Synthesis and Biological Evaluation of (−)- and (+)-Debromoflustramine B and Its Analogues as Selective Butyrylcholinesterase Inhibitors

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A series of pyrrolidinoindolines have been synthesized as debromoflustramine B (**4a**) analogues for their evaluation as cholinesterase inhibitors. Structure−activity studies of this series revealed the optimum pharmacophoric elements required for activity and resulted in the discovery of selective butyrylcholinesterase inhibitors with micromolar potency. Biological testing demonstrated that (−)-**4a** was 7500 times more potent than its enantiomer (+)-**4b**. The most active inhibitor against BChE in the series was demethyldebromoflustramine B (**5a**), with an IC_{50} value of 0.26 μM. X-ray crystallography of **15** and docking studies of selected compounds into human BChE (PDB 1POI) are presented. Molecular modeling studies showed that π−hydrogen bond, classical hydrogen bond, and cation−π interactions are critical for optimum potency.

Cholinesterase inhibitors have been used as therapeutic targets in Alzheimer's disease (AD)[a], one of the most common type of adult-onset dementia.[1] The cholinergic hypothesis postulates that memory impairments in patients with AD result from a deficit of cholinergic function in the brain.[2] Indeed, the cholinergic system is the earliest and most profoundly affected neurotransmitter system in AD, in which decreasing levels of neurotransmitter acetylcholine (ACh) and its hydrolyzing enzyme acetylcholinesterase (AChE) correlate positively with losses of cholinergic neurons and synapses occurring in the forebrain, cortex, and hippocampus.[3] Studies in AD patients with severe pathology have shown that these changes occur concomitantly with a significant increase of butyrylcholinesterase (BChE), while AChE is reduced in specific brain regions.[4] The survival of AChE knockout mice with normal levels and localization of BChE shows that this enzyme is likely to play a constitutive role in the hydrolysis of ACh in the normal brain.[5] Therefore, both enzymes are likely to have involvement in regulating ACh levels and represent therapeutic targets to ameliorate the cholinergic deficit. Recent evidence suggests that BChE may also have a role in the etiology and progression of AD beyond regulation of synaptic ACh levels.[6] Studies examining the relationship between BChE polymorphisms and the progression of cognitive impairment in dementia with Lewy bodies and AD suggests that BChE is present in key brain areas and may influence the aggregation of neuritic β-amyloid (Aβ) plaques to form the neurofibrillary plaques causing dementia.[7,8] These accumulating data suggest that BChE may be particularly important in individuals with more severe dementia as BChE activity increases with disease development. Therefore, the development of selective BChE inhibitors may be of great interest to clarify the physiological role of this enzyme in the normal, aging, and diseased brain and to provide therapeutics for various diseases, including AD. Current treatment for AD with the use of reversible dual cholinesterase inhibitors, such as rivastigmine, support a role for the central inhibition of BChE in addition to AChE based on the high correlation of the former with cognitive improvement.[9] The use of the more selective BChE inhibitors tacrine and tetrahydroaminoacridine are limited by its hepatotoxicity as well as side effects stemming from their low target specificity.[10] Recently, selective, reversible cymserine-based BChE inhibitors were synthesized, improving cognition and modulating neuropathological markers of AD.[11]

Although highly similar (50−60%), the enzymes AChE and BChE are encoded by different genes and clearly differ in substrate specificity and sensitivity to inhibitors, likely because of a larger void at the BChE active site gorge and/or structural differences in the catalytic site. The existence of a peripheral site at the lip of the gorge of equine and human BChEs was hypothesized using molecular docking techniques, and potent tacrine-based BChE inhibitors were developed in order to validate such hypothesis.[12] To define the role of BChE in brain, potent analogues of phenserine were designed based on the X-ray crystallographic structure of the binding sites for ACh that differentiate BChE from AChE.[13]

Besides the discovery of naturally occurring physostigmine (**1**) as a potent cholinesterase inhibitor,[14] there is a continuing search for new classes of natural products capable of alleviating some of the symptoms of AD (Figure 1). Between them, huperzine A (**2**), a *Lycopodium* alkaloid isolated from the Chinese herb, *Huperzia serrata*, is a reversible, potent, and selective AChE inhibitor.[15] Another selective AChE inhibitor, galanthamine (**3**), is an alkaloid isolated from the common snowdrop *Galanthus nivalis*.[16] In addition, several different types of steroids, terpenoids, and tropan alkaloids have been shown to inhibit BChE.[17] At this point, we previously reported the synthesis of racemic and enantiomerically pure debromof-

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[a] Abbreviations: Aβ, β-amyloid plaques; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; APCIMS, atmospheric pressure chemical ionization mass spectrometry; BChE, butyrylcholinesterase; ΔG_{bind}, estimated binding free energy for clusters; DMSO, dimethylsulfoxide; ESI, electrospray ionization; GC/MS, gas chromatography coupled to mass spectrometry; HRMS, high-resolution mass spectrometry; IC_{50}, half-maximal inhibitory concentration; LAH, lithium aluminum hydride; PDB, protein data bank; pK_a, minus the decimal logarithm of acid dissociation constants; rmsd, root-mean-square deviation; SAR, structure−activity relationship; TBAHS, tetrabutylammonium bisulfate; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, tetramethylsilane; 3D, three-dimension; CH_2-4Py, pyridin-4-ylmethyl. Single-letter and three-letter abbreviations are used for amino acids.

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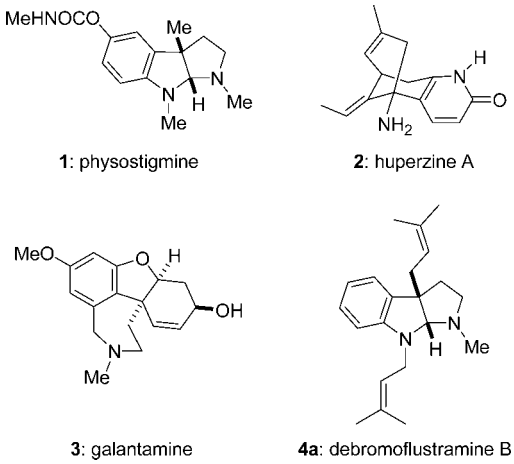


Figure 1. Structures of cholinesterase inhibitor alkaloids **1**−**4a**.

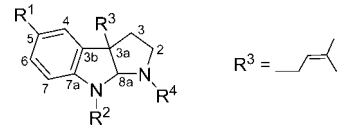
lustramine B (**4**),[18,19] a naturally occurring prenylated pyrrolidinoindoline isolated from the cheilostome bryozoan *Flustra foliacea*,[20] lacking the carbamate pharmacophore of physostigmine (**1**). In this article, we describe in vitro anticholinesterases evaluation of (−)- and (+)-debromoflustramine B (**4a** and **4b**). On the basis of a rational approach, a series of racemic structural analogous were designed and a discussion of their structure−activity relationships is reported.

Chemistry

The structures of all evaluated compounds are shown in Tables 1 and 2. In Table 1, the prenyl group at C(3a) (R^3) was kept in all cases, and the substituents R^2 and R^4 were varied between prenyl, benzyl, and methyl groups. Further modification of the scaffold molecule include the replacement of the substituent prenyl at C(3a) with either an aromatic core, such as benzyl or pyridin-4-ylmethyl (CH_2-4Py), or with an alkyl group varied from methyl to 2-methylbutyl, as shown in Table 2. The synthesis of the target molecules **4**−**22** and **27** was accomplished using our previously developed methodology.[18,19] Scheme 1 represents the synthesis of **4c** and derivatives **5**−**9**, **14**, and **16**−**22**, in which the alkyl groups at C(3a) and N(8) are the same. Commercially available 3-acetonitrilindole **23a** or its 5-methoxy derivative **23b**[21] were converted to oxindoles **24a** and **24b**, respectively, by treatment with a mixture of DMSO/HCl and served as late-stage intermediates for rapid analogue preparation. Facile N- and C-alkylation of **24a**,**b** with the proper alkyl halide under mild phase-transfer conditions gave dialkylated oxindoles **25a**−**h**, which by subsequent reductive cyclization and either N(1)-prenylation, N(1)-benzylation, or one-pot selective N(1)-monomethylation of the resulting pyrrolidinoindolines **5a**−**h** allowed access to **4c** and a variety of analogues **5**−**9**, **14**, **16**−**18**, and **20**-**22** in four steps. Compound **19** ($R^2 = R^3$ = 2-methylbutyl) was prepared from **4c** ($R^2 = R^3$ = prenyl) by hydrogenation on 10% Pd/C.

The synthesis of differentially 3a,8-dialkylated pyrrolidinoindolines **10**−**13** and **15** required introduction of the alkyl group at the N(1) position of the corresponding indole prior to the oxidation step (Scheme 2). Thus, alkylation of **23a**,**b** by reaction with the proper alkyl bromide gave **23c**−**e**, oxidation with DMSO/HCl then furnished **24c**−**e**. These oxindole intermediates were C(3)-alkylated to give **25i**−**l** and transformed into desired analogues **10**−**13** and **15** in two or three steps involving reductive ring closure to pyrrolidinoindolines **5i**−**l** and N(1)-benzylation of **5j** to give **13**, or one-pot N(1)-monomethylation by reaction of **5i**−**l** with CH_2O, MeOH, and then $NaBH_4$ to give **10**−**12** and **15**.

Table 1. Structures of C(3a) Prenylated Pyrrolidinoindolines **4a**−**c** and **5a**−**13** and Their in Vitro Inhibition of BChE



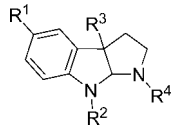
cmpd	R^1	R^2	R^4	IC_{50} (μM)[a]
(-)-**4a**	H		Me	1.37 ± 0.13
(+)-**4b**	H		Me	10.32 x 10^3 ± 315
(±)-**4c**	H		Me	2.59 ± 0.15
5a	H		H	0.26 ± 0.06
6	H			1.72 ± 0.08
7	H		Bn	n i[b]
8	OMe		Me	4.59 ± 0.19
9	OMe		Bn	49.98 ± 7.11
10	H	Me	Me	n i[b]
11	H	Bn	Me	10.00 ± 0.75
12	OMe	Bn	Me	7.54 ± 1.43
13	OMe	Bn	Bn	n i[b]

[a] Human BChE was used. The IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity by 50% and are the average of three independent measurements, each performed in triplicate. [b] ni = No inhibition a < 10000 μM.

To test whether the nitrogen atom at 1-position in pyrrolidines is crucial for good inhibitory activity, we decided to synthesize the furoindoline analogue **27** (Scheme 3). Thus, reductive cyclization of the sodium salt of 2-oxo-3-indolyl acetic acid **26**[19] with LAH/THF after cooling the reaction mixture in an ice/water bath gave the desired furoindoline **27** in 87% yield, together with a small amount (<5%) of alcohol **28**. It is noteworthy that similar transformation under reflux produced alcohol **28** in 93% yield.

Analysis of NMR spectral data and crystal structure determination of **15** (Figure 2) led to the assignment of the compounds. A prominent structural feature of **15** arising from the X-ray study is that the N(8)-benzyl group remains nearly perpendicular to the indole plane, whereas the pyridinylmethyl group is projected toward the *exo*-surface of the indole portion. This feature persists in solution, as demonstrated by the observed diagnostic cross-peak between H(8a) (δ 4.30) and one of the diastereotopic methylene protons (δ 2.84) of the pyridinylmethyl group in the NOESY spectrum. In the same way, the observed cross-peaks between H(8a) and the vinylic proton of the prenyl group at C(3a) in the NOESY spectra measured for pyrrolidinoindolines **4c** (δ 4.71, 4.99), **5a** (δ 4.65, 5.05), and **6** (δ 4.41, 4.99) suggest that these molecules exist in solution in a

Table 2. Structures of Pyrrolidinoindolines **14**−**22** and Their in Vitro Inhibition of BChE



cmpd	R^1	R^2	R^3	R^4	IC_{50} (μM)[a]
14	H	Bn	Bn	Me	22.06 ± 0.68
15	H	Bn	CH_2(4Py)	Me	n i[b]
16	H	CH_2(4Py)	CH_2(4Py)	Me	n i[b]
17	OMe	Bn	Bn	Me	5.89 ± 0.11
18	OMe	Bn	Bn	Bn	n i[b]
19	H			Me	n i[b]
20	H	*n*-Pr	*n*-Pr	Me	n i[b]
21	H	Et	Et	Me	n i[b]
22	H	Me	Me	Me	n i[b]

[a] Human BChE was used. The IC_{50} values represent the concentration of inhibitor required to decrease enzyme activity by 50% and are the average of the three independent measurements, each performed in triplicate. [b] ni = No inhibition at <10000 μM.

contributing conformation in which the C-prenyl group is positioned over the *exo*-surface of the pyrrolidinoindoline core.

