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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	25922-819.306
First Inventor	Joseph J. Buggy
Title	***THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)***
Electronically filed	April 24, 2013

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form** (e.g., PTO/SB/17)
2. ☐ **Applicant claims small entity status**. See 37 CFR 1.27.
3. ☒ **Specification** *[Total Pages 199]*
   Both the claims and abstract must start on a new page
   (For information on the preferred arrangement, see MPEP 608.01(a))
4. ☒ **Drawing(s)** (35 U.S.C. 113) *[Total Sheets 39]*
5. ☐ **Oath or Declaration** *[Total Sheets _____]*
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d))
   (for continuation/divisional with Box 18 completed)
   i. ☐ DELETION OF INVENTOR(S)
   Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ **Application Data Sheet**. See 37 CFR 1.76
7. ☐ **CD-Rom or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission**
   (if applicable, items a.-c. are required)
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
   i. ☐ CD-ROM or CD-R (2 copies); or
   ii. ☐ Paper
   c. ☐ Statement verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
P.O. Box 1450
Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers** (cover sheet & document(s))
   Name of Assignee _____
10. ☐ **37 CFR 3.73(b) Statement** ☐ **Power of Attorney**
    (when there is an assignee)
11. ☐ **English Translation Document** *(if applicable)*
12. ☐ **Information Disclosure** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment**
14. ☐ **Return Receipt Postcard** (MPEP 503)
    (Should be specifically itemized)
15. ☐ **Certified Copy of Priority Document(s)**
    (if foreign priority is claimed)
16. ☐ **Nonpublication Request under** 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☒ Other: Application Cover Sheet (2 pages)

18. **If a CONTINUING APPLICATION**, *check appropriate box, and supply the requisite information below in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No.: 13/153,317

Prior application information: *Examiner* Ramachandran, Umamaheswari *Art Unit:* 1629

19. CORRESPONDENCE ADDRESS

☒ *The address associated with Customer Number:* 021971 *OR* ☐ Correspondence address below

Name					
Address					
City		*State*		*Zip Code*	
Country		*Telephone*		*Email*	

Signature	/Michael Hostetler/	*Date*	April 24, 2013
Name (Print/Type)	Michael J. Hostetler, Ph.D.	*Registration No. (Attorney/Agent)*	47,664

This collection of information is required by 37 CFR 1.53(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

BeiGene Exhibit 1023.001

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)
First Named Inventor/Applicant Name:	Joseph J. Buggy
Filer:	Michael J. Hostetler/Kelley Brown/Uale Taotafa
Attorney Docket Number:	25922-819.306

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Utility Appl Size fee per 50 sheets >100	1081	2	400	800
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**800**

Electronic Acknowledgement Receipt	
EFS ID:	15603761
Application Number:	13869700
International Application Number:	
Confirmation Number:	4966
Title of Invention:	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)
First Named Inventor/Applicant Name:	Joseph J. Buggy
Customer Number:	21971
Filer:	Michael J. Hostetler/Kelley Brown/Uale Taotafa
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	25922-819.306
Receipt Date:	24-APR-2013
Filing Date:	
Time Stamp:	17:33:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$800
RAM confirmation Number	4661
Deposit Account	232415
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Application Data Sheet	25922_819_306_ADS.pdf	1433685 e06db0226c1e1d7651fbc7f370044fd0f1a76564	no	8
Warnings:					
Information:					
2		25922_819_306_App.pdf	3876816 dc07f8e68c012e24b8c5d342280f37c174c70d93	yes	240
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	186	
	Claims		187	200	
	Abstract		201	201	
	Drawings-only black and white line drawings		202	240	
Warnings:					
Information:					
3	Transmittal of New Application	25922_819_306_UtilityTM.pdf	317022 88a2cb4e58b7fb55ea353b0f7c60ce99c8347b92	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	30218 c215e40b70db0907a254ba5b510ecb72cc956461	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	5657741		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Joseph	J.	Buggy	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Mountain View	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	858 Cuesta Drive		
Address 2			
City	Mountain View	State/Province	CA
Postal Code	94040	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Laurence		Elias	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Berkeley	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	41 Alvarado Road		
Address 2			
City	Berkeley	State/Province	CA
Postal Code	94705	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Gwen		Fyfe	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

BeiGene Exhibit 1023.007

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

City	San Francisco	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	20 La Ferrera Terrace		
Address 2			
City	San Francisco	State/Province	CA
Postal Code	94133	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Eric		Hedrick	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Summit	State/Province	NJ	Country of Residence i	US

Mailing Address of Inventor:

Address 1	59 Hobart Avenue		
Address 2			
City	Summit	State/Province	NJ
Postal Code	07901	Country i	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	J.	Loury	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	San Jose	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	7130 Galli Drive		
Address 2			
City	San Jose	State/Province	CA
Postal Code	95129	Country i	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Tarak	D.	Mody	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Sunnyvale	State/Province	CA	Country of Residence i	US

BeiGene Exhibit 1023.008

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

Mailing Address of Inventor:

Address 1	955 La Mesa Terrace #E		
Address 2			
City	Sunnyvale	**State/Province**	CA
Postal Code	94086	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	21971		
Email Address	PATENTDOCKET@WSGR.COM	Add Email	Remove Email

Application Information:

Title of the Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)		
Attorney Docket Number	25922-819.306	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	39	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	21971		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13/153317	2011-06-03
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/351130	2010-06-03
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/351655	2010-06-04
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/351793	2010-06-04
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/351762	2010-06-04
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/419764	2010-12-03
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/153317	non provisional of	61/472138	2011-04-05

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

Remove

Application Number	Country i	Filing Date (YYYY-MM-DD)	Priority Claimed
			◯ Yes ◉ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◯ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

Name of the Deceased or Legally Incapacitated Inventor :	
If the Applicant is an Organization check here. ☐	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:			
Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

Remove

If the Assignee is an Organization check here. ☒	
Organization Name	Pharmacyclics, Inc.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	25922-819.306
	Application Number	
Title of Invention	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

Mailing Address Information:			
Address 1	995 East Arques Avenue		
Address 2			
City	Sunnyvale	**State/Province**	CA
Country i	US	Postal Code	94085
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications					
Signature	/Michael Hostetler/			Date (YYYY-MM-DD)	2013-04-24
First Name	Michael	Last Name	Hostetler	Registration Number	47664

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

BeiGene Exhibit 1023.013

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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NON-PROVISIONAL PATENT APPLICATION

THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

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I hereby certify that the attached Utility Application and all marked attachments are being deposited by Electronic Filing on April 24, 2013 by using the EFS – Web patent filing system and addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: /Kelley Brown/ Date: April 24, 2013
Kelley Brown

THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

RELATED APPLICATIONS

[0001] The present application claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed June 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed June 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed December 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed April 5, 2011; all of which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0003] Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm,* **2000,** 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* **2000,** 282-288). In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor–mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. *See, e.g.,* C. A. Jeffries, et al., (2003), *Journal of Biological Chemistry* 278:26258-26264; N. J. Horwood, et al., (2003), *The Journal of Experimental Medicine* 197:1603-1611; Iwaki *et al.* (2005), *Journal of Biological Chemistry* 280(48):40261-40270; Vassilev *et al.* (1999), *Journal of Biological Chemistry* 274(3):1646-1656, and Quek *et al.* (1998), *Current Biology* 8(20):1137-1140.

SUMMARY OF THE INVENTION

[0004] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the

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malignancy. In some embodiments, the hematological malignancy is CLL. In some embodiments, the treating the hematological malignancy comprises managing the hematological malignancy. In some embodiments, the hematological malignancy is a B-cell malignancy. In some embodiments, the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid. In some embodiments, the mobilized cells are myeloid cells or lymphoid cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises preparing a biomarker profile for a population of cells isolated from the plurality of cells, wherein the biomarker profile indicates the expression of a biomarker, the expression level of a biomarker, mutations in a biomarker, or the presence of a biomarker. In some embodiments, the biomarker is any cytogenetic, cell surface molecular or protein

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or RNA expression marker. In some embodiments, the biomarker is: ZAP70; t(14,18); β-2 microglobulin; p53 mutational status; ATM mutational status; del(17)p; del(11)q; del(6)q; CD5; CD11c; CD19; CD20; CD22; CD25; CD38; CD103; CD138; secreted, surface or cytoplasmic immunoglobulin expression; V_H mutational status; or a combination thereof. In some embodiments, the method further comprises providing a second cancer treatment regimen based on the biomarker profile. In some embodiments, the method further comprises not administering based on the biomarker profile. In some embodiments, the method further comprises predicting the efficacy of a treatment regimen based on the biomarker profile. In some embodiments, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the hematological malignancy is follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, or extranodal marginal zone B cell lymphoma. In some embodiments, the hematological malignancy is chronic myelogenous (or myeloid) leukemia, or acute lymphoblastic leukemia. In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, relapsed or refractory follicular lymphoma, relapsed or refractory CLL; relapsed or refractory SLL; relapsed or refractory multiple myeloma. In some embodiments, the Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog. In some embodiments, the irreversible Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some embodiments, the amount of the irreversible Btk inhibitor is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some embodiments, the Btk inhibitor is administered orally. In some embodiments, the Btk inhibitor is administered once per day, twice per day, or three times per day. In some embodiments, the Btk inhibitor is administered until disease progression, unacceptable

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toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some embodiments, the Btk inhibitor treats a refractory hematological malignancy. In some embodiments, the Btk inhibitor is a maintenance therapy. In some embodiments, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises bendamustine, and rituximab. In some embodiments, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises dexamethasone and lenalidomide. In some embodiments, the inhibitor of Bruton's tyrosine kinase is a reversible inhibitor. In some embodiments, the inhibitor of Bruton's tyrosine kinase is an

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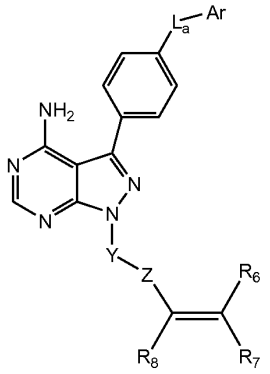
irreversible inhibitor. In some embodiments, the inhibitor of Bruton's tyrosine kinase forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog. In some embodiments, the inhibitor of Bruton's tyrosine kinase has the structure of Formula (D):



Formula (D)

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

Z is C(=O), OC(=O), NHC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NHS(=O)_x$, where x is 1 or 2;

R_7 and R_8 are independently H; or

R_7 and R_8 taken together form a bond;

R_6 is H; and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof. In some embodiments, the Bruton's tyrosine kinase inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some embodiments, La is O. In some embodiments, Ar is phenyl. In some embodiments, Z is C(=O), NHC(=O), or $S(=O)_2$. In some embodiments, each of R_7 and R_8 is H. In some embodiments, Y is a 4-, 5-, 6-, or 7-membered cycloalkyl ring; or Y is a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring.

[0005] Disclosed herein, in certain embodiments, is a method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-

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d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some embodiments, the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, or relapsed or refractory follicular lymphoma. In some embodiments, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered orally. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered once per day, twice per day, or three times per day. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some embodiments, (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is a second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some embodiments, the Btk inhibitor is a maintenance therapy. In some embodiments, the method further comprises administering a second cancer treatment regimen. In some embodiments, the second cancer treatment regimen is administered after mobilization of a plurality of lymphoid cells from the non-Hodgkin's lymphoma. In some embodiments, the second

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cancer treatment regimen is administered after lymphocytosis of a plurality of lymphoid cells from the non-Hodgkin's lymphoma. In some embodiments, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises bendamustine, and rituximab. In some embodiments, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some embodiments, the second cancer treatment regimen comprises dexamethasone and lenalidomide.

[0006] Disclosed herein, in certain embodiments, is a method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the method further comprises diagnosing the individual with diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), by determining the gene sequence of one or more biomarkers in a plurality of lymphoid cells isolated from the diffuse large B-cell lymphoma. In some embodiments, the irreversible Btk

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inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some embodiments, the ABC-DLBCL is characterized by a CD79B mutation. In some embodiments, the CD79B mutation is a mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some embodiments, the CD79B mutation is a missense mutation of the first immunoreceptor tyrosine-based activation motif (ITAM) tyrosine. In some embodiments, the CD79B mutation increases surface BCR expression and attenuates Lyn kinase activity. In some embodiments, the ABC-DLBCL is characterized by a CD79A mutation. In some embodiments, the CD79A mutation is in the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some embodiments, the CD79A mutation is a splice-donor-site mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some embodiments, the CD79A mutation deletes the immunoreceptor tyrosine-based activation motif (ITAM) signaling module. In some embodiments, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some embodiments, the MyD88 mutation is the amino acid substitution L265P in the MYD88 Toll/IL-1 receptor (TIR) domain. In some embodiments, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some embodiments, the irreversible Btk inhibitor is administered orally. In some embodiments, the irreversible Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the irreversible Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the irreversible Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy. In some embodiments, the irreversible Btk inhibitor treats a refractory hematological malignancy. In some embodiments, the irreversible Btk inhibitor is a maintenance therapy. In some embodiments, the method further comprises administering at least one additional cancer treatment regimen. In some embodiments, the additional cancer treatment regimen comprises a chemotherapeutic agent, an immunotherapeutic agent, a steroid, radiation therapy, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises an antibody, B cell receptor signaling

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inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, in certain embodiments is a damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

[0007] Disclosed herein, in certain embodiments, is a method of determining a cancer treatment regimen for an individual with a hematological malignancy, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; (b) analyzing the mobilized plurality of cells; and (c) selecting a cancer treatment regimen. In some embodiments, the cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the cancer treatment regimen comprises a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof. In some embodiments, the cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof. In some embodiments, the cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab. In some embodiments, the cancer treatment regimen comprises bendamustine, and rituximab. In some embodiments, the cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab. In some embodiments, the cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally,

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rituximab. In some embodiments, the cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab. In some embodiments, the cancer treatment regimen comprises dexamethasone and lenalidomide.

BRIEF DESCRIPTION OF THE FIGURES

[0008] Fig. 1 depicts the role of Btk activity in a number of processes in a CLL cell that contribute to the pathogenesis of the disease

[0009] Fig. 2 presents the absolute lyphocyte count during the course of treatment with an irreversible Btk inhibitor for an individual with CLL.

[0010] Fig. 3 presents change in the sum of the product of the diameters of lymph node (LN) in patients with CLL and SLL who are treated with an irreversible Btk inhibitor.

[0011] Fig. 4 depicts LN response in patient suffering from CLL. Left panel depicts LN prior to treatment with an irreversible Btk inhibitor and Right panel depicts LN post-treatment with an irreversible Btk inhibitor.

[0012] Fig. 5 depicts the effect of an irreversible Btk inhibitor on LN disease burden and lymphocytosis over time in the patients suffering with CLL and/or SLL.

[0013] Fig. 6 depicts adverse effects in patients treated with an irreversible Btk inhibitor. Grades 1-4 represent severity of effects with 1 representing very mild to 4 representing extreme discomfort.

[0014] Fig. 7 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to individuals with follicular lymphoma who achieved complete or partial response (CR/PR). The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. All Patients (except Pt 32009) were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. Note the increases of ALC during most cycles of most patients, and the fall of ALC at the beginning of subsequent cycles. This pattern is often blunted in later cycles as patients responded to treatment. Patient 32009 received treatment without interruption and did not show this cyclic pattern, but did show an increase at Cycle 1, day15, and gradual increases during Cycles 2 to 5.

[0015] Fig. 8 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to individuals with follicular lymphoma who had Stable Disease (SD) during treatment. The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by

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cycle number and day in the X axis. All Patients were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. Note the gradual increase of blood ALC mobilization of Patient 32004, who initially was stable but later had Progressive Disease (PD).

[0016] Fig. 9 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to PD individuals with follicular lymphoma. The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. All Patients except 38010 were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. Note lack of mobilization, especially patients 38010 and 32001. Patient 323001 had limited treatment before being taken off study. The lymphocyte response suggests that this patient might had responded if it had been possible to stay on treatment longer.

[0017] Fig. 10 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to PR and SD individuals with DLBCL. The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. Patient 38011 was treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for this patient. Patients 38008 and 324001 were treated with continuous daily doses.

[0018] Fig. 11 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to PD individuals with DLBCL. The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. All Patients were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. Note lack of mobilization for 3 of the 4 patients. Patient 32002 received only one cycle of treatment.

[0019] Fig. 12 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day after administering a Btk inhibitor to individuals with mantle cell lymphoma. The Y Axis shows the Absolute Lymphocyte Counts (ALC) at each time point by cycle number and day in the X axis. Patients 32006, 38003, and 38004 were treated on schedule of 4 weeks on treatment followed by one week off. Thus, day1 of each cycle follows one week off drug for these patients. The other patients were treated with continuous daily dosing. Note that the patient with initial PD (32014) failed to show mobilization.

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[0020] Fig. 13 depicts the absolute lymphocyte count (ALC)/109 L vs. Cycle Day for after administering a Btk inhibitor to the individuals with mantle cell lymphoma shown in Figure 12. The axis has been changed, as compared to Fig. 12, to demonstrate low amplitude fluctuations. Note that all responding patients showed some degree of mobilization.

[0021] Fig. 14 demonstrates that lymphocyte mobilization, specifically B Cell type, consistent with lymphoma cells, decreases as disease responds. Patient 32007, Cohort 4, had follicular lymphoma, grade 3, which gradually regressed from SD to CR. Although the changes of ALC in this case are not dramatic, the B cell fraction is undergoing characteristic cyclic increases in response to treatment with a Btk inhibitor. Also note the decreasing cycle by cycle magnitude of shifts consistent with cumulative disease control.

[0022] Fig. 15 demonstrates that there is increased B Cell mobilization with disease progression. Patient 32004, Cohort 2, had follicular lymphoma, grade 1, which progressed from SD initially to PD following Cycle 6.

[0023] Fig. 16 depicts early mobilization and eventual decrease of a $CD45^{DIM}$ B cell subpopulation in responding mantle cell lymphoma patient 200-005. This subpopulation has a typical MCL immunophenotype ($CD45^{DIM}$) and is different than that of normal lymphocytes.

[0024] Fig. 17 depicts abnormal high light scatter $CD19^{+}$ cells mobilizing and then regressing in CR DLBCL Pt 324001. These $CD45^{+}$ cells with light scatter (SSC-H) in the upper panels were gated upon and their CD3 vs CD19 staining displayed in the lower panels. Here the putative malignant cells were "hidden" in the large MNC window normally defining monocytes. The sequence of mobilization followed by response is similar to other examples.

[0025] Figure 18 presents the responses for a clinical trial involving administering a Btk inhibitor to elderly patients with CLL or SLL, who are naïve for drug intervention. Individuals were administered 420 mg/day of a Btk inhibitor.

[0026] Figure 19 presents the responses for a clinical trial involving administering a Btk inhibitor to R/R patients with CLL or SLL. Individuals were administered 420 mg/day of a Btk inhibitor.

[0027] Figure 20 presents the responses for a clinical trial involving administering a Btk inhibitor to individuals with high risk CLL.

[0028] Figure 21 presents the response over time for a clinical trial involving administering a Btk inhibitor to individuals with CLL or SLL.

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[0029] Figure 22 presents the best responses for all patients in a clinical trial involving administering a Btk inhibitor to individuals with CLL or SLL.

[0030] Figure 23 presents the best responses for abstract patients in a clinical trial involving administering a Btk inhibitor to individuals with CLL or SLL.

[0031] Figure 24 presents the best response by prognostic factor in CLL or SLL patients involved in a clinical trial involving administering a Btk inhibitor.

[0032] Figure 25 presents initial (Cycle 2) response assessment and best response (420mg Cohorts) in CLL or SLL patients involved in a clinical trial involving administering a Btk inhibitor.

[0033] Figure 26 presents initial (Cycle 2) response assessment by dose in relapsed/refractory CLL or SLL patients involved in a clinical trial involving administering a Btk inhibitor.

[0034] Figure 27 presents improvements in hematological parameters in CLL or SLL patients involved in a clinical trial involving administering a Btk inhibitor.

[0035] Figure 28 present data showing the results of a combination of a Btk inhibitor and Carboplatin or Velcade in DoHH2 cells.

[0036] Figure 29 present data showing the results of a combination of a Btk inhibitor and Dexamethasone or Lenalidomide in DoHH2 cells.

[0037] Figure 30 present data showing the results of a combination of a Btk inhibitor and Temsirolimus or R406 in DoHH2 cells.

[0038] Figure 31 present data showing the results of a combination of a Btk inhibitor and Gemcitabine or Doxorubicin in DoHH2 cells.

[0039] Figure 32 present data showing the results of a combination of a Btk inhibitor and Cal-101 in TMD8 cells.

[0040] Figure 33 present data showing the results of a combination of a Btk inhibitor and R406 in TMD8 cells.

[0041] Figure 34 present data showing the results of a combination of a Btk inhibitor and vincristine in TMD8 cells.

[0042] Figure 35 present data showing the results of a combination of a Btk inhibitor and doxorubicin in TMD8 cells.

[0043] Figure 36 present data showing the results of a combination of a Btk inhibitor and lenolidomide in TMD8 cells.

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[0044] Figure 37 present data showing the results of a combination of a Btk inhibitor and velcade in TMD8 cells.

[0045] Figure 38 present data showing the results of a combination of a Btk inhibitor and Fludarabine in TMD8 cells.

[0046] Figure 39 present data showing the results of a combination of a Btk inhibitor and taxol in TMD8 cells.

DETAILED DESCRIPTION OF THE INVENTION

[0047] There is currently a need for methods of treating (including, diagnosing) hematological malignancies, including relapsed and refractory B cell malignancies, and ABC-DLBCL. The present application is based, in part, on the unexpected discovery that Btk inhibitors induce mobilization (or, in some cases, lymphocytosis) of lymphoid cells in solid hematological malignancies. Mobilization of the lymphoid cells increases their exposure to additional cancer treatment regimens and their availability for biomarker screening. The inventors have also found that Btk inhibitors are useful for treating relapsed and refractory malignancies and ABC-DLBCL.

[0048] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. Disclosed herein, in certain embodiments, is a method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

Certain Terminology

[0049] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that

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such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

[0050] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0051] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0052] Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification.

[0053] It is to be understood that the methods and compositions described herein are not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as

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such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the methods and compositions described herein, which will be limited only by the appended claims.

[0054] All publications and patents mentioned herein are incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications, which might be used in connection with the methods, compositions and compounds described herein. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors described herein are not entitled to antedate such disclosure by virtue of prior invention or for any other reason.

[0055] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl moiety may be a "saturated alkyl" group, which means that it does not contain any alkene or alkyne moieties. The alkyl moiety may also be an "unsaturated alkyl" moiety, which means that it contains at least one alkene or alkyne moiety. An "alkene" moiety refers to a group that has at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group that has at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic. Depending on the structure, an alkyl group can be a monoradical or a diradical (i.e., an alkylene group). The alkyl group could also be a "lower alkyl" having 1 to 6 carbon atoms.

[0056] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . C_1-C_x.

[0057] The "alkyl" moiety may have 1 to 10 carbon atoms (whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, *i.e.*, the alkyl chain is selected from among methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Thus C_1-C_4 alkyl includes C_1-C_2 alkyl and C_1-C_3 alkyl. Alkyl groups can be substituted or unsubstituted. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

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[0058] As used herein, the term "non-cyclic alkyl" refers to an alkyl that is not cyclic (i.e., a straight or branched chain containing at least one carbon atom). Non-cyclic alkyls can be fully saturated or can contain non-cyclic alkenes and/or alkynes. Non-cyclic alkyls can be optionally substituted.

[0059] The term "alkenyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a double bond that is not part of an aromatic group. That is, an alkenyl group begins with the atoms –C(R)=C(R)-R, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. The alkenyl moiety may be branched, straight chain, or cyclic (in which case, it would also be known as a "cycloalkenyl" group). Depending on the structure, an alkenyl group can be a monoradical or a diradical (i.e., an alkenylene group). Alkenyl groups can be optionally substituted. Non-limiting examples of an alkenyl group include $–CH=CH_2$, $-C(CH_3)=CH_2$, $-CH=CHCH_3$, $–C(CH_3)=CHCH_3$. Alkenylene groups include, but are not limited to, –CH=CH–, $–C(CH_3)=CH–$, $–CH=CHCH_2–$, $–CH=CHCH_2CH_2–$ and $–C(CH_3)=CHCH_2–$. Alkenyl groups could have 2 to 10 carbons. The alkenyl group could also be a "lower alkenyl" having 2 to 6 carbon atoms.

[0060] The term "alkynyl" refers to a type of alkyl group in which the first two atoms of the alkyl group form a triple bond. That is, an alkynyl group begins with the atoms –C≡C-R, wherein R refers to the remaining portions of the alkynyl group, which may be the same or different. The "R" portion of the alkynyl moiety may be branched, straight chain, or cyclic. Depending on the structure, an alkynyl group can be a monoradical or a diradical (i.e., an alkynylene group). Alkynyl groups can be optionally substituted. Non-limiting examples of an alkynyl group include, but are not limited to, $–C≡CH$, $-C≡CCH_3$, $–C≡CCH_2CH_3$, –C≡C–, and $–C≡CCH_2–$. Alkynyl groups can have 2 to 10 carbons. The alkynyl group could also be a "lower alkynyl" having 2 to 6 carbon atoms.

[0061] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[0062] "Hydroxyalkyl" refers to an alkyl radical, as defined herein, substituted with at least one hydroxy group. Non-limiting examples of a hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl.

[0063] "Alkoxyalkyl" refers to an alkyl radical, as defined herein, substituted with an alkoxy group, as defined herein.

[0064] An "alkenyloxy" group refers to a (alkenyl)O- group, where alkenyl is as defined herein.

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[0065] The term "alkylamine" refers to the $-N(alkyl)_xH_y$ group, where x and y are selected from among x=1, y=1 and x=2, y=0. When x=2, the alkyl groups, taken together with the N atom to which they are attached, can optionally form a cyclic ring system.

[0066] "Alkylaminoalkyl" refers to an alkyl radical, as defined herein, substituted with an alkylamine, as defined herein.

[0067] An "amide" is a chemical moiety with the formula -C(O)NHR or -NHC(O)R, where R is selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). An amide moiety may form a linkage between an amino acid or a peptide molecule and a compound described herein, thereby forming a prodrug. Any amine, or carboxyl side chain on the compounds described herein can be amidified. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[0068] The term "ester" refers to a chemical moiety with formula -COOR, where R is selected from among alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference in its entirety.

[0069] As used herein, the term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (e.g., aryls and cycloalkyls), heterocycles (e.g., heteroaryls and non-aromatic heterocycles), aromatics (e.g. aryls and heteroaryls), and non-aromatics (e.g., cycloalkyls and non-aromatic heterocycles). Rings can be optionally substituted. Rings can be monocyclic or polycyclic.

[0070] As used herein, the term "ring system" refers to one, or more than one ring.

[0071] The term "membered ring" can embrace any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridine, pyran and thiopyran are 6-membered rings and cyclopentyl, pyrrole, furan, and thiophene are 5-membered rings.

[0072] The term "fused" refers to structures in which two or more rings share one or more bonds.

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[0073] The term "carbocyclic" or "carbocycle" refers to a ring wherein each of the atoms forming the ring is a carbon atom. Carbocycle includes aryl and cycloalkyl. The term thus distinguishes carbocycle from heterocycle ("heterocyclic") in which the ring backbone contains at least one atom which is different from carbon (i.e a heteroatom). Heterocycle includes heteroaryl and heterocycloalkyl. Carbocycles and heterocycles can be optionally substituted.

[0074] The term "aromatic" refers to a planar ring having a delocalized π-electron system containing 4n+2 π electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term "aromatic" includes both carbocyclic aryl (*e.g.*, phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

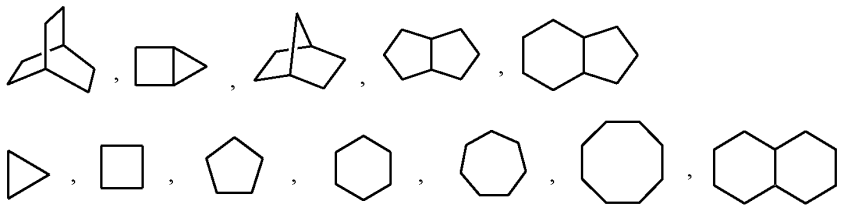
[0075] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

[0076] An "aryloxy" group refers to an (aryl)O- group, where aryl is as defined herein.

[0077] "Aralkyl" means an alkyl radical, as defined herein, substituted with an aryl group. Non-limiting aralkyl groups include, benzyl, phenethyl, and the like.

[0078] "Aralkenyl" means an alkenyl radical, as defined herein, substituted with an aryl group, as defined herein.

[0079] The term "cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, partially unsaturated, or fully unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include the following moieties:



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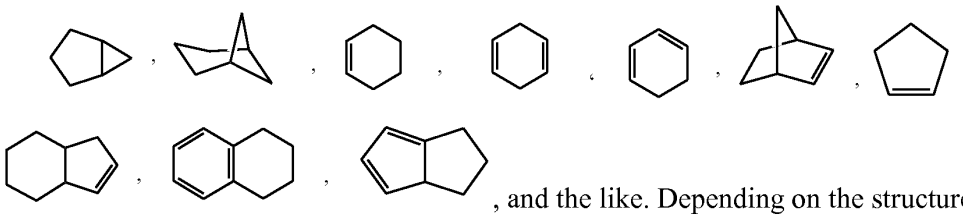 , and the like. Depending on the structure, a cycloalkyl group can be a monoradical or a diradical (e.g., an cycloalkylene group). The cycloalkyl group could also be a "lower cycloalkyl" having 3 to 8 carbon atoms.

[0080] "Cycloalkylalkyl" means an alkyl radical, as defined herein, substituted with a cycloalkyl group. Non-limiting cycloalkylalkyl groups include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.

[0081] The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (e.g., C_1-C_6 heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as "C_1-C_6 heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. It is understood that the heterocylic ring can have additional heteroatoms in the ring. Designations such as "4-6 membered heterocycle" refer to the total number of atoms that are contained in the ring (i.e., a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In heterocycles that have two or more heteroatoms, those two or more heteroatoms can be the same or different from one another. Heterocycles can be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl,

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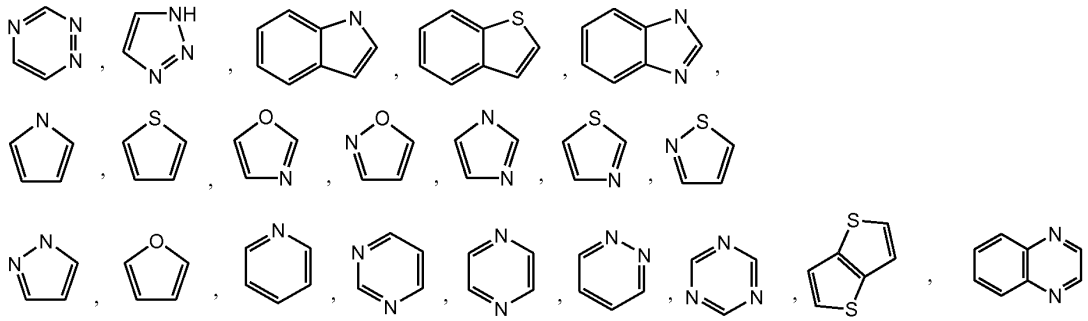
piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, may be C-attached or *N*-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. Depending on the structure, a heterocycle group can be a monoradical or a diradical (i.e., a heterocyclene group).

[0082] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. An *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. Illustrative examples of heteroaryl groups include the following moieties:



and the like. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroarylene group).

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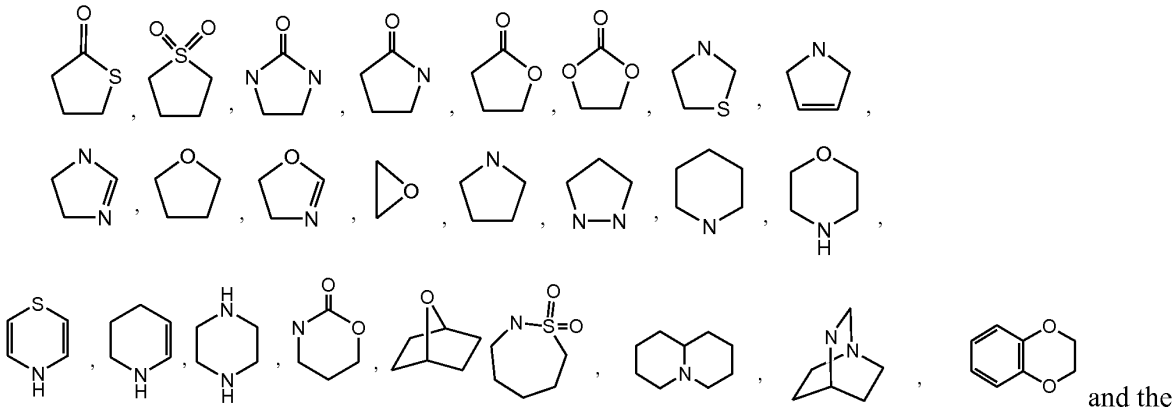
[0083] As used herein, the term "non-aromatic heterocycle", "heterocycloalkyl" or "heteroalicyclic" refers to a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. A "non-aromatic heterocycle" or "heterocycloalkyl" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Heterocycloalkyl rings can be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heterocycloalkyl rings can be optionally substituted. In certain embodiments, non-aromatic heterocycles contain one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of heterocycloalkyls include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:



and the like. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Depending on the structure, a heterocycloalkyl group can be a monoradical or a diradical (i.e., a heterocycloalkylene group).

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[0084] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo and iodo.

[0085] The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another. In other embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another.

[0086] The term "fluoroalkyl," as used herein, refers to alkyl group in which at least one hydrogen is replaced with a fluorine atom. Examples of fluoroalkyl groups include, but are not limited to, $-CF_3$, $-CH_2CF_3$, $-CF_2CF_3$, $-CH_2CH_2CF_3$ and the like.

[0087] As used herein, the terms "heteroalkyl" "heteroalkenyl" and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals in which one or more skeletal chain atoms is a heteroatom, *e.g.*, oxygen, nitrogen, sulfur, silicon, phosphorus or combinations thereof. The heteroatom(s) may be placed at any interior position of the heteroalkyl group or at the position at which the heteroalkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-CH_2-NH-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-N(CH_3)-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. In addition, up to two heteroatoms may be consecutive, such as, by way of example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[0088] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from among oxygen, sulfur, nitrogen, silicon and phosphorus, but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can all be the same as one another, or some or all of the two or more heteroatoms can each be different from the others.

[0089] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[0090] An "isocyanato" group refers to a -NCO group.

[0091] An "isothiocyanato" group refers to a -NCS group.

[0092] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

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[0093] A "sulfinyl" group refers to a -S(=O)-R.

[0094] A "sulfonyl" group refers to a -$S(=O)_2$-R.

[0095] A "thioalkoxy" or "alkylthio" group refers to a –S-alkyl group.

[0096] A "alkylthioalkyl" group refers to an alkyl group substituted with a –S-alkyl group.

[0097] As used herein, the term "O-carboxy" or "acyloxy" refers to a group of formula RC(=O)O-.

[0098] "Carboxy" means a -C(O)OH radical.

[0099] As used herein, the term "acetyl" refers to a group of formula -$C(=O)CH_3$.

[00100] "Acyl" refers to the group -C(O)R.

[00101] As used herein, the term "trihalomethanesulfonyl" refers to a group of formula $X_3CS(=O)_2$- where X is a halogen.

[00102] As used herein, the term "cyano" refers to a group of formula -CN.

[00103] "Cyanoalkyl" means an alkyl radical, as defined herein, substituted with at least one cyano group.

[00104] As used herein, the term "N-sulfonamido" or "sulfonylamino" refers to a group of formula $RS(=O)_2NH$-.

[00105] As used herein, the term "O-carbamyl" refers to a group of formula -$OC(=O)NR_2$.

[00106] As used herein, the term "N-carbamyl" refers to a group of formula ROC(=O)NH-.

[00107] As used herein, the term "O-thiocarbamyl" refers to a group of formula -OC(=S)NR2.

[00108] As used herein, the term "N-thiocarbamyl" refers to a group of formula ROC(=S)NH-.

[00109] As used herein, the term "C-amido" refers to a group of formula -C(=O)NR2.

[00110] "Aminocarbonyl" refers to a -CONH2 radical.

[00111] As used herein, the term "N-amido" refers to a group of formula RC(=O)NH-.

[00112] As used herein, the substituent "R" appearing by itself and without a number designation refers to a substituent selected from among from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[00113] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s) individually and independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, cyano, halo, acyl, nitro, haloalkyl, fluoroalkyl, amino, including mono- and di-substituted amino groups, and the protected derivatives

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thereof. By way of example an optional substituents may be L_sR_s, wherein each L_s is independently selected from a bond, -O-, -C(=O)-, -S-, -S(=O)-, -S(=O)$_2$-, -NH-, -NHC(O)-, -C(O)NH-, S(=O)$_2$NH-, -NHS(=O)$_2$, -OC(O)NH-, -NHC(O)O-, -(substituted or unsubstituted C_1-C_6 alkyl), or -(substituted or unsubstituted C_2-C_6 alkenyl); and each R_s is independently selected from H, (substituted or unsubstituted C_1-C_4alkyl), (substituted or unsubstituted C_3-C_6cycloalkyl), heteroaryl, or heteroalkyl. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, above.

[00114] The term "Michael acceptor moiety" refers to a functional group that can participate in a Michael reaction, wherein a new covalent bond is formed between a portion of the Michael acceptor moiety and the donor moiety. The Michael acceptor moiety is an electrophile and the "donor moiety" is a nucleophile.

[00115] The term "nucleophile" or "nucleophilic" refers to an electron rich compound, or moiety thereof. An example of a nucleophile includes, but in no way is limted to, a cysteine residue of a molecule, such as, for example Cys 481 of Btk.

[00116] The term "electrophile", or "electrophilic" refers to an electron poor or electron deficient molecule, or moiety thereof. Examples of electrophiles include, but in no way are limited to, Micheal acceptor moieties.

[00117] The term "acceptable" or "pharmaceutically acceptable", with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated or does not abrogate the biological activity or properties of the compound, and is relatively nontoxic.

[00118] "B-cell lymphoproliferative disorders (BCLD) biomarkers", as used herein, refer to any biological molecule (found either in blood, other body fluids, or tissues) or any chromosomal abnormality that is a sign of a BCLD-related condition or disease.

[00119] "Tumor," as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. "Neoplastic," as used herein, refers to any form of dysregulated or unregulated cell growth, whether malignant or benign, resulting in abnormal tissue growth. Thus, "neoplastic cells" include malignant and benign cells having dysregulated or unregulated cell growth.

[00120] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but

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are not limited to, B-cell lymphoproliferative disorders (BCLDs), such as lymphoma and leukemia, and solid tumors. By "B cell-related cancer" or "cancer of B-cell lineage" is intended any type of cancer in which the dysregulated or unregulated cell growth is associated with B cells.

[00121] By "refractory" in the context of a cancer is intended the particular cancer is resistant to, or non-responsive to, therapy with a particular therapeutic agent. A cancer can be refractory to therapy with a particular therapeutic agent either from the onset of treatment with the particular therapeutic agent (i.e., non-responsive to initial exposure to the therapeutic agent), or as a result of developing resistance to the therapeutic agent, either over the course of a first treatment period with the therapeutic agent or during a subsequent treatment period with the therapeutic agent.

[00122] By "agonist activity" is intended that a substance functions as an agonist. An agonist combines with a receptor on a cell and initiates a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand.

[00123] By "antagonist activity" is intended that the substance functions as an antagonist. An antagonist of Btk prevents or reduces induction of any of the responses meidated by Btk.

[00124] By "significant" agonist activity is intended an agonist activity of at least 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% greater than the agonist activity induced by a neutral substance or negative control as measured in an assay of a B cell response. Preferably, "significant" agonist activity is an agonist activity that is at least 2-fold greater or at least 3-fold greater than the agonist activity induced by a neutral substance or negative control as measured in an assay of a B cell response. Thus, for example, where the B cell response of interest is B cell proliferation, "significant" agonist activity would be induction of a level of B cell proliferation that is at least 2-fold greater or at least 3-fold greater than the level of B cell proliferation induced by a neutral substance or negative control.

[00125] A substance "free of significant agonist activity" would exhibit an agonist activity of not more than about 25% greater than the agonist activity induced by a neutral substance or negative control, preferably not more than about 20% greater, 15% greater, 10% greater, 5% greater, 1% greater, 0.5% greater, or even not more than about 0.1% greater than the agonist activity induced by a neutral substance or negative control as measured in an assay of a B cell response.

[00126] In some embodiments, the Btk inhibitor therapeutic agent is an antagonist anti-Btk antibody. Such antibodies are free of significant agonist activity as noted above when bound to a Btk antigen in a human cell. In one embodiment of the invention, the antagonist anti-Btk antibody is free

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of significant agonist activity in one cellular response. In another embodiment of the invention, the antagonist anti-Btk antibody is free of significant agonist activity in assays of more than one cellular response (e.g., proliferation and differentiation, or proliferation, differentiation, and, for B cells, antibody production).

[00127] By "Btk-mediated signaling" it is intended any of the biological activities that are dependent on, either directly or indirection, the activity of Btk. Examples of Btk-mediated signaling are signals that lead to proliferation and survival of Btk-expressing cells, and stimulation of one or more Btk-signaling pathways within Btk-expressing cells.

[00128] A Btk "signaling pathway" or "signal transduction pathway" is intended to mean at least one biochemical reaction, or a group of biochemical reactions, that results from the activity of Btk, and which generates a signal that, when transmitted through the signal pathway, leads to activation of one or more downstream molecules in the signaling cascade. Signal transduction pathways involve a number of signal transduction molecules that lead to transmission of a signal from the cell-surface across the plasma membrane of a cell, and through one or more in a series of signal transduction molecules, through the cytoplasm of the cell, and in some instances, into the cell's nucleus. Of particular interest to the present invention are Btk signal transduction pathways which ultimately regulate (either enahnce or inhibit) the activation of NF-κB via the NF-κB signaling pathway.

[00129] The methods of the present invention are directed to methods for treating cancer that, in certain embodiments, utilize antibodies for determining the expression or presence of certain BCLD biomarkers in these methods. The following terms and definitions apply to such antibodies.

[00130] Antibodies" and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. The terms are used synonymously. In some instances the antigen specificity of the immunoglobulin may be known.

[00131] The term "antibody" is used in the broadest sense and covers fully assembled antibodies, antibody fragments that can bind antigen (e.g., Fab, $F(ab')_2$, Fv, single chain antibodies, diabodies, antibody chimeras, hybrid antibodies, bispecific antibodies, humanized antibodies, and the like), and recombinant peptides comprising the forgoing.

[00132] The terms "monoclonal antibody" and "mAb" as used herein refer to an antibody obtained from a substantially homogeneous population of antibodies, i.e., the individual antibodies

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comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

[00133] Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy-chain variable domains.

[00134] The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. Variable regions confer antigen-binding specificity. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) or hypervariable regions, both in the light chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are celled in the framework (FR) regions. The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-pleated-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-pleated-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies (see, Kabat et al. (1991) NIH PubL. No. 91-3242, Vol. I, pages 647-669). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as Fc receptor (FcR) binding, participation of the antibody in antibody-dependent cellular toxicity, initiation of complement dependent cytotoxicity, and mast cell degranulation.

[00135] The term "hypervariable region," when used herein, refers to the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarily determining region" or "CDR" (i.e., residues 24-34 (L1), 50-56 (L2), and 89-97 (L3) in the light-chain variable domain and 31-35 (H1), 50-65 (H2), and 95-102

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(H3) in the heavy-chain variable domain; Kabat et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institute of Health, Bethesda, Md.) and/or those residues from a "hypervariable loop" (i.e., residues 26-32 (L1), 50-52 (L2), and 91-96 (L3) in the light-chain variable domain and (H1), 53-55 (H2), and 96-101 (13) in the heavy chain variable domain; Clothia and Lesk, (1987) J. Mol. Biol., 196:901-917). "Framework" or "FR" residues are those variable domain residues other than the hypervariable region residues, as herein deemed.

[00136] "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab, F(ab')2, and Fv fragments; diabodies; linear antibodies (Zapata et al. (1995) Protein Eng. 10:1057-1062); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

[00137] "Fv" is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[00138] The Fab fragment also contains the constant domain of the light chain and the first constant domain (C_{H1}) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain C_{H1} domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. Fab' fragments are produced by reducing the F(ab')2 fragment's heavy chain disulfide bridge. Other chemical couplings of antibody fragments are also known.

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[00139] The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[00140] Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of human immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Different isotypes have different effector functions. For example, human IgG1 and IgG3 isotypes have ADCC (antibody dependent cell-mediated cytotoxicity) activity.

[00141] The word "label" when used herein refers to a detectable compound or composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable.

[00142] The term “acceptable” or “pharmaceutically acceptable”, with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated or does not abrogate the biological activity or properties of the compound, and is relatively nontoxic.

[00143] As used herein, the term “agonist” refers to a compound, the presence of which results in a biological activity of a protein that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the protein, such as, for example, Btk.

[00144] As used herein, the term “partial agonist” refers to a compound the presence of which results in a biological activity of a protein that is of the same type as that resulting from the presence of a naturally occurring ligand for the protein, but of a lower magnitude.

[00145] As used herein, the term “antagonist” refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a protein. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a protein, such as, for example, Btk. In certain embodiments, an antagonist is an inhibitor.

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[00146] The term "Bruton's tyrosine kinase (Btk)," as used herein, refers to Bruton's tyrosine kinase from *Homo sapiens*, as disclosed in, e.g., U.S. Patent No. 6,326,469 (GenBank Accession No. NP_000052).

[00147] The term "Bruton's tyrosine kinase homolog," as used herein, refers to orthologs of Bruton's tyrosine kinase, e.g., the orthologs from mouse (GenBank Accession No. AAB47246), dog (GenBank Accession No. XP_549139.), rat (GenBank Accession No. NP_001007799), chicken (GenBank Accession No. NP_989564), or zebra fish (GenBank Accession No. XP_698117), and fusion proteins of any of the foregoing that exhibit kinase activity towards one or more substrates of Bruton's tyrosine kinase (e.g. a peptide substrate having the amino acid sequence "AVLESEEELYSSARQ").

[00148] The terms "co-administration" or "combination therapy" and the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00149] The term "effective amount," as used herein, refers to a sufficient amount of a Btk inhibitory agent or a Btk inhibitor compound being administered which will result in an increase or appearance in the blood of a subpopulation of lymphocytes (e.g., pharmaceutical debulking). For example, an "effective amount" for diagnostic and/or prognostic uses is the amount of the composition including a compound as disclosed herein required to provide a clinically significant decrease an increase or appearance in the blood of a subpopulation of lymphocytes without undue adverse side effects. An appropriate "effective amount" in any individual case may be determined using techniques, such as a dose escalation study.

[00150] The term "therapeutically effective amount," as used herein, refers to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms s B-cell lymphoproliferative disorder (BCLD). The result can be reduction and/or alleviation of the signs, symptoms, or causes of BCLD, or any other desired alteration of a biological system. The term "therapeutically effective amount" includes, for example, a prophylactically effective amount. An "effective amount" of a compound disclosed herein is an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. It is understood that "an effect amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of the compound of any of Formula (A),

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Formula (B), Formula (C), or Formula (D), age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician. By way of example only, therapeutically effective amounts may be determined by routine experimentation, including but not limited to a dose escalation clinical trial.

[00151] The terms "enhance" or "enhancing" means to increase or prolong either in potency or duration a desired effect. By way of example, "enhancing" the effect of therapeutic agents refers to the ability to increase or prolong, either in potency or duration, the effect of therapeutic agents on during treatment of a disease, disorder or condition. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of a therapeutic agent in the treatment of a disease, disorder or condition. When used in a patient, amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[00152] The term "homologous cysteine," as used herein refers to a cysteine residue found with in a sequence position that is homologous to that of cysteine 481 of Bruton's tyrosine kinase, as defined herein. For example, cysteine 482 is the homologous cysteine of the rat ortholog of Bruton's tyrosine kinase; cysteine 479 is the homologous cysteine of the chicken ortholog; and cysteine 481 is the homologous cysteine in the zebra fish ortholog. In another example, the homologous cysteine of TXK, a Tec kinase family member related to Bruton's tyrosine, is Cys 350. See also the sequence alignments of tyrosine kinases (TK) published on the world wide web at kinase.com/human/kinome/phylogeny.html.

[00153] The term "identical," as used herein, refers to two or more sequences or subsequences which are the same. In addition, the term "substantially identical," as used herein, refers to two or more sequences which have a percentage of sequential units which are the same when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using comparison algorithms or by manual alignment and visual inspection. By way of example only, two or more sequences may be "substantially identical" if the sequential units are about 60% identical, about 65% identical, about 70% identical, about 75% identical, about 80% identical, about 85% identical, about 90% identical, or about 95% identical over a specified region. Such percentages to describe the "percent identity" of two or more sequences. The identity of a sequence can exist over a region that is at least about 75-100 sequential units in length, over a region that is about 50 sequential units in length, or, where not specified, across the entire sequence. This definition also

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refers to the complement of a test sequence. By way of example only, two or more polypeptide sequences are identical when the amino acid residues are the same, while two or more polypeptide sequences are "substantially identical" if the amino acid residues are about 60% identical, about 65% identical, about 70% identical, about 75% identical, about 80% identical, about 85% identical, about 90% identical, or about 95% identical over a specified region. The identity can exist over a region that is at least about 75-100 amino acids in length, over a region that is about 50 amino acids in length, or, where not specified, across the entire sequence of a polypeptide sequence. In addition, by way of example only, two or more polynucleotide sequences are identical when the nucleic acid residues are the same, while two or more polynucleotide sequences are "substantially identical" if the nucleic acid residues are about 60% identical, about 65% identical, about 70% identical, about 75% identical, about 80% identical, about 85% identical, about 90% identical, or about 95% identical over a specified region. The identity can exist over a region that is at least about 75-100 nucleic acids in length, over a region that is about 50 nucleic acids in length, or, where not specified, across the entire sequence of a polynucleotide sequence.

[00154] The terms "inhibits", "inhibiting", or "inhibitor" of a kinase, as used herein, refer to inhibition of enzymatic phosphotransferase activity.

[00155] The term "irreversible inhibitor," as used herein, refers to a compound that, upon contact with a target protein (e.g., a kinase) causes the formation of a new covalent bond with or within the protein, whereby one or more of the target protein's biological activities (e.g., phosphotransferase activity) is diminished or abolished notwithstanding the subsequent presence or absence of the irreversible inhibitor.

[00156] The term "irreversible Btk inhibitor," as used herein, refers to an inhibitor of Btk that can form a covalent bond with an amino acid residue of Btk. In one embodiment, the irreversible inhibitor of Btk can form a covalent bond with a Cys residue of Btk; in particular embodiments, the irreversible inhibitor can form a covalent bond with a Cys 481 residue (or a homolog thereof) of Btk or a cysteine residue in the homologous corresponding position of another tyrosine kinase.

[00157] The term "isolated," as used herein, refers to separating and removing a component of interest from components not of interest. Isolated substances can be in either a dry or semi-dry state, or in solution, including but not limited to an aqueous solution. The isolated component can be in a homogeneous state or the isolated component can be a part of a pharmaceutical composition that comprises additional pharmaceutically acceptable carriers and/or excipients. By way of example

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only, nucleic acids or proteins are "isolated" when such nucleic acids or proteins are free of at least some of the cellular components with which it is associated in the natural state, or that the nucleic acid or protein has been concentrated to a level greater than the concentration of its in vivo or in vitro production. Also, by way of example, a gene is isolated when separated from open reading frames which flank the gene and encode a protein other than the gene of interest.

[00158] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes, such as, oxidation reactions) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Further information on metabolism may be obtained from The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996). Metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells *in vitro* and analysis of the resulting compounds. Both methods are well known in the art. In some embodiments, metabolites of a compound are formed by oxidative processes and correspond to the corresponding hydroxy-containing compound. In some embodiments, a compound is metabolized to pharmacologically active metabolites.

[00159] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00160] As used herein, the term "modulator" refers to a compound that alters an activity of a molecule. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more

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activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[00161] As used herein, the term "selective binding compound" refers to a compound that selectively binds to any portion of one or more target proteins.

[00162] As used herein, the term "selectively binds" refers to the ability of a selective binding compound to bind to a target protein, such as, for example, Btk, with greater affinity than it binds to a non-target protein. In certain embodiments, specific binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, 1000 or more times greater than the affinity for a non-target.

[00163] As used herein, the term "selective modulator" refers to a compound that selectively modulates a target activity relative to a non-target activity. In certain embodiments, specific modulator refers to modulating a target activity at least 10, 50, 100, 250, 500, 1000 times more than a non-target activity.

[00164] The term "substantially purified," as used herein, refers to a component of interest that may be substantially or essentially free of other components which normally accompany or interact with the component of interest prior to purification. By way of example only, a component of interest may be "substantially purified" when the preparation of the component of interest contains less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, or less than about l% (by dry weight) of contaminating components. Thus, a "substantially purified" component of interest may have a purity level of about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or greater.

[00165] The term "subject" as used herein, refers to an animal which is the object of treatment, observation or experiment. By way of example only, a subject may be, but is not limited to, a mammal including, but not limited to, a human.

[00166] As used herein, the term "target activity" refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, binding affinity, signal transduction, enzymatic activity, tumor growth, effects on particular biomarkers related to B-cell lymphoproliferative disorder pathology.

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[00167] As used herein, the term "target protein" refers to a molecule or a portion of a protein capable of being bound by a selective binding compound. In certain embodiments, a target protein is Btk.

[00168] The terms "treat," "treating" or "treatment", as used herein, include alleviating, abating or ameliorating a disease or condition, or symptoms thereof; managing a disease or condition, or symptoms thereof; preventing additional symptoms; ameliorating or preventing the underlying metabolic causes of symptoms; inhibiting the disease or condition, e.g., arresting the development of the disease or condition; relieving the disease or condition; causing regression of the disease or condition, relieving a condition caused by the disease or condition; or stopping the symptoms of the disease or condition. The terms "treat," "treating" or "treatment", include, but are not limited to, prophylactic and/or therapeutic treatments.

[00169] As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as inhibition of Btk, in an assay that measures such response.

[00170] As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

Hematological Malignancies

[00171] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, the hematological malignancy is CLL. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the

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peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time. In some embodiments, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the hematological malignancy is follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, or extranodal marginal zone B cell lymphoma. In some embodiments, the hematological malignancy is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia. In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, relapsed or refractory follicular lymphoma, relapsed or refractory CLL; relapsed or refractory SLL; relapsed or refractory multiple myeloma. In some embodiments, the hematological malignancy is a hematological malignancy that is classified as high-risk. In some embodiments, the hematological malignancy is high risk CLL or high risk SLL.

[00172] B-cell lymphoproliferative disorders (BCLDs) are neoplasms of the blood and encompass, inter alia, non-Hodgkin lymphoma, multiple myeloma, and leukemia. BCLDs can originate either in the lymphatic tissues (as in the case of lymphoma) or in the bone marrow (as in

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the case of leukemia and myeloma), and they all are involved with the uncontrolled growth of lymphocytes or white blood cells. There are many subtypes of BCLD, e.g., chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). The disease course and treatment of BCLD is dependent on the BCLD subtype; however, even within each subtype the clinical presentation, morphologic appearance, and response to therapy is heterogeneous.

[00173] Malignant lymphomas are neoplastic transformations of cells that reside predominantly within lymphoid tissues. Two groups of malignant lymphomas are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Both types of lymphomas infiltrate reticuloendothelial tissues. However, they differ in the neoplastic cell of origin, site of disease, presence of systemic symptoms, and response to treatment (Freedman et al., "Non-Hodgkin's Lymphomas" Chapter 134, Cancer Medicine, (an approved publication of the American Cancer Society, B.C. Decker Inc., Hamilton, Ontario, 2003).

Non-Hodgkin's Lymphomas

[00174] Disclosed herein, in certain embodiments, is a method for treating a non-Hodgkin's lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, the hematological malignancy is CLL. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of

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cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00175] Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. In some embodiments, the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, or relapsed or refractory follicular lymphoma.

[00176] Non-Hodgkin lymphomas (NHL) are a diverse group of malignancies that are predominately of B-cell origin. NHL may develop in any organs associated with lymphatic system such as spleen, lymph nodes or tonsils and can occur at any age. NHL is often marked by enlarged lymph nodes, fever, and weight loss. NHL is classified as either B-cell or T-cell NHL. Lymphomas related to lymphoproliferative disorders following bone marrow or stem cell transplantation are usually B-cell NHL. In the Working Formulation classification scheme, NHL has been divided into low-, intermediate-, and high-grade categories by virtue of their natural histories (see "The Non-Hodgkin's Lymphoma Pathologic Classification Project," Cancer 49(1982):2112-2135). The low-grade lymphomas are indolent, with a median survival of 5 to 10 years (Horning and Rosenberg (1984) N. Engl. J. Med. 311:1471-1475). Although chemotherapy can induce remissions in the majority of indolent lymphomas, cures are rare and most patients eventually relapse, requiring further therapy. The intermediate- and high-grade lymphomas are more aggressive tumors, but they have a greater chance for cure with chemotherapy. However, a significant proportion of these patients will relapse and require further treatment.

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[00177] A non-limiting list of the B-cell NHL includes Burkitt's lymphoma (e.g., Endemic Burkitt's Lymphoma and Sporadic Burkitt's Lymphoma), Cutaneous B-Cell Lymphoma, Cutaneous Marginal Zone Lymphoma (MZL), Diffuse Large Cell Lymphoma (DLBCL), Diffuse Mixed Small and Large Cell Lympoma, Diffuse Small Cleaved Cell, Diffuse Small Lymphocytic Lymphoma, Extranodal Marginal Zone B-cell lymphoma, follicular lymphoma, Follicular Small Cleaved Cell (Grade 1), Follicular Mixed Small Cleaved and Large Cell (Grade 2), Follicular Large Cell (Grade 3), Intravascular Large B-Cell Lymphoma, Intravascular Lymphomatosis, Large Cell Immunoblastic Lymphoma, Large Cell Lymphoma (LCL), Lymphoblastic Lymphoma, MALT Lymphoma, Mantle Cell Lymphoma (MCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), extranodal marginal zone B-cell lymphoma-mucosa-associated lymphoid tissue (MALT) lymphoma, Mediastinal Large B-Cell Lymphoma, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma, primary mediastinal B-cell lymphoma, lymphoplasmocytic lymphoma, hairy cell leukemia, Waldenstrom's Macroglobulinemia, and primary central nervous system (CNS) lymphoma. Additional non-Hodgkin's lymphomas are contemplated within the scope of the present invention and apparent to those of ordinary skill in the art.

DLBCL

[00178] Disclosed herein, in certain embodiments, is a method for treating a DLCBL in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the

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method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00179] As used herein, the term "Diffuse large B-cell lymphoma (DLBCL)" refers to a neoplasm of the germinal center B lymphocytes with a diffuse growth pattern and a high-intermediate proliferation index. DLBCLs represent approximately 30% of all lymphomas and may present with several morphological variants including the centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic and plasmoblastic subtypes. Genetic tests have shown that there are different subtypes of DLBCL. These subtypes seem to have different outlooks (prognoses) and responses to treatment. DLBCL can affect any age group but occurs mostly in older people (the average age is mid-60s).

[00180] Disclosed herein, in certain embodiments, is a method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day. The ABC subtype of diffuse large B-cell lymphoma (ABC-DLBCL) is thought to arise from post germinal center B cells that are arrested during plasmatic differentiation. The ABC subtype of DLBCL (ABC-DLBCL) accounts for approximately 30% total DLBCL diagnoses. It is considered the least curable of the DLBCL molecular subtypes and, as such, patients diagnosed with the ABC-DLBCL typically display significantly reduced survival rates compared with individuals with other types of DLCBL. ABC-DLBCL is most commonly associated with chromosomal translocations deregulating the germinal center master

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regulator BCL6 and with mutations inactivating the PRDM1 gene, which encodes a transcriptional repressor required for plasma cell differentiation.

[00181] A particularly relevant signaling pathway in the pathogenesis of ABC-DLBCL is the one mediated by the nuclear factor (NF)-κB transcription complex. The NF-κB family comprises 5 members (p50, p52, p65, c-rel and RelB) that form homo- and heterodimers and function as transcriptional factors to mediate a variety of proliferation, apoptosis, inflammatory and immune responses and are critical for normal B-cell development and survival. NF-κB is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. As such, many different types of human tumors have misregulated NF-κB: that is, NF-κB is constitutively active. Active NF-κB turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause it to die via apoptosis.

[00182] The dependence of ABC DLBCLs on NF-kB depends on a signaling pathway upstream of IkB kinase comprised of CARD11, BCL10 and MALT1 (the CBM complex). Interference with the CBM pathway extinguishes NF-kB signaling in ABC DLBCL cells and induces apoptosis. The molecular basis for constitutive activity of the NF-kB pathway is a subject of current investigation but some somatic alterations to the genome of ABC DLBCLs clearly invoke this pathway. For example, somatic mutations of the coiled-coil domain of CARD11 in DLBCL render this signaling scaffold protein able to spontaneously nucleate protein-protein interaction with MALT1 and BCL10, causing IKK activity and NF-kB activation. Constitutive activity of the B cell receptor signaling pathway has been implicated in the activation of NF-kB in ABC DLBCLs with wild type CARD11, and this is associated with mutations within the cytoplasmic tails of the B cell receptor subunits CD79A and CD79B. Oncogenic activating mutations in the signaling adapter MYD88 activate NF-kB and synergize with B cell receptor signaling in sustaining the survival of ABC DLBCL cells. In addition, inactivating mutations in a negative regulator of the NF-kB pathway, A20, occur almost exclusively in ABC DLBCL.

[00183] Indeed, genetic alterations affecting multiple components of the NF-κB signaling pathway have been recently identified in more than 50% of ABC-DLBCL patients, where these lesions promote constitutive NF-κB activation, thereby contributing to lymphoma growth. These include mutations of CARD11 (~10% of the cases), a lymphocyte-specific cytoplasmic scaffolding protein that—together with MALT1 and BCL10—forms the BCR signalosome, which relays signals from antigen receptors to the downstream mediators of NF-κB activation. An even larger fraction of

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cases (~30%) carry biallelic genetic lesions inactivating the negative NF-κB regulator A20. Further, high levels of expression of NF-κB target genes have been observed in ABC-DLBCL tumor samples. *See, e.g.,* U. Klein et al., (2008), *Nature Reviews Immunology* 8:22-23; R.E. Davis et al., (2001), *Journal of Experimental Medicine* 194:1861-1874; G. Lentz et al., (2008), *Science* 319:1676-1679; M. Compagno et al., (2009), *Nature* 459:712-721; and L. Srinivasan et al., (2009), *Cell* 139:573-586).

[00184] DLBCL cells of the ABC subtype, such as OCI-Ly10, have chronic active BCR signalling and are very sensitive to the Btk inhibitors described herein. The irreversible Btk inhibitors described herein potently and irreversibly inhibit the growth of OCI-Ly10 (EC50 continuous exposure = 10 nM, EC50 1 hour pulse = 50 nM). In addition, induction of apoptosis, as shown by capsase activation, Annexin-V flow cytometry and increase in sub-G0 fraction is observed in OCILy10. Both sensitive and resistant cells express Btk at similar levels, and the active site of Btk is fully occupied by the inhibitor in both as shown using a fluorescently labeled affinity probe. OCI-Ly10 cells are shown to have chronically active BCR signalling to NF-kB which is dose dependently inhibited by the Btk inhibitors described herein. The activity of Btk inhibitors in the cell lines studied herein are also characterized by comparing signal transduction profiles (Btk, PLCγ, ERK, NF-kB, AKT), cytokine secretion profiles and mRNA expression profiles, both with and without BCR stimulation, and observed significant differences in these profiles that lead to clinical biomarkers that identify the most sensitive patient populations to Btk inhibitor treatment. *See* U.S. Patent No. 7,711,492 and Staudt *et al.*, **Nature**, Vol. 463, Jan. 7, 2010, pp. 88-92, the contents of which are incorporated by reference in their entirety.

Follicular Lymphoma

[00185] Disclosed herein, in certain embodiments, is a method for treating a follicular lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration

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before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00186] As used herein, the term "follicular lymphoma" refers to any of several types of non-Hodgkin's lymphoma in which the lymphomatous cells are clustered into nodules or follicles. The term follicular is used because the cells tend to grow in a circular, or nodular, pattern in lymph nodes. The average age for people with this lymphoma is about 60.

CLL/SLL

[00187] Disclosed herein, in certain embodiments, is a method for treating a CLL or SLL in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the CLL or SLL is high-risk. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells.

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In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00188] Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are commonly thought as the same disease with slightly different manifestations. Where the cancerous cells gather determines whether it is called CLL or SLL. When the cancer cells are primarily found in the lymph nodes, lima bean shaped structures of the lymphatic system (a system primarily of tiny vessels found in the body), it is called SLL. SLL accounts for about 5% to 10% of all lymphomas. When most of the cancer cells are in the bloodstream and the bone marrow, it is called CLL.

[00189] Both CLL and SLL are slow-growing diseases, although CLL, which is much more common, tends to grow slower. CLL and SLL are treated the same way. They are usually not considered curable with standard treatments, but depending on the stage and growth rate of the

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disease, most patients live longer than 10 years. Occasionally over time, these slow-growing lymphomas may transform into a more aggressive type of lymphoma.

[00190] Chronic lymphoid leukemia (CLL) is the most common type of leukemia. It is estimated that 100,760 people in the United States are living with or are in remission from CLL. Most (>75%) people newly diagnosed with CLL are over the age of 50. Currently CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy ("de-bulking" swollen lymph nodes). Though CLL progresses slowly in most cases, it is considered generally incurable. Certain CLLs are classified as high-risk. As used herein, “high risk CLL” means CLL characterized by at least one of the following 1) 17p13-; 2) 11q22-; 3) unmutated IgVH together with ZAP-70+ and/or CD38+; or 4) trisomy 12.

[00191] CLL treatment is typically administered when the patient's clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient's quality of life.

[00192] Small lymphocytic leukemia (SLL) is very similar to CLL described supra, and is also a cancer of B-cells. In SLL the abnormal lymphocytes mainly affect the lymph nodes. However, in CLL the abnormal cells mainly affect the blood and the bone marrow. The spleen may be affected in both conditions. SLL accounts for about 1in 25 of all cases of non-Hodgkin lymphoma. It can occur at any time from young adulthood to old age, but is rare under the age of 50. SLL is considered an indolent lymphoma. This means that the disease progresses very slowly, and patients tend to live many years after diagnosis. However, most patients are diagnosed with advanced disease, and although SLL responds well to a variety of chemotherapy drugs, it is generally considered to be incurable. Although some cancers tend to occur more often in one gender or the other, cases and deaths due to SLL are evenly split between men and women. The average age at the time of diagnosis is 60 years.

[00193] Although SLL is indolent, it is persistently progressive. The usual pattern of this disease is one of high response rates to radiation therapy and/or chemotherapy, with a period of disease remission. This is followed months or years later by an inevitable relapse. Re-treatment leads to a response again, but again the disease will relapse. This means that although the short-term prognosis of SLL is quite good, over time, many patients develop fatal complications of recurrent

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disease. Considering the age of the individuals typically diagnosed with CLL and SLL, there is a need in the art for a simple and effective treatment of the disease with minimum side-effects that do not impede on the patient's quality of life. The instant invention fulfills this long standing need in the art.

Mantle Cell Lymphoma

[00194] Disclosed herein, in certain embodiments, is a method for treating a Mantle cell lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second

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cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00195] As used herein, the term, "Mantle cell lymphoma" refers to a subtype of B-cell lymphoma, due to CD5 positive antigen-naive pregerminal center B-cell within the mantle zone that surrounds normal germinal center follicles. MCL cells generally over-express cyclin D1 due to a t(11:14) chromosomal translocation in the DNA. More specifically, the translocation is at t(11;14)(q13;q32). Only about 5% of lymphomas are of this type. The cells are small to medium in size. Men are affected most often. The average age of patients is in the early 60s. The lymphoma is usually widespread when it is diagnosed, involving lymph nodes, bone marrow, and, very often, the spleen. Mantle cell lymphoma is not a very fast growing lymphoma, but is difficult to treat.

Marginal Zone B-cell Lymphoma

[00196] Disclosed herein, in certain embodiments, is a method for treating a marginal zone B-cell lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as

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compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00197] As used herein, the term "marginal zone B-cell lymphoma" refers to a group of related B-cell neoplasms that involve the lymphoid tissues in the marginal zone, the patchy area outside the follicular mantle zone. Marginal zone lymphomas account for about 5% to 10% of lymphomas. The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas including extranodal marginal zone B-cell lymphomas, nodal marginal zone B-cell lymphoma, and splenic marginal zone lymphoma.

MALT

[00198] Disclosed herein, in certain embodiments, is a method for treating a MALT in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of

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time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00199] The term "mucosa-associated lymphoid tissue (MALT) lymphoma", as used herein, refers to extranodal manifestations of marginal-zone lymphomas. Most MALT lymphoma are a low grade, although a minority either manifest initially as intermediate-grade non-Hodgkin lymphoma (NHL) or evolve from the low-grade form. Most of the MALT lymphoma occur in the stomach, and roughly 70% of gastric MALT lymphoma are associated with Helicobacter pylori infection. Several cytogenetic abnormalities have been identified, the most common being trisomy 3 or t(11;18). Many of these other MALT lymphoma have also been linked to infections with bacteria or viruses. The average age of patients with MALT lymphoma is about 60.

Nodal Marginal Zone B-Cell Lymphoma

[00200] Disclosed herein, in certain embodiments, is a method for treating a nodal marginal zone B-cell lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the

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mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00201] The term "nodal marginal zone B-cell lymphoma" refers to an indolent B-cell lymphoma that is found mostly in the lymph nodes. The disease is rare and only accounts for 1% of all Non-Hodgkin's Lymphomas (NHL). It is most commonly diagnosed in older patients, with women more susceptible than men. The disease is classified as a marginal zone lymphoma because the mutation occurs in the marginal zone of the B-cells. Due to its confinement in the lymph nodes, this disease is also classified as nodal.

Splenic Marginal Zone B-Cell Lymphoma

[00202] Disclosed herein, in certain embodiments, is a method for treating a splenic marginal zone B-cell lymphoma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the

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method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00203] The term "splenic marginal zone B-cell lymphoma" refers to specific low-grade small B-cell lymphoma that is incorporated in the World Health Organization classification. Characteristic features are splenomegaly, moderate lymphocytosis with villous morphology, intrasinusoidal pattern of involvement of various organs, especially bone marrow, and relative indolent course. Tumor progression with increase of blastic forms and aggressive behavior are observed in a minority of patients. Molecular and cytogenetic studies have shown heterogeneous results probably because of the lack of standardized diagnostic criteria.

Burkitt Lymphoma

[00204] Disclosed herein, in certain embodiments, is a method for treating a Burkitt lymphoma in an individual in need thereof, comprising: (a) administering to the individual an

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amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00205] The term "Burkitt lymphoma" refers to a type of Non-Hodgkin Lymphoma (NHL) that commonly affects children. It is a highly aggressive type of B-cell lymphoma that often starts and involves body parts other than lymph nodes. In spite of its fast-growing nature, Burkitt's lymphoma is often curable with modern intensive therapies. There are two broad types of Burkitt's lymphoma – the sporadic and the endemic varieties:

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[00206] Endemic Burkitt's lymphoma: The disease involves children much more than adults, and is related to Epstein Barr Virus (EBV) infection in 95% cases. It occurs primarily is equatorial Africa, where about half of all childhood cancers are Burkitt's lymphoma. It characteristically has a high chance of involving the jawbone, a rather distinctive feature that is rare in sporadic Burkitt's. It also commonly involves the abdomen.

[00207] Sporadic Burkitt's lymphoma: The type of Burkitt's lymphoma that affects the rest of the world, including Europe and the Americas is the sporadic type. Here too, it's mainly a disease in children. The link between Epstein Barr Virus (EBV) is not as strong as with the endemic variety, though direct evidence of EBV infection is present in one out of five patients. More than the involvement of lymph nodes, it is the abdomen that is notably affected in more than 90% of the children. Bone marrow involvement is more common than in the sporadic variety.

Waldenstrom Macroglobulinemia

[00208] Disclosed herein, in certain embodiments, is a method for treating a Waldenstrom macroglobulinemia in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment

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regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00209] The term "Waldenstrom macroglobulinemia", also known as lymphoplasmacytic lymphoma, is cancer involving a subtype of white blood cells called lymphocytes. It is characterized by an uncontrolled clonal proliferation of terminally differentiated B lymphocytes. It is also characterized by the lymphoma cells making an antibody called immunoglobulin M (IgM). The IgM antibodies circulate in the blood in large amounts, and cause the liquid part of the blood to thicken, like syrup. This can lead to decreased blood flow to many organs, which can cause problems with vision (because of poor circulation in blood vessels in the back of the eyes) and neurological problems (such as headache, dizziness, and confusion) caused by poor blood flow within the brain. Other symptoms can include feeling tired and weak, and a tendency to bleed easily. The underlying etiology is not fully understood but a number of risk factors have been identified, including the locus 6p21.3 on chromosome 6. There is a 2- to 3-fold risk increase of developing WM in people with a personal history of autoimmune diseases with autoantibodies and particularly elevated risks associated with hepatitis, human immunodeficiency virus, and rickettsiosis.

Multiple Myeloma

[00210] Disclosed herein, in certain embodiments, is a method for treating a myeloma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration

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of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00211] Disclosed herein, in certain embodiments, is a method for treating a multiple myeloma in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the

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duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00212] Multiple myeloma, also known as MM, myeloma, plasma cell myeloma, or as Kahler's disease (after Otto Kahler) is a cancer of the white blood cells known as plasma cells. A type of B cell, plasma cells are a crucial part of the immune system responsible for the production of antibodies in humans and other vertebrates. They are produced in the bone marrow and are transported through the lymphatic system.

Leukemia

[00213] Disclosed herein, in certain embodiments, is a method for treating a leukemia in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen

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occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00214] Leukemia is a cancer of the blood or bone marrow characterized by an abnormal increase of blood cells, usually leukocytes (white blood cells). Leukemia is a broad term covering a spectrum of diseases. The first division is between its acute and chronic forms: (i) acute leukemia is characterized by the rapid increase of immature blood cells. This crowding makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children; (ii) chronic leukemia is distinguished by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group. Additionally, the diseases are subdivided according to which kind of blood cell is affected. This split divides leukemias into lymphoblastic or lymphocytic leukemias and myeloid or myelogenous leukemias: (i) lymphoblastic or lymphocytic leukemias, the cancerous change takes

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place in a type of marrow cell that normally goes on to form lymphocytes, which are infection-fighting immune system cells; (ii) myeloid or myelogenous leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

[00215] Within these main categories, there are several subcategories including, but not limited to, Acute lymphoblastic leukemia (ALL), Acute myelogenous leukemia (AML), Chronic myelogenous leukemia (CML), and Hairy cell leukemia (HCL).

Btk inhibitors

[00216] Also presented herein are methods for treating a cancer such as by way of example only, a BCLD, in a subject wherein the subject has been treated with a dosing regimen of a Btk inhibitor. In the following description of irreversible Btk compounds suitable for use in the methods described herein, definitions of referred-to standard chemistry terms may be found in reference works (if not otherwise defined herein), including Carey and Sundberg "Advanced Organic Chemistry 4th Ed." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the ordinary skill of the art are employed. In addition, nucleic acid and amino acid sequences for Btk (e.g., human Btk) are known in the art as disclosed in, e.g., U.S. Patent No. 6,326,469. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[00217] The Btk inhibitor compounds described herein are selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk. Generally, an irreversible inhibitor compound of Btk used in the methods described herein is identified or characterized in an *in vitro* assay, e.g., an acellular biochemical assay or a cellular functional assay. Such assays are useful to determine an *in vitro* IC_{50} for an irreversible Btk inhibitor compound.

[00218] For example, an acellular kinase assay can be used to determine Btk activity after incubation of the kinase in the absence or presence of a range of concentrations of a candidate

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irreversible Btk inhibitor compound. If the candidate compound is in fact an irreversible Btk inhibitor, Btk kinase activity will not be recovered by repeat washing with inhibitor-free medium. See, e.g., J. B. Smaill, *et al*. (1999), *J. Med. Chem.* 42(10):1803-1815. Further, covalent complex formation between Btk and a candidate irreversible Btk inhibitor is a useful indicator of irreversible inhibition of Btk that can be readily determined by a number of methods known in the art (e.g., mass spectrometry). For example, some irreversible Btk-inhibitor compounds can form a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction).

[00219] Cellular functional assays for Btk inhibition include measuring one or more cellular endpoints in response to stimulating a Btk-mediated pathway in a cell line (e.g., BCR activation in Ramos cells) in the absence or presence of a range of concentrations of a candidate irreversible Btk inhibitor compound. Useful endpoints for determining a response to BCR activation include, e.g., autophosphorylation of Btk, phosphorylation of a Btk target protein (e.g., PLC-γ), and cytoplasmic calcium flux.

[00220] High throughput assays for many acellular biochemical assays (e.g., kinase assays) and cellular functional assays (e.g., calcium flux) are well known to those of ordinary skill in the art. In addition, high throughput screening systems are commercially available (see, e.g., Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments, Inc. Fullerton, CA; Precision Systems, Inc., Natick, MA, etc.). These systems typically automate entire procedures including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. Automated systems thereby allow the identification and characterization of a large number of irreversible Btk compounds without undue effort.

[00221] In some embodiments, the Btk inhibitor is selected from the group consisting of a small organic molecule, a macromolecule, a peptide or a non-peptide.

[00222] In some embodiments, the Btk inhibitor provided herein is a reversible or irreversible inhibitor. In certain embodiments, the Btk inhibitor is an irreversible inhibitor.

[00223] In some embodiments, the irreversible Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog.

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[00224] Irreversible Btk inhibitor compounds can use for the manufacture of a medicament for treating any of the foregoing conditions (e.g., autoimmune diseases, inflammatory diseases, allergy disorders, B-cell proliferative disorders, or thromboembolic disorders).

[00225] In some embodiments, the irreversible Btk inhibitor compound used for the methods described herein inhibits Btk or a Btk homolog kinase activity with an *in vitro* IC_{50} of less than 10 μM. (e.g., less than 1 μM, less than 0.5 μM, less than 0.4 μM, less than 0.3 μM, less than 0.1, less than 0.08 μM, less than 0.06 μM, less than 0.05 μM, less than 0.04 μM, less than 0.03 μM, less than less than 0.02 μM, less than 0.01, less than 0.008 μM, less than 0.006 μM, less than 0.005 μM, less than 0.004 μM, less than 0.003 μM, less than less than 0.002 μM, less than 0.001, less than 0.00099 μM, less than 0.00098 μM, less than 0.00097 μM, less than 0.00096 μM, less than 0.00095 μM, less than 0.00094 μM, less than 0.00093 μM, less than 0.00092, or less than 0.00090 μM).

