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Synthesis and evaluation of 4-alkoxy-[1′-cyclobutyl-spiro(3,4-dihydrobenzopyran-2,4′-piperidine)] analogues as histamine-3 receptor antagonists

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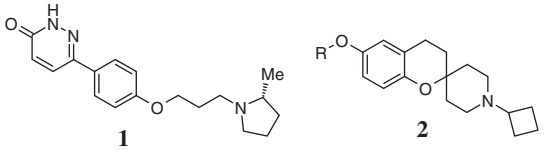
ABSTRACT

A novel class of 4-alkoxy-[1′-cyclobutyl-spiro(3,4-dihydrobenzopyran-2,4′-piperidine)] analogues were designed and synthesized as H_3R antagonists. Structure–activity relationship identified sulfone **27** with excellent H_3R affinities in both humans and rats, and acceptable pharmacokinetic properties. Further, compound **28** achieved single digit nanomolar H_3R affinities in both species with minimum hERG activity.

Histamine-3 receptors (H_3Rs) are predominantly located in the central nervous system (CNS) and function as presynaptic autoreceptors regulating histamine release and as presynaptic heteroreceptors regulating the release of multiple neurotransmitters including acetylcholine, dopamine, norepinephrine, and serotonin.[1–10] Thus, H_3R antagonists have potential use for the treatment of a variety of central nervous system (CNS) diseases such as sleep disorders, cognitive disorders, attention-deficit hyperactivity disorder (ADHD) and Alzheimer's disease (AD).[3–9] H_3Rs have attracted a lot of attention from the pharmaceutical industry in the development of H_3R ligands for the treatment of CNS disorders.[3–9] We identified a novel class of pyridazin-3-one H_3R antagonists/inverse agonists with exceptional drug-like properties, and in vivo profiles.[11,12] 6-{4-[3-(*R*)-2-Methylpyrrolidin-1-yl)propoxy]-phenyl}-2*H*-pyridazin-3-one **1** (Irdabisant; CEP-26401) (Fig. 1) was selected as a clinical candidate and recently completed phase I.[12] During our H_3 discovery project research, we actively pursued a variety of structural core modifications.[13,14] One strategy was to evaluate the constrained spiro-3,4-dihydrobenzopyran-2,4′-piperidine fragment as an amine replacement and optimize the western portion of the core. This letter describes the synthesis of 4-alkoxy-[1′-cyclobutyl-spiro(3,4-dihydrobenzopyran-2,4′-piperidine)] ether analogues **2** and evaluation of their H_3R binding SAR, pharmacokinetics (PK), selectivity and drug-like properties.[15]

The synthesis of compounds **8**–**12** is shown in Scheme 1. Cyclocondensation of 2,5-dihydroxyacetonphenone **3** with 4-oxo-piperidine-1-carboxylic acid *t*-butyl ester provided compound **4** in a good yield.[16] Reduction of ketone **4** and simultaneous elimination of the Boc group afforded compound **5**.[16,17] Reductive amination of **5** with excess cyclobutanone gave the key phenol intermediate **6**. Alkylation of phenol **6** with various electrophiles, such as (2-bromo-ethoxymethyl)-benzene resulted in compound **7**. Debenzylation of **7** gave primary alcohol **8**. Similarly, reaction of **6** with propylene oxide, (*R*)-2-ethyl-oxirane, (*S*)-2-ethyl-oxirane, and 1,2-epoxy-2-methylpropane provided compounds **9**–**12**.[18]

The synthesis of ethers **13**–**23** was accomplished by O-alkylation of phenol **6** with the corresponding alkyl and heterocyclic halides or mesylate intermediates (Scheme 2). The alkyl and cyclic mesylates were synthesized from the corresponding alcohol precursors and methanesulfonyl chloride. Oxidation of sulfur compounds **14**, **15**, **22**, and **23** was accomplished with oxone or hydrogen peroxide to afford the sulfone targets **24**–**28** in good yields.



1 (Irdabisant; CEP-26401) **2**

Figure 1.

