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Synthesis and structure–activity relationships of 8-azabicyclo[3.2.1]octane benzylamine NK_1 antagonists

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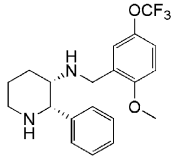
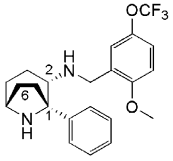
Abstract—A series of 8-azabicyclo[3.2.1]octane amine hNK_1 antagonists has been investigated and structure–activity relationships of the benzylamine and 6-*exo* substituents described. Acidic substituents at C6 give a series of high affinity compounds for hNK_1 with selectivity over the hERG channel.

The action of the mammalian tachykinin, substance P, at the human neurokinin-1 (hNK_1) receptor has been implicated in inflammatory conditions such as migraine,[1] rheumatoid arthritis,[2] asthma[3] and inflammatory bowel disease,[4] as well as mediation of the emetic reflex.[5] Hence, non-peptide antagonists for the hNK_1 receptor in the central nervous system are potential therapeutic agents for these indications.



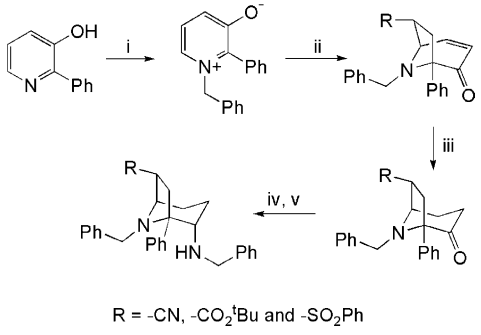
CP-122721



1b

Compound **CP-122721** is a high affinity antagonist at hNK_1 (hNK_1 IC_{50} 0.14 nM).[6] To explore conformationally restrained piperidine derivatives of **CP-122721** as hNK_1 antagonists, a two carbon bridge was appended to the positions adjacent to the *endocyclic* nitrogen, to give a series of 8-azabicyclo[3.2.1]octanes such as **1b**.

Synthesis of this series centres upon a [3+2] cycloaddition reaction (Scheme 1) giving the azabicyclic core with varied substitution on the bridge. This core can be readily modified to give ethers via reduction of the ketone produced followed by alkylation or amines by reductive amination. Both C6 and C7, *exo* and *endo* isomers at the bridge are formed in the cycloaddition, but these are separable by



R = -CN, -$CO_2{}^t$Bu and -SO_2Ph

Scheme 1. Reagents: (i) $PhCH_2Br$, toluene, followed by ion exchange; (ii) vinyl-R, 1,4-dioxane; (iii) Pd/C, MeOH, EtOAc, H_2; (iv) $PhCH_2NH_2$, TsOH, toluene; (v) $NaBH_4$, MeOH.

Keywords: Bicyclic diamine; Azabicyclo[3.2.1]octane; NK_1 antagonist; Substance P; Selectivity.
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chromatography and crystallisation. Early studies of structure–activity relationships (SAR) in a related ether series[7] showed the 6-substituted compounds to have higher affinity than 7-substituted isomers at hNK_1. The reaction was carried out in an analogous manner using 2-(4-fluorophenyl)-3-hydroxypyridine to give the corresponding 4-fluorophenyl bicyclic core, in an attempt to block metabolism at the 4-position of the phenyl group. This had little effect on binding to hNK_1 or hERG receptors.

Studies showed that the C2 amine gave higher affinity compounds if *exo* to the bicyclic core. Reduction of the imine formed from condensation of benzylamine and the ketone with sodium borohydride gave an exclusively *exo*-benzylamine rather than the *exo*/*endo* mixture obtained by reduction with sodium cyanoborohydride.

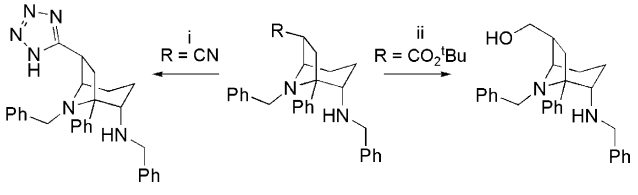
Bicyclic diamines substituted with 6-*exo* cyano, *tert*-butyl ester and phenyl sulfone groups could be obtained using this methodology, and these were further manipulated to give a range of functionalities such as tetrazole and hydroxymethyl at C6 (Scheme 2).

