Synthesis, Nicotinic Acetylcholine Receptor Binding, and Antinociceptive Properties of 2′-Fluoro-3′-(substituted phenyl)deschloroepibatidine Analogues. Novel Nicotinic Antagonist

F. Ivy Carroll,*,† Roy Ware,† Lawrence E. Brieaddy,† Hernán A. Navarro,† M. I. Damaj,‡ and Billy R. Martin‡

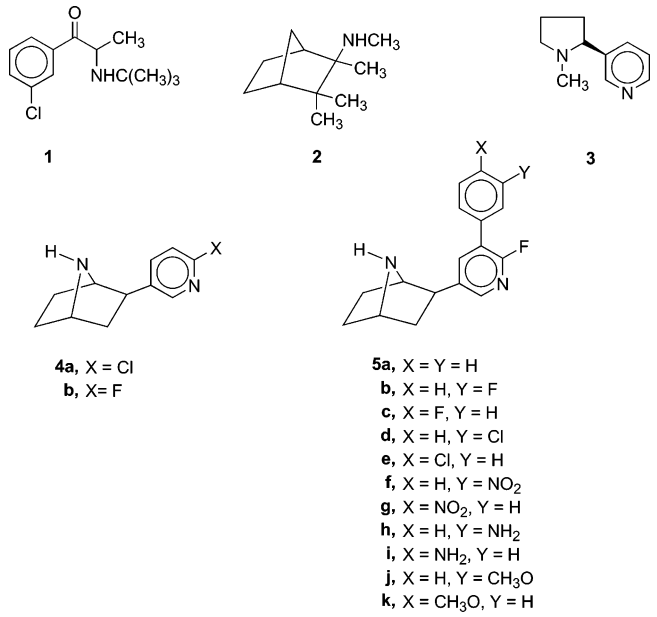
Chemistry and Life Sciences, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, North Carolina 27709, and Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia 23298

Received March 31, 2004

A series of 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogues (**5a**−**k**) showed high affinity for α4β2 binding with no affinity at α7 nAChRs. The most potent compound was 2′-fluoro-3′-(4-nitrophenyl)deschloroepibatidine (**5g**) which possessed a K_i value of 0.009 nM. Surprisingly, none of the compounds showed agonist effects in pain tests and body temperature changes in mice even when tested at 10−15 mg/kg with the exception of **5b**, which showed only very weak agonist effects. In contrast, all the compounds were potent functional antagonists of nicotine-induced antinociception. Interestingly, the 3′-substituted phenyl analogues **5b**−**k** were 10−870-fold more effective as antagonists in the tail-flick test versus the hot-plate procedure. They failed to antagonize nicotine-induced hypothermia. The 4-chlorophenyl analogue (**5e**) (AD_{50} = 0.0003 in the tail-flick test) was the most potent and selective analogue. These results suggest that these compounds will be highly useful for identifying which specific receptor subtypes are involved in each of nicotine's pharmacological effects. These compounds also deserve consideration as potential pharmacotherapies for treatment of smoking cessation.

During the past several years, considerable efforts have been directed toward the development of ligands for nicotinic acetylcholine receptors (nAChRs) in the brain. These compounds are of interest because of their potential therapeutic utility in the treatment of central nervous system (CNS) disorders including Alzheimer's and Parkinson's disease, pain, schizophrenia, anxiety, depression, Tourette's syndrome, and smoking cessation.[1] Most of the efforts have been directed toward nAChR agonists. However, interest in nAChR antagonists has increased since studies have shown that bupropion (**1**, Zyban), the antidepressant that has proven useful in treatment for smoking cessation, is a noncompetitive nAChR antagonist.[2,3] In addition, the noncompetitive nAChR antagonist mecamylamine (**2**) alone and in combination with nicotine (**3**) is under clinical evaluation for treatment of nicotine dependence.[4]

To further characterize the nAChR subtypes and to develop potential pharmacotherapies for treating smokers, we have been conducting structure−activity relationship studies on the alkaloid epibatidine (**4a**, *exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane).[5−9] In this study, we report the synthesis, nAChR binding affinity and pharmacological properties of 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogues (**5a**−**k**). All of the analogues, **5a**−**k,** showed high affinity for nAChR, but unlike epibatidine, showed no agonist activity in the mouse antinociception and body temperature tests. However, all compounds were potent nAChR functional antagonists in the tail-flick procedure. Preliminary results from some of these studies have been reported.[5]

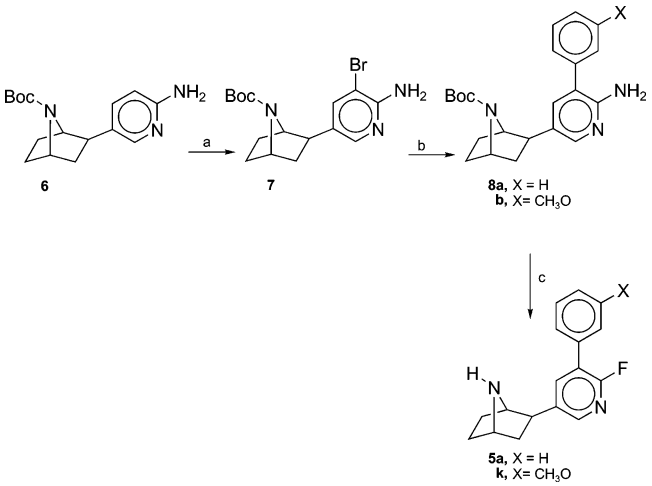


Chemistry. The synthesis of **5a** and **5k** is outlined in Scheme 1. Bromination of *tert*-butoxycarbonyl-2-*exo*-2-(2′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**6**)[7] using bromine in acetic acid provided the 2′-amino-3′-bromo intermediate **7**. Palladium acetate-catalyzed reaction of **7** with phenylboronic acid or 3-methoxyphenylboronic acid in dimethoxyethane (DME) in the presence of tri-(*o*-tolyl)phosphine and sodium carbonate gave the *tert*-butoxycarbonyl-protected 2′-amino-3′-phenyl analogue **8a** and **8b**, respectively. Diazotization of **8a,b** using sodium nitrite in pyridine containing 70% hydro-

* To whom correspondence should be addressed. Phone: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.
† Research Triangle Institute.
‡ Virginia Commonwealth University.

10.1021/jm040078g CCC: $27.50
Published on Web 07/27/2004

Scheme 1[a]



[a] Reagents: (a) Br_2, HOAc; (b) $C_6H_5B(OH)_2$ or $CH_3OC_6H_4B(OH)_2$, $Pd(OAc)_2$, P(*o*-toly)$_3$, DME, Na_2CO_3; (c) $NaNO_2$, pyridine·HF.

