Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 746–754
Bioorganic & Medicinal Chemistry

Synthesis, nicotinic acetylcholine receptor binding, and pharmacological properties of 3′-(substituted phenyl)deschloroepibatidine analogs

F. Ivy Carroll,[a,*] Yasuno Yokota,[a] Wei Ma,[a] Jeffrey R. Lee,[a] Lawrence E. Brieaddy,[a] Jason P. Burgess,[a] Hernán A. Navarro,[a] M. I. Damaj[b] and Billy R. Martin[b]

[a]*Organic and Medicinal Chemistry, Research Triangle Institute, PO Box 12194, Research Triangle Park, NC 27709, USA*
[b]*Department of Pharmacology and Toxicology, Medical College of Virginia Commonwealth University, Richmond, VA 23298, USA*

Received 14 August 2007; revised 1 October 2007; accepted 10 October 2007
Available online 13 October 2007

Abstract—A series of 3′-(substituted phenyl)deschloroepibatidine analogs (**5a–j**) were synthesized. The α4β2* and α7 nicotinic acetylcholine receptor (nAChR) binding properties and functional activity in the tail-flick, hot-plate, locomotor, and body temperature tests in mice of **5a–j** were compared to those of the nAChR agonist, nicotine (**1**), epibatidine (**4**), and deschloroepibatidine (**13**), the partial agonist, varenicline (**3**), and the antagonist 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs (**7a–j**). Unlike epibatidine and deschloroepibatidine, which are potent agonists in the tail-flick test, **5a–k** show no or very low antinociceptive activity in the tail-flick or hot-plate test. However, they are potent antagonists in nicotine-induced antinociception in the tail-flick test, but weaker than the corresponding 2′-fluoro-3′-(substituted phenyl)deschloroepibatidines.
© 2007 Elsevier Ltd. All rights reserved.

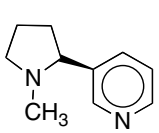
1. Introduction

The use of tobacco products is believed to be in large part due to addiction to nicotine (**1**), which is one of the most abused reinforcing agents. It is estimated that there are four million smoking-related deaths annually from diseases such lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular disease.[1] Consequently, there is great interest in the development of pharmacotherapies for aiding people to stop smoking.[2] Present FDA-approved drugs for treating smoking cessation include nicotine (**1**) replacement medication in the form of gum, patch, lozenge, sublingual tablet, nasal spray, and vapor inhaler, the antidepressant bupropion (**2**), and the α4β2* nAChR partial agonist varenicline (**3**).[2–4]

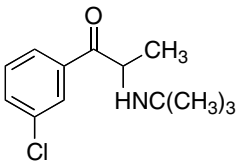
During the last few years, we have conducted structure–activity studies (SAR) using the potent nAChR agonist epibatidine (**4**) as a lead structure to identify pharmacophores for the nAChR. These studies have identified nAChR agonists as more potent than epibatidine as well as analogs that showed pure antagonist or partial agonist activity.[5–12] These studies showed that introduction of a substituted phenyl group at the 3′-position on the pyridine ring of epibatidine exerted a profound influence on both receptor binding (recognition) and receptor activation. Interestingly, substitution of different groups at the 2′-position distinguished between agonist and antagonist properties. In this study, we report the comparison of the nAChR binding and pharmacological properties of the 3′-(substituted phenyl)deschloroepibatidine analogs (**5a–j**) to those of the nAChR agonist nicotine (**1**), epibatidine (**4**), and deschloroepibatidine (**6**), the partial agonist varenicline (**3**), and the corresponding 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs (**7a–j**). The analogs **5a–j** showed α4β2* nAChR binding affinity as well as nAChR agonist and antagonist activity in mouse antinociceptive, hypothermia, and spontaneous activity test more like the partial agonist varenicline (**3**) than the nAChR agonist nicotine (**1**), epibatidine (**4**), and deschloroepibatidine (**6a**). Like the 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs **7a–j**, most of the 3-(substituted phenyl)deschloroepibatidine analogs **5a–j** were antagonist of nicotine-induced antinociception in the tail-flick test.

Keywords: Nicotinic antagonist; Varenicline; nAChR binding; Epibatidine analogs.
* Corresponding author. Tel.: +1 919 541 6679; fax: +1 919 541 8868; e-mail: fic@rti.org

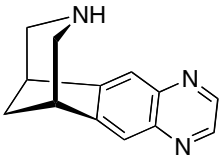
0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.10.027



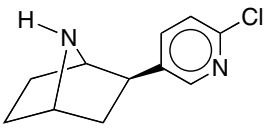
1



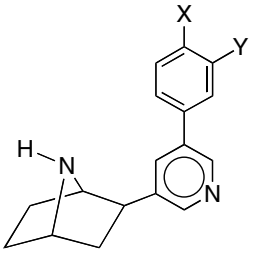
2



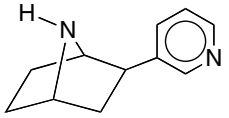
3



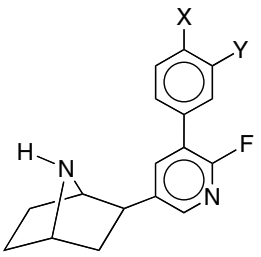
4



5a, X = Y = H
b, X = Cl, Y = H
c. X = H, Y = Cl
d, X = F, Y = H
e, X = H, Y = F
f, X = NO_2, Y = H
g, X = H, Y = NO_2
h, X = NH_2, Y = H
i, X = H, Y = NH_2
j, X = H, Y CH_3O



6a, X = H
b, X = F



7a, X = Y = H
b, X = Cl, Y = H
c. X = H, Y = Cl
d, X = F, Y = H
e, X = H, Y = F
f, X = NO_2, Y = H
g, X = H, Y = NO_2
h, X = NH_2, Y = H
i, X = H, Y = NH_2
j, X = H, Y = CH_3O

