Tandem Cleavage of Hydrogenated β- and γ-Carbolines − New Practical Synthesis of Tetrahydroazocino[4,5-*b*]indoles and Tetrahydroazocino[5,4-*b*]-indoles Showing Acetylcholinesterase Inhibitory Activity

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Hydrogenated γ-carbolines underwent tandem piperidine ring cleavage on treatment with dimethyl acetylenedicarboxylate (DMAD) or ethyl propiolate (EP) in the presence of alcohols, producing 3-alkoxymethyl-substituted indoles in high yields. These compounds were cyclized to tetrahydroazocino[4,5-*b*]indoles in the presence of $AlCl_3$. Hydrogenated β-carbolines produced tetrahydroazocino[5,4-*b*]indoles directly upon treatment with EP in ethanol. The resulting azocinoindole derivatives were subjected to a preliminary evaluation of their in vitro acetylcholinesterase (AChE) inhibitory activities. Most of them were found to inhibit AChE with IC_{50} values in the micromolar range, compound **17** being the most potent (IC_{50} = 8.7 μm).

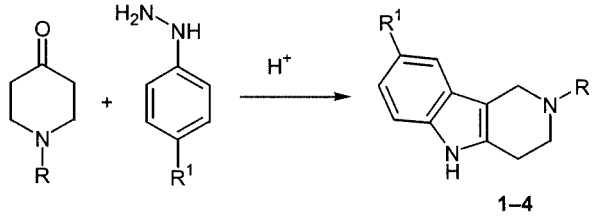
Introduction

Because of their wide occurrence in many biologically active compounds,[1,2] eight-membered (azocine) and larger *N*-containing fused ring systems deserve more investigation efforts from the point of view of organic chemistry. The azocine fragment, for example, occurs in many indole alkaloids,[3−6] but one barrier to their exploitation is a general lack of satisfactory preparative methods. Known synthetic pathways toward this class of indole derivatives include ring expansion of azetopyridoindoles through the [1,2]-Meisenheimer rearrangement of the corresponding *N*-oxides,[7] Fisher indolization of the appropriate azacyclanones,[8] cationic domino processes,[9] and catalytic hydrogenation of the 2-(2-benzylaminoethyl)-3-cyanoethylindoles.[10] These procedures are either based on poorly available (and thus very expensive) starting materials or require relatively inefficient, multi-step procedures. There is therefore a need for new synthetic approaches to produce azocine-containing heterocycles from readily available compounds.

We have recently reported tandem piperidine ring cleavage in tetrahydropyrrolopyridines (THPPs) on treatment with dimethyl acetylenedicarboxylate (DMAD) in aprotic solvents, resulting in the formation of α- and β-vinylpyrroles[11,12] or parallel pyrroloazocine formation in low yields.[13] THPP derivatives were also demonstrated to undergo cleavage in alcohols on treatment with DMAD, producing β-alkoxy(hydroxy)alkylpyrroles in moderate to high yields.[14] Here we report on a new practical synthesis of tetrahydroazocino[5,4-*b*]indole and tetrahydroazocino[4,5-*b*]indole derivatives, starting from readily obtainable hydrogenated β- and γ-carbolines and DMAD or ethyl propiolate. The preliminary results from an evaluation of their in vitro activities as acetylcholinesterase inhibitors (AChE-Is) are also reported.

Results and Discussion

The starting γ-carbolines **1**−**4** were obtained by the well known Fischer indolization of the appropriate *N*-alkyl-4-piperidones (see Scheme 1, Table 1).



Scheme 1

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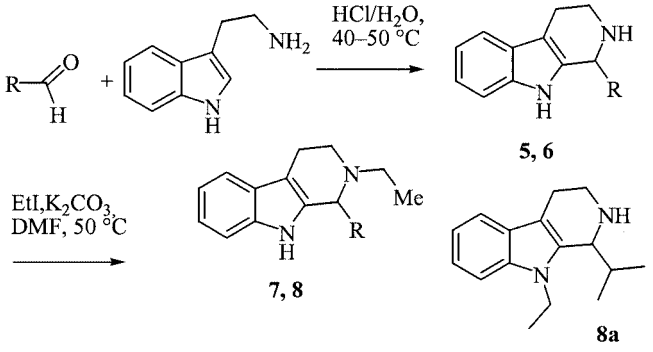
Table 1. R substituents for carbolines **1**−**8**, alkoxymethylindoles **9**−**15**, and azocinoindoles **17**−**22**

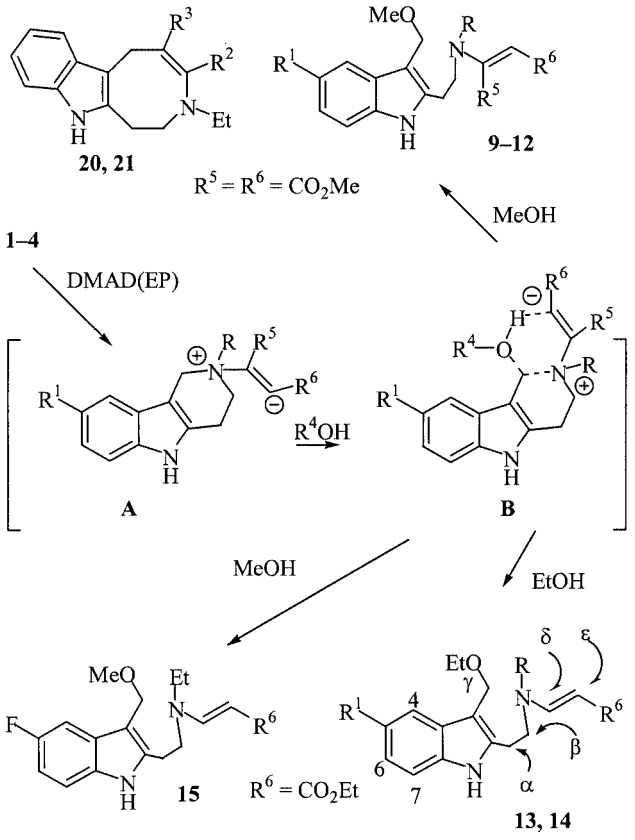
Carbolines			Alkoxymethylindoles			Azocinoindoles				
	R	R^1		R	R^1		R	R^1	R^2	R^3
1	Et	H	**9**	Et	F	**17**	Et	F	COOMe	COOMe
2	Et	F	**10**	*i*Pr	F	**18**	*i*Pr	F	COOMe	COOMe
3	*i*Pr	F	**11**	Et	OMe	**19**	Et	OMe	COOMe	COOMe
4	Et	OMe	**12**	Et	H	**20**	Et	H	COOMe	COOMe
5	Me	−	**13**	Et	H	**21**	Et	H	H	COOEt
6	*i*Pr	−	**14**	Et	OMe	**22**	Et	F	H	COOEt
7	Me	−	**15**	Et	F					
8	*i*Pr	−								

N-Ethyl-β-carbolines **7** and **8** were synthesized by Pictet−Spengler condensation of tryptamine with acetaldehyde or isobutyraldehyde, followed by *N*-ethylation of the intermediate tetrahydro-β-carbolines **5** and **6** (Scheme 2) (Table 1). All reactions proceeded smoothly, giving the desired products in good to high yields, except for the *N*-ethylation of **6**; the isolation of the target product required column chromatography in this case. The main by-product isolated was the N(9)−Et isomeric carboline **8a**. The structure of **8a** was assigned from its IR and ^{1}H NMR spectroscopic data as well as its mass spectrum. The proton NMR spectrum of **8a** lacks the N(9)−H signal, which in the case of **8** resonates at δ = 8.21 ppm (br. s, 1 H). We relate this unusual alkylation to the presence of the bulky isopropyl group in the position α to the piperidine NH in **6**.



