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A New Class of Histamine H_3-Receptor Antagonists: Synthesis and Structure–Activity Relationships of 7,8,9,10-Tetrahydro-6H-cyclohepta[*b*]quinolines

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Abstract—The synthesis and biological evaluation of novel cycloheptaquinoline antagonists of the human H_3 receptor are described. Two series of compounds, bearing either an amino substituent or an alkyne linker at the 11-position, were investigated. Modifications of the amino substituents, optimization of chain length and the effect of conformational restraints are described. Several compounds with high affinity and selectivity for the H_3 receptor were discovered.

Histamine is believed to exert its pharmacological effects in the CNS and periphery via the modulation of at least four distinct G-protein coupled receptor subtypes.[1] The identification of the H_1 and the H_2 receptors, and the subsequent determination of their respective physiological roles, have allowed the development of selective antagonists of these receptors with therapeutic applications in the treatment of allergic conditions (H_1 mediated)[2] and gastric ulcers (H_2 mediated).[3] The histamine H_3-receptor (H_3R), first characterized in 1983,[4] was originally described as a presynaptic autoreceptor regulating the production and release of histamine. Evidence has since accumulated suggesting that H_3R are also colocalized heteroreceptors present on cholinergic, dopaminergic, noradrenergic, peptidergic and serotonergic neurons.[5] Current pharmacological interest is focused on the potential role for selective ligands of H_3R in the treatment of several diseases and neurological disorders, for example, epilepsy, schizophrenia, obesity, arousal and sleep disorders, memory and learning deficits, and Alzheimer's disease.[6]

The search for selective ligands for H_3R has resulted in the identification of several potent and selective inhibitors. Many of the early approaches have focused on structural modification of the endogenous ligand, histamine, and several very potent series of imidazole-containing H_3 antagonists have emerged, such as thioperamide,[7] GT-2331,[8] FUB 470,[9] and ciproxifan.[10] It has been proposed that the basic imidazole moiety of these ligands interacts with an active site aspartate.[11] This has prompted the search for other basic groups as replacements for imidazole and a number of non-imidazole H_3R antagonists have recently been discovered, including guanidine containing compounds such as JB 98064[12] and tacrine derivatives.[13] We have also focused on developing non-imidazole H_3R antagonists and have recently published on several novel series.[14]

Following a high throughput screen of our internal compound library, we identified an 11-amino cycloheptaquinoline **1** as a ligand with high affinity for the H_3 receptor. We synthesized a series of both amino analogues and also alkyne bioisosteres (Fig. 1).

The synthetic strategy used to prepare both the 11-amino and 11-alkynyl series is shown in Scheme 1. Heating commercially available anthranilic acid and cycloheptanone afforded the tricycle **5**.[15] Halogenation of **5** was accomplished by heating with $POCl_3$ or $POBr_3$. The required amines were prepared by amination of *N*-3-bromopropylphthalimide and subsequent cleavage of the intermediate **10** with hydrazine to give the primary

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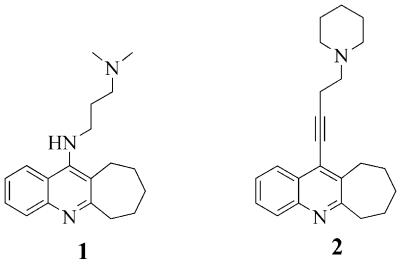


Figure 1.

