Bioorganic & Medicinal Chemistry Letters 22 (2012) 1073–1077

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and structure–activity relationship of 5-pyridazin-3-one phenoxypiperidines as potent, selective histamine H_3 receptor inverse agonists

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ARTICLE INFO

Article history:
Received 21 October 2011
Revised 22 November 2011
Accepted 28 November 2011
Available online 4 December 2011

Keywords:
Phenoxypiperidine
5-pyridazin-3-one
Histamine H_3 receptor
CEP-26401 irdabisant
Sleep–wake

ABSTRACT

Optimization of the R^2 and R^6 positions of (5-{4-[3-(*R*)-2-methylpyrrolin-1-yl-propoxy]phenyl}-2*H*-pyridazin-3-one) **2a** with constrained phenoxypiperidines led to the identification of 5-[4-(cyclobutyl-piperidin-4-yloxy)-phenyl]-6-methyl-2*H*-pyridazin-3-one **8b** as a potent, selective histamine H_3 receptor antagonist with favorable pharmacokinetic properties. Compound **8b** had an excellent safety genotoxocity profile for a CNS-active compound in the Ames and micronucleus tests, also displayed potent H_3R antagonist activity in the brain in the rat dipsogenia model and robust wake activity in the rat EEG/EMG model.

Histamine plays an important role in different physiological processes by four G-protein coupled receptors (H_1R–H_4R) and exerts a variety of functions in the central nervous system (CNS).[1] The histamine H_3 receptor (H_3R) is predominantly expressed in the central nervous system (CNS), where it functions both as an autoreceptor to modulate histamine release and as an inhibitory heteroreceptor regulating the release of multiple neurotransmitters including acetylcholine, histamine, norepinephrine, and dopamine.[2] H_3R antagonists are currently being evaluated as potential therapeutic agents for the treatment of cognitive deficits associated with a variety of CNS disease states including Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD) and schizophrenia.[3]

There have been a number of H_3R antagonists advance to preclinical and clinical development studies (Fig. 1). For example, ABT-239 (**1a**) was nominated for clinical development for cognition promotion, but was halted because of QTc prolongation observed in monkeys.[1,3g,f] MK-0249 (**1b**) from Merck has completed Phase II trails for ADHD, AD and cognitive impairment associated with schizophrenia.[1,3g,f] JNJ-31001074 (bavisant, **1c**) is reported in Phase II for ADHD.[1a] Pfizer has reported PF-03654746 (**1d**) in Phase II trail for ADHD and was discontinued.[3f] GSK-189254 (**1e**) enhanced cognitive performance pre-clinically and advanced to Phase II for narcolepsy and was in early clinical trails for AD.[3f] We recently reported a novel class of pyridazin-3-one H_3R antagonists/inverse agonists with excellent drug properties, safety and in vivo profiles and advanced CEP-26401 **1f** as a clinical candidate, which recently completed Phase I.[5]

As part of our H_3R discovery project studying the structure–activity relationships (SAR) around **1f**, we synthesized and reported the profile of the 5-regiomer **2a** (5-{4-[3-(*R*)-2-methylpyrrolin-1-yl-propoxy]-phenyl}-2*H*-pyridazin-3-one) (Fig. 2). Compound **2a** had

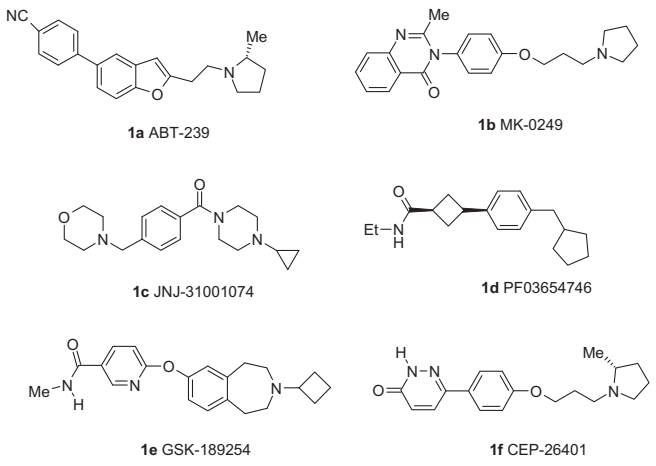

Figure 1. Structure of pre-clinical and clinical H_3R antagonists.

