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Investigation of 4-piperidinols as novel H_3 antagonists

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ABSTRACT

Compounds containing a substituted 4-piperidinol core have been found to be potent antagonists of the human H_3 receptor. The compounds exhibited up to a 60-fold preference for inhibiting the human H_3 receptor over the mouse and showed a low binding affinity for the hERG channel.

The histamine H_3 receptor is a G-protein coupled receptor that is primarily located in the CNS and regulates the synthesis and release of the neurotransmitter histamine via a negative-feedback mechanism. H_3 receptor activation also plays a role in the release of several other neurotransmitters in the CNS, including dopamine, serotonin, GABA, and acetylcholine, and is therefore suspected to possess promising therapeutic potential. Sought after indications for H_3 modulators include treatments for Alzheimer's disease,[1] attention-deficit hyperactivity disorder (ADHD), cognition,[2] and obesity.[3] Drug discovery efforts to modulate the histamine H_3 receptor have been ongoing in both academia and the pharmaceutical industry since its discovery in 1983.[4] Although significant progress has been made in finding compounds that effectively target the H_3 receptor, no candidates have yet received clinical approval. However, there are presently several compounds being evaluated in early to late-stage clinical trials.[5]

Early small molecule research efforts targeting the H_3 receptor revealed that imidazole-containing compounds such as clobenpropit showed very potent antagonistic activity. However, these compounds showed metabolic liabilities and poor CNS penetration likely attributable to the imidazole moiety. Potent H_3 antagonists were eventually discovered that lacked the imidazole core and exhibited an improved CNS and metabolic profile.[6] A common feature present in these 'non-imidazole' H_3 modulators is a basic amine group that is tethered to an aryl system via an alkyl chain having a high degree of rotational freedom as in JNJ-5207852[7] (Fig. 1). However, there are examples of potent H_3 modulators in the literature that have reduced conformational flexibility[8] including a rigidified analog of JNJ-5207852.[9] Generally, this is a desirable physico-chemical property as it has been described that reducing the number of rotatable bonds tends to improve oral bioavailability.[10] After a high-throughput screening campaign, we were pleased to find that the relatively rigid and racemic compound **1**[11] was a potent antagonist of the human H_3 (hH_3) receptor (Table 1). Interestingly, compound **1** showed a significant difference in IC_{50} potencies between mouse and human H_3 in the FLIPR assays.[12] However, the control H_3 antagonist clobenpropit did not

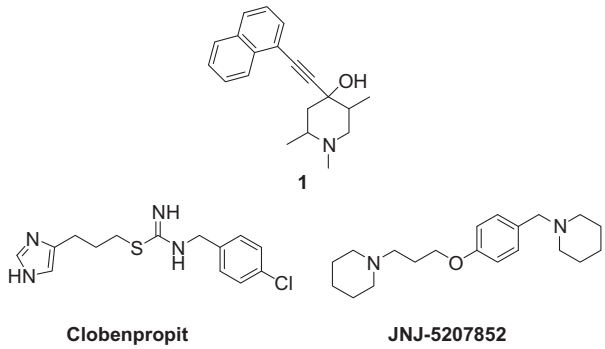

Figure 1. Structure of lead compound **1**, imidazole and non-imidazole based H_3 antagonists.

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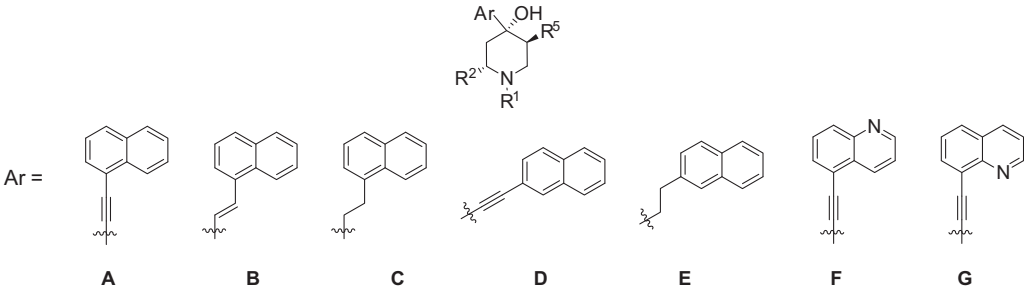
Table 1
Potency of piperidinols against mouse and human H_3

