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The Design and Synthesis of Novel NK_1/NK_2 Dual Antagonists

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Abstract—Functional probing of the backbone of the Sanofi NK_2 antagonist SR 48968 has resulted in the discovery of two new classes of NK_1/NK_2 dual antagonists: the diamine class and the oxime class. The addition of the amino or the oxime functional group results in the reversal of the stereochemical preference of the NK_2 receptor.

Introduction

The neurokinin oligopeptides, substance P (SP) and neurokinin A (NKA) bind to the neurokinin receptors, NK_1 and NK_2, respectively, with moderate selectivity.[1] These peptides have been implicated in bronchoconstriction, vasodilation, smooth muscle contraction, edema, and neurogenic inflammation.[2] The pathophysiological effects mediated by either the NK_1 or NK_2 receptor in asthmatics are related to pulmonary dysfunction.[3] Damage to airway epithelium leads to the local release of SP and NKA from sensory pulmonary C fibers resulting in the various pathophysiological responses related to asthma (bronchospasm, edema, inflammatory cell recruitment, plasma extravasation, and mucous gland secretion).[4] Additionally, lung tissues derived from asthmatics overexpress both NK_1 and NK_2 receptors.[5]

Antagonists of either SP or NKA have been shown to have beneficial effects in asthma models; namely, inhibition of microvascular leakage by NK_1 antagonists and reduction of bronchospasm by NK_2 antagonists.[2] Since inhibition of either receptor carries potential benefits for asthma, the simultaneous blockade of both receptors may lead to a new, more efficacious approach to asthma therapy. Thus, the design and synthesis of single digit or lower nanomolar *dual* NK_1/NK_2 antagonists was the major focus of our efforts at the onset of the program.

Design Strategy

Considerable structure–activity relationship (SAR) work around NK_1 antagonists had been reported in the literature by Pfizer,[6] Merck,[7] Rhone Poulenc,[8] Ciba-Geigy,[9] Sanofi,[10] and Lilly.[11] It appeared from the literature that there was substantial structural variability among the known NK_1 antagonists. In contrast, the SAR information for selective NK_2 antagonists was extremely limited. Only one nonpeptidic selective NK_2 antagonist discovered by Sanofi (SR 48968) had been reported with limited SAR disclosed.[12]

The rational design of antagonists with dual activity is an emerging field in medicinal chemistry. When our program was initiated, the only known dual NK_1/NK_2 antagonist was FK 224, a cyclic peptide discovered by Fujisawa with binding $IC_{50} = 37$ and 72 nM for the NK_1 and NK_2 receptors, respectively.[13] Although there were selective NK_1 and NK_2 nonpeptidic antagonists reported by several groups, there were no dual nonpeptidic antagonists in the literature in the neurokinin area at the commencement of our effort.

During the course of our investigation several groups have also looked at the feasibility of designing dual NK_1/NK_2 antagonists. Both Hoechst Marion Roussel[14] (MDL 105,212) and Merck[15] (spiroindolines) have worked from SR 48968 to build in impressive dual activity.

The strategy described herein focuses on the development of dual antagonists by imparting NK_1 activity to the scaffold of a known active NK_2 antagonist. The first generation effort was to understand the effects of systematically appending various functional groups to the

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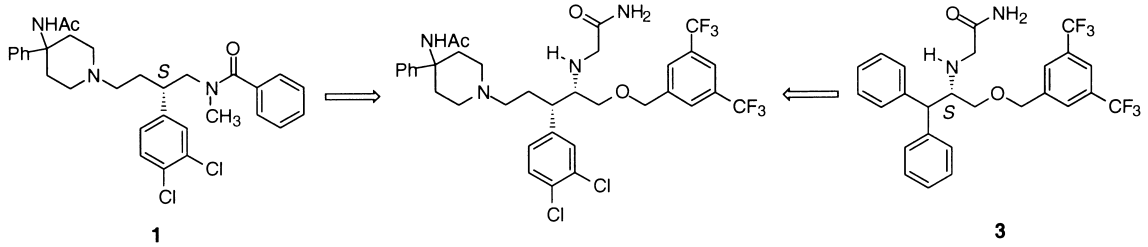


1
Sanofi SR 48968
K_i (NK_2) = 0.5 nM

2
Proposed Branched Dual Antagonist

3
Merck
K_i (NK_1) = 0.9 nM

carbon backbone of SR 48968 to probe this structure for building points that the NK_2 receptor would tolerate. This functionality was then used to construct branched dual antagonists by the incorporation of an NK_1 pharmacophore into the NK_2 antagonist backbone.

