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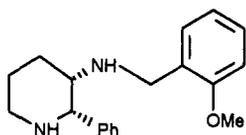
MORPHAN BASED SUBSTANCE P ANTAGONISTS¹

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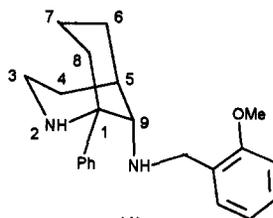
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Abstract: A bridged derivative of the substance P antagonist CP 99,994 has been prepared and shown to possess potent affinity for the NK₁ receptor.

Substance P, an eleven amino acid neuropeptide, is implicated in numerous disease states including arthritis,³ asthma,⁴ migraine⁵ and pain.⁶ The biological effects of substance P are mediated through the neurokinin NK₁ receptor. There is a great deal of reporting in the scientific literature on the development of nonpeptide NK₁ antagonists of diverse structural type.⁷ One of the most potent non-peptide NK₁ antagonists discovered to date is the 2-phenylpiperidine derivative CP 99,994.⁸ This class of compound shows in a ferret model of emesis a broad spectrum of anti-emetic activity,^{9,10} and therefore may offer a valuable novel therapy for the treatment of emesis associated with cancer chemotherapy.



CP 99,994

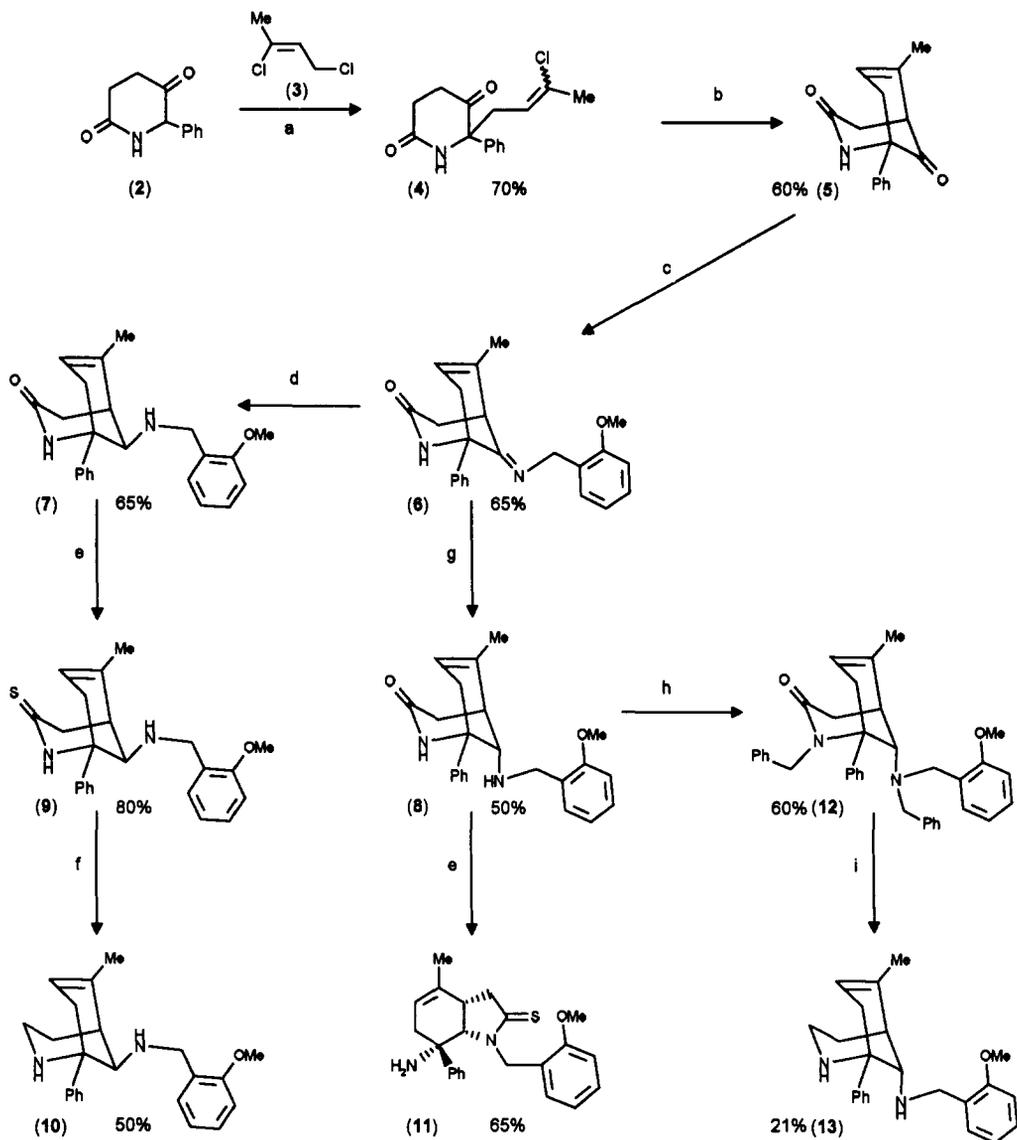


(1)

The chair/twist-boat flexibility of the piperidine ring does not allow the conformation of CP 99,994 at the receptor to be fully defined.¹¹ As part of a program investigating the bioactive conformation, we have prepared various ring constrained analogues. One such type is represented by the bridged bicyclic structure (1), a derivative of the novel 1-phenylmorphan skeleton.