2. Chemistry

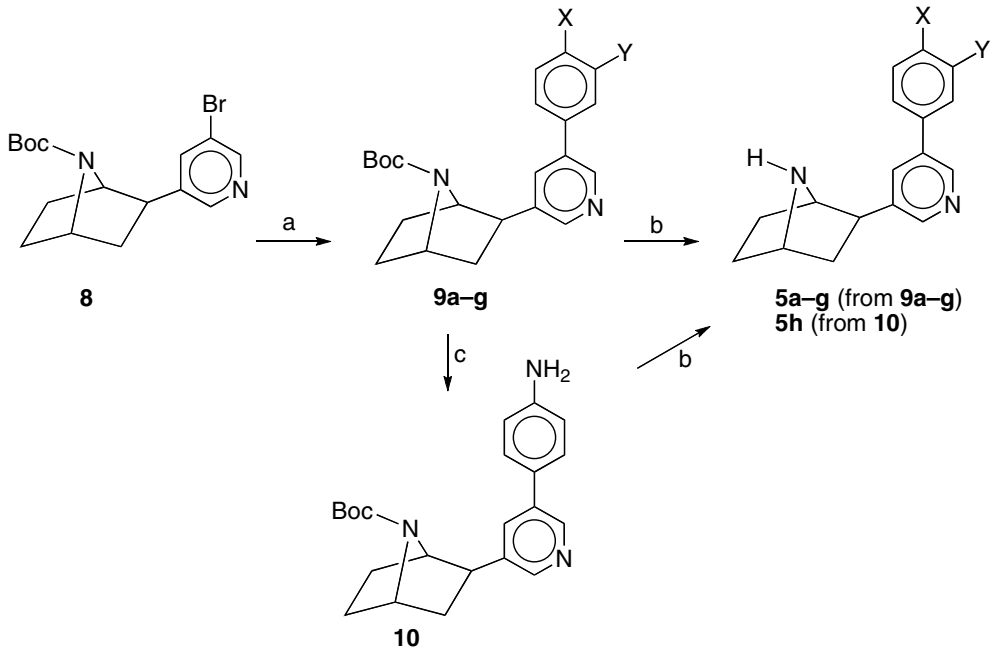
The synthesis of **5a**–**h** is shown in Scheme 1. Palladium acetate catalyzed coupling of *tert*-butoxycarbonyl-3′-bromodeschloroepibatidine (**8**)[10] with the appropriately substituted phenylboronic acid in dimethoxyethane (DME) in the presence of tri-(*o*-tolyl)phosphine and sodium carbonate gave the *tert*-butoxycarbonyl-protected 3′-(substituted phenyl)deschloroepibatidine analogs (**9a**–**g**). Reduction of the 4-nitrophenyl intermediate **9g** with iron powder in hydrochloric acid gave the 4-aminophenyl compound **10**. Treatment of **9a**–**g** and **10** with trifluoroacetic acid in methylene chloride removed the protecting *tert*-butoxycarbonyl group and afforded the desired 3-(substituted phenyl)deschloroepibatidine analogs **5a**–**h**.

The 3′-(3-aminophenyl)- and 3′-(3-methoxyphenyl)deschloroepibatidine analogs **5i** and **5j**, respectively, were synthesized as outlined in Scheme 2. Palladium acetate catalyzed addition of 3-nitrophenylboronic acid or 3-methoxyphenylboronic acid to 7-*tert*-butoxycarbonyl-2-*exo*-2-(2-amino-3-bromo-8-pyridinyl)-7-azabicyclo[2.2.1]-heptane (**11**)[10] provided the *tert*-butoxycarbonyl-protected 3′-(3-nitrophenyl)- and 3′-(3-methoxyphenyl)-deschloroepibatidine **12a** and **12b**, respectively. Diazotization of **12a** and **12b** using sodium nitrite in hydrochloric acid yielded 3′-(3-methoxyphenyl)epibatidine **13a** and **13b**, respectively. Catalytic hydrogenation of **13a** and **13b** using 10% palladium on carbon catalyst in methanol yielded the desired **5i** and **5j**, respectively.

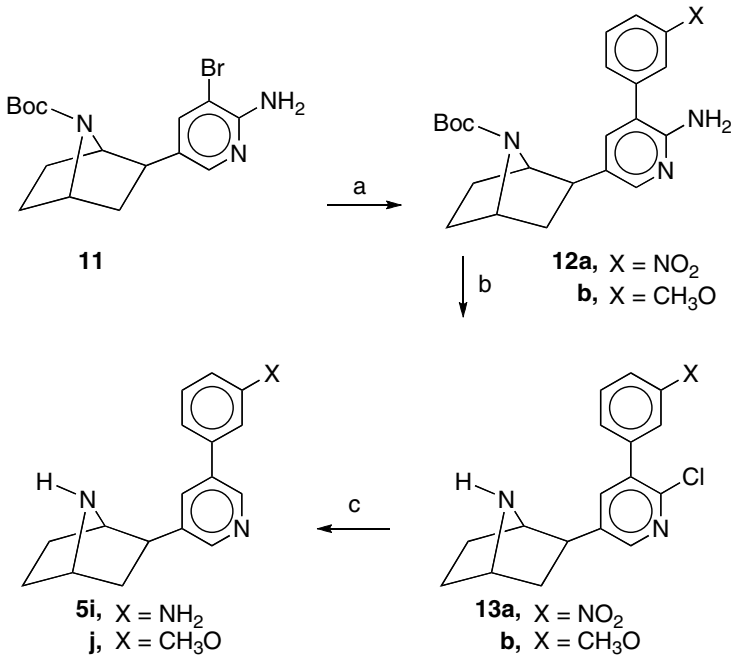
3. Biology

The K_i values for the inhibition of [^{3}H]epibatidine binding at the $\alpha4\beta2^*$ nAChR in male rat cerebral cortex for compounds **5a**–**j** are compared to values for nicotine (**1**), epibatidine (**4**), varenicline (**3**), and 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs (**7a**–**j**) (Table 1). The binding assays were conducted and the K_i values calculated as previously described.[8] Compounds (10 μM) were also evaluated for inhibition of binding to α7 nAChR using [^{125}I] iodoMLA as previously reported.[8]

The above compounds were evaluated in two acute pain models, the tail-flick and the hot-plate tests, and the results are listed in 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



Scheme 1. Reagents: (a) $Pd(OAc)_2$, P(*o*-toly)$_3$, Na_2CO_3, (X,Y)$C_6H_4B(OH)_2$, DME; (b) CF_3CO_2H; (c) Fe, HCl (H_2O).



Scheme 2. Reagents: (a) $Pd(OAc)_2$, P(*o*-toly)$_3$, Na_2CO_3, DME, H_2O, 3-$NO_2C_6H_4B(OH)_2$ or $CH_3OC_6H_4B(OH)_2$; (b) $NaNO_2$, HCl; (c) 10% Pd/C, CH_3OH.

determination. Antinociceptive response was calculated as percentage of maximum possible effect (% MPE, where % MPE = [(test − control)/(maximum latency − control) × 100]).

