Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 16, pp. 1903-1908, 1994
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0960-894X/94 $7.00+0.00

0960-894X(94)00259-2

ACYCLIC NK-1 ANTAGONISTS: 2-BENZHYDRYL-2-AMINOETHYL ETHERS

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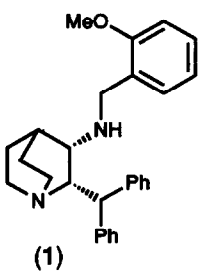
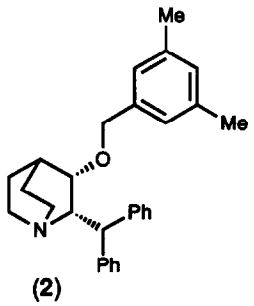
Abstract. A series of 2-aminoethyl ethers based on diphenylalaninol have been shown to have significant affinity for the human NK_1 receptor and reduced affinity at the L-type Ca^{++} channel compared with quinuclidines related to CP 96,345.

The tachykinins are a family of peptides containing a structurally related C-terminal amino-acid sequence "Phe-X-Gly-Leu-Met-NH_2".[1] The tachykinins have been implicated in a number of physiological processes and antagonists have potential in the treatment of neurogenic inflammation,[2] rheumatoid arthritis,[3] pain[4] and migraine.[5]

The initial discovery of the quinuclidine CP-96,345 (1)[6] as a selective non-peptide NK-1 antagonist has been rapidly followed by reports of tachykinin antagonist activity displayed by a range of other structural classes, such as *cis*-fused perhydroisoindolones[7], fused benzimidazoles[8], piperidines[9] and tryptophan derivatives.[10]



(1)



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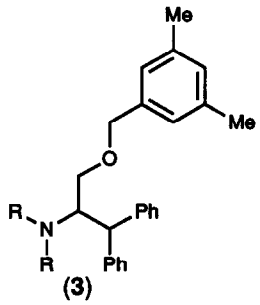


(3)

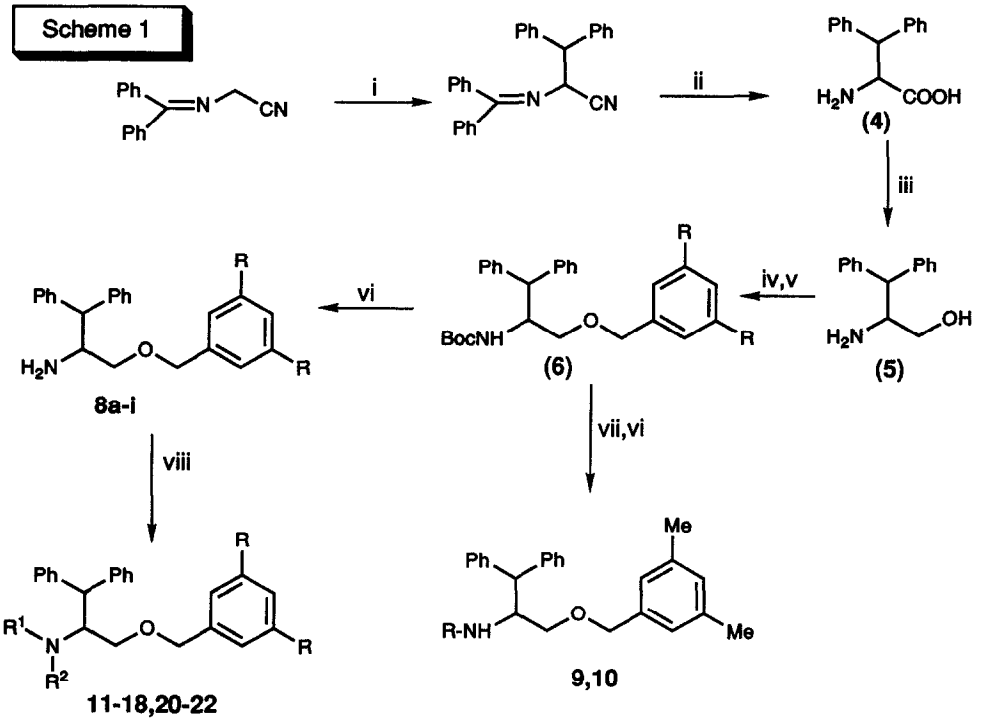
Detailed structure-activity relationships of CP-96,345 indicated that a *cis*-2,3 relationship between a benzhydryl group and a *o*-methoxybenzylamine group was essential for high affinity.[11] The NH of the linking group between the benzyl and the quinuclidine functions in particular was thought to be required for hydrogen bonding[12] and hence high receptor affinity. However, a recent

