4,4-Disubstituted Piperidines: A New Class of NK_1 Antagonist

Graeme I. Stevenson,* Angus M. MacLeod, Ian Huscroft, Margaret A. Cascieri,† Sharon Sadowski,† and Raymond Baker

Department of Medicinal Chemistry, Neuroscience Research Centre, Merck, Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, England, and Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories, Rahway, New Jersey 07065

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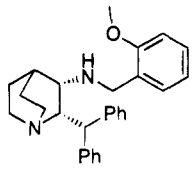
The recent discovery of selective non-peptide substance P antagonists, such as CP-96,345 (**1**),[1] together with the availability of the cloned human NK_1 receptor[2] has led to an intense exploration of the pharmacology of substance P. Subsequently, several non-peptide antagonists from structurally different classes have been identified, including the quinuclidinium-based SR 140333 (**2**),[3] piperidine CP 99,994 (**3**),[4] the tryptophan L-732,138 (**4**),[5] and the diarylpiperazine **5**.[6] The actions of substance P at the NK_1 receptor have been implicated in neurogenic inflammation,[7] transmission of pain,[8] vasodilation,[9] airway smooth muscle contraction,[10] and the regulation of the immune response.[11] Consequently an NK_1 antagonist may be of therapeutic use in the treatment of chronic pain, migraine, and rheumatoid arthritis.



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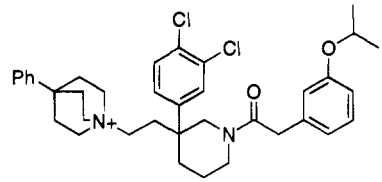

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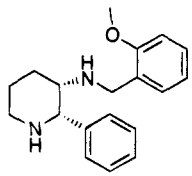

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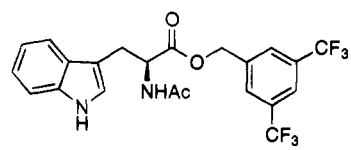

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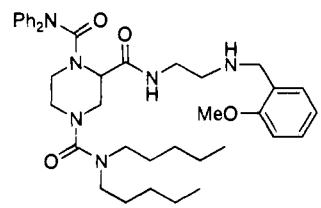

(5)

Studies on CP-96,345 carried out in our laboratories have shown that, with the appropriate choice of aryl substituent, the benzylamine can be replaced by a benzylic ether.[12] Subsequently, an acyclic series of NK_1 antagonists was derived by partial deletion of the quinuclidine ring of CP-96,345 and replacement of the benzhydryl moiety by a phenyl group to afford the phenylglycine derivative **6** with an IC_{50} of 13.5 nM.[13] This type of system probably contains the minimum pharmacophore required for binding to the human NK_1 receptor. However, although ligands such as **6** have good affinity for the NK_1 receptor, with six freely rotatable bonds such a flexible system probably suffers a loss in binding through entropic factors and consequently has lower affinity than **1**. Incorporation of **6** into a piperidine ring by linking N_1 to C_2 provided the potent 3-[[3,5-bis(trifluoromethyl)benzyl]oxy]piperidine (L-733,060, **7**; Figure 1) with IC_{50} = 1.0 nM at the human NK_1 receptor.[14] As part of our ongoing studies in this area, we examined novel conformationally restricted analogues of the pharmacophore present in **6**.

Initially this was carried out by incorporation of **6** into a piperidine ring through linking N_1 to C_1 (rather than C2 as in **7**) which resulted in the 2,2-geminally disubstituted system **8**[15] in which the unsubstituted phenyl group occupies an axial position, Figure 1. A good overlay of the main pharmacophoric elements of **7** and **8** could be achieved in modeling studies, and both compounds had the same binding affinity (IC_{50} = 1.0 nM), indicating the carbon framework of the piperidine ring acts as a molecular scaffold without any specific interaction with the receptor. We have now extended this approach by exploring the consequences of altering the proximity of the basic nitrogen to the rest of the receptor pharmacophore—the two aryl rings and the putative hydrogen-bond-accepting ether oxygen,[12] using the 3,3- and the 4,4-disubstituted piperidine systems, **9** and **10**, respectively.