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doi:10.1016/j.bmcl.2011.11.118

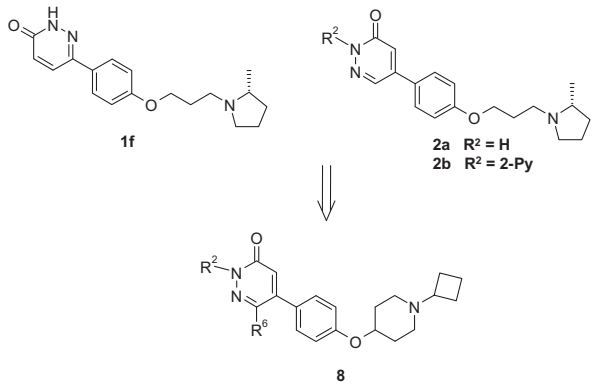


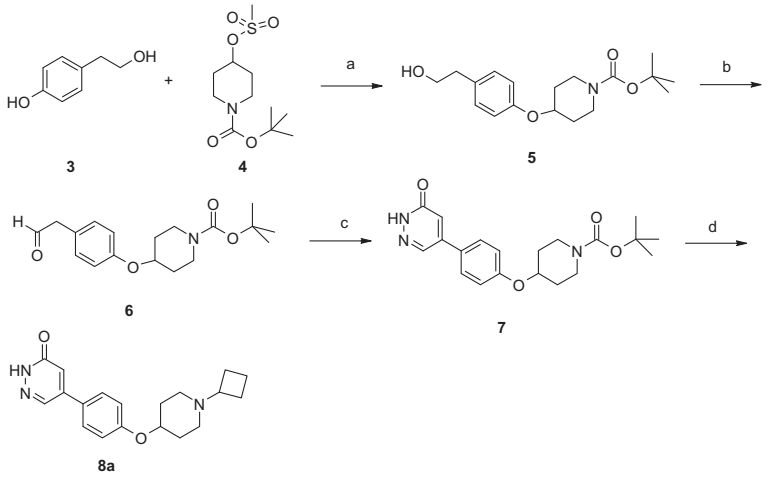
Figure 2. Pyridazinone H_3R antagonists.

high affinity for both the human (hH_3R K_i = 2.8 nM) and rat H_3Rs (rH_3R K_i = 8.5 nM), but displayed low oral bioavailability (%F = 24) in the rat.[5] To explore the structure–activity relationships (SAR) of 5-pyridazin-3-one core R^2 and R^6 positions around **2a** with a focus on improving the pharmacokinetic (PK) properties**,** we identified 5-{4-[3-(*R*)-2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-2-pyridin-2-yl-2*H*-pyridazin-3-one **2b** (hH_3R K_i = 1.7 nM and rH_3R K_i = 3.7 nM) with favorable oral bioavailability (%F = 78 in rat).[6] However, **2b** showed positive results in the Ames test, and was discontinued for development.

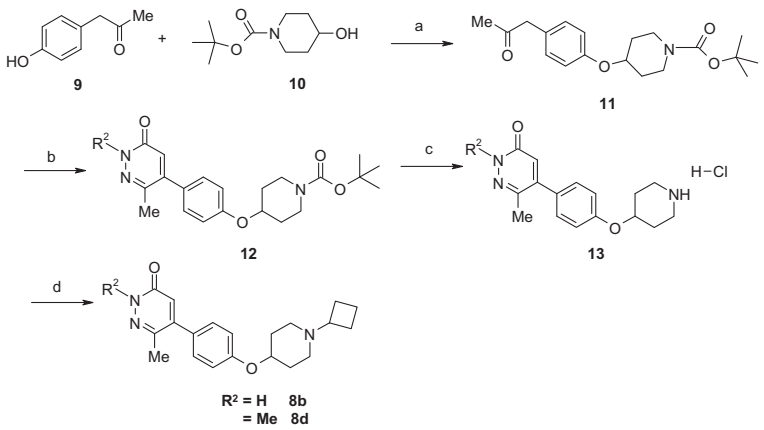
Most non-imidazole H_3R antagonists reported share common structural features: a basic tertiary amine attached to an aromatic ring through a linker-space group; for example, the propyloxy, and its constrained piperidinyloxy moiety.[7,1a] There have been many reports describing a variety of histamine H_3R receptor antagonist pharmacophores in the past few years.[4,1a] One design strategy we used in our search for 5-aryl analogs with a clean genotoxicity profile and to improved PK was to rigidify the core to reduce in the number of rotatable bonds.[7d] Based on this, we synthesized a series of 5-regiomers **8** (5-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-2*H*-pyridazin-3-one) where the pyrrolidinylpropyloxy side chain was constrained as the *N*-cyclobutylpiperidinyloxy moiety; a maneuver explored by the Merck and Johnson and Johnson groups on their respective cores.[7e] In this Letter, we report the synthesis, SAR, selectivity, pharmacokinetics (PK) and the in vivo activities of 5-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-6-methyl-2*H*-pyridazin-3-one **8b** in the rat dipsogenia model and in the rat EEG/EMG model of wakefulness.

