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Octahydropyrrolo[3,4-*c*]pyrrole: A Diamine Scaffold for Construction of Either α4β2 or α7-Selective Nicotinic Acetylcholine Receptor (nAChR) Ligands. Substitutions that Switch Subtype Selectivity

William H. Bunnelle,*,† Karin R. Tietje,† Jennifer M. Frost,† Dan Peters,‡ Jianguo Ji,† Tao Li,† Marc J. C. Scanio,† Lei Shi,† David J. Anderson,† Tino Dyhring,‡ Jens H. Grønlien,† Hilde Ween,† Kirsten Thorin-Hagene,† and Michael D. Meyer†

Neuroscience Research, Abbott Laboratories, Department R47W, Building AP9A, Abbott Park, Illinois 60064-6117, and NeuroSearch A/S, 93 Pederstrupvej, DK-2750 Ballerup, Denmark

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A series of 5-(pyridine-3-yl)octahydropyrrolo[3,4-*c*]pyrroles have been prepared that exhibit high affinity to α4β2 and/or α7 nicotinic acetylcholine receptors (nAChRs). Simple substitution patterns have been identified that allow construction of ligands that are highly selective for either nAChR subtype. The effects of substitution on subtype selectivity provide some insight into the differences in the ligand binding domains of the α4β2 and α7 receptors, especially in regions removed from the cation binding pocket.

Introduction

Nicotinic acetylcholine receptors have become prominent targets for drug discovery efforts aimed at treating a wide range of CNS[a] disorders, including cognitive dysfunction (attention-deficit hyperactivity disorder, cognitive deficits in schizophrenia), neurodegenerative conditions (Alzheimer's disease, Parkinson's disease), substance abuse, and pain, among others.[1−4] Consequently, the nAChR pharmacology offers great potential for the development of new drugs in areas of significant unmet medical need. A plethora of nAChR subtypes exist in the brain, and much current effort is devoted to understanding the structure, distribution, and function of each.[5,6] An early and still useful categorization divides neuronal nAChRs into two major families, namely those with high (nanomolar) affinity to (*S*)-nicotine and a distinct population that is labeled selectively by the snake venom component α-bungarotoxin. The former group consists mainly of receptors constructed from heteropentameric combinations of α4 and β2 subunits, probably with stoichiometry $(\alpha4)_2(\beta2)_3$, while the latter is represented mainly by a homopentamer of the α7 subunit.[6] The α4β2 and α7 subtypes are differentially distributed in the CNS, but both are expressed in brain regions (cortex, hippocampus) that are important for cognitive processes, where their main function appears to be to modulate the release of neurotransmitters (including acetylcholine, glutamate, GABA, dopamine, and serotonin) that are important for a wide range of CNS functions.[7−9] The α7 nAChR is a rapid-opening, rapidly desensitizing ion channel that is implicated in learning, memory, and information processing,[10−14] including gating deficits that are common in schizophrenia,[15,16] while peripheral α7 nAChRs have been shown to play a role in inflammation response.[17,18] Central α4β2 nAChRs have been identified as key mediators of the analgesic effects of nicotinic agonists[19−22] but are also linked to learning, memory, and attentional effects.[23−28] A number of selective α4β2 and α7 nAChR ligands, including AZD-3480 (**1**),[29,30] ABT-089 (**2**),[31,32] MEM-3454,[33,34] PHA-543613 (**3**),[35] and GTS-21 (**4**),[36,37] among others (Figure 1), have been advanced to human clinical trials for treatment of cognitive disorders.

Structural features of the nAChR agonist binding site were originally inferred from site-specific mutagenesis and photoaffinity labeling studies[38] and nicely confirmed by the three-dimensional structure of the acetylcholine binding protein (AChBP) isolated from snail glia.[39] A key feature is the convergence of several tyrosine and tryptophan side chains to form a pocket that receives the protonated or quaternized amine that is an essential element of the nicotinic agonist pharmacophore.[40,41] A π-cation interaction has been established as a substantial contributor to binding of acetylcholine[42] but appears less important for nicotine.[43,44] Hydrogen-bonding interactions have been proposed to account for charge compensation of protonated amines within that site.[45−47] General features of the cation binding site are well-conserved across nAChR subtypes, including α4β2 and α7, and do not provide much basis for designing subtype-selective ligands. On the other hand, homology models based on AChBP structures have revealed differences in the ligand binding site outside of the cation binding domain,[48,49] and it has been suggested that the α7 binding site is more lipophilic and presents a less negative electrostatic surface than that for the α4β2 subtype.[50] Although it has not been very difficult to develop ligands that exhibit high selectivity for either α4β2 or α7 subtype over the other, to our knowledge, there have been no systematic studies of structure and substitution effects that determine this selectivity. We have identified a series of *N*-pyridinyldiamines that exhibit high selectivity for either α4β2 or α7 nAChR subtype depending upon simple changes

*To whom correspondence should be addressed. Phone: (847) 938-9765. Fax: (847) 937-9195. E-mail: William.h.bunnelle@abbott.com. Address: Abbott Laboratories, R4DE, AP9A, 100 Abbott Park Road, Abbott Park, IL 60064.

† Abbott Laboratories.

‡ NeuroSearch A/S.

[a] Abbreviations: CNS, central nervous system; nAChR, nicotinic acetylcholine receptor; AChBP, acetylcholine binding protein; GABA, gamma aminobutyric acid; FLIPR, fluorometric light-imaging plate reader; POETs, parallel oocyte elctrophysiology test station.

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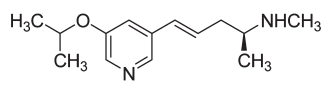
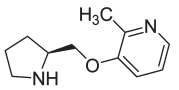
in substitution patterns. In addition to providing a general scaffold for preparation of ligands for either subtype, the SAR trends have the potential to clarify pharmacophore models of the α4β2 and α7 binding sites.

α4β2 selective:

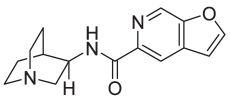


1 (AZD-3480)

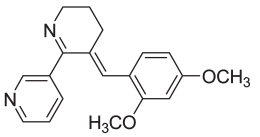


2 (ABT-089)

α7 selective:



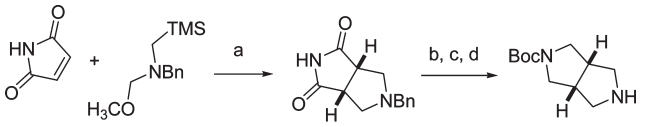
3 (PHA-543613)



4 (GTS-21)

Figure 1. Selective nAChR ligands advanced to human clinical trials.

Scheme 1. Preparation of the Diamine[a]



5

[a] Reagents and conditions: (a)CF_3CO_2H, CH_2C_{12}, 5 °C (83%); (b) $LiAlH_4$, THF, 70 °C; (c) Boc_2O, CH_2Cl_2, 20 °C; (d) H_2 (60 psi), Pd $(OH)_2$, CH_3OH, 50 °C (75%).

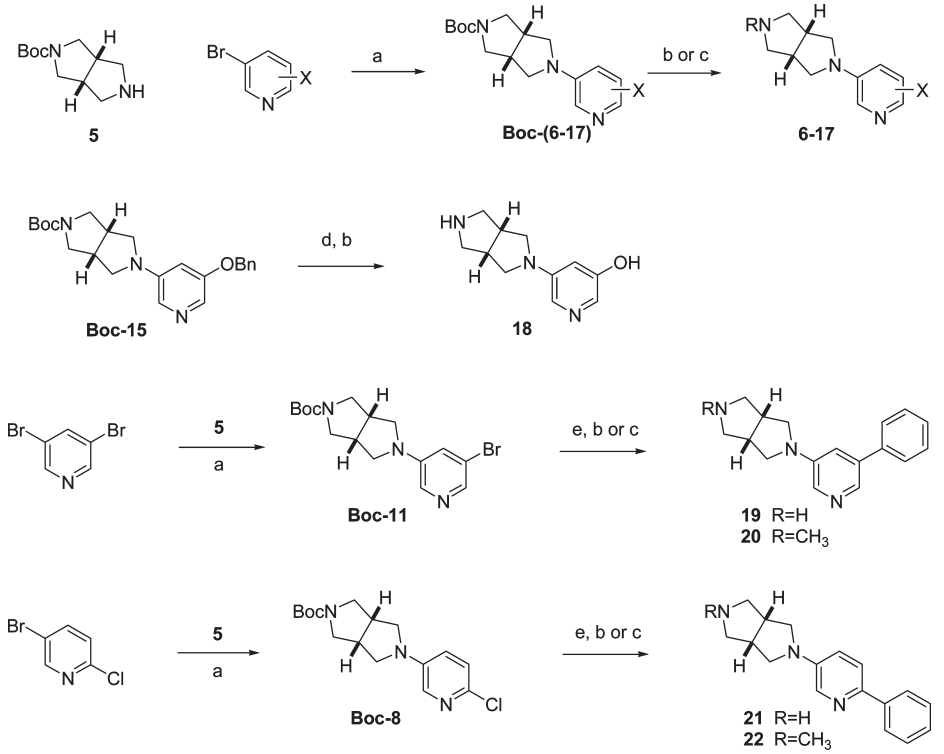
Chemistry

The Boc-protected diamine **5** was prepared (Scheme 1) by a four-step process involving azomethine ylide cycloaddition[51] to maleimide, reduction of the imide, and exchange of protecting groups. *N*-Arylation was accomplished either by base-mediated nucleophilc aromatic substitution (for activated heteroaryl halides) or through Pd-catalyzed amination of less reactive aryl and heteroaryl halides.[52−54] Thus, a variety of 3-bromopyridines reacted smoothly with **5** under Buchwald−Hartwig conditions to provide the pyridinyl amines **Boc-6** to **Boc-17** (Scheme 2). Removal of the Boc group with acid provided the amines **6**−**17**. The liberated secondary amine could be further substituted by reductive alkylation. Alternatively, Boc removal and *N*-methylation could be carried out in a single step under Eschweiler−Clarke conditions.

Other substituents were accessible by straightforward manipulation of the pyridine coupling products. Hydrogenolysis of the benzyl ether **Boc-15** provided the hydroxylpyridine **18** after deprotection. Monoamination of 3,5-dibromopyridine and 5-bromo-2-chloropyridine provided **Boc-11** and **Boc-8**, respectively, which could be elaborated by Suzuki−Miyaura coupling to the arylated analogues **19**−**22**.

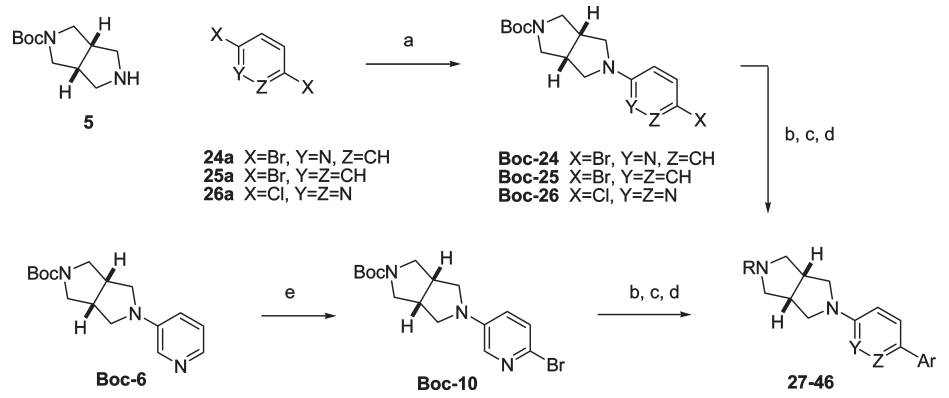
Other dihalogenated aromatics were also efficiently monoaminated (Scheme 3). Thus, symmetrical dihalides **25a** and **26a** proceeded to the corresponding aminoarylhalides **Boc-25** and **Boc-26**. Amination of 2,5-dibromopyridine (**24a**) reacted, as previously reported,[54] with substitution at C(2) to provide **Boc-24**. The regioisomeric **Boc-10** was easily prepared by electrophilic bromination of **Boc-6**. All of these halogenated derivatives were useful substrates for coupling with arylboronic acids to provide biaryl derivatives **27**−**46**.

Scheme 2[a]



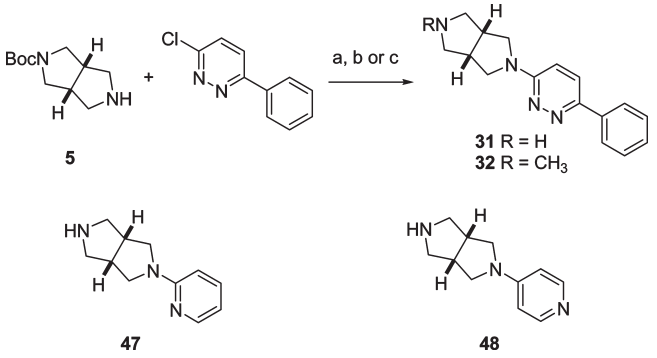
[a] Reagents and Conditions: (a) Pd_2dba_3, *rac*-BINAP, NaO*t*-Bu, toluene, 85 °C; (b) H^+, 0−20 °C; (c) $HCHO/H_2O$, HCO_2H, 100 °C, (d) H_2, $Pd(OH)_2$, 50 °C; (e) $PhB(OH)_2$, Pd(0), Na_2CO_3(aq)/toluene or Cs_2CO_3/dioxane, 80 °C.

Scheme 3[a]



[a] Reagents and conditions: (a) Pd_2dba_3, rac-BINAP, NaO*t*-Bu, toluene, 85 °C; (b) $PhB(OH)_2$, Pd(0), Na_2CO_3(aq)/toluene or Cs_2CO_3/dioxane, 80 °C; (c) H^+, 0−20 °C; (d) HCHO, $NaBH(OAc)_3$; (e) *N*-bromosuccinimide, CH_3CN, 0−20 °C.

Scheme 4[a]



[a] Reagents and conditions: (a) *i*Pr_2NEt, DMSO, 105 °C; (b) H^+, 0−20 °C; (c) HCHO, HCO_2H, 100 °C.

Direct coupling of **5** to 3-chloro-6-phenylpyridazine, accomplished with base in DMSO, provided more convenient access to **31** and **32** (Scheme 4). Similar conditions sufficed for amination of 2-chloropyridine to form **47**, but 4-bromopyridine reacted very sluggishly, and Pd catalysis was required for synthesis of **48**.

Biological Assays

The affinities of these ligands for native α4β2 and α7 nAChR subtypes in rat brain membranes were measured by radioligand binding using previously reported methods.[55,56] Briefly, displacement of [^{3}H]-cytisine was taken to represent binding to the α4β2 subtype, while the α7 affinities were determined by displacement of the α7-selective agonist [^{3}H]-A-585539.[56]

Selected compounds were also evaluated for agonist activity at the α4β2 and α7 receptor subtypes. For the heteromeric nAChR, functional activity was determined from calcium influx detected by fluorometric light-imaging plate reader (FLIPR) methodology, according to the reported methods,[57,58] employing an HEK-293 cell line expressing recombinant α4β2 nAChR. Experiments were run in 96-well plate format, and responses were normalized to that of 100 μM (−)-nicotine on the same plate.

The rapid desensitization of the α7 nAChR precludes use of FLIPR methodology for this subtype, so agonist activity was measured in oocytes expressing the human α7 nAChR using the automated electrophysiological robotic system parallel oocyte electrophysiology test (POET station).[59] Responses were normalized to the average of those to 10 mM ACh, applied to the same oocyte before and after the test compound.

