

SYNTHESIS OF NOVEL TRYPTAMINE AND AZEPINOINDOLE DERIVATIVES

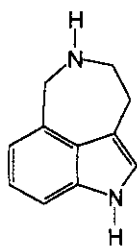
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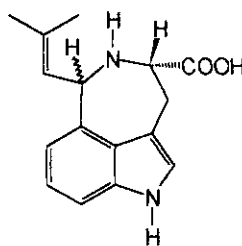
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Abstract - A novel one-pot synthesis of azepinoindoles (9) *via* reaction of tryptamines (4) with formaldehyde is described. The scope and generality of this new procedure and the preparation of the starting compounds are also discussed.

The tricyclic tetrahydroazepinoindole structure (1) forms the skeleton of clavicipitic acid isolated from *Claviceps* strain.^{1,2} Due to its unique biosynthetic connection with ergot alkaloids, namely both types of alkaloids are biosynthesized from the same intermediate, considerable synthetic efforts had been devoted to their preparations.²⁻⁵ Furthermore, several azepinoindoles possess analgesic properties or display 5-HT_{1A} receptor affinity.⁵⁻⁷



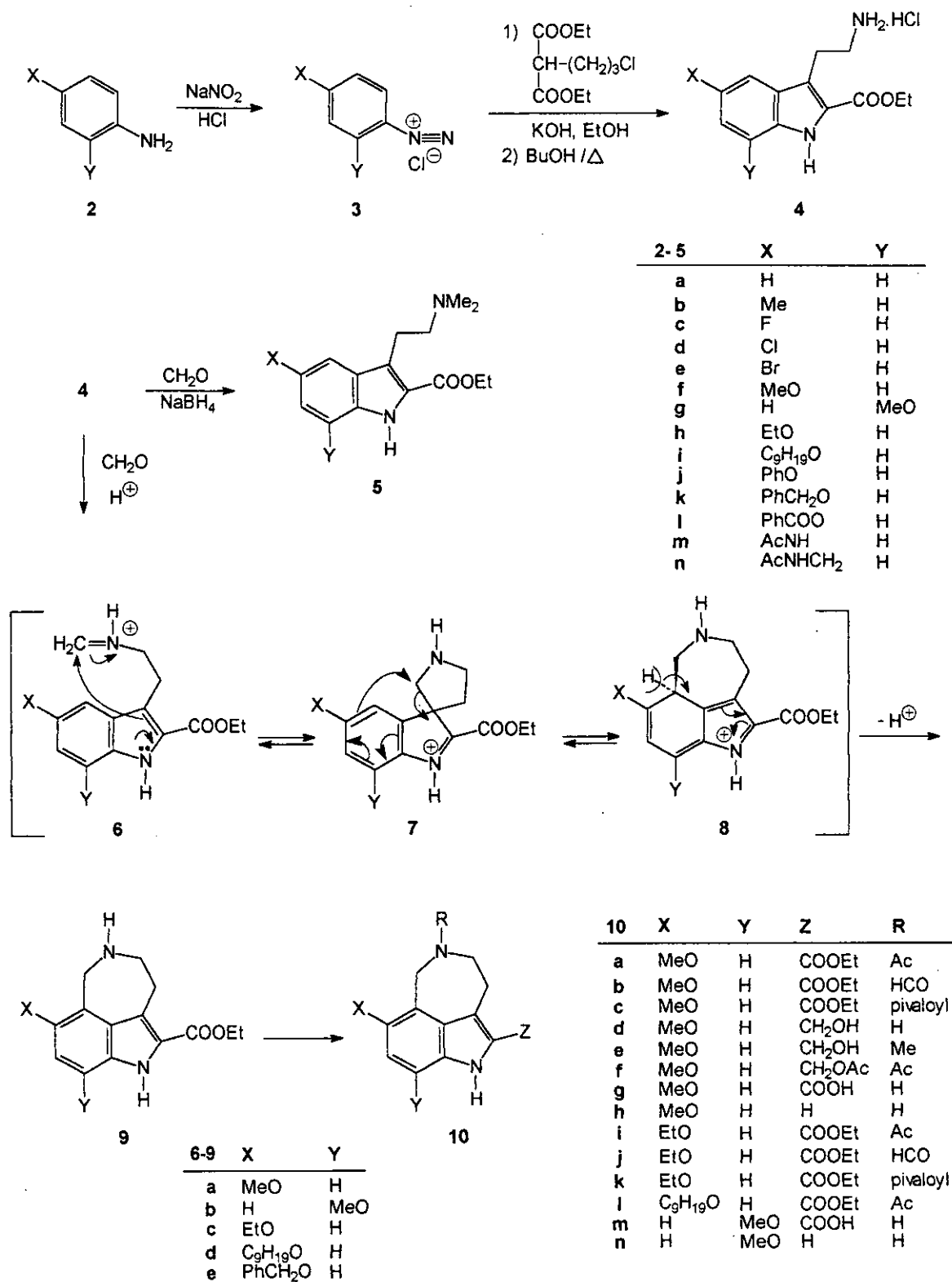
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Clavicipitic acid

Recently we were engaged in developing new methods for the preparation of bioactive indole derivatives. As a part of this research, we have examined the reactions of tryptamine derivatives with electrophiles. Now, we report the syntheses of new tryptamine derivatives. We also discuss a new method for the preparation of novel azepinoindole derivatives (Scheme 1).

Tryptamine derivatives (4a-n) were prepared from the corresponding anilines (2a-n) as outlined at the top of Scheme 1. This method^{8,9} started with the partial hydrolysis of diethyl 3-chloropropylmalonate followed by the coupling reaction with the diazonium salt (3) and rearrangement of the resulting Japp-Klingemann's product.¹⁰ The multistep reactions proceeded smoothly, usually in acceptable yields, and



Scheme 1.

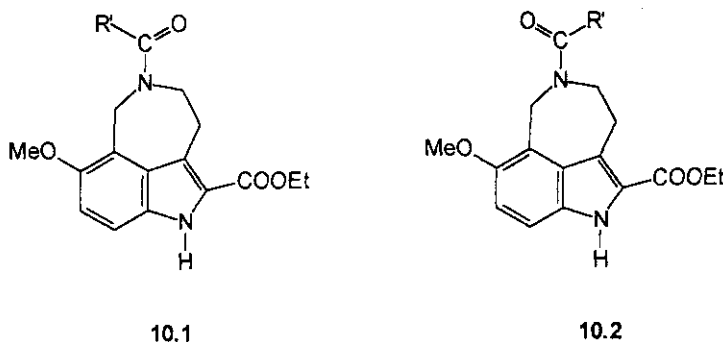
afforded tryptamines bearing ethoxycarbonyl group in position 2 and diverse substituents on the benzene ring.

The *N,N*-dimethyl derivatives of the above tryptamines (**5**) were prepared in conventional manner: the reaction with formaldehyde probably resulted the formation of iminium intermediate (**6**), which was then reduced by sodium borohydride. Although this alkylation reaction proceeded highly efficiently, generally in good to excellent yields (For selected examples see Experimental), in some cases when electron donating group was attached to the ring, side product was also isolated and characterised. For instance, compound (**4f**) bearing electron donating methoxy group in position 5 afforded 10% yield of a side product besides the major product (**5f**). The former was identified as tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivative (**9a**) by spectral analyses.

When we performed the reaction between **4f** and formaldehyde under acidic conditions and without using reducing agent, we isolated the azepinoindole (**9a**) as sole product in good yield.

Two reaction pathways may be considered for the formation of compound (**9a**). The reaction between tryptamine (**4f**) and formaldehyde gives rise to iminium intermediate (**6f**) which undergoes an intramolecular electrophilic substitution at position 3 to produce a 3,3-*spiro*-cyclicindolenine (**7f**). This intermediate then rearranges to yield azepinoindole (**9a**). An alternate mechanism for the formation of **9a** may be a direct intramolecular electrophilic substitution at position 4 of tryptamine derivative (**6f**→**8f**).¹¹⁻¹³

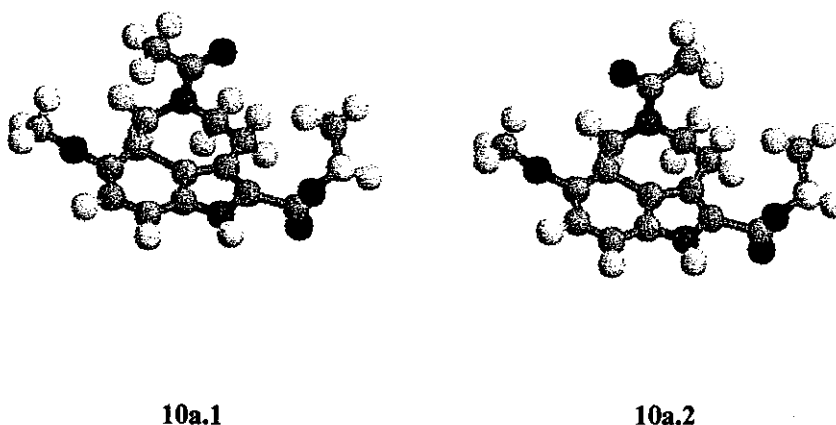
To extend the scope of this new reaction, we examined the reactions of tryptamines (**4a-n**). As expected, compounds having electron donating group in position 5 or 7 of the indole nucleus (**4b**, **4f-k**) reacted smoothly with formaldehyde to give compounds (**9b-e**) in good yields, respectively. However, tryptamines without electron donating group or with electron withdrawing group (**4a** and **4c-e**, respectively) were unreactive towards cyclization with formaldehyde, under normal or drastic conditions. In order to get more information about the reactivity of these azepinoindoles (**9**) and prepare their novel representatives, we investigated their reactions. Thus, azepinoindole (**9a**) was acylated in conventional manner. ¹H- and ¹³C- NMR spectra of the product (**10a**) indicated the presence of two rotamers in the ratio 3:1 (Scheme 2; **10a.1** and **10a.2**, respectively).



