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Discovery of 4-(5-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (CP-810,123), a Novel α7 Nicotinic Acetylcholine Receptor Agonist for the Treatment of Cognitive Disorders in Schizophrenia: Synthesis, SAR Development, and in Vivo Efficacy in Cognition Models

Christopher J. O'Donnell,* Bruce N. Rogers,* Brian S. Bronk, Dianne K. Bryce, Jotham W. Coe, Karen K. Cook, Allen J. Duplantier, Edelweiss Evrard, Mihaly Hajós, William E. Hoffmann, Raymond S. Hurst, Noha Maklad, Robert J. Mather, Stafford McLean, Frank M. Nedza, Brian T. O'Neill, Langu Peng, Weimin Qian, Melinda M. Rottas, Steven B. Sands, Anne W. Schmidt, Alka V. Shrikhande, Douglas K. Spracklin, Diane F. Wong, Andy Zhang, and Lei Zhang

Pfizer Global Research and Development, Groton Laboratories, Eastern Point Road, Groton, Connecticut 06340

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A novel α7 nAChR agonist, 4-(5-methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (**24**, CP-810,123), has been identified as a potential treatment for cognitive deficits associated with psychiatric or neurological conditions including schizophrenia and Alzheimer's disease. Compound **24** is a potent and selective compound with excellent pharmaceutical properties. In rodent, the compound displays high oral bioavailability and excellent brain penetration affording high levels of receptor occupancy and in vivo efficacy in auditory sensory gating and novel object recognition. The structural diversity of this compound and its preclinical in vitro and in vivo package support the hypothesis that α7 nAChR agonists may have potential as a pharmacotherapy for the treatment of cognitive deficits in schizophrenia.

Introduction

Schizophrenia is a chronic and highly debilitating psychiatric disease that afflicts about 1−2% of the world population.[1] This complex disorder is characterized by variable expression of three major symptomologies: positive, negative, and cognitive. Psychotic, or positive, symptoms include hallucinations and delusions, while negative symptoms include apathy, anhedonia, and social or emotional withdrawal. Cognitive symptoms, including disorganized thoughts, decreased attention, and memory deficits, have more recently become a focus in schizophrenia research.[2] Significant therapeutic advances have been made in the treatment of the positive and negative symptoms of schizophrenia,[3] but the vast majority of schizophrenic patients (over 85%) also suffer from cognitive deficits that are poorly addressed with current agents.[4] Although both genetic and environmental components contribute to schizophrenia, studies of twins show that the disease is predominantly a genetic disorder, with an 80% estimated risk of heritability.[5] Considerable genetic evidence implicates the α7 nicotinic acetylcholine receptor (nAChR[a]), including the subunit gene CHRNA7, and a linkage to impaired auditory gating (P50).[6,7] Additionally, cholinergic deficits in hippocampal regions that mediate stimulus processing have been attributed to attentional disorders and cognitive deficits.[8] A hypothesis has been constructed from the observation of diminished suppression of the P50 gating response following auditory stimulation and the observed reduction in α7 nAChRs found in schizophrenic patients.[9] The gating deficit in schizophrenic patients and their first degree relatives is transiently improved or normalized by nicotine, also supporting a connection to the α7 nAChR. In addition, heavy tobacco smoking in schizophrenic patients is well documented and interpreted as a potential form of self-medication.[10,11] As such, the α7 nAChR has received considerable attention as a promising target for schizophrenia therapy, in particular for the cognitive symptoms,[12] and may also offer promise for other cognitive disorders such as Alzheimer's disease and attention deficit hyperactivity disorder (ADHD).

Neuronal nAChRs, so named because they are activated by the alkaloid nicotine, are a well-defined subset of ligand-gated ion channels permeable to cations such as Na^+, K^+, and Ca^{2+}.[13,14] Formed by five individual subunits, the family of nAChRs is potentially vast, as 17 distinct nAChR subunits are known and can assemble in many different combinations to form a pentameric channel. These subunits assemble into homopentamers (e.g., α7, α9) or more commonly into heteropentamers.[15] The homopentameric α7 nAChR consists of five α7 subunits, and each subunit provides an orthosteric binding site for its endogenous ligand, acetylcholine.[16] Interest in the development of α7 nAChR agonists has greatly expanded

*To whom correspondence should be addressed. For C.J.O.: phone, 860-715-4118; fax, 860-686-5158; e-mail, christopher.j.odonnell@pfizer.com. For B.N.R.: phone, 860-686-0545; fax, 860-686-5403; e-mail, bruce.n.rogers@pfizer.com.

[a]Abbreviations: ACh, acetylcholine; ADME, absorption, distribution, metabolism, and excretion; ADHD, attention deficit hyperactivity disorder; AMP, amphetamine; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BTX, bungarotoxin; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; EEG, electroencephalography; hERG, human ether-a-go-go-related gene; FLIPR, fluorescence imaging plate reader; HLM, human liver microsomes; IVMN, in vitro micronucleus; MED, minimally effective dose; MDCK, Madin−Darby canine kidney; MW, molecular weight; nAChR, nicotinic acetylcholine receptor; NCS, *N*-chlorosuccinimide; NMP, *N*-methylpyrrolidone; NOR, novel object recognition; NSVT, nonsustained ventricular tachycardia; P-gp, P-glycoprotein; RLM, rat liver microsomes; RT, room temperature; SAR, structure−activity relationship; sc, subcutaneous; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TPSA, topological polar surface area.

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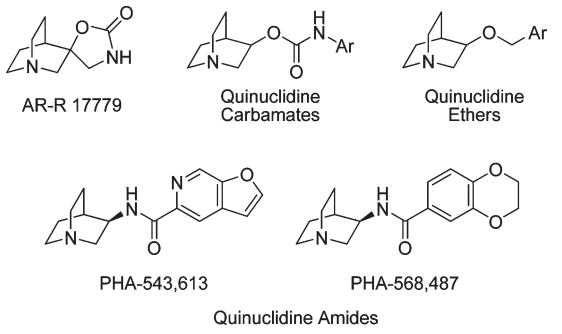


Figure 1. Known quinuclidne-based α7 nAChR ligands.

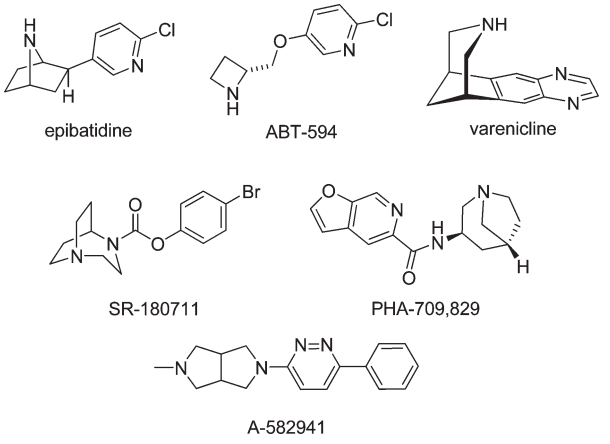


Figure 2. Non-quinuclidine amine templates in the nAChR field.

over the past decade, with the identification of many novel and selective chemical entities. The literature in the area has been extensively reviewed,[17] with the majority of ligands derived from various quinuclidine amine containing scaffolds, including such structures as spiro-oxazolidinones (AR-R17779),[18] carbamates,[19] ethers,[20] and amides (Figure 1).[21] Our previous efforts led to the identification of two phase I clinical candidates from the quinuclidine amide arena, PHA-543613 and PHA-568487,[22] both of which were discontinued because of cardiovascular findings of nonsustained ventricular tachycardia (NSVT).[23]

While several α7 nAChR agonists, such as GTS-21,[24] are reported to have entered human clinical trials, there remains a need for novel ligands with improved safety profiles. The structural diversity of α7 nAChR agonists has been limited and generally focuses around quinuclidine amine based ligands. Within the nAChR field, however, a wide variety of amine scaffolds are prevalent among ligands for α4β2 nAChRs and include compounds such as epibatidine,[25] ABT-594,[26] and the recently approved partial agonist varenicline (Figure 2).[27] In the α7 nAChR area, recent disclosures including SR-180711,[28] PHA-709829,[29] and A-582941[30] demonstrate that novel scaffolds can be identified, and we believed that additional opportunities remained to identify structural variants with a well tolerated safety profile in the α7 nAChR arena.[31]

We recently described the structure−activity relationship (SAR) of a 1,4-diazabicyclo[3.2.2]nonane aryl carbamate series of α7 nAChR agonists **1** (Figure 3).[32] One key finding in this work was that the carbamate oxygen atoms were critical for α7 nAChR potency and functional activity, possibly forming productive hydrogen bonds with the receptor.

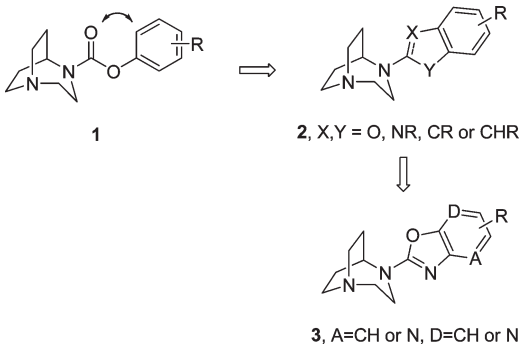
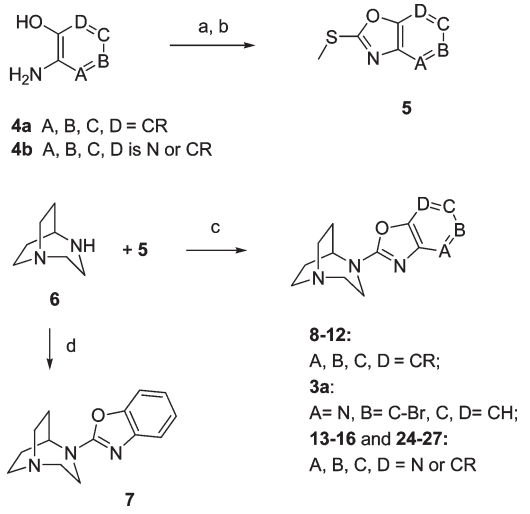


Figure 3. Design of the benzoxazole and azabenzoxazole series from the carbamate series.

Scheme 1[a]



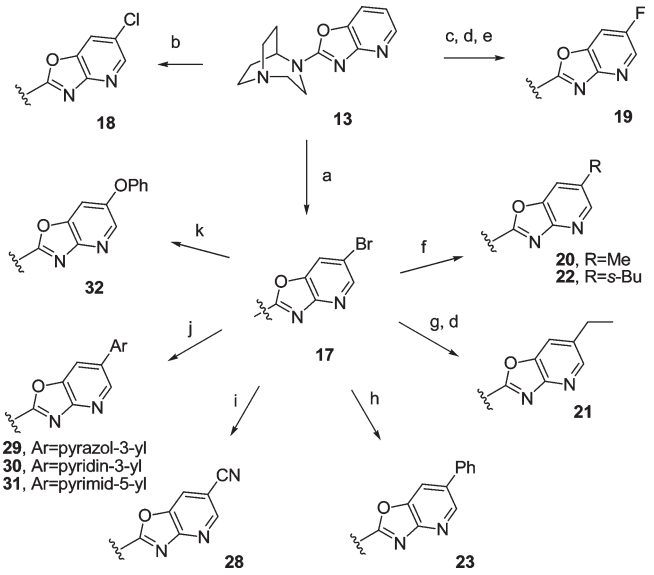
[a] Reagents and conditions: (a) thiophosgene, THF, RT, or potassium ethyl xanthate, EtOH, 90 °C; (b) MeI, K_2CO_3, DMF, RT; (c) *i*-PrOH, Et_3N, heat; (d) 2-chlorobenzoxazole, *i*-Pr_2NEt, toluene, 35%, RT.

We became interested in retaining this putative hydrogen bond while improving the potency while maintaining full agonist activity of the carbamate series, and we envisioned replacing the carbamate linkage with heterocyclic motifs as represented by **2**. We describe herein the exploration of benzoxazole and azabenzoxazole (**3**) replacements of the carbamate functional group and the development of the SAR within this heterocyclic motif.

