Synthesis and Structure−Activity Relationship Studies of 3,6-Diazabicyclo[3.2.0]heptanes as Novel α4β2 Nicotinic Acetylcholine Receptor Selective Agonists

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A series of novel, potent neuronal nicotinic acetylcholine receptor (nAChR) ligands derived from 3,6-diazabicyclo[3.2.0]heptane have been synthesized and evaluated for binding affinity and agonist activity at the α4β2 nAChR subtype. Structure−activity relationship studies of these novel nAChR ligands focused on substitution effects on the pyridine ring, as well as stereo- and regiochemical influences of the 3,6-diazabicyclo[3.2.0]heptane core. Small 5-substituents on the pyridine ring had a modest impact on the binding affinities and functional activities. 6-Bromo, 6-chloro, and 6-methyl substituents on the pyridine ring led to increased binding affinities and improved functional activities. Most of the 6-*N*-pyridinyl-substituted 3,6-diazabicyclo[3.2.0]heptanes are selective for the α4β2 nAChR subtype. Compounds (1*R*,5*S*)-**25**, (1*R*,5*S*)-**55**, and (1*R*,5*S*)-**56** were virtually inactive as agonists at the hα3β4 nAChR but retained potency and efficacy at the hα4β2 nAChR subtype. 3-*N*-Pyridinyl-substituted series demonstrated more complex SAR. (1*R*,5*R*)-**39**, (1*R*,5*R*)-**41**, and (1*R*,5*R*)-**42** were found to be much more potent at the hα3β4 nAChR subtype, whereas (1*R*,5*R*)-**38** and (1*R*,5*R*)-**40** were very selective at the hα4β2 nAChR subtype. The SAR studies of these novel ligands led to the discovery of several compounds with interesting *in vitro* pharmacological profiles.

Introduction

Commonly prescribed analgesic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids,[1] have safety concerns, as well as unpleasant side effects.[2] To satisfy significant unmet medical need and achieve optimal analgesic efficacy without undesirable side effects, the search for novel and efficacious analgesics with improved therapeutic window continues to receive considerable attention.[3] Among a number of novel approaches to pain relief currently under investigation, nicotinic acetylcholine receptors (nAChRs) hold considerable potential as therapeutic targets for the development of analgesic drugs.[4] nAChRs are pentameric ligand-gated ion channel proteins that are widely expressed throughout the central and peripheral nervous systems (CNS and PNS). nAChRs are derived from multiple α (α2-α10) and β (β2-β4) subunit genes. Each distinct subunit gene composition defines a certain nAChR subtype with characteristic pharmacological and biophysical properties.[5] Accordingly, drug discovery efforts have been focused on the development of subtype-selective nAChR ligands for the potential treatment of Alzheimer's disease (AD), Parkinson's disease, Tourette's syndrome, schizophrenia, depression, and pain.[6] Of particular interest is the α4β2 receptor subtype, a major target involved in the analgesic response elicited by nAChR agonists.[7] On the other hand, the α3β4 nAChR subtype that predominates in the autonomic ganglia and mediates the systemic release of multiple neurotransmitters is correlated to adverse events.[8] Consequently, the discovery of potent α4β2 nAChR subtype selective (vs α3β4) agonists has been critical for the advancement of novel nAChR-based analgesics with improved safety profiles.[4b]

Despite the mild analgesic effects of nicotine (**1**) (Scheme 1) reported decades ago,[9] the potential of nAChR ligands as pain relievers was not appreciated until the early 1990s when epibatidine (**2**), a novel nAChR agonist isolated from the skin of a poisonous Ecuadorian tree frog, demonstrated potent analgesic effects,[10] surpassing even opioids such as morphine (**3**).[8,11] Epibatidine demonstrates poor binding selectivity among nAChR subtypes (especially α4β2 vs α3β4 nAChR),[12] and its toxicity profile is unacceptable for clinical use.[13] In the search for nAChR analgesics with an improved therapeutic window, the structural diversity of nAChR ligands, primarily comprising series of nicotine and epibatidine analogues, has been extensively studied over the past decade with a focus on the identification of α4β2 nAChR subtype selective agonists.[4b] For an example, tebanicline (**4**), a potent nAChR agonist with moderate enhancement of α4β2 (vs α3β4) nAChR subtype selectivity as compared to **2**, demonstrated analgesic effects across a broad range of preclinical models of nociceptive and neuropathic pain.[14] However, tebanicline exhibited only a modest therapeutic window and showed dose-limiting gastrointestinal side effects. To identify novel nAChR agonists with superior α4β2 nAChR subtype selectivity and with reduced adverse effects, our ongoing efforts focused on novel nAChR pharmacophores and their structure−activity relationships (SARs) for further exploration of analgesic agents with clinical potential.

A few pharmacophore models for α4β2 nAChR ligands have been proposed to integrate binding interactions of nAChR ligands.[15] However, these are generally not useful for novel ligand design.[15b] According to Beers and Reich's early hypothesis,[15f] nicotinic agonists require a Columbic interaction involving the cationic center and a hydrogen bond acceptor feature that interacts with a receptor-based hydrogen bond donor site. Glennon et al. suggested an improved vector pharmacophore model stating that the spatial relationship between these two pharmacophoric elements is very important for ligand binding affinities toward α4β2 nAChR.[15c] From structural analysis of various nAChR ligands developed during the past decade, one simple conclusion is that most of the nAChR ligands

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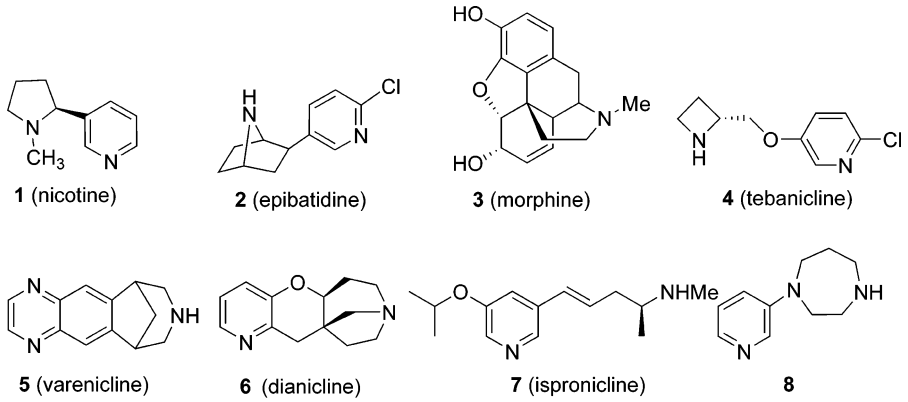
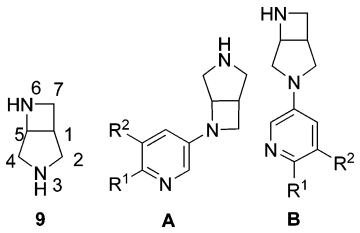
Scheme 1



Scheme 2



are generally composed of an sp^3 nitrogen atom, a heteroaryl group possibly containing an sp^2 nitrogen atom, and a linker that connects the sp^3 nitrogen atom to the heteroaryl group. The linkers play an important role by determining the internitrogen ($N^{sp^3}-N^{sp^2}$) distance and orientation in the ligand's binding conformation. The structural motif of many unique linkers often is constructed with a rigidified skeleton of $N^{sp^3}-(C)_n-X-$, wherein $-(C)_n-X-$ can be a simple −C− (nicotine **1**), −CC− (epibatidine **2**,[10] varenicline **5**[16]), −CCC− (dianicline, **6**[17]), −CCCC− (ispronicline **7**[18]), −CCO− (tebanicline **4**),[14] and −CCN− (**8**).[19] With regards to the ligands with the −NCCN− motif, compound **8** shows potent binding affinity ([^{3}H]cytisine, $IC_{50} = 1.9$ nM)[19b] but holds a relatively flexible homopiperazine linker, which provides the ligand with multiple conformational possibilities varying the internitrogen ($N^{sp^3}-N^{sp^2}$) distance and orientation. To gain more insight into the SAR of ligands with the −NCCN− motif, we proposed that a rigidified −NCCN− motif linker, such as 3,6-diazabicyclo[3.2.0]heptane (**9**), should reduce the conformational complexity of ligands and might lead to novel $\alpha4\beta2$ nAChR agonists with enhanced subtype selectivity. This paper describes the chiral synthesis and pharmacological profiles of 3,6-diazabicyclo[3.2.0]heptane-derived pyridine analogues **A** (6-*N*-pyridinyl-substituted series) and **B** (3-*N*-pyridinyl-substituted series) (Scheme 2).

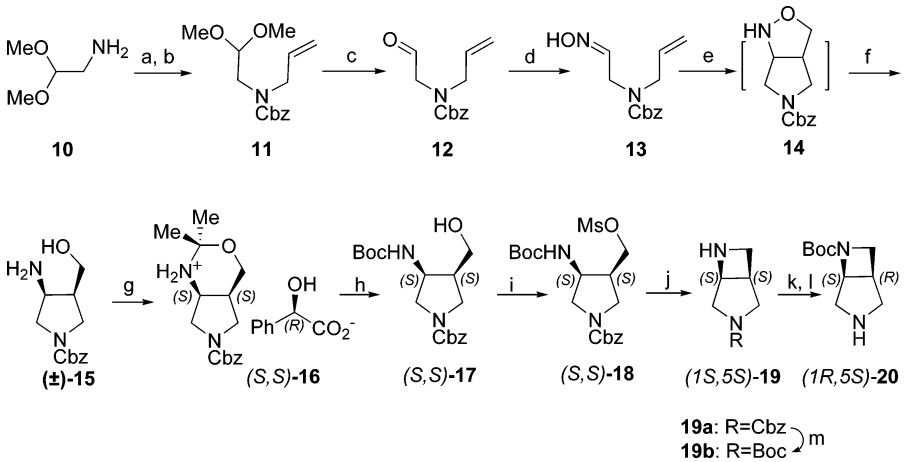
Results and Discussion

Chemistry. Scheme 3 outlines the chiral synthesis of intermediates (1*S*,5*S*)-**19** and (1*R*,5*S*)-**20**.[20] Oxime **13** was synthesized through a convenient process[21] including the *N*-Cbz protection of 2,2-dimethoxyethylamine (**10**) and the subsequent *N*-allylation to offer dimethyl acetal **11**, hydrolysis of **11** to produce aldehyde **12**, and oxime formation with hydroxyamine. Intramolecular 1,3-dipolar cycloaddition of oxime **13** afforded the racemic intermediate isoxazolidine (±)-**14**, which was then converted to (*cis*)-3-amino-4-(hydroxymethyl)pyrrolidine (±)-**15** by reductive cleavage of the N−O bond in (±)-**14** using Zn/HOAc. To minimize the facile air oxidation of **14** to isoxazoline[22] impurities as often detected by LC/MS, cyclization of **13** and reduction of **14** were carried out in a single pot providing (±)-**15** in an overall 90% yield. The optimized six-step process from **10** to (±)-**15** required neither distillation nor chromatographic purification.

Resolution of (±)-**15** with (*R*)-mandelic acid was then investigated. According to the procedure reported by Ohta,[23] amino alcohol (±)-**15** was initially treated with (*R*)-mandelic acid in cyclohexanone at −20 °C for 48 h. The reaction consistently gave enantiomerically enriched salt in 35−44% yield with maximal 94% ee. Replacing cyclohexanone with anhydrous acetone under identical conditions gave (*S*,*S*)-**16** with excellent enantioselectivity (>98% ee) but with much lower chemical yield (<10%). After additional optimization, the recovery of (*S*,*S*)-**16** was improved to 44% (>98% ee) by simply pretreating (±)-**15** with 2-methoxypropene. This modification also allows the chiral resolution to proceed at ambient temperature without sacrificing optical purity or chemical yield. The enantiomeric excess was determined by chiral high-performance liquid chromatography (HPLC) assay of the corresponding amino-alcohol intermediate (3*S*,4*S*)-**17**. The latter was easily obtained by acidic hydrolysis of salt (*S*,*S*)-**16**, followed by treatment with Boc_2O under basic conditions. Although the role of 2-methoxypropene in the reaction is not very clear at the present time, the formation of the fused 1,3-oxazinane that is actually resolved through chiral salt (*S*,*S*)-**16** was accelerated. The best resolution condition involved premixing 2 equiv of 2-methoxypropene with (±)-**15** for 1.0 h followed by treatment with 1 equiv of (*R*)-mandelic acid in anhydrous acetone at ambient temperature for 48 h. Crystalline (*S*,*S*)-**16** was isolated in 44% yield (vs maximal 50%) with over 98% enantiomeric excess. The crystallization of (*S*,*S*)-**16** also served as the first purification in the seven-step sequence from **10**.

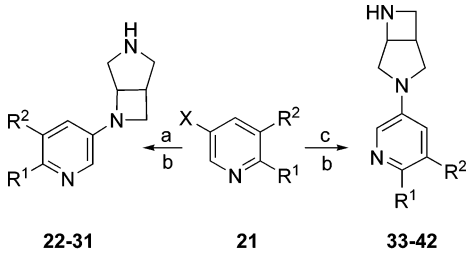
(*S*,*S*)-**16** was hydrolyzed with aqueous H_2SO_4, then basified to pH 10, and treated with di-*tert*-butyldicarbonate to give (3*S*,4*S*)-**17** in excellent chemical yield. The reaction of (3*S*,4*S*)-**17** with methanesulfonyl chloride gave mesylate (3*S*,4*S*)-**18**, which was smoothly transformed to (1*S*,5*S*)-**19a** (R = Cbz) by removal of the *N*-Boc-protecting group under acidic conditions, followed by basification to liberate the nucleophilic amine. The five-step process from (*S*,*S*)-**16** to (1*S*,5*S*)-**19a** did not require chromatographic purification and gave (1*S*,5*S*)-**19a** in 90% overall yield. (1*S*,5*S*)-**19a** was transformed to (1*R*,5*S*)-**20** by initial 6-*N*-Boc protection of (1*S*,5*S*)-**19a** with di-*tert*-butyldicarbonate and then *N*-Cbz deprotection under catalytic hydrogenation conditions with Pd/C. (1*S*,5*S*)-**19a** was also converted to (1*R*,5*S*)-**19b** (R = Boc) through a sequence involving 6-*N*-CF_3CO protection of (1*S*,5*S*)-**19a** with $(CF_3CO)_2O$, a swap of 3-*N*-Cbz for the 3-*N*-Boc-protecting group under catalytic hydrogenation conditions with Pd/C, and last the deprotection of azetidine nitrogen with K_2CO_3 in MeOH. The opposite

Scheme 3. Synthesis of Optically Pure 3,6-Diazabicyclo[3.2.0]heptane[a]



[a] Reagents and conditions: (a) CbzCl, NaOH (aqueous), toluene, r.t., 4 h, 91%. (b) Allyl-Br, KOH, $Et_3BnN^+Cl^-$, r.t., 14 h, 96%. (c) HCO_2H, r.t., 15 h, 99%. (d) $HONH_2$·HCl, NaOAc, MeCN, r.t., 20 h, 98%. (e) Xylene, 130 °C, 10 h. (f) Zn/HOAc, r.t., 3 h, 90%. (g) (1) 2-Methoxypropene, acetone, r.t., 1 h; (2) (*R*)-mandelic acid, r.t., 48 h, 44% yield, >98% ee. (h) (1) H_2SO_4 (aqueous), EtOH, r.t., 16 h; (2) NaOH (aqueous), Boc_2O, 65 °C, 4 h, 98%. (i) MsCl, Et_3N, CH_2Cl_2, −10 °C, 0.5 h, 97%. (j) (1) CF_3CO_2H, CH_2Cl_2, 0−20 °C, 1 h; (2) NaOH (aqueous), EtOH, pH=10, 60 °C, 10 h, 95%. (k) Boc_2O, CH_2Cl_2, Et_3N, r.t., 10 h, 95%. (l) Pd/C, H_2, EtOH, r.t. 4 h, 89%. (m) (1) $(CF_3CO)_2O$, Et_3N, THF, −20 to 0 °C, 4 h, 96%; (2) Pd/C, H_2, Boc_2O, MeOH, r.t., 10 h, 82%; (3) K_2CO_3, MeOH, 65 °C, 1 h, 80%.

Scheme 4. Synthesis of Pyridine-Substituted 3,6-Diazabicyclo[3.2.0]heptanes[a]



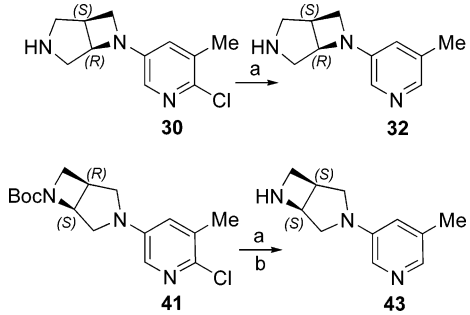
22	X=Br	R^1=H	R^2=H	**33**
23	X=Br	R^1=H	R^2=Br	**34**
24	X=Br	R^1=H	R^2=Cl	**35**
25	X=Br	R^1=H	R^2=CN	**36**
26	X=Br	R^1=H	R^2=OMe	**37**
27	X=Br	R^1=Me	R^2=Me	**38**
28	X=Br	R^1=Me	R^2=CN	**39**
29	X=Br	R^1=Cl	R^2=H	**40**
30	X=Br	R^1=Cl	R^2=Me	**41**
31	X=Br or I	R^1=Cl	R^2=Cl	**42**

[a] Reagents and conditions: (a) Compound **19a** (1.0 equiv), **21** (1.5 equiv), $Pd_2(dba)_3$ (0.02 equiv), *rac*-BINAP or xantphos (0.06 equiv), ^{t}BuONa or Cs_2CO_3 (1.5 equiv) in toluene (0.2 M), at 100−110 °C, 10−40 h. (b) CF_3CO_2H, or TsOH, or Pd/C−H_2. (c) Compound **20** (1.0 equiv), **21** (1.5 equiv), $Pd_2(dba)_3$ (0.02 equiv), *rac*-BINAP or xantphos (0.06 equiv), ^{t}BuONa or Cs_2CO_3 (1.5 equiv) (1.5 equiv) in toluene (0.2 M), at 100−110 °C, 10−40 h.

enantiomers, (1*R*,5*R*)-**19** and (1*S*,5*R*)-**20**, were obtained by resolution of (±)-**15** with (*S*)-mandelic acid and using the same sequence described above.