Our synthetic route to structures of this type was *via* the readily accessible keto-lactam (2).⁸ Alkylation of (2) with 1,3-dichloro-2-butene (3) was regiospecific giving the chlorobutene derivative (4).¹² Under acidic conditions the chlorobutene (4) underwent the Wichterle cyclisation to give the crystalline bridged ketone (5) in 60% yield. This 9-oxo-1-phenylmorphan (5) was the key intermediate for our synthetic strategy and the structure was confirmed by X-ray crystallography. Treatment with *o*-methoxybenzylamine under azeotropic conditions, in the presence of acid, gave the crystalline imine (6). Reduction of the imine with sodium borohydride or sodium triacetoxyborohydride gave the *trans* amino amide (7) as the major product. The structure was confirmed by X-ray crystallography. When the imine was reduced under catalytic conditions the *cis* isomer (8) was the major product.

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Reagents and Conditions

(a) NaH, DMF, 5°C; (b) H₂SO₄, 5°C, 4 h; (c) *o*-methoxybenzylamine, PhCH₃, PTSA, reflux, 16 h; (d) MeOH, NaBH₄; (e) Lawesson's reagent, PhCH₃, reflux, 2 h; (f) Raney Ni, EtOH, reflux, 3 h; (g) 10% Pd-C, H₂, EtOH; (h) PhCH₂Br, NaH, DMF (i) LiAlH₄ (15 equiv), THF, 21°C, 48 h.

Reduction of the amide (7) to the corresponding amine using diborane or lithium aluminium hydride was unsuccessful, possibly due to complex formation between the reagents and substrate. In the *trans* series the

desired reduction was achieved *via* the thioamide (9). Desulphurisation with Raney nickel gave the amine (10) which was characterised as the crystalline dihydrochloride salt.

To our surprise, treatment of the amide (8) with Lawesson's reagent gave rise not to the expected thioamide but to the rearranged thioamide (11). The structure and stereochemistry was confirmed by NMR and single crystal X-ray data.

Attempted reduction of the *cis*-amide (8) with diborane or lithium aluminium hydride similarly was unsuccessful. However, treatment of the dibenzyl derivative (12) with an excess of lithium aluminium hydride reduced the amide function with concomitant removal of both benzyl groups to give the required *cis*-amine (13). Compound (13) was fully characterised as the crystalline dihydrochloride salt.

An overlay of the X-ray crystallographic structure of CP 99,994 with (13) (both as dihydrochloride salts) demonstrates a close fit of the bicyclic analogue to the parent piperidine (Figure 1). Furthermore, both compounds possess similar high affinity for the NK₁ receptor (Table 1).¹³ The results show that bridging between positions 2 and 4 of the piperidine ring in this class of antagonist maintains the bioactive conformation, and that bulk added over the top face of the molecule is tolerated at the receptor.

Table 1

COMPOUND	NK ₁ pKi
CP99,994	9.4 (±0.1)
(10)	<5.5
(13)	9.2 (±0.4)

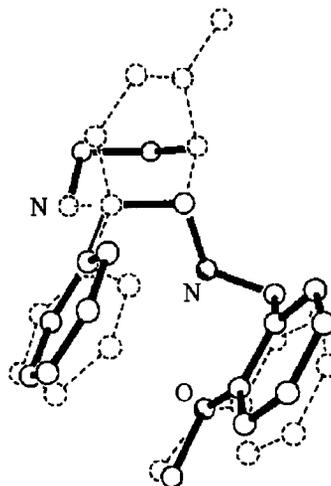


Figure 1. Overlay of CP99,994 (solid lines) with compound (13) (dotted lines)

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References and Footnotes

- Part of this work was reported as a poster in the 209th ACS National Meeting, April 2-6, 1995, Anaheim, CA. *ACS Abstr. Papers*. Division of Medicinal Chemistry **MEDI 94**. Chuen Chan, J Derek Cocker, H Geoffrey Davies, Chiara Ghiron, Peter Ward. Conformationally Constrained NK₁ Receptor Antagonists Based on 2-Azabicyclo[3.3.1]Nonene.

