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SERINE DERIVED NK_1 ANTAGONISTS 1: THE EFFECT OF MODIFICATIONS TO THE SERINE SUBSTITUENTS.

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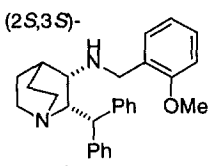
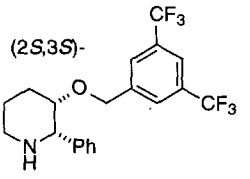
Abstract: A series of novel serine derived NK_1 antagonists is described. The effect of variations in the *N*-benzyl, *O*-benzyl and serine groups are used to define the elements which are necessary for binding.

Substance P is a member of the tachykinin family of neuropeptides which binds selectively to the NK_1 receptor.[1] The release of Substance P has been implicated in the pathogenesis of a wide range of disease conditions, including neurogenic inflammation, transmission of pain and emesis.[2,3] More recently, clinical results have suggested that NK_1 receptor antagonists may be effective as anti-depressants.[4,5] This has further intensified efforts to identify new NK_1 receptor antagonists which may have utility for the clinical treatment of disease.



1.



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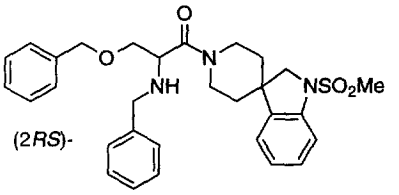

3.

Early work in this area focussed on peptide based antagonists,[1,3] but the discovery of non-peptide antagonists, such as CP-96,345 (**1**)[6] was a key breakthrough. Subsequent work in a number of laboratories has led to several highly potent antagonists, such as CP-99,994,[7] CP-122,721,[8] GR205171,[9] and L-733,060 (**2**).[10] We have discovered a novel series of serine based NK_1 receptor antagonists which have different structural requirements from previously reported classes, allowing us to develop a new pharmacophore model (discussed in the subsequent communication[11]).

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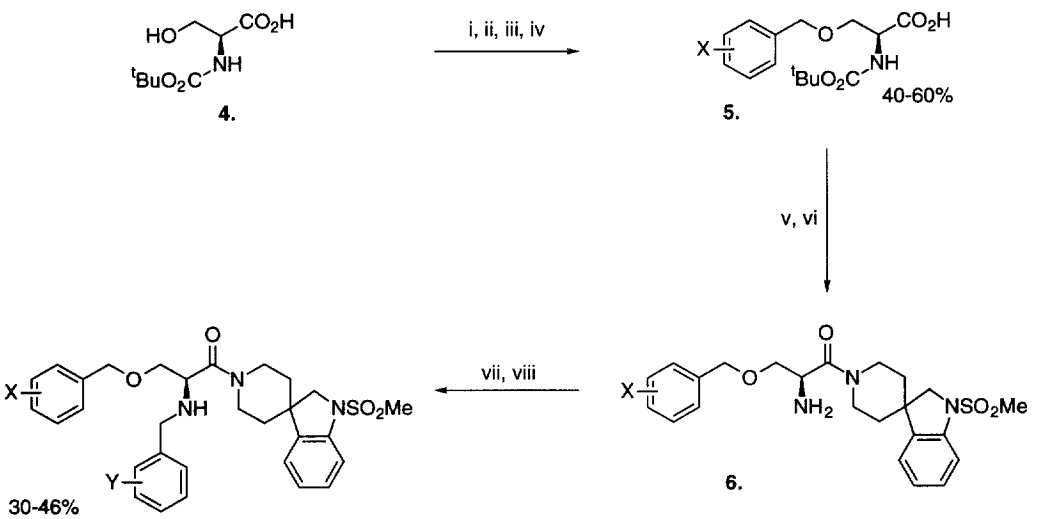
The lead compound **3**, 1,2-dihydro-1-(methylsulfonyl)spiro[3*H*-indole-3,4′-piperidine] coupled to an *N,O*-bis-benzylated serine, showed promising affinity for the NK_1 receptor (hNK_1 IC_{50} 80 nM[12]). In this communication, we report the effect of variations in the serine derived portion. The subsequent communication will describe the effect of modifications to the spirocycle.[11]