Scheme 2. Rotamers of compounds (**10a-c**)

(**a**: R' = Me; **b**: R' = H; **c**: R' = CMe₃)

The structure of these rotamers followed principally from the chemical shifts of the C-6 methylene protons in the ^1H NMR spectrum. In the spectrum of the minor rotamer (10a.2) these protons deshielded by carbonyl group showed a downfield shift by 0.14 ppm. As expected, taking the NMR measurement at elevated temperature (60°C) the spectrum showed fast interconversion of the two rotamers. The *N*-formyl derivative (10b) showed essentially the same ratio of rotamers (4:1). However, the *N*-pivaloyl derivative (10c) existed solely in rotamer (10c.1). These results showed that the equilibrium between the two rotamers was mainly determined by the steric interaction of the alkyl moiety of acyl group with the methylene groups at positions 3 and 4. The MM2 energy calculations also favored rotamer (10.1). We got considerably higher energies of rotamer (10.2) than the values for 10.1 (10a: $\Delta\Delta E = 1.4$ kcal/mol; 10c: $\Delta\Delta E = 7.0$ kcal/mol).



Scheme 3. Minimum-energy structure of 10a calculated by MM2.

Lithium aluminum hydride reduction of 9a afforded the corresponding alcohol (10d), which was then acylated with acetic anhydride to yield 10f. This compound also existed as a mixture of two rotamers (ratio 4:1).

Finally, azepinoindoles (9a) and (9b) were smoothly hydrolyzed to their corresponding carboxylic acids (10g and 10m) and decarboxylations led to the formation of methoxyazepinoindoles (10h) and (10n), respectively.

In conclusion, we have established a novel one-pot synthesis of tetrahydro-1*H*-azepino[5,4,3-*cd*]indole derivatives (9) by the reaction of tryptamine-2-carboxylic acid derivatives (4) with formaldehyde. This convenient synthetic method is applicable for tryptamine derivatives having electron donating substituent in 5- and/or 7-positions.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on Spekord 75 IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained with a Bruker DRX-500 spectrometer internal standard TMS. Splitting patterns are designated as "s, d, t, q, m, and br"; these symbols indicate "singlet, doublet, triplet, quartet, multiplet, and broad", respectively. MS measurements were carried out with a Kratos MS-25 RFA combined GC/MS system. Only selected peaks from IR and MS spectra are quoted. HPLC chromatographic analyses were performed with a Waters 600 equipped with a photodiode array detector 990. Stationary phase: Nucleosil C-18 (250 x 4 mm).

All solvents were dried by means of standard methods. All reactions were performed under argon and followed by thin-layer chromatography (TLC) on Merck precoated silica gel 60 F₂₅₄ plates. Merck Kieselgel[®] 60 was employed for column chromatography. Substrates 3-(2-aminoethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**4a**),⁸ its 5-methoxy analogue (**4f**),⁸ and the 5-bromo derivative (**4e**),⁹ were prepared according to the literature.

3-(2-Aminoethyl)-1*H*-indole-2-carboxylic acid ethyl esters (4b-n**); General Procedure.** To a stirred solution of 2-(3-chloropropyl)malonic acid diethyl ester (23.65 g, 0.1 mol) in dry ethanol (100 mL) was added a solution of potassium hydroxide (5.88 g, 0.105 mol) in dry ethanol (90 mL), and the resulting solution was stirred for 2 h at rt. Meanwhile, the appropriate benzenediazonium salt (**3**) was prepared as follows: A solution of sodium nitrite (7.25 g, 0.105 mol) in water (20 mL) was added portionwise to a stirred cold solution of the corresponding aniline derivative (**2**) in a mixture of water and conc. hydrochloric acid (30 mL), while keeping the temperature between 0-5°C. Afterwards the solution was neutralized by the addition of 10% aqueous sodium carbonate solution.

The former solution was then cooled to -7°C where to it, the solution of diazonium compound was added dropwise at -5°C. The pH of the resulting mixture was then adjusted to 8 by the addition of 10% aqueous sodium carbonate and stirring was continued at 0°C for 1 h. The mixture was acidified with acetic acid (pH= 6) and left overnight at rt.

The reaction mixture was then diluted with water (500 mL) and extracted with CH_2Cl_2 . The organic layer was washed with 2*N* aqueous NaOH and water, dried over MgSO_4 and solvent was evaporated in vacuo. The residue was dissolved in *n*-butanol (100 mL) containing some drops of water and refluxed under argon for 15 h. Upon cooling crystals dropped out which were collected with filtration, washed several times with cold acetone, and recrystallized from ethanol.

3-(2-Aminoethyl)-5-methyl-1*H*-indole-2-carboxylic acid ethyl ester Hydrochloride (4b**).** Following the general procedure, this compound was prepared from **2b** in 28% yield, mp 246-248°C (EtOH). TLC: R_f = 0.44 ($\text{CHCl}_3/\text{MeOH}$ 10:1, v/v, satur. with NH_3). HPLC: R_t = 9.31 min (acetonitrile/ H_2O 20:80 + 0.5% H_3PO_4). IR ν (KBr) cm^{-1} : 3360 (NH), 1710 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.43 (3H, t, J = 7.5 Hz, ester CH_3), 2.42 (3H, s, CH_3), 3.10 (2H, t, J = 8 Hz, CH_2), 3.46 (2H, t, J = 8 Hz, $\text{CH}_2\text{-N}$), 4.40 (2H, q, J = 7.5 Hz, $\text{CH}_2\text{-O}$), 7.08 (1H, dd, J = 8 and 1 Hz, H-6), 7.38 (1H, d, J = 8 Hz, H-7), 7.53 (1H, d, J = 1 Hz, H-4),

8.28 (3H, br s, NH_3^+), 11.16 (1H, s, NH). MS: m/z (%): 246 (M^+ , 14), 217 (100), 188 (22), 171 (99), 170 (98). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}_2\text{Cl}$: C, 59.46; H, 6.77; N, 9.91. Found: C, 59.17; H, 6.74; N, 9.81.

3-(2-Aminoethyl)-5-fluoro-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4c). The title compound was prepared as above from **2c** in 29% yield, mp 251-252°C (EtOH), TLC: R_f = 0.21 ($\text{CHCl}_3/\text{MeOH}$ 10:1, v/v, satur. with NH_3). HPLC: R_t = 5.23 min (acetonitrile/ H_2O 20:80+0.5% H_3PO_4). IR ν (KBr) cm^{-1} : 3430, 3300 (NH), 1705 (CO). ^1H NMR (DMSO-d_6 , δ , ppm): 1.38 (3H, t, J = 6 Hz, CH_3), 2.99 (2H, t, J = 4 Hz, CH_2), 3.36 (2H, t, J = 4 Hz, N- CH_2), 4.38 (2H, q, J = 6 Hz, O- CH_2), 7.18 (1H, m, H-6), 7.47 (1H, m, H-7), 7.65 (1H, m, H-4), 8.2 (3H, br s, NH_3^+), 11.86 (1H, s, NH). MS: m/z (%): 250 (M^+ , 8), 221 (100), 192 (23), 175 (79), 174 (76), 146 (47). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{FCl}$: C, 54.45; H, 5.63; N, 9.77. Found: C, 54.32; H, 5.41; N, 9.90.

3-(2-Aminoethyl)-5-chloro-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4d). Following the general procedure, this compound was prepared from **2d** in 25.3% yield, mp 249-250°C (EtOH). TLC: R_f = 0.53 ($\text{CHCl}_3/\text{MeOH}$ 9:1, v/v, satur. with NH_3). HPLC: R_t = 1.18 min (acetonitrile/ H_2O 40:60+0.5% H_3PO_4). IR ν (KBr) cm^{-1} : 3420 (NH), 1710 (CO). ^1H NMR (DMSO-d_6 , δ , ppm): 1.39 (3H, t, J = 6 Hz, CH_3), 2.98 (2H, m, CH_2), 3.35 (4H, m, CH_2), 4.38 (2H, q, J = 6 Hz, O- CH_2), 7.28 (1H, dd, J = 8 and 1 Hz, H-6), 7.46 (1H, d, J = 8 Hz, H-7), 7.80 (1H, d, J = 1 Hz, H-4), 8.16 (3H, br s, NH_3^+), 11.86 (1H, s, NH). ^{13}C NMR (DMSO-d_6 , δ , ppm): 14.44 (CH_3), 22.59 (C-1'), 39.42 (C-2'), 60.81 (O- CH_2), 114.49 (C-7), 117.46 (C-3), 119.56 (C-6), 124.67 (C-2), 125.35 (C-4), 125.56 (C-5), 128.26 (C-3a), 134.77 (C-7a), 161.36 (CO). MS: m/z (%): 266 (M^+ , 4), 239 (30), 238 (18), 237 (100), 208 (22), 193 (35), 192 (37), 191 (90), 162 (32). Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2\text{Cl}_2$: C, 51.45; H, 5.32; N, 9.24. Found: C, 51.70; H, 5.51; N, 5.34.

