4-Phenoxypiperidines: Potent, Conformationally Restricted, Non-Imidazole Histamine H_3 Antagonists

Curt A. Dvorak,*,† Richard Apodaca,† Ann J. Barbier,† Craig W. Berridge,‡ Sandy J. Wilson,† Jamin D. Boggs,† Wei Xiao,† Timothy W. Lovenberg,† and Nicholas I. Carruthers†

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., 3210 Merryfield Row, San Diego, California 92121, and Department of Psychology, University of Wisconsin, 1202 W. Johnson Street, Madison, Wisconsin 53706

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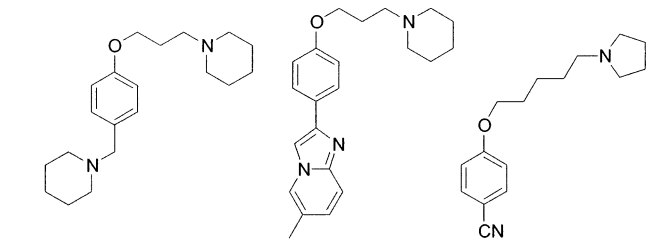
Two new series of 4-(1-alkyl-piperidin-4-yloxy)-benzonitriles and 4-(1-isopropyl-piperidin-4-yloxy)-benzylamines have been prepared. In vitro activity was determined at the recombinant human H_3 receptor and several members of these new series were found to be potent H_3 antagonists. The present compounds contain a 4-phenoxypiperidine core, which behaves as a conformationally restricted version of the 3-amino-1-propanol moiety common to the many previously described non-imidazole histamine H_3 ligands. One selected member of the new series, 4-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-morpholine (**13g**), was found to be a potent, highly selective H_3 receptor antagonist with in vivo efficacy in a rat EEG model of wakefulness at doses as low as 1 mg/kg sc.

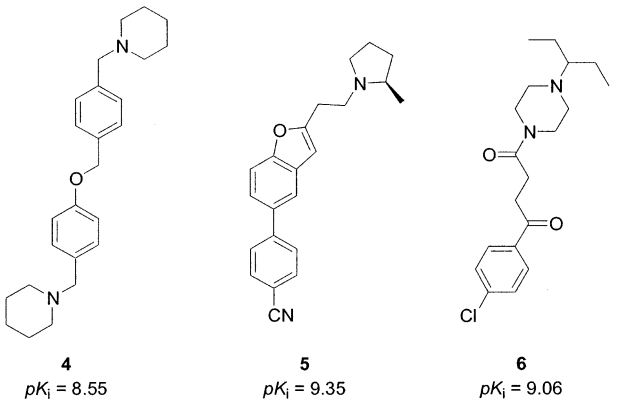
Introduction

Histamine[1] directs a complex array of physiological actions through four distinct G protein-coupled receptors known simply as H_1, H_2, H_3 and H_4.[2] The histamine H_1 and H_4 receptors are associated with inflammatory and immune responses while the H_2 receptor mediates gastric acid secretion. The H_3 receptor,[3] which has been cloned and subsequently found to be predominantly expressed in the central nervous system (CNS),[4] has been determined to be a presynaptic autoreceptor regulating the synthesis[5] and release of histamine through negative feedback. In addition, H_3 receptors were found to have a modulatory effect on the release of other neurotransmitters in the CNS including dopamine, noradrenalin, GABA, serotonin, and acetylcholine.[6] These effects, in turn, have prompted suggestions for therapeutic applications of H_3 agonists and antagonists in the areas of Parkinson's and Alzheimer's diseases, schizophrenia, memory, learning and sleep disorders.[7] There have also been reports that H_3 antagonists alone or in combination with a H_1 antagonist may be useful for the treatment of upper airway allergic responses.[8] Compared with the successes of marketed drugs targeting H_1 and H_2 receptors, the potential of histamine H_3 receptor antagonists or agonists has yet to be fully realized.[9]

Since the discovery of the H_3 receptor in 1983, many research groups have been interested in developing potent and selective ligands. Through the late 1990s, most efforts in the field were directed toward the discovery of imidazole-based ligands, many of which have found utility as pharmacological tools.[10] The basic structural motif common to these ligands was the 4(5)-substituted imidazole ring, which is present in the endogenous ligand histamine, linked to a polar group and a lipophilic residue. However, the imidazole heterocycle is a potential metabolic liability[11] and early efforts to identify imidazole replacements were met with only moderate success.[12] The more recent identification of imidazole-free ligands represents a significant advancement in the histamine H_3 field.[13] Examples of non-imidazole H_3 ligands include 4-(aminoalkoxy)benzylamine **1**,[14] imidazopyridine **2**,[15] *N*-(5-phenoxypentyl)-pyrrolidine **3**,[13a] 1-(4-(phenoxymethyl)benzyl)piperidine **4**,[16] 2-aminoethylbenzofuran **5**,[17] and 1-alkyl-4-acylpiperazine **6**[18] (Chart 1).

Chart 1. Representative Non-Imidazole Antagonists with Activities at the Cloned Recombinant Human Histamine H_3 Receptor or Rat Cortex





* To whom correspondence should be addressed. Phone: 858-784-3284. Fax: 858-450-2089. E-mail: cdvorak@prdus.jnj.com.
† Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
‡ University of Wisconsin.

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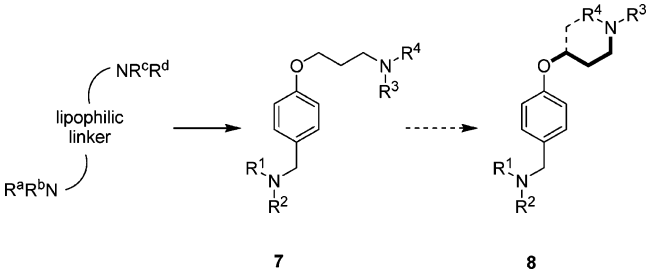
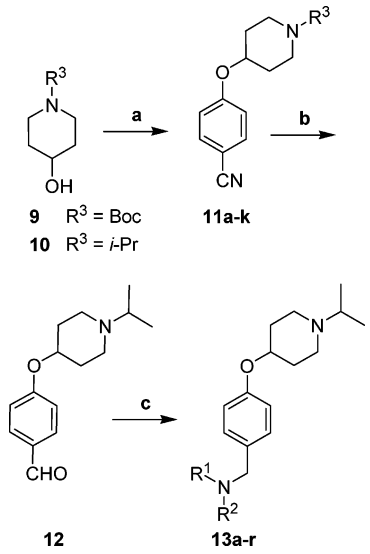


Figure 1. Design of 4-phenoxypiperidines (**8**).

As previously reported, our ligand design began with an attempt to develop a pharmacophore model to account for the activity of the structurally diverse nonimidazole H_3 ligands in the literature as well as those found in our own compound collection. Three common structural motifs were identified: (1) a basic nitrogen atom; (2) an aromatic ring; and (3) an additional polar functional group adjacent to the lipophilic core. A readily accessible chemical series that incorporates these structural features is depicted by the generic structure **7**, seen in Figure 1, which ultimately led to the discovery of the potent H_3 antagonist **1**, JNJ-5207852.[19] Having identified a general template for the design of H_3 antagonists, we set out to further explore this model by examining modifications to the ubiquitous propyloxy piperidinyl side chain present in **1**. Thus, we now report the discovery of a conformationally restricted replacement of the propyloxy piperidine moiety. We envisioned that this could be accomplished by simply "tying back" one of the alkyl residues present on the basic amine onto the carbon chain of the propyloxy linker (Figure 1). This would result in a cyclic structure for the tether linking the basic amine to the central aromatic core with an overall reduction in the number of rotatable bonds.[20] A key design element was to conserve the number of atoms between the central aromatic ring and the basic amine. Thus, we chose to explore 4-hydroxypiperidine as a potential replacement for the 3-amino-1-propanol functionality. Another design element for the development of this new ligand template was that the chemistry must be concise, modular and driven by carbon−heteroatom bond connections[21] allowing for the rapid synthesis of target compounds. This report describes the synthesis, human H_3 binding affinities and functional activities of several members of this new series. Behavioral data are also presented for a selected member of the series.

