# Coaxing a Pyridine Nucleus To Give Up Its Aromaticity: Synthesis and Pharmacological Characterization of Novel Conformationally Restricted Analogues of Nicotine and Anabasine[#]

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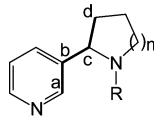
A series of novel nicotine and anabasine related conformationally restricted compounds including those with $\pi$-bonds in the connecting tether were synthesized following the hitherto unprecedented phenylsulfanyl group assisted generation of pyridine *o*-quinodimethane intermediates and their trapping by an intramolecular Diels−Alder reaction. Pharmacological characterization of some of these analogues at activating $\alpha3\beta4$ nAChRs was investigated, and constrained anabasine analogues **35** and **43** as well as constrained nicotine analogue **42** were found to exhibit moderately potent nicotinic agonist activity. Of special note is the fact that the pyrrolidinic nitrogen in these compounds is bound to a carbomethoxy group and, therefore, is not free to be protonated unlike all the known analogues of nicotine and anabasine, specifically designed as nAChRs agonists/antagonists. The structure−activity relationship studies indicate that when $\pi$−cation interaction is absent, the position of chlorine atom in the pyridine ring and steric bulk at the connecting tether between the pyridine and pyrrolidine ring of the constrained nicotinic ligands are important descriptors for their binding affinity at $\alpha4\beta2$ and $\alpha3\beta4$ nAChRs as well as the subtype selectivity issue. These findings are likely to improve our understanding of the structural requirements for selectivity, which, at present, is probably the most important goal in the field of nicotinic ligands.

## Introduction

In the last several decades, pharmacologists and chemists have focused an immense amount of research on the nicotinic receptor.[1−6] The critical neurotransmission pathway is found in both mammals and insects, and, in humans, the nicotinic pathway is associated with pain[7] and other chronic neurological disorders such as Alzheimer's disease,[8−10] Parkinson's disease,[10−12] Tourette's syndrome,[13] schizophrenia,[4] attention-deficit/hyperactivity disorder,[14] and depression.[15] Critical limitations for the potential use of nicotine as a therapeutic agent are its peripheral side effects that are due to the nonselective profile of nicotine. Compounds that target specific nAChR subtypes in the CNS may not induce these adverse effects and yet retain the beneficial effects of nicotine. One way to achieve this goal is to modify the parent biomolecule, e.g. **1/2** (Figure 1), in such a way that its original conformational mobility is severely limited to one particular conformation.[6] In light of this a variety of constrained nicotine analogues, e.g. **3**−**18** (Figure 2), have been synthesized.[16−31] Among these, analogues **4**, **8**, **10**, and **14** were evaluated as agonists, while **7** and **9** were evaluated as antagonists for neuronal nicotinic acetylcholine receptors (nAChRs). In particular, compound **4** ($n$ = 1), which selectively




**1**: R = Me, n = 1
**2**: R = H, n = 2

**Figure 1.** Structures for nicotine and anabasine.

activates human recombinant $\alpha2\beta4$ and $\alpha4\beta4$ nAChRs, has been shown to be active in animal models of Parkinson's disease and pain.[23] In order to develop novel conformationally restricted analogues of nicotine and anabasine, we settled on **19** (Figure 3), a reported constrained analogue of nicotine, because it provides a reasonable mimic of a trans conformer of nicotine that is supported by crystal structure data.[20,31] It may be mentioned here that, for the monoprotonated species of nicotine in aqueous solution, there are four major conformations present, of which the two approximately isoenergetic trans rotamers are preferred over their cis counterparts by >10:1 (Figure 4).[32] We envisioned that the ability to "freeze out" the conformational dynamics of nicotine at various torsion angles (*abcd*) maintaining skew orientation of pyridine and pyrrolidine rings as in **19** might help to identify conformational factors which appear to be critical for the interaction with various nAChR subtypes.

The binding units or additional substituents which may be used to restrict the conformational flexibility of nicotine may themselves interact with the portion of binding site, either favorably or unfavorably, and in turn impart some selectivity for one subtype or another.

[#] This paper is dedicated to Professor Tim Gallagher for his outstanding contribution to the development of new nicotinic agonists.

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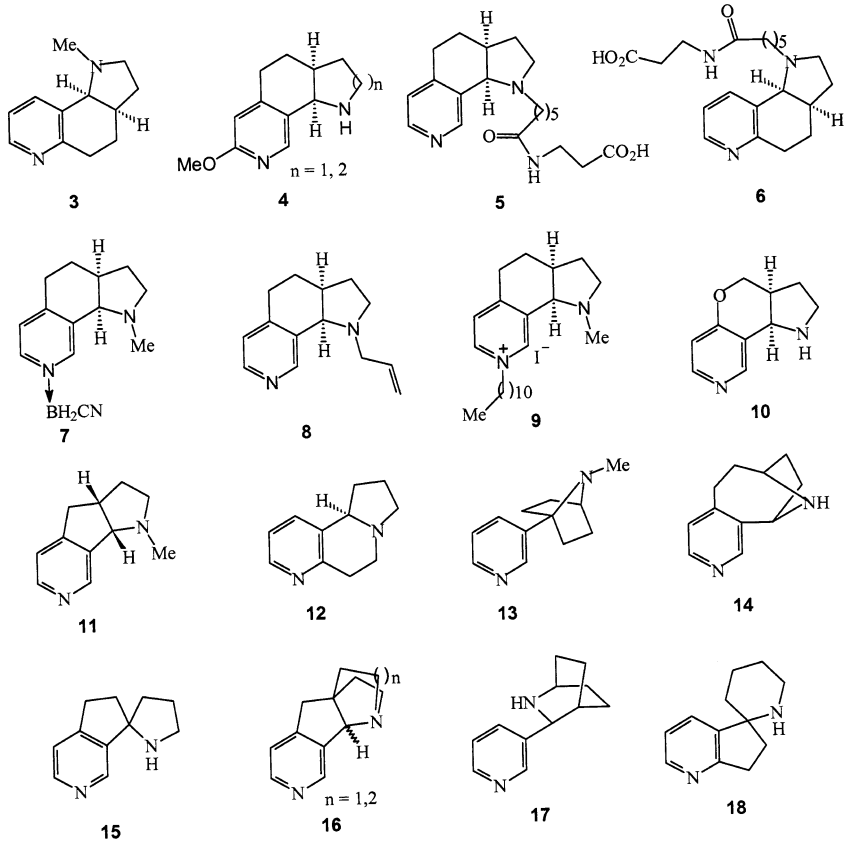



**Figure 2.** Selected conformationally constrained analogues of nicotine and anabasine.

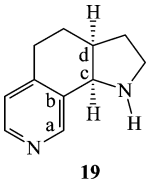



**Figure 3.** A mimic of a trans conformer of nicotine.

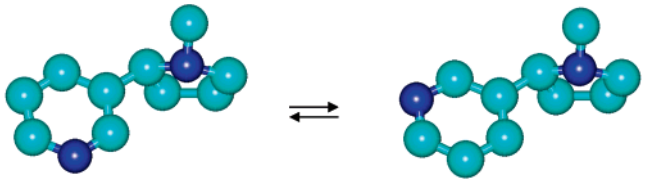
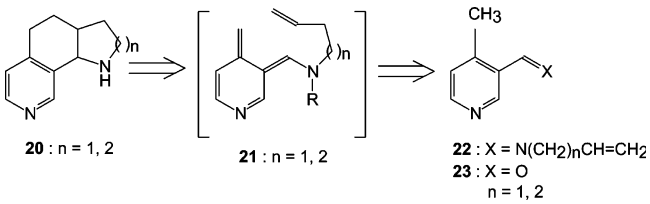


**Figure 4.** The major conformational isomers of nicotine in aqueous solution.

Disappointingly, the single synthetic route[17,20,21,23,27,28,31] followed over a period of two decades for the ring systems **4** − **9** does not appear to be viable for the synthesis of a large diversity of bridged nicotines and anabasines required to probe the conformation of (*S*)-nicotine which induces ion channel opening. Therefore, development of an alternate route which is easy, high-yielding, and flexible was desirable. Recently, we demonstrated a route to constrained anabasines (cf. **4**, $n$ = 2) involving a domino [4 + 2] cycloaddition/ring opening−elimination sequence of 3-amino-substituted furo-[3,4-*c*]pyridines.[33] Unfortunately, this approach turned out to be inefficient in the case of constrained nicotines (cf. **4**, $n$ = 1).[33,34] In this article we describe an alternative synthesis of both conformationally restricted analogues of nicotine and anabasine and their pharmacological activity for the α4$\beta$2 and α3$\beta$4 subtypes of the nicotinic receptor.

