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Rational design of novel pyrrolidine derivatives as orally active neurokinin-3 receptor antagonists

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ABSTRACT

The rational design of a novel series of pyrrolidine derivatives as neurokinin-3 receptor antagonists is reported starting from a selective neurokinin-1 receptor antagonist. Typical representatives in this series showed in vivo efficacy after oral administration in a NK3 mediated functional assay. This series of NK3 antagonists shows promise to deliver a novel antipsychotic.

Schizophrenia is a severe, disabling, lifelong disorder that affects 1% of the population and is characterized by positive symptoms (such as hallucinations, delusions, and paranoia), negative symptoms (such as flattened affect and apathy) and cognitive impairment (e.g., deficits in working memory and attention).[1] There is evidence that hyperactivity of the mesolimbic dopaminergic pathway is associated with positive symptoms of the disease, whereas hypoactivity of the mesocortical dopaminergic pathway is associated with negative and cognitive symptoms. Moreover, hypoactivity of the corticolimbic glutamatergic system may contribute to the underlying pathophysiology of this disorder. Most currently approved antipsychotic drugs reduce dopaminergic function by D_2 receptor blockade leading to the alleviation of positive symptoms, but the induction of side effects such as extrapyramidal symptoms (EPS) and elevated prolactin levels.

Neurokinin $(NK)_3$ receptors are G-protein-coupled receptors which have been shown to modulate monaminergic systems within regions of the brain implicated in schizophrenia.[2] Preclinical data suggest that NK_3 receptor antagonists have the potential to attenuate subcortical dopaminergic output and to enhance cortical dopaminergic output, which would be predicted to have beneficial effects in the treatment of positive and cognitive symptoms of schizophrenia, respectively. The selective NK_3 receptor antagonist osanetant (SR 142801; Fig. 1) was administered to hospitalized schizophrenic patients for 6 weeks at 200 mg/day in a double-blind placebo controlled clinical Phase 2 trial and significantly improved positive symptoms, with no difference in magnitude from haloperidol.[3] A structurally distinct compound, talnetant (SB223412; Fig. 1), has also been shown to improve positive symptoms as well as cognition in a sub-set of schizophrenic patients with high plasma exposure following 6 weeks treatment at 200 mg/day in a double-blind, placebo-controlled trial.[4] Both compounds had an improved side effect profile compared to existing antipsychotics. More recently, AZD-2624 (Fig. 1) structurally related to talnetant, failed to show efficacy in hospitalized schizophrenic patients administered 40 mg/day for 4 weeks.[5]

The development of all three compounds has been discontinued: osanetant possibly due to poor pharmacokinetic profile (high clearance and low oral bioavailability), talnetant likely due to a

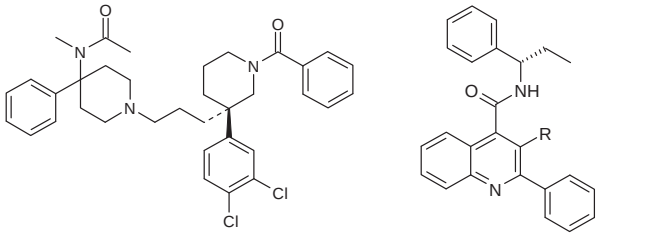

Figure 1. Three phase II compounds (osanetant, talnetant, AZD-2624).

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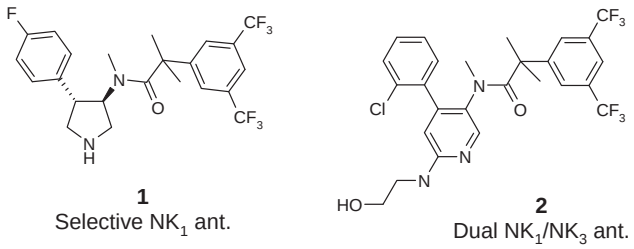


Figure 2. Selective NK_1 **1** and dual NK_1/NK_3 **2** antagonists.

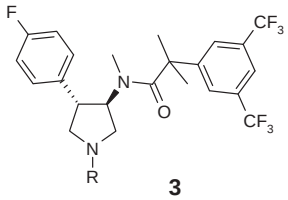
poor brain penetration and formulation issues; AZD-2624 due to lack of efficacy in schizophrenia. Therefore, in our novel NK_3 antagonist program, we aimed to discover highly potent compounds with an improve brain penetration, a high oral bioavailability and good physico-chemical properties.

