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Acyclic NK_1 antagonists: Replacements for the benzhydryl group.

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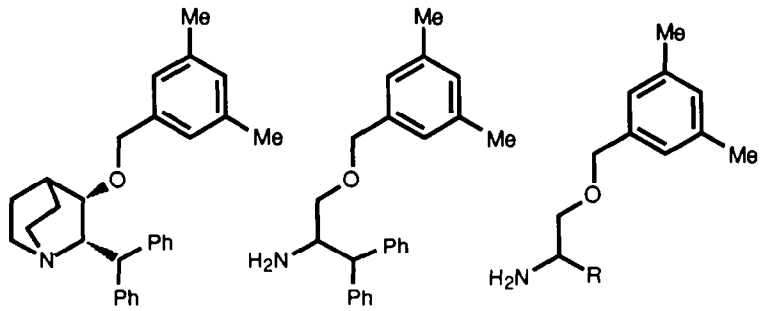
Abstract: An exploration of benzhydryl replacements is described. Whilst bridged and fused polynuclear aromatic systems both incur a reduction in affinity it was possible to replace the benzhydryl by a single phenyl ring with only a modest reduction in affinity. In contrast to the analogous diphenylalanyl ethers the binding was also shown to be stereoselective.

The tachykinins are a family of peptides that share the common C-terminal sequence "Phe-X-Gly-Leu-Met-NH_2". There are four mammalian tachykinins:- substance P (SP), neurokinin A (NKA), neurokinin B (NKB) and neuropeptide K (an N-terminally extended form of NKA). The biological actions of the tachykinins are mediated through specific cell-surface receptors; three subtypes, designated NK_1, NK_2 and NK_3, were identified on the basis of marked differences in the rank order of potencies of agonist peptides in different tissues, with SP being the preferred agonist for NK_1 receptors, NKA for NK_2 receptors and NKB for NK_3 receptors. The existence of three receptor subtypes has been confirmed by the cloning and sequencing of three distinct genes from mammalian sources[1,2,3]. A number of non-peptide antagonists of the NK_1 receptor have been reported[4], with Pfizer reporting the discovery of the first non-peptide substance P antagonist (CP 96,345)[5].

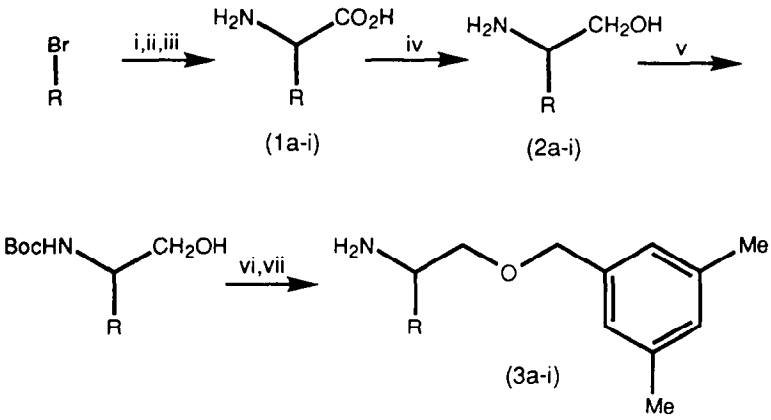


Recently we reported a novel series of acyclic NK_1 antagonists[6] derived from ring fission of the corresponding quinuclidine ethers[7]. Whilst the quinuclidines had provided an excellent framework for the exploration of the benzyl ether structure-activity-relationships, the difficulty of synthesis precluded a detailed examination of benzhydryl replacements. The acyclic series however

provided a ready entry into this area of exploration. Results from the quinuclidine series suggested that only one of the aryl rings of the benzhydryl was essential for high affinity[8]. In order to investigate this hypothesis a variety of alternative aryl systems were prepared and evaluated.

All the analogues were prepared (Scheme 1) by reduction of the corresponding amino acids (1a-i); subsequent Boc-protection of the amino alcohol (2a-i) followed by alkylation and deprotection afforded the desired benzyl ethers (3a-i). The amino acids were either commercially available (1d,g,h,i), or prepared by alkylation of dimethyl acetamidomalonate followed by hydrolysis and decarboxylation (1b,c,e,f), or as described previously (1a)[6].

Scheme 1

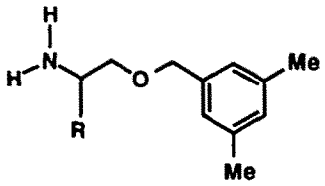


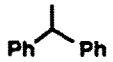
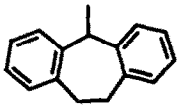
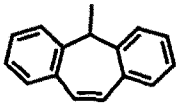
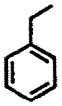
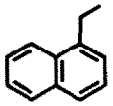
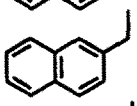
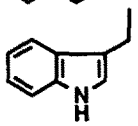
Reagents: i) Dimethylacetamidomalonate, THF, NaH; ii) NaOH; iii) Heat ; iv) $LiAlH_4$, THF, reflux; v) Boc_2O, DMAP, CH_2Cl_2 ; vi) NaH, DMF, 3,5-dimethylbenzyl bromide; vii) MeOH,HCl

Efforts to constrain the benzhydryl group met with limited success (Table 1), replacement by the dibenzoazepines (1b) or (1c) resulted in a 10 fold loss in affinity, perhaps reflecting steric constraints. Deletion of one of the phenyl rings (1d) resulted in a 50 fold loss in affinity possibly due to the increased conformational flexibility. Introduction of fused aromatic rings (1e, 1f or 1g) resulted in a further reduction in affinity. However, it was possible to replace the benzhydryl by a single phenyl ring without the linking methylene (1h) with only a 5 fold reduction in affinity, all the activity residing in the (S) enantiomer (1h). This compound is a selective NK_1 antagonist having negligible affinity at either NK_2 or NK_3 (>10,000 nM).

These results are consistent with the hypothesis that only one of the rings of the benzhydryl is involved in ligand binding, and that the second ring acts as a conformational anchor. Further results supporting this hypothesis will be published in subsequent communications.

Table 1: Binding Affinity of NK_1 antagonists determined from inhibition of [^{125}I] substance P binding to the hNK_1 receptor in CHO cells



Number	R[a]	IC_{50} (nM)[b]
1a		9.3 ± 6.2
1b		93 ± 5
1c		80 ± 8
1d		483 ± 165
1e		1160 ± 481
1f		2333 ± 1027
1g		2333 ± 850
1h	S-Enantiomer 	55 ± 4
1i	R-Enantiomer	2500 ± 408

[a] All compounds are racemic unless stated otherwise

[b] All results are the mean of three determinations[9]

Furthermore, in contrast to the diphenylalanyl ethers in which both enantiomers display similar affinity for the NK_1 receptor[6], the observed enantioselectivity is in accord with that observed for both the amines and ethers in the quinuclidine series[5,8] with the S-enantiomer showing the highest affinity.

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