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Discovery of potent, balanced and orally active dual NK_1/NK_3 receptor ligands

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ABSTRACT

During a program directed at selective NK_1 receptor antagonists, we serendipitously discovered an NK_1 receptor ligand with additional affinity for the NK_3 receptor. Recognising an opportunity for a drug discovery program aiming for dual NK_1/NK_3 receptor antagonists, we prepared a series of analogues from a novel, versatile building block. From this series emerged compounds with high and balanced affinities for the NK_1 and the NK_3 receptors. Typical representatives of this series were active in the gerbil foot tapping assay after oral administration.

Schizophrenia affects about 1% of the population and is characterised by hallucinations and delusions (positive symptoms) as well as anhedonia and social withdrawal (negative symptoms).[1] The introduction of the first antipsychotic drug, chlorpromazine, in 1952 revolutionised the treatment of the disease.[2] However, it soon became apparent that this and other antipsychotic drugs had serious side effects, a high non-responder rate, and did not substantially improve negative symptoms. Despite 50 years of research, a therapy that alleviates positive as well as negative symptoms, and that has a benign side effect profile, remains elusive.[3]

The neurokinin (NK) receptors 1–3 are the receptors for the three main mammalian tachykinins, substance P, neurokinin A and neurokinin B, and are present in brain areas which regulate mood and emotion. The NK receptors have been evaluated preclinically as potential targets for the treatment of psychiatric disorders, and several NK receptor ligands are in clinical trials for a variety of indications.[4]

The NK_3 receptor antagonists osanetant and talnetant are novel investigational drugs, which improved, in clinical phase II studies, the psychotic (positive) symptoms in schizophrenic patients, but had little effect on negative symptoms.[5] The NK_1 receptor antagonists aprepitant, L-759274, and CP-122,721 reduced symptoms of depression in phase II studies,[6] which may indicate their potential efficacy in treating the negative symptoms of schizophrenia. Although the antidepressant effect of aprepitant was not substantiated in a phase III trial,[7] several NK_1 receptor antagonists are currently in clinical development for depression[8] and other psychiatric disorders, such as anxiety.[4] Selective NK_3 and NK_1 receptor antagonists did not show the severe side effects of established antipsychotic drugs. Together, these results provide a rationale for dual NK_1/NK_3 receptor antagonists as a novel treatment for schizophrenia, addressing both positive and negative symptoms, while having an improved side effect profile.[9]

During our NK_1 receptor antagonist project,[10] we discovered compound **1** (Fig. 1, Table 1) with high human (h)NK_1 receptor affinity, and 10-fold lower affinity for the human (h)NK_3 receptor. We

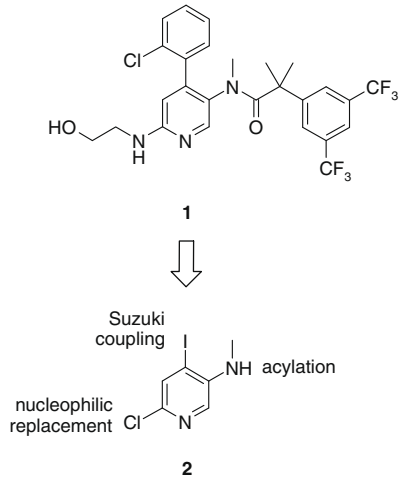

Figure 1. A versatile, modular approach for the synthesis of analogues of **1** was based on building block **2**.

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Table 1
Dual affinities of compounds **10** for the hNK_1 and hNK_3 receptors

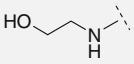
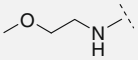
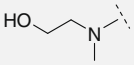
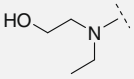
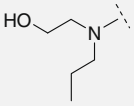
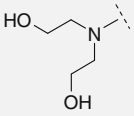
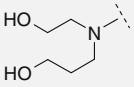
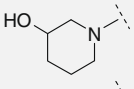
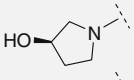
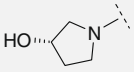
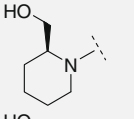
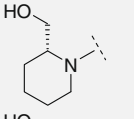
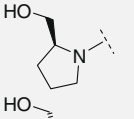
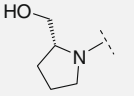
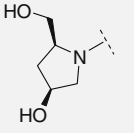
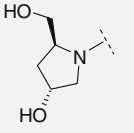
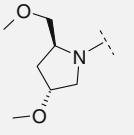
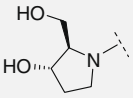
Compd	R_2N =	K_i[a] (hNK_1, nM)	K_i[b] (hNK_3, nM)
1		1.12	11.36
10a		3.05	93.25
10b		0.78	2.91
10c		3.37	12.22
10d		2.24	5.40
10e		1.15	0.91
10f		1.38	0.95
10g		1.72	15.10
10h		2.62	6.87
10i		0.86	8.38
10j		11.10	7.72
10k		2.27	29.73
10l		1.00	0.74
10m		1.58	7.27
10n		0.51	1.48
10o		0.61	1.12
10p		0.91	29.79

Table 1 (*continued*)

