Synthesis, Nicotinic Acetylcholine Receptor Binding, and Antinociceptive Properties of 3′-Substituted Deschloroepibatidine Analogues. Novel Nicotinic Antagonists

F. Ivy Carroll,*,† Wei Ma,† Yasuno Yokota,† Jeffrey R. Lee,† 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, Medical College of Virginia Commonwealth University, Richmond, Virginia 23298

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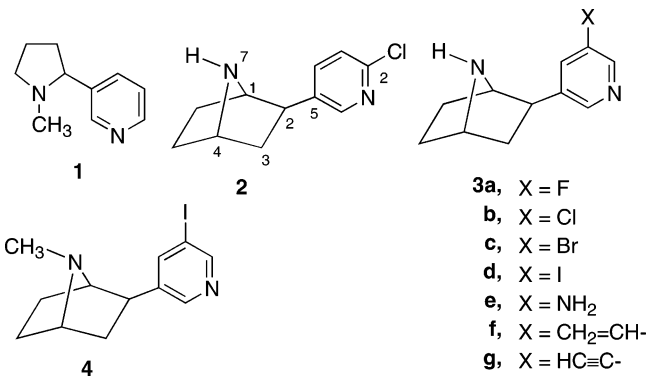
A series of 3′-substituted deschloroepibatidine analogues (**3a**−**g** and **4**) showed high affinity for α4β2 binding and relatively weak affinity for α7 nAChRs. The 3′-ethynyl (**3g**) and 3′-fluoro (**3a**) analogues with K_i values of 0.02 and 0.037 nM, respectively, were the most potent. Even though the α4β2 binding affinity of several of the analogues were equal to that of epibatidine, all of the compounds were weak agonists in the antinociceptive, hypothermia, and spontaneous activity test in mice. In contrast, all of the compounds were functional antagonists of nicotine-induced antinociception. In general, compounds **3a**−**g** and **4** were more potent in the tail-flick assay than the hot-plate test. For example, the 3′-fluoro analogue **3a** and the *N*-methyl-3′-iodo analogue **4** showed AD_{50} values of 0.07 and 0.04 μg/kg, respectively, in the tail flick test and only 35 and 0% inhibition at 20 and 10 μg/kg in the hot-plate assay, respectively. 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. The high affinity of the *N*-methyl-3′-iodo analogue **4** combined with its weak agonist and potent antagonist activity suggests that carbon-11 and iodine-123 analogues may be useful as PET and SPECT ligands, respectively, for studying nAChRs in vivo.

Nicotine (**1**) produces a number of behavioral effects and is one of the most abused reinforcing agents.[1] It is well documented that nicotinic cholinergic receptor (nAChR) ligand gated ion channels are the body's target for nicotinic actions.[2] These receptors exist in multiple subtypes and are widely distributed throughout the central and peripheral nervous systems including several regions of the brain, and there is wide diversity in the structure of nAChRs.[3,4] There are currently two major classes of neuronal nicotinic receptors identified in rat and human brain based on whether they demonstrate high affinity binding for either [^{3}H]nicotine ([^{3}N]-**1**) or [^{125}]α-bungarotoxin ([^{125}I]α-BTX)[5] now known to predominately, if not exclusively, correlate with a α4β2 nAChR[6,7] and α7 nAChR, respectively.[5,8−13] The fact that nAChRs plays a role in various neuropathological and physiological states, including Parkinson's disease, Alzheimer's disease, pain, tobacco dependency, schizophrenia, anxiety, and depression, has resulted in a renewed interest in characterizing the pharmacophore for the α4β2 nAChR.[14−18]

Epibatidine (**2**), a compound isolated from the skin of the Ecuadorian frog, *Epipidobates tricolor*, is a high affinity nonselective ligand for nAChRs.[14,19] To further characterize the nAChR pharmacophores, we, and others, have been conducting structure−activity relationship (SAR) studies on epibatidine (**2**).[20,21] In this study, we report the synthesis, nAChR binding affinity, and pharmacological properties of 3′-substituted deschloroepibatidine analogues (**3a**−**g**). The 3′-iodo analogue **3d** was converted to the *N*-methyl analogue **4** and prepared as a potential positron emission tomography (PET) ligand.



All of the analogues **3a**−**g** and **4** showed high affinity for nAChR; however, relative to epibatidine, they showed weak agonist activity in the mouse antinociception and body temperature tests. Importantly, all compounds were potent nAChR functional antagonists of nicotine's antinociceptive effects in the tail-flick procedure.

Chemistry. Scheme 1 outlines the synthesis of 3′-substituted deschloroepibatidine analogues of **3a**,**b**,**d**,**e** and **4**. Catalytic reductive dechlorination of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-amino-2′-chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**5**)[22] using 10% palladium on carbon catalyst in ethanol provided the intermediate 7-*tert*-butoxy-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo-

