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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 1443–1446

4-[6-(2-Aminoethyl)naphthalen-2-yl]benzonitriles are potent histamine H_3 receptor antagonists with high CNS penetration

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Received 16 October 2006; revised 16 November 2006; accepted 29 November 2006
Available online 1 December 2006

Abstract—4-[6-(2-Tertiaryaminoethyl)naphthalen-2-yl]benzonitriles are conformationally constrained histamine H_3 receptor antagonists with high potency and selectivity. The analogs were designed around a naphthalene core, with the goal of enhancing lipophilicity and CNS penetration, as compared to a previously reported benzofuran series. The SAR of the tertiary amine moiety is similar to that reported for the benzofuran series, with analogs bearing a 2-methylpyrrolidine substituent possessing the greatest rat and human H_3 receptor binding affinities.

Histamine H_3 receptors (H_3R) are constitutively active, located on presynaptic nerve terminals, and modulate the release of the neurotransmitters histamine, acetylcholine, dopamine, serotonin, and glutamate.[1] Activation of H_3R by the endogenous ligand, histamine (**1**), reduces neurotransmitter release, while antagonism of the H_3R leads to enhanced neurotransmitter release.[2] This enhanced neurotransmitter release is thought to be responsible for the reported efficacy observed in animal models where improvements in cognition,[3] attention,[3] wakefulness,[4] nasal congestion,[5] and in some cases an anti-obesity effect[6] have been observed upon administration of H_3R antagonists. This desirable profile suggests that H_3R antagonists have potential to treat human diseases such as attention-deficit disorder, Alzheimer's disease, schizophrenia, rhinitis, and obesity. To date, several H_3R antagonists have reportedly entered clinical trials and research continues in search of a H_3R antagonist suitable for human use.[7]

Several selective H_3R antagonists have been described in the literature, including early imidazole-based agents such as ciproxifan[8] (**2**) and thioperamide[9] (**3**), as well as later non-imidazole structures such as UCL-2190[10] (**4**), A-331440[11] (**5**), JNJ-5207852[12] (**6**), and ABT-239[13] (**7**). Many non-imidazole H_3R antagonists share a common structural element: a tertiary amine appended to an aromatic ring via a four-atom linker, typically the

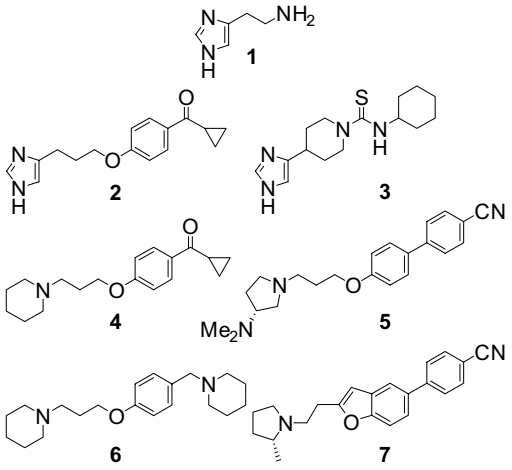

Figure 1. Structures of histamine (**1**), imidazole-based H_3 antagonists (**2** and **3**), and non-imidazole H_3 antagonists (**4**–**7**).

Keywords: Histamine H3 receptor antagonists; Naphthalene; High CNS penetration.
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doi:10.1016/j.bmcl.2006.11.073

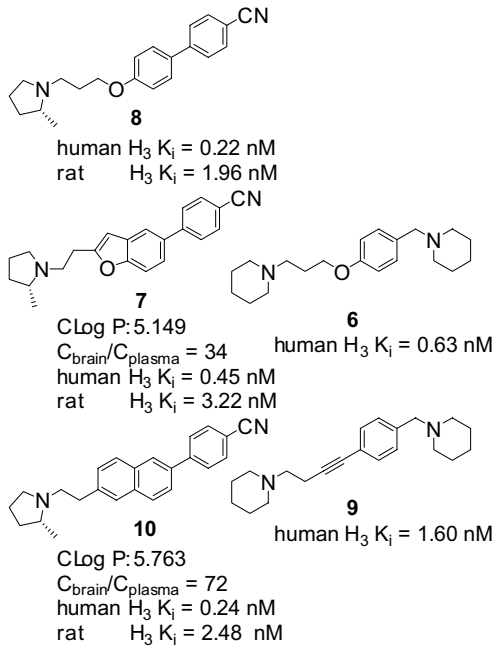


Figure 2. Comparison of H_3R antagonists with fully flexible propyloxy links to H_3R antagonists with more rigid, extended conformation links. (C log *P* calculated in ChemDraw™ 9.0, CambridgeSoft).

propyloxy group (see **4**–**6**, Fig. 1).[7d] With ABT-239 (**7**), the highly flexible propyloxy link was partially rigidified in an extended conformation by incorporating the oxygen and the proximal carbon into a furan ring fusion to the pharmacophore benzene, producing a benzofuran. This conformationally restricted derivative retains most of the high binding affinity possessed by the related flexible analog **8** (Fig. 2), while potentially providing a more drug-like profile.[14] Another reported variation on this theme involved replacement of the oxygen and proximal methylene of **6** with an acetylene to again provide a more conformationally restricted analog, **9**,[15] with similar potency to the parent. This latter example also indicated that the oxygen atom in the link is not absolutely essential for high H_3R binding affinity.

