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Synthesis and evaluation of pyridone-phenoxypropyl-*R*-2-methylpyrrolidine analogues as histamine H_3 receptor antagonists

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ABSTRACT

6-{4-[3-(*R*)-2-Methylpyrrolidin-1-yl)propoxy]-phenyl}-2*H*-pyridazin-3-one **6** (Irdabisant; CEP-26401) was recently reported as a potent H_3R antagonist with excellent drug-like properties and in vivo activity that advanced into clinical evaluation. A series of pyridone analogs of **6** was synthesized and evaluated as H_3R antagonists. Structure–activity relationships revealed that the 5-pyridone regiomer was optimal for H_3R affinity. *N*-Methyl **9b** showed excellent H_3R affinity, acceptable pharmacokinetics and pharmaceutical properties. In vivo evaluation of **9b** showed potent activity in the rat dipsogenia model and robust wake-promoting activity in the rat EEG model.

Histamine elicits physiological responses mediated by four G-protein coupled receptors (H_1R–H_4R) and exerts a variety of functions in the central nervous system (CNS).[1,2] H_3Rs are highly expressed in the CNS and function as presynaptic autoreceptors regulating histamine release and as presynaptic heteroreceptors regulating release of multiple neurotransmitters including acetylcholine, dopamine, norepinephrine and serotonin.[3,4] H_3R antagonists therefore have potential use for treatment of a variety of CNS diseases including sleep disorders, cognitive disorders, attention-deficit hyperactivity disorder (ADHD) and Alzheimer's disease (AD).[3,4]

A number of H_3R antagonists have advanced to pre-clinical and clinical development stages (Fig. 1). For example, ABT-239 (**1**) was nominated for clinical development as a cognition enhancing agent but was ultimately terminated due to cardiovascular liabilities.[5,11] GSK-189254 (**2**), a potent and selective H_3R ligand advanced into clinical trials for narcolepsy and AD.[6,11] The Merck compound MK-0249 (**4**) completed phase II trials for ADHD, AD and cognitive impairments in schizophrenia.[8,11] The Pfizer compound PF-3654746 (**5**) failed a Phase II ADHD trial and was discontinued while JNJ-31001074 (Bavisant, **3**) is reportedly still in Phase II for ADHD.[7,9,11] We identified a novel class of pyridazin-3-one H_3R antagonists/inverse agonists with exceptional drug-like properties and in vivo profiles.[10] 6-{4-[3-(*R*)-2-Methylpyrrolidin-1-yl)propoxy]-phenyl}-2*H*-pyridazin-3-one **6** (Irdabisant; CEP-26401) was selected as a clinical candidate and recently completed phase I.[10] As part of our H_3 discovery project studying the structure–activity relationships (SAR) around **6**, we actively pursued a variety of structural core modifications. One strategy, which is the focus of this Letter, was to synthesize and evaluate the pyridone replacements for the pyridazinone and evaluate the H_3R binding SAR, pharmacokinetics (PK), selectivity and drug-like properties for a series of pyridone-phenoxypropyl-*R*-2-methylpyrrolidine analogues.

A general synthesis of pyridones **9** and **10** is shown in Scheme 1. Alkylation of 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)-phenol (**7**) with 1-bromo-3-chloropropane and the subsequent reaction of the terminal chloride with (*R*)-2-methylpyrrolidine gave compound **8**.[10] Suzuki coupling of **8** with various bromopyridones provided analogs **9** and **10**.[12] *N*-Methyl-bromopyridone fragments leading to compounds **9b-e** were synthesized by simple N-methylation of their commercially available bromopyridones with MeI in the present of K_2CO_3 in DMSO at room temperature. Syntheses of the required bromopyridone precursors to compounds **10a–e** are shown in Scheme 2. N-Arylation of **11** with arylboronic acids provided compound **12a–b**.[13] N-Benzylation of 5-bromopyridone **11** with BnBr gave compound **13**. N-Methylation of pyridone **14** with MeI provided compound **15**. Bromopyridone **17** was synthesized in a three steps sequence: N-methylation of 3-bromopyridone **16** with MeI, then Suzuki coupling of the bromide group with $PhB(OH)_2$, followed by region selective bromination at the 5-position with NBS.[14a]

