First highly stereocontrolled synthesis of tetrahydro *trans*-β-carboline derivatives by exploiting the influence of a cyclic amide

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Dedicated to Professor Richard R. Schmidt on the occasion of his 78th anniversary

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Abstract
Stereocontrolled synthesis of *trans*-β-carboline derivatives by employing amidation strategy is presented.

Keywords: Stereocontrolled, tryptophan, β-carboline, diketopiperazine, tadalafil, mixed anhydride

Introduction

Carbolines and tetrahydro-β-carbolines as shown in Figure 1 are the key building blocks of many drug candidates and are abundantly found in natural products.[1] Considering their medicinal significance, many synthetic pathways have been developed.[2] There are few functionalized tetrahydro-β-carboline derivatives that were identified as selective PDE5 inhibitors and anti-hypertensive agents.[3] Of these, (6*R*,12a*R*)-6-(1,3-benzodioxol-5-yl)-2-methyl-1,2,3,4,6,7,12,12a-octahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione, tadalafil (**1c**; Figure 1) is a potent orally active phosphodiesterase (PDE5) inhibitor[3] discovered by GlaxoSmithKline, which is widely used for the management of erectile dysfunction (ED) under the trade names Cialis® and Adcirca®.

The Pictet-Spengler reaction[4] that involves the cyclization of relatively electron-rich aromatic framework by involving imine or iminium moieties is method of choice for constructing

carbolines.[5] This strategy has been employed in the total synthesis of numerous natural products including azatoxin, **1**a[6] and alstophylline **1b**.[7,8] Additionally, tetrahydro-β-carboline-hydantoin and tetrahydro-β-carboline piperazinedione scaffolds were also identified to have anti-cancer[9] and anti-HIV activities.[10]

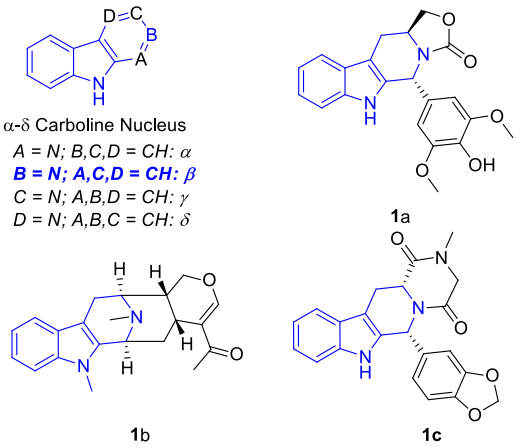


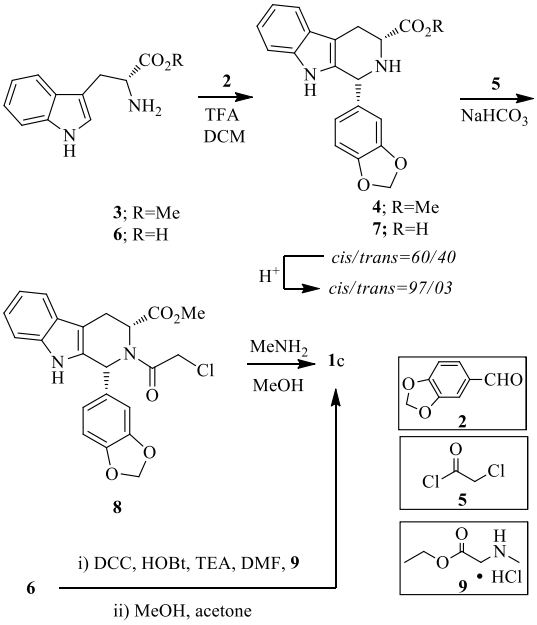
Figure 1. Core structure of carbolines and medicinally relevant entities.

We were interested to work on tadlafil and its isomers and the literature search revealed that the first synthesis of tadalafil **1c** was described by two groups Martin *et al*.[11] and Daugan *et al*.[12] Both the approaches involve cyclization of D-tryptophan methyl ester **3** with piperonal **2** using trifluoroacetic acid (TFA) in dichloromethane that afforded (1*R*,3*R*)-*cis*-pyrido-indole derivative **4** via isomerization (*cis*/*trans*: from 60/40 to 97/03). Thereafter, acylation of **4** with chloroacetyl chloride **5** yielded the chloroacetyl derivative **8**, which was finally subjected to cyclization with methylamine in methanol to yield **1c** as shown in Scheme 1. Moreover, direct activation of tryptophan **6** with DCC/HOBt followed by reaction with **9** afforded tadalafil **1c**.

