Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 3055–3058

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Evaluation of Potent Pyrrolidine H_3 Antagonists

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Received 7 May 2002; accepted 6 August 2002

Abstract—The synthesis and biological evaluation of novel antagonists of the rat H_3 receptor are described. These compounds differ from prototypical H_3 antagonists in that they do not contain an imidazole moiety, but rather a substituted aminopyrrolidine moiety. A systematic modification of the substituents on the aminopyrrolidine ring was performed using pre-formatted precursor sets, where applicable, to afford several compounds with high affinity and selectivity for the H_3 receptor.
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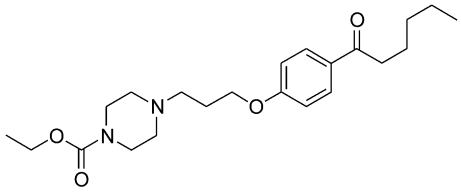
Histamine is thought to exert its actions in the CNS and periphery via the modulation of at least four distinct receptor subtypes.[1] The demonstration of the existence of the H_1 and the H_2 receptors, followed by an understanding of the physiological role of these receptors has resulted in the clinical applications of selective antagonists of these receptors in the treatment of allergic conditions (H_1 receptor antagonists) and gastric ulcers (H_2 receptor antagonists). Since the identification of the H_3 receptor in 1983,[2] several efforts aimed at gaining a better understanding of the functions modulated by this receptor subtype via the synthesis of selective ligands have been underway.[3] It has been found that H_3 receptors not only regulate the release of histamine, but also act as heteroreceptors involved in the regulation of the release of other neurotransmitters such as acetylcholine, dopamine, noradrenaline and serotonin.[4] Radiolabeling studies have shown the highest concentration of H_3 receptors to be in distinct areas of the CNS, suggesting a potential role for selective ligands of this receptor subclass in the treatment of various neurological and psychiatric diseases, such as epilepsy, schizophrenia, and attention deficit disorder (ADD).[5]

Attempts to identify selective ligands for the H_3 receptor have resulted in the identification of several potent and selective inhibitors, some of which are shown in Figure 1. Most of the initial approaches have focused on structural modification of the endogenous ligand, histamine, and have resulted in a series of very potent imidazole-containing H_3 antagonists, such as thioperamide,[6] GT-2331,[7] FUB 470,[8] and ciproxifan.[9] It has been speculated recently that the basic imidazole moiety of these compounds interacts with an active site aspartate.[10] Replacement of the potentially toxic isothiourea moiety in ligands similar to thioperamide resulted in the identification of guanidine containing compounds such as JB 98064.[11] Unsubstituted-imidazole containing compounds are known to interact with, and inhibit the cytochrome P450 system.[12] Though this feature can potentially be modulated by judicious substitution on the imidazole ring,[13] we have focused on developing non-imidazole H_3 antagonists. While this work was in progress, reports of non-imidazole containing H_3 antagonists have appeared in the literature.[14]



A-923

Compound A-923 was identified via high-throughput screening of the Abbott compound collection as a potent ($K_i = 2$ nM) rat H_3 antagonist.

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PII: S0960-894X(02)00685-6

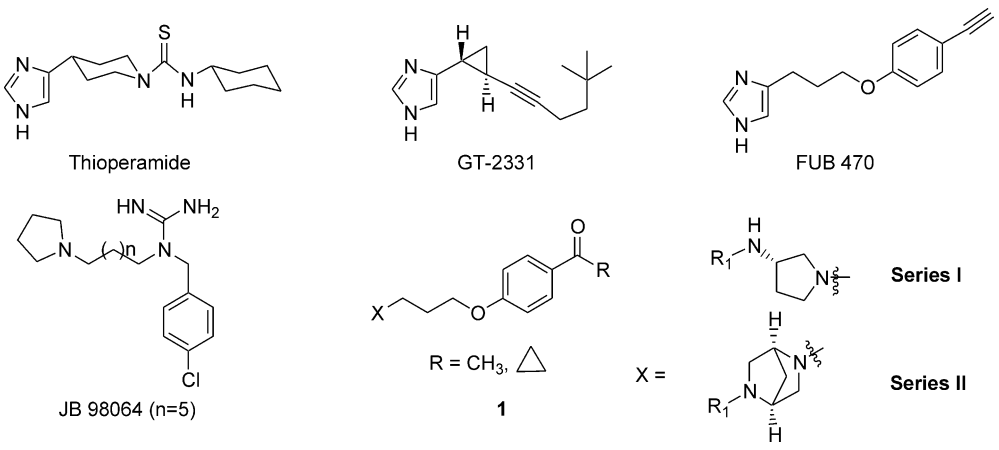
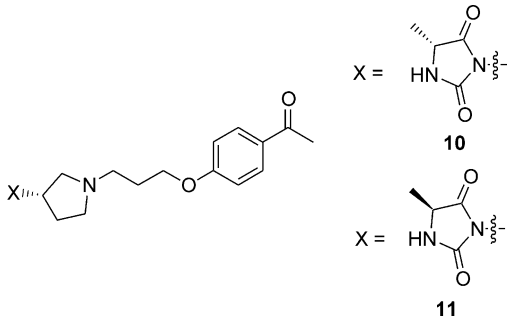


