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Preparation of Oxime Dual NK_1/NK_2 Antagonists with Reduced NK_3 Affinity

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Abstract—By employing a stereosimplification approach, a thorough SAR exploration of the piperidine region of Sch 206272 was possible through a practical and efficient synthesis of substituted cyclic ureas. This SAR study led to the identification of a benzimidazolinone series of compounds which display single digit nanomolar NK_1/NK_2 affinity and near micromolar binding for the NK_3 receptor.

Activation of sensory C afferent nerves by irritants and/or inflammatory mediators results in the co-release of the neurokinin oligopeptides, substance P (SP) and neurokinin A (NKA) in pulmonary tissue.[1] These neuropeptides bind to the NK_1 and NK_2 receptors respectively resulting in bronchoconstriction, vasodilation, smooth muscle contraction, edema, and neurogenic inflammation.[2] The involvement of these tachykinin neuropeptides in the pathophysiology of asthma makes them an attractive target for a new approach to asthma therapy by means of simultaneous blockade of the corresponding NK_1 and NK_2 receptors.

A third neuropeptide, neurokinin B (NKB), interacts primarily with the NK_3 receptor, however, similar to SP and NKA, there is overlapping specificity with the other NK receptors. The NK_3 receptor is present in the CNS as well as peripheral tissues. Although no NK_3 receptors have been localized in the respiratory tract,[3] SR 142801, an NK_3 antagonist, has been shown to affect cough, histamine potentiated microvasculature leakage, and airway hyperresponsiveness to acetylcholine.[4] Furthermore, there have been recent disclosures of the involvement of NKB, as well as possibly SP and NKA in the hypothalamic–pituitary axis.[5]

Since each of these three neuropeptides is capable of eliciting responses from all three neurokinin receptors, the overlapping specificity of agonist activity provides a challenging problem in understanding the nature of the neurokinin–endocrine relationship.

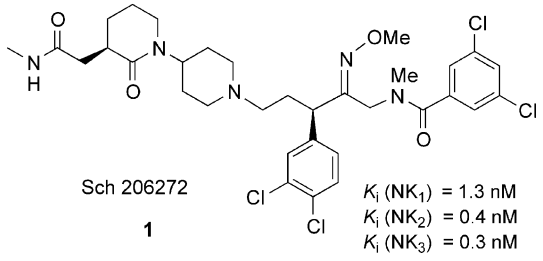

Figure 1.

The design and synthesis of NK_1/NK_2 dual antagonists is an active area of research in our labs as well as many others.[6] Structural modification[7] of an oxime lead structure[8] resulted in the identification of Sch 206272 (Fig. 1) as a potent dual NK_1/NK_2 antagonist that is quite active in vivo in both guinea pig and dog.[9] In addition to functioning as an effective NK_1/NK_2 dual antagonist, the binding affinity of Sch 206272 for the NK_3 receptor, is quite potent ($K_i = 0.3$ nM). Interestingly, a recent disclosure of the effect of *selective* NK_3 antagonists on testosterone and gonadotrophins[10] suggests that the NK_3 receptor may play a major role in the control of androgen/gonadotrophin production/secretion. While

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targeting NK_3 may be an interesting goal as an anti-androgen therapeutic, our interest in developing a dual NK_1/NK_2 antagonist for use in asthma prompted us to minimize NK_3 binding to avoid any potential NK_3 mediated effects controlled by the hypothalamic–pituitary axis.

Rapid second-generation exploration of the bipiperidine fragment to probe for diminished NK_3 binding was envisioned by utilizing a stereosimplification approach. The corresponding cyclic urea could allow for rapid access to a large number of structurally divergent groups driven by amine availability. Critical to this strategy was a practical and robust synthesis for the appropriately protected aldehyde **4**, wherein the protective group on the exocyclic amine could serve as the carbonyl source for the urea (Fig. 2).

