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Synthesis, nicotinic acetylcholine receptor binding, in vitro and in vivo pharmacology properties of 3′-(substituted pyridinyl)-deschloroepibatidine analogs

Pauline W. Ondachi[a], **Zhuo Ye**[b], **Ana H. Castro**[b], **Charles W. Luetje**[b], **M. Imad Damaj**[c], **S. Wayne Mascarella**[a], **Hernán A. Navarro**[a], and **F. Ivy Carroll**[a,*]

[a]Center for Drug Discovery, Research Triangle Institute, PO Box 12194, Research Triangle Park, NC 27709-2194

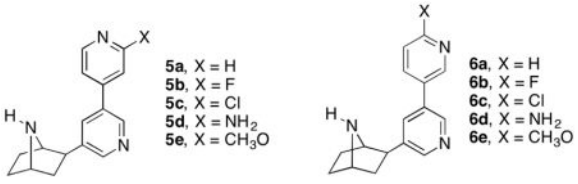
[b]Department of Molecular and Cellular Pharmacology, Miller School of Medicine, University of Miami, Miami, Florida 33101

[c]Department of Pharmacology and Toxicology, Virginia Commonwealth University Medical Campus, P.O. Box 980615, Richmond, Virginia 23298

Abstract

Over the last several years we have synthesized and studied the in vitro and in vivo nAChR pharmacological properties of epibatidine (**4**) analogs. In this study we report the synthesis, nAChR in vitro and in vivo pharmacological properties of 3′-(substituted pyridinyl)-deschloroepibatidine analogs (**5a–e** and **6a–e**). All of the analogs had high binding affinity for α4β2*-nAChRs. Several of the analogs were potent antagonists of α4β2-nAChRs in in vitro efficacy tests and were potent antagonists of nicotine-induced antinociception in the mouse tail-flick test. Compound **6b** had a K_i = 0.13 nM in the binding assay, 25- and 46-fold selectivity for the α4β2*-nAChR relative to the α3β4- and α7-nAChR, respectively, in the in vitro efficacy test and an AD_{50} = 0.13 μg/kg in the tail-flick test. Combined with favorable calculated physiochemical properties compared to varenicline, our findings suggest that **6b** should be considered for development as a potential pharmacotherapy for treating nicotine addiction and other CNS disorders.

Graphical abstract



*Corresponding author: Dr. F. Ivy Carroll, Research Triangle Institute, Post Office Box 12194, Research Triangle Park, NC 27709-2194, Telephone: 919 541-6679, Fax: 919 541-8868 fic@rti.org.

Keywords

Nicotine receptor; epibatidine analogs; nAChR antagonist; varenicline; in vitro/in vivo study

1. Introduction

Tobacco use is the leading preventable cause of disease, disability, and death. Each year, smoking-related diseases are responsible for nearly 6 million premature deaths globally[1] and approximately 443,000 premature deaths in the United States.[2] The continued use of tobacco products is due to addiction to nicotine (**1**), which is present in the various tobacco products. Nicotine exerts its effects through action at nicotinic receptors (nAChRs), a family of acetylcholine gated ion channels. These receptors exist in the periphery and in the CNS and are expressed in various brain regions involved in neuronal development, learning and memory formation, pain and reward. Neuronal nicotinic acetylcholine receptors are pentamers of homomeric or heteromeric combinations of alpha (alpha2-alpha10) and beta (beta2-beta4) subunits, which have different pharmacological and biophysical properties and locations in the brain. The major contributor to high affinity nAChR binding in the brain is the α4β2-nAChR.[3] A primary function of nAChRs in the CNS is modulation of the release of various neurotransmitters, including dopamine, glutamate, GABA, norepinephrine and acetylcholine.[4–6] Even though nicotine (**1**) dependence has a huge impact on global health, drugs for treating tobacco use remain limited. At present, bupropion (**2**), varenicline (**3**), and nicotine replacement therapies (NRT) are the only Food and Drug Administration (FDA)-approved therapies. Since only about 20% of smokers are able to maintain long-term (12-months) abstinence with present therapies,[7, 8] new and improved pharmacotherapies are needed. Over the last several years we have synthesized and studied the nAChR properties of a number of epibatidine (**4**) analogs [9–16] as a way to identify compounds that have the potential as pharmacotherapies useful for treating smokers. In this study we report the synthesis, nAChR in vitro and in vivo pharmacological properties of 3′-(substituted pyridinyl)-deschloroepitatidine analogs (**5a–e** and **6a–e**).

2. Chemistry

The synthesis of compounds **5a–e** is given in Scheme 1. Suzuki cross-coupling of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane(**7**)[12] with 4-pyridine boronic acid in the presence of tetrakis(triphenylphosphine) palladium(0), potassium carbonate in a mixture of 1,2-dimethoxyethane and water, heated at 100 °C for 24 h in a sealed tube provided **8a**. Suzuki cross-couplings of racemic **7** with commercially available 2-fluoropyridine-4-boronic acid or 2-chloropyridine-4-boronic acid in the presence palladium diacetate, tri-*o*-tolylphosphine, sodium carbonate in a 1,2-dimethoxyethane and water mixture heated at 80 °C for 5 h furnished the bipyridine derivatives **8b** and **8c**, respectively. Removal of the Boc-protection in compounds **8a–c** was accomplished using trifluoroacetic acid in methylene chloride stirred at room temperature for 1 h to provide analogs **5a–c**. In order to prepare **5d** and **5e**, compound **7** was first transformed to boronic ester **9** by cross-coupling using bis(pinacolato)diboron in the presence of potassium acetate, and palladium(II) dichloride [$PdCl_2$(dppf)] in 1,4-dioxane, heated at 110 °C overnight. The

resulting boronic ester **9** was further subjected to cross-coupling reactions with either 2-amino-4-bromopyridine or 4-bromo-2-methoxypyridine in the presence of tetrakis(triphenylphosphine) palladium(0), potassium carbonate in a 1,4-dioxane and water mixture heated at 110 °C in a sealed tube overnight to furnish the compounds **8d** and **8e**. Removal of the Boc-protecting group with trifluroacetic acid provided the amines **5d** and **5e** respectively.

Compounds **6a–e** were synthesized by procedures similar to those used to prepare **5a–e** (Scheme 2). Thus, Suzuki cross-coupling reactions of **7** with either 2-flouro-5-boronic acid or 2-chloro-5-boronic acid in the presence of palladium diacetate, tri-*o*-tolylphosphine, sodium carbonate in a 1,2-dimethoxyethane and water mixture heated at 80 °C for 5 h furnished the bipyridine derivatives **10b** and **10c**. In a similar fashion, pyridine-3-boronic acid, 2-aminopyridine-5-boronic acid and 2-methoxypyridine-5-boronic acid were subjected to cross coupling reactions with compound **7** in the presence of tetrakis(triphenylphosphine) palladium (0), potassium carbonate, heated at reflux for 24 h in a 1,4-dioxane, and water mixture to provide the desired cross-coupled products **10a, d,** and **e** in good yields. Removal of the Boc protecting group in compounds **10a–e** was accomplished using trifluoroacetic acid in methylene chloride to provide analogs **6a–e**.

3. Results and Discussion

The nAChR binding affinities and the in vitro functional nicotinic pharmacological properties of 3′-(substituted pyridinyl) deschloroepibatadine analogs **5a–e** and **6a–e** were determined. The K_i values for inhibition of [^{3}H]epibatidine binding at the α4β2*-nAChR for compounds **5a–e** and **6a–e** along with reference compounds nicotine (**1**), nat-epibatidine (**4**), and varenicline (**3**) are given in Table 1. Compounds **5a–e** and **6a–e** all had sub-nanomolar K_i values. The K_i values for **5a–e** ranged from 0.094 for **5e** to 0.38 nM for **5d** and for **6a–e**, from 0.12 for **6a** to 0.90 nM for **6d** compared to 1.5, 0.026, and 0.12 for nicotine, epibatidine, and varenicline, respectively. The 4′-pyridyl and 3′-pyridyl analogs **5a** and **6a**, respectively, had K_i values of 0.22 and 0.81 nM, respectively. Substitution of **5a** and **6a** with 3′- and 4′-substituents, respectively, had only small effects on the α4β2*-nAChR binding affinity. Analyses of the data show that the presence of 3′- or 4′-substituents on the 4′-pyridyl (**5b–e**) and 3′-pyridyl ring (**6b–e**) did not show any clear structure binding affinity pattern to the K_i values. However, with the exception of the chloro substituent, each of the 3′-substituted **5b–e** analogs with K_i values of 0.094 to 0.38 nM, were slightly more potent than the corresponding 4′-substituted **6b–e** analogs, which had K_i values of 0.12 to 0.90 nM. In the case of the **6b–e** series, the two highest affinity compounds were the electron-donating 3′-methoxy analogue **5e** (K_i = 0.094 nM) and the electron-withdrawing 3′-fluoro analogue (K_i = 0.18 nM). For the 4′-substituted 3′-pyridyl analogs the 4′-chloro and 4′-fluoro electron-withdrawing analogs **6c** and **6b** (K_i = 0.12 and 0.13 nM, respectively) had lower K_i values than the 3′-amino and 3′-methoxy electron-donating analogs **6d** and **6e** (K_i = 0.90 and 0.27 nM, respectively).

