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Synthesis, Nicotinic Acetylcholine Receptor Binding, and Antinociceptive Properties of 2′-Fluoro-3′-(substituted pyridinyl)-7-deschloroepibatidine Analogues

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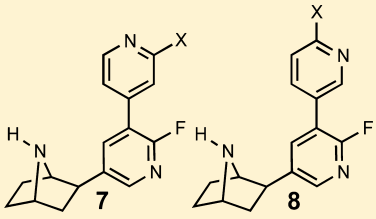
Supporting Information

ABSTRACT: 2′-Fluoro-3-(substituted pyridine)epibatidine analogues **7a−e** and **8a−e** were synthesized, and their in vitro and in vivo nAChR properties were determined. 2′-Fluoro-3′-(4″-pyridinyl)deschloroepibatidine (**7a**) and 2′-fluoro-3′-(3″-pyridinyl)-deschloroepibatidine (**8a**) were synthesized as bioisosteres of the 4′-nitrophenyl lead compounds **5a** and **5g**. Comparison of the in vitro nAChR properties of **7a** and **8a** to those of **5a** and **5g** showed that **7a** and **8a** had in vitro nAChR properties similar to those of **5a** and **5g** but both were more selective for the $\alpha4\beta2$-nAChR relative to the $\alpha3\beta4$- and $\alpha7$-nAChRs than **5a** and **5g**. The in vivo nAChR properties in mice of **7a** were similar to those of **5a**. In contrast, **8a** was an agonist in all four mouse acute tests, whereas **5g** was active only in a spontaneous activity test. In addition, **5g** was a nicotine antagonist in both the tail-flick and hot-plate tests, whereas **8a** was an antagonist only in the tail-flick test.



INTRODUCTION

Tobacco use continues to be the leading cause of preventable deaths in the United States as well as globally. Current statistics reveal that smoking-related diseases are responsible for nearly 6 million premature deaths globally annually.[1] In the United States, tobacco use is responsible for nearly 1 in 5 deaths that is approximately 443 000 premature deaths.[2] In 2010, an estimated 23% (58.3 million) of U.S. adults were current cigarette smokers.[3] Tobacco use increases the risk of multiple cancers such as cancers of the lung, mouth, nasal cavities, larynx, pharynx, esophagus, stomach, colorectum, liver, pancreas, kidney, bladder, uterine, cervix, ovary, and myeloid cells. Therefore, smoking accounts for at least 30% of all cancer deaths and 87% of lung cancer deaths.[4]

Due to the well-documented negative heath consequences, approximately 70% of smokers want to quit and about 40% try to quit every year. Of those who try to quit, only about 7% stay off nicotine for more than a year. The vast majority do not make it even a week without cigarettes. The major factor that is attributed to the initiation and sustaining of smoking is the presence of nicotine (**1**), the addictive substance in tobacco. Nicotine can produce a myriad of behavioral effects and is unquestionably one of the most popular and powerful reinforcing agents. Both the psychological and physiological effects of tobacco smoke are a result of nicotine's activation of various nicotinic acetylcholine receptor (nAChR) subtypes. For example, nicotine interacts with $\alpha4\beta2$-, $\alpha4\beta2\alpha6$*-, $\alpha4\beta2\alpha5$*, and $\alpha7$-nAChR in the dopaminergic mesolimbic pathway, a brain system thought to mediate the pleasurable and rewarding effects of most substances of abuse, including nicotine.[5] In addition, currently, the few treatments for nicotine dependence include nicotine replacement therapies (NRT); the antidepressant buproprion[6,7] (**2**), which acts as a dopamine uptake inhibitor in addition to its properties as a nicotinic antagonist of $\alpha3\beta4$- and $\alpha4\beta2$-nAChRs;[8] and the FDA-approved varenicline[9,10] (**3**), which acts as a partial nicotine agonist at the $\alpha4\beta2$ and a full agonist at the $\alpha3\beta4$- and $\alpha7$-nAChRs.[11] In addition, varenicline has affinity for $\alpha6\beta2$*-nAChR equal to that at $\alpha4\beta2$-nAChR, but functionally varenicline was more potent in stimulating $\alpha6\beta2$* versus $\alpha4\beta2$* mediated [^{3}H]dopamine release from rat striatal synaptosomes.[12] However, side effects such as gastrointestinal disturbances (nausea and vomiting) and neuropsychiatric effects (trouble sleeping, unusual dreams, violent or suicidal ideation) were frequently reported with the use of varenicline. In addition, recent evidence suggests that varenicline produces increased risk of heart attack, stroke, and/or other cardiovascular problems.[13] Therefore, there is need for development of new and improved pharmacotherapies for smoking cessation.

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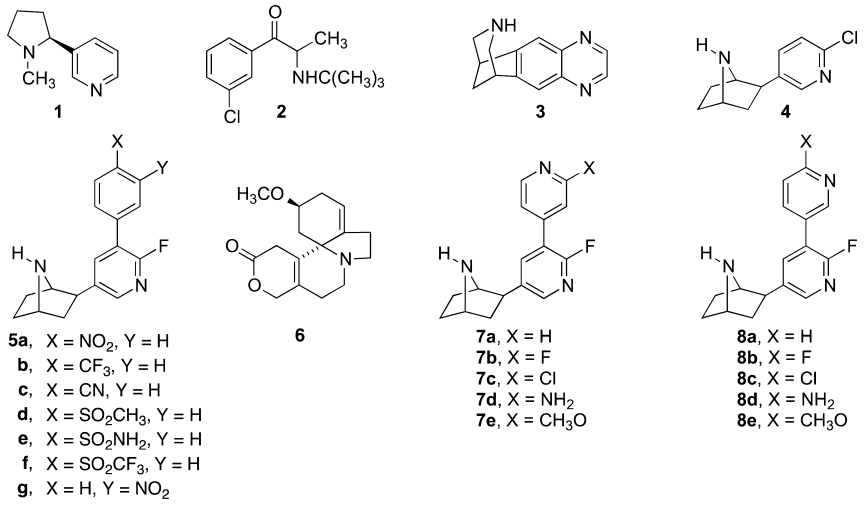
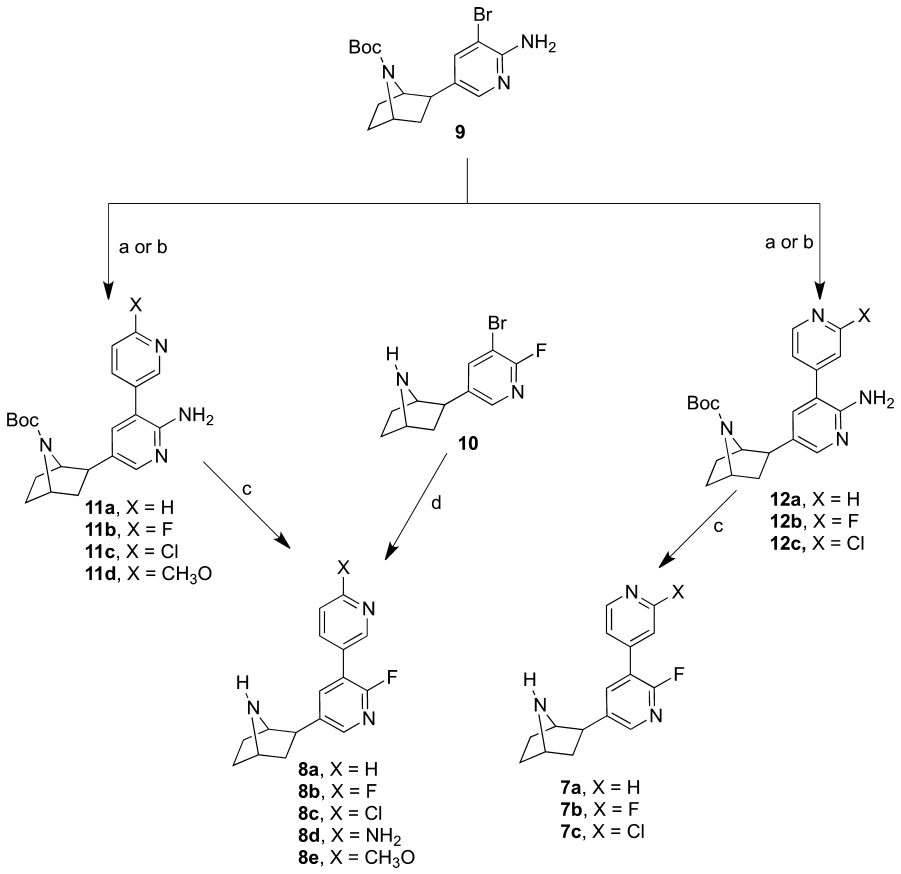
Chart 1. Structures of Compounds 1−4, 5a−g, 6, 7a−e, and 8a−e



Scheme 1[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, pyridinyl boronic acid, Na_2CO_3, DME, H_2O, 80 °C, 5 h for the preparation of **11b**, **11c**, **12b**, and **12c**; (b) pyridinyl boronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, H_2O, reflux, 24 h for the preparation of **11a**, **11d** and **12a**; (c) 70% HF−pyridine, $NaNO_2$; (d) 2-aminopyridine-5-pinacol boronic ester, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 110 °C, 18 h.

The natural alkaloid epibatidine (**4**, *exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane) is an important lead structure in the development of pharmacotherapies for treating nicotine addiction as well as other central nervous system (CNS) disorders including Alzheimers and Parkinson's diseases, pain, schizophrenia, anxiety, depression, and Tourette's syndrome among others.[14] Since its isolation and structural determination in 1992,[15] epibatidine has drawn a lot of interest because of its very high affinity for the $\alpha4\beta2$*-nAChRs.[16,17] In previous studies, we reported the synthesis, nAChR binding affinity, and pharmacological properties of a number of epibatidine analogues.[18,19] Interestingly, some analogues retained high affinity for nAChR but unlike epibatidine showed no agonist activity in the acute mouse antinociception test and were antagonists of nicotine-induced antinociception in these assays.[18−20] For example, we identified

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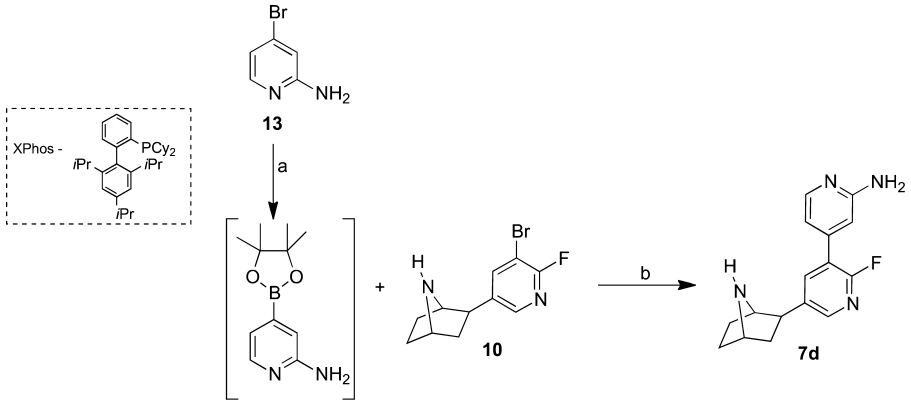
Scheme 2[a]



[a]Reagents and conditions: (a) bis(pinacolato)diboron, Pd_2dba_3 (3 mol %), XPhos (16 mol %), 1,4-dioxane, 110 °C, 4 h; (b) Pd_2dba_3 (3 mol %), K_3PO_4 (2.3 equiv), 1,4-dioxane, 110 °C, 18 h.

