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QUINUCLIDINE-BASED NK-1 ANTAGONISTS I: 3-BENZYLOXY-1-AZABICYCLO[2.2.2]OCTANES

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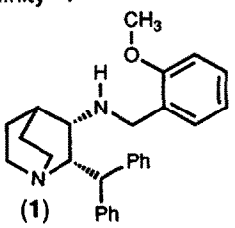
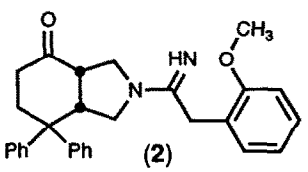
Abstract: A series of 3-benzyloxy-derivatives of CP-96,345 has been evaluated and found to have significant affinity for the human NK_1 receptor. 3,5-Disubstitution of the benzyl ether has been identified to be essential for high affinity.

Substance P is a member of the neurokinin family of bioactive peptides and mediates its biological effects *via* binding to the neurokinin-1 (NK_1) receptor.[1,2] There is considerable evidence for the role of substance P in neurogenic inflammation,[3] in the transmission of pain and in the regulation of the immune response.[4] Accordingly, NK_1 antagonists may be of clinical benefit in a variety of disorders, including rheumatoid arthritis,[5] migraine[6] and pain.[7] Structural modification of the endogenous agonist has led to the development of high affinity antagonists[8,9] but peptides are of little value as pharmacological probes, since they suffer from metabolic instability and poor oral bioavailability.

The recent discovery of two high affinity and selective *nonpeptide* antagonists represents an important breakthrough in the neurokinin field.[10,11] The first study disclosed CP-96,345 (**1**), a dibasic amino quinuclidine in which the *o*-methoxybenzylamine sidechain was reported to be essential for high affinity[12].

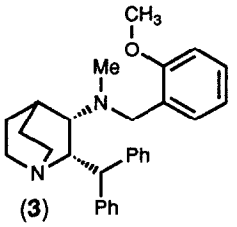


(**1**)



(**2**)

The second report described RP-67,580 (**2**), a *cis*-fused perhydroisoindolone which also incorporates an *o*-methoxybenzyl group.[11] It is noteworthy that the sidechain contains a basic linking group.



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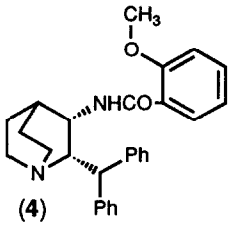
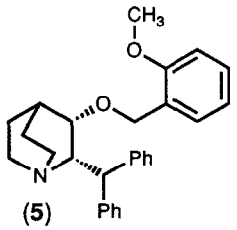


(4)

Structure-activity relationship studies on analogues of CP-96,345 (**1**) have highlighted the importance of the linking heteroatom to binding: methylation to give the tertiary amine **3**, conversion to the nonbasic amide **4**, or replacement with oxygen to afford the benzyl ether **5**, all resulted in reduced binding at the NK_1 receptor.[12,13]

Molecular modelling studies[14], carried out in our laboratory, suggest that in the global energy minimum conformation there exists an intramolecular hydrogen-bonding interaction between the methoxy oxygen and the N-H of the benzylamine in **1** which may play an important role in stabilizing the receptor-bound conformation. The hydrogen-bonding interaction is replaced by a destabilising lone pair-lone pair repulsion in the corresponding *o*-methoxybenzyl ether **5** resulting in quite different low energy conformations. Thus, a comparison of the *o*-methoxybenzyl analogues **1** and **5** is not valid and it is essential to include the unsubstituted benzylamine **6** in any comparative study to obtain a meaningful evaluation of the contribution of the linking heteroatom to binding.

We herein report the results of a systematic study to replace the benzylamine of **6** with alternative linking groups; affinity in this series was then explored with appropriate aromatic ring substitution.



