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Piperidine-Ether Based hNK$_1$ Antagonists 1: Determination of the Relative and Absolute Stereochemical Requirements

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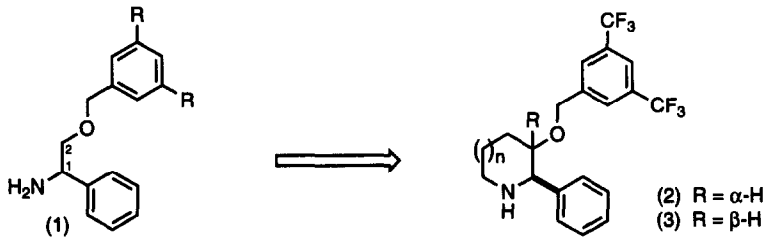
Abstract: The synthesis of a new series of piperidine-based ethers is described and the relative and absolute stereochemical requirements necessary for high affinity binding to the hNK$_1$ receptor established. The synthesis of the corresponding pyrrolidine derivative is also presented.

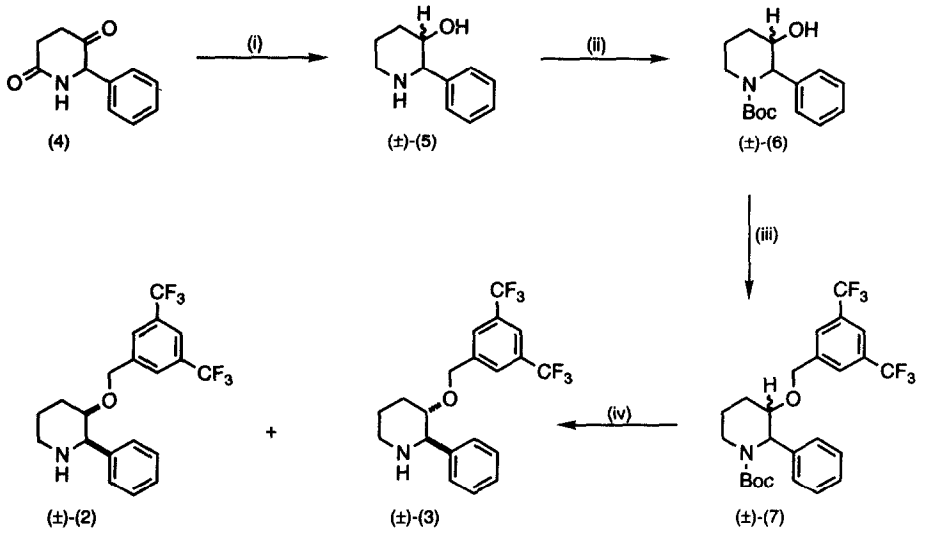
The role of the neurokinin substance P in a variety of biological responses including neurogenic inflammation[1], pain transmission and regulation of the immune response[2] is well documented. Accordingly, substance P antagonists may show clinical utility in a variety of disorders including migraine[3], rheumatoid arthritis[4] and pain[5]. The recent discovery of the first non-peptidic substance P antagonist CP-96,345 [6] has paved the way toward the realisation of this goal.

A recent publication from this laboratory has described the evolution of a series of acyclic phenyl-glycine derived substance P antagonists (eg **1**)[7]. These structures were ultimately derived from a quinuclidine ether series by ring scission followed by identification of a benzhydryl group replacement. In this communication we describe the synthesis of the *cis*- and *trans*- piperidine ethers (**2**) and (**3**) in which a ring has been built between C-2 and the N-atom, and demonstrate that *cis*- 2,3-substitution is essential for high-affinity binding to the human NK$_1$ (hNK$_1$) receptor. Furthermore, in analogy with the recently described piperidine amine series[8], activity resides almost exclusively in the (2S, 3S) enantiomer of (**2**). Finally, we describe the synthesis of the pyrrolidine analogue of (**2**) and demonstrate that high affinity binding to the hNK$_1$ receptor is retained when the ring size is decreased. The design and synthesis of alternative *gem*- disubstituted systems in which a ring is formed between C-1 and the nitrogen atom in (**1**) will be reported in due course.



The synthesis of the racemic *cis*- and *trans*- piperidine ethers (**2**) and (**3**) is shown in Scheme 1. Reduction of the keto-lactam (**4**)[9] with lithium aluminium hydride provided a 3:1 mixture of *cis*- and *trans*- amino alcohols (**5**), which were not separated but treated with di-*t*-butyl dicarbonate to provide carbamates (**6**). O-Alkylation with 3,5-bis(trifluoromethyl)benzyl bromide followed by removal of the nitrogen protecting group and separation of the isomers on silica gel provided the requisite racemic amino-ethers (±)-(**2**) and (±)-(**3**).

Scheme 1



Reagents: (i) $LiAlH_4$, THF, reflux, (72%) ; (ii) di-*t*-butyl dicarbonate, CH_2Cl_2, (98%); (iii) NaH, DMF, 3,5-bis(trifluoromethyl) benzyl bromide (47%); (iv) trifluoroacetic acid, (81%).