Scheme 2

γ-Carbolines, unlike THPP derivatives, are cleaved by DMAD in aprotic solvents, producing multicomponent mixtures of products, which were not identified. Compounds **1**−**4** and **7** and **8** were treated with DMAD or ethyl propiolate (EP) at room temperature in absolute methanol or ethanol. In the case of γ-carbolines **1**−**4** a tandem cleavage process involving one molecule of solvent took place (Scheme 3).

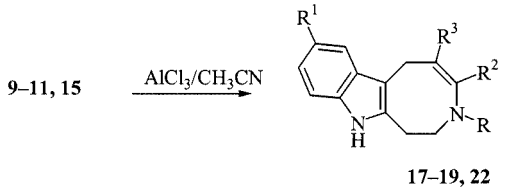


Scheme 3

In the case of carboline **1**, the target azocinoindoles **20** and **21** were isolated as almost the only products; the formation of the corresponding β-alkoxymethylindoles **12** and **13** in the course of the reaction was demonstrated with the aid of LCMS analysis of the crude reaction mixture. We presume that the reaction proceeds via the intermediate zwitterion **A**, the result of Michael addition of the tertiary nitrogen to DMAD or EP. The cleavage of the C(1)−N bond occurs through the formation of the six-membered transition state **B**, in which a molecule of alcohol facilitates the S_N reaction. The electronic effects of R^1 define the symmetry of the transition state (loose or tight) and the direction of further transformations: the formation of alkoxymethylindoles or azocinoindoles. EP is more active than DMAD in the reaction with carbolines; this may be explained in terms of different delocalization of the negative charge in the anionic part of **B**. The proton NMR spectra of indoles **9**−**11** and **14** and **15** have similar characteristics: the enamine protons of **9**−**11** resonate at δ = 4.50−4.70 ppm, whereas the enamine protons of **14** and **15** appear as two doublets at δ = 4.70−4.82 ppm and δ = 7.45−7.62 ppm with *J* = 13.0−13.8 Hz, such high vicinal coupling constant values indicating the *trans* configuration of the enamine fragment. This observation is in agreement with the data on cleavage of tetrahydropyrrolopyridines (THPPs) on treatment with DMAD in protic solvents.[14]

Compounds **9**−**11** and **15** underwent intramolecular cyclization on treatment with $AlCl_3$ in acetonitrile to give

the target azocinoindoles **17**−**19** and **22** in good (except for **19**) yields (Scheme 4).



Scheme 4

Our attempts to isolate the target azocinoindole failed in the case of the cyclization of **14**. The reaction was accompanied by significant tarring, and a multicomponent reaction mixture was formed.

We relate this result (along with the low yield of azocine in the case of **11**) to the presence of the OCH_3 group at the C(8) position. This can be alternatively attacked by the molecule of $AlCl_3$, thus destabilizing the transition state **B** and activating the methoxy group towards intermolecular nucleophilic displacement.

An X-ray crystallographic analysis was carried out on the tricyclic tetrahydroazocino[4,5-*b*]indole **17**, obtained as a suitable monocrystal by recrystallisation from ethyl acetate through slow evaporation at room temperature, to obtain unequivocal structural assignment and to elucidate its three-dimensional structure. The refined X-ray crystal structure of **17** is shown in Figure 1.

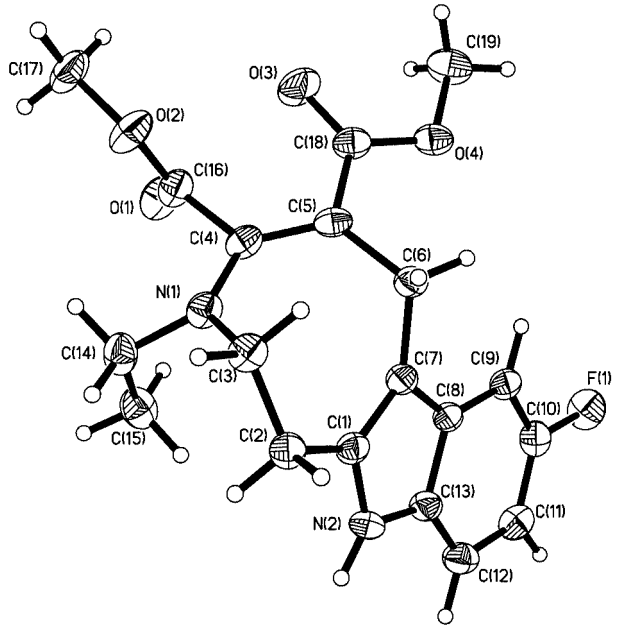
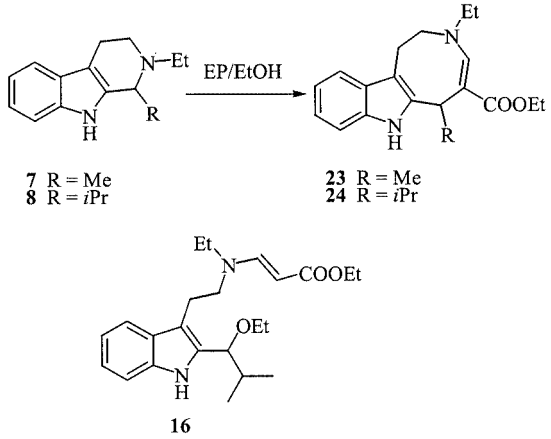


Figure 1. X-ray crystal structure of **17**

The conformation of the eight-membered ring is a twisted boat, in which the C(1), C(7), N(1), and C(4) atoms are almost coplanar, whilst the C(2), C(3), C(5), and C(6) atoms are located on the same side of this plane within 0.78, 1.26, 0.45, and 0.84 Å, respectively. The N(1)−C(4) bond is shorter than the N(1)−C(3) (1.364 and 1.469 Å respectively), indicating the presence of conjugation in the enamine [N(1)−C(4)−C(5)] fragment. β-Carbolines **7** and **8**, upon treatment with EP in absolute ethanol, directly provided target tetrahydroazocino[5,4-*b*]indoles **23** and **24** in good yield; in the case of **8** the corresponding α-(ethoxy)isobutylindole derivative **16** was also isolated (Scheme 5).