Compd	R_2N =	K_i[a] (hNK_1, nM)	K_i[b] (hNK_3, nM)
10q		1.58	0.91

Compounds **10e**,**f**,**l**,**n**,**o** emerged as particularly potent and balanced dual ligands. Determination of radioligand binding affinity (K_i) of (a) human NK_1 receptor using [^{3}H]substance P, in transiently transfected CHO-cell membranes, or (b) human NK_3 receptor, using [^{3}H]SR142801, in transiently transfected HEK-293-EBNA cells. Data represent n = 2–5 determinations in duplicate; SD <0.2 pK_i.

hypothesised that the hydroxyethylamine substituent, which is a unique feature of compound **1**, is needed for the NK_3 receptor affinity. We recognised this finding as an opportunity for a medicinal chemistry program towards dual NK_1/NK_3 receptor antagonists for the treatment of schizophrenia. To provide a lead structure with a balanced NK_1/NK_3 receptor affinity profile for such a program, we decided to synthesise analogues of **1**, in which the hydroxyethylamine unit is replaced by similar substituents. An X-ray crystal structure analysis[11] (Fig. 2) revealed that the N–CH_2–CH_2–OH unit adopts the *gauche* conformation which is typical for such motifs, if the nitrogen is bound to an sp^2 carbon,[12] and a *syn* orientation with respect to the pyridine N; alternative substituents should have a similar distance and directionality between the nitrogen and the hydroxy function.

The original synthesis leading to **1** introduced the N-substituent in an early step; moreover, the compound was available only in low quantities. To provide a more practical and versatile synthetic access, we envisaged **2** (Fig. 1) as a central building block for a modular approach.

Building block **2** was prepared as outlined in Scheme 1. The preparation of **5** via **4** from commercially available **3** proceeded uneventfully. Attempts to *N*-methylate **5**, followed by an iodination to give **7** failed; however this problem could be circumvented by a reversal of these synthetic steps. Thus, iodination of **5** gave **6** in reasonable yields, which could then be methylated to yield **7**. Deprotection under standard conditions provided the desired building block, **2**. This procedure was scalable to multi-gram

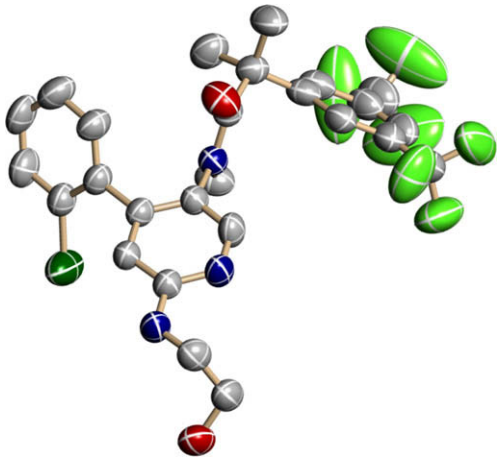
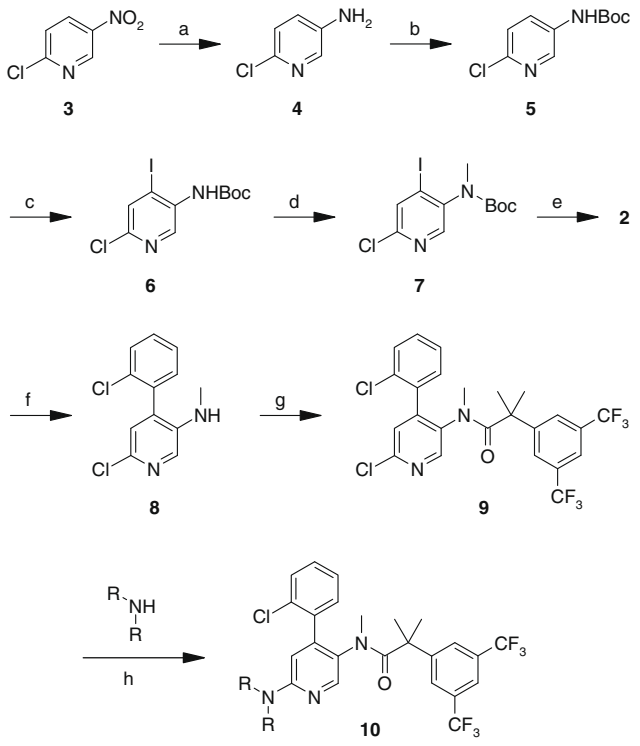


Figure 2. X-ray crystal structure of **1**.[11] The N–CH_2–CH_2–OH unit adopts a gauche conformation.