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

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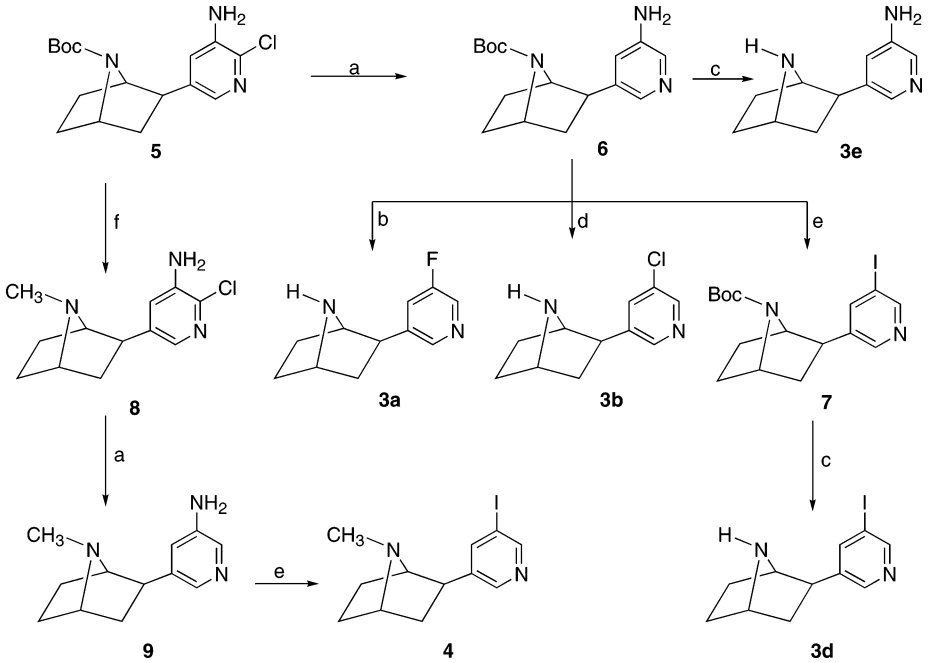
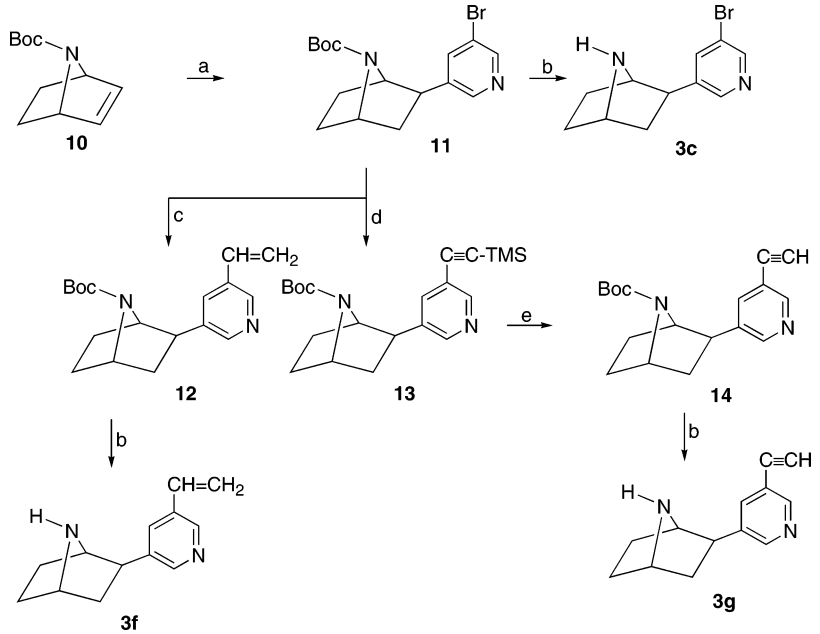
Scheme 1[a]



[a] Reagents and conditions: (a) 10% Pd/C, C_2H_5OH; (b) HF−pyridine, $NaNO_2$; (c) CF_3CO_2H (d) HCl, CuCl, $NaNO_2$; (e) isoamyl nitrate, CH_2I_2 HI; (f) $LiAlH_4$, THF.

Scheme 2[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, $(n\text{-}C_4H_9)_4N^+Cl^-$, KO_2CH, DMF, 80 °C, 3,5-dibromopyridine; (b) CF_3CO_2H, CH_2Cl_2; (c) $CH_2{=}CHSn(C_4H_9)_3$, $Pd_2(dba)_3$, NMP, TFP, 80 °C; (d) HC≡CTMS, $Pd(Cl)_2[PC_6H_5)_3]_2$, $[(CH_3)_2CH]_2NH$, CuI; (e) $C_4H_9)_4N^+F^+$, THF.

[2.2.1]heptane (**6**). Diazotization of **6** with sodium nitrite in pyridine containing 70% hydrogen fluoride−pyridine affected conversion of the 3-amino group to a fluoro group and deprotection of the *N*-*tert*-butoxycarbonyl group to give the 3-fluoro analogue **3a**. Diazotization of **6** with sodium nitrite in hydrochloric acid in the presence of cuprous chloride yielded the 3-chloro analogue **3b**. Diazotization of **6** with isoamyl nitrite containing hydroioidic acid in methylene iodide gave the 3-iodo intermediate **7**. Treatment of **6** and **7** with trifluoroacetic acid provided the 3-amino and 3′-iodo analogues **3e** and **3d**, respectively. Resolution of **3d** with (+)- and (−)-di-*p*-toluoyltartaric acid afforded (−)- and (+)-**3d**. The *N*-methyl-3′-iodo analogue **4** was prepared from **5.** Lithium aluminum hydride reduction of **5** yielded 7-methyl-2-*exo*-(2′-chloro-3′-amino-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**). Catalytic reductive dechlorination of **8** using 10% palladium on carbon as catalyst provided the *N*-methyl-3′-amino intermediate **9**. Diazotization of **9** using isoamyl nitrite in methylene iodide in the presence of hydroiodic acid yielded **4**.

The 3-bromo- (**3c**), 3-vinyl- (**3f**), and the 3-ethynyl- (**3g**) analogues were prepared as shown in Scheme 2. Reductive palladium acetate-catalyzed addition of 3,5-dibromopyridine to 7-*tert*-butoxycarbonyl-7-azabicyclo-[2.2.1]hept-2-ene (**10**) in DMF containing tetrabutylam-

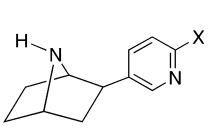
monium chloride and potassium formate at 80 °C provided the intermediate 7-*tert*-butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**11**). Coupling of **11** with vinyltributyltin, catalyzed by tris(dibenzylideneacetonyl)bis-palladium, in 1-methyl-2-pyrrolidinone (NPM) containing tris(2-furyl)phosphine (NSP) at 80 °C, afforded the butoxycarbonyl-protected 3′-vinyl intermediate **12**. The reaction of **11** with trimethylsilylacetylene in the presence of a catalytic amount of copper(I) iodide and bis(triphenylphosphine)-palladium(II) chloride in degassed disopropylamine in a sealed tube at 50 °C produced **13**. Removal of the silyl protecting group with tetrabutylammonium fluoride in THF afforded the *tert*-butoxycarbonyl 3′-ethynyl intermediate **14**. Treatment of **11**, **12**, and **14** with trifluoroacetic acid in methylene chloride yielded the 3′-bromo, 3′-vinyl, and 3′-ethynyl analogues **3c**,**f**,**g**, respectively.