Chemistry

In order to fully explore the SAR associated with the α7 nAChR, we sought to probe both steric and electronic requirements by efficiently and systematically installing substituents around the heteroaromatic ring system. The unsubstituted benzoxazole analog **7** was prepared by reacting commercially available 2-chlorobenzoxazole with 1,4-diazabicyclo[3.2.2]nonane, **6**,[33] in the presence of Hünig's base in 35% yield. Compounds bearing substitution about the benzoxazole ring (**8**−**12**) were prepared from the corresponding 2-aminophenols **4a** (Scheme 1). Cyclization of **4a** with either thiophosgene or potassium ethyl xanthate followed by methyl iodide alkylation of the resulting 2-mercaptobenzoxazole afforded methyl sulfide intermediates **5**.[34] Intermediate **5** was then coupled with diamine **6** in the presence of triethylamine in warm isopropanol to generate

Scheme 2[a]



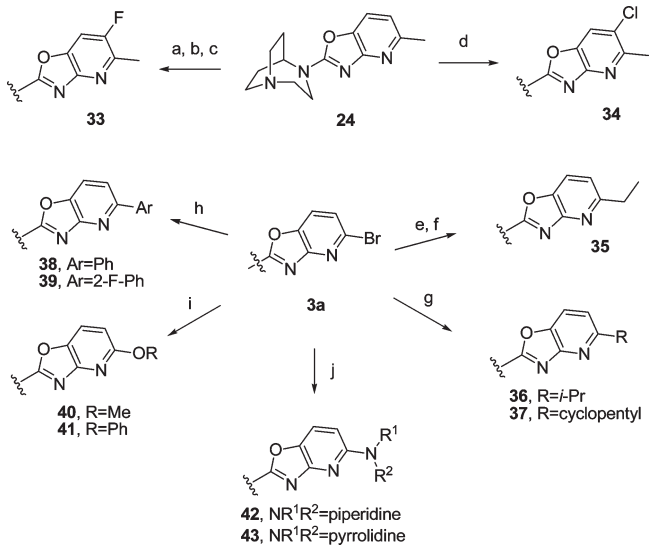
[a] Reagents and conditions: (a) Br_2, NaOAc, AcOH, H_2O, ↑↓, 2 h, 78%; (b) NCS, $CHCl_3$, microwave, 150 °C, 10 min, 33%; (c) HNO_3, H_2SO_4; (d) Pd/C, H_2 (45 psi), 1:1 EtOH/MeOH; (e) HCl, $NaNO_2$, HPF_6, H_2O, 32% (three steps); (f) $ZnMe_2$, Pd(dppf)Cl_2, 1,4-dioxane, microwave, 150 °C, 10 min, 70%, or *sec*-butylboronic acid, Pd(PPh_3)$_4$, Na_2CO_3, EtOH, H_2O, 85 °C; (g) (H_2C═CH)$SnBu_3$, Pd(PPh_3)$_2Cl_2$, toluene, ↑↓, 68%; (h) Pd(OAc)$_2$, Et_3N, 2-(*N*,*N*-dimethylamino)-2′-dicyclohexylphosphinobiphenyl, $PhB(OH)_2$, CsF, DME, 27%; (i) $Zn(CN)_2$, Pd(dppf)Cl_2, DMF, microwave, 220 °C, 10 min, 78%; (j) $ArB(OH)_2$, Pd(PPh_3)$_4$, K_2CO_3, 9:1 EtOH/H_2O, microwave, 150 °C, 10 min (15−24%); (k) phenol, CuCl, tetramethylheptane-3,5-dione, Cs_2CO_3, DMF, microwave, 200 °C, 40 min, 16%.

1,4-diazabicyclo[3.2.2]nonane-4-benzoxazole analogues **8**−**12** in 50−60% yields. This synthetic route was applied to the preparation of azabenzoxazole analogues to give compounds **3a**, **13**−**16**, and **24**−**27** from the corresponding aminohydroxypyridine **4b**.

The unsubstituted azabenzoxazole **13** was used as a key intermediate for preparing the 6-halo analogues **17**−**19** as shown in Scheme 2. The 6-bromo (**17**) and 6-chloro (**18**) analogues were prepared by direct halogenation of **13** using bromine and *N*-chlorosuccinimide (NCS), respectively. The 6-fluoro analogue **19** was attained via the 6-amino intermediate, itself derived by nitration of **13** under acidic conditions followed by catalytic hydrogenation of the nitro group, through a Sandmeyer reaction using HPF_6 as the fluoride source. The 6-bromo analogue **17** was a versatile intermediate, giving rapid access to a variety of 6-substituted azabenzoxazoles: alkylation with dimethylzinc or *s*-butylboronic acid via palladium catalysis afforded compounds **20** and **22**, respectively; tributyl(vinyl)stannane Stille coupling followed by hydrogenation gave **21**; Suzuki couplings afforded compounds **23**, **29**−**31**; cyanation using zinc cyanide yielded **28**, and aryl ether formation in the presence of copper chloride provided **32**.

Disubstituted analogues **33** and **34** were prepared from 5-methylazabenzoxazole **24** as depicted in Scheme 3. Nitration at the 6-position of **24** afforded the corresponding 6-nitro-5-methyl intermediate. Nitro reduction followed by a HPF_6 mediated Sandmeyer reaction gave the 6-fluoro-5-methyl analogue **33**. The corresponding 6-chloro-5-methyl compound **34** was prepared by direct chlorination of **24** with NCS. Again, the 5-bromo intermediate **3a** proved to be

Scheme 3[a]



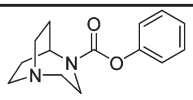
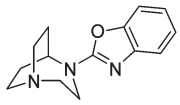
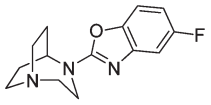
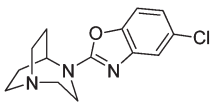
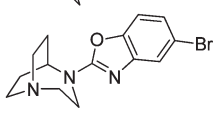
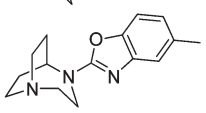
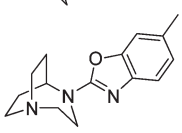
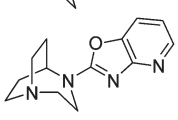
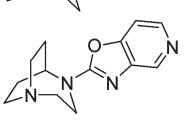
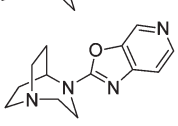
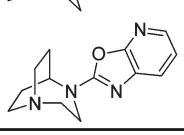
[a] Reagents and conditions: (a) HNO_3, H_2SO_4, ↑↓, 33%; (b) Pd/C, H_2 (45 psi), EtOH/MeOH (1:1); (c) HCl, $NaNO_2$, HPF_6, H_2O, 6% for two steps; (d) NCS, $CHCl_3$, microwave, 150 °C, 10 min, 70%; (e) (H_2C═CH)$SnBu_3$, Pd(PPh_3)$_2Cl_2$, toluene, ↑↓; (f) Pd/C, H_2 (45 psi), 1:1 EtOH/MeOH, 43% for two steps; (g) R-MgCl/$ZnCl_2$, Pd(dppf)Cl_2, THF, microwave, 37% for both **36** and **37**; (h) $ArB(OH)_2$, Pd(PPh_3)$_4$, Na_2CO_3, toluene, MeOH, H_2O, 22% for **38**, 32% for **39**; (i) R−OH, CuCl, tetramethylheptane-3,5-dione, Cs_2CO_3, NMP, microwave, 200 °C, 10 min, 46% for **40**, 32% for **41**; (j) R^1R^2NH, Pd(OAc)$_2$, BINAP, NaO*t*-Bu, toluene, 100 °C, 32% for **42**, 53% for **43**.

extremely versatile (Scheme 3): tributyl(vinyl)stannane Stille coupling followed by hydrogenation gave **35**; alkylation with alkylzinc reagents afforded **36** and **37**; Suzuki coupling afforded **38** and **39**; aryl ether formation gave **40** and **41**, and arylamine formation under Buchwald conditions[35] provided access to **42** and **43**.

Results and Discussion

The α7 nAChR and 5-HT_3 binding activities and α7 nAChR functional data for a number of monosubstituted benzoxazole and nonsubstituted azabenzoxazole analogues are shown in Table 1. The unsubstituted benzoxazole analogue **7** was characterized as a full agonist in a *Xenopus* oocyte assay with good α7 nAChR affinity and equivalent potency at the 5-HT_3 receptor. As is apparent from the data, replacing the carbamate functional group with a heterocyclic benzoxazole proved to be a viable option, as **7** was ∼32-fold more potent than **1** at the α7 nAChR. Paralleling SAR trends observed with the carbamate series of compounds recently described by our group,[32] the SAR about the 5- and 6-positions of the benzoxazole ring improved affinity for the α7 nAChR (**8**−**12**). However, these substitutions at the 5- and 6-positions also introduced significant affinity for the 5-HT_3 receptor, an activity we had not observed in the carbamate series.[32] Substitution at the distal position of the benzoxazole ring with a halogen or alkyl group generally increased potency for the α7 nAChR, but these substitutions did not improve 5-HT_3 selectivity.[36] Four monoazabenzoxazole regioisomers (**13**−**16**) were also prepared in an attempt to broadly define the SAR for this core. Both the 4-azabenzoxazole **13** and 7-azabenzoxazole **16** demonstrated potent α7 nAChR affinities, maintained full agonist activity as shown in the functional assay, and demonstrated potential for improved selectivity over the

Table 1. Structure−Activity Relationships of Benzoxazoles (**7**−**12**) and Azabenzoxazoles (**13**−**16**)

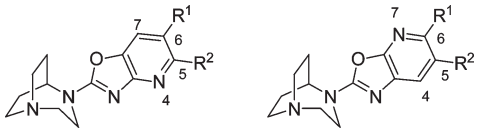
Compound	Structure	α7 Ki (nM)[a]	α7 agonist activity[b]	5-HT_3 Ki (nM)[c]
1		739 nM (340-1,610 n=2)	99%	3993
7		22.5 (4.85-104, n=5)	183%	13
8		20.7 (n=1)	315%	3.9
9		1.92 (1.27-2.91, n=4)	122%	1.2
10		2.15 (0.0938-49.1, n=3)	78%	< 17
11		33.6 (n=1)	287%	3.4
12		17.9 (n=1)	197%	< 17
13		30.3 (10.9-84.5, n=4)	220%	579
14		312 (164-594, n=4)	156%	2120
15		309 (200-476, n=4)	186%	162
16		40.6 (17.4-95.2, n=4)	182%	92

[a] Binding assay for rat α7 nAChR expressed in GH_4C_1 cells using [^{125}I]BTX as the radioligand. Each assay (*n*) represents an average of a six-point concentration−response curve run in triplicate, with geometric mean (95% confidence interval).[37] [b] Rat α7 expressed in *Xenopus* oocytes. All test compounds were measured at 32 μM and are reported as % control versus nicotine response at 50 μM.[38] [c] Binding assay for mouse 5-HT_3 receptors expressed in HEK293 cells using [^{3}H]LY278584 as the radioligand. All values represent an average of three six-point concentration−response curves run in triplicate in a single assay.[39]

5-HT_3 receptor, pointing to a promising direction for additional SAR studies.

As a key objective of our program, we sought compounds that were high affinity ligands at the α7 nAChR with potent and full functional responses. To rapidly understand the SAR in this series, each compound was evaluated in the α7 nAChR binding assay and a high-throughput FLIPR-based functional assay that utilized SH-EP1 cells expressing the α7/5-HT_3 chimera, in parallel. This chimera, combining the ligand binding domain of the α7 nAChR and the transmembrane domains of the 5-HT_3 receptor, was previously established as a rapid and viable option to develop SAR[21,40] and linked the data to previous clinical candidates from our group.[22,29] Starting from compounds **13** and **16**, the SARs of 4-azabenzoxazoles (**A**) and 7-azabenzoxazoles (**B**) were further explored at the 5- and 6-positions (R^2 and R^1, respectively, Table 2). In general, compounds in the 4-azabenzoxazoles template (**A**) displayed greater binding affinity at the α7 nAChR than their counterparts in the 7-azabenzoxazole template (**B**) (for example, see **18** vs **25**, **24** vs **27**) with the exception of the 5-phenyl substitution, which displayed essentially identical α7 nAChR binding affinities (**23** vs **26**). Halogens, −CN, and small alkyl groups (−Me) were preferred at the 6-position of template **A** (**17**−**20**, **28**), with the chloro analogue **18** displaying the greatest binding affinity for the α7 nAChR. Extension of the methyl group of **20** to ethyl (**21**) resulted in reduced affinity; however, replacing the methyl group with a branched alkyl group such as *sec*-butyl (**22**) greatly reduced α7 nAChR affinity, suggesting steric limitations at the 6-position. In addition, substitution of this position with a sp^2-hybridized

Table 2. Structure−Activity Relationship of the 4-Azabenzoxazole and 7-Azabenzoxazole Templates