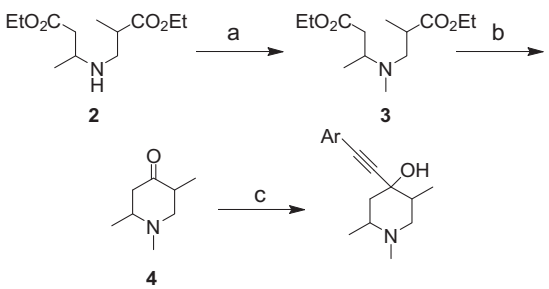


Compound[a]	Ar	R^1	R^2	R^5	FLIPR IC_{50}[b] (nM)		hERG
					mH_3	hH_3	
Clobenpropit					1	1	nd
1	A	Me	Me	Me	280 (±92)[c]	11 (±2)[c]	nd
5	A	Me	Me	Me	119 (±19)[c]	9 (±3)[c]	15% @ 50 μM
ent-**5**	A	Me	Me	Me	1318[d]	41[e]	nd
1 (*O*-acetate)	A	Me	Me	Me	>10,000[e]	5508[e]	nd
6	B	Me	Me	Me	570[d]	20[d]	20% @ 10 μM
7	C	Me	Me	Me	480 (±300)[c]	17[d]	15% @ 10 μM
8	C	Me	Me	Me	85[d]	2[d]	16% @ 10 μM
9	D	Me	Me	Me	810[e]	84[e]	nd
10	E	Me	Me	Me	122[e]	2[e]	0% @ 10 μM
13	A	$(-CH_2)_3$		Me	280[e]	5[e]	23% @ 10 μM
14	C	$(-CH_2)_3$		Me	345[e]	14[e]	nd
15	F	Me	Me	Me	690[e]	12[e]	3% @ 10 μM
16	G	Me	Me	Me	9730[e]	709[e]	nd

[a] Compounds **5**, *ent*-**5**, and **8** are single enantiomers. All other compounds are racemic.
[b] Measured reduction of intracellular calcium flux induced by agonist (*R*)-α-methylhistamine.
[c] Mean of at least three experiments, standard error of the mean.
[d] Average of two determinations.
[e] Single determination.

show a bias in potency toward either species. In addition to its high potency as a lead compound against hH_3, the unique structure of **1** generated interest in further exploration of this scaffold for improved H_3 receptor antagonism.

The general synthesis of compounds **1** and **5–10** is described in Scheme 1. The piperidone intermediate **4** was synthesized using a modification of a previously reported procedure.[13] Compound **2**, prepared from ethyl 3-aminobutyrate and ethyl methacrylate, was subjected to Eschweiler–Clarke conditions to give the N-methylated product **3**. Dieckmann cyclization of **3** and subsequent decarboxylation gave the piperidone **4** as an unresolved mixture of diastereomers. Final compounds were accessed via deprotonation of aryl acetylenes using BuLi followed by addition to piperidone **4**. There was concern that the creation of a third chiral center would yield a mixture of piperidinol diastereomers that may be difficult to purify. However, the major diastereomer formed in the addition reaction was easily isolated by silica gel chromatography.



Scheme 1. Reagents and conditions: (a) (i) $(CH_2O)_n$, Toluene-*n*BuOH; then (ii) HCO_2H, reflux; (b) (i) Na, EtOH, xylenes, reflux; (ii) 20% aq HCl, reflux; (c) Ar-CCH, *n*BuLi, THF, 0 °C.

A classical resolution was used to isolate each enantiomer of pure diastereomer **1**. Re-crystallization of the salt formed from optically pure di-*p*-toluoyl-(L)-tartaric acid gave an enantiomer having >95% de[14] X-ray crystal structure determination of the salt (Fig. 2) provided the absolute stereochemistry of **5**.[15] The crystal structure also confirmed the mode of aryl acetylene addition as being axial. The free base of **5** showed a 2- to 3-fold improvement in potency against mH_3 over the racemate **1**, but no improvement in hH_3 potency. The antipode **ent-5** was isolated from recrystallization of the di-*p*-toluoyl-(D)-tartrate salt of **1** and was found to be much less potent than **5** against both mH_3 and hH_3. Another observation was that the free 4-hydroxyl group was important for potency as the corresponding acetate of **1** was not active against mH_3 and very weakly active against hH_3 at the highest concentrations tested (Table 1).

