Bioorganic & Medicinal Chemistry Letters 22 (2012) 1504–1509

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

4-Phenoxypiperidine pyridazin-3-one histamine H_3 receptor inverse agonists demonstrating potent and robust wake promoting activity

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ARTICLE INFO

Article history:
Received 22 November 2011
Revised 4 January 2012
Accepted 9 January 2012
Available online 13 January 2012

Keywords:
Histamine H_3 receptor
H_3 inverse agonist
Pyridazin-3-one
CEP-26401
Irdabisant
Sleep–wake

ABSTRACT

Structure–activity relationships for a series of phenoxypiperidine pyridazin-3-one H_3R antagonists/inverse agonists are disclosed. The search for compounds with improved hERG and DAT selectivity without the formation of in vivo active metabolites identified 6-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-4,4-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one **17b**. Compound **17b** met discovery flow criteria, demonstrated potent H_3R functional antagonism in vivo in the rat dipsogenia model and potent wake activity in the rat EEG/EMG model at doses as low as 0.1 mg/kg ip.

The histamine H_3 receptor (H_3R) functions in the brain both as an autoreceptor modulating histamine release and as an inhibitory heteroreceptor regulating the release of multiple neurotransmitters, including acetylcholine, dopamine, norepinephrine and serotonin thought to be involved in attention, sleep and cognition.[1] Activation of the H_3R results in the inhibition of

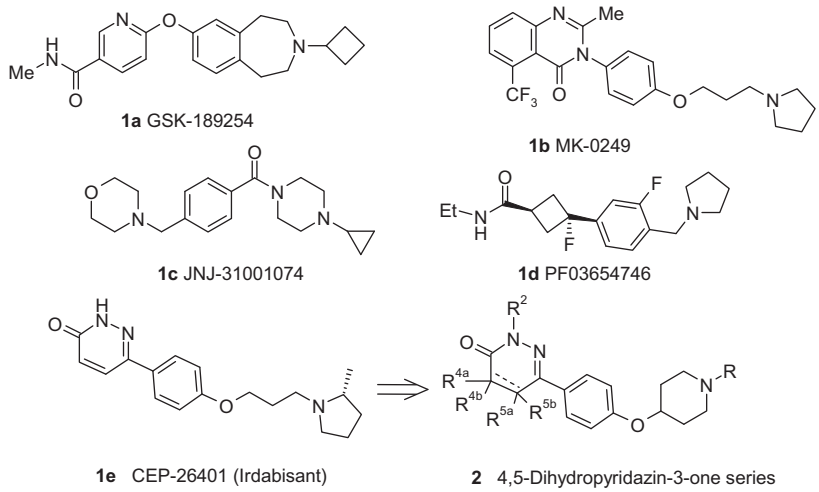

Figure 1. Structures of clinical candidates and 4,5-dihydropyridazin-3-one core.

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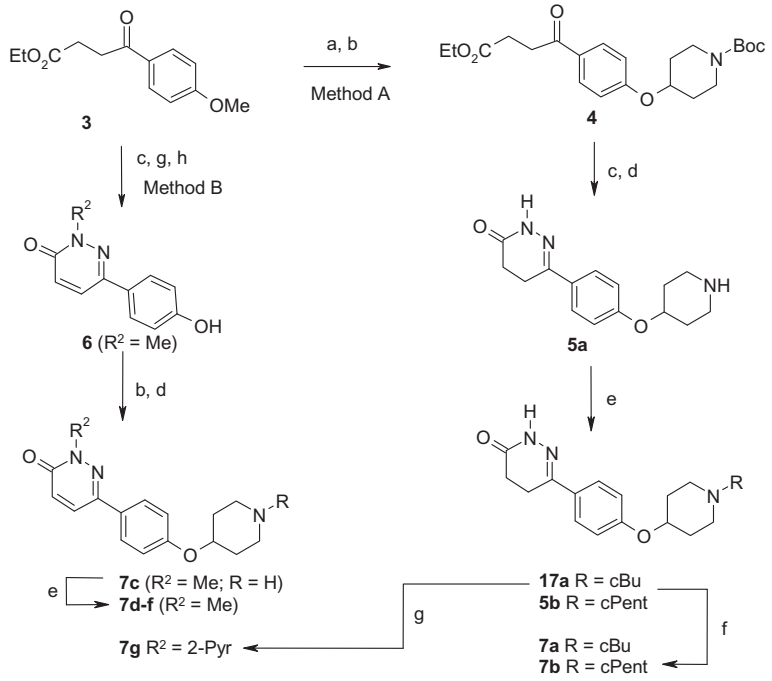
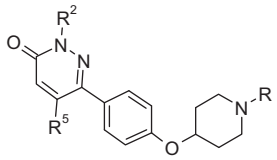
doi:10.1016/j.bmcl.2012.01.026