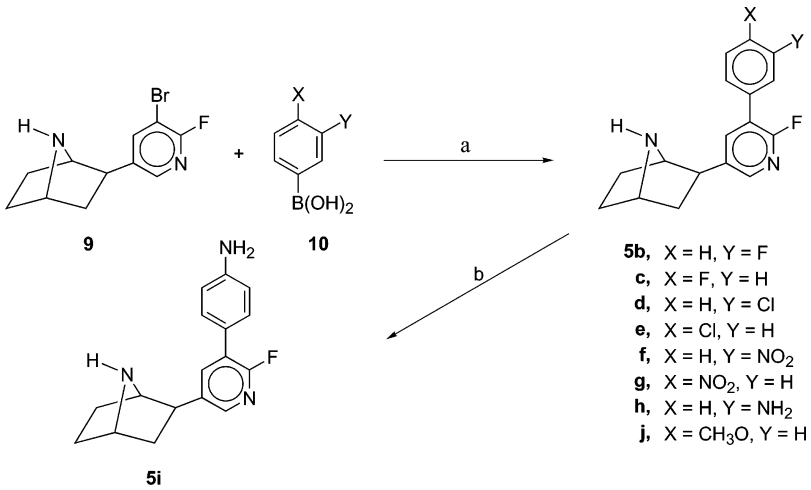
gen fluoride/pyridine yielded the desired compounds **5a** and **5k**, respectively. Resolution of **5a** using (+)- and (−)-di-*p*-toluoyltartaric acid afforded (+)- and (−)-**5a**. After completion of the synthesis of **5a** and **5k**, we discovered that the palladium-catalyzed coupling of arylboronic acids could be carried out without protecting the azabicyclo[2.2.1]heptane amino group. This provided a more efficient route to compounds **5b**−**j**, which is outlined in Scheme 2. Palladium acetate-catalyzed reaction of **9**[9] with the appropriate 3- or 4-substituted phenyboronic acid (**10**) in dimethoxyethane (DME) in the presence of tri-(*o*-tolyl)phosphine and sodium carbonate gave the desired compounds **5b**−**h** and **5j**. Reduction of the 4′-nitro analogue **5g** using iron and hydrochloride acid afforded the 4′-amino analogue **5i**.

Results and Discussion

The nAChR binding affinities and the antinociception properties of several 2′-fluoro-3′-(substituted phenyl)-epibatidine analogues are listed in Table 1. The K_i values for the inhibition of [^{3}H]epibatidine and [^{125}I]iodo-MLA binding at the $\alpha4\beta2$ and $\alpha7$ nAChRs, respectively, for compounds **5a**−**k**, (+)-**5a**, and (−)-**5a** along with the reference compounds (+)- and (−)-epibatidine [(+)- and (−)-**4a**], 2′-fluorodeschloroepibatidine (**4b**), and nicotine are listed in Table 1. In a preliminary letter, we reported a K_i value of 0.24 nM for unsubstituted 3′-phenyl analogue (racemic **5a**), which is 9-fold lower than that for (+)-**4a** or the 2′-fluoro epibatidine analogue **4b**. The K_i values of both (+)- and (−)-**5a** were essentially identical to that of racemic **5a**. All of the 3′-(substituted phenyl) analogues **5b**−**k** were more potent at inhibition of [^{3}H]epibatidine binding than the unsubstituted phenyl analogue **5a**. The K_i values ranged from 0.009 nM for the 4-nitro analogue **5g** to 0.16 nM for the 3′-amino analogue **5h**. In all cases, the 4′-substituted analogues (**5c**, **5e**, **5g**, **5i**, and **5k**) were more potent than the 3′-substituted analogue (**5b**, **5d**, **5f**, **5h**, and **5j**). Compounds possessing either electron-withdrawing 4′-substituents (**5c**, **5e**, and **5g**) or electron-releasing substituents (**5i** and **5k**) were highly potent. In contrast, the 3′-substituted analogues possessing an electron-withdrawing group (**5b**, **5d**, and **5f**) were two- to three-times more potent than analogues **5h** and **5j**, which contain an electron-releasing group. None of the compounds possessed appreciable affinity for the $\alpha7$ nAChR. Only **5b** demonstrated any agonist effects in the in vivo mouse models. It was equipotent to nicotine in hypothermia and spontaneous activity and less potent than nicotine in tail-flick and hot-plate assays despite its very high affinity for [^{3}H]epibatidine binding (17-fold higher affinity). All of the other compounds were devoid of agonist effects in tests of pain and body temperature even when tested at high doses (10 and 15 mg/kg). They produced very modest effects on spontaneous activity and only at high doses. The most potent analogue (**5g**) was 220-fold less potent than epibatidine, whereas the others were several 1000-fold less potent.

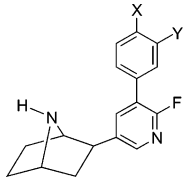
Since all the 2′-fluoro-3′-(substituted phenyl) analogues **5a**−**k** show high affinity for the nAChR and are devoid of agonist effects (with the exception of the weak agonist effects of **5b**), they are ideal candidates for antagonists. Indeed, all the analogues proved to be effective in antagonizing the antinociceptive effects of nicotine with potencies similar to or greater than that of mecamylamine. [10] In contrast to the agonist activity of epibatidine, the antagonist effect of racemic **5a** was enantioselective with (−)-**5a** being 13 times more potent

Scheme 2[a]



[a] Reagents: (a) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DME, Na_2CO_3; (b) Fe, HCl.

Table 1. Radioligand Binding and Antinociception Data for 2′-Fluoro-3′-(substituted phenyl)deschloroepibatidine Analogues[a]



