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Use of the Pictet–Spengler reaction for the synthesis of 1,4-disubstituted-1,2,3,4-tetrahydro-β-carbolines and 1,4-disubstituted-β-carbolines: formation of γ-carbolines

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Abstract

Microwave-assisted conjugate addition of indole on nitro-olefins furnished nitro compounds, which were reduced to tryptamines. Further, by using Pictet–Spengler condensation, new 1,4-disubstituted-1,2,3,4-tetrahydro-β-carbolines were synthesized in diastereoselective manner. Dehydrogenation of the tetrahydro-β-carbolines produced new 1,4-disubstituted-β-carbolines. As a new observation, in some of the cases, Pictet–Spengler condensation and dehydrogenation gave two products, namely 1,4-disubstituted-β-carbolines and 1,4-disubstituted-γ-carbolines. A mechanism is proposed for this observation.

Keywords: 1,4-Disubstituted-β-carboline; 1,4-Disubstituted-γ-carboline; Pictet–Spengler reaction; 1,4-Disubstituted-1,2,3,4-tetrahydro-β-carboline; 1,4-Disubstituted-1,2,3,4-tetrahydro-γ-carboline

1. Introduction

Tetrahydro-β-carbolines (THβCs) are potent neuroactive alkaloids.[1] THβCs as pharmacophores have exhibited a wide range of pharmacological properties. They have been shown to inhibit monoamine oxidase A and bind with nanomolar affinity to serotonin receptors.[2] THβCs also bind to GABA, a receptor ion channel and modulate molecular mechanisms controlling anxiety, convulsions, and sleep.[3a,b] β-Carbolines exhibit many important biological activities like mutagenic and co-mutagenic properties, significant anti-tumor and anti-HIV activities, and inhibition of topoisomerase I.[4a–c]

The Pictet–Spengler condensation is the most widely used and extensively studied method for the synthesis of tetrahydro-β-carbolines. Amongst the variously substituted THβCs, very few reports are available typically for the 1,4-disubstituted THβCs,[5a–c] and also for 1,4-disubstituted-β-carbolines.[6a–d] Recently, we have reported preliminary results about the conjugate addition of indole on nitro-olefins using microwave technology.[7] In continuation with those results we report herein further conversion of the nitro compounds to new 1,4-disubstituted-tetrahydro-β-carbolines and then to new β-carbolines. Surprisingly γ-carbolines are also obtained during the Pictet–Spengler condensation and dehydrogenation in some cases.

2. Results and discussions

Initially, indole was treated with methyl magnesium iodide to get indolyl magnesium iodide, which on reaction with nitrostyrene **1** at room temperature gave the expected Michael addition product **12a** in 71% yield in 5 min (Scheme 1). The same product **12a** was obtained in 80% yield when indole and nitrostyrene **1** in dry benzene were heated at 120 °C in a sealed tube for 2 days. When the reactants were loaded on silica gel and kept at room temperature for 1 or 2 h, the product **12a** was produced in quantitative yields. A microwave-assisted reaction was also carried where indole and nitrostyrene **1** were loaded on silica gel (60–120 mesh) and then irradiated

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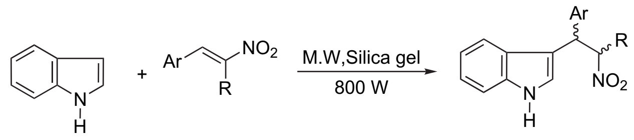


12a: Ar = phenyl, R = H; **12b**: Ar = 3,4-dimethoxyphenyl, R = H;
12c: Ar = 3,4-methylenedioxyphenyl, R = H; **12d**: Ar = 2-furyl, R = H;
12e: Ar = *p*-nitrophenyl, R = H; **12f**: Ar = 2-thienyl, R = H;
12g: Ar = *p*-methoxyphenyl, R = H; **12h**: Ar = *m*-methoxyphenyl, R = H;
12i: Ar = 2-furyl, R = CH_3, **12j**: Ar = *p*-methoxyphenyl, R = CH_3;
12k: Ar = *p*-nitrophenyl, R = CH_3

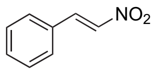
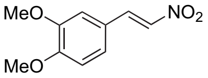
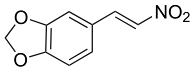
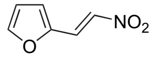
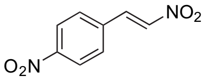
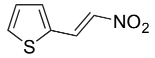
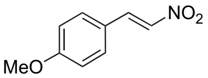
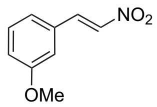
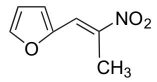
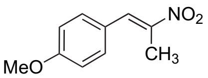
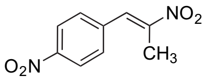
Scheme 1.

in a microwave oven (domestic Daewoo 616T) for 2 min to get **12a** in 95% yield. From these results, it was concluded that the microwave-assisted reaction was the most efficient method with respect to time and yield.

Reactions of various other nitro-olefins (**2**–**8**) and indole under microwave irradiation furnished products (**12b**–**12h**) in good yields (Scheme 1, Table 1). Alkylation of indole with α-methyl-nitro-alkenes (**9**–**11**) using microwave irradiation produced the corresponding Michael addition products (**12i**–**12k**) in good yields (Scheme 1, Table 1). The ^{1}H NMR spectra of **12i**–**12k** revealed the presence of diastereomers in the ratio of 2.3:1 for **12i**, 1.1:1 for **12j** and 1:1 for **12k**.

After generalizing the conjugate addition of indole, the nitro compound **12a** was reduced using freshly prepared Raney Nickel in methanol to obtain the substituted tryptamine **13a**. Treatment of amine **13a** with benzaldehyde in the presence of trimethylsilylchloride in dichloromethane furnished 1,4-di-substituted-tetrahydro-β-carboline **14a**. The product **14a** was a single diastereomer (probably *trans* isomer similar to the earlier report[5]), which was confirmed using ^{1}H NMR, ^{13}C NMR, IR, DEPT, elemental analysis and mass spectra. Further

Table 1
Time and yields for Michael adducts **12a**–**12k**

Entry	Electrophile	Product	Grignard reaction		Sealed tube reaction		Microwave reaction	
			Time	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)
1		**12a**	5 min	71	48[a]	80	2	95
2		**12b**	20 h	73	72[b]	53	10	80
3		**12c**	20 h	73	72[b]	60	10	89
4		**12d**	5 min	60	48[a]	85	2	86
5		**12e**	5 min	35	48[b]	65	10	84
6		**12f**	5 min	58	48[a]	82	2	93
7		**12g**		—	—	—	10	92
8		**12h**	—	—	—	—	10	94
9		**12i**	—	—	—	—	20	96
10		**12j**	—	—	—	—	1	87
11		**12k**	—	—	—	—	1	82

[a] Heating at 120 °C.
[b] Heating at 140 °C.

dehydrogenation by refluxing with Pd/C (5%) in xylene furnished 1,4-disubstituted-β-carboline **15a**. There is a report of formation of two diastereomers in a similar Pictet–Spengler condensation using sulfuric acid in water.[5a] In contrast to this, condensation using trimethylsilylchloride in dichloromethane gave diastereoselectively only one product **14a**.