Scheme 1. Reagents and conditions: (a) (i) 48% HBr, reflux, (ii) EtOH, 94%; (b) 4-hydroxy-1-Boc-piperidine, PPh_3, THF, DEAD, rt, 92%; (c) NH_2NH_2, or $MeNHNH_2$, 2-propanol, reflux, R^2 = H 50%, R^2 = Me 94%; (d) TFA, DCM, 25 °C, 100%; (e) cyclobutanone or, cyclopentanone, $NaCNBH_3$, DMF, MeOH, AcOH, 60 °C, 34–42%; (f) Cs_2CO_3, DMSO, air, 130 °C, 33–37%; (g) MnO_2, xylenes, 155 °C, 75%; (h) BBr_3, DCM, 5 °C → rt, 98%; (g) 2-bromopyridine, K_2CO_3, CuI, DMF, 150 °C, 45%.

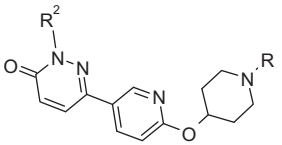
Table 1
Pyridazin-3-one H_3R binding data[a]



Entry	R^2	R^5	R	hH_3R (K_i) (nM)	rH_3R (K_i) (nM)
1e				2.0	7.2
7a	H	H	cButyl	1.9	2.2
7b	H	H	cPentyl	5.1	7.0
7c	Me	H	H	695	>1000
7d	Me	H	*i*Pr	9.2	46
7e	Me	H	cButyl	2.4	3.1
7f	Me	H	cPentyl	2.7	6.0
7g	2-Pyr	H	cButyl	9.8	15
7h	H	Me	cButyl	4.4	6.3

[a] K_i Values are an average of two or more determinations. The assay-to-assay variation was typically within 2.5-fold; 2-Pyr = 2-pyridy.

Table 2
Central ring pyridyl analogs[a]