The introduction of substituents on the *N*-benzyl ring was examined first. Compounds were prepared by coupling of a suitable *N*-protected, *O*-benzyl serine **5**[13] to 1,2-dihydro-1-(methylsulfonyl)spiro[3*H*--indole-3,4′-piperidine][14] using standard peptide coupling conditions.[15] The serine nitrogen was then deprotected to give **6** which was alkylated *via* a reductive amination (Scheme 1). This route was initially carried out using racemic **4**, but enantiomerically pure products could be prepared from resolved **4**, with no detectable racemisation during the sequence (product ee's >99% by chiral HPLC†). Treatment of the amine **6** with acid chlorides or sulfonyl chlorides gave the amides and sulfonamide of Table 2.

Scheme 1.

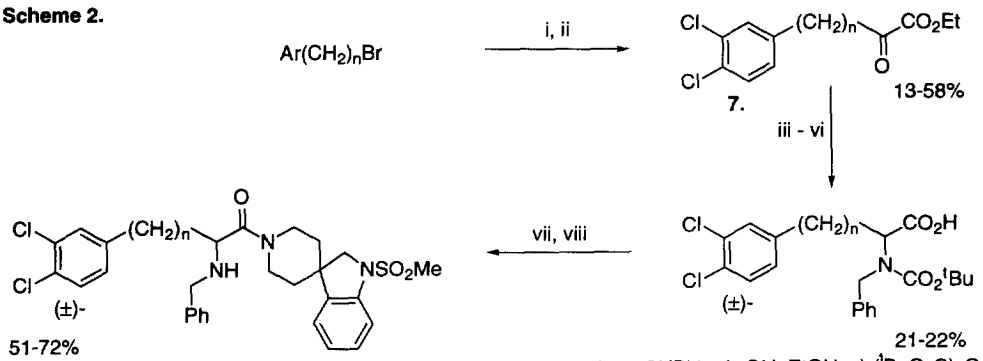


Reagents: i) NaH, DMF; ii) $ArCH_2Br$; iii) Cyclohexylamine, recrystallize from EtOAc/Hexane; iv) HCl-H_2O, EtOAc; v) N-[1-Methanesulfonylspiro(3*H*-indole-3,4'-piperidine) hydrochloride, BOP-Cl, Et_3N, CH_2Cl_2; vi) HCl, MeOH; vii) ArCHO, Et_3N, $MgSO_4$, CH_2Cl_2; viii) $NaBH_4$, MeOH.

Compounds in which the serine oxygen was replaced by a methylene, and chain shortened analogs, were prepared as racemates from the keto esters **7** by reductive amination (Scheme 2), followed by hydrolysis and coupling as above. *N*-Benzyl serine was protected and cyclized under Mitsonobu conditions to give the β-lactone **8**,[16] which was ring opened with 3,4-dichlorobenzylmercaptan to give compounds in which the serine oxygen was replaced by a sulfur (Scheme 3). The sulfide was oxidized to the corresponding sulfone by treatment with MCPBA. Compounds in which the serine oxygen was replaced with a nitrogen were prepared (as racemates) by Michael addition of 3,4-dichlorobenzylamine to the unsaturated ester **9**,[17] prepared by dehydration of protected serine (Scheme 4).

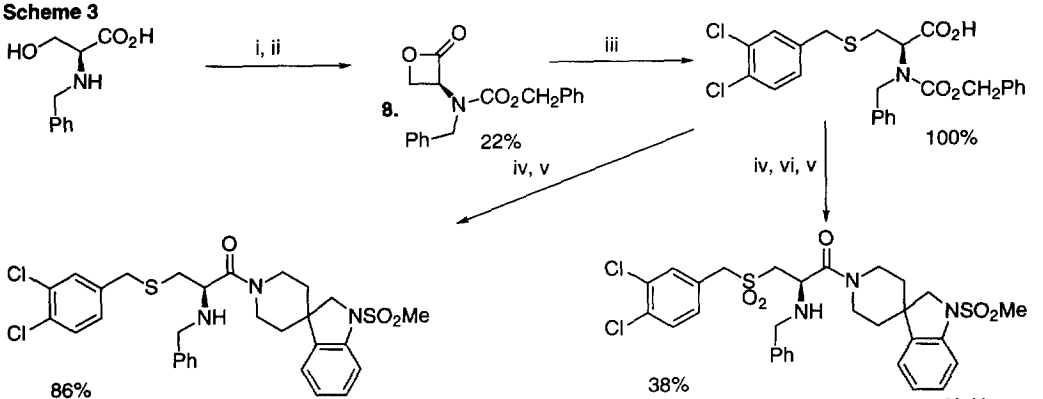
† Chiralcel OD (250 x 4.6 mm id 10 μM); 40 °C
hexane/ethanol (50:50); 1 ml/min; det. 230 nm.

