

## Cyclic urea derivatives as potent NK<sub>1</sub> selective antagonists

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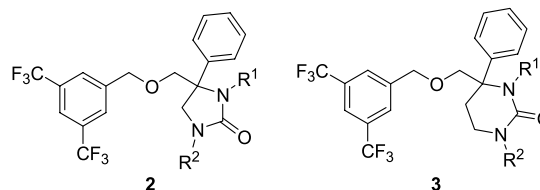
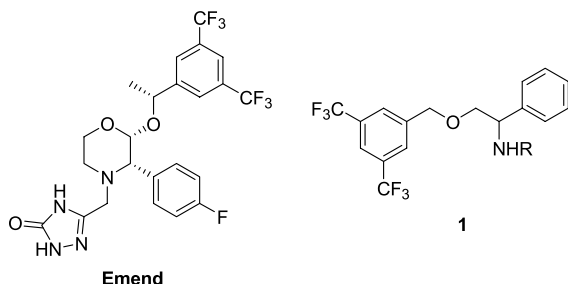
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**Abstract**—A series of novel five- and six-membered ring urea derivatives have been described as potent and selective NK<sub>1</sub> receptor antagonists. Several compounds in this series exhibited good oral activity and brain penetration. Syntheses of these compounds are also described herein.

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Substance P is a member of the tachykinin family of neurotransmitters that selectively binds to the NK<sub>1</sub> receptor. Substance P has been implicated in a number of pathological disorders in the central nervous system (CNS) and peripheral tissues,<sup>1,2</sup> including pain, inflammation, depression, emesis and cough.<sup>3–6</sup> Consequently, an antagonist of the NK<sub>1</sub> receptor has potential therapeutic use in the treatment of cough,<sup>6</sup> inflammation,<sup>7</sup> asthma,<sup>8</sup> pain,<sup>9</sup> chemotherapy-induced emesis,<sup>10</sup> migraine,<sup>11</sup> anxiety, and depression.<sup>12</sup> Recently, Emend was approved for the treatment of CINV (chemotherapy-induced nausea and vomiting), and several NK<sub>1</sub> antagonists are in clinical trials for anxiety and depression.<sup>13</sup>

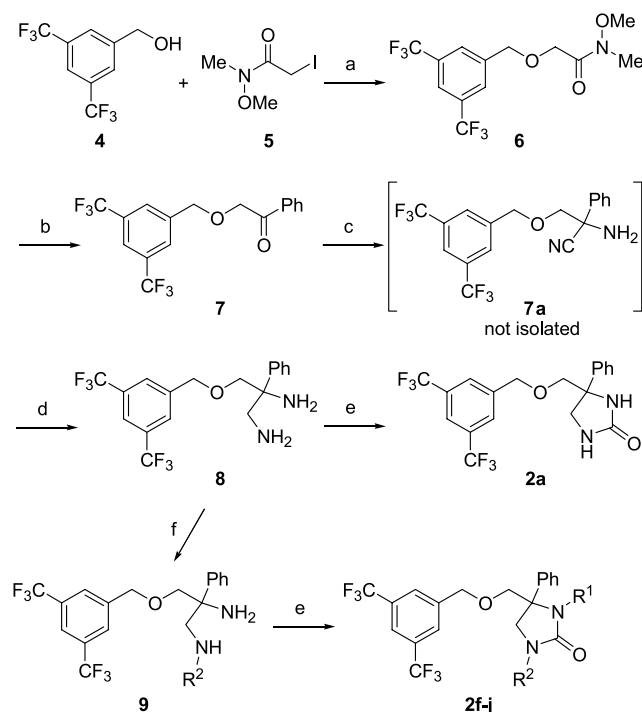


Herein, we report the discovery of novel cyclic urea derivatives **2** and **3** as potent and selective NK<sub>1</sub> antagonists that are orally active and have good CNS penetration. These cyclic ureas provide structural novelty while possessing the minimal pharmacophoric elements of phenylglycinol-derived NK<sub>1</sub> antagonists of type **1**.<sup>14</sup>