The synthesis of 5-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-pyridazinone analog **8a** is shown in Scheme 1. Alkylation of 4-hydroxy-phenyl ethanol **3** with 4-methanesulfonyloxy-1-Boc-piperidine **4** in the presence of cesium carbonate in DMF afforded the ether **5**. Dess–Martin oxidation of **5**, followed by condensation with glyoxylic acid, and subsequent cyclization with hydrazine hydrate yielded the pyridazinone **7**.[8] Deprotection of **7** with HCl in dioxane, followed by reductive amination with cyclobutanone in the presence of $NaCNBH_3$ gave **8a**. The 6-methyl substituted pyridazinones **8b** and **8d** were synthesized as shown in Scheme 2. Mitsunobu coupling of 4-hydroxyphenyl acetone **9** and 4-hydroxy-1-Boc-piperidine **10** in the presence of 40% of diethylazodicarboxylate in toluene and triphenylphosphine gave ether **11**. Condensation of **11** with glyoxylic acid, followed by cyclization with hydrazine afforded the 6-methyl pyridazinone **12**. Final targets **8b** and **8d** were synthesized following the same steps as described in Scheme 1. The synthesis of 5-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one **8c** is shown in Scheme 3. Alkylation of **11** with ethyl bromoacetate in the presence of KHMDS, and cyclization with hydrazine yielded the Boc-piperidinyl-6-methyl dihydropyridazinone **14**. Deprotection and reductive amination as described in Scheme 1 gave **8c**. The 2-aryl substituted pyridazinone analogs **8e–h** were synthesized as shown in Scheme 4. The 5-(4-methoxy-phenyl)-6-methyl-2*H*-pyridazin-3-one **16** was coupled with aryl bromide in the presence of copper(I) iodide in DMF to give 2-aryl substituted **17**.[9] Deprotection of **17** with BBr_3, followed by alkylation with 1-Boc-4-methanesulfonyloxy-piperidine **4** afforded **12**. Deprotection and reductive amination as shown in Scheme 1 gave the 2-aryl pyridazinones **8e–h**. The synthesis of **24** is shown in Scheme 5. Suzuki coupling 2-chloropyridyl-4-boronic acid **20** with 2-hydroxymethyl-5-iodo-2*H*-pyridazin3-one, followed by substitution with 4-hydroxy-1-Boc-piperidine afforded the Boc-protected pyridyl pyridazinone **22**. Deprotection of **22** with HCl in dioxane, and reductive amination gave compound **24**.

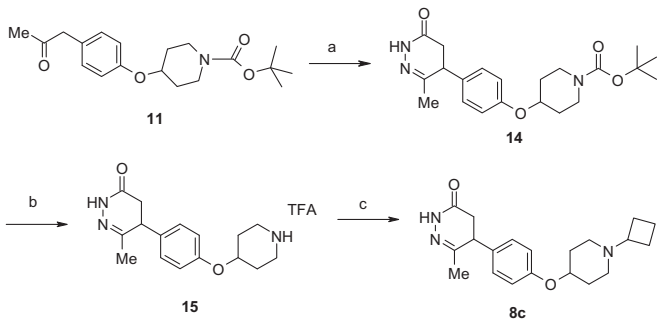
The substituted pyridazinone analogs were tested using in vitro binding assays by displacement of [^{3}H]N-α-methylhistamine ([^{3}H]NAMH) in membranes isolated from CHO cells transfected with cloned human H_3 or rat H_3 receptors.[10] Rat and human H_3R binding data for the analogs is shown in Table 1 in comparison with **2a**.[5] The *N*-cyclobutyl was established to be optimum and was fixed for comparison while exploring SAR.[11] As previously reported, the 5-pyridazin-3-one regiomer of **2a** had high affinity (hH_3R K_i = 2.8 nM, rH_3R K_i = 8.5 nM), but displayed low oral