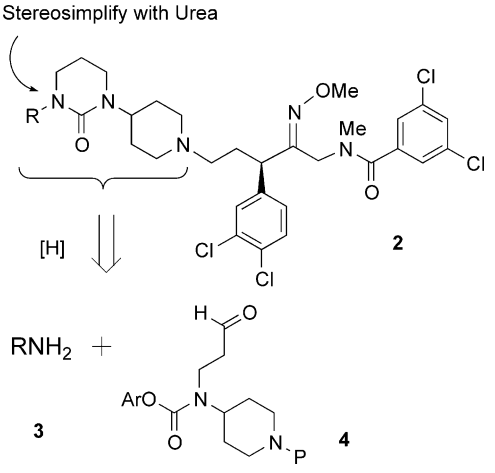
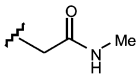
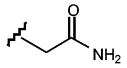
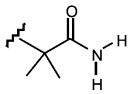
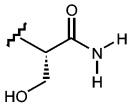
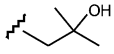
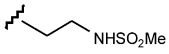
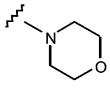
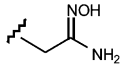
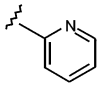
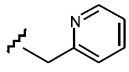
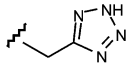
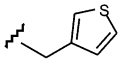
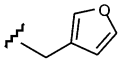
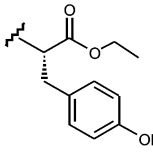
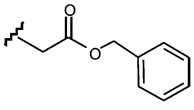
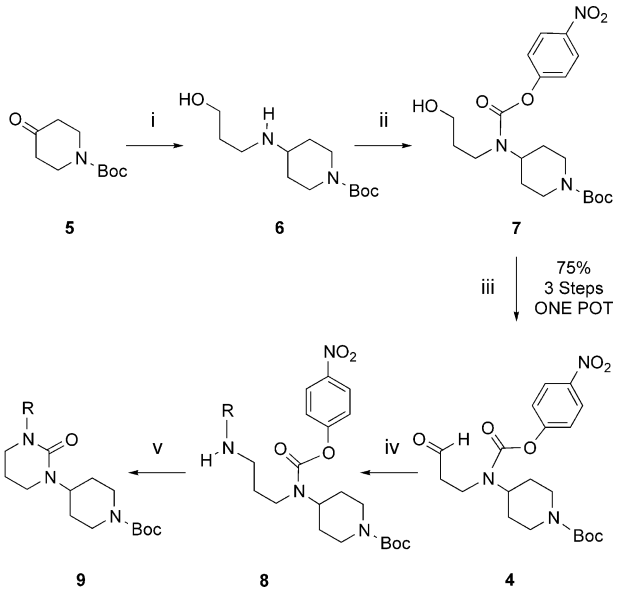


Figure 2.

Thus, synthetically, a one-pot procedure was developed for the preparation of aldehyde **4** (Scheme 1). The reductive amination of 3-amino-1-propanol with *N*-Boc-4-piperidone in 1,2-dichloroethane provided the amino alcohol **6**. Addition of saturated aqueous sodium bicarbonate to the reductive amination mixture followed by carbamate formation with *p*-nitrophenyl chloroformate proceeded smoothly. These biphasic conditions were then employed for the subsequent alcohol oxidation employing bleach/sodium bromide with a catalytic amount of TEMPO to give the aldehyde **4** in excellent overall yield over three steps in a one-pot procedure. Subsequent reductive amination with the desired amine is followed by spontaneous cyclization with unhindered amines to give the desired *N*-Boc protected piperidines. More hindered amines such as isopropyl amine or less reactive amines such as amino pyridines require heating in DMF for the cyclization to occur. Derivatives with N–O bonds (derived from hydroxyl or alkoxyl amines), N–N bonds (derived from hydrazines) and *N*-heterocyclic groups are readily and rapidly prepared in the urea series. The route is quite general (works well with other amino alcohols), and is amenable to large scale synthesis (over 150 g of pure, stable aldehyde (**4**) has been prepared in yields greater than 75%). The synthesis of targets is for the most part dependent on securing the appropriate amine.

