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4,4-Disubstituted Cyclohexylamine NK_1 Receptor Antagonists I

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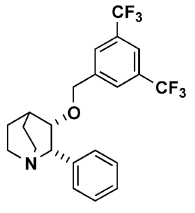
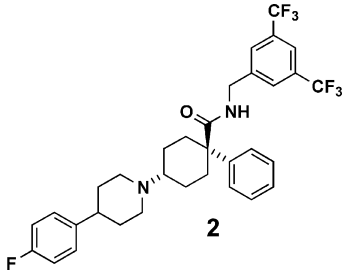
Abstract—A series of novel 4,4-disubstituted cyclohexylamine based NK_1 antagonists is described. The effect of changes to the C_1–C_4 relative stereochemistry on the cyclohexane ring and replacements for the flexible linker are discussed, leading to the identification of compounds with high affinity and good in vivo duration of action.

Substance P (SP) is a member of the tachykinin family of neuropeptides which binds selectively to the NK_1 receptor. The release of SP has been implicated in the pathogenesis of a wide range of disease conditions, including neurogenic inflammation, transmission of pain, emesis and depression.[1]



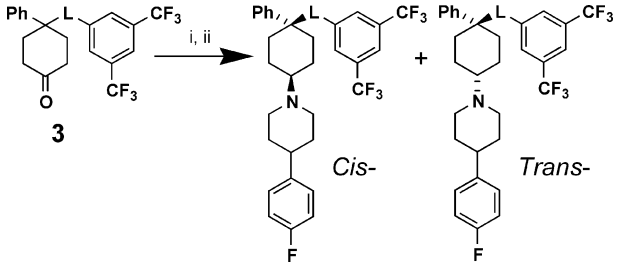
1



2

The key elements for high-affinity binding in known NK_1 antagonists (such as **1**, hNK_1 IC_{50} 0.2 nM) are two aromatic rings flanking a heteroatom.[2] Targeted screening has now identified the 1,1-disubstituted cyclohexane **2** as a high affinity ligand (hNK_1 IC_{50} 0.34 nM). Data (not shown) for binding of **2** to mutant receptors show that it occupies the same site as antagonists such as **1**. Comparison of the structures of quinuclidine **1** and cyclohexane **2** suggests that the *N*-[3,5-bis(trifluoromethyl)benzyl]phenylacetamide in **2** provides the key elements for binding to the NK_1 receptor; the cyclohexane (which would be predicted to adopt a chair conformation with the bulky C-1 substituent equatorial) serves to deliver these elements. This paper describes the initial work on optimisation of the *N*-[3,5-bis(trifluoromethyl)benzyl]phenylacetamide and the stereochemical requirements for NK_1 binding.

Compounds were synthesised from ketones **3** by reductive amination with 4-(4-fluorophenyl)piperidine. In most cases, the reactions were not stereoselective, leading to mixtures of isomers where the amine and linker L were either *cis*- or *trans*- to one another (Scheme 1).



3

Scheme 1. Reagents and conditions: (i) 4-(4-fluorophenyl)piperidine, $NaCN(BH_3)$, $ZnCl_2$, MeOH, rt or 4-(4-fluorophenyl)piperidine, $NaBH(OAc)_3$, 1,2-dichloroethane, rt; (ii) separate isomers.

