

Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists

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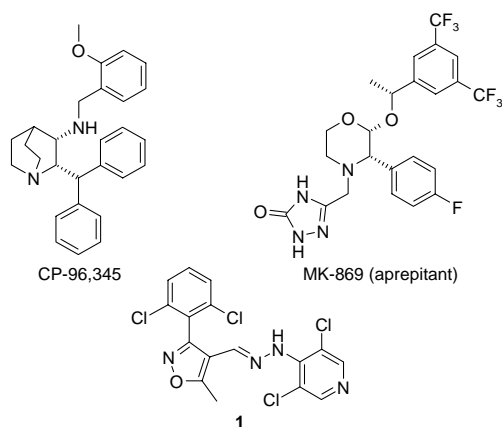
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Abstract—The discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK₁) receptor antagonists is described. The evaluation of this class is briefly outlined, leading to the identification of netupitant **21** and befetupitant **29**, two new proprietary chemical entities with high affinity and excellent CNS penetration.
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Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK₁, NK₂ and NK₃. The endogenous ligand for NK₁ receptors is the 11 amino acid neuropeptide substance P.¹ Following the discovery of the first non-peptide NK₁ receptor antagonist CP-96,345 in 1991,² a remarkable number of small molecule NK₁ receptor antagonists were identified by many pharmaceutical companies in the last decade.³



Moreover, recent clinical trials have demonstrated an important therapeutic application for NK₁ receptor antagonists in the control of cancer chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression.⁴ MK-869 (aprepitant) was the first NK₁ receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.⁵

Following random screening of our corporate library, a unique compound cluster of achiral aryl-substituted isoxazole derivatives was discovered which showed moderate affinity at the human NK₁ receptor (e.g., **1**, $K_i = 15$ nM). We hypothesized that **1** might be able to adopt conformations which are in agreement with the pharmacophore model described by researchers from Merck.⁶ Moreover this structural class, which displays simple achiral features, had previously not been described in the patent literature either as an NK₁ lead structure or as a pharmaceutically active chemical class per se. Consequently, we decided to embark on the optimization of this compound class during a focused lead generation and optimization program.

During the initial steps of our optimization efforts, it was discovered that the 5-membered heterocyclic isoxazole backbone of **1** could be replaced by a simple isocyclic benzene core (**2a–e** Table 1). Subsequently the *N*-(4-pyridyl)-hydrazone substituent, which was associated with potential toxicity liabilities, was replaced by the

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Table 1. hNK₁ binding affinity of biphenyl derivatives **2** and **3**

Compound	R ¹	R ²	hNK ₁ K _i ^a (nM)
2a	H	H	933
2b	CH ₃	H	316
2c	Cl	H	174
2d	Br	H	49
2e	Cl	Cl	93
3a	H	—	51
3b	CH ₃	—	17
3c	Cl	—	22
3d	Br	—	45

^a Displacement of [³H]-labelled substance P from cloned human receptor expressed in CHO cells.¹⁰ Values are means of two experiments with maximal standard deviations below ±0.25 logarithmic units.

well-documented *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methyl-carboxamide group (**3a–d** Table 1).⁷ This modification also led to a significant increase in binding affinity. Notably the potency at the NK₁ receptor is markedly enhanced by increasing the steric demand of the *ortho*-substitution (R¹ and R² in derivatives **2** and **3**) and thus the torsion angle of the biaryl system.⁸

