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In vitro SAR of pyrrolidine-containing histamine H_3 receptor antagonists: Trends across multiple chemical series

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Abstract—Structure–activity relationships (SAR) were analyzed within a library of diverse yet simple compounds prepared as histamine H_3 antagonists. The libraries were constructed with a variety of low molecular weight pyrrolidines, selected from (*R*)-2-methylpyrrolidine, (*S*)-2-methylpyrrolidine, and pyrrolidine.

The histamine H_3 receptor (H_3R), primarily located in the CNS, is a presynaptic auto-receptor that has been shown to regulate the release of histamine and other important neurotransmitters such as serotonin, dopamine, and acetylcholine.[1] Due to the wide distribution of H_3R in the mammalian CNS, many therapeutic targets have been proposed and explored in animal models of disease, including attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), schizophrenia, and obesity.[2] The efforts of a number of laboratories have been directed toward discovering potent H_3 antagonists for the treatment of these and other indications, with a wide variety of structural motifs found to have potent histamine H_3 antagonist activity.[3] Recent efforts focus on so- called non-imidazoles. Most H_3 antagonists under active investigation share some common broad structural elements: a basic amine, connected through a flexible propyloxy or alkyl chain to a lipophilic aromatic group.[4]

Previous studies of histamine H_3 receptor antagonists have often incorporated either piperidine or pyrrolidine moieties (Fig. 1a and b). The SAR of these basic amine moieties was examined in a benzofuran series of H_3 antagonists, and it was found that the methylated pyrrolidine had high in vitro potency.[5] One compound,

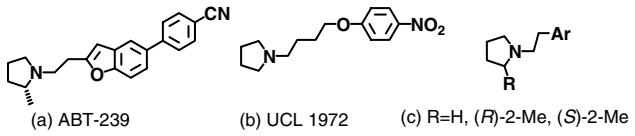
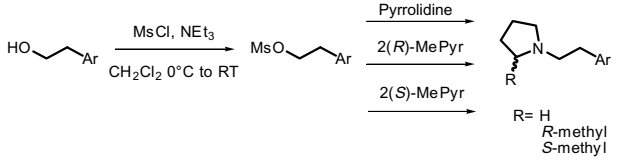


Figure 1. (a) The structure of a benzofuran (ABT-239) with potent in vitro activity and behavioral efficacy. (b) The structure of UCL 1972 one of the first examples of a potent non-imidazole H_3 antagonists.[3a] (c) General structure of histamine H_3 antagonists prepared in library form, specifically with pyrrolidines as the amine moiety.

ABT-239, had particularly high potency, in both in vitro and in vivo behavioral efficacy models. An early SAR study examining receptor binding potencies suggested that (*R*)-2-methylpyrrolidine was a superior amine in the benzofuran-2-ethylamine series.[5b] To better understand the SAR trends in other pyrrolidine-containing non-imidazoles outside the benzofuran-2-ethylamine series, in more diverse structural families, we made and tested libraries of new analogs spanning many different core moieties (Fig. 1c). For each core moiety, three



Scheme 1. Synthesis of aryl amines.

Keywords: Histamine H_3; ADHD; Serotonin; Imidazoles.
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Table 1. The in vitro H_3 affinity (nM) of the compounds of the library[7]

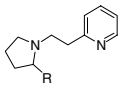
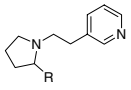
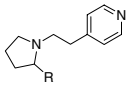
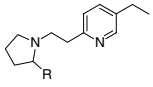
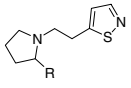
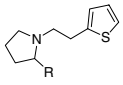
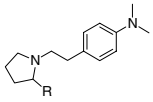
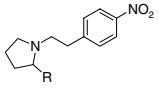
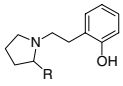
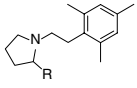
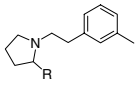
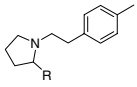
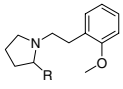
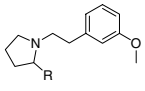
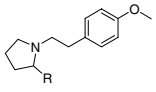
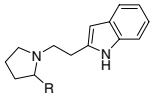
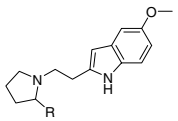
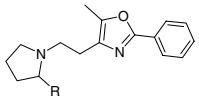
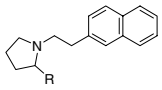
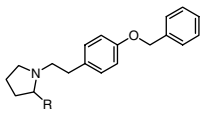
#	Structure	R = H K_i (nM)		R = (*S*)-CH_3 K_i (nM)		R = (*R*)-CH_3 K_i (nM)	
		Hum	Rat	Hum	Rat	Hum	Rat
1		>350	320	340	>330	200	>320
2		>340	>320	>330	>320	300	320
3		350	320	140	>320	70	320
4		230	160	300	>320	34	150
5		190	>320	33	160	17	81
6		>360	>340	110	340	34	140
7		>360	>340	43	230	6.0	43
8		360	>340	20	260	96	280
9		270	340	96	220	21	240
10		400	230	10	72	11	35
11		200	>340	32	240	5.0	30
12		81	>340	27	330	5.0	37
13		340	260	31	240	35	110
14		260	>330	65	170	16	160
15		41	370	8.9	63	2.3	12
16		219	>340	18	340	132	>340