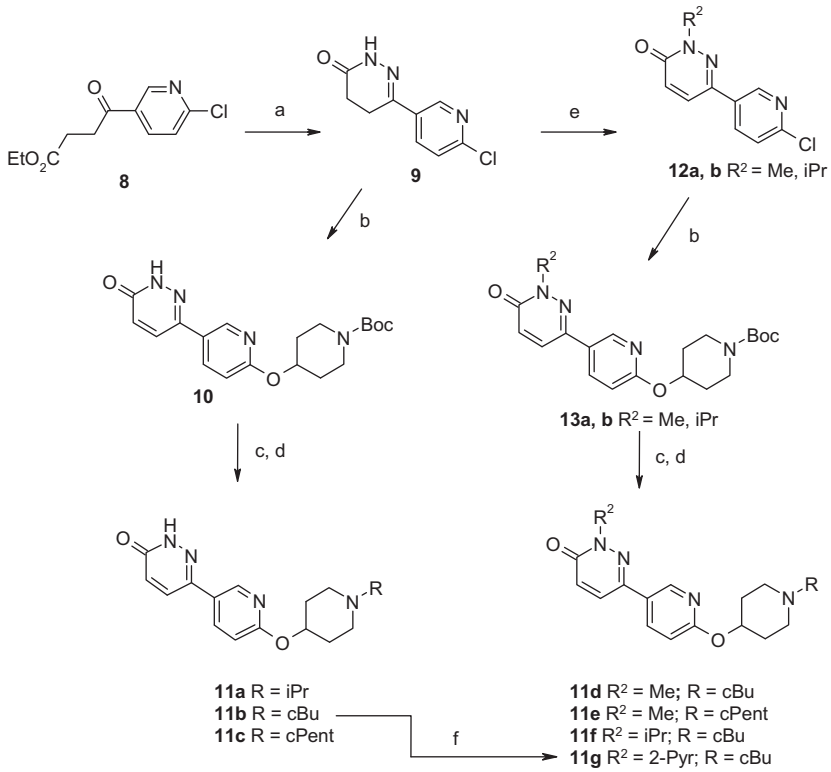


Entry	R^2	R	hH_3R (K_i) (nM)	rH_3R (K_i) (nM)
11a	H	*i*Pr	15	101
11b	H	cButyl	6.3	19
11c	H	cPentyl	26	51
11d	Me	cButyl	1.8	8.6
11e	Me	cPentyl	5.9	12
11f	*i*Pr	cButyl	6.5	9.4
11g	2-Pyr	cButyl	34	82

[a] K_i Values are an average of two or more determinations. The assay-to-assay variation was typically within 2.5-fold; 2-Pyr = 2-pyridyl.

neurotransmitter release, while blockade of H_3R by selective antagonists or inverse agonists reverses histamine-mediated inhibition and enhances neurotransmitter release. Clinically H_3R antagonists are of interest for potential treatment of multiple CNS disorders associated with attention and cognitive deficits, including sleep/wake activity, attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, and the cognitive deficits in schizophrenia.[1] Several clinical candidates (**1a**–**1e**) have advanced into trials (Fig. 1).[1a,f–l] We recently disclosed a novel class of pyridazin-3-one H_3R antagonists/inverse agonists and the profile of the first clinical compound **1e** (CEP-26401, irdabisant).[2] A series of publications outlined the pyridazinone phenoxypropyl amine structure–activity relationships (SAR) including the 4,5-dihydropyridazin-3-one series and amine replacements.[3] An exhaustive SAR direction investigated to identify second-generation pyridazinone H_3R antagonists to irdabisant was to replace the 4-phenoxypropylamine with the conformational restricted 4-phenoxypiperidine fragment in both the pyridazin-3-one and non-aromatic 4,5-dihydropyridazin-3-one subseries **2**. A similar maneuver was explored by the Merck and Johnson and Johnson groups on their respective cores.[4] In this Letter, we report the identification and potent wake promoting profile of 6-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-4,4-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one **17b**.

The 6-[4-(piperidin-4-yloxy)-phenyl]-pyridazin-3-ones **7a–f** were synthesized using a Mitsunobu reaction as outlined in Scheme 1.[3b,5] The pyridazinone NH analogs **7a** and **7b** were synthesized via intermediate **4**, which was produced in three steps from 4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester **3** (Method

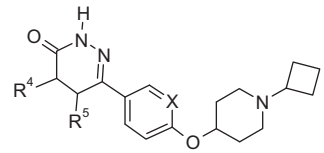


Scheme 2. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, EtOH, 80 °C, 79%; (b) 4-hydroxy-1-Boc-piperidine, 1 M KOtBu, DMSO, 100 °C, 100%; (c) 4 N HCl, dioxane, 50 °C, 100%; (d) acetone (**11a**), cyclobutanone (**11b**,**d**), cyclopentanone (**11c**,**e**), $NaCNBH_3$, DMF, MeOH, AcOH, 80 °C, 10–30%; (e) MeI or *i*PrI, Cs_2CO_3, DMSO, air, 100 °C, 79%; (f) 2-bromopyridine, K_2CO_3, CuI, DMF, 150 °C, 33%.