**Scheme 1**

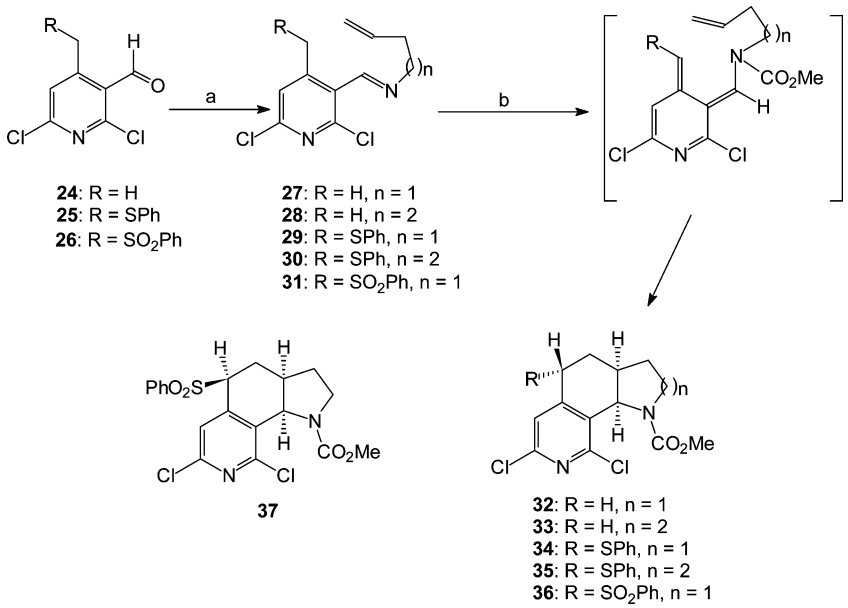



## Results and Discussion

**Chemistry.** A simple retrosynthetic analysis for both conformationally constrained nicotines and anabasines **20** shows that these compounds are also derivable via the generation of pyridine *o*-quinodimethane intermediates **21** through formal imine tautomerization of **22**, available from the corresponding aldehyde **23**, and its subsequent intramolecular trapping (Scheme 1). Although the chemistry of heterocyclic *o*-quinodimethanes has registered a burgeoning growth in recent years,[35−44] they have found, in general,[45−47] and pyridine *o*-quinodimethanes,[41] in particular, only limited applications in the synthesis of natural products.

To investigate the feasibility of this approach, we synthesized imines **27** and **28** from the dichloro-substituted aldehyde **24**[48] (Scheme 2). The choice of chloro substituents flanking the pyridine nitrogen was crucial for this study: the C-2 chloro group was selected for enhanced *cis*-stereoselectivity at the ring juncture in the Diels−Alder step, while the C-6 chloro group was

**Scheme 2**[a]




[a] (a) $CH_2{=}CHCH_2(CH_2)_nNH_2$, benzene; (b) $^iPr_2NEt$, $ClCO_2Me$, xylene.

chosen for stronger binding affinity of constrained nicotines and anabasines toward nAChRs, as will be apparent from a later discussion. Unfortunately, treatment of **27** or **28** with methyl chloroformate in the presence of Hünig's base and refluxing the mixture in xylene for an extended period[49] did not give any traces of **32** or **33**. This failure may be due to (i) the low acidity of methyl hydrogen which does not lend itself to rapid abstraction, (ii) recalcitrance of the pyridine nucleus to give up its aromaticity, or (iii) in situ generated *o*-quinodimethane intermediate being not sufficiently reactive to allow a Diels−Alder reaction to occur. It should be borne in mind that the aromaticity of pyridine is of the same order as that of benzene,[50] and the previous generation of indole 2,3-*o*-quinodimethanes[49] (or pyrrole *o*-quinodimethanes[51]) via a formal imine tautomerization protocol necessitated inductive deactivation of the indolic nitrogen lone pair of electrons by an arylsulfonyl[47] or a carboalkoxy group.[52] In order to overcome these problems we deemed it important to replace one of the hydrogens on the methyl group in the imine by a substituent which would not only make the methyl hydrogens more acidic (cf. **22**) but also stabilize the *o*-quinodimethane intermediates (cf. **21**). A phenylsulfanyl group appeared to fulfill these criteria; also it lends itself to easy reductive removal. In the event, we prepared imine **29** from **25**, an aldehyde which was prepared from commercially available ethyl 4-chloroacetoacetate.[53,54] With **29** in hand, we then carried out the formal imine tautomerization reaction using methyl chloroformate in the presence of diisopropylethylamine and were pleased to note that the desired constrained nicotine **34** was formed as a white crystalline solid (mp 156−157 °C) in 44% yield. The structure and stereochemistry of **34** were assigned on the basis of extensive NMR measurements and finally confirmed by X-ray crystallographic study (Figure 5). Interestingly, no other diastereomers could be traced in the crude reaction product by NMR spectroscopy.

The exclusive formation of **34** is explicable in terms of transition state **38** (exo-*E*,*E*) which is favored over

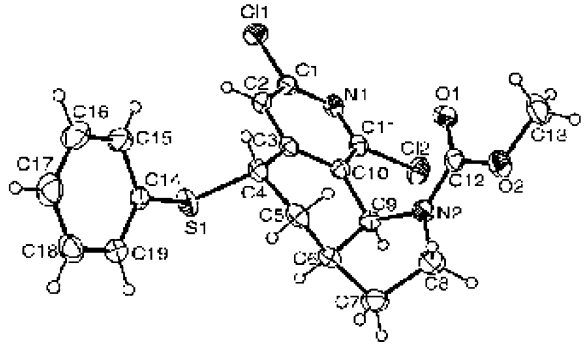
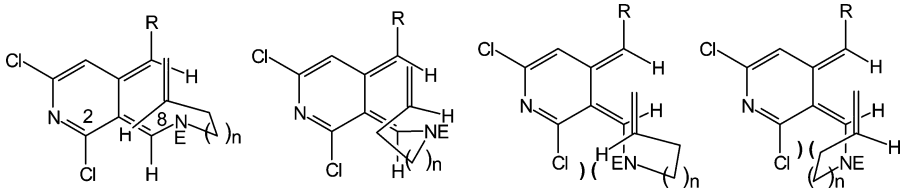



**Figure 5.** ORTEP perspective view of **34**.

the alternate transition state **39** (endo-*E*,*E*) as the latter is badly strained (Figure 6). The other most likely transition states, e.g. **40** (exo-*Z*,*E*) and **41** (endo-*Z*,*E*), are disfavored due to steric interaction between the substituents at C-2 and C-8.

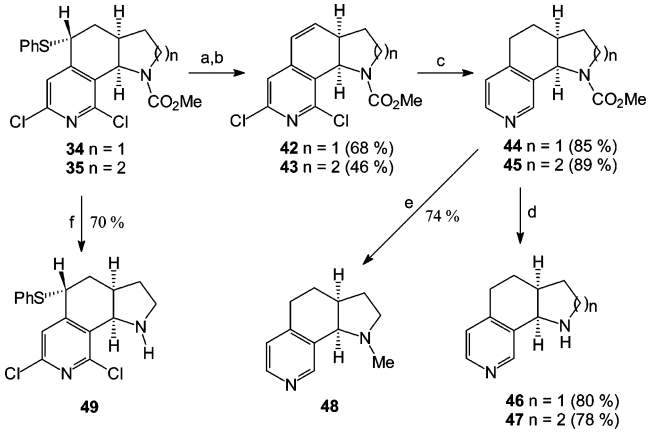
In order to explore the scope and limitations of this methodology we have also examined the formal imine tautomerization protocol for the synthesis of conformationally constrained anabasines. Thus, under conditions similar to those described for **34**, treatment of imine **30** with methyl chloroformate in the presence of diisopropylethylamine followed by preparative thin-layer chromatography gave an oil in 40% yield which was homogeneous on TLC. Proton NMR of this oil showed that it was a mixture of diastereomers corresponding to the desired Diels−Alder adducts. The diastereomers do not resolve on TLC (silica gel), and their relative abundance (69:25:6) was determined by LC−MS analysis. Finally, the major diastereomer **35** (mp 154−155 °C) was separated by preparative HPLC (column: ZORBAX SIL, 4.6 mm × 25 mm, ethyl acetate:hexane = 1:9). Unlike **34**, we failed to grow suitable crystals of **35** for X-ray analysis. The structure and stereochemistry of **35** were settled by a combination of $^1H$ and $^{13}C$ NMR, 1D homonuclear decoupling experiments, COSY, HMQC, NOESY, and HRMS studies. The transition state **38** (exo-*E*,*E*) is once again favored in this case.