The affinities of the two diastereoisomers for the hNK_1 receptor stably expressed in CHO cells were determined by competition with ^{125}I-SP[10,11], and the results are shown in Table 1.

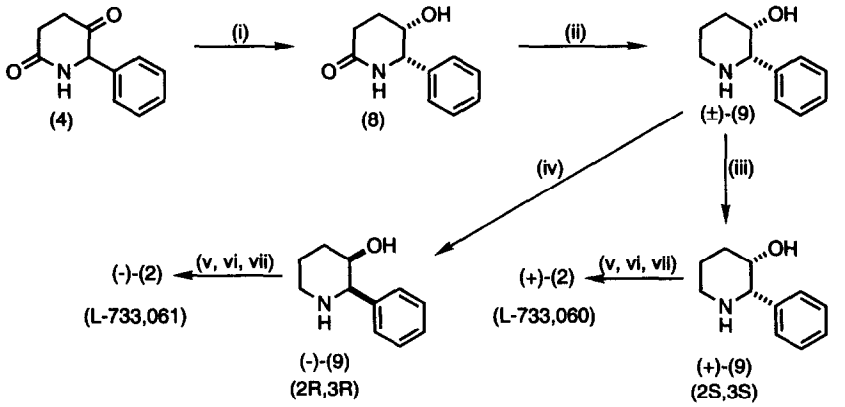
Table 1 : Displacement of [^{125}I] Substance P from hNK_1 receptor in CHO cells

Number	IC_{50} (nM)
(±)-2	1.4
(±)-3	300
(+)-2 (2S, 3S)	1.0
(-)-2 (2R, 3R)	350
(±)-15	7
CP-96,345	0.7

The finding that *cis*- 2,3-relative stereochemistry is essential for high affinity binding is in contrast to the situation in the corresponding benzhydryl-substituted quinuclidine ether series, in which it has been proposed that the presence of two aromatic rings on the benzhydryl group allows one ring of the benzhydryl to attain the bioactive conformation in both the *cis*- and *trans* - isomers[12].

Determination of the absolute stereochemistry required for high affinity hNK_1 binding was achieved by resolution of the racemic *cis* - amino alcohol (±)-(**9**). This compound could be obtained with high selectivity (>10:1 *cis* : *trans*) by initial reduction of the keto-lactam (**4**) using sodium borohydride at -20°C to provide the hydroxy-lactam (**8**) followed by reduction of the lactam carbonyl using borane. After resolution of (**9**) using dibenzoyl tartaric acid the individual enantiomers were converted to the enantiomeric benzyl ethers (+)-(**2**) (L-733,060) and (-)-(**2**) (L-733,061) (Scheme 2). The absolute configuration of the (2S, 3S) enantiomer (+)-(**9**) was determined by single crystal X-ray analysis of the derived (-)-dibenzoyl tartrate salt[13].

Scheme 2



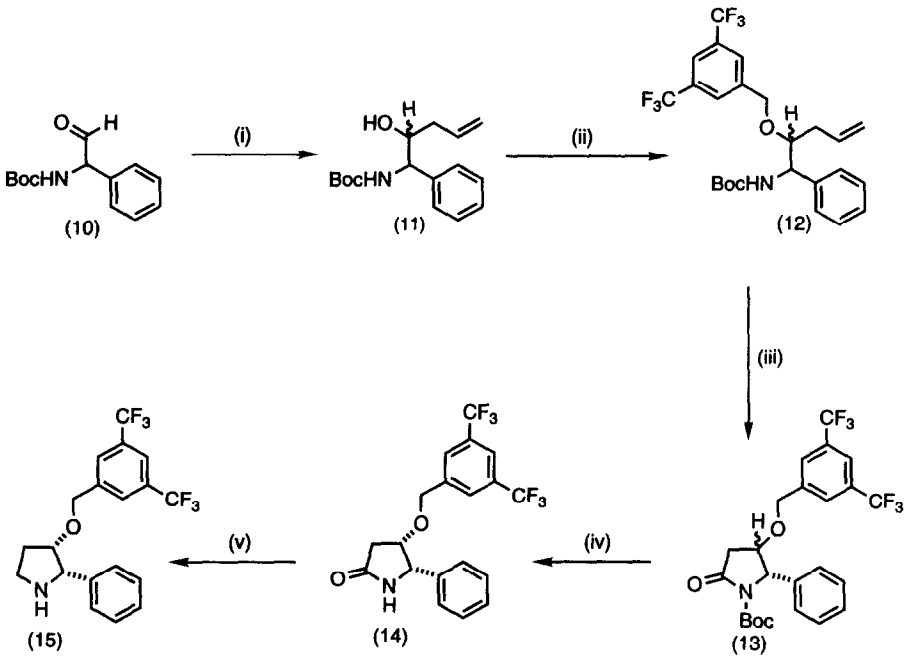
Reagents : (i) $NaBH_4$, MeOH, -20°C; (ii) BH_3.THF, reflux, then *p*-TsOH, (76%); (iii) Na_2CO_3, (-)-dibenzoyl tartaric acid; (iv) Na_2CO_3, (+)-dibenzoyl tartaric acid; (v) di-*t*-butyl dicarbonate, CH_2Cl_2, (99%); (vi) NaH, DMF, 3,5-bis(trifluoromethyl)benzyl bromide, (82%); (vii) trifluoroacetic acid (99%).