A). Intermediate **4** was condensed with hydrazine to give the 4,5-dihydropyridazinone intermediate, followed by deprotection of the Boc with TFA to produce **5a**. Reductive amination of **5a** with cyclobutanone or cyclopentanone gave 4,5-dihydropyridazinones **17a** and **5b**, respectively. Oxidation of **17a** and **5b** (DMSO/cesium carbonate) gave targets **7a** and **7b** in low yield. The route to *N*-R^2-methyl pyridazinone targets **7d–f** was accomplished using Method B (Scheme 1). Phenol **6** was produced in three steps from **3** and then converted to **7c** via Mitsunobu reaction with 4-hydroxy-1-boc-piperidine and Boc deprotection as described previously. Reductive amination with piperidine **7c** and acetone, cyclobutanone or cyclopentanone gave targets **7d–f**. The *N*-R^2 2-pyridyl analog **7g** was synthesized from the 4,5-dihydropyridazinone **17a** and 2-bromopyridine via copper mediated coupling (Scheme 1). The central ring 3-pyridyl analogs **11a–g** in Table 2 were synthesized as outlined in Scheme 2. 4-(6-Chloro-pyridin-3-yl)-4-oxo-butyric acid ethyl ester **8** was reacted with hydrazine hydrate to produce 6-(6-chloro-pyridin-3-yl)-4,5-dihydro-2*H*-pyridazin-3-one **9** in high yield. SnAr reaction of **9** with 4-hydroxy-1-Boc-piperidine and KOtBu in DMSO gave aromatized pyridazinone **1.** Deprotection and reductive amination gave targets **11a–c**. The pyridazinone N-R^2 substituted analogs **11d–f** were synthesized by alkylation and aromatization of **9** to **12a** and **12b**. SnAr reaction, Boc deprotection and reductive amination as described previously gave **11d**–**f**. The *N*-2-pyridyl **11g** was produced by copper mediated coupling **11b** analogous to **7g**.

The 4,5-dihydro targets in Table 3 were synthesized using procedures outlined in Schemes 3–5. 6-[4-(1-Cyclobutyl-piperidin-4-yloxy)-phenyl]-4,4-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one **17b** was produced from 4-(4-methoxy-phenyl)-2,2-dimethyl-4-oxo-butyric acid as outlined in Scheme 3 using analogous procedures described in Scheme 1 for **7a–f**. Likewise, 4-(3-fluoro-4-methoxy-phenyl)-2,2-dimethyl-4-oxo-butyric acid gave 3-fluoro **17g**. The

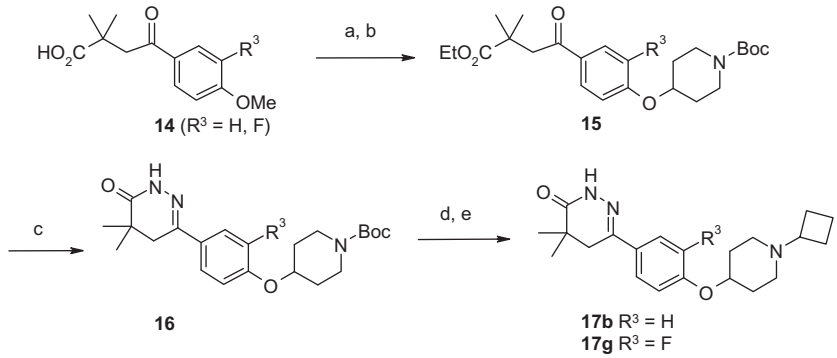
Table 3
4,5-Dihydropyridazin-3-one H_3R binding data[a]



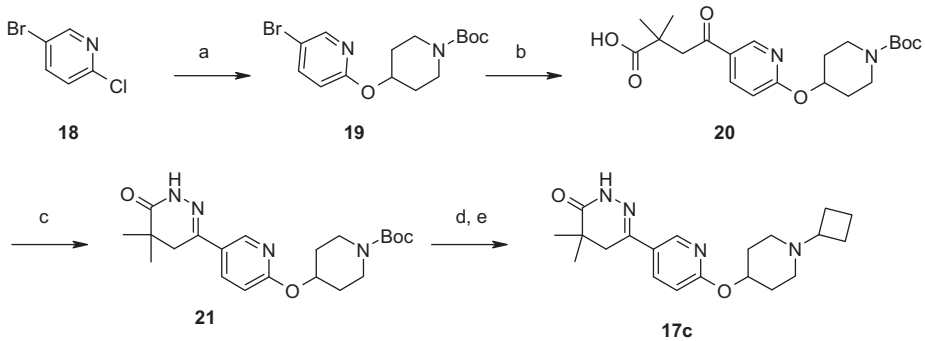
Entry	R^{4a}/R^{4b}	R^{5a}/R^{5b}	X	hH_3R (K_i) (nM)	rH_3R (K_i) (nM)
17a	H	H	CH	3.7	6.7
17b	Me/Me	H	CH	2.7	4.4
17c	Me/Me	H	N	12	28
17d	Me/Me	H	CF	7.1	7.2
R(+)17e	H	Me	CH	5.6	9.6
S(-)17e	H	Me	CH	7.8	13

