The Alkaloid Conessine and Analogues as Potent Histamine H_3 Receptor Antagonists

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The naturally occurring alkaloid, conessine (**6**), was discovered to bind to histamine H_3 receptors in a radioligand-based high-throughput screen. Conessine displayed high affinity at both rat and human H_3 receptors ($pK_i = 7.61$ and 8.27) and generally high selectivity against other sites, including histamine receptors H_1, H_2, and H_4. Conessine was found to efficiently penetrate the CNS and reach very high brain concentrations. Although the very slow CNS clearance and strong binding to adrenergic receptors discouraged focus on conessine itself for further development, its potency and novel steroid-based skeleton motivated further chemical investigation. Modification based on introducing diversity at the 3-nitrogen position generated a new series of H_3 antagonists with higher in vitro potency, improved target selectivity, and more favorable drug-like properties. One optimized analogue (**13c**) was examined in detail and was found to be efficacious in animal behavioral model of cognition.

Introduction

Histamine plays an important role in different physiological processes by acting through the four discovered histamine receptors H_1, H_2, H_3, and H_4.[1] The histamine H_3 receptor is a G-protein coupled receptor (GPCR), predominantly expressed in the central nervous system (CNS), where it modulates the release of multiple neurotransmitters including histamine, dopamine, noradrenaline, acetylcholine, glutamate, and serotonin.[2] Histamine H_3 receptor antagonists can stimulate the release of other neurotransmitters and have been posited to offer a promising approach to the treatment of several CNS disorders,[3,4] including attention deficit hyperactivity (ADHD),[5] sleep disorders,[6] epilepsy,[7] schizophrenia,[8] and obesity.[9]

The histamine H_3 receptor was first described in 1983[10] and later cloned in 1999.[11] Antagonists of this receptor have been divided into two broad structural groups—imidazole and nonimidazole analogues.[12] Most of the earliest potent compounds were imidazole derivatives.[13] Representative imidazole-containing compounds include **1** (thioperamide),[14] **2** (ciproxifan),[15] and **3** (GT-2331)[16] (Figure 1). While these antagonists have been found to be effective in a number of cognition models in rodents, they had several drawbacks, including reports of affinity for other receptors, e.g. H_4 receptors,[17] relatively poor CNS penetration, and most importantly, the known potential to perpetrate drug−drug interactions, through binding of the imidazole moiety to the heme-Fe engaged in hepatic cytochrome P_{450} enzymes.[18]

More recently, attention in the field has turned to the nonimidazole class of H_3-antagonists in the search for more drug-like compounds. SAR studies across a number of series have demonstrated that tertiary amines can effectively replace the imidazole moiety, reducing the potential for CYP inhibition, as well as promoting other drug-like properties, and better CNS penetration.[12,19] Most of the reported nonimidazole H_3 antagonists possess an "aromatic ring−spacer−basic amine" motif:

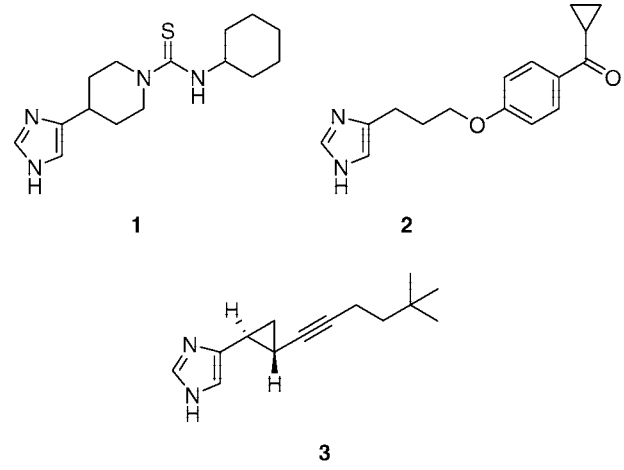

Figure 1

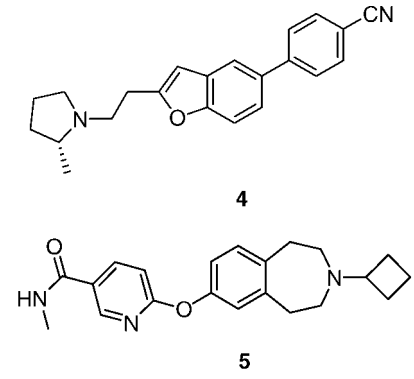

Figure 2

($Ar-X(CH_2)_n-NR_1R_2$). Notable examples of this class include **4** (ABT-239)[20,21] and **5** (GSK-189254)[22] (Figure 2). Compared to the earlier imidazole-based ligands, these compounds offer improvements in binding affinity (especially human H_3), receptor selectivity, CNS penetration, pharmacokinetic and metabolic

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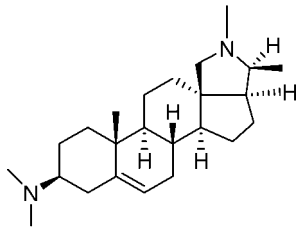
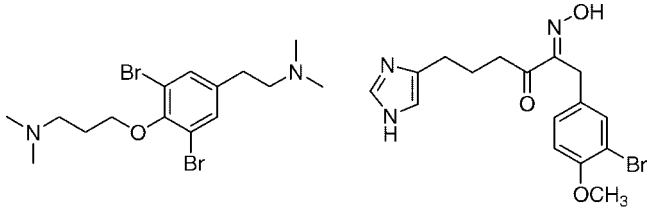


6 (Conessine)

Figure 3



7 8

Figure 4

profiles, and especially lower potential for CYP inhibition than imidazole derivatives.