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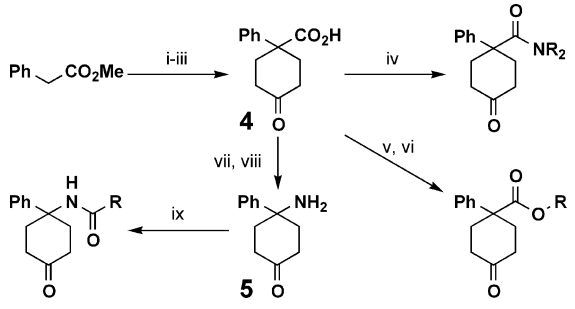
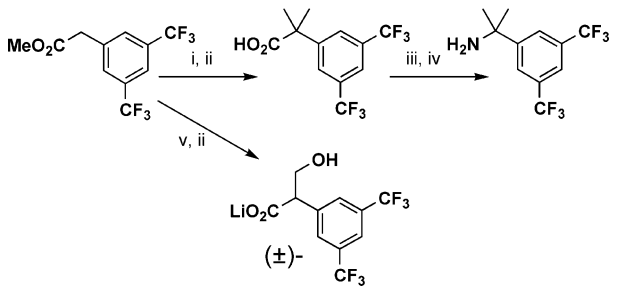
The syntheses of the ketones **3** with ester and amide linkers are shown in Scheme 2. Dialkylation of methyl phenylacetate with methyl acrylate, followed by in situ cyclisation and ester hydrolysis gave the key acid **4**. Curtius rearrangement of acid **4** with diphenylphosphoryl azide gave the amine **5**. Acid **4** and amine **5** were used to prepare amides and esters. The syntheses of key amine and acid components which are not commercially available are shown in Scheme 3.

Protection of ketone **6**, followed by DIBAL-H reduction, hydrolysis and further reduction gave the alcohol **7** (Scheme 4). Acylation with 3,5-bis(trifluoromethyl)-benzoyl chloride introduced the ester linker. Methylenation of this ester with dimethyl titanocene[3] followed by hydrogenation or hydroboration gave the corresponding α-methyl and α-hydroxymethyl ethers. Reductive amination of **6** followed by hydrogenation of the nitrile led to the amine **8** as a mixture of *cis*- and *trans*-isomers. Further reductive amination with 3,5-bis(trifluoromethyl)benzaldehyde and separation of isomers gave individual *cis*- and *trans*-secondary amines. Similarly, amine **8** was acylated with 3,5-bis(trifluoromethyl)benzoyl chloride and separated to give the corresponding amides.

Compounds without a heteroatom in the linker were prepared via a modified Julia coupling[4] of the sulfone **9** (Scheme 5).



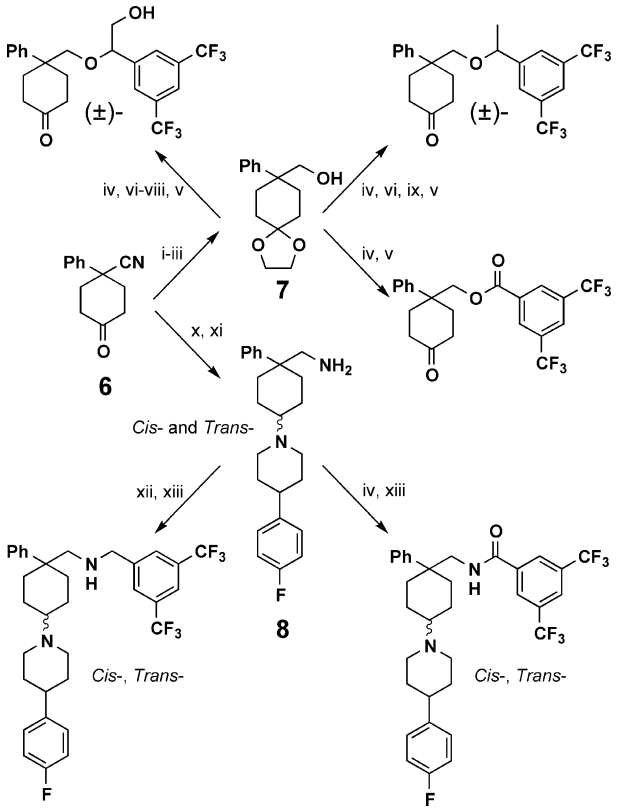
Scheme 2. Reagents and conditions: (i) methyl acrylate, NaH, DMF, 0 °C to rt; (ii) LiOH, MeOH, THF, H_2O, reflux; (iii) HCl, H_2O, rt; (iv) RNH_2, 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBT), Et_3N, DMF, rt or RNH_2, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl), Et_3N, CH_2Cl_2, rt; (v) $(COCl)_2$, DMF, $PhCH_3$, rt; (vi) ROH, DMAP, $PhCH_3$, reflux; (vii) $(PhO)_2PON_3$, Et_3N, $PhCH_3$, 90 °C; (viii) HCl, H_2O, reflux; (ix) RCO_2H, EDC, HOBT, Et_3N, DMF, rt.



