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SERINE DERIVED NK_1 ANTAGONISTS 2: A PHARMACOPHORE MODEL FOR ARYLSULFONAMIDE BINDING.

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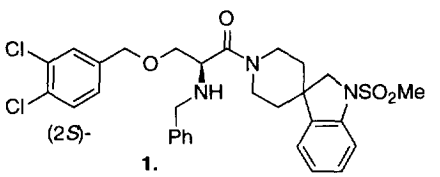
Abstract: Modifications to the spirocyclic aryl sulfonamide portion of serine derived NK_1 antagonists allow a partial pharmacophore model to be developed.

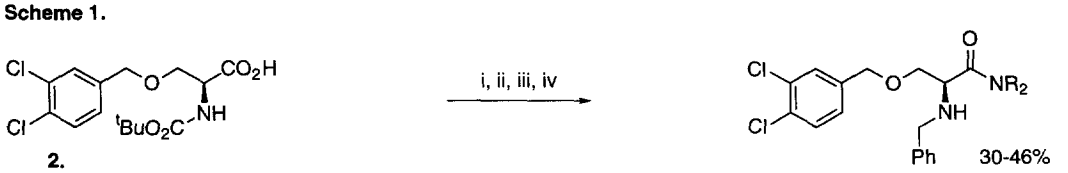
We have previously described our development of a novel class of serine based NK_1 receptor antagonists to give **1** (hNK_1 IC_{50} 1.0 nM).[1] In this communication, we discuss the effect of variations to the rigid spirocyclic portion of the molecule.



1.

Compounds were prepared by coupling of a suitable amine† to the enantiomerically pure acid **2**[1] followed by deprotection and *N*-benzylation (Scheme 1). The syntheses of those amines which are not commercially available are shown in Scheme 2.

Scheme 1.



2.

Reagents: i) R_2NH, BOP-Cl, Et_3N, CH_2Cl_2; ii) HCl, EtOH; iii) PhCHO, Et_3N, $MgSO_4$, CH_2Cl_2; iv) $NaBH_4$, MeOH.

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†1,2-Dihydro-1-(methylsulfonyl)spiro[3*H*-indole-3,4′-piperidine] and 2,3-dihydrospiro[1*H*-indene-1,4′--piperidine] were prepared by published methods.[2,3] 1-(2-Methoxyphenyl)piperazine and 1-(2-methylphenyl)piperazine were purchased from Aldrich Chemical Co.