After establishing the route from nitro compound **12a** to β-carboline **15a**, all nitro compounds (**12b**–**12f** and **12i**) were reduced with freshly prepared Raney Nickel in methanol to amino compounds (**13b**–**13f** and **13i**). The nitro compound **12e** gave reduction of aromatic nitro group (**13l**) initially. After continuing the reaction for longer time, both the nitro groups were reduced to get **13e**.

Further, treatment of amino compounds (**13b**–**13f**) with benzaldehyde in the presence of trimethylsilylchloride in dichloromethane furnished new 1,4-disubstituted THβCs (**14b**–**14f**, Scheme 2). In this reaction, amines **13a** and **13d**–**13f** gave only one product in each reaction while the amines **13b** and **13c** furnished two products. The products were separated and characterized. On the basis of the spectral data, the products were initially considered to be diastereomeric mixture of **14b** and **14c**, respectively. Surprisingly during the Pictet–Spengler reaction with **13d**, 1,4-disubstituted-β-carboline was also detected in 10% yield along with THβC **14d**. In all other similar reactions, TLC indicated the presence of dehydrogenated product in minor amount.

In the last step, refluxing THβCs (**14b**–**14d**) with Pd/C in xylene furnished 1,4-disubstituted-β-carbolines (**15b**–**15d**). Surprisingly, when the diastereomeric mixture of **14b** was dehydrogenated, two products were resulted, which was not expected from the mixture of diastereomers of tetrahydro-β-carbolines. Both of them were showing only aromatic protons and carbons in ^{1}H NMR and ^{13}C NMR, respectively. The mass spectrum showed M^+ at 380 for both the compounds. The spectral data was not sufficient to confirm the structures of these compounds. Finally these products were shown to be β-carboline **15b** and γ-carboline **17b** by single crystal X-ray analysis (Figs. 1 and 2). It was noted from ^{1}H NMR data that β-carboline showed C_3–H (8.45), upfield than that of γ-carboline (8.56). Protons of two methoxyl groups were resonating at different positions (4.01 and 3.91) in the case of β-carboline, however, they showed a singlet (3.96) in γ-carboline. Surprisingly, in ^{13}C NMR, β-carboline showed only one singlet (56.0) for both the methoxyls while γ-carboline indicated two singlets (56.1 and 56.0).

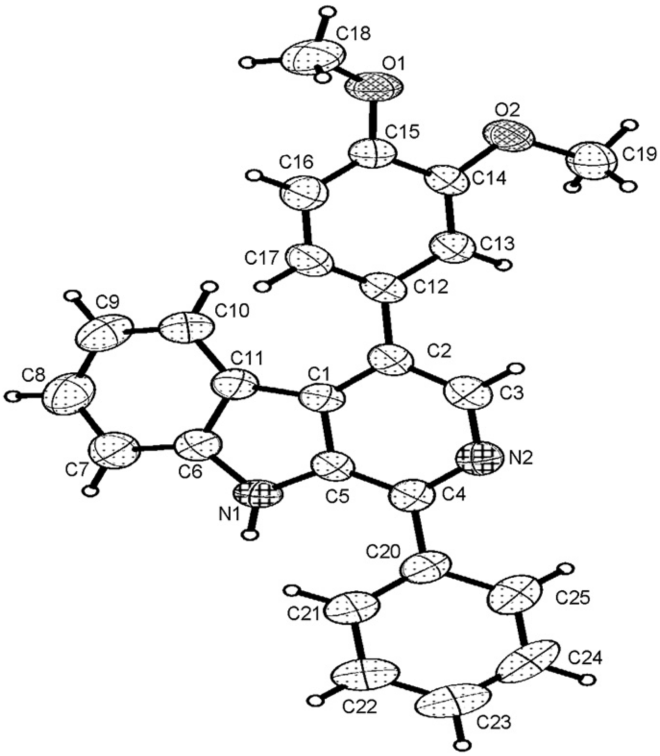
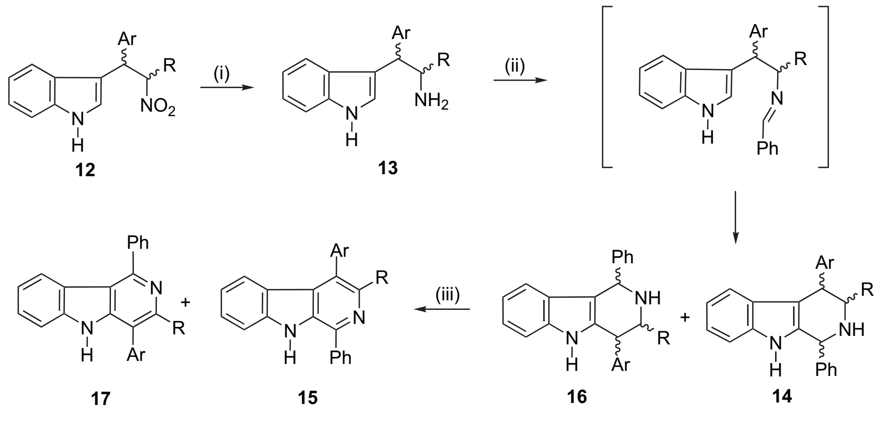


Figure 1. ORTEP diagram of the **15b** molecule with 50% probability.

The formation of two dehydrogenated products ruled out the possibility of formation of two diastereomers of THβCs in the previous reaction. From the mode of formation, the two products formed in the Pictet–Spengler condensation were shown



12a, **13a**, **14a**, **15a**: Ar = phenyl, R = H; **12b**, **13b**, **14b**, **15b**, **16b**, **17b**: Ar =3,4-dimethoxyphenyl, R = H; **12c**, **13c**, **14c**, **15c**, **16c**, **17c**: Ar = 3,4-methylenedioxyphenyl, R = H; **12d**, **13d**, **14d**, **15d**: Ar = 2-furyl, R = H; **12e**, **13e**, **14e**: Ar = *p*-aminophenyl, R = H; **12f**, **13f**, **14f**: Ar = 2-thienyl, R = H; **12i**, **13i**: Ar = 2-furyl, R = methyl.