Considering the presence of two chiral centres, most of the synthesis of **1c** employed the commercially available D-tryptophan derivative that has predisposed systemic chirality, and the second chiral center was generated through substrate controlled Pictet-Spengler type cyclization followed by acid mediated transformation of the *trans* isomer to the desired *cis* isomer predominantly as shown in Figure 2.[13] Unlike to amino ester, β-carboline *trans*-**4**, isomerization of *trans*-tadalafil **12** to tadalafil **1c** was unsuccessfully attempted (Figure 2).

An alternative synthesis of **1c** was reported[14] starting from L-tryptophan in seven steps. Another approach employed sarcosine ester **9** through double amidation[15] based two-step synthesis of **1c**. Recently, Shi. *et al*.[16] has published the synthesis of **1c** using an improved acid catalyzed stereoselective Pictet-Spengler reaction. So far, to the best of our knowledge, apart from substrate controlled stereocontrolled synthesis disclosed by Cook *et al*.,[17] there is no methodology reported that describes the synthesis of exclusively *trans*-β-carboline derivatives by manipulating amide functionalty. Herein, we disclose a methodology that enabled us to

synthesize *trans*-β-carboline derivative in a stereocontrolled manner using the diketopiperazine moiety present in the substrate.



Scheme 1. Precedented approaches for tadalafil synthesis.

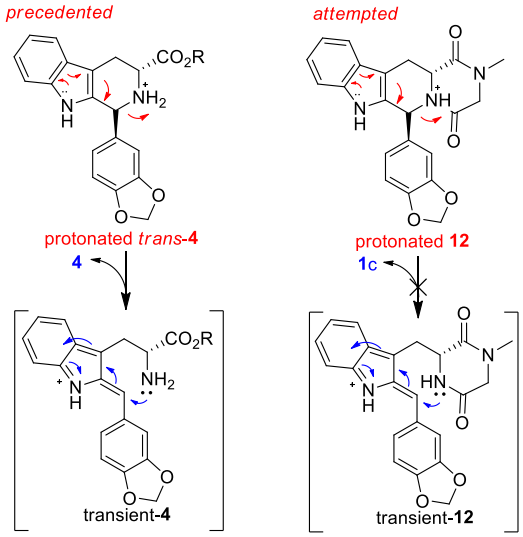
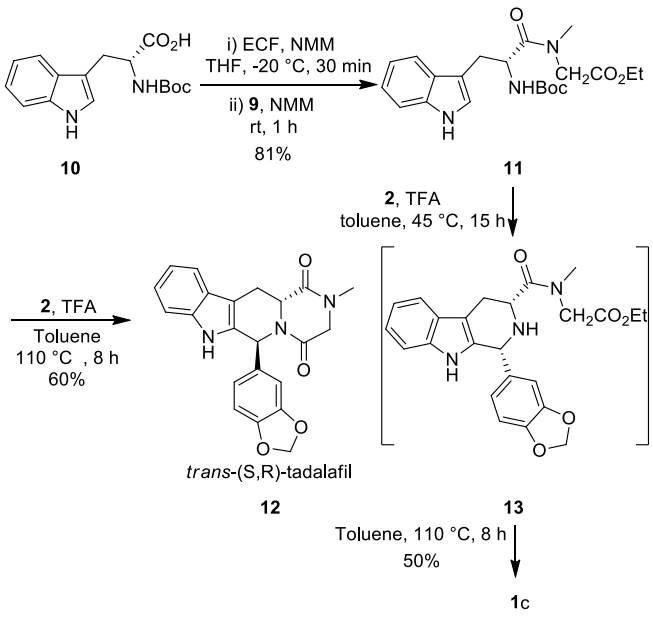


Figure 2. Acid mediated *trans-cis* isomerisation.