**38** (exo-*E,E*) **39** (endo-*E,E*) **40** (exo-*Z,E*) **41** (endo-*Z,E*)

**Figure 6.** Plausible transition structures for the formation of **34**.

**Scheme 3**[a]



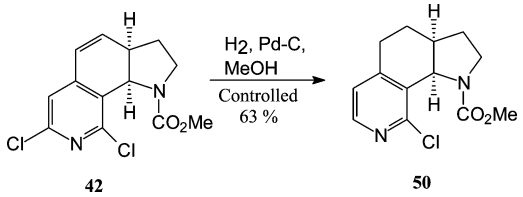
**34** n = 1
**35** n = 2
**42** n = 1 (68 %)
**43** n = 2 (46 %)
**44** n = 1 (85 %)
**45** n = 2 (89 %)
**46** n = 1 (80 %)
**47** n = 2 (78 %)
**49**
**48**

[a] (a) $NaIO_4$, MeOH−$H_2O$, room temperature; (b) Δ, $CH_2Cl_2$; (c) $H_2$, Pd−C, NaOAc, MeOH; (d) KOH, MeOH; (e) LAH,THF, room temperature; (f) TMSI, $CH_3CN$.

During the course of our studies, it appeared to us that better yield of the bridged products may be achieved by further enhancing the stability of the in situ generated pyridine *o*-quinodimethane intermediates. For this purpose, we have also investigated the chemistry of the closely related sulfone-substituted imine **31**, available from **26**, which in turn was prepared by oxidation ($RuCl_3$/$NaIO_4$) of **25**. However, an inseparable (TLC, $SiO_2$) mixture of two diastereomers is formed in a ratio of 65:35 (42%), which were separated by preparative HPLC to give **36** (mp 213−214 °C) and **37** (mp 210−211 °C). The structure and stereochemistry of **36** and **37** are based on extensive NMR ($^1H$ and $^{13}C$ NMR, 1D homonuclear decoupling experiments, COSY, HSQC, NOESY) as well as HRMS studies. Obviously, the major diastereomer **36** is forming via the transition state **38** (exo-*E,E*) as encountered before. We attribute transition state **41** (endo-*Z,E*) for the formation of minor diastereomer **37** where steric interactions presumably twist the nitrogen atom of the dieneamine segment out of conjugation with the diene system which is effectively stabilized by the phenylsulfonyl group.

The feasibility of our approach for the preparation of some constrained nicotines of proven bioactivity, e.g. **46**[23,28] and **48**,[20] has been shown in Scheme 3. Thus, $NaIO_4$ oxidation of **34** and thermally induced syn elimination of the resulting sulfoxide gave **42** (mp 172−173 °C) in 68% overall yield. One-pot reductive elimination of chlorine atoms and saturation of the π-bond in **42** followed by deprotection of the carbamate group under alkaline conditions yielded **46**. The compound **44** can be transformed into **48**, also of known bioactivity, in good yield by exposure of **44** to $LiAlH_4$ in $Et_2O$ at room temperature for 3 h. Subsequently, **35** was elaborated into conformationally constrained anabasine **47** following the same route developed for **46**. In addition, the carbamate group in **34** can be removed only by refluxing the mixture of **34** and TMSI in acetonitrile giving **49** in 70% yield. It may be mentioned here that **49** is a highly acid sensitive compound, and even traces of acid present in $CDCl_3$, $CHCl_3$, etc. are able to decompose it. Therefore, further studies with **49** ought to be carried out very carefully, and acetone, DMSO, etc. are found suitable solvents for this purpose.

**Scheme 4**



**42** **50**

**Table 1.** Conformational Parameters for Compounds **34** and **42**, Obtained from X-ray Study

| compd | torsion angle (deg) C11−C10−C9−C6 | torsion angle (deg) C11−C10−C9−N2 | N−N distance (Å) |
|---|---|---|---|
| **34** | −156.24 | 86.06 | 4.638 |
| **42** | −144.38 | 101.21 | |

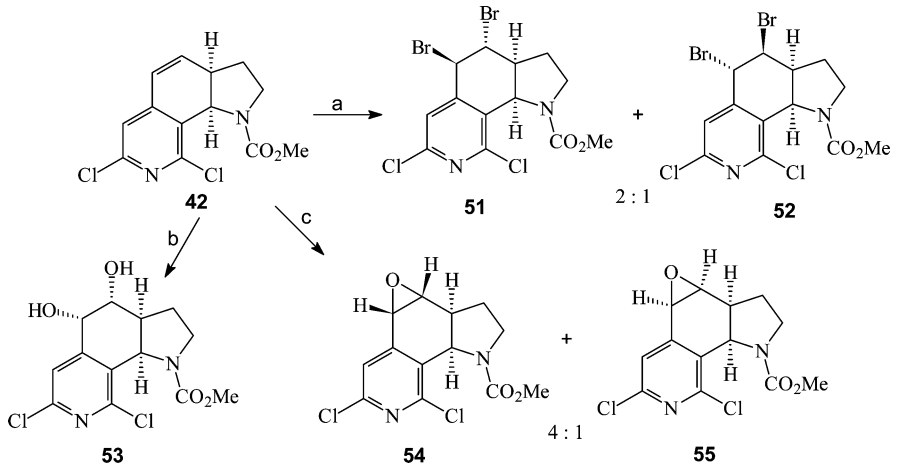
Furthermore, controlled hydrogenation of **42** using 10% Pd−C catalyst gives monochlorinated product **50**, the structural assignment of which was based on the $^1H$ NMR spectroscopic data (Scheme 4).

It may be mentioned here that **34**−**37**, **42**−**45**, **49**, and **50** are novel constrained nicotine and anabasine analogues. X-ray crystallographic data indicates that conformationally constrained nicotine analogue **42**[55] has a somewhat different conformation than **34** (Table 1).

With **42** and **43** in hand, we embarked upon a program to modify the tether with the hope of generating a large number of conformationally restricted biomolecules having altered torsion angles (*abcd*). Thus, bromination of **42** was carried out in dichloromethane at 0 °C, and the resulting brominated product was found to be as a mixture of two diastereomers **51** and **52** in a ratio of 2:1 (NMR), respectively (Scheme 5). Epoxides **54** and **55** were synthesized by a standard synthetic protocol and isolated as a chromatographically (silica gel) inseparable mixture (4:1). The diol **53** was obtained as a pure crystalline solid after chromatographic separation from the other minor *cis*-diol. The ratio of **53** and the other minor *cis*-diol was not determined. Semiempirical PM3 calculations showed that the torsion angle (*abcd*) in each of these compounds **51**−**55** is different from the others.

**Pharmacology.** Of the set of novel conformationally constrained analogues of nicotine and anabasine listed in this paper, compounds **34**, **35**, **36**, **42**, **43**, **47**, **49**, **50**, and **54/55** were tested for their functional activities at

**Scheme 5**[a]




[a] (a) $Br_2$, $CH_2Cl_2$, 0 °C; (b) $OsO_4$, Py, dioxane; (c) mCPBA, $CH_2Cl_2$.

