Bioorganic & Medicinal Chemistry Letters 20 (2010) 5004–5008

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

The synthesis and structure–activity relationship of 4-benzimidazolyl-piperidinylcarbonyl-piperidine analogs as histamine H_3 antagonists

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ARTICLE INFO

Article history:
Received 17 May 2010
Revised 9 July 2010
Accepted 13 July 2010
Available online 16 July 2010

Keyword:
Histamine H_3 antagonist

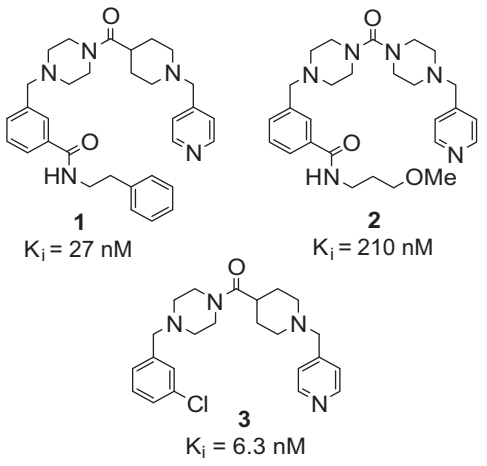
ABSTRACT

A structure–activity relationship study of the lead piperazinylcarbonylpiperidine compound **3** resulted in the identification of 4-benzimidazolyl-piperidinylcarbonyl-piperidine **6h** as a histamine-3 (H_3) receptor antagonist. Additional optimization of **6h** led to the identification of compounds **11i–k** with $K_i \leqslant 0.5$ nM and good in vivo activity.

The histamine H_3 receptor is a G-protein-coupled receptor in the histamine receptor family (H_1, H_2, H_3, and H_4) discovered by Arrang and co-workers in 1983.[1] It is a presynaptic receptor located in both the peripheral and central nervous system and acts as a negative feedback monitor by inhibiting the release of histamine as well as other neurotransmitters including serotonin, acetyl-choline, norepinephrine, dopamine, and GABA.[2] Therefore, a selective histamine H_3 antagonist will modulate neurotransmitter levels and may have potential use in a number of conditions such as metabolic syndrome, cognitive disorders, sleep, migraine, and inflammatory diseases.[3,4] Recently, the role of the H_3 receptor in CNS disorders has expanded.[5–7] In fact, many companies have entered clinical trials with H_3 ligands including Johnson and Johnson, GlaxoSmithKline, Merck, Sanofi Aventis, and Pfizer.[8,9]

Our initial research efforts on H_3 antagonists focused on imidazole based structures which often exhibited undesired liver enzyme P450 inhibitory activity.[10] Interest in the design and synthesis of H_3 antagonists which are an improvement over the early generations of imidazole based structures has escalated and is the subject of two reviews.[11,12] Current research efforts are directed at a variety of non-imidazole based structures.

Screening of a library, which originated from a collaboration with Pharmacopeia, produced a number of hits represented by compounds **1** and **2**. An analysis of the structure–activity relationship (SAR) from these hits indicated that the substituent on the piperazine ring was quite tolerant to change, and replacement of the *meta* amide group with a chlorine resulted in compound **3**, with 6 nM affinity in the H_3 binding assay.[13] Compound **3** was confirmed to be a full antagonist in a guinea pig ileum functional assay.[14]



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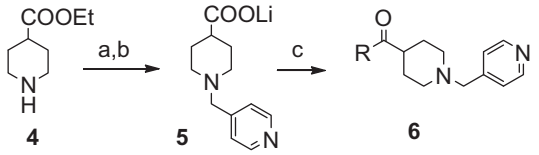
doi:10.1016/j.bmcl.2010.07.052

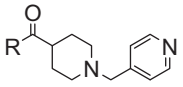


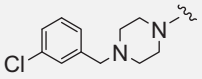
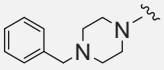
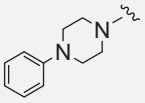
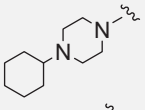
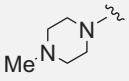
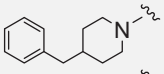
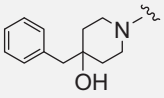
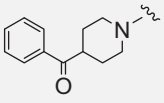
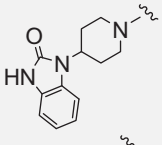
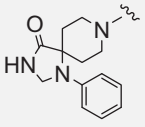
Scheme 1. Reagents: (a) 4-pyridylcarboxaldehyde, $NaB(OAc)_3H$, $ClCH_2CH_2Cl$, 3A sieves, 100%; (b) LiOH, MeOH, H_2O, 100%; (c) DCC, HOBT, CH_2Cl_2.

