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Synthesis and Structure–Activity Relationships of Oxime Neurokinin Antagonists: Discovery of Potent Arylamides

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Abstract—The structural modification of the benzylic ether region of oxime **1** has resulted in the identification of several novel aryl amides as selective or dual NK_1/NK_2 antagonists.

Substance P (SP) and neurokinin A (NKA) which bind to the neurokinin receptors, NK_1 and NK_2, respectively, have been implicated in many pathophysiological effects related to pulmonary dysfunction.[1] Since antagonists of either SP or NKA carries potential benefits for asthma, concomitant blockade of both receptors may lead to a new approach to asthma therapy. The administration of a single entity with both NK_1 and NK_2 affinity is one approach to achieve such simultaneous antagonism.

The discovery and optimization of potent *dual* NK_1/NK_2 antagonists is an active area in medicinal chemistry. We recently reported the design and synthesis of a new class of oxime antagonists that are equipotent at the NK_1 and NK_2 receptors.[2] Toward the further optimization of this series, we now report the structure–activity relationships (SAR) involved in the modification of the benzylic ether region of oxime **1** (Fig. 1).

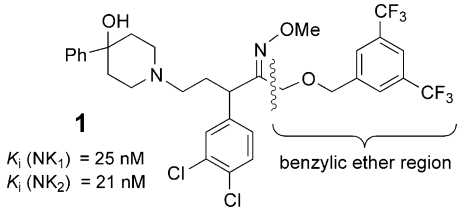
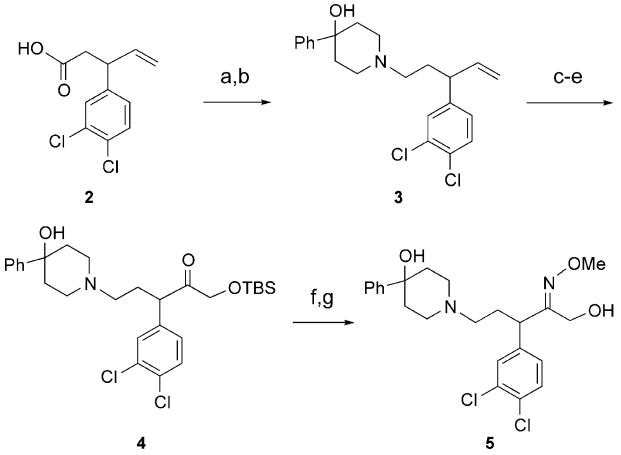


Figure 1.

Synthesis

We identified the oxime alcohol **5** as a versatile synthetic intermediate for the preparation of the modifications of the ether region. The synthesis of **5** (Scheme 1) employs carboxylic acid **2** prepared from 3,4-dichlorocinnamic acid.[2] Standard coupling and reduction give rise to the amine olefin **3**. Subsequent dihydroxylation followed by selective silylation and oxidation afford the TBS ketone **4**. Oxime formation followed by deprotection then provides the desired oxime alcohol **5** as a single isomer. This intermediate is functionalized appropriately using standard chemistry to access the analogues in Table 1.



Scheme 1. Reagents and conditions: (a) EDC, 4-hydroxyl-4-phenylpiperidine, CH_2Cl_2; (b) LAH/THF; (c) OsO_4/NMO; (d) $TBSCl/NEt_3/CH_2Cl_2$; (e) PDC/CH_2Cl_2; (f) NH_2OMe/NaOAc, aq EtOH; (g) TBAF.

