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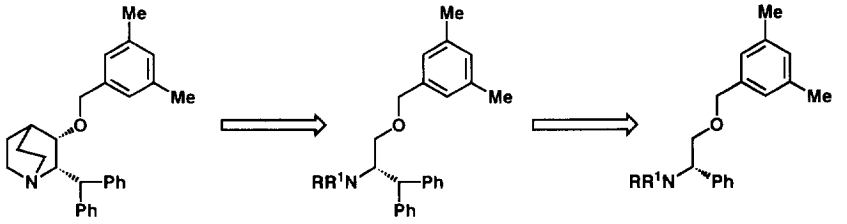
Phenyl-Glycinol Based NK_1 Receptor Antagonists - Towards the Minimum Pharmacophore

A.P. Owens*, B.J. Williams, T. Harrison, C.J. Swain, R. Baker, S. Sadowski[§] and M.A. Cascieri[§].

Department of Medicinal Chemistry, Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.
[§]*Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories, Rahway, New Jersey 07065*

Abstract: The effects of alternative benzyl ether substitution and the introduction of steric constraints on the binding affinity for the hNK_1 receptor of a phenylglycinol based Substance P antagonist is described.

A recent publication from this laboratory has described the design and synthesis of a novel series of acyclic human NK_1 receptor (hNK_1R) antagonists (eg. **3**). This series, the carbon backbone of which originates from phenyl glycinol, was derived from the previously reported[1] benzhydryl substituted quinuclidine ether series by ring fission followed by identification of a replacement for the benzhydryl group (Scheme 1)[2].

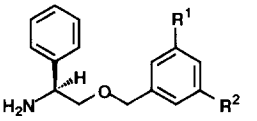


1 **2** **3**

Scheme 1

The fact that the benzhydryl group of the diphenyl-alaninol derived ethers **2** could be replaced by a single phenyl ring with only a modest decrease in binding affinity to the hNK_1 receptor suggests that only one phenyl ring of the benzhydryl group is involved in binding to the receptor, while the other functions as a conformational lock. Furthermore, in the phenyl-glycinol derived series, hNK_1R binding shows a marked dependence on the chirality of the phenyl-bearing centre, with the (S)-enantiomer showing much higher affinity than the (R)-enantiomer[2]. This is in contrast to the situation in the diphenyl-alaninol series where little or no dependance on the chirality of the benzhydryl-bearing centre is observed[3]. We therefore propose that phenyl-glycinol derived hNK_1R antagonists **3** are approaching the minimum pharmacophore required for high-affinity binding to the hNK_1R (*vis a vis* two optimally substituted aromatic rings connected by an appropriate linking group containing a hydrogen bond acceptor, and a polar substituent (in this series the amine) which projects toward the extracellular fluid). In this communication we describe the effects of changes to the proposed minimum pharmacophore.

Table 1 summarises the effects of varying the substitution in the aromatic ring of the benzyl ether. Since previous work has identified 3,5-di-substitution as being optimal for high affinity hNK_1R binding in the ether series[1], this substitution pattern was investigated in detail. All of the compounds shown in Table 1 were prepared by alkylation of N-Boc-phenylglycinol with the appropriate benzyl bromide or chloride (K_2CO_3, DMF) followed by N-deprotection using trifluoroacetic acid.