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

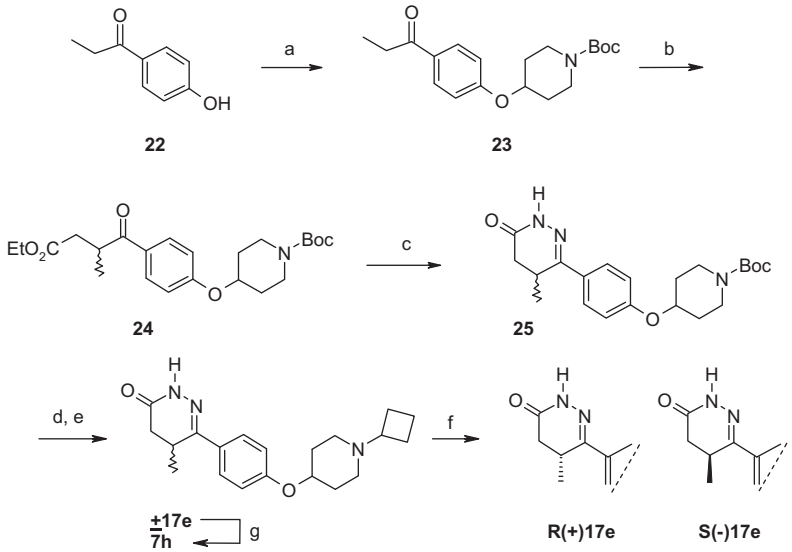
4,4-dimethyl pyridyl **17c** was produced starting with 5-bromo-2-chloro-pyridine as shown in Scheme 4. The key step was conversion of **19** to **20** via metal halogen exchange and reaction of the 3-lithiopyridyl intermediate with 3,3-dimethylsuccinic anhydride. The 5-methyl racemate **17e** was synthesized in five efficient steps starting with 1-(4-hydroxyphenyl)-propan-1-one (Scheme 5). Compound **17e** was separated using chiral SCF chromatography to give both isomers in >99% ee. The structure of peak 2 (ChiraPak 1A 4.6 × 250 mm, 2.5 mL/min, 55% MeOH/0.3% DEA, peak 1 rt = 3.2 min, peak 2 rt = 6.2 min) as the HCl salt was solved by single crystal X-ray crystallography and the stereochemistry assigned as the 5-*S*-methyl isomer. The specific rotations were, peak 1 **R(+)-17** $[\alpha]_D^{24}$ + 30.5 (c 0.1, MeOH) and peak 2 **S(−)-17** $[\alpha]_D^{24}$ − 29.2 (c 0.1, MeOH).



Scheme 3. Reagents and conditions: (a) (i) 48% HBr, reflux, (ii) ethanol 90%; (b) 4-hydroxy-1-Boc-piperidine, PPh_3, THF, DEAD, R^3 *F* = 45%, R^3 *H* = 93%; (c) NH_2NH_2, 2-propanol, reflux, 89%; (d) TFA, DCM, 25 °C, 100%; (e) cyclobutanone, $NaCNBH_3$, DMF, MeOH, AcOH, 60 °C, 35–58%.



Scheme 4. Reagents and conditions: (a) 4-Hydroxy-1-Boc-piperidine, 1 M KOtBu, toluene, 80 °C, 68%; (b) 3,3-dimethyl-dihydro-furan-2,5-dione, 1.4 M sec-BuLi, ether, −78 °C, 35%; (c) $NH_2NH_2{\cdot}H_2O$, 2-propanol, 120 °C, 97%; (d) TFA, DCM, 25 °C, 100%; (e) cyclobutanone, $NaCNBH_3$, DMF, MeOH, AcOH, 60 °C, 65%.