Chemistry. The syntheses of 4-(1-alkyl-piperidin-4-yloxy)-benzonitriles **11a**−**k** and 4-(1-isopropyl-piperidin-4-yloxy)-benzylamines **13a**−**r** were completed according to the route shown in Scheme 1. To install the aryl ether unit, the sodium salt of *N*-Boc-4-hydroxypiperidine or *N*-isopropyl-4-hydroxypiperidine was prepared in DMF with sodium hydride and then treated with 4-chlorobenzonitrile thus affording 4-phenoxypiperidines **10** via nucleophilic aromatic substitution. For compounds **11a**−**d** and **11f**−**k**, the *tert*-butyl carbamate (R^3 = Boc) group was removed with HCl and the resulting secondary amine provided a flexible intermediate that was alkylated via reductive amination.[22] The installation of the second basic polar group present in 4-(1-isopropyl-piperidin-4-yloxy)-benzylamines **13a**−**r** required a simple functional group interconversion of the aromatic nitrile moiety into the requisite benzaldehyde. This was accomplished with diisobutylaluminum hydride (DIBAL-H), providing the key aldehyde **12** directly from benzonitrile **11e**. Benzaldehyde **12** was then condensed with various primary and secondary amines by reductive amination to give the corresponding benzylamines.

Scheme 1. Synthesis of Conformationally Restricted H_3 Ligands[a]



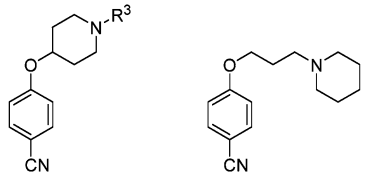
[a] Reagents and conditions: (a) **9** (R^3 = Boc): i. NaH, DMF, 4-chlorobenzonitrile, 65 °C; ii. HCl, MeOH, rt., 81% overall; iii. carbonyl analogue, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt. (a) **10** (R^3 = *i*-Pr): NaH, DMF, 4-chlorobenzonitrile, 80 °C, 79% (b) DIBAL-H, CH_2Cl_2, 0 °C, 95% (c) HNR^1R^2, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt.

Results and Discussion

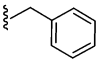
The objectives of the SAR study were to: (1) quickly assess the alkyl residue on the basic nitrogen atom of the 4-phenoxypiperidine; (2) explore the second basic polar group adjacent to the lipophilic core; and, (3) ultimately determine if the 4-hydroxypiperidine moiety is a suitable replacement for the propyloxypiperidine unit in our ligand model. The histamine H_3 receptor binding affinities of 4-phenoxypiperidines **11a**−**k** and (1-isopropyl-piperidin-4-yloxy)-benzylamines **13a**−**r** were determined and are summarized in Tables 1 and 2. In addition, the potency of (1-isopropyl-piperidin-4-yloxy)-benzylamines **13a**−**r** as antagonists of the human recombinant H_3 receptor were also obtained (Table 2).

The SAR of the alkyl group on the piperidine nitrogen was initially examined (Table 1). The 4-phenoxypiperidine **11a** with the free NH lacked significant activity at the H_3 receptor with a $pK_i < 5$. The addition of carbon atoms onto the piperidine nitrogen in a linear succession (**11b**−**d**) revealed a large gain in activity of more than two log units with the *N*-ethyl substitution (**11c**) from the initial unsubstituted parent compound (**11a** vs **11c**). The alpha branched *N*-isopropyl analogue **11e** was favored over the straight chain *N*-propyl compound **11d** (pK_i 7.55 vs 6.97). The *sec*-butyl substituted phenoxypiperidine **11g** gave a slight increase in activity over the isopropyl analogue **11e**. The addition of a hydroxyl group (**11f**) on the isopropyl moiety resulted in over a 10-fold decrease in activity from **11e** while the isobutyl substituted phenoxypiperidine **11h**, extending out the isopropyl unit, gave only a slight decrease in binding affinity over **11e**. The ring substituted analogues **11i**

Table 1. Binding Affinities at the Human H_3 Receptor



11a-k 14

id	R^3	pK_i[a]
11a	H	< 5
11b		5.37 ± 0.07
11c		7.09 ± 0.07
11d		6.97 ± 0.10
11e		7.55 ± 0.04
11f		6.12 ± 0.21
11g		7.82 ± 0.13
11h		7.18 ± 0.08
11i		7.89 ± 0.09
11j		7.49 ± 0.14
11k		5.27 ± 0.03
14		7.60
	thioperamide	7.54 ± 0.06

[a] Displacement of [^{3}H]-N^{α}-methylhistamine from human H_3 receptors expressed in SK-N-MC cells. Values reported as the mean ± SEM of at least three independent determinations in triplicate.

and **11j** were also very potent H_3 ligands with the *N*-cyclopentyl substitution found to be the most potent of this series. The *N*-benzyl analogue **11k** resulted in a more than 100-fold loss of activity. In comparison to the propyloxypiperidine **14**,[23] the *N*-isopropyl phenoxypiperidine **11e** has an identical molecular formula, fewer rotatable bonds and comparable potency at the H_3 receptor. Thus, it was determined to explore the addition of a second polar group for the fully assembled ligand model (i.e. NR^1R^2, Figure 1) with the *N*-isopropyl substituted 4-hydroxypiperidine as a possible replacement tether from the central aromatic ring.

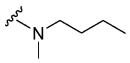
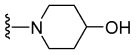
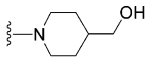
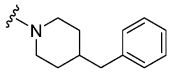
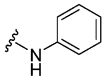
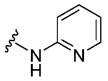
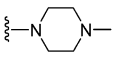
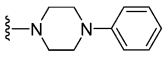
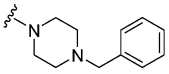
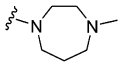
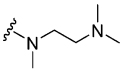
Table 2 lists the potency of compounds **13a**−**r** at the human H_3 receptor. All compounds were found to be antagonists with good correlation between the binding affinities (pK_i) and functional activities (pA_2). The replacement of the benzonitrile group in **11e** with a benzyldimethylamine moiety (**13a**) resulted in a 10-fold increase in affinity at the H_3 receptor (pK_i 7.55 vs 8.52). This improvement in activity with the addition of a second basic amine was also observed in the chemical series leading to **1**.[14] Increasing the size of the carbon chain substituted on the benzyl nitrogen gave compounds with improved activity (**13a**−**c**). The three cyclic amine substitutions (**13d**−**f**) from pyrrolidine to azepine provided excellent potency with the piperidine analogue (**11e)** being the most active with $pK_i = 9.20 \pm 0.10$ and having a $pA_2 = 9.90 \pm 0.04$. The introduction of a heteroatom into the cyclic piperidine ring, either within the ring by replacement of a carbon atom (**13g** and **13n**) or by simple attachment onto the ring (**13h**−**i**) was well tolerated with only a minimal loss of functional activity. The placement of larger groups on the ring (**13j**, **o**−**p**) was also allowed. Secondary amines **13k**−**m** are also acceptable substrates with good affinity. Finally, the piperazine **13n**, homo-piperazine **13q** and the ring opened analogue **13r** all exhibited comparable activity. In general, the benzylamine portion of the molecule confers potency on a wide array of substituents representing a key area where modifications could be made to "fine-tune" the physical properties without jeopardizing potency.

