Synthesis, Nicotinic Acetylcholine Receptor Binding, and Antinociceptive Properties of 2-*exo*-2-(2′-Substituted 5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes. Epibatidine Analogues

F. Ivy Carroll,*,† Feng Liang,† Hernán A. Navarro,† Lawrence E. Brieaddy,† Philip Abraham,† M. I. Damaj,‡ and Billy R. Martin‡

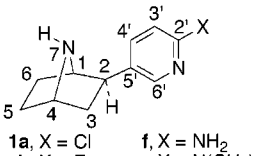
Chemistry and Life Sciences, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, North Carolina 27709, and Department of Pharmacology and Toxicology, Medical College of Virginia Commonwealth University, Richmond, Virginia 23298

Received January 11, 2001

A convenient, high-yield synthesis of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (**5**), which involved the addition of tributyltin hydride to 7-*tert*-butoxycarbonyl-2-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]hept-2-ene (**4**) followed by elimination of the tributyltin and *p*-tolylsulfonyl groups using tetrabutylammonium fluoride was developed. The addition of 2-amino-5-iodopyridine to **5** under reductive Heck conditions provided 7-*tert*-butoxycarbonyl-2-*exo*-(2′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**6**). Compound **6** was the key intermediate used to prepare epibatidine analogues where the 2′-chloro group on the pyridine ring was replaced with a fluorine (**1b**), bromine (**1c**), iodine (**1d**), hydroxy (**1e**), amino (**1f**), dimethylamino (**1g**), trifluoromethanesulfonate (**1h**), and hydrogen (**1i**) group. (+)- and (−)-Epibatidine and compounds **1b**−**d** and **1i** all possess similar binding affinities at the $\alpha_4\beta_2$ nAChR receptors labeled by [^{3}H]epibatidine. Compound **1f** has affinity similar to nicotine, whereas compounds **1e**, **1g**, and **1h** have much lower affinity. The binding affinity appears to be dependent upon the electronic nature of the substituent. However, other factors are also involved. None of the compounds possesses appreciable affinity for the α_7 nAChR labeled by [^{125}I]iodo-MLA. With the exception of **1f** and **1g**, all the epibatidine analogues are full agonists (tail flick test) in producing antinociception after intrathecal injection in mice.

Introduction

It is now well recognized that the natural alkaloid epibatidine (**1a**, *exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane) binds to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR) with much greater affinity than nicotine.[1,2] Since the nAChRs have been targeted for the development of drugs for Alzheimer's disease, anxiety, attention deficit hyperactivity disorder (ADHD), Parkinson's disease, analgesia, inflammatory bowel disorder, schizophrenia, anxiety, depression, Tourette's syndrome, and smoking cessation, there is current interest in characterizing the pharmacophore for the $\alpha_4\beta_2$ nAChR.[1,3−6] In this study we report the synthesis, nAChR binding properties, and antinociceptive effects of the *exo*-2-(2′-substituted-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptanes (**1a**−**i**). A preliminary account on the



1a, X = Cl
b, X = F
c, X = Br
d, X = I
e, X = OH
f, X = NH_2
g, X = $N(CH_3)_2$
h, X = CF_3SO_3
i, X = H

synthesis and nAChR binding properties of *exo*-2-(2′-fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**1b**) has been published.[2] In addition, we have reported the synthesis of [^{18}F]-**1b** and described its mapping of the nAChRs in baboons[7−9] using positron emission tomography (PET) and in rodent and human brain using in vitro and ex vivo autoradiographic studies.[10] We have also reported the synthesis and in vivo binding properties of [^{3}H]-2-*exo*-(3′-pyridinyl)-7-azabicyclo[2.2.1]heptane ([^{3}H]-**1i**).[11] Davila-Garcia and co-workers have reported the synthesis and pharmacological characterization of [^{125}I]-*exo*-2-(2-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane ([^{125}I]-**1d**).[12]

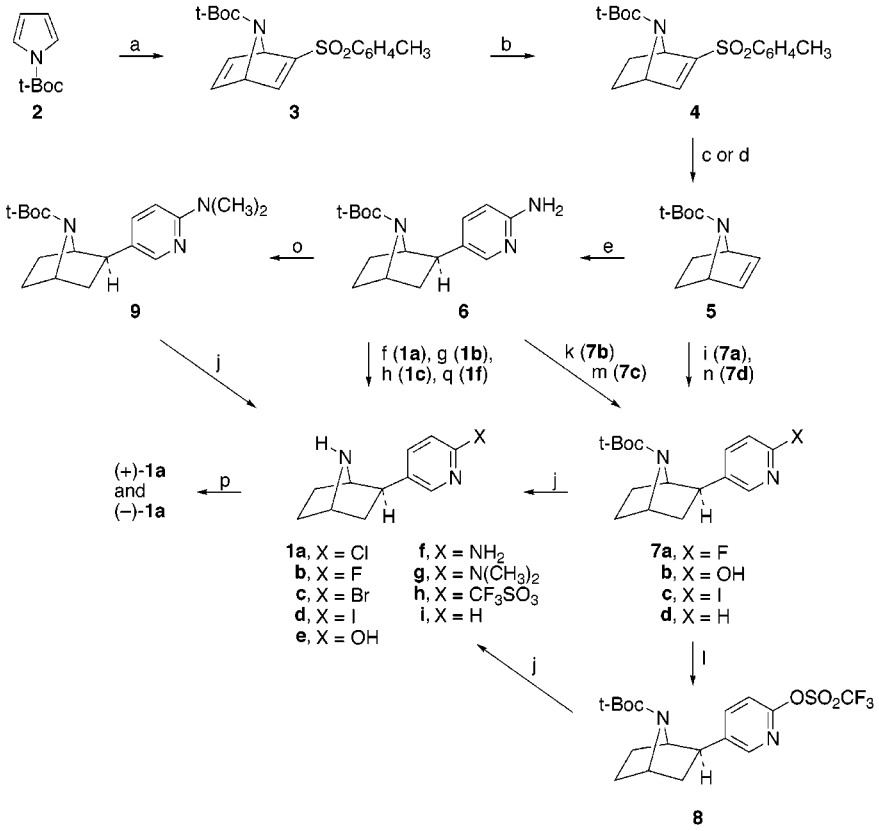
Chemistry

The routes used to synthesize epibatidine analogues **1a**−**i** are outlined in Scheme 1. Heating a solution of *N*-(*tert*-butoxycarbonyl)pyrrole[13] and *p*-tolylsulfonylacetylene[14] at 80 °C yielded 65% of the diene **3**. Selective reduction of the 5,6-double bond using nickel boride[15] in ethanol gave 86% of the monoolefin **4**. Originally the desulfonation of **4** to give **5** was carried out in 55% yield using 2.5% sodium amalgam in a 1:1 mixture of ethyl acetate and *tert*-butyl alcohol containing disodium hydrogen phosphate.[2] Later we discovered that **4** could be converted to **5** in higher yield and on larger scale by adding tributyltin hydride to **4** in benzene containing 2,2′-azabisisobutyronitrile (AIBN) followed by treatment of the resulting addition product with tetrabutylammonium fluoride in tetrahydrofuran. A preliminary account of this new synthesis of **5** has been reported.[16] Coupling of **5** with 2-amino-5-iodopyridine using palladium acetate as catalyst in dimethylformamide containing tetrabutylammonium chloride and potassium formate at 100 °C for 12 h provided 68% of 7-*tert*-butoxycarbonyl-

* Corresponding author. Tel: 919-541-6679. Fax: 919-541-8868. E-mail: fic@rti.org.
† Research Triangle University.
‡ Medical College of Virginia Commonwealth University.

