Synthesis and Evaluation of Nicotine Analogs as Neuronal Nicotinic Acetylcholine Receptor Ligands

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A series of 3′-, 4′-, and 5′-substituted nicotine analogs have been synthesized and evaluated as ligands of the neuronal nicotinic acetylcholine receptor. The compounds prepared were found to have binding affinities ranging from 4 to 3500 nM. The results indicate that only a small substituent or functionality is well tolerated at the C4′ position of nicotine and that binding affinity is affected by both steric and electronic properties of the substituent. On the other hand, the C3′ and C5′ positions seem to be the more sensitive toward bulky substituents. The best compound, 4′-methylnicotine, is nearly equipotent to nicotine. It possesses the most favorable binding affinity.

Introduction

Alzheimer's disease, senile dementia of Alzheimer type (AD/SDAT), is a progressive neurodegenerative disorder characterized by a global deterioration of cognitive function, afflicting mainly the elderly.[1] Neurochemical studies of autopsied brain tissue have shown that AD/SDAT is accompanied by multiple changes in numerous brain transmitter systems.[2–5] Although there are a number of neurotransmitter systems affected by Alzheimer's disease, the observed decline in the cholinergic system, and especially a severe depletion of cholinergic neurons, is one hallmark feature of the disease.[6] Moreover, the degree of cognitive impairment in patients with dementia is positively correlated with decreases in markers of cholinergic neuronal function, measured in a postmortem study.[7] More specifically, substantial reductions (30–50%) in nicotinic cholinergic receptors have been consistently reported in the brains of patients with Alzheimer's disease, whereas changes in muscarinic acetylcholine receptors are less remarkable and more dependent on receptor subtype.[8,9] There is currently no totally effective treatment for AD/SDAT, although tacrine has recently been approved by the FDA for use in the Alzheimer's patient, and numerous other clinical trials are underway with agents designed to increase cholinergic tone in the CNS.

Degeneration of the cholinergic neurotransmitter system is not limited to individuals suffering from dementia. Reduction in cholinergic markers in the basal forebrain, decreases in cortical activities of the biosynthetic and degradative enzymes for acetylcholine, decreases in the ability to release acetylcholine from tissue slices, and decreases in numbers of cortical nicotinic acetylcholine receptors have all been reported in otherwise healthy aged individuals.[10] Consistent with these findings are pharmacological studies suggesting that cholinergic deficits are, at least in part, responsible for the memory disturbances in aged animals and humans not suffering from Alzheimer's disease.[11,12]

Recent clinical evidence suggests that the characteristic perfusion abnormality observed in Alzheimer's disease patients reflects regional nicotinic cholinergic deficits,[13] and epidemiological evidence suggests a negative correlation between Alzheimer's disease and smoking. Pilot clinical studies suggest that nicotine may be useful for the acute treatment of deficits in attention and information processing associated with Alzheimer's disease.[14,15] These clinical findings are supported by animal studies showing that both acutely- and chronically-administered nicotine enhances cognitive function in rats, an effect that is preserved in aged animals.[16] These results point to the potential of nicotinic agonists for treatment of cholinergic deficits in AD/SDAT. In addition, a neuroregenerative action of chronically-administered nicotine on both neuronal and vascular functions following hemitransection or MPTP-induced destruction of the nigrostriatal dopamine system has also been demonstrated.[17,18]

It may therefore be possible to reverse memory impairment and improve cognitive function of AD/SDAT patients with a nicotinic acetylcholine receptor agonist such as nicotine. It has been demonstrated that chronic nicotine administration to rats enhances cognitive function.[19] Evidence indicates that nicotine might act upon a diverse range of receptor subtype to produce its wide spectrum of behavioral effects. Therefore, it may be possible to design nicotinic acetylcholine agonists which have beneficial effects on learning and memory but, unlike nicotine, do not affect the cardiovascular system nor produce nausea and vomiting. Furthermore, there has been no systematic structure–activity relationship (SAR) on the pyrrolidine ring[20] of nicotine to determine if more potent and/or selective compounds could be prepared for binding to neuronal nicotinic receptors. Therefore, a series of pyrrolidine-modified nicotine analogs have been synthesized with the goal of identifying a compound with an improved pharmacological profile for use as a therapeutic agent for treatment of Alzheimer's disease. We report here the synthesis and the receptor-binding affinity of a series of 3′,4′-disubstituted and 3′-, 4′-, and 5′-substituted nicotine analogs.

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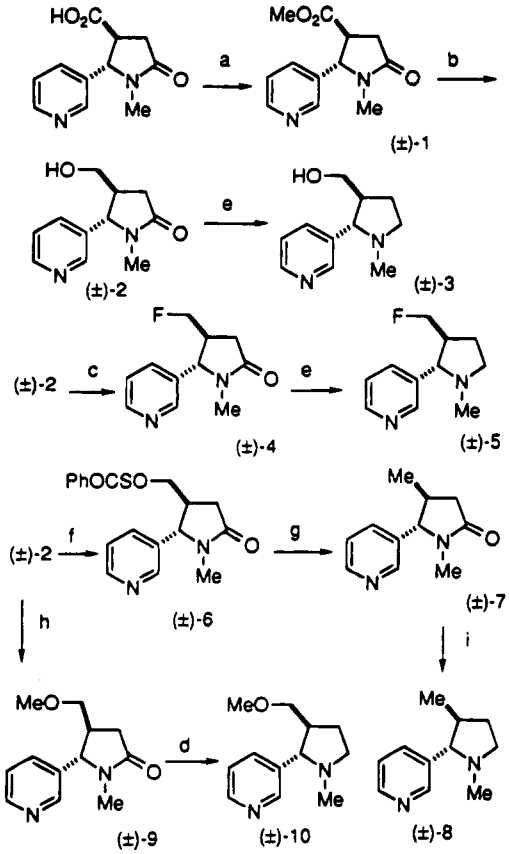
Scheme 1[a]

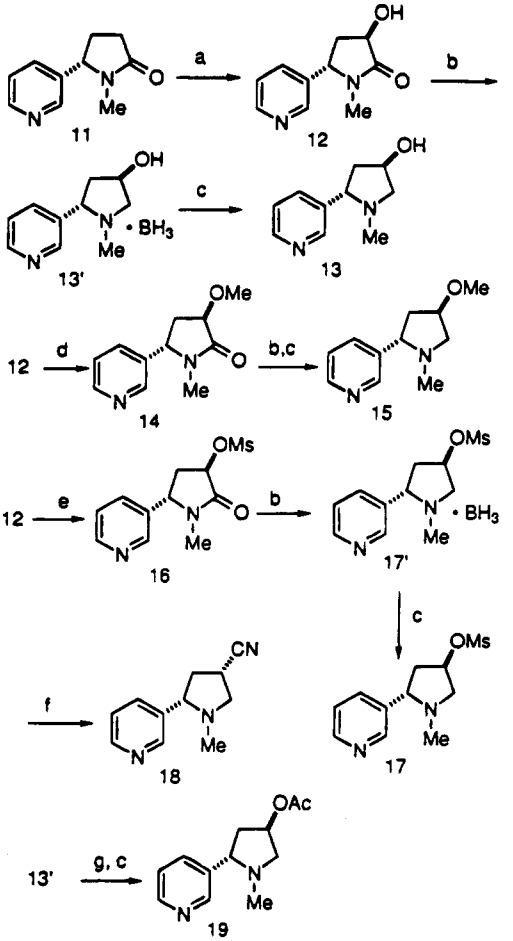


[a] Reagents: (a) HCl, MeOH; (b) $NaBH_4$, MeOH, 0 °C; (c) MsCl, NEt_3, then TBAF, THF; (d) BH_3, THF, reflux, then CsF, EtOH; (e) BH_3, THF, reflux, then H^+; (f) ClCSOPh, pyridine; (g) $(Me_3Si)_3SiH$, AIBN; (h) KOH, MeI, DMSO; (i) BH_3, THF, reflux, then CsF, dioxane.

Chemistry

The synthesis of 3′-substituted nicotine analogs is as shown in Scheme 1. Thus, the commercially-available[21] (±)-*trans*-4-cotininecarboxylic acid was esterified with methanol in the presence of hydrochloric acid to give the methyl ester **1**, which was then selectively reduced with sodium borohydride to give (±)-*trans*-4′-(hydroxymethyl)cotinine (**2**). Reduction of **2** with borane in THF followed by borane decomplexation with hydrochloric acid provided the hydoxymethyl analog **3**. The alcohol functionality of **2** was reacted with methanesulfonyl chloride to form the mesylate followed by treatment with tetrabutylammonium fluoride in THF to provide (±)-*trans*-4′-(fluoromethyl)cotinine (**4**). Reduction of **4** with borane in THF followed by borane decomplexation with hydrochloric acid gave the desired substituted nicotine compound **5**. Attempts to synthesize 3′-methylnicotine, following the literature procedure,[22] by treatment of the mesylate with various hydride sources such as lithium aluminum hydride or Superhydride failed to provide the desired methylcotinine in reasonable yield. Thus, the alcohol **2** was reacted with phenyl chlorothionoformate to give compound **6**, which was treated with tris(trimethylsilyl)silane[23] in the presence of AIBN to give 4′-methylcotinine (**7**). This compound was reduced with borane followed by treatment with cesium fluoride, yielding the desired (±)-*trans*-3′-methylnicotine analog (**8**). Treatment of alcohol **2** with potassium hydroxide and methyl iodide in DMSO provided (±)-*trans*-4′-(methoxymethyl)cotinine (**9**) which was then reduced with borane followed by cleavage of the borane complex with cesium fluoride to give (±)-*trans*-3′-(methoxymethyl)nicotine (**10**).

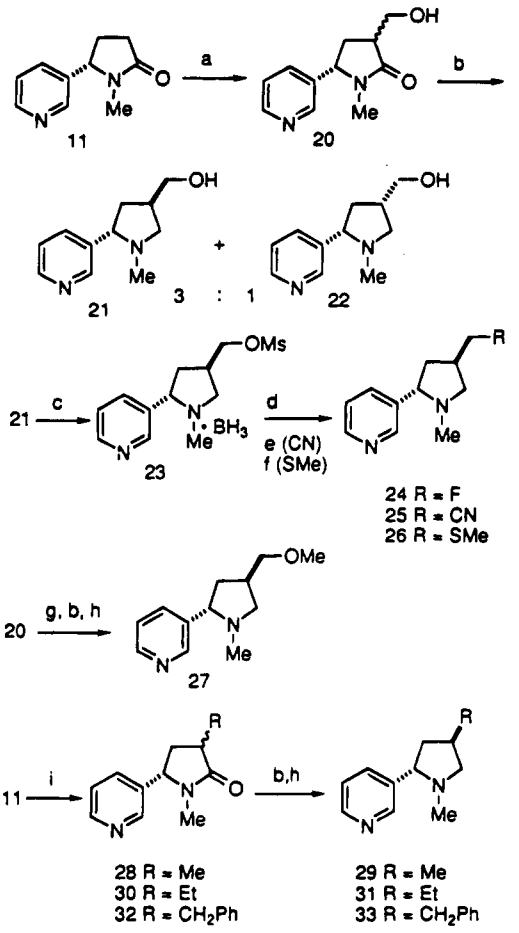
Scheme 2[a]



[a] Reagents: (a) LDA, oxaziridine; (b) BH_3, THF; (c) CsF, EtOH, reflux; (d) NaH, MeI, $(Bu)_4NI$; (e) MsCl, NEt_3, CH_2Cl_2; (f) NaCN, DMSO, H_2O; (g) Ac_2O, pyridine.