Scheme 2. Reagents and conditions: (i) Raney Nickel/MeOH; (ii) $Si(CH_3)_3Cl$, PhCHO, DCM, 88 h, 0–25 °C; (iii) Pd/C (5%), xylene, reflux.

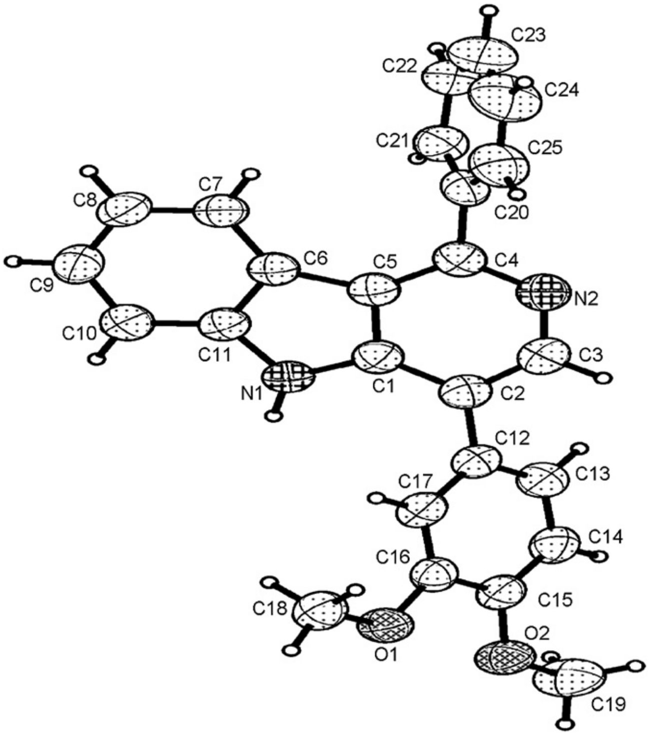
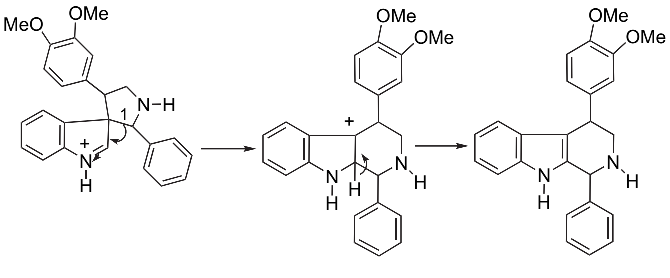
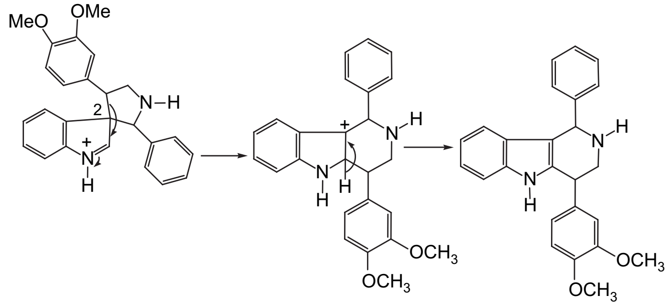


Figure 2. ORTEP diagram of the **17b** molecule with 50% probability.



Bond 1 migration.



Bond 2 migration.

Scheme 3.

to be tetrahydro-β-carboline **14b** and tetrahydro-γ-carboline **16b**. Dehydrogenation of **14c** gave similar results (Table 2).

The formation of two diastereomers of **14a** in the reported[5a] reaction using sulfuric acid in water was confirmed by the dehydrogenation of the mixture of diastereomers using Pd/C (5%), which resulted in the formation of only one product **15a**.

The formation of two regioisomers **14b** and **16b** could be explained as follows. The reported mechanism for the Pictet–Spengler condensation is through the five-membered spiro intermediate,[8] which would rearrange to six-membered heterocyclic ring. There are two possibilities for this rearrangement. Migration of bond 1 would give 1,4-disubstituted-tetrahydro-β-carboline **14b**, while bond 2 migration would furnish the formation of 1,4-disubstituted-tetrahydro-γ-carboline **16b** (Scheme 3). In the above two cases the migratory aptitude of bond 2 would be increased due to electron donating methoxy groups present on the phenyl ring, thus migration of both the bonds 1 and 2 would furnish β-carboline and γ-carboline, respectively. In all other cases probably there would be a large difference in the migratory aptitudes resulting in selective migration of bond 1 and formation of only THβCs. This is the first report showing the migration of both the bonds, furnishing tetrahydro β- and γ-carbolines, which can be explained only by involvement of a spiroindolenium intermediate.

3. Conclusions

Using Pictet–Spengler condensation, five new 1,4-disubstituted THβCs and two THγCs were synthesized. Further dehydrogenation gave four new 1,4-disubstituted β-carbolines and two γ-carbolines. A successful use of microwave-assisted reaction was demonstrated in one of the steps in the whole sequence. Formation of all products as THβCs, THγCs, β-carboline, and γ-carboline gave a strong evidence for a spiroindolenium intermediate. The migration of both the bonds in the spiro intermediate, giving regioisomers, was demonstrated for the first time after confirmation by single crystal X-ray analysis.

4. Experimental

4.1. General

Thin-layer chromatographic analysis was performed using silica gel on glass plates and was detected under UV. All recorded melting points are uncorrected. The ^1H and ^{13}C NMR spectra were recorded as δ values in $CDCl_3$ (DMSO-d_6 when required) with reference to TMS as internal standard on a Varian Mercury instrument (300 MHz for ^1H and 75 MHz for ^{13}C). FTIR spectra were recorded on a Perkin–Elmer 1600. Mass spectra were recorded on a Shimadzu QP 5050. Elemental analysis was recorded on Flash E.A. 1112 Thermo.

Table 2
Yields and ratios of **16/14** and **17/15**

Compounds number	Total yield (%)	Ratio
16b/14b	40	1:4
17b/15b	81	1:4
16c/14c	49	1:4.4
17c/15c	70	1:4.4

4.2. General procedure for reaction of nitro-olefins with indole using microwave irradiation

A mixture of indole (0.0012 mol) and nitro-olefin (0.001 mol) was loaded on silica gel (60−120 mesh) and irradiated in a microwave oven. The completion of the reaction was confirmed by TLC. The same silica gel was loaded on a silica-gel column, and chromatographic separation using hexane−ethyl acetate furnished the products (**12a**−**12k**).

