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Structure–Activity Relationships of Oxime Neurokinin Antagonists: Oxime Modifications

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Abstract—A thorough SAR study of the oxime region of the dual NK_1/NK_2 antagonist **1** revealed several modifications that result in potent dual antagonists. Follow up SAR studies on a second-generation scaffold demonstrate that certain polar groups on the oxime can improve the dual binding affinity to the subnanomolar range.

Introduction

The neurokinin oligopeptides, substance P (SP) and neurokinin A (NKA), which bind to the neurokinin receptors NK_1 and NK_2, respectively, have been implicated in bronchoconstriction, vasodilation, smooth muscle contraction, edema, and neurogenic inflammation.[1] Since inhibition of either receptor carries potential benefits for asthma,[2] the simultaneous blockade of both receptors was the goal of our efforts toward a more efficacious approach to asthma therapy.

We recently reported a new class of oxime antagonists that are equipotent at the NK_1 and NK_2 receptors.[3] The discovery that the incorporation of an oxime moiety into a selective NK_2 active scaffold imparts dual activity provided several avenues of investigation from a design standpoint. In particular, the presence of this oxime group or similar isosteric replacements could provide a functional handle to modify the polarity or pharmacokinetic properties of this class of compounds.

Toward the further optimization of this lead, we now report the structure–activity relationships (SAR) involved in the modification of the oxime ether region of compound **1** (Fig. 1) and a second generation lead, compound **23** (Fig. 2).

Isosteric Replacements

We have previously reported that geometry of the oxime moiety is critical to dual activity. Hence, the directionality of the oxime nitrogen lone pair of electrons may be a very important contributor to one or both receptor interactions. Additionally, the space occupied by the oxime methoxy group fixed by the *Z*-geometry of the oxime may induce a conformational preference to the flexible antagonist more closely resembling the bioactive conformation. To gain some insight into these interesting questions, the corresponding vinyl ether, hydrazone, olefin, allylic amine and semicarbazones were prepared and evaluated. All of the analogues were prepared using standard chemistry via ketone **2** whose synthesis was previously described.[3]

The NK_1 binding of the ketone starting material and most of the oxime analogues is relatively unaffected by the subtle changes of the isosteric replacements (Table 1).[4] The NK_2 affinity, however, does vary with electronic and geometric alterations. Diminished NK_2 binding of

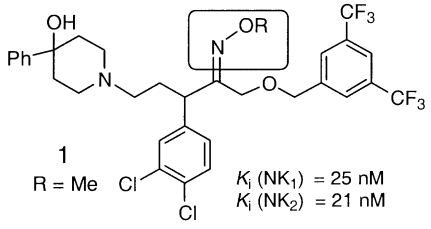

Figure 1.

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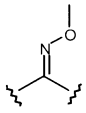
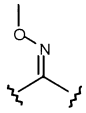
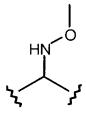
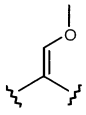
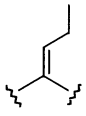
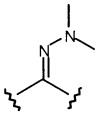
Table 1. Structure–activity relationships of oxime isosters

Compd	Oxime isoster	K_i or %I (1 μM)	
		NK_1	NK_2
1		25 nM	21 nM
2		15 nM	236 nM
3		25 nM	35%
4		25 nM	350 nM
5		33 nM	35%
6		57 nM	28%
7		38 nM	24 nM

the *E*-oxime isomer **3** suggests the position of the *Z*-oxime methoxy group and/or the directionality of the lone pair from the oxime nitrogen is critical for NK_2 affinity.

The recovery of some, albeit diminished, NK_2 affinity with the ketone, which contains a lone pair isosteric to the oxime nitrogen lone pair, suggests the lone pair is not sufficient to restore potent NK_2 affinity. Changing the basicity and directionality of the nitrogen lone pair by reduction to the methoxyamine **4** results in lower NK_2 affinity. The lower NK_2 affinity of the vinyl ether **5**, and the fully carbogenic isoster **6** highlights the importance of the oxime nitrogen lone pair. Finally, the restored NK_2 affinity of hydrazone **7** supports the notion that the space occupied by the *Z*-oxime methoxy group *and* the directionality of the nitrogen lone pair from the oxime are critical for controlling NK_2 affinity. The SAR in modulating the steric and electronic parameters on the *Z*-oxime functional group was the focus of a large effort, the results of which are reported below.

Z-Oxime Modifications

The synthesis of the oxime analogues described in Tables 2–3 resulted from the alkylation of the geometrically pure oxime derived from the reaction of ketone **2** with hydroxylamine.[5] Several targets required some standard functional group transformations; however, most of the syntheses were straightforward.[6] It is clear from the initial SAR screening that alkyl groups larger than methyl are not tolerated by either the NK_1 or NK_2 receptor (entries 8–12). Introduction of oxygenated functionality, however, restores dual binding affinity (entries 13–15). The NK_2 binding is diminished with the introduction of a carboxyl group or a tertiary amino group (entries 17 and 18). The nitrile, the corresponding amides, and hydroxyamidine (entries 19–22) retain the dual binding affinity of the parent oxime compound.