2′-fluoro-3′-(4-nitrophenyl)deschloroepibatidine (**5a**), also referred to as RTI-7527-102 and 4-nitro-PFEB, as an nAChR ligand with a K_i value of 0.009 nM for inhibition of [^{3}H]epibatidine binding. This compound also showed potent antagonism of nicotine-induced antinociception in the tail-flick and hot-plate tests in mice.[21] In a separate study, we showed that **5a** was a competitive antagonist of human $\alpha4\beta2$-nAChRs with a potency 17-fold higher than that of dihydro-β-erythroidine (**6**) with very low efficacy at $\alpha3\beta4$- and $\alpha7$-nAChRs.[22] In a more recent study, the $\alpha4\beta2$-nAChR antagonist **5a** attenuated the discriminative stimulus effects of nicotine, reduced nicotine's ability to facilitate intracranial self-stimulation (ICSS), blocked conditioned place preference (CPP) produced by nicotine in mice, and dose-dependently blocked nicotine self-administration in rats.[23] Thus, **5a** has both in vitro and in vivo properties thought to be favorable for a potential pharmacotherapy to treat smokers. However, the presence of a nitro-substituted phenyl group, a system that is associated with toxicity via partial reduction in vivo to the hydroxylamine, which can undergo metabolic activation to an electrophilic nitroso species of **5a**, raises concern about its future development. In a recent study, we reported that replacement of the 4-nitro group in **5a** by other strong electron-withdrawing groups led to compounds **5b–g** that retained high affinity for $\alpha4\beta2$-nAChRs and potent antagonist activity in the tail-flick test.[24]

In this study, we report the synthesis, nAChR binding, and pharmacological properties of compounds **7a–e** and **8a–e**. Compound **7a** is a bioisosteric analogue of **5a** where the nitrophenyl group has been replaced by a pyridine nitrogen. Compound **8a** is a similar bioisosteric analogue of **5g**, a compound that has a K_i value of 0.053 nM of affinity for inhibition of [^{3}H]epibatidine binding and AD_{50} values of 0.5 and 130 μg/kg in the tail-flick and hot-plate tests.[24] The syntheses and evaluation of analogues **7b–e** and **8b–e** allowed a determination of the effects of electron-withdrawing and -donating groups on the pyridine ring. See Chart 1 for the structures of the compounds described in the above paragraphs.

Chemistry. The synthetic route to the **7a–c** and **8a–e** analogues commenced with the intermediate 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-3′-bromo-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**) prepared in several steps from *N*-Boc pyrrole as reported in earlier work.[25,26] As outlined in Scheme 1, the Suzuki cross-couplings of the haloboronic acids, that is, 2-fluoropyridine-5-boronic acid, 2-fluoropyridine-4-boronic acid, 2-chloropyridine-5-boronic acid, and 2-chloropyridine-4-boronic acid with the 2′-amino-3′-bromo compound **9**, carried out in the presence of palladium diacetate, tri-(*o*-tolyl)phosphine, and sodium carbonate, heated at 80 °C in 1,2-dimethoxyethane and water for 5 h furnished the bipyridine intermediates **11b**, **11c**, **12b**, and **12c**.[27] Suzuki cross-coupling of pyridine-4-boronic acid, pyridine-3-boronic acid, and 2-methoxypyridine-5-boronic acids with **9** in the presence of tetrakis-(triphenylphosphine) palladium(0) as the catalyst, potassium carbonate as the base, and toluene (15 mL), ethanol (1.5 mL), and water (1.5 mL) as solvents and heating at reflux for 24 h in a sealed tube provided the cross-coupled products **11a**, **11d**, and **12a** in good yields. Conversion of the amino group to the fluoro group along with a concomitant removal of the *tert*-butyloxycarbonyl protecting group in the intermediates **11a–d** and **12a–c** performed through the diazotization reaction with sodium nitrite in the presence of hydrogen fluoride in pyridine (70%) furnished the products **8a–e** and **7a–c**. Compound **8d** was synthesized by subjecting 2-*exo*-(2′-fluoro-3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane **10**[21] to a Suzuki–Miyaura cross-coupling with 2-aminopyridine-5-pinacol boronic ester in the presence of tetrakis(triphenylphosphine) palladium(0), potassium carbonate, 1,4-dioxane, and water, heated at 110 °C in a sealed tube overnight. The reaction furnished the diamine **8d** in a 67% yield (Scheme 1).

The synthesis of the 2-*exo*-[2′-fluoro-3′-(2-aminopyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane **7d**, was accomplished in a "one-pot" reaction that combined the borylation and the Suzuki–Miyaura steps (Scheme 2). The borylation reaction was accomplished using Buchwald's dialkylphosphinobiphenyl ligand, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), and tris(dibenzylideneacetone)dipalladium (0) as the catalytic system.[28,29] Cross-coupling of 2-amino-4-bromopryidine (**13**) and bis(pinacolato)diborane in the presence of XPhos, tris(dibenzylideneacetone)dipalladium (0), and potassium acetate heated at 110 °C in 1,4-dioxane converted **13** to the boronic ester, which was carried on to the next step directly by addition of 2′-fluoro-3′-bromo intermediate **10**, tribasic potassium phosphate as base, and an additional 3 mol % of tris(dibenzylideneacetone)dipalladium (0) and heating at 110 °C for 18 h to provide **7d**. Compound **7e** was synthesized as shown in Scheme 3. Borylation of **14** was achieved by cross-coupling with bis(pinacolato)diborane heated

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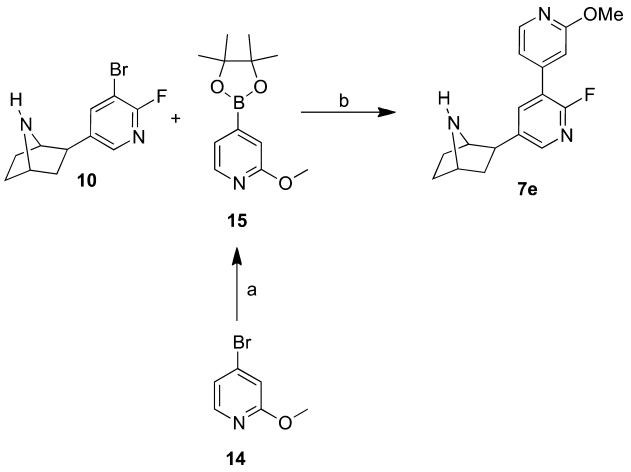
Scheme 3[a]



[a]Reagents and conditions: (a) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), DMF, 80 °C; (b) $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, 110 °C, 18 h.

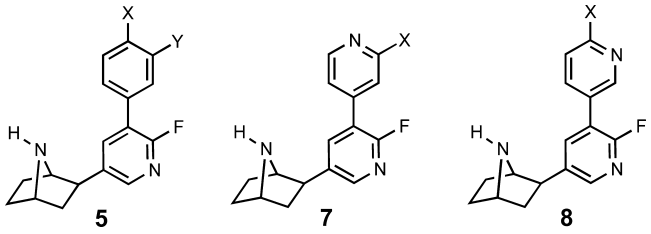
at 80 °C in the presence of 1,1′-bis(diphenylphosphino)-ferrocene-palladium(II)dichloride, potassium acetate, and dimethylformamide as the solvent to provide the pinacol boronic ester **15** (Scheme 3). Compound **15** was cross-coupled with 2′-fluoro-3′-bromo intermediate **10** to furnish 2-*exo*-[2′-fluoro-3′-(2-methoxypyridin-4-yl)-5′-pyridinyl]-7-azabicyclo-[2.2.1]heptane (**7e**).

Biology. The inhibition of [^{3}H]epibatidine binding at $\alpha4\beta2$*-nAChRs were conducted as previously reported.[21] The binding assays were performed using tissue homogenates prepared from freshly collected cerebral cortices from adult male Sprague–Dawley rats. These homogenates were frozen at −80 °C until use. It should be noted that, although this brain region contains a variety of nAChRs, $\alpha4\beta2$ is the predominant (>90%) subtype. The epibatidine analogues were tested for agonist and antagonist activity at rat $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChRs in an in vitro electrophysiology assay as previously described.[24] The epibatidine analogues were tested in mice for their effects on body temperature and two pain models (tail-flick and hot-plate assays) after acute administration as previously described.[21] For the antagonist experiments, male ICR adult mice were pretreated subcutaneously (sc) with either saline or epibatidine analogues 10 min before nicotine. Nicotine was administered at a dose of 2.5 mg/kg, sc (an ED_{84} dose), and mice were tested 5 min later. ED_{50} and AD_{50} values with 95% confidence limits were determined.

RESULTS AND DISCUSSION

The nAChR binding affinities and the functional nicotinic pharmacological properties of 2′-fluoro-3′-(substituted pyridine)deschloroepibatidine analogues **7a–e** and **8a–e** were determined. The K_i values for the inhibition of [^{3}H]epibatidine

Table 1. Radioligand Binding and Efficacy Profile Data for 2′-Fluoro-3′-(substituted pyridine)deschloroepibatidine Analogues



compd[a]	X	Y	$\alpha4\beta2$* [^{3}H]epibatidine[b] (K_i, nM) (Hill slope)	agonist activity at 100 μM (% of max ACh activity)[d]			antagonist activity at 100 μM (% ACh response remaining)[e]		
				$\alpha4\beta2$	$\alpha3\beta4$	$\alpha7$	$\alpha4\beta2$	$\alpha3\beta4$	$\alpha7$
nicotine[c]			1.50 ± 0.30	40 ± 1	37 ± 3	43 ± 5	nd	nd	nd
nat-epibatidine			0.026 ± 0.002	131 ± 13	97 ± 4	150 ± 8	nd	nd	nd
varenicline			0.12 ± 0.02	13 ± 0.4	66 ± 4	74 ± 5	38 ± 2	nd	nd
5a[f]	NO_2	H	0.009 ± 0.001	0	4 ± 1	6 ± 1	6 ± 1	9 ± 2	55 ± 6
5g[f]	H	NO_2	0.053 ± 0.004	1.0 ± 0.1	1.3 ± 0.2	6 ± 1	5 ± 1	2.1 ± 0.4	17 ± 3
7a	H		0.12 ± 0.03	1.5 ± 0.3	7 ± 1	8 ± 2	6 ± 1	34 ± 4	45 ± 4
7b	F		0.067 ± 0.01	3 ± 0.3	5 ± 0.4	2 ± 0.5	10 ± 1	27 ± 2	44 ± 4
7c	Cl		1.18 ± 0.14	1.2 ± 0.2	4 ± 0.4	3 ± 0.3	7 ± 1	20 ± 1	31 ± 3
7d	NH_2		0.13 ± 0.005	3.9 ± 0.5	0	10 ± 4	8 ± 1	9 ± 1	32 ± 10
7e	CH_3		0.04 ± 0.012	0	1.5 ± 0.2	2.1 ± 0.8	4 ± 1	6 ± 1	12 ± 4
8a	H		0.35 ± 0.038	2 ± 0.3	3 ± 0.5	7 ± 2	7 ± 1	15 ± 2	54 ± 9
8b	F		0.049 ± 0.02	9 ± 1	9 ± 1	8 ± 0.7	24 ± 4	73 ± 8	75 ± 18
8c	Cl		0.063 ± 0.08	1 ± 0.2	14 ± 1	0	8 ± 1	23 ± 2	32 ± 4
8d	NH_2		0.25 ± 0.033	2.7 ± 0.3	1.3 ± 0.3	5 ± 2	7 ± 1	9 ± 1	50 ± 6
8e	CH_3O		0.13 ± 0.027	5 ± 0.1	9 ± 2	22 ± 4	14 ± 1	23 ± 6	41 ± 2

[a]All compounds were tested as their (±)-isomers. [b]The K_d for (±)-[^{3}H]epibatidine is 0.02 nM. [c]Data taken from ref 21. [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 $\alpha4\beta2$, 110 μM for $\alpha3\beta4$) or an EC_{50} concentration (300 μM for $\alpha7$) 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 $\alpha4\beta2$, 200 μM for $\alpha3\beta4$, 300 μM for $\alpha7$) in the presence of 100 μM of each compound to the mean current response of three preceding applications of ACh alone. [f]Data taken from ref 24.