The morpholine analogue **13g** (JNJ-7737782), was selected for further profiling over the more potent piperidine, **13e**, based on a preliminary pharmacokinetic evaluation of both compounds in the rat. Thus **13e** exhibited a longer half-life and more extensive tissue distribution compared to **13g**, which we tentatively attribute to differences in Log P of the compounds and differences in pK_a of the piperidine versus the morpholine fragments of the two molecules. Selectivity of **13g** was examined versus a panel of 50 monoamine and hormone receptors, ion channels and neurotransmitter uptake sites preformed by CEREP. A 1 μM screen revealed no cross reactivity (<18% inhibition at all targets). This promising selectivity profile was further confirmed by in vitro autoradiography studies in rats. As shown in Figure 2A, incubation of sagittal rat brain slices with [^{3}H]-**13g** showed preferential binding in the cortex, striatum and substantia nigra, regions which are known to be rich in H_3 receptors.[24] Most importantly, the binding of [^{3}H]-**13g** is likely localized specifically to histamine receptors, since incubation with an excess of histamine was able to completely block the binding of [^{3}H]-**13g** to the slices (Figure 2B). The potency of **13g** at the rat histamine H_3 receptor was determined to be 7.81 ± 0.01 (pK_i). There were slight differences observed between the rat and human H_3 binding affinities of **13g** (rH_3 $pK_i = 7.81$ vs hH_3 $pK_i = 8.67$). However, contrasting ligand affinities between rat and human H_3 receptors have been well documented.[25]

Given the excellent selectivity and specificity of **13g**, its in vivo efficacy was examined in a model indicative of H_3 receptor antagonist activity. The role of the H_3 receptor in the regulation of sleep/wake states has been extensively studied. Histamine H_3 antagonists have been consistently shown to increase waking and suppress sleep in various animals such as rats[26] and mice.[27] We used a rat EEG model to evaluate the acute effects of **13g** on sleep-waking behavior.

Three doses of **13g** (0.1, 1 and 10 mg/kg) or vehicle were administered subcutaneously to rats. Time spent in distinct sleep-wake states were monitored from EEG and EMG recordings for 2 intervals of 30 min prior to, and 3 intervals of 30 min after administration of vehicle or test compound. As can be seen in Figure 3, administration of vehicle causes a small, transient increase in waking in the first 30 min, probably as a consequence

Table 2. Binding Affinities and Functional Activity Values at the Human H_3 Receptor

id	NR^1R^2	pA_2[a]	pK_i[b]
13a		8.93 ± 0.01	8.52[c]
13b		9.33 ± 0.02	8.91 ± 0.09
13c		9.47 ± 0.03	8.83 ± 0.09
13d		9.45 ± 0.04	8.71 ± 0.09
13e		9.90 ± 0.04	9.20 ± 0.10
13f		9.76 ± 0.01	8.77 ± 0.07
13g		9.32 ± 0.02	8.67 ± 0.03
13h		9.48 ± 0.01	8.85 ± 0.10
13i		9.59 ± 0.03	9.00[c]
13j		9.09 ± 0.06	8.84 ± 0.09
13k		9.34 ± 0.05	8.79 ± 0.10
13l		8.57 ± 0.02	8.26 ± 0.04
13m		9.13 ± 0.02	8.65 ± 0.04
13n		9.59 ± 0.03	9.13 ± 0.21
13o		8.99 ± 0.05	8.70 ± 0.01
13p		9.18 ± 0.06	8.70 ± 0.01
13q		9.49 ± 0.01	9.00 ± 0.01
13r		9.67 ± 0.04	8.94 ± 0.06
	thioperamide	7.36 ± 0.19	7.54 ± 0.06

[a] pA_2 values are reported as the mean ± SEM of at least three independent determinations in triplicate and are derived from Schild regression analysis of the compound-induced rightward shifts in dose−response curves of histamine-induced inhibition of forskolin-stimulated cAMP accumulation in SK-N-MC cells overexpressing the human histamine H_3 receptor. [b] Displacement of [^{3}H]-N^{α}-methylhistamine from human H_3 receptors expressed in SK-N-MC cells. Values reported as the mean ± SEM of at least three independent determinations in triplicate. [c] $n = 1$.

of the manipulation during sc injection of the animals. At 10 mg/kg, **13g** elicited a clear and statistically significant increase in total time spent awake in the first half hour after dosing, as compared to vehicle (Figure 3A). This wake-promoting effect was maintained for the next 30-minute observation interval. In the 1 mg/kg group an increase in waking was observed in the second 30-min interval after dosing only, possibly reflecting a longer time required to achieve sufficient brain levels. At the lowest dose (0.1 mg/kg) there was no statistically significant effect on waking or on any of the other variables measured. The increase in waking was predominantly manifested as quiet waking, reaching statistical significance in the 10 mg/kg group (Figure 3B). There appeared to be a trend toward an increase in time spent in an active waking state, although the effect did not reach statistical significance (Figure 3C). Slow-wave sleep was significantly suppressed in the second 30 min observation interval in both the 1 and 10 mg/kg groups, mirroring the effect on total awake time (Figure 3E).

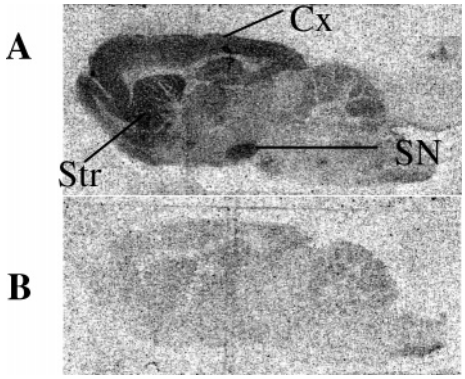


Figure 2. A. In vitro autoradiography of **13g** in sagittal sections from rat brain. Cortex (Cx), Substantia Nigra (SN), and Striatum (Str) are indicated by arrows. Nonspecific binding (B) was determined in the presence of 100 μM histamine.

No statistically significant differences were seen in the treated versus the vehicle group for REM sleep (Figure 3D). Thus, as expected, **13g** induced a state of increased arousal and wakefulness in rats, which was accompanied by a decrease in time spent asleep. The wake-promoting effect of **13g** is consistent with previous animal studies using H_3 receptor antagonists, such as thioperamide,[28,27b] carboperamide[26b] and ciproxifan.[27a] In our hands, for instance, an intracerebroventricular dose of thioperamide (80 μg, $n = 8$) caused the animals to spend an average time of 1619 $\pm$ 110 seconds awake, with a suppression of non-REM sleep to a level of 181 $\pm$ 110 sec.

Although no human data are available, there is considerable interest in the possible therapeutic applications of H_3 receptor antagonists. Therapeutic indications ranging from Alzheimer's disease[7a] to obesity[29] have been proposed. The wake-promoting effects demonstrated in this paper with **13g** could be beneficial for conditions associated with excessive daytime sleepiness, such as narcolepsy, sleep apnea, fibromyalgia and multiple sclerosis. The mild stimulant effect could also