Although early nonimidazole H_3 antagonists displayed high binding affinity and drug-like properties, there was a desire for greater structural diversity. This was one of our motivations for carrying out a high-throughput screen (HTS) to search for novel structural classes of H_3 antagonists. One particularly intriguing hit that emerged from this early HTS screen was compound **6**, conessine (Figure 3), a natural product based on a steroidal skeleton.[23] Conessine is an alkaloid with a history of use in folk medicine[24] and has even been reported to have some activity as an antibiotic agent.[25]

Natural products have over the years served as a rich source of pharmacologically active agents. Some of these have occasionally been developed into drugs, but more commonly they have some shortcomings that must be corrected during an optimization process requiring substantial structural modification. All in all, the interesting structures and properties of natural products make them an important source of inspiration and leads for drug discovery efforts that resulted in clinically useful entities, e.g., paclitaxel[26] and morphine.[27]

Three natural products have been reported as H_3 receptor antagonists. In fact, one of the earliest nonimidazole H_3 antagonists was aplysamine (**7**)[28] (Figure 4), an alkaloid present in a marine sponge. This compound is a weak functional H_3 receptor antagonist, with an IC_{50} of 0.34 μg/mL (0.83 μM) in a guinea pig ileum assay. Another natural product from the marine sponge *Verongula gigantean*, verongamine (**8**)[29] (Figure 4), also displayed weak H_3 receptor activity (IC_{50} of 0.19 μg/mL (0.50 μM) in a guinea pig ileum assay). More recently, carcinine, an imidazole-containing dipeptide (β-alanyl histamine) from the crustacean *Carcinus maenas*, has been found to be moderately active as a histamine H_3 ligand (rat H_3 K_i = 294 nM).[30] Compared to these natural products, conessine is a much more potent and selective H_3 antagonist. Its novel structure may serve as a starting point for the design of new classes of H_3 antagonists.[31]

Results and Discussion

Conessine exhibited high affinity for both human and rat histamine H_3 receptors, with pK_i values of 8.27 and 7.61 (K_i = 5.37 and 24.5 nM), respectively (Table 1), in radioligand binding assays.[32] Conessine had higher affinity for the human H_3 receptor than rat H_3 receptor, in contrast to the widely used reference H_3 antagonist standards, thioperamide and ciproxifan, which are 10- and 100-fold less potent respectively at the human H_3 receptor than at the rat receptor. Conessine had very good selectivity for H_3 receptors compared to the other histamine receptors. It displayed negligible binding affinity for human histamine H_1 and H_2 receptors, similar to ciproxifan and thioperamide. However, conessine is much more selective for human H_3 versus the H_4 receptor (>1860-fold) than the imidazole-based ciproxifan (30-fold selective) and thioperamide (only 1.5-fold selective). Conessine was also found to exhibit low binding affinity for most other rodent and human G-protein coupled receptors and ligand activated ion channels, with the notable exception of potent affinity for the human alpha$_{2C}$-adrenergic receptor subtype (pK_i = 7.98, K_i = 10.6 nM; Table 1).

Table 1. Comparison of Conessine, Ciproxifan, and Thioperamide Binding at Histamine Receptors and Other receptors

	mean pK_i ± SEM		
receptor	conessine	ciproxifan	thioperamide
human H_3	8.27 ± 0.10	7.20 ± 0.05	7.14 ± 0.06
rat H_3	7.91 ± 0.10	9.29 ± 0.09	8.44 ± 0.07
human cortex H_3	8.46 ± 0.34	7.05 ± 0.06	7.18 ± 0.08
rat cortex H_3	7.61 ± 0.08	9.20 ± 0.04	8.15 ± 0.06
human H_1	<5.00	<5.00	<5.00
human H_2	<5.00	<5.00	<5.00
human H_4	<5.00	5.73 ± 0.09	7.32 ± 0.25
human α_2C_4	7.98 ± 0.18	7.20 ± 0.13	6.46 ± 0.11
human α_2C_{10}	6.18 ± 0.19	7.37 ± 0.07	6.90 ± 0.08
rat $5HT_1$	5.72 ± 0.06	4.78 ± 0.18	4.95 ± 0.28
rat $5HT_2$	<5.00	4.73 ± 0.10	5.25 ± 0.39
rat $5HT_3$	<5.00	6.52 ± 0.19	5.64 ± 0.13

As can be seen in the data compiled in Table 2, conessine was found to act as an antagonist of H_3 receptor in cell- and tissue-based functional assays.[32] These functional assays assess the ability of compounds to block H_3 agonist-stimulated GTPγS binding, adenylate cyclase activity or Ca^{2+} intracellular increase (FLIPR). Consistent with the binding potency trends, conessine had high functional potency at the human H_3 receptor, several-fold higher than ciproxifan and thioperamide, in human H_3 GTP$_\gamma$S and human H_3 FLIPR assays, but several-fold weaker potency at rodent receptor (adenylate cyclase and electric field stimulated guinea pig ileum tissue assay).

In a pharmacokinetic study in rat, conessine efficiently crossed the brain−blood barrier, achieving high brain/plasma ratios (46- to 114-fold) at all time points (Table 3). The absolute brain concentrations reached a very high level of 6570 ng/gm one hour after 1 mg/kg ip dosing. Such efficient brain penetration is often deemed an advantage of a CNS-targeted drug, however, the extremely slow rate of CNS clearance is atypical and was deemed undesirable. Even after 24 h, 4140 ng/gm (>60%) remained in brain, not much changed from the one-hour time point. The prospect for CNS accumulation and consequent elevated risk for toxicity upon repeated dosing presented a potential liability. We believe it is likely that the high CNS concentrations and low CNS clearance arose from the lipophilic dibasic nature of the molecule. An additional drawback of this dibasic character of conessine is the potential to induce toxicity due to phospholipidosis, as it has been reported that dibasic compounds are more likely to induce phospholipidosis than monobasic congeners.[33] Overall, therefore, despite favorable high potency, conessine (**6**) itself lacks good drug-likeness. However, structural characteristics of this alkaloidal core, a novel highly rigid skeleton with no aromatic or heteroaromatic