Results and Discussion

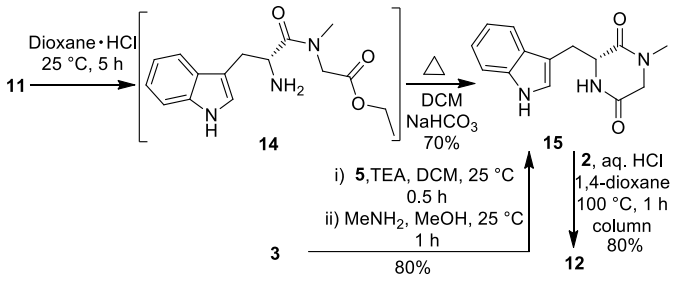
In our endeavors, we attempted the synthesis of **1c** and its isomer *via* new intermediates starting from the commercially available *N*-Boc-D-tryptophan **10**. In this approach, mixed anhydride methodology was adopted for amidation using sarcosine moiety. Considering the thermodynamic stability of *trans*-β-carboline over its *cis* isomer as reported,[9,16-19] we first explored the possibility of a stereocontrolled synthesis of the *S,R* diastereomer of *trans* tadalafil **12**.

As shown in Scheme 2, substrate **10** was treated with ethyl chloroformate (ECF) to generate its mixed anhydride *in situ* followed by reaction with **9** to yield an intermediate **11**. Thereafter, at higher temperature, we were able to construct piperazine ring in a *trans* (*S,R*) fashion yielding **12** while at lower temperature *R,R* isomer, tadalafil **1c** was observed. Predominant formation of **1c**, at low temperature, is due to the fact that the slow reaction rate of piperazine ring construction led to an epimerization of the *trans* isomer to *cis* isomer **13**[13,16,20] followed by intramolecular amidation.



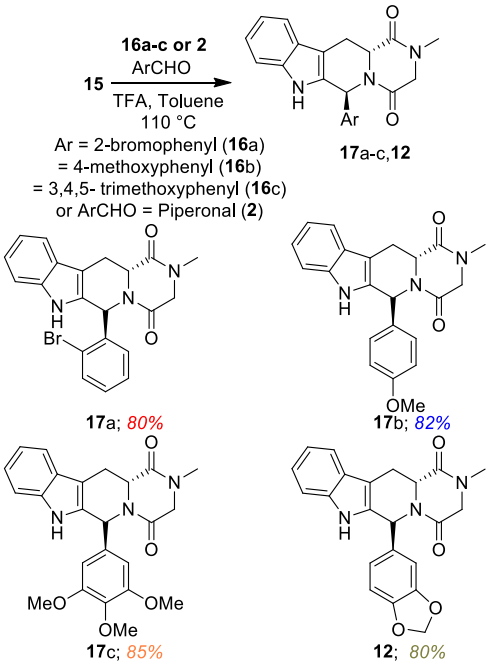
Scheme 2. New synthetic approach for tadalafil **1c** and its *trans* isomer **12**.

Secondly, we examined the transformation switch strategy where the piperazine ring was constructed first either starting from intermediate **11** or **3** to access **15**. Thereafter, reaction of **15** with aldehyde **2** afforded stereocontrolled *trans* isomer **12** in excellent yield as shown in Scheme 3.



Scheme 3. Transformation switch strategy for *trans* tadalafil **12**.

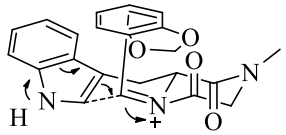
Encouraged by the outcome of Scheme 3, we intended to establish a generality of this approach by diversifying the intermediate **15** to synthesize few derivatives of *trans* tadalafil **12**. Such an approach led to a new methodology (Schemes 3 and 4) for modified stereocontrolled Pictet-Spengler reaction to synthesize β-carboline derivatives starting from 1,4-diketopiperazine scaffold. This type of diketopiperazine derivatives e.g. *S* isomer of **15** are recently disclosed in different context by using the Ugi reaction strategy.[21] Hitherto known procedures for modified Pictet-Spengler reaction were found to utilize amines, substituted amines[1,3,12,14,15,22] or carbamates[23] for β-carboline synthesis. However, in our approach, we utilized amide **15** to yield β-carboline derivatives **17**a-c and **12** as shown in Scheme 4.



Scheme 4. Synthesis of congeners of *trans* tadalafil **12**.