Figure 1.

This compound demonstrated poor oral bioavailability, as well as a lack of selectivity for other G-protein coupled receptors. We have previously reported on the structure–activity relationships of piperazine-containing H_3 antagonists, aimed at tackling some of these issues.[15] As part of our continuing effort to identify efficacious, orally bioavailable, non-imidazole containing ligands at the H_3 receptor, we wish to report preliminary results of novel ring-contracted analogues of A-923 wherein the piperidine ring was replaced with a pyrrolidine moiety. Prior SAR[15] had demonstrated that the methyl ketone of A-923 was equipotent, and hence preliminary SAR investigations were performed with this variant.

Most lead-optimization exercises tend to traditionally fall into two categories. In the first approach, some knowledge of the interactions between the ligand and the protein is available, either from prior SAR or structural information. In cases like this, a more structured or focused experimental design involving traditional analoging strategies outlined by Topliss,[16] Craig,[17] Wermuth,[18] and others is desirable. The second and perhaps more common lead-optimization exercise is one in which no ligand-protein information exists, which necessitates the synthesis of a diverse set of analogues, with the purpose of identifying an unexpected group or functionality that addresses some deficiency in the lead structure. We have recently reported on the feasibility of streamlining the experimental design comprising these two types of experiments to generate a set of automated medicinal chemistry approaches that can be applied for rapid and efficient lead-optimization.[19] The starting point for the delineation of optimal substitution patterns on the pyrrolidine nitrogen was the observation that the 3-*S*-amino isomer was about 35-fold more potent than the 3-*R* isomer in its binding affinity to the rat H_3 receptor (30 nM vs 811 nM, respectively, data not shown). Since the ring-contracted analogues were deemed to be a novel structural class, a concise set of experiments aimed at probing diverse substituents and linking elements, commencing with amides, attached to the pyrrolidine nitrogen of Series I was attempted. Incorporation of L and D-amino acids (Table 1, **5**–**9**) resulted in a significant reduction in binding affinity at the H_3 receptor. Further, there was only a modest preferential binding for the D-amino acids as compared to the L-amino acids, contrary to that observed in prior studies.[15] Conformational restriction of these side-chain amino acids via incorporation into hydantoins **10** and **11**, did not result in an improvement in binding affinity compared to the amino acids.

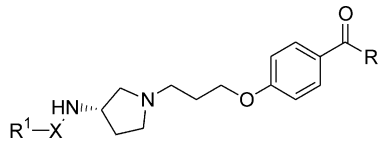


Acylation of the exocyclic amine with aryl groups afforded compounds **12**–**15** with reasonable binding affinity, but in general, these compounds were weaker than the original screening hit. Replacement of the acetyl moiety with a cyclopropyl ketone, as in **16** did not afford a measurable improvement in binding affinity at the H_3 receptor.