Scheme 4 outlines the synthesis of 3,6-diazabicyclo[3.2.0]-heptanyl pyridine analogues **22**−**31** and **33**−**42**. Monoprotected 3,6-diazabicyclo[3.2.0]heptanes **19a** or **20** were condensed with halopyridines **21** via a palladium-mediated procedure initially developed by Buchwald and Hartwig.[24] The Buchwald and Hartwig amination of numerous pyridines **21** with a variety of 5- and/or 6-substitutents, including bromo, chloro, cyano, methoxy, and methyl, proceeded smoothly and provided the corresponding coupling products with moderate-to-excellent chemical yield (40−95%). The protecting groups of the coupling products were then removed under acidic conditions (CF_3CO_2H for the removal of *N*-Boc or *N*-Cbz groups) or catalytic

Scheme 5[a]



[a] Reagents and conditions: (a) Pd/C, H_2, EtOH, r.t., 10 h, >87%. (b) CF_3CO_2H, CH_2Cl_2, r.t., 1 h, 85%.

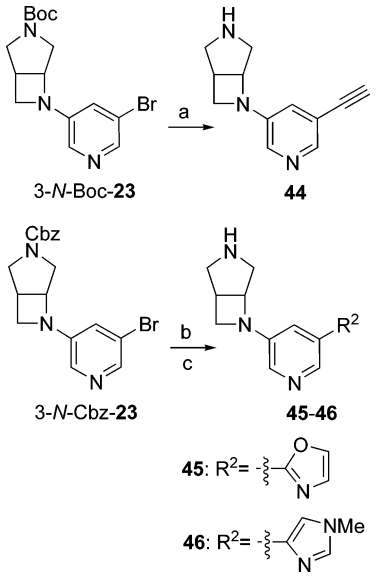
hydrogenation conditions (Pd/C−H_2 for the deprotection of *N*-Cbz group). 5-Methyl-substituted analogues **32** and **43** can be prepared through a convenient palladium-mediated hydrogenation of **30** and **41**, respectively (Scheme 5).

Scheme 6 illustrates the further transformation of the Buchwald−Hartwig coupling products 3-*N*-Boc-**23** and 3-*N*-Cbz-**23**. Under standard Sonogashira reaction conditions,[25] reaction of 3-*N*-Boc-**23** with ethynyltrimethylsilane, followed by the deprotection of trimethylsilyl and *N*-Boc groups, provided **44**. Under typical Stille coupling conditions,[26] reaction of 3-*N*-Cbz-**23** with 2-(tributylstannyl)oxazole or 1-methyl-4-(tributylstannyl)imidazole installed oxazole or imidazole groups on the 5-position, leading to **45** and **46**.

Several of the Buchwald−Hartwig coupling products (Scheme 7) could be further elaborated with a 6-bromo substituent by the reaction with NBS in MeCN to provide compounds **47**−**49** and **51**−**54**. The directive effect of the 3-amino group dominates, so that bromination at the 6-position was the major product regardless of the 5-substitutents. Minor amounts of 2-bromo and 2,6-dibromo byproducts were observed in some cases. These could be minimized by control of reaction temperature, amount, and rate of addition of NBS. These byproducts were easily removed by chromatography. Compound **50** was prepared by the reaction of 3-*N*-Boc-**48** with urea·H_2O_2 and the deprotection of the *N*-Boc group with CF_3CO_2H in CH_2Cl_2.

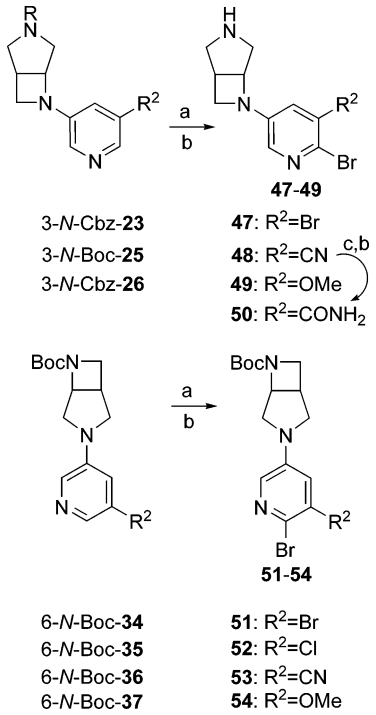
Scheme 8 outlines the further transformation of (1*S*,5*S*)-*tert*-butyl 6-(5-cyanopyridin-3-yl)-3,6-diazabicyclo[3.2.0]heptane-

Scheme 6. Transformation of 5-Bromopyridines[a]



[a] Reagents and conditions: (a) (1) TMSC≡CH (2.5 equiv), $PdCl_2(PPh_3)_2$, (0.02 equiv), CuI (0.1 equiv), Et_3N, DMF, 70 °C, 10 h, >60%; (2) $Bu_4N^+F^-$, THF, r.t., 1 h; (3) CF_3CO_2H, CH_2Cl_2, r.t., 2 h, 94%. (b) R^2SnBu_3 (2.0 equiv), $PdCl_2(PPh_3)_2$, (0.02 equiv), MeCN, 80 °C, 6 h, 99%. (c) Pd/C, H_2, EtOH, r.t., 2 h, >60%.

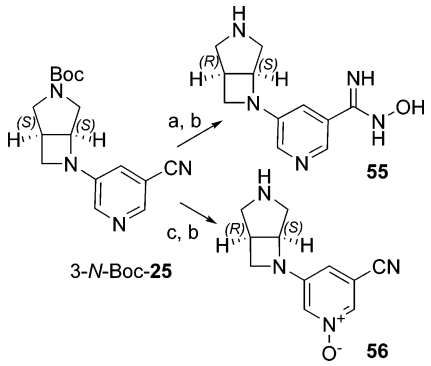
Scheme 7. Preparation of 6-Bromopyridin-3-yl-Substituted 3,6-Diazabicyclo[3.2.0]heptanes[a]



[a] Reagents and conditions: (a) NBS (1.0 equiv), MeCN, −20 to 20 °C, 0.5−1 h. (b) For deprotection of *N*-Boc group: CF_3CO_2H, CH_2Cl_2, r.t., 1 h; for deprotection of *N*-Cbz group: CF_3CO_2H, 65 °C, 1 h. (c) 3-*N*-Boc **48** (1.0 equiv), urea·H_2O_2 (10.1 equiv), K_2CO_3 (0.1 equiv), acetone−water, r.t., 10 h, 51%.

3-carboxylate (3-*N*-Boc-**25**). The reaction of (1*S*,5*S*)-3-*N*-Boc-**25** with hydroxylamine gave *N*-hydroxynicotinimidamide, and the deprotection of *N*-Boc with CF_3CO_2H provided 5-[(1*R*,5*S*)-3,6-diazabicyclo[3.2.0]heptan-6-yl]-*N*-hydroxynicotinimidamide **55**. Oxidation of (1*S*,5*S*)-3-*N*-Boc-**25** with *m*-CPBA, followed by the deprotection of *N*-Boc group, afforded 3-[(1*R*,5*S*)-3,6-diazabicyclo[3.2.0]heptan-6-yl]-5-cyanopyridine 1-oxide **56**.

Scheme 8[a]



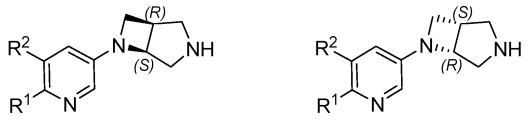
[a] Reagents and conditions: (a) NH_2OH·HCl, Et_3N, EtOH, r.t., 10 h, 76%. (b) CF_3CO_2H, CH_2Cl_2, r.t., 1 h. (c) *m*-CPBA (1.28 equiv), MeCN, r.t., 10 h, 97%.

Biology. The predominant receptor with high affinity for [^{3}H]nicotine and (−)-[^{3}H]cytisine in rodent brain is composed of α4 and β2 subunits.[27] As a primary screen, the binding affinities of ligands at nAChRs were determined by assessing their ability to compete with (−)-[^{3}H]cytisine in binding to rat brain membranes ($n \geq 3$).[28] In addition to (−)-[^{3}H]cytisine binding, fluorometric imaging plate reader (FLIPR) cellular assays[29] using recombinant human receptors were employed to evaluate the functional activities and subtype nAChR selectivity in all lines expressing recombinant human receptors.[30] Serial log dilutions of test compound were applied, and the corresponding changes in intracellular calcium were assessed. Data were normalized to the response evoked by 100 μM nicotine, and EC_{50} and maximal efficacy values were determined.

Exploration of SARs for the 3,6-diazabicyclo[3.2.0]heptane was focused on 6-*N*- and 3-*N*-pyridin-3-yl-substituted 3,6-diazabicyclo[3.2.0]heptanes (structures **A** and **B**, Scheme 2), especially on the extensive variations of substitutions on the 5- and/or 6-positions of pyridine ring. The results are shown in Tables 1 and 2. Typically, only those nAChR ligands with high affinity (K_i < 50 nM) were selected for functional evaluation. In functional assays, compounds with EC_{50} > 100 μM or less than 20% maximal peak response were generally considered to be weak or partial agonists. Comparison of EC_{50} and efficacy at recombinant hα4β2 and hα3β4 nAChR subtypes provides an estimate of nAChR subtype selectivity. Ideally, selective hα4β2 nAChR agonists should give high efficacy and potency at hα4β2 but not at hα3β4 nAChRs. As noted earlier, compounds with optimal subtype selectivity (hα4β2 vs hα3β4) hold the potential for achieving analgesic efficacy with a low incidence of undesired side effects.

Examination of the (−)-[^{3}H]cytisine binding indicated that most of the 6-*N*-substituted 3,6-diazabicyclo[3.2.0]heptanes (structure **A**) demonstrated comparable binding affinities (0.2−29 nM) to (*S*)-nicotine **1** (0.96 nM) and much weaker than epibatidine **2** (0.05 nM) (Table 1). Small substituents on the 5-position of the pyridine ring, such as hydrogen (**22**), bromo (**23**), chloro (**24**), nitrile (**25**), methoxy (**26**), methyl (**32**), and ethynyl (**44**), had little impact on binding affinities (K_i = 0.6−7.2 nM) (Table 1). On the other hand, placement of oxazol-2-yl and 1-methyl-imidazol-4-yl on 5-position (**45** and **46**, respectively) diminished binding affinities 15−20-fold (**45** and **46** vs **22**, Table 1). 6-Chloro analogue **29** exhibited comparable binding affinities to **22**. With regards to 5,6-disubstituted pyridin-3-yl analogues, 6-halo (chloro or bromo) substituents boost binding affinities 4−15-fold, as exemplified by compounds with a 6-chloro substitutent, (1*R*,5*S*)-**31** (K_i = 0.3 nM) vs (1*R*,5*S*)-**24** (K_i = 3.0 nM) and (1*R*,5*S*)-**30** (K_i = 0.2 nM) vs (1*R*,5*S*)-**32** (K_i = 1.1 nM), as well as compounds with a 6-bromo substitutent, (1*R*,5*S*)-**47** (K_i = 0.5 nM) vs (1*R*,5*S*)-**23** (K_i = 3.1

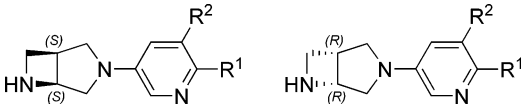
Table 1. Binding and Functional Activity of 6-*N*-Substituted 3,6-Diazabicyclo[3.2.0]heptanes



			Ca^{2+} Flux (FLIPR)							
			[^{3}H]-cytisine binding		hα4β2			hα3β4		
Compd.	R^1	R^2	pK_i ± SEM	K_i[a] (nM)	pEC_{50} ± SEM	EC_{50}[b] (μM)	Max (%)[c]	pEC_{50} ± SEM	EC_{50}[b] (μM)	Max (%)[c]
1			9.03 ± 0.31	1.0	5.18 ± 0.06	6.6	101 ± 3	5.10 ± 0.04	8.0	89 ± 3
2			10.33 ± 0.13	0.05	7.27 ± 0.04	0.05	133 ± 13	7.92 ± 0.07	0.01	103 ± 15
(*1R,5S*)-**22**	H	H	8.88 ± 0.02	1.3	5.74 ± 0.06	1.9	116 ± 6	4.53 ± 0.02	29.4	62 ± 11
(*1S,5R*)-**22**	H	H	9.15 ± 0.01	0.7	5.57 ± 0.05	2.8	101 ± 3	5.01 ± 0.03	9.7	97 ± 3
(*1R,5S*)-**23**	H	Br	8.51 ± 0.08	3.1	5.39 ± 0.08	4.4	31 ± 2	nc[d]	nc[d]	< 10
(*1S,5R*)-**23**	H	Br	8.83 ± 0.06	1.5	5.06 ± 0.36	11.4	20 ± 2	5.51 ± 0.43	6.6	23 ± 1
(*1R,5S*)-**24**	H	Cl	8.53 ± 0.04	3.0	5.14 ± 0.10	8.1	88 ± 6	4.64 ± 0.02	23.0	81 ± 2
(*1R,5S*)-**25**	H	CN	8.50 ± 0.17	3.2	5.29 ± 0.10	5.9	65 ± 0	nc[d]	nc[d]	16 ± 2
(*1S,5R*)-**25**	H	CN	9.07 ± 0.05	0.9	5.04 ± 0.34	11.4	34 ± 0	4.91 ± 0.15	13.7	47 ± 8
(*1R,5S*)-**26**	H	OMe	9.12 ± 0.02	0.8	5.47 ± 0.06	3.6	90 ± 8	4.60 ± 0.04	25.8	72 ± 3
(*1S,5R*)-**26**	H	OMe	8.14 ± 0.09	7.2	4.64 ± 0.19	24.7	43 ± 3	4.51 ± 0.02	31.2	64 ± 2
(*1R,5S*)-**27**	Me	Me	8.10 ± 0.03	8.0	5.69 ± 0.02	2.1	85 ± 1	5.38 ± 0.03	4.2	86 ± 3
(*1S,5R*)-**27**	Me	Me	8.51 ± 0.04	3.1	5.83 ± 0.01	1.5	83 ± 1	4.92 ± 0.03	12.3	78 ± 3
(*1R,5S*)-**28**	Me	CN	8.95 ± 0.03	1.1	5.42 ± 0.06	3.9	128 ± 13	5.68 ± 0.03	2.1	96 ± 2
(*1S,5R*)-**28**	Me	CN	9.18 ± 0.04	0.7	6.30 ± 0.07	0.5	116 ± 7	5.80 ± 0.01	1.6	95 ± 3
(*1R,5S*)-**29**	Cl	H	8.91 ± 0.05	1.2	6.27 ± 0.04	0.6	127 ± 6	5.95 ± 0.01	1.1	104 ± 3
(*1S,5R*)-**29**	Cl	H	8.90 ± 0.05	1.3	6.49 ± 0.05	0.3	107 ± 4	5.92 ± 0.02	1.2	94 ± 3
(*1R,5S*)-**30**	Cl	Me	9.70 ± 0.02	0.2	6.64 ± 0.05	0.2	133 ± 8	6.22 ± 0.03	0.6	97 ± 3
(*1S,5R*)-**30**	Cl	Me	9.70 ± 0.14	0.2	6.21 ± 0.07	0.6	134 ± 5	5.66 ± 0.02	2.2	89 ± 2
(*1R,5S*)-**31**	Cl	Cl	9.55 ± 0.08	0.3	6.58 ± 0.05	0.3	117 ± 10	6.00 ± 0.03	1.0	92 ± 3
(*1S,5R*)-**31**	Cl	Cl	8.93 ± 0.33	1.2	6.04 ± 0.02	0.9	110 ± 6	5.58 ± 0.01	2.6	87 ± 2
(*1S,5R*)-**32**	H	Me	8.94 ± 0.16	1.1	5.00 ± 0.05	10.4	68 ± 5	4.77 ± 0.02	16.9	74 ± 3
(*1R,5S*)-**44**	H		8.63 ± 0.08	2.4	5.31 ± 0.28	13.4	77 ± 11	4.11 ± 0.08	86.9	57 ± 13
(*1S,5R*)-**44**	H		9.21 ± 0.06	0.6	4.87 ± 0.17	20.4	45 ± 0	4.48 ± 0.01	33.2	33 ± 3
(*1R,5S*)-**45**	H		7.69 ± 0.07	20.2	nc[d]	nc[d]	< 10	nc[d]	nc[d]	< 10
(*1R,5S*)-**46**	H		7.58 ± 0.11	26.4	nc[d]	nc[d]	< 10	nc[d]	nc[d]	< 10
(*1R,5S*)-**47**	Br	Br	9.35 ± 0.02	0.5	6.17 ± 0.04	6.9	131 ± 4	5.96 ± 0.02	1.1	94 ± 2
(*1R,5S*)-**48**	Br	CN	9.60 ± 0.08	0.3	6.49 ± 0.07	0.4	100 ± 4	5.71 ± 0.05	2.0	95 ± 12
(*1R,5S*)-**49**	Br	OMe	9.68 ± 0.13	0.2	6.07 ± 0.06	0.9	118 ± 4	5.74 ± 0.03	1.8	94 ± 2
(*1R,5S*)-**50**	Br	$CONH_2$	8.19 ± 0.10	6.5	5.95 ± 0.02	1.1	155 ± 3	4.68 ± 0.02	21.2	88 ± 4
(*1R,5S*)-**55**	H		7.54 ± 0.05	29.1	5.17 ± 0.06	7.2	76 ± 2	nc[d]	nc[d]	< 10
(*1R,5S*)-**56**			7.74 ± 0.08	18.6	5.34 ± 0.02	7.5	69 ± 8	nc[d]	nc[d]	< 10

[a] Displacement studies with [^{3}H]cytisine using rat brain homogenates. The K_i represents mean values obtained from independent experiments where $n \geq 3$. [b] Values represents mean potencies of compounds, as assessed by measuring fluorescence changes using FLIPR technology in HEK 293 cell lines expressing human α4β2 and α3β4 nAChRs. [c] Max values represent the maximal response of the ligand relative to the peak response for the positive control of 100 μM nicotine. [d] nc, EC_{50} not reliably calculable for agonists with a maximal response below 20%.

