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Identification of a Novel 1′-[5-((3,5-Dichlorobenzoyl)methylamino)-3-(3,4-dichlorophenyl)-4-(methoxyimino)pentyl]-2-oxo-(1,4′-bipiperidine) as a Dual NK_1/NK_2 Antagonist

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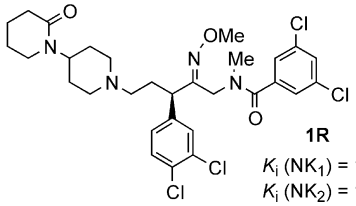
Abstract—A novel series of dual NK_1/NK_2 receptor antagonists, based on the 2-oxo-(1,4′-bipiperidine) template, has been prepared. Compound **10R** is a potent dual NK_1/NK_2 antagonist and demonstrates excellent in vivo activity and good oral plasma levels in the dog.

Introduction

The neurokinins are a family of peptides which can be found throughout the central and peripheral nervous system. They may play a role in allergic and inflammatory conditions such as asthma, arthritis, and cough as well as in central nervous system disorders such as migraine, emesis, anxiety, and depression.[1] Barnes and coworkers have proposed that both Substance P (SP) and neurokinin A (NKA), which bind to the seven transmembrane G-protein coupled NK_1 and NK_2 receptors respectively, are involved in plasma extravasation and airway constriction, which are the hallmarks of the asthmatic condition.[2] This hypothesis has been confirmed in a guinea pig model of bronchoconstriction by the synergistic effect observed with combining selective NK_1 and NK_2 receptor antagonists.[3]



1R

K_i (NK_1) = 1 nM

K_i (NK_2) = 1 nM

We have identified compound **1R**, the *Z* oxime isomer and the *R* enantiomer, as a potent dual NK_1/NK_2 antagonist with good in vivo activity, but moderate pharmacokinetic (PK) profile with only 5% bioavailability in the dog.[4] In this communication, we describe a series of analogues that have an additional substituent on the piperidone ring which results in a significant improvement in the PK profile.

Chemistry

The substituted 2-oxo-(1,4′-bipiperidine) analogues **8** were prepared as diastereomeric mixtures by the synthetic route diagrammed in Scheme 1. We have previously reported our synthesis of the versatile intermediate **2** which allowed us to vary the right-hand side amide, the center oxime, or the left-hand side piperidine moieties for our structure–activity relationship (SAR) studies.[5] In this case, Swern oxidation[6] of intermediate **2** followed by subsequent reductive amination[7] with methylamine and acylation with 3,5-dichlorobenzoyl chloride defined the right-hand side moiety as the desired amide **3**. Stepwise deprotection of compound **3** can be accomplished with hydrofluoric acid to remove the silyl protecting group and mercuric perchlorate to remove the dithiane protecting group.[8] The center oxime moiety was then fixed as the methoxyoxime. Formation of the oxime with methoxylamine in pyridine yields a 1.2:1.0 mixture of the *Z*/*E* oxime isomers which are separable by flash silica gel chromato-