To measure the effect of analogs on spontaneous activity, mice were placed into individual Omnitech photocell activity cages (28 cm × 16.5 cm) 5 min after sc administration of either 0.9% saline or the epibatidine analog. Interruptions of the photocell beams (two banks of eight cells each) were then recorded for the next 10 min. Data were expressed as 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 either saline or epibatidine analogs. 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.

Table 1. Comparison of radioligand binding and antinociception data of 3′-(substituted phenyl)deschloroepibatidine analogs to standard nAChR agonist, partial agonist, and antagonist

Compound[a]	X	Y	α4β2* [^{3}H]Epibatidine (K_i, nM)[b]	α_7 [^{125}I]iodo MLA (K_i, nM)[b]	ED_{50} tail-flick[c] (mg/kg)	ED_{50} hot-plate[c] (mg/kg)	ED_{50} hypothermia[c] (mg/kg)	ED_{50} spontaneous activity[c] (mg/kg)	AD_{50}[c] (μg/kg)		
									Tail-flick	Hot-plate	Body temperature
Epibatidine (**4**)			0.026 ± 0.002	198 ± 4	0.006	0.004	0.004	0.001			
6a[d]			0.020 ± 0.001		0.002						
6b[d]			0.027 ± 0.001								
Nicotine (**1**)			1.5 ± 0.3	670 ± 33	1.3	0.65	1.0	0.5			
Varenicline (**3**)			0.12 ± 0.02	32.5 ± 1.3	11% at 10	10% at 10	2.8	2.1	0.2	470	0% at 10,000
5a	H	H	0.50 ± 0.03	7% at 50 nM	6% at 10	30% at 10	1.5 (1.2–3.3)	0.5 (0.13–2)	300 (100–3000)	10% at 1000	0% at 1000
5b	Cl	H	0.21 ± 0.03	>2000	1% at 10	11% at 10	2% at 10	10.5 (8.2–15.5)	0% at 10	0% at 10	5% at 1000
5c	H	Cl	0.17 ± 0.021	>2000	1% at 20	10% at 20	0% at 20	3.8 (0.36–41)	0.01 (0.001–0.1)	0% at 1000	0% at 1000
5d	F	H	0.15 ± 0.003	>2000	3% at 10	13% at 10	−1.6% at 10	3.0 (2.2–3.9)	13 (2–70)	10% at 100	0% at 1000
5e	H	F	0.20 ± 0.04	>2000	2% at 10	8% at 10	0% at 10	5 (3.2–7.9)	3.1 (0.07–1)	3000 (2500–3600)	0% at 10
5f	NO_2	H	0.34 ± 0.005	>2000	1% at 10	26% at 10	2.9 (2.1–3.5)	0.66 (0.1–3.9)	47 (0.7–33)	10% at 100	0% at 100
5g	H	NO_2	0.17 ± 0.009	>2000	5% at 20	21% at 20	37.6 (30–45)	4.7 (0.25–8.5)	2.5 (0.4–18)	11,000 (900–13,300)	0% at 2000
5h	NH_2	H	0.34 ± 0.05	>2000	6% at 10	10% at 10	0% at 10	15% at 10	1 (0.1–4)	45% at 2000	0% at 20
5i	H	NH_2	1.16 ± 0.14	>2000	6.3 (3.8–10.3)	5.4 (3.2–9.1)	3.8 (2.8–4.8)	1.5 (0.5–4.5)	NT	NT	
5j	H	CH_3O	0.43 ± 0.05	>2000	1% at 10	20% at 10	0% at 10	2.9 (0.8–10)	0% at 10	0% at 10	0% at 10
7a[e]	H	H	0.24	>2000	3% at 15	4% at 15	−0.5 °C at 10	4.7	500	1200	
7b[e]	Cl	H	0.044		2% at 10	7% at 10	0% at 10	5% at 10	0.3	260	0% at 1000
7c[e]	F	H	0.073		3% at 10	14% at 10	0% at 10	15% at 10	12	450	0% at 1000
7d[e]	H	F	0.029		2% at 10	15% at 10	10% at 10	2	0.5	230	0% at 100
7e[e]	H	F	0.087		3.5	3.3	1.8	0.36	5	2% at 1000	0% at 1000
7f[e]	NO_2	H	0.009		5% at 10	10% at 10	3.5	0.22	3	120	0% at 1000
7g[e]	H	NO_2	0.053		3% at 10	20% at 10	0% at 10	6.5	0.5	130	5% at 500
7h[e]	NH_2	H	0.095		2% at 10	10% at 10	0% at 10	6	5	1800	0% at 5000
7i[e]	H	NH_2	0.16		1% at 10	4% at 10	0% at 10	8.5	9	820	5% at 5000
7j[e]	H	CH_3O	0.12		0% at 10	8% at 10	0% at 10	6	8	2000	0% at 10

[a] All epibatidine analogs with the exception of **5b** and **5d** were tested as hydrochloride salts and all were racemates.

[b] Data represent means ± SE from at least three independent experiments.

[c] Results are provided as ED_{50} or AD_{50} values (±confidence limits) or as a percent effect at the individual dose.

[d] Data taken from Ref. 9.

[e] Data taken from Ref. 11.

For the antagonist experiments, mice were pretreated sc with either saline or epibatidine analogs 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.

4. Results and discussion

The desired target compounds **5a–j** could be synthesized by a procedure similar to that used to prepare the previously reported 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs (**7a–k**).[11] The key step in both syntheses is palladium acetate catalyzed Suzuki[17,18] cross coupling of a 3-bromopyridine starting material **8** and **11** with the appropriately substituted phenylboronic acids.

Binding affinities for the 3′-(3- and 4-substituted phenyl)deschloroepibatidine analogs **5a–j** at α4β2* and α7 nAChRs along with data for nicotine (**1**), epibatidine (**4**), deschloroepibatidine (**6a**), 2′-fluorodeschloroepibatidine (**6b**), varenicline (**3**), and the corresponding 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs **7a–j** are listed in Table 1. 3′-Phenyldeschloroepibatidine has a K_i = 0.5 nM for the α4β2 nAChR. Substitution of the 3′-phenyl group with a 3′- or 4′-position electron withdrawing or releasing substituent had only small effects on binding affinity. The K_is varied between 0.15 and 0.43 nM for **5b–i**. The 3′-(4-fluorophenyl) and 3′-(3-chlorophenyl) analogs **5d** and **5c** with K_is = 0.15 and 0.17 nM, respectively, possessed the highest affinity and are almost identical to the K_i for varenicline (K_i = 0.12 nM), but are much lower than the K_is of 0.026 and 0.020 nM for epibatidine (**4**) and deschloroepibatidine (**6**). All compounds have >2000 nM affinity for the α7 nAChR compared to a K_i = 32.5 nM for varenicline. In every case, the K_i values of the deschloroepibatidine analogs **5a–j** were larger (weaker affinity) than the K_i values for the corresponding 2′-fluoro-(substituted phenyl)deschloroepibatidine analogs **7a–j**. Since deschloroepibatidine (**6a**) and 2′-fluorodeschloroepibatidine (**6b**) have almost identical K_i values (Table 1) for α4β2 AChR binding, the difference between the K_i values of **5a–j** and **7a–j** is apparently due to different types of effects of the 3-(substituted phenyl) groups in each series.