Table 2. Binding and Functional Activity of 3-*N*-Substituted 3,6-Diazabicyclo[3.2.0]heptanes



					Ca^{2+} flux (FLIPR)					
			[^{3}H]-cytisine binding		hα4β2			hα3β4		
compd	R^1	R^2	pK_i ± SEM	K_i[a] (nM)	pEC_{50} ± SEM	EC_{50}[b] (μM)	max (%)[c]	pEC_{50} ± SEM	EC_{50}[b] (μM)	max (%)[c]
(1*S*,5*S*)-**33**	H	H	8.92 ± 0.06	1.2	5.81 ± 0.04	1.6	122 ± 5	5.22 ± 0.02	6.1	90 ± 3
(1*R*,5*R*)-**33**	H	H	9.96 ± 0.02	0.1	6.53 ± 0.08	0.3	181 ± 14	6.22 ± 0.03	0.6	119 ± 4
(1*S*,5*S*)-**34**	H	Br	8.84 ± 0.04	1.4	5.21 ± 0.07	6.5	53 ± 5	5.04 ± 0.02	9.1	68 ± 2
(1*R*,5*R*)-**34**	H	Br	10.20 ± 0.10	0.1	5.97 ± 0.05	1.1	161 ± 6	6.62 ± 0.03	0.2	115 ± 4
(1*S*,5*S*)-**35**	H	Cl	8.72 ± 0.04	1.9	5.03 ± 0.02	11.4	66 ± 6	4.60 ± 0.03	25.3	57 ± 2
(1*S*,5*S*)-**36**	H	CN	8.77 ± 0.06	1.7	4.88 ± 0.08	14.6	102 ± 6	5.15 ± 0.03	7.1	84 ± 3
(1*R*,5*R*)-**36**	H	CN	9.92 ± 0.05	0.1	6.38 ± 0.17	0.6	123 ± 5	6.49 ± 0.02	0.3	102 ± 2
(1*S*,5*S*)-**37**	H	OMe	8.52 ± 0.06	3.0	4.88 ± 0.13	15.8	55 ± 5	4.33 ± 0.04	48.1	44 ± 3
(1*R*,5*R*)-**37**	H	OMe	9.96 ± 0.06	0.1	6.04 ± 0.06	1.0	130 ± 7	5.99 ± 0.02	1.0	99 ± 4
(1*S*,5*S*)-**38**	Me	Me	8.65 ± 0.13	2.2	5.93 ± 0.02	1.2	76 ± 2	5.49 ± 0.01	3.3	85 ± 3
(1*R*,5*R*)-**38**	Me	Me	9.59 ± 0.08	0.3	6.68 ± 0.02	0.2	124 ± 4	5.49 ± 0.01	3.3	96 ± 2
(1*S*,5*S*)-**39**	Me	CN	9.20 ± 0.03	0.6	6.14 ± 0.09	0.8	119 ± 4	6.04 ± 0.03	0.9	94 ± 3
(1*R*,5*R*)-**39**	Me	CN	10.22 ± 0.62	0.06	7.36 ± 0.07	0.5	136 ± 7	7.06 ± 0.02	0.09	101 ± 2
(1*S*,5*S*)-**40**	Cl	H	9.24 ± 0.11	0.6	6.79 ± 0.02	0.2	162 ± 6	6.35 ± 0.02	0.4	110 ± 3
(1*R*,5*R*)-**40**	Cl	H	9.77 ± 0.04	0.2	7.61 ± 0.08	0.03	126 ± 2	7.46 ± 0.03	0.4	105 ± 2
(1*S*,5*S*)-**41**	Cl	Me	10.10 ± 0.10	0.08	6.52 ± 0.03	0.3	134 ± 6	6.17 ± 0.01	0.7	100 ± 2
(1*R*,5*R*)-**41**	Cl	Me	10.40 ± 0.04	0.04	7.14 ± 0.02	0.7	228 ± 9	6.75 ± 0.06	0.2	119 ± 4
(1*S*,5*S*)-**42**	Cl	Cl	9.53 ± 0.05	0.3	6.35 ± 0.21	0.4	110 ± 5	5.84 ± 0.07	1.5	92 ± 1
(1*R*,5*R*)-**42**	Cl	Cl	10.40 ± 0.06	0.04	7.38 ± 0.05	0.4	162 ± 6	7.27 ± 0.04	0.05	98 ± 2
(1*S*,5*S*)-**43**	H	Me	8.61 ± 0.04	2.5	4.51 ± 0.15	39.9	76 ± 7	4.42 ± 0.03	38.5	74 ± 2
(1*S*,5*S*)-**51**	Br	Br	9.52 ± 0.05	0.3	5.93 ± 0.07	1.2	122 ± 6	5.90 ± 0.02	1.3	90 ± 3
(1*S*,5*S*)-**52**	Br	Cl	9.62 ± 0.09	0.2	6.41 ± 0.09	0.4	108 ± 5	6.23 ± 0.08	0.6	92 ± 2
(1*S*,5*S*)-**53**	Br	CN	9.51 ± 0.04	0.3	6.11 ± 0.05	0.8	146 ± 9	6.24 ± 0.01	0.6	91 ± 2
(1*S*,5*S*)-**54**	Br	OMe	8.71 ± 0.21	1.9	5.66 ± 0.05	2.2	64 ± 2	5.40 ± 0.03	4.0	72 ± 1
(1*R*,5*R*)-**54**	Br	OMe	10.15 ± 0.05	0.07	6.83 ± 0.01	0.2	159 ± 6	7.00 ± 0.01	0.1	113 ± 5

[a] Displacement studies with [^{3}H]cytisine using rat brain homogenates. The K_i represents mean values obtained from independent experiments where $n \geq 3$. [b] Values represents mean potencies of compounds, as assessed by measuring fluorescence changes using FLIPR technology in HEK 293 cell lines expressing human α4β2 and α3β4 nAChRs. [c] Max values represent the maximal response of the ligand relative to the peak response for the positive control of 100 μM nicotine

nM) and (1*R*,5*S*)-**48** (K_i = 0.3 nM) vs (1*R*,5*S*)-**25** (K_i = 3.2 nM) and (1*R*,5*S*)-**49** (K_i = 0.2 nM) vs (1*R*,5*S*)-**26** (K_i = 0.8 nM). On the other hand, the 6-methyl substituent revealed similar binding affinity [for example, (1*R*,5*S*)-**28** (K_i = 1.1 nM) vs (1*R*,5*S*)-**25** (K_i = 3.2 nM)]. Slight differences in binding affinities between (1*R*,5*S*)- and (1*S*,5*R*)-enantiomers were sometimes noted, but no clear SAR trends of stereochemical effect on binding affinities could be predicted.

As shown in Table 1, functional data from the 6-*N*-substituted 3,6-diazabicyclo[3.2.0]heptanes showed that all compounds, with the exception of **45** and **46**, demonstrated substantial agonist activities at recombinant human α4β2 and/or α3β4 nAChR subtypes. (1*R*,5*S*)-**22** was slightly more potent (EC_{50} = 1.9 μM) and efficacious (maximal response, 116%) at the recombinant hα4β2 nAChR subtype than (*S*)-nicotine **1** (EC_{50} = 6.6 μM; maximal response, 101%) but is weaker (EC_{50} = 29.4 μM) and less efficacious (maximal response, 62%) than (*S*)-nicotine **1** (EC_{50} = 8.0 μM; maximal response, 89%) at the recombinant hα3β4 nAChR subtype. As compared to **22**, 5-Cl, 5-MeO, 5-Me, and 5-ethynyl analogues (**24**, **26**, **32**, and **44**) revealed slightly weaker agonist activities at the recombinant hα4β2 nAChR subtypes. 5-Br and 5-nitrile analogues (**23** and **25**) showed stereochemical effects of 3,6-diazabicyclo[3.2.0]-heptane core on nAChR subtype selectivity. Both (1*S*,5*R*)-**23** and (1*S*,5*R*)-**25** demonstrated weak and nonselective agonist activity at the recombinant hα4β2 and hα3β4 nAChR subtypes. However, enantiomers (1*R*,5*S*)-**23** and (1*R*,5*S*)-**25** showed agonist activity at hα4β2 nAChR subtype but did not show detectable functional potency at hα3β4 nAChR subtype due to low efficacy. Ligands **45** and **46**, with oxazol-2-yl and 1-methyl-imidazol-4-yl substituents at the 5-position of the pyridine ring, lacked agonist activity at either hα4β2 or hα3β4 nAChR subtypes. A 6-chloro substituent (**29**) increased agonist activity at both recombinant hα4β2 and hα3β4 nAChR subtypes relative to **22**. Similar trends were observed for other 6-chloro, 6-methyl, and 6-bromo analogues (**27**−**31** and **47**-**50**). In spite of the modest stereochemical influence of 3,6-diazabicyclo[3.2.0]-heptane core on [^{3}H]cytisine binding K_i values, ligands of structure **A** with (1*R*,5*S*)-stereochemistry, with the exception of compounds **27**−**29**, demonstrated substantially more potent agonist activity at recombinant hα4β2 nAChR subtypes relative to (1*S*,5*R*)-enantiomers. On the basis of the functional data in Table 1, several compounds deserve particular attention because of the significant differentiation between functional activities at hα4β2 and hα3β4 nAChR subtypes. (1*R*,5*S*)-**22** and (1*R*,5*S*)-**50** showed full agonist activity at both hα4β2 and hα3β4 nAChR subtypes, but EC_{50} values at recombinant hα4β2 nAChR subtype were approximately 15−19-fold more potent than at the hα3β4 nAChR subtype. Compounds (1*R*,5*S*)-**25**, (1*R*,5*S*)-**55**, and (1*R*,5*S*)-**56** were virtually inactive as agonists at the hα3β4 nAChR but retained potency and efficacy at the hα4β2 nAChR subtype. (1*R*,5*S*)-**25**, (1*R*,5*S*)-**55**, and (1*R*,5*S*)-**56** offered, thus far, the highest degree of subtype selective for agonist activity at hα4β2 nAChR with very weak hα3β4 nAChR agonist activity.

Likewise, 3-*N*-substituted 3,6-diazabicyclo[3.2.0]heptanes (structure **B**) have also been tested in [^{3}H]cytisine binding and FLIPR functional assays (Table 2). As compared to the ligands of structure **A**, many of the compounds with chemical structure **B** showed more potent binding affinities (0.04−3.0 nM) and

agonist activity. Monosubstitution on the 5-position of the pyridine ring (**34**−**37** and **43** vs **33**) had little influence on binding affinities (0.1−3.0 vs 0.1−1.2 nM) but reduced functional agonist activities at both hα4β2 and hα3β4 nAChR subtypes. 6-Methyl-, 6-chloro-, and 6-bromo-substituted pyridine analogues (**38**−**42** and **51**−**54**) demonstrated more potent binding affinities and agonist activities relative to the corresponding 6-unsubstituted pyridine analogues (**33**−**37** and **43**). In contrast to the 6-*N*-substituted series (structure **A**), the 3-*N*-substituted series (structure **B**) showed significant stereochemical effects on binding affinity and functional potency. (1*R*,5*R*)-Enantiomers demonstrated approximately 5−30-fold more potent binding affinity than (1*S*,5*S*)-enantiomers. In many cases, (1*R*,5*R*)-enantiomers also exhibited more potent functional agonist activities than (1*S*,5*S*)-enantiomers. For instance, (1*S*,5*S*)-**33** showed an approximately 12-fold weaker K_i value (K_i = 1.2 nM) and 5-fold less potent EC_{50} value at hα4β2 nAChR subtype (EC_{50} = 1.6 μM; maximal response, 122%), as well as a 10-fold higher EC_{50} value at hα3β4 nAChR subtype (EC_{50} = 6.1 μM; maximal response, 90%) than (1*R*,5*R*)-**33** (K_i = 0.1 nM; hα4β2 nAChR: EC_{50} = 0.3 μM; maximal response, 181%; hα3β4 nAChR: EC_{50} = 0.6 μM; maximal response, 119%) (Table 2). Similar trends were noticed for compounds **34** and **36**−**42** as well. With regard to subtype selectivity, it is apparent that most of the ligands with (1*S*,5*S*)-absolute stereochemistry are generally hα4β2 nAChR subtype selective (see Table 2). Compounds with (1*R*,5*R*)-absolute stereochemistry, on the other hand, gave a more complex SAR. For example, (1*R*,5*R*)-**38** and (1*R*,5*R*)-**40** are potent and efficacious hα4β2 nAChR subtype selective agonists. (1*R*,5*R*)-**34**, (1*R*,5*R*)-**39**, (1*R*,5*R*)-**41**, and (1*R*,5*R*)-**42** revealed substantially more potent hα3β4 (vs hα4β2) nAChR agonist activity (Table 2). Additionally, several other ligands with (1*R*,5*R*)-absolute chemistry, such as (1*R*,5*R*)-**33** and (1*R*,5*R*)-**37**, showed low to moderate hα4β2 nAChR subtype selectivity. At the present time, the prediction of subtype selectivity resulting from substitution on the pyridine ring of (1*R*,5*R*)-stereoisomers remains difficult.

Data presented in Tables 1 and 2 also indicate a few other important SAR trends for stereo- and regiochemistry effects of the 3,6-diazabicyclo[3.2.0]heptane core. The 3-*N*-pyridinyl-substituted 3,6-diazabicyclo[3.2.0]heptanes (structure **B**) are, in general, more potent than the 6-*N*-substituted series (structure **A**) in the [^{3}H]cytisine binding assay. The 3-*N*-substituted series also demonstrate more potent agonist activities (Table 2) than the corresponding 6-*N*-substituted series (Table 1) at both hα4β2 and hα3β4 nAChR subtypes. The 6-*N*-substituted series generally has a preference for activation of the hα4β2 nAChR subtype.

In conclusion, we have explored 3,6-diazabicyclo[3.2.0]-heptane as a useful core for the optimization of novel selective hα4β2 nAChR agonists. Both absolute enantiomers of 3,6-diazabicyclo[3.2.0]heptane have been synthesized and employed to prepare 6-(*N*)- and 3-(*N*)-pyridin-3-yl-substituted analogues (structures **A** and **B**). SAR studies of these novel nAChR ligands explored substitution effects of the pyridine ring and stereo- and regiochemical influences of the 3,6-diazabicyclo[3.2.0]-heptane core. Small 5-substituents on the pyridine ring had modest impact on the binding affinities and functional activities. 6-Bromo and 6-chloro substituents on the pyridine led to an increase in binding affinities and functional activities. 6-*N*-Pyridinyl-substituted 3,6-diazabicyclo[3.2.0]heptanes were typically found to be hα4β2 nAChR subtype selective. (1*R*,5*S*)-**25**, (1*R*,5*S*)-**55**, and (1*R*,5*S*)-**56** are hα4β2 nAChR subtype selective agonists with almost no agonist efficacy at the hα3β4 nAChR. The 3-*N*-substituted series, especially those ligands with a (1*R*,5*R*)-3,6-diazabicyclo[3.2.0]heptane stereochemical skeleton, demonstrated complex SARs. (1*R*,5*R*)-**38** and (1*R*,5*R*)-**40** preferentially activated hα4β2 (vs hα3β4) nAChR subtypes with excellent potency and high efficacy. On the other hand, (1*R*,5*R*)-**34**, (1*R*,5*R*)-**39**, (1*R*,5*R*)-**41**, and (1*R*,5*R*)-**42** demonstrated substantially stronger potency at hα3β4 (vs hα4β2) nAChR subtype. (1*R*,5*R*)-**42** and (1*R*,5*R*)-**41** are compounds with the lowest K_i values (K_i = 0.04 nM) in the entire 3,6-diazabicyclo-[3.2.0]heptane series. (1*R*,5*R*)-**40** is the most potent hα4β2 nAChR (EC_{50} = 0.03 μM; maximal response, 126%) agonist. The SAR studies of novel 3,6-diazabicyclo[3.2.0]heptane nAChR ligands led to the identification of several nAChR subtype selective compounds that were advanced to in vivo testing in models of efficacy and tolerability. Examples of such prototypes will be reported elsewhere.

Experimental Section

Chemistry General. ^{1}H NMR spectra were recorded on GE QE-300 (300 MHz) and Bruker AMX-400 (400 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, and br = broad), coupling constant(s), integration, and peak assignment. ^{13}C NMR spectra were recorded on a GE QE-300 (75 MHz) spectrometer using broad band proton decoupling. Chemical shifts are reported in ppm downfield from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) or MeOH-d_4 (49.0 ppm) as an internal standard. Mass spectra were acquired on a Jeol JMS-SX-102 spectrometer. HPLC analyses were carried out on Hitachi system model D-7000. Elemental analyses were performed by QTI Quantitative Technologies Inc. (Whitehouse, NJ). Unless otherwise specified, all reagents and solvents were obtained from commercial suppliers.

Benzyl Allyl-(2,2-dimethoxyethyl)carbamate (11).[31,32] Step 1: Benzyl chloroformate (95%, 231.3 g, 1.29 mol) was added gradually to a mixture of aminoacetaldehyde dimethyl acetal (**10**) (152.0 g, 1.45 mol) in toluene (750 mL) and aqueous NaOH (72.8 g, 1.82 mol, in 375 mL of water) at 10−20 °C. After the addition was completed, the mixture was stirred at ambient temperature for 4 h. The organic layer was separated and washed with brine (2 × 100 mL). It was then concentrated to afford benzyl 2,2-dimethoxy-ethyl-carboxylate as an oil (281.5 g, 91.0% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.33 (t, J = 6.0 Hz, 2H), 3.39 (s, 6H), 4.37 (t, J = 6.0 Hz, 1H), 5.11 (s, 2H), 7.30 (m, 5H). MS (DCI/NH_3) m/z 257 $(M + NH_4)^+$, 240 $(M + H)^+$.

Step 2: Under N_2, powdered KOH (291.2 g, 5.20 mol) and triethyl-benzylammonium chloride (4.40 g, 19.4 mmol) were added to a 2 L three-necked flask containing the solution of benzyl 2,2-dimethoxyethylcarbamate (281.0 g, 1.18 mol) in dry toluene (1.0 L). A solution of allyl bromide (188.7 g, 1.56 mol) in toluene (300 mL) was then added dropwise over 1 h at 20−30 °C. The mixture was stirred at ambient temperature for 14 h. The reaction was slowly quenched with water (300 mL) at 20−30 °C over 20 min. The organic layer was separated, and the aqueous phase was extracted with toluene (2 × 300 mL). The combined organic extracts were washed with brine (2 × 100 mL) and concentrated to give **11** as an oil (315.6 g, 96% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.32 (s, 3H), 3.37 (m, 5H), 3.97 (d, J = 5.40 Hz, 2H), 4.45 (m, 1H), 5.15 (m, 4H), 5.75 (m, 1H), 7.23 (m, 5H). MS (DCI/NH_3) m/z 297 $(M + NH_4)^+$, 280 $(M + H)^+$.