Biology. The K_i values for the inhibition of [^{3}H]-epibatidine ([^{3}H]-**2**) binding at the α4β2 nAChR in male rat cerebral cortex for the 3-substituted epibatidine analogues **3a**−**g** and **4** as well as for nicotine and (+)-epibatidine [(+)-**3**] are listed in Table 1. The binding assays were conducted and the K_i values calculated as previously described.[22] The compounds were also evaluated at 50 nM for inhibition of [^{125}I]iodo-MLA binding at the α7 nAChR using conditions previously reported except that the assays were run in a volume of 0.25 mL, and the final assay concentration of [^{125}I]iodo-MLA was 45 pM.[23] The K_i value was determined for any compound that inhibited [^{125}I]iodo-MLA binding by at least 50% using procedures similar to those described for [^{3}H]-1 binding[24] and an [^{125}I]iodo-MLA K_d of 1.98 nM.

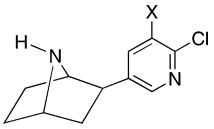
Compounds **3a**−**g** were evaluated in two acute pain models, the tail-flick and the hot-plate tests, and the results for compounds **3a**−**g** and **4** along with results for epibatidine and nicotine are listed in the Table 1.[25] In the tail-flick method of D'Amour and Smith,[26] the tail is exposed to a heat lamp and the amount of time taken for the animal to move (flick) its tail away from the heat is recorded. A control response (2−4 s) was determined for each mouse before treatment, and a test latency was determined after drug administration. The method used for the hot-plate test is a modification of those described by Eddy and Leimbach[27] and Atwell and Jacobson.[28] 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 8−12 s. The reaction time was scored when the animal jumped or licked its paws. The mice were tested 5 min after sc injections of nicotinic ligands for the dose−response evaluation. Antinociceptive response was calculated as percentage of maximum possible effect (% MPE, where %MPE = [(test − control)/(maximum latency − control) × 100]). Eight mice per dose were injected sc and tested at various times thereafter to establish a time course when needed. The effects of the compounds on body temperature and spontaneous activity were also measured (Table 1). ED_{50} values with 95% confidence limits for behavioral data were calculated by unweighted least squares linear regression as described by Tallarida and Murray.[29] For the antagonist experiments, mice were pretreated sc with either saline or epibatidine analogues 10 min before nicotine. Nicotine was administered at a dose of 2.5 mg/kg, sc (an ED_{84} dose), and mice were tested 5 min later. ED_{50} and AD_{50}values with 95% confidence limits were determined.

Results and Discussion

A number of epibatidine analogues have been prepared, and their nAChR radioligand binding and pharmacological properties have been determined.[20] For example, replacement of the 2′-chloro group of epibatidine with a hydrogen, fluoro, bromo, or iodo group provided analogues **16a**−**d** with affinity for the α4β2 nAChR essentially identical to that of epibatidine.[24] Replacement of the 2′-chloro group with an amino group resulted in an analogue **16e** with nearly the same affinity as nicotine.



16a, X = H
b, X = F
c, X = Br
d, X = I
e, X = NH_2

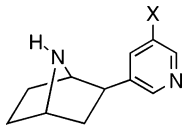


17a, X = Cl
b, X = F
c, X = Br
d, X = I
e, X = NH_2
f, X = C_6H_5
g, X = N_3

The K_i values of a number of 3′-substituted epibatidine analogues **17a**−**g** at α4β2 nAChR were also very similar to the K_i values of epibatidine (**2**).[22] In contrast, the affinity for α7 nAChR of **17a**,**b**,**e**,**g** were much greater than that of epibatidine. With the exception of **17e**, all the analogues were agonists in the tail-flick and hot-plate assays. Compound **17e** was a potent nAChR antagonist with weak agonist activity in the tail-flick test. In this study, we report the α4β2- and α7-nAChR binding affinity and pharmacological properties of the 3′-substituted deschloroepibatidine analogues **3a**−**g** and the *N*-methyl analogue **4** (Table 1). The analogues **3a**−**d** possessing electron-withdrawing 3′-fluoro, 3′-chloro, 3′-bromo, and 3′-iodo substitutents, respectively, as well as the electron-releasing 3′-amino analogue **3e** and the 3′-ethynyl analogue **3g** have affinity for the α4β2 nAChR similar to epibatidine. The K_i values of both (+)- and (−)-**3d** were essentially identical to that of racemic (±)−**3d**. The 3′-ethynyl (**3g**) and 3′-fluoro (**3a**) analogues with K_i values of 0.02 and 0.037 nM relative to epibatidine of 0.026 nM were the most potent. The 3′-vinyl (**3f**) analogue was an order of magnitude less potent than epibatidine at α4β2 nAChR. *N*-Methylation of **3d** to give **4** resulted in a doubling of the α4β2 affinity. With the exception of compound **4**, the analogues showed equal or less potency for α7 nAChR than epibatidine. Compound **4** with a K_i value of 33.2 nM was six times more potent at α7 nAChR than epibatidine.

Compounds **3a**−**g** and **4** were tested for antinociception using the tail-flick and hot-plate tests in male ICR mice using previously reported procedures.[25,26] The effects of the compounds on body temperature and locomotor activity were also measured (Table 1). Even though compounds **3a**−**g** had affinities for the α4β2 nAChR similar to epibatidine and compounds **3f** and **3g** were only 1 order of magnitude lower than epibati-

Table 1. Radioligand Binding and Antinociception Data for 3′-Substituted Deschloroepibatidine Analogues[a]