Scheme 5. Reagents and conditions: (a) 4-Hydroxy-1-Boc-piperidine, PPh3, THF, DEAD, 60%; (b) LDA, ethyl bromoacetate, THF, 0 °C; (c) $NH_2NH_2.H_2O$, 2-propanol, 110 °C, 65% two steps; (d) TFA, DCM, 25 °C, 100%; (e) cyclobutanone, $NaCNBH_3$, DMF, MeOH, AcOH, 60 °C, 60% two steps; (f) SCF chiral separation; (g) Cs_2CO_3, DMSO, air, 100 °C, 94%.

The phenoxypiperidine–pyridazinone analogs were tested using in vitro binding assays by displacement of [^{3}H]NAMH in membranes isolated from CHO cells transfected with cloned human H_3 or rat H_3 receptors as shown in Tables 1–3.[2,3] Replacing the *R*-2-methyl-pyrrolidinyl propoxy fragment of irdabisant **1e** with *N*-cyclobutylpiperidinyl (**7a** hH_3R K_i = 1.9 nM, rH_3R K_i = 2.2 nM) and *N*-cyclopentylpiperidinyl (**7b** hH_3R K_i = 5.1 nM, rH_3R K_i = 7.0 nM) showed comparable affinity (Table 1). Likewise, the *N*-methyl pyridazinones **7e** and **7f** were equally well tolerated,[3b] although the 2-pyridyl **7g** had slightly weaker H_3R binding affinity. The SAR at the piperidine nitrogen with compounds **7c**–**f** showed that the cyclobutyl was optimum. The *N*-isopropyl **7d** produced a large drop in affinity compared to *N*-cyclobutyl **7e**, while the piperidine NH compound **7c** was essentially inactive. Com-

Table 4
Pharmacokinetic properties in rat[a]

		7a	17b	S-17e
iv	$t_{½}$ (h)	2.3 ± 0.4	1.9 ± 0.9	4.4 ± 1.2
	V_d (L/kg)	2.5 ± 0.6	3.1 ± 0.4	7.6 ± 0.3
CL (mL/min/kg)		13 ± 3	18 ± 2	23 ± 6
po	AUC	1535 ± 117	1235 ± 162	1226 ± 78
C_{max} (ng/mL)		441 ± 22	270 ± 47	253 ± 21
	F (%)	35 ± 1	33 ± 4	56 ± 5
	B/P[b]	1.9 ± 0.1	4.0 ± 0.6	5.3 ± 0.3

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

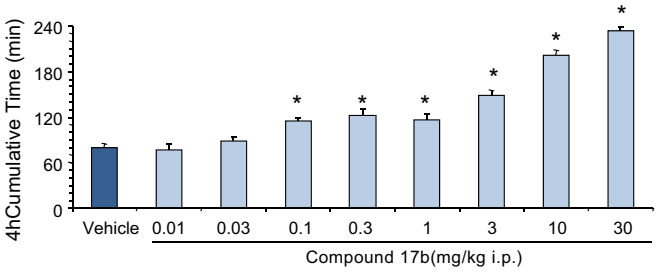


Figure 3. Compound **17b**-induced wake promotion. Cumulative time awake for 4 h (4 h AUC) following administration of vehicle or compound **17b** in chronically implanted rats. Mean ± SEM, n = 8–14/group. $^*p < 0.05$, Dunnett's post-hoc test versus vehicle.