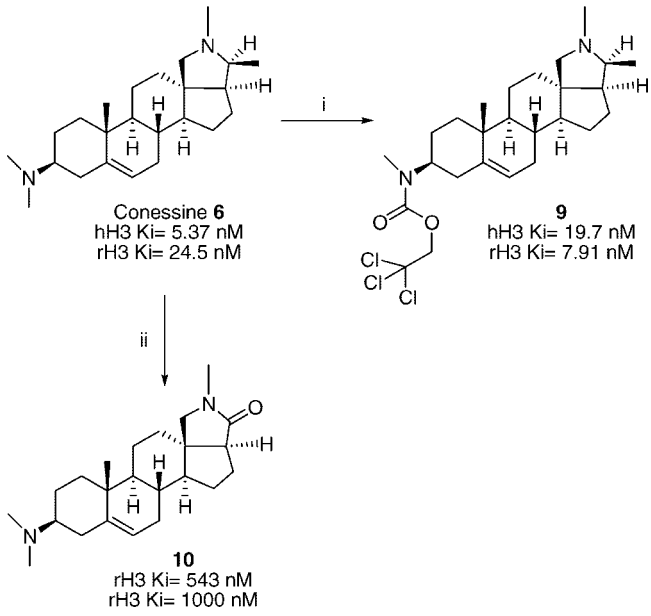
Table 2. Comparison of Antagonist Potencies of Conessine, Thioperamide, and Ciproxifan in Histamine H_3 Receptor Functional Assays

	mean (±SEM) [*n*]		
functional assay	conessine	ciproxifan	thioperamide
human H_3 GTPγS (pK_b)	7.96 ± 0.03 [3]	7.07 ± 0.13 [4]	7.39 ± 0.04 [4]
rat H_3 GTPγS (pK_b)	ND	8.78 ± 0.12 [5]	8.13 ± 0.14 [5]
human H_3 adenylate cyclase (pK_b)	6.14 ± 0.00 [1]	6.59 ± 0.04 [9]	6.10 ± 0.12 [6]
rat H_3 adenylate cyclase (pK_b)	6.99 ± 0.07 [3]	9.20 ± 0.10 [4]	7.61 ± 0.14 [3]
human H_3 FLIPR (pK_b)	8.08 ± 0.11 [4]	6.84 ± 0.08 [12]	6.82 ± 0.06 [11]
rat H_3 FLIPR (pK_b)	ND	9.42 ± 0.11 [8]	9.11 ± 0.14 [4]
EFS guinea pig ileum (pA_2)	6.55 ± 0.31 [17]	8.12 ± 0.56 [21]	8.44 ± 0.49 [20]

Table 3. Mean Blood and Brain Concentrations of Conessine **6** after a 1 mg/kg Concomitant ip Dosing in Rat

	1 h	5 h	24 h
plasma (μg/mL)	0.148	0.089	0.037
blood (μg/mL)	0.444	0.306	0.102
brain (μg/g)	6.57	6.80	4.14
C_b/C_p (ratio)	46.0	95.4	114.4
FRBC	0.819	0.849	0.805

Scheme 1. Preparation and Binding Affinity of Conessine Analogues [a]



[a] Reagents and conditions: (i) Troc-Cl, benzene, reflux, 4h, 48%; (ii) NBS, acetone/H_2O, 48h, rt, 85%.

moiety, may confer advantages in selectivity, toxicity, pharmacokinetics, or metabolic profile and lead to a novel class of H_3 antagonists.

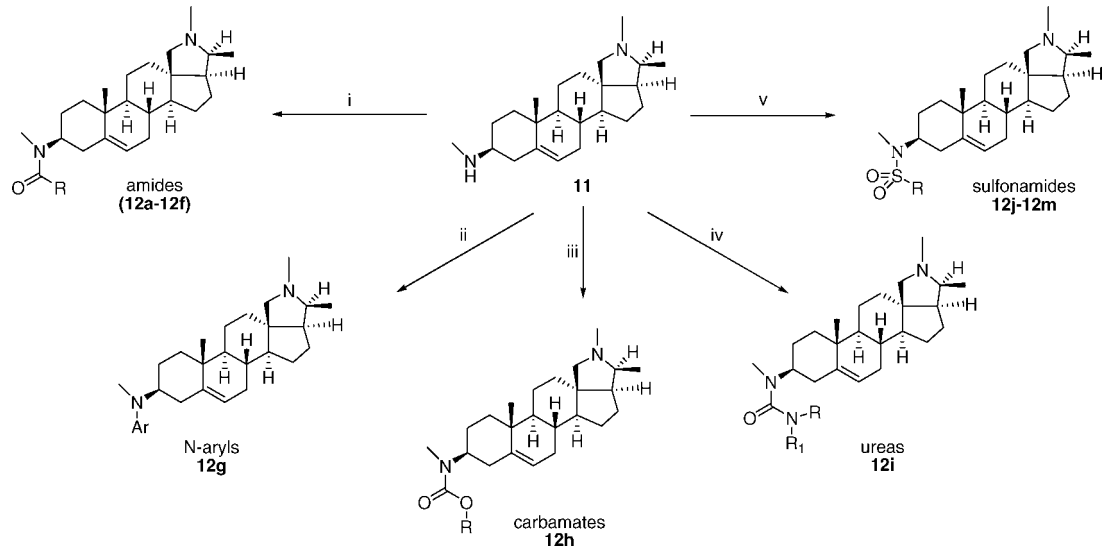
Based on the fact that all reported structural families of potent nonimidazole H_3 antagonists have at a minimum one basic amine, we hypothesized that it might be possible to alter or eliminate one of the two basic sites present in conessine without compromising the H_3 potency. To determine which of the two basic nitrogen atoms might be necessary, compounds **9** and **10** were synthesized as shown in Scheme 1. Conessine was demethylated by treatment with Troc-Cl in refluxing benzene to give 47% yield of carbamate **9**.[34] The lactam **10** was prepared in 85% yield by treating conessine **6** with an oxidizing agent (NBS in aqueous acetone), using the procedure reported by Bhutani et al.[35]

Testing of the resulting analogues in H_3 receptor radioligand binding assays revealed that carbamate **9**, which retains only the basic nitrogen of the pyrrolidine ring, maintained the high binding affinity (hH_3 K_i = 19.7 nM) of the parent compound conessine **6** (hH_3 K_i = 5.31 nM). In contrast, lactam **10**, with the basic dimethylamine moiety, displayed more than 100-fold weaker affinity (hH_3 K_i = 543 nM). This comparison of **9** versus **10** strongly suggested that the basic nitrogen in the pyrrolidine ring is critical for H_3 binding in conessine and conessine-like steroid structures (Scheme 1), whereas the basic nitrogen at the 3-position of the steroid skeleton was not important for H_3 binding. On the basis of these findings, the principle strategy to probe the SAR relied on retaining the conessine skeleton constant and introducing diversity at the 3-nitrogen position. The key intermediate des-methyl-conessine (isoconessimine, **11**)[36] was easily prepared from the Troc-conessine **9**, following a reported literature method.[37] Modification of the 3-position of conessine targeted five categories of substituents to be appended to the nitrogen: amides, *N*-aryls, carbamates, ureas, and sulfonamides (Scheme 2). Analogues with equal or better potency than conessine were found in several series. Of these, the most interesting examples are shown in Table 4 as compounds **12a**−**12m**.

