Synthesis and Biological Evaluation at Nicotinic Acetylcholine Receptors of *N*-Arylalkyl- and *N*-Aryl-7-Azabicyclo[2.2.1]heptanes

Jie Cheng,[†] Chunming Zhang,[†] Edwin D. Stevens,[†] Sari Izenwasser,[‡] Dean Wade,[‡] Shaoyi Chen,[‡] Dennis Paul,[§] and Mark L. Trudell*[,†]

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148, Department of Neurology, University of Miami School of Medicine, Miami, Florida 33136, and Department of Pharmacology, Louisiana State University Health Sciences Center, New Orleans, Louisiana 70112

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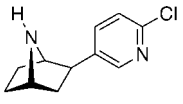
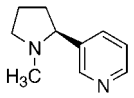
A new series of *N*-arylalkyl-substituted 7-azabicyclo[2.2.1]heptanes and *N*-aryl-substituted 7-azabicyclo[2.2.1]heptanes were synthesized and evaluated as potential ligands for neuronal nicotinic acetylcholine receptors. The in vitro binding affinities (K_i) of the 7-azabicyclo[2.2.1]-heptane derivatives were measured by inhibition of [^{3}H]cytisine binding to rat brain tissue. The most potent ligand of the series was found to be *N*-(3-pyridylmethyl)-7-azabicyclo[2.2.1]-heptane (**5b**, K_i = 98 nM). The chloro analogue (**5a**, K_i = 245 nM) **5a** and epibatidine (**1**) produced dose-dependent analgesia in both hotplate and tail-flick tests when administered subcutaneously. However, when compounds **1** and **5a**,**b** were administered intrathecally, all produced analgesia in the tail-flick test but only **5a** produced analgesia in the hotplate test.

Introduction

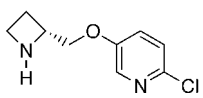
Since the natural product (−)-epibatidine (**1**) was first isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers,[1] its remarkable biological activity[2−4] and unique 7-azabicyclo-[2.2.1]heptane ring system have led to numerous investigations of the synthesis and biological activity of **1** as well as structurally related analogues.[5−19] Extensive pharmacological evaluations have demonstrated that **1** is a highly potent agonist at several central nervous system nicotinic acetylcholine receptor (nAChR) subtypes, including α4β2 and α7 subtypes, as well as at nAChRs in peripheral autonomic ganglia and skeletal muscle.[4,15] The binding affinity of **1** at nAChRs is several orders of magnitude greater than nicotine (**2**), and the remarkable analgesic activity of epibatidine is 200 times more potent than morphine.[1] The analgesic properties of **1** are thought to be mediated through α4β2 subtype nAChRs,[20] and in mice, this effect is thought to be mediated primarily by spinal nAChRs.[21,22] However, the therapeutic potential of epibatidine is limited due to its acute toxicity at doses only slightly higher than its effective analgesic dose.[23−26]



1 (-)-Epibatidine



2 (S)-Nicotine



3 ABT-594

To date, numerous structure−activity studies based upon the novel structure of epibatidine have been performed in search of nontoxic, nonnarcotic, analgesic agents.[8−19] The azetidine derivative ABT-594 (**3**) was recently identified as a potent nAChR analgesic with reduced toxicity.[15,27−29] The structural differences between **1**, **2**, and **3** suggest that further elucidation of the structure−activity relationships of nAChRs is warranted for the development of new analgesic agents with reduced side effects and/or toxicity. In an effort to explore the structure−activity relationships of epibatidine and the importance of the 7-azabicyclo[2.2.1]-heptane ring system as a scaffold for molecular recognition of at nAChRs, a series of novel *N*-arylalkyl- and *N*-aryl-7-azabicyclo[2.2.1]heptanes were prepared. Herein, we report the synthesis and in vitro and in vivo evaluation of congeners of epibatidine.

Chemistry

Multigram quantities of 7-azabicyclo[2.2.1]heptane hydrochloride (**4**) were readily prepared by a short and highly efficient synthetic sequence recently developed in our laboratories.[30,31] With **4** in hand, the *N*-arylalkyl-7-azabicyclo[2.2.1]heptane derivatives **5** were synthesized in a straightforward fashion (Table 1). A mixture of **4** and the corresponding arylmethyl chlorides was refluxed in a mixture of triethylamine and ethanol for 18−24 h. This furnished the desired *N*-arylmethyl-7-azabicyclo[2.2.1]heptane derivatives (**5a**,**e**−**g**) in 51−79% yield. The homologues **5c**,**d** were prepared in a similar fashion from the 3-pyridylalkyl mesylates **6a**,**b**, respectively. The derivative **5b** was obtained in 95% yield from **5a** by hydrogenolysis over 10% palladium on carbon.

