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Synthesis and SAR studies of benzimidazolone derivatives as histamine H_3-receptor antagonists

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ABSTRACT

A novel series of benzimidazolone-containing histamine H_3-receptor antagonists were prepared and their structure–activity relationship was explored. These benzimidazolone analogs demonstrate potent H_3-receptor binding affinities, no P450 enzyme inhibition, and strong H_3 functional activity. Compound **1o** exhibits the best overall profile with H_3K_i = 0.95 nM and rat AUC = 12.9 μM h.

The H_3 receptor is a G-protein coupled receptor in the histamine receptor family. It was originally characterized as an autoreceptor to regulate the synthesis and release of histamine from histaminergic neurons.[1] Thereafter it was also shown to mediate other neurotransmitters such as dopamine,[2] serotonin,[3] noradrenaline,[4] GABA,[5] and acetylcholine.[6] Therefore, histamine H_3 receptor ligands have been proposed as potential therapeutics for several central nervous system (CNS) indications such as obesity, attention deficit/hyperactivity disorder (ADHD), Alzheimer's disease, and schizophrenia.[7]

Known histamine H_3 antagonists can be structurally divided into imidazole (**GT-2227**, and **SCH 79687**) and nonimidazole-based analogs (**UCL 1972**, Fig. 1).[8] Although some of the imidazole-based antagonists show good potency and acceptable exposure, they have not advanced in the clinic because of their significant cytochrome P450 (CYP) enzyme inhibition liability. **SCH 79687** was the first imidazole-based H_3 antagonist lead from our laboratories. While **SCH 79687** showed excellent binding affinity, strong H_3 functional activity, and good oral bioavailability,[8c] it also, unsurprisingly, significantly inhibited P450 enzymes and lowered cholesterol levels in rat toxicology studies, and as a result, was not advanced for development.

In order to minimize the P450 enzyme liability, we decided to explore a new class of nonimidazole analogs. In the previous communication, a novel series of nonimidazole H_3 antagonists (**2**, Fig. 2) was reported.[9] Although many of these antagonists showed good in vitro activity, none of these compounds achieved an acceptable oral exposure in rats. In addition, many of them exhibited unacceptable levels of CYP3A4 and CYP2D6 inhibition. This communication details the structure–activity relationship (SAR) of compounds of general structure **1** with significantly improved enzyme profiles and pharmacokinetic properties.

The pharmacophore consists of four cyclic elements, that is, a benzimidazol-2-one moiety, two piperidine rings, and a pyridine heterocycle. The survey of a number of potential structural scaffolds on the right-hand side indicated that pyridine moiety is essential to binding affinity. The key change was the introduction of the 2-amino group in the pyridine which significantly improves the P450 enzyme profile. With this discovery, we focused on the modifications in the benzimidazol-2-one region to improve pharmacokinetic profile.

The preparation of benzimidazol-2-one-based H_3 antagonists of type **1** is illustrated in Scheme 1. Commercially available aminopyridine **3** was protected as the di-*N*-*tert*-butoxycarbonyl (BOC) derivative **4**. Compound **4** was brominated under standard *N*-bromosuccinimide (NBS) conditions to produce bromide **5**, which, in turn, was reacted with methyl isonipecotate to generate ester **6**. The hydrolysis of **6** with lithium hydroxide in tetrahydrofuran (THF) and water provided lithium salt **7** for the further coupling reactions without purification.

Diamines **8** were prepared conveniently from a substituted nitrobenzene and ethyl 4-amino-1-piperidinecarboxylate according to the literature method.[10] When the diamines **8** were treated with triphosgene in dichloromethane in the presence of triethylamine at 0 °C, benzimidazolones **9** were obtained in good yields. The available N-positions of benzimidazolones **9** were alkylated under two different conditions. One method was the biphasic

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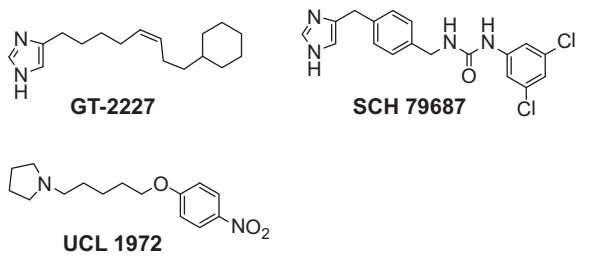


Figure 1. Representative H_3 antagonists.

