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Brief Article

Synthesis and Pharmacological Characterization of *exo*-2-(2‘-Chloro-5-pyridinyl)-7-(*endo* and *exo*)-aminobicyclo[2.2.1]heptanes as Novel Epibatidine Analogues

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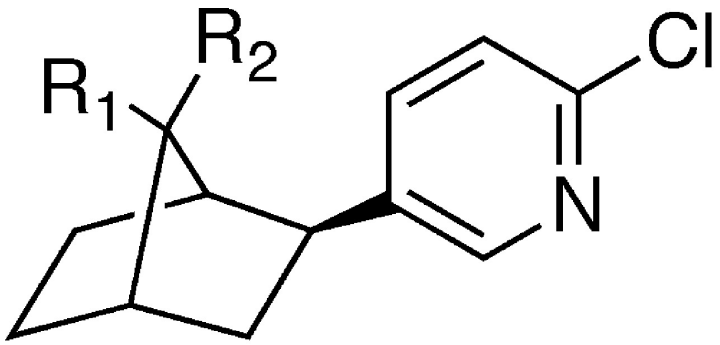

3a, $R_1 = H, R_2 = NH_2$

b, $R_1 = NH_2, R_2 = H$

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Synthesis and Pharmacological Characterization of *exo*-2-(2′-Chloro-5-pyridinyl)-7-(*endo* and *exo*)-aminobicyclo[2.2.1]heptanes as Novel Epibatidine Analogues

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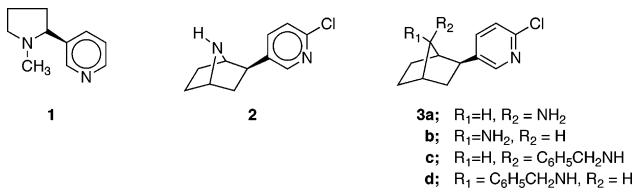
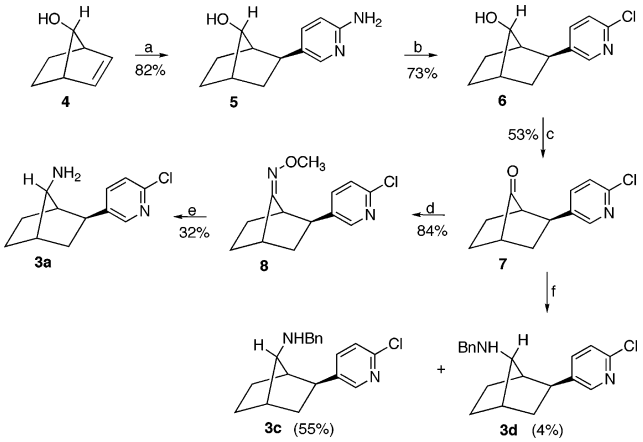
Procedures were developed for the synthesis of *exo*-(2′-chloro-5-pyridinyl)-7-(*endo* and *exo*)-amino[2.2.1]heptanes (**3a** and **3b**). The compounds were evaluated for binding to the α4β2 and α7 nicotinic acetylcholine receptors (nAChRs), for pharmacological activity in the mouse tail-flick and hot-plate assays, and for hypothermia and locomotor activity. Compounds **3a** and **3b** possessed α4β2 nAChR binding properties similar to those of (−)-nicotine and were nAChR agonists in all four mouse assays.

The nicotinic acetylcholine receptor (nAChR) subtype of acetylcholine (ACh) receptors is based on the agonist activities of the natural alkaloid nicotine (**1**). Since