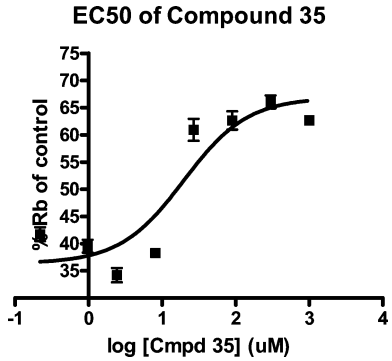



**Figure 7.** The dose−response curve ($EC_{50}$) of compound **35** (quadruplicate test of concentrations ranging from 0.279 $\mu$M to 1 mM) for the $\alpha3\beta4$ nicotinic receptor was determined by nonlinear regression of experimental data using sigmoidal dose−response curve fitting in Graph Pad Prism software. The stimulation of [$^{86}Rb^+$] efflux was measured and was expressed as a percentage of total [$^{86}Rb^+$] loaded.

**Table 2.** Functional Activity for Multiple Compounds Using the Rubidium Efflux Assay for the $\alpha3\beta4$ Subtype of the Nicotinic Receptor and Maximal Effect Reported Relative to Nicotine

| compd | $EC_{50}$ ($\mu$M) | % maximal response |
|---|---|---|
| epibatidine | $(28.25 \pm 1.63) \times 10^{-3}$ | na |
| **43** | $13.80 \pm 2.99$ | 75 |
| **35** | $18.24 \pm 3.40$ | 100 |
| nicotine | $19.83 \pm 1.61$ | 100 |
| **42** | $20.81 \pm 2.92$ | 100 |
| **49** | $26.36 \pm 1.78$ | 35 |
| **50** | >1000 | 10 |
| **36** | >1000 | 10 |
| **34** | >1000 | 10 |
| **54/55** | >300 | 40 |
| **47** | >1000 | 10 |

$\alpha3\beta4$ nAChRs, stably expressed by the KX$\alpha3\beta4$R2 cell line. The nAChRs ligand-stimulated $^{86}Rb^+$ efflux from KX$\alpha3\beta4$R2 cells was monitored by liquid scintillation counting. A representative concentration−response curve for our tested compounds is shown in Figure 7, and $EC_{50}$ values are also summarized in Table 2. The data from these studies demonstrate that the constrained anabasine analogue **43** has statistically similar potency to nicotine with regard to activation of $\alpha3\beta4$ nAChRs with $EC_{50}$ values of $13.8 \pm 2.99$ $\mu$M and $19.83 \pm 1.61$ $\mu$M, respectively, but it was significantly less potent than epibatidine [$EC_{50} = (28.25 \pm 1.63) \times 10^{-3}$ $\mu$M]. Interestingly, constrained anabasine analogue **35** ($18.24 \pm 3.40$ $\mu$M) and conformationally constrained nicotine analogue **42** ($20.81 \pm 2.92$ $\mu$M) have equivalent $EC_{50}$ values relative to nicotine ($19.83 \pm 1.61$ $\mu$M). However, in the case of **49**, although the $EC_{50}$ value was similar to that of nicotine, the maximum agonist response was 35% of the response obtained with nicotine, suggesting that the compound had partial agonist/antagonist properties. A mixture of epoxides **54** and **55** is found to have a weak $EC_{50}$ value (>300 $\mu$M), whereas compounds **34**, **36**, **47**, and **50** show no functional activity at a concentration of 1 mM and are considered to be ineffective agonists for $\alpha3\beta4$ nAChRs subtype.

Previous pharmacological models based on the $\alpha4\beta2$ receptor have suggested that the $\pi$−cation interaction is a key element.[1−7] Very recently, using the X-ray structure of acetylcholine binding protein (AChBP)[56] as template, a structural model of $\alpha3\beta4$ neuronal nicotinic receptor binding domain has been developed.[57] In this model the quaternary ammonium group of nicotine is found to form a $\pi$−cation interaction with αTyr194 and long-range electrostatic interaction with the αTyr90 side chain, in accordance with the experimentally characterized residues essential for nicotine binding. In addition, ACh ammonium group as well as cytisine ammonium group are also bound to the same region as nicotine, forming a $\pi$−cation interaction. However, it should be noted that the pyrrolidinic nitrogen of **35**, **42**, and **43** is bound to a carbomethoxy moiety and, therefore, should not be protonated. Thus, the $\pi$−cation interaction does not appear to play a role in the activity of these compounds.

To address the issue of binding selectivity among $\alpha4\beta2$ and $\alpha3\beta4$ nAChRs subtypes, binding affinity studies have also been carried out by displacement chromatographic experiments utilizing immobilized nAChRs stationary phase; a detailed discussion of the chromatographic studies is contained in a recent communication.[58] Some data from this work are listed in Table 3. In these studies the Δ mL (displacement of $^3H$-epibatidine) produced by the addition of nicotine or test ligands is equivalent to the binding affinities of the ligands. The greater the displacement of epibatidine (Δ mL), the greater the affinity. The chromatographic

**Table 3.** Determination of Binding Affinities of Constrained Nicotine and Anabasine Analogues Using Immobilized α4β2 and α3β4 nAChRs Based Liquid Chromatographic Stationary Phases

| sample | Δ $^3$H-epibatidine for α4β2 nAChRs (mL) | Δ $^3$H-epibatidine for α3β4 nAChRs (mL) |
|---|---|---|
| $^3$H-epibatidine | | |
| **42** | 0.28 | 0.28 |
| nicotine | 0.26 | 0.16 |
| **44** | 0.23 | 0.12 |
| **50** | 0.18 | −0.32 |
| **34** | 0.17 | −0.04 |
| **36** | 0.13 | −0.12 |

studies have demonstrated that various ligands have the following rank orders of potency for binding to each α4β2 and α3β4 nAChRs subtype: for α4β2, epibatidine > **49** > **42** > **54/55** ≈ nicotine > **44** > **43** > **50** > **34** > **36** > **35** > carbachol > **37**; for α3β4, epibatidine > **49** > **42** ≈ **54/55** > **43** > nicotine > **44** > **35** > carbachol ≈ **37** ≈ **34** > **36** > **50**.

These rank order profiles of compound potencies at α4β2 and α3β4 nAChRs demonstrate an interesting and significant relationship between structures and activity (SAR).

Binding data of **49** are fully corroborated with the fact that π−cation interaction is a primary determinant in high affinity binding.[1−7,59−61] This is also supported by the observations that many of the constrained analogues, e.g. **34** and **44** where the *N*-atom of the pyrrolidine ring is attached to the electron-withdrawing $CO_2Me$ group, show lower affinity toward nicotinic acetylcholine receptors. The binding data of these ligands including that of **42** suggests that when π−cation interaction is absent, the key factors that control the activity of the ligands are (i) position of chlorine atom in the pyridine ring and (ii) steric bulk at the connecting tether between pyridine and pyrrolidine rings of our ligands. An in-depth discussion of these points follows.

The binding data for **42**, **44**, and **50** for α4β2 nAChRs are consistent with observations that reported by Casida et al.[62] In that paper they suggested that the position of chlorine atom in the pyridine ring of the nicotinic ligand is important. Thus, in **50**, loss of binding affinity for α4β2 nAChRs may be due to the presence of one chlorine atom at the C-2 position of pyridine ring. But in the case **44**, the C-2 chlorine atom is absent and, therefore, binding affinity is somewhat better. In **42** the effect of one chlorine atom at C-6 overwhelms the effect of the other chlorine atom at C-2 and thereby enhances its affinity to the α4β2 nAChRs in comparison to that of **50**.