The 3′-(substituted phenyl)deschloroepibatidine analogs **5a–j** were also evaluated for their in vivo nAChR properties in mice and compared to similar properties of varenicline and the 2-fluoro-(substituted phenyl)deschloroepibatidine analogs **7a–j** (Table 1). With the exception of the 3′-(3-aminophenyl) analog **5i**, which has an ED_{50} = 6.3 mg/kg, no compound possessed antinociceptive activity in the tail-flick or hot-plate test. This contrasts sharply with deschloroepibatidine (**6**), which has an ED_{50} = 0.002 mg/kg in this test, but is very similar to the results obtained with the 2-fluoro-(substituted phenyl)deschloroepibatidine analogs **7a–j**. Compounds **5a**, **5f**, and **5i** showed weak activity in the hypothermia test (ED_{50} = 0.5–3.8 mg/kg) similar to that of varenicline (ED_{50} = 2.8 mg/kg). All compounds with the exception of **5b** and **5h** showed activity in the spontaneous activity test similar to varenicline; ED_{50} = 0.5–5 mg/kg compared to 2.1 mg/kg for varenicline. Even though there was not a one-to-one correlation between the analogs **5a–j** and **7a–j**, most of the 2-fluoro-(substituted phenyl)-deschloroepibatidine analogs (**7a–j**) showed similar potency in this test.

All analogs with the exception of the 3′-(3-methoxyphenyl) analog **5j** were potent antagonists in the tail-flick test. The 3-substituted phenyl analogs **5c**, **5e**, and **5g** were more potent antagonists than the 4-substituted analogs **5c**, **5d**, and **5f**. The 3′-(3-chlorophenyl) analog **5c** with an AD_{50} = 0.01 μg/kg was the most potent analog. The 3′-(3-fluorophenyl) and 3′-(3-nitrophenyl) analogs **5e** and **5g** with AD_{50}s = 3000 and 11,000 μg/kg, respectively, were weak antagonists in the hot-plate test; the other compounds were inactive in this test. No compound antagonized nicotine-induced hypothermia.

For comparison, varenicline[19] blocked nicotine-induced antinociception in the tail-flick and hot-plate tests with ED_{50}s of 0.2 and 470 μg/kg, respectively. Interestingly, compound **5c** was almost 20 times more potent in blocking nicotine's effects on the tail-flick test than varenicline, suggesting that **5c** is a more potent antagonist or partial agonist. However, our in vivo models cannot discriminate between these two properties. Interestingly, compared to varenicline, the differential in vivo blockade potency in the different tests suggests a better in vivo and possibly in vitro selectivity at nAChRs. While there was lack of a good correlation, the 2-fluoro-(substituted phenyl)deschloroepibatidine analogs **7a–j** had potencies as antagonist in the tail-flick similar to those of **5a–j**. In contrast, **7a–j** tended to be more potent antagonist in the hot-plate test than **5a–j**.

In summary, the addition of a 3′-phenyl or 3′-(substituted phenyl) group to deschloroepibatidine (**6**) provided compounds **5a–j**, which showed binding affinity at the α4β2* nAChR similar to that of nicotine (**1**) and varenicline (**3**), but considerably less than that of deschloroepibatidine (**6**), epibatidine (**4**), and 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs **7a–j**. In contrast to varenicline (**3**), the analogs **5a–k** had no affinity for the α7 nAChR. Unlike deschloroepibatidine (**6**), which is a potent agonist in the tail-flick test, **5a–h** and **5i** show no antinociceptive activity in the tail-flick or hot-plate test.

Similar to varenicline, 2′-fluoro-3′-(substituted phenyl)deschloroepibatidine analogs **7a–j** are modest activators of locomotor activity and are potent antagonists of nicotine-induced antinociception in the tail-flick test. However, unlike varenicline (**3**) and the 2-fluoro-(substituted phenyl)-deschloroepibatidine analogs **7a–j**, which had good potency as antagonist in the hot-plate test, the 3-phenyldeschloroepibatidine analogs **5a–j** had weak or no activity in this test. Additionally, the 3-substituted phenyl analogs exhibited greater antagonistic activity than the corresponding 4-substituted phenyl analogs.

5. Experimental

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 (CMA80).

The [^{3}H]epibatidine was purchased from Perkin-Elmer Inc. (Boston, MA). The [^{125}]iodo-MLA was synthesized as previously reported.[20]

5.1. 7-*tert*-Butoxycarbonyl-2-exo-[3-phenyl-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9a)

To a resealab1e reaction tube under nitrogen were added **8**[10] (300 mg, 0.85 mmol), $Pd(OAc)_2$ (16 mg, 0.071 mmol), P(*o*-tolyl)$_3$ (43 mg, 0.2 mmol), sodium carbonate (190 mg, 1.8 mmo1), phenylboronic acid (171 mg, 1.4 mmol), degassed water (1 mL), and DME (10 mL). The reaction mixture was heated at 80 °C overnight, cooled, and added to a saturated sodium bicarbonate solution. The mixture was extracted with CH_2C1_2, 4× 50 mL. The extracts were dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (3:1), to yield 0.28 g (95%) of **9a** as an oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.42 (s, 9H), 1.53–1.66 (m, 2H), 1.87–1.93 (br s, 3H), 2.00–2.07 (m, 1H), 2.93–2.98 (m, 1H), 4.28 (br s, 1H), 4.41 (br s, 1H), 7.36–7.48 (m, 3H), 7.57–7.59 (d, 2H), 7.87 (s, 1H), 8.48 (s, 1H), 8.70 (s, 1H).