In this work, we report on the synthesis and amine SAR of a new series of naphthalene-based H_3R antagonists that combines aspects of these two concepts—rigidification by ring fusion and replacement of oxygen by carbon. Relative to the flexible analog **8**, we envisioned that the more rigid naphthalenes might retain or enhance the H_3R selectivity and the favorable drug-like characteristics seen in the earlier benzofuran series. More importantly, a key motivation for incorporation of the naphthalene moiety was a belief that the higher lipophilicity relative to the benzofuran series (Fig. 2) would increase drug distribution to the brain, potentially resulting in improved access to H_3Rs in the CNS, thereby boosting efficacy relative to peripherally mediated side effects. Indeed, in rats one hour after a 5 mg/kg iv dose, the ratio of brain concentration to plasma concentration for naphthalene **10** was determined to be twice that of benzofuran **7** (Fig. 2).

The synthesis of the naphthalene-based H_3R antagonists began with commercially available ester **11**, which was reduced to the benzylic alcohol **12** with LAH (Fig. 3). Treatment of **12** with thionyl chloride produced **13**, which was reacted with NaCN to give the acetonitrile **14**. Sulfuric acid-catalyzed hydrolysis yielded the acetic acid **15**, which upon borane–THF reduction provided the ethanol **16**. Suzuki coupling of **16** with 4-cyanophenylboronic acid gave **17**, which was transformed into the corresponding mesylate **18**. Final products (**10**, **19**–**37**) were obtained after **18** was reacted with the appropriate amines in the presence of Cs_2CO_3.

Structure–activity relationships (SAR) for the amines surveyed are summarized by the data presented in Table 1. Good potency at rat as well as human receptors was desirable, since the majority of behavioral models were conducted with rats. While all examples displayed superior binding affinity at the cloned human H_3R relative to the rat cortex H_3R, we were gratified to find several compounds (**10**, **19**, **20**, **21**, **27**, **28**, and **33**) with high potency at the rat H_3R (K_i < 15 nM). Similar to the amine SAR reported for the benzofuran series,[7f] the pyrrolidine **21**, the 2-methylpyrrolidines (*R*: **10**, *S*: **19**, and racemate **20**), the (2*S*)-hydroxymethylpyrrolidine **27**, and the (2*S*)-fluoromethylpyrrolidine **28** possessed the greatest potency in the naphthyl derivatives studied. Importantly, the naphthalene analogs were found to be generally more potent than the corresponding benzofurans.

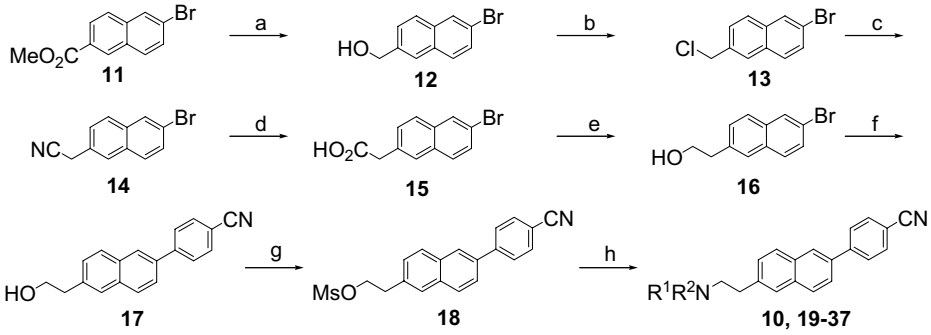
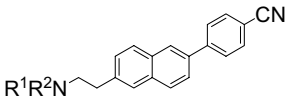


Figure 3. Synthesis of the 4-[6-(2-tertiaryaminoethyl)naphthalen-2-yl]benzonitrile H_3R antagonists. (a) LAH, THF, −10 °C, 95%; (b) $SOCl_2$, $ZnCl_2$, dioxane, −10 °C, 99%; (c) NaCN, CH_3CN, H_2O, reflux, 97%; (d) conc. H_2SO_4, AcOH, H_2O, reflux, 93%; (e) $BH_3 \cdot$ THF, THF, −15 °C, 96%; (f) 4-CN-$C_6H_4B(OH)_2$, $PdCl_2(PPh_3)_2$, K_3PO_4, *i*-PrOH, H_2O, 65 °C, 73%; (g) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 93%; (h) R^1R^2NH, Cs_2CO_3, CH_3CN, 50 °C, 20–60%.

