Diastereoselective synthesis of 1,1,4-trisubstituted-2,3,4,9-tetrahydrospiro-*β*-carbolines via glacial acetic acid catalyzed Pictet - Spengler reaction

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Abstract

The Pictet-Spengler reaction of substituted tryptamines with cyclic ketones using glacial acetic acid afforded only one diastereomer of unreported 1,1,4-trisubstituted-2,3,4,9-tetrahydrospiro-*β*-carbolines. The stereoselectivity in the reaction has been demonstrated using unsymmetrical ketones and single- crystal X-ray analysis of one of the spiro products in the form of base, its sulfate and hydrochloride salts, which indicated the formation of only the *R,R* diastereomer.

Keywords: 1,1,4-Trisubstituted-2,3,4,9-tetrahydrospiro-*β*-carbolines, diastereoselective Pictet-Spengler reaction, *β*-substituted tryptamine, glacial acetic acid

Introduction

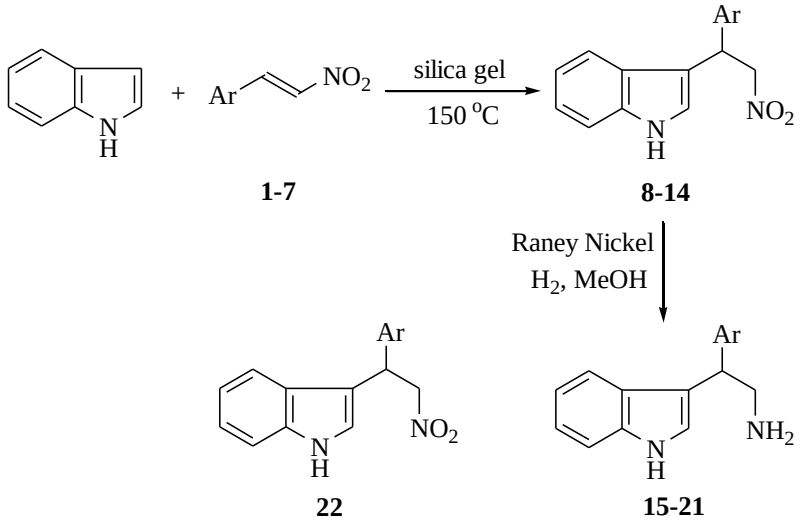
Tetrahydrospiro-*β*-carbolines (THS*β*Cs) are important indole alkaloids since they show various biological activities like anticonvulsant,[1] antispasmodic activity,[2] GHSR inhibitory activity with Ki = 60 nM,[3] receptor affinity,[4] and antidepressant activity.[5]

The Pictet-Spengler reaction[6] has been extensively studied in the areas of synthesis of different biologically important heterocyclic systems.[7] Asymmetric Pictet-Spengler reactions have attracted much attention,[8-15] because it is an important and useful tool to construct chiral synthons containing tetrahydro-isoquinoline or tetrahydro-*β*-carboline (TH*β*C) structural moieties. Therefore, the main challenge of this cyclization is stereoselectivity and the ratio of isomers. Different conditions, by changing temperature, solvent and acid-catalysts, were studied to improve the selectivity of Pictet-Spengler reaction.[16-20] Other synthetic strategies used to influence the stereoselectivity of the Pictet-Spengler condensation include the use of chiral catalysts,[11] chiral auxiliaries,[13,21] or optically active carbonyl compounds.[22] Amongst the variously substituted TH*β*Cs very few reports are available typically for 1,4-disubstituted TH*β*Cs

and also for 1,1,4-trisubstituted THβCs.[23-25] We now report a highly diastereoselective method for synthesizing 1,1,4-trisubstituted THSβCs by the Pictet–Spengler reaction of β–substituted tryptamine with symmetric and unsymmetric ketones using glacial acetic acid as a catalyst.

Results and Discussion

Use of silica gel as a solid and mildly acidic catalyst is well reported and is receiving considerable attention from synthetic chemists.[26,27] In the present study silica gel was used for conjugate addition reaction. Thus, indole and nitro olefin **1** were loaded on silica gel and then heated for 2 min. at 150 ^{o}C to get a solid product in 97% yield. The structure was shown to be **8** by comparing with the reported[27d] values. Further reactions of various other nitro olefins **2-7** and indole by using the same method furnished products **9-14** in good yields and in short time. The results are shown in Scheme 1 and Table 1. Thus, a new efficient method was established for the conjugate addition of indole on nitro olefins.



Compd.	Ar	Compd.	Ar
1, **8**, **15**	Phenyl	**5**, **12**	4-Nitrophenyl
2, **9**, **16**	4-Methoxyphenyl	**19**, **22**	4-Aminophenyl
3, **10**, **17**	3,4-Methylenedioxyphenyl	**6**, **13**, **20**	2-Thienyl
4, **11**, **18**	2-Furyl	**7**, **14**, **21**	3,4-Dimethoxyphenyl

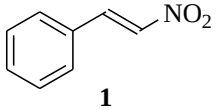
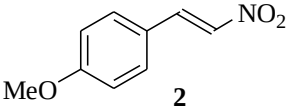
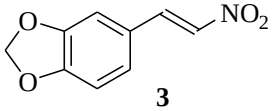
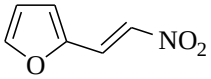
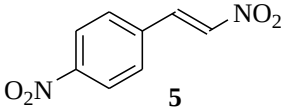
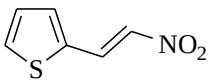
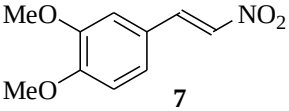
Scheme 1

Further reduction of the nitro compound **8-14** using freshly prepared Raney nickel in methanol furnished the β-phenyltryptamines **15-21**. In the case of the nitro compound **12**, initial

reduction of aromatic nitro group furnished product **22**. After continuing the reaction for longer time, both the nitro groups were reduced to give **19** (Scheme 1).