Biological

All synthesized compounds, including enantiopure (**4a**, **4b**) and racemic (**4c**) debromoflustramine B, were evaluated in vitro for their inhibitory action in both AChE and BChE. Compounds were first screened at 1 mM, and those compounds that showed good inhibitory activities (% inhibition >30%) were further tested at nine concentration levels to generate concentration-dependent curves from which the IC_{50} values were derived. Each tested compound was assayed three times for triplicate. Experimental screening of 20 compounds showed nine to be active as BChE inhibitors, while all of them had very little if any inhibitory activity on AChE. The effect on BChE inhibitory activity of alterations made to R^1−R^4 of the pyrrolidinoindoline scaffold is summarized in Tables 1 and 2. The role of chirality was initially examined. Synthetic racemic debromoflustramine B (**4c**) was determined to have an IC_{50} value of 2.59 ± 0.15 μM, whereas the corresponding natural occurring 3a*S*,8a*R*-(−) enantiomer **4a** was about 2 times more potent than **4c**, while the 3a*R*,8a*S*-(+) enantiomer **4b** was found to be inactive, in agreement with the established enantioselective behavior of the classical AChE inhibitor physostigmine (**1**).[14,22]

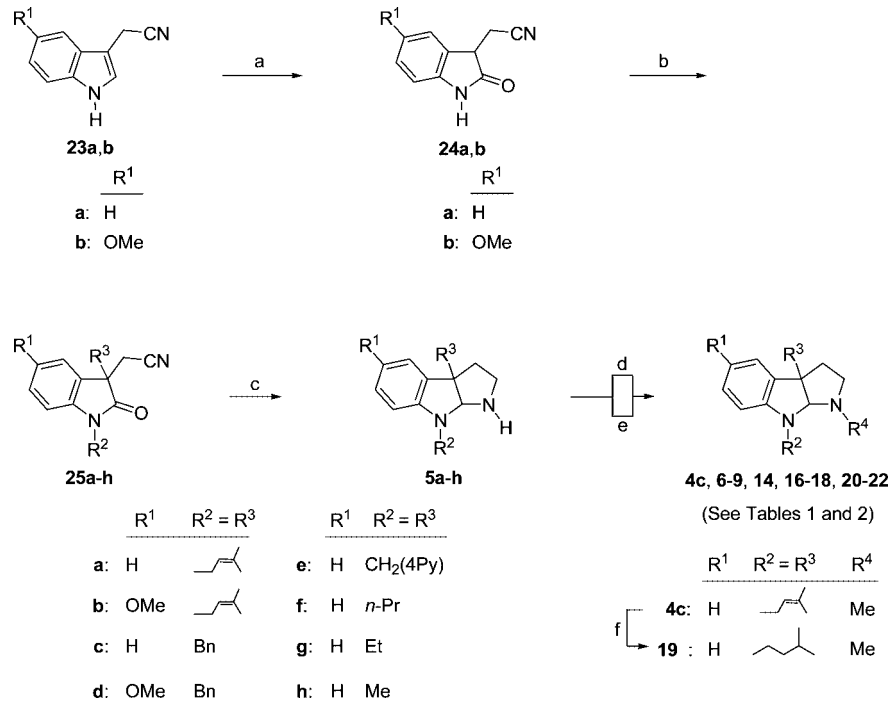
Compounds **5a**−**22** and **27** were evaluated as racemic mixtures, and some general observations can be made from SAR studies on R^1−R^4. The more active inhibitors against BChE in the series, **4a**, **4c**, **5a**, **6**, and **8**, are R^2 and R^3 prenyl substituted. Removal of the methyl group on the racemic parent compound **4c** was beneficial, enhancing the inhibition activity 10-fold (**5a**, Table 1). Replacement of the prenyl groups at R^2 and R^3 positions of **4c** by benzyl groups caused a 8.5-fold drop in inhibitory activity (**14**, Table 2), while replacement of a single aromatic CH with nitrogen in the benzyl portion or replacing it by alkyl groups resulted in complete loss of activity (**16**, **19**−**22** Table 2). Having determined the importance of retaining the prenyl substituents, we were focused to clarify if both prenyl groups are required for the best biological response. It was found that the R^2-Bn analogues **11** and **12** (Table 1) displayed greater or almost equal inhibitory potency than their dibenzylated counterparts **14** and **17** (Table 2) but exhibited ca. 4- and 2-time less loss of inhibitory activity as compared to their diprenylated counterparts **4c** and **8** (Table 1). In addition, compound **10**, which replace the prenyl group with methyl at the R^2 position, or compound **15**, which replace the benzyl group with pyridinylmethyl at the R^3 position, were associated with complete loss of inhibition activity.

Evaluation of the R^4-substituted analogues revealed that this was also a sensitive area for activity where the R^4-benzylated analogues **7**, **9**, **13**, and **18** resulted in significant (**9**) or total loss of inhibition activity, while replacement of methyl with a prenyl group at the R^4 position of racemic parent **4c** was well-tolerated, as demonstrated in the analogue **6**, which was roughly equipotent with **4a**. Unlike the SAR studies on carbamate-based cholinesterase inhibitors, in which the replacement of the N(1) and N(8) atoms with oxygen did not change significantly the in vitro activity,[14] in compound **27**, this type of replacement abolished the activity (data not shown). In addition, the effect of adding a methoxy group at the R^1 position was examined. As the data indicated (Tables 1 and 2), such substitution resulted in quite different outcomes for the activity. Minor effects were observed for the R^1-methoxylated analogues **8** and **12**, moderated effects for **17**, while the inactive demethoxylated analogue **7** turned to be active **9** upon methoxylation (IC_{50} = 49.98 ± 7.11 μM), suggesting that the conformation was a critical factor for receptor affinity.

Discussion

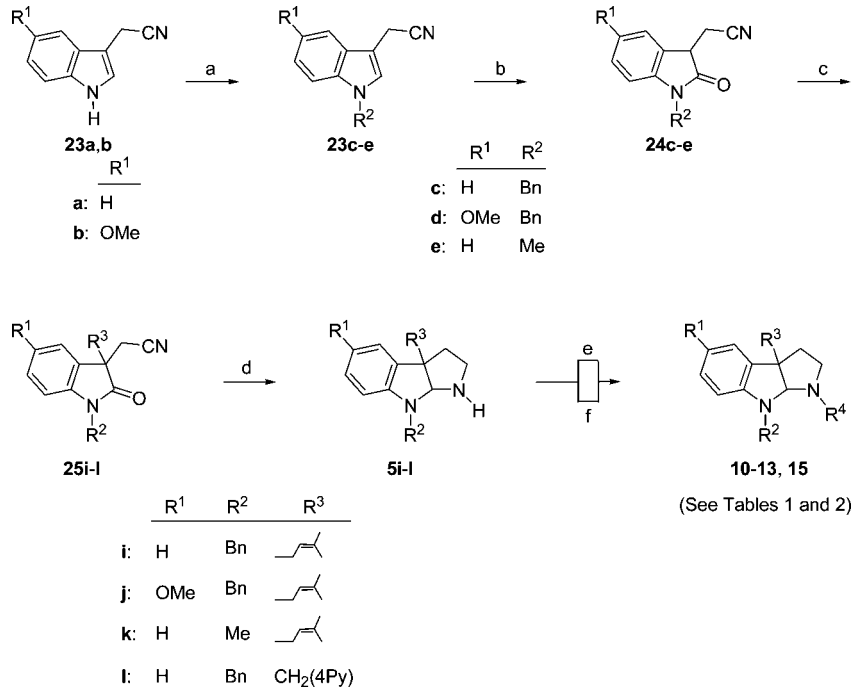
On the basis of the fact that R^1 carbamoylated pyrrolidinoindolines with a sterically bulky phenyl group at the R^3 position are known to lack cholinesterase inhibition activity,[23] it is surprising to find R^3-prenyl substituted pyrrolidinoindolines lacking the carbamate group that are micromolar cholinesterase inhibitors. Close examination of the data is consistent, in any case, with π−hydrogen bond interactions between the substrate with the enzyme, as the most plausible mechanism. On the basis of the SAR results outlined above, we postulated that the double bond of the prenyl groups at the R^2 and R^3 positions is interacting as a very specific π−hydrogen bond acceptor with the enzyme. Because the π-cloud of aromatic rings can act also as proton-acceptor site, it could be suggested that H-bonding may play a significant role in the BChE inhibitory action of benzylated compounds (**11**, **12**, **14**, and **17**), whereas the replacement of prenyl groups by heterocyclic aromatic rings could result in a diminished ability of the π-cloud to form H-bond interactions, resulting in complete loss of activity (**15** and **16**), in line with the π-electron density decrease in the order benzene > pyridine > pyrimidine.[24] In addition, not only does the π-electron density matter but also the ring flexibility is important, as this reveals the beneficial presence of the benzylic methylene spacer, which made it easer to adopt the appropriate conformation for interaction/binding of the compounds with BChE to allow enzyme inhibition. To see how the aromatic core benzyl or pyridinylmethyl compared, we calculated the low-energy conformations of **14** and **15** and superimposed the resulting structures (Figure 3a). The two low-energy conformations superimpose well (the structures are off-set slightly for illustrative purposes). Moreover, superposition of **14** with

Scheme 1. Synthesis of Pyrrolidinoindolines Equally Substituted at N(1) and C(3a)[a]



[a] Reagents and conditions: (a) DMSO/37% aq HCl (1:5), rt, 1 h, 77−90%; (b) 15% aq NaOH, TBAHS, CH_2Cl_2, MeI or R^2Br ($R^2Br = R^3Br$, 2.1 equiv), rt, 1.5−5 h, 72−91%; (c) LAH, THF, reflux, 1.5 h, 47−76%; (d) for **5a**, **5b**, **5d**: 15% aq NaOH, TBAHS, CH_2Cl_2, R^4Br (1.1 equiv), rt, 5−22 h, 48−65%; (e) for **5a**−**h**: CH_2O, MeOH, rt, 3 h, then $NaBH_4$, 43−67%; (f) H_2/10% Pd/C, MeOH, rt, 28 h, 64%.

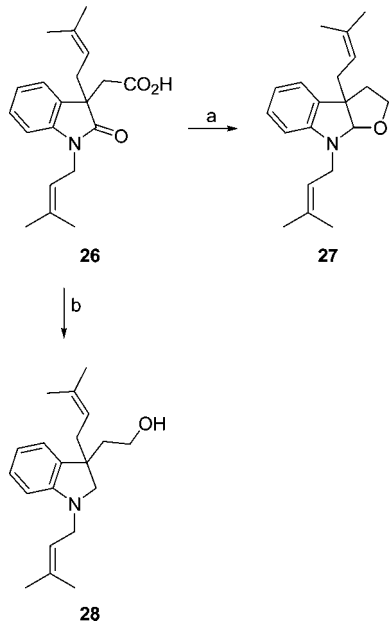
Scheme 2. Synthesis of Pyrrolidinoindolines Differentially Substituted at N(1) and C(3a)[a]



[a] Reagents and conditions: (a) 15% aq NaOH, TBAHS, CH_2Cl_2, MeI or R^2Br (1.1 equiv), rt, 24−72 h, 60−87%; (b) DMSO/37% aq HCl (1:5), rt, 1 h, 58−76%; (c) 15% aq NaOH, TBAHS, CH_2Cl_2, R^3Br (1.1 equiv), rt, 3−5 h, 70−77%; (d) LAH, THF, reflux, 1.5 h, 65−86%; (e) for **5j**: 15% aq NaOH, TBAHS, CH_2Cl_2, BnBr (1.1 equiv), rt, 24 h, 20%; (f) for **5i**−**l**: CH_2O, MeOH, rt, 3 h, then $NaBH_4$, rt, 1 h, 54−79%.

debromoflustramine B (**4a**) reveals that the alignment of the π-electrons of the benzyl groups of **14** and the π-electrons of the prenyl groups of **4a** are nearly coincident (Figure 3b). These results also suggest that the loss in activity observed upon replacement of a single aromatic CH with nitrogen in the benzyl moiety is likely due to the diminished H-bond interaction rather than due to an unfavorable conformational change. Finally, in our study, the crucial pharmacophore role of the N1(H, CH_3) group, as demonstrated by the SAR analysis, is consistent with a salt-bridge inhibitory mechanism because the basic N1-methyl group of physostigmine ($pK_a = 8.46$) and analogues is presumed to be largely protonated in the receptor to form a quaternary

Scheme 3. Synthesis of Furoindoline **27**[a]



[a] Reagents and conditions: (a) NaH, THF, 5 °C 30 min, then LAH, 5 °C 3 h, 87%; (b) NaH, THF, 5 °C 30 min, then LAH, reflux 3 h, 93%.

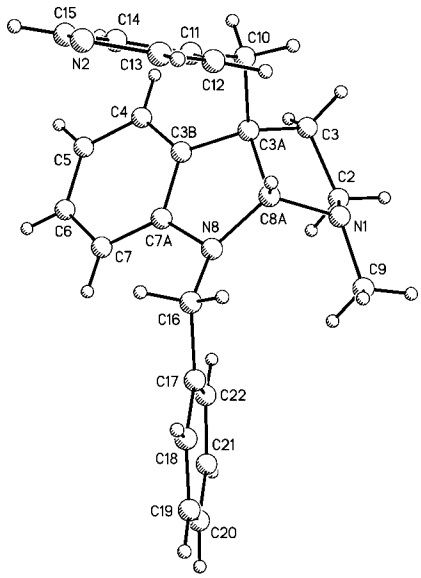


Figure 2. X-ray crystal structure of **15**.

ammonium group. The presence of a prenyl group at the R^4 position (**6**) introduces an additional double bond, which might participate in additional π−hydrogen bond that probably compensates for the loss of activity caused by an increase in sterically bulky substitution.

Molecular Modeling Studies. Our SAR studies identified that N(1), C(3a), and N(8) substitution in the pyrrolidinoindoline skeleton by bulky π-electron-rich prenyl groups provided the resulting compounds with a selectivity that favored BChE versus AChE, in agreement with the larger void at the BChE active site gorge.[25] To explore the ligand's protein-bound conformation responsible for biological activity that explains the above-described SAR studies, a molecular docking study was carried out on selected conformers of ligands (−)-**4a**, (+)-**4b**, and (−)-**5a**. Docking was carried out using the automated docking program AutoDock,[26] which allows torsional flexibility in the ligand and incorporates an efficient Lamarckian genetic search

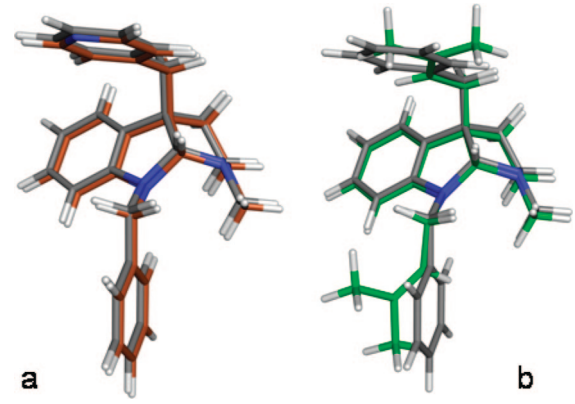


Figure 3. Minimum-energy conformations of compounds **4a** (green), **14** (gray), and **15** (brown) and their aligned structures. (a) Superposition of **14** and **15**. (b) Superposition of **4a** and **14**.

