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# Piperazinyl oxime ethers as NK-1 receptor antagonists

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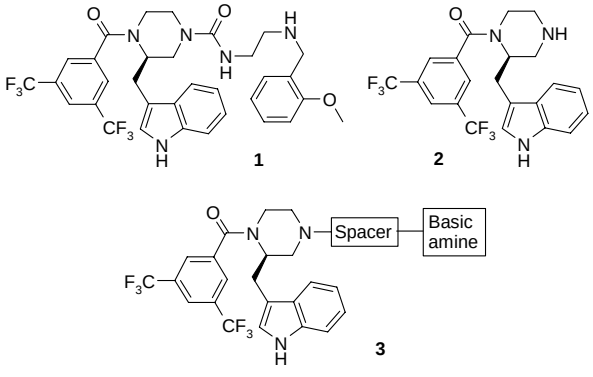
**Abstract**—The synthesis and structure–activity relations for a new class of centrally active NK-1 receptor antagonists are described. The new compounds are based on piperazine **2** and contain an oxime ether functionality. Several new compounds have high affinity for the NK-1 receptor and show good antagonistic activity in the gerbil foot-tapping assay.


The neuropeptide Substance P and its Neurokinin-1 (NK-1) receptor have been related to various biological disorders such as anxiety, depression,[1] emesis,[2] asthma and inflammatory bowel disease (IBD).[3] Furthermore, the first brain penetrant NK-1 receptor antagonist (Aprepitant; MK-869) has reached the market for the treatment of chemotherapy induced nausea and vomiting (CINV) and NK-1 receptor antagonists have shown their clinical effectiveness in Phase II studies for depression.[4] The latter result prompted us to examine a centrally acting NK-1 receptor antagonist for our CNS-drug discovery programme.

We have previously reported on a series of indolyl methyl-*N*,*N*′-bisacylpiperazines, a representative of which is **1**,[5] as potent NK-1 receptor antagonists (see Table1); however, **1** did not penetrate the brain[6] and thus showed no activity in the gerbil foot-tapping assay.[7] Based on in-house experience with poor brain penetration of compounds containing a urea function, it was postulated that the urea function, solely serving as a spacer unit between the required basic amine pharmacophore and the piperazine scaffold, was the cause of inactivity. Therefore, a programme was initiated to synthesise NK-1 receptor antagonists starting from the key pharmacophoric fragment **2** and introducing the essential basic element via an alternative spacer giving **3**. Due to our longstanding experience with oxime ethers,[8] having good brain penetration (i.e., fluvoxamine), an oxime ether function was selected as the key moiety in the spacer. Herein we report a series of novel compounds with several oxime ether spacers that act as highly potent CNS available NK-1 antagonists.




At first, a series of compounds was synthesised in which the influence of spacer length and spacer substitution was studied, whereas the basic amine was kept constant as a morpholino-group. Recently, researchers of Fujisawa reported a morpholine as the optimal basic pharmacophore in NK-1 antagonists.[9]

*Keywords*: Neurokinin; Synthesis; SAR; Oxime ethers.
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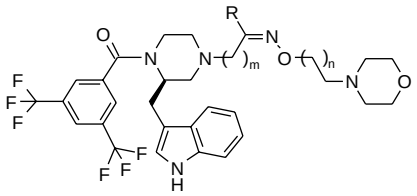
**Table 1.** Chain length and substituent variations