3-(2-Aminoethyl)-7-methoxy-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4g). Following the general procedure, compound **4g** was prepared from **2g** in 15% yield, mp 220-222°C (EtOH). TLC: R_f = 0.27 ($\text{CHCl}_3/\text{MeOH}$ 10:1, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3400, 3200 (NH), 1690 (CO). ^1H NMR (DMSO-d_6 , δ , ppm): 1.36 (3H, t, J = 7 Hz, CH_3), 2.96 (2H, m, CH_2), 3.40 (2H, m, CH_2), 3.90 (3H, s, O- CH_3), 4.33 (2H, q, J = 7 Hz, O- CH_2), 6.79 (1H, d, J = 7.7 Hz, H-6), 7.02 (1H, t, J = 7.9 Hz, H-5), 7.39 (1H, d, J = 7.9 Hz, H-4), 8.34 (3H, br s, NH_3^+), 11.58 (1H, s, NH). ^{13}C NMR (DMSO-d_6): 14.42 (CH_3), 22.96 (C-1'), 39.52 (C-2'), 55.55 (O- CH_3), 60.49 (O- CH_2), 104.96 (C-6), 112.59 (C-4), 118.61 (C-3), 120.75 (C-5), 124.34 (C-2), 127.28 (C-7a), 128.83 (C-3a), 146.91 (C-7), 161.49 (CO). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_3\text{Cl}$: C, 56.28; H, 6.41. Found: C, 55.95; H, 6.14.

3-(2-Aminoethyl)-5-ethoxy-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4h). This compound was prepared from **2h** in 12% yield, mp 145-147°C (BuOH). TLC: R_f = 0.2 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5:1, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3410 (NH), 1705 (CO). ^1H NMR ($\text{DMSO-d}_6\text{-CDCl}_3$, δ , ppm): 1.40 (3H, t, J = 7 Hz, CH_3), 1.48 (3H, t, J = 7 Hz, CH_3), 3.00 (2H, m, CH_2), 3.35 (2H, m, CH_2), 4.05 (2H, q, J = 7 Hz, $\text{CH}_2\text{-O}$), 4.38 (2H, q, J = 7 Hz, $\text{CH}_2\text{-O}$), 6.85 (1H, dd, J = 8 and 1 Hz, H-6), 7.28 (1H, d, J = 8 Hz, H-7), 7.32 (1H, d, J = 1 Hz, H-4), 8.25 (3H, br s, NH_3^+), 11.50 (1H, s, NH). Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{O}_3\text{N}_2\text{Cl}$: C, 57.59; H, 6.77; N, 8.96. Found: C, 57.32; H, 6.94; N, 8.68.

3-(2-Aminoethyl)-5-nonyloxy-1*H*-indole-2-carboxylic acid ethyl ester Hydrochloride (4i). Following the general procedure, this compound was prepared from **2i**¹⁴ in 12.5% yield, mp 121-122°C (EtOH). TLC: R_f = 0.7 (benzene/PrOH/MeOH 2:1:1, v/v). IR ν (KBr) cm^{-1} : 3410 (NH), 1690 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 0.84 (3H, t, J = 7 Hz, CH_3), 1.25 (8H, m, 4 CH_2), 1.32 (2H, m, CH_2), 1.36 (3H, t, J = 7 Hz, CH_3), 1.42 (2H, m, CH_2), 1.71 (2H, m, CH_2), 2.96 (2H, m, CH_2), 3.34 (2H, m, CH_2), 3.99 (2H, t, J = 7 Hz, O- CH_2), 4.34 (2H, q, J = 7 Hz, O- CH_2), 6.91 (1H, dd, J = 8 and 1 Hz, H-6), 7.31 (1H, d, J = 1 Hz, H-4), 7.32 (1H, d, J = 8 Hz, H-7), 8.25 (3H, br s, NH_3^+), 11.54 (1H, s, NH). ^{13}C NMR (DMSO- d_6): 14.11 (C-9"), 14.50 (CH_3), 22.26 (C-8"), 22.77 (C-1'), 25.85 (C-3"), 28.84 (C-6"), 29.04 (C-5"), 29.08 (C-4"), 29.17 (C-2"), 31.46 (C-7"), 39.44 (C-2'), 60.42 (O- CH_2), 68.07 (C-1"), 101.54 (C-4), 113.63 (C-7), 117.08 (C-6), 117.43 (C-3), 124.24 (C-2), 127.61 (C-3a), 131.74 (C-7a), 153.39 (C-5), 161.61 (CO). Anal. Calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_3\text{Cl}$: C, 64.29; H, 8.58; N, 6.82. Found C, 64.02; H, 8.67; N, 6.54.

3-(2-Aminoethyl)-5-phenoxy-1*H*-indole-2-carboxylic acid ethyl ester Hydrochloride (4j).¹⁵ This compound was prepared from **2j** in 11.8% yield, mp 234°C (EtOH). TLC: R_f = 0.19 (hexane/acetone 5:2, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3350, 3250 (NH), 1705 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.37 (3H, t, J = 7 Hz, CH_3), 2.96 (2H, m, CH_2), 3.34 (2H, t, J = 7.5 Hz, CH_2), 4.37 (2H, q, J = 7 Hz, O- CH_2), 6.92 (2H, d, J = 8 Hz, H-2" and H-6"), 7.02 (1H, t, J = 6.5 Hz, H-4"), 7.03 (1H, dd, J = 9 and 2 Hz, H-6), 7.31 (2H, t, J = 8 Hz, H-3" and H-5"), 7.50 (1H, d, J = 9 Hz, H-7), 7.53 (1H, d, J = 2 Hz, H-4), 8.26 (3H, br s, NH_3^+), 11.83 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.48 (CH_3), 22.76 (C-1'), 39.45 (C-2'), 60.67 (O- CH_2), 110.45 (C-4), 114.30 (C-6), 117.00 (C-2" and C-6"), 117.81 (C-3), 119.41 (C-7), 122.33 (C-4"), 125.29 (C-2), 127.84 (C-3a), 129.97 (C-3" and C-5"), 133.58 (C-7a), 149.41 (C-5), 158.89 (C-1"), 161.53 (CO). MS: m/z (%): 325 (M^+ , 21), 296 (100), 267 (11), 249 (95), 248 (55), 220 (27). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3\text{Cl}$: C, 63.24; H, 5.87. Found C, 62.98; H, 5.87.

3-(2-Aminoethyl)-5-benzyloxy-1*H*-indole-2-carboxylic acid ethyl ester Hydrochloride (4k). This compound was prepared from **2k**¹⁶ in 14% yield, mp 220-222°C (EtOH). TLC: R_f = 0.43 (hexane/acetone 1:1, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3350, 3150 (NH), 1700 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.37 (3H, t, J = 7 Hz, CH_3), 2.99 (2H, br s, CH_2), 3.39 (2H, m, CH_2), 4.35 (2H, q, J = 7 Hz, O- CH_2), 5.16 (2H, s, CH_2O), 7.01 (1H, dd, J = 9 and 1.7 Hz, H-6), 7.32 (1H, t, J = 7 Hz, H-4"), 7.36 (1H, d, J = 9 Hz, H-7), 7.39 (2H, t, J = 8 Hz, H-3" and H-5"), 7.51 (2H, d, J = 7.5 Hz, H-2" and H-6"), 8.34 (3H, br s, NH_3^+), 11.59 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.51 (CH_3), 22.82 (C-1'), 39.87 (C-2'), 60.47 (O- CH_2), 69.98 (CH_2O), 102.33 (C-4), 113.72 (C-7), 117.23 (C-6), 117.54 (C-3), 124.37 (C-2), 127.63 (C-3a), 127.90 (C-4"), 128.10 (C-2" and C-6"), 128.53 (C-3" and C-5"), 131.90 (C-7a), 137.61 (C-1"), 153.00 (C-5), 161.63 (CO). Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3\text{Cl}$: C, 64.08; H, 6.18. Found: C, 63.82; H, 6.02.

3-(2-Aminoethyl)-5-benzoyloxy-1*H*-indole-2-carboxylic acid ethyl ester Hydrochloride (4l). Following the general procedure, this compound was prepared from **2l**¹⁷ in 11% yield, mp 232-234°C (EtOH). TLC: R_f = 0.25 ($\text{CHCl}_3/\text{MeOH}$ 10:1, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3500, 3220 (NH), 1720, 1705 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.38 (3H, t, J = 7 Hz, CH_3), 2.97 (2H, m, CH_2), 3.38 (2H, t, J = 7.8 Hz, CH_2), 4.37 (2H, q, J = 7 Hz, O- CH_2), 7.19 (1H, dd, J = 8.8 and 1 Hz, H-6), 7.52 (1H, d, J = 8.8

Hz, H-7), 7.61 (1H, t, $J = 7.6$ Hz, H-3" and H-5"), 7.72 (1H, br s, H-4), 7.74 (1H, t, $J = 7.5$ Hz, H-4"), 8.14 (2H, d, $J = 7.5$ Hz, H-2" and H-6"), 8.30 (3H, br s, NH_3^+), 11.90 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.50 (CH_3), 22.75 (C-1'), 39.45 (C-2'), 60.75 (O- CH_2), 112.33 (C-4), 113.57 (C-7), 118.04 (C-3), 120.27 (C-6), 125.42 (C-2), 127.33 (C-7a), 129.18 (C-3" and C-5"), 129.32 (C-3a), 129.87 (C-2" and C-6"), 134.15 (C-4"), 144.49 (C-5), 161.52 (CO), 165.43 (CO). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_4\text{Cl}$: C, 61.77; H, 5.44. Found: C, 62.05; H, 5.71.