10.1021/jm0100178 CCC: $20.00
Published on Web 05/23/2001

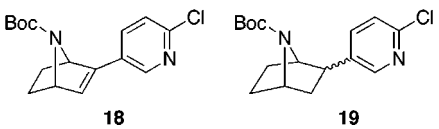
Scheme 1[a]



[a] Reagents: (a) $HC{\equiv}CSO_2C_6H_5CH_3$, 80 °C; (b) Ni_2B, EtOH; (c) NaHg (2.5%), Na_2HPO_4,EtOAc:*t*-BuOH (1:1); (d) (i) $(C_4H_9)_3SnH$, AlBN, benzene, (ii) $(C_4H_9)_4NF$, THF; (e) 2-amino-5-iodopyridine, $Pd(OAc)_2$, *n*-$Bu_4N^+Cl^-$, KO_2CH, DMF, 100 °C, 12 h; (f) $NaNO_2$, HCl, CuCl; (g) $NaNO_2$, pyridine·HF; (h) $NaNO_2$, Br_2, HBr; (i) 2-fluoro-5-iodopyride, $Pd(OAc)_2$, *n*-$Bu_4N^+Cl^-$, KO_2CH, DMF, 100 °C, 4 days; (j) CF_3CO_2H; (k) $NaNO_2$, HOAc, K_2CO_3; (l) $(CF_3SO_2)_2O$, pyridine; (m) isoamyl nitrite, CH_2I_2, HI; (n) 3-iodopyridine, $Pd(OAc)_2$, *n*-$Bu_4N^+Cl^-$, KO_2CH, DMF, 80 °C, 24 h; (o) $NaBH_3CN$, H_2CO, CH_3OH; (p) resolution using *p*-toluoyl tartaric acid; (q) HCl, CH_3OH.

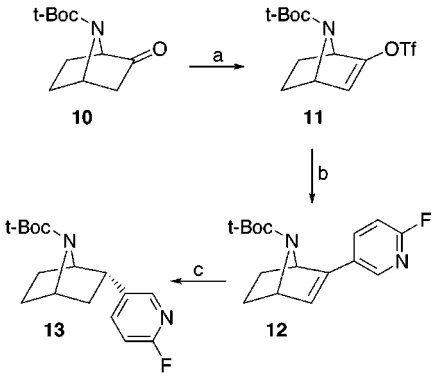
exo-2-(2′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (**6**). The 2-*exo* stereochemistry assigned to **6** was based on an analysis of the ^1H NMR ($CDCl_3$) spectrum. The spectrum showed a doublet of doublets at 2.74 ppm for the H-2 proton with $J_{2\alpha,3\beta} = 5.0$ Hz, $J_{2\alpha,3\alpha} = 8.8$ Hz, $J_{2\alpha,1} = 0$ Hz, which is characteristic of the 2-*exo* stereochemistry.[15] Diazotization[17] of **6** in pyridine containing 70% hydrogen fluoride effected conversion of the 2-amino group to a fluoro group, and deprotection of the *N*-Boc group to give 46% of **1b**. Compound **1b** could also be obtained by direct reductive Heck coupling of 2-fluoro-5-iodopyridine (obtained by diazotization of 2-amino-5-iodopyridine[14] in pyridine·HF) with **5** to give intermediate **7a**, which gave the desired **1b** on removal of the *N*-Boc-protecting group with trifluoroacetic acid. However, this route was less desirable since the overall yield was 39% and the coupling of 2-fluoro-5-iodopyridine with **5** took 4 days, whereas the coupling of 2-amino-5-iodopyridine with **5** was complete in 12 h. We also found that diazotization of **6** in hydrochloric acid in the presence or absence of cuprous chloride gave a 76% yield of epibatidine (**1a**) which was identical to an authentic sample.[15] This provided additional support for the 2-*exo* structural assignment of **6**. Epibatidine (**1a**) was resolved into (+)- and (−)-**1a** using di-*p*-toluyl-*d*-tartaric acid.[15] Diazotization of **6** using sodium nitrite in hydrobromic acid containing bromine or acetic acid containing sodium carbonate gave the 2′-bromo analogues **1c** and the *N*-*tert*-butoxycarbonyl 2′-hydroxy compound **7b**, respectively. Treatment of **7b** with trifluoromethanesulfonic anhydride gave the 2′-triflate **8**. Diazotization of **6** with isoamyl nitrite in methylene iodide containing hydrogen iodide afforded the *N*-*tert*-butoxycarbonyl 2′-iodo compound **7c**. Reduction Heck coupling of **5** with 3-iodopyridine yielded *N*-*tert*-butoxycarbonyl 2′-norchloro analogue **7d**. Reductive methylation of **6** with formaldehyde using sodium cyanoborohydride yielded the *N*-*tert*-butoxycarbonyl 2′-dimethylamino analogue **9**. Treatment of **7a**−**d**, **8**, and **9** with trifluoroacetic acid yielded the 2′-substituted epibatidine analogues **1d**−**i**.

We also attempted to synthesize the 2′-fluoro analogue **1b** by the route outlined in Scheme 2. Thus, the additions of phenyltriflimide to a tetrahydrofuran solution of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-one (**10**)[18] provided the triflate **11**. Reaction of **11** with 2-fluoro-5-pyridineboronic acid (**17**), prepared as shown in Scheme 3, in refluxing dimethoxyethane using tetrakis(triphenylphosphine)palladium(O) yielded 7-*tert*-butoxycarbonyl-2-(2′-fluoro-5′-pyridinyl)-7-azabicyclo-[2.2.1]hept-2-ene (**12**). Since Fletcher et al.[18] reported that reduction of 7-*tert*-butoxycarbonyl-2-(2′-chloro-5-pyridinyl)-7-azabicyclo[2.2.1]hept-2-ene (**18**) yielded a



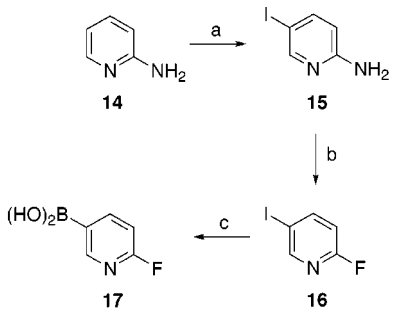
4:1 mixture of 2-*endo*- and 2-*exo*-7-*tert*-butoxycarbonyl-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**19**),

Scheme 2[a]



[a] Reagents: (a) $NaN[Si(CH_3)_3]_2$, $C_6H_5N(Tf)_2$, THF, −78 °C, 1 h, then 5 °C, 5 days; (b) 2-fluoro-5-pyridineboronic acid (**17**), $Pd[P(C_6H_5)_3]_4$, LiCl, Na_2CO_3, DME reflux 1 h; (c) H_2, PtO_2, EtOAc, 25 °C, 48 h.

Scheme 3[a]



[a] Reagents: (a) I_2, aq HOAc, H_2SO_4, H_5IO_6, 80 °C, 4 h; (b) pyridine−HF, $NaNO_2$, 0 °C, 15 min, then 90 °C, 2 h; (c) nC_4H_9Li, $[(CH_3)_2CHO]_3B$, THF, −78 °C; (d) 3 N NaOH.

we expected that a similar reduction of **12** would lead to a 2-*endo*- and 2-*exo*-2-(2′-fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane. However, we found that a similar reduction of **12** gave only the 2-*endo*-isomer **13**. Moreover, since reports from both our laboratory[15] and Merck Sharp and Dohme Research Laboratories[18] showed that 2-*endo*-**19** could be isomerized to 2-*exo*-**19**, we expected that **13** could be isomerized to the 2-*exo* isomer. However, we were unable to successfully convert **13** to the 2-*exo*-isomer. Any conditions strong enough to affect isomerization resulted in decomposition. Apparently, the 2′-fluoro compound **13** is much more sensitive to alkaline reagents than compound **19**.

Biology

The K_i values for the inhibition of [^{3}H]epibatidine ([^{3}H]**1a**) binding at the $\alpha_4\beta_2$ nAChR in male rat cerebral cortex for nicotine, (−)- and (+)-epibatidine [(−)- and (+)-**1a**, respectively], and the 2-substituted epibatidine analogues **1b**−**i** are listed in Table 1. The cerebral cortex homogenates were incubated with 0.5 nM [^{3}H]epibatidine and 10−12 different concentrations of the test compound. Nonspecific binding was determined in the presence of 300 μM nicotine. The IC_{50} values were determined from at least three independent experiments, and the K_i values were calculated using the Cheng−Prusoff equation.[19] The compounds were also evaluated once at 50 nM for inhibition of [^{125}I]iodo-MLA binding at the α_7 nAChR using conditions previously reported.[20]

Male ICR mice were tested for antinociception in the tail-flick test after intrathecal (i.t.) injection, and the results are listed in the table. Intrathecal injections were performed free-hand between the L4 and L6 lumbar space in unanesthetized male mice according to the method of Hylden and Wilcox.[21] Antinociception was assessed by the tail-flick method of D'Amour and Smith.[22] A control response (2−4 s) was determined for each mouse before treatment, and a test latency was determined after drug administration. The mice were tested 5 min after i.t. injections of nicotinic ligands for the dose−response evaluation. ED_{50} values with 95% CL for behavioral data were calculated by unweighted least-squares linear regression as described by Tallarida and Murray.[23]

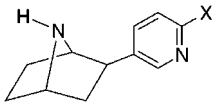
Results and Discussion

A number of 2′-substituted epibatidine analogues have been prepared and their nAChR binding properties determined using various radioligands.[1] In this study we determined the nAChR binding properties of a set of 2′-substituted epibatidine analogues using [^{3}H]epibatidine and [^{125}I]iodo-MLA. When appropriate, the data are compared to previously reported results. The set of compounds from this study possess both electron-withdrawing and electron-releasing substituents as well as substituents having variation in size and lipophilicity, thus, revealing new structure−activity relationships (SAR) information about the epibatidine class of nAChR ligands.