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binding at the $\alpha4\beta2$*-nAChRs for compounds **7a−e** and **8a−e** along with reference compounds nat-epibatidine (**4**), varenicline (**3**), and the lead compounds **5a** and **5g** are listed in Table 1. The reference standards nat-epibatidine and varenicline and lead compounds **5a** and **5g** have K_i values of 0.026, 0.12, 0.009, and 0.053 nM for the $\alpha4\beta2$*-nAChR, respectively.[24] The pyridine bioisosteres **7a** and **8a** of **5a** and **5b**, respectively, had K_i values of 0.12 and 0.35 nM, respectively, for $\alpha4\beta2$*-nAChR. Even though **7a** and **8a** have K_i values slightly less than **5a** and **5g**, respectively, their K_i values are still subnanomolar and thus have potent affinity for nAChRs labeled by [^{3}H]epibatidine.

Substitution of the 4′-pyridyl and 3′-pyridyl rings of analogues **7a** and **8a**, respectively, with 3′- and 4′-substituents, respectively, had only small effects on $\alpha4\beta2$*-nAChR binding affinity. The K_i values varied from 0.04 to 1.18 nM. With the exception of the 3′-chloro analogue **7c**, all the 3′-substituted 4′-pyridyl analogues **7b−e** had very high affinity for $\alpha4\beta2$*-nAChRs. The K_i values ranged from 0.04 for **7e** to 0.13 nM for **7d**. Even the 3′-chloro substituted analogue had a K_i value of 1.18 nM. All the 4′-substituted 3′-pyridyl analogues had K_i values of 0.04−0.35 nM and thus very high affinity for $\alpha4\beta2$*-nAChR. The presence of 3′-substituents on the 4′-pyridyl analogues **7b−e** or 4′-substituents on the 3′-pyridyl analogues **8b−e** did not show any clear structure affinity patterns. In the case of the **7a−e** series, the two highest affinity compounds were the electron-withdrawing 3′-fluoro analogue **7b** (K_i = 0.067) and the electron-donating methoxy analogue **7e** (K_i = 0.04). For the 4′-substituted 3′-pyridyl analogues, the 4′-fluoro and 4′-chloro electron-withdrawing analogues **8b** and **8c** (K_i = 0.049 and 0.063 nM) had higher $\alpha4\beta2$*-nAChR affinity than the 3′-amino and 3′-methoxy electron-donating analogues **8d** and **8e** (K_i = 0.25 and 0.13 nM). However, all four compounds have subnanomolar K_i values.

The receptor subtype selectivity of **7a−e** and **8a−e** was assessed in an electrophysiological assay using rat $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChRs expressed in *Xenopus* oocytes and assayed by a two-electrode voltage clamp. Compounds were compared to previously determined values for nicotine, nat-epibatidine, varenicline, and compounds **5a** and **5g** (Table 1). Current responses to a high concentration (100 μM) of each compound were compared to the maximum response that can be achieved with acetylcholine. All compounds differed dramatically from nat-epibatidine (a full agonist at $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChRs). Compounds **7a**, **7c**, **7e**, **8a**, and **8c** displayed little or no agonist activity at $\alpha4\beta2$ in this initial screen, while **7b**, **7d**, **8b**, and **8d−e** had a low level of agonist activity at this subtype. Compounds **7d** and **8d** had little or no agonist activity at $\alpha3\beta4$, while **7a−c**, **8a−c**, and **8e** had a low level of agonist activity at this subtype. At $\alpha7$-nAChRs, compounds **7b**, **7e**, and **8c** had little or no agonist activity, compounds **7a**, **7c−d**, **8a−b**, and **8d** displayed low levels of agonist activity, and compound **8e** showed a moderate level of agonist activity (22 ± 4% of the maximal acetylcholine response). Compounds **7a−e** and **8a−e** all showed lower agonist activity at $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChR than did varenicline (a partial agonist at $\alpha4\beta2$- and a full agonist at $\alpha3\beta4$- and $\alpha7$-nAChRs).

As an initial screen of antagonist properties, we measured the current response to an EC_{50} concentration of acetylcholine in the presence of 100 μM of each compound and compared this to a preceding current response to acetylcholine alone (Table 1). Compounds **7a−e** and **8a−e** antagonized, to varying extents, the $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChR subtypes in this preliminary screen. This contrasts with varenicline, which can antagonize $\alpha4\beta2$ receptors but is a full agonist at $\alpha3\beta4$- and $\alpha7$-nAChRs. The ability of **8e** to both activate and antagonize the $\alpha7$-nAChR subtype indicates that **8e** is a partial agonist at this receptor. The results from this initial screen suggested that some compounds in this series may be selective $\alpha4\beta2$ antagonists, and **7a**, **7c**, and **8a** were selected for more detailed studies.

We examined the subtype selectivity of antagonist activity of compounds **7a**, **7c**, and **8a** in more detail by generating concentration−inhibition curves (Table 2) and compared the

Table 2. Comparison of Antagonist Potency (IC_{50} Values) for Several Epibatidine Analogues at $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChRs

	antagonist activity[a] IC_{50} (μM)		
compd	$\alpha4\beta2$	$\alpha3\beta4$	$\alpha7$
varenicline	0.20 ± 0.03[b]	[d]	[d]
5a	3.2 ± 0.2[c]	7.9 ± 0.5[c]	32 ± 12[c]
5g	4.3 ± 0.6	3.9 ± 0.3	23 ± 5
7a	1.4 ± 0.1	8 ± 1	75 ± 16
7c	2.0 ± 0.4	8.8 ± 0.9	56 ± 10
8a	1.7 ± 0.2	18 ± 3	99 ± 24

[a]Antagonist activity of **7a**, **7c**, and **8a** was assessed in the in vitro electrophysiology assay at a range of concentrations to generate concentration−inhibition curves. Data were fit to the following equation: $I = I_{max}/[1+(IC_{50}/X)^n]$, where I is the current response at a compound concentration (X), I_{max} is the maximum current, IC_{50} is the compound concentration producing half-maximal inhibition of the current response, and n is the Hill coefficient. [b]Data taken from ref 11. [c]Data taken from ref 24. [d]Varenicline is an agonist at $\alpha3\beta4$- and $\alpha7$-nAChRs, with an EC_{50} of 55 ± 8 and 18 ± 6 μM, respectively (ref 11).

IC_{50} values to the lead nitro compounds **5a** and **5g**. Compound **7a**, the bioisosteric analogue of **5a**, where the nitro group has been replaced by a pyridine nitrogen, displayed an improved $\alpha4\beta2$ selectivity. While **5a** was 2.5-fold selective for $\alpha4\beta2$ over $\alpha3\beta4$ and 10-fold selective for $\alpha4\beta2$ over $\alpha7$, compound **7a** was 5.7-fold selective for $\alpha4\beta2$ over $\alpha3\beta4$ and 54-fold selective for $\alpha4\beta2$ over $\alpha7$. Similarly, compound **8a**, the bioisosteric analogue of **5g**, where the nitro group has been replaced by a pyridine nitrogen, displayed an improved $\alpha4\beta2$ selectivity. While **5g** was nonselective between $\alpha4\beta2$ and $\alpha3\beta4$ and 5-fold selective for $\alpha4\beta2$ over $\alpha7$, compound **8a** was 11-fold selective for $\alpha4\beta2$ over $\alpha3\beta4$ and 58-fold selective for $\alpha4\beta2$ over $\alpha7$. We also examined **7c** but found it to be less selective for $\alpha4\beta2$ than was **7a**. None of these compounds was as potent an antagonist as varenicline at $\alpha4\beta2$-nAChRs. The ability of these compounds to antagonize $\alpha3\beta4$- and $\alpha7$-nAChRs differs markedly from varenicline, which is a full agonist at these subtypes.

The 3′-substituted 4′-pyridyl analogues **7a−e** and the 4′-substituted 3-pyridyl analogues (**8a−e**) were evaluated for their in vivo nAChR properties in mice, and the results were compared to the properties of lead compounds **5a** and **5g** and varenicline (Table 3). Similar to **5a**, the pyridine bioisostere **7a** does not have agonist activity in the tail-flick and hot-plate tests but like **5a** and varenicline did show activity in the hypothermia and spontaneous-activity tests. The ED_{50} values for **7a** in the hypothermia and spontaneous-activity tests were 1.69 and 0.38 mg/kg compared to 0.21 and 0.22 mg/kg for **5a**. Similar to **5a**, **7a** antagonized nicotine-induced antinociception in the tail-flick and hot-plate tests with AD_{50} values of 12 and 290 μg/kg, respectively, compared to 3 and 120 μg/kg for **5a**. Thus, **7a** is a

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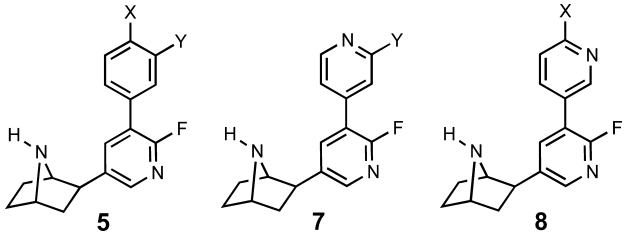
Table 3. Antinociception, Hypothermia, and Spontaneous Activity Profile Data for 2′-Fluoro-3′-(substituted pyridine)deschloroepibatidine Analogues



			ED_{50} (mg/kg)				AD_{50} (μg/kg)	
compd[a]	X	Y	tail-flick	hot-plate	hypothermia	spontaneous activity	tail-flick	hot-plate
nicotine[b]			1.3 (0.5–1.8)	0.65 (0.25–0.85)	1.0 (0.6–2.1)	0.5 (0.15–0.78)		
nat-epibatidine			0.006 (0.001–0.01)	0.004 (0.001–0.008)	0.004 (0.002–0.008)	0.001 (0.0005–0.005)		
varenicline			11% @ 10	10% @ 10	2.8	2.1	0.2	470
5a[c]	NO_2	H	5% @ 10	10% @ 10	0.21 (0.04–1.9)	0.22 (0.04 ± 1.2)	3 (0.8–45)	120 (10–900)
5g[c]	H	NO_2	3% @ 10	20% @ 10	0% @ 10	6.5 (5.3 ± 8.3)	0.5 (0.3–5)	130 (50–290)
7a	H		13% @ 10	40% @ 10	1.69 (1.1–2.6)	0.38 (0.2–2.7)	12 (10–172)	290 (19–991)
7b	F		5% @ 10	18% @ 10	1.58 (0.97–2.1)	0.17 (0.08–1.5)	4 (0.1–70)	117 (110–1100)
7c	Cl		11% @ 10	19% @ 10	2.74 (1.89–3.5)	1.01 (0.27–3.7)	320 (45–3262)	1370 (180–1430)
7d	NH_2		11% @ 10	12% @ 10	1.87 (0.1–35)	0.61 (0.04–9.1)	9 (0.4–19)	10% @ 10000
7e	CH_3O		5% @ 10	10% @ 10	8.5 (1.9–38.6)	1.82 (0.4–8.4)	0.3 (0.02–5.7)	40% @ 10000
8a	H		4.9 (3.6–6.7)	5 (3.7–6.7)	3.7 (2.9–4.5)	0.69 (0.4–12.8)	3 (0.5–24)	10% @ 1000
8b	F		3.6 (2.7–4.7)	3.27 (2.1–5.3)	0.68 (0.52–1.1)	0.38 (0.13–1.1)	1% @ 100	1% @ 100
8c	Cl		10% @ 10	27% @ 10	3.11 (1.5–5.1)	1.58 (0.5–4.4)	9 (2–38)	2001 (297–3610)
8d	NH_2		5% @ 10	8% @ 10	2.8 (2–3.8)	184 (0.5–6.3)	30 (3–35)	50% @ 10
8e	CH_3O		4.22 (3–5.3)	1.72 (0.9–3.4)	0.77 (0.51–1.2)	0.53 (0.19–1.1)	21 (3–125)	0% @ 100

[a]All compounds were tested as their (±)-isomers. [b]Data taken from ref 21. [c]Data taken from ref 24.