The *trans*-alkene **6** was obtained after lithium aluminum hydride reduction of alkyne **1** and showed a loss in activity against both mH_3 and hH_3. This result was not surprising given the altered spatial arrangement of the naphthyl ring. The alkene was further reduced to alkane **7** using standard Pd-catalyzed hydrogenation conditions. We anticipated a recovery in H_3 potency for **7** due to the increased conformational flexibility of the ethyl chain, but no improvements were seen over the alkene. However, upon chiral resolution of **7**, as previously described, enantiomer **8** was found to possess excellent potency against hH_3.

Altering the position of the alkyne moiety to the 2′-position of the naphthyl ring gave compound **9** that was less potent than the corresponding 1′-substituted analog **1** in both mH_3 (~3-fold) and hH_3 (~8-fold). However, the opposite trend was observed upon reduction of alkyne **9** to the alkane **10**. Comparison of

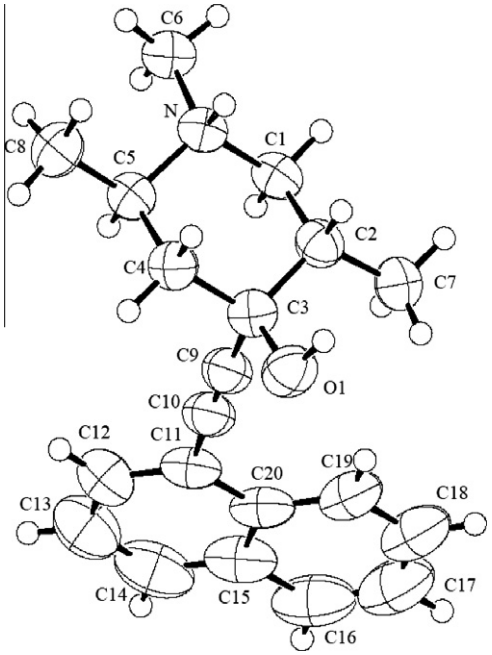


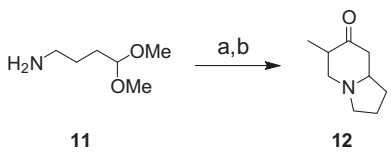
Figure 2. X-ray structure of **5**. Di-*p*-toluoyl-(L)-tartaric acid counter ion not shown for clarity.

reduced compounds **10** and **7** showed that 2′-substitution was more potent than the corresponding 1′-substitution. Although it was satisfying that mH_3 activity for **10** improved over compound **9**, it was not nearly as dramatic as the improvement in hH_3 potency.

A more rigid indolizidine ring system was also explored that was conveniently prepared from 4-aminobutyraldehyde dimethylacetal (Scheme 2) using a modified literature procedure.[16] Addition of the lithium salt of **A** to **12** gave a mixture of diastereomers. The major diastereomer **13** was isolated and was found to be the most potent constituent of the mixture and showed similar potencies against mH_3 and hH_3 as its acyclic counterpart **1** with preference for hH_3. Interestingly, the isolated minor diastereomer was able to be predominantly equilibrated to **13** (~4:1) by exposure to KOH/EtOH at 50 °C.[17] Following the same protocol as discussed previously, the alkyne was fully reduced to give compound **14** which showed similar potency to its counterpart **7**.

A sensitive structure–activity relationship was seen for quinoline isomers **15** and **16**. Alkyne substitution at the 5-position of the quinoline ring (**15**) showed similar activity against both mH_3 and hH_3 as the corresponding naphthyl series (**A–E**). However, alkyne substitution at the 8-position of the quinoline ring (**16**) showed a dramatic decrease in H_3 activity.

Historical H_3 modulators had showed a tendency to bind to the hERG ion channel which represents a potential safety liability.[18] Recently however, this problem has been successfully addressed.[19] As part of our compound safety profiling, H_3 antagonists of interest were evaluated for their potential to inhibit the hERG ion channel and all compounds tested showed minimal inhibition of hERG.



11 12

Scheme 2. Reagents and conditions: (a) 3-methyl-3-butene-2-one, MeOH, 0 °C; (b) 5% aq AcOH, reflux.