In agreement with published results, both (+)-natural and (−)-epibatidine (**1a**) possess high affinity for the $\alpha_4\beta_2$ nAChR.[1,24,25] In addition, we found that unnatural (−)-**1a** with a K_i value of 18 pM is slightly more potent than the natural isomer (+)-**1a**, which has a K_i value of 26 pM. This is in agreement with the reported 45 and 58 pM K_i values for (−)- and (+)-**1a** using [^{3}H]nicotine.[1,24] Houghtling has reported almost identical K_i values of 61 and 62 pM for (+)- and (−)-**1a**.[24,25] More recently, Gnädisch et al. reported K_i values of 7.2 and 7.5 pM for natural epibatidine using [^{3}H]epibatidine and (−)-[^{3}H]cytisine, respectively.[26] In our preliminary communication,[2] we reported a K_{app} of 20 pM for the 2′-fluoro analogue **1b**, which compares favorably with the K_i value of 27 pM found in this study using [^{3}H]-epibatidine as well as a recently reported value by Horti et al. of 37 pM.[27] K_i values of 31 pM using [^{3}H]nicotine[19] and 45 pM using [^{3}H]-**1a** have been reported for the norchloroepibatidine analogue **1i** and the 2′-bromo analogue **1c**, respectively. We find K_i values 20, 23, and 70 pM for **1i**, **1c**, and **ld**, respectively.

From an SAR point of view, it is interesting to note that epibatidine (**1a**), the 2′-fluoro, 2′-bromo, 2′-iodo, and 2′-norchloro analogues **1b**, **1c**, **1d**, and **1i**, respectively, all possess essentially the same K_i values. These results show that replacing the 2′-chloro group with a relatively large iodo group or small hydrogen had no effect on binding affinity. Compounds **1a**−**c**, which have electron-withdrawing halogen groups, all possess much higher affinity than the compounds **1e**−**g** containing the electron-donating 2′-hydroxy, 2′-amino, and 2′-dimethylamino groups, respectively. However, other factors must be involved since compound **1h**, which has a strongly electron-withdrawing 2′-trifluoromethanesulfo-

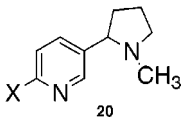
Table 1. Radioligand Binding Data and Antinociceptive Potencies of 2-*Exo*-(2′-Substituted 5′-pyridinyl)-7-azabicyclo[2.2.1]heptanes



compd[a]	X	$\alpha_4\beta_2$ [^{3}H]epibatidine[b] (K_i, nM)	Hill slope	[^{3}H]nicotine[c] (K_i, nM)	ED_{50}[d] nmol/mouse ± CL
nicotine		1.50 ± 0.30	0.90 ± 0.4	1.01	74 (37−137)
(+)-**1a**[e]	Cl	0.026 ± 0.002	0.98 ± 0.05	0.045	0.5 (0.11−5)
(−)-**1a**	Cl	0.018 ± 0.001	1.02 ± 0.07	0.058	0.6 (0.49−0.82)
1b	F	0.027 ± 0.001	0.90 ± 0.02		0.31 (0.26−0.98)
1c	Br	0.023 ± 0.001	0.90 ± 0.03		0.33 (0.29−0.37)
1d	I	0.070 ± 0.004[f]		0.48	NT[g]
1e	OH	107 ± 0.5	1.0 ± 0.05		52.4 (30−87)
1f	NH_2	1.3 ± 0.1	1.0 ± 0.01		27% @ 112
1g	$(CH_3)_2N$	26.4 ± 1.4	1.0 ± 0.01		10% @ 32.5
1h	CF_3SO_3	8.5 ± 0.2	1.1 ± 0.02		19.2 (4.5−77)
1i	H	0.020 ± 0.001	0.80 ± 0.02	0.031	0.2 (0.15−0.23)

[a] All compounds were assayed as their hydrochloride salts. [b] K_d = 20 pM. [c] Taken from ref 22. [d] Tail-flick test. [e] Compound (+)-**1a** is natural epibatidine hydrochloride. It has an $[\alpha]_D^{25}$ value of +42.6 (0.31, CH_3OH). Its enantiomer (−)-**1b** hydrochloride has an $[\alpha]_D^{25}$ value of −42.9 (0.29, CH_3OH). [f] K_{app} determined using [^{3}H]norchloroepitadine (ref 2). [g] Not tested.

Table 2. Radioligand Binding Data for the Nicotine Analogues[a]



20

compd	X	(K_i, nM)
20a	-H	1.26
20b	-Br	0.45
20c	-Cl	0.63
20d	-F	1.03
20e	-NH_2	81.0
20f	-OH	1072

[a] Data taken from ref 28.

nyl group, has lower affinity than the 2′-halogenated analogues and, as mentioned above, the norchloro analogue **1i**, which possesses an electronic neutral hydrogen substituent, has an affinity almost identical to that of epibatidine. Interestingly, the 2-amino analogue **1f** with a K_i value of 1.3 nM is considerably more potent than the 2-hydroxy analogue **1e**, which has a K_i value of 107 nM. Changing the 2-amino compound to the *N*,*N*-dimethyl analogue **1g** also results in loss of affinity.

In a previous study, the inhibition of [^{3}H] nicotine binding for several 6-substituted nicotine analogues was studied.[28] QSAR studies suggested that the affinities were related to the lipophibicity of the 6-position substitutent and was further influenced by the size of the substituents. The structure and K_i values of the nicotine analogues which have 6-substituents identical to the 2-substituent epibatidine analogues in this study are listed in Table 2. A correlation of 0.99 was found between the binding affinity of **20a**−**f** and the similarly substituted epibatidine analogues **1a**−**f** and **1e**. This provides additional evidence that 6-substituted nicotine analogues and 2′-substituent epibatidine analogues are binding to the nAChR in a similar fashion.

Since α_7 nAChR receptors are thought to be involved in learning, memory, and neuroprotection,[1] the compounds **1a**−**i** were assayed at 50 nM concentration for inhibition of [^{125}I]iodo-MLA binding to determine if any of the compounds possessed appreciable affinity at this site.[20] The 2′-fluoro analogue **1b** which showed only 20% inhibition was the most potent analogue. Thus, none of the compounds showed appreciable affinity for the α_7 nAChR.

Nicotine and epibatidines in vivo results in the tail-flick test are similar to those previously reported. Most compounds tested, except for **1f** and **1g**, are agonists in producing antinociception after intrathecal injection in mice. Furthermore, a good correlation (a coefficient of 0.96) exists between the K_i (nM) binding affinity values to brain [^{3}H]epibatidine sites and the ED_{50} (nmol/mouse) values for antinociceptive potency for the 2-substituted epibatidine analogues if **1e** (which is 10 000 less potent than epibatidine) was excluded. If **1e** was included in the correlation, a 0.75 coefficient was obtained. The weak antinociceptive activity of compound **1f** is unexpected, since its binding affinity was equal to that of nicotine.

Experimental Section

7-*tert*-Butoxycarbonyl-2-*p*-tolylsulfonyl-7-azabicyclo-[2.2.1]hepta-2,5-diene (3). A stirred solution of 11.7 g (0.065 mol) of *p*-tolylsulfonylacetylene in 19.5 g (0.116 mol) of *N*-*tert*-butoxycarbonylpyrrole (**2**) was heated to 80 °C under N_2. After 6 days, the excess *N*-*tert*-butoxycarbonylpyrrole was distilled from the resulting tarry reaction mixture under high vacuum at 85 °C. The residue was recrystallized from an ethyl ether and petroleum ether mixture. The mother liquor was concentrated under reduced pressure and filtered through a two-inch pad of silica gel, eluting with 5% chloroform in 25% ethyl acetate and hexane to give a total of 14.1 g (65%) of **3**: ^{1}H NMR ($CDCl_3$) δ 1.27 (br s, 9H), 2.45 (s, 3H), 5.18 (br s, 1H), 5.39 (br s, 1H), 6.88 (m, 2H), 7.34 (d, J = 8.2, 2H), 7.58 (s, 1H), 7.76 (d, J = 8.3, 2H). Anal. ($C_{18}H_{21}NO_4S$) C, H, N, S.

