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Synthesis, Modelling and NK_1 Antagonist Evaluation of a Non-Rigid Cyclopropane-Containing Analogue of CP-99,994

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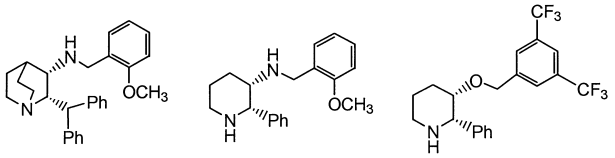
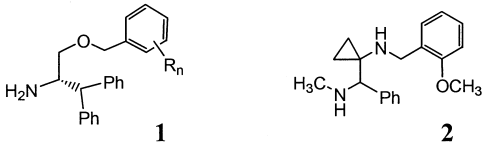
Abstract—A non-rigid cyclopropane-containing diamine analogue of CP-99,994 was synthesised and was found to have only moderate NK_1 receptor binding affinity. Molecular dynamics calculations of the conformational space of the former compound gave good correlation between observed activity and a recently published pharmacophore model, lending predictive value to the latter.

The discoveries of CP-96,345[1] then CP-99,994[2] as the first selective non-peptide NK_1 antagonists stimulated intensive studies of structural analogues throughout the 1990s, in which various aromatic substituents, heteroatom replacements and modified molecular frameworks have been investigated. This research has led to new potent antagonists, such as L-733,060,[3] while 'minimum pharmacophore' studies have been carried out to identify the importance of appropriately placed heteroatoms and substituted aromatic systems, as in structures **1**.[4–6] Modelling studies have kept pace with the evolution of experimental results, culminating in the recent publication by Marshall's group of a model for the bioactive conformation of compounds structurally related to CP-99,345, based on a thorough study of 17 known NK_1 antagonists.[7] This work identified a precise arrangement of the aromatic rings as determinant for antagonist activity.



CP-96,345 CP-99,994 L-733,060



1 **2**

As a contribution to structure–activity studies, we decided to investigate the cyclopropane compound **2**, conceived as a structural analogue of CP-99,994 by rupture of the piperidine C5–C6 bond and creation of a C5–C3 bond. Although **2** lacks the rigidity imposed by a piperidine (or other) heterocycle, it differs from freely rotating analogues studied hitherto in that both amine functions are retained in the target structure, while the cyclopropane moiety might be expected to impose more conformational restriction[8] than in structures such as **1**. This study also presented a timely opportunity to test Marshall's pharmacophore model with an 'unknown' structural analogue of CP-99,994.

Compound **2** was prepared in racemic form using a strategy designed for 1,2-diamine synthesis using a simple α-aminonitrile as the starting material,[9] as shown in Scheme 1. Double alkylation of **3** using ethylene sulfate gave cyclopropane **4** which was transformed into **5** in three steps. This key intermediate had appropriately-substituted carbon atoms of the diamine fragment and

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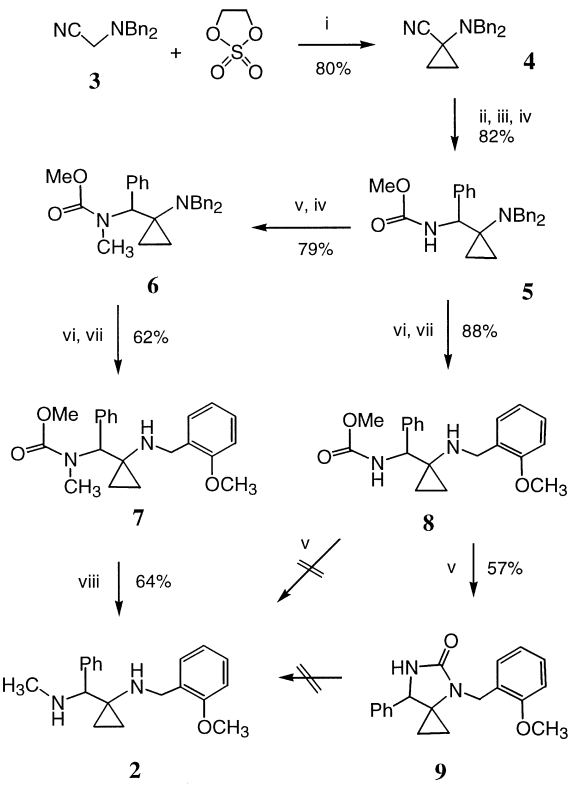
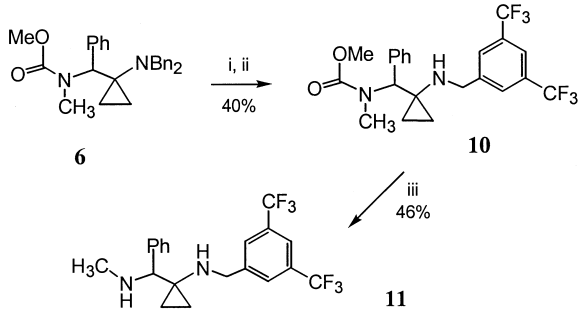