On the other hand, **34** and **36** bind to the receptor moderately due to the presence of bulky substituents such as −SPh group and $-SO_2Ph$ group at the axial position (cf. Figure 5) in the middle ring, whereas because of the presence of a less sterically demanding connecting tether in **42** it binds to the receptor with high affinity. It seems, therefore, that lesser steric bulk at the connecting tether is favorable for affinity. Interestingly, steric bulk at the equatorial position in the middle ring of constrained nicotines is least favorable for α4β2 nAChRs; this might be the reason why **37** is as inactive as carbachol. Unlike **34**, **49** is active in spite of the presence of a bulky substituent at the connecting tether due to the presence of a dominant π−cation interaction. In the case of **35** replacement of pyrrolidine ring by piperidine ring tolerates bulkiness of the group at the connecting tether during its binding to the α3β4 nAChRs at the activated state; therefore, ring size might be a factor for functional activity. From this study it is clear that a steric bulk effect between the pyridine and pyrrolidine rings of nicotine may be considered as a parameter in refining the nAChRs pharmacophore model.[63−65]

From the binding studies it appears to us that when π−cation interaction is absent, tolerability of the abovementioned steric bulk at the axial position of the connecting tether of the ligand by α4β2 nAChRs is higher than that by α3β4 nAChRs (Table 3). This means that greater steric bulk due to an axial benzylic substituent in the connecting tether of the ligand will make it more α4β2 subtype selective, although it requires steric balance for affinity. For example, **34** and **36** are selective for α4β2 subtype over the α3β4 subtype. However, when steric bulk in the connecting tether is absent, steric bulk associated with the chloro substituent at the C-2 position of the pyridine ring makes **50** α4β2 subtype selective. In addition, when both the 2- and 6-positions of the pyridine ring of the constrained nicotine are occupied by chloro substituents, then the effect of the chloro substituent at the C-6 position will be the dominating factor. This might have a favorable impact on α3β4 subtype selectivity. For example if we compare α4β2 and α3β4 chromatographic data of **42** and nicotine itself, it is clear that **42** shows somewhat more α3β4 subtype selectivity. Our observations might play a crucial role for further development of subtype selective nAChRs ligands.

## Conclusion

In conclusion, we have demonstrated for the first time that phenylsulfanyl group assisted generation of pyridine *o*-quinodimethanes provides an alternative synthesis of constrained nicotine and anabasine analogues. This route offers new possibilities in drug development because of its considerable flexibility for the synthesis of a variety of constrained nicotine and anabasine analogues. In addition, from a series of novel conformationally restricted analogues, four new nAChRs agonists have been identified. The constrained anabasine analogues **35** and **43** as well as constrained nicotine analogue **42** are found to elicit moderately potent nicotinic agonist activity via occupation of α3β4 nAChRs subtype. The structure−activity relationships of these conformationally restricted analogues where the pyrrolidinic nitrogen is not free to be protonated should be useful in further studies aimed at the elucidation of nAChR pharmacophore. The modified imine tautomerization protocol may also be useful for rapid construction of the tricyclic skeleton as present in the biologically significant sceletium alkaloids, e.g. sceletium-A4.[66]

## Experimental Section

**Chemistry.** All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: Tetrahydrofuran, benzene, and $Et_2O$ from sodium benzophenone ketyl; dichloromethane and acetonitrile from $P_2O_5$; DMSO and DMF from $CaH_2$; $Et_3N$, pyridine, and diisopropylamine from solid KOH; and methanol from Mg. After drying, organic

extracts were evaporated under reduced pressure and the residue was flash chromatographed on silica gel (Acme's, particle size 230−400 mesh) using an ethyl acetate−petroleum ether (60−80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plates (Merck, silica gel 60 F254) or $SiO_2$ (Glaxo, Sd 60−120 mesh, Acme 100−200 mesh).

**2,6-Dichloro-4-[(phenylthio)methyl]nicotinaldehyde (25).** To a stirred solution of 2,6-dichloro-4-[(phenylthio)-methyl]nicotinonitrile (4 g, 13.56 mmol) in $CH_2Cl_2$ (60 mL) cooled to −78 °C was added a 1.0 M solution of DIBAL-H (15 mL) in toluene dropwise over a period of 1 h. The resulting mixture was allowed to attain room temperature. After 2 h stirring at room temperature it was quenched with saturated aqueous $NH_4Cl$ at 0 °C, stirred for another 1 h at that temperature, and then acidified with 3 N HCl. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The crude residue was purified by chromatography (EtOAc: petroleum ether 1:99) to give 2.5 g (62%) of aldehyde **25** as a white crystalline solid. Mp: 61−62 °C. IR (KBr): 1688, 1565, 1526, 1317 $cm^{-1}$. $^1H$ NMR (200 MHz $CDCl_3$:$CCl_4$ 7:3): $\delta$ 4.37 (s, 2H), 7.00 (s, 1H), 7.28 (bs, 5H), 10.44 (s, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 36.0 (t), 113.9 (s), 124.9 (d), 127.8 (d), 129.0 (d), 131.9 (d), 133.3 (s), 158.3 (s), 153.9 (s), 154.2 (s), 190.0 (d). Anal. Calcd for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.03; N, 4.69. Found: C, 52.23; H, 3.19; N, 4.68.

**7,9-Dichloro-5-phenylsulfanyl-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (34).** A solution of but-3-enylamine (40 mg, 0.6 mmol) in dry benzene (1 mL) was added to a stirred solution of aldehyde **25** (100 mg, 0.34 mmol). After stirring for 2 h at room temperature, anhydrous $Na_2SO_4$ was added and stirring continued for a further 2 h. The mixture was then filtered and the filtrate allowed to stand over 4 Å molecular sieves overnight at room temperature. It was then filtered once again, and the filtrate was concentrated in vacuo. The crude product was immediately dissolved in dry xylene (15 mL) and cooled to 10 °C, and diisopropylethylamine (0.1 mL, 0.58 mmol) was added. The mixture was then treated with methyl chloroformate (0.5 mL, 6.5 mmol) at 0 °C. After stirring for 10 min, the mixture was then allowed to reflux for 3 h. After concentration under reduced pressure, the crude product was purified by column chromatography (silica gel, EtOAc−petroleum ether 10: 90) to give **34** as a yellowish oil, which on crystallization from methanol gives a white crystalline solid (70 mg, 44% yield). Mp: 156−157 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.45 (s, 1H), 7.40−7.26 (m, 5H, phenyl group), 5.07 (d, 1H, $J$ = 5.6 Hz), 4.25 (dd, 1H, $J_1$ = 9.6 Hz, $J_2$ = 4.8 Hz), 3.8−3.65 (m, 1H), 3.57 (s, 3H), 3.43 (td, 1H, $J_1$ = 10.9 Hz, $J_2$ = 7.2 Hz), 2.70 (tt, 1H, $J_1$ = 5.6 Hz, $J_2$ = 5.6 Hz), 2.26−2.13 (m, 1H), 2.01(ddd, 1H, $J_1$ = 14 Hz, $J_2$ = 5.2 Hz, $J_3$ = 5.2 Hz), 1.91−1.79 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 155.5 (s), 152.5 (s), 152.3 (s), 148.9 (s), 133.8 (s), 131.8 (d), 129.5 (d), 128.8 (s), 128.0 (d), 121.8 (d), 56.3 (d), 52.3 (q), 46.5 (d), 46.5 (t), 35.8 (d), 33.8 (t), 31.7 (t). HRMS (FAB): calcd for $C_{19}H_{19}N_2O_2SCl_2$ (M + H) 409.0544, found 409.0539.

**8,10-Dichloro-6-phenylsulfanyl-3,4,4a,5,6,10b-hexahydro-2*H*-[1,9]-phenanthroline-1-carboxylic Acid Methyl Ester (35).** Similar to the preparation of **34**, imine **30** was prepared first from aldehyde **25** (100 mg, 0.34 mmol) and pent-4-enylamine (50 mg, 0.58 mmol). The crude imine **30** was then treated with methyl chloroformate (0.5 mL, 6.5 mmol) in the presence of diisopropylethylamine (0.1 mL, 0.58 mmol), and the resulting mixture was heated at reflux for 3 h. The solvent was evaporated under reduced pressure, and the crude residue was purified by column chromatography to give a yellow oil (80 mg, 40% yield). HPLC−MS analysis of the yellow oil shows that it is a mixture of three diastereomers in a ratio of 69:25:6. The major diastereomer was purified by preparative HPLC (column: ZORBAX SIL, 4.6 mm × 25 mm, ethyl acetate: hexane = 1:9) to give **35** as a white crystalline solid. Mp: 154−155 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.54 (s, 1H), 7.42−7.30 (m, 5H, phenyl group), 4.92 (bs, 1H), 4.41 (t, 1H, $J$ = 6.4 Hz), 3.60 (s, 3H), 3.60−3.45 (m, 1H), 3.30−2.98 (m, 1H), 2.36−2.26 (m, 1H), 2.25−2.15 (m, 1H), 1.95−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.62−1.45 (m, 3H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 155.9, 152.4, 150.3, 148.2, 133.3, 132.9, 129.4, 129.2, 128.6, 124.1, 53.8, 52.7, 45.3, 43.3, 32.9, 31.6, 27.0, 23.5. HRMS (FAB): calcd for $C_{20}H_{21}N_2O_2SCl_2$ (M + H) 423.0701, found 423.0698.