[00226] In one embodiment, the irreversible Btk inhibitor compound selectively and irreversibly inhibits an activated form of its target tyrosine kinase (e.g., a phosphorylated form of the tyrosine kinase). For example, activated Btk is transphosphorylated at tyrosine 551. Thus, in these embodiments the irreversible Btk inhibitor inhibits the target kinase in cells only once the target kinase is activated by the signaling events.

[00227] In other embodiments, the Btk inhibitor used in the methods describe herein has the structure of any of Formula (A), Formula (B), Formula (C), Formula (D), Formula (E), or Formula (F). Also described herein are pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically active metabolites, and pharmaceutically acceptable prodrugs of such compounds. Pharmaceutical compositions that include at least one such compound or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, pharmaceutically active metabolite or pharmaceutically acceptable prodrug of such compound, are provided. In some embodiments, when compounds disclosed herein contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. In certain embodiments, isomers and chemically protected forms of compounds having a structure represented by any of Formula (A), Formula (B), Formula (C), Formula (D), Formula (E), or Formula (F), are also provided.

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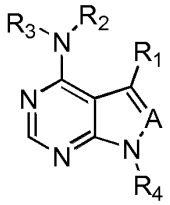
[00228] Formula (A) is as follows:



Formula (A)

wherein:

A is independently selected from N or CR_5;

R_1 is H, L_2-(substituted or unsubstituted alkyl), L_2-(substituted or unsubstituted cycloalkyl), L_2-(substituted or unsubstituted alkenyl), L_2-(substituted or unsubstituted cycloalkenyl), L_2-(substituted or unsubstituted heterocycle), L_2-(substituted or unsubstituted heteroaryl), or L_2-(substituted or unsubstituted aryl), where L_2 is a bond, O, S, -S(=O), -$S(=O)_2$, C(=O), -(substituted or unsubstituted C_1-C_6 alkyl), or -(substituted or unsubstituted C_2-C_6 alkenyl);

R_2 and R_3 are independently selected from H, lower alkyl and substituted lower alkyl;

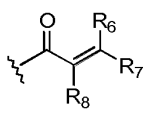
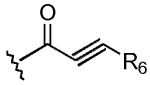
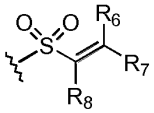
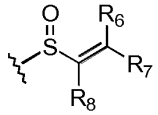
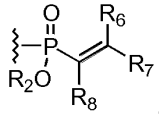
R_4 is L_3-X-L_4-G, wherein,

L_3 is optional, and when present is a bond, optionally substituted or unsubstituted alkyl, optionally substituted or unsubstituted cycloalkyl, optionally substituted or unsubstituted alkenyl, optionally substituted or unsubstituted alkynyl;

X is optional, and when present is a bond, O, -C(=O), S, -S(=O), -$S(=O)_2$, -NH, -NR_9, -NHC(O), -C(O)NH, -NR_9C(O), -C(O)NR_9, -$S(=O)_2$NH, -$NHS(=O)_2$, -$S(=O)_2NR_9$-, -$NR_9S(=O)_2$, -OC(O)NH-, -NHC(O)O-, -OC(O)NR_9-, -NR_9C(O)O-, -CH=NO-, -ON=CH-, -NR_{10}C(O)NR_{10}-, heteroaryl, aryl, -$NR_{10}C(=NR_{11})NR_{10}$-, -$NR_{10}C(=NR_{11})$-, -$C(=NR_{11})NR_{10}$-, -OC(=$NR_{11}$)-, or -C(=$NR_{11}$)O-;

L_4 is optional, and when present is a bond, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycle;

or L_3, X and L_4 taken together form a nitrogen containing heterocyclic ring;

G is  ,  ,  ,  , or  , wherein,

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R_6, R_7 and R_8 are independently selected from among H, lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl;

R_5 is H, halogen, -L_6-(substituted or unsubstituted C_1-C_3 alkyl), -L_6-(substituted or unsubstituted C_2-C_4 alkenyl), -L_6-(substituted or unsubstituted heteroaryl), or –L_6-(substituted or unsubstituted aryl), wherein L_6 is a bond, O, S, -S(=O), $S(=O)_2$, NH, C(O), -NHC(O)O, -OC(O)NH, -NHC(O), or -C(O)NH;

each R_9 is independently selected from among H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl;

each R_{10} is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or

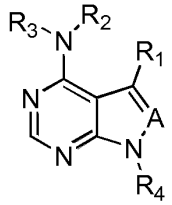
two R_{10} groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

R_9 and R_{10} can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

each R_{11} is independently selected from H, $–S(=O)_2R_8$, $–S(=O)_2NH_2$, -C(O)R_8, -CN, -NO_2, heteroaryl, or heteroalkyl; and

pharmaceutically active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00229] In one aspect are compounds having the structure of Formula (A1):



Formula (A1),

wherein

A is independently selected from N or CR_5;

R_1 is H, L_2-(substituted or unsubstituted alkyl), L_2-(substituted or unsubstituted cycloalkyl), L_2-(substituted or unsubstituted alkenyl), L_2-(substituted or unsubstituted cycloalkenyl), L_2-(substituted or unsubstituted heterocycle), L_2-(substituted or unsubstituted heteroaryl), or L_2-(substituted or unsubstituted aryl), where L_2 is a bond, O, S, -S(=O), $-S(=O)_2$, C(=O), -(substituted or unsubstituted C_1-C_6 alkyl), or -(substituted or unsubstituted C_2-C_6 alkenyl);

R_2 and R_3 are independently selected from H, lower alkyl and substituted lower alkyl;

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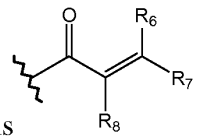
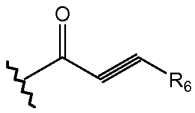
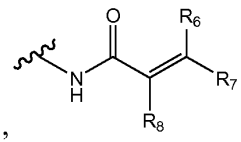
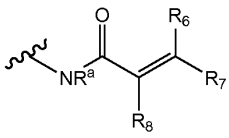
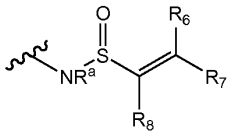
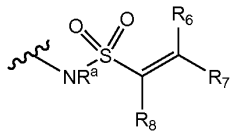
R_4 is L_3-X-L_4-G, wherein,

L_3 is optional, and when present is a bond, or an optionally substituted group selected from alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;

X is optional, and when present is a bond, O, -C(=O), S, -S(=O), -S(=O)$_2$, -NH, -NR$_9$, -NHC(O), -C(O)NH, -NR$_9$C(O), -C(O)NR$_9$, -S(=O)$_2$NH, -NHS(=O)$_2$, -S(=O)$_2$NR$_9$-, -NR$_9$S(=O)$_2$, -OC(O)NH-, -NHC(O)O-, -OC(O)NR$_9$-, -NR$_9$C(O)O-, -CH=NO-, -ON=CH-, -NR$_{10}$C(O)NR$_{10}$-, heteroaryl, aryl, -NR$_{10}$C(=NR$_{11}$)NR$_{10}$-, -NR$_{10}$C(=NR$_{11}$)-, -C(=NR$_{11}$)NR$_{10}$-, -OC(=NR$_{11}$)-, or -C(=NR$_{11}$)O-;

L_4 is optional, and when present is a bond, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycle;

or L_3, X and L_4 taken together form a nitrogen containing heterocyclic ring, or an optionally substituted group selected from alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, or alkylheterocycloalkyl;

G is  ,  ,  ,  ,  , or,  where R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

R_7 and R_8 are H;

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

R_6 and R_8 are H;

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R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_6 and R_8 taken together form a bond;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_5 is H, halogen, -L_6-(substituted or unsubstituted C_1-C_3 alkyl), -L_6-(substituted or unsubstituted C_2-C_4 alkenyl), -L_6-(substituted or unsubstituted heteroaryl), or –L_6-(substituted or unsubstituted aryl), wherein L_6 is a bond, O, S, -S(=O), $S(=O)_2$, NH, C(O), -NHC(O)O, -OC(O)NH, -NHC(O), or -C(O)NH;

each R_9 is independently selected from among H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl;

each R_{10} is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or

two R_{10} groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

R_9 and R_{10} can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

each R_{11} is independently selected from H, $–S(=O)_2R_8$, $–S(=O)_2NH_2$, -C(O)R_8, -CN, -NO_2, heteroaryl, or heteroalkyl; and pharmaceutically active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00230] In another embodiment are provided pharmaceutically acceptable salts of compounds of Formula (A1). By way of example only, are salts of an amino group formed with inorganic acids

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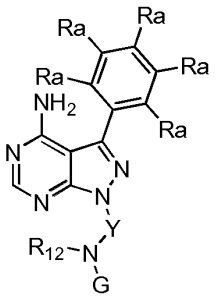
such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid. Further salts include those in which the counterion is an anion, such as adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate. Further salts include those in which the counterion is an cation, such as sodium, lithium, potassium, calcium, magnesium, ammonium, and quaternary ammonium (substituted with at least one organic moiety) cations.

[00231] In another embodiment are pharmaceutically acceptable esters of compounds of Formula (A1), including those in which the ester group is selected from a formate, acetate, propionate, butyrate, acrylate and ethylsuccinate.

[00232] In another embodiment are pharmaceutically acceptable carbamates of compounds of Formula (A1). In another embodiment are pharmaceutically acceptable N-acyl derivatives of compounds of Formula (A1). Examples of N-acyl groups include N-acetyl and N-ethoxycarbonyl groups.

[00233] In a further embodiment, the compound of Formula (A) has the following structure of Formula (B):



Formula (B)

wherein:

Y is alkyl or substituted alkyl, or a 4-, 5-, or 6-membered cycloalkyl ring;

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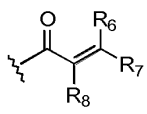
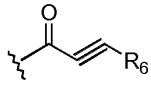
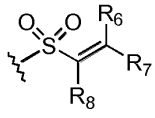
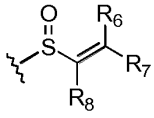
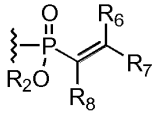
each R_a is independently H, halogen, $-CF_3$, -CN, $-NO_2$, OH, NH_2, $-L_a$-(substituted or unsubstituted alkyl), $-L_a$-(substituted or unsubstituted alkenyl), $-L_a$-(substituted or unsubstituted heteroaryl), or $-L_a$-(substituted or unsubstituted aryl), wherein L_a is a bond, O, S, -S(=O), $-S(=O)_2$, NH, C(O), CH_2, -NHC(O)O, -NHC(O), or -C(O)NH;

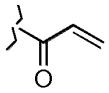
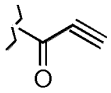
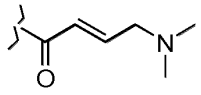
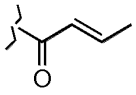
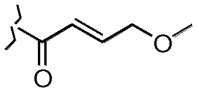
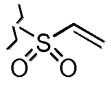
G is  ,  ,  ,  , or  , wherein,

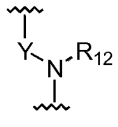
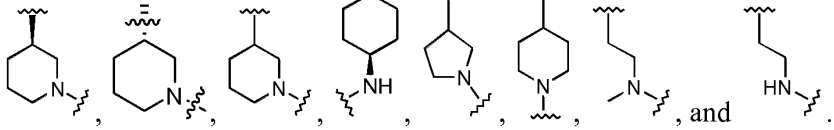
R_6, R_7 and R_8 are independently selected from among H, lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl;

R_{12} is H or lower alkyl; or

Y and R_{12} taken together form a 4-, 5-, or 6-membered heterocyclic ring; and

pharmaceutically acceptable active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00234] In further embodiments, G is selected from among  ,  ,  ,  ,  , and  .

[00235] In further embodiments,  is selected from among  .

[00236] In a further embodiment, the compound of Formula (A1) has the following structure of Formula (B1):

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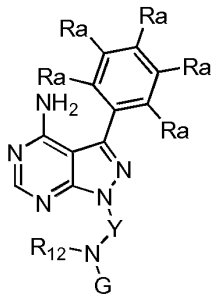
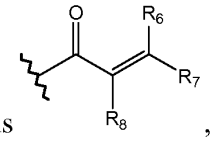
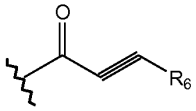
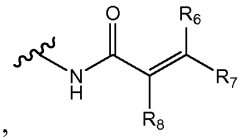
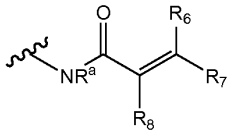
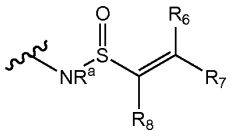
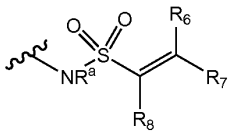


Formula (B1),

wherein:

Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, alkylenearylene, alkyleneheteroarylene, and alkyleneheterocycloalkylene;

each R_a is independently H, halogen, $-CF_3$, -CN, $-NO_2$, OH, NH_2, $-L_a$-(substituted or unsubstituted alkyl), $-L_a$-(substituted or unsubstituted alkenyl), $-L_a$-(substituted or unsubstituted heteroaryl), or $-L_a$-(substituted or unsubstituted aryl), wherein L_a is a bond, O, S, -S(=O), $-S(=O)_2$, NH, C(O), CH_2, -NHC(O)O, -NHC(O), or -C(O)NH;

G is  ,  ,  ,  ,  ,  , or, where R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

R_7 and R_8 are H;

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

R_6 and R_8 are H;

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R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

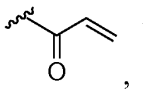
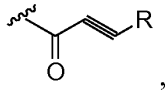
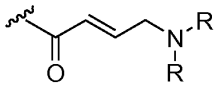
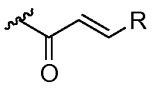
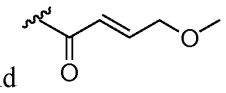
R_6 and R_8 taken together form a bond;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

R_{12} is H or lower alkyl; or

Y and R_{12} taken together form a 4-, 5-, or 6-membered heterocyclic ring; and

pharmaceutically acceptable active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00237] In further embodiments, G is selected from among  ,  ,  ,  , , , and  ., where R is H, alkyl, alkylhydroxy, heterocycloalkyl, heteroaryl, alkylalkoxy, alkylalkoxyalkyl.

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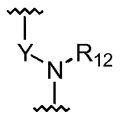
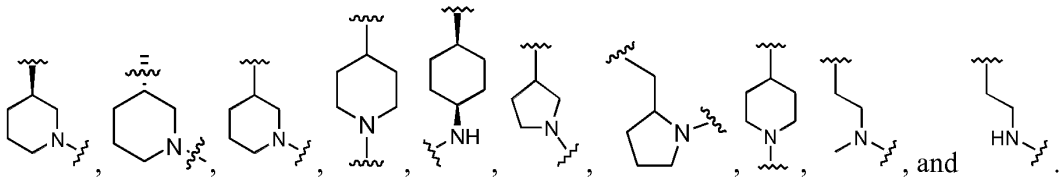
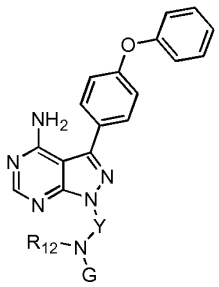
[00238] In further embodiments,  is selected from among  , and .

[00239] In a further embodiment, the compound of Formula (B) has the following structure of Formula (C):

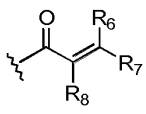
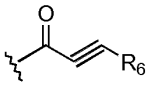
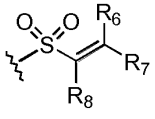
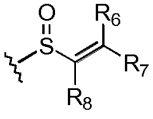
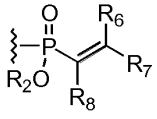


Formula (C)

Y is alkyl or substituted alkyl, or a 4-, 5-, or 6-membered cycloalkyl ring;

R_{12} is H or lower alkyl; or

Y and R_{12} taken together form a 4-, 5-, or 6-membered heterocyclic ring;

G is  ,  ,  ,  , or  , wherein,

R_6, R_7 and R_8 are independently selected from among H, lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl; and

pharmaceutically acceptable active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00240] In further embodiment, the compound of Formula (B1) has the following structure of Formula (C1):

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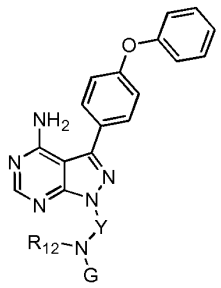
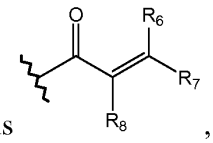
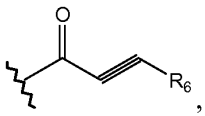
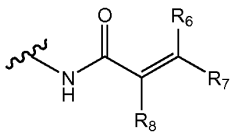
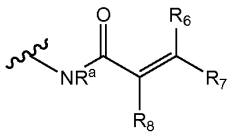
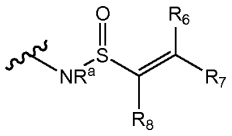
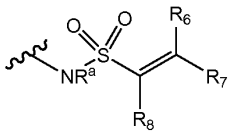


Formula (C1),

Y is an optionally substituted group selected from among alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, alkylheteroaryl, and alkylheterocycloalkyl;

R_{12} is H or lower alkyl; or

Y and R_{12} taken together form a 4-, 5-, or 6-membered heterocyclic ring;

G is  ,  ,  ,  ,  ,  , or, where R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

R_7 and R_8 are H;

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

R_6 and R_8 are H;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or

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unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_6 and R_8 taken together form a bond;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); and

pharmaceutically acceptable active metabolites, pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00241] In a further or alternative embodiment, the "G" group of any of Formula (A1), Formula (B1), or Formula (C1) is any group that is used to tailor the physical and biological properties of the molecule. Such tailoring/modifications are achieved using groups which modulate Michael acceptor chemical reactivity, acidity, basicity, lipophilicity, solubility and other physical properties of the molecule. The physical and biological properties modulated by such modifications to G include, by way of example only, enhancing chemical reactivity of Michael acceptor group, solubility, *in vivo* absorption, and *in vivo* metabolism. In addition, *in vivo* metabolism includes, by way of example only, controlling *in vivo* PK properties, off-target activities, potential toxicities associated with cypP450 interactions, drug-drug interactions, and the like. Further, modifications to G allow for the tailoring of the *in vivo* efficacy of the compound through the modulation of, by way of example, specific and non-specific protein binding to plasma proteins and lipids and tissue distribution *in vivo*.

[00242] In another embodiment, provided herein is a compound of Formula (D). Formula (D) is as follows:

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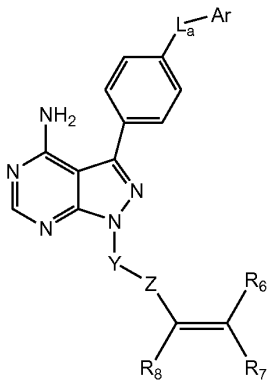

Formula (D)

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

Z is C(=O), OC(=O), NHC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NHS(=O)_x$, where x is 1 or 2;

R_6, R_7, and R_8 are each independently selected from among H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4alkyl(aryl), substituted or unsubstituted C_1-C_4alkyl(heteroaryl), substituted or unsubstituted C_1-C_4alkyl(C_3-C_8cycloalkyl), or substituted or unsubstituted C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_7 and R_8 taken together form a bond; and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00243] In one embodiment are compounds having the structure of Formula (D1):

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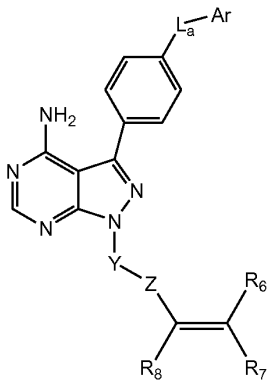

Formula (D1)

wherein

L_a is CH_2, O, NH or S;

Ar is an optionally substituted aromatic carbocycle or an aromatic heterocycle;

Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, alkylenearylene, alkyleneheteroarylene, and alkyleneheterocycloalkylene, or combination thereof;

Z is C(=O), NHC(=O), $NR^aC(=O)$, $NR^aS(=O)_x$, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

R_7 and R_8 are H;

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

R_6 and R_8 are H;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-

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C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_6 and R_8 taken together form a bond;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

or combinations thereof; and

pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00244] In another embodiment are provided pharmaceutically acceptable salts of compounds of Formula (D1). By way of example only, are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid. Further salts include those in which the counterion is an anion, such as adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate. Further salts include those in which the counterion is an cation, such as sodium, lithium, potassium, calcium, magnesium, ammonium, and quaternary ammonium (substituted with at least one organic moiety) cations.

[00245] In another embodiment are pharmaceutically acceptable esters of compounds of Formula (D1), including those in which the ester group is selected from a formate, acetate, propionate, butyrate, acrylate and ethylsuccinate.

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[00246] In another embodiment are pharmaceutically acceptable carbamates of compounds of Formula (D1). In another embodiment are pharmaceutically acceptable N-acyl derivatives of compounds of Formula (D1). Examples of N-acyl groups include N-acetyl and N-ethoxycarbonyl groups.

[00247] In a further embodiment, L_a is O.

[00248] In a further embodiment, Ar is phenyl.

[00249] In a further embodiment, Z is C(=O), NHC(=O), or $NCH_3C(=O)$.

[00250] In a further embodiment, each of R_1, R_2, and R_3 is H.

[00251] In one embodiment is a compound of Formula (D1) wherein R_6, R_7, and R_8 are all H. In another embodiment, R_6, R_7, and R_8 are not all H.

[00252] For any and all of the embodiments, substituents can be selected from among from a subset of the listed alternatives. For example, in some embodiments, L_a is CH_2, O, or NH. In other embodiments, L_a is O or NH. In yet other embodiments, L_a is O.

[00253] In some embodiments, Ar is a substituted or unsubstituted aryl. In yet other embodiments, Ar is a 6-membered aryl. In some other embodiments, Ar is phenyl.

[00254] In some embodiments, x is 2. In yet other embodiments, Z is C(=O), OC(=O), NHC(=O), $S(=O)_x$, $OS(=O)_x$, or $NHS(=O)_x$. In some other embodiments, Z is C(=O), NHC(=O), or $S(=O)_2$.

[00255] In some embodiments, R_7 and R_8 are independently selected from among H, unsubstituted C_1-C_4 alkyl, substituted C_1-C_4alkyl, unsubstituted C_1-C_4heteroalkyl, and substituted C_1-C_4heteroalkyl; or R_7 and R_8 taken together form a bond. In yet other embodiments, each of R_7 and R_8 is H; or R_7 and R_8 taken together form a bond.

[00256] In some embodiments, R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_6alkoxyalkyl, C_1-C_2alkyl-$N(C_1$-C_3alkyl$)_2$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_4alkyl(C_3-C_8cycloalkyl), or C_1-C_4alkyl(C_2-C_8heterocycloalkyl). In some other embodiments, R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_6alkoxyalkyl, C_1-C_2alkyl-$N(C_1$-C_3alkyl$)_2$, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_4alkyl(C_3-C_8cycloalkyl), or C_1-C_4alkyl(C_2-C_8heterocycloalkyl). In yet other embodiments, R_6 is H, substituted or unsubstituted C_1-C_4alkyl, $-CH_2$-O-(C_1-C_3alkyl), $-CH_2$-$N(C_1$-C_3alkyl$)_2$, C_1-C_4alkyl(phenyl), or C_1-C_4alkyl(5- or 6-membered heteroaryl). In some embodiments, R_6 is H, substituted or unsubstituted

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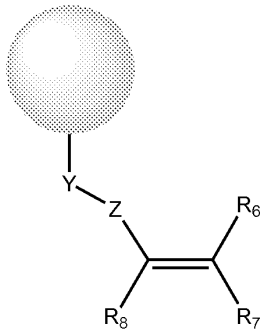
C_1-C_4alkyl, -CH_2-O-(C_1-C_3alkyl), -CH_2-N(C_1-C_3alkyl)$_2$, C_1-C_4alkyl(phenyl), or C_1-C_4alkyl(5- or 6-membered heteroaryl containing 1 or 2 N atoms), or C_1-C_4alkyl(5- or 6-membered heterocycloalkyl containing 1 or 2 N atoms).

[00257] In some embodiments, Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl. In other embodiments, Y is an optionally substituted group selected from among C_1-C_6alkyl, C_1-C_6heteroalkyl, 4-, 5-, 6- or 7-membered cycloalkyl, and 4-, 5-, 6- or 7-membered heterocycloalkyl. In yet other embodiments, Y is an optionally substituted group selected from among C_1-C_6alkyl, C_1-C_6heteroalkyl, 5-, or 6-membered cycloalkyl, and 5-, or 6-membered heterocycloalkyl containing 1 or 2 N atoms. In some other embodiments, Y is a 5-, or 6-membered cycloalkyl, or a 5-, or 6-membered heterocycloalkyl containing 1 or 2 N atoms.

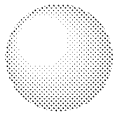
[00258] Any combination of the groups described above for the various variables is contemplated herein. It is understood that substituents and substitution patterns on the compounds provided herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those set forth herein.

[00259] In one embodiment the irreversible inhibitor of a kinase has the structure of Formula (E):



Formula (E)

wherein:

wherein  is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

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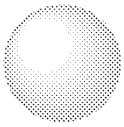
Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, heterocycloalkylene, cycloalkylene, alkylenearylene, alkyleneheteroarylene, alkylenecycloalkylene, and alkyleneheterocycloalkylene;

Z is C(=O), OC(=O), NHC(=O), $NCH_3C(=O)$, C(=S), $S(=O)_x$, $OS(=O)_x$, $NHS(=O)_x$, where x is 1 or 2;

R_6, R_7, and R_8 are each independently selected from among H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4alkyl(aryl), substituted or unsubstituted C_1-C_4alkyl(heteroaryl), substituted or unsubstituted C_1-C_4alkyl(C_3-C_8cycloalkyl), or substituted or unsubstituted C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

R_7 and R_8 taken together form a bond; and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

[00260] In some embodiments,  is a substituted fused biaryl moiety selected from

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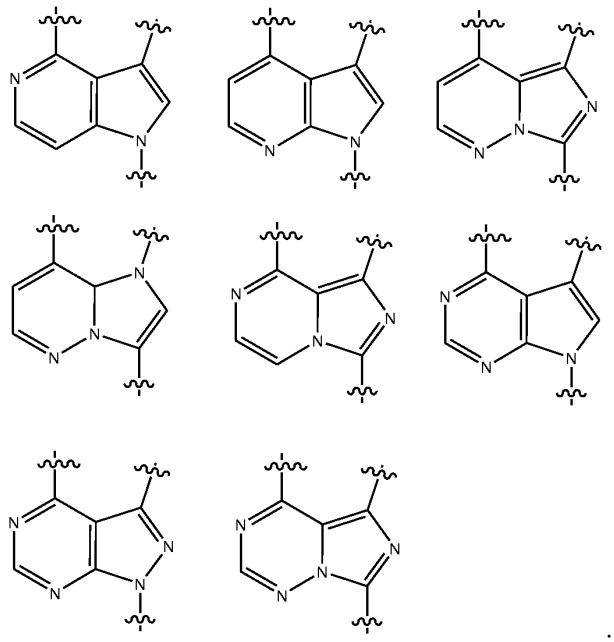
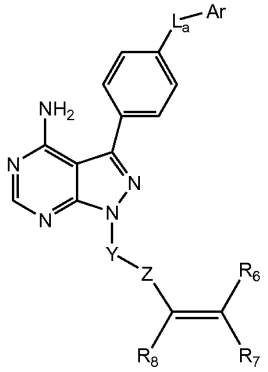


[00261] In one aspect, provided herein are compounds of Formula (F). Formula (F) is as follows:



Formula (F)

wherein

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; and either

(a) Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, alkylenearylene, alkyleneheteroarylene, alkylenecycloalkylene and alkyleneheterocycloalkylene;

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Z is C(=O), NHC(=O), $NR^aC(=O)$, $NR^aS(=O)_x$, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

(i) R_6, R_7, and R_8 are each independently selected from among H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4alkyl(aryl), substituted or unsubstituted C_1-C_4alkyl(heteroaryl), substituted or unsubstituted C_1-C_4alkyl(C_3-C_8cycloalkyl), or substituted or unsubstituted C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

(ii) R_6 and R_8 are H;

R_7 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8 hydroxyalkylaminoalkyl, C_1-C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

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(iii) R_7 and R_8 taken together form a bond;

R_6 is selected from among H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4alkyl(aryl), substituted or unsubstituted C_1-C_4alkyl(heteroaryl), substituted or unsubstituted C_1-C_4alkyl(C_3-C_8cycloalkyl), or substituted or unsubstituted C_1-C_4alkyl(C_2-C_8heterocycloalkyl) or

(b) Y is an optionally substituted group selected from cycloalkylene or heterocycloalkylene;

Z is C(=O), NHC(=O), $NR^aC(=O)$, $NR^aS(=O)_x$, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

(i) R_7 and R_8 are H;

R_6 is substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8 hydroxyalkylaminoalkyl, C_1-C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

(ii) R_6 and R_8 are H;

R_7 is substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8 hydroxyalkylaminoalkyl, C_1-C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or

(iii) R_7 and R_8 taken together form a bond;

R_6 is substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_8alkylaminoalkyl, C_1-C_8hydroxyalkylaminoalkyl, C_1-C_8alkoxyalkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_1-C_8alkylC_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-

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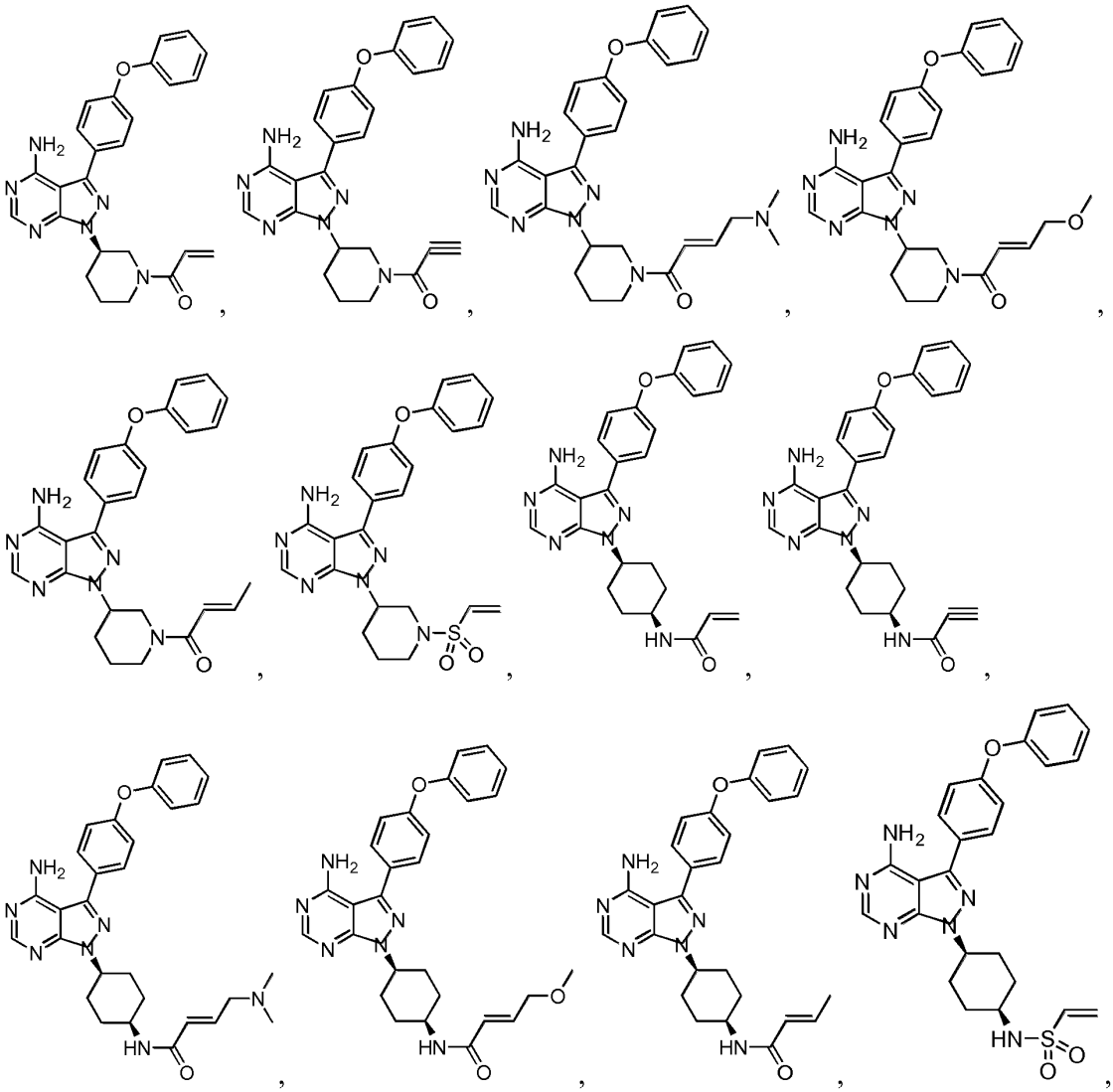
C_8alkylethers, C_1-C_8alkylamides, or C_1-C_4alkyl(C_2-C_8heterocycloalkyl); and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof

[00262] Further embodiments of compounds of Formula (A), Formula (B), Formula (C), Formula (D), include, but are not limited to, compounds selected from the group consisting of:



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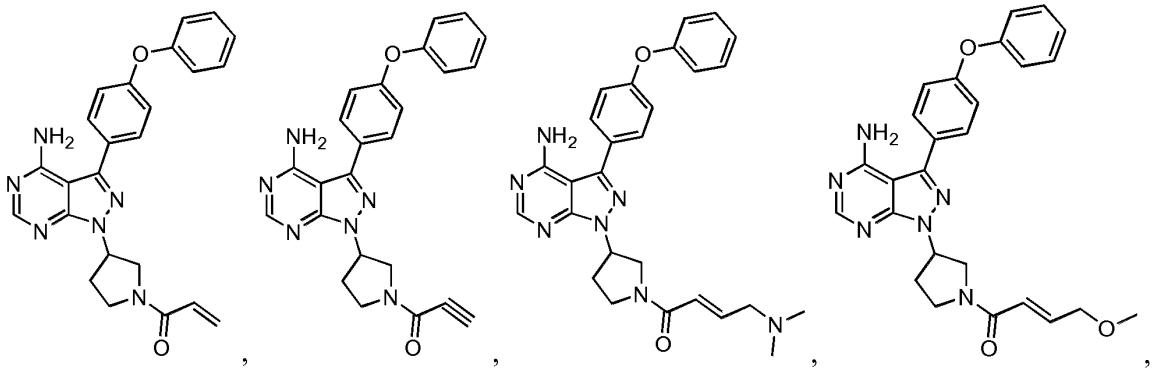

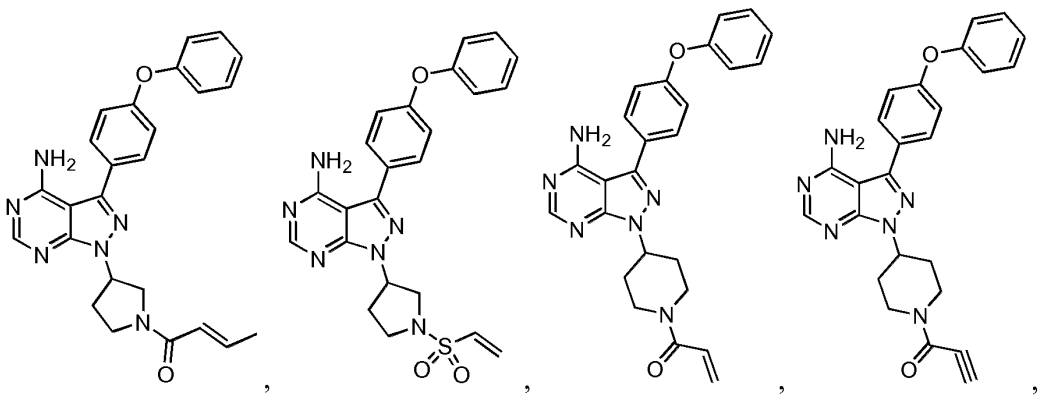

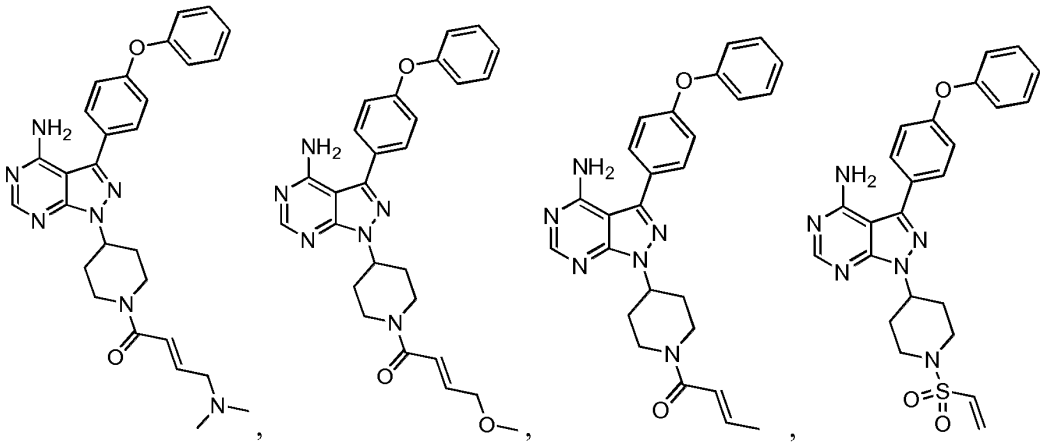

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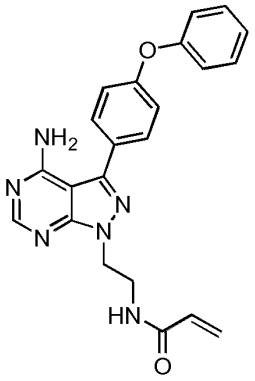
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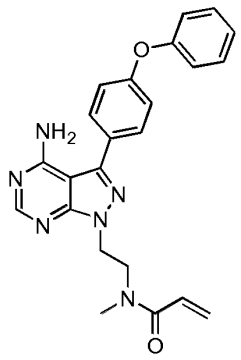
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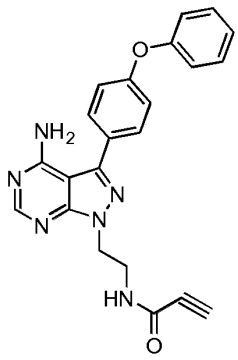
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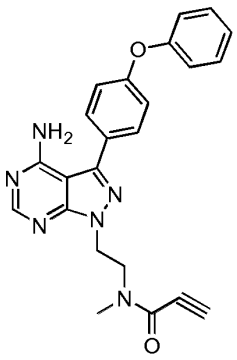
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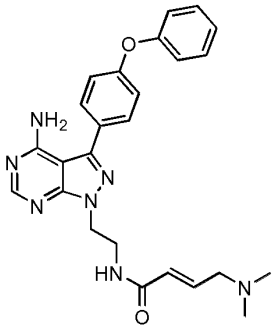
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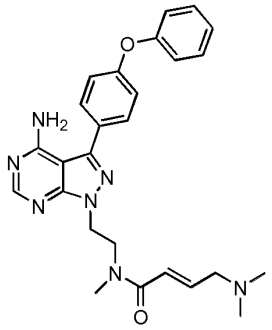
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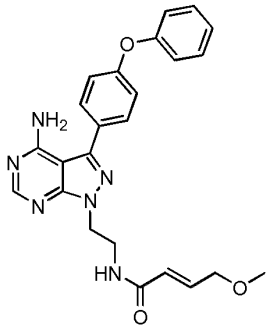
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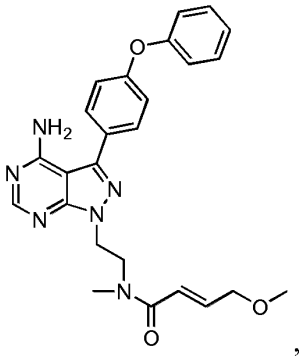
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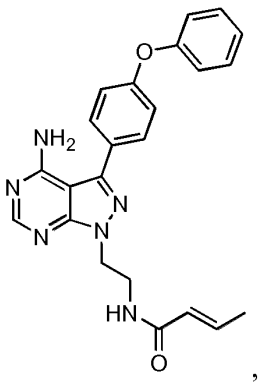
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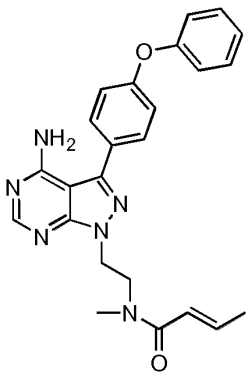
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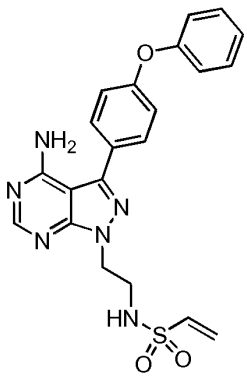
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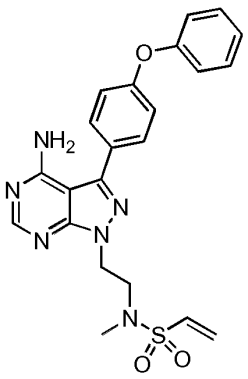
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[00263] In still another embodiment, compounds provided herein are selected from among:

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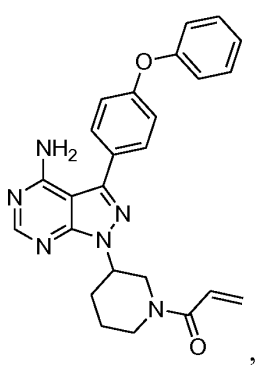
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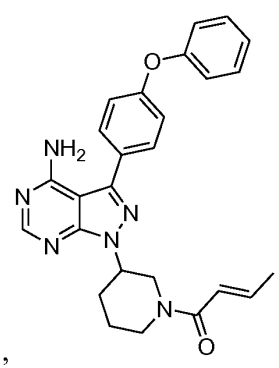
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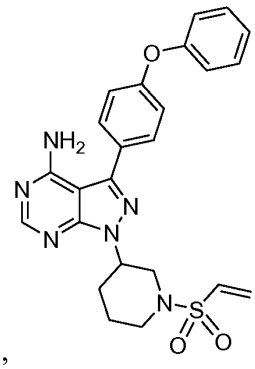
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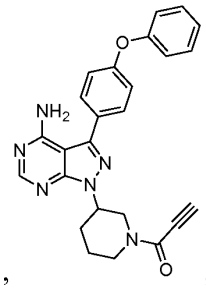
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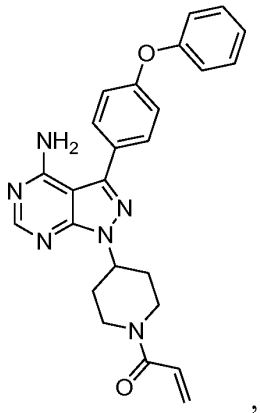
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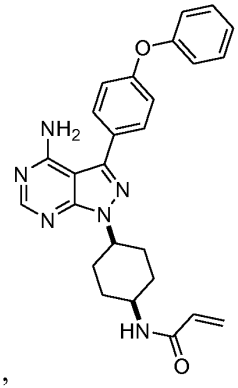
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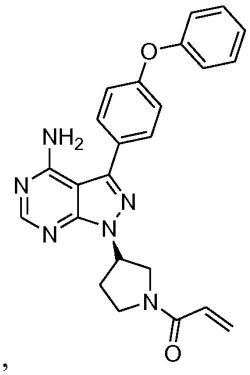
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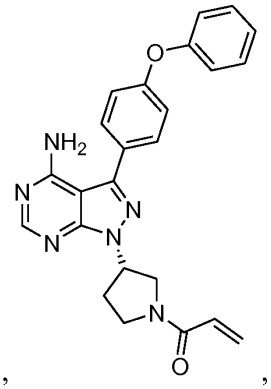
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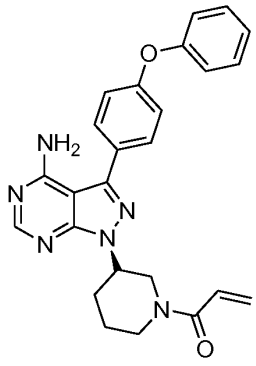
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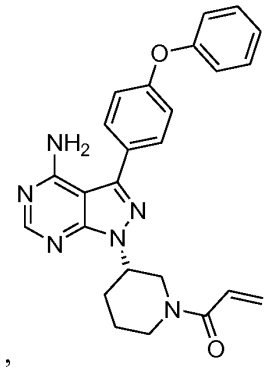
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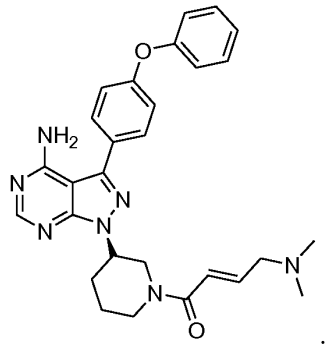
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[00264] In one aspect, provided herein is a compound selected from among: 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound **4**); (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)but-2-en-1-one (Compound **5**); 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)sulfonylethene (Compound **6**); 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-yn-1-one (Compound **8**); 1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound **9**);

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N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide (Compound **10**); 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound **11**); 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound **12**); 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound **13**); 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound **14**); and (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound **15**).

[00265] In some embodiments, the Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

[00266] In one embodiment, the Btk inhibitor is α-cyano-β-hydroxy-β- methyl-*N*-(2,5-dibromophenyl)propenamide (LFM-A13), AVL-101, 4-tert-butyl-N-(3-(8-(phenylamino)imidazo[1,2-a]pyrazin-6-yl)phenyl)benzamide, 5-(3-amino-2-methylphenyl)-1-methyl-3-(4-(morpholine-4-carbonyl)phenylamino)pyrazin-2(1H)-one, N-(2-methyl-3-(4-methyl-6-(4-(morpholine-4-carbonyl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)acetamide, 4-tert-butyl-N-(2-methyl-3-(4-methyl-6-(4-(morpholine-4-carbonyl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide, 5-(3-(4-tert-butylbenzylamino)-2-methylphenyl)-1-methyl-3-(4-(morpholine-4-carbonyl)phenylamino)pyrazin-2(1H)-one, 5-(3-(3-tert-butylbenzylamino)-2-methylphenyl)-1-methyl-3-(4-(morpholine-4-carbonyl)phenylamino)pyrazin-2(1H)-one, 3-tert-butyl-N-(2-methyl-3-(4-methyl-6-(4-(morpholine-4-carbonyl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide, 6-tert-butyl-N-(2-methyl-3-(4-methyl-6-(4-(morpholine-4-carbonyl)phenylamino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)nicotinamide, and terreic acid.

[00267] Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[00268] In certain embodiments, any of the Btk inhibitors and/or the second agent provided herein for the invention methods is included in a pharmaceutical composition comprising: i) a physiologically acceptable carrier, diluent, and/or excipient.

[00269] In some embodiments, the Btk inhibitor of the invention methods is administered at a dose of from about 1.25 mg/kg/day to about 12.5 mg/kg/day. In certain embodiments, the Btk

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inhibitor is administered at a dose selected from the group consisting of about 1.25 mg/kg/day, about 2.5 mg/kg/day, about 5 mg/kg/day, about 8.3 mg/kg/day, or about 12.5 mg/kg/day.

[00270] In some embodiments provide the biomarkers in accordance with the practice of the present invention is selected from ZAP-70, CD5, t(14;18), CD38, β-2 microglobulin, p53 mutational status, ATM mutational status, chromosome 17p deletion, chromosome 11q deletion, surface or cytoplasmic immunoglobulin, CD138, CD25, 6q deletion, CD19, CD20, CD22, CD11c, CD 103, chromosome 7q deletion, and V_H mutational status.

[00271] In some embodiments, determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes is of a combination of biomarkers. In certain embodiments, the combination of biomarkers is CD19 and CD5 or CD20 and CD5.

[00272] In other embodiments, the second agent is administered at a dose of from about 1.25 mg/kg/day to about 12.5 mg/kg/day. In certain embodiments, the second agent is administered at a dose selected from the group consisting of about 1.25 mg/kg/day, about 2.5 mg/kg/day, about 5 mg/kg/day, about 8.3 mg/kg/day, or about 12.5 mg/kg/day. The dosage of the second agent is based on the determined expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes. A person skilled in the art such as a physician can readily determine the suitable regimen (e.g. dosage of the second agent) based on the diagnostic results.

[00273] In other embodiments, the present invention provides methods for treating a cancer comprising determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes in a subject that has received a dose of a Btk inhibitor; and administering a second agent based on the determined expression profile.

[00274] In other embodiments, the present invention also provides methods for treating a cancer comprising administering a Btk inhibitor sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping; and administering a second agent once the increase or appearance in the blood of the subpopulation of lymphocytes is determined.

[00275] In some embodiments, the subject is a human.

[00276] In some embodiments, the Btk inhibitors are orally administered.

[00277] In any of the aforementioned aspects are further embodiments in which administration is enteral, parenteral, or both, and wherein (a) the effective amount of the Btk inhibitor is systemically administered to the mammal; (b) the effective amount of the Btk inhibitor is

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administered orally to the mammal; (c) the effective amount of the Btk inhibitor is intravenously administered to the mammal; (d) the effective amount of the Btk inhibitor administered by inhalation; (e) the effective amount of the Btk inhibitor is administered by nasal administration; or (f) the effective amount of the Btk inhibitor is administered by injection to the mammal; (g) the effective amount of the Btk inhibitor is administered topically (dermal) to the mammal; (h) the effective amount of the Btk inhibitor is administered by ophthalmic administration; or (i) the effective amount of the Btk inhibitor is administered rectally to the mammal.

[00278] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the Btk inhibitor, including further embodiments in which (i) the Btk inhibitor is administered once; (ii) the Btk inhibitor is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00279] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the Btk inhibitor, including further embodiments in which (i) the Btk inhibitor is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the Btk inhibitor is administered to the mammal every 8 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the Btk inhibitor is temporarily suspended or the dose of the Btk inhibitor being administered is temporarily reduced; at the end of the drug holiday, dosing of the Btk inhibitor is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[00280] In any of the aforementioned aspects are further embodiments in which administration is enteral, parenteral, or both, and wherein (a) the effective amount of the second agent is systemically administered to the mammal; (b) the effective amount of the second agent is administered orally to the mammal; (c) the effective amount of the second agent is intravenously administered to the mammal; (d) the effective amount of the second agent administered by inhalation; (e) the effective amount of the second agent is administered by nasal administration; or (f) the effective amount of the second agent is administered by injection to the mammal; (g) the effective amount of the second agent is administered topically (dermal) to the mammal; (h) the effective amount of the second agent is administered by ophthalmic administration; or (i) the effective amount of the second agent is administered rectally to the mammal.

[00281] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of second agent, including further embodiments in which (i)

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the second agent is administered once; (ii) the second agent is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[00282] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the second agent, including further embodiments in which (i) the second agent is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the second agent is administered to the mammal every 8 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the second agent is temporarily suspended or the dose of the second agent being administered is temporarily reduced; at the end of the drug holiday, dosing of the second agent is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[00283] \In any of the aforementioned aspects the second agent is selected from the group consisting of alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

Preparation of Compounds

[00284] Compounds of Formula D may be synthesized using standard synthetic techniques known to those of skill in the art or using methods known in the art in combination with methods described herein. In additions, solvents, temperatures and other reaction conditions presented herein may vary according to those of skill in the art. As a further guide the following synthetic methods may also be utilized.

[00285] The reactions can be employed in a linear sequence to provide the compounds described herein or they may be used to synthesize fragments which are subsequently joined by the methods described herein and/or known in the art.

Formation of Covalent Linkages by Reaction of an Electrophile with a Nucleophile

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[00286] The compounds described herein can be modified using various electrophiles or nucleophiles to form new functional groups or substituents. Table 1 entitled "Examples of Covalent Linkages and Precursors Thereof" lists selected examples of covalent linkages and precursor functional groups which yield and can be used as guidance toward the variety of electrophiles and nucleophiles combinations available. Precursor functional groups are shown as electrophilic groups and nucleophilic groups.

Table 1: Examples of Covalent Linkages and Precursors Thereof

Covalent Linkage Product	Electrophile	Nucleophile
Carboxamides	Activated esters	amines/anilines
Carboxamides	acyl azides	amines/anilines
Carboxamides	acyl halides	amines/anilines
Esters	acyl halides	alcohols/phenols
Esters	acyl nitriles	alcohols/phenols
Carboxamides	acyl nitriles	amines/anilines
Imines	Aldehydes	amines/anilines
Hydrazones	aldehydes or ketones	Hydrazines
Oximes	aldehydes or ketones	Hydroxylamines
Alkyl amines	alkyl halides	amines/anilines
Esters	alkyl halides	carboxylic acids
Thioethers	alkyl halides	Thiols
Ethers	alkyl halides	alcohols/phenols
Thioethers	alkyl sulfonates	Thiols
Esters	alkyl sulfonates	carboxylic acids
Ethers	alkyl sulfonates	alcohols/phenols
Esters	Anhydrides	alcohols/phenols
Carboxamides	Anhydrides	amines/anilines
Thiophenols	aryl halides	Thiols
Aryl amines	aryl halides	Amines
Thioethers	Azindines	Thiols
Boronate esters	Boronates	Glycols

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Carboxamides	carboxylic acids	amines/anilines
Esters	carboxylic acids	Alcohols
hydrazines	Hydrazides	carboxylic acids
N-acylureas or Anhydrides	carbodiimides	carboxylic acids
Esters	diazoalkanes	carboxylic acids
Thioethers	Epoxides	Thiols
Thioethers	haloacetamides	Thiols
Ammotriazines	halotriazines	amines/anilines
Triazinyl ethers	halotriazines	alcohols/phenols
Amidines	imido esters	amines/anilines
Ureas	Isocyanates	amines/anilines
Urethanes	Isocyanates	alcohols/phenols
Thioureas	isothiocyanates	amines/anilines
Thioethers	Maleimides	Thiols
Phosphite esters	phosphoramidites	Alcohols
Silyl ethers	silyl halides	Alcohols
Alkyl amines	sulfonate esters	amines/anilines
Thioethers	sulfonate esters	Thiols
Esters	sulfonate esters	carboxylic acids
Ethers	sulfonate esters	Alcohols
Sulfonamides	sulfonyl halides	amines/anilines
Sulfonate esters	sulfonyl halides	phenols/alcohols
Alkyl thiol	α,β-unsaturated ester	thiols
Alkyl ethers	α,β-unsaturated ester	alcohols
Alkyl amines	α,β-unsaturated ester	amines
Alkyl thiol	Vinyl sulfone	thiols
Alkyl ethers	Vinyl sulfone	alcohols
Alkyl amines	Vinyl sulfone	amines
Vinyl sulfide	Propargyl amide	thiol

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Use of Protecting Groups

[00287] In the reactions described, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Protecting groups are used to block some or all reactive moieties and prevent such groups from participating in chemical reactions until the protective group is removed. In one embodiment, each protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions fulfill the requirement of differential removal. Protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and t-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, but not limited to, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as t-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

[00288] Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be protected by conversion to simple ester compounds as exemplified herein, or they may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

[00289] Allyl blocking groups are useful in then presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a Pd^0-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

[00290] Typically blocking/protecting groups may be selected from:

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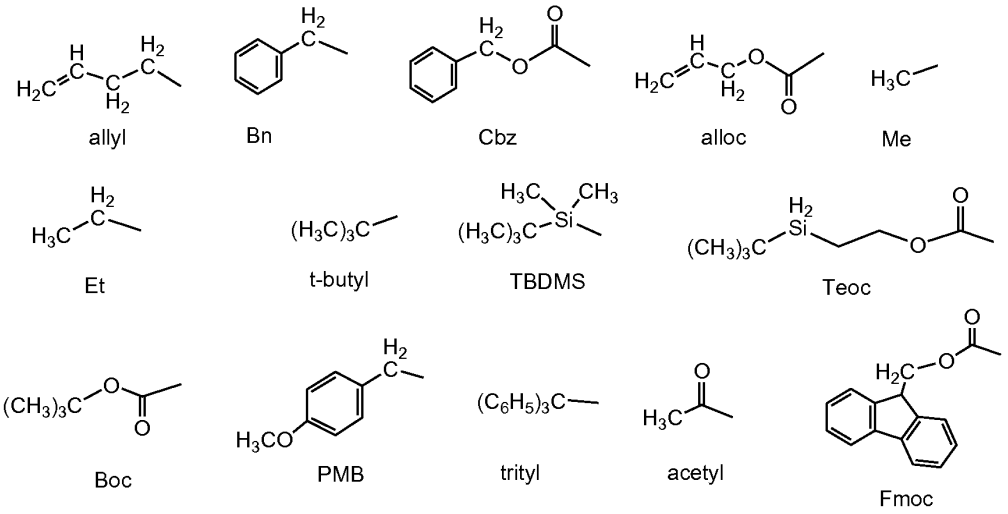

[00291] Other protecting groups, plus a detailed description of techniques applicable to the creation of protecting groups and their removal are described in Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, and Kocienski, Protective Groups, Thieme Verlag, New York, NY, 1994, which are incorporated herein by reference in their entirety.

Further Forms of Compounds

[00292] The compounds described herein may possess one or more stereocenters and each center may exist in the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns.

[00293] Diasteromeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known, for example, by chromatography and/or fractional crystallization. In one embodiment, enantiomers can be separated by chiral chromatographic columns. In other embodiments, enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers, and mixtures thereof are considered as part of the compositions described herein.

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[00294] The methods and formulations described herein include the use of *N*-oxides, crystalline forms (also known as polymorphs), or pharmaceutically acceptable salts of compounds described herein, as well as active metabolites of these compounds having the same type of activity. In some situations, compounds may exist as tautomers. All tautomers are included within the scope of the compounds presented herein. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00295] Compounds of Formula D in unoxidized form can be prepared from N-oxides of compounds of Formula D by treating with a reducing agent, such as, but not limited to, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like in a suitable inert organic solvent, such as, but not limited to, acetonitrile, ethanol, aqueous dioxane, or the like at 0 to 80°C.

[00296] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound described herein, which is administered as an ester (the "prodrug") to facilitate transmittal across a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to the carboxylic acid, the active entity, once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized to reveal the active moiety. In certain embodiments, upon *in vivo* administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically active form of the compound. In certain embodiments, a prodrug is enzymatically metabolized by one or more steps or processes to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, a pharmaceutically active compound is modified such that the active compound will be regenerated upon *in vivo* administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of

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pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound. (see, for example, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392; Silverman (1992), The Organic Chemistry of Drug Design and Drug Action, Academic Press, Inc., San Diego, pages 352-401, Saulnier *et al*., (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985).

[00297] Prodrug forms of the herein described compounds, wherein the prodrug is metabolized *in vivo* to produce a derivative as set forth herein are included within the scope of the claims. In some cases, some of the herein-described compounds may be a prodrug for another derivative or active compound.

[00298] Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues. In some embodiments, the design of a prodrug increases the effective water solubility. See, e.g., Fedorak et al., *Am. J. Physiol.*, 269:G210-218 (1995); McLoed et al., *Gastroenterol*, 106:405-413 (1994); Hochhaus et al., *Biomed. Chrom.,* 6:283-286 (1992); J. Larsen and H. Bundgaard, *Int. J. Pharmaceutics,* 37, 87 (1987); J. Larsen et al., *Int. J. Pharmaceutics*, 47, 103 (1988); Sinkula et al., *J. Pharm. Sci*., 64:181-210 (1975); T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series; and Edward B. Roche, *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, all incorporated herein in their entirety.

[00299] Sites on the aromatic ring portion of compounds of Formula D can be susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures, such as, by way of example only, halogens can reduce, minimize or eliminate this metabolic pathway.

[00300] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulas and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen,

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fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements.

[00301] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

[00302] Compounds described herein may be formed as, and/or used as, pharmaceutically acceptable salts. The type of pharmaceutical acceptable salts, include, but are not limited to: (1) acid addition salts, formed) by reacting the free base form of the compound with a pharmaceutically acceptable: inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion; or coordinates with an organic base. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like.

[00303] The corresponding counterions of the pharmaceutically acceptable salts may be analyzed and identified using various methods including, but not limited to, ion exchange

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chromatography, ion chromatography, capillary electrophoresis, inductively coupled plasma, atomic absorption spectroscopy, mass spectrometry, or any combination thereof.

[00304] The salts are recovered by using at least one of the following techniques: filtration, precipitation with a non-solvent followed by filtration, evaporation of the solvent, or, in the case of aqueous solutions, lyophilization.

[00305] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[00306] It should be understood that a reference to a salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[00307] Compounds described herein may be in various forms, including but not limited to, amorphous forms, milled forms and nano-particulate forms. In addition, compounds described herein include crystalline forms, also known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

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[00308] The screening and characterization of the pharmaceutically acceptable salts, polymorphs and/or solvates may be accomplished using a variety of techniques including, but not limited to, thermal analysis, x-ray diffraction, spectroscopy, vapor sorption, and microscopy. Thermal analysis methods address thermo chemical degradation or thermo physical processes including, but not limited to, polymorphic transitions, and such methods are used to analyze the relationships between polymorphic forms, determine weight loss, to find the glass transition temperature, or for excipient compatibility studies. Such methods include, but are not limited to, Differential scanning calorimetry (DSC), Modulated Differential Scanning Calorimetry (MDCS), Thermogravimetric analysis (TGA), and Thermogravi-metric and Infrared analysis (TG/IR). X-ray diffraction methods include, but are not limited to, single crystal and powder diffractometers and synchrotron sources. The various spectroscopic techniques used include, but are not limited to, Raman, FTIR, UVIS, and NMR (liquid and solid state). The various microscopy techniques include, but are not limited to, polarized light microscopy, Scanning Electron Microscopy (SEM) with Energy Dispersive X-Ray Analysis (EDX), Environmental Scanning Electron Microscopy with EDX (in gas or water vapor atmosphere), IR microscopy, and Raman microscopy.

[00309] Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

Cancer Treatment Regimens

[00310] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the

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mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time. In some embodiments, analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor. In some embodiments, administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood. In some embodiments, analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor. In some embodiments, the method further comprises administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

[00311] In some embodiments, administering a Btk inhibitor before a second cancer treatment regimen reduces immune-mediated reactions to the second cancer treatment regimen. In some embodiments, administering a Btk inhibitor before ofatumumab reduces immune-mediated reactions to ofatumumab.

[00312] In some embodiments, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

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[00313] In some embodiments, the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof.

[00314] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab.

[00315] In some embodiments, the second cancer treatment regimen comprises bendamustine, and rituximab.

[00316] In some embodiments, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab.

[00317] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab.

[00318] In some embodiments, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab.

[00319] In some embodiments, the second cancer treatment regimen comprises dexamethasone and lenalidomide.

[00320] Additional cancer treatment regimens include Nitrogen Mustards such as for example, bendamustine, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan, prednimustine, trofosfamide; Alkyl Sulfonates like busulfan, mannosulfan, treosulfan; Ethylene Imines like carboquone, thiotepa, triaziquone; Nitrosoureas like carmustine, fotemustine, lomustine, nimustine, ranimustine, semustine, streptozocin; Epoxides such as for example, etoglucid; Other Alkylating Agents such as for example dacarbazine, mitobronitol, pipobroman, temozolomide; Folic Acid Analogues such as for example methotrexate, permetrexed, pralatrexate, raltitrexed; Purine Analogs such as for example cladribine, clofarabine, fludarabine, mercaptopurine, nelarabine, tioguanine; Pyrimidine Analogs such as for example azacitidine, capecitabine, carmofur, cytarabine, decitabine, fluorouracil, gemcitabine, tegafur; Vinca Alkaloids such as for example vinblastine, vincristine, vindesine, vinflunine, vinorelbine; Podophyllotoxin Derivatives such as for example etoposide, teniposide; Colchicine derivatives such as for example demecolcine; Taxanes such as for example docetaxel, paclitaxel, paclitaxel poliglumex; Other Plant Alkaloids and Natural Products such as for example trabectedin; Actinomycines such as for example dactinomycin; Antracyclines

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such as for example aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pirarubicin, valrubicin, zorubincin; Other Cytotoxic Antibiotics such as for example bleomycin, ixabepilone, mitomycin, plicamycin; Platinum Compounds such as for example carboplatin, cisplatin, oxaliplatin, satraplatin; Methylhydrazines such as for example procarbazine; Sensitizers such as for example aminolevulinic acid, efaproxiral, methyl aminolevulinate, porfimer sodium, temoporfin; Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazonanib, sorafenib, sunitinib, temsirolimus; Other Antineoplastic Agents such as for example alitretinoin, altretamine, amzacrine, anagrelide, arsenic trioxide, asparaginase, bexarotene, bortezomib, celecoxib, denileukin diftitox, estramustine, hydroxycarbamide, irinotecan, lonidamine, masoprocol, miltefosein, mitoguazone, mitotane, oblimersen, pegaspargase, pentostatin, romidepsin, sitimagene ceradenovec, tiazofurine, topotecan, tretinoin, vorinostat; Estrogens such as for example diethylstilbenol, ethinylestradiol, fosfestrol, polyestradiol phosphate; Progestogens such as for example gestonorone, medroxyprogesterone, megestrol; Gonadotropin Releasing Hormone Analogs such as for example buserelin, goserelin, leuprorelin, triptorelin; Anti-Estrogens such as for example fulvestrant, tamoxifen, toremifene; Anti-Androgens such as for example bicalutamide, flutamide, nilutamide, , Enzyme Inhibitors, aminoglutethimide, anastrozole, exemestane, formestane, letrozole, vorozole; Other Hormone Antagonists such as for example abarelix, degarelix; Immunostimulants such as for example histamine dihydrochloride, mifamurtide, pidotimod, plerixafor, roquinimex, thymopentin; Immunosuppressants such as for example everolimus, gusperimus, leflunomide, mycophenolic acid, sirolimus; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; Other Immunosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide; and Radiopharmaceuticals such as for example, iobenguane.

[00321] Additional cancer treatment regimens include interferons, interleukins, Tumor Necrosis Factors, Growth Factors, or the like.

[00322] Additional cancer treatment regimens include Immunostimulants such as for example ancestim, filgrastim, lenograstim, molgramostim, pegfilgrastim, sargramostim; Interferons such as for example interferon alfa natural, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-n1, interferon beta natural, interferon beta-1a, interferon beta-1b, interferon gamma, peginterferon alfa-2a, peginterferon alfa-2b; Interleukins such as for example aldesleukin, oprelvekin; Other Immunostimulants such as for example BCG vaccine, glatiramer acetate,

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histamine dihydrochloride, immunocyanin, lentinan, melanoma vaccine, mifamurtide, pegademase, pidotimod, plerixafor, poly I:C, poly ICLC, roquinimex, tasonermin, thymopentin; Immunosuppressants such as for example abatacept, abetimus, alefacept, antilymphocyte immunoglobulin (horse), antithymocyte immunoglobulin (rabbit), eculizumab, efalizumab, everolimus, gusperimus, leflunomide, muromab-CD3, mycophenolic acid, natalizumab, sirolimus; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, etanercept, golimumab, infliximab; Interleukin Inhibitors such as for example anakinra, basiliximab, canakinumab, daclizumab, mepolizumab, rilonacept, tocilizumab, ustekinumab; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; Other Immunosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide.

[00323] Additional cancer treatment regimens include Adalimumab, Alemtuzumab, Basiliximab, Bevacizumab, Cetuximab, Certolizumab pegol, Daclizumab, Eculizumab, Efalizumab, Gemtuzumab, Ibritumomab tiuxetan, Infliximab, Muromonab-CD3, Natalizumab, Panitumumab, Ranibizumab, Rituximab, Tositumomab, Trastuzumab, or the like, or a combination thereof.

[00324] Additional cancer treatment regimens include Monoclonal Antibodies such as for example alemtuzumab, bevacizumab, catumaxomab, cetuximab, edrecolomab, gemtuzumab, ofatumumab, panitumumab, rituximab, trastuzumab, , Immunosuppressants, eculizumab, efalizumab, muromab-CD3, natalizumab; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, golimumab, infliximab, , Interleukin Inhibitors, basiliximab, canakinumab, daclizumab, mepolizumab, tocilizumab, ustekinumab, , Radiopharmaceuticals, ibritumomab tiuxetan, tositumomab; Others Monoclonal Antibodies such as for example abagovomab, adecatumumab, alemtuzumab, anti-CD30 monoclonal antibody Xmab2513, anti-MET monoclonal antibody MetMab, apolizumab, apomab, arcitumomab, basiliximab, bispecific antibody 2B1, blinatumomab, brentuximab vedotin, capromab pendetide, cixutumumab, claudiximab, conatumumab, dacetuzumab, denosumab, eculizumab, epratuzumab, epratuzumab, ertumaxomab, etaracizumab, figitumumab, fresolimumab, galiximab, ganitumab, gemtuzumab ozogamicin, glembatumumab, ibritumomab, inotuzumab ozogamicin, ipilimumab, lexatumumab, lintuzumab, lintuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, monoclonal antibody CC49, necitumumab, nimotuzumab, ofatumumab, oregovomab, pertuzumab, ramacurimab, ranibizumab, siplizumab, sonepcizumab, tanezumab, tositumomab, trastuzumab, tremelimumab, tucotuzumab celmoleukin, veltuzumab, visilizumab, volociximab, zalutumumab.

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[00325] Additional cancer treatment regimens include agents that affect the tumor micro-enviroment such as cellular signaling network (e.g. phosphatidylinositol 3-kinase (PI3K) signaling pathway, signaling from the B-cell receptor and the IgE receptor). In some embodiments, the second agent is a PI3K signaling inhibitor or a syc kinase inhibitor. In one embodiment, the syk inhibitor is R788. In another embodiment is a PKCγ inhibitor such as by way of example only, enzastaurin.

[00326] Examples of agents that affect the tumor micro-environment include PI3K signaling inhibitor, syc kinase inhibitor, Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazonanib, sorafenib, sunitinib, temsirolimus; Other Angiogenesis Inhibitors such as for example GT-111, JI-101, R1530; Other Kinase Inhibitors such as for example AC220, AC480, ACE-041, AMG 900, AP24534, Arry-614, AT7519, AT9283, AV-951, axitinib, AZD1152, AZD7762, AZD8055, AZD8931, bafetinib, BAY 73-4506, BGJ398, BGT226, BI 811283, BI6727, BIBF 1120, BIBW 2992, BMS-690154, BMS-777607, BMS-863233, BSK-461364, CAL-101, CEP-11981, CYC116, DCC-2036, dinaciclib, dovitinib lactate, E7050, EMD 1214063, ENMD-2076, fostamatinib disodium, GSK2256098, GSK690693, INCB18424, INNO-406, JNJ-26483327, JX-594, KX2-391, linifanib, LY2603618, MGCD265, MK-0457, MK1496, MLN8054, MLN8237, MP470, NMS-1116354, NMS-1286937, ON 01919.Na, OSI-027, OSI-930, Btk inhibitor, PF-00562271, PF-02341066, PF-03814735, PF-04217903, PF-04554878, PF-04691502, PF-3758309, PHA-739358, PLC3397, progenipoietin, R547, R763, ramucirumab, regorafenib, RO5185426, SAR103168, SCH 727965, SGI-1176, SGX523, SNS-314, TAK-593, TAK-901, TKI258, TLN-232, TTP607, XL147, XL228, XL281RO5126766, XL418, XL765.

[00327] Further examples of anti-cancer agents for use in combination with a Btk inhibitor compound include inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).

[00328] Other anti-cancer agents that can be employed in combination with a Btk inhibitor compound include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin

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hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin Il (including recombinant interleukin II, or rlL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-l a; interferon gamma-l b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

[00329] Other anti-cancer agents that can be employed in combination with a Btk inhibitor compound include: 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin;

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acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-such as for example growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-

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N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1 -based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylerie conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators;

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single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[00330] Yet other anticancer agents that can be employed in combination with a Btk inhibitor compound include alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, ete.), or triazenes (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[00331] Examples of alkylating agents that can be employed in combination a Btk inhibitor compound include, but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethlymelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazenes (decarbazine, ete.). Examples of antimetabolites include, but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin.

[00332] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules and which can be used in combination with a Btk inhibitor compound

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include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCI), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCI, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, lnanocine (also known as NSC-698666), 3-lAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tuiarik, also known as T-900607), RPR- 115781

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(Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, lsoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

Biomarkers

[00333] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, analyzing the mobilized plurality of cells comprises preparing a biomarker profile for a population of cells isolated from the plurality of cells. In some embodiments, the biomarker expression profile is used to diagnose, determine a prognosis, or create a predictive profile of a hematological malignancy. In some embodiments, the biomarker profile indicates the expression of a biomarker, the expression level of a biomarker, mutations in a biomarker, or the presence of a biomarker. In some embodiments, the biomarker is any cytogenetic, cell surface molecular or protein or RNA expression marker. In some embodiments, the biomarker is: ZAP70; t(14,18); β-2 microglobulin; p53 mutational status; ATM mutational status; del(17)p; del(11)q; del(6)q; CD5; CD11c; CD19; CD20; CD22; CD25; CD38; CD103; CD138; secreted, surface or cytoplasmic immunoglobulin expression; V_H mutational status; or a combination thereof. In some embodiments, the method further comprises providing a second cancer treatment regimen based on the biomarker profile. In some embodiments, the method further comprises not administering based on the biomarker profile. In some embodiments, the method further comprises predicting the efficacy of a treatment regimen based on the biomarker profile.

[00334] In certain embodiments, the methods comprise diagnosing, determining a prognosis, or creating a predictive profile of a hematological malignancy based upon the expression or presence of certain biomarkers. In other embodiments, the methods further comprise stratifying patient

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populations based upon the expression or presence of certain biomarkers in the affected lymphocytes. In still other embodiments, the methods further comprise determining a therapeutic regimen for the subject based upon the expression or presence of certain biomarkers in the affected lymphocytes. In yet other embodiments, the methods further comprise predicting a response to therapy in a subject based upon the expression or presence of certain biomarkers in the affected lymphocytes.

[00335] In certain aspects, provided herein are methods of diagnosing, determining a prognosis, or creating a predictive profile of a hematological malignancy in a subject comprising: (a) administering a Btk inhibitor to the subject sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes; and (b) determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes; wherein the expression or presence of one or more biomarkers is used to diagnose the hematological malignancy, determine the prognosis of the hematological malignancy, or create a predictive profile of the hematological malignancy. In one embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by immunophenotyping. In another embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by fluorescent activated cell sorting (FACS).

[00336] In other aspects, provided herein are methods of stratifying a patient population having a hematological malignancy comprising: (a) administering a Btk inhibitor to the subject sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes; and (b) determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes; wherein the expression or presence of one or more biomarkers is used to stratify patients for treatment of the hematological malignancy. In one embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by immunophenotyping. In another embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by fluorescent activated cell sorting (FACS).

[00337] In still other aspects, provided herein are methods of determining a therapeutic regimen in a subject having a hematological malignancy comprising: (a) administering a Btk inhibitor to the subject sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes; and (b) determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes; wherein the expression or presence of

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one or more biomarkers is used to determine the therapeutic regimen for the treatment of the hematological malignancy. In one embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by immunophenotyping. In another embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by fluorescent activated cell sorting (FACS).

[00338] In yet other aspects, provided herein are methods of predicting a response to therapy in a subject having a hematological malignancy comprising: (a) administering a Btk inhibitor to the subject sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes; and (b) determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes; wherein the expression or presence of one or more biomarkers is used to predict the subject's response to therapy for the hematological malignancy. In one embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by immunophenotyping. In another embodiment, the increase or appearance in the blood of a subpopulation of lymphocytes is determined by fluorescent activated cell sorting (FACS).

[00339] In certain aspects, provided herein are methods of diagnosing, determining a prognosis, or creating a predictive profile of a hematological malignancy in a subject comprising determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes in a subject that has received a dose of a Btk inhibitor wherein the expression or presence of one or more biomarkers is used to diagnose the hematological malignancy, determine the prognosis of the hematological malignancy, or create a predictive profile of the hematological malignancy. In one embodiment, the dose of Btk inhibitor is sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping. In another embodiment, the determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes further comprises isolating, detecting or measuring one or more type of lymphocyte. In still another embodiment, the Btk inhibitor is a reversible or irreversible inhibitor.

[00340] In other aspects, provided herein are methods of stratifying a patient population having a hematological malignancy comprising determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes in a subject that has received a dose of a Btk inhibitor wherein the expression or presence of one or more biomarkers is used to stratify patients for treatment of the hematological malignancy. In one embodiment, the dose of Btk

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inhibitor is sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping. In another embodiment, the determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes further comprises isolating, detecting or measuring one or more type of lymphocyte. In still another embodiment, the Btk inhibitor is a reversible or irreversible inhibitor.

[00341] In still other aspects, provided herein are methods of determining the therapeutic regimen in a subject having a hematological malignancy comprising determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes in a subject that has received a dose of a Btk inhibitor wherein the expression or presence of one or more biomarkers is used to determine the therapeutic regimen for the treatment of the hematological malignancy. In one embodiment, the dose of Btk inhibitor is sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping. In another embodiment, the determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes further comprises isolating, detecting or measuring one or more type of lymphocyte. In still another embodiment, the Btk inhibitor is a reversible or irreversible inhibitor.

[00342] In yet other aspects, provided herein are methods of predicting a response to therapy in a subject having a hematological malignancy comprising determining the expression or presence of one or more biomarkers from one or more circulating lymphocytes in a subject that has received a dose of a Btk inhibitor wherein the expression or presence of one or more biomarkers is used to predict the subject's response to therapy for the hematological malignancy. In one embodiment, the dose of Btk inhibitor is sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping. In another embodiment, the determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes further comprises isolating, detecting or measuring one or more type of lymphocyte. In still another embodiment, the Btk inhibitor is a reversible or irreversible inhibitor.

[00343] As contemplated herein, any biomarker related to hematological malignancies are in some embodiments utilized in the present methods. These biomarkers include any biological molecule (found either in blood, other body fluids, or tissues) or any chromosomal abnormality that is a sign of a hematological malignancy. In certain embodiments, the biomarkers include, but are not limited to, TdT, CD5, CD11c, CD19, CD20, CD22, CD79a, CD15, CD30, CD38, CD138, CD103,

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CD25, ZAP-70, p53 mutational status, ATM mutational status, mutational status of IgV_H, chromosome 17 deletions (del 17p), chromosome 6 deletions (del 6q), chromosome 7 deletions (del 7q), chromosome 11 deletions (del 11q), trisomy 12, chromosome 13 deletions (del 13 q), t(11:14) chromosomal translocation, t(14:18) chromosomal translocation, CD10, CD23, beta-2 microglobulin, bcl-2 expression, CD9, presence of *Helicobacter pylori*, CD154/CD40, Akt, NF-κB,WNT, Mtor, ERK, MAPK, and Src tyrosine kinase expression. In certain embodiments, the biomarkers include ZAP-70, CD5, t(14;18), CD38, β-2 microglobulin, p53 mutational status, ATM mutational status, chromosome 17p deletion, chromosome 11q deletion, surface or cytoplasmic immunoglobulin, CD138, CD25, 6q deletion, CD19, CD20, CD22, CD11c, CD 103, chromosome 7q deletion, V_H mutational status, or a combination thereof.