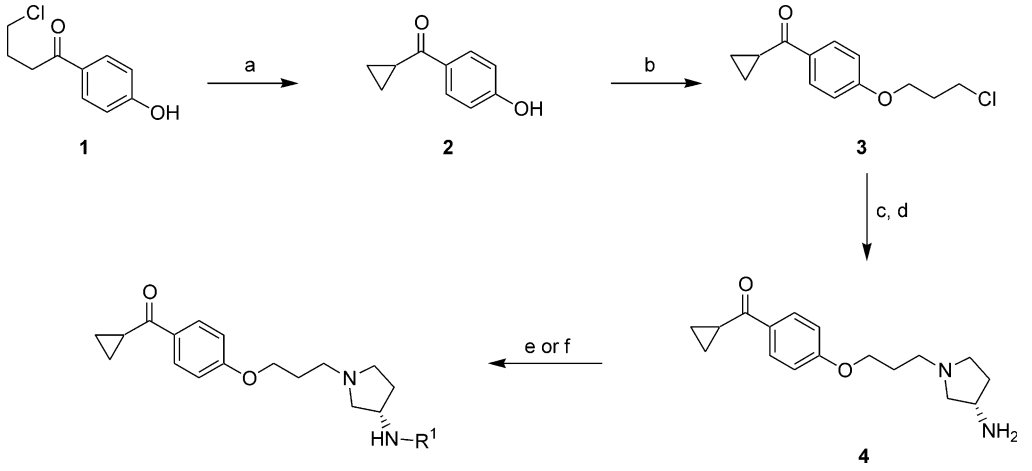
A representative synthesis of cyclopropyl-substituted compounds from Series I is shown in Scheme 1. Base-promoted cyclopropanation of **1**, followed by alkylation with 1-bromo-3-chloropropane, and a second alkylation with 3-*N*(*tert*-butoxycarbonyl)-amino pyrrolidine, afforded, after TFA treatment, the scaffold **4**, for investigation of the optimal substituent on the pyrrolidine ring.

Replacing the pyrrolidine ring in these compounds with the (*R*,*R*) enantiomer of 2,5-diazabicyclo[2.2.1]heptane, followed by acylation, afforded interesting results (Table 2). The receptor demonstrates a 7-fold preference for the Boc-protected D-amino acid compared to the D-amino acid side chain, while the deprotected compounds are equipotent (**17**–**20**). Acylation with alkyl, aryl and heteroaryl groups afforded equipotent compounds; however, branching beta to the carbonyl of the amide with hydrophobic groups results in a precipitous drop in potency. Incorporation of a β-alanine residue afforded **27** and **28**, which are the most potent compounds in this series.

Table 1. Binding affinities (K_i, nM) at rat cortical H_3 receptors and human H_1 and H_2 receptors[21]



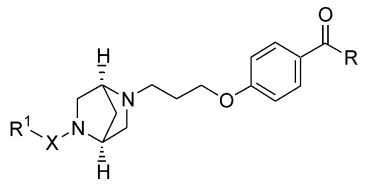
Compd	R	X	R^1	H_3	H_2	H_1
5	CH_3	CO	Boc L-Ala	901	24,000	60,000
6	CH_3	CO	Boc D-Ala	307	40,000	56,000
7	CH_3	CO	Boc L-Ser	587	46,000	75,000
8	CH_3	CO	Boc D-Ser	310	100,000	80,000
9	CH_3	CO	L-Ser	151	22,000	43,000
10	CH_3	—	—	1721	50,000	90,000
11	CH_3	—	—	676	31,000	100,000
12	CH_3	CO	2-Pyrazinyl	202	5000	10,000
13	CH_3	CO	3-Pyridyl	37	3500	7400
14	CH_3	CO	4-Thiazol[2-(3-pyridyl)]yl	55	6200	11,000
15	CH_3	CO	*p*-CN phenyl	40	6100	13,000
16	Cyclopropyl	CO	4-Thiazol[2-(3-pyridyl)]yl	50	4000	37,000
31	CH_3	SO_2	*p*-CN phenyl	6	2300	14,000
32	Cyclopropyl	SO_2	*p*-CN phenyl	4	1600	20,000
33	Cyclopropyl	SO_2	Phenyl	3	1200	9100
34	Cyclopropyl	SO_2	*o*-F phenyl	2.7	1550	9400
35	Cyclopropyl	SO_2	*m*-F phenyl	1.6	1600	5900
36	Cyclopropyl	SO_2	*p*-F phenyl	3.5	500	9200
37	Cyclopropyl	SO_2	*o*-Cl phenyl	3.7	1000	4500
38	Cyclopropyl	SO_2	*m*-Cl phenyl	3.0	700	3600
39	Cyclopropyl	SO_2	*p*-Cl phenyl	3.8	290	2500
40	Cyclopropyl	SO_2	*o*-CN phenyl	11	710	6200
41	Cyclopropyl	SO_2	*m*-CN phenyl	2.8	900	8900
42	Cyclopropyl	SO_2	*o*-CH_3 phenyl	11	2200	16,000
43	Cyclopropyl	SO_2	*m*-CH_3 phenyl	2.7	1800	6600
44	Cyclopropyl	SO_2	*p*-CH_3 phenyl	4.2	380	5500
45	Cyclopropyl	SO_2	*p*-OCH_3 phenyl	2.9	1000	4400
46	Cyclopropyl	SO_2	4-(*t*-butyl) phenyl	5.2	730	2300
47	Cyclopropyl	SO_2	*p*-Br phenyl	5	290	1500
48	Cyclopropyl	SO_2	4-(CH_2CH_3) phenyl	4.6	330	2300
49	Cyclopropyl	SO_2	*N*-CH_3-imidazol-4-yl	10	7100	91,000