Table 2. Structure–activity relationships for *Z*-oxime modifications of compound **1**

Compd	R	K_i or %I (1 μM)	
		NK_1	NK_2
8	Ethyl	81 nM	107 nM
9	*i*-Butyl	43%	11%
10	Allyl	100 nM	215 nM
11	*t*-Butyl	46%	28%
12	Phenyl	32%	23%
13	CH_2OMe	49 nM	42 nM
14	CH_2CH_2OMe	7 nM	50 nM
15	CH_2CH_2OH	20 nM	14 nM
16	CH_2CO_2Me	25 nM	198 nM
17	CH_2CO_2H	8 nM	20%
18	$CH_2CH_2NMe_2$	103 nM	11%
19	CN	15 nM	19 nM
20	$CH_2C(O)NH_2$	17 nM	58 nM
21	$CH_2C(O)NHMe$	24 nM	45 nM
22	$CH_2C(NOH)NH_2$	17 nM	19 nM

Second generation optimization

We recently reported on the optimization of both the piperidine portion[7] and the benzylic ether portion[8] of methoxyoxime **1**, which resulted in the identification of **23** as a more potent dual antagonist.[9] With the discovery that various polar functional groups on oxime **1** led to retention of the binding affinity, we sought to further explore this finding on the more potent scaffold of compound **23**.

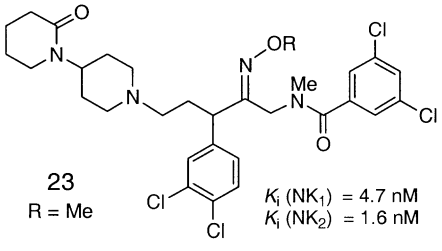
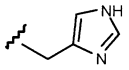
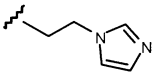
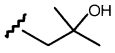
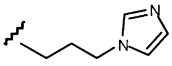
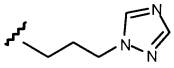
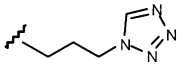
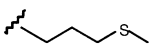
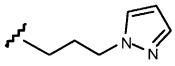
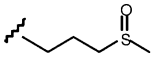
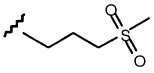
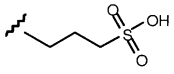
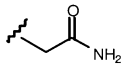
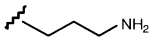
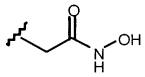
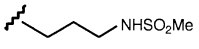
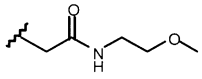
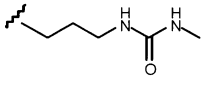
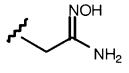
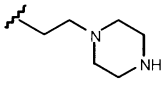
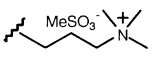


Figure 2.

Replacement of the oxime methyl group with cyanomethyl (entry 24) leads to a slight improvement in NK_1 binding, whereas the hydroxyethyl group on the oxime (entry 25) leads to a potent subnanomolar dual antagonist. Bulkier alcohols, longer chains, or methyl ether

capping (entries 26–28) does not lead to any significant advantages in binding in the carbinol series. A thioether (entry 29) leads to reduced affinity at both receptors, while the corresponding sulfoxide and sulfone (entries 30 and 31) introduces subnanomolar NK_1 and retains reasonable NK_2 binding. The charged sulfonic acid (entry 32) retains surprisingly good binding given the drastic electrostatic contrast to the parent methyl oxime. Analogues containing nitrogen on a carbogenic tether introduce a complementary change in the electronic environment since the amine would presumably carry a positive charge at physiological pH. The trend, however is that basic amine groups diminish NK_2 binding (entry 33). The neutral sulfonamide and urea (entries 34–35) restore reasonable dual activity. Both a larger piperazine (entry 36) and a quaternary nitrogen (entry 37) emphasize the lack of tolerance for bulky positively charged groups in the corresponding space occupied in the NK_2 receptor. Heterocyclic amine groups somewhat restore reasonable binding, however, no obvious advantages are gained with heterocycles in this region (entries 38–43). The carboxylic acid derivative (entry 44) is a very potent selective NK_1 antagonist. In contrast with the sulfonic acid (entry 32), the carboxyl group, which is assumed to be of similar charge at physiological pH as the sulfonic acid has significantly reduced NK_2