Scheme 1. Reagents and conditions: (a) Cs_2CO_3, DMF, 100 °C, 59%; (b) Dess–Martin [O], CH_2Cl_2, 0 °C to rt, 35%; (c) (i) $HCOCOOH{\cdot}H_2O$, 135 °C; (ii) NH_2NH_2, EtOH, 90 °C, 34% in 2 steps; (d) (i) 4 N HCl in dioxane, 50 °C; (ii) cyclobutanone, $NaCNBH_3$, DMF/MeOH/acetic acid, 60 °C, 1 h, 56%.

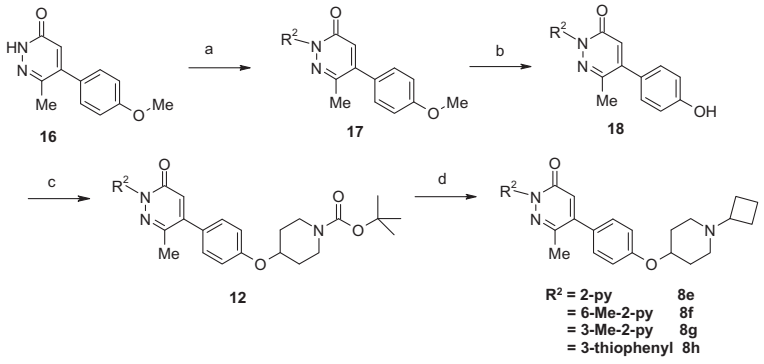


Scheme 2. Reagents and conditions: (a) DEAD, PPh_3, THF, 0 °C→rt, 63%; (b) (i) $HCOCOOH{\cdot}H_2O$, 135 °C; (ii) R^2NHNH_2, EtOH, 90 °C, 23% in 2 steps; (c) 4 N HCl in dioxane, dioxane, 50 °C; (d) cyclobutanone, $NaCNBH_3$, DMF/MeOH/acetic acid, 60 °C, 2 h, 80%.

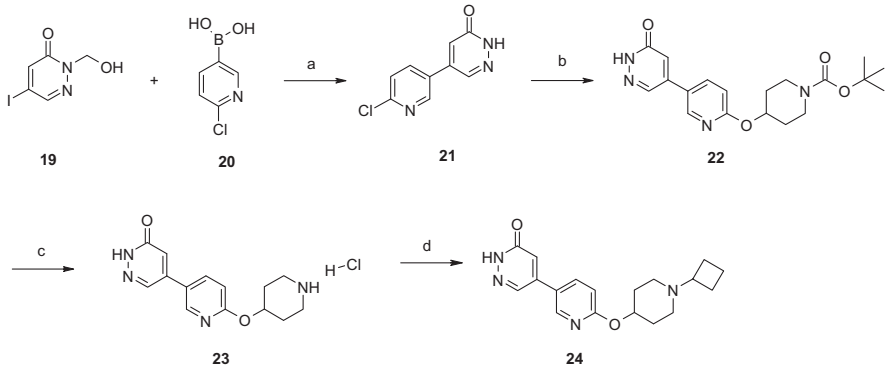


Scheme 3. Reagents and conditions: (a) (i) KHMDS, $BrCH_2COOEt$, THF, −78 °C; (ii) NH_2NH_2, EtOH, 90 °C, 56% in 2 steps; (b) TFA, CH_2Cl_2, 0 °C to rt; (c) cyclobutanone, $NaCNBH_3$, DMF/MeOH/acetic acid, 60 °C, 2 h, 30%.

