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Synthesis of Substituted 4(*Z*)-(Methoxyimino)pentyl-1-piperidines as Dual NK_1/NK_2 Inhibitors

Pauline C. Ting,* Joe F. Lee, John C. Anthes, Neng-Yang Shih and John J. Piwinski

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033-1300, USA

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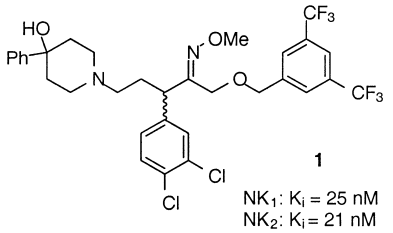
Abstract—The NK_1 and NK_2 receptor activity of a series of 5-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-3-(3,4-dichlorophenyl)-4(*Z*)-(methoxyimino)pentyl-1-piperidines was evaluated. Compounds **11d**, **11e**, **11f**, **12a**, and **12k** were found to be our most potent inhibitors.

Introduction

The tachykinins are a family of neuropeptides that share a common C-terminal sequence of Phe-X-Gly-Leu-Met-NH_2 and are found throughout the central and peripheral nervous system.[1] There exists three G-protein linked neurokinin receptors (NK_1, NK_2, and NK_3) through which the biological effects are transmitted. Although each neurokinin can act as an agonist at all three receptors, Substance P (SP), Neurokinin A (NKA), and Neurokinin B (NKB) have the highest affinity for the NK_1, NK_2, and NK_3 receptor, respectively.[2] The neurokinins may play an important role in several disease states, which include migraine, emesis, pain, arthritis, depression, anxiety, and asthma.[3] Our research interest lies in the theory that both SP and NKA are responsible for the excessive mucus secretion, airway constriction, and plasma extravasation found in the pathology of asthma.[4]

Our goal was to design and synthesize a compound that will block both the NK_1 and NK_2 receptors as a means of alleviating asthma. Compound **1** was identified as a potent dual NK_1 and NK_2 receptor antagonist.[5] In this communication, we describe a series of analogues that have diverse substituents at the 4-position of the piperidine ring.



1

NK_1: K_i = 25 nM
NK_2: K_i = 21 nM

Results and Discussion

The substituted 4(*Z*)-(methoxyimino)pentyl-1-piperidines were prepared as the racemates by the synthetic route outlined in Scheme 1. Reductive amination[6] of *N*-benzyl-4-piperidone (**2**) and subsequent hydrogenation[7] provided amine **3**. Coupling of amine **3** with 1-[[3,5-bis(trifluoromethyl)phenyl]methoxy]-3-(3,4-dichlorophenyl)-5-formyl-2(*Z*)-pentanone *O*-methyl-oxime (**4**)[8] produced the analogues **5**.[9] The synthesis of compounds **9** began with the protection of 4-hydroxymethylpiperidine (**6**) as its *t*-BOC derivative. Swern oxidation[10] of **6** followed by reductive amination and acid catalyzed removal of the *t*-BOC group afforded amine **8**. Addition of amine **8** to aldehyde **4** yielded the targets **9**.

The NK_1 and NK_2 biological activity of piperidines **10a–f** are reported in Table 1.[11] Replacement of the 4-hydroxy-4-phenylpiperidine subunit of **1** with the 4-(carbon linked amide)piperidines **10a** or **10b** increases NK_1 potency, but appears to decrease NK_2 potency.

*Corresponding author. Fax: +1-908-740-7152; e-mail: pauline.ting@spcorp.com

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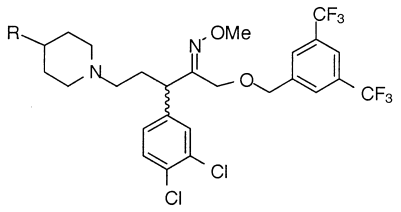
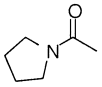
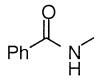
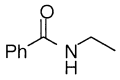
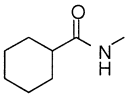
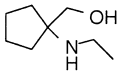
Table 1. NK_1 and NK_2 antagonistic activity of the piperidines **10a–f**