5-Acetylamino-3-(2-aminoethyl)-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4m).

Following the general procedure, this compound was prepared from **2m**¹⁸ in 9% yield, mp 244°C (EtOH). TLC: $R_f = 0.08$ ($\text{CHCl}_3/\text{MeOH}$ 10:1, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3280, 3220 (NH), 1690, 1660 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.37 (3H, t, $J = 7$ Hz, CH_3), 2.05 (3H, s, CH_3), 2.97 (2H, m, CH_2), 3.31 (2H, m, CH_2), 4.36 (2H, q, $J = 7$ Hz, O- CH_2), 7.31 (1H, dd, $J = 8.8$ and 1.6 Hz, H-6), 7.37 (1H, d, $J = 8.8$ Hz, H-7), 8.07 (1H, d, $J = 1.6$ Hz, H-4), 8.15 (3H, br s, NH_3^+), 9.99 (1H, s, NH), 11.65 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.50 (CH_3), 22.84 (C-1'), 24.02 (CH_3), 39.78 (C-2'), 60.55 (O- CH_2), 109.92 (C-4), 112.82 (C-7), 117.48 (C-3), 119.94 (C-6), 124.58 (C-2), 126.82 (C-3a), 132.36 (C-7a), 133.24 (C-5), 161.56 (CO), 168.11 (CONH). Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_3\text{Cl}$: C, 55.30; H, 6.19. Found C, 55.56; H, 6.02.

5-Acetylaminoethyl-3-(2-aminoethyl)-1H-indole-2-carboxylic acid ethyl ester Hydrochloride (4n).

Following the general procedure, this compound was prepared from **2n**¹⁹ in 17.8% yield, mp 268°C (EtOH). TLC: $R_f = 0.12$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 5:2, v/v, satur. with NH_3). IR ν (KBr) cm^{-1} : 3400, 3250 (NH), 1700, 1635. ^1H NMR (DMSO- d_6 , δ , ppm): 1.37 (3H, t, $J = 7$ Hz, CH_3), 1.88 (3H, s, CH_3), 2.98 (2H, br s, CH_2), 3.36 (2H, m, CH_2), 4.32 (2H, d, $J = 5.5$ Hz, N- CH_2), 4.36 (2H, q, $J = 7$ Hz, O- CH_2), 7.20 (1H, d, $J = 8.5$ Hz, H-6), 7.39 (1H, d, $J = 8.5$ Hz, H-7), 7.66 (1H, br s, H-4), 8.21 (3H, br s, NH_3^+), 8.37 (1H, t, $J = 5.5$ Hz, NH), 11.68 (1H, br s, NH). ^{13}C NMR (DMSO- d_6): 14.48 (CH_3), 22.75 (C-1'), 22.82 (CH_3), 39.90 (C-2'), 42.85 (C-1"), 60.56 (O- CH_2), 112.77 (C-7), 117.68 (C-3), 118.74 (C-6), 124.36 (C-2), 125.60 (C-4), 126.9 (C-3a), 131.13 (C-5), 135.60 (C-7a), 161.61 (CO), 169.17 (CO-NH). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_3\text{Cl}$: C, 56.55; H, 6.53. Found C, 56.72; H, 6.32.

3-(2-Dimethylaminoethyl)-5-methoxy-1H-indole-2-carboxylic acid ethyl ester (5f). To a stirred solution of **4f** (14.9 g, 50 mmol) in methanol (70 mL) was added formaldehyde (67 mL, 0.8 mol, 36% aqueous solution) during 15 min and the resulting mixture was stirred at 30°C for 1 h. NaBH_4 (15.1 g, 0.4 mol) was then added portionwise and stirring was maintained for 8 h. The solvent was evaporated in vacuo, the residue was taken up with CH_2Cl_2 (300 mL) and water (150 mL), the layers separated, and the water layer extracted with CH_2Cl_2 . The combined organic extracts were dried over MgSO_4 , the solvent evaporated in vacuo, and the residue recrystallized from benzene to yield **5f** (8.5 g, 59%). mp 130-132°C. TLC: $R_f = 0.26$ (benzene/ PrOH/MeOH 2:1:1, v/v). IR ν (KBr) cm^{-1} : 3350 (NH), 1695 (CO). ^1H NMR (CDCl_3 , δ , ppm): 1.30 (3H, t, $J = 7$ Hz, CH_3), 2.18 (6H, s, 2 CH_3), 2.60 (2H, m, CH_2), 3.12 (2H, m, CH_2), 3.80 (3H, s, O- CH_3), 4.42 (2H, q, $J = 7$ Hz, O- CH_2), 7.10 (1H, d, $J = 8$ Hz, H-6), 7.25 (1H, d, $J = 8$ Hz, H-7), 7.40 (1H, br s, H-4). Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_3$: C, 66.18; H, 7.64. Found: C, 65.91; H, 7.38.

3-(2-Dimethylaminoethyl)-5-fluoro-1H-indole-2-carboxylic acid ethyl ester (5c). As described for the preparation of **5f**, **4c** reacted with formaldehyde to give **5c** in 92% yield, mp 122-123°C (EtOH). TLC: R_f = 0.4 (CHCl₃/MeOH 10:1, v/v). IR ν (KBr) ppm: 3350 (NH), 1705 (CO). ¹H NMR (CDCl₃, δ , ppm): 1.38 (3H, t, J = 6 Hz, CH₃), 2.35 (6H, s, 2 CH₃), 2.50 (2H, m, CH₂), 3.16 (2H, m, CH₂), 4.42 (2H, q, J = 6 Hz, O-CH₂), 7.18 (1H, m, H-6), 7.45 (1H, m, H-7), 7.72 (1H, dd, J = 8 and 1 Hz, H-4), 11.15 (1H, br s, NH). Anal. Calcd for C₁₅H₁₉N₂O₂F: C, 64.73; H, 6.88. Found: C, 64.52; H, 7.09.

5-Chloro-3-(2-dimethylaminoethyl)-1H-indole-2-carboxylic acid ethyl ester (5d). As described for the preparation of **5f**, **4d** reacted with formaldehyde to give **5d** in 83% yield, mp 134-135°C. TLC: R_f = 0.46 (CHCl₃/MeOH 10:1, v/v). IR ν (KBr) cm⁻¹: 3200 (NH), 1710 (CO). ¹H NMR (CDCl₃, δ , ppm): 1.43 (3H, t, J = 6 Hz, CH₃), 2.35 (6H, s, 2 CH₃), 2.60 (2H, m, CH₂), 3.25 (2H, m, CH₂), 4.42 (2H, q, J = 6 Hz, CH₂-O), 7.22 (2H, m, H-6 and H-7), 7.65 (1H, d, J = 1 Hz, H-4), 9.22 (1H, s, NH). MS: m/z (%): 295 (M⁺, 3), 249 (3), 190 (4), 165 (2), 164 (4), 163 (4), 58 (100). Anal. Calcd for C₁₅H₁₉N₂O₂Cl: C, 61.11; H, 6.50. Found: C, 61.40; H, 6.42.

5-Bromo-3-(2-dimethylaminoethyl)-1H-indole-2-carboxylic acid ethyl ester (5e). In a similar manner as described for the preparation of **5f**, **4e** reacted with formaldehyde to afford **5e** in 94.3% yield, mp 126-127°C. TLC: R_f = 0.48 (CHCl₃/MeOH 10:1, v/v, satur. with NH₃). ¹H NMR (CDCl₃, δ , ppm): 1.42 (3H, t, J = 6 Hz, CH₃), 2.25 (6H, s, 2 CH₃), 2.55 (2H, m, CH₂), 3.24 (2H, m, CH₂), 4.40 (2H, q, J = 6 Hz, O-CH₂), 7.18 (2H, m, H-6 and H-7), 7.75 (1H, br s, H-4), 8.90 (1H, br s, NH), MS: m/z (%): 341 (80), 340 (22), 339 (M⁺, 100), 296 (13), 295 (16), 294 (16), 293 (16), 236 (40), 208 (36). Anal. Calcd for C₁₅H₁₉N₂O₂Br: C, 53.11; H, 5.65. Found: C, 53.00; H, 5.86.

5-Acetylaminomethyl-3-dimethylaminoethyl-1H-indole-2-carboxylic acid ethyl ester (5n). As described for the preparation of **5f**, **4n** reacted with formaldehyde to afford **5n** in 60% yield, mp 172-174°C. IR ν (KBr) cm⁻¹: 3380, 3300 (NH), 1700, 1650 (CO). ¹H NMR (DMSO-d₆, δ , ppm): 1.38 (3H, t, J = 7 Hz, CH₃), 1.98 (3H, s, CH₃), 2.32 (6H, s, 2 CH₃), 2.55 (2H, m, CH₂), 3.20 (2H, m, CH₂), 4.38 (2H, q, J = 7 Hz, O-CH₂), 6.24 (1H, m, NH), 7.13 (1H, d, J = 8 Hz, H-6), 7.35 (1H, d, J = 8 Hz, H-7), 7.59 (1H, br s, H-4), 9.35 (1H, br s, NH). Anal. Calcd for C₁₈H₂₅N₃O₃: C, 65.23; H, 7.60. Found: C, 65.50; H, 7.61.

3,4,5,6-Tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester Hydrochloride (9).