The 3,3-disubstituted piperidine **9** was prepared as shown in Scheme 1. Alkylation of diethyl phenylmalonate **11** with acrylonitrile followed by catalytic hydrogenation gave the lactam **12**, which was then subjected to further reduction and N-protection to afford the key intermediate (hydroxymethyl)piperidine **13**. Alkylation of **13** followed by deprotection produced the racemic ether **9**. This compound suffered a 20-fold loss in affinity compared to **8**, consistent with proposed models of antagonist binding to the NK_1 receptor in which the position of the basic nitrogen is an important feature.[3,16]

The 4,4-geminally disubstituted analogue **10** was prepared from the commercially available piperidinecarboxylic acid **14** (Scheme 2). Reduction followed by *in situ* protection of the piperidine nitrogen provided the 4-phenyl-4-(hydroxymethyl)piperidine **15**. This was then alkylated and deprotected to give the ether **10**. Remarkably, this achiral compound was found to be equal in affinity to **8** with an IC_{50} = 0.95 nM. This is in marked contrast to the stereochemical requirements observed in other series of NK_1 antagonists.[13,16]

The 3,5-bis(trifluoromethyl)phenyl moiety has now found application in a number of NK_1 antagonists,[4,12-15] playing a key role in providing compounds with high receptor affinity. In common with these other classes of antagonist, the pattern of substitution on the ether linked aryl ring is a critical determinant of the level of binding achieved. In this series, deletion of one of the trifluoromethyl groups (**16**) resulted in a 50-fold loss in affinity, while replacement by dimethyl (**17**) or dichloro

* Address correspondence to this author at Merck, Sharp and Dohme Research Laboratories.
† Merck Research Laboratories.

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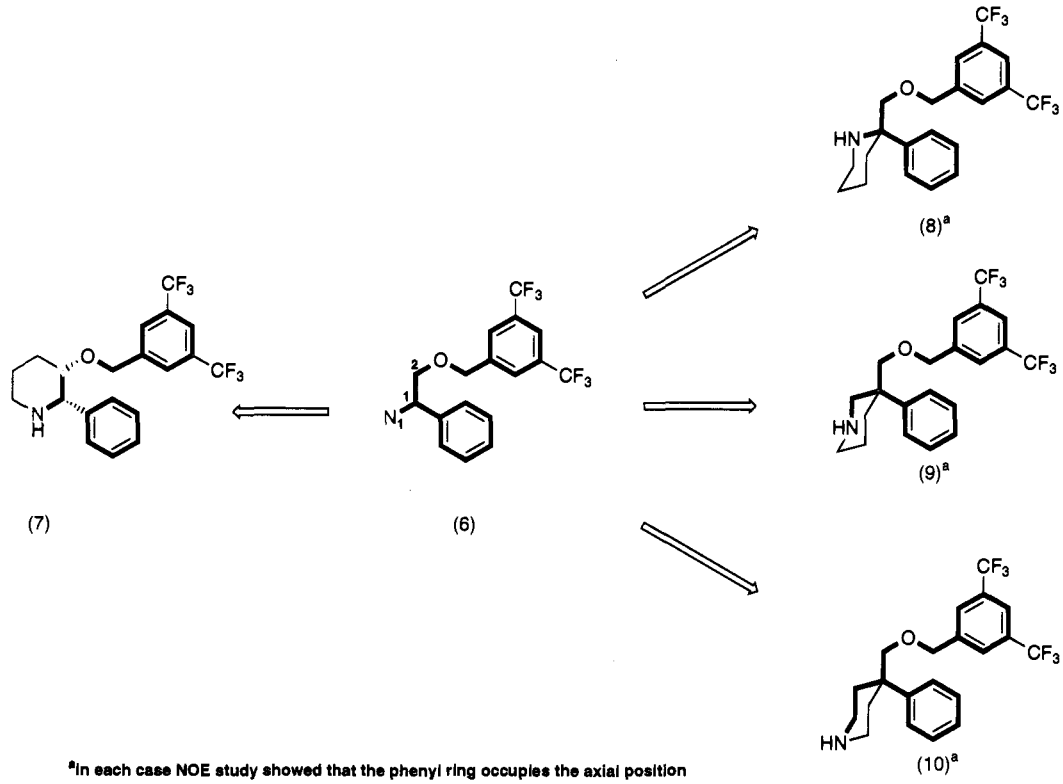
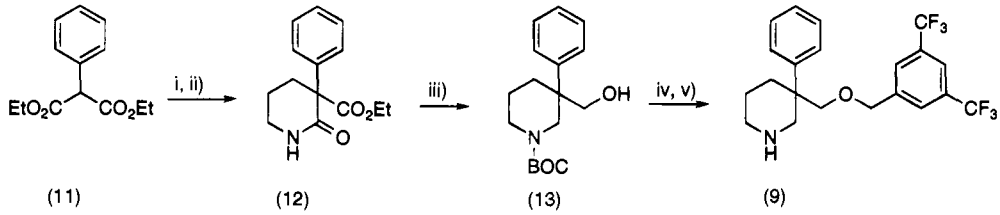