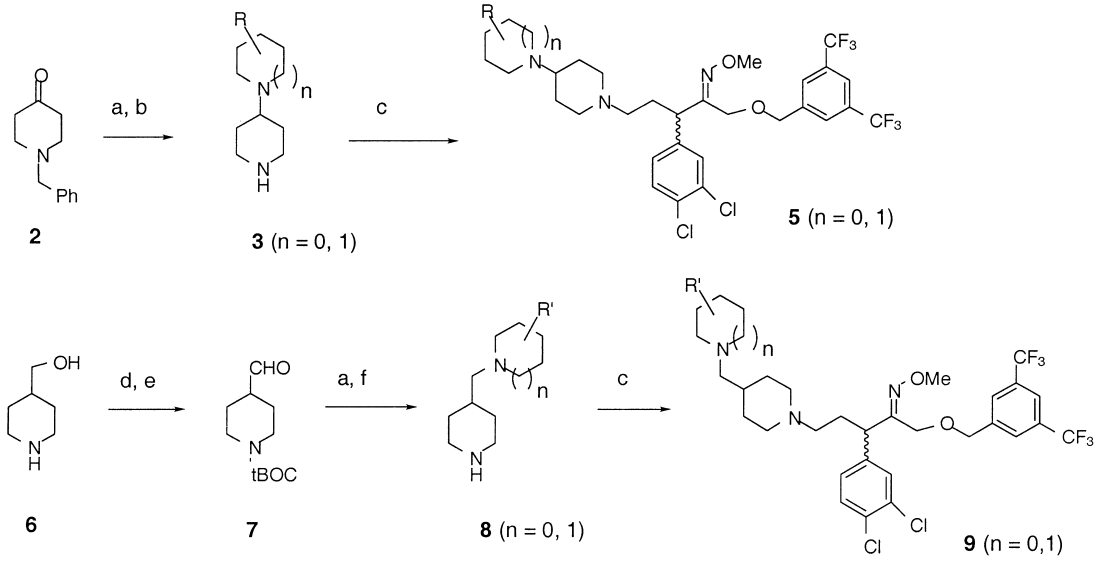
Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
10a		8 (±3)	67
10b		6 (±2)	59
10c		18 (±4)	144
10d		112	137
10e		44	146
10f		24 (±7)	16 (±8)

[a]Values are means of two experiments. If values are means of three experiments, standard deviation is given in parentheses.

The 4-(nitrogen linked amide)piperidines **10c–e** show greatly reduced NK_2 activity. In this set of racemic analogues, only the hydroxyamino substituted piperidine **10f** is equipotent to our lead structure **1**.

Additional analogues that have a second piperidine or pyrrolidine ring attached to the 4-position of the piperidine are summarized in Table 2. The piperidone **11a**[12] shows increased potency for both the NK_1 and NK_2 receptors relative to the 4-hydroxy-4-phenylpiperidine **1**. Similarly, the corresponding pyrrolidone analogue **11f** and the thiopyrrolidine analogue **11g** both retain this desired dual NK_1/NK_2 profile. In contrast, the pyrrolidine analogue **11h** reduces NK_2 potency to a much greater extent than NK_1 potency. Introduction of a hydroxy moiety on the piperidine ring as in **11b** or the pyrrolidine ring as in **11i** retains NK_1 and NK_2 activity. A carboxyamide group can also be added to the piperidine ring as in **11d** or the pyrrolidine ring as in **11e** and produces potent NK_1 and NK_2 receptor affinity. However, a less polar carboxyester substituent as in **11c** or a carbamate substituent as in **11j** shows decreased biological activity.

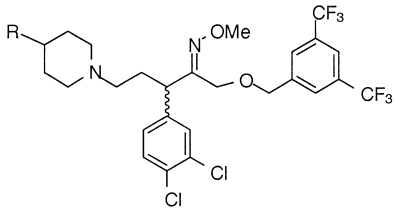
In Table 3 our analogues that have a methylene linker between the two piperidine rings are tabulated. The parent piperidone **12a** and the pyrrolidone analogue **12d** possess increased NK_1 and NK_2 potency relative to our lead structure **1**. The thiopiperidone **12c** and the reduced piperidine analogue **12b** are slightly less active. Alkylation at the α-position of the piperidone **12a** gives analogues **12e–h**. Steric size appears to be detrimental to biological activity as evident by the benzyl analogue **12e**. Hydroxy groups are well-tolerated as in analogue **12h**. When the second piperidine ring is a morpholine ring as in **12i**, NK_1 activity is retained and NK_2 activity

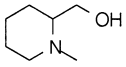
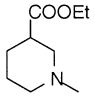
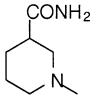
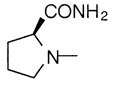
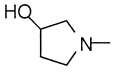
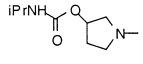