Benzyl Allyl-(2-oxo-ethyl)carbamate (12).[32] A solution of **11** (314.0 g, 1.125 mol) in formic acid (88%, 350 mL) was stirred under N_2 at ambient temperature for 15 h. Most of the formic acid was then removed under reduced pressure at 40−50 °C. The residue was extracted with EtOAc (3 × 500 mL). The combined extracts were washed with brine until the wash had a pH of 6−7. The

organic solution was then concentrated to provide **12** as an oil (260.0 g, 98.8% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.20 (m, 1H), 3.97 (m, 2H), 4.10 (m, 1H), 5.10 (m, 4H), 5.75 (m, 1H), 7.45 (m, 5H), 9.50 (d, J = 6.40 Hz, 1H). MS (DCI/NH_3) m/z 234 $(M + H)^+$.

Benzyl Allyl-(2-hydroxyiminoethyl)carbamate (13). A solution of $NaOAc\cdot 3H_2O$ (170.6 g, 1.254 mol, in 0.75 L of water) was added to a flask containing the solution of **12** (260.0 g, 1.115 mol) and $NH_2OH\cdot HCl$ (98.0 g, 1.41 mol) in MeCN (1.5 L) and then stirred at ambient temperature for 20 h. The volatiles were then removed under reduced pressure, and the residue was extracted with EtOAc (2 × 750 mL). The combined extracts were washed with brine until the wash had a pH of 7. The organic solution was concentrated to provide **13** as an oil (271.0 g 97.6% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.94 (m, 2H), 3.98 (d, J = 5.43 Hz, 1H), 4.17 (d, J = 4.41 Hz, 1H), 5.30 (m, 4H), 5.62 (m, 1H), 7.27−7.36 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1, 155.9, 149.8, 149.4, 147.0, 136.2, 132.8, 132.6, 128.4, 128.0, 127.8, 118.1, 117.8, 117.5, 117.3, 67.5, 50.8, 50.4, 49.5, 49.0, 45.4, 45.1, 42.4, 42.0 ppm. MS (DCI/NH_3) m/z 266 $(M + NH_4)^+$, 249 $(M + H)^+$. Anal. ($C_{13}H_{16}N_2O_3$) C, H, N.

(±)-Benzyl 3-Amino-4-hydroxymethyl-pyrrolidine-1-carboxylate [(±)-15].[23,33] A solution of **13** (20.0 g, 80.6 mmol) in xylene (100 mL) was stirred under N_2 at 130 °C for 10 h. The brown solution was cooled to ambient temperature, and HOAc (100 mL) was then added. Zinc powder (10.0 g, 154 mmol) was added gradually at 10 °C. After the addition was completed, the reaction mixture was stirred at ambient temperature for 3 h. The inorganic solid was removed by filtration. The xylene solution was then stirred with water (100 mL) for 10 min and separated. The aqueous layer was extracted with xylene (4 × 40 mL). The combined extracts were concentrated under reduced pressure. The residue was basified to pH 9−10 by cautious addition of saturated aqueous Na_2CO_3. The precipitated white solid was removed by filtration. The aqueous solution was extracted with $CHCl_3$ (3 × 60 mL). The combined extracts were washed with saturated aqueous Na_2CO_3 (2 × 10 mL) and dried over anhydrous Na_2CO_3. The mixture was then filtered through a short column of diatomaceous earth and concentrated to provide (±)-**15** as an oil (18.2 g, 90.3% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 2.40 (m, 1H), 3.32 (m, 2H), 3.52−3.80 (m, 5H), 5.10 (s, 2H), 7.35 (m, 5H) ppm. ^{13}C NMR (CD_3OD, 75 MHz): 156.7, 138.2, 19.4, 129.0, 128.8, 67.9, 60.6, 55.4, 55.1, 52.8, 52.0, 47.9, 47.7, 46.1, 45.3 ppm. MS (DCI/NH_3) m/z 251 $(M + H)^+$.

(3*S*,4*S*)-Benzyl 2,2-Dimethyl-hexahydro-pyrrolo[3,4-d][1,3]oxazine-6-carboxylate (16) [(*R*)-Mandelate].[23] 2-Methoxypropene (5.5 mL, 56.0 mmol) was added to the solution of (±)-**15** (7.0 g, 28.0 mmol) in anhydrous acetone (10 mL). The solution was stirred at ambient temperature for 1 h and subsequently concentrated under reduced pressure to remove the volatiles. The residue was then dissolved in anhydrous acetone (140 mL) and stirred with (*R*)-mandelic acid (4.25 g, 28.0 mmol) at ambient temperature for 48 h. The precipitate was obtained by filtration and dried under reduced pressure to provide (3*S*,4*S*)-**16** as a white solid (5.46 g, 44% yield); mp 113.7−115.8 °C. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.30 [s (br.), 3 H], 2.09 (s, 3 H), 3.30 (m, 1 H), 3.48−3.75 (m, 6 H), 4.20 (m, 1 H), 5.10 (m, 3 H), 7.25−7.52 (m, 10 H) ppm. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 206.4, 174.4, 141.5, 137.1, 128.3, 127.7, 127.6, 127.5, 127.4, 126.9, 126.4, 82.7, 72.8, 65.9, 65.6, 58.9, 58.0, 57.6, 53.3, 53.2, 52.7, 51.0, 50.4, 50.2, 49.5, 48.6, 46.2, 45.6, 45.5, 45.0, 42.9, 42.0, 35.1, 34.3, 30.6, 30.0, 28.9, 20.3, 18.4 ppm. MS (DCI/NH_3) m/z 291 $(M + H)^+$; $[\alpha]_D^{20} = -45.70°$ (c = 0.37, MeOH). Anal. ($C_{16}H_{22}N_2O_3\cdot 1.0C_8H_8O_3$) C, H, N.

Benzyl (3*S*,4*S*)-3-*tert*-Butoxycarbonylamino-4-hydroxymethyl-pyrrolidine-1-carboxylate (17). A solution of (3*S*,4*S*)-**16** (56.0 g, 127 mmol) in EtOH (50 mL) was stirred with aqueous H_2SO_4 (5%, 100 mL) at ambient temperature for 16 h. It was then basified to pH ∼10 with 20% aqueous NaOH (50 mL). A solution of di-*tert*-butyl dicarbonate (41.5 g, 190 mmol) in EtOH (50 mL) was cautiously added at 10−20 °C. After the addition was completed, it was allowed to stir at 65 °C for 4 h. The volatiles were removed under reduced pressure, and the residue was extracted with EtOAc (3 × 500 mL). The combined extracts were washed with brine (2 × 100 mL) and concentrated to give (*S*,*S*)-**17** as a solid (43.7 g, 98% yield). The optical purity (>98% ee) was determined by HPLC (HPLC conditions: Chiracel AD column; eluents, EtOH/hexanes = 20/80; flow rate, 1.0 mL/min; UV, 215 nm; retention time for (*S*,*S*)-**17** as the more mobile isomer, 10.8 min; and retention time for (*R*,*R*)-**17** as the less mobile isomer, 13.9 min); mp 149.0−150.8 °C. ^{1}H NMR (CD_3OD, 400 MHz): δ 1.46 (s, 9 H), 2.50 (m, 1 H), 3.25 (m, 1 H), 3.40 (m, 1 H), 3.50−3.75 (m, 4 H), 4.20 (m, 1 H), 5.10 (s, 2 H), 7.35 (m, 5 H) ppm. ^{13}C NMR (CD_3OD, 75 MHz): δ 158.4, 156.7, 138.2, 129.5, 129.0, 128.8, 80.6, 68.1, 60.8, 53.1, 52.9, 52.1, 48.0, 47.8, 45.7, 44.9, 28.7 ppm. MS (DCI/NH_3) m/z 368 $(M + NH_4)^+$, 351 $(M + H)^+$; $[\alpha]_D^{20} = 17.50°$ (c = 0.67, MeOH). Anal. ($C_{18}H_{26}N_2O_5$) C, H, N.

Benzyl (3*S*,4*S*)-3-*tert*-Butoxycarbonylamino-4-methylsulfonyloxymethyl-pyrrolidine-1-carboxylate (18).[34] A solution of methanesulfonyl chloride (12.6 mL, 163 mmol) in anhydrous CH_2Cl_2 (50 mL) was added to the solution of (*S*,*S*)-**17** (43.7 g, 125 mmol) and Et_3N (25.2 g, 250 mmol) in anhydrous CH_2Cl_2 (600 mL) at −10 °C over 30 min. The reaction was then allowed to warm to ambient temperature and stirred for 1 h and quenched with water (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL). The combined organic solution was washed with brine (2 × 100 mL) and concentrated to give (*S*,*S*)-**18** as an oil (52.0 g, 97% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (s, 9H), 2.80 (m, 1 H), 3.08 (s, 3 H), 3.40 (m, 2 H), 3.70 (m, 2 H), 4.10 (m, 2 H), 4.75 (m, 1 H), 5.16 (s, 2 H), 7.30 (m, 5 H). MS (DCI/NH_3) m/z 446 $(M + NH_4)^+$, 429 $(M + H)^+$.

Benzyl (1*S*,5*S*)-3,6-Diaza-bicyclo[3.2.0]heptane-3-carboxylate (19a). A solution of (*S*,*S*)-**18** (43.7 g, 125 mmol) in CH_2Cl_2 (150 mL) was stirred with CF_3CO_2H (50 mL) at 0−20 °C for 1 h. It was then concentrated under reduced pressure. The residue was dissolved in EtOH (250 mL), basified to pH ∼10 with 10% aqueous NaOH, and stirred at 60 °C for 10 h. It was cooled to ambient temperature and concentrated under reduced pressure to remove most of the volatiles. The residue was extracted with $CHCl_3$ (2 × 500 mL). The combined extracts were washed with brine (3 × 50 mL) and then passed through a short column of diatomaceous earth. The filtrate was concentrated to give (1*S*,5*S*)-**19a** (28.0 g, 95% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.16−3.30 (m, 3 H), 3.36 (m, 1 H), 3.75−3.86 (m, 3 H), 4.55 (m, 1 H), 5.20 (s, 2 H), 7.36 (m, 5 H). ^{13}C NMR (CD_3OD, 75 MHz): δ 157.4, 138.2, 129.5, 129.1, 129.0, 68.2, 63.6, 54.8, 52.9, 50.6, 38.3. MS (DCI/NH_3) m/z 250 $(M + NH_4)^+$, 233 $(M + H)^+$; $[\alpha]_D^{20} = -18.97°$ (c = 0.39, MeOH). Anal. ($C_{13}H_{16}N_2O_2$) C, H, N.

Synthesis of *tert*-Butyl (1*S*,5*S*)-3,6-Diaza-bicyclo[3.2.0]heptane-3-carboxylate (19b). Step 1: A solution of $(CF_3CO)_2O$ (2.77 g, 13.2 mmol) in tetrahydrofuran (THF) (anhydrous, 10 mL) was slowly added to a flask containing the solution of (1*S*,5*S*)-**19a** (2.80 g, 12 mmol) and Et_3N (1.82 g, 18 mmol) in anhydrous THF (20 mL) under N_2 at −20 °C. The reaction was then warmed to 0 °C and stirred for 4 h. The volatiles were removed under reduced pressure. The residue was diluted with EtOAc (100 mL), washed with brine (2 × 10 mL), and concentrated to give benzyl (1*S*,5*S*)-6-trifluoroacetyl-3,6-diaza-bicyclo[3.2.0]heptane-3-carboxylate (3.80 g, 96.5% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11−3.42 (m, 3 H), 3.56−3.77 (m, 0.7 H, rotamer), 3.79−4.05 (m, 1.3 H, rotamer), 4.09−4.33 (m, 1.7 H, rotamer) 4.47 (t, J = 8.75 Hz, 0.3 H, rotamer), 4.85 (t, J = 5.98 Hz, 0.7 H, rotamer), 4.93 (t, J = 6.00 Hz, 0.3 H, rotamer), 5.03−5.33 (m, 2 H), 7.18−7.44 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 155.2, 136.2, 128.4, 128.1, 127.8, 105.4, 67.4, 67.3, 56.1, 52.8, 50.4, 49.9, 48.3 ppm. MS (DCI/NH_3) m/z 346 $(M + NH_4)^+$, 329 $(M + H)^+$. $[\alpha]_D^{20} = -85.87°$ (c = 0.39, MeOH).

Step 2: A solution of benzyl (1*S*,5*S*)-6-trifluoroacetyl-3,6-diaza-bicyclo[3.2.0]heptane-3-carboxylate (3.77 g, 11.5 mmol) in MeOH (50 mL) was stirred with Pd/C (10 wt %, 0.38 g) under H_2 at ambient temperature for 2 h. It was then degassed and purged with N_2 three times. Boc_2O (4.36 g, 22 mmol) was added, and the mixture was stirred at ambient temperature for 10 h. The catalyst

was cautiously removed by filtration through a short column of diatomaceous earth. The filtrate was concentrated to give *tert*-butyl (1*S*,5*S*)-6-trifluoroacetyl-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate as an oil (2.80 g, 82.6% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (s, 9 H), 3.22 (dd, J = 12.12, 6.29 Hz, 1 H), 3.29 (dd, J = 13.96, 5.37 Hz, 1 H), 3.32−3.43 (m, 1 H), 3.71 (dd, J = 10.74, 5.52 Hz, 1 H), 3.80 (d, J = 11.97 Hz, 1 H), 4.12−4.30 (m, 2 H), 4.90 (t, J = 6.14 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 154.8, 80.8, 63.2, 50.2, 49.7, 48.3, 35.9, 28.2 ppm. MS (DCI/NH_3) m/z 312 $(M + NH_4)^+$, 295 $(M + H)^+$; $[\alpha]_D^{20} = -22.32°$ (c = 0.36, MeOH).

Step 3: The solution of (*tert*-butyl (1*S*,5*S*)-6-trifluoroacetyl-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (2.70 g, 9.2 mmol) in MeOH (20 mL) was stirred with saturated K_2CO_3 (aqueous, 5 mL) at 65 °C for 1 h. It was then extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were washed with brine (2 × 10 mL), passed through a short column of diatomaceous earth, and then concentrated to give (1*S*,5*S*)-**19b** (1.50 g, 79.8% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 1.49 (s, 9 H), 3.09−3.29 (m, 4 H), 3.62−3.73 (m, 2 H), 3.77 (t, J=7.97 Hz, 1 H), 4.38 (m, 1 H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ 157.06, 80.99, 63.45, 54.82, 52.68, 50.69, 39.14, 28.80, 25.34 ppm. MS (DCI/NH_3) m/z 199 $(M + H)^+$; $[\alpha]_D^{20} = -32.14°$ (c = 0.28, MeOH). Anal. ($C_{10}H_{18}N_2O_2$) C, H, N.

(1*R*,5*S*)-3-Benzyl 6-*tert*-Butyl 3,6-Diazabicyclo[3.2.0]heptane-3,6-dicarboxylate (3-*N*-Cbz-20). A solution of (1*S*,5*S*)-**19a** (6.96 g, 30.0 mmol) in CH_2Cl_2 (100 mL) was stirred with Et_3N (4.04 g, 40 mmol) and Boc_2O (8.72 g, 40.0 mmol) at ambient temperature for 10 h. It was then concentrated, and the residue was purified with chromatography on silica gel (EtOAc/hexanes, v. 1/1, R_f = 0.4) to provide (1*R*,5*S*)-3-benzyl 6-*tert*-butyl 3,6-diazabicyclo[3.2.0]-heptane-3,6-dicarboxylate [(1*R*,5*S*)-3-*N*-Cbz-**20**] (9.50 g, yield, 95.4%). ^{1}H NMR (CD_3OD, 400 MHz): δ 1.41 (s, 9 H), 2.98−3.17 (m, 2 H), 3.21−3.29 (m, 1 H), 3.39−3.52 (m, 1 H), 3.86 (d, J = 11.9 Hz, 1 H), 3.95−4.11 (m, 2 H), 4.67 (dd, J = 6.4, 4.4 Hz, 1 H), 5.05−5.26 (m, 2 H), 7.08−7.62 (m, 5 H) ppm. MS (DCI/NH_3) m/z 350 $(M + NH_4)^+$, 333 $(M + H)^+$.

(1*R*,5*S*)-*tert*-Butyl 3,6-Diazabicyclo[3.2.0]heptane-6-carboxylate (20). A solution of [(1*R*,5*S*)-3-*N*-Cbz-**20**] (7.5 g, 22.6 mmol) in EtOH (50 mL) was stirred with Pd/C (10 wt %, 0.75 g) under H_2 for 4 h. The catalyst was cautiously removed by filtration through a short column of diatomaceous earth. The filtrate was concentrated to give (1*R*,5*S*)-*tert*-butyl 3,6-diazabicyclo[3.2.0]heptane-6-carboxylate (**20**) as an oil (4.0 g, yield, 89.4%). ^{1}H NMR (CD_3OD, 400 MHz): δ 1.43 (s, 9 H), 2.46 (dd, J = 12.9, 3.7 Hz, 1 H), 2.62 (dd, J = 12.2, 6.1 Hz, 1 H), 2.90−3.00 (m, 1 H), 3.03 (d, J = 12.5 Hz, 1 H), 3.22 (d, J = 12.9 Hz, 1 H), 3.37−3.57 (m, 1 H), 3.95 (t, J = 7.6 Hz, 1 H), 4.64 (dd, J = 6.1, 3.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 199 $(M + H)^+$.

Buchwald−Hartwig Coupling Reaction: Representative Procedure "C(a)". The mixture of (1*S*,5*S*)-**19a** (230 mg, 1.0 mmol), 3-bromopyridine (236 mg, 1.50 mmol), and ^{t}BuONa (144 mg, 1.50 mmol) in anhydrous toluene (10.0 mL) was degassed and purged with nitrogen three times before the addition of *rac*-BINAP (37.3 mg, 0.06 mmol) and $Pd_2(dba)_3$ (18.3 mg, 0.02 mmol). It was then heated to 110 °C and stirred at this temperature for 10 h. After it was cooled down to ambient temperature, it was diluted with EtOAc (20.0 mL) and washed with brine (2 × 5.0 mL). The organic solution was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 4:1) to give (1*S*,5*S*)-3-*N*-Cbz-**22** (R_f = 0.30, 190 mg, 61% yield).