Scheme 5

The three-dimensional structure of compound **24** was also investigated by X-ray diffraction method. The monocrystal was obtained by recrystallisation from an ethyl acetate/hexane mixture by slow evaporation at room temperature, and the refined X-ray crystal structure of **24** is shown in Figure 2. The conformation of the eight-membered ring is a flat boat, in which the C(7), C(13), N(2), and C(10) atoms are coplanar, whilst the C(9), C(11), C(12), and C(19) atoms are located on the same side of this plane, within 1.09, 0.41, 0.90 and 2.42 Å, respectively.

The isopropyl group in azocine moiety is pseudoaxially oriented. The N(2)−C(10) bond is shorter than the N(2)−C(9) (1.364 and 1.469 Å, respectively), once again indicating the presence of conjugation in the enamine [N(2)−C(10)−C(11)] fragment.

We evaluated the synthesized azocinoindoles for their abilities to inhibit AChE, in the context of a research program aimed at testing the neuroprotective potential of new heterocyclic candidates.[15] AChE inhibition represents a major pharmacological approach to the treatment of Alzheimer's disease (AD).[16]

Our azocinoindoles were preliminarily tested as inhibitors of bovine AChE, by Ellman's method,[17] and their mean inhibitory concentrations (IC_{50}s) were estimated from the best-fitting inhibition-concentration curves, as shown in Figure 3 for compound **17**. The biological data showed compound **17** to be the best AChE inhibitor of the tetrahydroazocino[4,5-*b*]indole derivatives tested, its IC_{50} value being 8.7 μM. The other derivatives, including tetrahydroazocino[5,4-*b*]indoles **23** and **24**, showed IC_{50}s ranging from 20 to 50 μM. Detailed kinetic studies and structure-activity relationships will be reported elsewhere in due course.

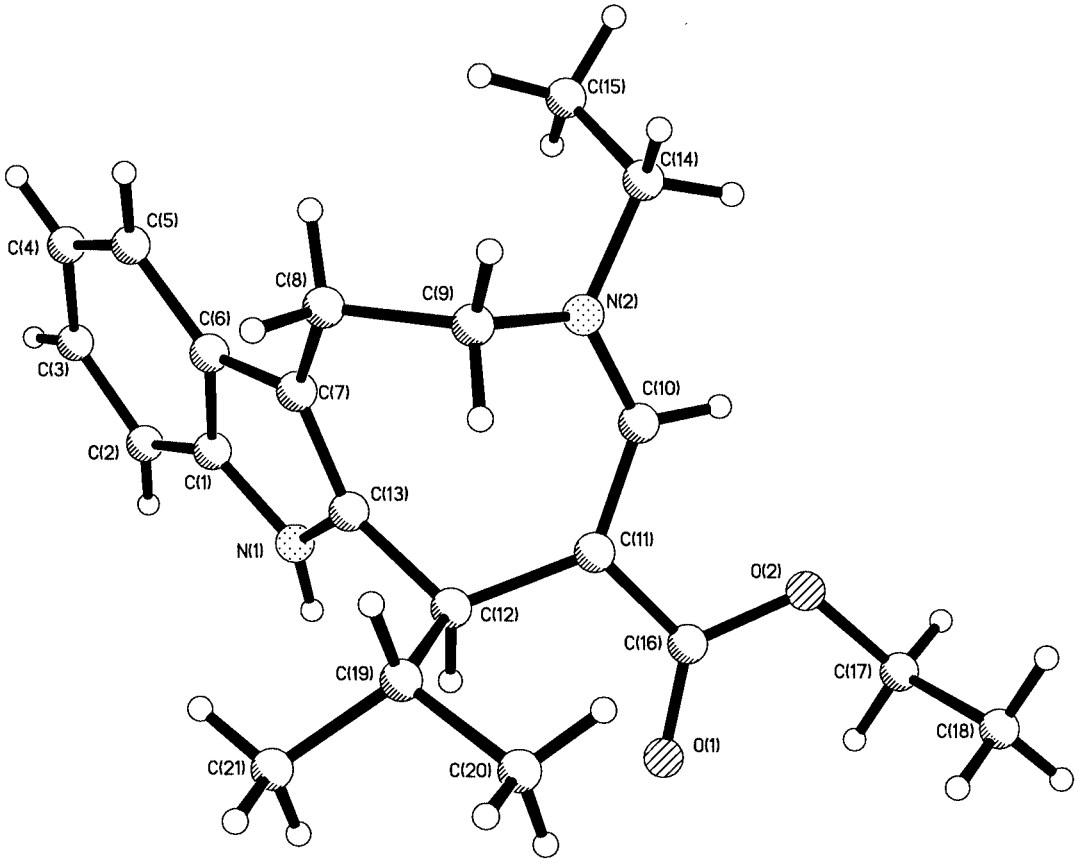


Figure 2. X-ray crystal structure of **24**

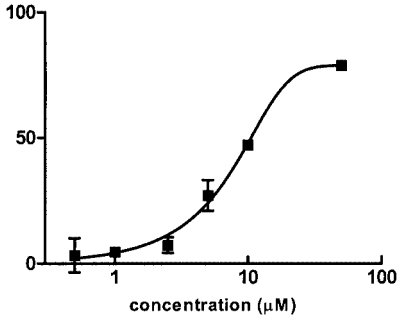


Figure 3. AChE inhibition curve for compound **17**; interpolation of the best-fitting curve gave an IC_{50} value of 8.7 μM; data points and error bars represent means and s.d. (n = 3−5), respectively

Conclusion

In conclusion, we offer a new, two-step procedure for the synthesis of azocino[4,5-*b*]indoles and azocino[5,4-*b*]indoles, starting from readily available γ- and β-carbolines. This reaction could represent a new powerful tool for the construction of fused azocine derivatives, shown to be endowed with different degrees of inhibitory activity toward AChE.

Experimental Section

General Remarks: All solvents were distilled and dried before use; DMAD and EP were purchased from Acros Organics and were used without any additional purification. Column chromatography was performed with alumina oxide 60 from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions, at 25 °C or in [D_6]DMSO solutions at 40 °C, with a Bruker WM 400 NMR spectrometer operating at 400 and 100 MHz, respectively; peak positions are given in parts per million (δ) with tetramethylsilane as the internal standard. For the protons indexes for compounds **9**−**11** and **14**, **15** see Scheme 3. ^{1}H-^{1}H COSY experiments were used for the assignment of the signals in the spectra of compounds **16** and **24**. Mass spectra were obtained by the EI technique (Finnigan-MAT 95 XL engine) or the ESI method (Agilent 1100 Series LC/MSD Trap System VL). IR spectra were recorded with a Perkin−Elmer Spectrum One instrument. Only noteworthy IR absorptions (cm^{-1}) are listed. Melting points were determined in a capillary tube and are uncorrected.

Starting Materials: γ-Carbolines **1**−**4** were synthesized by the previously described method,[18] and β-carbolines **5** and **6** were synthesized by a previously described procedure.[19] The structures of compounds **1**−**6** were confirmed by ^{1}H NMR and MS data.