Table 3. Structure–activity relationships for *Z*–oxime modifications of **23**

Compd	R	K_i or %I (1 μM)		Compd	R	K_i or %I (1 μM)	
		NK_1	NK_2			NK_1	NK_2
24	CH_2CN	1.5 nM	1.4 nM	**38**		2.2 nM	8.5 nM
25	CH_2CH_2OH	0.6 nM	0.8 nM	**39**		2.8 nM	5.4 nM
26		1.9 nM	23 nM	**40**		1.6 nM	6.8 nM
27	$CH_2CH_2CH_2OH$	0.7 nM	1.5 nM	**41**		0.7 nM	4.8 nM
28	CH_2CH_2OMe	2.4 nM	3.1 nM	**42**		0.8 nM	17 nM
29		7.4 nM	11.5 nM	**43**		1.7 nM	25 nM
30		0.8 nM	3.5 nM	**44**	CH_2CO_2H	0.7 nM	394 nM
31		0.9 nM	3.2 nM	**45**	CH_2CO_2Me	4.7 nM	16.7 nM
32		3.3 nM	2.7 nM	**46**		0.9 nM	2.0 nM
33		0.7 nM	8.8 nM	**47**		1.2 nM	4.2 nM
34		1.2 nM	4.5 nM	**48**		2.2 nM	48 nM
35		1.0 nM	1.7 nM	**49**		0.7 nM	0.7 nM
36		0.5 nM	50 nM	**50**	CHF_2	1.7 nM	5.0 nM
37		1.8 nM	590 nM	**51**	CH_2F	0.8 nM	0.8 nM

binding. While the ester (entry 45) restores some NK_2 binding, small neutral amides have very good dual activity. While extended functionalized amides reduce NK_2 affinity (entry 48), the hydroxyamidine (entry 49) has excellent dual antagonist binding. Finally, fluoro-substituted analogues were investigated as a strategy to retain the benefits of the methoxyloxime with a moiety more stable to metabolic cleavage. Although the difluoromethyl oxime (entry 50) suffered from lower NK_2 affinity, the monofluoromethyl analogue (entry 51) showed excellent binding with subnanomolar affinity at both the NK_1/NK_2 receptors.

Characterization in functional and in vivo assays differentiate compound **49** from analogues with similar binding affinity (data not shown). Synthesis of the optically pure hydroxyl amidine[6] derivative of **49** provides compound **52** (Fig. 3). Along with subnanomolar NK_1/NK_2 binding affinity, this analogue also has good PK in the rat with an $AUC_{0-6\ h}$ of 3 μM h (dosed orally @ 30 mpk).[10] This translates into excellent in vivo potency as this compound shows 91 and 94% inhibition at 10 mpk, po in the guinea pig NK_1 and NK_2 models, respectively.[11]

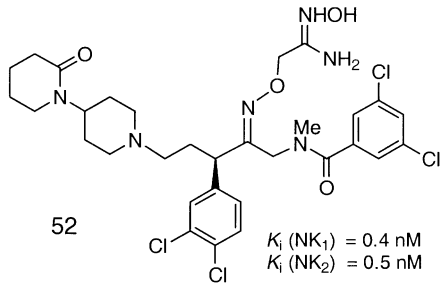


Figure 3.

A thorough SAR study of the oxime region of our lead oxime dual NK_1/NK_2 antagonist **1** revealed several modifications that result in more potent dual antagonists. A study of oxime isosters led to our focus on potency modulation by modification of the *Z*-oxime parent compound. Initial studies revealed that polar functionality on the oxime resulted in retention of dual binding affinity. A thorough follow-up study on the more potent lead compound **23** resulted in the discovery of several subnanomolar dual antagonists.

Acknowledgements

The authors thank Mr. C. Richard and Mr. Z. Zhan for performing the NK binding studies. We also thank Dr. Richard Chapman and his group for the assessment of compound **52** in the in vivo assays, and Dr. Amin Nomeir and his group for evaluation of compound **52** in the rapid rat assay.

References and Notes

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2. (a) Barnes, P. J. *Lancet* **1986**, *1*, 242. (b) Barnes, P. J.; Chung, F. K.; Page, C. P. *Pharmacol. Rev.* **1988**, *40*, 49.
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4. Receptor binding assays were performed on membrane preparations containing recombinant human NK_1 or NK_2 receptors in CHO cells. [^{3}H]Sar SP and [^{3}H]NKA were used as the ligands for the NK_1 and NK_2 receptor assays, respectively, at the experimentally derived K_ds. K_is were obtained according to the Cheng and Prussoff equation. CP-96345 and SR-48968 were run as NK_1 and NK_2 standards, respectively, revealing an inter-run variability within 2-fold.
5. The *E*/*Z* isomers of the parent oxime were separated chromatographically prior to alkylation.
6. Reichard, G. A.; Alaimo, C. A.; Shih, N.-Y.; Ting, P. C.; Carruthers, N. I.; Lavey, B. J. US Patent 6063926, 2000; *Chem. Abstr.* **2000**, *132*, 334363.
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10. The AUC of compound **23** is at least an order of magnitude lower than that of compound **52** in the rat.
11. In vivo NK_1 and NK_2 antagonist activity was measured by the inhibition of SP-induced microvascular permeability of the airways and inhibition of β-ala-NKA (4–10) induced bronchospasm, respectively.