An initial SAR study of the left hand side piperazine moiety was undertaken first. The construction of selected analogs **6a**–i followed the synthetic route depicted in Scheme 1.[15] Reductive amination of ethyl isonipecotate (**4**) with 4-pyridylcarboxaldehyde and subsequent saponification with lithium hydroxide afforded the lithium salt **5**. Intermediate **5** coupled in moderate yields with a variety of piperidines and piperazines (DCC, HOBT) to afford compounds **6a–i**.

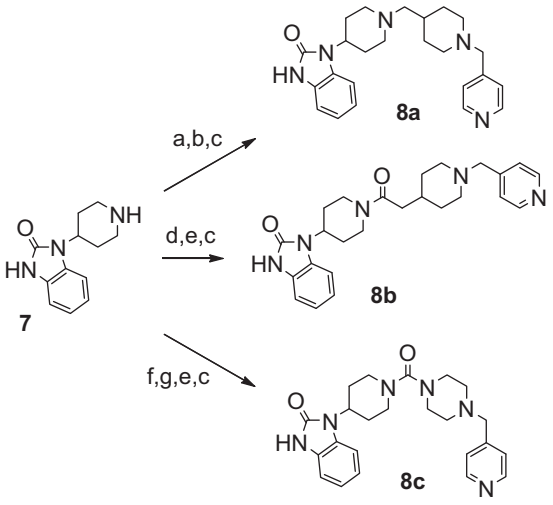
Compounds were tested for H_3 receptor binding activity, and the biological data are summarized in Table 1.[13] Replacement of the 3-chlorophenyl group with the benzyl, phenyl, or cyclohexyl group in **6a–c** resulted in a slight reduction of H_3 activity. The smaller methyl substitution in **6d** was significantly less active. H_3 affinity was unchanged for the benzyl piperidine analog **6e** relative to the benzyl piperazine **6a** while the benzylhydroxypiperidine **6f** and keto analog **6g** showed slightly less affinity. The structurally different benzimidazolyl-4-piperidine compound **6h** displayed good H_3 binding affinity in comparison to the spiro structure **6i** and was utilized in subsequent SAR studies.

Table 1
In vitro H_3 receptor binding affinity of left hand side analogs **6a–i**



Compd	R	K_i[a] (nM)
3		6.3
6a		28
6b		40
6c		14
6d		355
6e		5.5
6f		30
6g		17
6h		2.0
6i		20

[a] Inhibition of $[^3H]N^{\alpha}$-methylhistamine binding to guinea pig brain receptor. H_3 binding K_i values are the average of at least two independent determinations. Variation from the mean is generally within ±50%.

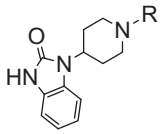


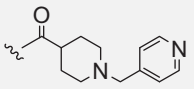
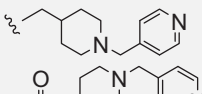
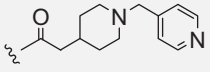
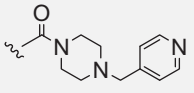
Scheme 2. Reagents: (a) N-CBZ-4-piperidinecarboxaldehyde, $NaB(OAc)_3H$, CH_2Cl_2, 92%; (b) H_2, 10% Pd/C, MeOH, DMF, 93%; (c) 4-pyridyl-carboxaldehyde, $NaB(OAc)_3H$, CF_3CH_2OH, 3A sieves, 29–59%; (d) DCC, HOBT, N-*t*BOC-4-piperidinemethylcarboxylic acid, CH_2Cl_2, 100%; (e) 4 N HCl in dioxane, CH_2Cl_2, 100%; (f) 4-nitrophenyl chloroformate, Et_3N, $ClCH_2CH_2Cl$, 100%; (g) *N*-BOC-piperazine, DMF, Δ, 41%.

Compounds **8a–c** were synthesized in order to verify that the piperidinylcarbonyl-piperidine core was essential for activity (Scheme 2). Removal of the carbonyl moiety in analog **8a**, insertion of a methylene linker in analog **8b**, and replacement of the piperidine ring with a piperazine ring in analog **8c** all decreased H_3 affinity (Table 2).