Schemes 2 and 3 outline the preparation of various 4′-substituted nicotine compounds. (*S*)-Cotinine (**11**) was reacted with lithium diisopropylamide (LDA) at −78 °C followed by addition of (+)-(camphorsulfonyl)-oxaziridine and acid workup to give the *trans*-3′-hydroxycotinine (**12**). The ^1H NMR spectrum of **12** is identical with that reported in the literature.[24] Compound **12** was reacted with methyl iodide to give the *trans*-3′-methoxycotinine (**14**), which was reduced to the *trans*-4′-methoxynicotine derivative (**15**) with borane/THF as described in Scheme 1. Alternately, *trans*-3′-hydroxycotinine (**12**) was treated with methanesulfonyl chloride in the presence of triethylamine to form the cotinine methanesulfonate **16**, which was reduced with borane in THF to give the nicotine borane complex **17′**. The mesylate **17′** was displaced with any of several nucleophiles to provide various analogs. By displacement with sodium cyanide, the nitrile **18** was formed.[25] It is interesting to note that the borane complex was cleaved in this reaction, leaving the free amine as the product. When *trans*-3′-hydroxycotinine (**12**) was reduced with borane in THF, the *trans*-4′-hydroxynicotine borane complex (**13′**) was formed. Acetylation of compound **13′** with acetic anhydride followed by treatment with cesium fluoride in ethanol gave the *trans*-4′-(acetyloxy)nicotine (**19**).

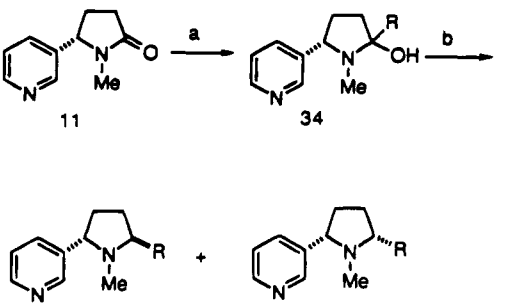
Scheme 3[a]



[a] Reagents: (a) LDA, H_2CO, −78 °C; (b) BH_3, THF, then CsF, EtOH; (c) BH_3, THF, then MsCl, pyridine; (d) TBAF, THF, reflux, 3 h; (e) NaCN, DMSO, H_2O; (f) NaSMe, DMF; (g) NaH, MeI, $(n\text{-}Bu)_4NI$; (h) separation of the major isomer; (i) LDA, RBr, THF, −78 °C.

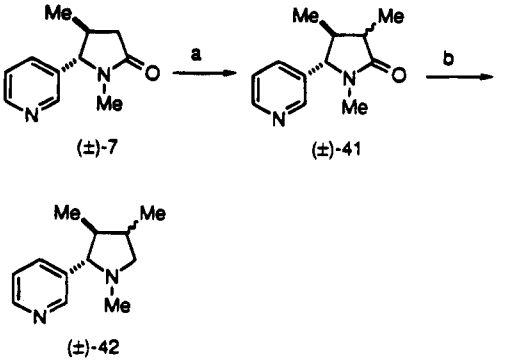
Treatment of (*S*)-cotinine with LDA at −78 °C followed by addition of formaldehyde afforded the 3′-(hydroxymethyl)cotinine (**20**) as a mixture of two diastereoisomers. Reduction of the lactam with borane followed by cleavage of the borane complex with cesium fluoride provided the two (hydroxymethyl)nicotine isomers **21** and **22** in a 3:1 ratio which were readily separated via silica gel column chromatography. The stereochemistry of compounds **21** and **22** were determined by NOE studies and comparing their spectra with those reported in the literature.[26] To avoid any complication in the displacement reactions due to the presence of the free amine functionality, the amino group of compound **21** was protected as the borane complex by reaction with borane in THF. Treatment of the borane complex derived from compound **21** with methanesulfonyl chloride in the presence of triethylamine provided compound **23** which subsequently could be converted to various analogs *via* displacement with nucleophiles. Displacement with fluoride in refluxing THF provided the *trans*-4′-(fluoromethyl)nicotine (**24**); displacement with sodium cyanide in a mixture of DMF and water provided the *trans*-4′-(cyanomethyl)nicotine compound (**25**), whereas displacement with sodium thiomethoxide provided the *trans*-4′-[(methylthio)methyl]nicotine compound (**26**). When compound **20** was treated with sodium hydride followed by methyl iodide in the presence tetrabutylammonium iodide, the corresponding (methoxymethyl)cotinine was formed. It should be noted that this reaction proceeded in very low yield without the presence of the phase transfer agent, tetrabutylammonium iodide. Reduction of the lactam with borane followed by decomplexation with cesium fluoride as described above gave the *trans*-4′-(methoxymethyl)nicotine analog (**27**).

Scheme 4[a]



[a] Reagents: (a) RLi, THF, −78 °C; (b) $NaCNBH_3$, H^+.

Scheme 5[a]



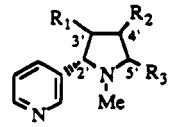
[a] Reagents: (a) LDA, MeI, THF, −78 °C; (b) BH_3, THF, reflux, then CsF, EtOH, reflux.

Various 4′-alkyl-substituted nicotine analogs were prepared by treatment of the enolate anion, which was generated by reaction of (*S*)-cotinine with LDA, with the corresponding alkyl halide followed by reduction with borane as shown in Scheme 3.[27]

The 5′-derivatives of nicotine were prepared in accordance with Scheme 4. Following the patent procedure,[28] (*S*)-cotinine (**11**) was reacted with an alkyllithium or phenyllithium in THF at −78 °C to give the amino alcohol intermediate **34**, which could be isolated in pure form via silica gel column chromatography. However, as a general practice, crude **34** was immediately treated with sodium cyanoborohydride in the presence of hydrochloric acid to provide the 5′-alkyl- or 5′-phenylnicotine as a mixture of two diastereoisomers that were readily separated by silica gel column chromatography. The stereochemistry was determined by comparing their ^1H NMR and optical rotation data with those reported in the literature.[28]

The 3′,4′-dimethylnicotine derivatives were prepared according to Scheme 5. The (±)-*trans*-4′-methylcotinine (**7**) obtained in Scheme 1 was treated with LDA and methyl iodide to produce the 3′,4′-dimethylcotinine (**41**), which upon reduction with borane/THF as described above was converted to the (±)-3′,4′-dimethylnicotine analog (**42**) as a mixture of two isomers.

Table 1. Binding Data for Pyrrolidine-Modified Nicotine Analogs



compound[a]	R_1	R_2	R_3	binding affinity,[b,c] K_i (nM)
(*S*)-nicotine	H	H	H	1.15 ± 0.4
3	(±)-β-CH_2OH	H	H	619.2 ± 12.4
5	(±)-β-CH_2F	H	H	98.5 ± 9.7
8	(±)-β-Me	H	H	24.9 ± 1.7
10	(±)-β-CH_2OMe	H	H	2032± 32
13	H	(β)-OH	H	27.6 ± 0.8
15	H	(β)-OMe	H	36.6 ± 0.8
17	H	(β)-OMs	H	363.6 ± 17.9
18	H	(α)-CN	H	82.0 ± 2.0
19	H	(β)-OAc	H	102.9 ± 16.7
21	H	(β)-CH_2OH	H	157.8 ± 7.4
22	H	(α)-CH_2OH	H	294.3 ± 11.0
24	H	(β)-CH_2F	H	11.1 ± 1.9
25	H	(β)-CH_2CN	H	52.0 ± 2.9
26	H	(β)-CH_2SMe	H	492.8 ± 19.2
27	H	(β)-CH_2OMe	H	510.0 ± 46.6
29	H	(β)-Me	H	4.23 ± 0.28
31	H	(β)-Et	H	50.2 ± 1.1
33	H	(β)-CH_2Ph	H	119.4 ± 18.5
35	H	H	(β)-Me	34.9 ± 1.9
36	H	H	(α)-Me	1205.3 ± 34.6
37	H	H	(β)-*n*-Bu	125.2 ± 4.7
38	H	H	(α)-*n*-Bu	1381.4 ± 209.0
39	H	H	(β)-Ph	1242.3 ± 12.4
40	H	H	(α)-Ph	3353.5 ± 196.9
42	Me	Me	H	96.4 ± 6.4

[a] Compounds are all enantiomerically pure unless otherwise noted. [b] Values are the means ± SEM. [c] IC_{50} values were converted to K_i values using the Cheng–Prusoff equation as described in the Experimental Section.

Results and Discussion

The present study evaluates the effects of substitutions at the 3′-, 4′-, and 5′-positions of nicotine which possesses a very high affinity for neuronal nicotinic acetylcholine receptors. The substituents at these positions were varied with respect to size, electronic character, and hydrophobic properties in order to determine the overall effect on ligand-binding affinity. Table 1 shows the K_i value of the 3′-, 4′-, and 5′-substituted and 3′,4′-disubstituted nicotine analogs. The binding procedure is detailed in the Experimental Section.

As shown in Table 1, replacement of the hydrogen at the C3′ position of nicotine with a methyl group (compound **8**) decreases the potency by a factor of 22. Replacement of the methyl group with a sterically larger fluoromethyl functionality (i.e., **5**, van der Waal radii, H = 1.2 Å, F = 1.35 Å) results in a further 4-fold decrease in the binding affinity. Changing the substituent to a hydroxymethyl group (compound **3**) reduces the K_i value to 619 nM. Replacement of the hydroxy group of **3** with a methoxy functionality (compound **10**) results in a 3-fold decrease in binding potency. These data are consistent with the hypothesis that binding potency of C3′-substituted analogs is predominantly governed by steric effects.

For 4′-substitution, the present study demonstrates that replacement of hydrogen at the C4′ position of nicotine with a polar hydroxy group (compound **13**) decreases the potency by a factor of 23. Replacement of the hydroxy group with a sterically larger acetoxy functionality (compound **19**) results in a 3.7-fold decrease in binding affinity. Changing this substituent to the sterically much larger (methylsulfonyl)oxy group (**17**) causes a further 3.6-fold decrease. Furthermore, it is demonstrated that extending certain functionalities such as hydroxy or methoxy *via* homologation decreases binding potency (**13** vs **21**, **15** vs **27**). Thus, the same steric effects we observed at the C3′ position has also been shown here. In addition, the same phenomenon has been observed with 4′α-substituted analogs. As shown in Table 1, the nitrile analog **18**, which is sterically smaller than hydroxymethyl, is 3.7-fold more potent than 4′-(hydroxymethyl)nicotine (**22**).

Although a 4′(*R*)-methyl analog, **29**, has comparable binding affinity when compared to (−)-nicotine, deleterious effects are also observed upon substitution with nonpolar groups larger than a methyl group. It is shown from the binding results in Table 1 that the order of binding potency for 4′-alkyl-substituted compounds is Me > Et > benzyl (**29**, **31**, **33**). Replacement of the methyl group with a polar fluoromethyl functionality (i.e., **24**) results in a 2.5-fold decrease in the binding affinity. Changing the substituent to a hydroxymethyl group (**21**) reduced the K_i value to 158 nM (14-fold decrease). Replacement of the hydroxy group of **21** with a methoxy functionality (i.e., **27**) results in a further 3.2-fold decrease in binding potency. The deleterious effect could be due to steric occlusion in this region of the receptor. The data in Table 1 indicate that steric volume of a methyl group may represent an upper limit which may be accommodated by the space in the receptor ligand-binding domain since a large decrease in binding was observed in going from a methyl to ethyl group. Thus, steric factors are clearly important for optimal binding potency for the substituents at the C4′

position of the pyrrolidine ring. However, it is noted that the 4′-benzyl analog **33**, which is sterically larger than the 4′-methoxymethyl analog **27**, is 4.3-fold more potent. In addition, further substitution with either an acetoxy (**19**) or cyanomethyl (**25**) group causes a less dramatic loss of affinity than with the smaller hydroxymethyl group (**21**). Therefore, electronic effects may play at least a minor role in influencing binding affinities.