compd[a]	X	αβ [^{3}H]-epibatidine[b] (K_i, nM) (Hill slope)	α7 [^{125}I]iodo-MLA (K_i, nM) (Hill slope)	tail-flick, ED_{50} μg/kg	hot-plate, ED_{50} μg/kg	hypothermia, ED_{50} μg/kg	spontaneous activity, ED_{50} μg/kg	AD_{50} (μg/kg) tail-flick	AD_{50} (μg/kg) hot-plate	AD_{50} (μg/kg) body temp
3a	F	0.037 ± 0.001 (0.90 ± 0.01)	>1000	80 (50−120)	50 (30−70)	150 (100−320)	23 (10−30)	0.07 (0.002−0.2)	35% @20	0% @ 0.02
3b	Cl	0.055 ± 0.001 (0.98 ± 0.01)	50.6 ± 6.2	300 (190−380)	230 (170−320)	150 (100−320)	40 (20−60)	0.2 (0.1−0.7)	15 (4−60)	0% @ 0.02
3c	Br	0.050 ± 0.002 (0.99 ± 0.02)	164 ± 10 (1.97 ± 0.15)	1200 (1000−1400)	570 (200−940)	70 (50−100)	100 (10−700)	15 (6−40)	0.78 (51−130)	0% @ 0.01
3d	I	0.059 ± 0.001 (0.86 ± 0.02)	150 ± 6.3 (1.82 ± 0.13)	800 (500−1300)	900 (500−1300)	780 (500−1100)	130 (30−500)	0.1 (0.09−0.2)	0.24 (0.1−0.3)	0% @ 0.01
(+)-**3d**	I	0.045 ± 0.007 (0.95 ± 0.07)	179 ± 30 (2.29 ± 1.1)	6% @ 5000	780 (460−1310)	60 (36−134)	91 (22−379)	1.2 (0.3−4.4)	15% @ 20	
(−)-**3d**	I	0.048 ± 0.007 (1.01 ± 0.03)	156 ± 42 (1.72 ± 0.26)	940 (600−1460)	210 (70−640)	480 (300−850)	351 (109−1134)	0.11 (0.05−0.3)	15% @ 10	
3e	NH_2	0.097 ± 0.007 (0.93 ± 0.05)	732 ± 89 (1.61 ± 0.18)	4700 (3200−680)	3100 (2400−4100)	2700 (2300−4000)	900 (500−1500)	1.6 (5−90)	6.9 (0.8−9)	0% @ 0.01
3f	$H_2C{=}C$	0.260 ± 0.015 (1.0 ± 0.04)	344 ± 52 (600−1500)	1000 (600−1500)	800 (500−1200)	450 (300−800)	200 (130−300)	2.4 (0.4−30)	100 (17−600)	0% @ 0.01
3g	$HC{\equiv}C$	0.020 ± 0.001 (1.02 ± 0.04)	5% @ 50 nM	1000 (700−1500)	560 (240−1300)	50 (10−90)	1.0 (3−10)	6.0 (3−30)	0% @ 0.1	0% @ 0.01
4	I	0.029 ± 0.003 (0.92 ± 0.16)	33.2 ± 8.8 (1.81 ± 0.22)	600 (400−800)	370 (250−500)	340 (10−80)	30 (90−120)	0.04 (0.01−0.8)	0% @ 10 μg/kg	0% @ 10 μg/kg
nicotine[c]		1.50 ± 0.30		1300 (500−1800)	650 (250−850)	1000 (600−2100)	500 (150−780)			
2		0.026 ± 0.002	198	6.0	4.0	4.0	1.0			

[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] This is the *N*-methyl analogue of **3d**. [c] All data taken from ref 20.

dine, they all were weak agonists. Compound **3a** with ED_{50} values of 80 and 50 μg/kg in the tail-flick and hot-plate assays was the most potent analogues; however, this potency is thirteen and eight times weaker than epibatidine in the tail-flick and hot-plate test, respectively. The remaining analogues **3b**−**g** were 50−783 and 58−775 times weaker than epibatidine in the tail-flick and hot-plate assays, respectively. The ethynyl analogue **3g** with ED_{50} values of 50 and 1.0 μg/kg in the hypothermia and spontaneous activity assays was the most potent analogue in these tests. The other compounds **3a**−**c** and **3f**−**g** were 15−675 and 23−900 times weaker than epibatidine in these two assays. Even though the binding affinity for (+)- and (−)-**3d** were almost identical, they showed differences in their antinociceptive, hypothermia, and spontaneous activity. Compound (−)-**3d** with ED_{50} values of 940 and 210 μg/kg in the tail-flick and hot-plate assays was more potent than (+)-**3d**, which showed 6% inhibition at 5000 μg/kg in the tail-flick and an ED_{50} value of 780 μg/kg in the hot-plate test. In contrast, (+)-**3d** with ED_{50} values of 60 and 91 μg/kg in the hypothermia and spontaneous test was more potent than (−)-**3d**, which showed ED_{50} values of 480 and 351 μg/kg in these two tests.

The high affinity of **3a**−**g** for α4β2 nAChR combined with their weak agonist activity suggested that these analogues may act as nAChR functional antagonists in vivo. Indeed, all the analogues were potent antagonists with AD_{50}s of 0.07−15 μg/kg in the tail flick assay. Compounds **3b**−**d** and **3e**−**f** were also antagonists in the hot-plate assay. Compounds **3b** and **3c**−**f** were 2.4−75 times less potent antagonists in the hot-plate than the tail-flick assay. The most potent antagonist in the hot-plate assay was **3d** with an AD_{50} of 0.24 μg/kg. It is interesting to note that (−)-**3d** with the AD_{50} value of 0.11 μg/kg in the tail-flick assay is an order of magnitude more potent than (+)-**3d**, which has an AD_{50} values of 1.2 μg/kg. Surprisingly, even though (+)-**3d** has AD_{50} value of 0.24 μg/kg in the hot-plate assay, (+)- and (−)-**3d** show only 15% inhibition at 20 and 10 μg/kg, respectively. Compounds **3a**, **3g**, and **4** were not active in the hot-plate assay. None of the compounds were antagonists in the body temperature assay.

It is interesting to note that *N*-methylation of **3d** to give **4** had little effect on the agonist activity. In contrast, the antagonistic potency of **4** in the tail-flick assay was increased by 2.5-fold (0.1 to 0.04 μg/kg). Interestingly, **3d** had an AD_{50} of 0.24 μg/kg in the hot-plate assay, whereas, **4** did not show any antagonism at 10 μg/kg.