Scheme 2.



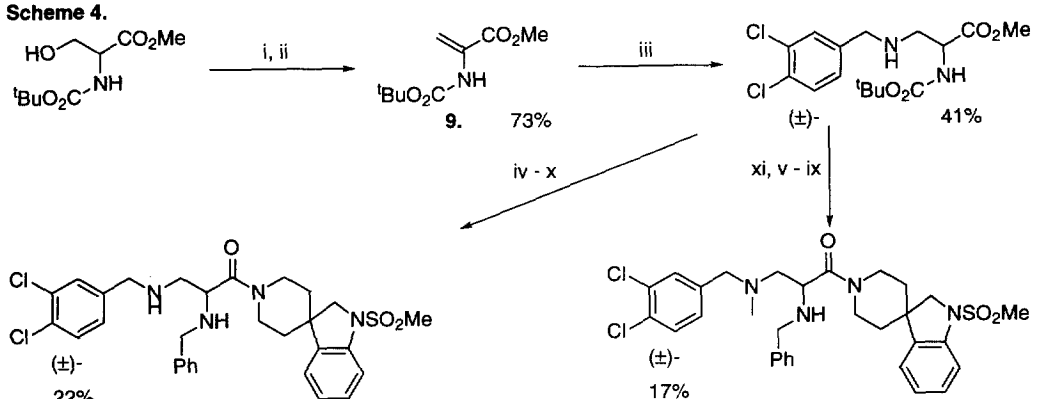
Reagents: i) Mg, Et_2O; ii) EtO_2CCO_2Et; iii) $PhCH_2NH_2$, EtOH; iv) $NaCNBH_3$, AcOH, EtOH; v) $(^tBuO_2C)_2O$, CH_2Cl_2; vi) LiOH, $THF\text{-}H_2O$; vii) N-[1-Methanesulfonylspiro(3*H*-indole-3,4'-piperidine) hydrochloride, BOP-Cl Et_3N, CH_2Cl_2; viii) HCl, EtOH.

Scheme 3



Reagents: i) $PhCH_2OCOCl$, NaOH, $THF\text{-}H_2O$; ii) DEAD, Ph_3P, THF; iii) 3,4-Dichlorobenzylmercaptan, NaH, DMF; iv) N-[1-Methanesulfonylspiro(3*H*-indole-3,4'-piperidine) hydrochloride, BOP-Cl, Et_3N, CH_2Cl_2; v) BBr_3, CH_2Cl_2; vi) MCPBA, CH_2Cl_2.

Scheme 4.

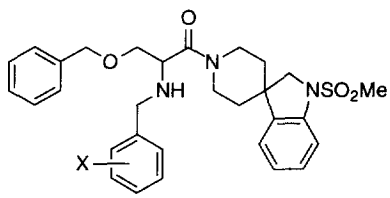


Reagents: i) $TolSO_2Cl$, Py, CH_2Cl_2; ii) Et_2NH, Et_2O, EtOAc; iii) 3,4-Dichlorobenzylamine, MeOH; iv) $PhCH_2CO_2Cl$, $NaHCO_3$, $THF\text{-}H_2O$; v) LiOH, $THF\text{-}H_2O$; vi) N-[1-Methanesulfonylspiro(3*H*-indole-3,4'-piperidine) hydrochloride, BOP-Cl, Et_3N, CH_2Cl_2; vii) TFA, CH_2Cl_2; viii) PhCHO, Et_3N, $MgSO_4$, CH_2Cl_2; ix) $NaBH_4$, MeOH; x) BBr_3, CH_2Cl_2; xi) HCHO, $NaCNBH_3$, AcOH, MeCN.