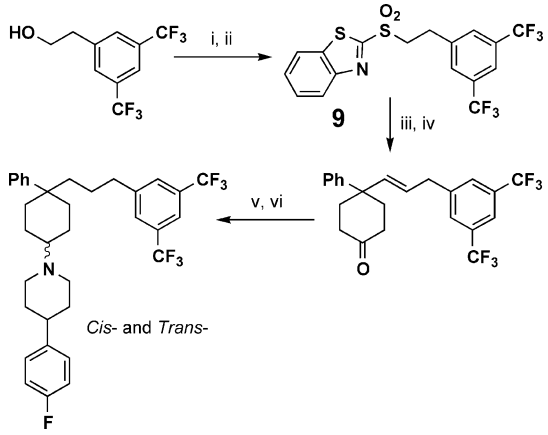
Scheme 3. Reagents and conditions: (i) NaH, MeI, DMF, rt; (ii) LiOH, THF, MeOH, H_2O, rt; (iii) $(PhO)_2PON_3$, Et_3N, $PhCH_3$, 90 °C; (iv) HCl, Et_2O, rt; (v) paraformaldehyde, $NaHCO_3$, DMSO, 45 °C.

Reduction of the phenylglycine adduct **10** gave the corresponding α-hydroxymethyl derivative (Scheme 6).

Table 1 summarises the effect of modifications to the amide linker of **2**. Throughout, *trans*-isomers have higher affinity than the corresponding *cis*-isomers. A

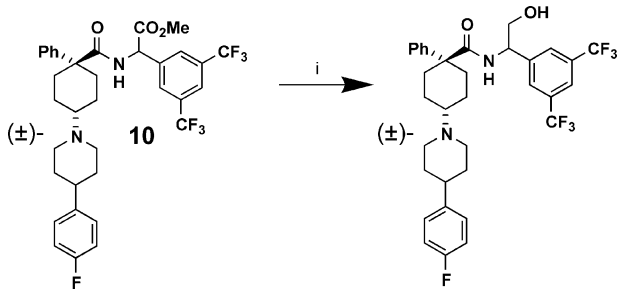


Scheme 4. Reagents and conditions: (i) $HOCH_2CH_2OH$, *p*TsOH, $PhCH_3$, reflux; (ii) DIBAL-H, $PhCH_3$, −78 °C; (iii) $NaBH_4$, EtOH, rt; (iv) 3,5-$(CF_3)_2$PhCOCl, CH_2Cl_2, rt; (v) HCl, H_2O, acetone, reflux; (vi) Cp_2TiMe_2, $PhCH_3$, 90 °C; (vii) BH_3·THF, THF, rt; (viii) H_2O_2, NaOH, THF, H_2O, rt; (ix) H_2, Pd/C, EtOAc, EtOH, rt; (x) 4-(4-fluorophenyl)piperidine, $NaCN(BH_3)$, $ZnCl_2$, MeOH, rt; (xi) H_2, Pd/C, HCl, MeOH, rt; (xii) 3,5-$(CF_3)_2$PhCHO, $NaCNBH_3$, $ZnCl_2$, MeOH, rt; (xiii) separate isomers.