A **B**

compd	template	R^1	R^2	α7 binding K_i (nM)[a]	α7 efficacy EC_{50} (nM)[b,d]	5-HT_3 K_i (nM)[c,d]
17	A	−Br	−H	2.08 (1.63−2.66 $n = 22$)	240 (64%)	926
18	A	−Cl	−H	1.00 (0.533−1.88 $n = 4$)	160 (83%)	1370
19	A	−F	−H	17.2 (11.7−25.3 $n = 4$)	213 (64%)	6200
20	A	−Me	−H	6.66 (4.25−10.3, $n = 4$)	1015 (55%)	3390
21	A	−Et	−H	22.5 ($n = 1$)	300 (53%)	> 5260
22	A	−*sec*-butyl	−H	> 1,000 ($n = 1$)	NT	NT
23	A	−Ph	−H	7.04 (1.34−37.1 $n = 4$)	320 (71%)	2117
24	A	−H	−Me	13.5 (7.31−24.9 $n = 6$)	244 (46%)	269
25	B	−H	−Cl	2.59 (2.11−3.18 $n = 4$)	227 (62%)	NT
26	B	−H	−Ph	2.31 (0.466−11.4 $n = 5$)	264 (69%)	3673
27	B	−Me	−H	88.6 (51.0−154 $n = 2$)	1200 (59%)	126
28	A	−CN	−H	6.20 ($n = 1$)	510 (58%)	> 5290
29	A	−pyrazol-3-yl	−H	23.0 (6.44−82.2 $n = 3$)	390 (68%)	> 5260
30	A	−pyridin-3-yl	−H	119 (38.3−370 $n = 4$)	430 (70%)	> 5350
31	A	−pyrimid-5-yl	−H	60 ($n = 1$)	NT	> 7140
32	A	−OPh	−H	4.16 ($n = 1$)	620 (75%)	1960
33	A	−F	−Me	15.3 (0.158−1490 $n = 2$)	2100 (36%)	547
34	A	−Cl	−Me	3.19 (0.941−10.8 $n = 4$)	160 (58%)	244
35	A	−H	−Et	18.7 (4.82−72.6 $n = 4$)	100 (34%)	> 5260
36	A	−H	−*i*-Pr	9.05 (2.18−37.5 $n = 3$)	580 (68%)	> 5290
37	A	−H	−cyclopentyl	5.30 (3.24−8.67 $n = 3$)	525 (54%)	> 5290
38	A	−H	−Ph	3.22 (0.802−12.9 $n = 4$)	320 (71%)	> 3580
39	A	−H	−2-fluoro-Ph	3.45 (2.80−4.26 $n = 4$)	160 (73%)	> 3770
40	A	−H	−OMe	24.9 ($n = 1$)	1000 (56%)	141
41	A	−H	−OPh	17.3 ($n = 1$)	380 (63%)	6830
42	A	−H	−piperidine	67.1 (15.8−284 $n = 3$)	1900 (30%)	1,140
43	A	−H	−pyrrolidine	1.91 (0.009−408 $n = 2$)	470 (67%)	6340

[a] Binding assay for rat α7 nAChR expressed in GH_4C_1 cells using [^{125}I]BTX as the radioligand. Each assay (n) represents an average of a six-point concentration−response curve run in triplicate, with geometric mean (95% confidence interval).[37] [b] α7 nAChR agonist EC_{50} and efficacy measured in a functional assay using the chimeric α7-5HT_3 receptor. Efficacy is reported as a percent of the response evoked by 100 μM nicotine.[21] [c] Binding assay for human 5-HT_3 receptors expressed in HEK293 cells using [^{3}H]LY278584 as the radioligand. All values represent an average of a six-point concentration−response curve run in triplicate.[39] [d] NT = not tested.

phenyl (**23**) or phenoxy (**32**) provided compounds with α7 nAChR affinity that was comparable to that of the 6-methyl analogue **20**. Replacing the phenyl group of **23** with 3-pyrazolyl, 3-pyridinyl, or 4-pyrimidinyl groups (**29**, **30**, or **31**, respectively) decreased α7 nAChR binding affinity, a finding consistent with the SAR observed in the previously reported carbamate series.[32]

Encouraging data from the SAR sparked further exploration of the 5-position of compounds such as **24** and the evaluation of combining the SAR of the 5- and 6-positions into a single molecule. Two 5,6-bis-substituted analogues were profiled (**33**−**34**), and the 6-chloro-5-methyl analogue **34** showed improved affinity for the α7 nAChR, thus translating into an improved selectivity over the 5-HT_3 receptor compared to **24**, suggesting that the SAR trends observed for the 5- and 6-positions independently translated into a combine synergistic effect. In contrast to the SAR trends observed with 6-mono substituted azabenzoxazoles, branched alkyl groups at the 5-position of template **A** were very potent (**35**−**37**). For example, when the 5-position of azabenzoxazole template **A** was substituted with an isopropyl (**36**) or cyclopentyl group (**37**), potent α7 nAChR affinity was observed, along with a substantial decrease in 5-HT_3 affinity. Simple phenyl substitution (**38**) led to a roughly 3-fold improvement in α7 nAChR affinity vs **24** while greatly increasing selectivity over the 5-HT_3 receptor (> 700-fold). Ortho-F substitution on the phenyl ring (**39**) further enhanced 5-HT_3 receptor selectivity, eliminating 5-HT_3 binding without impacting α7 potency. Alkoxy or amino substituents (**40**−**43**) also increased α7 nAChR potency and selectivity over the 5-HT_3 receptor (**41**−**43**).

Through these SAR efforts, we successfully identified a cohort of compounds with both high affinity (< 20 nM) and potent functional responses (EC_{50} < 250 nM) such as compounds **17**−**19**, **24**−**26**, **34**−**35**, and **39**. Derivatives that exhibited a disconnect between the binding and functional activity (e.g., **20**, **23**, **28**, **29**, **32**−**33**, **36**−**38**, and **43**) or were simply less active in either assay were deprioritized. All analogues in Table 2 were agonists as demonstrated by their percent maximal response in the functional assay relative to the response of 100 μM nicotine. As a class, the azabenzoxazole analogues also afford good to excellent binding selectivity for the α7 nAChR over the 5-HT_3 receptor (> 100-fold) with three notable exceptions (**24**, **27**, and **34**).

Table 3. Structure−Activity Relationship of the 4-Azabenzoxazole and 7-Azabenzoxazole Templates

compd	α7 binding K_i (nM)[a]	5-HT$_3$ binding K_i (nM)[b,e]	5-HT$_3$ function IC_{50} (nM)[c,e]	hERG IC_{50} (nM)[d,e]	IVMN[e]
17	2.08 (1.63−2.66 n = 22)	926	779	2300	pos
18	1.00 (0.533−1.88 n = 4)	1370	484	3300	NT
19	17.2 (11.7−25.3 n = 4)	6200	2480	8700	pos
24	13.5 (7.31−24.9 n = 6)	269	5	40000	neg
25	2.59 (2.11−3.18 n = 4)	NT	NT	2200	NT
34	3.19 (0.941−10.8 n = 4)	244	70	16200	neg
35	18.7 (4.82−72.6 n = 4)	5260	3310	27700	neg
39	3.45 (2.80−4.26 n = 4)	> 3770	> 7310	2800	neg

[a] Binding assay for rat α7 nAChR expressed in GH_4C_1 cells using [^{125}I]BTX as the radioligand. Each assay (n) represents an average of a six-point dose−response curve run in triplicate.[37] [b] Binding assay for human 5-HT$_3$ receptors expressed in HEK293 cells using [^{3}H]LY278584 as the radioligand. All values represent an average of a six-point dose−response curve run in triplicate.[39] [c] 5-HT$_3$ functional antagonist assay in human skin epithelial cells. [d] Blockade of the hERG potassium channel in HEK293 cells.[44] [e] NT = not tested.

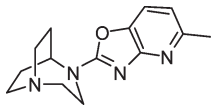
As summarized in Table 3, a group of high interest compounds (**17**−**19**, **24**, **25**, **34**, **35**, and **39**) were further profiled in key selectivity assays. Given the high degree of homology between orthosteric sites in α7 nAChRs and 5-HT$_3$ receptors,[41] some degree of cross-reactivity was anticipated and we were therefore interested in identifying compounds that afforded reasonable binding selectivity and were functional antagonists at the 5-HT$_3$ receptor. We postulated that the risk associated with 5-HT$_3$ receptor antagonism was minimal and, in fact, could be beneficial, since recent clinical studies suggest that the potent and selective 5-HT$_3$ receptor antagonist ondansetron is well tolerated in patients with schizophrenia for over 12 weeks of treatment and may provide benefits to tardive dyskinesia and psychotic symptoms.[42] In constrast, compounds that displayed functional 5-HT$_3$ agonism were not of interest because of the potential link between this pharmacology and cardiovascular events.[43] All of the compounds tested in this series displayed antagonist activity as measured in a functional selectivity assay for the 5-HT$_3$ receptor.

Prolongation of the QT interval is believed to increase the risk of cardiac arrhythmia in humans, potentially leading to ventricular fibrillation,[45] and blockade of the hERG potassium channel has become an important preclinical parameter to assess a compound's proarrhythmic potential.[46] As such, the set of compounds in Table 3 were evaluated in a patch clamp assay to assess potential hERG liability (hERG IC_{50}). Monosubstituted compounds with bromide, chloride, fluoride, or aryl substituents on the azabenzoxazole ring demonstrated more potent hERG inhibition (**17**−**19**, **25**, and **39**), whereas substitution at the 5-position (**24**, **35**) or 5,6-disubstitution (**34**) displayed reduced hERG inhibition. In particular, compounds **24**, **34**, and **35** stood out as promising compounds with hERG IC_{50} values of > 15 μM.

The potential for genetic toxicity was assessed in an in vitro micronucleus (IVMN) assay (Table 3).[47] 6-Halogen substituted azabenzoxazoles **17** and **19** were positive in the IVMN assay upon metabolic activation. Compounds substituted at the 5-position of the azabenzoxazole ring such as **24**, **34**, **35**, and **39** proved to be negative in the IVMN assay, indicating the vital role of the 5-substituent on the azabenzoxazole ring to avoid this potential risk. The overall in vitro potency and selectivity profiles at α7 nAChR, 5-HT$_3$, hERG, and IVMN prompted further evaluation of compound **24** in nicotinic selectivity assays, in vitro and in vivo ADME studies, and our in vivo efficacy models.

The physicochemical properties, in vitro characteristics, ADME, and pharmacokinetic data for compound **24** are captured in Table 4. The physicochemical properties are clearly in alignment with our design goals of low molecular weight (MW), low cLogP and cLogD, and topological polar surface area (TPSA) consistent with CNS drugs.[48] Compound **24** had been identified as a potent α7 nAChR ligand in a binding assay using the rat receptor (13.5 nM, Table 3), and this potency was confirmed to be 16.4 nM using a human receptor. The functional agonism of **24** was also confirmed with native α7 nAChRs utilizing rat α7 nAChR expressed in *Xenopus* oocytes (195% vs 50 μM nicotine). In evaluating

Table 4. Selected Physicochemical Properties, in Vitro Characteristics, ADME, and Pharmacokinetic Data for **24**



24 (CP-810123)

parameter	value
MW	258.33
cLogP	1.57
log D at pH 7.4	0.36
TPSA	45.4
α7 K_i (human)[a]	16.4 nM
% agonist vs nicotine (oocyte)[b]	195%
α4β2 K_i[c]	1350 nM
α3β4 K_i[d]	5370 nM
aq solubility	> 2.4 mg/mL
$T_{1/2}$[e]	> 120 min
HLM Clh[f]	< 5.3 (mL/min)/kg
MDR1 BA/AB[g]	0.8
MDCK AB[h]	18.0×10^{-6} cm/s
plasma protein binding (f_u) (rat)	0.78
brain/plasma[i]	1.5
F (rat)	73%

[a] Binding assay for human α7 nAChR expressed in IMR-32 cells using [^{125}I]BTX as the radioligand. Each assay (n) represents an average of a six-point concentration−response curve run in triplicate. [b] Rat α7 nAChR expressed in *Xenopus* oocytes. The test compound was measured at 32 μM and is reported as % control versus nicotine response at 50 μM.[38] [c] Rat brain homogenate binding assay using [^{3}H]nicotine as the radioligand. This value represents an average of a six-point dose−response curve run in triplicate.[51] [d] IMR32 cells binding assay using [^{3}H]epibatidine as the radioligand. This value represents an average of a six-point concentration−response curve run in triplicate.[52] [e] Derived from human liver microsomes. [f] Predicted hepatic clearance (hCL_h) from human liver microsomal stability assay. [g] Ratio of (basal → apical) to (apical → basal) transfer rate of a test compound at 2 μM across contiguous monolayers of MDR1-transfected MDCK (Madin−Darby canine kidney) cells. [h] MS-based quantification of apical → basolateral transfer rate of a test compound at 2 μM across contiguous monolayers of MDCK cells. [i] Determined in rat at 40 min postdose (1 mg/kg, sc).

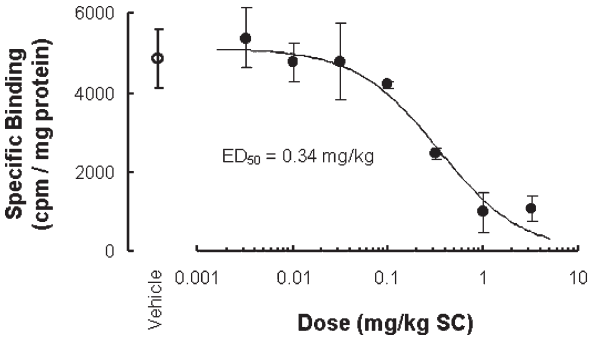


Figure 4. Ex vivo binding of **24** in rat hippocampal homogenate.

nicotinic selectivity, **24** was found to be selective against the predominant ganglionic nAChR ($\alpha3\beta4$) and the high affinity neuronal nAChR ($\alpha4\beta2$) as shown in Table 4. In addition, **24** was screened in a broad selectivity panel at 10 μM and found to have no significant additional activities.[49]

Compound **24** possessed excellent solubility and ADME attributes (Table 4). In vitro ADME data showed that **24** was metabolically stable in the presence of human liver microsomes ($hCL_h < 5.3$ (mL/min)/kg), resulting in a long projected half-life. The compound was also well absorbed (MDCK A → B, $\geq 18 \times 10^{-6}$ cm/s) with no evidence of P-gp efflux liability (MDR1 B → A/A → B, ~1).[50] Subsequent in vivo studies validated these in vitro results, as compound **24** demonstrated high oral bioavailability and favorable brain/plasma ratios in rats (Table 4), with no evidence of impaired brain penetration using the P-gp knockout mouse model (data not shown). Furthermore, in these P-gp knockout mice, the ratio [CSF]/[total plasma] vs fraction unbound was 0.8, suggesting that there is no disequilibrium and the compound readily distributes to the target site of the brain.