The benzyl-protecting groups were removed by hydrogenolysis (Scheme 3) and the less sterically hindered *exo*-amine reacted with a substituted benzaldehyde by reductive amination to yield the target compounds. In the case of the phenyl sulfone derivative, removal of the benzyl groups first, followed by reductive cleavage of the carbon–sulfur bond of **2a**, provided the most efficient route to **2b**.

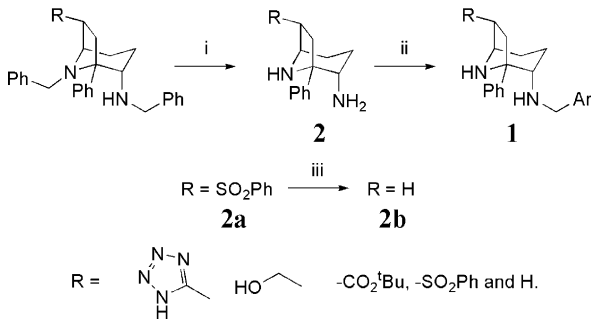
The *tert*-butyl ester group could be carried through the synthesis to give a late stage intermediate (**3**) (Scheme 4). This could be deprotected to give the diamino acid (**4**), which was further elaborated to give acyl sulfonamides and amides. The primary amide was reduced to the amino methyl compound, and this reacted with sulfonyl chlorides to give sulfonamides. Attempts to convert the 6-hydroxymethyl compound (**5a**) to the corresponding halide or mesylate, followed by displacement by sulfonamides, resulted in very poor yields.

The diamino acid (**6**) could be used to form 1,2,4-triazol-3-one on the bridge by condensation with semicarbazide, followed by cyclisation under basic conditions (Scheme 5). The benzyl groups were removed, and the *exo*-amine reductively alkylated as in Scheme 3 to give **5e**.

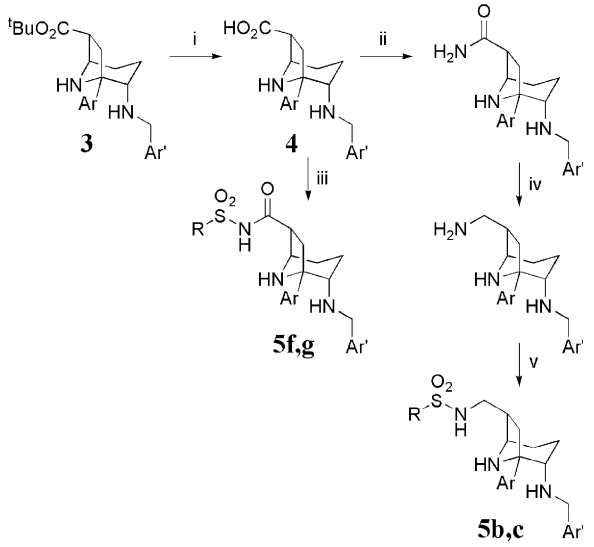
Initially, a number of substitution patterns on the benzylamine side chain, which are known[6,8,9] to exhibit



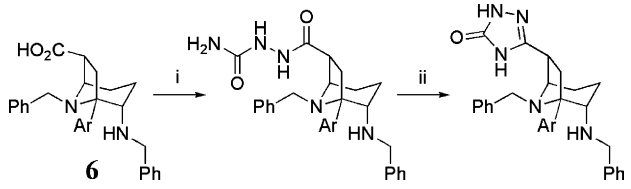
Scheme 2. Reagents: (i) NaN_3, $Et_3N{\cdot}HCl$, NMP; (ii) DIBAL-H, toluene.



Scheme 3. Reagents: (i) Pd/C, NH_4O_2CH, EtOH; (ii) ArCHO, $NaBH(OAc)_3$, DCE; (iii) Na/Hg, Na_2HPO_4, MeOH.



Scheme 4. Reagents: (i) TFA, DCM; (ii) *N*,*N*′-carbonyldiimidazole, Et_3N, NH_3, THF; (iii) *N*,*N*′-carbonyldiimidazole, Et_3N, RSO_2NH_2, THF; (iv) $BH_3{\cdot}SMe_2$, toluene; (v) RSO_2Cl, NaOH, DCM, H_2O.