Although the effect of stereochemistry of substituents on the pyrrolidine ring has not been reported in the literature, it is interesting to note that the configuration at the C4′ position has only a small effect on activity. Specifically, the C4′ epimer of (*R*)-(hydroxymethyl)-nicotine **21**, (*S*)-(hydroxymethyl)nicotine **22**, is 2-fold less potent than **21**. However, the limited number of compounds with α stereochemistry at the C4′ position makes it difficult to draw any conclusions regarding the effect of stereochemistry on SAR.

The effect of substitution on binding affinity at the C5′ position was also examined. Replacement of the C5′ hydrogen of nicotine with an alkyl or phenyl group results in a decrease in binding potency ranging by factors of 35−3353. Specifically, the potency of the β-methyl analog **35** is reduced by a factor of 35, and the β-butyl analog **37** has an affinity over 125-fold lower than that of nicotine. Changing the substituent to a β-phenyl group (**39**) led to a 1240-fold drop in potency. These results suggest that any β substitution at this position is not well tolerated. Likewise, C5′α substituents are not well tolerated, with the α-methyl analog **36** demonstrating greater than 1000-fold decrease in binding affinity compared to that of (−)-nicotine. This unfavorable steric interaction appears to be more severe in the C5′α-substituted series than in the C5′β-substituted series, a phenomenon not observed with C4′-substituted analogs. Thus the K_i value of the α-methyl isomer **36** is 30-fold greater than that of the β isomer **35**, and the K_i value of the α-butyl analog **38** is over 10-fold higher than that of the β-butyl analog **37**. Although the substituents at the C5′ position might change the bioactive conformation of the molecule, the reduction in potency might also result from the steric interaction between the α-alkyl substituents and the nicotinic acetylcholine receptor. It has been shown by NMR analysis[29] that nicotine in solution exists primarily in a conformation in which the methyl group on the pyrrolidine ring is trans to the pyridine ring; the pyrrolidine ring is in an envelope conformation, and the relative orientation of pyrrolidine and pyridine rings is orthogonal. Using this NMR conformational analysis as a starting point, we have carried out molecular mechanics calculations[30] to understand the binding potency difference between α and β isomers. However, our calculations failed to provide any conclusive results. Since the bioactive conformation of 5′-substituted analogs is not known at the present time, we assumed that either steric or conformational effects or a combination of both may account for the observed result. Since the C5′ position is directly adjacent to the pyrrolidine nitrogen atom, which is believed to constitute a critical binding point,[31] close contact with the protein in this region is quite plausible. The effect of stereochemistry of substituents on binding affinity will require additional studies.

We have also demonstrated that the substitution position of a functional group has dramatic effects on binding affinity. Hence, the 5′β-methylnicotine analog (**35**) is significantly less potent in binding than its 4′-substitution counterpart, **29**, while the 3′-methylnicotine analog (**8**) exhibits intermediate activity. However, it should be noted that the 3′-substituted analogs examined in this study are all racemates. Thus, these analogs may possess affinity even higher that those shown here had each enantiomer been synthesized and evaluated. The 3′,4′-dimethyl analog **42** exhibits weaker potent binding affinity than either compound **8** or **29**. The reduction in potency might result from the steric interaction between the methyl substituents and the nicotinic acetylcholine receptor.

In conclusion, pyrrolidine-modified nicotine analogs possessing various substituents at the 3′-, 4′-, and 5′-positions have been synthesized and evaluated for binding potency to the neuronal nicotinic acetylcholine receptor. The SAR generated has provided valuable information concerning the structural requirements of the pyrrolidine ring of nicotine and its analogs. Although it has been demonstrated that the nicotinic acetylcholine channel protein possesses five subunits,[32] the makeup of which may complicate the interpretation of SAR data, these data can be used to help begin to define the volume of available space in the pyrrolidine ring region of the receptor ligand-binding domain. On the basis of this initial information, novel nicotinic acetylcholine ligands are currently being synthesized to further characterize the nicotinic acetylcholine receptor binding domain and the ligand receptor interaction.

Experimental Section

Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz) and a General Electric GN-300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) relative to Me_4Si as an internal standard unless otherwise indicated. Mass spectra were obtained with a Hewlett Packard HP5965 spectrometer. Elemental analyses and the above determinations were performed by the Analytical Research Department, Abbott Laboratories.

Thin-layer chromatography (TLC) was carried out by using E. Merck precoated silica gel F-254 plates (thickness 0.25 mm). Flash chromatography was carried out using Merck silica gel 60, 200−400 mesh.

Melting points are uncorrected and were determined on a Buchi melting point apparatus. Optical rotation data were obtained on a Perkin-Elmer Model 241 polarimeter. All reactions were performed under anhydrous conditions unless otherwise noted. The following abbreviations are used in the Experimental Section: THF, tetrahydrofuran; DMF, *N*,*N*-dimethylformamide; D_2O, deuterium oxide; $CDCl_3$, deuteriochloroform, DMSO-d_6, deuteriodimethyl sulfoxide; BOC, *tert*-butyloxycarbonyl; CBZ, benzyloxycarbonyl; Bn, benzyl; Ms, methanesulfonyl; PAW, pyridine/acetic acid/water (20:6:11); DCC, dicyclohexylcarbodiimide; DIBAL-H, diisobutylaluminum hydride; DIEA, diisopropylethylamine; DPPA, diphenyl phosphorazidate; EDCI, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; EtOH, ethanol; IBCF, isobutyl chloroformate; HOAc, acetic acid; HOBt, 1-hydroxybenzotriazole; LAH, lithium aluminum hydride; NH_4OAc, ammonium acetate; NMM, *N*-methylmorpholine.

(±)-4′-*trans*-(Hydroxymethyl)cotinine (2). A sample of methyl *trans*-4-cotininecarboxylate (557 mg, 2.38 mmol) (prepared from the acid, which is available from Aldrich Chemical Co.) in methanol (20 mL) was cooled to 0 °C. Sodium borohydride (135 mg, 3.57 mmol) was added portionwise to the reaction mixture under nitrogen at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was warmed to room

temperature and allowed to stir for an additional 2 h. After the reaction was completed, it was quenched by addition of saturated aqueous sodium bicarbonate solution. The desired product was extracted into chloroform from water by a continuous extraction method. The solvent was removed under reduced pressure to give a light yellow oil which was chromatographed on silica gel, eluting with chloroform/methanol (10:1), to provide the title compound (477 mg, 97% yield) as a colorless oil. MS (DCI/NH_3): *m/z* 207 $(M + H)^+$, 224 $(M + NH_3)^+$. ^1H NMR ($CDCl_3$): δ 2.30–2.41 (m, 2H), 2.49 (s, 3H), 2.65–2.77 (m, 1H), 3.70–3.76 (m, 2H), 4.49 (d, J = 6 Hz, 1H), 7.35 (dd, J = 4.5, 9.0 Hz), 7.55 (dt, J = 2.5, 9.0 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H), 8.61 (dd, J = 2.5, 4.5 Hz, 1H).

(±)-3′-*trans*-(Hydroxymethyl)nicotine (3). Compound **2** (640 mg, 3.10 mmol) in THF (20 mL) was treated dropwise with a 1 M solution of borane (9.3 mL, 9.3 mmol) in THF at room temperature. After the mixture was refluxed for 3 h, the reaction was quenched by addition of a large excess of methanol. The resultant solution was allowed to stir at room temperature for an additional 15 min. Solvent was then removed under reduced pressure to give a white solid. The crude reaction product was dissolved in methanol (12 mL) and treated with 6 N aqueous hydrochloric acid (0.4 mL). After the pH of the solution was adjusted to 2.0 by addition of 15% aqueous sodium hydroxide solution, the solvent was concentrated *in vacuo*. The resultant crude product was purified by flash column chromatography on silica gel, eluting with chloroform/methanol (10:1), to give 343 mg of the title compound (58%) as a colorless oil. MS (DCI/NH_3): *m/z* 193 $(M + H)^+$, 210 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.65–1.80 (m, 1H), 2.16 (s, 3H), 2.10–2.48 (m, 2H), 2.94 (br d, J = 8 Hz, 1H), 3.26 (br t, J = 8.0 Hz, 1H), 3.55–3.70 (m, 2H), 7.29 (dd, 1H, J = 2.5, 5.0 Hz, overlap with $CDCl_3$), 7.55 (m, 1H), 8.51 (d, J = 2.5, 5.0 Hz, 1H), 8.54 (d, J = 2.5 Hz, 1H). Anal. ($C_{11}H_{14}N_2O \cdot 0.55H_2O$) C, N; H: calcd, 7.60; found, 8.05.

(±)-4′-*trans*-(Fluoromethyl)cotinine (4). In a 50 mL round-bottomed flask equipped with a rubber septum and a magnetic stir bar were placed **2** (363 mg, 1.76 mmol) and dichloromethane (20 mL). To this stirring solution, at room temperature, was added triethylamine (0.248 mL, 1.94 mmol) followed by methanesulfonyl chloride (0.164 mL, 2.11 mmol). The reaction mixture was stirred for 30 min and then the reaction quenched with methanol to destroy excess methanesulfonyl chloride. The reaction mixture was concentrated with a rotary evaporator to obtain a dark yellow oil. This crude material (499 mg, 1.76 mmol) was placed in a 25 mL round-bottomed flask, and 1 M tetra-*n*-butylammonium fluoride (7.39 mL, 7.39 mmol) in THF was added to the system. This solution was refluxed under nitrogen for 30 min. The reaction mixture was concentrated, and the residue was taken up with chloroform. After washing with saturated aqueous sodium bicarbonate solution, the organic layer was dried and concentrated under reduced pressure to give a yellow oil. The crude material was purified by flash column chromatography (50 g of silica gel), eluting with chloroform/methanol (100:3), to provide 131 mg (36% yield) of the title compound as a light yellow oil. MS (DCI/NH_3): *m/z* 209 $(M + H)^+$, 226 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 2.36 (d, J = 9.0, 15 Hz, 1H), 2.42–2.58 (m, 1H), 2.71 (s, 3H), 2.74 (dd, J = 9.0, 15 Hz, 1H), 4.52 (d, J = 5.2 Hz, 1H), 4.48 (ddd, J = 2.6, 5.1, 47 Hz, 2H), 7.47 (dd, J = 5.2, 7.7 Hz, 1H), 7.66 (dt, J = 1.9, 8.1 Hz, 1H), 8.57 (d, J = 1.1 Hz, 1H), 8.66 (m, 1H).

(±)-3′-*trans*-(Fluoromethyl)nicotine Oxalate (5). Following the same procedure as described in the preparation of **3**, compound **4** (131 mg, 0.62 mmol) in THF (10 mL) was treated with borane (1.25 mL, 1.25 mmol) to give 59 mg of the title compound (49%) as a colorless oil. MS (DCI/NH_3): *m/z* 195 $(M + H)^+$, 212 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.70–1.82 (m, 1H), 2.15 (s, 3H), 2.16–2.20 (m, 1H), 2.32–2.45 (m, 2H), 2.97 (d, J = 9 Hz, 1H), 3.24 (t, J = 9.0 Hz, 1H), 4.47 (ddd, J = 4.5, 9.0, 48 Hz, 2H), 7.28 (m, 1H, overlap with $CDCl_3$), 7.72 (dt, J = 2.5, 9.0 Hz, 1H), 8.53 (dd, J = 2.5, 5.0 Hz, 1H), 8.57 (d, J = 2.5 Hz, 1H).

To the solution of the product obtained from above in diethyl ether (1.5 mL) was added oxalic acid in diethyl ether (5 mL) dropwise at 0 °C. After the mixture was stirred at 0 °C for 15 min, the precipitate was collected by centrifugation, washed with diethyl ether three times, and dried *in vacuo* to yield the title compound as a white powder. Mp: 86–89 °C. MS (DCI/NH_3): *m/z* 195 $(M + H)^+$, 212 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.18–2.32 (m, 1H), 2.41–2.58 (m, 1H), 2.82 (s, 3H), 3.07–3.30 (m, 1H), 3.36–3.51 (m, 1H), 4.38–4.74 (m, 2H, overlap with D_2O peak), 4.85–4.98 (m, 1H), 7.76 (dd, J = 5.0, 7.5 Hz, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.75 (d, J = 5.0 Hz, 1H), 8.79 (s, 1H). Anal. ($C_{11}H_{15}N_2F \cdot 1.6C_2H_2O_4 \cdot 1.0H_2O$) C, H, N.

