Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 22, pp. 2671-2676, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00481-5

SPIRO-PIPERIDINE NON-PEPTIDE NEUROKININ-1 RECEPTOR ANTAGONISTS

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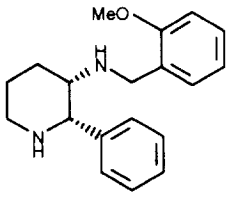
Abstract: The synthesis and activity of a novel spiro-piperidine non-peptide antagonist (2) of the neurokinin-1 (NK_1) receptor is described. Despite having essentially the same solution conformation as CP 99,994 (1) at physiological pH, (2) has reduced affinity for the NK_1 receptor.

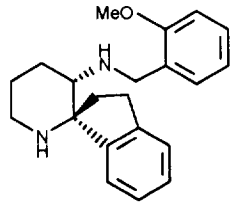
Introduction

The therapeutic potential of neurokinin-1 (NK_1) receptor antagonists in a range of disease states such as chronic pain, arthritis, migraine and asthma has been well documented[1]. Recently Bountra *et al.*[2] reported the effectiveness of the NK_1 receptor antagonist CP 99,994 (1) in the blockade of emesis in the ferret against a range of emetogens, further stimulating our own efforts to find a non-peptide NK_1 receptor antagonist.

Many structurally diverse non-peptide NK_1 antagonists have now been identified of which CP 99,994 (1) is one of the most potent in vitro, (K_i = 0.17 nM)[3]. The minimum energy conformation of (1) has the 2-phenyl ring orthogonal to the piperidine ring and so, if this is indeed the bioactive conformation then the spiro-constrained piperidine (2) should have enhanced affinity for the receptor as a consequence of favourable entropic factors.



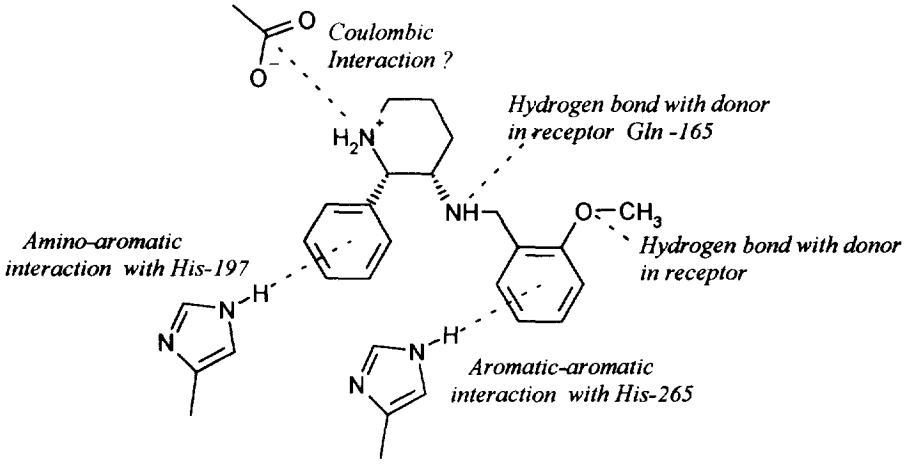
CP 99,994 (1)



(2)

A series of elegant papers[4] have described the identification of many of the key interactions between various related NK_1 receptor antagonists and the NK_1 receptor using site-directed mutagenesis, leading to a postulated pharmacophore model (figure 1). While many aspects of the pharmacophore model for the binding of CP 99,994 (1) remain open to debate, particularly with regard to the putative ion-pair interaction[5], most workers[6] have assumed that the two phenyl rings of the piperidine analogue CP 99,994 (1) lie in a π- stacked conformation. This assumption is based on X-ray crystallographic and modelling study evidence, and is entirely consistent with the low energy conformation of the spiro-constrained analogue (2).

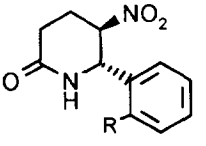
Figure 1.