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11. Piperidine ring constrained analogues of CP 99,994 have been synthesised but no biological activities have been reported: Desai, M.C.; Lefkowitz, S.L. *Tetrahedron Lett.* **1994**, 35, 4701-4704. For cyclic constrained analogues of the side-chain in CP 99,994 see: Desai, M.C.; Vincent, L.A.; Rizzi, J.P. *J. Med. Chem.*, **1994**, 37, 4263-4266.
12. All compounds described had correct microanalyses, (except compound (12) which was used directly in the next reaction) and spectral data to support their structural assignment.
Spectroscopic data for key compounds is included below :
Compound 6: $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ 7.29-7.48 (m, 5H), 7.18 (td, $J=7$ & 2, 1H), 7.00 (d, $J=7$, 1H), 6.77-6.88 (m, 2H), 5.79 (broad s, 1H), 5.58 (dm, $J=4$, 1H), 4.51 & 4.63 (ABq, $J=15$, 2H), 3.81 (s, 3H), 3.51 (bs, 1H), 3.29 (d, $J=16$, 1H), 2.51-2.80 (m, 3H), 1.80 (s, 3H).
Compound 7: $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ 7.30-7.42 (m, 5H), 7.19 (td, $J=7$ & 2, 1H), 6.90 (dd, $J=7$ & 2, 1H), 6.80 (t, $J=7$, 1H), 6.70 (d, $J=7$, 1H), 5.53-5.59 (m, 1H), 5.48 (bs, 1H), 3.52 & 3.71 (ABq, $J=14$, 2H), 3.48 (s, 3H), 3.15 (d, $J=16$, 1H), 2.92 (s, 1H), 2.43-2.56 (m, 2H), 2.19 (dd, $J=17$ & 4, 1H), 1.79 (s, 3H).
Compound 10: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.43 (d, 2H), 7.30-7.18 (m, 4H), 7.08 (dd, 1H), 6.85 (t, 1H), 6.78 (d, 1H), 5.73 (m, 1H), 3.76 (d, $J=13.5$, 1H), 3.63 (s, 3H), 3.62 (d, $J=13.5$, 1H), 3.25 (d, $J=2.5$, 1H), 2.96-2.85 (m, 2H), 2.64-2.59 (m, 2H), 2.40 (m, 1H), 1.82 (m, 1H), 1.72 (s, 3H), 1.53 (m, 1H).
Compound 11: $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ 7.24-7.43 (m, 5H), 7.17 (td, $J=7.5$ & 2, 1H), 6.75-6.89 (m, 2H), 6.71 (d, $J=7.5$, 1H), 5.48 (dm, $J=4$, 1H), 5.37 (d, $J=15$, 1H), 4.54 (d, $J=8$, 1H), 3.58 (s, 3H), 3.43 (d, $J=15$, 1H), 3.40 (t, $J=8$, 1H), 2.96-3.28 (m, 2H), 2.52 (dm, $J=17$, 1H), 2.13 (dd, $J=17$ & 6, 1H), 1.81 (s, 3H).
Compound 13 (as dihydrochloride salt): $^1\text{H-NMR}$ (400 MHz, D_2O) δ 7.55-7.45 (m, 5H), 7.25 (m, 3H), 7.0 - 6.92 (m, 2H), 5.70 (br. s, 1H), 4.35 (d, $J=12$, 1H), 4.14 (d, $J=12$, 1H), 4.09 (s, 1H), 3.63 (s, 3H), 3.52 (m, 1H), 3.06 (m, 1H), 2.83 (d, $J=19$, 1H), 2.69 (d, $J=19$, 1H), 2.18 (m, 1H), 2.01 (m, 1H), 1.84 (s, 3H).
13. Human NK₁ receptor (U373 MG cells) binding protocol:
An assay volume of 200 μl was used, consisting of 50 μl of wash buffer (pH 7.4, containing 50mM HEPES and 3mM MnCl_2) or test compound, 100 μl membrane suspension (25-35 μg protein) in assay buffer (pH 7.4, containing 50mM HEPES, 0.04% bovine serum albumin, 80 μgml^{-1} bacitracin, 8 μgml^{-1} leupeptin, 2 μM phosphoramidon and 3mM MnCl_2) and 50 μl of [^3H]-substance P in wash buffer (final ligand concentration of 0.7-1.0nM). The incubation was carried out at 22 $^\circ\text{C}$ for 40min. The reaction was terminated by rapid filtration through Whatman GF/B filters pre-soaked in 0.5% Triton-X containing polyethylenimine (0.2%). Filters were washed 3 times with HEPES wash buffer and radioactivity bound to filters was determined in a liquid scintillation counter. Non-specific binding was defined by the addition of CP99,994 (1 μM). Inhibition curves were analysed using the curve fitting program ALLFIT and inhibition constants (K_i values) were determined.

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