The overall properties of compound **24** prompted further characterization in models to fully understand its potential in vivo. Ex vivo binding studies evaluated exposure of **24** at the target site following systemic administration. Receptor binding under these conditions is dependent on the access of the compound to the receptor and is therefore influenced by brain uptake, protein binding, and other partitioning that may occur in the brain. Receptor occupancy was determined in the hippocampal brain regions of rats 30 min after subcutaneous (sc) injections of **24** or vehicle (3 animals/dose group) using [^{125}I]α-bungarotoxin. The dose and ex vivo derived receptor occupancy relationship yielded an ED_{50} of 0.34 mg/kg for **24** (Figure 4). These results are consistent with in vitro potencies reported in Table 2 and reveal that the compound enters the brain and binds to native hippocampal α7 nAChRs at pharmacologically relevant doses.

It has been hypothesized that impaired auditory gating (P50), observed in patients with schizophrenia, may relate to inefficient sensory processing and disturbed perception common to the disease.[53] P50 was measured in a rat model of auditory sensory gating in which normal auditory gating was disrupted by systemic administration of amphetamine.[54] Previous work has shown that amphetamine-induced gating deficits can be restored by partial and full α7 nAChR agonists.[53,55,56] Compound **24** significantly improved auditory gating at 0.3 and 1.0 mg/kg sc ($p < 0.05$; Figure 5A). Lower doses (0.03 and 0.1 mg/kg) trended toward reversing amphetamine-induced deficits, but the effect was not statistically significant. These data were used to establish a minimally effective dose (MED) of **24** in the gating assay of 0.3 mg/kg.

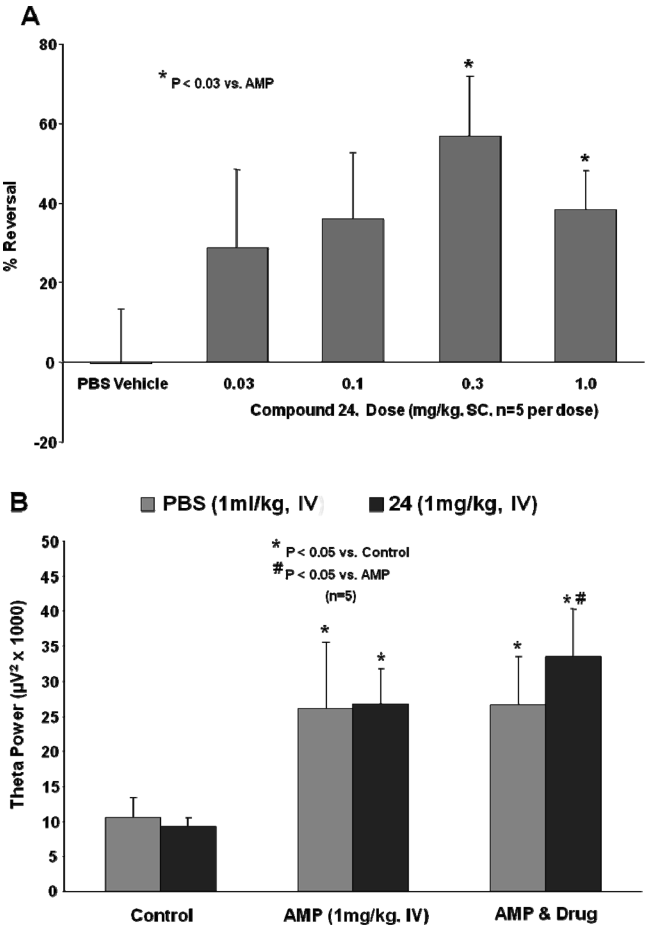


Figure 5. (A) Efficacy of **24** (0.03−1 mg/kg, sc) on amphetamine (AMP)-induced auditory gating deficit in rats, expressed as reversal of amphetamine-induced deficit. Significant ($p < 0.05$) differences in gating after amphetamine and α7 nAChR agonists administration are indicated by an asterisk (∗). Vehicle treatment (PBS) did not significantly impact amphetamine-induced gating deficit. (B) Power of hippocampal θ oscillation induced by amphetamine (AMP) significantly augmented by administration of **24** (1 mg/kg, sc, (#) $p < 0.05$ vs AMP) but not vehicle (PBS).

The free plasma exposure achieved in rats given 0.3 mg/kg, sc, of **24** was 326 nM, approximately 40 min after dosing. On the basis of the measured brain to plasma ratio (Table 4) and a lack of P-gp efflux, there is low likelihood of disequilibrium between drug concentrations in plasma and brain; therefore, free brain concentrations should be comparable.

Consistent with previous findings,[57] amphetamine administration resulted in θ band synchronization of hippocampal EEG. Quantitative EEG analysis showed that subsequent administration of **24** but not vehicle (PBS, 1 mL/kg iv) significantly enhanced θ band power (Figure 5B), in line with our previous observations.[58] These results demonstrate that α7 nAChRs agonists can synchronize ongoing hippocampal oscillations, leading to a significantly augmenting θ power, suggesting that it could be one of the contributing mechanisms to procognitive actions of α7 nAChRs agonists. Importantly, doses at which efficacy was observed in auditory gating for **24** were consistent with ex vivo binding.

The rat novel object recognition task (NOR) is thought to be comparable to delayed-matching-to-sample tasks that are commonly utilized in both nonhuman primates and humans to study working memory performance.[59] Results in rat indicate that **24** significantly improved the scopolamine-impaired

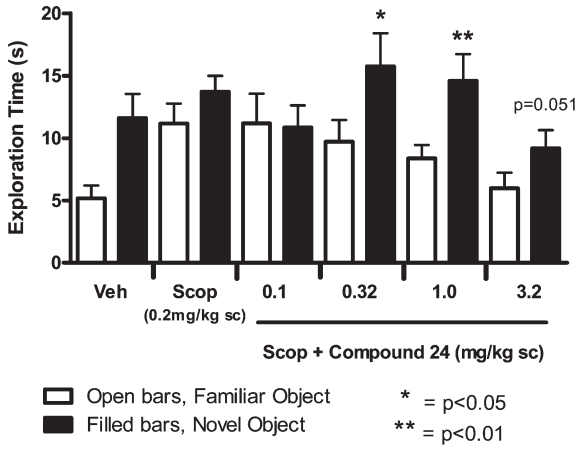


Figure 6. Efficacy of **24** in rat novel object recognition assay. Rats were habituated to the test arena for 3 min on day 1. The following day, animals (10−15 per group) were first dosed (sc) with either vehicle or test compound followed 30 min later by injection of either vehicle or (−)-scopolamine (0.2 mg/kg, sc). After an additional 30 min, two identical objects were presented for 3 min. Two and a half hours later, rats were exposed to one novel and one familiar object for 3 min. The time spent exploring each object (mean time (s) ± SEM) is plotted.

performance at both 0.32 and 1.0 mg/kg (sc) (Figure 6). This is consistent with prior reports demonstrating efficacy of α7 nAChR agonists in object recognition in mouse and further supports the notion that selective activation of this receptor may improve some aspects of cognitive function.[22a,60] Additionally, the effective doses of **24** in NOR are in complete alignment with the effective doses in both the ex vivo binding and (AMP)-induced auditory gating assays.

Conclusions

The synthesis and in vitro and in vivo evaluation of a series of 1,4-diazabicyclo[3.2.2]nonane azabenzoxazole α7 nAChR agonists have been described. Of the azabenzoxazoles evaluated, compound **24** (CP-810,123) exhibited an excellent balance of potency, selectivity and high affinity agonist activity at the α7 nAChR. The compound's in vitro profile is complemented by excellent brain penetration, high oral bioavailability in rats, and an acceptable preclinical cardiovascular safety profile with a favorable hERG and genetic toxicology profile. It demonstrates high receptor occupancy at low doses, in vivo efficacy in an amphetamine induced P50 gating deficit model, and improved performance in novel object recognition test. A good correlation between the in vitro data, ex vivo binding, and exposure required for in vivo efficacy demonstrates the solid in vitro to in vivo correlation for **24**. The structural diversity of this class of compounds, when compared to our previous clinical entries, combined with its preclinical evaluation package supports the hypothesis that α7 nAChR agonists may have potential as a pharmacotherapy for the treatment of cognitive deficits in schizophrenia.

Experimental Section

Biology. α7 Nicotinic Receptor Binding. Membrane preparations were made for nicotinic receptors expressed in GH_4C_1 cell line. Briefly, 1 g of cells by wet weight was homogenized with a Polytron in 25 mL of buffer containing 20 mM HEPES, 118 mM NaCl, 4.5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, pH 7.5. The homogenate was centrifuged at 40000*g* for 10 min at 4 °C, and the resulting pellet was homogenized and centrifuged again as described above. The final pellet was resuspended in 20 mL of the same buffer. Radioligand binding was carried out with [^{125}I]α-bungarotoxin from New England Nuclear, specific activity of about 16 μCi/μg, used at 0.4 nM final concentration in a 96-well microtiter plate. The plates were incubated at 37 °C for 2 h with 25 μL of drugs or vehicle for total binding, 100 μL of [^{125}I]bungarotoxin, and 125 μL of tissue preparation. Nonspecific binding was determined in the presence of methyllycaconitine at 1 μM final concentration. The reaction was terminated by filtration using 0.5% polyethylene imine treated Whatman GF/B glass fiber filters (Brandel Biomedical Research & Development Laboratories, Inc., Gaithersburg, MD) on a Skatron cell harvester (Molecular Devices Corp., Sunnyvale, CA) with ice-cold buffer; filters were dried overnight and counted on a Beta plate counter using Betaplate Scint (Wallac Inc., Gaithersburg, MD). Data are expressed as IC_{50} values (concentration that inhibits 50% of the specific binding) or as an apparent K_i, $IC_{50}/(1 + [L]/K_D)$, where [L] is the ligand concentration and K_D is the affinity constant for [^{125}I] ligand determined in a separate experiment.

α7 Nicotinic Receptor Functional Assay in Oocyte. *Xenopus* oocytes were harvested surgically and treated with collagenase (1.3 mg/mL) for 3 h to remove the follicular layer. The oocytes were injected with 10−50 ng of rat α7 neuronal nicotinic receptor cRNA and stored in Barth's saline for up to 2 weeks. Electrophysiological recordings were performed 4−10 days later using a two-electrode voltage clamp. The oocytes were placed in the recording chamber and superfused with Ringer's saline (in mM: 115 NaCl, 2.5 KCl, 0.4 $BaCl_2$, 0.1 $CaCl_2$, 10 HEPES, pH 7.5) containing agonists or antagonists. Electrodes are filled with 3 M KCl. Holding potential (V_h) was −60 or −90 mV. Currents induced by the application of drugs were digitized by a Data Translation analog/digital board and analyzed with Axodata software. All test compounds were tested at 32 μM and are compared to a test dose of nicotine at 50 μM. Data are reported as % nicotine response with the response of nicotine at 50 μM set at 100%.

Construction and Expression of the Chimeric α7-5HT$_3$ Receptor. The cDNA encoding the N-terminal 201 amino acids from the human α7 nAChR that contain the ligand binding domain of the ion channel was fused to the cDNA encoding the pore forming region of the mouse $5HT_3$ receptor as described by Eisele.[40] The chimeric α7-$5HT_3$ ion channel was inserted into pGS175 and pGS179 which contain the resistance genes for G-418 and hygromycin B, respectively. Both plasmids were simultaneously transfected into SH-EP1 cells, and cell lines were selected that were resistant to both G-418 and hyrgromycin B. Cell lines expressing the chimeric ion channel were identified by their ability to bind fluorescent α-bungarotoxin on their cell surface. The cells with the highest amount of fluorescent α-bungarotoxin binding were isolated using a fluorescent activated cell sorter (FACS). Cell lines that stably expressed the chimeric α7-$5HT_3$ were identified by measuring fluorescent α-bungarotoxin binding after growing the cells in minimal essential medium containing nonessential amino acids supplemented with 10% fetal bovine serum, L-glutamine, 100 U/mL penicillin/streptomycin, 250 ng/mg fungizone, 400 μg/mL hygromycin B, and 400 μg/mL G-418 at 37 °C with 6% CO_2 in a standard mammalian cell incubator for at least 4 weeks in continuous culture.