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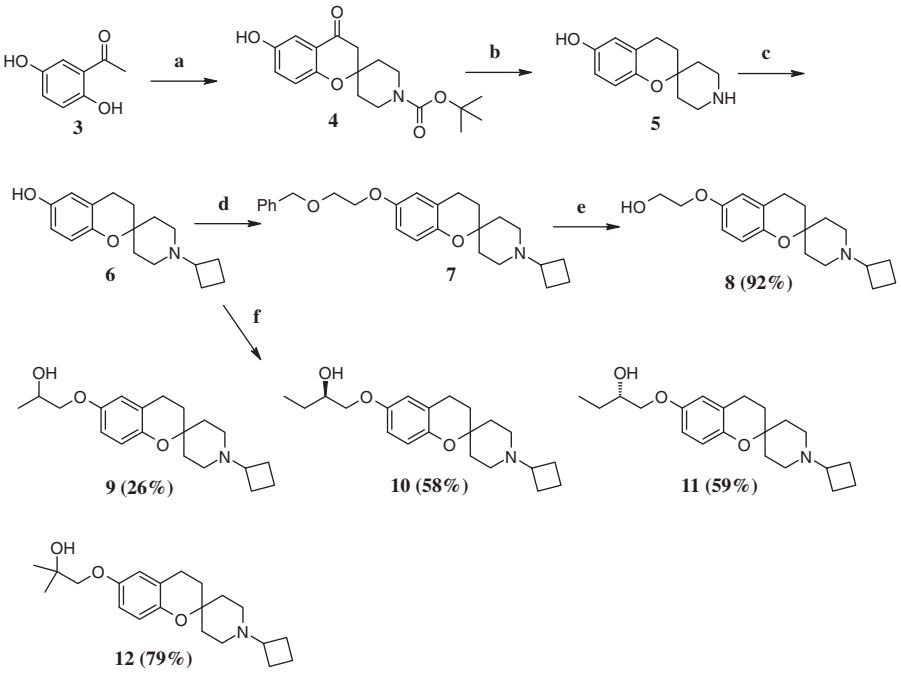
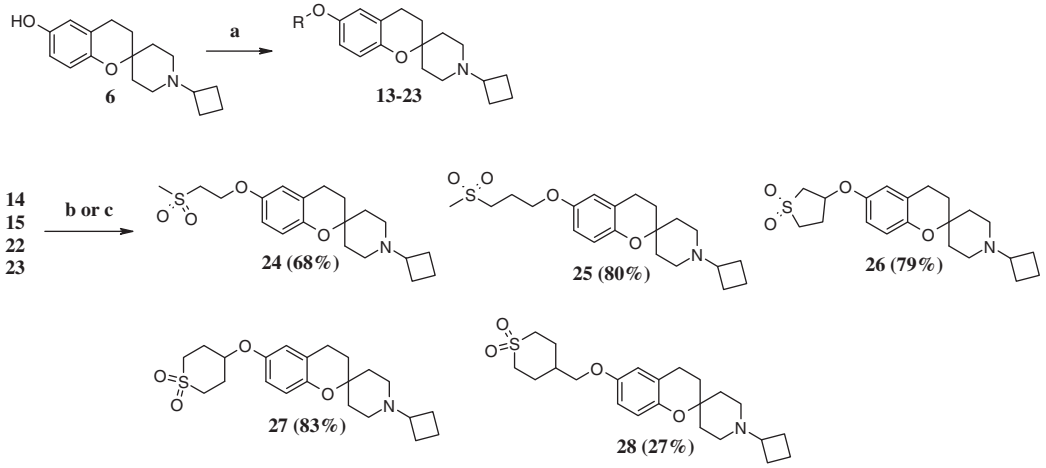


Scheme 1. Reagents and conditions: (a) 4-oxo-piperidine-1-carboxylic acid *t*-butyl ester, pyrrolidine, MeOH, reflux, 18 h, 87%; (b) $NaBH_4$, MeOH, 0 °C, 1 h; Et_3SiH, TFA, CH_2Cl_2, rt, 24 h, 95%; (c) cyclobutanone, $NaCNBH_3$, AcOH, THF, rt, 5 h, 74%; (d) (2-bromo-ethoxymethyl)-benzene, NaH, DMF, 65 °C, 4 h, 67%; (e) H_2, Pd/C, MeOH, cat. HCl, MeOH, 45 psi, 4 h, 92%; (f) propylene oxide/(*R*)-2-ethyl-oxirane/(*S*)-2-ethyl-oxirane/1,2-epoxy-2-methylpropane, 1 N NaOH, rt, 12 h.