nicotine produces a number of behavioral effects and is one of the most abused reinforcing agents, there has been considerable interest in the characterization of the pharmacophore for the α4β2 nAChR, a major subtype found in the brain.[1−5] Epibatidine (**2**), a compound isolated from the skin of the Ecuadorian frog, *Epipidobates tricolor*, has high affinity for α4β2 nAChRs but does have appreciable affinity for other nAChR subtypes.[5,6] To further characterize the nAChR pharmacophores, we and others have been conducting structure−activity relationship (SAR) studies on epibatidine (**2**).[7,8] In this study, we report the synthesis, nAChR binding affinity, and pharmacological properties of epibatidine analogues where the nitrogen in the 7-azabicyclo[2.2.1]-heptane ring has been moved outside the ring. Procedures were developed for the synthesis of *exo*-(2′-chloro-5-pyridinyl)-7-(*endo* and *exo*)-amino[2.2.1]heptanes **(3a** and **3b)** where the nitrogen has an *exo* or *endo* relationship to the pyridine ring. Benzyl substitutions on the *exo*- and *endo*-nitrogens (**3c** and **3d**) provided information about steric bulk. The compounds were evaluated for binding to the α4β2 and α7 nAChR and for effects on nociception, spontaneous activity, and rectal temperature. Compounds **3a** and **3b** were nAChR agonists with binding and pharmacological properties similar to those of (−)-nicotine. Thus, like (−)-nicotine, they were much less potent than epibatidine as nAChR agonists.

Scheme 1[a]



[a] Reagents: (a) 2-amino-5-iodopyridine, $Pd(OAc)_2$, KO_2CH, DMF, $(n\text{-}C_4H_9)_4N^+Cl^-$, 110 °C; (b) $NaNO_2$, HCl; (c) pyridine sulfur trioxide, $(C_2H_5)_3N$, DMSO; (d) CH_3ONH_2, K_2CO_3, C_2H_5OH; (e) B_2H_6, THF; (f) $C_6H_5CH_2NH_2$, benzene (Dean−Stark trap), $NaCNBH_3$.

Failure of **3c** and **3d** to bind to either receptor subtype reveals volume limitations at this site. The discovery that **3a** and **3b** bind to nicotinic receptors provides a new template for further exploration of the SAR of epibatidine.

Chemistry

The synthesis of **3a**, **3c**, and **3d** is outlined in Scheme 1. The reductive palladium acetate catalyzed addition of 2-amino-5-iodopyridine to *exo*-7-hydroxybicyclo[2.2.1]-heptane (**4**)[9] in dimethylformamide (DMF) containing potassium formate and tetrabutylammonium chloride at 110 °C provided an 82% yield of less sterically hindered *exo*-2-(2′-amino-5′-pyridinyl)-7-*exo*-hydroxybicyclo[2.2.1]heptane (**5**).[10,11] Diazotization of **5** using sodium nitrite in concentrated hydrochloric acid afforded the 2′-chloro compound (**6**) in a 73% yield. Oxidation of **6** using a pyridine sulfur trioxide complex in DMSO provided a 50% yield of the 7-oxo compound **7**. Potassium carbonate catalyzed condensation of **7** with methoxylamine in ethanol provided an 84% yield of the

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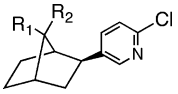
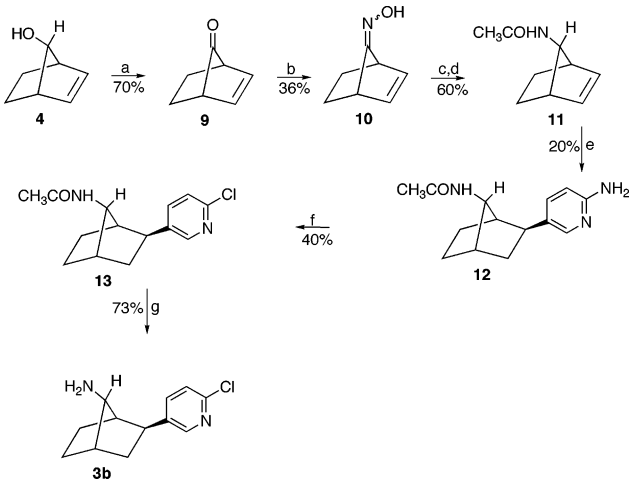
Table 1. Radioligand Binding Data for Norborane Epibatidine Analogues