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very good bioisostere analogue of **5a**. In contrast, the 3′-pyridyl compound **8a**, which is the pyridine bioisostere of **5g**, was an agonist in all four mice acute tests, whereas **5g** was active only in the spontaneous-activity test. In addition, whereas **5g** was an antagonist of nicotine-induced antinociception in the tail-flick and hot-plate tests with AD_{50} values of 0.5 and 130 μg/kg, respectively, **8a** was an antagonist in only the tail-flick test with an AD_{50} value of 3 μg/kg. Somewhat surprisingly, the in vivo properties of **8a** are quite different from those of **5g**, and thus, even though it is an interesting partial agonist, it is not a good bioisosteric analogue of **5g** in the mice in vivo test. These discrepancies between the in vivo and in vitro effects of **5g** and **8a** could also be related to many factors such as differences in the metabolic profile and brain penetrability of these two analogues as well as the fact that we used expressed receptors systems and not native receptors preparations. Furthermore, since the agonistic response of nicotine in these two tests is largely mediated by $\alpha4\beta2^*$ nAChR subtypes, it is possible that **5g** and **8a** differ in their affinity/activity at the various $\alpha4\beta2^*$ nAChR subtypes mediating their pharmacological responses. In addition, in vivo regulation of nicotinic receptors such as $\alpha4\beta2^*$ nAChR subtypes by these two analogues may differ also. For example, it is possible that, since **5g** was more potent than **8a** as a functional blocker in the tail-flick and hot-plate tests, in vivo desensitization/blockade of $\alpha4\beta2^*$ receptors by **5g** is more pronounced. We recently reported that varenicline (**3**) and sazetidine, two $\alpha4\beta2^*$ nicotinic partial agonists that differ in their desensitization properties, differ in their potency to act as functional antagonists of nicotine in these tests.[30,31]

Similar to the unsubstituted analogue **7a**, none of the 3′-substituted 4-pyridyl analogues **7b**−**e** had any agonist activity in the tail-flick and hot-plate tests (Table 3). In the case of the 4′-substituted 3′-pyridyl analogues, the 4′-fluoro and 4′-methoxy analogues **8b** and **8e** had agonist activity in the tail-flick and hot-plate tests. Similar to **5a**, **5g**, and varenicline, **7b**−**e** and **8b**−**e** had activity in the hypothermia and spontaneous-activity tests.

Analogues **7b**−**e** and **8c**−**e** antagonized nicotine-induced antinociception in the tail-flick test (Table 3). Analogues **7b**−**c** and **8c** also antagonized nicotine-induced antinociception in the hot-plate test with AD_{50} values ranging from 117 to 1370 μg/kg. Compounds **7a** and **7b**, which have AD_{50} values of 290 and 117 μg/kg, respectively, in the hot-plate test, compared to 470 μg/kg for varenicline strongly suggest that these compounds have good brain penetration. Unlike any of the other pyridine substituted analogues, the 3′-fluoro-4′-pyridyl analogue **8b** was an agonist in all four acute mouse tests and had no antagonist properties.

Calculated physicochemical properties such as lipophilicity (clogP), topological polar surface area (TPSA), and derived values such as logBB can be used as an indication of the potential of a compound for development as a CNS drug. These molecular descriptors were calculated for lead compounds **5a** and **5g**, bioisosteric analogues **7a** and **8a**, respectively, as well as compounds **7b**−**e**, **8b**−**e** and reference compounds nicotine, epibatidine, and varenicline (Table 4). In general, CNS drugs have a clogP in the range 2−4,[32] TPSA less than 76 Å,[33] and logBB greater than −1.[34] All of the compounds have clogP values within or close to the desirable range and logBB values between −0.54 and +0.08. In addition, all of the compounds have TPSA values of less than 76 Å. A comparison of the logP, TPSA, and logBB values of 1.99, 37.81, and −0.12, respectively, for bioisosteric analogues **7a** and **8a** to the corresponding values of 3.14, 70.74, and −0.43 for lead compounds **5a** and **5g** show that these two bioisosteric analogues (**7a** and **8a**) have at least as favorable if not better calculated physicochemical properties than lead compounds **5a** and **5g**. In addition, both **7a** and **8a** have calculated logBB values somewhat better than that of varenicline.

Table 4. Calculated Physiochemical Properties of 5a, 5g, 7a−e, 8a−e, Nicotine, Nat Epibatidine, and Varenicline

compd	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	3.14	70.74	−0.43
5g	3.14	70.74	−0.43
7a	1.99	37.81	−0.12
7b	2.52	37.81	−0.04
7d	1.75	63.83	−0.54
7c	2.81	37.81	0.01
7e	2.12	37.81	−0.10
8a	1.99	37.81	−0.12
8b	2.52	37.81	−0.04
8c	2.81	37.81	0.01
8d	1.75	63.83	−0.54
8e	2.42	47.04	−0.19

[a]ChemAxon Calculator Plugins, Marvin 6.1.0, 2013. [b]logBB = −0.0148 × TPSA + 0.152 × clogP + 0.139 (from ref 34).

In summary, 2′-fluoro-3-(substituted pyridine)epibatidine analogues **7a**−**e** and **8a**−**e** were synthesized and evaluated for the ability to inhibit [^{3}H]epibatidine binding to nAChR, tested for agonist and antagonist activity at $\alpha4\beta2$-, $\alpha3\beta4$-, and $\alpha7$-nAChR in an electrophysiology assay, and evaluated for agonist effects in the tail-flick, hot-plate, spontaneous-activity, and hypothermia tests in the mouse and as antagonists of nicotine-induced antinociception in the tail-flick and hot-plate tests in the mouse. A comparison of the nAChR binding and electrophysiology of bioisosteres **7a** and **8a** to those of the nitrophenyl lead compounds **5a** and **5g**, respectively, showed that **7a** and **8a** had in vitro nAChR properties similar to those of **5a** and **5g** but were more selective for the $\alpha4\beta2$-nAChR relative to the $\alpha3\beta4$- and $\alpha7$-nAChRs than **5a** and **5g**. Similar to **5a**, **7a** did not have agonist activity in the tail-flick and hot-plate tests and like **5a** was a potent antagonist of nicotine-induced antinociception in these two tests. Thus, **7a** is a very good bioisosteric analogue of **5a**. In contrast, **8a** unlike **5g** was an agonist in both the tail-flick and hot-plate tests and was an antagonist of nicotine-induced antinociception only in the tail-flick test, whereas **5g** was an antagonist in both tests. Even though **8a** is not a good bioisosteric analogue of **5g** in the mice test, it is an interesting partial agonist. A comparison of the AD_{50} value of **7a** to that of varenicline in the hot-plate test, strongly suggest that this compound penetrates the brain in mice. Calculated logBB values for **7a** and **8a** also suggest that this compound will have good blood−brain barrier penetration. Since both nAChR antagonists and partial agonists are of interest as possible pharmacotherapies for treating smokers, both **7a** and **8a** are candidates for development as pharmacotherapies to treat nicotine addiction.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-temp (Laboratory Devices, Inc.) capillary tube apparatus. NMR spectra were recorded on a Bruker

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Avance 300 or AMX 500 spectrometer using tetramethylsilane as internal standard. Mass spectra were determined on a Perkin−Elmer Sciex API 150EX mass spectrometer outfitted with APCI and ESI sources. Melting point was determined on a Laboratory Devices MEL-TEMP II. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross GA. The purity of the compounds (>95%) was established by elemental analysis. Analytical thin-layer chromatography (TLC) was carried out on plates precoated 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.

Suzuki Cross-Coupling Reaction: General Procedure (Method A). To a resealable reaction vessel under nitrogen was added 1.0 equiv of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**9**), $Pd(OAc)_2$ (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, sealed, and heated on a sand bath at 80 °C for 5 h. The mixture was cooled, poured into 20 mL of a saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered through Celite, and the solvent was removed under reduced pressure. The resultant residue was purified on silica gel by flash chromatography eluted with $CHCl_3$−MeOH (50:1 to 10:1).

Suzuki Cross-Coupling Reaction: General Procedure (Method B). To a resealable reaction vessel under nitrogen was added 1.0 equiv of the 3′-bromo compound **9**, $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (2.0 equiv) and the respective pyridinyl boronic acid (1.3 equiv), toluene (12 mL), ethanol (1.5 mL), and water (1.5 mL). The mixture was degassed through bubbling nitrogen, sealed, and heated on a sand bath at 110 °C. After 24 h, the mixture was cooled, poured into 30 mL of H_2O, and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered through Celite, and the solvent was removed in vacuo. The resultant residue was purified by flash chromatography on a silica gel column using hexanes−isopropanol (80:20 to 25:75) or $CHCl_3$−MeOH (30:1 to 10:1) as the eluent.

General Procedure C: Removal of the Boc-Protecting Group. A solution of 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 and 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, and concentrated in vacuo, and the residue was purified by flash chromatography using a silica gel column eluted with $CHCl_3$−MeOH (10%) to provide the respective amine.

2-*exo*-[2′-Fluoro-3′-(pyridin-4-yl)-5′-pyridinyl]-7-azabicyclo-[2.2.1]heptane (7a) Fumarate. A solution of **12a** (378 mg, 1.03 mmol, 1.0 equiv) in 70% HF in pyridine (1.5 mL) was stirred at 0 °C for 30 min. Sodium nitrite (806 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH−H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on a silica gel column using $CHCl_3$−MeOH as the eluent to provide 192 mg (69%) of **7a** as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 1.50−1.78 (m, 6H), 2.01−2.08 (dd, J = 9.0, 11.2 Hz, 1H), 3.02−3.07 (dd, J = 8.7, 5.2 Hz, 1H), 3.66 (s, 1H), 3.77 (br s, 1H), 7.70−7.73 (m, 2H), 8.13 (dd, J = 2.4, 9.4 Hz, 1H), 8.18 (s, 1H), 8.64 (d, J = 1.5 Hz, 1H), 8.65 (d, J = 1.5 Hz, 1H); ^{13}C NMR (CD_3OD) δ 30.0, 31.8, 41.1, 45.7, 57.9, 63.7, 121.2, 125.1, 141.3, 142.1, 144.2, 147.8, 148.0, 150.6, 158.6, 161.7; MS (ESI) m/z 270.2 $(M + H)^+$.

A solution of **7a** (302 mg, 1.12 mmol) in chloroform (2 mL) was placed in vial and treated with 1.1 equiv of fumaric acid (0.65 M in MeOH). After 24 h, the white solid obtained was recrystallized from a MeOH−Et_2O mixture to provide the salt **7a**·$C_4H_4O_4$ as a white solid: mp 192−195 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.86−2.22 (m, 6H), 2.44−2.51 (dd, J = 9.0, 11.0 Hz, 1H), 3.50−3.55 (m, 1H), 4.35 (br s, 1H), 4.56 (d, J = 3.9 Hz, 1H), 6.63 (s, 1H), 7.72−7.75 (m, 2H), 8.20 (dd, J = 2.4, 9.0 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.67 (m, 2H); ^{13}C NMR (CD_3OD) δ 27.0, 29.0, 37.7, 43.4, 60.2, 64.1, 121.6, 125.1, 136.2, 137.6, 141.3, 143.9, 147.8, 148.0, 150.7, 159.0, 162.2, 171.4; MS (ESI) m/z 270.1 [(M − fumaric)$^+$, M = $C_{16}H_{16}FN_3$·$C_4H_4O_4$]. Anal. ($C_{20}H_{20}FN_3O_4$·0.25 H_2O) C, H, N.