Functional Assay for the Chimeric α7-5HT$_3$ Receptor Agonist Activity. To assay the activity of the α7-$5HT_3$ ion channel, cells expressing the channel were plated into each well of either a 96- or 384-well dish (Corning no. 3614) and grown to confluence prior to assay. On the day of the assay, the cells were loaded with a 1:1 mixture of 2 mM Calcium Green 1, AM (Molecular Probes) dissolved in anhydrous DMSO, and 20% pluronic F-127 (Molecular Probes). This solution was added directly to the growth media of each well to achieve a final concentration of 2 μM. The cells were incubated with the dye for 60 min at 37 °C

and were washed with a modified version of Earle's balanced salt solution (MMEBSS) as described in WO 00/73431.[40b] The ion conditions of the MMEBSS was adjusted to maximize the flux of calcium ion through the chimeric α7-5HT$_3$ ion channel as described in WO 00/73431.[40b] The activity of compounds on the chimeric α7-5HT$_3$ ion channel was analyzed on FLIPR. The instrument was set up with an excitation wavelength of 488 nm using 500 mW of power. Fluorescent emission was measured above 525 nm with an appropriate F-stop to maintain a maximal signal-to-noise ratio. Agonist activity of each compound was measured by directly adding the compound to cells expressing the chimeric α7-5HT$_3$ ion channel and measuring the resulting increase in intracellular calcium that is caused by the agonist-induced activation of the chimeric ion channel. The assay is quantitative such that concentration-dependent increase in intracelluar calcium is measured as concentration-dependent change in Calcium Green fluorescence. The effective concentration needed for a compound to cause a 50% maximal increase relative to 100 μM nicotine in intracellular calcium is termed the EC$_{50}$.

5-HT$_3$ Receptor Binding. Radioligand binding studies were performed according to Wong with some modifications.[39] Briefly, frozen cell paste (HEK293 cells expressing mouse or human 5-HT$_{3A}$ receptors) was homogenized using a Brinkman Polytron model PT3000 (setting 15 000 rpm, 15 s) in 50 mM Tris-HCl buffer, pH 7.4, containing 2 mM $MgCl_2$. The homogenate was centrifuged for 10 min at 40000*g*, washed, and recentrifuged. The final pellet was resuspended in 20 mM Tris-HCl buffer, pH 7.4, at 37 °C containing 154 mM NaCl (3.5 mg/mL). Incubations were initiated by the addition of tissue homogenate to wells of 96-well plates containing ^{3}H-LY-278584 (1 nM, final concentration) and varying concentrations of test compound, buffer, or 10 μM ICS205-930 in a final volume of 250 μL. Nonspecific binding was defined as the radioactivity remaining in the presence of a saturating concentration of ICS205-390. After a 60 min incubation at 37 °C, assay samples were filtered onto GF/B filtermats presoaked in 0.5% polyethylenimine, using a Skatron cell harvester (Molecular Devices), and washed with ice-cold 50 mM Tris buffer, pH 7.4, at 4 °C. Radioactivity was quantified by liquid scintillation counting (Betaplate, Wallac Instruments). The IC$_{50}$ value (concentration at which 50% inhibition of specific binding occurs) was calculated by linear regression of the concentration−response data. K_i values were calculated according to Cheng and Prusoff, where $K_i = IC_{50}/(1 + (L/K_d))$, where L is the concentration of the radioligand used in the experiment and the K_d value is the dissociation constant for the radioligand (determined previously by saturation analysis). The data reported in the tables represent the average of three six-point dose−response curves that were run in a single assay. Tropisetron was used as an internal standard in each assay and had $K_i = 2.26 \pm 0.29$ nM ($n = 11$).

Functional Assay for 5-HT$_3$ Receptor Antagonist Activity. The human 5-HT$_{3A}$ receptor was stably expressed in human skin epithelial cells. Functional activity was evaluated as calcium flux using the fluorescence imaging plate reader (FLIPR, Molecular Devices). Cells were grown in DMEM supplemented with 10% FBS, L-glutamine, sodium pyruvate, 500 μg/mL Geneticin, and 100 units/mL penicillin/streptomycin. The cells were trypsinized and plated in 384-well plates with dark side walls and clear bottoms at a density of 15 000 cells/well 2 days before analysis. Cells were loaded in a 1:1 mixture of 8 mM Fluo-4 stock and 20% Pluronic F-127 (Molecular Probes). This reagent was added directly to the growth medium of each well to achieve a final concentration of 8 μM Fluo-4 in plating medium (same as above but without Geneticin). Cells were then incubated in the dye for 1 h at 37 °C and then washed 4 times in assay buffer comprising Hank's balanced salt solution supplemented with 20 mM Tris-HEPES and 1 μM atropine. $CaCl_2$ was added to achieve 4 mM Ca^{2+}, and the pH was asjusted to 7.4. FLIPR was used to measure changes in intracellular Ca^{2+}. After 30 s of baseline recording, test compounds were added to each well of the assay plate for 2 min from a 4× stock solution. Antagonist activity was determined as the inhibition of the fluorescence signal in response to a subsquent challenge with 5-HT for an additional 2 min (250 nM final from a 4× stock).

α7 Nicotinic ex Vivo Binding. Each hippocampus was homogenized with a Polytron in 4.5 mL of buffer containing 20 mM HEPES, 118 mM NaCl, 4.5 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgSO_4$, pH 7.5. Radioligand binding was carried out with [^{125}I]α-bungarotoxin from New England Nuclear, specific activity of about 16 μCi/μg, used at 0.4 nM final concentration in a 96-well microtiter plate. The plates were incubated at 37 °C for 2 h with 0.4 nM [^{125}I]bungarotoxin and 750 μL of tissue homogenates in a 1 mL assay. Nonspecific binding was determined in the presence of methyllycaconitine at 1 μM final concentration. The reaction was terminated by filtration using 0.5% polyethylene imine treated Whatman GF/B glass fiber filters (Brandel Biomedical Research & Development Laboratories, Inc., Gaithersburg, MD) on a Skatron cell harvester (Molecular Devices Corp., Sunnyvale, CA) with ice-cold buffer; filters were dried overnight and counted on a Beta plate counter using Betaplate Scint (Wallac Inc., Gaithersburg, MD). Data are expressed as ED$_{50}$ values (concentration that inhibits 50% of the specific binding).

Auditory Gating Assay. Experiments were performed on male Sprague−Dawley rats (weighing 250−300 g) under chloral hydrate anesthesia (400 mg/kg, ip). The femoral vein was cannulated for drug administration or additional doses of anesthetic. Unilateral hippocampal field potential (EEG) was recorded by a metal monopolar macroelectrode placed into the CA3 region (coordinates: 3.0−3.5 mm posterior from the bregma, 2.6−3.0 mm lateral, and 3.8−4.0 mm ventral). Field potentials were amplified, filtered (0.1−100 Hz), displayed, and recorded for on-line and off-line analysis; quantitative EEG analysis was performed by means of fast Fourier transformation (Spike3). The auditory stimulus consisted of a pair of 10 ms, 5 kHz tone bursts with a 0.5 s delay between the first "conditioning" stimulus and second "test" stimulus. Auditory-evoked responses were computed by averaging of responses to 50 pairs of stimuli presented with an interstimulus interval of 10 s. Amphetamine (*d*-amphetamine sulfate, 1 mg/kg, iv) was administered in order to disrupt sensory gating. By use of fast Fourier transform, the relative θ power was determined by calculating the percentage of total power that occurred in the θ (3.5−5.5 Hz) frequency band compared with the 0−15 Hz frequency band. Statistical significance was determined by means of two-tailed paired Student's *t*-test.

Chemistry. General Methods. Solvents and reagents were of reagent grade and were used as supplied by the manufacturer. All reactions were run under a N_2 atmosphere. Organic extracts were routinely dried over anhydrous Na_2SO_4. Concentration refers to rotory evaporaration under reduced pressure. Chromatography refers to flash chromatography using disposable RediSepR_f 4−120 g silica columns or Biotage disposable columns on a CombiFlash Companion or Biotage Horizon automatic purification system. Microwave reactions were carried out in a microwave reactor manufactured by Smithcreator of Personal Chemistry. Purification by mass-triggered HPLC was carried out using Waters XTerra PrepMS C_{18} columns, 5 μm, 30 mm × 100 mm steel. Compounds were presalted as TFA salts and diluted with 1 mL of dimethyl sulfoxide. Samples were purified by mass triggered collection using a mobile phase of 0.1% TFA in water and acetonitrile with a starting gradient of 100% aqueous to 100% acetonitrile over 10 min at 20 mL/min flow rate. Elemental analyses were performed by QTI, Whitehouse, NJ. All target compounds were analyzed using ultrahigh performance liquid chromatography/ultraviolet/evaporative light scattering detection coupled to time-of-flight mass spectrometry (UHPLC/UV/ELSD/TOFMS). Unless otherwise noted, all tested compounds were found to be ≥95% pure by this method.

UPLC/MS Analysis. The UPLC was performed on a Waters ACQUITY UPLC system (Waters, Milford, MA), which was equipped with a binary solvent delivery manager, column manager, and sample manager coupled to ELSD and UV detectors (Waters, Milford, MA). Detection was performed on a Waters LCT premier XE mass spectrometer (Waters, Milford, MA). The instrument was fitted with an Acquity BEH (bridged ethane hybrid) C18 column (30 mm × 2.1 mm, 1.7 μm, Waters, Milford, MA) operating at 60 °C.

4-Benzoxazo-2-yl-1,4-diazabicyclo[3.2.2]nonane (7). 2-Chlorobenzoxazole (99 μL, 0.87 mmol) was added to a solution of 1,4-diazabicyclo[3.2.2]nonane **6** (100 mg, 0.79 mmol) in methanol (2.65 mL) at 0 °C. The reaction mixture was allowed to slowly warm to RT. After a period of 16 h *i*-Pr_2NEt (138 μL, 0.79 mmol) was added and the mixture was stirred at RT for 4.5 h, at which time it was diluted with $CHCl_3$ and $NaHCO_3$. The layers were partitioned, and the aqueous layer was extracted with $CHCl_3$ (×3). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by chromatography (Biotage, 12 L), eluting with 4% MeOH in $CHCl_3$ containing 20 drops of NH_4OH per liter of eluent to afford 67 mg (35%) of the free base of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, 1H, *J* = 7.5 Hz), 7.19 (d, 1H, *J* = 7.9 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 6.94 (t, 1H, *J* = 7.9 Hz), 4.46 (s, 1H), 3.87 (t, 2H, *J* = 5.8 Hz), 3.12−2.92 (m, 6H), 2.15−2.05 (m, 2H), 1.79−1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.8, 148.9, 143.7, 124.1, 120.3, 116.1, 108.7, 57.3, 50.3, 46.5, 44.4, 27.1; MS (APCI) *m*/*z* 244.3 (M + 1).

4-(5-Bromobenzoxazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane (10). Step 1. Potassium ethyl xanthate (416 mg, 2.60 mmol) was added to a solution of 2-amino-4-bromophenol (**4a**, 244 mg, 1.30 mmol) in EtOH (3.24 mL). The reaction mixture was heated at reflux for 4 h. Upon cooling to RT, the mixture was concentrated and the resulting residue was dissolved in water. Acetic acid was added until pH 5 was obtained and a white solid precipitated from the solution. The solid was filtered, washed with water, and dried to afford 270 mg (90%) of 5-bromo-3*H*-benzooxazole-2-thione as a tan powder which was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 14.02 (s, 1H), 7.47−7.38 (m, 3H); ^{13}C (DMSO-d_6, 400 MHz) δ 181.4, 148.1, 133.7, 127.1, 117.8, 118.8, 112.2; MS (CI) *m*/*z* 229.8 (M − 1).

Step 2. 5-Bromo-3*H*-benzooxazole-2-thione (530 mg, 2.30 mmol) was dissolved in DMF (5.75 mL). Potassium carbonate (318 mg, 2.30 mmol) and iodomethane (172 μL, 2.76 mmol) were added, and the reaction mixture was allowed to stir at RT for 3.5 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated to afford 538 mg (96%) of 5-bromo-2-methylsulfanylbenzooxazole (**5**) as a dark-brown solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, ^{1}H, *J* = 2.1 Hz), 7.36−7.26 (m, 2H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 151.2, 143.8, 126.9, 121.6, 117.3, 111.2, 14.8; MS (CI) *m*/*z* 244.0 (M + 1).

Step 3. 1,4-Diazabicyclo[3.2.2]nonane (57%, 731 mg, 3.31 mmol) was added to a solution of 5-bromo-2-methylsulfanylbenzooxazole (538 mg, 2.20 mmol) in *i*-PrOH (4.4 mL). The mixture was placed in an oil bath at 90 °C, and the solvent was evaporated. The mixture was allowed to stir neat at 90 °C for 18 h. Upon cooling to RT, the mixture was purified by chromatography (Biotage, 25 M), eluting with 4% MeOH in $CHCl_3$ with 20 drops of NH_4OH per liter of eluent to afford 392 mg (55%) of compound **10** as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (t, 1H, *J* = 1.2 Hz), 7.05 (d, 2H, *J* = 1.2 Hz), 4.46−4.43 (m, 1H), 3.87 (t, 2H, *J* = 5.8 Hz), 3.14−2.93 (m, 6H), 2.13−2.06 (m, 2H), 1.81−1.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 148.0, 145.6, 122.9, 119.0, 116.8, 109.8, 57.2, 50.5, 46.5, 44.4, 27.0; MS (CI) *m*/*z* 322.0 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a solution of 2.5 N HCl in ethyl acetate.