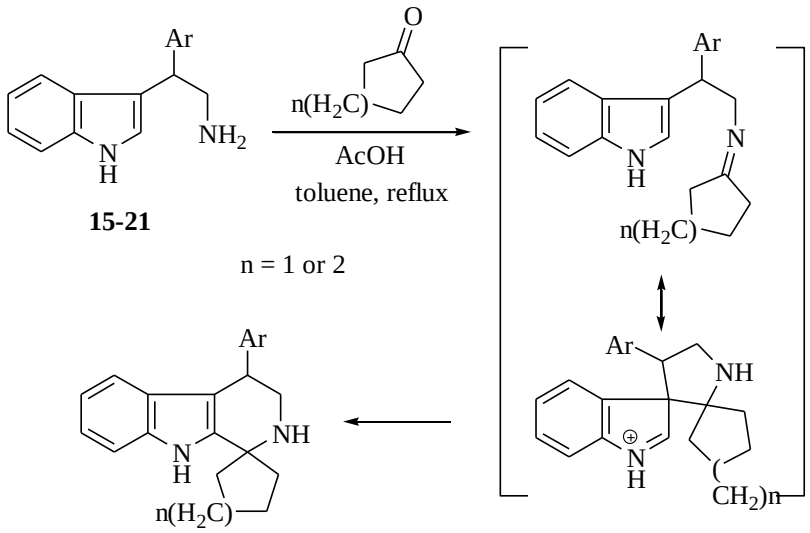
To check the catalytic activity of glacial acetic acid for Pictet-Spengler cyclization initially the condensation reaction of amine **15** and cyclohexanone in the presence of catalytic amount of glacial acetic acid was carried out by refluxing in toluene to furnish a new compound **23** (Scheme 2, Table 2) in 91% yield. The spectral and analytical data was consistent with the structure **23** which was confirmed by DEPT experiment. In the ^{13}C NMR, signal at 52.3 was assigned to the spiro carbon C_1 which was absent in the DEPT experiment where all protonated carbons are seen. One CH at 40.8 for C_4 and five -CH_2 groups with one strong signal at 21.7 were observed in the aliphatic region of the DEPT experiment. This data supported for Pictet-Spengler cyclization in presence of glacial acetic acid.

Table 1. Time and yield for the Michael addition reactions using nitro olefins **1**-**7**

Entry	Electrophile	Products	Time (min.)	Yield (%)
1	 **1**	**8**	2	97
2	 **2**	**9**	4	91
3	 **3**	**10**	5	90
4	 **4**	**11**	2	90
5	 **5**	**12**	5	87
6	 **6**	**13**	2	93
7	 **7**	**14**	7	89

After getting this successful cyclization, similar Pictet-Spengler cyclizations of the amino compounds **16**-**21** with cyclohexanone and of compounds **15** and **17** with cyclopentanone, furnished eight new 1,1,4-trisubstituted THS*β*Cs **24**-**29** and **30**-**31** respectively (Scheme 2, Table 2). Although spiro compounds are known to show dissymmetry, only one racemic product was expected, as the ketones used were symmetric.

To explore the stereoselectivity in the reaction, unsymmetrical ketones such as isatin, α-tetralone and 2-methylcyclopentane-1,3-dione were used for the Pictet-Spengler cyclization. Treatment of **15** with isatin in the presence of a catalytic amount of glacial acetic acid furnished a solid product. ^{1}H and ^{13}C NMR indicated it to be a single diastereomer of base **32** (Scheme 3). The stereochemistry of base **32** was investigated using single crystal X-ray analysis, indicating the *R, R* configuration at C_1 and C_4 (Figure 1).



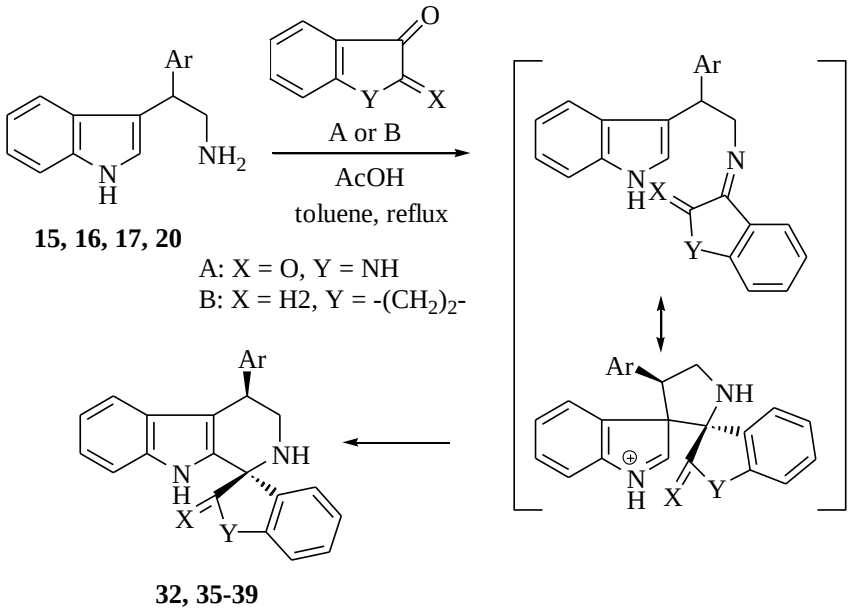
Compd.	**Ar**	**n**	Compd.	**Ar**	**n**
23	Phenyl	2	**24**	4-methoxyphenyl	2
25	3,4-methylenedioxyphenyl	2	**26**	2-furyl	2
27	4-aminophenyl	2	**28**	2-thienyl	2
29	3,4-dimethoxyphenyl	2	**30**	Phenyl	1
31	3,4-methylenedioxyphenyl	1			

Scheme 2

A literature survey revealed that there is a report for the formation of mixture of the two diastereomers of sulfate form of base **32** in a similar Pictet-Spengler condensation using sulfuric acid in water as a catalyst in 46% yield. In this report,[24] the major diastereomer was shown to have *R,R* configuration using 2D NMR of the mixture without isolating the individual isomers.

However, in the present study using acetic acid as a catalyst we could achieve the formation of only one diastereomer of base **32** in 88% yield exclusively and also confirmed the stereochemistry of base **32** as *R,R* unambiguously using single crystal X-ray analysis. The sterically preferred spiro transition state (Scheme 3) having the *trans* arrangement of substituents

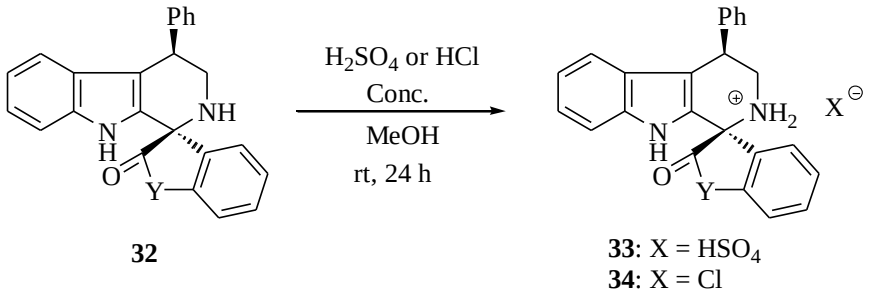
at C_1 and C_4 in presence of glacial acetic acid as a mild acidic catalyst explained the exclusive formation of diastereomer **32**.