Table 3. Results of 100 Independent Docking Runs for (−)-**4a**, (+)-**4b**, and (−)-**5a**

compd	cluster[a]	f_{occ}[b]	ΔG_{bind}[c]
(−)−**4a**	1	65	−8.5
	2	5	−8.4
(+)−**4b**	1	4	−8.0
	2	12	−7.9
	3	7	−7.8
	4	5	−7.7
	5	20	−7.7
	6	8	−7.6
(−)−**5a**	1	22	−8.5
	2	35	−8.2

[a] The assessment of conformational cluster sizes was determined as function of the root-mean-square deviation (rmsd) of 0.3 Å between conformers. [b] The number of results contained in the clusters is given by the frequency of occurrence, f_{occ}. [c] ΔG_{bind} is the estimated free energy of binding for the clusters and is given in kcal/mol.

algorithm together with an empirical free energy function. Compounds (−)-**4a**, (+)-**4b**, and (−)-**5a** were docked into the binding pocket of human BChE (PDB code 1POI),[27] and the results of prevailing clusters of each ligand, ranked according to the total docking energy (ΔG_{bind}), are summarized in Table 3. The binding modes derived from docking simulations of the two enatiomers of **4** were characterized by significant different score values (Table 3), which are consistent with the inhibition data.

A hierarchical cluster analysis, carried out on 100 independent dockings runs performed for (−)-**4a**, revealed that all the docking poses could be collected in one prevalent geometric group associated with the highest frequency of occurrence (f_{occ}) and therefore with low cost of the loss in conformational entropy upon binding, within an rmsd value of 0.3 Å. Figure 4a (top panel) shows the most favorable binding mode identified for (−)-**4a** (ΔG_{bind} = −8.5 kcal/mol, f_{occ} = 65) in the mid-gorge of hBChE and therefore the bioactive one. As already noted, the docking results (Figure 5a) reveals a cation−π interaction between the ammonium nitrogen atom of (−)-**4a** and Trp82, consistent with a distance between them of 3.5 Å. The ammonium N(1) atom also favorably interacted with the anionic residue Glu197 (5.2 Å). In addition, the C(3a) prenyl group come close to the oxyanion hole,[25] delimited by Gly116, Gly117, and Ala199, with the prenyl double bond interacting as π−hydrogen bond acceptor with the hydroxylic residues of Thr120 (4.6 Å) and Tyr128 (4.2 Å). In the same way, the prenyl double bond at N(8) is engaged in a π−hydrogen bond interaction with Tyr332 (4.9 Å) and a weaker interaction with Tyr440 (6.9 Å). In particular, it is reported that His438 is

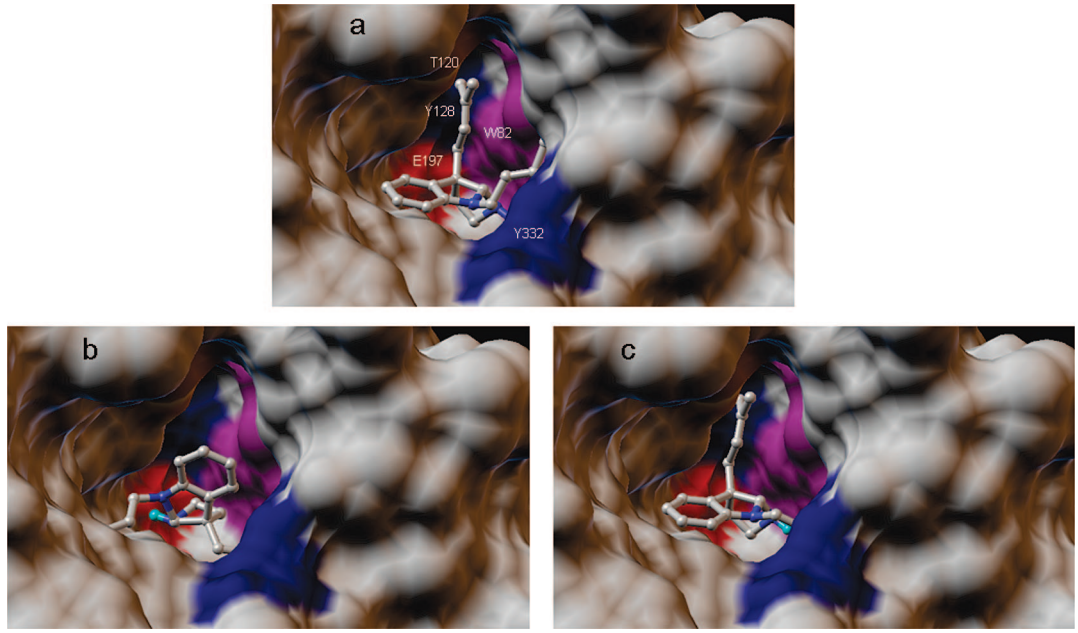


Figure 4. Accessible surface of active site gorge of hBChE showing docked BChEIs (−)-**4a** (a) and (−)-**5a** (b,c).

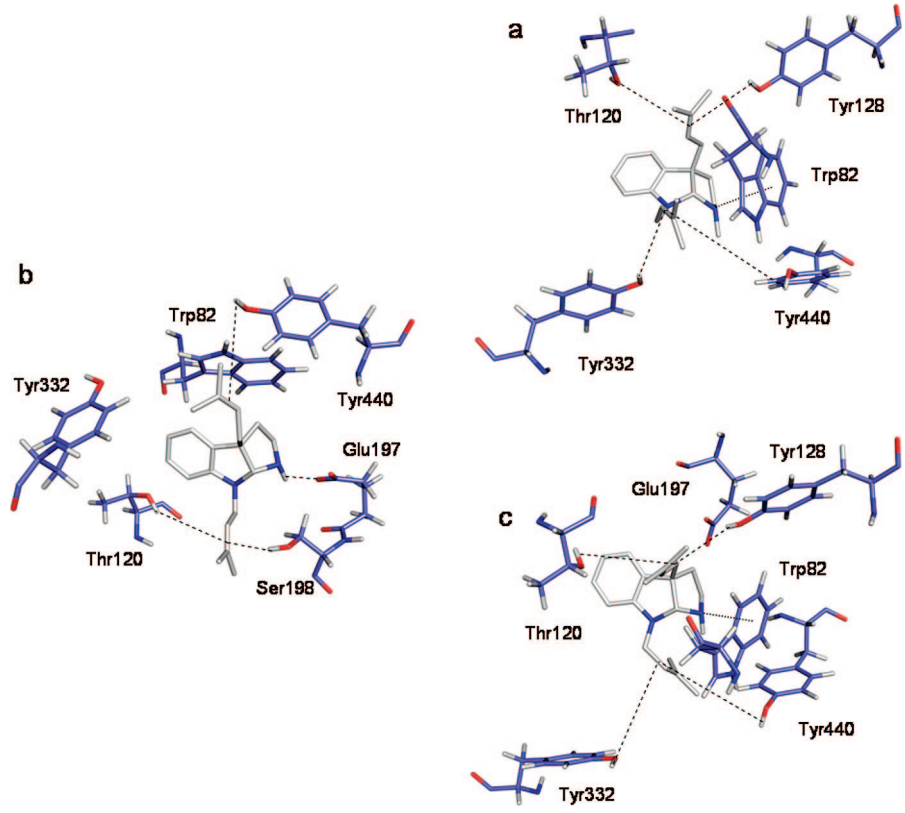


Figure 5. Binding mode of BChEIs (−)-**4a** (a) and (−)-**5a** (b,c) as outcomes of docking simulations. (a) Glu197 has been omitted for clarity. (b) Tyr128 has been omitted for clarity. Cation−π interactions are shown as dotted lines, classical hydrogen bond and π−hydrogen bonds are shown as dashed lines.

important for BChE enzyme function, and it has been proposed together with Ser198 as catalytic site for cocaine hydrolysis;[28] however, the docking simulation of (−)-**4a** indicates that the pharmacophore prenyl groups lie in an opposite region in space to make any significant interaction with the catalytic triad Ser198-His438-Glu325 (Figure S1 in Supporting Information). Comparing the above results with the docking simulation and cluster analyses of enantiomer (+)-**4b** reveals that this ligand scored poorly against hBChE (Table 3) and consequently make poorer interactions than those of their active enantiomer with Trp82 (anionic site) and with the hydroxylic residues of Thr120, Tyr128, Tyr332, and Tyr440.

Docking simulations of (−)-**5a**, which possesses the highest anti-BChE activity (Table 1), revealed a very clear preference for two prevailing clusters (Figure 4b,c) within an rmsd value of 0.3 Å (Table 3). The top-ranking results ($\Delta G_{bind} = -8.5$ kcal/mol, $f_{occ} = 22$) clearly show that the N(1)-H is responsible for anchoring the molecule at the BChE gorge by forming a

strong H-bond with the carboxylate group of Glu197 (H−O 2.0 Å, Figure 5b) treated as deprotonated at physiological pH. A closer look at the model of (−)-**5a** (Figure 5b) showed additional π−hydrogen bond interactions between the prenyl double bond at C(3a) and Tyr440 (5.0 Å) as well as between the prenyl double bond at N(8) and the hydroxyl oxygen atom of catalytic Ser198 (2.4 Å). It seem clear that the H-bond formation causes rotation of the tricyclic structure by nearly 180°, pointing the C(3a)-prenyl group toward Trp82. A significant alternative to this position is given by the second-ranked solution ($\Delta G_{bind} = -8.2$ kcal/mol, $f_{occ} = 35$), which resemble that of prevailing cluster of (−)-**4a**. The main cation−π interaction was observed between the ammonium nitrogen atom of (−)-**5a** and Trp82 (3.2 Å) as well as π−hydrogen bond interactions between the prenyl double bonds at C(3a) and N(8) with the hydroxylic residues of Thr120, Tyr128, Tyr332, and Tyr440 (Figure 5c).

Conclusion

We have evaluated several substituted modified analogues of natural occurring debromoflustramine B (−)-**4a** as cholinesterase inhibitors. An efficient parallel array synthesis of pyrrolidinoindolines led to rapid SAR development. A variety of alkyl substitution produces analogues with micromolar cholinesterase inhibitory activity. On the basis of docking studies, enhanced potency for the conformationally rather rigid pyrrolidinoindolines containing prenyl substituents at C(3a) and N(8) appears to be the result of favorable π−hydrogen bond interactions between the inhibitor and the hydroxylic amino acid residues of Thr120, Tyr128, Tyr332, Tyr440, and Ser198. In addition, cation−π interactions and classical hydrogen bond seems to be critical for optimum potency. The most significant outcomes from this study is that a clear in vitro activity of (−)-**4a** as selective, reversible BChE inhibitor has been demonstrated and that the prenyl groups are fundamental for properly anchoring the molecule at the enzyme gorge. This information can be used to design a second generation of prenylated pyrrolidinoindolines, tailored to the BChE gorge, to produce a drug with both high affinity and high degree of selectivity for this enzyme.

Experimental Section

All reagents are of commercial quality and obtained from Sigma-Aldrich (St. Louis, MO). Solvents were dried, where necessary, using standard procedures. Melting points (mp) were determined using a Fisher−Johns apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets, silica gel 60 F254) with detection by UV light or with ceric ammonium sulfate in H_2SO_4 followed by heating. Flash chromatography was performed on silica gel 60 (230−400 mesh). IR spectra were obtained using a Perkin-Elmer 16 FPC FT spectrophotometer. NMR spectra were recorded on Mercury spectrometers working at 300 and 75 MHz for ^{1}H and ^{13}C, respectively; chemical shifts are measured in ppm (δ) relative to internal tetramethylsilane (TMS) and coupling constants (J) are in Hz. The spectral assignments were confirmed by standard procedures (gHMBC, gHSQC, NOESY). Signals, when declared, are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad); signals due to NH protons were located by deuterium exchange with D_2O. LRMS were recorded on a Varian Saturn 2000 or Hewlett-Packard 5989A spectrometers working at 20 and 70 eV, respectively. HRMS were recorded at the University of California, Riverside CA.

Starting indole **23a** is commercially available. Indoles **23b**[21] and **23e**,[18a] oxindoles **24a**,[18a] **24e**,[18a] **25a**,[18a] **25h**,[29] and **25k**,[18a] as well as pyrrolidinoindolines **4a**−**c**,[18,19] **5a**,[18a] **5h**,[30] **5k**,[18a] **10**,[18a] and **22**,[31] are known and were synthesized using procedures described from this laboratory.

General Procedure 1 for the Preparation of Indoles 23c and 23d. To a solution of the corresponding indole (**23a** or **23b**) (0.013 mol) in CH_2Cl_2 (65 mL) were added 15% aq NaOH (30 mL), TBAHS (0.14 g, 0.41 mmol), and benzyl bromide (0.015 mol). The resulting mixture was stirred at room temperature until TLC analysis showed complete loss of starting material. After completion (24−30 h), the organic layer was collected and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with brine (2 × 60 mL), dried, and concentrated under reduced pressure. The resulting indoles were purified by flash chromatography on silica gel.