4-(5-Fluorobenzoxazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane (8). The free base of the title compound was prepared from 2-amino-4-fluorophenol by the methods described for the preparation of **10** in 54% overall yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (dd, 1H, *J* = 8.7, 4.6 Hz), 7.01 (dd, 1H, *J* = 9.1, 2.5 Hz), 6.70−6.65 (m, 1H), 4.54−4.51 (m, 1H), 3.94 (t, 2H, *J* = 5.8 Hz), 3.24−3.17 (m, 4H), 3.11−3.03 (m, 2H), 2.21−2.14 (m, 2H), 1.90−1.82 (m, 2H); MS (CI) *m*/*z* 262.1 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-(5-Chlorobenzoxazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane (9). The free base of the title compound was prepared from 2-amino-4-chlorophenol by the methods described for the preparation of **10** in 48% overall yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, 1H, *J* = 2.1 Hz), 7.09 (d, 1H, *J* = 8.3 Hz)), 6.91 (dd, 1H, *J* = 8.3, 2.1 Hz), 4.49−4.47 (m, 1H), 3.90 (t, 2H, *J* = 5.8 Hz), 3.20−3.12 (m, 4H), 3.07−2.99 (m, 2H), 2.17−2.09 (m, 2H), 1.85−1.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.4, 147.5, 145.0, 129.4, 120.2, 116.2, 109.3, 57.0, 50.4, 46.3, 44.0, 26.7; MS (APCI) *m*/*z* 278.1 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-(5-Methylbenzoxazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane (11). The free base of the title compound was prepared from 2-amino-4-methylphenol by the methods described for the preparation of **10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (s, 1H), 7.10 (d, 1H, *J* = 7.9 Hz), 6.80 (dd, 1H, *J* = 7.9, 0.8 Hz), 4.55−4.53 (m, 1H), 3.95 (t, 2H, *J* = 5.8 Hz), 3.24−3.17 (m, 4H), 3.10−3.03 (m, 2H), 2.38 (s, 3H), 2.22−2.15 (m, 2H), 1.89−1.81 (m, 2H); MS (APCI) *m*/*z* 258.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-(6-Methylbenzoxazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane (12). The free base of the title compound was prepared from 2-amino-5-methylphenol by the methods described for the preparation of **10** in 55% overall yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (d, 1H, *J* = 7.9 Hz), 7.06 (s, 1H), 6.96 (d, 1H, *J* = 8.3 Hz), 4.55−4.52 (m, 1H), 3.94 (t, 2H, *J* = 5.8 Hz), 3.23−3.15 (m, 4H), 3.09−3.01 (m, 2H), 2.39 (s, 3H), 2.22−2.14 (m, 2H), 1.89−1.80 (m, 2H); MS (APCI) *m*/*z* 258.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-Oxazolo[4,5-*b*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane (13). The free base of the title compound was prepared from 2-(methylthio)oxazolo[4,5-*b*]pyridine[34] by the methods described for the preparation of **10** in 98% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (dd, 1H, *J* = 5.0, 1.2 Hz), 7.34 (dd, 1H, *J* = 7.5, 1.2 Hz), 6.81 (dd, 1H, *J* = 7.8, 5.0 Hz), 4.50 (s, 1H), 3.90 (t, 2H, *J* = 5.8 Hz), 3.13−3.05 (m, 4H), 2.98−2.91 (m, 2H), 2.13−2.05 (m, 2H), 1.79−1.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1, 158.7, 144.7, 141.4, 115.4, 114.8, 57.1, 50.6, 46.4, 46.3, 44.4, 30.3, 26.9; MS (APCI) *m*/*z* 245.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-Oxazolo[4,5-*c*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane (14). The free base of the title compound was prepared from 2-(methylthio)oxazolo[4.5-*c*]pyridine[34] by the methods described for the preparation of **10** in 32% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (s, 1H), 8.21 (d, 1H, *J* = 5.4 Hz), 7.16 (d, 1H, *J* = 5.4 Hz), 4.46−4.45 (m, 1H), 3.88 (t, 2H, *J* = 5.8 Hz), 3.14−3.03 (m, 4H), 3.00−2.93 (m, 2H), 2.13−2.06 (m, 2H), 1.82−1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 154.3, 142.0, 141.4, 138.0, 104.9, 62.3, 57.1, 50.8, 46.3, 44.6, 30.3, 26.9; MS (APCI) *m*/*z* 245.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-Oxazolo[5,4-*c*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane (15). The free base of the title compound was prepared from 2-(methylthio)oxazolo[5,4-*c*]pyridine[34] by the methods described for the preparation of **10** in 67% yield: ^{1}H NMR

($CDCl_3$, 400 MHz) δ 8.44 (s, 1H), 8.27 (d, 1H, J = 5.0 Hz), 7.19 (d, 1H, J = 5.3 Hz), 4.48 (s, 1H), 3.90 (t, 2H, J = 5.8 Hz), 3.14−3.07 (m, 4H), 3.00−2.93 (m, 2H), 2.12−2.07 (m, 2H), 1.82−1.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 150.9, 147.5, 145.5, 129.8, 111.6, 62.3, 50.9, 46.4, 44.7, 30.3, 26.9; MS (APCI) m/z 245.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-Oxazolo[5,4-*b*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane (16). The free base of the title compound was prepared from 2-(methylthio)oxazolo[5.4-*b*]pyridine[34] by the methods described for the preparation of **10** in 72% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, 1H, J = 5.0, 1.2 Hz), 7.47 (dd, 1H, J = 7.5, 1.2 Hz), 7.04 (dd, J = 7.5, 5.0 Hz), 4.49−4.47 (m, 1H), 3.89 (t, 2H, J = 5.8 Hz), 3.13−3.05 (m, 4H), 3.00−2.92 (m, 2H), 2.13−2.06 (m, 2H), 1.81−1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 158.4, 138.6, 136.3, 122.7, 120.7, 57.1, 50.4, 46.4, 44.2, 26.9; MS (APCI) m/z 245.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

4-(6-Bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (17). Bromine (0.12 mL, 2.29 mmol) was added to a solution of 4-oxazolo[4,5-*b*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane **13** (560 mg, 2.29 mmol) and sodium acetate (2.26 g, 27.5 mmol) in water (12 mL) and acetic acid (12 mL). The resulting mixture was heated to reflux for 2 h. The mixture was cooled and extracted with ethyl acetate (3×). The combined organic layers were washed with water (2×) and brine (1×) and dried over sodium sulfate, filtered, and concentrated. The crude residue was purified by chromatography (Biotage, 25 M) using a gradient elution from 4% MeOH/$CHCl_3$ containing 0.1% NH_4OH to 8% MeOH/$CHCl_3$ containing 0.1% NH_4OH, giving 578 mg (78%) of the free base of the title compound as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, 1H, J = 1.7 Hz), 7.50 (d, 1H, J = 1.7 Hz), 4.51 (br s, 1H), 3.92 (br s, 2H), 3.16−3.04 (m, 4H), 3.02−2.94 (m, 2H), 2.17−2.01 (m, 2H), 1.83−1.74 (m, 2H); MS (APCI) m/z 325.0/323.0 (M + 1).

4-(6-Chlorooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (18). 4-Oxazolo[4,5-*b*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane **13** (300 mg, 1.2 mmol) and *N*-chlorosuccinimide (239 mg, 1.8 mmol) were dissolved in chloroform, sealed in a microwave reactor tube, and heated at 150 °C for 10 min in a microwave reactor. The crude material was cooled and purified by chromatography, eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (0.5/9.5/90) to give 111 mg (33%) of the free base of the title compound as a sticky solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 2.1 Hz), 7.34 (d, 1H, J = 2.1 Hz), 4.42−4.53 (m, 1H), 3.82−3.96 (m, 2H), 3.02−3.16 (m, 4H), 2.88−3.02 (m, 2H), 1.98−2.16 (m, 2H), 1.68−1.83 (m, 2H); LCMS m/z 279.2 (M + 1).

4-(6-Fluorooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (19). The free base of the title compound was prepared from 4-oxazolo[4,5-*b*]pyridin-2-yl-1,4-diazabicyclo[3.2.2]nonane **13** by the methods described for the preparation of **33** in 32% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (t, 1H, J = 2.3 Hz), 7.25 (dd, 1H, J = 7.5, 2.5 Hz), 4.55 (m, 1H), 3.92−3.98 (m, 2H), 3.11−3.22 (m, 4H), 2.98−3.07 (m, 2H), 2.10−2.21 (m, 2H), 1.77−1.89 (m, 2H); MS (APCI) m/z 263.2 (M + 1).

4-(6-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (20). 4-(6-Bromo-oxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (50 mg, 0.15 mmol), dimethylzinc (2 M solution in toluene, 0.15 mL, 0.31 mmol), and Pd(dppf)Cl_2 (4 mg, 0.03 mmol) were dissolved in 1,4-dioxane (1 mL), sealed in a microwave reactor tube, and heated at 150 °C for 10 min in a microwave reactor. The reaction mixture was diluted with MeOH and filtered through a pad of Celite. The filtrate was purified by chromatography, eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (0.5/9.5/90) to give 27 mg (70%) of the free base of the title compound as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H), 7.24 (s, 1H), 4.53−4.58 (m, 1H), 3.95 (s, 2H), 3.11−3.21 (m, 4H), 2.97−3.07 (m, 2H), 2.36 (s, 3H), 2.10−2.20 (m, 2H), 1.76−1.87 (m, 2H); LCMS m/z 259.2 (M + 1).

4-(6-Ethyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (21). Step 1. Tributyl(vinyl)stannane (117 mg, 0.37 mmol) and Pd(PPh_3)$_2Cl_2$ (11 mg, 0.015 mmol) were added to a stirred solution of 4-(6-bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (100 mg, 0.31 mmol) in toluene. The reaction mixture was heated to reflux. After cooling to RT, the mixture was concentrated, hydrolyzed with water, and extracted with CH_2Cl_2 (10×, 10 mL). Organic extracts were combined, dried ($MgSO_4$), concentrated, and purified by chromatography, eluting with 5% MeOH in CH_2Cl_2 containing 5% NH_4OH to give 57 mg (68%) of 2-(6-vinyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo-[3.2.2]nonane: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.09 (s, 1H), 7.80 (s, 1H), 6.77 (dd, 1H, J = 17.6, 11.0 Hz), 5.77 (d, 1H, J = 17.6 Hz), 5.26 (d, 1H, J = 11.2 Hz), 4.63 (m, 1H), 4.10 (m, 2H), 3.35 (m, 2H), 3.28 (m, 4H), 2.30 (m, 2H), 2.07 (m, 2H); LCMS m/z 271.0 (M + 1).

Step 2. 10% Pd/C (10 mg) was added to a solution of 2-(6-vinyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane (55 mg) in 1:1 EtOH/MeOH (10 mL). The mixture was shaken under H_2 (45 psi) for 2 h in a PARR apparatus and filtered through a pad of Celite and the filtrate was concentrated to give 55 mg (99% yield) of the free base of the title compound as a viscous oil: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.97 (s, 1H), 7.57 (s, 1H), 4.61 (m, 1H), 4.10 (m, 2H), 3.36 (m, 2H), 3.30 (m, 4H), 2.70 (q, 2H, J = 7.5 Hz), 2.29 (m, 2H), 2.05 (m, 2H), 1.26 (t, 3H, J = 7.5 Hz); LCMS m/z 273.0 (M + 1).

4-(6-*sec*-Butyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (22). The compound was prepared in a library format using the following protocol: a stock solution of 4-(6-bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (20 mg in 0.75 mL) in 1,2-dichloroethane/methanol (1/1) was added to an 8 mL reaction vial with the corresponding boronic acid (0.12 mmol). The resulting mixture was then evaporated in vacuo, and the residue was dissolved in ethanol (0.65 mL), followed by addition of sodium carbonate aqueous solution (19 mg, 0.18 mmol in 0.085 mL) and a solution of tetrakis-(triphenylphosphine)palladium(0) in toluene (3.4 mg, 0.003 mmol in 0.1 mL). The reaction vial was then heated to 85 °C for 18 h. When the mixture was cooled to RT, 1 N NaOH (1.5 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 2.5 mL). The combined organic layer was loaded onto a solid phase extraction (SPE) cartridge and eluted with ethyl acetate (5 mL) followed by methanol (5 mL) into a waste container. The column was then eluted with 1 N triethylamine in methanol (5 mL) to a collecting container. The filtrate was concentrated in vacuo to afford crude product, which was converted to the trifluoroacetic acid salt by adding a 1 mL of a 15/485 trifluoroacetic acid/dichloromethane solution. The crude was purified by mass triggered HPLC and analyzed using the general HPLC conditions. LCMS retention time 1.71 min, m/z 323.03 (M + Na).