Compd.	Ar	X	Y
32	Phenyl	O	NH
35	4-Methoxyphenyl	O	NH
36	3,4-Methylenedioxyphenyl	O	NH
37	2-Thienyl	O	NH
38	Phenyl	H_2	$-(CH_2)_2-$
39	4-Methoxyphenyl	H_2	$-(CH_2)_2-$

Scheme 3

To compare the reported[24] and the present results, base **32** was treated with sulfuric acid (conc.) in methanol to furnish the corresponding sulfate **33** in 95% yield (Scheme 4). The ^{1}H NMR and ^{13}C NMR data of sulfate **33** were consistent with that of the reported major isomer.



32

33: X = HSO_4
34: X = Cl

Scheme 4

The report[2] of good biological activity for the hydrochloride of similar base without a substituent at 4-position led us to convert base **32** to the hydrochloride **34** (94% yield, Scheme 4).

Table 2. Time and yield for Pictet- Spengler reactions using *β*-substituted tryptamines

Entry	Compd.	Ketones	Ar	THS*β*Cs	
				Time (h)	Yield %
1	**15**, **23**	Cyclohexanone	Phenyl	9.5	91
2	**16,24**	Cyclohexanone	4-Methoxyphenyl	7.5	90
3	**17,25**	Cyclohexanone	3,4-Methylenedioxyphenyl	7.5	89
4	**18**, **26**	Cyclohexanone	2-Furyl	8.5	85
5	**19,27**	Cyclohexanone	4-Aminophenyl	10.0	71
6	**20,28**	Cyclohexanone	2-Thienyl	8.5	87
7	**21,29**	Cyclohexanone	3,4-Dimethoxyphenyl	7.5	88
8	**15,30**	Cyclopentanone	Phenyl	13.5	82
9	**17,31**	Cyclopentanone	3,4-Methylenedioxyphenyl	11.5	79
10	**15,32**	Isatin	Phenyl	18.5	88
11	**16**, **35**	Isatin	4-Methoxyphenyl	18.0	84
12	**17**, **36**	Isatin	3,4-Methylenedioxyphenyl	18.5	85
13	**20**, **37**	Isatin	2-Thienyl	18.0	81
14	**15**, **38**	α-Tetralone	Phenyl	17.5	76
15	**16** , **39**	α-Tetralone	4-Methoxyphenyl	17.5	72

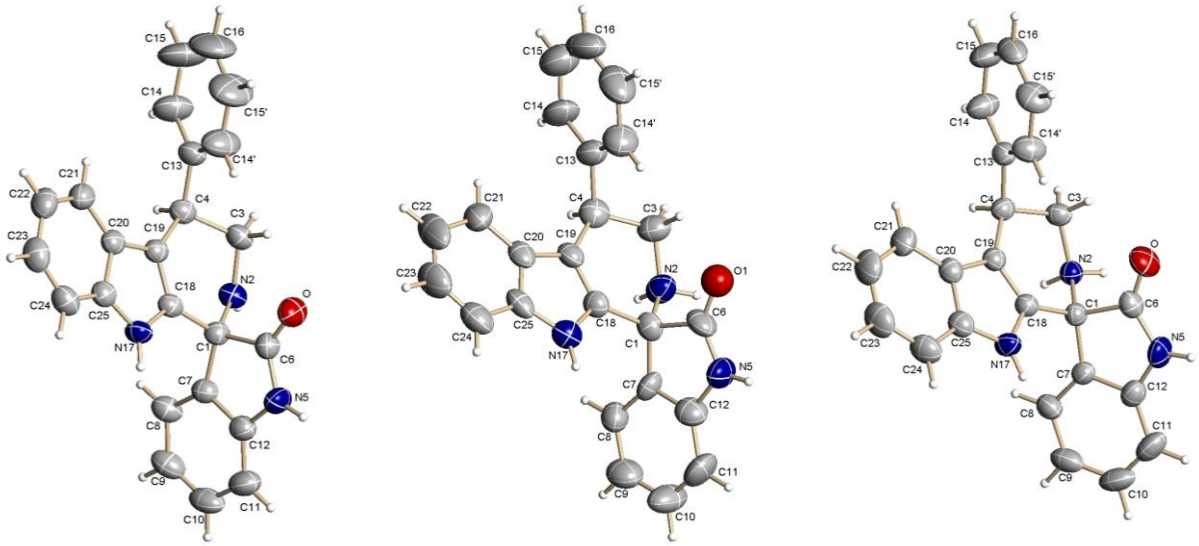
In the ^{1}H NMR of salts **33** and **34**, the assignments of C_3H_2 and C_4H are different from those of base **32**, as shown in Table 3. In both the salts, the protons at C_3 are shifted downfield due to the proximity of quaternary nitrogen. The C_4H appeared as a dd with J = 6.1 and 12.1 Hz as Ja,e and Ja,a, respectively showing coupling with two protons at C_3.

Table 3. Comparison of ^{1}H NMR spectra of compounds **32, 33** and **34**

Entry	Assignment	Base **32**			Sulfate **33**			Hydrochloride **34**		
		C_3H	C_3H	C_4H	C_3H_a	C_3H_e	C_4H	C_3H_a	C_3H_e	C_4H
1	Chemical shift (δ)	3.56	3.75	4.41	4.14	4.72	3.84	4.17	4.83	3.71
2	Multiplicity	dd	dd	t	t	dd	dd	t	dd	dd
3	J Hz	5.5, 13.4	6.7, 13.4	6.7	10.7	6.1, 10.7	6.1, 12.1	11.3	6.1, 10.6	6.1, 12.1

This indicated the axial position of C_4H in both the salts **33** and **34**. However, in base **32** C_4H appeared at 4.41 as a triplet, J = 6.7 Hz, indicating rapid flipping of the nitrogen containing ring in solution.

As compared to the chemical shift of C_4H in base, this proton, being axial was shifted to up field position in both the salts. In contrast to this the stereochemistry of salts **33** and **34** was shown to be same as the base **32** as *R,R* using X-ray analysis (Figure 1 and 2). The difference in the two results from ^{1}H NMR and X-ray analysis can be attributed to the solution state where rapid flipping is possible in ^{1}H NMR and rigid solid state in X-ray analysis.



32 **33** **34**

Figure 1. ORTEP diagram of base **32,** sulfate **33** and hydrochloride **34** ellipsoids are drawn at 50% probability.

To generalize the stereoselectivity in the reaction using glacial acetic acid, the substituents at 1 and 4-positions were changed. Treatment of amino compounds **16, 17** and **20** with isatin and **15** and **16** with α-tetralone afforded products **35**-**37** and **38**-**39** respectively (Scheme 3, Table 2). The similarity in the ^{1}H and ^{13}C NMR of these products, with that of **32** indicated formation of only one diastereomer in each case.