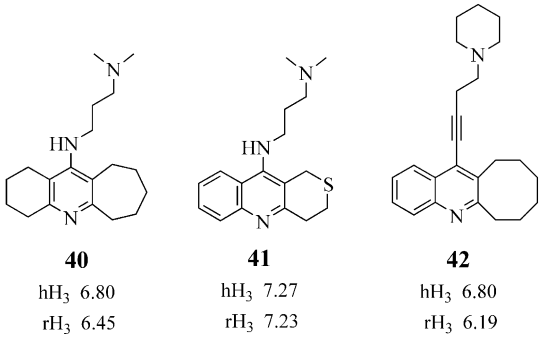
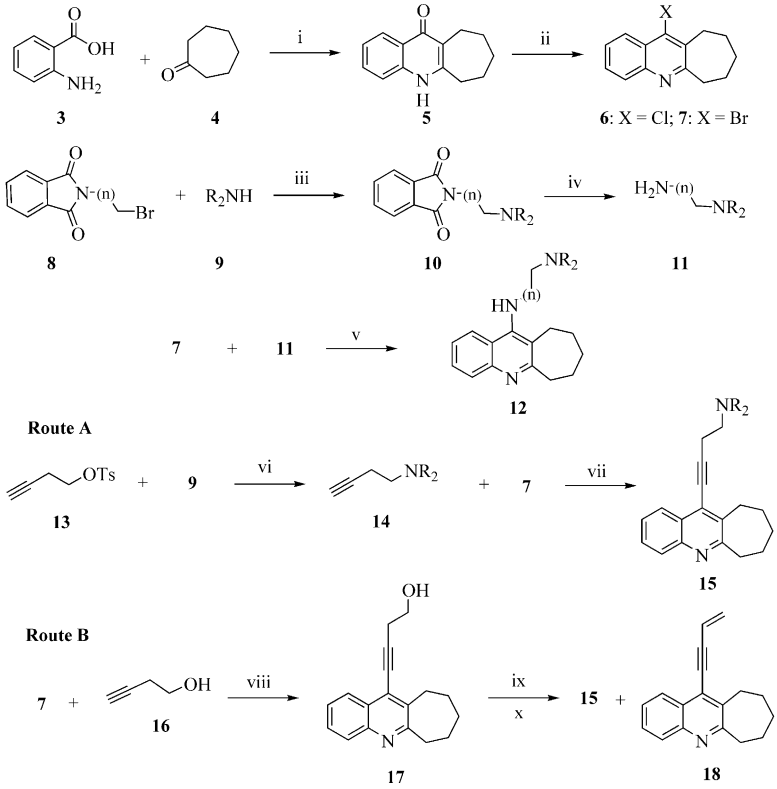


Figure 2.

amine **11**.[16] Reaction of **11** with the brominated tricycle **7** (lower yields were obtained using the chloro analogue) in the presence of copper bronze and a catalytic quantity of iodine, gave the desired 11-amino compounds **12**. Compounds **26** and **31** were prepared from **25** and **30**, respectively by TFA cleavage of the *N*-Boc group. The 4-thio cyclohexyl analogue **41** (Fig. 2) was obtained by employing tetrahydrothiopyran-4-one in the initial formation of the tricyclic core.

The alkynyl compounds were obtained by two approaches. In Route A, 3-butynyl-*p*-toluenesulfonate was treated with an amine to give the amino alkyne intermediate **14**. The Pd–Cu mediated coupling of **7** with the alkyne **14**, under mild conditions, was used to give the acetylenic product **15**. All attempts to employ the chloro intermediate **6** in this coupling were unsuccessful. In the more divergent Route B, the Pd coupling is conducted using 1-butynol and the coupled product **17** is converted to the mesylate. This can be aminated with a range of primary and secondary amines in parallel fashion. A by-product resulting from elimination of the mesylate is the vinylogous alkyne **18**, typically observed in yields of 12–20%. The cis alkene **39** was obtained by catalytic reduction of **2** using Pd/C.

Compounds were evaluated for H_3 potency[17] using a radioligand assay measuring the inhibition of binding of the agonist, [^{3}H]-*N*-α-methyl histamine (RAMH), to rat H_3R using rat cortex homogenates. Functional antagonism was demonstrated by the compound's inhibition of the reversal of cAMP formation by RAMH. Affinity for the human H_3 was comparably determined with receptors expressed in C-6 cells. Selectivity was assessed against HEK cells expressing human H_1 receptors

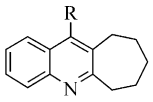


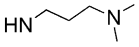
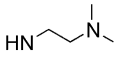
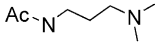
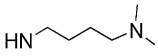
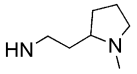
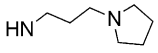
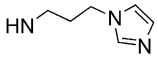
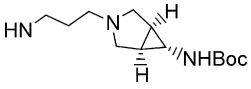
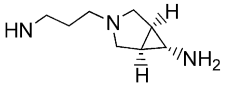
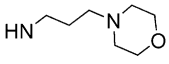
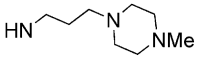
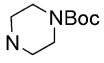
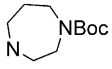
Scheme 1. Reagents and reaction conditions: (i) Xylene, 140 °C, 15 h (76%); (ii) POX_3, reflux, 3 h (X = Cl, 76%; X = Br, 70%); (iii) K_2CO_3, DMF, 90 °C, 4 h; (iv) $N_2H_2{\cdot}H_2O$, EtOH, 3 h; (v) Cu (s), I_2 (cat), 180 °C, 18 h; (vi) K_2CO_3, DMF, 80 °C, 15 h; (vii) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, CH_2Cl_2, reflux, 22 h; (viii) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, CH_2Cl_2, reflux, 18 h; (65%); (ix) $MeSO_2Cl$, Hunig's base, CH_2Cl_2, 0 °C–rt, 1 h; (x) R_2NH, CH_2Cl_2, DMF, 70 °C, 15 h.

labeled with [^{3}H]-mepyramine or human H_2 receptors labeled with [^{3}H]-tiotidine.

