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Design of a New Histamine H_3 Receptor Antagonist Chemotype: (3a*R*,6a*R*)-5-Alkyl-1-aryl-octahydropyrrolo[3,4-*b*]pyrroles, Synthesis, and Structure−Activity Relationships

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A new histamine H_3 receptor (H_3R) antagonist chemotype **1** was designed by combining key pharmacophoric elements from two different precursor structural series and then simplifying and optimizing the resulting combined structural features. First, analogues were made based on a previously identified conessine-based H_3R antagonist series. While the first analogues **11** and **15** showed no antagonistic activity to H_3R, the mere addition of a key moiety found in the reference compound **7** (ABT-239) elevated the series to high potency at H_3R. The hybrid structure (**16b**) was judged too synthetically demanding to enable an extensive SAR study, thus forcing a strategy to simplify the chemical structure. The resulting (3a*R*,6a*R*)-5-alkyl-1-aryl-octahydropyrrolo[3,4-*b*]pyrrole series proved to be highly potent, as exemplified by **17a** having a human H_3 K_i of 0.54 nM, rat H_3 K_i of 4.57 nM, and excellent pharmacokinetics (PK) profile in rats (oral bioavailability of 39% and $t_{1/2}$ of 2.4 h).

Introduction

The histamine H_3 receptor (H_3R) was first described in 1983[1] and cloned in 1999.[2] It is a G-protein coupled receptor (GPCR[a]) predominantly expressed in the central nervous system (CNS) and is known to modulate the release of multiple neurotransmitters, including histamine, acetylcholine, dopamine, and noradrenaline.[3] Antagonists of the H_3 receptor are well-known to induce the release of these neurotransmitters in vitro and in vivo and have been found effective in diverse CNS behavioral animal models.[4] Thus, there is extensive preclinical data supporting the notion that H_3 antagonists offer a promising approach for the treatment of several CNS disorders including Alzheimer's disease,[5] sleep disorders,[6] attention deficit hyperactivity (ADHD),[7] and cognitive dysfunctions of schizophrenia.[8] We report herein the retrodesign and optimization of a new highly potent and selective structural class of histamine H_3 antagonists (**1**) with excellent PK profiles and CNS penetration (Chart 1).

We recently reported the discovery of **2** (conessine)[9] as an H_3 antagonist in an HTS screen (Scheme 1).[10] **2** was potent at H_3R in vitro but possessed some significant shortcomings including very low selectivity at adrenergic receptors, slow CNS clearance (> 60% remaining in brain 24 h after dosing in rats), and key structural features (two dibasic amines, highly lipophilic steroid skeleton) that have been causally associated with the induction of phospholipidosis. SAR studies were carried out in a first attempt to address those shortcomings. Of the two key analogues made (**3a** and **3b**), only compound **3a** retained potency, highlighting the critical basic site for H_3R ligands. The SAR identified a minimal H_3 binding pharmacophore as the A, B, C, and D rings of the steroid skeleton plus the basic pyrrolidine, as depicted by the portion of the structure encircled in compound **3a**. Further SAR studies on this pharmacophore led to compound **4**,[10] which had 10−25× greater H_3R potency in vitro, along with significantly reduced off-target bindings with the exception of M1 receptor (K_i 11 nM). Despite otherwise good properties, this compound (**4**) retained extremely slow CNS clearance ($t_{1/2}$ 77 h), which was viewed as likely a detrimental profile for a drug candidate. We hypothesized that these problems might be addressed if additional, likely extensive, changes were made through designing new structures.

Results and Discussion

The earlier studies on analogues of **3** and **4** relied on the readily available **2** to allow the semisynthesis of steroid-based structures. However, to make yet more diverse analogues with such a steroid skeleton would require a prohibitively demanding dedication of synthetic resources to develop methods to install and orient all the chiral centers and rings. A compromise series was thus targeted, which contained the putative C and D rings of the steroidal lead as well as the key pyrrolidine. Compound **5** was previously reported by Meyers[11] as a synthetic intermediate toward a formal total synthesis of **2**. We hypothesized that intermediate compound **5** might still retain just enough structural similarity to the pharmacophore identified for **3a** to be active as H_3R antagonist and justify SAR studies and further optimization into a viable series. It was also hypothesized that the aromatic ring in **5** might mimic the saturated B ring of **2**, whereas the methoxy group in **5** could act

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[a] Abbreviations: SAR, structure−activity relationships; HTS, high throughput screening; hERG, human ether-a-go-go related gene; M1, muscarinic acetylcholine receptor; GPCR, G-protein coupled receptor; CNS, central nervous system; PK, pharmacokinetics.

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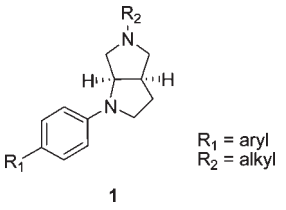
Chart 1



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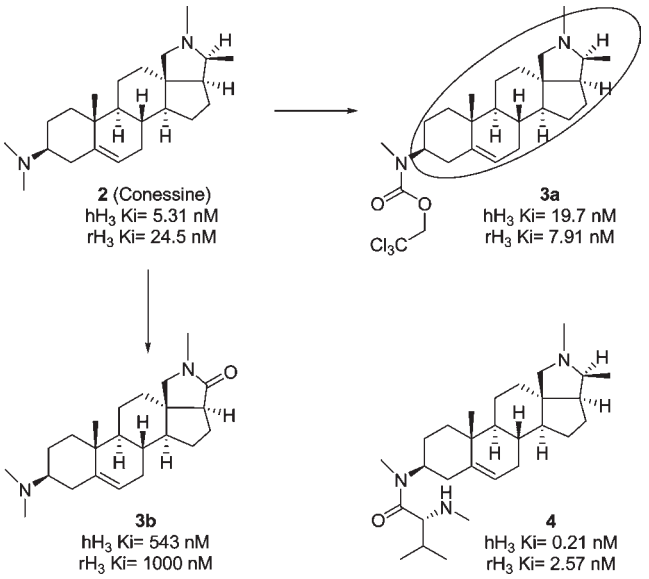
Scheme 1. Preparation and Binding Affinity of **2** Analogues



as a useful synthetic "handle" for new analogues (**6**) . As such, the selection of the appropriate R group in the aromatic ring, a 4-cyano and 4-acetyl were preferred, as we had already found that these motifs conferred good drug likeness when present in benzofurans such as **7** (ABT-239) (Figure 1).[12]

The key intermediate **8** was synthesized in nine steps with 27% overall yield following the previously reported method by Meyers.[11] This 3:1 mixture of isomers could be separated, contrary to what was stated in Meyer's paper, to yield compounds **9** and **10.** The *S*-isomer **9** was methylated via reductive amination to give **11**, which was then treated with BBr_3 to afford the hydroxyl analogue **12**. The latter was then converted to the reactive triflate **13**, suitable for the coupling reaction to afford the desired target compounds **14**. The *R*-isomeric compounds **16a**−**b** were made from **10** by the same reaction sequence as was used to prepare **14** from **9**. The in vitro binding data of the analogues at histamine H_3 receptors is shown in Table 1. We were disappointed to find that neither of the epimeric anisoles **11** and **15** had activity at H_3R (K_i > 1000 nM). However, the addition of an extra aromatic ring, as seen with homologated analogues **14** and **16a**−**b**, led to a significant boost in affinity. Of these, the *S*-isomeric compound (**14)** was found active, although significantly less potent than **2** at human (21-fold) and rat H_3R (17-fold) despite possessing the same configuration (*S*) as **2**. However, the new R-isomeric compounds (**16a** and **16b**) both displayed potent binding affinity, only a few-fold weaker than **2** itself. This was surprising in light of the fact that compounds **16a** and **16b** have an *R* configuration at the benzyl-H, which is opposite to that present in **2**.