Isomerisation of β-carbolines[9,19] are well documented and the literature findings reveal that the use of bulky moieties e.g. esters of tryptophan result in *trans* isomers predominantly at higher

temperature however at lower temperature the *cis* isomer can preferably be obtained.[9,17,19,20,22-23] Considering the low reactivity than amines and structural attributes of amide, it is quite apparent that the intermediate **15** can offer conformationally locked six membered sterically constrained amide ring system which is amenable to afford *trans* products **17a-c** including **12** plausibly due the iminium transition state where the carboline ring might form from top of the plane as depicted in the Figure 3.



TS

Figure 3. Transition state disposed for affording *trans* product.

We also observed the influence of acid and solvent in the condensation to obtain *in situ* iminium species followed by carboline ring formation. Aq. HCl in 1,4-dioxane was found to be suitable to affect the carboline ring formation at 100 °C in 95% conversion as shown in Table 1 (entry 2).

Table 1. Acid screening for β-carboline synthesis

Entry	Acid/solvent	Temp (°C)	Time (h)	Trans (%)
1	PTSA/toluene	105	8*	70
2	aq. HCl/1,4-dioxane	100	7	95
3	aq. HCl/acetonitrile	82	10	15
4	aq. HCl/2-propanol	85	10	10
5	aq. HCl/ethanol	78	10	10
6	aq. HCl	100	10	10
7	BF_3/Ether	25	5*	-

*reaction did not proceed to completion.

Conclusions

In summary, we have successfully demonstrated an unprecedented stereocontrolled synthesis of *trans* isomer of tadalafil **12** and β-carboline derivatives **17a-c**. The method disclosed here is the first of its kind for the synthesis of β-carbolines that employs the less reactive amide rather than the amine.

Experimental Section

General. All starting materials were commercial substances. LR grade solvents and commercial reagents were used without further purification. The FT IR spectra were recorded as KBr pallet and only diagnostic and/or intense peaks are reported. Mass spectra (70 eV) were recorded on LC-MS spectrometer. The melting points were determined by using the capillary method and are uncorrected. ^{1}HNMR spectra were recorded in $CDCl_3$ and DMSO-d6 using a 400 MHz instrument. ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d6 using a 400 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (J) corresponds to the order of multiplicity assignment. TLC analyses were performed on silica gel precoated-plates (250 μm layers). We note that our stereo chemical assignments are supported by comparisons with the literature. HPLC analysis was performed with Waters Symmetry shield RP18 (250X4.6 mm, 5μ) column by using gradient elution and monitored at 220 nm.

(*R*)-Ethyl 2-(2-((tert-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)-*N*-methyl propanamido) acetate (11). A mixture of *N*-Boc-D-tryptophan (5 g, 16.4 mmol) and THF (25 mL) was cooled to -20 °C under nitrogen atmosphere. To the mixture charged *N*-methyl morpholine (1.83 g, 18 mmol) and stirred for 20 min. Thereafter, a solution of ethyl chloroformate (1.95 g, 18 mmol) in THF (2 mL) was slowly added and stirred the reaction mass for 30 min. Subsequently, a solution of sarcosine ethyl ester in THF (5 mL) was prepared by treating sarcosine ethyl ester hydrochloride (2.76 g, 18 mmol) with *N*-methyl morpholine (2 g). This solution was added to the solution of mixed anhydride in THF drop wise at -20 °C. The reaction mass was allowed to attain ambient temperature and maintained for 1 h. After completion of the reaction, solvent was removed by distillation (CAUTION: THF forms peroxides while distillation and hence PPE should be wear during concentration of THF) and to the obtained residue water and DCM were charged. After stirring, organic layer was separated and 2N HCl washings (2 x 10 mL) were given followed by bicarbonate washing (1 x 10 mL). The organic layer was evaporated to give compound **11** in 5.4 g, 81% yield; mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* 7.2 Hz), 1.42 (s, 9H), 2.77 (s, 3H), 3.13-3.24 (m, 2H), 3.9-4.08 (m, 2H), 4.17 (q, 2H, *J* 7.2 Hz), 4.99 (dd, 1H, *J* 7.8 Hz), 5.41-5.43 (d, 1H), 7.1-7.35 (m, 4H), 7.6 (d, 1H, *J* 7.8 Hz), 8.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.9, 25.6, 28.3, 29.3, 33.9, 36.2, 49.6, 50.8, 51.0, 61.2, 77.6, 110.2, 111.1, 118.7, 119.5, 121.9, 123.3, 136.0, 155.2, 168.9, 172.8; IR (KBr) ν 3295, 3060, 2981, 2933, 1750, 1688, 1645, 1459, 1203, 1171, 746 cm^{-1}; $[\alpha]_D^{28.4}$ -4.65 (c 0.50, CH_3OH); HRMS (ESI) calcd for $C_{21}H_{30}N_3O_5$ [M^++H]: 404.2185; Found: 404.2171.