7-*tert*-Butoxycarbonyl-2-(*p*-tolylsulfonyl)-7-azabicyclo-[2.2.1]hepta-2-ene (4). To a solution of 0.64 g (0.0025 mol) of nickel tetraacetate in 2.5 mL of ethanol under N_2 at 25 °C was added dropwise 0.097 g (0.0025 mol) of sodium borohydride in 2.5 mL of ethanol at room temperature. After 10 min, 0.174 g (0.0005 mol) of the cycloadduct **7** in 2.5 mL of THF was added to the resulting black slurry followed by dropwise addition of 0.42 mL (5 mmol) of concentrated hydrochloric acid. After 1 h or until judged complete as evidenced by TLC analysis [bright fluorescent spot above starting material (3:1 hexane/ethyl acetate)], the reaction mixture was filtered through Celite, the slurry was washed with 10 mL of ethylene chloride, and the filtrate was rendered basic (pH 8−9) using

saturated sodium bicarbonate solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated under vacuum to give 0.28 g of crude product which was extracted in ether and concentrated to obtain 0.15 g (86%) of **4** as a yellowish white solid: ^{1}H NMR ($CDCl_3$) δ 1.21 (br s, 9H), 1.27−1.47 (m, 2H), 2.01 (m, 2H), 2.45 (s, 3H), 4.76 (m, 1H), 4.83 (br s, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.35 (m, 2H), 7.81 (m, 2H). Anal. ($C_{18}H_{23}NO_4S$) C, H, N, S.

2-(*p*-Tolylsulfonyl)-3-tributylstannyl-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane. To a stirred solution of **4** (23.4 g, 0.067 mol) and AIBN (0.60 g, 0.0036 mol) in 250 mL of benzene was added tributyltin hydride (40.1 g, 0.138 mol) via a syringe. The reaction was refluxed for a period of 3 h and cooled to room temperature, and 70 g of silica gel was added. The slurry was concentrated in vacuo to a paste and chromatographed on silica gel using hexanes to remove the excess tributyltin hydride (19.3 g). Using hexane/EtOAc (9:1) mixtures as the eluent, 32.8 g of the addition product (78%) was isolated as a thick, clear oil. Upon standing, the oil solidified to waxy solid (mp 54−57 °C): ^{1}H NMR ($CDCl_3$) δ (ppm) 0.79 (br s, 4H), 0.85−0.94 (t, 6H), 1.25−1.90 (m, 18H), 1.41 (s, 9H), 2.44 (s, 3H), 2.57−2.63 (m, 1H), 3.67−3.70 (m, 1H), 4.20−4.26 (m, 2H), 7.33−7.36 (d, 2H), 7.71−7.75 (d, 2H). Anal. ($C_{30}H_{51}NO_4SSn$) C, H, N.

7-*tert*-Butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (5) (Method A). To a solution of the above intermediate (52.3 g, 0.0832 mol) in 480 mL of tetrahydrofuran was added 166 mL (0.166 mol) of 1 M tetrabutylammonium fluoride in THF. The reaction mixture was stirred at reflux for 17 h, then cooled to room temperature, and concentrated in vacuo. The oily residue was chromatographed on silica gel using hexane/EtOAc (9:1) mixtures as the eluent to afford 15.6 g (98%) of **5** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.08−1.11 (d, 2H), 1.41 (s, 9H), 1.82−1.87 (br d, 2H), 4.65 (br s, 2H), 6.21 (br s, 2H).

Method B. To a stirred mixture of 337 g (0.288 mol) of 2.5% sodium amalgam, 10 g (0.072 mol) of Na_2HPO_4, and 8.6 g (0.072 mol) of NaH_2PO_4 at 0 °C under N_2 was added 5.04 g (0.0144 mol) of **4** in 200 mL of 1:1 ethyl acetate and *tert*-butyl alcohol. The reaction mixture was warmed to room temperature over a 1 h period. After 24 h, the top layer was poured into 500 mL of water and extracted with three 50 mL portions of ethyl acetate. The bottom layer (Hg layer) was washed with two 50 mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 4.6 g of a white oily solid. This material was purified by filtration through a short pad of silica gel, eluting with hexanes to give 1.56 g (55%) of **5** as a colorless oil, which was dried by azeotropation with toluene and further dried under high vacuum.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (6). To a stirred mixture of 1.93 g (0.00985 mol, dried by azeotropation with toluene and under high vacuum) of **5**, 4.3 g (0.0197 mol) of 2-amino-5-iodopyridine, 700 mg (2.5 mmol) of *n*-Bu_4NCl, 1.66 g (0.0197 mol) of KO_2CH in 40 mL of DMF at room temperature under nitrogen was added 55 mg (0.25 mmol) of $Pd(OAc)_2$. The reaction vessel was inserted into a 100 °C oil bath. After 12 h, another 55 mg (0.25 mmol) of $Pd(OAc)_2$ was added. After 12 h, the reaction mixture was diluted with 100 mL of ethyl acetate and filtered through a Celite pad into 100 mL of 1:1 NH_4OH and H_2O. The aqueous phase was extracted with two 50 mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting brown oil was redissolved into 50% of ethyl acetate in hexanes, allowed to stand for 3 h (to precipitate all the white solid), and filtered. The filtrate was concentrated under reduced pressure to give a yellow solid. This material was purified by recrystallization from acetone to give 1.56 g of **6** as colorless crystals. The mother liquor was purified by column chromatography, eluting with 30% Et_3N in Et_2O to give an additional 229 mg of the same product (68% total) as a white solid (mp 135−136 °C): ^{1}H NMR ($CDCl_3$) δ (ppm) 1.43 (s, 9H), 1.43−1.59 (m, 3H), 1.81 (m, 2H), 1.93 (dd, J = 8.8, 12.3, 1H), 2.74 (dd, J = 5.0, 8.8, 1H), 4.10 (m, 1H), 4.36 (m, 3H), 6.46 (d, J = 8.5, 1H), 7.42 (d, J = 8.5, 1H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 28.31, 28.31, 29.52, 40.15, 44.62, 55.91, 62.29, 79.53, 108.68; 136.51, 146.50, 156.97; IR (neat, NaCl) υ 3485, 3000, 1686, 1618, 1499, 1409, 1384, 1360, 1151, 1094 cm^{-1}. Anal. ($C_{16}H_{23}N_3O_2$) C, H, N.

2-*exo*-(2′-Fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1b) Hydrochloride from 6. To 17 mg (0.058 mmol) of **6** at room temperature under nitrogen in a plastic vessel was added 0.02 mL (0.7 mmol, 70% HF in pyridine) of HF-Py with stirring. After 1 h, a solution of 26 mg of $NaNO_2$ (0.38 mmol) in 0.2 mL of H_2O was added, followed by warming to 80 °C for 2 h. The reaction mixture was slowly poured into 25 mL of a 50% aqueous NH_4OH solution. The water phase was saturated with NaCl and extracted with three 25 mL portions of Et_2O. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 5.6 mg of a brown oil. This material was purified by column chromatography (silica gel), eluting with 30% Et_3N in Et_2O to give 4.5 mg (46%) of 2-*exo*-(2′-fluoro-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**1b**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.55−1.65 (m, 5H), 1.90 (dd, J = 8.9, 12.2, 1H), 2.78 (dd, J = 5.0, 9.0, 1H), 3.55 (m, 1H), 3.78 (m, 1H), 6.83 (dd, J = 3.0, 8.5, 1H), 7.87 (ddd, J = 2.6, 8.3, 8.5, 1H), 8.07 (d, J = 2.6, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 30.18, 31.38, 40.49, 44.40, 56.43, 62.83, 109.03 (d, J = 36.7 Hz), 140.04 (br d, J = 7.7 Hz), 146.11 (d, J = 14.0 Hz), 160.48, 164.25; IR (neat, NaCl) υ 3335, 2945, 1590, 1473, 1394, 1243, 910, 837, 639 cm^{-1}.

