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Novel H_3 receptor antagonists with improved pharmacokinetic profiles

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ABSTRACT

A new series of H_3 antagonists derived from the natural product Conessine are presented. Several compounds from these new series retain the potency and selectivity of earlier diamine based analogs while exhibiting improved PK characteristics. One compound (**3u**) demonstrated functional antagonism of the H_3 receptor in an in vivo pharmacological model.

The histamine H_3 receptor is one of four members of the G-protein coupled receptor (GPCR) super-family which bind histamine.[1] H_3 receptors are expressed primarily on presynaptic neurons of the central nervous system (CNS) where they regulate the synthesis and release of several neurotransmitters including histamine, acetylcholine, dopamine and serotonin.[2] The central role of H_3 receptors in these signaling pathways has led to a significant effort to develop H_3 antagonists as potential treatments for a diverse collection of CNS related disorders.[3] Several H_3 antagonists are currently being investigated in clinical trials,[4] and preliminary results suggest that an H_3 antagonist can increase wakefulness in narcolepsy patients.[5]

We recently reported early data from our effort to develop novel H_3 antagonists/inverse agonists as wake promoting agents.[6] Utilizing the known H_3 antagonist natural product Conessine (**1**)[7] as a structural starting point, we prepared a series of simplified diamines, exemplified by **2**, which exhibited potent antagonism and inverse agonism of the H_3 receptor (Chart 1). While diamines such as **2** were suitable for preliminary in vivo studies, they frequently exhibited delayed absorption and long half-lives. We considered these characteristics less than ideal in a potential wake promoter and sought to develop new compounds in this series with pharmacokinetic (PK) profiles more consistent with our goal of developing a rapidly absorbed, short-acting drug. We have previously demonstrated that the basic phenethylamine portion of these compounds is required for activity at the H_3 receptor,[6] and describe here the effect of changes in the bicyclic core on H_3 receptor binding, PK characteristics and in vivo activity.

Alteration of the bicyclic portion of these molecules was examined in analogs **3a–o** (Scheme 1). Previously described single isomer bicyclic ketone **4**[6] was reacted with the lithium reagent derived from 4-bromo-phenethylpyrrolidine **6a** to give the alcohol derivative **7a**. Deprotection of the *N*-benzyl group of **7a** followed by dehydration with HCl provided diamine **8a**. Subsequent reaction of **8a** with various acid chlorides, sulfonyl chlorides or isocyanates provided the amide, sulfonamide and urea analogs **3a–o**, which contained the preferred (**3a***R*, **6a***R*) stereochemistry found in our earlier studies.

Compounds **3a–o** were tested in a rat cortex *N*-[^{3}H]-methylhistamine displacement assay,[8] the results of which are shown in Table 1. It was readily apparent that the new analogs were significantly less potent H_3 antagonists than the diamines prepared in our earlier study. For example, the urea derivatives **3a–d**, whose K_i's ranged from 12 to 20 nM, and the sulfonamide analogs **3e–h** (K_i = 12–27 nM) were approximately 200-fold less potent than diamine **2**. With the exception of phenyl amide **3i** (K_i = 21 nM), the amide analogs **3j–o** (K_i = 3–7 nM) were slightly more potent than either the ureas or sulfonamides and approximately 70-times less potent than diamine **2**. Notwithstanding the differences observed between various functional groups, no significant potency trends were observed within the amide, urea or sulfonamide series.

In order to focus subsequent efforts on compounds with promising in vivo characteristics, the PK properties of several com-

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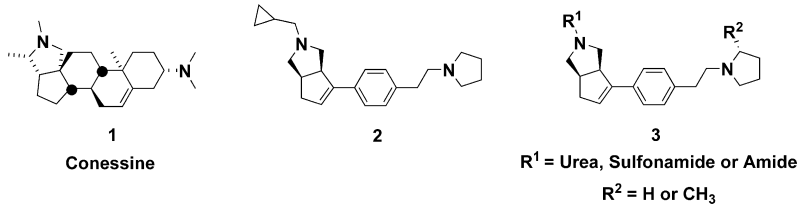
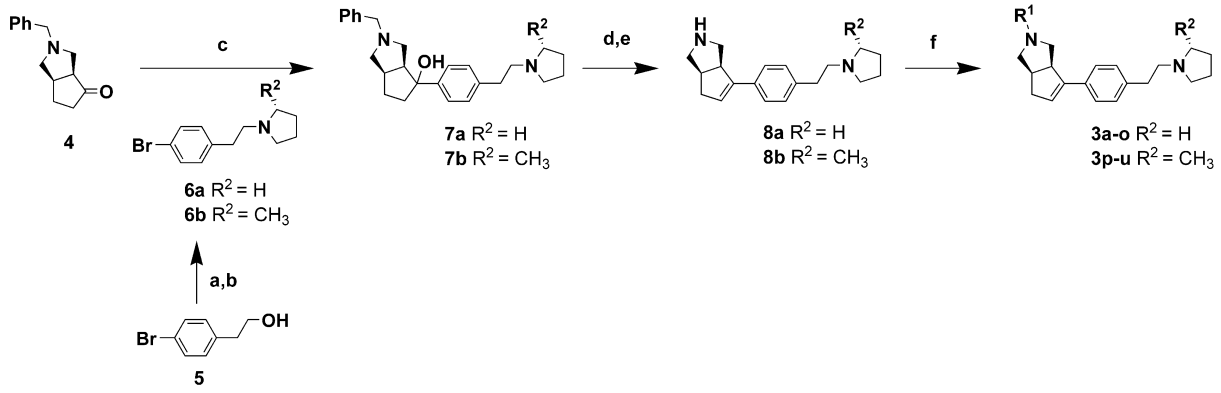
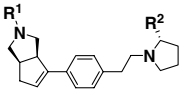