5.2. 3-Phenyldeschloroepibatidine (5a) dihydrochloride

To a stirred solution of **9a** (280 mg, 0.797 mmol) in methylene chloride (5 mL) at 0 °C was added trifluoroacetic acid (5 mL). After stirring at 25 °C for 2 h, the reaction mixture was poured into 150 mL of a solution of concentrated NH_4OH/H_2O (1:1). The mixture was extracted with CH_2Cl_2 (4× 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with CMA80/ethyl acetate (1:3), to yield 180 mg (90%) of **5a**. ^{1}H NMR ($CDCl_3$) δ 1.51–1.76 (m, 5H), 1.92–2.00 (m, 1H, CH_2), 2.85–2.90 (m, 1H, CH), 3.65 (br s, 1H), 3.81 (br s, 1H), 7.35–7.48 (m, 3H), 7.57–7.60 (d, 2H), 7.91 (s, 1H), 8.50 (s, 1H), 8.66 (s, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm) (I7-C): 30.5, 31.8, 40.7, 45.8; 56.9, 63.2, 127.6(2C), 128.3, 129.3(2C), 133.5, 136.7, 138.5, 142.3, 146.3, 148.3.

The free base was dissolved in CH_3OH and excess 2 M ethereal HCl was added. The solvents were removed and the resulting solid was recrystallized from a CH_3OH and Et_2O mixture. The dihydrochloride salt had mp 170–175 °C, anal ($C_{17}H_{20}Cl_2N_2{\cdot}1.5H_2O$) C, H, N.

5.3. 7-*tert*-Butoxycarbonyl-2-exo-[3-(4-chlorophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9b)

Using a procedure similar to that described for **9a**, compound **8** (400 mg, 1.13 mmol) was coupled to 292 mg (1.86 mmol) of 4-chlorophenylboronic acid to give 0.40 g (97%) of **9b** as a white solid; mp 119–120 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.53–1.66 (m, 2H), 1.86–1.93 (m, 3H), 2.00–2.08 (m, 1H), 2.93–2.98 (m, 1H), 4.27 (br s, 1H), 4.41 (br s, 1H), 7.43 (d, J = 10.5 Hz, 2H), 7.51 (d, J = 10.5, 2H), 7.83 (t, J = 2.1 Hz, 1H), 8.48 (s, J = 2.1 Hz, 1H), 8.65 (s, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 155.3, 148.5, 146.4, 136.8, 135.6, 134.6, 132.8, 129.5, 128.8, 80.1, 62.2, 56.3, 45.9, 40.8, 30.2, 29.2, 28.7 ESI-MS (*m*/*z*): 385.5 (M+1); Anal. ($C_{22}H_{25}ClN_2O_2$) C, H, N.

5.4. 3-(4-Chlorophenyl)deschloroepibatidine (5b)

To a solution of **9b** (400 mg, 1.04 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added trifluoroacetic acid (7 mL). After 2 h at 25 °C, the reaction mixture was poured into 200 mL of concentrated NH_4OH/H_2O (1:1), extracted with CH_2Cl_2 (5× 70 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–2:3) to give 184 mg (62%) of **5b** as a crystalline solid; mp 118–119 °C. ^{1}H NMR ($CDCl_3$) δ 1.50–1.76 (m, 5H), 1.92–2.00 (m, 1H), 2.84–2.89 (m, 1H), 3.65 (br s, 1H), 3.82 (br s, 1H), 7.04 (d, J = 8.04 Hz, 2H), 7.52 (d, J = 7.52, 2H), 7.90 (t, J = 2.1 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 8.63 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 30.6, 31.9, 40.8, 45.7, 56.9, 63.2, 128.9, 129.5, 133.3, 134.5, 135.6, 137.1, 142.5, 146.1, 148.7; ESI-MS (*m*/*z*): 285.5 (M+1); Anal. ($C_{17}H_{17}ClN_2$) C, H, N.

5.5. 7-*tert*-Butoxycarbonyl-2-exo-[3-(3-chlorophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9c)

Using a procedure similar to that described for **9a**, compound **8** (600 mg, 1.70 mmol) was coupled to 440 mg (2.80 mmol) of 3-chlorophenylboronic acid to give 0.67 g (>100%) of **9c** as a noncrystalline solid. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.39–1.57 (m, 2H), 1.78–1.82 (m, 3H), 1.91–1.98 (m, 1H), 2.84–2.89 (m, 1H), 4.20 (br s, 1H), 4.32 (br s, 1H), 7.227.46 (m, 3H), 7.46 (s, br, 1H), 7.76 (s, br, 1H), 8.40 (s, br, 1H), 8.56 (br s, 1H; ^{13}C NMR ($CDCl_3$) δ 28.6, 29.1, 30.1, 40.7, 45.7, 56.2, 62.2, 80.0, 125.6, 127.5, 128.3, 130.6, 133.0, 135.2, 135.3, 140.0, 141.6, 146.2, 148.5, 155.2.

5.6. 3′-(3-Chlorophenyl)deschloroepibatidine (5c) dihydrochloride

To a stirred solution of **9c** (600 mg, 1.56 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added trifluoroacetic acid (10 mL). After 2 h at 25 °C, the reaction mixture was poured into 300 mL of concentrated NH_4OH/H_2O (1:1) extracted with CH_2Cl_2 (5× 80 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–4:3), to yield 430 mg (98%) of **5c**. ^{1}H NMR ($CDCl_3$) δ 1.47–1.75 (m, 5H), 1.89–1.96 (m, 1H), 2.02–2.05 (m,

1H), 2.81–2.86 (m, 1H), 3.62 (br s, 1H), 3.80 (br s, 1H), 7.29–7.45 (m, 3H), 7.54 (s, br, 1H), 7.91 (s, br, 1H), 8.52 (5, br, 1H), 8.61 (5, br, 1H); ^{13}C NMR ($CDCl_3$) δ 30.5, 31.8, 40.5, 45.6, 56.8, 63.1, 125.8, 127.6, 128.3, 130.6, 133.4, 135.2, 135.3, 140.3, 142.4, 146.1, 148.9.

The dihydrochloride salt had mp 227–230 °C; Anal ($C_{17}H_{19}Cl_3N_2{\cdot}1.5H_2O$) C, H, N.

5.7. 7-*tert*-Butoxycarbonyl-2-exo-[3-(4-fluorophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9d)

Using a procedure similar to that described for **9a**, compound **8** (1.0 g, 0.0028 mol) was coupled to 650 mg (4.67 mmol) of 4-fluorophenylboronic acid to give 1.04 g (97%) of **9d** as a noncrystalline solid. ^{1}H NMR ($CDCl_3$) δ 1.43 (5, 9H), 1.58–1.64 (m, 2H), 1.87–1.93 (m, 3H), 2.00–2.08 (m, 1H), 2.96–2.98 (m, 1H), 4.29 (br s, 1H), 4.42 (br s, 1H), 7.14 (m, 2H), 7.55 (m, 2H), 7.84 (m, 1H), 8.05 (br s, 1H), 8.65 (br s, 1H).