Buchwald−Hartwig Coupling Reaction: Representative Procedure "C(b)". A mixture of (1*S*,5*S*)-**19a** (460 mg, 2.0 mmol), 5-bromo-nicotinonitrile (550 mg, 3.0 mmol), Cs_2CO_3 (1312 mg, 4.0 mmol), *rac*-BINAP (74.8 mg, 0.12 mmol), and $Pd_2(dba)_3$ (36.6 mg, 0.04 mmol) in anhydrous toluene (20 mL) was stirred under N_2 at 110 °C for 40 h. After it was cooled to ambient temperature, it was then diluted with EtOAc (50.0 mL), washed with brine (2 × 5.0 mL), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 4:1) to give (1*S*,5*S*)-3-*N*-Cbz-**25** (R_f = 0.30, 610 mg, 91.3% yield).

***N*-Cbz Deprotection: Representative Procedure "D(a)".** A solution of (1*S*,5*S*)-3-*N*-Cbz-**22** (190 mg) in methanol (10 mL) was stirred with Pd/C (wt 10%, 100 mg) under H_2 for 2 h. The catalyst was cautiously removed by filtration through a short column of diatomaceous earth. The filtrate was concentrated to give (1*R*,5*S*)-**22** (100 mg, 94% yield).

***N*-Cbz Deprotection: Representative Procedure "D(b)".** A solution of (1*S*,5*S*)-3-*N*-Cbz-**23** (180 mg, 0.46 mmol) in trifluoroacetic acid (3.0 mL) was stirred at 65 °C for 1 h. It was then concentrated under reduced pressure. The residue was treated with NaOH aqueous solution (5%) to pH 8−9. It was subsequently extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (2 × 10 mL) and concentrated. The residue was purified by chromatography (SiO_2, solvent: v. CH_2Cl_2:MeOH:NH_3·H_2O = 90:10:2) to give (1*R*,5*S*)-**23** (R_f = 0.15, 80 mg, 69% yield).

***N*-Boc Deprotection: Representative Procedure "D(c)"**. A solution of (1*R*,5*S*)-6-*N*-Boc-**33** (430 mg, 1.56 mmol) in CH_2Cl_2 (5 mL) was stirred with trifluoroacetic acid (1 mL) at ambient temperature for 1 h. It was then concentrated, and the residue was purified with chromatography on silica gel (solvent: v. CH_2Cl_2: MeOH:NH_3·H_2O = 90:10:2) to give (1*S*,5*S*)-**33** (R_f = 0.1, 230 mg, 84%).

***N*-Boc Deprotection: Representative Procedure "D(d)"**. A solution of (1*R*,5*S*)-6-*N*-Boc-**38** (280 mg, 0.92 mmol) in EtOAc (10 mL) was stirred with TsOH·H_2O (351 mg, 1.85 mmol) at 80 °C for 6 h. The precipitate was filtered and dried to give (1*S*,5*S*)-**38** tosylate (320 mg, 81% yield).

Salt Formation: Representative Procedure "S(a)" for Fumarate Formation. A solution of fumaric acid (66 mg, 0.57 mmol) in EtOH (1 mL) was added to a solution of (1*R*,5*S*)-**22** (100 mg, 0.57 mmol) in EtOAc (10 mL). The mixture was then stirred at ambient temperature for 16 h. The white precipitate was filtered and dried to give (1*R*,5*S*)-**22**-fumarate (120 mg, 73% yield).

Salt Formation: Representative Procedure "S(b)" for Tosylate Formation. (1*R*,5*S*)-**25** (1.40 g, 7 mmol) was dissolved in ^{i}PrOH (50 mL) and heated to 80 °C. The solution of TsOH·H_2O (2.66 g, 14.0 mmol) in EtOAc (50 mL) was slowly added to the above solution at 80 °C over 0.5 h. After the addition was finished, the mixture was cooled to ambient temperature and stirred for 10 h. The solid was filtered and dried to give (1*R*,5*S*)-**25** bis(tosylate) as a white solid (3.20 g, 84.0% yield).

Salt Formation: Representative Procedure "S(c)" for Trifluoroacetate Formation. A solution of (1*R*,5*S*)-6-*N*-Boc-**41** (480 mg, 1.48 mmol) in CH_2Cl_2 (5 mL) was stirred with trifluoroacetic acid (5 mL) at ambient temperature for 2 h. It was then concentrated, and the residue was stirred in *i*-PrOAc (5 mL) at ambient temperature overnight. The precipitate was filtered and dried to give (1*S*,5*S*)-**41** trifluoroacetate (310 mg, 62% yield).

(1*R*,5*S*)-6-Pyridin-3-yl-3,6-diaza-bicyclo[3.2.0]heptane (22) Fumarate. This was prepared according to the representative procedures C(a), D(a), and S(a) using (1*S*,5*S*)-**19a** and 3-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.18 (dd, J = 12.6, 3.4 Hz, 1 H), 3.35 (m, 1 H), 3.46 (m, 1 H), 3.75 (m, 3 H), 4.04 (t, J = 7.8 Hz, 1 H), 4.90 (m, 1 H), 6.58(s, 2.5 H), 7.04 (ddd, J = 8.2, 2.7, 1.3 Hz, 1 H), 7.27 (dd, J = 8.2, 4.8 Hz, 1 H), 7.87 (d, J = 2.7 Hz, 1 H), 7.95 (dd, J = 4.8, 1.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 176 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3$·$1.25C_4H_4O_4$·$0.30H_2O$) C, H, N.

(1*S*,5*R*)-6-Pyridin-3-yl-3,6-diaza-bicyclo[3.2.0]heptane (22) Fumarate. This was prepared according to the representative procedures C(a), D(a), and S(a) using (1*R*,5*R*)-**19a** and 3-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.18 (dd, J = 12.2, 3.4 Hz, 1 H), 3.35 (m, 1 H), 3.46 (m, 1 H), 3.75 (m, 3 H), 4.04 (t, J = 7.5 Hz, 1 H), 4.90 (m, 1 H), 6.58(s, 2.7 H), 7.04 (ddd, J = 8.2, 2.7, 1.3 Hz, 1 H), 7.27 (dd, J = 8.2, 4.8 Hz, 1 H), 7.87 (d, J = 2.7 Hz, 1 H), 7.95 (dd, J = 4.8, 1.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 176 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3$·$1.36C_4H_4O_4$·$0.24H_2O$) C, H, N.

(1*R*,5*S*)-6-(5-Bromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (23) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*S*,5*S*)-**19a** and 3,5-dibromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.15 (dd, J = 12.6, 3.4 Hz, 1 H), 3.30 (m, 1 H), 3.45 (m, 1 H), 3.67 (d, J = 11.5 Hz, 1 H), 3.75 (m, 2 H), 4.06 (t, J = 8.1 Hz, 1 H), 4.94

(m, 1 H), 6.30 (s, 2.0 H), 7.22 (t, $J = 2.3$ Hz, 1 H), 7.84 (d, $J = 2.3$ Hz, 1 H), 8.04 (d, $J = 1.7$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 256 $(M + H)^+$, 254 $(M + H)^+$. Anal. ($C_{10}H_{12}BrN_3 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*S*,5*R*)-6-(5-Bromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (23) Bisfumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*R*,5*R*)-**19a** and 3,5-dibromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.20 (dd, $J = 12.7$, 3.7 Hz, 1 H), 3.30−3.45 (m, 2 H), 3.70−3.82 (m, 3 H), 4.05 (t, $J = 8.1$ Hz, 1 H), 4.96 (dd, $J = 6.6$, 3.7 Hz, 1 H), 6.30 (s, 4.9 H), 7.22 (t, $J = 2.3$ Hz, 1 H), 7.84 (d, $J = 2.3$ Hz, 1 H), 8.04 (d, $J = 1.7$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 256 $(M + H)^+$, 254 $(M + H)^+$. Anal. ($C_{10}H_{12}BrN_3 \cdot 2.45C_4H_4O_4 \cdot 1.00H_2O$) C, H, N.

(1*R*,5*S*)-6-(5-Chloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (24) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*S*,5*S*)-**19a** and 3-bromo-5-chloropyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.14 (dd, $J = 12.9$, 3.4 Hz, 1 H), 3.31−3.36 (m, 1 H), 3.39−3.52 (m, 1 H), 3.65−3.74 (m, 2 H), 3.77 (dd, $J = 8.1$, 3.1 Hz, 1 H), 4.05 (t, $J = 8.0$ Hz, 1 H), 4.93 (dd, $J = 6.6$, 3.6 Hz, 1 H), 6.69 (s, 2 H), 7.07 (t, $J = 2.2$ Hz, 1 H), 7.79 (d, $J = 2.4$ Hz, 1 H), 7.93 (d, $J = 2.0$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 212 $(M + H)^+$, 210 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.00C_4H_4O_4 \cdot 0.30H_2O$) C, H, N.

(1*R*,5*S*)-6-(5-Cyanopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (25) Bis(tosylate). This was prepared according to the representative procedures C(b), D(b), and S(b) using (1*S*,5*S*)-**19a** and 5-bromo-nicotinonitrile; mp 240−243 °C. ^{1}H NMR (MeOH-d_4, 400 MHz): δ 2.36 (s, 6 H), 3.23 (dd, $J = 13.0$, 3.8 Hz, 1 H), 3.34 (dd, $J = 12.6$, 7.1 Hz, 1 H), 3.73 (d, $J = 12.3$ Hz, 1 H), 3.82−3.98 (m, 3 H), 4.18 (t, $J = 8.6$ Hz, 1 H), 5.13 (dd, $J = 6.4$, 3.7 Hz, 1 H), 7.21 (d, $J = 8.0$ Hz, 4 H), 7.64 (d, $J = 8.0$ Hz, 4 H), 7.83 (dd, $J = 2.6$, 1.4 Hz, 1 H), 8.22 (d, $J = 2.5$ Hz, 1 H), 8.42 (d, $J = 0.9$ Hz, 1 H) ppm. ^{13}C NMR (CD_3OD, 100 MHz): δ 148.0, 143.3, 141.9, 133.2, 130.2, 129.9, 129.3, 126.8, 115.2, 113.9, 68.7, 56.0, 50.9, 35.4, 25.3, 21.3. MS (DCI/NH_3) *m/z* 218 $(M + NH_4)^+$, 201 $(M + H)^+$; $[\alpha]_D^{25} = -108.0°$ (0.47, MeOH). Anal. ($C_{11}H_{12}N_4 \cdot 2.00C_7H_8SO_3$) C, H, N.

(1*S*,5*R*)-6-(5-Cyanopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (25) Bisfumarate. This was prepared according to the representative procedures C(b), D(b), and S(a) using (1*R*,5*R*)-**19a** and 5-bromo-nicotinonitrile. ^{1}H NMR (CD_3OD, 400 MHz): δ 3.20 (dd, $J = 12.7$, 3.7 Hz, 1 H), 3.38 (m, 1 H), 3.50 (m, 1H), 3.70−3.85 (m, 3 H), 4.10 (t, $J = 8.1$ Hz, 1 H), 5.00 (dd, $J = 6.5$, 3.8 Hz, 1 H), 6.70 (s, 5.0 H), 7.36 (d, $J = 2.7$, 1.7 Hz, 1 H), 8.10 (d, $J = 3.0$ Hz, 1 H), 8.26 (d, $J = 1.4$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 218 $(M + NH_4)^+$, 201 $(M + H)^+$. Anal. ($C_{11}H_{12}N_4 \cdot 2.50C_4H_4O_4 \cdot 0.70H_2O$) C, H, N.

(1*R*,5*S*)-6-(5-Methoxypyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (26) Tosylate. This was prepared according to the representative procedures C(a), D(a), and S(b), using (1*S*,5*S*)-**19a** and 3-bromo-5-methoxypyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.37 (s, 3 H), 3.20 (dd, $J = 12.6$, 3.7 Hz, 1 H), 3.35 (m, 1 H), 3.45 (m, 1 H), 3.72 (m, 3 H), 3.83 (s, 3 H), 4.16 (t, $J = 8.2$ Hz, 1 H), 4.90 (dd, $J = 6.5$, 3.8 Hz, 1 H), 6.54 (t, $J = 2.4$ Hz, 1 H), 7.22 (d, $J = 6.0$ Hz, 2 H), 7.47 (d, $J = 2.8$ Hz, 1 H), 7.67 (d, $J = 2.8$ Hz, 1 H), 7.69 (d, $J = 6.0$ Hz, 2 H) ppm. MS (DCI/NH_3) *m/z* 206 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3O \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*S*,5*R*)-6-(5-Methoxypyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (26) Tosylate. This was prepared according to the representative procedures C(a), D(a), and S(b), using (1*R*,5*R*)-**19a** and 3-bromo-5-methoxypyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 3 H), 3.18 (dd, $J = 12.5$, 3.4 Hz, 1 H), 3.32−3.38 (m, 1 H), 3.38−3.50 (m, 1 H), 3.66−3.80 (m, 3 H), 3.84 (s, 3 H), 4.01 (t, $J = 8.0$ Hz, 1 H), 4.90 (dd, $J = 6.4$, 3.4 Hz, 1 H), 6.55 (t, $J = 2.4$ Hz, 1 H), 7.22 (d, $J = 7.8$ Hz, 2 H), 7.47 (d, $J = 2.4$ Hz, 1 H), 7.67 (d, $J = 2.8$ Hz, 1 H), 7.69 (d, $J = 6.0$ Hz, 2 H) ppm. MS (DCI/NH_3) *m/z* 206 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3O \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*R*,5*S*)-6-(5,6-Dimethylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (27) Tosylate. This was prepared according to the representative procedures C(b), D(a), and S(b) using (1*S*,5*S*)-**19a** and 3-bromo-5,6-dimethylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.27 (s, 3 H), 2.36 (s, 3 H), 2.37 (s, 3 H), 3.16 (dd, $J = 12.5$, 3.4 Hz, 1 H), 3.30−3.50 (m, 2 H), 3.70 (d, $J = 12.5$ Hz, 2 H), 3.73 (dd, $J = 7.8$, 2.0 Hz, 1 H), 3.96 (t, $J = 8.0$ Hz, 1H), 4.81−4.84 (m, 1 H), 6.87 (d, $J = 3.1$ Hz, 1 H), 7.22 (d, $J = 7.8$ Hz, 2 H), 7.55 (d, $J = 2.4$ Hz, 1 H), 7.70 (d, $J = 8.5$ Hz, 2 H) ppm. MS (DCI/NH_3) *m/z* 204 $(M + H)^+$. Anal. ($C_{12}H_{17}N_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*S*,5*R*)-6-(5,6-Dimethylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (27) Tosylate. This was prepared according to the representative procedures C(b), D(a), and S(b) using (1*R*,5*R*)-**19a** and 3-bromo-5,6-dimethylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.27 (s, 3.3 H), 2.37 (s, 3 H), 2.38 (s, 3 H), 3.16 (dd, $J = 12.7$, 3.6 Hz, 1 H), 3.32−3.46 (m, 2 H), 3.70 (d, $J = 11.5$ Hz, 2 H), 3.75 (dd, $J = 7.8$, 2.4 Hz, 1 H), 3.96 (t, $J = 7.8$ Hz, 1 H), 4.76−4.87 (m, 1 H), 6.89 (d, $J = 1.7$ Hz, 1 H), 7.23 (d, $J = 8.1$ Hz, 2.2 H), 7.56 (d, $J = 2.7$ Hz, 1 H), 7.70 (d, $J = 8.5$ Hz, 2.2 H) ppm. MS (DCI/NH_3) *m/z* 204 $(M + H)^+$. Anal. ($C_{12}H_{17}N_3 \cdot 1.11C_7H_8SO_3$) C, H, N.

(1*R*,5*S*)-6-(5-Cyano-6-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (28) Trifluoroacetate. This was prepared according to the representative procedures C(b), D(b), and S(c) using (1*S*,5*S*)-**19a** and 3-bromo-5-cyano-6-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.60 (s, 3 H), 3.14 (dd, $J = 12.7$, 3.6 Hz, 1 H), 3.33−3.56 (m, 2 H), 3.70 (d, $J = 12.4$ Hz, 1 H), 3.72 (d, $J = 12.4$ Hz, 1 H), 3.77 (dd, $J = 8.1$, 3.1 Hz, 1 H), 4.04 (t, $J = 8.1$ Hz, 1 H), 4.92 (dd, $J = 6.4$, 3.7 Hz, 1 H), 7.31 (d, $J = 3.1$ Hz, 1 H), 7.99 (d, $J = 3.1$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 215 $(M + H)^+$. Anal. ($C_{12}H_{14}N_4 \cdot 1.00CF_3CO_2H$) C, H, N.

(1*S*,5*R*)-6-(5-Cyano-6-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (28) Fumarate. This was prepared according to the representative procedures C(b), D(b), and S(a) using (1*R*,5*R*)-**19a** and 3-bromo-5-cyano-6-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.60 (s, 3 H), 3.15 (dd, $J = 12.9$, 3.4 Hz, 1 H), 3.27−3.36 (m, 1 H), 3.45 (ddd, $J = 14.3$, 7.4, 2.7 Hz, 1 H), 3.71 (dd, $J = 12.4$, 10.3 Hz, 2 H), 3.77 (dd, $J = 8.1$, 3.1 Hz, 1 H), 4.03 (t, $J = 8.0$ Hz, 1 H), 4.92 (dd, $J = 6.4$, 3.4 Hz, 1 H), 6.67 (s, 2 H), 7.31 (d, $J = 2.7$ Hz, 1 H), 7.99 (d, $J = 3.1$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 215 $(M + H)^+$. Anal. ($C_{12}H_{14}N_4 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*R*,5*S*)-6-(6-Chloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (29) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*S*,5*S*)-**19a** and 5-bromo-2-chloropyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.15 (dd, $J = 12.8$, 3.7 Hz, 1 H), 3.35 (m, 1 H), 3.40 (m, 1 H), 3.45 (m, 1 H), 3.76 (m, 2 H), 4.00 (t, $J = 7.8$ Hz, 1 H), 4.88 (m, 1 H), 6.70 (s, 2.9 H), 7.05 (dd, $J = 8.8$, 3.0 Hz, 1 H), 7.28 (d, $J = 8.4$ Hz, 1 H), 7.68 (d, $J = 3.0$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 212 $(M + H)^+$, 210 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.45C_4H_4O_4$) C, H, N.