Chart 1. Structure of conessine and representative H_3 antagonists.



Scheme 1. Synthesis of target compounds **3**. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 95%; (b) pyrrolidine or 2-*R*-methylpyrrolidine, K_2CO_3, CH_3CN, 25 °C, 65–70%; (c) *n*-BuLi, THF, −78 °C, 60–64%; (d) ammonium formate, $Pd(OH)_2/C$, MeOH, 96–98%; (e) HCl, *i*-PrOH, 60 °C, 98%; (f) i—R_2NCO, CH_2Cl_2, 25 °C, 29–40%; or ii—RSO_2Cl, CH_2Cl_2, Et_3N, 25 °C, 31–43%; or iii—RCOCl, CH_2Cl_2, Et_3N, 25 °C, 32–46%.

Table 1
Binding affinities (K_i and pK_i) of compounds **3a–r** at rat H_3 receptor[a]



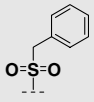
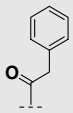
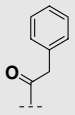
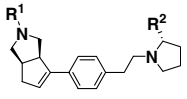
Compound	R^1	R^2	Rat H_3 K_i[b] (nM)	Rat pK_i[b]
2		H	0.07 (**h Antag.** = **0.9**, **Inverse Ag.** = **1.0**)[c]	10.17 ± 0.21
3a		H	20	7.69 ± 0.15
3b		H	16	7.78 ± 0.38
3c		H	13	7.89 ± 0.10
3d		H	12	7.91 ± 0.13
3e		H	27	7.56 ± 0.16
3f		H	12	7.92 ± 0.26
3g		H	12	7.93 ± 0.16
3h		H	17	7.77 ± 0.03
3i		H	21	7.67 ± 0.26
3j		H	6	8.21 ± 0.04

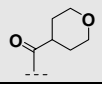
Table 1 (*continued*)

Compound	R^1	R^2	Rat H_3K_i[b] (nM)	Rat pK_i[b]
3k		H	7	8.15 ± 0.08
3l		H	5	8.26 ± 0.16
3m		H	3	8.49 ± 0.17
3n		H	4	8.42 ± 0.10
3o		H	6	8.20 ± 0.22
3p		CH_3	0.4	9.42 ± 0.21
3q		CH_3	0.4	9.46 ± 0.19
3r		CH_3	3	8.57 ± 0.13
3s		CH_3	1	8.97 ± 0.18
3t		CH_3	0.3	9.53 ± 0.14
3u		CH_3	0.7 (**h Antag.** = **2**, **Inverse Ag.** = **4**)[c]	9.13 ± 0.23

[a] Displacement of *N*-[^{3}H]-methylhistamine from rat cortex membranes.[6]
[b] Values are reported as average of $n \geqslant 3$ independent measurements for all compounds. Errors are ±log SD.
[c] Antagonism determined by displacement of [^{3}H] R(−)-α-methylhistamine from recombinant CHO–K1 cells expressing the human H_3 receptor ($n = 1$). Inverse agonism determined by GTPγS binding in CHO–K1 cells expressing the human H_3 receptor in the absence of agonist ($n = 1$).[10]

Table 2
PK characteristics of selected compounds in the rat



Compound	R^1	R^2	$t_{1/2}$[a] (h)	T_{max}[a] (h)	%F[a]
2		H	6	6	78
3a		H	7.3	0.3	22
3f		H	5	0.2	3
3o		H	1.8	0.6	39
3u		CH_3	2.5	0.3	66

[a] After PO dose (10 mg/kg, $n = 3$).

pounds from the initial series (**3a**–**o**) were examined in rats (Table 2). Unfortunately, selected examples from the urea series exhibited many of the same shortcomings we observed with the diamine series. For example, although compound **3a** was rapidly absorbed (T_{max} = 0.3 h), its long half-life (7.3 h) and modest oral bioavailability (F = 22%) offered no improvement over diamine analog **2**. The PK characteristics of the sulfonamides were also disappointing. This is demonstrated for isopropyl sulfonamide **3f**, which had a half-life that was similar to **3a** and exhibited very low bioavailability (F = 3%). We were gratified to find that some, though not all, of the amide analogs possessed desirable PK characteristics. For example, compound **3o** exhibited a short half-life (1.8 h), rapid absorption (T_{max} = 0.6 h) and good bioavailability (F = 39%).

