



Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1845–1850

BIOORGANIC &
MEDICINAL CHEMISTRY
LETTERS

SERINE DERIVED NK₁ ANTAGONISTS 1: THE EFFECT OF MODIFICATIONS TO THE SERINE SUBSTITUENTS.

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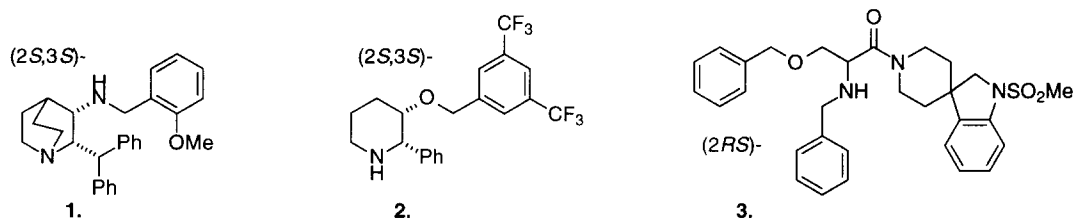
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Received 31 March 1998; accepted 16 June 1998

Abstract: A series of novel serine derived NK₁ 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.

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Substance P is a member of the tachykinin family of neuropeptides which binds selectively to the NK₁ 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 NK₁ receptor antagonists may be effective as anti-depressants.^{4,5} This has further intensified efforts to identify new NK₁ receptor antagonists which may have utility for the clinical treatment of disease.



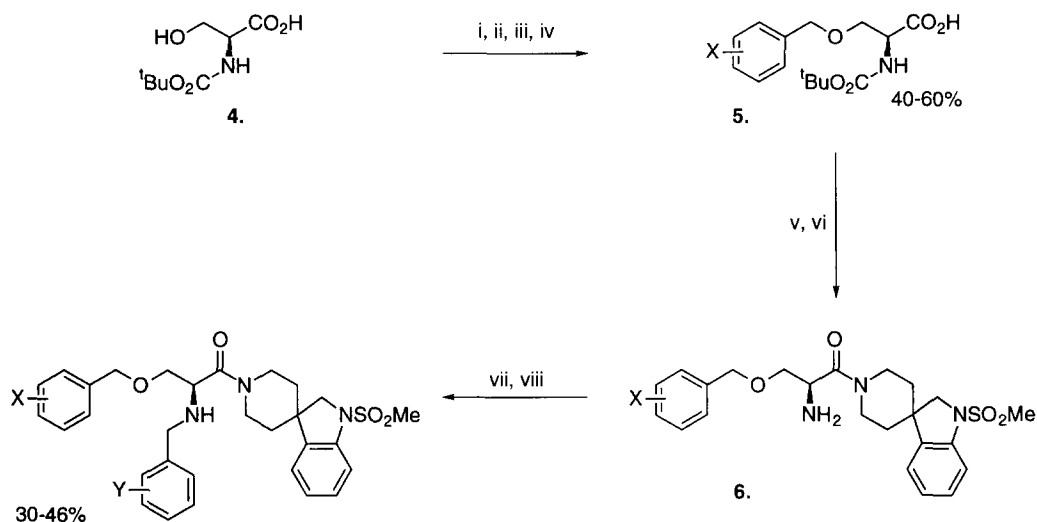
Early work in this area focussed on peptide based antagonists,^{1,3} but the discovery of non-peptide antagonists, such as CP-96,345 (**1**)⁶ was a key breakthrough. Subsequent work in a number of laboratories has led to several highly potent antagonists, such as CP-99,994,⁷ CP-122,721,⁸ GR205171,⁹ and L-733,060 (**2**).¹⁰ We have discovered a novel series of serine based NK₁ receptor antagonists which have different structural requirements from previously reported classes, allowing us to develop a new pharmacophore model (discussed in the subsequent communication¹¹).

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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 NK₁ receptor (hNK₁ IC₅₀ 80 nM¹²). 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.

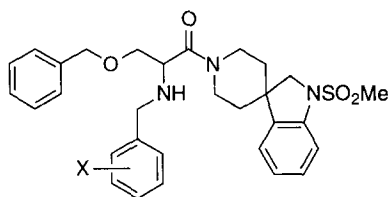


Reagents: i) NaH, DMF; ii) ArCH₂Br; iii) Cyclohexylamine, recrystallize from EtOAc/Hexane; iv) HCl-H₂O, EtOAc; v) N-[1-Methanesulfonylspiro(3*H*-indole-3,4'-piperidine) hydrochloride, BOP-Cl, Et₃N, CH₂Cl₂; vi) HCl, MeOH; vii) ArCHO, Et₃N, MgSO₄, CH₂Cl₂; viii) NaBH₄, MeOH.

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 Mitsunobu 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).

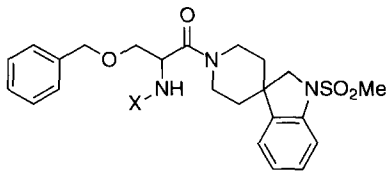
[†] Chiralcel OD (250 x 4.6 mm id 10 μM); 40 °C
hexane/ethanol (50:50); 1 ml/min; det. 230 nm.