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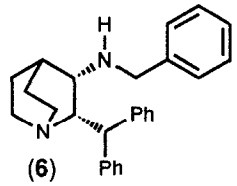
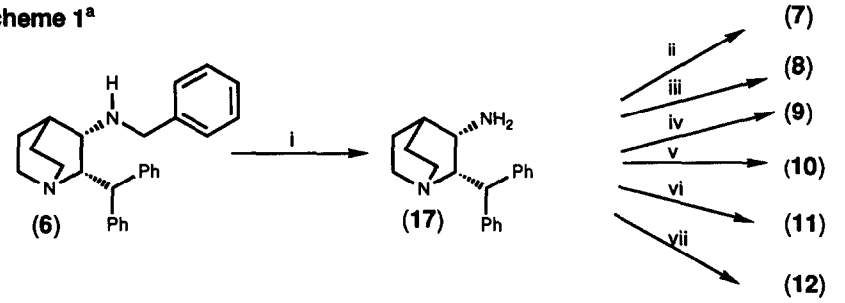


(6)

The key intermediate in the synthesis of compounds **6-12** (Scheme 1) and compounds **13-15g** (Scheme 2) was the quinuclidinone **16** which was prepared by the method of Warawa *et al.*[15] The ketone was reacted according to the method of Lowe,[16] to give the parent benzylamine **6.** The benzyl group was removed by hydrogenolysis over palladium hydroxide to give amine **17.**

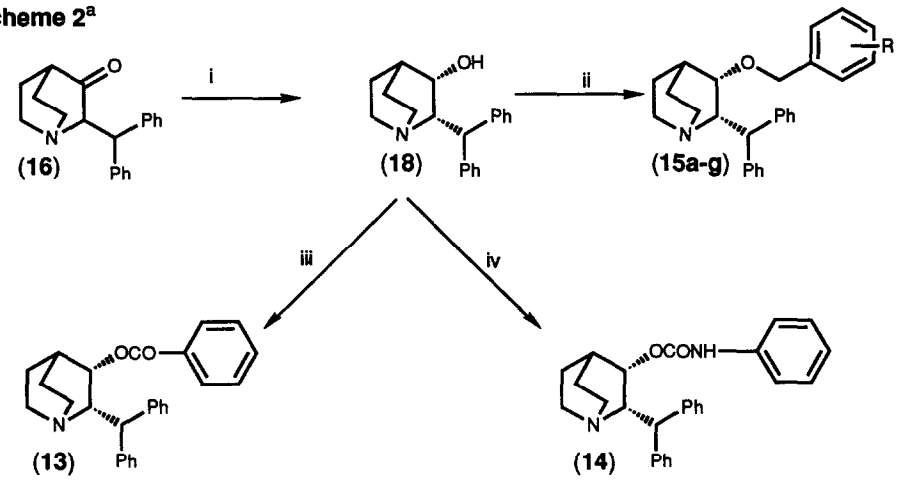
Scheme 1[a]



[a]Reagents: i) H_2, $Pd(OH)_2$; ii) $PhCH_2CH_2Br$, K_2CO_3, DMF; iii) KH, PhCOCl, DMAP, DME; iv) PhOCOCl, Et_3N, DCM; v) PhNCO, Et_3N, DCM; vi) PhNCS, Et_3N, DCM; vii) $PhSO_2Cl$, Et_3N, DCM;

Reaction of **17** with the appropriate alkyl halide, acid chloride, chloroformate, isocyanate, isothiocyanate, or sulfonyl chloride afforded the phenethyl derivative **7**, amide **8**, carbamate **9**, urea **10**, thiourea **11** and sulfonamide **12** respectively.

Scheme 2[a]

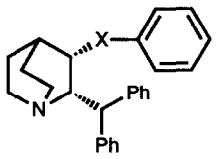


[a]Reagents: i) $LiEt_3BH$, THF; ii) $KN(SiMe_3)_2$, $ArCH_2Br$, DME; iii) PhOCOCl, Et_3N, DCM; iv) PhNCO, Et_3N, DCM.

The ketone **16** was stereoselectively reduced with lithium triethylborohydride in tetrahydrofuran to afford the *cis* alcohol **18** (Scheme 2). Treatment of **18** with the appropriate acid chloride or isocyanate afforded ester **13** and carbamate **14** respectively. Compound **18** was alkylated under Williamson ether conditions, using potassium hexamethyldisilazide as base and the resultant alkoxide quenched with the appropriate benzyl bromide, to afford benzyl ethers **15a-g**. The bulky diphenylmethyl group effectively shields the highly nucleophilic quinuclidine nitrogen from reaction with the benzyl bromide and no quaternization was observed.