Among the five series of analogues, amides were found particularly interesting due to high potency and the easy access to reagents for diversification. The 2-(thiophen-2-yl)acetamide **12f** displayed a 2-fold increase in both rat and human binding affinity and good CNS penetration and clearance compared to conessine, but unfortunately this compound had only 4.5% oral bioavailability in rat.

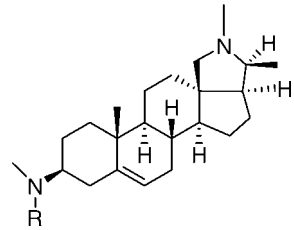
Additional SAR studies of amides pointed us to conessine analogues with appended amino acid side chains, which showed significant improvements (>10 fold) in binding potencies compared with conessine (**6**) (Table 5). A good representative, exemplifying this series, was the *N*-methyl-D-valine analogue **13c**. It showed high affinity at both human and rat H_3 receptors (K_i = 0.21 and 2.57 nM), and was selective against other histamine receptor subtypes (H_1, H_2, and H_4, K_i > 10000 nM). In a more general screen, compound **13c** exhibited minimal or no binding affinity (K_i > 10000 nM) to most receptors (e.g., dopamine, serotonin, and cholinergic subtypes), except for potent binding to one off-target receptor (muscarinic-M_1, K_i = 11 nM). In particular, **13c** had reduced affinity for the human alpha$_{2C}$ adrenergic receptor (α_2C_4 K_i = 77.6 nM, hH_3/α_2C_4 = 370) and greatly improved selectivity compared to conessine **6** (α_2C_4 K_i = 10.6 nM, hH_3/α_2C_4 = 2.0). The compound was further characterized in functional assays and showed potent (K_b = 4 nM) H_3 antagonism in adenylate cyclase and Ca^{2+} flux assays and inverse agonism (EC_{50} 3.3 nM) in a GTP$_\gamma$S assay.[38,39] The compound was highly orally bioavailable in rats (F = 65%), and demonstrated efficient CNS penetration (brain/blood ranges 12−49×), with a very long half-life (77 h). The compound was found to have no notable CNS side effects at 1.3−13 mg/kg (ip). It was also free of genotoxicity[40] and did not inhibit CYP enzymes (IC_{50} > 10 μM). Although the core structure of compound **13c** is a steroid, no binding (K_i > 30000 nM) to

Scheme 2. Preparation of Conessine analogues **12a**−**12m** [a]



[a] Reagents and conditions: (i) acid chloride, Et_3N, CH_2Cl_2; (ii) aryl bromide, $Pd_2(dba)_3$, BINAP, NaOtBu; (iii) chloroformate, Et_3N, CH_2Cl_2, or 4-nitrophenyl-ester, Et_3N, THF; (iv) carbamoyl chloride, Et_3N, CH_2Cl_2; (v) sulfonyl chloride, Et_3N, CH_2Cl_2.

Table 4. Binding Affinities of Conessine **6** and Its Derivatives **11** and **12a**−**12m** at Human and Rat H_3R[a]



compound	R group	human H_3 pK_i ± SEM	human H_3 K_i (nM)	rat H_3 pK_i ± SEM	rat H_3 K_i (nM)
6	Me	8.27 ± 0.10	5.37	7.61 ± 0.08	24.5
11	H	7.42 ± 0.01	38.0	6.52 ± 0.00	302
12a	COMe	6.96 ± 0.29	110	6.59 ± 0.09	257
12b	CO(cyclopropyl)	7.22 ± 0.10	60.3	6.42 ± 0.16	380
12c	COPh	7.91 ± 0.18	12.3	7.42 ± 0.11	38.0
12d	CO(Ph-4-CN)	7.40 ± 0.22	39.8	6.71 ± 0.13	195
12e	CO(4-Py)	7.79 ± 0.05	16.2	6.81 ± 0.09	155
12f	$COCH_2$(thiophen-2-yl)	8.48 ± 0.21	3.31	7.95 ± 0.18	11.2
12g	Ph-4-CN	8.78 ± 0.04	1.66	7.62 ± 0.09	24.0
12h	CO_2Me	7.22 ± 0.13	60.3	6.59 ± 0.39	257
12i	$CONMe_2$	7.30 ± 0.15	50.1	6.53 ± 0.25	295
12j	SO_2NMe_2	7.51 ± 0.28	30.9	6.62 ± 0.25	240
12k	SO_2-Et	7.63 ± 0.17	23.4	6.85 ± 0.01	141
12l	SO_2−Ph	8.11 ± 0.12	7.76	7.21 ± 0.16	61.7
12m	SO_2-(Ph-4-CN)	7.72 ± 0.10	19.0	6.86 ± 0.11	138

[a] Binding potencies were assessed by displacement of ^{3}H-*N*-α-methyl histamine. The human H_3 values were from cloned human H_3 expressed in C6 cells, while rat H_3 values were from rat cortical membranes. The pK_i (−log K_i) ± the standard error of the mean (SEM) are reported.