2-*exo*-[2′-Fluoro-3′-(2-fluoropyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (7b) Fumarate. A solution of **12b** (230 mg, 0.60 mmol, 1.0 equiv) in 70% HF in pyridine (1.5 mL) was stirred at 0 °C for 30 min. Sodium nitrite (413 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH−H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on a silica gel column using $CHCl_3$−MeOH as the eluent to provide 121 mg (70%) of **7b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56−1.68 (m, 6H), 1.92−1.98 (dd, J = 9.1, 11.2 Hz, 1H), 2.81−2.86 (m, 1H), 3.60 (s, 1H), 3.83 (br s, 1H), 7.17 (d, J = 1.0 Hz, 1H), 7.43 (ddd, J = 1.6, 4.9, 6.9 Hz, 1H), 8.15−8.19 (m, 2H), 8.23 (d, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4, 31.5, 40.7, 44.2, 56.4, 62.9, 109.0, 119.4, 121.1, 139.6, 141.5, 147.5, 157.1, 160.3, 162.6, 162.7; MS (ESI) m/z 288.3 $(M + H)^+$.

A solution of **7b** (141 mg, 0.49 mmol) in CH_2Cl_2 in a vial was treated with 1.2 equiv of fumaric acid (0.65 M) in MeOH, and the vial was allowed to stand in a refrigerator overnight. The excess solvent was then removed in vacuo from the salt and then redissolved in a minimal amount of MeOH, and the fumarate salt was recrystallized from MeOH using diethyl ether to provide 110 mg (55%) of the salt **7b**·$C_4H_4O_4$ as a white crystalline solid: mp 203−205 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.87−2.20 (m, 5H), 2.45−2.50 (dd, J = 9.3, 13.2 Hz, 1H), 3.50−3.53 (m, 1H), 4.34−4.35 (br s, 1H), 4.56 (d, J = 3.9 Hz, 1H), 6.64 (s, 2H), 7.41 (s, 1H), 7.61−7.63 (m, 1H), 8.21 (dd, J = 2.4, 9.3 Hz, 1H), 8.28 (d, J = 1.0 Hz, 1H), 8.32 (d, J = 5.3 Hz, 1H); ^{13}C NMR (CD_3OD) δ 25.8, 27.8, 36.5, 42.2, 59.0, 62.8, 109.4, 121.6, 135.0, 136.5, 140.1, 147.2, 147.8, 158.3, 160.2, 163.4, 165.3, 170.2; MS (ESI) m/z 288.3 [(M − fumaric)$^+$, M = $C_{16}H_{15}F_2N_3$·$C_4H_4O_4$]. Anal. ($C_{20}H_{19}F_2N_3O_4$) C, H, N.

2-*exo*-[2′-Fluoro-3′-(2-chloropyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (7c) Fumarate. A solution of **12c** (130 mg, 0.32 mmol, 1.0 equiv) in 70% HF in pyridine (1.5 mL) was stirred at 0 °C for 30 min. Sodium nitrite (224 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH−H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on a silica gel column using $CHCl_3$−MeOH as the eluent to provide 86 mg (87%) of **7c** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54−1.67 (m, 6H), 1.92−1.98 (dd, J = 9.1, 11.2 Hz, 1H), 2.81−2.86 (m, 1H), 3.60 (s, 1H), 3.83 (br s, 1H), 7.46 (dd, J = 1.2, 5.2 Hz, 1H), 7.56 (s, 1H), 8.12−8.15 (m, 2H), 8.47 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4, 31.6, 40.7, 44.3, 56.4, 62.9, 119.2, 122.1, 139.6, 141.5, 145.1, 147.2, 149.9, 152.1, 157.1, 160.3; MS (ESI) m/z 304.3 $(M + H)^+$.

A solution of **7c** (106 mg, 0.35 mmol) in CH_2Cl_2 in a vial was treated with 1.2 equiv of fumaric acid (0.65 M) in MeOH, and the vial was allowed to stand in a refrigerator overnight. The excess solvent was then removed in vacuo from the salt and then redissolved in a minimal amount of MeOH, and the fumarate salt was recrystallized from MeOH using diethyl ether to provide 62 mg (42%) of the salt **7c**·$C_4H_4O_4$ as a white crystalline solid: mp 193−194 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.87−2.21 (m, 5H), 2.45−2.50 (dd, J = 9.2, 13.2 Hz, 1H), 3.50−3.53 (m, 1H), 4.34−4.35 (br s, 1H), 4.56 (d, J = 3.9 Hz, 1H), 6.63 (s, 2H), 7.67 (dd, J = 1.4, 9.3 Hz, 1H), 7.80 (s, 1H), 8.21 (dd, J = 2.4, 9.3 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 4.9 Hz, 1H); ^{13}C NMR (CD_3OD) δ 25.7, 27.8, 36.5, 42.2, 59.0, 62.9, 119.4,

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122.7, 135.0, 136.6, 140.1, 145.4, 147.3, 149.9, 151.8, 158.3, 160.3, 170.1; MS (ESI) m/z 304.0 [(M − fumaric)$^+$, M = $C_{16}H_{15}ClFN_3$·$C_4H_4O_4$]. Anal. ($C_{20}H_{19}ClFN_3O_4$·0.25 H_2O) C, H, N.

2-Fluoro-3-(2′-amino-4′-pyridinyl)deschloroepibatidine (7d) Hydrochloride. A solution of 2-amino-4-bromopyridine (200 mg, 1.16 mmol, 1.0 equiv), bispinacolato diborane (307 mg, 1.21 mmol, 1.05 equiv), Pd_2dba_3 (36 mg, 0.035 mmol, 3 mol %), Xphos (88 mg, 0.185 mmol, 16 mol %), and KOAc (272 mg, 2.77 mmol, 2.4 mmol) in dioxane placed in a resealable pressure vessel was degassed through bubbling nitrogen for 40 min then heated at 110 °C for 4 h. A TLC check revealed that all the bromopyridine had been converted to the boronic ester. The reaction was allowed to cool to room temperature, and K_3PO_4 (613 mg, 2.89 mmol, 2.5 equiv), a solution of **10** (270 mg, 1.0 mmol, 0.87 equiv) in dioxanes, an additional 3 mol % of Pd_2dba_3, and H_2O (1 mL) were added to the reaction. The mixture was degassed for 30 min and heated for 18 h at 110 °C. The reaction was cooled to room temperature and extracted with EtOAC (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered through Celite, and the solvent was removed in vacuo. Two purifications of the residue by flash chromatography through an ISCO column using $CHCl_3$−MeOH (10:1) as the eluent provided 60 mg (21%) of **7d** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.71 (m, 5H), 1.90−1.97 (m, 1H), 2.36 (br s, 1H), 2.80−2.85 (dd, J = 3.8, 5.0 Hz, 1H), 3.61 (s, 1H), 3.81 (d, J = 2.7 Hz, 1H), 4.66 (br s, 2H), 6.72 (s, 1H), 6.84 (d, J = 5.3 Hz, 1H), 8.02 (dd, J = 2.3, 9.5 Hz, 1H), 8.11 (s, 1H), 8.13 (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.4, 40.5, 44.3, 56.5, 62.9, 108.1, 113.9, 139.4, 140.6, 143.7, 145.9, 148.5, 157.4, 158.8, 160.6; MS (ESI) m/z 285.5 (M + H)$^+$.

A solution of **7d** (122 mg, 0.43 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 excess solvent was filtered off, and the obtained salt was washed with ether and then dried to provide 94 mg of the salt **7d**·HCl as a white solid: mp 205−208 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.83−2.28 (m, 5H), 2.46−2.53 (dd, J = 3.8, 9.6 Hz, 1H), 3.52−3.57 (dd, J = 3.1, 5.5 Hz, 1H), 4.37 (d, J = 3.6 Hz, 1H), 4.59 (d, J = 2.7 Hz, 1H), 7.02−7.05 (dd, J = 1.6, 6.1 Hz, 1H), 7.10 (s, 1H) 7.98 (d, J = 6.1 Hz, 1H) 8.16 (dd, J = 2.3, 9.2 Hz, 1H) 8.28 (s, 1H); ^{13}CNMR (CD_3OD) δ 26.8, 28.9, 37.5, 43.3, 60.5, 64.2, 112.0, 113.8, 137.4, 141.3, 143.2, 148.0, 148.2, 158.8, 158.9, 162.1; MS (ESI) m/z 285.7 [(M − HCl)$^+$, M = $C_{16}H_{17}FN_4$·2HCl]. Anal. ($C_{16}H_{19}Cl_2FN_4$) C, H, N.

2-*exo*-[2′-Fluoro-3′-(2-methoxypyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (7e) Fumarate. To a resealable reaction pressure vessel under nitrogen was added compound **10** (180 mg, 0.66 mmol, 1.0 equiv), compound **16** (188 mg, 0.80 mmol, 1.2 equiv), $(Pd(PPh_3)_4$ (38 mg, 0.03 mmol, 5 mol %), K_2CO_3 (184 mg, 1.33 mmol, 2.0 equiv), 1,4-dioxane (10 mL), and water (0.80 mL). The reaction mixture was degassed through bubbling nitrogen for 40 min, sealed, and heated over a sand bath at 110 °C for 18 h. After cooling, the solvent was removed under reduced pressure, and to the residue was added 20 mL of H_2O. The organic product was extracted using EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and filtered through Celite, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel using MeOH−$CHCl_3$ as the eluent provided 100 mg (50%) of **7e** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.68 (m, 5H), 1.89−1.96 (dd, 3.8, 9.6 Hz, 1H), 1.98 (broad signal 1H), 2.79−2.84 (dd, J = 3.4, 5.5 Hz, 1H), 3.59 (s, 1H), 3.81 (s, 1H), 3.96 (s, 3 H), 6.96 (s, 1H), 7.07−7.10 (dt, J = 5.3, 1.5 Hz, 1H), 8.06 (dd, J = 2.4, 9.6 Hz, 1H), 8.11 (s, 1H), 8.21 (d, J = 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2. 31.4, 40.5, 44.3, 53.5, 56.4, 62.9, 110.5, 116.6, 139.6, 140.8, 144.6, 146.2, 146.4, 147.2, 160.5, 164.6; MS (ESI) m/z (300.4) (M + H)$^+$.

A solution of **7e** (156 mg, 0.52 mmol) in CH_2Cl_2 in a vial was treated with 1.2 equiv of fumaric acid (0.65 M) in MeOH, and the vial was allowed to stand in a refrigerator overnight. The excess solvent was then removed in vacuo from the salt that was then redissolved in a minimal amount of MeOH, and the fumarate salt was recrystallized from MeOH using diethyl ether to provide 164 mg (74%) of the salt **7e**·$C_4H_4O_4$ as a white solid: mp 160−164 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.85−2.19 (m, 5H), 2.43−2.50 (dd, J = 9.3, 13.2 Hz, 1H), 3.48−3.53 (m, 1H), 3.96 (s, 3H), 4.34 (br s, 1H), 4.55 (s, 1H), 6.65 (s, 2H), 7.07 (s, 1H), 7.22 (dd, J = 1.2, 4.1 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 8.22−8.23 (m, 2H); ^{13}C NMR (CD_3OD) δ 26.9, 29.0, 37.7, 43.4, 54.2, 60.2, 64.1, 111.6, 117.9, 136.1, 137.5, 141.2, 145.9, 147.5, 147.6, 148.3, 162.2, 166.2, 171.1; MS (ESI) m/z 300.3 [(M − fumaric)$^+$, M = $C_{17}H_{18}FN_3O$·$C_4H_4O_4$]. Anal. ($C_{21}H_{22}FN_3O_5$) C, H, N.