[00344] In certain embodiments, subpopulations of patients having a hematological malignancy cancer or pre- that would benefit from a known treatment regimen are identified by screening candidate subjects for one or more clinically useful biomarkers known in the art. Any clinically useful prognostic marker known to those of skill in the art can be used. In some embodiments, the subpopulation includes patients having chronic lymphocytic leukemia (CLL), and the clinically useful prognostic markers of particular interest include, but are not limited to, ZAP-70, CD38, .beta.2 microglobulin, and cytogenetic markers, for example, p53 mutational status, ATM mutational status, chromosome deletions, such as the chromosome 17p deletion and the chromosome 11q deletion, all of which are clinically useful prognostic markers for this disease.

[00345] ZAP-70 is a tyrosine kinase that associates with the zeta subunit of the T cell antigen receptor (TCR) and plays a pivotal role in T cell activation and development (Chan et al. (1992) Cell 71:649-662). ZAP-70 undergoes tyrosine phosphorylation and is essential in mediating signal transduction following TCR stimulation. Overexpression or constitutive activation of tyrosine kinases has been demonstrated to be involved in a number of malignancies including leukemias and several types of solid tumors. For example, increased ZAP-70 RNA expression levels are a prognostic marker of chronic lymphocytic leukemia (CLL) (Rosenwald et al. (2001) J. Exp. Med. 194:1639-1647). ZAP-70 is expressed in T-cells and natural killer cells, but is not known to be expressed in normal B-cells. However, ZAP-70 is expressed at high levels in the B-cells of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients, and more particularly in the subset of CLL patients who tend to have the more aggressive clinical course that is found in CLL/SLL patients with unmutated Ig genes (Wiestner et al. (2003) Blood 101: 4944-4951; U.S.

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Patent Application Publication No. 20030203416). Because of the correlation between ZAP-70 expression levels and Ig gene mutation status, ZAP-70 can be used as a prognostic indicator to identify those patients likely to have severe disease (high ZAP-70, unmutated Ig genes), and who are therefore candidates for aggressive therapy.

[00346] CD38 is a signal transduction molecule as well as an ectoenzyme catalyzing the synthesis and degradation of cyclic ADP ribose (cADPR). CD38 expression is present at high levels in bone marrow precursor B cells, is down-regulated in resting normal B cells, and then is re-expressed in terminally differentiated plasma cells (Campana et al. (2000) Chem. Immunol. 75:169-188). CD38 is a reliable prognostic indicator in B-CLL, with the expression of CD38 generally indicating a less favorable outcome (D'Arena et al. (2001) Leuk. Lymphoma 42:109; Del Poeta et al. (2001) Blood 98:2633; Durig et al. (2002) Leukemia 16:30; Ibrahim et al. (2001) Blood 98:181; Deaglio et al. (2003) Blood 102:2146-2155). The unfavorable clinical indications that CD38 expression has been associated with include an advanced stage of disease, poor responsiveness to chemotherapy, a shorter time before initial treatment is required, and a shorter survival time (Deaglio et al. (2003) Blood 102:2146-2155). Initially, a strong correlation between CD38 expression and IgV gene mutation was observed, with patients having unmutated V genes displaying higher percentages of CD38.sup.+ B-CLL cells than those with mutated V genes (Damle et al. (1999) Blood 94:1840-1847). However, subsequent studies have indicated that CD38 expression does not always correlate with the rearrangement of the IgV genes (Hamblin et al. (2002) Blood 99:1023; Thunberg et al. (2001) Blood 97:1892).

[00347] p53 is a nuclear phosphoprotein that acts as a tumor suppressor. Wild-type p53 is involved in regulating cell growth and division. p53 binds to DNA, stimulating the production of a protein (p21) that interacts with a cell division-stimulating protein (cdk2). When p21 is bound to cdk2, the cell is blocked from entering the next stage of cell division. Mutant p53 is incapable of binding DNA effectively, thus preventing p21 from acting as the stop signal for cell division, resulting in uncontrolled cell division, and tumor formation. p53 also regulates the induction of programmed cell death (apoptosis) in response to DNA damage, cell stress or the aberrant expression of some oncogenes. Expression of wild type p53 in some cancer cell lines has been shown to restore growth suppression control (Casey et al. (1991) Oncogene 6:1791-1797; Takahashi et al. (1992) Cancer Res. 52:734-736). Mutations in p53 are found in most tumor types, including tumors of the colon, breast, lung, ovary, bladder, and many other organs. p53 mutations have been

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found to be associated with Burkitt's lymphoma, L3-type B-cell acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia (Gaidano et al. (1991) Proc. Natl. Acad. Sci. U.S.A. 88:5413-5417). p53 abnormalities have also been found associated with B-cell prolymphocytic leukemia (Lens et al. (1997) Blood 89:2015-2023). The gene for p53 is located on the short arm of chromosome 17 at 17p13.105-p12.

[00348] B-2-microglobulin is an extracellular protein that is noncovalently associated with the .alpha. chain of the class I major histocompatibility complex (MHC). It is detectable in the serum, and is an adverse prognostic indicator in CLL (Keating et al. (1998) Blood 86:606a) and Hodgkin's lymphoma (Chronowski et al. (2002) Cancer 95:2534-2538). It is clinically used for lymphoproliferative diseases including leukemia, lymphoma, and multiple myeloma, where serum β-2-microglobulin levels are related to tumor cell load, prognosis, and disease activity (Bataille et al. (1983) Br. J. Haematol. 55:439-447; Aviles et al. (1992) Rev. Invest. Clin. 44:215-220). P2 microglobulin is also useful in staging myeloma patients (Pasqualetti et al. (1991) Eur. J. Cancer 27:1123-1126).

[00349] Cytogenetic aberrations may also be used as markers to create a predictive profile of a hematological malignancy. For example, chromosome abnormalities are found in a large percentage of CLL patients and are helpful in predicting the course of CLL. For example, a 17p deletion is indicative of aggressive disease progression. In addition, CLL patients with a chromosome 17p deletion or mutation in p53, or both, are known to respond poorly to chemotherapeutics and rituximab. Allelic loss on chromosome 17p may be also be a useful prognostic marker in colorectal cancer, where patients with a 17p deletion are associated with an increased tendency of disease dissemination in colorectal cancer (Khine et al. (1994) Cancer 73:28-35).

[00350] Deletions of the long arm of chromosome 11 (11q) are one of the most frequent structural chromosome aberrations in various types of lymphoproliferative disorders. CLL patients with chromosome 11q deletion and possibly ATM mutations have a poor survival compared to patients without either this defect or the 17p deletion. Furthermore, an 11q deletion is often accompanied by extensive lymph node involvement (Dohner et al. (1997) Blood 89:2516-2522). This deletion also identifies patients who are at high risk for disease persistence after high-dose therapy and autologous transplantation.

[00351] The ataxia telangiectasia mutated (ATA4) gene is a tumor suppressor gene that is involved in cell cycle arrest, apoptosis, and repair of DNA double-strand breaks. It is found on

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chromosome 11. ATMmutations are associated with increased risk for breast cancer among women with a family history of breast cancer (Chenevix-Trench et al. (2002) J. Natl. Cancer Inst. 94:205-215; Thorstenson et al. (2003) Cancer Res. 63:3325-3333) and/or early-onset breast cancers (Izatt et al. (1999) Genes Chromosomes Cancer 26:286-294; Teraoka et al. (2001) Cancer 92:479-487). There is also a high frequency of association of rhabdomyosarcoma with ATM gene mutation/deletion (Zhang et al. (2003) Cancer Biol. Ther. 1:87-91).

[00352] Methods for detecting chromosomal abnormalities in a patient are well known in the art (see, for example, Cuneo et al. (1999) Blood 93:1372-1380; Dohner et al. (1997) Blood 89:2516-2522). Methods to measure mutated proteins, such as ATM, are well known in the art (see, for example, Butch et al. (2004) Clin. Chem. 50: 2302-2308).

[00353] Thus, the biomarkers that are evaluated in the methods described herein include the cell survival and apoptotic proteins described *supra*, and proteins involved in hematological malignancy-related signaling pathways. Determining the expression or presence can be at the protein or nucleic acid level. Thus, the biomarkers include these proteins and the genes encoding these proteins. Where detection is at the protein level, the biomarker protein comprises the full-length polypeptide or any detectable fragment thereof, and can include variants of these protein sequences. Similarly, where detection is at the nucleotide level, the biomarker nucleic acid includes DNA comprising the full-length coding sequence, a fragment of the full-length coding sequence, variants of these sequences, for example naturally occurring variants or splice-variants, or the complement of such a sequence. Biomarker nucleic acids also include RNA, for example, mRNA, comprising the full-length sequence encoding the biomarker protein of interest, a fragment of the full-length RNA sequence of interest, or variants of these sequences. Biomarker proteins and biomarker nucleic acids also include variants of these sequences. By "fragment" is intended a portion of the polynucleotide or a portion of the amino acid sequence and hence protein encoded thereby. Polynucleotides that are fragments of a biomarker nucleotide sequence generally comprise at least 10, 15, 20, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, or 1,400 contiguous nucleotides, or up to the number of nucleotides present in a full-length biomarker polynucleotide disclosed herein. A fragment of a biomarker polynucleotide will generally encode at least 15, 25, 30, 50, 100, 150, 200, or 250 contiguous amino acids, or up to the total number of amino acids present in a full-length biomarker protein of the invention. "Variant" is intended to mean substantially similar sequences. Generally, variants of a particular biomarker of the invention

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will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to that biomarker as determined by sequence alignment programs known in the art.

[00354] As provided above, any method known in the art can be used in the methods for determining the expression or presence of biomarker described herein. Circulating levels of biomarkers in a blood sample obtained from a candidate subject, can be measured, for example, by ELISA, radioimmunoassay (RIA), electrochemiluminescence (ECL), Western blot, multiplexing technologies, or other similar methods. Cell surface expression of biomarkers can be measured, for example, by flow cytometry, immunohistochemistry, Western Blot, immunoprecipitation, magnetic bead selection, and quantification of cells expressing either of these cell surface markers. Biomarker RNA expression levels could be measured by RT-PCR, Qt-PCR, microarray, Northern blot, or other similar technologies.

[00355] As previously noted, determining the expression or presence of the biomarker of interest at the protein or nucleotide level can be accomplished using any detection method known to those of skill in the art. By "detecting expression" or "detecting the level of" is intended determining the expression level or presence of a biomarker protein or gene in the biological sample. Thus, "detecting expression" encompasses instances where a biomarker is determined not to be expressed, not to be detectably expressed, expressed at a low level, expressed at a normal level, or overexpressed.

[00356] In certain aspects of the method provided herein, the one or more subpopulation of lymphocytes are isolated, detected or measured. In certain embodiments, the one or more subpopulation of lymphocytes are isolated, detected or measured using immunophenotyping techniques. In other embodiments, the one or more subpopulation of lymphocytes are isolated, detected or measured using fluorescence activated cell sorting (FACS) techniques.

[00357] In certain embodiments of the methods provided herein, the one or more biomarkers comprises ZAP-70, CD5, t(14;18), CD38, β-2 microglobulin, p53 mutational status, ATM mutational status, chromosome 17p deletion, chromosome 11q deletion, surface or cytoplasmic immunoglobulin, CD138, CD25, 6q deletion, CD19, CD20, CD22, CD11c, CD 103, chromosome 7q deletion, VH mutational status, or a combination thereof.

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[00358] In certain aspects, the methods described herein, the determining step requires determining the expression or presence of a combination of biomarkers. In certain embodiment, the combination of biomarkers is CD19 and CD5 or CD20 and CD5.

[00359] In certain aspects, the expression or presence of these various biomarkers and any clinically useful prognostic markers in a biological sample can be detected at the protein or nucleic acid level, using, for example, immunohistochemistry techniques or nucleic acid-based techniques such as in situ hybridization and RT-PCR. In one embodiments, the expression or presence of one or more biomarkers is carried out by a means for nucleic acid amplification, a means for nucleic acid sequencing, a means utilizing a nucleic acid microarray (DNA and RNA), or a means for in situ hybridization using specifically labeled probes.

[00360] In other embodiments, the determining the expression or presence of one or more biomarkers is carried out through gel electrophoresis. In one embodiment, the determination is carried out through transfer to a membrane and hybridization with a specific probe.

[00361] In other embodiments, the determining the expression or presence of one or more biomarkers carried out by a diagnostic imaging technique.

[00362] In still other embodiments, the determining the expression or presence of one or more biomarkers carried out by a detectable solid substrate. In one embodiment, the detectable solid substrate is paramagnetic nanoparticles functionalized with antibodies.

[00363] In another aspect, provided herein are methods for detecting or measuring residual lymphoma following a course of treatment in order to guide continuing or discontinuing treatment or changing from one therapeutic regimen to another comprising determining the expression or presence of one or more biomarkers from one or more subpopulation of lymphocytes in a subject wherein the course of treatment is treatment with a Btk inhibitor.

[00364] Methods for detecting expression of the biomarkers described herein, and optionally cytokine markers, within the test and control biological samples comprise any methods that determine the quantity or the presence of these markers either at the nucleic acid or protein level. Such methods are well known in the art and include but are not limited to western blots, northern blots, ELISA, immunoprecipitation, immunofluorescence, flow cytometry, immunohistochemistry, nucleic acid hybridization techniques, nucleic acid reverse transcription methods, and nucleic acid amplification methods. In particular embodiments, expression of a biomarker is detected on a protein level using, for example, antibodies that are directed against specific biomarker proteins. These

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antibodies can be used in various methods such as Western blot, ELISA, multiplexing technologies, immunoprecipitation, or immunohistochemistry techniques. In some embodiments, detection of cytokine markers is accomplished by electrochemiluminescence (ECL).

[00365] Any means for specifically identifying and quantifying a biomarker (for example, biomarker, a biomarker of cell survival or proliferation, a biomarker of apoptosis, a biomarker of a Btk-mediated signaling pathway) in the biological sample of a candidate subject is contemplated. Thus, in some embodiments, expression level of a biomarker protein of interest in a biological sample is detected by means of a binding protein capable of interacting specifically with that biomarker protein or a biologically active variant thereof. Preferably, labeled antibodies, binding portions thereof, or other binding partners may be used. The word "label" when used herein refers to a detectable compound or composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (e.g., radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable.

[00366] The antibodies for detection of a biomarker protein may be monoclonal or polyclonal in origin, or may be synthetically or recombinantly produced. The amount of complexed protein, for example, the amount of biomarker protein associated with the binding protein, for example, an antibody that specifically binds to the biomarker protein, is determined using standard protein detection methodologies known to those of skill in the art. A detailed review of immunological assay design, theory and protocols can be found in numerous texts in the art (see, for example, Ausubel et al., eds. (1995) Current Protocols in Molecular Biology) (Greene Publishing and Wiley-Interscience, NY)); Coligan et al., eds. (1994) Current Protocols in Immunology (John Wiley & Sons, Inc., New York, N.Y.).

[00367] The choice of marker used to label the antibodies will vary depending upon the application. However, the choice of the marker is readily determinable to one skilled in the art. These labeled antibodies may be used in immunoassays as well as in histological applications to detect the presence of any biomarker or protein of interest. The labeled antibodies may be polyclonal or monoclonal. Further, the antibodies for use in detecting a protein of interest may be labeled with a radioactive atom, an enzyme, a chromophoric or fluorescent moiety, or a colorimetric tag as described elsewhere herein. The choice of tagging label also will depend on the detection limitations desired. Enzyme assays (ELISAs) typically allow detection of a colored product formed by

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interaction of the enzyme-tagged complex with an enzyme substrate. Radionuclides that can serve as detectable labels include, for example, I-131, I-123, I-125, Y-90, Re-188, Re-186, At-211, Cu-67, Bi-212, and Pd-109. Examples of enzymes that can serve as detectable labels include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, and glucose-6-phosphate dehydrogenase. Chromophoric moieties include, but are not limited to, fluorescein and rhodamine. The antibodies may be conjugated to these labels by methods known in the art. For example, enzymes and chromophoric molecules may be conjugated to the antibodies by means of coupling agents, such as dialdehydes, carbodiimides, dimaleimides, and the like. Alternatively, conjugation may occur through a ligand-receptor pair. Examples of suitable ligand-receptor pairs are biotin-avidin or biotin-streptavidin, and antibody-antigen.

[00368] In certain embodiments, expression or presence of one or more biomarkers or other proteins of interest within a biological sample, for example, a sample of bodily fluid, is determined by radioimmunoassays or enzyme-linked immunoassays (ELISAs), competitive binding enzyme-linked immunoassays, dot blot (see, for example, Promega Protocols and Applications Guide (2nd ed.; Promega Corporation (1991), Western blot (see, for example, Sambrook et al. (1989) Molecular Cloning, A Laboratory Manual, Vol. 3, Chapter 18 (Cold Spring Harbor Laboratory Press, Plainview, N.Y.), chromatography, preferably high performance liquid chromatography (HPLC), or other assays known in the art. Thus, the detection assays can involve steps such as, but not limited to, immunoblotting, immunodiffusion, immunoelectrophoresis, or immunoprecipitation.

[00369] In certain other embodiments, the methods of the invention are useful for identifying and treating hematological malignancies, including those listed above, that are refractory to (i.e., resistant to, or have become resistant to) first-line oncotherapeutic treatments.

[00370] The expression or presence of one or more of the biomarkers described herein may also be determined at the nucleic acid level. Nucleic acid-based techniques for assessing expression are well known in the art and include, for example, determining the level of biomarker mRNA in a biological sample. Many expression detection methods use isolated RNA. Any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA (see, e.g., Ausubel et al., ed. (1987-1999) Current Protocols in Molecular Biology (John Wiley & Sons, New York). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process disclosed in U.S. Pat. No. 4,843,155.

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[00371] Thus, in some embodiments, the detection of a biomarker or other protein of interest is assayed at the nucleic acid level using nucleic acid probes. The term "nucleic acid probe" refers to any molecule that is capable of selectively binding to a specifically intended target nucleic acid molecule, for example, a nucleotide transcript. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled, for example, with a radioactive label, a fluorescent label, an enzyme, a chemiluminescent tag, a colorimetric tag, or other labels or tags that are discussed above or that are known in the art. Examples of molecules that can be utilized as probes include, but are not limited to, RNA and DNA.

[00372] For example, isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to an mRNA or genomic DNA encoding a biomarker, biomarker described herein above. Hybridization of an mRNA with the probe indicates that the biomarker or other target protein of interest is being expressed.

[00373] In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in a gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoding the biomarkers or other proteins of interest.

[00374] An alternative method for determining the level of a mRNA of interest in a sample involves the process of nucleic acid amplification, e.g., by RT-PCR (see, for example, U.S. Pat. No. 4,683,202), ligase chain reaction (Barany (1991) Proc. Natl. Acad. Sci. USA 88:189-193), self-sustained sequence replication (Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86:1173-1177), Q-Beta Replicase (Lizardi et al. (1988) Bio/Technology 6:1197), rolling circle replication (U.S. Pat. No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection

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schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the invention, biomarker expression is assessed by quantitative fluorogenic RT-PCR (i.e., the TaqMan® System).

[00375] Expression levels of an RNA of interest may be monitored using a membrane blot (such as used in hybridization analysis such as Northern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See U.S. Pat. Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The detection of expression may also comprise using nucleic acid probes in solution.

[00376] In one embodiment of the invention, microarrays are used to determine expression or presence of one or more biomarkers. Microarrays are particularly well suited for this purpose because of the reproducibility between different experiments. DNA microarrays provide one method for the simultaneous measurement of the expression levels of large numbers of genes. Each array consists of a reproducible pattern of capture probes attached to a solid support. Labeled RNA or DNA is hybridized to complementary probes on the array and then detected by laser scanning. Hybridization intensities for each probe on the array are determined and converted to a quantitative value representing relative gene expression levels. See, U.S. Pat. Nos. 6,040,138, 5,800,992 and 6,020,135, 6,033,860, and 6,344,316, which are incorporated herein by reference. High-density oligonucleotide arrays are particularly useful for determining the gene expression profile for a large number of RNA's in a sample.

[00377] Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, e.g., U.S. Pat. No. 5,384,261, incorporated herein by reference in its entirety. Although a planar array surface is preferred, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be peptides or nucleic acids on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate, see U.S. Pat. Nos. 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992, each of which is hereby incorporated in its entirety for all purposes. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of an all-inclusive device. See, for example, U.S. Pat. Nos. 5,856,174 and 5,922,591, herein incorporated by reference.

Pharmaceutical Compositions/Formulations

[00378] Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate

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processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art. A summary of pharmaceutical compositions described herein may be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery* Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference in their entirety.

[00379] A pharmaceutical composition, as used herein, refers to a mixture of a compound described herein, such as, for example, compounds of Formula D or the second agent, with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. In practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds described herein are administered in a pharmaceutical composition to a mammal having a disease, disorder, or condition to be treated. Preferably, the mammal is a human. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00380] In certain embodiments, compositions may also include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00381] In other embodiments, compositions may also include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

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[00382] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound described herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound described herein and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00383] The pharmaceutical formulations described herein can be administered to a subject by multiple administration routes, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes. The pharmaceutical formulations described herein include, but are not limited to, aqueous liquid dispersions, self-emulsifying dispersions, solid solutions, liposomal dispersions, aerosols, solid dosage forms, powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[00384] Pharmaceutical compositions including a compound described herein may be manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00385] "Antifoaming agents" reduce foaming during processing which can result in coagulation of aqueous dispersions, bubbles in the finished film, or generally impair processing. Exemplary anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

[00386] "Antioxidants" include, for example, butylated hydroxytoluene (BHT), sodium ascorbate, ascorbic acid, sodium metabisulfite and tocopherol. In certain embodiments, antioxidants enhance chemical stability where required.

[00387] In certain embodiments, compositions provided herein may also include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing

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substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[00388] Formulations described herein may benefit from antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[00389] "Binders" impart cohesive qualities and include, e.g., alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crosspovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[00390] A "carrier" or "carrier materials" include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility with compounds disclosed herein, such as, compounds of any of Formula D and the second agent, and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. "Pharmaceutically compatible carrier materials" may include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, polyvinylpyrrollidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphotidylcholine, sodium chloride,

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tricalcium phosphate, dipotassium phosphate, cellulose and cellulose conjugates, sugars sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Fo*rms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[00391] "Dispersing agents," and/or "viscosity modulating agents" include materials that control the diffusion and homogeneity of a drug through liquid media or a granulation method or blend method. In some embodiments, these agents also facilitate the effectiveness of a coating or eroding matrix. Exemplary diffusion facilitators/dispersing agents include, e.g., hydrophilic polymers, electrolytes, Tween ® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcelluloses (e.g., HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), vinyl pyrrolidone/vinyl acetate copolymer (S630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)), polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyvinylpyrrolidone/vinyl acetate copolymer (S-630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, polysorbate-80, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone,

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carbomers, polyvinyl alcohol (PVA), alginates, chitosans and combinations thereof. Plasticizers such as cellulose or triethyl cellulose can also be used as dispersing agents. Dispersing agents particularly useful in liposomal dispersions and self-emulsifying dispersions are dimyristoyl phosphatidyl choline, natural phosphatidyl choline from eggs, natural phosphatidyl glycerol from eggs, cholesterol and isopropyl myristate.

[00392] Combinations of one or more erosion facilitator with one or more diffusion facilitator can also be used in the present compositions.

[00393] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In certain embodiments, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); mannitol, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[00394] The term "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. "Disintegration agents or disintegrants" facilitate the breakup or disintegration of a substance. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crosspovidone, a cross-linked polyvinylpyrrolidone,

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alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00395] "Drug absorption" or "absorption" typically refers to the process of movement of drug from site of administration of a drug across a barrier into a blood vessel or the site of action, e.g., a drug moving from the gastrointestinal tract into the portal vein or lymphatic system.

[00396] An "enteric coating" is a substance that remains substantially intact in the stomach but dissolves and releases the drug in the small intestine or colon. Generally, the enteric coating comprises a polymeric material that prevents release in the low pH environment of the stomach but that ionizes at a higher pH, typically a pH of 6 to 7, and thus dissolves sufficiently in the small intestine or colon to release the active agent therein.

[00397] "Erosion facilitators" include materials that control the erosion of a particular material in gastrointestinal fluid. Erosion facilitators are generally known to those of ordinary skill in the art. Exemplary erosion facilitators include, e.g., hydrophilic polymers, electrolytes, proteins, peptides, and amino acids.

[00398] "Filling agents" include compounds such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00399] "Flavoring agents" and/or "sweeteners" useful in the formulations described herein, include, e.g., acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium

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saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sylitol, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof.

[00400] "Lubricants" and "glidants" are compounds that prevent, reduce or inhibit adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl fumerate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex®), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (e.g., PEG-4000) or a methoxypolyethylene glycol such as Carbowax™, sodium oleate, sodium benzoate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid™, Cab-O-Sil®, a starch such as corn starch, silicone oil, a surfactant, and the like.

[00401] A "measurable serum concentration" or "measurable plasma concentration" describes the blood serum or blood plasma concentration, typically measured in mg, □g, or ng of therapeutic agent per ml, dl, or l of blood serum, absorbed into the bloodstream after administration. As used herein, measurable plasma concentrations are typically measured in ng/ml or □g/ml.

[00402] "Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

[00403] "Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

[00404] "Plasticizers" are compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. In some embodiments, plasticizers can also function as dispersing agents or wetting agents.

[00405] "Solubilizers" include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium doccusate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl

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cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200-600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide and the like.

[00406] "Stabilizers" include compounds such as any antioxidation agents, buffers, acids, preservatives and the like.

[00407] "Steady state," as used herein, is when the amount of drug administered is equal to the amount of drug eliminated within one dosing interval resulting in a plateau or constant plasma drug exposure.

[00408] "Suspending agents" include compounds such as polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, vinyl pyrrolidone/vinyl acetate copolymer (S630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose acetate stearate, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00409] "Surfactants" include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. Some other surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40. In some embodiments, surfactants may be included to enhance physical stability or for other purposes.

[00410] "Viscosity enhancing agents" include, e.g., methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate stearate, hydroxypropylmethyl cellulose phthalate, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

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[00411] "Wetting agents" include compounds such as oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium docusate, sodium oleate, sodium lauryl sulfate, sodium doccusate, triacetin, Tween 80, vitamin E TPGS, ammonium salts and the like.

Dosage Forms

[00412] The compositions described herein can be formulated for administration to a subject via any conventional means including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal, rectal or transdermal administration routes. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[00413] Moreover, the pharmaceutical compositions described herein, which include a compound of any of Formula D or the second agent can be formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00414] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00415] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic

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solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00416] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[00417] In some embodiments, the solid dosage forms disclosed herein may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder) a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations described herein may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[00418] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of a compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the particles of the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also include film coatings, which disintegrate

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upon oral ingestion or upon contact with diluent. These formulations can be manufactured by conventional pharmacological techniques.

[00419] Conventional pharmacological techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, e.g., Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00420] The pharmaceutical solid dosage forms described herein can include a compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the formulation of the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6). In one embodiment, some or all of the particles of the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), are coated. In another embodiment, some or all of the particles of the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), are microencapsulated. In still another embodiment, the particles of the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), are not microencapsulated and are uncoated.

[00421] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[00422] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate,

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calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethycellulose (HPMC), hydroxypropylmethycellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00423] In order to release the compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00424] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacoat-603, hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer,

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crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[00425] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. Formulators skilled in art can determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[00426] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, and the like.

[00427] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like.

[00428] The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm^3, e.g. Avicel, powdered cellulose), and talc.

[00429] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

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[00430] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, polaxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like.

[00431] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00432] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[00433] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[00434] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

[00435] Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the

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compressed tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of the compound of of any of Formula D or the second agent, from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

[00436] A capsule may be prepared, for example, by placing the bulk blend of the formulation of the compound of any of Formula D or the second agent, described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the formulation is delivered in a capsule form.

[00437] In various embodiments, the particles of the compound of any of Formula D or the second agent, and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[00438] In another aspect, dosage forms may include microencapsulated formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00439] Materials useful for the microencapsulation described herein include materials compatible with compounds of any of Formula D or the secodn agent, which sufficiently isolate the compound of any of Formula D or the secodn agent, from other non-compatible excipients.

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Materials compatible with compounds of any of Formula D or the secodn agent, are those that delay the release of the compounds of of any of Formula D or the secodn agent, *in vivo*.

[00440] Exemplary microencapsulation materials useful for delaying the release of the formulations including compounds described herein, include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucel® or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Methocel®-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel®-A, hydroxypropylmethylcellulose acetate stearate Aqoat (HF-LS, HF-LG,HF-MS) and Metolose®, Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®, Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol®, carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®, monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, Eudragit® NE30D, and Eudragit® NE 40D, cellulose acetate phthalate, sepifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

[00441] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the microencapsulation material is Klucel. In still other embodiments, the microencapsulation material is methocel.

[00442] Microencapsulated compounds of any of Formula D or the secodn agent, may be formulated by methods known by one of ordinary skill in the art. Such known methods include, e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ

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polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating may also be used.

[00443] In one embodiment, the particles of compounds of any of Formula D or the secodn agent, are microencapsulated prior to being formulated into one of the above forms. In still another embodiment, some or most of the particles are coated prior to being further formulated by using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000).

[00444] In other embodiments, the solid dosage formulations of the compounds of any of Formula D or the second agent, are plasticized (coated) with one or more layers. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

[00445] In other embodiments, a powder including the formulations with a compound of any of Formula D or the secodn agent, described herein, may be formulated to include one or more pharmaceutical excipients and flavors. Such a powder may be prepared, for example, by mixing the formulation and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also include a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units.

[00446] In still other embodiments, effervescent powders are also prepared in accordance with the present disclosure. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the compositions described herein are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence." Examples of effervescent salts include, e.g., the following ingredients: sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric

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acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

[00447] In some embodiments, the solid dosage forms described herein can be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[00448] The term "delayed release" as used herein refers to the delivery so that the release can be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. In some embodiments the method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the methods and compositions described herein to achieve delivery to the lower gastrointestinal tract. In some embodiments the polymers described herein are anionic carboxylic polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

(a) Shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH >7;

(b) Acrylic polymers. The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in

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the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

(c) Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH >6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP psuedolatex with particles <1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions; Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00449] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

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[00450] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[00451] In other embodiments, the formulations described herein, which include compounds of Formula D or the secodn agent, are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, plyanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983, each of which is specifically incorporated by reference.

[00452] In some embodiments, pharmaceutical formulations are provided that include particles of the compounds of any of Formula D or the secodn agent, described herein and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00453] Liquid formulation dosage forms for oral administration can be aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 754-757 (2002). In addition to the particles of compounds of Formula (A1-A6), the liquid dosage forms may include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions can further include a crystalline inhibitor.

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[00454] The aqueous suspensions and dispersions described herein can remain in a homogenous state, as defined in The USP Pharmacists' Pharmacopeia (2005 edition, chapter 905), for at least 4 hours. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[00455] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®; a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum® HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[00456] In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, for example, hydrophilic polymers, electrolytes, Tween ® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, hydroxypropylmethyl-cellulose

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acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (Plasdone®, e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)). In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes; Tween ® 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L); hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g. HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M, and Pharmacoat® USP 2910 (Shin-Etsu)); carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethyl-cellulose phthalate; hydroxypropylmethyl-cellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); or poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®).

[00457] Wetting agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, but are not limited to, cetyl alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)), and polyethylene glycols (e.g., Carbowaxs 3350® and 1450®, and Carbopol 934® (Union Carbide)), oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, triacetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphotidylcholine and the like

[00458] Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben), benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such

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as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth.

[00459] Suitable viscosity enhancing agents for the aqueous suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdon® S-630, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

[00460] Examples of sweetening agents suitable for the aqueous suspensions or dispersions described herein include, for example, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cylamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In one embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.001% to about 1.0% the volume of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.005% to about 0.5% the volume of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.01% to about 1.0% the volume of the aqueous dispersion.

[00461] In addition to the additives listed above, the liquid formulations can also include inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and

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emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, sodium lauryl sulfate, sodium doccusate, cholesterol, cholesterol esters, taurocholic acid, phosphotidylcholine, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[00462] In some embodiments, the pharmaceutical formulations described herein can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration, which ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563, each of which is specifically incorporated by reference.

[00463] It is to be appreciated that there is overlap between the above-listed additives used in the aqueous dispersions or suspensions described herein, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in formulations described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

Intranasal Formulations

[00464] Intranasal formulations are known in the art and are described in, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452, each of which is specifically incorporated by reference. Formulations that include a compound of any of Formula (A1-A6), Formula (B1-B6), Formula (C1-C6), or Formula (D1-D6), which are prepared according to these and other techniques

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well-known in the art are prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, Ansel, H. C. et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of nasal dosage forms and some of these can be found in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st edition, 2005, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, or buffering and other stabilizing and solubilizing agents may also be present. The nasal dosage form should be isotonic with nasal secretions.

[00465] For administration by inhalation, the compounds of any of Formula D or the second agent, described herein may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

Buccal Formulations

[00466] Buccal formulations that include compounds of any of Formula D or the second agent may be administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136, each of which is specifically incorporated by reference. In addition, the buccal dosage forms described herein can further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. The buccal dosage form is fabricated so as to erode gradually over a predetermined time period, wherein the delivery of the compound of any of Formula D or the second agent, is provided essentially throughout. Buccal drug delivery, as will be

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appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. With regard to the bioerodible (hydrolysable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the compound of any of Formula D or the second agent, and any other components that may be present in the buccal dosage unit. Generally, the polymeric carrier comprises hydrophilic (water-soluble and water-swellable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer). Other components may also be incorporated into the buccal dosage forms described herein include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.

Transdermal Formulations

[00467] Transdermal formulations described herein may be administered using a variety of devices which have been described in the art. For example, such devices include, but are not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144, each of which is specifically incorporated by reference in its entirety.

[00468] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In one embodiments, the transdermal formulations described herein include at least three components: (1) a formulation of a compound of any of Formula D or the secodn agent; (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation can further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

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[00469] Formulations suitable for transdermal administration of compounds described herein may employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches can provide controlled delivery of the compounds of any of Formula D or the second agent. The rate of absorption can be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier can include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Injectable Formulations

[00470] Formulations that include a compound of any of Formula D or the secodn agent, suitable for intramuscular, subcutaneous, or intravenous injection may include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

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[00471] For intravenous injections, compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, appropriate formulations may include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

[00472] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Other Formulations

[00473] In certain embodiments, delivery systems for pharmaceutical compounds may be employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein can also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00474] In some embodiments, the compounds described herein may be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such

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pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00475] The compounds described herein may also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

Dosing and Treatment Regimens

[00476] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: (a) administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and (b) analyzing the mobilized plurality of cells. In some embodiments, the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy. In some embodiments, the amount of the irreversible Btk inhibitor is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is about 420 mg/day. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL. In some embodiments, the AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL. In some embodiments, the Btk inhibitor is administered orally. In some embodiments, the Btk inhibitor is administered once per day, twice per day, or three times per day. In some embodiments, the Btk inhibitor is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is a maintenance therapy.

[00477] The compounds described herein can be used in the preparation of medicaments for the inhibition of Btk or a homolog thereof, or for the treatment of diseases or conditions that would benefit, at least in part, from inhibition of Btk or a homolog thereof, including a patient and/or

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subject diagnosed with a hematological malignancy. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing at least one compound of any of Formula (A), Formula (B), Formula (C), or Formula (D), described herein, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[00478] The compositions containing the compound(s) described herein can be administered for prophylactic, therapeutic, or maintenance treatment. In some embodiments, compositions containing the compounds described herein are administered for therapeutic applications (e.g., administered to a patient diagnosed with a hematological malignancy). In some embodiments, compositions containing the compounds described herein are administered for therapeutic applications (e.g., dministered to a patient susceptible to or otherwise at risk of developing a hematological malignancy). In some embodiments, compositions containing the compounds described herein are administered to a patient who is in remission as a maintenance therapy.

[00479] Amounts of a compound disclosed herein will depend on the use (e.g., therapeutic, prophylactic, or maintnenace). Amounts of a compound disclosed herein will depend on severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial). In some embodiments, the amount of the irreversible Btk inhibitor is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of the Btk inhibitor is from 400 mg/day up to, and including, 860 mg/day. In some embodiments, the amount of the Btk inhibitor is about 360 mg/day. In some embodiments, the amount of the Btk inhibitor is about 420 mg/day. In some embodiments, the amount of the Btk inhibitor is about 560 mg/day. In some embodiments, the amount of the Btk inhibitor is about 840 mg/day. In some embodiments, the amount of the Btk inhibitor is from 2 mg/kg/day up to, and including, 13 mg/kg/day. In some embodiments, the amount of the Btk inhibitor is from 2.5 mg/kg/day up to, and including, 8 mg/kg/day. In some embodiments, the amount of the Btk inhibitor is from 2.5 mg/kg/day up to, and including, 6 mg/kg/day. In some

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embodiments, the amount of the Btk inhibitor is from 2.5 mg/kg/day up to, and including, 4 mg/kg/day. In some embodiments, the amount of the Btk inhibitor is about 2.5 mg/kg/day. In some embodiments, the amount of the Btk inhibitor is about 8 mg/kg/day.

[00480] In some embodiments, a Btk inhibitior disclosed herein is administered daily. In some embodiments, a Btk inhibitor disclosed herein is administered every other day.

[00481] In some embodiments, a Btk inhibitior disclosed herein is administered once per day. In some embodiments, a Btk inhibitior disclosed herein is administered twice per day. In some embodiments, a Btk inhibitior disclosed herein is administered here times per day. In some embodiments, a Btk inhibitior disclosed herein is administered times per per day.

[00482] In some embodiments, the Btk inhibitor is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice.

[00483] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday can vary between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[00484] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00485] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely

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determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, or from about 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00486] The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative. In some embodiments, each unit dosage form comprises 210 mg of a compound disclosed herein. In some embodiments, an individual is administerd 1 unit dosage form per day. In some embodiments, an individual is administerd 2 unit dosage forms per day. In some embodiments, an individual is administerd 3 unit dosage forms per day. In some embodiments, an individual is administerd 4 unit dosage forms per day.

[00487] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00488] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and

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therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Kits/Articles of Manufacture

[00489] The present invention also encompasses kits for carrying out the methods of the present invention. For example, the kit can comprise a labeled compound or agent capable of detecting a biomarker described herein, e.g., a biomarker of apoptosis, cellular proliferation or survival, or a Btk-mediated signaling pathway, either at the protein or nucleic acid level, in a biological sample and means for determining the amount of the biomarker in the sample (for example, an antibody or an oligonucleotide probe that binds to RNA encoding a biomarker of interest) following incubation of the sample with a BCLD therapeutic agent of interest. Kits can be packaged to allow for detection of multiple biomarkers of interest by including individual labeled compounds or agents capable of detecting each individual biomarker of interest and means for determining the amount of each biomarker in the sample.

[00490] The particular choice of the second agent used will depend upon the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol of the Btk inhibitors.

EXAMPLES

[00491] The following specific and non-limiting examples are to be construed as merely illustrative, and do not limit the present disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present disclosure to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

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Example 1: Treatment of Non-Hodgkin Lymphoma by Administering a Btk inhibitor to Induce Pharmaceutical Debulking

[00492] Two groups of patients with Non-Hodgkin Lymphoma (15 each) are treated with or without a Btk inhibitor followed by administering a second agent (Taxane). Group 1 is subject to the second agent treatment only (Taxane) and Group 2 is subject to a Btk inhibitor treatment for 2 days followed by administering the second agent based on the determined expression or presence of one or more B-cell lymphoproliferative disorder (BCLD) biomarkers from one or more subpopulation of lymphocytes.

Example 2. Determining the Expression or Presence of BCLD after Administering the Btk inhibitor for the Treatment of Non-Hodgkin Lymphoma

[00493] Determining the expression or presence of BCLD after administering compound 15 to a patient of Group 1 is used by the known procedures.

Example 3. Use of Taxane for the treatment of Non-Hodgkin Lymphoma

[00494] Following determination of the expression or presence of one or more B-cell lymphoproliferative disorder (BCLD) biomarkers from one or more subpopulation of lymphocytes in the patient, Taxane is used for Group 2 patients.

Example 4: Clinical Example of Determination of BCLDs Using a Btk inhibitor

[00495] A patient with BCLD completes treatment with a Btk inhibitor or another treatment, and appears to be in complete remission. After this treatment is stopped, a short course of the Btk inhibitor is then given. If cells with markers of the malignant cells appear in the peripheral blood, in some embodiments it is an indication for continued treatment or for starting another treatment. One example of the cell subpopulation investigated for in the peripheral blood is cells bearing both the CD5 and CD20 markers, which is typical of CLL/SLL and Mantle Cell Lymphoma. These markers can be detectable by flow cytometry. A further example of cell type is follicular lymphoma, which is characterized by cells with t(14;18) which in other embodiments are detectable by PCR or in situ hybridization in cells harvested from the peripheral blood.

[00496] Based on the markers of the malignant cells as determined in the peripheral blood, a suitable second treatment regimen is administered.

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Example 5: Pharmaceutical Compositions:

[00497] The compositions described below are presented with a compound of Formula (D) for illustrative purposes; any of the compounds of any of Formulas (A), (B), (C), or (D) can be used in such pharmaceutical compositions.

Example 5a: Parenteral Composition

[00498] To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula (D) is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 5b: Oral Composition

[00499] To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (D) is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

Example 5c: Sublingual (Hard Lozenge) Composition

[00500] To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, mix 100 mg of a compound of Formula (D), with 420 mg of powdered sugar mixed, with 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

Example 5d: Inhalation Composition

[00501] To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (D) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

Example 5e: Rectal Gel Composition

[00502] To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (D) is mixed with 2.5 g of methylcellulose (1500 mPa), 100 mg of methylparapen, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

Example 5f: Topical Gel Composition

[00503] To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (D) is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of

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isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

Example 5g: Ophthalmic Solution Composition

[00504] To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (D) is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

Example 6—Clinical Trial to Determine Efficacy of a Btk irreversible inhibitor in CLL and SLL patients

Patients with CLL and/or SLL:

[00505] The data provided herein is a pooled analysis of patients with CLL or SLL from two clinical trials of a Btk irreversible inhibitor. The initial trial (Study 04753) was a Phase 1A multi-cohort, first-in-human, dose escalation trial of a Btk irreversible inhibitor in patients with relapsed or refractory B-cell. 56 patients were enrolled between March 2009 and September 2010 and two doses were evaluated, namely oral once-daily dosing of a Btk irreversible inhibitor with a 28-day-on, 7-day-off schedule, and a continuous daily oral dosing schedule. Of the 56 patients enrolled, 16 CLL/SLL patients are included in this pooled analysis.

[00506] The second trial (Study 1102) is a Phase 1B/II trial of two once-daily oral doses of a Btk irreversible inhibitor in 2 populations of patients with CLL or SLL; a cohort containing patients with relapsed of refractory disease after at least 2 prior treatment regimens, and a second cohort of elderly patients with treatment-naïve disease. This study began enrollment in May 2010, and has enrolled 56 patients to date. For the purpose of this pooled analysis, 38 patients, with a minimum of 28 days follow-up and 28 patients with on study tumor assessments are included in this analysis. In sum, 56 patients from the two studies are included in this analysis.

[00507] The baseline characteristics of patients enrolled to the two studies are summarized here. In study 04753, the median age was 66, there were 11 patients with CLL and 5 patients with SLL. The median # of prior therapies was 3, with a range of 1-10. x% of patients had received prior nucleoside analogues, and x% had received prior anti-CD20 agents.

[00508] In study 1102, the median age was 68, 32 patients had CLL and 2 patients had SLL. Of the patients with CLL, 10 had del 17p. 15 patients had bulky disease, defined as a nodal mass >5 cm diameter. In the relapsed/ refractory cohort, the median # of prior regimens was x.3 Per the

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eligibility requirements, all patients had received a nucleoside analogue-based regimen. 93% had received prior anti-CD20 agents, 9% alemtuzumab, and 19% bendamustine.

[00509] Objectives of the analysis

[00510] The objective of this pooled analysis is to characterize the nature and kinetics of the response to a Btk irreversible inhibitor in CLL. The Btk irreversible inhibitor compound is one of a new class of BCR signaling inhibitors, and, similar to other inhibitors of this pathway, the kinetics of response differ between the peripheral blood and the nodal compartments. The second objective was to summarize the current status of the two studies with respect to best response, patient disposition, and time on treatment. The final objective was the summarization of the adverse event profile of the Btk inhibitor on a larger and more diverse population of patients with CLL or SLL.

Response criteria

[00511] Different response criteria were applied to patients with CLL and SLL respectively in these trials. Though considered biologically similar (or identical) diseases, given the phenotypic differences in presentation, the IW criteria for CLL are based on improvement in circulating lymphocytes, nodal/ splenic/ marrow-based disease, and normalization of hematologic parameters. In contrast, the NHL criteria used to gauge the lymphomatous presentation of this disease (or SLL) are based only on improvement in lymphadenopathy and organomegaly.

Lymphocyte count

[00512] Figure 5 depicts the change with treatment in the lymphocyte count for a 57 year-old patient with disease relapse following multiple prior therapies and the poor-risk cytogenetic feature del11q began treatment with a Btk irreversible inhibitor nearly 6 months ago. Typical of the majority of CLL patients treated with a Btk irreversible inhibitor, there was an initial, rapid, and prominent reduction in nodal disease and spleen size, with a corresponding rise in the circulating lymphocyte count, likely a consequence of the inhibitory effects of a Btk irreversible inhibitor on lymphocyte homing to the nodal and splenic compartments. Simultaneous with these changes, patients reported symptomatic improvement consistent with the resolution of bulky disease. Over time, the initial rise in lymphocytes returns to pre-treatment levels in spite of sustained reductions in adenopathy and splenomegaly. Cases such as this seen with a Btk irreversible inhibitor and similar agents, highlights the difficulty in applying standard response criteria to newer agents.

Effect of treatment on Lymph Node SPD

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[00513] As shown in Figure 6, patients treated with a Btk irreversible inhibitor had an immediate and marked nodal response to treatment. 85% of evaluable patients achieved a partial response and even more had some LN shrinkage. 80% of patients with measurable LN disease achieved a 50% reduction in their SPD within 2 cycles of therapy. Figure 7 shows the remarkable shrinkage in Lymph node post-treatment for the 57 year-old patient described supra.

Change in Lymph Node and absolute lymphocyte count (ALC)

[00514] Figure 8 depicts the effect of a Btk irreversible inhibitor on LN disease burden and lymphocytosis over time in the patients from the Phase Ia trial. Summary statistics from the patients with an early lymphocytosis show a similar pattern in the median percent change over time in both ALC and in LN disease burden measured by the SPD. Immediately following treatment, patients develop an early lymphocytosis which decreases with time to pre-treatment or normal levels. There is a sustained decrease in disease burden shown by the LN sum of perpendicular diameters. Thus, with some variability in timing, many patients show a marked decrease in tumor burden in both peripheral blood and in LN disease with sustained treatment.

Adverse Effects

[00515] Adverse effects seen as a side effect of the treatment were monitored as outlined in Figure 9. The effects were categorized by severity into grades 1-4. Grade 3 or greater events have been very uncommon. The vast majority of events have been mild in severity. Diarrhea, nausea, and fatigue have been the most commonly reported adverse events, with most of the reports occurring early in treatment

[00516] Thus, the oral Btk inhibitor has marked activity in patients with CLL and SLL including high-risk pts. It provides good disease control with longer follow-up commonly exceeds 6 months. There is no evidence of drug-related myelosuppression or cumulative toxicity.

Example 7 Clinical Trial to Determine Safety and Efficacy of Compounds of Formula (D)

[00517] The purpose of this clinical trial is to study the side effects and best dose of a compound of Formula (D) and to determine its efficacy in the treatment of patients diagnosed with recurrent B-cell lymphoma.

STUDY DESIGN

[00518] Cohorts of 6 patients each receive a compound of Formula (D) at 1.25, 2.5, 5.0, 8.3, 12.5, 17.5 mg/kg/d until the MTD is established. In cases where MTD is not reached, dosing levels

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are increased beyond 17.5mg/kg/d by 33% increments. Patients receive daily treatment for 28 days followed by a 7 day rest period (one cycle). Tests for Btk occupancy by the drug ("occupancy") are performed on Day 1, 2, 8, 15 and 29 during Cycle 1 and on Day 1 and 15 of Cycles 3, 5, 7, 9, and 11. If ≤ 1 DLT ("dose-limiting toxicity") is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Patients are enrolled in the next cohort if four of the six patients enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining two patients are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher is suspended and the MTD is established as the previous cohort. Patients are allowed to continue dosing at the MTD. If ≥ 2 DLTs are seen at the 5.0 mg/kg/d cohort an additional cohort of 6 patients can be added at 3.75 mg/kg/d.

[00519] Upon determination of the MTD, a cohort of 6 patients is enrolled to receive a compound of Formula (D) at the MTD or "preferred occupying dose" continuously for 35 days with no rest period (one cycle).

STUDY POPULATION

[00520] Up to 52 patients with recurrent surface immunoglobulin positive B cell non-Hodgkin's lymphoma according to WHO classification (including small lymphocytic lymphoma /chronic lymphocytic leukemia)

STUDY OBJECTIVES

[00521] 1. Primary Objectives include:

[00522] A. Determine pharmacokinetics (PK) of an orally administered compound of Formula (D).

[00523] B. Evaluate tumor response. Patients have screening (i.e., baseline) disease assessments within 30 days before beginning treatment. Patients undergo follow-up disease assessments following specified dosing cycles. Patients without evidence of disease progression on treatment are followed for a maximum of 6 months off treatment for disease progression. At screening, a computed tomography (CT) (with contrast unless contraindicated) and positron-emission tomography (PET) or CT/PET scan of the chest, abdomen, and pelvis are required. At other visits, a CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis are obtained. A CT/PET or PET is required to confirm a complete response. Bone marrow biopsy is optional. In patients known to have positive bone marrow before treatment with study drug, a repeat biopsy should be done to confirm a complete response following treatment. All patients are

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evaluated for response based on International Working Group Revised Response Criteria for Malignant Lymphoma, Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia14, or Uniform Response Criteria in Waldenstrom's Macroglobulinemia.

[00524] C. Measure pharmacodynamic (PD) parameters to include drug occupancy of Btk, the target enzyme, and effect on biological markers of B cell function. Specifically, this study examines the pharmacodynamics (PD) of the drug in peripheral blood mononuclear cells (PBMCs) using two PD assays. The first PD assay measures occupancy of the Btk active site by the drug using a specially designed fluorescent probe. The second PD assay measures inhibition of B cell activation by stimulating the PBMCs ex vivo at the BCR with anti-IgM/IgG, and then assaying cell surface expression of the activation marker CD69 by flow cytometry The PD biomarkers are measured in vitro from a blood sample removed from patients 4-6 hours following an oral dose of the drug. These assays determine what drug levels are required to achieve maximal occupancy of Btk and maximal inhibition of BCR signaling. When possible, similar studies are conducted on circulating tumor cells isolated from blood of patients.

[00525] 2. Secondary Objectives include:

[00526] A. To analyze tumor biopsy samples (when possible) for apoptotic biomarker expression analysis.

Inclusion Criteria

[00527] To be eligible to participate in this study, a patient must meet the following criteria:

- Women and men ≥ 18 years of age
- Body weight ≥ 40 kg
- Recurrent surface immunoglobulin positive B cell non-Hodgkin's lymphoma (NHL) according to WHO classification, including small lymphocytic lymphoma/ chronic lymphocytic leukemia (SLL/CLL) and lymphoplasmacytic lymphoma, including Waldenstrom's Macroglobulinemia (WM)
- Measurable disease (for NHL, bidimensional disease ≥ 2 cm diameter in at least one dimension, for CLL ≥ 5000 leukemia cells/mm3, and for WM presence of immunoglobulin M paraprotein with a minimum IgM level ≥ 1000 mg/dL and infiltration of bone marrow by lymphoplasmacytic cells)

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- Have failed ≥ 1 previous treatment for lymphoma and no standard therapy is available. Patients with diffuse large B cell lymphoma must have failed, refused or be ineligible for autologous stem cell transplant
- ECOG performance status of ≤ 1
- Ability to swallow oral capsules without difficulty
- Willing and able to sign a written informed consent

Exclusion Criteria

[00528] A patient meeting any of the following criteria will be excluded from this study:

- More than four prior systemic therapies (not counting maintenance rituximab), except for CLL patients. Salvage therapy/conditioning regimen leading up to autologous bone marrow transplantation is considered to be one regimen
- Prior allogeneic bone marrow transplant
- Immunotherapy, chemotherapy, radiotherapy or experimental therapy within 4 weeks before first day of study drug dosing
- Major surgery within 4 weeks before first day of study drug dosing
- CNS involvement by lymphoma
- Active opportunistic infection or treatment for opportunistic infection within 4 weeks before first day of study drug dosing
- Uncontrolled illness including but not limited to: ongoing or active infection, symptomatic congestive heart failure (New York Heart Association Class III or IV heart failure), unstable angina pectoris, cardiac arrhythmia, and psychiatric illness that would limit compliance with study requirements
- History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty and/or stenting within the past 6 months
- Known HIV infection
- Hepatitis B sAg or Hepatitis C positive
- Other medical or psychiatric illness or organ dysfunction which, in the opinion of the investigator, would either compromise the patient's safety or interfere with the evaluation of the safety of the study agent

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- Pregnant or lactating women (female patients of child-bearing potential must have a negative serum pregnancy test within 14 days of first day of drug dosing, or, if positive, a pregnancy ruled out by ultrasound)
- History of prior cancer < 2 years ago, except for basal cell or squamous cell carcinoma of the skin, cervical cancer in situ or other in situ carcinomas

Results:

[00529] 29 pts (12 follicular, 7 CLL/SLL, 4 DLBCL, 4 mantle, 2 marginal) with a median of 3 prior therapies have been enrolled on cohorts 1-4. Therapy was well tolerated with most adverse events < grade 2. One protocol defined DLT (dose delay > 7 d due to neutropenia) was observed. 19/22 pts from cohorts 1-3 are evaluable. The ORR is 42%; 1 CR (SLL), 7 PR (4 CLL/SLL, 2 MCL and 1FL). In cohort 2, PD demonstrate complete occupancy of Btk by a compound of Formula (D), with >95% enzyme occupancy 4 hours post dose in all pts. Basophil degranulation, a Btk-dependent cellular process, was completely inhibited up to 24 hrs. T-cell responses were not affected, and no significant depletion of peripheral blood B, T or NK cell counts was observed. Positive correlation (R2 = 0.93) was found between Btk active-site occupancy in PBMCs (mean of Days 1 and 8) and a compound of Formula (D) plasma AUC0 -° (Day 1) at the 1.25 mg/kg dose.

Example 8: Clinical Example of Diagnosis of BCLDs Using a Btk inhibitor

[00530] A patient with BCLD completes treatment with a Btk inhibitor or another treatment, and appears to be in complete remission. After this treatment is stopped, a short course of the Btk inhibitor is then given. If cells with markers of the malignant cells appear in the peripheral blood, in some embodiments it is an indication for continued treatment or for starting another treatment. One example of the cell subpopulation investigated for in the peripheral blood is cells bearing both the CD5 and CD20 markers, which is typical of CLL/SLL and Mantle Cell Lymphoma. These markers can be detectable by flow cytometry. A further example of cell type is follicular lymphoma, which is characterized by cells with t(14;18) which in other embodiments are detectable by PCR or in situ hybridization in cells harvested from the peripheral blood.

[00531] For patients initially starting on treatment an increase of the malignant subpopulation can be an early predictive marker of response or duration of response.

[00532] For patients who have previously received treatment and are suspected of progressing based upon changes (for example in a scan) that are non-diagnostic, the BTK test for peripheral blood cell increases could add diagnostic information that enable earlier treatment of relapse. This

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would be valuable in determining whether to re-start treatment for BCLD or to watch or to pursue an alternative diagnosis.

[00533] The test could yield better diagnostic information for patients whose BCLD is suspected to be transforming into a more aggressive cellular form. For example both CLL/SLL and lower grade follicular lymphoma can transform into a higher grade process which may resemble diffuse large B cell lymphoma, and require more aggressive treatment.

Example 9: Patient Selection

[00534] Patient selection screens are performed to identify an individual with the ABC subtype of DLBCL. Gene expression profiling is conducted using FFPE biopsy material, using RNA amplified with a Nugen kit and assayed on an Affymetrix U133Plus 2.0 arrays.

[00535] Samples are screened for recurrent somatic mutations. This is accomplished by conventional resequencing of candidate genes in the NF-kB and B cell receptor signaling pathways (e.g. CARD11, CD79A, CD79B, MYD88, TNFAIP3) plus p53 by exon amplification and standard dideoxy automated DNA sequencing.

[00536] The patient selection screen also identifies patients with ABC DLBCL that are particularly sensitive or resistant to Btk inhibitors. A positive result for a CARD11 mutation indicates that the individual is resistant to Btk inhibitors because CARD11 mutations activate the NF-kB pathway at a step that is downstream of BTK.

[00537] Genomic copy number analysis is also required to adequately assess the activity of oncogenic pathways that may be relevant for the response to Btk inhibitors as well as to assess prognosis. In particular, ABC DLBCLs harbor genomic deletions of the *TNFAIP3* locus, which encodes A20, a negative regulator of NF-kB. Thus, a full assessment of A20 status requires both resequencing to look for somatic mutations and copy number analysis to look for deletions. In addition, patients are identified with DLBCL tumors that harbor genomic deletions in the INK4a/ARF locus or have trisomy of chromosome 3 because these genomic aberrations are associated with poor prognosis in ABC DLBCL. A single pass high throughput DNA sequencing is performed using the Illumina HiSeq2000 platform to assess genomic copy number globally.

Example 10: PK and Efficacy of a Btk inhibitor in Individuals with CLL or SLL

[00538] A Btk inhibitor was administered to 33 individuals diagnosed with CLL or SLL. Efficacy and PK was determined.

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No.	Dose mg	Patient_ID	Group	Sex	Day 8 AUC0-24 (ng.h/mL)	Cycle	IWG Resp Mar 2011
1	420	073-203	Naïve	Female	102	7	PR
2	420	217-107	R/R	Male	120	8	PR
3	420	217-202	Naïve	Female	121	7	SD
4	420	032-110	R/R	Male	155	6	PR
5	420	217-104	R/R	Male	176	8	PR
6	420	032-201	Naïve	Male	177	9	PR
7	420	217-103	R/R	Female	206	8	Nodal
8	420	032-104	R/R	Male	227	8	PR
9	420	217-102	R/R	Male	243	9	Nodal
10	420	217-106	R/R	Female	267	8	Nodal
11	420	032-109	R/R	Male	318	7	Nodal
12	420	217-110	R/R	Female	407	7	Nodal
13	420	038-101	R/R	Male	428	7	PR
14	420	217-111	R/R	Male	473	7	PR
15	420	217-109	R/R	Male	498	7	Nodal
16	420	032-107	R/R	Male	502	8	Nodal
17	420	073-201	Naïve	Male	532	2	SD
18	420	032-105	R/R	Male	534	8	PR
19	420	217-101	R/R	Male	570	9	CR
20	420	073-101	R/R	Male	593	4	PR
21	420	217-105	R/R	Female	594	8	PR
22	420	032-101	R/R	Female	643	9	Nodal
23	420	073-202	Naïve	Male	648	9	PR
24	420	217-112	R/R	Female	653	7	SD
25	420	217-201	Naïve	Male	687	9	PR
26	420	073-204	Naïve	Male	784	1	NE
27	420	217-108	R/R	Male	809	1	PD
28	420	032-108	R/R	Male	907	7	PR
29	420	032-106	R/R	Male	1200	8	Nodal
30	420	032-102	R/R	Male	1210	2	NE
31	420	217-113	R/R	Male	1270	4	Cri
32	420	032-202	Naïve	Female	1670	8	PR
33	420	038-201	Naïve	Female	2000	7	CR

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Example 11: Clinical Trial with Btk inhibitor

[00539] A phase Ib/II clinical trial was performed to study the effects of a Btk inhibitor on individuals with CLL.

[00540] Study Type: Interventional

[00541] Allocation: Non-Randomized

[00542] Endpoint Classification: Safety Study

[00543] Intervention Model: Parallel Assignment

[00544] Masking: Open Label

[00545] Primary Purpose: Treatment

[00546] Group I (elderly, naïve, individuals) received 420 mg/day of the Btk inhibitor. Group II (R/R individuals, who had twice been treated with fludara) received 420 mg/day of the Btk inhibitor. Group III (R/R individuals, who had twice been treated with fludara) received 840 mg/day of the Btk inhibitor.

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Patient Characteristics

	Treatment-Naive 420 mg (N=23)	Relapsed/Refractory 420 mg (N=27)	Relapsed/Refractory 840 mg (N=33)
Age, y			
Median:	71	64	65
Range:	66 – 84	40 – 81	44 – 80
Dx, # pts			
CLL:	22 (96%)	26 (96%)	32 (97%)
SLL:	1 (4%)	1 (4%)	1 (3%)
Prior Rx, #			
Median:	0	3	5
Range:		2 – 10	2 – 12
Prior therapy, %			
Nucleoside analog	0 (0%)	27 (100%)	33 (100%)
Rituximab	0 (0%)	25 (93%)	32 (97%)
Alkylator	0 (0%)	24 (89%)	27 (82%)
Alemtuzumab	0 (0%)	5 (19%)	3 (9%)
Bendamustine	0 (0%)	8 (30%)	13 (39%)
Ofatumumab	0 (0%)	8 (30%)	10 (30%)

	Treatment-Naive 420 mg (N=23)	Relapsed/ Refractory 420 mg (N=27)	Relapsed/ Refractory 840 mg (N=33)
Cytopenia at baseline, %			
ANC < 1500/UL	1 (4%)	6 (22%)	17 (52%)
HGB < 11g/dL	7 (30%)	4 (15%)	19 (58%)
Platelets < 100,000/uL	9 (39%)	8 (30%)	22 (67%)
Prognostic Markers, %*			
IgVH unmutated:	8/16 (50%)	17/24 (71%)	18/24 (75%)
Del(17p):	2/17 (12%)	9/24 (38%)	10/25 (40%)
Del(11q):	0/17 (0%)	8/24 (33%)	12/25 (48%)
β Microglobin < 3mg/L	10/16(62%)	14/23(61%)	8/25(32%)
β Microglobin ≥ 3mg/L	6/16(38%)	9/23(39%)	17/25(68%)

[00547] Tumor assessment was performed every 2 treatment cycles.

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Objectives

[00548] Describe the characteristics of the antitumor effect of a Btk inhibitor in individuals with CLL/SLL, e.g., reduction in lymphadenopathy/splenomegaly, and kinetics of change in absolute lymphocyte count (ACL).

[00549] Summarize the safety profile of the Btk inhibitor.

Inclusion Criteria

[00550] FOR TREATMENT-NAIVE GROUP ONLY: Men and women ≥ 65 years of age with confirmed diagnosis of CLL/SLL, who require treatment per NCI or International Working Group guidelines11-14

[00551] FOR RELAPSED/REFRACTORY GROUP ONLY: Men and women ≥ 18 years of age with a confirmed diagnosis of relapsed/refractory CLL/SLL unresponsive to therapy (ie, failed ≥ 2 previous treatments for CLL/SLL and at least 1 regimen had to have had a purine analog [eg, fludarabine] for subjects with CLL)

[00552] Body weight ≥ 40 kg

[00553] ECOG performance status of ≤ 2

[00554] Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children

[00555] Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

[00556] Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

Exclusion Criteria

[00557] A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Btk inhibitor PO, or put the study outcomes at undue risk

[00558] Any immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first dose of study drug (corticosteroids for disease-related symptoms allowed but require 1-week washout before study drug administration)

[00559] Central nervous system (CNS) involvement by lymphoma

[00560] Major surgery within 4 weeks before first dose of study drug

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[00561] Creatinine > 1.5 x institutional upper limit of normal (ULN); total bilirubin > 1.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related

[00562] Concomitant use of medicines known to cause QT prolongation or torsades de pointes

[00563] Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc > 470 msec

[00564] Lactating or pregnant

Response Criteria

[00565] NHL IWG criteria1 were applied to SLL cases without modification

[00566] The 2008 CLL IWG criteria were applied to CLL cases with the following modifications:

a. An isolated lymphocytosis, in the absence of other parameters meeting the criteria for PD, was not considered PD
b. Patients experiencing a lymphocytosis, but obtaining a PR by other measurable parameters, were classified as "nodal" response until there was a 50% reduction in ALC from baseline in which case they were categorized as PR.
c. Patients with a normal ALC (<5K) at baseline with treatment-related lymphocytosis required normalization to <5K to be categorized as PR.

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Results

Subject Disposition

		Treatment-Naive 420 mg (N=23)	Relapsed/ Refractory 420 mg (N=27)	Relapsed/ Refractory 840 mg (N=33)
Number of subjects		23	27	33
Follow-up	Median (months)	6.3	7.8	4.6
	Range	1.4 - 9.2	0.7 - 9.5	0.3 - 6.5
Subjects still on study		21 (91%)	22 (81%)	28 (85%)
Subject Discontinued		2 (9%)	5 (19%)	5 (15%)
Primary Reasons for Discontinuation				
Disease Progression		0 (0%)	2 (7%)	1 (3%)
Death		0 (0%)	0 (0%)	2 (6%)
Adverse Event		1 (4%)	1 (4%)	1 (3%)
Other		1 (4%)	2 (7%)	1 (3%)

Best Response

	Treatment-Naive 420mg	Relapsed/ Refractory 420mg
N	21	27
CR	1 (5%)	1 (4%)
PR	13 (62%)	12 (44%)
ORR%	67%	48%
Nodal	4 (19%)	11 (41%)
SD	2 (10%)	1 (4%)
PD	0	1 (4%)
NE	1 (5%)	1 (4%)

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Best Response by Risk Features

		Best Response	
Molecular Risk Feature	N	IWG Response	Nodal Response
Overall	**27**	**48%**	**41%**
Del17p	9	44%	33%
Del11q	8	63%	37%
IgVH unmutated	17	53%	29%

[00567] Results further summarized in Figs. 18 - 27. Figure 18 presents the responses for the naive, 420 mg/day group. Figure 19 presents the responses for the R/R, 420 mg/day group. Figure 20 presents the responses by prognostic factors. Figure 21 presents responses over time. Figure 22 presents the best responses for all patients. Figure 23 presents the best responses for abstract patients. Figure 24 presents the best response by prognostic factor. Figure 25 presents initial (Cycle 2) response assessment and best response (420mg Cohorts). Figure 26 presents initial (Cycle 2) response assessment by dose: relapsed/refractory. Figure 27 presents improvements in hematological parameters.

Conclusions

[00568] The interim Phase II data confirm that a Btk inhibitor is highly active in both treatment-naïve and relapsed/ refractory CLL/ SLL patients

[00569] Class-specific rapid lymph node reduction with concurrent lymphocytosis seen in the majority of patients

[00570] 2008 CLL IWG objective responses (PR + CR) and nodal responses appear to be durable and independent of high risk genomic features

[00571] A high proportion (85%) of relapsed or refractory patients are free-of-progression at 6 months (420mg cohort)

Example 12: Long Term Follow-Up Trial for Individuals Taking Btk inhibitor

[00572] The purpose of this study is to determine the long-term safety of a fixed-dose, daily regimen of Btk inhibitor PO in subjects with B cell lymphoma or chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL).

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[00573] Study Type: Interventional

[00574] Allocation: Non-Randomized

[00575] Endpoint Classification: Safety Study

[00576] Intervention Model: Single Group Assignment

[00577] Masking: Open Label

[00578] Primary Purpose: Treatment

[00579] Intervention: 420 mg/day of a Btk inhibitor

[00580] Applicable conditions: B-cell Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma; Diffuse Well-Differentiated Lymphocytic Lymphoma; B Cell Lymphoma; Follicular Lymphoma; Mantle Cell Lymphoma; Non-Hodgkin's Lymphoma; Waldenstrom Macroglobulinemia; Burkitt Lymphoma; B-Cell Diffuse Lymphoma

Primary Outcome Measures:

[00581] Adverse Events/ Safety Tolerability [Time Frame: 30 days after last dose of study drug] - frequency, severity, and relatedness of adverse events

Secondary Outcome Measures:

[00582] Tumor Response [Time Frame: frequency of tumor assessments done per standard of care] - tumor response will be assessed per established response criteria. This study will capture time to disease progression and duration of response.

[00583] Tumor Response [Time Frame: Time to disease progression] - Duration of response as measured by established response criteria for B cell lymphoma and chronic lymphocytic leukemia

Inclusion Criteria

[00584] Men and women with B cell lymphoma or CLL/small lymphocytic lymphoma (SLL) who had stable disease or response to Btk inhibitor PO for at least 6 months on a prior Btk inhibitor study and want to continue study drug or who had disease progression on PCYC-04753 and want to try a higher dose

[00585] Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2

[00586] Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children

[00587] Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

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[00588] Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

Exclusion Criteria

[00589] A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Btk inhibitor PO, or put the study outcomes at undue risk

[00590] Concomitant immunotherapy, chemotherapy, radiotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day), or experimental therapy

[00591] Concomitant use of medicines known to cause QT prolongation or torsades de pointes

[00592] Central nervous system (CNS) involvement by lymphoma

[00593] Creatinine > 1.5 x institutional upper limit of normal (ULN); total bilirubin > 1.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related

[00594] Lactating or pregnant

Example 13: Phase II Study of Btk inhibitor in R/R MCL

[00595] The purpose of this study is to: Evaluate the efficacy of Btk inhibitor in relapsed/refractory subjects with MCL who have not had prior bortezomib, and who have had prior bortezomib

[00596] The secondary objective is to evaluate the safety of a fixed daily dosing regimen of Btk inhibitor capsules in this population.

[00597] Study Type: Interventional

[00598] Allocation: Non-Randomized

[00599] Endpoint Classification: Safety/Efficacy Study

[00600] Intervention Model: Parallel Assignment

[00601] Masking: Open Label

[00602] Primary Purpose: Treatment

[00603] Intervention: 560 mg/day of a Btk inhibitor

Primary Outcome Measures

[00604] To Measure the Number of Participants with a Response to Study Drug [Time Frame: Participants will be followed until progression of disease or start of another anti-cancer treatment.]

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Secondary Outcome Measures

[00605] To Measure the Number of Participants with Adverse Events as a Measure of Safety and Tolerability [Time Frame: Participants will be followed until progression of disease or start of another anti-cancer treatment.]

[00606] To Measure the Number of Participants Pharmacokinetics to Assist in Determining How the Body Responds to the Study Drug [Time Frame: Procedure to be Performed During the First Month of Receiving Study Drug.]

[00607] Patient Reported Outcomes [Time Frame: Participants will be followed until progression of disease or start of another anti-cancer treatment.]

[00608] To measure the number of participants reported outcomes in determining the health related quality of life.

Inclusion Criteria:

[00609] Men and women ≥ 18 years of age

[00610] ECOG performance status of ≤ 2

[00611] Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions

[00612] Documented failure to achieve at least partial response (PR) with, or documented disease progression disease after, the most recent treatment regimen

[00613] At least 1, but no more than 5, prior treatment regimens for MCL (Note: Subjects having received ≥2 cycles of prior treatment with bortezomib, either as a single agent or as part of a combination therapy regimen, will be considered to be bortezomib-exposed.)

[00614] Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

[00615] Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

Major exclusion criteria:

[00616] Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug

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[00617] Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Btk inhibitor capsules, or put the study outcomes at undue risk

[00618] Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification

[00619] Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

[00620] Any of the following laboratory abnormalities:

a. Absolute neutrophil count (ANC) < 750 cells/mm3 (0.75 x 109/L) unless there is documented bone marrow involvement
b. Platelet count < 50,000 cells/mm3 (50 x 109/L) independent of transfusion support unless there is documented bone marrow involvement
c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
d. Creatinine > 2.0 x ULN

Example 14: Phase II Study of Btk inhibitor + ofatumumab in R/R CLL

[00621] The purpose of this study was to determine the efficacy and safety of a fixed-dose, daily regimen of orally administered Btk inhibitor combined with ofatumumab in subjects with relapsed/refractory CLL/SLL and related diseases

[00622] Study Type: Interventional

[00623] Allocation: Non-Randomized

[00624] Endpoint Classification: Safety Study

[00625] Intervention Model: Single Group Assignment

[00626] Masking: Open Label

[00627] Primary Purpose: Treatment

[00628] Intervention: 420 mg/day of a Btk inhibitor, standard dose of ofatumumab

[00629] Applicable conditions: B-cell Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma; Diffuse Well-Differentiated Lymphocytic Lymphoma; Prolymphocyctic Leukemia; Richter's Transformation

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Primary Outcome Measures:

[00630] Response and safety of Btk inhibitor [Time Frame: At the end of cycles 1 and 3]

[00631] Response rate as defined by recent guidelines in Chronic Lymphocytic Leukemia

Secondary Outcome Measures:

[00632] Pharmacokinetic/Pharmacodynamic assessments [Time Frame: during 1-2 cycles]

[00633] Pharmacodynamics of Btk inhibitor (ie, drug occupancy of Btk and effect on biological market 1/2) of Btk inhibitor.

[00634] Tumor Response [Time Frame: at the end of Cycles 2,4 and 6 (28 days for each cycle)]

[00635] Overall response rate as defined by recent guidelines on CLL

Inclusion Criteria:

[00636] Subjects with histologically confirmed chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), prolymphocytic leukemia (PLL) as defined by WHO classification of hematopoietic neoplasms, or Richter's transformation arising out of CLL/SLL and satisfying ≥ 1 of the following conditions:

[00637] Progressive splenomegaly and/or lymphadenopathy identified by physical examination or radiographic studies

[00638] Anemia (<11 g/dL) or thrombocytopenia (<100,000/μL) due to bone marrow involvement

[00639] Presence of unintentional weight loss > 10% over the preceding 6 months

[00640] NCI CTCAE Grade 2 or 3 fatigue

[00641] Fevers > 100.5 degree or night sweats for > 2 weeks without evidence of infection

[00642] Progressive lymphocytosis with an increase of > 50% over a 2 month period or an anticipated doubling time of < 6 months

[00643] Need for cytoreduction prior to stem cell transplant

[00644] Subjects must have failed ≥ 2 prior therapies for CLL including a nucleoside analog or ≥ 2 prior therapies not including nucleoside analog if there is a contraindication to such therapy

[00645] > 10% expression of CD20 on tumor cells

[00646] ECOG performance status ≤ 2

[00647] Life expectancy ≥ 12 weeks

[00648] Subjects must have organ and marrow function as defined below:

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[00649] Absolute neutrophil count (ANC) ≥ 1000/μL in the absence of bone marrow involvement Platelets ≥ 30,000/μL Total bilirubin ≤ 1.5 x institutional upper limit of normal unless due to Gilbert's disease AST(SGOT) ≤ 2.5 x institutional upper limit of normal unless due to infiltration of the liver Creatinine ≤ 2.0 mg/dL OR creatinine clearance ≥ 50 mL/min

[00650] No history of prior anaphylactic reaction to rituximab

[00651] No history of prior exposure to ofatumumab

[00652] Age ≥ 18 years

[00653] Body weight ≥ 40 kg

[00654] Able to swallow capsules without difficulty and no history of malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

Exclusion Criteria:

[00655] A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Btk inhibitor PO, or put the study outcomes at undue risk

[00656] Any anticancer immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first dose of study drug. Corticosteroids for disease-related symptoms are allowed provided 1 week washout occurs.

[00657] Active central nervous system (CNS) involvement by lymphoma

[00658] Major surgery within 4 weeks before first dose of study drug

[00659] Lactating or pregnant

[00660] History of prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for at least 2 years or which will not limit survival to < 2 years

[00661] History of Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy.

Results

[00662] 6 Patients have been evaluated for DLT through end of cycle 2. 0 DLTs occurred in these patients.

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[00663] 4 patients have had end of cycle 3 scans and blood counts. 3 of 4 are responder per IWG criteria. Our response rate is 75% for these pts.

Example 15: Phase II Study of Btk inhibitor + BR or FCR in R/R CLL

[00664] The purpose of this study is to establish the safety of orally administered Btk inhibitor in combination with fludarabine/cyclophosphamide/rituximab (FCR) and bendamustine/rituximab (BR) in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma(SLL).

[00665] Study Type: Interventional

[00666] Allocation: Non-Randomized

[00667] Endpoint Classification: Safety Study

[00668] Intervention Model: Single Group Assignment

[00669] Masking: Open Label

[00670] Primary Purpose: Treatment

[00671] Intervention: 420 mg/day of a Btk inhibitor, standard FCR or BR regimen

[00672] Applicable conditions: B-cell Chronic Lymphocytic Leukemia; Small Lymphocytic Lymphoma; Diffuse Well-differentiated Lymphocytic Lymphoma

Primary Outcome Measures:

[00673] To measure the number of participants with prolonged hematologic toxicity [Time Frame: 8 weeks from first dose]

Secondary Outcome Measures:

[00674] To measure the number of participants with adverse events as a measure of safety and tolerability [Time Frame: For 30 days after the last dose of Btk inhibitor]

[00675] To measure the number of patients who respond to treatment by measuring the increase or decrease of disease in the lymph nodes and/or blood test results [Time Frame: Patients may remain on study until the last subject enrolled completes a maximum of 12 cycles of Btk inhibitor. Any subjects still receiving Btk inhibitor at that time may enroll in a long-term follow-up study to continue to receive Btk inhibitor capsules]

Inclusion Criteria:

[00676] Histologically confirmed CLL or SLL and satisfying at least 1 of the following criteria for requiring treatment:

[00677] Progressive splenomegaly and/or lymphadenopathy identified by physical examination or radiographic studies

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[00678] Anemia (<11 g/dL) or thrombocytopenia (<100,000/μL) due to bone marrow involvement

[00679] Presence of unintentional weight loss > 10% over the preceding 6 months

[00680] NCI CTCAE Grade 2 or 3 fatigue

[00681] Fevers > 100.5° or night sweats for > 2 weeks without evidence of infection

[00682] Progressive lymphocytosis with an increase of > 50% over a 2 month period or an anticipated doubling time of < 6 months

[00683] 1 to 3 prior treatment regimens for CLL/SLL

[00684] ECOG performance status of ≤ 1

[00685] ≥ 18 years of age

[00686] Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty

[00687] Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)

Exclusion Criteria:

[00688] Any chemotherapy, therapeutic antineoplastic antibodies (not including radio- or toxin immunoconjugates), radiation therapy, or experimental antineoplastic therapy within 4 weeks of first dose of study drug Radio- or toxin-conjugated antibody therapy within 10 weeks of first dose of study drug

[00689] Concomitant use of medicines known to cause QT prolongation or torsades de pointes

[00690] Transformed lymphoma or Richter's transformation

[00691] Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Btk inhibitor PO, or put the study outcomes at undue risk

[00692] Any of the following laboratory abnormalities:

a. Absolute neutrophil count (ANC) < 1000 cells/mm3 (1.0 x 109/L)
b. Platelet count < 50,000/mm3 (50 x 109/L)
c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
d. Creatinine > 2.0 x ULN or creatinine clearance < 40 mL/min

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Example 16: Phase II Study of Btk inhibitor in R/R DLBCL

[00693] The purpose of this study is to evaluate the efficacy of Btk inhibitor in relapsed/refractory de novo activated B-cell (ABC) and germinal-cell B-Cell (GCB) Diffuse Large B-cell Lymphoma (DLBCL).