compd	X	Y	αβ [^{3}H]-epibatidine[a] (K_i, nM) (Hill slope)	α_7 [^{125}I]iodo-MLA (K_i, nM) (Hill slope)	ED_{50} mg/kg tail flick	ED_{50} mg/kg hot plate	ED_{50} mg/kg hypothermia	ED_{50} mg/kg spontaneous activity	AD_{50} tail flick	AD_{50} hot plate	AD_{50} body temperature
nicotine[b]			1.50 ± 0.30		1.3 (0.5−1.8)	0.65 (0.25−0.85)	1 (0.6−2.1)	0.5 (0.15−0.78)			
(+)-**4a**[b]			0.026 ± 0.002								
(−)-**4a**[b]			0.018 ± 0.001		0.006 (0.001−0.01)	0.004 (0.001−0.008)	0.004 (0.002−0.008)	0.001 (0.0005−0.005)			
4b			0.027 ± 0.001	*c*							
(±)-**5a**	H	H	0.24 ± 0.02 (0.98 ± 0.05)	>2000	3% @ 15	4% @ 15	−0.5 °C @ 10	4.7 (3.5−8.5)	0.5 (0.25−1.5)	1.2 (0.9−2.1)	
(+)-**5a**	H	H	0.24 ± 0.02 (1.13 ± 0.13)	>2000	7% @ 15	8 @ 15	−0.4 °C @ 10	NT	1.0 (0.5−1.5)	2.4 (1.9−3.8)	
(−)-**5a**	H	H	0.26 ± 0.05 (0.78 ± 0.05)	>2000	5% @ 15	10%@ 15	−0.8 °C @ 10	NT	0.08 (0.03−0.2)	0.7 (0.1−2.5)	
5b	H	F	0.087 ± 0.001 (0.79 ± 0.03)	*c*	3.5 (2.6−4.7)	3.3 (2.3−4.7)	1.8 (1.2−3.1)	0.36 (0.1−1.67)	0.005 (0.004−0.1)	20% @ 1	0% @ 1
5c	F	H	0.029 ± 0.001 (0.92 ± 0.03)	*c*	2% @ 10	15%@ 10	10% @ 10	2 (1−3)	0.0005 (0.0001−0.003)	0.23 (0.02−3.2)	0% @ 1
5d	H	Cl	0.073 ± 0.006 (0.78 ± 0.02)	*c*	3% @ 10	14%@ 10	0% @ 10	15% @ 10	0.012 (0.002−0.06)	0.45 (0.04−1.4)	0% @ 10
5e	Cl	H	0.044 ± 0.002 (1.03 ± 0.02)	*c*	2% @ 10	7%@ 10	0% @ 10	50% @ 10	0.0003 (0.00005−0.003)	0.26 (0.02−2.6)	0% @ 10
5f	H	NO_2	0.053 ± 0.004 (1.04 ± 0.04)	*c*	3% @ 10	20% @ 10	0% @ 10	6.5 (5.3−8.3)	0.0005 (0.00005−0.005)	0.13 (0.05−0.29)	5% @ 5
5g	NO_2	H	0.009 ± 0.001 (0.68 ± 0.09)	*c*	5% @ 10	10% @ 10		0.22 (0.04−1.2)	0.003 (0.0008−0.045)	0.12 (0.01−0.9)	0% @ 1
5h	H	NH_2	0.16 ± 0.03 (0.85 ± 0.08)	*c*	1% @ 10	4% @ 10	0% @ 10	8.5 (7.1−11.2)	0.009 (0.003−0.025)	0.82 (0.3−2.2)	5% @ 5
5i	NH_2	H	0.095 ± 0.007 (0.99 ± 0.03)	*c*	2% @ 10	10% @ 10	0% @ 10	6 (4.5−7.8)	0.005 (0.0004−0.08)	1.8 (0.5−7.1)	0% @ 5
5j	H	CH_3O	0.12 ± 0.02 (0.78 ± 0.07)	*c*	0% @ 10	8% @ 10	0% @ 10	6 (4.9−8.1)	0.008 (0.001−0.06)	2 (0.4−9.8)	0% @ 10
5k	CH_3O	H	0.06 ± 0.01 (1.01 ± 0.08)	*c*	2% @ 10	16% @ 10	0% @ 10	3.6 (0.7−14)	0.05 (0.01−0.12)	0.52 (0.07−3.0)	10% @ 1

[a] Results were presented as ED_{50} or AD_{50} values (± confidence limits) in mg/kg or as a percent effect at the individual dose. [b] All data take from ref 5. [c] All had <50% inhibition at 50 nM in MLA assay.

than (+)-**5a**. All the 3′-substituted phenyl analogues were more potent nicotinic antagonists in the tail-flick test than the unsubstituted phenyl analogue **5a**. The ED_{50} values ranged from 0.0003 mg/kg for the 4-chlorophenyl analogue **5e** to 0.012 mg/kg for the 3′-chlorophenyl analogue **5d**. The 4-substituted analogues **5c**, **5e**, and **5g** possessing electron-withdrawing fluoro, chloro, and nitro groups, respectively, were more potent than the 3-substituted analogues **5b**, **5d**, and **5f**. In the case of electron-releasing groups, it was dependent upon the aromatic substituent. The 4-amino analogue, **5i**, was slightly more potent than the 3-amino analogue, **5h**, whereas the 3-methoxy analogue, **5j**, was more potent than the 4-methoxy analogue **5k**. With the exception of the 3-fluoro analogue **5b**, all substituted phenyl compounds were also more potent antagonists in the hot-plate test than unsubstituted analogue **5a**. This differential sensitivity supports earlier findings that analgesia measured in the hot-plate and tail-flick tests are subserved by different nicotine receptor subtypes.[11] Further studies will be necessary to characterize the affinities of these antagonists to additional receptor subpopulations.

In a preliminary report,[5] we described the conversion of the very potent agonist epibatidine to an antagonist by the addition of a bulky phenyl group at the 3′ position and a fluoro at the 2′ position. The results presented herein extend this original observation regarding structural features that are critical for delineating receptor recognition from activation. The bulky substituent at the 3′ position does not interfere with receptor recognition as illustrated by the high affinity of these compounds for [^{3}H]epibatidine binding. On the other hand, this bulky phenyl substituent did interfere with receptor activation as evidenced by lack of agonist effects at very high doses. The present results demonstrate that antagonist potency can be greatly enhanced through additional substitutions on the 3′-phenyl moiety. Substitutions with either electron-withdrawing or -releasing groups increased antagonist potency several 100-fold in the tail-flick procedure. The resulting compounds represent a new class of nicotinic antagonist in that they exhibit the highest potency of any competitive antagonist of nicotine.

One of the most intriguing observations is the differential potency of these antagonists in blocking different effects of nicotine. The antagonists were 10−870-fold more effective in blocking nicotine's analgesic effects in the tail-flick procedure versus the hot-plate test. The 2′-fluoro-3′-(4-chlorophenyl)deschloroepibatidine (**5e**) with an AD_{50} value of 0.0003 mg/kg in the tail-flick test was the most potent and selective analogue. Equally important is the failure of these compounds to block nicotine-induced hypothermic effects. This pattern is dramatically distinct from that of the noncompetitive antagonist mecamylamine and the competitive antagonist dihydro-

β-erythroidine, neither of which exhibit appreciable differential sensitivity in blocking these three pharmacological effects of nicotine.[10] As a result, these compounds will serve as important tools for identifying the specific receptor subtypes involved in each of nicotine's pharmacological effects. For example, β_2 knock-out mice fail to elicit nicotine-induced analgesia in the hot-plate test, a supraspinally mediated event; yet, these animals retain some nicotine-induced analgesia in the tail-flick procedure, a spinally mediated effect.[11] The antagonists **5a**−**k** may be useful in further establishing which nAChR subtypes are involved in spinally and supraspinally mediated analgesia. It is unfortunate that the characterization of the action of these antagonists at all nicotine receptor subtypes is beyond the scope of the present investigation. However, information on receptor selectivity of these compounds will provide insight into the roles of specific receptor subtypes in nicotine's actions. In addition, these antagonists will likely serve as guides for the development of selective probes for nicotine receptor subtypes.