General Procedure. To a stirred solution of ester (**4**; 13 mmol) in ethanol (80 mL) was added dropwise formaldehyde (37% solution in water; 17 mL, 0.2 mol) at 70° and the pH of the mixture was adjusted to 4.5 by the addition of acetic acid. After stirring for 2 h at the same temperature, the solution became turbid, but stirring was continued for further 5 h. Upon cooling, light yellow crystals dropped out which were collected by filtration, washed with cold acetone, and recrystallized from EtOH to afford **9**.

7-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester Hydrochloride (9a). Following the general procedure, this compound was prepared from **4f** in 77% yield, mp 234-236°C (EtOH). TLC: R_f = 0.53 (benzene/PrOH/MeOH 2:1:1, v/v/v), IR ν (KBr) cm⁻¹: 3400 (NH),

1710 (CO). ^1H NMR (DMSO- d_6 -CDCl $_3$, δ , ppm): 1.42 (3H, t, J = 7 Hz, CH $_3$), 3.56 (4H, br s, 2 CH $_2$), 3.88 (3H, s, O-CH $_3$), 4.37 (2H, q, J = 7 Hz, O-CH $_2$), 4.50 (2H, s, CH $_2$), 7.13 (1H, d, J = 9 Hz, H-6), 7.46 (1H, d, J = 9 Hz, H-7), 9.88 (2H, br s, NH $_2^+$), 11.70 (1H, s, NH). ^{13}C NMR (DMSO- d_6 -CDCl $_3$, δ , ppm): 12.57 (CH $_3$), 23.63 (C-3), 45.04 (C-4), 45.25 (C-6), 55.02 (O-CH $_3$), 58.58 (O-CH $_2$), 109.77 (C-8), 110.74 (C-2a), 110.95 (C-9), 116.32 (C-6a), 122.18 (C-2), 123.05 (C-2b), 130.44 (C-9a), 147.83 (C-7), 159.62 (CO). Anal. Calcd for C $_{15}$ H $_{19}$ N $_2$ O $_3$ Cl: C, 57.97; H, 6.16; N, 9.02. Found: C, 57.97; H, 6.24; N, 9.07.

9-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester Hydrochloride (9b). This compound was obtained from **4g** in 58% yield according to the general procedure. mp 245-247°C. TLC: R_f = 0.36 (CHCl $_3$ /MeOH 10:1, v/v, satur. with NH $_3$). IR ν (KBr) cm $^{-1}$: 3410, 3300 (NH), 1705 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.35 (3H, t, J = 7 Hz, CH $_3$), 3.51 (4H, m, 2 CH $_2$), 3.92 (3H, s, O-CH $_3$), 4.31 (2H, q, J = 7 Hz, O-CH $_2$), 4.49 (2H, s, CH $_2$), 6.80 (1H, d, J = 8 Hz, H-8), 6.96 (1H, d, J = 8 Hz, H-7), 9.92 (2H, br s, NH $_2^+$), 11.79 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.41 (CH $_3$), 24.77 (C-3), 47.38 (C-4), 50.82 (C-6), 55.71 (O-CH $_3$), 60.51 (O-CH $_2$), 104.45 (C-8), 119.50 (C-7), 119.61 (C-6a), 120.56 (C-2a), 123.19 (C-2), 126.24 (C-2b), 127.40 (C-9a), 146.45 (C-9), 161.48 (CO). Anal. Calcd for C $_{15}$ H $_{19}$ N $_2$ O $_3$ Cl: C, 57.97; H, 6.16; N, 9.02. Found: C, 57.70; H, 6.00; N, 9.19.

7-Ethoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester Hydrochloride (9c). Following the general procedure, this compound was prepared from **4h** in 70% yield, mp 229-231°C. TLC: R_f = 0.52 (CHCl $_3$ /MeOH 10:1, v/v, satur. with NH $_3$). IR ν (KBr) cm $^{-1}$: 3280 (NH), 1705 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.49 (3H, t, J = 7 Hz, CH $_3$), 1.51 (3H, t, J = 7 Hz, CH $_3$), 3.57 (4H, m, 2 CH $_2$), 4.15 (2H, q, J = 7 Hz, O-CH $_2$), 4.41 (2H, q, J = 7 Hz, O-CH $_2$), 4.52 (2H, s, CH $_2$), 7.23 (1H, d, J = 8.5 Hz, H-8), 7.48 (1H, d, J = 7.5 Hz, H-9), 9.98 (2H, br s, NH $_2$), 11.83 (1H, s, NH). Anal. Calcd for C $_{16}$ H $_{21}$ N $_2$ O $_3$ Cl: C, 59.16; H, 6.52; N, 8.63. Found: C, 59.00; H, 6.62; N, 8.75.

7-Benzyloxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester Hydrochloride (9e). This compound was obtained from **4k** in 48% yield, mp 233-235°C. TLC: R_f = 0.50 (CHCl $_3$ /MeOH 10:1, v/v, satur. with NH $_3$). IR ν (KBr) cm $^{-1}$: 3420 (NH), 1715 (CO). ^1H NMR (DMSO- d_6 , δ , ppm): 1.36 (3H, t, J = 7 Hz, CH $_3$), 3.52 (4H, m, 2 CH $_2$), 4.35 (2H, q, J = 7 Hz, O-CH $_2$), 4.51 (2H, s, CH $_2$), 5.17 (2H, s, CH $_2$ -O), 7.28 (1H, d, J = 8.9 Hz, H-8), 7.34 (1H, t, J = 7 Hz, H-4"), 7.41 (2H, t, J = 7 Hz, H-3" and H-5"), 7.43 (1H, d, J = 8.9 Hz, H-9), 7.48 (2H, d, J = 7.5 Hz, H-2" and H-6"), 9.94 (2H, s, NH $_2^+$), 11.81 (1H, s, NH). ^{13}C NMR (DMSO- d_6 , δ , ppm): 14.49 (CH $_3$), 25.46 (C-3), 46.75 (C-4 and C-6), 60.60 (O-CH $_2$), 71.24 (O-CH $_2$), 112.69 (C-9), 113.69 (C-8), 113.91 (C-2a), 119.01 (C-6a), 123.81 (C-2), 124.98 (C-2b), 127.75 (C-2" and C-6"), 128.05 (C-4"), 128.65 (C-3" and C-5), 132.45 (C-9a), 137.53 (C-1"), 148.73 (C-7), 161.53 (CO). Anal. Calcd for C $_{21}$ H $_{23}$ N $_2$ O $_3$ Cl: C, 65.19; H, 5.99. Found: C, 64.90; H, 6.12.

5-Acetyl-7-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester (10a). To a stirred solution of **9a** (2.0 g, 6.4 mmol) in pyridine (70 mL) was added acetic anhydride (0.72 g, 7 mmol) and the resulting solution was stirred at rt overnight. Pyridine was then evaporated in vacuo and the pH of the remaining oil was adjusted to 10 by the addition of 25% NH $_4$ OH solution and extracted

with CH_2Cl_2 . The extract was washed with water, dried over MgSO_4 and concentrated in vacuo. The residue was subjected to chromatography ($\text{CHCl}_3/\text{CH}_3\text{OH}$ 10:0.1, v/v) to give **10a** (1.5 g, 74%) as white crystals. mp 197-198°C. TLC: R_f = 0.55 ($\text{CHCl}_3/\text{MeOH}$ 10:0.5, v/v). IR ν (KBr) cm^{-1} : 3200 (NH), 1705, 1640 (CO). ^1H NMR (CDCl_3 , δ , ppm): A 3:1 mixture of rotamers. Major component: 1.40 (3H, t, J = 6.5 Hz, CH_3), 2.11 (3H, s, CH_3), 3.52 (2H, m-t, J = 6 Hz, CH_2), 3.89 (3H, s, O- CH_3), 3.92 (2H, m-t, J = 6 Hz, CH_2 -N), 4.39 (2H, q, J = 6.5 Hz, O- CH_2), 4.90 (2H, s, CH_2), 7.06 (1H, d, J = 8 Hz, H-8), 7.28 (1H, d, J = 8 Hz, H-9), 8.78 (1H, br s, NH). Minor component: 1.42 (3H, t, J = 6.5 Hz, CH_3), 2.23 (3H, s, CH_3), 3.49 (2H, m-t J = 6 Hz, CH_2), 3.88 (2H, m-t, J = 6 Hz, CH_2 -N), 3.88 (3H, s, O- CH_3), 4.42 (2H, q, J = 6.5 Hz, O- CH_2), 5.08 (2H, s, CH_2), 7.05 (1H, d, J = 8 Hz, H-8), 7.22 (1H, d, J = 8 Hz, H-9), 8.72 (1H, br s, NH). MS: m/z (%): 316 (M^+ , 85), 287 (100), 273 (16), 245 (45), 199 (43), 184 (32). Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.26; H, 6.48; N, 8.62.