Table 1 (*continued*)

#	Structure	R = H K_i (nM)		R = (*S*)-CH_3 K_i (nM)		R = (*R*)-CH_3 K_i (nM)	
		Hum	Rat	Hum	Rat	Hum	Rat
17		230	>360	100	>360	15	41
18		26	210	28	440	3.5	62
19		30	>240	14	89	1.3	7.1
20		5.0	40	1.6	5.9	0.39	3.9

amine analogs were made, with (*R*)-2-methylpyrrolidine (2(*R*)-MePyr), (*S*)-2-methylpyrrolidine (2(*S*)-MePyr), and pyrrolidine (Pyr) installed to allow direct comparison of in vitro potency across series.

To develop the SAR in the most timely and efficient manner, molecular simplicity and synthetic tractability were priorities. The compounds in each core series were prepared in two steps as shown in Scheme 1, using commercially available arylethylalcohols and the three target pyrrolidines. The (*R*)-2-methylpyrrolidine and (*S*)-2-methylpyrrolidine were prepared in enantiomerically pure form (>98% ee) by fractional crystallization of the tartrate salts.[5d] The alcohols were converted to mesylates in high yields using mesyl chloride and triethylamine in CH_2Cl_2. The reaction was efficient, so the mesylates were typically not purified. Mesylates were found to react directly and cleanly with each of the three amines in CH_3CN at ambient temperature. Final products were purified to >90% (95% NMR or HPLC) by reversed phase HPLC, elution with acetonitrile/aqueous CF_3CO_2H. Compounds were all assayed for in vitro histamine H_3 potency in competition binding assays using human H_3R from cell membranes and rat H_3 receptors from membranes derived from cortical homogenates.[6] In all a total of 60 new analogs were prepared comprising 20 different core moieties, each incorporating Pyr, 2(*R*)-MePyr, or 2(*S*)-MePyr (Table 1).

The three series incorporating pyrrolidine (Pyr), 2(*S*)-methylpyrrolidine (2(*S*)-MePyr), and 2(R)-methylpyrrolidine (2(*R*)-MePyr) were compared using the data in Table 1 (values are reported as nonamolar potencies; $n \geqslant 3$ SEM typically <0.08) and Fig. 2. We first examined the SAR at the human H_3 receptor, where several important trends became clear.[9] In no series did any of the pyrrolidine analogs exceed the potency of either the (*R*) or the (*S*)-methylpyrrolidine analogs, leading to the conclusion that methylation of pyrrolidine moieties increased the in vitro potency across all series. Averages of the ratios calculated from human H_3 binding assays indicated that for 18 of the 20 series, compounds containing (*S*)-2-methylpyrrolidine were more potent (average of 4-fold) than the corresponding unmethylated pyrrolidine analogs. Analogs containing (*R*)-2-methylpyrrolidine were yet more potent (up to 14-fold) than the corresponding non-methylated pyrrolidine analogs. In the great majority of the series (18 of 20 series) the (*R*)-2-methylpyrrolidine analogs exceeded the potency of the (*S*)-2-methylpyrrolidine analogs.