The receptor subtype selectivity of **5a–e** and **6a–e** was initially assessed in an electrophysiological assay using rat α4β2-, α3β4-, and α7-nAChRs expressed in Xenopus oocytes and assayed by a two-electrode voltage clamp. Compounds were compared to

previously determined values for nicotine, [9] nat-epibatidine, [9] and varenicline [9] (Table 1). To assess potential agonist activity, current responses to a high concentration (100 μM) of each compound were compared to the maximum response that can be achieved with acetylcholine. Unlike nat-epibatidine, which is a full agonist at α4β2-, α3β4-, and α7-nAChRs, compounds **5a–e** and **6a–e** showed little or no agonist activity at α4β2-nAChR. The 3′- and 4′-amino analogs **5d** and **6d**, respectively, had little or no agonist activity at α3β4-nAChRs, while all the other **5** and **6** analogs displayed a low level of agonist activity at this subtype. At α7-nAChRs, compounds **6b** and **6e** had little or no agonist activity, compounds **5a–c**, **6a**, and **6c–d** displayed low levels of agonist activity and compounds **5d** and **5e**, with 12 and 16% of the maximal ACh response, showed moderate levels of agonist activity. All of the compounds **5a–e** and **6a–e** showed substantially lower agonist activity at α4β2-, α3β4-, and α7-nAChRs than varenicline.

As an initial assessment of potential antagonist activity, a high concentration (100 μM) of each compound was tested for the ability to inhibit current responses to an EC_{50} concentration of ACh (Table 1). Compounds **5a–c, 5e, 6a** and **6c** displayed a similar selectivity profile, with substantial antagonist activity at α4β2-nAChRs, somewhat less antagonist activity at α3β4-nAChRs and much less antagonist activity at α7-nAChRs. Compound **6e** had a similar rank order of activity (α4β2> α3β4 > α7), but the antagonist activity at α7-nAChRs was still substantial (> 80% inhibition). Compounds **5d** and **6d** showed similarly strong inhibition at α4β2- and α3β4-nAChRs, with less antagonist activity at α7-nAChRs. Compound **6b** showed strong inhibition at α4β2-nAChRs, with similarly lesser antagonist activity at α3β4- and α7-nAChRs.

Compounds **5a–c, 5e**, **6a–c** and **5e** were examined for subtype selectivity in more detail by generating IC_{50} values from concentration-inhibition curves (Table 2). Each of these compounds was a more potent antagonist at α4β2-nAChRs than at α3β4- and α7-nAChRs. In addition, each of the compounds was less potent at the α7- than the α3β4 and α4β2-nAChR. The most potent compounds at α4β2-nAChRs were **5b, 5e, 6b,** and **6e**, which had IC_{50} values of 2.9, 1.2, 1.3, and 1.8 μM, respectively. Compound **6b**, with 25- and 46-fold selectively for α4β2-nAChRs, relative to the α3β4 and α7-nAChRs, respectively, was the most α4β2-selective compound. Compound **6e**, with an IC_{50} value of 8.2 μM was the most potent compound at the α3β4-nAChR. All of the compounds showed IC_{50} values of 30 μM or greater at the α7-nAChR.

The 3′-substituted 4′-pyridyl analogs **5a–e** and the 4′-substituted 3-pyridyl analogs **6a–e** were evaluated for their in vivo nAChR properties in mice, and the results were compared to the properties of varenicline (Table 1). None of the **5a–e** or **6a–e** compounds displayed any agonist activity in the mice tail-flick or hot-plate tests. Similar to varenicline all of the compounds except **5d** had agonist activity in the hypothermia and spontaneous activity assays. In the hypothermia test the ED_{50} values ranged form 2.78 mg/kg for **6b** to 10 mg/kg for **5e**, compared to an ED_{50} = 2.8 mg/kg for varenicline. For the spontaneous activity the ED_{50} values varied from 0.56 mg/kg for both **6c** and **6e** to 4 mg/kg for **5e**, compared to an ED_{50} = 2.1 mg/kg for varenicline. The discrepancy between the high binding affinity of **5a–e** and **6a–e** for α4β2*-nAChR and their absence of agonist effects in the tail-flick and hot-

plate antinociceptive tests suggested that these compounds might act as functional nAChR antagonists in the two pain tests. As expected, all of the compounds were antagonists of nicotine-induced antinociception in the tail-flick test, with AD_{50} values of 0.3, 0.5, 0.5, 0.68, 1, 1.5, and 2 μg/kg for **5e**, **6c**, **6e**, **6a**, **5d**, **6d**, and **6b**. Even **5a** and **5c** had AD_{50} values of 39 and 110 μg/kg in the tail-flick test. Varenicline has an AD_{50} = 0.2 μg/kg in the tail-flick test. Compounds **5a** and **6a** have AD_{50} values of 900 and 2,000 μg/kg in the hot plate test, compared to 470 μg/kg for varenicline.

Calculated lipophilicity (clogP), topological polar surface area (TPSA), and logBB derived values provide information as to the potential of a compound for development as a pharmacotherapy for treating CNS disorders. These molecular descriptors were calculated for compounds **5a–e** and **6a–e** as well as reference compounds nicotine, epibatidine, and varenicline (Table 3). Note that compounds **5a–e** have the same molecular formula as the respective compounds **6a–e** and thus, identical calculated values. In general, successful drugs used for treating CNS disorders have a clogP in the range 2–4, [17] TPSA less than 76Å, [18] and logBB greater than −1. [19] With the exception of possibly **5d** and **6d**, which have clogP values of 1.21, all the other compounds have clogP values within or close to the desirable range. All of the compounds have TPSA values of less than 76Å and logBB values between −0.62 and −0.08. For comparison varenicline has clogP, TPSA, and logBB values of 1.01, 37.81Å, and 0.27, respectively. The calculated values for **5a–e** and **6a–e** also compare favourably to the values of epibatadine.

4. Conclusions

In conclusion, the 3′-(substituted pyridinyl)deschloroepibatidine analogs **5a–e** and **6a–e** were synthesized and evaluated in vitro for their ability to inhibit [^{3}H]epibatidine binding at nAChR and for agonist and antagonist efficacy at α4β2-, α3β4-, and α7-nAChR using an electrophysiology assay. In addition, the compounds were evaluated for agonist effects in the tail-flick, hot-plate, spontaneous activity, and hypothermia tests in the mouse and antagonists of nicotine-induced antinociception in the tail-flick and hot-plate tests in the mouse. All of the 3′-(substituted pyridinyl)deschloroepibatidine analogs had high binding affinity for α4β2* nAChRs. Several of the analogs were potent antagonists of α4β2-nAChRs in in vitro efficacy tests and were potent antagonists of nicotine-induced antinociception in the mouse tail-flick test. Compound **6b**, with a K_i of 0.13 nM in the binding assay, had the greatest selectivity for the α4β2-nAChR in the electrophysiological assay, with an IC_{50} of 1.3 μM at this receptor, a 25- and 46-fold selectivity relative to the α3β4- and α7-nAChRs, respectively. Compound **6b** also had an AD_{50} of 0.13 μg/kg in the tail-flick test. These data, combined with favorable calculated physicochemical properties compared to varenicline, suggest that **6b** will be a valuable pharmacological tool for studying nAChRs and should be considered for development as a potential pharmacotherapy for treating nicotine addiction and other CNS disorders.

5. Experimental

Melting points were determined on a Mel-temp (Laboratory Devices, Inc.) capillary tube apparatus. NMR spectra were recorded on a Brunker Avance 300 or AMX 500 Spectrometer

using tetramethylsilane as internal standard. Mass Specs were determined on a Perkin-Elmer Sciex API 150EX mass spectrometer outfitted with an APCI and ESI sources. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross GA. Analytical thin-layer chromatography (TLC) was carried out on plates pre-coated with silica gel (60 F_{254}). TLC visualization was accomplished with a UV lamp or in an iodine chamber. Purifications by flash chromatography were performed on a Combiflash® Teledyne ISCO instrument.

General Procedure - Cross-coupling of boronic acids - Method A

To a resealable reaction vessel under nitrogen was added 1.0 equiv of compound **7**, $Pd(OAc)_2$ (0.1 equiv), P(*o*-tolyl)$_3$ (0.2 equiv), sodium carbonate (2.0 equiv) and the respective pyridinyl boronic acid (1.6 equiv), DME (6 mL) and water (0.7 mL). The mixture was degassed through bubbling nitrogen for 40 min, sealed and heated in an oilbath at 80 °C for 5 h. The mixture was cooled, poured into 20 mL of a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent removed under reduced pressure. The resultant residue was purified on a silica gel ISCO column and eluted with EtOAc/hexanes.