Overall, the hypothesis that structures such as **14** and **16** would be active was proven true, but the more elaborate

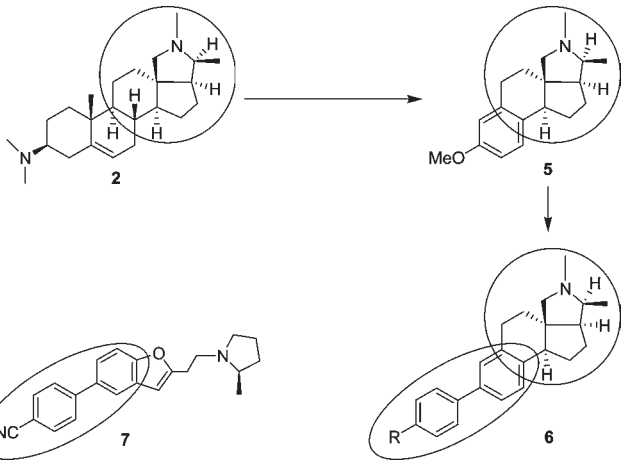
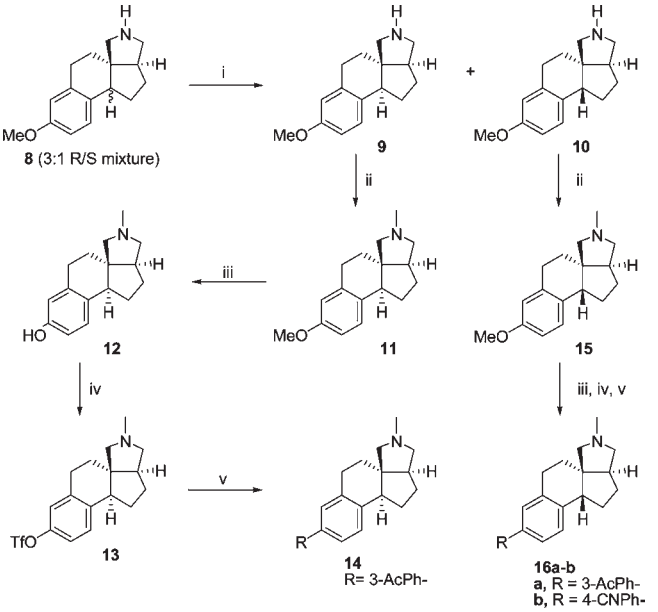


Figure 1. Design of hybrid series combining elements of **2** with **7**.

Scheme 2. Synthetic Route for the Preparation of Benzo[4,5] hydrindeno[1,7a-*c*]-1-benzylpyrrolidine Derivatives[a]



[a] Reagents and conditions: (i) Silica gel flash column chromatography; 10%CH_3OH/CH_2Cl_2 + 1%NH_4OH; (ii) HCOH, $NaBH_3CN$, CH_3OH; (iii) BBr_3, CH_2Cl_2; (iv) Tf_2O, Et_3N, CH_2Cl_2; (v) R-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, EtOH, H_2O.

synthesis (14 steps), together with the moderate potency for H_3R, could not justify additional work within the series. Nevertheless, there were some advantages inherent in the series: structures such as **16** are highly rigidified, and we have previously used the principle of rigidifying structures to improve the PK properties, selectivity, and drug-likeness of H_3R antagonists.[13] Therefore, with the goal of designing a simplified structural core that would retain the rigidity and the overall 3D shape of **14** and **16**, yet support a more straightforward synthesis to facilitate SAR optimization, we proposed a new structural series based on a retro-design by combining several hypotheses.

First, the 2*S*-methyl substituent on the pyrrolidine moiety of **6** possibly was not absolutely necessary for H_3R activity because both **14** and **16** lack this 2*S*-methyl yet have significant binding potency. Second, we proposed a possible structural overlap of **6** and **7** (Figure 2), which if operative would imply

Table 1. Binding Affinities of Benzo[4,5]hydrindeno[1,7*a*−*c*]-1-benzylpyrrolidine Derivatives at Human and Rat H_3R[a]

compd	R group	human H_3 p*Ki* ± SEM	human H_3*Ki* (nM)	rat H_3 p*Ki* ± SEM	rat H_3*Ki* (nM)
2		8.27 ± 0.10	5.37	7.61 ± 0.08	24.5
11	CH_3O−	> 6.00	< 1000	> 6.00	< 1000
15	CH_3O−	> 6.00	< 1000	> 6.00	< 1000
14	3-AcPh−	6.94 ± 0.14	115	6.38 ± 0.45	417
16a	3-AcPh−	7.81 ± 0.06	15.5	6.84 ± 0.25	145
16b	4-CNPh−	7.84 ± 0.06	14.5	7.34 ± 0.30	45.7
7	4-CNPh−	9.35 ± 0.04	0.45	8.49 ± 0.04	3.22

[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 ($n \geq 3$).

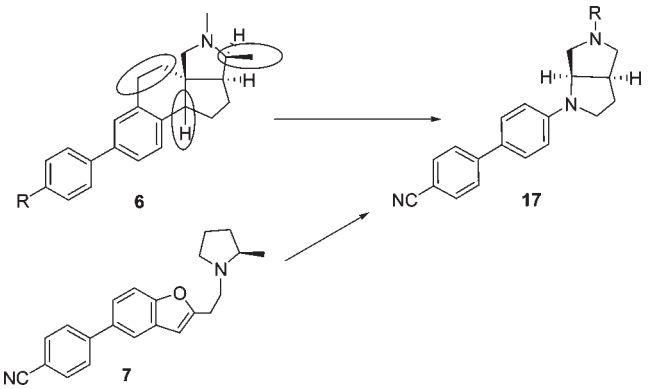
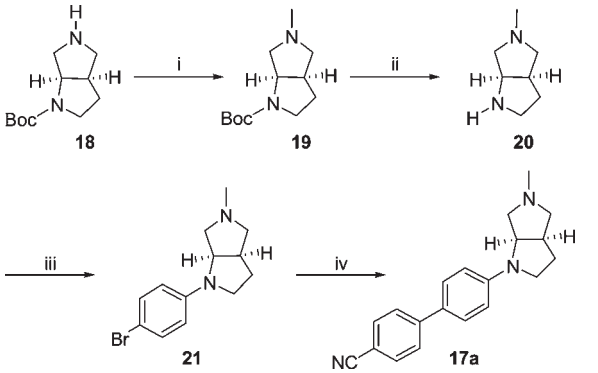


Figure 2. Design of aryl-octahydropyrrolo[3,4-*b*]pyrrole series **17** based on combining elements of **6** and **7**.

that the two methylenes forming the cyclohexane ring of **6** could be deleted, as the highly potent **7** lacks a similarly situated substituent or ring. Third, we hypothesized that the benzylic carbon might be replaced with a nitrogen atom, which would greatly simplify synthesis by imparting the benefit of eliminating one chiral center and allowing facile formation of the C−N bond via well-precedented cross-coupling procedures. Lastly, the implementation of this plan was enabled by the availability of the pyrrolidinylpyrrolidine intermediate **20** in optically pure form.[14]

The route shown in Scheme 3 was used to synthesize the first targeted analogue **17a**. First, the synthetic intermediate **18**[14]

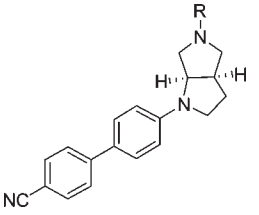
Scheme 3. Synthetic Route for the Preparation of (3a*R*,6a*R*)-Octahydropyrrolo[3,4-*b*]pyrrole Derivatives **17a**[a]



[a] Reagents and conditions: (i) HCOH, $NaBH_3CN$, CH_3OH; (ii) 3 N HCl, CH_3OH; (iii) 1,4-dibromobenzene, $Pd_2(dba)_3$, BINAP, *t*-BuONa, Toluene, 70 °C; (iv) 4-CN-Ph-$B(OH)_2$, $Pd(OAc)_2$, K_3PO_4, $(Cy)_2$P-Ph-Ph, Toluene/*i*-PrOH/H_2O, 70 °C.

was methylated with $NaBH_3CN$ and formaldehyde and then deprotected by treatment with acid to give **20**, which was then subjected to Pd-catalyzed cross-coupling with 1,4-dibromobenzene to give **21**. This versatile intermediate bromide was then treated with 4-cyanobenzene boronic acid under cross-coupling conditions to yield **17a**. In addition to the first analogue, **17a**, which had an *N*-methyl substituent, a series of *N*-alkylated analogues (**17c**−**h**) were made to probe the SAR at this position. For these compounds, the synthetic

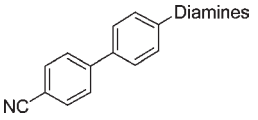
Table 2. SAR Summary of R_1 Alkyls in Analogue **17**[a]

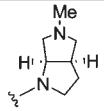
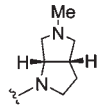
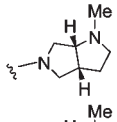
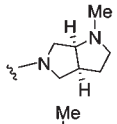
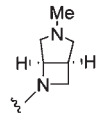
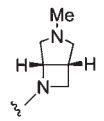
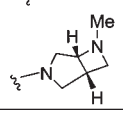


compd	R group	human H_3 p*Ki* ± SEM	human H_3*Ki* (nM)	rat H_3 p*Ki* ± SEM	rat H_3*Ki* (nM)
17a	Me−	9.27 ± 0.20	0.54	8.34 ± 0.04	4.57
17b	H−	6.49 ± 0.04	324	> 6.00	< 1000
17c	Et−	8.18 ± 0.08	6.61	7.45 ± 0.13	35.5
17d	*i*-Pr−	7.37 ± 0.04	42.7	6.07 ± 0.07	851
17e	*c*-Pr-CH_2−	7.26 ± 0.17	55.0	6.40 ± 0.13	398
17f	*n*-Pr−	7.15 ± 0.03	70.8	6.27 ± 0.07	537
17g	*i*-Bu−	6.64 ± 0.17	229	> 6.00	< 1000
17h	*n*-Bu−	6.26 ± 0.26	550	> 6.00	< 1000

[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 ($n \geq 3$).