**5-Benzenesulfonyl-7,9-dichloro-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (36 and 37).** A flask is charged with a magnetic stirrer, $CCl_4$ (2 mL), $CH_3CN$ (2 mL), $H_2O$ (6 mL), aldehyde **25** (120 mg, 0.4 mmol), and $NaIO_4$ (0.34 g, 1.6 mmol). To this biphasic solution was added a catalytic amount of $RuCl_3 \cdot xH_2O$ (∼5−10 mg), and the resulting mixture was stirred vigorously for 2 h at room temperature. Then $CH_2Cl_2$ (∼10 mL) was added, and the phases were separated. The upper aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The resulting residue was diluted with ether (15 mL), filtered through a Celite pad, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel) and afforded sulfone group bearing aldehyde **26** (80 mg, 60% yield).

Following the standard procedure, the aldehyde **26** (80 mg, 0.24 mmol) was then exposed to but-3-enylamine (30 mg, 0.42 mmol) in dry benzene (5 mL). The crude imine, thus prepared, was directly treated with methyl chloroformate (0.36 mL, 4.6 mmol) in the presence of diisopropylethylamine (0.08 mL, 0.4 mmol) at 0 °C, and resulting mixture was heated at 148 °C for 3 h. Concentration and chromatographic purification of the residue gave a white solid (50 mg, 42%). LC−MS analysis shows that it is a mixture of two diastereomers in a ratio of 65:35. These two diastereomers were separated by preparative HPLC (column: ZORBAX SIL, 4.6 mm × 25 mm, ethyl acetate: hexane 1:9) to give **36** (mp 213−214 °C) and **37** (mp 210−211 °C). Constrained nicotine analogue **36** exhibited the following properties. Mp: 213-214 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.85−7.72 (m, 3H), 7.68−7.57 (m, 2H), 7.05 (bs, 1H). 4.84 (d, 1H, $J$ = 4.5 Hz), 4.27 (dd, 1H, $J$ = 6 and 4 Hz), 3.51 (s, 3H), 3.60−3.42 (m, 2H), 2.88−2.75 (m, 1H), 2.31 (dt, 1H, $J$ = 14.5 and 4.5 Hz), 2.21−2.08 (m, 1H), 1.95−1.82 (m, 1H), 1.68 (t, 1H, $J$ = 10.5 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$): 156.8 (s), 155.3 (s), 154.6 (s), 148.4 (s), 136.8 (s), 134.8 (d), 129.7 (d), 129.2 (d), 128.8 (s), 123.6 (d), 63.5 (d), 55.9 (d), 52.4 (q), 45.2 (t), 34.2 (d), 29.1 (t), 24.9 (t). ESI-MS: *m/z* (relative intensity) 441 [(M + H)$^+$, 100], 405 [(M − Cl), 39]. HRMS (FAB): calcd for $C_{19}H_{19}N_2O_4SCl_2$ (M + H) 441.0442, found 441.0453.

Constrained nicotine analogue **37** exhibited the following properties. Mp: 210−211 °C. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.58−7.47 (m, 3H), 7.52−7.41 (m, 2H), 7.27 (s, 1H), 4.66−4.53 (bs, 1H), 4.51 (t, $J$ = 9.2 Hz, 1H), 3.58−3.12 (bm, 5H), 2.39−2.26 (bm, 1H), 2.26−2.17 (m, 1H), 2.14−2.02 (m, 1H), 1.95−1.75 (m, 2H). $^{13}C$-DEPT 45 (100 MHz, $CDCl_3$): 135.2, 129.6, 129.1, 123.3, 63.6, 55.8, 52.0, 45.0, 31.5, 23.5, 22.6. ESI-MS: *m/z* (relative intensity) 441 [(M + H)$^+$, 100], 463 [(M + Na), 83]. HRMS (FAB): calcd for $C_{19}H_{19}N_2O_4SCl_2$ (M + H) 441.0442, found 441.0444.

**7,9-Dichloro-2,3,3a,9b-tetrahydropyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (42).** To a stirred solution of **34** (180 mg, 0.44 mmol) in methanol (4 mL) and a small amount of $CH_2Cl_2$ (∼0.5 mL) was added a solution of $NaIO_4$ (0.15 g, 0.70 mmol) in $H_2O$ (3 mL) dropwise. After the solution was stirred for 5−6 days at room temperature, water and $CH_2Cl_2$ were added, the aqueous layer was extracted with $CH_2Cl_2$, and the combined organic fractions were washed with water, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was purified by chromatography (silica gel, ethyl acetate/petroleum ether 15:85) to give **42** as a white crystalline solid (50 mg, 38% yield) and the other unconverted diastereomeric sulfoxide of **34** (70 mg). This sulfoxide (70 mg) was then dissolved in $CH_2Cl_2$ (6 mL) and was heated at reflux for 4 h. After concentration under reduced pressure, the crude product was purified by silica gel chromatography to give

another crop of **42** (40 mg, 81% yield). The combined yield of **42** from **34** is ~68%. Constrained nicotine analogue **42** exhibited the following properties. Mp: 172−174 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.97 (s, 1H), 6.46 (dd, 1H, $J_1$ = 2.2 Hz, $J_2$ = 9.6 Hz), 6.00 (d, 1H, $J$ = 9.6 Hz), 4.93 (d, 1H, $J$ = 5.2 Hz), 3.70 (t, 1H, $J$ = 9.2 Hz), 3.54 (s, 3H), 3.46−3.10 (m, 2H), 2.42−2.05 (m, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 155.2 (s), 152.6 (s), 149.5 (s), 144.8 (s), 136.6 (d), 126.1 (d), 124.1 (s), 120.1 (d), 54.2 (d), 52.2 (q), 46.9 (t), 40.7 (d), 29.7 (t). LC−MS: *m/z* 299 [(M + H)$^+$].

**2,3,3a,4,5,9b-Hexahydropyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (44).** A mixture of **42** (90 mg, 0.3 mmol), fused NaOAc (0.12 g, 1.46 mmol), 10% Pd−C (120 mg), and dry methanol (6 mL) was stirred overnight under a hydrogen atmosphere at room temperature. The solution was then filtered through a small pad of Celite and the filtrate concentrated in vacuo. The resulting residue was purified by chromatography (silica gel, ethyl acetate:petroleum ether 20:80) to afford **44** as a colorless oil (60 mg, 85% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.73 (bs, 1H), 8.34 (bs, 1H), 6.99 (d, 1H, $J$ = 4.6 Hz), 4.99 (bs, 1H), 4.62−4.08 (bm, 1H), 3.76 (s, 3H), 3.68−3.46 (m, 1H), 3.46−3.27 (m, 1H), 2.94−2.51 (m, 3H), 2.22−1.88 (m, 2H), 1.87−1.51 (m, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 156.8 (s), 150.1 (d), 146.8 (d), 146.0 (s), 133.2 (s), 122.8 (d), 55.7 (d), 52.5 (q), 45.8 (t), 36.6 (d), 28.1 (t), 25.0 (t), 23.2 (t). LC−MS: *m/z* 233 [(M + H)$^+$].

**2,3,3a,4,5,9b-Hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (46).** To a stirred solution of **44** (50 mg, 0.21 mmol) in methanol (1 mL) was added a 40% aqueous solution of KOH (5 mL) dropwise, and the resulting mixture was heated at reflux for 3 h. After removal of most of the methanol under reduced pressure, the mixture was extracted with ether. The combined ethereal extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was then purified by column chromatography (basic alumina, ethyl acetate:petroleum ether 25:75) to give **46** as a colorless oil (30 mg, 80% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.57 (s, 1H), 8.30 (d, 1H, $J$ = 5 Hz), 7.00 (d, 1H, $J$ = 5 Hz), 4.01 (d, 1H, $J$ = 6.7 Hz), 3.26−3.02 (m, 1H), 3.02−2.88 (m, 1H), 2.88−1.32 (m, 8H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 151.1 (d), 147.3 (d), 146.6 (s), 133.0 (s), 123.1 (d), 56.8 (d), 45.6 (t), 37.0 (d), 32.6 (t), 28.2 (t), 25.5 (t).