*4.3. Catalytic hydrogenation of 2-(aryl)-2-(3-indolyl)-1-nitroethane (**12a**−**12f** and **12i**)*[9]

2-(Aryl)-2-(3-indolyl)-1-nitroethane (0.002 mol) in methanol and Raney Nickel were treated with hydrogen at 70 psi in Parr low pressure hydrogen apparatus for 2−48 h. The catalyst was filtered off and the filtrate was concentrated by vacuum distillation. Ether was added so that the products (**13a**−**13f** and **13i**) readily separated out.

*4.3.1. 2-Phenyl-2-(3-indolyl)-1-aminoethane (**13a**)*

Brown solid; yield 95%; mp 130 °C (lit[10] mp 131−132 °C); [Found: C, 81.80; H, 6.48; N, 11.71. $C_{16}H_{16}N_2$ requires: C, 81.32; H, 6.82; N, 11.85%]; ν_{max} (KBr) 3411, 3348, 3143 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.54 (2H, br s, exchangeable with D_2O, NH_2), 3.30 (1H, dd, J=7.0, 12.8 Hz, C_1H), 3.44 (1H, dd, J=7.0, 12.8 Hz, C_1H), 4.24 (1H, t, J=7.0 Hz, C_2H), 7.02 (2H, t, J=7.0, indole ring protons), 7.12−7.22 (2H, m, ArH), 7.24−7.39 (5H, m, ArH), 7.46 (1H, d, J=7.9 Hz, C_4H of indole ring), 8.31 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$) 46.6, 47.1, 111.1, 117.2, 119.3, 122.1, 126.4, 126.9, 128.4, 136.4, 142.7; MS m/z 236 (M^+), 206 (100%).

*4.3.2. 2-(3,4-Dimethoxyphenyl)-2-(3-indolyl)-1-aminoethane (**13b**)*

White solid; yield 92%; mp 195 °C; [Found: C, 72.48; H, 6.30; N, 9.92. $C_{18}H_{20}N_2O_2$ requires: C, 72.95; H, 6.80; N, 9.45%]; ν_{max} (KBr) 3275 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$) 1.88 (2H, br s, exchangeable with D_2O, NH_2), 3.25 (1H, m, C_1H), 3.40 (1H, m, C_1H), 3.8 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.20 (1H, t, J=6.3 Hz, C_2H), 6.72−6.9 (3H, m, ArH), 6.94−7.08 (2H, m, ArH), 7.13 (1H, t, J=7.4 Hz, ArH), 7.30 (1H, d, J=7.7 Hz, C_7H of indole ring), 7.44 (1H, d, J=7.7 Hz, C_4H of indole ring), 8.28 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, CD_3OD) 42.3, 45.1, 56.5, 112.5, 112.9, 113.2, 114.9, 119.5, 120.0, 121.4, 122.8, 123.1, 127.5, 134.5, 138.4, 149.7, 151.0; MS m/z 296 (M^+), 266 (100%), 265, 250, 234, 204, 178, 130, 76.

*4.3.3. 2-(3,4-Methylenedioxyphenyl)-2-(3-indolyl)-1-aminoethane (**13c**)*

White solid; yield 88%; mp 219 °C; [Found: C, 72.96; H, 5.87; N, 10.30. $C_{17}H_{16}N_2O_2$ requires: C, 72.84; H, 5.75; N, 9.99%]; ν_{max} (KBr) 3325 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$) 3.0−3.4 (4H, 2×br m changes to 2×m after D_2O exchange, C_1H_2+NH_2), 4.2 (1H, br t, J=6.6 Hz, C_2H), 5.84, 5.86 (2H, 2×br s, OCH_2O), 6.55−6.8 (3H, m, ArH), 6.9−7.02 (2H, m, ArH), 7.1 (1H, t, J=7.4 Hz, ArH), 7.3 (1H, d, J=8.0 Hz, C_7H of indole ring), 7.38 (1H, d, J=8.0 Hz, C_4H of indole ring), 8.4 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 42.5, 44.2, 99.2, 106.5, 106.8, 110.0, 113.9, 117.0, 117.2, 119.5, 119.8, 120.2, 125.1, 135.1, 144.4, 146.0; MS m/z 280 (M^+), 278, 252, 250 (100%), 220, 204, 191, 115.

*4.3.4. 2-(2-Furyl)-2-(3-indolyl)-1-aminoethane[11] (**13d**)*

Blackish solid; yield 88.5%; mp 142−143 °C; [Found: C, 74.40; H, 6.41; N, 12.80. $C_{14}H_{14}N_2O$ requires: C, 74.31; H, 6.24; N, 12.38%]; ν_{max} (Nujol) 3356, 3292 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.6 (2H, br s, exchangeable with D_2O, NH_2), 3.26−3.42 (2H, m, C_1H_2), 4.33 (1H, t, J=7.3 Hz, C_2H), 6.12 (1H, dd, J=2.3, 0.9 Hz, furyl ring proton), 6.3 (1H, t, J=2.3 Hz, furyl ring proton), 7.03−7.16 (2H, m, indole ring+furyl ring protons), 7.2 (1H, t, J=7.9 Hz, indole ring proton), 7.36 (2H, br d, J=8.5 Hz, C_2H and C_7H of indole ring), 7.57 (1H, d, J=7.9 Hz, C_4H indole ring), 8.18 (1H, br s, exchangeable with D_2O NH); δ_C (75 MHz, $CDCl_3$) 40.9, 45.9, 106.3, 110.4, 111.6, 114.7, 119.4, 119.7, 122.3, 122.6, 126.7, 136.6, 141.5, 156.4; MS m/z 226 (M^+), 196 (100%), 195, 167, 141, 139, 115.

*4.3.5. 2-(4-Aminophenyl)-2-(3-indolyl)-1-aminoethane (**13e**)*

Brown solid; yield 80%; mp 125−127 °C; [Found: C, 76.34; H, 6.77; N, 16.88. $C_{16}H_{17}N_3$ requires: C, 76.46; H, 6.82; N, 16.72%]; ν_{max} (KBr) 3645, 3570 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.8 (4H, br s, exchangeable with D_2O, 2×NH_2), 3.13 (1H, dd, J=7.2, 12.4 Hz, C_1H), 3.28 (1H, dd, J=7.2, 12.4 Hz, C_1H), 4.07 (1H, t, J=7.2 Hz, C_2H), 6.54 (2H, d, J=8.0 Hz, ArH *ortho* to NH_2), 6.88 (1H, t, J=7.7 Hz, indole ring proton), 6.9−7.05 (4H, m, *meta* to NH_2+indole ring protons), 7.3 (1H, d, J=8.0 Hz, C_7H indole ring), 7.36 (1H, d, J=7.7 Hz, C_4H of indole ring), 10.37 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 44.7, 46.2, 110.1, 113.4, 115.9, 117.1, 117.7, 119.9, 120.1, 125.7, 127.3, 130.8, 135.3, 144.4; MS m/z 251 (M^+), 221 (100% $M^+-CH_2NH_2$), 204, 192, 177.

