

Novel Benzamide-Based Histamine H₃ Receptor Antagonists: The Identification of Two Candidates for Clinical Development

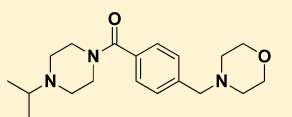
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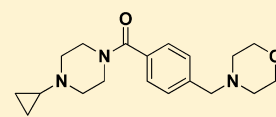
Supporting Information

ABSTRACT: The preclinical characterization of novel phenyl(piperazin-1-yl)methanones that are histamine H₃ receptor antagonists is described. The compounds described are high affinity histamine H₃ antagonists. Optimization of the physical properties of these histamine H₃ antagonists led to the discovery of several promising lead compounds, and extensive preclinical profiling aided in the identification of compounds with optimal duration of action for wake promoting activity. This led to the discovery of two development candidates for Phase I and Phase II clinical trials.

KEYWORDS: Histamine H₃ antagonists, phenyl(piperazin-1-yl)methanones, histamine



11h
human H₃R K_i=2.5 nM
human H₃R pA₂=8.94
human t_{1/2}=49.1-56.1 h



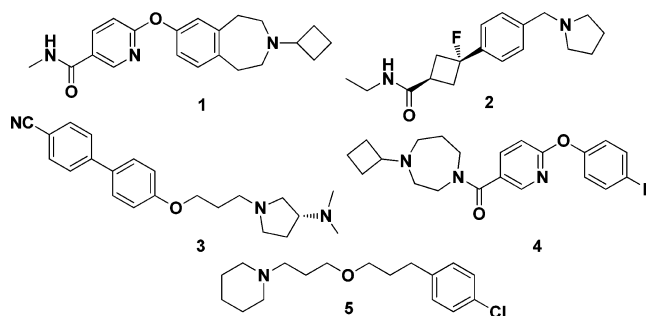
11j: Bavisant
human H₃R K_i=5.4 nM
human H₃R pA₂=8.36
human t_{1/2}=13.9-22.1 h

Following the discovery that the histamine H₃ receptor is abundantly expressed in the brain, numerous research groups have investigated the effects of modulation of the histamine H₃ receptor on brain function. These efforts have demonstrated that histamine H₃ receptors regulate the sleep-wake cycle and that histamine H₃ antagonists promote wake and have potential utility for the treatment of a variety of indications, including excessive daytime sleepiness, narcolepsy, and attention deficit hyperactivity disorder (ADHD), among others.¹ More recently, several pharmaceutical companies embarked on medicinal chemistry efforts to advance histamine H₃ antagonists into the clinic for a variety of indications, and numerous clinical trials have been conducted over the past 5–10 years. The details of these efforts have been reviewed multiple times.^{1–6}

Select examples of compounds that have been reported to advance into the clinic include the GSK compound GSK-189,254 (1), Pfizer's PF-03654746 (2),⁷ A-331440 (3) from Abbott, and JNJ-39220675 (4).⁸ Several of these compounds have advanced into Phase II trials for therapeutic intervention in narcolepsy, ADHD, and allergic rhinitis. To date, the most advanced candidate appears to be pitolisant (5).⁹

Janssen's efforts toward the preclinical characterization and clinical development of histamine H₃ antagonists have been ongoing for quite some time. During this research a variety of potent histamine H₃ antagonists were discovered, and several compounds advanced into preclinical toxicology studies. However, while advancing these compounds it was noted that some of the compounds induced varying degrees of

phospholipidosis, a phenomenon that has also been noted by other researchers in the field.^{7,10}



As it is well-known that phospholipidosis can be associated with cationic amphiphilic drugs, efforts to generate optimized histamine H₃ antagonists with respect to physical properties and duration of action were pursued in order to advance compounds into the clinic devoid of phospholipidosis potential while maintaining a duration of action appropriate for a compound that promotes wakefulness. This report describes one aspect of the progress toward those goals with a series of phenyl(piperazin-1-yl)methanones.

