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Reduction of hERG inhibitory activity in the 4-piperidinyl urea series of H3 antagonists

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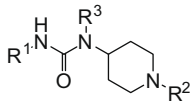
ABSTRACT

Structural features of the substituted 4-piperidinyl urea analogs **1**, responsible for the H3 antagonist activity, have been identified. Structure–activity relationship of the H3 receptor affinity, hERG ion channel inhibitory activity and their separation is described. Preliminary pharmacokinetic evaluation of the compounds of the series is addressed.

Histamine acts biologically by interacting with four distinct histaminergic receptor subtypes, namely the H1, H2, H3, and H4 receptors. H3 receptors are $G_{i/o}$ coupled, and are expressed primarily in the CNS on histaminergic neurons, which project into all main areas of the brain and part of the spinal cord. The H3 receptor was first recognized as a presynaptic autoreceptor inhibiting histamine synthesis and release via negative feedback.[1] In addition, the H3 receptor is involved in regulation of other neurotransmitter systems, such as glutamate, acetylcholine, norepinephrine, dopamine, GABA, and serotonin, owing to its expression on other types of neurons as a presynaptic heteroreceptor,[2] thus adding to the potentially broad application of H3-based drug therapy. Evidence from in vivo studies in animals suggests that H3 receptor ligands may be useful in the treatment of CNS disorders, characterized by deficient neurotransmitter signaling, such as ADHD, Alzheimer disease, and sleep-related disorders.[3] Additionally, given the known role of central histamine in the control of appetite, H3 receptor ligands can be expected and have been reported active in animal models of obesity.[4] Finally, H3 receptor-mediated modulation of norepinephrine levels in the sympathetic nervous system has been proposed as a means of maintaining vascular tone and relieving nasal congestion associated with allergic rhinitis.[5] While currently there are no marketed drugs acting at the H3 receptor, several companies have candidates in phase I and phase II clinical trials for dementia, narcolepsy, neuropathic pain, ADHD, schizophrenia, obesity, diabetes, and allergic rhinitis.[3,6]

Cardiovascular side effects—specifically, QT prolongation in monkeys—have been previously quoted as a major reason for the discontinued development of at least one promising clinical H3 candidate, ABT-239.[7] Attempting to foresee this issue at the lead optimization stage translates into the in vitro monitoring of hERG channel inhibitory activity for the structural series of interest.[8] Minimization of this activity as part of the ongoing H3 antagonist lead optimization program in the series defined by the 4-piperidinyl urea scaffold **1** is described.



1

Work in the current series was initiated after *N*-aryl-*N*′-benzyl-*N*-piperidinyl urea **2** was identified in screening as a structurally novel lead with moderate H3 in vitro activity (K_i (hH3R) = 36 nM). However, the high level of the accompanying hERG inhibition, initially suggested by the high-throughput Rb efflux screen[9] (see Table 1), necessitated efforts to minimize the potential liability of the series. Investigation of the three peripheral regions of the molecule, R^1, R^2, and R^3, while maintaining the piperidinyl urea core of **1** intact, was undertaken.

The SAR trends are presented in Table 1. In addition to the Rb efflux assay, most promising and/or prototypical compounds were characterized in the medium-throughput hERG IonWorks assay.[10]

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Table 1
H3 receptor affinity, Rb efflux, and hERG IonWorks SAR in the 4-piperidinyl urea series **1**