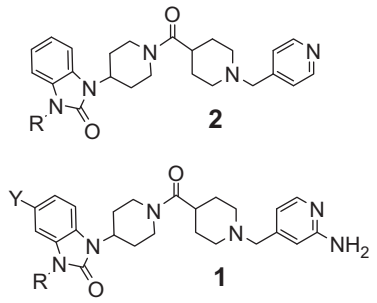
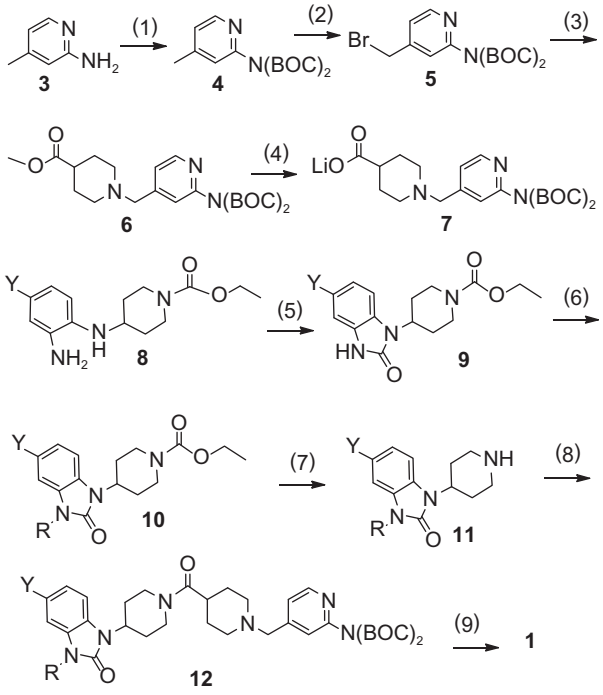


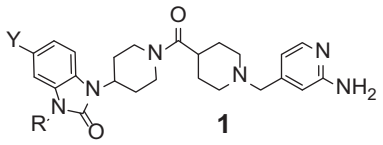
Figure 2.

reaction of **9** and an appropriate alkyl chloride in toluene in the presence of a base, such as a mixture of NaOH, potassium carbonate and phase-transfer reagent, such as tetra-*n*-butyl ammonium bisulfate. The other method involved using an aryl boronic acid to prepare *N*-aryl substituted analogs. This reaction was conveniently carried out at room temperature in the presence of copper(II) chloride and triethylamine. Both methods gave acceptable yields. The subsequent deprotection of **10** was completed with sodium hydroxide in water under reflux to produce **11**, which was coupled with lithium salt **7** to produce **12**. The coupling reaction was conducted with HATU and 4-dimethylaminopyridine (DMAP)



Scheme 1. Reagents and conditions: (1) $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2; (2) NBS, benzoyl peroxide, CCl_4; (3) methyl isonipecotate, triethylamine, DMF; (4) LiOH, THF, H_2O; (5) triphosgene, Et_3N, CH_2Cl_2, 0 °C; (6) alkyl chloride, $(n\text{-}Bu)_4NHSO_4$, NaOH–K_2CO_3, totuene, or aryl boronic acid, $CuCl_2$, triethylamine, CH_2Cl_2. (7) NaOH, water, reflux; (8) **7**, HATU, DMAP, DMF; (9) HCl, 1,4-dioxane.

Table 1
H_3 binding affinity (K_i), enzyme (3A4 and 2D6) inhibition and functional activity (pA_2) of compounds **1**[11]



Compound	R	Y	H_3 K_i (nM)[a]	IC_{50} 3A4 (μM)[b]	IC_{50} 2D6 (μM)[b]	pA_2[c]
1a	H	H	0.6	>30	>30	N/A
1b	F_3C	H	4.7	>30	>30	8.1
1c	Cl, Cl	H	77	N/A	N/A	N/A
1d	F	H	420	N/A	N/A	N/A
1e	O	H	1.5	>30	>30	8.0
1f	O, N	H	0.7	~30	>30	8.7
1g	O, N	F	2.3	>30	>30	N/A
1h	F_3C	F	3.8	~30	>30	8.9
1i		F	7.6	>30	>30	8.6
1j	F_3C	F	1.5	>30	>30	8.7
1k		F	2.2	~30	>30	8.7
1l		F	5.1	22	>30	8.2
1m		F	19	>30	>30	7.9
1n	F, F	F	2.8	>30	>30	8.3
1o	F, F	F	0.95	>30	>30	8.7
1p	N	F	2.5	>30	>30	7.8
1q	N, N	F	4.0	>30	>30	8.0
1r	N, N	F	0.5	>30	>30	N/A

Not determined.