General Procedure - Cross-coupling of boronic acids – Method B

To a resealable reaction pressure vessel under nitrogen was added racemic **7** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), potassium carbonate (2.0 equiv), the respective pyridine boronic acid (1.3 equiv), 1,4-dioxane (10 mL) and water (2 mL). The mixture was degassed through bubbling nitrogen for 30 min and heated at 110 °C for 24 h. After cooling to room temperature the mixture was poured into a 30 mL of aqueous solution of $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The resultant residue was purified on silica gel eluted with hexanes/EOAc to furnish the respective products.

General Procedure C: Removal of the Boc-protecting group

The Boc-protected compound in methylene chloride (5 mL) was treated with TFA (1.5 mL) and stirred at room temperature overnight. In some cases the solution was heated at 40 °C for 2 h then stirred at room temperature overnight. The solvent was then removed in vacuo and the residue was treated with a solution of NH_4Cl (20 mL) and extracted with $CHCl_3$/MeOH (10%) (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo* and the residue was purified by flash chromatography on a silica gel column eluted with MeOH/CH_2Cl_2 or $CHCl_3$ (10/90) to provide the desired product.

General Procedure D: Conversion to the Fumarate Salts

A solution of the amine in ether (2 mL) was treated with a solution of fumaric acid (1.2 equivalent) in MeOH. The mixture was left to stand in a refrigerator overnight. Filtration and washing of the filter cake with ether, followed by recrystallization from MeOH-ether to provide the fumarate salt as a crystalline solid.

2-*exo*-[3′-(Pyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (5a) Fumarate—A solution of **8a** (175 mg, 0.498 mmol) was treated according to the General Procedure C to provide 102 mg (84%) of compound **5a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.88 (m, 7H), 1.93 – 2.00 (dd, *J* = 9.0, 11.2 Hz, 1H), 2.85 – 2.90 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.65 (s, 1H), 3.82 (br s 1H), 7.53 (d, *J* = 5.6 Hz, 2H), 8.04 (t, *J* = 2.0 Hz, 1H), 8.60 – 8.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.5, 40.4, 45.2, 56.4, 62.8, 121.6, 133.0, 133.5, 142.5, 145.6, 149.6, 150.4; MS (ESI) m/z 252.3 $(M+H)^+$.

A solution of **5a** (102 mg, 0.404 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (92.4 mg) as white crystalline solid. M.p 182 – 186 °C: ^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.85 (d, *J* = 1.74 Hz, 1H), 8.66 – 8.67 (m, 2H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.21 – 8.22 (m, 1H), 7.83 – 7.84 (m, 2H), 6.69 (s, 2H), 4.63 (d, *J* = 3.83 Hz, 1H), 4.37 (br s, 1H), 3.57 (dd, *J* = 6.10, 9.59 Hz, 1H), 2.52 (dd, *J* = 9.59, 13.42 Hz, 1H), 2.15 – 2.26 (m, 1H), 1.97 – 2.15 (m, 4H), 1.82 – 1.97 (m, 1H); ^{13}C NMR (500 MHz, METHANOL-d_4) δ 27.03, 29.07, 37.72, 44.01, 60.44, 64.00, 123.57, 135.07, 135.33, 135.90, 139.60, 147.17, 147.30, 150.14, 151.06, 170.06; MS (ESI) m/z 252.3 $[(M\text{-fumarate})^+$, $M=C_{16}H_{17}N_3{\bullet}C_4H_4O_4]$. Anal. calcd. for $C_{20}H_{21}N_3O_4$: C, 63.06; H, 5.95; N, 11.03. Found: C, 62.97; H, 5.74; N, 10.46.

2-*exo*-[3′-(2-Fluoropyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (5b) Fumarate—A solution of **8b** (217 mg, 0.587 mmol) was treated according to the General Procedure C to provide 102 mg (65%) of compound **5b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.75 (m, 6H), 1.82 (br s, 1 H), 1.94 – 2.01 (dd, *J* = 9.0, 11.2 Hz, 1H), 2.85 – 2.90 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.65 (s, 1H), 3.84 (br s 1H), 7.17 (s, 1H), 7.43 (dt, *J* = 1.6, 5.2 Hz, 1H), 8.07 (t, *J* = 2.1 Hz, 1H), 8.29 (d, *J* = 5.2 Hz, 1H) 8.63 (d, *J* = 2.0 Hz, 1H), 8.71 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 31.5, 40.1, 45.1, 56.4, 62.8, 107.0, 119.5, 133.1, 142.7, 145.6, 148.2, 148.4, 151.2, 162.8, 166; MS (ESI) m/z 270.4 $(M+H)^+$.

A solution of **5b** (85 mg, 0.314 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (80 mg) as white crystalline solid. Mp. 210 – 214 °C; ^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.87 (d, *J* = 1.74 Hz, 1H), 8.65 (d, *J* = 1.74 Hz, 1H), 8.33 (d, *J* = 5.23 Hz, 1H), 8.22 – 8.23 (m, 1H), 7.72 (td, *J* = 1.70, 5.32 Hz, 1H), 7.52 (s, 1H), 6.671 (s, 2H), 4.63 (br s, 1H), 4.35 – 4.37 (br s, 1H), 3.55 – 3.57 (m, 1H), 3.57 (d, *J* = 5.93 Hz, 1H), 2.50 (d, *J* = 9.76 Hz, 3H), 2.52 (d, *J* = 9.76 Hz, 3H), 2.21 (s, 6H), 1.98 – 2.16 (m, 17H), 1.87 – 1.908 (m, 6H); ^{13}C (500 MHz, METHANOL-d_4) δ 27.3, 29.1, 37.7, 44.0, 60.4, 64.0, 108.6, 121.2, 135.1, 136.0, 139.7, 147.3, 149.5, 149.6, 150.6, 170.5; MS (ESI) m/z 270.2 $[(M\text{-fumarate})^+$, $M=C_{16}H_{16}FN_3{\bullet}C_4H_4O_4]$. Anal. calcd. for $C_{20}H_{20}FN_3O_4{\bullet}0.5H_2O$: C, 60.92; H, 5.37; N, 10.65. Found: C, 60.72; H, 5.15; N, 10.49.

2-*exo*-[3′-(2-Chloropyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (5c) Fumarate—A solution of **8c** (175 mg, 0.454 mmol) was treated according to the General Procedure C to provide 98.3 mg (76%) of compound **5c** as a coloress oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 – 1.74 (m, 6H), 1.93 – 2.00 (dd, *J* = 9.1, 11.2 Hz, 1H), 2.85 – 2.89 (m, 1H), 3.65 (s, 1H), 3.83 (br s 1H), 7.45 (dd, *J* = 1.5, 5.2 Hz, 1H), 7.56 (s, 1H), 8.05 (t, *J* = 2.1 Hz, 1H), 8.47 (d, *J* = 5.2 Hz, 1H) 8.62 (d, *J* = 2.0 Hz, 1H), 8.68 (d, *J* = 2.2 Hz, 1H); ^{13}C

NMR ($CDCl_3$) δ 30.3, 31.6, 40.4, 45.1, 56.4, 62.8, 120.5, 122.1, 132.3, 133.1, 142.7, 145.6, 148.8, 150.2, 152.4; MS (ESI) m/z 286.5 $(M+H)^+$.

A solution of **5c** free base (104 mg, 0.365 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide 95 mg of the fumarate salt as a white crystalline solid. M.p 205 – 208 °C. ^{1}H NMR (500 MHz, METHANOL-d_4) δ 8.85 (d, *J* = 1.95 Hz, 1H), 8.65 (d *J* = 1.85 Hz, 1H), 8.48 (d, *J* = 5.35 Hz, 1H), 8.20 – 8.23 (m, 1H), 7.90 – 7.93 (m, 1H), 7.77 (dd, *J* = 1.66, 5.27 Hz, 1H), 6.69 (s, 2H), 4.61 – 4.64 (br s, 1H), 4.35 – 4.38 (br s, 1H), 3.53 – 3.59 (m, 1H), 2.47 – 2.55 (m, 1H), 2.21 – 2.21 (m, 1H), 2.07 – 2.11 (m, 1H), 1.98 – 2.07 (m, 1H), 1.89 – 1.97 (m, 1H); ^{13}C NMR (500 MHz, METHANOL-d_4) δ 27.0, 29.1, 37.8, 44.0, 60.4, 64.0, 122.3, 123.7, 134.3, 135.1, 136.0, 139.7, 147.4, 150.0, 150.7, 151.5, 153.5, 170.5; MS (ESI) m/z 286.5 $[(M\text{-fumarate})^+$, M=$C_{16}H_{16}ClN_3 \bullet C_4H_4O_4]$. Anal. calcd. for $C_{20}H_{20}ClN_3O_4$: C, 59.78; H, 5.02; N, 10.46. Found: C, 59.76; H, 4.97; N, 10.40.