5.8. 3′-(4-Fluorophenyl)deschloroepibatidine (5d)

To a stirred solution of **9d** (1.38 g, 0.0038 mmol) in CH_2Cl_2 (23 mL) at 0 °C was added trifluoroacetic acid (23 mL). After 2 h, the reaction mixture was poured into 500 mL of concentrated NH_4OH/H_2O (1:1), extracted with CH_2Cl_2 (5× 100 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–2:3), to yield 0.81 g (81%) of **5d** as a crystalline solid; mp 115–116 °C. ^{1}H NMR ($CDCl_3$) δ 1.46–1.76 (m, 5H), 1.92–1.99 (m, 1H), 2.84–2.89 (m, 1H), 3.65 (br s, 1H), 3.82 (br s, 1H), 7.16 (t, J = 9.6 Hz, 2H), 7.55 (m, 2H), 7.89 (m, 1H), 8.50 (br s, 1H), 8.62 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.6, 31.9, 40.8, 45.7, 56.9, 63.2, 116.3 (d, J_{CF} = 21.6 Hz), 129.3 (d, J_{CF} = 8.1 Hz) 133.2, 134.7, 135.8, 142.4, 146.2, 148.4, 163.0 (d, J_{CF} = 236.3) ; ESI-MS (*m*/*z*); 269.1 (M+l); Anal. ($C_{17}H_{17}FN_2$) C, H, N.

5.9. 7-*tert*-Butoxycarbonyl-2-exo-[3-(3-fluorophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9e)

Using a procedure similar to that described for **9a**, compound **8** (600 mg, 1.70 mmol) was coupled to 392 mg (2.80 mmol) of 3-fluorophenylboronic acid to give 0.63 g (96%) of **9e** as a noncrystalline solid. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.49–1.67 (m, 2H), 1.87–1.94 (m, 3H), 2.01–2.08 (m, 1H), 2.94–2.99 (m, 1H), 4.29 (br s, 1H), 4.42 (br s, 1H), 7.07 (m, 1H), 7.26–7.46 (m, 3H), 7.87 (m, 1H), 8.50 (br s, 1H), 8.68 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.8, 29.8, 40.4, 45.4, 55.9, 61.9, 79.7, 114.4 (m), 122.8, 130.6, 132.7, 135.1, 140.2, 141.3, 145.9, 148.2, 154.9, 161.6, 164.8.

5.10. 3′-(3-Fluorophenyl)deschloroepibatidine (5e) dihydrochloride

To a solution of **9e** (600 mg, 1.63 mmol) in CH_2Cl_2 (27 mL) at 0 °C was added trifluoroacetic acid (27 mL). After 2 h, the reaction mixture was poured into 300 mL of NH_4OH/H_2O (1:1), extracted with CH_2Cl_2 (5× 80 mL), dried ($Na_2SO)_4$, and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–1:1) to give 0.39 g (90%) of **5e**. ^{1}H NMR ($CDCl_3$) δ 1.48–1.61 (m, 5H), 1.68–1.76 (m, 1H, CH_2), 1.90–1.97 (m, 1H, CH), 2.82–2.87 (m, 1H), 3.63 (br s, 1H), 3.80 (br s, 1H), 7.02–7.08 (m, 1H), 7.26–7.30 (m, 1H), 7.34–7.44 (m, 2H), 7.93 (m, 1H), 8.53 (br s, 1H), 8.63 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.2, 31.4, 40.4, 42.3, 56.5, 62.8, 113.9 (d, J_{CF} = 22.4 Hz), 114.7 (d, J_{CF} = 21.1 Hz), 122.9 (d, J_{CF} = 2.9 Hz), 131.0 (d, J_{CF} = 8.2 Hz), 133.0, 135.1, 140.0 (d, J_{CF} = 9.1 Hz), 138.3, 148.4, 148.1, 163.2 (d, J_{CF} = 246.2 Hz).

The dihydrochloride salt had mp 165–167 °C; Anal. ($C_{17}H_{19}Cl_2N_2{\cdot}1.5H_2O$) C, H, N.

5.11. 7-*tert*-Butoxycarbonyl-2-exo-[3-(4-nitrophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9f)

Using a procedure similar to that described for **9a**, compound **8** (400 mg, 2.40 mmol) was coupled to 312 mg (1.87 mmol) of 4-nitrophenylboronic acid to give 0.40 g (90%) of **9f** as a solid. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.58–1.75 (m, 2H), 1.89–1.94 (m, 3H), 2.04–2.11 (m, 1H), 2.97–3.01 (m, 1H), 4.29 (br s, 1H), 4.42 (br s, 1H), 7.75 (d, J = 8.7 Hz, 2H), 7.93 (br s, 1H), 8.33 (d, J = 8.4 Hz, 2H), 8.56 (br s, 1H), 8.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 29.2, 30.0, 40.7, 45.7, 56.3, 62.1, 80.0, 124.5, 128.2, 133.1, 134.3, 141.8, 144.7, 146.4, 147.8, 149.6, 155.2.

5.12. 3′-(4-Nitrophenyl)deschloroepibatidine (5f) dihydrochloride

To a stirred solution of **9f** (390 mg, 0.99 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added trifluoroacetic acid (6 mL). After 2 h, the reaction mixture was poured into 150 mL of concentrated NH_4OH/H_2O (1:1), extracted with CH_2Cl_2 (5× 70 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–2:3), to yield 0.25 g (77%) of **5f**. ^{1}H NMR ($CDCl_3$) δ 1.52–1.86 (m, 5H), 1.95–2.02 (m, 1H), 2.88–2.93 (m, 1H), 3.61 (br s, 1H), 3.84 (br s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 8.07 (br s, 1H), 8.30 (d, J = 8.7, 2H), 8.61 (s, 1H), 8.70 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 29.9, 38.8, 43.5, 54.8, 61.2, 122.5, 126.3, 131.7, 132.3, 140.9, 143.0, 144.1, 145.7, 147.8.

The dihydrochloride salt had mp 215–216 °C; Anal. ($C_{17}H_{19}Cl_2N_3O_2$) C, H, N.