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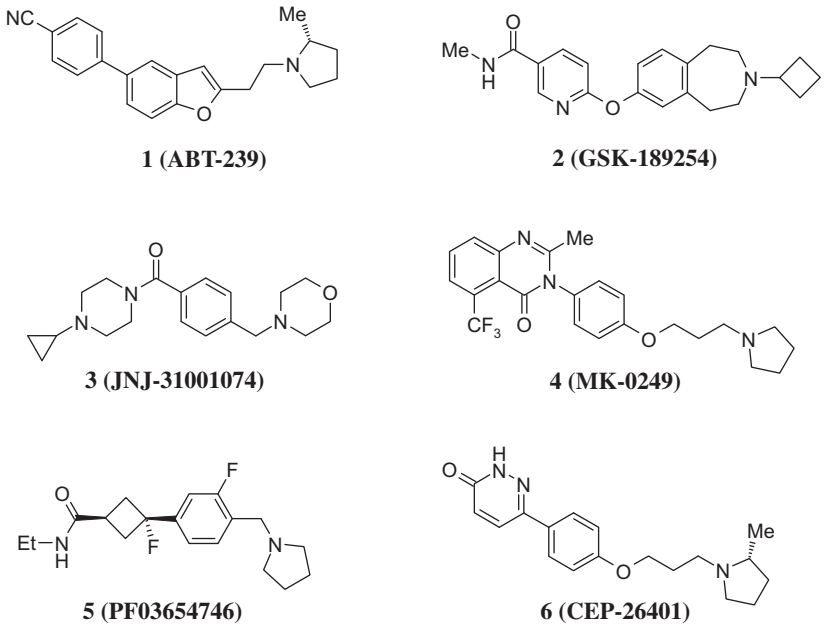
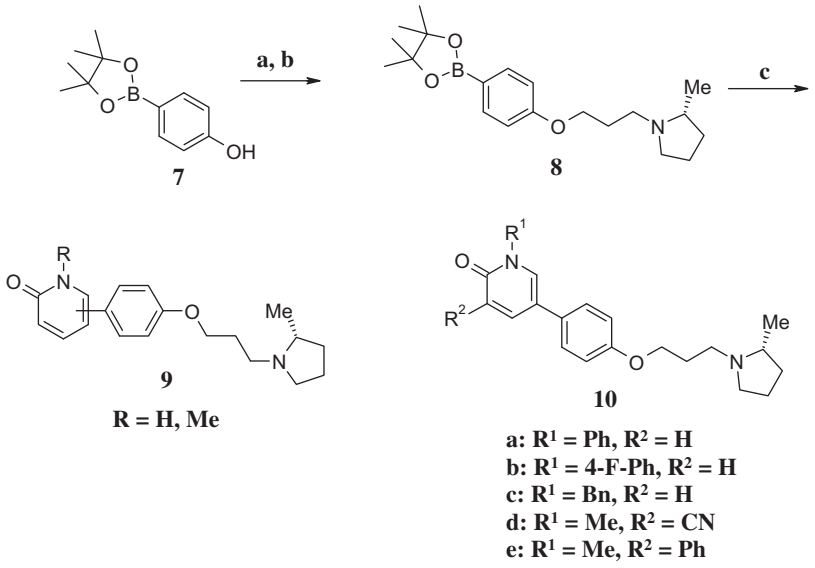


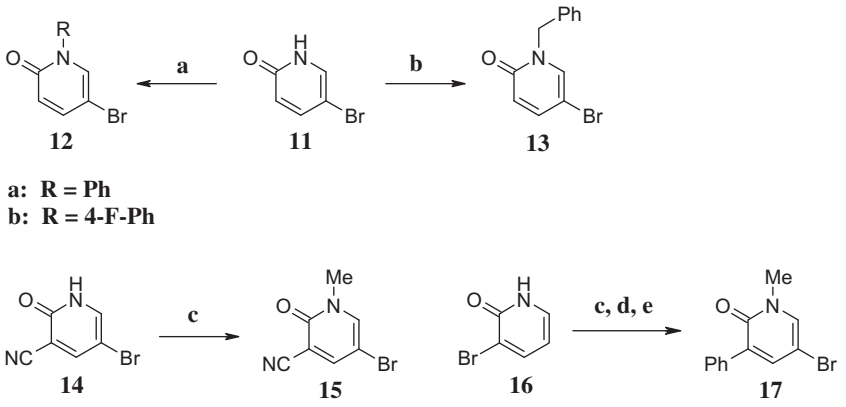
Figure 1. Structures of pre-clinical and clinical H_3R antagonists.