2-Ethyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (7): Ethyl iodide (1.3 g, 8 mmol) was added to a stirred solution of **5** (1.0 g, 5.4 mmol) and K_2CO_3 (1.6 g, 16 mmol) in DMF (10 mL), and stir-

ring was continued at 50 °C for 5 h. The crude reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 70 mL). Solvents were evaporated under reduced pressure to give **7** (600 mg, 52%) as a light brown oil. ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, *J* = 7.3 Hz, 3 H, *CH*$_3$−CH$_2$), 1.40 (d, *J* = 6.7 Hz, 3 H, *CH*$_3$−CH), 2.61−2.95 (m, 5 H, *CH*$_2$−CH$_3$, CH$_2$-3, 4-H), 3.18−3.20 (m, 1 H, 4-H), 3.85 (q, *J* = 7.3 Hz, 1 H, 1-H), 7.06−7.1 (m, 2 H, 6-H, 7-H), 7.3 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.50 (d, *J* = 7.6 Hz, 1 H, 8-H), 7.75 (br. s, 1 H, NH) ppm. EI MS: *m*/*z* (%) = 214 (20) [M$^+$], 199 (100), 157 (40), 144 (10), 130 (15). $C_{14}H_{18}N_2$ (214.31): calcd. C 78.46, H 8.47, N 13.07; found C 78.32, H 8.53, N 12.95.

2-Ethyl-1-isopropyl-1,2,3,4-tetrahydro-β-carboline (8) and 9-Ethyl-1-isopropyl-1,2,3,4-tetrahydro-β-carboline (8a): Ethyl iodide (1.1 g, 7 mmol) was added to a stirred solution of **6** (1.0 g, 4.7 mmol) and K_2CO_3 (1.4 g, 14 mmol) in DMF (10 mL), and stirring was continued at 50 °C for 6 h. The crude reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 70 mL). Solvents were evaporated under reduced pressure, and the residue (750 mg) was purified by column chromatography with ethyl acetate/heptane (1:3) as eluent. The first fraction provided **8** (590 mg, 53%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 1.05 (d, *J* = 6.8 Hz, 3 H, *CH*$_3$−CH), 1.13 (t, *J* = 7.3 Hz, 3 H, CH$_3$−CH$_2$), 1.21 (d, *J* = 6.8 Hz, 3 H, *CH*$_3$−CH), 2.0 (m, 1 H, *CH* *i*Pr), 2.45−2.60 (m, 3 H, *CH*$_2$−CH$_3$, 4-H), 2.90 (m, 1 H, 4-H), 3.05 (m, 1 H, 3-H), 3.20−3.30 (m, 2 H, 1-H, 3-H), 7.10 (t, *J* = 7.6 Hz, 1 H, 6-H), 7.15 (t, *J* = 7.6 Hz, 1 H, 7-H), 7.25 (d, *J* = 7.6 Hz, 1 H, 5-H), 7.50 (d, *J* = 7.6 Hz, 1 H, 8-H), 7.71 (br. s, 1 H, NH) ppm. ESI MS: *m*/*z* = 243 [M$^+$ + 1]. $C_{16}H_{22}N_2$ (242.36): calcd. C 79.29, H 9.15, N 11.56; found C 78.98, H 9.13, N 11.32.

Further elution provided **8a** (100 mg, 9%) as light yellow crystals, m.p. 142−143 °C. ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, *J* = 6.6 Hz, 3 H, *CH*$_3$−CH), 1.01 (t, *J* = 7.1 Hz, 3 H, CH$_3$−CH$_2$), 1.08 (d, *J* = 6.6 Hz, 3 H, *CH*$_3$−CH), 1.85 (td, *J* = 13.2, 4.2 Hz, 1 H, 4-H$_a$), 2.27−2.28 (m, 2 H, CH$_2$−N), 2.45 (m, 1 H, CH *i*Pr), 2.60−2.71 (m, 2 H, 4-H$_e$, 3-H$_a$), 3.07 (d, *J* = 11.0 Hz, 1 H, 1-H), 3.51 (td, *J* = 12.3, 2.8 Hz, 1 H, 3-H$_e$), 7.20 (t, *J* = 7.4 Hz, 1 H, 6-H), 7.30−7.40 (m, 2 H, 5-H, 7-H), 7.52 (d, *J* = 7.6 Hz, 1 H, 8-H) ppm. ESI MS: *m*/*z* = 243 [M$^+$ + 1]. $C_{16}H_{22}N_2$ (242.36): calcd. C 79.29, H 9.15, N 11.56; found C 79.13, H 9.18, N 11.64.

General Synthetic Procedure for the Synthesis of Alkoxyindoles 9−11, 14, and 15: DMAD or EP (1.2 mmol) was added to a solution of the carboline derivative **2**−**4** (1 mmol) in methyl (ethyl) alcohol (10 mL). The reaction mixture was stirred for 4−6 h at room temperature (TLC monitoring). The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography with ethyl acetate/hexane (1:2) as eluent. The first fraction provided the corresponding β-alkoxy derivatives **9**−**11** and **14** and **15**.

Dimethyl (2*E*)-2-(Ethyl{2-[5-fluoro-3-(methoxymethyl)-1*H*-indol-2-yl]ethyl}amino)but-2-enedioate (9): Colorless oil. Yield 270 mg (70%). ^{1}H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 7.3 Hz, 3 H, *CH*$_3$−CH$_2$) 2.95 (q, *J* = 7.3 Hz, 2 H, *CH*$_2$−CH$_3$), 2.95 (t, *J* = 6.7 Hz, 2 H, CH$_2$-α), 3.39 (s, 3 H, OCH$_3$), 3.42 (t, *J* = 6.7 Hz, 2 H, N−CH$_2$-β), 3.67 (s, 3 H, OCH$_3$), 3.95 (s, 3 H, OCH$_3$), 4.56 (s, 2 H, O−CH$_2$), 4.74 (s, 1 H, H-ε), 6.90 (ddd, *J* = 11.7 Hz, 9.2 Hz, 2.4 Hz, 1 H, CH$_{6'\text{-indolyl}}$), 7.20−7.27 (m, 2 H, CH$_{4'\text{-indolyl}}$, CH$_{7'\text{-indolyl}}$), 8.32 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 12.5, 22.1, 46.3, 51.2, 52.3, 55.0, 57.1, 66.3, 86.2, 103.2 (d, $^2J_{C,F}$ = 26 Hz), 107.9 (d, $^2J_{C,F}$ = 26 Hz), 110.4 (d, $^3J_{C,F}$ = 9 Hz), 110.5, 131.4, 135.2, 136.8, 150.7, 157.3 (d, $^1J_{C,F}$ = 230 Hz), 168.2, 169.1 ppm. EI MS: *m*/*z* (%) = 392 (6) [M$^+$], 333 (21), 301 (79), 271 (18), 241 (10), 200 (100), 185 (15), 133 (11), 59 (15). $C_{20}H_{25}FN_2O_5$ (392.42): calcd. C 61.21, H 6.42, N 7.14; found C 61.30, H 6.51, N 7.35.

