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Novel histamine H_3 receptor antagonists based on the 4-[(1*H*-imidazol-4-yl)methyl]piperidine scaffold

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Abstract—We report the discovery of novel histamine H_3 receptor antagonists based on 4-[(1*H*-imidazol-4-yl)methyl]piperidine. The most potent compounds in the series (e.g., **7**) result from the attachment of a substituted aniline amide to the main pharmacophore piperidine via a two-methylene linker.

Histamine H_3 receptors have been reported to modulate a number of neurotransmitters including histamine,[1] serotonin,[2] acetylcholine,[3] norepinephrine,[4] dopamine,[5] and neuropeptides[6] in both the central and peripheral nervous systems. As a result, various therapeutic applications for H_3 agonists and antagonists have been envisioned.[7] In addition, recent evidence in animals and humans suggests that H_3 antagonism may have a nasal decongestant effect when combined with H_1 antagonism.[8] Downregulation of norepinephrine levels through activation of presynaptic H_3 heteroreceptors by histamine released from mast cells results in vasodilation. H_3 antagonism would reestablish the release of norepinephrine and lead to vasoconstriction (decongestion). This hypothesis was demonstrated in a histamine-driven cat model of nasal congestion.[9] Allergic rhinitis affects 10–30% of U.S. population alone, and current treatments for the congestion associated with rhinitis include oral decongestants such as pseudoephedrine, topical decongestants such as oxymetazoline, and nasal steroids, all of which are known to have side effects such as hypertension, agitation or insomnia. Our goal has been to discover a novel, selective H_3 antagonist that can be used in combination with an H_1 antagonist for the treatment of the allergic and congestive nasal symptoms of seasonal or allergic rhinitis.

A number of H_3 agonist and antagonist structural types have been reported in recent years, divided between classical imidazole-based[10] and non-imidazole series.[11] It has been observed that imidazole-based H_3 antagonists often share a common structural motif wherein a nitrogen containing heterocycle is linked usually by an alkyl chain to a polar group which is then linked to a lipophilic residue.[12] A qualitative model describing receptor–inhibitor binding interactions for imidazole-based ligands was proposed by Timmerman and co-workers.[13] Previously, Timmerman reported [(1*H*-imidazol-4-yl)methyl]piperidine **1** (Table 1) to be a potent H_3 agonist (K_i = 0.3 nM, pD_2 = 8.0).[14] According to the model, compound **1** possesses the structural requirements for H_3 receptor affinity, but lacks the lipophilic element necessary for H_3 antagonism. We initiated the efforts to vary the R group of **1** with the aim of improving H_3 antagonism.

All the compounds employed in this study were prepared from key intermediate **4** (Scheme 1). Trityl-protected 4-iodoimidazole **2** was converted to the corresponding Grignard reagent as described by

Keywords: Histamine; H_3 antagonists; Imidazole series; 4-[(1*H*-Imidazol-4-yl)methyl]piperidine; Norepinephrine; Allergic rhinitis; Decongestion.
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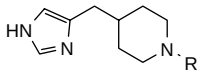
Table 1. Histamine H_3 receptor affinity and antagonist potency