Subsequently, treatment of amino compound **15** with 2-methylcyclopentane-1,3-dione, under the same conditions led to formation of a new product in 89% yield. The spectral data was not consistent with the expected structure. Even the attempts for cyclization using strong acid TFA were unsuccessful (Scheme 5). Thus single crystal X-ray analysis was used to assign structure **40** to the new unexpected product (Figure 3). The formation of compound **40** can be explained by bond isomerization in the imine intermediate to achieve the stable conjugated system.

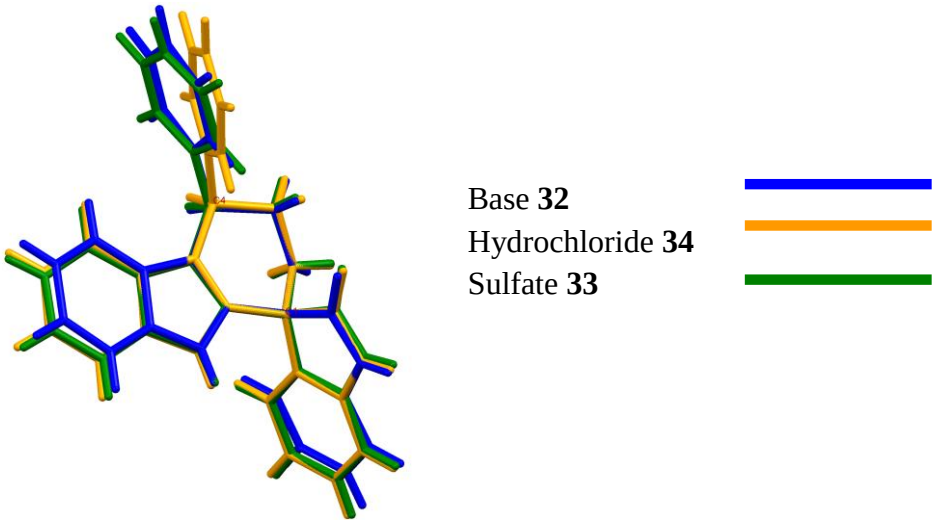
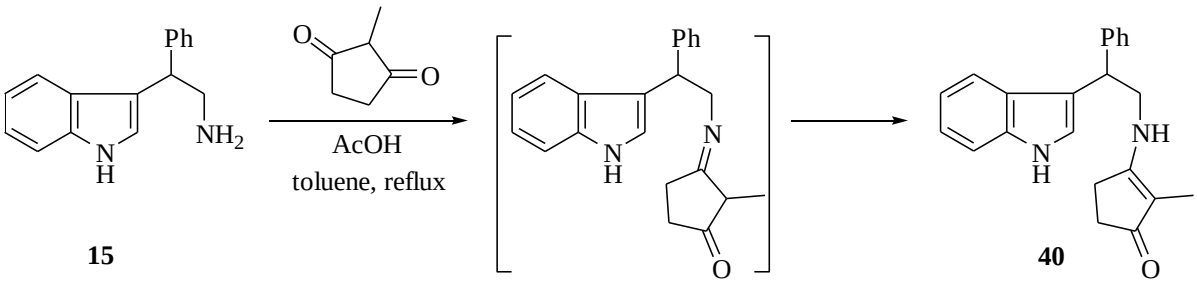


Figure 2. X-ray structures overlapping of compounds **32**, **33** and **34**.



Scheme 5

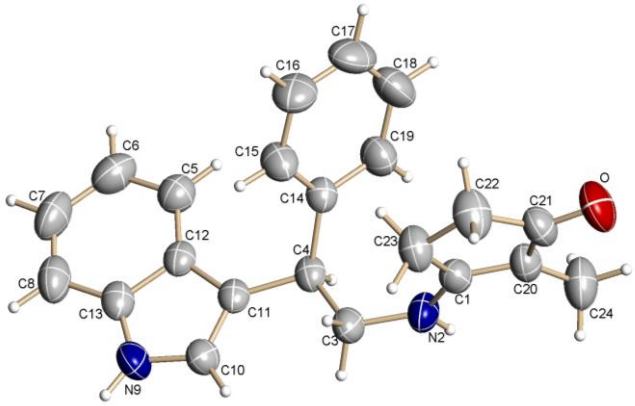


Figure 3. ORTEP diagram of compound **40,** ellipsoids is drawn at 50% probability.

Conclusions

In conclusion, catalytic activity of glacial acetic acid in Pictet–Spengler reaction has been demonstrated using symmetric ketones like cyclohexanone and cyclopentanone which furnished new spiro products. Using the same catalyst with unsymmetrical ketones, such as isatin and tetralone, one diastereomer of new THS*β*Cs resulted exclusively. The structures of the base **32**, sulfate **33**, and hydrochloride **34** were confirmed using single crystal X-ray analysis, from which the absolute configuration of the products **32**, **33** and **34** was confirmed as *R*,*R*. Thus, in the present study a diastereoselective and high yielding method for the synthesis of THS*β*Cs was established using glacial acetic acid.

Experimental Section

General. Melting points recorded are uncorrected. All solvents were of reagent grade and, when necessary, were purified and dried by standard methods. Commercially available glacial acetic acid (from Merck) was used. Reactions and products were routinely monitored by thin layer chromatography (TLC) on silica gel (Kieselgel 60 F254, Merck). Column chromatographic purifications were performed using 60-120 mesh silica gel. Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on Shimadzu 8400 instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Varian Mercury instrument using TMS as internal standard. ^{1}H NMR peaks expressed as s, bs, d, dd, t, m correspond to singlet, broad-singlet, doublet, doublet of doublet, triplet, and multiplet, respectively. Mass were recorded on Shimadzu QP 5050. Elemental analyses were recorded on a Vario EL III elemental analyzer instrument.

General procedure for Michael addition of indole on nitro olefins and further reduction to *β*-substituted tryptamines

A mixture of indole (2.4 mmol) and nitro olefin (2 mmol) was loaded on silica gel (60–120 mesh, 0.25 g) and heated in silica gel bath at 150 ^{o}C. After the reaction was complete as judged by TLC, the same silica gel was loaded on a silica-gel column. Chromatographic separation using hexane/ethyl acetate (9:1) furnished the products **8-14**. The *β*-Substituted tryptamines **15-21** were prepared using reported[25] procedure.