2-*exo*-[3′-(2-Aminopyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (5d) Hydrochloride—A solution of **8d** (180 mg, 0.491 mmol) was treated according to the General Procedure C to provide 88 mg (67%) of compound **5d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.76 (m, 6H), 1.86 (br s, 1H) 1.92 – 1.99 (dd, *J* = 9.0, 11.2 Hz, 1H), 2.84 – 2.88 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.64 (s, 1H), 3.83 (br s 1H), 4.69 (br s, 2H) 6.70 (s, 1H), 6.85 (dd, *J* = 1.1, 5.3 Hz, 1H), 7.85 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 5.3 Hz, 1H), 8.55 (d, *J* = 1.8 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.5, 40.4, 45.2, 56.5, 62.8, 106.2, 112.5, 132.9, 134.1, 142.2, 145.6, 147.4, 148.9, 149.3, 159.1; MS (ESI) m/z 267.1 $(M+H)^+$.

A solution of **5d** (88.4 mg, 0.332 mmol) in chloroform in a vial was treated with a 2.0 equiv solution of HCl in diethyl ether and allowed to stand at room temperature. The solid obtained was recrystallized from MeOH/diethyl ether to provide 80.2 mg (66%) of **5d**•HCl as an off white solid. Mp. 209 – 214 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 1.90 – 2.0 (m, 4H), 2.10 – 2.34 (m, 1H), 2.52 – 2.60 (dd, *J* = 9.0, 11.2 Hz, 1H), 3.64 – 3.69 (dd, *J* = 3.9, 6.9 Hz, 1H), 4.42 (s, 1H), 4.70 (br s 1H), 7.38 (dd, *J* = 1.6, 6.8 Hz, 1H), 7.49 (s, 1H), 8.01 (d, *J* = 6.7 Hz, 1H), 8.49 (s, 1H), 8.82 (s, 1H), 8.96 (s, 1H); ^{13}CNMR (CD_3OD) δ 26.8, 28.9, 37.4, 43.9, 60.5, 64.0, 112.5, 112.7, 137.3, 137.4, 140.3, 145.9, 149.9, 153.2; MS (ESI) m/z 267.2 $[(M\text{-}HCl)^+$, M = $C_{16}H_{18}N_4 \bullet 2HCl]$; Anal. calcd. for $C_{16}H_{20}Cl_2N_4 \bullet 1.5H_2O$: C, 52.46; H, 6.33; N 15.30. Found: C, 52.81; H, 6.07; N, 15.17.

2-*exo*-[3′-(2-Methoxypyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (5e) Fumarate—A solution of **8e** (270 mg, 0.708 mmol) was treated according to the General Procedure C to provide 138 mg (69%) of compound **5e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.76 (m, 6H), 1.86 (br s, 1H) 1.92 – 1.99 (dd, *J* = 9.0, 11.2 Hz, 1H), 2.84 – 2.88 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.64 (s, 1H), 3.83 (br s 1H), 4.69 (br s, 2H) 6.70 (s, 1H), 6.85 (dd, *J* = 1.1, 5.3 Hz, 1H), 7.85 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 5.3 Hz, 1H), 8.55 (d, *J* = 1.8 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 31.3, 40.2, 45.5, 55.2, 56.5, 62.8, 107.3, 108.4, 133.1, 134.6, 141.8, 145.8, 149.4, 151.2, 156.8, 166.4; MS (ESI) m/z 282.5 $(M+H)^+$.

A solution of **5e** free base (117.4 mg, 0.417 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (156 mg) as white crystalline solid. Mp. 160 – 164 °C; ^{1}H NMR (300 MHz, METHANOL-d_4) δ (d, J = 1.74 Hz, 1H) 8.60 (d, J = 1.71 Hz, 1H), 8.51 (d, J = 5.85 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.04 (dd, J = 2.4, 5.82 Hz, 1H), 6.68 (s, 1H), 4.60 (d, J = 2.0 Hz, 1H), 4.37 (br s, 1H), 3.98 (s, 3H), 3.57 (dd, J = 3.3, 9.3 Hz, 1H), 2.45 – 2.53 (m, 1H), 1.86 – 2.26 (m, 6H); ^{13}C NMR (300 MHz, METHANOL-d_4) δ 26.99, 28.84, 37.33, 43.91, 56.32, 60.33, 64.15, 109.52, 110.58, 134.72, 135.87, 138.97, 147.41, 149.72, 152.18, 157.20, 170.89; MS (ESI) m/z 282.4 [(M-fumarate)$^{+}$, M=$C_{16}H_{16}FN_3$•$C_4H_4O_4$]. Anal. calcd. for $C_{20}H_{20}FN_3O_4$•0.5H_2O: C, 59.42; H, 6.17; N, 9.90. Found: C, 59.38, H, 5.92, N, 8.83.

2-*exo*-[3′-(Pyridin-3″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (6a) Fumarate—A solution of **10a** (177 mg, 0.504 mmol) was treated according to the General Procedure C to provide 106 mg (84%) of compound **6a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 – 1.76 (m, 6H), 1.93 – 2.00 (dd, J = 9.0, 11.2 Hz, 1H), 2.86 – 2.90 (dd, J = 3.9, 6.9 Hz, 1H), 3.66 (s, 1H), 3.83 (br s 1H), 7.37 – 7.42 (m, 1H), 7.89 (dt, J = 2.0, 8.0 Hz, 1H), 7.98 (t, J = 2.0 Hz, 1H), 8.58 (d, J = 2.0 Hz, 1H), 8.63 – 8.66 (m, 2H) 8.85 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.4, 40.4, 45.2, 56.4, 62.8, 123.6, 133.1, 133.8, 134.4, 142.4, 145.7, 148.3, 148.8, 149.1; MS (ESI) m/z 252.2 (M+H)$^{+}$.

A solution of **6a** free base (106 mg, 0.430 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (103 mg) as white crystalline solid. M.p 169 – 172 °C; ^{1}H NMR (300 MHz, METHANOL-d_4) δ 1.91 – 2.22 (m, 5H), 2.47 – 2.55 (dd, J = 9.0, 11.2 Hz, 1H), 3.53 – 3.58 (dd, J = 3.9, 6.9 Hz, 1H), 4.35(s, 1H), 4.63 (br s 1H), 6.65 (s, 2H), 7.57 – 7.61 (dd, J = 3.0, 5.3 Hz, 1H), 8.17 (t, J = 1.9 Hz, 1H), 8.22 (dt, J = 2.0, 6.2 Hz, 1H), 8.60 – 8.63 (m, 2H), 8.77 (d, J = 1.9 Hz, 1H), 8.91 (d, J = 2.0 Hz, 1H); ^{13}C NMR (300 MHz, METHANOL-d_4) δ 27.1, 29.2, 37.8, 44.1, 60.4, 64.1, 125.8, 135.8, 136.3, 137.1, 139.6, 147.3, 148.8, 149.2, 150.1, 171.4; MS (ESI) m/z 252.2 [(Mfumarate)$^{+}$, M=$C_{16}H_{17}N_3$•$C_4H_4O_4$]; Anal. calcd. for $C_{20}H_{21}N_3O_4$•0.5H_2O: C, 63.82; H, 5.89; N 11.16. Found: C, 63.53; H, 5.89; N, 11.02.

2-*exo*-[3′-(2″-Fluoropyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (6b) Fumarate—A solution of **10b** (170 mg, 0.461 mmol) was treated according to the General Procedure C to provide 76 mg (61%) of compound **6b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 – 1.73 (m, 6H), 1.93 – 2.00 (m, 1H), 2.82 – 2.86 (m, 1H), 3.62 (s, 1H), 3.80 (br s 1H), 7.01 (dd, J = 3.0, 8.5 Hz, 1H), 7.92 – 8.00 (m, 2H), 8.39 (d, J = 1.9 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.5, 40.4, 45.2, 56.4, 62.8, 109.4, 132.1, 133.1, 139.9, 142.5, 145.6, 145.9, 148.9, 161.8, 165.1; MS (ESI) m/z 270.3 (M+H)$^{+}$.

A solution of **6b** free base (141 mg, 0.525 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (142 mg) as white crystalline solid. M.p 205 – 207 °C; ^{1}H NMR (300 MHz, METHANOL-d_4) δ 1.85 – 2.24 (m, 5H), 2.47 – 2.55 (m, 1H), 3.53 – 3.58 (dd, J = 3.9, 6.9 Hz, 1H), 4.35 (s, 1H), 4.62 (br s 1H), 6.67 (s, 3H), 7.22 (dd, J = 2.6, 8.6 Hz, 1H), 8.13 (s, 1H), 8.31 (td, J = 2.6, 8.2 Hz, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.59 (d, J = 1.9 Hz, 1H), 8.76 (d, J = 1.8 Hz, 1H); ^{13}C NMR (300 MHz, METHANOL-d_4) δ 27.1, 29.1, 37.7, 44.1, 60.5, 64.1, 111.0, 135.0, 136.0, 139.5,

142.2, 147.2, 147.4, 149.1, 163.5, 167.0, 170.5; MS (ESI) m/z 270.4 [(M-fumarate)$^+$, M=$C_{16}H_{16}FN_3$•1.5$C_4H_4O_4$]; Anal. calcd for $C_{22}H_{22}FN_3O_6$: C, 59.59; H, 5.00; N, 9.48. Found, C, 59.46; H, 5.00; N, 9.54.

