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2-, 5-, and 6-Halo-3-(2(*S*)-azetidinylmethoxy)pyridines: Synthesis, Affinity for Nicotinic Acetylcholine Receptors, and Molecular Modeling

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3-(2(*S*)-Azetidinylmethoxy)pyridine (A-85380) has been identified recently as a ligand with high affinity for nicotinic acetylcholine receptors (nAChRs). Here we report the synthesis and in vitro nAChR binding of a series of 10 pyridine-modified analogues of A-85380. The novel compounds feature a halogen substituent at position 2, 5, or 6 of the 3-pyridyl fragment. Those with the substituents at position 5 or 6, as well as the 2-fluoro analogue, possess subnanomolar affinity for nAChRs in membranes from rat brain. For these ligands, K_i values range from 11 to 210 pM, as measured by competition with (±)-[^{3}H]epibatidine. In contrast, 2-chloro, 2-bromo, and 2-iodo analogues exhibit substantially lower affinity. AM1 quantum chemical calculations demonstrate that the bulky substituents at position 2 cause notable changes in the molecular geometry. The high-affinity members of the series and (+)-epibatidine display a tight fit superposition of low-energy stable conformers. The new ligands with high affinity for nAChRs may be of interest as pharmacological probes, potential medications, and candidates for developing radiohalogenated tracers to study nAChRs.

Over the past few years, considerable efforts have been directed toward the identification and characterization of ligands for nicotinic acetylcholine receptors (nAChRs). The interest in these compounds stems in part from accumulating evidence that agents acting at nAChRs may have therapeutic utility in the treatment of a variety of central nervous system (CNS) disorders,[1,2] including Alzheimer's and Parkinson's[3] diseases, attention deficit/hyperactivity disorder,[4] Tourette's syndrome,[5] and depression.[6] The therapeutic usefulness of the prototypical agonist for nAChRs, (*S*)-nicotine, however, is limited by a variety of untoward effects.

In parallel, observations of abnormalities in the densities of nAChRs in the brains of smokers[7] and patients with various CNS disorders[3] have suggested that noninvasive in vivo imaging and quantification of cerebral nAChRs, using such techniques as positron emission tomography (PET) and single-photon emission computed tomography (SPECT), could be useful in studies of the progression of these pathological states. The only tracer currently available for such studies[8] is the long-known (*S*)-[^{11}C]nicotine,[9] which shows considerable nonspecific binding and rapid clearance from brain.[10] During the past few years, several promising PET[11,12] and SPECT[13,14] tracers for nAChRs have been developed. Nevertheless, none is optimal for human subjects, and there is still a need for potent nAChR ligands with high selectivity for CNS receptors and a favorable in vivo profile.

Recently, a novel series of compounds with subnanomolar affinity for central neuronal nAChRs has been reported.[15] These compounds include 3-pyridyl ethers which incorporate a saturated azacyclic fragment, such as 2-pyrrolidinyl or 2-azetidinyl. An initial report was followed by intensive structure−activity studies of both branches of the series.[16−18] In the "pyrrolidine" branch, these efforts led to the identification of ABT-089, an orally bioavailable nAChR ligand[19] with neuroprotective[20] and cognition-enhancing[21] properties. Another pyrrolidine-based ligand, A-84543, was labeled with carbon-11,[22] and the labeled compound showed moderate specific binding to nAChRs in vivo in mice.[23]

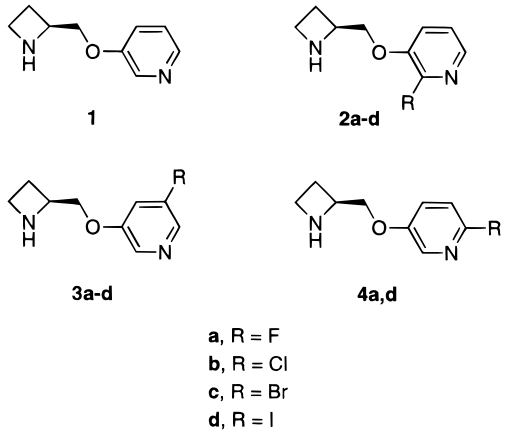

Figure 1. Structures of A-85380 and its halogenated analogues.

The parent compound of the azetidine-based series of ligands, 3-(2(*S*)-azetidinylmethoxy)pyridine, A-85380 (**1**; Figure 1), showed a remarkable combination of properties. It displayed exceptionally high affinity for central nAChRs,[15] almost identical to that of (±)-epibatidine (Figure 2), the most potent nAChR ligand identified so far. However, in functional in vitro assays,

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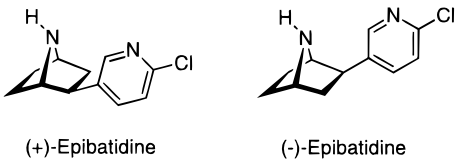


Figure 2. Stereoisomers of epibatidine.

A-85380 was 40-fold less potent than (±)-epibatidine to activate central nAChRs and 100-fold less potent to activate ganglionic-type nAChRs.[15] Since the ganglionic-type nAChRs are believed to mediate at least some untoward effects of nicotinic agonists, A-85380 may be expected to have a wider safety margin than epibatidine.[24] Indeed, comprehensive examination of in vitro pharmacological properties of A-85380 suggested that this compound may serve as a potent and highly selective probe for the neuronal nAChRs.[24] Subsequently ^{3}H-labeled A-85380 has been identified as an excellent tool for studying nicotinic acetylcholine receptors in vitro.[25] The most recently reported member of the "azetidine" series, ABT-594,[26] also showed extremely high affinity for nAChRs and appeared to produce a nonopioid-mediated analgesia in rodent models, with efficacy equal to that of morphine.

To gain further insight into the structure−activity relationship for azetidine-based 3-pyridyl ether compounds, we have prepared a number of pyridine-modified derivatives of A-85380 and screened them for binding affinity for central nAChRs. In this paper, we describe the synthesis and in vitro receptor binding properties of a series of halogenated analogues: **2a**−**d**, **3a**−**d**, and **4a**,**d** (Figure 1). Isomers with halogen substituents at position 4 of the pyridine nucleus were excluded from consideration as such derivatives are known to be chemically unstable.[27]

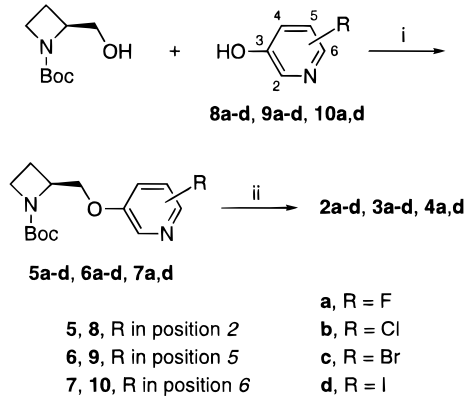
By targeting the halo derivatives we aimed at identifying nAChR ligands, which might represent suitable candidates for developing ^{18}F-, ^{76}Br-, and $^{123/125}$I-labeled probes for studying the receptors both in vivo, using PET/SPECT, and in vitro.

Results and Discussion

Chemistry. Throughout this report, compounds with the **a** designation are fluoro derivatives, whereas the **b**, **c**, and **d** designations denote, respectively, chloro, bromo, and iodo compounds. All target compounds were synthesized by the etherification of the respective halo-3-pyridinols with 1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinemethanol under Mitsunobu conditions followed by the removal of the protecting group (Scheme 1).