(±)-4′-*trans*-[[[Phenoxy(thiocarbonyl)]oxy]methyl]cotinine (6). In a 50 mL round-bottomed flask equipped with a rubber septum and a magnetic stir bar were placed 4-(hydroxymethyl)cotinine (**2**) (468 mg, 2.27 mmol) and dichloromethane (15 mL). To this stirring solution, at room temperature, was added pyridine (0.733 mL, 9.0 mmol) followed by chlorophenoxythiocarbonate (0.373 mL, 2.72 mmol). The reaction mixture was stirred at room temperature for 2 h and at 0–5 °C for 19 h. The reaction was then quenched with methanol to destroy excess chloride. The reaction mixture was concentrated with a rotary evaporator to obtain a dark yellow oil. This crude material was subjected to flash column chromatography (50 g of silica gel), gradually increasing the polarity of the eluent from 2:1 hexane/acetone to 1:1 hexane/acetone, to obtain 576 mg (74% yield) of the phenoxythiocarbonate as a white solid. MS (DCI/NH_3): *m/z* 343 $(M + H)^+$, 360 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 2.43 (dd, J = 6, 15 Hz, 1H), 2.68–2.89 (m, 2H), 2.72 (s, 3H), 4.54–4.62 (m, 2H), 4.49 (d, J = 6.0 Hz, 1H), 7.06–7.12 (m, 1H), 7.31–7.35 (m, 1H), 7.36–7.48 (m, 3H), 7.59 (dt, J = 8.5, 2 Hz, 1H), 8.57 (s, 1H), 8.65 (m, 1H).

(±)-4′-*trans*-Methylcotinine (7). To a solution of the compound **6** (392 mg, 1.14 mmol) in toluene (15 mL) containing azobis(isobutyronitrile) (30 mg, 0.38 mmol) was added tris(trimethylsilyl)silane (0.52 mL, 1.72 mmol). The resultant solution was degassed under nitrogen. After 2 h at 90 °C, the toluene was removed under reduced pressure and the residue was allowed to stand on a silica gel column for 30 min prior to elution with chloroform/methanol, 100:7. There was obtained 246 mg (76%) of the title compound as a colorless oil. MS (DCI/NH_3): *m/z* 191 $(M + H)^+$, 208 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.19 (d, J = 7.5 Hz, 3H), 2.12–2.26 (m, 2H), 2.67 (s, 3H), 2.69–2.83 (m, 1H), 4.11 (d, J = 6.0 Hz, 1H), 7.54 (m, 1H), 7.74 (d, J = 7.5 Hz, 1H), 8.58 (s, 1H), 8.65 (d, J = 4.5 Hz, 1H).

(±)-3′-*trans*-Methylnicotine Dioxalate (8). Compound **7** (112 mg, 0.59 mmol) in THF (6 mL) was treated dropwise with a 1 M solution of borane (1.76 mL, 1.76 mmol) in THF at room temperature. After the solution was refluxed for 2 h, the reaction was quenched by addition of a large excess of methanol. The resultant solution was allowed to stir at room temperature for an additional 15 min. Solvent was then removed under reduced pressure to give a white solid. The crude reaction product (110 mg) was dissolved in a mixture of dioxane (3 mL) and ethanol (6 mL). This reaction mixture was then treated with cesium fluoride (204 mg, 1.76 mmol) and refluxed overnight. The crude product was purified by flash column chromatography on silica gel, eluting with hexane/acetone (1:1), to give 22 mg (21% yield for two steps) of the title compound as a colorless oil. MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_3)^+$. ^1H NMR ($CDCl_3$): δ 0.98 (d, J = 6.0 Hz, 1H), 1.41–1.59 (m, 1H), 1.55–1.79 (m, 1H), 2.16 (s, 3H), 2.33–2.50 (m, 1H), 2.59–2.72 (m, 1H), 3.20–3.40 (m, 1H), 3.68–3.74 (m, 1H), 7.25–7.34 (m, 1H, overlap with $CDCl_3$ peak), 7.67–7.83 (m, 1H), 8.50–8.59 (m, 2H).

To the solution of the product obtained above in diethyl ether (1.5 mL) was added oxalic acid in diethyl ether dropwise at 0 °C. After stirring at 0 °C for 15 min, the precipitate was collected by centrifugation, washed with diethyl ether three times, and dried *in vacuo* to yield the title compound as a white powder. Mp: 98–101 °C. MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 1.05 (d, J = 6.6 Hz, 3H), 1.93–2.09 (m, 1H), 2.41–2.55 (m, 1H), 2.70–2.90 (m, 1H, overlap with 2.83 peak), 2.83 (s, 3H), 3.36–3.52 (m, 1H), 3.84–4.03 (m, 1H), 4.21 (d, J = 9.0 Hz, 1H), 8.01 (dd, J = 5.5, 9.0 Hz, 1H), 8.49–8.58 (m, 1H), 8.86 (dd, J = 1.5, 5.5 Hz, 1H), 8.90 (d, J = 3 Hz, 1H). Anal. ($C_{11}H_{16}N_2 \cdot 2.4C_2H_2O_4$) C, H, N.

(±)-4′-*trans*-(Methoxymethyl)cotinine (9). A sample of 3-*trans*-(hydroxymethyl)cotinine (143 mg, 0.69 mmol) was dissolved in DMSO (1.5 mL) containing potassium hydroxide (154 mg, 2.76 mmol) and stirred at room temperature for 15 min. Methyl iodide (0.086 mL, 1.38 mmol) was then added to the reaction mixture, and after stirring at room temperature for 1 h, the solvent was evaporated under reduced pressure. The crude product was purified on a flash silica gel column, eluting with chloroform/methanol (10:1), to give 66 mg (43%) of the title compound. MS (DCI/NH_3): *m/z* 221 $(M + H)^+$, 238 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 2.46–2.58 (m, 3H), 2.69 (s, 3H), 3.38 (s, 3H), 3.42 (d, *J* = 6 Hz, 2H), 4.43 (d, *J* = 6 Hz, 1H), 7.37 (dd, *J* = 4.5, 6 Hz, 1H), 7.56 (m, 1H), 8.52 (m, 1H), 8.61 (m, 1H).

(±)-3′-*trans*-(Methoxymethyl)nicotine Dioxalate (10). Compound **9** (66 mg, 0.30 mmol) was treated with borane followed by cesium fluoride as described in the preparation of compound **8**. The crude product was purified by flash chromatography on silica gel, eluting with acetone/hexane (1:1), to give 36 mg (23%) of the free base. By the procedure described in **8**, the product described above was converted to the oxalate salt in quantitative yield to give 64 mg of the title compound as a very hygroscopic salt. MS (DCI/NH_3): *m/z* 207 $(M + H)^+$, 224 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.05–2.19 (m, 1H), 2.40–2.55 (m, 1H), 2.83 (s, 3H), 3.01–3.16 (m, 1H), 3.22 (s, 3H), 3.40–3.53 (m, 1H), 3.56 (dd, *J* = 3.0, 6.0 Hz, 1H), 3.93 (br s, 1H), 4.88 (m, 1H), 4.52 (m, 1H), 8.06 (dd, *J* = 5, 8.1 Hz, 1H), 8.61 (m, 1H), 8.87 (d, *J* = 5.6 Hz, 1H), 8.96 (m, 1H). Anal. ($C_{12}H_{18}N_2O{\cdot}1.5C_2H_2O_4$) C, H, N.

(3′*R*,5′*S*)-3′-Hydroxycotinine (12). A sample of (*S*)-cotinine (1.2 g, 6.8 mmol; from Aldrich Chemical Co.) was dissolved in THF (30 mL) and cooled to −78 °C. LDA solution (1.5 M in hexane, 13.6 mmol) was added, and the solution was stirred and warmed to 0 °C for 30 min. The solution was cooled to −78 °C, and (+)-(camphorylsulfonyl)oxaziridine (2.5 g, 10.9 mmol) dissolved in THF (24 mL) was added. The reaction mixture was stirred for 2 h and the reaction quenched by addition of methanol. This mixture was stirred for 15 min, and the solvent was removed. The residue was subjected to flash chromatography on silica gel using chloroform/methanol (100:7) as eluent. The title compound was isolated as an oil (1.1 g, 84% yield). $[\alpha]_D$ +39° (*c* 0.48, MeOH) (lit.[24] $[\alpha]_D$ +42.2° (*c* 2.5, MeOH). MS (DCI/NH_3): *m/z* 193 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 2.34 (ddd, *J* = 13.5, 9.0, 3.0 Hz, 1H), 2.51 (m, 1H), 2.78 (s, 3H), 4.57 (t, *J* = 7.5 Hz, 1H), 4.66 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.45 (m, 1H), 7.35 (dd, *J* = 9.0, 6.0 Hz), 8.61 (dd, *J* = 5.6, 3 Hz, 1H), 8.49 (d, *J* = 3 Hz, 1H).

(2′*S*,4′*R*)-4′-Hydroxynicotine Dioxalate (13). A 1 M solution of borane (3.71 mL, 3.71 mmol) in THF was added dropwise over a period of 5 min to compound **12** (357 mg, 1.86 mmol) in THF (2 mL) under nitrogen. After the mixture was refluxed for 2 h, methanol was added dropwise and the reaction mixture stirred for an additional 15 min. The solvent was then removed *in vacuo*, affording a white solid borane complex. This solid was dissolved in anhydrous ethanol, cesium fluoride (1.30 g, 11.16 mmol) was added, and the resultant solution was refluxed overnight. Evaporation of the solvent provided a white solid which was purified on a silica gel column, eluting with chloroform/methanol (10:1), to give 105 mg of the desired alcohol as an oil in 32% yield. MS (DCI/NH_3): *m/z* 179 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 2.03–2.10 (m, 2H), 2.18 (s, 3H), 2.33 (dd, *J* = 5.2, 10 Hz, 1H), 3.52 (dd, *J* = 7.3, 9.5 Hz), 3.59 (dd, *J* = 6.7, 10.3 Hz, 1H), 4.47 (m, 1H), 7.43 (dd, *J* = 5.2, 7.7 Hz, 1H), 7.85 (dt, *J* = 5.9, 1.8 Hz, 1H), 8.45 (dd, *J* = 5.2, 1.5 Hz, 1H), 8.50 (d, *J* = 1.5 Hz, 1H).

A solution of the amine obtained from above (34 mg, 0.19 mmol) in ethanol was added dropwise to a stirred solution of oxalic acid (25 mg, 0.28 mmol) in diethyl ether at room temperature. The resultant white precipitate was then collected by centrifugation and triturated with three portions of diethyl ether. The hygroscopic solid was obtained in 50% yield (25.4 mg). Mp: 208–211 °C. $[\alpha]_D$ −15.5° (*c* 0.11, MeOH). MS (DCI/NH_3): *m/z* 179 $(M + H^+)$, 196 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.55 (dd, *J* = 6, 13 Hz), 2.73 (m, 2H), 2.96 (s, 3H), 3.37 (m, 1H), 4.19 (m, 1H), 4.93 (m, 1H), 7.82 (m, 1H), 8.32 (d, *J* = 9 Hz, 1H), 8.71 (d, *J* = 6 Hz), 8.82 (s, 1H). Anal. ($C_{10}H_{14}N_2O{\cdot}C_2H_2O_4{\cdot}H_2O$) C, H, N.