Table 3. SAR Summary of Bicyclic Diamine Cores[a]



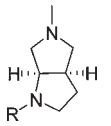
Compound	Diamines	Human H_3[b] pK_i ± SEM	Human H_3 K_i (nM)	Rat H_3[b] pK_i ± SEM	Rat H_3 K_i (nM)
17a		9.27 ± 0.20	0.54	8.34 ± 0.04	4.57
22		6.11 ± 0.02	776	<6.00	>1000
23		6.26 ± 0.25	550	6.05 ± 0.03	891
24		7.21 ± 0.56	61.7	<6.00	>1000
25		7.80 ± 0.11	15.9	7.22 ± 0.19	60.3
26		6.27 ± 0.06	537	<6.00	>1000
27		7.05 ± 0.19	89.1	6.70 ± 0.20	200

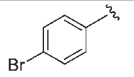
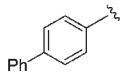
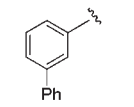
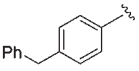
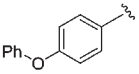
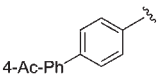
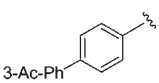
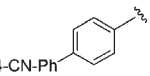
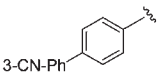
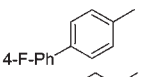
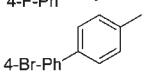
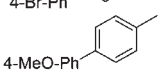
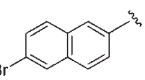
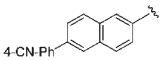
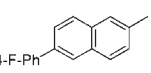
[a] Binding potencies were assessed by displacement of ^{3}H-*N*-α-methyl histamine. The human H_3 values were from cloned human H_3 expressed in C6 cells, while rat H_3 values were from rat cortical membranes. The pK_i (−log K_i) ± the standard error of the mean (SEM) are reported ($n \geq 3$).

sequence was modified in order to put the alkyl groups more efficiently. The intermediate **18** was first protected by Cbz, followed by Boc removal, the resulting (3a*R*,6a*R*)-hexahydropyrrolo[3,4-b]pyrrole-5-carboxylic acid benzyl ester was coupled with trifluoro-methanesulfonic acid 4′-cyano-biphenyl-4-yl ester under palladium coupling condition. The Cbz group was finally removed to give the N−H analogue **17b**, which was alkylated under reductive amination or alkylation conditions to give the desired *N*-alkyl analogues **17c**−**h**. The in vitro potencies on H_3R of these compounds are shown in Table 2.

We were gratified to find that the first targeted analogue **(17a)** was highly potent at human H_3R (0.54 nM) and rat H_3 (4.57 nM), which is a significant improvement compared to the earlier series of analogues **14** and **16a**−**b**. The SAR of the *N*-alkyl substituent showed clear trends for in vitro potency. The N−H analogue **17b** had only weak activity, which was in line with our finding that tertiary amine H_3R antagonists are significantly more potent than secondary amines. On the other hand, the effect of the size of alkyl groups was quite unexpected: as groups grew larger than methyl, a rapid reduction in potency was seen. This was a surprising finding in light of the many reports on diverse H_3R antagonists series where typically an isopropopyl or comparably sized cyclobutyl confers higher potency than methyl substituents.[15,16]

Table 4. SAR Summary of (3a*R*,6a*R*)-1-Aryl-5-methyl-octahydropyrrolo[3,4-*b*]pyrrole Analogues[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)
21		7.00 ± 0.11	100	6.17 ± 0.01	676
28		7.88 ± 0.17	13.2	6.84 ± 0.19	145
29		6.29 ± 0.16	512	<6.00	>1000
30		7.58 ± 0.30	26.3	6.86 ± 0.19	138
31		7.60 ± 0.14	25.1	7.03 ± 0.16	93.3
32		8.49 ± 0.14	3.24	7.66 ± 0.09	21.9
33		8.23 ± 0.37	5.89	7.40 ± 0.34	39.8
17a		9.27 ± 0.20	0.54	8.34 ± 0.04	4.57
34		8.31 ± 0.33	4.90	7.53 ± 0.11	29.5
35		7.97 ± 0.16	10.7	6.95 ± 0.12	112
36		7.91 ± 0.18	12.3	6.78 ± 0.02	166
37		8.82 ± 0.16	1.51	7.61 ± 0.13	24.6
38		6.74 ± 0.11	182	<6.00	>1000
39		8.38 ± 0.19	4.14	7.19 ± 0.23	64.6
40		7.69 ± 0.19	20.4	6.34 ± 0.12	457

[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 ($n \geq 3$).

With the new finding that the (3a*R*,6a*R*)-octahydropyrrolo [3,4-*b*]pyrrole ring conferred good in vitro H_3 potency to the series **17**, an investigation was undertaken to understand how broad the SAR for this bicyclic diamine moiety would be. For this purpose, compounds **22**−**27** were synthesized with different ring sizes and stereochemistries. First, with compound **22** (the opposite enantiomer of **17a**), the absolute stereochemistry was found to be critical because **22** was 1440-fold lower in H_3R potency than **17a**. Next, the effect of orientation of the

Table 5. Rat Pharmacokinetic Properties of Selected H_3 Antagonists[a]

	1 mg/kg iv dose			1 mg/kg oral dose		
compd	$t_{1/2}$	AUC	CL_b	C_{max}	AUC	F
17a	2.4	432.9	2.37	21.8	170.7	39.4
32	1.6	178.6	5.79	6.7	26.3	14.7
37	2.0	225.0	4.49	18.8	119.9	53.3

[a] 1 mg/kg dose of each compound simultaneously in each rat. Units: $t_{1/2}$ (h); C_{max} (ng/mL); AUC (ng·hr/ml); F (%); CL_b (l/h·kg); $n = 3$. Unable to estimate plasma elimination half-life.

pyrrolidinylpyrrolidine moiety was examined. Both **23** and **24** were much less potent than **17a**, and this observation proved that not only stereochemistry but the point of attachment to the diamine was critical for H_3R binding affinity. To further probe the effect of the bicyclic ring size and orientation, three different 3,6-diazabicyclo[3.2.0]heptane diamines, **25**, **26**, and **27**, were prepared. While all of them had detectable activity at histamine H_3 receptors and **25** had quite good potency (15.9 nM at human H_3), none of the diamines demonstrated affinity comparable to the high potency seen in **17a**. Overall, of diverse diamines investigated, it was concluded that although all of them were able to support some degree of H_3 binding when attached to the 4-cyanobiaryl moiety, the first diamine investigated, (3a*R*,6a*R*)-octahydropyrrolo[3,4-*b*]pyrrole, was superior.

We next turned our attention to a series of analogues (**28**−**40**) with diverse aryl groups to replace the 4-cyanophenyl moiety of **17a**. These compounds were synthesized via cross coupling reactions from the bromine intermediate **21**, which was itself active (100 nM at human H_3R) but not so much as the other analogues that were larger in size. While none of the new analogues matched the high potency of **17a**, the new analogues **28**−**40** (with the exception of **29**) were still highly potent, significantly more than **21**, suggesting a benefit of most groups larger than bromine in this series.

The pharmacokinetic properties of selected compounds were investigated in rat, with the data summarized in Table 5. The most potent compound **17a** displayed a favorable PK profile in rats, with an oral bioavailability of 39.4% and $t_{1/2}$ of 2.4 h. All three compounds tested in this (3a*R*,6a*R*)-5-methyl-1-aryl-octahydropyrrolo[3,4-*b*]pyrrole series had moderate to good PK profiles. The drawback to this series is its high binding for the hERG channel. The highlighted compound **17a**, interacted potently with this channel (dofetilide binding $K_i = 282$ nM). This is also an issue previously found for **7**.

In summary, a new series of histamine H_3R antagonists was retro-designed by incorporating structural elements from two diverse structural classes to produce the new series of H_3R antagonist (**1**). These novel (3a*R*,6a*R*)-5-methyl-1-aryl-octahydropyrrolo[3,4-*b*]pyrroles, compared with **2**, its analogue **4**, and the hybrid motif **6**, have reduced molecular weight, improved properties, and greatly simplified syntheses, which increased the ability to make new analogues while retaining the high rigidity seen in earlier series. The most potent member **17a** had subnanomolar potency (0.45 nM) at human H_3 receptor and good bioavailability (good %F, low clearance and acceptable half-life in rats). Further modification of this novel series to reduce the interaction with hERG channels and improve the overall drug likeness while retaining high potency will be reported elsewhere.