Conclusion

The addition of a phenyl or substituted phenyl group to the highly potent nAChR agonist 2′-fluorodeschloroepibatidine (**4b)** provided compounds **5a**−**k**. Like **4b**, these compounds possess high affinity for the $\alpha4\beta2$ nAChR, but unlike **4b**, they have no agonist activity in the tail-flick, hot-plate, spontaneous activity, and hypothermia tests in the mouse. However, these compounds are potent functional antagonists of nicotine-induced antinociception in both the tail-flick and hot-plate test. Since some of these analogues such as 2′-fluoro-3′-(4-chlorophenyl)deschloroepibatidine (**5e**) were 870-fold more effective in the tail-flick versus the hot plate test, they will be important tools for characterization of nicotinic pharmacological effects with specific receptor subtypes. In addition, future studies may show that one of these analogues have use as a pharmacotherapy for treatment of smoking cessation.

Experimental Section

Melting points were determined on a Mel-temp (Laboratory Devices, Inc.) capillary tube apparatus. NMR spectra were recorded on a Bruker Avance 300 or AMSX 500 Spectrometer using tetramethylsilane as internal standard. Thin-layer chromatography was carried out on Whatman silica gel 60 plates. Visualization was accomplished under UV or in an iodine chamber. Microanalysis was carried out by Atlantic Microlab, Inc. Flash chromatography was carried out using silica gel 60 (230−400 mesh) using hexanes combined with a solvent mixture of 80% cholorform, 18% methanol, and 2% concentrated ammonium hydroxide (CMA).

The [^{3}H]epibatidine was purchased from Perkin-Elmer Inc., (Boston, MA). The [^{125}I]iodo-MLA was synthesized as previously reported.[12]

(±)-7-*tert*-Butoxycarbonyl-2-*exo*-(2′-amino-3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (7). To a stirred solution of 968 mg (3.30 mmol) of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**6**) in methylene chloride (8 mL) and acetic acid (7 mL) under nitrogen at 0 °C was added bromine (0.260 mL, 5.05 mmol) followed by triethylamine (0.260 mL). After stirring the reaction for 16 h, the mixture was poured into 100 mL of NH_4OH/H_2O (1:2) solution and extracted three times with chloroform. The combined organic extracts were dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography using 4:1 ether/triethylamine to give 1.04 g (85%) of **7** as a colorless solid: mp 129−130 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 1.44 (s, 9H), 1.40−1.55 (m, 2H), 1.70−1.84 (m, 3H), 1.90 (dd, J = 9.0, 12.3 Hz, 1H), 2.70 (dd, J = 4.8, 8.8 Hz, 1H), 4.08 (br s, 1H), 4.33 (br s, 1H), 7.62 (s, 1H, pyridyl CH), 7.83 (s, 1H, pyridyl CH); ^{13}C NMR ($CDCl_3$) δ (ppm) 28.3 (3C), 28.7, 29.7, 40.3, 44.6, 55.7, 62.0, 79.7, 104.6, 132.9, 138.8, 145.5, 154.0, 154.9. Anal. ($C_{16}H_{22}BrN_3O_2$) C, H, N.

(±)-7-*tert*-Butoxycarbonyl-2-*exo*-(2′-amino-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (8a). To a resealable reaction tube under nitrogen were added 403 mg (1.08 mmol) of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-3′-bromopyridinyl)-7-azabicyclo[2.2.1]heptane (**7**), $Pd(OAc)_2$ (25 mg, 0.011 mmol), P(o-tolyl)$_3$ (60 mg, 0.02 mmol), sodium carbonate (230 mg, 2.17 mmol), phenylboronic acid (210 mg, 1.72 mmol), degassed (nitrogen bubbling) water (0.800 mL), and DME (4 mL). The reaction was heated at 80 °C for 1.5 h. The reaction mixture was poured into saturated sodium bicarbonate and extracted three times with ethyl acetate. The organic layers were dried with sodium sulfate and concentrated. The residue was purified by flash chromatography using hexane/ethyl acetate (1:2) as eluent to provide 347 mg (88%) of **8** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.38 (br s, 9H), 1.38−1.65 (m, 2H), 1.75−2.0 (m, 4H), 2.78 (dd, J = 5.2, 8.6 Hz, 1H), 4.16 (s, 1H), 4.35 (s, 1H), 4.60 (br s, 2 NH), 7.3−7.45 (m, 6H), 7.92 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 28.2(2C), 28.8, 29.7, 40.2, 44.8, 55.5, 62.1, 79.3, 121.6, 127.5, 128.6(2C), 128.8(2C), 131.7, 136.5, 138.2, 145.6, 154.3, 154.8. Anal. ($C_{22}H_{27}N_3O_2$) C, H, N.

(±)-2-*exo*-(2′-Fluoro-3′-phenyl-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (5a) Hydrochloride. A solution of 150 mg (0.410 mmol) of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**) in 70% hydrofluoric acid/pyridine (0.6 mL) was prepared in a plastic vessel. Sodium nitrite (110 mg, 1.6 mmol) was added and the reaction mixture stirred for 45 min at room temperature followed by heating to 100 °C for 1 h. The mixture was poured into a solution of 50 mL of NH_4OH/H_2O (1:1) and extracted with ethyl acetate. The combined organic layers were dried with magnesium sulfate and concentrated. The residue was purified via flash chromatography using $CHCl_3/CH_3OH/NH_4OH$ (45:9:1) to give 91 mg (83%) of **5a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.45−1.76 (m, 4H), 1.93 (dd, J = 9.3, 12.3 Hz, 2H), 2.04 (s, 1H), 2.83 (dd, J = 6.0, 9.3 Hz, 1H), 3.62 (br s, 1H), 3.80 (br s, 1H), 7.33−7.60 (m, 5H), 7.98 (dd, J_F = 2.4, 9.6 Hz, 1H), 8.07 (t, J_F = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 29.97, 31.23, 40.32, 44.35, 56.36, 62.74, 123.01(d, J_{CF} = 28.5 Hz), 128.5 (m, 4C), 134.15 (d, J_{CF} = 5.1 Hz), 139.70 (d, J_{CF} = 4.2 Hz), 140.34 (d, J_{CF} = 18.9 Hz), 144.59 (d, J_{CF} = 57 Hz), 157.39, 160.55.

To a stirred solution of 91 mg (0.339 mmol) of **5a** in methylene chloride (2.5 mL) was added 1 M HCl in ether (1.6 mL). After 30 min at room temperature, the solvent was removed under reduced pressure, and the remaining solid was pumped overnight to give 90 mg (81%) of **5a**·HCl as a colorless solid. Anal. ($C_{17}H_{18}ClFN_2\cdot H_2O$) C, H, N.