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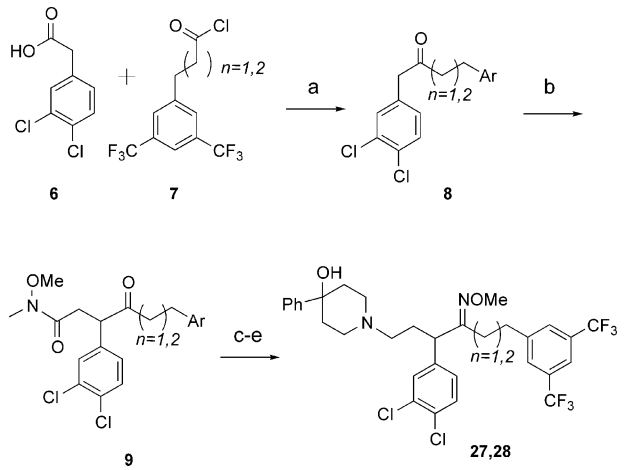
The amine-based analogues (Tables 2 and 3) are prepared by oxidation of oxime alcohol **5**, followed by standard reductive amination. Functionalization to those tabulated analogues in Tables 2 and 3 is straightforward. The carbogenic analogues (entries 27 and 28, Table 2) require a different route (Scheme 2).



Scheme 2. Reagents and conditions: (a) 2 equiv LHMDS @ −78 °C; then, add **7**, warm to 23 °C; (b) LHMDS, $Me(MeO)N(CO)CH_2Cl$; cat. KI; (c) NH_2OMe HCl/pyridine; (d) DIBAL-H/THF; (e) 4-hydroxyl-4-phenylpiperidine, $NaBH_3CN$, MeOH.

Ketone **8** is accessed via the addition of the dianion of 3,4-dichlorophenylacetic acid to the appropriate acid chloride **7**[3] followed by decarboxylation. Two-carbon homologation of ketone **8** is performed via alkylation with the α-chloro-Weinreb amide. Conversion to the oxime, followed by formation of the aldehyde and reductive amination provides the carbogenic analogues (entries 27 and 28).

Discussion

We initially set out to explore the tolerance of both receptors for different types of aryl and alkyl ethers. The parent unsubstituted benzyl ether (entry 2) shows a significant loss of NK_1 binding,[4] however, the NK_2 binding is retained. Positional modulation of a single methyl group indicates a preference, albeit diminished, for dual activity with the 3-substituted analogue (entry 4). Alkyl substituents in the 4-position leads to NK_2 selective compounds. In fact, bulky *alkyl* ethers (entries 7 and 8) show excellent selective NK_2 binding with the adamantyl analogue completely selective for the NK_2 over the NK_1 receptor. Larger aryl and heteroaryl ethers continue the trend of NK_2 selectivity (entries 9–13). However, the pyridyl, oxadiazole, and fluoronaphthyl derivatives (entries 14–16) show modest dual activity. Focusing on 3,5-disubstituted-phenyl[5] modifications led to a consistent series of dual active analogues. The smaller difluoro substitution (entry 17) have diminished NK_1 affinity compared to the dimethyl, dichloro, and dibromo derivatives (entries 18–20). Both receptors seem to accommodate the 3,5-dimethoxy and 3,4,5-tri-methoxy substituents found in reported dual antagonists.[6] However, at this point in our SAR survey, there was no clear advantage for

Table 1. Structure–activity relationships for alkyl and aryl ether analogues

Compd	K_i (nM) or %I (1 μM)		Compd	K_i (nM) or %I (1 μM)		Compd	K_i (nM) or %I (1 μM)	
	NK_1	NK_2		NK_1	NK_2		NK_1	NK_2
1	25	21	**9**	2%	38	**17**	113	42
2	33%	40	**10**	37%	12	**18**	26	6
3	34%	136	**11**	23%	20	**19**	10	15
4	140	14	**12**	29%	17	**20**	32	8
5	48%	9	**13**	48%	21	**21**	33	18
6	6%	4	**14**	115	43	**22**	53	28
7	21%	13	**15**	100	1	**23**	96	10
8	0%	7	**16**	70	21	**24**	19%	130

this substitution pattern. The di-*t*-butyl analogue (entry 24) reveals the lack of tolerance for large alkyl substitution at the 3,5-positions at the NK_1 receptor binding site.

With 3,5-substituted aryl ethers representing a promising dual active series, it was interesting to investigate alternate linkages to the ether unit (Fig. 2). The 3,5-bis(trifluoromethyl)phenyl group was held constant and several heteroatom and carbogenic linkers were prepared (Table 2).