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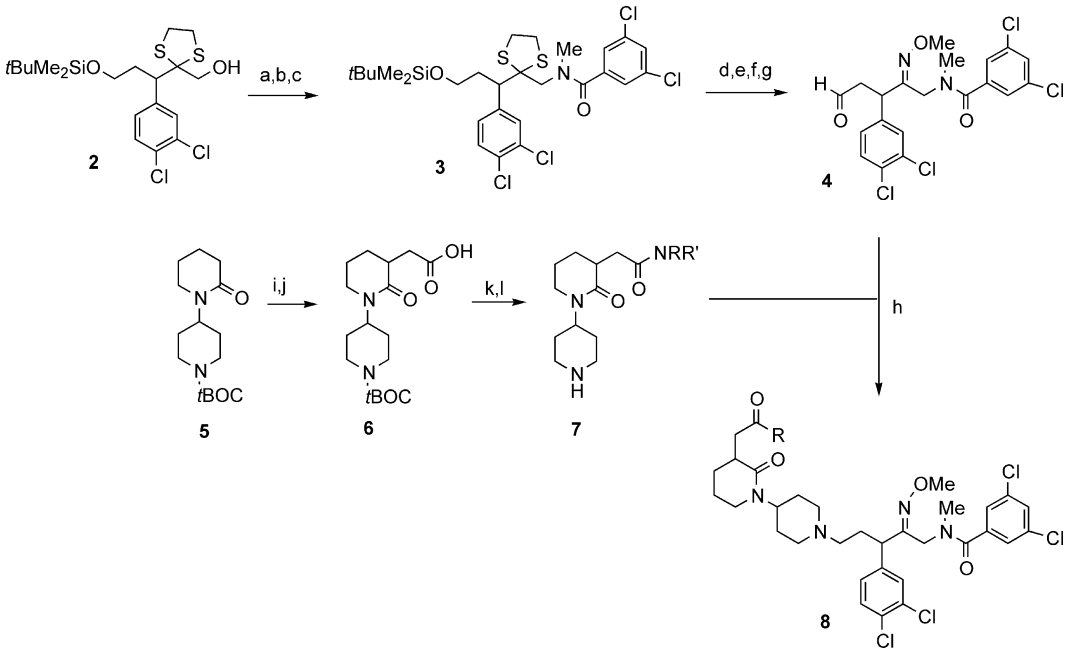


Scheme 1. Reagents and conditions: (a) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, 100%; (b) $MeNH_2$, $NaCNBH_3$, CF_3CH_2OH, 44%; (c) 3,5-dichlorobenzoyl chloride, pyridine, CH_2Cl_2, 97%; (d) HF, CH_3CN, 80%; (e) $HgClO_4$, $CaCO_3$, THF, H_2O, 100%; (f) $MeONH_2$–HCl, pyridine, 28% of *Z* isomer and 22% of *E* isomer; (g) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, 100%; (h) $NaCNBH_3$, CF_3CH_2OH, 26–70%; (i) $LiN(TMS)_2$, THF, allyl bromide, 93%; (j) RuO_2, $NaIO_4$, EtOAc, H_2O, 90%; (k) amine, DEC, HOBT, CH_2Cl_2, 31–100%; (l) TFA, CH_2Cl_2, 100%.

graphy. From previous SAR studies, we know that the *Z* oxime isomer is critical for dual NK_1/NK_2 activity. All compounds described in this paper are *Z* oxime isomers. Swern oxidation provided the key intermediate aldehyde **4**. Reductive amination of aldehyde **4** with a number of piperidines **7** yielded the target 2-oxo-(1,4′-bipiperidines) **8**.[9] The piperidines **7** were synthesized by alkylation of the known piperidone **5**[10] with allyl bromide, and oxidation of the double bond with ruthenium dioxide catalysis and sodium metaperiodate to provide the carboxylic acid **6**. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, DEC, promoted amide formation of acid **6** and subsequent acid catalyzed removal of the *t*BOC protecting group produced the piperidines **7**.

The individual stereoisomers of the target compound **8** were initially obtained by separation on a Chiracel[11] AD and/or OD HPLC column with 80:20 hexane:isopropanol and 0.25% by volume diethylamine as the eluant. Assignment of the absolute stereochemistry was determined by a chiral synthesis and single crystal X-ray analysis.[12]

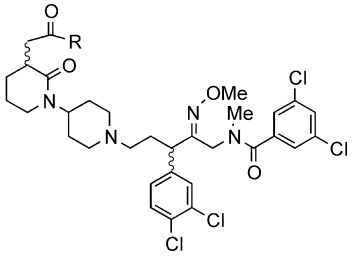
Results and Discussion

Our screening protocol was to analyze target compounds in our binding and functional assays as diastereomeric or enantiomeric mixtures and subsequently determine the in vivo biological and pharmacokinetic profile of the individual stereoisomers for the more active analogues.

Therefore, in Table 1 are the NK_1 and NK_2 receptor binding and NK_2 functional data[13] for selected 2-oxo-(1,4′-bipiperidine) analogues **8a**–**g** as the mixture of stereoisomers. The racemate of our lead structure **1R** is the piperidone **1**.