In summary, substitution with either an electron-donating or -withdrawing group at position-3 dramatically reduced agonist potency in all behavioral measures while having relatively little effect on receptor affinity. On the other hand, these analogues were extremely potent antagonists of nicotine-induced effects in the tail-flick test, and to a lesser degree, in the hot-plate test. The high antagonist potency of these compounds in the tail-flick test, compared to that of the hot-plate test, indicates that spinal pain pathways were antagonized preferentially over supraspinal ones. Interestingly, none of the compounds altered the hypothermic effect of nicotine. The differing potencies of these compounds in the three pharmacological tests suggest that different nAChR subtypes may be mediating the effect of nicotine. Since the tissue preparation used in our assays contains predominately α4β2 nAChRs, selectivity of these compounds at other αβ nAChR subtypes expressed at lower levels cannot be detected. Thus, the weak correlation we observed between αβ binding affinity and antagonist potency may be the result of effects coupled to non-α4β2 nAChRs. Moreover, for the most potent antagonists, we do not believe α7 nAChRs play a predominant role in these effects, since based on their AD_{50} and [^{125}I]iodo MLA K_i values, the proportion of occupied α7 receptors would be approximately 2% or lower, compared to 85% or greater receptor occupancy for α4β2-containing nAChRs. Electrophysiological experiments using these compounds, which are beyond the scope of the present study, may shed light on the nAChR subtypes subserving spinal and supraspinal pain.

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 AMX 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 various solvents combined with a solvent mixture of 80% chloroform, 18% methanol, and 2% concentration ammonium hydroxide (CMA).

The [^{3}H]epibatidine was purchased from Perkin-Elmer, Inc. (Boston, MA). The [^{125}]iodo-MLA was synthesized as previously reported.[23]

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (6). 7-*tert*-Butoxycarbonyl-2-*exo*-(3′-amino-2′-chloro-5′-pyridinyl-7-azabicyclo[2.2.1]heptane (**5**) (1.65 g, 0.0051 mol) was dissolved in EtOH (20 mL), and 10% Pd/C (1 g) was added. The mixture was shaken at 50 psi of hydrogen for 17 h at room temperature. The catalyst was removed by filtration through Celite. Removal of the solvent by rotary evaporation afforded 1.20 g of **6** (83%) as beige solid: mp 181−183 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.47−1.61 (m, 2H), 1.61−1.83 (m 2H), 1.84 (m, 1H), 2.78 (m, 1), 3.64 (br s, 2H), 4.10 (br s, 1H), 4.36 (br s, 1H), 6.92 (s, 1H), 7.88 (s, 1H), 7.93 (s, 1H).

2-*exo*-(3′-Fluoro-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Hydrochloride (3a). To a solution of 7-*tert*-butoxycarbonyl-2-*exo*(3′-amino-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane (**6**) (150 mg, 0.51 mmol) in 70% solution of HF−pyridine (3 mL) at 0 °C was added sodium nitrite (300 mg, 4.4 mmol), and stirring was continued for an additional 30 min. The mixture was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 3 × 50 mL of ethyl acetate, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography using (6:1) ethyl acetate:CMA to yield 70 mg (72%) of 2-*exo*-(3′-fluoro-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane (**3a**). ^{1}H NMR ($CDCl_3$) δ 1.50−1.66 (m, 5H), 1.89−1.96 (dd, 1H), 2.80−2.84 (dd, 1H), 3.60 (br s, 1H), 3.80 (br s, 1H), 7.55−7.59 (d, 1H), 8.28−8.32 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 30.17, 31.34, 40.34, 44.62, 56.29, 62.67, 121.23(121.47) ($^2J_{C-F}$ = 18.1 Hz), 135.37(135.676) ($^2J_{C-F}$ = 23.2 Hz), 144.18(144.23) ($^3J_{C-F}$ = 3.3 Hz), 144.90(144.941) ($^4J_{C-F}$ = 3.45 Hz), 157.99(161.38) ($^1J_{C-F}$ = 254 Hz).

To a stirred solution of 70 mg (0.365 mmol) of **3a** in 4 mL of methanol was added dropwise 1 M HCl in ether (4 mL) over 30 min at room temperature. The solvent was removed under reduced pressure. The residue was recrystallized from methanol/ether mixtures to give **3a** 2HCl: mp 155−160 °C; Anal. ($C_{11}H_{15}Cl_2FN_2 \cdot 1.75H_2O$) (C, H, N).

2-*exo*-(3′-Chloro-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Dihydrochloride (3b). To a solution of 7-*tert*-butoxy-

carbonyl-2-*exo*-(3′-amino-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane (**6**) (136 mg, 0.464 mmol) in concentrated hydrochloric acid (5 mL) were added sodium nitrite (800 mg, 11.6 mmol) and copper (I) chloride (800 mg, 8.0 mmol) in portions over 30 min, and stirring was continued for 1 h at 0 °C. After 3 h at room temperature, the mixture was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 3 × 50 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography using (6:1) ethyl acetate:CMA to yield 60 mg (61.7%) of **3b**. ^{1}H NMR ($CDCl_3$) δ 1.52−1.68 (m, 5H), 1.88−2.01 (dd, 1H), 2.76−2.81 (dd, 1H), 3.60 (br s, 1H), 3.81 (br s, 1H), 7.82 (s, 1H), 8.38 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 30.57, 31.77, 40.69, 45.18, 56.75, 63.05, 132.31, 134.87, 142.0, 146.61, 147.37. Compound **3b** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 188−191 °C; Anal. ($C_{11}H_{15}Cl_3N_2 \cdot 2H_2O$).

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (11). To a resealable reaction tube containing DMF (22 mL) were added 7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]-hept-2-ene (**10**) (1 g, 5.1 mmol), 3,5-dibromopyridine (3 g, 12.5 mmol), $Pd(OAc)_2$ (60.7 mg, 0.27 mmol), tetrabutylammonium chloride (355.7 mg, 1.28 mmol), and potassium formate (1.05 g, 12.5 mmol). The reaction tube was sealed under nitrogen, placed into an 80 °C oil bath, and stirred for 48 h. The reaction mixture was poured into NH_4OH/H_2O (1:1) and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic extracts were dried with sodium sulfate and concentrated. The residue was purified by flash chromatography, eluting with (2:1) hexane/ethyl acetate to yield 0.42 (22%) of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane as a colorless solid (**11**); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H) 1.50−1.85 (m, 5H), 1.95−2.04 (m, 1H, CH_2), 2.85−2.89 (m, 1H, m, CH), 4,29 (br s, 1H), 4,39 (br s, 1H), 7.81 (s, 1H, pyridinyl), 8.40 (s, 1H, m, pyridinyl) 8.51 (s, 1H, m, pyridinyl).