4-(6-Phenyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (23). Et_3N (5 μL) was added to a solution of palladium(II) acetate (0.7 mg, 3.1 μmol) and 2-(*N*,*N*-dimethylamino)-2′-dicyclohexylphosphinobiphenyl (1.8 mg, 4.65 μmol) in 1,2-dimethoxyethane (0.5 mL) under a nitrogen atmosphere at RT. 4-(6-Bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (50 mg, 0.155 mmol), phenylboronic acid (32 mg, 0.233 mmol), and CsF (70 mg, 0.465 mmol) were added to the solution, and the mixture was heated in an oil bath (80 °C) for a period of 16 h. The reaction mixture was cooled to RT, filtered through a pad of Celite, and concentrated in vacuo. The crude residue was purified by chromatography, eluting with 4% MeOH in $CHCl_3$ with 1 mL of NH_4OH per liter to give 14 mg (27%) of the free base of the title compound as a film: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (d, 1H, J = 2.1 Hz), 7.62 (d, 1H, J = 2.1 Hz), 7.57−7.55 (m, 2H), 7.47−7.43 (m, 2H), 7.40−7.34 (m, 1H), 4.62 (br s, 1H), 4.00 (t, 2H, J = 5.8 Hz), 3.20−3.15 (m, 4H), 3.08−3.01 (m, 2H),

2.19−2.08 (m, 2H), 1.90−1.81 (m, 2H); MS (APCI) *m*/*z* 321.2 (M + 1).

4-(5-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]-nonane (24). The free base of the title compound was prepared from 5-methyl-2-methylsulfanyloxazolo[4,5-*b*]pyridine (prepared from 6-methyl-2-nitropyridin-3-ol) by the methods described for the preparation of **10** in 67% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22 (d, 1H, J = 7.9 Hz), 6.65 (d, 1H, J = 7.9 Hz), 4.49 (s, 1H), 3.89 (t, 2H, J = 5.8 Hz), 3.13−3.05 (m, 4H), 2.99−2.90 (m, 2H), 2.47 (s, 3H), 2.13−2.06 (m, 2H), 1.78−1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 158.2, 153.5, 139.8, 114.9, 114.3, 57.1, 50.5, 46.4, 44.3, 26.9, 24.1; MS (APCI) *m*/*z* 259.2 (M + 1). The hydrochloride salt was prepared by diluting in ethyl acetate and adding a 2.5 N HCl solution in ethyl acetate.

2-(6-Chlorooxazolo[5,4-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (25). Step 1. 5-Chloro-3-nitropyridin-2-ol (2 g, 11.46 mmol), $Na_2S_2O_4$ (20 g, 114.58 mmol), and KOH (11.9 g, 212.01 mmol) were dissolved in water (40 mL) and stirred at RT overnight. The reaction mixture was extracted with EtOAc (5×). The organic extracts were combined, dried over Na_2SO_4, and concentrated to give 0.8 g (48%) of 3-amino-5-chloropyridin-2-ol: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.40−11.73 (m, 1 H), 6.71 (d, 1 H, J = 2.5 Hz), 6.37 (d, 1 H, J = 2.9 Hz), 5.39−5.46 (m, 2 H); LCMS *m*/*z* 144.9 (M + 1).

Step 2. Thiophosgene (815 μL, 10.7 mmol) was added to a solution of 3-amino-5-chloropyridin-2-ol in THF (15 mL) under N_2 and stirred at RT for 1.5 h. A solution of NaOH (1.0 N aqueous solution) was added to adjust the pH to ∼3. The mixture was concentrated, and another solution of NaOH (1.0 N aqueous solution) was added to adjust the pH to ∼5. The mixture was filtered, concentrated, dissolved in EtOAc, filtered again, concentrated, and purified by chromatography to give 306 mg (30%) of 6-chlorooxazolo[5,4-*b*]pyridine-2-thiol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1 H, J = 2.5 Hz), 7.55 (d, 1 H, J = 2.1 Hz); LCMS *m*/*z* 187.0 (M + 1).

Step 3. 6-Chloro-2-(methylthio)oxazolo[5,4-*b*]pyridine was prepared from 6-chlorooxazolo[5,4-*b*]pyridine-2-thiol by the methods described for the preparation of **10** (step 2) in 85% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1 H, J = 2.1 Hz), 7.85−7.86 (m, 1 H), 2.77 (s, 3 H); LCMS *m*/*z* 201.0 (M + 1).

Step 4. The free base of the title compound was prepared from 6-chloro-2-(methylthio)oxazolo[5,4-*b*]pyridine by the methods described for the preparation of **10** (step 3) in 20% yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.87−7.96 (m, 1 H), 7.63−7.70 (m, 1 H), 4.71−4.80 (m, 1 H), 4.24 (t, 2 H, J = 5.6 Hz), 3.68 (t, 2 H, J = 5.8 Hz), 3.59 (t, 4 H, J = 7.9 Hz), 2.37−2.54 (m, 2 H), 2.16−2.35 (m, 2 H); LCMS *m*/*z* 279.1 (M + 1).

4-(6-Phenyloxazolo[5,4-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]-nonane (26). The free base of the title compound was prepared 6-phenyl-2-methylsulfanyloxazolo[5,4-*b*]pyridine by the methods described for the preparation of **10** in 50% yield as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, J = 2.1 Hz), 7.72 (d, 1H, J = 2.1 Hz), 7.57−7.55 (m, 2H), 7.47−7.44 (m, 2H), 7.39−7.36 (m, 1H), 4.58 (br s, 1H), 3.98 (t, 2H, J = 5.8 Hz), 3.22−3.14 (m, 4H), 3.11−3.01 (m, 2H), 2.22−2.15 (m, 2H), 1.89−1.82 (m, 2H); MS (APCI) *m*/*z* 321.2 (M + 1).

2-(5-Methyloxazolo[5,4-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (27). The free base of the title compound was prepared from 3-amino-6-methylpyridin-2-ol by the methods described for the preparation of **25** (steps 2−4) in 9% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, 1H, J = 7.9 Hz), 7.08 (d, 1H, J = 7.9 Hz), 4.43−4.49 (m, 1H), 3.97 (s, 2H), 2.99−3.18 (m, 6H), 2.49 (s, 3H), 2.12−2.28 (m, 2H), 1.85−1.96 (m, 2H); LCMS *m*/*z* 259.2 (M + 1).

4-(6-Cyanooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]-nonane (28). 4-(6-Bromo-oxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (500 mg, 1.5 mmol), dicyanozinc (217 mg, 1.9 mmol), and Pd(dppf)Cl_2 (36 mg, 0.045 mmol) were dissolved in DMF (5 mL), sealed in a microwave reactor tube and heated at 220 °C for 10 min in a microwave reactor. The crude material was cooled and filtered through a pad of Celite. The filtrate was purified by chromatography, eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (0.5/9.5/90) to give 316 mg (78%) of **28** as a solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (s, 1H), 7.56 (s, 1H), 4.59 (s, 1H), 3.84−4.17 (m, 2H), 3.12−3.22 (m, 4H), 2.96−3.06 (m, 2H), 2.04−2.25 (m, 2H), 1.79−1.91 (m, 2H); MS (APCI) *m*/*z* 270.2 (M + 1).

2-(6-(1*H*-Pyrazol-3-yl)oxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane (29). 4-(6-Bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (291 mg, 0.9 mmol), 1*H*-pyrazol-3-ylboronic acid (100 mg, 0.9 mmol), K_2CO_3 (497 mg, 3.6 mmol), and Pd(PPh_3)$_4$ (21 mg, 0.018 mmol) were dissolved in a solution of 10% water/ethanol (2.2 mL), sealed in a microwave reactor tube, and heated at 150 °C for 110 min in a microwave reactor. The crude material was cooled and filtered through a pad of Celite. The solvent was removed in vacuo and the residue was purified by preparative HPLC to give 41 mg (15%) of **29** as an oil: ^{1}H NMR (CD_3OD, 400 MHz) 8.58 (s, 1H), 8.38 (br s, 1H), 8.01 (d, 1H, J = 1.7 Hz), 7.72 (d, 1H, J = 2.5 Hz), 6.71 (d, 1H, J = 2.1 Hz), 4.75 (s, 1H), 4.20−4.26 (m, 2H), 3.61−3.66 (m, 2H), 3.48−3.59 (m, 4H), 2.38−2.50 (m, 2H), 2.17−2.29 (m, 2H); LCMS *m*/*z* 311.2 (M + 1).

2-(6-(Pyridin-3-yl)oxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo-[3.2.2]nonane (30). The title compound was prepared from 4-(6-bromooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** and pyridin-3-ylboronic acid by the methods described in compound **29** in 24% yield and converted to HCl salt by the method described for compound **8**: ^{1}H NMR (CD_3OD, 400 MHz) δ 9.34 (s, 1H), 9.01 (d, 1H, J = 7.9 Hz), 8.94 (d, 1H, J = 5.4 Hz), 8.74 (s, 1H), 8.58 (s, 1H), 8.25 (dd, 1H, J = 7.7, 6.0 Hz), 4.36−4.42 (m, 2H), 3.73−3.79 (m, 2H), 3.60−3.67 (m, 4H), 3.35 (s, 1H), 2.46−2.59 (m, 2H), 2.28−2.41 (m, 2H); LCMS *m*/*z* 322.2 (M + 1).

2-(6-(Pyrimidine-5-yl)oxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane (31). The title compound was prepared in a library format using the same protocol described for the preparation of **22** from pyrimidin-5-ylboronic acid: LCMS retention time 1.37 min, *m*/*z* 323.16 (M + 1).

2-(6-Phenoxyoxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (32). 4-(6-Bromo-oxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **17** (100 mg, 0.31 mmol), phenol (44 mg, 0.46 mmol), CuCl (15 mg, 0.15 mmol), tetramethylheptane-3,5-dione (14 mg, 0.08 mmol), and Cs_2CO_3 (150 mg, 0.46 mmol) were dissolved in DMF (1 mL)), sealed in a microwave reactor tube, and heated at 200 °C for 40 min in a microwave reactor. The crude material was cooled and filtered through a pad of Celite. The filtrate was purified by chromatography, eluting with a solution of NH_4OH/MeOH/CH_2Cl_2 (0.5/9.5/90) to give 17 mg (16%) of **32**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.28−7.35 (m, 2H), 7.20 (d, 1H, J = 2.5 Hz), 7.08 (t, 1H, J = 7.3 Hz), 6.96 (d, 2H, J = 7.9 Hz), 4.52−4.58 (m, 1H), 3.95 (s, 2H), 3.11−3.21 (m, 4H), 2.97−3.07 (m, 2H), 2.10−2.21 (m, 2H), 1.76−1.87 (m, 2H); MS (APCI) *m*/*z* 337.3 (M + 1).

4-(6-Fluoro-5-methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane (33). Step 1. 4-(5-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **24** (0.6 g) was dissolved in sulfuric acid (95 − 98%, 4.0 mL) and cooled to 0 °C in an ice bath. A chilled mixture of sulfuric acid (95−98%, 2.0 mL) and nitric acid (> 90%, 2 mL) was added slowly, and the resulting mixture was allowed to stir at ambient temperature for 16 h and then slowly poured over $NaHCO_3$ (15.0 g). A solution of NaOH (1.0 N aqueous solution) was added to adjust the pH to ∼14. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified using flash chromatography (silica gel, 0−9.5% MeOH in CH_2Cl_2 with 0.5% NH_4OH) to give 4-(5-methyl-6-nitrooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane in 33% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (s, 1H), 4.39−4.76 (m, 1H), 3.83−4.16 (m, 2H), 3.09−3.25 (m, 4H), 2.94−3.09 (m, 2H), 2.89

(s, 3H), 1.95−2.29 (m, 2H), 1.75−1.94 (m, 2H); MS (ESI+) for $C_{14}H_{17}N_5O_3$ *m/z* 304.3 (M + 1).

Step 2. 10% Pd/C (50 mg) was added to a solution of 4-(5-methyl-6-nitrooxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]-nonane (0.208 g) in 1:1 EtOH/MeOH (100 mL). The mixture was shaken under H_2 (45 psi) for 2 h in a PARR apparatus and filtered through a pad of Celite and the filtrate was concentrated to give 2-(1,4-diazabicyclo[3.2.2]non-4-yl)-5-methyloxazolo-[4,5-*b*]pyridin-6-ylamine: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (s, 1H), 4.45−4.57 (m, 1H), 3.88−3.95 (m, 2H), 3.08−3.20 (m, 4H), 2.96−3.07 (m, 2H), 2.42 (s, 3H), 2.10−2.21 (m, 2H), 1.73−1.84 (m, 2H); MS (ESI+) for $C_{14}H_{19}N_5O$ *m/z* 274.3 (M + 1).