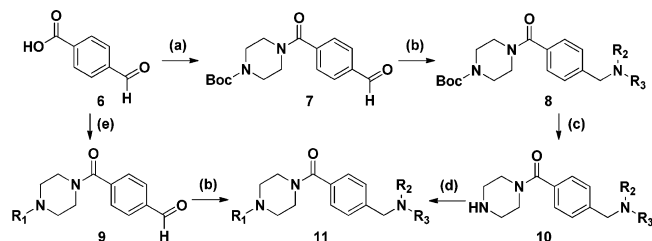
These piperazine amides shown were synthesized by one of the two routes shown in Scheme 1. As such, 4-formylbenzoic acid (6) was combined with *tert*-butyl piperazine-1-carboxylate

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Scheme 1. Synthesis of Compounds 11^a

^aReagents and conditions: (a) (dimethylamino)propyl-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate, *N*-methylmorpholine, *tert*-butyl piperazine-1-carboxylate, CH₂Cl₂; (b) R₂R₃NH, HOAc, NaBH(OAc)₃, CH₂Cl₂; (c) trifluoroacetic acid, CH₂Cl₂; (d) various aldehydes, HOAc, NaBH(OAc)₃, CH₂Cl₂; (e) (dimethylamino)propyl-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate, various piperazines, CH₂Cl₂.

to form 7, which was then condensed with an amine to form 8. Removal of the protecting group followed by a reductive amination gave the desired compounds 11. Alternately, 4-formylbenzoic acid reacts with a substituted piperazine to directly install R₁, and the resulting aldehyde 9 is converted to the desired compounds 11 via reductive amination. The required piperazines can be made from *tert*-butyl piperazine-1-carboxylate by known methods.

The initial set of structures that were prepared were high affinity compounds with human binding affinities of <100 nM (11a–11d, Table 1).¹¹ The histamine H₃ receptor affinity could be further improved by installing larger/more lipophilic substituents on the benzyl amine (i.e., 11e–g); however, efforts focused on the smallest/most polar groups that provided sufficient histamine H₃ affinity to move forward. This work led to the preparation of the morpholine derivatives 11h–11j, all of which are high affinity human histamine H₃ antagonists. In addition, since one focus of these efforts was to modify the physical properties of our leads, a few 4-fluoropiperidines were made (11k–11m) and were also found to be high affinity antagonists. The morpholines 11h–j and the 4-fluoropiperidines 11k–m were expected to have pK_as lower than the piperidine 11g, and the 4-fluoropiperidines have the highest A log P_s as shown in Table 1. As two examples, comparing 11g to 11h (piperidine vs morpholine) installation of the morpholine lowers the A log P and the pK_a of the benzyl nitrogen, whereas comparing 11h to 11k (piperidine vs 4-fluoropiperidine) the A log P is higher for the 4-fluoropiperidine and the calculated pK_a of the benzyl nitrogen is slightly lower.¹²

Next, focusing on the basicity of the piperazine nitrogen, several cyclopropyl and cyclobutyl piperazines were prepared and profiled. Again, high affinity compounds were obtained (11i–11j, 11l–11m), and again, these changes (i.e., isopropyl to cyclopropyl or cyclobutyl) were expected to modulate the pK_a of the piperazine nitrogen to which these groups were attached.

Rat affinity data for a select group of the compounds in Table 1 as well as pA₂ data in rat and human, which demonstrate that the key compounds in this series are all high affinity histamine H₃ antagonists, are detailed in Table S1 in the Supporting Information.

Table 2 shows liver microsomal stability, hERG data, and Caco-2 data for some of the more interesting compounds that were prepared. The compounds have moderate to high liver microsomal stability, none have significant interactions with the

Table 1. Binding Data for the Human H₃ Receptor for Compounds 11

Compd	R ₁	-NR ₂ R ₃	MW (Alog P) ^a	Human H ₃ K _i (nM) ^b
11a,	H ₃ C-		301.43 (1.98)	24 ^c
11b,	H ₃ C-		303.40 (0.75)	22 ^c
11c,	<i>i</i> -Pr-		289.42 (1.79)	5.0 ^c
11d,	<i>i</i> -Pr-		317.47 (2.49)	6.0 ^c
11e,	<i>i</i> -Pr-		315.46 (2.25)	1.0 ^c
11f,	<i>i</i> -Pr-		343.51 (3.16)	1.0 ^c
11g,	<i>i</i> -Pr-		329.49 (2.71)	1.3 ± 0.4
11h,	<i>i</i> -Pr-		331.46 (1.48)	2.5 ± 0.4
11i,	<i>c</i> -Bu-		343.47 (1.70)	1.3 ± 0.4
11j,	<i>c</i> -Pr-		329.44 (1.24)	5.4 ± 0.8
11k,	<i>i</i> -Pr-		347.48 (2.16)	1.5 ^d
11l,	<i>c</i> -Bu-		359.49 (2.38)	0.7 ^e
11m,	<i>c</i> -Pr-		345.46 (1.92)	2.0 ^d

^aCalculated A log P. ^bK_is are the mean of at least three experiments in triplicate, unless otherwise stated. ^cn = 1 (in triplicate), ^dn = 2 (in triplicate); K_i ± SD is reported.

hERG channel, and all compounds tested were highly permeable with low to moderate efflux potential. Consequently, these compounds were tested in vivo for oral exposure, duration of action, and target engagement as measured by ex vivo autoradiography.