Having identified the promising PK characteristics of compounds from the amide series, we sought to improve the potency of these compounds prior to selecting a compound for in vivo pharmacology studies. To this end, a new series of amides (**3p**–**u**), which incorporated a distal *R*-2-methylpyrrolidine group, were prepared starting from compound **6b** (Scheme 1). We were gratified to find that the inclusion of this group afforded compounds with binding affinities six to 23 times greater than their respective

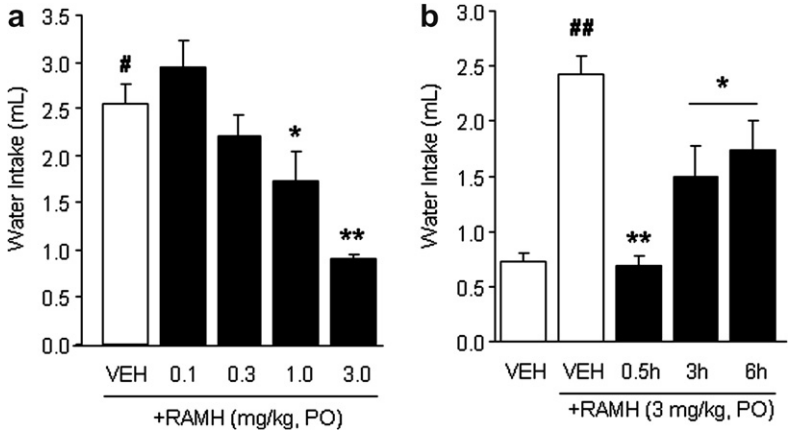


Figure 1. (a) Inhibition of (*R*)-α-methylhistamine induced drinking 0.5 h after oral administration of compound **3u** (0.1, 0.3, 1 and 3 mg/kg). (b) Inhibition of (*R*)-α-methylhistamine induced drinking 0.5 h, 3 h and 6 h after oral administration of compound **3u** (3 mg/kg).

pyrrolidine analogs (Table 1). The *R*-2-methylpyrrolidine group has been reported to enhance H_3 potency in vitro in other series.[6,9] Among several new analogs in this series was THP-amide analog **3u**, which displayed sub-nanomolar potency against the rat H_3 receptor (K_i = 0.7 nM). Further examination of **3u** demonstrated high affinity (K_i = 2 nM) and potent inverse agonist activity (K_i = 4 nM) at the human H_3 receptor. This compound also showed >1000-fold selectivity for the H_3 receptor versus a panel of over 100 human GPCRs, including H_1, H_2 and H_4.[10] Compound **3u** was ultimately chosen for in vivo pharmacological testing after rat PK experiments demonstrated that it was rapidly absorbed, had a relatively short half-life and excellent bioavailability (Table 2).

Compound **3u** demonstrated functional antagonism of the H_3 receptor in vivo in a rat dipsogenia model, in which an acute drinking response induced by an H_3 agonist is attenuated by pre-administration of an H_3 antagonist.[11] Specifically, **3u** (0.1, 0.3, 1 and 3 mg/kg) or vehicle were administered orally to rats 0.5 hour prior to administration of (*R*)-α-methylhistamine (10 mg/Kg, SC). As shown in Figure 1a, **3u** inhibited agonist induced drinking in a dose dependent manner with a minimum effective dose of 1 mg/kg. In a subsequent experiment designed to examine this compound's time profile, **3u** (3 mg/kg) was administered 0.5, 3 and 6 h prior to injection of the H_3 agonist. The results of this experiment (Fig. 1b) suggest a relatively short duration of action for **3u** that is consistent with data obtained from our PK experiments.

In summary, the alteration of substituents on the bicyclic nitrogen in this series of compounds can result in significant changes in their PK profiles. These changes are often accompanied by a significant loss of potency, a deficiency that can be rectified by the inclusion of a distal *R*-methyl pyrrolidine group. Among the analogs studied, certain members of the amide series (e.g., **3u**) possess the most promising profiles including excellent potency and selectivity at the H_3 receptor as well as rapid absorption and short half-life.