The series of *N*-aryl-7-azabicyclo[2.2.1]heptane derivatives **7** were prepared by palladium-catalyzed amination of heteroaryl halides with **4** employing the bisimidazolium salt **8** (DiIPr·HCl) as a ligand precursor for formation of the palladium−bisimdazol-2-ylidene complex to catalyze the C−N bond formation.[30,32] A wide

* To whom correspondence should be addressed. Tel.: (504)280-7337. Fax: (504)280-6860. E-mail: mtrudell @uno.edu.
[†] University of New Orleans.
[‡] University of Miami School of Medicine.
[§] Louisiana State University Health Sciences Center.

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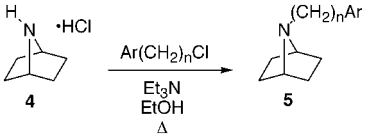
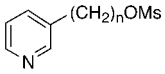
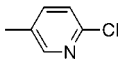
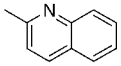
Table 1. *N*-Arylalkyl-7-azabicyclo[2.2.1]heptane Derivatives (**5**)





6a n = 2
6b n = 3

cmpd	n	Ar	yield (%)[a]
5a	1		56
5b[b]	1		95
5c	2		46
5d	3		36
5e	1		79
5f	1		69
5g	1		77

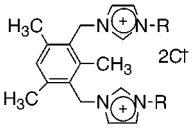
[a] Isolated yield. [b] Prepared from **5a** by hydrogenolysis over 10% Pd/C.

variety of heterocylic halides underwent the amination reaction and furnished the desired *N*-aryl-7-azabicyclo-[2.2.1]heptane derivatives in moderate to good yields (36−71%, Table 2). It is noteworthy that under these conditions, the 2-chloro-5-iodopyridine gave a predominant coupling product at the 2-position to yield **7e** as the major product.

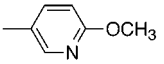
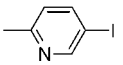
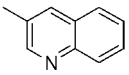
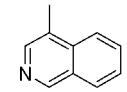
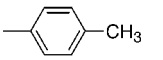
Results and Discussion

The binding affinities of the *N*-arylalkyl-7-azabicyclo-[2.2.1]heptanes (**5a**−**g**) and *N*-aryl-7-azabicyclo[2.2.1]-heptanes (**7a**−**h**), summarized in Table 3, were determined by the inhibition of [^{3}H]cytisine binding in homogenates of rat striatum. There are a variety of nACHRs subtypes that exist in the central nervous system; however, the α4β2 subtype is the predominant nAChR in rat striatum tissue.[15] Therefore, the binding affinities reported in Table 3 correspond to the α4β2 subtype affinity of epibatidine and related compounds. As shown in Table 3, both the *N*-arylalkyl- and the *N*-aryl-7-azabicyclo[2.2.1]heptane derivatives **5** and **7** exhibited significantly lower binding affinities when compared to (−)-, (±)-, and (+)-epibatidine. The *N*-arylalkyl derivatives **5a**−**e** were found to possess higher binding affinity than the *N*-aryl derivatives **7a**−**h**. Compounds **5f**,**g** and **7a**−**h** did not fully inhibit [^{3}H]-cytisine binding at the highest dose tested (100 μM); hence, the binding affinities are reported as the percent inhibition at 100 μM. Among all *N*-arylalkyl-7-azabicyclo-

Table 2. *N*-Aryl-7-azabicyclo[3.3.1]heptane Derivatives (**7**)[a]



DiIPr (**8**) R = 2,4,6-triisopropylphenyl

cmpd	X	Ar	yield (%)
7a	Br		67
7b	Br		71
7c	Br		58
7d	Br		36
7e	Cl		56
7f	Br		67
7h	Br		71
7g	Cl		66

[a] See ref 30 for synthetic details.

Table 3. Inhibition of [^{3}H]Cytisine Binding and [^{3}H]Dopamine Release at α4β2 Subtype NAChRs in Rat Brain

compd	binding affinity K_i (nM)[a]	dopamine release EC_{50} (nM)[a]
(−)-epibatidine (**1**)	0.079 ± 0.016	0.2 ± 0.1
(±)-epibatidine	0.14 ± 0.02	0.4 ± 0.3
(+)-epibatidine	0.16 ± 0.03	1.3 ± 1.3
(−)-cytisine	4.2 ± 0.5	8.8 ± 4.4
(*S*)-nicotine (**2**)	8.0 ± 4.5	7.3 ± 2.6
(*R*)-nicotine	87 ± 45	
5a[b]	245 ± 35	79 ± 38
5b[b]	98 ± 9	1.4 ± 0.3
5c[b]	2230 ± 275	
5d[b]	27 200 ± 200	8140 ± 880
5e[b]	31 300 ± 800	
5f[b]	<50%[c]	
5g[b]	<50%[c]	
7a−**h**[b]	<50%[c]	

[a] All values are the mean ± SEM of three experiments performed in triplicate. [b] Tested as the oxalate salt. [c] Percent inhibition at highest dose tested (100 μM).