Dimethyl (2*E*)-2-[{2-[5-Fluoro-3-(methoxymethyl)-1*H*-indol-2-yl]-ethyl}(isopropyl)amino]but-2-enedioate (10): White crystals, m.p. 100−102 °C (ethyl acetate/hexane), yield 230 mg (56%). ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, *J* = 6.4 Hz, 3 H, CH$_3$ *i*Pr), 1.01 (d, *J* = 6.4 Hz, 3 H, CH$_3$ *i*Pr), 3.05 (t, *J* = 7.2 Hz, 2 H, N−CH$_2$-α), 3.32 (t, *J* = 7.2 Hz, 2 H, N−CH$_2$-β), 3.40 (s, 3 H, OCH$_3$), 3.54 (sept, *J* = 6.4 Hz, 1 H, CH *i*Pr), 3.65 (s, 3 H, OCH$_3$), 3.94 (s, 3 H, OCH$_3$), 4.55 (s, 2 H, O−CH$_2$), 4.79 (s, 1 H, H-ε), 6.87 (ddd, *J* = 10.5 Hz, 8.9 Hz, 2.3 Hz, 1 H, CH$_{6'\text{-indolyl}}$), 7.23−7.19 (m, 2 H, CH$_{4'\text{-indolyl}}$, CH$_{7'\text{-indolyl}}$), 8.38 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 20.1, 20.1, 23.9, 43.6, 50.9, 52.5, 57.8, 65.0, 65.0, 86.2, 103.3 (d, $^2J_{C,F}$ = 24 Hz), 110.0 (d, $^2J_{C,F}$ = 24 Hz), 110.1, 111.2 (d, $^3J_{C,F}$ = 9 Hz), 128.7, 131.9, 136.6, 153.3, 158.1 (d, $^1J_{C,F}$ = 234 Hz), 166.8, 168.1 ppm. EI MS: *m*/*z* (%) = 406 (5) [M$^+$], 375 (8), 347 (12), 315 (5), 271 (5), 214 (100), 174 (15), 172 (18), 161 (25), 140 (50), 112 (20), 44 (15). $C_{21}H_{27}FN_2O_5$ (406.45): calcd. C 62.06, H 6.65, N 6.90; found C 62.30, H 6.51, N 6.45.

Dimethyl (2*E*)-2-(Ethyl{2-[5-methoxy-3-(methoxymethyl)-1*H*-indol-2-yl]ethyl}amino)but-2-enedioate (11): Pale yellow oil. Yield 280 mg (70%). ^{1}H NMR ($CDCl_3$): δ = 1.05 (t, *J* = 6.7 Hz, 3 H, *CH*$_3$−CH$_2$), 2.95 (q, *J* = 6.7 Hz, 2 H, *CH*$_2$−CH$_3$), 3.06 (t, *J* = 7.2 Hz, 2 H, N−CH$_2$−*CH*$_2$), 3.38 (s, 3 H, OCH$_3$), 3.41 (t, *J* = 7.2 Hz, 2 H, N−CH$_2$), 3.66 (s, 3 H, OCH$_3$), 3.85 (s, 3 H, OCH$_3$), 3.95 (s, 3 H, OCH$_3$), 4.58 (s, 2 H, O−CH$_2$), 4.73 (s, 1 H, H-ε), 6.81 (dd, *J* = 8.7 Hz, 1.9 Hz, 1 H, CH$_{6'\text{-indolyl}}$), 7.04 (d, *J* = 1.9 Hz, 1 H, CH$_{4'\text{-indolyl}}$), 7.22 (d, *J* = 8.7 Hz, 1 H, CH$_{7'\text{-indolyl}}$), 8.21 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.8, 24.9, 46.7, 50.7, 51.2, 53.4, 56.4, 58.1, 65.5, 85.1, 100.1, 110.0, 111.8, 112.2, 129.2, 130.9, 135.5, 153.7, 154.9, 166.9, 168.6 ppm. EI MS: *m*/*z* (%) = 404 (5) [M$^+$], 373 (8), 372 (20), 345 (15), 313 (25), 200 (100), 173 (85), 158 (20), 96 (15), 45 (15). $C_{21}H_{28}N_2O_6$ (404.46): calcd. C 62.36, H 6.98, N 6.93; found C 62.02, H 7.12, N 6.90.

Ethyl (2*E*)-3-[{2-[3-(Ethoxymethyl)-5-methoxy-1*H*-indol-2-yl]ethyl}-(ethyl)amino]acrylate (14): Pale yellow oil. Yield 230 mg (61%). ^{1}H NMR: δ = 1.05 (t, *J* = 7.2 Hz, 3 H, N−CH$_2$−*CH*$_3$), 1.22 (t, *J* = 7.0 Hz, 3 H, O−CH$_2$−*CH*$_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, O−CH$_2$−*CH*$_3$), 2.95 (t, *J* = 7.5 Hz, 2 H, CH$_2$-α), 3.05 (q, *J* = 7.2 Hz, 2 H, N−*CH*$_2$−CH$_3$), 3.48 (t, *J* = 7.5 Hz, 2 H, N−CH$_2$-β), 3.52 (q, *J* = 7.0 Hz, 2 H, O−*CH*$_2$−CH$_3$), 3.85 (s, 3 H, O−CH$_3$), 4.25 (q, *J* = 7.1 Hz, 2 H, O−*CH*$_2$−CH$_3$), 4.52 (s, 2 H, O−CH$_2$-γ), 4.54 (d, *J* = 13.2 Hz, 1 H, H-ε), 6.80 (dd, *J* = 8.7 Hz, 1.9 Hz, 1 H, CH$_{6'\text{-indolyl}}$), 7.04 (d, *J* = 2.2 Hz, 1 H, CH$_{4'\text{-indolyl}}$), 7.19 (d, *J* = 8.7 Hz, 1 H, CH$_{7'\text{-indolyl}}$), 7.42 (d, *J* = 13.2 Hz, 1 H, H-δ), 8.22 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4, 14.6, 15.4, 24.7, 55.9, 55.9, 59.0, 63.2, 63.2, 65.3, 84.5, 100.6, 109.7, 111.3, 111.6, 128.9, 130.5, 135.2, 150.7, 154.3, 169.9 ppm. ESI MS: *m*/*z* = 375 [M + 1]. $C_{21}H_{30}N_2O_4$ (374.47): calcd. C 67.35, H 8.07, N 7.48; found C 67.39, H 8.31, N 7.25.