The introduction of *N*-benzyl substituents generally has modest effects on binding (Table 1). While substitution at the 2-position is detrimental, both electron donating and electron withdrawing substituents at the 3- and 4-positions are tolerated. Interestingly, binding is also insensitive to the stereochemistry at the 2-position of the serine. Both enantiomers of **16** had good affinity, with the *S*-enantiomer (**18**) slightly more active than the *R*-enantiomer (**17**). This is in contrast to the *cis*-disubstituted piperidines, where NK_1 activity is limited to a single enantiomeric series [For example (2*S*,3*S*)-L-733,060 (**2**), is a potent NK_1 antagonist (IC_{50} 1.0 nM), but the (2*R*,3*R*)-enantiomer is much less active (IC_{50} 350 nM)].[10] Further modification of the group attached to the serine nitrogen shows even greater tolerance for variation (Table 2), with phenylacetamide (**30**) and phenylsulfonamide (**31**) substituents giving significant affinity. Only complete removal of the substituent abolishes affinity (**32**).

Table 1.

N-Benzyl Substitution

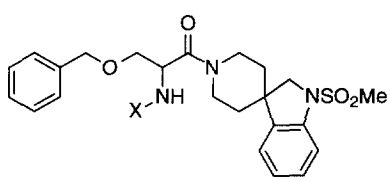


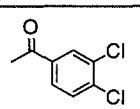
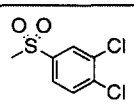
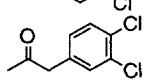
	Stereochemistry	X	hNK_1 IC_{50} (nM)[a]		Stereochemistry	X	hNK_1 IC_{50} (nM)[a]
3.	2*RS*	H	80 ±4	**19.**	2*RS*	3,5-Cl_2	79 ±8
10.	2*RS*	2-Cl	542 ±24	**20.**	2*RS*	3-F	157 ±51
11.	2*RS*	3-Cl	58 ±2	**21.**	2*RS*	3-Br	60 ±5
12.	2*RS*	4-Cl	27 ±3	**22.**	2*RS*	2-OMe	163 ±15
13.	2*RS*	2,3-Cl_2	153 ±47	**23.**	2*RS*	3-OMe	71 ±25
14.	2*RS*	2,4-Cl_2	100 ±17	**24.**	2*RS*	4-OMe	57 ±8
15.	2*RS*	2,6-Cl_2	895 ±359	**25.**	2*RS*	4-NMe_2	33 ±6
16.	2*RS*	3,4-Cl_2	12 ±3	**26.**	2*RS*	3-NO_2	120 ±26
17.	2*R*	3,4-Cl_2	42 ±9	**27.**	2*RS*	3-Me	55 ±9
18.	2*S*	3,4-Cl_2	18 ±7	**28.**	2*RS*	3-CN	152 ±42

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[12]

Table 2.

N-Benzyl Replacements



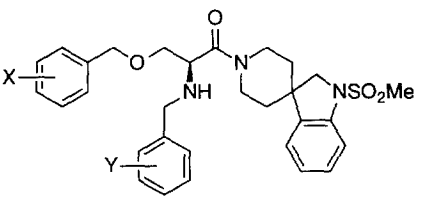
	Stereochemistry	X	hNK_1 IC_{50} (nM)[a]		Stereochemistry	X	hNK_1 IC_{50} (nM)[a]
29.	2*RS*		260 ±115	**31.**	2*RS*		88 ±34
30.	2*RS*		43 ±13	**32.**	2*RS*	-H	2000 ±173

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[12]

The introduction of substituents on the *O*-benzyl ring has profound effects on binding. Chlorine substitution, especially at the 3- and 4-positions of the aromatic ring causes a significant improvement in affinity (Table 3). The effect is additive, with 3,4-dichloro substitution giving the most potent compound in this series (**36**) (hNK_1 IC_{50} 1.0 nM). In contrast, 3,5-bis(trifluoromethyl) substitution, which is highly favored in *cis*-disubstituted piperidines such as L-733,060 (**2**), is not tolerated (**41**, hNK_1 1300 ± 80 nM).