(1-Benzyl-1*H*-indol-3-yl)acetonitrile (23c). Prepared by stirring **23a** for 30 h according to general procedure 1. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **23c** as colorless crystals (2.78 g, 87%); mp 94−95 °C (Lit. 94−95 °C). The spectral and analytical data were consistent with those reported.[31]

(1-Benzyl-5-methoxy-1*H*-indol-3-yl)acetonitrile (23d). Prepared by stirring **23b** for 24 h according to general procedure 1. Upon workup, the crude product was purified by flash chromatography (1:6 EtOAc/hexane) to give **23d** as pale-yellow oil (2.74 g, 77%). The elemental composition was consistent with that reported.[32] To our knowledge, the NMR data are unreported and therefore follow. ^{1}H NMR ($CDCl_3$) δ 7.31−7.25 (m, 3H), 7.17 (dd, J = 8.9, 0.6 Hz, 1H), 7.11 (br s overlap, 1H), 7.09 (br d, overlap, 2H), 6.99 (br d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.9, 2.4 Hz, 1H), 5.24 (s, 2H), 3.86 (s, 3H), 3.79 (d, J = 0.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 154.4, 137.0, 131.9, 128.8 (2C), 127.8, 127.2, 127.0, 126.8 (2C), 118.2, 112.9, 111.0, 103.0, 99.9, 55.8, 50.3, 14.4. EIMS m/z (relative intensity) 276 (M+, 100), 91 (100), 65 (19). HRMS (ESI/APCIMS) calcd for $C_{18}H_{16}N_2O$ + H, 277.1341; found, 277.1338.

General Procedure 2 for the Preparation of Oxindoles 24b−24d. To a solution of the corresponding 3-indolylacetonitrile (**23b**, **23c**, or **23d**) (8.5 mmol) in DMSO (7 mL) was added dropwise and under stirring 37% aq HCl (35 mL). The resulting mixture was stirred at room temperature until TLC analysis showed complete loss of starting material. After completion (1−24 h), the resulting mixture was cooled to 5 °C, diluted with water (15 mL), and solid K_2CO_3 was added until pH ca. 7−8. The mixture was allowed to warm to room temperature and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried, and concentrated under reduced pressure. The resulting oxindoles were purified by flash chromatography on silica gel.

(5-Methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (24b). Prepared by stirring **23b** for 1 h according to general procedure 2. Upon workup, the crude product was purified by flash chromatography (1:1 EtOAc/hexane) to give **24b**[33] as pale-yellow oil (1.32 g, 77%); R_f 0.25 (1:1 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3436, 3206, 3020, 2254, 1716, 1494 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.16 (very br s, 1H), 7.10 (br s, 1H), 6.84 (m, 2H), 3.81 (s, 3H), 3.69 (ddd, J = 8.9, 4.8, 1.0 Hz, 1H), 3.10 (dd, J = 16.9, 4.8 Hz, 1H), 2.75 (dd, J = 16.9, 8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 176.0, 156.2, 134.3, 127.4, 117.0, 114.2, 111.4, 110.7, 55.8, 42.2, 18.8. EIMS m/z (relative intensity) 202 (M+, 100), 162 (80), 131 (9). HRMS (ESI/APCIMS) calcd for $C_{11}H_{10}N_2O_2$ + H, 203.0821; found, 203.0818.

(1-Benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (24c). Prepared by stirring **23c** for 24 h according to general procedure 2. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **24c** as colorless solid (1.29 g, 58%); mp 152−154 °C (Lit. 150−151 °C). The elemental composition was consistent with that reported.[34] To our knowledge, the NMR data are unreported and therefore follow. ^{1}H NMR ($CDCl_3$) δ 7.50 (br d, J = 7.3 Hz, 1H), 7.35−7.20 (m, 5H), 7.24 (tm, J = 7.9 Hz, 1H), 7.08 (td, J = 7.5, 0.9 Hz, 1H), 6.77 (br d, J = 7.9 Hz, 1H), 4.95 and 4.89 (AB, J = 15.7 Hz, 2H), 3.76 (dd, J = 8.7, 4.7 Hz, 1H), 3.15 (dd, J = 16.8, 4.7 Hz, 1H), 2.77 (dd, J = 16.8, 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 174.3, 143.2, 135.1, 129.3, 128.8 (2C), 127.8, 127.2 (2C), 125.5, 124.2, 123.1, 117.1, 109.6,

44.0, 41.4, 19.9. EIMS *m/z* (relative intensity) 262 (M+, 100), 222 (36), 91 (75), 65 (12). HRMS (ESI/APCIMS) calcd for $C_{17}H_{14}N_2O$ + H, 263.1184; found, 263.1185.

(1-Benzyl-5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (24d). Prepared by stirring **23d** for 2 h according to general procedure 2. Upon workup, the crude product was purified by flash chromatography (1:1 EtOAc/hexane) to give **24d** as colorless solid (0.96 g, 62%); mp 144−145 °C (acetone/CH_2Cl_2); R_f 0.48 (1:1 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3016, 2254, 1710, 1602, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34−7.24 (m, 5H), 7.12 (dd, J = 2.2, 0.8 Hz, 1H), 6.76 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 6.65 (br d, J = 8.8 Hz, 1H), 4.94 and 4.87 (AB, J = 15.7 Hz, 2H), 3.78 (s, 3H), 3.74 (dd, overlap, J = 8.8, 4.7 Hz, 1H), 3.15 (dd, J = 16.8, 4.7 Hz, 1H), 2.79 (dd, J = 16.8, 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 174.0, 156.3, 136.5, 135.2, 128.8 (2C), 127.8, 127.2 (2C), 126.8, 117.1, 113.7, 111.5, 110.1, 55.8, 44.1, 41.8, 19.2. EIMS *m/z* (relative intensity) 292 (M+, 100), 252 (38), 91 (76), 65 (12). HRMS (ESI/APCIMS) calcd for $C_{18}H_{16}N_2O_2$ + H, 293.1290; found, 293.1283.

General Procedure 3 for the Preparation of Oxindoles 25b−25l. To a solution of the corresponding oxindole (**24a−e**) (0.01 mol) in CH_2Cl_2 (65 mL) were added 15% aq NaOH (23 mL, 86.2 mmol), TBAHS (0.14 g, 0.41 mmol), and the corresponding halide [ethyl bromide, *n*-propyl bromide, prenyl bromide, benzyl bromide, or 4-(bromomethyl)pyridine] [0.025 mol (**24a**, **24b**), or 0.015 mol (**24c−e**)]. The resulting mixture was stirred at room temperature until TLC analysis showed complete loss of starting material. After completion (2−7 h), the organic layer was collected and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with brine (2 × 60 mL), dried, and concentrated under reduced pressure. The resulting oxindoles were purified by flash chromatography on silica gel. Data for the new compounds (**25b−g**, **25i**, **25j**, and **25l**) follow.

[5-Methoxy-1,3-bis(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25b). Prepared by stirring **24b** with prenyl bromide for 2 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **25b** as pale-yellow oil (2.81 g, 83%); R_f 0.39 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3028, 2972, 2254, 1705, 1602, 1436 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.05 (d, J = 2.2 Hz, 1H), 6.83 (dd, J = 8.6, 2.6 Hz, 1H), 6.73 (br d, J = 8.3 Hz, 1H), 5.07 (tm, J = 6.6 Hz, 1H), 4.74 (tm, J = 7.5 Hz, 1H), 4.38 (br dd, J = 15.5, 6.6 Hz, 1H), 4.19 (br dd, J = 15.5, 6.8 Hz, 1H), 3.81 (s, 3H), 2.86 and 2.62 (AB, J = 16.7 Hz, 2H), 2.61 (br d, J = 7.5 Hz, 2H), 1.80 (br s, 3H), 1.71 (br s, 3H), 1.56 (br s, 3H), 1.54 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 176.0, 156.0, 136.8 (2C), 136.1, 130.7, 118.2, 116.6, 116.1, 113.3, 110.8, 109.4, 55.8, 49.2, 38.2, 34.9, 25.8, 25.6, 24.8, 18.1, 18.0. EIMS *m/z* (relative intensity) 338 (M+, 100), 270 (46), 215 (51), 175 (15), 69 (17), 41 (22). HRMS (ESI/APCIMS) calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073; found, 339.2076.

[1,3-Dibenzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25c). Prepared by stirring **24a** with benzyl bromide for 5 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **25c** as colorless solid (3.17 g, 90%); mp 139−140 °C (EtOAc/hexane); R_f 0.54 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3020, 2920, 2256, 1714, 1614 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.58 (m, 1H), 7.20−7.04 (m, 8H), 6.87 (dm, J = 8.0 Hz, 2H), 6.64 (dm, J = 7.6 Hz, 2H), 6.45 (m, 1H), 4.97 and 4.50 (AB, J = 16.2 Hz, 2H), 3.38 and 3.27 (AB, J = 12.9 Hz, 2H), 3.03 and 2.78 (AB, J = 16.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 176.0, 142.5, 134.5, 134.2, 130.0 (2C), 129.2, 128.6 (2C), 128.2, 128.1 (2C), 127.3, 127.1, 126.5 (2C), 123.8, 122.9, 116.5, 109.8, 50.6, 43.7, 41.9, 26.0. EIMS *m/z* (relative intensity) 352 (M+, 100), 261 (53), 235 (22), 91 (84). HRMS (ESI/APCIMS) calcd for $C_{24}H_{20}N_2O$ + H, 353.1654; found, 353.1657.

[1,3-Dibenzyl-5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25d). Prepared by stirring **24b** with benzyl bromide for 3 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **25d** as colorless solid (3.13 g, 82%); mp 150−151 °C (acetone/Et_2O); R_f 0.34 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3014, 2920, 2256, 1710, 1604, 1496 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.20−7.10 (m, 5H), 7.09 (tm, J = 7.1 Hz, 2H), 6.90 (dm, J = 6.9 Hz, 2H), 6.66 (dd, J = 8.6, 2.7 Hz, 1H), 6.65 (dm, J = 7.1 Hz, 2H), 6.35 (d, J = 8.5 Hz, 1H), 4.94 and 4.48 (AB, J = 15.9 Hz, 2H), 3.80 (s, 3H), 3.35 and 3.26 (AB, J = 12.9 Hz, 2H), 3.01 and 2.79 (AB, J = 16.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 175.7, 156,1, 135.9, 134.7, 134.3, 130.1 (2C), 129.6, 128.6 (2C), 128.1 (2C), 127.3, 127.1, 126.5 (2C), 116.4, 113.6, 111.0, 110.2, 55.8, 51.0, 43.8, 42.0, 26.1. EIMS *m/z* (relative intensity) 382 (M+, 93), 291 (68), 266 (33), 91 (100), 65 (19). HRMS (ESI/APCIMS) calcd for $C_{25}H_{22}N_2O_2$ + H, 383.1760; found, 383.1767.

[2-Oxo-1,3-bis(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25e). Prepared by stirring **24a** with 4-(bromomethyl)pyridine for 6 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (EtOAc) to give **25e** as pale-yellow oil (2.72 g, 77%); R_f 0.17 (4:1 EtOAc/acetone). IR ($CHCl_3$) ν_{max} 3022, 2258, 1718, 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.43 (dm, J = 4.4 Hz, 2H), 8.32 (dm, J = 4.4 Hz, 2H), 7.65 (m, 1H), 7.23 (m, 2H), 6.78 (dm, J = 4.4 Hz, 2H), 6.54 (dm, J = 4.4 Hz, 2H), 6.45 (m, 1H), 4.87 and 4.58 (AB, J = 16.6 Hz, 2H), 3.37 and 3.29 (AB, J = 12.8 Hz, 2H), 3.08 and 2.86 (AB, J = 16.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 175.4, 150.0 (2C), 149.4 (2C), 143.6, 143.2, 141.9, 129.9, 127.3, 125.1 (2C), 123.9, 123.7, 121.2 (2C), 115.9, 109.6, 50.3, 42.7, 41.1, 26.2. EIMS *m/z* (relative intensity) 354 (M+, 100), 314 (11), 262 (76), 93 (47). HRMS (EIMS) calcd for $C_{22}H_{18}N_4O$, 354.1481; found, 354.1480.

[2-Oxo-1,3-di(*n*-propyl)-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25f). Prepared by stirring **24a** with *n*-propyl bromide for 7 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (2:3 EtOAc/hexane) to give **25f** as pale-yellow oil (1.84 g, 72%); R_f 0.54 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3028, 2968, 2256, 1712, 1614 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41 (ddd, J = 7.4, 1.3, 0.5 Hz, 1H), 7.33 (td, J = 7.8, 1.2 Hz, 1H), 7.12 (td, J = 7.6, 1.1 Hz, 1H), 6.91 (br d, J = 7.6 Hz, 1H), 3.66 (dt, J = 13.4, 6.7 Hz, 1H) 3.63 (dt, J = 13.4, 6.7 Hz, 1H), 2.83 and 2.59 (AB, J = 16.5 Hz, 2H), 1.94 (m, 2H), 1.71 (sextet, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.95 (m, overlap, 2H), 0.80 (br t, overlap, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.8, 142.9, 129.4, 128.9, 123.2, 122.8, 116.4, 108.7, 48.9, 41.7, 38.3, 26.0, 20.6, 17.3, 13.8, 11.3. EIMS *m/z* (relative intensity) 256 (M+, 100), 214 (96), 187 (53), 174 (33), 158 (25). HRMS (EIMS) calcd for $C_{16}H_{20}N_2O$, 256.1575; found, 256.1574.