			K_i, nM		ED_{50}, mg/kg			
compd[a]	R_1	R_2	α4β2 [^{3}H]epibatidine (Hill slope)	α7 [^{125}I]iodo-MLA	tail-flick	hot-plate	hypothermia	locomotor activity
(−)-nicotine			1.5 ± 0.30		1.3 (0.5−1.8)	0.65 (0.25−0.85)	1.0 (0.6−2.1)	0.5 (0.15−0.75)
epibatidine			0.026 ± 0.002	198	0.006 (0.001−0.01)	0.004 (0.001−0.008)	0.004 (0.002−0.008)	0.001
3a	H	NH_2	8.2 ± 0.08 (1.2 ± 0.04)	>700	4.5 (3.5−6.0)	2.9 (2.0−4.0)	3.4 (2.8−5.0)	NT[b]
3b	NH_2	H	10.9 ± 0.91 (1.3 ± 0.06)	>700	4.5 (3.6−5.6)	4.4 (3.1−6.3)	2.3 (1.8−3.6)	1.1 (0.7−2.1)
3c	H	$C_6H_5CH_2NH$	>1000	>700	NT[b]	NT[b]	NT[b]	NT[b]
3d	$C_6H_5CH_2NH$	H	>1000	>200	NT[b]	NT[b]	NT[b]	NT[b]

[a] Compounds were tested as hydrochloride salts. [b] NT = not tested.

Scheme 2[a]



[a] Reagents: (a) $(COCl)_2$, DMSO $(C_2H_5)_3N$; (b) NH_2OH HCl, NaOAc; (c) $LiAlH_4$, Et_2O; (d) Ac_3O, pyridine; (e) KO_2CH, 2-amino-5-iodopyridine, Bu_4NCl, $(Pd(OAc)_2$, DMF; (f) $NaNO_2$, HCl; (g) KOH, $HO(CH_2)_2OH$.

O-methyloxime compound **8**. Reduction of the *O*-methyloxime analogue **8** from the least hindered face with diborane in tetrahydrofuran afforded *exo*-2-(2′-chloro-5-pyridinyl)-7-*endo*-aminobicyclo[2.2.1]heptane (**3a**) in 32% yield. Treatment of **7** with benzylamine in benzene, using a Dean−Stark trap to remove the water to force the reaction to completion, followed by reduction of the intermediate obtained with sodium cyanoborohydride in methanol gave the 7-*endo*- and 7-*exo*-benzylamine analogues **3c** (55%) and **3d** (4%), respectively.

All attempts to synthesize *exo*-2-(2′-chloro-5-pyridinyl)-7-*exo*-aminobicyclo[2.2.1]heptane **(3b)** by reduction of **8** with diborane or $NaBH_4$ led to the *endo* isomer. The 7-*exo*-benzylamine analogue **3d** was subjected to several different catalytic N-debenzylation procedures and transfer hydrogenation conditions in attempts to obtain **3b**. Either no reduction or concomitant reductive dechlorination occurred. We were finally able to obtain **3b** by the route shown in Scheme 2. Swern oxidation of **4** using oxalyl chloride, dimethyl sulfoxide, and triethylamine gave the ketone **9** in 70% yield. Treatment of **9** with hydroxylamine hydrochloride in aqueous methanol containing sodium acetate provided a 36% yield of the oxime **10**. Lithium aluminum hydride reduction of **10** followed by acetylation gave the *N*-acetamido protected intermediate **11** (69%). Reductive palladium acetate catalyzed addition of 2-amino-5-iodopyridine to **11** in DMF containing potassium formate and tetrabutylammonium chloride yielded 20% of the less sterically hindered *exo*-2-[(2′-amino-5-pyridinyl]-7-exo-acetamidobicyclo[2.2.1]heptane **(12)**.[10,11] Diazotization of **12** using sodium nitrite in concentrated hydrochloric acid afforded a 40% yield of 2′-chloro compound **13**. Removal of the protecting acetyl group from **13** using potassium hydroxide in ethylene glycol at 150 °C provided the desired **3b** in 73% yield.