The racemic 4,4-disubstituted-2-imidazolidinones (**2a–j**) shown in Table 1 were prepared by the synthetic route illustrated in Scheme 1.<sup>15</sup> Alkylation of 3,5-bis(trifluoromethyl)benzyl alcohol **4** with 2-iodo-*N*-methoxy-*N*-methylacetamide **5**, which was prepared in acetone from its chloride derivative using sodium iodide, afforded Weinreb amide **6**. The coupling of Weinreb amide **6** with phenyllithium gave the ketone **7** in excellent yield (80%). Treatment of ketone **7** with trimethylsilyl cyanide and ammonia in presence of zinc iodide afforded amine–nitrile intermediate **7a**, which was subsequently reduced without isolation to give the diamine compound **8**. The

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**Scheme 1.** Reagent and conditions: (a)  $\text{KN}(\text{TMS})_2/\text{THF}$ , 0–25 °C, 18 h, 60%; (b)  $\text{PhLi}/\text{THF}$ , –78 °C, 1.5 h then rt, 80%; (c)  $\text{TMSCN}/\text{ZnI}_2/\text{THF}$ , rt, 1 h, filtered, concd then  $\text{NH}_3/\text{MeOH}$ , 45 °C, 2 h then filtered, concd; (d)  $\text{LiAlH}_4/\text{ether}$ , –78 °C then rt, 18 h, 25–35% from 7; (e)  $\text{CDI}/\text{THF}$ , rt, 18 h, 97%; (f) ketone, aldehyde/ $\text{NaBH}(\text{OAc})_3/\text{CH}_2\text{Cl}_2$ , rt or  $\text{NaBH}_3\text{CN}/\text{MeOH}$  or alkyl halide/ $\text{DMF}$ .

**Table 1.**  $\text{NK}_1$  receptor binding affinity and GFT inhibition for compounds **2a–j**

Compound <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	$\text{NK}_1^b$ $K_i$ (nM)	GFT <sup>b</sup> (%inh.)
<b>2a</b>	–H	–H	16	NT <sup>c</sup>
<b>2b</b> ( <i>S</i> )	–H	–H	332	NT <sup>c</sup>
<b>2c</b> ( <i>R</i> )	–H	–H	6	54
<b>2d</b> ( <i>R</i> )	–CH <sub>3</sub>	–H	94	NT <sup>c</sup>
<b>2e</b> ( <i>R</i> )	–H	–CH <sub>3</sub>	8	0
<b>2f</b>	–H		4	18
<b>2g</b>	–H		0.7	23
<b>2h</b>	–H		1	68
<b>2i</b>	–H		0.5	15
<b>2j</b>	–H		1	0

<sup>a</sup> Unless defined as (*R*) or (*S*), the compounds in the table are racemic.

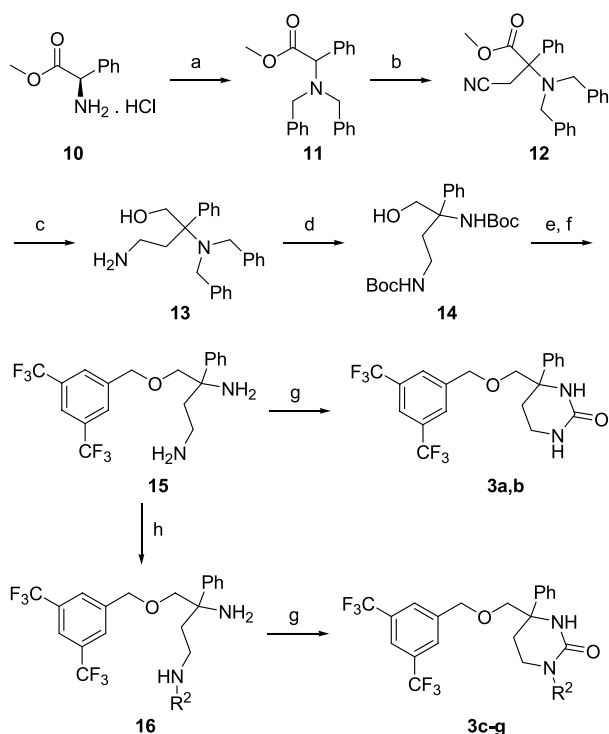
<sup>b</sup> See Ref. 17–20.