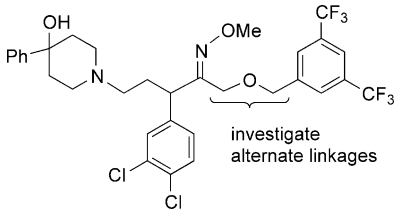


Figure 2.

We discovered that a heteroatom is necessary but not sufficient along a five- or six-atom chain between the two aryl rings in order to maintain dual activity. The addition of a carbonyl group between the ether oxygen and the aromatic ring (entry 25) diminishes NK_1 binding yet retains NK_2 affinity. Methylation of the opposing carbon (entry 26) diminshes binding at both receptors. The all carbon analogue (entry 27) is also less active at both receptors. Shortening the carbon chain to four atoms between the aryl rings (entry 28), surprisingly restores NK_1 activity, but diminishes NK_2 activity. By reinstalling the ether linkage for a four-atom analogue (entry 29) the same preference for the NK_1 receptor is observed, however, the binding is diminished. The six-atom saturated ether chain restores some NK_2 activity, however, NK_1 binding is poor for the unsaturated analogue (entries 30 and 31). Interestingly, the allyl ether with a seven-atom chain (entry 32) restores NK_2 affinity. The secondary amine (entry 33) suffers reduced NK_2 binding, however, by switching to the methyl amine derivative (entry 34) the dual activity is maintained. The corresponding retroamide (entry 35) is very active in the NK_1 assay, however, NK_2 binding is poor. The sulfonamide (entry 36) shows very poor activity at both receptors. The carbamate (entry 37) looked promising, as did the urea (entry 38), however, stability problems upon exposure to low pH tempered interest in this series. The more stable reversed carbamate (entry 39) shows excellent dual activity. The corresponding amide analogues (entries 40 and 41) improves the dual activity to single digit affinity at both receptors. From our study of the different linkages between the oxime and the 3,5-bis(trifluoromethyl)phenyl moiety, the NK_1 and NK_2 receptors are highly sensitive to this region. Although several linkages have been identified which modulate the relative selectivity for the NK_1 or NK_2 receptors, the amide is the most promising linker identified for dual active antagonists.

Table 2. Structure–activity relationships for 3,5-bis(trifluoromethyl)phenyl analogues

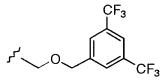
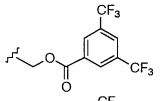
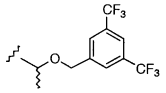
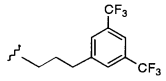
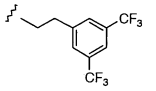
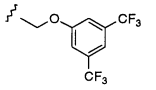
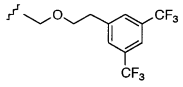
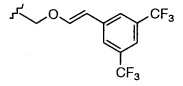
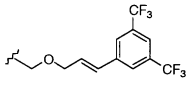
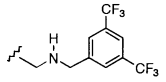
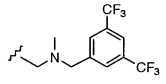
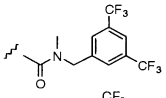
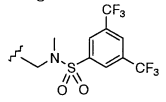
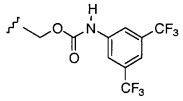
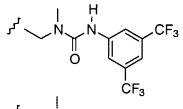
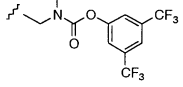
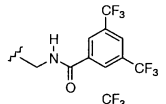
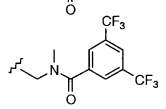
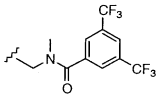
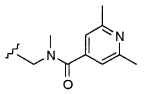
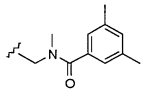
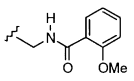
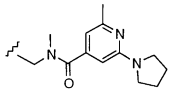
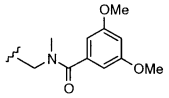
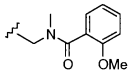
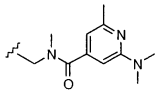
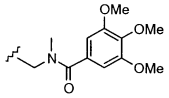
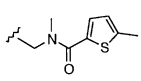
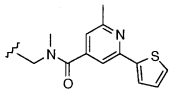
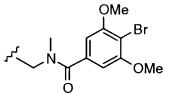
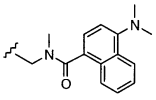
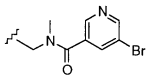
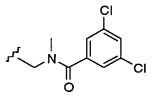
Compd		K_i (nM) or %I (1 μM)	
		NK_1	NK_2
1		25	21
25		168	25
26		75	157
27		92	332
28		23	51%
29		81	31%
30		39	118
31		20%	100
32		36%	20
33		50	130
34		42	22
35		6	167
36		435	286
37		32	35
38		5	8
39		6	11
40		2	2
41		4	9