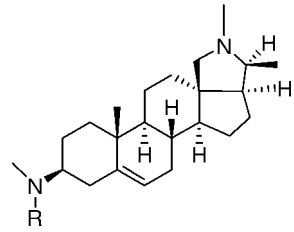
glucocorticoid, androgen, estrogen, or progesterone receptors was detected. Since it was reported that dibasic compounds have sometimes been associated with induction of phospholipidosis,[33] compound **13c** was scrutinized in an in vitro phospholipidosis assay. It only weakly induced phospholipidosis (P.I. = 0.42 at 6.25 μM), where the P.I. is the phospholipidosis index,[33] a ratio of the test compound's propensity to induce phospholipidosis compared to the reference standard toxin amiodarone (P.I. = 1.00 at 10 μM). In further in vivo studies, compound **13c** was found to be effective in a 24 h inhibitory avoidance behavioral model tested in mice at 0.01 mg/kg (ip), consistent with the fact that many histamine H_3 receptor antagonists with in vitro potency in the similar range have been shown to improve performance in a number of rodent behavioral models.[3,20,41]

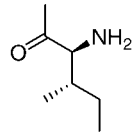
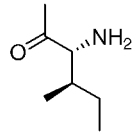
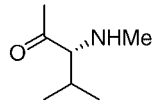
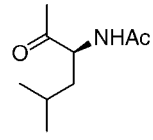
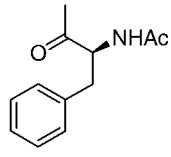
In summary, the conessine analogues described in this paper represent a novel structural class of histamine H_3 receptor antagonists—aliphatic azasteroids. They are highly potent, selective, and some members of the class were found to have good drug likeness by most measures.

Experimental Section

Chemistry Methods. Unless otherwise noted, all commercially available solvents, chemicals, and reagents were used without purification. ^{1}H NMR spectra were obtained on a Varian Mercury plus 300 or Varian UNITY plus 300 MHz instrument, with chemical shifts (δ, ppm) determined using TMS as internal standard. Abbreviations used in description of NMR spectra: s = singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, m = multiplet, br = broad singlet. Mass spectra were obtained on a Kratos MS-50 instrument, and unless otherwise indicated, all MS instruments were operated in the +APCI or +DCI mode to detect positively charged ions. Elemental analysis was performed by Quantitative Technologies, Inc. Flash column chromatography was

Table 5. Binding Affinities of Conessine **6** and Its Derivatives **13a**−**13e** at Human and Rat H_3R[a]



Compound	R group	Human H_3 pK_i ± SEM	Human H_3 K_i (nM)	Rat H_3 pK_i ± SEM	Rat H_3 K_i (nM)
6	Me	8.27 ± 0.10	5.37	7.61 ± 0.08	24.5
13a		9.65 ± 0.07	0.22	9.31 ± 0.02	0.49
13b		9.43 ± 0.05	0.37	8.54 ± 0.09	2.88
13c		9.68 ± 0.07	0.21	8.59 ± 0.08	2.57
13d		8.79 ± 0.13	1.62	8.17 ± 0.18	6.76
13e		8.94 ± 0.06	1.15	8.64 ± 0.15	2.29

[a] Binding potencies were assessed by displacement of ^{3}H-*N*-α-methyl histamine. The human H_3 values were from cloned human H_3 expressed in C6 cells, while rat H_3 values were from rat cortical membranes. The pK_i (−log K_i) ± the standard error of the mean (SEM) are reported.

performed with prepacked ISCO cartridges. Thin-layer chromatography was performed on 250 mm silica gel 60 glass-backed plates from Merck with F254 as indicator.

Methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,11b*S*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-carbamic Acid 2,2,2-trichloro-ethyl Ester (9). 2,2,2-Trichloroethylchloroformate (5.94 g, 28 mmol) was added dropwise to a stirred solution of conessine (6, 10 g, 28 mmol) in 200 mL of benzene. The reaction mixture became a very thick gel. It was then heated at reflux for 4 h (oil bath temperature 90 °C), then cooled down to room temperature, quenched with water, adjusted the pH with 25 mL of saturated sodium bicarbonate, and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give crude product, which was purified by flash chromatography (silica gel, 20:1:0.1 CH_2Cl_2/CH_3OH/NH_4OH) to provide 8.8 g (61%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.96 (s, 3H), 1.04−1.26 (m, 7H), 1.34−1.43 (m, 3H), 1.55 (s, 3H), 1.64−1.92 (m, 9H), 2.04−2.13 (m, 2H) 2.21 (s, 3H), 2.35−2.52 9 (m, 2H), 2.91 (s, 3H), 3.89 (m, 1H), 4.74 (s, 2H), 5.35 (m, 1H). MS (DCI/NH_3): *m*/*z* 517 $(M + H)^+$.

Methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amine (11). Preparation of 10% Pb/Cd couple:[37] yellow lead oxide (PbO, 108 mg, 0.49mmol) was dissolved in 5 mL of 50% aqueous AcOH, and the solution was slowly added to a vigorously stirred suspension of Cd dust (100 mesh, 546 mg, 4.9 mmol) in deionized water (10 mL). The Cd darkened as Pb deposited on its surface and formed clumps that were gently broken up with a glass rod. The dark, nonpyrophoric Pb/Cd couple was filtered, washed with water and acetone, then vaccuum-dried, crushed, and stored in a closed vessel. This gives the 10% Pb/Cd couple (4.9 mmol Cd in 654 mg couple).

Then 10% Pb/Cd couple (1.2 g, 9 mmol Cd) was added to a rapidly stirred mixture of compound **9** (800 mg, 1.54 mmol), THF (6 mL), and aqueous 1N NH_4OAc (6 mL). The mixture was stirred for 5 h, then another portion of 10% Pb/Cd couple (1.0 g) was added and then stirred overnight. The solid was filtered, the filtrate was diluted with water, and adjusted the pH with saturated sodium bicarbonate, then extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to give crude product, which was purified by flash chromatography (silica gel, 20:1:0.1 CH_2Cl_2/CH_3OH/NH_4OH) to provide 397 mg (75%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.94 (s, 3H), 0.98 (m, 1H), 1.06 (d, J = 6.1 Hz, 3H), 1.09−1.26 (m, 5H), 1.33−1.46 (m, 4H), 1.58−1.67 (m, 3H), 1.72−1.91 (m, 6H), 2.05−2.12 (m, 2H), 2.22 (s, 3H), 2.46 (s, 3H), 3.01 (d, J = 10.4 Hz, 1H), 5.35 (m, 1H). MS (DCI/NH_3): *m*/*z* 343 $(M + H)^+$.

