Bioorganic & Medicinal Chemistry Letters 21 (2011) 5543–5546

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Amine-constrained pyridazinone histamine H_3 receptor antagonists

Babu G. Sundar *, Thomas Bailey, Edward Bacon, Lisa Aimone, Zeqi Huang, Jacquelyn Lyons, Rita Raddatz, Robert Hudkins

Discovery Research, Cephalon Inc., 145 Brandywine Parkway, West Chester, PA 19380, United States

ARTICLE INFO

Article history:
Received 6 May 2011
Revised 17 June 2011
Accepted 20 June 2011
Available online 21 July 2011

Keywords:
H_3R antagonist
Pyridazinone
Rat PK

ABSTRACT

Pyridazinone **1** was recently reported as a potent H_3R antagonist with good drug-like properties and in vivo activity. A series of constrained amine analogs of **1** was synthesized to identify compounds with improved pharmacokinetic profiles. From these efforts, a new class of (*S*)-2-pyrrolidin-1-ylmethyl-1-pyrrolidinyl amides was identified.

© 2011 Elsevier Ltd. All rights reserved.

The histamine H_3 receptor (H_3R) is an attractive central nervous system (CNS) therapeutic target due to its ability to affect various CNS functions. H_3Rs are predominantly expressed in presynaptic neurons, and function as inhibitory auto- and heteroreceptors. Therefore, antagonists of H_3R can modulate the release of a variety of neurotransmitters including histamine, GABA, acetylcholine, norepinephrine, serotonin and dopamine.[1] As a result of their potential to modulate multiple CNS functions, H_3R antagonists are being clinically evaluated for the treatment of different CNS disorders including neuropathic pain and deficits in sleep/wake and cognition (Fig. 1).[2] ABT-239, an early clinical candidate and one of the most widely published H_3R antagonist reference compounds, showed efficacy in cognition models. However, development of ABT-239 was ultimately halted due to cardiovascular liabilities.[3] The benzazepine GSK-189254 advanced into clinical trials for Alzheimer's disease, pain and narcolepsy and BF-2649 advanced for cognitive enhancement in schizophrenic patients, daytime sleepiness in Parkinson's disease and sleep apnea syndrome.[4]

Based on established pharmacophores for H_3R antagonists, the project objective was to identify proprietary series with a combination of in vitro potency and acceptable preclinical pharmacokinetic properties. Initial amine-based H_3 antagonists suffered from undesirable pharmacokinetic properties including high brain to plasma ratio and high brain residence time, issues that were addressed early in the lead optimization process in this project.[5,6] Over the last several years, compounds with improved pharmacokinetic and drug-like properties have been identified. We recently reported on our lead pyridazinone phenoxypropylamine candidate and the *N*-methyl pyridazinone, **1**.[7] In this paper, we report on novel series of constrained analogs of **1** with improved pharmacokinetic properties. While designing these changes, the goal was to maintain the ACD-*c* Log *P* below 3 in order to mitigate potential safety issues such as phospholipidosis and hERG inhibition.[7,8]

By changing the *R*-α-methylpyrroldinyl-propyloxy moiety of **1** (Table 1) to a 4-piperidinyloxy moiety, high affinity was retained for both rat and human H_3R with K_i values below 10 nM (**2** and **3**; see Ref. 7 for the assay details). Piperazine and homopiperazine replacements for the propyloxyamine (**4**–**7**) provided compounds with greatly reduced human and rat H_3R binding affinity ($K_i \geqslant 100$ nM). Next, it was reasoned that introducing a carbonyl moiety as a spacer between the aryl ring and the piperazine may improve the affinity due to distance similarity of the aryl to amine spacing in the piperidinoxy core. In order to test this hypothesis, amides **8**–**10** were synthesized, which are analogous to **5**–**7**. Similar to the amine analogs, amides **8**–**10** also displayed weak binding affinity for both human and rat H_3R (K_i >100 nM, Table 2). The next strategy was to move the basic amine moiety exocyclic to the amide by introducing the *S*-pyrrolidinemethyl pyrrolidine ring. This manipulation produced compound **11**, which demonstrated potent hH_3R affinity with moderate rH_3R affinity (K_i = 10 and 84 nM, respectively).

Select compounds which met the affinity criteria were tested for metabolic stability in liver microsomes of various species (mouse, rat, dog and human). With the exception of **2**, which had relatively reduced stability in mouse microsomes ($t_{1/2}$ = 35 min), **1**, **11** and **12** had good stability across species ($t_{1/2}$ >40 min) and were screened for rat pharmacokinetic properties (Table 3). For comparison, compound **1** showed acceptable in vitro metabolic stability ($t_{1/2}$ >40 min) and rat pharmacokinetic properties.