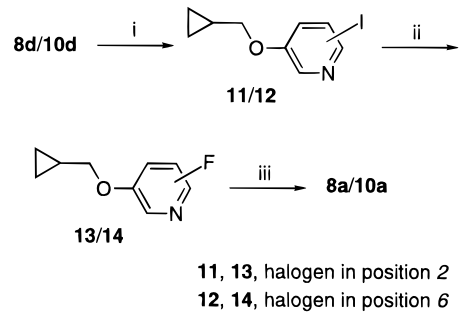
Previously unknown fluoropyridinols **8a** and **10a** were synthesized via halogen exchange starting from the available iodopyridinols **8d** and **10d**,[28] respectively. Here, we employed a technique proved effective for a bromo-to-fluoro exchange in a nonactivated pyridine ring.[11] Our initial attempts to carry out a iodo-to-fluoro substitution directly in iodopyridinol **8d** yielded only tarlike decomposition products. In contrast, the displacement did take place when the methyl ether of **8d** was brought into the reaction (data not presented), thereby indicating the necessity of protecting the hydroxyl group. Eventually we found that protection with a cyclopropylmethyl group was an adequate strategy (Scheme 2). This group tolerated the halogen-exchange

Scheme 1[a]



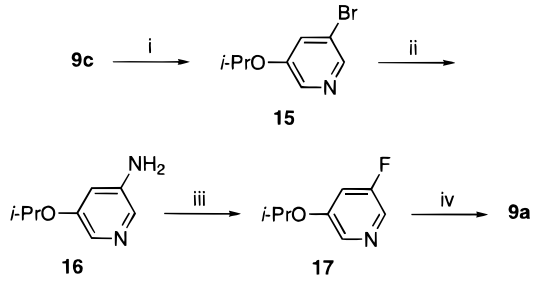
[a] (i) Diethyl azodicarboxylate, Ph_3P, THF; (ii) TFA, CH_2Cl_2.

Scheme 2[a]



[a] (i) *O*-(Cyclopropylmethyl)-*N*,*N*′-dicyclohexylisourea, benzene; (ii) KF, Kryptofix 222, DMSO; (iii) HBr, CH_3COOH. For position numbering, see Scheme 1.

Scheme 3[a]

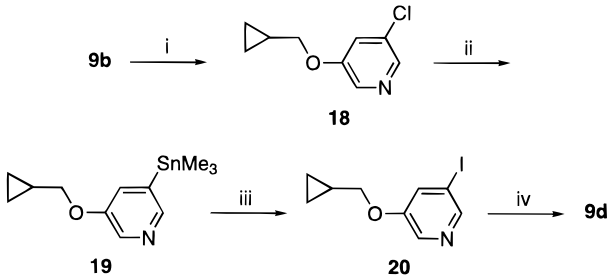


[a] (i) *O*-Isopropyl-*N*,*N*′-dicyclohexylisourea, benzene; (ii) aq NH_3, $CuSO_4$; (iii) $NaNO_2$, HF, pyridine; (iv) HBr, CH_3COOH.

conditions (DMSO, 165 °C, tens of hours) and could be removed under sufficiently mild ones (HBr−acetic acid, room temperature, 3 h). As would be expected, compound **12** was less reactive in the nucleophilic iodo-to-fluoro displacement than isomer **11,** having the iodine atom in the vicinity of the electron-withdrawing oxygen. One may suppose that, due to a close similarity in structures of **11**, **12** and **5d**, **7d**, the latter two could also undergo the halogen-exchange nucleophilic fluorination to provide a pathway to radiofluorinated analogues of A-85380.

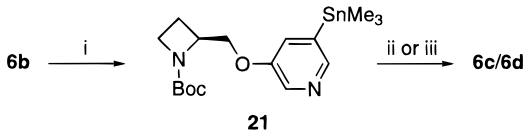
It is well-known that β-halogens in the pyridine ring generally resist exchange fluorination, although their displacement by a base is a practical route to 3(5)-substituted pyridines.[27] Hence we developed a strategy for the synthesis of the previously unknown fluoropyridinol **9a** starting from bromopyridinol **9c** (Scheme 3). The latter was protected with an isopropyl group to give derivative **15**, which was converted into amine **16**

Scheme 4[a]



[a] (i) *O*-(Cyclopropylmethyl)-*N*,*N*′-dicyclohexylisourea, benzene; (ii) $NaSnMe_3$, $MeOCH_2CH_2OMe$; (iii) I_2, $CHCl_3$; (iv) HBr, CH_3-COOH.

Scheme 5[a]



[a] (i) $NaSnMe_3$, $MeOCH_2CH_2OMe$; (ii) Br_2, $CHCl_3$; (iii) I_2, $CHCl_3$.

using a modification of a published procedure.[29] The amine, in turn, was transformed into fluoropyridine **17** via diazotization−fluorodediazonization[30] in HF−pyridine medium. Finally, deprotection of **17** gave the desired fluoropyridinol **9a** in a 12% overall yield. In this synthesis, we used the isopropyl protecting group to ensure stability of the ether bond during the fluorodediazonization step, which occurs in an acidic medium at elevated temperature (HF−pyridine, 50 °C, 1 h).

Previously unknown iodopyridinol **9d** was prepared starting from a commercially available chloropyridinol **9b**. The key steps of the reaction sequence (Scheme 4) are the synthesis of an organotin compound **19** and its iododestannylation, which were carried out according to a published method.[31]

The halodestannylation was also used successively in an alternative synthesis of compounds **6c**,**d** (Scheme 5) to reveal a useful precursor (**21**) for future development of radiobrominated and radioiodinated analogues of A-85380.

The syntheses of alkoxypyridines **11**, **12**, **15**, and **18** (the first step in Schemes 2−4) were accomplished using a modification of a published method for O-alkylation of phenols with *O*-alkyl-*N*,*N*′-dicyclohexylisoureas.[32]

In Vitro Receptor Binding. The binding affinity of each ligand for nAChRs was determined by measuring its ability to compete with (±)-[^{3}H]epibatidine for specific binding sites in rat brain. Our studies showed that the specific binding of the used radioligand to crude synaptic membranes of rat forebrain, at concentrations up to 1 nM, is characterized by a single population of binding sites with $K_d = 10 \pm 1$ pM ($n = 6$). It has been previously found that the predominant receptor with high affinity for [^{3}H]nicotine, (−)-[^{3}H]cytisine, and (±)-[^{3}H]epibatidine in rat brain is composed of α4 and β2 subunits.[33,34] Therefore, the affinities, measured in the present work, presumably reflect interactions of ligands primarily with the α4β2 subtype of nAChR.

As shown in Table 1, competition assays yielded a K_i value of 8.4 ± 0.2 pM for (+)-epibatidine. This result is consistent with both recently reported[33] and our own direct measurements of the affinity of (±)-[^{3}H]epibatidine for nAChR in rodent brain. Compared to (+)-epibatidine, A-85380 showed somewhat lower affinity ($K_i = 17 \pm 1$ pM). This pattern agrees with the findings of an earlier work[15] where K_i values for (±)-epibatidine and A-85380 (43 and 52 pM, respectively) were determined using (−)-[^{3}H]cytisine. The discrepancy in absolute values might be ascribed to an overestimation of competitor concentrations in the assays with (−)-[^{3}H]cytisine due to inadequate consideration of removal of the competitors from the incubation medium.