[2.2.1]heptane derivatives **5a**−**g**, the *N*-(3-pyridylmethyl)-7-azabicyclo[2.2.1]heptane (**5b**) exhibited the most potent binding affinity of the series. The derivative **5b** (K_i = 98 nM) was found to be equipotent with (*R*)-nicotine (K_i = 87 nM) and only 10-fold less potent than

Table 4. ED_{50} Values of Subcutaneously Administered **1** and **5a**,**b** for Tail-Flick and Hotplate Analgesia[a]

compd	tail-flick ED_{50} (mg/kg) [95% CI]	hotplate ED_{50} (mg/kg) [95% CI]
1	0.000 46 [0.000 232−0.000 92]	0.000 72 [0.000 30−0.0017]
5a	11.1 [2.42−51.3]	12.23 [1.26−118.9]
5b	12.4 [4.40 − 34.9]	5.36 [2.68−10.3]

[a] ED_{50} values were determined using nonlinear regression analysis.

natural (*S*)-nicotine (K_i = 8 nM). The des-chloro analogue **5b** was 2-fold more potent than the 6-chloro analogue **5a** (K_i = 245 nM). This result is opposite of that observed for **1** and **3**.[15,27,29] Even though these compounds have much lower affinities for nAChRs as compared to epibatidine, the affinities still fall within a useful range. Epibatidine has an exceptionally high affinity, both in producing nicotinic agonist effects and in producing side effects, and this contributes greatly to the problems with its clinical usefulness.

To determine the potential for functional agonist activity at nAChRs, selected compounds were examined in [^{3}H]dopamine release studies.[33−35] As shown in Table 3, the nAChR agonists epibatidine, cytisine, and nicotine were potent dopamine-releasing agents. Of the epibatidine analogues tested, **5b** was found to be equipotent with (±)-epibatidine and was 3−4-fold more potent than (−)-nicotine (**2**) and (−)-cytisine. Unexpectedly, the chloro analogue **5a** was 50-fold less potent than **5b**, while the extended tethered derivative **5d** was over 6000-times less potent. All of the compounds produced approximately 100% efficacy (based on the stimulation of dopamine release by nicotine) except for compound **5b**, which was only 50% efficacious at the highest concentration tested (100 μM). There was a significant correlation (r^2 = 1 if the original values are used, r^2 = 0.804 if log values of binding K_i and release EC_{50} are used) between binding and dopamine release. While we tried to use conditions that would prefer the $\alpha4\beta2$ site, it is not possible to know which nicotinic receptor subtype is involved in the release of dopamine in these studies. Further studies aimed at elucidating the specific nicotinic sites to which these compounds bind will help us to better understand the mechanisms involved in these functions.

Compounds **5a**,**b** were further characterized in vivo for analgesic agonist activity. Accordingly, the analgesic effects of subcutaneously and intrathecally administered **1** and analogues **5a**,**b** were assessed using the tail-flick and hotplate assays.[36−38] It has been reported that nicotinic agonists also induce a reduction in body temperature.[39] The thermoregulatory effects of these drugs following subcutaneous administration activity were also determined. Like **1**, compounds **5a**,**b**, when injected subcutaneously, produced dose-dependent analgesia in both the tail-flick and the hotplate tests (Table 4). Over the same dose range, all three drugs produced a dose-dependent reduction in body temperature (Figure 1). However, at a dose of 32 μg/kg, both compounds **5a**,**b** caused fatal seizures before the animals could be tested.

In contrast, when administered spinally, all three drugs produced analgesia in the tail-flick assay (Figure 2), whereas only compound **5a** produced analgesia in the hotplate assay. Spinally administered **1** produced hyperalgesia (an increased sensitivity to painful stimuli) in the hotplate assay (Figure 3), similar to that seen in rats.[20] At the highest doses (10 and 32 μg), compounds **5a**,**b** produced signs of spinal seizures. Thus, the safety of compounds **5a**,**b** is less than or equal to that of epibatidine. Others have stressed the importance of spinal nAChRs in the mediation of the analgesia produced by nicotinic agonists.[20−22] In these studies, analgesic models using spinal reflexes were used. The