SAR studies were conducted by varying the R substituent at the 11-position of the tricycle core (Table 1). In the amine series, comparison of **19**, **1** and **21** shows that a 3 C linker between the two N's is optimal. Acylation of the NH (**20**) results in a 50-fold drop in potency. Constraint of the tertiary N into a five-membered ring (**22** and **23**) gives a moderate increase in potency and the addition of a fused cyclopropyl group (**26**) is well tolerated, even with a bulky *N*-Boc group attached (**25**). However, replacing the pyrrolidine ring with imidazole is unfavorable (**24**). Incorporation of an *N*-Me piperazine moiety (**28**) gave moderate potency but introduction of a morpholine moiety (**27**) gave a further 12-fold reduction. All attempts to incorporate the two N's into a cyclic system (**29**–**31**) were detrimental to activity.

Table 1. Synthesis of 11-amino compounds and binding affinities[a] at human cloned H_3 and rat cortical H_3 receptors



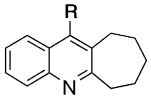
Compd[b]	R	Method of preparation	Yield	Rat cortex H_3-HR pK_i	Human H_3L pK_i
1		A	44	7.66	8.01
19		A	52	6.83	7.32
20		—	85	<6	6.00
21		A	31	7.41	7.36
22		A	39	7.74	8.18
23		A	43	8.60	8.76
24		A	30	<6	<6
25		A	40	7.29	7.33
26		—	87	7.13	7.35
27		A	43	6.40	6.12
28		A	52	7.01	7.29
29		A	44	<6	<6
30		A	44	<6	<6
31		—	74	<6	<6

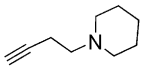
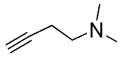
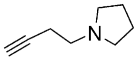
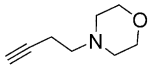
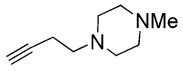
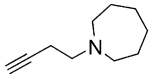
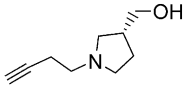
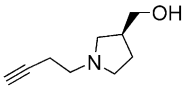
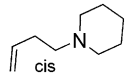
[a]Values are the mean of three or more experiments (SEM $\leq$0.2).
[b]Satisfactory ^{1}H NMR, MS spectra and combustion analysis were obtained for all compounds.

As with the amine analogues, we see a pattern in the alkyne series (Table 2) where the five- and six-membered ring analogues are the most active (**2** and **33**). An interesting stereochemical preference for the (*S*) enantiomer is observed in the case of the 3-hydroxymethylpyrrolidines **37** and **38**. The alkene derivative **39** was found to be of similar potency to its alkyne counterpart. In Figure 2, we see that reduction of the aromatic ring reduces potency (**40**) while the introduction of a thiocyclohexyl ring is better tolerated (**41**). The most active amino analogues were much more potent than the corresponding alkyne derivatives (e.g., **1** 100-fold $>$**33**) but this ratio drops to parity for weaker analogues. The expansion of the cycloalkyl ring from seven- to eight-membered (**42**) is detrimental to activity.

A selection of the most potent compounds was also evaluated for H_3 selectivity with respect to the H_1 and H_2 receptors (Table 3). The amino substituted analogues were highly selective for H_3: 600–6000-fold selective over H_1 and 500–1000-fold selective over H_2. The selectivity was markedly lower for the alkynyl analogue **2** with 13- and 24-fold ratios, respectively.

Table 2. Synthesis of 11-alkynyl compounds and binding affinities[a] at human cloned H_3 and rat cortical H_3 receptors



Compd	R	Method of Preparation	Yield	Rat cortex H_3-HR pK_i*	Human H_3L pK_i*
2		B	59	6.39	7.10
32		B	29	6.16	6.41
33		C	77	6.19	6.67
34		C	50	<6	<6
35		C	38	<6	6.14
36		C	19	<6	6.36
37		C	37	6.21	6.60
38		C	41	<6	6.02
39		—	99	6.56	7.06

[a]See corresponding footnote for Table 1.

Table 3. Binding affinities of selected compounds at human H_3, H_1 and H_2 receptors

Compd	Human H_3L K_i (nM)	Human H_1-HR K_i (nM)	Human H_2-HR K_i (nM)
1	9.7	7696	10,131
2	80	1000	1729
22	6.6	4085	3781
23	1.7	15,733	3211

Values are the mean of four experiments.