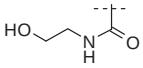
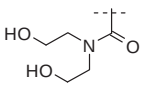
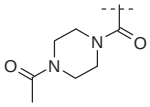
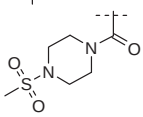
During a former NK_1 project, we discovered compound (±)-**1** (Fig. 2, Table 1) as a highly potent and selective NK_1 receptor antagonist (inactive at the NK_3 receptor). More recently, we reported the discovery of a potent and dual NK_1/NK_3 ligand **2** (Fig. 2).[6]

Based on the alignment between (±)-**1** and **2** (Fig. 3), we hypothesized that the introduction of a hydrogen bond acceptor bearing side-chain on the nitrogen of the pyrrolidine will allow us to pick up NK_3 affinity.

In order to confirm this hypothesis, several pyrrolidine derivatives containing a side-chain with a hydrogen bond acceptor moiety (±)-**3a–d** were prepared (Table 1).[7] Gratifyingly, these derivatives exhibit a decent affinity at NK_3 receptor and were therefore considered as a good entry point towards a novel class of NK_3 antagonists. In contrast, (±)-**3e** containing a benzyl side-chain was inactive.

Table 1
Affinities of compounds (±)-**1** and (±)-**3** for the hNK_1 and hNK_3 receptors



Compd	R =	K_i[a] (hNK_1, nM)	K_i[b] (hNK_3, nM)
(±)-**1**	H	0.9	Inactive
(±)-**3a**		0.6	298
(±)-**3b**		1.1	192
(±)-**3c**		1.4	370
(±)-**3d**		2.1	165
(±)-**3e**		No data	Inactive

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.

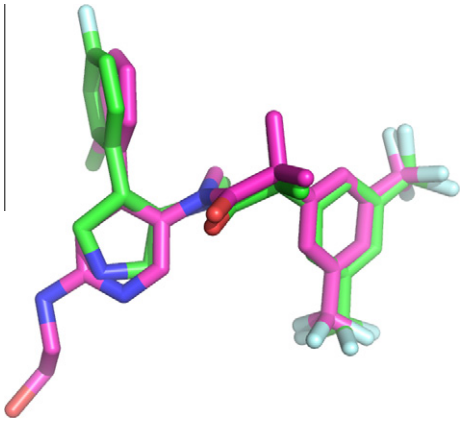
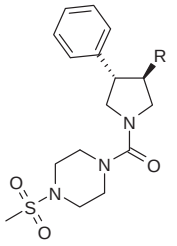
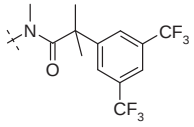
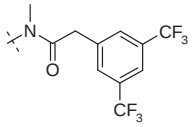
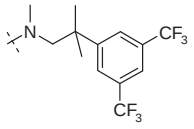
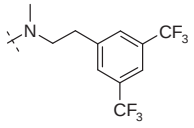
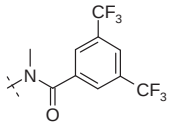
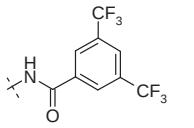
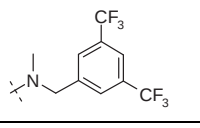


Figure 3. Alignment between **1** (green) and **2** (magenta).

Table 2
Affinities of compounds (±)-**4** for the hNK_3 receptors



Compd	R =	K_i[a] (hNK_3, nM)
(±)-**4a**		160
(±)-**4b**		Inactive
(±)-**4c**		Inactive
(±)-**4d**		Inactive
(±)-**4e**		Inactive
(±)-**4f**		Inactive
(±)-**4g**		1300

[a] Determination of radioligand binding affinity (K_i) human NK_3 receptor, using [^{3}H]SR142801, in transiently transfected HEK-293-EBNA cells.

Nevertheless, further development of a compound from the sub-class (±)-**3** was hampered by a high lipophilicity and a poor aqueous solubility.