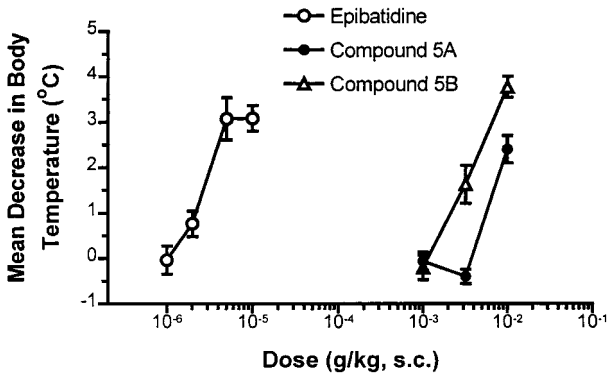


Figure 1. Reduction of body temperature produced by subcutaneous epibatidine (**1**) and **5a**,**b**. Groups of mice ($n \geq 10$) were injected sc with the indicated dose of **1** and **5a**,**b**, and rectal temperature was assessed immediately before tail-flick testing. Data are expressed as mean ± SEM.

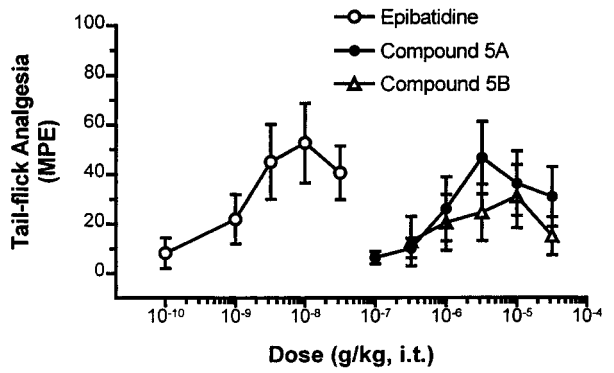


Figure 2. Tail-flick analgesia produced by intrathecal **1** and **5a**,**b**. Groups of mice ($n \geq 10$) were injected ip with the indicated dose of **1** and **5a**,**b** and tested for tail-flick analgesia 10 min later. Data are expressed as mean ± SEM.

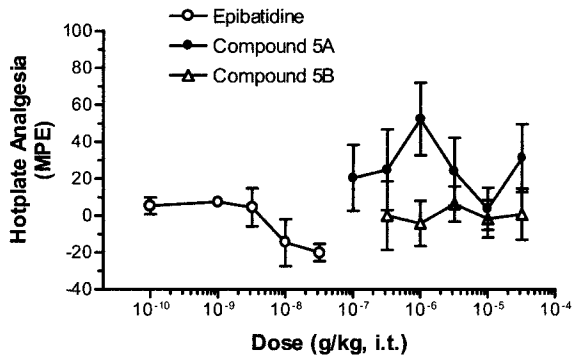


Figure 3. Hotplate analgesia produced by intrathecal **1** and **5a**,**b**. Groups of mice ($n \geq 10$) were injected it with the indicated dose of **1** and **5a**,**b** and tested for hotplate analgesia immediately after tail-flick testing. Data are expressed as mean ± SEM. Only compound **5a** produced significant analgesia. At a dose of 32 ng, **1** produced hyperalgesia.

hotplate assay requires the mouse to make a coordinated response (licking of the hind paw) involving supraspinal circuitry. The finding that **1** and compound **5b** produced hotplate analgesia when injected subcutaneously, but not when injected intrathecally, is evidence that hotplate analgesia is not mediated by spinal nAChRs.

The structure−activity relationships of the *N*-substituted 7-azabicyclo[2.2.1]heptanes offer some interesting insights into the neuronal nAChR pharmacophore. The low binding affinities of compounds **7a**−**h** can be attributed to the reduced basicity of the bridging nitrogen atom of the 7-azabicyclo[2.2.1]heptane moiety due to the electron-withdrawing effects of the aryl groups. Even the structural isomer of des-chloro-epibatidine, **7b**, did not fully inhibited [^{3}H]cytisine binding at the highest does tested (100 μM). This is consistent with pharmacophore models that require a basic tertiary nitrogen for protonation forming an onium site on the molecule. Similar to **1** and **2**, the attachment of the alicyclic amine residue to the 3-position of the pyridine ring exhibited the optimal effect on binding affinity (**5b** > **5e** > **5f**).

It is apparent from the structure−activity studies of this relatively homogeneous series of compounds that the *N*−*N* distance between the onium-nitrogen (*N*7) and the hydrogen bond acceptor nitrogen (pyridyl-*N*) has some relevance for high affinity binding at neuronal $\alpha4\beta2$ nAChRs. From X-ray crystallographic studies (4.737 Å)[40] and computational studies (4.71 Å),[41] the *N*−*N* distance of **5b** was found to be consistent with the optimal *N*−*N* distances proposed in the Sheridan nAChR phamacophore model.[42] The analogues **5c**,**d**, which possessed significantly longer *N*−*N* distances than **5b**,[41] approaching that of the potent ligands cytisine[43] and epibatidine,[44] exhibited low binding affinities. The compound **5e** with a shortened *N*−*N* distance of 3.4 Å[41] also exhibited diminished binding affinity. However, the isomer **5f** (5.1 Å),[41] which also possesses a *N*−*N* distance within the idealized range of several nAChR pharmacophore models,[42−45] exhibited very low affinity at nAChRs. It has been noted that *N*−*N* distance is not sufficient to provide a pharmacophore model that can accurately predict the binding affinities and activity for a diverse set of nAChR ligands;[44,45] it appears that within this series of compounds, an optimal *N*−*N* distance of ≈4.7 Å is required for potent binding at $\alpha4\beta2$ nAChRs.