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 performed with prepacked Analogix cartridges. Thin-layer chromatography was performed on 250 mm silica gel 60 glass-backed plates from Merck with F254 as indicator. All target compounds possessed a purity of at least 95% as determined by elemental analysis.

(4b*S*,6a*S*,9a*R*)-2-Methoxy-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrole (9) and (4b*R*,6a*S*,9a*R*)-2-Methoxy-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]-pyrrole (10). 8-Benzyl-2-methoxy-6a,7,8,9,10,11-hexahydro-6*H*-benzo[4,5]indeno[1,7*a*−*c*]pyrrole (prepared according to the procedure of Meyers[10]) (1.0 g, 3.0 mmol) and 10% Pd/C (200 mg) were stirred in ethanol (30 mL) under hydrogen for 2 h. The reaction mixture was filtered and concentrated under vacuum to provide 617.8 mg (84.2%) of 2-Methoxy-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benzo[4,5]indeno[1,7*a*−*c*]pyrrole (**8**) as a 3:1 mixture of *R*/*S* isomers. MS (DCI/NH_3): m/z 244 $(M + H)^+$.

The mixture **8** was separated by flash chromatography (silica gel, 20:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide pure **9** and **10**.

9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (dd, 1H, $J = 8.7$, 1.2 Hz), 6.66 (s, 1H), 6.64 (d, 1H, $J = 3.0$ Hz), 3.76 (s, 3H), 3.16 (dd, 1H, $J = 11.5$, 6.0 Hz), 3.00 (dd, 1H, $J = 19$, 9.0 Hz), 2.92 (dd, 1H, $J = 18.0$, 9.0 Hz), 2.89 (m, 1H), 2.84 (dd, 1H, $J = 11.0$, 2.0 Hz), 2.55 (d, 1H, $J = 12.0$ Hz), 2.45 (d, $J = 12.0$ Hz), 2.24 (m, 1H), 2.13 (m, 2H), 2.04 (ddd, 1H, $J = 12.7$, 8.2, 2.5 Hz). 1.91 (m. 1H), 1.58 (m, 1H), 1.56 (m, 1H). MS (DCI/NH_3): m/z 244 $(M + H)^+$.

10. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, 1H, $J = 14.0$ Hz), 6.73 (dd, 1H, $J = 14.0$, 4.5 Hz), 6.62 (d, $J = 4.5$ Hz), 3.77 (s, 3H), 3.01 (dd, 1H, $J = 18.0$, 12.0 Hz), 2.89 (d, 1H, $J = 18.0$ Hz), 2.74 (dd, 1H, $J = 19.0$, 5.5 Hz), 2.6- 2.83 (m, 2H), 2.60 (d, 1H, $J = 19.0$ Hz), 2.13−2.21 (m, 2H), 1.79−1.98 (m, 4H), 1.50−1.68 (m, 2H), 1.33 (m, 1H). MS (DCI/NH_3): m/z 244 $(M + H)^+$.

(4b*S*,6a*S*,9a*R*)-2-Methoxy-8-methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrole (11). Compound **9** (109.0 mg, 0.45 mmol) and paraformaldehyde (403 mg, 13.4 mmol) were stirred in methanol (5 mL) at rt for 30 min. $NaBH_3CN$ (560 mg, 9.0 mmol) was added, and stirring was continued for 60 min. The mixture was quenched with 1 N NaOH (10 mL), extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum 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 102.0 mg (88.5%) of the title compound (**11**) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, 1H, $J = 9.15$ Hz, 1 H), 6.67 (s, 1 H). 6.66 (d, $J = 6.44$ Hz, 1 H), 3.77 (s, 3H), 2.95 (m, 2H), 2.72 (m, 2H), 2.44 (m. 1H), 2.22 (s. 3H), 2.07−1.55 (m, 9H). MS (DCI/NH_3): m/z 258 $(M + H)^+$.

(4b*S*,6a*S*,9a*R*)-8-Methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrol-2-ol (12). Compound **11** (100.0 mg, 0.39 mmol) and tetrabutylammonium iodide (158 mg, 0.43 mmol) were dissolved in CH_2Cl_2 (10 mL) and cooled to −78 °C. BCl_3 (0.97 mL, 1 M in CH_2Cl_2) was added dropwise. The mixture was stirred at −78 °C for 30 min and 0 °C for 5 h. It was then quenched with aq. satd. $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum 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 26.0 mg (27.5%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.10 (s, 1H), 6.96 (d, 1H, $J = 18.5$ Hz), 6.57 (dd,

1H, J = 14, 3.5 Hz), 6.48 (s, 3H), 1.29−3.50 (m, 14H). MS (DCI/NH_3): m/z 244 $(M + H)^+$.

Trifluoro-methanesulfonic Acid (4b*S*,6a*S*,9a*R*)-8-Methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benzo[4,5]indeno[1,7*a*−*c*]pyrrol-2-yl Ester (13). Compound **12** (25.0 mg, 0.11 mmol) and triethylamine (21 μL, 0.12 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C. Trifluoromethane sulfonic anhydride (21 μL, 0.15 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h. It was then quenched with water (2 mL), extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum to give the crude product, which was purified by flash chromatography (silica gel, 10:1 CH_2Cl_2/CH_3OH) to provide 52 mg (>100%) of the title compound as a colorless oil. MS (DCI/NH_3): m/z 376 $(M + H)^+$.

1-[3-((4b*S*,6a*S*,9a*R*)-8-Methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrol-2-yl)-phenyl]-ethanone (14). Compound **13** (0.1 mmol) and 3-acetylphenylboronic acid (33 mg, 0.20 mmol) were dissolved in toluene (2 mL) and ethanol (0.5 mL). Then 0.3 mL of 1 M Na_2CO_3 solution was added. Nitrogen was bubbled through the reaction mixture for 10 min. Tetrakis(triphenylphosphine)palladium (12.0 mg, 0.01 mmol) was then added. The mixture was stirred at 80 °C for 6 h. The reaction mixture was quenched with water (2 mL), extracted with CH_2Cl_2 (5 mL x 4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum 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 5.3 mg (15.3%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85−3.14 (m, 14 H) 2.47 (s, 3 H) 2.65 (s, 3 H) 7.00 (m, 2 H) 7.13 (m, 1 H) 7.48 (m, 1 H) 7.98 (m, 1 H) 8.14 (m, 1 H) 8.53 (m, 1 H). MS (DCI/NH_3): m/z 346 $(M + H)^+$.

(4b*R*,6a*S*,9a*R*)-2-Methoxy-8-methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrole (15). Compound **15** (203.1 mg, 98.9%) was prepared by using the procedure for making compound **11** except substituting Compound **10** for Compound **9**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, 1H, J = 8.4 Hz), 6.72 (dd, 1H, J = 10.5, 2.1 Hz). 6.62 (s, 1H), 3.77 (s, 3H), 2.92 (m, 1H), 2.73 (m, 1H), 2.64 (m. 2H), 2.44 (m. 1H), 2.34 (s, 3H), 2.15 (m, 2H), 2.04 (m, 1H), 1.95 (m, 1H), 1.79 (m, 1H), 1.68 (m, 1H), 1.55 (m, 3H). MS (DCI/NH_3): m/z 258 $(M + H)^+$.

1-[3-((4b*R*,6a*S*,9a*R*)-8-Methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrol-2-yl)-phenyl]-ethanone (16a). Compound **16a** (3.9 mg, 14.1%) was prepared by using the procedures for making compound **14**, except substituting Compound **15** for Compound **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53−3.05 (m, 14 H) 2.34 (s, 3 H) 2.65 (s, 3 H) 7.00 (m, 1 H) 7.34 (d, J = 1.50 Hz, 1 H) 7.40 (dd, J = 8.48, 1.50 Hz, 1 H) 7.51 (t, J = 7.80 Hz, 1 H) 7.77 (d, J = 8.48 Hz, 1 H) 7.91 (d, J = 7.80 Hz, 1 H) 8.16 (m, 1 H). MS (DCI/NH_3): m/z 346 $(M + H)^+$.