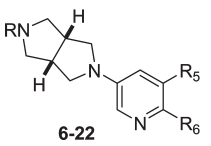
Results and Discussion

Binding affinities for native α4β2 and α7 receptors in rat brain are collected in Table 1. It should be noted that typical "nonselective" (a characterization that refers to activity across heteromeric receptor subtypes) nAChR ligands like (−)-nicotine and epibatidine actually exhibit significantly higher affinity for the α4β2 nAChR compared to the α7 subtype: for these examples approximately 200-fold and 60-fold differences, respectively. The parent compound of the series, **6**, exhibits potent (subnanomolar) affinity for the α4β2 subtype and approximately 400-fold weaker α7 activity.

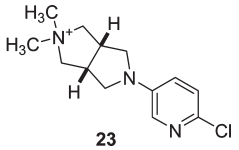
The SAR trends for **6** follow the patterns established for other pyridine-based nAChR ligands.[60−67] In particular, only the 3-pyridinyl attachment affords compounds with potent binding affinity, while the 2- and 4-pyridinyl analogues (**47** and **48**, respectively) are substantially weaker at both α4β2 and α7 subtypes. Also typical of most pyridinyl diamines,[64,68] *N*-methylation (**7**, **9**) causes a very sharp (ca. 200-fold) attenuation of α4β2 binding, which in these instances is mirrored by a similar decrease in α7 affinity. The *N*,*N*-dimethylated quaternary ammonium salt **23** shows a further drop in potency at the α4β2 receptor, but enhanced α7 affinity relative to **9**, so that **23** is essentially nonselective for binding to these major brain subtypes. The effect of sequential *N*-methylation on the α4β2 activity of other diamines has been studied;[68] quaternization generally improved potency relative to the tertiary amine. In this context, **23** resembles the analogous homopiperazine system where the lower activity of the quaternary dimethyl ammonium derivative was attributed to a slight change in ligand orientation in the cation binding domain that pivoted the 6-substituent of the heteroaryl group, resulting in an unfavorable interaction with a leucine residue at the remote edge of the ligand binding site.[69] Because the α7 nAChR already accommodates larger substituents in this position than does the α4β2 subtype (see below), it seems reasonable that quaternization might have a differential effect on α7 vs α4β2 binding.

The effects of pyridine substituents on α4β2 activity have been extensively investigated, with remarkable consistency across a wide range of structure types.[60−67] In general, only small (e.g., halogen) substitutents are tolerated at the pyridine

Table 1. Binding Affinities at α4β2 (Cytisine Binding) and α7 (A-585539 Binding) in Rat Brain



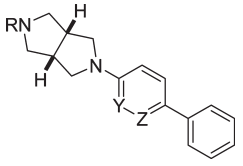
6-22



23

structure				cytisine binding		A-585539 binding		selectivity
example	NR	R5	R6	K_i (nM)	SEM range	K_i (nM)	SEM range	(α4β2:α7)
(−)-nicotine				0.94	(0.46−1.9)	176	(120−260)	190
epibatidine				0.047	(0.035−0.063)	2.7	(2.5−3.0)	57
6	H	H	H	0.12	(0.11−0.14)	51	(43−62)	420
7	CH_3	H	H	26	(23−29)	1590	(1550−1630)	61
8	H	H	Cl	0.20	(0.14−0.28)	180	(90−360)	900
9	CH_3	H	Cl	38	(34−42)	> 10000		> 260
10	H	H	Br	0.28	(0.21−0.39)	290	(200−420)	1000
11	H	Br	H	0.060	(43−85)	66	(58−76)	1100
12	H	OCH_3	H	0.081	(0.073−0.089)	240	(190−320)	2900
13	H	OCH_2CH_3	H	0.035	(0.031−0.040)	1440	(870−2400)	41000
14	H	$OCH_2CH_2CH_3$	H	0.041	(0.036−0.047)	> 10000		> 240000
15	H	$OCH_2C_6H_5$	H	0.058	(0.038−0.089)	> 10000		> 170000
16	H	$OCH(CH_3)_2$	H	0.051	(0.045−0.058)	> 10000		> 200000
17	H	morpholin-4-yl	H	47	(44−52)	> 10000		> 210
18	H	OH	H	0.75	(0.66−0.85)	> 10000		> 13000
19	H	C_6H_5	H	0.16	(0.13−0.20)	4560	(3200−6500)	28000
20	CH_3	C_6H_5	H	51	(43−61)	> 10000		> 190
21	H	H	C_6H_5	96	(80−114)	8.4	(6.2−11.4)	0.09
22	CH_3	H	C_6H_5	28000	(22000−35000)	9.6	(9.1−10.2)	0.0003
23	$(CH_3)_2$	H	Cl	210	(190−240)	340	(280−400)	1.6
47	H	H	H	260	(250 280)	> 10000		> 38
48	H	H		> 10,000		> 10000		

Table 2. Effect of Aminoaryl Group on nAChR Affinity

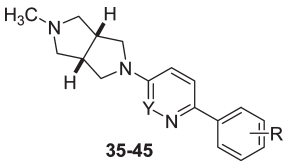


structure				cytisine binding		A-585539 binding		selectivity
example	R	Y	Z	K_i (nM)	(SEM range)	K_i (nM)	(SEM range)	(α7:α4β2)
21	H	CH	N	96	(80−114)	8.4	(6.2−11.4)	11
22	CH_3	CH	N	28000	(22000−35000)	9.6	(9.1−10.2)	2900
27	H	N	CH	> 100000		30	(27−35)	> 3300
28	CH_3	N	CH	> 100000		17	(11−28)	> 6000
29	H	CH	CH	> 10000		28	(26−30)	> 350
30	CH_3	CH	CH	> 100000		12	(8.8−16.1)	> 8300
31	H	N	N	5320	(2800−10000)	17.5	(17.1−18.0)	300
32	CH_3	N	N	> 100000		10.8	(9.0−12.9)	> 9200
33	Et	N	N	> 100000		330	(180−620)	> 300
34	$(CH_3)_2$	N	N	> 10000		5.98	(5.0−7.1)	> 1600

6-position, while the 5-position accommodates a much broader range of groups. Not surprisingly, the data in Table 1 reinforce this trend for effects on α4β2 affinity. Substituents at the pyridine 5-position ranging from Br (**11**), straight and branched chain alkyl ethers (**12**−**16**), and phenyl (**19**) maintain or even improve the affinity for the α4β2 nAChR. In contrast, the morpholino group (**17**) has a detrimental effect on nAChR affinity. The 5-hydroxyl substitution results in a 6-fold drop in binding potency, but **18** remains a subnanomolar compound. Likewise, while halogen (**8**, **10**) substitution at the 6-position is well-tolerated, a 6-phenyl group (**21**) results in a nearly 800-fold loss of affinity for the α4β2 nAChR.

To our knowledge, the effect of pyridine substitutions on α7 binding affinity has not been studied systematically. Studies of epibatidine SAR indicate that analogues with small groups at the pyridine 5-position retain α7 activity,[65,66] but phenyl substitution is not tolerated.[67] The results in Table 1 extend those findings to the *N*-pyridinyl diamine scaffold and illustrate that pyridine substitutions have nearly opposite effects on α7 binding as compared to α4β2 activity. For example,

Table 3. Effects of Biaryl Substituents on nAChR Binding Affinities



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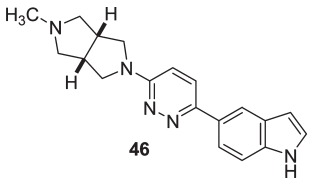


46

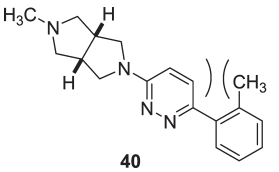
structure			cytisine binding		A-585539 binding		selectivity
example	Y	R	(α7:α4β2)	SEM range	K_i (nM)	SEM range	(α7:α4β2)
35	N	4-methyl	> 100000		11.6	(7.4−18.1)	> 8600
36	N	3-methyl	> 100000		4.42	(3.7−5.3)	> 22000
37	CH	3-methyl	750	(590−930)	6.7	(6.0−7.2)	112
38	CH	3-phenyl	9800	(8400−11500)	44	(40−48)	220
39	N	3,5-dimethyl	> 100000		> 10000		
40	N	2-methyl	> 10000		690	(620−770)	> 14
41	N	4-methoxy	> 100000		22	(15−32)	> 4500
42	N	4-hydroxy	> 10000		5.3	(5.0−5.7)	> 1800
43	CH	3-methoxy	> 100000		5.0	(4.5−5.5)	> 2000
44	N	3-hydroxy	21000	(18000−25000)	7.9	(5.2−12)	2660
45	CH	3-nitro	2600	(22000−29000)	30	(25−35)	87
46			> 100000		0.24	(0.21−0.28)	> 400000

nearly all substitutions at the pyridine 5-position that are compatible with high α4β2 affinity attenuate α7 binding. Only 5-Br (**11**) and 5-OMe (**12**) retain submicromolar α7 affinity, and the potency drops rapidly as the size of the alkoxy group increases. The 5-phenyl substituent (**19**) causes a 90-fold loss of binding affinity relative to the parent **6**. On the other hand, 6-phenyl substitution (**21**) results in a 6-fold enhancement of potency (compared to **6**) at the α7 nAChR. Coupled with the decreased affinity for α4β2, **21** achieved 11-fold selectivity for binding to the α7 vs α4β2 nAChR. Somewhat surprisingly in light of the effect of *N*-methylation on binding for **7** and **9**, *N*-methylation of the 6-phenyl analogue (as in **22**) does not change α7 affinity significantly, although it does cause the expected loss of α4β2 potency. The combination of *N*-methylation and 6-phenyl substitution, then, results in a shift of selectivity from a compound that has 400-fold selectivity for α4β2 (**6**) to **22**, with ~2900-fold selectivity for α7 binding.

High selectivity for α4β2 binding, on the other hand, is favored by a pyrrolidine NH and substitutions on the pyridine 5-position. Nearly 3000-fold selectivity is achieved already with a 5-methoxy group (**12**) and larger substituents (**13**−**16**) drive the affinity ratio still higher.

Further SAR studies reveal that α7 binding affinity is much less sensitive to the nature of the *N*-aryl ring than is α4β2 binding. While a shift in the aza-ring position from **6** to **47** results in a 2000-fold loss of potency at α4β2, the corresponding 5-phenyl-2-pyridinyl α7 ligand (**28**) is nearly as potent as the 6-phenyl-3-pyridinyl isomer **22**. In fact, the pyridine can be replaced with a phenyl ring (**30**) without loss of α7 affinity. These, and the pyridazine analogue **32**, actually show enhanced α7 vs α4β2 selectivity compared to **22** due to replacement of the 3-pyridinyl pharmacophore that is critical for potent α4β2 binding. The high α7 affinity of the biphenyl analogues **29** and **30** is consistent with the suggestion that the α7 ligand binding domain is more lipophilic than that for α4β2[50] and further suggests that hydrogen bonding to the *N*-aryl group is not a prerequisite for strong binding. Nevertheless, the more hydrophilic pyridine and pyridazine linking rings are certainly well-tolerated. We have demonstrated that **32**, in particular, is an exceptionally useful compound for evaluating α7 nAChR activity in vitro and in vivo and have shown that it is potent and efficacious across several animal models of learning, memory, and attention.[70,71]

Scheme 5



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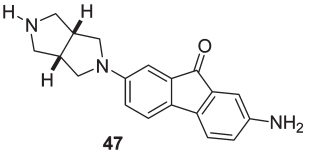

47

Similar to **21** and **22**, the α7 activities of the biaryl diamines **27**−**32** are barely influenced by methylation of the basic amine group. In fact, the *N*-methyl derivatives **28**, **30**, and **32** exhibit slightly greater α7 binding potency than the corresponding *des*-methyl analogues **27**, **29**, and **31**. Homologation to an *N*-ethyl group, on the other hand, causes a 30-fold loss of binding potency (**33** vs **32**), while the *N*,*N*-dimethyl quaternary salt (**34**) retains high affinity for the α7 nAChR.

The terminal phenyl ring of the biaryl system accommodates further substitution. A *para*- (**35**) or *meta*-methyl group (**36**, **37**) does not change α7 affinity, and even a *meta*-phenyl substituent (**38**) is tolerated with only a small decrease in potency. On the other hand, substitution at both meta positions (**39**) completely eliminates α7 binding, suggesting that one edge of the terminal phenyl ring already makes close contact with receptor protein in the α7 binding pocket. Likewise, even a single ortho-substituent (**40**) causes a sharp drop in in potency. In this case, it seems likely that a coplanar geometry of the biaryl system is preferred for α7 binding and the *ortho*-methyl prevents that arrangement. This explanation is consistent with the potent α7 affinity reported for the structurally related, but conformationally constrained analogue **47** (Scheme 5).[72]

Electron donating (**41**−**44**) groups appear to be slightly preferred to electron-withdrawing (**45**) groups, but the effect is not dramatic. The notion that a para-situated hydrogen bond donor (**42** vs **41**) seemed to enhance α7 binding affinity was inspiration for replacement of the terminal phenyl by an

Table 4. Agonist Activity for Selected Compounds at Recombinant h$\alpha4\beta2$ and h$\alpha7$ nAChRs Expressed in Vitro

example	$\alpha4\beta2$ FLIPR		$\alpha7$ POETs	
	EC_{50} (μM) (SEM range)	max	EC_{50} (μM) (SEM range)	max
(−) nicotine[a]	6.6 (5.9−7.4)	101 ± 3	91 (78−104)	74 ± 3
6	0.040 (0.034−0.046)	146 ± 16	4.47 (2.42−8.27)	129 ± 25
13	0.37 (0.27−0.51)	118 ± 10	> 100	37[b]
19	> 100	< 10	> 100	< 10
31	> 100	< 10	1.15 (0.62−2.15)	29 ± 4
32	> 100	< 10	4.26 (2.64−6.61)	52 ± 5
46	> 100	< 10	0.32 (0.14−0.66)	87 ± 11

[a] Nicotine data published previously.[62,73] [b] Maximum response at 100 μM.

indolyl group, resulting in the most potent $\alpha7$ ligand (**46**) identified in this series.

Having established structural modifications that can be manipulated to design ligands with high selectivity for binding to either $\alpha4\beta2$ or $\alpha7$ nAChRs, it remained to evaluate the functional activity of selective ligands. Binding experiments reflect interaction of the ligand with a desensitized, inactive state of the receptor and do not provide information about channel-activating (agonist) activity that is considered to be important for selective nAChR ligands that have advanced to clinical trials.[29,32,34,35] Agonist data for selected compounds is presented in Table 4. It can be seen that **6** is a full agonist at both $\alpha4\beta2$ and $\alpha7$ nAChRs and significantly more potent than (−)-nicotine. Comparison of agonist potencies across $\alpha4\beta2$ and $\alpha7$ subtypes must be done with caution because the assays are run in different systems, but **6** is clearly more selective toward activating the $\alpha4\beta2$ nAChR than is nicotine. More to the point, the 5-ethoxy derivative **13**, which exhibits high selectivity for $\alpha4\beta2$ in the binding assay, is also a potent full agonist at this receptor but only partially activates the $\alpha7$ nAChR at high concentrations. It can be noted that the size of the 5-substituent does eventually affect the agonist activity of these ligands; the 5-phenyl analogue **19**, also a highly selective $\alpha4\beta2$ ligand, fails to activate the receptor in functional assays. It is likewise inactive at the $\alpha7$ subtype.