2-*exo*-[3′-(2″-Chloropyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (6c) Fumarate—A solution of **10c** (112 mg, 0.290 mmol) was treated according to the General Procedure C to provide 71 mg (86%) of compound **6c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 – 1.76 (m, 6H), 1.93 – 2.00 (dd, *J* = 9.1, 11.2 Hz, 1H), 2.85 – 2.89 (m, 1H), 3.65 (s, 1H), 3.83 (br s 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.85 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.97 (t, *J* = 2.1 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H) 8.62 (dd, *J* = 2.2, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 31.5, 40.4, 45.2, 56.4, 62.8, 124.4, 131.9, 132.9, 133.1, 137.3, 142.6, 145.6, 148.0, 149.2, 151.1; MS (ESI) m/z 286.6 (M+H)$^+$.

A solution of **6c** free base (71 mg, 0.247 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (70 mg) as white crystalline solid. M.p 199 – 202 °C; ^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ 1.88 – 2.24 (m, 5H), 2.47 – 2.54 (dd, *J* = 9.1, 11.2 Hz, 1H), 3.53 – 3.58 (dd, *J* = 3.9, 6.9 Hz, 1H), 4.37 (s, 1H), 4.63 (br s 1H), 6.67 (s, 3H), 7.59 (d, *J* = 8.3 Hz, 1H), 8.15 (s, 1H), 8.18 (dd, *J* = 2.6, 8.4 Hz, 1H), 8.6 (d, *J* = 2.0 Hz, 1H) 8.77 (dd, *J* = 2.0, 8.3 Hz, 1H); ^{13}C NMR (300 MHz, METHANOL-*d*$_4$) δ 27.1, 29.1, 37.7, 44.1, 60.4, 64.0, 126.1, 133.8, 134.1, 135.0, 136.0, 139.6, 147.2, 149.3, 149.4, 152.6, 170.6; MS (ESI) m/z 286.6 [(M-fumarate)$^+$, M=$C_{16}H_{16}ClN_3$•1.5$C_4H_4O_4$]; Anal. calcd. for $C_{22}H_{22}ClN_3O_6$•0.75H_2O: C, 55.82; H, 5.00; N 8.88. Found: C, 56.17; H, 4.84; N, 9.04.

2-*exo*-[3′-(2″-Aminopyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (6d) Fumarate—A solution of **10d** (157 mg, 0.429 mmol) was treated according to the General Procedure C to provide 91.2 mg (80%) of compound **6d**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 – 1.84 (m, 6H), 1.92 – 1.99 (dd, *J* = 9.0, 10.9 Hz, 1H), 2.84 – 2.89 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.65 (s, 1H), 3.82 (br s 1H), 4.58 (br s, 2H), 6.58 (d, *J* = 8.5 Hz, 1H), 7.68 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.83 (t, *J* = 2.2 Hz, 1H), 8.31 (d, *J* = 2.3 Hz, 1H), 8.48 (d, *J* = 2.1 Hz, 1H), 8.59 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.3, 40.3, 45.3, 56.5, 62.7, 108.6, 124.0, 132.1, 133.7, 136.5, 141.9, 145.1, 146.5, 147.5, 158.3; MS (ESI) m/z 267.1 (M+H)$^+$.

A solution of **6d** free base (91.2 mg, 0.342 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (72 mg) as white crystalline solid. M.p 157 – 160 °C; ^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ 1.84 – 2.20 (m, 5H), 2.45 – 2.53 (dd, *J* = 9.6, 9.7 Hz, 1H), 3.49 – 3.54 (dd, *J* = 3.3, 7.8 Hz, 1H), 4.34 (s, 1H), 4.59 (br s 1H), 6.68 (s, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.02 (t, *J* = 1.9 Hz, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 8.46 (d, *J* = 1.8 Hz, 1H), 8.64 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (300 MHz, METHANOL-*d*$_4$) δ 27.1, 29.2, 37.8, 44.1, 53.8, 60.5, 64.1, 111.1, 123.3, 133.7, 136.2, 138.6, 139.3, 145.7, 146.2, 147.5, 160.7, 171.0; MS (ESI) m/z 267.2 [(M-fumarate)$^+$, M=$C_{16}H_{18}N_4$•1.5$C_4H_4O_4$]; Anal. calcd. for $C_{21}H_{23}N_3O_5$•0.75H_2O: C, 58.21; H, 5.66; N 12.34. Found: C, 57.85; H, 5.69; N, 12.73.

2-*exo*-[3′-(2″-Methoxypyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (6e)—A solution of **10e** (111 mg, 0.291 mmol) was treated according to the General

Procedure C to provide 71 mg (86%) of compound **6e**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.76 (m, 6H), 1.86 (br s, 1H) 1.92 – 1.99 (dd, *J* = 9.0, 11.2 Hz, 1H), 2.84 – 2.88 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.65 (s, 1H), 3.82 (br s 1H), 3.98 (s, 3H) 6.83 (d, *J* = 8.6 Hz, 1H), 7.8 (dd, *J* = 2.6, 8.6 Hz, 1H), 7.88 (t, *J* = 2.1 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.61 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 31.4, 40.3, 45.3, 53.6, 56.5, 62.7, 111.0, 127.1, 132.6, 133.2, 137.4, 142.1, 145.1, 145.4, 148.0, 164.0; MS (ESI) m/z 282.5 $(M+H)^+$.