Ethyl (2*E*)-3-[(Ethyl){2-[5-fluoro-3-(methoxymethyl)-1*H*-indol-2-yl]-ethyl}amino]acrylate (15): Yellow crystals. M.p. 83−84 °C (ethyl acetate). Yield 255 mg (73%). ^{1}H NMR ($CDCl_3$): δ = 1.07 (t, *J* = 7.2 Hz, 3 H, N−CH$_2$−*CH*$_3$), 1.26 (t, *J* = 7.0 Hz, 3 H, O−CH$_2$−*CH*$_3$), 2.95 (t, *J* = 8.3 Hz, 2 H, CH$_2$-α), 3.01 (q, *J* = 7.3 Hz, 2 H, N−*CH*$_2$−CH$_3$), 3.39 (s, 3 H, OCH$_3$), 3.41 (t, *J* = 8.3 Hz, 2 H, N−CH$_2$-β), 4.15 (q, *J* = 7.3 Hz, 2 H, O−*CH*$_2$−CH$_3$), 4.55 (s, 2 H, O−CH$_2$-γ), 4.68 (bd, *J* = 13.1 Hz, 1 H, H-ε), 6.90 (td, *J* = 8.9, 2.4 Hz, 1 H, CH$_{6'\text{-indolyl}}$), 7.17−7.27 (m, 2 H, CH$_{4'\text{-indolyl}}$, CH$_{7'\text{-indolyl}}$), 7.44 (d, *J* = 13.1 Hz, 1 H, H-δ), 8.21 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.1, 19.4, 30.8, 52.1, 58.2, 59.5,

60.1, 65.5, 85.2, 97.8, 103.8 (d, $J^2_{C,F}$ = 37 Hz), 110.5 (d, $^2J_{C,F}$ = 37 Hz), 111.2 (d, $^3J_{C,F}$ = 14 Hz), 129.3, 132.7, 136.8, 151.2, 158.6 (d, $^1J_{C,F}$ = 240 Hz), 170.4 ppm. EI MS: *m*/*z* (%) = 348 (10) [M$^+$], 261 (5), 161 (7), 156 (100), 142 (5), 128 (20), 82 (10). $C_{19}H_{25}FN_2O_3$ (348.41): calcd. C 65.50, H 7.23, N 8.04; found C 65.34, H 7.33, N 8.42.

Use of the same procedure in the case of the carboline **1** resulted in the isolation of the azocinoindoles **20** and **21** (LCMS analysis of the crude reaction mixtures carried out within 2 h of the start of the reaction showed small peaks corresponding to **12** and **13**).

Dimethyl 3-Ethyl-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]indole-4,5-dicarboxylate (20): Yield 170 mg (50%), m.p. 116−118 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ = 1.00 (t, *J* = 7.1 Hz, 3 H, CH_2-CH_3), 3.00 (q, *J* = 7.1 Hz, 2 H, CH_2-CH_3), 3.17 (t, *J* = 6.0 Hz, 2 H, CH_2-1), 3.73 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.94 (t, *J* = 6.0 Hz, 2 H, CH_2-2), 4.04 (s, 2 H, CH_2-6), 7.07−7.01 (m, 2 H, 8-H, 9-H), 7.25 (m, 1 H, 7-H), 7.41 (m, 1 H, 10-H), 7.95 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.4, 21.6, 27.9, 45.6, 48.2, 51.7, 52.3, 103.0, 110.0, 110.1, 118.1, 119.2, 121.1, 129.0, 132.5, 135.8, 152.5, 167.8, 169.5 ppm. EI MS: *m*/*z* (%) = 342 (15) [M$^+$], 297 (10), 283 (50), 214 (15), 200 (20), 143 (100). $C_{19}H_{22}N_2O_4$ (342.39): calcd. C 66.65, H 6.48, N 8.18; found C 66.54, H 6.09, N 8.25.

Ethyl 3-Ethyl-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]indole-5-carboxylate (21): Yield 135 mg (45%), m.p. 122−124 °C (ethyl acetate/hexane). ^{1}H NMR: δ = 1.19 (t, *J* = 7.2 Hz, 3 H, N−CH_2-CH_3), 1.29 (t, *J* = 7.1 Hz, 3 H, O−CH_2-CH_3), 3.00 (q, *J* = 7.2 Hz, 2 H, N−CH_2-CH_3), 3.22 (t, *J* = 5.7 Hz, *J* = 6.2 Hz, 2 H, CH_2-1), 3.92 (bt, 2 H, CH_2-2), 4.06 (s, 2 H, CH_2-6), 4.14 (q, *J* = 7.1 Hz, 2 H, O−CH_2), 7.01−7.11 (m, 2 H, 8-H, 9-H), 7.23 (m, 1 H, 7-H), 7.39 (s, 1 H, 4-H), 7.41 (m, 1 H, 10-H), 7.77 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 15.3, 15.6, 19.1, 30.3, 45.3, 51.6, 59.2, 96.6, 110.7, 112.0, 117.9, 118.6, 120.7, 129.1, 133.7, 136.2, 149.8, 169.5 ppm. EI MS: *m*/*z* (%) = 298 (38) [M$^+$], 269 (8), 253 (15), 225 (20), 167 (18), 156 (60), 143 (100). $C_{18}H_{22}N_2O_2$ (298.38): calcd. C 72.46, H 7.43, N 9.39; found C 73.21, H 7.55, N 9.52.

General Synthetic Procedure for the Synthesis of Azocinoindoles 17−19 and 22: Anhydrous $AlCl_3$ (3 mg, 23 μmol) was added to a stirred solution of the alkoxy indole derivative **9**−**11** or **15** (0.6 mmol) in dry acetonitrile (10 mL), and stirring was continued for 24 h at room temperature (TLC monitoring: alufoil, hexane/ethyl acetate, 1:1). The reaction mixture was concentrated under reduced pressure, and the resulting dark, oily residue was dissolved in ethyl acetate (200 mL) and percolated through a short column of alumina oxide (*h* = 3 cm, *d* = 3 cm). Evaporation of the solvent provided the target azocinoindole derivatives **17**−**19** and **22**.

Dimethyl 3-Ethyl-8-fluoro-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]indole-4,5-dicarboxylate (17): Yield 130 mg (60%), white crystals, m.p. 141−143 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3 H, CH_2-CH_3), 3.00 (q, *J* = 7.4 Hz, 2 H, CH_2-CH_3), 3.19 (t, *J* = 6.7 Hz, 2 H, CH_2-1), 3.75 (s, 6 H, 2 × OCH_3), 3.85 (t, *J* = 6.7 Hz, 2 H, CH_2-2), 3.95 (s, 2 H, CH_2-6), 6.9 (td, $J_{9H,F}$ = $J_{9H,10H}$ = 8.7, $J_{9H,7H}$ = 2.0 Hz, 1 H, 9-H), 7.17 (dd, $J_{10H,9H}$ = 8.7, $J_{10H,F}$ = 4.5 Hz, 1 H, 10-H), 7.24 (dd, $J_{7H,F}$ = 8.7, $J_{7H,9H}$ = 2.0 Hz, 1 H, 7-H), 7.90 (br. s, 1 H, NH) ppm. EI MS: *m*/*z* (%) = 360 (35) [M$^+$], 328 (10), 301 (62), 271 (12), 185 (20), 161 (100), 133 (11), 59 (15). $C_{19}H_{21}FN_2O_4$ (360.38): calcd. C 63.32, H 5.87, N 7.77; found C 63.30, H 6.01, N 7.45.