2-*exo*-(3′-Bromo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Dihydrochloride (3c). To a solution of 7-*tert*-butoxycarbonyl-2-*exo*(3′-bromo-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane (**11**) (100 mg, 0.283 mmol) in methylene chloride (3 mL) at 0 °C was added trifluoroacetic acid (3 mL), and the mixture was allowed to stir at room temperature for 30 min. The reaction mixture was poured into NH_4OH/H_2O (1:1, 100 mL), extracted with 3 × 30 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography eluted with (1:3) ethyl acetate:CMA to yield 58 mg (80%) of 2-*exo*(3′-bromo-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane **(3c)** as colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.53−1.66 (m, 5H), 1.90−1.93 (m, 1H, CH2), 2.77−2.80 (m, 1H, CH), 2.90 (br s, 1H, NH), 3.64 (br s, 1H), 3.94 (br s, 1H) 7.96 (s, 1H, pyridinyl), 8.43 (s, 1H, pyridinyl), 8.49 (s, 1H, pyridinyl); ^{13}C NMR ($CDCl_3$) δ 30.29, 31.59, 40.48, 45.14, 56.89, 63.05, 121.25, 137.71, 144.04, 147.67, 148.86.

Compound **3c** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 189−192 °C; Anal. ($C_{11}H_{15}Cl_2Br \cdot 2.5\ H_2O$): C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (7). A solution of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**6**) (150 mg, 0.51 mmol), methylene iodide (5 mL), and isoamyl nitrite (1.35 mL) was allowed to stir at room temperature for 30 min. HI (0.015 mL) was then added. After 24 h, the reaction mixture was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 3 × 50 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography eluting with (9:1) ethyl acetate:CMA to yield 70 mg (34%) of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**7**). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.50−1.62 (m, 2H), 1.79−1.86 (m, 3H), 1.86−2.03 (m, 1H), 2.80−2.84 (m, 1H), 4.20 (br s, 1H), 4.39 (br s, 1H), 7.27 (s, 1H), 8.43 (s, 1H), 8.67 (s. 1H); ^{13}C NMR ($CDCl_3$) δ 28.73, 29.67, 40.13, 45.28, 55.70, 61.62, 79.92, 93.71, 142.51, 143.14, 147.3, 153,60, 154.84.

2-*exo*-(3′-Iodo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Dihydrochloride (3d). To a solution of 7-*tert*-butoxycarbonyl-2-*exo*(3′-iodo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**7**) (70 mg, 0.173 mmol) in methylene chloride (2 mL) at 0 °C was added trifluoroacetic acid (2 mL), and the mixture was allowed to stir at room temperature for 30 min. The reaction mixture was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 3 × 50 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography, eluting with (3:1) ethyl acetate:CMA to yield 47 mg (90%) of 2-*exo*-(3′-iodo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**3d**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.48−1.69 (m, 5H), 1.86−1.94 (m, 1H, CH2) 2.69−2.74 (m, 1H, CH), 3.59 (br s, 1H), 3.79 (br s, 1H), 8.13 (s, 1H, pyridinyl) 8.45 (s. 1H, pyridinyl), 8.64 (s, 1H, pyridinyl); ^{13}C NMR ($CDCl_3$) δ 30.12, 31.35, 40.25, 44.87, 56.29, 62.56, 93.71, 142.87, 144.28, 147.59, 153.23.

Compound **3d** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 223−226 °C; Anal. ($C_{11}H_{15}Cl_2IN_2 \cdot 0.25\ H_2O$): C, H, N.

Preparation of (−)- and (+)-2-*exo*(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane Dihydrochloride (−)-3d and (+)-3d). To a solution of (±)-2-*exo*(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**3d**) (1.79 g, 5.97 mmol) in EtOH (100 mL) was added (+)-di-*p*-toluoyl-D-tartaric acid (2.42 g, 6.27 mmol) in EtOH (100 mL). The reaction was kept at room temperature for 24 h. The first crystals were separated by filtration and dried under vacuum. The residual solution was concentrated and kept refrigerated. A second crop was separated by filtration and dried under vacuum. Six recrystallizations from EtOH gave material with $[\alpha]_D = +62.0°$ ($c = 0.49$, MeOH), HPLC (Chrown Tech Chiral-AGP, 4 × 150 mm, 5 μm, solvent A: 10 mM $KH_2PO_4 + K_2HPO_4$, pH = 7.0, B: CH_3OH, 5%B, flow rate: 1.0 mL/min, 235 nm) indicated >99% ee. The salt was treated with an aqueous solution of Na_2CO_3, extracted with Et_2O, dried over Na_2SO_4, concentrated, and dried under vacuum. The free amine (100 mg) was dissolved in 5 mL of absolute MeOH. To this stirred solution was added dropwise 3 mL of 1 M HCl in Et_2O. The solid obtained on concentration was dissolved in 1 mL of absolute MeOH and kept in a container filled with dry Et_2O for a day. The crystals that formed were separated by filtration, dried under vacuum, crushed into powder, and dried under vacuum for a week to give (−)-2-*exo*-(3′-iodo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane dihydrochloride [(−)-**3d**]: mp 233−244 °C; $[\alpha]_D = -30.6°$ ($c = 0.25$, MeOH). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.66−2.0 (m, 5H), 2.25−2.33 (m, 1H), 3.32−3.37 (m, 1H), 4.22 (s, 1H), 4.40 (s, br, 1H), 8.38 (s, 1H), 8.64 (s, br, 1H), 8.77 (s, 1H); mass 301.6 (ESI, turbo spray, M + 1). Anal. ($C_{11}H_{15}Cl_3IN_2\ 2H_2O$): C, H, N.