4-((4b*R*,6a*S*,9a*R*)-8-Methyl-5,6,6a,7,8,9,10,11-octahydro-4b*H*-benz[4,5]indeno[1,7*a*−*c*]pyrrol-2-yl)-benzonitrile (16b). Compound **16b** (6.2 mg, 30.8%) was prepared by using the procedures for making compound **14**, except substituting Compound **15** for Compound 11 and substituting 4-cyanophenylboronic acid for 3-acetylphenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (q, 4H), 7.37 (dd, 1H), 7.29−7.31 (m, 2H), 3.33−1.25 (m, 17H). MS (DCI/NH_3): m/z 329 $(M + H)^+$.

(3a*R*,6a*R*)-5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrole-1-carboxylic Acid *tert*-Butyl Ester (19). To a solution of (3a*R*,6a*R*)-hexahydro-pyrrolo[3,4-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester[14] (**18**, 18.31 g, 0.86 mol) in methanol (450 mL) was added paraformaldehyde (52 g, 1.72 mol) and the mixture was stirred at room temperature for 1 h. Sodium cyanoborohydride was then added, and the mixture was stirred at room temperature for 10 h, diluted with 1 N NaOH (450 mL), and extracted with dichloromethane (5 × 200 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to provide the crude title compound (20.85 g, >100%) which could be used in the next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 4.18 (m, 1 H) 3.47−3.59 (m, 1 H) 3.34−3.46 (m, 2 H) 2.75−2.90 (m, 1 H) 2.71 (m, 1 H) 2.44−2.60 (m, 2 H) 2.29 (s, 3 H) 1.89−2.06 (m, 1 H) 1.65−1.81 (m, 1 H) 1.42−1.49 (m, 9 H). MS (DCI/NH_3): m/z 226 $(M + H)^+$.

(3a*R*,6a*R*)-5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrole (20). To a solution of compound **19** (20.8 g, 0.86 mol) in methanol (450 mL) was added aq 3 N HCl (300 mL). The mixture was stirred at room temperature overnight and concentrated to dryness at 30 °C under vacuum. The residue was treated with aq 1 N NaOH to obtain a pH of 9−10. The mixture was concentrated to dryness again. The residue was stirred with 200 mL of 10:1 CH_2Cl_2/CH_3OH overnight and then filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 10:1:0.1 CH_2Cl_2/CH_3OH/NH_4OH) to provide 12.4 g of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.12−4.17 (m, 1 H) 3.31−3.43 (m, 1 H) 3.19−3.30 (m, 1 H) 3.12 (d, J = 11.53 Hz, 1 H) 2.88−3.01 (m, 1 H) 2.69 (dd, J = 9.49, 2.37 Hz, 1 H) 2.40−2.52 (m, 2 H) 2.33 (s, 3 H) 2.12−2.28 (m, 1 H) 1.82−1.95 (m, 1 H). MS (DCI/NH_3): m/z 127 $(M + H)^+$.

3a*R*,6a*R*)-1-(4-Bromo-phenyl)-5-methyl-octahydro-pyrrolo [3,4-*b*]pyrrole (21). Compound **20** (1.0 g, 7.92 mmol), 1,4-dibromobenzene (2.24 g, 9.50 mmol), tris(dibenzylideneacetone)dipalladium (145 mg, 0.16 mmol), racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (200 mg, 0.32 mmol) and sodium *tert*-butoxide (1.14 g, 11.9 mmol) were dissolved in 10 mL of toluene and heated to 70 °C under N_2 for 5 h. The mixture was cooled to room temperature, diluted with water, and extracted with dichloromethane (20 mL × 4). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 40:1:0.1 CH_2Cl_2/CH_3OH/NH_4OH) to provide 1.81 g (81.2%) of the title compound as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.25−7.30 (m, 2 H) 6.41−6.46 (m, 2 H) 4.07(m, 1 H) 3.47 (ddd, J = 9.1, 7.7, 5.9 Hz, 1 H) 3.19 (dt, J = 8.9, 7.3 Hz, 1 H) 2.95 (m, 1 H) 2.68 (dd, J = 9.0, 3.0 Hz, 1 H) 2.55−2.60 (m, 3 H) 2.32 (s, 3 H) 2.13−2.22 (m, 1 H) 1.88−1.98 (m, 1 H). MS (DCI/NH_3): m/z 281/283 $(M + H)^+$.

(3a*R*,6a*R*)-4′-(5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-carbonitrile (17a). Compound **21** (30.0 mg, 0.11 mmol), 4-cyanophenylboronic acid (18.8 mg, 0.13 mmol), palladium(II) acetate (1.2 mg, 0.005 mmol), 2-(dicyclohexylphosphino)biphenyl (3.8 mg, 0.01 mmol), and potassium phosphate (K_3PO_4) (75 mg, 0.35 mmol) were dissolved in 1 mL of toluene, 0.5 mL of isopropyl alcohol, and 0.5 mL of water. The mixture was stirred at 60 °C under N_2 for 5 h. The mixture was cooled to room temperature, diluted with water, and extracted with dichloromethane (5 mL × 5). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 20:1 CH_2Cl_2/CH_3OH) to provide 23.1 mg (71.3%) of the title compound as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.60−7.68 (m, 4 H) 7.47−7.53 (m, 2 H) 6.61−6.68 (m, 2 H) 4.14−4.22 (m, 1 H) 3.51−3.60 (m, 1 H) 3.28−3.35 (m, 1 H) 2.93−3.01 (m, 1 H) 2.71−2.75 (m, 1 H) 2.48−2.61 (m, 3 H) 2.32 (s, 3 H) 2.14−2.25 (m, 1 H) 1.96 (d, J = 7.12 Hz, 1 H). MS (DCI/NH_3): m/z 304 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.2CH_3OH$) C, H, N.

(3a*R*,6a*R*)-4′-(Hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-carbonitrile (17b). Trifluoro-methanesulfonic Acid 4′-Cyano-biphenyl-4-yl Ester (SM-1 of 17b). 4-cyano-4′-hydroxybiphenyl was dissolved in dichloromethane. Triethylamine (2.5 equiv) was added, and the mixture was stirred at room temperature. Triflic anhydride (1.3 equiv) was added slowly, and the resulting solution was stirred for 2 h. The mixture was diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography to provide the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm

7.76 (d, J = 8.82 Hz, 2 H) 7.66 (d, J = 8.82 Hz, 4 H) 7.40 (d, J = 8.82 Hz, 2 H). MS (DCI/NH_3): m/z 328 $(M + H)^+$.

(3a*R*,6a*R*)-Hexahydro-pyrrolo[3,4-*b*]pyrrole-1,5-dicarboxylic Acid 5-Benzyl Ester 1-*tert*-Butyl Ester (SM-2 of 17b). Compound **18** and *N*-(benzyloxycarbonyloxy)succinimide (3.42 g, 13.7 mmol) were mixed in 15 mL of dichloromethane. The mixture was stirred at room temperature overnight and then concentrated under vacuum to provide the crude product. The residue was purified by flash chromatography (silica gel, 5:1 hexane/EtOAc) to provide 4.50 g of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.29−7.43 (m, 5 H) 5.13 (s, 2 H) 4.15−4.33 (m, 1 H) 3.39−3.74 (m, 5 H) 3.20−3.37 (m, 1 H) 2.84−2.96 (m, 1 H) 1.92−2.03 (m, 1 H) 1.66−1.82 (m, 1 H) 1.46 (s, 9 H). MS (DCI/NH_3): m/z 347 $(M + H)^+$.

(3a*R*,6a*R*)-Hexahydro-pyrrolo[3,4-*b*]pyrrole-5-carboxylic Acid Benzyl Ester (SM-3 of 17b). Compound SM-2 **of 17b** (4.5 g, 12.5 mmol) was stirred with a mixture of dichloromethane and trifluoroacetic acid (15 mL/15 mL) for 2 h. The solvent was removed under reduced pressure, and the residue was basified with saturated sodium bicarbonate and then extracted with dichloromethane (50 mL × 3). The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 15:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 1.26 g (39.4%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.28−7.40 (m, 5 H) 5.12 (s, 2 H) 3.74−3.87 (m, 1 H) 3.53−3.71 (m, 2 H) 3.36−3.48 (m, 1 H) 3.18−3.32 (m, 1 H) 3.01−3.13 (m, 1 H) 2.88−3.01 (m, 1 H) 2.70−2.83 (m, 1 H) 1.87−2.03 (m, 1 H) 1.58−1.76 (m, 1 H). MS (DCI/NH_3): m/z 247 $(M + H)^+$.