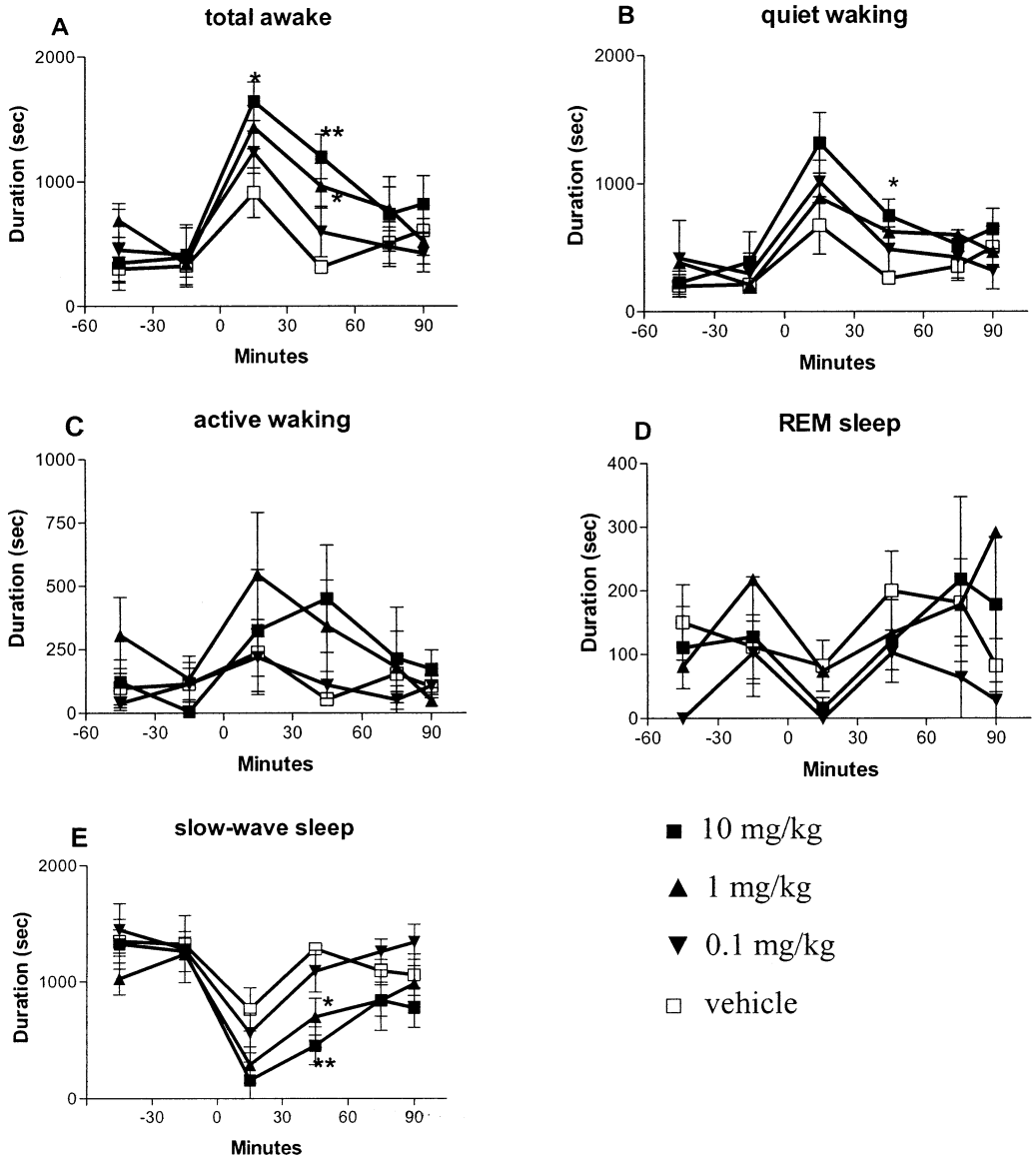


Figure 3. Arousal response to 0.1, 1 and 10 mg/kg (sc) of **13g** in the rat. The compound or vehicle was administered sc at $t = 0$ min. Sleep-wake behavior was monitored for 2 epochs of 30 min prior to, and 4 epochs after dosing and expressed as average time spent in each of the sleep/waking states. A, total time awake; B, quiet waking; C, active waking; D, REM sleep; E, slow-wave sleep. Data are shown as average $\pm$ SEM of four animals. * $p < 0.05$, ** $p < 0.01$, statistically significant from vehicle.

be beneficial for the treatment Attention Deficit Disorder with Hyperactivity, a disease for which low doses of stimulants have been shown to improve attention.[30]

Conclusions

We have refined our previously described H_3 antagonist template, replacing the piperidinyl propyloxy fragment found in **1** with a conformationally restricted 4-hydroxypiperidine moiety. These two fragments were determined to be freely interchangeable in our pharmacophore design model. This has led to a new series of H_3 antagonists described herein. One selected member of the new series, 4-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-morpholine **13g**, was found to be a potent, highly selective H_3 receptor antagonist with in vivo efficacy in a rat EEG model of wakefulness at doses as low as 1 mg/kg sc.

Experimental Section

General Procedures. Reagents were purchased from commercial suppliers and were used without purification. Anhydrous solvents were obtained from a GlassContour Solvent Dispensing System. Reactions were performed at room temperature (20−23 °C) under an atmosphere of N_2 unless otherwise noted. Chromatography was performed using prepacked ISCO RediSep silica cartridges utilizing gradient elution. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 MHz spectrometers. Chemical shifts are reported in parts per million downfield from an internal standard (Me_4-Si). All spectra were taken in $CDCl_3$ unless otherwise noted. Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in either positive or negative modes as indicated. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} 2.5 cm × 7.5 cm 250 μm or 5.0 cm × 10.0 cm 250 μm precoated silica gel plates. Preparative thin-layer chromatography was performed using EM Science silica gel 60 F_{254} 20 cm × 20 cm 0.5 mm precoated plates with a 20 cm × 4 cm concentrating zone. Melting points are uncorrected and were obtained on a MelTemp apparatus. Analytical reverse phase HPLC was preformed on a Hewlett-Packard Series 1100 instrument with an Agilent ZORBAX Bonus RP, column utilizing an acetonitrile/water (0.05%TFA) gradient. Combustion analyses were performed by Desert Analytics or NuMega Resonance Labs.

1-Isopropyl-piperidin-4-ol (10). To a solution of 1-isopropyl-piperidin-4-one (60.0 g, 425 mmol) in 600 mL of absolute ethanol cooled to 0 °C (ice bath) was added $NaBH_4$ (8.5 g, 225 mmol) in several portions. After the addition was complete the mixture was stirred at room temperature for 24 h. The solvent was then removed and the yellow paste was partitioned between CH_2Cl_2 (300 mL) and 1.0 M NaOH (300 mL). This mixture was stirred for 6 h (reaches clarity). The layers were separated and the aqueous was extracted with CH_2Cl_2 (4 × 100 mL) and the combined organics were dried over sodium sulfate. The solvent was removed and the yellow oil distilled bulb to bulb to reveal 39.3 g (bp 68 °C @ 1.5 mmHg, 65%) of a clear oil that solidified on standing to a waxy solid. ^{1}H NMR (400 MHz) δ 3.69−3.61 (m, 1H), 2.80−2.66 (m, 3H), 2.28−2.20 (m, 2H), 1.94−1.86 (m, 2H), 1.61−1.51 (m, 2H), 1.02 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 68.2, 54.2, 46.1, 34.7, 18.3; MS *m/z* 144.1 (M + H$^+$).

4-(Piperidin-4-yloxy)-benzonitrile (11a). A solution of 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (14.99 g, 74.5 mmol) and 4-chlorobenzonitrile (10.35 g, 75.2 mmol) in DMF (100 mL) was treated with sodium hydride (60%, 3.8 g). The resulting dark mixture was then heated to 65 °C for 16 h. The cooled mixture was poured into water (1 L) and then extracted with ether (3 × 400 mL). The combined organic phases were evaporated, and the brown oil was dissolved in methanol (500 mL) and treated with concentrated hydrochloric acid (20 mL). After 24 h the methanol was removed, 5% aqueous sodium hydroxide (300 mL) and water (300 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic phases were dried over sodium sulfate, and the solvent removed to reveal 12.23 g of an off-white waxy solid (81%). ^{1}H NMR (400 MHz) δ 7.57 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.48−4.41 (m, 1H), 3.18−3.11 (m, 2H), 2.79−2.71 (m, 2H), 2.05−1.98 (m, 2H), 1.73−1.65 (m, 2H); ^{13}C NMR (125 MHz) δ 160.4, 133.9, 118.9, 116.0, 103.4, 71.5, 42.0, 29.9; MS *m/z* 203.1 (M + H$^+$); Anal. ($C_{12}H_{14}N_2O$) H; C: calcd. 71.26; found 69.51; N: calcd. 13.85; found 12.36.

General Procedure for Reductive Amination (Method A). A solution of amine (1 equiv), the carbonyl analogue (1.2 equiv), and acetic acid (1 equiv) in CH_2Cl_2 (0.1 M) was treated with $NaBH(OAc)_3$ (1.6 equiv). After 16 h, the resulting mixture was treated with 10% sodium hydroxide (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over sodium sulfate and evaporated. Chromatography of the residue (1−7% 2M methanolic ammonia/CH_2Cl_2) provided the desired product.

General Procedure for Reductive Amination (Method B). A solution of the aldehyde (1 equiv), the amine analogue (1.2 equiv), and acetic acid (1.2 equiv) in CH_2Cl_2 or THF (0.1 M) was treated with $NaBH(OAc)_3$ (1.6 equiv). After 16 h, the resulting mixture was treated with 10% sodium hydroxide (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over sodium sulfate and evaporated. Chromatography of the residue (1−7% 2M methanolic ammonia/CH_2Cl_2) provided the desired product.