In summary, we have identified a unique piperidinol-based pharmacophore that shows potent human H_3 inhibition and a very good overall hERG profile. However, this series showed a significant disparity in potency between the human and mouse H_3 receptors as only moderate potency was achieved against the mouse, The lack of mH_3 potency was disappointing because in vivo assays were to be performed in mouse. This result is somewhat surprising given the reported high H_3 receptor homology (94%) between mouse and human.[20] A few antagonists have been reported that are biased toward hH_3 over mH_3 albeit to a much lesser extent than our observations with the piperidinol series.[21] In our case, the observed differences in potency between the two species appear to result from the human H_3 receptor being much more accommodating for the piperidinol pharmacophore.

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References and notes

1. Medhurst, A. D.; Atkins, A. R.; Beresford, I. J.; Brackenborough, K.; Briggs, M. A.; Calver, A. R.; Cilia, J.; Cluderay, J. E.; Crook, B.; Davis, J. B.; Davis, R. K.; Davis, R. P.; Dawson, L. A.; Foley, A. G.; Gartlon, J.; Gonzalez, M. I.; Heslop, T.; Hirst, W. D.; Jennings, C.; Jones, D. N. C.; Lacroix, L. P.; Martyn, A.; Ociepka, S.; Ray, A.; Regan, C. M.; Roberts, J. C.; Schogger, J.; Southam, E.; Stean, T. O.; Trail, B. K.; Upton, N.; Wadsworth, G.; Wald, J. A.; White, T.; Witherington, J.; Woolley, M. L.; Worby, A.; Wilson, D. M. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1032.
2. Esbenshade, T. A.; Browman, K. E.; Bitner, R. S.; Strakhova, M.; Cowart, M. D.; Brioni, J. D. *Br. J. Pharmacol.* **2008**, *154*, 1166.
3. Yoshimoto, R.; Miyamoto, Y.; Shimamura, K.; Ishihara, A.; Takahashi, K.; Kotani, H.; Chen, A. S.; Chen, H. Y.; MacNeil, D. J.; Kanatani, A.; Tokita, S. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 13866.
4. Arrang, J.-M.; Garbarg, M.; Schwartz, J. C. *Nature* **1983**, *302*, 832.
5. Sander, K.; Kottke, T.; Stark, H. *Biol. Pharm. Bull.* **2008**, *31*, 2163.
6. Ganellin, C. R.; Leurquin, F.; Piripitsi, A.; Arrang, J.-M.; Garbarg, M.; Ligneau, X.; Schunack, W.; Schwartz, J.-C. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 395.
7. (a) Apodaca, R.; Dvorak, C. A.; Xiao, W.; Barbier, A. J.; Boggs, J. D.; Wilson, S. J.; Lovenberg, T. W.; Carruthers, N. I. *J. Med. Chem.* **2003**, *46*, 3938; (b) Barbier, A. J.; Berridge, C.; Dugovic, C.; Laposky, A. D.; Wilson, S. J.; Boggs, J.; Aluisio, L.; Lord, B.; Mazur, C.; Pudiak, C. M.; Langlois, X.; Xiao, W.; Apodaca, R.; Carruthers, N. I.; Lovenberg, T. W. *Br. J. Pharmacol.* **2004**, *143*, 649.
8. (a) Kitbunnadaj, R.; Zuiderveld, O. P.; De Esch, I. J. P.; Vollinga, R. C.; Bakker, R.; Lutz, M.; Spek, A. L.; Cavoy, E.; Deltent, M.-F.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. *J. Med. Chem.* **2003**, *46*, 5445; (b) Cowart, M.; Pratt, J. K.; Stewart, A. O.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 689; (c) Zhao, C.; Sun, M.; Bennani, Y. L.; Gopalakrishnan, S. M.; Witte, D. G.; Miller, T. R.; Krueger, K. M.; Browman, K. E.; Thiffault, C.; Wetter, J.; Marsh, K. C.; Hancock, A. A.; Esbenshade, T. A.; Cowart, M. D. *J. Med. Chem.* **2008**, *51*, 5423.
9. Dvorak, C. A.; Apodaca, R.; Barbier, A. J.; Berridge, C. W.; Wilson, S. J.; Boggs, J. D.; Xiao, W.; Lovenberg, T. W.; Carruthers, N. I. *J. Med. Chem.* **2005**, *48*, 2229.
10. (a) Varma, M. V. S.; Obach, R. S.; Rotter, C.; Miller, H. R.; Chang, G.; Steyn, S. J.; El-Kattan, A.; Troutman, M. D. *J. Med. Chem.* **2010**, *53*, 1098; (b) Vieth, M.; Siegel, M. G.; Higgs, R. E.; Watson, I. A.; Robertson, D. H.; Savin, K. A.; Durst, G. L.; Hipskind, P. A. *J. Med. Chem.* **2004**, *47*, 224.
11. Prostakov, N. S.; Kholdarova, T.; Pleshakov, V. G.; Govor, S. Ya.; Shalimov, V. P. *Chem. Heterocycl. Compd.* **1973**, *9*, 323.
12. The FLIPR assay was performed using HT1080 cells expressing chimeric Gqαi5 and either mH_3 or hH_3 and measured a compound's ability to inhibit the increase of intracellular Ca^{+2} induced with the H_3 agonist (*R*)-α-methylhistamine. Song, J.; Doucette, C.; Hanniford, D.; Hunady, K.; Wang, N.; Sherf, B.; Harrington, J. J.; Brunden, K. R.; Stricker-Krongrad, A. *Assay Drug Dev. Technol.* **2005**, *3*, 309.
13. Thomas, J. B.; Herault, X. M.; Rothman, R. B.; Atkinson, R. N.; Burgess, J. P.; Mascarella, S. W.; Dersch, C. M.; Xu, H.; Flippen-Anderson, J. L.; George, C. F.; Carroll, F. I. *J. Med. Chem.* **2001**, *44*, 972.
14. The same resolution technique was used on a compound similar to **1**. Fries, D. S.; Portoghese, P. S. *J. Med. Chem.* **1976**, *19*, 1155.
15. Crystallographic data (excluding structure factors) for structure **5** (di-*p*-toluoyl-(L)-tartrate salt) in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 752416. Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 335033] or email: data_request@ccdc.cam.ac.uk.
16. King, F. D. *Tetrahedron Lett.* **1983**, *24*, 3281.
17. Litvinenko, G. S.; Iskakova, T. K. *Chem. Heterocycl. Compd.* **1991**, *27*, 859.
18. (a) Wijtmans, M.; Leurs, R.; de Esch, I. *Expert Opin. Investig. Drugs* **2007**, *16*, 967; (b) Gemkow, M. J.; Davenport, A. J.; Harich, S.; Ellenbroek, B. A.; Cesura, A.; Hallett, D. *Drug Discovery Today* **2009**, *14*, 509.

