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MORPHAN BASED SUBSTANCE P ANTAGONISTS[1]

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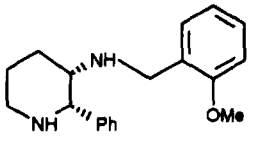
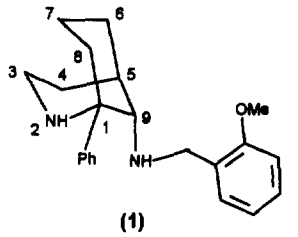
Abstract: A bridged derivative of the substance P antagonist CP 99,994 has been prepared and shown to possess potent affinity for the NK_1 receptor.

Substance P, an eleven amino acid neuropeptide, is implicated in numerous disease states including arthritis,[3] asthma,[4] migraine[5] and pain.[6] The biological effects of substance P are mediated through the neurokinin NK_1 receptor. There is a great deal of reporting in the scientific literature on the development of nonpeptide NK_1 antagonists of diverse structural type.[7] One of the most potent non-peptide NK_1 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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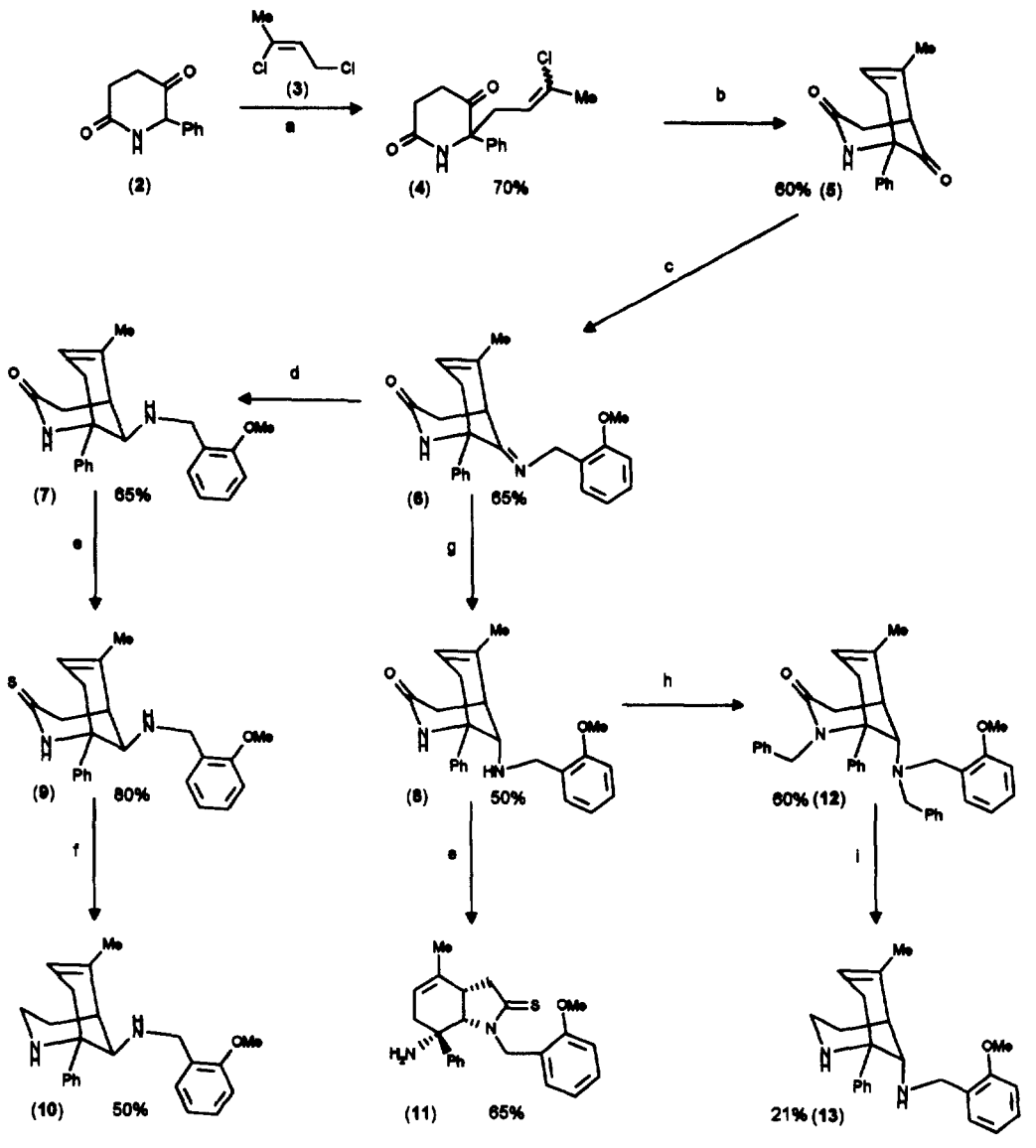

Reagents and Conditions

(a) NaH, DMF, 5°C; (b) H_2SO_4, 5°C, 4 h; (c) *o*-methoxybenzylamine, $PhCH_3$, PTSA, reflux, 16 h; (d) MeOH, $NaBH_4$; (e) Lawesson's reagent, $PhCH_3$, reflux, 2 h; (f) Raney Ni, EtOH, reflux, 3 h; (g) 10% Pd-C, H_2, EtOH; (h) $PhCH_2Br$, NaH, DMF (i) $LiAlH_4$ (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 NK_1 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)

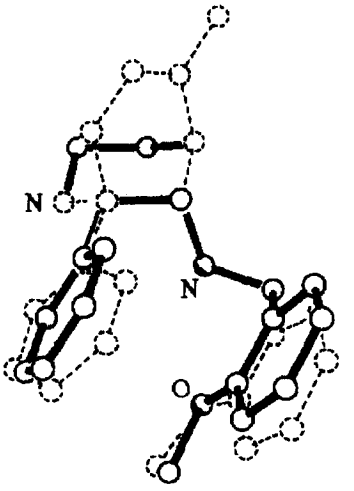

Figure 1. Overlay of CP99,994 (solid lines) with compound (**13**) (dotted lines)

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References and Footnotes

1. 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 NK_1 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}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}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}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}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}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 NK_1 receptor (U373 MG cells) binding protocol:
An assay volume of 200μl was used, consisting of 50μl of wash buffer (pH 7.4, containing 50mM HEPES and 3mM $MnCl_2$) or test compound, 100μl membrane suspension (25-35μg protein) in assay buffer (pH 7.4, containing 50mM HEPES, 0.04% bovine serum albumin, 80μgml^{-1} bacitracin, 8μgml^{-1} leupeptin, 2μM phosphoramidon and 3mM $MnCl_2$) and 50μl of [^{3}H]-substance P in wash buffer (final ligand concentration of 0.7-1.0nM). The incubation was carried out at 22°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 (1μM). Inhibition curves were analysed using the curve fitting program ALLFIT and inhibition constants (K_i values) were determined.

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