Compound	R	K_i (nM)[a]	pA_2[b]	Synthesis
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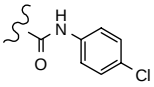
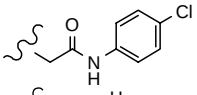
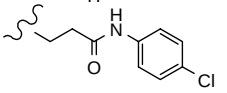
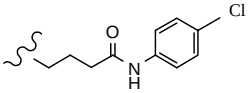
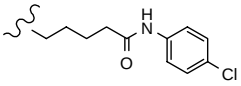
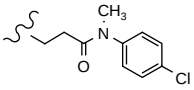
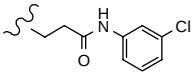
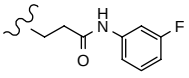
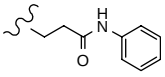
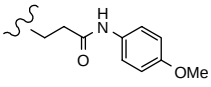
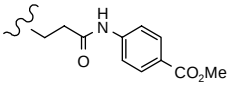
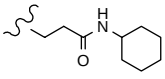
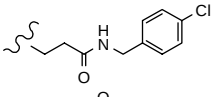
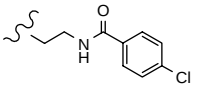
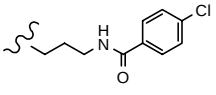
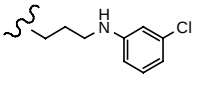
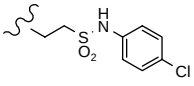
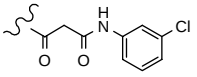
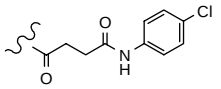
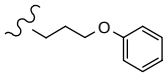
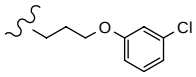
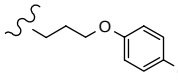
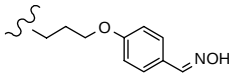
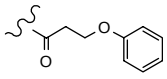
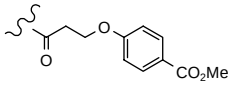
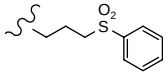
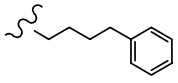
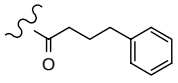
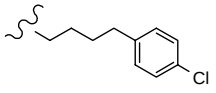
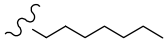
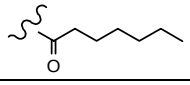
5		160	ND[c]	a, b
6		90	ND	c, b
7		0.4	10.1	d, e, f, b
8		17	8.3	g, h, e, f, b
9		40	ND	i, e, f, b
10		60	ND	d, e, f, b
11		0.2	9.8	d, e, f, b
12		0.2	9.9	d, e, f, b
13		2	8.9	d, e, f, b
14		3	8.8	d, e, f, b
15		3	8.8	d, e, f, b
16		3	8.2	d, e, f, b
17		21	ND	d, e, f, b
18		9	7.9	j, k, l, b
19		13	ND	m, k, l, b
20		2	8.4	n, k, b
21		170	ND	o, b
22		50	ND	p, b

Table 1 (*continued*)

Compound	R	K_i (nM)[a]	pA_2[b]	Synthesis
23		970	ND	p, b
24		4	8.3	p, k, b
25		2	7.9	p, k, b
26		20	ND	d, k, q, r
27[d]		44	ND	d, k, s, b, t
28		5	7.8	p, b
29		625	ND	u, v, f, b
30		25	7.1	p, k, b
31		5	8.2	p, k, b
32		9	7.8	p, b
33		6	8.8	p, k, b
34		2	8.6	p, k, b
35		18	7.4	p, b

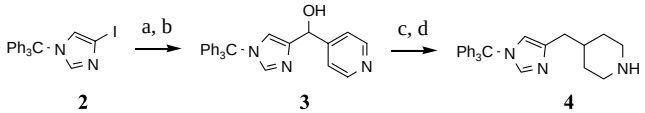
Synthesis: (a) **4**, ArNCO, CH_2Cl_2; (b) HCl, MeOH; (c) **4**, $BrCH_2CONHAr$, 2,6-lutidine; (d) **4**, $CH_2{=}CHCO_2Me$, MeOH; (e) LiOH, THF–H_2O; (f) R^1R^2NH, EDC, HOBT, CH_2Cl_2; (g) **4**, $BrCH_2CH{=}CHCO_2Et$, Et_3N, DMF; (h) H_2, Pd/C; (i) **4**, $Br(CH_2)_4CO_2Et$, NaH, DMF; (j) **4**, $BrCH_2CN$, K_2CO_3, KI, DMF; (k) $LiAlH_4$, THF; (l) RCO_2H, EDC, HOBT, DMF; (m) **4**, $CH_2{=}CHCN$, MeOH; (n) **4**, $CH_2{=}CHCONHAr$, MeOH; (o) **4**, $CH_2{=}CHSO_2NHAr$, MeOH; (p) **4**, RCO_2H, EDC, HOBT, DMF; (q) 4-hydroxybenzamide, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF; (r) $POCl_3$, $CHCl_3$; (s) 4-hydroxybenzaldehyde, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF; (t) $NH_2OH{\cdot}HCl$, pyridine; (u) methyl 4-hydroxybenzoate, $HOCH_2CH_2CH_2OH$, 1,1′-(azodicarbonyl)dipiperidine, Bu_3P, THF; (v) CrO_3, H_2SO_4, H_2O.

[a] Inhibition of [^{3}H]-*N*-α-methylhistamine binding to guinea pig brain receptor.[16] H_3 binding K_i values are the average of at least two independent determinations. The assay-to-assay variation was generally ± 2-fold.

[b] Antagonist potency in an electrically stimulated guinea pig ileum.[17] pA_2 values are the average of at least four independent determinations. The assay-to-assay maximum variability in the series was ±0.2.

[c] Not determined.

[d] Single oxime isomer, undetermined stereochemistry.