bioavailability in the rat (%*F* = 24).[5] Replacement of (*R*)-2-methylpyrrolidinylpropoxy of 5-pyridazin-3-one with the constrained cyclobutylpiperidinyloxy (**8a**) showed high affinity in both human and rat H_3R (hH_3R K_i = 2 nM, rH_3R K_i = 2 nM), but did not show improvement on rat oral bioavailability (%*F* = 21) compared to **2a**. Further profiling showed **8a** had moderate selectivity for the hERG channel in a patch clamp assay (IC_{50} = 2 μM). Compound **8b**, with a methyl substitution at the 6-position, designed to increase the torsional angle between the two rings, retained high affinity in both human and rat H_3R (hH_3R K_i = 5 nM, rH_3R K_i = 6 nM), and displayed acceptable in vitro metabolic stability in liver microsomes from rat, dog and human ($t_{½}$ >40 min), and showed weak CYP inhibition (IC_{50} >30 μM, 5 CYP isoforms). Compound **8b** had an improved PK profile in rat (%*F* = 68, Table 2). The dihydropyridazinone analog **8c** showed ~2–5-fold weaker affinity compared to **2a** (hH_3R K_i = 15 nM, rH_3R K_i = 13 nM). Compound **8c** had acceptable in vitro metabolic stability in liver microsomes from rat, dog and human ($t_{½}$ >40 min) and weak CYP inhibition (IC_{50} >30 μM, 5 CYP isoforms). However, plasma levels of **8c** were low following oral administration (%*F* = 6, C_{max} = 73 ng/mL, AUC = 370 ng∗h/mL), and **8c** was extensively aromatized to the metabolite **8b** (~40% in plasma, C_{max} = 34 ng/mL, AUC = 152 ng∗h/mL) in a rat PK experiment. The *N*-2-methyl analog **8d**, with high affinity, acceptable in vitro metabolic stability in liver microsomes from rat, dog and human ($t_{½}$ >40 min) and weak CYP inhibition (IC_{50} >30 μM, 5 CYP isoforms), was profiled in a rat PK experiment. Following oral administration of **8d** (%*F* = 19, C_{max} = 107 ng/mL, AUC = 337 ng∗h/mL) in the rat, high levels of the demethylated active metabolite **8b** (~95% in plasma, C_{max} = 68 ng/mL, AUC = 320 ng∗h/mL) was formed in plasma, therefore the compound was not further advanced. The *N*-2-pyridyl analog **8e** was synthesized with the goal to find metabolically stable R^2 analogs while maintaining a low log*P* value (<3).[6] Compound **8e** had high affinity in both human and rat H_3R and displayed acceptable in vitro metabolic stability in liver microsomes from rat, dog and human ($t_{½}$ >40 min), and weak CYP inhibition (IC_{50} >30 μM for 5 CYP isoforms). Further profiling showed **8e** displayed an acceptable PK profile (Table 2), weak hERG activity in a patch clamp assay (IC_{50} >30 μM), and showed high selectivity against hH_1, hH_2, and hH_4 receptor subtypes (<30% inhibition at 10 μM). However, it had moderate affinity for the muscarinic M_2 subtype (IC_{50} = 0.34 μM) when screened against

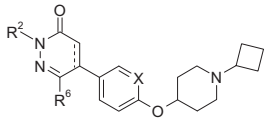


Scheme 4. Reagents and conditions: (a) K_2CO_3, ArBr, CuI, DMF, 150 °C, 36–87%; (b) BBr_3, CH_2Cl_2, 0 °C to rt, ~80%; (c) 4-methanesulfonyloxy-piperidine-1-carboxylic acid *tert*-butyl ester, Cs_2CO_3, DMF, 100 °C, 40–70%; (d) (i) 4 N HCl in dioxane, dioxane, 50 °C, (ii) cyclobutanone, $NaCNBH_3$, DMF/MeOH/acetic acid, 60 °C, 1 h, ~70%.



Scheme 5. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, DME/water, 85 °C, 36%; (b) 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester, K_2CO_3, DMSO, 110 °C, 54%; (c) 4 N HCl in dioxane, dioxane, 50 °C; (d) cyclobutanone, $NaCNBH_3$, DMF/MeOH/acetic acid, 60 °C, 1 h, 56%.