report from this laboratory has shown that an oxygen linking group is a suitable replacement for the nitrogen atom in a series of high affinity *cis*-2,3-quinuclidine ethers substituted with a benzhydryl group and a 3,5-substituted benzyl ether (2).[13] In general however, quinuclidine-based NK-1 antagonists such as CP 96,345 display adverse cardiovascular effects *in vivo*, which is possibly a consequence of antagonist activity at L-type Ca^{++} channels (as seen by their ability to displace [^{3}H]diltiazem and enhance [^{3}H]nitrendipine binding).[14] One factor we believed to be contributing to the high L-channel activity was the basicity of the quinuclidine nitrogen.

In this present study we investigate whether the presence of the quinuclidine framework plays an important role in establishing the correct conformation for recognition by the NK-1 receptor, and if modification of the nitrogen atom can be used to reduce activity at the L-type Ca^{++} channel.

Molecular modelling indicated very little conformational mobility for quinuclidines with either ether- or amine- linked benzyl groups (1 and 2). Scission of the quinuclidine ring from (2) generates the 2-benzhydryl-2-aminoethyl ether (3) which still retains the elements thought essential for receptor binding but with significantly increased conformational freedom. Furthermore, the presence of the primary amine allows for the introduction of alternative substituents which can be used to control the basicity of the nitrogen.

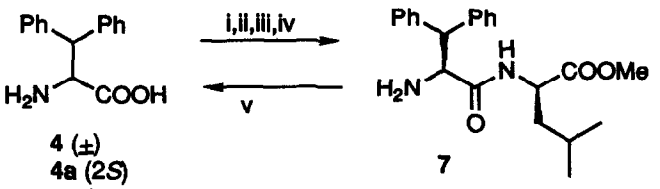
Scheme 1



Reagents: i, Ph_2CHBr / NaOH; ii, 0.5M HCl, 140°C, 48h; iii, $LiAlH_4$; iv, $(Boc)_2O$; v, $ArCH_2Br$ / NaH; vi, TFA; vii, MeI or EtI / NaH; viii, H_2CO / $NaCNBH_3$ (for 14-16); or alkyl-bromide / K_2CO_3(for 11-13); methyl bromoacetate / K_2CO_3 followed by NH_3/ MeOH (for 20-22); or acyl anhydride (for 17 and 18).

Synthesis of the 2-benzhydryl-2-aminoethyl ether (3) required the amino acid diphenylalanine, which we prepared in racemic form (Scheme 1) and as the single enantiomers (Scheme 2). Preparation of the racemic amino acid 4 utilized alkylation of N-(diphenylmethylene) aminoacetonitrile with benzhydryl bromide under the phase transfer conditions of O'Donnell[15] followed by acid hydrolysis. This route was found to be convenient on a large scale. Reduction to the amino alcohol 5 by $LiAlH_4$, protection of the amino group with di-t-butyldicarbonate and alkylation under standard Williamson conditions gave the protected amino ether (6) in high yield. Preparation of the mono alkyl derivatives 9 and 10 was achieved by alkylation of 6 prior to removal of the Boc protecting group. The N,N-dialkyl- derivatives 14-16, N-acyl derivatives 17 and 18, and the remaining mono-alkyl derivatives were prepared by removal of the Boc protecting group from 6 followed by alkylation or acylation under standard mild base conditions.