(3′*R*,5′*S*)-3′-Methoxycotinine (14). A sample of hydroxycotinine (80 mg, 2 mmol) was dissolved in THF containing sodium hydride and stirred at room temperature for 15 min. Tetrabutylammonium iodide (20 mg, 0.05 mmol) and methyl iodide (0.020 mL, 0.32 mmol) were then added to the reaction mixture. After stirring at room temperature for 20 h, the solvent was evaporated under reduced pressure. The crude product was purified on a flash silica gel column. Elution with chloroform/methanol (20:1) gave 17 mg (53%) of the title compound. MS (DCI/NH_3): *m/z* 207 $(M + H)^+$, 224 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 2.14–2.26 (m, 1H), 2.42–2.55 (m, 1H), 2.73 (s, 3H), 3.32–3.43 (m, 3H), 3.58 (s, 3H), 4.12 (m, 1H), 4.66 (m, 1H), 7.36 (m, 1H), 7.47 (m, 1H), 8.5 (m, 1H), 8.62 (m, 1H).

(2′*S*,4′*R*)-4′-Methoxynicotine Dioxalate (15). Compound **14** (170 mg, 0.83 mmol) was treated with borane followed by cesium fluoride as described in the preparation of **13**. The crude product was purified by flash chromatography on silica gel, eluting with acetone/hexane (1:1), to give 36 mg (23% yield for two steps). MS (DCI/NH_3): *m/z* 191 $(M + H)^+$, 208 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 1.4–1.52 (m, 1H), 1.88–197 (m, 2H), 2.09–2.12 (m, 1H), 2.15 (s, 3H), 2.6–2.7 (m, 1H), 3.13–3.41 (m, 2H), 3.37 (s, 3H), 7.25–7.29 (m, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.53 (d, *J* = 1.5 Hz, 1H).

By the procedure described in the preparation of salt **13**, the product obtained above was converted to the oxalate salt in quantitative yield to give 64 mg of the title compound as a very hygroscopic salt. Mp: 150–152 °C. $[\alpha]_D$ −2.56° (*c* 0.19, MeOH). MS (DCI/NH_3): *m/z* 193 $(M + H)^+$, 210 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.60–2.70 (m, 1H), 2.74–2.81 (m, 1H), 2.92 (s, 3H), 3.42 (s, 3H), 3.46–3.55 (m, 1H), 4.25 (m, 1H), 4.88 (m, 1H), 4.44 (m, 1H), 8.09 (dd, *J* = 5, 8.1 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.89 (d, *J* = 5.6 Hz, 1H), 8.99 (s, 1H). Anal. ($C_{11}H_{16}N_2O{\cdot}2.8C_2H_2O_4{\cdot}H_2O$) C, H, N.

(3′*R*,5′*S*)-3′-[(Methylsulfonyl)oxy]cotinine (16). In a 50 mL round-bottomed flask equipped with a rubber septum and a magnetic stir bar were placed product **12** (554 mg, 2.89 mmol) and dichloromethane (20 mL). To this stirring solution, at room temperature, was added triethylamine (0.59 mL, 4.62 mmol) followed by methanesulfonyl chloride (0.34 mL, 4.34 mmol). The reaction mixture was stirred for 19 h and then the reaction quenched with methanol to destroy excess methanesulfonyl chloride. The reaction mixture was concentrated with a rotary evaporator to obtain a dark yellow oil. This crude material was subjected to flash chromatography (50 g of silica gel), gradually increasing the polarity of the eluent from 100:5 chloroform/methanol to 100:7 chloroform/methanol, to obtain 420 mg (57% yield) of the methanesulfonate ester as a pale yellow viscous oil. MS (DCI/NH_3): *m/z* 257 $(M + H)^+$, 264 $(M + NH_4)^+$. ^1H NMR (CD_3OD): δ 2.24 (s, 3H), 2.65–2.61 (m, 2H), 3.65–3.74 (m, 1H), 3.07 (s, 3H), 3.75–3.85 (m, 1H), 4.25–4.32 (m, 2H), 5.24–5.34 (m, 1H), 7.62 (dd, *J* = 6, 7.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 6 Hz, 1H), 8.59 (s, 1H).

(2′*S*,4′*R*)-4′-[(Methylsulfonyl)oxy]nicotine Dioxalate (17). To compound **16** (652 mg, 2.41 mmol) in THF (15 mL) was added under nitrogen and dropwise over a period of 5 min a 1 M solution of borane (6.03 mL, 6.03 mmol) in THF. After the mixture was stirred under reflux for 2 h, methanol was added dropwise and the reaction mixture stirred for an additional 1 h. The solvent was then removed *in vacuo*, affording a white solid borane complex, **17′**. A sample of the borane complex (312 mg) was dissolved in anhydrous ethanol, cesium fluoride (334 mg) was added, and the resultant solution was refluxed overnight. Evaporation of the solvent provided a white solid which was purified on a silica gel column, eluting with chloroform/methanol (10:7) to give 117 mg of the desired mesylate. Following the procedure for the preparation of salt **13** above, a 35 mg sample of the oxalate salt was prepared. Mp: 122–125 °C. $[\alpha]_D$ −6.55° (*c* 0.28, $CHCl_3$). MS (DCI/NH_3): *m/z* 257 $(M + H)^+$. ^1H NMR (D_2O): δ 2.85 (m, 5H), 3.35 (s, 3H), 3.77 (d, *J* = 14 Hz, 1H), 4.38 (dd, *J* = 5.5, 13, 1H), 5.0

(m, 1H), 5.7 (m, 1H), 7.87 (m, 1H), 8.37 (dt, J = 8, 1.5 Hz, 1H), 8.79 (m, 1H), 8.82 (m, 1H). Anal. ($C_{11}H_{16}N_2O_3S \cdot 1.7C_2H_2O_4$) C, H, N.

(2′*S*,4′*S*)-4′-Cyanonicotine Dioxalate (18). The amine borane complex **17′** (100 mg, 0.39 mmol) was dissolved in DMF (4 mL) and sodium cyanide (190 mg) was added. This solution was heated at 105 °C under nitrogen for 16 h. The reaction mixture was concentrated with a rotary evaporator, and the residue was taken up in chloroform. The crude material was purified by flash chromatography (50 g of silica gel), eluting with chloroform/methanol (100:0.7), to provide 24 mg (33% yield) of the title compound as a yellow oil. MS (DCI/NH_3): m/z 188 $(M + H)^+$, 205 $(M + NH_4)^+$. ^{1}H NMR ($CDCl_3$): δ 2.02–2.13 (m, 1H), 2.21 (s, 3H), 2.62–2.72 (m, 1H), 3.06–3.16 (m, 1H), 3.21–3.31 (m, 1H), 3.51 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 4.8, 7.7 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.53–8.60 (m, 2H).

The oil from above was dissolved in diethyl ether to which was added, dropwise, a solution of oxalic acid (13 mg, 0.14 mmol) in diethyl ether. The resultant precipitate was collected by centrifugation to give 37 mg of the title compound. Mp: 130–133 °C. $[\alpha]_D$ −50.4° (c 0.10, MeOH). MS (DCI/NH_3): m/z 188 $(M + H)^+$, 205 $(M + NH_4)^+$. ^{1}H NMR (D_2O): δ 2.60 (s, 3H), 2.60–2.70 (m, 1H), 3.02–3.22 (m, 1H), 3.51 (dd, J = 9.2, 12.1 Hz, 1H), 3.75–3.88 (m, 1H), 3.99 (dd, J = 3.6, 11.7 Hz, 1H), 4.37 (dd, J = 7.7, 10.0 Hz, 1H), 7.84 (ddd, J = 0.8, 8.1, 5.2 Hz, 1H), 8.35 (dt, J = 1.8, 8.1 Hz, 1H), 8.75 (dd, J = 1.4, 5.4 Hz, 1H), 8.78 (d, J = 1.5 Hz, 1H). Anal. ($C_{11}H_{13}N_3 \cdot 2.0C_2H_2O_4$) C, H, N.

(2′*S*,4′*R*)-4′-(Acetyloxy)nicotine Dioxalate (19). To a sample of 4′-hydroxynicotine (95 mg, 0.53 mmol) (as the borane complex intermediate from compound **13** shown above) in methylene chloride (3 mL) were added acetic anhydride (0.075 mL, 0.80 mmol) and pyridine (0.086 mL, 1.06 mmol), and the solution was allowed to stir at room temperature for 16 h. The solvent was then removed, and the residue was dissolved in ethanol (4 mL). To this was added CsF (184.2 mg, 1.8 mmol), and the mixture was stirred at 57 °C for 16 h. The solvent was removed and the residue purified by chromatography on silica gel, eluting with chloroform/methanol (100:7), to give the product as an oil. This was converted to the dioxalate salt following the procedure described above giving a white solid. Mp: 58–60 °C. $[\alpha]_D$ +6.67° (c 0.24, MeOH). MS (DCI/NH_3): m/z 221 $(M + H)^+$, 238 $(M + NH_4)^+$. ^{1}H NMR (D_2O): δ 2.18 (s, 3H), 2.7–2.9 (m, 2H), 2.94 (s, 3H), 3.61 (d, J = 14 Hz, 1H), 4.33 (dd, J = 5.5, 14, 1H), 5.04 (q, J = 6.2 Hz, 1H), 5.59 (br t, 1H), 8.05 (dd, J = 5.5, 8.5 Hz, 1H), 8.61 (d, J = 8.5 Hz, 1H), 8.88 (d, J = 5.5 Hz, 1H), 8.97 (s, 1H). Anal. ($C_{12}H_{16}N_2O_2 \cdot 2.2C_2H_2O_4$) C, H; N: calcd, 6.70; found, 6.17.

(3′*RS*,5′*S*)-3′-(Hydroxymethyl)cotinine (20). The enolate of cotinine was generated by dropwise addition of a 1.5 M solution of lithium diisopropyl amide solution (1.67 mL, 2.5 mmol) in THF to cotinine (352 mg, 2.00 mmol) in THF (18 mL) at −78 °C. After the mixture was stirred at −78 °C for 15 min, the reaction temperature was raised to 0 °C and the resultant solution allowed to stirred for an additional 30 min. The enolate solution was cooled to −78 °C followed by passage of anhydrous gaseous formaldehyde in a stream of nitrogen (the formaldehyde was generated by the thermal depolymerization of paraformaldehyde at 160 °C). After 2 h at −78 to −20 °C, the reaction was quenched at 0 °C with methanol and the organic solvent was concentrated *in vacuo* to give a dark yellow oil. The oil was purified by flash column chromatography on silica gel, eluting with chloroform/methanol (100:7), to give 242 mg (59% yield) of the title compound as a colorless oil. MS (DCI/NH_3): m/z 207 $(M + H)^+$, 224 $(M + NH_4)^+$. ^{1}H NMR ($CDCl_3$): δ 1.68–1.80 (m, 1H, overlap with water peak), 2.05 (ddd, J = 3.0, 6.0, 9.0 Hz, 1H), 2.23 (m, 1H), 2.41 (dt, J = 12, 9 Hz, 1H), 2.65 (s, 1H), 2.76 (s, 2H), 3.72–3.83 (m, 1H), 3.93–4.05 (m, 1H), 4.52 (t, J = 7.5 Hz, $^1/_3$H), 4.60 (dd, J = 9, 3.0 Hz, $^2/_3$H), 7.47–7.53 (m, $^2/_3$H), 7.59–7.64 (m, $^1/_3$H), 8.47–8.66 (m, 1H), 8.57–8.66 (m, 1H).