Next we examined SAR trends at the rat H_3R and found them similar to the human H_3 receptor. Compounds containing (*R*)-2-methylpyrrolidine were up to 9-fold more potent than the corresponding unmethylated pyrrolidine analogs. (*S*)-2-Methylpyrrolidine containing compounds were up to 2.5-fold more potent than unmethylated analogs. Overall, binding potencies at the human receptor in the present series were generally greater than those at the rat receptor (as much as 10-fold), consistent with some previous reports on other non-imidazole structures.[5c,d,8]

Moving beyond the SAR analysis of the pyrrolidine moiety, to an examination of the SAR of the core moieties of the 20 series, the data in Table 1 point to weak human H_3R affinity for small polar aromatic groups (e.g., compounds **1**–**3**). However, compounds with polar substituents in the para position show moderate affinity (e.g., compounds **7** and **8**). Enhanced affinity for the human H_3 receptor is clearly seen with non-polar aromatic groups (e.g., compounds **10**–**15**) which show 10- to 100-fold increases in potency compared to compounds containing heterocycles and polar substituents (e.g., compounds **1**–**3** and **17**). Of all the series made, those with large non-polar groups show the highest affinity (e.g., **18**–**20**).

GTPγS binding using H_3 receptor-transfected cells demonstrated that compounds **19**-(*S*)-CH_3 and **20**-(R)-CH_3 function as antagonists at both the human (h) and rat (r) H_3 receptor subtypes ($pK_b = 7.75 \pm 0.06$ (h), 6.98 ± 0.06 (r); 8.93 ± 0.04 (h), 8.24 ± 0.05 (r), respectively). The GTPγS functional data were consistent with