[1,3-Diethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25g). Prepared by stirring **24a** with ethyl bromide for 7 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (2:3 EtOAc/hexane) to give **25g** as pale-yellow oil (1.91 g, 84%); R_f 0.47 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3028, 2980, 2252, 1710, 1614, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40 (ddd, J = 7.4, 1.1, 0.6 Hz, 1H), 7.34 (td, J = 7.8, 1.4 Hz, 1H), 7.12 (td, J = 7.4, 1.1 Hz, 1H), 6.93 (br d, J = 7.6 Hz, 1H), 3.81 (dq, J = 14.0, 7.0 Hz, 1H), 3.78 (dq, J = 14.0, 7.0 Hz, 1H), 2.83 and 2.62 (AB, J = 16.7 Hz, 2H), 2.00 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H), 0.60 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 176.2, 142.5, 128.9, 128.8, 123.1, 122.7, 116.3, 108.4, 49.2, 34.6, 29.2, 25.4, 12.4, 8.1. EIMS *m/z* (relative intensity) 228 (M+, 100), 200 (14), 188 (88), 160 (54), 132 (10). HRMS (EIMS) calcd for $C_{14}H_{16}N_2O$, 228.1263; found, 228.1262.

[1-Benzyl-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25i). Prepared by stirring **24c** with prenyl bromide for 5 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **25i** as yellow crystals (2.54 g, 77%); mp 90−92 °C (acetone/Et_2O); R_f 0.47 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3028, 2916, 2256, 1714, 1614, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45 (ddd, J = 7.5, 1.3, 0.7 Hz, 1H), 7.27−7.25 (m, 5H), 7.21 (td, J = 7.8, 1.5 Hz, 1H), 7.08 (td, J = 1.2, 7.6 Hz, 1H), 6.72 (br d, J = 7.8 Hz, 1H), 5.14 and 4.70 (AB, J = 15.8 Hz, 2H), 4.76 (tm, J = 7.9 Hz, 1H), 2.92 and 2.68 (AB, J = 16.6 Hz, 2H), 2.71 (br d, J = 7.5 Hz, 2H), 1.56 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 176.9, 142.6, 137.1, 135.3, 129.1, 129.0, 128.7 (2C), 127.6, 127.0 (2C), 123.4, 123.0, 116.5, 116.3, 109.5, 49.1, 43.9, 35.0, 25.8, 25.2, 18.0. EIMS *m/z* (relative intensity) 330 (M+, 9), 262 (100), 235 (42), 184 (10), 171 (8), 91

(33), 69 (36). HRMS (ESI/APCIMS) calcd for $C_{22}H_{22}N_2O$ + H, 331.1810; found, 331.1814.

[1-Benzyl-5-methoxy-3-(3-methylbut-2-enyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25j). Prepared by stirring **24d** with prenyl bromide for 3 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (3:7 EtOAc/hexane) to give **25j** as pale-yellow oil (2.84 g, 79%); R_f 0.36 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3032, 2928, 2256, 1712, 1602, 1436 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.32−7.23 (m, 5H), 7.06 (d, J = 2.2 Hz, 1H), 6.73 (dd, J = 8.6, 2.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 5.12 and 4.67 (AB, J = 15.8, Hz, 2H), 4.77 (tm, J = 7.5 Hz, 1H), 3.78 (s, 3H), 2.91 and 2.69 (AB, J = 16.7 Hz, 2H), 2.70 (m, overlap, 2H), 1.58 (br s, 3H), 1.57 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 176.5, 156.2, 137.1, 135.9, 135.4, 130.4, 128.7 (2C), 127.6, 127.0 (2C), 116.6, 116.3, 113.3, 110.7, 110.0, 55.7, 49.5, 44.0, 34.9, 25.8, 25.3, 18.1. EIMS *m*/*z* (relative intensity) 360 (M+, 54), 292 (64), 265 (100), 91 (68). HRMS (ESI/APCIMS) calcd for $C_{23}H_{24}N_2O_2$ + H, 361.1916; found, 361.1913.

[1-Benzyl-2-oxo-3-(pyridin-4-ylmethyl)-2,3-dihydro-1*H*-indol-3-yl]acetonitrile (25l). Prepared by stirring **24c** with 4-(bromomethyl)pyridine for 5 h according to general procedure 3. Upon workup, the crude product was purified by flash chromatography (1:1 EtOAc/hexane) to give **25l** as pale-yellow oil (2.47 g, 70%); R_f 0.21 (1:1 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3028, 2996, 2256, 1716, 1614, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.23 (dm, J = 4.4 Hz, 2H), 7.60 (dd, J = 7.0, 1.3 Hz, 1H), 7.15 (m, 4H), 7.13 (td, J = 7.7, 1.3 Hz, 1H), 6.73 (dm, J = 4.4 Hz, 2H), 6.68 (br dm, J = 4.4 Hz, 2H), 6.53 (br dd, J = 6.9, 1.7 Hz, 1H), 4.87 and 4.54 (AB, J = 15.8 Hz, 2H), 3.35 and 3.26 (AB, J = 12.7 Hz, 2H), 3.05 and 2.77 (AB, J = 16.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 175.1, 149.2 (2C), 142.9, 142.2, 134.2, 129.5, 128.6 (2C), 127.4, 127.3, 126.3 (2C), 124.8 (2C), 123.5, 123.1, 116.0, 109.8, 50.1, 43.9, 41.1, 26.5. EIMS *m*/*z* (relative intensity) 353 (M+, 93), 261 (68), 91 (100), 65 (26). HRMS (ESI/APCIMS) calcd for $C_{23}H_{19}N_3O$ + H, 354.1606; found, 354.1609.

General Procedure 4 for the Preparation of Pyrroloindolines 5b−5j and 5l. To a precooled (5 °C) stirred suspension of LAH (0.57 g, 15.0 mmol) in anhydrous THF (20 mL) and under argon atmosphere was added the corresponding oxindole (**25b−25j** or **25l**) (2.0 mmol) in THF (20 mL), and the mixture was heated at reflux for 1.5 h. After cooling, the reaction mixture in an ice/water bath, the reaction was quenched by adding, in sequence, EtOAc (10 mL) and water (5 mL). The solids were removed by filtration and washed with EtOAc (2 × 15 mL). The combined organic phases were washed with brine, dried, and concentrated under reduced pressure. The resulting pyrroloindolines were purified by flash chromatography on silica gel. Data for the new compounds (**5b−5g**, **5i**, **5j**, and **5l**) follow.

5-Methoxy-3a,8-bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5b). Prepared from **25b** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (4:1 EtOAc/acetone) to give **5b** as pale-yellow oil (0.43 g, 66%); R_f 0.28 (7:3 EtOAc/acetone). IR ($CHCl_3$) ν_{max} 3376, 3020, 2932, 1670, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.65 (d, J = 2.4 Hz, 1H), 6.62 (dd, J = 8.3, 2.6 Hz, 1H), 6.27 (d, J = 8.3, 1H), 5.22 (tm, J = 6.6 Hz, 1H), 5.06 (tm, J = 7.2 Hz, 1H), 4.58 (s, 1H), 3.76 (m, overlap, 2H), 3.74 (s, overlap, 3H), 2.99 (ddd, J = 10.3, 6.7, 2.4 Hz, 1H), 2.75 (ddd, J = 10.3, 10.3, 6.2 Hz, 1H), 2.41 (br d, J = 7.3 Hz, 2H), 1.93 (very br s, 1H), 1.92 (m, 2H), 1.71 (br s, 3H), 1.70 (br s, 3H), 1.68 (s, 3H), 1.59 (s, 3H). ^{13}C NMR δ 152.3, 145.6, 136.3, 134.8, 133.8, 121.0, 120.5, 112.1, 110.8, 106.0, 87.7, 56.6, 56.0, 45.5, 44.5, 40.6, 37.7, 25.9, 25.8, 18.1, 18.0. EIMS *m*/*z* (relative intensity) 326 (M+, 57), 257 (89), 240 (100), 189 (67), 160 (26), 97 (26), 69 (51). HRMS (ESI/APCIMS) calcd for $C_{21}H_{30}N_2O$ + H, 327.2436; found, 327.2440.

3a,8-Dibenzyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5c). Prepared from **25c** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (4:1 EtOAc/acetone) to give **5c** as pale-yellow oil (0.51 g, 75%); R_f 0.20 (EtOAc). IR ($CHCl_3$) ν_{max} 3346, 3016, 2930, 1660, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.23−7.14 (m, 6H), 7.00−6.92 (m, 6H), 6.63 (td, J = 7.3, 0.8 Hz, 1H), 6.14 (dd, J = 8.2, 0.7 Hz, 1H), 4.79 (s, 1H), 4.35 and 4.27 (AB, J = 16.3 Hz, 2H), 3.23 and 2.90 (AB, J = 13.4 Hz, 2H), 2.96 (ddd, J = 11.2, 6.8, 1.5 Hz, 1H), 2.65 (ddd, J = 11.2, 11.0, 5.4 Hz, 1H), 2.11 (ddd, J = 11.9, 5.4, 1.5 Hz, 1H), 2.01 (ddd, J = 11.9, 11.2, 6.8 Hz, 1H), 1.87 (very br s, 1H). ^{13}C NMR ($CDCl_3$) δ 151.3, 138.6, 138.3, 133.0, 130.1 (2C), 128.4 (2C), 128.0, 127.9 (2C), 126.9 (2C), 126.6, 126.2, 123.6, 116.5, 104.9, 85.9, 57.8, 48.1, 45.9, 45.1, 42.1. EIMS *m*/*z* (relative intensity) 340 (M+, 40), 249 (100), 220 (15), 158 (8), 91 (27). HRMS (ESI/APCIMS) calcd for $C_{24}H_{24}N_2$ + H, 341.2018; found, 341.2024.

3a,8-Dibenzyl-5-methoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5d). Prepared from **25d** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (9:1 EtOAc/acetone) to give **5d** as pale-yellow oil (0.50 g, 68%); R_f 0.21 (EtOAc). IR ($CHCl_3$) ν_{max} 3344, 3012, 2938, 1664, 1598 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.25−7.17 (m, 6H), 7.02−6.96 (m, 4H), 6.60 (br d, J = 2.4 Hz, 1H), 6.56 (dd, J = 8.4, 2.6 Hz, 1H), 6.07 (br d, J = 8.4 Hz, 1H), 4.75 (s, 1H), 4.29 and 4.16 (AB, J = 16.0 Hz, 2H), 3.72 (s, 3H), 3.19 and 2.89 (AB, J = 13.4 Hz, 2H), 2.96 (ddd, J = 10.8, 6.8, 2.0 Hz, 1H), 2.67 (ddd, J = 11.0, 10.8, 5.5 Hz, 1H), 2.11 (ddd, J = 12.1, 5.5, 2.0 Hz, 1H), 2.00 (ddd, J = 12.1, 11.0, 6.8 Hz, 1H), 1.88 (very br s, 1H). ^{13}C NMR ($CDCl_3$) δ 152.0, 145.9, 138.9, 138.2, 134.6, 130.2 (2C), 128.3 (2C), 127.9 (2C), 127.1 (2C), 126.6, 126.3, 112.5, 111.2, 105.5, 86.7, 58.0, 56.0, 49.4, 45.9, 44.9, 41.5. EIMS *m*/*z* (relative intensity) 370 (M+, 86), 279 (100), 250 (16), 188 (9), 173 (8), 91 (25). HRMS (ESI/APCIMS) calcd for $C_{25}H_{26}N_2O$ + H, 371.2123; found, 371.2124.

3a,8-Bis(pyridin-4-ylmethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5e). Prepared from **25e** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (3:7 MeOH/acetone) to give **5e** as pale-yellow oil (0.53 g, 77%); R_f 0.27 (3:7 MeOH/acetone). IR ($CHCl_3$) ν_{max} 3290, 3018, 2962, 1602, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.43 (dm, J = 4.4 Hz, 2H), 8.39 (dm, J = 4.5 Hz, 2H), 7.07 (dd, J = 7.8, 1.1 Hz, 1H), 7.02 (td, J = 7.8, 1.1 Hz, 1H) 6.83 (br d, J = 4.4 Hz, 2H), 6.73 (br d, J = 4.4 Hz, 2H), 6.71 (td, J = 7.3, 1.1 Hz, 1H), 6.05 (br d, J = 7.8 Hz, 1H), 4.72 (s, 1H), 4.35 and 4.21 (AB, J = 17.1 Hz, 2H), 3.32 and 2.88 (AB, J = 13.2 Hz, 2H), 3.07 (ddd, J = 11.3, 6.9, 1.1 Hz, 1H), 2.67 (ddd, J = 11.6, 11.3, 5.2 Hz, 1H), 2.25 (ddd, J = 11.8, 5.2, 1.1 Hz, 1H), 2.03 (very br s, 1H), 2.01 (ddd, overlap, J = 11.8, 11.6, 6.9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.9, 149.8 (2C), 149.4 (2C), 147.9, 147.2, 131.5, 128.6, 125.2 (2C), 123.7, 121.7 (2C), 117.3, 105.0, 86.1, 57.8, 47.2, 46.0, 44.6, 43.1. EIMS *m*/*z* (relative intensity) 342 (M+, 100), 250 (91), 221 (28), 92 (12), (18). HRMS (ESI/APCIMS) calcd for $C_{22}H_{22}N_4$ + H, 343.1923; found, 343.1925.