*4.3.6. 2-(4-Aminophenyl)-2-(3-indolyl)-1-nitroethane (**13l**)*

Orange solid; yield 10%; mp 138−140 °C; [Found: C, 68.41; H, 5.80; N, 15.38. $C_{16}H_{15}N_3O_2$ requires: C, 68.31; H, 5.37; N, 14.94%]; ν_{max} (KBr) 3425, 3348, 3288, 1547, 1380 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.57 (2H, br s, exchangeable with D_2O, NH_2), 4.80 (1H, dd, J=7.7, 11.3 Hz, C_1H), 4.93−5.05 (2H, m, C_1H+C_2H), 6.55 (2H, d, J=7.4 Hz, ArH *ortho* to NH_2), 6.89 (1H, s, C_2H of indole ring), 7.03 (3H, m, *meta* to NH_2+indole ring proton), 7.13 (1H, t, J=7.7 Hz, indole ring proton), 7.26 (1H, d, J=8.0 Hz, C_7H of indole ring), 7.40 (1H, d, J=7.7 Hz, C_4H of indole ring), 8.03 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$) 40.9, 79.8, 111.2, 114.7, 115.3, 118.9, 119.7, 121.4, 122.4, 126.0, 128.5, 128.8, 136.3, 145.5; MS m/z 281 (M^+), 247, 234, 221 (100%), 204, 143, 130, 117.

4.3.7. 2-(2-Thienyl)-2-(3-indolyl)-1-aminoethane[11] *(**13f**)*

Brown solid; yield 91%; mp 121 °C; [Found: C, 69.50; H, 5.98; N, 12.02. $C_{14}H_{14}N_2S$ requires: C, 69.39; H, 5.82; N, 11.56%]; ν_{max} (KBr) 3358, 3296, 3450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.5 (2H, br s, exchangeable with D_2O, NH_2), 3.28–3.5 (2H, m, C_1H_2), 4.52 (1H, t, J=7.0 Hz, C_2H), 6.94 (2H, d, J=3.5 Hz, thienyl ring protons), 7.1 (1H, t J=7.9 Hz, indole ring proton), 7.05–7.24 (3H, m, ArH+thienyl ring protons), 7.38 (1H, d, J=7.9 Hz, C_7H of indole ring), 7.55 (1H, d, J=7.9 Hz, C_4H of indole ring), 8.11 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 38.7, 39.0, 110.8, 115.0, 117.9, 118.0, 120.6, 121.4, 122.6, 123.4, 125.7, 135.8, 146.7; MS m/z 212 ($M^+-CH_2NH_2$), 58, 44, 42 (100%), 40.

*4.3.8. 1-Methyl-2-(2-furyl)-2-(3-indolyl)-1-aminoethane (**13i**)*

Blackish solid; yield 95%; mp 152–153 °C; [Found: C, 75.29; H, 6.88; N, 11.76. $C_{15}H_{16}N_2O$ requires: C, 74.97; H, 6.71; N, 11.66%]; ν_{max} (KBr) 3649, 3568 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.15 (3H, d, J=2.8 Hz, CH_3), 2.3 (2H, br s, exchangeable with D_2O, NH_2), 3.7 (1H, m, C_1H), 4.18 (1H, d, J=7.7 Hz, C_2H), 6.13 (1H, br s, furyl ring proton), 6.27 (1H, br s, furyl ring proton), 7.0–7.4 (5H, m, ArH+furyl ring protons), 7.68 (1H, d, J=7.7 Hz, C_4H indole ring), 8.44 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 21.2, 45.1, 50.1, 105.9, 109.7, 111.2, 113.1, 118.8, 121.3, 122.8, 126.7, 136.0, 140.6, 156.0 (minor signals probably of other diastereomer are also seen in the spectrum); MS m/z 196 ($M^+-CH_3CHNO_2$), 167, 115.

*4.4. General procedure for synthesis of tetrahydro β- or γ-carboline from amino compounds (**13a–13f**)*

To the solution of amino compounds (0.002 mol) in dichloromethane, benzaldehyde (0.0024 mol) was added, the solution was cooled and trimethylsilylchloride (0.004 mol) was added to it. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 41 h. Trimethylsilylchloride (0.004 mol) was added again and stirring was continued further for 47 h. The reaction mixture was diluted with dichloromethane, washed with 10% NaOH and brine. The combined organic layer was dried over sodium sulfate and concentrated. The crude product obtained was chromatographed on silica gel using pet-ether and ethyl acetate as an eluent yielding tetrahydro β- or γ-carboline.

*4.4.1. 1,4-Diphenyl-1,2,3,4-tetrahydro-β-carboline (**14a**)*

Yellow solid; yield 48.5%; mp 189 °C; [Found: C, 84.93; H, 6.38; N, 8.28. $C_{23}H_{20}N_2$ requires: C, 85.15; H, 6.21; N, 8.63%]; ν_{max} (KBr) 3406, 3686 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.87 (1H, br s, exchangeable with D_2O, NH), 3.02 (1H, dd, J=7.2, 12.7 Hz, C_3H), 3.53 (1H, dd, J=7.2, 12.7 Hz, C_3H), 4.37 (1H, br t, J=7.2 Hz, C_4H), 5.25 (1H, s, C_1H), 6.83 (2H, m, ArH), 7.04 (1H, t, J=7.7 Hz, ArH), 7.12–7.40 (11H, m, ArH), 7.64 (1H, br s, exchangeable with D_2O, NH of indole ring); δ_C (75 MHz, $CDCl_3$) 41.7, 52.9, 58.2, 110.7, 112.5, 119.3, 119.8, 121.5, 126.5, 126.7, 128.4, 128.5, 128.9, 135.8, 135.9, 141.4, 143.0, 182.0; MS m/z 324 (M^+), 295 (100%), 218; DEPT showed the presence of one CH_2 group and 11 CH groups, CH_3 group was absent.