To address these physico-chemical issues, we thought that the replacement of the (3,5-bis-trifluoromethyl-phenyl)-*N*-methyl-isobutyramide tail was mandatory. Several alternative tails, containing a two or three atom linker were therefore evaluated (Table 2). Removal of the *gem*-dimethyl substituent led to a complete loss of affinity ((±)-**4b**). The analogous phenethyl amines (±)-**4c** and (±)-**4d** were inactives as well as the two-atom linker amides (±)-**4e** and (±)-**4g**. More surprisingly the compound containing a benzyl amine fragment ((±)-**4g**) was the only one which displayed a moderate but promising affinity in the low micromolar.

Encouraged by these results, we then examined the influence of the substitution pattern of both phenyl rings from (±)-**4g** (Fig. 4). First, a screening of alternative benzylic amine fragments showed that the 3,5-bis-trifluoromethyl substituents from (±)-**4g** could be advantageously replaced by a 3-fluoro, 4-trifluoromethyl, which drastically increased (14-fold) the NK_3 receptor affinity (**5**, Fig. 4, K_i hNK_3: 91 nM). Second, we evaluated the substitution pattern of the phenyl ring directly attach on the pyrrolidine. In analogy to osanetant (Fig. 1), 3,4-bis-chloro substitution was the best as a further boost (13-fold) of the NK_3 affinity was achieved ((±)-**6**, Fig. 4, K_i hNK_3: 7 nM). The optimal substitution of both phenyl rings had a profound impact on the NK_3 affinity as an increase from 1300 nM for (±)-**4g** to 7 nM for (±)-**6** was achieved. However, the physico-chemical properties of (±)-**6** needed to be optimized, in particular its poor aqueous solubility and high lipophilicity (solubility: <1 μg/mL; Log *D*: >4). This was addressed by the replacement of the methyl sulfone by a dimethyl-amine ethyl moiety. For instance, (+)-**7** (Fig. 4) was highly potent at the NK_3 receptor (K_i hNK_3: 3 nM), had a lipophilicity in a good range for a CNS drug (Log *D*: 2.9) and a high aqueous solubility (495 μg/mL). The blood brain barrier permeability of (+)-**7** was assessed in a rat pharmacokinetic study and found to be high (brain/plasma ratio: ~2) in sharp contrast to talnetant (brain/plasma ratio: ~0.1).

The overall profile of (+)-**7** was suitable for a in vivo evaluation in gerbils.[8] Oral administration of (+)-**7** at 30 mg/kg significantly reverse the senktide-induced locomotor activity in gerbils with a similar potency as the positive control osanetant at 100 mg/kg

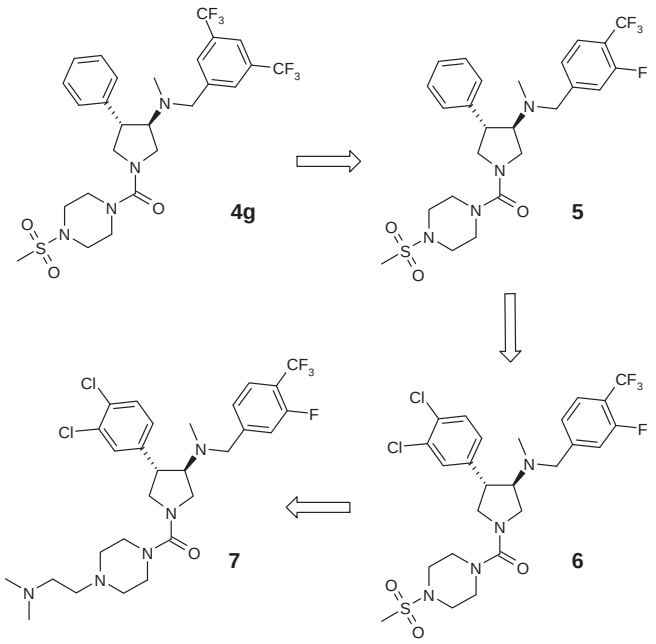


Figure 4. Sequential optimization of hNK_3 affinity and solubility.