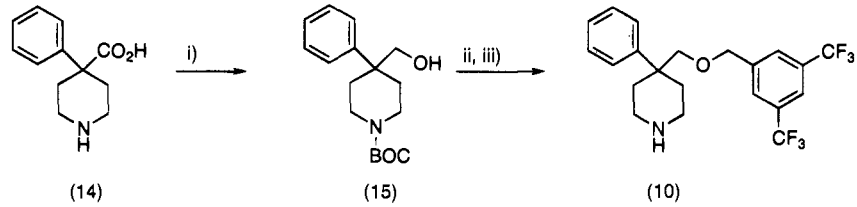
Figure 1.

Scheme 1[a]



[a] Reagents: (i) acrylonitrile/^{t}BuOH, KOH, MeOH; (ii) PtO_2/H_2; (iii) $LiAlH_4$, THF/BOC_2O; (iv) KHMDS, THF/3,5-bis(trifluoromethyl)benzyl bromide; (v) HCl/Et_2O.

Scheme 2[a]



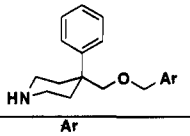
[a] Reagents: (i) $LiAlH_4$, BOC_2O; (ii) NaH, DMF/3,5-bis(trifluoromethyl)benzyl bromide; (iii) HCl/Et_2O.

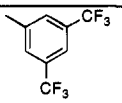
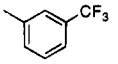
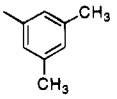
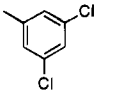
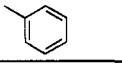
(**18**) caused only a 3–4-fold decrease. The contribution of the bis(trifluoromethyl) substitution is best illustrated by comparison with the unsubstituted system **19** which is 1000-fold less active (Table 1). In established classes of NK_1 antagonists, although the substitution type and pattern of one of the phenyl rings is important, various different substitutions have been utilised to achieve subnanomolar affinities.[1,3,4] Our initial results show that, in this series, disubstitution of the ether-linked aryl ring is important for high-affinity binding and that the lipophilicity of the substituents on this ring predominate over electron-withdrawing effects.

The 4-phenylpiperidine ring system is a common feature of central nervous system (CNS)-active compounds, and 4,4-geminally disubstituted systems are also common. With many such systems, selectivity is often a major issue. We have evaluated compound **10** in binding assays for the NK_2, NK_3, μ opioid, D_1–D_4, 5-HT_{1A}, 5-HT_{1D}, 5-HT_2, and 5-HT_3 receptors[17] and have established that it is highly selective (>1000-fold) for NK_1 with IC_{50} values greater than 3 μM for all the receptors tested. Using an established procedure,[18] **10** was shown to inhibit the substance P-induced accumulation of inositol phosphate in CHO cells. Schild analysis of this effect was linear with a slope of 1.0, thus establishing that **10** behaves as a competitive antagonist at the NK_1 receptor with a K_b of 4.5 ± 0.18 nM.

In conclusion, we have developed a series of novel, high-affinity, achiral NK_1 antagonists by the incorporation of a derived minimum pharmacophore into a 4,4-geminally disubstituted piperidine ring. These compounds have been shown to be selective for the NK_1

Table 1. Variation of Benzylic Substitution



Compound	Ar	hNK1 IC_{50} nM[a]
10		0.95 +/- 0.41
16		57 +/- 25
17		9.0 +/- 6
18		4.6 +/- 2.3
19		1100 +/- 300

[a] Displacement of ^{125}I-labeled substance P from the cloned receptor expressed in CHO cells.

receptor. A full exploration of the SAR and optimization of this type of NK_1 antagonist will be reported subsequently.

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(17) Receptor sources: NK_2, NK_3, stable transfected CHO cells; D_1, rat striatal membranes; D_2, D_3, stable transfected CHO cells; D_4, stable transfected HEK cells; 5-HT_{1A}, pig cortical membranes; 5-HT_{1D}, pig caudate membranes; 5-$HT_{2/3}$, rat cortical membranes; μ-opioid, rat cortical membranes.

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