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Synthesis and SAR of novel histamine H_3 receptor antagonists

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Abstract—The synthesis and biological evaluation of novel tetrahydroisoquinoline, tetrahydroquinoline, and tetrahydroazepine antagonists of the human and rat H_3 receptors are described. The substitution around these rings as well as the nature of the substituent on nitrogen is explored. Several compounds with high affinity and selectivity for the human and rat H_3 receptors are reported.

Histamine is known to play an important role in the human body, with actions spanning diverse physiological roles, from acting as a neurotransmitter in the central nervous system (CNS) to peripheral effects on gastric acid secretion and smooth muscle contraction.[1] The action of histamine is mediated through four distinct receptors known to date as histamine H_1, H_2, H_3, and H_4 receptors.[2] Centrally administered histamine H_3 antagonists lead to increased histamine levels[3] and may consequently be useful for the treatment of a variety of CNS disorders such as attention deficit and hyperactivity disorder, cognitive disorders, schizophrenia or obesity.[4]

Attempts to identify selective non-imidazole containing ligands for the H_3 receptors have resulted in the identification of several potent antagonists (Fig. 1) such as UCL 2190 (**1**)[5], A-923 (**2**)[6], JNJ-5205872 (**3**)[7], ABT-239 (**4**)[8], and compounds **5**[9] and **6**.[10]

Initial efforts employing a medium throughput screen identified a novel tetrahydroisoquinoline (**7**) as a potent

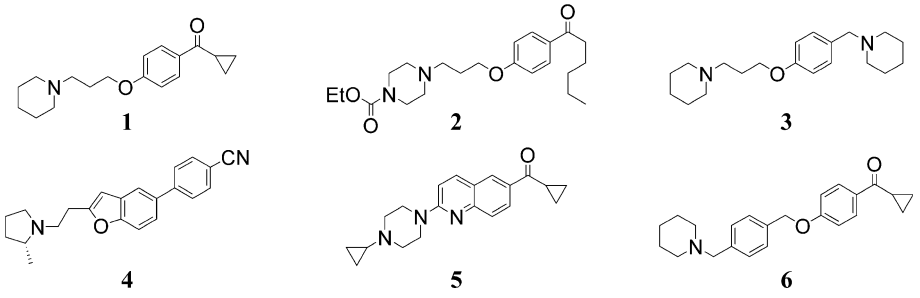

Figure 1. Structures of non-imidazole based histamine H_3 antagonists.

Keywords: Histamine H_3 receptor antagonist; Tetrahydroisoquinolines; Tetrahydroquinolines; Tetrahydroazepines.
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antagonist[11] (K_i = 2.4 nM, IC_{50} = 6.6 nM) at human histamine H_3 receptor in vitro (Fig. 2). We were intrigued by this water-soluble compound and sought to further explore this structure type. This paper reports the SAR of a number of tetrahydroisoquinolines, tetrahydroquinolines, and tetrahydroazepines.

The synthesis of 6-hydroxy tetrahydroisoquinoline compounds is outlined in Scheme 1. 6-Hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **8**[12] was alkylated with 1-(3-chloro-propyl)-piperidine, followed by removal of the Boc group, and further elaboration of the newly unmasked nitrogen by reaction with aldehydes, ketones, acid chlorides, sulfonyl chlorides, and isocyanates to give the final products (**11**).

The other tetrahydroisoquinoline regioisomers were prepared as described in Scheme 1 from the corresponding hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester intermediates.[13] The 8-hydroxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylic acid *tert*-butyl ester **12** was prepared as detailed in Scheme 2. The indanone **13** was prepared in two steps from 3-(3-methoxyphenyl)propanoic acid.[14] The bromo substituent, whose role was to assure the desired regiochemistry, was removed by hydrogenation. Curtius rearrangement of the resulting ketone **14** provided the isoquinolinone **15**, which was reduced to the corresponding isoquinoline **16**,[15] demethylated, and protected with a Boc group.