(1*S*,5*R*)-6-(6-Chloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (29) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*R*,5*R*)-**19a** and 5-bromo-2-chloropyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.15 (dd, $J = 12.8$, 3.7 Hz, 1 H), 3.35 (m, 1 H), 3.40 (m, 1 H), 3.45 (m, 1 H), 3.76 (m, 2 H), 4.00 (t, $J = 7.8$ Hz, 1 H), 4.88 (m, 1 H), 6.70 (s, 2.8 H), 7.05 (dd, $J = 8.8$, 3.0 Hz, 1 H), 7.28 (d, $J = 8.4$ Hz, 1 H), 7.68 (d, $J = 3.0$ Hz, 1 H) ppm. MS (DCI/NH_3) *m/z* 212 $(M + H)^+$, 210 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.38C_4H_4O_4$) C, H, N.

(1*R*,5*S*)-6-(6-Chloro-5-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (30) Tosylate. This was prepared according to the representative procedures C(a), D(b), and S(b) using (1*S*,5*S*)-**19a** and 5-bromo-2-chloro-3-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.31 (s, 3 H), 2.36 (s, 3 H), 3.17 (dd, $J = 12.5$, 3.4 Hz, 1 H), 3.33−3.37 (m, 1 H), 3.43 (ddd, $J = 14.3$, 7.5, 2.9 Hz, 1 H), 3.69 (d, $J = 2.7$ Hz, 1 H), 3.74 (dd, $J = 8.3$, 2.9 Hz, 2 H), 3.98 (t, $J = 8.0$ Hz, 1 H), 4.87 (dd, $J = 6.4$, 3.4 Hz, 1 H), 6.97 (d, $J = 3.1$ Hz, 1 H), 7.21 (d, $J = 7.8$ Hz, 2 H), 7.49 (d, $J = 2.7$ Hz, 1 H), 7.69 (d, $J = 8.1$ Hz, 2 H) ppm. MS (DCI/NH_3) *m/z* 226 $(M + H)^+$, 224 $(M + H)^+$. Anal. ($C_{11}H_{14}ClN_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*S*,5*R*)-6-(6-Chloro-5-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (30) Tosylate. This was prepared according to the representative procedures C(b), D(b), and S(b) using (1*R*,5*R*)-**19a** and 5-bromo-2-chloro-3-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.31 (s, 3 H), 2.36 (s, 3 H), 3.17 (dd, J = 12.5, 3.4 Hz, 1 H), 3.32−3.37 (m, 1 H), 3.43 (ddd, J = 14.1, 7.5, 2.9 Hz, 1 H), 3.69 (d, J = 3.1 Hz, 1 H), 3.74 (dd, J = 8.0, 2.9 Hz, 2 H), 3.98 (t, J = 7.8 Hz, 1 H), 4.87 (dd, J = 6.4, 3.4 Hz, 1 H), 6.97 (d, J = 3.1 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 2 H), 7.49 (d, J = 2.4 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 2 H) ppm. MS (DCI/NH_3) m/z 226 $(M + H)^+$, 224 $(M + H)^+$. Anal. ($C_{11}H_{14}ClN_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*R*,5*S*)-6-(5,6-Dichloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (31) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*S*,5*S*)-**19a** and 2,3-dichloro-5-iodopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.14 (dd, J = 12.9, 3.7 Hz, 1 H), 3.32−3.35 (m, 1 H), 3.45 (ddd, J = 14.5, 7.4, 3.2 Hz, 1 H), 3.70 (dd, J = 12.4, 10.3 Hz, 2 H), 3.76 (dd, J = 8.0, 3.2 Hz, 1 H), 4.04 (t, J = 8.1 Hz, 1 H), 4.92 (dd, J = 6.4, 3.4 Hz, 1 H), 6.67 (s, 2 H), 7.20 (d, J = 2.7 Hz, 1 H), 7.63 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 246 $(M + H)^+$, 244, $(M + H)^+$. Anal. ($C_{10}H_{11}Cl_2N_3 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*S*,5*R*)-6-(5,6-Dichloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (31) Fumarate. This was prepared according to the representative procedures C(a), D(b), and S(a) using (1*R*,5*R*)-**19a** and 2,3-dichloro-5-iodopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.14 (dd, J = 12.9, 3.4 Hz, 1 H), 3.32−3.34 (m, 1 H), 3.45 (ddd, J = 14.2, 7.4, 3.2 Hz, 1 H), 3.64−3.73 (m, 2 H), 3.76 (dd, J = 8.0, 3.2 Hz, 1 H), 4.04 (t, J = 8.1 Hz, 1 H), 4.92 (dd, J = 6.4, 3.4 Hz, 1 H), 6.67 (s, 2 H), 7.21 (d, J = 2.7 Hz, 1 H), 7.63 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 246 $(M + H)^+$, 244, $(M + H)^+$. Anal. ($C_{10}H_{11}Cl_2N_3 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*S*,5*R*)-6-(5-Methylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (32) Hydrochloride. A solution of (1*S*,5*R*)-**30** (0.62 g, 2.77 mmol) in EtOH (15 mL) was stirred with Pd/C (10 wt %, 0.2 g) under H_2 (1 atm) at ambient temperature for 10 h. The catalyst was filtered off, and the organic solution was concentrated to give (1*S*,5*R*)-**32** hydrochloride (0.54 g, 87% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 2.30 (s, 3 H), 3.18 (dd, J = 12.5, 3.4 Hz, 1 H), 3.31−3.39 (m, 1 H), 3.44 (ddd, J = 14.2, 7.5, 2.7 Hz, 1 H), 3.71 (dd, J = 12.2, 2.4 Hz, 2 H), 3.77 (dd, J = 7.8, 3.1 Hz, 1 H), 4.00 (t, J = 7.8 Hz, 1 H), 4.89 (dd, J = 6.3, 3.6 Hz, 1 H), 6.84−6.94 (m, 1 H), 7.67 (d, J = 2.4 Hz, 1 H), 7.81 (d, J = 1.0 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 190 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3 \cdot 1.00HCl \cdot 0.25H_2O$) C, H, N.

(1*S*,5*S*)-3-(Pyridin-3-yl)-3,6-diazabicyclo[3.2.0]heptane (33) Bis(tosylate). This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*R*,5*S*)-**20** and 3-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 6 H), 3.23 (dd, J = 10.5, 6.4 Hz, 1 H), 3.36 (dd, J = 10.8, 5.5 Hz, 1 H), 3.50−3.67 (m, 1 H), 3.76 (dd, J = 11.2, 5.1 Hz, 1 H), 4.00 (d, J = 10.8 Hz, 1 H), 4.19−4.37 (m, 2 H), 5.11 (dd, J = 6.8, 5.4 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 4 H), 7.69 (d, J = 8.5 Hz, 4 H), 7.81 (dd, J = 8.8, 5.1 Hz, 1 H), 7.92 (ddd, J = 8.8, 2.7, 1.0 Hz, 1 H), 8.18 (d, J = 5.4 Hz, 1 H), 8.32 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 176 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3 \cdot 2.00C_7H_8SO_3$) C, H, N.

(1*R*,5*R*)-3-(Pyridin-3-yl)-3,6-diazabicyclo[3.2.0]heptane (33) Tosylate. This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*S*,5*R*)-**20** and 3-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 3 H), 3.01 (dd, J = 10.3, 5.9 Hz, 1 H), 3.11 (dd, J = 12.4, 4.9 Hz, 1 H), 3.43−3.56 (m, 1 H), 3.74 (dd, J = 11.0, 5.3 Hz, 1 H), 3.92 (d, J = 10.5 Hz, 1 H), 4.14 (d, J = 12.2 Hz, 1 H), 4.26 (dd, J = 10.9, 8.5 Hz, 1 H), 5.04 (dd, J = 7.1, 4.7 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2 H), 7.30−7.44 (m, 2 H), 7.70 (d, J = 8.5 Hz, 2 H), 8.04 (dd, J = 4.4, 1.4 Hz, 1 H), 8.21 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 176 $(M + H)^+$. Anal. ($C_{10}H_{13}N_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*S*,5*S*)-3-(5-Bromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (34) Hemifumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*R*,5*S*)-**20** and 3,5-dibromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.08 (dd, J = 10.3, 6.3 Hz, 1 H), 3.15 (dd, J = 12.2, 5.1 Hz, 1 H), 3.43−3.56 (m, 1 H), 3.66 (dd, J = 10.7, 4.9 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.2 Hz, 1 H), 4.20 (dd, J = 10.7, 8.3 Hz, 1 H), 4.98 (dd, J = 7.0, 4.9 Hz, 1 H), 6.66 (s, 1 H), 7.47−7.59 (m, 1 H), 8.07 (d, J = 2.0 Hz, 1 H), 8.16 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 256 $(M + H)^+$, 254 $(M + H)^+$. Anal. ($C_{10}H_{12}BrN_3 \cdot 0.50C_4H_4O_4$) C, H, N.

(1*R*,5*R*)-3-(5-Bromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (34) Tosylate. This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*S*,5*R*)-**20** and 3,5-dibromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.32 (s, 3H), 3.06 (dd, J = 10.5, 6.1 Hz, 1 H), 3.16 (dd, J = 12.5, 5.1 Hz, 1 H), 3.43−3.60 (m, 1 H), 3.73 (dd, J = 11.2, 5.1 Hz, 1 H), 3.91 (d, J = 10.5 Hz, 1 H), 4.13 (d, J = 12.2 Hz, 1 H), 4.26 (dd, J = 11.2, 8.5 Hz, 1 H), 5.05 (dd, J = 7.1, 5.1 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 1 H), 7.49−7.56 (m, 1 H), 7.69 (d, J = 8.5 Hz, 2 H), 8.09 (d, J = 2.0 Hz, 1 H), 8.16 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 256 $(M + H)^+$, 254 $(M + H)^+$. Anal. ($C_{10}H_{12}BrN_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*S*,5*S*)-3-(5-Chloropyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (35) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*R*,5*S*)-**20** and 3-bromo-5-chloropyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.08 (dd, J = 10.5, 6.1 Hz, 1 H), 3.17 (dd, J = 12.4, 4.9 Hz, 1 H), 3.44−3.59 (m, 1 H), 3.71 (dd, J = 11.2, 5.1 Hz, 1 H), 3.92 (d, J = 10.5 Hz, 1 H), 4.13 (d, J = 12.5 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.1, 4.7 Hz, 1 H), 6.67 (s, 2 H), 7.39 (t, J = 2.2 Hz, 1 H), 8.00 (d, J = 2.0 Hz, 1 H), 8.13 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 212 $(M + H)^+$, 210 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.05C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-5-(3,6-Diaza-bicyclo[3.2.0]hept-3-yl)nicotinonitrile (36) Tosylate. This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*R*,5*S*)-**20** and 5-bromonicotinonitrile. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.30 (s, 4.2 H), 3.16 (dd, J = 10.7, 6.3 Hz, 1 H), 3.25 (dd, J = 12.8, 7.8 Hz, 1 H), 3.47−3.62 (m, 1 H), 3.74 (dd, J = 11.2, 5.1 Hz, 1 H), 3.98 (d, J = 10.5 Hz, 1 H), 4.20 (d, J = 12.5 Hz, 1 H), 4.28 (dd, J = 11.0, 8.6 Hz, 1 H), 5.08 (dd, J = 6.8, 5.1 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 2.8 H), 7.69 (d, J = 8.5 Hz, 2.8 H), 7.76 (dd, J = 2.7, 1.7 Hz, 1 H), 8.39 (d, J = 1.7 Hz, 1 H), 8.47 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 201 $(M + H)^+$. Anal. ($C_{11}H_{12}N_4 \cdot 1.40C_7H_8SO_3$) C, H, N.

(1*R*,5*R*)-5-(3,6-Diaza-bicyclo[3.2.0]hept-3-yl)nicotinonitrile (36) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*S*,5*R*)-**20** and 5-bromonicotinonitrile. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.14 (dd, J = 10.6, 6.2 Hz, 1 H), 3.24 (dd, J = 12.8, 5.0 Hz, 1 H), 3.55 (m, 1 H), 3.75 (dd, J = 11.0, 5.0 Hz, 1 H), 3.96 (d, J = 10.6 Hz, 1 H), 4.18 (d, J = 12.2 Hz, 1 H), 4.28 (dd, J = 10.9, 8.4 Hz, 1 H), 5.00 (dd, J = 6.8, 4.8 Hz, 1 H), 6.40 (s, 2 H), 7.65 (dd, J = 2.9, 1.2 Hz, 1 H), 8.33 (d, J = 1.2 Hz, 1 H), 8.45 (d, J = 2.8 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 201 $(M + H)^+$. Anal. ($C_{11}H_{12}N_4 \cdot 1.00C_4H_4O_4 \cdot 0.50H_2O$) C, H, N.

(1*S*,5*S*)-3-(5-Methoxypyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (37) Tosylate. This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*R*,5*S*)-**20** and 3-bromo-5-methoxypyridine. ^{1}H NMR (MeOH-d_4, 300 MHz): δ 2.36 (s, 4.2 H), 3.13 (dd, J = 10.7, 6.3 Hz, 1 H), 3.23 (dd, J = 12.5, 5.1 Hz, 1 H), 3.45−3.61 (m, 1 H), 3.75 (dd, J = 11.2, 5.1 Hz, 1 H), 3.87−4.01 (m, 4 H), 4.18 (d, J = 12.5 Hz, 1 H), 4.27 (dd, J = 11.0, 8.6 Hz, 1 H), 5.07 (dd, J = 7.3, 5.3 Hz, 1 H), 7.13 (t, J = 2.4 Hz, 1 H), 7.22 (d, J = 8.1 Hz, 2.8 H), 7.69 (d, J = 8.1 Hz, 2.8 H), 7.85 (d, J = 2.4 Hz, 1 H), 7.90 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 206 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3O \cdot 1.40C_7H_8SO_3 \cdot 0.10H_2O$) C, H, N.

(1*R*,5*R*)-3-(5-Methoxypyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (37) Tosylate. This was prepared according to the representative procedures C(a), D(c), and S(b) using (1*S*,5*R*)-**20** and 3-bromo-5-methoxypyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 3.5 H), 3.08 (dd, J = 10.7, 5.9 Hz, 1 H), 3.18 (dd, J = 12.5, 5.1 Hz, 1 H), 3.44−3.59 (m, 1 H), 3.75 (dd, J = 11.0, 4.9 Hz, 1 H), 3.86−3.98 (m, 4 H), 4.15 (d, J = 12.5 Hz, 1 H), 4.26

(dd, J = 11.0, 8.3 Hz, 1 H), 5.05 (dd, J = 7.1, 5.1 Hz, 1 H), 7.02 (t, J = 2.4 Hz, 1 H), 7.22 (d, J = 8.5 Hz, 2.3 H), 7.69 (d, J = 8.1 Hz, 2.3 H), 7.81 (d, J = 2.4 Hz, 1 H), 7.86 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 206 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3O \cdot 1.15C_7H_8SO_3 \cdot 0.60H_2O$) C, H, N.

(1*S*,5*S*)-3-(5,6-Dimethylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (38) Tosylate. This was prepared according to the representative procedures C(a) and D(d) using (1*R*,5*S*)-**20** and 3-bromo-5,6-dimethylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.30 (s, 3 H), 2.36 (s, 3.8 H), 2.40 (s, 3 H), 2.93 (dd, J = 10.3, 5.9 Hz, 1 H), 3.02 (dd, J = 12.2, 4.7 Hz, 1 H), 3.40−3.54 (m, 1 H), 3.72 (dd, J = 10.8, 5.1 Hz, 1 H), 3.86 (d, J = 10.2 Hz, 1 H), 4.07 (d, J = 12.2 Hz, 1 H), 4.23 (dd, J = 10.8, 8.8 Hz, 1 H), 4.99 (dd, J = 7.1, 4.7 Hz, 1 H), 7.19 (d, J = 2.7 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2.5 H), 7.70 (d, J = 8.1 Hz, 2.5 H), 7.87 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 204 $(M + H)^+$. Anal. ($C_{12}H_{17}N_3 \cdot 1.27C_7H_8SO_3 \cdot 0.20H_2O$) C, H, N.

(1*R*,5*R*)-3-(5,6-Dimethylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (38) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*S*,5*R*)-**20** and 3-bromo-5,6-dimethylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.31 (s, 3 H), 2.40 (s, 3 H), 2.95 (dd, J = 10.3, 5.9 Hz, 1 H), 3.04 (dd, J = 12.2, 4.7 Hz, 1 H), 3.40−3.57 (m, 1 H), 3.74 (dd, J = 11.0, 5.3 Hz, 1 H), 3.88 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.2 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.02 (dd, J = 6.8, 5.1 Hz, 1 H), 6.68 (s, 2.6 H), 7.22 (d, J = 2.7 Hz, 1 H), 7.88 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 204 $(M + H)^+$. Anal. ($C_{12}H_{17}N_3 \cdot 1.30C_4H_4O_4 \cdot 0.20H_2O$) C, H, N.

(1*S*,5*S*)-3-(5-Cyano-6-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (39) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*R*,5*S*)-**20** and 3-bromo-5-cyano-6-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.63 (s, 3 H), 3.05 (dd, J = 10.5, 6.1 Hz, 1 H), 3.15 (dd, J = 12.4, 4.9 Hz, 1 H), 3.43−3.56 (m, 1 H), 3.73 (dd, J = 11.2, 5.1 Hz, 1 H), 3.93 (d, J = 10.5 Hz, 1 H), 4.14 (d, J = 12.5 Hz, 1 H), 4.26 (dd, J = 11.2, 8.5 Hz, 1 H), 5.04 (dd, J = 7.0, 4.9 Hz, 1 H), 6.68 (s, 2 H), 7.62 (d, J = 3.1 Hz, 1 H), 8.33 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 215 $(M + H)^+$. Anal. ($C_{12}H_{14}N_4 \cdot 1.00C_4H_4O_4 \cdot 0.10H_2O$) C, H, N.