Table 1. nAChR Binding Affinities, Distances between Pharmacophoric Elements, Relative Energies, and Superposition rms Deviations for (+)-Epibatidine, A-85380, and Halogenated Analogues **2a**−**d**, **3a**−**d**, and **4a,d**

compound	K_i[a] (pM)	A−B[b] (Å)	A−C[c] (Å)	ΔE[d] (kcal/mol)	rms[e] (Å)
(+)-Epibatidine	8.4 ± 0.2	4.47	4.27	0.18	0.00
1 (A-85380)	17 ± 1	4.39	4.43	0.33	0.09
2a (R = 2-F)[f]	46 ± 5[g]	4.81	4.13	0.59	0.21
2b (R = 2-Cl)	(8.4 ± 0.6) × 10^3 [h]	5.10	4.24	0.63	0.34
2c (R = 2-Br)	(240 ± 10) × 10^3	5.25	4.32	0.88	0.40
2d (R = 2-I)	>1 × 10^6	5.32	4.36	1.52	0.42
3a (R = 5-F)	25 ± 1	4.37	4.40	0.42	0.09
3b (R = 5-Cl)	30 ± 3	4.36	4.39	0.32	0.09
3c (R = 5-Br)	21 ± 1	4.34	4.36	0.25	0.09
3d (R = 5-I)	11 ± 1	4.33	4.35	0.24	0.09
4a (R = 6-F)	25 ± 3	4.33	4.37	0.35	0.09
4d (R = 6-I)	150 ± 8	4.36	4.40	0.36	0.09

[a] Values represent mean ± SEM obtained from n independent experiments where $n = 6-9$, except for **2d** where $n = 3$. [b] Distance between sp^3 nitrogen atom and pyridine ring nitrogen atom. [c] Distance between sp^3 nitrogen atom and pyridine ring centroid. [d] Energy of the stable conformer with reference to the lowest-energy conformer. [e] rms deviation of the three pharmacophoric elements from those of (+)-epibatidine. [f] For position numbering, see Scheme 1. [g] $K_i = 150$ pM against [^{3}H]cytisine.[18] [h] $K_i = 2.5$ nM against [^{3}H]cytisine.[18]

As seen from Table 1, most of the synthesized halopyridyl ethers retained subnanomolar affinity to central nAChRs. The apparent exceptions were 2-substituted analogues **2b**−**d** whose affinity diminished drastically with an increase in the substituent size. The affinity of the iodo compound **2d** dropped into the micromolar range. As shown below, the bulky substituents at position 2 of the pyridine nucleus distort the molecular conformation of the ligands and affect the intramolecular N−N distance. This parameter is believed to be crucial for high-affinity binding to nAChRs.[35−37] A relatively small fluorine substituent at position 2 causes minimal conformational distortion. As a result, the fluoro compound **2a** showed a 2-fold lower affinity compared to isomers **3a** and **4a**, which have the fluorine atom at positions 5 and 6, respectively.

Substituents at position 6, the other α-position of the pyridine ring, exerted a much smaller impact on the binding affinity. Still, the iodo representative of this series, ligand **4d**, was about 1 order of magnitude less potent than the parent compound **1**.

Substitution at position 5 of the 3-pyridyl moiety had the smallest effect on the binding affinity of the compounds under consideration. Of the 5-substituted analogues studied, the least potent ligand, chloro derivative **3b**, showed a 2-fold lower affinity than A-85380.

Of all the synthesized ligands, the most potent one was compound **3d**, featuring an iodine atom at position 5. The affinity of **3d** ($K_i = 11 \pm 1$ pM) was even

somewhat higher than that of prototype **1**. The emerging trend, that the presence of a bulkier substituent at position 5 of the 3-pyridyl moiety contributes to a higher affinity, is similar to the pattern found recently for derivatives of A-84543.[16,17] The reasons for this interesting phenomenon are currently under investigation.

Computational Studies. The pharmacophore concept is one of the cornerstones of medicinal chemistry. Deducing a pharmacophore requires identification of chemical groups essential for a particular biological activity and determination of their three-dimensional arrangement that is recognized by a single receptor. With regard to the nicotinic pharmacophore, the most recently developed model[35] suggests that the essential groups are (A) a cationic center (e.g., a basic or quaternized sp^3 nitrogen atom), (B) an electronegative atom capable of formation of a hydrogen bond (e.g., a pyridine-like nitrogen or a carbonyl oxygen), and (C) a dummy point or an atom to define a line along which the hydrogen bond may form. The latter element can be exemplified by the pyridine ring centroid or the carbonyl carbon. Optimal distances between the three pharmacophoric elements were estimated[35] as follows: A−B, 4.7 ± 0.3 Å; A−C, 4.0 ± 0.3 Å; B−C, 1.2 Å.

A more recent molecular modeling study[36] cast some doubt on these parameters. In that work, it was found that the lowest-energy conformer of epibatidine had the internitrogen (i.e., A−B) distance of 5.51 Å, a value far beyond the range previously proposed. Since epibatidine is one of the most potent nAChR ligands known, the suggestion has been made[36,37] that the optimal internitrogen distance for high-affinity binding should be closer to 5.5 Å. Subsequently, computational studies[15] assumed that in A-85380, which binds to nAChRs almost equipotently to epibatidine, nitrogen atoms might be even farther apart.

Given these findings, we decided to use molecular modeling in order to get some idea why a substitution at position 2, unlike one at position 5 or 6 of the 3-pyridyl fragment in A-85380, has such a profound impact on the ligand affinity. To this end, we performed quantum chemical calculations on molecules of compounds **1**, **2a**−**d**, **3a**−**d**, and **4a,d** using the semiempirical AM1[38] method. The calculations revealed that the lowest-energy conformers of A-85380 and analogues **2a**−**d**, **3a**−**d**, and **4a**,**d** had almost identical geometries with the distance between the azetidine and pyridine nitrogen atoms ranging from 5.50 Å (in **2b**) to 5.74 Å (in **1**), which could not explain the wide variations in binding affinity.

It is commonly recognized,[15,35] however, that the receptor-bound conformations of ligands may not be the same as the lowest-energy conformations either in a vacuum or in solution. Hence, we reexamined the geometry of the epibatidine molecule which has been shown to possess another stable conformer with a shorter N−N distance.[15] Our calculations substantiated that the lowest-energy conformer of epibatidine had the internitrogen distance of 5.50 Å. The other stable conformer found, with a relative energy of only 0.18 kcal/mol, featured the N−N distance of 4.47 Å and the A−C parameter (a distance between the sp^3 nitrogen atom and the pyridine ring centroid) of 4.27 Å that fit perfectly into the nicotinic pharmacophore model.[35]

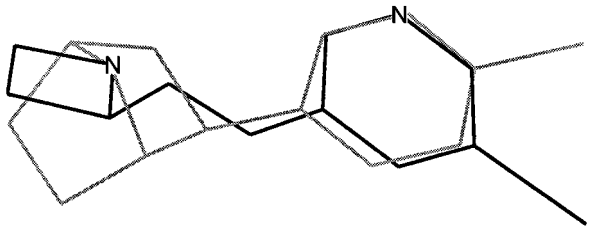


Figure 3. Superposition of **3d** (solid black) on (+)-epibatidine by the three pharmacophoric elements.