Table 1
5-Pyridazin-3-one in vitro binding data



Compd	Bond	X	R^2	R^6	hH_3 (K_i, nM)	rH_3 (K_i, nM)
8a	Double	CH	H	H	2	2
8b	Double	CH	H	Me	5	6
8c	Single	CH	H	Me	15	13
8d	Double	CH	Me	Me	4	8
8e	Double	CH	2-Py	Me	3	9
8f	Double	CH	6-Me-2-py	Me	4	10
8g	Double	CH	3-Me-2-py	Me	6	17
8h	Double	CH	3-Thiophenyl	Me	3	8
24	Double	N	H	H	14	20

K_i values are an average of two or more determinations. The assay-to-assay variation was typically within 2.5-fold.

71 GPCRs, ion channels and enzymes (MDS Pharma Services, Lead Profiler). The methyl substituted N^2-2-pyridine analogs **8f**, and **8g** also showed high affinity for both human and rat H_3R, good in vitro metabolic stability, weak CYP inhibition (IC_{50} >30 μM, 5 CYP isoforms), and acceptable hERG selectivity (IC_{50} >30 μM) in a patch clamp assay. However, it showed no improvement in rat PK compared to **2a** (Table 2). Further R^2 modification, the *N*-2-(3)-thiophene analog **8h** also showed high affinity for both human and rat H_3R but had significantly lower solubility. Changing the central phenyl ring to pyridyl **24** was designed to lower the *c*log*P* and potentially improve hERG activity. However, this maneuver showed much weaker H_3R affinity compared to **8a**.

Compound **8b** was further tested for H_3R functional activity using a [^{35}S]GTPγS hH_3R binding assay and displayed full inverse agonist activity with an EC_{50} = 1.1 nM.[10] Compound **8b** showed high selectivity against hH_1, hH_2, and hH_4 receptor subtypes (<20% inhibition at 10 μM) and in a panel of 101 GPCRs, ion channels and enzymes inhibited the α-adrenergic receptor subtype greater than 50% at 10 μM. It showed acceptable hERG selectivity with an IC_{50} value of 7 μM and displayed acceptable drug-like properties with high water solubility (pH 2 and pH 7.4 >0.14 mg/mL), low lipophilicity (*c*log*P* = 1.5), and high permeability in the Caco-2 assay ($P_{app} = 14.9 \times 10^{-6}$ cm/s). Compound **8b** had low binding to plasma proteins of rat (54%), dog (43%), and human (58%) in vitro. In genotoxicity profiling, **8b** did not induce mutation in the Ames assay (*Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537) both in the presence and absence of rat liver S9 metabolic activation and did not induce micronuclei in vitro in a micronucleus test in mouse lymphocytes with and without metabolic activation.

The rat dipsogenia model was used as an in vivo surrogate measure of H_3R functional inhibition in the brain following peripheral administration, and the activity in this model may be predictive of efficacy in cognitive models. Histamine and the H_3R-selective agonist, *R*-α-methylhistamine (RAMH), induce water drinking in the rat when administered either peripherally or centrally, an effect that is blocked by H_3R antagonists.[12] Compound **8b** inhibited RAMH-induced water drinking, demonstrating potent inhibition of central H_3R following ip administration of compound with an ED_{50} value of 0.02 mg/kg, consistent with the high brain exposure

Table 2
Pharmacokinetic properties in rat

	2a[a]	**8b**[a]	**8e**[b]	**8f**[b]	**8g**[b]
iv[c]					
$t_{½}$ (h)	1.0 ± 0.1	1.5 ± 0.5	1.3 ± 0.0	1.1 ± 0.1	1.1 ± 0.1
Vd (L/kg)	0.8 ± 0.1	3.4 ± 1.5	1.4 ± 0.1	1.7 ± 0.6	1.1 ± 0.2
CL (mL/min/kg)	9.6 ± 1.0	25 ± 4	13 ± 1.3	16 ± 4	11 ± 2.4
po[c]					
AUC (ng h/mL)	4209 ± 258	4869 ± 524	1502 ± 103	1273 ± 300	1860 ± 347
C_{max} (ng/mL)	446 ± 65	673 ± 44	287 ± 31	332 ± 129	505 ± 137
T_{max} (h)	2 ± 0	1 ± 0	3.2 ± 0.7	2.0 ± 1.0	2.3 ± 0.9
F (%)	24 ± 2	68 ± 7	22 ± 2	20 ± 5	23 ± 4
B/*P*[d]	1.8 ± 0.2	2.3 ± 0.1	1.6 ± 0.2	1.6 ± 0.1	1.0 ± 0.0