(+)- and (−)-2-*exo*-(2′-Fluoro-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (+)- and (−)-5a. To a mixture of 520 mg (1.94 mmol) of racemic 2-*exo*-(2′-fluoro-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1] heptane (**5a**) and 0.80 g (0.0020 mol) of di-*p*-toluoyl-D-tartaric acid was added 45 mL of (4:1) 2-propanol/water. The resulting mixture was warmed to dissolution and allowed to stand at room-temperature overnight. The resulting crystals were filtered to give 0.83 g of the di-*p*-toluoyl salt of **5a**. This salt was recrystallized twice from 2-propanol/water (4:1) mixtures to give 0.27 g of the tartrate salt. This salt was neutralized with aqueous Na_2CO_3 and extracted with CH_2Cl_2 to give 100 mg of the free base. The free base was converted to the hydrochloride salt and recrystallized from EtOAc/MeOH mixtures to give 42 mg of (−)-2-*exo*-(2′-fluoro-3′-phenyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane hydrochloride: mp 239−242 °C; $[\alpha]_D$ = −11.4 (*c* 0.35, MeOH). Anal. ($C_{17}H_{18}ClFN_2\cdot 0.5H_2O$) C, H, N.

The mother liquors from above were combined and evaporated to dryness, dissolved in water, basified with Na_2CO_3, and extracted with CH_2Cl_2. The dried extracts (Na_2SO_4) were

evaporated to give 0.25 g of solid. To the solids was added 0.378 g of di-*p*-toluoyl-L-tartaric acid and 20 mL of (4:1) 2-propanol/water and crystallized as above to afford 0.32 g of the tartrate salt of **5a**. The salt was converted to its free base as above to afford 0.13 g. The free base was converted to the hydrochloride salt and recrystallized from EtOAc/MeOH mixtures to afford 56 mg of (+)- 2-*exo*-(2′-fluoro-3′-phenyl-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane hydrochloride hydrate: mp 240−242 °C; $[\alpha]_D$ = +11.1 (*c* = 0.28, MeOH). Anal. ($C_{17}H_{18}ClFN_2$**.**$0.33H_2O$) C, H, N.

(±)-7-*tert*-Butoxycarbonyl-2-*exo*-[2′-amino-3′-(3-methoxyphenyl)-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (8b). To a resealable reaction vessel under nitrogen were added 515 mg (1.4 mmol) of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**7**), $Pd(OAc)_2$ (31 mg, 0.14 mmol), P(o-tolyl)$_3$ (85 mg, 0.28 mmol), sodium carbonate (30 mg, 2.8 mmol), and 3-methoxyphenylboronic acid (340 mg, 2.24 mmol), degassed (nitrogen bubbling) water (1.1 mL), and DME (6 mL). The reaction was heated at 80 °C for 3.5 h, cooled, poured into 50 mL of saturated $NaHCO_3$, and extracted with EtOAc (4 × 5 mL). The residue obtained on evaporation was subjected to flash chromatography using (1:1; EtOAc/hexanes initially, then 2:1 mixture followed by a 3:1 mixture of EtOAc/hexanes to give 470 mg (82%) of **8b** as a viscous oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s 9H), 1.54 (m, 2H), 1.81−1.98 (m, 4H), 2.79 (m, 1H), 3.83 (s, 3H), 4.14 (m, 1H), 4.35 (bs, 1H), 4.51 (bs, 2H), 6.88 (d, 1H), 6.98 (m, 2H), 7.27 (m, 2H), 7.94 (s, 1H). This material was used directly in the next step.

(±)-2-*exo*-[2′-Fluoro-3′-(3-methoxyphenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5k). A solution of 180 mg (0.40 mmol) of 7-*tert*-butoxycarbonyl-2-exo-[2′-amino-3′-(3-methoxyphenyl)- 5′-pyridinyl]-7-azabicyclo[2.2.1]-heptane (**8b**) in 70% hydrofluoric acid/pyridine was cooled to 0 °C in an ice bath. Sodium nitrite (303 m, 4.39 mmol) was added, and the reaction in a plastic vessel was warmed to room temperature and stirred for 2 h. The reaction mixture was poured into 40 mL of NH_4OH/H_2O (1:1) and extracted with ethyl acetate (5 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexanes/CMA) to afford **5k** (86 mg, 66%) as a yellow, viscous oil. Compound **5k** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp 211−213 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.87−2.18 (m 5H), 2.48 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.51 (dd, *J* = 6.0, 9.5 Hz, 1H), 3.85 (s, 3H), 4.34−4.35 (m, 1H), 4.57 (d, *J* = 3.1 Hz, 1H) 7.02−7.07 (m 2H), 7.56−7.61 (m 2H), 8.00 (dd, *J* = 2.5, 9.3 Hz, 1H), 8.10 (br s, 1H); ^{13}C NMR (CD_3-OD, 75 MHz) δ 30.5, 32.6, 41.3, 47.0, 59.6, 64.2, 69.0, 116.8, 119.0, 128.5 (d, *J* = 28.2 Hz), 130.7, 135.0 (d, *J* = 3.5 Hz), 140.8, 144.6 (d, *J* = 4.7 Hz), 148.5 (d, *J* = 14.5 Hz), 162.2; Anal. ($C_{18}H_{19}FN_2O$·HCl) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(3-fluorophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5b). To a resealable reaction vessel under nitrogen were added 192 mg (0.71 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (16 mg, 0.07 mmol), P(*o*-tolyl)$_3$ (43 mg, 01.4 mmol), sodium carbonate (150 mg, 1.42 mmol), 3-fluorophenylboronic acid (154 mg, 1.13 mmol), degassed (nitrogen bubbling) water (0.5 mL), and DME (2.0 mL). The reaction was heated at 75 °C for 3 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (2:1; hexanes/CMA) to afford **5b** (180 mg, 89%) as a colorless, viscous oil. Compound **5b** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 225 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.88−2.17 (m 5H), 2.49 (dd, *J* = 9.6, 13.3 Hz, 1H), 3.50−3.55 (m, 1H), 4.35 (br s, 1H), 4.58 (br s, 1H), 7.17−7.23 (m 1H), 7.41−7.56 (m, 3H), 8.07 (dd, *J* = 2.2, 9.1 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.3, 116.5 (d, *J* = 21.1), 116.9 (d, *J* = 22.7 Hz), 123.7 (d, *J* = 27.1 Hz), 126.0, 131.7 (d, *J* = 8.4 Hz), 137.1 (d,*J* = 5.1 Hz), 137.2 (d, *J* = 5.2 Hz), 141.4, 146.1 (d, *J* = 12.6 Hz), 160.6 (d, *J* = 239.9 Hz), 164.3 (d, *J* = 245.1 Hz); Anal. ($C_{17}H_{16}F_2N_2$·HCl) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(4-fluorophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5c). To a resealable reaction vessel under nitrogen were added 190 mg (0.70 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (16 mg, 0.07 mmol), P(*o*-tolyl)$_3$ (43 mg, 0.14 mmol), sodium carbonate (149 mg, 1.40 mmol), 4-fluorophenylboronic acid (157 mg, 1.12 mmol), degassed (nitrogen bubbling) water (0.5 mL), and DME (2.6 mL). The reaction was heated at 75 °C for 5 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexanes/CMA) to afford **5c** (140 mg, 70%) as a light gray, viscous oil. Compound **5c** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp 263−264 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.87−2.19 (m 5H), 2.49 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.52 (dd, *J* = 6.0, 9.3 Hz, 1H), 4.34 (dd, *J* = 3.5 Hz, 1H), 4.57 (dd, *J* = 2.8 Hz, 1H), 7.20−7.27 (m 2H), 7.65−7.71 (m, 2H), 8.04 (dd, *J* = 2.4, 9.3 Hz, 1H), 8.16 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.3, 116.6 (d, *J* = 22.0 Hz), 124.0 (d, *J* = 29.4 Hz), 131.1, 132.1 (d, *J* = 7.7 Hz), 137.1 (d, *J* = 4.9 Hz), 141.3 (d, *J* = 3.9 Hz), 145.7 (d, *J* = 14.8 Hz), 160.7 (d, *J* = 239.7 Hz), 164.5 (d, *J* = 247.9 Hz); Anal. ($C_{17}H_{16}F_2N_2$·HCl) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(3-chlorophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5d). To a resealable reaction vessel under nitrogen were added 190 mg (0.70 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (20 mg, 0.09 mmol), P(*o*-tolyl)$_3$ (53 mg, 0.18 mmol), sodium carbonate (186 mg, 1.76 mmol), 3-chlorophenylboronic acid (220 mg, 1.41 mmol), degassed (nitrogen bubbling) water (0.6 mL), and DME (3.3 mL). The reaction was heated at 60 °C for 14 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (2:1; hexanes/CMA) to afford **5d** (170 mg, 64%) as a colorless, viscous oil. Compound **5d** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 254 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.89−2.18 (m 5H), 2.49 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.53 (dd, *J* = 6.0, 9.4 Hz, 1H), 4.35 (d, *J* = 3.4 Hz, 1H), 4.58 (d, *J* = 3.0 Hz, 1H), 7.44−7.52 (m 2H), 7.57−7.61 (m, 1H), 7.68−7.69 (m, 1H), 8.07 (dd, *J* = 2.6, 8.9 Hz, 1H), 8.19−8.20 (m, 1H); ^{13}C NMR (CD_3-OD, 75 MHz) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.3, 123.5 (d, *J* = 28.3 Hz), 128.5 (d, *J* = 2.2 Hz), 129.8, 129.9, 131.4, 135.7, 136.9 (d, *J* = 5.0 Hz), 137.2 (d, *J* = 4.8 Hz), 141.4 (d, *J* − 3.9 Hz), 146.5 (d, *J* = 14.4 Hz), 160.6 (d, *J* = 239.9 Hz); Anal. ($C_{17}H_{16}$-$ClFN_2$·HCl) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(4-chlorophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5e). To a resealable reaction vessel under nitrogen were added 210 mg (0.78 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (17 mg, 0.08 mmol), P(*o*-tolyl)$_3$ (47 mg, 0.16 mmol), sodium carbonate (164 mg, 1.55 mmol), 4-chlorophenylboronic acid (194 mg, 1.24 mmol), degassed (nitrogen bubbling) water (0.5 mL), and DME (2.0 mL). The reaction was heated at 80 °C for 14 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexanes/CMA) to afford **5e** (180 mg, 89%) as a colorless,