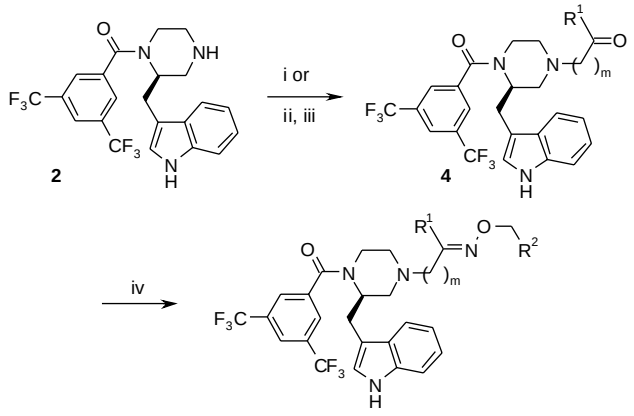


| Compound | R | *m* | *n* | hNK-1 p$K_i$[a] | hNK-1 p$A_2$[b] | Gerbil FT $ED_{50}$ (mg/kg po)[c] |
|---|---|---|---|---|---|---|
| **1** | | | | 8.6 ± 0.2 (3) | 8.9 ± 0.1 (3) | >10 |
| **8** | Me | 1 | 1 | 8.0 ± 0.2 (3) | 9.8 ± 0.2 (3) | 1.3 |
| **9** | Me | 1 | 2 | 7.9 ± 0.2 (3) | 9.8 ± 0.2 (6) | 7.4 |
| **10** | Me | 2 | 1 | 9.4 ± 0.2 (4) | 8.9 ± 0.3 (3) | 2.0 |
| **11** | Me | 2 | 2 | 9.7 ± 0.5 (3) | 9.0 ± 0.5 (4) | 5.5 |
| **12** | Me | 3 | 1 | 8.9 ± 0.3 (4) | 8.8 ± 0.3 (3) | 2.0 |
| **13** | Ph | 1 | 1 | 7.7 ± 0.2 (3) | 8.5 ± 0.4 (4) | n.d. |
| **14** | Ph | 1 | 2 | 8.2 ± 0.3 (3) | 8.9 ± 0.3 (4) | >10 |
| **15** | Ph | 2 | 1 | 8.0 ± 0.3 (4) | 8.9 ± 0.3 (3) | >10 |
| **16** | H | 1 | 1 | 8.9 ± 0.2 (3) | 9.2 ± 0.1 (4) | 2.0 |
| **17** | H | 1 | 2 | 8.9 ± 0.3 (4) | 9.2 ± 0.2 (4) | 2.3 |

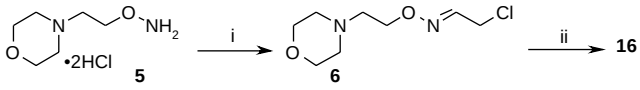
[a] Displacement of [$^3$H]-labelled Substance P from the cloned hNK-1 receptor expressed in CHO cells.
[b] Effect on $IP_3$ turnover by phospholipaseC positively linked to hNK-1 receptor expressed in CHO cells.
[c] Inhibition of foot-tapping by po administration of test compound 60 min prior to icv infusion of GR-73632. The duration of foot-tapping was recorded for 5 min.

Most oxime ethers were made from the corresponding ketones and aldehydes **4** by reaction with the appropriate alkoxyamine (Scheme 1), except for compound **16**. All oxime ethers were obtained as *E*/*Z*-mixtures. The ketones **4** were obtained from **2** by alkylation with a suitable alkylating agent, in those cases where the carbonyl was protected, the alkylating step was followed by acidic hydrolysis (see legend to Scheme 1 for details).

Compound **16** was made by direct alkylation of **2** with 2-chloroacetaldehyde oxime ether; the required oxime ether **6** was made by condensation of chloroacetaldehyde with the corresponding alkoxy amine **5** (Scheme 2).[10]



**Scheme 1.** Reagents and conditions: (i) chloroacetone, DIPEA, $CH_3CN$, rt or methylvinylketone, toluene, rt or 3-chloropropiophenone, DIPEA, $CH_3CN$, 70 °C or chloroacetophenone, DIPEA, $CH_3CN$, rt; (ii) 5-chloro-2-pentanone ethylene ketal, DIPEA, $CH_3CN$, reflux or 2-(2-bromoethyl)-1,3-dioxolane, DIPEA, $CH_3CN$, 75 °C; (iii) HCl, dioxane, $H_2O$ 50 °C; (iv) $RCH_2ONH_2 \cdot HCl$, NaOAc, EtOH, 70 °C.