The hydrochloride salt had a melting point of 177−179 °C: ^{1}H NMR (DMSO-d_6) δ (ppm) 1.61−1.95 (m, 4H), 2.22 (m, 1H), 2.37 (m, 1H), 3.25 (m, 1H), 4.13 (m, 1H), 4.34 (m, 1H), 7.09 (dd, J = 2.5, 8.5, 1H), 8.05 (ddd, J = 2.6, 8.5, 8.5, 1H), 8.17 (d, J = 2.6, 1H), 8.95 (s, 1H), 9.57 (s, 1H). Anal. ($C_{11}H_{14}ClFN_2$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (7a). To a stirred mixture of 138 mg (0.70 mmol) of **5**, 157 mg (0.704 mmol) of 2-fluoro-5-iodopyridine, 196 mg (0.704 mmol) of *n*-Bu_4NCl, and 89 mg (1.06 mmol) of KO_2CH in 1.0 mL of DMF at room temperature under nitrogen was added 16 mg (0.07 mmol) of $Pd(OAc)_2$. After 4 days, the reaction mixture was diluted with 50 mL of 25% ethyl acetate in hexanes, filtered through a Celite pad, and concentrated under reduced pressure to give 150 mg of a yellow oil. This material was purified by radial PLC (silica gel) eluting with a solvent mixture of CH_2Cl_2:$CHCl_3$:CH_3OH:NH_4OH (450:40:9:1) to give 106 mg (51%) of **7a** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.34−1.71 (m, 3H), 1.36 (s, 9H), 1.93 (dd, J = 9.0. 12.3, 1H), 2.81 (dd, J = 5.0, 9.0, 1H), 4.08 (m, 1H), 4.30 (m, 1H), 6.78 (dd, J = 3.0, 8.5, 1H), 7.70 (ddd, J = 2.2, 8.5, 8.5, 1H), 7.99 (d, J = 2.2, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 28.24, 28.72, 29.60, 40.48, 44.71, 56.14, 62.02, 79.80, 109.22 (d, J = 37.2 Hz), 139.25 (d, J = 31.6 Hz), 146.06 (d, J = 14.3 Hz), 155.24, 160.48, 164.25; IR (neat, NaCl) υ 2956, 1703, 1593, 1403, 1359, 1251, 1151, 1092 cm^{-1}. Anal. ($C_{16}H_{21}FN_2O_2$) C, H, N.

2-*exo*-(2′-Fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1b) from 7a. To a stirred solution of 60 mg (0.205 mmol) of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**11**) in 1 mL of CH_2Cl_2 at 0 °C under nitrogen was added dropwise 1.0 mL of CF_3CO_2H. After 0.5 h, 25 mL of a saturated aqueous K_2CO_3 solution was added. The reaction mixture was extracted with two 50 mL portions of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 43 mg of a yellow oil. This material was purified with column chromatography, eluting with a solvent mixture of CH_2Cl_2:$CHCl_3$:CH_3OH:NH_4OH (50:40:9:1) to give 30 mg (77%) of **1b** as a colorless oil. The ^{1}H NMR spectrum was identical to the sample of **1b** prepared from compound **6**.

2-*exo*-(2′-Chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane [1a, (±)-Epibatidine]. To 115 mg (0.358 mmol) of **6** at 0 °C was added 1.5 mL of a 36% hydrochloric acid with stirring, and 500 mg of $NaNO_2$ was added in three portions. The reaction mixture was warmed to room temperature, and 1.5 g of CuCl was added as a solid. After 1 h, the reaction

mixture was poured into 25 mL of 3:1 NH_4OH and H_2O, and it was extracted with three 50 mL portions of $CHCl_3$. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 60 mg (72%) of pure (±)-epibatidine (**1a**) as a colorless oil. The ^1H NMR and R_f values are identical to the reported values.[14,15]

2-*exo*-(2′-Bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1c). To 105 mg (0.358 mmol) of **6** at 0 °C was added 0.41 mL of a 48% HBr solution in acetic acid (3.58 mmol) with stirring. After 0.5 h, 0.02 mL of Br_2 was added dropwise followed by a solution of $NaNO_2$ in 0.5 mL of water. After 0.5 h, the resulting tarry reaction mixture was diluted with 25 mL of 1:1 NH_4OH (concentrated) and H_2O then extracted with three 25 mL portions of 10% MeOH in $CHCl_3$. The combined organic phase was washed with a saturated aqueous Na_2SO_3 solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 120 mg of a brown oil. This material was purified by column chromatography, eluting with 20% triethylamine in ether to give 35 mg (36%) of a colorless oil, which was purified again with column chromatography, eluting with a solution of 96:3:1 $CHCl_3$:MeOH:NH_4OH to give 31 mg of 2-*exo*-(2′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane as a colorless oil. ^1H NMR ($CDCl_3$) δ (ppm) 1.55−1.73 (m, 3H), 1.82 (m, 2H), 1.93 (dd, J = 8.8, 12.4, 1H), 2.78 (dd, J = 5.0, 8.8, 1H), 3.64 (m, 1H), 4.88 (m, 1H), 7.40 (d, J = 8.2, 1H), 7.71 (dd, J = 2.4, 8.2, 1H), 8.27 (d, J = 2.4, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 149.45, 140.15, 139.16, 137.53, 127.90. 62.77, 56.87, 44.24, 39.53, 30.76, 29.09.

To a stirred solution of 31 mg of **1c** free base (0.114 mmol) in 0.5 mL of 2:1 Et_2O and MeOH at room temperature was added dropwise 1.0 mL of a 1.0 M HCl solution in Et_2O (1 mmol). After 2 h, the solvents were removed under reduced pressure, and the resulting white solid was redissolved into MeOH, filtered, and recrystallized from MeOH and Et_2O to give 31 mg of 2-*exo*-(2′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (**1c**) dihydrochloride as a white solid (mp 183−185 °C). Anal. ($C_{11}H_{15}BrCl_2N_2$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-hydroxy-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (7b). To a stirred solution of 52 mg (0.18 mmol) of **6** in 1 mL of AcOH at 0 °C was added 62 mg of $NaNO_2$ (0.86 mmol) in 1.0 mL of water. After 2 h, 8 mL of saturated aqueous solution of Na_2CO_3 was added (until pH ≥ 10), and the reaction mixture was warmed to room temperature. After 1 h, the reaction mixture was poured into 25 mL of 1:1 NH_4OH and H_2O and extracted with three 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 40 mg of pure **7b** as a colorless oil. This material was used without further purification.

2-*exo*-(2′-Hydroxy-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1e) Dihydrochloride. Trifluoroacetic acid (2.0 mL, 0.026 mol) was added to compound **7b** (0.45 g, 0.0015 mol) in CH_2Cl_2 (5 mL). The reaction was stirred at room temperature for 1 h then concentrated in vacuo. The residue was purified by silica gel column chromatography using 80 CMA as eluent to afford **1e** (0.24 g, 84%) as an oil. The HCl salt was prepared by dissolving the free base in ether and adding ethereal HCl to give solids that were crystallized from MeOH/EtOAc mixtures to afford a beige solid (mp 220−223 °C): ^1H NMR (MeOD, base) δ 1.89−2.16 (m, 5H), 2.43 (m, 1H), 3.48 (m, 1H), 4.36 (m, 1H), 4.54 (m, 1H), 7.19 (d, 1H), 8.13 (s, 1H), 8.27 (d, 1H). Anal. ($C_{11}H_{16}C1_2N_20$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-trifluoromethanesulfonyloxy-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (8). To a stirred solution of 40 mg (0.34 mmol) of **7b** in 4.0 mL of pyridine at room temperature was added 0.5 mL of $(CF_3SO_2)_2O$ (3.4 mmol). After 8 h, the reaction mixture was poured into 25 mL of 1:1 NH_4OH and H_2O and extracted with three 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 60 mg of a yellow oil. This material was filtered through a 1 in. pad of silica gel, eluting with 25% ethyl acetate in hexanes to give 53 mg (88%) of **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ (ppm) 1.44 (s, 9H), 1.52−1.69, (m, 2H), 1.79−1.86 (m, 3H), 2.03 (dd, J = 9.7, 13.4, 1H), 3.93 (dd, J = 5.3, 9.8, 1H), 4.20 (m, 1H), 4.38 (m, 1H), 7.11 (d, J = 9.1, 1H), 7.88 (dd, J = 2.6, 9.1, 1H), 8.25 (d, J = 2.7, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 155.69, 154.78, 147.78, 142.74, 139.76, 118.57 (q, J = 320), 115.37, 80.48, 61.88, 56.16, 44.79, 40.40, 30.01, 29.60, 28.73, 28.63.