<sup>c</sup> NT = not tested.

cyclization of diamine **8** in the presence of *N,N'*-carbonyldiimidazole (CDI) afforded the unsubstituted urea compound **2a**. An alternative four-step sequence to compound **2a** from compound **4** in higher overall yield has previously been reported.<sup>16</sup> Treatment of compound **8** with 1 equiv of ketone/aldehyde in the presence of a reducing agent, such as sodium triacetoxyborohydride, or an alkylating reagent, followed by CDI cyclization afforded the *N*-substituted cyclic ureas **2f–j**. In order to determine the effect of the absolute stereochemistry on binding activity, compound **2a** was resolved to the enantiomers **2b** and **2c** by chiral HPLC on a Daicel Chiralpak AD<sup>®</sup> column. The assignment of absolute configuration of enantiomer **2c** was made based on the established chiral synthesis.<sup>16</sup> The chiral *N*-methylated compounds (**2d** and **2e**) were prepared by alkylation of the chiral compound **2c** with methyl iodide in the presence of sodium hydride in *N,N*-dimethylformamide.

The in vitro  $\text{NK}_1$  binding and in vivo  $\text{NK}_1$  agonist-induced gerbil foot-tapping (GFT) inhibition data for 4,4-disubstituted-2-imidazolidinones (**2a–j**) are listed in Table 1. The  $\text{NK}_1$  binding assay determines the affinity of these compounds (**2a–j**) toward the  $\text{NK}_1$  receptor while the GFT inhibition measures the potency of these compounds antagonizing an  $\text{NK}_1$  receptor-mediated CNS effect. As shown in Table 1, the unsubstituted five membered urea analogue **2a** exhibited good  $\text{NK}_1$  binding affinity ( $K_i = 16$  nM). It was noted that enantiomer **2c** (*R*-isomer) had higher affinity for the  $\text{NK}_1$  receptor than the enantiomer **2b** (*S*-isomer) (6 vs 330 nM). In addition, compound **2c** was active in the GFT assay (54% inhibition of foot-tapping at 1 mg/kg po after a 2 h pretreatment time) which demonstrated CNS penetration and  $\text{NK}_1$  antagonist activity. In order to understand the importance of the urea NH protons for affinity, the *N*-methyl derivatives of **2c** were synthesized. When the hindered NH of the urea ring was methylated (**2d**), the binding affinity was greatly reduced ( $K_i = 94$  nM). On the other hand, when the less hindered NH was methylated (**2e**), retention of the binding affinity was observed ( $K_i = 8$  nM). This suggested that the NH proton adjacent to the tertiary position of the cyclic urea is more important for  $\text{NK}_1$  receptor binding. Consequently, substitutions at the less hindered NH were further explored. We found that a polar amide side chain improved potency (e.g., **2f**,  $K_i = 4$  nM). Further increase in polarity from a neutral substitution to basic amino group containing side chains, significantly improved  $\text{NK}_1$  affinity and in some cases (**2g** and **2i**) picomolar binding was achieved. Both the acyclic **2g** and cyclic (**2h–j**) amine side chains were well tolerated and the position of the basic nitrogen did not significantly affect the binding (**2g**,  $K_i = 0.7$  nM and **2j**,  $K_i = 1$  nM). The best representative of the amine side chain containing compounds was analogue **2h**, which bound with high affinity ( $K_i = 1$  nM) and produced good activity (68% inhibition) in the GFT assay.

A series of racemic six-membered cyclic urea derivatives (**3a–g**) were prepared by the synthetic route shown in Scheme 2<sup>15</sup> and their biological data are listed in Table 2. The chiral compounds **3a** and **3b** were prepared by



**Scheme 2.** Reagent and conditions: (a)  $\text{PhCH}_2\text{Br}$ ,  $\text{Et}_3\text{N}/\text{THF}/80^\circ\text{C}$ , 48 h, 46%; (b)  $\text{LDA}/\text{ICH}_2\text{CN}/\text{THF}$ ,  $-78^\circ\text{C}$  to  $-20^\circ\text{C}$ , 51%; (c)  $\text{LAH}/\text{THF}$ ,  $-78^\circ\text{C}$  to rt, 64%; (d)  $t\text{-BOC-anhydride}/20\% \text{Pd}(\text{OH})_2\text{-C}$ ,  $\text{H}_2$ , 50 psi, 18 h, 85%; (e)  $\text{Ag}_2\text{O}/\text{DMF}$ , 3,5-bis(trifluoromethyl)benzyl bromide, rt, 18 h, 64%; (f)  $\text{HCl}/\text{Et}_2\text{O}$ , rt, 18 h, 99%; (g)  $\text{CDI}/\text{THF}$ ,  $0-25^\circ\text{C}$ , 18 h, 48–63%; (h) ketone/ $\text{HOAc}/\text{NaBH}_3\text{CN}/\text{MeOH}$ , or  $\text{CH}_3/\text{K}_2\text{CO}_3/\text{DMF}$  or  $\text{R}^2\text{CH}_2\text{Br}/\text{DMF}$ .