2-*exo*-[2′-Fluoro-3′-(pyridin-3-yl)-5′-pyridinyl]-7-azabicyclo-[2.2.1]heptane (8a) Hemifumarate. A solution of **11a** (394 mg, 1.08 mmol, 1.0 equiv) in 70% HF in pyridine (1.5 mL) was stirred at 0 °C for 30 min. Sodium nitrite (742 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH−H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using $CHCl_3$−MeOH as the eluent to provide 203 mg (70%) of **8a** as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 1.49−1.79 (m, 6H), 2.01−2.08 (dd, J = 9.1, 11.2 Hz, 1H), 3.02−3.07 (dd, J = 3.3, 5.4 Hz, 1H), 3.67 (s, 1H), 3.77 (br s, 1H), 7.54 (dd, J = 2.6, 7.8 Hz, 1H), 8.08−8.15 (m, 3H), 8.58−8.60 (d, 2H), 8.58 (d, J = 1.4 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (CD_3OD) δ 29.9, 31.8, 40.6, 41.1, 45.7, 57.8, 63.9, 121.1, 125.2, 138.4, 141.4, 142.0, 147.0, 150.1, 158.7, 161.8; MS (ESI) m/z 270.3 (M + H)$^+$.

A solution of **8a** (246 mg, 0.91 mmol) in chloroform (2 mL) was placed in vial and treated with 1.1 equiv of fumaric acid (0.65 M in MeOH). After 24 h, the white solid obtained was recrystallized from MeOH using Et_2O to provide the salt **8a**·0.5$C_4H_4O_4$ as a white solid: mp 155−159 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.86−2.22 (m, 6H), 2.44−2.51 (dd, J = 9.0, 11.0 Hz, 1H), 3.49−3.54 (dd, J = 3.0, 5.1 Hz, 1H), 4.35 (br s, 1H), 4.56 (d, J = 3.9 Hz, 1H), 6.63 (s, 1H), 7.56−7.60 (dd, J = 2.3, 7.5 Hz, 1H), 8.12−8.16 (m, 2H), 8.23 (s, 1H), 8.61 (dd, J = 1.4, 6.0 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (CD_3OD) δ 27.4, 29.4, 38.2, 43.8, 59.8, 64.0, 121.0, 125.4, 136.8, 138.2, 138.5, 141.4, 147.0, 147.2, 150.0, 159.1, 162.3, 171.5; MS (ESI) m/z 270.2 [(M − fumaric)$^+$, M = $C_{16}H_{16}FN_3$·0.5$C_4H_4O_4$]. Anal. ($C_{18}H_{18}FN_3O_2$·0.5 H_2O) C, H, N.

2-*exo*-[2′-Fluoro-3′-(6-fluoropyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (8b) Hemifumarate. Compound **11b** (250 mg, 0.65 mmol, 1.0 equiv) was placed in a plastic vessel and was treated dropwise with 1.5 mL of 70% HF in pyridine, and the mixture was stirred at 0 °C for 30 min. Sodium nitrite (449 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH−H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using $CHCl_3$−MeOH as the eluent to provide 170 mg (91%) of **8b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54−1.70 (m, 6H), 1.92−1.99 (dd, J = 9.0, 11.2 Hz, 1H), 2.82−2.87 (m, 1H), 3.61 (s, 1H), 3.83 (br s, 1H), 7.04 (dd, J = 3.0, 8.4 Hz, 1H), 7.99−8.09 (m, 2H), 8.14 (br s, 1H), 8.42 (d, J = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 31.5, 40.6, 44.3, 56.4, 62.9, 109.3, 118.5, 139.5, 141.3, 145.8, 147.5, 157.3, 160.4, 161.7, 164.9; MS (ESI) m/z 288.3 (M + H)$^+$.

A solution of **8b** (198 mg, 0.69 mmol) in chloroform (2 mL) was placed in a vial and treated with 1.1 equiv of fumaric acid (0.65 M in MeOH). After 24 h, the white solid obtained was recrystallized from MeOH using Et_2O to provide 200 mg (84%) of the salt **8b**·0.5$C_4H_4O_4$ as a white crystalline solid: mp 197−199 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.81−2.15 (m, 5H), 2.38−2.43 (dd, J = 9.3, 13.2 Hz, 1H), 3.42−3.46 (m, 1H), 4.43 (br s, 1H), 6.57 (s, 1H), 7.21 (dd, J = 2.4, 8.3 Hz, 1H), 8.14 (dd, J = 2.4, 8.2 Hz, 1H), 8.21−8.25 (m, 2H), 8.48 (br s, 1H); ^{13}C NMR (CD_3OD) δ 27.5, 29.5, 38.3, 43.8, 59.9, 64.1, 111.0, 120.5, 137.0, 141.4, 143.8, 147.2, 148.8, 159.7, 161.6, 164.1, 166.0, 174.0; MS (ESI) m/z 288.3 [(M − fumaric)$^+$, M = $C_{16}H_{15}F_2N_3$·0.5$C_4H_4O_4$]. Anal. ($C_{18}H_{17}F_2N_3O_2$) C, H, N.

2-*exo*-[2′-Fluoro-3′-(6-chloropyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (8c) Fumarate. Compound **11c** (300

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mg, 0.75 mmol, 1.0 equiv) was placed in a plastic vessel and was treated dropwise with 3 mL of 70% HF in pyridine, and the mixture was stirred at 0 °C for 30 min. Sodium nitrite (559 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH-H_2O (40 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using $CHCl_3$–MeOH as the eluent to provide 142 mg (62%) of **8c** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54–1.71 (m, 6H), 1.92–1.98 (dd, J = 9.1, 11.2 Hz, 1H), 2.81–2.86 (m, 1H), 3.61 (s, 1H), 3.81 (br s, 1H), 7.42 (dd, J = 0.6, 8.3 Hz, 1H), 7.88 (ddd, J = 0.8, 4.1, 8.3 Hz, 1H), 8.06 (dd, J = 2.4, 9.6 Hz, 1H), 8.15 (br s, 1H), 8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4, 31.5, 40.6, 44.3, 56.4, 62.9, 118.5, 124.1, 129.2, 139.5, 141.3, 146.1, 149.2, 151.2, 157.3, 160.5; MS (ESI) m/z 304.3 $(M + H)^+$.

A solution of **8c** (138 mg, 0.46 mmol) in chloroform (2 mL) was placed in a vial and treated with 1.1 equiv of fumaric acid (0.65 M in MeOH). After 24 h, the white solid obtained was recrystallized from MeOH using Et_2O to provide 105 mg (55%) of the salt of **8c**·$0.5C_4H_4O_4$ as a white crystalline solid: mp 194–195 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 1.89–2.20 (m, 5H), 2.45–2.49 (dd, J = 9.2, 13.2 Hz, 1H), 3.49–3.52 (dd, J = 3.5, 9.5 Hz, 1H), 4.34 (br s, 1H), 4.56 (d, J = 3.5 Hz, 1H), 6.63 (s, 2H), 7.60 (d, J = 8.5 Hz, 1H), 8.09–8.15 (m, 2H), 8.23 (d, J = 2.4 Hz, 1H), 8.64 (br s, 1H); ^{13}C NMR (CD_3OD) δ 27.1, 29.1, 37.8, 43.5, 60.3, 64.2, 120.4, 125.8, 130.6, 136.3, 137.8, 141.3, 147.4, 150.6, 152.6, 159.8, 161.7, 171.5; MS (ESI) m/z 304.5 $[(M - \text{fumaric})^+$, M = $C_{16}H_{15}ClFN_3 \cdot C_4H_4O_4]$. Anal. ($C_{20}H_{19}ClFN_3O_4$) C, H, N.

2′-Fluoro-3′-(2″-amino-5″-pyridinyl)deschloroepibatidine (8d) Hydrochloride. To a resealable reaction pressure vessel under nitrogen was added 2-*exo*-(2′-fluoro-3′-bromo)-7-azabicyclo[2.2.1]-heptane (**10**) (125 mg, 0.46 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (27 mg, 5 mol %), K_2CO_3 (128 mg, 0.92 mmol, 2.0 equiv), 1,4-dioxane (10 mL), water (0.80 mL), and 2-aminopyridine-5-pinacolate boronic ester (122 mg, 0.55 mmol, 1.2 equiv). The mixture was degassed through bubbling nitrogen for 40 min and heated at 110 °C for 18 h. After cooling, the solvent was removed under reduced pressure, and to the residue was added 20 mL of H_2O. The organic product was extracted using EtOAc (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and filtered through Celite, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel using MeOH–$CHCl_3$ as the eluent provided 88 mg (67%) of the desired product **8d** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.67 (m, 5H), 1.85–1.92 (m, 2H), 2.76–2.80 (dd, J = 3.8, 5.0 Hz, 1H), 3.56 (s, 1H), 3.75 (d, J = 2.7 Hz, 1H), 4.82 (s, 2H), 6.53 (d, J = 8.6 Hz, 1H), 7.63 (dt, J = 1.9, 8.6 Hz, 1H), 7.87 (dd, J = 2.3, 9.5 Hz, 1H), 7.98 (s, 1H), 8.23 (s, 1H); ^{13}CNMR ($CDCl_3$) δ 30.2, 31.4, 40.5, 44.5, 56.4, 62.8, 108.2, 120.2, 138.0, 138.7, 140.7, 144.2, 147.9, 157.5, 158.3, 160.6; MS (ESI) m/z 285.7 $(M + H)^+$.

A solution of the diamine **8d** (217 mg, 0.76 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 excess solvent was filtered off, and the obtained salt washed with ether and then dried to provide 246 mg (90%) of **8d**·HCl as a white solid: mp 202–205 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 1.88–2.24 (m, 5H), 2.44–2.52 (dd, J = 3.8, 9.6 Hz, 1H), 3.51–3.56 (dd, J = 3.1, 5.5 Hz, 1H), 4.37 (d, J = 3.4 Hz, 1H), 4.58 (d, J = 2.7 Hz, 1H), 7.11 (dd, J = 1.9, 8.2 Hz, 1H), 8.18–8.28 (m, 4H); ^{13}CNMR (CD_3OD) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.4, 114.7, 119.3, 120.4, 137.6, 140.6, 145.1, 147.2, 155.8, 158.9, 162.1; MS (ESI) m/z 285.6 $[(M - HCl)^+$, M = $C_{16}H_{17}FN_4 \cdot 2HCl]$. Anal. ($C_{16}H_{19}Cl_2FN_4 \cdot 1.25\ H_2O$) C, H, N.