4-(1-Methyl-piperidin-4-yloxy)-benzonitrile (11b). Prepared according to Method A (40%). ^{1}H NMR (400 MHz) δ 7.57 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 4.40 (m, 1H), 2.69 (br, 2H), 2.37−2.29 (br, 2H), 2.32 (s, 3H), 2.03 (m, 2H), 1.87 (m, 2H); ^{13}C NMR (125 MHz) δ 160.8, 133.9, 119.1, 116.1, 103.6, 72.4, 52.3, 46.0, 30.5; MS *m/z* 217.1 (M + H$^+$); Anal. ($C_{13}H_{16}N_2O$) C, H, N.

4-(1-Ethyl-piperidin-4-yloxy)-benzonitrile (11c). Prepared according to Method A (26%). ^{1}H NMR (400 MHz) δ 7.53 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.37 (m, 1H), 2.71 (m, 2H), 2.41 (q, J = 7.1, 2H), 2.28 (m, 2H), 1.99 (m, 2H), 1.82 (m, 2H), 1.07 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz) δ 160.9, 133.9, 119.2, 116.1, 103.6, 72.9, 52.2, 49.9, 30.5, 12.1; MS *m/z* 231.1 (M + H$^+$); Anal. ($C_{14}H_{18}N_2O$) C, H, N.

4-(1-Propyl-piperidin-4-yloxy)-benzonitrile (11d). Prepared according to Method A (48%). ^{1}H NMR (400 MHz) δ 7.57 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 4.42 (br, 1H), 2.76 (br, 2H), 2.35 (br, 3H), 2.05 (br, 2H), 1.87 (br, 2H), 1.56 (br, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz) δ 160.9, 133.9, 119.2, 116.1, 103.5,73.2, 60.5, 50.4, 30.5, 20.2, 11.9; MS *m/z* 245.1 (M + H); Anal. ($C_{15}H_{20}N_2O$) C, H, N.

4-(1-Isopropyl-piperidin-4-yloxy)-benzonitrile (11e). To a suspension of 4-chlorobenzonitrile (38.4 g, 280 mmol) and NaH (95%, 7.68 g) in DMF (200 mL) cooled to 0 °C was added slowly a solution of 1-isopropyl-piperidin-4-ol **10** (39.3 g, 274 mmol) in DMF (100 mL). After the addition was complete, the mixture was stirred at room temperature for 1 h then heated to 80 °C for 12 h. The cooled reaction mixture was then poured into water (1.5 L) and allowed to stand for 3 h. The product was collected by suction filtration and the cake washed with water and dried. The residual 4-chlorobenzonitrile was removed by sublimation to reveal 52.9 g (79%) of a light brown solid. ^{1}H NMR (400 MHz) δ 7.56 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 4.37 (m, 1H), 2.81−2.72 (m, 3H), 2.41 (m, 4H), 2.06−1.98 (m, 2H), 1.87−1.77 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz) δ 161.0, 133.9, 119.2, 116.1, 103.5, 73.5, 54.3, 45.5, 30.9, 18.4; MS *m/z* 245.2 (M + H$^+$); Anal. ($C_{15}H_{20}N_2O$) C, H, N.

4-[1-(2-Hydroxy-1-methyl-ethyl)-piperidin-4-yloxy]-benzonitrile (11f). Prepared according to Method A (61%). ^{1}H NMR (400 MHz) δ 7.57 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.42 (m, 1H), 3.42 (m, 1H), 3.32 (m, 1H), 2.88 (m, 2H), 2.64 (m, 2H), 2.33 (m, 1H), 2.03 (m, 2H), 1.84 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz) δ 160.8, 134.0,

119.1, 116.1, 103.7, 73.0, 62.3, 60.1, 31.1, 30.9; MS *m/z* 261.1 (M + H$^+$); Anal. ($C_{16}H_{20}N_2O_2$) H, N; C: calcd. 69.20; found, 68.76.

4-(1-*sec*-Butyl-piperidin-4-yloxy)-benzonitrile (11g). Prepared according to Method A (34%). ^{1}H NMR (400 MHz) δ 7.56 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 4.36 (br, 1H), 2.77 (br, 2H), 2.50 (br, 2H), 2.37 (br, 1H), 2.02 (br, 2H), 1.81 (br, 2H), 1.58 (br, 1H), 1.30 (m, 1H), 1.0 (br, d, J = 6.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz) δ 161.0, 133.9, 119.2, 116.1, 103.5, 73.4, 60.8, 44.8, 31.1, 26.3, 13.8, 11.4; MS *m/z* 259.1 (M + H$^+$); Anal. ($C_{16}H_{22}N_2O$) C, H, N.

4-(1-Isobutyl-piperidin-4-yloxy)-benzonitrile (11h). Prepared according to Method A (72%). ^{1}H NMR (400 MHz) δ 7.56 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 4.37 (br, 1H), 2.69 (br, 2H), 2.22 (br, 2H), 2.09 (br, 2H), 1.98 (br, 2H), 187−1.73 (m, 3H), 0.90 (d, br, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz) δ 161.0, 133.9, 119.2, 116.1, 103.4, 73.5, 66.7, 50.8, 30.6, 25.7, 20.8; MS *m/z* 259.1 (M + H$^+$); Anal. ($C_{16}H_{22}N_2O$) C, H, N.

4-(1-Cyclopentyl-piperidin-4-yloxy)-benzonitrile (11i). Prepared according to Method A (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 4.40 (br, 1H), 2.91−2.23 (br, m, 5H), 2.13−1.35 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 133.9, 119.2, 116.1, 103.6, 73.1, 67.3, 49.3, 30.6, 30.5, 24.1; MS *m/z* 271.1 (M + H$^+$); Anal. ($C_{17}H_{22}N_2O$) C, H, N.

4-(1-Cyclohexyl-piperidin-4-yloxy)-benzonitrile (11j). Prepared according to Method A (79%). ^{1}H NMR (400 MHz) δ 7.56 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.37 (m, 1H), 2.84 (m, 2H), 2.47 (m, 2H), 2.32 (br, 1H), 2.01 (br, 2H), 1.89−1.77 (m, 6H), 1.63 (m, 1H), 1.30−1.17 (m, 4H), 1.10 (m, 1H); ^{13}C NMR (125 MHz) δ 161.0, 133.9, 119.2, 116.1, 103.4, 73.6, 63.6, 45.9, 31.1, 28.8, 26.2, 25.9; MS *m/z* 285.1 (M + H$^+$); Anal. ($C_{18}H_{24}N_2O$) C, H, N.

4-(1-Benzyl-piperidin-4-yloxy)-benzonitrile (11k). Prepared according to Method A (38%). ^{1}H NMR (400 MHz) δ 7.56 (d, J = 8.8 Hz, 2H), 7.33 (m, 3H), 7.27 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.40 (br, 1H), 3.54 (br, 2H), 2.73 (br, 2H), 2.32 (br, 2H), 1.99 (br, 2H), 1.84 (br, 2H), 1.56 (br, 1H); ^{13}C NMR (100 MHz) δ 160.9, 138.2, 133.9, 129.0, 128.2, 127.0, 119.2, 116.1, 103.6, 73.2, 62.9, 50.3, 30.6; MS *m/z* 293.0 (M + H$^+$); Anal. ($C_{18}H_{20}N_2O$) H, N; C: calcd. 78.05; found 77.54.