General procedure for the Pictet-Spengler cyclization

The mixture of the amino compound **15-21**, (2 mmol), ketone (8 mmol), and glacial acetic acid (0.1- 0.5 equiv.), was heated at 120 ^{o}C in dry toluene under nitrogen atmosphere in a Dean-Stark apparatus for 7.5-18.5 h. The heating was continued till the full consumption of the amino compound. Completion of the reaction was confirmed by TLC. The reaction mixture was diluted with ethyl acetate, washed with 10% $NaHCO_3$ and brine. The combined organic layer was dried

over sodium sulfate and the solvent was evaporated under reduced pressure. The crude product obtained was submitted to column chromatography using hexane/ethyl acetate to give the products **23-32** and **35-40**.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (23). Yield 91%; yellowish solid; mp 185-187 ºC; R_f (50% ethyl acetate/hexane) 0.35; IR (KBr): ν 3402 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.48-1.95 (m, 11H, -($C\underline{H}_2$)$_5$-, including N$\underline{H}$, exchangeable with D_2O), 3.02 (dd, *J* = 5.5, 13.5 Hz, 1H, $C_3\underline{H}$), 3.39 (dd, *J* = 5.2, 13.5 Hz, 1H, $C_3\underline{H}$), 4.15 (t, *J* = 5.2 Hz, 1H, $C_4\underline{H}$), 6.84-6.94 (m, 2H, Ar$\underline{H}$), 7.06 (dt, *J* = 1.4, 8.0 Hz, 1H, Ar$\underline{H}$), 7.11-7.30 (m, 6H, Ar$\underline{H}$), 7.85 (br s, 1H, exchangeable with D_2O, N$\underline{H}$ of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4 (st.), 25.8, 36.4, 37.2, 40.8, 48.5, 52.3, 109.7, 110.5, 119.1, 119.2, 121.3, 126.1, 126.8, 128.1 (st.), 128.2 (st.), 135.4, 142.3, 143.7; *m/z*: 316 (M^+). Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50; H, 7.64; N, 8.85. Found: C, 83.25; H, 7.89; N, 8.57%.

4-(4-Methoxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (24). Yield 90%; white solid; mp 187-189 ºC; R_f (60% ethyl acetate/hexane) 0.29; IR (KBr): ν 3373, 3308 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 1.49-2.12 (m, 11H, -($C\underline{H}_2$)$_5$- including N$\underline{H}$, exchangeable with D_2O), 2.95 (dd, *J* = 5.8, 13.2 Hz, 1H, $C_3\underline{H}$), 3.35 (dd, *J* = 5.2, 13.2 Hz, 1H, $C_3\underline{H}$), 3.76 (s, 3H, $OC\underline{H}_3$), 4.11 (t, *J* = 5.2 Hz, 1H, $C_4\underline{H}$), 6.76-6.99 (m, 4H, Ar$\underline{H}$), 7.04 (t, *J* = 7.9 Hz, 3H, Ar$\underline{H}$), 7.32 (d, *J* = 7.9 Hz, 1H, Ar$\underline{H}$), 9.59 (br s, 1H, exchangeable with D_2O, N$\underline{H}$ of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 20.5 (st.), 24.9, 35.0, 35.8, 39.7, 47.8, 51.6, 54.2, 107.9, 110.0, 112.6 (st.), 117.3, 117.8, 119.5, 125.6, 128.1 (st.), 134.9, 135.2, 141.9, 156.8; *m/z*: 346 (M^+); Anal. Calcd. for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.51; H, 7.69; N; 7.85%.

4-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (25). Yield 89%; white solid; mp 201-203 ºC; R_f (70% ethyl acetate/hexane) 0.40; IR (KBr): ν 3412 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.55-2.16 (m, 11H, -($C\underline{H}_2$)$_5$- including N$\underline{H}$, exchangeable with D_2O), 2.98 (dd, *J* = 5.5, 13.5 Hz, 1H, $C_3\underline{H}$), 3.38 (dd, *J* = 5.0, 13.5 Hz, 1H, $C_3\underline{H}$), 4.09 (t, *J* = 5.2 Hz, 1H, $C_4\underline{H}$), 5.89 (d, *J* = 2.2 Hz, 2H, $OC\underline{H}_2O$), 6.63 (d, *J* = 9.1 Hz, 2H, Ar$\underline{H}$), 6.71 (d, *J* = 7.9 Hz, 1H, Ar$\underline{H}$), 6.90 (t, *J* = 7.7 Hz, 1H, Ar$\underline{H}$), 7.00 (d, *J* = 7.4 Hz, 1H, Ar$\underline{H}$), 7.09 (t, *J* = 7.4 Hz, 1H, Ar$\underline{H}$), 7.30 (d, *J* = 7.9 Hz, 1H, Ar$\underline{H}$), 7.83 (br s, 1H, exchangeable with D_2O, N$\underline{H}$ of indole ring); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 20.4 (st.), 24.8, 34.7, 35.7, 39.6, 47.6, 51.5, 99.6, 106.8, 107.4, 107.6, 109.9, 117.3, 117.7, 119.5, 119.9, 125.4, 134.9, 137.2, 141.8, 144.6, 146.3; *m/z*: 360 (M^+). Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N,7.77. Found: C, 76.39; H, 6.58; N, 7.98%.

4-(2-Furyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (26). Yield 85%; white solid; mp 260-262 ºC; R_f (50% ethyl acetate/hexane) 0.41; IR (KBr): ν 3300 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.39-1.99 (m, 11H, -($C\underline{H}_2$)$_5$- including N$\underline{H}$, exchangeable with D_2O), 3.18 (br s, 2H, $C_3\underline{H}_2$), 4.08 (br s, 1H, $C_4\underline{H}$), 5.78 (s, 1H, Ar$\underline{H}$), 6.11 (s, 1H, Ar$\underline{H}$), 6.88 (distorted d, *J* = 7.2 Hz, 1H, Ar$\underline{H}$), 6.98 (t, *J* = 7.4 Hz, 1H, Ar$\underline{H}$),7.12 (m, 3H, Ar$\underline{H}$), 7.78 (s, 1H, exchangeable with D_2O, N$\underline{H}$ of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.4, 25.8, 33.8, 35.4, 37.9,

44.4, 52.3, 106.6, 107.8, 109.9, 110.6, 118.6, 119.3, 121.3, 126.8, 135.2, 141.3, 142.1, 156.9; *m/z*: 306 (M^+). Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.19; H, 7.07; N, 9.02%.

4-(4-Aminophenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (27). Yield 71%; white solid; mp 224-226 ºC; R_f (70% ethyl acetate/hexane) 0.13; IR (KBr): ν 3458, 3346, 3225 (br) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 1.43-2.05 (m, 13H, -(C<u>H</u>$_2$)$_5$- including N<u>H</u>, N<u>H</u>$_2$, exchangeable with D_2O), 2.75 (dd, *J* = 7.4, 13.2 Hz, 1H, C_3<u>H</u>), 3.15 (dd, *J* = 7.7, 13.2 Hz, 1H, C_3<u>H</u>), 3.90 (br s, overlapped on DMSO signal, 1H, C_4<u>H</u>), 6.45 (d, *J* = 7.9 Hz, 2H, Ar<u>H</u>), 6.59-6.85 (m, 4H, Ar<u>H</u>), 6.94 (t, *J* = 5.5 Hz, 1H, Ar<u>H</u>), 7.25 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 10.79 (br s, 1H, exchangeable with D_2O, N<u>H</u> of indole ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.9, 21.5, 25.5, 35.7 (st.), 40.3, 48.5, 52.2, 109.3, 110.8, 113.9 (st.), 117.8, 118.6, 120.0, 126.3, 128.4 (st.), 131.2, 135.5, 142.4, 146.6; *m/z*: 331(M^+). Anal. Calcd. for $C_{22}H_{25}N_3$: C, 79.72; H, 7.60; N, 12.68. Found: C, 79.49; H, 7.35; N, 12.39%.