(2′*S*,4′*R*)- and (2′*S*,4′*S*)-4′-(Hydroxymethyl)nicotine (21 and 22). Compound **20** (735 mg, 3.57 mmol), a mixture of diastereoisomers, in THF (10 mL) was treated dropwise with a 1 M solution of borane (10.7 mL, 10.7 mmol) in THF at room temperature. After the solution was refluxed for 3 h, the reaction was quenched by addition of a large excess of methanol. The resultant solution was allowed to stir at room temperature for an additional 15 min. Solvent was then removed under reduced pressure to give a white solid. One-fifth of this crude reaction product (160 mg, 0.83 mmol) was dissolved in dioxane (8 mL) and treated with cesium fluoride (290 mg, 2.50 mmol) as described in the preparation of compound **13**. The crude product was purified by flash column chromatography on silica gel, eluting with chloroform/methanol (10:1), to give, in order of elution, 23 mg of (2′*S*,4′*S*)-4′-(hydroxymethyl)nicotine (**22**)[26] (14% for two steps) and 69 mg of (2′*S*,4′*R*)-4′-(hydroxymethyl)nicotine (**21**)[26] as a colorless oil.

4′*S* Isomer. MS (DCI/NH_3): m/z 193 $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 1.65–1.78 (m, 1H), 2.18 (s, 3H), 2.51–2.63 (m, 1H), 3.13–3.30 (m, 2H), 3.66 (dd, J = 4.5, 9.0 Hz, 1H), 3.79 (dd, J = 4.5, 9.0 Hz, 1H), 7.29 (m, 1H, overlap with $CDCl_3$), 7.83 (d, J = 7.5 Hz, 1H), 8.53 (m, 2H). Anal. ($C_{11}H_{16}N_2O \cdot 0.05CHCl_3$) C, H, N.

4′*R* Isomer. MS (DCI/NH_3): m/z 193 $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 1.88–2.10 (m, 2H), 2.19 (s, 3H), 2.54–2.72 (m, 1H), 3.24 (t, J = 7.5 Hz, 1H), 3.45 (t, J = 8.0 Hz, 1H), 3.66 (m, 2H), 7.28 (m, 1H, overlap with $CDCl_3$), 7.76 (d, J = 7.5 Hz, 1H), 8.52 (dd, J = 3.0, 4.5 Hz, 1H), 8.54 (d, J = 3.0 Hz, 1H). Anal. ($C_{11}H_{16}N_2O$) C, H, N.

(2′*S*,4′*R*)-4′-[(Methylsulfonyl)oxy]methylnicotine (23). A sample of 4-(hydroxymethyl)nicotine (**21**) (384 mg, 2.0 mmol) in THF (10 mL) was treated dropwise with a 1 M solution of borane (3.0 mL, 3.0 mmol) in THF at room temperature. After the mixture was refluxed for 3 h, the reaction was quenched by addition of a large excess of methanol. The resultant solution was allowed to stir at room temperature for an additional 15 min. The solvent was then removed under reduced pressure to give a white solid, which was used for next the reaction without further purification. Thus, in a 50 mL round-bottomed flask equipped with a rubber septum and a magnetic stir bar were placed the product (440 mg, 2.0 mmol) from the previous reaction and dichloromethane (25 mL). To this stirred solution was added pyridine (0.34 mL, 8.0 mmol) followed by methanesulfonyl chloride (0.42 mL, 3.0 mmol) at room temperature. The reaction mixture was stirred for 19 h and then the reaction quenched with methanol to destroy excess methanesulfonyl chloride. The reaction mixture was concentrated with a rotary evaporator to obtain a dark yellow oil. This crude material was subjected to flash column chromatography on silica gel, gradually increasing the polarity of the eluent from 2:1 hexane/acetone to 1:1 hexane/acetone, to obtain 350 mg (65% yield) of the borane complex of the methanesulfonate ester as a pale yellow viscous oil. MS (DCI/NH_3): m/z 271 $(M + H)^+$, 300 $(M + BNH_4)^+$. ^{1}H NMR ($CDCl_3$): δ 1.88–1.95 (m, 1H), 2.10–2.20 (m, 1H), 2.32 (s, 1H), 2.50 (s, 2H), 2.78–2.96 (m, 2H), 3.04 (s, 1H), 3.09 (s, 2H), 3.30–3.48 (m, 1H), 3.70–3.88 (m, 1H), 4.25–4.34 (m, 2H), 7.53–7.62 (m, 1H), 8.24 (d, J = 9.0 Hz, $^1/_3$H), 8.40 (d, J = 9 Hz, $^2/_3$H), 8.50–8.72 (m, 2H).

(2′*S*,4′*R*)-4′-(Fluoromethyl)nicotine Dioxalate (24). Compound **23** (104 mg, 0.39 mmol) was placed in a 10 mL round-bottomed flask, and 1 M tetra-*n*-butylammonium fluoride (2.31 mL, 2.31 mmol) in THF was added. This solution was heated at reflux for 3 h. The reaction mixture was concentrated, and the residue was taken up in chloroform. The crude material was purified by flash column chromatography (50 g of silica gel), eluting with hexane/acetone (1:2), to provide 12 mg (16% yield) of the title compound as a yellow oil. MS (DCI/NH_3): m/z 195 $(M + H)^+$, 212 $(M + NH_4)^+$. ^{1}H NMR ($CDCl_3$): δ 1.92–2.17 (m, 2H), 2.23 (s, 3H), 2.60–2.92 (m, 1H), 3.11–3.47 (m, 1H), 3.40–3.60 (m, 1H), 4.43 (dd, J = 6.0, 48 Hz, 2H), 7.25 (m, 1H, overlap with $CDCl_3$ peak), 7.65–7.90 (m, 1H), 8.55 (m, 2H).

To the solution of the product from above in diethyl ether (1.5 mL) was added oxalic acid in diethyl ether (5 mL) dropwise at 0 °C. After stirring at 0 °C for 15 min, the precipitate was collected by centrifugation, washed with diethyl ether three times, and dried *in vacuo* to yield the title compound as a white powder. Mp: 89–92 °C. $[\alpha]_D$ +9.6° (c 0.12, MeOH). MS (DCI/NH_3): m/z 195 $(M + H)^+$, 212 $(M + NH_4)^+$. ^{1}H NMR

(D_2O): δ 2.52–2.76 (m, 2H), 2.84 (s, 3H), 3.0–3.23 (m, 1H), 3.30–3.43 (m, 1H), 4.01–4.13 (m, 1H), 4.64 (dd, J = 56.0, 48 Hz, 2H), 4.67–4.80 (m, 1H, overlap with D_2O peak), 7.91 (dd, J = 7.5, 4.5 Hz, 1H), 8.45 (d, J = 9.0, 1H), 8.81 (d, J = 6.1 Hz, 1H), 8.87 (s, 1H). Anal. ($C_{11}H_{15}N_2F \cdot 2.1C_2H_2O_4 \cdot 0.5Et_2O$) C, H, N.

(2′S,4′R)-4′-(Cyanomethyl)nicotine Dioxalate (25). A sample of **23** (65 mg, 0.24 mmol) and NaCN (118 mg, 2.4 mmol) were dissolved in DMF (2.5 mL) and water (0.4 mL) and stirred at 100 °C for 16 h. The solvent was removed by evaporation, and the residue was purified on a silica gel column, eluting with 1:1 acetone/hexane. Removal of the solvent gave 32 mg of the free base, which was converted to the oxalate salt as described above. Mp: 55–58 °C. $[\alpha]_D$ +5.33° (c 0.15, MeOH). MS (DCI/NH_3): m/z 202 $(M + H)^+$, 219 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.5–2.6 (m, 1H), 2.7–2.92 (m, 7H), 3.1–3.2 (m, 1H), 3.21–3.41 (m, 1H), 4.12 (m, 1H), 7.85 (dd, J = 8.1, 5.2 Hz, 1H), 8.37 (dt, J = 8, 1.6 Hz, 1H), 8.78 (dd, J = 5.5, 1.5 Hz, 1H), 8.83 (d, J = 1.8 Hz, 1H). Anal. ($C_{12}H_{15}N_3 \cdot 2C_2H_2O_4$) C, N, H.

(2′S,4′R)-4′-[(Methylthio)methyl]nicotine Dioxalate (26). A sample of **23** (260 mg, 1.01 mmol) and NaSMe (175 mg, 2.50 mmol) were dissolved in DMF (4.0 mL) and water (0.4 mL) and stirred at 55 °C for 16 h. The solvent was removed by evaporation, and the residue was purified on a silica gel column, eluting with 20:1 chloroform/methanol. Removal of the solvent gave 65 mg (29%) of the free base, which was converted to the oxalate salt as described above. Mp: 117–120 °C. $[\alpha]_D$ +13° (c 0.10, MeOH). MS (DCI/NH_3): m/z 223 $(M + H)^+$, 240 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.14 (s, 3H), 2.48–2.59 (m, 1H), 2.61–2.72 (m, 1H), 2.78–2.89 (m, 2H), 2.85 (s, 3H), 2.97–3.17 (m, 1H), 3.17–3.34 (m, 1H), 3.60–3.80 (m, 1H), 4.08 (m, 1H), 8.08 (dd, J = 8.1, 5.5 Hz, 1H), 8.64 (m, 1H), 8.88 (d, J = 5.5, 1H), 8.96 (m, 1H). Anal. ($C_{12}H_{18}N_2S \cdot 2.2C_2H_2O_4$) C, H, N.

(2′S,4′R)-4′-(Methoxymethyl)nicotine Dioxalate (27). Compound **20** (195 mg, 0.95 mmol) was dissolved in THF (9 mL) containing sodium hydride (90 mg, 2.25 mmol) and stirred at room temperature for 15 min. Tetrabutylammonium iodide (185 mg, 0.5 mmol) and methyl iodide (0.095 mL, 1.53 mmol) were then added to the reaction mixture. After stirring at room temperature for 20 h, the solvent was evaporated under reduced pressure. The crude product was used directly for the next reaction without further purification. The compound obtained from above was treated with borane followed by cesium fluoride as described in the preparation of compound **13**. The crude product was purified by flash chromatography on silica gel, eluting with acetone/hexane (2:1), to give 24 mg of (2′S,4′R)-4′-(methoxymethyl)nicotine (12% for three steps). The product from above was converted to the oxalate salt by the procedure described in the preparation of compound **13** in quantitative yield to give 45 mg of the title compound as a very hygroscopic salt. Mp: 102–105 °C. $[\alpha]_D$ +15.9° (c 0.19, MeOH). MS (DCI/NH_3): m/z 207 $(M + H)^+$, 224 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 1.60–1.70 (m, 1H), 2.41–2.68 (m, 1H), 2.82 (s, 3H), 3.14–3.30 (m, 2H), 3.42 (s, 3H), 3.61 (m, 2H), 4.01 (br s, 1H), 7.97 (dd, J = 5, 8.1 Hz, 1H), 8.49 (m, 1H), 8.82 (d, J = 5.6 Hz, 1H), 8.88 (m, 1H). Anal. ($C_{12}H_{18}N_2O \cdot 2.18C_2H_2O_4 \cdot 0.3H_2O$) C, H, N.

(3′RS,5′S)-3′-Methylcotinine (28). 1.5 M solution of lithium diisopropyl amide solution (3.40 mL, 5.11 mmol) in THF was added dropwise to a solution of cotinine (819 mg, 4.65 mmol) in THF (30 mL) at −78 °C. After the mixture was stirred at −78 °C for 15 min, the reaction temperature was raised to 0 °C and the resultant solution was stirred for an additional 30 min. The solution was cooled to −78 °C, and then methyl iodide (0.304 mL, 4.88 mmol) was added dropwise. After 2 h at −78 to −20 °C, the reaction was quenched at 0 °C with methanol. The organic solvent was concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography on silica gel, eluting with acetone/hexane (3:1), to give 683 mg (77%) of the title compound as a colorless oil. MS (DCI/NH_3): m/z 190 $(M + H)^+$, 208 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.27 (d, J = 7.5 Hz, 3H), 2.12–2.20 (m, 2H), 2.63–2.74 (m, 1H), 2.74 (s, 3H), 4.54 (dd, J = 4.5, 8.0 Hz, 1H), 7.33 (ddd, J = 1.0, 4.5, 8.0 Hz, 1H), 7.48 (dt, J = 2.5, 8.0 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H), 8.59 (dd, J = 2.0, 4.5 Hz, 1H).

