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High Affinity Phenylglycinol-Based NK_1 Receptor Antagonists

A.P. Owens*, T. Harrison, J.D. Moseley, C.J. Swain, S. Sadowski§, M.A. Cascieri§

Department of Medicinal Chemistry, Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, U.K.

§Department of Molecular Pharmacology and Biochemistry, Merck Research Laboratories, Rahway, New Jersey 07065

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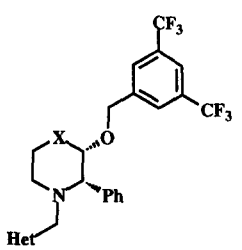
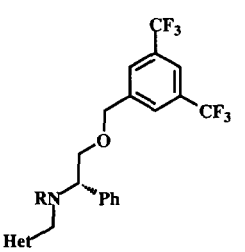
Abstract: Heterocyclic replacements for the carboxamido group of the previously disclosed phenylglycinol-based human NK_1 (hNK_1) receptor antagonists have been investigated, ultimately leading to acyclic compounds with sub-nanomolar affinity for the hNK_1 receptor.

It has recently been shown that certain heterocyclic moieties can be introduced into piperidine- or morpholine-derived human NK_1 (hNK_1) receptor antagonists[1,2] resulting in compounds of type **1** which possess increased potency, both *in vitro* and *in vivo*, over previous lead structures. In this publication we investigate the effect of the introduction of certain of these heterocycles into the phenylglycinol-derived acyclic series of NK_1 receptor antagonist of type **3**[3] as replacements for the potentially metabolically labile carboxamido moiety to obtain compounds of type **2**. The heterocycles chosen for this initial investigation were triazole, triazolinone and tetrazole. In addition, the effects of introducing alternative N-alkyl substituents and of alternative benzyl ether substitution patterns were investigated.



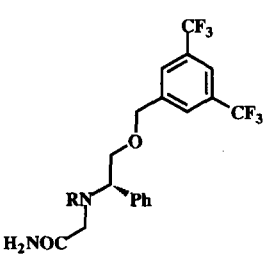
X = O, CH_2

1



2

R = H or Me



3

The triazole moiety was introduced by synthesis of the (chloromethyl)amidrazone **6** (Scheme 1) which was coupled with enantiomerically pure **11a**[3] at 40°C with K_2CO_3 in DMF, followed by cyclization at 140°C to give **12a** (Scheme 2). The tertiary amine derivative **12b** was prepared by BOC protection of **11a** followed by methylation with NaH/MeI, and subsequent deprotection with TFA to give **11b** which was alkylated with **6** followed by cyclization, as previously described (Scheme 2). The triazolinone moiety was introduced in a similar fashion to the triazole by synthesis of **7** (Scheme 1) which was coupled with **11a** or **11b**, followed by cyclization to give the secondary amine derivative **13a** and the tertiary amine derivative **13b** (Scheme 2).