[00694] Study Type: Interventional

[00695] Allocation: Non-Randomized

[00696] Endpoint Classification: Safety Study

[00697] Intervention Model: Single Group Assignment

[00698] Masking: Open Label

[00699] Primary Purpose: Treatment

[00700] Intervention: 560 mg/day Btk inhibitor

Primary Outcome Measures:

[00701] To measure the number of patients with a response to study drug [Time Frame: 24 weeks from first dose]

[00702] Participants will be followed until progression of disease or start of another anti-cancer treatment.

Secondary Outcome Measures:

[00703] To measure the number of patients with adverse events as a measure of safety and tolerability. [Time Frame: For 30 days after the last dose of Btk inhibitor]

[00704] Participants will be followed until progression of the disease or start of another anticancer treatment.

[00705] To measure the number of participants pharmacokinetics to assist in determining how the body responses to the study drug. [Time Frame: Procedure will be performed during the first month of receiving study drug.]

Inclusion Criteria:

[00706] Men and women $\geq$ 18 years of age.

[00707] Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$ 2.

[00708] Pathologically confirmed de novo DLBCL; subjects must have available archival tissue for central review to be eligible.

[00709] Relapsed or refractory disease, defined as either: 1) recurrence of disease after a complete remission (CR), or 2) partial response (PR), stable disease (SD), or progressive disease

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(PD) at completion of the treatment regimen preceding entry to the study (residual disease):Subjects must have previously received an appropriate first-line treatment regimen. Subjects with suspected residual disease after the treatment regimen directly preceding study enrollment must have biopsy demonstration of residual DLBCL. Subjects who have not received high dose chemotherapy/autologous stem cell transplant (HDT/ASCT) must be ineligible for HDT/ASCT as defined by meeting any of the following criteria: Age ≥ 70 years ,Diffuse lung capacity for carbon monoxide (DLCO) < 50% by pulmonary function test (PFT), Left ventricular ejection fraction (LVEF) < 50% by multiple gated acquisition(MUGA)/echocardiograph (ECHO), Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment-related morbidity, Subject refusal of HDT/ASCT.

[00710] Subjects must have ≥ 1 measurable (> 2 cm in longest dimension) disease sites on computed tomography (CT) scan.

Exclusion Criteria:

[00711] Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue [MALT] lymphoma)

[00712] Primary mediastinal (thymic) large B-cell lymphoma (PMBL)

[00713] Known central nervous system (CNS) lymphoma

[00714] Any chemotherapy, external beam radiation therapy, or anticancer antibodies within 3 weeks of the first dose of study drug

[00715] Radio- or toxin-immunoconjugates within 10 weeks of the first dose of study drug

[00716] Major surgery within 2 weeks of first dose of study drug

[00717] Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, or put the study outcomes at undue risk

[00718] Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification

[00719] Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

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[00720] Any of the following laboratory abnormalities:

a. Absolute neutrophil count (ANC) < 750 cells/mm3 (0.75 x 109/L) unless there is documented bone marrow involvement
b. Platelet count < 50,000 cells/mm3 (50 x 109/L) independent of transfusion support unless there is documented bone marrow involvement
c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 upper limit of normal (ULN)
d. Creatinine > 2.0 x ULN

Example 17: Assay of Drug Combinations

[00721] Combinations of a Btk inhibitor and additional cancer treatment agents were assayed using DoHH2 cells.

[00722] DOHH2 is a DLBCL (diffuse large B-cell lymphoma) cell line, from a transformed follicular lymphoma patient. It is moderately sensitive to a Btk inhibitor.

[00723] The Btk inhibitor was incubated with other cancer drugs for 2 days. Assay was an alamar blue assay.

[00724] The combinations were:

a. Btk inhibitor and Gemicitabine;
b. Btk inhibitor and Dexamethasone;
c. Btk inhibitor and Lenalinomide;
d. Btk inhibitor and R-406;
e. Btk inhibitor and Temsirolimus;
f. Btk inhibitor and Carboplatin;
g. Btk inhibitor and Bortezomib; and
h. Btk inhibitor and Doxorubicin.

[00725] Results are presented in figures 28-31.

Example 18: Assay of Drug Combinations

[00726] Combinations of a Btk inhibitor and additional cancer treatment agents were assayed using TMD8 cells.

[00727] TMD8 is a NF-kB signalling-dependent ABC-DLBCL cell line. It is sensitive to BTK inhibitors alone at low nanomolar concentrations (GI50 ~1-3 nM). A Btk inhibitor was incubated with other cancer drugs for 2 days. Assay was an alamar blue assay.

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[00728] The combinations were:

a. Btk inhibitor and CAL-101;
b. Btk inhibitor and Lenalinomide;
c. Btk inhibitor and R-406;
d. Btk inhibitor and Bortezomib;
e. Btk inhibitor and Vincristine;
f. Btk inhibitor and Taxol;
g. Btk inhibitor and Fludarabine; and
h. Btk inhibitor and Doxorubicin.

[00729] Results are presented in figures 32-39.

Example 19: Clinical Trial of Btk Inhibitor in Combination with BR

[00730] A clinical trial was performed to determine the effects of combining a Btk inhibitor with BR (bendamustine and rituximab). The Btk inhibitor was administered. Following an increase in the concentration of lymphoid cells in the peripheral blood, BR was administered. Initial results indicated that the combination of the Btk inhibitor and BR resulted in substantially no lymphoid cells in the peripheral blood.

Example 20: Clinical Trial of Btk Inhibitor in Combination with Ofatumumab

[00731] A clinical trial was performed to determine the effects of combining a Btk inhibitor with ofatumumab. The Btk inhibitor was administered. Following an increase in the concentration of lymphoid cells in the peripheral blood, ofatumumab was administered. Initial results indicated that the combination of the Btk inhibitor and ofatumumab resulted in a decrease in lymphoid cells in the peripheral blood.

BeiGene Exhibit 1023.200

WHAT IS CLAIMED IS:

1. A method for treating a hematological malignancy in an individual in need thereof, comprising:

    a. administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy; and

    b. analyzing the mobilized plurality of cells.

2. The method of claim 1, wherein the amount of the irreversible Btk inhibitor is sufficient to induce lymphocytosis of a plurality of cells from the malignancy.

3. The method of claim 2, wherein the malignancy is CLL.

4. The method of claim 1, wherein treating the hematological malignancy comprises managing the hematological malignancy.

5. The method of claim 1, wherein the hematological malignancy is a B-cell malignancy.

6. The method of claim 1, wherein the hematological malignancy is a leukemia, lymphoproliferative disorder, or myeloid.

7. The method of claim 1, wherein the mobilized cells are myeloid cells or lymphoid cells.

8. The method of claim 1, wherein analyzing the mobilized plurality of cells comprises measuring the peripheral blood concentration of the mobilized plurality of cells.

9. The method of claim 8, further comprising administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells increases as compared to the concentration before administration of the Btk inhibitor.

10. The method of claim 8, wherein administering the second cancer treatment regimen occurs after a subsequent decrease in peripheral blood concentration of the mobilized plurality of cells.

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11. The method of claim 1, wherein analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the peripheral blood concentration of the mobilized plurality of cells as compared to the concentration before administration of the Btk inhibitor.

12. The method of claim 11, further comprising administering a second cancer treatment regimen after the peripheral blood concentration of the mobilized plurality of cells has increased for a predetermined length of time.

13. The method of claim 1, wherein analyzing the mobilized plurality of cells comprises counting the number of mobilized plurality of cells in the peripheral blood.

14. The method of claim 13, further comprising administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood increases as compared to the number before administration of the Btk inhibitor.

15. The method of claim 14, wherein administering the second cancer treatment regimen occurs after a subsequent decrease in the number of mobilized plurality of cells in the peripheral blood.

16. The method of claim 1, wherein analyzing the mobilized plurality of cells comprises measuring the duration of an increase in the number of mobilized plurality of cells in the peripheral blood as compared to the number before administration of the Btk inhibitor.

17. The method of claim 16, further comprising administering a second cancer treatment regimen after the number of mobilized plurality of cells in the peripheral blood has increased for a predetermined length of time.

18. The method of claim 1, wherein analyzing the mobilized plurality of cells comprises preparing a biomarker profile for a population of cells isolated from the plurality of cells, wherein the biomarker profile indicates the expression of a biomarker, the expression level of a biomarker, mutations in a biomarker, or the presence of a biomarker.

19. The method of claim 18, wherein the biomarker is any cytogenetic, cell surface molecular or protein or RNA expression marker.

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20. The method of claim 18, wherein the biomarker is: ZAP70; t(14,18); β-2 microglobulin; p53 mutational status; ATM mutational status; del(17)p; del(11)q; del(6)q; CD5; CD11c; CD19; CD20; CD22; CD25; CD38; CD103; CD138; secreted, surface or cytoplasmic immunoglobulin expression; V_H mutational status; or a combination thereof.

21. The method of claim 18, further comprising providing a second cancer treatment regimen based on the biomarker profile.

22. The method of claim 18, further comprising not administering based on the biomarker profile.

23. The method of claim 18, further comprising predicting the efficacy of a second cancer treatment regimen based on the biomarker profile.

24. The method of claim 1, wherein the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma.

25. The method of claim 1, wherein the hematological malignancy is follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, multiple myeloma, marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, or extranodal marginal zone B cell lymphoma.

26. The method of claim 1, wherein the hematological malignancy is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia.

27. The method of claim 1, wherein the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, relapsed or refractory follicular lymphoma, relapsed or refractory CLL; relapsed or refractory SLL; relapsed or refractory multiple myeloma.

28. The method of claim 1, wherein the Btk inhibitor forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog.

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29. The method of claim 1, wherein the irreversible Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

30. The method of claim 1, wherein the amount of the irreversible Btk inhibitor is from 300 mg/day up to, and including, 1000 mg/day.

31. The method of claim 1, wherein the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day.

32. The method of claim 1, wherein the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day.

33. The method of claim 1, wherein the amount of the irreversible Btk inhibitor is about 420 mg/day.

34. The method of claim 1, wherein the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL.

35. The method of claim 34, wherein AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL.

36. The method of claim 1, wherein the Btk inhibitor is administered orally.

37. The method of claim 1, wherein the Btk inhibitor is administered once per day, twice per day, or three times per day.

38. The method of claim 1, wherein the Btk inhibitor is administered until disease progression, unacceptable toxicity, or individual choice.

39. The method of claim 1, wherein the Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice.

40. The method of claim 1, wherein the Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice.

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41. The method of claim 1, wherein the Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy.

42. The method of claim 1, wherein the Btk inhibitor treats a refractory hematological malignancy.

43. The method of claim 1, wherein the Btk inhibitor is a maintenance therapy.

44. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof.

45. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises a B cell receptor pathway inhibitor.

46. The method of claim 45, wherein the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof.

47. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

48. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof.

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49. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab.

50. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises bendamustine, and rituximab.

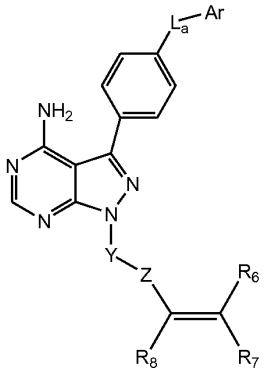
51. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab.

52. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab.

53. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab.

54. The method of claim 9, 10, 12, 14, 15, 17, or 21, wherein the second cancer treatment regimen comprises dexamethasone and lenalidomide.

55. The method of claim 1, wherein the irreversible Btk inhibitor has the following structure:



Formula (D)

wherein:

L_a is CH_2, O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

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Z is C(=O), OC(=O), NHC(=O), C(=S), $S(=O)_x$, $OS(=O)_x$, $NHS(=O)_x$, where x is 1 or 2;
R_6, R_7, and R_8 are each independently selected from among H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted C_2-C_6heterocycloalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted C_1-C_4alkyl(aryl), substituted or unsubstituted C_1-C_4alkyl(heteroaryl), substituted or unsubstituted C_1-C_4alkyl(C_3-C_8cycloalkyl), or substituted or unsubstituted C_1-C_4alkyl(C_2-C_8heterocycloalkyl); or
R_7 and R_8 taken together form a bond; and pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

56. The method of Claim 55, wherein La is O.

57. The method of Claim 55, wherein Ar is phenyl.

58. The method of Claim 55, wherein: Z is C(=O), NHC(=O), or $S(=O)_2$.

59. The method of Claim 55, wherein:
each of R_7 and R_8 is H.

60. The method of Claim 55, wherein:
Y is a 4-, 5-, 6-, or 7-membered cycloalkyl ring; or
Y is a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring.

61. A method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

62. The method of claim 61, wherein the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, or relapsed or refractory follicular lymphoma.

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63. The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 300 mg/day up to, and including, 1000 mg/day.

64. The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 420 mg/day up to, and including, 840 mg/day.

65. The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day, about 560 mg/day, or about 840 mg/day.

66. The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day.

67. The method of claim 61, wherein the AUC_{0-24} of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is between about 150 and about 3500 ng*h/mL.

68. The method of claim 67, wherein AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL.

69. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered orally.

70. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered once per day, twice per day, or three times per day.

71. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice.

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72. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice.

73. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered daily until disease progression, unacceptable toxicity, or individual choice.

74. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered every other day until disease progression, unacceptable toxicity, or individual choice.

75. The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is a second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy.

76. The method of claim 61, wherein the Btk inhibitor is a maintenance therapy.

77. The method of claim 61, further comprising administering a second cancer treatment regimen.

78. The method of claim 77, wherein the second cancer treatment regimen is administered after mobilization of a plurality of lymphoid cells from the non-Hodgkin's lymphoma.

79. The method of claim 77, wherein the second cancer treatment regimen is administered after lymphocytosis of a plurality of lymphoid cells from the non-Hodgkin's lymphoma.

80. The method of claim 77, wherein the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof.

81. The method of claim 77, wherein the second cancer treatment regimen comprises a B cell receptor pathway inhibitor.

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82. The method of claim 81, wherein the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof.

83. The method of claim 77, wherein the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

84. The method of claim 77, wherein the second cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof.

85. The method of claim 77, wherein the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab.

86. The method of claim 77, wherein the second cancer treatment regimen comprises bendamustine, and rituximab.

87. The method of claim 77, wherein the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab.

88. The method of claim 77, wherein the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab.

89. The method of claim 77, wherein the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab.

90. The method of claim 77, wherein the second cancer treatment regimen comprises dexamethasone and lenalidomide.

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91. A method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day.

92. The method of claim 91, further comprising diagnosing the individual with diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), by determining the gene sequence of one or more biomarkers in a plurality of lymphoid cells isolated from the diffuse large B-cell lymphoma.

93. The method of claim 91, wherein the irreversible Btk inhibitor is (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

94. The method of claim 91, wherein the Activated B cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by a CD79B mutation.

95. The method of claim 94, wherein the CD79B mutation is a mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module.

96. The method of claim 94, wherein the CD79B mutation is a missense mutation of the first immunoreceptor tyrosine-based activation motif (ITAM) tyrosine.

97. The method of claim 94, wherein the CD79B mutation increases surface BCR expression and attenuates Lyn kinase activity.

98. The method of claim 91, wherein the Activated B cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by a CD79A mutation.

99. The method of claim 98, wherein the CD79A mutation is in the immunoreceptor tyrosine-based activation motif (ITAM) signaling module.

100. The method of claim 98, wherein the CD79A mutation is a splice-donor-site mutation of the immunoreceptor tyrosine-based activation motif (ITAM) signaling module.

101. The method of claim 98, wherein the CD79A mutation deletes the immunoreceptor tyrosine-based activation motif (ITAM) signaling module.

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102. The method of claim 91, wherein the Activated B cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) is characterized by a mutation in MyD88, A20, or a combination thereof.

103. The method of claim 102, wherein the MyD88 mutation is the amino acid substitution L265P in the MYD88 Toll/IL-1 receptor (TIR) domain.

104. The method of claim 91, wherein the amount of the irreversible Btk inhibitor is from 420 mg/day up to, and including, 840 mg/day.

105. The method of claim 91, wherein the amount of the irreversible Btk inhibitor is about 420 mg/day, about 560 mg/day, or about 840 mg/day.

106. The method of claim 91, wherein the amount of the irreversible Btk inhibitor is about 420 mg/day.

107. The method of claim 91, wherein the AUC_{0-24} of the Btk inhibitor is between about 150 and about 3500 ng*h/mL.

108. The method of claim 107, wherein AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL.

109. The method of claim 91, wherein the irreversible Btk inhibitor is administered orally.

110. The method of claim 91, wherein the irreversible Btk inhibitor is administered daily until disease progression, unacceptable toxicity, or individual choice.

111. The method of claim 91, wherein the irreversible Btk inhibitor is administered every other day until disease progression, unacceptable toxicity, or individual choice.

112. The method of claim 91, wherein the irreversible Btk inhibitor is a front line therapy, second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy.

113. The method of claim 91, wherein the irreversible Btk inhibitor treats a refractory hematological malignancy.

114. The method of claim 91, wherein the irreversible Btk inhibitor is a maintenance therapy.

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115. The method of claim 91, further comprising administering at least one additional cancer treatment regimen.

116. The method of claim 115, wherein the additional cancer treatment regimen comprises a chemotherapeutic agent, an immunotherapeutic agent, a steroid, radiation therapy, a targeted therapy, or a combination thereof.

117. The method of claim 116, wherein the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

118. A method of determining a cancer treatment regimen for an individual with a hematological malignancy, comprising:

a. administering to the individual an amount of an irreversible Btk inhibitor sufficient to mobilize a plurality of cells from the malignancy;

b. analyzing the mobilized plurality of cells; and

c. selecting a cancer treatment regimen.

119. The method of claim 118, wherein the cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof.

120. The method of claim 118, wherein the cancer treatment regimen comprises a B cell receptor pathway inhibitor.

121. The method of claim 118, wherein the cancer treatment regimen comprises a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCγ inhibitor, a PKCβ inhibitor, or a combination thereof.

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122. The method of claim 118, wherein the cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

123. The method of claim 118, wherein the cancer treatment regimen comprises chlorambucil, ifosphamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, pentostatin, endostatin, or a combination thereof.

124. The method of claim 118, wherein the cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab.

125. The method of claim 118, wherein the cancer treatment regimen comprises bendamustine, and rituximab.

126. The method of claim 118, wherein the cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab.

127. The method of claim 118, wherein the cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab.

128. The method of claim 118, wherein the cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab.

129. The method of claim 118, wherein the cancer treatment regimen comprises dexamethasone and lenalidomide.

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THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

ABSTRACT

[00732] Disclosed herein are methods for treating a cancer comprising: a. administering a Btk inhibitor to a subject sufficient to result in an increase or appearance in the blood of a subpopulation of lymphocytes defined by immunophenotyping; b. determining the expression profile of one or more biomarkers from one or more subpopulation of lymphocytes; and c. administering a second agent based on the determined expression profile.

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Fig. 1

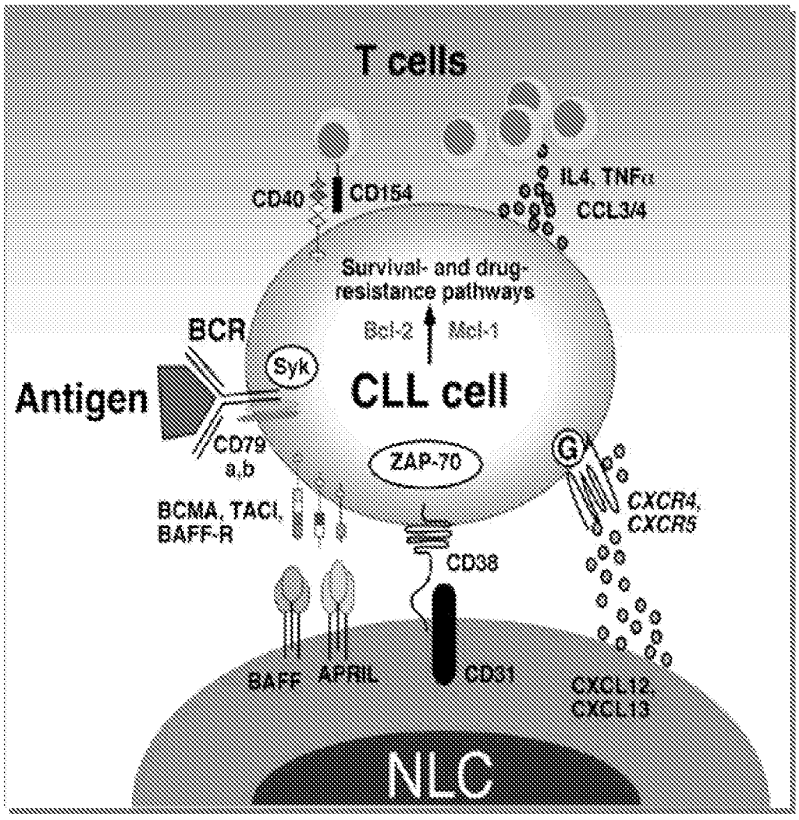

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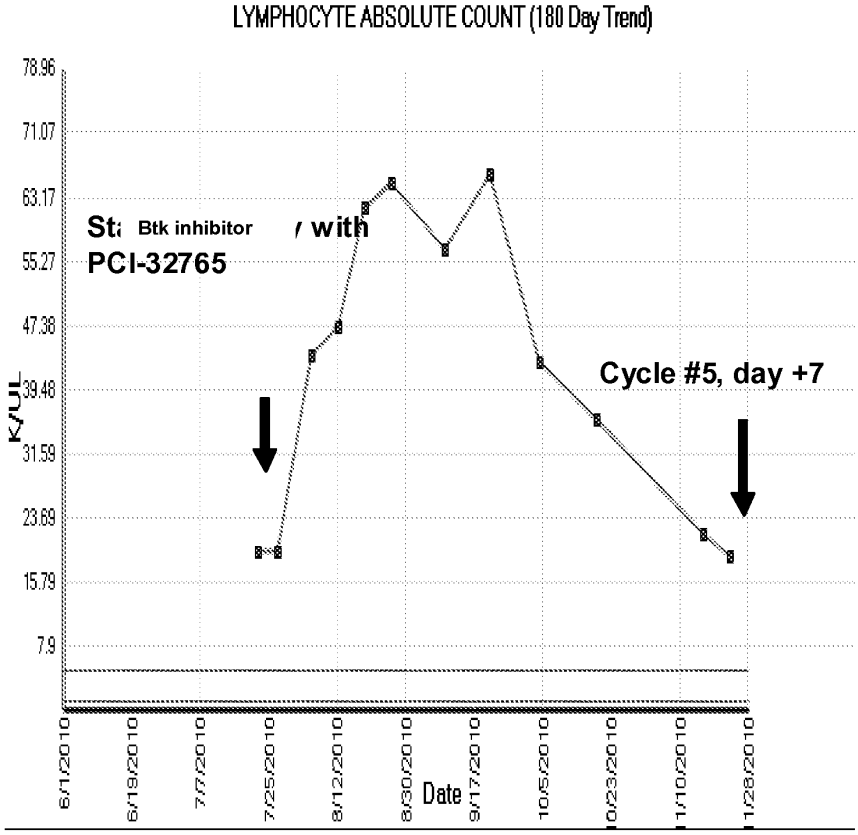
Fig. 2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71.07
63.17
55.27
47.38
39.48
31.59
23.69
15.79
7.9
K/UL
St: Btk inhibitor r with
PCI-32765
Cycle #5, day +7
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6/19/2010
7/7/2010
7/25/2010
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11/28/2010
Date

Fig. 3

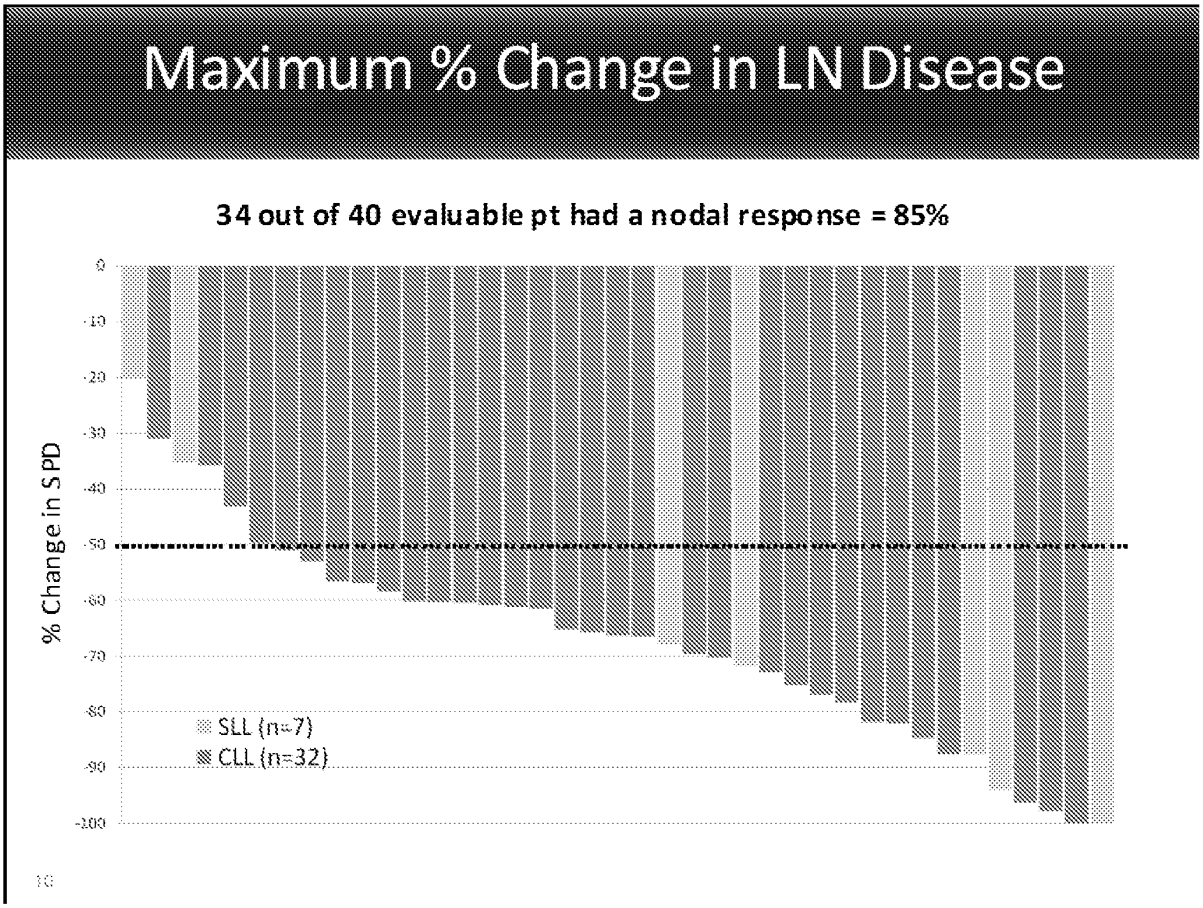
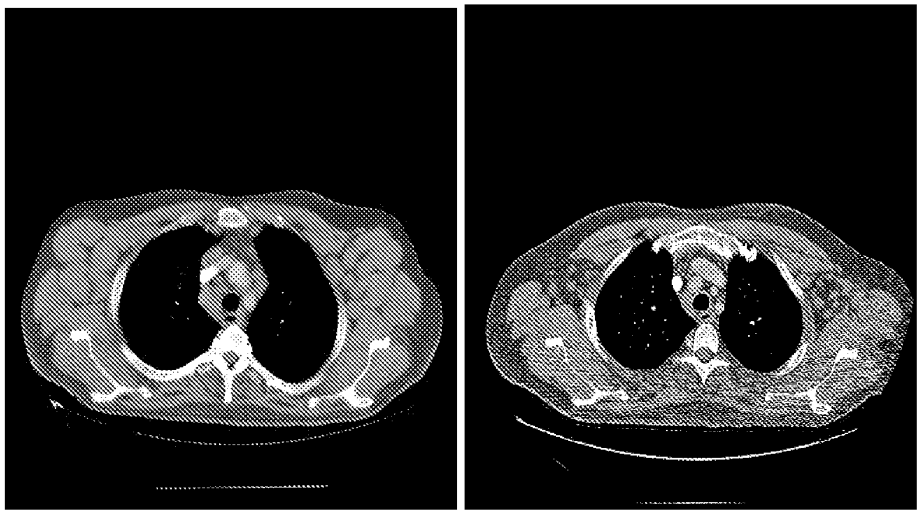

Maximum % Change in LN Disease
34 out of 40 evaluable pt had a nodal response = 85%
% Change in SPD
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
SLL (n=7)
CLL (n=32)

Fig. 4



Pre-treatment with Btk inhibitor **Post-treatment with Btk inhibitor**

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Fig. 5

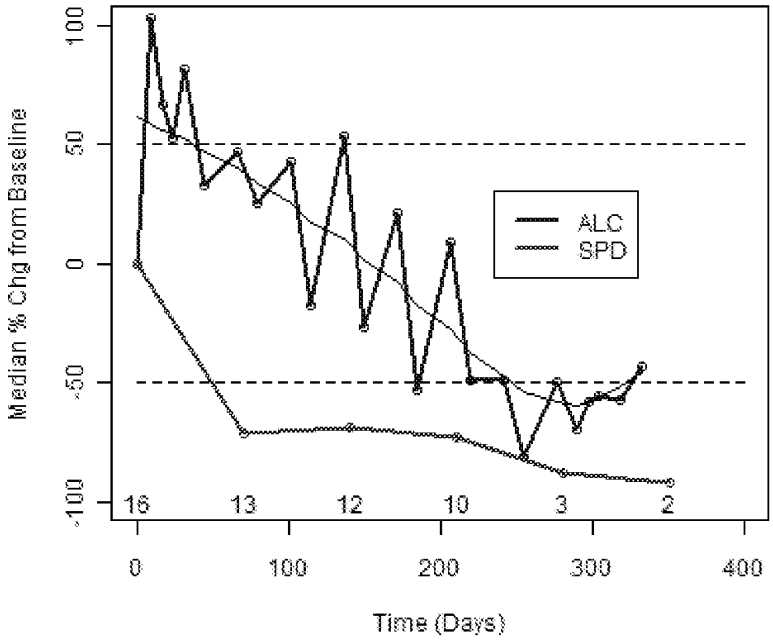

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Fig. 6

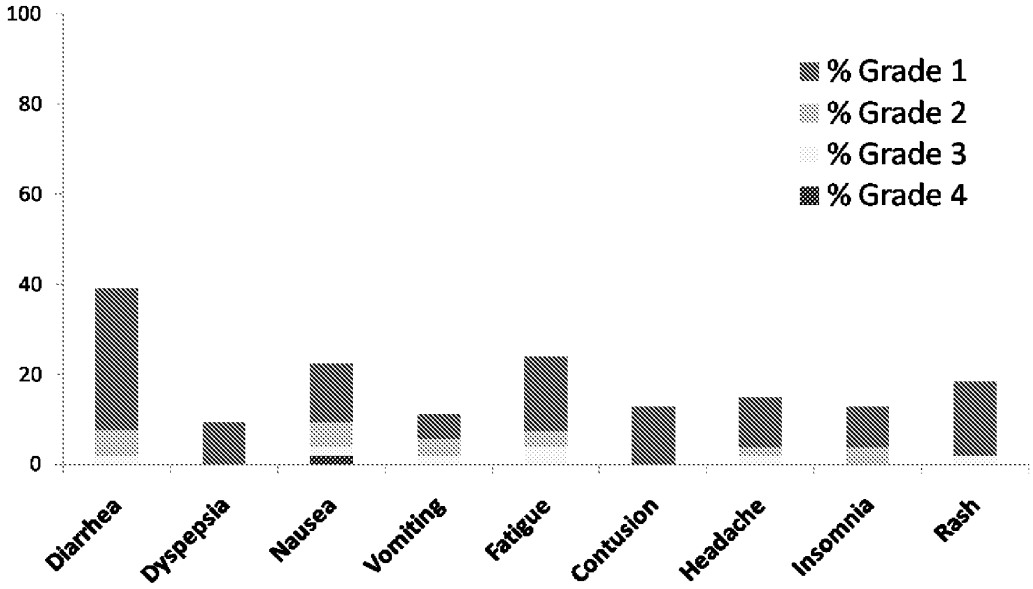

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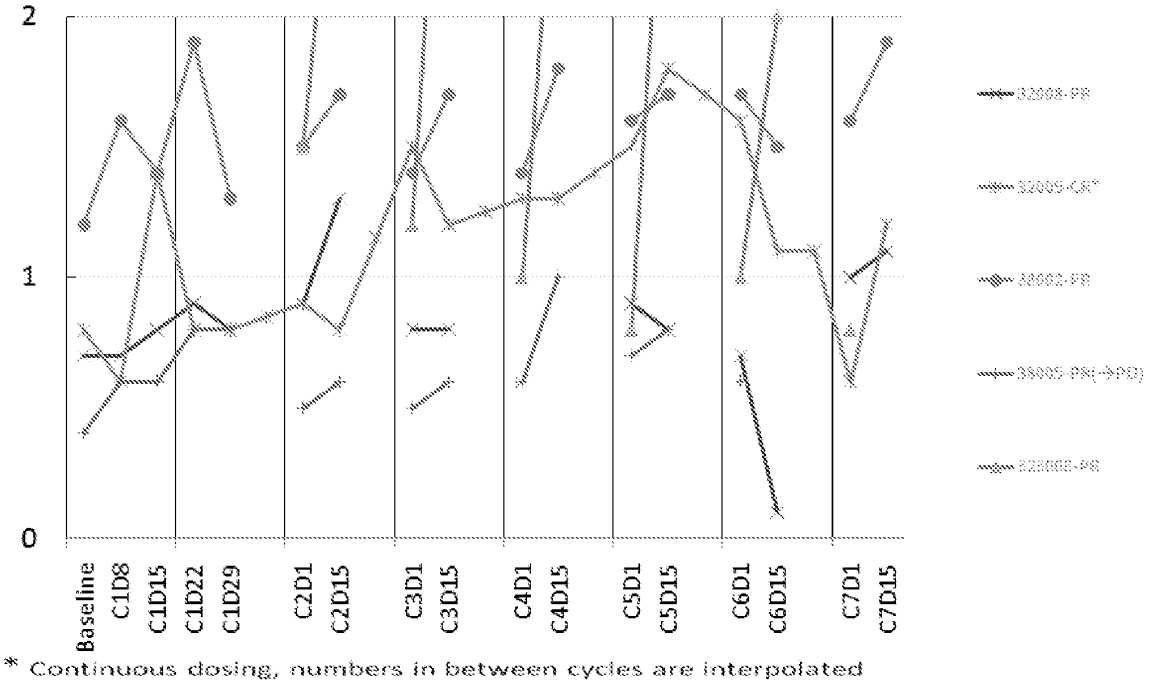
Fig. 7



* Continuous dosing, numbers in between cycles are interpolated

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Fig. 8

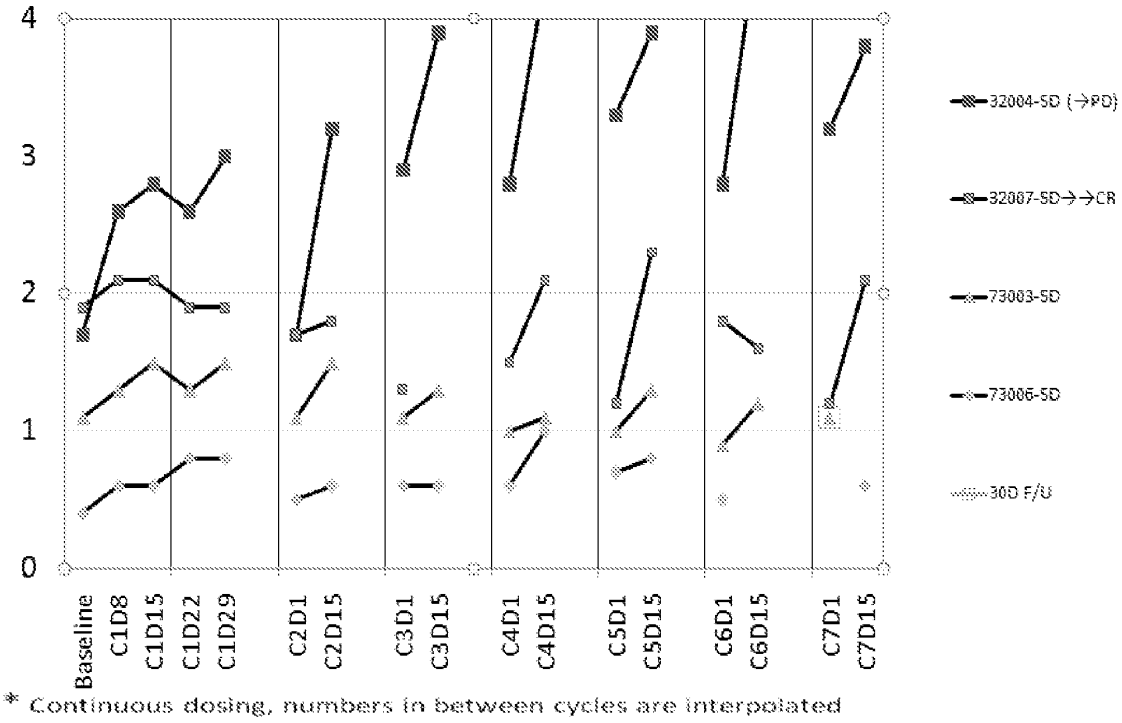

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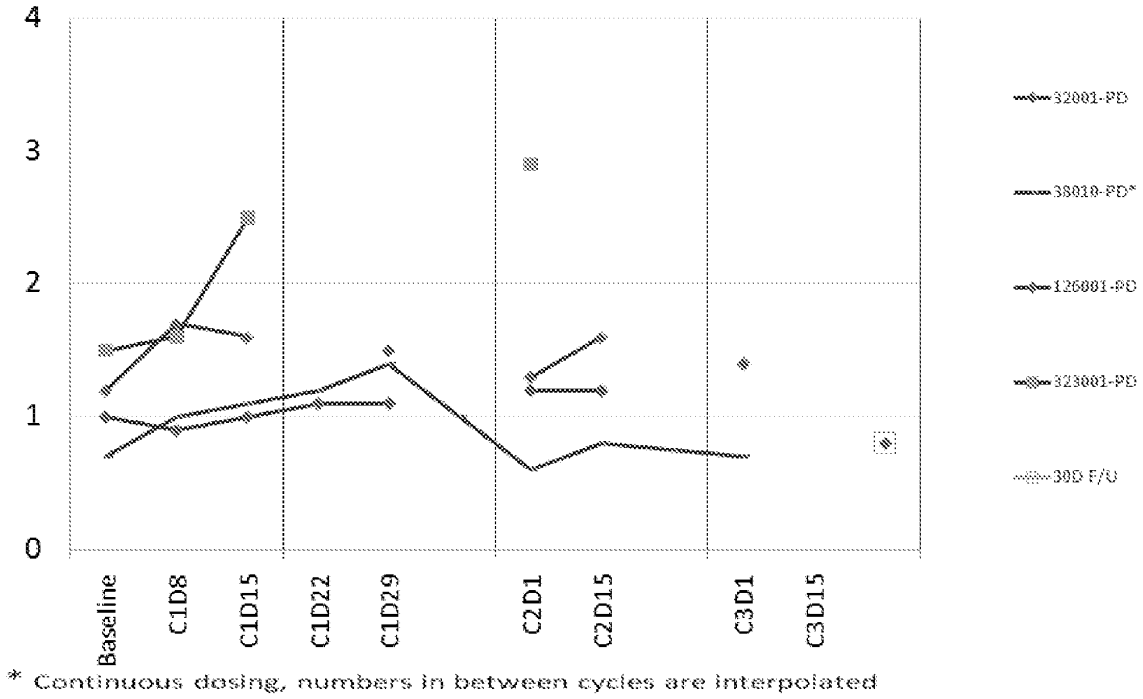
Fig. 9



* Continuous dosing, numbers in between cycles are interpolated

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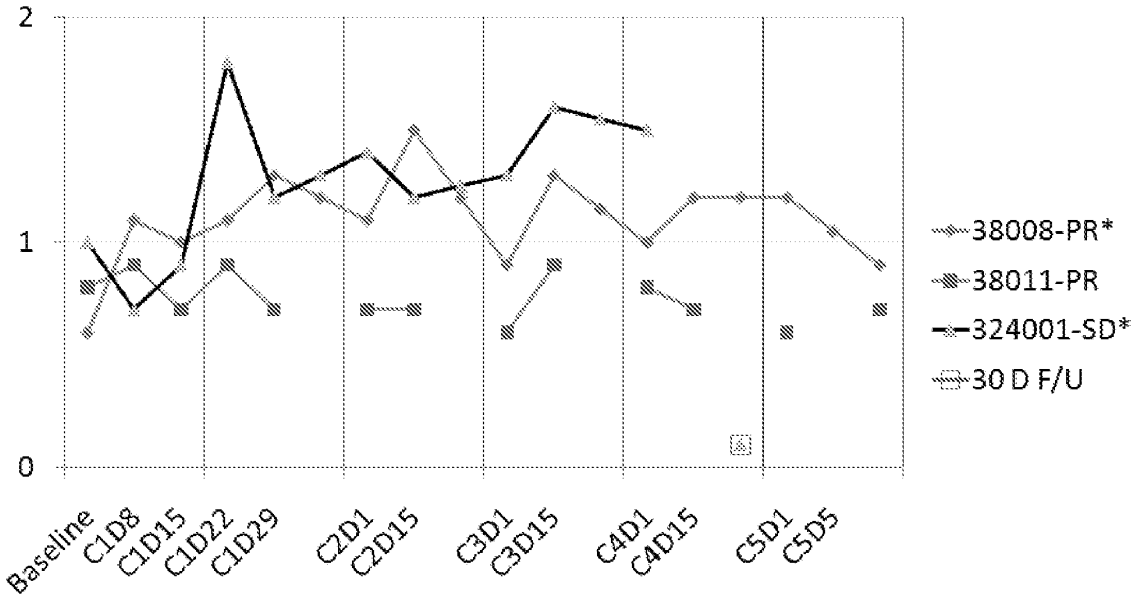
Fig. 10



* Continuous dosing, numbers in between cycles are interpolated

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Fig. 11

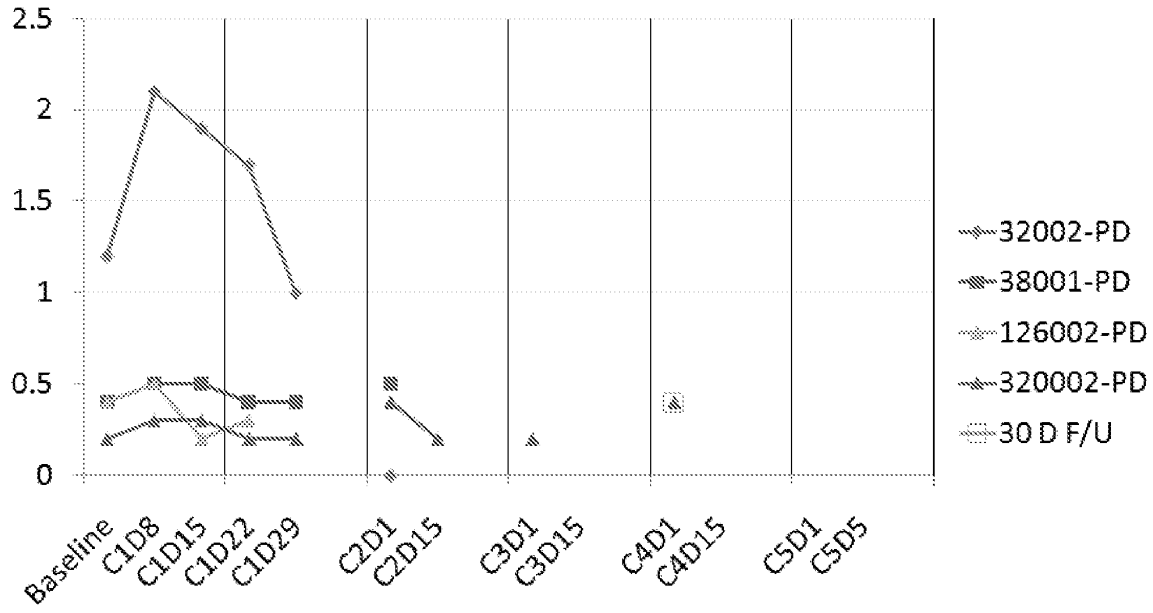

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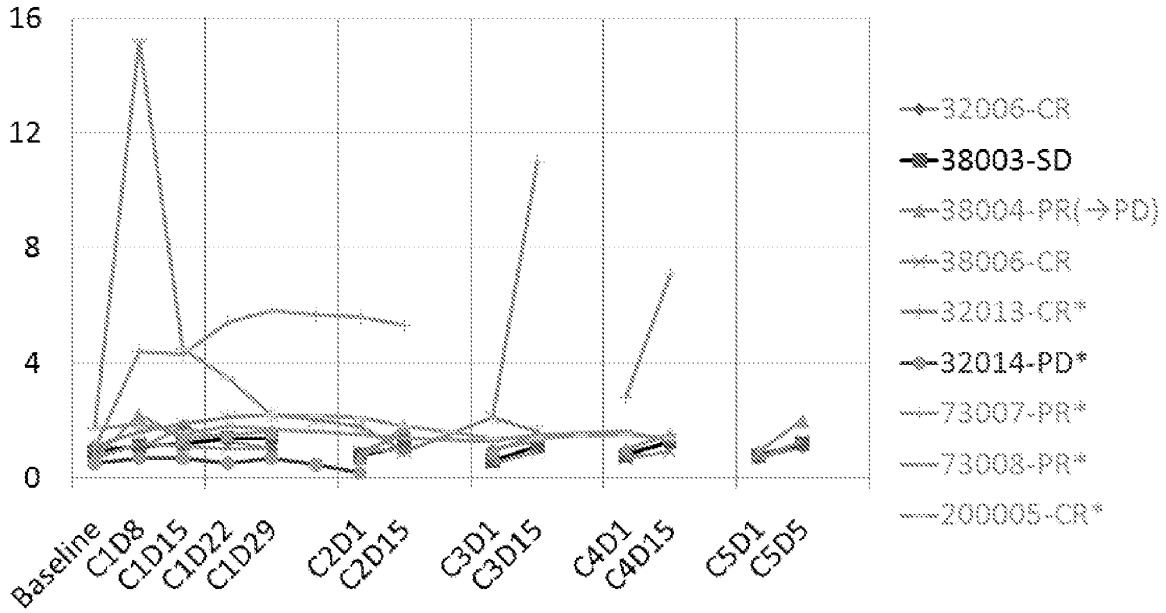
Fig. 12



* Continuous dosing, numbers in between cycles are interpolated

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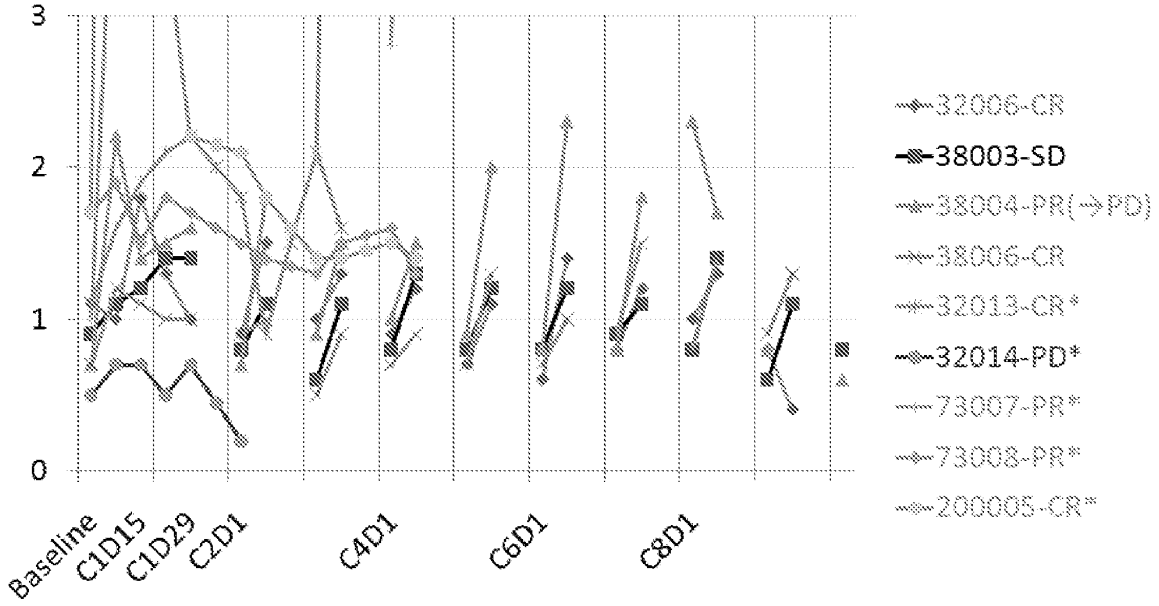
Fig. 13



* Continuous dosing, numbers in between cycles are interpolated

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Fig. 14

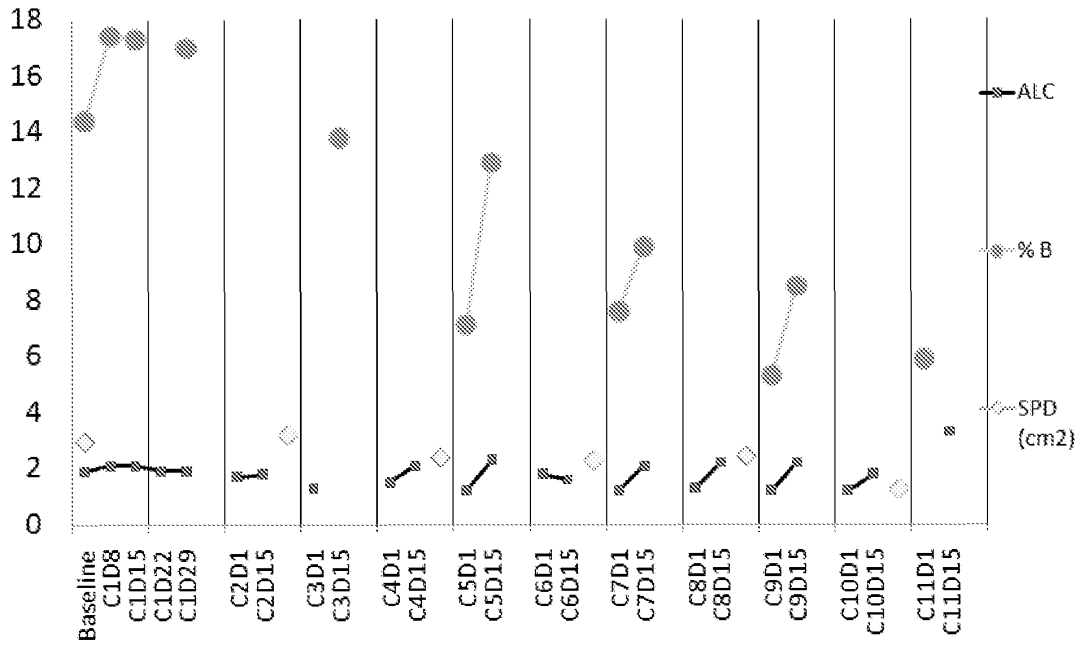

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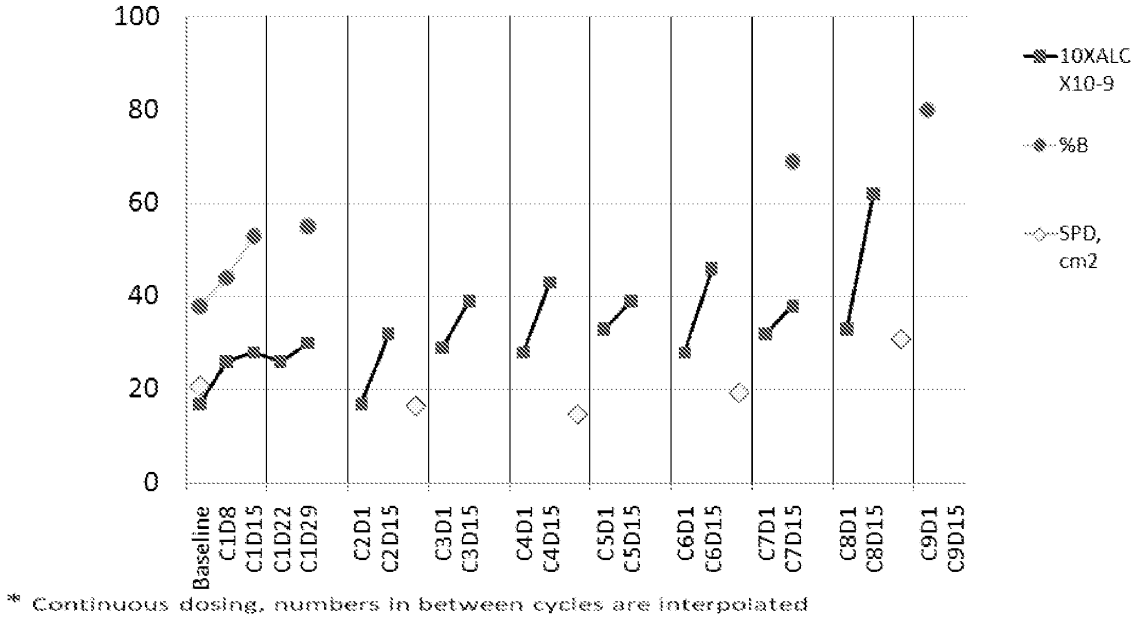
Fig. 15



* Continuous dosing, numbers in between cycles are interpolated

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Fig. 16

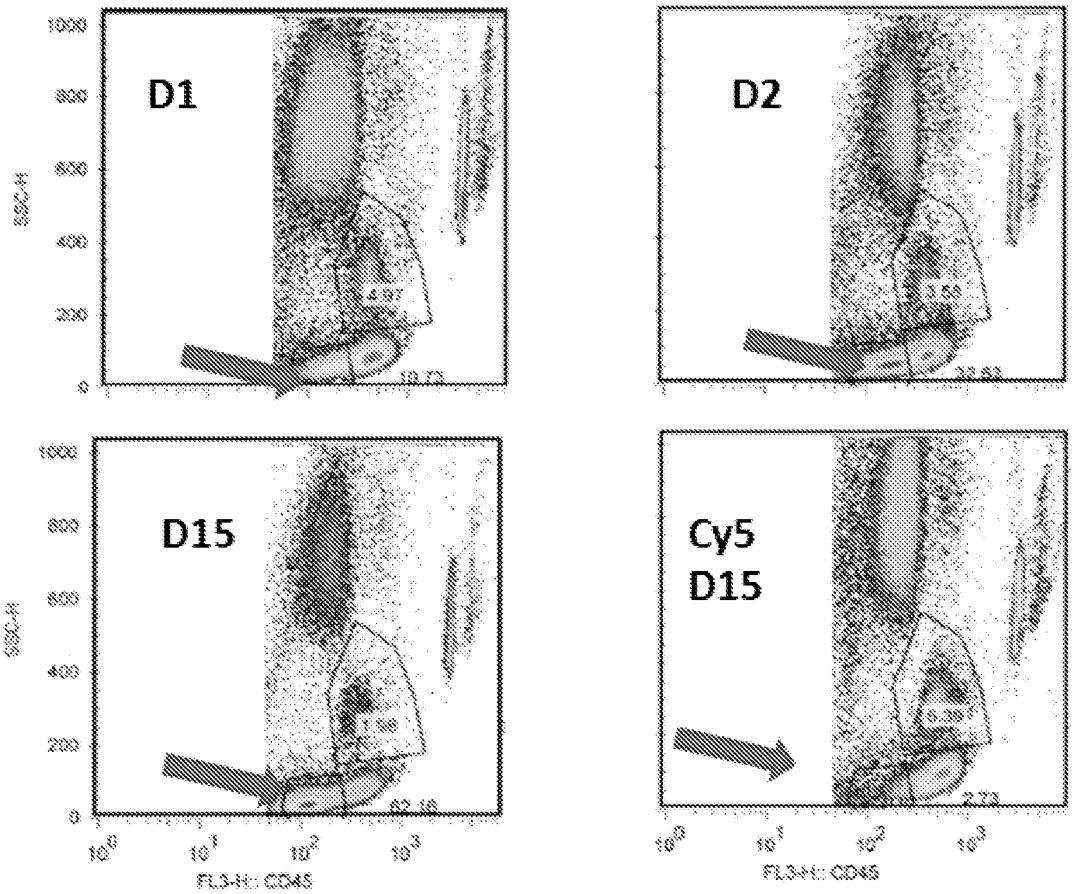

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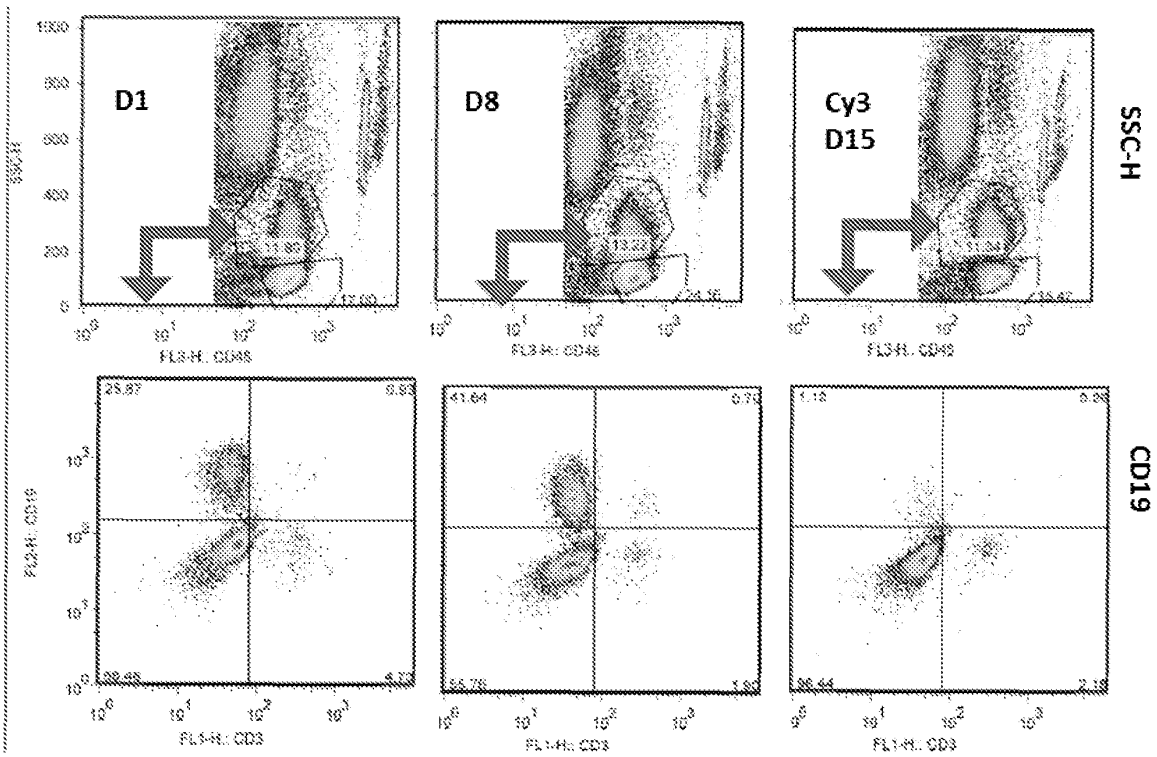
Fig. 17



BeiGene Exhibit 1023.232

Fig. 18

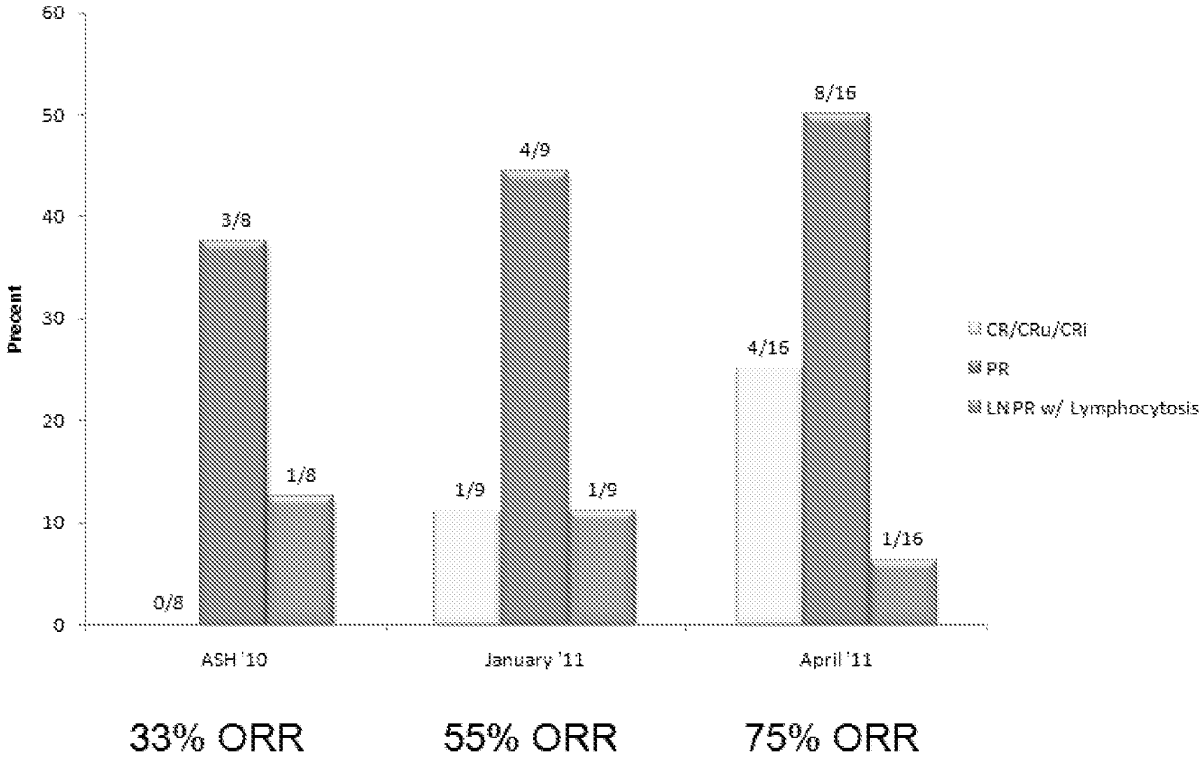

60
50
40
30
20
10
0
Precent
0/8
3/8
1/8
1/9
4/9
1/9
4/16
8/16
1/16
ASH '10
January '11
April '11
CR/CRu/CRi
PR
LN PR w/ Lymphocytosis
33% ORR
55% ORR
75% ORR

Fig. 19

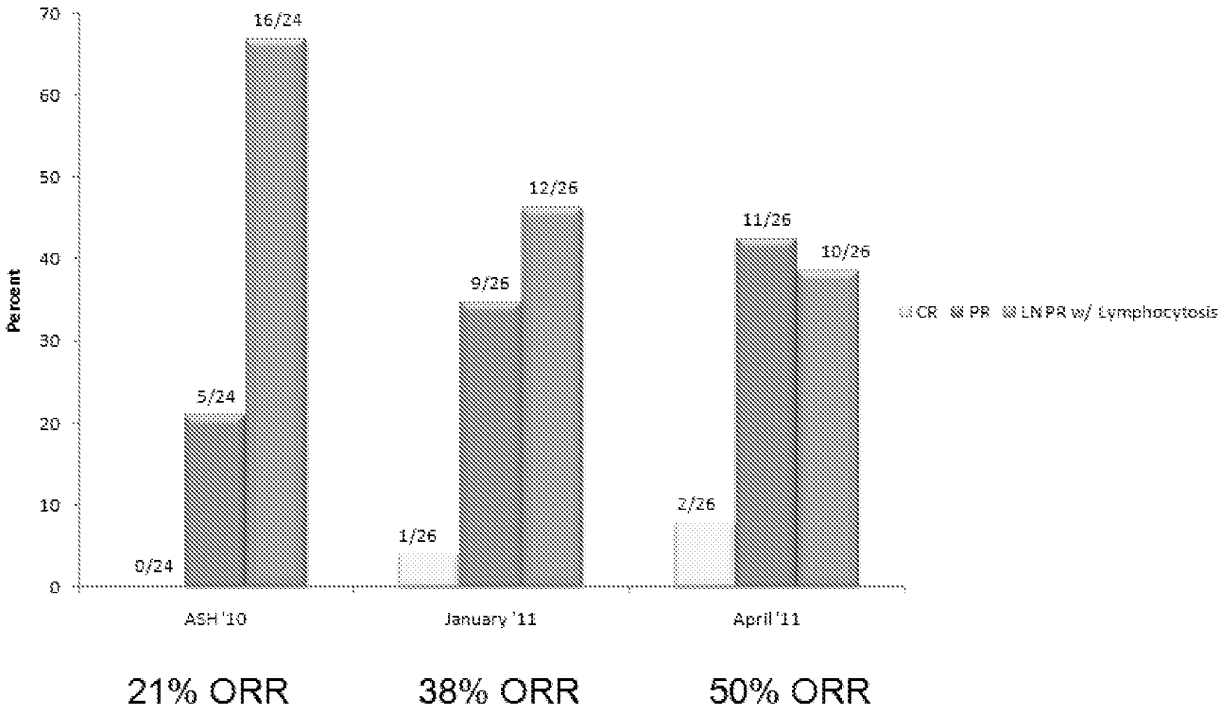
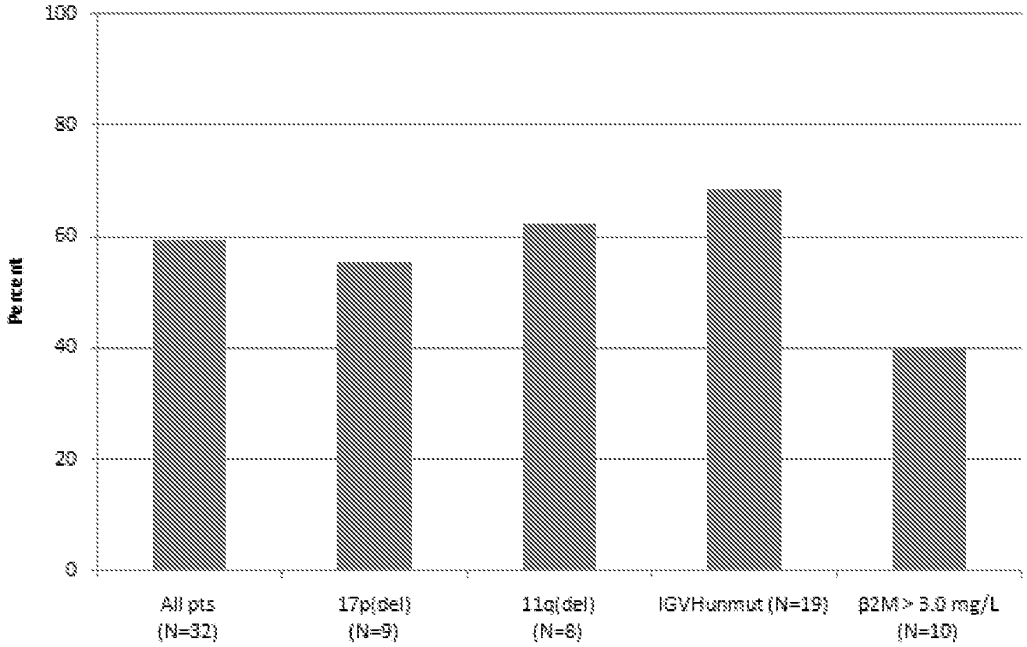
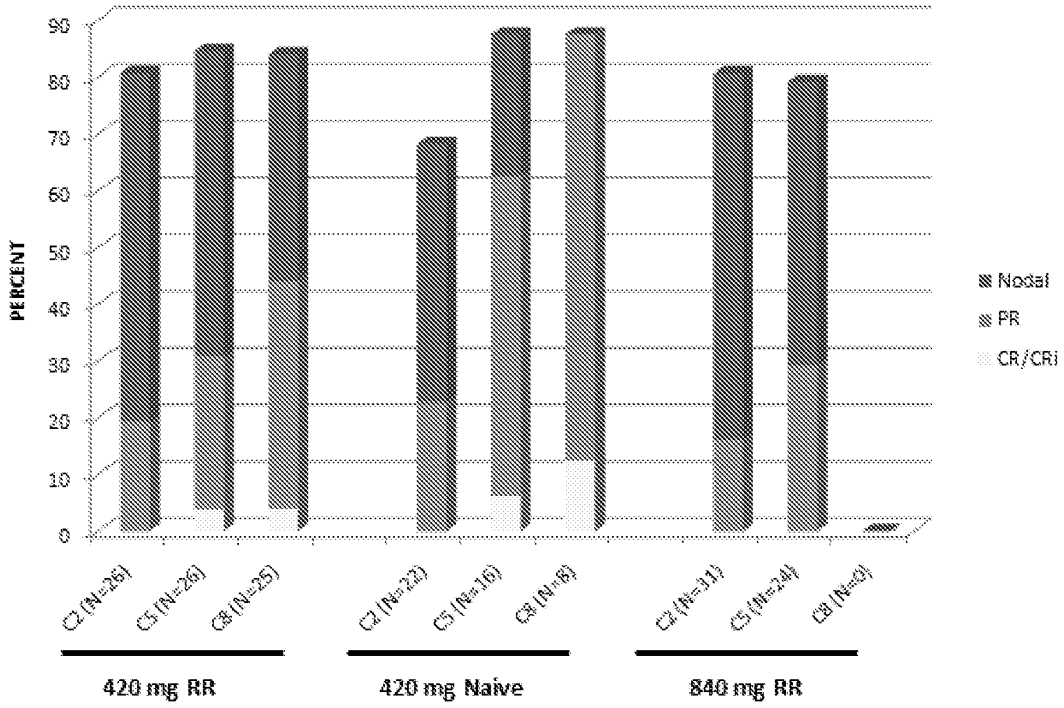

70
60
50
40
30
20
10
0
Percent
16/24
5/24
0/24
12/26
9/26
1/26
11/26
10/26
2/26
CR
PR
LN PR w/ Lymphocytosis
ASH '10
January '11
April '11
21% ORR
38% ORR
50% ORR

Fig. 20



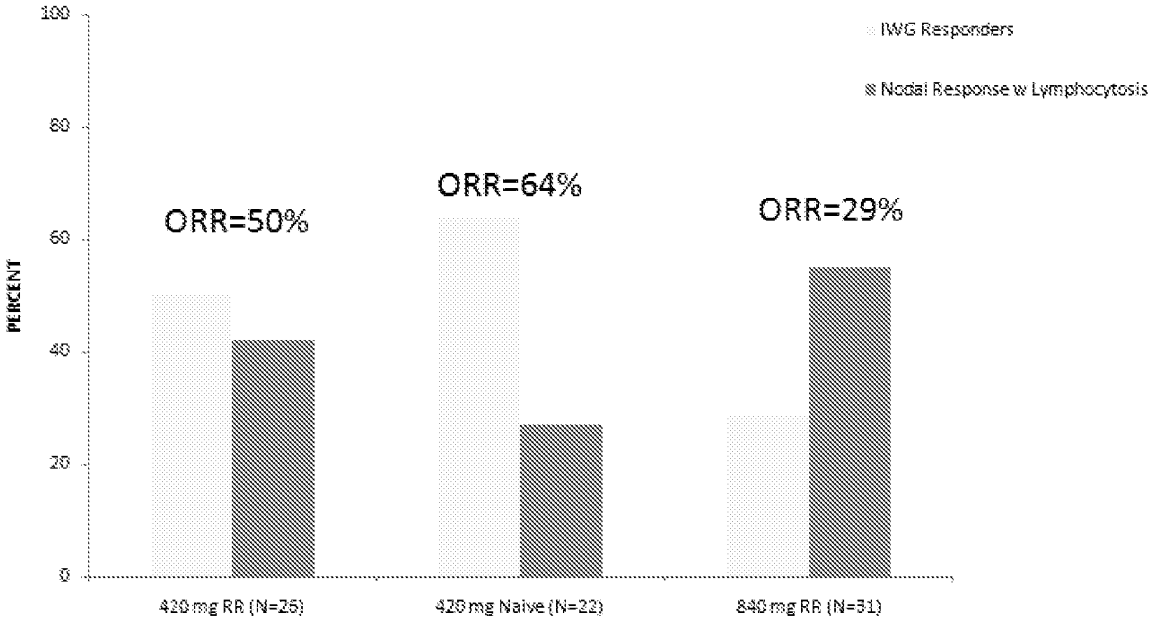
BeiGene Exhibit 1023.235

Fig. 21



BeiGene Exhibit 1023.236

Fig. 22



BeiGene Exhibit 1023.237

Fig. 23

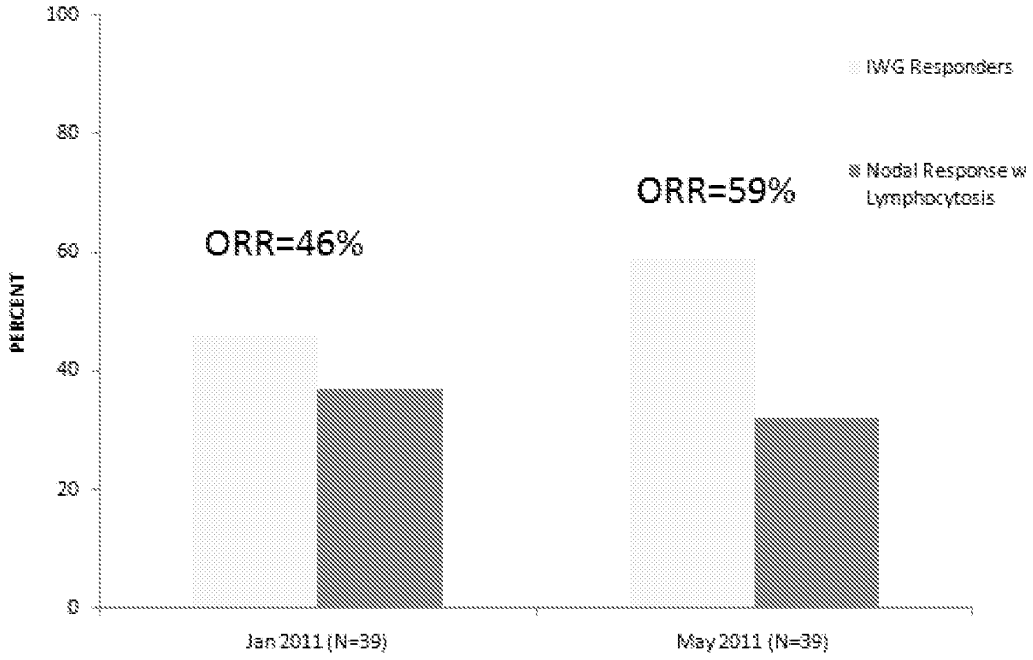

100
80
60
40
20
0
PERCENT
IWG Responders
≥ Nodal Response w Lymphocytosis
ORR=46%
ORR=59%
Jan 2011 (N=39)
May 2011 (N=39)