Scheme 2



4 (±)
4a (2*S*)
4b (2*R*)

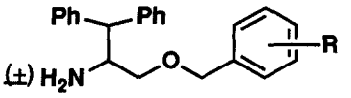
7

Reagents: i, Boc_2O / Et_3N; ii, L- or D-Leu-OMe.HCl / 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide / HOBt; iii, fractional crystallization or chromatographic separation of diastereomers; iv, TFA, extraction of the free base with Na_2CO_3; v, 5.5M-HCl, reflux 48h.

Resolution of 4 into the L- and D- enantiomers 4a and 4b (Scheme 2) was achieved by derivatization with D-Leucine methyl ester followed by fractional crystallization or chromatography to give the pure diastereomer L-diphenylalaninyl-D-leucine methyl ester (7) (absolute stereochemical assignment was determined by X-ray analysis and by enantiospecific synthesis using standard Schollkopf synthesis[16]). Acid hydrolysis gave the hydochloride salt of L-diphenylalanine 4a.

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). These results indicate that simple benzyl ethers show significant affinity for the human NK_1 receptor although the best of these 8d is still some 9 times less active than the corresponding quinuclidine 2. Appropriate benzylic substitution does contribute significantly to the NK_1 affinity with 8d having an increase of 40 fold over the unsubstituted benzyl ether 8a. In contrast to the quinuclidines 1 and 2, which offer limited scope for variation and substitution of the nitrogen atom, these acyclic amino ethers 8d and 8e were used as the basis of an extensive programme to investigate the effects of nitrogen substitution.

Table 1 Displacement of [^{125}I]Substance P from hNK$_1$ receptors in CHO cells



No	R		[a]IC$_{50}$ nM (±SEM)	
2			1.0	(± 0.7)
8a	H	H	367	(± 170)
8b	3-Cl	H	75	(± 35)
8c	3-I	H	77	(± 45)
8d	3-Me	5-Me	9.3	(± 6.2)
8e	3-CF_3	5-CF_3	10.7	(± 3.1)
8f	3-Cl	5-Cl	11.3	(± 7.7)
8g	3-Br	5-Br	13.3	(± 10.4)
8h	3-Br	5-Me	9.7	(± 7.3)
8i	2-Me	5-Me	150	(± 108)

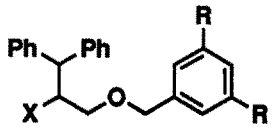
[a] binding affinity for hNK$_1$ (at least n=3)

The effect of nitrogen substitution on the binding affinity of **8d** and **8e** at the hNK$_1$ receptor is shown in Table 2. Mono alkylation by small alkyl groups maintains receptor affinity (**9**,methyl and **10**,ethyl) however with larger alkyl groups (**11**, i-propyl; **12**, cyclopropylmethyl; **13**, benzyl) affinity declines rapidly. Introduction of a second methyl group increases affinity slightly (**14**, hNK$_1$ IC$_{50}$ 4.4nM) over the mono methyl derivative (**9**). Synthesis of the individual enantiomers (2*S*,**15** and 2*R*,**16**) of the dimethyl- derivative (**14**) in enantiomerically pure form (enantiomeric excess >99%) showed only marginal selectivity for the receptor (hNK$_1$ IC$_{50}$ 5.5 and 14nM respectively). Acylation of **8d** with formyl (**17**,hNK$_1$ IC$_{50}$ 11nM) and acetyl (**18**,hNK$_1$ IC$_{50}$ 21nM) groups reduces receptor affinity, however this reduction is approximately equivalent to the reduction seen for the corresponding isosteric alkyl group (ethyl and i-propyl, hNK$_1$ IC$_{50}$ 12.7nM and 55nM respectively). This indicates that the presence of a basic amino group is not required by the receptor. This was confirmed by the synthesis of **19**, which is the analogue of **8d** in which the primary amino group has been replaced by a hydroxy- group. High binding affinity at the hNK$_1$ receptor (hNK$_1$ IC$_{50}$ 17nM) is maintained.

