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High Affinity, Selective Neurokinin 2 and Neurokinin 3 Receptor Antagonists from a Common Structural Template

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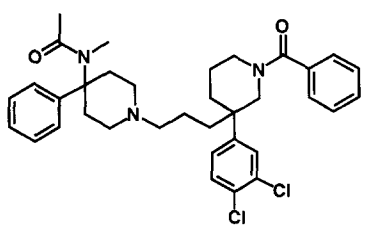
Abstract: High affinity, selective hNK_2 or hNK_3 ligands can be prepared from the common template **1** in a few simple chemical operations. The hNK_3 ligands **3** antagonise the calcium mobilisation caused by activation of hNK_3 receptors expressed in CHO cells as measured using fura-2 microspectrofluorimetry. © 1998 Elsevier Science Ltd. All rights reserved.

The neurokinins are a family of peptides that share the common C-terminal sequence *Phe-X-Gly-Leu-Met(NH_2)*. There are three neurokinin receptors (NK_1, NK_2 and NK_3), each of which is G-protein linked to secondary messenger systems. Substance P, NKA and NKB have highest affinity at the NK_1, NK_2 and NK_3 receptors respectively, although it should be noted that all three of these neurokinins have a relatively high affinity for, and are able to act as full agonists at, all three receptor subtypes[1]. The neurokinins have been implicated in a number of disease states including migraine, emesis, pain, arthritis, asthma, depression and anxiety.[2]

In order to investigate fully the roles of the various neurokinins, ligands selective for the three receptors are required. While much recent effort has focussed on the identification of non-peptide antagonists for the NK_1 receptor, by contrast NK_2 and NK_3 receptor antagonists have received much less attention[3]. A recent disclosure from Sanofi has described SR-142,801, a non-peptidic human NK_3 (hNK_3) antagonist which may have potential in psychosis and anxiety.[4]



SR-142,801

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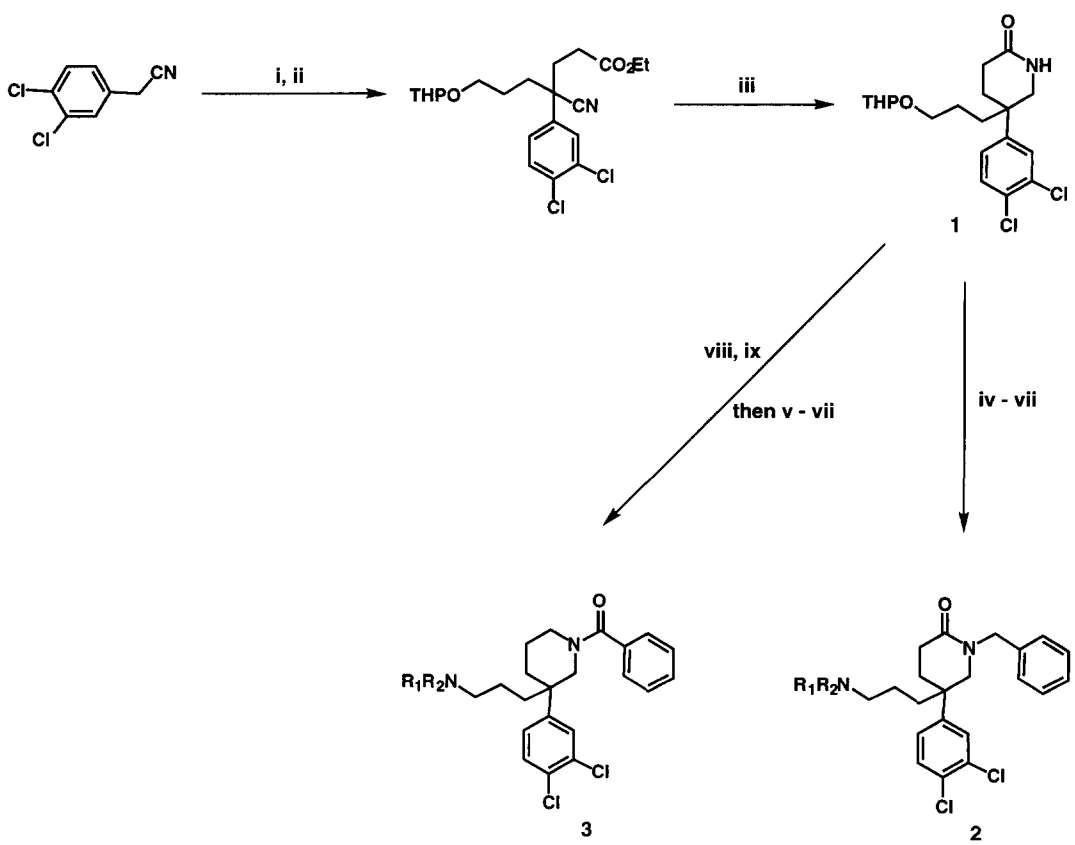
In this communication we describe a new series of lactam derivatives in which the amide carbonyl of SR-142,801 has been transposed into the piperidine ring and which contain a range of novel cyclic amines replacing the phenyl acetamidopiperidine moiety. The effect of incorporating these novel cyclic amines into the amide series is also presented. Finally, the ability of a series of high affinity non-peptide hNK_3 ligands to antagonise the calcium mobilisation caused by activation of hNK_3 receptors expressed in CHO cells is discussed.