(6*R*,12a*R*)-6-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6] pyrido[3,4-*b*]indole-1,4(6*H*,7*H*)-dione (1c). A mixture of toluene (10 mL), compound **11** (1 g,

12.4 mmol) and compound **2** (0.36 g, 12.65 mmol) were stirred for 10 min. Trifluoroacetic acid was added slowly and the reaction mass was heated to 45-50 °C, maintained at the same temperature for 15 h and concentrated under vacuum. To the obtained residue, charged water (5 mL) and dichloromethane (5 mL) and the mixture was neutralized with saturated sodium bicarbonate solution. Organic layer was separated and concentrated below 35 °C under vacuum. Charged toluene (5 mL) to the obtained residue and the mixture was heated to reflux. After stirring for 8 h, reaction mass was cooled to ambient temperature and the product separated was filtered to give tadalafil, **1c** in 0.39 g, 50% yield; mp 301-303 °C; purity by HPLC 99.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (s, 3H), 3.18-3.25 (m, 1H), 3.77 (dd, 1H, *J* 4.4Hz, 16.1Hz), 3.93 (d, 1H, *J* 17.7 Hz), 4.08 (d, 1H, *J* 17.7 Hz), 4.29-4.31 (m, 1H), 5.85 (s, 2H), 6.15 (s, 1H), 6.67-6.73 (m, 2H), 6.84-6.86 (m, 1H), 7.14-7.18 (m, 2H), 7.26-7.28 (m, 1H), 7.61(d, 1H, *J* 6.4), 7.9 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 33.6, 52.1, 56.2, 56.6, 101.1, 106.4, 107.4, 108.2, 111.2, 118.6, 120.0, 120.6, 122.4, 126.1, 132.8, 135.3, 136.5, 147.1, 147.8, 166.4, 166.8; IR (KBr) ν 3327, 3061, 2904, 1677, 1650, 1627, 1438, 1323, 1242, 1041, 939, 922, 746 cm^{-1}; $[\alpha]_D^{26.8}$ 70.54 (c 0.99, $CHCl_3$); HRMS calcd for $C_{22}H_{20}N_3O_4$ [M^++H]: 390.1454; Found: 390.1454.

(*R*)-3-((1*H*-Indol-3-yl)methyl)-1-methyl piperazine-2, 5-dione (15). Method a. A mixture of compound **11** (2 g, 12.4 mmol) and hydrochloric acid in dioxane (20 mL, 4N) and stirred at ambient temperature for 5 h. Thereafter, reaction mass was concentrated under reduced pressure. Charged DCM and washed with saturated sodium bicarbonate solution (15 mL). Then, solvent was evaporated under reduced pressure to get the desired compound **15** in 0.9 g, 70% yield. **Method b.** A suspension of HCl salt of compound **3** (1.17 g, 4.58 mmol) in chloroform (10 mL), to that added aqueous ammonia solution (2 mL) and water (10 mL) and stirred at ambient temperature for 10 min. Organic layer was separated and solvent was evaporated under reduced pressure. The obtained residue was diluted with chloroform (10 mL) then added triethyl amine (0.394 g, 3.894 mmol) and cooled to 0 °C. Compound **5** (0.66 g, 5.84 mmol) was added and the reaction mass was stirred for 1 h. Thereafter, water (10 mL) was added to the mass below 10 °C, and organic layer was separated and washed with saturated sodium bicarbonate solution followed by water. Finally, organic layer was distilled under vacuum. To the obtained compound, methylamine (0.42 g, 13.548 mmol) in methanol (10 mL) was added and stirred for 6 h at 55 °C for completion of the reaction. Subsequently, the reaction mass was cooled to ambient temperature and separated solids were filtered. The filtrate was evaporated to get the desired compound **15** in 0.95 g, 80% yield; mp 234-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H), 2.98 (dd, 1H, *J* 4.4 Hz, 14.4 Hz), 3.27 (dd, 1H, *J* 3.9 Hz, 14.4 Hz), 3.36 (s, 3H), 4.1 (br s, 1H), 6.9-7.1 (m, 3H), 7.34 (d, 1H, *J* 7.9 Hz), 7.43 (d, 1H, *J* 7.9 Hz) 8.18 (br s, 1H, NH), 11.0 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ 30.1, 32.8, 50.4, 55.5, 107.9, 111.3, 118.3, 118.7, 121.0, 125.0, 127.2, 136.0, 165.1, 166.3; IR (KBr) ν 3250, 3057, 2931, 1686, 1650, 1630, 1474, 1321, 1189, 1103, 1028, 738, 712 cm^{-1}; $[\alpha]_D^{28.4}$ -133.5 (c 0.49, CH_3OH); HRMS calcd. for $C_{14}H_{16}N_3O_2$ (M^++H) 258.1243; found (M^++H) 258.1246.