Dimethyl 8-Fluoro-3-isopropyl-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]indole-4,5-dicarboxylate (18): Yield 135 mg (60%), yellow crystals, m.p. 160−162 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, *J* = 6.6 Hz, 6 H, 2 × CH_3 *i*Pr), 3.15 (t, *J* = 6.0 Hz, 2 H, CH_2-1), 3.40 (m, 1 H, CH *i*Pr), 3.70 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.90 (t, *J* = 6.0 Hz, 2 H, CH_2-2), 3.93 (s, 2 H, CH_2-6), 6.83 (td, $J_{9H,F}$ = $J_{9H,10H}$ = 8.6, $J_{9H,7H}$ = 2.5 Hz, 1 H, 9-H), 7.30−7.21 (m, 2 H, 7-H, 10-H), 7.76 (br. s, 1 H, NH) ppm. IR (KBr): ṽ = 3395.9, 2952.0, 1715.8, 1669.5, 1546.3 cm^{-1}. ESI MS: *m*/*z* = 375 [M$^+$ + 1]. $C_{20}H_{23}FN_2O_4$ (374.41): calcd. C 64.16, H 6.19, N 7.48; found C 64.11, H 6.15, N 7.09.

Dimethyl 3-Ethyl-8-methoxy-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]-indole-4,5-dicarboxylate (19): Yield 60 mg (25%), yellow oil, ^{1}H NMR ($CDCl_3$): δ = 1.01 (t, *J* = 7.1 Hz, 3 H, CH_2-CH_3), 3.01 (q, *J* = 7.1 Hz, 2 H, CH_2-CH_3), 3.16 (t, *J* = 6.2 Hz, 2 H, CH_2-1), 3.73 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.93 (t, *J* = 6.2 Hz, 2 H, CH_2-2), 4.00 (s, 2 H, CH_2-6), 6.76 (dd, *J* = 8.7 Hz, 2.3 Hz, 1 H, 9-H), 7.09 (d, *J* = 2.3 Hz, 1 H, 7-H), 7.12 (d, *J* = 8.7 Hz, 1 H, 10-H), 7.75 (br. s, 1 H, NH) ppm. ESI MS: *m*/*z* = 373 [M$^+$ + 1]. $C_{20}H_{24}N_2O_5$ (372.42): calcd. C 64.50, H 6.50, N 7.52; found C 64.87, H 6.35, N 7.53.

Ethyl 3-Ethyl-8-fluoro-2,3,6,11-tetrahydro-1*H*-azocino[4,5-*b*]indole-5-carboxylate (22): Yield 125 mg (65%), white crystals, m.p. 218−220 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) :δ = 1.17 (t, *J* = 7.2 Hz, 3 H, N−CH_2-CH_3), 1.30 (t, *J* = 7.1 Hz, 3 H, O−CH_2CH_3), 3.16 (q, *J* = 7.2 Hz, 2 H, N−CH_2-CH_3), 3.20 (t, *J* = 5.4 Hz, 2 H, CH_2-1), 3.98 (m, 4 H, CH_2-6, CH_2-2), 4.17 (q, *J* = 7.1 Hz, 2 H, O−CH_2), 6.9 (td, $J_{9H,F}$ = $J_{9H,10H}$ = 8.6, $J_{9H,7H}$ = 2.5 Hz, 1 H, 9-H), 7.09 (dd, $J_{10H,9H}$ = 8.6, $J_{10H,F}$ = 4.3 Hz, 1 H, 10-H), 7.32 (dd, $J_{7H,F}$ = 9.7, $J_{7H,9H}$ = 2.5 Hz, 1 H, 7-H), 7.35 (s, 1 H, 4-H), 7.87 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 14.8, 18.9, 30.3, 44.9, 51.6, 59.6, 97.2, 103.4 (d, $^2J_{C,F}$ = 23 Hz), 109.3 (d, $^2J_{C,F}$ = 23 Hz), 110.4 (d, $^3J_{C,F}$ = 9 Hz), 113.4, 129.3, 132.2, 133.6, 149.2, 157.7 (d, $^1J_{C,F}$ = 240 Hz), 170.0 ppm. ESI MS: *m*/*z* = 317 [M$^+$ + 1]. $C_{18}H_{21}FN_2O_2$ (316.37): calcd. C 68.34, H 6.69, N 8.85; found C 68.31, H 6.42, N 8.63.

Ethyl 3-Ethyl-6-methyl-1,2,3,6-tetrahydroazocino[5,4-*b*]indole-5-carboxylate (23): A solution of β-carboline **7** (200 mg, 0.9 mmol) and ethyl propiolate (110 mg, 1.1 mmol) in absolute ethanol (10 mL) was stirred at room temp. for 5 h. The solvent was evaporated under reduced pressure, and dry diethyl ether (10 mL) was added to the oily residue. White crystals of **23** (150 mg, 52%) were filtered off and dried, m.p. 188−190 °C. ^{1}H NMR ($CDCl_3$) :δ = 1.16 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2−N), 1.28 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2−O), 1.59 (d, *J* = 7.3 Hz, 3 H, CH_3−CH), 3.05 (dt, *J* = 14.5 Hz, 2.8 Hz, 1 H, 1-H$_e$), 3.25 (m, 3 H, N−CH_2CH_3, 1-H$_a$), 3.57 (dt, *J* = 14.5, 2.8 Hz, 1 H, 2-H$_e$), 4.08 (td, *J* = 14.5, 2.8 Hz, 1 H, 2-H$_a$), 4.18 (q, *J* = 7.1 Hz, OCH_2CH_3), 4.69 (q, *J* = 7.3 Hz, 1 H, 6-H), 7.05−7.16 (m, 2 H, 9-H, 10-H), 7.25 (d, *J* = 7.6 Hz, 1 H, 11-H), 7.45 (d, *J* = 7.6 Hz, 1 H, 8-H), 7.61 (s, 1 H, 4-H), 7.95 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 15.4, 15.6, 26.4, 27.1, 31.6, 49.8, 51.8, 59.5, 98.6, 107.4, 111.1, 118.0, 118.7, 121.0, 130.0, 134.8, 139.0, 151.6, 169.7 ppm. IR (KBr): ṽ = 3295.0, 2974.1, 1647.6, 1598.0 cm^{-1}. EI MS: *m*/*z* (%) = 312 (100) [M$^+$], 297 (27), 267 (20), 255 (13), 239 (54), 223 (9), 209 (9), 194 (16), 182 (25), 170 (61), 143 (64), 122 (50). $C_{19}H_{24}N_2O_2$ (312.41): calcd. C 73.05, H 7.74, N 8.97; found C 73.18, H 7.87, N 8.59.