3a,8-Di(*n*-propyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5f). Prepared from **25f** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (1:19 MeOH/CH_2Cl_2) to give **5f** as pale-ellow oil (0.34 g, 70%); R_f 0.21 (1:9 MeOH/CH_2Cl_2). IR ($CHCl_3$) ν_{max} 3664, 3054, 2962, 1666, 1602, 1492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.03 (td, J = 7.6, 1.1 Hz, 1H), 6.96 (dd, J = 7.2, 1.3 Hz, 1H), 6.58 (td, J = 7.3, 0.7 Hz, 1H), 6.30 (br d, J = 7.9 Hz, 1H), 4.69 (s, 1H), 3.18 (m, 2H), 2.97 (ddd, J = 10.8, 6.8, 1.8 Hz, 1H), 2.65 (ddd, J = 11.0, 10.8, 5.5 Hz, 1H), 2.27 (very br s, 1H), 2.00 (ddd, J = 11.9, 5.5, 1.5 Hz, 1H), 1.80 (m, 2H), 1.63 (m, 3H), 1.29 (m, 1H), 1.12 (m, 1H), 0.94 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 151.3, 133.7, 127.6, 123.1, 116.1, 104.5, 87.4, 56.6, 46.8, 45.4, 42.4, 42.2, 20.9, 18.9, 14.6, 11.7. EIMS *m*/*z* (relative intensity) 244 (M+, 100), 215 (63), 201 (25), 186 (41), 172 (87). HRMS (ESI/APCIMS) calcd for $C_{16}H_{24}N_2$ + H, 245.2018; found, 245.2018.

3a,8-Diethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5g). Prepared from **25g** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (4:1 EtOAc/acetone) to give **5g** as pale-yellow oil (0.20 g, 47%); R_f 0.22 (1:1 EtOAc/acetone). IR ($CHCl_3$) ν_{max} 3566, 3018, 2968, 1662, 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.04 (td, J = 7.8, 1.5 Hz, 1H), 6.97 (ddd, J = 7.3, 1.3, 0.4 Hz, 1H), 6.60 (td, J = 7.4, 1.1 Hz, 1H), 6.32 (br d, J = 7.5 Hz, 1H), 4.70 (s, 1H), 3.32 (dq, J = 12.2, 7.0 Hz, 1H), 3.29 (dq, J = 12.2, 7.0 Hz, 1H), 2.99 (ddd, J = 10.8, 6.8,

1.8 Hz, 1H), 2.69 (ddd, J = 10.8, 11.0, 5.7 Hz, 1H), 2.10 (very br s, 1H), 1.98 (ddd, J = 11.9, 5.7, 1.8 Hz, 1H), 1.87 (dq, J = 14.7, 7.4 Hz, 1H), 1.81 (ddd, J = 11.9, 11.0, 6.8 Hz, 1H), 1.68 (dq, J = 14.7, 7.4 Hz, 1H), 1.17 (t, J = 7.3 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 150.9, 133.7, 127.7, 123.2, 116.3, 104.8, 86.4, 57.0, 45.5, 41.8, 39.2, 32.4, 12.3, 9.9. EIMS m/z (relative intensity) 216 (M+, 100), 201 (19), 186 (34), 172 (57), 158 (76), 144 (37). HRMS (ESI/APCIMS) calcd for $C_{14}H_{20}N_2$ + H, 217.1705; found, 217.1710.

8-Benzyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5i). Prepared from **25i** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (3:2 EtOAc/hexane) to give **5i** as pale-yellow oil (0.53 g, 84%); R_f 0.39 (7:3 acetone/hexane). IR ($CHCl_3$) ν_{max} 3336, 3020, 2932, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.31−7.21 (m, 5H), 7.04 (dd, J = 7.4, 0.8 Hz, 1H), 7.01 (td, J = 7.7, 1.4 Hz, 1H), 6.62 (td, J = 7.4, 0.8, Hz, 1H), 6.26 (br d, J = 8.0 Hz, 1H), 5.06 (tm, J = 7.3 Hz, 1H), 4.70 (s, 1H), 4.47 (br s, 2H), 3.01 (ddd, J = 11.0, 6.9, 1.5 Hz, 1H), 2.76 (ddd, J = 11.0, 11.0, 5.5 Hz, 1H), 2.47 (m, 2H), 2.04 (very br s, 1H), 2.03 (ddd, J = 12.1, 5.5, 1.5 Hz, 1H), 1.90 (ddd, J = 12.1, 11.0, 6.9 Hz, 1H), 1.67 (br s, 3H), 1.55 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 151.1, 139.0, 133.9, 134.0, 128.5 (2C), 127.8, 127.2 (2C), 126.8, 123.2, 120.4, 116.6, 104.7, 87.1, 56,9, 48.5, 45.8, 41.5, 37.6, 25.9, 18.1. EIMS m/z (relative intensity) 318 (M+, 36), 249 (100), 220 (15), 158 (12), 91 (44). HRMS (ESI/APCIMS) calcd for $C_{22}H_{26}N_2$ + H, 319.2174; found, 319.2176.

8-Benzyl-5-methoxy-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5j). Prepared from **25j** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (3:2 EtOAc/hexane) to give **5j** as pale-yellow oil (0.45 g, 65%); R_f 0.30 (7:3 acetone/hexane). IR ($CHCl_3$) ν_{max} 3342, 3024, 2966 cm^{-1}. ^{1}H NMR (CD_2Cl_2) δ 7.33−7.21 (m, 5H), 6.67 (d, J = 2.8 Hz, 1H), 6.52 (dd, J = 8.4, 2.7 Hz, 1H), 6.10 (br d, J = 8.5 Hz, 1H), 5.07 (tm, J = 7.3 Hz, 1H), 4.66 (s, 1H), 4.40 and 4.33 (AB, J = 16.0, 2H), 3.69 (s, 3H), 2.98 (ddd, J = 10.9, 7.1, 1.9 Hz, 1H), 2.65 (ddd, J = 10.9, 10.7, 5.6 Hz, 1H), 2.45 (m, 2H), 2.01 (very br s, 1H), 1.98 (ddd, J = 12.1, 5.6, 1.9 Hz, 1H), 1.86 (ddd, J = 12.1, 10.7, 7.1 Hz, 1H), 1.67 (br s, 3H), 1.56 (br s, 3H). ^{13}C NMR (CD_2Cl_2) δ 152.6, 146.1, 140.0, 136.1, 134.1, 128.7 (2C), 127.7 (2C), 127.0, 120.9, 112. 2, 111.2, 105,1, 88.4, 57.3, 56.2, 49.9, 46.2, 41.7, 37.8, 26.0, 18.2. EIMS m/z (relative intensity) 348 (M+, 55), 279 (100), 188 (31), 173 (19), 91 (27). HRMS (ESI/APCIMS) calcd for $C_{23}H_{28}N_2O$ + H, 349.2280; found, 349.2282.

8-Benzyl-3a-(pyridin-4-ylmethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (5l). Prepared from **25l** according to general procedure 4. Upon workup, the crude product was purified by flash chromatography (1:1 acetone/hexane) to give **5l** as pale-yellow oil (0.59 g, 86%); R_f 0.15 (7:3 acetone/hexane). IR ($CHCl_3$) ν_{max} 3344, 3030, 2964, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.36 (dm, J = 4.4 Hz, 2H), 7.25−7.19 (m, 3H), 7.02 (td, J = 7.5, 1.3 Hz, 1H), 7.00 (br d, overlap, J = 7.0 Hz, 1H), 6.89 (br m, 2H), 6.81 (dm, J = 4.4 Hz, 2H), 6.66 (td, J = 7.3, 0.9 Hz, 1H), 6.18 (dd, J = 7.7, 0.9 Hz, 1H), 4.71 (s, 1H), 4.32 and 4.25 (AB, J = 16.0 Hz, 2H), 3.26 and 2.86 (AB, J = 13.2 Hz, 2H), 3.02 (ddd, J = 11.2, 6.8, 1.3 Hz, 1H), 2.68 (ddd, J = 11.2, 11.2, 5.3 Hz, 1H), 2.20 (br ddd, J = 11.4, 5.3, 1.3 Hz, 1H), 2.17 (very br s, 1H), 2.00 (ddd, J = 11.4, 11.2, 6.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 151.4, 149.3 (2C), 147.2, 138.3, 131.7, 128.5 (2C), 128.4, 126.9 (2C), 126.8, 125.3 (2C), 123.5, 116.8, 105.2, 85.7, 57.4, 48.1, 45.7, 44.6, 42.6. EIMS m/z (relative intensity) 341 (M+, 68), 249 (100), 221 (26), 207 (12), 91 (49), 65 (18). HRMS (ESI/APCIMS) calcd for $C_{23}H_{23}N_3$ + H, 342.1970; found, 342.1964.

General Procedure 5 for the Preparation of Pyrroloindolines 6, 7, 9, 13, and 18. To a solution of the corresponding pyrroloindoline (**5a**, **5b**, **5d**, or **5j**) (1.31 mmol) in CH_2Cl_2 (20 mL) were added 15% aq NaOH (4 mL, 15.0 mmol), TBAHS (14.0 mg, 0.041 mmol), and the corresponding halide (prenyl bromide or benzyl bromide) (1.5 mmol). The resulting mixture was stirred at room temperature until TLC analysis showed complete loss of starting material. After completion (5−22 h), the organic layer was collected and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed wit brine (2 × 10 mL), dried, and concentrated under reduced pressure. The resulting N(1)-alkylated pyrroloindolines were purified by flash chromatography on silica gel. Data for the new compounds (**6**, **7**, **9**, **13**, and **18**) follow.

1,3a,8-Tris(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (6). Prepared by stirring **5a** with prenyl bromide for 22 h according to general procedure 5. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **6** as pale-yellow oil (0.29 g, 60%); R_f 0.45 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3016, 2930, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.03 (td, J = 7.8, 1.3 Hz, 1H), 6.96 (dd, J = 7.0, 0.9 Hz, 1H), 6.63 (td, J = 7.3, 0.9 Hz, 1H), 6.39 (br d, J = 7.9 Hz, 1H), 5.34 (tm, J = 6.6 Hz, 1H), 5.15 (tm, J = 6.5 Hz, 1H), 4.99 (tm, J = 7.0 Hz, 1H), 4.41 (s, 1H), 3.91 (dd, J = 16.3, 5.5 Hz, 1H), 3.80 (dd, J = 16.3, 7.3 Hz, 1H), 3.30 (br d, J = 6.4 Hz, 2H), 2.75 (ddd, J = 9.7, 6.6, 3.0 Hz, 1H), 2.55 (ddd, J = 9.9, 9.7, 5.9 Hz, 1H), 2.43 (br d, J = 7.0 Hz, 2H), 2.03 (ddd, J = 12.1, 9.9, 6.6 Hz, 1H), 1.88 (ddd, J = 12.1, 5.9, 3.0 Hz, 1H), 1.73 (br s, 3H), 1.69 (br s, 6H), 1.65 (br s, 6H), 1.58 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 151.8, 135.5, 133.9, 133.8, 133.4, 127.5, 122.8, 122.6, 121.5, 120.9, 117.1, 107.0, 90.4, 56.8, 50.3, 49.1, 45.9, 38.8, 38.3, 25.9, 25.8, 25.7, 18.1, 18.1, 18.0. EIMS m/z (relative intensity) 364 (M+, 9), 296 (100), 227 (11), 212 (26), 199 (38), 130 (20), 69 (18). HRMS (ESI/APCIMS) calcd for $C_{25}H_{36}N_2$ + H, 365.2951; found, 365.2953.

1-Benzyl-3a,8-bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (7). Prepared by stirring **5a** with benzyl bromide for 5 h according to general procedure 5. Upon workup, the crude product was purified by flash chromatography (1:9 EtOAc/hexane) to give **7** as pale-yellow oil (0.33 g, 65%); R_f 0.66 (1:4 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3016, 2930, 1602 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.39 (dm, J = 7.7 Hz, 2H), 7.30 (tm, J = 8.0 Hz, 2H), 7.22 (tm, J = 7.2 Hz, 1H), 7.04 (td, J = 7.7, 1.1 Hz, 1H), 6.98 (dd, J = 7.3, 1.0 Hz, 1H), 6.64 (td, J = 7.3, 1.1 Hz, 1H), 6.41 (br d, J = 7.7 Hz, 1H), 5.12 (tm, overlap, J = 6.1 Hz, 1H), 5.10 (tm, overlap, J = 7.7 Hz, 1H), 4.48 (s, 1H), 3.92 and 3.84 (AB, J = 14.0 Hz, 2H), 3.80 (br dd, J = 15.9, 5.9 Hz, 1H), 3.65 (br dd, J = 15.9, 7.4 Hz, 1H), 2.69 (ddd, J = 9.6, 6.9, 2.2 Hz, 1H), 2.56 (ddd, J = 9.6, 9.6, 5.8 Hz, 1H), 2.41 (br d, J = 7.4 Hz, 2H), 2.08 (ddd, J = 11.6, 9.6, 6.9 Hz, 1H), 1.85 (ddd, J = 11.6, 5.8, 2.2 Hz, 1H), 1.69 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.49 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 152.1, 139.9, 135.8, 133.9, 133.4, 128.2 (4C), 127.5, 126.7, 122.8, 121.4, 120.9, 117.2, 107.1, 89.9, 56.8, 54.9, 50.4, 46.3, 38.6, 38.2, 26.0, 25.7, 18.1, 17.8. EIMS m/z (relative intensity) 386 (M+, 13), 317 (100), 249 (21), 212 (21), 198 (45), 130 (22), 91 (45). HRMS (ESI/APCIMS) calcd for $C_{27}H_{34}N_2$ + H, 387.2800; found, 387.2797.