Fax:+44 1279 440390; e-mail: andrew_owens@merck.com

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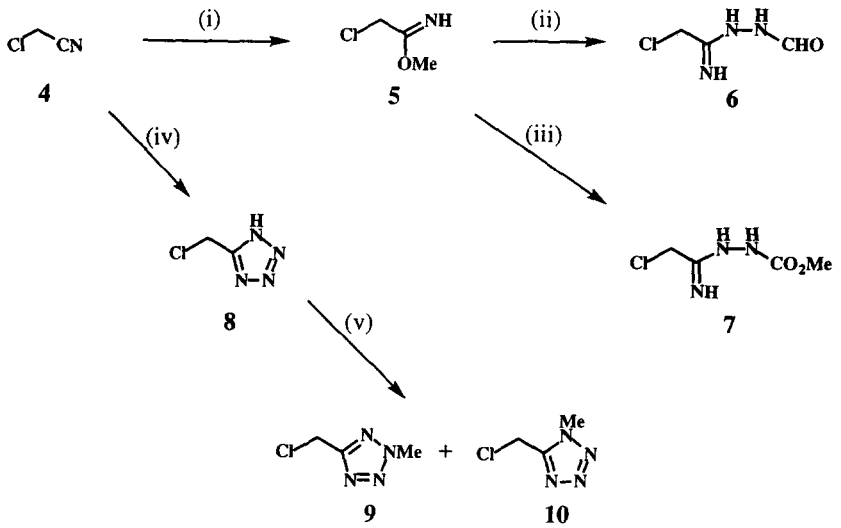
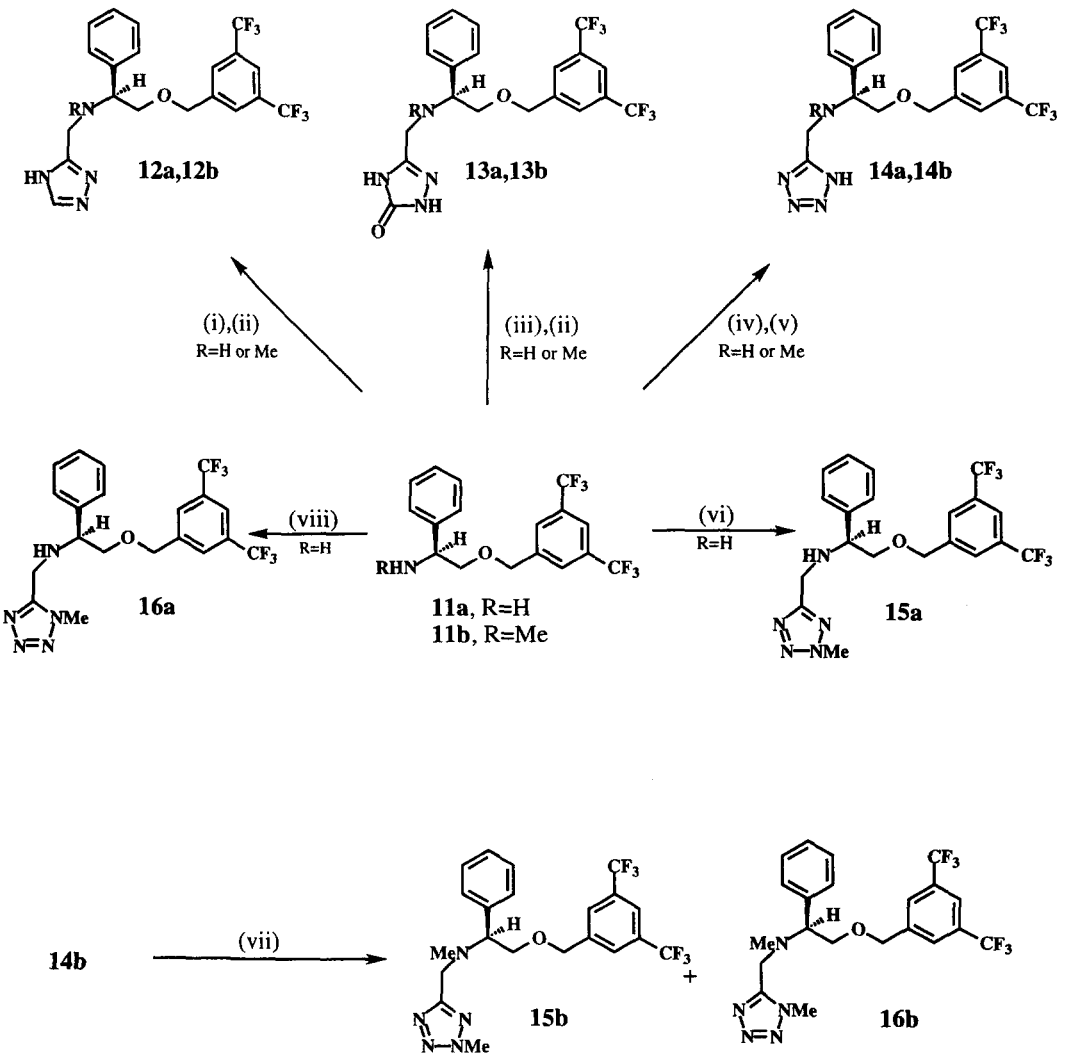
The tetrazole containing compounds (**14-16a,b**) were formed by various methods. The unsubstituted tetrazoles **14a** and **14b** were formed by alkylation of **11a** and **11b** respectively with bromoacetonitrile in DMF in the presence of K_2CO_3, followed by cycloaddition with sodium azide in 1-methyl-2-pyrrolidinone (Scheme 2). Compound **14b** was subsequently alkylated with diazomethane in ether to give the two isomers **15b** and **16b** which were separated by flash silica gel chromatography (Scheme 2). The secondary amines **15a** and **16a** were formed by alkylation of **11a** with the N-methylated (chloromethyl)tetrazole isomers **9** and **10** (Scheme 2) which were made by diazomethane methylation of **8** derived from reacting chloroacetonitrile with $Al(N_3)_3$ in THF at reflux (Scheme 1).[4]



Reagents: (i) NaOMe, MeOH; (ii) CH_3CO_2H, NH_2NHCHO; (iii) CH_3CO_2H, NH_2NHCO_2Me; (iv) $AlCl_3$, NaN_3, THF, reflux; (v) CH_2N_2, Et_2O, 0°C.

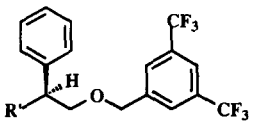
Scheme 1

Table 1 summarises the effects of heterocyclic replacements of the carboxamido group of **3** on the hNK_1 binding affinity. The N-Me group, resulting in series **b**, was included as it had previously been shown to have a beneficial effect in the phenylglycinol-based series on hNK_1 binding affinity.[3] It can be seen that introduction of either the triazole or the triazolinone heterocycles into the secondary amine series **12a** and **13a** is tolerated and gives a slight improvement in affinity for the hNK_1 receptor over the unsubstituted compound **11a**, whereas introduction of the tetrazole moiety to give **14a**, shows no improvement in binding affinity. Removing the acidity of the tetrazole, by the introduction of a methyl group on the ring, compounds **15a** and**16a**, again gives no improvement in binding affinity. N-Methylation to give the tertiary amines (series **b**) has a slight detrimental effect on the affinity of the tetrazole **14b**, but little effect on **15b** and **16b**, however N-methylation results in a 4-6 fold improvement in affinity in the triazole and triazolinone cases **12b** and **13b**. Compound **13b** has a 30 fold improved receptor affinity compared to the original unsubstituted compound **11a**.