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**−**d** and for nicotine and (+)-epibatidine [(+)-**2**] are listed in Table 1. The binding assays were conducted, and the K_i values were calculated as previously described.[12]

Compounds **3a**,**b** were evaluated in two acute pain models, the tail-flick and the hot-plate tests, and the results for **3a**,**b** and for epibatidine and nicotine are listed in the Table 1.[13] In the tail-flick method of D'Amour and Smith,[14] 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[15] and Atwell and Jacobson.[16] 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 a percentage of the maximum possible effect (% MPE, where % MPE = [(test − control)/(maximum latency − control) × 100]). To measure the effect of analogues on spontaneous activity, mice were placed in individual Omnitech photocell activity cages (28 cm × 16.5 cm) 5 min after sc administration of 0.9% saline or epibatidine analogues. Interruptions of the photocell beams (two banks of eight cells each) were then recorded for the next 10 min. Data were expressed as the number

of photocell interruptions. Rectal temperature was measured by a thermistor probe (inserted 24 mm) and digital thermometer (Yellow Springs Instrument Co., Yellow Springs, OH). Readings were taken just before and at different times after the sc injection of saline or epibatidine analogues. The difference in rectal temperature before and after treatment was calculated for each mouse. The ambient temperature of the laboratory varied from 21 to 24 °C from day to day. ED_{50} values with 95% confidence limits for behavioral data were calculated by unweighted least-squares linear regression as described by Tallarida and Murray.[17]

Results and Discussion

The K_i values for the inhibition of [^{3}H]epibatidine and [^{125}I]iodo-MLA binding at the α4β2 and α7 nAChRs, respectively, for **3a**−**d** along with the reference compounds epibatidine and (−)-nicotine are listed in Table 1. Compounds **3a** and **3b** possess an *endo*- and *exo*-amino, respectively, at the 7-position of the bicyclo[2.2.1]-heptane ring. Compounds **3a** and **3b** have K_i values of 8.2 and 10.9 nM, respectively, compared to nicotine with a K_i of 1.5 nM at the α4β2 nAChR. Compounds **3c** and **3d** possess *endo*- and *exo*-benzylamino groups at the 7-position of the bicyclo ring. Both compounds showed K_i values of >1000 nM at the α4β2 nAChR. None of the compounds showed appreciable affinity for the α7 nAChR.

Compounds **3a** and **3b** were agonists in all four pharmacological tests. Both compounds showed an ED_{50} value of 4.5 mg/kg in the tail-flick test, compared to 1.3 mg/kg for (−)-nicotine. In the hot-plate test, **3a** had an ED_{50} of 2.9 mg/kg compared to 4.4 and 0.65 for **3b** and (−)-nicotine, respectively. In the hypothermia test, (−)-nicotine has an ED_{50} of 1.0 mg/kg compared to 3.4 and 2.3 for **3a** and **3b**, respectively. Compound **3b** was slightly more potent in decreasing locomotor activity compared to other behavioral effects. In addition, pharmacological effects of **3a** and **3b** were blocked by pretreatment with mecamylamine, a nicotinic antagonist (data not shown). Epibatidine with a K_i value of 0.026 nM at the α4β2 nAChR and ED_{50} values of 0.006, 0.004, and 0.004 mg/kg in the tail-flick, hot-plate, and hypothermia tests had much higher receptor affinity and was much more potent in vivo than (−)-nicotine, **3a**, and **3b**. Analogues **3c** and **3d** were not evaluated in vivo because they failed to bind to either receptor subtype.

Epibatidine is a 7-azabicyclo[2.2.1]heptane possessing a *syn*-(2-chloro-5-pyridinyl) group at the 2-position of the azabicyclo ring. Compounds **3a** and **3b** have a 2-chloro-5-pyridinyl group in the 2-position of a bicyclo[2.2.1]-heptane ring system that is syn to the 7-position of the bicyclo ring. In contrast to epibatidine, **3a** and **3b** have an amino group connected to the 7-position in an *endo*- and *exo*-position relative to the 2-chloro-5-pyridinyl group. Even though these represent small changes in the epibatidine structure, they led to compounds with nicotine agonist activity more like nicotine than epibatidine. Addition of bulky benzyl substituents led to the inactive analogues **3c** and **3d** that demonstrated steric constraints at this position.