1-Benzyl-5-methoxy-3a,8-bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (9). Prepared by stirring **5b** with benzyl bromide for 6 h according to general procedure 5. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **9** as pale-yellow oil (0.26 g, 48%); R_f 0.56 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3024, 2966, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.39 (dm, J = 6.9 Hz, 2H), 7.30 (tm, J = 7.2 Hz, 2H), 7.22 (tm, J = 6.9 Hz, 1H), 6.63 (dd, overlap, J = 9.3, 2.5 Hz, 1H), 6.63 (d, overlap, J = 2.2 Hz, 1H), 6.36 (d, J = 9.4 Hz, 1H), 5.11 (br m, 2H), 4.44 (s, 1H), 3.93 and 3.84 (AB, J = 14.0 Hz, 2H), 3.74 (s, overlap, 3H), 3.73 (br dd, J = 16.0, 4.1 Hz, 1H), 3.59 (dd, J = 16.0, 7.7 Hz, 1H), 2.69 (ddd, J = 9.4, 6.9, 2.0 Hz, 1H), 2.55 (ddd, J = 10.2, 9.4, 5.5 Hz, 1H), 2.44 (br d, J = 6.9 Hz, 2H), 2.05 (ddd, J = 11.8, 10.2, 6.9 Hz, 1H), 1.83 (ddd, J = 11.8, 5.5, 2.0 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 152.7, 146.7, 139.9, 137.5, 133.8, 133.4, 128.2 (2C), 128.1 (2C), 126.7, 121.5, 120.9, 112.2, 110.0, 108.1, 90.4, 56.9, 55.9, 54.5, 50.3, 47.8, 38.7, 38.1, 26.0, 25.7, 18.1, 17.8. EIMS m/z (relative intensity) 416 (M+, 51), 347 (100), 280 (20), 241 (56), 91 (41), 130 (20), 69 (18). HRMS (ESI/APCIMS) calcd for $C_{28}H_{36}N_2O$ + H, 417.2906; found, 417.2909.

1,8-Dibenzyl-5-methoxy-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (13). Prepared by stirring **5j** with benzyl bromide for 5 h according to general procedure 5. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **13** as pale-yellow oil (0.11 g, 20%); R_f 0.71 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3018, 2932, 1494 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29−7.17 (m, 10H), 6.66 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.4, 2.6 Hz, 1H), 6.21 (d, J = 8.4 Hz, 1H), 5.08 (tm, J = 7.3 Hz, 1H), 4.50 (s, 1H), 4.31 and 4.15 (AB, J = 16.5 Hz, 2H), 3.77 (br s, 2H), 3.73 (s, 3H), 2.73 (m, 2H), 2.43 (m, 2H), 2.09 (ddd, J = 12.1, 9.2, 7.9 Hz, 1H), 1.89 (ddd, J = 12.1, 4.8, 3.3 Hz, 1H), 1.68 (br s, 3H), 1.54 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 152.7, 146.7, 139.7, 139.6, 137.0, 133.7, 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.2 (2C), 126.7, 126.6, 120.7, 112.0, 110.3, 107.0, 91.7, 57.0, 56.0, 55.1, 53.6, 50.6, 38.6, 38.0, 26.0, 18.1. EIMS *m*/*z* (relative intensity) 438 (M+, 92), 369 (94), 278 (44), 250 (73), 91 (100). HRMS (ESI/APCIMS) calcd for $C_{30}H_{34}N_2O$ + H, 439.2749; found, 439.2744.

1,3a,8-Tribenzyl-5-methoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (18). Prepared by stirring **5d** with benzyl bromide for 5 h according to general procedure 5. Upon workup, the crude product was purified by flash chromatography (1:4 EtOAc/hexane) to give **18** as pale-yellow oil (0.36 g, 59%); R_f 0.76 (3:7 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3016, 2932, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.27−7.12 (m, 11H), 6.99−6.91 (m, 4H), 6.57 (d, overlap, J = 2.4 Hz, 1H), 6.56 (dd, J = 9.2, 2.6 Hz, 1H), 6.18 (d, J = 9.2 Hz, 1H), 4.54 (s, 1H), 4.15 and 3.92 (AB, J = 16.3 Hz, 2H), 3.72 (s, 3H), 3.62 (br s, 2H), 3.07 and 2.88 (AB, J = 13.4 Hz, 2H), 2.66 (m, 2H), 2.23 (ddd, J = 11.8, 8.6, 8.3 Hz, 1H), 1.97 (ddd, J = 11.8, 4.0, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 152.6, 146.7, 139.6, 139.4, 138.2, 136.2, 130.4 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.9 (2C), 127.2 (2C), 126.7, 126.6, 126.3, 112.7, 110.6, 107.5, 90.7, 58.2, 56.0, 55.4, 53.1, 50.6, 45.4, 38.4. EIMS *m*/*z* (relative intensity) 460 (M+, 100), 370 (60), 279 (16), 251 (28), 91 (49). HRMS (ESI/APCIMS) calcd for $C_{32}H_{32}N_2O$ + H, 461.2593; found, 461.259.

General Procedure 6 for the Preparation of Pyrroloindolines 8, 10−12, 14−17, and 20−22. To a solution of the corresponding pyrroloindoline (**5b**−**5l**) (1.19 mmol) in MeOH (9 mL) at room temperature was added 37% aq CH_2O (0.8 mL, 9.87 mmol). The resulting mixture was stirred at this temperature for 3 h, then cooled to 0 °C, and $NaBH_4$ (0.19 g, 5.13 mmol) was added portionwise over 5 min. After stirring the mixture for 1 h at room temperature, the solvent was removed under reduced pressure, the residue was treated with H_2O (14 mL) and Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL) and the combined organic layers were washed with brine (1 × 40 mL), dried, and concentrated under reduced pressure to afford the corresponding N(1)-methylated pyrroloindolines (**8**, **10**−**12**, **14**−**17**, and **20**−**22**). Data for the new compounds (**8**, **12**, **15**−**17**, **20**, and **21**) follow.

5-Methoxy-1-methyl-3a,8-bis(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (8). Prepared from **5b** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (4:1 EtOAc/hexane) to give **8** as pale-yellow oil (0.27 g, 67%); R_f 0.19 (EtOAc). IR ($CHCl_3$) ν_{max} 3022, 2934, 1594 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.63 (dd, overlap, J = 7.9, 2.6, 1H), 6.61 (d, overlap, J = 2.6 Hz, 1H), 6.38 (dd, J = 7.9, 0.9 Hz, 1H), 5.18 (tm, J = 6.6 Hz, 1H), 4.97 (tm, J = 7.2 Hz, 1H), 4.26 (br s, 1H), 3.86 (br dd, J = 16.1, 5.7 Hz, 1H), 3.74 (br dd, J = 16.1, 6.8 Hz, 1H), 3.74 (s, overlap, 3H), 2.71 (br ddd, J = 9.4, 6.6, 3.3 Hz, 1H), 2.54 (ddd, J = 9.4, 9.3, 5.9 Hz, 1H), 2.48 (s, overlap, 3H), 2.41 (br d, J = 7.0 Hz, 2H), 2.06 (ddd, J = 12.1, 9.3, 6.6 Hz, 1H), 1.91 (ddd, J = 12.1, 5.9, 3.3 Hz, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.66 (br s, 3H), 1.58 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 153.0, 146.3, 137.1, 134.2, 133.6, 121.5, 120.6, 112.4, 109.9, 108.4, 92.0, 57.3, 55.9, 52.6, 48.3, 38.9, 38.3, 37.3, 25.9, 25.7, 18.1, 18.0. EIMS *m*/*z* (relative intensity) 340 (M+, 76), 271 (100), 240 (95), 229 (48), 203 (23), 160 (21), 69 (15). HRMS (ESI/APCIMS) calcd for $C_{22}H_{32}N_2O$ + H, 341.2587; found, 341.2593.

8-Benzyl-1-methyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (11). Prepared from **5i** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (7:3 EtOAc/hexane) to give **11** as pale-yellow oil (0.28 g, 72%). The spectral and analytical data were consistent with those reported.[35]

8-Benzyl-5-methoxy-1-methyl-3a-(3-methylbut-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (12). Prepared from **5j** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (7:3 EtOAc/hexane) to give **12** as pale-yellow oil (0.23 g, 54%); R_f 0.14 (1:1 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3024, 2934, 1596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34−7.20 (br m, 5H), 6.66 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.3, 2.6 Hz, 1H), 6.21 (d, J = 8.3 Hz, 1H), 4.99 (tm, J = 7.2 Hz, 1H), 4.46 and 4.34 (AB, J = 16.5 Hz, 2H), 4.25 (s, 1H), 3.72 (s, 3H), 2.70 (ddd, J = 10.2, 8.4, 5.9 Hz, 1H), 2.65 (ddd, J = 10.2, 6.8, 4.3 Hz, 1H), 2.41 (br d, J = 7.3 Hz, 2H), 2.38 (s, 3H), 2.07 (ddd, J = 12.1, 8.4, 6.8 Hz, 1H), 1.95 (ddd, J = 12.1, 5.9, 4.3 Hz, 1H), 1.66 (d, J = 1.1 Hz, 3H), 1.56 (br s, 3H). ^{13}C NMR ($CDCl_3$) δ 152.9, 146.3, 139.4, 137.0, 133.7, 128.4 (2C), 127.3 (2C), 126.7, 120.6, 112.1, 110.2, 107.7, 93.8, 57.3, 55.9, 54.3, 52.8, 38.8, 38.4, 38.3, 25.9, 18.1. EIMS *m*/*z* (relative intensity) 362 (M+, 100), 293 (96), 250 (83), 202 (48), 187 (32), 91 (39). HRMS (ESI/APCIMS) calcd for $C_{24}H_{30}N_2O$ + H, 363.2436; found, 363.2435.

3a,8-Dibenzyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (14). Prepared from **5c** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (7:3 EtOAc/hexane) to give **14** as pale-yellow oil (0.23 g, 55%). The spectral and analytical data were consistent with those reported.[36]

8-Benzyl-1-methyl-3a-(pyridin-4-ylmethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (15). Prepared from **5l** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (2:3 EtOAc/hexane) to give **15** as colorless crystals (0.33 g, 79%); mp 113−115 °C (acetone/CH_2Cl_2); R_f 0.17 (EtOAc). IR ($CHCl_3$) ν_{max} 3034, 2966, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.36 (br d, J = 6.0 Hz, 2H), 7.22 (m, 3H), 6.98 (m, 4H), 6.77 (br d, J = 6.0 Hz, 2H), 6.71 (td, J = 7.4, 0.7 Hz, 1H), 6.20 (br d, J = 7.8 Hz, 1H), 4.30 (s, 1H), 4.26 and 4.12 (AB, J = 16.4 Hz, 2H), 3.20 and 2.84 (AB, J = 13.2 Hz, 2H), 2.72 (ddd, J = 9.4, 8.4, 5.8 Hz, 1H), 2.67 (ddd, J = 9.4, 6.5, 4.3 Hz, 1H), 2.36 (s, 3H), 2.21 (ddd, J = 11.9, 8.4, 6.5 Hz, 1H), 2.12 (ddd, J = 11.9, 5.8, 4.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 151.7, 149.3 (2C), 147.2, 138.4, 133.3, 128.4 (2C), 128.3, 126.9 (2C), 126.8, 125.3 (2C), 123.2, 117.6, 107.2, 91.8, 57.7, 52.7, 52.1, 45.1, 39.6, 38.9. EIMS *m*/*z* (relative intensity) 355 (M+, 100), 298 (39), 263 (73), 220 (78), 172 (32), 91 (41). HRMS (EI) calcd for $C_{24}H_{25}N_3$, 355.2048; found, 355.2044.

1-Methyl-3a,8-bis(pyridin-4-ylmethyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (16). Prepared from **5e** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (1:1 EtOH/acetone) to give **16** as pale-yellow oil (0.27 g, 64%); R_f 0.20 (1:1 EtOH/acetone). IR ($CHCl_3$) ν_{max} 3074, 2966, 1602 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.45 (dm, J = 4.6 Hz, 2H), 8.38 (dm, J = 4.4 Hz, 2H), 7.09 (dd, J = 7.4, 1.1 Hz, 1H), 7.00 (td, J = 7.8, 1.3 Hz, 1H), 6.90 (br d, J = 4.4 Hz, 2H), 6.79 (br d, overlap, J = 4.4 Hz, 2H), 6.76 (td overlap, J = 7.5, 1.0 Hz, 1H), 6.06 (br d, J = 7.8 Hz, 1H), 4.26 (s, 1H), 4.17 and 4.07 (AB, J = 17.5 Hz, 2H), 3.27 and 2.88 (AB, J = 13.1 Hz, 2H), 2.72 (m, 2H), 2.35 (s, 3H), 2.24 (ddd, J = 12.0, 6.6, 3.8 Hz, 1H), 1.96 (ddd, J = 12.0, 5.9, 4.4, Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 151.2, 149.8 (2C), 149.2 (2C), 148.1, 147.1, 133.2, 128.4, 125.2 (2C), 123.3, 121.8 (2C), 118.3, 106.9, 92.8, 57.9, 52.6, 51.4, 45.2, 39.7, 39.1. EIMS *m*/*z* (relative intensity) 356 (M+, 98), 299 (32), 264 (90), 221 (100), 172 (58), 92 (16). HRMS (EI) calcd for $C_{23}H_{24}N_4$, 356.2001; found, 356.2004.

3a,8-Dibenzyl-5-methoxy-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (17). Prepared from **5d** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (4:1 EtOAc/hexane) to give **17** as pale-yellow oil (0.31 g, 68%); R_f 0.17 (EtOAc). IR ($CHCl_3$) ν_{max} 3022, 2936, 1598

cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.25−7.16 (m, 6H), 7.09−7.06 (m, 2H), 6.92−6.89 (m, 2H), 6.60 (d, J = 2.2 Hz, 1H), 6.54 (dd, J = 8.5, 2.3 Hz, 1H), 6.12 (d, J = 8.5 Hz, 1H), 4.24 (s, 1H), 4.03 and 3.96 (AB, J = 16.0 Hz, 2H), 3.71 (s, 3H), 3.17 and 2.82 (AB, J = 13.5 Hz, 2H), 2.69 (ddd, J = 9.5, 7.7, 6.1 Hz, 1H), 2.59 (ddd, J = 9.5, 6.6, 4.7 Hz, 1H), 2.27 (br s, 3H), 2.21 (ddd, J = 11.9, 7.7, 6.6 Hz, 1H), 2.06 (ddd, J = 11.9, 6.1, 4.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 152.9, 146.4, 139.3, 138.2, 136.3, 130.2 (2C), 128.3 (2C), 127.9 (2C), 127.3 (2C), 126.6, 126.3, 112.7, 110.5, 108.4, 93.2, 58.4, 55.9, 54.1, 52.8, 45.8, 39.1, 38.6. EIMS m/z (relative intensity) 384 (M+, 100), 293 (9), 250 (62), 202 (20), 91 (41), 65 (11). HRMS (ESI/APCIMS) calcd for $C_{26}H_{28}N_2O$ + H, 385.2280; found, 385.2279.