19. (a) Covel, J. A.; Santora, V. J.; Smith, J. M.; Hayashi, R.; Gallardo, C.; Weinhouse, M. I.; Ibarra, J. B.; Schultz, J. A.; Park, D. M.; Estrada, S. A.; Hofilena, B. J.; Pulley, M. D.; Smith, B. M.; Ren, A.; Suarez, M.; Frazer, J.; Edwards, J.; Hauser, E. K.; Lorea, J.; Semple, G.; Grottick, A. J. *J. Med. Chem.* **2009**, *52*, 5603; (b) Black, L. A.; Liu, H.; Diaz, G. J.; Fox, G. B.; Browman, K. E.; Wetter, J.; Marsh, K. C.; Miller, T. R.; Esbenshade, T. A.; Brioni, J.; Cowart, M. D. *Inflamm. Res.* **2008**, *57*, S45.
20. Chen, J.; Liu, C.; Lovenberg, T. W. *Eur. J. Pharmacol.* **2003**, *467*, 57.
21. (a) Rouleau, A.; Heron, A.; Cochois, V.; Pillot, C.; Schwartz, J.-C.; Arrang, J.-M. *J. Neurochem.* **2004**, *90*, 1331; (b) Ligneau, X.; Perrin, D.; Landais, L.; Camelin, J.-C.; Calmels, T. P. G.; Berrebi-Bertrand, I.; Lecomte, J.-M.; Parmentier, R.; Anaclet, C.; Lin, J.-S.; Bertaina-Anglade, V.; Drieu la Rochelle, C.; d'Aniello, F.; Rouleau, A.; Gbahou, F.; Arrang, J.-M.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J.-C. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 365.