Scheme 1. Preparation of building block **2**, and final products **10**. Reagents and conditions: (a) Fe, HCl, H_2O, 30 min, 90 °C, 70%; (b) NaHMDS, Boc_2O, THF, 2 h, rt, 81%; (c) BuLi, TMEDA, I_2, Et_2O, 16 h, rt, 50%; (d) NaH, MeI, DMF, 3.5 h, −10 °C, quant.; (e) TFA, CH_2Cl_2, 2 h, rt, quant.; (f) 2-chlorophenylboronic acid, $Pd(OAc)_2$, PPh_3, 2 N Na_2CO_3, DME, 80 °C, 2 h, 89%; (g) KHMDS, add 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride,[13] THF, rt, 30 min, 80%; (h) typical conditions: R_2NH/DMSO = 1:1, 130 °C, 1–3 d.[14]

amounts. Although the use of building block **2** would allow for a derivatisation of three vectors (Fig. 1), we decided initially to focus on the amine substituent, which was likely responsible for the NK_3 receptor affinity of **1**. To this end, we converted **2** via **8** into the advanced building block **9** by a Suzuki coupling with a sterically hindered *ortho*-substituted arylboronic acid, followed by an acylation. Both steps proceeded in good overall yields. The 2-chloropyridine motif in **9** was found to be quite unreactive towards amines, and high temperatures, a large excess of amines, and long reaction times were necessary to obtain the desired target compounds, **10**.[14] Nevertheless, this final step (Scheme 1, h) was well amenable to parallel chemistry, and numerous end-products **10** were obtained from **9** and a variety of amines.[15]

Affinities of compounds **10a–q** for the hNK_1 and the hNK_3 receptors were determined using radioligand binding assays;[14] the results for selected compounds are presented in Table 1. Almost all compounds had low- to sub-nanomolar affinities for the NK_1 receptor. A comparison of **1** with **10a** demonstrated that the methylation of the hydroxyl function leads to a ~eightfold reduction in NK_3 receptor affinity, which supported our working hypothesis, that a free hydroxyl group is needed for high NK_3 affinity. The introduction of an *N*-methyl substituent improved the NK_3 receptor affinity (**10b** compared to **1**). Homologues (**10c** and **10d**) had no further increased NK_3 affinities, but the introduction of a second hydroxyl function into this side chain led to potent and balanced NK_1/NK_3 receptor ligands (**10e** and **10f**). The modulation of the receptor binding profile by conformational locking was further explored with cyclic amine substituents. The 'endocyclic' incorporation of the ethylene linker into a piperidine or a pyrrolidine ring led to compounds with retained affinities for both receptors (**10g–i** compared to **1**). 'Exocyclic' linker incorporation resulted in **10j–m**,

Table 2
Inhibition of NK_1 agonist (GR73632)-induced foot tapping behaviour in Mongolian gerbils after oral pretreatment of animals with **1** and **10** 2 h prior to intracerebroventricular (icv) administration of the agonist[15]

Compd	ID_{50} (mg/kg, po)	Single dose, 10 mg/kg, po
1	1.0	
10c		100% inhibition
10d		100% inhibition
10n	1.3	
10o	1.1	

out of which one compound, **10l**, had a greatly improved NK_3 receptor affinity and a balanced profile. Interestingly, the N–C–C–OH conformation of such 'exocyclic' derivatives overlaps with the conformation observed in the X-ray analysis of **1** (Fig. 2), and **10l** may thus be regarded as a conformationally restricted analogue of **1**. Compound **10l** was further modified by the introduction of additional OH groups, which was postulated to further improve the NK_3 receptor affinity (see above). This led to **10n** and **10o**, which may be regarded as locked analogues of **10e**. Although the NK_3 receptor affinity of **10n** and **10o** was not improved in comparison to **10e** or **10l**, both compounds had high and balanced NK_1/NK_3 receptor affinities. A comparison of **10p** and **10o** demonstrates that a free hydroxyl group is still needed for high NK_3 receptor affinity in these compounds: methylation of the hydroxyl groups of **10o** leads to a ~15-fold reduction of NK_3 receptor affinity. Finally, **10q** was found to be another bis-hydroxylated analogue of **10l** with a well-balanced affinity ratio. Formally, **10q** is a ring-closed analogue of **10e**, although binding conformations and the spacial orientation of the hydroxyl groups may be different. Out of these and many similar compounds, **10e,f,l,n,o** emerged as being best in terms of high and balanced affinities for the hNK_1 and the hNK_3 receptors.

In a preliminary evaluation of in vivo properties, **10n** and **10o** dose-dependently inhibited NK_1 agonist (GR73632)-induced foot tapping behaviour in gerbils[16] with an ID_{50} of 1.3 and 1.1 mg/kg, respectively, indicating NK_1 antagonistic activity after oral administration (Table 2). Similarly, **10c** and **10d** led to a complete blockade of NK_1 agonist induced foot tapping after 10 mg/kg (single dose po). These results demonstrate that the molecular properties of these compounds are suitable to reach the intended target in the CNS after oral administration, and to elicit the expected pharmacodynamic response with a reasonable dose.

In conclusion, the serendipitously discovered dual NK_1/NK_3 receptor ligand **1** was optimised into a lead series represented by **10e,f,l,o** with high and balanced affinities for the NK_1 and NK_3 receptors. Compounds **10n** and **10o** elicited a dose-dependent pharmacodynamic response in vivo. A novel synthetic access to compounds **10** via a versatile building block **2** was developed, and a preliminary SAR for NK_3 receptor affinity was elucidated. These results provided the basis for a lead optimisation program towards a novel antipsychotic treatment.

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