Conclusion

From a series of novel epibatidine analogues, two new nAChR agonists have been identified. The *N*-(3-pyridylmethyl)-7-azabicyclo[2.2.1]heptane (**5b**) and the corresponding 6′-chloro derivative **5a** were found to elicit moderately potent nicotinic agonist activity via occupation of $\alpha4\beta2$ subtype nAChRs. In addition, like epibatidine, these novel nAChR agonists produced dose-dependent analgesic activity when administered subcutaneously in both tail-flick and hotplate tests. However, **5a** exhibited anomalous activity in spinally administered hotplate tests, producing analgesic effects, while **1** and **5b** did not. The structure−activity relationships of these structurally simple epibatidine analogues should be useful in the further studies aimed at the elucidation of nAChR pharmacophore.

Experimental Section

All chemicals and reagents not otherwise noted were purchased from Aldrich Chemical Co. Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were dried by distillation from Na and benzophenone. The spectral data for all compounds are reported for the free base. The free base was then converted into the oxalate salt to give a hygroscopic solid used for microanalysis and biological testing. Microanalysis for C, H, and N was performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Multiprobe 400 MHz spectrometer. Melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected.

Preparation of 5a,e−g (General Procedure). A solution of the corresponding aryl−alkyl halide (1.5 mmol), triethylamine (2 mmol, 280 μL), and 7-azabicyclo[2.2.1]heptane hydrochloride (1 mmol, 133 mg) in ethanol (8 mL) was refluxed and monitored by thin-layer chromatography (TLC). After 18−24 h, the solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (20 mL), and water (10 mL) was added. Saturated aqueous Na_2CO_3 solution was carefully added to adjust the pH to 10−11. The organic layer was removed, and the water layer was then extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (K_2CO_3) and evaporated under reduced pressure. The resulting residue was purified by chromatography (CH_2Cl_2/MeOH/Et_3N, 80:2:1) to afford the corresponding amine.

***N*-[(2-Chloro-5-pyridyl)methyl]-7-azabicyclo[2.2.1]heptane (5a).** Colorless oil (56%). ^{1}H NMR ($CDCl_3$): δ 8.30 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 8.0, 2.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 3.52 (s, 2H), 3.21-(quintet, J = 2.4 Hz, 2H), 1.73 (d, J = 7.2 Hz, 4H), 1.31 (d, J = 7.6 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 150.1, 149.7, 139.5, 134.6, 124.2, 59.5 (2), 48.6, 28.5 (4). IR (NaCl, thin film): 3405, 1568, 1458, 1102, 827 cm^{-1}. MS (CI): m/z 223 (MH^+, 100) 187 (30); mp 156−158 °C (oxalate salt). Anal. ($C_{12}H_{15}N_2Cl\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

***N*-(2-Pyridylmethyl)-7-azabicyclo[2.2.1]heptane (5e).** Colorless oil (79%). ^{1}H NMR ($CDCl_3$): δ 8.29 (d, J = 4.8 Hz, 1H), 7.42 (dt, J = 7.6, 1.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 6.93−6.89 (m, 1H), 3.52 (s, 2H), 3.13 (quintet, J = 2.4 Hz, 2H), 1.67−1.64 (m, 4H), 1.12 (d, J = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 149.4, 137.3, 135.5, 124.7, 123.1, 61.4 (2), 53.0, 27.9 (4). IR (NaCl, thin film): 3392, 1639, 1596, 1472, 879, 762 cm^{-1}. MS (CI): m/z 189 (MH^+, 100), 188 (M^+, 70); mp 104−106 °C (oxalate salt). Anal. ($C_{12}H_{16}N_2\cdot C_2H_2O_4\cdot 0.25H_2O$) C, H, N.

