Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2333–2335

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and NK_1/NK_2 Receptor Activity of Substituted-4(*Z*)-(methoxyimino)pentyl-1-piperazines

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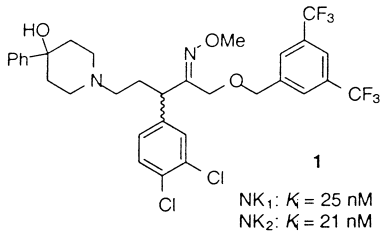
Received 9 June 2000; accepted 7 August 2000

Abstract—A series of 5-[(3,5-bis(trifluoromethyl)phenyl)methoxy]-3-(3,4-dichlorophenyl)-4(*Z*)-(methoxyimino)pentyl-1-piperazines was prepared and their affinity for the NK_1 and NK_2 receptors investigated. Compounds **7f**, **10o**, **10r**, and **10s** were found to be our most potent inhibitors.

Introduction

Substance P (SP), neurokinin A (NKA), and neurokinin B (NKB) are members of 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 systems.[1] These peptides exert their biological effect through three neurokinin receptors (NK_1, NK_2, and NK_3), which are each G-protein linked to secondary messenger systems. Although each neurokinin can act as an agonist at all three receptor subtypes, 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 a number of disease states including migraine, emesis, pain, arthritis, depression, anxiety, and asthma.[3] In particular, it is believed that both SP and NKA are responsible for the excessive mucus secretion, airway constriction, and plasma extravasation found in the pathology of asthma.[4] Therefore, our goal was to discover a compound which could block both the NK_1 and NK_2 receptors as a therapy for the treatment of asthma.



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

Biological screening[5] of directed targets and synthetic intermediates in the program identified oxime **1** to be a potent dual NK_1 and NK_2 receptor antagonist.[6] In this communication, we describe a series of analogues in which the piperidine ring has been replaced by an array of substituted piperazines.

Results and Discussion

The target piperazines **7a**–**f** were prepared as the racemates by the synthetic route shown in Scheme 1.[7] 1,4-Addition of ethyl 1,3-dithiolane-2-carboxylate (**2**) to methyl *trans*-3,4-dichlorocinnamate gave the diester **3**.[8] Reduction of the diester **3** with lithium aluminum hydride and selective protection of the less hindered primary alcohol afforded the *t*-butyldimethylsilyl ether **4**. Alkylation of alcohol **4** with 3,5-bis(trifluoromethyl) benzyl bromide and removal of the silyl protecting group yielded compound **5**. Hydrolysis of the dithiane **5**,[9] treatment with methoxylamine,[10] and Swern oxidation[11] provided aldehyde **6**. Reductive amination[12] with aldehyde **6** produced the piperazines **7a**–**f**.

The biological activity of piperazines **7a**–**f** are summarized in Table 1. These results indicate that the unsubstituted piperazine **7a**, the alkylsubstituted piperazines **7b** and **7c**, and the arylsubstituted piperazines **7d** and **7e** all bind to the NK_1 receptor in favor of the NK_2 receptor. In this set of analogues, only the (pyrrolidinocarbonylmethyl)piperazine **7f** stands out as a dual NK_1/NK_2 antagonist.

Additional analogues based on the (pyrrolidinocarbonylmethyl)piperazine lead structure **7f** are reported in

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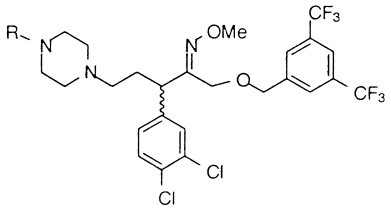
0960-894X/00/$ - see front matter
PII: S0960-894X(00)00464-9