Although the receptor displayed only limited steric tolerance for simple alkyl groups, it was found that alkyl groups containing a range of polar substituents were well tolerated and in many cases gave improved receptor affinity. The carboxamidomethyl- derivative **20** (hNK$_1$ 2.2nM) is approximately isosteric with the cyclopropylmethyl derivative **12** (hNK$_1$ 93nM) but displays

significantly higher receptor affinity. Both the racemic and the resolved carboxamidomethyl-derivative **21** and **22** show subnanomolar affinity with 3,5-bis(trifluoromethyl)benzyl ether substitution.

Table 2 Effects of amino substitution on binding affinity on **8d** and **8e** (displacement of [^{125}I]Substance P from hNK$_1$ receptors in CHO cells).



No	X	R	stereo	[a]IC$_{50}$ nM (±SEM)	
8d	H_2N-	Me	(±)	9.3	(± 6.2)
9	MeNH-	Me	(±)	6.8	(± 2.2)
10	EtNH-	Me	(±)	12.7	(± 5.2)
11	^{i}PrNH-	Me	(±)	55	(± 29)
12	^{c}PrCH$_2$NH-	Me	(±)	93	(± 49)
13	BnNH-	Me	(±)	82	(± 120)
14	Me_2N-	Me	(±)	4.4	(± 3.2)
15	Me_2N-	Me	(S)	5.5	(± 3.7)[b]
16	Me_2N-	Me	(R)	14	(± 3)[b]
17	HCONH-	Me	(±)	11	(± 13)
18	CH_3CONH-	Me	(±)	21	(± 28)
19	HO-	Me	(±)	17	(± 9)
20	NH_2COCH_2NH-	Me	(±)	2.2	(± 0.6)
21	NH_2COCH_2NH-	CF_3	(±)	0.85	(± 0.59)
22	NH_2COCH_2NH-	CF_3	(S)	0.53	(± 0.21)[b]

[a] affinity for hNK$_1$ receptors (at least n=3) [b] enantiomeric excess >99% by chiral hplc

In conclusion, the rigid *cis*-2,3-quinuclidine framework does play a role in establishing the precise conformation required by the receptor. However, the corresponding acyclic compounds are also able to achieve high binding affinity in the absence of this conformational constraint. With the appropriate N-substitution the binding affinity can be increased further to sub-nanomolar levels which are equivalent to those found in the quinuclidine series. Furthermore substitution of the nitrogen with polar groups is anticipated to cause a reduction in the basicity of the nitrogen. The acyclic aminoethers can be clearly shown to have reduced L-channel Ca^{++} activity compared with quinuclidines such as CP 96,345, **1** (inhibition of [^{3}H]diltiazem binding, IC$_{50}$ 0.24μM). Whilst the N,N-dimethyl analogue **15** showed reduced L-channel Ca^{++} activity ([^{3}H]diltiazem binding IC$_{50}$

0.98μM) this can be decreased further by introduction of electron withdrawing groups on the nitrogen such as the N-carboxamidomethyl group (20, 22 [^{3}H]diltiazem binding IC_{50} 5.5μM, 1.67μM respectively). Thus 22 shows a 2-fold increase in binding affinity at the hNK-1 receptor compared with 2, it is some 7 fold less active as an L-channel Ca^{++} antagonist.

Acknowledgements

The authors would like to thank M. Ahmed, K. Mahmood and N. Smith for their technical assistance, A. Watt for the determination of chiral purity and R. Ball for X-ray crystallographic data on 7. L-channel Ca^{++} antagonist activity at the diltiazem binding site was provided by P. Hutson.

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(*Received in Belgium* 17 *May* 1994)