2-*exo*-[2′-Fluoro-3′-(6-methoxypyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (8e) Hemifumarate. Compound **11d** (480 mg, 1.21 mmol, 1.0 equiv) was placed in a plastic vessel and was treated dropwise with 3 mL of 70% HF in pyridine, and the mixture was stirred at 0 °C for 30 min. Sodium nitrite (835 mg, 10 equiv) was added in small portions, and the reaction mixture was stirred at room temperature. After 1 h, the mixture was poured into a 1:1 aqueous solution of NH_4OH-H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using $CHCl_3$–MeOH as the eluent to provide 227 mg (94%) of **8e** as a colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 1.48–1.76 (m, 6H), 1.94–2.05 (m, 2H), 2.96–3.01 (dd, J = 3.4, 5.5 Hz, 1H), 3.65 (s, 3H), 3.77 (br s, 1H), 6.83 (d, J = 8.7 Hz, 1H), 7.88 (tt, J = 0.7, 1.7, 8.7 Hz, 1H), 7.99 (dd, J = 2.4, 9.6 Hz, 1H), 8.04 (d, J = 0.8 Hz, 1H), 8.34 (d, J = 1.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 29.9, 31.7, 40.9, 45.7, 54.3, 57.7, 63.7, 111.7, 121.3, 124.5, 140.8, 141.6, 145.8, 147.9, 158.6, 161.8, 165.5; MS (ESI) m/z 300.3 $(M + H)^+$.

A solution of **8e** (169 mg, 0.53 mmol) in CH_2Cl_2 in a vial was treated with a 1.2 equiv of fumaric acid (0.65 M) in MeOH, and the vial was allowed to stand in a refrigerator overnight. The excess solvent was removed in vacuo from the salt that was then redissolved in a minimal amount of MeOH, and the fumarate salt was recrystallized from MeOH using diethyl ether to provide 159 mg of the salt **8e**·$0.5C_4H_4O_4$: mp 193–195 °C. ^{1}H NMR (300 MHz, methanol-d_4) δ 1.80–2.15 (m, 6H), 2.36–2.43 (dd, J = 9.3, 13.2 Hz, 1H), 3.40–3.45 (m, 1H), 3.96 (s, 3H), 4.27 (br s, 1H), 4.42 (s, 1H), 6.61 (s, 1H), 6.91 (dd, J = 0.7, 7.6 Hz 1H), 7.95 (dt, J = 0.8, 2.4, 8.8 Hz, 1H), 8.06 (dd, J = 1.9, 8.8 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 8.41 (br s, 1H); ^{13}C NMR (methanol-d_4) δ 26.9, 29.0, 37.7, 43.4, 54.3, 60.2, 64.1, 111.7, 124.2, 136.2, 137.4, 140.6, 140.8, 145.8, 148.0, 159.1, 162.3, 165.8, 171.3; MS (ESI) m/z 300.5 $[(M - \text{fumaric})^+$, M = $C_{17}H_{18}FN_3O \cdot 0.5C_4H_4O_4]$. Anal. ($C_{19}H_{20}FN_3O_3 \cdot 0.25\ H_2O$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(pyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (11a). A solution of compound **9** (322 mg, 0.87 mmol, 1.0 equiv), pyridine-3-boronic acid (140 mg, 1.14 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (50 mg, 0.044 mmol, 5 mol %), and K_2CO_3 (242 mg, 1.75 mmol, 2.0 equiv) in toluene (10 mL), EtOH (2 mL), and water (2 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 110 °C for 22 h. After cooling to room temperature, 20 mL of H_2O was added, and the organic product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using *i*-PrOH–hexanes as the eluent to provide 263 mg (82%) of **11a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (br s, 9H), 1.48–1.61 (m, 2H), 1.75–1.86 (m, 3H), 1.96–2.04 (m, 1H), 2.79–2.83 (dd, J = 3.8, 5.0 Hz, 1H), 4.16 (s, 1H), 4.35 (br s, 1H), 4.66 (s, 2 NH), 7.34 (d, J = 2.5 Hz, 1H), 7.38 (d, J = 4.9 Hz, 1H), 7.80 (dt, J = 7.9, 1.9 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 8.59 (dd, J = 4.9, 1.6 Hz, 1H), 8.69 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.3, 44.9, 55.9, 62.2, 79.5, 118.0, 123.6, 132.1, 134.1, 136.2, 136.9, 146.6, 148.9, 149.7, 154.5, 154.9; MS (ESI) m/z 367.6 $(M + H)^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(6-fluoropyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (11b). A solution of compound **9** (241 mg, 0.65 mmol, 1.0 equiv), 5-fluoropyridine-4-boronic acid (148 mg, 1.05 mmol, 1.6 equiv), $Pd(OAc)_2$ (15 mg, 0.065 mmol, 10 mol %), P(*o*-tolyl)$_3$ (40 mg, 0.131 mmol, 20 mol %), and Na_2CO_3 (139 mg, 1.31 mmol, 2.0 equiv) in DME (8 mL) and water (0.9 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 80 °C for 5 h. After cooling to room temperature, the mixture was poured into 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 concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using EtOAc–hexanes as the eluent to provide 250 mg (99%) of **11b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (br s, 9H), 1.51–1.59 (m, 2H), 1.81–1.85 (m, 3H), 1.94–2.00 (m, 1H), 2.79–2.84 (m, 1H), 4.16 (s, 1H), 4.35 (br s, 1H), 4.70 (s, 2 NH), 7.02 (dd, J = 2.9, 8.4 Hz, 1H), 7.34 (d, J = 2.25 Hz, 1H), 7.91 (ddd, J = 2.5, 8.4, 16 Hz, 1H), 7.96 (d, J = 2.25 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2 (3 C), 28.8, 29.7, 40.3, 44.8, 55.9, 62.1, 79.5, 109.5, 116.8, 132.0, 136.9, 141.5, 146.8, 147.5, 154.6, 154.9, 161.3, 164.5; MS (ESI) m/z 385.5 $(M + H)^+$.

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7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(6-chloropyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (11c). A solution of compound **9** (304 mg, 0.83 mmol, 1.0 equiv), 5-chloropyridine-4-boronic acid (208 mg, 1.32 mmol, 1.6 equiv), $Pd(OAc)_2$ (19 mg, 0.083 mmol, 10 mol %), P(*o*-tolyl)$_3$ (51 mg, 0.166 mmol, 20 mol %), and Na_2CO_3 (176 mg, 1.66 mmol, 2.0 equiv) in DME (6 mL) and water (0.7 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 80 °C for 5 h. After cooling to room temperature, the mixture was poured into 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 concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using EtOAc−hexanes as the eluent to provide 305 mg (99%) of **11c** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (br s, 9H), 1.43−1.50 (m, 2H), 1.72−1.76 (m, 3H), 1.85−1.92 (m, 1H), 2.70−2.74 (m, 1H), 4.06 (s, 1H), 4.26 (br s, 1H), 4.60 (s, 2 NH), 7.25 (d, J = 2.25 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.71 (dd, J = 2.5, 8.2 1H), 7.88 (d, J = 2.2 Hz, 1H), 8.38 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.3, 44.8, 55.9, 62.1, 79.5, 116.7, 124.2, 132.2, 133.1, 136.9, 139.0, 147.0, 149.5, 150.6, 154.4, 155.0; MS (ESI) m/z 401.5 (M + H)$^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(6-methoxypyridin-3-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (11d). A solution of **9** (337 mg, 0.92 mmol, 1.0 equiv), 2-methoxypyridine-5-boronic acid (182 mg, 1.2 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (53 mg, 0.046 mmol, 5 mol %), and K_2CO_3 (253 mg, 1.83 mmol, 2.0 equiv) in toluene (12 mL), EtOH (2 mL), and H_2O (2 mL) was placed in a resealable pressure vessel and degassed through bubbling nitrogen for 20 min. The vessel was sealed and placed on a sand bath that was heated at 110 °C overnight. After cooling to room temperature, H_2O (20 mL) was added, and the organic product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using EtOAc−hexanes as the eluent to furnish compound **11d** (310 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (br s, 9H), 1.50−1.59 (m, 2H), 1.76−1.88 (m, 3H), 1.91−1.98 (m, 1H), 2.77−2.81 (dd, J = 3.7, 5.0 Hz, 1H), 3.94 (s, 3H), 4.16 (s, 1H), 4.34 (br s, 1H), 4.78 (s, 2 NH), 6.79 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.3 Hz, 1H), 7.65 (dd, J = 8.4, 2.4 Hz, 1H), 7.93 (d, J = 2.3 Hz, 1H) 8.22 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1 (3 C), 28.4, 28.6, 40.1, 44.8, 53.3, 55.3, 62.1, 79.3, 110.8, 118.1, 126.9, 128.4, 131.8, 136.7, 138.9, 145.8, 146.6, 154.8, 163.5; MS (ESI) m/z 397.5 (M + H)$^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(pyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (12a). A solution of compound **9** (354 mg, 0 0.96 mmol, 1.0 equiv), pyridine-4-boronic acid (154 mg, 1.25 mmol, 1.3 equiv), $Pd(PPh_3)_4$ (56 mg, 0.048 mmol, 5 mol %), and K_2CO_3 (266 mg, 1.92 mmol, 2.0 equiv) in toluene (10 mL), EtOH (2 mL), and water (2 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 110 °C for 22 h. After cooling to room temperature, 20 mL of H_2O was added, and the organic product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using *i*-PrOH−hexanes as the eluent to provide 340 mg (97%) of **12a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (br s, 9H), 1.44−1.59 (m, 2H), 1.81−1.84 (m, 3H), 1.93−2.00 (m, 1H), 2.79−2.84 (dd, J = 3.8, 5.0 Hz, 1H), 4.16 (s, 1H), 4.36 (br s, 1H), 4.67 (s, 2 NH), 7.39−7.43 (m, 3H), 7.99 (d, J = 2.3 Hz, 1H), 8.66 (dd, J = 6.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.4, 44.8, 55.8, 62.1, 79.5, 118.7, 123.4 (2 C), 132.2, 136.5, 146.4, 147.2, 150.5 (2 C), 153.9, 154.9; MS (ESI) m/z 367.6 (M + H)$^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(2-fluoropyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (12b). A solution of compound **9** (319 mg, 0.87 mmol, 1.0 equiv), 2-fluoropyridine-4-boronic acid (196 mg, 1.39 mmol, 1.6 equiv), $Pd(OAc)_2$ (20 mg, 0.087 mmol, 10 mol %), P(*o*-tolyl)$_3$ (53 mg, 0.173 mmol, 20 mol %), and Na_2CO_3 (184 mg, 1.73 mmol, 2.0 equiv) in DME (6 mL) and water (0.7 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 80 °C for 5 h. After cooling to room temperature, the mixture was poured into 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 concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using EtOAc−hexanes as the eluent to provide 300 mg (92%) of **12b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (br s, 9H), 1.52−1.59 (m, 2H), 1.82−1.84 (m, 3H), 1.94−1.98 (m, 1H), 2.79−2.84 (m, 1H), 4.16 (s, 1H), 4.36 (br s, 1H), 4.77 (s, 2 NH), 7.06 (s, 1H), 7.34 (ddd, J = 1.6, 5.13, 8.4 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 8.0 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 5.16 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.5, 44.8, 55.9, 62.1, 79.7, 108.8, 121.1, 132.5, 136.5, 147.8, 148.3, 152.0, 153.7, 155.0, 162.8, 166.0. MS (ESI) m/z 385.3 (M + H)$^+$.

7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(2-chloropyridin-4-yl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane (12c). A solution of compound **9** (192 mg, 0.52 mmol, 1.0 equiv), 2-chloropyridine-4-boronic acid (131 mg, 0.83 mmol, 1.6 equiv), $Pd(OAc)_2$ (12 mg, 0.052 mmol, 10 mol %), P(*o*-tolyl)$_3$ (32 mg, 0.104 mmol, 20 mol %), and Na_2CO_3 (111 mg, 1.04 mmol, 2.0 equiv) in DME (6 mL) and water (0.7 mL) was degassed through bubbling nitrogen for 20 min. The mixture was sealed and heated over a sand bath at 80 °C for 5 h. After cooling to room temperature, the mixture was poured into 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 concentrated in vacuo. The resultant residue was purified by flash chromatography on silica gel using EtOAc−hexanes as the eluent to provide 112 mg (54%) of **12c** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (br s, 9H), 1.49−1.61 (m, 2H), 1.77−1.83 (m, 3H), 1.94−2.00 (m, 1H), 2.78−2.83 (m, 1H), 4.16 (s, 1H), 4.36 (br s, 1H), 4.54 (s, 2 NH), 7.37 (dd, J = 1.4, 5.13 Hz, 1H), 7.40 (d, J = 2.22 Hz, 1H), 7.45 (s, 1H), 8.0 (d, J = 2.22 Hz, 1H), 8.44 (d, J = 5.10 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3 (3 C), 28.8, 29.7, 40.5, 44.8, 55.9, 62.1, 79.6, 117.4, 122.0, 123.8, 132.4, 136.5, 147.8, 149.6, 150.2, 152.4, 153.8, 154.9; MS (ESI) m/z 401.3 (M + H)$^+$.