* Corresponding author. Tel.: +1 610 738 6348; fax: +1 610 738 6558.
E-mail address: bsundar@cephalon.com (B.G. Sundar).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.06.094

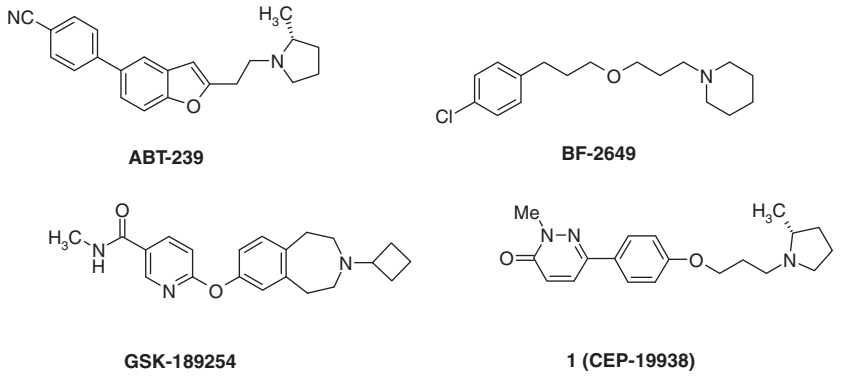
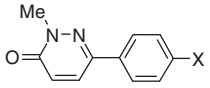
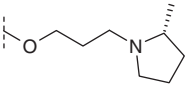
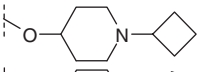
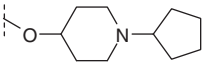
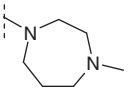
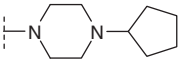
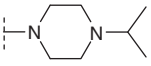
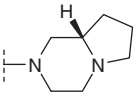


Figure 1. Structure of clinical and H_3 lead compounds.

Table 1
Pyridazinone amines and ethers



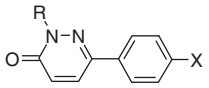
Compound	X	hH_3R[a] (K_i, nM)	rH_3R (K_i, nM)	*c* Log *P*
1		1	6	2.8
2		3	3	2.1
3		3	6	2.6
4		>500	>1000	1.4
5		93	255	2.7
6		110	419	2.3
7		308	>1000	1.7

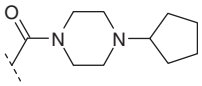
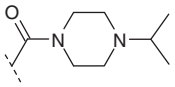
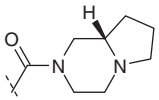
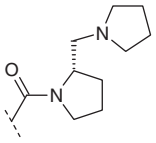
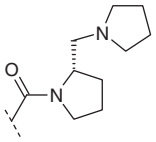
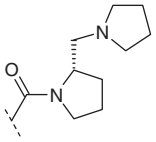
[a] [^{3}H]NAMH binding in membranes prepared from cells transfected with human or rat H_3R.

Following iv (1 mg/kg) administration, **1** had a $t_{1/2}$ of 1.6 h, higher than desired clearance (45 mL/min/kg) and volume of distribution (V_d) of 6.5 L/kg. Following administration of a single 5 mg/kg po dose, **1** was rapidly absorbed (T_{max} = 1 h) with an estimated oral bioavailability of 28% based on 6 h AUC data and demonstrated good brain partitioning. The brain to plasma ratio was 3.9 one hour after a 10 mg/kg ip dose (3440 ng/g brain concentration). Amide **11** also showed acceptable metabolic stability across all species ($t_{1/2}$ >40 min) and lack of activity (IC_{50} >30 μM) against cytochrome P450 isoforms (1A2, 2C19, 2C9, 2D6, and 3A4), which prompted further pharmacokinetic profiling (Table 3). In a rat pharmacokinetic experiment, amide **11** showed an iv $t_{1/2}$ of 1.6 h, clearance of 18 mL/min/kg and V_d of 2.5 L/kg. Following administration of a single 5 mg/kg po dose, plasma levels were higher relative to **1** based on C_{max} (412 ng/mL) and AUC (2184 ng/h/mL) with an estimated oral bioavailability of 45% and a brain to plasma ratio of 0.37. A rat pharmacokinetic comparison was also made with the reference compound GSK-189254 using our in house conditions. GSK-189254 demonstrated good oral (C_{max} = 435 ng/mL, 6 h AUC = 2596 ng/h/mL, *F* = 51%) and good brain exposure (ip 1 h brain concentration 1656 ng/g; *B*/*P* = 1.4). The iv and po data for **11** was comparable with GSK-189254 with only the brain partitioning being lower. With the goal to improve brain exposure of **11** by increasing the lipophilicity, the pyridazinone *N*-methyl was replaced with *N*-4-fluorophenyl (**12**). Amide **12** had significantly increased lipophilicity (*c* Log *P* = 3.0) compared to **11** (*c* Log *P* = 1.4) and acceptable binding affinity (hH_3R, K_i = 16 nM; rH_3R, K_i = 92 nM) for additional profiling. However, evaluation of the rat pharmacokinetic properties showed that brain concentrations were only marginally improved compared to **11** (ip 1 h concentration = 529 ng/g, *B*/*P* = 0.7).