In contrast, the 6-aryl analogues like **31** and **32** are fairly potent partial agonists of the $\alpha7$ nAChR and highly selective for that subtype because they do not activate the $\alpha4\beta2$ receptor. It is interesting to note that **31** appears to be a little more potent as an agonist than is **32**, opposite to their relative binding affinities, but **32** exhibits higher agonist efficacy than **31**. The partial efficacy (30−50% of the maximal response achieved by the native transmitter acetylcholine) observed in the electrophysiological assay does not appear to be a limitation for the in vivo pharmacological effects; the $\alpha7$ partial agonists MEM-3454 and GTS-21[36,37] have been shown to enhance cognitive performance in human clinical trials, and we have reported that **32** achieves full efficacy in a variety of preclinical animal models of cognition, memory, and attention.[70,71] Nevertheless, the data for **46** demonstrates that it is possible to identify ligands in this series with nearly full agonist efficacy while maintaining the $\alpha7$-selective profile.

Summary

We have identified an *N*-aryldiamine scaffold that can be manipulated to produce ligands that are highly selective for binding to either the $\alpha4\beta2$ or $\alpha7$ nAChRs. Beginning with **6**, incorporation of substituents at the pyridine 5-position leads to highly selective $\alpha4\beta2$ ligands, mainly by strong attenuation of binding to the $\alpha7$ subtype. On the other hand, potent $\alpha7$ binding is favored by an aryl group at the pyridine 6-position, which also disfavors $\alpha4\beta2$ binding. *N*-Methylation improves $\alpha7$ further, mainly by reducing affinity at the $\alpha4\beta2$ nAChR. These simple structure changes on a common scaffold should help to illuminate the differences in the ligand binding domains for $\alpha4\beta2$ and $\alpha7$ nAChRs, particularly in the regions extending away from the conserved cation binding pocket.

Experimental Section

General. Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers and were used without further purification. Flash chromatography was performed using silica gel (230−400 mesh) from EM Science or prepacked columns supplied by Analogix, Isco, or Silicycle. Proton NMR spectra were recorded at 300 MHz in the solvent indicated, and chemical shifts are listed in ppm downfield of internal tetramethylsilane. Mass spectra were obtained in chemical ionization mode, and only parent ions are listed. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ) or QTI Inc. (Whitehouse, NJ). Compounds for biological testing were typically prepared as water-soluble salts in ≥95% purity, in accord with results from combustion analysis.

Preparation of *t*-Butyl *cis*-Hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (5). Step 1. *cis*-5-Benzyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3-dione. A solution of *N*-benzyl-*N*-methoxymethyl-*N*-(trimethylsilyl)methylamine[51] (76.68 g, 0.29 mol) in dichloromethane (130 mL) was added to an ice-cooled mixture of maleimide (25.53 g, 0.26 mol) and trifluoroacetic acid (2.2 mL, 0.028 mol) in dichloromethane (350 mL) over 40 min so that the reaction temperature remained between 0 and 5 °C. The resulting bright-yellow solution was allowed to warm gradually and stirred at room temperature for 27 h. The mixture was washed with saturated $NaHCO_{3(aq)}$ (80 mL), and the organic phase was dried ($MgSO_4$) and concentrated under vacuum. The residual oil was stirred with 10% EtOAc−heptane (300 mL) for 15 h, and the resulting precipitate was isolated by filtration, washed with 10% EtOAc−heptane (150 mL) and dried under vacuum at 50 °C to provide a white solid (54.25 g), contaminated by variable amounts of the *N*-(*N*-benzyl-*N*-methylaminomethyl) Mannich base of the title compound. The crude product was stirred with methanol (500 mL) and 50% aqueous H_2NOH (4.2 mL) at room temperature for 20 h. This mixture was concentrated under vacuum, and the residue was taken up in EtOAc (500 mL) and filtered to remove some insoluble material. The filtrate was concentrated under vacuum to leave the title compound as an off-white solid (49.9 g, 83% yield), sufficiently pure to use in the next step. An analytical sample was obtained by crystallization from EtOAc. ^{1}H NMR (CD_3OD) δ 2.32−2.43 (m, 2 H), 3.18 (d, J = 9.8 Hz, 2 H), 3.20−3.26 (m, 2 H), 3.59 (s, 2 H), 7.13−7.35 ppm (m, 5 H). MS m/z 231 $(MH)^+$. Anal. ($C_{13}H_{14}N_2O_2$) C, H, N.

Step 2. *t*-Butyl *cis*-5-Benzylhexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate. A three-necked, 2 L flask with mechanical stirrer, thermometer, and addition funnel was charged with $LiAlH_4$ (16.9 g, 0.445 mol) and THF (200 mL). The slurry was cooled in ice under a nitrogen atmosphere as a solution of

cis-5-benzyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3-dione (49.0 g, 0.202 mol) in THF (250 mL) was added dropwise over 20 min such that the temperature remained below 14 °C. After the addition was complete, the reaction mixture was stirred for 40 min with ice cooling and then heated at reflux for 3 h. The mixture was again cooled in ice and quenched by gradual, successive addition of water (17 mL), 15% $NaOH_{(aq)}$ (17 mL), and water (51 mL). The resulting slurry was filtered and the cake washed well with EtOAc (2 × 400 mL). The combined filtrate and wash was concentrated under vacuum to provide a colorless oil (43.5 g), which was dissolved in dichloromethane (200 mL). The solution was stirred with ice cooling as di-*t*-butyl dicarbonate (46.3 g, 0.212 mol) was added gradually (gas evolution), and the resulting solution was allowed to warm to room temperature and stirred for 1 h. Aspartic acid (5.3 g, 0.04 mol) was added, and the mixture was stirred for 30 min and then transferred to a separatory funnel and washed with 1 N $NaOH_{(aq)}$ (100 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide the titled compound as a colorless oil, sufficiently pure for use in the next step (64.73 g, 108%). ^{1}H NMR (CD_3OD) δ 1.45 (s, 9 H), 2.34 (dd, J = 9.3, 3.9 Hz, 2 H), 2.69−2.78 (m, 2 H), 2.78−2.88 (m, 2 H), 3.20−3.30 (m, 2 H), 3.39−3.50 (m, 2 H), 3.59 (s, 2 H), 7.15−7.39 ppm (m, 5 H). MS m/z 303 $(MH)^+$.

Step 3. *t*-Butyl *cis*-Hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (5). The crude *t*-butyl *cis*-5-benzylhexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (64.70 g, 0.212 mol) was dissolved in methanol (250 mL). Pearlman's catalyst ($Pd(OH)_2$, 20% on C, 6.5 g) was added, and the mixture was shaken at 50 °C under hydrogen (60 psi) for 4 h. The mixture was cooled to room temperature, filtered under nitrogen to remove the catalyst, and the filtrate was concentrated under vacuum to leave a pale oil (46.55 g). This was dissolved in ether (150 mL), applied to a column of silica gel (300 g), and eluted with ether (1 L). The column was then eluted with methanol (2 L), and the methanol fraction was concentrated under vacuum. The residue was taken up in EtOAc (500 mL), filtered to remove insoluble material, and concentrated under vacuum to provide the title compound as an off-white solid (33.84 g, 75% yield over two steps), sufficiently pure for use in subsequent operations. ^{1}H NMR (CD_3OD) δ 1.45 (s, 9 H), 2.65 (dd, J = 11.5, 4.4 Hz, 2 H), 2.75−2.89 (m, 2 H), 3.01−3.11 (m, 2 H), 3.20 (dd, J = 11.5, 3.7 Hz, 2 H), 3.47−3.58 ppm (m, 2 H).

3-Bromo-5-ethoxypyridine. Freshly cleaned sodium metal (1.46 g, 63.3 mmol) was added gradually to ethanol (50 mL) and stirred until the metal had reacted completely to give a clear solution (1 h). The solution was concentrated under vacuum, and the residue was suspended in dry toluene (20 mL) and concentrated to a white solid (toluene treatment repeated a second time). The solid was taken up in dry DMF (60 mL), and 3,5-dibromopyridine (10.0 g, 42.2 mmol) was added. The mixture was heated at 70 °C for 2.5 h, then cooled to room temperature and poured into ice water (250 g). The mixture was extracted with ethyl ether (2 × 100 mL), and the combined extract was washed successively with water (50 mL) and saturated brine (50 mL), dried (Na_2SO_4), and concentrated. The residual brown oil was purified by flash chromatography (silica, hexanes−EtOAc 80:20) to provide the title compound as a pale oil (5.83 g, 69% yield). ^{1}H NMR ($CDCl_3$) δ1.43 (t, J = 7.0 Hz, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 7.34 (dd, J = 2.5, 1.7 Hz, 1 H), 8.22 (d, J = 2.5 Hz, 1 H), 8.26 ppm (d, J = 1.7 Hz, 1 H). MS m/z 202/216 $(MH)^+$.

3-Bromo-5-propyloxypyridine. Freshly cleaned sodium metal (0.73 g, 32 mmol) was stirred with 1-propanol (20 mL) until the metal had reacted completely to give a clear solution (3 h). The solution was concentrated under vacuum, and the residue was suspended in dry toluene (20 mL) and concentrated to a white solid (toluene treatment repeated a second time). The solid was taken up in dry DMF (30 mL), and 3,5-dibromopyridine (5.0 g, 21 mmol) was added. The mixture was heated at 70 °C for 4 h and then cooled to room temperature and poured onto ice−water (100 g). The mixture was extracted with ethyl ether (2 × 50 mL), and the combined extract was washed with satd brine (40 mL), dried (Na_2SO_4), and concentrated. The residual oil (a mixture of starting dibromide and product, with some DMF) was purified by flash chromatography (silica, hexanes−EtOAc 80:20) to provide the title compound (1.15 g, 25% yield). ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.4 Hz, 3 H), 1.83 (tq, J = 7.0, 6.8 Hz, 2 H), 3.96 (t, J = 6.4 Hz, 2 H), 7.36 (dd, J = 2.6, 1.8 Hz, 1 H), 8.23 (d, J = 2.6 Hz, 1 H), 8.27 ppm (d, J = 1.8 Hz, 1 H). MS m/z 216/218 $(MH)^+$.

3-Bromo-5-isopropyloxypyridine. Solid K_2CO_3 (1.3 g, 9.44 mmol) was added to a solution of 5-bromopyridin-3-ol (705 mg, 4.05 mmol) and 2-iodopropane (1.70 g, 1.00 mmol) in DMF (10 mL). The mixture was purged with a nitrogen stream for 15 min and then heated under nitrogen at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with water (100 mL), and extracted with hexanes (2 × 50 mL). The combined extract was washed with water (50 mL), satd brine (40 mL), dried (Na_2SO_4), and concentrated to a pale-yellow oil. Bulb-to-bulb distillation (115−120 °C air bath/21 Torr) provided the title compound as a colorless oil (0.78 g, 88% yield). ^{1}H NMR ($CDCl_3$)δ 1.36 (d, J = 6.1 Hz, 6 H), 4.56 (heptet, J = 6.0 Hz, 1 H), 7.35 (dd, J = 2.4, 1.7 Hz, 1 H), 8.20 (d, J = 2.4 Hz, 1 H), 8.25 ppm (d, J = 1.7 Hz, 1 H). MS m/z 216/218 $(MH)^+$.

4-(5-Bromopyridin-3-yl) Morpholine. Morpholine (0.33 g, 3.83 mmol), 3,5-dibromopyridine (1.09 g, 4.60 mmol), racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (rac-BINAP, 0.14 g, 0.23 mmol), tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 70 mg, 0.08 mmol), and sodium *t*-butoxide (0.55 g, 5.75 mmol) were combined with toluene (25 mL). The suspension was evacuated and purged with nitrogen. The mixture was heated at 115 °C under nitrogen for 18 h. The residue was filtered through a pad of silica, followed by an EtOAc (150 mL) rinse. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (hexanes−EtOAc, 50:50) to provide the title compound (0.66 g, 71% yield). ^{1}H NMR (CD_3OD) δ 3.20−3.26 (m, 4 H), 3.77−3.87 (m, 4 H), 7.50−7.60 (m, 1 H), 8.03 (d, J = 1.7 Hz, 1 H), 8.20 ppm (d, J = 2.4 Hz, 1 H). MS m/z 243/245 $(MH)^+$.

General Pyridine−Amine Coupling Procedure (A). *t*-Butyl *cis*-5-(3-Pyridinyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (Boc-6). A solution of **5** (0.52 g, 2.45 mmol) in toluene (30 mL) was dried by azeotropic distillation under N_2 (1 atm) to a volume of ~20 mL. The solution was cooled to 35 °C and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) (45 mg, 0.049 mmol) and racemic-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (rac-BINAP, 75 mg, 0.12 mmol) were added. The mixture was warmed to 85 °C for 10 min and then cooled to 35 °C. Sodium *t*-butoxide (371 mg, 3.86 mmol) and 3-bromopyridine (426 mg, 2.70 mmol) were added, and the mixture was warmed to 85 °C under N_2 for 2 h. The mixture was cooled to 30 °C and filtered through diatomaceous earth with an EtOAc (100 mL) rinse. The filtrate was concentrated under reduced pressure to provide a red oil, which was purified by flash chromatography (CH_2Cl_2−CH_3OH, 16:1) to provide the title compound as a pale-yellow solid (0.62 g, 87% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.96−3.12 (m, 2 H), 3.24 (dd, J = 9.5, 4.1 Hz, 2 H), 3.34 (m, 2 H), 3.55 (dd, J = 9.5, 7.5 Hz, 2 H), 3.60−3.72 (m, 2 H), 6.81 (dd, J = 8.3, 1.9 Hz, 1 H), 7.13 (dd, J = 8.3, 4.6 Hz, 1 H), 7.89−8.07 ppm (m, 2 H). MS m/z 290 $(MH)^+$.

General Procedure for Boc Deprotection with HCl. *cis*-2-(3-Pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole Dihydrochloride (6). HCl/dioxane (4M, 2 mL, 8 mmol) was added to a solution of **Boc-6** (310 mg, 1.07 mmol) in ethanol (5 mL), and the solution was stirred at 20 °C for 4 h. The solution was concentrated under reduced pressure, and the residual solid was crystallized from ethanol:EtOAc (1:5) to provide the title compound as a white solid (203 mg, 72% yield). mp 250−252 °C (dec). ^{1}H NMR (CD_3OD) δ 3.32 (m, 4H), 3.57 (dd, J = 10.7, 3.0 Hz, 2H), 3.65

(m, 4H), 7.78 (m, 1H), 7.83 (dd, J = 8.2, 5.1 Hz, 1H), 8.09 (d, J = 5.1 Hz, 1H), 8.12 ppm (d, J = 2.2 Hz, 1H). MS m/z 190 $(MH)^+$. Anal. ($C_{11}H_{15}N_3 \cdot 2HCl$) C, H, N.