In summary, **3a** and **3b** demonstrate the importance of the location of the nitrogen in epibatidine. Moving the nitrogen outside the azabicyclo ring of the epibatidine system reduces α4β2 nAChR potency but does not eliminate receptor affinity. The net results of these structural alterations are compounds with nAChR affinity and in vivo functional activity comparable to that of nicotine. Bulky substitutions on the externalized nitrogens (**3c** and **3d**) preclude receptor interactions. These structural alterations provide further insight into the requirements for epibatidine binding and insight into development of a new structural template for nicotine agonists and antagonists.

Experimental Section

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

The [^{3}H]epibatidine was purchased from Perkin-Elmer Inc. (Boston, MA).

***exo*-2-(2′-Amino-5-pyridinyl)-7-*exo*-hydroxybicyclo[2.2.1]-heptane (5).** To DMF (20 mL) in a closed reaction vessel was added *exo*-7-hydroxybicyclo[2.2.1]heptane (**4**) (2.0 g, 0.018 mol), 2-amino-5-iodopyridine (7.9 g, 0.036 mol), KO_2CH (3.0 g, 0.036 mol), tetrabutylammonium chloride (1.3 g, 0.0045 mol), and palladium(II) acetate (0.26 g, 0.0012 mol). The mixture was stirred at 110 °C for 24 h and cooled. Then brine (100 mL) and EtOAc (100 mL) were added. The mixture was filtered, and the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give an orange oil. The oil was purified by silica gel chromatography using 2:1:1 80 CMA−hexanes−EtOAc, then 1:1 80 CMA−EtOAc as eluents to afford 3.0 g (82%) of **5** as a white solid: mp 159−160 °C; ^{1}H NMR (MeOD) δ 1.33−2.07 (m, 8H), 2.60 (m, 1H), 4.12 (m, 1H), 6.53 (d, 2H), 7.35 (dd, 2H), 7.73 (d, 1H). Anal. ($C_{12}H_{16}N_2O\cdot0.25H_2O$) C, H, N.

***exo*-2-(2′-Chloro-5-pyridinyl)-7-*exo*-hydroxybicyclo[2.2.1]-heptane (6) Hydrochloride.** Compound **5** (4.0 g, 0.019 mol) was added to ice-chilled 12 N HCl (60 mL) followed by $NaNO_2$ (24.3 g, 0.35 mol) in portions over a 40 min period. The mixture was removed from the ice bath, was allowed to stir at room temperature for 1 h, and then was added to NH_4OH (300 mL). The mixture was extracted with $CHCl_3$, dried (Na_2SO_4), and concentrated in vacuo to yield 3.84 g (73%) of **6** as an orange oil. An analytical sample was prepared by dissolving the free base in ether and adding ethereal HCl to give a light-yellow solid: mp 114−115 °C; ^{1}H NMR ($CDCl_3$, base) δ 1.36−2.20 (m, 8H), 2.76 (m, 1H), 4.21 (s, 1H), 7.24 (d, 1H), 7.50 (dd, 1H), 8.23 (d, 1H). Anal. ($C_{12}H_{15}Cl_2NO\cdot0.25H_2O$) C, H, N.

***exo*-2-(2′-Chloro-5-pyridinyl)-7-oxobicyclo[2.2.1]-heptane (7) Hydrochloride.** Pyridine sulfur trioxide complex (2.2 g, 0.014 mol) was added to a stirred mixture of **6** (1.04 g, 0.0046 mol) and Et_3N (1.4 g, 0.014 mol) in DMSO (1 mL at 8−10 °C). The mixture was stirred for 2.5 h, added to brine (300 mL), and extracted with EtOAc. The EtOAc layer was separated, dried (Na_2SO_4), and concentrated to give an orange oil. The oil was purified by silica gel chromatography using 70% hexanes−EtOAc to yield 0.51 g (50%) of **7** as a white solid: mp 63−64 °C; ^{1}H NMR ($CDCl_3$) δ 1.66−2.27 (m, 8H), 3.06 (m, 1H), 7.25 (d, 1H), 7.43 (dd, 1H), 8.19 (d, 1H). The free base was converted to the hydrochloride salt with ethereal HCl to give a white solid: mp 115−118 °C. Anal. ($C_{12}H_{12}ClNO$) C, H, N.

