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Quinuclidine-Based NK_1 Antagonists, the Role of the Benzhydryl.

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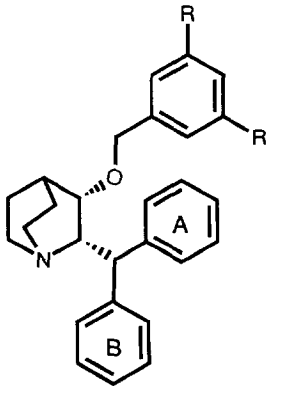
Abstract: Initial work on a series of quinuclidine based antagonists suggested that only one of the rings of the benzhydryl was involved in receptor binding. This communication endeavors to test this hypothesis and to identify which of the phenyl rings interacts with Histidine 197.

The tachykinins are a family of peptides that share the common C-terminal sequence "Phe-X-Gly-Leu-Met-NH_2". A number of high affinity non-peptide antagonists of the NK_1 receptor have been reported[1,2], and have been shown to be active in a variety of animal models that would be predictive of clinical utility.

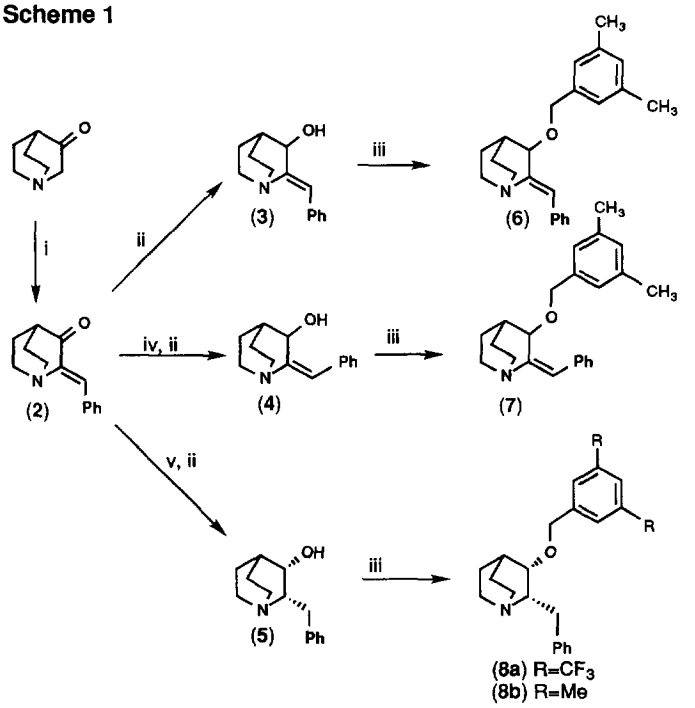
As part of our early work in this area we proposed that in a series of quinuclidine-based NK_1 antagonists **1a,b** only one of the phenyl rings of the benzhydryl group was involved in binding to the NK_1 receptor and that the second ring acted as a conformational anchor[3,4]. In order to test this hypothesis a series of compounds have been prepared in which one of the rings has been deleted and a double bond introduced to reduce conformational freedom. In addition, these studies have also enabled the identification of which of the rings (A or B) of the benzhydryl interacts with histidine-197 of the hNK_1 receptor, a residue which has previously been shown to be involved in the interaction of the benzhydryl moiety with the receptor[5].



(1a) R=CF_3
(1b) R=CH_3

The key intermediate alcohols were prepared by aldol condensation between 3-quinuclidinone and benzaldehyde to afford the enone 2 [6] (Scheme 1), sodium borohydride reduction of the enone afforded the unsaturated alcohol 3 which was then alkylated to give the benzyl ether 6. Alternatively, isomerisation followed by reduction afforded 4 and alkylation yielded the corresponding Z-isomer 7. The structures of these isomers were confirmed by noe studies[7]. Reduction of the enone 2 by catalytic hydrogenation and subsequent treatment with sodium borohydride afforded the saturated alcohol 5 which was alkylated to give ether 8.

Scheme 1



Reagents: i) PhCHO, NaOH, EtOH ; ii) $NaBH_4$, MeOH; iii)$KN(SiMe_3)_2$, THF, $ArCH_2Br$; iv) $CHCl_3$, HCl; v) H_2, Pd/C;

These compounds were then evaluated in two binding assays, firstly for their affinity for the wild type receptor[8] and secondly for their affinity for a mutant receptor in which His-197 has been replaced by alanine (H197A). The parent compounds **1a,b** are high affinity NK_1 antagonists (Table 1) and show reduced affinity for the H197A mutant. Removal of one of the phenyl rings of the benzhydryl **8a** or **8b** results in approximately a 100 fold reduction for the wild type receptor, this reduction in affinity is probably due to the increased conformational flexibility of the ligand. However **8a** and **8b** still retain some

sensitivity to the H197A mutant suggesting that these ligands still interact with His-197, possibly through the remaining phenyl ring however it is not possible to determine whether this remains a direct interaction.

Introduction of the double bond as a conformational restraint affords two isomers; the unsubstituted phenyl ring of each isomer can then mimic the position of one or the other of the phenyl rings of the benzhydryl. As anticipated, whilst isomer **7** retains respectable affinity for the wild type receptor the other isomer **6** shows only very weak affinity. In addition, whilst isomer **6** is insensitive to the H197A mutation, isomer **7** retains sensitivity to the mutation suggesting that the phenyl ring in this isomer is still interacting with the histidine in a similar manner to **1**. The reduced affinity for the wild type receptor observed for compound **7** is probably due to conjugation between the unsubstituted phenyl ring and the double bond raising the energy of the receptor bound conformation in which the phenyl is probably not coplanar with the double bond.

Table 1 Summary of Receptor Binding Studies

Number[a]	Wild Type IC_{50} (nM)	H197A IC_{50} (nM)
1a	2±0.3 (4)	330± 50 (5)
1b	2±0.7 (11)	196± 84 (2)
8a	197 ± 75 (3)	500 (1)
8b	292±114(2)	845±114(2)
7	129±20 (6)	615±91 (3)
6	8200± 1800 (6)	7500± 1800 (3)

[a] All compounds are racemic

These studies serve to support our original hypothesis that only one of the phenyl rings of the benzhydryl is involved in receptor binding. They also suggest that it is ring A **1** that is involved in the interaction with His 197 and thus enable us to refine further our model of the antagonist binding site.

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