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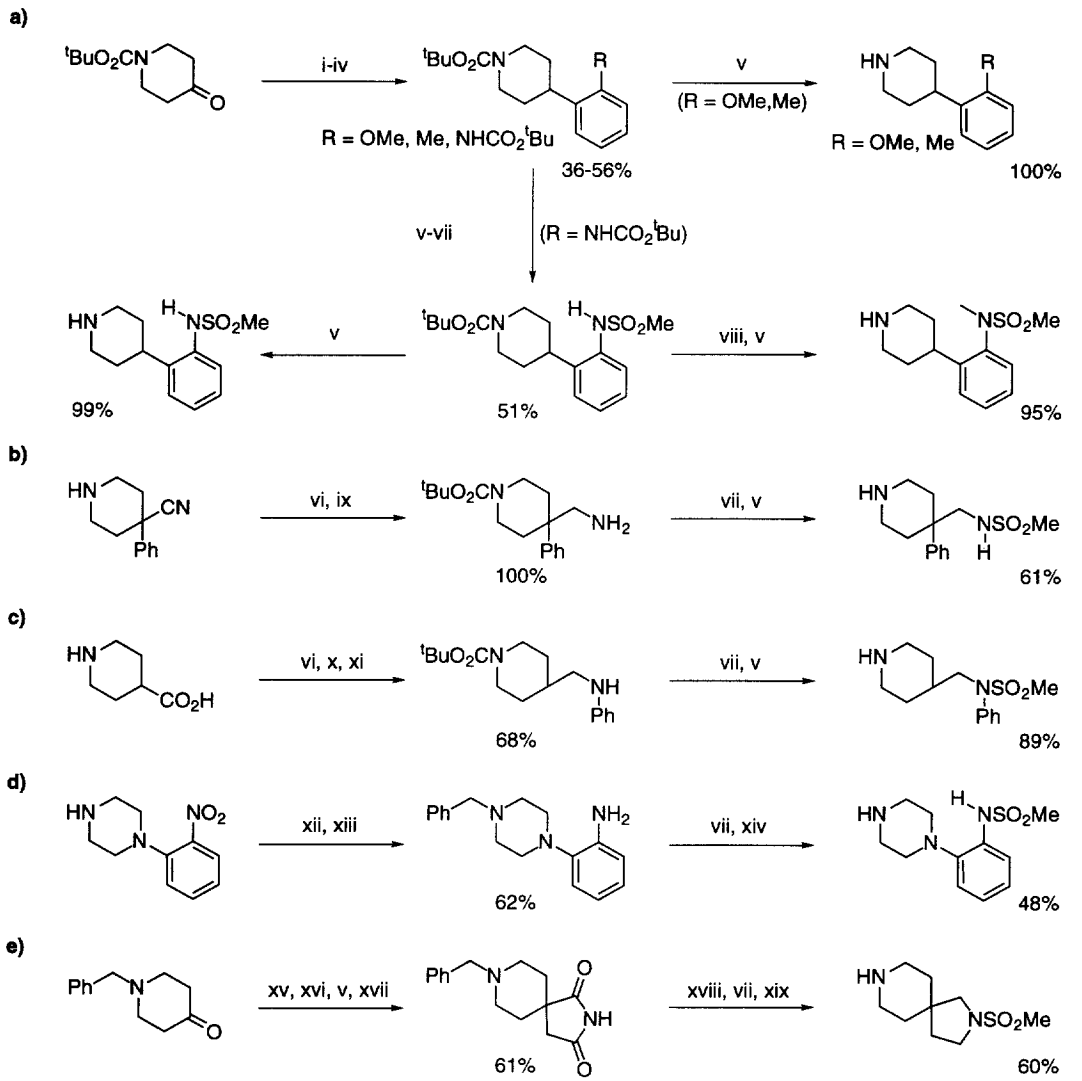
PII: S0960-894X(98)00319-9

Scheme 2.



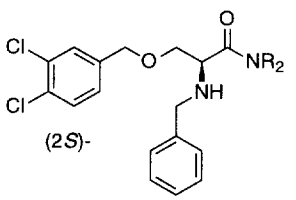
Reagents: i) LDA, THF; ii) $PhN(SO_2CF_3)_2$; iii) $ArB(OH)_2$, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, DME-H_2O; iv) H_2 (50 psi), Pd-C, EtOH; v) HCl, MeOH; vi) $(^tBuO_2C)_2O$, CH_2Cl_2; vii) $MeSO_2Cl$, Pyridine, CH_2Cl_2; viii) NaH, MeI, THF; ix) H_2 (50 psi), PtO_2, AcOH-EtOH; x) $PhNH_2$, BOP-Cl, Et_3N, CH_2Cl_2; xi) BH_3.THF, THF; xii) $PhCH_2Br$, K_2CO_3, DMF; xiii) $SnCl_2$, EtOH; xiv) Pd-C, $NH_4.HCO_2$, HCO_2H, MeOH; xv) EtO_2CCH_2CN, AcOH, $PhCH_3$; xvi) NaCN, EtOH-H_2O; xvii) H_2SO_4, AcOH; xviii) $LiAlH_4$, THF; xix) Pd-C, HCO_2H, EtOH.