Preparation of 2-Methoxypyidine-4-boronic Acid Pinacol Ester (15). A solution of 4-bromo-2-methoxypyridine (**14**) (462 mg, 2.46 mmol, 1.0 equiv), bis(pinacolato)diboron (749 mg, 2.95 mmol, 1.2 equiv), $PdCl_2$(dppf) (54 mg, 0.074 mmol, 3 mol %), and KOAc (724 mg, 7.37 mmol, 3.0 equiv) in DMF (6 mL) in a resealable pressure vessel was degassed through bubbling nitrogen for 20 min. The reaction mixture was sealed and heated over a sand bath at 85 °C overnight. After cooling to room temperature, the mixture was diluted with EtOAc and filtered through a plug of Celite and anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel using EtOAc−MeOH as the eluent to provide 427.4 mg (74%) of **15** as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 12H), 3.93 (s, 3H), 7.13 (s, 1H), 7.18 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 5.0 Hz, 1H).

[^{3}H]Epibatidine Binding Assay. The inhibition of [^{3}H]-epibatidine binding at rat brain $\alpha4\beta2$*-nAChRs was conducted as previously reported.[21]

Electrophysiology. The electrophysiology assays with rat $\alpha4\beta2$-, $\alpha3\beta4$, and $\alpha7$-nAChRs were conducted as previously described.[24]

In Vivo Test. The antinociception (tail-flick and hot-plate), locomotor, and body temperature tests were all conducted in mice as previously described.[21]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

NRT, nicotine replacement therapy; CDC, Centers for Disease Control; nAChR, nicotinic acetylcholine receptor; ICSS, intracranial self-stimulation; CPP, conditioned place preference; DD, drug discrimination; SA, self-administration; $PdCl_2$(dppf), 1,1′-bis(diphenylphosphino)ferrocene-palladium-(II) dichloride; MCPBA, *meta*-chloroperoxybenzoic acid; MPE, maximum potential effect; DHβE, dihydro-β-erythroidine; AD_{50}, the antagonist dose that blocks 50% of the nicotine response

■ REFERENCES

(1) World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2011; Warning about the Dangers of Tobacco*; 2011.

(2) Center for Disease Control and Prevention.. Vital Signs: Current cigarette smoking among adults aged ≥18 years: United States, 2009. *Morbidity and Mortality Weekly Report* **2010**, *59*, 1135−1140.

(3) SAMHSA. *(Substance Abuse and Mental Health Services Administration) Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings*; U. S. Department of Health and Human Services: Washington, DC, 2011.

(4) American Cancer Society. *Cancer Facts & Figures 2011*; American Cancer Society: Atlanta, Georgia, 2011.

(5) De Biasi, M.; Dani, J. A. Reward, addiction, withdrawal to nicotine. *Annu. Rev. Neurosci.* **2011**, *34*, 105−130.

(6) Hurt, R. D.; Sachs, D. P.; Glover, E. D.; Offord, K. P.; Johnston, J. A.; Dale, L. C.; Khayrallah, M. A.; Schroeder, D. R.; Glover, P. N.; Sullivan, C. R.; Croghan, I. T.; Sullivan, P. M. A comparison of sustained-release bupropion and placebo for smoking cessation. *N. Engl. J. Med.* **1997**, *337*, 1195−1202.

(7) Hayford, K. E.; Patten, C. A.; Rummans, T. A.; Schroeder, D. R.; Offord, K. P.; Croghan, I. T.; Glover, E. D.; Sachs, D. P.; Hurt, R. D. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br. J. Psychiatry* **1999**, *174*, 173−178.

(8) Slemmer, J. E.; Martin, B. R.; Damaj, M. I. Bupropion is a nicotinic antagonist. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 321−327.

(9) Coe, J. W.; Brooks, P. R.; Vetelino, M. G.; Wirtz, M. C.; Arnold, E. P.; Huang, J.; Sands, S. B.; Davis, T. I.; Lebel, L. A.; Fox, C. B.; Shrikhande, A.; Heym, J. H.; Schaeffer, E.; Rollema, H.; Lu, Y.; Mansbach, R. S.; Chambers, L. K.; Rovetti, C. C.; Schulz, D. W.; Tingley, F. D., III; O'Neill, B. T. Varenicline: An $\alpha4\beta2$ nicotinic receptor partial agonist for smoking cessation. *J. Med. Chem.* **2005**, *48*, 3474−3477.

(10) Coe, J. W.; Brooks, P. R.; Wirtz, M. C.; Bashore, C. G.; Bianco, K. E.; Vetelino, M. G.; Arnold, E. P.; Lebel, L. A.; Fox, C. B.; Tingley, F. D., III; Schulz, D. W.; Davis, T. I.; Sands, S. B.; Mansbach, R. S.; Rollema, H.; O'Neill, B. T. 3,5-Bicyclic aryl piperidines: A novel class of $\alpha4\beta2$ neuronal nicotinic receptor partial agonists for smoking cessation. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4889−4897.

(11) Mihalak, K. B.; Carroll, F. I.; Luetje, C. W. Varenicline is a partial agonist at $\alpha4\beta2$ and a full agonist at $\alpha7$ neuronal nicotinic receptors. *Mol. Pharmacol.* **2006**, *70*, 801−805.

(12) Bordia, T.; Hrachova, M.; Chin, M.; McIntosh, J. M.; Quik, M. Varenicline is a potent partial agonist at $\alpha6\beta2$* nicotinic acetylcholine receptors in rat and monkey striatum. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 327−334.

(13) U.S. Food and Drug Administration. FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease (Safety Announcement June 16, 2011). http://www.fda.gov/Drugs/Drugsafety/ucm259161.htm (accessed September 2013).

(14) Lloyd, G. K.; Williams, M. Neuronal nicotinic acetylcholine receptors as novel drug targets. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461−467.

(15) Spade, T. E.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. Epibatidine: A novel (chloropyridyl)-azabicycloheptane with potent analgesic activity from an Ecuadoran poison frog. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478.

(16) Badio, B.; Daly, J. W. Epibatidine, a potent analgetic and nicotinic agonist. *Mol. Pharmacol.* **1994**, *45*, 563−569.

(17) Badio, B.; Shi, D.; Garraffo, M.; Daly, J. W. Antinociceptive effects of the alkaloid epibatidine: Further studies on involvement of nicotinic receptors. *Drug Dev. Res.* **1995**, *36*, 46−59.

(18) Carroll, F. I. Epibatidine structure−activity relationships. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889−1896.

(19) Carroll, F. I. Epibatidine analogs synthesized for characterization of nicotinic pharmacophores—A review. *Heterocycles* **2009**, *79*, 99−120.

(20) Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2′-substituted-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptanes. Novel nicotinic antagonist. *J. Med. Chem.* **2001**, *44*, 4039−4041.

(21) Carroll, F. I.; Ware, R.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2′-fluoro-3′-(substituted phenyl)-deschloroepibatidine analogs. Novel nicotinic antagonist. *J. Med. Chem.* **2004**, *47*, 4588−4594.

(22) Abdrakhmanova, G. R.; Damaj, M. I.; Carroll, F. I.; Martin, B. R. 2-Fluoro-3-(4-nitro-phenyl)deschloroepibatidine is a novel potent competitive antagonist of human neuronal $\alpha4\beta2$ nAChRs. *Mol. Pharmacol.* **2006**, *69*, 1945−1952.

(23) Tobey, K. M.; Walentiny, D. M.; Wiley, J. L.; Carroll, F. I.; Damaj, M. I.; Azar, M. R.; Koob, G. F.; George, O.; Harris, L. S.; Vann, R. E. Effects of the specific $\alpha4\beta2$ nAChR antagonist, 2-fluoro-3-(4-nitrophenyl)deschloroepibatidine, on nicotine reward-related behaviors. *Psychopharmacology (Berlin, Ger.)* **2012**, *223*, 159−168.

(24) Ondachi, P.; Castro, A.; Luetje, C. W.; Damaj, M. I.; Mascarella, S. W.; Navarro, H. A.; Carroll, F. I. Synthesis and nicotinic acetylcholine receptor in vitro and in vivo pharmacological properties of 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogues of 2′-fluoro-3′-(4-nitrophenyl)deschloroepibatidine. *J. Med. Chem.* **2012**, *55*, 6512−6522.

(25) Brieaddy, L. E.; Liang, F.; Abraham, P.; Lee, J. R.; Carroll, F. I. New synthesis of 7-(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene. A key intermediate in the synthesis of epibatidine and analogs. *Tetrahedron Lett.* **1998**, *39*, 5321−5322.

(26) Carroll, F. I.; Liang, F.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2′-substituted 5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes. Epibatidine analogues. *J. Med. Chem.* **2001**, *44*, 2229−2237.

(27) Gao, Y.; Horti, A. G.; Kuwabara, H.; Ravert, H. T.; Hilton, J.; Holt, D. P.; Kumar, A.; Alexander, M.; Endres, C. J.; Wong, D. F.; Dannals, R. F. Derivatives of (-)-7-methyl-2-(5-(pyridinyl)pyridin-3-yl)-7-azabicyclo[2.2.1]heptane are potential ligands for positron emission tomography imaging of extrathalamic nicotinic acetylcholine receptors. *J. Med. Chem.* **2007**, *50*, 3814−3824.

(28) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. Palladium-catalyzed borylation of aryl chlorides: Scope, applications, and computational studies. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359−5363.

(29) Martin, T.; Laguerre, C.; Hoarau, C.; Marsais, F. Highly efficient borylation Suzuki coupling process for 4-bromo-2-ketothiazoles: straightforward access to micrococcinate and saramycetate esters. *Org. Lett.* **2009**, *11*, 3690−3693.
(30) AlSharari, S. D.; Carroll, F. I.; McIntosh, J. M.; Damaj, M. I. The antinociceptive effects of nicotinic partial agonists varenicline and sazetidine-A in murine acute and tonic pain models. *J. Pharmacol. Exp. Ther.* **2012**, *342*, 742−749.
(31) Ortiz, N. C.; O'Neill, H. C.; Marks, M. J.; Grady, S. R. Varenicline blocks β2*-nAChR-mediated response and activates β4*-nAChR-mediated responses in mice in vivo. *Nicotine Tob. Res.* **2012**, *14*, 711−719.
(32) Summerfield, S. G.; Read, K.; Begley, D. J.; Obradovic, T.; Hidalgo, I. J.; Coggon, S.; Lewis, A. V.; Porter, R. A.; Jeffrey, P. Central nervous system drug disposition: The relationship between in situ brain permeability and brain free fraction. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 205−213.
(33) Ghose, A. K.; Herbertz, T.; Hudkins, R. L.; Dorsey, B. D.; Mallamo, J. P. Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. *ACS Chem. Neurosci.* **2012**, *3*, 50−68.
(34) Clark, D. E. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 2. Prediction of blood−brain barrier penetration. *J. Pharm. Sci.* **1999**, *88*, 815−821.