The residues from above were treated with an aqueous solution of Na_2CO_3, extracted with Et_2O, dried over Na_2SO_4, concentrated, dried under vacuum, and weighed. This solid (1.00 g) was dissolved in EtOH (100 mL), and (−)-di-*p*-toluoyl-L-tartaric acid (1.35 g, 3.50 mmol) in EtOH (100 mL) was added and kept at room temperature for 24 h. The resulting solids were recrystallized five times from ethanol to give crystals with $[\alpha]_D = +62.4°$ ($c = 0.51$, MeOH). The salt was basified with an aqueous solution of Na_2CO_3, extracted with Et_2O, dried over Na_2SO_4, concentrated, and dried under vacuum. The free amine (100 mg) was dissolved in 5 mL of absolute MeOH. To this solution was added 3 mL of 1 M HCl in Et_2O dropwise. The solid obtained was concentrated and dissolved in 1 mL of absolute MeOH and kept in a container filled with dry Et_2O for a day. The crystals that formed were separated by filtration, dried under vacuum, crushed into powder, and dried under vacuum for a week to give (+)-2-*exo*-(3′-iodo-5′pyridinyl)-7-azabicyclo[2.2.1]heptane dihydrochloride [(+)-**3d**]: mp 224−226 °C; $[\alpha]_D = +31.0°$ ($c = 0.26$, MeOH). ^{1}H NMR (MeOH-*d*, 300 MHz): Identical to the salt of (+) isomer and ($C_{11}H_{15}Cl_3IN_2$): C, H, N.

2-*exo*-(3′-Amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane Dihydrochloride (3e). Trifluoroacetic acid (2.0 mL) was

added to **6** (0.49 g, 0.0017 mol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temperature for 1 h and then added to NH_4OH/H_2O (1:1, 50 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography using CMA as eluent to afford **3e** (0.077 g, 24%) as an oil. The HCl salt was prepared by dissolving the free base in CH_2Cl_2 and adding ethereal HCl to give solids. The solids were dried in a heating pistol at 65 °C to afford **3e** as a beige solid: mp 252−254 °C; ^{1}H NMR (DMSO-d_6) δ 1.66−1.94 (m, 5H), 2.34 (t, 1H), 3.35 (m, 2H), 4.22 (bs, 1H), 4.51 (br s, 1H), 7.55 (s, 1H), 7.92 (s, 1H), 8.15 (s, 1H), 9.00 (br s, 1H), 9.48 (bs, 1H). Anal. ($C_{11}H_{17}Cl_2N_3 \cdot 0.33H_2O$): C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-vinyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (12). A solution of 7-*tert*-Butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**11**) (600 mg, 1.7 mmol) was dissolved in anhydrous NMP (10 mL) and treated with tris(2-furyl)phosphine (32.5 mg, 0.14 mmol), tris(dibenzylideneacetonyl)bis-palladium (32 mg, 0.07 mmol), and then with vinyltributyltin (1.1 mL, 3.82 mmol). The mixture was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 3 × 50 mL CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography eluting with (2:1) hexane/ethyl acetate to yield 240 mg (47%) of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-vinyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**12**). ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.49−1.88 (m, 5H), 1.96−2.04 (m, 1H, CH_2), 2.87−2.90 (m, 1H, CH), 4.23 (br s, 1H), 4.39 (br s, 1H), 5.33−5.38 (dd, 1H ABX), 5.78−5.86 (dd, 1H, ABX), 6.64−6.73 (dd, 1H, ABX), 7.69 (s, 1H, pyridinyl), 8.37 (s, 1H, pyridinyl), 8.45 (s, 1H, pyridinyl).

2-*exo*-(3′-Vinyl-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Dihydrochloride (3f). To a solution of 7-*tert*-butoxycarbonyl-2-*exo*(3′-vinyl-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**12**) (240 mg, 0.8 mmol) in methylene chloride (5 mL) at 0 °C, trifluoroacetic acid (5 mL) was added and allowed to stir at room temperature for 1 h. The reaction was poured into NH_4OH/H_2O (1:1, 150 mL), extracted with 4 × 50 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography using (1:1) ethyl acetate:CMA to yield 110 mg (69%) of 2-*exo*(3′-vinyl-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**3f**). ^{1}H NMR ($CDCl_3$) δ 1.47−172 (m, 5H), 1.80 (br s, 1H, NH), 1.88−1.96 (m, 1H, CH_2), 2.79−2.83 (m, 1H, CH), 3.60 (br s, 1H), 3.80 (br s, 1H), 5.33−5.37 (dd, 1H, ABX), 5.80−5.86 dd, 1H, ABX), 6.64−6.74 (dd, 1H, ABX), 7.75 (s, 1H, pyridinyl), 8.40 (s, 1H, pyridinyl), 8.45 (s, 1H, pyridinyl); ^{13}C NMR ($CDCl_3$) δ 30.39, 31.70, 40.58, 45.59, 56.82, 63.04, 116.25, 131.67, 133.02, 134.10, 142. 06, 146.18, 148.76

Compound **3f** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 278−280 °C; Anal. ($C_{13}H_{18}Cl_2N_2 \cdot 0.25H_2O$): C, H, N.

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-trimethylsilylacetylene-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (13). A solution of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-bromo-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**11**) (100 mg, 0.283 mmol) in 10 mL of diisopropylamine in an ACE pressure tube was deaerated by bubbling nitrogen through the mixture for 30 min. To this stirred solution were added CuI (0.106 g, 0.056 mmol) and bis-(triphenylphospine)-palladium (II) chloride (69.4 mg, 0.099 mmol) followed by trimethylsilylacetylene (0.142 mL, 0.99 mmol). The solution became dark quickly and solidified. The solution was briefly degassed as before. The vessel was sealed and stirred at 50 °C for 3 h and then at room temperature for 72 h. The reaction mixture was poured into NH_4OH/H_2O (1:1, 150 mL) and extracted with 3 × 50 mL CH_2Cl_2. The combined organic extracts were dried with sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with (3:1) hexane/ethyl acetate to produce 100 mg (98%) of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-trimethylsilylacetylene-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**13**). ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.45 (s, 9H), 1.50−1.86 (m, 5H), 1.95−2.03 (dd, 1H, CH_2), 2.85−2.89 (m, 1H, CH), 4.19 (br s, 1H), 4.41 (br s, 1H), 7.72 (s, 1H, pyridinyl), 8.39 (s, 1H, pyridinyl), 8.52 (s, 1H, pyridinyl).