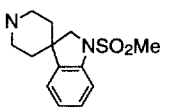
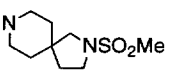
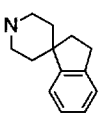
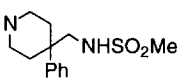
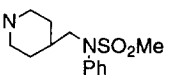
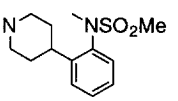
If either the spirocyclic aromatic ring or sulfonamide are removed, the resulting compounds (**3, 4**) have much lower affinity for the NK_1 receptor than the lead compound **1** (Table 1), suggesting that both groups are crucial for binding. The rigidity of the spirocyclic linkage also appears to be important as compounds in which indoline bonds are (effectively) cleaved also lose affinity (**5, 6**). Only **7**, corresponding to cleavage of the 2,3-bond of the indoline, shows significant affinity, although approximately 60-fold less than **1**.

Further exploration of the SAR around **7** shows that removal of the *N*-methyl group (**8**) gains some affinity but replacement of the methanesulfonamide with methyl (**9**) or methoxy (**10**) is not favored (Table 2). However, replacement of the piperidine with a piperazine improves affinity (**11**, **13**). In combination with 2-methanesulfonamido substitution, this gives **11** which has only marginally lower affinity than the lead 1,2-dihydro-1-(methylsulfonyl)spiro[3*H*-indole-3,4′-piperidine] **1**.

Table 1.

Spirocycle Replacements

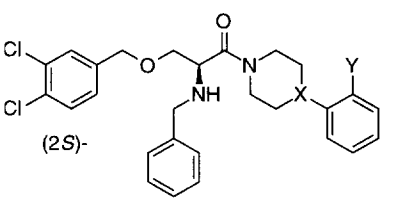


	X	hNK_1 IC_{50} (nM)[a]
1.		1.0 ±0.6[b]
3.		2500 ±1054
4.		602 ±233
5.		382 ±180
6.		547 ±254
7.		61 ±26

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[4] [b]n = 4.

Table 2.

4-Aryl Piperidines and piperazines



	X	Y	hNK_1 IC_{50} (nM)[a]
8.	CH	$NHSO_2Me$	17 ±18
9.	CH	Me	330 ±87
10.	CH	OMe	263 ±115
11.	N	$NHSO_2Me$	4.8 ±3.3
12.	N	Me	558 ±158
13.	N	OMe	13 ±3

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[4]

We have already established that the aromatic ring of the *O*-benzyl group plays a key role in binding to the receptor.[1] These results show that the aryl sulfonamide is also important. We believe that the function of the serine derived backbone is to deliver the two groups to appropriate binding sites on the receptor, although the relationship between the sites is not known. We can, however, use the SAR described here to define a partial pharmacophore model for the arylsulfonamide portion of the molecule.

Simplified molecular models[‡] of the spirocycle **1** suggest a modest preference for the conformation in which the aryl group is equatorial to the piperidine (the conformation in which the aryl group is axial is higher in energy by 1 kcal/mol). On its own, this result would be insufficient to exclude the possibility that **1** could adopt an axial-aryl conformation, and it would be possible to construct two possible pharmacophore models in which the aryl group is either equatorial or axial. However, the non-spirocyclic 4-aryl piperidines (**7-10**) are calculated to have rather larger preferences for equatorial-aryl conformations (up to 3.5 kcal/mol). Thus, the SAR is more consistent with the hypothesis that it is the equatorial-aryl conformation of **1** (Figure 1) which is involved in receptor binding. The low affinity of **4**, which is calculated to adopt a conformation very similar to **1**, suggests that the sulfonamide group is needed for binding to the receptor, probably acting as a hydrogen bond acceptor. Similarly, the low affinity of **3**, which lacks an aromatic ring, shows that the aryl group of **1** is needed to exploit a hydrophobic or π-interaction with the receptor. Thus we can propose a minimum pharmacophore for the aryl sulfonamide which involves these two interactions (Figure 2).