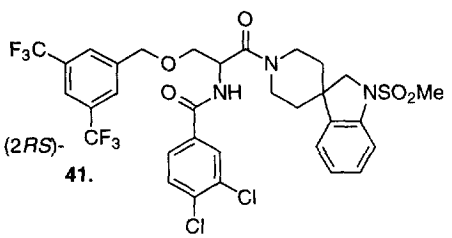
Table 3.

O-Benzyl Substitution

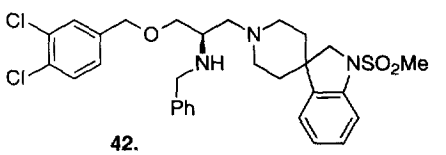


	Stereochemistry	X	Y	hNK_1 IC_{50} (nM)[a]		Stereochemistry	X	Y	hNK_1 IC_{50} (nM)[a]
33.	2*S*	2-Cl	H	36 ±12	**37.**	2*S*	2-Cl	3,4-Cl_2	34 ±14
34.	2*S*	3-Cl	H	7.7 ±1.5	**38.**	2*S*	3-Cl	3,4-Cl_2	11 ±8
35.	2*S*	4-Cl	H	6.6 ±0.8	**39.**	2*S*	4-Cl	3,4-Cl_2	23 ±28
36.	2*S*	3,4-Cl_2	H	1.0 ±0.6[b]	**40.**	2*S*	3,4-Cl_2	3,4-Cl_2	1.7 ±1.0

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[12] [b]n = 4.



41.

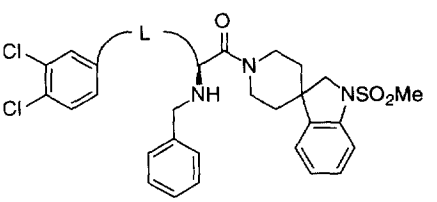


42.

Reduction of the amide of **36** (BH_3, THF) significantly reduces affinity (**42**, hNK_1 170 ± 17 nM), but replacement of the ether oxygen by methylene (**43**) is well tolerated (Table 4). Ether replacements such as sulfide (**45**), sulfone (**46**) or amines (**47, 48**) retain moderate affinity, but shortening the chain (**44**) causes a much greater loss.

Table 4.

Ether Replacements



	Stereochemistry	L	hNK_1 IC_{50} (nM)[a]			Stereochemistry	L	hNK_1 IC_{50} (nM)[a]	
43.	2*RS*	$CH_2CH_2CH_2$	3.3	±1.0	**46.**	2*S*	$CH_2SO_2CH_2$	63	±42
44.	2*RS*	CH_2CH_2	455	±178	**47.**	2*RS*	CH_2NHCH_2	24	±4
45.	2*S*	CH_2SCH_2	13	±8	**48.**	2*RS*	$CH_2NMe.CH_2$	54	±23

[a]Displacement of [^{125}I]substance P from hNK_1 receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.[12]

These results allow us to define the structural elements of the serine derived portion of the molecule which are necessary for binding to the NK_1 receptor. The significant effects of substitution on the benzyloxy aromatic ring suggest that this group plays a crucial role in binding. However, the benzyloxy oxygen is not involved in an interaction with the receptor as the methylene analog **43** has similar affinity to **36**. This is unlike the benzyloxy group of the *cis*-disubstituted piperidine class of antagonists, where the oxygen is believed to participate in a hydrogen bond to the receptor.[18] We have found that the spirocyclic aryl sulfonamide is also crucial for binding to the receptor,[11] but the SAR is remarkably tolerant of changes to the central portion of the molecule. The most important factor for binding is the length of the backbone, suggesting that the function of the serine derived core of the molecule is to deliver the benzyloxy and arylsulfonamide groups to the receptor with appropriate relative positions. Thus, changes to the nitrogen substituent, the absolute stereochemistry or the ether have little effect, but shortening the backbone (**44**) or replacement of the planar amide with a tetrahedral amine (**42**) disrupts the ability to deliver the two end groups correctly, resulting in poor binding.

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References and Notes

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