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 NK₁ activity is limited to a single enantiomeric series [For example (2*S*,3*S*)-L-733,060 (**2**), is a potent NK₁ antagonist (IC₅₀ 1.0 nM), but the (2*R*,3*R*)-enantiomer is much less active (IC₅₀ 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 <i>RS</i>	H	80 ±4	19.	2 <i>RS</i>	3,5-Cl ₂	79 ±8
10.	2 <i>RS</i>	2-Cl	542 ±24	20.	2 <i>RS</i>	3-F	157 ±51
11.	2 <i>RS</i>	3-Cl	58 ±2	21.	2 <i>RS</i>	3-Br	60 ±5
12.	2 <i>RS</i>	4-Cl	27 ±3	22.	2 <i>RS</i>	2-OMe	163 ±15
13.	2 <i>RS</i>	2,3-Cl ₂	153 ±47	23.	2 <i>RS</i>	3-OMe	71 ±25
14.	2 <i>RS</i>	2,4-Cl ₂	100 ±17	24.	2 <i>RS</i>	4-OMe	57 ±8
15.	2 <i>RS</i>	2,6-Cl ₂	895 ±359	25.	2 <i>RS</i>	4-NMe ₂	33 ±6
16.	2 <i>RS</i>	3,4-Cl ₂	12 ±3	26.	2 <i>RS</i>	3-NO ₂	120 ±26
17.	2 <i>R</i>	3,4-Cl ₂	42 ±9	27.	2 <i>RS</i>	3-Me	55 ±9
18.	2 <i>S</i>	3,4-Cl ₂	18 ±7	28.	2 <i>RS</i>	3-CN	152 ±42

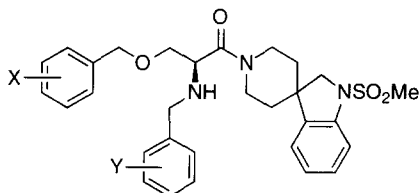
^aDisplacement of [¹²⁵I]substance P from hNK₁ receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.¹²

Table 2.*N*-Benzyl Replacements

	Stereochemistry	X	hNK ₁ IC ₅₀ (nM) ^a		Stereochemistry	X	hNK ₁ IC ₅₀ (nM) ^a
29.	2 <i>RS</i>		260 ±115	31.	2 <i>RS</i>		88 ±34
30.	2 <i>RS</i>		43 ±13	32.	2 <i>RS</i>	-H	2000 ±173

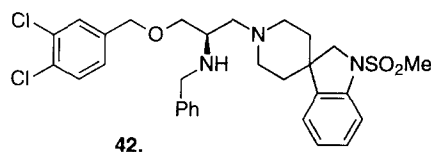
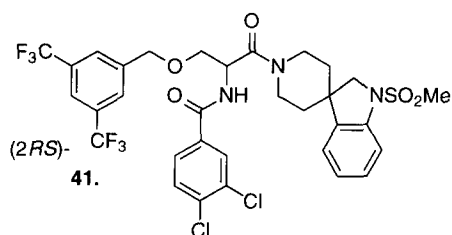
^aDisplacement of [¹²⁵I]substance P from hNK₁ receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations.¹²

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**) (hNK₁ IC₅₀ 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**, hNK₁ 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 <i>S</i>	2-Cl	H	36 ± 12	37.	2 <i>S</i>	2-Cl	3,4-Cl ₂	34 ± 14
34.	2 <i>S</i>	3-Cl	H	7.7 ± 1.5	38.	2 <i>S</i>	3-Cl	3,4-Cl ₂	11 ± 8
35.	2 <i>S</i>	4-Cl	H	6.6 ± 0.8	39.	2 <i>S</i>	4-Cl	3,4-Cl ₂	23 ± 28
36.	2 <i>S</i>	3,4-Cl ₂	H	1.0 ± 0.6 ^b	40.	2 <i>S</i>	3,4-Cl ₂	3,4-Cl ₂	1.7 ± 1.0

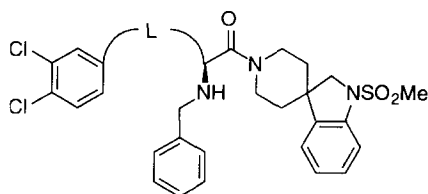
^aDisplacement of [¹²⁵I]substance P from hNK₁ receptors in CHO cells. Data are mean ± S.D. for n = 3 determinations. ¹²_bn = 4.



Reduction of the amide of **36** (BH₃, THF) significantly reduces affinity (**42**, hNK₁ 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 <i>RS</i>	CH ₂ CH ₂ CH ₂	3.3 ± 1.0	46.	2 <i>S</i>	CH ₂ SO ₂ CH ₂	63 ± 42
44.	2 <i>RS</i>	CH ₂ CH ₂	455 ± 178	47.	2 <i>RS</i>	CH ₂ NHCH ₂	24 ± 4
45.	2 <i>S</i>	CH ₂ SCH ₂	13 ± 8	48.	2 <i>RS</i>	CH ₂ NMe.CH ₂	54 ± 23

^aDisplacement of [¹²⁵I]substance P from hNK₁ 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 NK₁ 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.

Acknowledgement: We thank A. Watt and H. P. Verrier for chiral purity determinations.

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