As we have previously reported, a thorough SAR study of the left-hand side piperidine moiety has been conducted, and we have found that an additional amide side chain α to the lactam is well-tolerated.[14] This is the basis for the design of target compounds **8a**–**g**, all of which retain both NK_1 ($K_i = 0.6$–3 nM) and NK_2 ($K_i = 0.7$–3 nM) binding potency relative to our lead

Table 1. NK_1 and NK_2 in vitro activity of 2-oxo-(1,4′-bipiperidines) **8a**–**g**



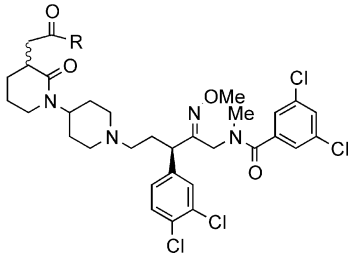
Compd	R	K_i, nM[a] (NK_1)	K_i, nM[a] (NK_2)	pA_2[b] (NK_2)
1	No side chain	5	2	7.3
8a	NMe_2	1	1	7.2
8b	NHMe	2	2	7.3
8c	NH_2	2	3	7.0
8d	3-Hydroxy-azetidine	3	2	7.6
8e	Morpholine	1	1	7.3
8f	Thiomorpholine	1	2	6.2
8g	*N*-Methyl-piperidine	0.6	0.7	6.8

[a]K_i values are the average of at least two independent determinations.
[b]In vitro guinea pig bronchus contraction assay.[13]

structure **1**. Although the thiomorpholinoamide **8f** and the *N*-methylpiperidinoamide **8g** possess good binding activity, they clearly exhibit less potent NK_2 functional activity ($pA_2 < 7.0$). Therefore, we decided to separate the stereoisomers of analogues **8a**–**8e** for complete in vitro and in vivo characterization since these compounds possess more potent NK_2 functional activity ($pA_2 \geq 7.0$).

From our previous work, we know that the stereochemistry of the 3,4-dichlorophenyl chiral center is *R* for optimal activity as in **1R**.[4] This SAR hypothesis has been verified for this series of 2-oxo-(1,4′-bipiperidines) with compounds **10R** and **10S**.[15] The in vitro profile for analogues **9**–**13**, in which the 3,4-dichlorophenyl stereocenter is fixed as the *R* enantiomer, is tabulated in Table 2. Overall, the NK_1 binding potency is similar for the *R* stereoisomer ($K_i = 0.6$–1.3 nM) versus the *S* stereoisomer ($K_i = 0.4$–1.5 nM) of the carboxamide side chain. This is also true for the NK_2 binding potency for the *R* stereoisomer ($K_i = 0.2$–0.5 nM) versus the S stereoisomer ($K_i = 0.3$–1 nM). However, these compounds can be distinguished based on their NK_2 functional activity. For example, the *N*-methylacetamide analogue exhibits a pA_2 for NK_2 of 7.8 for the isomer **10R** in comparison to 7.4 for the isomer **10S**. Likewise, acetamide **11R** has a pA_2 for NK_2 of 8.0 relative to 7.3 for **11S**. This trend holds for the 3-hydroxyazetidinoamide **12R** (pA_2 for NK_2 of 7.3) over **12S** (pA_2 for NK_2 of 6.3) and the morpholinoamide **13R** (pA_2 for NK_2 of 7.9) over **13S** (pA_2 for NK_2 of 6.9). The sole exception is the *N*,*N*-dimethylacetamides **9R** and **9S** which show the same level of NK_2 functional potency of 7.4.