The affinities of the compounds for the human NK_1 receptor (stably expressed in CHO cells) were determined according to the method of Cascieri *et al.*[17]

Table 1 Displacement of [^{125}I]Substance P Binding from hNK_1 Receptors in CHO Cells



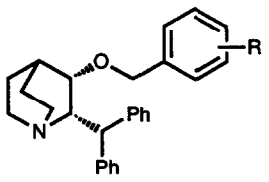
No.	X	[a]IC_{50} (μM)
6	$-NHCH_2-$	0.15 ± 0.05
7	$-NHCH_2CH_2-$	0.70
8	-NHCO-	>1
9	-NHCOO-	>1
10	-NHCONH-	>1
11	-NHCSNH-	>1
12	$-NHSO_2-$	>1
13	-OCO-	>1
14	-OCONH-	>1
15a	$-OCH_2-$	0.11 ± 0.02

[a] ± SEM

The results in Table 1 show that homologation of the aminomethyl linkage in **6** to afford the phenethyl analogue **7** results in a marked reduction in affinity. A number of other derivatives, including the amide **8**, carbamate **9**, urea **10**, thiourea **11** and sulfonamide **12**, were essentially inactive. Similarly, the oxygen-linked derivatives, ester **13** and carbamate **14**, had no measurable binding to the NK_1 receptor. When the benzylamine was replaced with a benzyl ether a full restoration of binding affinity was achieved (**15a**, IC_{50} = 110nM; **6**, IC_{50} = 150nM) suggesting that it is possible to replace the secondary nitrogen of **1** with alternative residues.

The poor affinity of compounds **7**, **9**, **10**, **11** and **14** can be rationalised in terms of the length of the 3-atom linking group which positions the phenyl ring in a different region of space. Also, the linking groups in **9**, **10**, **11** and **14** all contain an sp^2 carbon atom which restricts conformational flexibility of the molecule. Previous studies attribute the poor affinity of **4** to the nonbasic character of the amide,[13] however, the present work shows that a basic centre is not essential in this position. A more likely explanation for the poor activity of amide **8** and ester **13** lies in the change in geometry which occurs on going from an sp^3 to an sp^2 centre.

Table 2 The Effect of Aromatic Substitution on the Displacement of [^{125}I]Substance P from Human NK_1 Receptors.



No.	R^1	R^2	[a]IC_{50} (nM)
15a	H	H	110 ± 22
15b	2-CH_3	H	183 ± 85
15c	3-CH_3	H	21 ± 7
15d	4-CH_3	H	290 ± 130
15e	2-CH_3	5-CH_3	48 ± 3
15f	3-CH_3	4-CH_3	197 ± 56
15g	3-CH_3	5-CH_3	1 ± 0.7
1	CP-96,345		0.5

[a] ± SEM

Using a methyl group as a probe to examine the influence of aromatic substitution, a series of mono- and dimethyl-substituted benzyl ether analogues (**15b-g**) were evaluated (Table 2). Ortho substitution (**15b**, IC_{50} = 183 nM) did not significantly affect binding, while para substitution was detrimental (**15d**, IC_{50} = 290 nM). However, meta substitution resulted in a five-fold increase in affinity (**15c**, IC_{50} = 21 nM) over the unsubstituted benzyl ether. When a methyl group occupies both meta and para positions the binding affinity is reduced (**15f**, IC_{50} = 197 nM), however, occupation of both meta positions afforded a remarkable increase in affinity (**15g**, IC_{50} = 1 nM), 100-fold more active than the parent compound and equipotent with CP-96,345.

3-Benzyloxyquinuclidines have been evaluated as antagonists at the human NK_1 receptor. A previous report suggested that these compounds were considerably less active than the corresponding benzylamines,[13] however, our work has shown that with appropriate benzyl ether substitution this series displays high affinity binding at the NK_1 receptor; the study highlights the importance of 3,5-disubstitution of the aromatic ring.

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