General Procedure for Boc Deprotection with Concomitant *N*-Methylation. *cis*-2-Methyl-5-(3-pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole Dihydrochloride (7). A mixture of **Boc-6** (200 mg, 0.69 mmol) in 88% formic acid (1.8 mL) and 37% formalin (3.5 mL) was warmed to 95 °C for 3 h. The solution was concentrated under reduced pressure, and the resulting pale-yellow solid was taken up in 20% aq KOH (5 mL) and extracted into ethyl acetate (2 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in EtOH (10 mL), treated with HCl/dioxane (4M, 2 mL), and concentrated under reduced pressure to leave an oily solid, which was crystallized from EtOH:ethyl acetate (1:20) to provide the title compound as an off-white, hygroscopic solid: mp 207−209 °C. ^{1}H NMR (CD_3OD) δ 2.93−2.98 (2 s, endo and exo CH_3, 3 H) 3.00−3.10 (m, 1 H) 3.32−3.39 (m, 1 H) 3.39−3.55 (m, 3 H) 3.58−3.65 (m, 2 H) 3.65−3.75 (m, 2 H) 3.94−4.07 (m, 1 H) 7.76−7.88 (m, 2 H) 8.05−8.20 ppm (m, 2 H). MS m/z 190 $(MH)^+$. Anal. ($C_{12}H_{17}N_3 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***t*-Butyl *cis*-5-(6-Chloro-3-pyridinyl)hexahydropyrrolo[3,4-*c*]pyrrole-2(1*H*)-carboxylate (Boc-8).** Diamine **5** (1.70 g, 8 mmol) and 5-bromo-2-chloropyridine (2.11 g, 8.8 mmol) were coupled according to procedure A (described for **Boc-6**) to provide the title compound as a yellow solid (1.18 g, 46% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.98−3.12 (m, 2 H), 3.20 (dd, J = 9.5, 4.0 Hz, 2 H), 3.24−3.41 (m, 2 H), 3.52 (dd, J = 9.3, 7.3 Hz, 2 H), 3.58−3.72 (m, 2 H), 6.79 (dd, J = 8.7, 3.2 Hz, 1 H), 7.12 (d, J = 8.7 Hz, 1 H), 7.68 ppm (d, J = 3.2 Hz, 1 H). MS m/z 324/326 $(MH)^+$.

***cis*-2-(6-Chloro-3-pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole Hydrochloride (8).** A solution of HCl in 1,4-dioxane (4M, 2 mL, 8 mmol) was added to **Boc-8** (360 mg, 1.11 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 2 h and then concentrated under vacuum. The residual yellow solid was crystallized from ethanol:EtOAc (2:1) after carbon treatment to provide the title compound as a white solid (198 mg, 69% yield): mp 230−236 °C (dec). ^{1}H NMR (CD_3OD) δ 3.28 (m, 4 H), 3.49 (m, 4 H), 3.62 (m, 2 H), 7.45 (dd, J = 8.8, 3.1 Hz, 1 H), 7.52 (d, J = 9 Hz, 1 H), 7.90 ppm (d, J = 3 Hz, 1 H). MS m/z 224/226 $(MH)^+$. Anal. ($C_{11}H_{14}N_3Cl \cdot HCl$) C, H, N.

***cis*-2-(6-Chloro-3-pyridinyl)-5-methyloctahydropyrrolo[3,4-*c*]pyrrole (9).** Aqueous 37% formalin (3.5 mL) was added to a mixture of **Boc-8** (207 mg, 0.64 mmol) and 88% formic acid (1.8 mL), and the solution was heated at 95 °C for 2 h. The solution was concentrated under reduced pressure, and the resulting solid was purified by chromatography (CH_2Cl_2:CH_3OH:Et_2NH, 94:5:1) to provide the title compound (135 mg, 88% yield). ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3 H) 2.53 (dd, J = 9.5, 3.2 Hz, 2 H) 2.65−2.75 (m, 2 H) 2.94−3.08 (m, 2 H) 3.19 (dd, J = 9.3, 3.0 Hz, 2 H) 3.35−3.48 (m, 2 H) 6.88 (dd, J = 8.7, 3.2 Hz, 1 H) 7.11 (d, J = 8.7 Hz, 1 H) 7.75 ppm (d, J = 2.8 Hz, 1 H). MS m/z 238/240 $(MH)^+$. Anal. ($C_{12}H_{16}N_3Cl$) C, H, N.

***t*-Butyl *cis*-5-(6-Bromo-pyridin-3-yl)-hexahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-10).** A solution of *N*-bromosuccinimide (0.62 g, 3.46 mmol) in CH_3CN (5 mL) was added dropwise over 15 min to a solution of **Boc-6** (1.0 g, 3.46 mmol) in CH_3CN (40 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature. The reaction was diluted with H_2O (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phase was washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give 1.24 g (3.38 mmol, 98% yield) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.95−3.08 (m, 2 H), 3.20 (dd, J = 9.8, 4.1 Hz, 2 H), 3.23−3.40 (m, 2 H), 3.52 (dd, J = 9.9, 7.5 Hz, 2 H), 3.60−3.73 (m, 2 H), 6.71 (dd, J = 8.8, 3.1 Hz, 1 H), 7.25 (d, J = 8.8 Hz, 1 H), 7.69 ppm (d, J = 3.4 Hz, 1 H). MS m/z 368/370 $(MH)^+$.

***cis*-5-(6-Bromo-pyridin-3-yl)-hexahydro-pyrrolo[3,4-*c*]pyrrole Trifluoroacetate (10).** Trifluoroacetic acid (3 mL) was added to a solution of **Boc-10** (100 mg, 0.27 mmol) in CH_2Cl_2 (4 mL), and the solution was stirred at room temperature for 30 min and then concentrated under vacuum. The residue was combined with toluene (3 mL) and concentrated under vacuum. This process was repeated once more to ensure removal of excess acid. The residual oil was taken up in EtOAc (2 mL), and ethyl ether (3 mL) was added gradually. The resulting suspension was stirred at room temperature for 16 h. The precipitate was isolated by filtration and dried under vacuum to provide the title salt (89 mg, 86% yield). ^{1}H NMR (CD_3OD) δ 3.18−3.28 (m, 4 H), 3.32−3.41 (m, 2 H), 3.46 (dd, J = 9.8, 2.2 Hz, 2 H), 3.54−3.65 (m, 2 H), 7.08 (dd, J = 8.8, 3.1 Hz, 1 H), 7.39 (d, J = 8.5 Hz, 1 H), 7.78 ppm (d, J = 3.4 Hz, 1 H). MS m/z 268/270 $(MH)^+$. Anal. ($C_{11}H_{14}N_3Br \cdot CF_3CO_2H \cdot 0.5H_2O$) C, H, N.

***t*-Butyl *cis*-5-(5-Bromopyridin-3-yl)hexahydro-pyrrolo[3,4-*c*]-pyrrole-2-carboxylate (Boc-11).** Prepared from **5** (212 mg, 1.0 mmol was coupled with 3,5-dibromopyridine (255 mg, 1.08 mmol) according to the procedure A as described for **Boc-6**. The crude product was purified by chromatography on silica gel, eluting with hexanes−EtOAc (1:1) to provide the title compound as a light-yellow solid (256 mg, 70% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.97−3.08 (m, 2 H), 3.23 (dd, J = 9.7, 3.8 Hz, 2 H), 3.26−3.40 (m, 2 H), 3.55 (dd, J = 9.1, 7.5 Hz, 2 H), 3.60−3.74 (m, 2 H), 6.95 (br s, 1 H), 7.88 (br s, 1 H), 8.00 ppm (br s, 1 H). MS m/z 368/370 $(MH)^+$.

***cis*-2-(5-Bromopyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Trifluoroacetate (11).** A solution of the product of **Boc-11** (30 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) was cooled in ice and treated with trifluoroacetic acid (500 μL). The pale-yellow solution was stirred at 0 − 5 °C for 1 h and then concentrated under vacuum. The residue was triturated with ether (3 mL), and the solvent was decanted. After a second trituration with 10% methanol-ether (3 mL), the resulting pale-yellow solid was isolated by filtration and dried under vacuum at 50 °C to provide the title compound (25 mg, 75% yield). ^{1}H NMR (CD_3OD) δ 3.20−3.30 (m, 4 H), 3.38−3.51 (m, 4 H), 3.55−3.65 (m, 2 H), 7.33 (t, J = 2.2 Hz, 1 H), 7.98 ppm (m, 2 H). MS m/z 268/270 $(MH)^+$. Anal. ($C_{11}H_{14}N_3Br \cdot CF_3CO_2H \cdot 0.5H_2O$) C, H, N.

***cis*-2-(5-Methoxy-3-pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole-Dihydrochloride (12).** Prepared from **5** (300 mg, 1.4 mmol) and 3-bromo-5-methoxypyridine (290 mg, 1.5 mmol) according to procedure A described for **Boc-6**, followed by deprotection with HCl in dioxane and EtOAc to provide the title compound as a white crystalline solid (150 mg, 37% yield). ^{1}H NMR (CD_3OD) δ 3.32 (m, 4 H), 3.58 (dd, J = 10.7, 3.1 Hz, 2 H), 3.63 (m, 4 H), 4.00 (s, 3 H), 7.21 (t, J = 2.2 Hz, 1 H), 7.78 (d, J = 2.4 Hz, 1 H), 7.85 ppm (d, J = 2.0 Hz, 1 H). MS m/z 220 $(MH)^+$. Anal. ($C_{12}H_{17}N_3O \cdot 2HCl$) C, H, N.

***cis*-2-(5-Ethoxy-3-pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole- Dihydrochloride (13).** Prepared from **5** (600 mg, 2.8 mmol) and 3-bromo-5-ethoxypyridine (625 mg, 3.1 mmol) by procedure A as described for **Boc-6**, followed by deprotection and salt formation with HCl in refluxing ethyl acetate−EtOH (3:1, 20 mL). After cooling, the mixture was filtered to provide the title compound as a white crystalline solid (435 mg, 51% yield): mp 226−227 °C. ^{1}H NMR (CD_3OD) δ 1.57 (t, J = 7.0 Hz, 3 H), 3.30 (m, 4 H), 3.55 (dd, J = 10.6, 2.9 Hz, 2 H), 3.61 (m, 4 H), 4.25 (q, J = 7.0 Hz, 2 H), 7.19 (dd, J = 2.4, 1.7 Hz, 1 H), 7.78 (d, J = 2.4 Hz, 1 H), 7.84 ppm (d, J = 1.7 Hz, 1 H). MS m/z 234 $(MH)^+$. Anal. ($C_{13}H_{19}N_3O \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***cis*-3-(5-Propyloxy-3-pyridinyl)-3,7-diazabicyclo[3.3.0]octane Semifumarate (14).** Prepared from **5** (300 mg, 1.4 mmol) and 3-bromo-5-(1-propyloxy)pyridine (333 mg, 1.5 mmol) according to procedure A as described for **Boc-6**, followed by deprotection with HCl in refluxing ethyl acetate−EtOH (4:1, 10 mL). After 3 h, the solution was concentrated and the residue was purified by flash chromatography (CH_2Cl_2−EtOH-NH_4OH, 96:3:0.5) to provide the free base of the title compound (70 mg). This was

dissolved in ethyl acetate (8 mL) and methanol (1 mL), and a solution of fumaric acid (34 mg) in methanol (1.2 mL) was added dropwise. The solution was diluted with diethyl ether (5 mL) and scratched to induce crystallization. The mixture was filtered and the solid dried under vacuum to provide the title compound (50 mg, 17% yield). ^{1}H NMR (CD_3OD) δ 1.06 (t, J = 7.5 Hz, 3 H), 1.81 (qt, J = 7.5, 6.4 Hz, 2 H), 3.20 (m, 4 H), 3.40 (m, 4 H), 3.54 (m, 2 H), 3.99 (t, J = 6.4 Hz, 2 H), 6.65 (s, 1 H), 6.68 (t, J = 2.4 Hz, 1 H), 7.62 ppm (m, 2 H). MS m/z 248 $(MH)^+$. Anal. ($C_{14}H_{21}N_3O \cdot 0.5\ C_4H_4O_4$) C, H, N.

***t*-Butyl *cis*-5-[5-(Benzyloxy)-3-pyridinyl]hexahydropyrrolo-[3,4-*c*]pyrrole-2(1*H*)-carboxylate (Boc-15).** Prepared from **5** (1.0 g, 4.7 mmol) and 3-(benzyloxy)-5-bromopyridine (1.37 g, 5.2 mmol) according to coupling procedure A described for **Boc-6** to provide the title compound as a solid (1.5 g, 81% yield). ^{1}H NMR (CD_3OD) δ 1.45 (s, 9 H), 2.96−3.11 (m, 2 H), 3.21 (dd, J = 9.9, 3.6 Hz, 2 H), 3.24−3.31 (m, 2 H), 3.52 (dd, J = 9.9, 7.1 Hz, 2 H), 3.64 (dd, J = 9.5, 7.1 Hz, 2 H), 5.13 (s, 2 H), 6.61 (t, J = 2.2 Hz, 1 H), 7.26−7.46 (m, 5 H), 7.51 (d, J = 2.4 Hz, 1 H), 7.61 ppm (d, J = 2.0 Hz, 1 H). MS m/z 396 $(MH)^+$.

***cis*- 2-(5-(Benzyloxy)pyridin-3-yl)octahydropyrrolo[3,4-*c*]pyrrole (15).** Trifluoroacetic acid (2 mL) was added to an ice-cooled solution of **Boc-15** (363 mg, 0.92 mmol) in CH_2Cl_2 (5 mL). The yellow solution was stirred with ice cooling for 1 h, then at room temperature for 16 h. The solution was concentrated under vacuum, and the residue was purified by chromatography (CH_2Cl_2−EtOH−NH_4OH, 90:10:1) to provide an off-white solid, which was triturated with ethyl ether (10 mL) and dried to provide the title compound (172 mg, 63% yield). ^{1}H NMR (CD_3OD) δ 2.81 (dd, J = 11.5, 3.6 Hz, 2 H), 3.19 (m, 2 H), 3.18 (dd, J = 11.5, 7.1 Hz, 2 H), 3.25 (dd, J = 9.9, 2.4 Hz, 2 H), 3.39 (dd, J = 9.5, 7.5 Hz, 2 H), 5.14 (s, 2 H), 6.69 (t, J = 2.2 Hz, 1 H), 7.29−7.47 (m, 5 H), 7.59 (d, J = 2.4 Hz, 1 H), 7.64 ppm (d, J = 2.0 Hz, 1 H). MS m/z 296 $(MH)^+$. Anal. ($C_{18}H_{21}N_3O \cdot 0.1H_2O$) C, H, N.

***cis*-3-(5-Isopropyloxy-3-pyridinyl)-3,7-diazabicyclo[3.3.0]octane Semi(fumarate) (16).** Prepared in 63% yield from **5** (0.73 mmol) and 3-bromo-5-isopropyloxypyridine according to the procedures described for **15**. ^{1}H NMR (CD_3OD) δ 1.32 (d, J = 6.1 Hz, 6 H), 3.11−3.25 (m, 4 H), 3.33−3.40 (m, 2 H), 3.44 (dd, J = 9.8, 2.4 Hz, 2 H), 3.47−3.61 (m, 2 H), 4.65 (heptet, J = 6.0 Hz, 1 H), 6.65 (s, 1 H), 6.66 (t, J = 2.4 Hz, 1 H), 7.60 ppm (d, J = 2.4 Hz, 2 H). MS m/z 148 $(MH)^+$. Anal. ($C_{14}H_{21}N_3O \cdot 0.5C_4H_4O_4$) C, H, N.

***cis*-4-(5-(Hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)pyridin-3-yl)morpholine Sesqui-fumarate (17).** Prepared from **5** (138 mg, 0.65 mmol) and 4-(5-bromopyridin-3-yl)morpholine (190 mg, 0.78 mmol) according to coupling procedure A as described for **Boc-6**, followed by deprotection with trifluoroacetic acid in CH_2Cl_2. The crude product was taken up with 1.0 M $Na_2CO_{3(aq)}$ (100 mL) and extracted with $CHCl_3$−*i*PrOH (4:1, 2 × 50 mL). The combined extract was dried (Na_2SO_4) and concentrated under vacuum. The residue was dissolved in a minimal amount of methanol (ca. 1 mL), and a solution of fumaric acid (50 mg, 0.43 mmol) in ether−methanol (10:1, 5.0 mL) was added dropwise with stirring over 5 min. After 1 h, the precipitate was collected by filtration, rinsed with ether, and dried to afford the title compound (83 mg, 25% yield). ^{1}H NMR (CD_3OD) δ 3.17−3.22 (m, 4 H), 3.23−3.39 (m, 6 H), 3.46−3.78 (m, 4 H), 3.80−3.86 (m, 4 H), 6.65 (t, J = 2.2 Hz, 1 H), 6.70 (s, 3.4 H; $C_4H_4O_4$), 7.54 (d, J = 2.4 Hz, 1 H), 7.68 ppm (d, J = 2.4 Hz, 1 H). MS m/z 275 $(MH)^+$. Anal. ($C_{15}H_{22}N_4O \cdot 1.7C_4H_4O_4$) C, H, N.