5-Formyl-7-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester (10b). Compound (**9a**) (0.78, 2.5 mmol) was dissolved in formic acid (5 mL) at 65°C and acetic anhydride (12.5 mL, 12.76 g, 0.125 mol) was added dropwise within 5 h. The resulting mixture was then left at rt for overnight. The reaction mixture was concentrated in vacuo and the residue was extracted with EtOAc. The organic solution was successively washed with satur. NaHCO_3 solution and water, dried, and concentrated. The residue was purified by column chromatography (hexane/acetone 10:1, v/v) to give **10b** (0.4 g, 53%). mp 203-205°C. TLC: R_f = 0.16 (hexane/acetone 5:2, v/v). IR ν (KBr) cm^{-1} : 3310 (NH), 1690, 1660 (CO). ^1H NMR (CDCl_3 - CD_3OD , δ , ppm): A 3:1 mixture of rotamers. Major component: 1.33 (3H, t, J = 7 Hz, CH_3), 3.41 (2H, t, J = 6 Hz, CH_2), 3.81 (3H, t, J = 6 Hz, CH_2), 3.82 (3H, s, J = 6 Hz, O- CH_3), 4.31 (2H, q, J = 7 Hz, O- CH_2), 4.78 (2H, s, CH_2), 6.96 (1H, d, J = 9 Hz, H-8), 7.22 (1H, d, J = 8 Hz, H-9), 8.14 (1H, s, H-CO). Minor component: 1.34 (3H, t, J = 7 Hz, CH_3), 3.38 (2H, t, J = 6 Hz, CH_2), 3.75 (3H, t, J = 6 Hz, CH_2), 3.84 (3H, s, J = 6 Hz, O- CH_3), 4.32 (2H, q, J = 7 Hz, O- CH_2), 4.92 (2H, s, CH_2), 6.95 (1H, d, J = 9 Hz, H-8), 7.17 (1H, d, J = 8 Hz, H-9), 8.23 (1H, s, H-CO). ^{13}C NMR (CDCl_3 - CD_3OD , δ , ppm): Major component: 14.74 (CH_3), 27.69 (C-3), 45.09 (C-4), 50.33 (C-6), 57.18 (O- CH_3), 61.36 (O- CH_2), 111.39 (C-9), 111.97 (C-8), 119.61 (C-6a), 121.59 (C-2a), 124.74 (C-2), 125.41 (C-2b), 132.68 (C-9a), 149.60 (C-7), 162.88 (CO), 163.23 (NCO). Minor component: 14.41 (CH_3), 28.32 (C-3), 44.22 (C-4), 48.83 (C-6), 57.54 (O- CH_3), 61.24 (O- CH_2), 111.34 (C-9), 112.90 (C-8), 119.61 (C-6a), 121.59 (C-2a), 124.74 (C-2), 125.41 (C-2b), 132.81 (C-9a), 149.60 (C-7), 162.84 (CO), 163.23 (NCO).

5-(2,2-Dimethylpropionyl)-7-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester (10c). To a stirred solution of **9a** (1.0 g, 3.2 mmol) in triethylamine (40 mL) was added pivaloyl chloride (0.67 g, 3.5 mmol) and the resulting solution was allowed to stand at rt overnight. Water was then added and the mixture was extracted with CH_2Cl_2 . The organic extract was washed with water, dried over MgSO_4 , and the solvent was evaporated under reduced pressure. The resultant solid residue was recrystallized from a mixture of ethanol and water to afford **10c** (0.65 g, 56%). mp 265°C. TLC: R_f = 0.80 ($\text{CHCl}_3/\text{MeOH}$ 10:1 v/v). IR ν (KBr) cm^{-1} : 3410, 3250 (NH), 1705, 1610 (NH). ^1H NMR (CDCl_3 , δ , ppm): 1.22 (9H, s, 3 CH_3), 1.40 (3H, t, J = 7 Hz, CH_3), 3.47 (2H, t, J = 6 Hz, CH_2), 3.90 (2H, m-t, J = 6 Hz,

CH₂), 3.91 (3H, s, O-CH₃), 4.39 (2H, q, $J = 7$ Hz, O-CH₂), 5.08 (2H, s, CH₂), 7.05 (1H, d, $J = 9$ Hz, H-8), 7.26 (1H, d, $J = 9$ Hz, H-9), 8.84 (1H, br s, NH). ¹³C NMR (CDCl₃, δ , ppm): 14.49 (CH₃), 27.49 (C-3), 28.32 (3CH₃), 38.75 (C-CO), 50.28 (C-4), 50.66 (C-6), 57.00 (O-CH₃), 60.92 (O-CH₂), 110.56 (C-9), 111.75 (C-8), 120.92 (C-6a), 122.49 (C-2a), 124.33 (C-2), 126.31 (C-2b), 132.38 (C-9a), 148.96 (C-7), 162.54 (CO), 176.75 (CON). MS: m/z (%): 358 (M^+ , 40), 329 (60), 273 (22), 245 (18), 184 (25), 57 (100). Anal. Calcd for C₂₀H₂₆N₂O₄: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.73, H, 7.23; N, 7.56.

5-Acetyl-7-ethoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester (10i)

As described for the preparation of 10a, 9c was reacted with acetic anhydride to give 10i in 56% yield, mp 173°C. TLC: $R_f = 0.71$ (CHCl₃/MeOH 10:1 v/v). IR ν (KBr) cm⁻¹: 3420, 3190 (NH), 1695, 1620 (CO). ¹H NMR: (DMSO-d₆, δ , ppm): A 3:1 mixture of rotamers. Major component: 1.31 (3H, t, $J = 7$ Hz, CH₃), 1.32 (3H, t, $J = 7$ Hz, CH₃), 1.91 (3H, s, CH₃), 3.30 (2H, m, CH₂), 3.75 (2H, t, $J = 5.6$ Hz, CH₂), 4.05 (2H, q, $J = 7$ Hz, O-CH₂), 4.30 (2H, q, $J = 7$ Hz, O-CH₂), 4.82 (2H, s, CH₂), 7.08 (1H, d, $J = 9$ Hz, H-8), 7.29 (1H, d, $J = 9$ Hz, H-9), 11.51 (1H, br s, NH). Minor component: 1.31 (3H, t, $J = 7$ Hz, CH₃), 1.32 (3H, t, $J = 7$ Hz, CH₃), 2.08 (3H, s, CH₃), 3.30 (2H, m, CH₂), 3.86 (2H, t, $J = 5.6$ Hz, CH₂), 4.01 (2H, q, $J = 7$ Hz, O-CH₂), 4.31 (2H, q, $J = 7$ Hz, O-CH₂), 4.90 (2H, s, CH₂), 7.05 (1H, d, $J = 9$ Hz, H-8), 7.26 (1H, d, $J = 9$ Hz, H-9), 11.50 (1H, br s, NH). ¹H NMR at 70°C: 1.34 (3H, t, $J = 7$ Hz, CH₃), 1.35 (3H, t, $J = 7$ Hz, CH₃), 2.00 (3H, br s, CH₃), 3.37 (2H, t, $J = 5.8$ Hz, CH₂), 3.83 (2H, br s, CH₂), 4.07 (2H, q, $J = 7$ Hz, O-CH₂), 4.34 (2H, q, $J = 7$ Hz, O-CH₂), 4.89 (2H, br s, CH₂), 7.04 (1H, d, $J = 9$ Hz, H-8), 7.30 (1H, d, $J = 9$ Hz, H-9), 11.07 (1H, br s, NH). ¹³C NMR (DMSO-d₆, δ , ppm): Major component: 14.53 (CH₃), 15.37 (CH₃), 21.14 (CH₃-CO), 26.47 (C-3), 44.04 (C-4), 49.70 (C-6), 60.33 (O-CH₂), 65.74 (O-CH₂), 111.82 (C-9), 114.31 (C-8), 120.30 (C-6a), 121.17 (C-2a), 123.75 (C-2), 125.30 (C-2b), 132.92 (C-9a), 147.87 (C-7), 161.80 (CO), 169.18 (CON). Minor component: 14.53 (CH₃), 15.37 (CH₃), 21.66 (CH₃-CO), 28.94 (C-3), 47.17 (C-4), 49.70 (C-6), 60.61 (O-CH₂), 65.64 (O-CH₂), 111.24 (C-9), 114.10 (C-8), 120.57 (C-6a), 120.97 (C-2a), 123.60 (C-2), 125.30 (C-2b), 132.89 (C-9a), 148.41 (C-7), 161.71 (CO), 168.74 (CON). MS: m/z (%): 330 (M^+ , 60), 301 (92), 287 (14), 259 (48), 213 (44), 184 (32), 43 (100). Anal. Calcd for C₁₈H₂₂N₂O₄: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.15; H, 6.48; N, 8.20.