5.13. 7-*tert*-Butoxycarbonyl-2-exo-[3-(3-nitrophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (9g)

Using a procedure similar to that described for **9a**, compound **8** (600 mg, 1.70 mmol) was coupled to 382 mg (3.60 mmol) of 3-nitrophenylboronic acid to give 0.53 g (79%) of **9g** as a oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.49–1.71 (m, 2H), 1.90–1.95 (m, 3H), 2.04–2.13 (m, 1H), 3.00–3.05 (m, 1H), 4.32 (br s, 1H), 4.44 (br s, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.94 (br s, 2H), 8.23–8.26 (m, 1H), 8.44 (s, br, 1H), 8.58 (s, br, 1H),

8.73 (s, br 1H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.8, 29.8, 40.4, 45.5, 56.1, 61.9, 79.8, 121.9, 122.7, 130.1, 132.8, 133.1, 134.1, 139.8, 141.5, 146.0, 148.8, 149.0, 155.0.

5.14. 3′-(3-Nitrophenyl)deschloroepibatidine (5g) dihydrochloride

To a stirred solution of **9g** (0.47 mg, 1.19 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added trifluoroacetic acid (8 mL). After 2 h, the reaction mixture was poured into 300 mL of concentrated NH_4OH/H_2O (1:1), extracted with CH_2Cl_2 (5× 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–1:1), to yield 0.25 g (71%) of **5g** as an oil. ^{1}H NMR ($CDCl_3$) δ 1.91–2.64 (m, 6H), 3.29–3.34 (m, 2H), 3.77–3.82 (m, 1H), 4.42–3.32 (m, 1H), 4.72–4.89 (m, 1H), 7.85–7.90 (m, 1H), 8.31–8.34 (m, 1H), 8.42–8.45 (m, 1H), 8.78–8.79 (m, 1H), 9.00 (br, 2, 2H), 9.23 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.6, 27.6, 35.8, 42.8, 59.2, 62.4, 122.6, 124.5, 130.8, 133.9, 135.7, 137.0, 139.1, 140.3, 142.1, 143.4, 149.3.

The dihydrochloride salt had mp 248–250 °C; Anal. ($C_{17}H_{19}Cl_2N_3O_2$) C, H, N.

5.15. 7-*tert*-Butoxycarbonyl-2-exo-[3-(4-aminophenyl)-5-pyridinyl)]-7-azabicyclo[2.2.1]heptane (10)

To a stirred solution of **9g** (0.34 g, 0.86 mmol) in EtOH (3 mL), water (0.6 mL), and concd HCl (0.1 mL), excess Fe powder was added in one portion over 1 min. After heating at 90 °C for 1 h, the reaction mixture was poured into 100 mL of NH_4OH/H_2O (1:1) solution, extracted with CH_2Cl_2 (5× 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with hexane/EtOAc (2:1–1:2), to yield 0.25 g (80%) of **10** as a solid. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.51–1.64 (m, 2H), 1.85–1.91 (m, 3H), 1.97–2.04 (m, 1H), 2.89–2.93 (m, 1H), 3.82 (br s, 2H), 4.27 (br s, 1H), 4.40 (br s, 1H), 6.74 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.79 (br s, 1H), 8.38 (br s, 1H), 8.63 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.7, 29.2, 30.3, 40.7, 45.9, 56.3, 62.3, 80.0, 115.8, 128.0, 128.4, 132.1, 136.7, 141.2, 145.9, 146.9, 147.2, 155.3.

5.16. 3-(4-Aminophenyl)deschloroepibatidine (5h) trihydrochloride

To a stirred solution of **10** (240 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added trifluoroacetic acid (4 mL). After 2 h, the reaction mixture was poured into 100 mL of concentrated NH_4OH/H_2O (1:1) solution, extracted with CH_2Cl_2 (5× 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/MeOH (2:1–1:1), to yield 0.17 g (95%) of **5h**. ^{1}H NMR ($CDCl_3$) δ 1.48–1.78 (m, 5H), 1.92–1.99 (m, 1H), 2.85–2.89 (m, 1H), 3.65 (br s, 1H), 3.80 (br s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.81 (s, 1H), 8.41 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.4, 31.7, 40.6, 45.9, 56.9, 63.2, 115.8, 128.3, 128.5, 132.5, 136.7, 142.1, 145.7, 147.1, 147.2.

The trihydrochloride salt had mp 238–240 °C; Anal ($C_{17}H_{21}Cl_3N_3 \cdot 1.5H_2O$) C, H, N.

5.17. 7-*tert*-Butoxycarbonyl-2-exo-[5′-(3′-(3-nitrophenyl)-2′-aminopyridinyl)]-7-azabicyclo[2.2.1]heptane (12a)

To a resealable reaction tube under nitrogen were added **11** (600 mg, 1.6 mmol), $Pd(OAc)_2$ (29.1 mg, 0.129 mmol), P(*o*-tolyl)$_3$ (78.5 mg, 0.258 mmol), sodium carbonate (348 mg, 3.28 mmol), 3-nitrophenylboronic acid (411 mg, 2.47 mmol), degassed water (1.65 mL), and DME (8.2 mL). The reaction mixture was heated at 80°C overnight, cooled and poured into saturated sodium bicarbonate solution, and extracted with ethyl acetate (3× 20 mL). The organic combination was dried (Na_2SO_4) and concentrated. The resulting residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (1:2), to yield 0.56 g (85%) of **12a** as an oil. ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.49–1.62 (m, 2H), 1.76–1.85 (br s, 3H), 1.94–2.01 (m, 1H), 2.79–2.84 (m, 1H), 4.16 (br s, 1H), 4.36 (br s, 1H), 4.56 (br s, 1H), 7.40 (s, 1H), 7.61–7.66 (t, 1H), 7.81–7.84 (d, 1H), 7.99 (s, 1H), 8.21–8.24 (d, 1H), 8.33 (s, 1H).

5.18. 3-(3-Nitrophenyl)epibatidine (13a)

To a solution of **12a** (158 mg, 0.192 mmol) in concentrated hydrochloric acid (2 ml) was added sodium nitrite 473 mg (6.86 mmol) in portions over 30 min and stirring continued for 1 h at 0 °C, then at room temperature for additional 3 h. The mixture was poured into 100 mL solution of concentrated NH_4OH/H_2O (1:1), extracted with $CHCl_3$ (3× 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography, eluting with CMA80/ethyl acetate (1:3), to yield 80 mg (63%) of **13a** as an oil. ^{1}H NMR ($CDCl_3$) δ 1.54–1.71 (m, 5H), 1.92–2.02 (dd, 1H), 2.80–2.85 (dd, 1H), 3.62 (br s, 1H), 3.81 (br s, 1H), 7.64–7.67 (t, 1H), 7.80–7.87 (m, 2H), 8.27–8.37 (m, 3H).