Table 3. Structure–activity relationships for amide analogues

Compd		K_i (nM)		Compd		K_i (nM)		Compd		K_i (nM)	
		NK_1	NK_2			NK_1	NK_2			NK_1	NK_2
41		4	9	**46**		9	6	**51**		1	2
42		33	54	**47**		2	3	**52**		5	2
43		58	4	**48**		2	1	**53**		13	3
44		10	2	**49**		2	6	**54**		5	8
45		12	7	**50**		7	4	**55**		2	4

Subsequent second-generation exploration of the SAR of the amide linked series via parallel and targeted synthesis results in a number of potent NK_1/NK_2 dual antagonists (Table 3). Utilization of the *ortho*-methoxyphenyl substitution pattern (entry 42) present in the Pfizer series of NK_1 antagonists[7] results in diminished activity in our oxime class. The *N*-methyl derivative (entry 43) shows improved NK_2 binding affinity. Several analogues which contain an alternate aryl group for the 3,5-disubstituted phenyl represent novel replacements for this group not only for selective NK antagonists, but for dual NK antagonists as well. The thiophene and aminonaphthyl amides have surprisingly good affinity for both receptors (entries 44 and 45). A similar active series was found for the pyridine class (entries 46–50). Aminopyridines (entries 47 and 48) are particularly potent dual NK antagonists. Finally, several 3,5-disubstituted benzamides are potent dual antagonists (entries 51–55). The 3,5-dichlorophenyl substitution is very promising in the NK binding assays; and many second generation derivatives of these compounds display excellent biological activity in more advanced assays (data not shown).

Summary

A thorough SAR study of the benzylic ether region of our lead oxime dual NK_1/NK_2 antagonist revealed several modifications, which results in more potent selective and dual antagonists. A study of different linkers between the oxime and the terminal aryl group identified the amide moiety as an improvement over the ether in the original lead oxime **1** with regard to maximizing dual activity. The generality of the 3,5-disubstituted phenyl substitution has been confirmed, in both the ether and amide series, and several novel aryl groups outside of this substitution pattern have been discovered which have excellent affinity for both receptors.

Acknowledgements

The authors wish to thank Mr. C. Richard and Mr. Z. Zhan for performing the NK binding studies.

References and Notes

1. (a) Barnes, P. J. *Lancet* **1986**, *1*, 242. (b) Barnes, P. J.; Chung, F. K.; Page, C. P. *Pharmacol. Rev.* **1988**, *40*, 49.
2. Reichard, G. A.; Ball, A. T.; Aslanian, R.; Anthes, J. C.; Shih, N.-Y.; Piwinski, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2329.
3. 3,5-Bis(trifluoromethyl)phenylpropionic acid ($n=1$) was prepared from 3,5-bis(trifluoromethyl)benzyl bromide using the 2 carbon homologation method by Meyers: Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36. Further homologation to 3,5-bis(trifluoromethyl)phenylbutyric acid ($n=2$) was performed by tosylation, displacement with KCN followed by standard acidic hydrolysis.
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_d's. K_i's were obtained according to the Cheng and Prussoff equation.

5. The 3,5-disubstituted pharmacophore for the NK_1 receptor, discovered by Merck, has been reported in a number of benzyl ether NK_1 receptor antagonists, see: Williams, B.; Teall, M.; McKenna, J.; Harrison, T.; Swain, C. J.; Cascieri, M.; Sodowski, S.; Strader, C.; Baker, R. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1903.
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