***N*-(4-Pyridylmethyl)-7-azabicyclo[2.2.1]heptane (5f).** Colorless oil (69%). ^{1}H NMR ($CDCl_3$): δ 8.49 (d, J = 5.6 Hz, 2H), 7.31 (d, J = 5.2 Hz, 2H), 3.57 (s, 2H), 3.26 (s, 2H), 1.90 (d, J = 7.2 Hz, 4H), 1.33 (d, J = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 157.9, 150.8 (2), 124.8 (2), 62.3, 59.9 (2), 27.6 (4). IR (NaCl, thin film): 3407, 2920, 2852, 1639, 1463 cm^{-1}. MS (CI): m/z 189 (MH^+, 100), 200 ($M+2H^+$, 20), 98 (65); mp 122−124 °C (oxalate salt). Anal. ($C_{12}H_{16}N_2\cdot C_2H_2O_4$) C, H, N.

***N*-(2-Quinolinylmethyl)-7-azabicyclo[2.2.1]heptane (5g).** Pink oil (77%). ^{1}H NMR ($CDCl_3$): δ 8.12 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.79−7.76 (m, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 3.88 (s, 2H), 3.31 (t, J = 2.0 Hz, 2H), 1.87 (d, J = 6.8 Hz, 4H), 1.33 (d, J = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 147.8, 136.5, 129.5, 129.2 (2), 127.7, 127.6, 126.1, 121.0, 60.2 (2), 54.8, 28.8 (4). IR (NaCl, thin film): 3397, 1601, 1503, 830 cm^{-1}. MS (CI): m/z 239 (MH^+, 100), 240 ($M+2H^+$, 30); mp 162−164 °C (oxalate salt, pink). Anal. ($C_{16}H_{18}N_2\cdot C_2H_2O_4$) C, H, N.

***N*-(3-Pyridylmethyl)-7-azabicyclo[2.2.1]heptane (5b).** A mixture of **5a** (115 mg, 0.52 mmol) and 10%Pd−C (10wt %, 12 mg) was added to methanol (10 mL). The mixture was hydrogenated (1 atm) overnight. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure. The residue was chromatographed (CH_2Cl_2/MeOH/Et_3N, 80:2:1) to give **5b** (280 mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.56 (d, J = 2.0 Hz, 1H), 8.48 (dd, J = 5.2, 2.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 1H), 7.26−7.23 (m, 2H), 3.53

(s, 2H), 3.21 (quintet, J = 2.4 Hz, 2H), 1.78 (d, J = 6.8 Hz, 4H), 1.31 (d, J = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 150.2, 148.7, 136.6 (2), 123.6, 59.6 (2), 49.5, 28.5 (4). IR (NaCl, thin film): 3392, 1648, 1517 cm^{-1}. MS (CI): *m*/*z* 189 (MH^+, 100), 98 (35); mp 166−168 °C (oxalate salt). Anal. ($C_{12}H_{16}N_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$) C, H, N.

***N*-[2-(3-Pyridylethyl)]-7-azabicyclo[2.2.1]heptane (5c) and *N*-(3-pyridylpropyl)-7-azabicyclo[2.2.1]heptane (5d) (Representative Procedure).** Compound **4** (200 mg, 1.5 mmol) was added to a solution of the corresponding 3-pyridylalkylmesylate (**6a**,**b**) (1 mmol) and Et_3N (3 mmol) in dimethylformamide (DMF) (5 mL) at room temperature. The mixture was heated to 120 °C for 24 h. The solution was allowed to cool to room temperature and concentrated under reduced pressure. The residue was poured in a saturated Na_2CO_2 solution (10 mL) and extracted with dichloromethane (4 × 10 mL). The solvent was removed under reduced pressure, and the residue was then purified by flash chromatography (CH_2Cl_2/MeOH,/Et_3N, 80:20:1) to give the corresponding free base.

***N*-[2-(3-Pyridylethyl)]-7-azabicyclo[2.2.1]heptane (5c).** Colorless oil (46%). ^{1}H NMR ($CDCl_3$): δ 8.43 (d, J = 2.0 Hz, 1H), 8.39 (dd, J = 4.8, 1.6 Hz, 1H), 7.49 (dt, J = 7.6, 2 Hz, 1H), 7.15 (dd, J = 7.2, 4.4 Hz, 1H), 3.28 (quintet, J = 2.4 Hz, 2H), 2.76 (t, J = 8.0 Hz, 2H), 2.55 (t, J = 8.0 Hz, 2H), 1.70 (dd, J = 8.8, 2.4 Hz, 4H), 1.25 (d, J = 7.2 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 150.2, 147.6, 136.2, 136.0, 123.3, 59.4 (2), 49.5, 33.5, 28.4 (4). IR (NaCl, thin film): 3407, 1548 cm^{-1}. MS (CI): *m*/*z* 203 (MH^+, 100), 204 ($M+2H^+$, 55); mp 136−138 °C (oxalate salt). Anal. ($C_{13}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