Table 1. NK_1 and NK_2 antagonistic activity of the piperazines **7a–f**



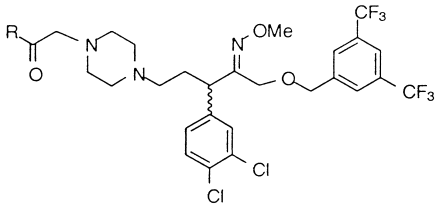
Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
7a	H	30	738
7b	Me	61	200
7c	Cyclohexyl	53	128
7d	Ph	181	978
7e	2-Pyrimidinyl	70	217
7f	*N*-PyrrolidinylCOCH$_2$	14	21

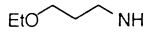
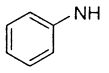
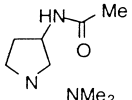
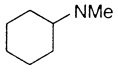
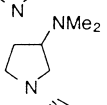
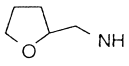
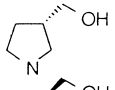
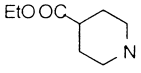
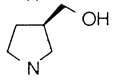
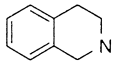
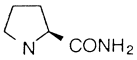
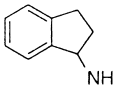
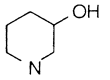
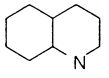
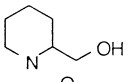
[a]Values are means of two experiments.

Table 2. These compounds were prepared by reductive amination of key aldehyde **6** with TROC-protected piperazine. Removal of the TROC moiety with zinc under buffered pH conditions avoided oxime isomerization which was observed under acidic conditions.[13] The analogues **10a–k** in Table 2 include a broad range of variation at the terminal amine position. Alkylation of piperazine **7a** in a parallel synthesis manner[14] gave target analogues **10a–k**. Relative to the standard **7f**, none of the piperazine analogues **10a–k** shows improved potency as a dual NK_1/NK_2 antagonist.

The analogues **10m–w** focus on a more specific structure–activity study of **7f**. Replacement of the pyrrolidine ring **7f** with the smaller azetidine ring as in **10m** or **10n** retains both NK_1 and NK_2 potency. The 3-position of pyrrolidine can be substituted with a hydroxy moiety as

Table 2. NK_1 and NK_2 antagonistic activity of the piperazines **l0a–w**



Compd	R	NK_1 K_i (nM)	NK_2 K_i (nM)	Compd	R	NK_1 K_i (nM)[a]	NK_2 K_i (nM)[a]
10a		82	208	**7f**		14 (±7)	21 (±7)
10b		62	259	**10m**		23 (±5)	33 (±8)
10c	$(iPr)_2N$	82	170	**10n**		22 (±5)	31 (±3)
10d		39	382	**10o**		16 (±4)	30 (±10)
10e		125	>680	**10p**		9 (±2)	48 (±25)
10f		113	368	**10q**		14 (±2)	95 (±26)
10g		20	266	**10r**		14 (±4)	13 (±2)
10h		24	409	**10s**		13 (±4)	24 (±6)
10i		125	566	**10t**		24 (±6)	26 (±8)
10j		136	>680	**10u**		13 (±3)	38 (±21)
10k		136	477	**10v**		47 (±24)	52 (±8)
				10w		19 (±4)	28 (±6)

[a]Values are the means of three experiments; standard deviation is given in parentheses.