Scheme 1. (a) NaOH, heat; (b) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone-reflux, 24 h; (c) 3*S*-(−)-3-(*tert*-butoxycarbonylamino)pyrrolidine, KI/K_2CO_3, 2-butanone, reflux, 64 h; (d) 5% TFA/CH_2Cl_2, 3 h; (e) R^1COOH, PS-DCC, cat. DMAP, DMF, (f) R^1SO_2Cl, PS-DMAP, CH_2Cl_2, 12 h.

Changing the linking element between the pyrrolidine nitrogen and the pendant substitution to a sulfonamide afforded significantly more potent compounds than the corresponding amides (**15** vs **31**). Given the increased metabolic stability, water solubility as well as hydrogen bonding potential of sulfonamides compared to amides,[20] these results were quite encouraging. Further, since it was observed that replacement of the acetyl functionality with a cyclopropyl ketone afforded comparable binding affinity at the H_3 receptor (**31** and **32**), all subsequent investigations were performed with the cyclopropyl ketone functionality. The sulfonyl chloride precursor inventory comprising both focused as well as diverse monomers (designed based on approaches mentioned previously) was used to synthesize sulfonamides, and several potent H_3 antagonists were identified from

Table 2. Binding affinities (K_i, nM) at rat cortical H_3 receptors and human H_1 and H_2 receptors[21]



Compd	R	X	R^1	K_i
17	Cyclopropyl	–CO—	Boc D-Ala	311
18	Cyclopropyl	–CO—	Boc L-Ala	2182
19	Cyclopropyl	–CO—	D-Ala	413
20	Cyclopropyl	–CO—	L-Ala	232
21	Cyclopropyl	–CO—	Cyclohexyl	134
22	Cyclopropyl	–CO—	Phenyl	344
23	Cyclopropyl	–CO—	*p*-F phenyl	258
24	Cyclopropyl	–CO—	2-Pyridyl	191
25	Cyclopropyl	–CO—	2-Furyl	208
26	Cyclopropyl	–CO—	$CH_2C(CH_3)_3$	10,000
27	Cyclopropyl	–CO—	Boc β-Ala	71
28	Cyclopropyl	–CO—	β-Ala	17
50	Cyclopropyl	$–SO_2–$	CH_2CH_3	120
51	Cyclopropyl	$–SO_2–$	Phenyl	19

this exercise, some of which are depicted in Table 1. Further, several substituents (F, Cl, CN, CH_3, OCH_3, and CH_2CH_3), which would be expected to impart varying pharmakokinetic and pharmacodynamic properties were identified. In addition, these compounds showed significant selectivity for the H_3 receptor compared to the H_1 and H_2 receptors (Table 1).

Incorporating similar substitution patterns in Series II did not improve the binding affinity as much as in the monocyclic pyrrolidine compounds, suggesting the importance of the hydrogen on the 3-amino substituent or the attenuated basicity of this series compared to Series I as being critical for affinity at the H_3 receptor. As a result, these compounds were not evaluated against H_1 and H_2 receptors.

In conclusion, a novel series of H_3 antagonists has been identified commencing with ring-contracted analogues of a screening hit, followed by systematic lead-optimization exercises using pre-formatted precursor sets to generate several extremely potent sulfonamide containing H_3 antagonists. Detailed in vivo studies on compounds identified from this study will be reported in the near future.

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