Figure 1

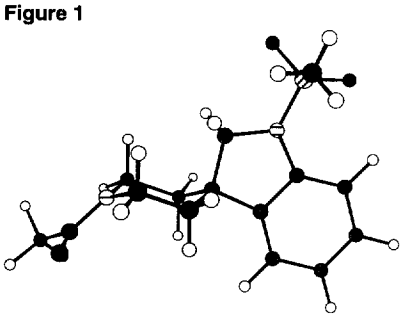
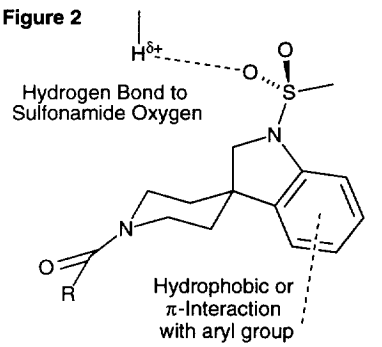


Figure 2

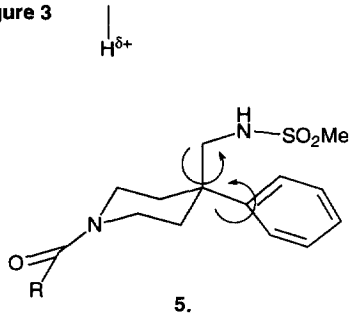


For compound **5**, the two conformers with the phenyl group axial or equatorial are calculated to have similar energies. Nevertheless, in the conformer which most closely matches **1** (equatorial-phenyl), both the phenyl and

‡ Compounds were modeled using semiempirical quantum mechanics [MOPAC 6 (J.J.P. Stewart, QCPE program 455) using AM1 with PRECISE convergence criteria and eigenvector following geometry optimisation]. The serine derived portion of the molecule was abbreviated to N-acetyl. A full conformational search was carried out on the spirocyclic portion of **1** using the systematic search module of Tripos' Sybyl suite (Tripos, Inc., St. Louis, Missouri) and initial conformers of subsequent compounds were constructed on the basis of similarity to the lowest energy (after AM1 minimisation) conformations of **1** found (piperidine/piperazine substituent axial and equatorial). In compounds where there were no conformational constraints, several possible orientations of the aryl ring and its substituent relative to one another and to the piperidine/piperazine were tried. Where significant conformational changes were observed during minimisation of these subsequent compounds, e.g. with **7**, a conformational search was carried out to confirm that there was no other low-lying energy minimum more similar to the reference conformations of **1**.

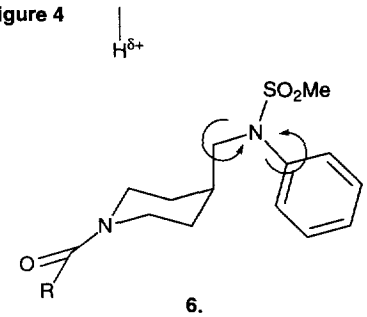
sulfonamide groups are free to rotate out of position, so binding is poor (Figure 3). Similarly, in **6** the flexible side chain fails to fix the key groups in the correct positions for binding (Figure 4).

Figure 3



5.
hNK_1 IC_{50} 382 nM

Figure 4



6.
hNK_1 IC_{50} 547 nM

Calculations on the 4-aryl piperidines (**7-10**) predict that the aryl group adopts an equatorial position; interactions between the aryl group and the hydrogens on the 3- and 5- positions of the piperidine are minimized if the aryl ring is orthogonal to the piperidine, with the 2-substituent close to the 4-axial hydrogen. In the case of **7** this results in a moderately good overlay with **1** but an unfavorable interaction between the *N*-methyl group and the 4-axial hydrogen forces the sulfonamide group to rotate away from the optimal position (Figure 5) (the barrier to rotating the sulfonamide back into a position similar to that in the spirocycle is over 7 kcal/mol). Removal of the *N*-methyl group (**8**) reduces this unfavorable steric interaction, improving the affinity. Finally, replacing the piperidine with a piperazine (**11**) removes the 4-axial hydrogen and, moreover, allows a hydrogen bond between the piperazine nitrogen and the sulfonamide to stabilize a conformation which closely mimics the spirocycle (Figure 6).