Proposed binding mode of CP 99,994 (1)

Chemistry

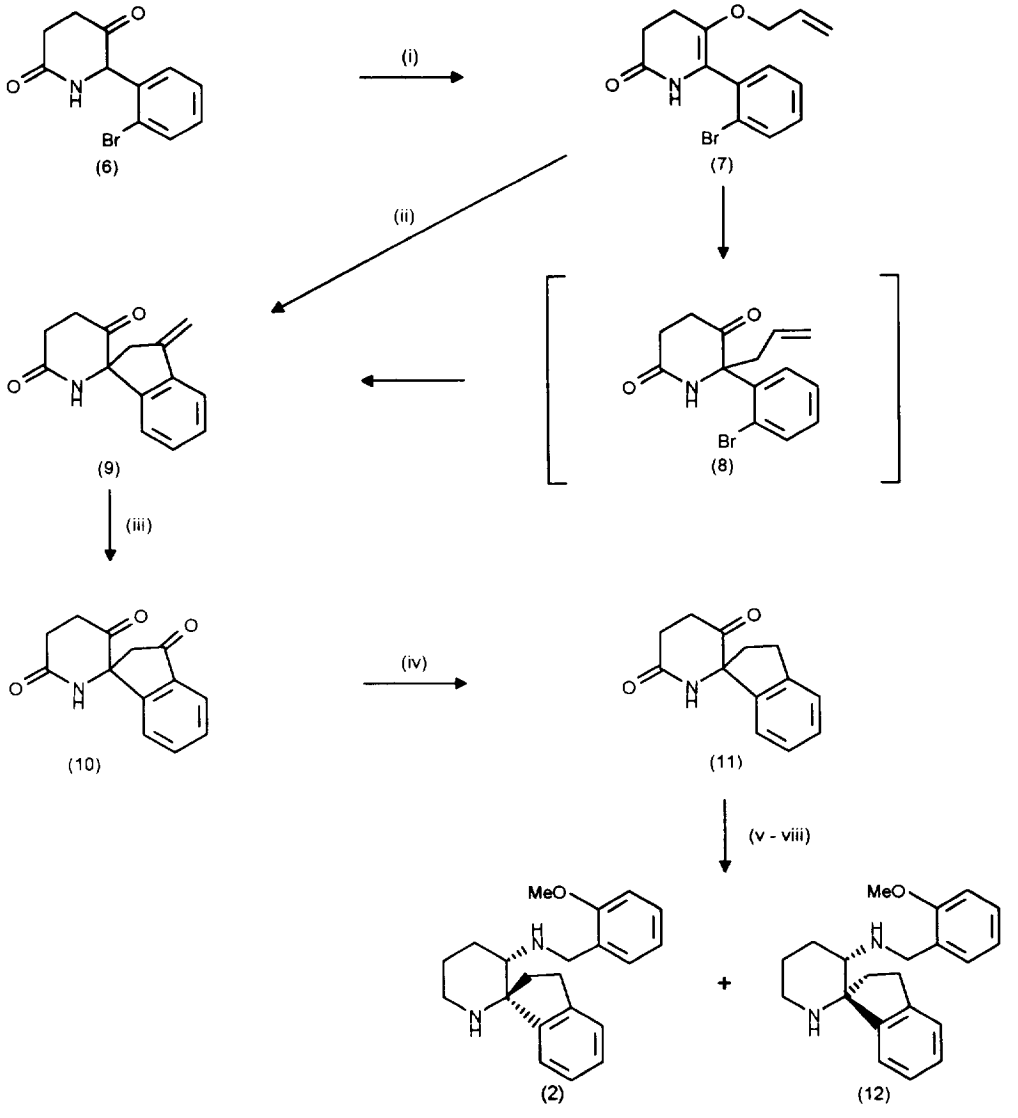
Typically CP 99,994 (1) is prepared from nitro-piperidine (4) which is in turn prepared by reaction of benzaldehyde, ethyl 4-nitrobutyrate and ammonium acetate.[7] An initial attempt to prepare (2) *via* the analogous cyclisation of ethyl 4-nitrobutyrate, ammonium acetate and 1-indanone proved unsuccessful. However we successfully prepared (2) according to the chemistry of scheme 1, the crucial step involving assembly of the spirocycle via a Heck arylation reaction.



(4) R = H
(5) R = Br

The ketone (6) is prepared in two steps via (5) using literature chemistry.[8] Alkylation with sodium hydride and allyl bromide affords predominantly O-alkylated (7) material. This mixture is converted to (9) *via* a tandem 1,3-allyl shift - Heck arylation reaction[9] - under palladium (0) catalysis (7) undergoes a 1,3 allyl shift rearrangement to give (8) which *in situ* is converted to (9) *via* a Heck reaction. Ozonolysis gives the diketone (10) which is carefully hydrogenated to allow selective removal of the benzylic ketone to provide (11). Imine formation, hydrogenolysis and borane reduction of the amide results in a 2:1 mixture of diastereomers which are separated by preparative reverse phase HPLC, giving the desired material (2)[10] as the minor component along with (12)[11].

Scheme 1.