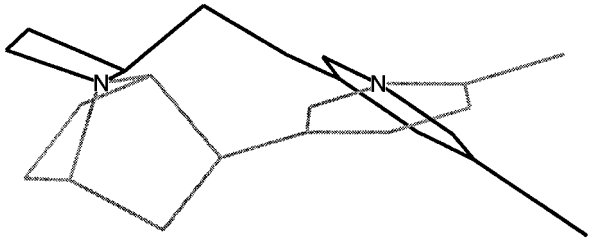


Figure 4. Superposition of **3d** (solid black) on (−)-epibatidine by the three pharmacophoric elements.

Subsequently, higher-than-minimum-energy conformers of compounds **1**, **2a**−**d**, **3a**−**d**, and **4a**,**d** were considered. We have found that molecules of parent A-85380 and analogues **3a**−**d** and **4a**,**d** have stable conformations with the relative energies not exceeding 0.42 kcal/mol and the internitrogen distances ranging from 4.33 to 4.39 Å (Table 1). The A−C parameters for these conformers vary from 4.35 to 4.43 Å. Although the obtained values do not fall exactly within the proposed[35] ranges, they are still very close to the parameters found for epibatidine. As a result, a tight fit superposition of each of these conformers on (+)-epibatidine was achieved. In all cases the pyridine rings of the overlaid structures were nearly coplanar (for example, see Figure 3), rms deviations were below 0.1 Å (Table 1), and the maximal distance between respective superimposed points did not exceed 0.13 Å. When superimposing the ligands on (−)-epibatidine, their pyridine rings formed a distinct dihedral angle and the aza fragments showed less overlap (Figure 4).

Quite different results were obtained for compounds **2a**−**d**. A stable conformation with the distance parameters complying with the nicotinic pharmacophore model was found only for the high-affinity fluoro derivative **2a**. For its chloro, bromo, and iodo analogues **2b**−**d**, no stable conformers could be located to have the N−N distance shorter than 5.10, 5.25, and 5.32 Å, respectively. Moreover, none of the identified conformers could be satisfactorily superimposed on any of the epibatidine stereoisomers (for example, see Figure 5). These results are consistent with the lower affinities exhibited by ligands **2b**−**d**. As seen from superposition of the isomeric iodo derivatives **2d** and **3d** (Figure 6), the bulky substituent at position 2 of the pyridine ring caused radical changes in the molecular geometry which apparently are beyond the limits allowed for high-affinity binding.

In summary, our computational studies have shown that epibatidine and the new high-affinity A-85380-based nAChR ligands possess stable conformers featuring similar spatial arrangement of pharmacophoric

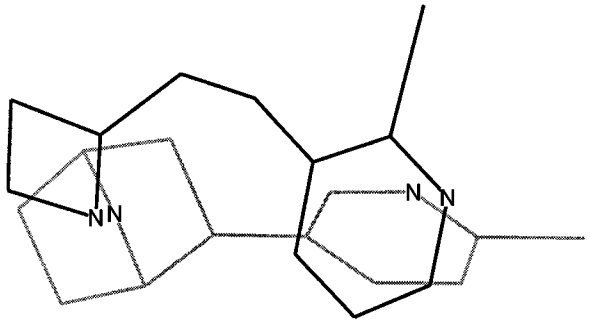


Figure 5. Superposition of **2d** (solid black) on (+)-epibatidine by the three pharmacophoric elements.

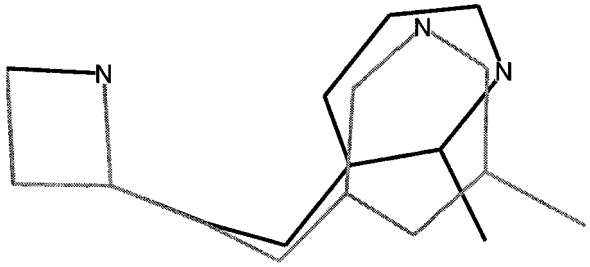


Figure 6. Superposition of **2d** (solid black) on **3d** by the azetidine cycles.

elements. This arrangement agrees well with the current nicotinic pharmacophore model. Reasons for the lower affinity of ligands **2b**−**d** for nAChRs can also be rationalized within the framework of this model. We must particularly emphasize, however, that it would be an oversimplification to assume that the affinity for nAChRs is determined solely by the limited set of distance parameters examined here. It is now recognized that more sophisticated models are needed to deal with ligand volumes and regions of bulk tolerance/intolerance.[39] Nonetheless, the employed simple approach has proven to be a useful tool for interpreting and rationalizing activity data.

Summary

We have shown that A-85380-based compounds, having a halogen atom as the substituent at position 5 or 6 of the 3-pyridyl fragment, are potent nAChR ligands. These compounds, as well as the 2-fluoro analogue, possess subnanomolar affinity for nAChRs in membranes from rat forebrain. Of these ligands, 5-iodo-3-(2(*S*)-azetidinylmethoxy)pyridine shows the highest affinity (K_i = 11 pM), exceeding that of A-85380 and comparable to the affinity of (+)-epibatidine. In contrast, compounds with a 2-chloro-, 2-bromo-, and 2-iodo-substituted pyridine ring exhibit substantially lower potency. Molecular modeling studies demonstrate that the bulky substituents at position 2 of the 3-pyridyl moiety distort the molecular geometry common to the high-affinity members of the series studied. For the latter compounds, a tight fit superposition of low-energy stable conformers on (+)-epibatidine is observed. The high affinity of 2-fluoro, 6-fluoro, 5-bromo, and 5-iodo analogues for nAChRs suggests that the respective radiohalogenated compounds are worth testing as potential PET/SPECT tracers. Precursors, suitable for the syntheses of these tracers, have been developed and are reported in the present work.

Experimental Section

Chemistry. Methods and Materials. Proton magnetic resonance spectra were recorded on a Bruker AM 300 instrument at 300 MHz. Chemical shifts are reported in ppm downfield from internal tetramethylsilane at 0.00 ppm. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

High-performance liquid chromatography (HPLC) was performed using a Hamilton PRP-1 column (7 × 305 mm) at flow rate of 7 mL/min and a fixed-wavelength (254 nm) UV detector. Flash chromatography was carried out using Merck silica gel (grade 9385, 230−400 mesh, 60 Å) obtained from Aldrich Chemical Co. (Milwaukee, WI).

2-Chloro-3-pyridinol (**8b**), 2-bromo-3-pyridinol (**8c**), and 5-chloro-3-pyridinol (**9b**) were purchased from Aldrich Chemical Co. 2-Iodo-3-pyridinol (**8d**) was purchased from Lancaster Synthesis Inc. (Windham, NH). 5-Bromo-3-pyridinol (**9c**),[40] 6-iodo-3-pyridinol (**10d**),[28] and 1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinemethanol[15] were prepared according to the literature procedures. All reactions were carried out under anhydrous conditions unless otherwise noted.

The following abbreviations are used in the Experimental Section: DME for ethylene glycol dimethyl ether, DMSO for dimethyl sulfoxide, EtOAc for ethyl acetate, TFA for trifluoroacetic acid, THF for tetrahydrofuran, t_R for retention time.

General Procedure for Preparation of Compounds 2a−d, 3a−d, and 4a,d. To a solution of an appropriate Boc-protected compound (**5a−d, 6a−d, 7a,d**; 0.5 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL), and the resulting solution was stirred at room temperature for 3 h. The volatiles were removed in vacuo, and the residue was purified by HPLC. The fraction containing the desired product was concentrated in vacuo at 40 °C using a rotary evaporator. During the evaporation, HPLC-grade acetonitrile was repeatedly added to the product for azeotropical removal of water. Finally, the product was dried in a vacuum-desiccator over P_2O_5 at 0.1 mmHg. Isolated yields ranged from 67% to 84%. The compounds were obtained as very viscous colorless syrups.