***N*-[3-(3-Pyridylpropyl)]-7-azabicyclo[2.2.1]heptane (5d).** Colorless oil (34%). ^{1}H NMR ($CDCl_3$): δ 8.42 (brs, 1H), 8.40 (brs, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.19 (dd, J = 8, 4.8 Hz, 1H), 3.31 (s, 2H), 2.64 (t, J = 8.0 Hz, 2H), 2.41 (t, J = 8.0 Hz, 2H), 1.86 (quintet, J = 8.1 Hz, 2H), 1.75−1.73 (m, 4H), 1.29 (d, J = 7.6 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 150.1, 147.7, 137.3, 136.0, 123.5, 59.8 (2), 47.0, 31.2, 30.4, 28.3 (4). IR (NaCl, thin film): 3365, 1654, 1580, 714, 606 cm^{-1}. MS (CI): *m*/*z* 217 (MH^+, 100), 218 ($M+2H^+$, 15); mp 120−122 °C (oxalate salt). Anal. ($C_{12}H_{15}N_2Cl \cdot 2C_2H_2O_4$) C, H, N.

2-(3-Pyridylethyl)mesylate (6a). 3-Pyridylacetic acid hydrochloride (1.7 g, 10 mmol) was added slowly to a slurry of $LiAlH_4$ (1.9 g, 50 mmol) in THF (30 mL) under argon at 0 °C. The mixture was refluxed for 24 h and cooled to room temperature. Methanol (10 mL) was added slowly to decompose the excess hydride, and water (20 mL) was added. The two layers were separated, and the aqueous layer was extracted with ether (4 × 25 mL). The combined organic phase was washed with 5% $NaHCO_3$ solution and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography of the residue (ethyl acetate) gave 0.76 g (62%) of 3-pyridinylethanol as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.29 (d, J = 4 Hz, 1H), 7.54 (dt, J = 8, 1.2 Hz, 1H), 7.18−7.15 (m, 1H), 4.2 (brs, 1H), 3.82 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H).

A solution of methanesulfonyl chloride (0.44 g, 3.8 mmol) in dichloromethane (2 mL) was added to a stirred solution of 3-pyridylethanol (3.2 mmol, 0.4 g) and Et_3N (5 mmol) in dichloromethane (15 mL) at 0−5 °C, and the mixture was stirred for 6 h. Saturated Na_2CO_3 solution (20 mL) was added to the mixture, which was then extracted with dichloromethane (4 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated to give the mesylate **6a** as a solid (0.56 g) for use without further purification. (>95% pure by ^{1}H NMR). 3-(3-Pyridylpropyl)mesylate (**6b**) was synthesized in similar fashion from commercially available 3-pyridyl-1-propanol.

[^{3}H]Cytisine Binding Assay. The binding affinities of **1**, (*S*)-nicotine (**2**), (*R*)-nicotine, the *N*-arylalkyl-7-azabicyclo-[2.2.1]heptanes (**5a**−**g**), and *N*-aryl-7-azabicyclo[2.2.1]heptanes (**7a**−**h**) were determined in homogenates of rat striatum. Rats were killed by decapitation, and their brains were quickly removed and dissected on an ice-cold platform removing the caudate putamen. The tissue was weighed and placed in 30 volumes of ice-cold Tris buffer (50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, and 2.5 mM $CaCl_2$, pH adjusted to 7.4). The tissue was homogenized for 30 s with a polytron (setting 4) and centrifuged at 35 000*g* for 10 min at 4 °C. The supernatant was discarded, and the resultant pellet was resuspended in fresh buffer. The membrane suspension was then added to tubes containing increasing concentrations of the drug being tested, with each concentration done in triplicate. Additional triplicate samples were incubated with [^{3}H]cytisine in the presence of 1 mM (−)-nicotine for determination of nonspecific binding. The tubes were quickly vortexed and incubated on ice for 5 min before adding [^{3}H]cytisine to each tube at a concentration of 3.5 nM per tube. The final volume in the tubes was 0.5 mL. The tubes were again quickly vortexed and were then incubated at 2 °C for 90 min. The assay was terminated by the addition of 3 mL of ice-cold Tris buffer and filtration with a Brandel Cell Harvester through GF/B glass fiber filters that had been soaked overnight in 0.5% polyethylenimine in water to reduce nonspecific binding. Two additional 3 mL washes were carried out, and the filters were transferred to scintillation vials containing 0.5 mL of absolute ethanol and 2.75 mL of Beckman Ready Value scintillation cocktail. The vials were counted 24 h later at an efficiency of approximately 25%. Under these conditions, the affinity of (−)-cytisine is 4.2 ± 0.5 nM.