In order to further demonstrate the specificity of these compounds, 11g–j were also tested in a commercial panel of

Table 2. RLM and HLM Stability, and in Vivo Data for Compounds 11g–m

compd	RLM stability ^a	HLM stability ^b	hERG ^c	Caco-2 ^d
11g	n.d.	n.d.	>30 μ M	12.4/14.8
11h	n.d.	65.0%	>10 μ M	22.4/20.9
11i	49.6%	85.4%	>10 μ M	71.2/22.4
11j	44.1%	96.1%	>10 μ M	108/37.8
11k	50.0%	84.8%	>10 μ M	n.d.
11l	n.d.	n.d.	>10 μ M	n.d.
11m	26.8%	83.6%	>10 μ M	n.d.

^aStability in rat liver microsomes. Data reported as percent remaining after a 15 min incubation. ^bStability in human liver microsomes. Data reported as percent remaining after a 15 min incubation. ^chERG IC₅₀ as measured in an [³H]-astemizole competition binding assay in HEK-293 cells expressing the hERG channel. ^dData shown are P_{app} A–B/B–A ($\times 10^{-6}$) cm/s.

50 ion channel, receptor, and transporter assays (Eurofins-CEREP, <http://www.eurofins.com/>). None of the compounds had any significant affinity (at 1 μ M) for any of these targets.

Table 3 shows rat PK parameters for compounds 11g–m. The i.v. $t_{1/2}$ s trend as expected. Comparing 11g with 11h, a

Table 3. Rat Pharmacokinetic Parameters for Compounds 11g–m

compd	C_l (mL/min/kg) ^a	V_{ss} (L/kg) ^b	$t_{1/2}$ (h) ^c	%F ^d
11g	26.1 \pm 5.3	39.4 \pm 8.0	20.0 \pm 4.7	52 \pm 26
11h	12.8 \pm 5.5	3.6 \pm 1.6	3.2 \pm 0.1	62 \pm 1
11i	34.9 \pm 12.9	6.4 \pm 2.9	2.1 \pm 0.1	85 \pm 26
11j	21.6 \pm 1.8	1.7 \pm 0.1	0.9 \pm 0.1	112 \pm 35
11k	44.2 \pm 12.5	29.2 \pm 10.2	7.6 \pm 1.1	17 \pm 7
11l	113.3 \pm 13.6	20.3 \pm 5.2	2.1 \pm 0.6	31 \pm 41
11m	41.4 \pm 17.1	3.9 \pm 1.7	1.1 \pm 0.2	14 \pm 10

^aClearance. ^bVolume of distribution at steady state. ^ci.v. half-life. ^dAll data are mean \pm SD.

change from piperidine to morpholine substantially reduced the half-life, and as expected, this appears to be driven primarily by a reduction in V_{ss} , which can be attributed to a reduction in log P and pK_a . Similarly, comparing 11h to 11j, the half-life is reduced as the expected pK_a is reduced even further.

The PK profile of both cyclobutyl compounds (11i and 11l) appears to be influenced by a combination of log P , pK_a , and increased clearance, possibly due to oxidation of the cyclobutyl group. Similar trends are observed with the 4-fluoropiperidine compounds 11k–m.

The pK_a s, log P s and log $D_{7,4}$ s of select compounds were calculated in order to confirm earlier estimations. A summary of this data is shown in Table 4.