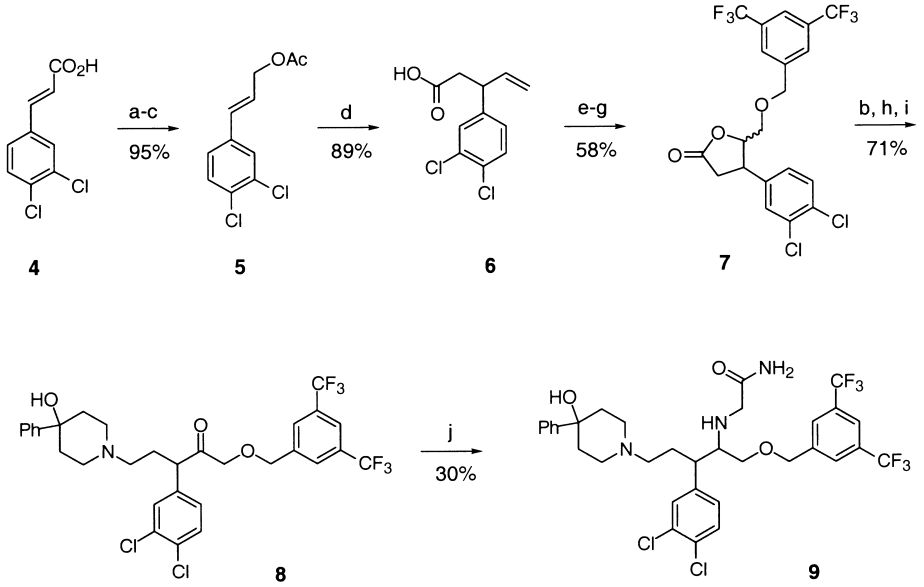
Acyclic NK_1 antagonists[7] developed at Merck were considered to be model pharmacophores to incorporate into backbone substituted analogues of the NK_2 antagonist SR 48968. Various modifications of the functional appendages were planned in order to optimize dual activity.

Synthesis and Binding Results

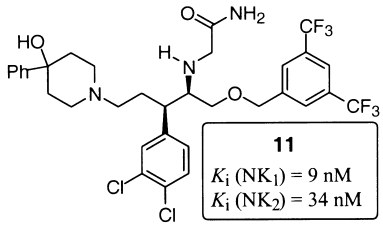
A stereo-divergent synthesis depicted in Scheme 1 was originally pursued in order to assess the biological activity of all four possible diastereomers of the proposed dual antagonist **2**. Thus, conversion of 3,4-dichlorocinnamic acid to the corresponding cinnamyl acetate followed by Ireland–Claisen rearrangement proceeded in 85% yield over four steps to give acid **6**. Subsequent epoxidation with *m*-CPBA followed by cyclization with Amberlyst 15 provided a 1:1 mixture of diastereomeric hydroxy lactones in 81% over two steps. Alkylation of the base sensitive hydroxy lactones with silver oxide and 3,5-bis(trifluoromethyl)benzyl bromide gave lactone ether **7** in 71%. Reduction of the lactone to the lactol using DIBAL-H, followed by reductive amination and Jones oxidation provided ketone **8** in >70% over three steps. Reductive amination with glycineamide provided a mixture of diastereomeric diamines **9**.