(3a*R*,6a*R*)-1-(4′-Cyano-biphenyl-4-yl)-hexahydro-pyrrolo [3,4-*b*]pyrrole-5-carboxylic Acid Benzyl Ester (SM-4 of 17b). Compound SM-3 of **17b** (1.46 g, 5.93 mmol), compound SM-1 of **17b** (1.94 g, 5.93 mmol), palladium acetate (53 mg, 0.24 mmol), racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 220 mg, 0.35 mmol), and sodium *tert*-butoxide (855 mg, 9.90 mmol) were mixed in 12 mL of toluene and heated at 85 °C under N_2 for 5.5 h. The mixture was cooled to room temperature, diluted with water, and extracted with dichloromethane (60 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 100:1 CH_2Cl_2/CH_3OH) to provide 0.75 g (29.9%) of the title compound. MS (DCI/NH_3): m/z 424 $(M + H)^+$.

(3a*R*,6a*R*)-4′-(Hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-carbonitrile (17b). Compound SM-4 of **17b** (750 mg, 1.77 mmol) was refluxed in 10 mL of trifluoroacetic acid for 2.5 h. The solution was concentrated and triturated with dichloromethane. The residue was redissolved in dichloromethane and stirred with sodium bicarbonate powder. The solution was loaded on a silica gel column and purified by flash chromatography (silica gel, 20:1 CH_2Cl_2/CH_3OH) to provide 330 mg (64%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 2.71 Hz, 4 H) 7.51 (d, J = 8.81 Hz, 2 H) 6.66 (d, J = 8.82 Hz, 2 H) 4.07−4.17 (m, 1 H) 3.50−3.65 (m, 1 H) 3.24−3.36 (m, 1 H) 2.86−3.10 (m, 5 H) 2.15−2.29 (m, 1 H) 1.74−1.93 (m, 1 H). MS (DCI/NH_3): m/z 290 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3 \cdot 0.35CH_3OH$) C, H, N.

(3a*R*,6a*R*)-1-(4-benzylphenyl)-5-methyloctahydropyrrolo[3,4-*b*]pyrrole (17c). Compound **17b** (22 mg, 0.076 mmol) was dissolved in 2.5 mL of anhydrous THF under nitrogen. Sodium hydride (95%, 4 mg, 0.167 mmol) was added, and the mixture was stirred at room temperature for 1 h. Iodoethane (18 μL, 0.225 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was diluted with water and extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 50:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 11.0 mg (46%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 1.36 Hz, 4 H) 7.50 (d, J = 8.82 Hz, 2 H) 6.65 (d, J = 8.82 Hz, 2 H) 4.14−4.23 (m, 1 H) 3.47−3.60 (m, 1 H) 3.27−3.39 (m, 1 H) 2.92−3.04 (m, 1 H) 2.70−2.81 (m, 1 H) 2.38−2.67 (m, 5 H) 2.11−2.25 (m, 1 H) 1.89−2.03 (m, 1 H) 1.08 (t, J = 7.12 Hz, 3 H). MS (DCI/NH_3): m/z 318 $(M + H)^+$. Anal. ($C_{21}H_{23}N_3 \cdot 0.15CH_3OH$) C, H, N.

4′-[(3a*R*,6a*R*)-5-Isopropylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-1,1′-biphenyl-4-carbonitrile (17d). To a solution of compound **17b** (26 mg, 0.09 mmol) in methanol (2 mL) was added acetone (132 μL, 1.8 mmol), and the mixture was stirred at room temperature for 1.5 h. Sodium cyanoborohydride (28 mg, 0.44 mmol) was added and the mixture stirred overnight. The mixture was diluted with 2 mL of 1 N NaOH and extracted with 20:1 dichloromethane/methanol (10 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 50:1:0.1 $CH_2Cl_2/CH_3OH/NH_4OH$) to provide 17 mg (57%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.63 (d, J = 3.74 Hz, 4 H) 7.50 (d, J = 9.05 Hz, 2 H) 6.64 (d, J = 8.73 Hz, 2 H) 4.16−4.22 (m, 1 H) 3.48−3.55 (m, 1 H) 3.31−3.38 (m, 1 H) 2.90−3.01 (m, 2 H) 2.74 (t, J = 7.96 Hz, 1 H) 2.46−2.52 (m, 2 H) 2.31−2.39 (m, 1 H) 2.10−2.20 (m, 1 H) 1.90−1.99 (m, 1 H) 1.06 (dd, J = 6.24, 1.87 Hz, 6 H). MS $(M + H)^+$ = 332. Anal. ($C_{22}H_{25}N_3 \cdot 0.1H_2O$) C, H, N.

4′-[(3a*R*,6a*R*)-5-(Cyclopropylmethyl)hexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-1,1′-biphenyl-4-carbonitrile (17e). Compound **17e** (19.0 mg, 61.5%) was prepared by using the procedure for making compound **17d** except substituting cyclo-propanecarbox-aldehyde for acetone. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 2.76 Hz, 4 H), 7.50 (d, J = 8.90 Hz, 2 H), 6.65 (d, J = 8.59 Hz, 2 H), 4.18−4.26 (m, 1 H), 3.51−3.59 (m, 1 H), 3.31−3.41 (m, 1 H), 2.87−3.09 (m, 2 H), 2.73−2.83 (m, 1 H), 2.56−2.70 (m, 2 H), 2.25−2.43 (m, 2 H), 2.12−2.23 (m, 1 H), 1.93−2.05 (m, 1 H), 0.85−0.96 (m, 1 H), 0.12 (d, J = 4.30 Hz, 2 H), 0.50 (d, J = 7.98 Hz, 2 H). MS (DCI/NH_3): m/z 344 $(M + H)^+$. Anal. ($C_{23}H_{25}N_3$) C, H, N.

4′-[(3a*R*,6a*R*)-5-Propylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-1,1′-biphenyl-4-carbonitrile (17f). Compound **17f** (14.0 mg, 55.5%) was prepared by using the procedure for making compound **17c** except substituting iodopropane for iodoethane. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 1.70 Hz, 4 H), 7.50 (d, J = 8.82 Hz, 2 H), 6.64 (d, J = 8.82 Hz, 2 H), 4.12−4.22 (m, 1 H), 3.46−3.57 (m, 1 H), 3.27−3.39 (m, 1 H), 2.88−3.02 (m, 1 H), 2.61−2.74 (m, 2 H), 2.49−2.58 (m, 2 H), 2.26−2.42 (m, 2 H), 2.10−2.23 (m, 1 H), 1.86−2.04 (m, 1 H), 1.40−1.54 (m, 2 H), 0.89 (t, J = 7.29 Hz, 3 H). MS (DCI/NH_3): m/z 332 $(M + H)^+$. Anal. ($C_{22}H_{25}N_3 \cdot 0.1H_2O$) C, H, N.

4′-((3a*R*,6a*R*)-5-Isobutyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-carbonitrile (17g). Compound **17g** (34.0 mg, 100%) was prepared by using the procedure for making compound **17d** except substituting isobutylaldehyde for acetone. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 1.36 Hz, 4 H), 7.50 (d, J = 8.82 Hz, 2 H), 6.64 (d, J = 8.82 Hz, 2 H), 4.13−4.25 (m, 1 H), 3.44−3.54 (m, 1 H), 3.29−3.41 (m, 1 H), 2.86−2.99 (m, 1 H), 2.44−2.70 (m, 4 H), 2.06−2.19 (m, 2 H), 1.86−2.02 (m, 2 H), 1.61−1.77 (m, 1 H), 0.82−0.98 (m, 6 H). MS (DCI/NH_3): m/z 346 $(M + H)^+$. Anal. ($C_{23}H_{27}N_3 \cdot 0.9CH_3OH$) C, H, N.

4′-[(3a*R*,6a*R*)-5-Butylhexahydropyrrolo[3,4-*b*]pyrrol-1(2*H*)-yl]-1,1′-biphenyl-4-carbonitrile (17h). Compound **17h** (10.0 mg, 32%) was prepared by using the procedure for making compound **17d** except substituting *n*-butylaldehyde for acetone. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.64 (d, J = 2.03 Hz, 4 H), 7.50 (d, J = 8.81 Hz, 2 H), 6.64 (d, J = 8.82 Hz, 2 H), 4.13−4.25 (m, 1 H), 3.46−3.59 (m, 1 H), 3.27−3.40 (m, 1 H), 2.87−3.04 (m, 1 H), 2.49−2.77 (m, 4 H), 2.29−2.46 (m, 2 H), 2.12−2.24 (m, 1 H), 1.86−2.03 (m, 1 H), 1.23−1.49 (m, J = 44.07 Hz, 4 H), 0.89 (t, J = 7.12 Hz, 3 H). MS (DCI/NH_3): m/z 346 $(M + H)^+$. Anal. ($C_{23}H_{27}N_3 \cdot 1.0CH_3OH$) C, H, N.

Compounds **22**−**27** were synthesized from corresponding known methyl or Boc or Cbz protected diamines using the procedures for making compounds **17**.