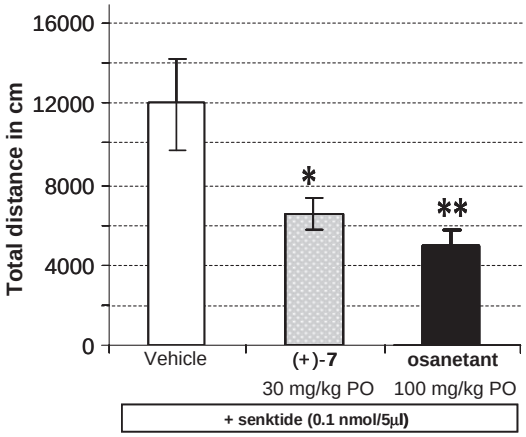
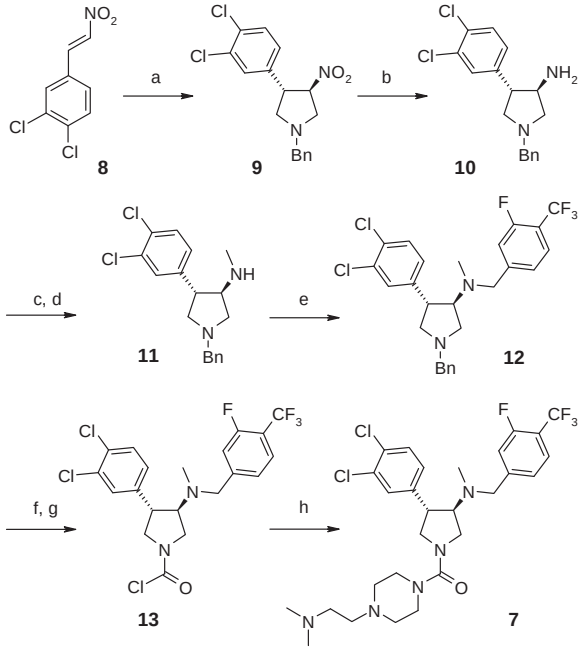


Figure 5. Reversal of the senktide-induced locomotor activity in gerbils after oral pretreatment of animals with test compounds prior to intracerebroventricular (icv) administration of the agonist. Statistical significance versus vehicle group: * p <0.05; ** p <0.01.

(Fig. 5). The brain/plasma ratio in gerbils was ~1.6, which is consistent with the data obtained in the rat PK study.

(+)-**7** was synthesized as outlined in Scheme 1.[9] A stereospecific 1,3-dipolar cycloaddition between the nitrostyrene **8** and the azomethine ylide generated in situ from the *N*-(methoxymethyl)-*N*-(phenylmethyl)-*N*-(trimethylsilyl) methylamine. The nitro group was reduced into an amine with tin dichloride. The amino moiety was then methylated in a two step sequence, involving first the preparation of the ethyl carbamate followed by its reduction with borane to give **11**. Reductive amination reaction with the corresponding benzaldehyde afforded **12**. The pyrrolidine was deprotected, converted into the carbamoyl chloride **13** with triphosgene



Scheme 1. Reagents and conditions: (a) *N*-methoxymethyl)-*N*-(phenylmethyl)-*N*-(trimethylsilyl)methylamine 1.5 equiv, TFA 1.0 equiv, CH_2Cl_2, rt, 62%; (b) $SnCl_2{\cdot}2H_2O$ 3.0 equiv, EtOAc reflux, 75%; (c) EtOCOCl 1.1 equiv, K_2CO_3 2.0 equiv, THF, rt, 98%; (d) $BH_3{\cdot}THF$ 3 equiv, THF, reflux, 75%; (e) 3-fluoro-4-trifluoromethyl-benzaldehyde 1.1 equiv, $NaBH_3CN$ 1.2 equiv, AcOH, MeOH, rt, 62%; (f) 2,2,2-trichloroethyl chloroformate 1.5 equiv, CH_3CN then Zn dust, AcOH, 53%; (g) triphosgene 0.4 equiv, pyridine 2.0 equiv, CH_2Cl_2, −78 °C to rt, 80%; (h) dimethyl-(2-piperazin-1-yl-ethyl)-amine 1.1 equiv, Et_3N 1.5 equiv, CH_2Cl_2, rt, 85%.

and then reacted with dimethyl-(2-piperazin-1-yl-ethyl)-amine to give the racemic **7**. The enantiomeric mixture was resolved by preparative chiral HPLC to give (+)-**7**.

In summary, we have developed a novel class of selective NK_3 antagonists starting from a selective NK_1 compound. We derived molecules with high potency, favorable physico-chemical properties and DMPK profile which led to in vivo efficacy after oral administration.

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