Separation of the diastereomers of diamine **9** and subsequent biological evaluation in NK_1 and NK_2 receptor binding assays revealed the major diastereomer of **9** to be a modest dual inhibitor with K_is of 4 and 34 nM, respectively.[16] Separation of this diastereomer by chiral HPLC provided the enantiomeric pair **11** and **12**. Biological evaluation showed that **11** retained the dual NK_1/NK_2 binding with K_is of 9 and 34 nM, respectively. Synthesis of optically pure **11** revealed the relative and absolute configuration to be *R,R*.[17]

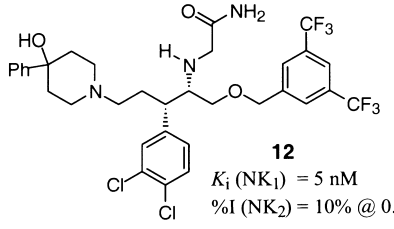
Biological evaluation of the *S,S* isomer **12** resulted in the identification of a potent NK_1 selective antagonist. The racemic *trans* diamine **13** proved to be an even more potent NK_1 selective antagonist with subnanomolar binding.



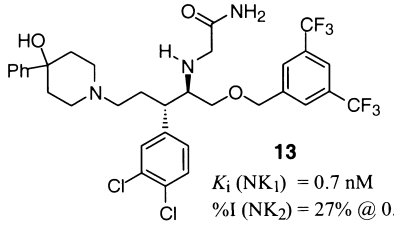
Scheme 1. Reagents and conditions: (a) Cs_2CO_3, MeI; (b) DIBAL-H; (c) acetyl chloride; pyridine, DMAP; (d) KHMDS, TESCl, THF, Δ, 3 h; (e) *m*-CPBA; (f) Amberlyst 15; (g) Ag_2O, 3,5-bis(trifluoromethyl)benzyl bromide, DMF, 23 °C, 48 h; (h) 4-hydroxy-4-phenylpiperidine, $NaBH_3CN$, 2,2,2-Trifluorethanol, 3 Å mol. sieves; (i) Jones; (j) gly-NH_2·HCl, $NaBH_3CN$, MeOH.



11
K_i (NK_1) = 9 nM
K_i (NK_2) = 34 nM

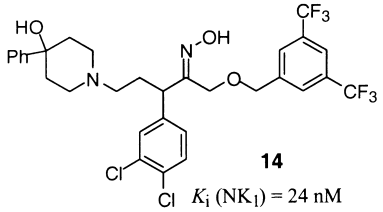


12
K_i (NK_1) = 5 nM
%I (NK_2) = 10% @ 0.1 μM

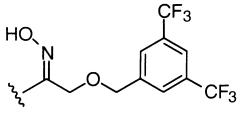


13
K_i (NK_1) = 0.7 nM
%I (NK_2) = 27% @ 0.1 μM

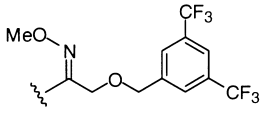
The disappointing 30% yield of the reductive amination of ketone **8** prompted further studies to optimize the transformation of **8** to diamine **9**. Since oximes are readily transformed into amines, and they represent an interesting moiety from an SAR perspective, we decided to utilize this group in this series. Thus, treatment of ketone **8** with both hydroxylamine and methoxylamine provided the corresponding oximes **14** through **17**. Although all attempts to reduce these oximes failed, subsequent biological evaluation of these intermediates revealed a new class of neurokinin dual antagonists. In all cases, regardless of the oxime geometry, the NK_1 activity is similar (i.e., $K_i = 25$ nM). Although the NK_2 activity varies as a function of oxime geometry and substitution, the Z-methyloxime, **17** shows very promising NK_2 binding with a $K_i = 21$ nM.



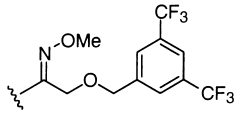
14
K_i (NK_1) = 24 nM
K_i (NK_2) = 122 nM