Ethyl 3-Ethyl-6-isopropyl-1,2,3,6-tetrahydroazocino[5,4-*b*]indole-5-carboxylate (24): A solution of β-carboline **8** (0.20 g, 0.8 mmol) and ethyl propiolate (100 mg, 1 mmol) in absolute ethanol (10 mL) was heated at reflux for 4 h. The solvent was evaporated under

reduced pressure, and dry diethyl ether (10 mL) was added to the oily residue, causing precipitation of **24** (120 mg, 44%); white crystals, m.p. 222−224 °C. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 6.2 Hz, 3 H, *CH*$_3$ *i*Pr), 1.06 (t, *J* = 6.8 Hz, 3 H, *CH*$_3$ *i*Pr), 1.16 (t, *J* = 7.2 Hz, 3 H, *CH*$_3$CH$_2$−N), 1.26 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$CH$_2$−O), 2.04 (m, 1 H, CH *i*Pr), 2.99 (dt, *J* = 16.1 Hz, 2.6 Hz, 1 H, 1-H$_e$), 3.23 (m, 3 H, N−*CH*$_2$CH$_3$, 1-H$_a$), 3.46 (ddt, *J* = 14.1, 2.9, 1.8 Hz, 1 H, 2-H$_e$), 4.09 (td, *J* = 14.1, 2.9 Hz, 1 H, 2-H$_a$), 4.18−4.11 (m, 3 H, 6-H, CH$_2$−O), 7.11−7.08 (m, 2 H, 9-H, 10-H), 7.25 (d, *J* = 7.6 Hz, 1 H, 11-H), 7.46 (d, *J* = 7.5 Hz, 1 H, 8-H), 7.64 (s, 1 H, 4-H), 8.07 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 15.0, 20.4, 22.6, 26.3, 39.2, 45.2, 48.7, 52.0, 59.8, 96.9, 106.9, 110.4, 117.5, 118.8, 120.9, 130.0, 134.2, 137.9, 151.0, 171.0 ppm. IR (KBr): $\tilde{\nu}$ = 3395.9, 2952.0, 1715.8, 1669.5, 1546.3 cm^{-1}. ESI MS: *m*/*z* = 341 [M$^+$ + 1]. $C_{21}H_{28}N_2O_2$ (340.46): calcd. C 74.08, H 8.29, N 8.23; found C 73.93, H 8.63, N 8.01. The solvent was evaporated from the mother liquor, and the residue was dissolved in ethyl acetate/hexane (1:10) and percolated through a short column with alumina oxide. Evaporation of the solvent provided **16** as white crystals (77 mg, 25%), m.p. 88−90 °C (ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ = 0.82 (d, *J* = 6.6 Hz, 3 H, CH$_3$ *i*Pr), 1.10 (d, *J* = 6.6 Hz, 3 H, CH$_3$ *i*Pr), 1.15 (t, *J* = 7.2 Hz, 3 H, *CH*$_3$CH$_2$N), 1.16 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$CH$_2$O), 1.27 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$CH$_2$O), 2.00 (m, 1 H, CH *i*Pr), 3.00 (m, 2 H, *CH*$_2$−CH$_2$−N), 3.15−3.17 (m, 2 H, N-*CH*$_2$CH$_3$), 3.30−3.42 (m, 4 H, CH$_2$*CH*$_2$N, OCH$_2$), 4.14 (d, *J* = 7.1 Hz, 1 H, CH−O), 4.14 (q, *J* = 7.1 Hz, 2 H, O*CH*$_2$CH$_3$), 4.70 (d, *J* = 12.2 Hz, 1 H, *CH*=CH−N), 7.11 (t, *J* = 8.0 Hz, 1 H, 5-H), 7.15 (t, *J* = 8.0 Hz, 1 H, 4-H), 7.34 (d, *J* = 8.0 Hz, 1 H, 6-H), 7.48 (d, *J* = 12.2 Hz, 1 H, CH=*CH*−N), 7.53 (d, *J* = 8.0 Hz, 1 H, 7-H), 8.21 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 15.2, 15.2, 19.0, 19.2, 20.4, 34.3, 58.8, 58.8, 64.9, 64.9, 79.5, 84.2, 110.4, 111.0, 118.2, 119.4, 121.9, 127.9, 135.2, 135.5, 150.8, 169.9. ESI MS: *m*/*z* = 387 [M$^+$ + 1]. $C_{23}H_{34}N_2O_3$ (386.53): calcd. C 71.45, H 8.87, N 7.25; found C 71.34, H 8.89, N 7.34.

X-ray Crystallographic Study: Crystal data were collected on a Bruker AXS SMART 1000 area detector diffractometer[20] (three-circle goniometer with 1 K CCD detector, Mo-K_α radiation, graphite monochromator).

Crystal Structure Analysis for 17: $C_{19}H_{21}FN_2O_4$, M_r = 360.38 g·mol^{-1}, monoclinic, space group $P2_1/c$, *a* = 8.7731(19), *b* = 17.636(4), *c* = 11.738(3) Å, β = 104.458(4) Å, *V* = 1758.6(7) Å^3, *Z* = 4, ρ = 1.361 g·cm^3, μ = 0.103 cm^{-1}, *F*(000) = 760. A total of 9800 reflections (2.13 < θ < 30.02°) were collected, of which 4145 were unique [*R*(int.) = 0.0337]. The structure was solved with the program SHELXS-97[21] and refined by use of SHELXL-97 [22] to R_1 = 0.0735 and $wR(F^2)$ = 0.1830 for 4145 reflections with $I > 2\sigma(I)$; max.\min. residual electron density 0.930 and −0.293e·Å^{-3}.

Crystal Structure Analysis for 24: $C_{21}H_{28}N_2O_2$, M_r = 340.45 g·mol^{-1}, monoclinic, space group $P2_1/c$, *a* = 10.432(2), *b* = 18.175(4), *c* = 11.302(2) Å, β = 113.62(3) Å, *V* = 1963.5(7) Å^3, *Z* = 4, ρ = 1.152 g·cm^3, μ = 0.103 cm^{-1}, *F*(000) = 736. A total of 4592 reflections (2.13 < θ < 27.96) were collected, of which 4323 were unique [*R*(int.) = 0.1185]. The structure was solved with the program SHELXS-97 and refined by use of SHELXL-97 to R_1 = 0.0683 and $wR(F^2)$ = 0.1877 for 4097 reflections with $I > 2\sigma(I)$; max./min. residual electron density 0.324 and −0.269e·Å^{-3}.

CCDC-218170 (for **17**) and -229769 (for **24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

AChE Inhibition Measurements: Enzyme inhibitory activities were determined by Ellman's[17] general method, with AChE from bovine erythrocytes (EC. 3.1.1.7, C-5021 from Sigma). The AChE activity was determined in a reaction mixture containing a solution of AChE (200 μL, 0.415 U/mL in 0.1 M phosphate buffer, pH 8.0), a solution of 5,5′-dithiobis(2-nitrobenzoic acid) (100 μL, 3.3 mM in 0.1 M phosphate-buffered solution pH 7.4), an aqueous solution of the substrate (5 mM, 100 μL), a solution of the inhibitor (100 μL) and phosphate buffer (pH 8, 0.1 M, 500 μL). Acetylthiocholine was used as the substrate, and five to seven concentrations of the examined compounds, ranging from 1×10^{-7} to 1×10^{-4} M, were spectrophotometrically tested for AChE inhibition (measurements of increase in absorbance at 412 nm was taken over 3.0 min at 25 °C).

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