***t*-Butyl *cis*-5-(5-Hydroxy-3-pyridinyl)hexahydropyrrolo[3,4-*c*]-pyrrole-2(1*H*)-carboxylate (Boc-18).** A solution of **Boc-15** (1.3 g, 3.8 mmol) in 2-propanol (100 mL) was shaken with 10% Pd/C (0.65 g) under hydrogen (4 atm) at ambient temperature for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with a minimum amount of EtOAc (ca. 2 mL) and filtered to provide the title compound as a solid (0.76 g, 66% yield). ^{1}H NMR (CD_3OD) δ 3.05 (m, 2 H), 3.20 (dd, J = 9.8, 4.1 Hz, 2 H), 3.28 (m, 2 H), 3.51 (dd, J = 9.8, 7.5 Hz, 2 H), 3.64 (m, 2 H), 6.42 (t, J = 2.4 Hz, 1 H), 7.40 (d, J = 2.4 Hz, 1 H), 7.43 ppm (d, J = 2.4 Hz, 1 H).

***cis*-2-(5-Hydroxy-3-pyridinyl)octahydropyrrolo[3,4-*c*]pyrrole-Dihydrochloride (18).** A solution of **Boc-18** (150 mg, 0.49 mmol) in EtOAc−CH_3OH (1:2, 15 mL) was treated with HCl/1,4-dioxane (4M, 1 mL, 4 mmol). The mixture was stirred at room temperature for 16 h and then cooled in ice to complete precipitation. The mixture was filtered to provide the title compound as a white solid (136 mg, 99% yield). ^{1}H NMR (CD_3OD) δ 3.30 (m, 4 H), 3.51 (dd, J = 10.3, 2.4 Hz, 2 H), 3.60 (m, 4 H), 7.06 (dd, J = 2.2, 1.8 Hz, 1 H), 7.62 (d, J = 1.8 Hz, 1 H), 7.69 ppm (d, J = 2.2 Hz, 1 H). MS m/z 206 $(MH)^+$. Anal. ($C_{11}H_{15}N_3O \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

***t*-Butyl *cis*-5-(5-Phenylpyridin-3-yl)hexahydro-pyrrolo[3,4-*c*]-pyrrole-2-carboxylate (Boc-19).** A mixture of **Boc-11** (158 mg, 0.43 mmol), phenylboronic acid (63 mg, 0.52 mmol) and tetrakis (triphenylphosphine)palladium (13 mg, 0.011 mmol) was combined with ethanol (6 mL) and 5% $Na_2CO_{3(aq)}$ (1 mL). The mixture was evacuated and purged with nitrogen (3 cycles) and stirred under nitrogen at 85 °C for 1 h. The mixture was cooled to 30 °C, diluted with water (25 mL), and extracted with ethyl acetate (2 × 25 mL). The combined extract was concentrated under vacuum, and the residue was purified by chromatography on silica gel, eluting with 1:1 hexanes−EtOAc to provide the title compound as a white foam (142 mg, 91% yield). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.06 (m, 2 H), 3.32 (dd, J = 9.7, 3.9 Hz, 2 H), 3.37 (br m, 2 H), 3.66 (m, 4 H), 7.03 (br s, 1 H), 7.46 (m, 3 H), 7.58 (m, 2 H), 7.95 (br s, 1 H), 8.20 ppm (br s, 1 H). MS m/z 366 $(MH)^+$.

***cis*-2-(5-Phenylpyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (19).** A solution of **Boc-19** (42 mg, 0.115 mmol) in CH_2Cl_2 (1.5 mL) was cooled in ice and treated with trifluoroacetic acid (800 μL). The pale-yellow solution was stirred at 0 °C for 1 h and then concentrated under vacuum. The residue was taken up in ether (5 mL) and concentrated under vacuum, then triturated with 10% methanol−ether. The resulting white precipitate was filtered and dried under vacuum at 50 °C to provide the title compound (45 mg, 80% yield). ^{1}H NMR (CD_3OD) δ 3.32 (m, 4 H), 3.63 (m, 6 H), 7.54 (m, 3 H), 7.73 (d, J = 1.4 Hz, 1 H), 7.76 (m, 2 H), 8.07 (d, J = 2.7 Hz, 1 H), 8.34 ppm (d, J = 1.4 Hz, 1 H). MS m/z 266 $(MH)^+$. Anal. ($C_{17}H_{19}N_3 \cdot 2CF_3CO_2H$) C, H, N.

***cis*-2-(5-Phenylpyridin-3-yl)-5-methyl-octahydro-pyrrolo[3,4-*c*]-pyrrole Sesqui-fumarate (20).** A solution of **Boc-19** (100 mg, 0.274 mmol) and 37% formalin (66 mg, 0.814 mmol) in 88% formic acid (1 mL) was warmed to 100 °C for 100 min. The mixture was cooled to 30 °C and concentrated under vacuum. The residue was taken up in 20% $K_2CO_{3(aq)}$ (4 mL) and 25% $NaOH_{(aq)}$ (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 8 mL). The combined extract was dried over K_2CO_3 and concentrated under vacuum. The residue was dissolved in 10% methanol−ether (3 mL) and treated with a solution of fumaric acid (33 mg, 0.284 mmol) in 10% methanol−ether (10 mL). The mixture was scratched until an even white suspension resulted, and the solid was isolated by filtration and dried under vacuum at 50 °C to provide the title compound (59 mg, 46% yield). ^{1}H NMR (CD_3OD) δ 2.91 (s, 3 H), (3.33 (m, 6 H), 3.64 (m, 4 H), 6.70 (s, 3 H, 1.5 fumaric acid), 7.48 (dd, J = 2.7, 2.7 Hz, 1 H), 7.41 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.3 Hz, 2 H), 7.64 (d, J = 7.4 Hz, 2 H), 8.05 (d, J = 2.7 Hz, 1 H), 8.20 ppm (d, J = 1.7 Hz, 1 H). MS m/z 280 $(MH)^+$. Anal. ($C_{18}H_{21}N_3 \cdot 1.5C_4H_4O_4 \cdot 0.2H_2O$) C, H, N.

***t*-Butyl *cis*-5-(6-Phenyl-pyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]-pyrrole-2-carboxylate (Boc-21).** A pressure tube was charged with **Boc-8** (200 mg, 0.62 mmol), phenylboronic acid (238 mg, 1.24 mmol), Pd_2dba_3 (20 mg, 0.022 mmol), Cs_2CO_3 (611 mg, 1.86 mmol), and *p*-dioxane (15 mL). Solid 1,3-bis(2,6-di(isopropyl) phenyl)imidazolium chloride (26 mg, 0.061 mmol) was added, and the tube was closed under a nitrogen purge. The mixture was heated at 85 °C for 13 h, and the mixture was cooled to room

temperature and filtered. The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography (hexanes−EtOAc, 50:50) to provide the title compound (200 mg, 88% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.99−3.09 (m, 2 H), 3.29 (dd, J = 9.8, 3.7 Hz, 2 H), 3.30−3.44 (m, 2 H), 3.55−3.74 (m, 4 H), 6.89 (dd, J = 8.6, 2.9 Hz, 1 H), 7.27−7.34 (m, 1 H), 7.38−7.46 (m, 2 H), 7.60 (d, J = 8.8 Hz, 1 H), 7.87−7.94 (m, 2 H), 8.07 ppm (d, J = 2.7 Hz, 1 H). MS m/z 366 $(MH)^+$.

***cis*-2-(6-Phenyl-pyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (21).** Trifluoroacetic acid (1 mL) was added to a solution of **Boc-21** (72 mg, 0.20 mmol) in CH_2Cl_2 (2 mL), and the solution was stirred at room temperature for 1 h and then concentrated under vacuum. Toluene (5 mL) was added to the residue, and the mixture concentrated under vacuum. This was repeated once more to remove excess acid. The residue was dissolved in EtOAc (1.5 mL), and ethyl ether (3 mL) was added gradually. The resulting suspension was stirred for 5 h and then cooled in ice. The precipitate was isolated by filtration and dried under vacuum to provide the title salt (72 mg, 74% yield). ^{1}H NMR (CD_3OD) δ 3.32 (m, 4 H), 3.62 (m, 6 H), 7.57 (m, 3 H), 7.68 (dd, J = 9.2, 2.7 Hz, 1 H), 7.81 (m, 2 H), 8.01 ppm (m, 2 H). MS m/z 266 $(MH)^+$. Anal. ($C_{17}H_{19}N_3 \cdot 2CF_3CO_2H$) C, H, N.

***cis*-2-Methyl-5-(6-phenyl-pyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole L-Tartrate (22).** Trifluoroacetic acid (2 mL) was added to a solution of **Boc-21** (200 mg, 0.55 mmol) in CH_2Cl_2 (4 mL), and the solution was stirred at room temperature for 1 h and then concentrated under vacuum. The residue was taken up in 20% $K_2CO_{3(aq)}$ (4 mL) and 15% $NaOH_{(aq)}$ (4 mL) and extracted with CH_2Cl_2 (6 × 8 mL). The combined extract was dried (Na_2SO_4) and concentrated to leave the free base (122 mg). This was dissolved in CH_3CN (5 mL), and formalin (37%, 4 mL) was added, followed by $NaBH(OAc)_3$ (134 mg, 0.60 mmol). The mixture was stirred at room temperature for 12 h and concentrated under vacuum. The residue was extracted with CH_2Cl_2 (4 × 5 mL), the combined organic phase was concentrated under vacuum, and the residue was purified by chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 95:5:0.7) to provide the *N*-methylated free base (46 mg). This was dissolved in warm EtOAc (4 mL) and a solution of L-tartaric acid (49 mg, 0.33 mmol, 2 equiv) in CH_3OH (1.5 mL) was added dropwise. The resulting suspension was stirred at room temperature for 1 h, then filtered and the solid dried under vacuum to provide the title compound (80 mg, 25% yield). ^{1}H NMR (CD_3OD) δ 2.87 (s, 3 H), 3.30 (m, 6 H), 3.60 (m, 4 H), 4.40 (s, 2 H), 7.29 (dd, J = 8.8, 2.7 Hz, 1 H), 7.35 (m, 1 H), 7.44 (m, 2 H), 7.71 (d, J = 8.5 Hz, 1 H), 7.83 (m, 2 H), 8.12 ppm (d, J = 3.1 Hz, 1 H). MS m/z 280 $(MH)^+$. Anal. ($C_{18}H_{21}N_3 \cdot C_4H_6O_6 \cdot 0.1H_2O$) C, H, N.

***cis*-5-(6-Chloropyridin-3-yl)-2,2-dimethyloctahydropyrrolo[3,4-*c*]-pyrrol-2-ium Iodide (23).** Methyl iodide (0.06 mL, 130 mg, 0.93 mmol) was added at room temperature to a solution of **9** (110 mg, 0.46 mmol) in CH_2Cl_2 (5 mL). A precipitate formed within 2 min, and the suspension was stirred for 1 h, and then filtered. The solid was washed with ethyl ether (3 mL) and dried under vacuum to provide the title compound (137 mg, 78% yield). ^{1}H NMR (CD_3OD) δ 3.07−3.16 (m, 2 H), 3.17 (s, 3 H), 3.27 (s, 3 H), 3.29−3.36 (m, 2 H), 3.38−3.51 (m, 2 H), 3.54−3.72 (m, 2 H), 3.87−4.05 (m, 2 H), 7.16−7.37 (m, 2 H), 7.88 ppm (br s, 1 H). MS m/z 252 $(M)^+$. Anal. ($C_{13}H_{19}N_3ClI$) C, H, N.

***t*-Butyl *cis*-5-(5-Bromo-pyridin-2-yl)-hexahydro-pyrrolo[3,4-*c*]-pyrrole-2-carboxylate (Boc-24).** Prepared from **5** (7.032 g, 33.2 mmol) and 2,5-dibromopyridine (**24a**, 22.03 g, 92.9 mmol) according to coupling procedure A as described for **Boc-6**. The crude product was purified by column chromatography (hexanes−EtOAc, 95:5−40:60) to provide the title compound as an off-white solid (7.71 g, 62% yield). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H) 2.94−3.14 (m, 2 H) 3.17−3.38 (m, 4 H) 3.51−3.76 (m, 4 H) 6.26 (d, J = 8.9 Hz, 1 H) 7.50 (dd, J = 9.0, 2.5 Hz, 1 H) 8.16 ppm (d, J = 2.4 Hz, 1 H). MS m/z 368/370 $(MH)^+$.

***t*-Butyl *cis*-5-(4-Bromo-phenyl)-hexahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-25).** Prepared from **5** (0.75 g, 3.53 mmol) and 1,4-dibromobenzene (**25a**, 0.83 g, 3.53 mmol) according to coupling procedure A as described for **Boc-6**, except the heating period was extended to 24 h at 100 °C. The crude product was purified by flash chromatography (hexanes−EtOAc, 70:30) to provide the title compound (0.65 g, 1.8 mmol, 50% yield). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.94−3.05 (m, 2 H), 3.17 (dd, J = 9.7, 3.9 Hz, 2 H), 3.20−3.42 (m, 2 H), 3.50 (dd, J = 8.8, 7.4 Hz, 2 H), 3.64 (dd, J = 11.2, 7.5 Hz, 2 H), 6.43 (d, J = 8.8 Hz, 2 H), 7.30 ppm (d, J = 8.8 Hz, 2 H). MS m/z 367/369 $(MH)^+$.

***t*-Butyl *cis*-5-(6-Chloro-pyridazin-3-yl)-hexahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-26).** A mixture of **5** (5.0 g, 23.6 mmol), 3,6-dichloropyridazine (**26a**, 4.70 g, 30.6 mmol), $Pd_2(dba)_3$, (944 mg, 1.03 mmol), 1,3-bis(2,6-di(isopropyl)phenyl)-imidazolium chloride (1.23 g, 2.90 mmol), and Cs_2CO_3 (23.2 g, 70.8 mmol) in *p*-dioxane (60 mL) was heated at 85 °C with stirring under nitrogen for 18 h. The reaction was cooled to room temperature, filtered, and concentrated under vacuum. The resulting solid was triturated with hexanes−EtOAc (50:10, 100 mL) and filtered to provide the title compound as an off-white solid (3.40 g). The filtrate was concentrated, and the residue was purified by flash chromatography (hexanes−EtOAc, 50:50−0:100) to provide additional product (total 4.44 g, 58% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.05 (s, 2 H), 3.21−3.57 (m, 4 H), 3.58−3.83 (m, 4 H), 6.61 (d, J = 9.5 Hz, 1 H), 7.19 ppm (d, J = 9.5 Hz, 1 H). MS m/z 325/327 $(MH)^+$.