(6*S*,12a*R*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6] pyrido[3,4-*b*]indole-1,4(6*H*,7*H*)-dione (12). Method a. A mixture of toluene (10 mL), compound **11** (1 g, 12.4 mmol) and compound **2** (0.36 g, 12.65 mmol) was stirred for 10 min. Trifluoroacetic acid was added slowly and the reaction mass was heated to reflux and maintained at the same temperature for 8 h. Thereafter, the reaction mass was cooled to ambient temperature and neutralize it with saturated sodium bicarbonate solution. Charge dichloromethane (15 mL) to the mass and stir for 10 min. Organic layer was separated and concentrated below 35 °C under vacuum and the product was purified by column chromatography to give pure *S,R* isomer of tadalafil, **12** in 0.7 g, 65% yield. **Method b.** A mixture of compound **15** (2 g, 7.78 mmol) and **2** (1.17 g, 7.78 mmol) is taken along with aqueous HCl (10 mL, 6N) and dioxane (10 mL) and stirred at reflux temperature for 1 h. Thereafter, reaction mass was concentrated under reduced pressure. Charged DCM and washed with saturated sodium bicarbonate solution (30 mL). Subsequently, solvent was evaporated under reduced pressure followed by purification through column chromatography using petroleum ethers: ethyl acetate (7:3) to give pure compound **12** in 2.4 g, 80% yield; mp 287-288 °C; purity by HPLC 99.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91-2.98 (m, 1H), 3.0 (s, 3H), 3.55 (dd, 1H, *J* 12 Hz, 4.4 Hz), 4.0 (s, 2H, *J* 17.7 Hz), 4.14 (d, 2H, *J* 17.6 Hz), 4.35 (dd, 1H, *J* 11.9 Hz, 4.4 Hz), 5.9 (s, 2H), 6.72 (s, 2H), 6.82 (s, 1H, Ar), 6.98 (s, 1H), 7.14-7.24 (m, 2H), 7.28 (d, 1H, *J* 7.8 Hz), 7.53 (d, 1H, *J* 7.8 Hz), 7.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 27.6, 33.4, 51.4, 51.8, 52.4, 101.3, 108.3, 109.0, 119.1, 111.1, 118.4, 120.0, 122.4, 122.7, 126.2, 129.7, 132.3, 136.3, 148.0, 148.1, 161.5, 165.4**;** IR (KBr) *ν* 3348, 3060, 2926, 1657, 1623, 1594, 1452, 1325, 1263, 1040, 934.9, 746.1 cm^{-1}; $[\alpha]_D^{28}$ 278 (c 1.03, $CHCl_3$); HRMS calcd for $C_{22}H_{20}N_3O_4$ [M^++H]: 390.1454. Found: 390.1460.

Procedure for preparation of compounds 17. A mixture of compound **15** (7.78 mmol) and **16** (7.78 mmol) in aqueous HCl (10 mL, 6N) and dioxane (10 mL) is stirred at reflux temperature. After stirring for 1 h, reaction mass was concentrated under reduced pressure and DCM was charged and washed with saturated sodium bicarbonate solution (30 mL). Theraafter, solvent was evaporated under reduced pressure to get crude compound **17** followed by its purification through column chromatography using petroleum ethers: ethylacetate (7:3) to give pure compound **17** in 80-85% yield range.