Scheme 1. (a) Substituted amine, $NaCNBH_3$, CF_3CH_2OH, 3 Å sieves, 42–83%; (b) H_2, Pd/C, MeOH, 83–100%; (c) 1-[[3,5-bis(trifluoromethyl)phenyl]methoxy]-3-(3,4-dichlorophenyl)-5-formyl-2(*Z*)-pentanone *O*-methyloxime, 3 Å sieves, $NaCNBH_3$, CF_3CH_2OH, 32–63%; (d) $(t\text{-BOC})_2O$, CH_2Cl_2, 100%; (e) ClCOCOCl, DMSO, CH_2Cl_2, Et_3N, 100%; (f) CF_3COOH, CH_2Cl_2, 100%.

decreases slightly. Substitution at the 2-position of the piperidine ring indicates that the hydroxyethyl side chain of **12k** is more active than the hydroxymethyl side chain of **12j**. Compounds **12l–p** vary the size and polarity of the moiety at the 3-position of the piperidine ring, and none of these analogues are as potent as the piperidone **12a**.

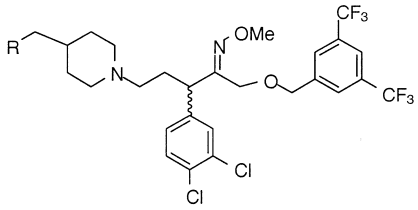
Table 2. NK_1 and NK_2 antagonistic activity of the piperidines **11a–j**

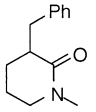
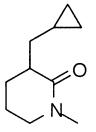
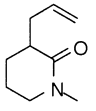
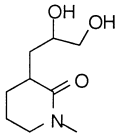
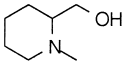
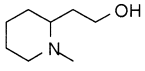
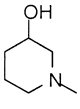
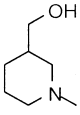


Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
11a		18 (±4)	4 (±1)
11b		14 (±3)	15 (±6)
11c		117	20
11d		13 (±4)	10 (±3)
11e		13 (±3)	11 (±3)
11f		9 (±2)	7 (±2)
11g		16 (±3)	23 (±8)
11h		36	195
11i		4	16
11j		19 (±7)	67 (±19)

[a]Values are means of two experiments. If values are means of three experiments, standard deviation is given in parentheses.

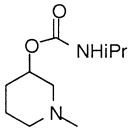
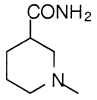
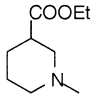
Table 3. NK_1 and NK_2 antagonistic activity of the piperidines **12a–p**



Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
12a		10 (±3)	12 (±2)
12b		36 (±23)	26 (±4)
12c		20 (±7)	23 (±6)
12d		8 (±3)	21 (±6)
12e		69	91
12f		14 (±5)	26 (±7)
12g		13	58
12h		7 (±4)	16 (±8)
12i		14 (±10)	39 (±11)
12j		20	53
12k		13 (±3)	14 (±3)
12l		38	47
12m		50 (±30)	39 (±9)

(continued on next page)

Table 3 (*continued*)

Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
12n		17 (±3)	33 (±5)
12o		25 (±10)	27 (±18)
12p		16 (±1)	28 (±7)

[a]Values are means of two experiments. If values are means of three experiments, standard deviation is given in parentheses.

Conclusion

In conclusion, the left hand region of our lead NK_1/NK_2 inhibitor structure **1** appears to be quite tolerant to structural modifications. We have found that the 4-hydroxy-4-phenyl substituent of piperidine **1** can be replaced by a piperidone ring as in compounds **11a** and **12a**. From this structure–activity relationship study, several diverse analogues including compounds **11d**, **11e**, **11f**, and **12k** were found to be our most potent dual inhibitors. The results of our efforts to further optimize the biological profile of this series of dual NK_1/NK_2 antagonists will be forthcoming.

Acknowledgements

The authors would like to thank Mr. Z. Zhan and Mr. Christian Richard for conducting the NK_1 and NK_2 receptor binding assays.

References and Notes

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9. All synthesized compounds were fully characterized by ^1H NMR, ^{13}C NMR, and high-resolution mass spectroscopy.
10. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
11. Binding data are the average of two or three independent determinations. Receptor binding assays were performed on membrane preparations containing recombinant human NK_1 or NK_2 receptors in CHO cells. [^3H]Sar SP and [^3H]NKA were used as the ligands for the NK_1 and NK_2 receptor assays, respectively, at the experimentally derived K_d values. K_i values were obtained according to the Cheng and Prussoff equation.
12. Miller, S. C. W.O. Patent 94/10 146, 1994; *Chem. Abstr.* **1994**, 122, 105675.