(1*R*,5*R*)-3-(5-Cyano-6-methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (39) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*S*,5*R*)-**20** and 3-bromo-5-cyano-6-methylpyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.63 (s, 3 H), 3.05 (dd, J = 10.5, 6.1 Hz, 1 H), 3.14 (dd, J = 12.4, 4.9 Hz, 1 H), 3.42−3.59 (m, 1 H), 3.72 (dd, J = 11.2, 5.1 Hz, 1 H), 3.93 (d, J = 10.5 Hz, 1 H), 4.13 (d, J = 12.5 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.04 (dd, J = 6.8, 5.1 Hz, 1 H), 6.67 (s, 2 H), 7.62 (d, J = 3.1 Hz, 1 H), 8.33 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 215 $(M + H)^+$. Anal. ($C_{12}H_{14}N_4 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-3-(6-Chloropyridin-3-yl)-3,6-diaza-bicyclo[3.2.0]-heptane (40) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*R*,5*S*)-**20** and 2-chloro-5-iodopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.02 (dd, J = 10.5, 6.1 Hz, 1 H), 3.12 (dd, J = 12.4, 4.9 Hz, 1 H), 3.43−3.59 (m, 1 H), 3.72 (dd, J = 11.0, 4.9 Hz, 1 H), 3.89 (d, J = 10.5 Hz, 1 H), 4.10 (d, J = 12.2 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.0, 4.9 Hz, 1 H), 6.68 (s, 2 H), 7.27−7.45 (m, 2 H), 7.98 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 212 $(M + H)^+$, 211 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.00C_4H_4O_4$): C, H, N.

(1*R*,5*R*)-3-(6-Chloropyridin-3-yl)-3,6-diaza-bicyclo[3.2.0]-heptane (40) Fumarate. This was prepared according to the representative procedures C(a), D(c), and S(a) using (1*S*,5*R*)-**20** and 2-chloro-5-iodopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.05 (dd, J = 10.1, 5.1 Hz, 1 H), 3.15 (dd, J = 12.6, 5.1 Hz, 1 H), 3.50 (m, 1 H), 3.75 (dd, J = 11.2, 3.10 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 4.10 (d, J = 12.2 Hz, 1 H), 4.25 (dd, J = 11.2, 8.8 Hz, 1 H), 5.05 (dd, J = 6.8, 4.8 Hz, 1 H), 6.68 (s, 2.4 H), 7.34 (d, J = 8.5 Hz, 1 H), 7.38 (dd, J = 8.9, 3.1 Hz, 1 H), 7.96 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 212 $(M + H)^+$, 210 $(M + H)^+$. Anal. ($C_{10}H_{12}ClN_3 \cdot 1.20C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-3-(6-Chloro-5-methylpyridin-3-yl)-3,6-diaza-bicyclo-[3.2.0]heptane (41) Trifluoroacetate. This was prepared according to the representative procedures C(a) and S(c) using (1*R*,5*S*)-**20** and 2-chloro-3-methyl-5-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.37 (s, 3 H), 3.00 (dd, J = 10.5, 6.1 Hz, 1 H), 3.10 (dd, J = 12.4, 4.9 Hz, 1 H), 3.41−3.58 (m, 1 H), 3.72 (dd, J = 11.2, 5.1 Hz, 1 H), 3.89 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.5 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.3, 5.3 Hz, 1 H), 7.34 (d, J = 3.1 Hz, 1 H), 7.83 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 226 $(M + H)^+$, 224 $(M + H)^+$. Anal. ($C_{11}H_{14}ClN_3 \cdot 1.00CF_3CO_2H$) C, H, N.

(1*R*,5*R*)-3-(6-Chloro-5-methylpyridin-3-yl)-3,6-diaza-bicyclo-[3.2.0]heptane (41) Tosylate. This was prepared according to the representative procedures C(a) and D(d) using (1*S*,5*R*)-**20** and 2-chloro-3-methyl-5-bromopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 6 H), 2.99 (dd, J = 10.3, 5.9 Hz, 1 H), 3.09 (dd, J = 12.5, 4.7 Hz, 1 H), 3.40−3.58 (m, 1 H), 3.73 (dd, J = 11.2, 5.1 Hz, 1 H), 3.88 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.5 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.0, 4.9 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2 H), 7.32 (d, J = 3.1 Hz, 1 H), 7.69 (d, J = 8.5 Hz, 2 H), 7.82 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 226 $(M + H)^+$, 224 $(M + H)^+$. Anal. ($C_{11}H_{14}ClN_3 \cdot 1.01C_7H_8SO_3$) C, H, N.

(1*S*,5*S*)-3-(5,6-Dichloropyridin-3-yl)-3,6-diaza-bicyclo[3.2.0]-heptane (42) Tosylate. This was prepared according to the representative procedures C(a) and D(d) using (1*R*,5*S*)-**20** and 3-bromo-5,6-dichloropyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 3 H), 3.06 (dd, J = 10.3, 6.3 Hz, 1 H), 3.17 (dd, J = 12.5, 5.1 Hz, 1 H), 3.41−3.61 (m, 1 H), 3.72 (dd, J = 10.8, 5.4 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 4.10 (d, J = 12.5 Hz, 1 H), 4.26 (dd, J = 11.0, 8.6 Hz, 1 H), 5.04 (dd, J = 7.1, 5.1 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2 H), 7.52 (d, J = 2.7 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 2 H), 7.95 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 248 $(M + H)^+$, 246 $(M + H)^+$, 244 $(M + H)^+$. Anal. ($C_{10}H_{11}Cl_2N_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*R*,5*R*)-3-(5,6-Dichloropyridin-3-yl)-3,6-diaza-bicyclo[3.2.0]-heptane (42) Tosylate. This was prepared according to the representative procedure C(a) and D(d) using (1*S*,5*R*)-**20** and 2,3-dichloro-5-iodopyridine. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.36 (s, 3 H), 3.06 (dd, J = 10.5, 6.1 Hz, 1 H), 3.16 (dd, J = 12.5, 5.1 Hz, 1 H), 3.42−3.59 (m, 1 H), 3.72 (dd, J = 11.2, 5.1 Hz, 1 H), 3.89 (d, J = 10.5 Hz, 1 H), 4.10 (d, J = 12.5 Hz, 1 H), 4.26 (dd, J = 11.2, 8.5 Hz, 1 H), 5.05 (dd, J = 7.1, 4.7 Hz, 1 H), 7.21 (d, J = 8.1 Hz, 2 H), 7.51 (d, J = 2.7 Hz, 1 H), 7.69 (d, J = 8.1 Hz, 2 H), 7.94 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 248 $(M + H)^+$, 246 $(M + H)^+$, 244 $(M + H)^+$. Anal. ($C_{10}H_{11}Cl_2N_3 \cdot 1.00C_7H_8SO_3$) C, H, N.

(1*R*,5*S*)-tert-Butyl 3-(5-Methylpyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane-6-carboxylate (6-*N*-Boc-43) Hydrochloride. A solution of (1*R*,5*S*)-6-*N*-Boc-**41** (350 mg, 1.00 mmol) in EtOH (20 mL) was stirred with Pd/C (10 wt %, 100 mg) under H_2 (1 atm) at ambient temperature for 10 h. The catalyst was filtered off, and the organic solution was concentrated to give (1*R*,5*S*)-6-*N*-Boc-**43**·HCl (300 mg, 92% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 1.44 (s, 9 H), 2.49 (s, 3 H), 3.10−3.19 (m, 1 H), 3.20−3.29 (m, 2 H), 3.53−3.67 (m, 1 H), 3.88 (d, J = 10.5 Hz, 1 H), 3.98 (d, J = 11.5 Hz, 1 H), 4.13 (t, J = 8.0 Hz, 1 H), 4.90 (dd, J = 6.6, 4.6 Hz, 1 H), 7.77 (s, 1 H), 7.96 (s, 1 H), 8.07 (s, 1 H) ppm. MS (DCI/NH_3) m/z 290 $(M + H)^+$.

(1*S*,5*S*)-3-(5-Methylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (43) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*R*,5*S*)-6-*N*-Boc-**43**·HCl. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.34 (s, 3 H), 3.00 (dd, J = 10.5, 6.1 Hz, 1 H), 3.09 (dd, J = 12.2, 4.7 Hz, 1 H), 3.41−3.60 (m, 1 H), 3.73 (dd, J = 10.8, 5.1 Hz, 1 H), 3.91 (d, J = 10.8 Hz, 1 H), 4.13 (d, J = 12.5 Hz, 1 H), 4.25 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.3, 4.9 Hz, 1 H), 6.68 (s, 2.2 H), 7.22 (s, 1 H), 7.17−7.29 (m, 1 H), 7.89 (s, 1 H), 7.89 (d, J = 1.0 Hz, 1 H), 8.01 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 190 $(M + H)^+$. Anal. ($C_{11}H_{15}N_3 \cdot 1.08C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-*tert*-Butyl 6-(5-Bromopyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane-3-carboxylate (3-*N*-Boc-23). This was prepared according to the representative procedure C(a) using (1*S*,5*S*)-**19b** (0.20 g, 1.0 mmol) and 3,5-dibromopyridine (0.35 g, 1.5 mmol) to provide (1*S*,5*S*)-3-*N*-Boc-**23** (0.16 g, 45.7% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 1.40 [s(br.), 9 H], 3.12 (dd, J = 12.7, 3.7 Hz, 1 H), 3.20−3.35 (m, 2 H), 3.65 (m, 1 H), 3.80−4.05 (m, 3 H), 4.73−4.76 (m, 1 H), 7.06 (t, J = 2.0 Hz, 1 H), 7.70 (d, J = 2.7 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 356 $(M + H)^+$, 354 $(M + H)^+$.

(1*S*,5*S*)-*tert*-Butyl 6-{5-[(Trimethylsilyl)ethynyl]pyridin-3-yl}-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (TMS-3-*N*-Boc-44). A solution of (1*S*,5*S*)-3-*N*-Boc-**23** (140 mg, 0.40 mmol), ethynyltrimethylsilane (100 mg, 1.0 mmol), Et_3N (122 mg, 1.2 mmol), $PdCl_2(PPh_3)_2$ (5.6 mg, 0.008 mmol), and CuI (7.6 mg, 0.004 mmol) in anhydrous DMF (5 mL) was stirred under N_2 at 60−70 °C for 10 h. It was then cooled to ambient temperature, quenched with water (10 mL), and extracted with EtOAc (3 × 50 mL). The combined extracts were concentrated, and the residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 1:1) to provide (1*S*,5*S*)-TMS-3-*N*-Boc-**44** (R_f = 0.50, 90 mg, 60% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 0.05 (s, 9 H), 1.40 [s (br.), 9 H], 3.16 (dd, J = 12.6, 3.6 Hz, 1H), 3.20−3.35 (m, 2 H), 3.65 (m, 1H), 3.85−4.05 (m, 3 H), 4.70 (m, 1 H), 6.68 (m, 1 H), 7.48 (d, J = 2,7 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 372 $(M + H)^+$.

(1*R*,5*S*)-6-(5-Ethynylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (44). A solution of (1*S*,5*S*)-TMS-3-*N*-Boc-**44** (90 mg, 0.24 mmol) in THF (5 mL) was stirred with $Bu_4N^+F^-$ (1 M in THF, 2 mL, 2.0 mmol) at ambient temperature for 1 h. It was then diluted with EtOAc (50 mL), washed with water (2 × 5 mL), and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and stirred with trifluoroacetic acid (1 mL) at ambient temperature for 2 h. The volatiles were removed under reduced pressure, and the residue was purified by chromatography on silica gel (v. CH_2Cl_2: MeOH:NH_3·H_2O = 90:10:2) to give (1*R*,5*S*)-**44** (R_f = 0.2, 45 mg, 94%). ^{1}H NMR (CD_3OD, 300 MHz): δ 2.75 (dd, J = 12.9, 3.4 Hz, 1 H), 2.90 (dd, J = 12.25, 6.4 Hz, 1 H), 3.10 (m, 1 H), 3.30 (d, J = 12.6 Hz, 1 H), 3.40 (d, J = 12.9 Hz, 1 H), 3.70 (dd, J = 7.8, 3.3 Hz, 1 H), 3.76 (s, 1H), 3.96 (t, J = 7.8 Hz, 1 H), 4.70 (dd, J = 6.1, 3.3 Hz, 1 H), 6.94 (dd, J = 2.7, 1.7 Hz, 1 H), 7.77 (d, J = 2.7 Hz, 1 H), 7.94 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 200 $(M + H)^+$.

(1*R*,5*S*)-6-(5-Ethynylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane(44) Fumarate. This was prepared according to the representative procedure S(a) using (1*R*,5*S*)-**44**. ^{1}H NMR (MeOH-d_4, 300 MHz): δ 3.16 (dd, J = 12.6, 3.7 Hz, 1 H), 3.35−3.40 (m, 2 H), 3.45 (m, 1 H), 3.70−3.85 (m, 3 H), 4.05 (t, J = 7.8 Hz, 1 H), 4.96 (dd, J = 6.1, 3.4 Hz, 1 H), 6.70 (s, 2.4 H), 7.10 (dd, J = 2.4, 2.0 Hz, 1 H), 7.85 (d, J = 3.0 Hz, 1 H), 7.96 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 200 $(M + H)^+$. Anal. ($C_{12}H_{13}N_3$·$1.20C_4H_4O_4$·$1.00H_2O$) C, H, N.

(1*R*,5*R*)-*tert*-Butyl 6-(5-Bromopyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane-3-carboxylate (3-*N*-Boc-23). A solution of (1*S*,5*R*)-**23** (510 mg, 2.0 mmol), di-*tert*-butyl dicarbonate (660 mg, 3.0 mmol), and Et_3N (404 mg, 4.0 mmol) in CH_2Cl_2 (20 mL) was stirred at ambient temperature for 10 h and then concentrated. The residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 1:1) to give (1*R*,5*R*)-3-*N*-Boc-**23** (R_f = 0.5, 700 mg, 98% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 1.40 [s(br.), 9 H], 3.14 (dd, J = 12.9, 4.0 Hz, 1 H), 3.20−3.35 (m, 2 H), 3.65 (m, 1 H), 3.85−4.05 (m, 3 H), 4.74 (dd, J = 5.4, 3.7 Hz, 1 H), 7.07 (t, J = 2.0 Hz, 1 H), 7.68 (d, J = 2.7 Hz, 1H), 7.90 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 356 $(M + H)^+$, 354 $(M + H)^+$.

(1*R*,5*R*)-*tert*-Butyl 6-{5-[(Trimethylsilyl)ethynyl]pyridin-3-yl}-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (TMS-3-*N*-Boc-44). This was prepared according to the procedure for (1*S*,5*S*)-TMS-3-*N*-Cbz-**44** using (1*R*,5*R*)-3-*N*-Boc-**23** (140 mg, 0.40 mmol) to provide (1*R*,5*R*)-TMS-3-*N*-Boc-**44** (120 mg, 80%). ^{1}H NMR (CD_3OD, 300 MHz): δ 0.05 (s, 9 H), 1.40 [s (br.), 9 H], 3.16−3.35 (m, 3 H), 3.50 (m, 1H), 3.85−4.05 (m, 3 H), 4.50 (m, 1 H), 6.68 (m, 1 H), 7.48 (d, J = 2.7 Hz, 1 H), 7.67 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 372 $(M + H)^+$.

(1*S*,5*R*)-6-(5-Ethynylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (44). This was prepared according to the procedure for (1*R*,5*S*)-**44** using (1*R*,5*R*)-TMS-3-*N*-Boc-**44** (120 mg, 0.32 mmol) to give (1*S*,5*R*)-**44** (60 mg, 93.7%). ^{1}H NMR (CD_3OD, 300 MHz): δ 2.57 (dd, J = 12.6, 4.1 Hz, 1 H), 2.75 (dd, J = 12.5, 6.4 Hz, 1 H), 3.10−3.30 (m, 3 H), 3.60 (dd, J = 7.8, 3.4 Hz, 1 H), 3.70 (s, 1H), 3.96 (t, J = 7.8 Hz, 1 H), 4.70 (dd, J = 6.1, 3.3 Hz, 1 H), 6.94 (dd, J = 2.7, 1.7 Hz, 1 H), 7.72 (d, J = 2.7 Hz, 1 H), 7.90 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 200 $(M + H)^+$.

(1*S*,5*R*)-6-(5-Ethynylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (44) Fumarate. This was prepared according to the representative procedure S(a) using (1*S*,5*R*)-**44** (60 mg, 0.30 mmol) to give (1*S*,5*R*)-**44** fumarate (86 mg, 92% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.16 (dd, J = 12.6, 3.4 Hz, 1 H), 3.35−3.40 (m, 2 H), 3.45 (m, 1 H), 3.70−3.85 (m, 3 H), 4.05 (t, J = 7.8 Hz, 1 H), 4.96 (dd, J = 6.4, 3.3 Hz, 1 H), 6.70 (s, 2.8 H), 7.10 (dd, J = 2.3, 1.7 Hz, 1 H), 7.85 (d, J = 2.7 Hz, 1 H), 8.00 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 200 $(M + H)^+$. Anal. ($C_{12}H_{13}N_3$·$1.42C_4H_4O_4$·$0.30H_2O$) C, H, N.

(1*S*,5*S*)-Benzyl 6-(5-(Oxazol-2-yl)pyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane-3-carboxylate (3-*N*-Cbz-45). A solution of (1*S*,5*S*)-3-*N*-Cbz-**23** (125 mg, 0.32 mmol), 2-(tributylstannyl)oxazole (230 mg, 0.64 mmol), and $PdCl_2(PPh_3)_2$ (5.6 mg, 0.008 mmol) in anhydrous MeCN (10 mL) was stirred under N_2 at 80 °C for 4 h. It was then cooled down to ambient temperature, concentrated under reduced pressure, and purified by chromatography on silica gel (v. EtOAc:hexanes = 4:1) to provide (1*S*,5*S*)-3-*N*-Cbz-**45** (R_f = 0.40, 120 mg, 99% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.25 (dd, J = 12.5, 3.7 Hz, 1 H), 3.31−3.42 (m, 1 H), 3.69 (dd, J = 7.8, 3.4 Hz, 1 H), 3.93−4.29 (m, 4 H), 4.73−4.81 (m, 1 H), 5.01−5.23 (m, 2 H), 7.04−7.30 (m, 3 H), 7.25−7.49 (m, 4 H), 7.86 (d, J = 2.7 Hz, 1 H), 8.04 (s, 1 H), 8.49 (d, J = 2.0 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 377 $(M + H)^+$.