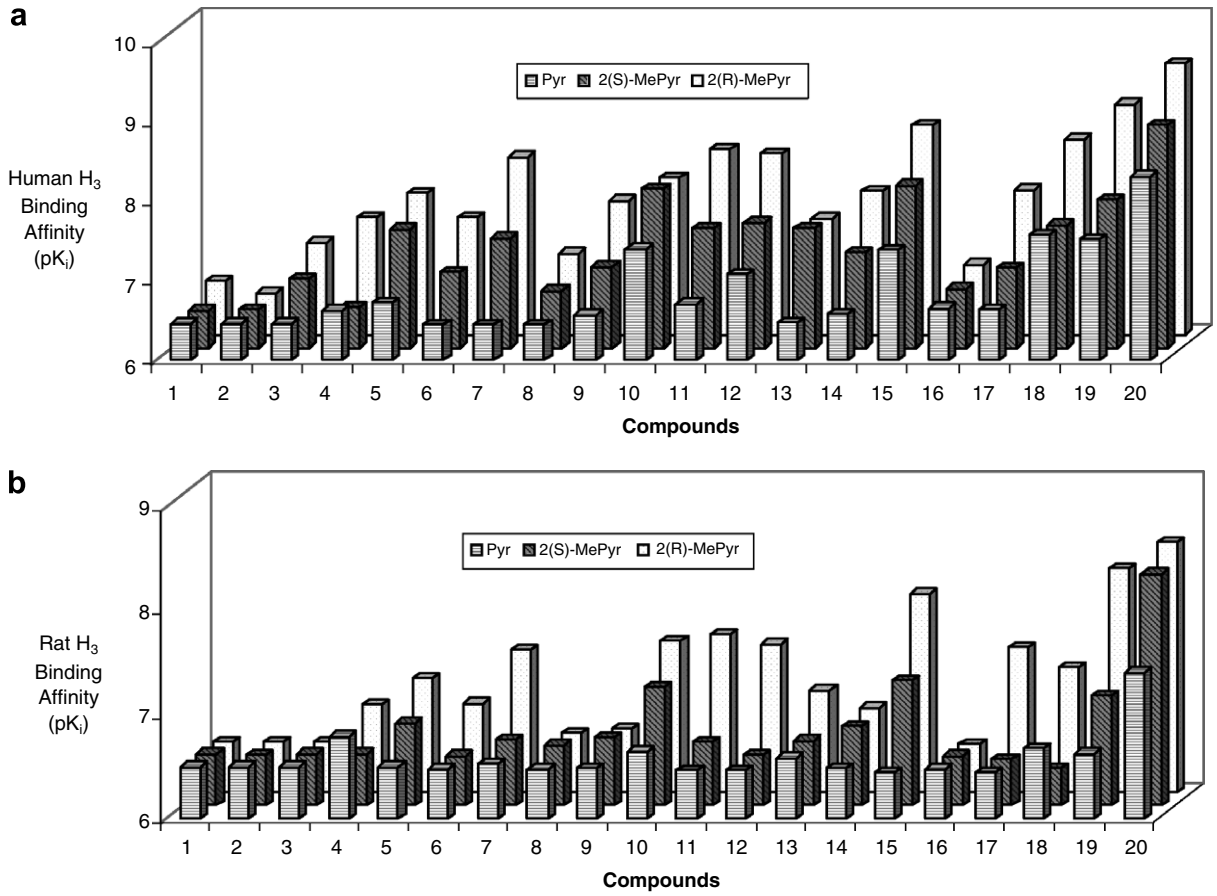


Figure 2. Graphical illustration of SAR trends. Compound chemical series are shown on the *x*-axis, with the H_3 receptor binding potency values on the *y*-axis, expressed as pK_i values for better graphical display. The pyrrolidine base groups are shown on the *z*-axis. (a) human histamine H_3 receptor, (b) rat histamine H_3 receptor.

the radioligand binding data where **19**-(*S*)-CH_3 had lower affinity than **20**-(*R*)-CH_3 for the H_3 receptor. The selectivity of these compounds was also tested at the other histamine receptor subtypes. Compounds **19**-(*S*)-CH_3 and **20**-(*R*)-CH_3 had $K_i > 1000$ nM at H_1, H_2, and H_4 receptors indicating that these compounds are selective for the H_3 receptor subtype.

Results of this extensive SAR study of 60 compounds in the presently examined 20 new series showed that the substitution of the pyrrolidine moiety with a methyl group at the 2-position reliably enhances in vitro potency over unsubstituted analogs at both human and rat histamine H_3 receptors. (*R*)-2-Methylpyrrolidine (95%) analogs were more potent than the (*S*)-2-methylpyrrolidine analogs. The results thus support the hypothesis that 2-methylpyrrolidine generally enhances in vitro potency across diverse chemical classes, and that the (*R*)-configuration is superior to the (*S*)-configuration. We posit that this finding will prove useful to design new histamine H_3 antagonists.

References and notes

1. (a) Hill, S. J.; Ganellin, C. R.; Timmerman, H.; Schwartz, J.-C.; Shankley, N. P.; Young, J. M.; Schunack, W.; Levi, R.; Haas, H. L. *Pharmacol. Rev.* **1997**, *49*, 253; (b) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. *Nature* **1983**, *302*, 832; (c) Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. *Trends Pharmacol. Sci.* **1998**, *19*, 177; (d) Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Jiang, X.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. *Mol. Pharmacol.* **1999**, *55*, 1101; (e) Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. P. *Nat. Rev. Drug Discov.* **2005**, *4*, 107.
2. (a) Stark, H.; Schlincher, E.; Schunack, W. *Drugs Fut.* **1996**, *21*, 507; (b) Tozer, M. J.; Kalindjian, S. B. *Exp. Opin. Ther. Patents* **2000**; (c) Bennani, Y. L.; Black, L. A.; Faghih, R.; Hancock, A. A.; Decker, M. W. *Behav. Brain Res.* **2002**, *131*, 151; (d) Halpern, M. T. *Curr. Opin. Cent. Peripher, Nerv. Syst. Invest. Drugs* **1999**, *1*, 524; (e) Ali, S. M.; Tedford, C. E.; Gregory, R.; Handley, M. K.; Yates, S. L.; Hirth, W. W.; Phillips, J. G. *J. Med. Chem.* **1999**, *42*, 903; (f) Fox, G. B.; Pan, J. G.; Esbenshade, T. A.; Switzerland, 2004; p 97; (g) Babier, 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; (h) Hancock, A. A. *Curr. Opin. Investig. Drugs* **2003**, *4*, 1190; (i) Hancock, A. A.; Bennani, Y. L.; Bush, E. N.; Esbenshade, T. A.; Faghih, R.; Fox, G. B.; Jacobson, P.; Knourek-Segal, V.; Krueger, K. M.; Nuss, M. E.; Pan, J. B.; Shapiro, R.; Witte, D. G.; Yao, B. B. *Eur. J. Pharmacol.* **2004**, *487*, 183; (j) Malmolof, K.; Zaragoza, F.; Golozoubova, V.; Refsgaard, H. H. F.; Cremers, T.; Raun, K.; Wulff, B. S.; Johansen, P. B.; Westerink, B.; Rimvall, K. *Int. J. Obesity* **2005**, *29*, 1402.