2-Fluoro-3-(2(*S*)-azetidinylmethoxy)pyridine (2a), salt with trifluoroacetic acid: HPLC t_R 4.6 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.61 (m, 1H), 3.00 (m, 1H), 4.75−4.92 (m, 3H), 5.01 (m, 1H), 5.74 (m, 1H), 7.31 (dd, J = 4.8, 7.9 Hz, 1H), 7.69 (ddd, J = 1.4, 7.9, 10.5 Hz, 1H), 7.81 (ddd, J = 1.4, 1.7, 4.8 Hz, 1H). Anal. ($C_9H_{11}FN_2O\cdot2.9C_2HF_3O_2$) C, H, N.

2-Chloro-3-(2(*S*)-azetidinylmethoxy)pyridine (2b), salt with trifluoroacetic acid: HPLC t_R 6.7 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.68 (m, 1H), 3.02 (m, 1H), 4.74−4.90 (m, 3H), 5.05 (m, 1H), 5.77 (m, 1H), 7.41 (dd, J = 4.7, 8.1 Hz, 1H), 7.63 (dd, J = 1.5, 8.1 Hz, 1H), 8.05 (dd, J = 1.5, 4.7 Hz, 1H). Anal. ($C_9H_{11}ClN_2O\cdot2C_2HF_3O_2$) C, H, N.

2-Bromo-3-(2(*S*)-azetidinylmethoxy)pyridine (2c), salt with trifluoroacetic acid: HPLC t_R 4.7 min (acetonitrile−water−TFA, 10:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.73 (m, 1H), 3.02 (m, 1H), 4.76 (m, 1H), 4.81−4.90 (m, 2H), 5.05 (m, 1H), 5.78 (m, 1H), 7.43 (dd, J = 4.8, 8.1 Hz, 1H), 7.56 (dd, J = 1.5, 8.1 Hz, 1H), 8.04 (dd, J = 1.5, 4.8 Hz, 1H). Anal. ($C_9H_{11}BrN_2O\cdot1.5C_2HF_3O_2$) C, H, N.

2-Iodo-3-(2(*S*)-azetidinylmethoxy)pyridine (2d), salt with trifluoroacetic acid: HPLC t_R 6.3 min (acetonitrile−water−TFA, 10:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.81 (m, 1H), 3.02 (m, 1H), 4.74 (m, 1H), 4.82−4.92 (m, 2H), 5.18 (m, 1H), 5.80 (m, 1H), 7.39 (dd, J = 3.9, 8.1 Hz, 1H), 7.42 (dd, J = 2.4, 8.1 Hz, 1H), 8.05 (dd, J = 2.4, 3.9 Hz, 1H). Anal. ($C_9H_{11}IN_2O\cdot3C_2HF_3O_2$) C, H, N.

5-Fluoro-3-(2(*S*)-azetidinylmethoxy)pyridine (3a), salt with trifluoroacetic acid: HPLC t_R 2.3 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.63 (m, 1H), 2.99 (m, 1H), 4.74−4.90 (m, 3H), 5.05 (m, 1H), 5.74 (m, 1H), 7.43 (ddd, J = 2.2, 2.5, 10.5 Hz, 1H), 8.22 (d, J = 2.5 Hz, 1H), 8.30 (dd, J = 1.2, 2.2 Hz, 1H). Anal. ($C_9H_{11}FN_2O\cdot2.8C_2HF_3O_2$) C, H, N.

5-Chloro-3-(2(*S*)-azetidinylmethoxy)pyridine (3b), salt with trifluoroacetic acid: HPLC t_R 5.1 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.63 (m, 1H), 2.99 (m, 1H), 4.74−4.89 (m, 3H), 5.05 (m, 1H), 5.74 (m, 1H), 7.61 (dd, J = 1.9, 2.3 Hz, 1H), 8.1−8.6 (br, 2H). Anal. ($C_9H_{11}ClN_2O\cdot2.5C_2HF_3O_2$) C, H, N.

5-Bromo-3-(2(*S*)-azetidinylmethoxy)pyridine (3c), salt with trifluoroacetic acid: HPLC t_R 6.9 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.63 (m, 1H), 2.99 (m, 1H), 4.74−4.89 (m, 3H), 5.05 (m, 1H), 5.73 (m, 1H), 7.74 (dd, J = 1.8, 2.6 Hz, 1H), 8.2−8.6 (br, 2H). Anal. ($C_9H_{11}BrN_2O\cdot2.5C_2HF_3O_2$) C, H, N.

5-Iodo-3-(2(*S*)-azetidinylmethoxy)pyridine (3d), salt with trifluoroacetic acid: HPLC t_R 4.4 min (acetonitrile−water−TFA, 10:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.64 (m, 1H), 2.99 (m, 1H), 4.75 (m, 1H), 4.80−4.90 (m, 2H), 5.05 (m, 1H), 5.73 (m, 1H), 7.87 (dd, J = 1.4, 2.4 Hz, 1H), 8.33−8.45 (br, 1H), 8.45−8.57 (br, 1H). Anal. ($C_9H_{11}IN_2O\cdot2.5C_2HF_3O_2$) C, H, N.

6-Fluoro-3-(2(*S*)-azetidinylmethoxy)pyridine (4a), salt with trifluoroacetic acid: HPLC t_R 5.3 min (acetonitrile−methanol−water−TFA, 6:4:90:0.2); ^{1}H NMR (acetone-d_6) δ 2.61 (m, 1H), 2.97 (m, 1H), 4.69−4.89 (m, 3H), 5.03 (m, 1H), 5.72 (m, 1H), 7.07 (ddd, J = 0.5, 3.3, 9.0 Hz, 1H), 7.69 (ddd, J = 3.3, 6.3, 9.0 Hz, 1H), 7.98 (ddd, J = 0.5, 1.8, 3.3 Hz, 1H). Anal. ($C_9H_{11}FN_2O\cdot1.7C_2HF_3O_2$) C, H, N.

6-Iodo-3-(2(*S*)-azetidinylmethoxy)pyridine (4d), salt with trifluoroacetic acid: HPLC t_R 8.4 min (acetonitrile−water−TFA, 12:88:0.2); ^{1}H NMR (acetone-d_6) δ 2.62 (m, 1H), 2.98 (m, 1H), 4.72 (m, 1H), 4.77−4.89 (m, 2H), 5.04 (m, 1H), 5.72 (m, 1H), 7.27 (dd, J = 3.3, 8.6 Hz, 1H), 7.76 (dd, J = 0.5, 8.6 Hz, 1H), 8.21 (dd, J = 0.5, 3.3 Hz, 1H). Anal. ($C_9H_{11}IN_2O\cdot2.5C_2HF_3O_2$) C, H, N.

General Procedure for Preparation of Compounds 5a−d, 6a−d, and 7a,d. To a stirred at 0 °C solution of an appropriate halo-3-pyridinol (**8a**−**d**, **9a**−**d**, **10a,d**; 2 mmol) and 1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinemethanol (560 mg, 3 mmol) in THF (8 mL) was added in one portion Ph_3P (786 mg, 3 mmol) followed by the dropwise addition of neat diethyl azodicarboxylate (522 mg, 3 mmol). The resulting solution was allowed to warm gradually and stirred at room temperature for 3 days. The solvent was removed under reduced pressure. The residue was extracted with hexanes−EtOAc (80:20) mixture (4 × 15 mL). The combined extract was washed with 10-mL portions of saturated $NaHCO_3$ and water and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo. The crude material was purified by flash chromatography (hexanes−EtOAc, 80:20 to 60:40) to give the desired product in 61−78% yields. Compounds **5a**,**d**, **6c**, and **7a** were obtained as colorless syrups, while **5b**,**c**, **6a**,**b**,**d**, and **7d** appeared to be white solids.