4-(2-Thienyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (28). Yield 87%; brown solid; mp 78-80 ºC; R_f (50% ethyl acetate/hexane) 0.53; IR (KBr): ν 3410, 3273 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40-1.89 (m, 11H, -(C<u>H</u>$_2$)$_5$- including N<u>H</u>, exchangeable with D_2O), 3.05 (dd, *J* = 3.3, 13.2 Hz, 1H, C_3<u>H</u>), 3.30 (dd, *J* = 3.8, 13.2 Hz, 1H, C_3<u>H</u>), 4.30 (distorted t, *J* = 3.8 Hz, 1H, C_4<u>H</u>), 6.68 (d, *J* = 2.8 Hz, 1H, Ar<u>H</u>), 6.78 (t, *J* = 3.8 Hz, 1H, Ar<u>H</u>), 6.87 (t, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.0 (d, *J* = 5.5 Hz, 2H, Ar<u>H</u>), 7.13 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 7.19 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 7.73 (br s, 1H, exchangeable with D_2O, N<u>H</u> of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.4, 25.9, 35.5 (st.), 37.9, 48.5, 52.3, 110.2, 110.6, 118.7, 119.3, 121.4, 123.4, 124.3, 126.5, 126.8, 135.3, 141.8, 148.5; *m/z*: 322 (M^+). Anal. Calcd. for $C_{20}H_{22}N_2S$: C, 74.49; H, 6.88; N 8.69. Found: C, 74.18; H, 6.56; N 8.42%.

4-(3,4-Dimethoxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclohexane] (29). Yield 88%; white solid; mp 260-262 ºC; R_f (70% ethyl acetate/hexane) 0.27; IR (KBr): ν 3358 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.49-1.98 (m, 11H, -(C<u>H</u>$_2$)$_5$- including N<u>H</u>, exchangeable with D_2O), 3.01 (dd, *J* = 5.2, 13.5 Hz, 1H, C_3<u>H</u>), 3.35 (dd, *J* = 4.7, 13.5 Hz, 1H, C_3<u>H</u>), 3.77 (s, 3H, OC<u>H</u>$_3$), 3.83 (s, 3H, OC<u>H</u>$_3$), 4.08 (t, *J* = 4.7 Hz, 1H, C_4<u>H</u>), 6.63 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 6.72-6.75 (m, 2H, Ar<u>H</u>), 6.89 (t, *J* = 7.4 Hz, 1H, Ar<u>H</u>), 6.98 (d, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.08 (t, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.30 (d, *J* = 7.9 Hz, 1H, Ar<u>H</u>), 7.82 (br s, 1H, exchangeable with D_2O, N<u>H</u> of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6) δ 20.4 (st.), 24.9, 34.8, 36.1, 39.7, 47.7, 51.4, 54.8 (st.), 107.7, 109.9, 110.0, 110.6, 117.2, 117.6, 119.1, 119.4, 125.6, 134.7, 136.0, 142.0, 146.1, 147.5; *m/z*: 376 (M^+). Anal. Calcd. for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.75; H, 7.65; N, 7.23%.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclopentane] (30). Yield 82%; brown solid; mp 133-135 ºC; R_f (50% ethyl acetate/hexane) 0.38; IR (KBr): ν 3425 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.81-2.15 (m, 9H, -(C<u>H</u>$_2$)$_4$-, including N<u>H</u>, exchangeable with D_2O), 3.03 (dd, *J* = 5.5, 13.5 Hz, 1H, C_3<u>H</u>), 3.43 (dd, *J* = 5.0, 13.5 Hz, 1H, C_3<u>H</u>), 4.14 (t, *J* = 5.0 Hz, 1H, C_4<u>H</u>), 6.83-6.92 (m, 2H, Ar<u>H</u>), 7.07 (t, *J* = 6.1 Hz, 1H, Ar<u>H</u>), 7.10-7.35 (m, 6H, Ar<u>H</u>), 7.75 (br s, 1H, exchangeable with D_2O, N<u>H</u> of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1(st.), 40.2,

40.7, 40.9, 50.0, 61.8, 110.5 (st.), 119.1, 119.2, 121.4, 126.2, 126.8, 128.1 (st.), 128.2 (st.), 135.6, 140.5, 143.5; *m/z*: 302 (M^+). Anal. Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.18; H, 7.59; N, 9.05%.

4-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-cyclopentane] (31). Yield 79%; white solid; mp 245-247 ºC; R_f (70% ethyl acetate/hexane) 0.44; IR (KBr): ν 3412 (br) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42-2.01 (m, 9H, -(CH_2)$_4$- including NH, exchangeable with D_2O), 2.90 (dd, *J* = 5.5, 13.2 Hz, 1H, C_3H), 3.26 (distorted t, *J* = 5.0 Hz, 1H, C_3H), 3.98 (br d, *J* = 4.4 Hz, 1H, C_4H), 5.77(d, *J* = 5.5 Hz, 2H, OCH_2O), 6.45-6.65 (m, 3H, ArH), 6.75-7.05 (m, 3H, ArH), 7.15 (t, = *J* 8.2 Hz, 1H, ArH), 7.76 (br s, 1H, exchangeable with D_2O, NH of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0(st.), 40.1, 40.3, 40.8, 50.0, 61.7, 100.7, 108.0, 108.4, 110.4, 110.5, 119.0, 119.2, 121.0, 121.4, 126.7, 135.6, 137.7, 140.4, 145.8, 147.4; *m/z*: 346 (M^+). Anal. Calcd. for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N 8.09. Found: C, 76.06; H, 6.61; N, 7.92%.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one (32). Yield 88%; Colorless crystal; mp 199-201ºC; R_f (60% ethyl acetate/hexane) 0.50; IR (KBr): ν 3296 (br.), 3263, 1722 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (br s, 1H, exchangeable with D_2O, NH), 3.56 (dd, *J* = 5.5, 13.4 Hz, 1H, C_3H), 3.75 (dd, *J* = 6.7, 13.4 Hz, 1H, C_3H), 4.41 (t, *J* = 6.7 Hz, 1H, C_4H), 6.89-6.96 (m, 3H, ArH), 6.99-7.1 (m, 2H, ArH), 7.15 (d, *J* = 7.9 Hz, 1H, ArH), 7.21-7.3 (m, 3H, ArH), 7.33 (t, *J* = 7.3 Hz, 2H, ArH), 7.41 (br d, *J* = 6.7 Hz, 2H, ArH), 7.61, 8.1 (2×br s, 2H, exchangeable with D_2O, 2×NH of isatyl ring and indole ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 40.3, 48.3, 61.8, 110.9, 111.1, 114.0, 119.2, 119.5, 122.1, 123.0, 124.6, 126.1, 126.5, 128.1, 128.3 (st.), 128.4 (st.), 129.8, 131.0, 136.3, 140.7, 142.6, 178.8; *m/z*: 365 (M^+). Anal. Calcd. for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.65; H, 5.39; N, 11.34%.