(2′S,4′R)-4′-Methylnicotine Dioxalate (29). Compound **28** (40 mg, 0.227 mmol) was treated dropwise with a 1 M solution of borane (0.45 mL, 0.45 mmol) in THF. After 3 h, the reaction was complete; the crude reaction product was treated with cesium fluoride as described in the preparation of the free amine **13**. The crude product was purified by flash column chromatography on silica gel, eluting with acetone/hexane (1:1), to give the title compound (32 mg, 81%) as a colorless oil.[26] MS (DCI/NH_3): m/z 177 $(M + H)^+$, 191 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.07 (d, J = 7.0 Hz, 3H), 1.78–1.83 (m, 1H), 1.93–2.0 (m, 2H), 2.16 (s, 3H), 2.42–2.50 (m, 1H), 3.21 (t, J = 8.1 Hz, 1H), 3.36 (dd, J = 7, 9.2 Hz, 1H), 7.26 (dd, J = 4.5, 8 Hz, 1H), 7.70 (dt, J = 2, 8 Hz, 1H), 8.49 (dd, J = 2, 4.5 Hz, 1H), 8.52 (d, J = 2 Hz, 1H).

To a solution of the product obtained above in diethyl ether (1.5 mL) was added oxalic acid in diethyl ether dropwise at 0 °C. The solution was stirred at 0 °C for 15 min, and the precipitate was collected by centrifugation, washed with diethyl ether three times, and dried *in vacuo* to yield the title compound as a white powder. Mp: 112–115 °C. $[\alpha]_D$ +16.3° (c 0.14, MeOH). MS (DCI/NH_3): m/z 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 1.23 (d, J = 6.6 Hz, 3H), 2.28–2.42 (m, 1H), 2.54–2.68 (m, 1H), 2.80 (m, 1H, overlap with 2.84 peak), 2.84 (s, 3H), 3.04 (m, 1H), 4.72 (br s, 1H), 3.98 (m, 1H), 7.98 (dd, J = 5.5, 8.0 Hz, 1H), 8.49 (d, J = 8.1, 1 Hz, 1H), 8.83 (d, J = 5.5 Hz, 1H), 8.89 (s, 1H). Anal. ($C_{11}H_{16}N_2 \cdot 2.4C_2H_2O_4 \cdot H_2O$) C, H, N.

(2′S,4′R)-4′-Ethylnicotine Dioxalate (31). Following a similar procedure as described for **28**, cotinine (300 mg, 1.70 mmol) was reacted with 1.5 mL of LDA (1.36 mL, 2.0 mmol) followed by treatment with ethyl iodide (0.204 mL, 2.55 mmol) to give 240 mg (69% yield) of 3′-ethylcotinine (**30**) as a colorless oil. MS (DCI/NH_3): m/z 205 $(M + H)^+$, 222 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 0.98 (t, J = 7.5 Hz, 3H), 1.50 (m, 1H), 1.94 (m, 1H), 2.23 (m, 1H), 2.58 (m, 1H), 2.73 (s, 3H), 4.54 (dd, J = 3, 9 Hz, 1H), 7.35 (m, 1H), 7.50 (m, 1H), 8.49 (br s, 1H), 8.60 (br s, 1H).

Following a similar procedure as described for **29**, the product (240 mg, 1.26 mmol) obtained from above was treated with borane (3.79 mL, 3.79 mmol) followed by decomplexation with cesium fluoride (292 mg, 2.52 mmol) to afford 136 mg of the title compound (56% yield for two steps) as a colorless oil. MS (DCI/NH_3): m/z 191 $(M + H)^+$, 208 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 0.92 (t, J = 7.5 Hz, 3H), 1.36 (dd, J = 7.5, 13.5 Hz, 1H), 1.44 (dd, J = 7.5, 13.5 Hz, 1H), 1.78–1.93 (m, 1H), 1.93–2.06 (m, 1H), 2.16 (s, 3H), 2.16–2.37 (m, 1H), 3.26 (m, 1H), 3.37 (m, 1H), 7.25 (m, 1H, overlap with $CHCl_3$), 7.71 (m, 1H), 8.49 (dd, J = 3.0, 6.0 Hz, 1H), 8.52 (d, J = 3 Hz, 1H).

The product obtained above was converted to the dioxalate salt following the procedure described in the preparation of **29**. Mp: 65–67 °C. $[\alpha]_D$ +12° (c 0.11, MeOH). MS (DCI/NH_3): m/z 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 0.97 (t, J = 7.5 Hz, 3H), 1.61 (m, 2H), 2.31–2.46 (m, 1H), 2.50–2.70 (m, 2H), 2.82 (s, 3H), 3.04–3.14 (m, 1H), 3.90–4.04 (m, 1H), 4.60–4.70 (m, 1H, overlap with D_2O peak), 7.79 (dd, J = 4.5, 8.0 Hz, 1H), 8.29 (d, J = 9.0, 1.5 Hz, 1H), 8.74 (d, J = 6.08 Hz, 1H), 8.78 (d, J = 1.5 Hz, 1H). Anal. ($C_{12}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

(3′R,5′S)-3′-Benzylcotinine (32). Following a similar procedure as described for **28**, cotinine (300 mg, 1.70 mmol) was reacted with 1.5 M of LDA (1.48 mL, 2.22 mmol), followed by treatment with benzyl bromide (0.303 mL, 2.25 mmol) to give 410 mg (90%) of the title compound as a colorless oil. MS (DCI/NH_3): m/z 267 $(M + H)^+$, 284 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 1.88–1.98 (m, 1H), 2.25–2.37 (m, 1H), 2.74 (s, 3H), 2.81 (dd, J = 8.0, 13.5 Hz, 1H), 2.90–3.01 (m, 1H), 3.22 (dd, J = 4.0, 13.5 Hz, 1H), 4.21 (dd, J = 4.0, 8.0 Hz, 1H), 7.16–7.43 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 8.41 (m, 1H), 8.57 (d, J = 4.5 Hz, 1H).

(2′S,4′R)-4′-Benzylnicotine Dioxalate (33). Following a similar procedure as described for **29**, the product **32** (410 mg, 1.54 mmol) obtained from above was treated with borane (4.62 mL, 4.62 mmol) followed by decomplexation with cesium fluoride (535 mg, 4.62 mmol) to afford the crude product. This

material was purified by flash column chromatography on silica gel, eluting with chloroform/methanol (10:1), to give 120 mg of the title compound (31% for two steps) as a colorless oil. MS (DCI/NH_3): *m/z* 253 $(M + H)^+$. ^1H NMR ($CDCl_3$): δ 8.53 (d, $J = 2.2$ Hz, 1H), 8.50 (d, $J = 4.4$ Hz, 1H), 7.6–7.7 (m, 1H), 7.10–7.31 (m, 6H), 3,16–3.45 (m, 2H), 2.73 (s, 3H), 2.19–2.33 (m, 4H), 1.92–2.19 (m, 2H).

To a solution of the product obtained above in diethyl ether (1.5 mL) was added oxalic acid in diethyl ether dropwise at 0 °C. After stirring at 0 °C for 15 min, the precipitate was collected by centrifugation, washed with diethyl ether (3×), and dried *in vacuo* to yield the title compound as a white powder. Mp: 63–65 °C. $[\alpha]_D$ +13.8° (*c* 0.17, MeOH). MS (DCI/NH_3): *m/z* 253 $(M + H)^+$, 270 $(M + NH_4)^+$. ^1H NMR (D_2O): δ 2.50–2.52 (m, 2H), 2.82 (s, 3H), 2.94 (d, $J = 8.1$ Hz, 1H), 3.01–3.24 (m, 1H), 3.14–3.27 (m, 1H), 3.82–3.96 (m, 1H), 4.6–4.83 (m, 1H, overlap with D_2O peak), 7.32–7.42 (m, 5H), 7.93 (dd, $J = 5.5$, 8.4 Hz, 1H), 8.43 (m, 1H), 8.79 (dd, $J = 1.5$, 5.6 Hz, 1H), 8.84 (d, $J = 2.9$ Hz, 1H). Anal. ($C_{17}H_{20}N_2 \cdot C_2H_2O_4$) C, H, N.

5′-Hydroxy-5′-methylnicotine (34). A sample of cotinine (0.95 g, 5.4 mmol; from Aldrich Chemical Co.) was dissolved in anhydrous ether (25 mL) flushed with nitrogen. The solution was cooled to 0 °C, and methyllithium (4.70 mL, 6.6 mmol) was slowly added via a syringe. A white precipitate formed, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with 1 M HCl (10 mL), and then potassium carbonate (0.7 g) was added. The layers were separated, the organic layer was removed, and the residue was dissolved in ethyl acetate. The aqueous layer was extracted overnight with ethyl acetate, and the two fractions were combined and then dried over sodium sulfate and concentrated to afford 1.11 g of a clear orange oil, which was purified on silica gel, eluting with chloroform/methanol (20:1) containing 1% ammonium hydroxide increasing to 7:1 containing 2% ammonium hydroxide. Removal of the solvent gave 0.27 g of the intermediate product.

(2′*S*,5′*S*)-5′-Methylnicotine Oxalate (36). Compound **34** (0.27 g, 1.4 mmol) was dissolved in anhydrous methanol (5.6 mL) under an nitrogen atmosphere and adjusted to the bromocresol green acidic end point (yellow) with 2 M HCl in anhydrous methanol. To this was added sodium cyanoborohydride (88 mg, 1.4 mmol), and the pH was again adjusted to acidic with the HCl. The reaction mixture was stirred for 0.5 h and the reaction quenched with 0.1 M sodium hydroxide (6 mL). The solution was adjusted to pH 12 with 15% sodium hydroxide solution; then solid sodium chloride and brine were added. The mixture was extracted with ethyl acetate, dried, and purified on silica gel, eluting with a series of increasingly polar mixtures of chloroform/methanol containing a small amount of ammonium hydroxide. Two fractions were isolated. Fraction A consisted of 95 mg (38%) of the 5′-(*S*)-methyl isomer. $[\alpha]_{546}$ −95.4° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_{546}$ −96.4° (*c* 0.6, MeOH). MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.54 (d, $J = 2.5$ Hz, 1H), 8.49 (dd, $J = 2.0$, 6.0 Hz, 1H), 7.73 (m, 1H), 7.25 (dd, $J = 3.0$, 7.5 Hz), 3.22 (t, $J = 8$ Hz, 1H), 2.33–2.46 (m, 1H), 2.11 (s, 3H), 1.91–2.04 (m, 1H), 1.47–1.73 (m, 2H), 1.21 (d, $J = 6.0$ Hz, 3H). Fraction B consisted of 34 mg (14%) of the 5′-(*R*)-methyl isomer. $[\alpha]_{546}$ −66.1° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_{546}$ −65.2° (*c* 0.23, MeOH). MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.51 (d, $J = 2.5$ Hz, 1H), 8.49 (dd, $J = 2.0$, 6.0 Hz, 1H), 7.64 (dt, $J = 3$, 7.5 Hz, 1H), 7.25 (dd, $J = 3.0$, 7.5 Hz), 3.71 (dd, $J = 6.0$, 9.0 Hz, 1H), 3.49 (m, 1H), 2.17–2.42 (m, 2H), 2.15 (s, 3H), 1.67–1.81 (m, 1H), 1.51–1.62 (m, 1H), 1.05 (d, $J = 6.0$ Hz, 3H). Each fraction was converted to the oxalate salt following the procedure described before.