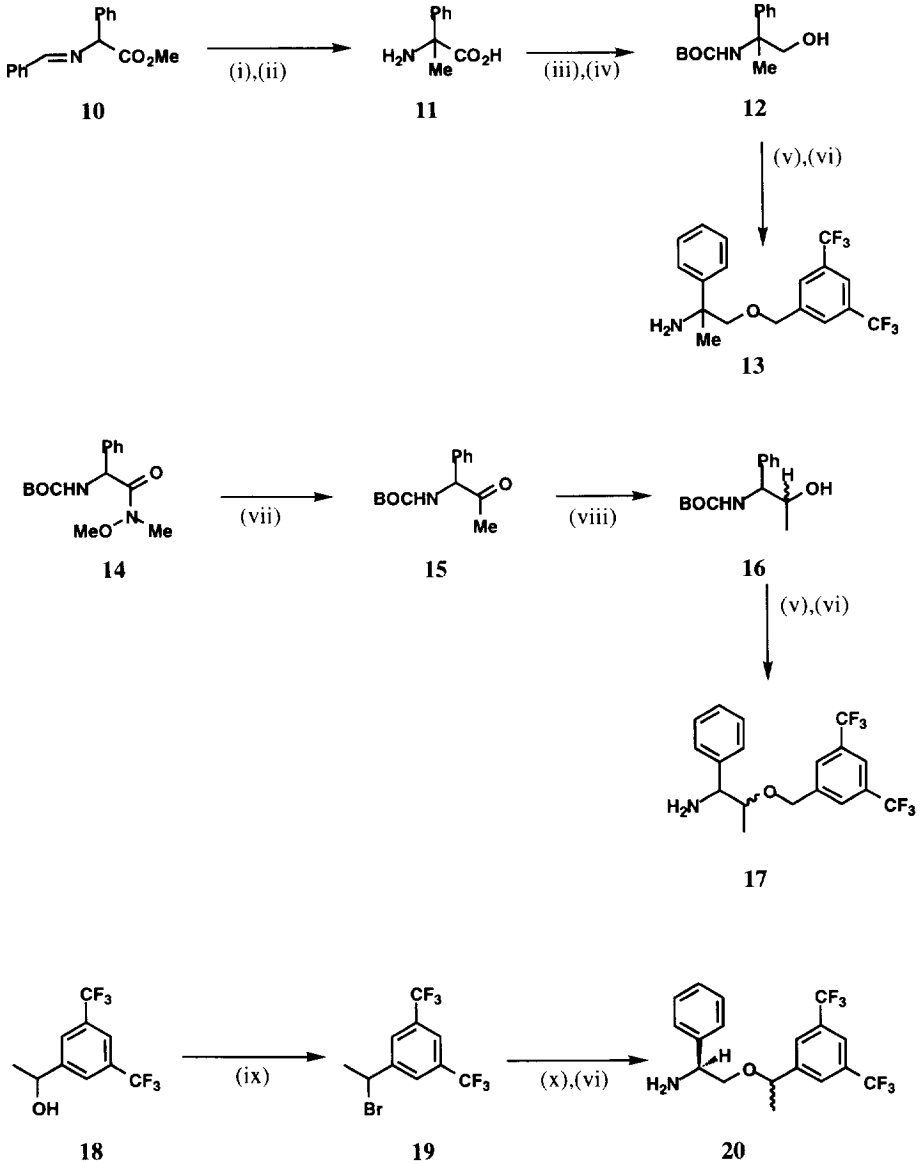


Cpd	R^1	R^2	hNK_1IC_{50} (nM)[4]
4	CH_3O	CH_3	135 ± 27
5	Cl	Cl	49± 9
6	CH_3	CH_3	55± 4
7	Br	CH_3	20± 6
8	^{t}Bu	CH_3	13.7± 0.6
9	CF_3	CF_3	13± 4 (n=4)

Table 1

It can be seen that in general lipophilic substituents are preferred and that there is a five-fold increase in affinity in moving from 3,5-dimethyl to the 3,5-bis (trifluoromethyl) substitution. This improvement in binding affinity is most pronounced in the phenyl glycinol series since both the quinuclidine ether and the diphenyl alaninol ether series showed little variation in binding affinity between these two substitution patterns.

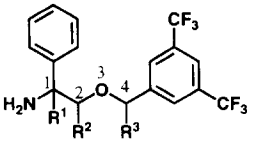
Having demonstrated that variation in benzyl substitution offers an increase in binding to the hNK_1R we next sought to further stabilise the bio-active conformation of **9** by introducing methyl groups along the carbon backbone as conformational constraints (Scheme 2). A similar strategy has been adopted in a series of dipeptide NK_2 receptor antagonists[5]. The C-1 methyl substituted derivative **13** was prepared by alkylation of the imine **10**[6] using lithium diisopropylamide (L.D.A.) and MeI followed by hydrolysis to give **11**. Reduction ($LiAlH_4$) followed by N-protection provided the alcohol **12** and subsequent ether formation and N-deprotection provided **13** as a racemate. The C-2 substituted diastereomers **17** were prepared by Grignard addition to the Weinreb amide of N-BOC-phenylglycine **14** to yield the ketone **15**, followed by reduction and subsequent introduction of the ether moiety as described previously. Introduction of a methyl group at the benzylic centre of **9** was achieved by alkylation of (S)-N-BOC phenyl glycinol with the bromide **19** followed by N-deprotection. The product **20** was obtained as an inseparable 2:1 mixture of diastereomers.



Reagents: (i) L.D.A., MeI, DMF; (ii) 6*M*HCl; (iii) $LiAlH_4$,THF; (iv) $(BOC)_2O$, CH_2Cl_2; (v) NaH, DMF, 3,5bis(CF_3)benzyl bromide; (vi) TFA; (vii) MeMgBr, THF; (viii) $NaBH_4$, EtOH; (ix) PBr_3; (x) NaH, (S)-N-BOC-phenylglycinol, DMF.

Scheme 2

The affinities of these methylated derivatives for the hNK_1 receptor are summarized in Table 2 :