2-Fluoro-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (5a): ^{1}H NMR (acetone-d_6) δ 1.38 (s, 9H), 2.24−2.45 (m, 2H), 3.84 (m, 2H), 4.25 (m, 1H), 4.43−4.58 (m, 2H), 7.25 (dd, J = 4.9, 7.9 Hz, 1H), 7.64 (ddd, J = 1.4, 7.9, 10.5 Hz, 1H), 7.93 (ddd, J = 1.4, 1.8, 4.9 Hz, 1H). Anal. ($C_{14}H_{19}FN_2O_3$) C, H, N.

2-Chloro-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (5b): mp 65−66 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.32−2.48 (m, 2H), 3.88 (m, 1H), 3.98 (m, 1H), 4.12 (m, 1H), 4.35−4.63 (m, 2H), 7.19 (dd, J = 4.5, 8.1 Hz, 1H), 7.29 (dd, J = 1.5, 8.1 Hz, 1H), 8.00 (dd, J = 1.5, 4.5 Hz, 1H). Anal. ($C_{14}H_{19}ClN_2O_3$) C, H, N.

2-Bromo-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (5c): mp 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 2.32−2.50 (m, 2H), 3.88 (m, 1H), 4.02 (m, 1H), 4.10 (m, 1H), 4.37−4.63 (m, 2H), 7.19 (dd, J = 3.7, 8.1 Hz, 1H), 7.23 (dd, J = 2.4, 8.1 Hz, 1H), 7.99 (dd, J = 2.4, 3.7 Hz, 1H). Anal. ($C_{14}H_{19}BrN_2O_3$) C, H, N.

2-Iodo-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (5d): ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.35−2.52 (m, 2H), 3.88 (m, 1H), 4.03−4.10 (m, 2H), 4.33−4.60 (m, 2H), 7.06 (dd, J = 1.4, 8.1 Hz, 1H), 7.18 (dd, J = 4.6, 8.1 Hz, 1H), 8.01 (dd, J = 1.4, 4.6 Hz, 1H). Anal. ($C_{14}H_{19}IN_2O_3$) C, H, N.

5-Fluoro-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (6a): mp 62−63 °C; ^{1}H NMR (acetone-d_6) δ 1.39 (s, 9H), 2.23−2.44 (m, 2H), 3.83 (m, 2H), 4.24 (m, 1H), 4.47 (m, 1H), 4.48−4.57 (m, 1H), 7.31 (ddd, J = 2.4, 2.4, 10.9 Hz, 1H), 8.11 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 1.2, 2.4 Hz, 1H). Anal. ($C_{14}H_{19}FN_2O_3$) C, H, N.

5-Chloro-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (6b): mp 82−83 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.22−2.42 (m, 2H), 3.89 (m, 2H), 4.13 (m, 1H), 4.29−4.39 (m, 1H), 4.52 (m, 1H), 7.28 (dd, J = 1.9, 2.7 Hz, 1H), 8.20 (d, J = 1.9 Hz, 1H), 8.25 (d, J = 2.7 Hz, 1H). Anal. ($C_{14}H_{19}ClN_2O_3$) C, H, N.

5-Bromo-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (6c): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.22−2.42 (m, 2H), 3.89 (m, 2H), 4.13 (m, 1H), 4.29−4.38 (m, 1H), 4.52 (m, 1H), 7.43 (dd, J = 1.8, 2.6 Hz, 1H), 8.28 (d, J = 2.6 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H). Anal. ($C_{14}H_{19}BrN_2O_3$) C, H, N.

5-Iodo-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (6d): mp 65−66 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.21−2.41 (m, 2H), 3.89 (m, 2H), 4.12 (m, 1H), 4.27−4.37 (m, 1H), 4.51 (m, 1H), 7.60 (dd, J = 1.6, 2.7 Hz, 1H), 8.30 (d, J = 2.7 Hz, 1H), 8.43 (d, J = 1.6 Hz, 1H). Anal. ($C_{14}H_{19}IN_2O_3$) C, H, N.

6-Fluoro-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (7a): ^{1}H NMR (acetone-d_6) δ 1.39 (s, 9H), 2.22−2.43 (m, 2H), 3.83 (m, 2H), 4.21 (m, 1H), 4.42 (m, 1H), 4.47−4.57 (m, 1H), 7.02 (ddd, J = 0.5, 3.5, 9.0 Hz, 1H), 7.61 (ddd, J = 3.2, 6.5, 9.0 Hz, 1H), 7.93 (ddd, J = 0.5, 1.6, 3.2 Hz, 1H). Anal. ($C_{14}H_{19}FN_2O_3$) C, H, N.

6-Iodo-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)-methoxy)pyridine (7d): mp 69−70 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.21−2.41 (m, 2H), 3.88 (m, 2H), 4.10 (m, 1H), 4.26−4.36 (m, 1H), 4.50 (m, 1H), 6.97 (dd, J = 3.2, 8.7 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 3.2 Hz, 1H). Anal. ($C_{14}H_{19}IN_2O_3$) C, H, N.

General Procedure for Preparation of Compounds 6c,d via Halodestannylation. A solution of, respectively, bromine (80 mg, 0.5 mmol) or iodine (127 mg, 0.5 mmol) in $CHCl_3$ (1.5 mL) was added dropwise to a stirred solution of **21** (214 mg, 0.5 mmol) in $CHCl_3$ (1.5 mL). The reaction mixture was stirred for 20 min at room temperature, and then saturated KF (2 mL) was added. The resulting mixture was made alkaline with saturated K_2CO_3 and thoroughly extracted with $CHCl_3$. The combined extract was washed with saturated KF, saturated $Na_2S_2O_3$, and water and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude material was purified by flash chromatography (hexanes−EtOAc, 60:40). Isolated yields were as follows: **6c**, 141 mg (82%); **6d**, 150 mg (77%). Properties of the compounds were identical to those described above.

General Procedure for Preparation of Compounds 8a, 9a,d, and 10a. A solution of HBr in acetic acid (45% w/v, 5 mL) was added dropwise to 2 mmol of an appropriate halo-3-alkoxypyridine (**13**, **17**, **20**, or **14**, respectively) while stirring and cooling with an ice−salt bath. The resulting solution was stirred at room temperature for 3 h (in the case of **17**, at 60 °C for 72 h), neutralized by the dropwise addition of 10 M NaOH (5.5 mL) while cooling with an ice bath, and extracted with ether (4 × 15 mL). The combined extract was washed with water (10 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The solid residue was purified by flash chromatography (**8a**, hexanes−ether, 30:70; **9a**, CH_2Cl_2−EtOAc, 75:25; **9d**, ether; **10a**, CH_2Cl_2−ether, 85:15). Isolated yields were as follows: **8a**, 61%; **9a**, 36%; **9d**, 78%; **10a**, 55%.