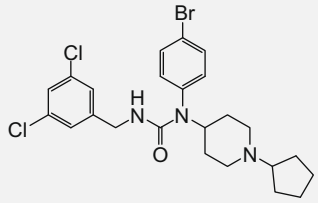
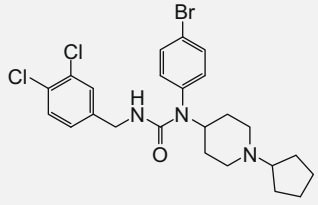
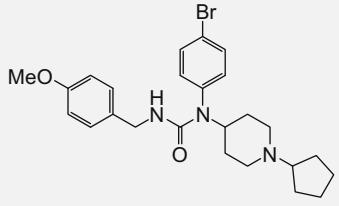
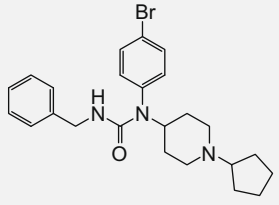
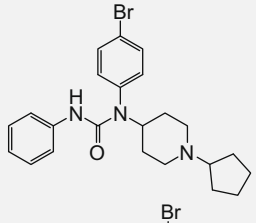
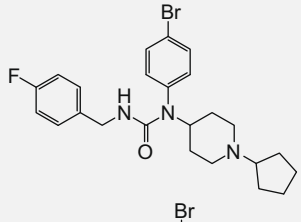
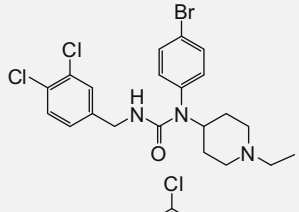
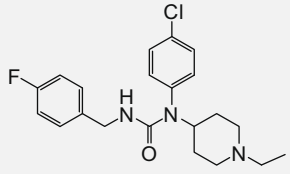
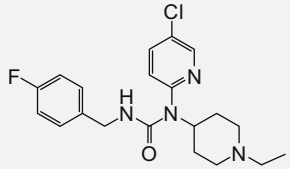
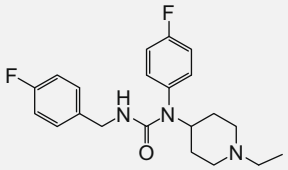
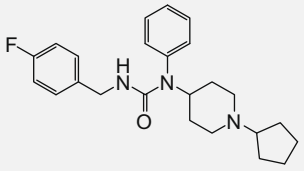
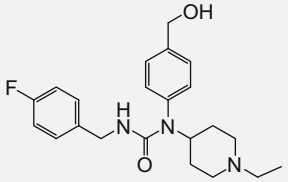
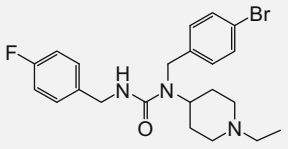
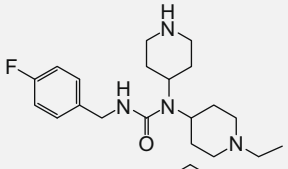
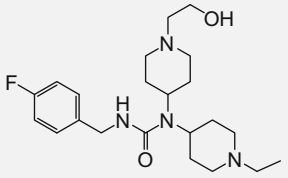
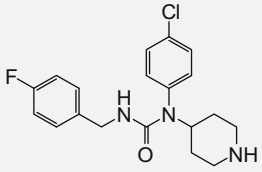
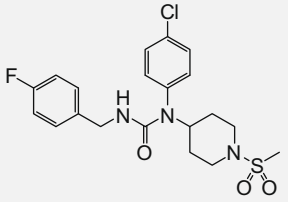
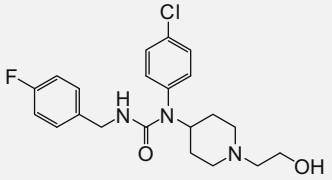
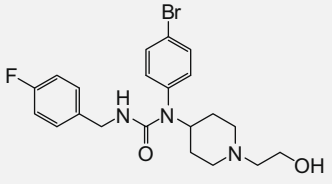
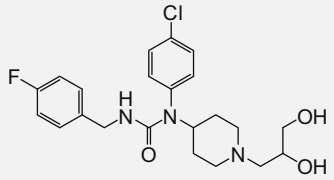
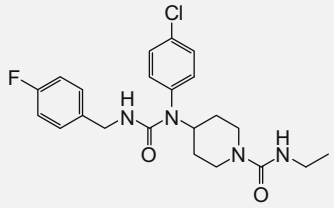
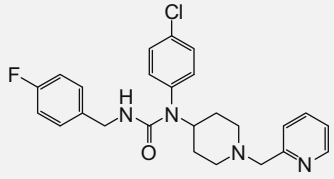
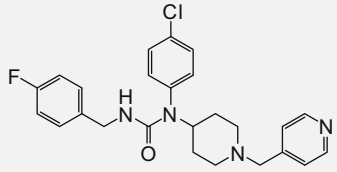
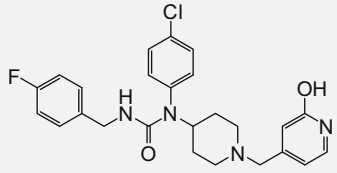
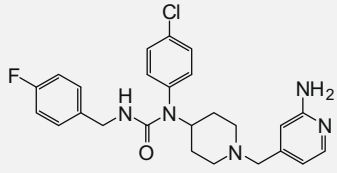
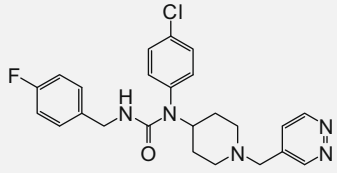
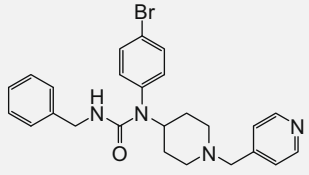
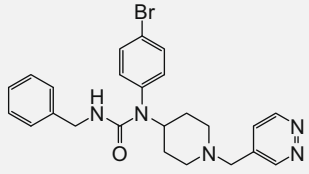
	Structure	K_i[a] (H3), nM	% Rb efflux inh[b] (5 μg/mL)	hERG IonWorks IC_{50}[c] (nM)
2		36	93	61
3		191	95	
4		47	78	
5		10	67	178
6		14	ND[d]	188
7		7	45	202
8		23	83	
9		7	42	6650
10		41	15	9190