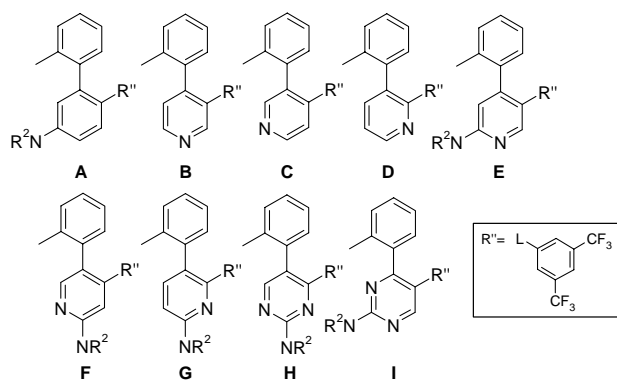
The unsubstituted biphenyl derivative **3a** was selected as a starting point to systematically explore a set of differently functionalized 3-atom linkers L (Table 2). *N*-Methyl substitution, which leads to orthogonal twist of the carboxamide plane with respect to the aromatic system,⁹ was found to be crucial for receptor binding (cf. **3a** and **4**). Geminal dimethyl substitution (**5** and **6**) did not lead to increased NK₁ receptor affinity. The *N*-methyl carboxamide linker can be replaced by the inverse amide linker with 10-fold loss of potency (cf. **3a** and **7**). However, in case of the inverse amide linker, geminal dimethyl substitution leads to a 10-fold increase in NK₁ receptor affinity and comparable potency (cf. **3a** and **8**). Again, *N*-methyl substitution was found to be important for receptor binding (cf. **8** and **9**). Amine (**10** and **11**) and ether (**12**) linker substitutions were not preferred over *N*-methyl-substituted carboxamides or inverse carboxamides.

Biphenyl derivatives **3a** and **8**, displaying the *N*-methyl-substituted carboxamide and inverse amide linker series, were selected for further optimization, while conserving the 3,5-bis(trifluoromethyl)phenyl group, which is characteristic of many potent NK₁ receptor antagonists.³ In parallel, 9 compound classes were explored with *ortho*-tolyl substitution and different amine substituents NR₂: Isocyclic biphenyl derivatives **A**, pyridine classes **B–G** and pyrimidine classes **H** and **I** (Fig. 1).

Table 2. Optimization of the 3-atom linker L

Compound	L	hNK ₁ K _i ^a (nM)
3a		51
4		>10,000
5		295
6		>10,000
7		562
8		68
9		1,380
10		724
11		372
12		224

^a Displacement of [³H]-labelled substance P from cloned human receptor expressed in CHO cells.¹⁰ Values are means of two experiments with maximal standard deviations below ±0.25 logarithmic units.

**Figure 1.** Compound classes **A–I** were explored with *ortho*-tolyl substitution and different amine substituents NR₂.

In all 9 classes **A–I**, potent NK₁ receptor antagonists were discovered.¹⁰ The structural variations allowed fine-tuning of: NK₁ receptor affinity and subtype selectivity; physicochemical properties, such as pK_a value,

Table 3. Potent NK₁ receptor antagonists from classes A–I (Fig. 1) NR₂ = *N*-methylpiperazinyl

Compound	Class	L	hNK ₁ K _i ^a (nM)
13	A		1.4
14	B		8.5
15	B		3.4
16	C		4.6
17	C		3.3
18	D		3.8
19	D		4.0
20	E		0.58
21	E		0.95
22	F		1.7
23	G		6.2
24	G		2.0
25	H		3.5
26	H		1.1
27	I		1.7
28	I		0.44

^a Displacement of [³H]-labelled substance P from cloned human receptor expressed in CHO cells.¹⁰ Values are means of two experiments with maximal standard deviations below ± 0.25 logarithmic units.

solubility and permeability; as well as DMPK parameters, such as half-life, clearance, volume of distribution, phase I metabolism and blood brain barrier permeability. Table 3 exemplifies a selection of 16 derivatives (13–28) from structural classes A–I displaying both carboxamide linkers L, with *N*-methylpiperazine as NR₂

substituent and an *ortho*-tolyl group. It is worthwhile to note that without exception all derivatives display low-nM to sub-nM affinity at the NK₁ receptor. Furthermore, NK₁ receptor antagonists 1–31 were found to be at least 100-fold sub-type selective over NK₂ and NK₃ receptors as assessed by displacement of the respective radiolabelled endogenous ligand from cloned NK₂ and NK₃ receptors in CHO cells, respectively. The functional antagonistic activity of these molecules was demonstrated by using a standard fluorescence imaging plate reader (FLIPR)-based assay measuring Ca²⁺ flux in vitro.