The measured data confirmed the assumption that a cyclopropyl substituent would substantially reduce the pK_a with little effect on log P , although as shown the calculated pK_a did not predict this observation.¹³ There is at least one literature report that suggests that cyclopropyl amines are

Table 4. Physical Chemical Data for Compounds 11h–j

compd	pK_a (calcd)	pK_a (meas)	log P	log $D_{7,4}$
11h	8.5, 6.2	7.6, 6.2	0.55	0.13
11i	7.8, 6.2	7.4, 6.5	2.09	1.77
11j	8.5, 6.2	6.5, 5.3	0.89	0.86

approximately ten times less basic than aliphatic amines;¹⁴ however no direct experimental evidence has been reported (although one reported calculation corroborates the literature suggestion).¹⁵ Illustrating the point, the measured pK_a values for 11j were significantly lower than that predicted through calculation (using the Pallas software package from CompuDrug, Inc.) and also were significantly lower than that measured for 11h and 11i. The data here corroborate literature suggestions.

Next, key compounds were profiled for their ability to distribute into the rat brain and bind to the histamine H₃ receptor. To do this, drug was administered and drug concentrations in the brain and plasma were measured along with histamine H₃ receptor occupancy. These data are shown in Table 5. As shown, all the compounds were able to penetrate

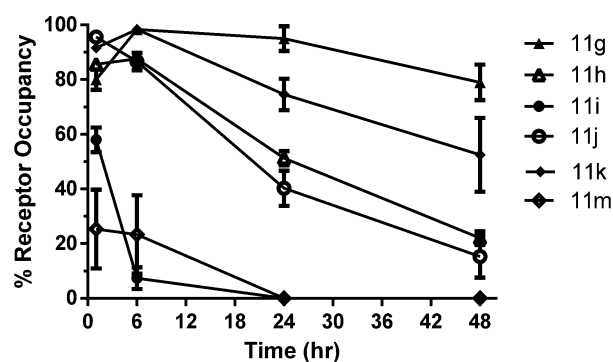
Table 5. Drug Levels in Rat Brain and Plasma and Levels of ex Vivo H₃ Receptor Occupancy for Compounds 11

compd	conc. (brain) ^{a,c}	R.O. ^{b,c}
11g	0.48 \pm 0.14	90 \pm 2
11h	5.37 \pm 1.09	86 \pm 1
11i	8.10 \pm 0.53	96 \pm 2
11j	2.54 \pm 0.36	58 \pm 8
11k	1.82 \pm 0.51	92 \pm 2
11m	0.54 \pm 0.14	25 \pm 25

^aConcentration in μ M at 1 h in brain following a 3 mg/kg p.o. dose. ^bReceptor Occupancy at 1 h Following a 3 mg/kg p.o. Dose. ^cMean \pm SD.

the brain and occupy the histamine H₃ receptor.¹⁶ Distribution into the brain varied, but the brain concentrations measured for all compounds was high, and with the exception of compound 11m, all of the compounds in Table 5 showed good receptor occupancy.

Considering the overall rat PK and distribution parameters observed, compounds 11g–k and 11m were all eventually chosen for further profiling. Toward that end, time course ex vivo H₃ receptor occupancy data in rat was generated for these compounds and are shown in Figure 1. This data provides an indication of duration of action. Dose response related to receptor occupancy is shown in Figure S1 and PK parameters for canine and mouse are shown in Table S2 (detailed in the Supporting Information). All of the compounds show robust target engagement, and as expected based on the half-lives reported in Table 3, the compounds had varying duration of

**Figure 1.** Ex vivo H₃ receptor occupancy with compounds 11g–k and 11m at 3 mg/kg in rat striatum: time dependency after oral administration.

action. In addition, the PK trends in canine and mouse are similar to those observed in rat. As an example, focusing on a comparison of **11h** and **11j**, volume, clearance, and $t_{1/2}$ were reduced in both cases for **11j**, which results in a reduced half-life observed for **11j**. Figure 1 compares compounds **11h** and **11j** demonstrating the shorter duration of action for the cyclopropyl compound **11j**.

Compounds **11a**–**11h** were the first set of compounds to be prepared and profiled; of that set it appeared that **11h** had the most desirable balance of potency, PK, target engagement, and duration of action. Therefore, this was the first compound in this series to be advanced into rat and dog safety toleration studies.

In order to support preclinical toleration studies and other first in human enabling studies, compound **11h** was prepared on larger scale by a slightly different synthetic route than the one used to enable medicinal chemistry profiling. The synthesis is described in detail in the Supporting Information.