***exo*-2-(2′-Chloro-5-pyridinyl)-7-oxobicyclo[2.2.1]-heptane Methoxyoxime (8).** Compound **7** (2.0 g, 0.009 mol), $CH_3ONH_2\cdot HCl$ (1.2 g, 0.0145 mol), and K_2CO_3 (2.0 g, 0.0145

mol) were stirred in EtOH (80 mL) at 40 °C for 24 h. The mixture was concentrated, and the residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed with brine, separated, dried (Na_2SO_4), and concentrated to give 1.90 g (84%) of **8** as a yellow oil. The oil was converted to its HCl salt: mp 97−99 °C; ^{1}H NMR (base, $CDCl_3$) δ 1.57−2.12 (m, 6H), 2.61 (m, 1H), 2.93 (m, 1H), 3.12 (m, 1H) 3.86 (s, 3H), 7.25 (d, 1H), 7.52 (d, 1H), 8.22 (s, 1H). Anal. ($C_{13}H_{16}Cl_2N_2O$) C, H, N.

***exo*-2-(2′-Chloro-5-pyridinyl)-7-*endo*-aminobicyclo[2.2.1]-heptane (3a) Dihydrochloride.** Diborane (1 M, 19.2 mL, 0.0192 mol) was added to an ice-chilled solution of **8** (1.2 g, 0.0048 mL) in THF (15 mL). The ice bath was removed, and the mixture was heated at reflux for a period of 2 h. The mixture was then chilled to 0 °C, and H_2O (5 mL) and 25% NaOH (5 mL) were added. The mixture was refluxed for 1 h and concentrated in vacuo. The residue was partitioned between brine and ether. The ether layer was separated, dried (Na_2SO_4), and concentrated to yield a yellow oil. The oil was purified by silica gel column chromatography using 90% CH_2Cl_2−MeOH as eluent to afford 0.40 g (32%) of **3a** as an oil. The oil was converted to its HCl salt: mp 222−223 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 2H), 1.72 (m, 2H), 2.09 (m, 2H), 2.31 (m, 1H), 2.85 (s, 1H), 2.85 (t, 1H), 3.03 (m, 1H), 7.44 (d, 1H), 7.79 (d, 1H), 7.96 (br s, 3H), 8.35 (s, 1H). Anal. ($C_{12}H_{18}Cl_2N_2$) C, H, N.

***exo*-2-(2′-Chloro-5-pyridinyl)-7-(*endo* and *exo*)-benzylaminobicyclo[2.2.1]heptane (3c and 3d) Hydrochloride.** Compound **7** (1.5 g, 0.0067 mol) and benzylamine (0.73 g, 0.0067 mol) were dissolved in benzene (120 mL) and heated to reflux in a Dean−Stark trap for 68 h. The mixture was concentrated to give an orange oil. This oil was dissolved in MeOH (15 mL), and $NaCNBH_3$ (0.30 g, 0.005 mol) in MeOH (15 mL) was then added. The mixture was stirred for 21 h, and 6N HCl was added until the mixture was acidic to litmus paper. The mixture was concentrated in vacuo, and the residue was partitioned between 5 N NaOH and EtOAc. The organic layer was separated, dried (Na_2SO_4), and concentrated to give an oil, which was chromatographed on silica gel using 95% toluene−EtOAc as the eluent to afford **3c** (1.17 g, 55%) as a colorless oil. A CHN sample 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 **3c**·HCl as a white solid: mp 232−234 °C; ^{1}H NMR (DMSO-d_6) δ 1.35−1.62 (m, 5H), 2.13 (m, 2H), 2.34 (m, 1H), 3.09 (m, 3H), 4.04 (m, 2H), 7.39−7.49 (m, 6H), 7.90 (d, 1H) 8.45 (s, 1H), 8.73 (br s, 1H), 9.03 (br s, 1H). Anal. ($C_{19}H_{22}Cl_2N_2$) C, H, N.

In the chromatography of **3c**, **3d** (0.070 g, 4%) was also isolated as an oil. The oil was converted to its HCl salt: mp 246−249 °C; ^{1}H NMR (base, $CDCl_3$) δ 1.29−1.32 (m, 3H), 1.56 (m, 1H), 1.70−1.96 (m 3H), 2.10 (s, 2H), 2.65 (m, 1H), 2.96 (s, 1H), 3.67 (s, 2H), 7.09−7.32 (m, 7H), 8.13 (s, 1H). Anal. ($C_{19}H_{23}Cl_3N_2$·0.25H_2O) C, H, N.