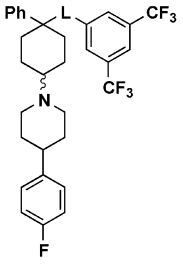
Scheme 5. Reagents and conditions: (i) 2,2′-dithiobis(benzothiazole), Bu_3P, THF, rt; (ii) OXONE®, Al_2O_3, $CHCl_3$, reflux; (iii) LiHMDS, 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxaldehyde, THF, −78 °C to rt; (iv) HCl, H_2O, acetone, reflux; (v) 4-(4-fluorophenyl)piperidine, $NaBH(OAc)_3$, 1,2-dichloroethane, rt; (vi) H_2, $Pd(OH)_2$, MeOH, rt.

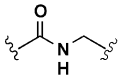
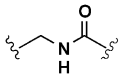
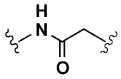
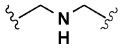
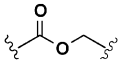
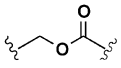
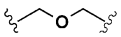
number of different linkers are tolerated, most notably the amides **2** and **15**, the amine **17** and ether **23**. The relatively poor affinity of the propyl linker **24** (hNK_1 IC_{50} 40 nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor.



Scheme 6. Reagents and conditions: (i) $LiBH_4$, THF, rt.

Table 1. Linker replacements



Compd	-L-	Stereochemistry	hNK_1 IC_{50} (nM)[a]
11		*cis*-	150±80
2		*trans*-	0.34±0.10
12		*cis*-	250±26
13		*trans*-	6.3±2.5
14		*cis*-	85±46
15		*trans*-	0.70±0.44
16		*cis*-	82±0
17		*trans*-	1.7±0.6
18		*cis*-	140±49
19		*trans*-	2.5±0.6
20		*cis*-	50% @ 1000
21		*trans*-	120±99
22		*cis*-	59±18
23		*trans*-	4.2±1.9
24		1:1 *cis*- and *trans*-	40±3

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean±SD ($n=3$).[5]

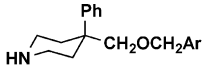
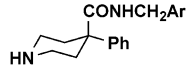
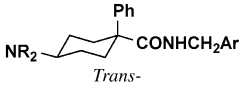
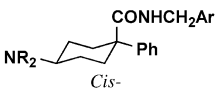
The large substituent at the 1-position of the cyclohexane locks the conformation of the ring, determining which of the *gem*-substituents is axial and which is equatorial.[6] Thus, the 1-substituent indirectly determines the conformation of the key parts of the molecule. The differences in affinity between the *cis*- and *trans*-isomers for the compounds in Table 1 demonstrates that the conformation in which the phenyl is axial and the linker is equatorial (*trans*-isomer) is necessary for good affinity. In contrast, the low affinity *cis*-isomers have the phenyl group equatorial and the linker axial.

This series has obvious similarities to the *gem*-piperidine series which has been extensively studied (Table 2).[7] In these compounds the geminal centre is free to invert, but NMR studies show that compounds with ether based linkers adopt a conformation in which the phenyl group is axial, giving good affinity (**25**, hNK_1 IC_{50} 0.95 nM). This is similar to the conformation adopted by the *trans*-cyclohexane compounds (**2**). In contrast, modelling studies on *gem*-piperidines with amide based linkers suggest that the preferred solution conformation has the phenyl group equatorial, resulting in low affinity (**26**, hNK_1 IC_{50} 130 nM). This is similar to the conformation adopted by the *cis*-cyclohexane compounds (**11**).

Introduction of methyl or hydroxymethyl substituents onto the lead amide and ether linkers is tolerated (Table 3). In the case of ether **28**, the hydroxymethyl substituent improves affinity. The amide **29** was separated by chiral HPLC (Chirobiotic V; MeOH/Et_3N/AcOH; 100:0.1:0.1; 1 mL/min; 260 nm) into its component enantiomers **29a** and **29b**. Interestingly, the difference in affinities for the two compounds is modest when compared to most other series of NK_1 antagonists where enantiomers show large differences in affinity.[8] It is also notable that achiral dimethyl substitution is well tolerated (**30**, **33**).