**1-Methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*h*]isoquinoline (48).** To a stirred suspension of lithium aluminum hydride (20 mg, 0.5 mmol) in dry THF (3 mL) was added a solution of **44** (50 mg, 0.21 mmol) in THF (1 mL) dropwise at room temperature. After the mixture was stirred for 3 h at the same temperature, solvent was removed in vacuo and ether was added. Excess lithium aluminum hydride was then quenched with saturated aqueous solution of $Na_2SO_4$ dropwise carefully to make a pasty mass (not layer), and solution was decanted. Further extraction of the pasty mass with ether, drying of combined ethereal extracts ($Na_2SO_4$), and concentration gave the crude residue, which was purified by column chromatography (basic alumina, ethyl acetate:petroleum ether 25:75) to afford **48** as a colorless oil (30 mg, 74% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.38 (d, 1H, $J$ = 4.6 Hz), 8.32 (s, 1H), 7.08 (d, 1H, $J$ = 4.8 Hz), 3.79−3.57 (m, 1H), 3.16−1.38 (m, 12H). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 150.2 (d), 149.5 (s), 148.0 (d), 132.2 (s), 123.4 (d), 64.4 (d), 55.6 (t), 40.3 (q), 36.0 (d), 29.7 (t), 28.9 (t) 26.1 (t). EI-MS: *m/z* (relative intensity) 188 [M$^+$, 96], 187 [(M − H)$^+$, 100], 160 [(M − $C_2H_4$)$^+$, 6], 144 [(M − $NMe_2$)$^+$, 23], 130 [(M − $N(CH_3)C_2H_5$)$^+$, 57], 117 [8], 96 [34], 69 [10], 59 [21]. HRMS (EI): calcd for $C_{12}H_{16}N_2$ 188.1313, found 188.1309.

**8,10-Dichloro-3,4,4a,10b-tetrahydro-2*H*-[1,9]-phenanthroline-1-carboxylic Acid Methyl Ester (43).** A sample of **35** (380 mg, 0.89 mmol) under conditions similar to those described for the preparation of **42** gave **43** as a white crystalline solid (130 mg, 46% yield). Mp: 132−134 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 6.94 (s, 1H), 6.40 (dd, $J$ = 9.6 and 5.8 Hz, 1H), 6.29 (d, $J$ = 9.6 Hz, 1H), 5.70 (d, $J$ = 6.5 Hz, 1H), 4.32−4.11 (m, 1H), 3.74 (s, 3H), 2.85−2.64 (m, 1H), 2.58−2.36 (m, 1H), 1.84−1.12 (m, 4H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 155.9 (s), 149.0 (s), 147.9 (s), 147.7 (s), 140.1 (d), 124.4 (d), 124.1 (s), 120.4 (d), 52.9 (q), 52.4 (d), 41.0 (t), 36.5 (d), 25.9 (t), 23.8 (t). MSI-MS: *m/z* (relative intensity) 352 [(M + K + H)$^+$, 37], 330 [(M + $H_2O$)$^+$, 100], 313 [(M + H)$^+$, 22], 277 [(M − Cl)$^+$, 92].

**3,4,4a,5,6,10b-Hexahydro-2*H*-[1,9]-phenanthroline-1-carboxylic Acid Methyl Ester (45).** Following the procedure for the synthesis of **44**, a sample of **43** (100 mg, 0.32 mmol) gave **45** as a colorless oil (70 mg, 89% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.54−8.16 (bs, 1H), 8.28 (s, 1H), 7.02 (d, $J$ = 4.9 Hz, 1H), 5.61−5.22 (m, 1H), 5.05−4.44 (bs, 1H), 4.32−3.82 (m, 2H), 3.66 (s, 3H), 2.98−1.14 (m, 8H).$^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 156.5 (s), 147.9 (d), 146.7 (2C; s and d), 130.6 (s), 123.5 (d), 52.8 (q), 52.1 (d), 39.2 (t), 32.9 (d), 26.4 (t), 25.2 (t), 23.9 (t), 23.7 (t). ESI-MS: *m/z* (relative intensity) 247 [(M + H)$^+$, 100]. Stereochemistry at the ring juncture is tentatively assigned.

**1,2,3,4,4a,5,6,10b-Octahydro-[1,9]-phenanthroline (47).** Following the conditions described for the preparation of **46**, a sample of **45** (60 mg, 0.24 mmol) gave **47** as a colorless oil (36 mg, 78% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.47 (bs, 1H), 8.31 (d, 1H), 7.00 (d, $J$ = 4.9 Hz, 1H), 3.83 (d, $J$ = 3 Hz, 1H), 3.18−1.34 (m, 12 H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 150.7 (d), 147.5 (d), 146.3 (s), 134.4 (s), 123.7 (d), 54.2 (d), 46.4 (t), 33.2 (d), 29.2 (t), 28.4 (t), 22.1 (t), 21.8 (t). EI-MS: *m/z* (relative intensity) 188 [M$^+$, 85], 187 [(M − H)$^+$, 100], 171 [(M − $NH_3$)$^+$, 18], 159 [(M − $C_2H_5$)$^+$, 18], 144 [(M − $C_2H_5NH$)$^+$, 10], 130 [(M − $C_3H_7NH$)$^+$, 48], 117 [7], 98 [20], 83 [10], 69 [18], 55 [15]. HRMS (EI): calcd for $C_{12}H_{16}N_2$ 188.1313, found 188.1312.

**7,9-Dichloro-5-phenylsulfanyl-2,3,3a,4,5,9b-hexahydro-1*H*- pyrrolo[3,2-*h*]isoquinoline (49).** To a stirred solution of **34** (100 mg, 0.24 mmol) and NaI (120 mg, 0.80 mmol) in $CH_3CN$ (3 mL) was added freshly distilled trimethylsilyl chloride (0.70 mL, 0.5 mmol) at room temperature. The mixture was then heated at reflux for 2 h. MeOH (1 mL) was added, and after stirring for 15 min at room temperature the mixture was evaporated to dryness under reduced pressure. NaOH (2 N) was added and the slurry extracted thoroughly with ethyl acetate. The combined organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was purified by column chromatography ($Al_2O_3$, ethyl acetate:petroleum ether 25:75) to afford **49** as a yellowish oil (60 mg, 70% yield). [**CAUTION**: The compound **49** is highly acid sensitive, even toward $CHCl_3$, $CDCl_3$, etc.]. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.62−7.31 (m, 5H), 7.21 (s, 1H), 4.81−4.70 (m, 1H), 3.99 (d, $J$ = 5.7 Hz, 1H), 2.98−2.82 (m, 2H), 2.82−2.59 (bm, 1H), 2.36−1.39 (m, 5H). $^{13}$C NMR (50 MHz, acetone-$d_6$): $\delta$ 152.3 (s), 152.1 (s), 147.8 (s), 134.6 (s), 133.8 (d), 130.1 (d), 129.0 (d), 124.3 (d), 56.3 (d), 47.7 (d), 44.9 (t), 33.3 (d), 31.8 (t), 30.2 (t). HRMS (ESI): calcd for $C_{17}H_{17}N_2SCl_2$ (M + H) 351.0484, found 351.04809.

**9-Chloro-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-h]isoquinoline-1-carboxylic Acid Methyl Ester (50).** The compound **42** (50 mg, 0.17 mmol), fused NaOAc (60 mg, 0.73 mmol), and 10% Pd−C (~50 mg) were stirred in methanol under a controlled hydrogen atmosphere. The mixture was filtered through Celite and evaporated under reduced pressure. The residue was chromatographed (silica gel, ethyl acetate:petroleum ether 20:80) to give **50** as a colorless oil (28 mg, 63% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.17 (d, $J$ = 4.8 Hz, 1H), 6.99 (d, $J$ = 4.8 Hz, 1H), 5.14 (d, $J$ = 5.8 Hz, 1H), 3.76 (t, $J$ = 9.8 Hz, 1H), 3.54 (s, 3H), 3.53−3.29 (m, 1H), 2.77−1.64 (m, 7H).