**Table 2.**  $\text{NK}_1$  receptor binding affinity and GFT inhibition for compounds **3a–g**

Compound <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	$\text{NK}_1$ <sup>b</sup> $K_i$ (nM)	GFT <sup>b</sup> (%inh.)
<b>3a</b> ( <i>S</i> )	–H	–H	350	NT <sup>c</sup>
<b>3b</b> ( <i>R</i> )	–H	–H	9	0
<b>3c</b>	–H	–CH <sub>3</sub>	14	18
<b>3d</b>	–H		9	16
<b>3e</b>	–H		3	47
<b>3f</b>	–H		2	2
<b>3g</b>	–H		0.5	56

<sup>a</sup> Unless defined as (*R*) or (*S*), the compounds in the table are racemic.

<sup>b</sup> See Ref. 17–20.

<sup>c</sup> NT = not tested.

the chiral HPLC separation of the racemic mixture **3a,b** on a Daicel Chiralpak AS<sup>®</sup> column.

As shown in Table 2, the six-membered ureas also exhibited good  $\text{NK}_1$  receptor binding affinities. Similar to five-membered urea derivatives, the activity of six-membered urea derivatives also resided mostly in the *R*-isomer, for an example, compound **3b** (*R*-isomer,  $K_i = 9$  nM) versus compound **3a** (*S*-isomer,  $K_i = 350$  nM). However, compound **3b** was found to be inactive in GFT assay. This may be due to a poorer pharmacokinetic profile of the latter. Based on the SAR of the five-membered ureas, the substitutions at the less hindered NH were subsequently explored in the six-membered series. The *N*-methyl derivative **3c** and acetylpiperidine derivative **3d** retained the binding while the pyran analogue **3e** showed improvement in both binding ( $K_i = 3$  nM), and in vivo activity (47% inhibition). As previously observed with five-membered analogues, incorporation of basic amine side chains (**3f,g**) improved the binding, and in the case of methyl-piperidine analogue (**3g**), sub-nanomolar  $\text{NK}_1$  affinity ( $K_i = 0.5$  nM) was achieved. The analogue **3g** showed the best GFT activity (56% inhibition) in the six-membered urea series which was comparable to the most potent five-membered series analogues **2c** and **2h**.

In conclusion, we have identified a novel series of cyclic urea derivatives of structures **2** and **3** as potent  $\text{NK}_1$  antagonists. Several compounds in these series exhibit good  $\text{NK}_1$  selectivity, are orally active and have good brain penetration. For example, compound **2c** (SCH 388714) showed an excellent selectivity ( $\text{NK}_2$ ,  $\text{NK}_3 > 1 \mu\text{M}$ ), good oral bioavailability (69% in rat) and it displayed very good brain penetration (brain/plasma ratio 4 in rat). Further details of the SAR effort to improve potency of this class of  $\text{NK}_1$  antagonist will be reported in due course.

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17. NK<sub>1</sub> assay: Binding data are the average of two or three independent determinations. Receptor binding assays were performed on membrane preparations from CHO cells in which recombinant human NK<sub>1</sub> receptors were expressed. [<sup>3</sup>H]-Sar-Met Substance P was used as the ligand for the NK<sub>1</sub> assay, at concentrations near the experimentally derived K<sub>d</sub> value. K<sub>i</sub> values were obtained using the Cheng and Prusoff equation.
18. The NK<sub>1</sub> agonist GR73632 (3 pmol in 5 μl) was administered centrally to female Mongolian gerbils via icv injection. Immediately following recovery from the anesthesia, gerbils were placed into clear Plexiglas boxes for 5 min, and the duration of foot tapping was measured. Foot tapping was defined as rhythmic, repetitive tapping of the hind feet. NK<sub>1</sub> antagonists were administered orally in 0.4% methylcellulose in distilled water at a dose of 1 mg/kg (unless otherwise stated) at various pretreatment times prior to injection of GR73632. Data are expressed as a percent decrease (% inhibition) in the amount of time spent foot tapping compared to vehicle-treated controls.
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