pound **7a** from this set was selected for additional profiling to identify potential issues and areas of improvement as a backup to irdabisant. Compound **7a** was a potent, full inverse agonist in the [^{35}S]GTPγS hH_3R binding assay (EC_{50} = 1.1 nM)[2] and displayed acceptable drug-like properties with low lipophilicity ($c\log P$ = 1.5), high permeability (Caco-2 $P_{app} = 16.5 \times 10^{-6}$ cm/s) and water solubility (pH 2 and pH 7.4 > 1 mg/mL). Compound **7a** showed acceptable in vitro metabolic stability across species in liver microsomes ($t_{½}$ > 40 min in mouse, rat, dog, monkey and human) and IC_{50} values >30 μM for inhibition of cytochrome P450 enzymes (CYP1A2, 2C9, 2C19, 2D6 and 3A4), indicating low potential for drug–drug interactions. Compound **7a** displayed excellent selectivity over hH_1, hH_2, and hH_4 receptor subtypes (<10% inhibition at 10 μM) and when screened against a panel of 63 GPCRs, ion channels and enzymes it showed activity only for the dopamine transporter (DAT, 63% inhibition at 10 μM; MDS Pharma Services, LeadProfile screen). The hERG IC_{50} was 8 μM in a patch clamp assay. The pharmacokinetic (PK) profile in rat showed **7a** had a iv half-life of 2.3 h, moderate clearance and acceptable oral bioavailability and brain exposure (brain concentration 6 h following a 5 mg/kg po dose = 1.4 μM) (Table 4). The hERG selectivity and the DAT activity required further improvement for a compound to be considered as a potential backup/second generation wake promoting agent to irdabisant.[2a]

The SAR of the central pyridyl analogs, designed to lower the $c\log P$ and potentially improve hERG activity, is shown in Table 2. In general, parallel changes in the pyridyl series showed weaker affinity compared to the phenyl series (compare **11b** to **7a**, and **11c** to **7b**). Pyridyl **11b** ($c\log P$ = 0.9) retained high affinity for hH_3R, but unfortunately did not show an improvement in hERG selectivity (IC_{50} = 9 μM) or rat oral bioavailability (%F = 21). Of note, an opposite SAR trend was observed compared to the phenyl series when changing the NH-pyridazinone to an *N*-methyl (compare **11d** to **11b**, and **11e** to **11c**).

We recently reported a series of non-aromatic 4,5-dihydropyridazin-3-one phenoxypropylamines and the wake promoting activity of compound **30** (Fig. 2).[3f] A key issue in the phenoxypropyl series was blocking in vivo metabolism of the 4,5-dihydropyridazinone ring. A similar SAR was explored on the phenoxypiperidine core for comparison. 4,5-Dihydro-2*H*-pyridazin-3-one **17a** had high H_3R affinity, but as we observed in the phenoxypropyl series, in vivo metabolite identification (ID) studies revealed **17a** was metabolized approximately 35% to **7a** in the rat, and about 20–25% in the dog. Based on the formation of an undesired active H_3R metabolite, and findings with the phenoxypropyl series, we next installed the 5-methyl to potentially block in vivo metabolite formation.[3f] Isomers **R-17e** and **S-17e** (Table 3) showed comparable H_3R binding affinity (Table 3), selectivity, functional activity (**R-17e** $K_{b,app}$ = 0.6, EC_{50} = 1.3 nM; **S-17e** $K_{b,app}$ = 0.7 nM, EC_{50} = 1.6 nM) and pharmacokinetics in rat (**S-17e**, Table 4). The in vivo rat metabolite ID study revealed **R-17e** was metabolized about 25% to **7h** following oral administration, while the *S*-isomer was stable. Further profiling showed incorporation of the *S*-methyl (**S-17e**) improved hERG activity (IC_{50} = 27 μM) and DAT selectivity (13% inhibition at 10 μM) compared to **7a**. However, this compound was later abandoned due to concerns with the fate of the *S*-isomer in higher species.

Subsequently, the 4,4-dimethyl phenoxypiperidine analog of **30**[3f] was synthesized and profiled (Fig. 2). Compound **17b** had high affinity for both human and rat H_3Rs, while the 3-pyridyl **17c** and 3-fluoro **17d** had slightly weaker binding affinity. Functionally, **17b** was a full inverse agonist (EC_{50} = 0.8 nM) and showed acceptable in vitro metabolic stability ($t_{½}$ > 40 min across species), and cytochrome P450 selectivity (IC_{50} > 30 μM). The hERG IC_{50} value was 21 μM and selectivity profiling showed **17b** had >1000-fold selectivity against hH_1, hH_2, and hH_4 receptor subtypes and against a panel of 172 GPCRs, ion channels and enzymes (<50% inhibition at 10 μM; DAT = 8%; MDS Pharma Services, LeadProfiler and Spectrum screen). The permeability was classified as high (Caco2 $P_{app} = 27 \pm 0.4 \times 10^{-6}$ cm/s) and plasma protein binding for rat, dog, and human was low to moderate (50–60%). In rat PK studies it showed an iv $t_{½}$ < 2 h, with acceptable oral bioavailability and brain exposure (brain concentration 6 h following a 5 mg/kg po dose = 2.1 μM) (Table 4).