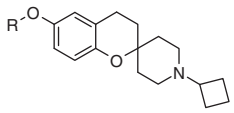
Scheme 2. Reagents and conditions: (a) ROMs/RBr/RCl, NaH, DMF, 85 °C, 1–18 h, 20–70%; (b) oxone, MeOH, rt, 4–24 h; (c) H_2O_2, AcOH, rt, 6 h (for **27**).

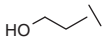
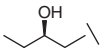
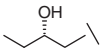
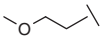
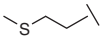
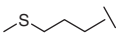
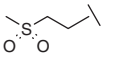
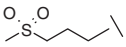
The structure–activity relationships (SARs) (Table 1) revealed that the acyclic alkyl alcohols, ethers, and thioethers, in general had favorable human H_3R binding affinities with K_i values less than 50 nM. The exception was the primary alcohol **8** (hH_3R K_i = 126 nM). To a lesser degree the rat H_3R affinity was weaker (K_i >50 nM) with the exclusion of **25** (rH_3R K_i = 41 nM). The order of hH_3R binding affinity in the alcohol series was tertiary > secondary ≫ primary (**12** > **9** ≫ **8**). In the case of the secondary alcohols, little difference was observed in the H_3R affinity between butan-2-ol isomers **10** and **11** and propan-2-ol **9**. Converting primary alcohol **8** to methylether **13** improved H_3R affinity by threefold. Replacing methoxy group with methylthio group (**13** to **14**) showed little affect on the H_3R affinity, and further increasing the alkyl chain from methylsulfanyl-ethoxy **14** (hH_3R K_i = 38 nM) to propoxy **15** (hH_3R K_i = 15 nM) improved hH_3R affinity by about twofold. The effect of the sulfur oxidation state on H_3R affinity was also investigated where the corresponding sulfone showed comparable affinity with the thioether (compare **14** with **24**, and **15** with **25**).

Next, the SAR was investigated with cyclic-ether and cyclic thioether analogues for comparison with their acyclic counterparts. In general, the cyclic derivatives showed improved H_3R affinity (Table 2). *S*-Tetrahydrofuran (THF) isomer **17** was about threefold more potent than methoxyethyloxy **13**, and the eudismic ratio for *S*-**17** was about 2 and 3 for human and rat H_3Rs compared to *R*-**16**. A number of changes in the cyclic series were tolerated, such as changing the THF to a tetrahydrothiophene (**18**) ring, expanding the THF to tetrahydropyran **21** (THP) and tetrahydrothiopyran **22**, or insertion of a methylene linker (**19**, **20**, and **23**) between the spiro-ether core and the cyclic group. In the five-member ring sulfur series oxidation of tetrahydrothiophene **18** to sulfone **26** showed little affect on H_3R affinity. However in the six-membered tetrahydrothiopyran series sulfur oxidation produced the most potent compounds in the series. The hH_3R K_i values were 7 nM for **27** and 4 nM for methylene spaced **28**.

Based on these results compounds **25**, **27**, and **28** were further profiled in the discovery flow. Compounds **25**, **27**, and **28** had

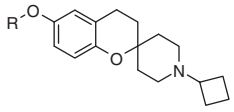
Table 1
H_3R binding data for sprio-benzopyran-piperidines

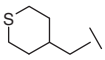
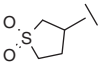
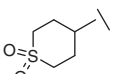
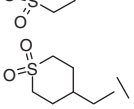


Compd	R	hH_3R K_i[a] (nM)	rH_3R K_i[a] (nM)
8		126	368
9		25	99
R-**10**		15	86
S-**11**		26	112
12		18	74
13		42	91
14		38	86
15		15	64
24		39	157
25		10	41

The assay-to-assay variation was typically within 2.5-fold.
[a] K_i values are an average of 2 or more determinations.