*4.4.2. 1-Phenyl-4-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-β-carboline (**14b**)*

Pale yellow solid; yield 32%; mp 190 °C; [Found: C, 78.60; H, 6.38; N, 7.70. $C_{25}H_{24}N_2O_2$ requires: C, 78.10; H, 6.29; N, 7.29%]; ν_{max} (KBr) 3446 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$) 3.06 (1H, dd, J=5.3, 12.8 Hz, C_3H), 3.58 (1H, dd, J=5.3, 12.8 Hz, C_3H), 3.78 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.35 (1H, m, C_4H), 4.66 (1H, br s, exchangeable with D_2O, NH), 5.39 (1H, br s, C_1H), 6.75–6.90 (5H, m, ArH), 7.07 (1H, t, J=5.9 Hz, ArH), 7.24 (1H, m, ArH), 7.37 (5H, br s, ArH), 7.59 (1H, br s, exchangeable with D_2O, NH of indole ring); δ_C (75 MHz, $CDCl_3$) 40.8, 52.1, 55.9, 57.7, 110.7, 111.1, 111.4, 112.6, 119.3, 120.0, 121.7, 128.7, 128.9, 134.3, 134.6, 135.9, 139.7, 147.6, 148.8; MS m/z 384 (M^+), 355 (100%), 340, 278, 218, 178.

*4.4.3. 4-Phenyl-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (**16b**)*

White solid; yield 8%; mp 210 °C; [Found: C, 78.55; H, 6.63; N, 7.78. $C_{25}H_{24}N_2O_2$ requires: C, 78.10; H, 6.29; N, 7.29%]; ν_{max} (KBr) 3346 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$+DMSO-d_6) 2.59 (1H, br s, exchangeable with D_2O, NH), 3.65–3.78 (2H, m, C_2H_2), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.69 (1H, br s, C_1H), 5.64 (1H, s, C_4H), 6.54 (1H, d, J=8.2 Hz, ArH), 6.74–6.84 (3H, m, ArH), 6.89 (1H, d, J=8.2 Hz, ArH), 7.0 (1H, t, J=7.7 Hz, ArH), 7.29 (1H, d, J=7.7 Hz, ArH), 7.36–7.42 (3H, m, ArH), 7.48–7.56 (2H, m, ArH), 10.21 (1H, br s, exchangeable with D_2O, NH of indole ring); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 40.3, 50.3, 54.7, 56.5, 110.3, 110.6, 117.2, 117.9, 119.8, 124.2, 126.9, 126.9, 127.8, 133.3, 134.9, 142.0, 146.5, 147.5; Ms m/z 384 (M^+), 355 (100%), 340, 278.

*4.4.4. 1-Phenyl-4-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-β-carboline (**14c**)*

Pale yellow solid; yield 40%; mp 189 °C; [Found: C, 77.99; H, 5.67; N, 7.30. $C_{24}H_{20}N_2O_2$ requires: C, 78.24; H, 5.47; N, 7.6%]; ν_{max} (Nujol) 3387, 3346 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.9 (1H, br s, exchangeable with D_2O, NH), 3.0 (1H, dd, J=5.2, 12.6 Hz, C_3H), 3.52 (1H, dd, J=5.2, 12.6 Hz, C_3H), 4.32 (1H, br t, J=5.2 Hz, C_4H), 5.30 (1H, br s, C_1H), 5.93 (2H, br s, OCH_2O), 6.7 (1H, s, ArH), 6.54–6.57 (2H, m, ArH), 6.94 (2H, m, ArH), 7.03–7.14 (1H, m, ArH), 7.21–7.27 (1H, d, J=8.2 Hz, ArH), 7.36 (5H, br m, ArH), 7.55 (1H, s, exchangeable with D_2O, NH of indole ring); δ_C (75 MHz, $CDCl_3$) 41.2, 52.7, 58.0, 100.8, 108.1, 108.6, 110.7, 112.5, 119.3, 119.8, 121.3, 121.5, 126.6, 128.3, 128.5, 128.8, 135.7, 135.9, 137.1, 141.4, 146.1, 147.6; MS m/z 277 ($M^+-C_7H_7$, 100%), 118 ($M^+-C_8H_8N$), 89, 76.

*4.4.5. 4-Phenyl-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (**16c**)*

Pale yellow solid; yield 9%; mp 195 °C; [Found: C, 78.52; H, 5.57; N, 7.91. $C_{24}H_{20}N_2O_2$ requires: C, 78.24; H, 5.47; N, 7.6%]; ν_{max} (KBr) 3446 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$) 1.61 (1H, br s, exchangeable with D_2O, N*H*), 3.22 (1H, br d, *J*=12.9 Hz, C_2H), 3.48 (1H, dd, *J*=5.0, 12.9 Hz, C_2H), 4.23 (1H, br s, C_1H), 5.22 (1H, br s, C_4H), 5.93 (2H, br s, OCH_2O), 6.70–6.90 (4H, m, Ar*H*), 7.0 (1H, t, *J*=7.3 Hz, Ar*H*), 7.1–7.22 (3H, m, Ar*H*), 7.33–7.50 (4H, br s, Ar*H*), 7.65 (1H, br s, exchangeable with D_2O, N*H* of indole ring); δ_C (75 MHz, $CDCl_3$) 39.2, 51.5, 57.9, 100.8, 108.1, 108.7, 110.8, 112.0, 119.1, 119.5, 121.3, 121.9, 126.9, 128.3, 128.5, 128.9, 135.6, 136.0, 138.1, 141.2, 146.1, 147.7; Ms *m/z* 368 (M^+) (339, 100%), 309, 307, 278, 262, 204.

4.4.6. 4-(2-Furyl)-1-phenyl-1,2,3,4-tetrahydro-β-carboline (*14d*)

Pale yellow solid; yield 49.3%; mp 150 °C; [Found: C, 79.98; H, 5.64; N, 8.83. $C_{21}H_{18}N_2O$ requires: C, 80.23; H, 5.77; N, 8.91%]; ν_{max} (KBr) 3400 cm^{-1} (broad); δ_H (300 MHz, $CDCl_3$) 1.25 (1H, br s, exchangeable with D_2O, N*H*), 3.25 (1H, dd, *J*=5.0, 12.7 Hz, C_3H), 3.48 (1H, dd, *J*=5.0, 12.7 Hz, C_3H), 4.42 (1H, t, *J*=5.0 Hz, C_4H), 5.20 (1H, br s, C_1H), 6.06 (1H, d, *J*=3.0 Hz, furyl ring proton), 6.3 (1H, dd, *J*=1.9, 3.0 Hz, furyl ring proton), 6.94–7.04 (1H, m, ArH), 7.1 (2H, distorted dt, *J*=3.6, 8.0 Hz, Ar*H*+furyl ring protons), 7.2–7.48 (7H, m, Ar*H*), 7.61 (1H, br s, exchangeable with D_2O, N*H* of indole ring); δ_C (75 MHz, $CDCl_3$) 34.4, 47.5, 57.2, 106.6, 110.1, 110.4, 110.8, 119.0, 119.4, 121.7, 126.5, 128.1, 128.5, 128.7, 135.0, 135.7, 141.3, 156.1; Ms *m/z* 314 (M^+) (285, 100%), 268, 256.