Fig. 24

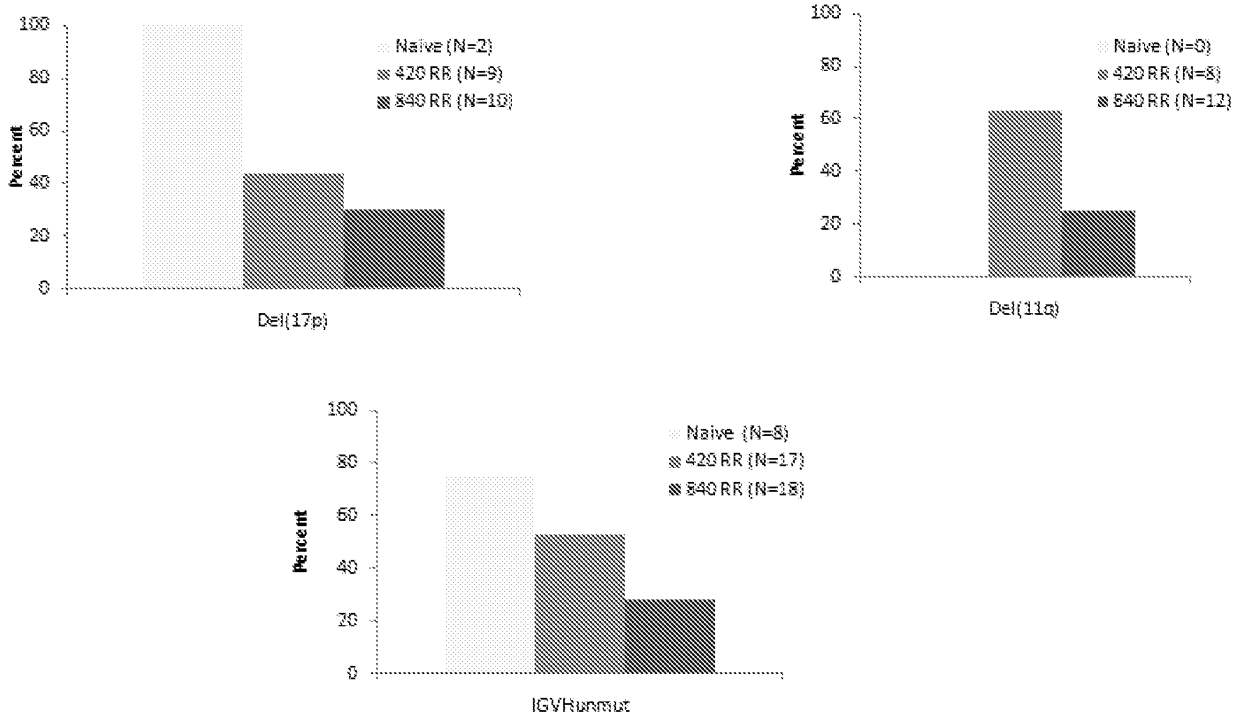
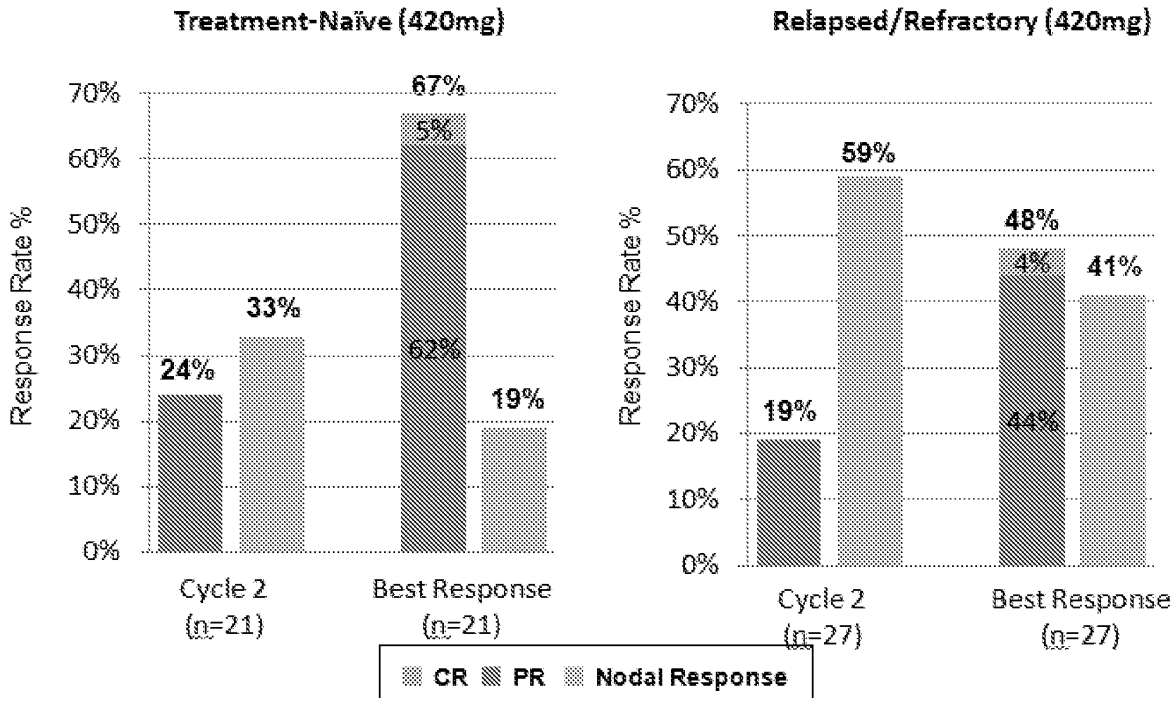
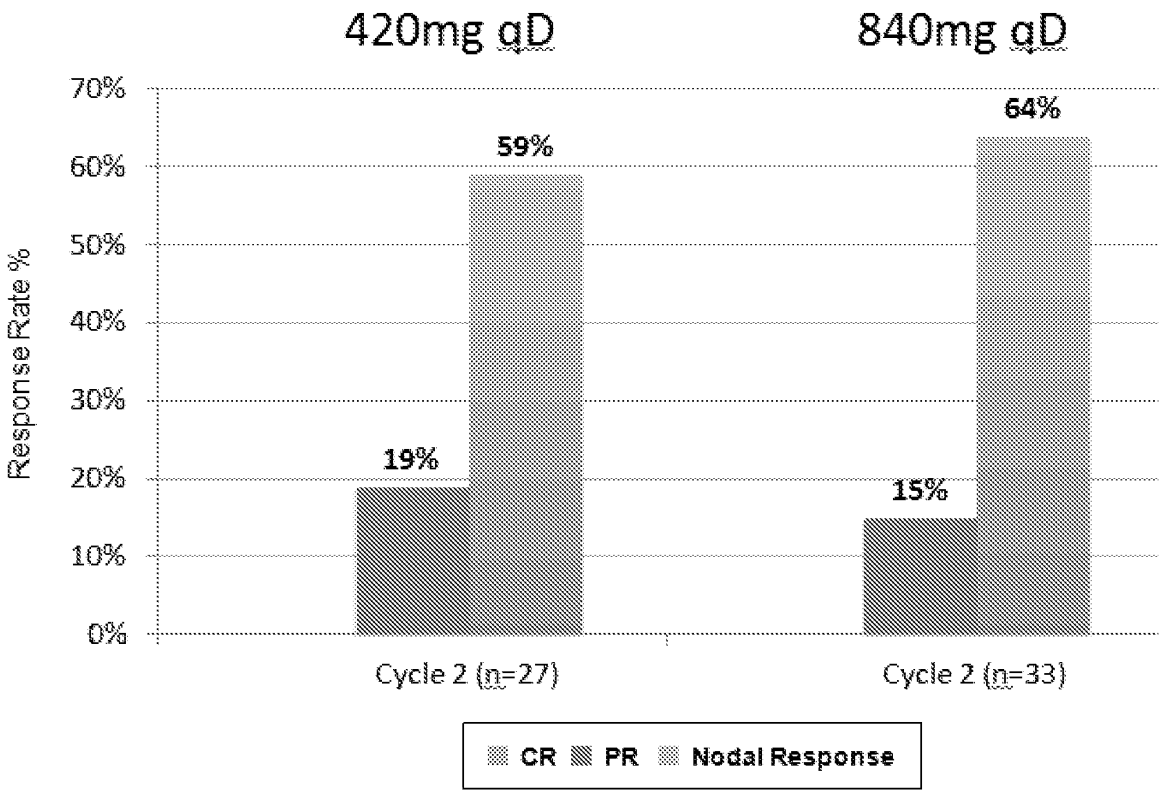

100
80
60
40
20
0
Percent
Naive (N=2)
420 RR (N=9)
840 RR (N=10)
Del(17p)
Naive (N=0)
420 RR (N=8)
840 RR (N=12)
Del(11q)
Naive (N=8)
420 RR (N=17)
840 RR (N=18)
IGVHunmut

Fig. 25



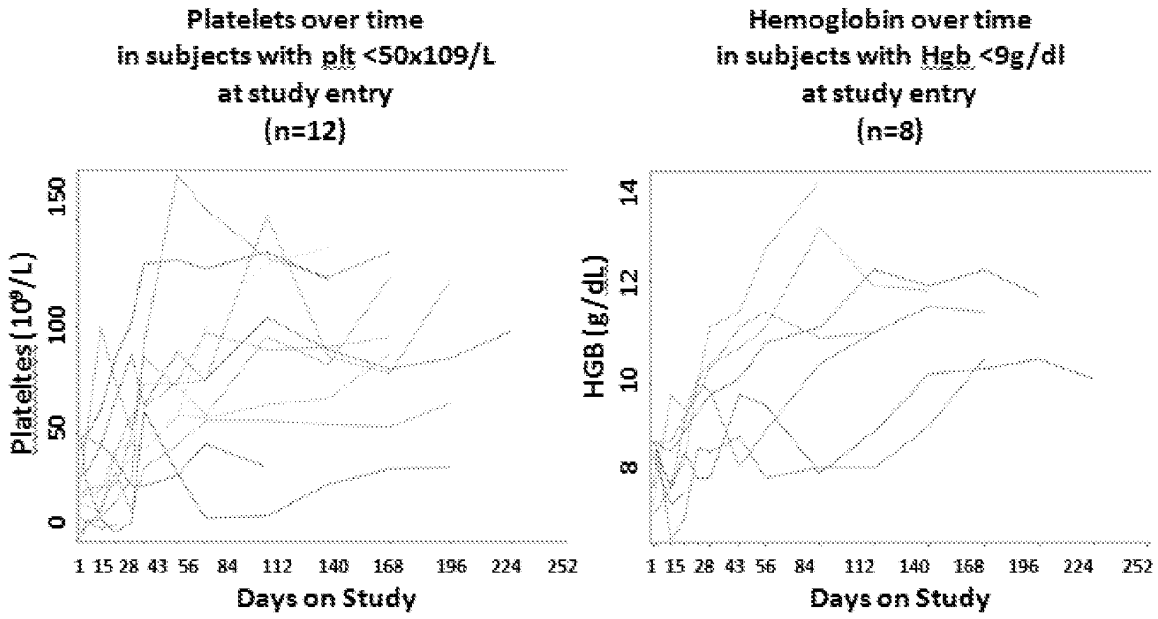
BeiGene Exhibit 1023.240

Fig. 26



BeiGene Exhibit 1023.241

Fig. 27

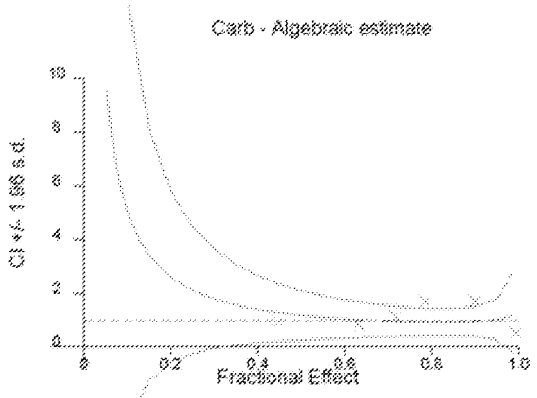


BeiGene Exhibit 1023.242

Fig. 28

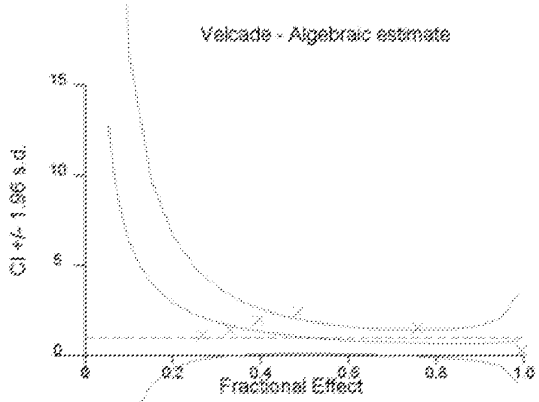
	Btk inhibitor (uM)	Carb(uM)
GI50	0.096	15.382
r:	0.994	0.990

	Btk inhibitor (uM)	Velcade(uM)
GI50	0.176	5.434
r:	0.986	0.850



CI For experimental values

Btk inhibitor (uM)	Carb (uM)	Fa	CI
0.03125	6.25	0.443223	0.954
0.0625	12.5	0.632339	0.826
0.125	25	0.715772	1.165
0.25	50	0.783398	1.718
0.5	100	0.899868	1.74
1	200	0.993211	0.564



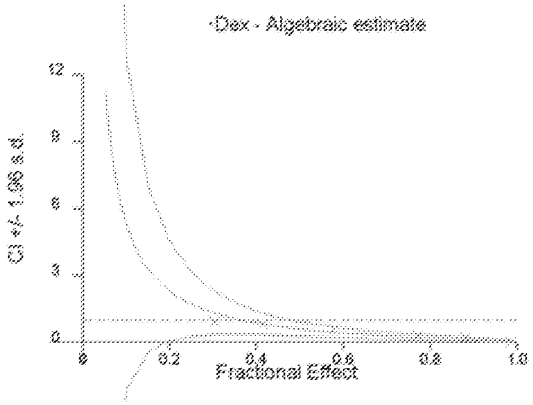
CI For experimental values

Btk inhibitor (uM)	Velcade (nM)	Fa	CI
0.03125	0.625	0.265657	1.16
0.0625	1.25	0.329518	1.487
0.125	2.5	0.394877	2.011
0.25	5	0.48706	2.488
0.5	10	0.756802	1.505
1	20	0.99494	0.314

BeiGene Exhibit 1023.243

Fig. 29

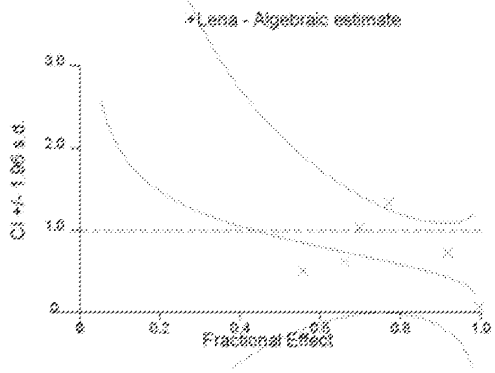
	Btk Inhibitor (uM)	Dex(uM)
GI50	0.177	45.850
r:	0.964	0.991



CI For experimental values

Btk Inhibitor	Dex	Fa	CI
(uM)	(uM)		
0.03125	3.125	0.300998	0.953
0.0625	6.25	0.41699	0.83
0.125	12.5	0.577051	0.606
0.25	25	0.769886	0.337
0.5	50	0.879476	0.249
1	100	0.988655	0.035

	Btk Inhibitor (uM)	Lena(uM)
GI50	0.183	12.653
r:	0.980	0.795



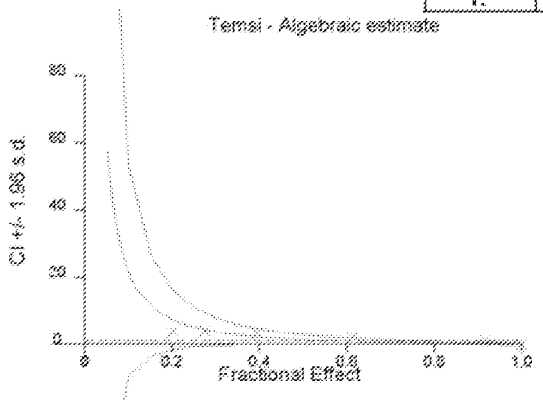
CI For experimental values

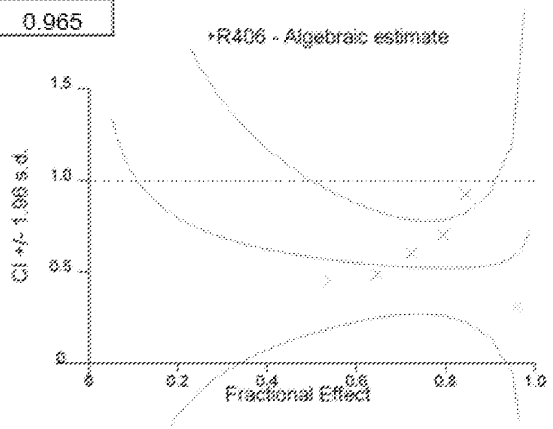
Btk Inhibitor	Lena	Fa	CI
(uM)	(uM)		
0.03125	6.25	0.558238	0.511
0.0625	12.5	0.663338	0.621
0.125	25	0.698831	1.034
0.25	50	0.773021	1.349
0.5	100	0.918456	0.722
1	200	0.994404	0.073

BeiGene Exhibit 1023.244

Fig. 30

	Btk inhibitor (uM)	Temsi(uM)	R406(uM)
GI50	0.099	1.774	12.750
r:	0.987	0.836	0.965





CI For experimental values

Btk inhibitor (uM)	Temsi (uM)	Fa	CI
0.03125	0.3125	0.200943	3.779
0.0625	0.625	0.275482	3.93
0.125	1.25	0.394234	3.529
0.25	2.5	0.614251	2.244
0.5	5	0.91765	0.907
1	10	0.99999	0.016

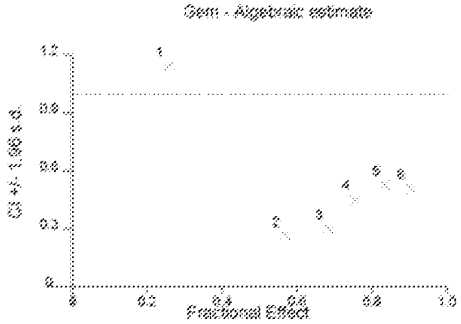
CI For experimental values

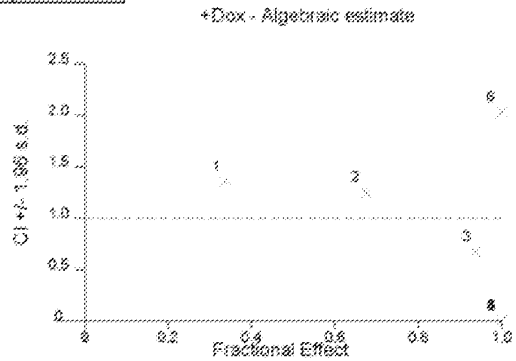
Btk Inhibitor (uM)	R406 (uM)	Fa	CI
0.03125	3.125	0.53672	0.455
0.0625	6.25	0.64571	0.484
0.125	12.5	0.722258	0.6
0.25	25	0.795651	0.709
0.5	50	0.844892	0.927
1	100	0.960979	0.307

BeiGene Exhibit 1023.245

Fig. 31

	Btk inhibitor (uM)	Gem(uM)	Dox(uM)
GI50	0.247	0.005	0.006
r:	0.996	0.897	0.892





CI For experimental values

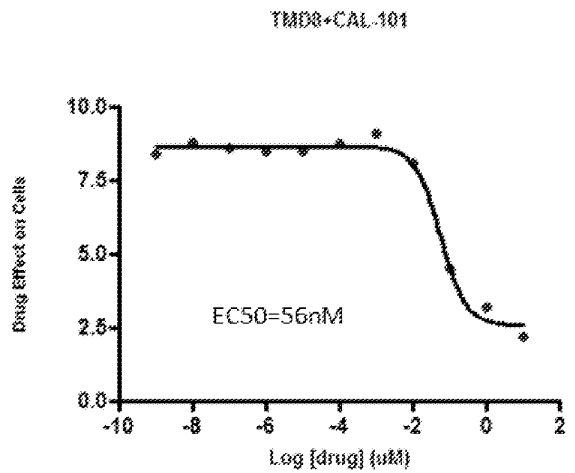
Btk inhibitor (uM)	Gem (uM)	Fa	CI
0.03125	0.000192	0.258111	1.144
0.0625	0.00096	0.569329	0.262
0.125	0.0048	0.683823	0.299
0.25	0.024	0.754917	0.456
0.5	0.12	0.836676	0.527
1	0.6	0.903074	0.51

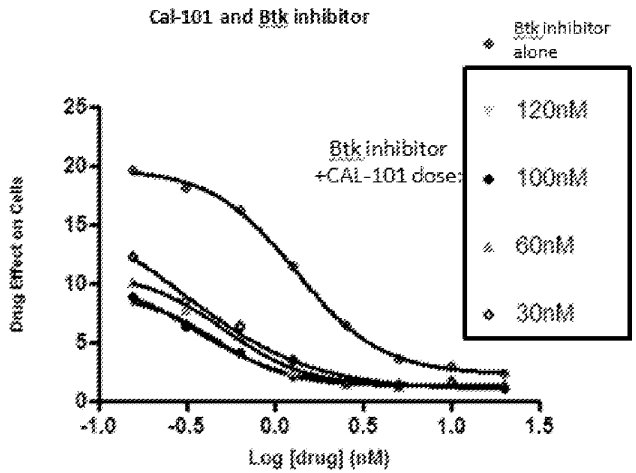
CI For experimental values

Btk inhibitor (uM)	Dox (uM)	Fa	CI
0.03125	0.0032	0.339005	1.358
0.0625	0.016	0.674194	1.256
0.125	0.08	0.939547	0.673
0.25	0.4	0.99999	0
0.5	2	0.99999	0.001
1	10	0.997935	2.032

BeiGene Exhibit 1023.246

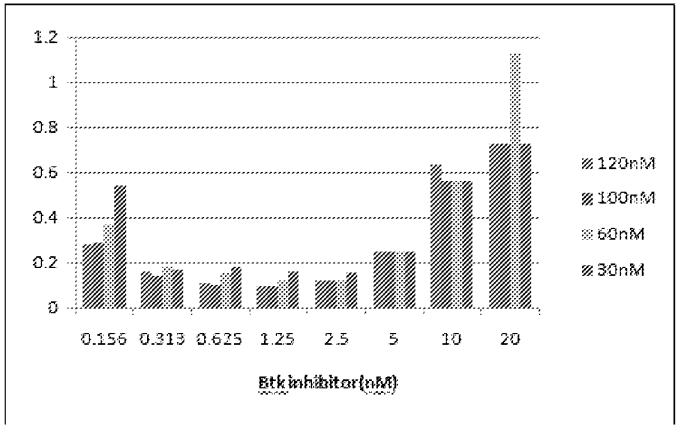
Fig. 32





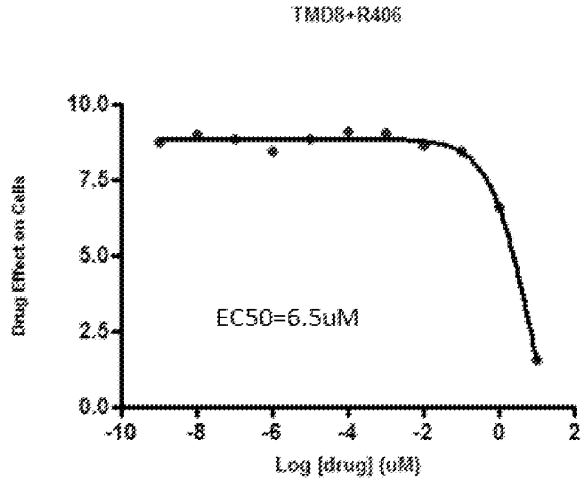
CI Values

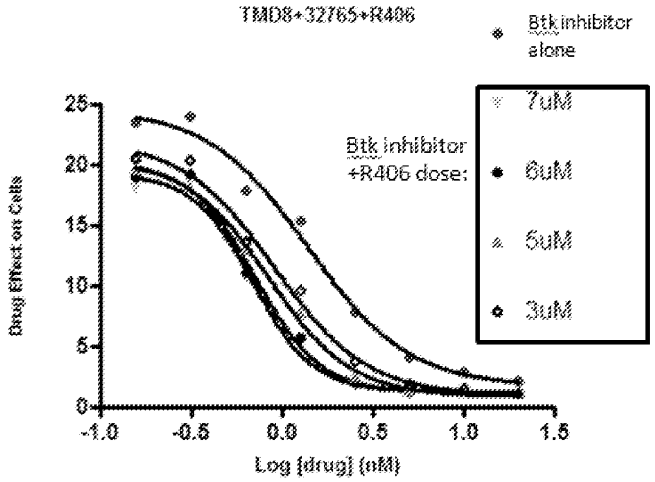
Btk inhibitor (nM)	CAL-101 120nM	100nM	60nM	30nM
0.156	0.282	0.293	0.37	0.541
0.313	0.166	0.141	0.186	0.173
0.625	0.108	0.106	0.159	0.18
1.25	0.098	0.098	0.125	0.161
2.5	0.125	0.125	0.125	0.159
5	0.25	0.25	0.25	0.25
10	0.635	0.567	0.567	0.567
20	0.73	0.73	1.133	0.73



BeiGene Exhibit 1023.247

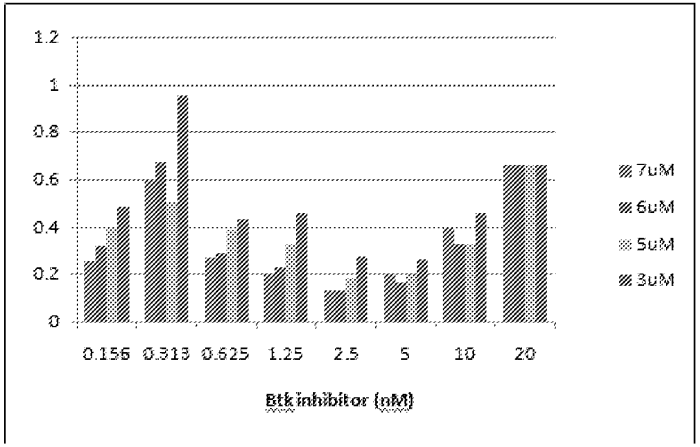
Fig. 33





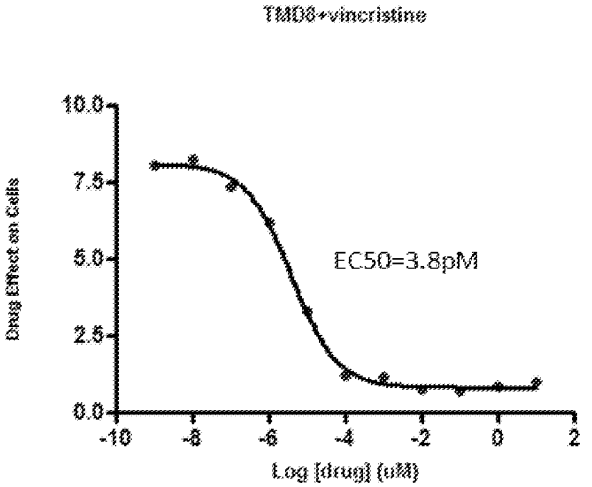
CI Values

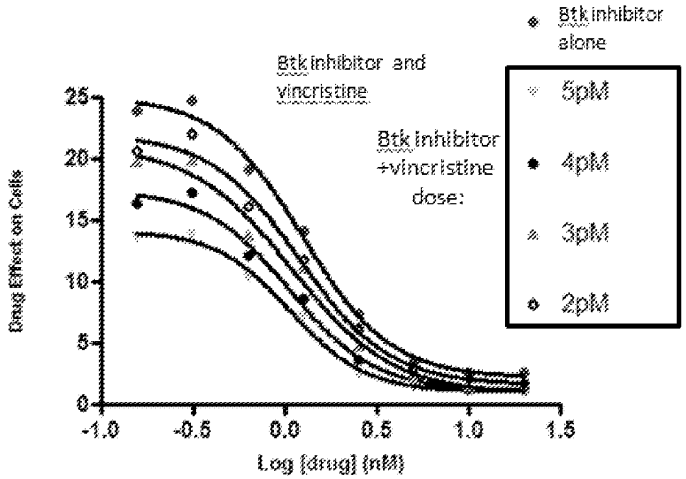
Btk inhibitor (nM)	R406 7uM	6uM	4uM	3uM
0.156	0.26	0.326	0.394	0.486
0.313	0.6	0.675	0.503	0.956
0.625	0.268	0.288	0.388	0.434
1.25	0.197	0.231	0.332	0.457
2.5	0.132	0.132	0.183	0.274
5	0.198	0.165	0.198	0.264
10	0.395	0.33	0.33	0.461
20	0.661	0.661	0.66	0.66



BeiGene Exhibit 1023.248

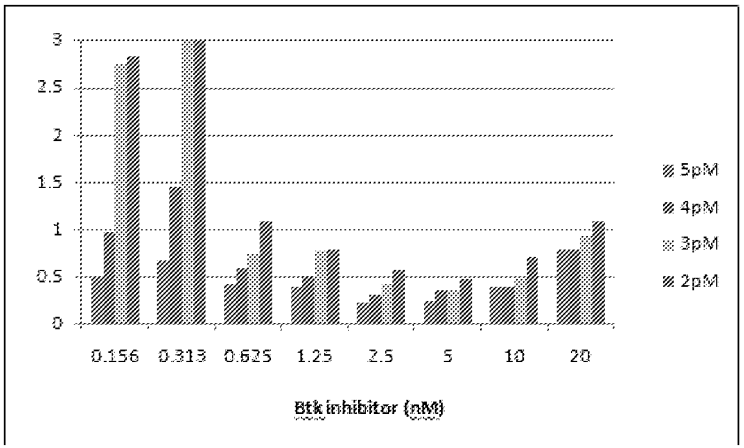
Fig. 34





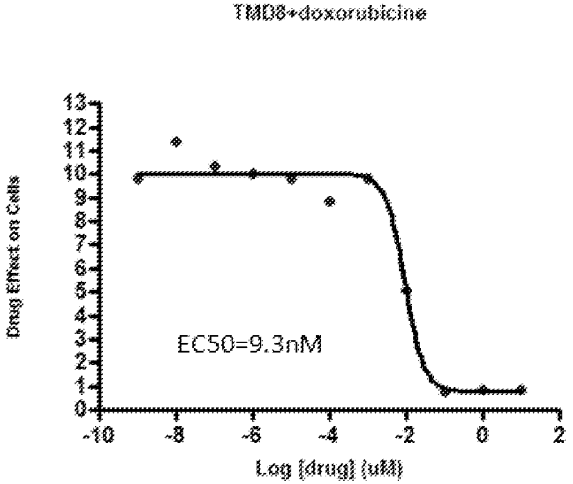
CI Values

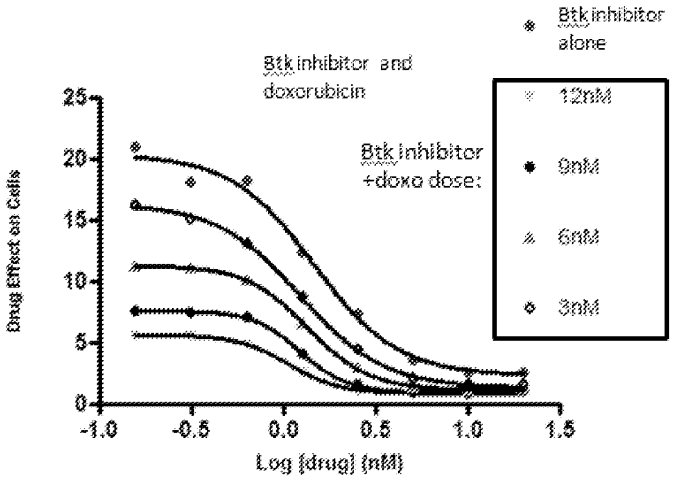
	Vincristine			
Btk inhibitor (nM)	5pM	4pM	3pM	2pM
0.156	0.512	0.976	2.746	2.837
0.313	0.67	1.449	3.14	8.836
0.625	0.429	0.587	0.748	1.096
1.25	0.391	0.503	0.774	0.798
2.5	0.221	0.308	0.424	0.578
5	0.237	0.354	0.353	0.474
10	0.395	0.394	0.471	0.704
20	0.788	0.788	0.94	1.094



BeiGene Exhibit 1023.249

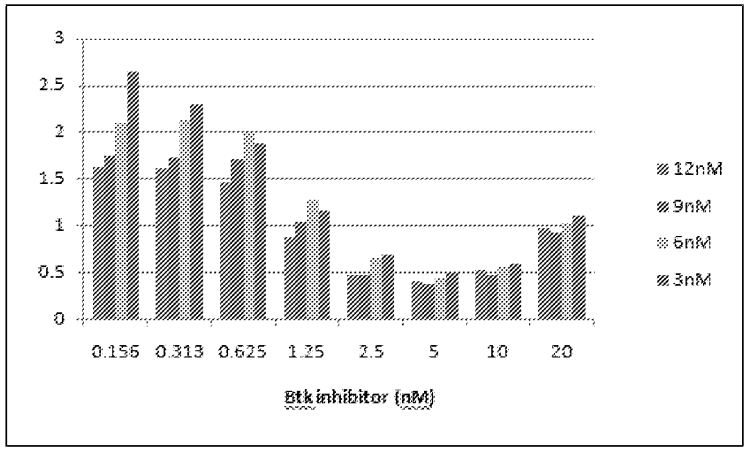
Fig. 35





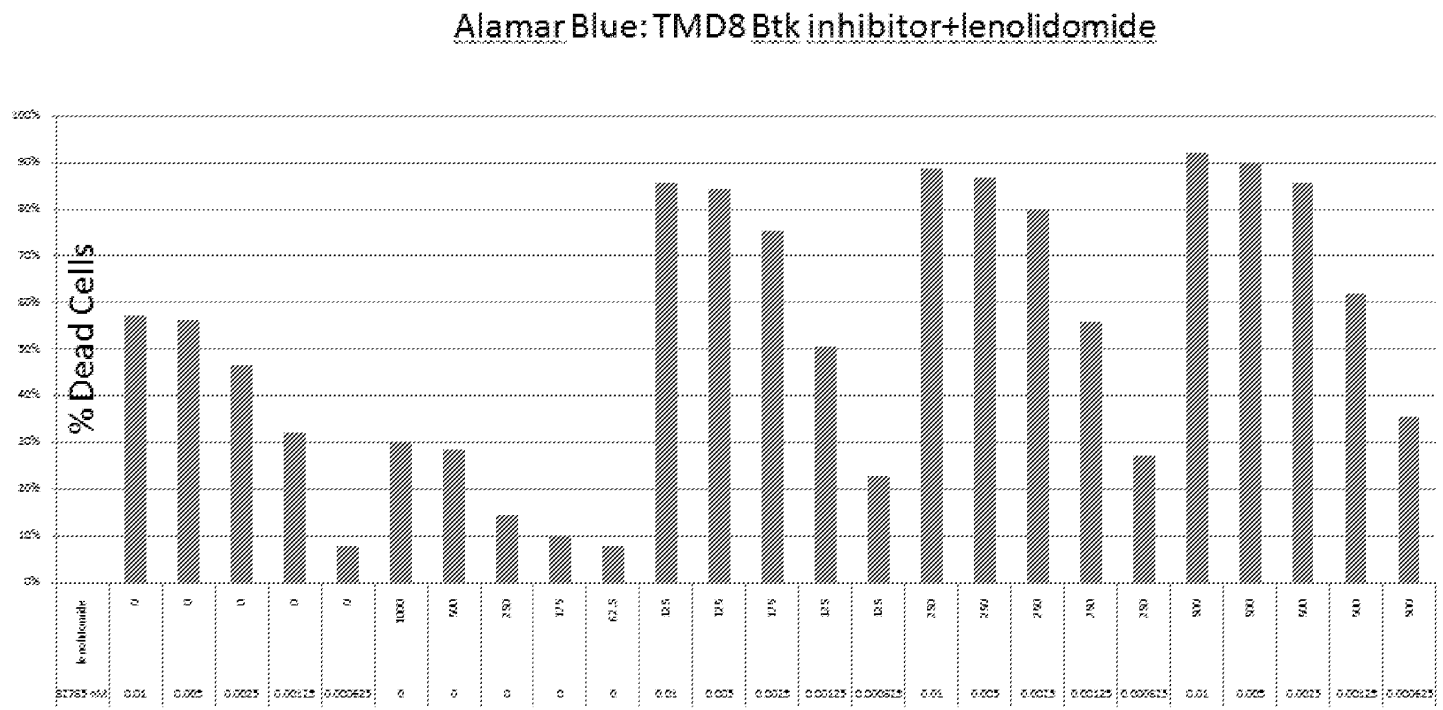
CI Values

Btk inhibitor (nM)	Doxorubicin 12nM	9nM	6nM	3nM
0.156	1.633	1.745	2.102	2.659
0.313	1.622	1.736	2.138	2.302
0.625	1.46	1.709	2.004	1.877
1.25	0.873	1.05	1.283	1.157
2.5	0.474	0.481	0.654	0.699
5	0.418	0.374	0.436	0.489
10	0.534	0.484	0.559	0.602
20	0.987	0.936	1.034	1.105



BeiGene Exhibit 1023.250

Fig. 36



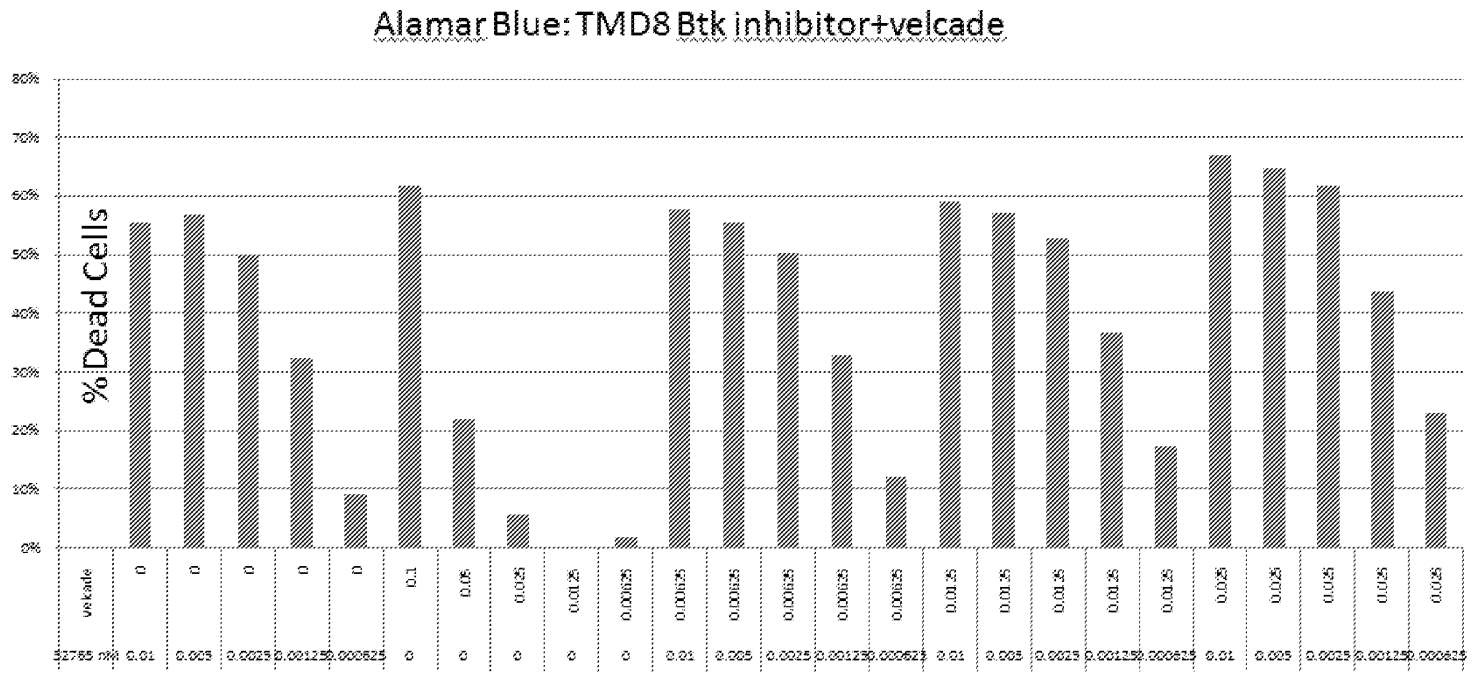
Btk inhibitor nM	lenolidomide nM	CI
0.000625	125	0.77
0.00125	125	0.311
0.0025	125	0.175
0.005	125	0.188
0.01	125	0.332

Btk inhibitor nM	lenolidomide nM	CI
0.000625	250	0.773
0.00125	250	0.271
0.0025	250	0.136
0.005	250	0.154
0.01	250	0.25

Btk inhibitor nM	lenolidomide nM	CI
0.000625	500	0.668
0.00125	500	0.244
0.0025	500	0.093
0.005	500	0.119
0.01	500	0.163

BeiGene Exhibit 1023.251

Fig. 37



Btk inhibitor nM	velcade nM	CI
0.000625	0.00625	1.486
0.00125	0.00625	0.701
0.0025	0.00625	0.601
0.005	0.00625	0.91
0.01	0.00625	1.043

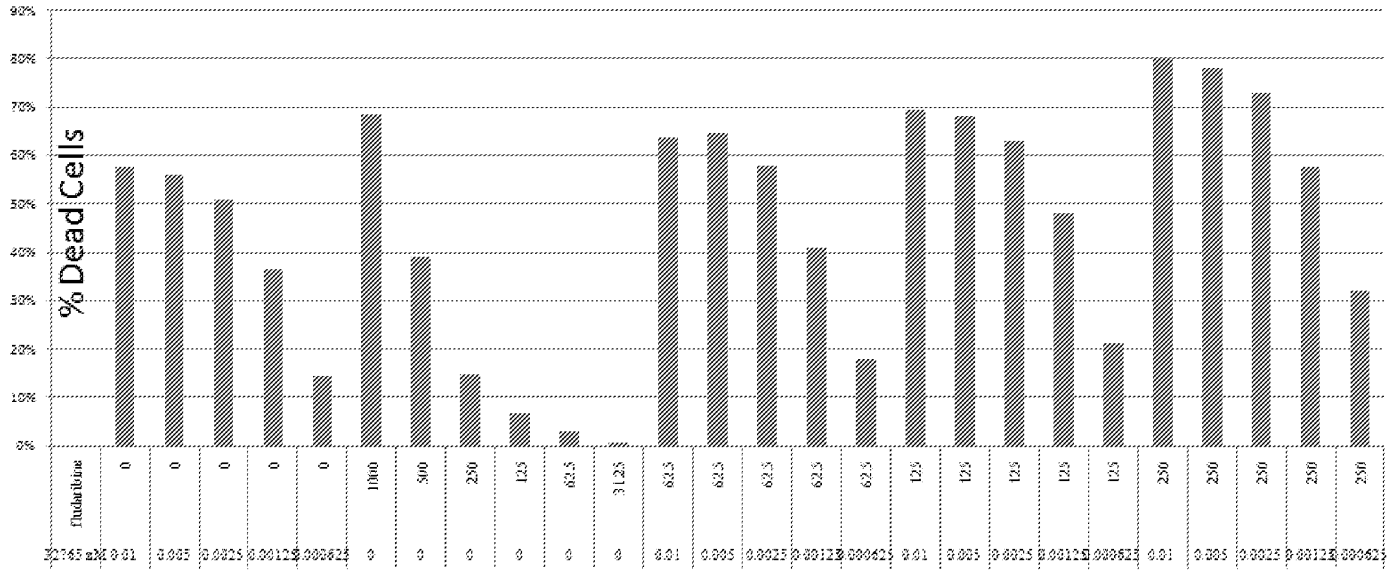
Btk inhibitor nM	velcade nM	CI
0.000625	0.0125	1.053
0.00125	0.0125	0.656
0.0025	0.0125	0.582
0.005	0.0125	0.888
0.01	0.0125	1.043

Btk inhibitor nM	velcade nM	CI
0.000625	0.025	0.942
0.00125	0.025	0.596
0.0025	0.025	0.472
0.005	0.025	0.691
0.01	0.025	1.169

BeiGene Exhibit 1023.252

Fig. 38

Alamar Blue: TMD8 Btk inhibitor+Fludarabine



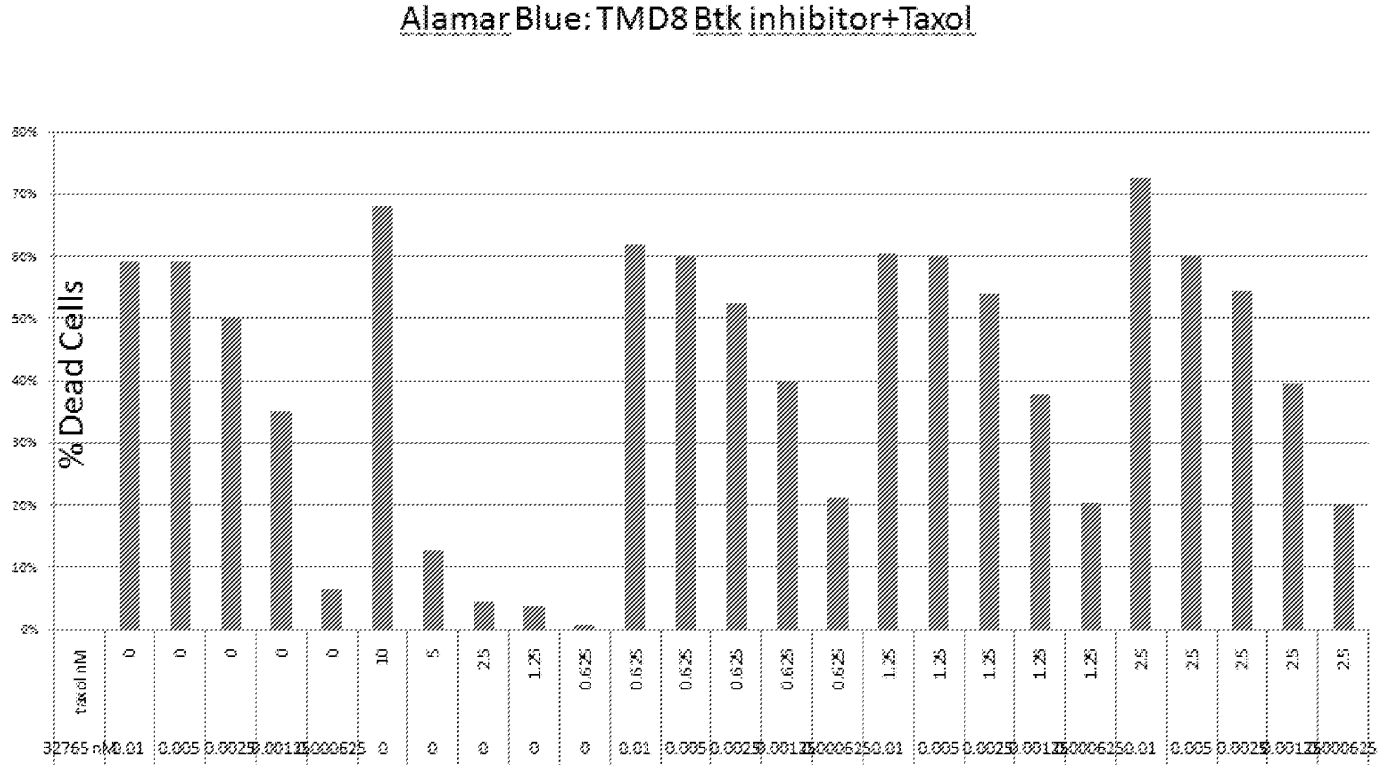
Btk inhibitor nM	fludarabine nM	CI
0.00125	62.5	0.636
0.0025	62.5	0.474
0.005	62.5	0.598

Btk inhibitor nM	fludarabine nM	CI
0.00125	125	0.548
0.0025	125	0.427
0.005	125	0.542
0.01	125	0.889

Btk inhibitor nM	fludarabine nM	CI
0.00125	250	0.518
0.0025	250	0.356
0.005	250	0.383
0.01	250	0.518

BeiGene Exhibit 1023.253

Fig. 39



Btk inhibitor nM	taxol nM	CI
0.000625	0.625	0.683
0.00125	0.625	0.535
0.0025	0.625	0.612
0.005	0.625	0.865
0.01	0.625	1.525

Btk inhibitor nM	taxol nM	CI
0.000625	1.25	0.85
0.00125	1.25	0.664
0.0025	1.25	0.634
0.005	1.25	0.918
0.01	1.25	1.710

Btk inhibitor nM	taxol nM	CI
0.000625	2.5	1.15
0.00125	2.5	0.784
0.0025	2.5	0.735
0.005	2.5	1.007
0.01	2.5	1.894

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DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 13869700 Document Date: 04/24/2013

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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Form Revision Date: February 8, 2006

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	1	of	17	Attorney Docket Number	25922-819.306

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2002-016460	2/7/2002	Snow et al.	
	2.	US-2003-0040461	2/27/2003	Mcatee	
	3.	US-2003-0125235	7/3/2003	Foxwell	
	4.	US-2004-0006083A1	1/8/2004	Hirst et al.	
	5.	US-2005-008640 A1	1/13/2005	Waegell et al.	
	6.	US-2005-0090499 A1	4/28/2005	Currie et al.	
	7.	US-2005-0101604 A1	5/12/2005	Currie et al.	
	8.	US-2005-0196851 A1	9/8/2005	Uckun	
	9.	US-2005-0209255 A1	9/22/2005	Jimenez et al.	
	10.	US-2006-0079494	4/13/2006	Santi et al.	
	11.	US-2006-0167090 A1	7/27/2006	Uckun et al.	
	12.	US-2007-0281907	12/6/2007	Watkins	
	13.	US-2008-0214501	9/4/2008	Pan	
	14.	US-2010-0022561 A1	1/28/2010	Honigberg et al.	
	15.	US-2010-0041677 A1	2/18/2010	Honigberg et al.	
	16.	US-2010-0254905	10/7/2010	Honigberg et al.	
	17.	US-2010-0324050 A1	12/23/2010	Honigberg et al.	
	18.	US-2011-0039868 A1	2/17/2011	Honigberg et al.	
	19.	US-2011-0086866	4/14/2011	Chen	
	20.	US-2011-0177011	7/21/2011	Currie et al.	
	21.	US-2011-0224235	9/15/2011	Honigberg et al.	
	22.	US-2011-0281322 A1	11/17/2011	Honigberg et al.	
	23.	US-2012-0065201	3/15/2012	Honigberg et al.	
	24.	US-2012-0071497	3/22/2012	Buggy et al.	
	25.	US-2012-0087915	4/12/2012	Buggy et al.	
	26.	US-2012-0088912 A1	4/12/2012	Honigberg et al.	
	27.	US-2012-0095026 A1	4/19/2012	Honigberg et al.	

Examiner Signature		Date Considered	

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				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	2	of	17	Attorney Docket Number	25922-819.306

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	28.	US-2012-0100138	4/26/2012	Buggy et al.	
	29.	US-2012-0101113	4/26/2012	Honigberg et al.	
	30.	US-2012-0101114	4/26/2012	Honigberg et al.	
	31.	US-2012-0108612 A1	5/3/2012	Honigberg et al.	
	32.	US-2012-0115889 A1	5/10/2012	Honigberg et al.	
	33.	US-2012-0122894 A1	5/17/2012	Honigberg et al.	
	34.	US-2012-0129821 A1	5/24/2012	Honigberg et al.	
	35.	US-2012-0129873 A1	5/24/2012	Honigberg et al.	
	36.	US-2012-0135944 A1	5/31/2012	Honigberg et al.	
	37.	US-2012-0165328	6/28/2012	Honigberg et al.	
	38.	US-2012-0178753	7/12/2012	Honigberg et al.	
	39.	US-2012-0183535	7/19/2012	Buggy et al.	
	40.	US-2012-0184013	7/19/2012	Honigberg et al.	
	41.	US-2012-0184567	7/19/2012	Honigberg et al.	
	42.	US-2012-0202264	8/9/2012	Honigberg et al.	
	43.	US-2012-0214826 A1	8/23/2012	Honigberg et al.	
	44.	US-2012-0252821 A1	10/4/2012	Honigberg et al.	
	45.	US-2012-0252822 A1	10/4/2012	Honigberg et al.	
	46.	US-2012-0277225	11/1/2012	Honigberg et al.	
	47.	US-2012-0277254 A1	11/1/2012	Honigberg et al.	
	48.	US-2012-0277255	11/1/2012	Honigberg et al.	
	49.	US-2012-0283276 A1	11/8/2012	Honigberg et al.	
	50.	US-2012-0283277 A1	11/8/2012	Honigberg et al.	
	51.	US-2012-0296089	11/22/2012	Honigberg et al.	
	52.	US-2012-0329130	12/27/2012	Honigberg et al.	
	53.	US-2013-0005746	1/3/2013	Honigberg et al.	
	54.	US-2013-0012525	1/10/2013	Honigberg et al.	
	55.	US-5,397,787	3/14/1995	Buzzetti	
	56.	US-6,160,010	12/12/2000	Uckun et al.	

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				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	3	of	17	Attorney Docket Number	25922-819.306

U.S. PATENT DOCUMENTS

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	57.	US-6,221,900	4/24/2001	Uckun et al.	
	58.	US-6,326,469	12/4/2001	Ullrich et al.	
	59.	US-6,506,769	1/14/2003	Snow et al.	
	60.	US-6,660,744	12/9/2003	Hirst et al.	
	61.	US-6,753,348	6/22/2004	Uckun et al.	
	62.	US-6,770.639	8/3/2004	Snow et al.	
	63.	US-6,921,763	7/26/2005	Hirst et al.	
	64.	US-7,138,420	11/21/2006	Bentzien et al.	
	65.	US-7,332,497	2/19/2008	Hirst et al.	
	66.	US-7,514,444	4/7/2009	Honigberg et al.	
	67.	US-7,718,662	5/18/2010	Chen	
	68.	US-7,732,454	6/8/2010	Erik Verner	
	69.	US-7,741,330	6/22/2010	Chen	
	70.	US-7,825,118	11/2/2010	Honigberg et al.	
	71.	US-7,960,396	6/14/2011	Honigberg et al.	
	72.	US-8,008,309	8/30/2011	Honigberg et al.	
	73.	US-8,088,781	1/3/2012	Honigberg et al.	
	74.	US-8,158,786	4/17/2012	Honigberg et al.	
	75.	US-8,232,280	7/31/2012	Honigberg et al.	
	76.	US-8,236,812	8/7/2012	Honigberg et al.	
	77.	US-2013-0005745	1/3/2013	Honigberg et al.	
	78.	US-2013-0035334 A1	02/07/2013	Honigberg et al.	
	79.	US-2013-0018060 A1	01/17/2013	Honigberg et al.	
	80.	US-2003-013125	1/16/2003	Braisted et al.	
	81.	US-2002-155505	10/24/2002	Wells et al.	
	82.	US-2005-084905	4/21/2005	Prescott et al.	
	83.	US-2009-0105209	4/23/2009	Dewdney et. al.	

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				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	4	of	17	Attorney Docket Number	25922-819.306

U.S. UNPUBLISHED PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	84.	US-13/890,498	5/9/2013	Honigberg et al.	
	85.	US-13/849,399	3/22/2013	Honigberg et al.	
	86.	US-13/654,173	10/17/2012	Honigberg et al.	
	87.	US-13/736,812	1/8/2013	Buggy et al.	
	88.	US-13/747,322	01/22/2013	Buggy et al.	
	89.	US-13/747,319	01/22/2013	Buggy et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	90.	WO-1997-028161	8/7/1997	Novartis AG		
	91.	WO-1999-054286	10/28/1999	Wayne Hughes Institute		
	92.	WO-2000-56737 A2	9/28/2000	Parker Hughes Institute		
	93.	WO-2001-044258 A1	6/21/2001	Ariad Pharmaceuticals		
	94.	WO-2001-019829 A2 + A3	3/22/2001	BASF		
	95.	WO-2001-041754	6/14/2001	Parker Hughes Institute		
	96.	WO-2001-25238 A2	4/12/2001	Boehringer Ingelheim Pharmacueticals, Inc.		
	97.	WO-2002-38797 A2	5/16/2002	Bristol-Myers Squibb		
	98.	WO-2002-076986 A1	10/3/2002	Abbott GMBH & CO.		
	99.	WO-2002-080926	10/17/2002	Abbott GMBH & CO.		
	100.	WO-2003-000187	1/3/2003	Ariad Pharmaceuticals		
	101.	WO-2003-097645	11/27/2003	Bayer Healthcare AG		
	102.	WO-2004-074290	9/2/2004	Merck Sharp & Dohme		

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	103.	WO-2004-100868 A2 + A3	11/25/2004	Abbott Laboratories		
	104.	WO-2004-096253	11/11/2004	Centre National de la Recherche Scientifique		
	105.	WO-2005-000197	1/6/2005	Univ California		
	106.	WO-2005-014599	2/17/2005	Cellular Genomics Inc		
	107.	WO-2005-037843	04/28/2005	Vertex Pharma Inc.		
	108.	WO-2005-005429	1/20/2005	Cellular Genomics Inc		
	109.	WO-2005-060956	7/7/2005	Univ. Maryland		
	110.	WO-2005-074603	8/18/2005	Abbott Laboratories		
	111.	WO-2006-036527	4/6/2006	Janssen Pharmaceutica NV		
	112.	WO-2006-053121	5/18/2006	CGI Pharmaceuticals, Inc.		
	113.	WO-2006-099075	9/21/2006	CGI Pharmaceuticals, Inc.		
	114.	WO-2006-050946	5/18/2006	Novartis Pharma GMBH		
	115.	WO-2006-124462	11/23/2006	IRM LLC		
	116.	WO-2007-002325	1/4/2007	Plexxikon Inc.		
	117.	WO-2007-136790	11/29/2007	Mannkind Corp.		
	118.	WO-2007-058832	5/24/2007	Boehringer Ingelheim Pharmacueticals, Inc.		
	119.	WO-2008-054827 A2	5/8/2008	Pharmacyclics, Inc.		
	120.	WO-2008-039218	4/3/2008	Pharmacyclics, Inc.		
	121.	WO-2008-121742	10/9/2008	Pharmacyclics, Inc.		
	122.	WO-2009-051822	4/23/2009	Avila Therapeutics, Inc.		
	123.	WO-2009-158571	12/30/2009	Avila Therapeutics, Inc.		
	124.	WO-2010-009342 A2, A3	1/21/2010	Pharmacyclics, Inc.		

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	125.	WO-2010-126960	11/4/2010	Locus Pharma.		
	126.	WO-2011-034907	3/24/2011	Avila Therapeutics, Inc.		
	127.	WO-2011-153514	12/8/2011	Pharmacyclics, Inc.		
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	129.	WO-2012-021444	2/16/2012	Avila Therapeutics, Inc.		
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	132.	EP-1473039	11/3/2004	Centre National de la Recherche Scientifique		
	133.	WO-2000-000823	1/6/2000	Sunesis Pharmaceuticals, Inc.		
	134.	WO-2003-046200	6/5/2003	Sunesis Pharmaceuticals, Inc.		

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				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	7	of	17	Attorney Docket Number	25922-819.306

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	135.	ADVANI et al. "The BTK inhibitor PCI-32765 is highly active and well tolerated in patients (PTS) with relapsed/refractory B cell malignancies: final results from a phase I study", Ann. Oncol., 22(suppl 4): abstract 153 (2011)	
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	146.	CZUCZMAN et al. "Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma", J. Clin. Oncol. 23(4):694-704 (February 1, 2005)	
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	162.	EP 12166296.9 Search Report and Written Opinion dated 8 November 2012	
	163.	EP 12166298.5 Search Report and Written Opinion dated 7 November 2012	
	164.	EP 12166300.9 Search Report and Written Opinion dated 31 October 2012	

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	166.	EP 12166302.5 Search Report and Written Opinion dated 6 November 2012	
	167.	EP 12166305.8 Search Report and Written Opinion dated 6 November 2012	
	168.	EP 12166306.6 Search Report and Written Opinion dated 8 November 2012	
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	171.	FABIAN et al. "A small molecule-kinase interaction map for clinical kinase inhibitors." *Nature Biotechnology,* 2005, 23(3): 329-336	
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		German Low-Grade Lymphoma Study Group", Blood (Epub August 25, 2005), 106(12):3725-3732 (December 2005)	
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	216.	SADA, K. and YAMAMURA, H., "Protein-Tyrosine Kinases and Adaptor Proteins in FceRI-Mediated Signaling in Mast Cells," Curr. Mol. Med., 3(1):85-94 (2003)	
	217.	SCHAEFFER, E.M. and SCHWARTZBERG, P.L., "Tec family kinases in lymphocyte signaling and function," Curr. Opin. Imm., 12:282-288 (2000)	
	218.	SCHWAMB et al. "B-cell receptor triggers drug sensitivity of primary CLL cells by controlling glucosylation of ceramides", Blood (Epub August 27, 2012), 120(19):3978-3985 (November 2012)	
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	220.	SCIENCE IP CAS Search, September 5, 2006	
	221.	SHAFFER et al." Lymphoid malignancies: the dark side of B-cell differentiation," Nature Rev. Immun., 2:920-932 (December 2002)	

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BeiGene Exhibit 1023.267

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	13	of	17	Attorney Docket Number	25922-819.306

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	222.	SMAILL et al. "Tyrosine Kinase Inhibitors. 15. 4-(Phenylamino)quinazoline and 4-(Phenylamino)prido[d]pyrimidine Acrylamides as Irreversible Inhibitors of the ATP Binding Site of the Epidermal Growth Factor Receptor," J. Med. Chem., 42(10):1803-1815 (1999)	
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	225.	TINMOUTH et al. "Fludarabine in alkylator-resistant follicular non-Hodgkin's lymphoma", Leuk. Lymphoma, 41(1-2):137-145 (2001)	
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	229.	U.S. Serial No. 11/617,645 Office Action mailed January 24, 2008	
	230.	U.S. Serial No. 11/617,645 Office Action mailed May 13, 2008	
	231.	U.S. Serial No. 11/692,870 Final Office Action mailed August 19, 2009	
	232.	U.S. Serial No. 11/692,870 Office Action mailed January 26, 2009	
	233.	U.S. Serial No. 12/356,498 Final Office Action mailed July 8, 2011	
	234.	U.S. Serial No. 12/356,498 Office Action mailed April 14, 2011	
	235.	U.S. Serial No. 12/499,002 Final Office Action mailed December 14, 2012	
	236.	U.S. Serial No. 12/499,002 Final Office Action mailed October 25, 2011	
	237.	U.S. Serial No. 12/499,002 Office Action mailed June 5, 2012	
	238.	U.S. Serial No. 12/499,002 Office Action mailed March 3, 2011	
	239.	U.S. Serial No. 12/499,005 Office Action mailed February 17, 2011	

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				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1629
				Examiner Name	Not Yet Assigned
Sheet	14	of	17	Attorney Docket Number	25922-819.306

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	240.	U.S. Serial No. 12/499,008 Office Action mailed July 19, 2011	
	241.	U.S. Serial No. 12/499,008 Office Action mailed March 9, 2011	
	242.	U.S. Serial No. 12/594,805 Office Action mailed October 15, 2012	
	243.	U.S. Serial No. 12/727,703 Final Office Action mailed July 19, 2011	
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	245.	U.S. Serial No. 12/887,428 Office Action mailed April 20, 2011	
	246.	U.S. Serial No. 13/011,258 Office Action mailed November 22, 2011	
	247.	U.S. Serial No. 13/162,449 Office Action mailed February 9, 2012	
	248.	U.S. Serial No. 13/249,066 Office Action mailed November 27, 2012	
	249.	U.S. Serial No. 13/312,606 Office Action mailed September 19, 2012	
	250.	U.S. Serial No. 13/328,718 Final Office Action mailed December 27, 2012	
	251.	U.S. Serial No. 13/328,718 Office Action mailed July 3, 2012	
	252.	U.S. Serial No. 13/340,276 Office Action mailed September 26, 2012	
	253.	U.S. Serial No. 13/361,733 Notice of Allowance mailed November 14, 2012	
	254.	U.S. Serial No. 13/361,733 Office Action mailed July 6, 2012	
	255.	U.S. Serial No. 13/404,422 Office Action mailed September 28, 2012	
	256.	U.S. Serial No. 13/410,110 Office Action mailed September 28, 2012	
	257.	U.S. Serial No. 13/439,775 Office Action mailed December 10, 2012	
	258.	U.S. Serial No. 13/526,161 Office Action mailed November 27, 2012	
	259.	U.S. Serial No. 13/526,163 Office Action mailed November 28, 2012	
	260.	U.S. Serial No. 13/607,036 Office Action mailed November 14, 2012	

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	261.	UCKUN et al. "Bruton's tyrosine kinase as a molecular target in treatment of leukemias and lymphomas as well as inflammatory disorders and autoimmunity." *Expert Opinion Ther. Patents* 2010, 20(11):1-14	
	262.	UCKUN, F.M., "Bruton's Tyrosine Kinase (BTK) as a Dual-Function Regulator of Apoptosis," Biochem. Pharmacology, 56:683-691 (1998)	
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	264.	UCKUN et al. "In Vivo Pharmacokinetic Features, Toxicity Profile, and Chemosensitizing Activity of α-Cyano-β-hydroxy-β-methyl-N-(2,5-dibromophenyl)propenamide (LFM-A13), a Novel Antileukemic Agent Targeting Bruton's Tyrosine Kinase," Clin. Cancer Res., 8:1224-1233 (2002)	
	265.	UCKUN et al. "The Anti-leukemic Bruton's Tyrosine Kinase Inhibitor α-cyano-β-hydroxy-β-mehyl-N-(2,5-dibromophenyl)Propenamide (LFM-A13) Prevents Fatal Thromboembolism," Leuk. Lymphoma, 44(9):1569-1577 (2003)	
	266.	VASSILEV, A.O. and UCKUN, F.M., "Therapeutic Potential of Inhibiting Bruton's Tyrosine Kinase, (BTK)," Current Pharmaceutical Design, 10:1757-1766 (2004)	
	267.	VASSILEV et al. "Bruton's Tyrosine Kinase as an Inhibitor of the Fas/CD95 Death-inducing Signaling Complex," J. Biol. Chem. 274(3):1646-1656 (1999)	
	268.	VIPPAGUNTA et al., "Crystalline Solids," Advanced Drug Delivery Reviews, 48:3-26 (2001)	
	269.	VOSE, J.M., "Mantle cell lymphoma: 2012 update on diagnosis, risk-stratification, and clinical management", Am. J. Hematol. 87(6):604-609 (June 2012)	
	270.	WILKINSON et al. "Selective tyrosine kinase inhibitors," Expert Opin. Emerging Drugs 5(3):287-297 (2000)	
	271.	WITZENS-HARIG et al. "Current treatment of mantle cell lymphoma: results of a national survey and consensus meeting", Ann Hematol. (Epub August 29, 2012), 91(11):1765-1772 (November 2012)	
	272.	WITZIG et al. "Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's lymphoma", J. Clin. Oncol. (Epub October 5, 2009), 27:5404-5409 (2009)	
	273.	WOLFF, M.E., "Burger's Medicinal Chemistry and Drug Discovery," 5th Ed. Part 1, pp. 975-977 (1995)	

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				Art Unit	1629
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	274.	YAMAMOTO et al. "The Orally Available Spleen Tyrosine Kinase Inhibitor 2-[7-(3,4-Dimethoxyphenyl)-imidazo[1,2-c]pyrimidin-5-ylamino]-nicotinamide Dihydrochloride (BAY61-3606) Blocks Antigen-Induced Airway Inflammation in Rodents," J. Pharma. And Exp. Therapeutics, 306(3):1174-1181 (2003)	
	275.	YASUHIRO et al. "ONO-WG-307, a Novel, Potent and Selective Inhibitor of Bruton's Tyrosine Kinase, in sustained inhibition of the Erk, Akt and PKD signaling pathways", 53rd American Society of Hematology Annual Meeting and Exposition, San Diego, CA, Poster #2021 (December 10-13, 2011)	
	276.	ZHU et al. "Calpain Inhibitor II Induces Caspase-dependent Apoptosis in Human Acute Lymphoblastic Leukemia and Non-Hodgkin's Lymphoma Cells as well as Some Solid Tumor Cells", Clin. Cancer Res. 6:2456-2463 (2000)	
	277.	EP 08744513.6 Examination Report dated 16 January 2013	
	278.	EP 12151943.3 Examination Report dated 05 February 2013	
	279.	EP 12172842.2 Partial Search Report dated 24 January 2013	
	280.	EP 12172843.0 Search Report and Written Opinion dated 18 January 2013	
	281.	U.S. Serial No. 13/341,695 Office Action mailed February 1, 2013	
	282.	U.S. Serial No. 13/003,811 Office Action mailed February 25, 2013	
	283.	CARRLE et al. "Current Strategies of Chemotherapy in Osteosarcoma", International Orthopaedics 30:445-451 (2006)	
	284.	MARINA et al. "Biology and Therapeutic Advances for Pediatric Osteosarcoma", The Oncologist 9:422-441 (2004)	
	285.	PICCI, P. "Osteosarcoma (Osteogenic Sarcoma)", Orphanet J. Rare Diseases 2(6):1-4 (2007)	
	286.	RITTER et al. "Osteosarcoma", Ann. Oncol. 21(Supplement 7):320-325 (2010)	
	287.	U.S. Serial No. 13/472,292 Office Action mailed March 13, 2013	
	288.	U.S. Serial No. 13/340,522 Office Action mailed March 13, 2013	
	289.	U.S. Serial No. 13/340,533 Final Office Action mailed February 25, 2013	

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	290.	PRNewswire, "Pharmacyclics, Inc. Announces Presentation of Interim Results from Phase I Trial of its First-in-Human Btk Inhibitor PCI-32765", December 7, 2009	
	291.	POLLYEA et al., "A Phase I Dose Escalation Study of the Btk Inhibitor PCI-32765 in Relapsed and Refractory B Cell Non-Hodgkin Lymphoma and Use of a Novel Fluorescent Probe Pharmacodynamic Assay", Poster Abstract #3713, 51st ASH Annual Meeting and Exposition (December 3, 2009)	
	292.	HIDDEMAN et al., "Rituximab Plus Chemotherapy in Follicular and Mantle Cell Lymphomas", Seminars in Oncology 30(1)Suppl.2:16-20 (February 2003)	
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	294.	AHN et al. "Michael acceptors as a tool for anticancer drug design", Current Pharmaceutical Design 2(3):247-262 (1996)	
	295.	U.S. Serial Number No. 13/312,606 Final Office Action mailed April 5, 2013	
	296.	U.S. Serial Number No. 13/404,422 Final Office Action mailed April 16, 2013	
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Electronic Acknowledgement Receipt	
EFS ID:	15798981
Application Number:	13869700
International Application Number:	
Confirmation Number:	4966
Title of Invention:	THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)
First Named Inventor/Applicant Name:	Joseph J. Buggy
Customer Number:	21971
Filer:	Michael J. Hostetler/Adriana Serrano/Alice Lee-Dutra
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	25922-819.306
Receipt Date:	16-MAY-2013
Filing Date:	
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Application Type:	Utility under 35 USC 111(a)

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket No. 25922-819.306
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: Joseph J. BUGGY, et al.	Group Art Unit: 1629
Serial Number: 13/869,700	Examiner: Not Yet Assigned
Filing Date: April 24, 2013	**CONFIRMATION NO: 4966**
Title: THE USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	

FILED ELECTRONICALLY ON: May 16, 2013

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.97

Madam:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP §609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in §1.56.

A. ☒ *37 CFR §1.97(b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under §1.53(d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in §1.491 in an international application;

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-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under §1.114.

B. ☐ *37 CFR §1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR §1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under §1.113, (2) a notice of allowance under §1.311, or (3) an action that otherwise closes prosecution on the merits, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97(e) provided concurrently herewith;

-- OR --

☐ a fee of $180.00 as set forth in §1.17(p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR §1.97(d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under §1.113 or (2) a notice of allowance under §1.311, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in §1.97(e);

-- AND --

ii. a fee of $180.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97(e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§1.97(d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e)(1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in a communication from a foreign patent office in a counterpart application that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98(a)(2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

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-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are NOT enclosed.

-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☒ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98(a)(2)(iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a)(3)(ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) Cite Nos. 85-297 were previously submitted in an Information Disclosure Statement, or cited by examiner, for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 13/153,317

Information Disclosure Statement(s) filed on: 5/3/2013, 2/15/2013, 8/5/2011

AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

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I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 23-2415 (Docket No. 25922-819.306).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI

Dated: May 16, 2013

By: /Michael Hostetler/
Michael J. Hostetler
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/869,700	04/24/2013	1629	800	25922-819.306	129	4

CONFIRMATION NO. 4966

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FILING RECEIPT

OC000000061524842

Date Mailed: 06/03/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Joseph J. Buggy, Mountain View, CA;
Laurence Elias, Berkeley, CA;
Gwen Fyfe, San Francisco, CA;
Eric Hedrick, Summit, NJ;
David J. Loury, San Jose, CA;
Tarak D. Mody, Sunnyvale, CA;

Applicant(s)

Joseph J. Buggy, Mountain View, CA;
Laurence Elias, Berkeley, CA;
Gwen Fyfe, San Francisco, CA;
Eric Hedrick, Summit, NJ;
David J. Loury, San Jose, CA;
Tarak D. Mody, Sunnyvale, CA;

Assignment For Published Patent Application

PHARMACYCLICS, INC., Sunnyvale, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/153,317 06/03/2011
which claims benefit of 61/351,130 06/03/2010
and claims benefit of 61/351,655 06/04/2010
and claims benefit of 61/351,793 06/04/2010
and claims benefit of 61/351,762 06/04/2010
and claims benefit of 61/419,764 12/03/2010
and claims benefit of 61/472,138 04/05/2011

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Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 05/24/2013
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/869,700**
Projected Publication Date: To Be Determined - pending completion of Missing Parts
Non-Publication Request: No
Early Publication Request: No
Title

USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

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community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13869700	

Applicant(s) Joseph Buggy

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
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	Indep	Depend	Indep	Depend	Indep	Depend
51		7				
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54		7				
55		1				
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58		1				
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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13869700	

Applicant(s) Joseph Buggy

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
101		1				
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Total Indep	4		0		0	
Total Depend	191	↵	0	↵	0	↵
Total Claims	195		0		0	

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/869,700	04/24/2013	Joseph J. Buggy	25922-819.306

CONFIRMATION NO. 4966

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

FORMALITIES LETTER

OC000000061524843

Date Mailed: 06/03/2013

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**280** to complete the basic filing fee for an undiscounted entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27) or make a certification of entitlement to micro entity status and pay the micro entity filing fee (37 CFR 1.29).*

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of $ **15200** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- A surcharge (for late submission of the basic filing fee, search fee, examination fee or inventor's oath or declaration) as set forth in 37 CFR 1.16(f) of $ **140** for an undiscounted entity, must be submitted.

SUMMARY OF FEES DUE:

Total fee(s) required within **TWO MONTHS** from the date of this Notice is $ **16940** for an undiscounted entity
- $ **280** Statutory basic filing fee.
- $ **140** Surcharge.
- The application search fee has not been paid. Applicant must submit $ **600** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $ **720** to complete the examination fee for an undiscounted entity.
- Total additional claim fee(s) for this application is $ **15200**
  - $ **420** for **1** independent claims over 3.
  - $ **14000** for **175** total claims over 20.

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• $ **780** for multiple dependent claim surcharge.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

• A properly executed inventor's oath or declaration has not been received for the following inventor(s):
All
Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/eggolla/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/869,700

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	195 minus 20 =	* 175			OR	x 80 =	14000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						800
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							780
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	17600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Inventor(s): Joseph J. BUGGY, et al. Serial No.: 13/869,700 Filed: April 24, 2013 Title: USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)	Group Art Unit: 1629 Examiner: Not Yet Assigned Confirmation No.: 4966 Customer No.: 021971 Certificate of Electronic Filing I hereby certify that the attached **Preliminary Amendment in Response to Notice to File Missing Parts** and all marked attachments are being deposited by Electronic Filing on August 5, 2013 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. By: /Lora Kim/ Lora Kim

Mail Stop Missing Parts
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS MAILED JUNE 3, 2013

Dear Madam:

Applicants hereby submit a response to the Notice to File Missing Parts of Non-Provisional Application mailed on June 3, 2013. This Response is being filed within the two-month statutory period for reply. Therefore, this response is timely filed and no fee should be due. Applicants respectfully request entry of the proposed amendments prior to examination and allowance of the pending claims.

Amendments to the Specification are on page **2**.

Amendments to the Claims begin on page **3**.

Remarks are on page **6**.

Conclusion is on page **7**.

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0001] on page 1 which currently reads:

[0001] The present application claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed June 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed June 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed December 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed April 5, 2011; all of which are herein incorporated by reference in their entirety.

With the following paragraph:

This application is a continuation of U.S. Application No. 13/153,317, filed June 3, 2011; which claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed June 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed June 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed December 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed April 5, 2011; all of which are herein incorporated by reference in their entirety.

Paragraph showing mark-up:

~~The present application~~ This application is a continuation of U.S. Application No. 13/153,317, filed June 3, 2011; which claims the benefit of priority from U.S. Provisional Patent Application No. 61/351,130, filed June 3, 2010; U.S. Provisional Patent Application No. 61/351,655, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,793, filed June 4, 2010; U.S. Provisional Patent Application No. 61/351,762, filed June 4, 2010; U.S. Provisional Patent Application No. 61/419,764, filed December 3, 2010; and U.S. Provisional Patent Application No. 61/472,138, filed April 5, 2011; all of which are herein incorporated by reference in their entirety.

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AMENDMENTS TO THE CLAIMS

This listing of claims replaces all prior versions and listing of claims in the above-referenced patent application. The following amendments do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Amendments to the claims were made for purposes of more clearly stating the claimed subject matter and do not add new matter or alter the scope of the claims. Deletions are denoted by [~~strikethrough~~] and additions are denoted by underline.

LISTING OF THE CLAIMS

1. – 60. (Cancelled)

61. (Currently Amended) A method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 300 mg/day up to, and including, 1000 mg/day.

62. (Currently Amended) The method of claim 61, wherein the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, ~~or~~ relapsed or refractory follicular lymphoma, relapsed or refractory chronic lymphocytic leukemia (CLL), relapsed or refractory small lymphocytic leukemia (SLL), or relapsed or refractory multiple myeloma.

63. (Cancelled)

64. (Original) The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is from 420 mg/day up to, and including, 840 mg/day.

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65. (Original) The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day, about 560 mg/day, or about 840 mg/day.

66. (Original) The method of claim 61, wherein the amount of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is about 420 mg/day.

67. (Original) The method of claim 61, wherein the AUC_{0-24} of (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is between about 150 and about 3500 ng*h/mL.

68. (Original) The method of claim 67, wherein AUC_{0-24} of the Btk inhibitor is between about 500 and about 1100 ng*h/mL.

69. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered orally.

70. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered once per day, twice per day, or three times per day.

71. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered until disease progression, unacceptable toxicity, or individual choice.

72. (Cancelled)

73. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is administered daily until disease progression, unacceptable toxicity, or individual choice.

74. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is

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administered every other day until disease progression, unacceptable toxicity, or individual choice.

75. (Original) The method of claim 61, wherein (R)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is a second line therapy, third line therapy, fourth line therapy, fifth line therapy, or sixth line therapy.

76. (Original) The method of claim 61, wherein the Btk inhibitor is a maintenance therapy.

77. – 129. (Cancelled)

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REMARKS

Amendment to the Specification

Applicants request entry of the amendment to the priority claim. No new matter is added by this amendment.

Amendments to the Claims

Claims 61 and 62 have been amended. Claims 1-60, 63, 72, and 77-129 have been cancelled. Applicants reserve the right to pursue the subject matter of the cancelled claims in this or any other appropriate patent application. Upon entry of the proposed claims, claims 61, 62, 64-71, and 73-76 will be under examination. Support for the amendments to the claims is found in the original claims and throughout the specification.

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CONCLUSION

Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned attorney at (858) 350-2300.

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. 23-2415, referencing Attorney Docket No. 25922-819.306.