Table 2
H_3R binding data for sprio-benzopyran-piperidine



Compd	R	hH_3R K_i[a] (nM)	rH_3R K_i[a] (nM)
R-**16**		27	119
S-**17**		15	39
18		17	42
19		18	49
20		16	50
21		15	42
22		23	62
23		12	48
26		23	44
27		7	24
28		4	9

The assay-to-assay variation was typically within 2.5-fold.
[a] K_i values are an average of 2 or more determinations.

Table 3
Rat pharmacokinetics for **25**, **27**, and **28**

	25	**27**	**28**
iv (1 mg/kg)			
$t_{1/2}$ (h)	0.9 ± 0.2	1.7 ± 0.1	1.9 ± 0.5
V_d (L/kg)	1.2 ± 0.1	2.8 ± 0.5	3.6 ± 0.8
CL (mL/min/kg)	16 ± 1	19 ± 3	23 ± 5
po (5 mg/kg)			
AUC_{0-t} (ng h/mL)	586 ± 89	1791 ± 220	713 ± 33
C_{max} (ng/mL)	142 ± 26	460 ± 108	157 ± 5
%F	13 ± 2	48 ± 6	22 ± 2
B/P[a]	0.73 ± 0.01	1.0 ± 0.1	0.73 ± 0.05

[a] Based on the 6 h time point after 5 mg/kg po dosing.

excellent selectivity over hH_1R, hH_2R, and hH_4R subtypes with K_i values >10 μM, and showed acceptable metabolic stability in liver microsomes from human, mouse, rat, and monkey ($t_{1/2}$ >40 min). Acyclic sulfone **25** had IC_{50} values >30 μM for inhibition of cytochrome P450 enzymes (CYPs) CYP1A2, 2C9, 2C19, 2D6, and 3A4, indicating low potential for drug-drug interactions. Compared to **25**, cyclic sulfones **27** and **28** showed moderate 2D6 activity (**27** = 6.6 μM, **28** = 11 μM). Based on the metabolic stability profiles **25**, **27**, and **28** were evaluated for pharmacokinetic (PK) properties in the rat (Table 3). Acyclic sulfone **25** had acceptable iv PK but showed low oral bioavailability and low brain to plasma ratio. Compounds **27** and **28** showed acceptable PK profiles with longer iv half-lives, comparable clearance, and higher volume of distribution. Overall **27** had high oral exposure based on C_{max}, AUC_{0-t} and oral bioavailability. Further profiling **27** and **28** hERG activity (MDS Pharma Services PatchExpress) showed a difference, the methylene spaced linker compound **28** had a hERG IC_{50} >30 μM, compared to **27**, which was 7 μM.

Compound **27** was further screened against a panel of 65 GPCRs, ion channels and enzymes (MDS Pharma Services, LeadProfile screen). The targets identified from the broad selectivity screen with activity >50% inhibition at 10 μM concentration were nicotinic acetylcholine receptor (nACh, 63%), alpha adrenergic subtypes 2C (α_{2C}, 78%) and 1D (α_{1D}, 50%). Compound **27** had moderate binding to plasma protein from humans (77%) and rats (73%) and it showed an acceptable 27% free fraction in the rat brain homogenate, comparable to the free fraction in rat plasma. Compound **27** was tested for proof-of-concept in the rats in the dipsogenia assay[10,19] and produced significant 61% inhibition of RAMH-induced drinking at the highest dose of 3 mg/kg po.

In summary, a new series of constrained 4-alkoxy-[1′-cyclobutyl-spiro(3,4-dihydrobenzopyran-2,4′-piperidine)] ether analogues were designed and evaluated as H_3R antagonists. In general the series had high H_3R affinity in humans with hH_3R K_i <50 nM in both alkyl and cyclic ethers series. The cyclic-tetrahydrothiopyran sulfones **27** and **28** achieved single digit nanomolar hH_3R binding affinity and the methylene spaced analogue **28** had weak hERG (IC_{50} >30 μM) activity. Proof-of-concept in vivo functional activity in the rat dipsogenia model using **27** showed a significant 61% inhibition of RAMH-induced drinking at 3 mg/kg po. Further optimization and evaluation of the spiro series will be reported in due course.

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