4.4.7. 1-Phenyl-4-(4-aminophenyl)-1,2,3,4-tetrahydro-β-carboline (*14e*)

Brown solid; yield 20%; mp 175 °C; [Found: C, 81.47; H, 6.50; N, 12.02. $C_{23}H_{21}N_3$ requires: C, 81.38; H, 6.24; N, 12.38%]; ν_{max} (KBr) 3421, 3336, 3174 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.0 (1H, t, *J*=10.5 Hz, C_3H), 3.50 (3H, m, with D_2O changes to dd, C_3H+NH_2), 4.36 (1H, m, C_4H), 5.30 (2H, d, with D_2O changes to s, NH+C_1H), 6.65 (2H, d, *J*=7.6 Hz, ArH), 6.95 (2H, br s, Ar*H*), 7.0–7.20 (3H, m, Ar*H*), 7.38 (6H, br s, Ar*H*), 7.52 (1H, br s, exchangeable with D_2O, N*H* of indole ring); δ_C (75 MHz, $CDCl_3$) 40.8, 58.1, 58.2, 110.7, 113.0, 115.3, 119.1, 120.0, 121.4, 126.8, 128.3, 128.6, 128.9, 129.2, 133.1, 135.7, 135.9, 141.5, 144.6; MS *m/z* 310 (M^+-CH_2NH), 233 (M^+-PhCH_2NH), 116 ($M^+-C_6H_6$).

4.4.8. 4-(2-Thienyl)-1-phenyl-1,2,3,4-tetrahydro-β-carboline (*14f*)

Brown solid; yield 42.9%; mp 190 °C; [Found: C, 76.12; H, 5.69; N, 8.64. $C_{21}H_{18}N_2S$ requires: C, 76.33; H, 5.49; N, 8.48%]; ν_{max} (Nujol) 3321, 3392 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.9 (1H, br s, exchangeable with D_2O, N*H*), 3.13 (1H, dd, *J*=7.4, 12.9 Hz, C_3H), 3.56 (1H, dd, *J*=7.4, 12.9 Hz, C_3H), 4.66 (1H, t, *J*=7.4 Hz, C_4H), 5.25 (1H, br s, C_1 *H*), 6.95–7.01 (3H, m, thienyl protons), 7.05–7.14 (2H, m, Ar*H*), 7.15–7.24 (2H, m, Ar*H*), 7.27–7.40 (5H, m, Ar*H*), 7.74 (1H, br s, exchangeable with D_2O, N*H* of indole ring); δ_C (75 MHz, $CDCl_3$) 34.8, 49.8, 55.8, 110.4, 110.7, 117.7, 117.8, 120.1, 122.6, 123.6, 125.4, 125.5, 126.8, 127.5, 127.7, 134.1, 135.3, 141.2, 147.1; MS *m/z* 301 (M^+-CH_2NH).

4.5. General procedure for dehydrogenation of THβCs or THγCs

A mixture of THβCs or THγCs (0.10 g), 5% Pd/C (50 mg), and dry xylene (5 ml) was refluxed for 1–4 h. The reaction mixture was cooled and ethyl acetate (10 ml) was added to it. The catalyst was filtered off through Celite and the filtrate was concentrated by vacuum distillation. The crude product obtained was chromatographed on neutral alumina using pet-ether and ethyl acetate as an eluent yielding β- and γ-carboline (**15a–15d** and **17b**, **17c**).

4.5.1. 1,4-Diphenyl-β-carboline (*15a*)

Yellow solid; yield 81%; mp 125 °C; [Found: C, 86.32; H, 5.35; N, 8.32. $C_{23}H_{16}N_2$ requires: C, 86.22; H, 5.03; N, 8.74%]; ν_{max} (KBr) 3427 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.0–7.1 (1H, m, Ph), 7.40–7.61 (8H, m, Ar*H*), 7.66 (3H, br d, *J*=7.4 Hz, Ar*H*), 7.94 (2H, d, *J*=8.0 Hz, Ar*H*), 8.4 (1H, s, C_3H), 9.0 (1H, br s, exchangeable with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 111.4, 119.8, 121.4, 123.4, 127.2, 128.1, 128.2, 128.6, 128.7, 129.1, 129.3, 130.9, 133.2, 137.5, 137.9, 139.4, 140.5, 141.6; MS *m/z* 320 (M^+ 100%), 291, 242, 241, 216, 215.

4.5.2. 1-Phenyl-4-(3,4-dimethoxyphenyl)-β-carboline (*15b*)

Pale yellow solid; yield 65.4%; mp 199 °C; [Found: C, 78.57; H, 5.50; N, 7.60. $C_{25}H_{20}N_2O_2$ requires: C, 78.93; H, 5.30; N, 7.36%]; ν_{max} (KBr) 3325 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 7.09 (2H, m, Ar*H*), 7.18–7.28 (2H, m, Ar*H*), 7.44–7.54 (3H, m, Ar*H*), 7.6 (2H, t, *J*=7.1 Hz, Ar*H*), 7.77 (1H, d, *J*=8.0 Hz, C_5H of indole ring), 7.97 (2H, d, *J*=7.2 Hz, Ar*H*), 8.45 (1H, s, C_3H), 8.65 (1H, br s, exchangeable with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 56.0, 111.3, 111.5, 112.4, 120.0, 121.5, 123.6, 128.1, 128.4, 128.9, 129.2, 129.9, 130.9, 133.2, 139.0, 140.7, 148.8; MS *m/z* 380 (M^+ 100%), 363.

4.5.3. 4-Phenyl-1-(3,4-dimethoxyphenyl)-γ-carboline (*17b*)

Pale yellow solid; yield 16.2%; mp 205 °C; [Found: C, 78.79; H, 5.51; N, 7.39. $C_{25}H_{20}N_2O_2$ requires: C, 78.93; H, 5.30; N, 7.36%]; ν_{max} (KBr) 3329 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.96 (6H, s, 2×OCH_3), 7.06 (1H, d, *J*=8.3 Hz, Ar*H*), 7.13 (1H, br t, *J*=9.9 Hz, Ar*H*), 7.19 (1H, d, *J*=1.9 Hz, Ar*H*), 7.24–7.32 (2H, m, Ar*H*+$CDCl_3$), 7.38–7.49 (2H, m, Ar*H*), 7.53–7.64 (3H, m, Ar*H*), 7.76 (1H, d, *J*=8.0 Hz, C_5H of indole ring), 7.86 (2H, dd, *J*=8.0, 1.7 Hz, Ar*H*), 8.56 (1H, s, C_2H), 8.84 (1H, br s, exchangeable with D_2O, N*H*); δ_C (75 MHz, $CDCl_3$) 56.0, 56.1, 111.0, 111.6, 111.7, 117.1, 119.4, 120.5, 120.7, 121.8, 122.5, 126.8, 128.0, 128.4, 128.8, 128.9, 139.5, 140.0, 142.7, 142.9, 148.9, 149.5, 153.2; MS *m/z* 380 (M^+ 100%), 363, 319, 305, 243, 190, 77.