4-(1-Isopropyl-piperidin-4-yloxy)-benzaldehyde (12). To a solution of 4-(1-isopropyl-piperidin-4-yloxy)-benzonitrile **11e** (48.6 g, 199 mmol) in CH_2Cl_2 (500 mL) cooled to 0 °C was added DIBAL-H (250 mL, 1.0 M CH_2Cl_2, 1.25 equiv) via syringe. The reaction was stirred at 0 °C for 30 min then quenched with ethyl acetate (30 mL). Aqueous Rochelle's salt (1.5 L) was added slowly. Caution! Gas Evolution! The resulting suspension was stirred for 12 h (reaches clarity). The layers were separated and the aqueous was extracted with CH_2Cl_2 (4 × 400 mL). The solvent was removed to reveal a thick syrup that was treated with HCl (300 mL, pH 1) and stirred for 2 h. Water (1.4 L) was added and the pH adjusted with 50% NaOH (pH ∼ 12). The produce was extracted with CH_2Cl_2 (5 × 300 mL) and washed with water and brine. The solvent was removed to reveal 46.6 g (95%) of a thick oil that solidified on standing to a light brown solid. ^{1}H NMR (400 MHz) δ 9.86 (s, 1H), 7.81 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 4.43 (m, 1H), 2.82−2.72 (m, 3H), 2.42 (m, 4H), 2.08−2.00 (m, 2H), 1.89−1.80 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 190.7, 162.8, 131.9, 129.6, 115.7, 73.2, 54.4, 45.5, 31.0, 18.4; MS *m/z* 248.3 (M + H$^+$).

[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-dimethyl-amine (13a). Prepared according to Method B (86%). ^{1}H NMR (400 MHz) δ 7.18 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.27 (m, 1H), 3.34 (s, 2H), 3.37 (s, 3H), 2.81−2.70 (m, 3H), 2.38 (m, 2H), 2.21 (s, 6H), 2.05−1.96 (m, 2H), 1.85−1.75 (m, 2H), 1.05 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.5, 130.9, 130.2, 115.8, 73.0, 63.7, 54.4, 45.7, 45.2, 31.2, 18.4; MS *m/z* 277.1 (M + H$^+$); Anal. ($C_{17}H_{28}N_2O$) H, N; C: calcd. 73.87; found 73.38.

Diethyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine (13b). Prepared according to Method B (37%). ^{1}H NMR (400 MHz) δ 7.21 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.49 (s, 2H), 2.82−2.70 (m, 4H), 2.50 (q, J = 7.1 Hz, 4H), 2.37 (m, 2H), 2.04−1.96 (m, 2H), 1.85−1.76 (m, 2H), 1.60 (m, 9H), 1.07−1.00 (m, 12H); ^{13}C NMR (100 MHz) δ 156.3, 130.0, 128.6, 115.7, 73.1, 56.7, 54.4, 46.4, 45.8, 31.2, 18.4, 11.6; MS *m/z* 305.1 (M + H$^+$); Anal. ($C_{19}H_{32}N_2O$) C, H, N.

Butyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-methyl-amine (13c). Prepared according to Method B (73%). ^{1}H NMR (400 MHz) δ 7.19 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.27 (m, 1H), 3.40 (s, 2H), 2.82−2.71 (m, 3H), 2.39 (m, 2H), 2.34 (m, 2H), 2.16 (s, 3H), 2.00 (m, 2H), 1.85−1.76 (m, 2H), 1.52−1.45 (m, 2H), 1.38−1.27 (m, 2H) 1.06 (d, J = 6.6 Hz, 6H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz) δ 156.4, 131.3, 130.1, 115.8, 73.2, 61.6, 57.1, 54.4, 45.7, 42.1, 31.2, 29.5, 20.6, 18.4, 14.0; MS *m/z* 319.2 (M + H$^+$); Anal. ($C_{20}H_{34}N_2O$) C, H, N.

1-Isopropyl-4-(4-pyrrolidin-1-ylmethyl-phenoxy)-piperidine (13d). Prepared according to Method B (70%). ^{1}H NMR (400 MHz) δ 7.21 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.26 (m, 1H), 3.53 (s, 2H), 2.82−2.71 (m, 3H), 2.48 (m, 4H), 2.37 (m, 2H), 2.03−1.96 (m, 2H), 1.85−1.74 (m, 6H), 1.05 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.4, 131.6, 130.0, 115.8, 73.2, 60.0, 54.0, 45.8, 31.2, 23.3, 18.4; MS *m/z* 303.1 (M + H$^+$); Anal. ($C_{19}H_{30}N_2O$) H, N; C: calcd. 75.45; found 75.03.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidine (13e). Prepared according to Method B (84%). ^{1}H NMR (400 MHz) δ 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.29−4.25 (m, 1H), 3.40 (s, 2H), 2.82−2.71 (m, 3H), 2.41−2.35 (m, 6H), 2.40−2.26 (m, 6H), 2.03−1.99 (m, 2H), 1.85−1.77 (m, 2H), 1.59−1.53 (m, 4H), 1.43−1.38 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.4, 130.5, 130.4, 115.6, 73.0, 63.2, 54.3, 45.7, 31.2, 25.9, 24.3, 18.4; MS *m/z* 317.1 (M + H$^+$); Maleate salt Anal. ($C_{24}H_{36}N_2O_5$) H, N; C: calcd. 66.64; found 65.99.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-azepane (13f). Prepared according to Method B (73%). ^{1}H NMR (400 MHz) δ 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.56 (s, 2H), 2.85−2.71 (m, 3H), 2.60 (m, 4H), 2.38 (m, 2H), 2.04−1.96 (m, 2H), 1.85−1.76 (m, 2H), 1.60 (m, 9H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.3, 132.0, 129.9, 115.7, 73.1, 62.0, 55.4, 54.4, 45.8, 31.2, 28.0, 27.0, 18.4; MS *m/z* 331.2 (M + H$^+$); Anal. ($C_{21}H_{34}N_2O$) C, H, N.

4-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-morpholine (13g). Prepared according to Method B (96%). ^{1}H NMR (400 MHz) δ 7.20 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.27 (m, 1H), 3.69 (m, 4H), 3.42 (s, 2H), 2.82−2.70 (m, 3H), 2.41 (m, 4H), 2.36 (m, 2H), 2.04−1.96 (m, 2H), 1.84−1.75 (m, 2H), 1.05 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.6, 130.3, 129.7, 115.8, 73.0, 66.9, 62.8, 54.4, 53.5, 45.7, 31.2, 18.4; MS *m/z* 319.3 (M + H$^+$). Maleate salt: Anal. ($C_{23}H_{34}N_2O_6$) C, H, N.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-ol (13h). Prepared according to Method B (74%). ^{1}H NMR (400 MHz) δ 7.17 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.25 (m, 1H), 3.64 (m, 1H), 3.42 (s, 1H), 3.40 (s, 2H), 2.80−2.69 (m, 5H), 2.36 (m, 2H), 2.08 (m, 2H), 2.02−1.94 (m, 2H), 1.87−1.74 (m, 2H), 1.55 (m, 2H), 1.04 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.5, 130.2, 130.3, 115.6, 72.9, 67.8, 62.2, 54.3, 50.2, 45.6, 34.4, 31.0, 18.3; MS *m/z* 333.1 (M + H$^+$); Anal. ($C_{20}H_{32}N_2O_2$) C, H, N.

{1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-yl}-methanol (13i). Prepared according to Method B (75%). ^{1}H NMR (400 MHz) δ 7.17 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.25 (m, 1H), 3.24 (d, J = 6.6 Hz, 2H), 3.39 (s, 2H), 2.87 (m, 2H), 2.80−2.69 (m, 3H), 2.37 (m, 2H), 2.02−1.94 (m, 2H), 1.90 (m, 2H), 1.83−1.74 (m, 2H), 1.69 (m, 2H) 1.45 (m, 1H), 1.23 (m, 2H), 1.04 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.4, 130.3, 130.4, 115.6, 72.8, 67.5, 62.7, 54.3, 53.2, 45.6, 38.5, 31.0, 28.7, 18.3; MS *m/z* 347.3 (M + H$^+$); Anal. ($C_{21}H_{34}N_2O_2$) H, N; calcd. 72.79; found 71.27.

{1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-piperidin-4-}-methylbenzene (13j). Prepared according to Method B (51%). ^{1}H NMR (400 MHz) δ 7.29−7.23 (m, 3H), 7.19−7.10 (m, 4H), 6.83 (m, 2H), 4.26 (m, 1H), 3.39 (s, 2H), 2.87−2.70

(m, 5H), 2.52 (d, J = 7.1 Hz, 2H), 2.38 (m, 2H), 2.03−1.96 (m, 2H), 1.59 (m, 2H), 1.50 (m, 1H), 1.29 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.4, 140.7, 130.4, 130.3, 129.0, 128.0, 125.6, 115.6, 73.0, 62.8, 54.4, 53.6, 45.7, 43.2, 37.9, 32.1, 31.1, 18.4; MS *m/z* 407.3 (M + H$^+$); Anal. ($C_{27}H_{38}N_2O$) C, H, N.