***N*-Methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-acetamide (12a).** Compound **11** (12 mg, 0.035 mmol) and triethylamine (15 μL, 3.0 equiv) were dissolved in dichloromethane (1 mL). Acetyl chloride (3.8 μL, 0.053 mmol, 1.5 equiv) was added to it dropwise. The mixture was stirred at room temperature for 2 h, then quenched with water and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over sodium sulfate and concentrated to

give the crude product, which was then purified by flash chromatography (silica gel, 20:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 10.5 mg (78.0%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.93 (m, 3H), 1.08 (m, 3H), 1.31 (m, 4H), 1.57 (m, 3H), 1.68 (m, 3H), 1.87 (m, 7H), 2.10 (m, 3H), 2.23 (m, 3H), 2.37 (m, 1H), 2.52 (m, 1H), 2.80 (m, 3H), 2.87 (m, 3H), 3.35 (m, 1H), 3.73 (m, 1H), 5.36 (m, 1H). MS (DCI/NH_3): *m*/*z* 385 $(M + H)^+$.

Cyclopropanecarboxylicacidmethyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amide (12b). Compound **12b** (12.8 mg, 88.6%) was prepared by using the procedure for making compound **12a**, except substituting cyclopropane carbonyl chloride for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.75 (m, 4H), 0.96 (s, 3H), 0.98 (s, 3H), 1.00−2.60 (m, 23H), 2.87 (s, 3H), 3.04 (s, 3H), 3.94 (m, 1H), 4.40 (m, 1H), 5.38 (m, 1H). MS (DCI/NH_3): *m*/*z* 411 $(M + H)^+$.

***N*-Methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-benzamide (12c).** Compound **12c** (13.0 mg, 83.1%) was prepared by using the procedure for making compound **12a**, except substituting benzoyl chloride for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.93 (s, 3H), 1.02−1.50 (m, 7H), 1.53 (s, 3H), 1.56 (s, 3H), 1.83−2.52 (m, 14H), 2.79 (d, J = 4.4 Hz, 3H), 3.02 (m, 1H), 3.35 (m, 1H), 3.74 (m, 1H), 5.32 (m, 1H), 7.33−7.40 (m, 5H). MS (DCI/NH_3): *m*/*z* 447 $(M + H)^+$.

4-Cyano-*N*-methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-benzamide (12d). Compound **12d** (8.0 mg, 48.5%) was prepared by using the procedure for making compound **12a**, except substituting 4-cyanobenzoyl chloride for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.95 (d, 3H), 1.00−1.48 (m, 7H), 1.53 (s, 3H), 1.56 (s, 3H), 1.84−2.65 (m, 14H), 2.79 (d, J = 4.4 Hz, 3H), 3.02 (m, 1H), 3.35 (m, 1H), 3.72 (m, 1H), 5.33 (m, 1H), 7.46 (m, 2H), 7.70 (d, J = 8.14 Hz, 2H). MS (DCI/NH_3): *m*/*z* 472 $(M + H)^+$.

***N*-Methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-isonicotinamide (12e).** Compound **12e** (8.8 mg, 56.2%) was prepared by using the procedure for making compound **12a**, except substituting isonicotinoyl chloride hydrochloride for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.91 (s, 3H), 0.96 (s, 3H), 1.00−2.75 (m, 21H), 2.80 (m, 3H), 3.03 (s, 3H), 3.27 (m, 1H), 3.71 (m, 1H), 4.47 (m, 1H), 5.30 (m, 1H), 7.39 (d, J = 4.07 Hz, 2H), 8.71 (d, J = 4.07 Hz, 2H). MS (DCI/NH_3): *m*/*z* 448 $(M + H)^+$.

***N*-Methyl-2-thiophen-2-yl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-acetamide (12f).** Compound **12f** (4.0 mg, 24.5%) was prepared by using the procedure for making compound **12a**, except substituting 2-thiopheneacetyl chloride for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.93 (s, 3H), 1.04 (d, 3H), 1.05−2.15 (m, 18H), 2.20 (s, 3H), 2.38 (m, 2H), 2.50 (m, 1H), 2.90 (d, 3H), 3.01 (m, 1H), 3.66 (m, 1H), 3.90 (d, 2H), 4.42 (m, 1H), 5.34 (m, 1H), 6.87 (m, 1H), 6.95 (m, 1H), 7.18 (m, 1H). MS (DCI/NH_3): *m*/*z* 467 $(M + H)^+$.

4-[Methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amino]-benzonitrile (12g). A mixture of compound **11** (20 mg, 0.058 mmol), 4-bromobenzonitrile (16 mg, 0.088 mmol), tris(dibenzylideneacetone)dipallidium (2.1 mg, 0.0023 mmol), racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) (2.2 mg, 0.0035 mmol), and cesium carbonate (29 mg, 0.088 mmol) in toluene (1 mL) were mixed and heated at 100 °C overnight. The reaction mixture was cooled, quenched with water, and extracted with dichloromethane (3 × 5 mL). The combined organic layer was dried over sodium sulfate, filtered, and concentrated to give the crude product, which was purified by flash chromatography (silica gel, 20:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 12 mg (46%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.99 (s, 3H), 1.09−1.27 (m, 7H), 1.38−1.42 (m, 2H), 1.55 (s, 6H), 1.63−1.68 (m, 4H), 1.79−1.85 (m, 3H), 1.93−1.20 (m, 2H), 2.06−2.13 (m, 3H), 2.43−2.52 (m, 2H), 2.88 (s, 3H), 3.63 (m, 1H), 5.39 (m, 1H), 6.69 (d, J = 8.80 Hz, 2H), 7.44 (d, J = 8.80 Hz, 2H). MS (DCI/NH_3): *m*/*z* 444 $(M + H)^+$.

Methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-carbamic acid methyl ester (12h). Compound **12h** (11.0 mg, 79.0%) was prepared by using the procedure for making compound **12a**, except substituting methyl chloroformate for acetyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.92 (s, 3H), 1.02−1.39 (m, 7H), 1.53 (s, 3H), 1.56 (s, 3H), 1.69−1.91 (m, 8H), 1.98−2.13 (m, 2H), 2.21−2.26 (m, 2H), 2.37−2.55 (m, 2H), 2.65 (m, 1H), 2.80 (d, 3H), 3.36 (m, 1H), 3.69 (s, 3H), 3.76 (m, 1H), 5.33 (m, 1H). MS (DCI/NH_3): *m*/*z* 401 $(M + H)^+$.