Reagents: (i) **6**, K_2CO_3, DMF, 40°C; (ii) 140°C; (iii) **7**, K_2CO_3, DMF, 40°C; (iv) $BrCH_2CN$, K_2CO_3, DMF, 60°C; (v) NaN_3, 1-methyl-2-pyrrolidinone, $Et_3N.HCl$; (vi) **9**, K_2CO_3, DMF; (vii) CH_2N_2, Et_2O, 0°C; (viii) **10**, K_2CO_3, DMF

Scheme 2



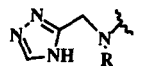
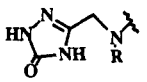
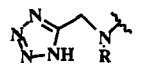
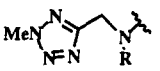
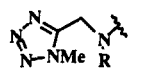
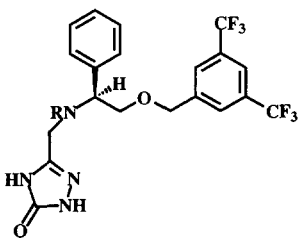
Cpd	R'	$hNK_1 IC_{50}(nM)$[5] R=H a	R=Me b
11	H_2N-	13 ± 4	-
3	H_2NCOCH_2RN-	8 ± 1	5.8 ± 2.2
12		5.0 ± 2.0	1.4 ± 0.3
13		2.4 ± 0.4	0.43 ± 0.12
14		23 ± 6	70 ± 13
15		15 ± 3	16 ± 1
16		10 ± 5	13 ± 0

Table 1

Compound **13b** was shown to display excellent selectivity over other neurokinin receptors (NK_2, NK_3 >1mM) whilst maintaining low affinity binding to the calcium channel (IC_{50}>1mM).[6] Compound **13b** has also a modest oral bioavailability of 16% in rat (C_{max} = 97ng/ml, T_{max} = 30min, plasma elimination half-life = 0.8h, steady state volume of distribution = 3.5 l/kg after *iv* dosing; *iv* and *po* dosing at 3mg/kg). Further studies on this compound in rat liver microsomes showed N-demethylation to be the major metabolic pathway *in vitro*. Replacement of the N-methyl group with less metabolically labile groups could be a method for improving bioavailability.

The observation that the inclusion of the N-methyl group in compound **13b** resulted in an improved affinity for the hNK_1 receptor was further investigated by the introduction of larger N-alkyl groups. Ethyl and n-propyl groups were introduced following sodium hydride deprotonation of BOC-protected **11a** in DMF, reaction with the appropriate alkyl halide followed by BOC deprotection using TFA. The triazolinone was then introduced as previously described to give compounds **17** and **18** (Table 2).

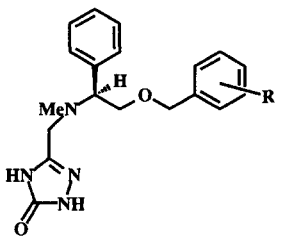


Cpd	R	$hNK_1IC_{50}(nM)^5$
13a	H	2.4 ± 0.4
13b	Me	0.43 ± 0.12
17	Et	0.8 ± 0.5
18	^nPr	2.0 ±0.5

Table 2

It can be seen that although N-ethylation and N-propylation are tolerated, affinity for the hNK_1 receptor is gradually reduced as the size of the alkyl group is increased.

Replacements for the 3,5-bis(trifluoromethyl)phenyl group of compound **13b** were then investigated using a previously described route.[3] The 3,5 disubstitution pattern was retained as this had been shown previously to be optimal.[7] Results of this investigation are shown in Table 3. The 3,5-dichloro substituted compound **19** and the 3-methyl, 5-chloro substituted compound **20** show reduced affinities compared to **13b**, whereas the 3-^{t}butyl, 5-methyl substitution pattern resulted in compound **21** which has an equivalent potency to **13b**.



Cpd	R	$hNK_1IC_{50}(nM)^5$
13b	3,5 bis CF_3	0.43 ± 0.12
19	3,5 Di Cl	1.5 ± 0.5
20	3Me, 5Cl	2.2 ± 0.7
21	3^{t}Bu, 5Me	0.42 ± 0.11

Table 3

In summary the triazole and triazolinone heterocycles have been shown to be acceptable replacements for the carboxamido moiety of compound **3**. When this modification is combined with N-methylation and appropriate benzyl substitution, the resulting compounds have sub-nanomolar affinity for the hNK_1 receptor.

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