4-(4-Methoxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one (35). Yield 84%, white solid; mp 280-281ºC; R_f (70% ethyl acetate/hexane) 0.47; IR (KBr): ν 3610, 3342, 3286, 1732 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 1H, exchangeable with D_2O, NH), 3.26 (distorted t, *J* = 5.0 Hz, 1H, C_3H), 3.50 (distorted t, *J* = 6.6 Hz, 1H, C_3H), 3.73 (s, 3H, OCH_3), 4.33 (t, *J* = 6.1 Hz, 1H, C_4H), 6.63-6.78 (m, 2H, ArH), 6.82-7.01 (m, 5H, ArH), 7.15 (t, *J* = 7.9 Hz, 2H, ArH), 7.20-7.33 (m, 3H, ArH), 10.53, 10.57 (2×s, 2H, exchangeable with D_2O, 2×NH of isatyl ring and indole ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 39.9, 48.5, 54.9, 61.0, 109.7, 111.0, 113.0, 113.4 (st.), 118.0, 118.6, 120.7, 121.6, 124.4, 125.7, 129.0 (st.), 132.3, 132.5, 135.5, 136.1, 142.2, 157.5, 177.9; *m/z*: 395 (M^+); Anal. Calc. for $C_{25}H_{21}N_3O_2$: C, 75.93; H, 5.35; N, 10.63. Found: C, 75.75; H, 5.09; N 10.45%.

4-(3,4-Methylenedioxyphenyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one (36). Yield 85%; yellowish solid; mp 266-268 ºC; R_f (70% ethyl acetate/hexane) 0.46; IR (KBr): ν 3398 (br), 3288, 1730 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.03 (s, 1H, exchangeable with D_2O, NH), 3.28 (dd, *J* = 5.3, 12.9 Hz, 1H, C_3H), 3.45 (dd, *J* = 6.6, 12.9 Hz, 1H, C_3H), 4.25 (t, *J* = 6.6 Hz, 1H, C_4H), 5.97 (s, 2H, OCH_2O), 6.76 (d, *J* = 5.9 Hz, 2H, ArH), 6.8 (d, *J* = 6.6 Hz, 1H, ArH), 6.86 (s, 2H, ArH), 6.91-6.99 (m, 3H, ArH), 7.15 (t, *J* = 9.9 Hz, 2H, ArH), 7.28 (t, *J* = 7.7 Hz, 1H, ArH), 10.55, 10.58 (2×s, 2H, exchangeable with D_2O, 2×NH of isatyl ring and indole

ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 39.8; 48.9, 61.6, 100.9, 108.1, 108.9, 110.4, 111.5, 113.1, 118.7, 119.1, 121.4, 121.5, 122.2, 124.8, 126.3, 129.4, 132.8, 132.9, 136.7, 138.2, 142.7, 146.1, 147.6, 178.4; *m/z*: 409 (M^+). Anal. Calcd. for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.14; H, 4.89; N 10.01%.

4-(2-Thienyl)-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one (37). Yield 81%; brown solid; mp 134-136 ºC; R_f (50% ethyl acetate/hexane) 0.46; IR (KBr): ν 3390, 3280, 3186, 1718 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.96 (br s, 1H, exchangeable with D_2O, NH), 3.44 (br s, 1H, C_3H), 3.53 (dd, *J* = 5.4, 12.0 Hz, 1H, C_3H), 4.62 (t, *J* = 5.5 Hz, 1H, C_4H), 6.8 (t, *J* = 7.6 Hz, 1H, ArH), 6.85-7.03 (m, 6H, ArH), 7.15 (t, *J* = 10.5 Hz, 2H, ArH), 7.19-7.3 (m, 2H, ArH), 10.58 (s, 2H, exchangeable with D_2O, 2×NH of isatyl ring and indole ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 35.1, 48.8, 61.1, 109.8, 111.0, 112.6, 118.2, 118.4, 120.9, 121.6, 123.7, 124.3, 124.6, 125.6, 126.3, 128.9, 132.0, 132.4, 136.1, 142.1, 147.3, 177.6; *m/z*: 371 (M^+). Anal. Calcd. for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31. Found: C, 70.91; H, 4.79; N 11.12%.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,1′-*α*-tetralone] (38). Yield 76%; white solid; mp 183-185ºC; R_f (50% ethyl acetate/hexane) 0.50; IR (KBr): ν 3437, 3421 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 2H), 2.05 (s, 1H), 2.17 (s, 3H), 3.81 (dd, *J* = 6.6, 13.2 Hz, 1H, C_3H), 4.04 (dd, *J* = 6.6, 13.2 Hz, 1H, C_3H), 4.4 (t, *J* = 7.6 Hz, 1H, C_4H), 5.71 (br s, 1H, exchangeable with D_2O, NH), 6.95-7.05 (m, 3H, ArH), 7.14 (t, *J* = 7.7 Hz, 2H, ArH), 7.22 (t, *J* = 7.7 Hz, 1H, ArH), 7.25-7.34 (m, 6H, ArH), 7.42 (d, *J* = 7.7 Hz, 1H, ArH), 8.64 (br s, 1H, exchangeable with D_2O, NH of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5 (st.), 30.1, 36.7, 67.2, 113.6 (st.), 120.4 (st.), 122.5, 123.1, 124.7 (st.), 126.3, 126.5 (st.), 128.9, 129.0 (st.), 133.6 (st.), 135.4, 137.8; *m/z*: 364 (M^+). Anal. Calcd. for $C_{26}H_{24}N_2$: C, 85.68; H, 6.64; N, 7.69. Found: C, 85.35; H, 6.89; N, 7.91%.