Table 1. Structure–activity relationships: modifications of **2**

Compd	R	K_i (nM)		
		NK_1	NK_2	NK_3
10		0.9	1.2	1.3
11		0.3	0.2	0.4
12		0.8	0.4	0.3
13		0.6	0.5	0.3
14	-Me	0.4	0.7	0.8
15		0.9	0.8	0.6
16		0.5	0.8	0.5
17	-OH	1.0	0.7	0.7
18		0.6	0.5	0.4
19		0.8	0.9	0.5
20		0.6	0.8	0.5
21		1.9	0.5	0.5
22		0.7	0.7	0.8
23		1.0	0.9	2.0
24		2.4	1.2	3.2
25		1.1	1.1	2.2
26		1.6	1.2	10.9
27		1.0	1.2	11.8

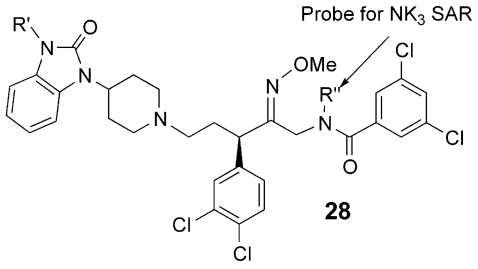


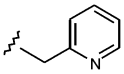
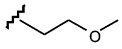
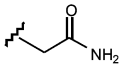
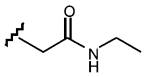
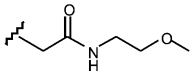
Scheme 1. Reagents and conditions: (i) aminopropanol, sodium triacetoxyborohydride, 2 h; (ii) add saturated sodium bicarbonate, followed by *p*-nitrophenylchloroformate; (iii) sodium bromide, TEMPO, sodium hypochlorite; (iv) RNH_2, sodium triacetoxy-borohydride, 2 h; (v) DMF, heat if needed.

The direct stereosimplified methyl amide analogue (Table 1, entry 10) of Sch 206272 revealed that removal of the piperidone chiral center has little effect on the binding affinity for the neurokinin receptors.[11] Subsequent alteration of the functionality stemming from the urea nitrogen showed that this region of the receptor tolerates a wide range of steric and functional modifications. A number of methyl carboxamides (entries 10–13) are quite active at all three NK receptors. Accordingly, simple alkyl groups such as methyl and isopropyl (entries 14 and 15) are accommodated as well. The hindered tertiary alcohol (entry 16) and the hydroxyl urea (entry 17) bind with excellent affinity to all of the neurokinin receptors, showing no bias against the NK_3 receptor. Substitution with amine functionality of various basicities ranging from neutral (entry 18) to a basic hydrazide (entry 19) to the more basic hydroxyamidine (entry 20) showed little effect on binding and no impact on reducing NK_3 affinity. Heterocyclic amines (entries 21–23) similarly had no effect on selectivity for the NK receptors. Although the tetrazole, thiazole and furan (entries 23–25) showed little effect on NK_3 binding, the neutral phenyl substituted changes (entries 26–27) did show a 7- to 10-fold selectivity for decreased NK_3 affinity over the NK_1 or NK_2 receptors. This prompted us to investigate a series of compounds containing a fused aryl ring with a fixed conformation relative to the cyclic urea functional group, the benzimidazolinone class.