The synthesis of compound **1** was described previously[7] (Scheme 1). Commercially available *p*-anisyl-oxo-butanoic acid was ring closed with *N*-methyl hydrazine and the resultant 4,5-dihydropyridazinone was dehydrogenated with SeO_2 or MnO_2. The 4-methoxy group was cleaved with BBr_3 and the resultant phenol was alkylated with bromochloropropane in refluxing acetonitrile. The chloroether was treated with a slight excess of the

Table 2
Pyridazinone amides



Compound	X	R	hH_3R[a] (K_i, nM)	rH_3R (K_i, nM)	*c* Log *P*
8		Me	134	186	1.8
9		Me	167	185	1.4
10		Me	>1000	>1000	0.8
11		Me	10	84	1.4
12		4-F-Ph	16	92	3.0
13		H	17	46	0.9

[a] [^{3}H]NAMH binding in membranes prepared from cells transfected with human or rat H_3R.

Table 3
Rat pharmacokinetic parameters

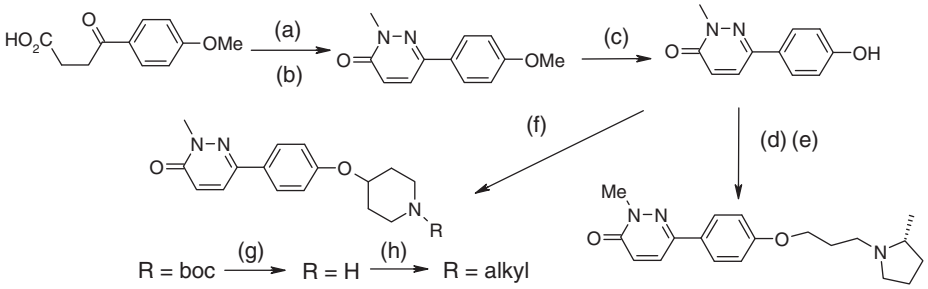
Rat PK parameters	**1**	**11**	**12**
iv (1 mg/kg)			
$t_{1/2}$ (h)	1.6	1.6	1.0
V_d (L/kg)	6.5	2.5	1.1
CL (mL/min/kg)	45	18	12
po (5 mg/kg)			
C_{max} (ng/mL)	123	412	180
6 h-AUC (ng/h/mL)	538	2184	1016
% *F*	28	45	13
i.p. (10 mg/kg)			
1 h-Brain concn (ng/g)	3440	454	529
B/*P*	3.9	0.37	0.7

iv vehicle: 3% DMSO, 30% Solutol, 67% PBS.
po vehicle: Compounds **11** and **12** were administered in Tween 80:propylene carbonate:propylene glycol (5:4:1). Compound **1** was administered in saline.

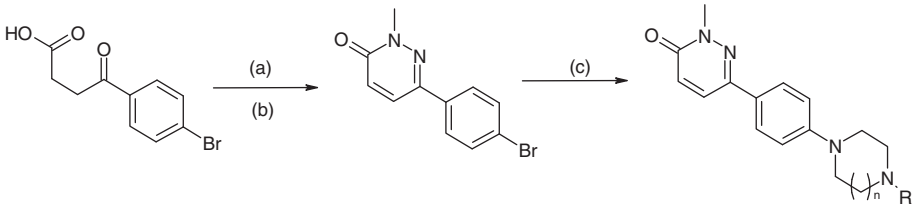
amine salt and NaI in the presence of K_2CO_3 in refluxing acetonitrile to produce **1**. Phenoxypiperidine analogs **2** and **3** were synthesized by Mitsunobu reaction with the phenol intermediate and boc-protected 4-piperidinol to afford the protected ether in good yields.[9] The boc group was removed under standard conditions (TFA/CH_2Cl_2) and the resultant secondary amines were readily alkylated by reductive amination with appropriate ketones.[10a,b]