viscous oil. Compound **5e** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 259 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85−2.19 (m 5H), 2.49 (dd, J = 9.5, 13.4 Hz, 1H), 3.47 (m, 1H), 4.35 (d, J = 3.2 Hz, 1H), 4.58 (br s, 1H), 7.46−7.52 (m 2H), 7.61−7.66 (m, 2H), 8.02−8.08 (m, 1H) 8.18 (br s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.3, 123.5 (d, J = 28.3 Hz), 128.5 (d, J = 2.2 Hz), 129.8, 129.9, 131.4, 135.7, 136.9 (d, J = 5.0 Hz), 137.2 (d, J = 4.8 Hz), 141.1, 146.5 (d, J = 14.4 Hz), 160.6 (d, J = 239.9 Hz); Anal. ($C_{17}H_{16}ClFN_2$·HCl) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(3-nitrophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5f). To a resealable reaction vessel under nitrogen were added 190 mg (0.70 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (28 mg, 0.12 mmol), P(*o*-tolyl)$_3$ (75 mg, 0.25 mmol), sodium carbonate (260 mg, 2.45 mmol), 3-nitrophenylboronic acid (327 mg, 1.96 mmol), degassed (nitrogen bubbling) water (0.8 mL), and DME (4.6 mL). The reaction was heated at 70 °C for 3 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexanes/CMA) to afford **5f** (270 mg, 70%) as a viscous, amber oil. Compound **5f** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp 142−143 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.85−2.19 (m 5H), 2.49 (dd, J = 9.5, 13.4 Hz, 1H), 3.47 (m, 1H), 4.35 (d, J = 3.2 Hz, 1H), 4.58 (br s, 1H), 7.46−7.52 (m 2H), 7.61−7.66 (m, 2H), 8.02−8.08 (m, 1H), 8.18 (br s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 26.8, 28.9, 37.6, 43.3, 60.5, 64.3, 123.5 (d, J = 28.3 Hz), 128.5 (d, J = 2.2 Hz), 129.8, 129.9, 131.4, 135.7, 136.9 (d, J = 5.0 Hz), 137.2 (d, J = 4.8 Hz), 141.1, 146.5 (d, J = 14.4 Hz), 160.6 (d, J = 239.9 Hz); Anal. ($C_{17}H_{17}ClFN_3O_2$) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(4-nitrophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5g). To a resealable reaction vessel under nitrogen were added 420 mg (1.55 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (34 mg, 0.16 mmol), P(*o*-tolyl)$_3$ (94 mg, 0.31 mmol), sodium carbonate (328 mg, 3.10 mmol), 4-nitrophenylboronic acid (414 mg, 2.48 mmol), degassed (nitrogen bubbling) water (1.1 mL), and DME (4.4 mL). The reaction was heated at 80 °C for 3.5 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (2:1; EtOAc/CMA) to afford **5g** (324 mg, 65%) as a viscous, light yellow oil. Compound **5g** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 266 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.86−2.20 (m 5H), 2.50 (dd, J = 9.6, 13.5 Hz, 1H), 3.55 (dd, J = 6.0, 9.5 Hz, 1H), 4.36 (t, J = 3.8 Hz, 1H), 4.60 (d, J = 3.0 Hz, 1H), 7.90−7.95 (m 2H), 8.15 (dd, J = 2.6, 11.8 Hz, 1H), 8.25−8.26 (m, 1H), 8.35−8.40 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz) δ 27.2, 29.2, 37.9, 43.6, 60.9, 64.6, 123.2 (d, J = 28.3 Hz), 125.2, 131.7 (d, J = 3.4 Hz), 137.8 (d, J = 5.0 Hz), 141.8 (d, J = 5.4 Hz), 142.0 (d, J = 4.0 Hz), 147.7 (d, J = 14.9 Hz), 149.7m 160.9 (d, J = 239.9 Hz); Anal. ($C_{17}H_{16}FN_3O_2$·HCl·0.75H_2O) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(3-aminophenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5h). To a resealable reaction vessel under nitrogen were added 426 mg (1.70 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (38 mg, 0.17 mmol), P(*o*-tolyl)$_3$ (104 mg, 0.34 mmol), sodium carbonate (361 mg, 3.41 mmol), 3-aminophenylboronic acid (436 mg, 2.73 mmol), degassed (nitrogen bubbling) water (1.2 mL), and DME (6.6 mL). The reaction was heated at 80 °C for 16 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:2; hexanes/CMA) to afford **5h** (435 mg, 90%) as a viscous, amber oil. Compound **5h** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 277 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.88−2.25 (m 5H), 2.50 (dd, J = 9.6, 13.3 Hz, 1H), 3.56 (dd, J = 6.2, 9.0 Hz, 1H), 4.36−4.37 (m, 1H), 4.61 (d, J = 2.7 Hz, 1H), 7.50 (dd, J = 1.4, 7.9 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 7.75−7.83 (m, 2H), 8.17 (dd, J = 2.1, 9.3 Hz, 1H), 8.24−8.26 (br s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 27.2, 29.3, 38.0, 43.7, 60.9, 64.7, 123.5 (d, J = 28.2 Hz), 124.7, 125.2 (d, J = 3.7 Hz), 131.2 (d, J = 2.6 Hz), 132.2 (d, J = 14.7 Hz), 137.5 (d, J = 5.0 Hz), 137.8 (d, J = 5.0 Hz), 142.0 (d, J = 5.0 Hz), 147.2, 147.4, 160.9 (d, J = 239.2 Hz); Anal. ($C_{17}H_{18}FN_3$·2.5HCl·0.5H_2O) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(4-methoxyphenyl)-5′-pyridinyl]-7-azabicyclo[2.2.1]heptane Hydrocholoride (5j). To a resealable reaction vessel under nitrogen were added 195 mg (0.72 mmol) of 2-*exo*-(2′-fluoro-3′-bromopyridinyl)-7-azabicyclo-[2.2.1]heptane (**9**), $Pd(OAc)_2$ (16 mg, 0.08 mmol), P(*o*-tolyl)$_3$ (44 mg, 0.14 mmol), sodium carbonate (152 mg, 1.44 mmol), 4-methoxyphenylboronic acid (175 mg, 1.15 mmol), degassed (nitrogen bubbling) water (0.5 mL), and DME (2.0 mL). The reaction was heated at 80 °C for 14 h. The reaction mixture was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexanes/CMA) to afford **5j** (175 mg, 81%) as a viscous, amber oil. Compound **5j** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp 198−200 °C; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.90−2.18 (m 5H), 2.49 (dd, J = 9.5, 13.5 Hz, 1H), 3.51 (dd, J = 6.2, 8.9 Hz, 1H), 3.85 (s, 3H), 4.32−4.34 (m, 1H), 4.58 (d, J = 2.4 Hz, 1H), 7.00−7.04 (m, 1H), 7.16−7.20 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H), 8.02 (dd, J = 2.4, 9.2 Hz, 1H), 8.15 (br s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 27.8, 29.9, 38.6, 44.2, 56.9, 61.4, 65.2, 115.9, 123.3, 125.8 (d, J = 28.1 Hz), 131.7, 136.9 (d, J = 4.6 Hz), 137.9, 142.5 (d, J = 3.9 Hz), 146.7 (d, J = 14.5 Hz), 161.5 (d, J = 239.7 Hz), 164.4(d, J = 239.5 Hz), 165.4; Anal. ($C_{18}H_{19}FN_2O_2$·HCl·0.25H_2O) C, H, N.