4′-((3a*S*,6a*S*)-5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-carbonitrile (22). Prepared from (3a*S*,6a*S*)-5-methyloctahydropyrrolo[3,4-*b*]pyrrole (CAS no. 876130-70-0)[17] (3.1 mg. 3.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.51 (d, J = 8.8, 2H), 6.63 (d, J = 8.8, 2H), 4.35 (m, 1H), 3.63 (m, 1H), 3.42 (m, 1H), 3.20 (m, 1H), 2.85−2.40 (m, 7H), 2.22 (m, 1H), 2.03 (m, 1H). MS (DCI/NH_3): m/z 304 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.95CH_3OH$) C, H, N.

4′-((3a*R*,6a*R*)-1-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-5-yl)-biphenyl-4-carbonitrile (23). Prepared from compound **18** (3.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.60 (m, 4H), 7.49 (d, J = 8.8, 2H), 6.69 (d, J = 8.8, 2H), 3.54 (d, J = 10.5, 1H), 3.43 (d, J = 8.8, 1H), 3.32 (dd, J = 4.9, 9.6, 1H), 3.26 (dd, J = 5.3, 10.4, 1H), 3.16 (t, J = 8.0, 1H), 2.99 (m, 2H), 2.42 (s, 3H), 2.38 (m, 1H), 2.25−2.10 (m, 1H), 1.87−1.71 (m, 1H). MS (DCI/NH_3): m/z 304 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.2CH_3OH$) C, H, N.

4′-((3a*S*,6a*S*)-1-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-5-yl)-biphenyl-4-carbonitrile (24). Prepared from (3a*S*,6a*S*)-*tert*-butyl hexahydropyrrolo[3,4-*b*]pyrrole-1(2*H*)-carboxylate (CAS no. 370880-16-3)[14,18] (20.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.59 (m, 4H), 7.49 (d, J = 8.8, 2H), 6.69 (d, J = 8.8, 2H), 3.55 (m, 1H), 3.45 (t, J = 9.0, 1H), 3.39−3.22 (m, 2H), 3.17 (m, 1H), 2.98 (m, 2H), 2.42 (m, 4H), 2.19 (m, 1H), 1.81 (m, 1H). MS (DCI/NH_3): m/z 304 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.1CH_2Cl_2$) C, H, N.

4′-((1*S*,5*R*)-3-Methyl-3,6-diaza-bicyclo[3.2.0]hept-6-yl)-biphenyl-4-carbonitrile (25). Prepared from (1*S*,5*R*)-3,6-Diazabicyclo[3.2.0]heptane-6-carboxylic acid, 1,1-dimethylethyl ester (CAS no. 370882-66-9)[14,19] (21.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (q, J = 8.7, 4H), 7.46 (d, J = 8.6, 2H), 6.48 (d, J = 8.6, 2H), 4.72−4.57 (m, 1H), 3.97 (t, J = 9.0, 1H), 3.94−3.80 (m, 1H), 3.47−3.35 (m, 1H), 3.34−3.15 (m, 2H), 2.57 (s, 3H), 2.39−2.05 (m, 2H). MS (DCI/NH_3): m/z 290 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3 \cdot 0.2H_2O$) C, H, N.

4′-((1*R*,5*S*)-3-Methyl-3,6-diaza-bicyclo[3.2.0]hept-6-yl)-biphenyl-4-carbonitrile (26). Prepared from (1*S*,5*S*)-benzyl 3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (CAS no. 370881-43-9)[19a] (10.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.57 (m, 4H), 7.45 (d, J = 8.7, 2H), 6.46 (d, J = 8.7, 2H), 4.60 (dd, J = 3.8, 6.8, 1H), 3.95 (t, J = 7.8, 1H), 3.81 (dd, J = 3.9, 7.5, 1H), 3.33 (d, J = 10.5, 1H), 3.22−3.10 (m, 2H), 2.48 (s, 3H), 2.22−2.10 (m, 1H), 2.05 (d, J = 11.7, 1H). MS (DCI/NH_3): m/z 290 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3 \cdot 0.2CH_2Cl_2$) C, H, N.

4′-((1*R*,5*R*)-6-Methyl-3,6-diaza-bicyclo[3.2.0]hept-3-yl)-biphenyl-4-carbonitrile (27). Prepared from (1*S*,5*R*)-3,6-Diazabicyclo[3.2.0]heptane-6-carboxylic acid, 1,1-dimethylethyl ester (CAS no. 370882-66-9)[14,19] (10.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.60 (m, 4H), 7.52 (d, J = 8.8, 2H), 6.80 (d, J = 8.7, 2H), 4.20−3.94 (m, 1H), 3.83−3.73 (m, 2H), 3.67−3.43 (m, 1H), 3.40−3.33 (m, 1H), 3.31−3.17 (m, 2H), 3.10−3.00 (m, 1H), 2.47 (s, 3H). MS (DCI/NH_3): m/z 290 $(M + H)^+$. Anal. ($C_{19}H_{19}N_3 \cdot 0.15CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-1-Biphenyl-4-yl-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (28). Compound **28** (30.0 mg, 54.4%) was prepared by using the procedure for making compound **21** except substituting 4-bromobiphenyl for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.45−7.58 (m, 4 H) 7.33−7.43 (m, 3 H) 6.61−6.67 (m, 2 H) 4.15−4.27 (m, 2 H) 3.50−3.65 (m, 1 H) 3.24−3.35 (m, 1 H) 2.95−3.09 (m, 1 H) 2.59−2.82 (m, 4 H) 2.39 (s, 3 H) 2.13−2.24 (m, 1 H) 1.92−2.03 (m, 1 H). MS (DCI/NH_3): m/z 279 (M + H)+. Anal. ($C_{19}H_{22}N_2 \cdot 1.0CH_2Cl_2 \cdot 0.3CH_3OH$) C, H, N.

(3a*R*,6a*R*)-1-Biphenyl-3-yl-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (29). Compound **29** (26.5 mg, 48.1%) was prepared by using the procedure for making compound **21** except substituting 3-bromobiphenyl for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.4, 8.3, 2H), 7.46−7.38 (m, 2H), 7.38−7.28 (m, 2H), 6.94 (d, J = 7.7, 1H), 6.76−6.72 (m, 1H), 6.56 (dd, J = 2.3, 8.1, 1H), 4.25 (dd, J = 6.7, 16.5, 1H), 3.60 (dd, J = 7.1, 15.0, 1H), 3.35 (dd, J = 7.6, 15.0, 1H), 3.15−2.94 (m, 1H), 2.88−2.71 (m, 2H), 2.71−2.58 (m, 1H), 2.42 (s, 3H), 2.25−2.11 (m, 1H), 2.06−1.88 (m, 1H). MS (DCI/NH_3): m/z 279 $(M + H)^+$. Anal. ($C_{19}H_{22}N_2 \cdot 0.9CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-1-(4-Benzyl-phenyl)-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (30). Compound **30** was prepared by using the procedure for making compound **21** except substituting 4-bromodiphenylmethane for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.22−7.30 (m, 3 H) 7.12−7.20 (m, 2 H) 7.05 (d, J = 8.48 Hz, 2 H) 6.43−6.56 (m, 2 H) 4.17−4.25 (m, 1 H) 3.89 (s, 2 H) 3.46−3.57 (m, 1 H) 3.22−3.34 (m, 1 H) 3.01−3.15 (m, 2 H) 2.89−3.00 (m, 1 H) 2.73 (m, 2 H) 2.50 (s, 3 H) 2.08−2.24 (m, 1 H) 1.89−1.99 (m, 1 H). MS (DCI/NH_3): m/z 293 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2 \cdot 0.6CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-5-Methyl-1-(4-phenoxy-phenyl)-octahydro-pyrrolo[3,4-*b*]pyrrole (31). Compound **31** (20.5 mg, 17.6%) was prepared by using the procedure for making compound **21** except substituting 4-bromodiphenylether for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.25−7.31 (m, 2 H) 6.87−7.05 (m, 5 H) 6.51−6.61 (m, 2 H) 4.03−4.14 (m, 1 H) 3.45−3.56 (m, 1 H) 3.15−3.26 (m, 1 H) 2.90−3.00 (m, 1 H) 2.69−2.76 (m, 1 H) 2.50−2.63 (m, 3 H) 2.34 (s, 3 H) 2.13−2.22 (m, 1 H) 1.85−2.00 (m, 1 H). MS (DCI/NH_3): m/z 295 $(M + H)^+$. Anal. ($C_{19}H_{22}N_2O \cdot 0.2CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-1-[4′-(5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-4-yl]-ethanone (32). Compound **32** (405.6 mg, 53.2%) was prepared by using the procedure for making compound **21** except substituting 4-(4-bromophenyl)acetophenone for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.96−8.00 (m, 2 H) 7.46−7.57 (m, 4 H) 6.65 (m, 2 H) 4.11−4.22 (m, 1 H) 3.49−3.62 (m, 1 H) 3.26−3.39 (m, 1 H) 2.97 (m, 1 H) 2.69−2.75 (m, 1 H) 2.61 (s, 3 H) 2.50−2.62 (m, 3 H) 2.32 (s, 3 H) 2.13−2.23 (m, 1 H) 1.91−2.01 (m, 1 H). MS (DCI/NH_3): m/z 321 $(M + H)^+$. Anal. ($C_{21}H_{24}N_2O \cdot 0.4CH_2Cl_2 \cdot 0.2CH_3OH$) C, H, N.