Cyclopropyl-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-amine (13k). Prepared according to Method B (30%). ^{1}H NMR (400 MHz) δ 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.25 (m, 1H), 3.74 (s, 2H), 2.81−2.69 (m, 3H), 2.37 (m, 2H), 2.12 (m, 1H), 2.03−1.95 (m, 2H), 1.83−1.74 (m, 2H), 1.04 (d, J = 6.6 Hz, 6H), 0.44−0.33 (m, 4H); ^{13}C NMR (100 MHz) δ 156.3, 132.7, 129.2, 115.9, 73.0, 54.3, 53.0, 45.6, 31.1, 29.9, 18.3, 6.3; MS *m/z* 289.1 (M + H$^+$); Anal. ($C_{18}H_{28}N_2O$) C, H, N.

[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-phenyl-amine (13l). A solution of benzaldehyde **12** (200 mg), aniline (104 mg), and acetic acid (0.05 mL) in DCE (3 mL) was treated with NaBH(OAc)$_3$ (257 mg). After 16 h, the resulting mixture was treated with 10% sodium hydroxide (1 mL), and the mixture was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried (magnesium sulfate) and evaporated. Chromatography of the residue (0−8% 2 M methanolic ammonia/CH_2Cl_2) gave 136 mg as a yellow amorphous solid. ^{1}H NMR (400 MHz) δ 7.27 (d, J = 8.2 Hz, 1H), 7.19−7.15 (m, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.73−6.69 (m, 1H), 6.65−6.62 (m, 2H), 4.31−4.23 (m, 3H), 3.96−3.90 (br s, 1H), 2.83−2.70 (m, 3H), 2.43−2.34 (m, 2H), 2.05−1.96 (m, 2H), 1.86−1.76 (m, 2H), 1.06 (d, J = 6.7, 6H);^{13}C NMR (100 MHz) δ 156.7, 148.1, 131.4, 129.2, 128.8, 117.4, 116.2, 112.7, 73.1, 54.4, 47.7, 45.7, 31.1, 18.4; MS *m/z* 325.5; (M + H$^+$); Maleate salt: Anal. ($C_{25}H_{32}N_2O_5$) C, H, N.

[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-pyridin-2-yl-amine (13m). To a solution of benzaldehyde **12** (5.19 g, 20.9 mmol) in THF (100 mL) was added 2-aminopyridine (2.19 g, 23.3 mmol) followed by NaBH(OAc)$_3$ (7.1 g, 33.5 mmol). This mixture was stirred at room temperature for 16 h. The mixture was quenched by addition of 1.0 M NaOH (40 mL) and poured into water (700 mL). The pH was adjusted with 50% NaOH (pH ∼ 10) and allowed to stand for 12 h. The resulting white solid was collected by filtration and the filter cake washed with water then dried (4.82 g, 71%). ^{1}H NMR (400 MHz) δ 8.10 (m, 1H), 7.40 (m, 1H), 7.28−7.24 (m, 2H), 6.9−6.85 (m, 2H), 6.58 (m, 1H), 6.37 (m, 1H), 4.77 (m, 1H), 4.41 (d, J = 5.8 Hz, 2H), 4.28 (m, 1H), 2.82−2.71 (m, 4H), 2.39 (m, 3H), 2.05−1.97 (m, 3H), 1.85−1.76 (m, 3H), 1.06 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz) δ 158.5, 156.7, 148.1, 137.3, 131.1, 128.7, 116.2, 113.0, 106.7, 72.9, 54.5, 45.8, 45.7, 31.0, 18.3; MS *m/z* 326.3 (M + H$^+$); Maleate salt: Anal. ($C_{24}H_{31}N_3O_5$) C, H, N.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-piperazine (13n). Prepared according to Method B (94%). ^{1}H NMR (400 MHz) δ 7.19 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.42 (s, 2H), 2.81−2.70 (m, 3H), 2.55−2.33 (m, 8H), 2.26 (s, 3H), 2.03−1.97 (m, 2H), 1.84−1.74 (m, 2H), 1.04 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100, MHz) δ 156.5, 130.3, 130.1, 115.7, 73.0, 62.4, 55.1, 54.3, 52.9, 46.0, 45.7, 31.2, 18.4; MS *m/z* 332.3 (M + H$^+$); Anal. ($C_{20}H_{33}N_3O$) H, N; C: calcd. 72.46; found 71.72.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-phenyl-piperazine (13o). Prepared according to Method B (35%). ^{1}H NMR (400 MHz) δ 7.30−7.22 (m, 4H), 6.65−6.82 (m, 5H), 4.29 (m, 1H), 3.50 (s, 2H), 3.19 (m, 2H), 3.16−3.12 (m, 2H), 2.83−2.71 (m, 3H), 2.59 (m, 2H), 2.39 (m, 2H), 2.06−1.99 (m, 2H), 1.87−1.78 (m, 2H), 1.07 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.6, 151.7, 151.3, 130.3, 129.0, 119.4, 116.0, 115.7, 72.9, 62.3, 52.9, 50.3, 49.0, 46.0, 31.1, 18.3; MS *m/z* 394.2 (M + H$^+$); Anal. ($C_{25}H_{35}N_3O$) H, N; C: calcd. 76.29; found 74.42.

1-Benzyl-4-[4-(1-isopropyl-piperidin-4-yloxy)-benzyl]-piperazine (13p). Prepared according to Method B (77%). ^{1}H NMR (400 MHz) δ 7.31−7.29 (m, 4H), 7.25−7.23 (m, 1H), 7.18 (d, J = 8.6 Hz, 2H) 6.84 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.50 (s, 2H), 3.43 (s, 2H), 2.82−2.70 (m, 3H), 2.54−2.34 (m, 9H), 2.03−1.96 (m, 2H), 1.84−1.75 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 157.0, 138.5, 130.8, 130.5, 129.6, 128.5, 127.3, 116.1, 73.5, 63.5, 62.8, 54.8, 53.4, 53.3, 46.2, 31.6, 18.9; MS *m/z* 408.3 (M + H$^+$); Anal. ($C_{26}H_{37}N_3O$) H, N; C: calcd. 76.62; found 76.11.

1-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-4-methyl-[1,4]diazepane (13q). Prepared according to Method B (50%). ^{1}H NMR (400 MHz) δ 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.55 (s, 2H), 2.82−2.72 (m, 3H), 2.71−2.63 (m, 6H), 2.61−2.57 (m, 2H), 2.41−2.36 (m, 2H), 2.35 (s, 3H), 2.00 (m, 2H), 1.85−1.76 (m, 4H), 1.06 (d, J = 6.6 Hz, 6H; ^{13}C NMR (100 MHz) δ 156.4, 131.5, 129.9, 115.7, 72.8, 62.1, 57.9, 56.7, 54.5, 54.1, 46.9, 45.7, 31.0, 27.2, 18.3; MS *m/z* 346.2 (M + H$^+$); Anal. ($C_{21}H_{35}N_3O$) C, H, N.

***N*-[4-(1-Isopropyl-piperidin-4-yloxy)-benzyl]-*N*,*N*′,*N*′-trimethyl-ethane-1,2-diamine (13r).** Prepared according to Method B (55%). ^{1}H NMR (400 MHz) δ 7.19 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.26 (m, 1H), 3.44 (s, 2H), 2.82−2.71 (m, 3H), 2.48−2.34 (m, 6H), 2.22 (s, 3H), 2.20 (s, 6H), 2.04−1.96 (m, 2H), 1.85−1.75 (m, 2H), 1.06 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz) δ 156.5, 131.0, 130.2, 115.8, 73.0, 62.2, 57.4, 55.0, 54.4, 45.8, 45.7, 42.3, 31.1, 18.4; MS *m/z* 334.2 (M + H); Anal. ($C_{20}H_{35}N_3O$) C, H, N.