(±)-2-*exo*-[2′-Fluoro-3′-(4-aminophenyl-5′-pyridinyl]-7-azabicyclo[2.2.1]-heptane Hydrochloride (5i). A solution of 2-*exo*-[2′-fluoro-3′-(4-nitrophenyl)-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**5g**), 484 mg (1.55 mmol) concentration hydrochloric acid (0.50 mL), water (2.5 mL), and ethanol (45 mL) was stirred for 10 min at room temperature. Iron (8.63 mg, 15.50 mmol) was added in one portion. The reaction mixture was heated at 100 °C for 4.5 h then cooled to room temperature. The mixture was poured over a saturated solution of sodium carbonate (50 mL) and extracted with ethyl acetate (3 × 75 mL). The organic layers were dried with sodium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography (1:2; hexanes/CMA) to afford **5i** (380 mg, 87%) as a yellow, viscous oil. Compound **5i** was converted to the hydrochloride salt by a procedure similar to that described for **5a** and recrystallized from methanol/ether to give a white solid: mp decomposed 260 °C: ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm) 1.90−2.20 (m, 5H), 2.50 (dd, J = 9.6, 13.4 Hz, 1H), 3.54 (dd, J = 6.1, 9.5 Hz, 1H), 4.36 (t, J = 3.7 Hz, 1H) 4.59 (d, J = 3.1 HZ, 1H) 7.53−7.57 (m 2H), 7.83−7.90 (m 2H), 8.12 (dd, J = 2.3, 94. Hz, 1H), 8.21−8.22 (m 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 27.2, 29.5, 38.0, 43.7, 60.9, 64.7, 123.7, (d, J = 4.9 Hz), 142.0 (d, J = 4.1 Hz), 147.1 (d, J = 14.6 Hz), 161.0 (d, J = 239.4 Hz); Anal. ($C_{17}H_{18}FN_3$·2.9HCl) C, H. N.

[^{3}H]Epibatidine Binding Assay. Adult male rat cerebral cortices (Pelfreeze Biological, Rogers, AK) were homogenized in 39 volumes of ice-cold 50 mM Tris buffer (pH 7.4 at 4 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$ and sedimented at 37 000*g* for 10 min at 4 °C. The supernatant was discarded, the pellet resuspended in the original volume of buffer, and the wash procedure repeated

twice more. After the last centrifugation, the pellet was resuspended in 1/10 its original homogenization volume and stored at −80 °C until needed. In a final volume of 0.5 mL, each assay tube contained 3 mg wet weight male rat cerebral cortex homogenate (added last), 0.5 nM [^{3}H]epibatidine (NEN Life Science Products, Wilmington, DE) and one of 10−12 different concentrations of test compound dissolved in buffer (pH 7.4 at room temperature) containing 10% DMSO resulting in a final DMSO concentration of 1%. Total and nonspecific bindings were determined in the presence of vehicle and 300 μM (−)-nicotine, respectively. After a 4-h incubation at room temperature, the samples were vacuum-filtered over GF/B filter papers presoaked in 0.03% polyethylenimine using a Brandel 48-well harvester and washed with 6 mL of ice-cold buffer. The amount of radioactivity trapped on the filter was determined by standard liquid scintillation techniques in a TriCarb 2200 scintillation counter (Packard Instruments, Meriden, CT) at approximately 50% efficiency. The binding data were fit using the nonlinear regression analysis routines in Prism (Graphpad, San Diego, CA). The K_i values for the test compounds were calculated from their respective IC_{50} values using the Cheng−Prusoff equation.