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: August 5, 2013 By: /Michael Hostetler/
Michael J. Hostetler, Ph.D.
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Electronic Patent Application Fee Transmittal

Application Number:	13869700
Filing Date:	24-Apr-2013
Title of Invention:	USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)
First Named Inventor/Applicant Name:	Joseph J. Buggy
Filer:	Michael J. Hostetler/UT/ Lora Kim
Attorney Docket Number:	25922-819.306

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1740

Electronic Acknowledgement Receipt	
EFS ID:	16506859
Application Number:	13869700
International Application Number:	
Confirmation Number:	4966
Title of Invention:	USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)
First Named Inventor/Applicant Name:	Joseph J. Buggy
Customer Number:	21971
Filer:	Michael J. Hostetler/UT/ Lora Kim
Filer Authorized By:	Michael J. Hostetler
Attorney Docket Number:	25922-819.306
Receipt Date:	05-AUG-2013
Filing Date:	24-APR-2013
Time Stamp:	21:17:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1740
RAM confirmation Number	7307
Deposit Account	232415
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		25922_819306_ResponseToMissingParts_AUG052013.pdf	26415 1dbde3da9fa45e85afd0baf60a3b14077c7a5191	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Applicant Response to Pre-Exam Formalities Notice	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	36898 a16577d195ee497c6bd0ee6a504b468732bb58cf	no	2

Warnings:

Information:

Total Files Size (in bytes):	63313

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/869,700	04/24/2013	1629	2540	25922-819.306	14	1

CONFIRMATION NO. 4966

UPDATED FILING RECEIPT

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

OC000000063104856

Date Mailed: 08/09/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Joseph J. Buggy, Mountain View, CA;
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Gwen Fyfe, San Francisco, CA;
Eric Hedrick, Summit, NJ;
David J. Loury, San Jose, CA;
Tarak D. Mody, Sunnyvale, CA;

Applicant(s)

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Laurence Elias, Berkeley, CA;
Gwen Fyfe, San Francisco, CA;
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David J. Loury, San Jose, CA;
Tarak D. Mody, Sunnyvale, CA;

Assignment For Published Patent Application

PHARMACYCLICS, INC., Sunnyvale, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/153,317 06/03/2011
which claims benefit of 61/351,130 06/03/2010
and claims benefit of 61/351,655 06/04/2010
and claims benefit of 61/351,793 06/04/2010
and claims benefit of 61/351,762 06/04/2010
and claims benefit of 61/419,764 12/03/2010
and claims benefit of 61/472,138 04/05/2011

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Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 05/24/2013
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/869,700**
Projected Publication Date: 11/21/2013
Non-Publication Request: No
Early Publication Request: No
Title

USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

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community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/869,700	04/24/2013	Joseph J. Buggy	25922-819.306

CONFIRMATION NO. 4966

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

NOTICE

OC000000063104857

Date Mailed: 08/09/2013

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  All
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/869,700

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	14 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						800
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	2400

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/869,700	04/24/2013	Joseph J. Buggy	25922-819.306

CONFIRMATION NO. 4966

21971
WILSON, SONSINI, GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

PUBLICATION NOTICE

Title:USE OF INHIBITORS OF BRUTON'S TYROSINE KINASE (BTK)

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PTO/SB/08a (07-09)
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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
				Examiner Name	RAMACHANDRAN, Umamaheswari
Sheet	1	of	13	Attorney Docket Number	25922-819.306

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1.	US-2007-0105136	5/10/2007	Staudt et al.	
	2.	US2014-0039186	2/6/2014	Honigberg et al.	
	3.	US-2012-0108547	5/3/2012	Jankowski, et al.	
	4.	US-2010-0016296	1/21/2010	Singh et al.	
	5.	US-2010-0185419	7/22/2010	Singh et al.	
	6.	US2014-0057907	2/27/2014	Honigberg et al.	

U.S. UNPUBLISHED PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Filing Date MM-DD-YYYY	Name of Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	7.	US-13/965,135	8/12/2013	Buggy et al.	
	8.	US-14/033,344	9/20/2013	Honigberg et al.	
	9.	US-14/073,543	11/6/2013	Honigberg et al.	
	10.	US-14/073,594	11/6/2013	Honigberg et al.	
	11.	US-14/079,508	11/14/2013	Honigberg et al.	
	12.	US-14/080,640	11/14/2013	Honigberg et al.	
	13.	US-14/080,649	11/14/2013	Honigberg et al.	
	14.	US-14/152,886	1/10/2014	Honigberg et al.	
	15.	US-14/156,247	1/15/2014	Honigberg et al.	
	16.	US-14/188,390	2/24/2014	Buggy et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] – Number[4] – Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	17.	WO-2006-071017	7/6/2006	Hanmi Science Co., Ltd.		

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	18.	U.S. Serial Number No. 13/526,161 Final Office Action mailed May 15, 2013	
	19.	U.S. Serial Number No. 13/526,163 Final Office Action mailed May 15, 2013	
	20.	U.S. Serial Number No. 13/249,066 Final Office Action mailed May 15, 2013	
	21.	EP 12172842.2 Extended Search Report dated 14 May 2013	
	22.	U.S. Serial Number No. 13/341,695 Final Office Action mailed June 7, 2013	
	23.	U.S. Serial Number No. 13/439,775 Final Office Action mailed June 17, 2013	
	24.	U.S. Serial Number No. 13/607,036 Final Office Action mailed June 24, 2013	
	25.	U.S. Serial Number No. 12/594,805 Final Office Action mailed June 27, 2013	
	26.	U.S. Serial Number No. 13/153,291 Office Action mailed July 5, 2013	
	27.	GORDON et al. "Somatic hypermutation of the B cell receptor genes B29 (Igβ, CD79b) and mb1 (Igα, CD79a)," PNAS 100(7):4126-4131 (2003)	
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	29.	FRIEDBERG et al. "Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia," Blood 115(13):2578-2585 (2010) [E-pub November 17, 2009]	
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	31.	KUGLSTATTER et al. "Insights into the conformational flexibility of Bruton's tyrosine kinase from multiple ligand complex structures," Protein Science 20(2):428-436 (2011) [E-pub December 17, 2010]	
	32.	DAVIS et al. "Chronic active B-cell receptor signalling in diffuse large B-cell lymphoma," Nature 463(7277):88-92 (2010)	
	33.	YANG et al. "Tyrosine kinase inhibition in diffuse large B-cell lymphoma: molecular basis for antitumor activity and drug resistance of dasatinib," Leukemia 22(9):1755-	

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		1766 (2008) [E-pub July 3, 2008]	
	34.	U.S. Serial Number No. 13/361,726 Office Action mailed July 18, 2013	
	35.	U.S. Serial Number No. 13/340,409 Office Action mailed July 19, 2013	
	36.	U.S. Serial Number No. 13/153,317 Office Action mailed July 29, 2013	
	37.	ADVANI et al. "Effect of Btk inhibitor PCI-32765 monotherapy on responses in patients with relapsed aggressive NHL: Evidence of antitumor activity from a phase I study." J. Clin. Oncol., 2010 ASCO Annual Meeting Proceedings (Post-Meeting Edition), 28(15 Supp):8012 (2010)	
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	41.	Science Daily "Counting tumor cells in blood predicts treatment benefit in prostate cancer." (July 7, 2008), http://www.sciencedaily.com/releases/2008/07/080706083142.htm , last accessed July 23, 2013	
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	46.	U.S. Serial Number No. 13/526,163 Office Action mailed August 2, 2013	
	47.	U.S. Serial Number No. 12/907,759 Office Action mailed August 13, 2013	

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	48.	U.S. Serial Number No. 13/479,053 Office Action mailed September 6, 2013	
	49.	U.S. Serial Number No. 13/340,276 Office Action mailed September 10, 2013	
	50.	U.S. Serial Number No. 13/003,811 Final Office Action mailed October 11, 2013	
	51.	U.S. Serial Number No. 13/542,440 Non-Final Office Action mailed October 31, 2013	
	52.	U.S. Serial Number No. 13/450,158 Non-Final Office Action mailed October 31, 2013	
	53.	U.S. Serial Number No. 13/606,949 Non-Final Office Action mailed October 29, 2013	
	54.	U.S. Serial Number No. 13/340,522 Final Office Action mailed November 1, 2013	
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	64.	PRNewswire, "Update on Preclinical Finding and Development Timeline for PCI-45292", March 2, 2011	
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	68.	Science Daily "Drug shows surprising efficacy as treatment for chronic leukemia, mantle cell lymphoma." (June 19, 2013), http://www.sciencedaily.com/releases/2013/06/130619195217.htm, last accessed January 30, 2014	
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	75.	U.S. Serial Number No. 13/439,775 Office Action mailed March 6, 2014	
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	79.	CHANG et al. "Egress of $CD19^{+}CD5^{+}$ cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor inbrutinib in mantel cell lymphoma patients", Blood, 122:2412-2424 (2013).	
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	82.	Ohio State University Comprehensive Cancer Center. PCI-32765 (Ibrutinib) in treating patients with relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, or B-cell prolymphocytic leukemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Apr 23- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01589302 NLM Identifier: NCT01589302.	
	83.	Janssen Research and Development, LLC. A study of PCI-32765 (Ibrutinib) in patients with refractory follicular lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jan 25- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01779791 NLM Identifier: NCT01779791.	
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	86.	Janssen Research and Development, LLC. A study to assess the effect of ketoconazole on the pharmacokinetics of ibrutinib in healthy participants. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Jun 18- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01626651 NLM Identifier: NCT01626651.	
	87.	Janssen Research and Development, LLC. A study on the Bruton's tyrosine kinase inhibitor, PCI-32765 (Ibrutinib), in combination with rituximab,	

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Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(Use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
				Examiner Name	RAMACHANDRAN, Umamaheswari
Sheet	7	of	13	Attorney Docket Number	25922-819.306

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		cyclophosphamide, doxorubicin, vincristine, and prednisone in patients with newly diagnosed non-germinal center B-cell subtype of diffuse large B-cell lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 May 14- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01855750 NLM Identifier: NCT01855750.	
	88.	Janssen Research and Development, LLC. A pharmacokinetic study in healthy participants to assess the pharmacokinetics and safety of a supratherapeutic dose of PCI-32765 (Ibrutinib) capsule and solution formulations administered with food. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Aug 19- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01969266 NLM Identifier: NCT01969266.	
	89.	National Center Institute (NCI). Lenalidomide and Ibrutinib in treating patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jun 24- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01886859 NLM Identifier: NCT01886859.	
	90.	Janssen Research and Development, LLC. A study to determine the effect of food on the pharmacokinetics of PCI-32765. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Mar 04- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01820936 NLM Identifier: NCT01820936.	
	91.	Janssen Research and Development, LLC. A study combining Ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in patients with CD20-positive B-cell non Hodgkin lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Mar 30- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01569750 NLM Identifier: NCT01569750.	
	92.	National Cancer Institute (NCI). Rituximab, lenalidomide, and ibrutinib in treating patients with previously untreated stage II-IV follicular lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Apr 09- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01829568 NLM Identifier: NCT01829568.	

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				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
				Examiner Name	RAMACHANDRAN, Umamaheswari
Sheet	8	of	13	Attorney Docket Number	25922-819.306

NON PATENT LITERATURE DOCUMENTS			
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	93.	Janssen Research and Development, LLC. A study of PCI-32765 (Ibrutinib) in combination with either bendamustine and rituximab or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in patients with previously treated indolent non-Hodgkin lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Oct 28- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01974440 NLM Identifier: NCT01974440.	
	94.	Janssen Research and Development, LLC. A study of the Bruton's tyrosine kinase inhibitor PCI-32765 (Ibrutinib) versus rituximab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Oct 25- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01973387 NLM Identifier: NCT01973387.	
	95.	Pharmacyclics, Inc. Study of the Bruton's tyrosine kinase inhibitor in combination with carfilzomib (Kyprolis), in subjects with relapsed or relapsed and refractory multiple myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Sept 27- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01962792 NLM Identifier: NCT01962792.	
	96.	Dana-Farber Cancer Institute. Ibrutinib (PCI-32765) in Waldenstrom's Macroglobulinemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 May 17- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01614821 NLM Identifier: NCT01614821.	
	97.	National Cancer Institute (NCI). Ibrutinib in treating patients with relapsed or refractory follicular lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 May 06- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01849263 NLM Identifier: NCT01849263.	
	98.	National Cancer Institute (NCI). Lenalidomide and ibrutinib in treating patients with relapsed or refractory B-Cell non-Hodgkin lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Sept 27- [cited 2013 Nov 22]. Available from:	

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				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
				Examiner Name	RAMACHANDRAN, Umamaheswari
Sheet	9	of	13	Attorney Docket Number	25922-819.306

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		http://clinicaltrials.gov/ct2/show/NCT01955499 NLM Identifier: NCT01955499.	
	99.	M.D. Anderson Cancer Center. Pilot study to determine effects of the Btk inhibitor PCI-32765 on leukemia cell kinetics and trafficking, using heavy water labeling in subjects with CLL and SLL. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Dec 13- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01752426 NLM Identifier: NCT01752426.	
	100.	Janssen Research and Development, LLC. A study to evaluate the efficacy and safety of ibrutinib, in patients with mantel cell lymphoma who progress after bortezomib therapy. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 May 14- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01599949 NLM Identifier: NCT01599949.	
	101.	Pharmacyclics, Inc. Study of the Bruton's tyrosine kinase inhibitor in combination with rituximab in previously untreated subjects with follicular lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Oct 24- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01980654 NLM Identifier: NCT01980654.	
	102.	Janssen Research and Development, LLC. A study of ibrutinib in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 May 15- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01611090 NLM Identifier: NCT01611090.	
	103.	M.D. Anderson Cancer Center. Phase 2 ibrutinib + rituximab in relapsed/refractory mantel cell lymphoma (R/R MCL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jun 14- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01880567 NLM Identifier: NCT01880567.	
	104.	Pharmacyclics, Inc. A phase 3 study of ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (RESONATE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Apr 11- [cited 2013 Nov 22]. Available	

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				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
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		from: http://clinicaltrials.gov/ct2/show/NCT01578707 NLM Identifier: NCT01578707.	
	105.	Janssen Research and Development, LLC. Study of ibrutinib (a Bruton's tyrosine kinase inhibitor), versus temsirolimus in patients with relapsed or refractory mantel cell lymphoma who have received at least one prior therapy. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Jul 18- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01646021 NLM Identifier: NCT01646021.	
	106.	Janssen Biotech, Inc. An open label treatment use protocol for ibrutinib in subjects with relapsed or refractory mantel cell lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Apr 06- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01833039 NLM Identifier: NCT01833039.	
	107.	Janssen Research and Development, LLC. A study of the Bruton's tyrosine kinase inhibitor ibrutinib given in combination with bendamustine and rituximab in patients with newly diagnosed mantel cell lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jan 24- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01776840 NLM Identifier: NCT01776840.	
	108.	National Cancer Institute (NCI). Ibrutinib in treating patients with relapsed hairy cell leukemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Apr 24- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01841723 NLM Identifier: NCT01841723.	
	109.	Janssen Research and Development, LLC. A study to assess the effect of rifampin on the pharmacokinetics of PCI-32765 in healthy participants. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jan 4- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01763021 NLM Identifier: NCT01763021.	
	110.	Pharmacyclics, Inc. A multicenter phase 2 study of PCI-32765 (Ibrutinib) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with 17p deletion. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Dec 03- [cited 2013	

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				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
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Sheet	11	of	13	Attorney Docket Number	25922-819.306

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		Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01744691 NLM Identifier: NCT01744691.	
	111.	Janssen Research and Development, LLC. A study to evaluate the pharmacokinetics of PCI-32765 in participants with varying degrees of hepatic impairment. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Jan 09- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01767948 NLM Identifier: NCT01767948.	
	112.	Ohio State University Comprehensive Cancer Center. Rituxan/Bendamustine/PCI-32765 in relapsed DLBCL, MCL, or indolent non-Hodgkin's lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 Nov 01- [cited 2014 Feb 6]. Available from: http://clinicaltrials.gov/ct2/show/NCT01479842 NLM Identifier: NCT01479842.	
	113.	Janssen Pharmaceutical K.K. A study to evaluate the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with recurrent mature B-cell neoplasms. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2012 Oct 09- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01704963 NLM Identifier: NCT01704963.	
	114.	Pharmacyclics, Inc. Study of the Bruton's tyrosine kinase inhibitor in subjects with relapsed/refractory marginal zone lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Oct 29- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01980628 NLM Identifier: NCT01980628.	
	115.	Pharmacyclics, Inc. Safety of PCI-32765 in chronic lymphocytic leukemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 Apr 13- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01105247 NLM Identifier: NCT01105247.	
	116.	National Heart, Lung, and Blood Institute (NHLBI). PCI-32765 for special cases of chronic lymphocytic leukemia or small lymphocytic lymphoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011 Dec 22- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01500733 NLM Identifier: NCT01500733.	
	117.	National Cancer Institute (NCI). A multicenter phase 2 study of the Bruton's	

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BeiGene Exhibit 1023.316

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				Application Number	13/869,700
				Filing Date	April 24, 2013
				First Named Inventor	Joseph J. BUGGY
				Art Unit	1627
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		tyrosine kinase inhibitor PCI-32765 for treatment of relapsed hairy cell leukemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013 Nov 2- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01981512 NLM Identifier: NCT01981512.	
	118.	Pharmacyclics, Inc. Safety and efficacy of PCI-32765 in subjects with relapsed/refractory mantel cell lymphoma (MCL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2010 Oct 18- [cited 2013 Nov 22]. Available from: http://clinicaltrials.gov/ct2/show/NCT01236391 NLM Identifier: NCT01236391.	
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(54) Title: QUINAZOLINE DERIVATIVES FOR INHIBITING CANCER CELL GROWTH AND METHOD FOR THE PREPARATION THEREOF

(57) Abstract: The present invention relates to a novel quinazoline derivative and a pharmaceutically acceptable salt thereof for inhibiting the growth of cancer cells, a method for the preparation thereof and a pharmaceutical composition comprising same as an active ingredient.

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QUINAZOLINE DERIVATIVES FOR INHIBITING CANCER CELL GROWTH AND METHOD FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to a novel quinazoline derivative and a pharmaceutically acceptable salt thereof for inhibiting the growth of cancer cells, a method for the preparation thereof and a pharmaceutical composition comprising same as an active ingredient.

Background of the Invention

Most of the traditional drugs used for treating cancers, e.g., taxanes such as paclitaxel and doxetaxel; vinca alkaloid such as vincristine, vinblastine and vinorelbin; anthracyclines such as daunomycin and doxorubicin; camptothecins such as topotecan, irinotecan; actinomycin; and etopocid are based on selective cytotoxicity, but such selectivity against cancer cells has been unsatisfactory to cause many side effects.

To overcome such a problem, recent studies have focused on specific molecular level targets in the cell to maximize the therapeutic effect of an anticancer agent without causing adverse side effects.

In cells, there are many signal transduction systems, which are fuctionally linked to each other to control the proliferation, growth, metastasis and apoptosis of cells. A breakdown of the intracellular controlling system by genetic and environmental influences may cause abnormal amplification or destruction of the signal transduction system so that the possibility for tumor cell generation occurs.

Protein tyrosine kinases play important roles in such cellular regulation, and their abnormal expression or mutation has been observed in cancer cells. Protein tyrosine kinase is an enzyme which catalyzes the transportation of phosphate groups from ATP to tyrosines located on the protein substrate. Many growth factor receptor proteins function as tyrosine kinases to transport

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cellular signals. The interaction between growth factors and their receptors normally controls the cellular growth, but abnormal signal transduction caused by the mutation or overexpression of any of the receptors may induce tumor cells or cancers.

Protein tyrosine kinases have been classified into many families in terms of growth factors, and epithelial cell growth factors (EGFs)-related EGF receptor (EGFR) tyrosine kinase have been intensely studied. An EGFR tyrosine kinase is composed of a receptor and tyrosine kinase, and delivers extracellular signals to the cell nuclear through the cellular membrane. The EGFR tyrosine kinases are classified by their structural differences into EGFR (Erb-B1), Erb-B2, Erb-B3, Erb-B4, and all of the above members can form a homodimer- or heterodimer- signal delivery complex. Also, overexpression of more than one member of the above mentioned homodimers is often observed in malignant cells.

Therefore, the inhibition of mutated or overexpressed EGFR tyrosine kinases has been considered to be useful for treating tumors, and many drugs have been developed therefor, e.g., Gefitinib, Erlotinib, Carnertinib, Lapatinib.

International Patent Publications WO 96/033981, WO 96/033979, WO 97/038994 and WO 96/033980 each discloses a quinazoline derivative substituted with an alkoxyalkylamino or alkylaminoalkoxy group, International Patent Publications WO 97/030034 and WO 96/016960 each discloses quinazoline substituted with aryl or heteroaryl, and International Patent Publications WO 2003/040109 and WO 2003/040108 disclose compounds having aminoalkoxy substituents at position 5 of quinazoline (Normaclature of quinazoline is according to a reference [J.A. Joule, Chapman & Hall, *Heterocyclic chemistry*, 3rd Ed., 189]).

International Patent Publication WO 95/019970 and United States Patents 5,654,307 and 5,679,683 each discloses various tricyclic heteroarylcompounds, International Patent Publications WO 99/006396, WO 99/006378, WO 97/038983, WO 2000/031048, WO 98/050038, WO 99/024037 and WO 2000/006555, and European Patent 787722 each discloses quinazoline compounds that inhibit the tyrosine kinase irreversably, United States Patent 6,225,318, European Patents 0387063 and 01292591, and International Patent

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Publications WO 2001/098277, WO 2003/045939 and WO 2003/049740 each discloses compounds having various alkenyl or alkynyl substituents at position 6 of quinazoline.

Also, International Patent Publications WO 98/043960, WO 2000/018761, WO 2001/047892, WO 2001/072711, WO 2003/050090, WO 99/09016, WO 2000/018740 and WO 2000/66583 disclose 3-cyanoquinoline compounds, International Patent Publications WO 98/002434, WO 98/002437, WO 99/035132, WO 99/035146, WO 2001/004111 and WO 2002/002552 each discloses various quinazoline compounds substituted with furan having various sulfonealkylamino substituents, and International Patent Publications WO 2003/053466 and WO 2001/094353 disclose specific thienopyrimidine compounds.

Further, International Patent Publications WO 2001/012227, WO 2004/014386, WO 2004/035057 and WO 2001/076586 disclose various methods for treating tumors that employ specific drugs that interact with EGFR tyrosine kinase in combination with radiation therapy.

However, the above mentioned conventional quinazoline derivatives have to be taken in large dose for intended treatments, which causes such side effects such as diarrhea and skin eruption. Accordingly, there has continued to exist a need to develop an effective drug that gives no adverse side effect.

Summary of the Invention

Accordingly, it is an object of the present invention to provide a novel quinazoline derivative which selectively inhibits the cancer cell growth caused by epitherial growth factor without any side effects, and a method for the preparation thereof.

It is another object of the present invention to provide a phamarceutical composition for inhibiting cancer cell growth comprising the quinazoline derivative as an active ingredient.

In accordance with one aspect of the present invention, there is provided a quinazoline derivative of formula (I) or a pharmaceutically acceptable salt

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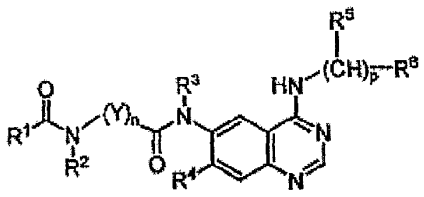
thereof:



(I)

wherein,

R^1 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, aryl or heteroaryl which is optionally substituted with X;

R^2 and R^3 are each independently hydrogen, hydroxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, hydroxyC_{1-5}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or C_{1-6}dialkylaminoC_{1-6}alkyl;

Y is $-(CR^{11}R^{12})-$, aryl or heteroaryl, R^{11} and R^{12} being each independently hydrogen, halogen, hydroxy, amino, nitro, cyano, thiol, carboxylic acid, carbamoyl; C_{1-6}alkyl, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkyloxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkanoyloxy, C_{1-6}alkyloxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkyl or C_{1-6}dialkylureido, C_{1-6}alkyl, C_{1-6}dialkylguanidino, aryl, or heteroaryl which is optionally substitutied with substituent Z; or optionally fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring;

R^4 is hydrogen, halogen, hydroxy, amino, or C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkylamino optionally substituted with R^{13}, R^{13} being halogen, cyano, trifluoromethyl, trifluoromethoxy, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-5}dialkylamino, aryl or heteroaryl);

R^5 is hydrogen or C_{1-3}alkyl;

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R^6 is R^{14}, aryl or heteroaryl optionally substituted with R^{15}, R^{14} and R^{15} being each independently hydrogen, halogen, trifluoromethyl, trifluoromethoxy, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, or aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylalkoxy, heteroarylalkoxy, aryloxy, heteroaryloxy, aryloxycarbonyl, heteroaryloxycarbonyl, arylcarbonyl, heteroarylcarbonyl, arylcarbamoyl, heteroarylcarbamoyl, arylsulfonyl or heteroarylsulfonyl optionally substituted with R^{16}, wherein R^{16} is halogen, nitro, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino or C_{1-6}dialkylamino;

n is an integer in the range of 1 to 6;

p is 0 or 1;

X and Z are each independently hydrogen, halogen, nitro, hydroxy, amino, cyano, thiol, carboxylic acid, carbamoyl, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, C_{1-6}alkylcarbonyl, C_{1-6}alkylthiocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbamoyl, C_{1-6}dialkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkoxycarbonyloxy, C_{1-6}alkylaminocarbonyloxy, C_{1-6}dialkylaminocarbonyloxy, C_{1-6}alkylthiocarbonyloxy, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkylureido, C_{1-6}dialkylureido, C_{1-6}alkylguanidino, C_{1-6}dialkylguanidino, C_{1-6}alkoxysulfonyl, C_{1-6}alkylaminosulfonyl, C_{1-6}dialkylaminosulfonyl, C_{1-6}alkylsulfamoyl, C_{1-6}alkylaminosulfamoyl, C_{1-6}dialkylaminosulfamoyl, aryl or heteroaryl; wherein

aryl is C_{5-12} monocylic or bicyclic aryl;

heteroaryl is a 5 to 13-membered heteroaromatic or non-aromatic group containing one or more of the elements selected from the group consisting of N, O, S, SO and SO_2; and

The optionally substituted aryl and heteroaryl each has one or more substituents selected from the group consisting of halogen, hydroxy, amino, nitro, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylamino and C_{1-6}dialkylamino.

Detailed Description of the Invention

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In the quinazoline derivative of formula (I) of the present invention, R^1 is preferably methyl, cyclopropyl, trifluoromethyl, cyanomethyl, chloromethyl, phenyl, methoxy, phenoxy, benzyloxy, methoxymethyl, acetoxymethyl, dimethylaminoethoxymethyl, methoxyethoxymethyl, methylthiomethyl, methanesulfinylmethyl, methanesulfonylmethyl, dimethylaminomethyl, morpholinomethyl, 4-methylpiperazinylmethyl, methanesulfonylethylaminomethyl, methoxyethylaminomethyl, ethoxycarbonyl, ethylamino, furan-3-yl, furan-2-yl-methylamino, benzamino, benzylamino, *t*-buthoxy, 3-methyl-isoxazol-5-yl, 5-methyl-isoxazol-4-yl, 1*H*-pyrazol-4-yl, vinyl, penta-1,3-dienyl, cyclopentenyl, 2-phenylvinyl, 2-methylvinyl, 2,2-dimethylvinyl, 1-methylvinyl, 2-phenylethynyl, 2-methylethynyl, 2-(bromomethyl)vinyl, 2-(dimethylaminomethyl)vinyl, 2-(morpholinomethyl)vinyl, 2-(4-methylpiperazinylmethyl)vinyl, 2-((*N*-methyl-(2-hydroxyethyl)amino)methyl)vinyl or 2-(methanesulfonylethylaminomethyl)vinyl;

R^2 and R^3 are preferably each independently hydrogen, methyl, ethyl or 3-(*N,N*-dimethylamino)propyl;

R^4 is preferably hydrogen, amino, hydroxyl, fluoro, chloro, methoxy, ethoxy, methoxyethoxy, methoxypropoxy, ethylsulfanyl, cyclopropylmethoxy, cyclopentyloxy, 2,2,2-trifluoroethoxy, 2-fluoroethoxy, *N,N*-dimethylamino, morpholinopropoxy or 4-methylpiperadinylmethoxy;

R^5 is preferably hydrogen;

R^6 is preferably 1-phenyl-ethyl, 3-ethynyl-phenyl, biphenyl, 3-chloro-4-fluoro-phenyl, 3-chloro-4-(3-fluoro-benzyloxy)-phenyl, 3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl, 4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenyl, *N*-phenyl-benzamid-4-yl, 3-chloro-4-(pyridin-2-ylmethoxy)-phenyl, 3-chloro-4-(pyridin-3-ylmethoxy)-phenyl, 3-chloro-4-(6-methyl-pyridin-2ylmethoxy)-phenyl, 3-chloro-4-(pyridin-4-ylmethoxy)-phenyl, 3-methyl-4-(pyridin-2-ylmethoxy)-phenyl, 1-pyridin-2-ylmethyl-1*H*-indazol-5-yl, 1-(3-fluoro-benzyl)-1*H*-indazol-5-yl, 1-penta-2,4-dienyl-1*H*-indazol-5-yl, 3-chloro-4-(2-fluoroethoxy)-phenyl, 2-methyl-1*H*-indol-5-yl or 1-benzyl-1*H*-indazol-5-yl;

Y is preferably -($CR^{11}R^{12}$)-, aryl or heteroaryl, R^{11} and R^{12} being each

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independently hydrogen, amino, hydroxyl, halogen, C_{1-6}alkyl, C_{1-3}alkenyl, C_{1-6}alkylC_{1-6}alkyl, hydroxylC_{1-3}alkyl, diC_{1-3}alkylaminoC_{1-3}alkyl, C_{1-3}alkoxyC_{1-3}alkyl, C_{1-3}alkylsulfonylC_{1-3}alkyl, C_{1-3}alkylsulfinylC_{1-3}alkyl, C_{1-3}alkylsulfanylC_{1-3}alkyl, carboxyC_{1-3}alkyl, C_{1-3}alkoxycarbonylC_{1-3}alkyl, diC_{1-3}alkylamino, C_{1-3}alkoxy, C_{1-6}alkanoyloxy, C_{1-6}alkylcarbamoyl, aryl, heteroaryl, or C_{1-3}alkylsubstitutied with aryl or heteroaryl, the aryl or heteroaryl is phenyl, naphtyl, furan, thiophene, imidazole, triazole, pyridine, oxazole, isoxazole, thiazole, indole, quinoline, isoquinoline, quinazoline, aziridine, azetidine, pyrrolidine, piperidine, morpholine, piperazine, thiomorpholine or 4-pyridone, or optionally fused to each other to form a 3 to 8-membered non-aromatic ring, or R^{11} or R^{12} may be fused to R^2 or R^3 to form together with the carbon and nitrogen they are attached to a 4 to 8-membered non-aromatic ring; and

Preferable n is an integer in the range of 1 to 4.

In the present invention, the term 'halo' refers to fluoro, chloro, bromo or iodo, unless otherwise indicated.

In the present invention, the term 'alkyl' refers to a monovalent saturated hydrocarbon compound having linear, circular or branced residue, 'alkenyl' and 'alkynyl' refer to the said alkylcompound having carbon-carbon double bond and triple bond, respectively, when the alkyl is composed of 2 or more carbon atoms.

In the present invention, the term 'alkoxy' refers to an oxygen derivative of the said alkyl, unless otherwise indicated.

In the present invention, the term 'aryl' refers to an aromatic hydrocarbon such as phenyl or naphtyl, unless otherwise indicated.

Examples of more preferred compounds of formula (I) according to the present invention are:

1) ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester;

2) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide;

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3) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methanesulfonyl-acetamide;

4) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

5) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide;

6) (1*S*)-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-3-methanesulfanyl-propyl)-carbamic acid *t*-butylester;

7) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide;

8) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methanesulfonyl-acetamino)-4-methanesulfanyl-butyramide;

9) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide;

10) (1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-cyclopropyl)-carbamic acid *t*-butylester;

11) (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-2-phenyl-acetamide;

12) (4*S*)-4-*t*-buthoxycarbonylamino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester;

13) 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester;

14) 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid;

15) 2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester;

16) 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

17) 1-(2-methanesulfonyl-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

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18) 1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

19) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

20) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

21) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

22) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

23) 3-phenyl-propionylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

24) hexa-2,4-dienonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

25) cyclopent-1-en carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

26) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-3-phenyl-acrylamide;

27) but-2-ynoylic acid(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

28) but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

29) 3-methyl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

30) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-methyl-acrylamide;

31) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-cyano-acetamide;

32) 3-methyl-isoxazol-5-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

33) furan-3-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

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34) 1*H*-pyrazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

35) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-benzamide;

36) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-oxalamic acid ethylester;

37) cyclopropylcarboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

38) acetic acid 2-*t*-buthoxycarbonylamino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester;

39) acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester;

40) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-hydroxyl-3-(2-methoxy-acetylamino)-propionamide;

41) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

42) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide;

43) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-2-methyl-propionamide;

44) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-acrylamide;

45) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-1-phenyl-ethyl)-carbamic acid *t*-butylester;

46) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide;

47) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-3-phenyl-propionamide;

48) 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

49) (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester;

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50) 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

51) *N*-(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

52) {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

53) *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

54) *N*-{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

55) 4-bromo-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

56) 4-dimethylamino-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

57) 4-morpholin-4-yl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

58) 4-(4-methyl-piperazin-1-yl)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

59) 4-[(2-hydroxyl-ethyl)-methyl-amino]-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

60) 4-(2-methanesulfonyl-ethylamino)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

61) 3-(2-chloro-acetylamide)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

62) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

63) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-dimethylamino-acetylamino)-propionamide;

64) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

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65) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethylamino)-acetylamino]-propionamide;

66) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-propionamide;

67) 3-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

68) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide;

69) 3-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

70) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide;

71) 3-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-methylamino]-quinazolin-6-yl}-propionamide;

72) 3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

73) *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

74) 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide;

75) *N*-{2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

76) *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide;

77) {2-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

78) *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

79) *N*-{2-[4-(1-benzyl-1*H*-imidazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

80) {2-[4-(4-phenylcarbamoyl-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester;

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81) 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide;

82) 4-[6-(3-acryloylamino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide;

83) *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide;

84) *N*-{2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

85) *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

86) (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester;

87) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide;

88) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfonyl-acetylamino)-butyramide;

89) 4-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

90) *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-benzamide;

91) *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-oxalamic acid ethylester;

92) cyclopropylcarboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

93) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-cyano-acetylamino)-butyramide;

94) furan-3-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

95) 1*H*-pyrazol-4-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide;

96) {3-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-propyl}-carbamic acid *t*-butylester;

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97) *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide;

98) 4-acryloylamino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide;

99) (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbonyl}-propyl)-carbamic acid *t*-butylester;

100) 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

101) 4-acryloylamino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

102) 4-(2-chloro-acetylamino)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

103) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

104) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-dimethylamino-acetylamino)-butyramide;

105) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

106) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methoxy-ethylamino)-acetylamino]-butyramide;

107) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-butyramide;

108) 4-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

109) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide;

110) 4-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

111) *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide;

112) 4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

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113) 4-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide;

114) (4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyl)-carbamic acid *t*-butylester;

115) 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide;

116) 5-(2-methanesulfonyl-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-pentylamino]-quinazolin-6-yl}-amide;

117) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfanyl-acetylamino)-propionamide;

118) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfinyl-acetylamino)-propionamide;

119) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2,2,2-trifluoro-acetylamino)-propionamide;

120) 3-acetylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide;

121) acetic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylcarbamoyl)-methylester;

122) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-dimethylamino-ethoxy)-acetylamino]-propionamide;

123) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-ethyl-ureido)-propionamide;

124) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-phenyl-ureido)-propionamide;

125) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-furan-2-ylmethyl-ureido)-propionamide;

126) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid methylester;

127) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid phenylester;

128) (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid benzylester;

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129) *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

130) *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

131) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

132) *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide;

133) *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide;

134) *N*-(2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

135) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethoxy)-acetylamino]-propionamide;

136) 5-methyl-isoxazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide;

137) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfanyl-acetylamino)-butyramide;

138) *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfinyl-acetylamino)-butyramide;

139) *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide;

140) *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-ethyl-carbamoyl)-ethyl]-acrylamide;

141) *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide;

142) *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

143) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide;

144) *N*-(2-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

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145) (2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

146) (2*S*)-1-(1-oxo-butyn-2-yl)-pyrrolidin-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

147) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

148) (3*R*,5*S*)-acetic acid 1-acryloyl-5-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidin-3-ylester;

149) (2*S*,4*R*)-1-acryloyl-4-hydroxyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

150) (2*S*,4*R*)-1-acryloyl-4-ethylsulfanyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

151) (2*S*,4*R*)-1-acryloyl-4-dimethylamino-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

152) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

153) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

154) 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-acetamide;

155) 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

156) 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

157) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-amide;

158) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-ethynyl-phenylamino)-quinazolin-6-yl]-amide;

159) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-amide;

160) (2*S*,4*R*)-1-acryloyl-4-ethanesulfonyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

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161) (2*S*,4*R*)-1-acryloyl-4-methoxy-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

162) 1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

163) 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

164) 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

165) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

166) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

167) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

168) (2*S*)-1-acryloyl-pyrrolidin-2-carboxylic acid {7-methoxy-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

169) 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide;

170) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

171) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethylsulfanyl-quinazolin-6-yl}-amide;

172) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopropylmethoxy-quinazolin-6-yl}-amide;

173) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopentyloxy-quinazolin-6-yl}-amide;

174) *N*-(2-{4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

175) (2*S*)-1-(4-dimethylamino-buten-2-oyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

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176) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-chloro-4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

177) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

178) *N*-(2-{7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

179) (2*S*)-1-acryloyl-2,5-dihydro-1*H*-pyrrol-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

180) (4*R*)-3-acryloyl-thiazolidin-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

181) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide;

182) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

183) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-6-yl]-amide;

184) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-dimethylamino-quinazolin-6-yl}-amide;

185) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

186) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

187) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-fluoro-ethoxy)-quinazolin-6-yl]-amide;

188) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-7-methoxy-quinazolin-6-yl}-amide;

189) (1*R*)-*N*-(1-{4-[3chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

190) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

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191) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}ethyl)-N-methyl-acrylamide;

192) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

193) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-penta-2,4-dienyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide;

194) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

195) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide;

196) 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

197) 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

198) 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

199) 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide;

200) 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

201) (3S)-1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

202) *N*-((1*S*)-1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-ethyl-acrylamide;

203) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(2-fluoro-ethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

204) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide;

205) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

206) *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-2-fluoro-ethyl)-acrylamide;

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207) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(1-methyl-piperidin-4-ylmethoxy)-quinazolin-6-yl}-amide;

208) (1*R*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxy-ethoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

209) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-yl}-amide;

210) *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

211) *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide;

212) (3*S*)-3-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-butyramide;

213) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

214) (1*S*)-*N*-{1-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide;

215) (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl]-amide;

216) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

217) *N*-{[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl]-methyl}-acrylamide;

218) *N*-({4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-ylcarbamoyl}-methyl]-acrylamide;

219) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylemthoxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl}-ethyl-acrylamide;

220) (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(3-methoxypropoxy)-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide;

221) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

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222) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(2-methoxyethoxy)-quinazolin-6-yl}-4-methylsulfanyl-butyramide;

223) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-4-methylsulfinyl-butyramide;

224) (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methyl-butyramide; and

225) (2*S*)-2-acryloylamino-4-methyl-pentanoic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide.

The compound of formula (I) of the present invention may be prepared by the procedure shown in Reaction Scheme (I):

Reaction Scheme (I)

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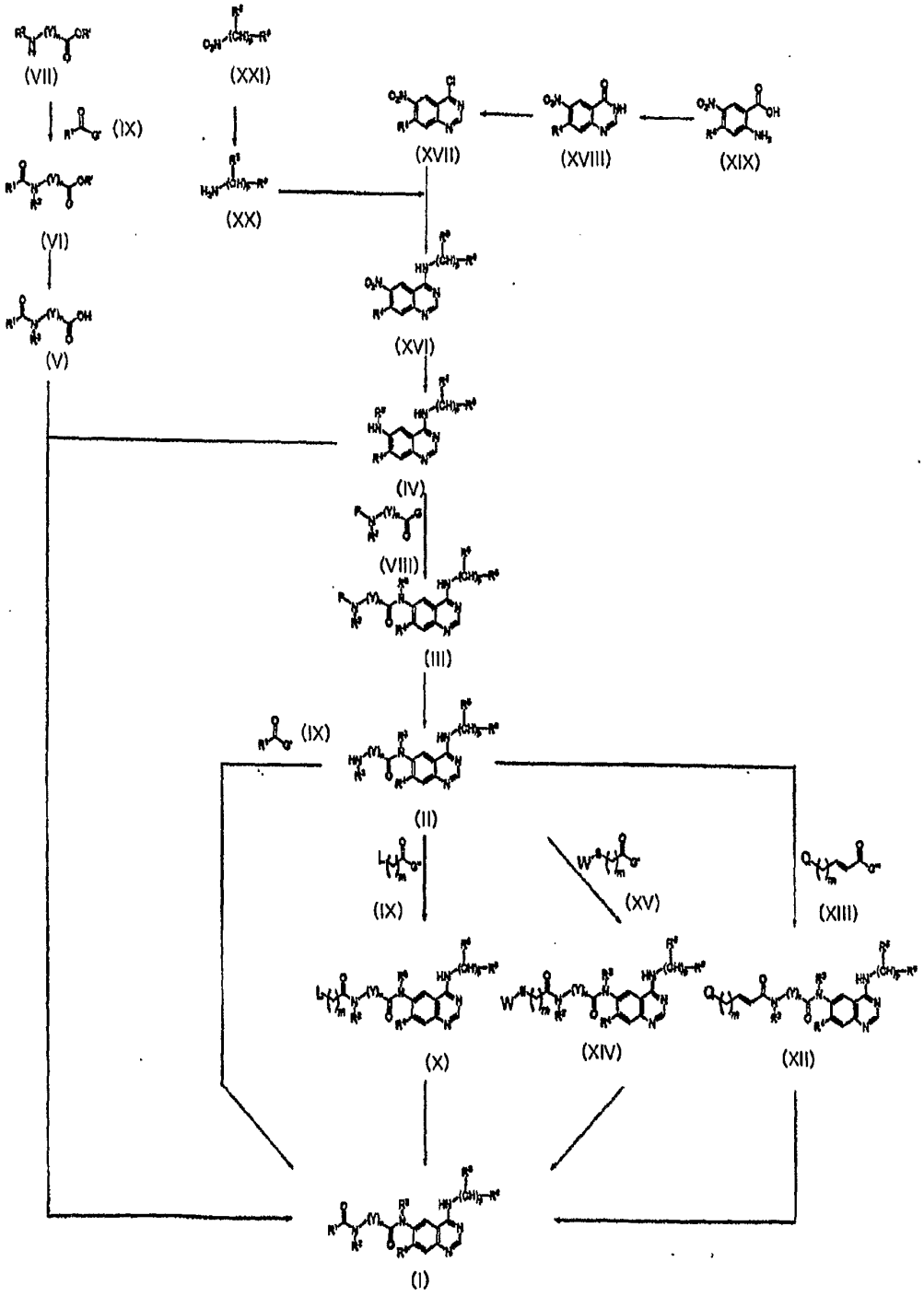

wherein,

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R^1, R^2, R^3, R^4, R^5, R^6, Y, n and p have the same meanings as defined preveiously while;

R' and W are each independently C_{1-6}alkyl;

G, G' and G" are each independently halogen, hydroxy or C_{1-6}alkanoyloxy;

L is halogen, C_{1-6}alkylsulfonyloxy or arylsulfonyloxy;

Q is halogen;

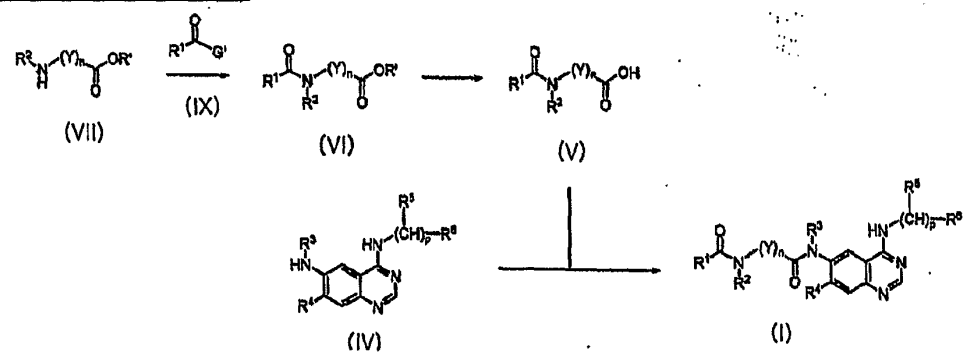
G"' is halogen, hydroxy or tri(C_{1-6}alkyl)silyloxy;

P is a *t*-buthoxycarbonyl or benzyloxycarbonylate amine protecting group; and

M is an integer in the range of 1 to 5.

Specifically, The compound of formula (I) of the present invention may be prepared by the procedure shown in Reaction Schemes (II) to (VI):

Reaction Scheme (II)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, R' and G' have same meanings as defined above.

In Reaction Scheme (II), a compound of formula (IV), the preparative procedure thereof is explained in Reacion Scheme (VII) in detail, is subjected to a condensation reaction with a compound of formula (V) to obtain a compound of formula (I). The condensation agent which may be used in this reaction is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate, carbonyldiimidazole or *O*-(1*H*-benzotriazol-1-yl)-

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N,N,N',N'-tetramethyluronium tetrafluoroborate, and the agent may be employed in an amount of 1 to 10 equivalentss, preferably 1 to 5 equivalentss based on the compound of formula (IV). The compound of formula (V) may be employed in an amount of 1 to 10 equivalentss, preferably 1 to 4 equivalentss based on the compound of formula (IV).

N,N-dimethylaminopyridine, *N,N*-hydroxysuccinimide or *N*-hydroxybenzotriazole can be added as a catalyst in an amount of 0.05 to 1 equivalent based on the compound of formula (IV). Also, triethylamine, *N,N*-diisopropylethylamine, pyridine or *N*-methylmorpholine can be added as a base in an amount of 1 to 5 equivalentss based on the compound of formula (IV).

The solvent used in this reaction may be methylene chloride, chloroform, *N,N*-dimethylformamide, tetrahydrofuran (THF), 1,4-dioxane or acetonitrile, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

The compound of formula (V) is commercially availavle and it can be prepared by hydrolysis of the compound of formula (VI). In this hydrolysis step, lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide may be used in an amount of 1 to 20 equivalentss, preferably 1 to 10 equivalents based on the compound of formula (VI). The hydrolysis can be carried out at a temperature ranging from -20℃ to 100℃, preferably 0 to 30℃ in a solvent selected from the group consisting of water, alcohol, ether and a mixture thereof.

The compound of formula (VII) is subjected to a condensation reaction with the compound of formula (IX) to obtain the compound of formula (VI), and the compound of formula (IX) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (VII). In case that the G' is halogen or alkanoyloxy, the compound of formula (VI) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (VI) may be prepared by using a condensation reagent selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate in an amount of 1 to 10 equivalents,

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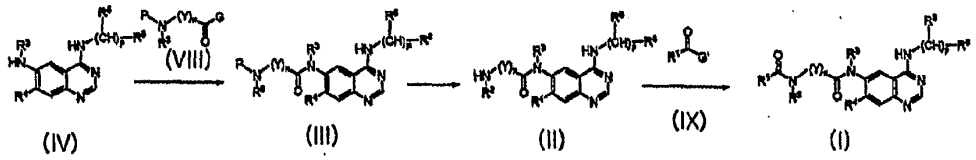
preferably 1 to 5 equivalents based on the compound of formula (VII).

In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (VII). Further, a base such as triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine may be optionally used in an amount of 1 to 5 equivalents. The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 10 to 40℃.

The compound of formula (VII) is commercially available and it can be prepared in accordance with the method described by Dieter Seebach *et al.*, [*Helvetica Chimica Acta*, 2003, *86*:1852].

The compound of formula (IX) is commercially available and it can be prepared in accordance with the method described by Hwei-Ru Tsou *et al.*, [*Journal of Medicinal Chemistry*, 2001, *44*:2719].

Reaction Scheme (III)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, G, G' and P have same meanings as defined above.

In Reaction Scheme (III), the compound of formula (II) is subjected to a condensation reaction with a compound of formula (IX) to obtain the compound of formula (I). The compound of formula (IX) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 5 equivalents based on the compound of formula (II). In case that the G' is halogen or alkanoyloxy, the compound of formula (I) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (I) may be

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prepared by using a condensation reagent selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate in an amount of 1 to 10 equivalents, preferably 1 to 5 equivalents based on the compound of formula (II).

In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (II). Further, a base such as triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine may be optionally used in an amount of 1 to 5 equivalents. The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

The compound of formula (IV), the preparative procedure thereof is explained in Reacion Scheme (VII) in detail, is subjected to a condensation reaction with a compound of formula (VIII) to obtain a compound of formula (III). Then, the compound of formula (III) is subjected to the deprotection (removing the protecting group 'P') to obtain the compound of formula (II).

The compound of formula (VIII) is commercially available and it can be prepared in accordance with the method described by Dieter Seebach *et al.*, [*Helvetica Chimica Acta*, 2003, *86*:1852].

The condensation agents which may be used in this reaction is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *N,N*-dicyclohexyldiimide, C_{1-6}alkylchloroformate, carbonyldiimidazole or *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate. The compound of formula (VIII) may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (IV). In case that the G' is halogen or alkanoyloxy, the compound of formula (VI) may be prepared by just adding a base without a condensation reagent, and in case that the G' is hydroxy, the compound of formula (VI) may be prepared by using the said condensation reagent. In this reaction, a solvent such as *N,N*-dimethylaminopyridine, *N,N*-

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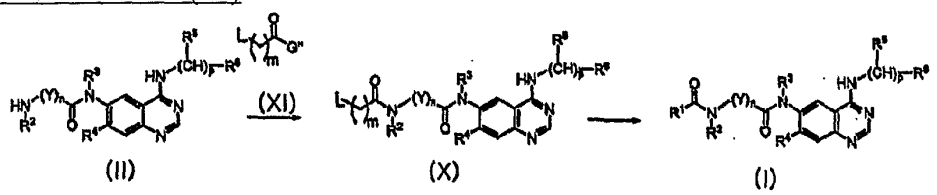
hydroxysuccinimide and *N*-hydroxybenzotriazole may be optionally used in an amount of 0.05 to 1 equivalent based on the compound of formula (IV). Also, triethylamine, *N,N*-diisopropylethylamine, pyridine and *N*-methylmorpholine can be optionally added as a base in an amount of 1 to 5 equivalents based on the compound of formula (IV). The solvent used in this reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to the boiling point of the solvent used, preferably 0 to 40℃.

While subjecting the compound of formula (III) to deprotection to obtain the compound of formula (II), hydrochloric acid, phosphoric acid, sulfuric acid or trifluoroacetic acid as a depretecting agent can be added or used as a solvent. Further, the compound of formula (II) can be obtained by using metal (for example, palladium, platinum or nickel) or metal oxide, carrying the reaction under hydrogen gas, or adding cyclohexene or cyclodihexene. The deprotection can be carried out at a temperature ranging from 0℃ to 10℃, preferably room temperature to 50℃ in accordance with the method described by Greene Wuts, [*Protective Groups in Organic Synthesis*, 3rd Ed., Wiley-Interscience].

Reaction Scheme (IV)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, L, G" and m have same meanings as defined above.

In Reaction Scheme (IV), when the R^1 is C_{1-6}alkylaminoC_{1-6}alkyl, C_{1-6}dialkylaminoC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl or C_{1-6}alkylthioC_{1-6}alkyl, the compound of formula (X) may be prepared by subjecting the compounds of

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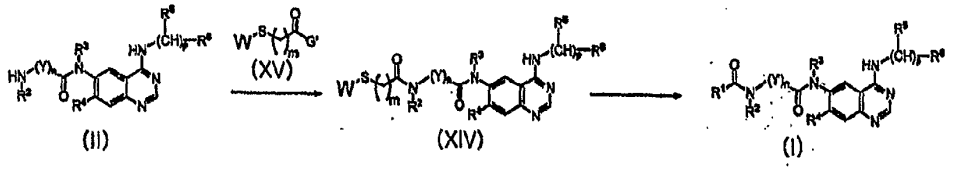
formula (II) and (XI) to condensation reaction, and then the compound of formula (I) may be prepared by adding amine, alcohol or thiol corresponding to R^1.

The condensation reaction to obtain the compoun (II) is carried out in similar condition of reaction to prepare the compound of formula (III) or by applying the reaction. The compound of formula (XI) is commercially available and it can be prepared in accordance with conventional methods.

The amine, alcohol or thiol added to the compound of formula (X) is commercially available and it can be prepared in accordance with conventional methods, and the compounds may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (X). Further, an inorganic or organic base such as potassium carbonate, sodium carbonate, sodium hydride, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and *N,N*-diisopropylethylamine may be used in an amount of 1 to 5 equivalents based on the compound of formula (X). The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, toluene, *N,N*-dimethylformamide, dimethoxyethane and a mixture thereof, and the reaction can be carried out at a temperature ranging from 0℃ to 150℃, preferably 0℃ to 100℃.

Reaction Scheme (V)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, W, G' and m have same meanings as defined above.

In Reaction Scheme (V), when the R^1 is C_{1-6}alkylsulfinyl or C_{1-6}alkylsulfonyl, the compound of formula (XIV) may be prepared by subjecting the compounds of formula (II) and (XV) to condensation reaction, and then the compound of formula (I) may be prepared by oxidizing the compound of

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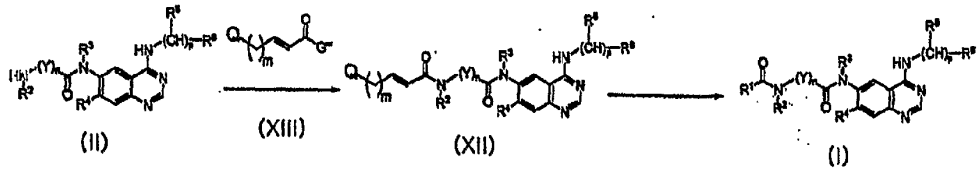
formula (XIV) in the presence of an oxidizing agent such as *m*-chloroperoxybenzoic acid (CPBA) or OXONE (Koichiro Matsumoto) in an amount of 1 to 5 equivalents based on the compound of formula (XIV), and as occasion demands, an inorganic base such as sodium carbonate or an aqueous solution thereof can be used. The reaction can be carried out at a temperature ranging from -20℃ to 50℃.

Reaction Scheme (VI)



wherein,

R^1, R^2, R^3, R^4, R^5, R^6, Y, n, p, Q, G''' and m have same meanings as defined above.

In Reaction Scheme (VI), when the R^1 is C_{1-6}alkenyl, the compound of formula (XII) may be prepared by subjecting the compounds of formula (II) and (XIII) to condensation reaction, and then the compound of formula (I) may be prepared by adding amine, alcohol or thiol corresponding to R^1.

The compound of formula (XIII) is commercially available and it can be prepared in accordance with the conventional method [*Synthesis*, 1983, 745]. In case that the G''' is halogen, the compound of formula (VI) may be prepared by just adding a base, and in case that the G''' is hydroxy or trialkylsilyloxy, the compound of formula (VI) may be prepared by using the base after substituting the G''' to halogen by using thionylchloride, oxalylchloride or phosphorousoxychloride at at a temperature ranging from 0℃ to room temperature. Further, during the substitution, *N,N*-dimethylformamide can be optionally added in an catalytic amount, and the compound of formula (XIII) may be employed in an amount ranging from 1 to 3 equivalents based on the compound of formula (II). In this reaction, the base such as triethylamine, *N,N*-diisopropylethylamine, pyridine or *N*-methylmorpholine may be employed in an amount ranging from 1 to 5 equivalents. The solvent used in this

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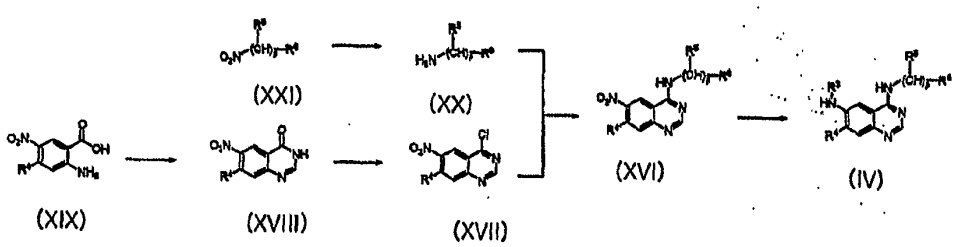
reaction may be selected from the group consisting of methylene chloride, chloroform, *N,N*-dimethylformamide, THF, 1,4-dioxane, acetonitrile and a mixture thereof, and the reaction can be carried out at a temperature ranging from -20℃ to 50℃, preferably 0 to room temperature.

The amine, alcohol or thiol added to the compound of formula (XII) is commercially available and it can be prepared in accordance with conventional methods, and the compounds may be employed in an amount of 1 to 10 equivalents, preferably 1 to 3 equivalents based on the compound of formula (XII). Further, an inorganic or organic base such as potassium carbonate, sodium carbonate, sodium hydride, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) and *N,N*-diisopropylethylamine may be used in an amount of 1 to 5 equivalents based on the compound of formula (XII). The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, toluene, *N,N*-dimethylformamide, dimethoxyethane and a mixture thereof, and the reaction can be carried out at a temperature ranging from 0℃ to 150℃, preferably 0℃ to 60℃.

The compound of formula (IV) forementioned in Reaction Schemes (II) and (III) can be prepared by reducing the compound of formula (XVI) after reacting compounds of formula (XVII) and (XVIII) to obtain the compound of formula (XVI).

Reaction Scheme (VII)



wherein,

R^3, R^4, R^5, R^6 and p have same meanings as defined above.

In Reaction Scheme (VII), the compound of formula (XVI) can be

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prepared by reacting compounds of formula (XVII) and (XVIII) to substitute a chloride of the compound of formula (XVII) to the compound of formula (XX). In this reaction, a base such as *N,N*-dimethylaniline can be added, and the reaction can be carried out in a solvent such as isopropanol and acetonitrile at a temperature ranging from 0℃ to 150℃, preferably room temperature to 100℃.

The reducing agent which used in this reaction may be selected from the group consisting of indium, palladium, platinum, iron, tartar, and oxide or chloride thereof, and employed in an amount of 1 to 5 equivalents based on the compound of formula (XVI). The reducing reaction can be carried out in the presence of hydrogen gas, and cyclohexene or cyclohexadien, or an inorganic or organic acid such as acetic acid, hydrochloric acid can be added thereto. The solvent used in this reaction may be selected from the group consisting of THF, 1,4-dioxane, ethylacetate, C_{1-6}alcohol, methylene chloride, chloroform, water, hexane, toluene and a mixture thereof.

The compound of formula (XX) is commercially available and it can be prepared in accordance with similar or identical method preparing the compound of formula (IV) from the compound of formula (XXI).

The compound of formula (XXI) is commercially available and it can be prepared in accordance with the method described by Yue-Mei Zhang *et al.*, [*Bioorganic and Medicinal Chemistry Letters*, 2004 *14*:111].

The compound of formula (XVII) can be prepared from the compound of formula (XIX) via the compound of formula (XVIII) ([Alexander J. Bridges *et al.*, *Journal of Medicinal Chemistry*, 1996 *39*:267]).

The compound of formula (I) of the present invention can also be used in the form of a pharmaceutically acceptable salt formed with an inorganic or organic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, acetic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, malic acid, mandelic acid, tartaric acid, citric acid, ascorbic acid, palmitic acid, maleic acid, hydroxymaleic acid, benzoic acid, hydroxybenzoic acid, phenylacetic acid, cinnamic acid, salicylic acid, methanesulfonic acid, benzenesulfonic acid and toluenesulfonic acid.

The inventive compound or a pharmaceutically acceptable salt thereof

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selectively inhibits the growth of cancer cells induced by epitelial cell growth factors, and provides enhanced anticancer effects when combined with other anticancer agents. Namely, the inventive compound or a pharmaceutically acceptable salt thereof is useful for enhancing the effects of anticancer agents selected from the group consisting of cell signal transduction inhibitors, mitosis inhibitors, alkylating agents, antimetabolites, antibiotics, growth factor inhibitors, cell cycle inhibitors, topoisomerase inhibitors, biological reaction modifiers, antihormonal agents and antiandrogen.

Therefore, the present invention provides a pharmaceutical composition for inhibiting cancer cell growth comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient

The inventive compound or a pharmaceutically acceptable salt thereof may be administered orally or parenterally as an active ingredient in an effective amount ranging from about 0.01 to 100 mg/kg, preferably 0.2 to 50 mg/kg body weight per day in case of mammals including human in a single dose or in divided doses. However, the foregoing dosage should be monitored, and change in consideration of idiosyncrasy and weight of the patient, kind and seriousness of illnesses, characteristics of the drug and interval and duration of drug.

The pharmaceutical composition of the present invention may be formulated for oral and parenteral administration, including intravenous, intraperitoneal, subcutaneous, rectal and topical routes of administration in accordance with conventional methods. The composition for administration may take various forms such as tablets, powder, soft and hard gelatin capsules, aqueous solutions, suspensions, emulsions, syrups, granules, aerosol elixirs, sterilized aqueous solution, sterilized powder, non-aqueous solution and lyophilized agent, and additionally includes conventional additives such as a diluent, lubricant, filler, extender, wetting agent, absorbent, colorant, flavor, sweetener, preservative, emulsifier and the like.

The inventive pharmaceutical composition for oral administration may be prepared by mixing the active ingredient with a carrier, diluent or excipient. Examples of the carrier, excipient and diluent are a disintegrator (e.g., starch, sugar and mannitol); a filler and extender (e.g., calcium phosphate and silicate

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derivatives); a binder (e.g., carboxymethylcellulose and a derivative thereof, gelatin, and polyvinylpyrrolidone); and a lubricant (e.g., talc, calcium stearate and magnesium stearate, and polyethylene glycol(s)).

Examples of the carrier employed in the injectable composition of the present invention is a water, saline solution, glucose solution, alcohol, glycol, ether (e.g., polyethylene glycol 400), oil, fatty acid, fatty acid ester, glyceride, surfactant, suspension or emulsifier.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1: Preparation of ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester

(1-1) Preparation of 6-nitro-3*H*-quinazolin-4-one

150 g of 2-amino-5-nitro-benzoylic acid was added to 200 ml of formamide, the resulting solution was heated to 170℃ for 4 hours, and cooled to 100℃. 500 ml of ice water was added thereto, stirred for 1 hour, and the resulting mixture was filtered under a reduced pressure. The resulting residue was washed with water to obtain a solid, which was dried at 40℃ for 15 hours to obtain the title compound of formula (140 g, 90%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.77 (d, *J*=2.7 Hz, 1H), 8.55 (dd, *J*=6.9 Hz, 1H), 8.36 (s, 1H), 7.84 (d, *J*=9 Hz, 1H).

(1-2) Preparation of 4-chloro-6-nitro-quinazoline hydrochloride

415 ml of thionylchloride and 123 ml of phosphorousoxy chloride were added to 80 g of the compound obtained in (1-1), and the mixture was stirred at 120℃ for 10 hours after adding 3 ml of *N,N*-dimethylformamide. The reacted solution was cooled to room temperature, concentrated under a reduced pressure, 240 ml of toluene was added thereto, and the resulting solution was

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concentrated under a reduced pressure again to obtain the title compound of formula (72 g, 69%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.80 (d, *J*=2.6 Hz, 1H), 8.57 (dd, *J*=3.9 Hz, 1H), 8.35 (s, 1H), 7.89 (d, *J*=9 Hz, 1H).

(1-3) Preparation of [3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-(6-nitro-quinazolin-4-yl)-amine hydrochloride

72 g of the compound obtained in (1-2) and 74 g of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine were added to 1,000 ml of isopropanol, and the solution was stirred at 100℃ for 17 hours. The mixture was cooled to room temperature and concentrated under a reduced pressure. The concentrate was washed with acetone and dried at 40℃ for 15 hours to obtain the tile compound (118 g, 91%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.82 (d, *J*=2 Hz, 1H), 8.97 (d, *J*=3 Hz, 1H), 8.75 (dd, *J*=6,9 Hz, 1H), 8.14 (d, *J*=9 Hz, 1H), 7.93 (d, *J*=3 Hz, 1H), 7.70 (dd, *J*=2.6, 9 Hz, 1H), 7.45-7.48 (m, 1H), 7.29-7.36 (m, 3H), 7.18 (t, *J*=6 Hz, 1H), 5.29 (s, 2H).

(1-4) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-quinazolin-4,6-diamine

700 ml of THF and 1,400 ml of water were added to 118 g of the compound obtained in (1-3), and 92 g of indium and 192 ml of HCl were added thereto sequentially. The reacted solution was stirred at room temperature for 10 hours, distilled under a reduced pressure to remove THF, and left at 0℃ for 30 mins. The resulting solid was filtered and stirred for 30 mins in 1,000 ml of saturated aqueous sodium bicarbonate solution. The resulting mixture was filtered under a reduced pressure, and the residue was washed with water and dried at 40℃ to obtain the title compound (80 g, 83%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.42 (s, 1H), 8.40(s, 1H), 8.03 (d, *J*=2 Hz, 1H), 7.73 (dd, *J*=2.4, 9 Hz, 1H), 7.43-7.53 (m, 2H), 7.29-7.33 (m, 3H), 7.18-7.25 (m, 3H), 5.61 (s, 2H), 5.24 (s, 2H).

(1-5) Preparation of ({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-carbamic acid *t*-butylester

297 mg of 1-hydroxylbenzotriazole and 959 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 664 mg of *t*-buthoxycarbonylacetic acid dissolved in 10 ml of THF, and the solution was reacted at room temperature for 2 hours after adding 1 g of the compound obtained in (1-4). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure to obtain impure residue, and the resulting residue was subjected to column chromatography (column- silica gel 60 (Merck, 107719); eluent- methylene chloride : methanol = 20 : 1) to obtain the title compound (1.35 g, 97%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.40 (br s, 1H), 8.67 (s, 1H), 8.34 (br s, 1H), 8.02 (d, 1H), 7.73 (m, 3H), 7.4 8(m, 2H), 7.35 (m, 2H), 7.15 (t, 1H), 7.07 (d, 1H), 5.63 (t, 1H), 5.26 (s, 2H), 4.16 (d, 2H), 1.59 (s, 9H).

Example 2: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide

(2-1) Preparation of (2-methoxy-acetylamino)-acetic acid ethylester

1.5 ml of triethylamine was added to 500 mg of amino-acetic acid ethylester hydrochloride dissolved in 5 ml of chloroform, and the solution was cooled to -78℃. 0.34 ml of methoxyacetylchloride diluted with 3 ml of chloroform was slowly added thereto, and the resulting solution was heated slowly to room temperature and reacted for 6 hours. The reacted solution was washed with distilled water, adjusted to pH 8 to 9 by adding saturated sodium bicarbonate solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (595 mg, 75%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.15 (br s, 1H), 4.26 (q, 2H), 4.11 (d, 2H), 3.98 (s, 2H), 3.48 (s, 3H), 1.33 (t, 3H).

(2-2) Preparation of (2-methoxy-acetylamino)-acetic acid

229 mg of lithium hydroxide was added to 595 mg of the compound obtained in (2-1) dissolved in 6 ml of 50% aqueous THF solution, and the solution was reacted for 4 hours. The reacted solution was washed with distilled water, adjusted to pH 2 by adding 1 N HCl solution, extracted with organic solvent several times, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (110 mg, 21%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 4.09 (s, 2H), 3.50 (s, 3H), 3.45 (d, 2H).

(2-3) Preparation of 2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-acetamide

25 ml of trifluoroacetic acid was added to 1.3 g of the compound obtained in (1-5) of Example 1 dissolved in 25 ml of methylene chloride, and the solution was reacted at room temperature for 2 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (394 mg, 36%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.93 (d, 1H), 8.80 (s, 1H), 7.99 (m, 2H), 7.66 (dd, 1H), 7.60 (dd, 1H), 7.44 (m, 1H), 7.35 (m, 2H), 7.08 (m, 2H), 5.27 (s, 2H), 3.6 7(s, 2H).

(2-4) Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methoxy-acetamide

110 mg of the compound obtained in (2-2) and 0.4 ml of triethylamine were dissolved in 5 ml of THF, and the solution was cooled to 0℃. 0.18 ml of isobutylchloroformate was added thereto, and the resulting solution was stirred

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for 20 mins. 134 mg of the compound obtained in (1-4) of Example 1 diluted with 2 ml of THF was added thereto, and the solution was reacted at -20℃ for 8 hours. The reacted solution was adjusted to pH 9 by adding saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (10 mg, 6%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.73 (m, 2H), 8.52 (s, 1H), 7.87 (m, 2H), 7.62 (s, 1H), 7.51 (td, 2H), 7.35 (m, 1H), 7.23 (m, 1H), 7.00 (m, 2H), 5.16 (s, 2H), 4.09 (s, 2H), 3.56 (s, 3H), 3.50 (m, 2H).

Example 3: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-2-methanesulfonyl-acetamide

16 mg of 1-hydroxylbenzotriazole and 53 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 18 mg of methanesulfonylacetic acid dissolved in 3 ml of THF, and the solution was reacted at room temperature for 2 hours after adding 50 mg of the compound obtained in (2-1) of Example 2. The reacted solution was extracted with distilled water, and the resulting residue was filtered under a reduced pressure to obtain the title compound (44 mg, 70%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.60 (s, 1H), 8.52 (s, 1H), 7.82 (d, 1H), 7.69 (m, 2H), 7.54 (dd, 1H), 7.31 (m, 2H), 7.21 (t, 2H), 6.97 (m, 2H), 5.12 (s, 2H), 4.12 (s, 2H), 4.03 (s, 2H), 3.14 (s, 3H).

Example 4: Preparation of *N*-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-methyl)-acrylamide

22 μl of acrylic acid dissolved in 2 ml of THF was cooled to 0℃, and 30 μl of pyridine was added thereto. 70 mg of the compound (2-1) of Example 2

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and 59 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added thereto, and the solution was reacted at 0℃ for 7.5 hours. The reacted solution was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (14.8 mg, 19%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.51 (d, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.64 (m, 2H), 7.48 (m,1H), 7.29 (m, 2H), 7.18 (m, 2H), 7.04 (d, 1H), 6.95 (t, 1H), 6.27 (d, 1H), 6.20 (dd, 1H), 5.64 (dd, 1H), 5.11 (s, 2H), 4.07 (s, 2H).

Example 5: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide

(5-1) Preparation of (2*S*)-2-(2-methoxy-acetylamino)-3-phenyl-propionic acid methylester

500 mg of 2-amino-3-phenyl-propionic acid methylester hydrochloride dissolved in 10 ml of chloroform was cooled to -78℃, 0.96 ml of triethylamine and 0.23 ml of methoxyacetylchloride were added thereto, and the solution was reacted at room temperature for 2 hours. The reacted solution dissolved in distilled water was adjusted to pH 9 by adding saturated sodium bicarbonate solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (427 mg, 73%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.27 (m, 5H), 7.13 (d, 2H), 6.92 (d, 1H), 4.92 (m, 1H), 3.88 (s, 2H), 3.72 (s, 3H), 3.35 (s, 3H), 3.14 (m, 2H).

(5-2) Preparation of (2*S*)-(2-methoxy-acetylamino)-3-phenyl-propionic acid

122 mg of lithium hydroxide was added to 427 mg of the compound obtained in (5-1) dissolved in 10 ml of 50% aqueous THF solution, and the

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solution was reacted for 2 hours. The reacted solution was diluted with distilled water, adjusted to pH 3 to 4 by adding 1 N HCl solution, extracted with organic solvent, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (120 mg, 100%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 7.28 (m, 3H), 7.19 (d, 2H), 6.95 (d, 1H), 4.91 (q, 1H), 3.89 (s, 2H), 3.34 (s, 3H), 3.25 (dd, 1H), 3.15 (dd, 1H).

(5-3) Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-3-phenyl-propionamide

76 mg of 1-hydroxylbenzotriazole, 244 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 200 mg of the compound obtained in (1-4) of Example 1 were added to 120 mg of the compound obtained in (5-2) dissolved in 8 ml of THF, and the solution was reacted at room temperature for 15 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (94 mg, 30%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.30 (br s, 1H), 8.58 (d, 1H), 8.08 (d, 1H), 7.86 (m, 2H), 7.63 (m, 2H), 7.48 (m, 1H), 7.29 (m, 7H), 7.00 (m, 2H), 5.15 (s, 2H), 4.93 (m, 1H), 3.93 (m, 2H), 3.37 (s, 3H), 3.30 (m, 1H), 3.16 (m, 1H).

Example 6: Preparation of (1*S*)-(1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-3-methanesulfanyl-propyl)-carbamic acid *t*-butylester

The procedure of (5-3) of Example 5 was repeated except for using 126 mg of 2-*t*-buthoxycarbonylamino-4-methanesulfanyl-butyric acid instead of the compound obtained in (5-2) of Example 5 to obtain the title compound (80 mg, 25%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (br s, 1H), 8.48 (s, 1H), 7.91 (d, 1H), 7.79 (m, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.34 (m, 3H), 7.18 (d, 1H), 7.08 (t, 1H), 5.24 (s, 2H), 4.40 (m, 1H), 2.67 (m, 2H), 2.14 (s, 3H), 2.08 (m, 2H), 1.46 (s, 9H); MS(ESI): [M+H+] 626.

Example 7: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide

(7-1) Preparation of (2*S*)-2-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide

10 ml of trifluoroacetic acid was added to 527 mg of the compound obtained in Example 6 dissolved in 10 ml of methylene chloride, and the solution was reacted at room temperature for 3 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was adjusted to pH 9 by adding saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (370 mg, 84%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.97 (br s, 1H), 8.82 (d, 1H), 8.68 (s, 1H), 7.85 (m, 2H), 7.51 (m, 2H), 7.37 (m, 1H), 7.23 (m, 2H), 7.00 (m, 2H), 5.16 (s, 2H), 3.74 (m, 1H), 2.70 (m, 2H), 2.35 (m, 1H), 2.15 (s, 3H), 1.88 (m, 1H).

(7-2) Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-4-methanesulfanyl-butyramide

108 mg of the compound obtained in (7-1) dissolved in 3 ml of chloroform was cooled to -78℃ after adding 70 μl of triethylamine, and 70 μl of methoxyacetylchloride dissolved in 2 ml of chloroform was added thereto. The reacted solution was washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (16 mg, 16%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.27 (s, 1H), 8.62 (s, 1H), 8.32 (m, 1H), 7.86 (m, 1H), 7.75 (m, 2H), 7.60 (m, 2H), 7.34 (m, 1H), 7.15 (m, 1H), 6.89 (m, 3H), 5.16 (s, 2H), 4.85 (m, 1H), 3.98 (m, 2H), 3.47 (s, 2H), 3.45 (s, 3H), 2.65 (m, 2H), 2.14 (s, 3H); MS(ESI): [M+H+] 598.

Example 8: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methanesulfonyl-acetamino)-4-methanesulfanyl-butyramide

43 mg of 1-hydroxylbenzotriazole, 103 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 150 mg of the compound obtained in (7-1) of Example 7 were added to 47.2 mg of methanesulfonylacetic acid dissolved in 6 ml of methylene chloride, and the solution was reacted at room temperature for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (40 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.31 (s, 1H), 8.51 (s, 1H), 8.39 (d, 1H), 8.24 (s, 1H), 7.72 (d, 1H), 7.52 (m, 3H), 7.33 (m, 1H), 7.18 (t, 2H), 7.00 (t, 1H), 6.83 (d, 1H), 5.03 (s, 2H), 4.85 (m, 1H), 4.18 (m, 2H), 3.15 (s, 3H), 2.61 (t, 2H), 2.18 (m, 2H), 2.03 (s, 3H); MS(ESI): [M+H+] 647.

Example 9: Preparation of (2*S*)-2-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-methanesulfanyl-butyramide

5 μl of acrylic acid dissolved in 5 ml of methylene chloride was cooled to 0℃, 20 μl of *N,N'*-diisopropylethylamine, 27 mg of *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate and 30 mg of the compound obtained in (7-1) of Example 7 were added thereto, and reacted for 2 hours.

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The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (6 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.13 (s, 1H), 8.49 (s, 1H), 7.79 (d, 2H), 7.69 (d, 1H), 7.54 (m, 3H), 7.34 (m, 1H), 7.20 (m, 2H), 7.01 (t, 1H), 6.88 (d, 1H), 6.30 (dd, 2H), 5.71 (dd, 1H), 5.09 (s, 2H), 5.02 (m, 1H), 2.72 (t, 2H), 2.02 (m, 2H), 2.13 (s, 3H).

Example 10: Preparation of (1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-cyclopropyl)-carbamic acid *t*-butylester

76 mg of 1-hydroxylbenzotriazole, 244 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 200 mg of the compound obtained in (1-4) of Example 1 were added to 180 mg of 1-*t*-buthoxycarbonylamino-cyclopropylcarboxylic acid dissolved in 15 ml of methylene chloride, and reacted at room temperature for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (160 mg, 55%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.92 (br s, 1H), 8.66 (m, 2H), 7.83 (m, 2H), 7.54 (dd, 1H), 7.39 (m, 2H), 7.22 (m, 2H), 6.98 (m, 2H), 5.15 (s, 2H), 1.70 (m, 2H), 1.50 (s, 9H), 1.18 (m, 2H).

Example 11: Preparation of (2*S*)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-(2-methoxy-acetylamino)-2-phenyl-acetamide

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38 mg of 1-hydroxylbenzotriazole and 121 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 68 mg of (2-methoxy-acetylamino)-phenyl-acetic acid dissolved in 5 ml of methylene chloride, and reacted at room temperature for 28 hours after adding 100 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (22 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.52 (s, 1H), 8.44 (s, 1H), 7.74 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 7.30 (m, 3H), 7.13 (m, 3H), 6.94 (m, 2H), 6.81 (m, 1H), 5.03 (s, 2H), 3.91 (s, 1H), 3.83 (s, 2H), 3.34 (s, 3H); MS(ESI): [M+H+] 602.

Example 12: Preparation of (4*S*)-4-*t*-buthoxycarbonylamino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester

109 mg of 1-hydroxylbenzotriazole and 350 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 230 mg of 2-*t*-buthoxycarbonylamino-pentanedionic acid-5-methylester dissolved in 10 ml of methylene chloride, and reacted at room temperature for 13 hours after adding 289 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (87 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 8.38 (s, 1H), 7.80 (d, 1H), 7.71 (d, 1H), 7.56 (m, 1H), 7.46 (m ,2H), 7.26 (m, 2H), 7.12 (m, 1H), 6.92 (m ,2H), 5.08 (s, 2H), 4.27 (m, 1H), 3.65 (s, 3H), 2.18 (m, 2H), 1.98 (m, 2H), 1.38 (s, 9H).

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Example 13: Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester

(13-1) Preparation of (4*S*)-4-amino-4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyric acid methylester

4.6 ml of trifluoroacetic acid was added to 80 mg of the compound obtained in Example 12 dissolved in 4.6 ml of methylene chloride, and reacted at room temperature for 4 hours. The reacted solution was distilled under a reduced pressure to obtain residue, and the residue was washed with saturated sodium bicarbonate, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (76 mg, 99%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.83 (s, 1H), 8.70 (s, 1H), 7.89 (m, 2H), 7.59 (m, 2H), 7.37 (m, 2H), 7.25 (m, 1H), 6.98 (m, 2H), 5.18 (s, 2H), 3.73 (s, 3H), 2.60 (t, 1H), 2.32 (m, 2H), 2.06 (m, 2H).