7-Oxobicyclo[2.2.1]heptane (9). To a solution of oxalyl chloride (26 mL, 0.052 mol, 2 M) in CH_2Cl_2 (100 mL) at −78 °C was added DMSO (8.3 g, 0.106 mol) in CH_2Cl_2 (50 mL). The mixture was stirred for 10 min, and **4** (4.9 g, 0.044 mol) in CH_2Cl_2 (100 mL) was added followed by Et_3N (23.2 g, 0.23 mol) in CH_2Cl_2 (10 mL). The mixture was stirred at bath temperatures for 30 min and then allowed to come to room temperature. Water (200 mL) was added, and the mixture was allowed to stir for 30 min. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give an orange liquid. Hexane (200 mL) was added, and the resultant colloidal suspension was filtered and concentrated to give 3.34 g (70%) of **9** as a light-orange liquid. ^{1}H NMR ($CDCl_3$) δ 1.22 (2H, m), 1.97 (2H, m), 2.82 (2H, s), 6.53 (2H, s).

7-Oxobicyclo[2.2.1]heptane Oxime (10). To a solution of **9** (12.1 g, 0.11 mol) in 70% MeOH−H_2O (300 mL) was added NH_2OH·HCl (8.8 g, 0.12 mol) and NaOAc·3H_2O (16.3 g, 0.12 mol). The mixture was stirred at room temperature overnight, then concentrated in vacuo, and extracted with ether to afford 7.7 g of a thick orange oil. The oil was chromatographed on silica gel using 70% hexanes−EtOAc as the eluent to yield 4.3 g (36%) of **10** as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.20 (2H, m), 1.85 (2H, m), 3.10 (1H, s), 3.77 (1H, s), 6.30 (2H, q), 7.81 (1H, s).

***exo*-7-Acetamidobicyclo[2.2.1]heptane (11).** Lithium aluminum hydride (16 mL, 0.016 mol, 1.0 M) in ether was added to a solution of **10** (1.0 g, 0.0092 mol) in ether (30 mL) and stirred at 30−35 °C for 17 h. The reaction was quenched with water, then a 20% Rochelle's salt solution (20 mL) was added followed by 10% NaOH (4 mL). The mixture was stirred for 20 min, filtered through a Celite pad, dried (Na_2SO_4), and concentrated to yield 0.87 g of a yellow liquid. Ethereal HCl was used to prepare the HCl salt, which was dissolved in pyridine (5 mL) and treated with Ac_2O (1 g). The mixture was stirred at 65 °C for 4 h. Then ice−water (200 g) was added, and the mixture was extracted with $CHCl_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated to give 0.71 g (60%) of **11** as a yellow solid. NMR showed a 1.5:1 mixture of syn and /anti isomers.

***exo*-2-[(2′-Amino-5-pyridinyl]-7-exoacetamidobicyclo-[2.2.1]heptane (12).** To a stirred mixture of **11** (1.0 g, 0.0066 mol), 2-amino-5-iodopyridine (2.9 g, 0.013 mol), KO_2CH (1.1 g, 0.013 mol), and *n*-Bu_4Cl (0.46 g, 0.001 65 mol) in DMF (6 mL) at room temperature were added $Pd(OAc)_2$ (0.090 g, 0.000 40 mol). The reaction vessel was inserted into a 100 °C oil bath, and the mixture was stirred for 21 h. The mixture was cooled, diluted with EtOAc (100 mL), and filtered, and NH_4OH (200 mL) was added. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford 1.2 g of an orange oil. The oil was subjected to silica gel chromatography using 40:25:25:9:1 $CHCl_3$−EtOAc−hexane−MeOH−NH_4OH as the eluent to yield 0.33 g (20%) of **12** as an orange oil. ^{1}H NMR ($CDCl_3$) δ 1.46 (2H, m), 1.77 (4H, m), 1.97 (3H, s), 2.31 (2H, br d), 2.68 (1H, m), 4.05 (1H, d), 4.32 (2H, br s), 5.44 (1H, br s), 6.47 (1H, d), 7.48 (1H, d), 7.92 (1H, s).