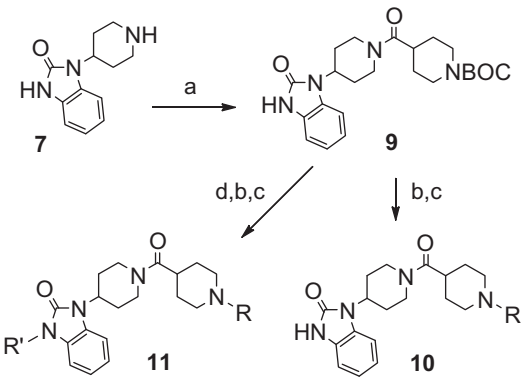
The next step was to examine the SAR of the right hand side pyridylmethyl moiety. Analogs were synthesized according to the

Table 2
In vitro H_3 receptor binding affinity of core analogues **8a–c**



Compd	R	K_i[a] (nM)
6h		2.0
8a		24
8b		180
8c		17

[a] Inhibition of $[^3H]N^{\alpha}$-methylhistamine binding to guinea pig brain receptor. H_3 binding K_i values are the average of at least two independent determinations. Variation from the mean is generally within ±50%.



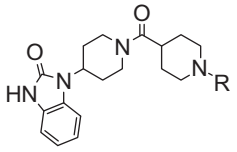
Scheme 3. Reagents: (a) *N*-BOC-isonipecotic acid, DCC, HOBT, CH_2Cl_2, 95%; (b) TFA, CH_2Cl_2, 100%; (c) RCHO, AcOH, $NaB(OAc)_3H$, CH_2Cl_2 or RCOCl, Et_3N, CH_2Cl_2; (d) NaOH, $nBu_4N(HSO_4)$, K_2CO_3, R′X.

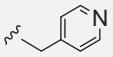
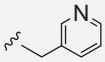
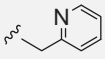
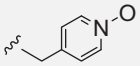
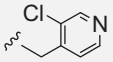
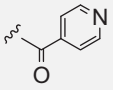
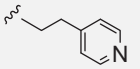
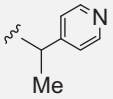
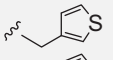
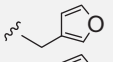
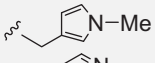
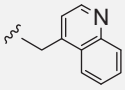
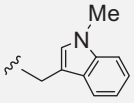
route outlined in Scheme 3.[15] Coupling of 4-(2-keto-1-benzimidazolinyl)piperidine (**7**) with *N*-BOC-isonipecotic acid formed intermediate **9**. Acid catalyzed removal of the BOC protecting group and further elaboration gave compounds **10a–l**. Alternatively, intermediate **9** could be alkylated before removal of the BOC protecting group, and additional elaboration provided compounds **11a–r**.

The SAR around the pyridylmethyl moiety appeared to be quite restricted (Table 3). Replacement of the 4-pyridyl ring in **6h** with the 3-pyridyl ring in **10a** or the 2-pyridyl ring in **10b** resulted in a reduction of H_3 affinity. The pyridine N-oxide **10c** and the 3-chloropyridyl analog **10d** were also less active. Furthermore, the methylene linker appeared to be important for biological activity. Conversion of the basic amine to an amide in compound **10e** or extension to the ethylene linker in compound **10f** significantly decreased H_3 receptor binding. Even addition of a single methyl group as in compound **10g** was not well-tolerated. Alternative heterocycles for the pyridine ring including the thiophene analog **10h**, the furan analog **10i**, the pyrrole analog **10j**, the quinoline analog **10k**, and the indole analog **10l**, all exhibited reduced H_3 affinity.

In contrast, the urea nitrogen of the left side benzimidazolone was very amenable to substitution (Table 4). H_3 antagonists, in particular structures which contain an imidazole moiety, displayed undesired cytochrome P450 inhibition, and therefore, we screened active analogs for CYP liver enzyme 3A4 and 2D6 inhibition.[14] The lead compound **6h** exhibited moderate 3A4 inhibition (9.5 μM) and minimal 2D6 inhibition (>20 μM). Target compounds which met the criteria of guinea pig K_i for H_3 <5 nM and IC_{50} for 3A4 >5 μM were tested for H_3 functional activity (pA2) in the guinea pig ileum assay.[14] In this assay, (*R*)-α-methylhistamine inhibited electrical field-stimulated contractions in guinea pig ileum segments. A H_3 antagonist dose dependently inhibited the (*R*)-α-methylhistamine activity. Overall, there was good correlation between the guinea pig receptor binding assay and the guinea pig functional assay. Introduction of an alkyl group such as the methyl in **11a** and the isobutyl in **11b** retained reasonable H_3 binding affinity and 3A4/2D6 profile. Ether chains as in compounds 11d–**h** were well-tolerated, but the more polar alcohol analog **11c** displayed good in vitro biological activity and improved (lower) 3A4 inhibition. This trend was also present with the more polar substituted amino side chains in compounds **11i–l** where $K_i \leqslant 0.5$ nM and IC_{50} for 3A4 inhibition is $\geqslant 30$ μM. Compounds **11j** and **11l** exhibited undesired 2D6 inhibition in comparison to compounds **11i** and **11k**. Introduction of a benzyl group with either an electron withdrawing chlorine atom as in analogs **11n–p** or an electron donating methoxy group as in analogs **11q and 11r** also displayed a high level of H_3 receptor binding affinity, but these