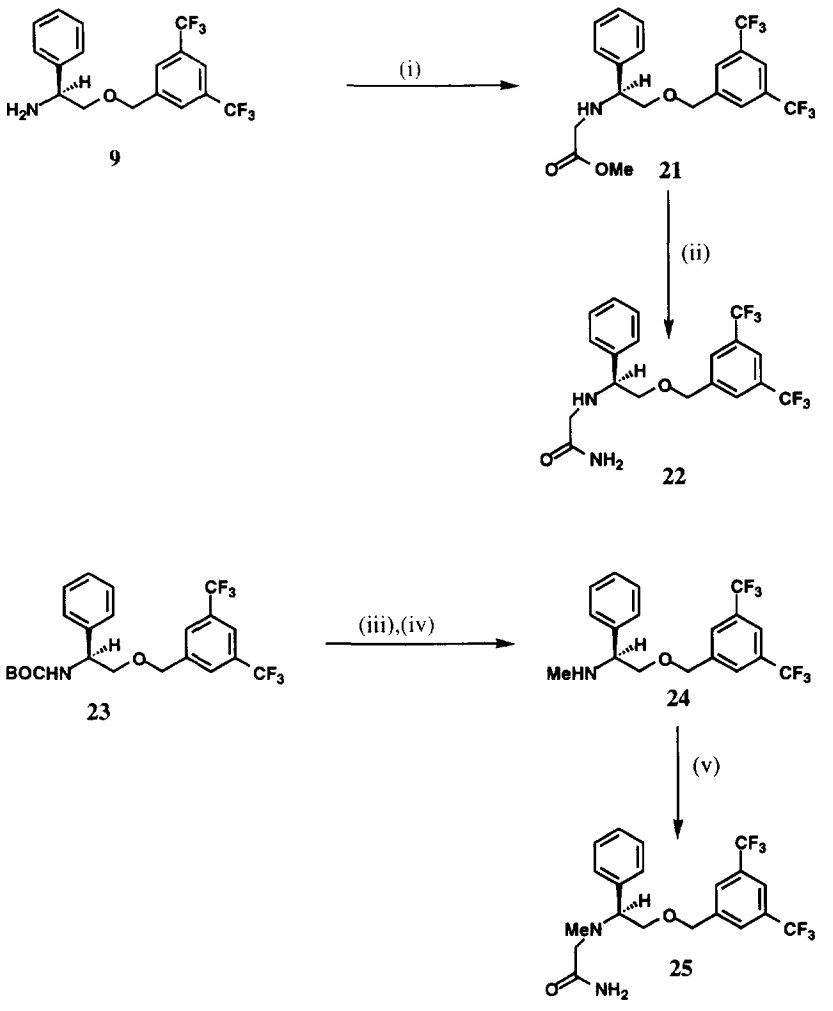


	Cpd	R^1	R^2	R^3	$hNK_1 IC_{50}$(nM)[4]
(1S)	**9**	H	H	H	13 ± 4 (n=4)
(±)	**13**	CH_3	H	H	30 ± 14
(±)	**17** (Diast A)	H	CH_3	H	95 ± 4
(±)	**17** (Diast B)	H	CH_3	H	7 ± 2
(1S)	**20** (2:1 mix of diastereomers)	H	H	CH_3	4.3 ± 1.8

Table 2

It can be seen that substitution at C-1 is well tolerated but does not improve binding affinity. Introduction of a methyl group at C-2 provides two diastereomers: one of these shows a much reduced affinity at the hNK_1 receptor while the other shows a modest improvement in binding over the unsubstituted compound. An increase in binding affinity is also observed following introduction of a methyl group at the C-4 benzylic centre (eg.Compound **20,** 2:1 mixture of diastereomers at C-4, hNK_1 IC_{50} = 4.3nM). These results provide further information to aid refinement of the pharmacophore.

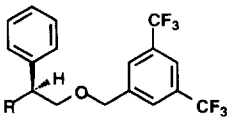
Phenylglycine derivatives such as **9** contain a basic nitrogen (pK_a=7.93)[7]. As may be expected **9** also shows relatively high affinity binding to the L-type calcium channel. Using a similar strategy to that described in the literature for the diphenylalaninyl and piperidine ether series[3,8], we were able to significantly reduce Ca^{2+} channel binding affinity whilst retaining high hNK_1R affinity by incorporation of the polar electron withdrawing carboxamidomethyl substituent on nitrogen. Thus, the secondary amine **22** was synthesised by alkylation of **9** with methyl bromoacetate to give **21** followed by ammonolysis (Scheme 3). The tertiary amine, derivative **25**, was prepared by methylation of **23** using NaH and MeI, followed by N-deprotection with TFA to give **24**, which was subsequently alkylated (iodoacetamide).



Reagents: (i) Methyl bromoacetate, NEt_3, THF; (ii) NH_3, MeOH; (iii) NaH, MeI, DMF; (iv) TFA; (v) iodoacetamide, $(iPr)_2EtN$, acetonitrile.

Scheme 3

The hNK_1R and Ca^{2+} channel binding data for the carboxamidomethyl derivatives **22** and **25** are summarised in Table 3.



Cpd	R	$hNK_1 IC_{50}$(nM)[4]	Ca^{2+}-binding[9]
9	H_2N-	13 ± 4 (n=4)	580nM
22	H_2NCOCH_2HN-	8 ± 1	2.3μM
25	H_2NCOCH_2MeN-	5.8 ± 2.2	>10μM

Table 3

Acknowledgement: We thank S.Patel for providing the Ca^{2+} channel binding data, S. Thomas and R.Herbert for helpful discussion, D. O'Connor for providing pK_a measurement and S.N. Owen for preparing **8**.

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9. (i) Ca^{2+} channel binding was determined using a method similar to that described by: Reynolds, I.; Snowman, A.M.; Snyder, S.H. *J. Pharmac. Exp. Therap.* **1986**, *237*, 731. (ii) All experiments were carried out using diltiazen as a positive control, n=1 for all experiments.

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