(3a*R*,6a*R*)-1-[4′-(5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-3-yl]-ethanone (33). Compound **33** was prepared by using the procedure for making compound **17a** except substituting 3-acetylphenylboronic acid for 4-cyanophenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.13 (t, J = 1.86 Hz, 1 H) 7.84 (d, J = 7.46 Hz, 1 H) 7.74 (d, J = 8.14 Hz, 1 H) 7.51 (t, J = 8.14 Hz, 2 H) 6.64 (d, J = 8.48 Hz, 2 H) 4.28−4.42 (m, 1 H) 3.55−3.67 (m, 1 H) 3.34−3.49 (m, 1 H) 3.12−3.27 (m, 1 H) 2.69−2.98 (m, 4 H) 2.65 (s, 3 H) 2.57 (s, 3 H) 2.15−2.30 (m, 1 H) 1.94−2.11 (m, 1 H). MS (DCI/NH_3): m/z 321 $(M + H)^+$. Anal. ($C_{21}H_{24}N_2O \cdot 0.25CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-4′-(5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-biphenyl-3-carbonitrile (34). Compound **34** (26.5 mg, 48.1%) was prepared by using the procedure for making compound **17a** except substituting 3-cyanophenylboronic acid for 4-cyanophenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.73−7.84 (m, 2 H) 7.39−7.54 (m, 4 H) 6.62−6.69 (m, 2 H) 4.13−4.23 (m, 1 H) 3.48−3.64 (m, 1 H) 3.25−3.41 (m, 1 H) 2.91−3.04 (m, 1 H) 2.69−2.76 (m, 1 H) 2.50−2.68 (m, 3 H) 2.33 (s, 3 H) 2.11−2.25 (m, 1 H) 1.91−2.02 (m, 1 H). MS (DCI/NH_3): m/z 304 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.3CH_3OH$) C, H, N.

(3a*R*,6a*R*)1-(4′-Fluoro-biphenyl-4-yl)-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (35). Compound **35** (16.5 mg, 52.1%) was prepared by using the procedure for making compound **17a** except substituting 4-fluorophenylboronic acid for 4-cyanophenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.40−7.50 (m, 4 H) 7.02−7.11 (m, 2 H) 6.58−6.67 (m, 2 H) 4.13−4.26 (m, 1 H) 3.50−3.63 (m, 1 H) 3.24−3.37 (m, 1 H) 3.01 (m, 1 H) 2.56−2.79 (m, 4 H) 2.38 (s, 3 H) 2.11−2.25 (m, 1 H) 1.91−2.01 (m, 1 H). MS (DCI/NH_3): m/z 297 $(M + H)^+$. Anal. ($C_{20}H_{21}N_3 \cdot 0.1CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-1-(4′-Bromo-biphenyl-4-yl)-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (36). Compound **36** (340 mg, 60%) was prepared by using the procedure for making compound **21** except substituting 4,4′-dibromobiphenyl for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.38−7.51 (m, 6 H) 6.60−6.66 (m, 2 H) 4.16−4.23 (m, 1 H) 3.51−3.63 (m, 1 H) 3.27−3.34 (m, 1 H) 3.06 (m, 1 H) 2.75 (m, 2 H) 2.61 (m, 2 H) 2.38 (s, 3 H) 2.13−2.24 (m, 1 H) 1.98−2.18 (m, 1 H). MS (DCI/NH_3): m/z 357, 359 $(M + H)^+$.

(3a*R*,6a*R*)-1-(4′-Methoxy-biphenyl-4-yl)-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (37). Compound **37** (20 mg, 23.3%) was prepared by using the procedure for making compound **21** except substituting 3-bromobiphenyl for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.47 (d, J = 9.15 Hz, 2 H) 7.42 (d, J = 9.15 Hz, 2 H) 6.94 (d, J = 8.81 Hz, 2 H) 6.63 (d, J = 8.81 Hz, 2 H) 4.11−4.19 (m, 1 H) 3.83 (s, 3 H) 3.50−3.60 (m, 1 H) 3.22−3.33 (m, 1 H) 2.91−3.03 (m, 1 H) 2.69−2.77 (m, 1 H) 2.52−2.62 (m, 3 H) 2.34 (s, 3 H) 2.11−2.26 (m, 1 H) 1.89−2.01 (m, 1 H). MS (DCI/NH_3): m/z 309 $(M + H)^+$. Anal. ($C_{20}H_{24}N_2O \cdot 0.3CH_3OH$) C, H, N.

(3a*R*,6a*R*)-1-(6-Bromo-naphthalen-2-yl)-5-methyl-octahydro-pyrrolo[3,4-*b*]pyrrole (38). Compound **38** (203.9 mg, 38.8%) was prepared by using the procedure for making compound **21** except substituting 2,6-dibromonaphthalene for 1,4-dibromobenzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 1.7, 1H), 7.62 (d, J = 7.9, 1H), 7.50 (d, J = 8.7, 1H), 7.42 (dd, J = 1.9, 8.9, 1H), 6.97 (dd, J = 2.4, 9.1, 1H), 6.69 (d, J = 2.3, 1H), 4.55−4.31 (m, 1H), 3.76−3.59 (m, 1H), 3.56−3.43 (m, 1H), 3.36−3.16 (m, 1H), 2.89−2.47 (m, 7H), 2.36−2.19 (m, 1H), 2.11−1.93 (m, 1H). MS (DCI/NH_3): m/z 331, 333 $(M + H)^+$.

4-[6-((3a*R*,6a*R*)-5-Methyl-hexahydro-pyrrolo[3,4-*b*]pyrrol-1-yl)-naphthalen-2-yl]-benzonitrile (39). Compound **39** (6.2 mg, 30.8%) was prepared by using the procedures for making compound **17a** except substituting compound **38** for compound **21**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 1.7, 1H), 7.81−7.69 (m, 4H), 7.61 (dd, J = 1.9, 8.6, 1H), 7.37 (m, 2H), 7.04 (dd, J = 2.5, 8.9, 1H), 6.77 (d, J = 2.3, 1H), 4.41−4.28 (m, 1H), 3.67 (dd, J = 6.9, 15.9, 1H), 3.44 (dd, J = 7.7, 15.0, 1H), 3.16−3.00 (m, 1H), 2.85−2.73 (m, 2H), 2.70−2.56 (m, 2H), 2.39 (s, 3H), 2.24 (dt, J = 7.8, 14.6, 1H), 2.02 (dt, J = 5.9, 18.6, 1H). MS (DCI/NH_3): m/z 353 $(M + H)^+$. Anal. ($C_{24}H_{23}N_3 \cdot 0.1CH_2Cl_2$) C, H, N.

(3a*R*,6a*R*)-1-[6-(4-Fluoro-phenyl)-naphthalen-2-yl]-5-methyl-octahydropyrrolo[3,4-*b*]pyrrole (40). Compound **40** (12.8 mg, 34.9%) was prepared by using the procedures for making compound **17a**, except substituting compound **38** for compound **21** and substituting 4-fluorophenylboronic acid for 4-cyanophenylboronic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 1.4, 1H), 7.76 (d, J = 8.9, 1H), 7.72 7.58 (m, 4H), 7.18−7.10 (m, 2H), 6.99 (dd, J = 2.4, 8.9, 1H), 6.75 (d, J = 2.1, 1H), 4.62−4.35 (m, 1H), 3.83−3.62 (m, 1H), 3.60−3.44 (m, 1H), 3.40−3.17 (m, 1H), 2.95−2.44 (m, 7H), 2.35−2.18 (m, 1H), 2.17−1.92 (m, 1H). MS (DCI/NH_3): m/z 347 $(M + H)^+$. Anal. ($C_{23}H_{23}FN_2 \cdot 0.1CH_2Cl_2$) C, H, N.

Note Added after ASAP Publication. This manuscript was released ASAP on July 9, 2009, with a couple of incorrect compound numbers and without Scheme 3 due to a production error. The correct version was posted on July 15, 2009.

Supporting Information Available: Combustion analysis of compounds **17a**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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