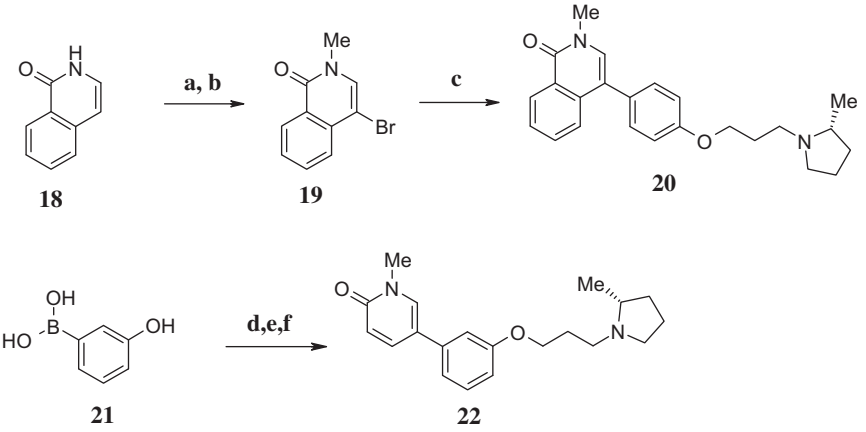
Scheme 1. Reagents and conditions: (a) $BrCH_2CH_2CH_2Cl$, K_2CO_3, CH_3CN, 80 °C, 18 h; (b) (*R*)-2-methylpyrrolidine–HCl, NaI, K_2CO_3, CH_3CN, 80 °C, 24 h, 88% two steps; (c) bromopyridones, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, $PhCH_3$–EtOH–H_2O (1:1:1.5), 100 °C, 18 h, 26–58% (except **9a** = 8%).

Syntheses of compounds **20** and **22** are presented in Scheme 3. N-Methylation of isoquinolinone **18** followed by region selective bromination at the 4-position gave compound **19**.[14b] Suzuki coupling of **19** with **8** afforded compound **20**. Suzuki coupling of **21** with 5-bromo-1-methyl-pyridin-2-one, and the subsequence alkylation of the phenol with 1-bromo-3-chloropropane followed by reaction of the terminal chloride with (*R*)-2-methylpyrrolidine provided compound **22**.

In general, the pyridone analogues bound the hH_3R with single digit nanomolar affinity comparable with the pyridazinone class. *N*-methyl pyridone **9b** (hH_3R K_i = 0.7 nM, rH_3R K_i = 8.5 nM) had excellent H_3R binding affinity for both human and rat receptors (Table 1) whereas the *N*-H pyridone **9a** (hH_3R K_i = 7.7 nM, rH_3R K_i = 9.0 nM) had 11-fold weaker hH_3R affinity but similar rH_3R affinity. The pyridone regiochemistry appeared to play an important role in the H_3R binding affinity. The 4-pyridone **9c** (hH_3R K_i = 3.2 nM, rH_3R K_i = 12 nM) and 6-pyridone regiomers **9d** (hH_3R K_i = 4.9 nM, rH_3R K_i = 21 nM) with the *meta*-carbonyl orientation had comparable H_3R binding affinities in both species. However, the 5-pyridone regiomer **9b** had 5–7-fold higher hH_3R affinity compared to **9c** and **9d**. The 6-regiomer **9e** (hH_3R K_i = 18 nM, rH_3R K_i = 144 nM) was over 16-fold weaker for both human and rat H_3R than **9b**. Thus, the optimum pyridone regiomer had the carbonyl oriented at the para-position.



Scheme 2. Reagents and conditions: (a) $ArB(OH)_2$, $Cu(OAc)_2$, pyridine, molecular sieves, CH_2Cl_2, 80–88%; (b) BnBr, K_2CO_3, DMSO, rt, 98%; (c) MeI, K_2CO_3, DMSO, rt, 97%; (d) $Ph(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, $PhCH_3$–EtOH–H_2O (1:1:1.5), 100 °C, 17 h; (e) NBS, $CHCl_3$, rt, 15 h, 78% (2 steps).



Scheme 3. Reagents and conditions: (a) MeI, K_2CO_3, DMSO, rt, 2 h; (b) NBS, $CHCl_3$, rt, 1 h, 42% (2 steps); (c) **8**, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, $PhCH_3$–EtOH–H_2O (1:1:1.5), 100 °C, 21 h, 37%; (d) 5-bromo-1-methyl-pyridin-2-one, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, $PhCH_3$–EtOH–H_2O (1:1:1.5), 100 °C, 5 h, 66%; (e) $ClCH_2CH_2CH_2Br$, K_2CO_3, CH_3CN, 80 °C, 24 h, 98%; (f) (*R*)-2-methylpyrrolidine–HCl, NaI, K_2CO_3, CH_3CN, 80 °C, 21 h, 33%.