Scheme 1. Reagents: (i) LDA–HMPA, THF, −70 °C; (ii) PhLi, THF, −70 °C to 0 °C; (iii) $NaBH_4$, MeOH; (iv) ClCOOMe, NaOH, $CHCl_3$; (v) $LiAlH_4$, THF; (vi) H_2, $Pd(OH)_2$-C, MeOH; (vii) *o*-anisaldehyde, $NaBH_3CN$, HOAc, MeOH; (viii) HBr–HOAc. All reactions at rt except where specified.



Scheme 2. Reagents: (i) H_2, $Pd(OH)_2$-C, MeOH; (ii) 3,5-bis(trifluoromethyl)benzaldehyde, $NaBH_3CN$, HOAc, MeOH; (iii) HBr–HOAc.

mutually-protected amine functions. The methyl group was generated by carbamate reduction and the amine reprotected, giving **6**. Liberation of the other amine function followed by reductive amination using *o*-anisaldehyde led to the penultimate derivative **7**, which furnished **2** upon acidic deprotection (21% overall yield).[10] It was necessary to construct the amine functions in this order, because the alternative intermediate **8** gave only the intractable imidazolidinone **9** under carbamate reduction conditions.

Pharmacological evaluation of (±)-**2** was carried out using standard procedures;[11] it had moderate NK_1 receptor binding affinity, with $K_i = 150 \pm 15$ nM (compared with $K_i = 3.1 \pm 0.9$ nM for CP-99,345 in a control experiment). This shows a similar trend to that observed for a range of amine-ether derivatives of type **1**, for which the binding affinities are reduced by between one and two orders of magnitude when compared with their rigid heterocyclic precursors.

A molecular dynamics conformational analysis was carried out on compound **2** (as its *S*-enantiomer), and also on CP-99,994 for comparison purposes.[12] For CP-99,994, two accessible conformer families were found, corresponding to the two chair forms of the piperidine ring (of which one was clearly preferred). The lowest energy conformer had a stacked arrangement of its two aromatic rings, but a perpendicular ('L-shaped') conformer (Fig. 1, left) was readily accessible ($\Delta E = 2.57$ kcal mol^{-1}), corresponding precisely to the bioactive conformer suggested by Marshall's studies.[7] Analogous calculations on **2** showed that three conformer families were more or less equally attainable, corresponding (approximately) to staggered conformations of the N–C–C–N torsion angle. In one of the families the minimum-energy conformer was found, again having a stacked aromatic system, and a low-energy L-shaped conformer (Fig. 1, right) was accessible ($\Delta E = 3.06$ kcal mol^{-1}). Superposition of the two L-shaped conformers (Fig. 1, centre) was achieved with very good correlation (rmsd = 0.215 for six points) and excellent matching of the pharmacophore aromatic rings.