***t*-Butyl *cis*-5-(5-Phenyl-pyridin-2-yl)-hexahydro-pyrrolo[3,4-*c*]-pyrrole-2-carboxylate (Boc-27).** A mixture of **Boc-24** (0.25 g, 0.68 mmol), phenylboronic acid (0.26 g, 1.36 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), 1,3-bis(2,6-di(isopropyl)phenyl)imidazolium chloride (52 mg, 0.12 mmol), and Cs_2CO_3 (0.67 g, 1.9 mmol) in 15 mL dioxane was heated at 85 °C for 16 h. The mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by chromatography (hexanes−EtOAc, 50:50) to provide the title compound (0.20 g, 80% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.96−3.10 (m, 2 H), 3.21−3.55 (m, 4 H), 3.58−3.83 (m, 4 H), 6.44 (d, J = 8.9 Hz, 1 H), 7.30 (dt, J = 7.0, 1.2 Hz, 1 H), 7.38−7.45 (m, 2 H), 7.47−7.55 (m, 2 H), 7.71 (d, J = 9.0 Hz, 1 H), 8.42 ppm (dd, J = 2.4, 0.7 Hz, 1 H). MS m/z 366 $(MH)^+$.

***cis*-2-(5-Phenyl-pyridin-2-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole-Bis-trifluoroacetate (27).** Deprotection and salt formation from **Boc-27** (0.20 g, 0.55 mmol) was accomplished with trifluoroacetic acid according to the procedure described for **15** to provide the title compound (233 mg, 84% yield). ^{1}H NMR (CD_3OD) δ 3.33 (m, 2 H), 3.40 (m, 2 H), 3.70 (m, 4 H), 3.92 (m, 2 H), 7.08 (d, J = 9.5 Hz, 1 H), 7.52 (m, 3 H), 7.65 (m, 2 H), 8.18 (br d, J = 2.4 Hz, 1 H), 8.25 ppm (dd, J = 9.5, 2.4 Hz, 1 H). MS m/z 266 $(MH)^+$. Anal. ($C_{17}H_{19}N_3 \cdot 2CF_3CO_2H$) C, H, N.

***cis*-2-Methyl-5-(5-phenyl-pyridin-2-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole 4-Toluenesulfonate (28).** $NaBH(OAc)_3$ (0.21 g, 0.57 mmol) was added to a solution of **27** (0.20 g, 0.40 mmol) in 37% formalin (7 mL), and the resulting mixture was stirred at room temperature for 8 h and then concentrated under vacuum. The residue was taken up in CH_2Cl_2 (3 mL) and purified by flash chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the methylated free base (74 mg, 66% yield). This was combined with *p*-toluenesulfonic acid (53 mg, 0.28 mmol) in warm EtOAc (10 mL) and the resulting precipitate was filtered and dried to provide the title compound (85 mg, 69% yield). ^{1}H NMR (CD_3OD) δ 2.35 (s, 3 H), 2.96 (s, 3 H), 3.22 (m, 2 H), 3.43 (m, 3 H), 3.66 (m, 4 H), 3.98 (m, 1 H), 6.82 (d, J = 9.2 Hz, 1 H), 7.22 (m, 2 H), 7.34 (tt, J = 7.1, 2.0 Hz, 1 H), 7.44 (m, 2 H), 7.56 (m, 2 H), 7.68 (m, 2 H), 7.92 (dd, J = 8.8, 2.4 Hz, 1 H), 8.32 ppm (d, J = 2.0 Hz, 1 H). MS m/z 280 $(MH)^+$. Anal. ($C_{18}H_{21}N_3 \cdot C_7H_8O_3S \cdot 0.6H_2O$) C, H, N.

***t*-Butyl *cis*-2-Biphenyl-4-yl-octahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-29).** Aqueous Na_2CO_3 (2 M, 3 mL) was added

to a mixture of **Boc-25** (250 mg, 0.68 mmol), $Pd_2(dba)_3$ (25 mg, 0.027 mmol), 1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride (29 mg, 0.068 mmol) and phenylboronic acid (262 mg, 1.37 mmol) in toluene (25 mL). The mixture was evacuated and purged with nitrogen (3 cycles) and stirred under nitrogen at 85 °C for 60 h. The mixture was cooled to room temperature, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (hexanes−EtOAc 70:30) to provide the title compound (160 mg, 64% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.93−3.08 (m, 2 H), 3.19−3.45 (m, 4 H), 3.51−3.72 (m, 4 H), 6.63 (d, J = 8.5 Hz, 2 H), 7.21−7.30 (m, 1 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.50 (d, J = 8.8 Hz, 2 H), 7.54 ppm (d, J = 7.5 Hz, 2 H). MS m/z 365 $(MH)^+$.

***cis*-2-Biphenyl-4-yl-octahydro-pyrrolo[3,4-*c*]pyrrole Trifluoroacetate (29).** Trifluoroacetic acid (4 mL) was added dropwise over 5 min to a solution of **Boc-29** (160 mg, 0.44 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 2 h and then concentrated under vacuum. Toluene (3 mL) was added to the residue and the mixture was concentrated under vacuum to remove excess acid (repeated once more). The residue was triturated with a mixture of EtOAc (2 mL) and ethyl ether (2 mL). The resulting suspension was filtered and the solid dried under vacuum to provide the title salt (144 mg, 83% yield). ^{1}H NMR (CD_3OD) δ 3.29 (m, 6 H), 3.52 (d, J = 8.8 Hz, 2 H), 3.61 (m, 2 H), 6.83 (m, 2 H), 7.23 (m, 1 H), 7.37 (m, 2 H), 7.52 ppm (m, 4 H). MS m/z 265 $(MH)^+$. Anal. ($C_{18}H_{20}N_2 \cdot CF_3CO_2H \cdot 0.2H_2O$) C, H, N.

***cis*-2-Biphenyl-4-yl-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole Dihydrochloride (30).** Solid $NaBH(OAc)_3$ (59 mg, 0.28 mmol) was added to a solution of **29** (105 mg, 0.21 mmol) in 37% formalin (3 mL). The mixture was stirred at room temperature for 2 h and then quenched by addition of satd $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (4 × 3 mL), and the combined extract was concentrated under vacuum. The residue was purified by flash chromatography (silica, CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the crude *N*-methylated free base (88 mg), contaminated with paraformaldehyde. This material was taken up in EtOAc (3 mL) and filtered to remove some insoluble matter. HCl/dioxane (4 M, 0.7 mL) was added to the filtrate, and the resulting suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration and dried under vacuum to provide the title salt (40 mg, 54% yield). ^{1}H NMR (CD_3OD) δ 2.92 (s, 3 H), 3.21 (m, 2 H), 3.40 (m, 4 H), 3.64 (m, 3 H), 3.98 (m, 1 H), 6.96 (m, 2 H), 7.25 (t, J = 7.8 Hz, 1 H), 7.38 (t, J = 7.6 Hz, 2 H), 7.54 ppm (m, 4 H). MS m/z 279 $(MH)^+$. Anal. ($C_{19}H_{22}N_2 \cdot 2HCl$) C, H, N.

***t*-Butyl *cis*-5-(6-Phenyl-pyridazin-3-yl)-hexahydro-pyrrolo-[3,4-*c*]pyrrole-2-carboxylate (Boc-31).** Solid 3-chloro-6-phenylpyridazine (2.82 g, 14.79 mmol) and **5** (3.14 g, 14.79 mmol) were charged to a 100 mL flask with stir bar and condenser. *N*,*N*-Diisopropylethylamine (9 mL, 51.5 mmol) and DMSO (9 mL) were added, and the slurry was heated at 105 °C under nitrogen for 49 h. The dark-amber solution was cooled to 40 −50 °C, diluted with water (50 mL), and stirred vigorously for 1 h. The precipitate was isolated by filtration, washed well with water, and sucked dry on the filter. The solid was triturated with ether (2 × 50 mL) to remove unreacted 3-chloro-6-phenylpyridazine, and filtered to provide the title compound as a beige solid (4.91 g, 91% yield). ^{1}H NMR (CD_3OD) δ 1.46 (s, 9 H), 3.03−3.17 (m, 2 H), 3.29−3.37 (m, 2 H), 3.50 (dd, J = 10.7, 4.0 Hz, 2 H), 3.61−3.74 (m, 2 H), 3.82 (dd, J = 11.1, 7.1 Hz, 2 H), 7.04 (d, J = 9.5 Hz, 1 H), 7.35−7.43 (m, 1 H), 7.47 (t, J = 7.3 Hz, 2 H), 7.85 (d, J = 9.5 Hz, 1 H), 7.92 ppm (d, J = 7.1 Hz, 2 H). MS m/z 367 $(MH)^+$.

***cis*-2-(6-Phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (31).** Deprotection of **Boc-31** (0.16 g, 0.44 mmol) with trifluoroacetic acid according to the procedure described for **19** provided the title salt as an off-white solid (0.30 mmol, 69% yield). ^{1}H NMR (CD_3OD) δ 3.36 (m, 4 H), 3.65 (m, 2 H), 3.75 (dd, J = 11.5, 3.1 Hz, 2 H), 3.89 (m, 2 H), 7.46 (d, J = 9.5 Hz, 1 H), 7.53 (m, 3 H), 7.96 (m, 2 H), 8.17 ppm (d, J = 9.8 Hz, 1 H). MS m/z 267 $(MH)^+$. Anal. ($C_{16}H_{18}N_4 \cdot 2CF_3CO_2H \cdot 0.2H_2O$) C, H, N.

***cis*-2-(6-Phenyl-pyridazin-3-yl)-5-methyloctahydro-pyrrolo[3,4-*c*]-pyrrole (32).** Aqueous formalin (37%, 1.1 mL, 14.7 mmol) was added to a solution of **Boc-31** (4.91 g, 13.40 mmol) in 88% formic acid (25 mL). The dark mixture was heated at 100 °C for 1 h and then cooled to room temperature and concentrated under vacuum. The dark-amber residue was combined with 20% Na_2CO_3(aq) (25 mL), and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extract was washed with brine (25 mL) and concentrated under vacuum. The residue was recrystallized from EtOAc (50 mL) to provide a slightly off-white, crystalline solid (2.00 g, 53%). ^{1}H NMR (CD_3OD) δ 2.35 (s, 3 H), 2.53 (dd, J = 9.5, 4.0 Hz, 2 H), 2.84 (dd, J = 9.5, 7.1 Hz, 2 H), 3.02−3.17 (m, 2 H), 3.56 (dd, J = 10.9, 3.0 Hz, 2 H), 3.71 (dd, J = 11.1, 8.0 Hz, 2 H), 7.08 (d, J = 9.5 Hz, 1 H), 7.37−7.51 (m, 3 H), 7.84 (d, J = 9.5 Hz, 1 H), 7.89−7.95 ppm (m, 2 H). MS m/z 281 $(MH)^+$. Anal.($C_{17}H_{20}N_4$) C, H, N.

***cis*-2-Ethyl-5-(6-phenyl-pyridazin-3-yl)-octahydro-pyrrolo[3,4-*c*]-pyrrole Bis-*p*-toluenesulfonate (33).** $NaBH(OAc)_3$ (112 mg, 0.53 mmol) was combined with **31** (200 mg, 0.40 mmol) and acetaldehyde (5 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under vacuum, and the residue was taken up in CH_2Cl_2 (15 mL) and washed successively with satd $NaHCO_{3(aq)}$ (2 × 5 mL) and brine (5 mL) and then dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the free base (31 mg). This was dissolved in EtOAc (3 mL) and a solution of *p*-toluenesulfonic acid monohydrate (42 mg, 2 equiv) In CH_3OH (1 mL) was added dropwise with stirring. The resulting precipitate was isolated by filtration and dried under vacuum to provide the title salt (38 mg, 15% yield). ^{1}H NMR (CD_3OD) δ 1.37 (q, J = 7.7 Hz, 3 H), 2.30 (s, 6 H), 3.41 (m, 6 H), 3.94 (m, 6 H), 7.18 (d, J = 7.8 Hz, 4 H), 7.58 (m, 3 H), 7.65 (d, J = 8.1 Hz, 4 H), 7.74 (dd, J = 28.1, 10.2 Hz, 1 H), 7.96 (d, J = 3.7 Hz, 2 H), 8.32 ppm (dd, J = 27.0, 10.0 Hz, 1 H). MS m/z 295 $(MH)^+$. Anal. ($C_{18}H_{22}N_4 \cdot 2C_7H_8O_3S \cdot 0.2H_2O$) C, H, N.

***cis*-5-(6-Phenylpyridazin-3-yl)-2,2-dimethyloctahydropyrrolo-[3,4-*c*]pyrrol-2-ium Iodide (34).** Iodomethane (0.2 mL) was added to a solution of **32** (39 mg, 0.14 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 12 h, then concentrated under vacuum. The residue was triturated with ether (5 mL) and filtered to provide the title salt as an off-white solid (52 mg, 88% yield). ^{1}H NMR (D_2O) δ 3.09 (s, 3 H), 3.17 (s, 3 H), 3.25−3.35 (m, 2 H), 3.45 (m, 4 H), 3.77 (d, J = 9.8 Hz, 2 H), 3.93 (br dd, J = 11.0, 4.2 Hz, 2 H), 7.17 (d, J = 9.5 Hz, 1 H), 7.43−7.53 (m, 3 H), 7.75−7.80 (m, 2 H), 7.82 ppm (d, J = 9.5 Hz, 1 H). MS m/z 295 $(M)^+$. Anal. ($C_{18}H_{23}N_4I$) C, H, N.

***cis*-2-(6-Chloro-pyridazin-3-yl)-5-methyl-octahydro-pyrrolo-[3,4-*c*]-pyrrole.** A solution of **Boc-26** (1.0 g, 3.1 mmol) in 37% formalin (10 mL) and 88% formic acid (20 mL) was heated at 100 °C for 2.5 h. The mixture was cooled to room temperature and concentrated under vacuum. The residual oil was purified by flash chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the title compound (0.43 g, 58% yield). ^{1}H NMR (CD_3OD) δ 2.41 (s, 3 H) 2.62 (dd, J = 10.0, 3.9 Hz, 2 H) 2.89 (dd, J = 10.3, 7.3 Hz, 2 H) 3.05−3.16 (m, 2 H) 3.50 (dd, J = 11.2, 3.1 Hz, 2 H) 3.65 (dd, J = 11.5, 8.1 Hz, 2 H) 7.04 (d, J = 9.5 Hz, 1 H) 7.41 ppm (d, J = 9.5 Hz, 1 H). MS m/z 239 $(MH)^+$.

***cis*-2-Methyl-5-(6-(4-methylphenyl)pyridazin-3-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Dihydrochloride (35).** A mixture of *cis*-2-(6-chloro-pyridazin-3-yl)-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole (0.23 g, 9.5 mmol), *p*-tolylboronic acid (0.17 g, 1.2 mmol), Cs_2CO_3 (0.93 g, 2.8 mmol), 1,3-bis(2,6-di-*i*-propylphenyl)imidazolium chloride (52 mg, 0.12 mmol), and $Pd_2(dba)_3$ (40 mg, 4.4 mmol) was charged to a glass pressure tube with 1,4-dioxane (15 mL). The mixture was stirred at 85 °C for 72 h then cooled to ambient temperature. The mixture was filtered, concentrated

under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the free base of the title product (0.13 g, 37% yield). This was dissolved in 10% CH_3OH−diethyl ether (5 mL) and 4 N HCl/dioxane (1 mL) was added. The suspension was stirred for 1 h, and the precipitate was collected by filtration, washed with ether, and dried to provide the title salt (0.11 g, 64% yield). ^{1}H NMR (CD_3OD) δ 2.43 (s, 3 H), 2.97 (s, 3 H), 3.17 (m, 2 H), 3.54 (m, 2 H), 3.93 (m, 6 H), 7.40 (d, J = 7.8 Hz, 2 H), 7.76 (m, 1 H), 7.88 (m, 2 H), 8.38 ppm (d, J = 9.5 Hz, 1 H). MS m/z 295 $(MH)^+$. Anal. ($C_{18}H_{22}N_4 \cdot 2HCl \cdot 1.5H_2O$) C, H, N.