The effect of substitution on the pyridone ring was also investigated (Table 2). Replacement of *N*-methyl with *N*-phenyl and *N*-benzyl groups (**10a–c**) or substitution at the 3-position of the pyridone ring with nitrile and phenyl (**10d** and **10e**) gave no improvement in hH_3R or rH_3R affinities with the exception of compound **10d** (rH_3R K_i = 3.0 nM). Interestingly, the 3,4-fused phenyl **20** (hH_3R K_i = 0.9 nM, rH_3R K_i = 2.4 nM) displayed about a 3-fold improvement in affinity compared to 3-phenyl **10e**. Moving the 3-((*R*)-2-methylpyrrolidin-1-yl)-propan-1-ol fragment from the 4- to the 3-position as in **22** resulted in significant loss of H_3R binding affinity, demonstrating that attachment of the pyridone at the 4-position of the central ring was clearly preferred.

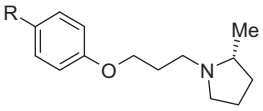
Based on the target affinities, analogues **9a**, **9b**, **10a**, **10c** and **20** were screened for PK properties in the rat. Compared to the pyridazinone series,[10] the pyridone series showed poor rat PK profiles. Compounds **9a**, **10a**, **10c** and **20** all suffered poor PK properties with high clearance (**9a** = 96 ml/min/kg, **10a** = 138 ml/min/kg, **10c** = 171 ml/min/kg, and **20** = 42 ml/min/kg), and low to no oral exposure (**9a** %*F* = 0, **10a** %*F* = 17, **10c** %*F* = 0, **20** %*F* = 8). *N*-Methyl **9b** demonstrated a slight improvement in the overall rat PK profile. The oral exposure was low (%*F* = 11), however the iv intrinsic properties were acceptable ($t_{½}$ = 1.4 h, V_d = 1.4 L/kg, CL = 11 mL/min/kg) (Table 3). Following oral administration, the brain exposure was acceptable (brain to plasma ratio B/P = 1.7) and following administration of a 10 mg/kg ip dose 1 h brain levels of 2.9 μM were achieved (B/P = 1.9), sufficient to allow for proof-of-concept in vivo evaluation. Further, the *N*-methyl analog **9b** had excellent hH_3R selectivity over hH_1R, hH_2R, and hH_4R subtypes (K_i >10 μM), acceptable drug-like properties with aqueous solubility at pH 7.4 (>0.3 mg/mL), stability in liver microsomes (human, mouse, rat, and monkey $t_{½}$ >40 min) and low to no inhibition of cytochrome P450 enzymes (CYP1A2, 2C9, 2C19, 2D6, and 3A4 IC_{50} >30 μM).

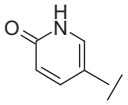
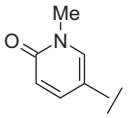
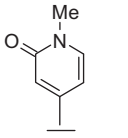
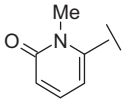
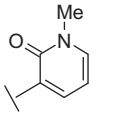
The pyridone analogues were potent antagonists and inverse agonists of H_3R activity in vitro, in the guanosine 5′-(γ thio) trisphosphate ([^{35}S]GTPγS) binding assay, as demonstrated with the pyridazinone series.[15] Compound **9b** inhibited *R*-α-methylhistamine (RAMH)-induced [^{35}S]GTPγS binding in membranes prepared from CHO cells recombinantly expressing hH_3R with a $K_{b,app}$ value of 0.2 nM and inhibited basal activity in this assay with an EC_{50} value of 0.7 nM.