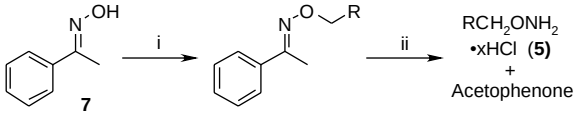


**Scheme 2.** Reagents and conditions: (i) chloroacetaldehyde, NaOH, $H_2O$, rt; (ii) **2**, DIPEA, $CH_3CN$, reflux.

The required alkoxy amines **5** were obtained by alkylation of acetophenone oxime **7** with an appropriate alkylating agent followed by acidic hydrolysis (Scheme 3).

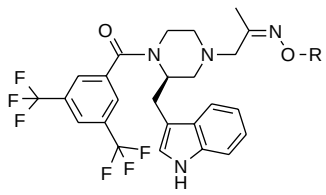
The biological results for compounds **8**–**17**, as shown in Table 1, indicate that the chain length between the piperazine-nitrogen and the morpholino-group does not have much effect on the affinity for the NK-1 receptor. A more noticeable effect is seen on the inositol turnover assay where the shorter chain lengths have a stronger antagonistic effect. A shorter distance between the morpholino-group and the oxime ether functionality is favoured. This effect is even more striking in the gerbil foot-tapping assay (compounds **8**, **10** and **12** versus **9** and **11**), a model predictive of central NK-1 activity.

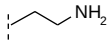
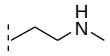
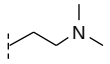
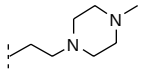
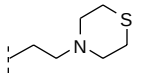
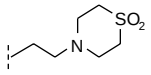
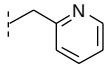
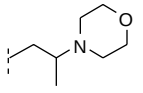
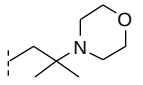
Whereas the spacer length has only a minor effect on the receptor affinity, a somewhat stronger effect is seen for the substituent in the spacer. A hydrogen-atom or methyl group is well tolerated; however, a phenyl group lowers the affinity and also reduces the antagonistic properties. Furthermore, the results from the gerbil



**Scheme 3.** Reagents and conditions: (i) $Bu_4NBr$, NaOH, toluene, $H_2O$, rt; (ii) HCl reflux.

**Table 2.** Variations of oxime ether side chain



| Compound | R | hNK-1 p$K_i$[a] | hNK-1 p$A_2$[b] | Gerbil FT $ED_{50}$ (mg/kg po)[c] |
|---|---|---|---|---|
| **18** | Me | 8.4 ± 0.1 (3) | 8.1 ± 0.3 (4) | n.d. |
| **19** |  | 9.1 ± 0.2 (4) | 9.8 ± 0.2 (4) | >10 |
| **20** |  | 8.7 ± 0.2 (4) | 9.5 ± 0.2 (4) | >10 |
| **21** |  | 9.1 ± 0.1 (3) | 8.1 ± 0.3 (4) | >10 |
| **22** |  | 8.8 ± 0.2 (3) | 8.8 ± 0.2 (3) | >10 |
| **23** |  | 8.2 ± 0.2 (6) | 8.9 ± 0.2 (3) | 10 |
| **24** |  | 8.6 ± 0.2 (5) | 10.0 ± 0.3 (3) | >10 |
| **25** |  | 8.0 ± 0.2 (4) | 8.9 ± 0.3 (4) | 4.1 |
| **26** |  | 8.5 ± 0.2 (4) | 8.7 ± 0.3 (3) | 2.6 |
| **27** |  | 8.2 ± 0.2 (3) | 8.3 ± 0.1 (3) | n.d. |