15
K_i (NK_1) = 34 nM
K_i (NK_2) = 358 nM

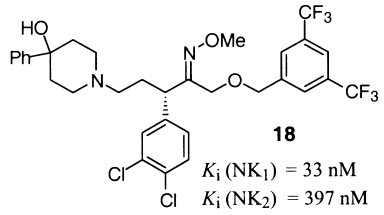


16
K_i (NK_1) = 25 nM
%I (NK_2) = 35% @ 1 μM

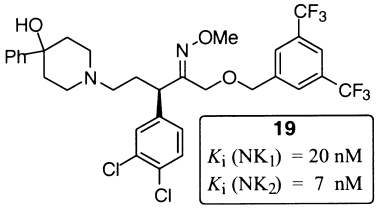


17
K_i (NK_1) = 25 nM
K_i (NK_2) = 21 nM

Resolution of the enantiomers of oxime **14** by chiral HPLC followed by methylation provided the optically pure methyloximes **18** and **19**. Subsequent biological evaluation revealed **19** to be a novel dual antagonist with K_is of 20 and 7 nM for the NK_1 and NK_2 receptors, respectively. Synthesis of **19** from optically pure intermediates confirmed the absolute stereochemistry to be the *R* configuration.[17]



18
K_i (NK_1) = 33 nM
K_i (NK_2) = 397 nM



19
K_i (NK_1) = 20 nM
K_i (NK_2) = 7 nM

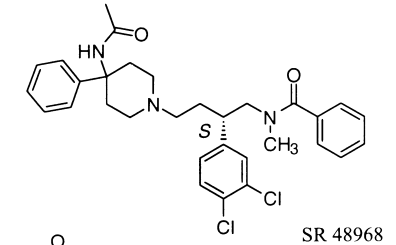
Discussion

Utilizing SR 48968, a selective NK_2 antagonist, as a scaffold, we have designed two unique classes of NK_1/NK_2 dual antagonists, diamines and oximes. It is very interesting to note that the usual stereochemical preference of known selective NK_2 receptor antagonists is the *S* enantiomer. This is not only the case for SR 48968, but also for the dual antagonists reported by both Merck and HMR during the course of our research. In fact, the design of MDL 105,212 utilized molecular modeling studies which showed very good overlap of the 3,4-dichlorophenyl ring, the benzamide aromatic ring, a hydrogen bond acceptor[14] and the piperidine nitrogen with SR 48968. Correspondingly, Merck's dual antagonists contain no functional backbone modifications to SR 48968; hence it is reasonable to assume the overlap of these groups with SR 48968 is very good.

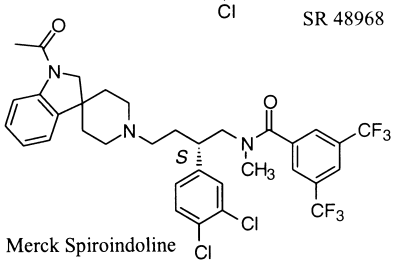
In our work we have found that in modifying the backbone of the Sanofi antagonist, the stereochemical preference can be significantly affected by functional groups adjacent to the benzylic center. In the case of our original designed amine branched antagonists, dual activity was imparted to the Sanofi scaffold by the introduction of the Merck NK_1 pharmacophore. Unexpectedly, the introduction of this unit in a stereospecific manner reverses the stereopreference for the NK_2 receptor. In this series, no isomers containing the *S* stereochemistry, show any appreciable affinity for the NK_2 receptor. The stereochemistry does not appreciably influence the NK_1 binding.

In the case of the oxime derivatives, the introduction of the achiral oxime functional group adjacent to the benzylic center also reverses the stereopreference for the NK_2 receptor such that the dual active compounds

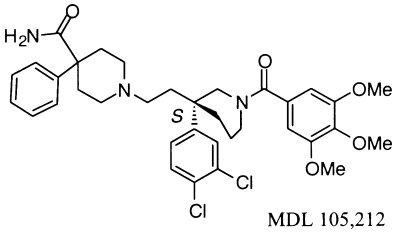
contain the *R* stereochemistry as well. Similarly, for this class, the NK_1 activity is relatively unaffected by the stereochemistry of the benzylic center.



SR 48968



Merck Spiroindoline



MDL 105,212

In summary, we have discovered two novel classes of NK_1/NK_2 dual antagonists. The novelty of the oxime class of compounds in particular, has prompted further SAR investigation of this class of compounds, the results of which will be the subject of future publications.

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16. 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.
17. Manuscript in preparation.