Table 1. In vitro SAR of amine derivatives in human and rat H_3R binding affinity assays



Compound	R^1R^2N	Human H_3[a]		Rat H_3[b]	
		K_i[c] (nM)	pK_i ± SEM	K_i[c] (nM)	pK_i ± SEM
10	(2*R*)-Methylpyrrolidine[d]	0.24 [0.45]	9.62 ± 0.06	2.48 [3.22]	8.61 ± 0.09
19	(2*S*)-Methylpyrrolidine[e]	0.12	9.92 ± 0.23	3.47	8.46 ± 0.10
20	(±2)-Methylpyrrolidine	0.18 [0.95]	9.75 ± 0.12	1.24 [6.46]	8.91 ± 0.17
21	Pyrrolidine	0.49 [4.26]	9.31 ± 0.16	6.42 [46.8]	8.19 ± 0.16
22	3-Pyrroline	3.31	8.48 ± 0.11	66.1	7.18 ± 0.07
23	(2*R*)-Ethylpyrrolidine[f]	8.61	8.06 ± 0.16	33.7	7.47 ± 0.14
24	(±2)-Isopropylpyrrolidine	27.3	7.56 ± 0.07	233	6.63 ± 0.29
25	(±2)-Isobutylpyrrolidine	273	6.56 ± 0.05	465	6.33 ± 0.21
26	(2*R*)-Hydroxymethylpyrrolidine	2.89 [17.8]	8.54 ± 0.02	42.8 [166]	7.37 ± 0.25
27	(2*S*)-Hydroxymethylpyrrolidine	0.44 [2.24]	9.36 ± 0.16	11.0 [25.7]	7.96 ± 0.11
28	(2*S*)-Fluoromethylpyrrolidine[g]	0.81	9.09 ± 0.13	9.77	8.01 ± 0.12
29	(3R)-Dimethylaminopyrrolidine	20.1 [15.8]	7.70 ± 0.18	100 [63.1]	7.00 ± 0.27
30	(3R)-Hydroxypyrrolidine	1.56 [8.91]	8.81 ± 0.10	30.9 [95.5]	7.51 ± 0.17
31	(2*R*)-Methylpiperidine	8.71	8.06 ± 0.12	141	6.85 ± 0.09
32	Dimethylamine	2.65	8.58 ± 0.14	45.3	7.34 ± 0.29
33	Diethylamine	0.84	9.07 ± 0.11	12.5	7.90 ± 0.16
34	Methylpropylamine	2.09	8.68 ± 0.19	25.7	7.59 ± 0.20
35	*tert*-Butylmethylamine	1.09	8.96 ± 0.18	27.9	7.56 ± 0.16
36	Ethylisopropylamine	4.62	8.34 ± 0.12	30.3	7.52 ± 0.03
37	2-Methylaminoethanol	10.5	7.98 ± 0.34	457	6.34 ± 0.26

Binding affinities determined by displacement of ^3H *N*-α-methylhistamine tested in:
[a] Membranes from cloned human H_3R expressed in C6 cells.
[b] Rat cortical membranes. The number of independent pK_i determinations was $\geqslant 3$ for all compounds.
[c] Bracketed K_i values show published data for the corresponding benzofuran derivatives.
[d] For synthesis, see Ref. 13d or by fractional recrystallization of L-tartrate salt.
[e] For synthesis, use preceding method starting with (2*R*)-hydroxymethylpyrrolidine.
[f] For synthesis, see Ref. 16.
[g] Prepared by DAST fluorination of *N*-Boc-(2*S*)-hydroxymethylpyrrolidine and subsequent HCl-induced deprotection.

Table 2. Rat pharmacokinetic data

Compound	iv (1 mg/kg)				po (1 mg/kg)			
	$t_{1/2}$ (h)	V_β (L/kg)	$AUC_{0-\infty}$ (ng h/mL)	Cl_b (L/h kg)	C_{max} (ng/mL)	$t_{1/2}$ (h)	$AUC_{0-\infty}$(ng h/mL)	*F* (%)
7	5.3	12	673	1.5	29	5.2	349	53
10	6.9	6	1640	0.6	48	6.5	890	55

The naphthyl analog **10** possessed the best overall profile in this series of compounds. This compound is highly selective, with a binding affinity over a thousand times more potent at the human H_3R relative to the human histamine H_1, H_2, and H_4 receptors. In addition to higher CNS distribution than the benzofuran analog **7** (ABT-239), **10** displayed improved potency in binding assays and a similar pharmacokinetic profile (Table 2).

Similar to the benzofuran series, these naphthyl compounds were also confirmed to be inverse agonists at the human H_3R in a functional assay, reducing basal GTPγS binding in transfected cells.[2b,17]

In summary, we have found that naphthalene is not only a suitable replacement for the benzofuran moiety in H_3R antagonists previously reported, but with regard to some key aspects, this series is actually superior. In general, this new series possesses higher rat and human potencies, higher lipophilicity, and similar amine SAR. Finally, in the specific case of the naphthalene **10**, the desired higher brain/plasma concentration ratio relative to the benzofuran **7** was achieved while maintaining a similar PK profile.

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