[a] Administration at 1 mg/kg iv and 10 mg/kg po.
[b] Administration at 1 mg/kg iv and 5 mg/kg po.
[c] iv formulation (3% DMSO, 30% solutol, 67% phosphate buffered saline) oral formulation (50% Tween 80, 40% propylene carbonate and 10% propylene glycol).
[d] *B*/*P* = brain to plasma ratio measured 6 h post 10 mg/kg ip dose.

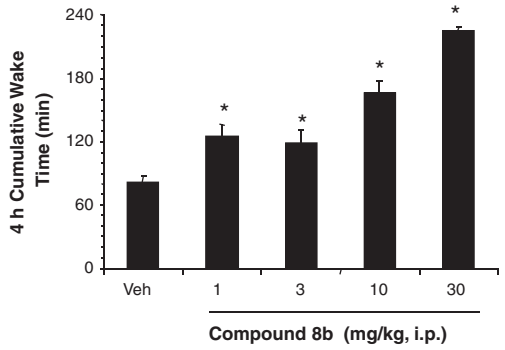


Figure 3. Compound **8b**-induced wake promotion. Cumulative wake time (min) for 4 h post dosing following administration of vehicle (Veh), Compound **8b** in rats chronically implanted with electrodes for recording EEG and EMG activity. Mean + SEM; $n = 6–7$/group. $^{*}p < 0.05$, Dunnett's test versus vehicle.

and potent rat H_3R affinity. Histamine-producing neurons are an important part of the monoaminergic arousal system and H_3R antagonists have been documented to increase wakefulness in a number of species. However, potency of H_3R antagonist in the rat dipsogenia model has been reported to correlate with lower levels of receptor occupancy compared with wake promotion, which required much higher doses, and 80–100% receptor occupy for robust wake activity.[13,14] Compound **8b** was evaluated in the rat EEG/EMG sleep–wake model. Wake-promoting activity in the rat was measured as previously described using male Sprague Dawley rats surgically implanted for chronic recording of EEG (electroencephalographic) and EMG (electromyographic) signals.[15] Cumulative wake time for 4 h post dosing was evaluated during the normal quiet period of the rat. While the wake activity at 1 and 3 mg/kg was significantly greater than vehicle, the corresponding slow-wave sleep onset values (34.9 ± 5.1, 35.3 ± 7.0, and 45.0 ± 7.5 for vehicle, 1, and 3 mg/kg groups, respectively) were not different. Compound **8b** significantly increased waking at 10 and 30 mg/kg ip (167 ± 11 min, and 226 ± 2.9 min) by 4 h AUC values (Fig. 3). Maximal cumulative wake surplus at 30 mg/kg was 163 min at 6 h post dosing, and dropped by only 20 min over the next 11 h (data not shown). At 30 mg/kg ip, **8b** demonstrated robust wake promotion, with the treated animals being awake 94% of the time up to 4 h post dose and the increase in wake time over vehicle = 145 min which is 178% of the vehicle wake time (Fig. 3). No hypersomnolence was observed in any group (data not shown).

In summary, optimization of the 5-pyridazin-3-one R^2 and R^6 positions of **8** with constrained phenoxypiperidine amine led to the identification of 5-[4-(cyclobutyl-piperidin-4-yloxy)-phenyl]-6-methyl-2*H*-pyridazin-3-one **8b** as a potent, selective histamine H_3 receptor antagonist. Compound **8b** showed favorable pharmacokinetic properties with improved oral bioavailability (%*F* = 61 in rat), and displayed an excellent safety genotoxicity profile for a CNS-active compound in the Ames and mouse lymphocyte micronucleus in vitro tests. Compound **8b** displayed potent H_3R antagonist activity in the brain in the rat dipsogenia model and robust wake activity in the rat EEG/EMG model.

Acknowledgments

The authors acknowledge the support and contributions from Edward R. Bacon, Mark A. Ator, Michael J. Marino, Mehran Yazdanizn, Amy Decamillo, Bob Bendesky, Nathalie Bourrit, and Debra Galinis.

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