Compound **11h** is a BCS Class I nonhygroscopic crystalline solid as the bis-maleate salt. It has a very high free fraction in human plasma (% bound 12.4%), and no CYP interactions were noted (IC_{50} s all >40 μ M at CYP 1A2, 2C9, 2C19, 2D6, and 3A4). Numerous additional in vitro and in vivo safety studies were completed in order to support potential first in human studies, and a summary of those studies is reported here.

In rats, after oral administration, **11h** penetrates the blood–brain barrier and occupied histamine H_3 receptor sites. As expected for this class of compound, administration of **11h** in rats during the light sleep phase produced a significant increase in time spent awake (~1 h) during the first 6 h post-treatment, and this was associated with a decrease in NREM sleep duration while REM sleep was not affected (Figure S2 in the Supporting Information). This occurred in the absence of any increase in locomotor activity and differentiates the compound from amphetamine like stimulants. Administration of **11h** also increased acetylcholine (ACh) levels in the frontal cortex of freely moving rats and in a 7-trial passive avoidance model, **11h** decreased the number of trials needed to increase the latency to enter the aversive chamber, consistent with pro-cognitive effects (data not shown).

Compound **11h** had no effect in models predictive of cardiovascular toxicity, including hERG channel binding and models of QTc prolongation. Overall, the compound was well tolerated in the mouse, rat, and dog. Administration of up to 250 mg/kg of **11h** orally to rats for up to 28 days induced mild and sporadic salivation and decreased activity. Minor decreases in body weight, food consumption, and clinical pathology alterations were considered related to **11h** treatment but nonadverse. The rat NOAEL was 25 mg/kg/day. In dogs, administration of **11h** for 5 days within the dose range of 10 to 75 mg/kg/day resulted in no adverse findings. These data supported progression to first in human studies. In human, the mean elimination half-life for the 2 and 5 mg dose groups of **11h** was 49.1 and 56.1 h, respectively. Given these data, and that fact that significant insomnia was reported upon dose escalation, the team looked for back-up compounds with significantly reduced duration of action.

One such compound, **11j**, appeared promising since this compound had significantly reduced duration of action in all preclinical species (Tables 3 and S2 (Supporting Information), and Figure 1). Compound **11j** is also a BCS Class I nonhygroscopic crystalline solid as the bis-HCl salt. In

human liver microsomes, **11j** is not a potent inhibitor of the various CYPs. In rats, **11j** penetrates the blood–brain barrier after systemic administration and effectively occupies histamine H_3 receptor sites (>80% receptor occupancy at 10 mg/kg SC, corresponding to a maximum plasma concentration [C_{max}] of 1933 ng/mL) (Figure S1, Supporting Information). Therefore, the anticipated plasma concentration for maximal receptor occupancy in humans was anticipated to be approximately 200 ng/mL as the potency of **11j** is about 10-fold higher for the human receptor than for the rat receptor.

In the rat, the administration of **11j** resulted in a significant increase in time spent awake, an increase in acetylcholine (ACh) levels in frontal cortex, and pro-cognitive effects in a 7-trial passive avoidance model.

Compound **11j** was devoid of any cardiovascular liability in preclinical species including QTc prolongation. The compound (Bavisant) was also well tolerated in rats and dogs and the safety margins supported first in human dosing for this compound. No evidence of phospholipidosis was observed in these studies. Following single oral doses, **11j** was rapidly absorbed with peak concentrations observed 0.5 to 4 h postdose. The C_{max} increased dose-proportionally over 100 to 400 mg. The area under the concentration–time curve extrapolated to infinity (AUC_{inf}) was dose-proportional between 10 and 30 mg and in the 100 to 400 mg dose range. The mean $t_{1/2}$ ranged from 13.9 to 22.1 h. The reduced human $t_{1/2}$ observed with **11j** validates our assertion that reduced duration of action in human could be achieved by modification of the physical properties of this series of H_3 antagonists.

In conclusion, we identified a series of novel, potent histamine H_3 antagonists that demonstrated that improved human pharmacokinetic profiles can be obtained by tuning the physical properties of these ligands in order to reduce tissue retention time and $t_{1/2}$ in vivo. Optimization of these ligands led to the discovery of Bavisant, a histamine H_3 ligand useful for clinical investigation of the utility of histamine H_3 antagonists.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details and analytical data for compounds **11a**–**m**, additional Figures and Tables. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

ADHD, attention deficit hyperactivity disorder; *i*-Pr, isopropyl; *c*-Pr, cyclopropyl; *c*-Bu, cyclobutyl; CYPs, cytochrome P450s

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