Compounds **4**–**7** were synthesized using standard amination conditions[11] with the appropriate amine in variable yields (Scheme 2). The bromo starting material was made from the corresponding *p*-bromo-phenyl oxo-butanoic acid as described above for the 4-methoxy-phenyl pyridazinones. The carboxylic acid starting material for the amides **8**–**13** was prepared as reported in the literature.[12] The 4-acetyl-phenylacetic acid was subjected to aldol condensation with glyoxylic acid and the resultant keto acid was reacted with *N*-methyl hydrazine to provide the pyridazinone phenylacetic acid (Scheme 3). The amides **8**–**13** were readily prepared via the acid chloride and the corresponding amines.[13]

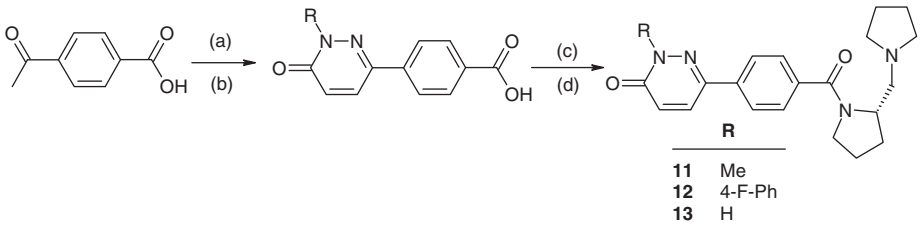
In summary, modification of pyridazinone lead **1** by constraining the amine part of the molecule produced a novel series of amides as potent H_3R antagonists. Lead compound **11** had high affinity for both the human and rat H_3Rs while maintaining a low *c* Log *P*. Compound **11** showed acceptable rat oral bioavailability and plasma exposure, comparable to GSK-189254 and **1**.



Scheme 1. Preparation of ethers **1–3**. Reagents and conditions: (a) $MeNHNH_2$, *i*-PrOH, reflux, 15 h, 95%; (b) MnO_2, xylene, reflux, 14 h, 75%; (c) BBr_3, CH_2Cl_2, 5 °C to rt, 5 h, 98%; (d) $Cl(CH_2)_3Br$, K_2CO_3, CH_3CN, reflux, 20 h, 91%; (e) α-methylpyrrolidine·HCl, K_2CO_3, NaI, CH_3CN, 90 °C, 15 h, 48%; (f) *N*-boc-4-hydroxypiperidine, DEAD, Ph_3P, THF, 0 °C to rt; (g) TFA, CH_2Cl_2, rt, 3 h; (h) ketone, $NaCNBH_3$, AcOH, MeOH, DMF, 60 °C.



Scheme 2. Preparation of amines **4–7**. Reagents and conditions: (a) $MeNHNH_2$, *i*-PrOH, reflux, 15 h; (b) SeO_2, AcOH, 100 °C, 16 h, 72%, 2 steps; (c) amine, Pd_2dba_3, BINAP, $NaOBu^t$, toluene, 80 °C, 40–70%.



R	
11	Me
12	4-F-Ph
13	H

Scheme 3. Preparation of amides **11–13**. Reagents and conditions: (a) glyoxylic acid, AcOH, 110 °C, 20 h; (b) $RNHNH_2$, 100 °C, 5 h; (c) $SOCl_2$, 70 °C, 1 h; (d) amine, Et_3N, CH_2Cl_2, 0 °C to rt, 72%.

Compound **11** may have advantages for peripheral indications of H_3R antagonists, such as allergic rhinitis, with good PK and lower brain levels.[14] Additional profiling and SAR around the pyridazinone cores will be disclosed in future reports.