(13-2) Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid methylester

17 mg of 1-hydroxylbenzotriazole and 53 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 20 μl of methoxyacetic acid dissolved in 5 ml of methylene chloride, and the solution was reacted at room temperature for 8 hours after adding 60 mg of the compound obtained in (13-1). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20 mg, 29%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.67 (s, 1H), 8.50 (s, 1H), 8.07 (s, 1H), 7.80 (d, 1H), 7.57 (d, 3H), 7.43 (d, 1H), 7.29 (m, 1H), 7.16 (t, 2H), 6.88 (m, 2H),

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5.08 (s, 2H), 4.56 (m, 1H), 3.92 (d, 2H), 3.65 (s, 3H), 3.40 (s, 3H), 2.50 (m, 2H), 2.25 (m, 2H).

Example 14: Preparation of 4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-4-(2-methoxy-acetylamino)-butyric acid

8 mg of the compound obtained in (13-2) of Example 13 dissolved in 2.4 ml of 50% aqueous THF solution was reacted for 13 hours after adding 1 mg of lithium hydroxide. The reacted solution was diluted with distilled water, adjusted to pH 4.8 by adding 1 N HCl aqueous solution, and filtered under a reduced pressure to obtain the title compound (6.2 mg, 80%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.53 (d, 1H), 8.37 (s, 1H), 7.81 (d, 1H), 7.75 (d, 1H), 7.67 (d, 1H), 7.50 (dd, 1H), 7.32 (m, 1H), 7.19 (m, 2H), 7.07 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 4.52 (m, 1H), 4.47 (s, 2H), 3.37 (s, 3H), 2.34 (t, 2H), 2.14 (m, 2H); MS(ESI): [M+H+] 596.

Example 15: Preparation of 2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

187 mg of 1-hydroxylbenzotriazole and 604 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 299 mg of proline-1,2-dicarboxylic acid-1-*t*-butylester dissolved in 5 ml of THF, and reacted at room temperature for 5 hours after adding 500 mg of the compound obtained in (1-4) of Example 1. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (459 mg, 61%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.24 (s, 1H), 8.47 (s, 1H), 7.93 (s, 1H), 7.73 (m, 4H), 7.35 (m, 2H), 7.24 (m, 1H), 7.00 (m, 2H), 5.15 (s, 2H), 4.66 (m, 1H), 3.68 (m, 1H), 3.53 (m, 1H), 2.25 (m, 4H), 1.46 (s, 9H).

Example 16: Preparation of 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

(16-1) Preparation of pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (13-1) of Example 13 was repeated except for using 448 mg of the compound obtained in Example 15 instead of the compound obtained in Example 12 to obtain the title compound (297 mg, 82%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.39 (br s, 1H), 8.93 (s, 1H), 8.83 (s, 1H), 8.06 (d, 1H), 7.79 (d, 1H), 7.69 (m, 2H), 7.54 (m, 1H), 7.40 (m, 2H), 7.18 (m, 2H), 5.33 (s, 2H), 4.20 (m, 1H), 3.31 (m, 2H), 2.46 (m, 1H), 2.28 (m, 1H), 2.02 (m, 2H).

(16-2) Preparation of 1-(2-methoxy-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

21 mg of 1-hydroxylbenzotriazole and 68 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 19 mg of methoxyacetic acid dissolved in 5 ml of THF, and reacted at room temperature for 9 hours after adding 70 mg of the compound obtained in (16-1). The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (73 mg, 91%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.51 (s, 1H), 7.96 (s, 1H), 7.83 (d, 1H), 7.67 (m, 2H), 7.56 (d, 1H), 7.26 (m, 1H), 7.17 (m, 1H), 6.93 (m, 2H), 5.09 (s,

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2H), 4.84 (m, 1H), 4.11 (d, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.40 (s, 3H), 2.19 (m, 2H).

Example 17: Preparation of 1-(2-methanesulfonyl-acetyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

21 mg of 1-hydroxylbenzotriazole and 67 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 30 mg of methanesulfonylacetic acid dissolved in 5 ml of THF, and reacted at room temperature for 9 hours after adding 70 mg of the compound obtained in (16-1) of Example 16. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (66 mg, 76%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.59 (s, 1H), 8.57 (s, 1H), 7.82 (d, 1H), 7.75 (d, 1H), 7.54 (m, 2H), 7.29 (m, 1H), 7.19 (m, 2H), 6.91 (m, 2H), 5.09 (s, 2H), 4.79 (m, 1H), 4.10 (dd, 2H), 3.92 (m, 1H), 3.69 (m, 1H), 3.13 (s, 3H), 2.41 (m, 1H), 2.12 (m, 3H).

Example 18: Preparation of 1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

40 μl of pyridine and 100 mg of the compound obtained in (16-1) of Example 16 dissolved in 4 ml of THF were added to 30 μl of acrylic acid dissolved in 1 ml of THF at 0℃, and reacted with 82 mg of the compound obtained in (16-1) of Example 16 for 6 hours. The reacted solution was washed with distilled water, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (30 mg, 27%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.56 (s, 1H), 8.49 (s, 1H), 7.90 (d, 1H), 7.75 (m, 3H), 7.44 (d, 1H), 7.37 (m, 1H), 7.25 (m, 2H), 7.05 (t, 1H), 7.10 (d, 1H), 6.60 (dd, 1H), 6.45 (dd, 1H), 5.81 (dd, 1H), 5.15 (s, 2H), 5.00 (m, 1H), 3.93 (m, 1H), 3.76 (m, 1H), 2.26 (m, 4H).

Example 19: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

0.29 g of 3-*t*-buthoxycarbonylamino-propionic acid, 0.6 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride 0.6 g and 0.2 g of hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were stirred at room temperature for 13 hours after adding 0.5 g of the compound obtained in (1-4) of Example 1 at room temperature for 13 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.3 g, 42%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.73 (s, 1H), 8.64 (s, 1H), 8.48 (s, 1H), 7.92 (d, 1H), 7.74 (m, 2H), 7.45 (d, 2H), 7.18 (m, 4H), 6.84 (t, 1H), 5.20 (s, 2H), 3.40 (t, 2H), 2.42 (t, 2H), 1.33 (s, 9H); MS(ESI): [M+H+] 566.

Example 20: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(20-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

0.42 g of the compound obtained in Example 19 dissolved in 13 ml of methylene chloride and 13 ml of trifluoroacetic acid was stirred at room temperature for 2 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was melted in 10 ml of methylene chloride

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while adding 20 ml of saturated sodium bicarbonate slowly, and filtered under a reduced pressure to obtain the title compound as solid (0.34 g, 98%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.47 (s, 1H), 7.90 (d, 1H), 7.76 (m, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.30 (m, 2H), 7.16 (d, 1H), 7.06 (t, 1H), 5.22 (s, 2H), 3.08 (m, 2H), 2.68 (t, 2H).

(20-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

0.07 ml of triethylamine was added to 0.08 g of the compound obtained in (20-1) dissolved in 3 ml of methylene chloride, and reacted with 0.03 ml of methoxyacetylchloride at -70 ℃ for 30 mins and at room temperature for 4 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 44%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.47 (s, 1H), 7.87 (d, 1H), 7.80 (s, 1H), 7.73 (s, 2H), 7.58 (dd, 1H), 7.36 (m, 1H), 7.30 (m, 2H), 7.13 (d, 1H), 7.04 (t, 1H), 5.21 (s, 2H), 3.90 (s, 2H), 3.66 (t, 2H), 3.42 (s, 3H), 2.72 (t, 2H).

Example 21: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

0.12 g of methanesulfonylacetic acid, 0.34 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.12 g of methylene chloride dissolved in 2 ml of methylene chloride was stirred at room temperature for 2 hours after adding 0.2 g of the compound obtained in (20-1) of Example 20. The reacted solution was filtered under a reduced pressure

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after adding saturated sodium bicarbonate to obtain the title compound as solid (0.2 g, 80%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.35 (s, 1H), 9.83 (s, 1H), 8.66 (s, 1H), 8.50 (m, 2H), 7.95 (s, 1H), 7.86 (d, 1H), 7.65 (m, 2H), 7.48 (m, 1H), 7.32 (m, 2H), 7.18 (m, 2H), 5.23 (s, 2H), 4.08 (s, 2H), 3.44 (m, 2H), 3.11 (s, 3H), 2.58 (t, 2H).

Example 22: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

0.03 ml of acrylic acid, 0.1 ml of diisopropylethylamine and 0.15 g of *O*-(1*H*-benzotriazolyl-1-yl)-*N,N,N'N'*-tetramethyluronium tetrafluoroborate dissolved in 10 ml of methylene chloride at 0 ℃ was reacted with 0.14 g of the compound obtained in (20-1) of Example 20 for 10 mins and at room temperature for 15 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.37 (s, 1H), 7.84 (d, 1H), 7.70 (s, 1H), 7.60 (d, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.21 (m, 2H), 7.04 (m, 2H), 6.23 (d, 2H), 5.65 (t, 1H), 5.17 (s, 2H), 3.66 (t, 2H), 2.72 (t, 2H); MS(ESI): [M+H+] 520.2.

Example 23: Preparation of 3-phenyl-propionylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

32.2 mg of phenylpropagylic acid dissolved in 1 ml of THF was cooled to 0℃, and reacted with 22 μl of pyridine, 50 mg of the compound obtained (20-1) of Example 20 and 41 mg of 1-(3-dimethylaminopropyl)-3-

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ethylcarbodiimide hydrochloride for 15 hours. The reacted solution was diluted with distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (16.9 mg, 26%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.46 (s, 1H), 8.24 (s, 1H), 7.67 (d, 1H), 7.53 (s, 2H), 7.34 (dd, 1H), 7.30 (m, 2H), 7.20 (m, 4H), 7.05 (m, 2H), 6.94 (d, 1H), 6.83 (t, 1H), 5.00 (s, 2H), 3.45 (t, 2H), 2.52 (t, 2H); MS(ESI): [M+H+] 594.

Example 24: Preparation of hexa-2,4-dienonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 25 mg of 2,4-hexadienonylic acid instead of phenylpropagylic acid. The resulting solution was poured into ice water after adding 4 droplets of saturated sodium bicarbonate solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the solution was recrystallized with hexane to obtain the title compound (36.1 mg, 58.2%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.58 (s, 1H), 8.01 (d, 1H), 7.87 (d, 2H), 7.72 (dd, 1H), 7.53 (m, 1H), 7.43 (m, 2H), 7.26 (m, 2H), 7.18 (m, 1H), 6.25 (m, 3H), 6.01 (d, 1H), 5.34 (s, 2H), 3.77 (t, 2H), 2.83 (t, 2H), 1.94 (d, 3H); MS(ESI): [M+H+] 560.

Example 25: Preparation of cyclopent-1-en carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 25 mg of 1-cyclopentene carboxylic acid instead of phenylpropagylic acid. 2 ml of distilled water was added to the resulting solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the

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solution was recrystallized with hexane to obtain the title compound (29.3 mg, 47.3%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.30 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (m, 1H), 6.47 (s, 1H), 5.13 (s, 2H), 3.55 (t, 2H), 2.63 (t, 2H), 2.41 (m, 4H), 1.87 (t, 2H); MS(ESI) : [M+H+] 560.

Example 26: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-3-phenyl-acrylamide

The procedure of Example 23 was repeated except for using 32.3 mg of cinnamic acid instead of phenylpropagylic acid. The resulting solution was poured into ice water after adding 4 droplets of saturated sodium bicarbonate solution to obtain solid. The solid was dissolved in a mixture of methylene chloride and methanol, and the solution was recrystallized with hexane to obtain the title compound (35.6 mg, 56%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.87 (s, 1H), 8.66 (s, 1H), 8.09 (d, 1H), 7.94 (m, 2H), 7.77 (m, 4H), 7.56 (m, 5H), 7.37 (d, 1H), 7.26 (m, 1H), 6.82 (d, 2H), 5.43 (s, 2H), 3.91 (t, 2H), 2.96 (t, 2H); MS(ESI): [M+H+] 596.

Example 27: Preparation of but-2-ynoylic acid(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 23 was repeated except for using 19 mg of 2-butenoylic acid instead of phenylpropagylic acid to obtain the title compound (11.8 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.62 (s, 2H), 7.46 (dd, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 7.04 (d, 1H), 6.93 (t, 1H), 5.10 (s, 2H), 3.47 (t, 2H), 2.57 (t, 2H), 1.82 (s, 3H); MS(ESI): [M+H+] 532.

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Example 28: Preparation of but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

0.64 ml of pyridine was added to 50 mg of the compound obtained (20-1) of Example 20, cooled to 0℃, and reacted with 12.5 μl of crotonylchloride dissolved in 0.26 ml of diethylether for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (12.6 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.65 (d, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.21 (m, 2H), 7.07 (d, 1H), 6.96 (td, 1H), 6.70 (dd, 1H), 5.84 (dd, 1H), 5.13 (s, 2H), 3.54 (t, 2H), 2.61 (t, 2H), 1.74 (dd, 2H); MS(ESI): [M+H] 534.

Example 29: Preparation of 3-methyl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 28 was repeated except for using 14.3 μl of 3,3-dimethylacryloylchloride instead of crotonylchloride. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred after adding distilled water, and filtered under a reduced pressure to obtain the title compound (47.9 mg, 81.2%).

^{1}H-NMR (CD_3OD, 300MHz)): δ 8.87 (s, 1H), 8.66 (s, 1H), 7.98 (d, 1H), 7.95 (dd, 1H), 7.86 (d, 1H), 7.69 (dd, 1H), 7.50 (m, 1H), 7.36 (m, 2H), 7.29 (d, 1H), 7.13 (t, 1H), 5.77 (s, 1H), 5.34 (d, 2H), 3.69 (t, 2H), 2.79 (t, 2H), 2.19 (d, 3H), 1.92 (d, 3H); MS(ESI): [M+H+] 548.

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Example 30: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-methyl-acrylamide

The procedure of Example 28 was repeated except for using 13 μl of metacryloy chloride instead of crotonylchloride to obtain the title compound (14.6 mg, 25.5%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (s, 1H), 8.66 (s, 1H), 8.09 (d, 1H), 7.95 (s, 2H), 7.80 (dd, 1H), 7.59 (m, 1H), 7.49 (m, 2H), 7.37 (d, 1H), 7.26 (t, 1H), 5.90 (s, 1H), 5.57 (s, 1H), 5.41 (s, 2H), 3.84 (t, 2H), 2.92 (t, 2H), 2.14 (s, 3H); MS(ESI): [M+H] 534.

Example 31: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-2-cyano-acetamide

The procedure of Example 21 was repeated except for using cyano acetic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.09 g, 88%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.28 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.49 (s, 1H), 8.35 (t, 1H), 7.97 (d, 1H), 7.83 (dd, 1H), 7.73 (d, 1H), 7.68 (dd, 1H), 7.45 (m, 1H), 7.29 (m, 2H), 7.23 (d, 1H), 7.17 (t, 1H), 5.24 (s, 2H), 3.61 (s, 2H), 3.41 (q, 2H), 2.59 (t, 2H).

Example 32: Preparation of 3-methyl-isoxazol-5-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using 3-methyl-isoxazol-5-carboxylic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.04 g, 58%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.46 (s, 1H), 7.90 (d, 1H), 7.40 (d, 2H), 7.60 (dd, 1H), 7.40 (m, 1H), 7.29 (m, 2H), 7.17 (d, 1H), 7.05 (t, 1H), 6.81 (s, 1H), 5.23 (s, 2H), 3.77 (t, 2H), 2.80 (t, 2H), 2.32 (s, 3H).

Example 33: Preparation of furan-3-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using furan-3-carboxylic acid instead of methanesulfonylacetic acid and 0.09 g of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 56%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.30 (s, 1H), 9.77 (s, 1H), 8.67 (d, 1H), 8.50 (s, 1H), 8.33 (t, 1H), 8.17 (t, 1H), 7.98 (d, 1H), 7.83 (dd, 1H), 7.72 (m, 3H), 7.47 (m, 1H), 7.31 (m, 2H), 7.24 (d, 1H), 7.18 (t, 1H), 6.85 (t, 1H), 5.25 (s, 2H), 3.55 (q, 2H), 2.68 (t, 2H).

Example 34: Preparation of 1*H*-pyrazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 21 was repeated except for using 1*H*-pyrazol-4-carboxylic acid and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methanesulfonylacetic acid to obtain the title compound (0.07 g, 65%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.89 (d, 1H), 8.69 (s, 1H), 8.03 (m, 3H), 7.86 (d, 1H), 7.81 (d, 1H), 7.60 (dd, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 7.17 (d, 1H), 7.04 (t, 1H), 5.22 (s, 2H), 3.76 (t, 2H), 2.81 (t, 2H).

Example 35: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-benzamide

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The procedure of (20-2) of Example 20 was repeated except for using benzoic acid and 0.05 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid to obtain the title compound (0.03 g, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.82(d, 1H), 8.61 (s, 1H), 7.88 (dd, 1H), 7.75 (d, 1H), 7.68 (m, 3H), 7.48 (dd, 1H), 7.38 (m, 1H), 7.30 (m, 3H), 7.13 (m, 3H), 6.95 (t, 1H), 5.12 (s, 2H), 3.70 (t, 2H), 2.73 (t, 2H); MS(ESI): [M+H+] 569.

Example 36: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-oxalamic acid ethylester

The procedure of (20-2) of Example 20 was repeated except for using oxalic acid monoethylester and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid, and subjecting column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.93 (s, 1H), 8.47 (d, 1H), 7.88 (m, 2H), 7.38 (d, 1H), 7.28 (m, 1H), 7.13 (m, 3H), 7.06 (d, 1H), 6.95 (t, 1H), 5.09 (s, 2H), 4.19 (q, 2H), 3.53 (t, 2H), 2.61 (t, 2H), 1.22 (t, 3H)

Example 37: Preparation of cyclopropylcarboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of (20-2) of Example 20 was repeated except for using cyclopropylcarboxylic acid and 0.09 g of the compound obtained in (20-1) of Example 20 instead of methoxyacetic acid, and subjecting column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.39 (s, 1H), 7.83 (d, 1H), 7.68 (s, 2H), 7.53 (dd, 1H), 7.33 (m, 1H), 7.23 (m, 2H), 7.10 (d, 1H), 6.99 (t,

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1H), 5.16 (s, 2H), 3.52 (t, 2H), 2.61 (t, 2H), 1.49 (m, 1H), 0.77 (m, 2H), 0.68 (m, 2H).

Example 38: Preparation of acetic acid 2-*t*-buthoxycarbonylamino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester

1.83 g of 2-acetoxy-3-*t*-buthoxycarbonylamino-propionic acid, 2.83 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1 g of 1-hydroxylbenzotriazole dissolved in 30 ml of methylene chloride was reacted with 1.46 g of the compound obtained in (1-4) of Example 1 at room temperature for 22 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with distilled saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (1.08 g, 47%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.37 (s, 1H), 8.55 (s, 1H), 8.15 (s, 2H), 7.76 (d, 1H), 7.50 (m, 3H), 7.32 (m, 1H), 7.22 (m, 2H), 6.99 (t, 1H), 6.86 (d, 1H), 5.53 (t, 1H), 5.29 (t, 1H), 5.07 (s, 2H), 3.72 (m, 2H), 2.19 (s, 3H), 1.40 (s, 9H).

Example 39: Preparation of acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester

(39-1) Preparation of acetic acid 2-amino-1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylester

0.12 g of the compound obtained in Example 38 dissolved in 3 ml of methylene chloride and 3 ml of trifluoroacetic acid was stirred at room temperature for 1.5 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 3 ml of methylene

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chloride while adding 10 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound (0.08 g, 84%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.53 (m, 2H), 7.81 (d, 1H), 7.76 (d, 1H), 7.63 (dd, 1H), 7.56 (dd, 1H), 7.30 (m, 1H), 7.15 (m, 2H), 6.96 (m, 2H), 5.08 (s, 2H), 4.28 (m, 1H), 3.65 (m, 2H), 2.02 (s, 3H).

(39-2) Preparation of acetic acid 1-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-2-(2-methoxy-acetylamino)-ethylester

0.4 g of metonym acetic acid, 1.69 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.6 g of 1-hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were reacted with 1.14 g of the compound obtained in (39-1) at room temperature for 6.5 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.7 g, 54%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.62 (s, 1H), 9.93 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.17 (t, 1H), 8.07 (d, 1H), 7.98 (d, 1H), 7.77 (m, 2H), 7.52 (m, 1H), 7.40 (m, 2H), 7.31 (d, 1H), 7.24 (t, 1H), 5.31 (s, 2H), 4.26 (m, 2H), 3.72 (m, 2H), 3.56 (m, 1H), 3.42 (s, 3H), 1.90 (s, 3H),

Example 40: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-hydroxyl-3-(2-methoxy-acetylamino)-propionamide

0.5 ml of ammonia water was added to 0.1 g of the compound obtained in (39-2) of Example 39 dissolved in 10 ml of methanol, and the solution was stirred at room temperature for 1.5 hours. The reacted solution was filtered under a reduced pressure after adding distilled water to obtain the title compound as solid (0.08 g, 86%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.00 (s, 1H), 9.80 (s, 1H), 8.72 (d, 1H), 8.58 (s, 1H), 8.14 (dd, 1H), 8.05 (m, 2H), 7.79 (m, 2H), 7.54 (m, 1H), 7.39

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(m, 2H), 7.34 (d, 1H), 7.23 (t, 1H), 6.22 (d, 1H), 5.31 (s, 2H), 4.26 (m, 1H), 3.61 (m, 1H), 3.36 (s, 3H), 3.28 (m, 1H), 1.90 (s, 2H).

Example 41: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester

0.44 g of 3-*t*-buthoxycarbonylamino-2-methyl-propionic acid, 0.83 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.29 g of 1-hydroxylbenzotriazole dissolved in 20 ml of methylene chloride were reacted with 0.43 g of the compound obtained in (1-4) of Example 1 at room temperature for 18 hours. The reacted solution was extracted with methylene chloride 3 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.32 g, 52%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.17 (s, 1H), 9.70 (s, 1H), 8.64 (s, 1H), 8.41 (s, 1H), 7.88 (d, 1H), 7.73 (t, 1H), 7.59 (m, 2H), 7.38 (m, 1H), 7.24 (m, 2H), 7.17 (d, 1H), 7.10 (t, 1H), 6.83 (t, 1H), 5.17 (s, 2H), 2.93 (m, 1H), 1.30 (s, 9H), 1.04 (d, 2H), 0.95 (d, 2H).

Example 42: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide

(42-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-2-methyl-propionamide

0.24 g of the compound obtained in Example 41 dissolved in 7 ml of methylene chloride and 7 ml of trifluoroacetic acid was stirred at room temperature for 8 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 4 ml of methylene chloride

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while adding 20 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound as solid (0.19 g, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 9.84 (s, 1H), 8.71 (s, 1H), 8.49 (s, 1H), 7.99 (d, 1H), 7.88 (dd, 1H), 7.72 (m, 2H), 7.46 (m, 1H), 7.32 (m, 2H), 7.26 (d, 1H), 7.15 (t, 1H), 5.25 (s, 2H), 2.75 (m, 2H), 2.40 (m, 1H), 1.12 (d, 3H); MS(ESI): [M+H+] 480.2.

(42-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-2-methyl-propionamide

0.02 g of methoxy acetic acid, 0.08 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.03 g of 1-hydroxylbenzotriazole dissolved in 3 ml of methylene chloride were reacted with 0.05 g of the compound obtained in (42-1) at room temperature for 46 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.4 g, 70%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29 (s, 1H), 9.82 (s, 1H), 8.74 (d, 1H), 8.52 (s, 1H), 8.00 (d, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 7.50 (m, 1H), 7.35 (m, 2H), 7.27 (d, 1H), 7.21 (t, 1H), 5.28 (s, 2H), 3.83 (s, 2H), 3.40 (m, 2H), 3.31 (s, 3H), 2.85 (m, 1H), 1.17 (d, 3H).

Example 43: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-2-methyl-propionamide

0.03 g of methanesulfonylacetic acid, 0.08 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.03 g of 1-hydroxylbenzotriazole dissolved in 3 ml of methylene chloride were reacted with 0.05 g of the compound obtained in (42-1) of Example 42 at room temperature for 46 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate solution to obtain the title compound as solid (0.4 g, 64%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29 (s, 1H), 9.79 (s, 1H), 8.71 (d, 1H), 8.49 (m, 2H), 7.98 (d, 1H), 7.85 (d, 1H), 7.73 (m, 2H), 7.46 (m, 1H), 7.25 (m,4H), 5.25 (s, 1H), 4.10 (s, 2H), 3.11 (s, 3H), 2.75 (m, 2H), 2.20 (m, 1H), 1.18 (d, 3H).

Example 44: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-acrylamide

0.02 g of acrylic acid, 0.1 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.04 g of 1-hydroxylbenzotriazole dissolved in 5 ml of methylene chloride were reacted with 0.06 g of the compound obtained in (42-1) of Example 42 at room temperature for 24 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.01 g, 15%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.31 (s, 1H), 7.74 (d, 1H), 7.60 (m, 2H), 7.44 (dd, 1H), 7.24 (m, 1H), 7.15 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.09 (m, 2H), 5.49 (m, 1H), 5.07 (s, 2H), 3.50 (m, 2H), 2.75 (m, 1H), 1.13 (d, 3H).

Example 45: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-1-phenyl-ethyl)-carbamic acid *t*-butylester

1.35 g of 3-*t*-buthoxycarbonylamino-3-phenyl-propionic acid, 1.95 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.69 g of 1-hydroxylbenzotriazole dissolved in 30 ml of methylene chloride were reacted with 1 g of the compound obtained in (1-4) of Example 1 at room temperature for 12 hours. The reacted solution was extracted with methylene chloride 2

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times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.7 g, 43%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.18 (s, 1H), 8.77 (s, 1H), 7.62 (s, 1H), 7.45 (s, 1H), 6.92 (d, 1H), 6.70 (m, 3H), 6.40 (m, 2H), 6.25 (m, 8H), 4.22 (s, 2H), 4.04 (m, 1H), 1.79 (d, 2H), 0.30 (s, 9H).

Example 46: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide

(46-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-phenyl-propionamide

0.64 g of the compound obtained in Example 45 dissolved in 20 ml of methylene chloride and 20 ml of trifluoroacetic acid was stirred at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 5 ml of methylene chloride while adding 20 ml of saturated sodium bicarbonate slowly and filtered under a reduced pressure to obtain the title compound as solid (0.53 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.46 (s, 1H), 9.77 (s, 1H), 8.55 (s, 1H), 8.50 (s, 1H), 8.10 (bs, 2H), 7.95 (d, 1H), 7.79 (dd, 1H), 7.72 (d, 1H), 7.70 (dd, 1H), 7.53 (d, 2H), 7.40 (m, 3H), 7.31 (m, 2H), 7.26 (d, 1H), 7.21 (t, 1H), 5.25 (s, 2H), 4.73 (t, 1H), 3.08 (d, 2H).

(46-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-3-phenyl-propionamide

0.03 g of methoxyacetic acid, 0.14 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.05 g of 1-hydroxylbenzotriazole dissolved in 5 ml of methylene chloride were reacted with 0.1 g of the

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compound obtained in (46-1) at room temperature for 23 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (0.05 g, 45%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 9.78 (s, 1H), 8.61 (s, 1H), 8.46 (s, 1H), 8.42 (d, 1H), 7.93 (d, 1H), 7.70 (m, 3H), 7.43 (m, 3H), 7.29 (m, 3H), 7.20 (m, 2H), 5.40 (m, 1H), 5.23 (s, 2H), 3.80 (s, 2H), 3.28 (s, 3H), 2.94 (m, 2H).

Example 47: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-3-phenyl-propionamide

0.08 g of methanesulfonylacetic acid, 0.21 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.08 g of 1-hydroxylbenzotriazole dissolved in 10 ml of methylene chloride were reacted with 0.15 g of the compound obtained in (46-1) of Example 46 at room temperature for 24 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.1 g, 55%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.29(s, 1H), 9.76 (s, 1H), 8.94 (d, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.94 (d, 1H), 7.71 (m, 3H), 7.30 (m, 8H), 5.36 (m, 1H), 5.23 (s, 2H), 4.10 (m, 2H), 3.36 (m, 2H), 3.04 (s, 3H); MS(ESI): [M+H+] 662.17.

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Example 48: Preparation of 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

0.11 g of 3-(2-methoxy-acetylamino)-thiophene-2-carboxylic acid, 0.19 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.1 g of 1-hydroxylbenzotriazole dissolved in 10 ml of methylene chloride were reacted with 0.1 g of the compound obtained in (1-4) of Example 1 at room temperature for 3 hours. The reacted solution was extracted with methylene chloride 2 times after adding saturated sodium bicarbonate solution, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.02 g, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.58 (d, 1H), 8.46 (d, 1H), 8.15 (d, 1H), 7.83 (m, 2H), 7.73 (m, 2H), 7.57 (d, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 7.01 (m, 2H), 5.16 (s, 2H), 4.05 (s, 2H), 3.53 (s, 3H).

Example 49: Preparation of (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

(49-1) Preparation of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine

The procedures of (1-1) to (1-4) of Example 1 were repeated except for using 3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamine instead of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine to obtain the title compound (0.38 g, 56%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.62 (s, 1H), 8.28 (d, 1H), 7.77 (d, 1H), 7.64 (d, 1H), 7.53 (dd, 1H), 7.24 (dd, 1H), 7.12 (m, 3H), 6.94 (m, 2H), 4.06(bs, 2H), 2.55 (s, 3H), 2.30 (s, 3H).

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(49-2) Preparation of (2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 0.36 g of the compound obtained in (49-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.28 g, 53%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.92 (bs, 1H), 8.77 (s, 1H), 8.68 (s, 1H), 8.26 (s, 1H), 7.82 (d, 1H), 7.61 (s, 1H), 7.53 (m, 2H), 7.12 (m, 2H), 6.90 (d, 1H), 5.23 (m, 1H), 3.57 (m, 2H), 2.70 (m, 2H), 2.51 (s, 3H), 2.24 (s, 3H), 1.37 (s, 9H).

Example 50: Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

(50-1) Preparation of 3-amino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of (20-1) of Example 20 was repeated except for using 1 g of the compound obtained in Example 49 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.79 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.63 (s, 2H), 8.81 (s, 1H), 8.70 (s, 1H), 8.21 (s, 1H), 8.01 (d, 1H), 7.82 (m, 3H), 7.70 (s, 1H), 7.59 (d, 1H), 7.29 (s, 2H), 6.98 (d, 1H), 3.14 (m, 2H), 2.81 (t, 2H), 2.46 (s, 3H), 2.24 (s, 3H).

(50-2) Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 21 was repeated except for using 0.03 g of the compound obtained in (50-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.02 g, 52%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.73 (s, 1H), 8.66 (s, 1H), 8.48 (s, 1H), 8.15 (bt, 1H), 8.14 (d, 1H), 7.72 (m, 4H), 7.20 (m, 2H), 6.90

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(d, 1H), 4.02 (s, 2H), 3.20 (m, 2H), 3.05 (s, 3H), 2.39 (s, 3H), 2.18 (s, 3H), 1.98 (m, 2H); MS(ESI): [M+H+] 549.25.

Example 51: Preparation of *N*-(2-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using 0.08 g of the compound obtained in (50-1) of Example 50 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.03 g, 34%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.74 (s, 1H), 8.68 (s, 1H), 8.26 (s, 1H), 7.82 (m, 1H), 7.60 (m, 2H), 7.53 (dd, 1H), 7.40 (d, 1H), 7.09 (m, 2H), 6.91 (d, 1H), 6.30 (m, 3H), 2.52 (s, 3H), 2.27 (m, 5H), 1.80 (m, 2H); MS(ESI): [M+H+] 483.22.

Example 52: Preparation of {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

(52-1) Preparation of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine

The procedures of (1-1) to (1-4) of Example 1 were repeated except for using 3-chloro-4-fluoro-phenylamine instead of 3-chloro-4-(3-fluoro-benzyloxy)-phenylamine to obtain the title compound (1.1 g, 48%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.49 (s, 1H), 8.36 (s, 1H), 8.21 (dd, 1H), 7.80 (m, 1H), 7.55 (d, 1H), 7.41 (t, 1H), 7.31 (s, 1H), 7.25 (dd, 1H), 5.65 (bs, 2H).

(52-2) Preparation of {2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 1 g of the compound obtained in (52-1) instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.7 g, 44%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.27 (s, 1H), 9.90 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.10 (dd, 1H), 7.78 (m, 3H), 7.44 (t, 1H), 6.87 (bt, 1H), 3.24 (m, 2H), 2.54 (t, 2H), 1.36 (s, 9H); MS(ESI): [M+H+] 460.02.

Example 53: Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(53-1) Preparation of 3-amino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-propionamide

The procedure of (20-1) of Example 20 was repeated except for using 0.55 g of the compound obtained in Example 52 instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (0.4 g, 93%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.69 (s, 1H), 8.51 (s, 1H), 8.11 (d, 1H), 7.79 (m, 3H), 7.40 (t, 1H), 2.88 (m, 2H), 2.55 (m, 2H).

(53-2) Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

The procedure of Example 21 was repeated except for using 0.08 g of the compound obtained in (53-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 57%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.36 (s, 1H), 9.92 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.47 (bt, 1H), 8.11 (d, 1H), 7.80 (m, 3H), 7.40 (t, 1H), 4.05 (s, 2H), 3.41 (m, 2H), 3.09 (s, 3H), 2.53 (m, 2H); MS(ESI): [M+H+] 480.04.

Example 54: Preparation of *N*-{2-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

The procedure of Example 22 was repeated except for using 0.1 g of the compound obtained in (53-1) of Example 53 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.09 g, 79%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.96 (s, 1H), 10.19 (s, 1H), 9.01 (s, 1H), 8.50 (s, 1H), 8.34 (m, 2H), 8.05 (m, 3H), 7.39 (t, 1H), 6.03 (m, 1H), 6.04 (m, 1H), 5.52 (dd, 1H), 3.19 (m, 2H), 2.60 (t, 2H); MS(ESI): [M+H+] 414.05.

Example 55: Preparation of 4-bromo-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

293 mg of 4-bromo-2-butenoylic acid trimethylsilylester dissolved in 3 ml of methylene chloride was stirred for 2 hours after adding 0.12 ml of oxalylchloride and 1 droplet of *N,N*-dimethylformamide, and the solution was distilled under a reduced pressure. The resulting residue dissolved in 5 ml of THF was reacted with 500 mg of the compound obtained (20-1) of Example 20 and 0.21 ml of *N,N'*-diisopropylethylamine dissolved in 10 ml of THF at 0℃ for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was dissolved in distilled water, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (393 mg, 60%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.95 (t, 1H), 6.74 (m, 1H), 6.12 (d, 1H), 5.13 (s, 2H), 4.13 (dd, 1H), 3.56 (t, 2H), 2.63 (t, 2H).

Example 56: Preparation of 4-dimethylamino-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

1.6 ml of 2 M dimethylamine dissolved in 1 ml of THF was cooled to 0℃, and reacted for 19 hours after adding 100 mg of the compound obtained in

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Example 55 dissolved in 3 ml of THF. The reacted solution was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20.5 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.48 (s, 1H), 7.91 (d, 1H), 7.77 (s, 2H), 7.62 (dd, 1H), 7.43 (m, 1H), 7.31 (m, 2H), 7.19 (d, 1H), 7.08 (t, 1H), 6.76 (m, 1H), 5.25 (s, 2H), 3.67 (t, 2H), 3.11 (d, 2H), 2.74 (t, 2H), 2.28 (s, 6H).

Example 57: Preparation of 4-morpholin-4-yl-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

100 mg of the compound obtained in Example 55 dissolved in 3 ml of THF was cooled to 0℃, and reacted at room temperature for 16 hours after adding 0.3 ml of morpholine. The reacted solution was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (41 mg, 41%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.36 (s, 1H), 7.79 (d, 1H), 7.64 (s, 2H), 7.50 (dd, 1H), 7.30 (m, 1H), 7.18 (m, 2H), 7.06 (d, 1H), 6.95 (t, 1H), 6.65 (m, 1H), 6.01 (d, 1H), 3.55 (m, 6H), 2.99 (d, 2H), 2.61 (t, 2H), 2.34 (br s, 4H).

Example 58: Preparation of 4-(4-methyl-piperazin-1-yl)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

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The procedure of Example 57 was repeated except for using 0.18 ml of 1-methylpiperazine instead of morpholine to obtain the title compound (20 mg, 38%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.65 (s, 2H), 7.51 (dd, 1H), 7.30 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 6.65 (m, 1H), 6.01 (d, 1H), 3.56 (t, 2H), 3.04 (d, 2H), 2.62 (t, 2H), 2.39 (br s, 4H), 2.17 (s, 3H).

Example 59: Preparation of 4-[(2-hydroxyl-ethyl)-methyl-amino]-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 57 was repeated except for using 0.13 ml of 2-(methylamino) ethanol instead of morpholine to obtain the title compound (10 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.37 (s, 1H), 7.80 (d, 1H), 7.66 (s, 2H), 7.51 (dd, 1H), 7.31 (m, 1H), 7.19 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 6.67 (m, 1H), 6.01 (d, 1H), 5.13 (s, 2H), 3.50 (m, 4H), 3.13 (d, 2H), 2.62 (t, 2H), 2.46 (t, 2H), 2.18 (s, 3H).

Example 60: Preparation of 4-(2-methanesulfonyl-ethylamino)-but-2-enonylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 57 was repeated except for using 12 mg of 2-methanesulfonyl-ethylamine instead of morpholine to obtain the title compound (11 mg, 21%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.82 (s, 1H), 8.48 (s, 1H), 7.92 (d, 1H), 7.77 (s, 2H), 7.60 (dd, 1H), 7.42 (m, 1H), 7.33 (m, 2H), 7.20 (d, 1H), 7.07 (m,

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1H), 6.79 (m, 1H), 6.11 (d, 1H), 5.24 (s, 2H), 3.67 (t, 2H), 3.39 (m, 2H), 3.32 (m, 2H), 3.07 (d, 2H), 3.02 (s, 3H), 2.73 (t, 2H).

Example 61: Preparation of 3-(2-chloro-acetylamide)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

0.7 g of the compound obtained in (20-1) of Example 20 dissolved in 10 ml of THF was cooled to 0℃, and the solution was reacted at room temperature for 2 hours after adding 0.25 ml of pyridine and 0.18 ml of chloroacetylchloride. The reacted solution was extracted with ethylacetate, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, removed solvent under a reduced pressure, and vacuum dried to obtain the title compound (0.68 g, 84%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.73 (s, 2H), 7.58 (dd, 1H), 7.38 (m, 1H), 7.27 (m, 2H), 7.15 (d, 1H), 7.04 (t, 1H), 5.21 (s, 2H), 4.05 (s, 2H), 3.62 (t, 2H), 2.70 (t, 2H).

Example 62: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide

0.07 g of the compound obtained in Example 61 dissolved in 5 ml of *N,N'*-dimethylformamide was reacted with 0.04 ml of morpholine and 0.04 g of potassium carbonate for 2 hours while heating to 100℃. The reacted solution was diluted with distilled water, extracted with ethylacetate, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 mg, 92%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.51 (s, 1H), 8.36 (s, 1H), 7.78 (d, 1H), 7.63 (s, 2H), 7.49 (dd, 1H), 7.30 (m, 1H), 7.17 (m, 2H), 7.03 (d, 1H), 6.95 (t, 1H), 5.10 (s, 2H), 3.55 (m, 6H), 2.92 (s, 2H), 2.61 (t, 2H), 2.38 (m, 4H).

Example 63: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-dimethylamino-acetylamino)-propionamide

The procedure of Example 62 was repeated except for using 0.25 ml of dimethylamine 2 M THF solution instead of morpholine to obtain the title compound (0.08 g, 88%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.49 (s, 1H), 8.47 (d, 1H), 7.79 (d, 1H), 7.68 (d, 1H), 7.53 (m, 2H), 7.25 (m, 1H), 7.12 (m, 2H), 6.87 (m, 2H), 5.06 (s, 2H), 3.53 (t, 2H), 2.85 (s, 2H), 2.58 (t, 2H), 2.15 (s, 6H).

Example 64: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.06 ml of 1-methylpiperazine instead of morpholine to obtain the title compound (0.07 g, 70%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.48 (d, 1H), 8.33 (s, 1H), 7.76 (d, 1H), 7.59 (m, 2H), 7.47 (dd, 1H), 7.28 (m, 1H), 7.13 (m, 2H), 6.94 (m, 2H), 5.04 (s, 2H), 3.55 (t, 2H), 2.92 (s, 2H), 2.60 (t, 2H), 2.38 (bd, 8H), 2.06 (s, 3H)

Example 65: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethylamino)-acetylamino]-propionamide

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The procedure of Example 62 was repeated except for using 0.07 ml of 2-methoxyethylamine instead of morpholine to obtain the title compound (0.08 g, 83%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 1H), 8.40 (s, 1H), 7.83 (d, 1H), 7.66 (s, 2H), 7.54 (dd, 1H), 7.36 (m, 1H), 7.23 (m, 2H), 7.07 (d, 1H), 7.03 (t, 1H), 5.14 (s, 2H), 3.59 (t, 2H), 3.38 (t, 2H), 3.24 (s, 3H), 3.21 (s, 2H), 2.66 (m, 4H).

Example 66: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-propionamide

The procedure of Example 62 was repeated except for using 0.1 g of 2-methanesulfonyl-ethylamine instead of morpholine to obtain the title compound (0.1 g, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.36 (s, 1H), 7.80 (m, 1H), 7.65 (s, 2H), 7.49 (dd, 1H), 7.32 (m, 1H), 7.18 (m, 2H), 7.07 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 3.54 (t, 2H), 3.25 (m, 5H), 2.96 (t, 2H), 2.86 (s, 2H), 2.62 (t, 2H); MS(ESI): [M+H+] 629.11.

Example 67: Preparation of 3-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 61 was repeated except for using 0.88 g of the compound obtained in (50-1) of Example 50 and 0.3 ml of chloroacetylchloride instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.6 g, 58%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.71 (s, 1H), 8.68 (s, 1H), 8.46 (s, 1H), 8.26 (s, 1H), 7.86 (d, 1H), 7.58 (m, 3H), 7.14 (m, 2H), 6.92 (d, 1H), 4.08 (s, 2H), 3.74 (q, 2H), 2.80 (t, 2H), 2.54 (s, 3H), 2.29 (s, 3H), 2.17 (s, 2H).

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Example 68: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-(2-morpholin-4-yl-acetylamino)-propionamide

The procedure of Example 62 was repeated except for using 0.09 g of the compound obtained in Example 67 and 0.05 ml of morpholine instead of the compound obtained in Example 61 to obtain the title compound (0.08 g, 81%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.94 (s, 1H), 8.60 (m, 2H), 8.38 (bs, 1H), 8.19 (s, 1H), 7.78 (t, 1H), 7.67 (m, 2H), 7.57 (s, 1H), 7.50 (d, 1H), 7.08 (m, 2H), 6.82 (d, 1H), 3.63 (m, 6H), 2.98 (s, 2H), 2.68 (t, 2H), 2.49 (s, 3H), 2.44 (m, 4H), 2.20 (s, 3H); MS(ESI): [M+H+] 556.24.

Example 69: Preparation of 3-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.08 g of the compound obtained in Example 67 and 0.24 ml of dimethylamine 2 M THF instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 50%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.85 (s, 1H), 8.65 (s, 1H), 8.62 (s, 1H), 8.22 (d, 1H), 7.80 (t, 1H), 7.70 (m, 2H), 7.61 (s, 1H), 7.51 (d, 1H), 7.12 (m, 2H), 6.86 (d, 1H), 3.68 (m, 2H), 2.99 (s, 2H), 2.72 (t, 2H), 2.44 (s, 3H), 2.26 (s, 6H), 2.23 (s, 3H).

Example 70: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(4-methyl-piperazin-1-yl)-acetylamino]-propionamide

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The procedure of Example 62 was repeated except for using 0.07 g of the compound obtained in Example 67 and 0.05 ml of 1-methylpiperazine instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 51%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.83 (s, 1H), 8.64 (s, 2H), 8.21 (s, 1H), 7.75 (m, 2H), 7.58 (m, 3H), 7.10 (m, 2H), 6.87 (d, 1H), 3.66 (m, 2H), 3.01 (s, 2H), 2.72 (m, 2H), 2.51 (bs, 8H), 2.38 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H).

Example 71: Preparation of 3-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-methylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.07 g of the compound obtained in Example 67 and 0.06 ml of 2-methoxyethylamine instead of the compound obtained in Example 61 to obtain the title compound (0.04 g, 54%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.87 (s, 1H), 8.61 (s, 2H), 8.21 (d, 1H), 8.01 (t, 1H), 7.71 (s, 2H), 7.61 (m, 1H), 7.50 (d, 1H), 7.12 (m, 2H), 6.86 (d, 1H), 3.66 (q, 2H), 3.40 (m, 2H), 3.37 (s, 2H), 3.30 (s, 3H), 2.72 (m, 4H), 2.52 (s, 3H), 2.20 (s, 3H); MS(ESI): [M+H+] 544.23.

Example 72: Preparation of 3-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 62 was repeated except for using 0.09 g of the compound obtained in Example 67 and 0.11 g of 2-methanesulfonyl-ethylamine instead of the compound obtained in Example 61 to obtain the title compound (0.03 g, 29%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.50 (m, 2H), 8.10 (m, 1H), 7.97 (s, 1H), 7.59 (s, 1H), 7.53 (m, 1H), 7.41 (d, 1H), 7.05 (m, 2H), 6.76 (m, 1H), 3.56 (m, 2H), 3.10 (m, 2H), 2.98 (m, 2H), 2.91 (s, 3H), 2.84 (s, 3H), 2.59 (m, 2H), 2.45 (s, 3H), 2.12 (s, 2H).

Example 73: Preparation of *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

(73-1) Preparation of 3-amino-*N*-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-yl]-propionamide

150 mg of 2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester dissolved in 5 ml of methylene chloride was reacted with 5 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (100 mg, 82%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.32 (s, 1H), 7.82 (dd, *J*=2,9 Hz, 1H) 7.79(d, *J*=9 Hz, 1H), 7.63 (s, 1H), 7.34 (d, *J*=8Hz, 1H), 7.21 (dd, *J*=2,9 Hz, 1H), 6.16 (s, 1H), 3.32 (m, 2H), 2.72 (m, 2H), 2.44 (s,3H).

(73-2) Preparation of *N*-{2-[4-(2-methyl-1*H*-indol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

106 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 58 μl of pyridine were added to 40 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (73-1) for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 9 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography

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(eluent- chloroform : methanol = 15 : 1) to obtain the title compound (5.2 mg, 9%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.32 (s, 1H), 7.81 (dd, *J*=2,9 Hz, 1H), 7.73 (d, *J*=9 Hz, 1H), 7.63 (s, 1H), 7.34 (d, *J*=8 Hz, 1H), 7.21 (dd, *J*=2,9 Hz, 1H), 6.24-6.60 (m, 2H), 6.16 (s, 1H), 5.64-5,68 (m, 1H), 3.69 (t, *J*=7 Hz, 2H), 2.75 (t, *J*=7 Hz, 2H), 2.44 (s, 3H).

Example 74: Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

(74-1) Preparation of 3-amino-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

250 mg of 2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester dissolved in 5 ml of methylene chloride was reacted with 5 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (90 mg, 52%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.37 (s, 1H), 7.79 (dd, *J*=2,9 Hz, 1H), 7.70 (d, *J*=9 Hz, 1H), 7.47 (d, *J*=7 Hz, 2H), 7.35 (t, *J*=7 Hz, 2H), 7.25 (t, *J*=7 Hz, 1H), 3.26 (m, 3H), 2.90 (t, *J*=6 Hz, 2H), 1.7 (d, *J*=7 Hz, 3H).

(74-2) Preparation of 3-(2-methanesulfonyl-acetylamino)-*N*-[4-(1-phenyl-ethylamino)-quinazolin-6-yl]-propionamide

40 mg of 1-hydroxylbenzotriazole and 114 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 41 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and reacted with 50 mg of the compound obtained in (74-1) at room temperature for 12 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled

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under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (3 mg, 6%).

^{1}H-NMR(CD_3OD, 300MHz): δ 8.59 (s, 1H), 8.39 (s, 1H), 7.79-7.68 (m, 2H), 7.22-7.46 (m, 5H), 4.04 (s, 2H), 3.65 (m, 3H), 2.73 (t, *J*=6 Hz, 2H), 1.70 (d, *J*=7 Hz, 3H).

Example 75: Preparation of *N*-{2-[4-(1-phenyl-ethylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

62 μl of pyridine and 114 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 41 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (74-2) of Example 74 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 9 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (4.8 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.37 (s, 1H), 7.69 (s, 2H), 7.47 (d, *J*=7.5 Hz, 2H), 7.32 (t, *J*=7 Hz, 2H), 7.23 (t, *J*=7 Hz, 1H), 6.29 (m, 2H), 5.67 (m, 1H), 3.66 (m, 2H), 2.66-2.76 (m, 3H), 1.7 (d, *J*=7 Hz, 3H).

Example 76: Preparation of *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide

(76-1) Preparation of 3-amino-*N*-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-yl)-propionamide

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800 mg of [2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2yl)-ethyl]phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-carbamic acid *t*-butylester dissolved in 16 ml of methylene chloride was reacted with 16 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 200 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (310 mg, 46%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.46 (s, 1H), 7.8 (d, *J*=9 Hz, 1H), 7.69-7.75 (m, 3H), 7.33 (d, *J*=7.5 Hz, 2H), 6.71 (d, *J*=9 Hz, 2H), 3.8 (s, 2H), 3.67 (s, 2H), 3.37 (m, 2H), 2.72-2.92 (m, 10H).

(76-2) Preparation of *N*-[2-(4-{4-[2-(6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethyl]-phenylamino}-quinazolin-6-ylcarbamoyl)-ethyl]-acrylamide

59 μl of pyridine and 109 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 39 μl of acrylic acid dissolved in 3 ml of THF, and the solution was reacted with 150 mg of the compound obtained in (76-1) at 0℃ for 30 mins and for 2 hours while heating to room temperature. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (22 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.43 (s, 1H), 7.74 (s, 2H), 7.68 (d, *J*=9 Hz, 2H), 7.33 (d, *J*=9 Hz, 2H), 6.70 (d, *J*=9 Hz, 2H), 6.71 (d, *J*=9 Hz, 2H), 6.22-6.24 (m, 2H), 5.67 (m, 1H), 3.79 (s, 6H), 3.78 (s, 2H), 3.67 (t, *J*=7 Hz, 2H), 2.81-2.93 (m, 8H), 2.71 (t, *J*=7 Hz, 2H).

Example 77: Preparation of {2-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

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1.1 g of 2-[3-cyano-4-(dimethylamino-methylene amino)-phenylcarbamoyl]-ethyl-carbamic acid *t*-butylester (see, *Journal of Medicinal Chemistry* 2004, 44:2719) dissolved in 6 ml of acetic acid was reacted with 1.05 g of 1-benzyl-1*H*-indazol-5-ylamine at 60℃ for 3 hours, and the resulting residue was stirred in 100 ml of saturated aqueous sodium bicarbonate solution at room temperature for 30 mins. The reacted solution was extracted with 30 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (810 mg, 66%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8.39 (s, 1H), 8.07-8.11 (m, 2H), 7.73 (s, 2H), 7.55-7.64 (m, 2H), 7.21-7.32 (m, 5H), 5.66 (s, 2H), 3.47 (t, *J*=7 Hz, 2H), 2.67 (t, *J*=7 Hz, 2H), 1.4 (s, 9H).

Example 78: Preparation of *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(78-1) Preparation of 3-amino-*N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-propionamide

815 mg of the compound obtained in Example 77 dissolved in 16 ml of methylene chloride was reacted with 16 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 100 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (490 mg, 53%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8.40 (s, 1H), 8.11 (d, *J*=8 Hz, 2H), 7.76-7.79 (m, 2H), 7.56-7.63 (m, 2H), 7.22-7.33 (m, 5H), 5.67 (s, 2H), 3.32 (m, 2H), 2.73 (m, 2H).

(78-2) Preparation of *N*-[4-(1-benzyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

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50 μl of pyridine and 87 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 63 mg of methanesulfonylacetic acid dissolved in 3 ml of THF at 0℃, reacted with 50 mg of the compound obtained in (78-1) at for 30 mins while heating to room temperature and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (11 mg, 17%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H), 8.46 (s, 1H), 8.09-8.12 (m, 3H), 7.76-7.79 (m, 2H), 7.59-7.65 (m, 2H), 7.25-7.32 (m, 5H), 5.69 (s, 2H), 4.05 (s, 2H), 3.58 (m, 2H), 3.24 (s, 3H), 2.90 (m, 2H).

Example 79: Preparation of *N*-{2-[4-(1-benzyl-1*H*-imidazol-5-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

71 μl of pyridine and 132 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 47 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 150 mg of the compound obtained in (78-1) of Example 78 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (13 mg, 8%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (s, 1H), 8.32 (s, 1H), 7.99-8.02 (m, 3H), 7.68-7.70 (m, 2H), 7.56-7.52 (m, 2H), 7.14-7.123 (m, 5H), 6.08-6.18 (m, 2H), 5.56-5.60 (m, 3H), 3.61 (t, *J*=7 Hz, 2H), 2.68 (t, *J*=7 Hz, 2H).

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Example 80: Preparation of {2-[4-(4-phenylcarbamoyl-phenylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-carbamic acid *t*-butylester

1 g of 2-[3-cyano-4-(dimethylamino-methylene amino)-phenylcarbamoyl]-ethyl-carbamic acid *t*-butylester (see, *Journal of Medicinal Chemistry* 2004, 44:2719) dissolved in 6 ml of acetic acid was reacted with 650 mg of 4-amino-*N*-phenyl-benzamide at 60℃ for 3 hours, and the resulting residue was stirred in 100 ml of saturated aqueous sodium bicarbonate solution at room temperature for 30 mins. The reacted solution was extracted with 30 ml of ethylacetate 3 times, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (350 mg, 25%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.51 (s, 1H), 7.92-8.01 (m, 3H), 7.87 (s, 1H), 7.67-7.69 (m, 4H), 7.36 (t, *J*=7.5 Hz, 2H), 7.14 (t, *J*=7.5 Hz, 1H), 3.47 (t, *J*=4 Hz, 2H), 2.65 (t, *J*=7 Hz, 2H), 1.4 (s, 9H).

Example 81: Preparation of 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide

(81-1) Preparation of 4-[6-(3-amino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide

350 mg of the compound obtained in Example 80 dissolved in 7 ml of methylene chloride was reacted with 7 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (250 mg, 89%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.75 (s, 1H), 8.59 (s, 1H), 8.00-8.07 (m, 4H), 7.80 (s, 2H), 7.73 (d, *J*=9 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.18 (t, *J*=7.5 Hz, 1H), 3.31 (m, 2H), 2.71 (t, *J*=7 Hz, 2H).

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(81-2) Preparation of 4-{6-[3-(2-methanesulfonyl-acetylamino)-propionylamino]-quinazolin-4-ylamino}-*N*-phenyl-benzamide

32 mg of hydroxyl-benzotriazole and 90 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 32 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and reacted with 50 mg of the compound obtained in (81-1) at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (10 mg, 16%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.62 (s, 1H), 8.00-8.07 (m, 4H), 7.82 (s, 2H), 7.73 (d, *J*=9 Hz, 2H), 7.41 (t, *J*=7.5 Hz, 2H), 7.17 (t, *J*=7.5 Hz, 1H), 4.08 (s, 2H), 3.67 (t, *J*=7 Hz, 2H), 3.14 (s, 3H) 2.77 (t, *J*=7 Hz, 2H).

Example 82: Preparation of 4-[6-(3-acryloylamino-propionylamino)-quinazolin-4-ylamino]-*N*-phenyl-benzamide

124 μl of pyridine and 228 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 82 μl of acrylic acid dissolved in 6 ml of THF at 0℃, reacted with 127 mg of the compound obtained in (81-1) of Example 81 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 10 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (15 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.74 (s, 1H), 8.59 (s, 1H), 8.00-8.07 (m, 4H), 7.82 (s, 2H), 7.72 (d, *J*=9 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.16 (t, *J*=7.5

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Hz, 1H), 6.25-6.27 (m, 2H), 5.61-5.69 (m, 1H), 3.68 (t, *J*=7 Hz, 2H), 2.73 (t, *J*=7 Hz, 2H).

Example 83: Preparation of *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

(83-1) Preparation of 3-amino-*N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-propionamide

480 mg of 2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl-carbamic acid *t*-butylester (prepared in accordance with the procedure of Example 80) dissolved in 10 ml of methylene chloride was reacted with 10 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 50 ml of saturated aqueous sodium bicarbonate for 30 mins, filtered under a reduced pressure, and dried to obtain the title compound (400 mg, 99%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.71 (s, 1H), 8.50 (s, 1H), 7.89 (d, *J*=9 Hz, 2H), 7.78-7.80 (m, 2H), 7.65-7.75 (m, 4H), 7.43 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5 Hz, 1H) 3.32 (t, *J*=7 Hz, 2H), 2.71 (t, *J*=7 Hz, 2H).

(83-2) Preparation of *N*-[4-(biphenyl-4-ylamino)-quinazolin-6-yl]-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of hydroxyl-benzotriazole and 160 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 58 mg of methanesulfonylacetic acid dissolved in 5 ml of THF, and reacted with 80 mg of the compound obtained in (83-1) at room temperature for 12 hours. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, and filtered and distilled under a reduced pressure. 5 ml of diethylether was added to the resulting residue dissolved in 0.5 ml of methanol to obtain solid, and the solid was filtered under a reduced pressure and dried to obtain the title compound (30 mg, 76%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H). 8.56 (s, 1H), 7.84-7.89 (m, 3H), 7.63-7.73 (m, 5H), 7.42 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5 Hz, 1H), 4.1 (s, 2H), 3.68 (t, *J*=7 Hz, 2H), 3.16(s, 3H), 2.77 (t, *J*=7 Hz, 2H).

Example 84: Preparation of *N*-{2-[4-(biphenyl-4-ylamino)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

54 μl of pyridine and 100 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 36 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 100 mg of the compound obtained in (83-1) of Example 83 for 30 mins while heating to room temperature, and the resulting solution was stirred at room temperature for 2 hours. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (11 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.42 (s, 1H), 7.78 (d, *J*=8Hz, 2H), 7.69-7.71 (m, 2H), 7.57-7.62 (m, 4H), 7.39 (t, *J*=7.5 Hz, 2H), 7.25 (t, *J*=7.5 Hz, 1H), 6.16-6.18 (m, 2H), 5.66-5.71 (m, 1H), 3.60 (t, *J*=7 Hz, 2H), 2.69 (t, *J*=7 Hz, 2H).

Example 85: Preparation of *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

(85-1) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-7-(3-morpholin-4-yl-propoxy)-quinazolin-4,6-diamine

353 mg of iron dissolved in aqueous 5% acetic acid solution was activated at 100℃. 450 mg of [3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-[7-(3-morpholin-4-yl-propoxy)-6-nitro-quinazolin-4-yl]-amine (see, *Journal of Medicinal Chemistry* 2000, *43*, 1380) dissolved in a mixture of ethylacetate and

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acetic acid (1 : 1) was added thereto dropwise, and refluxed. The hot reacted solution was filtered under a reduced pressure through celite pad, and the pad was washed with ethylacetate. The washed solvent was washed with saturated sodium bicarbonate solution several times. The organic layer was dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (353 mg, 83%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.22 (s, 1H), 8.32 (s, 1H), 8.03 (d, 1H), 7.71 (dd, 1H), 7.46 (m, 1H), 7.39 (s, 1H), 7.32 (m, 2H), 7.19 (m, 2H), 7.06 (s, 1H), 5.28 (br s, 2H), 5.23 (s, 2H), 4.19 (t, 2H), 3.59 (t, 4H), 2.50 (t, 2H), 2.40 (br s, 4H), 1.99 (m, 2H); MS(ESI): [M+H+] 537.

(85-2) Preparation of *N*-{2-[4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-7-(3-morpholin-4-yl-propoxy)-quinazolin-6-ylcarbamoyl]-ethyl}-acrylamide

The procedure of Example 4 was repeated except for using 250 mg of the compound obtained in Example (85-1) and 60 μl of acrylic acid instead of the compound obtained in (2-3) of Example 2 to obtain the title compound (10 mg, 4%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.73 (s, 1H), 8.40 (s, 1H), 7.82 (d, 1H), 7.53 (dd, 1H), 7.39 (m, 1H), 7.29 (m, 2H), 7.09 (m, 3H), 6.25 (m, 2H), 5.66 (dd, 1H), 5.19 (s, 2H), 4.24 (t, 2H), 3.71 (t, 4H), 3.67 (t, 2H), 2.80 (t, 2H), 2.60 (t, 2H), 2.53 (br s, 4H), 2.12 (m, 2H); MS(ESI): [M+H+] 662.

Example 86: Preparation of (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-carbamic acid *t*-butylester

1.54 g of 4-*t*-buthoxycarbonylamino-butyric acid, 2.9 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.03 g of 1-hydroxylbenzotriazole dissolved in 25 ml of methylene chloride was reacted with 1.5 g of the compound obtained in (1-4) of Example 1 at room temperature for 14 hours. Saturated sodium bicarbonate solution was added to the reacted

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solution, and the resulting solution was filtered under a reduced pressure to obtain the title compound as solid (0.9 g, 41%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.76 (s, 1H), 8.68 (d, 1H), 8.48 (s, 1H), 7.96 (d, 1H), 7.70 (m, 3H), 7.45 (m, 1H), 7.31 (m, 4H), 6.86 (m, 1H), 5.24 (s, 2H), 2.99 (q, 2H), 2.37 (t, 2H), 1.73 (m, 2H), 1.37 (s, 9H).

Example 87: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide

(87-1) Preparation of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

0.76 g of the compound obtained in Example 86 dissolved in 22 ml of methylene chloride and 22 ml of trifluoroacetic acid was stirred at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred in 5 ml of methylene chloride while adding 50 ml of saturated aqueous sodium bicarbonate slowly, and filtered under a reduced pressure to obtain the title compound as solid (0.62 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.58 (s, 1H), 8.38 (s, 1H), 7.87 (s, 1H), 7.73 (d, 1H), 7.62 (m, 2H), 7.35 (m, 1H), 7.20 (m, 2H), 7.15 (d, 1H), 7.08 (t, 1H), 5.15 (s, 2H), 2.56 (m, 2H), 2.33 (t, 2H), 1.65 (m, 2H).

(87-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methoxy-acetylamino)-butyramide

The procedure of (20-2) of Example 20 was repeated except for using 0.1 g of the compound obtained in (87-1) instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was filtered under a reduced pressure to obtain the title compound as solid (0.06 g, 53%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.28 (s, 1H), 9.78 (bs, 1H), 8.67 (d, 1H), 8.44 (s, 1H), 7.95 (d, 1H), 7.84 (m, 2H), 7.67 (m, 2H), 7.43 (m, 1H), 7.26 (m, 2H), 7.20 (d, 1H), 7.12 (t, 1H), 5.21 (s, 2H), 3.76 (s, 2H), 3.26 (s, 3H), 3.15 (q, 2H), 2.38 (t, 2H), 1.77 (m, 2H).

Example 88: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfonyl-acetylamino)-butyramide

The procedure of Example 21 was repeated except for using 0.1 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was filtered under a reduced pressure to obtain the title compound as solid (0.05 g, 40%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.41 (s, 1H), 9.85 (bs, 1H), 8.72 (s, 1H), 8.48 (m, 1H), 7.99 (s, 1H), 7.87 (d, 1H), 7.68 (m, 2H), 7.46 (m, 1H), 7.33 (m, 2H), 7.24 (d, 1H), 7.17 (t, 1H), 5.23 (s, 2H), 4.06 (s, 2H), 3.18 (m, 2H), 3.11 (s, 3H), 2.43 (t, 2H), 1.79 (m, 2H).

Example 89: Preparation of 4-acryloylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

36 μl of pyridine, 100 mg of the compound obtained in (87-1) of Example 87 and 80 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 30 μl of acrylic acid dissolved in 2 ml of THF, and reacted at 0℃ for 5 hours. The reacted solution was washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (14 mg, 13%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (s, 1H), 8.45 (s, 1H), 7.87 (d, 1H), 7.73 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.28 (m, 2H), 7.11 (m, 2H), 6.22 (m, 2H), 5.65 (dd, 1H), 5.19 (s, 2H), 3.39 (t, 2H), 2.50 (t, 2H), 1.94 (m, 2H).

Example 90: Preparation of *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-benzamide

The procedure of Example 35 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide to obtain the title compound (0.05 g, 69%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.95 (d, 1H), 8.84 (s, 1H), 8.12 (dd, 1H), 8.04 (d, 1H), 7.98 (dd, 2H), 7.93 (d, 1H), 7.78 (dd, 1H), 7.58 (m, 4H), 7.42 (m, 2H), 7.34 (d, 1H), 7.21 (t, 1H), 5.37 (s, 2H), 3.72 (t, 2H), 2.75 (t, 2H), 2.26 (m, 2H); MS(ESI): [M+H+] 583.

Example 91: Preparation of *N*-(3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-oxalamic acid ethylester

The procedure of Example 36 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 g, 65%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.21 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.69 (m, 3H), 7.45 (m, 2H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 5.23 (s, 2H), 4.20 (q, 2H), 3.20 (q, 2H), 2.37 (t, 2H), 1.82 (m, 2H), 1.24 (t, 3H).

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Example 92: Preparation of cyclopropylcarboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 37 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 30%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.22 (s, 1H), 9.76 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.73 (m, 3H), 7.46 (m, 2H), 7.28 (m, 2H), 7.21 (d, 1H), 7.15 (t, 1H), 5.23 (s, 2H), 3.13 (q, 2H), 2.39 (t, 2H), 1.76 (m, 2H), 1.50 (m, 1H), 0.76 (m, 2H), 0.62 (m, 2H).

Example 93: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-cyano-acetylamino)-butyramide

The procedure of Example 31 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 44%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.48 (s, 1H), 8.33 (s, 1H), 7.76 (d, 1H), 7.59 (s, 2H), 7.46 (dd, 1H), 7.28 (m, 1H), 7.17 (m, 2H), 6.99 (d, 1H), 6.92 (t, 1H), 5.06 (s, 2H), 3.22 (m, 4H), 2.40 (t, 2H), 1.84 (m, 2H).

Example 94: Preparation of furan-3-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 33 was repeated except for using 0.06 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-

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chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 56%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (d, 1H), 8.44 (s, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 7.71 (m, 2H), 7.57 (dd, 1H), 7.53 (t, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.10 (d, 1H), 7.04 (t, 1H), 6.79 (t, 1H), 5.17 (s, 2H), 3.48 (t, 2H), 2.54 (t, 2H), 2.04 (m, 2H).

Example 95: Preparation of 1*H*-pyrazol-4-carboxylic acid (3-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-propyl)-amide

The procedure of Example 34 was repeated except for using 0.09 g of the compound obtained in (87-1) of Example 87 instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.04 g, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.80 (d, 1H), 8.67 (s, 1H), 8.01 (s, 2H), 7.96 (dd, 1H), 7.86 (d, 1H), 7.76 (d, 1H), 7.59 (dd, 1H), 7.38 (m, 1H), 7.26 (m, 2H), 7.17 (d, 1H), 7.03 (t, 1H), 5.20 (s, 2H), 3.45 (t, 2H), 2.55 (t, 2H), 2.03 (m, 2H).

Example 96: Preparation of {3-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-ylcarbamoyl]-propyl}-carbamic acid *t*-butylester

The procedure of Example 86 was repeated except for using 0.5 g of N^4-(3-chloro-4-fluoro-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.39 g, 57%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.21 (s, 1H), 9.89 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.10 (dd, 1H), 7.78 (m, 3H), 7.40 (t, 1H), 6.84 (bt, 1H), 2.98 (q, 2H), 2.36 (t, 2H), 1.72 (m, 2H), 1.35 (s, 9H).

Example 97: Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide

(97-1) Preparation of 4-amino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide

The procedure of (87-1) of Example 87 was repeated except for using 0.08 g of the compound obtained in Example 96 instead of the compound obtained in Example 86 to obtain the title compound (0.06 g, 96%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.75 (d, 1H), 8.51 (s, 1H), 8.12 (bt, 1H), 7.82 (m, 3H), 7.40 (t, 1H), 2.80 (m, 2H), 2.43 (m, 2H), 1.72 (m, 2H).

(97-2) Preparation of *N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-4-(2-methanesulfonyl-acetylamino)-butyramide

The procedure of Example 21 was repeated except for using 0.05 g of the compound obtained in (97-1) instead of 4-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 44%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.69 (s, 2H), 7.98 (dd, 1H), 7.85 (d, 1H), 7.61 (m, 2H), 7.16 (t, 1H), 6.92 (m, 1H), 3.48 (m, 2H), 3.15 (s, 2H), 2.52 (t, 2H), 2.17 (s, 3H), 1.60 (m, 2H); MS(ESI): [M+H+] 494.09.

Example 98: Preparation of 4-acryloylamino-*N*-[4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-butyramide

The procedure of Example 22 was repeated except for using 0.1 g of the compound obtained in (97-1) of Example 97 instead of 4-amino-*N*-{4-[3-

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chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide to obtain the title compound (0.04 g, 35%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.26 (s, 1H), 9.90 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.11 (m, 2H), 7.78 (m, 3H), 7.40 (t, 1H), 6.20 (m, 1H), 6.04 (m, 1H), 5.55 (dd, 1H), 3.19 (q, 2H), 2.40 (t, 2H), 1.79 (m, 2H); MS(ESI): [M+H+] 428.07.

Example 99: Preparation of (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylcarbonyl}-propyl)-carbamic acid *t*-butylester

The procedure of Example 86 was repeated except for using 1.2 g of N^4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1, and the resultant was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (1.58 g, 87%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.17 (s, 1H), 9.74 (s, 1H), 8.67 (d, 1H), 8.47 (s, 1H), 8.15 (d, 1H), 7.78 (dd, 1H), 7.70 (m, 2H), 7.63 (dd, 1H), 7.18 (m, 2H), 6.92 (d, 1H), 6.84 (bt, 1H), 2.98 (q, 2H), 2.41 (s, 3H), 2.36 (t, 2H), 2.18 (s, 3H), 1.72 (m, 2H), 1.35 (s, 9H).

Example 100: Preparation of 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

(100-1) Preparation of 4-amino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of (87-1) of Example 87 was repeated except for using 1.51 g of the compound obtained in Example 99 instead of the compound obtained in example 86 to obtain the title compound (1.21 g, 98%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 12.60 (bs, 1H), 10.64 (s, 1H), 9.55 (s, 1H), 8.61 (d, 1H), 8.47 (s, 1H), 8.26 (m, 2H), 8.17 (d, 1H), 7.63 (d, 1H), 7.20 (m, 2H), 6.92 (d, 2H), 3.12 (m, 2H), 2.40 (m, 5H), 2.17 (s, 3H), 1.75 (m, 2H).

(100-2) Preparation of 4-(2-methanesulfonyl-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 88 was repeated except for using 0.1 g of the compound obtained in (100-1) instead of the compound obtained in (87-1) of Example 87 to obtain the title compound (0.04 g, 32%).

^{1}H-NMR(DMSO-d_6, 300MHz): δ 10.22 (s, 1H), 9.75 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.39 (bt, 1H), 8.15 (d, 1H), 7.70 (m, 4H), 7.17 (m, 2H), 6.91 (d, 1H), 4.03 (s, 2H), 3.19 (q, 2H), 3.09 (s, 3H), 2.39 (m, 5H), 2.18 (s, 3H), 1.78 (m, 2H); MS(ESI [M+H+] 563.19.

Example 101: Preparation of 4-acryloylamino-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 89 was repeated except for using 0.15 g of the compound obtained in (100-1) of Example 100 instead of the compound obtained in (87-1) of Example 87 to obtain the title compound (0.03 g, 18%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (d, 1H), 8.44 (s, 1H), 8.11 (d, 1H), 7.75 (m, 2H), 7.66 (d, 1H), 7.58 (dd, 1H), 7.28 (m, 2H), 6.97 (d, 1H), 6.23 (d, 1H), 6.20 (s, 1H), 5.63 (dd, 1H), 3.38 (t, 2H), 2.52 (m, 5H), 2.24 (s, 3H), 1.96 (m, 2H); MS(ESI): [M+H+] 497.19.

Example 102: Preparation of 4-(2-chloro-acetylamino)-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 61 was repeated except for using 0.3 g of the compound obtained in (87-1) of Example 87 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.33 g, 95%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (d, 1H), 8.46 (s, 1H), 7.87 (d, 1H), 7.74 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.04 (t, 1H), 5.20 (s, 2H), 4.05 (s, 2H), 3.36 (t, 2H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 103: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide

The procedure of Example 62 was repeated except for using 0.04 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 42%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.75 (m, 2H), 7.58 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.05 (t, 1H), 5.20 (s, 2H), 3.68 (m, 4H), 3.35 (t, 2H), 3.00 (s, 2H), 2.50 (m, 6H), 1.95 (m, 2H).

Example 104: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-dimethylamino-acetylamino)-butyramide

The procedure of Example 63 was repeated except for using 0.04 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 45%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.63 (s, 1H), 8.46 (s, 1H), 7.90 (d, 1H), 7.76 (m, 2H), 7.60 (dd, 1H), 7.40 (m, 1H), 7.28 (m, 2H), 7.15 (d, 1H), 7.07 (t, 1H), 5.22 (s, 2H), 3.37 (t, 2H), 3.02 (s, 2H), 2.51 (t, 2H), 2.32 (s, 6H), 1.97 (m, 2H).

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Example 105: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide

The procedure of Example 64 was repeated except for using 0.02 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.01 g, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 8.52 (s, 1H), 7.88 (d, 1H), 7.80 (m, 2H), 7.66 (dd, 1H), 7.37 (m, 1H), 7.24 (m, 2H), 7.04 (m, 2H), 5.18 (s, 2H), 3.41 (t, 2H), 3.07 (s, 2H), 2.63 (bs, 4H), 2.46 (t, 2H), 2.03 (m, 6H), 1.43 (s, 3H).

Example 106: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methoxy-ethylamino)-acetylamino]-butyramide

The procedure of Example 65 was repeated except for using 0.07 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 28%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.73 (m, 2H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.28 (m, 2H), 7.13 (d, 1H), 7.05 (t, 1H), 5.19 (s, 2H), 3.47 (t, 2H), 3.35 (t, 2H), 3.30 (s, 3H), 3.28 (s, 2H), 2.75 (t, 2H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 107: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-butyramide

The procedure of Example 66 was repeated except for using 0.09 g of the compound obtained in Example 102 instead of the compound obtained in Example 61 to obtain the title compound (0.02 g, 20%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.60 (d, 1H), 8.45 (s, 1H), 7.88 (d, 1H), 7.75 (m, 2H), 7.58 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.14 (d, 1H), 7.05 (t, 1H), 5.20 (s, 2H), 3.37 (m, 4H), 3.27 (s, 2H), 3.05 (m, 5H), 2.50 (t, 2H), 1.98 (m, 2H).

Example 108: Preparation of 4-(2-chloro-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

1 g of the compound obtained in (100-1) of Example 100 dissolved in 20 ml of THF was cooled to 0℃, and reacted with 0.4 ml of pyridine and 0.3 ml of chloroacetylchloride at room temperature for 5 hours. Saturated sodium bicarbonate solution was added to the reacted solution, and the resulting solution was extracted with chloroform, washed with saturate saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure. The resulting residue was vacuum dried to obtain the title compound (0.4 g, 35%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.89 (s, 1H), 9.01 (s, 1H), 8.71 (s, 1H), 8.50 (s, 1H), 8.14 (m, 2H), 7.75 (m, 4H), 7.21 (m, 2H), 6.92 (d, 1H), 4.04 (s, 2H), 3.18 (m, 2H), 2.42 (m, 5H), 2.18 (s, 3H), 1.75 (m, 2H); MS(ESI): [M+H+] 519.08.

Example 109: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-(2-morpholin-4-yl-acetylamino)-butyramide

0.07 g of the compound obtained in Example 108 dissolved in 5 ml of *N,N'*-dimethylformamide was reacted with 0.02 ml of morpholine and 0.04 g of potassium carbonate for 10 hours while heating to 100℃. The reacted solution was diluted with distilled water, extracted with ethylacetate, washed with saturated saline solution, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected

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to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.03 g, 38%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.62 (s, 1H), 8.42 (s, 1H), 8.10 (d, 1H), 7.72 (m, 2H), 7.63 (d, 1H), 7.57 (d, 1H), 7.24 (m, 2H), 6.94 (d, 1H), 3.67 (m, 4H), 3.35 (t, 2H), 2.99 (s, 2H), 2.48 (m, 9H), 2.22 (s, 3H), 1.94 (m, 2H); MS(ESI): [M+H+] 570.28.

Example 110: Preparation of 4-(2-dimethylamino-acetylamino)-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using dimethylamine 2 M THF instead of morpholine to obtain the title compound (0.03 g, 37%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.27 (s, 1H), 8.76 (s, 1H), 8.66 (s, 1H), 8.25 (d, 1H), 8.12 (bs, 1H), 7.80 (s, 2H), 7.58 (m, 3H), 7.11 (m, 2H), 6.87 (d, 1H), 3.44 (q, 2H), 2.88 (s, 2H), 2.52 (s, 3H), 2.40 (m, 2H), 2.32 (s, 6H), 2.24 (s, 3H), 1.94 (m, 2H).

Example 111: Preparation of *N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-4-[2-(4-methyl-piperazin-1-yl)-acetylamino]-butyramide

The procedure of Example 109 was repeated except for using 1-methyl-piperazine instead of morpholine to obtain the title compound (0.05 g, 56%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.22 (s, 1H), 8.65 (s, 1H), 8.53 (s, 1H), 8.24 (s, 2H), 7.79 (s, 2H), 7.53 (m, 3H), 7.10 (m, 2H), 6.87 (d, 1H), 3.44 (m, 2H), 3.07 (s, 2H), 2.57 (bs, 4H), 2.51 (s, 3H), 2.40 (m, 6H), 2.29 (s, 3H), 2.23 (s, 3H), 1.92 (m, 2H).