5.19. 3′-(3-Aminophenyl)deschloroepibatidine (5i) trihydrochloride

Compound **13a**, (70 mg, 0.211 mmol), 10% Pd/C (110 mg), and methanol (20 m1) were placed into a Fisher–Porter tube under nitrogen. The tube was evacuated and refilled with hydrogen gas (50 psi). The reaction mixture was allowed to shake for 7 h, filtered through a Celite pad and the solvent was removed. The resulting residue was purified by flash chromatography eluting with CMA80/ethyl acetate (1:1), to yield 45 mg (80%) of **5i**. ^{1}H NMR (CD_3OD) δ 1.50–1.68 (m, 5H), 1.91–1.98 (dd, 1H), 2.89–2.94 (dd, 1H), 3.57 (br s, 1H), 3.66 (br s, 1H), 6.64–6.67 (d, 1H), 6.84–6.90 (m, 2H), 7.07–7.12 (t, 1H), 7.85 (s, 1H), 8.31 (s, 1H), 8.44 (s, 1H); ^{13}C NMR (CD_3OD) δ 30.2, 32.1, 41.3, 46.8, 58.3, 63.9, 115.2, 116.8, 118.2, 131.3, 135.2, 139.2, 139.9, 143.6, 146.3, 148.2, 150.1.

The trihydrochloride salt had mp 209 °C (dec); Anal. ($C_{17}H_{22}Cl_3N_3 \cdot 1.25H_2O$) C, H, N.

5.20. 7-*tert*-Butoxycarbonyl-2-exo-[2-amino-3-(3-methoxyphenyl)-5-pyridinyl]-7-azabicyclo[2.2.1]heptane (12b)

Using a procedure similar to that described for **12a** (997 mg, 2.7 mmol) of **11** was coupled to 3-methoxyphenylboronic acid (649 mg, 4.3 mmol) to give 959 mg (90%) of **12b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.45–1.65 (m, 3H), 1.7–20 (m, 3H), 2.78 (dd, J = 4.9, 7.7 Hz, 1H), 3.82 (s, 3H), 4.16 (s, 1H), 4.34 (s, 1H), 4.66 (s, 2H), 6.85–7.07 (m, 3H), 7.28–7.40 (m, 2H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1 (3C), 28.6, 29.7, 40.1, 44.8, 55.1, 55.7, 62.1, 79.3, 113.1, 114.1, 120.8, 121.4, 129.9, 131.5, 136.5, 139.5, 145.5, 154.3, 154.9, 159.8.

5.21. 3′-(3-Methoxyphenyl)epibatidine (13b)

Using a procedure similar to that described for **13a**, (167 mg, 0.422 mmol) of **12b** was converted to 83 mg (63%) of **13b** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.4-1.8 (m, 4H), 1.8–2.05 (m, 2H), 2.81 (dd, J = 5.0, 8.8 Hz, 1H), 3.62 (br s, 1H), 3,78 (br s, 1H), 3.84 (s, 3H), 6.8–7.1 (m, 3H), 7,31 (t, J = 7.9 Hz, 1H), 7.76 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 31.3, 40.2, 44.5, 55.3, 56.4, 62.7, 113.5, 115.1, 121.7, 129.2, 136.1, 138.5, 139.0, 141.2, 146.9, 147.4, 159.2.

5.22. 3-(3-Methoxyphenyl)deschloroepibatidine (5j) dihydrochloride

Deschlorohydrogenation of **13b** (80 mg, 0.254 mmol) using conditions similar to those described for **12b** yielded 28 mg (39%) of **5j** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.45–1.80 (m, 4H), 1.86 (s, 1H), 1.94 (dd, J = 8.9, 12.3 Hz, 1H), 2.87 (dd, J = 5.1, 8.7 Hz, 1H), 3.65 (br s, 1H), 3.80 (br s, 1H), 3.86 (s, 3H), 6.9–7.5 (m, 4H), 7.88 (s, 1H), 8.50 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 31.3, 40.3, 45.5, 55.4, 56.5, 62.8, 113.2, 113.2, 119.7 (2C), 130.0, 133.1, 136.2, 139.7, 141.8, 146.0, 148.0

The dihydrochloride salt had mp 242 °C (dec); Anal ($C_{18}H_{22}Cl_2N_2O\cdot H_2O$) C, H, N.

Acknowledgment

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

Supplementary data

Elemental analysis data. This material is available free of charge via the internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.10.027.

References and notes

1. Ezzati, M.; Lopez, A. D. *Lancet* **2003**, *362*, 847.
2. Henningfield, J. E.; Fant, R. V.; Buchhalter, A. R.; Stitzer, M. L. *CA Cancer J. Clin.* **2005**, *55*, 281.
3. Keating, G. M.; Siddiqui, M. A. A. *CNS Drugs* **2006**, *20*, 945.
4. Niaura, R.; Jones, C.; Kirkpatrick, P. *Nat. Rev. Drug Discov.* **2006**, *5*, 537.
5. Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889.
6. Carroll, F. I.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2005**, *48*, 7491.
7. Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2001**, *44*, 4039.
8. Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755.
9. Carroll, F. I.; Liang, F.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2001**, *44*, 2229.
10. Carroll, F. I.; Ma, W.; Yokota, Y.; Lee, J. R.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2005**, *48*, 1221.
11. Carroll, F. I.; Ware, R.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2004**, *47*, 4588.
12. Abdrakhmanova, G. R.; Damaj, M. I.; Carroll, F. I.; Martin, B. R. *Mol. Pharmacol.* **2006**, *69*, 1945.
13. Damaj, M. I.; Glassco, W.; Aceto, M. D.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 390.
14. D'Amour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74.
15. Eddy, N. B.; Leimbach, D. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385.
16. Atwell, L.; Jacobson, A. E. *Lab. Anim.* **1978**, *7*, 42.
17. Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866.
18. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.
19. Rollema, H.; Chambers, L. K.; Coe, J. W.; Glowa, J.; Hurst, R. S.; Lebel, L. A.; Lu, Y.; Mansbach, R. S.; Mather, R. J.; Rovetti, C. C.; Sands, S. B.; Schaeffer, E.; Schulz, D. W.; Tingley, F. D., 3rd; Williams, K. E. *Neuropharmacology* **2007**, *52*, 985.
20. Navarro, H. A.; Xu, H.; Zhong, D.; Abraham, P.; Carroll, F. I. *Synapse* **2002**, *44*, 117.