2-*exo*-(2′-Trifluoromethanesulfonyloxy-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (1h) Hydrochloride. To a stirred solution of 53 mg of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-trifluoromethanesulfonyloxy-5′-pyridinyl)-7-azabicyclo[2.2.l]-heptane (0.12 mmol) in 0.5 mL of CH_2Cl_2 at room temperature was added 0.5 mL of TFA. After 1 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 50 mL of $CHCl_3$ and washed with 50 mL of 1:1 NH_4-OH (concentrated) and H_2O. The aqueous phase was extracted with two 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 39 mg of 2-*exo*-(2′-trifluoromethanesulfonyloxy-5′-pyridyl)-7-azabicyclo[2.2.1]heptane as a yellow oil (100%): ^1H NMR ($CDCl_3$) δ (ppm) 1.11−1.18 (m, 2H), 1.41−1.59 (m, 3H), 1.85 (dd, J = 9.7, 13.4, 1H), 2.73 (dd, J = 5.3, 9.8, 1H), 3.51 (m, 1H), 3.74 (m, 1H), 7.01 (d, J = 9.1, 1H), 7.97 (dd, J = 2.6, 9.1, 1H), 8.21 (d, J = 2.7, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 154.19, 147.46, 143.58, 139.86, 118.67 (q, J = 320), 114.72, 62.69, 56.35, 44.42, 40.54, 31.47, 30.35.

To a stirred solution of 39 mg of **1h** free base and 0.5 mL of Et_2O in MeOH at room temperature under N_2 was added 1.0 mL of 1.0 M solution of HCl (1.0 mmol) in Et_2O. After 2 h, the stirrer was stopped, and the solvents were removed with a pipet. The resulting white solid was washed with two 0.5 mL portions of Et_2O and dried under vacuum to give 39 mg of 2-*exo*-(2′-trifluoromethanesulfonyloxy-5′-pyridyl)-7-azabicyclo-[2.2.l]heptane (**1h**) hydrochloride as a white solid (mp 204−205 °C). Anal. ($C_{12}H_{14}ClF_3N_2SO_3$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (7c). To a stirred mixture of 50 mg (0.172 mmol) of **6** and 1 mL of CH_2I_2 under N_2 at room temperature was added 0.35 mL of isoamyl nitrite (3.43 mmol). After 0.5 h, 0.005 mL of HI was added. After 12 h, the reaction mixture was poured into 50 mL of 1:1 NH_4OH and H_2O and extracted with two 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 202 mg of a brown oil. This material was azeotroped with 10:1 MeOH and acetone followed by column chromatography, eluting with 25% ethyl acetate in hexanes to give 57 mg (79%) of **7c** as a colorless oil. ^1H NMR ($CDCl_3$) δ (ppm) 1.43 (s, 9H), 1.55−1.73 (m, 3H), 1.82 (m, 2H), 1.99 (dd, J = 9.6, 13.4, 1H), 2.81 (dd, J = 5.3, 9.6, 1H), 4.15 (m, 1H), 4.37 (m, lH), 7.31 (dd, J = 2.5, 8.8, 1H), 7.63 (d, J = 8.8, 1H), 8.23 (d, J = 2.5, 1H); ^1C NMR ($CDCl_3$) β (ppm) 149.97, 140.88, 136.30, 134.65, 115.20, 79.90, 61.78, 56.35, 43.84, 39.92, 29.95, 28.41, 28.26.

2-*exo*-(2′-Iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1d) Hydrochloride. To a stirred solution of 63 mg (0.126 mmol) of **7c** and 0.5 mL of CH_2Cl_2 under N_2 at 0 °C was added 0.5 mL of trifluoroacetic acid (6.49 mmol). The reaction mixture was warmed to room temperature in a 4 h period. After an additional 4 h, the reaction mixture was poured into 20 mL of 1:1 NH_4OH and H_2O and extracted with two 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 44 mg of a brown oil. This material was filtered through a 1 in. pad of silica gel, eluting with 50% ethyl acetate in hexanes to give 38 mg (79%) of **1d** as a colorless oil: ^1H NMR ($CDCl_3$) δ (ppm) 1.51−1.63 (m, 5H), 1.90 (dd, J = 9.6, 13.08, 1H), 2.71 (dd, J = 5.4, 9.6, 1H), 3.55 (m, 1H), 3.78 (m, 1H), 7.45 (dd, J = 2.6, 8.8, 1H), 7.62 (d, J = 8.8, 1H), 8.26 (d, J = 2.6, 1H); ^{13}C NMR ($CDCl_3$) β (ppm) 150.17, 141.92, 136.75, 134.47, 117.80, 62.70, 56.37, 44.58, 40.28, 31.39, 30.15.

To a stirred solution of 38 mg of **1d** in 1 mL of 2.5% MeOH in Et_2O under N_2 at room temperature was added dropwise 0.3 mL of 1 M HCl solution in Et_2O. After an additional 0.5 h, the solvent was removed, and the residue was recrystallized

from MeOH and Et_2O to give the hydrochloride salt as a light yellow solid (mp 178−179 °C). Anal. ($C_{11}H_{14}ClN_2$) C, H, N.

2-*exo*-(2′-Amino-5′-pyridinyl)-7-azabicyclo[2.2.1]-heptane (1f) Dihydrochloride. To a stirred solution of 23 mg (0.079 mmol) of **6** in 0.5 mL of MeOH at room temperature under nitrogen was added dropwise 2 mL of 36% aqueous HCl solution. After 8 h, the reaction mixture was concentrated under reduced pressure to give 25 mg of a yellow oil. This material was purified by recrystallization in MeOH and Et_2O to give 18 mg of 2-*exo*-(2′-amino-5′-pyridinyl)-7-azabicyclo-[2.1.1]heptane (**1f**) dihydrochloride as a colorless crystal (mp 270 °C (dec)): ^{1}H NMR (CD_3OD) δ (ppm) 1.85−2.12 (m, 5H), 2.39 (dd, J = 5.0, 8.8, 1H), 3.36 (m, 1H), 4.34 (m, 1H), 4.48 (m, 1H), 7.05 (d, J = 8.5, 1H), 7.84 (s, 1H), 7.96 (d, J = 8.5, 1H). Anal. ($C_{11}H_{17}Cl_2N_3$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-pyridinyl)]-7-azabicyclo-[2.2.1]heptane (7d). To a stirred mixture of 230 mg (1.17 mmol) of **5**, 481 mg of 3-iodopyridine (2.34 mmol), 82 mg of *n*-Bu_4NCl (0.29 mmol), and 198 mg of KO_2CH (2.34 mmol) in 2.0 mL of DMF at room temperature under nitrogen was added 26 mg of $Pd(OAc)_2$ (0.12 mmol). The reaction mixture was warmed to 80 °C. After 24 h, the reaction mixture was warmed to 120 °C. After 1 h, the reaction mixture was diluted with 50 mL of 25% ethyl acetate in hexanes, filtered through a 1 in. pad of Celite, and concentrated under reduced pressure to give 500 mg of a yellow oil. This material was purified by chromatatron, eluting with 25% followed by 50% ethyl acetate in hexanes to give 306 mg (94%) of **7d** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.43 (s, 9H), 1.45 (m, 1H), 1.57 (m, 1H), 1.86−1.94 (m, 2H), 2.00 (dd, J = 8.8, 12.4, 1H), 2.89 (dd, J = 5.0, 8.8, 1H), 4.22 (m, 1H), 4.38 (m, 1H), 7.21 (dd, J = 3.7, 7.9, 1H), 7.65 (d, J = 7.9, 1H), 8.44 (dd, J = 1.9, 3.7, 1H), 8.48 (d, J = 1.9, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 155.12, 148.94, 147.60, 140.97, 134.21, 123.45, 79.64, 61.87, 55.74, 45.47, 39.64, 29.96, 28.59, 28.23.