[a] Inhibition of [^{3}H]-*N*-α-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] Human liver microsome assay. IC_{50} values are the average of at least three independent determinations. The assay-to-assay variability is ±15%.

[c] Antagonist potency in an electrically stimulated guinea pig ileum. pA_2 values are the average of at least four independent determinations. The assay-to-assay variability is ±0.2.[15]

Table 2
Rat oral AUC data of selected compounds[16]

Compound	Rat AUC (μM h)	Concentration @ 6 hour (μM)
1e	0.1	0
1f	0	0
ig	0	0
1h	4.1	0.51
1j	1.2	0.13
1k	3.5	0.26
1l	1.8	0.20
1n	5.1	0.68
1o	12.9	1.85
1p	10.9	1.2
1r	3.7	0.50

in dimethylformamide (DMF). The final deprotections were realized using HCl in 1,4-dioxane at room temperature to afford the target compounds **1**.[11]

The histamine H_3 receptor binding affinity (K_i) of the compounds was evaluated in a radioligand binding assay in guinea-pig brain homogenates utilizing the selective H_3 histamine agonist [^{3}H]-*N*-α-methyl histamine as the radioligand.[12,1b] We began the studies from the parent compound **1a** (Table 1). We were pleased to see that **1a** showed a K_i value of 0.6 nM. Next, we rapidly examined the tolerability of an alkyl group at the distal N-position. When 4,4,4-trifluorobutyl group was incorporated, the resulted antagonist **1b** showed slightly reduced affinity. The increase in bulkiness (**1c** and **1d**) in this region substantially reduced affinity. In particular, the affinity was very sensitive to the steric effect from the carbon connected to the N-position.[13] In contrast, the external alkyl chain with a more polar substituent in **1e** or **1f** helped the compound to maintain good affinity. These results suggested that a polar substituent in the remote position favored binding affinity. The most active compounds **1e** and **1f** were then dosed orally to Sprague–Dawley rats; plasma levels of both were negligible (Table 2). We reasoned that the poor pharmacokinetic profiles of these compounds could be due to low lipophilicity (*C*log*P* = 0.41 and 0.33, respectively),[14] which limited their absorption. Further SAR study was undertaken with a more lipophilic alkyl group on the left-hand side. Additionally, a small and electron-withdrawing group, such as fluoro, was introduced to the benzimidazolone core to reduce electron density in this region (**1g**–**r**). Not surprisingly, compound **1g** (*C*log*P* = 0.60) displayed low plasma levels due to its low lipophilicity, while the more lipophilic **1h** (*C*log*P* = 1.51) did show a significantly improved pharmacokinetic (PK) profile (Table 2). We were encouraged by this result and prepared a few structurally similar compounds (**1i**–**m**). As shown in the Table 1, other alkyl groups such as 2,2,2-trifluoroethyl (**1j**), cyclopropymethyl (**1k**), and cyclopentyl (**1l**) helped maintain good activity. The larger cyclohexylmethyl (**1m**) was not tolerated at this position. Compounds **1k** and **1l** displayed moderate plasma concentrations when dosed to rats (Table 2).[16]

The lipophilicity of analogs could be further increased by an *N*-aryl substituent. Thus, we decided to continue the SAR studies by incorporating a 3,4-difluorophenyl group in this region. We were very satisfied to find that **1n** displayed very good affinity (K_i = 2.8 nM) and rat PK (rat AUC = 5.1 μM h at a dose of 10 mg/kg). The binding affinity and PK were even better when a 3,5-difluorophenyl substituent was attached to the N-position (**1o**). This compound showed binding affinity of 0.95 nM and rat oral AUC of 12.9 μM h. In order to examine if a more polar heteroaryl substituent was favorable to H_3 affinity, compounds **1p** and **1r** were prepared. Interestingly, these compounds maintained high affinity (0.5–4.0 nM). Compound **1p** also displayed excellent plasma concentration, while **1r** exhibited slightly decreased oral PK compared to **1o**.

In summary, a novel series of H_3 receptor antagonists were optimized by modification of the benzimidazolone N-position. Lipophilicity of the substituent played an important role in the plasma levels of the molecule. As the best compounds in the series, both **1o** and **1p** showed good H_3 affinity. In addition, they displayed significantly improved rat oral pharmacokinetics, which supports our hypothesis that optimum lipophilicity could help the absorption. Furthermore, the new version of the series showed no inhibition of P450 enzymes and good potency in the functional assay.

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