***exo*-2-[(2′-Chloro-5-pyridinyl]-7-exoacetamidobicyclo-[2.2.1]heptane (13).** To **12** (1.48 g, 0.0060 mol) at 0 °C was added 36% hydrochloric acid (22 mL) and $NaNO_2$ (7.5 g, 0.109 mol) in four portions. The mixture was stirred at bath temperatures for 30 min and then at room temperature for 2 h. The heterogeneous mixture was then added to NH_4OH (100 mL) and extracted with $CHCl_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated to give an oil that was columned on silica gel, using 40:25:25:9:1 $CHCl_3$−EtOAc−hexane−MeOH−NH_4OH as the eluent, to yield 0.64 g (40%) of **13** as a light-yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.44−1.90 (6H, m), 1.99 (3H, s), 2.34 (1H, br s), 2.42 (1H, br s), 2.80 (1H, m), 4.01 (1H, d), 5.35 (1H, br s), 7.30 (1H, d), 7.69 (1H, d), 8.24 (1H, s).

2-*exo*-[(2′-Chloro-5-pyridinyl]-7-exoaminobicyclo[2.2.1]-heptane Hydrochloride (3b). Compound **13** (0.30 g, 0.0011 mol) was added to ethylene glycol (4 mL)/water (1 mL) containing KOH (0.36 g, 0.0064 mol). The mixture was stirred at 150 °C for 4 h and then at room temperature overnight. Brine (50 mL) and $CHCl_3$ (50 mL) were added to the mixture. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to yield an oil that was columned on silica gel, using 50:40:9:1 CH_2Cl_2−$CHCl_3$−MeOH−NH_4OH as the eluent, to afford 0.18 g (73%) of **3b** as a yellow oil. The free base was converted to the hydrochloride salt with ethereal HCl and recrystallized from MeOH−EtOAc to yield 0.133 g of a white solid: mp 223−224 °C; ^{1}H NMR ($CDCl_3$, free base) δ 1.35−1.44 (4H, m), 1.67−1.99 (4H, m), 2.06 (2H, br s), 2.75 (1H, m), 3.26 (1H, s), 7.23 (1H, d), 7.51 (1H, d), 8.24 (1H, s). Anal. ($C_{12}H_{16}Cl_2N_2$) C, H, N.

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

References

(1) *Treating Tobacco Use and Dependence*; U.S. Department of Health and Human Services, Public Health Service: Washington, DC, 2000.

(2) 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.

(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.; 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.

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

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

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

(9) Story, P. R. 7-Substituted norbornadienes. *J. Org. Chem.* **1961**, *26*, 287−290.

(10) Arcadi, A.; Marinelli, F.; Bernocchi, E.; Cacchi, S.; Ortar, G. Palladium-catalyzed preparation of exo-aryl derivatives of the norbornane skeleton. *J. Organomet. Chem.* **1989**, *368*, 249−256.

(11) Larock, R. C.; Johnson, P. L. Palladium-catalysed intermolecular arylation and alkenylation of bicyclic alkenes. *Chem. Commun.* **1989**, 1368−1370.

(12) Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2′,3′-disubstituted 5′-pyridinyl)-7-azabicyclo[2.2.1]-heptanes: epibatidine analogues. *J. Med. Chem.* **2002**, *45*, 4755−4761.

(13) Damaj, M. I.; Glassco, W.; Aceto, M. D.; Martin, B. R. Antinociceptive and pharmacological effects of metanicotine, a selective nicotinic agonist. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 390−398.

(14) D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74−79.

(15) Eddy, N. B.; Leimbach, D. Synthetic analgesics: II. Dithienybutenyl- and benzomorphans. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385−939.

(16) Atwell, L.; Jacobson, A. E. The search for less harmful analgesics. *Lab. Anim.* **1978**, *7*, 42−47.

(17) Tallarida, R. J.; Murray, R. B. *Manual of Pharmacological Calculations with Computer Programs*; Springer-Verlag: New York, 1987.

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