A solution of **6e** free base (78.5 mg, 0.279 mmol) in ether was converted to the fumarate salt according to the General Procedure D to provide the fumarate salt (50 mg) as white crystalline solid. M.p 96 – 100 °C; ^{1}H NMR (300 MHz, METHANOL-*d*$_4$) δ 1.85 – 2.22 (m, 5H), 2.46 – 2.53 (dd, *J* = 9.0, 11.2 Hz, 1H), 3.50 – 3.55 (dd, *J* = 3.9, 6.9 Hz, 1H), 3.97 (s, 3H) 4.34 (s, 1H), 4.60 (br s 1H), 6.65 (s, 2H), 6.92 (d, *J* = 8.8 Hz, 1H), 8.03 (dd, *J* = 2.6, 8.7 Hz, 1H), 8.08 (t, *J* = 2.1 Hz, 1H), 8.48 (d, *J* = 1.8 Hz, 1H), 8.52 (d, *J* = 2.5 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (300 MHz, METHANOL-*d*$_4$) δ 27.1, 29.2, 37.8, 44.1, 54.4, 60.4, 64.1, 112.3, 127.5, 134.5, 136.3, 137.1, 139.3, 146.6, 146.7, 148.2, 166.0, 171.4; MS (ESI) m/z 282.4 $[(M\text{-fumarate})^+$, $M=C_{17}H_{19}N_3 \bullet C_4H_4O_4]$; Anal. calcd. for $C_{21}H_{23}N_3O_5 \bullet H_2O$: C, 60.71; H, 6.07; N 10.11. Found: C, 60.88; H, 5.99; N, 10.05.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(pyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (8a)—To a resealable reaction pressure vessel under nitrogen was added racemic **7** (215 mg, 0.607 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (70 mg, 0.061 mmol, 10 mol %), potassium carbonate (168 mg, 1.22 mmol, 2.0 equiv), pyridine 4-boronic acid (104.4 mg, 0.849 mmol, 1.2 equiv), DME (15 mL) and water (2 mL). The mixture was degassed through bubbling nitrogen and heated at 100 °C for 24 h. After cooling to room temperature the mixture was poured into 30 mL of H_2O and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The resultant residue was purified on a silica gel column eluted with hexanes/isopropanol to furnish 175 mg (82%) of **8a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (br s, 9H), 1.58 – 1.66 (m, 2H), 1.87 – 1.94 (m, 3H), 1.93 – 2.00 (m, 1H), 2.04 – 2.11 (dd, *J* = 9.0 Hz, 1H), 2.97 – 3.02 (m, 1 H), 4.29 (s, 1H), 4.43 (br s, 1H), 7.51 – 7.56 (m, 2H), 7.93 (d, *J* = 1.9 Hz, 1H), 8.56 (d, *J* = 1.9 Hz, 1H) 8.69 – 8.74 (m, 3H); ^{13}C NMR ($CDCl_3$) δ; 28.3 (3 C), 28.8, 29.8, 40.4, 45.4, 55.9, 61.8, 79.8, 121.5, 132.5, 133.5, 141.4, 145.3, 145.9, 149.4, 150.4, 154.8; MS (ESI) m/z 352.3 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2-flouropyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (8b)—Racemic compound **7** (386 mg, 1.09 mmol) and 2-fluoropyridine-4-boronic acid (200 mg, 1.42 mmol, 1.3 equiv) were cross-coupled according to the General Procedure A to provide 243 mg (60%) of **8b** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (br s, 9H), 1.48 – 1.69 (m, 2H), 1.87 – 1.93 (m, 3H), 2.05 – 2.12 (dd, *J* = 9.0 Hz, 1H), 2.99 – 3.03 (m, 1H), 4.29 (s, 1H), 4.43 (br s, 1H), 4.54 (s, 2 NH), 7.16 (s, 1H), 7.42 – 7.44 (dt, *J* = 1.7, 5.2 Hz, 1H), 7.95 (t, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 5.3 Hz, 1H), 8.59 (d, *J* = 2.0 Hz, 1H), 8.73 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.5, 45.3, 56.0, 61.8, 79.9, 107.4, 119.4, 132.5, 141.6, 145.8, 148.2, 150.0, 150.9, 154.9, 162.9, 166.0; MS (ESI) m/z 386.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2-chloropyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (8c)—Racemic compound **7** (194 mg, 0.549 mmol) and 2-chloropyridine-4-boronic acid (138 mg, 0.878, 1.6 equiv) were cross-coupled according to the General Procedure A to provide 175 mg (83%) of **8a** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (br s, 9H), 1.48 – 1.69 (m, 2H), 1.87 – 1.91 (m, 3H), 2.05 – 2.12 (m, 1H), 2.98 – 3.03 (m, 1H), 4.29 (s, 1H), 4.43 (br s, 1H), 4.54 (s, 2 NH), 7.46 (dd, *J* = 1.5, 4.2 Hz, 1H), 7.55 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 8.71 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.5, 45.3, 55.9, 61.7, 79.9, 120.3, 122.0, 132.4, 132.5, 141.7, 145.8, 148.5, 150.0, 150.2, 152.4, 154.9; MS (ESI) m/z 386.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2-aminopyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (8d)—To a resealable reaction pressure vessel under nitrogen was added 1.0 equiv of **9** (265 mg, 0.662 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 5 mol %), K_2CO_3 (184 mg, 1.324 mmol, 2.0 equiv), 2-amino-4-bromopyridine (137 mg, 0.794 mmol, 1.2 equiv), dioxane (12 mL) and water (1 mL). The mixture was degassed through bubbling nitrogen for 40 min, sealed and heated at 110 °C for 20 h. After cooling to room temperature, water (10 mL) was added and the organic product was extracted using EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The residual was purified on a silica get column eluted with EtOAc/hexanes to provide 180 mg (74%) of **8d** as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (br s, 9H), 1.53–1.66 (m, 2H), 1.80 – 1.91 (m, 3H), 2.01 – 2.08 (m, 1H), 2.94 – 2.98 (m, 1H), 4.27 (s, 1H), 4.41 (br s, 1H), 4.76 (s, 2 NH), 6.70 (s, 1H), 6.85 (d, *J* = 4.3 Hz, 1H), 7.85 (s, 1H), 8.13 (d, *J* = 5.3 Hz, 1H), 8.52 (d, *J* = 1.7 Hz, 1H), 8.67 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.8, 40.4, 45.5, 55.9, 61.8, 79.8, 106.2, 112.3, 132.5, 134.2, 141.2, 145.9, 147.1, 148.8, 149.1, 154.9, 159.1; MS (ESI) m/z 367.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2-methoxypyridin-4-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (8e)—To a resealable reaction pressure vessel under nitrogen was added 1.0 equiv of **9** (266 mg, 0.665 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol, 5 mol %), K_2CO_3 (184 mg, 1.33 mmol, 2.0 equiv), 2-methoxy-4-bromopyridine (137 mg, 0.732 mmol, 1.1 equiv), dioxane (20 mL) and water (2 mL). The mixture was degassed through bubbling nitrogen for 40 min and heated at 110 °C overnight. After cooling to room temperature, water (20 mL) was added and the organic product was extracted using EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite and the solvent removed *in vacuo*. The residual was purified on a silica gel column eluted with EtOAc/hexanes to provide 160 mg (63%) of **8e** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 9H), 1.49 – 1.63 (m, 2H), 1.86 – 1.98 (m, 3H), 2.00 – 2.07 (m, 1H), 2.96 – 3.01 (m, 1H), 3.92 (s, 3H), 4.30 (s, 1H), 4.42 (br s, 1H), 6.81 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 1H), 8.22 (t, *J* = 1.9 Hz, 1H), 8.53 (d, *J* = 5.7 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 9.00 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.9, 40.2, 45.8, 55.9, 61.8, 79.7, 107.2, 108.6, 132.9, 134.7, 140.9, 146.2, 149.1, 151.1, 155.0, 156.7, 166.5; MS (ESI) m/z 382.7 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[5′-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3′-pyridnyl]-7-azabicyclo[2.2.1]heptane (9)—To a resealable reaction pressure vessel under nitrogen was added a solution of racemic **7** (209 mg, 0.590 mmol, 1.0 equiv), Bis(pinacolato)diboron (225 mg, 0.886 mmol, 1.5 equiv), $PdCl_2$(dppf) (22 mg, 0.0295 mmol, 5 mol %), and KOAc (180 mg, 1.83 mmol, 3.0 equiv) in 1,4-dioxane (10 mL). The mixture was degassed through bubbling nitrogen for 40 min then heated at between 100 and 110 °C for 24 h. After cooling to room temperature the reaction was diluted in EtOAc and filtered through a plug of Celite and anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluted with ethyl acetate to provide 199 mg (84%) of **9** as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 12H) 1.44 (br s, 9H), 1.53 – 1.60 (m, 2H), 1.80 – 1.88 (m, 2H), 1.91 – 2.08 (m, 1H), 2.87 – 2.96 (m, 2H), 4.22 (s, 1H), 4.42 (br s, 1H), 8.02 (d, *J* = 5.3 Hz, 1H), 8.52 (d, *J* = 1.7 Hz, 1H), 8.67 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 24.8, 24.9, 25.0, 28.3 (3 C), 28.8, 29.8, 39.9, 45.8, 55.7, 61.7, 79.6, 84.1, 140.1, 140.6, 147.4, 148.8, 151.0, 153.1, 162.5; MS (ESI) m/z 367.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(pyridin-3″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (10a)—Racemic compound **7** (334 mg, 0.944 mmol) and pyridine-3-boronic acid (150 mg, 1.23, 1.3 equiv) were cross-coupled according to the General Procedure B to provide 176 mg (53%) of **10a** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (br s, 9H), 1.50 – 1.68 (m, 2H), 1.90 – 1.95 (m, 3H), 2.03 – 2.10 (m, 1H), 2.96 – 3.01 (m, 1H), 2.97 – 3.02 (m, 1 H), 4.29 (s, 1H), 4.43 (br s, 1H), 7.38 – 7.43 (m, 1H), 7.87 – 7.91 (m, 2H), 8.54 (d, *J* = 1.9 Hz, 1H), 8.65 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.69 (d, *J* = 2.2 Hz, 1H), 8.85 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ; 28.3 (3 C), 28.8, 29.8, 40.4, 45.5, 55.9, 61.8, 79.8, 123.7, 133.3, 133.6, 134.4, 141.3, 146.0, 148.2, 148.6, 149.3, 154.9; MS (ESI) m/z 352.4 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2″-flouropyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (10b)—Racemic compound **7** (240 mg, 0.680 mmol) and 2-flouropyridine-5-boronic acid (124 mg, 0.883, 1.3 equiv) were cross-coupled according to the General Procedure A to provide 170 mg (68%) of **10b** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (br s, 9H), 1.55 – 1.68 (m, 2H), 1.80 – 1.93 (m, 3H), 2.03 – 2.12 (m, 1H), 2.96 – 3.00 (m, 1H), 4.28 (s, 1H), 4.42 (br s, 1H), 7.03 – 7.07 (dd, *J* = 3.0, 8.5 Hz, 1H), 7.83 (t, *J* = 2.1 Hz, 1H), 7.98 (td, *J* = 7.6, 2.6 Hz, 1H), 8.42 (d, *J* = 2.6 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.8, 40.4, 45.5, 56.0, 61.8, 79.9, 109.5, 123.5, 132.6, 139.8, 141.5, 145.8, 148.7, 154.9, 161.9, 165.1; MS (ESI) m/z 370.4 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2″-chloropyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (10c)—Racemic compound **7** (213 mg, 0.602 mmol) and 2-chloropyridine-5-boronic acid (114 mg, 0.722, 1.2 equiv) were cross-coupled according to the General Procedure A to provide 69 mg (30%) of **10c** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (br s, 9H), 1.50 – 1.68 (m, 2H), 1.87 – 2.03 (m, 3H), 2.05 – 2.10 (m, 1H), 2.96 – 3.00 (m, 1H), 4.28 (s, 1H), 4.42 (br s, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.83 – 7.87 (m, 2H), 8.55 (d, *J* = 1.8 Hz, 1H), 8.61 (d, *J* = 2.5 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR

($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.5, 45.5, 56.0, 61.8, 79.9, 124.4, 122.0, 132.1, 132.6, 137.2, 141.7, 145.9, 147.9, 149.0, 151.2, 155.0; MS (ESI) m/z 386.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2″-aminopyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (10d)—Racemic compound **7** (303 mg, 0.857 mmol) and 2-aminopyridine-5-pinacoboronic ester (245 mg, 1.11, 1.3 equiv) were cross-coupled according to the General Procedure B to provide 166 mg (53%) of **10d** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 9H), 1.53 – 1.66 (m, 2H), 1.80 – 1.91 (m, 3H), 2.01 – 2.10 (m, 1H), 2.92 – 2.96 (m, 1H), 4.27 (s, 1H), 4.41 (br s, 1H), 4.70 (s, 2 NH), 6.58 (d, *J* = 8.6 Hz, 1H), 7.65 (dd, *J* = 2.3, 8.5 Hz, 1H), 7.76 (t, *J* = 2.0 Hz, 1H), 8.29 (d, *J* = 2.2 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.60 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.8, 40.3, 45.6, 56.0, 61.9, 79.7, 108.6, 112.3, 123.9, 131.7, 133.8, 136.4, 141.1, 145.3, 146.4, 147.3, 155.0, 158.3; MS (ESI) m/z 367.6 $(M+H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[3′-(2″-methoxypyridin-5″-yl)-5′-pyridnyl]-7-azabicyclo[2.2.1]heptane (10e)—Racemic compound **7** (304 mg, 0.859 mmol) and 2-methoxypyridine-5-boronic acid (171 mg, 1.12, 1.3 equiv) were cross-coupled according to the General Procedure B to provide 118 mg (36%) of **10e** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (br s, 9H), 1.49 – 1.63 (m, 2H), 1.86 – 1.98 (m, 3H), 2.00 – 2.07 (m, 1H), 2.96 – 3.01 (m, 1H), 3.92 (s, 3H), 4.30 (s, 1H), 4.42 (br s, 1H), 6.81 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 1H), 8.22 (t, *J* = 1.9 Hz, 1H), 8.53 (d, *J* = 5.7 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 9.00 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8 (3 C), 28.3, 29.3, 39.8, 45.0, 55.5, 61.4, 79.3, 110.6, 126.4, 132.9, 136.9, 134.7, 140.7, 145.2, 147.3, 154.5, 163.6; MS (ESI) m/z 382.4 $(M+H)^+$.

[^{3}H]Epibatidine Binding Assay

The inhibition of [^{3}H] binding at rat brain α4β2*-nAChRs was conducted as previously reported.[13]

Electrophysiology

The electrophysiology assays with rat α4β2-, α3β4-, and α7-nAChRs were conducted as previously described.[20]

In vivo testing

The antinociception (tail-flick and hot-plate), locomotor, and body temperature tests were all conducted as previously described.[13]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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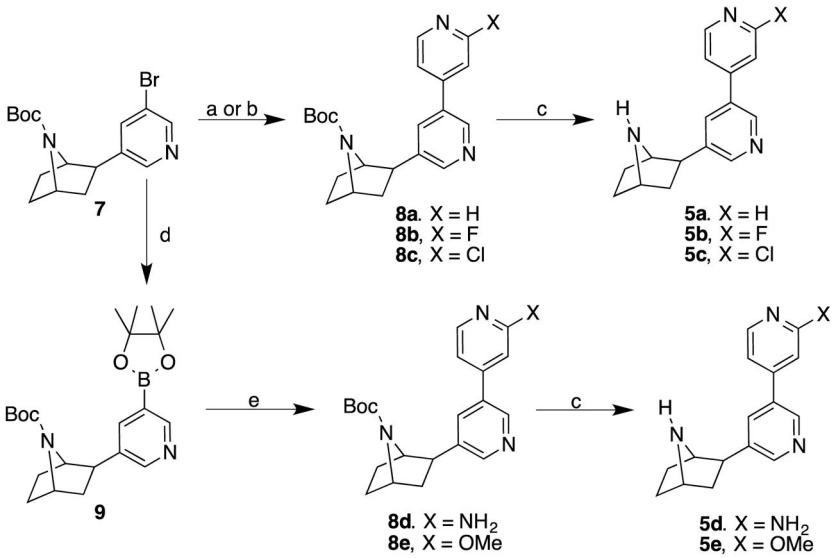
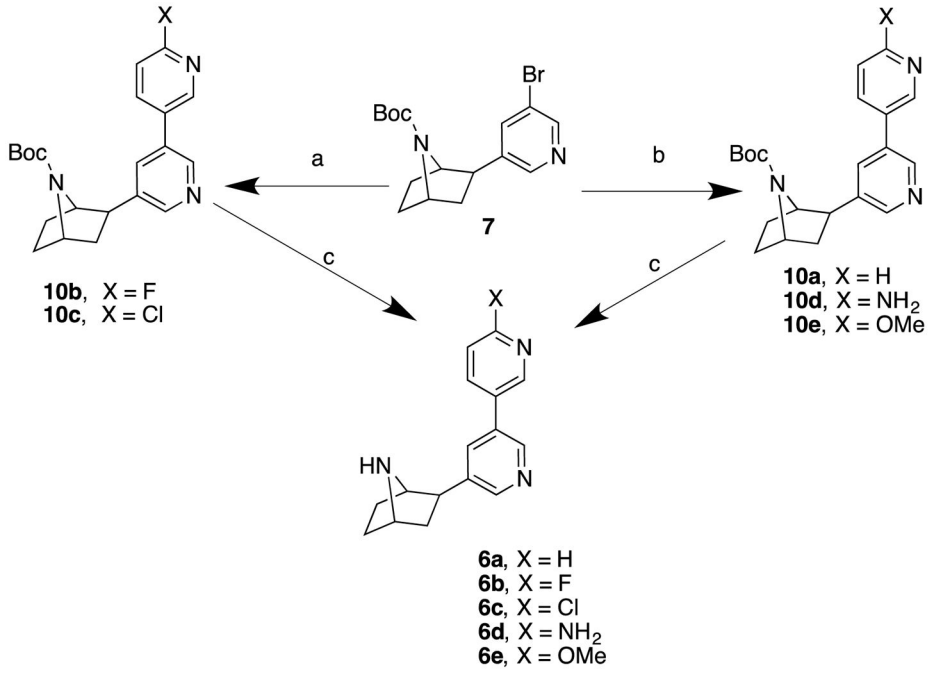


Scheme 1.

Reagents and conditions: (a) 4-Pyridine boronic ester, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 100 °C, 24 h (for **5a**); (b) 2-fluoropyridine-4-boronic acid (for **5b**) or 2-Chloropyridine-4-boronic acid (for **5c**), $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Na_2CO_3, DME, H_2O, 80 °C, 5 h; (c) TFA, CH_2Cl_2, rt, 3 h; (d) Bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), 1,4-dioxane, 110 °C, 18 h; (e) 3-amino-4-bromopyridine (for **8d**), 4-bromo-2-methoxypyridine (for **8e**), $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 110 °C, overnight.



Scheme 2.

Reagents and conditions: (a) 2-Fluoro-5-boronic acid (for **10b**) or 2-Chloro-5-boronic acid (for **10c**), $Pd(OAc)_2$, $P(o\text{-tolyl})_3$, Na_2CO_3, DME, H_2O, 80 °C, 5 h; (b) Pyridine-3-boronic acid (for **10a**), or 2-methoxypyridine-5-boronic acid (for **10e**), or 2-aminopyridine-5-boronic (for **10d**), $Pd(PPh_3)_4$, K_2CO_3, dioxane, H_2O, reflux, 24 h; (c) TFA, CH_2Cl_2, rt, 2 h.