In summary, we have identified a novel structural class of H_3 antagonists based upon a cycloheptaquinoline core. Two series of compounds, bearing either an amino substituent or an alkyne linker at the 11-position, were shown to have moderate to high affinity and selectivity for the H_3 receptor.

References and Notes

1. (a) Leurs, R.; Watanabe, T.; Timmerman, H. *Trends Pharmacol. Sci.* **2001**, *22*, 337. (b) Hough, B. L. *Mol. Pharmacol.* **2001**, *59*, 415. (c) Oda, T.; Morikawa, N.; Saito, Y.; Masuho, Y.; Matsumoto, S. *J. Biol. Chem.* **2000**, *275*, 36781.
2. Kinsolving, C. R.; Munro, N. L.; Carr, A. A. *Pharmacologist* **1973**, *15*, 221.
3. Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, E. M. *Nature* **1972**, *236*, 385.
4. Arrang, J. M.; Garbarg, M.; Schwartz, J. C. *Nature* **1983**, *302*, 832.
5. Schlicker, E.; Kathmann, M. In *The Histamine H3 Receptor; A Target for New Drugs*, 1st ed.; Leurs, R., Timmermman, H., Eds.; Elsevier Science: Amsterdam, 1998; p 59.
6. (a) Tedford, C. E. In *The Histamine H3 Receptor; A Target for New Drugs*, 1st ed.; Leurs, R., Timmermman, H., Eds.; Elsevier Science: Amsterdam, 1998; p 269. (b) Leurs, R., Vollinga, R. C., Timmerman, H. In *Progress in Drug Research*, Jacker, E., Ed., Birkhausser: Basel, 1995; p 107.
7. Arrang, J.-M.; Garbarg, M.; Lancelot, J. C.; Lecomte, J. M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. *Nature* **1987**, *327*, 117.
8. Tedford, C. E.; Hoffmann, M.; Seyedi, N.; Maruyama, R.; Levi, R.; Yates, S. L.; Ali, S. M.; Phillips, J. G. *Eur. J. Pharmacol.* **1998**, *351*, 307.
9. Krause, M.; Ligneau, X.; Stark, H.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1998**, *41*, 4171.
10. Ligneau, X.; Lin, J. S.; Vanni-Mercier, G.; Jouvet, M.; Muir, J. L.; Ganellin, C. R.; Stark, H.; Elz, S.; Schunack, W.; Schwartz, J.-C. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 658.
11. De Esch, I. J.; Mills, J. E.; Perkins, T. D.; Romeo, G.; Hoffmann, M.; Wieland, K.; Leurs, R.; Menge, W. M.; Nederkoorn, P. H.; Dean, P. M.; Timmerman, H. J. *J. Med. Chem.* **2001**, *44*, 1666.
12. Linney, I. D.; Buck, I. M.; Harper, E. A.; Kalindjian, S. B.; Pether, M. J.; Shankley, N. P.; Watt, G. F.; Wright, P. T. *J. Med. Chem.* **2000**, *43*, 2362.
13. Apelt, J.; Ligneau, X.; Pertz, H. H.; Arrang, J.-M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *J. Med. Chem.* **2002**, *45*, 1128.
14. (a) Faghih, R.; Dwight, W.; Gentles, R. G.; Phelan, K.; Esbenshade, T. A.; Ireland, L.; Miller, T.; Kang, C. H.; Fox, G. B.; Gopalakrishnan, S.; Hancock, A. A.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2031. (b) Faghih, R.; Dwight, W.; Black, L.; Liu, H.; Gentles, R. G.; Phelan, K.; Esbenshade, T. A.; Ireland, L.; Miller, T.; Kang, C. H.;

Kreuger, K.; Fox, G. B.; Hancock, A. A.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2035. (c) Vasudevan, A.; Connor, S. E.; Gentles, R. G.; Faghih, R.; Liu, H.; Dwight, W.; Ireland, L.; Kang, C. H.; Esbenshade, T. A.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3077. (d) Faghih, R.; Dwight, W.; Vasudevan, A.; Dinges, J.; Connor, S. E.; Esbenshade, T. A.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3077.

15. Lee, C.-M. *J. Med. Chem.* **1968**, *11*, 388.
16. Baldwin, A. W.; Robinson, R. *J. Chem. Soc.* **1934**, 1264.
17. Comparative pK_i's for reference standards ciproxifan and thioperamide, respectively: human H_3L 7.20 and 7.14; rat cortex H_3-HR 9.20 and 8.15.