In a similar manner, the tetrahydroquinoline compounds were synthesized from the corresponding hydroxy-3,4-dihydro-2*H*-quinoline-1-carboxylic acid *tert*-butyl esters which were obtained by reduction of the substituted quinolines (**17**) as illustrated in Scheme 3.[16]

The 7-hydroxy-1,3,4,5-tetrahydro-benzo[*c*]azepine-2-carboxylic acid *tert*-butyl ester was prepared in an analogous manner as that described in Scheme 2 from 6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one.[17] The corresponding 7-hydroxy-1,2,4,5-tetrahydro-benzo[*d*]azepine-3-carboxylic acid *tert*-butyl ester was prepared as described in the literature.[18]

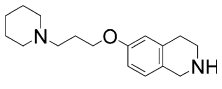

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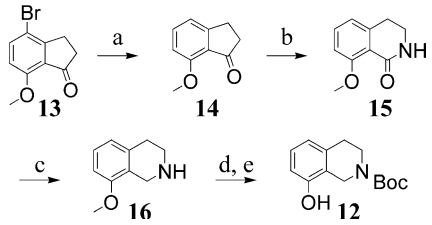
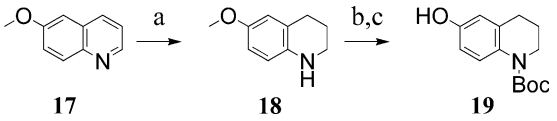
Figure 2. Initial Screen Hit.

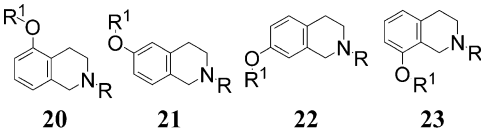


Scheme 2. Reagents and conditions: (a) H_2, 10% Pd/C, $NaOAc{\cdot}3H_2O$, EtOH, 60 psi, 4 h, 72%; (b) NaN_3, H_2SO_4, toluene, 4 h, 79%; (c) LAH, THF, 5 h, 70%; (d) BBr_3, CH_2Cl_2, −78 °C, 3.5 h; (e) Boc_2O, NaOH, dioxane, 18 h, 89% (two steps).

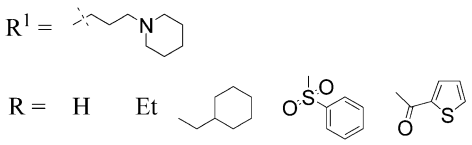


Scheme 3. Reagents and conditions: (a) H_2, PtO_2, MeOH, 60 psi, 12 h, 100%; (b) BBr_3, CH_2Cl_2, 4 h, −78 °C; (c) Boc_2O, NaOH, dioxane, 77% (two steps).

Table 1. Binding affinities (nM) of tetrahydroisoquinolines at the human H_3 receptor[a]



20 **21** **22** **23**

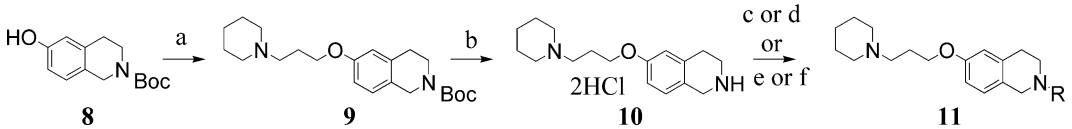


a **b** **c** **d** **e**

R	K_i[b], nM ± SEM			
	20	**21**	**22**	**23**
a	>300	2.4 ± 0.7	0.60 ± 0.10	154 ± 32
b	84.2 ± 13.7	0.54 ± 0.13	0.34 ± 0.07	95.2 ± 2.9
c	15.4 ± 1.3	1.01 ± 0.43	0.35 ± 0.09	59 ± 20
d	>300	7.4 ± 0.92	0.53 ± 0.19	>300
e	>300	2.1 ± 0.6	8.1 ± 0.81	>300

[a] Binding potencies were assessed by displacement of [^{3}H]*N*-α-methylhistamine using cloned human H_3 receptors.
[b] Values are means of at least three experiments.

