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

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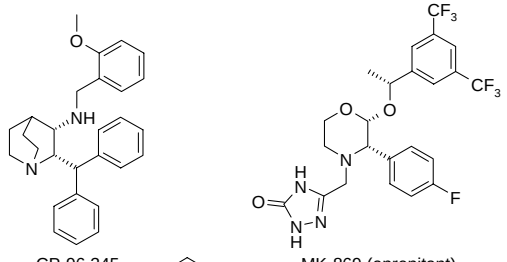
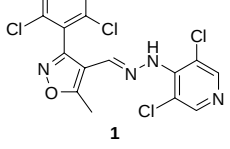
Abstract—The discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK_1) receptor antagonists is described. The evaluation of this class is briefly outlined, leading to the identification of netupitant **21** and befetupitant **29**, two new proprietary chemical entities with high affinity and excellent CNS penetration.

Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK_1, NK_2 and NK_3. The endogenous ligand for NK_1 receptors is the 11 amino acid neuropeptide substance P.[1] Following the discovery of the first non-peptide NK_1 receptor antagonist CP-96,345 in 1991,[2] a remarkable number of small molecule NK_1 receptor antagonists were identified by many pharmaceutical companies in the last decade.[3]





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Moreover, recent clinical trials have demonstrated an important therapeutic application for NK_1 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 NK_1 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 NK_1 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 NK_1 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

Keywords: NK_1 receptor antagonist; G-protein coupled receptor; Drug design and synthesis.
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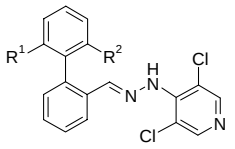
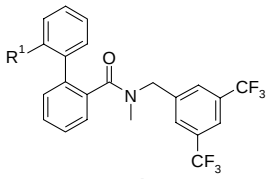
Table 1. hNK_1 binding affinity of biphenyl derivatives **2** and **3**



2a-e



3a-d

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

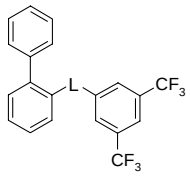
[a] Displacement of [^{3}H]-labelled substance P from cloned human receptor expressed in CHO cells.[10] Values are means of two experiments with maximal standard deviations below ± 0.25 logarithmic units.

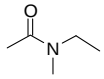
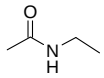
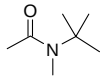
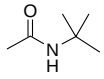
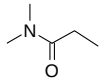
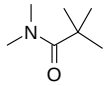
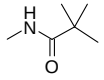
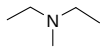
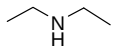
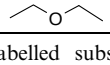
well-documented *N*-[3,5-bis(trifluoromethyl)benzyl]-*N*-methyl-carboxamide group (**3a**–**d** Table 1).[7] This modification also led to a significant increase in binding affinity. Notably the potency at the NK_1 receptor is markedly enhanced by increasing the steric demand of the *ortho*-substitution (R^1 and R^2 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 NK_1 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 NK_1 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 NK_1 receptor antagonists.[3] In parallel, 9 compound classes were explored with *ortho*-tolyl substitution and different amine substituents NR_2: 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 [^{3}H]-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.

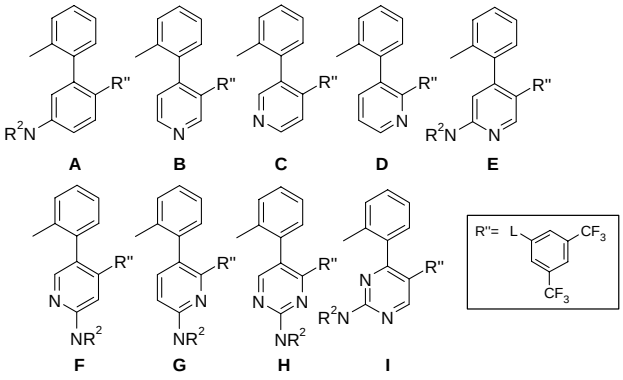


Figure 1. Compound classes **A**–**I** were explored with *ortho*-tolyl substitution and different amine substituents NR^2.

In all 9 classes **A**–**I**, potent NK_1 receptor antagonists were discovered.[10] The structural variations allowed fine-tuning of: NK_1 receptor affinity and subtype selectivity; physicochemical properties, such as pK_a value,

Table 3. Potent NK_1 receptor antagonists from classes **A**–**I** (Fig. 1) NR_2 = *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

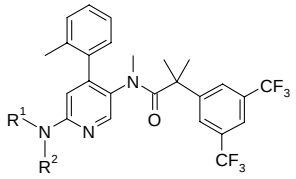
[a] Displacement of [^{3}H]-labelled substance P from cloned human receptor expressed in CHO cells.[10] Values are means of two experiments with maximal standard deviations below ± 0.25 logarithmic units.