2-*exo*-(3′-Pyridinyl)-7-azabicyclo[2.2.1]heptane (1i) Dihydrochloride. To a stirred solution of 45 mg of **7d** in 2.5 mL of 5:1 Et_2O and MeOH at room temperature under nitrogen was added dropwise 2 mL of a 1 M solution of HCl in ethyl ether (excess). After 8 h, the reaction mixture was concentrated under reduced pressure to give 50 mg of a white solid. This material was purified by recrystallization in MeOH and Et_2O to give 35 mg of the dihydrochloride salt as a white solid (mp 239 °C (dec)): ^{1}H NMR (CD_3OD) δ (ppm) 1.84−2.54 (m, 6H), 3.66 (dd, J = 5.0, 8.8, 1H), 4.43 (m, 1H), 4.68 (m, 1H), 7.39 (s, 1H), 8.04 (dd, J = 3.7, 7.9, 1H), 8.66 (d, J = 3.7, 1H), 8.69 (d, J = 7.9, 1H), 9.08 (s, 1H). Anal. ($C_{11}H_{16}Cl_2N_2 \cdot 0.25H_2O$) C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(2′-*N*,*N*-dimethylamino-5′-pyridinyl)-7-aza-bicyclo-[2.2.1]heptane (9). To a stirred solution of 102 mg (0.348 mmol) of **6** in MeCN at room temperature under N_2 was added 1.5 mL (20 mmol) of a 37% polyformaldehyde solution in H_2O followed by 450 mg (6.8 mmol) of $NaBH_3CN$ as a solid. After 2 h, 0.5 mL of HOAc was added dropwise, and the reaction mixture was poured into 50 mL of a 10% aqueous NaOH solution and extracted with three 50 mL portions of $CHCl_3$. The combined organic phase was washed with a saturated aqueous NaCl solution, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give 130 mg of a white solid. This material was purified by column chromatography, eluting with 50% ethyl acetate in hexanes to give 97 mg (87%) of **9** as a white solid: mp 99.5−100 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 1.43 (s, 9H), 1.49−1.60 (m, 2H), 1.77−1.87 (m, 3H), 1.94 (m, 1H), 2.74 (m, 1H), 3.05 (s, 6H), 4.09 (m, 1H), 4.34 (m, 1H), 6.48 (d, J = 8.8, 1H), 7.45 (dd, J = 2.4, 8.8, 1H), 8.00 (d, J = 2.4, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 158.36, 155.42, 146.45, 135.80, 128.66, 105.96, 79.42, 67.89, 58.35, 48.20, 41.40, 38.28, 30.71, 28.34.

2-*exo*-(2′-*N*,*N*-Dimethylamino-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (1g) Dihydrochloride. To a stirred solution of 66 mg of 7-*tert*-butoxycarbonyl-2-*exo*-(2′-(dimethylamino)-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (0.21 mmol) in 0.5 mL of CH_2Cl_2 at room temperature was added 0.5 mL of TFA. After 1 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 50 mL of $CHCl_3$ and washed with 50 mL of 1:1 of NH_4OH and H_2O. The aqueous phase was extracted with two 25 mL portions of $CHCl_3$. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 37 mg (95%) of **1g** as a yellow oil. This material was converted into HCl salt without further purification and recrystallized from MeOH and Et_2O to give 15 mg of 2-*exo*-(2′-*N*,*N*-dimethylamino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane dihydrochloride monohydrate as a light yellow solid (mp 222 °C dec): ^{1}H NMR ($CDCl_3$) δ (ppm) 1.46−1.57, (m, 3H), 1.72−1.84 (m, 3H), 2.63 (dd, J = 5.5, 9.6, 1H), 2.95 (s, 6H), 3.39 (m, 1H), 3.63 (m, 1H), 6.38 (d, J. = 9.5, 1H), 7.36 (dd, J = 2.7, 9.5, 1H), 7.92 (d, J = 2.7, 1H): ^{13}C NMR ($CDCl_3$) δ (ppm) 158.14, 146.20, 136.11, 128.98, 105.80, 62.96, 56.37, 44.67, 39.81, 38.20, 30.67, 29.71. Anal. ($C_{13}H_{23}Cl_2N_3O$) C, H, N.

7-*tert*-Butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene-2-trifluoromethylsulfonate (11). To a stirred solution of 590 mg of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one (**16**) (2.78 mmol) in 2.5 mL of THF at −78 °C under nitrogen was added 4.2 mL of a 1.0 M solution of $NaN[(SiCH_3)]_2$ (4.2 mmol) in THF. After 3 h, 2.0 g of $C_6H_5N(Tf)_2$ (5.6 mmol) was added as a solid, and the reaction mixture was warmed to 0 °C. After 0.5 h, the reaction mixture was warmed to 5 °C. After 5 days, the reaction mixture was poured into 150 mL of a saturated aqueous NH_4Cl solution and extracted with three 100 mL portions of hexanes. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1 g of a yellow solid. This material was purified by column chromatography, eluting with 10% ethyl acetate in hexanes to give 650 mg (68%) of 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene-2-trifluoromethylsulfonate (**11**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.32−1.55 (m, 2H), 1.43 (s, 9H), 2.05 (m, 2H), 4.69 (d, J = 6.6, 1H), 4.75 (m, 1H), 5.96 (m, 1H); ^{13}C NMR δ (ppm) 24.18, 25.23, 27.98, 60.25, 60.25, 80.96, 118.48 (q, J = 321.2), 120.38, 153.69, 154.78; IR (neat, NaCl) υ 2975, 1719, 11619, 1427, 1361, 1289, 1246, 1216, 1150, 1083, 922, 817 cm^{-1}; Anal. ($C_{12}H_{16}F_3N_2O_5S$) C, H, N.

7-*tert*-Butoxycarbonyl-2-[(2′-fluoro-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptene (12). A mixture of 55 mg of **11** (0.218 mmol), 45 mg of 2-fluoro-5′-pyridineboronic acid (**17**) (0.327 mmol), 15 mg of LiCl (0.65 mmol), 0.3 mL of a saturated aqueous Na_2CO_3 solution, and 15 mg of $Pd(PPh_3)_4$ (0.01 mmol) in 0.7 mL of DME under nitrogen was heated to reflux. After 0.5 h, the reaction mixture was cooled to room temperature, diluted with 20 mL of Et_2O, filtered through a 1 in. pad of Celite into 50 mL of a 1:1 NH_4OH and water solution. The water phase was extracted with two 50 mL portions of Et_2O. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 50 mg of a yellow wax. This material was purified by column chromatography, eluting with 25% ethyl acetate in hexanes to give 32 mg (69%) of 7-*tert*-butoxycarbonyl-2-[(2′-fluoro-5′-pyridinyl)]heptene (**12**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 1.17−1.33 (m, 2H), 1.41 (s, 9H), 1.47 (m, 1H), 1.96−2.05 (m, 2H), 4.80 (m, 1H), 5.02 (d, J = 3.6, 1H), 6.48 (d, J = 2.3, 1H), 6.91 (dd, J = 3.0, 8.6, 1H), 7.78 (ddd, J = 2.5, 7.6, 8.6, 1H), 8.23 (m, 1H).

7-*tert*-Butoxycarbonyl-2-*endo*-[(2′-fluoro-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (13). To a stirred solution of 16 mg of **12** (0.055 mmol) in 0.5 mL of ethyl acetate at room temperature under nitrogen was added 2 mg of PtO_2, and the mixture was then exposed to H_2. After 48 h, the reaction mixture was diluted with 50 mL of ethyl acetate, filtered through a one-inch pad of Celite, and concentrated under reduced pressure to give 16 mg (95%) of 7-*tert*-butoxycarbonyl-2-*endo*-[(2′-fluoro-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**13**) a yellow oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.41−1.51 (m, 3H), 1.49 (s, 9H), 1.55−1.62 (m, 2H), 1.84 (m, 1H), 2.32 (m, 1H), 3.46 (m, 1H), 4.32 (m, 1H), 6.91 (dd, J = 3.0, 8.3, 1H), 7.62 (ddd, J = 2.5, 8.3, 8.3, 1H), 8.07 (m, 1H).

2-Fluoro-5-iodopyridine (16). To a powder of 820 mg of 2-amino-5-iodopyridine[2] (3.73 mmol) in a plastic vessel at room

temperature under nitrogen was added 5 mL of HF-pyridine (70% HF in Py) with stirring. After 20 min, 775 mg of $NaNO_2$ (11.2 mmol) was added in small portions in a 15 min period. After 1 h, the resulting blue solution was warmed to 100 °C, and the brown fume was led to a good vent. After 1 h, the resulting yellow reaction mixture was slowly poured into 100 mL of a 1:1 NH_4OH and water solution and extracted with three 50 mL portions of 50% ethyl acetate in hexanes. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1 g of a yellow oil. This material was sublimated from room temperature to −78 °C, giving 500 mg (60%) of 2-fluoro-5-iodopyridine (**16**) as a colorless solid (mp 31.2−31.7 °C): ^{1}H NMR ($CDCl_3$) δ (ppm) 6.72 (dd, J = 3.0, 8.6, 1H), 7.97 (ddd, J = 2.5, 7.6, 8.6, 1H), 8.32 (m, 1H); ^{13}C NMR δ (ppm) 119.97 (d, J = 38.1), 149.05 (d, J = 7.8), 153.60 (d, J = 14.5), 161.22, 165.04. Anal. (C_5H_3FIN) C, H, N.