1,1,3-Trimethyl-3-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-urea (12i). Compound **11** (15.0 mg, 0.044 mmol) and triethylamine (25 μL, 4.0 equiv) were dissolved in dichloromethane (1 mL). Dimethylcarbamyl chloride (6 μL, 0.065 mmol, 1.5 equiv) was added to it dropwise. The mixture was stirred at room temperature overnight. The resulting clear solution was directly loaded on silica gel column and eluted with 20:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$ to provide 14.0 mg (76.9%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.95 (s, 3H), 1.04−1.39 (m, 10H), 1.55 (s, 6H), 1.60−1.92 (m, 10H), 2.02−2.10 (m, 2H), 2.20 (m, 2H), 2.35 (m, 1H), 2.45−2,55 (m, 1H) 2.72 (s, 3H), 2.78 (s, 3H), 3.47 (m, 1H), 5.35 (m, 1H). MS (DCI/NH_3): *m*/*z* 414 $(M + H)^+$.

1,1-Dimethyl-3-methyl-3-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*][phenanthren-9-yl)-sulfamide (12j). Compound **12j** (10.0 mg, 50.5%) was prepared by using the procedure for making compound **12i**, except substituting dimethylsulfomoyl chloride for dimethylcarbamyl chloride. ^{1}H NMR ($CDCl_3$): δ δ ppm 0.93 (s, 3H), 0.99−1.44 (m, 10H), 1.55 (s, 6H), 1.62−1.92 (m, 10H), 2.02−2.12 (m, 2H), 2.22 (m, 2H), 2.35 (m, 1H), 2.42−2,53 (m, 1H) 2.76 (s, 3H), 2.77 (s, 3H), 3.57 (m, 1H), 5.38 (m, 1H). MS (DCI/NH_3): *m*/*z* 450 $(M + H)^+$.

Ethanesulfonic acid methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amide (12k). Compound **12k** (12.5 mg, 82.0%) was prepared by using the procedure for making compound **12i**, except substituting ethanesulfonyl chloride for dimethylcarbamyl chloride. ^{1}H NMR ($CDCl_3$): δ δ ppm 0.91 (s, 3H), 1.06−1.26 (m, 10H), 1.34 (t, J = 7.5 Hz, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 1.66−1.90 (m, 10H), 2.08 (m, 1H), 2.24 (m, 1H), 2.52 (m, 1H), 2.83 (s, 3H), 2..96 (q, J = 7.46 Hz, 2H), 3.72 (m, 1H), 5.36 (m, 1H). MS (DCI/NH_3): *m*/*z* 435 $(M + H)^+$ and 452 $(M + NH_4)^+$.

***N*-Methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-benzenesulfonamide (12l).** Compound **12l** (12.5 mg, 82.0%) was prepared by using the procedure for making compound **12i**, except substituting benzenesulfonyl chloride for dimethylcarbamyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.85 (s, 3H), 0.95 (m, 1H), 1.03 (d, 3H), 1.10−1.45 (m, 9H), 1.50−1.90 (m, 9H), 2.03 (m, 1H), 2.18 (m, 3H), 2.34 (m, 2H), 2.78 (s, 3H), 2.95 (m, 1H), 3.76 (m, 1H), 5.22 (m, 1H), 7.48 (m, 2H), 7.57 (m, 1H), 7.81 (m, 2H). MS (DCI/NH_3): *m*/*z* 483 $(M + H)^+$ and 500 $(M + NH_4)^+$.

4-Cyano-*N*-methyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadeca-hydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-benzenesulfonamide (12m). Compound **12m** (20.0 mg, 89.5%) was prepared by using the procedure for making compound **12i**, except substituting 4-cyanobenzenesulfonyl chloride for dimethylcarbamyl chloride. ^{1}H NMR ($CDCl_3$): δ ppm 0.88 (s, 3H), 1.04−2.39 (m, 10H), 1.55 (s, 6H), 1.60−1.84 (m, 7H), 2.02 (m, 1H), 2.19 (m, 2H), 2.33 (m, 2H), 2.81 (s, 3H), 2.96 (m, 1H), 3.75 (m, 1H), 5.25 (m, 1H), 7.80 (m, 2H), 7.93 (m, 2H). MS (DCI/NH_3): *m*/*z* 508 $(M + H)^+$.

2-Amino-3-(*S*)-methyl-pentanoicacidmethyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,11b*S*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amide L-Tartrate (13a). A mixture of compound **11** (1.0 g, 2.92 mmol), *N*-Boc-L-isoleucine (811 mg, 3.51 mmol, 1.2 equiv), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (840 mg, 4.38 mmol, 1.5 equiv), and 1-hydroxybenzotriazole (590 mg, 4.37 mmol, 1.5 equiv) in dichloromethane (15 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in minimum amount of dichloromethane and purified by flash chromatography (silica gel, 30:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 1.57 g (96.9%) of the Boc protected title compound. It was dissolved in a mixture dichloromethane (20 mL) and TFA (20 mL) and stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was triturated with dichloromethane (3×). The residue was then dissolved in ethyl acetate, stirred with sodium bicarbonate powder for 30 min, and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 25:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 0.87 g (65.4%) of the free base. It was dissolved in methanol (100 mL) and stirred with L-tartaric acid (573 mg, 3.82 mmol, 2 equiv) at room temperature overnight, concentrated, and dried on high vacuum to provide 1.44 g (100%) of the title compound. 1H NMR (300 MHz, DMSO-d_6) δ ppm 0.80−0.96 (m, 9 H), 0.99−1.07 (m, 1H), 1.12 (d, J = 6.44 Hz, 3H), 1.16−1.22 (m, 4H), 1.32−1.53 (m, 8H), 1.53−1.71 (m, 5H), 1.72−1.96 (m, 5H), 1.97−2.10 (m, 2H), 2.30 (d, J = 11.53 Hz, 1H), 2.43 (s, 3H), 2.57 (m, 1H), 2.93 (s, 3H), 3.22 (d, J = 11.19 Hz, 1H), 3.94 (s, 4H), 4.08 (t, J = 6.27 Hz, 1H), 4.12 − 4.25 (m, 1H), 5.07 (br, 8H), 5.34 (m, 1H). MS (DCI/NH_3): m/z 456 $(M + H)^+$.