Compound **17b** met all discovery criteria and advanced into in vivo evaluation in the rat dipsogenia and the rat EEG/EMG sleep–wake models. The rat dipsogenia model was used as an in vivo surrogate measure of H_3R functional inhibition in the brain following peripheral administration. Histamine and the

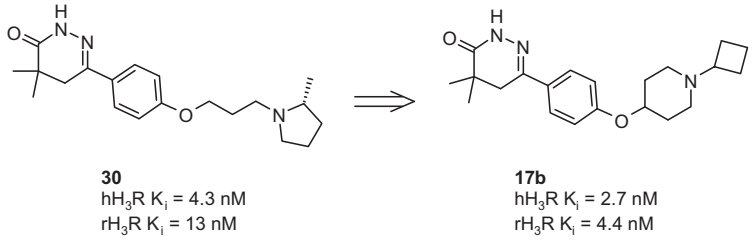


Figure 2. Design of **17b** based on profile of **30**.

H_3-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.[1k,2,6] Compound **17b** potently and dose-dependently inhibited RAMH-induced dipsogenia with an ED_{50} value of 0.14 mg/kg ip. H_3R antagonists including irdabisant and its analogs demonstrated wake promoting activity in the rat.[2b,3a,3f,7] Wake-promoting activity of **17b** in the rat was measured from 0.01 to 30 mg/kg ip as previously described using rats surgically implanted for chronic recording of EEG (electroencephalographic) and EMG (electromyographic) signals enabling wake, slow-wave sleep, and rapid eye-movement sleep to be scored by standard criteria.[2b,8,9] The cumulative wake time at 4 h after dosing (5 h after lights on) was evaluated during the normal quiet period of the rat. Compound **17b** significantly and dose-dependently increased wake at doses from 0.1 up to 30 mg/kg ip by 4 h AUC values ($P < 0.001$ ANOVA) (Fig. 3). Doses of 0.1–1 mg/kg increased wake 45–50% above the vehicle value, from 80 ± 5 min (vehicle group) to 115 ± 4 (0.1 mg/kg), 122 ± 9 min (0.3 mg/kg), and 116 ± 7 min (1 mg/kg). At 10 mg/kg, percent time awake was maintained over 90% for the first 2 h after dosing. Wake in the 10 and 30 mg/kg groups was increased to 201 ± 7 and 234 ± 4 min at 4 h (152% and 193%, respectively, compared to vehicle, equivalent to 84% and 98% time awake for 4 h). At 30 mg/kg, maximal cumulative wake surplus (excess wake time compared to the vehicle group) was 196 min at 7 h post dosing, which was maintained up to 22 h. Sleep rebound was not observed in any of the treatment groups. Compound **17b** thus demonstrated very potent wake promotion in rat at doses as low as 0.1 mg/kg ip and robust wake at higher doses.

In summary, optimization of the phenoxypiperidine core led to the identification of target molecules meeting H_3R target potency, selectivity and rat pharmacokinetic criteria. The search for compounds with improved hERG and DAT selectivity and lacking in vivo active metabolites identified 6-[4-(1-cyclobutyl-piperidin-4-yloxy)-phenyl]-4,4-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one **17b**. Compound **17b** met all discovery criteria, including demonstration of potent functional H_3R antagonism in vivo in the rat dipsogenia model and potent wake activity in the rat EEG/EMG model at doses as low as 0.1 mg/kg ip.

Acknowledgments

The authors thank Emily Kordwitz, Mark Olsen, Gilbert Moachon, Nicole Lepallec, Isabelle Kanmacher, Véronique Agathon, Mehran Yazdanian and Val Marcy for their assistance and support.

References and notes

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