Reagents and Conditions :

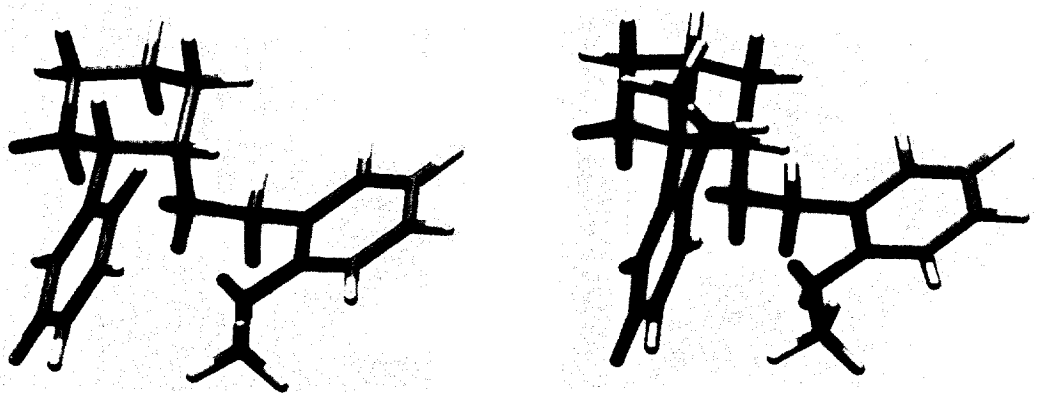
(i) NaH, DMF then $BrCH_2CH{=}CH_2$, 60% (ii) Pd $(PPh_3)_4$, Et_3N, CH_3CN, 53% (iii) O_3 then PPh_3, 82% (iv) H_2 50 psi, 10% Pd/C, AcOH, 40 °C, 78% (v) 2-methoxybenzylamine, TsOH, toluene, reflux, 100% (vi) H_2, 10% Pd/C, EtOH, 41% (vii) BH_3.THF, 40% (viii) Reverse-phase HPLC

Conformational Analysis

Since the pK_as of the mono- and di-protonated forms of CP 99,994 (1) are 8.4 and 4.7 [12] and reported structure activity relationships indicate that the 3-benzylamine substituent can be replaced with a 3-benzyloxy substituent[13] we believe that the bioactive species is likely to be the monocation protonated on the piperidine

nitrogen (cf Figure 1). ^{1}H NMR studies established that the conformation of the piperidine ring in monoprotonated (2) is comparable to that of (1) as the mono-protonated species in aqueous solution; in both cases the benzylamine substituent is found to be axial and the 2-aryl ring equatorial[14]. Additionally computer modelling studies[15] indicated that (1) and (2) as mono-protonated species have similar global minimum energy conformations (Figure 2). Thus, on purely conformational grounds one would expect the affinity of (2) to be enhanced over that of CP 99,994 (1).

Figure 2.

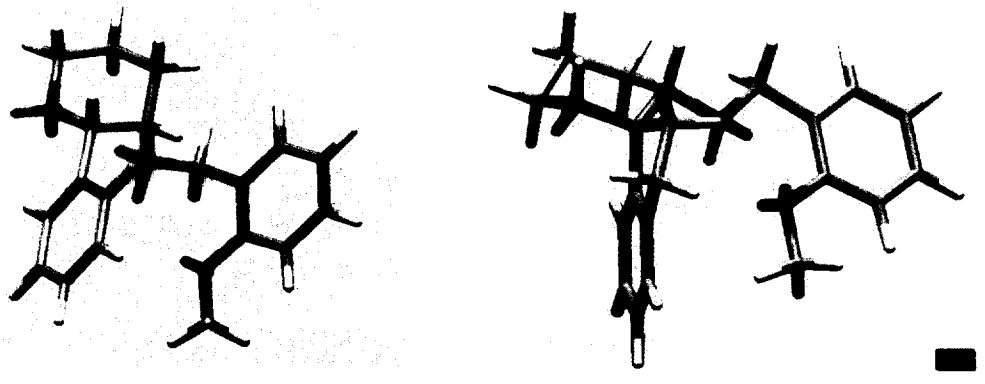


mono-protonated
CP 99,994 (1)

mono-protonated
(2)

However ^{1}H NMR studies indicated that whereas the solution conformation of the piperidine in CP 99,994 (1) is essentially independent of its state of protonation, the diprotonated form of (2) has a different aqueous solution conformation such that the 3-benzylamine substituent lies equatorial (Figure 3)[14]. Hence, if the bioactive species is actually diprotonated the affinity of (2) is likely to be reduced with respect to CP 99,994 (1).