2-Amino-3-(*R*)-methyl-pentanoicacidmethyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,11b*S*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-amide L-Tartrate (13b). Compound **13b** (104.3 mg, 59.2%) was prepared by using the procedure for making compound **13a**, except substituting *N*-Boc-D-isoleucine for *N*-Boc-L-isoleucine. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.82−0.96 (m, 9 H), 1.03−1.07 (m, 1H), 1.15 (d, J = 6.78 Hz, 3H), 1.21−1.45 (m, 12H), 1.57−1.68 (m, 5H), 1.77−1.95 (m, 5H), 1.98−2.09 (m, 2H), 2.40 (d, J = 8.48 Hz, 1H), 2.45 (s, 3H), 2.57 (m, 1H), 2.93 (s, 3H), 3.27 (d, J = 11.19 Hz, 1H), 3.99 (s, 4H), 4.13 (m, 1H), 4.15−4.31 (m, 1H), 5.20 (br, 8H), 5.30 (m, 1H). MS (DCI/NH_3): m/z 456 $(M + H)^+$.

3-(*R*)-Methyl-*N*-methyl-2-methylamino-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-butyramide L-Tartrate (13c). Compound **13c** (3.2, 80.0%) was prepared by using the procedure for making compound **13a**, except substituting *N*-Boc-D-valine for *N*-Boc-L-isoleucine. ^{1}H NMR ($CDCl_3$): δ 0.95 ppm (m, 12H), 1.00−2.20 (m, 19H), 2.25 (s, 3H), 2.29 (s, 3H), 2.40−2.80 (m, 3H), 2.91 (d, 3H), 3.05 (m, 3H), 3.65 (m, 1H), 4.48 (m, 1H), 5.38 (m, 1H). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.91−0.96 (m, 9 H), 1.03−1.07 (m, 1H), 1.15 (d, J = 6.78 Hz, 3H), 1.22−1.40 (m, 8H), 1.46−1.54 (m, 1H), 1.60−1.70 (m, 5H), 1.77−1.97 (m, 5H), 2.01−2.12 (m, 2H), 2.35 (s, 3H), 2.57 (m, 1H), 2.94 (s, 3H), 3.11 (m, 1H), 3.17 (s, 3H), 3.32 (d, J = 11.53 Hz, 1H), 3.88 (m, 1H), 4.00 (s, 4H), 4.19 − 4.26 (m, 1H), 4.76 (br, 8H), 5.34 (m, 1H). MS (DCI/NH_3): m/z 456 $(M + H)^+$.

2-Acetylamino-4-(*S*)-methyl-pentanoic acid methyl-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,11b*S*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]-phenanthren-9-yl)-amide (13d). A mixture of compound **11** (15 m g, 0.044 mmol), *N*-acetyl-L-leucine (9.0 mg mg, 0.053 mmol, 1.2 equiv), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (13 mg, 0.068 mmol, 1.5 equiv), and 1-hydroxybenzotriazole (9 mg, 0.068 mmol, 1.5 equiv) in dichloromethane (1 mL) and THF (0.5 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in minimum amount of dichloromethane and purified by flash chromatography (silica gel, 30:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 16.0 g (73.1%) of the title compound. ^{1}H NMR ($CDCl_3$): δ ppm 0.87−1.02 (m, 10H), 1.15−1.26 (m, 4H), 1.34−1.51 (m, 6H), 1.55 (s, 6H), 1.65−1.91 (m, 4H), 1.80−1.93 (m, 4H) 1.98 (d, J = 4.4 Hz, 3H), 2.13−2.64 (m, 4H), 2.85 (s, 2H), 2.95 (s, 3H), 4.30 (m, 1H), 5.00 (m, 1H), 5.36 (m, 1H), 6.30 (m, 1H). MS (DCI/NH_3): m/z 498 $(M + H)^+$.

2-((*S*)-Acetylamino)-*N*-methyl-3-phenyl-*N*-((3*S*,3a*S*,5a*S*,5b*R*,9*S*,11a*R*,13a*R*)-2,3,11a-trimethyl-2,3,3a,4,5,5a,5b,6,8,9,10,11,11a,11b,12,13-hexadecahydro-1*H*-2-aza-pentaleno[1,6a-*a*]phenanthren-9-yl)-propionamide (13e). Compound **13e** (18.2 mg, 78.0%) was prepared by using the procedure for making compound **13d**, except substituting *N*-acetyl-L-phenylalanine for *N*-acetyl-L-leucine. ^{1}H NMR ($CDCl_3$): δ ppm 0.88 (m, 3H), 0.96 (m, 1H), 1.03 (s, 3H), 1.14−1.23 (m, 5H), 1.34−1.41 (m, 3H), 1.54 (m, 1H), 1.60−1.87 (m, 10H), 1.99 (s. 3H), 2.08 (m, 1H), 2.19 (s, 3H), 2.31−2.35 (m, 2H), 2.78 (s, 3H), 2.97 (m, 2H), 4.27 (m, 1H), 5.15 (m, 1H), 5.35 (m, 1H), 6.39 (m, 1H), 7.14−7.30 (m, 5H). MS (DCI/NH_3): m/z 532 $(M + H)^+$.

Method for 24 h Inhibitory Avoidance Test. Mice were injected ip with test compound (or in the case of control animals, with identical carrier vehicle) in a volume of 10 mL/kg and placed back into their home cage. Twenty minutes afterward, a training was begun by placing mice in the light side of a two-chambered compartment. The latency to enter the adjoining dark compartment was recorded; upon entering the darkened compartment, an inescapable footshock (0.2 mA, 1 s duration) was presented to the mouse. In the memory retention test 24 h later, the mouse was retested using methods identical to those on the training day, with the latency to enter the darkened compartment recorded, with learning evidenced by a statistically significant ($p < 0.05$) increase in the latency to enter the darkened chamber.

Supporting Information Available: Combustion analysis of compounds **12a**−**12m** and **13a**−**13e** and graphical result of compound **13c** in the rodent inhibitory avoidance behavioral model. This material is available free of charge via the Internet at http://pubs.acs.org.

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