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Gem- Disubstituted Amino-Ether Based Substance P Antagonists

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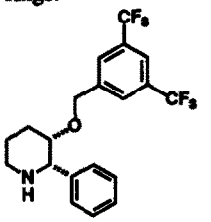
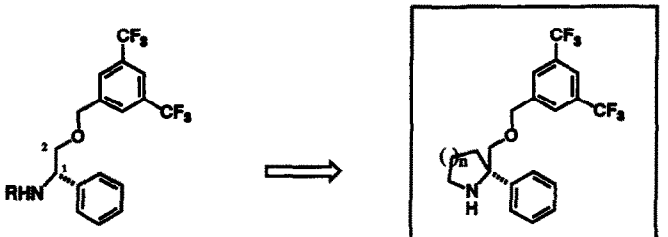
Abstract: The design and syntheses of new series of *gem*- disubstituted pyrrolidine and piperidine derivatives (eg. 2 and 3) is described.

A recent publication from this laboratory has described the development of a new series of high affinity piperidine ether based human NK_1 (hNK-1) antagonists (eg L-733,060, hNK_1 IC_{50} 1nM)[1]. Molecular modelling studies[1] have demonstrated that in the lowest energy conformation of L-733,060 the phenyl ring at the 2-position occupies an equatorial position on the piperidine ring while the benzyloxy substituent at the 3-position is axial. Furthermore, there is an edge to face π -π interaction between the two aromatic rings.



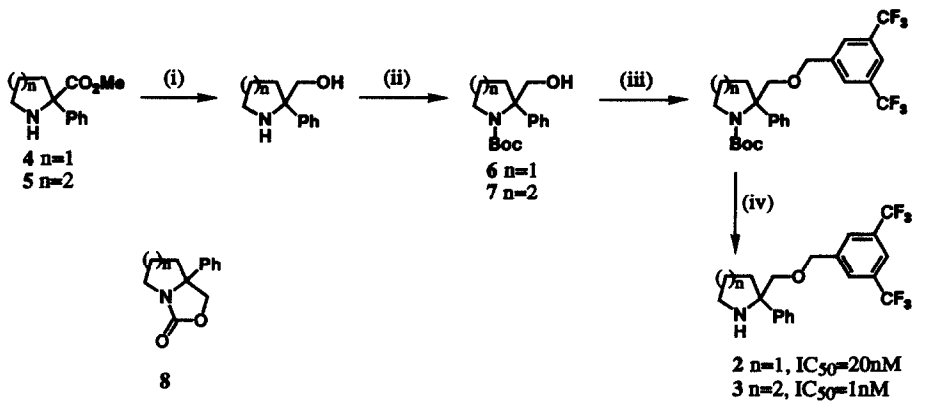
L-733,060

Piperidine derivatives such as L-733,060 can be considered as cyclic analogues of the previously described phenyl glycine based hNK_1 antagonists (eg 1)[2] in which a ring has been constructed between C-2 and the nitrogen atom. We considered that there might exist an alternative connection between C-1 and the nitrogen atom which could generate a new series of novel *gem*- disubstitued amino-ether derivatives (eg 2, 3). In this communication we describe the syntheses of 2 and 3 and demonstrate that high affinity binding to the hNK_1 receptor can be retained when this new ring-constraint is applied.



1 **2** n=1
3 n=2

The syntheses of the amino-ethers 2 and 3 began from the known racemic amino-esters 4 and 5 (Scheme 1)[4]. Thus reduction of the ester moiety provided the corresponding amino alcohols, which were N-Boc protected under standard conditions. Addition of NaH to a premixed solution of the alcohol 6 or 7 and 3,5-bis(trifluoromethyl)benzyl bromide in DMF furnished the corresponding ethers. If the alkoxide of 6 or 7 is preformed prior to addition of the alkylating agent, then the bicyclic derivative 8 is the major product. Finally removal of the N-Boc group using TFA provided the desired amino-ethers 2 and 3.



Reagents: (i) $LiAlH_4$, THF, reflux (n=1, 97%; n=2, 90%); (ii) di-*t*- butyl dicarbonate, CH_2Cl_2, 23°C (n=1, 90%; n=2, 95%); (iii) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 23°C (n=1, 74%; n=2, 65%); (iv) trifluoroacetic acid, 23°C (n=1, 92%; n=2, 87%).

Scheme 1

It can be seen there is a relatively large increase in binding affinity in moving from the pyrrolidine (2, IC_{50} 20nM) to the piperidine (3, IC_{50} 1nM) ring system. This observation is in qualitative agreement with molecular modelling studies which showed that in the minimum energy conformation of the piperidine 3 there was almost perfect overlay of the two aromatic rings and the ether oxygen (the key pharmacophoric determinants) with those of L-733,060.[3] The exact superimposition of these three determinants could not be achieved when the minimum energy conformations of L-733,060 and the pyrrolidine 2 were compared.

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References and Notes

1. Harrison,T.; Williams, B.J.; Swain, C.J.; Ball, R.G. *BioMed. Chem. Lett.* **1994**, manuscript submitted.

2. Swain, C.J.; Cascieri, M.A.; Owens, A.P.; Saari, W.; Sadowski, S.; Strader, C.; Teall, M.;Van Niel, M.B.; Williams, B.J. *BioMed. Chem. Lett.*, **1994**, *in press.*

3. The minimum energy conformations were generated using Grid search within SYBYL, all conformations within 10kcal of the global minima were then minimised using the Tripos force field parameters. The minimum energy conformations were then superimposed using the basic nitrogen, the ether oxygen and the aryl centroids.

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5. The affinities of 2 and 3 for the hNK_1 receptor stably expressed in CHO cells were determined by competition with ^{125}I-SP, see: (i) Cascieri, M.A.; Ber, E.; Fong, T.M.; Sadowski, S.; Bansal, A.; Swain, C.; Seward, E.; Frances, B.; Burns, D.; Strader, C.D. *Mol. Pharm.*, **1992**, *42*, 458. (ii) Fong, T.M.; Anderson, S.A.; Yuh, H.; Huang, R.R.C.; Strader, C.D. *Mol. Pharm.* **1992**, *41*, 24.

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