Both the amide series **3** and the lactam series **2** were constructed from the common lactam **1**[5] as shown in Scheme 1. In the lactam series, N-benzylation was followed by O-deprotection, conversion to the mesylate and displacement using an appropriate amine. Alternatively, the lactam **1** was reduced with $LiAlH_4$, the resultant piperidine benzoylated and the amine introduced as described previously to provide amides **3**.

Scheme 1



Reagents and conditions: i) $THPO(CH_2)_3Br$, THF, NaH (84%); ii) ethyl acrylate, triton B, dioxane (95%);iii) H_2, Raney Ni, EtOH (76%); iv) NaH, BnBr, THF (87%); v) HCl, MeOH; vi) MsCl, Et_3N, CH_2Cl_2; vii) R_1R_2NH, K_2CO_3, DMF; viii) $LiAlH_4$, THF (60%); ix) PhCOCl, Et_3N, CH_2Cl_2 (83%).

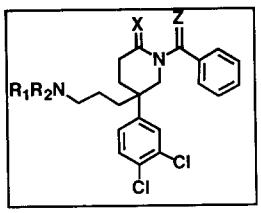


Table 1 - Lactam Series (X=O, Z=H_2)

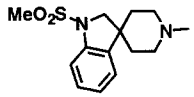
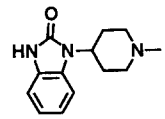
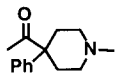
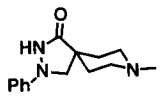
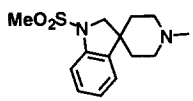
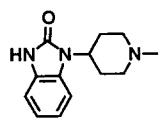
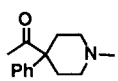
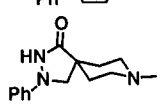
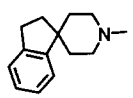
Compound	R_1R_2N	hNK_1	IC_{50} (nM)[6] hNK_2	hNK_3
2a		763	2.2	25
2b		743	6.4	539
2c		1026	3.9	19
2d		892	2.5	127

Table 2 - Amide Series (X=H_2, Z=O)

Compound	R_1R_2N	hNK_1	IC_{50} (nM)[6] hNK_2	hNK_3
3a		497	177	1.2
3b		379	348	7.9
3c		460	389	1.5
3d		108	50	6.8
3e		272	204	2.6

It can be seen by reference to Table 2 that in the amide series **3** all of the new cyclic amines are well tolerated providing a series of compounds with high affinity for the hNK_3 receptor and with good selectivity over other hNK receptors. Interestingly, when the amide carbonyl is transposed into the piperidine ring a complete reversal of selectivity is achieved to provide a series of compounds with high affinity for the hNK_2 receptor and generally good selectivity over other hNK receptors (Table 1). Thus, from the common precursor **1** high affinity ligands with good selectivity for both the hNK_2 and the hNK_3 receptor can be prepared in a few simple chemical steps.

Before using these high affinity, selective ligands as biological probes we were interested in demonstrating that they acted as functional antagonists. Thus the ability of the hNK_3 ligands to antagonise the calcium mobilisation caused by activation of hNK_3 receptors expressed in CHO cells was studied using Fura-2 microspectrofluorimetry, as described for hNK1 transfected cells[7].

Activation of hNK_3 receptors in CHO cells caused a concentration-dependent and oscillatory increase in $[Ca^{2+}]_i$ (Figure 1). The rank order of agonist potency was NKB = senktide > NKA > SP (Table 3).

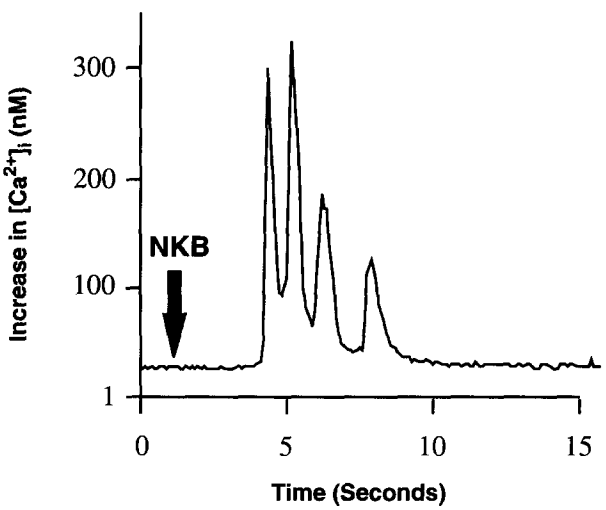


Figure 1

This was comparable to the ability of these ligands to displace [^{3}H]-NKB binding in this cell line (Table 3).