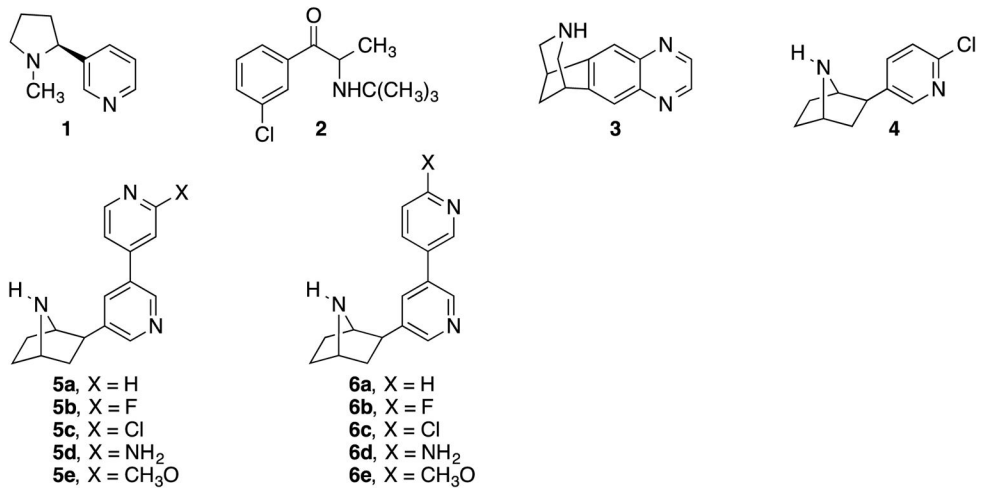
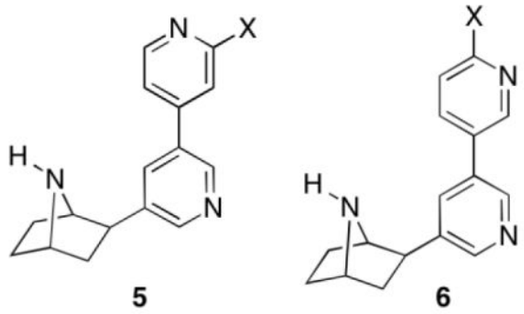


Chart 1.
Structures of Compounds **1–4, 5a–e** and **6a–e**.

Table 1

Radioligand binding, antinociception, and efficacy profile data for 3′-(substituted pyridine)deschloroepibatidine analogs



Structure[a]	X	αβ [^{3}H]Epibatidine (K_i, nM)[b] (Hill slope)	mg/kg				AD$_{50}$ (μg/kg)		Agonist Activity (% of max ACh at 100 μM)[d]			Antagonist Activity (% EC_{50} ACh remaining at 100 μM)[e]		
			ED_{50} Tail-Flick	ED_{50} Hot-Plate	ED_{50} Hypothermia	ED_{50} Spontaneous Activity	Tail-Flick	Hot-Plate	α4β2	α3β4	α7	α4β2	α3β4	α7
nicotine[c]		1.50 ± 0.30	1.3 (0.5–1.8)	0.65 (0.25–0.85)	1.0 (0.6–2.1)	0.5 (0.15–0.78)			40 ± 1	37 ± 3	43 ± 5	nd	nd	nd
nat epibatidine		0.026 ± 0.002	0.006 (0.001–0.01)	0.004 (0.001–0.008)	0.004 (0.002–0.008)	0.001 (0.0005–0.005)			131 ± 13	97 ± 4	150 ± 8	nd	nd	nd
varenicline		0.12 ± 0.02	11% @ 10	10% @ 10	2.8	2.1	0.2	470	13 ± 0.4	66 ± 4	74 ± 5	38 ± 2	nd	nd
5a	H	0.22 ± 0.02	7% @ 10	4% @ 10	5 (2–13)	1.76 (0.6–5.4)	39 (4–63)	20%1000	1.0 ± 0.2	9.5 ± 1.4	8.1 ± 1.3	3.9 ± 0.8	11 ± 2	69 ± 8
5b	F	0.18 ± 0.04	13% @ 10	34% @ 10	5.2 (1.9–13.6)	1.78 (0.7–4.3)	1.2 (0.3–6.7)	46% @ 1000	0	9.5 ± 1.8	5.7 ± 1.3	8.1 ± 2.3	18 ± 2	90 ± 11
5c	Cl	0.29 ± 0.03	10% @ 10	30% @ 10	6.2 (3–12.5)	1.6 (0.4–5.8)	110 (20–645)	36% @ 1000	0	6.5 ± 1.4	8.1 ± 2.4	5.7 ± 1.7	10 ± 1	47 ± 6
5d	NH_2	0.38 ± 0.10	1% @ 10	5% @ 10	0% @ 10	20% @ 10	1 (0.13–1.4)	32% @ 1000	0	1.2 ± 0.1	12 ± 2	5.2 ± 0.9	4.2 ± 0.8	44 ± 11
5e	CH_3O	0.094 ± 0.012	14% @ 10	50% @ 10	10 (1–114)	4 (1.2–13.4)	0.3 (0.04–20)	900 (487–1687)	0	6.1 ± 0.7	16 ± 2	4.0 ± 1.0	7.2 ± 0.9	47 ± 8
6a	H	0.81 ± 0.08	3% @ 10	14% @ 10	7.0 (3.5–9.3)	3 (0.3–2.7)	0.68 (0.11–4)	2000 (300–13700)	0	4.5 ± 0.8	5.8 ± 1.1	5.3 ± 0.9	14 ± 0.5	59 ± 5
6b	F	0.13 ± 0.02	10% @ 10	10% @ 10	2.78 (0.8–8.80)	0.69 (0.08–6.5)	2 (0.4–9)	10% @ 1000	0	5.5 ± 0.8	0	7.9 ± 1.2	41 ± 10	36 ± 3
6c	Cl	0.12 ± 0.01	8% @ 10	17% @ 10	5.5 (3.7–8)	0.56 (0.1–1.9)	0.5 (0.05–4.7)	10% @ 1000	0	3.1 ± 0.9	4.8 ± 0.6	4.8 ± 0.6	12 ± 1	38 ± 3
6d	NH_2	0.90 ± 0.02	3% @ 10	14% @ 10	0% @ 10	20% @ 10	1.5 (0.5–4.1)	50% @ 10000	0	0	7.0 ± 1.5	5.7 ± 0.9	5.4 ± 0.7	46 ± 3
6e	CH_3O	0.27 ± 0.03	8% @ 10	17% @ 10	5.5 (3.7–8)	0.56 (0.1–1.9)	0.5 (0.05–4.7)	10% @ 1000	0	2.4 ± 0.5	1.2 ± 0.3	4.5 ± 0.7	8.4 ± 2.3	18 ± 2

[a] All compounds were tested as their (±)- isomers.

[b] The K_d for (±)-epibatidine is 0.02 nM.

[c] Data taken from ref 5.

[d] Assessed by comparing the current response to 100 μM of each compound to the mean current response of three preceding applications of ACh, applied at an EC_{20} concentration (20 μM for α4β2, 100 μM for α3β4) or an EC_{50} concentration (300 μM for α7) and expressed as a percentage of the maximal response to ACh.

[e] Assessed by comparing the current response to an EC_{50} concentration of ACh (70 μM for α4β2, 200 μM for α3β4, 300 μM for α7) in the presence of 100 μM of each compound to the mean current response of three preceding applications alone.

Table 2

Comparison of antagonist potency values, **5a–c** and **5e**, and **6a–c** and **5e** at α4β2-, α3β4- and α7-nAChRs[a]

	Antagonist Activity IC_{50}, μM		
Compounds	**α4β2**	**α3β4**	**α7**
varenicline	0.20 ± 0.03[b]	na	na
5a	7.1 ± 1.0	23 ± 2	179 ± 34
5b	2.9 ± 0.4	23 ± 3	233 ± 40
5c	11 ± 1	20 ± 2	97 ± 17
5e	1.2 ± 0.2	13 ± 3	114 ± 20
6a	6.4 ± 0.8	22 ± 3	117 ± 22
6b	1.3 ± 0.2	33 ± 8	60 ± 9
6c	2.7 ± 0.6	24 ± 0.3	66 ± 9
6e	1.8 ± 0.3	8.2 ± 1.5	30 ± 6

[a] Current responses of rat nAChRs expressed in *Xenopus* oocytes were recorded under two-electrode voltage clamp. IC_{50} values for **5a–c** and **5e** and **6a–c** and **5e** inhibition of α4β2-, α3β4- and α7-nAChRs are derived from concentration-inhibition curves, in which the current response to an EC_{50} concentration of acetylcholine (70 μM for α4β2, 200 μM for α3β4, 300 μM for α7) in the presence of various concentrations of each compound are compared to the response to acetylcholine alone.

[b] Data taken from ref 5.

Table 3

Calculated physiochemical properties of **5a–e** and **6a–e**, nicotine, epibatidine, and varenicline

Compd ID	LogP[a]	TPSA[a]	logBB[b]
nicotine	1.16	16.13	0.08
epibatidine	1.84	24.92	0.05
varenicline	1.01	37.81	−0.27
5a	1.45	37.81	−0.20
5b	1.99	37.81	−0.12
5c	2.27	37.81	−0.08
5d	1.21	63.83	−0.62
5e	1.89	47.04	−0.27
6a	1.45	37.81	−0.20
6b	1.99	37.81	−0.12
6c	2.27	37.81	−0.08
6d	1.21	63.83	−0.62
6e	1.89	47.04	−0.27

[a] ChemAxon Calculator Plugins, Marvin 6.1.0, 2013.

[b] logBB = −0.0148 * TPSA + 0.152 * LogP + 0.139 (from ref. 15).