Preferred compounds were tested for their potential to pharmacologically block central NK₁ receptors in gerbils. Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK₁-selective receptor agonist GR73632.¹¹ Excellent oral antagonist activity was observed for the pyridine derivatives from class E as exemplified for netupitant (21), befetupitant (29) and structurally closely related compounds such as 30 and 31 (Table 4).¹²

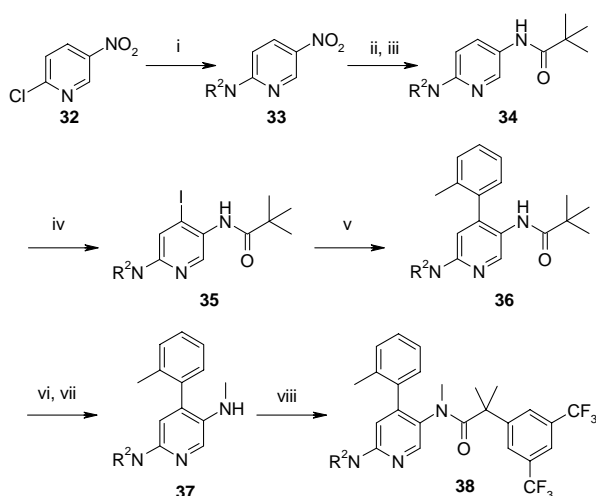
Pyridine derivatives from class E were synthesized as outlined in Scheme 1. 2-Chloro-5-nitropyridine 32 was treated with the respective amine to yield amine-substituted nitropyridines 33. The nitro group was catalytically reduced with hydrogen and the resulting aniline immediately trapped with pivaloyl chloride to yield derivatives 34. The pivaloyl amide group served as directing group for *ortho*-lithiation with an excess of

Table 4. Pyridines: amine substitution in the 6-position

Compound	NR ¹ R ²	hNK ₁ K _i ^a (nM)	Gerbil foot tapping ^b (ID ₅₀ mg/kg po)
21 (netupitant)		0.95	0.5
29 (befetupitant)		1.0	0.2
30		0.40	0.5
31		1.3	0.8

^a Displacement of [³H]-labelled substance P from cloned human receptor expressed in CHO cells.¹⁰ Values are means of two experiments with maximal standard deviations below ± 0.25 logarithmic units.

^b Inhibition of agonist (GR73632)-induced foot tapping behaviour in gerbils after oral pretreatment of animals with test compounds 2 h prior to intracerebroventricular (icv) administration of the agonist.¹¹



Scheme 1. Reagents and conditions: (i) R^2NH , THF, reflux; (ii) H_2 (1 atm), Pd/C, MeOH, 45 °C; (iii) PivCl, Et_3N , THF, rt; (iv) $tBuLi$, TMEDA, 2,2,6,6-tetramethylpiperidine, THF, -78 to -30 °C; I_2 , -78 to 0 °C; (v) *o*-tolyl-B(OH) $_2$, $(PPh_3)_4Pd$, Na_2CO_3 , toluene, 80 °C; (vi) 3 N HCl, reflux; (vii) $HC(OCH_3)_3$, TFA (cat.), 130 °C; $LiAlH_4$, THF, 0 °C to rt; (viii) [3,5-(CF_3) $_2C_6H_3$]C(CH_3) $_2COCl$, Pr_2NEt , CH_2Cl_2 , 0 °C to reflux.

$tBuLi$ in the presence of TMEDA at -78 °C. The intermediate lithium organic pyridine derivative was trapped with an excess of iodine at this temperature to give iodopyridine derivatives **35**.¹³ Suzuki coupling with *ortho*-tolyl boronic acid under standard conditions gave 4-arylpyridine derivatives **36**. The pivaloyl group was cleaved under acidic conditions and the resulting 3-aminopyridines were mono-methylated using the reductive *ortho*-ester standard procedure to give **37**. Mono-methylated aminopyridines were acylated with 2-[3,5-bis(trifluoromethyl)phenyl]-2-methyl-propionyl chloride to yield NK $_1$ receptor antagonists **38** of class **E** with the inverse amide linker. Detailed experimental procedures including the first description of 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride have been published in a series of patent applications.^{10,12}

In conclusion, rapid multidimensional optimization of the aryl-substituted isoxazole screening hit cluster (e.g., **1**) gave rise to 9 novel achiral structural classes (**A–I**) of highly potent and selective NK $_1$ receptor antagonists.¹⁰ Pyridine derivatives from class **E** have been shown to potently inhibit NK $_1$ agonist-induced foot tapping behaviour in gerbils after oral administration.¹²

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