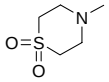
solubility and permeability; as well as DMPK parameters, such as half-life, clearance, volume of distribution, phase I metabolism and blood brain barrier permeability. Table 3 exemplifies a selection of 16 derivatives (**13**–**28**) from structural classes **A**–**I** displaying both carboxamide linkers L, with *N*-methylpiperazine as NR_2 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 NK_1 receptor. Furthermore, NK_1 receptor antagonists **1**–**31** were found to be at least 100-fold sub-type selective over NK_2 and NK_3 receptors as assessed by displacement of the respective radiolabelled endogenous ligand from cloned NK_2 and NK_3 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 Ca^{2+} flux in vitro.

Preferred compounds were tested for their potential to pharmacologically block central NK_1 receptors in gerbils. Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK_1-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

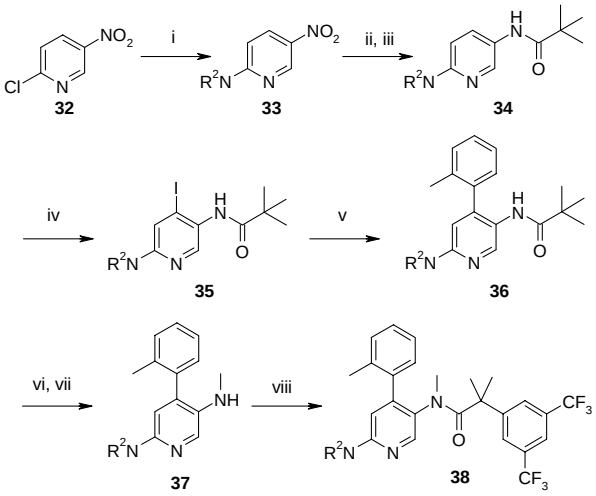
Table 4. Pyridines: amine substitution in the 6-position



Compound	NR^1R^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 [^{3}H]-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) ^{n}BuLi, 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) $[3,5\text{-}(CF_3)_2C_6H_3]C(CH_3)_2COCl$, $^i Pr_2NEt$, CH_2Cl_2, 0 °C to reflux.

^{n}BuLi 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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References and notes

1. Almeida, T. A.; Rojo, J.; Nieto, P. M.; Pinto, F. M.; Hernandez, M.; Martin, J. D.; Candenas, M. L. *Curr. Med. Chem* **2004**, *11*, 2045, and references cited therein.
2. Snider, R. M.; Constantine, J. W.; Lowe, J. A., 3rd; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W. *Science* **1991**, *251*, 435.
3. Albert, J. S. *Expert Opin. Ther. Patents* **2004**, *14*, 1421, and references cited therein.
4. Duffy, R. A. *Expert Opin. Emerg. Drugs* **2004**, *9*, 9, and references cited therein.
5. Dando, T. M.; Perry, C. M. *Drugs* **2004**, *64*, 777.
6. Swain, C. J.; Sewart, E. M.; Cascieri, M. A.; Fong, T. M.; Herbert, R.; MacIntyre, D. E.; Merchant, K. J.; Owen, S. N.; Owens, A. P.; Sabin, V.; Teall, M.; VanNiel, M. B.; Williams, B. J.; Sadowski, S.; Strader, C.; Ball, R. G.; Baker, R. *J. Med. Chem.* **1995**, *38*, 4793.
7. Natsugari, H.; Ikeura, Y.; Kiyota, Y.; Ishichi, Y.; Ishimaru, T.; Saga, O.; Shirafuji, H.; Tanaka, T.; Kamo, I.; Doi, T.; Otsuka, M. *J. Med. Chem.* **1995**, *38*, 3106.
8. Eliel, E. L.; Wilen, S. H.; Mander, N. L. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994, p 1143ff.
9. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277.
10. (a) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. EP 1035115, 2000; (b) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. WO 2000050401; (c) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. WO 2000053572; (d) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. WO 2000073278; (e) Bös, M.; Branca, Q.; Galley, G.; Godel, T.; Hoffmann, T.; Hunkeler, W.; Schnider, P.; Stadler, H. WO 2000073279.
11. Bristow, L. J.; Young, L. *Eur. J. Pharmacol.* **1994**, *253*, 245.
12. (a) Ballard, T. M.; Higgins, G. A.; Hoffmann, T.; Poli, S. M.; Sleight, A. J. EP 1103545, 2001.; (b) Hoffmann, T.; Schnider, P.; Stadler, H. WO 2002008232.; (c) Ballard, T. M.; Hoffmann, T.; Poli, S. M.; Schnider, P.; Sleight, A. J. WO 2003011860.
13. The procedure was optimized by Dr. François Montavon, F. Hoffmann-La Roche Ltd, Kilolaboratories Basel, Switzerland.