These modelling studies suggest that the presence of the cyclopropane ring does not severely restrict the accessible conformational space of compound **2**. Nevertheless, one low-energy conformer corresponds closely

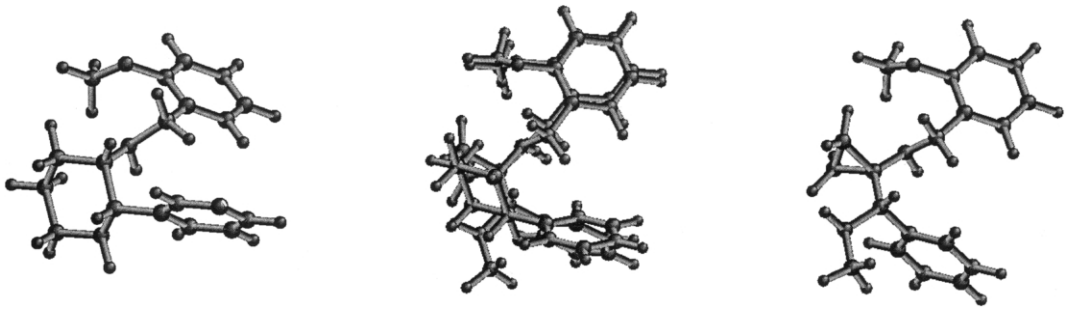


Figure 1. L-shaped conformer of CP-99,994 (left). Superposition of the two L-shaped conformers (centre). L-shaped conformer of (*S*)-**2** (right).

to the putative bioactive conformation of NK_1 receptor antagonists. From these calculations, it would appear reasonable to predict that structure **2** could behave as an antagonist, but perhaps not with great potency. This is indeed borne out by the pharmacology results.

Similarly, reduced binding affinity was also observed for another non-rigid cyclopropane-containing analogue **11**, this time a hybrid between the CP-99,994 diamine structure and the ether-amine L-733,060. The previous synthetic scheme was adapted easily for the preparation of this compound from intermediate **6**, via carbamate **10** (Scheme 2). Pharmacological evaluation[11] of (±)-**11** showed relatively poor receptor binding affinity, with $K_i = 620 \pm 30$ nM.

In conclusion, this work shows that the above-noted non-rigid diamine analogues of the CP-99,994-derived NK_1 antagonist family behave similarly to non-rigid amine-ether derivatives in that they possess diminished binding affinity compared with their heterocyclic precursors, and demonstrates that Marshall's recent pharmacophore model may have useful predictive value.

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10. Data for compound **2**: NMR ($CDCl_3$): δ_H 0.44 (1H, m), 0.53–0.72 (3H, br m), 2.02 (1H, br s), 2.30 (3H, s), 3.67 (1H, s), 3.73 (1H, d, $J = 12.8$), 3.81 (3H, s), 3.99 (1H, d, $J = 12.8$), 5.20 (1H, br s), 6.83 (1H, d, $J = 7.6$), 6.89 (1H, t, $J = 7.6$), 7.18–7.37 (7H, m); δ_C 11.1 (t), 11.7 (t), 35.3 (q), 43.8 (s), 46.4 (t), 55.3 (q), 68.3 (d), 110.3, 120.7, 127.2, 127.7, 128.2, 129.6 (each d), 129.4, 141.2, 157.6 (each s); IR (cm^{-1}): 3533, 3415, 3400 br; MS(IC): *m/z* 297 $[MH]^+$; Analytical sample as dihydrochloride; mp 147 °C ($CHCl_3$–*i*Pr_2O). Anal. calcd for $C_{19}H_{24}N_2O \cdot 2HCl \cdot H_2O$: C, 58.91; H, 7.29; N, 7.23. Found: C, 59.14; H, 7.09; N, 6.99.
11. Inhibition of [^{3}H][Pro^9]-SP was measured using hNK_1 receptors expressed in CHO cells, as previously described: Sagan, S.; Chassaing, G.; Pradier, L.; Lavielle, S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 1039.
12. Molecular modelling studies were performed on a Silicon Graphics SGI Power Indigo2 R8000 workstation, using SYBYL 6.5 software package (Tripos Associates Inc., St Louis, USA). Structures of CP-99,994 and (*S*)-**2** were built within SYBYL, the potential types and binding parameters of the cyclopropane carbons of the latter being defined using the semi-empirical GEOMOS method (Rinaldi, D.; Hoggan, P. E.; Cartier, A. GEOMOS, QCPE 584). The energy of the molecules was calculated in vacuo with the Tripos force field Maximin2, and minimised directly to ensure the system was in a low energy state. An elevated temperature of 800 K was applied for 1000 fs then was reduced to 0 K for 2500 fs. This process was repeated for 100 cycles so that multiple conformations could be generated. Conformers devoid of kinetic energy were retained, and results were interpreted graphically for each molecule.