Table 1 (*continued*)

	Structure	K_i[a] (H3), nM	% Rb efflux inh[b] (5 μg/mL)	hERG IonWorks IC_{50}[c] (nM)
11		447	18	
12		>1000	13	
13		560	ND	
14		>1000	ND	
15		>1000	9	
16		>1000	ND	
17		>1000	1	
18		858	0	
19		86	11	12,700
20		67	14	7880

(*continued on next page*)

Table 1 (*continued*)

	Structure	K_i[a] (H3), nM	% Rb efflux inh[b] (5 μg/mL)	hERG IonWorks IC_{50}[c] (nM)
21		>1000	4	
22		>1000	5	
23		>1000	33	
24		16	46	3810
25		624	28	
26		3	94	384
27		49	2	12,000
28		2	66	2310
29		10	38	13,800

[a] Recombinant human receptor binding assay. Values are means of two determinations. The range of duplicate values was typically less than threefold.
[b] Rb efflux assay. Values are means of at least two experiments. The standard deviation was generally no more than twofold.
[c] hERG IonWorks assay. Values are means of three experiments. The standard deviation was no more than ±30%.
[d] Not determined.

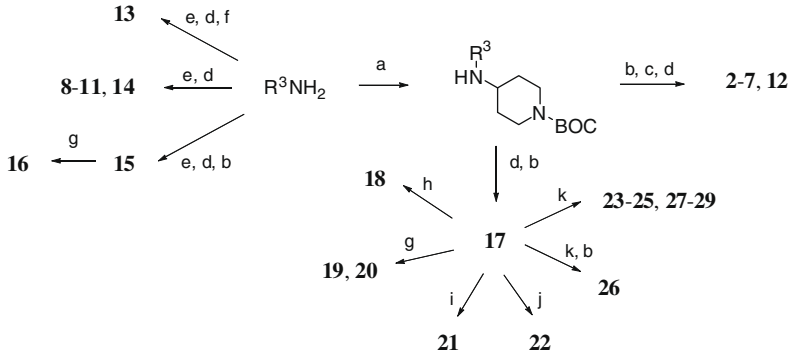


Figure 1. Synthetic approaches to the compounds of Table 1. (a) 1-BOC-4-Piperidone, $NaCNBH_3$, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) cyclopentanone, $NaBH(OAc)_3$, CH_2Cl_2; (d) R^1–NCO, Et_3N, THF, reflux; (e) 1-ethyl-4-piperidone, $NaBH(OAc)_3$, CH_2Cl_2; (f) TBAF, THF; (g) $BrCH_2CH_2OH$, Et_3N, THF, reflux; (h) CH_3SO_2Cl, Et_3N, CH_2Cl_2; (i) $BrCH_2CH(OH)CH_2OH$, K_2CO_3, DMF, 70 °C; (j) Et-NCO, Et_3N, THF; (k) Ar-CHO, $NaBH(OAc)_3$, CH_2Cl_2.

As discussed below, compounds from the series displayed similar trends in both assays, while a favorable combination of data from both assays was relied upon for compound selection. It was assumed from the beginning that viability of the series depended on the ability to maintain low nanomolar H3 receptor affinity. A benzyl group on the monosubstituted urea nitrogen (R^1) appeared to be well positioned for preserving H3 potency, while a 4-fluoro substituent was identified as a comparable alternative to hydrogen, both somewhat superior to the bulkier options (compounds **2**–**5**, **7**). Although some examples in which R^2 is an ethyl group showed a noticeable advantage over cyclopentyl analogs with regard to H3 receptor affinity (e.g., **8** vs **3**), overall these two substituents appeared comparable and were used interchangeably. The original 4-bromophenyl substituent, present in **2**, could be replaced with 4-chlorophenyl (e.g., **9**), but otherwise could not be changed without drastic reduction in H3 receptor affinity. In particular, while a reduction in lipophilicity was achieved by transition to 4-fluorine (**11**), 4-hydrogen (**12**), or 4-hydroxymethyl (**13**) and was counted on to reduce hERG inhibitory activity, a significant drop in H3 activity was observed.