Step 3. 2-(1,4-Diazabicyclo[3.2.2]non-4-yl)-5-methyloxazolo-[4,5-*b*]pyridin-6-ylamine (0.180 g) was dissolved in a solution of HCl (36%, 0.4 mL) and water (2 mL). The resulting mixture was heated to 100 °C for 20 min and then cooled to −10 °C in an ice−NaCl bath. A solution of $NaNO_2$ (0.055 g) in water (2 mL) was added, followed by the addition of HPF_6 (60%, 0.17 mL). The resulting suspension was stirred at −10 °C for additional 30 min. The mixture was then filtered to give a solid, which was transferred to a vial and heated to 165 °C in an oil bath for 20 min. The residue was purified using reverse phase HPLC to give the title compound in 6% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, 1 H, J = 8.3 Hz), 4.50−4.60 (m, 1H), 3.95 (t, 2H, J = 5.8 Hz), 3.12−3.24 (m, 4H), 2.97−3.10 (m, 2H), 2.50 (d, 3H, J = 3.7 Hz), 2.11−2.23 (m, 2H), 1.76−1.90 (m, 2H); MS (ESI+) for $C_{14}H_{17}FN_4O$ *m/z* 277.3 (M + 1).

4-(6-Chloro-5-methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo-[3.2.2]nonane (34). 4-(5-Methyloxazolo[4,5-*b*]pyridin-2-yl)-1,4-diazabicyclo[3.2.2]nonane **24** (0.1 g) and *N*-chlorosuccinimide (0.051 g) were dissolved in $CHCl_3$, sealed in a microwave reactor tube (Smith process vial), and heated to 150 °C for 10 min in a microwave reactor. The mixture was filtered, and the solvent was removed in vacuo. The residue was dissolved in MeOH, and HCl in 1,4-dioxane (4 M, 0.4 mL) was added. The solvent was removed in vacuo and the residue was dissolved in MeOH and triturated with CH_2Cl_2 to give **34** in 70% yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.27 (s, 1H), 4.84−4.89 (m, 1H), 4.34 (t, 2H, J = 5.8 Hz), 3.73 (t, 2H, J = 5.8 Hz), 3.61 (t, 4H, J = 7.9 Hz), 2.69 (s, 3H), 2.42−2.54 (m, 2H), 2.26−2.37 (m, 2H); MS (ESI+) for $C_{14}H_{17}ClN_4O$ *m/z* 293.0 (M + 1).

2-(5-Bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (3a). Step 1. Sodium methoxide (25% in methanol, 44.6 mL, 178.5 mmol) was added to a solution of 2-nitropyridin-3-ol (25 g, 178.5 mmol) in methanol under N_2. The mixture was stirred at RT for 30 min before cooling to 0 °C. Bromine was added dropwise, and the mixture was stirred for 1 h. Acetic acid (3.1 mL) was added, and the mixture was concentrated to give a yellow solid. The yellow solid was triturated with CH_2Cl_2 to give a white solid which was dissolved in boiling methanol (5 mL) followed by addition of water (12 mL). The mixture was cooled to RT. The resulting precipitate was filtered and washed with water to give 6-bromo-2-nitropyridin-3-ol as a white solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.78 (d, 1H, J = 8.7 Hz), 7.56 (d, 1H, J = 8.7 Hz).

Step 2. Iron (11.7 g, 20.9 mmol) and calcium chloride (4.6 g, 41.9 mmol) were added to a solution of 6-bromo-2-nitropyridin-3-ol (10.2 g, 46.6 mmol) in EtOH containing 20% water. The reaction mixture was refluxed for 1 h and cooled to RT. The mixture was filtered through a pad of Celite and washed with methanol. The filtrate was concentrated and purified by flash chromatography (Biotage, 25 L) using a gradient elution from 100% CH_2Cl_2 to 15% MeOH/CH_2Cl_2 to give 7.45 g of 2-amino-6-bromopyridin-3-ol as an orange solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 6.77 (d, 1H, J = 7.9 Hz), 6.60 (d, 1H, J = 7.9 Hz).

Step 3. The free base of the title compound was prepared from 2-amino-6-bromopyridin-3-ol by the methods described for the preparation of **10**: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.53 (d, 1H, J = 7.9 Hz), 7.16 (d, 1H, J = 7.9 Hz), 4.48−4.56 (m, 1H), 3.97−4.05 (m, 2H), 3.00−3.19 (m, 6H), 2.14−2.27 (m, 2H), 1.85−1.98 (m, 2H); LCMS *m/z* 323.1, 325.1 (M + 1).

2-(5-Ethyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (35). The free base of the title compound was synthesized from 2-(5-bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo-[3.2.2]nonane **3a** following the method described for the preparation of **21** in 43% overall yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.53 (d, 1H, J = 8.3 Hz), 6.88 (d, 1H, J = 7.9 Hz), 4.51−4.57 (m, 1H), 3.99−4.05 (m, 2H), 3.00−3.18 (m, 6H), 2.77 (q, 2H, J = 7.5 Hz), 2.15−2.27 (m, 2H), 1.85−1.97 (m, 2H), 1.25−1.31 (t, 3H, J = 7.5 Hz); LCMS *m/z* 273.3 (M + 1).

2-(5-Isopropyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (36). 2-(5-Bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane **3a** (800 mg, 0.62 mmol), isopropylmagnesium chloride (2 M solution in THF, 928 μL, 1.85 mmol), Pd(dppf)Cl_2 (50 mg, 0.06 mmol), and zinc chloride (solution in THF, 3.7 mL, 1.85 mmol) were dissolved in THF, sealed in a microwave reactor tube, and heated at 170 °C for 10 min in a microwave reactor. The mixture was diluted with 1 N NaOH (20 mL) and CH_2Cl_2 (20 mL). The layers were partitioned, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by chromatography using a gradient elution from 100% CH_2Cl_2 to 7% MeOH in CH_2Cl_2 to give a brown oil. The brown oil was dissolved in a minimum amount of methanol, followed by addition of 1 N HCl in Et_2O. The mixture was triturated with ether and filtered to give 83 mg (37%) of the HCl salt of the title compound as a beige solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.17 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 4.30−4.45 (m, 2H), 3.71−3.77 (m, 2H), 3.57−3.67 (m, 4H), 3.20−3.30 (m, 2H), 2.41−2.58 (m, 2H), 2.26−2.40 (m, 2H), 1.42 (d, J = 7.1 Hz, 6H); MS (APCI) *m/z* 287.3 (M + 1).

2-(5-Cyclopentyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo-[3.2.2]nonane (37). The HCl salt of the title compound was prepared from cyclopentylmagnesium chloride by the methods described for the preparation of **36** in 37% yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.15 (d, 1H, J = 8.3 Hz), 7.33 (d, 1H, J = 7.9 Hz), 4.27−4.46 (m, 2H), 3.70−3.77 (m, 2H), 3.58−3.66 (m, 4H), 3.20−3.30 (m, 2H), 2.41−2.56 (m, 2H), 2.28−2.40 (m, 2H), 2.19−2.28 (m, 2H), 1.87−1.98 (m, 2H), 1.73−1.86 (m, 4H); MS (APCI) *m/z* 313.3 (M + 1).

2-(5-Phenyloxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (38). $Pd(PPh_3)_4$ (43 mg, 0.04 mmol), Na_2CO_3 (197.4 mg, 1.86 mmol), and phenylboronic acid (1.36 mg, 1.1 mmol) were added to a solution of 2-(5-bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane **3a** (300 mg, 0.93 mmol) in toluene. The reaction mixture was heated at reflux overnight. Upon cooling to RT, the mixture was diluted with CH_2Cl_2 and extracted with saturated Na_2CO_3 solution, dried (Na_2SO_4), and concentrated to give a brown oil. The oil was purified by flash chromatography using a gradient elution from 100% CH_2Cl_2 to 7% MeOH in CH_2Cl_2 and converted to HCl salt to give 80 mg (22% yield) of the title compound: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.28 (d, 1H, J = 8.3 Hz), 7.80−7.86 (m, 2H), 7.61−7.69 (m, 4H), 4.36−4.44 (m, 2H), 3.73−3.79 (m, 2H), 3.60−3.67 (m, 5H), 2.44−2.59 (m, 2H), 2.29−2.42 (m, 2H); LCMS *m/z* 321.2 (M + 1).

2-(5-(2-Fluorophenyl)oxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane (39). The HCl salt of the title compound was prepared from 2-fluorophenylboronic acid by the methods described for the preparation of **38** in 32% yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.24 (d, 1H, J = 7.9 Hz), 7.70−7.76 (m, 1H), 7.61−7.69 (m, 1H), 7.58 (d, 1H, J = 8.3 Hz), 7.34−7.46 (m, 2H), 4.91−4.97 (m, 1H), 4.36−4.43 (m, 2H), 3.75 (t, 2H, J = 5.6 Hz), 3.63 (t, 4H, J = 7.9 Hz), 2.44−2.57 (m, 2H), 2.29−2.41 (m, 2H); MS (APCI) *m/z* 339.3 (M + 1).

2-(5-Methoxyoxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (40). 2-(5-Bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane **3a** (100 mg, 0.31 mmol), CuI (5.9 mg, 0.031 mmol), 1,10-phenanthrene (11.1 mg, 0.06 mmol), and

Cs_2CO_3 (141 mg, 0.43 mmol) were dissolved in MeOH (1 mL), sealed in a tube, and heated at 120 °C for 3 h. The mixture was diluted with CH_2Cl_2/*i*-PrOH (3:1) and extracted with saturated NH_4Cl solution. The organic extract was dried (Na_2SO_4), concentrated, and purified by HPLC to afford 39.4 mg (46%) of the title compound as a solid. The hydrochloride salt was prepared by addition of 2 equiv of 4.0 N HCl in dioxane: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.52 (d, 1H, J = 8.3 Hz), 6.35 (d, 1H, J = 8.7 Hz), 4.40−4.49 (m, 1H), 3.95 (t, 2H, J = 5.8 Hz), 3.86 (s, 3H), 2.96−3.14 (m, 6H), 2.10−2.23 (m, 2H), 1.80−1.93 (m, 2H); LCMS m/z 275.2 (M + 1).

2-(5-Phenoxyoxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]-nonane (41). 2-(5-Bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane **3a** (100 mg, 0.31 mmol), CuCl (15.3 mg, 0.155 mmol), phenol (58 mg, 0.62 mmol), tetramethylheptane 3,5-dione (34 mg), and Cs_2CO_3 (201 mg, 0.62 mmol) were dissolved in NMP (2 mL), sealed in a tube, and heated at 120 °C for 4 h. The mixture was cooled to RT and filtered through a pad of Celite. The filtrate was concentrated to give an oil. The oil was diluted with CH_2Cl_2/*i*-PrOH (3:1) and washed with water/brine. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative HPLC to give 34 mg (32%) of the title compound. The hydrochloride salt was prepared by addition of 2 equiv of 4.0 N HCl in dioxane: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.77 (d, 1H, J = 8.7 Hz), 7.37−7.44 (m, 2H), 7.17−7.23 (m, 1H), 7.10 (d, 2H, J = 7.5 Hz), 6.59 (d, 1H, J = 8.7 Hz), 4.72−4.78 (m, 1H), 4.19−4.27 (m, 2H), 3.64−3.70 (m, 2H), 3.54−3.62 (m, 3H), 3.24−3.28 (m, 1H), 2.38−2.50 (m, 2H), 2.19−2.31 (m, 2H); LCMS m/z 337.2 (M + 1)).

2-(5-(Piperidin-1-yl)oxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo-[3.2.2]nonane (42). 2-(5-Bromooxazolo[4,5-*b*]pyridin-2-yl)-2,5-diazabicyclo[3.2.2]nonane **3a** (250 mg, 0.77 mmol), piperidine (91.4 mL, 0.92 mmol), $Pd(OAc)_2$ (6.9 mg, 0.03 mmol), BINAP (20.3 mg, 0.03 mmol), NaO*t*-Bu (103.6 mg, 1.1 mmol) were dissolved in toluene (4 mL) and heated at 100 °C overnight. The mixture was cooled to RT, filtered through a pad of Celite, concentrated, and purified by flash chromatography (Biotage, 12 L) using a gradient elution from 100% CH_2Cl_2 to 7% MeOH in CH_2Cl_2 to give 82 mg (32%) of the title compound as a white solid. The hydrochloride salt was prepared by addition of 2 equiv of 4.0 N HCl in dioxane: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.93−7.99 (m, 1H), 6.92−7.02 (m, 1H), 4.78−4.84 (m, 1H), 4.25−4.33 (m, 2H), 3.68−3.74 (m, 2H), 3.56−3.65 (m, 8H), 2.39−2.53 (m, 2H), 2.23−2.35 (m, 2H), 1.82−1.95 (m, 4H), 1.74−1.83 (m, 2H); MS (APCI) m/z 328.3 (M + 1).

2-(1,4-Diazabicyclo[3.2.2]nonan-4-yl)-5-(pyrrolidin-1-yl)oxazolo-[4,5-*b*]pyridine (43). The HCl salt of the title compound was prepared from pyrrolidine by the methods described for the preparation of **42** in 53% yield: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (d, 1H, J = 8.1 Hz), 6.40 (d, 1H, J = 8.3 Hz), 4.78 (m, 1H), 4.23 (m. 2H), 3.64 (m, 2H), 3.56 (m, 8H), 2.40 (m, 2H), 2.25 (m, 2H), 2.10 (m, 4H); MS (APCI) m/z 314.2 (M + 1).

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