Table 3
In vitro H_3 receptor binding affinity of right hand side analogues **8a–l**



Compd	R	K_i[a] (nM)
6h		2.0
10a		174
10b		40%[b]
10c		440
10d		222
10e		11%[b]
10f		537
10g		20
10h		104
10i		204
10j		42%[b]
10k		681
10l		30%[b]

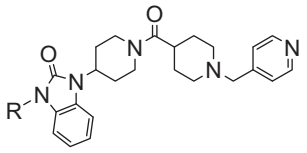
[a] Inhibition of [^{3}H]N$^\alpha$-methylhistamine binding to guinea pig brain receptor. H_3 binding K_i values are the average of at least two independent determinations. Variation from the mean is generally within ±50%.
[b] % Inhibition at 1 μM ($n = 2$).

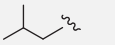
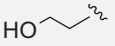
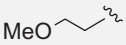
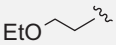
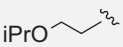
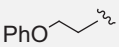
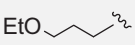
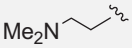
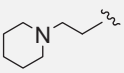
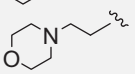
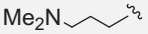
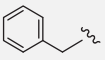
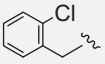
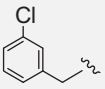
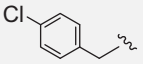
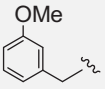
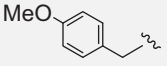
compounds were unfortunately potent inhibitors of the CYP3A4 enzyme. In addition, compounds **6h** and **11i–l** showed no liver enzyme 2C9 inhibition (>20 μM).

Due to their acceptable guinea pig binding, guinea pig functional H_3 activity, and P450 profile (3A4, 2D6, 2C9), compounds **11i–k** were validated in the guinea pig CNS-induced hypertension assay.[16] In this in vivo model, (*R*)-α-methylhistamine inhibited the CNS-induced hypertension caused by electrical stimulation to the medullary cardiopressor area. All three compounds **11i–k** exhibited in vivo efficacy by attenuating the effect of (*R*)-α-methylhistamine with an ED_{50} <0.3 mg/kg po. Compounds **11i–k** displayed AUC(0–6 h) of 240 nM h when dosed in the rat at 10 mg/kg po, minimal hERG inhibition (<10%) at 10 μM, and reasonable clearance levels in rat and human hepatocytes (<10 μL/min/million cells).

In conclusion, a new series of H_3 receptor antagonists was discovered. Optimization of the original lead compound **1** led to the key intermediate **6h**, and further studies of **6h** identified the biologically active compounds **11i–k**. Initial studies focused on

Table 4
In vitro H_3 receptor binding affinity, functional activity, and CYP3A4/CYP2D6 inhibition profile of benzimidazolone analogs **6h** and **11a–r**



Compd	R	K_i[a] (nM)	pA2[b]	IC_{50}[c] 3A4 (μM)	IC_{50}[c] 2D6 (μM)
6h	H	2.0	8.1	9.5	>20
11a	Me	4.3	8.3	7.5	>20
11b		0.4	ND[d]	1.5	1.9
11c		0.95	8.2	>30	>20
11d		2.0	8.8	11	>20
11e		1.7	8.7	13.5	>20
11f		0.65	9.3	6	>20
11g		2.0	9.1	9	20
11h		0.80	8.5	10.6	>20
11i		0.20	9.3	>30	10.5
11j		0.15	8.9	30	3.7
11k		0.50	9.1	30	>20
11l		0.20	9.7	>30	1.6
11m		0.20	8.9	0.4	9.1
11n		4.5	ND	0.5	6.7
11o		2.0	ND	0.3	4.2
11p		0.90	ND	0.4	5.8
11q		0.30	ND	0.2	5.6
11r		0.25	ND	0.4	20

[a] Inhibition of [^{3}H]N$^\alpha$-methylhistamine binding to guinea pig brain receptor. H_3 binding K_i values are the average of at least two independent determinations. Variation from the mean is generally within ±50%.
[b] Antagonist potency in an electrically stimulated guinea pig ileum. pA2 values are the average of at least four independent determinations. The assay-to-assay variability is ±0.2.
[c] Human liver microsome assay. IC_{50} values are the average of at least three independent determinations. The assay-to-assay variability is ±15%.
[d] Not determined.

delineating the PK/PD correlation of this series of H_3 antagonists. Additional structure–activity investigations targeting the optimization of the pharmacokinetic profile and in vivo activity will be reported in due course.

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