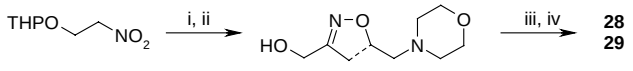
[a] Displacement of [$^3$H]-labelled Substance P from the cloned hNK-1 receptor expressed in CHO cells.
[b] Effect on $IP_3$ turnover by phospholipaseC positively linked to hNK-1 receptor expressed in CHO cells.
[c] Inhibition of GR-73632 induced foot-tapping in gerbils after oral administration.

foot-tapping assay show greater variability than would be expected from the in vitro data, suggesting that pharmacokinetic properties for brain penetration may not be favourable in all cases. A possible explanation for the latter fact could be the increase in molecular weight.

To study the effect of the basic amine, a series of compounds was made wherein the basic amine was varied. All compounds were made from **4** ($m = 1$, R = Me) and the distance between the basic amine and the oxygen-atom from the oxime ether was kept constant at a C-2 distance. First of all **18** was made; the result clearly indicated the importance of a basic amine, not only for functional activity but even for good receptor binding. For receptor binding and functional activity in vitro, the presence of a basic amine is sufficient, however, when the amine is too basic (cp$K_b$ < 5); oral in vivo activity is lost, probably caused by the less favourable pharmacokinetics of the compounds.

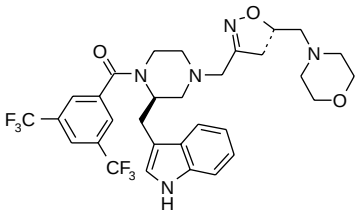
Furthermore, increasing the steric bulk around the basic nitrogen, as in **26** and **27**, reduced the affinity for the receptor and the antagonistic potency. While one methyl group is allowed (**26**), two methyl groups α to the basic nitrogen decrease the affinity and especially lower the antagonistic potency (Table 2).

In order to reduce the number of rotatable bonds in **8**, and to fix the oxime ether configuration, with the aim of increasing the affinity for the NK-1 receptor, the oxime ether functionality was replaced by an isoxazole




**Scheme 4.** Reagents and conditions: (i) *N*-allylmorpholine or *N*-propargylmorpholine, PhNCO, $Et_3N$, toluene, 55 °C; (ii) PPTS, MeOH, reflux; (iii) MsCl, DIPEA, $CH_2Cl_2$, rt; (iv) **2**, DIPEA, $CH_3CN$, reflux.

**Table 3.** Replacement of oxime ether by heterocycles



| Compound | Dotted bond | hNK-1 p$K_i$[a] | hNK-1 p$A_2$[b] | Gerbil FT $ED_{50}$ (mg/kg po)[c] |
|---|---|---|---|---|
| **28** | Single (isoxazoline) | 8.6 ± 0.2 (3) | 9.2 ± 0.1 (3) | 6.4 |
| **29** | Double (isoxazole) | 7.9 ± 0.1 (3) | 9.1 ± 0.3 (4) | 4.6 |

[a] Displacement of [$^3$H]-labelled Substance P from the cloned hNK-1 receptor expressed in CHO cells.
[b] Effect on $IP_3$ turnover by phospholipaseC positively linked to hNK-1 receptor expressed in CHO cells.
[c] Inhibition of GR-73632 induced foot-tapping in gerbils after oral administration.

or isoxazoline moiety (Scheme 4). The required isoxazole and isoxazoline were conveniently obtained by 1,3-dipolar cycloaddition of a nitrile oxide with *N*-allyl- or *N*-propargylmorpholine.[11] The isoxazoline **28** was isolated as a mixture of diastereomers and tested as such. The results are shown in Table 3, although the results in vitro were encouraging, the potency after oral dosing was decreased.

The best compound overall, **8**, was separated in the two oxime-isomers (ratio ~3:1) and the major isomer (*E*) was tested. As this isomer had very similar activities compared to those of mixture of isomers, ***E*-8** was selected as a preclinical candidate.

## Acknowledgments

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