References and notes

1. (a) Hill, S.; Ganellin, C.; Timmerman, H.; Schwartz, J.; Shankley, N.; Young, J.; Schunack, W.; Levi, R.; Haas, H. *Pharmacol. Rev.* **1997**, *49*, 253; (b) Hough, L. B. *Mol. Pharmacol.* **2001**, *59*, 415.
2. (a) Schwartz, J. C.; Arrang, J.-M.; Garbarg, M.; Pollard, H.; Ruat, M. *Physiol. Rev.* **1991**, *71*, 1; (b) Leurs, R.; Smit, M. J.; Timmerman, H. *Pharmacol. Ther.* **1995**, *66*, 413; (c) Morisset, S. A.; Rouleau, A.; Ligneau, X.; Gbahou, F.; Tardivel-Lacombe, J.; Stark, H.; Schunack, W.; Ganellin, C. R.; Schwartz, J.-C.; Arrang, J.-M. High. J.-M. *Nature* **2000**, *408*, 860; (d) Garduno-Torres, B.; Trevino, M.; Gutierrez, R.; Arias-Montano, J.-A. *Neuropharmacology* **2007**, *52*, 527; (e) Threlfell, S.; Cragg, S.; Kallo, I.; Turi, G.; Coen, C.; Greenfield, S. *J. Neurosci.* **2004**, *24*, 8704.
3. (a) Medhurst, A.; Briggs, M.; Bruton, G.; Calver, A.; Chessell, I.; Crook, B.; Davis, J.; Davis, R.; Foley, A.; Heslop, T.; Hirst, W.; Medhurst, S.; Ociepka, S.; Ray, A.; Regan, C. M.; Sargent, B.; Schogger, J.; Stean, T.; Trail, B.; Upton, N.; White, T.; Orlek, B.; Wilson, D. *Biochem. Pharmacol.* **2007**, *73*, 1182; (b) Passani, M.; Lin, J.-S.; Hancock, A.; Crochet, S.; Blandina, P. *Trends Pharmacol. Sci.* **2004**, *25*, 618; (c) Hancock, A.; Brune, M. *Expert Opin. Investig. Drugs* **2005**, *14*, 223; (d) Bernaerts, P.; Lamberty, Y.; Tirelli, E. *Behav. Brain Res.* **2004**, *154*, 211; (e) Parmentier, R.; Anaclet, C.; Guhennec, C.; Brousseau, E.; Bricout, D.; Giboulot, T.; Bozyczko-Coyne, D.; Spiegel, K.; Ohtsu, H.; Williams, M.; Lin, J. S. *Biochem. Pharmacol.* **2007**, *73*, 11571; (f) Esbenshade, T.; Fox, G.; Cowart, M. *Mol. Interventions* **2006**, *59*, 77.
4. Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, J. P. I. *Drug Discov. Today* **2005**, *10*, 1613.
5. Lin, J.-S.; Dauvilliers, Y.; Arnulf, I.; Bastuji, H.; Anaclet, C.; Parmentier, R.; Kocher, L.; Yanagisawa, M.; Lehert, P.; Ligneau, X.; Perrin, D.; Robert, P.; Roux, M.; Lecomte, J.-M.; Schwartz, J.-C. *Neurobiol. Dis.* **2008**, *30*, 74.
6. Santora, V. J.; Covel, J. A.; Hayashi, R.; Hofilena, B. J.; Ibarra, J. B.; Pulley, M. D.; Weinhouse, M. I.; Sengupta, D.; Duffield, J. J.; Semple, G.; Webb, R. R.; Sage, C.; Ren, A.; Pereira, G.; Knudsen, J.; Edwards, J. E.; Suarez, M.; Frazer, J.; Thomsen, W.; Hauser, E.; Whelan, K.; Grottick, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1490.
7. Zhao, Chen; Bennani, Y. L.; Gopalakrishnan, S.; Sun, M.; Esbenshade, T. A.; Krueger, K. M.; Miller, T. R.; Witte, D. G.; Marsh, Kennan C.; Cowart, M. D.; Hancock, A. A. Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, August 28–September 1, **2005**, MEDI-104.
8. Esbenshade, T.; Fox, G.; Krueger, K.; Miller, T.; Kang, C.; Denny, L.; Witte, D.; Yao, B.; Pan, L.; Wetter, J.; Marsh, K.; Bennani, Y.; Cowart, M.; Sullivan, J.; Hancock, A. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 165.
9. Nersesian, D. L.; Black, L. A.; Miller, T. R.; Vortherms, T. A.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 355.
10. Human H_3 binding and functional (GTPγS) assays were performed by MDS Pharma Services, Taiwan (http://www.mdsps.com).
11. Clapham, J.; Kilpatrick, G. J. *Eur. J. Pharmacol.* **1993**, *232*, 99.