***cis*-2-Methyl-5-(6-(3-methylphenyl)pyridazin-3-yl)-octahydropyrrolo[3,4-*c*]pyrrole Dihydrochloride (36). Step 1. Procedure for Anhydrous Miyaura−Suzuki Coupling.** To a solution of **Boc-26** (1.45 g, 4.47 mmol) in 50 mL *p*-dioxane was added *m*-tolylboronic acid (0.79 g, 5.82 mmol), $Pd_2(dba)_3$ (0.24 g, 0.26 mmol), 1,3-bis(2,6-di-i-propylphenyl)imidazolium chloride (0.312 g, 0.73 mmol), and Cs_2CO_3 (4.4 g, 13.4 mmol). This mixture was warmed to 85 °C and stirred for 20 h. The reaction was then cooled to room temperature and concentrated under vacuum. Diethyl ether (25 mL) and hexanes (25 mL) were added to the crude material, and the resulting solid was filtered to provide the title compound (1.28 g, 75% yield). ^{1}H NMR ($CDCl_3$) δ1.46 (s, 9 H), 2.43 (s, 3 H), 2.99−3.12 (m, 2 H), 3.21−3.45 (m, 2 H), 3.46−3.65 (m, 2 H), 3.63−3.74 (m, 2 H), 3.75−3.91 (m, 2 H), 6.70 (d, J = 9.5 Hz, 1 H), 7.21 (d, J = 7.5 Hz, 1 H), 7.35 (t, J = 7.6 Hz, 1 H), 7.64 (d, J = 9.5 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 7.86 ppm (s, 1 H). MS m/z 381 $(MH)^+$.

Step 2. Deprotection and *N*-Methylation. Trifluoroacetic acid (10 mL) was added to a solution of the product from Step 1 (1.18 g, 3.1 mmol) in CH_2Cl_2 (20 mL), and the solution was stirred at room temperature for 90 min and then concentrated under vacuum. Toluene (15 mL) was added to the residue, and the mixture concentrated under vacuum—this was repeated once more to remove excess acid. The residue was taken up in EtOAc (15 mL), and the amine salt was precipitated by dropwise addition of diethyl ether (8 mL). The solid was filtered and dried (1.5 g). This material was dissolved in 37% formalin (25 mL) and $NaBH(OAc)_3$ (0.82 g, 3.84 mmol) was added. The mixture was stirred for 18 h at room temperature and then concentrated under vacuum. The residue was diluted with satd $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined extract was washed with brine (10 mL) and concentrated under vacuum. The residue was dissolved in 10% ethanol−EtOAc (15 mL) and a solution of 4 N HCl/dioxane (4 mL) was added. The solution was stirred at room temperature as ethyl ether (8 mL) was added gradually to produce a precipitate. The mixture was filtered and the collected solid was washed with ether and dried to provide the title compound (1.0 g, 81% yield). ^{1}H NMR (CD_3OD) δ 2.45 (s, 3 H), 2.96 and 3.02 (endo/exo NHMe, s, 3 H), 3.20 (m, 1 H), 3.48 (m, 2 H), 3.61 (m, 1 H), 3.79 (m, 1 H), 3.98 (m, 5 H), 7.44 (m, 2 H), 7.81 (m, 3 H), 8.41 and 8.44 ppm (endo/exo salt, d, J = 9.8 Hz, 1 H). MS m/z 295 $(MH)^+$. Anal. ($C_{18}H_{22}N_4 \cdot 2HCl \cdot 2H_2O$) C, H, N.

***cis*-2-Methyl-5-(6-*m*-tolyl-pyridin-3-yl)-octahydro-pyrrolo[3,4-*c*]-pyrrole Bis-L-tartrate (37).** Prepared in 39% overall yield from **Boc-8** (200 mg, 0.62 mmol) and *m*-tolylboronic acid (96 mg, 0.68 mmol) according to the anhydrous Miyaura−Suzuki coupling and *N*-methylation procedures described for **36**. The free base (45 mg) was combined with L-tartaric acid (46 mg) in methanol (1 mL) and EtOAc (2 mL) and the precipitate was isolated to provide the title salt. ^{1}H NMR (CD_3OD) δ 1.24 (m, 2 H), 2.41 (s, 3 H), 2.93 (s, 3 H), 3.31 (m, 4 H), 3.62 (d, J = 8.8 Hz, 2 H), 3.69 (m, 2 H), 4.45 (s, 4 H), 7.18 (d, J = 7.5 Hz, 1 H), 7.31 (m, 2 H), 7.61 (d, J = 7.8 Hz, 1 H), 7.66 (s, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 8.11 (d, J = 2.7 Hz, 1 H). MS m/z 294 $(MH)^+$. Anal. ($C_{19}H_{23}N_3 \cdot 2.3C_4H_6O_6$) C, H, N.

***cis*-2-(6-Biphenyl-3-yl-pyridin-3-yl)-5-methyl-octahydro-pyrrolo-[3,4-*c*]pyrrole *p*-Toluenesulfonate (38).** Prepared in 34% yield from **Boc-10** and 3-biphenylboronic acid according to the coupling, deprotection and *N*-methylation procedures described for **36**. The free base (34 mg) was dissolved in EtOAc (2 mL) and a solution of *p*-toluenesulfonic acid (19 mg, 0.096 mmol) in 10% CH_3OH−EtOAc (1 mL) was added with stirring. After 30 min, the precipitate was isolated by filtration and dried to provide the title salt (35 mg, 68% yield for the salt). ^{1}H NMR (CD_3OD) δ 2.34 (s, 3 H), 2.96 (s, 3 H), 3.35 (m, 6 H), 3.62 (m, 4 H), 7.21 (m, 2 H), 7.36 (m, 2 H), 7.46 (m, 2 H), 7.53 (m, 1 H), 7.63 (ddd, J = 7.8, 1.7, 1.0 Hz, 1 H), 7.69 (m, 4 H), 7.81 (ddd, J = 7.8, 1.7, 1.0 Hz, 1 H) 7.82 (m, 1 H), 8.10 (dd, J = 2.0, 1.4 Hz, 1 H), 8.15 ppm (br d, J = 2.7 Hz, 1 H). MS m/z 356 $(MH)^+$. Anal. ($C_{24}H_{25}N_3 \cdot C_7H_8O_3S \cdot 0.5H_2O$) C, H, N.

***cis*-2-[6-(3,5-(Dimethylphenyl)pyridazin-3-yl]-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole Dihydrochloride (39).** Prepared in 51% yield (73% coupling, 70% methylation and salt formation) from **Boc-26** and 3,5-dimethylphenylboronic acid according to the procedures described for 36. ^{1}H NMR (CD_3OD) δ 2.41 (s, 6 H), 2.97 (s, 3 H), 3.17 (m, 1 H), 3.52 (m, 3 H), 3.91 (m, 6 H), 7.25 (s, 1 H), 7.58 (s, 2 H), 7.78 (t, J = 9.2 Hz, 1 H), 8.39 ppm (m, 1 H). MS m/z 309 $(MH)^+$. Anal. ($C_{19}H_{24}N_4 \cdot 2HCl \cdot 1.7H_2O$) C, H, N.

***cis*-2-Methyl-5-(6-(2-methylphenyl)pyridazin-3-yl)-octahydropyrrolo[3,4-*c*]pyrrole Bis-L-tartrate (40). Step 1: Biphasic Miyaura−Suzuki Coupling.** Toluene (10 mL) was added to a mixture of **Boc-26** (150 mg, 0.46 mmol), *o*-tolylboronic acid (126 mg, 0.93 mmol), $Pd_2(dba)_3$ (20 mg, 0.021 mmol), 1,3-bis(2,6-di(isopropyl)phenyl)imidazolium chloride (26 mg, 0.062 mmol). Aqueous Na_2CO_3 (2M, 1 mL) was added and the mixture was stirred at 85 °C for 16 h and then cooled to room temperature. The mixture was diluted with EtOAc (40 mL) and washed successively with water (15 mL) and brine (15 mL). The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash chromatography (hexanes−EtOAc, 20:80) to provide the title compound as a white solid (167 mg, 95% yield). ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 2.42 (s, 3 H), 3.02−3.11 (m, 2 H), 3.28−3.46 (m, 2 H), 3.46−3.63 (m, 2 H), 3.63−3.75 (m, 2 H), 3.78−3.91 (m, 2 H), 6.69 (d, J = 9.5 Hz, 1 H), 7.26−7.31 (m, 3 H), 7.34 (d, J = 9.5 Hz, 1 H), 7.38−7.43 ppm (m, 1 H). MS m/z 381 $(MH)^+$.

This material was deprotected and *N*-methylated (50% yield) according to the methods described for **36**, and the free base was converted to the L-tartrate salt as described for **37** to provide the title salt. ^{1}H NMR (CD_3OD) δ 2.31 (s, 3 H), 2.94 (s, 3 H), 3.26 (m, 2 H), 3.40 (m, 2 H), 3.67 (m, 4 H), 3.80 (m, 2 H), 4.45 (s, 4 H), 7.17 (d, J = 9.5 Hz, 1 H), 7.32 (m, 4 H), 7.56 ppm (d, J = 9.5 Hz, 1 H). MS m/z 295 $(MH)^+$. Anal. ($C_{18}H_{22}N_4 \cdot 2C_4H_6O_6$) C, H, N.

***cis*-2-[6-(4-Methoxy-phenyl)-pyridazin-3-yl]-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole *p*-Toluenesulfonate (41). Step 1. *t*-Butyl *cis*-5-[6-(4-Methoxyphenyl)pyridazin-3-yl]-octahydro-pyrrolo-[3,4-*c*]pyrrole-2-carboxylate (41a).** Aqueous Na_2CO_3 (2 M, 2 mL) was added to a mixture of **Boc-26** (200 mg, 0.62 mmol), 4-(methoxy)phenylboronic acid (187 mg, 1.23 mmol), $Pd_2(dba)_3$ (23 mg, 0.025 mmol), and 1,3-bis(2,6-di(isopropyl)phenyl)imidazolium chloride (26 mg, 0.062 mmol) in toluene (20 mL). The mixture was evacuated and purged with nitrogen (3 cycles) and then heated under nitrogen at 85 °C for 60 h. The reaction was cooled to room temperature, filtered through a pad of diatomaceous earth, and concentrated under vacuum. The residue was purified by flash chromatography (silica, eluted with hexanes−EtOAc 20:80) to provide the title compound as a beige solid (180 mg, 74% yield). ^{1}H NMR (CD_3OD) δ 1.46 (s, 9 H), 3.05−3.17 (m, 2 H), 3.31−3.36 (m, 2 H), 3.48 (dd, J = 10.9, 3.7 Hz, 2 H), 3.67 (dd, J = 9.3, 7.3 Hz, 2 H), 3.81 (dd, J = 10.9, 7.5 Hz, 2 H), 3.84 (s, 3 H), 7.01 (d, J = 9.5 Hz, 1 H), 7.03 (d, J = 8.6 Hz, 2 H), 7.79 (d, J = 9.5 Hz, 1 H), 7.86 ppm (d, J = 8.8 Hz, 2 H). MS m/z 397 $(MH)^+$.

Step 2. *cis*-2-[6-(4-Methoxyphenyl)pyridazin-3-yl]-octahydropyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (41b). Trifluoroacetic acid (2 mL) was added to a stirring solution of **41a** (180 mg, 0.45 mmol) in CH_2Cl_2 (5 mL). After 1 h, the solution was concentrated under vacuum, and the residue was stirred with toluene (3 mL) and concentrated under vacuum to remove

excess acid. The residue was taken up in EtOAc (2 mL) to give a solution from which the salt soon crystallized. The solid was collected by filtration and dried to provide the title compound (215 mg, 90% yield). ^{1}H NMR (CD_3OD) δ 3.32−3.46 (m, 4 H), 3.66 (dd, J = 11.5, 7.1 Hz, 2 H), 3.74 (dd, J = 11.7, 3.2 Hz, 2 H), 3.93 (dd, J = 11.9, 7.4 Hz, 2 H), 6.89−6.99 (m, 2 H), 7.65 (d, J = 9.8 Hz, 1 H), 7.80−7.85 (m, 2 H), 8.29 ppm (d, J = 9.8 Hz, 1 H). MS m/z 283 $(MH)^+$.

Step 3. *cis*-2-[6-(4-Methoxyphenyl)pyridazin-3-yl]-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole *p*-Toluenesulfonate (41). A solution of **41b** (215 mg, 0.41 mmol) in 37% formalin (5 mL) was stirred at room temperature as $NaBH(OAc)_3$ (113 mg, 0.53 mmol) was added. After 14 h, the reaction was quenched by addition of satd $NaHCO_{3(aq)}$ (2 mL). The mixture was extracted with CH_2Cl_2 (4 × 4 mL) and the combined extract was dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2−CH_3OH−NH_4OH, 90:10:1) to provide the free base of the title compound (100 mg). This was dissolved in EtOAc (3 mL) and EtOH (0.3 mL) and pTsOH·H_2O (64 mg, 1 equiv) was added with warming to dissolve. The solution was cooled to room temperature and ether (1 mL) was added gradually. The resulting suspension was stirred at room temperature for 14 h and then filtered and the solid dried to provide the title compound (141 mg, 64% yield). ^{1}H NMR (CD_3OD) δ 2.35 (s, 3 H), 2.95 (s, 3 H), 3.37 (m, 4 H), 3.65 (m, 4 H), 3.78 (m, 2 H), 3.85 (s, 3 H), 7.04 (m, 2 H), 7.15 (d, J = 9.5 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 2 H), 7.69 (m, 2 H), 7.86 ppm (m, 3 H). MS m/z 311 $(MH)^+$. Anal. ($C_{18}H_{22}N_4O\cdot C_7H_8O_3S$) C, H, N.

***cis*-4-[6-(5-Methyl-hexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-pyridazin-3-yl]-phenol Bis-*p*-toluenesulfonate (42). Step 1. *cis*-4-[6-(Hexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-pyridazin-3-yl]-phenol Hydrobromide (42a).** A solution of BBr_3 (1 M in heptane, 7.3 mL, 7.3 mmol) was added dropwise under nitrogen to a cold (−70 °C) solution of **41a** (725 mg, 1.83 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was kept at −70 °C for 30 min after the addition and then allowed to warm gradually to room temperature and stirred for 14 h. The mixture was cooled to −20 °C and quenched by dropwise addition of CH_3OH (20 mL) and allowed to warm to room temperature for 1 h. The suspension was filtered and the solid dried to provide the crude title salt (728 mg, >100% yield) used directly in the next reaction. ^{1}H NMR (CD_3OD) δ 3.35−3.50 (m, 4 H), 3.61−3.73 (m, 2 H), 3.81 (dd, J = 11.4, 2.5 Hz, 2 H), 3.98 (dd, J = 11.5, 7.1 Hz, 2 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.76 (d, J = 9.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H), 8.37 ppm (d, J = 9.8 Hz, 1 H). MS m/z 283 $(MH)^+$.

Step 2. *cis*-4-[6-(5-Methyl-hexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-pyridazin-3-yl]-phenol Bis-*p*-toluenesulfonate (42). The crude salt **42a** (91 mg, 0.23 mmol) was carried through reductive methylation according to the procedure described for **36** to provide the *N*-methylated free base (62 mg, 91% yield). This was dissolved in 10% ethanol in EtOAc (3 mL) and *p*-toluenesulfonic acid (83 mg, 0.44 mmol) in 1 mL 10% ethanol in EtOAc was added. The resulting solids were recrystallized from ethanol to provide the title compound (34 mg, 23% yield). ^{1}H NMR (CD_3OD) δ 2.31 (s, 6 H), 3.00 (s, 3 H), 3.20 (m, 1 H), 3.47 (m, 3 H), 3.89 (m, 6 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.1 Hz, 4 H), 7.65 (d, J = 8.1 Hz, 4 H), 7.67 (m, 1 H), 7.81 (d, J = 8.5 Hz, 2 H), 8.24 ppm (m, 1 H). MS m/z 297 $(MH)^+$. Anal. ($C_{17}H_{20}N_4O\cdot 2C_7H_8O_3S$) C, H, N.