A representative subset of compounds based on the tetrahydroisoquinoline core is shown in Table 1. The receptor shows a preference for the orientation



8 **9** **10** **11**

Scheme 1. Reagents and conditions: (a) 1-(3-chloro-propyl)-piperidine, Cs_2CO_3, KI, DMF, 90 °C, 18 h, 67%; (b) 4 M HCl in dioxane, CH_2Cl_2, rt, 4 h, 87%; (c) aldehyde, MP-$CNBH_3$, CH_2Cl_2/MeOH (9:1), rt, 18 h; (d) acid chloride, Et_3N, CH_2Cl_2, rt, 18 h; (e) sulfonyl chloride, Et_3N, CH_2Cl_2, rt, 18 h; (f) isocyanate, Et_3N, CH_2Cl_2, rt, 18 h.

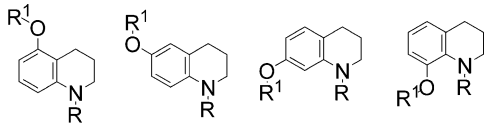
provided by the 6- and 7-substituted tetrahydroisoquinolines (**21 a–e** and **22 a–e**). The dibasic compounds (**22a–c**) have subnanomolar affinity for the human H_3 receptor as does the monobasic compound **22d**.

The data on a representative set of tetrahydroquinoline compounds are shown in Table 2. In general, these compounds were less active than the most closely homologous tetrahydroisoquinoline regioisomers shown in Table 1.

Encouraged by the data on the 6- and 7-hydroxy tetrahydroisoquinolines, tetrahydrobenzazepines were prepared and evaluated at both the human and rat histamine H_3 receptors (Table 3). Reports in the literature[19] (for different chemical series) have described significant potency differences between the human and rat receptors. Likewise, we also saw a species difference with all the compounds being less potent at the rat receptor. We selected compounds **22b** and **28f** based on their high affinity for human H_3 receptors for further evaluation.[20] These compounds potently inhibited the ex vivo binding of [^{3}H]*R*-α-methylhistamine in rat brain homogenates (IC_{50} = 1.1 and 5.3 mg/kg, po, for **22b** and **28f**, respectively). The oral bioavailability of compounds **22b** and **28f** in rat after a dose of 10 mg/kg was found to be 69% and ⩾100%, respectively.

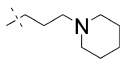
In conclusion, we have discovered highly potent ligands for both the human and rat H_3 receptors. The full biological profile of these compounds will be published in due course.

Table 2. Binding affinities (nM) of tetrahydroquinolines at the human H_3 receptor[a]

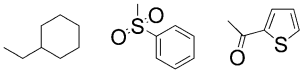


24 **25** **26** **27**

R^1 =



R = H Et

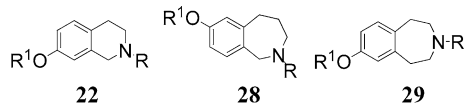


a **b** **c** **d** **e**

R	K_i[b], nM ± SEM			
	24	**25**	**26**	**27**
a	>300	54 ± 10	129 ± 27	>300
b	>300	41 ± 4	156 ± 24	>300
c	141 ± 19	31 ± 8	187 ± 11	>300
d	—	18 ± 2.9	7.3 ± 0.5	>300
e	—	—	22.6 ± 6	>300

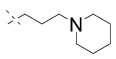
[a] Binding potencies were assessed by displacement of [^{3}H]*N*-α-methylhistamine using cloned human H_3 receptors.
[b] Values are means of at least three experiments.

Table 3. Binding affinities (nM) of tetrahydroisoquinolines and tetrahydroazepines at the human and rat H_3 receptors[a]

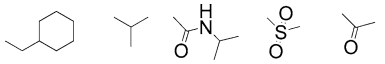


22 **28** **29**

R^1=



R= Et



b **c** **f** **h** **i** **j**

R	K_i[b] (nM)					
	22		**28**		**29**	
	hH_3	rH_3	hH_3	rH_3	hH_3	rH_3
b	0.34	0.64	0.34	0.56	0.26	1.1
c	0.28	0.46	0.20	0.80	0.53	0.97
f	0.17	0.89	0.20	1.29	0.72	1.6
h	4.9	39.6	17.1	32.5	42.3	—
i	23.8	74.5	2.9	70.1	12.1	38.1
j	19.4	36.7	—	—	11.6	48.8

[a] Binding potencies were assessed by displacement of [^{3}H]*N*-α-methylhistamine using cloned human H_3 and rat H_3 receptors.
[b] Values are means of at least three experiments.

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