Ligand	IC_{50} (nM)	EC_{50} (nM)
senktide	1	7 ± 0.3
neurokinin B	3	6 ± 2
neurokinin A	45	53 ± 11
SP	125	793 ± 10

Table 3 - Comparison of binding (IC_{50} for displacement of [^{3}H]-NKB binding) and functional (EC_{50} for increase in $[Ca^{2+}]_i$) data for a series of ligands at the hNK_3 receptor

Since responses in NK_3-CHO cells exhibited pronounced tachyphylaxis with repeated agonist applications, the ability of antagonists to block responses to a known concentration of agonist was examined (Figure 2).

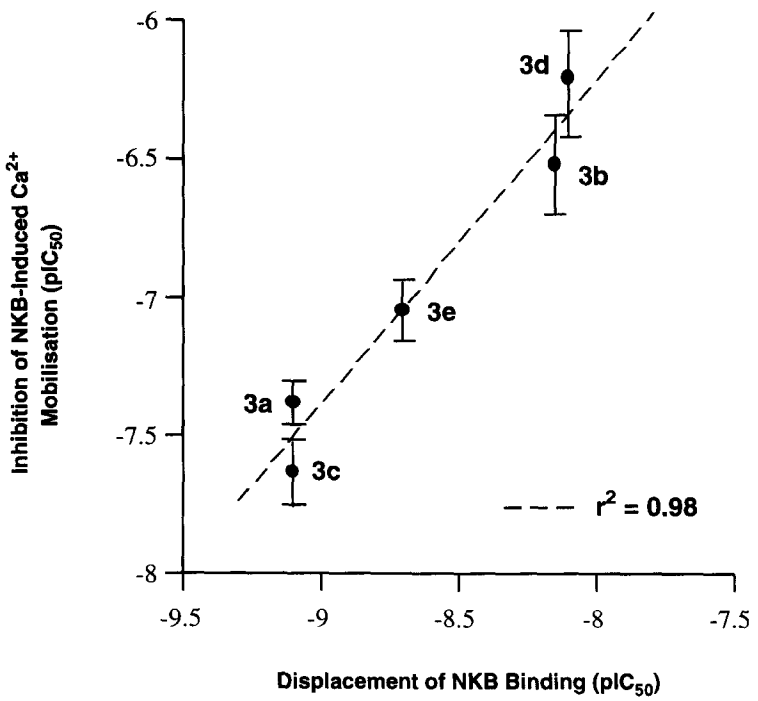


Figure 2

It can be seen (Figure 2) that there is good correlation between the IC_{50} for inhibition of NKB-induced Ca^{2+} mobilisation and the IC_{50} for displacement of NKB binding. The functional IC_{50} for **3c** was 23nM (pIC_{50} = 7.64

± 0.12). The functional IC_{50} values were approximately 30-fold weaker than the binding IC_{50} values which is consistent with the concentration of agonist used (100nM NKB) relative to its EC_{50} (6nM).

In conclusion, high affinity ligands for human cloned NK_2 and NK_3 receptors can be prepared from a common structural template based upon SR-142,801 simply by transposing the carbonyl oxygen from an exocyclic to an endocyclic position on the piperidine ring. These compounds should be useful in helping to define the pharmacophore for hNK_2 and hNK_3 receptors and to further clarify the functional significance of neurokinin receptor subtypes in the central nervous system.

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6. The affinities of the compounds for the $NK_{1/2/3}$ receptors were determined by displacement of the appropriate radioligand from the cloned human receptor in CHO cells as follows: NK_1: [^{125}I]Substance P, see (i) Cascieri, M.A.; Ber, E.; Fong, T.M.; Sadowski, S.; Bansal, A.; Swain, C.J.; Seward, E.; Frances, B.; Burns, D. and Strader, C.D. *Mol. Pharm.*, **1992**, *42*, 458. (ii) Fong, T.M.; Anderson, S.A.; Yuh, H.; Huang, R.R.C. and Strader, C.D. *Mol. Pharm.*, **1992**,*41*, 24; NK_2: [^{125}I]NKA, see Cascieri, M.A.; Huang, R.R.CT.M. Fong, T.M.; Cheung, A.H.; Sadowski, S.; Ber, E. and Strader, C.D. *Mol. Pharm.*, **1992**, *41*, 1096; NK_3: [^{125}I]NKB, see Sadowski, S.; Huang, R.R.C.; Fong, T.M.; Marko, O. and Cascieri, M.A. *Neuropeptides*, **1993**, *24*, 317. Binding data are the mean of 3 independent determinations. All new compounds described are racemic.

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