3. (a) Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, I. J. P. *Drug Discov. Today* **2005**, *10*, 1613; (b) Esbenshade, T. A.; Fox, G. B.; Cowart, M. D. *Mol. Interventions* **2006**, *6*, 77; (c) Arrang, J. M.; Morisset, S.; Rouleau, A.; Gbahou, F.; Ligneau, X.; Tardivel-Lacombe, J.; Stark, H.; Schunack, W.; Ganellin, C. R.; Schwartz, J.-C. *Int. Congr. Ser.* **2003**, *1249*, 139; (d) Stark, H. *Exp. Opin. Ther. Pat.* **2003**, *13*, 851.
4. (a) Meier, G.; Apelt, J.; Reichert, U.; Grassman, S.; Ligneau, X.; Elz, S.; Leurquin, F.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. *Eur. J. Pharmacol. Sci.* **2001**, *12*, 249; (b) Faghih, R.; Dwight, W.; Vasudevan, A.; Dinges, J.; Conner, S. E.; Esbenshade, T. A.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3077; (c) 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; (d) sbenshade, T. A.; Fox, G. B.; Krueger, K. M.; Miller, T. R.; Kang, C. J.; Denny, L. I.; Witte, D. G.; Yao, B. B.; Pan, L.; Wetter, J.; Marsh, K.; Bennani, Y. L.; Cowart, M. D.; Sullivan, J. P.; Hancock, A. A. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 165; (e) Fox, G. B.; Esbenshade, T. A.; Pan, J. B.; Radek, R. J.; Krueger, K. M.; Yao, B. B.; Browman, K. E.; Buckley, M. J.; Ballard, M. E.; Komater, V. A.; Miner, H.; Zhang, M.; Faghih, R.; Rueter, L. E.; Bitner, R. S.; Drescher, K. U.; Wetter, J.; Marsh, K.; Lemaire, M.; Porsolt, R. D.; Bennani, Y. L.; Sullivan, J. P.; Cowart, M. D.; Decker, M. W.; Hancock, A. A. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 176; (f) Veber, D. F.; Johnson, S. R.; Chen, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615; (g) Wenlock, M. C.; Austin, R. P.; Barton, P.; Davis, A. M.; Leeson, P. D. *J. Med. Chem.* **2003**, *46*, 1250.
5. (a) Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A.; Bennani, Y. L.; Black, L. A.; Pan, L.; Marsh, K. C.; Sullivan, J. P.; Esbenshade, T. A.; Fox, G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38; (b) Cowart, M. D.; Pratt, J. K.; Stewart, A. O.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 689; (c) Black, L. A.; Nersesian, D. L.; Sharma, P.; Ku, Y.-Y.; Bennani, Y. L.; Marsh, K. C.; Miller, T. R.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1443; (d) Gfesser, G. A.; Faghih, R.; Bennani, Y. L.; Curtis, M. C.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Biorg. Med. Chem. Lett.* **2005**, *15*, 2559; (e) Cowart, M. D.; Gfesser, G. A.; Browman, K. E.; Faghih, R.; Miller, T. R.; Milicic, I.; Baranowski, J. L.; Krueger, K. M.; Witte, D. G.; Molesky, A. L.; Komater, V. A.; Buckley, M. J.; Diaz, B. J.; Gagne, G. D.; Zhou, D.; Deng, X.; Pan, L.; Roberts, E. M.; Diehl, M. S.; Wetter, J. M.; Marsh, K. C.; Fox, G. B.; Brioni, J. D.; Esbenshade, T. A.; Hancock, A. A. *J. Biochem. Pharmacol.* **2007**, *73*, 1243.
6. Esbenshade, T. A.; Fox, G. B.; Krueger, L. M.; Miller, T. R.; Kang, C. H.; Denny, L. I., et al. *J. Pharmacol Exp. Ther.* **2005**, *313*, 165.
7. These were determined from the mean of at least three pK_i determinations, for the compounds, the standard error of the mean pK_i (SEM) were typically <0.08.
8. Faghih, R.; Dwight, W.; Pan, J. B.; Fox, G. B.; Krueger, K. M.; Esbenshade, T. A.; McVey, J. M.; Marsh, K.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2002**, *13*, 1325.
9. Potencies were compared by calculation of the ratio of potencies across series according to these formulae: $\frac{2(R)-\text{MePyr}}{2(S)-\text{MePyr}}$, $\frac{2(R)-\text{MePyr}}{\text{Pyr}}$, $\frac{2(S)-\text{MePyr}}{\text{Pyr}}$.