7-Ethoxy-5-formyl-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid ethyl ester (10j)

As described for the preparation of 10b, 9c reacted with formic acid and acetic anhydride to afford 10j (0.48 g, 58%). mp 164-165°C. TLC: $R_f = 0.82$ (CHCl₃/MeOH) 10:1, v/v). IR ν (KBr) cm⁻¹: 3180 (NH), 1700, 1660 (CO). ¹H NMR (CDCl₃, δ , ppm): A 3:1 mixture of rotamers. Major component: 1.39 (3H, t, $J = 7$ Hz, CH₃), 1.44 (3H, t, $J = 7$ Hz, CH₃), 3.49 (2H, t, $J = 6$ Hz, CH₂), 3.87 (2H, t, $J = 6$ Hz, CH₂), 4.09 (2H, q, $J = 7$ Hz, O-CH₂), 4.38 (2H, q, $J = 7$ Hz, O-CH₂), 4.86 (2H, s, CH₂), 7.01 (1H, d, $J = 9$ Hz, H-8), 7.26 (1H, d, $J = 9$ Hz, H-9), 8.26 (1H, s, HCO), 9.27 (1H, br s, NH). Minor component: 1.39 (3H, t, $J = 7$ Hz, CH₃), 1.44 (3H, t, $J = 7$ Hz, CH₃), 3.44 (2H, t, $J = 6$ Hz, CH₂), 3.80 (2H, t, $J = 6$ Hz, CH₂), 4.05 (2H, q, $J = 7$ Hz, O-CH₂), 4.39 (2H, q, $J = 7$ Hz, O-CH₂), 5.01 (2H, s, CH₂), 6.98 (1H, d, $J = 9$ Hz, H-8), 7.21 (1H, d, $J = 9$ Hz, H-9), 8.34 (1H, s, HCO), 9.21 (1H, br s, NH). ¹³C NMR (CDCl₃, δ , ppm): Major component: 14.44 (CH₃), 15.32 (CH₃), 27.41 (C-3), 44.64 (C-4), 50.01 (C-6), 60.93 (O-CH₂), 65.32 (O-CH₂), 110.96

(C-9), 112.88 (C-8), 119.84 (C-6a), 121.35 (C-2a), 124.35 (C-2), 125.70 (C-2b), 132.34 (C-9a), 148.52 (C-7), 162.30 (HCO), 162.40 (CO). Minor component: 14.22 (CH₃), 15.07 (CH₃), 26.71 (C-3), 44.04 (C-4), 48.33 (C-6), 60.80 (O-CH₂), 65.67 (O-CH₂), 110.56 (C-9), 112.30 (C-8), 119.99 (C-6a), 120.73 (C-2a), 123.76 (C-2), 125.89 (C-2b), 132.22 (C-9a), 149.45 (C-7), 162.06 (CO), 162.69 (HCO). MS: *m/z* (%): 316 (M⁺, 82), 287 (100), 270 (23), 241 (45), 213 (42), 185 (38), 169 (22). Anal. Calcd for C₁₇H₂₀N₂O₄: C, 64.54; H, 6.37. Found: C, 64.41; H, 6.62.

5-(2,2-Dimethylpropionyl)-7-ethoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester (10k). In a similar manner as described before for the preparation of 10c, 9c reacted with pivaloyl chloride to give 10k in 59% yield, mp 215°C (EtOH-H₂O). TLC: R_f = 0.85 (CHCl₃/MeOH 10:1, v/v). IR ν (KBr) cm⁻¹: 3280 (NH), 1695, 1610 (CO). ¹H NMR (CDCl₃, δ, ppm): 1.21 (9H, s, 3CH₃), 1.38 (3H, t, *J* = 7 Hz, CH₃), 1.43 (3H, t, *J* = 7 Hz, CH₃), 3.45 (2H, t, *J* = 5.7 Hz, CH₂), 3.89 (2H, t, *J* = 5.7 Hz, CH₂), 4.09 (2H, q, *J* = 7 Hz, O-CH₂), 4.37 (2H, q, *J* = 7 Hz, O-CH₂), 5.22 (2H, s, CH₂), 7.00 (1H, d, *J* = 9 Hz, H-8), 7.23 (1H, d, *J* = 9 Hz, H-9), 8.26 (1H, s, HCO), 9.11 (1H, br s, NH). ¹³C NMR (CDCl₃, δ, ppm): 14.48 (CH₃), 15.44 (CH₃), 27.53 (C-3), 28.31 (3CH₃), 38.74 (CO-C), 50.28 (C-4), 50.74 (C-6), 60.89 (O-CH₂), 65.36 (O-CH₂), 110.67 (C-9), 113.01 (C-8), 121.16 (C-6a), 122.49 (C-2a), 124.22 (C-2), 126.23 (C-2b), 132.50 (C-9a), 148.23 (C-7), 162.68 (CO), 176.74 (NCO). MS: *m/z* (%): 372 (M⁺, 40), 343 (58), 287 (18), 259 (16), 242 (28), 213 (16), 57 (100). Anal. Calcd for C₂₁H₂₈N₂O₄: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.46; H, 7.47; N, 7.52.

(7-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indol-2-yl)methanol (10d). To stirred suspension of lithium aluminum hydride (1.5 g, 40 mmol) in dry tetrahydrofuran (170 mL) was added 9a (4.0 g, 13 mmol) portionwise at 0°C, and the resulting mixture was stirred at 0°C for 20 min, and then heated up to 55°C for 4 h. After cooling, the reaction was quenched by the dropwise addition of water and the precipitate was filtered off. The organic layer was separated and extracted three times with CH₂Cl₂. The combined organic solutions were washed with water, dried over MgSO₄ and the evaporation of solvent in vacuo gave 10d (2.0 g, 67%), mp 202-203°C. TLC: R_f = 0.1 (MeOH/CHCl₃/*i*-PrOH 1:1:1, v/v/v). IR ν (KBr) cm⁻¹: 3300 (NH), 3260 (OH). ¹H NMR (DMSO-*d*₆-CDCl₃, δ, ppm): 2.90 (2H, t, *J* = 4 Hz, CH₂), 3.14 (2H, t, *J* = 4 Hz, CH₂), 3.20 (2H, m, OH, NH), 3.78 (3H, s, O-CH₃), 4.24 (2H, s, CH₂), 4.62 (2H, s, CH₂), 6.74 (1H, d, *J* = 8.5 Hz, H-8), 7.13 (1H, d, *J* = 8.5 Hz, H-9), 10.15 (1H, s, NH). ¹³C NMR (DMSO-*d*₆-CDCl₃, δ, ppm): 30.27 (C-3), 50.10 (C-4), 50.57 (C-6), 55.72 (O-CH₃), 57.12 (CH₂-O), 107.39 (C-8), 108.79 (C-9), 110.03 (C-2a), 122.47 (C-4a), 126.95 (C-2b), 131.78 (C-2), 135.53 (C-9a), 148.55 (CO). Anal. Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94. Found: C, 66.94; H, 7.04.

(7-Methoxy-5-methyl-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indol-2-yl)methanol (10e). The title compound was isolated as a side product of the above reaction. mp 208-210°C. TLC: R_f = 0.22 (benzene/PrOH/MeOH 2:1:1, v/v/v). ¹H NMR (DMSO-*d*₆-CDCl₃, δ, ppm): 2.48 (3H, s, N-CH₃), 2.89 (2H, m, CH₂), 2.96 (2H, m, CH₂), 3.74 (3H, s, O-CH₃), 3.98 (2H, s, CH₂), 4.55 (2H, d, *J* = 5.5 Hz, CH₂-O), 4.99 (1H, t, *J* = 5.5 Hz, OH), 6.72 (1H, d, *J* = 9 Hz, H-8), 7.12 (1H, d, *J* = 9 Hz, H-9), 10.48 (1H, br s, NH). ¹³C NMR (DMSO-*d*₆-CDCl₃, δ, ppm): 25.36 (C-3), 43.85 (N-CH₃), 54.98 (C-4), 56.17 (C-6), 56.68 (O-

CH₃), 57.50 (CH₂-O), 107.32 (C-8), 108.12 (C-9), 109.43 (C-2a), 119.24 (C-6a), 126.38 (C-6a), 130.79 (C-2), 134.24 (C-9a), 148.55 (C-7). MS: *m/z* (%): 246 (M⁺, 86), 245 (52), 228 (32), 215 (14), 213 (16), 203 (100), 186 (52), 172 (23).

(5-Acetyl-7-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indol-2-yl)methyl Acetate (10f). To a stirred solution of **10d** (1.6 g, 7 mmol) in dry pyridine (50 mL) was added acetic anhydride (1.67 g, 17 mmol) and the resultant mixture was stirred at rt overnight. Pyridine was then evaporated in vacuo and the pH of the oily residue was adjusted to 10 by the addition of 25% NH₄OH solution, and then extracted with CH₂Cl₂. The organic layer was washed with 2N NaOH solution and water, and dried over MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with hexane/acetone (2:1) as eluent to afford **10f** (1.1 g, 51%), mp 153-155°C. TLC: R_f = 0.8 (CHCl₃/MeOH 10:1, v/v). IR ν (KBr) cm⁻¹: 3300 (NH), 1720, 1640, 1625 (CO). ¹H NMR (CDCl₃, δ , ppm): A 4:1 mixture of rotamers. Major component: 2.07 (3H, s, CH₃), 2.10 (3H, s, CH₃), 3.18 (2H, t, *J* = 5.5 Hz, CH₂), 3.87 (3H, s, O-CH₃), 3.92 (2H, t, *J* = 5.5 Hz, CH₂-N), 4.88 (2H, s, CH₂), 5.16 (2H, s, O-CH₂), 6.90 (1H, d, *J* = 9 Hz, H-8), 7.19 (1H, d, *J* = 9 Hz, H-9), 8.58 (1H, br s, NH). Minor component: 2.08 (3H, s, CH₃), 2.22 (3H, s, CH₃), 3.18 (2H, t, *J* = 5.5 Hz, CH₂), 3.85 (3H, s, O-CH₃), 3.92 (2H, t, *J* = 5.5 Hz, CH₂-N), 5.08 (2H, s, CH₂), 5.18 (2H, s, O-CH₂), 6.88 (1H, d, *J* = 9 Hz, H-8), 7.15 (1H, d, *J* = 9 Hz, H-9), 8.52 (1H, br s, NH). MS: *m/z* (%): 316 (M⁺, 18), 256 (85), 213 (33), 197 (52), 43 (100). Anal. Calcd for C₁₇H₂₀N₂O₄: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.26; H, 6.29; N, 8.58.