Dopamine Release Assays. Dopamine release was measured essentially as described previously.[31,32] Male Sprague−Dawley rats (350−500 g, Hilltop, Scottdale, PA) were killed by decapitation, and their brains were removed to an ice-cooled dish for dissection of the striatum. The tissue was weighed and chopped into 250 μm slices on a Sorvall TC2 tissue slicer with two successive cuts at an angle of 90°. The strips of tissue were suspended in oxygenated modified Krebs-HEPES buffer (MKB) consisting of 127 mM NaCl, 5 mM KCl, 1.3 mM NaH_2PO_4, 1.2 mM $MgSO_4$ (where indicated), 15 mM HEPES acid, and 10 mM glucose (adjusted to pH 7.4 with NaOH), which was presaturated with 95% O_2/5% CO_2 and warmed to 37 °C. The tissue was rinsed three times, each in approximately 20 volumes of buffer. The tissue slice suspensions were then incubated in 20 mL of buffer containing [^{3}H]dopamine (final concentration 15 nM) and 0.1 mM ascorbic acid at 37 °C for 30 min. The tissue was then washed twice in 20 mL of MKB and once in MKB containing domperidone, which was included in all subsequent steps of the experiment to prevent feedback inhibition by released [^{3}H]dopamine. The tissue was suspended a final time in MKB and distributed in 275 μL aliquots between glass-fiber filter disks into chambers of a BRANDEL (Gaithersburg, MD) superfusion apparatus. MKB was superfused over the tissue at a flow rate of 0.6 mL/min. A low, stable baseline release, of approximately 1.1%/collection interval of 2 min, was established over a 30 min period. The tissue was then stimulated to release [^{3}H]dopamine by a 2 min exposure to a test compound (Stimulus 1, S1). The inflow was then returned to a nonstimulating buffer (interstimulus interval) for a period of 10 min. The tissue was then stimulated a second time for 2 min with 10 mM K^+ (Stimulus 2, S2). Inflow was again returned to nonstimulating buffer to allow a return to baseline release before the final extraction of radioactivity remaining in the tissue by a 45 min exposure to 0.2 N HCl. Concentration−response curves for the test compounds were established using five concentrations of each drug. Superfusates were collected at 2 min intervals in scintillation vials, and the glass-fiber filter disks and tissue were collected into the final vials. Released radioactivity was determined by liquid scintillation spectroscopy. Data were expressed as radioactivity released above baseline during the collection interval as a fraction of total radioactivity in the tissue at the beginning of the collection interval (percent fractional release) to allow visualization of absolute amounts of release. All data were statistically analyzed as ratios (S1/S2). Data were analyzed as ratios so that each tissue sample could serve as its own control. Under the experimental conditions used, the released radioactivity has been shown to be primarily dopamine.[31] Curves were generated, and EC_{50} values were determined with GraphPad Prism software.

Analgesia Paradigms. Subjects. Male CD-1 mice (25−35 g) were used in all analgesia experiments and maintained on a 12/12 h light/dark cycle with food and water available ad libitum. Subcutaneous injections (sc) were made on the back in a volume of 10 mL/kg. Intrathecal (it) injections were made under light halothane anesthesia (4%) with a 10 μL syringe fitted to a 30 ga needle with PE10 tubing by lumbar puncture.[38] The 30 ga needle was inserted sc and then inserted between two lumbar vertebrae. A flinch of the tail or a leg was taken as a positive sign of insertion. The injection volume was 1 μL. Exposure to halothane produced a drop in body temperature of approximately 2 °C. Therefore, thermoregulatory effects were not studied after intrathecal injections.

Data Analysis. For analgesia studies, mean percent effect (MPE) was calculated for each mouse using the formula: MPE = (test latency − baseline latency)/(12 − baseline latency). ED_{50} values ± CI95 were determined from dose−response curves using nonlinear regression analysis.

Tail-Flick Analgesia.[36] Each mouse's tail was exposed to a focused light beam, and the latency to move the tail was measured using a photocell. The mean of two determinations was taken as the mouse's tail-flick latency. The mean postdrug latencies were compared to predrug baseline latencies. A 12 s maximal latency was used to minimize tissue damage.

Hotplate Analgesia.[37] For animals tested using the hotplate assay, baseline latencies were determined in a single trial by placing each animal on a 52 °C hotplate apparatus (IITC, Inc., Woodland Hills, CA) and measuring the time until the mouse licked its hind paws or jumped. A maximal latency of 30 s was used to minimize tissue damage.

Thermoregulation. Immediately before baseline and postinjection tail-flick and hotplate testing, the body temperature of each mouse was assessed rectally using a telethermometer (Cole-Parmer, Vernon Hills, IL).

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Supporting Information Available: X-ray crystallographic data and an ORTEP diagram of **5b** and tail-flick and hotplate analgesia data for subcutaneous adminstration of **1** and **5a**,**b**. This material is free of charge via the Internet at http://pubs.acs.org.

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