The region of the molecule adjacent to the piperidine ring (R^2) was then considered for structural modifications. In view of the strongly lipophilic nature of R^1 and R^3 possibly contributing to the hERG activity, an overall increase in hydrophilicity, coupled with the attenuation of basicity of the piperidine nitrogen, seemed to be a prudent approach.[11] Attention was primarily concentrated on the 4-chlorophenyl subseries, derived from the piperidine **17**, with an anticipated advantage in hERG profile over the bromo analogs, as suggested by IonWorks data on analog **9**.

As can be seen from Table 1, H3 SAR of the R^2 region remains tight, similarly to the other parts of the molecule. Most of the substitutions, targeted to increase the hydrophilicity of the molecule or reduce the pK_a of the piperidine nitrogen, resulted in a drastic reduction of H3 activity (e.g., **18**, **21**, **22**). β-Hydroxyethyl substitution (**19** and **20**) was a notable exception. In a further effort to improve H3 receptor affinity, select heterocycles—in particular, 4-aza-6-membered heteroaryls—were identified as the best option. The extent of their substitution, however, was greatly limited by the combined H3 and hERG SAR requirements, as evidenced by compounds **25** and **26**. While the basic 2-amino group in **26** retained H3 activity, it negatively affected the hERG profile. Ultimately, compound **29** appeared to offer the best balance between H3 activity and reduced hERG inhibition, with the effect of 4-bromophenyl substituent largely neutralized by the pyridazine ring. Not surprisingly, hERG activity of the current series appears to correlate positively with the overall lipophilicity.[11] As gauged by *c*log *P*, a drastic lipophilicity decrease from **2** (*c*log *P* = 6.56)[12] to **29** (*c*log *P* = 2.98) is accompanied by a sharp reduction in hERG inhibition. In fact, compounds **29** and **27** (*c*log *P* = 2.98) have the lowest *c*log *P* values among compounds in Table 1, except for the completely H_3-inactive **16**. While this *c*log *P*–IonWorks IC_{50} correlation is observed for compounds of functional continuity—such as haloaryl analogs **7** (*c*log *P* = 5.27) and **9** (*c*log *P* = 4.44))—*c*log *P* values do not seem to predict well the effects of the noncontinuous functional changes, also previously referred to as 'discrete structural modifications'.[11] For example, 2-aminopyridine **26** shows substantially higher activity in the hERG IonWorks assay than 2-unsubstituted pyridine **24**, despite the lower *c*log *P* value (3.88 vs 4.20, respectively). Furthermore, one could argue that the anticipated effect of hydroxy group in **19** is overpredicted by its lower *c*log *P* value (3.37) relative to the deshydroxy analog **9** (*c*log *P* = 4.44), considering their comparable IonWorks profiles. Overall, the link between the physicochemical properties and hERG profiles of the compounds of the current series appears traceable but tentative. Synthetic approaches to the compounds of Table 1 are shown in Figure 1.

Preliminary pharmacokinetic evaluation revealed oral bioavailability of **29** in the rat ($AUC_{0-6\ h}$ = 3020 h nM (10 mg/kg, po)),[13] although with a half-life just close to 1 h. PK limitations of **29** appear to be likely caused by rapid metabolism rather than inadequate absorption as suggested by high in vitro permeability and solubility characteristics (Caco-2: 269 nm/s; aqueous kinetic solubility (pH 7.4) >250 μM). However, more in-depth pharmacokinetic or metabolic studies were not conducted at this point. The profile of **29** clearly benefits from the increased polarity. Thus, more lipophilic analogs **7** and **10** produced lower exposures after the same oral dose in the rat ($AUC_{0-6\ h}$ of 250 and 340 h nM, respectively), while still showing no sign of potential problem with permeability (Caco-2: 116 and 72 nm/s, respectively). Compound **29** was selected for further profiling, results of which will be reported in due course. Among other issues, in vivo implications of the reduced hERG inhibitory activity in vitro would certainly be of major interest.

In conclusion, a novel series of H3 antagonists, based on the 4-piperidinyl urea core, has been identified. Excellent separation between H3 activity and hERG ion channel inhibition has been achieved, and preliminary oral bioavailability in rats has been demonstrated.

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