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Example 112: Preparation of 4-[2-(2-methanesulfonyl-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using 2-methanesulfonylethylamine instead of morpholine to obtain the title compound (0.04 g, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.83 (s, 1H), 8.64 (s, 2H), 8.23 (d, 1H), 7.80 (m, 3H), 7.64 (s, 1H), 7.54 (d, 1H), 7.12 (m, 2H), 6.88 (d, 1H), 3.42 (m, 2H), 3.34 (s, 2H), 3.20 (m, 4H), 3.02 (s, 3H), 2.52 (s, 3H), 2.42 (m, 2H), 2.25 (s, 3H), 1.96 (m, 2H).

Example 113: Preparation of 4-[2-(2-methoxy-ethylamino)-acetylamino]-*N*-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-butyramide

The procedure of Example 109 was repeated except for using 2-methoxyethylamine instead of morpholine to obtain the title compound (0.05 g, 60%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.27 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.23 (d, 1H), 7.82 (m, 3H), 7.61 (d, 1H), 7.53 (dd, 1H), 7.08 (m, 2H), 6.86 (d, 1H), 3.44 (m, 4H), 3.35 (s, 5H), 2.78 (m, 2H), 2.51 (s, 3H), 2.39 (m, 2H), 2.23 (s, 3H), 1.91 (m, 2H).

Example 114: Preparation of (4-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-butyl)-carbamic acid *t*-butylester

The procedure of Example 19 was repeated except for using 0.4 g of 5-*t*-buthoxycarbonylamino-pentanoic acid instead of 3-*t*-buthoxycarbonylamino-propionic acid to obtain the title compound (0.6 g, 40%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.19 (s, 1H), 9.77 (s, 1H), 8.69 (s, 1H), 8.48 (s, 1H), 7.97 (d, 1H), 7.71 (m, 2H), 7.45 (m, 1H), 7.33 (m, 2H), 7.24 (d, 1H), 7.16 (t, 1H), 6.81 (s, 1H), 5.25 (s, 2H), 2.94 (m, 2H), 2.38 (t, 2H), 1.61 (m, 2H), 1.44 (m, 2H), 1.36 (s, 9H).

Example 115: Preparation of 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

(115-1) Preparation of 5-amino-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (20-1) of Example 20 was repeated except for using 0.42 g of the compound obtained in Example 114 instead of the compound obtained in Example 19 to obtain the title compound (0.34 g, 98%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.83 (m, 1H), 7.68 (m, 2H), 7.44 (m, 1H), 7.25 (m, 4H), 5.24 (s, 2H), 3.35 (m, 2H), 2.37 (t, 2H), 1.65 (m, 2H), 1.42 (m, 2H).

(115-2) Preparation of 5-(2-methoxy-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (20-2) of Example 20 was repeated except for using 0.09 g of the compound obtained in (115-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.06 g, 59%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.20 (s, 1H), 9.77 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 7.96 (d, 1H), 7.71 (m, 4H), 7.46 (m, 1H), 7.32 (m, 2H), 7.24 (d, 1H), 7.18 (t, 1H), 5.25 (s, 2H), 3.77 (s, 2H), 3.29 (s, 3H), 3.13 (q, 2H), 2.39 (t, 2H), 1.62 (m, 2H), 1.50 (m, 2H).

Example 116: Preparation of 5-(2-methanesulfonyl-acetylamino)-pentanoic acid {4-[3-chloro-4-(3-fluoro-benzyloxy)-pentylamino]-quinazolin-6-yl}-amide

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The procedure of Example 21 was repeated except for using 0.09 g of the compound obtained in (115-1) of Example 115 instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.05 g, 45%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.19 (s, 1H), 9.76 (s, 1H), 8.67 (s, 1H), 8.48 (s, 1H), 8.34 (d, 1H), 7.96 (s, 1H), 7.70 (m, 3H), 7.45 (m, 1H), 7.25 (m, 4H), 5.24 (s, 2H), 4.02 (s, 2H), 3.13 (m, 2H), 3.05 (s, 3H), 2.40 (m, 2H), 1.65 (m, 2H), 1.39 (m, 2H).

Example 117: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfanyl-acetylamino)-propionamide

The procedure of Example 21 was repeated except for using 0.19 ml of methylthioacetic acid instead of methanesulfonylacetic acid to obtain the title compound (520 mg, 87%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.31 (s, 1H), 9.80 (s, 1H), 8.69 (s, 1H), 8.51 (s, 1H), 8.13 (t, 1H), 7.99 (d, 1H), 7.83 (dd, 1H), 7.72 (m, 2H), 7.47 (m, 1H), 7.31 (m, 2H), 7.26 (d, 1H), 7.20 (t, 1H), 5.26 (s, 2H), 3.42 (q, 2H), 3.33 (s, 3H), 3.08 (s, 2H), 2.61 (t, 2H).

Example 118: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfinyl-acetylamino)-propionamide

100 mg of the compound obtained in (20-1) of Example 20 dissolved in 5 ml of THF and 5 ml of saturated aqueous sodium bicarbonate solution was reacted with 40 mg of *m*-CPBA at room temperature for 27 hours, and the reacted solution was diluted with distilled water and chloroform, and filtered under a reduced pressure to obtain the title compound as solid (80 mg, 78%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.23 (s, 1H), 9.75 (s, 1H), 8.66 (s, 1H), 8.48 (s, 1H), 8.34 (t, 1H), 7.92 (s, 1H), 7.79 (dd, 1H), 7.65 (m, 2H), 7.43 (m, 1H), 7.29 (m, 2H), 7.19 (m, 2H), 5.21 (s, 2H), 3.60 (dd, 2H), 3.39 (q, 2H), 2.56 (s, 3H), 2.52 (t, 2H); MS(ESI): [M+H+] 569.99.

Example 119: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(2,2,2-trifluoro-acetylamino)-propionamide

80 mg of the compound obtained in (20-1) of Example 20 dissolved in 3 ml of THF at 0℃ was reacted with 0.03 mg of pyridine and 0.03 ml of anhydrous trifluoroacetic acid for 4 hours while heating to room temperature. The reacted solution was diluted with saturated sodium bicarbonate solution, extracted with ethylacetate, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (40 mg, 42%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.58 (s, 1H), 8.42 (s, 1H), 7.84 (d, 1H), 7.66 (m, 2H), 7.54 (dd, 1H), 7.35 (m, 1H), 7.21 (m, 2H), 7.05 (m, 2H), 5.15 (s, 2H), 3.67 (t, 2H), 2.74 (t, 2H).

Example 120: Preparation of 3-acetylamino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-propionamide

The procedure of Example 119 was repeated except for using 0.03 ml of anhydrous acetic acid instead of trifluoroacetic acid to obtain the title compound (60 mg, 69%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.25 (s, 1H), 9.76 (s, 1H), 8.65 (s, 1H), 8.46 (s, 1H), 7.94 (m, 2H), 7.79 (dd, 1H), 7.66 (m, 2H), 7.43 (m, 1H), 7.30 (m, 2H), 7.21 (d, 1H), 7.13 (t, 1H), 5.22 (s, 2H), 3.38 (t, 2H), 2.52 (t, 2H), 1.77 (s, 3H).

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Example 121: Preparation of acetic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethylcarbamoyl)-methylester

The procedure of Example 119 was repeated except for using 0.03 ml of acetoxyacetylchloride instead of trifluoroacetic acid to obtain the title compound (80 mg, 74%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.35 (s, 1H), 9.81 (s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 8.16 (t, 1H), 7.99 (d, 1H), 7.83 (dd, 1H), 7.74 (m, 2H), 7.46 (m, 1H), 7.32 (m, 2H), 7.25 (d, 1H), 7.16 (t, 1H), 5.25 (s, 2H), 4.44 (s, 2H), 3.43 (t, 2H), 2.60 (t, 2H), 2.10 (s, 3H).

Example 122: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-dimethylamino-ethoxy)-acetylamino]-propionamide

44 mg of sodium hydride (60%, oil suspension) dissolved in 2 ml of THF was reacted with 0.03 ml of dimethylethanol for 30 mins, 100 mg of the compound obtained (20-1) of Example 20 dissolved in 5 ml of THF was added thereto at 0℃, and the resulting solution was reacted for 3 hours while heating to room temperature. The reacted solution was diluted with saturated sodium bicarbonate solution, extracted with chloroform, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (70 mg, 64%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.53 (d, 1H), 8.37 (s, 1H), 7.81 (d, 1H), 7.67 (m, 2H), 7.51 (dd, 1H), 7.36 (m, 1H), 7.21 (m, 2H), 7.02 (m, 2H), 5.09 (s, 2H), 3.91 (s, 2H), 3.62 (t, 2H), 3.56 (t, 2H), 2.66 (t, 2H), 2.48 (t, 2H), 2.20 (s, 6H).

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Example 123: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-ethyl-ureido)-propionamide

80 mg of the compound obtained in (20-1) of Example 20 dissolved in 5 ml of chloroform was reacted with 0.02 ml of ethylisocyanate at room temperature for 2 hours. The reacted mixture was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (70 mg, 77%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.26 (s, 1H), 9.77 (s, 1H), 8.66 (s, 1H), 8.47 (s, 1H), 7.95 (d, 1H), 7.79 (dd, 1H), 7.72 (d, 1H), 7.68 (dd, 1H), 7.45 (m, 1H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 5.88 (q, 2H), 5.23 (s, 2H), 2.97 (m, 2H), 2.51 (m, 2H), 0.94 (t, 3H).

Example 124: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-phenyl-ureido)-propionamide

The procedure of Example 123 was repeated except for using 0.02 ml of phenylisocyanate instead of ethylisocyanate to obtain the title compound (73 mg, 73%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.40 (s, 1H), 9.82 (s, 1H), 8.71 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.00 (d, 1H), 7.89 (dd, 1H), 7.72 (m, 2H), 7.30 (m, 8H), 6.92 (m, 2H), 6.39 (t, 1H), 5.23 (s, 2H), 3.42 (q, 2H), 2.60 (t, 2H).

Example 125: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-(3-furan-2-ylmethyl-ureido)-propionamide

The procedure of Example 123 was repeated except for using 0.02 ml of furfurylisocyanate instead of ethylisocyanate to obtain the title compound (80 mg, 80%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.34 (s, 1H), 9.80 (s, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 7.98 (d, 1H), 7.83 (dd, 1H), 7.69 (m, 2H), 7.51 (s, 1H), 7.44 (m, 1H), 7.30 (m, 2H), 7.22 (d, 1H), 7.16 (t, 1H), 6.38 (t, 1H), 6.16 (d, 1H), 6.05 (t, 1H), 5.23 (s, 2H), 4.16 (d, 2H), 3.38 (m, 2H), 2.56 (m, 2H).

Example 126: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid methylester

The procedure of Example 119 was repeated except for using 0.02 ml of methylchloroformate instead of ethylisocyanate to obtain the title compound (60 mg, 67%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (s, 1H), 8.45 (s, 1H), 7.87 (d, 1H), 7.81 (s, 2H), 7.57 (dd, 1H), 7.38 (m, 1H), 7.29 (m, 2H), 7.12 (d, 1H), 7.04 (t, 1H), 5.20 (s, 2H), 3.64 (s, 3H), 3.51 (t, 2H), 2.66 (t, 2H).

Example 127: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid phenylester

The procedure of Example 119 was repeated except for using 0.03 ml of phenylchloroformate instead of ethylisocyanate to obtain the title compound (20 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.54 (s, 1H), 8.07 (s, 1H), 7.80 (d, 1H), 7.69 (d, 1H), 7.57 (m, 2H), 7.30 (m, 3H), 7.13 (m, 2H), 6.98 (m, 5H), 5.08 (s, 2H), 3.56 (t, 2H), 2.68 (t, 2H).

Example 128: Preparation of (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid benzylester

The procedure of Example 119 was repeated except for using 0.04 ml of benzylchloroformate instead of ethylisocyanate to obtain the title compound (50 mg, 49%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.27 (s, 1H), 9.77 (s, 1H), 8.68 (s, 1H), 8.49 (s, 1H), 7.96 (d, 1H), 7.83 (dd, 1H), 7.75 (d, 1H), 7.70 (dd, 1H), 7.49 (m, 1H), 7.37 (m, 6H), 7.28 (d, 1H), 7.20 (t, 1H), 5.14 (s, 2H), 5.00 (s, 2H), 3.38 (q, 2H), 2.60 (t, 2H).

Example 129: Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(129-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-propionamide

350 mg of 2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester dissolved in 7 ml of methylene chloride was reacted with 7 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred with 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (280 mg, 97%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (s, 1H) 8.57 (s, 1H), 8.50 (s, 1H), 7.92-7.94 (m, 2H), 7.72-7.78 (m, 3H), 7.59-7.62 (m, 1H), 7.40 (t, *J*=5 Hz, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.29 (s, 2H), 3.53 (bs, 2H), 2.65 (bs, 2H).

(129-2) Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

30 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 17 μl of methoxyacetic acid dissolved in 3 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (129-1). The reacted solution was extracted with ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, distilled under a reduced pressure, and the resulting residue was subjected to column chromatography

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(eluent- chloroform : methanol = 15 : 1) to obtain the title compound (15 mg, 26%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.90 (s, 1H), 8.71-8.75 (m, 2H), 8.08-8.11 (m, 2H), 7.92-7.95 (m, 3H), 7.79 (m, 1H), 7.63 (t, *J*=5 Hz, 1H), 7.39 (d, *J*=9 Hz, 1H), 5.47 (s, 2H), 4.08 (s, 2H), 3.85 (t, *J*=6 Hz, 2H) 3.53 (s, 3H), 2.93 (bs, 2H).

Example 130: Preparation of *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 mg of methanesulfonylacetic acid dissolved in 2 ml of THF, and the solution was reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (129-1) of Example 129. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (5.2 mg, 8%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.66 (s, 1H), 8.54 (bs, 1H), 8.47 (s, 1H), 7.93 (m, 2H), 7.70 - 7.75 (m, 3H), 7.58 (m, 1H), 7.39 (t, *J* = 5 Hz, 1H), 7.17 (d, *J* = 9 Hz, 1H), 5.29 (s, 2H), 4.03 (s, 2H), 3.64 (t, *J* = 6 Hz, 2H), 3.29 (s, 3H), 2.72 (t, *J* = 6 Hz, 2H).

Example 131: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 46 μl of pyridine were added to 31 μl of acrylic acid dissolved in 3 ml of THF, and reacted with 100 mg of the compound obtained

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in (129-1) of Example 129 at 0℃ for 30 mins. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (7 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.67 (s, 1H), 8.56 (bs, 1H), 8.48 (s, 1H), 7.89-7.94 (m, 2H), 7.72-7.76 (m, 3H), 7.64 (dd, *J*=6,9 Hz, 1H), 7.42 (t, *J*=5 Hz, 1H), 7.17 (d, *J*=9 Hz, 1H), 6.24-6.26 (m, 2H), 5.66-5.68 (m, 1H), 5.29 (s, 2H), 3.69 (t, *J*=6 Hz, 2H), 2.76 (t, *J*=6 Hz, 2H).

Example 132: Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

(132-1) Preparation of 3-amino-*N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-propionamide

280 mg of 2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-carbamic acid *t*-butylester dissolved in 6 ml of methylene chloride was reacted with 6 ml of trifluoroacetic acid at room temperature for 4 hours. The residue obtained from distillation of the reacted solution under a reduced pressure was stirred with 50 ml of saturated aqueous sodium bicarbonate solution for 30 mins, filtered under a reduced pressure and dried to obtain the title compound (220 mg, 96%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (bs, 1H), 8.63 (s, 1H), 8.50 (bs, 1H), 8.44 (s, 1H), 8.00 (d, *J*=8 Hz, 1H), 7.90 (d, *J*=2.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.63 (dd, *J*=9, 2.5 Hz, 1H), 7.46-7.50 (m, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.24 (s, 2H), 3.30 (bs, 2H), 2.63 (bs, 2H).

(132-2) Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methoxy-acetylamino)-propionamide

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30 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 17 μl of methoxyacetic acid dissolved in 3 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (132-1). The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (5 mg, 9%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (bs, 1H), 8.63 (s, 1H), 8.50 (bs, 1H), 8.44 (s, 1H), 8.00 (d, *J*=8 Hz, 1H), 7.90 (d, *J*=2.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.63 (dd, *J*=9, 2.5 Hz, 1H), 7.46-7.50 (m, 1H), 7.19 (d, *J*=9 Hz, 1H), 5.24 (s, 2H), 3.30 (bs, 2H), 2.63 (bs, 2H).

Example 133: Preparation of *N*-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-(2-methanesulfonyl-acetylamino)-propionamide

56 mg of 1-hydroxylbenzotriazole and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 mg of methansulfonylacetic acid dissolved in 2 ml of THF, and reacted at room temperature for 12 hours after adding 50 mg of the compound obtained in (132-1) of Example 132. The reacted solution was extracted with 10 ml of ethylacetate 3 times after adding 5 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (16 mg, 25%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 8.74 (s, 1H), 8.70 (s, 1H), 8.66 (d, *J*=2 Hz, 1H), 8.50 (s, 1H), 8.21 (d, *J*=8 Hz, 1H), 8.11 (d, *J*=2.5 Hz, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, *J*=9, 2.5 Hz, 1H), 7.69 (bs, 1H), 7.43 (d, *J*=9 Hz, 1H),

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5.29 (s, 2H), 4.11 (s, 2H), 3.71 (t, *J*=6 Hz, 2H), 3.16 (s, 3H), 2.79 (t, *J*=6 Hz, 2H).

Example 134: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

46 μl of pyridine and 85 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added to 31 μl of acrylic acid dissolved in 3 ml of THF at 0℃, reacted with 100 mg of the compound (132-1) of Example 132 for 30 mins, and stirred for 2 hours while heating to room temperature. The reacted solution was extracted with 6 ml of ethylacetate 3 times after adding 4 ml of water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (20 mg, 18%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (bs, 1H), 8.85 (s, 1H), 8.73 (bs, 1H), 8.72 (s, 1H), 8.21 (d, *J*=8 Hz, 1H), 8.11 (d, *J*=2.5 Hz, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, *J*=9, 2.5 Hz, 1H), 7.69 (bs, 1H), 7.43 (d, *J*=9 Hz,1H), 6.37-6.44 (m, 2H), 5.82-5.86 (m, 1H), 5.46 (s, 2H), 3.87 (t, *J*=6 Hz, 2H), 2.94 (t, *J*=6 Hz, 2H).

Example 135: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-[2-(2-methoxy-ethoxy)-acetylamino]-propionamide

0.04 ml of 2-(2-methoxyethoxy) acetic acid, 0.05 g of 1-hydroxylbenzotriazole and 0.13 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride dissolved in 5 ml of dichloromethane were reacted at room temperature for 21 hours after adding 0.08 g of the compound obtained in (20-1) of Example 20. The reacted solution was extracted with chloroform 2 times after adding saturated sodium bicarbonate, washed with saturated saline solution, dried over anhydrous magnesium sulfate, filtered and

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distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.07 g, 71%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.59 (d, 2H), 7.48 (dd, 1H), 7.28 (m, 1H), 7.15 (m, 2H), 6.94 (m, 2H), 5.07 (s, 2H), 3.90 (s, 2H), 3.53 (m, 4H), 3.42 (m, 2H), 3.20 (s, 3H), 2.62 (t, 2H).

Example 136: Preparation of 5-methyl-isoxazol-4-carboxylic acid (2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-amide

The procedure of Example 140 was repeated except for using 0.05 g of 5-methylisoxazol-4-carboxylic acid instead of 2-(2-methoxyethoxy)acetic acid to obtain the title compound (0.05 g, 51%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.53 (s, 1H), 8.38 (s, 1H), 7.80 (m, 1H), 7.65 (m, 2H), 7.50 (dd, 1H), 7.32 (m, 1H), 7.19 (m, 2H), 7.07 (d, 1H), 6.98 (t, 1H), 5.13 (s, 2H), 3.65 (t, 2H), 2.70 (t, 2H), 2.57 (s, 3H).

Example 137: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfanyl-acetylamino)-butyramide

The procedure of Example 135 was repeated except for using 0.3 g of the compound obtained in (20-1) of Example 20 and 0.11 ml of methylthioacetic acid 0.11 ml to obtain the title compound (0.3 g, 85%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (s, 1H), 8.47 (s, 1H), 7.89 (d, 1H), 7.73 (m, 2H), 7.59 (dd, 1H), 7.40 (m, 1H), 7.27 (m, 2H), 7.17 (d. 1H), 7.02 (t, 1H), 5.23 (s, 2H), 3.15 (s, 2H), 2.51 (t, 2H), 2.15 (s, 3H), 1.96 (t, 2H).

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Example 138: Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-4-(2-methanesulfinyl-acetylamino)-butyramide

The procedure of Example 118 was repeated except for using 0.11 g of the compound obtained in Example 137 instead of the compound obtained in Example 117 to obtain the title compound (70 mg, 61%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (d, 1H), 8.43 (s, 1H), 7.88 (d, 1H), 7.69 (m, 2H), 7.57 (dd, 1H), 7.38 (m, 1H), 7.25 (m, 2H), 7.08 (d, 1H), 7.02 (t, 1H), 5.16 (s, 2H), 3.82 (d, 1H), 3.63 (d, 1H), 3.38 (m, 2H), 2.75 (s, 3H), 2.51 (t, 2H), 1.95 (m, 2H).

Example 139: Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide

(139-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-formamide

2 g of the compound obtained in (1-4) of Example 1 and 0.78 ml of formic acid dissolved in 20 ml of dichloromethane was reacted with 1.64 ml of pyridine and 3.88 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at room temperature for 3 hours. The reacted solution was filtered under a reduced pressure after adding saturated sodium bicarbonate to obtain the title compound as solid (1.8 g, 84%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.64 (d, 1H), 8.46 (d, 1H), 8.30 (d, 1H), 7.88 (d, 1H), 7.76 (d, 1H), 7.72 (d, 1H), 7.58 (dd, 1H), 7.39 (m, 1H), 7.27 (m, 2H), 7.12 (d, 1H), 7.03 (t, 1H), 5.21 (s, 2H).

(139-2) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-*N*6-methyl-quinazolin-4,6-diamine

1 g of the compound obtained in (139-1) dissolved in 20 ml of THF was added to 0.45 g of lithium aluminum hydride dissolved in 5 ml of THF at 0℃,

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and reacted for 4 hour while heating the solution slowly to 60℃. The reacted solution was dried over magnesium sulfate after adding 0.5 ml of distilled water, 2.8 ml of 1 N aqueous sodium hydroxide solution and 1 ml of distilled water sequentially, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.6 g, 62%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.57 (s, 1H), 7.79 (s, 1H), 7.71 (d, 1H), 7.52 (dd, 1H), 7.32 (m, 1H), 7.15 (m, 3H), 6.98 (m, 3H), 6.52 (s, 1H), 5.14 (s, 2H), 2.96 (s, 3H).

(139-3) Preparation of [2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-carbamic acid *t*-butylester

0.55 g of the compound obtained in (139-2) and 1.02 g of 3-*t*-buthoxycarbonylamino-propionic acid dissolved in 15 ml of pyridine were reacted with 1.29 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride at room temperature for 2 hours. The reacted solution was distilled under a reduced pressure to remove solvent, and saturated sodium bicarbonate was added thereto. The resultant was extracted with chloroform 2 times, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.62 g, 80%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.78 (s, 1H), 8.38 (s, 1H), 7.91 (m, 2H), 7.70 (d, 1H), 7.59 (m, 1H), 7.34 (m, 1H), 7.23 (m, 2H), 6.97 (m, 2H), 5.17 (s, 2H), 3.42 (m, 2H), 3.35 (s, 3H), 2.55 (m, 2H), 1.2 5(s, 9H).

(139-4) Preparation of 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-*N*-methyl-propionamide

0.58 g of the compound obtained in (139-3) dissolved in 10 ml of dichloromethane and 10 ml of trifluoroacetic acid was stirred at room temperature for 1 hour. The residue obtained from distillation of the reacted

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solution under a reduced pressure was dissolved in small amount of dichloromethane and stirred while adding saturated sodium bicarbonate. The resulting solution was extracted with chloroform, washed with saturated saline solution, dried over magnesium sulfate, and filtered and distilled under a reduced pressure to obtain the title compound (0.4 g, 83%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.75 (s, 1H), 8.38 (s, 1H), 7.97 (m, 3H), 7.59 (m, 2H), 7.33 (m, 1H), 7.20 (m, 2H), 6.98 (m, 2H), 5.15 (s, 2H), 3.36 (s, 3H), 2.98 (m, 2H), 2.37 (m, 2H); MS(ESI): [M+H+] 480.

(139-5) Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-methyl-carbamoyl)-ethyl]-acrylamide

The procedure of Example 22 was repeated except for using 0.5 g of the compound obtained in (139-4) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.25 g, 45%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.30 (s, 1H), 8.74 (s, 1H), 8.13 (s, 1H), 7.93 (m, 2H), 7.71 (d, 1H), 7.57 (dd, 1H), 7.35 (m, 1H), 7.23 (m, 2H), 6.98 (m, 3H), 6.15 (m, 2H), 5.63(dd, 1H), 5.15 (s, 2H), 3.55 (m, 2H), 3.34 (s, 3H), 2.55 (t, 2H).

Example 140: Preparation of *N*-[2-({4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-ethyl-carbamoyl)-ethyl]-acrylamide

The procedure of (139-5) of Example 139 was repeated except for using 3-amino-*N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-*N*-ethyl-propionamide instead of the compound obtained in (139-4) of Example 139 to obtain the title compound (15 mg, 5%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.21 (s, 1H), 8.77 (s, 1H), 7.95 (s, 2H), 7.88 (d, 1H), 7.72 (dd, 1H), 7.56 (dd, 1H), 7.33 (m, 1H), 7.22 (m, 2H), 7.00 (m, 2H), 6.71 (bt, 1H), 6.18 (m, 2H), 5.67 (dd, 1H), 5.17 (s, 2H), 3.84 (m, 2H), 3.57 (m, 2H), 2.50 (m, 2H), 1.09 (t, 3H).

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Example 141: Preparation of *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide

(141-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-acrylamide

The procedure of Example 22 was repeated except for using 8.8 g of the compound obtained in (1-4) of Example 1 instead of the compound obtained in (139-4) of Example 139 to obtain the title compound (5 g, 50%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.77 (s, 1H), 10.01 (s, 1H), 8.95 (s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 8.09 (d, 1H), 7.86-7.92 (m, 2H), 7.58-7.63 (m, 1H), 7.32-7.46 (m, 4H), 6.61-6.65 (m, 1H), 6.50 (d, 1H), 5.99 (d, 1H), 5.39 (s, 2H).

(141-2) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-dimethylamino-propionamide

6 ml of dimethylamine 2 M THF was added to 534 mg of the compound obtained in (141-1) and 113 mg of *p*-toluene sulfonic acid dissolved in 15 ml of THF, and reacted for 5 hour while heating the solution slowly to 50℃. The reacted solution was cooled to room temperature, extracted with ethylacetate 3 times after adding saturated sodium bicarbonate, washed with saturated saline solution, dried over magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (0.4 g, 68%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.50 (s, 1H), 8.40 (s, 1H), 7.83 (d, 1H), 7.63 (s, 2H), 7.52 (dd, 1H), 7.3 (m, 1H), 7.19 (m, 2H), 6.97 (m, 2H), 5.08 (s, 2H), 2.76 (t, 2H), 2.61 (t, 2H), 2.33 (s, 6H).

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(141-3) Preparation of N^4-[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]-N^6-(3-dimethylamino-propyl)-quinazolin-4,6-diamine

The procedure of (139-2) of Example 139 was repeated except for using 0.13 g of the compound obtained in (141-2) instead of the compound obtained in (139-1) of Example 139 to obtain the title compound (0.12 g, 93%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.22 (s, 1H), 7.80 (s, 1H), 7.48 (m, 3H), 7.31 (m, 1H), 7.22 (m, 3H), 7.04 (m, 2H), 5.06 (s, 2H), 3.19 (bt, 2H), 2.41 (t, 2H), 2.25 (s, 6H), 1.83 (m, 2H).

(141-4) Preparation of *N*-{2-[{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-(3-dimethylamino-propyl)-carbamoyl]-ethyl}-acrylamide

The procedure of Example 139 was repeated except for using 335 mg of the compound obtained in (141-3) instead of the compound obtained in (139-2) of Example 139 to obtain the title compound (80 mg, 23%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.55 (s, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 7.85 (d, 1H), 7.74 (d, 1H), 7.6 1(d, 1H), 7.37 (m, 1H), 7.25 (m, 2H), 7.14 (d, 1H), 7.03 (t, 1H), 6.14 (m, 2H), 5.57 (m, 1H), 5.19 (s, 2H), 3.84 (t, 2H), 3.46 (t, 2H), 2.37 (m, 4H), 2.24 (s, 6H), 1.77 (m, 2H).

Example 142: Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

(142-1) Preparation of *N*-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-yl}-3-methylamino-propionamide

The procedure of (141-2) of Example 141 was repeated except for using methylamine instead of dimethylamine to obtain the title compound (0.41 g, 96%).

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^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (d, 1H), 8.35 (s, 1H), 7.78 (d, 1H), 7.66 (m, 2H), 7.49 (dd, 1H), 7.32 (m, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.96 (t, 1H), 5.13 (s, 2H), 2.85 (t, 2H), 2.57 (t, 2H), 2.34 (s, 3H).

(142-2) Preparation of *N*-(2-{4-[3-chloro-4-(3-fluoro-benzyloxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

The procedure of Example 22 was repeated except for using 0.38 g of the compound obtained in (142-1) instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (0.04 g, 10%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.06 (s, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 8.08 (bs, 1H), 7.81 (d, 1H), 7.71 (m, 2H), 7.53 (dd, 1H), 7.36 (m, 1H), 7.22 (m, 2H), 7.02 (t, 1H), 6.92 (d, 1H), 6.59 (m, 1H), 6.36 (d, 1H), 5.77 (d, 1H), 5.12 (s, 2H), 3.87 (t, 2H), 3.12 (s, 3H), 2.79 (t, 2H).

Example 143: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-methyl-acrylamide

The procedure of Example 22 was repeated except for using *N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-3-methylamino-propionamide instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (80 mg, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.80 (s, 1H), 8.38 (m, 3H), 7.64 (d, 1H), 7.52 (m, 3H), 7.43 (d, 1H), 7.28 (d, 1H), 7.02 (t, 1H), 6.77 (d, 1H), 6.39 (m, 1H), 6.18 (d, 1H), 5.57 (d, 1H), 5.06 (s, 2H), 3.66 (t, 2H), 2.96 (s, 3H), 2.61 (t, 2H).

Example 144: Preparation of *N*-(2-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using 3-amino-*N*-{4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-

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yl}-propionamide instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (47 mg, 12%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.61 (s, 1H), 8.42 (s, 1H), 7.88 (d, 1H), 7.70 (m, 3H), 7.55 (dd, 1H), 7.47 (d, 1H), 7.21 (d, 1H), 7.10 (d, 1H), 6.19 (m, 2H), 5.62 (dd, 1H), 5.18 (s, 2H), 3.60 (t, 2H), 2.70 (t, 2H), 2.51 (s, 3H).

Example 145: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

(145-1) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(6-nitro-quinazolin-4-yl)-amine hydrochloride salt

The procedure of (1-3) of Example 1 was repeated except for using 3.13 g of the compound obtained in (1-2) of Example 1 and 2.99 g of 3-chloro-4-(pyridin-2-ylmethoxy)-phenylamine instead of 3-chloro-4-(3-fluorobenzyloxy)-phenylamine to obtain the title compound (5 g, 88%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.80 (s, 1H), 8.95 (s, 1H), 8.75 (dd, 1H), 8.69 (d, 1H), 8.11 (d, 1H), 8.05 (t, 1H), 7.97 (d, 1H), 7.72 (m, 2H), 7.68 (t, 1H), 7.36 (d, 1H), 5.41 (s, 2H).

(145-2) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-quinazolin-4,6-diamine

The procedure of (1-4) of Example 1 was repeated except for using 4.5 g of the compound obtained in (145-1) instead of the compound obtained in (1-3) of Example 3 to obtain the title compound (2 g, 47%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.33 (s, 1H), 8.60 (d, 1H), 8.30 (s, 1H), 8.06 (d, 1H), 7.88 (t, 1H), 7.74 (dd, 1H), 7.59 (d, 1H), 7.50 (d, 1H), 7.38 (m, 2H), 7.22 (d, 2H), 5.41 (s, 2H), 5.56 (bs, 2H), 5.27 (s, 2H).

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(145-3) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

The procedure of (1-5) of Example 1 was repeated except for using 414 mg of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of 2-*t*-butoxycarbonylamino-ethanoic acid and 368 mg of the compound obtained in (145-2) to obtain the title compound (200 mg, 35%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (s, 1H), 8.58 (d, 1H), 8.49 (s, 1H), 7.90-7.93 (m, 2H), 7.72-7.79 (m, 2H), 7.63 (dd, 1H), 7.42 (t, 1H), 7.20 (d, 1H), 5.29 (s, 2H), 4.35 (m, 1H), 3.59 (m, 2H), 2.04 (m, 4H), 1.43 (m, 9H).

(145-4) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of (2-3) of Example 2 was repeated except for using 200 mg of the compound obtained in (145-3) instead of the compound obtained in (1-5) of Example 1 to obtain the title compound (130 mg, 79%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.57 (s, 2H), 8.49 (s, 1H), 7.93 (m, 3H), 7.75 (t, 1H), 7.60 (d, 1H), 7.39 (t, 1H), 7.10 (d, 1H), 5.26 (s, 2H), 4.85 (m, 1H), 3.85 (m, 1H), 3.75 (m, 1H), 1.80 - 2.20 (m, 4H).

(145-5) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 18 was repeated except for using the compound obtained in (145-4) instead of the compound obtained in (16-1) of Example 16 to obtain the title compound (32 mg, 22%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.65 (d, 1H), 8.65 (d, 1H), 8.58 (s, 1H), 7.88-7.93 (m, 3H), 7.70-7.80 (m, 2H), 7.65 (t, 1H), 7.40 (t, 1H), 7.20 (d, 1H), 6.55-6.79 (m, 1H), 6.30 (dd, 1H), 5.80 (dd, 1H), 5.27 (s, 2H), 4.60-4.70 (m, 1H), 3.80 (m, 2H), 2.26 (m, 4H).

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Example 146: Preparation of (2*S*)-1-(1-oxo-butyn-2-yl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 18 was repeated except for using 2-butynoic acid instead of acrylic acid to obtain the title compound (43 mg, 13%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.70 (s, 1H), 8.92 (s, 1H), 8.61 (s, 2H), 7.85 (s, 1H), 7.75 (t, 1H), 7.67 (d, 2H), 7.51 (dd, 1H), 7.43 (s, 1H), 6.92 (d, 1H), 7.26 (m, 2H), 5.77 (t, 1H), 5.29 (s, 2H), 4.82 (d, 1H), 4.05 (s, 3H), 3.77 (m, 2H), 2.60 (m, 1H), 1.92 - 2.13 (m, 3H), 2.02 (s ,3H).

Example 147: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-quinazolin-4,6-diamine as a starting material to obtain the title compound (250 mg, 66%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.59 (s, 1H), 8.48 (s, 1H), 8.15 (bs, 1H), 7.95 (d, 1H), 7.79 (m, 2H), 7.62 (t, 1H), 7.51 (bs, 1H), 7.46 (d, 1H), 7.36 (d, 1H), 7.08 (d, 1H), 6.98 (d, 1H), 6.60 (m, 1H), 6.39 (dd, 1H), 5.78 (dd, 1H), 5.26 (s, 2H), 5.02 (m, 1H), 3.93 (m, 1H), 3.74 (m, 1H), 2.58 (s, 3H), 2.39 (m, 2H), 2.28 (m, 1H), 2.15 (m, 1H).

Example 148: Preparation of (3*R*,5*S*)-acetic acid 1-acryloyl-5-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-pyrrolidin-3-ylester

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-acetoxy-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-

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pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (300 mg, 46%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.50 (s, 1H), 8.60 (d, 1H), 8.47 (s, 1H), 8.18 (bs, 1H), 7.94 (d, 1H), 7.75 (m, 4H), 7.50 (s, 1H), 7.34 (d, 1H), 7.25 (t, 1H), 7.06 (d, 1H), 6.53 (m, 1H), 6.40 (m, 1H), 5.81 (d, 1H), 5.57 (m, 1H), 5.29 (s, 2H), 5.08 (t, 1H), 4.20 (m, 1H), 3.89 (d, 1H), 2.67 (m, 1H), 2.52 (m, 1H), 2.12 (s, 3H).

Example 149: Preparation of (2*S*,4*R*)-1-acryloyl-4-hydroxyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

0.32 ml of ammonia water was added to 130 mg of the compound obtained in Example 148 diluted with 10 ml of methanol, and the solution was refluxed with stirring at 80℃ for 26 hours. The reacted solution was cooled to room temperature, and filtered under a reduced pressure to obtain solid. The solid was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (80 mg, 66%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.48 (s, 1H), 8.59 (d, 1H), 8.52 (s, 1H), 7.97 (m, 1H), 7.88 (m, 2H), 7.76 (m, 2H), 7.66 (m, 2H), 7.45 (d, 1H), 7.01 (d, 1H), 6.52 (m, 1H), 6.40 (d, 1H), 5.79 (d, 1H), 5.29 (s, 2H), 5.12 (t, 1H), 4.78 (m, 1H), 3.92 (m, 1H), 3.75 (m, 1H), 2.60 (m, 1H), 2.17 (m, 1H).

Example 150: Preparation of (2*S*,4*R*)-1-acryloyl-4-ethylsulfanyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-ethylsulfanyl-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 36%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.35 (s, 1H), 8.60 (d, 1H), 8.50 (s, 1H), 8.04 (bs, 1H), 7.97 (d, 1H), 7.70 (m, 5H), 7.42 (d, 1H), 7.25 (t, 1H), 7.01 (d, 1H), 6.68 (m, 1H), 6.40 (dd, 1H), 5.82 (dd, 1H), 5.30 (s, 2H), 4.92 (t, 1H), 4.18 (m, 1H), 3.70 (t, 1H), 3.47 (m, 1H), 2.73 (m, 1H), 2.68 (m, 2H), 2.43 (m, 1H), 1.33 (t, 3H).

Example 151: Preparation of (2*S*,4*R*)-1-acryloyl-4-dimethylamino-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-dimethylamino-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (60 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.28 (s, 1H), 8.64 (d, 1H), 8.59 (s, 1H), 7.97 (d, 1H), 7.76 (m, 6H), 7.56 (d, 1H), 7.30 (t, 1H), 7.05 (d, 1H), 6.55 (m, 2H), 5.89 (dd, 1H), 5.40 (m, 1H), 5.34 (s, 2H), 5.10 (m, 1H), 4.14 (m, 1H), 3.95 (m, 1H), 2.95 (s, 3H), 2.87 (s, 3H), 2.80 (m, 1H), 2.58 (m, 1H).

Example 152: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (19 mg, 14%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.72 (s, 1H), 8.67 (s, 1H), 8.55 (m, 1H), 8.51 (s, 1H), 7.93 (t, 1H), 7.92 (d, 1H), 7,82 (d, 1H), 7.80 (m, 1H), 7.60 (dd, 1H), 7.50 (dd, 1H), 7.26 (d, 1H), 6.35 (dd, 1H), 5.84 (d, 1H), 5.45 (d, 1H), 5.29 (s, 2H), 4.70 (m, 1H), 3.70 (m, 2H), 2.00 - 2.20 (m, 4H).

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Example 153: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (8.3 mg, 10%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.60 (m, 3H), 7.94 (dd, 2H), 7.80 (d, 1H), 7.60 (m, 3H), 7.20 (d, 1H), 6.70 (dd, 1H), 6.30 (d, 1H), 5.80 (d, 1H), 5.20 (s, 2H), 4.80 (m, 1H), 3.80 (m, 2H), 2.20 (m, 4H).

Example 154: Preparation of 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-acetamide

The procedure of Example 145 was repeated except for using 2-carboxymethyl-pyrrolidine-1-carboxylic acid *t*-butylester (see, *J. Med. Chem.* 1991, 34(2):717) instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 13%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.23 (br s, 1H), 8.66 (s, 1H), 8.60 (br s, 2H), 7.89 (d, 1H), 7.65 - 7.83 (m, 3H), 7.56 (m, 2H), 7.24 (t, 1H), 7.01 (d, 1H), 6.48 (m, 2H), 5.79 (m, 1H), 5.30 (s, 2H), 4.50 (m, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 2.92 (dd, 1H), 2.60 (dd, 1H), 2.11 (m, 4H).

Example 155: Preparation of 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using pyrrolidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (29 mg, 10%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.59 (m, 3H), 7.61-7.76 (m, 5H), 7.45 (d, 1H), 7.23 (t, 1H), 6.93 (d, 1H), 6.32 (m, 2H), 5.68 (m, 1H), 5.24 (s, 2H), 4.88 (br s, 1H), 3.80 (m, 2H), 3.58 (m, 1H), 3.15 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H).

Example 156: Preparation of 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,4-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (35 mg, 11%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.76 (s, 1H), 8.69 (s, 1H), 8.60 (d, 1H), 7.85 (m, 2H), 7.75 (m, 1H), 7.66 (m, 1H), 7.50 (m, 2H), 7.42 (d, 1H), 7.01 (d, 1H), 6.58 (dd, 1H), 6.30 (dd, 1H), 5.73 (dd, 1H), 5.29 (s, 2H), 4.70 (br s, 1H), 3.20 (m, 1H), 2.80 (m, 2H), 2.50 (m, 1H), 1.82 (m, 4H).

Example 157: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using N^4-[3-methyl-4-(6-methyl-pyridin-3-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (170 mg, 29%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.79 (s, 1H), 8.70 (d, 1H), 8.49 (s, 1H), 8.17 (d, 1H), 7.84 (dd, 1H), 7.74 (m, 2H), 7.65 (dd, 1H), 7.22 (m, 2H), 6.95 (d, 1H), 6.60 (dd, 1H), 6.18 (d, 1H), 5,69 (d, 1H), 4.50 (m, 1H), 3.60 (m, 2H), 2.44 (s, 3H), 2.21 (m, 1H), 2.20 (s, 3H), 2.01 (m, 3H).

Example 158: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-ethynyl-phenylamino)-quinazolin-6-yl]-amide

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The procedure of Example 145 was repeated except for using N^4-(3-ethynyl-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (69 mg, 10%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.32 (br s, 1H), 9.81 (s, 1H), 8.65 (s, 1H), 8.48 (s, 1H), 7.93 (s, 1H), 7.79 (m, 2H), 7.73 (m, 2H), 7.31 (t, 1H), 7.13 (d, 1H), 6.61 (m, 1H), 6.08 (dd, 1H), 5.66 (dd, 1H), 4.53 (t, 1H), 4.11 (s, 1H), 3.63 (m, 2H), 1.96 (m, 4H).

Example 159: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-(3-chloro-4-fluoro-phenylamino)-quinazolin-6-yl]-amide

The procedure of Example 145 was repeated except for using N^4-(3-chloro-4-fluoro-phenyl)-quinazolin-4,6-diamine instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (109 mg, 19%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.38 (br s, 1H), 9.92 (s, 1H), 8.72 (s, 1H), 8.71 (s, 1H), 8.31 (m, 1H), 7.81 (m, 3H), 6.66 (m, 1H), 6.16 (dd, 1H), 5.70 (dd, 1H), 4.60 (t, 1H), 3.69 (m, 2H), 2.09 (m, 2H), 1.98 (m, 2H).

Example 160: Preparation of (2*S*,4*R*)-1-acryloyl-4-ethanesulfonyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-ethanesulfonyl-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (10 mg, 9%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.42 (m, 3H), 7.79 (d, 1H), 7.65 (m, 3H), 7.46 (m, 2H), 7.16 (t, 1H), 6.90 (d, 1H), 6.32 (m, 1H), 5.98 (m, 1H), 5.68 (m,

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1H), 5.15 (s, 2H), 4.69 (m, 1H), 4.28 (t, 1H), 4.0 5(m, 2H), 3.75 (m, 1H), 2.7 2(m, 1H), 2.53 (m 2H), 1.32 (t, 3H).

Example 161: Preparation of (2*S*,4*R*)-1-acryloyl-4-methoxy-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using (2*S*,4*R*)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 42%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.61 (d, 1H), 8.60 (s, 1H), 8.17 (s, 1H), 7.91 (dd, 1H), 7.76 (m, 2H), 7.69 (s, 1H), 7.59 (s, 1H), 7.25 (t, 1H), 7.01 (d, 1H), 6.50 (m, 2H), 5.82 (m, 1H), 5.30 (s, 2H), 5.01 (t, 1H), 4.93 (m, 1H), 4.35 (m, 1H), 4.02 (m, 1H), 3.43 (s, 3H), 2.75 (m, 1H), 2.48 (m, 1H).

Example 162: Preparation of 1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (130 mg, 43%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.63(s, 1H), 8.76 (s, 1H), 8.68 (s, 1H), 8.60 (d, 1H), 7.84 (m, 2H), 7.76 (m, 2H), 7.66 (d, 1H), 7.55 (m, 2H), 7.02 (d, 1H), 6.59 (dd, 1H), 6.39 (d, 1H), 5.8 1(d, 1H), 5.30 (s, 2H), 4.43 (d, 1H), 6.39 (d, 1H), 5.81(d, 1H), 5.30 (s, 2H), 4.43 (d, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 3.49 (m, 1H), 2.80 (m, 1H), 2.48 (m, 1H), 1.70 (m, 3H).

Example 163: Preparation of 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

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The procedure of Example 145 was repeated except for using azetidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (85 mg, 34%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.76 (s, 1H), 8.67 (s, 1H), 8.63 (d, 1H), 8.30 (s, 1H), 7.8 (m, 3H), 7.67 (d, 1H), 7.49 (t, 2H), 6.99 (d, 1H), 6.31 (d, 1H), 6.23 (dd, 1H), 5.73 (d, 1H), 5.29 (s, 2H), 4.60 (m, 1H), 4.29 (m, 3H), 3.49 (m, 1H).

Example 164: Preparation of 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using piperidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (67 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.27 (s, 1H), 8.65 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.90 (d, 1H), 7.76 (t, 2H), 7.67 (d, 1H), 7.54 (m, 3H), 7.30 (d, 1H), 6.65 (dd, 1H), 6.44 (dd, 1H), 5.85 (dd, 1H), 4.00 (d, 1H), 3.25 (t, 1H), 2.30 (d, 1H), 1.58 - 2.03 (m, 6H).

Example 165: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

(165-1) Preparation of 4-chloro-7-fluoro-6-nitro-quinazoline

Preparation of the compound was carried out in accordance with Examples of International patent publication WO 00/031048.

(165-2) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(7-fluoro-6-nitro-quinazolin-4-yl)-amine hydrochloride salt

72 g of the compound obtained in (165-1) and 74 g of 3-chloro-4-(pyridin-2-ylmethoxy)-phenylamine was stirred at 100℃ for 17 hours after

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adding 1,000 ml of isopropanol. The reacted solution was cooled, filtered under a reduced pressure, washed with acetone and dried at 40℃ for 15 hours to obtain the title compound (118 g, 91%).

(165-3) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine

The procedure of (1-4) of Example 1 was repeated except for using 1.5 g of the compound obtained in (165-2) instead of the compound obtained in (1-3) of Example 1 to obtain the title compound (1.3 g, 91%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.23 (s, 1H), 8.59 (d, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.91 (s, 1H), 7.71 (t, 1H), 7.58 (dd, 1H), 7.35 (m, 2H), 7.22 (t, 1H), 7.05 (m, 1H), 5.32 (s, 2H), 5.25 (s, 2H).

(165-4) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

The procedure of (145-3) of Example 145 was repeated except for using 1.74 g of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester and 0.8 g of the compound obtained in (165-3) instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (1.1 g, 89%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 9.49 (d, 1H), 8.90 (d, 1H), 8.65 (d, 1H), 8.41 (s, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.25 (s, 2H), 4.50 (m, 1H), 1.80-2.18 (m, 6H).

(165-5) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

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The procedure of (145-4) of Example 145 was repeated except for using 1.1 g of the compound obtained in (165-4) instead of the compound obtained in (145-3) of Example 145 to obtain the title compound (0.8 g, 90%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.40 (s, 1H), 9.75 (s, 1H), 9.06 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.65 (dd, 1H), 7.59 (d, 1H), 7.35 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.01 (s, 3H), 2.99 (m, 1H), 2.84 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.61 (m, 2H).

(165-6) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

The procedure of (145-5) of Example 145 was repeated except for using 474 mg of the compound obtained in (165-5) instead of the compound obtained in (145-5) of Example 145 to obtain the title compound (260 mg, 49%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.70 (s, 1H), 8,51 (d, 1H), 8.35 (s, 1H), 7.88 (m, 2H), 7.71 (d, 1H), 7.55 (dd, 1H), 7.30 (t, 1H), 7,12 (m, 2H), 6,71 (dd, 1H), 6,35 (d, 1H), 5.81 (d, 1H), 5.21 (s, 2H), 4.80 (m, 1H), 3.80 (m, 2H), 2.03 - 2.30 (m, 4H).

Example 166: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

(166-1) Preparation of [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(7-methoxy-6-nitro-quinazolin-4-yl)-amine

100 ml of dimethylsulfoxide and 5.84 g of sodium methoxide were added to 5 g of the compound obtained in (165-2) of Example 165, and the mixture was stirred at room temperature for 20 hours. The resultant was

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stirred for 30 mins after adding water, filtered under a reduced pressure and dried 40℃ to obtain the title compound (4.7 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.13(s,1H) 8.45(d,1H) 8.49(s,1H) 7.91(s,1H) 7.81(t,1H) 7.55(m,2H) 7.23(m,2H) 7.07(m,1H) 5.24(s,2H) 3.99(s,3H)

(166-2) Preparation of N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine

3 g of iron was refluxed with stirring at 100℃ for 1 hour after adding 100 ml of 50% aqueous ethanol solution and 0.358 ml of HCl, the mixture was refluxed with stirring after adding 4.7 g of the compound obtained in (166-1) for 1 hour. The resultant was filtered under a reduced pressure through celite pad, and the pad was washed with ethylacetate. The organic layer was dried over magnesium sulfate, and distilled under a reduced pressure to obtain the title compound (3.4 g, 79%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.23 (s, 1H), 8.59 (d, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.70 (t, 1H), 7.58 (dd, 1H), 7.36 (m, 2H), 7.22 (t, 1H), 7.07 (m, 1H), 5.31 (s, 2H), 5.28 (s, 2H), 3.95 (s, 3H).

(166-3) Preparation of (2*S*)-2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-pyrrolidine-1-carboxylic acid *t*-butylester

3.75 g of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester and 30 ml of pyridine were added to 3.4 g of the compound obtained in (166-2), and the mixture was stirred for 5 hours after adding 3.53 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. The reacted solution was extracted with ethylacetate after adding water, dried over anhydrous magnesium sulfate, filtered and distilled under a reduced pressure, and the resulting residue was subjected to column chromatography (eluent-chloroform : methanol = 15 : 1) to obtain the title compound (3.4 g, 68%).

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^{1}H-NMR (DMSO-d_6, 300MHz): δ 9.71 (s, 1H), 9.49 (d, 1H), 8.95 (d, 1H), 8.60 (d, 1H), 8.46 (s, 1H), 8.30 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.51 (m, 1H), 4.03 (s, 3H), 1.80-2.18 (m, 6H).

(166-4) Preparation of (2*S*)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

60 ml of dimethylene chloride and 60 ml of trifluoroacetic acid were added to 3.3 g of the compound obtained in (166-3). After 4 hours, the reacted solution was distilled under a reduced pressure, distilled with small amount of water, and neutralized with saturated aqueous sodium bicarbonate solution. The solution was filtered under a reduced pressure and dried at 40℃ for 15 hours to obtain the title compound (2.8 g, 99%).

^{1}H-NMR (DMSO-d_6, 300MHz): δ 10.46 (s, 1H), 9.71 (s, 1H), 9.06 (s, 1H), 8.60 (d, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.88 (t, 1H), 7.67 (dd, 1H), 7.59 (d, 1H), 7.38 (t, 1H), 7.21 (m, 2H), 5.28 (s, 2H), 4.03 (s, 3H), 3.81 (s, 1H), 2.99 (m, 1H), 2.84 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 1.64 (m, 2H).

(166-5) Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

0.489 ml of acrylic acid dissolved in 50 ml of THF was reacted with 1.77 ml of pyridine, 1.37 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.8 g of the compound obtained in (166-4) for 4 hours. The reacted solution was diluted with water, extracted with ethylacetate, dried over anhydrous magnesium sulfate, and the resulting residue was subjected to column chromatography (eluent- chloroform : methanol = 15 : 1) to obtain the title compound (743 mg, 37%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.76 (s, 1H), 8,55 (d, 1H), 8.40 (s, 1H), 7.88 (m, 2H), 7.71 (d, 1H), 7.55 (dd, 1H), 7.33 (t, 1H), 7,12 (m, 2H), 6,71 (dd,

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1H), 6,36 (d, 1H), 5.82 (d, 1H), 5.23 (s, 2H), 4.85 (m, 1H), 4.02 (s, 3H), 3.81 (m, 2H), 2.03 - 2.27 (m, 4H).

Example 167: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using 3-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid 1-*t*-butylester to obtain the title compound (80 mg, 21%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.85 (s, 1H), 8.57 (t, 1H), 8.45 (s, 1H), 7.93 (m, 2H), 7.75 (d, 1H), 7.60 (dd, 1H), 7.41 (t, 1H), 7.22 (s, 1H), 7.19 (d, 1H), 6.26 (m, 2H), 5.69 (dd, 1H), 5.29 (s, 2H), 4.07 (s, 3H), 3.69 (t, 2H), 2.01 (t, 2H).

Example 168: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-methoxy-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (230 mg, 23%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.85 (s, 1H), 9.02 (s, 1H), 8.67 (m, 2H), 7.79 (m, 1H), 7.64 (d, 1H), 7.50 (m, 2H), 7.41 (s, 1H), 7.28 (m, 2H), 6.96 (d, 1H), 6.60 (m, 2H), 5.89 (m, 1H), 5.31 (s, 2H), 4.98 (m, 1H), 4.09 (s, 3H), 3.80 (m, 1H), 3.71 (m, 1H), 2.60 (m, 1H), 2.44 (s, 3H), 2.20 (m, 3H).

Example 169: Preparation of 2-(1-acryloyl-pyrrolidin-2-yl)-*N*-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-acetamide

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The procedure of Example 166 was repeated except for using 2-carboxymethyl-pyrrolidine-1-carboxylic acid *t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (72 mg, 14%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.56 (s, 2H), 8.00 (s, 1H), 7.79 (s, 1H), 7.72 (m, 1H), 7.61 (m, 1H), 7.48 (d, 1H), 7.29 (m, 1H), 7.19 (t, 1H), 6.91 (d, 1H), 6.43 (m, 2H), 5.69 (dd, 1H), 5.23 (s, 2H), 4.42 (br s, 1H), 3.95 (s, 3H), 3.55 (m, 2H), 3.05 (m, 1H), 2.59 (m, 1H), 2.02 (m, 4H).

Example 170: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (170 mg, 28%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.8 1(s, 1H), 8.79 (s, 1H), 8.57 (m, 2H), 8.08 (s, 1H), 7.80 (d, 1H), 7.73 (td, 1H), 7.64 (d, 1H), 7.52 (dd, 1H), 7.22 (t, 1H), 6.99 (s, 1H), 6.94 (d, 1H), 6.48 (m, 2H), 5.78 (dd, 1H), 5.25 (s, 2H), 4.98 (d, 1H), 3.96 (m, 2H), 3.73 (m, 1H), 3.62 (m, 1H), 2.52 (m, 1H), 2.07 (m, 3H), 1.44 (t, 3H).

Example 171: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethylsulfanyl-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethylsulfanyl-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 32%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.95 (s, 1H), 8.58 (d, 1H), 8.46 (s, 1H), 8.17 (s, 1H), 8.00 (s, 1H), 7.74 (m, 2H), 7.63 (m, 2H), 7.35 (s, 1H), 7.23 (t, 1H), 6.94 (d, 1H), 6.54 (m, 1H), 6.37 (dd, 1H), 5.74 (dd, 1H), 5.27 (s, 2H), 5.12 (m, 1H), 3.88 (m, 1H), 3.70 (m, 1H), 2.71 (m, 2H), 2.60 (m, 1H), 2.25 (m, 3H), 1.29 (t, 3H).

Example 172: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopropylmethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethylsulfanyl-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 32%).

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-cyclopropylmethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (19 mg, 5%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.61 (m, 1H), 7.92 (s, 1H), 7.77 (m, 2H), 7.69 (d, 2H), 7.20-7.40 (m, 3H), 7.01 (m, 1H), 6.43 (d, 1H), 6.19 (dd, 1H), 5.92 (d, 1H), 5.25 (s, 2H), 4.45 (m, 1H), 4.02 (m, 2H), 3.74 (m, 1H), 2.77 (m, 1H), 2.00 (m, 5H), 0.89 (t, 2H), 0.63 (d, 2H), 0.40 (q, 2H).

Example 173: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-cyclopentyloxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-cyclopentyloxy-quinazolin-4,6-

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diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (300 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.86 (s, 1H), 8.88 (s, 1H), 8.52 (s, 2H), 7.76 (s, 1H), 7.67 (m, 1H), 7.57 (d, 2H), 7.41 (dd, 1H), 7.21 (m, 3H), 6.92 (d, 1H), 6.89 (m, 2H), 5.77 (t, 1H), 5.21 (s, 2H), 4.90 (m, 2H), 3.55 (m, 2H), 2.55 (m, 1H), 1.60-2.10 (m, 10H).

Example 174: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using N^4-[3-chloro-4-(pyridin-4-ylmethoxy)-phenyl]-quinazolin-4,6-diamine instead of the compound obtained in (1-4) of Example 1 to obtain the title compound (10 mg, 13%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.77 (s, 1H), 8.60 (m, 3H), 7.94 (dd, 2H), 7.80 (d, 1H), 7.60 (m, 3H), 7.20 (d, 1H), 6.90 (m, 1H), 6.50 (d, 1H), 6.20 (m, 1H), 5.30 (s, 2H), 3.60 (t, 2H), 2.80 (t, 2H).

Example 175: Preparation of (2*S*)-1-(4-dimethylamino-buten-2-oyl)-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using 4-dimethylamino-buten-2-oic acid instead of acrylic acid to obtain the title compound (100 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ :9.84 (s, 1H), 8.88 (s, 1H), 8.59 (s, 2H), 7.83 (s, 1H), 7.77 (t, 1H), 7.68 (d, 1H), 7.57 (s, 1H), 7.51 (d, 1H), 7.26 (m, 1H), 7.15 (s, 1H), 7.06 (m, 2H), 6.36 (d, 1H), 5.28 (s, 2H), 4.92 (d, 2H), 3.95 (s, 3H), 3.73 (m, 2H), 3.13 (d, 2H), 2.52 (m, 1H), 2.27 (s, 6H), 1.92-2.13 (m, 3H).

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Example 176: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-chloro-4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-chloro-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (250 mg, 31%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.71 (s, 1H), 8.60 (m, 2H), 8.20 (s, 1H), 7.74 (m, 2H), 7.68 (m, 1H), 7.60 (s, 1H), 7.49 (m, 1H), 7.23 (m, 1H), 6.96 (d, 1H), 6.27 (m, 1H), 6.00 (m, 1H), 5.72 (m, 1H), 5.31 (s, 2H), 4.90 (m, 1H), 4.16 (m, 2H), 4.00 (m, 1H), 3.33 (m, 1H), 3.07 (m, 1H), 2.65 (m, 1H).

Example 177: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (220 mg, 36%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.35 (s, 1H), 8.90 (d, 1H), 8.65 (m, 2H), 7.77 (m, 1H), 7.6 1(m, 2H), 7.53 (d, 1H), 7.46 (m, 2H), 7.26 (m, 1H), 6.92 (d, 1H), 6.57 (m, 2H), 5.88 (m, 1H), 5.28 (s, 2H), 5.02 (m, 1H), 3.80 (m, 1H), 3.66 (m, 1H), 2.68 (m, 1H), 2.41 (s, 3H), 2.20 (m, 1H), 2.02 (m, 2H).

Example 178: Preparation of *N*-(2-{7-fluoro-4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 22 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-fluoro-quinazolin-4,6-diamine

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instead of the compound obtained in (20-1) of Example 20 to obtain the title compound (100 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.98 (bd, 1H), 8.82 (bs, 1H), 8.60 (m, 2H), 7.74 (m, 2H), 7.67 (bs, 1H), 7.54 (m, 2H), 7.41 (m, 2H), 7.26 (m, 1H), 6.88 (d, 1H), 6.61 (m, 1H), 6.30 (m, 1H), 5.72 (m, 1H), 5.23 (s, 2H), 3.80 (m, 2H), 2.82 (m, 2H), 2.36 (s, 3H).

Example 179: Preparation of (2*S*)-1-acryloyl-2,5-dihydro-1*H*-pyrrol-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (2*S*)-dihydro-1*H*-pyrrol-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (15 mg, 3%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.43 (bs, 1H), 8.92 (s, 1H), 8.60 (m, 2H), 7.85 (d, 1H), 7.74 (m, 1H), 7.65 (d, 1H), 7.48 (m, 2H), 7.19 (m, 2H), 6.98 (d, 1H), 6.52 (d, 2H), 6.07 (m, 2H), 5.85 (t, 1H), 5.54 (m, 1H), 5.28 (s, 2H), 4.52 (m, 2H), 4.00 (s, 3H).

Example 180: Preparation of (4*R*)-3-acryloyl-thiazolidin-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (4*R*)-thiazolidin-3,4-dicarboxylic acid-3-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (150 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.48 (bs, 1H), 8.9 1(s, 1H), 8.60 (m, 2H), 7.83 (d, 1H), 7.74 (t, 1H), 7.65 (d, 1H), 7.56 (bs, 1H), 7.48 (dd, 1H), 7.23 (m,

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1H), 7.21 (s, 1H), 6.98 (d, 1H), 6.55 (m, 2H), 5.89 (m, 1H), 5.33 (m, 1H), 5.28 (s, 2H), 4.81 (m, 1H), 4.68 (m, 1H), 4.00 (s, 3H), 3.67 (m, 1H), 3.23 (m, 1H).

Example 181: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-quinazolin-6-yl}-amide

The procedure of Example 145 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (153 mg, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.81 (s, 1H), 8.67 (s, 1H), 8.60 (d, 1H), 8.50 (s, 1H), 7.90 (d, 1H), 7.82 (d, 1H), 7.73 (td, 1H), 7.68 (m, 2H), 7.55 (m, 2H), 7.02 (d, 1H), 6.51 (d, 1H), 6.26 (dd, 1H), 5.87 (dd, 1H), 5.30 (s, 2H), 5.22 (m, 1H), 4.27 (t, 2H), 2.90 (m, 1H), 2.59 (m, 1H).

Example 182: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 181 was repeated except for using the compound obtained in (166-2) of Example 166 instead of the compound obtained in (145-2) of Example 145 to obtain the title compound (106 mg, 17%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.34 (s, 1H), 8.97 (s, 1H), 8.63 (s, 1H), 8.60 (d, 1H), 7.87 (d, 1H), 7.76 (td, 1H), 7.67 (d, 1H), 7.51 (dd, 1H), 7.42 (s, 1H), 7.23 (s, 1H), 7.01 (d, 1H), 6.51 (dd, 1H), 6.26 (dd, 1H), 5.83 (dd, 1H), 5.30 (s, 2H), 5.16 (m, 1H), 4.25 (t, 2H), 4.04 (s, 3H), 2.87 (m, 1H), 2.62 (m, 1H).

Example 183: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-6-yl]-amide

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The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-(2,2,2-trifluoro-ethoxy)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (70 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.96 (s, 1H), 8.80 (s, 1H), 8.60 (m, 2H), 7.86 (d, 1H), 7.76 (m, 2H), 7.66 (d, 1H), 7.53 (dd, 1H), 7.12 (s, 1H), 7.00 (d, 1H), 6.52 (m, 2H), 5.82 (t, 1H), 5.30 (s, 2H), 4.98 (m, 1H), 4.43 (m, 2H), 3.77 (m, 1H), 3.65 (m, 1H), 2.53 (m, 1H), 2.09 (m, 1H).

Example 184: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-dimethylamino-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-dimethylamino-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (190 mg, 44%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.61 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 8.53 (d, 1H), 7.79 (d, 1H), 7.68 (td, 1H), 7.59 (d, 1H), 7.52 (m, 3H), 7.17 (d, 1H), 6.94 (d, 1H), 6.45 (m, 2H), 5.76 (dd, 1H), 5.23 (s, 2H), 4.86 (m, 1H), 3.69 (m, 1H), 3.60 (m, 1H), 2.70 (s, 6H), 2.47 (m, 1H), 2.06 (m, 3H).

Example 185: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide

The procedure of Example 166 was repeated except for using 7-methoxy-N^4-(1-pyridin-2-ylmethyl-1*H*-indazol-5-yl)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (160 mg, 29%).

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^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.74 (s, 1H), 8.97 (s, 1H), 8.58 (s, 1H), 8.05 (m, 2H), 7.88 (bs, 1H), 7.55 (dd, 1H), 7.27 (m, 2H), 7.23 (s, 1H), 6.99 (m, 2H), 6.88 (m, 1H), 6.51 (m, 2H), 5.80 (m, 1H), 5.57 (s, 2H), 4.92 (m, 1H), 3.98 (s, 3H), 3.74 (m, 1H), 3.60 (m, 1H), 3.22 (m, 2H), 2.53 (m, 1H), 2.12 (m, 1H).

Example 186: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-methyl-4-(pyridin-2-ylmethoxy)-phenyl]-7-ethoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (130 mg, 15%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.81 (s, 1H), 9.45 (s, 1H), 8.95 (s, 1H), 8.57 (m, 2H), 7.66 (m, 1H), 7.50 (d, 1H), 7.22 (d, 1H), 7.18 (d, 2H), 6.75 (d, 1H), 6.54 (m, 2H), 5.84 (m, 1H), 5.18 (s, 2H), 4.95 (d, 1H), 4.24 (m, 2H), 3.76 (m, 1H), 3.64 (m, 1H), 2.39 (s, 1H), 2.28 (s, 3H), 2.04 (m, 3H), 1.27 (t, 3H).

Example 187: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-(2-fluoro-ethoxy)-quinazolin-6-yl]-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-7-(2-fluoro-ethoxy)-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (155 mg, 33%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 10.05 (s, 1H), 8.85 (s, 1H), 8.52 (m, 2H), 7.77 (d, 1H), 7.68 (td, 1H), 7.59 (d, 1H), 7.55 (m, 1H), 7.44 (dd, 1H), 7.18 (d, 1H), 7.12 (d, 1H), 6.94 (d, 1H), 6.48 (d, 2H), 5.76 (t, 1H), 5.22 (s, 2H), 4.92 (m, 2H), 4.80 (m, 1H), 4.34 (m, 1H), 4.25 (m, 1H), 3.70 (m, 1H), 3.56 (q, 1H), 2.55 (m, 1H), 2.05 (m, 3H).

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Example 188: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-ylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[1-(3-fluoro-benzyl)-1*H*-indazol-5-yl)-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (150 mg, 25%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.71 (s, 1H), 8.92 (s, 1H), 8.52 (s, 1H), 7.98 (m, 2H), 7.73 (bs, 1H), 7.48 (dd, 1H), 7.19 (m, 3H), 6.91 (m, 2H), 6.82 (m, 1H), 6.46 (m, 2H), 5.74 (m, 1H), 5.51 (s, 2H), 4.84 (m, 1H), 4.01 (s, 3H), 3.73 (m, 1H), 3.55 (m, 1H), 2.98 (m, 2H), 2.47 (m, 1H), 2.05 (m, 1H).

Example 189: Preparation of (1*R*)-*N*-(1-{4-[3chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 166 was repeated except for using (2*S*)-2-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (49 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.69 (s, 1H), 8.49 (d, 1H), 8.35 (s, 1H), 7.81 (m, 2H), 7.64 (d, 1H), 7.51 (dd, 1H), 7.33 (m, 1H), 7.10 (d, 1H), 6.30 (d, 1H), 6.26 (d, 1H), 5.68 (dd, 2H), 5.20 (s, 2H), 4.67 (q, 1H), 4.01 (s, 3H), 1.44 (d, 3H).

Example 190: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

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The procedure of Example 166 was repeated except for using (2*R*)-2-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (32 mg, 7%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.72 (s, 1H), 8.45 (d, 1H), 8.32 (s, 1H), 7.80 (td, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.47 (dd, 1H), 7.30 (m, 1H), 7.10 (s, 1H), 7.05 (d, 1H), 6.25 (d, 2H), 6.23 (d, 1H), 5.66 (dd, 1H), 5.17 (s, 2H), 4.64 (m, 1H), 3.95 (s, 3H), 1.39 (d, 3H).

Example 191: Preparation of (1*S*)-*N*-(1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}ethyl)-*N*-methyl-acrylamide

The procedure of Example 166 was repeated except for using (2*R*)-2-(*t*-buthoxycarbonyl-methyl-amino)-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (24 mg, 6%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.56 (s, 1H), 8.43 (d, 1H), 8.26 (s, 1H), 7.79 (td, 2H), 7.72 (d, 1H), 7.58 (d, 1H), 7.41 (dd, 1H), 7.26 (m, 1H), 6.9 7(s, 1H), 6.94 (dd, 1H), 6.68 (d, 1H), 5.73 (d, 1H), 5.24 (m, 1H), 5.22 (s, 3H), 4.45 (br s, 1H), 3.87 (s, 3H), 3.20 (s, 3H), 1.41 (d, 3H).

Example 192: Preparation of *N*-(2-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-ylcarbamoyl}-ethyl)-acrylamide

The procedure of Example 165 was repeated except for using (3-*t*-buthoxycarbonylamino-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (60 mg, 19%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.79 (m, 1H), 8.55 (m, 2H), 7.86 (s, 1H), 7.76 (t, 1H), 7.66 (m, 2H), 7.52 (m, 3H), 7.22 (m, 1H), 7.01 (d, 1H), 6.30 (m, 1H), 6.10 (m, 1H), 5.65 (m, 1H), 5.26 (s, 2H), 3.65 (m, 2H), 2.74 (m, 2H); MS(ESI): [M+Na]+ 543.

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Example 193: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid [7-methoxy-4-(1-penta-2,4-dienyl-1*H*-indazol-5-ylamino)-quinazolin-6-yl]-amide 의

The procedure of Example 166 was repeated except for using N^4-[1-benzyl-1*H*-indazol-5-yl)-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (52 mg, 22%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.81 (s, 1H), 8.99 (s, 1H), 8.61 (s, 1H), 8.00 (s, 2H), 7.72 -7.69 (m, 2H), 7.55-7.51 (m, 2H), 7.37 (m, 5H), 6,54 (dd, 2H), 5.84 (d, 1H), 5.60 (s, 2H), 4.23 (m, 1H), 4.04 (s, 3H), 3.75-3.63 (m, 2H), 2.54 (m, 1H), 1.98 (m, 3H).

Example 194: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(6-methyl-pyridin-2-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (113 mg, 21%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.76 (s,1H), 8.89 (s,1H), 8.59 (s,1H), 7.83 (d,1H), 7,71 (s,1H), 7.50 (t,1H), 7.49 (dd,1H), 7.43 (d,1H), 7.25 (s,1H), 7.19 (s,1H), 7.09 (d,1H), 6.95 (d,1H), 6.51 (m,2H), 5.83 (dd,1H), 5.78 (s,2H), 4.92 (d, 1H), 3.99 (s, 3H) 3.75-3.62(m,2H) 2.57(s,3H) 2.55(m,1H) 2.08(m,3H).

Example 195: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-fluoro-quinazolin-6-yl}-amide

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The procedure of Example 165 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (82 mg, 20%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.97 (d, 1H), 8.57 (d, 1H), 8.49 (s, 1H), 7.92 (m, 2H), 7.73 (d, 1H), 7.60 (dd, 1H), 7.51 (d, 1H), 7.40 (m, 1H), 7.17 (d, 1H), 6.39 (m, 2H), 5.84 (dd, 1H), 5.29 (s, 2H), 5.20 (m, 1H), 4.35 (t, 2H), 2.66 (m, 2H).

Example 196: Preparation of 1-acryloyl-piperidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 9%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.07 (bs, 1H), 8.95 (s, 1H), 8.60 (m, 2H), 7.86 (d, 1H), 7.76 (m, 2H), 7.67 (d, 1H), 7.52 (dd, 1H), 7.23 (m, 2H), 6.99 (d, 1H), 6.70 (m, 1H), 6.41 (m, 1H), 5.82 (m, 1H), 5.48 (m, 1H), 5.29 (s, 2H), 4.00 (m, 1H), 3.97 (s, 3H), 3.20 (m, 1H), 2.39 (m, 1H), 1.70 (m, 5H).

Example 197: Preparation of 1-acryloyl-piperidine-4-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,4-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (210 mg, 17%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.96 (s, 1H), 8.58 (m, 2H), 8.15 (s, 1H), 7.93 (bs, 1H), 7.84 (d, 1H), 7.75 (m, 1H), 7.65 (d, 1H), 7.47 (dd, 1H), 7.28 (s, 1H), 7.22 (m, 1H), 6.97 (d, 1H), 6.59 (m, 1H), 6.29 (m, 1H), 5.71 (m, 1H), 5.27

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(s, 2H), 4.70 (m, 1H), 4.04 (s, 3H), 3.24 (m, 1H), 2.85 (m, 1H), 2.34 (m, 4H), 1.82 (m, 2H).

Example 198: Preparation of 1-acryloyl-pyrrolidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (110 mg, 27%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.86 (s, 1H), 8.53 (m, 2H), 8.15 (d, 1H), 7.86 (bs, 1H), 7.75 (m, 1H), 7.65 (m, 1H), 7.58 (d, 1H), 7.41 (dd, 1H), 7.17 (m, 2H), 6.88 (d, 1H), 6.35 (m, 2H), 5.64 (m, 1H), 5.19 (s, 2H), 3.94 (s, 3H), 3.81 (m, 3H), 3.55 (m, 1H), 3.14 (m, 1H), 2.27 (m, 2H).

Example 199: Preparation of 1-acryloyl-azetidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-ethoxy-quinazolin-6-yl}-amide

The procedure of Example 170 was repeated except for using azetidine-1,2-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (85 mg, 25%).

^{1}H-NMR (CD_3OD, 300MHz): δ 9.10 (d, 1H), 8.74 (d, 1H), 8.64 (d, 1H), 8.09 (m, 2H), 7.90 (d, 1H), 7.77 (m, 2H), 7.57 (m, 1H), 7.35 (m, 1H), 6.53 (m, 2H), 6.02 (dd, 1H), 5.46 (s, 2H), 5.36 (m, 1H), 4.51 (m, 2H), 2.84 (m, 2H).

Example 200: Preparation of 1-acryloyl-azetidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

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The procedure of Example 166 was repeated except for using azetidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (70 mg, 26%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.04 (s, 1H), 8.64 (m, 2H), 8.20 (s, 1H), 7.98 (bs, 1H), 7.89 (d, 1H), 7.80 (m, 1H), 7.70 (d, 1H), 7.54 (dd, 1H), 7.27 (m, 2H), 7.02 (d, 1H), 6.43 (m, 1H), 6.26 (m, 1H), 5.76 (m, 1H), 5.32 (s, 2H), 4.61 (m,1 H), 4.40 (m, 3H), 4.07 (s, 3H), 3.61 (m, 1H).

Example 201: Preparation of (3S)-1-acryloyl-piperidine-3-carboxylic acid {4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using (3*S*)-piperidine-1,3-dicarboxylic acid-1-*t*-butylester instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (50 mg, 30%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.95 (bs, 1H), 8.60 (m, 3H), 8.29 (bs, 1H), 7.84 (d, 1H), 7.75 (m, 1H), 7.66 (d, 1H), 7.50 (dd, 1H), 7.24 (m, 2H), 6.98 (d, 1H), 6.57 (m, 1H), 6.31 (m, 1H), 5.73 (m, 1H), 5.28 (s, 2H), 4.78 (m, 1H), 4.02 (m, 1H), 3.97 (s, 3H), 3.20 (m, 1H), 2.57 (m, 1H), 2.18 (m, 3H), 1.90 (m, 1H), 1.57 (m, 1H).

Example 202: Preparation of *N*-((1*S*)-1-{4-[3-chloro-4-(pyridin-2-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-ylcarbamoyl}-ethyl)-*N*-ethyl-acrylamide

The procedure of Example 166 was repeated except for using (2*S*)-2-(*t*-buthoxycarbonyl-ethyl-amino)-propionic acid instead of (2*S*)-pyrrolidine-1,2-dicarboxylic acid-1-*t*-butylester to obtain the title compound (7 mg, 7%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 9.17 (s, 1H), 8.83 (s, 1H), 8.53 (m, 2H), 7.78 (m, 1H), 7.70 (td, 1H), 7.61 (s, 1H), 7.58 (d, 1H), 7.45 (dd, 1H), 7.16 (s,

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1H), 7.14 (s, 1H), 6.92 (d, 1H), 6.53 (m, 1H), 5.75 (dd, 1H), 5.21 (s, 2H), 4.08 (m, 1H), 3.95 (s, 3H), 3.48 (q, 2H), 1.45 (d, 3H), 1.19 (t, 3H).

Example 203: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(2-fluoro-ethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(2-fluoro-ethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (110 mg, 34%).

^{1}H-NMR ($CDCl_3$, 300MHz): δ 8.99 (s, 1H,) 8.62 (s, 1H), 7.83 (d, 1H), 7.60 (s, 1H), 7.56 (dd, 1H), 7.00 (d, 1H), 6.51 (m, 2H), 5.83 (dd, 1H), 4.88 (t, 1H), 4.73 (t, 1H), 4.50 (m, 1H), 4.35 (t, 1H), 4.26 (t, 1H), 3.98 (s, 3H), 3.48 (m, 2H), 2.20 (m, 1H), 1,98 (m,1H), 1.89 (m,2H).

Example 204: Preparation of (2*S*)-1-acryloyl-pyrrolidine-2-carboxylic acid {4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenylamino]-7-methoxy-quinazolin-6-yl}-amide

The procedure of Example 166 was repeated except for using N^4-[3-chloro-4-(pyridin-3-ylmethoxy)-phenyl]-7-methoxy-quinazolin-4,6-diamine instead of the compound obtained in (166-2) of Example 166 to obtain the title compound (19 mg, 11%).

^{1}H-NMR (CD_3OD, 300MHz): δ 8.86 (s, 1H), 8.85 (s, 1H), 8.73 (s, 1H), 8.72 (s, 1H), 8.21 (d, 1H), 8.11 (d, 1H), 7.93-7.98 (m, 2H), 7.85 (dd, 1H), 7.43 (d, 1H), 6.37-6.44 (m, 2H), 5.82-5.86 (m, 1H), 5.46 (s, 2H), 4.80 (m, 1H), 3.96 (s, 3H), 3.51 (m, 2H), 2.24 (m, 1H), 1.78-1.99 (m, 3H).

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