2-Fluoro-3-pyridinol (8a): mp 125−126 °C; ^{1}H NMR (acetone-d_6) δ 7.14 (ddd, J = 1.1, 4.8, 7.8 Hz, 1H), 7.42 (ddd, J = 1.6, 7.8, 10.6 Hz, 1H), 7.70 (ddd, J = 1.6, 1.8, 4.8 Hz, 1H). Anal. (C_5H_4FNO) C, H, N.

5-Fluoro-3-pyridinol (9a): mp 167−168 °C; ^{1}H NMR (acetone-d_6) δ 7.04 (ddd, J = 2.4, 2.4, 10.5 Hz, 1H), 8.02 (d, J

= 2.4 Hz, 1H), 8.21 (dd, J = 1.2, 2.4 Hz, 1H). Anal. (C_5H_4FNO) C, H, N.

5-Iodo-3-pyridinol (9d): mp 208−209 °C; ^{1}H NMR (acetone-d_6) δ 7.62 (dd, J = 1.6, 2.7 Hz, 1H), 8.20 (d, J = 2.7 Hz, 1H), 8.32 (d, J = 1.6 Hz, 1H). Anal. (C_5H_4INO) C, H, N.

6-Fluoro-3-pyridinol (10a): mp 156−157 °C; ^{1}H NMR (acetone-d_6) δ 6.91 (dd, J = 3.5, 9.0 Hz, 1H), 7.40 (ddd, J = 3.2, 6.5, 9.0 Hz, 1H), 7.75 (dd, J = 1.8, 3.2 Hz, 1H). Anal. (C_5H_4FNO) C, H, N.

General Procedure for Preparation of Compounds 11, 12, 15, and 18. A mixture of cyclopropanemethanol (0.79 g, 11 mmol), 1,3-dicyclohexylcarbodiimide (2.06 g, 10 mmol), and copper(I) chloride (20 mg) was stirred at 60 °C for 6 h. (For preparation of **15**, 2-propanol (0.66 g, 11 mmol) was used instead of cyclopropanemethanol.) The reaction mixture was diluted with benzene (10 mL), and 10 mmol of an appropriate halo-3-pyridinol (**8d**, **10d**, **9c**, or **9b**, respectively) was added. This mixture was heated to reflux while stirring for 24 h. A precipitate that formed was filtered off, and the solution was concentrated under reduced pressure. The residue was extracted with hexanes−EtOAc (80:20) mixture (4 × 20 mL). The combined extract was washed with 20-mL portions of saturated $NaHCO_3$ and water and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo. The crude material was purified by flash chromatography (hexanes−EtOAc, 90:10 to 80:20) to give the desired product in 34−48% yields. Compounds **11**, **12**, and **15** were obtained as colorless liquids, while **18** appeared to be a white solid.

2-Iodo-3-(cyclopropylmethoxy)pyridine (11): ^{1}H NMR ($CDCl_3$) δ 0.43 (m, 2H), 0.68 (m, 2H), 1.31 (m, 1H), 3.92 (d, J = 6.6 Hz, 2H), 6.97 (dd, J = 1.3, 8.2 Hz, 1H), 7.16 (dd, J = 4.6, 8.2 Hz, 1H), 7.99 (dd, J = 1.3, 4.6 Hz, 1H). Anal. ($C_9H_{10}INO$) C, H, N.

6-Iodo-3-(cyclopropylmethoxy)pyridine (12): ^{1}H NMR ($CDCl_3$) δ 0.36 (m, 2H), 0.67 (m, 2H), 1.26 (m, 1H), 3.82 (d, J = 7.0 Hz, 2H), 6.90 (dd, J = 3.2, 8.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 3.2 Hz, 1H). Anal. ($C_9H_{10}INO$) C, H, N.

5-Bromo-3-isopropoxypyridine (15): ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 6.0 Hz, 6H), 4.56 (sept, J = 6.0 Hz, 1H), 7.34 (dd, J = 1.8, 2.7 Hz, 1H), 8.20 (d, J = 2.7 Hz, 1H), 8.24 (d, J = 1.8 Hz, 1H). Anal. ($C_8H_{10}BrNO$) C, H, N.

5-Chloro-3-(cyclopropylmethoxy)pyridine (18): mp 47−48 °C; ^{1}H NMR ($CDCl_3$) δ 0.37 (m, 2H), 0.68 (m, 2H), 1.28 (m, 1H), 3.85 (d, J = 7.2 Hz, 2H), 7.19 (dd, J = 2.1, 2.6 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 8.20 (d, J = 2.6 Hz, 1H). Anal. ($C_9H_{10}ClNO$) C, H, N.

General Procedure for Preparation of Compounds 13 and 14. A mixture of, respectively, **11** or **12** (1.1 g, 4 mmol), Kryptofix 222 (1.5 g, 4 mmol), and spray-dried KF (11.6 g, 200 mmol) in DMSO (80 mL) was stirred under argon at 165 °C for 24 or 72 h, respectively. The reaction mixture was diluted with water (160 mL) and extracted with CCl_4 (3 × 40 mL). The combined extract was washed with water (3 × 20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed at 35 °C under reduced pressure. The crude material was purified by flash chromatography (hexanes−ether, 70:30) to give the desired product as a colorless liquid in 38−46% yields.

2-Fluoro-3-(cyclopropylmethoxy)pyridine (13): ^{1}H NMR (acetone-d_6) δ 0.38 (m, 2H), 0.63 (m, 2H), 1.29 (m, 1H), 3.97 (d, J = 7.0 Hz, 2H), 7.22 (ddd, J = 0.9, 4.8, 7.9 Hz, 1H), 7.53 (ddd, J = 1.4, 7.9, 10.4 Hz, 1H), 7.70 (ddd, J = 1.4, 1.7, 4.8 Hz, 1H). Anal. ($C_9H_{10}FNO$) C, H, N.

6-Fluoro-3-(cyclopropylmethoxy)pyridine (14): ^{1}H NMR ($CDCl_3$) δ 0.36 (m, 2H), 0.67 (m, 2H), 1.27 (m, 1H), 3.83 (d, J = 7.0 Hz, 2H), 6.84 (dd, J = 3.5, 8.7 Hz, 1H), 7.33 (ddd, J = 3.2, 6.5, 8.7 Hz, 1H), 7.81 (dd, J = 1.9, 3.2 Hz, 1H). Anal. ($C_9H_{10}FNO$) C, H, N.

5-Amino-3-isopropoxypyridine (16). A mixture of **15** (1.08 g, 5 mmol), $CuSO_4 \cdot 5H_2O$ (230 mg, 0.92 mmol), and concentrated NH_4OH (7.5 mL) was heated in a high-pressure vessel at 135 °C for 20 h while being vigorously stirred with a Teflon-coated magnetic stirring bar. Then the mixture was brought to pH 10 with 20% NaOH, saturated with NaCl, and extracted with ether (2 × 20 mL). The combined extract was dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure. The crude material was purified by flash chromatography (hexanes−ether, 30:70) to give 0.68 g (89%) of the title compound as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.0 Hz, 6H), 3.87 (br s, 2H), 4.50 (sept, J = 6.0 Hz, 1H), 6.51 (dd, J = 1.8, 2.6 Hz, 1H), 7.69 (br m, 2H). Anal. ($C_8H_{12}N_2O$) C, H, N.