Benzimidazolinone analogues (Table 2) were prepared by standard protection and subsequent alkylation/functionalization from the commercially available parent 4-(2-keto-1-benzimidazolinyl)piperidine. It was interesting to find the parent unsubstituted benzimidazolinone (entry 29) showed an 8- to 10-fold selectivity in affinity of NK_1 and NK_2 over NK_3 binding. Functionalization of the urea nitrogen revealed a fairly consistent selectivity over NK_1 and NK_2, as illustrated by the methyl, carbomethoxymethyl and carboxymethyl analogues (entries 30–32). Alteration of the benzamide methyl group resulted in targets with significantly reduced NK_3 affinity. While the *N*-ethyl derivative (entry 33) displayed greater than 30-fold selectivity over NK_3, the monofluoroethyl derivatives (entries 34 and 35) were the first analogues to show 50- to 100-fold selectivity in binding for NK_1 and NK_2 over NK_3. Although this selectivity was encouraging, potential toxic metabolites arising from the monofluoroethyl moiety stemmed further interest in these analogues. Interestingly, the *N*-cyclopropyl derivative (entry 37) showed a similar effect on NK_2 and NK_3 binding, however, the NK_1 affinity was significantly diminished, thus providing an avenue for designing NK_2 selective compounds in this class, if desired. Since we were concentrating on NK_1/NK_2 selective antagonists, we focussed our subsequent SAR around the *N*-ethyl benzamide benzimidazolinone class. Preparation of the 2-piperidinylmethyl, methoxymethyl and cyanomethyl analogues (entries 38–40) provided selectivities ranging from around 100 to over 250-fold of NK_1 and NK_2 over

Table 2. Structure–activity relationships: benzimidazolinone series



Compd	R′	R″	K_i (nM)		
			NK_1	NK_2	NK_3
29	-H	$-CH_3$	1.2	1.0	10
30	$-CH_3$	$-CH_3$	1.5	1.5	20
31	$-CH_2COOMe$	$-CH_3$	1.3	1.8	29
32	$-CH_2COOH$	$-CH_3$	1.3	1.7	11
33	$-CH_2COOH$	$-CH_2CH_3$	2.4	5.2	176
34	$-CH_2COOH$	$-CH_2CH_2F$	1.2	3.1	304
35	-H	$-CH_2CH_2F$	3.2	4.9	231
36	-H	$-CH_2CH_3$	2.5	2.6	97
37	-H		157	2.5	103
38		$-CH_2CH_3$	2.7	2.8	312
39		$-CH_2CH_3$	2.0	4.0	572
40	$-CH_2CN$	$-CH_2CH_3$	2.3	2.5	674
41		$-CH_2CH_3$	2.4	4.8	167
42		$-CH_2CH_3$	3.0	3.6	281
43		$-CH_2CH_3$	1.9	4.1	945

NK_3 binding. Finally, refocusing on amide derivatives (entries 41–43) of the pivotal carboxymethyl lead (entry 33) led to the discovery of the methoxyethyl methyl carboxamide, **43** which has single digit nanomolar NK_1/NK_2 affinity and near micromolar binding for the NK_3 receptor.

Summary

Subsequent to the identification of Sch 206272 as a potent subnanomolar NK_1/NK_2/NK_3 antagonist and the emerging literature on the involvement of neurokinins in the hypothalamic-pituitary axis, a study was undertaken to reduce the NK_3 binding in this class. By employing a stereosimplification approach, a thorough SAR exploration of the piperidine region of Sch 206272 was possible through a practical and efficient synthesis of substituted cyclic ureas. This SAR study led to the identification of the benzimidazolinone series of compounds illustrated by compound **43** which displays single digit nanomolar NK_1/NK_2 affinity and near micromolar binding for the NK_3 receptor.

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11. Receptor binding assays were performed on membrane preparations containing recombinant human NK_1, NK_2 or NK_3 receptors in CHO cells. [^{3}H]Sar SP, [^{3}H]NKA and [^{125}I][MePhe]NKB were used as ligands for the NK_1, NK_2, and NK_3 receptor binding assays, respectively, at the experimentally derived K_ds. K_is were obtained according to the Cheng and Prussoff equation. CP-96345, SR-48968 and SR-142801 were run as NK_1, NK_2, and NK_3 standards, respectively, revealing an inter-run variability within 2-fold.