4.5.4. 1-Phenyl-4-(3,4-methylenedioxyphenyl)-β-carboline (*15c*)

Pale yellow solid; yield 57%; mp 155 °C; [Found: C, 79.34; H, 4.62; N, 7.44. $C_{24}H_{16}N_2O_2$ requires: C, 79.11; H, 4.43; N, 7.69%]; ν_{max} (KBr) 3304 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.1

(2H, br s, OCH_2O), 7.0 (1H, d, J=8.5 Hz, ArH), 7.06–7.2 (3H, m, ArH), 7.44–7.52 (3H, m, ArH), 7.58 (2H, t, J=7.2 Hz, ArH), 7.8 (1H, d, J=8.3 Hz, C_5H of indole ring), 7.98 (2H, d, J=8.3 Hz, ArH), 8.40 (1H, s, C_3H), 8.74 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$) 101.2, 108.5, 109.7, 111.4, 119.8, 121.4, 122.8, 123.5, 127.2, 128.05, 128.1, 128.7, 129.1, 130.6, 131.3, 133.2, 138.0, 139.5, 140.5, 141.5, 147.5, 147.7; MS m/z 364 (M^+ 100%), 335, 181, 153.

4.5.5. 4-Phenyl-1-(3,4-methylenedioxyphenyl)-γ-carboline (*17c*)

Pale yellow solid; yield 13%; mp 234 °C; [Found: C, 79.20; H, 4.02; N, 7.52. $C_{24}H_{16}N_2O_2$ requires: C, 79.11; H, 4.43; N, 7.69%]; ν_{max} (KBr) 3420 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.9 (2H, s, OCH_2O), 6.90 (1H, d, J=7.7 Hz, ArH), 7.02–7.20 (3H, m, ArH), 7.45 (1H, t, J=7.7, Hz, indole ring proton), 7.5–7.67 (4H, m, ArH), 7.72 (1H, d, J=7.9 Hz, C_5H of indole ring), 7.85 (2H, br s, ArH), 8.40 (1H, s, C_2H), 9.9 (1H, br s, exchangeable with D_2O, NH); δ_c (75 MHz, $CDCl_3$+DMSO-d_6) 99.9, 107.6, 107.7, 110.6, 115.6, 118.0, 118.4, 119.6, 120.3, 120.9, 125.1, 127.0, 127.3, 127.5, 127.9, 138.7, 139.2, 141.0, 141.2, 145.9, 146.6, 151.2; MS m/z 364 (M^+ 100%), 363, 333, 167, 152.

4.5.6. 4-(2-Furyl)-1-phenyl-β-carboline (*15d*)

Orange solid; yield 60%; mp 115 °C; [Found: C, 81.70; H, 4.90; N, 9.52. $C_{21}H_{14}N_2O$ requires: C, 81.27; H, 4.55; N, 9.03%]; ν_{max} (KBr) 3435 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.67 (1H, d, J=1.2 Hz, furyl ring proton), 6.87 (1H, d, J=3.0 Hz, furyl ring proton), 7.18–7.3 (1H, m, ArH), 7.4–7.62 (5H, m, ArH), 7.75 (1H, br s, furyl ring proton), 7.90 (2H, d, J=8.0 Hz, ArH), 8.3 (1H, d, J=8.0 Hz, C_5H of indole ring), 8.7 (1H, s, C_3H), 8.9 (1H, br s, exchangeable with D_2O, NH); δ_C (75 MHz, $CDCl_3$) 109.0, 111.3, 111.8, 119.8, 120.1, 121.2, 124.3, 128.1, 128.4, 128.8, 129.1, 133.4, 137.8, 138.5, 140.6, 142.1, 142.7, 151.4; MS m/z 310 (M^+ 100%) 243, 203, 155, 141.

5. Crystallography

X-ray data for **15b** and **17b** have been deposited at the Cambridge Crystallographic Data Centre, deposition numbers CCDC 630523 and CCDC 630524. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

5.1. Crystal data

The X-ray data of the two compounds were collected at room temperature on a SMART APEX CCD single crystal X-ray diffractometer with omega and phi scan mode and different number of scans and exposure times for different crystals using λ (Mo Kα)=0.71073 Å radiation, at T=293(2) K with Oscillation/frame −0.3°, maximum detector swing angle=−30.0°, beam center=(260.2,252.5), in plane spot width=1.24. All the data were corrected for Lorentzian, polarization, and absorption effects using SAINT and SADABS programs. SHELX-97 (ShelxTL)[12] was used for structure solution and full matrix least squares refinement on F^2. The regiochemistry of all the molecules was confirmed by single crystal X-ray analysis like difference in the pattern of H-bonding (Supplementary data).

5.1.1. Crystal data for *15b* ($C_{25}H_{20}N_2O_2$)

M=380.43, yellow colored crystal, grown from a mixture of ethanol and water, approximate size 0.32×0.25×0.04 mm, multiscan data acquisition. Total scans=5, total frames=3030, exposure/frame=15.0 s/frame, θ range=2.06–25.00°, completeness to θ of 25.0° is 100%. Monoclinic, space group $P2_1/n$, a=10.7329(4), b=16.7366(7), c=17.2684(7) Å, β=101.608(1)°, V=3038.5(2) Å,[3] Z=4, D_c=1.517 mg m^{-3}, μ(Mo Kα)=0.770 mm^{-1}, 31,910 reflections measured, 5356 unique [$I>2\sigma(I)$], R value=0.0320, $wR2$=0.0803.

5.1.2. Crystal data for *17b* ($C_{25}H_{20}N_2O_2$)

M=380.43, yellow colored crystal, grown from a mixture of ethanol and water, approximate size 0.32×0.25×0.04 mm, multiscan data acquisition. Total scans=5, total frames=3030, exposure/frame=15.0 s/frame, θ range=2.06–25.00°, completeness to θ of 25.0° is 100%. Monoclinic, space group $P2_1/n$, a=10.7329(4), b=16.7366(7), c=17.2684(7) Å, β=101.608(1)°, V=3038.5(2) $Å^3$, Z=4, D_c=1.517 mg m^{-3}, μ(Mo Kα)=0.770 mm^{-1}, 31,910 reflections measured, 5356 unique [$I>2\sigma(I)$], R value=0.0320, $wR2$=0.0803.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.008.

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