**4,5-Dibromo-7,9-dichloro-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (51 and 52).** Bromine (0.014 mL, 0.28 mmol) in $CH_2Cl_2$ (0.7 mL) was added dropwise with stirring to a solution of **42** (80 mg, 0.21 mmol) in $CH_2Cl_2$ (4 mL) at 0 °C. After the mixture was stirred for 30 min at the same temperature, solvent was removed in vacuo. The residue was purified by preparative thin-layer chromatography (silica gel, ethyl acetate:petroleum ether 15:85) to give **51** and **52** in a ratio of 2:1 (62 mg, 51% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.41 (s, 1H), 5.46 (d, $J$ = 6 Hz, minor diastereomer **52**) and 5.38 (d, $J$ = 5.3 Hz, major diastereomer **51**) [1H], 5.17 (d, $J$ = 7 Hz, minor diastereomer **52**) and 5.14 (d, $J$ = 5.9 Hz, major diastereomer **51**) [1H], 4.63

(dd, $J = 6.4$ and 6.2 Hz, minor diastereomer **52**) and 4.56 (dd, $J = 6.6$ and 5.5 Hz, major diastereomer **51**) [1H], 3.88−3.39 (m, 2H), 3.64 (s, minor diastereomer **52**) and 3.63 (s, major diastereomer **51**) [3H], 3.32−3.05 (m, minor diastereomer **52**) and 3.06−2.82 (m, major diastereomer **51**) [1H], 2.56−1.82 (m, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$ 155.3 (s), 153.5 (s), 149.3 (s), 149.0 (s), 147.7 (s), 126.0 (s), 125.9 (s), 123.8 (d), 55.4 (d), 52.5 (q), 51.8 (d), 51.0 (d), 48.4 (d), 47.2 (d), 46.8 (d), 44.8 (t), 44.4 (t), 40.7 (d), 28.8 (t), 26.7 (t). HRMS (ESI): calcd for $C_{13}H_{13}N_2O_2Cl_2Br_2$ (M + H) 456.8715, found 456.8716.

**7,9-Dichloro-4,5-dihydroxy-2,3,3a,4,5,9b-hexahydropyrrolo[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (53).** To a stirred solution of **42** (70 mg, 0.23 mmol) in dry pyridine (4 mL) was added a solution of $OsO_4$ (70 mg, 0.28 mmol) in dry pyridine (1 mL) dropwise. Stirring was continued at room temperature in the dark for 12 h. The mixture was then poured into a saturated solution of $NaHSO_3$, stirred overnight, and extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was then purified by preparative thin-layer chromatography (silica gel, ethyl acetate:petroleum ether 40:60) to give **53** contaminated with a minor amount of the other diastereomer as a white crystalline solid (50 mg, 64% yield). A pure sample of **53** can be obtained by further purification of the mixture of diastereomers by preparative thin-layer chromatography. The constrained nicotine analogue **53** exhibited the following properties. Mp: 210−212 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.55 (s, 1H), 5.16 (d, $J = 6.1$ Hz, 1H), 4.69 (m, 1H), 4.08 (d, $J = 3$ Hz, 1H), 3.94−3.68 (m, 1H), 3.57 (s, 3H), 3.40−3.16 (m, 1H), 2.68−2.54 (m, 1H), 2.40−2.01 (m, 2H). $^{13}$C NMR (50 MHz, acetone-$d_6$): $\delta$ 156.5 (s), 154.7 (s), 149.6 (s), 147.4 (s), 128.6 (s), 120.2 (d), 74.7 (d), 69.4 (d), 54.4 (d), 52.2 (q), 47.0 (t), 45.3 (d), 29.3 (t). HRMS (ESI): calcd for $C_{13}H_{15}N_2O_4Cl_2$ (M + H) 333.0403, found 333.0405.

**7,9-Dichloro-4,5-epoxy-2,3,3a,4,5,9b-hexahydropyrrolo-[3,2-*h*]isoquinoline-1-carboxylic Acid Methyl Ester (54 and 55).** *m*-Chloroperbenzoic acid was first recrystallized by being dissolved in a mixture of 3 parts of petroleum ether (bp 60−80 °C) and 1 part ether using about 4−5 mL per gram, seeding, and cooling to −20 °C. The freshly recrystallized mCPBA (70 mg, 0.4 mmol) was then added to a stirred solution of **42** (70 mg, 0.23 mmol) in dry dichloromethane (2 mL) at room temperature overnight. Water was then added, and organic fractions were separated out. The combined organic extracts were washed with aqueous sodium hydrogen carbonate and with brine, dried ($Na_2SO_4$), and evaporated under reduced pressure. The crude residue was then purified to give a diastereomeric mixture of epoxides **54** and **55** as a colorless oil in a ratio of 4:1 (34 mg, 47% yield). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.40 (s, minor diastereomer **55**) and 7.36 (s, major diastereomer **54**) [1H]; 5.17 (d, $J = 6.3$ Hz, major diastereomer **54**) and 5.01 (d, $J = 4.7$ Hz, minor diastereomer **55**) [1H], 3.91−3.88 (m, 1H), 3.72 (s, 3H), 3.72−3.57 (m, 1H), 3.38−3.16 (m, 1H), 3.12−2.89 (m, 1H), 2.61−1.45 (m, 3H). HRMS (ESI): calcd for $C_{13}H_{13}N_2O_3Cl_2$ (M + H) 315.02977, found 315.02979.

**Biology.** Minimum essential medium with Earle's salts and L-glutamine (MEM), fetal bovine serum (FBS), penicillin-streptomycin (P/S), and geniticin were purchased from Gibco (Carlsbad, CA). Poly D-lysine, HEPES, NaCl, KCl, $MgSO_4$, $CaCl_2$, and glucose were purchased from Sigma Chemical Company (St.Louis, MO). $^{86}$Rubidium chloride ($[^{86}Rb^+]$) was purchased from Perkin-Elmer (Boston, MA). Twenty-four-well plates were purchased from Fisher Scientific (Fairlawn, NJ).

**Nicotine Stimulated $^{86}Rb^+$ Efflux Experiments on the KX$\alpha$3$\beta$4R2 Cells.** The KX$\alpha$3$\beta$4R2 cells were provided by Dr. Kenneth J. Kellar (Georgetown University, Washington, DC) and were established and maintained as previously described.[67] The functional studies were carried out on the nicotinic receptors using the rubidium efflux assay as previously described.[68] Briefly, cells were grown in selection growth medium (500 mL MEM, 10% FBS, 1% p/s, 350 mg of geniticin). Once the cells reached greater than 90% confluence, they were plated (1 mL/well) on 24-well plates coated with poly (D-lysine) (>300000 MW). These plates were then incubated for 48 h at 37 °C to reach greater than 90% confluence. The medium was then removed, and the cells were incubated with 0.5 mL of $[^{86}Rb^+]$ (2 $\mu$Ci/well) in growth medium for 4 h at 37 °C. The medium was then aspirated, and the cells were washed for 2 min with 1 mL of buffer A (15 mM Hepes, 140 mM NaCl, 2 mM KCl, 1 mM $MgSO_4$, 1.8 mM $CaCl_2$, 11 mM glucose, pH 7.4) per well. The process was repeated two additional times, first with a wash of 2 min and then with a final wash of 7 min. One milliliter solutions of either buffer A (control) or buffer A with the test compounds (experimental) were then added to the wells for 2 min, after which they were collected into scintillation vials and counted for $[^{86}Rb^+]$ efflux using liquid scintillation counting. The $EC_{50}$ values of the test compounds (quadruplicate test of concentrations ranging from 0.279 $\mu$M to 1 mM) were determined by nonlinear regression of experimental data using sigmoidal dose−response curve fitting in Graph Pad Prism software.[69]

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of all compounds; COSY, HMQC/HSQC, HMBC, and NOESY/TROESY of **34**−**37** and **51**−**55** including complete discussion regarding stereochemical assignments; MS and HRMS of **34**−**37**, **43**, **45**, **47**−**49**, and **51**−**55**; LC traces of **35**−**37**; NOE spectra of **43**, **46**, **51/52**, and **54/55**; decoupled spectra of **43**, **44**, **51/52**, and **54/55**; X-ray crystallographic data of **34**; response vs concentration graphs ($EC_{50}$) of **36**, **42**, **43**, **50**, and **54/55**. This material is available free of charge via the Internet at http://pubs.acs.org.

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