(6*S*,12a*R*)-6-(2-Bromophenyl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4(6*H*,7*H*)-dione (17a). 80% Isolated yield; mp 283-284 °C; purity by HPLC 99.9%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92-2.96 (m, 1H), 3.02 (s, 3H), 3.49 (dd, 1H, *J* 15.6 Hz, 4.3 Hz), 4.07-4.13 (m, 2H), 4.33 (dd, 1H, *J* 11.95 Hz, 4.4 Hz), 6.84 (d, 1H, *J* 9.3 Hz), 7.16-7.26 (m, 5H), 7.32 (d, 1H, *J* 7.8 Hz), 7.52 (d, 1H, *J* 7.8 Hz), 7.65 (d, 1H, *J* 9.3 Hz), 7.97 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.3, 29.7, 33.3, 51.4, 52.2, 53.0, 60.4, 108.7, 111.3, 118.3, 120.0, 122.7, 124.1, 126.2, 127.5, 129.8, 130.3, 131.1, 133.7, 136.3, 136.7, 163.2, 166.1; IR (KBr) ν 3305, 3057, 2930, 1668, 1655, 1621, 1453, 1328, 1041, 743.5 cm^{-1}; $[\alpha]_D^{29.6}$ 199.78 (c 0.50, $CHCl_3$); EI-MS *m/z* 422 [M^-].

(6*S*,12a*R*)-6-(4-Methoxyphenyl)-2-methyl-2,3,12,12a-tetrahydropyrazino[1',2':1,6]pyrido-[3,4-*b*]indole-1,4(6*H*,7*H*)-dione (17b). 82% Isolated yield; mp 245-246 °C; purity by HPLC

99.0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.92-2.96 (m, 1H), 2.99 (s, 3H), 3.56 (dd, 1H, *J* 15.5 Hz, 4.4 Hz), 3.8 (s, 3H), 3.99 (d, 1H, *J* 17.6 Hz), 4.1 (d, 1H, *J* 17.6 Hz), 4.34 (dd, 1H, *J* 11.95 Hz, 4.4 Hz), 6.84 (m, 2H), 7.0 (s, 1H), 7.16-7.23 (m, 4H), 7.31 (d, 1H, *J* 7.8 Hz), 7.52 (d, 1H, *J* 7.6 Hz), 7.86 (brs,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 33.3, 51.3, 51.5, 52.3, 55.3, 108.7, 111.1, 114.1, 118.3, 119.8, 122.5, 126.2, 130.0, 130.5, 136.3, 159.8, 161.4, 165.4; IR (KBr) ν 3333, 3057, 2932, 1658, 1648, 1591, 1459, 1329, 1237, 1126, 1004, 745, 708 cm^{-1}; $[\alpha]_D^{29.4}$ 202.63 (c 0.49, $CHCl_3$); EI-MS *m/z* 374 [M^-].

(6*S*,12a*R*)-2-Methyl-6-(3,4,5-trimethoxyphenyl)-2,3,12,12a-tetrahydropyrazino[1',2':1,6]-pyrido[3,4-*b*]indole-1,4(6*H*,7*H*)-dione (17c**).** 85% Isolated yield; mp 239-240 °C; purity by HPLC 99.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93-2.98 (m, 1H), 3.08 (s, 3H), 3.58 (dd, 1H, *J* 15.6 Hz, 4.4 Hz,), 3.7 (s, 3H), 3.8 (s, 6H), 4.01 (d, 1H, *J* 17.6 Hz), 4.15 (d, 1H, *J* 17.6 Hz), 4.4 (dd, 1H, *J* 12.2 Hz, 3.9 Hz,), 6.51 (s, 2H), 6.98 (s, 1H), 7.15-7.26 (m, 2H), 7.33 (d, 1H, *J* 7.9 Hz), 7.55 (d, 1H, *J* 7.9 Hz), 8.03 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 33.3, 51.3, 52.3, 52.8, 55.9, 60.5, 105.5, 108.5, 111.2, 118.2, 119.5, 122.3, 126.0, 134.1, 136.4, 137.4, 152.9, 161.5, 165.5; IR (KBr) ν 3266, 3058, 2925, 1655, 1464, 1329, 1248, 1175, 1158, 744 cm^{-1} $[\alpha]_D^{29.4}$: 220.19 (c 0.50, $CHCl_3$); EI-MS *m/z* 434 [M^-].

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