1-Methyl-3a,8-di(*n*-propyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (20). Prepared from **5f** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (EtOAc) to give **20** as pale-yellow oil (0.18 g, 60%); R_f 0.11 (EtOAc). IR ($CHCl_3$) ν_{max} 3018, 2962, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.03 (td, J = 7.6, 1.3 Hz, 1H), 6.94 (ddd, J = 7.3, 1.3, 0.5 Hz, 1H), 6.62 (td, J = 7.3, 1.0 Hz, 1H), 6.39 (br d, J = 8.0 Hz, 1H), 4.28 (s, 1H), 3.31 (m, 1H), 3.14 (m, 1H), 2.63 (ddd, J = 9.4, 6.7, 3.9 Hz, 1H), 2.54 (ddd, overlap, J = 9.4, 8.8, 5.8 Hz, 1H), 2.50 (s, 3H), 2.00 (ddd, J = 11.9, 8.8, 6.7 Hz, 1H), 1.92 (ddd, J = 11.9, 5.8, 3.9 Hz, 1H), 1.71 (m, 2H), 1.62 (m, 2H), 1.27 (m, 1H), 1.07 (m, 1H), 0.91 (t, J = 7.1 Hz, 3H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 151.4, 135.2, 127.4, 122.8, 116.8, 106.5, 92.1, 57.1, 52.7, 50.3, 42.9, 39.4, 38.6, 20.2, 18.8, 14.6, 11.6. EIMS m/z (relative intensity) 258 (M+, 100), 229 (22), 214 (18), 200 (99), 186 (48), 172 (56), 158 (16). HRMS (EI) calcd for $C_{17}H_{26}N_2$, 258.2096; found, 258.2102.

3a,8-Diethyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (21). Prepared from **5g** according to general procedure 6. Upon workup, the crude product was purified by flash chromatography (9:1 acetone/hexane) to give **21** as pale-yellow oil (0.12 g, 43%); R_f 0.26 (9:1 acetone/hexane). IR ($CHCl_3$) ν_{max} 3020, 2966, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.05 (td, J = 7.8, 1.3 Hz, 1H), 6.94 (dd, J = 7.4, 1.2 Hz, 1H), 6.64 (td, J = 7.4, 0.9 Hz, 1H), 6.42 (br d, J = 8.0 Hz, 1H), 4.31 (s, 1H), 3.45 (dq, J = 14.6, 7.2 Hz, 1H), 3.26 (dq, J = 14.6, 7.2 Hz, 1H), 2.66 (ddd, J = 9.3, 6.6, 3.5 Hz, 1H), 2.55 (ddd, J = 9.3, 9.2, 6.0 Hz, 1H), 2.50 (s, 3H), 2.01 (ddd, J = 11.9, 9.2, 6.6 Hz, 1H), 1.92 (ddd, J = 11.9, 6.0, 3.5 Hz, 1H), 1.82 (dq, J = 14.9, 7.4 Hz, 1H), 1.69 (dq, J = 14.9, 7.4 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 151.3, 135.1, 127.5, 122.8, 117.1, 106.8, 90.8, 57.4, 52.6, 42.7, 39.3, 37.9, 32.8, 11.9, 9.9. EIMS m/z (relative intensity) 230 (M+, 100), 186 (56), 172 (55), 158 (78), 144 (35), 130 (24). HRMS (EI) calcd for $C_{15}H_{22}N_2$, 230.1783; found, 230.1775.

Preparation of Pyrroloindoline 19. 1-Methyl-3a,8-bis(2-methylbutyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (19). A suspension of **4a** (60 mg, 0.19 mmol) and 10% Pd−C (60 mg) in MeOH (7 mL) was stirred under a hydrogen atmosphere (1 atm) at room temperature for 28 h. The reaction mixture was filtered through a plug of celite with rinsing by EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (EtOAc) to give **19** as pale-yellow oil (39.0 mg, 64%); R_f 0.15 (EtOAc). IR ($CHCl_3$) ν_{max} 3050, 2958, 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.05 (td, J = 7.4, 1.4 Hz, 1H), 6.94 (dd, J = 7.4, 1.4 Hz, 1H), 6.63 (td, J = 7.4, 1.1 Hz, 1H), 6.39 (br d, J = 7.7 Hz, 1H), 4.29 (s, 1H), 3.38 (dt, J = 13.9, 6.9 Hz, 1H), 3.19 (dt, J = 13.9, 6.9 Hz, 1H), 2.66 (ddd, J = 9.4, 6.6, 3.6 Hz, 1H), 2.55 (ddd, overlap, J = 9.4, 8.9, 5.8 Hz, 1H), 2.51 (s, overlap, 3H), 2.01 (ddd, J = 11.8, 8.9, 6.6 Hz, 1H), 1.91 (ddd, J = 11.8, 5.8, 3.6 Hz, 1H), 1.76 (dt, J = 13.5, 4.6 Hz, 1H), 1.65 (dt, overlap, J = 13.5, 4.6 Hz, 1H), 1.58 (m, 1H), 1.47 (m, 2H), 1.45 (m, 1H), 1.14 (m, 1H), 0.95 (br d, overlap, J = 1.4 Hz, 3H), 0.94 (m, overlap, 1H), 0.92 (br d, overlap, J = 1.6 Hz, 3H), 0.84 (br d, J = 4.7 Hz, 3H), 0.82 (br d, J = 4.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 151.4, 135.4, 127.5, 122.8, 116.9, 106.5, 91.6, 56.9, 52.6, 46.6, 39.4, 38.3, 38.1, 35.5, 34.5, 28.5, 26.3, 22.7, 22.6, 22.5, 22.4. EIMS m/z (relative intensity) 314 (M+, 100), 270 (17), 257 (65), 228 (67), 214 (69), 200 (47), 172 (17), 158 (15), 144 (14). HRMS (EI) calcd for $C_{21}H_{34}N_2$, 314.2721; found, 314.2722.

Preparation of Furoindoline 27 and Indoline 28. 3a,8-Bis(3-methylbut-2-enyl)-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (27). To a precooled (0 °C) solution of the oxindole-3-acetic acid **26**[19] (0.17 g, 0.52 mmol) in dry THF (20 mL) was added NaH (30 mg, 1.25 mmol), and the reaction mixture was stirred for 30 min at room temperature. After cooling at 0 °C, LAH (80 mg, 2.11 mmol) was added and stirring continued at this temperature for 3 h. The reaction was quenched by adding, in sequence, EtOAc (10 mL) and water (10 mL). The solids were removed by filtration and washed with EtOAc (2 × 15 mL). The combined organic phases were washed with brine, dried, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (1:9 EtOAc/hexane) to afford furoindoline **27** (134 mg, 87%), followed by alcohol **28** (<5%) as pale-yellow oils. Compound **27** has spectroscopic data, which closely match those reported.[30]

2-[1,3-Bis(3-methylbut-2-enyl)-2,3-dihydro-1*H*-indol-3-yl]ethanol (28). Compound **28** was prepared as described above for **27**, except reduction with LAH was effected under reflux for 3 h. The crude product was purified by flash chromatography on silica gel (1:4 EtOAc/hexane) to afford alcohol **28** (144 mg, 93%) as pale-yellow oil; R_f 0.66 (7:3 EtOAc/hexane). IR ($CHCl_3$) ν_{max} 3566, 3048, 2930, 1602 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.12 (td, J = 7.7, 1.4 Hz, 1H), 6.99 (dd, J = 7.1, 1.1 Hz, 1H), 6.78 (td, J = 7.4, 1.1 Hz, 1H), 6.62 (br d, J = 8.0 Hz, 1H), 5.27 (tm, J = 7.1 Hz, 1H), 5.14 (tm, J = 7.4 Hz, 1H), 3.80 (dd, J = 14.3, 6.6 Hz, 1H), 3.52 (dd, J = 14.3, 6.7 Hz, 1H), 3.49 (m, overlap, 1H), 3.40 (very br s, 1H), 3.32 and 3.00 (AB, J = 9.1 Hz, 2H), 3.19 (ddd, J = 11.5, 9.9, 4.1 Hz, 1H), 2.51 (dd, J = 14.4, 8.2 Hz, 1H), 2.34 (dd, J = 14.4, 4.5 Hz, 1H), 2.07 (ddd, J = 14.0, 9.6, 4.9 Hz, 1H), 1.74 (br s, 3H), 1.70 (br s, 6H), 1.61 (br s, 3H), 1.61 (m, overlap, 1H). ^{13}C NMR ($CDCl_3$) δ 151.9, 136.1, 136.0, 134.1, 127.7, 122.8, 119.9, 119.4, 119.2, 108.9, 63.4, 60.2, 46.9, 46.8, 42.9, 38.2, 26.0, 25.7, 18.0, 17.9. EIMS m/z (relative intensity) 299 (M+, 19), 230 (100), 162 (68), 144 (91), 69 (31). HRMS (ESI/APCIMS) calcd for $C_{20}H_{29}NO$ + H, 300.2327; found, 300.2327.

X-ray Crystal Structure of 15. The X-ray data were measured on a Bruker-Nonius CAD4 diffractometer with Cu K_α radiation (λ = 1.54184 Å). The data were collected in the $\omega-2\theta$ scan mode. Unit cell refinements were carried out by using the CAD4 Express v2.0 software. The structure was solved by direct methods using the SHELXS-97 program included in the WINGX v1.64.05 crystallographic software package. For the structure refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms included in the structure factor calculation were refined isotropically. Compound **15** crystallized as colorless blocks in the orthorhombic space group $P2_12_12_1$ with cell dimensions a = 9.777(2) Å, b = 12.432(2) Å, c = 16.241(2) Å and was refined to final R indices (all data) R (%) = 4.9, Rw (%) = 13.2. The CCDC deposition number is 686711.

Determination of the Inhibitory Effect on AChE and BChE Activities. The method of Ellman et al.[37] was followed. Physostigmine was used as reference compound. Rat brain homogenate and human plasma were used as a source of AChE and BChE, respectively. Nine different concentrations ($10^{-3}-10^{-7}$ M) of each compound were used to obtain inhibition of AChE or BChE activity comprised between 20% and 80%. The assay solution consisted of a 0.1 M phosphate buffer, pH 8.0, with the addition of 340 μM substrate (acetylthiocoline iodide or butyrylthiocholine iodide). Test compounds were added to the assay solution and preincubated at 37 °C with the enzyme for 20 min followed by the addition of substrate. Assays were done with a blank containing all components except AChE or BChE to account for nonenzymatic reaction. The percentage of inhibition due to the presence of test compounds was calculated. Each concentration was analyzed three times in triplicate, and IC_{50} values were determined graphically transforming the percent of activity into probit format[38] and then plotted as function of its log concentration.

Computational Studies. The 3D models of compounds (−)-**4a**, (+)-**4b**, (−)-**5a**, (−)-**14**, and (−)-**15** were built using ab initio calculations[39] and geometry optimized at the density functional level

of theory (B3LYP/6-31G*) by means of the software Gaussian 03.[40] Docking simulations for (−)-**4a**, (+)-**4b**, and (−)-**5a**, were carried out by means of the AutoDock software (v. 4.0).[26] To search the low-energy docked conformation of the ligand on the receptor, the empirical free energy function and the Lamarckian genetic algorithm were used. In this approach, the ligand performs a random walk around the static protein. At each time step, the ligand is moved by small increments in global translation and orientation at each of the rotational torsion angles. Depending on the input parameter values for the number of generations and the total number of energy evaluations, configurations are generated for grid points on the protein surface. The energy of the configurations is calculated based on a previously defined grid surface. Interaction energies are calculated with a free-energy-based expression. The docked energies are listed in increasing order of energy.

The crystal structure of human BChE was obtained from the RCSB protein database (PDB code 1POI).[27] Protonation states were assumed to be those most common at pH 7, that is, lysines, arginines, histidines, aspartates, and glutamates, were considered in ionized form. Water molecules and ions were removed. For the protein receptor, polar hydrogens were added and Kollman charges were assigned, whereas the Gasteiger−Marsili partial charges were used for the ligands. The ligand binding site was defined using a grid map of 60 × 60 × 60 points (Å^3), centered on the hydroxyl oxygen atom of Ser198, with 0.375 Å grid-point spacing applying a standard protocol with an initial population of 100 randomly placed individuals and a maximum number of 2.5×10^7 energy evaluations per run. All other parameters were maintained at their default settings. A total of 100 binding conformations were carried out for each ligand generated by the program and then clusterized by means of AutoDock Tools.[26] Cutoffs for clustering were set at 0.3 Å rmsd and were represented by the result with the most favorable free energy binding (ΔG_{bind}). The poses reported in Figures 4 and 5 for compounds (−)-**4a** and (−)-**5a** are the low and the two low-energy conformations, respectively, representative of the most populated clusters that, according to the Chauvenet criterion,[41] were statistically populated. The fitness score is taken as the negative of the sum of the energy terms so that larger fitness scores indicate a better binding. The docked structures were analyzed using AutoDock Tools for hydrogen bonding and hydrophobic interactions.

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Supporting Information Available: GC/MS plots, ^{1}H and ^{13}C NMR spectra for tested compounds **4**−**22** as well as Figure S1, illustrating docking experiments of (−)-**4** and (−)-**5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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