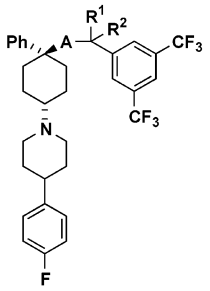
The in vivo CNS penetration of selected compounds was assessed in gerbils by their ability to block the foot-tapping response induced by central infusion of the NK_1-selective agonist GR73632.[9] In this assay, **2** is

Table 2. Effect of conformation

Compd	Structure[a]	hNK_1 IC_{50} (nM)[b]
25		0.95±0.41
26		130±80
2	 *Trans-*	0.34±0.10
11	 *Cis-*	150±80

[a]NR_2 = 4-(4-fluorophenyl)piperidinyl; Ar = 3,5-$(CF_3)_2$Ph.
[b]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean±SD ($n=3$).[5]

Table 3. Linker substitution



Compd	-A-	R^1	R^2	Stereo	hNK_1 IC_{50} (nM)[a]
23		H	H		4.2±1.9
27		CH_3	H	(±)-	5.3±2.5
28		CH_2OH	H	(±)-	0.75±0.21
2		H	H		0.34±0.10
29		CH_3	H	(±)-	0.77±0.11
29a		CH_3	H	(+)-	0.35±0.11
29b		CH_3	H	(−)-	1.5±0.7
30		CH_3	CH_3		0.62±0.23
31		CH_2OH	H	(±)-	0.29±0.09
15		H	H		0.70±0.44
32		CH_3	H	(±)-	0.63±0.45
33		CH_3	CH_3		0.49±0.24
34		CH_2OH	H	(±)-	0.44±0.11

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean±SD ($n=3$).[5]

moderately active when the NK_1 agonist challenge immediately follows dosing (ID_{50} 1.9 mg/kg iv), but has poor duration of action (15% inhibition at 3 mg/kg iv when the NK_1 agonist challenge is given 2 h after dosing). The α-methyl amide **32** shows the most promising in vivo profile; it has affinity similar to **2** and shows similar blockade of foot-tapping immediately following dosing (ID_{50} 1.7 mg/kg iv). However, activity improves after 2 h (ID_{50} 0.6 mg/kg iv), suggesting slow brain penetration, and is maintained to 24 h (ID_{50} 1.8 mg/kg iv).

In conclusion, we have explored the effect of changes to C_1–C_4 relative stereochemistry on the cyclohexane ring and replacements for the amide linker of a new series of high affinity NK_1 antagonists based on 4,4-disubstituted cyclohexylamine. Throughout, there is a clear preference for *trans*- relative stereochemistry across the cyclohexane ring, which is consistent with the results for the related *gem*-piperidine series. A heteroatom in the linking chain is beneficial, although this can be as part of either an amide or an ether. Substitution on the side chain with methyl, dimethyl or hydroxymethyl groups is well tolerated. Combining these features gives a range of compounds with high affinity. The α-methyl amide **32** also shows long duration of action in an animal model of central NK_1 activity.

References and Notes

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6. ^{1}H NMR experiments (400 MHz, CD_3OD) show that, in both isomers, the cyclohexyl ring adopts a chair conformation with the C-1 hydrogen axial. In *cis*-isomers (such as **11**), NOE's are seen from the *o*-hydrogens of the 4-phenyl group to both axial and equatorial C-3 hydrogens, indicating that the 4-phenyl group is equatorial. In *trans*-isomers (such as **2**), NOE's are seen from the *o*-hydrogens of the 4-phenyl group to the equatorial C-3 hydrogens and to the axial C-2 hydrogens, indicating that the 4-phenyl group is axial.
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8. For example, the 2*R*,3*R* enantiomer of **1** displays a 1000-fold loss in affinity.[2]
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