4-(4-Methoxyphenyl)-2,3, 4,9-tetrahydrospiro[*β*-carboline-1,1′-*α*-tetralone] (39). Yield 72%; oily; R_f (60% ethyl acetate/hexane) 0.45; IR (KBr): ν 3404, 3302 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 1H), 1.91 (s, 2H), 2.2 (s, 3H), 3.72-3.89 (m, 4H, C_3H and OCH_3), 4.03 (dd, *J* = 7.6, 13.5 Hz, 1H, C_3H), 4.38 (t, *J* = 7.6 Hz, 1H, C_4H), 5.53 (brs, 1H, exchangeable with D_2O, NH), 6.81 (t, *J* = 8.8 Hz, 3H, ArH), 6.95-7.07 (m, 3H, ArH), 7.11-7.27 (m, 4H, ArH), 7.34 (d, *J* = 8.2 Hz, 1H, ArH), 7.42 (d, *J* = 7.6 Hz, 1H, ArH), 8.33 (brs, 1H, exchangeable with D_2O, NH of indole ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.3 (st.), 27.6, 34.2, 54.7, 66.7, 113.6 (st.), 120.3 (st.), 121.4, 123.3, 124.0 (st.), 124.9 (st.), 126.6 (st.), 128.5, 129.1 (st.), 133.7 (st.), 135.2, 137.8, 155.1; *m/z*: 394 (M^+). Anal. Calcd. for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 81.93; H, 6.89; N 7.33%.

Compound (40). Yield 89%; colorless crystal; mp 191-193 ºC; R_f (70% ethyl acetate/hexane) 0.11; IR (KBr): ν 3367 (br) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 3H, CH_3), 2.15-2.62 (m, 4H, -(CH_2)$_2$-), 3.85 (dd, *J* = 6.4, 13.8 Hz, 1H, C_3H), 4.02 (dd, *J* = 6.3, 12.7 Hz, 1H, C_3H), 4.49 (t, *J* = 7.2 Hz, 1H, C_4H), 6.63 (br s, 1H, exchangeable with D_2O, NH), 6.93 (t, *J* = 7.2 Hz, 1H, ArH), 7.09 (t, *J* = 7.2 Hz, 2H, ArH), 7.13-7.50 (m, 7H, ArH), 10.46 (br s, 1H, exchangeable with D_2O, NH of indole ring). ^{13}C NMR (75 MHz, DMSO-d_6) δ 6.7, 23.8, 32.5, 43.4, 48.5, 105.1, 111.3, 115.3, 118.2, 118.5, 120.9, 122.0, 126.1, 126.5, 128.0 (st.), 136.1, 143.1, 173.1,

199.5; *m/z*: 330 (M^+). Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.64; H, 6.99; N, 8.27%.

General procedure for preparation of compounds (33 and 34)

A few drops of concentrated H_2SO_4 or HCl were added to compound **32** (0.2 g, 0.55 mmol) dissolved in methanol (3 mL). The reaction mixture stirred with heating till the solution became clear and kept at room temperature for 24 h. Completion of the reaction was confirmed by TLC. The solvent was removed and the crystals were washed twice with methanol to furnish the expected product 1,1-isatyl-4-phenyl-2,3,4,9-tetrahydrospiro-*β*-carboline sulfate **33** or hydrochloride **34**.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one sulfate (33). Yield 95%; colorless crystals; mp above 300 ºC; R_f (50% acetone/hexane) 0.10; IR (KBr): ν 3389, 3244 (br), 1725 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.84 (dd, *J* = 6.1, 12.1 Hz, 1H, C_4H), 4.14 (t, *J* = 10.7 Hz, overlapped on DMSO-d_6 1H, C_3Ha), 4.72 (dd, *J* = 6.1, 10.7 Hz, 1H, C_3He), 6.54 (d, *J* = 7.7 Hz, 1H, ArH), 6.77 (t, *J* = 7.2 Hz, 1H, ArH), 7.03 (t, *J* = 8.3 Hz, 1H, ArH), 7.1-7.24 (m, 3H, ArH), 7.32-7.45 (m, 6H, ArH), 7.53 (t, *J* = 7.7 Hz, 1H, ArH), 10.55, 11.02 and 11.41 (4x br s, 4H, exchangeable with D_2O, 2xNH of isatyl ring and indole ring and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.8, 44.7, 59.5, 111.3, 111.9 (st.), 119.3 (st.), 122.4, 123.0, 124.4, 124.8, 126.4, 126.9, 127.6, 128.5 (st.), 128.8 (st.), 132.1, 136.9, 140.4, 143.2, 172.1; *m/z*: 435 (M^+-28). Anal. Calcd. for $C_{24}H_{21}N_3O_5S$: C, 62.19; H, 4.57; N, 9.07. Found: C, 61.98; H, 4.71; N 8.81%.

4-Phenyl-2,3,4,9-tetrahydrospiro[*β*-carboline-1,3′-indol]-2′(1′*H*)-one hydrochloride (34). Yield 94%, colorless crystals; mp 255-257 ºC; R_f (90% ethyl acetate/hexane) 0.40; IR (KBr): ν 3306, 3248, 3217 (br), 1739 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 3.71 (dd, *J* = 6.1, 12 .1 Hz, 1H, C_4H), 4.17 (t, *J* = 11.3 Hz, 1H, C_3Ha), 4.83 (dd, *J* = 6.1, 10.6 Hz, 1H, C_3He), 6.54 (d, *J* = 8.0 Hz, 1H, ArH), 6.76 (t, *J* = 7.4 Hz, 1H, ArH), 7.02 (t, *J* = 7.7 Hz, 1H, ArH), 7.13 (t, *J* = 7.7 Hz, 2H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 7.39 (br s, 5H, ArH), 7.51 (t, *J* = 7.7 Hz, 1H, ArH), 7.63 (d, *J* = 7.4 Hz, 1H, ArH), 10.97, 11.4 (2x br s, 4H, exchangeable with D_2O, 2xNH of isatyl ring and indole ring and NH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ 38.8, 48.3, 60.9, 109.7, 111.0, 112.6, 118.0, 118.5, 120.7, 121.5, 124.4, 125.6, 126.0, 127.9(st.), 128.0 (st.), 128.9, 132.2, 132.5, 136.0, 142.2, 143.6, 177.8; *m/z*: 365 (M^+-36). Anal. Calcd. for $C_{24}H_{20}ClN_3O$: C, 71.73; H, 5.02; N, 10.46. Found: C, 71.52; H, 4.81; N, 10.22%.

Crystallography

Crystallographic data in this paper have been deposited with the Cambridge Crystallographic Data Centre. Deposition numbers are CCDC 752864 for **33**, CCDC 752865 for **40**, CCDC 752866 for **32** and CCDC 752867 for **34**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

Crystal data. The X-ray data of all the four compounds were collected at *T* = 296 K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a

maximum θ range of 25.00°. The structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL)[28] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

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