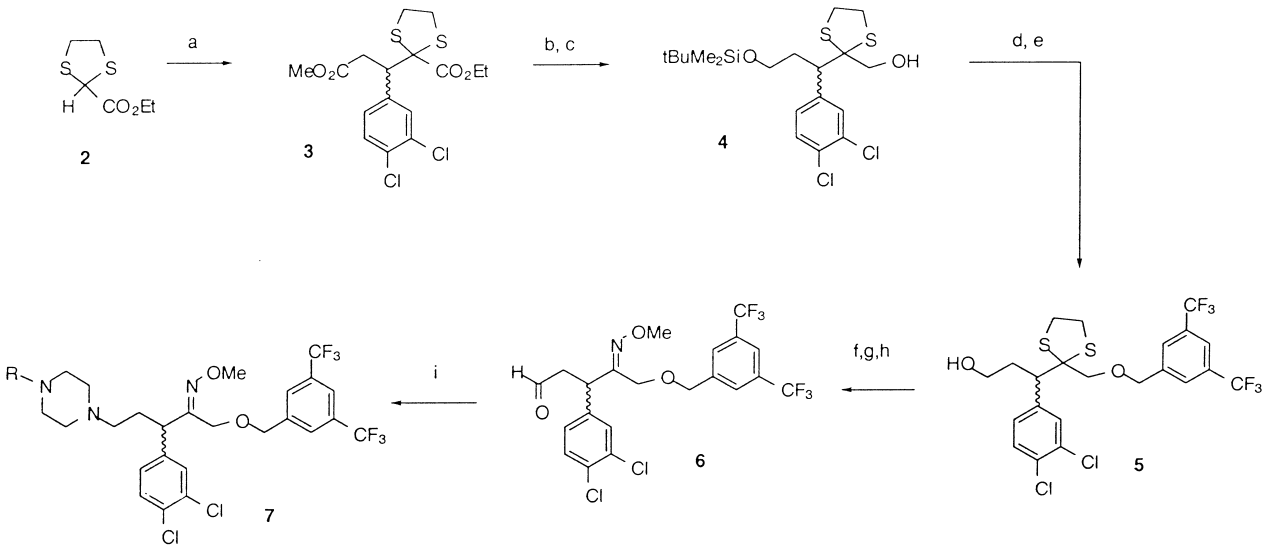


Figure 1. (a) $LiN(TMS)_2$, THF, −78°C, methyl *trans*-3,4-dichlorocinnamate, 87%; (b) $LiAlH_4$, THF, 0°C–23°C, 92%; (c) *t*-$BuMe_2SiCl$, Et_3N, DMAP, THF, 0°C–23°C, 96%; (d) $KN(TMS)_2$, THF, 3,5-bis(trifluoromethyl)benzyl bromide, 0°C–23°C, 88%; (e) HF, CH_3CN, 100%; (f) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, 100%; (g) $MeONH_2$-HCl, NaOAc, EtOH, H_2O, Δ, 58% of *Z* isomer and 25% of *E* isomer; (h) ClCOCOCl, DMSO, CH_2Cl_2, Et_3N, 100%; (i) substituted piperazine, $NaCNBH_3$, CF_3CH_2OH, 3 A sieves, 20–40%.

in **10o** and maintain biological activity. However, the larger acetamide group as in **10p** or the dimethylamino group as in **10q** both tend to decrease NK_2 potency but not NK_1 potency. The 2-position of the pyrrolidine is tolerant to substitution by a hydroxymethyl moiety as in the stereoisomers **10r** and **10s** or a carboxamide moiety as in **10t** and retains the dual neurokinin antagonist profile. In comparison to the hydroxypiperidine analogue **10u,** the hydroxymethylpiperidine **10v** shows a slight decrease in both NK_1 and NK_2 potency. The morpholine analogue **10w** possesses potent dual NK_1/NK_2 activity.

Conclusion

In conclusion, we have found that the 4-hydroxy-4-phenylpiperidine ring of compound **1** can be replaced by a totally different structural subunit—the (pyrrolidinocarbonylmethyl)piperazine **7f**. Modification of the pyrrolidine ring of **7f** with a hydroxy group retains biological activity, and analogues such as **10o**, **10r**, and **10s** are equipotent to **1** as a dual NK_1/NK_2 antagonist. Further structure–activity relationship studies will be reported in future publications.

Acknowledgements

We 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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5. 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. [^{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 values. K_i values were obtained according to the Cheng and Prussoff equation.
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14. Our parallel synthesis procedure was to react 11 different amines with bromoacetyl bromide in separate vials and subsequently treat with piperazine **7a**. The reaction mixtures underwent water work up, extraction, and analysis by mass spectroscopy.