2-{5-[(1*R*,5*S*)-3,6-Diazabicyclo[3.2.0]heptan-6-yl]pyridin-3-yl}oxazole (45) Bisfumarate. This was prepared according to the representative procedures D(a) and S(a) using (1*S*,5*S*)-3-*N*-Cbz-**45**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.22 (dd, J = 12.5, 3.4 Hz, 1 H), 3.38 (d, J = 7.5 Hz, 1 H), 3.43−3.56 (m, 1 H), 3.74 (d, J = 12.5 Hz, 1 H), 3.80 (d, J = 12.5 Hz, 1 H), 3.84 (dd, J = 8.1, 3.1 Hz, 1 H), 4.12 (t, J = 8.0 Hz, 1 H), 5.01 (dd, J = 6.4, 3.4 Hz, 1 H), 6.70 (s, 4 H), 7.36 (d, J = 1.0 Hz, 1 H), 7.54 (dd, J = 2.7, 1.7 Hz, 1 H), 8.00 (d, J = 3.1 Hz, 1 H), 8.06 (s, 1 H), 8.59 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 243 $(M + H)^+$. Anal. ($C_{13}H_{14}N_4O$·$2.00C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-Benzyl 6-[5-(1-Methyl-1H-imidazol-5-yl)pyridin-3-yl]-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (3-*N*-Cbz-46). This was prepared according to the procedure for the synthesis of (1*S*,5*S*)-3-*N*-Cbz-**45** using (1*S*,5*S*)-3-N-Cbz-**23** (200 mg, 0.52 mmol) and 1-methyl-5-(tributylstannyl)-1H-imidazole (385 mg, 1.04 mmol) to provide (1*S*,5*S*)-3-*N*-Cbz-**46** (200 mg, 99% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.23 (dd, J = 12.7, 3.9 Hz, 1 H), 3.30−3.41 (m, 1 H), 3.62−3.84 (m, 5 H), 3.89−4.26 (m, 3 H), 4.78 (dd, J = 6.3, 3.9 Hz, 1 H), 5.00−5.24 (m, 2 H), 6.92 (dd, J = 2.7, 2.0 Hz, 1 H), 7.11 (s, 1 H), 7.16−7.46 (m, 5 H), 7.74 (s, 1 H), 7.77 (d, J = 2.7 Hz, 1 H), 7.96 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 390 $(M + H)^+$.

(1*R*,5*S*)-6-(5-(1-Methyl-1H-imidazol-5-yl)pyridin-3-yl)-3,6-diazabicyclo[3.2.0]heptane (46) Bisfumarate. This was prepared according to the representative procedures D(a) and S(a) using (1*S*,5*S*)-3-*N*-Cbz-**46**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.19 (dd, J = 12.5, 3.4 Hz, 1 H), 3.32−3.39 (m, 1 H), 3.41−3.57 (m, 1 H), 3.75 (t, J = 12.7 Hz, 2 H), 3.74 (s, 3 H), 3.82 (dd, J = 8.1, 3.1 Hz, 1 H), 4.09 (t, J = 7.8 Hz, 1 H), 4.98 (dd, J = 6.4, 3.4 Hz, 1 H), 6.71 (s, 4 H), 7.08 (dd, J = 2.7, 2.0 Hz, 1 H), 7.16 (d, J = 1.0 Hz, 1 H), 7.81 (d, J = 0.7 Hz, 1 H), 7.90 (d, J = 2.7 Hz, 1 H), 8.07 (d, J = 2.0 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 256 $(M + H)^+$. Anal. ($C_{14}H_{17}N_5$·$2.00C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-Benzyl 6-(5,6-Dibromopyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane-3-carboxylate (3-*N*-Cbz-47): Representative Pro-

cedure for Bromination. A solution of *N*-bromosuccinimide (92 mg, 0.52 mmol) in MeCN (5 mL) was slowly added to the solution of (1*S*,5*S*)-3-*N*-Cbz-**23** (200 mg, 0.52 mmol) in MeCN (10 mL) at −20 to 0 °C over 5 min. The mixture was then stirred at 0−20 °C for 1 h and quenched with water (5 mL). It was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 5 mL) and then concentrated. The residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 1:1) to provide (1*S*,5*S*)-3-*N*-Cbz-**47** (R_f = 0.5, 100 mg, 42% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.11−3.23 (m, 2 H), 3.33−3.43 (m, 1 H), 3.59 (dd, J = 8.0, 3.6 Hz, 1 H), 3.90−4.12 (m, 3 H), 4.72 (dd, J = 6.1, 4.1 Hz, 1 H), 4.99−5.33 (m, 2 H), 7.13 (d, J = 2.4 Hz, 1 H), 7.17−7.44 (m, 5 H), 7.52 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 470 $(M + H)^+$, 468 $(M + H)^+$, 466 $(M + H)^+$.

(1*R*,5*S*)-6-(5,6-Dibromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (47) Bis(tosylate). This was prepared according to the representative procedures D(b) and S(b) using (1*S*,5*S*)-3-*N*-Cbz-**47**. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.37 (s, 6 H), 3.17 (dd, J = 12.7, 3.2 Hz, 1 H), 3.33−3.38 (m, 1 H), 3.40−3.52 (m, 1 H), 3.65−3.80 (m, 3 H), 4.03 (t, J = 8.0 Hz, 1 H), 4.89−4.98 (m, 1 H), 7.23 (d, J = 8.5 Hz, 4 H), 7.31 (d, J = 2.7 Hz, 1 H), 7.66 (d, J = 2.7 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 4 H) ppm. MS (DCI/NH_3) m/z 336 $(M + H)^+$, 334 $(M + H)^+$, 332 $(M + H)^+$. Anal. ($C_{10}H_{11}Br_2N_3 \cdot 2.00C_7H_8SO_3 \cdot 0.48H_2O$) C, H, N.

(1*R*,5*S*)-6-(6-Bromo-5-cyano-pyridin-3-yl)-3,6-diaza-bicyclo-[3.2.0]heptane (48) Bisfumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*S*,5*S*)-3-*N*-Boc-**48**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.20 (dd, J = 12.0, 3.0 Hz, 1 H), 3.28−3.38 (m, 2 H), 3.45 (m, 1 H), 3.68−3.72 (m, 2 H), 4.08 (t, J = 8.8 Hz, 1 H), 4.95 (m, 1 H), 6.70 (s, 4.00 H), 7.40 (d, J = 3.0 Hz, 1 H), 7.90 (d, J = 3.0 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 281 $(M + H)^+$, 279 $(M + H)^+$. Anal. ($C_{11}H_{11}BrN_4 \cdot 2.00C_4H_4O_4$) C, H, N.

(1*R*,5*S*)-6-(6-Bromo-5-methoxy-pyridin-3-yl)-3,6-diaza-bicyclo-[3.2.0]heptane (49) Trifluoroacetate. This was prepared according to the representative procedures D(b) and S(c) using (1*S*,5*S*)-3-*N*-Cbz-**49**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.18 (dd, J = 12.5, 3.7 Hz, 1 H), 3.32−3.39 (m, 2 H), 3.46 (ddd, J = 14.1, 7.3, 2.7 Hz, 1 H), 3.66−3.81 (m, 3 H), 3.90 (s, 3 H), 4.04 (t, J = 8.0 Hz, 1 H), 4.93 (dd, J = 6.4, 3.4 Hz, 1 H), 6.58 (d, J = 2.4 Hz, 1 H), 7.25 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 286 $(M + H)^+$, 284 $(M + H)^+$. Anal. ($C_{11}H_{14}N_3OBr \cdot 1.00CF_3CO_2H \cdot 0.50H_2O$) C, H, N.

(1*S*,5*S*)-*tert*-Butyl 6-(6-Bromo-5-carbamoylpyridin-3-yl)-3,6-diazabicyclo[3.2.0]heptane-3-carboxylate (3-*N*-Boc-50). A solution of (1*S*,5*S*)-3-*N*-Boc-**48** (383 mg, 1.0 mmol), urea hydrogen peroxide (953 mg, 10.1 mmol), and K_2CO_3 (14 mg, 0.1 mmol) in acetone−water (v., 1:1, 10 mL) was stirred at ambient temperature for 10 h. It was then diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous NH_4Cl solution (2 × 5 mL) and brine (2 × 5 mL). The organic solution was concentrated, and the residue was purified by chromatography on silica gel (v. EtOAc:hexanes = 1:1) to provide (1*S*,5*S*)-3-*N*-Boc-**50** (R_f = 0.3, 203 mg, 51% yield). ^{1}H NMR (CD_3OD, 300 MHz): δ 1.44 (s, 9 H), 3.14 (dd, J = 13.6, 4.1 Hz, 1 H), 3.27−3.40 (m, 2 H), 3.66 (dd, J = 8.1, 3.1 Hz, 1 H), 3.87 (d, J = 10.5 Hz, 1 H), 3.93 (d, J = 12.9 Hz, 1 H), 4.01 (t, J = 8.0 Hz, 1 H), 4.71 (dd, J = 5.8, 3.7 Hz, 1 H), 6.92 (d, J = 3.1 Hz, 1 H), 7.60 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 399 $(M + H)^+$, 397 $(M + H)^+$.

5-[(1*R*,5*S*)-3,6-Diazabicyclo[3.2.0]heptan-6-yl]-2-bromonicotinamide (50) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*S*,5*S*)-3-*N*-Boc-**50**. ^{1}H NMR (D_2O, 300 MHz): δ 3.22 (dd, J = 12.7, 3.2 Hz, 1 H), 3.32−3.44 (m, 1 H), 3.45−3.61 (m, 1 H), 3.77−3.83 (m, 3 H), 4.08 (t, J = 8.0 Hz, 1 H), 4.99 (dd, J = 5.9, 3.2 Hz, 1 H), 6.57 (s, 2 H), 7.10 (d, J = 3.1 Hz, 1 H), 7.74 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 299 $(M + H)^+$, 297 $(M + H)^+$. Anal. ($C_{11}H_{13}BrN_4O \cdot 1.00C_4H_4O_4 \cdot 0.20H_2O$) C, H, N.

(1*S*,5*S*)-3-(5,6-Dibromopyridin-3-yl)-3,6-diazabicyclo[3.2.0]-heptane (51) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*R*,5*S*)-6-*N*-Boc-**51**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.06 (dd, J = 10.5, 6.1 Hz, 1 H), 3.16 (dd, J = 12.4, 4.9 Hz, 1 H), 3.43−3.60 (m, 1 H), 3.71 (dd, J = 11.0, 5.3 Hz, 1 H), 3.89 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.2 Hz, 1 H), 4.25 (dd, J = 11.2, 8.8 Hz, 1 H), 5.03 (dd, J = 7.0, 5.3 Hz, 1 H), 6.69 (s, 2 H), 7.63 (d, J = 2.7 Hz, 1 H), 7.99 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 336 $(M + H)^+$, 334 $(M + H)^+$, 332 $(M + H)^+$. Anal. ($C_{10}H_{11}Br_2N_3 \cdot 1.00C_4H_4O_4$) C, H, N.

(1*S*,5*S*)-3-(6-Bromo-5-chloropyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (52) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*R*,5*S*)-6-*N*-Boc-**52**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.07 (dd, J = 10.5, 6.4 Hz, 1 H), 3.17 (dd, J = 12.5, 5.1 Hz, 1 H), 3.44−3.59 (m, 1 H), 3.71 (dd, J = 11.2, 5.1 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 4.09 (d, J = 12.5 Hz, 1 H), 4.24 (dd, J = 11.2, 8.5 Hz, 1 H), 5.03 (dd, J = 7.1, 5.1 Hz, 1 H), 6.68 (s, 2 H), 7.50 (d, J = 2.7 Hz, 1 H), 7.96 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 292 $(M + H)^+$, 290 $(M + H)^+$, 288 $(M + H)^+$. Anal. ($C_{10}H_{11}BrClN_3 \cdot 1.00C_4H_4O_4$) C, H, N.

5-[(1*S*,5*S*)-3,6-Diazabicyclo[3.2.0]heptan-3-yl]-2-bromonicotinonitrile (53) Tosylate. This was prepared according to the representative procedures D(c) and S(b) using (1*R*,5*S*)-6-*N*-Boc-**53**. ^{1}H NMR (CD_3OD, 300 MHz): δ 2.37 (s, 3 H), 3.10 (dd, J = 11.0, 6.3 Hz, 1 H), 3.21 (dd, J = 12.7, 5.3 Hz, 1 H), 3.45−3.62 (m, 1 H), 3.72 (dd, J = 10.8, 5.4 Hz, 1 H), 3.93 (d, J = 10.5 Hz, 1 H), 4.13 (d, J = 12.2 Hz, 1 H), 4.26 (dd, J = 11.2, 8.8 Hz, 1 H), 5.06 (dd, J = 6.8, 4.7 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 2 H), 7.63−7.84 (m, 3 H), 8.22 (d, J = 3.1 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 281 $(M + H)^+$, 279 $(M + H)^+$. Anal. ($C_{11}H_{11}BrN_4 \cdot 1.03C_7H_8SO_3 \cdot 0.70H_2O$) C, H, N.

(1*S*,5*S*)-3-(6-Bromo-5-methoxypyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (54) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*R*,5*S*)-6-*N*-Boc-**54**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.06 (dd, J = 10.3, 5.9 Hz, 1 H), 3.15 (dd, J = 12.4, 4.9 Hz, 1 H), 3.41−3.59 (m, 1 H), 3.73 (dd, J = 11.2, 5.1 Hz, 1 H), 3.93 (d, J = 12.5 Hz, 1 H), 3.94 (s, 3 H), 4.11 (d, J = 12.2 Hz, 1 H), 4.26 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.1, 5.1 Hz, 1 H), 6.68 (s, 2 H), 6.94 (d, J = 2.7 Hz, 1 H), 7.58 (d, J = 2.4 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 286 $(M + H)^+$, 284 $(M + H)^+$. Anal. ($C_{11}H_{14}BrN_3O \cdot 1.02C_4H_4O_4 \cdot 0.80H_2O$) C, H, N.

(1*R*,5*R*)-3-(6-Bromo-5-methoxypyridin-3-yl)-3,6-diazabicyclo-[3.2.0]heptane (54) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*S*,5*R*)-6-*N*-Boc-**54**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.05 (dd, J = 10.5, 6.1 Hz, 1 H), 3.15 (dd, J = 12.5, 5.1 Hz, 1 H), 3.44−3.60 (m, 1 H), 3.73 (dd, J = 10.8, 5.1 Hz, 1 H), 3.93 (d, J = 12.5 Hz, 1 H), 3.94 (s, 3 H), 4.12 (d, J = 12.5 Hz, 1 H), 4.26 (dd, J = 11.0, 8.6 Hz, 1 H), 5.03 (dd, J = 7.1, 5.1 Hz, 1 H), 6.68 (s, 2 H), 6.94 (d, J = 2.7 Hz, 1 H), 7.57 (d, J = 2.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 286 $(M + H)^+$, 284 $(M + H)^+$. Anal. ($C_{11}H_{14}BrN_3O \cdot 1.00C_4H_4O_4 \cdot 0.40H_2O$) C, H, N.

5-[(1*R*,5*S*)-3,6-Diazabicyclo[3.2.0]heptan-6-yl]-*N*-hydroxynicotinimidamide (55) Fumarate. This was prepared according to the representative procedures D(c) and S(a) using (1*S*,5*S*)-3-*N*-Boc-**55**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.15 (dd, J = 12.5, 3.4 Hz, 1 H), 3.32−3.36 (m, 1 H), 3.38−3.50 (m, 1 H), 3.70 (d, J = 12.2 Hz, 1 H), 3.74 (d, J = 12.6 Hz, 1 H), 3.79 (dd, J = 7.8, 3.1 Hz, 1 H), 4.06 (t, J = 8.0 Hz, 1 H), 4.93 (dd, J = 6.4, 3.4 Hz, 1 H), 6.68 (s, 2 H), 7.20 (dd, J = 2.7, 2.0 Hz, 1 H), 7.89 (d, J = 2.7 Hz, 1 H), 8.24 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 234 $(M + H)^+$. Anal. ($C_{11}H_{15}N_5O \cdot 1.00C_4H_4O_4$) C, H, N.

3-{(1*R*,5*S*)-3,6-Diazabicyclo[3.2.0]heptan-6-yl}-5-cyanopyridine 1-oxide (56) Fumarate. This was prepared according to the representative procedure D(c) and S(a) using 3-*N*-Boc-**56**. ^{1}H NMR (CD_3OD, 300 MHz): δ 3.18 (dd, J = 12.5, 3.4 Hz, 1 H), 3.33−3.38 (m, 1 H), 3.39−3.51 (m, 1 H), 3.66−3.86 (m, 3 H), 4.06 (t, J = 8.0 Hz, 1 H), 4.94 (dd, J = 6.3, 3.6 Hz, 1 H), 6.68 (s, 2 H), 7.21 (dd, J = 2.7, 2.0 Hz, 1 H), 7.89 (d, J = 2.7 Hz, 1 H), 8.25 (d, J = 1.7 Hz, 1 H) ppm. MS (DCI/NH_3) m/z 234 $(M + NH_4)^+$. Anal. ($C_{11}H_{12}N_4O \cdot 1.10C_4H_4O_4 \cdot 1.05H_2O$) C, H, N.

Binding Assay. Binding assay conditions were modified from the procedures described in Pabreza et al.[28b] 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 was 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} values using the Cheng−Prusoff equation, where $K_i = IC_{50}/(1 + [\text{ligand}]/K_D)$.

Functional Assay. HEK-293 cell lines expressing the recombinant human nAChRs α4β2 and α3β4 subunit combinations were used in the determination of functional nAChR agonist activity by measuring intracellular calcium changes using the fluorometric imaging plate reader (FLIPR; 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 (Sigma, 75 μL/well of 0.01 g/L solution ≥ 30 min) and allowed to incubate for 24−48 h at 37 °C in 5% CO_2 in a humidified environment. After the media were aspirated off, the cell lines 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 (Sigma, United Kingdom) in NMDG 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 NMDG 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 reference peak response for the positive control of 100 μM nicotine. Dose−response data were fitted using a single sigmoidal function in GraphPad Prism (San Diego, CA) for determination of EC_{50} and maximum response. Data are expressed as means ± SEM (*n* of six represents two replicates across three separate plates).

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Supporting Information Available: Experimental details and spectra data for (1*R*,5*R*)-**19a**, (1*S*,5*R*)-**20**, and intermediates of **22**−**31**, **33**−**43**, **45**−**49**, and **51**-**56** as well as elemental analysis for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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