***cis*-2-[6-(3-Methoxy-phenyl)-pyridin-3-yl]-5-methyl-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-L-tartrate (43).** Prepared from **Boc-8** and 3-(methoxy)phenylboronic acid according to the anhydrous coupling procedure described for **36** (78% yield), followed by deprotection, reductive methylation, and salt formation as described for **37** to provide the title salt. ^{1}H NMR (CD_3OD) δ 2.93 (s, 3 H), 3.30 (m, 6 H), 3.61 (m, 2 H), 3.70 (m, 2 H), 3.85 (m, 3 H), 4.44 (m, 4 H), 6.92 (m, 1 H), 7.32 (m, 4 H), 7.71 (d, J = 8.8 Hz, 1 H), 8.12 ppm (d, J = 3.1 Hz, 1 H). MS m/z 310 $(MH)^+$. Anal. ($C_{19}H_{23}N_3O\cdot 2C_4H_6O_6\cdot 2H_2O$) C, H, N.

***cis*-3-[6-(5-Methyl-hexahydro-pyrrolo[3,4-c]pyrrol-2-yl)-pyridazin-3-yl]-phenol dihydrochloride (44).** Prepared from **Boc-26** and 3-(methoxy)phenylboronic acid using the biphasic Miuaura−Suzuki coupling method described for **40** (83% yield) and further processed according to the methods described for **42** to provide the free base of the title compound. This (16 mg) was dissolved in 10% CH_3OH in EtOAc (1 mL), and excess 4 N HCl/dioxane (0.2 mL) was added. The resulting precipitate was isolated via filtration to give 20 mg of the title compound (20 mg, overall 42% yield). ^{1}H NMR (CD_3OD) δ 2.96 (s, 3 H), 3.31 (m, 4 H), 3.61 (m, 6 H), 6.86 (ddd, J = 7.9, 2.5, 1.2 Hz, 1 H), 7.16 (d, J = 9.5 Hz, 1 H), 7.29 (t, J = 7.8 Hz, 1 H), 7.37 (m, 2 H), 7.86 ppm (d, J = 9.5 Hz, 1 H). MS m/z 297 $(MH)^+$. Anal. ($C_{17}H_{20}N_4O\cdot 2.5HCl\cdot 0.75H_2O$) C, H, N.

***cis*-2-Methyl-5-[6-(3-nitrophenyl)-pyridin-3-yl]-octahydro-pyrrolo[3,4-c]pyrrole p-toluenesulfonate (45).** Prepared from **Boc-8** and 3-nitrophenylboronic acid by the anhydrous Miyaura−Suzuki coupling procedure as described for **36** (20% yield), followed by deprotection and *N*-methylation as described for b (82% yield). The free base (28 mg, 0.86 mmol) was dissolved in EtOAc (1 mL), and MeOH (3 drops) was added. A solution of *p*-toluenesulfonic acid monohydrate (17 mg, 0.86 mmol) in warm EtOAc (1 mL) was added, and the resulting solution was stirred at room temperature as a precipitate formed slowly. After 16 h, the solid was isolated by filtration and dried to provide the title salt (33 mg, 73% yield). ^{1}H NMR (CD_3OD) δ 2.35 (s, 3 H), 2.94 (s, 3 H), 3.26 (m, 3 H), 3.43 (m, 3 H), 3.68 (m, 3 H), 3.99 (m, 1 H), 7.22 (m, 2 H), 7.33 (m, 1 H), 7.69 (m, 3 H), 7.88 (d, J = 8.8 Hz, 1 H), 8.21 (m, 2 H), 8.28 (m, 1 H), 8.77 ppm (dd, J = 1.9, 1.9 Hz, 1 H). MS m/z 325 $(MH)^+$. Anal. ($C_{18}H_{20}N_4O_2\cdot C_7H_8O_3S\cdot H_2O$) C, H, N.

***cis*-5-[6-(5-Methyl-hexahydro-pyrrolo[3,4-*c*]pyrrol-2-yl)-pyridazin-3-yl]-1*H*-indole Bis-*p*-toluenesulfonate (46).** Prepared from **Boc-26** and indol-5-ylboronic acid according to the procedures described for **36**. ^{1}H NMR (C_5D_5N) δ 2.17 (s, 6 H) 3.01 (s, 3 H) 3.26−3.39 (m, 4 H) 3.52 (dd, J = 10.7, 6.8 Hz, 2 H) 3.78−3.92 (m, J = 9.8 Hz, 4 H) 6.80−6.85 (m, 1 H) 6.94 (d, J = 9.2 Hz, 1 H) 7.18 (d, J = 8.0 Hz, 4 H), 7.60 (t, J = 2.8 Hz, 1 H) 7.79 (d, J = 9.0 Hz, 1 H) 7.91 (d, J = 9.0 Hz, 1 H) 8.31 (d, J = 9.2, 1.5 Hz, 1 H) 8.33 (d, J = 8.0 Hz, 4 H) 8.63 (m, 1 H) 12.30 ppm (s, 1 H). MS m/z 320 $(MH)^+$. Anal. $C_{19}H_{21}N_5\cdot 2C_7H_8O_3S\cdot H_2O$: C, H, N.

***t*-Butyl *cis*-5-(Pyridin-2-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-47).** 2-Chloropyridine (120 mg, 1.06 mmol) and Na_2CO_3 (95.8 mg, 0.90 mmol) were added to a solution of **5** (109.7 mg, 0.52 mmol) in DMSO (1.5 mL). The mixture was heated at 130 °C for 18 h and then cooled to room temperature and diluted with methanol (1 mL). The solution was purified by preparative HPLC (Phenomenex Luna C8(2) 5 μm 100 Å AXIA column (30 mm × 75 mm), eluted with acetonitrile/0.1% aqueous trifluoroacetic acid, 10:90−90:10) to provide the title compound as a white solid (69.8 mg, 47% yield). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.92−3.06 (m, 2 H), 3.18−3.51 (m, 4 H), 3.59−3.75 (m, 4 H), 6.35 (d, J = 8.7 Hz, 1 H), 6.56 (dd, J = 6.5, 5.4 Hz, 1 H), 7.45 (ddd, J = 8.5, 6.9, 2.0 Hz, 1 H), 8.16 ppm (ddd, J = 5.2, 2.0, 0.8 Hz, 1 H). MS m/z 290 $(MH)^+$.

***cis*-2-(Pyridin-2-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (47).** Trifluoroacetic acid (1 mL) was added to a solution of **Boc-47** (64.8 mg, 0.22 mmol) in CH_2Cl_2 (5 mL), and the solution was stirred at 20 °C for 1 h. The solution was concentrated under vacuum, and the residue was triturated with 10% CH_3OH−ethyl ether to produce an even suspension. The solid was filtered, washed with ethyl ether, and dried under vacuum to provide the title compound as a light-yellow solid (80 mg, 86% yield). ^{1}H NMR (CD_3OD) δ 3.32−3.47 (m, 4 H), 3.59−3.72 (m, 4 H), 3.80−3.92 (m, 2 H), 6.98 (ddd, J = 7.1, 6.1, 0.8 Hz, 1 H), 7.07 (dt, J = 8.8, 1.0 Hz, 1 H), 7.95−8.03 ppm (m, 2 H). MS m/z 190 $(MH)^+$. Anal. ($C_{11}H_{15}N_3\cdot 2CF_3CO_2H$) C, H, N.

***t*-Butyl *cis*-5-(Pyridin-4-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole-2-carboxylate (Boc-48).** A 100 mL flask with stir bar and

condenser was charged with **5** (234 mg, 1.10 mmol) and 4-bromopyridine hydrochloride (225 mg, 1.157 mmol). Toluene (15 mL) was added, followed by triethylamine (6 mL, 43.0 mmol). A solution of $Pd_2(dba)_3$ (25 mg) and rac-BINAP (21 mg) in toluene (2 mL) was added, followed by NaOtBu (250 mg). The mixture was warmed at reflux under nitrogen for 8 h and then cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography (silica, CH_2Cl_2−MeOH−NH_4OH (95:5:0−90:10:1) to provide the adduct as an orange−brown solid (202 mg, 63% yield). ^{1}H NMR (CD_3OD) δ 1.35−1.57 (m, 9 H), 2.97−3.13 (m, J = 1.7 Hz, 2 H), 3.20−3.29 (m, 4 H), 3.50−3.74 (m, 4 H), 6.53 (d, J = 6.4 Hz, 2 H), 8.05 ppm (d, J = 6.4 Hz, 2 H). MS m/z 290 $(MH)^+$.

***cis*-2-(Pyridin-4-yl)-octahydro-pyrrolo[3,4-*c*]pyrrole Bis-trifluoroacetate (48).** Trifluoroacetic acid (1 mL) was added over 5 min to an ice-cooled solution of **Boc-48** (200 mg, 0.691 mmol) in CH_2Cl_2 (5 mL). The cold solution was allowed to warm gradually to room temperature and stirred overnight. The orange solution was concentrated under vacuum, and the residue was suspended in ether (15 mL) and concentrated (repeat twice) to remove residual trifluoroacetic acid. Finally, the residue was stirred with 10% MeOH−ether (15 mL) for 2 h. The tan solid was collected by filtration, washed with 10% MeOH−ether (2 × 4 mL), and dried under vacuum to provide the title compound (243 mg, 84% yield). ^{1}H NMR (CD_3OD) δ 3.31−3.46 (m, 4 H), 3.57−3.72 (m, 4 H), 3.82−3.95 (m, J = 7.5 Hz, 2 H), 6.91 (d, J = 7.8 Hz, 2 H), 8.17 ppm (d, J = 7.8 Hz, 2 H). MS m/z 190 $(MH)^+$. Anal. ($C_{11}H_{15}N_3 \cdot 2C_2HO_2F_3$) C, H, N.

Experimental [^{3}H]-Cytisine Binding. Binding conditions were modified from the procedures described.[74] Membrane enriched fractions from rat brain minus cerebellum (ABS Inc., Wilmington, DE) were slowly thawed at 4 °C, washed, and resuspended in 30 volumes of BSS-Tris buffer (120 mM NaCl/5 mM KCl/2 mM $CaCl_2$/2 mM $MgCl_2$/50 mM Tris-Cl, pH 7.4, 4 °C). Samples containing 100−200 μg of protein and 0.75 nM [^{3}H]-cytisine (30 C_i/mmol; Perkin-Elmer/NEN Life Science Products, Boston, MA) were incubated in a final volume of 500 μL for 75 min at 4 °C. Seven log-dilution concentrations of each compound were tested in duplicate. Nonspecific binding was determined in the presence of 10 μM (−)-nicotine. Bound radioactivity was isolated by vacuum filtration onto prewetted glass fiber filter plates (Millipore, Bedford, MA) using a 96-well filtration apparatus (Packard Instruments, Meriden, CT) and were then rapidly rinsed with 2 mL of ice-cold BSS buffer (120 mM NaCl/5 mM KCl/2 mM $CaCl_2$/2 mM $MgCl_2$). Packard MicroScint-20 scintillation cocktail (40 μL) was added to each well and radioactivity determined using a Packard TopCount instrument. The IC_{50} values were determined by nonlinear regression in Microsoft Excel software. K_i values were calculated from the IC_{50}s using the Cheng−Prusoff equation, where $K_i = IC_{50}/1 + [Ligand]/K_D$].

[^{3}H]-A-585539 Binding. [^{3}H]-(*S*,*S*)-2,2-dimethyl-5-(6-phenyl-pyridazin-3-yl)-5-aza-2-azonia-bicyclo[2.2.1]heptane iodide ([^{3}H]-A-585539), binding to the α7 nAChR subtype was determined using membrane enriched fractions from rat brain minus cerebellum or human cortex (ABS Inc., Wilmington, DE) as previously described.[56] Pellets were thawed at 4 °C, washed, and resuspended with a Polytron at a setting of 7 in 30 volumes of BSS-Tris buffer (120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, and 50 mM Tris-Cl, pH 7.4, 4 °C). Seven log-dilution concentrations of test compounds containing 100−200 μg of protein and 0.5 nM [^{3}H]A-585539 (62.8 Ci/mmol; R46 V, Abbott Laboratories) were incubated in a final volume of 500 μL for 75 min at 4 °C in duplicate. Nonspecific binding was determined in the presence of 10 μM methyllycaconitine. Bound radioactivity was collected on Millipore MultiScreen harvest plates FB presoaked with 0.3% PEI using a Packard cell harvester, washed with 2.5 mL ice-cold buffer, and radioactivity was determined using a Packard TopCount Microplate β counter. IC_{50} values were determined by nonlinear regression in Microsoft Excel or Assay Explorer. K_i values were calculated from the IC_{50}s using the Cheng−Prusoff equation, where $K_i = IC_{50}/1 + [Ligand]/K_D$].

Functional Assays. Ca^{2+} Signaling in FLIPR. An HEK-293 cell line expressing the recombinant human $\alpha4\beta2$ subunit combination was used to measure functional agonist activity by measuring intracellular calcium changes using the fluorometric imaging plate reader (GFLIPR; Molecular Devices, Sunnyvale, CA). Cells were plated at densities of 25000−50000 cells/well in Dulbecco's modified Eagle's medium (Gibco) supplemented with 10% fetal bovine serum (Gibco) in 96-well clear bottom black-walled plates precoated with poly-D-lysine and allowed to incubate for 24−48 h at 37 °C in 5% CO_2 in a humidified environment. After the media was aspirated off, the cells were incubated in the dark at room temperature for ~0.75−1 h with 2−4 μM Fluo-4 AM calcium indicator dye (Molecular Probes, Eugene, OR) dissolved in 0.1−0.2% v/v of DMSO in Ringer buffer (in mM: 140 NMDG, 5 KCl, 1 $MgCl_2$, 10 HEPES, and 10 $CaCl_2$, pH 7.4). Cells were placed in the FLIPR, and 50 μL of 3× stock concentrations of test compounds or buffer prepared in the same Ringer buffer was added. Raw fluorescence data were corrected by subtracting fluorescence values from wells that received buffer-only additions. Peak fluorescent values were exported to Microsoft Excel, corrected for background signal, and expressed as a percentage of the peak response for the positive control of 100 μM nicotine. Dose−response data for half-log concentration increments were fitted using a single sigmoidal function in GraphPad Prism for determination of EC_{50} and maximum response. Data are expressed as means ± SEM for at least n = 6 (two replicates across three different plates).

Electrophysiological Measurements. Functional evaluation at human α7 nAChR was performed using recombinant receptors expressed in *Xenopus laevis* oocytes. Responses were measured at room temperature using the two-electrode voltage clamp (−60 mV) in the presence of 0.5 μM atropine to block endogenous muscarinic receptors. Assays were sonducted in the POETs apparatus[58,59] using a robotic pipettor. Responses were measured as the peak (maximal) inward current relative to the baseline holding current and were normalized to the maximal response to acetylcholine (10 mM) determined in the each oocyte before and after application of each test compound. Dose−response data for half-log concentration increments were fitted using a single sigmoidal function in GraphPad Prism for determination of EC_{50} and maximum response. Data are expressed as means ± SEM.

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