Figure 3.



di-protonated
CP 99,994 (1)[16]

di-protonated
(2)

Pharmacology

The affinities of *racemic* CP 99,994 (1), (2) and (12) for the NK_1 receptor were determined by displacement of tritiated radiolabelled substance P from cloned human NK_1 receptor expressed in CHO cell membranes[17] (Table 1). Surprisingly (2) has reduced affinity for the NK_1 receptor even though mono-protonated (2) has essentially the same minimum energy conformation as CP 99,994 (1). These results probably reflect a destabilising steric interaction with the receptor. However we cannot completely exclude the possibility that the bioactive species is diprotonated,resulting in reduced affinity due to an unfavourable conformational change, nor can we exclude the possibility that our initial assumption that minimum energy conformation of the 2-phenyl ring is the bioactive conformation of CP 99,994 (1) may be incorrect.

Table 1.

Compound	pK_i	SEM	n
racemic (2)	7.4	0.2	4
racemic (12)	<6	-	4
racemic CP 99,994 (1)	9.1	0.1	4

Conclusion

The synthesis of a novel spiro-constrained NK_1 receptor antagonist (2) using a tandem 1,3 allyl shift - Heck arylation reaction has been described. This compound shows reduced (circa 50 fold) potency for the NK_1 receptor suggesting that although the mono-protonated form (2) has essentially the same minimum energy conformation as CP 99,994 (1), the area of space occupied by the molecular constraint is not well tolerated by the receptor. However we cannot completely exclude a number of other possibilities (see above) that could also explain this surprising reduction in activity.

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6. While Viti *et al.*[7] have recently reported the synthesis of a benzo[b}-1,5-naphthyridine derivative as "a potential constrained NK_1 receptor antagonist" no biological data was reported for this compound.
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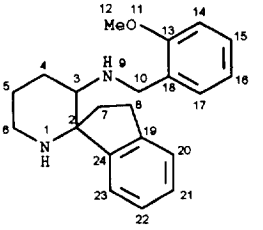
9. Watson, S. P.; Knox, G. R.; and Heron, N. M., *Tet. Lett.* **1994**, *35*, 9763.
10. Di-trifluoroacetate salt of (2) : ^{1}NMR (D_2O, 400 MHz) δ 1.79-2.58 (6H, m, H4, H5 and H7), 3.01-3.40 (4H, m, H6 and H8), 3.57 (1H, dd, H3, J= 11,5 Hz), 3.84 (3H, s, H12), 4.3, 4.42 (2H, AB, H10), 7.07 (1H, td, H16), 7.11 (1H, dd, H14), 7.36 (1H, dd, H17), 7.43-7.83 (5H, m, aromatics).
Since H3 has an 11Hz coupling it is probably axial.
No n.O.e. is observed between H3 and H23.



NMR numbering system for (2) and (12)

11. Di-trifluoroacetate salt of (12) : ^{1}NMR (D_2O, 400 MHz) δ 1.88-2.7 (6H, m, H4, H5 and H7), 3.08-3.27 (2H, m, H8), 3.34 (2H, dd, H6, J= 8, 3 Hz), 3.55 (3H, s, H12), 3.69 (1H, dd, H3 (ax), J= 12, 3 Hz), 4.29, 4.37 (2H, AB, H10, J= 14 Hz), 6.67 (1H, dd, H23), 7.26-7.62 (7H, m, aromatics).
Since H3 has a 12 Hz coupling it is probably axial.
Irradiation of H3 gives a n.O.e. to H23.
12. Determined by measuring the change of NMR chemical shift of CH protons alpha to the basic amine centres with increasing pH in D_2O solution.
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14. Compound (2) at pH 1.9 proton H3 in the ^{1}H NMR (D_2O, 400 MHz) spectrum has δ 3.57 ppm and is a doublet of doublets with J=11 and 5 Hz, and is therefore axial. At pH 6.9, proton H3 in the ^{1}H NMR (D_2O, 400 MHz) spectrum has δ 2.73 ppm and is a triplet with J= 5 Hz, and is therefore equatorial.
15. Macromodel V4.5 using Monte-Carlo searching and MM2 forcefield; Mohamadi, F.; Richards, N. G. S.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T. and Still, W. C.; *J. Comput. Chem.*; **1990**, *11*, 440..
16. The picture of di-protonated CP 99,994 was generated using the published crystal structure, see reference 3.
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Acknowledgements.
We would like to acknowledge the contributions of T. Hawcock, A. Jones, P. Brush, D. O'Brien, S. Jackson, T. Underwood and M. Congreve to this work.

(*Received in Belgium* 17 *February* 1995; *accepted* 5 *October* 1995)