2 **3** **4**

Scheme 1. Reagents and conditions: (a) EtMgBr, CH_2Cl_2; (b) 4-pyridinecarboxaldehyde, 100% (two steps); (c) Ac_2O, DMAP, CH_2Cl_2, 85%; (d) H_2, PtO_2, AcOH, 60 psi, 96%.

Ley and co-workers.[15] Subsequent treatment with 4-pyridinecarboxaldehyde provided the alcohol **3**. We found it necessary to convert the alcohol **3** to the corresponding acetate prior to hydrogenation to achieve both reduction of the pyridine ring and hydrogenolysis of the benzylic position to afford **4** in a single operation. Prepared compounds along with the corresponding synthetic routes are listed in Table 1.

The most potent H_3 antagonists are obtained when the lipophilic right-side region of the molecule consists of an aniline amide separated from the piperidine ring by a two-methylene linker. For example, compound **7** is the most potent antagonist of the series ($pA_2 = 10.10 \pm 0.15$), equipotent with clobenpropit.[18] Moderate variation in the halogen substitution of the phenyl ring is well tolerated (**11** and **12**). In addition, these compounds were shown to have excellent affinity for human brain H_3 receptor with K_i's of 1.7, 0.4, and 1.9 nM for **7**, **11**, and **12**, respectively.[19,20] Linker length is critical to H_3 activity, as compounds with shorter (**5** and **6**) and longer (**8** and **9**) linkers display dramatic drop in H_3 receptor affinity. Most variations of the amide system of **7**, such as phenyl ring substitutions **13**–**15** or nitrogen substitution as in **10**, lead to decreased activity. A drop in activity is also observed with reversed amide **18**, aniline **20** and, especially, sulfonamide **21**. Simple phenyl ethers, tethered to the piperidine ring by a three-methylene fragment, although noticeably less active than **7**, maintained single-digit H_3 receptor affinity (**24** and **25**). So did the piperidine amide analog **28**, as well as, in both cases, their all-carbon-linked analogs **31** and **32**. However, attempted substitution of the benzene ring drastically reduced activity in all cases (**26**, **27**, and **29**). Combination of the aniline amide with the piperidine amide provided, depending on the linker, either a strong drop or almost complete loss of activity (**22** and **23**). Although noticeably less potent than **7**, straight-chain analog **34** still demonstrates good H_3 affinity and antagonism.

Despite the attractive in vitro H_3 profile of the 4-[(1*H*-imidazol-4-yl)methyl]piperidine series, efforts to advance a compound toward further development were hindered, not totally unexpectedly, by the unfavorable CYP450 inhibitory profile of the series, a known liability of aromatic nitrogen heterocycles in general and imidazoles in particular.[21] In fact, the most potent compounds, **7** and **12**, strongly inhibited CYP2D6 human enzyme with IC_{50}'s of 40 and 100 nM, respectively, when assayed in human liver microsomes.[22] CYP2D6 inhibition was also observed with other compounds in the series at comparable levels. While CYP2D6 represents only 2% of total liver cytochrome P450, it is estimated to be involved in the metabolism of 30% of marketed drugs and its inhibition therefore increases the chance of adverse drug–drug interactions.[23] Inhibition of the more abundant CYP3A4 appears not to be an issue with this series with IC_{50}'s estimated to be above 20 μM for both **7** and **12**. The inhibition of the CYP450 enzymes by nitrogen heterocycles is believed to be primarily due to the coordination of the nitrogen lone pair with the heme iron.[21a,24] While it has been demonstrated that substitution at the imidazole 2-position or 4,5-disubstitution would sterically disrupt this binding interaction and diminish enzyme inhibition,[21a] that substitution pattern also leads to the loss of H_3 activity.[25] The imidazole ring therefore seems to be off limits for structural modification purposes in this series. To prevent enzyme inhibition, one then might attempt to accomplish a destabilizing drug–enzyme interaction through an appropriate substitution of the lipophilic side chain of 4-[(1*H*-imidazol-4-yl)methyl]piperidines. The success of this approach would be essential for further interest in the imidazole-based series.

In conclusion, substitution of the piperidine ring of the known H_3 pharmacophore 4-[(1*H*-imidazol-4-yl)methyl]piperidine with lipophilic functional groups resulted in some of the most potent H_3 antagonists known today. The compounds of this series possess high inhibitory activity against CYP2D6 human enzyme, the efforts to minimize which are described in the next paper.

References and notes

1. (a) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. *Nature* **1983**, *302*, 832; (b) Onodera, K.; Yamatodani, A.; Watanabe, T.; Wada, H. *Prog. Neurobiol.* **1994**, *42*, 685.
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