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Piperazinyl oxime ethers as NK-1 receptor antagonists

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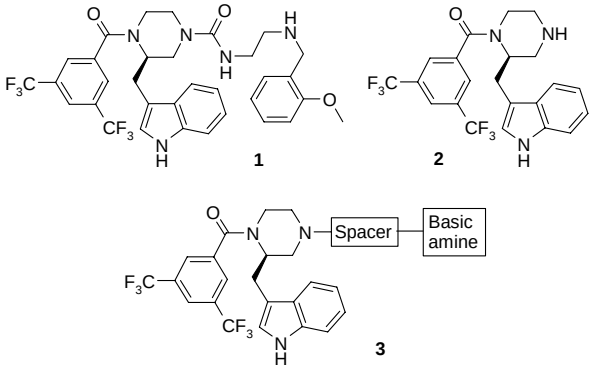
Abstract—The synthesis and structure–activity relations for a new class of centrally active NK-1 receptor antagonists are described. The new compounds are based on piperazine **2** and contain an oxime ether functionality. Several new compounds have high affinity for the NK-1 receptor and show good antagonistic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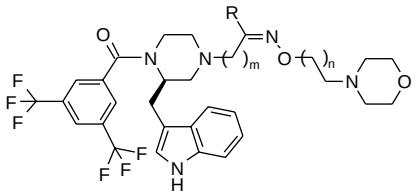
Table 1. Chain length and substituent variations

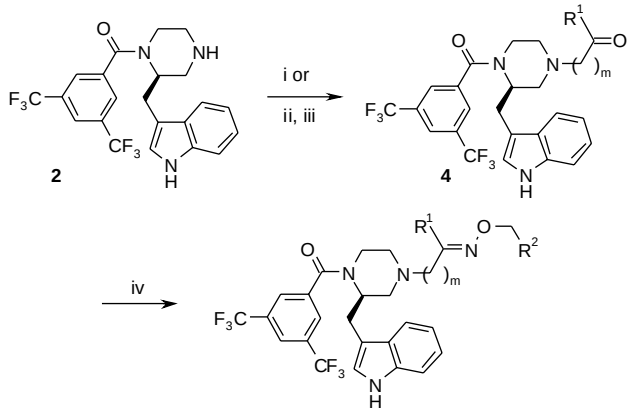


Compound	R	*m*	*n*	hNK-1 pK_i[a]	hNK-1 pA_2[b]	Gerbil FT ED_{50} (mg/kg po)[c]
1				8.6 ± 0.2 (3)	8.9 ± 0.1 (3)	>10
8	Me	1	1	8.0 ± 0.2 (3)	9.8 ± 0.2 (3)	1.3
9	Me	1	2	7.9 ± 0.2 (3)	9.8 ± 0.2 (6)	7.4
10	Me	2	1	9.4 ± 0.2 (4)	8.9 ± 0.3 (3)	2.0
11	Me	2	2	9.7 ± 0.5 (3)	9.0 ± 0.5 (4)	5.5
12	Me	3	1	8.9 ± 0.3 (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

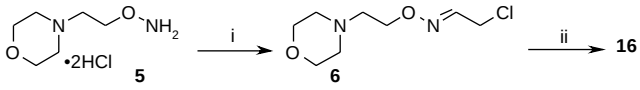
[a] Displacement of [^{3}H]-labelled Substance P from the cloned hNK-1 receptor expressed in CHO cells.
[b] Effect on IP_3 turnover by phospholipaseC positively linked to hNK-1 receptor expressed in CHO cells.
[c] Inhibition of foot-tapping by po administration of test compound 60 min prior to icv infusion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

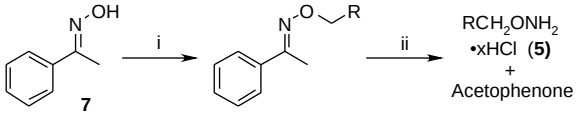


Scheme 2. Reagents and conditions: (i) chloroacetaldehyde, NaOH, H_2O, rt; (ii) **2**, DIPEA, CH_3CN, reflux.

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.