In Vitro Pharmacology. Human and Rat Histamine H_3 Binding Assays. Binding of compounds to the cloned human H_3 receptor, stably expressed in SK-N-MC cells, was performed as described earlier.[25d] Briefly, cell pellets from SK-N-MC cells expressing either the rat or human H_3 receptor were homogenized in 50 mM Tris-HCl/5 mM EDTA and recentrifuged at 30 000*g* for 30 min. Pellets were rehomogenized in 50 mM Tris/5 mM EDTA (pH 7.4). Membranes were incubated with 0.8 nM [^{3}H]-N^α-methylhistamine plus/minus test compounds for 60 min at 25 °C and harvested by rapid filtration over GF/C glass fiber filters (pretreated with 0.3% polyethylenimine) followed by four washes with ice-cold buffer. Nonspecific binding was defined in the presence of 10 μM histamine. IC_{50} values were determined by a single site curve-fitting program (GraphPad, San Diego, CA) and converted to K_i values based on a [^{3}H]-N^α-methylhistamine K_d of 800 pM and a ligand concentration of 800 pM.[31]

CEREP Binding Panel. The compound was screened at a concentration of 1 μM against a panel of 50 drug targets (receptors, ion channels, transporters) by CEREP (15318 NE 95th Street, Redmond WA; www.cerep.com).

Human Histamine H_3 Functional Assay. Sublines of SK-N-MC cells were created that expressed a reporter construct and the human H_3 receptor. The reporter gene was β-galactosidase under the control of multiple cyclic AMP responsive elements. In 96-well plates, histamine was added directly to the cell media followed 5 min later by an addition of forskolin (5 μM final concentration). After a 6-h incubation at 37 °C, the media was aspirated and the cells were washed with 200 μL of phosphate-buffered saline followed by a second aspiration. Antagonists were added 10 min prior to the addition of histamine. Cells were lysed with 25 μL 0.1 × assay buffer (10 mM Na-phosphate, pH 8, 0.2 mM $MgSO_4$, 0.01 mM $MnCl_2$) and incubated at room temperature for 10 min. Cells were then incubated for 10 min with 100 μL of 1 × assay buffer containing 0.5% Triton and 40 mM β-mercaptoethanol. Color was developed using 25 mL of 1 mg/mL substrate solution (cholorphenolred β-D-galactopyranoside; Roche Molecular Biochemicals, Indianapolis, IN). Color was quantitated on a microplate reader at absorbance 570 nm. The pA_2 values were calculated by Schild regression analysis of the EC_{50} values.

In Vitro Autoradiography. Tissue slices for autoradiography were prepared as described by Bonaventure et al.[32] Briefly, rats were asphyxiated by carbon dioxide and decapitated. The brains were removed and frozen on dry ice. Sections (20 μM thickness) were cut using a cryostat-microtome (Microm HM505E, Microm International GmbH, Walldorf, Germany) and thaw-mounted on adhesive microscope slides (Superfrost$^+$ Plus, VWR, West Chester, PA). The sections were kept at −70 °C until further use, when they were incubated for 10 min at room temperature in 0.5 × PBS with the radioligand. The concentration of [^{3}H]-**13g** was 45 nM. The slides were then washed three times for 20 s with agitation in

ice-cold 0.5 × PBS. After dipping in water, the slides were dried and put on Fujifilm BAS TR2025 for 5 days prior to developing. Nonspecific binding was determined in the presence of 100 μM histamine.

[^{3}H]-**13g** (26 Ci/mmol) was prepared through a contract with Sibtech (Newington, CT). Radiochemical purity 99.6% by HPLC analysis with radioactive flow detection. Analysis was performed using a 4.6 × 250 mm Vydac TP C18 column operated at a flow rate of 1 mL/min at 20 °C with a gradient of acetonitrile and 50 mM pH 3 phosphate buffer with radioactive flow detection using a 0.5 mL flow cell and In−Flow ES cocktail at 2 mL/min.

In Vivo EEG. All animal work reported in this paper was performed in accordance with the Declaration of Helsinki.

Animals and Surgery. Male Sprague−Dawley rats (Charles River, Wilmington, MA) weighing 280−350 g were used in all studies. Stereotaxic surgery was performed using halothane anesthesia administered through a nose cone, with the incisor bar set at 11.5 mm below ear bar zero and body temperature was maintained at approximately 36 °C. Animals were housed in pairs prior to and following surgery. The postsurgical recovery time was 5−7 days. All procedures conformed to university, U.S. Department of Agriculture, and National Institutes of Health guidelines for the care and use of laboratory animals. Electroencephalography and electromyography (EEG and EMG) electrodes were implanted as described below. EEG/EMG electrodes were cemented in position with acrylic cement (Plastics One, Roanoke, VA).

EEG and EMG Recording and Analysis. EEG and EMG were recorded as described previously.[33] Briefly, a bipolar EEG electrode was implanted into the frontal cortex (A + 3.0; L ± 1.5), two EMG electrodes were implanted into the neck muscle, and a ground screw electrode was placed over the cerebellum. The free ends of the EEG, EMG and ground electrodes were inserted into a five-pin plastic connector that was cemented in place, along with the cannula, using acrylic cement (Plastics One). EEG and EMG signals were amplified, filtered (0.3−50.0 Hz band-pass), and continuously recorded on a polygraph and on VCR recording tape using a four-channel headstage FET amplifier connected to standard EEG amplifiers.

On the day prior to testing, pairs of animals were weighed and transferred to testing chambers where they were housed individually.[33] The animals had free access to food and water. On the day of testing, animals were connected to an EEG/EMG recording FET headstage. Testing was conducted between the hours of 10:00 AM and 3:00 PM. Following 60-min of collection of baseline data, animals were injected subcutaneously with 0.1, 1.0, 10.0 mg/kg **13g** or vehicle. Recording of behavior and EEG/EMG data was continued for the subsequent 120-min. Each animal was tested with both doses of **13g**. Testing sessions were separated by 3−4 days. All compounds were dissolved in artificial extracellular fluid (147 mM NaCl, 1.3 mM $CaCl_2$, 0.9 mM $MgCl_2$, 2.5 mM KCl, 5.0 mM NaH_2P0_4, pH 7.4).

EEG and EMG were manually scored for the following behavioral state categories: (1) slow-wave sleep (high-voltage EEG, low-voltage EMG); (2) REM sleep (low-voltage EEG combined with EMG activity of approximately 50% lower amplitude than that observed in slow-wave sleep, with occasional short-duration, large-amplitude deflections due to muscle twitches); (3) quiet waking (low-voltage EEG with EMG activity of an average amplitude twice that observed in slow-wave sleep); active-waking (low-voltage EEG, sustained high-voltage EMG of approximately twice that observed in quiet waking, with occasional movement deflections). To be scored as a distinct epoch, the appropriate EEG and EMG activity patterns needed to persist for a minimum of 15 s. The time spent in each state was scored and totaled for the five 30-min epochs of the observation period. These included the two segments immediately prior to injection (PRE1: 0−30 min; PRE2: 30−60 min) and the three segments that followed the injections (POST1 = 60−90 min; POST2 = 90−120 min; POST3 = 120−150 min). All measurements were conducted by observers blind to experimental conditions.

Statistical Analysis. EEG/EMG effects were analyzed using a one-way or two-way ANOVA with time as a repeated-measures variable (five levels corresponding to five 0.5 h epochs: the first two epochs corresponding to the preinjection portion and the last three epochs corresponding to the postinjection portion of the experiment) and, when appropriate, treatment as a between-subjects variable. When ANOVA indicated a statistically significant effect of time, treatment or a significant treatment × time interaction ($P < 0.05$), posthoc analyses were conducted using Tukey's HSD test (between-subject analyses) or means-comparison contrasts (within-subject analyses).

Supporting Information Available: Results from combustion analysis and ^{1}H NMR of **11a**, **11f**, **11k**, **13a**, **13d**, **13e**, **13i**, **13l**, **13n**, **13o** and **13p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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