5-Acetyl-7-nonyloxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-*cd*]indole-2-carboxylic acid ethyl ester (10l). To a stirred solution of **4i** (1.0 g, 2.5 mmol) in ethanol (20 mL) was added dropwise formaldehyde (37% solution in water, 3 mL, 37 mmol) at 60°C and the pH of the solution was adjusted to 4.5 by the addition of acetic acid. Stirring was continued for 20 h at the same temperature and the solvent was evaporated in vacuo. The yellow residue (crude **9d**) was dissolved in pyridine (10 mL) and after adding acetic acid anhydride (0.2 g, 1.96 mmol), the resulting mixture was left at rt overnight. The pyridine was evaporated in vacuo and the residue was purified by column chromatography (hexane/acetone 1:1, v/v) to afford **10l** (0.2 g, 19.2 %) as a 3:1 mixture of rotamers. mp 104-107 °C. TLC: R_f = 0.76 (hexane/acetone 5:2, v/v). IR ν (KBr) cm⁻¹: 3400 (NH), 1700, 1635, 1625 (CO). ¹H NMR (CDCl₃, δ , ppm): A 3:1 mixture of rotamers. Major component: 0.88 (3H, t, *J* = 7 Hz, CH₃), 1.29 (8H, m, 4CH₂), 1.36 (2H, m, CH₂), 1.40 (3H, t, *J* = 7.1 Hz, CH₃), 1.49 (2H, m, CH₂), 1.81 (2H, m, CH₂), 2.11 (3H, s, CH₃), 3.51 (2H, t, *J* = 5.8 Hz, CH₂), 3.92 (2H, t, *J* = 5.8 Hz, CH₂), 4.02 (2H, t, *J* = 6.5 Hz, O-CH₂), 4.38 (2H, q, *J* = 7 Hz, O-CH₂), 4.91 (2H, s, CH₂) 7.02 (1H, d, *J* = 9 Hz, H-8), 7.25 (1H, d, *J* = 9 Hz, H-9), 8.97 (1H, br s, NH). Minor component: 0.88 (3H, t, *J* = 7 Hz, CH₃), 1.29 (8H, m, 4CH₂), 1.36 (2H, m, CH₂), 1.41 (3H, t, *J* = 7 Hz, CH₃), 1.49 (2H, m, CH₂), 1.81 (2H, m, CH₂), 2.24 (3H, s, CH₃), 3.48 (2H, t, *J* = 5.8 Hz, CH₂), 3.90 (2H, t, *J* = 5.8 Hz, CH₂), 4.00 (2H, t, *J* = 6.5 Hz, O-CH₂), 4.40 (2H, q, *J* = 7 Hz, O-CH₂), 5.09 (2H, s, CH₂) 7.00 (1H, d, *J* = 9 Hz, H-8), 7.19 (1H, d, *J* = 9 Hz, H-9), 8.90 (1H, br s, NH). ¹³C NMR (CDCl₃, δ , ppm): Major component: 14.10 (C-9'), 14.47 (CH₃), 21.97 (CH₃-CO), 22.67 (C-8'), 26.26 (C-3'), 26.97 (C-3), 29.27 (C-6'), 29.42 (C-4'), 29.59 (C-5'), 29.77 (C-2'), 31.89 (C-7'), 47.86 (C-4), 50.39 (C-6), 60.92 (O-CH₂),

70.11 (C-1'), 110.89 (C-9), 113.20 (C-8), 120.11 (C-6a), 122.01 (C-2a), 124.31 (C-2), 126.27 (C-2b), 132.22 (C-9a), 148.71 (C-7), 162.45 (CO), 170.74 (NCO). Minor component: 14.10 (C-9'), 14.52 (CH₃), 21.32 (CH₃-CO), 22.61 (C-8'), 26.16 (C-3'), 29.22 (C-3), 29.31 (C-6'), 29.50 (C-4'), 29.55 (C-5'), 29.81 (C-2'), 31.89 (C-7'), 46.85 (C-6), 49.53 (C-4), 60.76 (O-CH₂), 70.67 (C-1'), 110.27 (C-9), 114.48 (C-8), 121.26 (C-6a), 121.35 (C-2a), 124.80 (C-2), 126.06 (C-2b), 132.22 (C-9a), 149.67 (C-7), 161.98 (CO), 169.91 (NCO).

7-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole (10h). A solution of **9a** (1.7 g, 5.5 mmol) in 4N NaOH (16 mL) was refluxed with stirring for 2 h. After cooling the solution to 0°C, the pH was adjusted to 3 by adding acetic acid and then the precipitate formed was collected by filtration and washed with water to furnish the acetic acid salt of **7-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid (10g)**, 1.08 g, 80%). mp 230 °C (decomp). TLC: R_f = 0.05 (CHCl₃/MeOH 10:1, v/v). IR (KBr) cm⁻¹: 3400, 3300, 1680, 1620. ¹H NMR: (DMSO-d₆, δ, ppm): 1.85 (3H, s, CH₃), 3.10 (2H, m, CH₂), 3.34 (2H, m, CH₂), 3.75 (3H, s, OCH₃), 4.20 (2H, s, CH₂), 6.86 (1H, d, J = 8.5 Hz, H-8), 7.19 (1H, d, J = 8.5 Hz, H-9), 10.53 (1H, s, NH). ¹³C NMR (DMSO-d₆, δ, ppm): 21.85 (CH₃), 30.66 (C-3), 49.27 (C-4), 57.19 (OCH₃), 109.54 (C-9), 109.96 (C-8), 126.78 (C-2b), 130.98 (C-9a), 148.26 (C-7), 166.05 (CO), 172.49 (CO).

A suspension of **10g** (1.0 g, 4 mmol) in 15% H₂SO₄ (17 mL) was refluxed with stirring for 2.5 h. After cooling, the reaction mixture was alkalized with aqueous 10% NaOH solution (pH = 8.5) and the precipitate solid was collected by filtration to afford **10h** (0.32 g, 40%). mp 250 °C. TLC: R_f = 0.20 (CHCl₃/MeOH 10:1, v/v). IR (KBr) cm⁻¹: 3410, 3320, 1580. ¹H NMR: (DMSO-d₆, δ, ppm): 2.90 (2H, m, CH₂), 2.98 (2H, m, CH₂), 3.73 (3H, s, OCH₃), 4.12 (2H, s, CH₂), 6.79 (1H, d, J = 8.8 Hz, H-8), 7.11 (1H, d, J = 8.8 Hz, H-9), 10.59 (1H, s, NH). MS: m/z (%) 203 (M+H⁺, 100), 188 (26), 175 (40), 174 (17).

9-Methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole (10n). A solution of **9b** (0.93 g, 3 mmol) in 4N NaOH (9 mL) was refluxed with stirring for 2 h. After cooling the solution to 0°C, the pH was adjusted to 3 by adding acetic acid and then the precipitate formed was collected by filtration to afford the acetic acid salt of **9-methoxy-3,4,5,6-tetrahydro-1H-azepino[5,4,3-cd]indole-2-carboxylic acid (10m)**, 0.6 g, 66%). mp 240 °C (decomp). TLC: R_f = 0.08 (CHCl₃/MeOH 10:1, v/v). IR (KBr) cm⁻¹: 3430, 3220, 1640, 1560. ¹H NMR: (DMSO-d₆, δ, ppm): 1.86 (3H, s, CH₃), 3.10 (2H, t, J = 5.5 Hz, CH₂), 3.34 (2H, t, J = 5.5 Hz, CH₂), 3.59 (3H, br s, OH, NH), 3.86 (3H, s, OCH₃), 4.16 (2H, s, CH₂), 6.56 (1H, d, J = 7.8 Hz, H-8), 6.63 (1H, d, J = 7.8 Hz, H-7), 9.79 (1H, s, NH). ¹³C NMR (DMSO-d₆, δ, ppm): 21.98 (CH₃), 30.57 (C-3), 50.11 (C-4), 54.91 (C-6), 55.49 (OCH₃), 102.11 (C-8), 115.81 (C-7), 116.61 (C-2a), 124.82 (C-2), 127.94 (C-6a), 128.06 (C-2b), 131.20 (C-9a), 144.65 (C-9), 165.68 (CO), 172.63 (CO).

A suspension of **10m** (0.5 g, 2 mmol) in 10% H₂SO₄ (10 mL) was refluxed with stirring for 3.5 h. After cooling, aqueous 10% NaOH solution was added to adjust the pH to 8-9 and the precipitated solid was collected by filtration. This solid was taken up into CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated in vacuo to yield **10n** (0.2 g, 50%). mp 179-183 °C. TLC: R_f = 0.19 (CHCl₃/MeOH 10:1, v/v). IR (KBr) cm⁻¹: 3400, 3300, 1600, 1580. ¹H NMR: (CDCl₃, δ, ppm): 2.66 (1H, br s, NH), 3.06 (2H, t, J =

5.5 Hz, CH₂), 3.25 (2H, t, J = 5.5 Hz, CH₂), 3.92 (3H, s, OCH₃), 4.30 (2H, s, CH₂), 6.45 (1H, d, J = 7.7 Hz, H-8), 6.73 (1H, d, J = 7.7 Hz, H-7), 6.95 (1H, s, H-2), 8.51 (1H, br s, NH). ¹³C NMR (CDCl₃, δ , ppm): 30.86 (C-3), 50.96 (C-4), 55.44 (OCH₃), 101.45 (C-8), 115.72 (C-2a), 116.21 (C-7), 120.70 (C-2), 126.95 (C-2b), 127.21 (C-6a), 128.46 (C-9a), 144.70 (C-9). MS: m/z (%): 203 (M+H⁺, 100), 188 (22), 186 (20), 176 (34), 161 (8).

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