The rat dipsogenia model was initially used in the project as an in vivo surrogate measure of H_3R functional inhibition in the brain following peripheral administration of compounds. Histamine and the H_3-selective agonist, RAMH induce water drinking in the rat when administered either peripherally or centrally, an effect that is blocked by H_3R antagonists.[16] **9b** potently and dose-dependently inhibited RAMH-induced dipsogenia with an ED_{50} value of 0.03 mg/kg ip. Following the demonstration of potent in vivo H_3R functional activity in the brain, **9b** was further evaluated for wake-promoting activity in the rat.[4,19,20]

A number of H_3R antagonists promote wake activity in preclinical species, and this effect has recently been reported in clinical trials with the H_3R antagonists pitolisant and MK-0249.[17,18]

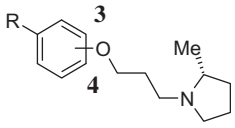
Table 1
Human and rat H_3Rs binding data for pyridone analogues[15]



Compounds	R	hH_3RK_i (nM)[a]	rH_3RK_i (nM)[a]
9a		7.7	9.0
9b		0.7	8.5
9c		3.2	12
9d		4.9	21
9e		18	144

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

Table 2
The substitution effect on pyridone ring[15]



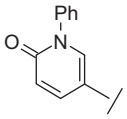
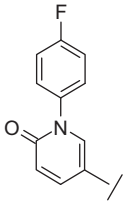
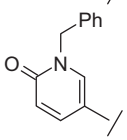
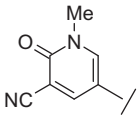
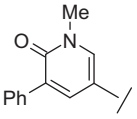
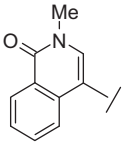
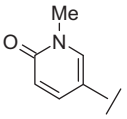
Compounds	R	Regiomer	hH_3RK_i (nM)[a]	rH_3RK_i (nM)[a]
10a		4-	1.8	19
10b		4-	4.7	9.6
10c		4-	2.0	10
10d		4-	3.4	3.0

Table 2 (*continued*)

Compounds	R	Regiomer	hH_3RK_i (nM)[a]	rH_3RK_i (nM)[a]
10e		4-	3.5	7.9
20		4-	0.9	2.4
22		3-	112	>500

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

Table 3
Rat PK data for compound **9b**

iv (1 mg/kg)	
$t_{1/2}$ (h)	1.4
V_d (L/kg)	1.4
CL (mL/min/kg)	11
po (5 mg/kg)	
AUC_{0-t} (ng h/mL)	867
C_{max} (ng/mL)	190
%F	11
B/P	1.7

Compound **9b** was tested in the rat EEG/EMG model of wake promotion as previously described (Fig. 2).[4,19,20] Compound **9b** increased wake activity dose dependently at 10 and 30 mg/kg ip based on cumulative wake 4 h post dosing (4 h AUC). AUC values were 160 ± 16 min at 10 mg/kg and 227 ± 5 min at 30 mg/kg ip compared to vehicle (114 ± 9 min). At 30 mg/kg the treated animals were awake 95% of the time for 4 h post dosing, a two-fold increase in wake time compared to the vehicle group. The maximal cumulative wake surplus (time awake compared to the vehicle group) at 30 mg/kg ip was 146 ± 8 min reached at 6 h post dosing. From 6 to 22 h post dosing, this group recovered sleep at a constant rate of 6.3 min per hour, and at 22 h post dosing, retained 35% of the surplus wake time (51 ± 27 min, p <0.05 vs 6 h, paired t-test). At 10 mg/kg ip, the maximum cumulative wake surplus was

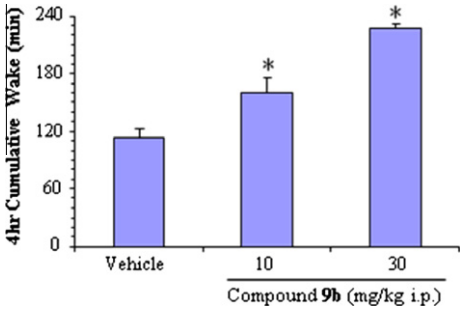


Figure 2. EEG wake activity of compound **9b**. Compound **9b**-induced wake promotion; cumulative wake 4 h AUC values shown for each dose (mean + SEM, n = 8, 5, and 10 for vehicle, 10, and 30 mg/kg groups). Compound administered i.p. to rats with chronically implanted electrodes for recording EEG and EMG activity. *p < 0.05 Dunnett's *post hoc* vs. vehicle.

53 ± 10 min at 3 h and was not different at 22 h (33 ± 12 min). No adverse EEG activity was observed in either treatment group.

In conclusion, a series of pyridone phenoxypropyl-*R*-2-methylpyrrolidine analogues were synthesized and evaluated as H_3R ligands. They were found to have excellent binding affinities for both hH_3R and rH_3R. The pyridone series in general displayed unacceptable rat PK properties compared to the pyridazinone series. However, results from this study demonstrated that *N*-methyl **9b** showed acceptable target affinity, PK exposure and pharmaceutical properties for in vivo proof of concept studies.

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