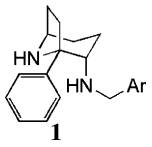


Scheme 5. Reagents and condition: (i) semicarbazide HCl, BOP-Cl, Et_3N, DCM; (ii) 1 M aqueous NaOH, reflux.

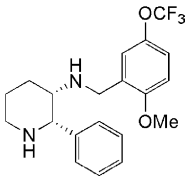
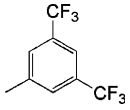
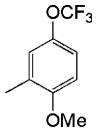
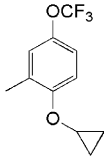
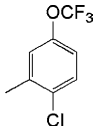
high affinity at the hNK_1 receptor in other series, were explored (Table 1).

The bicyclic core followed the trend displayed by **CP-122721** and analogues by requiring 2,5-disubstitution on the benzylamine for maximum affinity, with 2-methoxy (**1b**) or cyclopropoxy (**1c**) 5-trifluoromethoxy compounds giving sub-nanomolar affinity. These compounds showed significant binding to the hERG channel,[12] however. This could be alleviated in **1d** with a 2-chloro substituent, reducing the hERG affinity to a micromolar level, but to the detriment of hNK_1 affinity. Therefore, the benzylamine substitution in **1c** was chosen to continue SAR studies in this series.

Table 1.

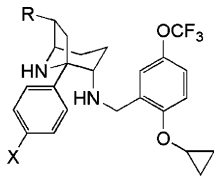


1

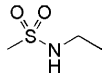
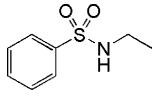
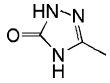
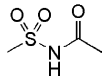
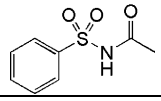
Compound	Ar	hNK_1 IC_{50}[a] (nM)	hERG K_i[b] (nM)
CP-122721[c]		0.14	1800
1a		3	—
1b		0.13	240
1c		0.10	360
1d		2.1	1400

Values represent geometric means of three determinations.
[a] Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells.[10]
[b] Displacement of [^{35}S]-labelled MK-499 from the cloned channel expressed in HEK cells.[11]
[c] CP-122721 is a single enantiomer. All 8-azabicyclo[3.2.1]octanes are racemic.

Table 2.



5

Compound	R	X	hNK_1 IC_{50}[a] (nM)	hERG K_i[b] (nM)
1c	H	H	0.10	360
5a		H	0.11	270
5b		F	0.09	420
5c		F	0.24	190
4	CO_2H	F	1.0	4800
5d		H	0.65	>6000
5e		F	0.61	5800
5f		F	1.2	>5000
5g		F	0.27	>6000

Values represent geometric means of three determinations.
[a] Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells.[10]
[b] Displacement of [^{35}S]-labelled MK-499 from the cloned channel expressed in HEK cells.[11]

A wide variety of substituents are tolerated at the 6-*exo* position (Table 2) showing that both large and polar groups give compounds of high hNK_1 affinity and can also modulate hERG affinity. It was not until intermediate **4** was profiled that it became apparent that acidic groups in this position maintain the good hNK_1 affinity, but have a marked effect on hERG.

The acidic heterocycles **5d** and **5e** show improved selectivity for hNK_1 over hERG, as does the acidic methyl acyl sulfonamide, **5f**. Replacement of the methyl with phenyl gave the highest affinity and the most selective compound from the series, the phenyl acyl sulfonamide, **5g**.

Compounds **1c**, **4**, **5a**, **5d**, and **5g** were tested in vivo in the gerbil foot-tap assay,[13] a measure of NK_1 activity in the brain. Compounds **1c** and **5a** showed activity, with an ID_{50} of 2.6 and 1.1 mg/kg, respectively. Unfortunately, the compounds bearing acidic substituents were inactive in this assay, indicating a potential lack of brain penetration.

A series of 8-azabicyclo[3.2.1]octane benzylamines has been explored leading to high affinity hNK_1 ligands. Inhibition of the hERG channel can be significantly reduced by substitution at the 6-position with acidic groups, whilst maintaining this high hNK_1 affinity. However, substitution with these acidic groups also abolishes in vivo activity.

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