Table 2. NK_1 and NK_2 in vitro activity of 2-oxo-(1,4′-bipiperidines) **9**–**13**



Compd	R	K_i, nM[a] (NK_1)	K_i, nM[a] (NK_2)	pA_2[b] (NK_1)	pA_2[b] (NK_2)
1R	No side chain	1.2	0.8	8.0	7.7
9R	NMe_2	0.8	0.2	7.9	7.4
9S	NMe_2	0.8	0.3	8.0	7.4
10R	NHMe	1.3	0.4	7.9	7.8
10S	NHMe	1.5	0.9	8.0	7.4
11R	NH_2	0.8	0.3	8.0	8.0
11S	NH_2	0.4	0.3	7.7	7.3
12R	3-Hydroxy-azetidine	0.6	0.3	8.0	7.3
12S	3-Hydroxy-azetidine	1.1	0.6	NT	6.3
13R	Morpholine	0.7	0.4	7.8	7.9
13S	Morpholine	0.8	0.8	8.2	6.9

[a]K_i values are the average of at least two independent determinations.
[b]In vitro guinea pig bronchus contraction assay.[13]
NT, not tested.

Table 3. NK_1 and NK_2 in vivo guinea pig activity of 2-oxo-(1,4′-bipiperidines) **9R**–**13R**

Compd	ED_{50}, mpk (NK_1)	ED_{50}, mpk (NK_2)
1R	1	3
9R	3	3
10R	1	3
11R	1	4
12R	45%[a]	64%[a]
13R	47%[a]	97%[a]

[a]% Inhibition @ 10 mpk.

Due to their encouraging in vitro activity, the in vivo activities of analogues **9R**–**13R** as dual NK_1 and NK_2 antagonists have been determined and are reported in Table 3. In vivo NK_1 activity in the guinea pig is characterized by the compound's ability to inhibit the increase in airway microvascular leakage (AML) produced by a SP challenge. In vivo NK_2 activity is characterized by the compound's ability to inhibit bronchoconstriction produced by a NKA challenge.[13] The *N*,*N*-dimethylacetamide **9R**, the *N*-methylacetamide **10R**, and the acetamide **11R** all exhibit in vivo guinea pig activity comparable to the lead structure **1R** with ED_{50} in the 1–4 mpk range. In contrast, the 3-hydroxyazetidinoamide **12R** and the morpholinoamide **13R** are significantly less potent as NK_1 inhibitors for the guinea pig in vivo, exhibiting only 45–50% inhibition at a 10 mpk dose.

Due to their encouraging biological activity in the guinea pig, analogues **9R**–**11R** were further evaluated for their pharmacokinetic profile in the dog. The results of these studies are shown in Table 4. Our lead structure **1R** and the *N*,*N*-dimethylacetamide analogue **9R** both possess lower blood levels with AUC < 4ug h/mL. However, the *N*-methylacetamide **10R** and the acetamide **11R** both show higher blood levels with AUC > 9 ug h/mL. Between **10R** and **11R**, the *N*-methylacetamide **10R** is the superior compound based on its higher bioavailability of 66% versus 37% for **11R**.

In conclusion, we have confirmed that the introduction of an amide side chain on the 2-oxo-(1,4′-bipiperidine) template as in analogues **8a**–**g** retains the superior in vitro dual NK_1 and NK_2 binding potency in comparison to our lead structure **1R**. This side chain amide can be the unsubstituted acetamide **8c** or substituted as the *N*,*N*-dimethylacetamide **8a**, *N*-methylacetamide **8b**, 3-hydroxyazetidinoamide **8d**, or morpholinoamide **8e** and retain NK_2 functional potency relative to **1R**. The R stereoisomer **9R**–**13R** of **8a**–**e** displays higher NK_2 functional activity than the corresponding S stereoisomer **9S**–**13S**. Evaluation of the in vivo activities of **9R**–**13R** in the guinea pig shows that the *N*,*N*-dimethyl-

Table 4. Pharmacokinetic data for 2-oxo-(1,4′-bipiperidines) **9R**–**11R**

Compd	$AUC_{0-24\ h}$, dog, po at 3 mpk (ug h/mL)	Bioavailabilty
1R	1.22	5%
9R	3.46	ND
10R	13.6	66%
11R	9.49	37%

ND, not determined.

acetamide **9R**, *N*-methylacetamide **10R**, and acetamide **11R** all possess good potency equivalent to that of our lead structure **1R**. Further evaluation of **9R**–**11R** for their pharmacokinetic profile in the dog distinguishes the *N*-methylacetamide **10R** with a significantly improved AUC level and bioavailability in comparison to our lead structure **1R**.

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