2-Fluoropyridine-5-boronic Acid (17). To a stirred solution of 700 mg of **16** (3.14 mmol) in 1.0 mL of THF at −78 °C under nitrogen was added 1.9 mL of a 2.5 M solution of *n*-BuLi (4.71 mmol) in hexanes dropwise down the side of the flask. After 0.5 h, 1.1 mL of $(I\text{-}PrO)_3B$ (4.71 mmol) was added, and the resulting brown slurry was warmed to 0 °C. After 1 h, the reaction mixture was warmed to room temperature, and 50 mL of 10% hydrochloric acid was added. After 15 min, the mixture was neutralized to pH = 7 with 3 N aqueous NaOH solution, saturated with NaCl, and extracted with three 70 mL portions of Et_2O. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 300 mg (68%) of 2-fluoropyridine-5-boric acid (**17**) as a white solid. The analytical sample was purified by recrystallization from ethyl acetate at room temperature (mp 190−191 °C): ^{1}H NMR (5 μL of CD_3OD in $CDCl_3$) δ (ppm) 3.59 (s, 2H), 6.94 (ddd, J = 1.9, 8.2, 1H), 8.22 (m, 1H), 8.50 (s, 1H). Anal. ($C_5H_5BFO_2N$) 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 37000*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 of 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 binding 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 35000*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 of 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 μM (−)-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.[22] 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 8−12 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. A total of 8−12 mice were treated per dose, and a minimum of four doses was performed for dose−response curve determination.

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

References

(1) Holladay, M. W.; Cosford, N. D. P.; McDonald, I. A. Natural products as a source of nicotinic acetylcholine receptor modulators and leads for drug discovery. In *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*; Arneric, S. P., Brioni, J. D., Eds.; Wiley-Liss: New York, 1999; pp 253−270.

(2) Liang, F.; Navarro, H. A.; Abraham, P.; Kotian, P.; Ding, Y.-S.; Fowler, J.; Volkow, N.; Kuhar, M. J.; Carroll, F. I. Synthesis and nicotinic acetylcholine receptor binding properties of exo-2-(2′-fluoro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane: A new positron emission tomography ligand for nicotinic receptors. *J. Med. Chem.* **1997**, *40*, 2293−2295.

(3) Decker, M. W.; Arneric, S. P. Nicotinic acetylcholine receptor-targeted compounds: A summary of the development pipeline and therapeutic potential. In *Neuronal Nicotinic Receptors: Pharmacology and Therapeutic Opportunities*; Arneric, S. P., Brioni, J. D., Eds.; Wiley-Liss: New York, 1999; pp 395−411.

(4) Glennon, R. A.; Dukat, M. Central nicotinic receptor ligands and pharmacophores. *Pharm. Acta Helv.* **2000**, *74*, 103−114.

(5) Holladay, M. W.; Dart, M. J.; Lynch, J. K. Neuronal nicotinic acetylcholine receptors as targets for drug discovery. *J. Med. Chem.* **1997**, *40*, 4169−4194.

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

(7) Ding, Y.-S.; Gatley, S. J.; Fowler, J. S.; Volkow, N. D.; Aggarwal, D.; Logan, J.; Dewey, S. L.; Liang, F.; Carroll, F. I.; Kuhar, M. J. Mapping nicotinic acetylcholine receptors with PET. *Synapse* **1996**, *24*, 403−407.

(8) Ding, Y.-S.; Liang, F.; Fowler, J. S.; Kuhar, M. J.; Carroll, F. I. Synthesis of [^{18}F]norchlorofluoroepibatidine and its *N*-methyl derivative: New PET ligands for mapping nicotinic acetylcholine receptors. *J. Labelled Compd. Radiopharm.* **1997**, *39*, 827−832.

(9) Ding, Y.-S.; Molina, P. E.; Fowler, J. S.; Logan, J.; Volkow, N. D.; Kuhar, M. J.; Carroll, F. I. Comparative studies of epibatidine derivatives [^{18}F]NFEP and [^{18}F]N-methyl-NFEP: Kinetics, nicotine effect, and toxicity. *Nucl. Med. Biol.* **1999**, *26*, 139−148.

(10) Gatley, S. J.; Ding, Y.-S.; Brady, D.; Gifford, A. N.; Dewey, S. L.; Carroll, F. I.; Fowler, J. S.; Volkow, N. D. In vitro and ex vivo autoradiographic studies of nicotinic acetylcholine receptors using [^{18}F]fluoronorchloroepibatidine in rodent and human brain. *Nucl. Med. Biol.* **1998**, *25*, 449−454.

(11) Scheffel, U.; Taylor, G. F.; Kepler, J. A.; Carroll, F. I.; Kuhar, M. J. In vivo labeling of neuronal nicotinic acetylcholine receptors with radiolabeled isomers of norchloroepibatidine. *NeuroReport* **1995**, *6*, 2483−2488.

(12) Davila-Garcia, M. I.; Musachio, J. L.; Perry, D. C.; Xiao, Y.; Horti, A.; London, E. D.; Dannals, R. F.; Kellar, K. J. [^{125}I]IPH, an epibatidine analog, binds with high affinity to neuronal nicotinic cholinergic receptors. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 445−451.
(13) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. Total synthesis of (±)-epibatidine. *Tetrahedron Lett.* **1994**, *35*, 9297−9300.
(14) Clayton, S. C.; Regan, A. C. A total synthesis of (±)-epibatidine. *Tetrahedron Lett.* **1993**, *34*, 7493−7496.
(15) Kotian, P. L.; Carroll, F. I. Synthesis of (+)- and (−)-epibatidine. *Synth. Commun.* **1995**, *25*, 63−71.
(16) 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.
(17) Danso-Danquah, R.; Bai, X.; Zhang, X.; Mascarella, S. W.; Williams, W.; Sine, B.; Bowen, W. D.; Carroll, F. I. Synthesis and σ binding properties of 2′-substituted 5,9α-dimethyl-6,7-benzomorphans. *J. Med. Chem.* **1995**, *38*, 2978−2985.
(18) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. Total synthesis and determination of the absolute configuration of epibatidine. *J. Org. Chem.* **1994**, *59*, 1771−1778.
(19) Cheng, Y.-C.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% inhibition (I_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(20) Navarro, H. A.; Zhong, D.; Abraham, P.; Xu, H.; Carroll, F. I. Synthesis and pharmacological characterization of [(^{125})I]iodomethyllycaconitine ([(^{125})I]iodo-MLA). A new ligand for the α_7 nicotinic acetylcholine receptor. *J. Med. Chem.* **2000**, *43*, 142−145.
(21) Hylden, J. L.; Wilcox, G. L. Intrathecal morphine in mice: A new technique. *Eur. J. Pharmacol.* **1980**, *67*, 313−316.
(22) D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74−79.
(23) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacologic Calculations with Computer Programs*; Springer-Verlag: New York, 1987.
(24) Badio, B.; Daly, J. W. Epibatidine, a potent analgetic and nicotinic agonist. *Mol. Pharmacol.* **1994**, *45*, 563−569.
(25) Houghtling, R. A.; Davila-Garcia, M. I.; Kellar, K. J. Characterization of (±)-[^{3}H]epibatidine binding to nicotinic cholinergic receptors in rat and human brain. *Mol. Pharmacol.* **1995**, *48*, 280−287.
(26) Gnadisch, D.; London, E. D.; Terry, P.; Hill, G. R.; Mukhin, A. G. High affinity binding of [^{3}H]epibatidine to rat brain membranes. *NeuroReport* **1999**, *10*, 1631−1636.
(27) Horti, A. G.; Scheffel, U.; Kimes, A. S.; Musachio, J. L.; Ravert, H. T.; Mathews, W. B.; Zhan, Y.; Finley, P. A.; London, E. D.; Dannals, R. F. Synthesis and evaluation of *N*-[^{11}C]methylated analogues of epibatidine as tracers for positron emission tomographic studies of nicotinic acetylcholine receptors. *J. Med. Chem.* **1998**, *41*, 4199−4206.
(28) Dukat, M.; Dowd, M.; Damaj, I.; Martin, B.; El-Zahabi, M. A.; Glennon, R. A. Synthesis, receptor binding and QSAR studies on 6-substituted nicotine derivatives as cholinergic ligands. *Eur. J. Med. Chem.* **1999**, *34*, 31−40.

JM0100178