5-Fluoro-3-isopropoxypyridine (17). Sodium nitrite (180 mg, 2.6 mmol) was added in small portions to a solution of **16** (380 mg, 2.5 mmol) in HF−pyridine mixture (7.5 mL) in a poly(ethylene) reaction vessel cooled with an ice−salt bath. The resulting solution was stirred at 0 °C for 30 min, then heated to 50 °C, and stirred at this temperature for 1 h. The reaction mixture was poured onto crushed ice (25 g), partially neutralized with cold saturated $NaHCO_3$, and extracted with ether (4 × 15 mL). The combined extract was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (hexanes−ether, 60:40) to give 318 mg (82%) of the title compound as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 6.0 Hz, 6H), 4.62 (sept, J = 6.0 Hz, 1H), 7.07 (ddd, J = 2.3, 2.3, 10.2 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H), 8.21 (dd, J = 0.7, 2.3 Hz, 1H). Anal. ($C_8H_{10}FNO$) C, H, N.

5-(Trimethylstannyl)-3-(cyclopropylmethoxy)pyridine (19). A solution of **18** (1.84 g, 10 mmol) in DME (6 mL) was added dropwise to a stirred at 0 °C filtrate containing trimethylstannyl sodium prepared according to the literature procedure[31] from trimethyltin chloride (2.5 g, 12.5 mmol) and sodium (0.9 g, 39 mmol) in DME (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The solvent was removed in vacuo at 35 °C; the residue was extracted with ether (4 × 25 mL). After removal of the ether, the resulting crude material was purified by flash chromatography (hexanes−ether, 50:50) to give 1.62 g (52%) of the title compound as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.35 (m, 9H), 0.37 (m, 2H), 0.67 (m, 2H), 1.28 (m, 1H), 3.85 (d, J = 7.0 Hz, 2H), 7.29 (m, 1H), 8.20 (m, 1H), 8.22 (d, J = 3.0 Hz, 1H). Anal. ($C_{12}H_{19}NOSn$) C, H, N.

5-Iodo-3-(cyclopropylmethoxy)pyridine (20). A solution of iodine (1.27 g, 5 mmol) in $CHCl_3$ (15 mL) was added dropwise to a stirred solution of **19** (1.56 g, 5 mmol) in $CHCl_3$ (15 mL). The reaction mixture was stirred for 20 min at room temperature, and then saturated KF (20 mL) was added. The resulting mixture was made alkaline with saturated K_2CO_3 and separated. The aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The organic layers were combined, washed with 10-mL portions of saturated KF, saturated $Na_2S_2O_3$ and water, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude material was purified by flash chromatography (hexanes−ether, 60:40) to give 1.14 g (83%) of the title compound as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 0.36 (m, 2H), 0.67 (m, 2H), 1.27 (m, 1H), 3.83 (d, J = 7.2 Hz, 2H), 7.53 (dd, J = 1.6, 2.7 Hz, 1H), 8.26 (d, J = 2.7 Hz, 1H), 8.41 (d, J = 1.6 Hz, 1H). Anal. ($C_9H_{10}INO$) C, H, N.

5-(Trimethylstannyl)-3-((1-(*tert*-butoxycarbonyl)-2(*S*)-azetidinyl)methoxy)pyridine (21) was prepared analogously to **19** starting from **3b** (747 mg, 2.5 mmol). The product, purified by flash chromatography (hexanes−EtOAc, 50:50), was obtained as a colorless liquid: yield 470 mg (44%); ^{1}H NMR ($CDCl_3$) δ 0.34 (m, 9H), 1.42 (s, 9H), 2.23−2.42 (m, 2H), 3.91 (m, 2H), 4.15 (m, 1H), 4.30−4.35 (m, 1H), 4.52 (m, 1H), 7.33 (m, 1H), 8.22 (m, 1H), 8.25 (m, 1H). Anal. ($C_{17}H_{28}N_2O_3Sn$) C, H, N.

In Vitro Binding Study. Materials. (±)-[^{3}H]Epibatidine (48 Ci/mmol) was obtained from New England Nuclear Corp. (Boston, MA). 3-(2(*S*)-Azetidinylmethoxy)pyridine dihydrochloride (A-85380, **1**) was purchased from Research Biochemicals International (Natick, MA). All other chemicals used were purchased from Sigma Chemical Co. (St. Louis, MO). Male Fischer rats were obtained from Charles River Breeding Laboratories (Wilmington, MA). Rats, shipped at age of 12 weeks, were housed in a temperature- and light-controlled vivarium for at least 2 weeks before being used for this study.

Membrane Preparation. After CO_2 euthanasia and decapitation, rat forebrain was obtained by a single cut just behind the colliculi and excluded the cerebellum and medulla. A crude membrane fraction (P2) was isolated as previously described[41] and stored in aliquots at −70 °C for at least 16 h but no more than 4 weeks before use. In contrast to the original procedure,[41] the pellets of the crude membrane fraction were washed just once on the day of assay instead of repeated washing. The pellets were homogenized in 30 volumes of a HEPES−salt solution (HSS) containing HEPES (15 mM), NaCl (120 mM), KCl (5.4 mM), $MgCl_2$ (0.8 mM), and $CaCl_2$ (1.8 mM). After centrifugation at 40000***g*** for 10 min, the resultant pellets were resuspended in a fresh HSS and used for binding assay.

Binding Assays. Binding assays for all of the compounds studied were carried out in HSS at 25 °C and performed in duplicate. Each assay sample of a total volume of 0.5 mL contained 64 μg of membrane protein, 0.5 nM (±)-[^{3}H]epibatidine, and a test compound in concentrations ranging from 0.03 to 30 times an expected IC_{50} value. Nonspecific binding was determined in the presence of (−)-nicotine (300 μM). After 90 min of incubation, samples were filtered through Whatman GF/B glass fiber filters, presoaked in 1% poly(ethylenimine), using a Brandel 96-channel cell harvester. Radioactivity was measured using a Beckman LS 3801 liquid scintillation counting system at an efficiency of 43%. Protein concentration was measured using a dye reagent (Bio-Rad, Richmond, CA) and bovine serum albumin as a standard.[42] K_i values were calculated by the Cheng−Prusoff equation[43] based on the measured IC_{50} values and K_d = 10 pM for binding of (±)-[^{3}H]epibatidine. The K_d value was obtained in six independent experiments.

Molecular Modeling. Quantum chemical calculations by the AM1 method were performed using MOPAC 6.0 molecular orbital package (QCPE[44] program no. 455). The conformational search on a molecule of epibatidine involved calculations on rotamers with a fixed angle of rotation of the pyridine ring about the bond between the pyridyl and azabicyclic fragments. All other geometric parameters were subject to optimization with gradient norm (GNORM) set to 0.1. The fixed angle was changed in a 5° increment.

A systematic conformational search on molecules of compounds **1**, **2a**−**d**, **3a**−**d**, and **4a,d** was performed with three simultaneously fixed parameters. Those were angles of rotation of the respective fragments about the bonds C(azetidine)−C(methylene), C(methylene)−O, and O−C(pyridine). Each of the three fixed angles was changed in a 30° increment to give 1728 structures for each of the compounds studied. GNORM was set to 0.5 for this coarse search. Subsequently, regions of interest were searched systematically with the increments of 5° and GNORM = 0.15. Finally, calculations with full optimization were performed for the low-energy conformers found.

In accordance with the nicotinic pharmacophore model,[35] pyridine ring centroids were placed along the C−N−C bond angle bisector at 1.2 Å from the nitrogen atom.

Superpositions of structures were generated using Chem3D Pro Version 3.5 software.[45] Minimum rms error and gradient were set to 0.05 and 0.002, respectively.

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