[^{125}I]Iodo-MLA Binding Assay. Adult male rat cerebral cortices (Pel-Freez Biologicals, Rogers, AK) were homogenized (polytron) in 39 volumes of ice-cold 50 mM Tris buffer (assay buffer; pH 7.4 at 4 °C) containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$. The homogenate was centrifuged at 35 000*g* for 10 min at 4 °C and the supernatant discarded. The pellet was resuspended in the original volume of buffer and the wash procedure repeated twice more. After the last centrifugation step, the pellet was resuspended in one-tenth the original homogenization volume and stored at −80 °C until needed. Triplicate samples were run in 1.4-mL polypropylene tubes (Matrix Technologies Corporation, Hudson, NH). Briefly, in a final volume of 0.5 mL, each assay sample contained 3 mg wet weight rat cerebral cortex (added last), 40−50 pM [^{125}I]MLA and 50 nM final concentration of test compound dissolved in buffer containing 10% DMSO, giving a final DMSO concentration of 1%. Total and nonspecific binding were determined in the presence of vehicle and 300 uM (−)-nicotine, respectively. After a 2-h incubation on ice, the samples were vacuum-filtered using a Multimate 96-well harvester (Packard Instruments, Meriden, CT) onto GF/B filters presoaked for at least 30 min in assay buffer containing 0.15% bovine serum albumin. Each well was then washed with approximately 3.0 mL of ice-cold buffer. The filter plates were dried, and 30 μL of Microscint20 (Packard) was added to each well. The amount of radioligand remaining on each filter was determined using a TopCount 12-detector (Packard) microplate scintillation counter at approximately 70% efficiency.

Tail-Flick Test. Antinociception was assessed by the tail-flick method of D'Amour and Smith.[13] A control response (2−4 s) was determined for each mouse before treatment, and a test latency was determined after drug administration. To minimize tissue damage, a maximum latency of 10 s was imposed. Antinociceptive response was calculated as percent maximum possible effect (% MPE), where %MPE = [(test − control)/(10 − control)] × 100. Groups of eight to twelve animals were used for each dose and for each treatment. The mice were tested 5 min after i.t. injections of epibatidine analogues for the dose−response evaluation. Eight to twelve mice were treated per dose, and a minimum of four doses were performed for dose−response curve determination.

Hot-Plate Test. Mice were placed into a 10 cm wide glass cylinder on a hot plate (Thermojust Apparatus) maintained at 55.0 C. Two control latencies at least 10 min apart were determined for each mouse. The normal latency (reaction time) was 8 to 12 s. Antinociceptive response was calculated as percent maximum possible effect (% MPE), where %MPE = [(test − control)/40 − control) × 100]. The reaction time was scored when the animal jumped or licked its paws. Eight mice per dose were injected sc with epibatidine analogues and tested 5 min thereafter in order to establish a dose−response curve.

Locomotor Activity. Mice were placed into individual Omnitech photocell activity cages (28 × 16.5 cm) 5 min after sc administration of either 0.9% saline or epibatidine analogues. Interruptions of the photocell beams (two banks of eight cells each) were then recorded for the next 10 min. Data were expressed as the number of photocell interruptions.

Body Temperature. Rectal temperature was measured by a thermistor probe (inserted 24 mm) and digital thermometer (Yellow Springs Instrument Co., Yellow Springs, OH). Readings were taken just before and at different times after the sc injection of either saline or epibatidine analogues. The difference in rectal temperature before and after treatment was calculated for each mouse. The ambient temperature of the laboratory varied from 21 to 24 °C from day to day.

Acknowledgment. This research was supported by the National Institute on Drug Abuse Grant DA12001.

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

References

(1) Lloyd, G. K.; Williams, M. Neuronal nicotinic acetylcholine receptors as novel drug targets. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461−467.
(2) Fryer, J. D.; Lukas, R. J. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine, and ibogaine. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 88−92.
(3) Slemmer, J. E.; Martin, B. R.; Damaj, M. I. Bupropion is a nicotinic antagonist. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 321−327.
(4) Rose, J. E.; Behm, F. M.; Westman, E. C. Nicotine-mecamylamine treatment for smoking cessation: the role of pre- cessation therapy. *Exp. Clin. Psychopharmacol.* **1998**, *6*, 331−343.
(5) 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.
(6) Brieaddy, L. E.; Mascarella, S. W.; Navarro, H. A.; Atkinson, R. N.; Damaj, M. I.; Martin, B. R.; Carroll, F. I. Synthesis of bridged analogs of epibatidine. 3-Chloro-5,7,8,9,9a,10-hexahydro-7,10-methanopyrrolo[1,2-b]-2,6-naphthyridine and 2-chloro-5,5a,6,7,8,-10-hexahydro-5,8-methanopyrrolo[2,1-b]-1,7-naphthyridine. *Tetrahedron Lett.* **2001**, *42*, 3795−3797.
(7) 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.
(8) Avalos, M.; Parker, M. J.; Maddox, F. N.; Carroll, F. I.; Luetje, C. W. Effects of pyridine ring substitutions on the affinity, efficacy, and subtype selectivity of the neuronal nicotinic receptor agonist epibatidine. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1246−1252.
(9) Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2′, 3′-disubstituted 5′-pyridinyl)-7-azabicyclo[2.2.1]-heptanes: epibatidine analogues. *J. Med. Chem.* **2002**, *45*, 4755−4761.
(10) Damaj, M. I.; Welch, S. P.; Martin, B. R. In vivo pharmacological effects of dihydro-β-erythroidine, a nicotinic antagonist in mice. *Psychopharmacology* **1995**, *117*, 67−73.
(11) Marubio, L. M.; del Mar Arroyo-Jimenez, M.; Cordero-Erausquin, M.; Lena, C.; Le Novere, N.; de Kerchove d'Exaerde, A.; Huchet, M.; Damaj, M. I.; Changeux, J. P. Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. *Nature* **1999**, *398*, 805−810.
(12) Navarro, H. A.; Xu, H.; Zhong, D.; Abraham, P.; Carroll, F. I. In vitro and In vivo characterization of [^{125}I]iodomethyllycaconitine in the rat. *Synapse* **2002**, *44*, 117−123.
(13) D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74−79.

JM040078G