As shown in Table 1 and anticipated on the basis of previous results[8,12] the (2S, 3S) absolute stereochemistry is required for high-affinity hNK_1 binding. The residual binding affinity of the (-)-enantiomer (e.e. >98% by chiral HPLC)[14] is possibly due to the presence of residual (+)-(**2**).

We next sought to investigate the effect of decreasing ring size by preparing (±)-(**15**), the pyrrolidine analogue of (**2**) (Scheme 3). Addition of allyl magnesium chloride to N-Boc phenyl glycine aldehyde (**10**)[15] provided a diastereoisomeric mixture of alcohols (**11**), which were

benzylated without separation of the individual isomers to provide benzyl ethers (**12**). Oxidative cleavage of the terminal olefin provided a mixture of aminals which were oxidised without further purification providing lactams (**13**). After removal of the N-protecting group and separation of the isomers by chromatography the *cis* -lactam (**14**) was isolated as an oil. The *cis* - relative stereochemistry of the phenyl ring and benzyloxy substituent was determined by n.O.e. spectroscopy. Borane reduction of the lactam carbonyl provided the desired pyrrolidine (±)-(**15**). As Table 1 shows, only a modest decrease in binding affinity is observed in moving from the piperidine to the pyrrolidine series. This is in accord with molecular modelling studies which show that in both series the key pharmacophoric determinants, the two aromatic rings, the ether oxygen and the basic nitrogen, are similarly disposed[16].

Scheme 3



Reagents:(i) allyl magnesium chloride, THF, 23°C; (ii) NaH, DMF, 3,5-bis(trifluoromethyl)benzyl bromide; (iii) O_3, CH_2Cl_2-MeOH, -78°C, quench with Me_2S then PCC, 4A mol sieves, CH_2Cl_2; (iv) trifluoroacetic acid then separate isomers; (v)borane-THF reflux then potassium carbonate, EtOH, reflux.

In summary we have described the synthesis of two new series of conformationally constrained phenyl glycine-based hNK_1 antagonists . The effects of further nuclear variations will be reported in due course.

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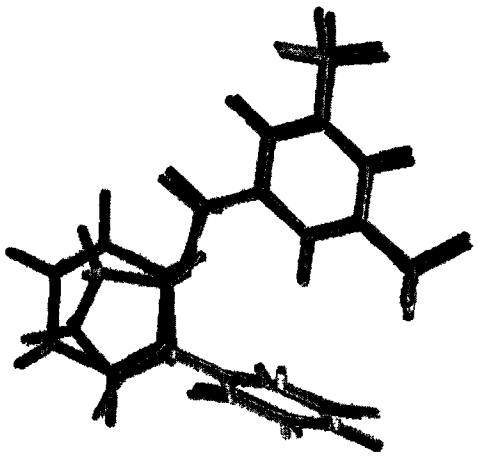
13. Crystal structure details: $C_{40}H_{44}N_2O_{10}$, M_r = 712.804, tetragonal, $P\,4_3$, α = 10.084 (1), c = 35.703 (2)A , V = 3630.4(9) A^3, Z = 4, D_x = 1.304 g cm^{-3}, monochromatized radiation λ(Cu K_α) = 1.541838 A, μ = 0.73 mm^{-1}, F (000) = 1512, T = 294 K. Data were collected on an Enraf-Nonius CAD4 Diffractometer to a θ ,limit of 70° and there were 3489 observed [$I > 3\sigma(I)$] reflections out of 3948 measured. The structure was solved by direct methods and refined using full-matrix least-squares on F using 468 parameters. All non-hydrogen atoms were refined with anisotropic thermal displacements. The final agreement statistics are: R = 0.045, ωR = 0.063, S = 2.43, $(\Delta/\sigma)_{max}$ = 2.13 with a weighting scheme of $1/\sigma^2(F)$. The maximum peak height in final difference fourier map is 0.34(7) eA^{-3} and it has no chemical significance. The authors have deposited the atomic

coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

14. HPLC conditions: Chiral AGP column, 18% CH_3CN in 10mM K_2HPO_4, pH 7, 0.9mL/min Retention times: (+)-(9) - 12.5min, (-)-(9) - 17.6min.

15. Prepared from N-Boc phenyl glycine following conversion to the corresponding Weinreb amide and $LiAlH_4$ reduction. For a review of the chemistry of N-protected α-amino aldehydes see: Jurczak, J., Golebiowski, A. *Chem Rev.*, **1989**, *89*, 149.

16.



Overlay of the minimum energy conformations of the piperidine (**2**) (dark lines) and pyrrolidine (**15**) (light lines). 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. It is interesting to note that although there is excellent overlap of the phenyl and benzyl rings and the ether oxygen in the two series, there is a significant deviation in the directionality of the substituent on nitrogen. The effects of nitrogen substitution will be reported in due course.

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