Figure 5

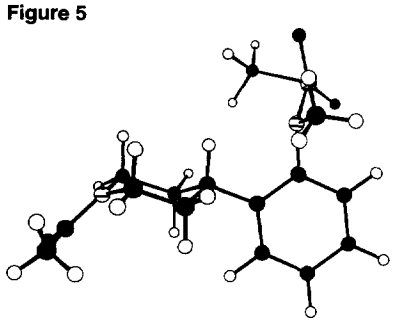
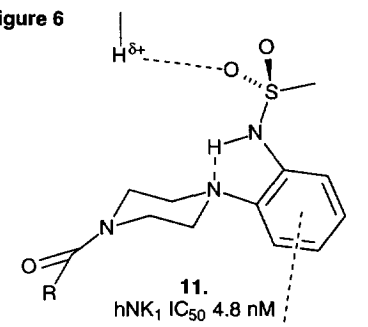


Figure 6



11.
hNK_1 IC_{50} 4.8 nM

The 2-methoxyphenylpiperazine **13** is an interesting anomaly. The low affinity of the piperidine analog **10** suggests that the methoxy oxygen is a poor hydrogen bond acceptor, despite a predicted conformation which places the aryl ring in the preferred equatorial, orthogonal position. Moreover, modeling studies on the piperazine **13** predict that repulsion between the lone pairs of the oxygen and nitrogen force the aryl ring to rotate away from the orthogonal orientation (Figure 7). This occurs despite steric crowding between the *o*-aromatic substituents and the hydrogens on the 3- and 5- positions of the piperidine. It is surprising therefore, that **13** actually has much greater affinity (hNK_1 IC_{50} 13 nM) than **10**. This result can be explained by the formation of a hydrogen bond to

both the oxygen and nitrogen. Since the lone pairs on both heteroatoms are involved in the hydrogen bond, the repulsion between them is reduced and the molecule can return to the preferred orthogonal conformation (Figure 8). A simplified model for this hydrogen bonded form is the protonated form of **13**. Calculations confirm that once the nitrogen is protonated, the aryl group returns to the orthogonal position (Figure 9), giving a much better overlay with **1** than the unprotonated form. While this form would not be expected to be significant in solution, it is a good model for a bound form in which there is a hydrogen bond to both the oxygen and nitrogen. Thus, a combination of electronic and steric repulsion destabilizes the non-hydrogen bonded form relative to the hydrogen bonded form, making **13** a much better hydrogen bond acceptor than **10**.

Figure 7

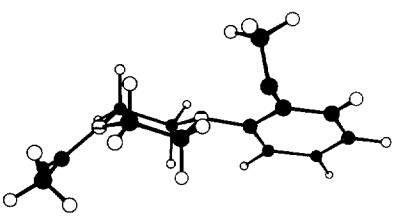
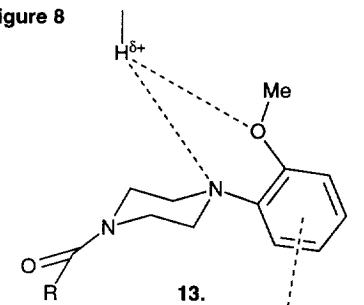
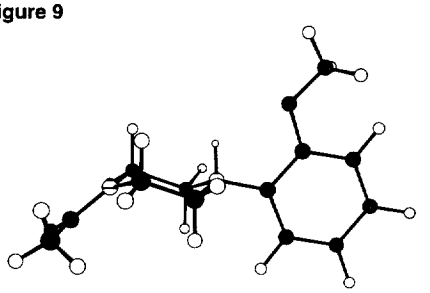


Figure 8



13.
hNK_1 IC_{50} 13 nM

Figure 9



The full pharmacophore model must also include the binding site for the *O*-benzyl ring, but the highly flexible nature of the serine backbone makes it impossible to determine a preferred conformation for **1**. However, the flexibility of the molecule is somewhat constrained by the rigid spirocycle, so it will be possible to place limits on the available conformations and thus further refine our pharmacophore model. We are currently exploring the conformational analysis of partially flexible molecules such as **1** in order to address this problem.

References and Notes

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