7-*tert*-Butoxycarbonyl-2-*exo*-(3′-vinyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (14). A solution of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-trimethylsilylacetylene-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**13**) (100 mg, 0.274 mmol) in 10 mL of anhydrous THF at 0 °C was added 1 mL (1 mmol) of 1.0 M tetrabutylammonium fluoride in THF dropwise. The solution was stirred for 2 h with warming to room temperature. The solution was diluted with saturated sodium bicarbonate solution and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic extracts were dried with sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with (3:1) hexane/ethyl acetate to produce 80 mg (100%) of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-vinyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**14**). ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.53−1.87 (m, 5H), 1.96−2.04 (dd, 1H, CH_2), 2.86−2.90 (m, 1H, CH), 3.21 (s, 1H, C≡CH), 4.20 (br s, 1H), 4.40 (br s, 1H), 7.75 (s, 1H, pyridinyl), 8.45 (s, 1H, pyridinyl), 8.55 (s. 1H, pyridinyl).

2-*exo*-(3′-Ethynyl-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane Dihydrochloride (3g). To a solution of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-ethynyl-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**14**) (80 mg, 0.273 mmol) in methylene chloride (3 mL) at 0 °C was added trifluoroacetic acid (3 mL), and the mixture was allowed to stir at room temperature for 30 min. The reaction mixture was poured into NH_4OH/H_2O (1:1, 150 mL) extracted with 3 × 50 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography using (1:4) ethyl acetate:CMA to yield 40 mg (70%) of 2-*exo*(3′-ethynyl-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**3g**). ^{1}H NMR ($CDCl_3$) δ 1.48−1.67 (m, 5H), 1.88−1.95 (m, 1H, CH_2), 2.76−2.81 (m, 1H, CH), 3.20 (s, 1H, C≡CH), 3.59 (br s, 1H), 7.87 (s, 1H, pyridinyl), 8.48 (s, 1H, pyridinyl), 8.54 (s, 1H, pyridinyl); ^{13}C NMR ($CDCl_3$) δ 30.54, 31.75, 40.60, 45.39, 56.81, 63.03, 80.56, 81.17, 119.22, 138.07, 141.97, 149.20, 150.70.

Compound **3g** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 89 °C (dec); Anal. ($C_{13}H_{16}Cl_2N_2 \cdot 1.25H_2O$): C, H, N.

7-Methyl-2-*exo*-(2′-chloro-3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (8). To a solution of $LiAlH_4$ (2.69 g, 70.9 mmol) in dry THF (60 mL) at 0 °C, a solution of 7-*tert*-butoxycarbonyl-2-*exo*-(3′-chloro-3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**5**) (2.55 g, 7.88 mmol) in dry THF (20 mL) was added dropwise over 30 min. The reaction mixture was stirred overnight at room temperature. The reaction was poured into 250 mL of Na_2CO_3 saturated solution, filtered through Celite pad, extracted with 4 × 100 mL of CH_2Cl_2, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography eluting with (1:6) ethyl acetate:CMA to produce 700 mg (37%) of 7-methyl-2-exo-(2′-chloro-3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**). ^{1}H NMR ($CDCl_3$) δ 1.65−1.93 (m 6H), 2.01 (s, 3H, CH_3), 2.55−2.59 (dd, 1H), 3.13 (br s, 1H), 3.29 (br s, 1H), 4.05 (br s, 2H, NH_2), 7.36 (s, 1H, pyridinyl), 7.67 (s, 1H, pyridinyl).

7-Methyl-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo-[2.2.1]heptane (9). A solution of 7-methyl-2-*exo*-(2′-chloro-3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**) (700 mg, 2.94 mmol), 10% Pd/C (1 g) and methanol (40 mL) was placed into a Fisher-Porter tube under nitrogen. The tube was evacuated and refilled with hydrogen gas at 40 psi, and then the reaction was allowed to shake overnight for 15 h. The mixture was filtered through a Celite pad and concentrated in vacuo. Flash chromatography of the residue with (1:1) ethyl acetate:CMA yielded 500 mg (84%) of 7-methyl-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**9**). ^{1}H NMR ($CDCl_3$) δ 1.70−1.94 (m, 6H), 2.25 (s, 3H, CH_3), 2.57−2.60 (dd, 1H), 3.18 (br s, 1H), 3.29 (br s, 1H), 3.68 (br s, 2H, NH_2), 7.23 (s, 1H, pyridinyl), 7.90 (s, 2H, pyridinyl).

7-Methyl-2-*exo*-(3′-iodo-5′-pyridinyl)]-7-azabicyclo[2.2.1]-heptane Dihydrochloride (4). A solution of 7-methyl-2-*exo*-(3′-amino-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane (**9**) (500 mg, 2.47 mmol) in methylene iodide (30 mL) and isoamyl nitrite

(6.54 mL) was allowed to stir at room temperature for 30 min. HI (0.08 mL) was then added. After 24 h, the reaction was poured into NH_4OH/H_2O (1:1, 200 mL), extracted with 4 × 50 mL of CH_2Cl_2, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting with (1:3) ethyl acetate:CMA to yield 210 mg (27%) of 7-methyl-2-*exo*(3′-iodo-5′-pyridinyl)]-7-azabicyclo[2.2.1]heptane (**4**). ^{1}H NMR ($CDCl_3$) δ 1.68−1.95 (m, 6H), 2.26 (s, 3H, CH_3), 2.67−2.62 (dd, 1H), 3.17 (br s, 1H), 3.34 (br s, 1H), 8.22 (s, 1H), 8.48 (s, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) (12-C): 23.48, 24.45, 32.64, 39.54, 43.88, 59.10, 65.31, 91.66, 141.22, 42.98, 145.78, 151.15.

Compound **4** was converted to the dihydrochloride salt by a procedure similar to that used for **3a** and recrystallized from methanol/ether mixtures: mp 248−250 °C; Anal. ($C_{12}H_{17}Cl_2IN_2$): C, H, N.

[^{3}H]Epibatidine Binding Assay. The [^{3}H]epibatidine binding assays were conducted as previously reported.[24]

[^{125}I]Iodo-MLA Binding Assay.[30] These assays were conducted as previously described with the following modifications: the assay volume was 0.25 mL, the assays were run in Corning 3371 round-bottom polypropylene plates (Corning, Inc., Corning, NY), the final radioligand concentration was 45 pM, the assay buffer contained 0.15% BSA, and the K_i values were calculated from competition binding curve IC_{50} values using the Cheng−Prusoff equation[31] and an [^{125}I]iodo-MLA K_d of 1.98 nM.

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

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