References and notes

1. (a) Hill, S. J.; Ganellin, C.; Timmermans, H.; Schwartz, J. C.; Shankley, N.; Yound, J. M.; Levi, R.; Haas, H. L. *Pharmacol. Rev.* **1997**, *49*, 253; (b) Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. *Trends Pharmacol.* **1998**, *19*, 177; (c) Repka-Ramirez, M. S. *Curr. Allergy Asthma Rep.* **2003**, *3*, 227; (d) Chazot, P. L.; Hann, V. *Curr. Opin. Invest. Drugs* **2001**, *2*, 1428.
2. (a) Hudkins, R. L.; Raddatz, R. *Annu. Rep. Med. Chem.* **2007**, *42*, 49; (b) Esbenshade, T. A.; Browman, K. E.; Bitner, R. S.; Strakhova, M.; Cowart, M. D.; Brioni, J. D. *Br. J. Pharmacol.* **2008**, *154*, 1166; (c) Gemkow, M. J.; Davenport, A. J.; Harich, S.; Ellenbroek, B. A.; Cesura, A.; Hallett, D. *Drug Discovery Today* **2009**, *14*, 509.
3. Hancock, A. A. *Biochem. Pharmacol.* **2006**, *71*, 1103.
4. Ligneau, X.; Perrin, D.; Landais, L.; Camelin, J.-C.; Calmels, T. P. G.; Berrebi-Bertrans, I.; Lecomte, J.-M.; Parmentier, R.; Anaclet, C.; Lin, J.-S.; Bertaina-Anglade, V.; Driwu la Rochell, 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.
5. (a) Bonaventure, P.; Letavic, M.; Dugovic, C.; Wilson, S.; Alusio, L.; Pudiak, C.; Lord, B.; Mazur, C.; Kamme, F.; Nishio, S.; Carruthers, N.; Lovenberg, T. *Biochem. Pharmacol.* **2007**, *73*, 1084; (b) Beavers, L. S.; Finley, D. R.; Gadski, R. A.; Hipskind, P. A.; Hornback, W. J.; Jesudasan, C. D.; Pickard, R. T.; Takawuwa, WO07005503, 2007.; (c) Hipskind, P. A.; Takawuwa, C. D.; Jesudasan, R. A.; Gadski, R. A.; Hornback, W. J.; Pickard, R. T.; Neavers, L. S. WO06107661, 2006.
6. Cowart, M.; Altenbach, R.; Black, L.; Faghih, R.; Zhao, C.; Hancock, A. A. *Mini-Rev. Med. Chem.* **2004**, *4*, 979.
7. Hudkins, R. L.; Raddatz, R.; Tao, M.; Mathiasen, J. R.; Aimone, L. D.; Becknell, N. C.; Prouty, C. P.; Knutsen, L.; Yazdanian, Y.; Moachon, G.; Ator, M. A.; Mallamo, J. P.; Marino, M. J.; Bacon, E. R.; Williams, M. *J. Med. Chem.* **2011**, *54*, 4781.
8. Ploemen, J. P.; Kelder, J.; Hafmans, T.; Sandt, H.; Van Burgsteden, J. A.; Salemink, P. J. M.; Van Esch, E. *Exp. Toxicol. Pathol.* **2004**, *55*, 347.
9. Furber, M.; Alcaraz, L.; Bent, J. E.; Beyerbach, A.; Bowers, A.; Braddock, M.; Caffrey, M. V.; Cladingboel, D.; Collington, J.; Donald, D. K.; Fagura, M.; Ince, F.; Kinchin, E. C.; Laurent, C.; Lawson, M.; Luker, T. J.; Mortimore, M. M.; Pimm, A. D.; Riley, R. J.; Roberts, N.; Robertson, M.; Theaker, J.; Thorne, P. V.; Weaver, R.; Webborn, P.; Wilis, P. *J. Med. Chem.* **2007**, *50*, 5882.
10. (a) Bacon, E.; Bailey, T.; Becknell, N. C.; Chatterjee, S.; Dunn, D.; Hostetler, G.; Hudkins, R. L.; Josef, K.; Knutsen, L.; Tao, M.; Zulli, A. WO08013838, 2008.; (b) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
11. Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
12. Bratt, E.; Chen, Y.; Granberg, K.; Nilsson, I. WO05065688, 2005.
13. Becknell, N. C.; Dandu, R.; Dunn, D.; Hudkins, R. L.; Josef, K.; Sundar, B. G.; Zulli, A. L. WO09142732, 2009.
14. Procopiou, P. A.; Ancliff, R. A.; Bamford, M. J.; Browning, C.; Connor, H.; Davies, S.; Fogden, S. T.; Holmes, B. E.; Looker, B. E.; Morris, K. M. L.; Parr, C. A.; Pickup, E. A.; Sehmi, S. S.; White, G. V.; Watts, C. J.; Wilson, D. M.; Woodrow, M. D. *J. Med. Chem.* **2007**, *50*, 6706.