Fraction A (5′*S* Isomer). Mp: 93–96 °C. $[\alpha]_D$ +30.3° (*c* 0.29, MeOH). MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR (CD_3OD): δ 1.53 (d, 3H), 2.05 (m, 1H), 2.35–2.6 (m, 4H), 2.76 (s, 3H), 3.62 (br m, 1H), 4.53 (t, 1H), 7.60 (q, 1H), 8.14 (dt, $J = 1.5$, 7.5 Hz, 1H), 8.67 (dd, $J = 2.5$, 6 Hz, 1H), 8.73 (d, $J = 2.5$ Hz, 1H). Anal. ($C_{11}H_{16}N_2 \cdot 1.3C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(2′*S*,5′*R*)-5′-Methylnicotine Oxalate (35). Fraction B (5′*R* Isomer). Viscous oil. MS (DCI/NH_3): *m/z* 177 $(M + H)^+$, 194 $(M + NH_4)^+$. ^1H NMR (CD_3OD): δ 1.47 (d, 3H), 1.93–2.07 (m, 1H), 2.4–2.6 (m, 4H), 2.58 (s, 3H), 3.95 (br s, 1H), 7.59 (q, 1H), 8.10 (dt, $J = 1.5$, 7 Hz, 1H), 8.67 (dd, $J = 2.5$, 6 Hz, 1H), 8.73 (d, $J = 2.5$ Hz, 1H). Anal. ($C_{11}H_{16}N_2 \cdot 1.5C_2H_2O_4 \cdot 0.4H_2O$) C, H, N.

(2′*S*,5′*S*)-5′-Butylnicotine Oxalate (38). Following a similar procedure as described above, cotinine (1.00 g, 5.67 mmol) was reacted with *n*-butyllithium (2.70 mL, 6.75 mmol) to afford 1.33 g of the amino alcohol as an oil. Following a similar procedure as described above, the aminal product was reduced with sodium cyanoborohydride. Chromatography provided two fractions; their physical data are shown below. Fraction A (5′*S* isomer) consisted of 360 mg (37%). $[\alpha]_D$ −36.2° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_D$ −37.6° (*c* 1.9, MeOH)). MS (DCI/NH_3): *m/z* 219 $(M + H)^+$, 236 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.53 (d, $J = 2.5$ Hz, 1H), 8.43 (dd, $J = 2.0$, 6.0 Hz, 1H), 7.71 (dt, $J = 3.0$, 7.5 Hz, 1H), 7.24 (dd, $J = 3.0$, 7.5 Hz), 3.23 (t, $J = 8$ Hz, 1H), 2.26–2.38 (m, 1H), 2.11 (s, 3H), 1.91–2.15 (m, 2H), 1.50–1.78 (m, 3H), 1.34–1.44 (m, 4H), 0.93 (t, $J = 7.5$ Hz, 3H). Fraction B consisted of 77 mg (8%) of the 5′-(*R*)-methyl isomer. $[\alpha]_D$ −86.7° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_D$ −85.1° (*c* 0.1, MeOH)). MS (DCI/NH_3): *m/z* 219 $(M + H)^+$, 236 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.48 (m, 1H), 7.61 (dt, $J = 3$, 7.5 Hz, 1H), 7.25 (dd, $J = 3.0$, 7.5 Hz), 3.79 (dd, $J = 6.0$, 7.5 Hz, 1H), 3.02–3.13 (m, 1H), 2.22–2.39 (m, 1H), 2.07–2.20 (m, 1H), 2.16 (s, 3H), 1.60–1.83 (m, 2H), 1.15–1.45 (m, 4H), 0.94 (t, $J = 7.5$ Hz, 3H). Each fraction was converted to the oxalate salt as described above. The physical data of each salt are shown below.

Fraction A (5′*S* Isomer). Mp: 67–70 °C. $[\alpha]_D$ +51.6° (*c* 0.18, MeOH). MS (DCI/NH_3): *m/z* 219 $(M + H)^+$, 236 $(M + NH_4)^+$, 437 $(2M + H)^+$. ^1H NMR (CD_3OD): δ 0.96 (m, 3H), 1.35–1.53 (m, 4H), 1.63–1.76 (m, 1H), 1.95–2.13 (m, 2H), 2.35–2.65 (m, 3H), 2.75 (s, 3H), 3.48 (br q, 1H), 4.49 (br t, 1H), 7.58 (q, 1H), 8.14 (dt, $J = 1.5$, 7.5 Hz, 1H), 8.67 (dd, $J = 2.5$, 6 Hz, 1H), 8.74 (d, $J = 2.5$ Hz, 1H). Anal. ($C_{14}H_{22}N_2 \cdot 1.4C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(2′*S*,5′*R*)-5′-Butylnicotine Oxalate (37). Fraction B (5′*R* Isomer). Viscous oil. $[\alpha]_D$ −4.68° (*c* 0.16, MeOH). MS (DCI/NH_3): *m/z* 219 $(M + H)^+$, 236 $(M + NH_4)^+$. ^1H NMR (CD_3OD): δ 0.97 (m, 3H), 1.35–1.53 (m, 4H), 1.64–1.76 (m, 1H), 1.90–2.05 (m, 2H), 2.45–2.6 (m, 7H), 3.70 (br s, 1H), 7.58 (q, 1H), 8.07 (dt, $J = 1.5$, 7.5 Hz, 1H), 8.67 (dd, $J = 2.5$, 6 Hz, 1H), 8.72 (d, $J = 2.5$ Hz, 1H). Anal. ($C_{14}H_{22}N_2 \cdot 1.4C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(2′*S*,5′*R*)-5′-Phenylnicotine Oxalate (40). Following a similar procedure as described above, cotinine (1.00 g, 5.67 mmol) was reacted with phenyllithium (4.25 mL, 8.50 mmol) to afford 1.33 g of the amino alcohol compound as an oil. Following a similar procedure as described above, the phenyl amino alcohol was reduced with sodium cyanoborohydride. Chromatography provided two fractions; their physical data are shown below. Fraction A (5′*R* isomer) consisted of 572 mg (40%). $[\alpha]_D$ −8.72° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_D$ −8.3° (*c* 6.1, MeOH)). MS (DCI/NH_3): *m/z* 238 $(M + H)^+$, 256 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.66 (d, $J = 2.5$ Hz, 1H), 8.52 (dd, $J = 2.0$, 6.0 Hz, 1H), 7.84 (dt, $J = 3.0$, 7.5 Hz, 1H), 7.27 (dd, $J = 3.0$, 7.5 Hz), 7.27–7.49 (m, 5H), 3.46 (m, 2H), 2.21–2.30 (m, 2H), 2.03 (s, 3H), 1.76–1.90 (m, 2H). Fraction B consisted of 77 mg (8%) of the 5′-(*S*)-phenyl isomer. $[\alpha]_D$ −89.2° (*c* 0.5, MeOH) (lit.[28] $[\alpha]_D$ −88.9° (*c* 1.26, MeOH)). MS (DCI/NH_3): *m/z* 238 $(M + H)^+$, 256 $(M + NH_4)^+$. ^1H NMR ($CDCl_3$): δ 8.55 (d, $J = 2.5$ Hz, 1H), 8.52 (dd, $J = 2.0$, 6.0 Hz, 1H), 7.84 (dt, $J = 3.0$, 7.5 Hz, 1H), 7.27 (dd, $J = 3.0$, 7.5 Hz), 7.27–7.49 (m, 5H), 3.46 (m, 2H), 2.21–2.30 (m, 2H), 2.03 (s, 3H), 1.76–1.90 (m, 2H). Each fraction was converted to the oxalate salt as described above. The physical data of each salt are shown below.

Fraction A (5′*R* Isomer). Mp: 105–107 °C. $[\alpha]_D$ −43.5° (*c* 0.14, MeOH). MS (DCI/NH_3): *m/z* 238 $(M + H)^+$, 256 $(M + NH_4)^+$. ^1H NMR (DMSO-d_6): δ 1.95 (s, 3H), 2.04–2.20 (m, 2H), 2.52–2.63 (m, 2H, overlap with DMSO), 4.31–4.51 (m, 2H), 7.33–7.48 (m, 1H), 7.89 (dd, $J = 5.2$, 1.5 Hz, 1H), 8.55

(dd, J = 5.2, 1.5 Hz, 1H), 8.64 (m, 1H). Anal. ($C_{16}H_{18}N_2 \cdot 1.9C_2H_2O_4$) C, H, N.

(2′S,5′S)-5′-Phenylnicotine Oxalate (39). Fraction B (5′S Isomer). Mp: 115–117 °C. $[\alpha]_D$ −3.33° (c 0.15, MeOH). MS (DCI/NH_3): m/z 238 $(M + H)^+$, 256 $(M + NH_4)^+$. ^{1}H NMR (DMSO-d_6): δ 1.76–1.98 (m, 2H), 1.97 (s, 3H), 2.20–2.32 (m, 2H), 3.50–3.68 (m, 2H), 7.25–7.52 (m, 1H), 7.93 (dd, J = 5.2, 1.5 Hz, 1H), 8.5 (m, 1H), 8.65 (m, 1H). Anal. ($C_{16}H_{18}N_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

(±)-3′,4′-Dimethylcotinine (41). A sample of (±)-*trans*-4-methylcotinine (**7**) (124 mg, 0.65 mmol) was dissolved in dry THF (8 mL), and LDA (0.52 mL, 0.78 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min and at 0 °C for 30 min. The temperature was again lowered to −78 °C, methyl iodide (0.045 mL, 0.72 mmol) was added, and the solution was stirred for 1.5 h. The reaction was quenched at 0 °C with methanol, the organic solvent was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel, eluting with acetone/hexane (1:1), to give 69 mg of the title product.

(±)-3′,4′-Dimethylnicotine Dioxalate (42). Product **41** was dissolved in THF (3 mL), and a 1 M solution of borane (1.0 mL, 1.0 mmol) in THF was added. The reaction was refluxed for 3 h. The reaction was quenched by stirring with methanol for 10 min, and the solvent was removed. The residue was treated with cesium fluoride (118 mg) in ethanol (4 mL) as described above. The crude product was purified by flash column chromatography on silica gel, eluting with acetone/hexane (3:4), to give 36 mg of the title compound as a colorless oil. The product was converted to the oxalate salt following the procedure described in the preparation of salt **13**. MS (DCI/NH_3): m/z 191 $(M + H)^+$, 208 $(M + NH_4)^+$. ^{1}H NMR (D_2O): δ 0.95 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 2.78–2.90 (m, 2H), 2.81 (br s, 3H), 3.05 (br q, 1H), 4.16 (br m, 1H), 4.28 (br m, 1H), 7.90 (m, 1H), 8.40 (dt, J = 6, 2 Hz, 1H), 8.82 (m, 2H). Anal. ($C_{12}H_{18}N_2O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

Binding Experiments. Binding of [^{3}H]cytisine to nicotinic acetylcholine receptors was determined using a modification of the method of Pabreza and co-workers.[33] Membrane-enriched fractions were prepared from whole rat brain following a published method.[34] The tissue was stored as pellets at −80 °C. Prior to use, pellets were slowly thawed, washed, and resuspended in binding buffer [BSS (basic salt solution); 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, and 50 mM Tris-Cl, pH 7.4, 4 °C]. Samples containing approximately 100 mg of protein were incubated at 4 °C for 75 min with 1.25 nM [^{3}H]cytisine. For concentration–inhibition studies, seven log dilutions of test compounds in duplicate were used. Three separate determinations were done for each compound. Nonspecific binding was determined in the presence of 10 mM (−)-nicotine. Bound radioactivity was isolated by vacuum filtration onto no. 32 glass fiber filters (S&S). The filters were prerinsed with 0.5% poly(ethylenimine) (PEI) prior to sample filtration and rapidly rinsed with 10 mL of ice cold BSS. Filters were counted in 3 mL of Ecolume (ICN). IC_{50} values were calculated with a four-parameter logistics program in RS/1 (BBN), and K_i values were determined using the Cheng–Prusoff equation[35] as shown below.

$$K_i = IC_{50}/(1 + [\text{ligand}]/K_D)$$

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