Pictet-Spengler Cyclization in Room Temperature Ionic Liquid: A Convenient Access to Tetrahydro β-carbolines

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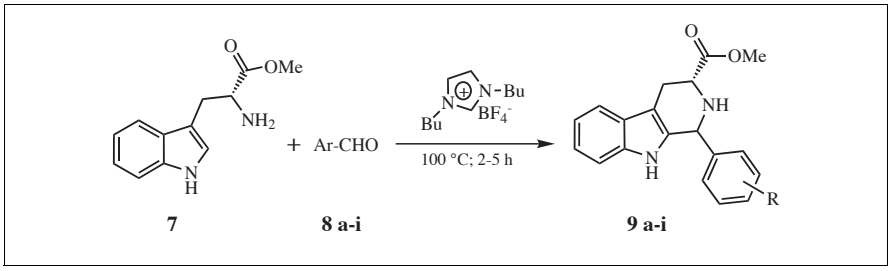

1,2,3,4-Tetrahydro-β-carbolines have been synthesized in moderate to good yields in short reaction time using the ionic liquid [bbim] BF_4 as reaction medium and promoter. There was no need for the use of an additional catalyst normally employed in Pictet-Spengler condensation.

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Introduction.

β-Carboline alkaloids are compounds that comprise the tricyclic pyrido[3,4]indole ring system with alkyl C1-constituents [1]. This class includes simple tricyclic eleagnines and harmines (**1**, Figure 1) as well as a number of structurally more complex examples such as yohimbine, ajmalicine and reserpine, which are long known as hallucinators [2]. The potential of β-carboline and 1,2,3,4-tetrahydro-β-carboline pharmacophore was well documented in various therapeutic areas such as alcohol abuse, mental illness, CNS [3], CCK receptor antagonists [4] and phosphodiesterase inhibitors [5]. The world drugs index for instance, contains over 200 listings of this pharmacophore [6]. HR22C16 (**3**, Figure 1), a tetrahydro-β-carboline fused to a hydantoin ring, was recently reported as a new cell-permeable small-molecule inhibitor of cell division [7]. Similarly, hydantoins GR30040X (**4**) and **5** are reported as potential candidates for the treatment of erectile dysfunction (ED) and their mode of action has been well established as the selective inhibition of PDE5 *vs* other PDEs (type 5 phospho-diesterase) [8]. Tadalafil (*Cialis*®) is a successful β-carboline derivative that is presently in the market for the treatment of ED related diseases [9].

The Pictet–Spengler reaction is a generally used method for the synthesis of tetrahydro-β-carboline derivatives. Normally, strong Brönsted/Lewis acids ranging from catalytic to stoichiometric amounts are employed to accomplish the Pictet–Spengler reaction. In the context of our ongoing research program dealing with drug discovery lead structure modification, we were encountered with a need for an efficient methodology for

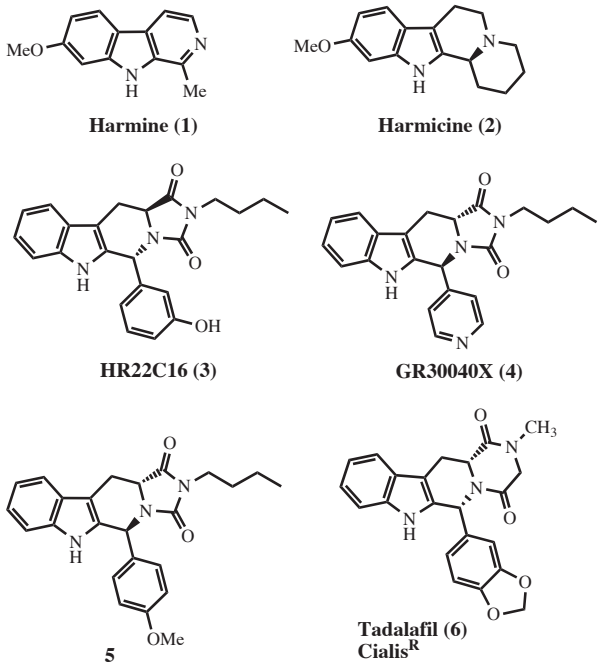
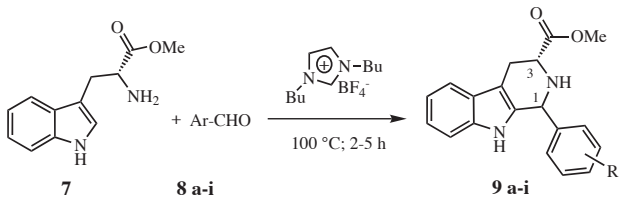


Figure 1. Medicinally Important Natural and Synthetic β-carbolines.

the synthesis of β-carboline libraries and we were interested to explore the possibility of conducting the Pictet-Spengler reaction in ionic liquids. Application of ionic liquids in chemical processes has blossomed only within the last decade. Room temperature ionic liquids have been utilized as clean solvents and catalysts for various organic transformations. Interest in this class of solvent stems from the properties they exhibit. No significant vapor pressure (thus create no volatile organic

components), easy separation of organic molecules by direct distillation/extraction without loss of the ionic liquids lead to recognize them as an attractive green alternative to conventional solvents. They are non-volatile, recyclable, non-explosive. Comprehensive information about this field may be found in the recent reviews by Seddon [10] and Holbrey [11] and Welton [12] and by Wasserscheid [13]. These provide an excellent and essential source of the physical and chemical properties of ionic liquids and catalog a range of reactions that can be carried out in ionic liquids. We herein describe an extremely facile and environmentally friendly synthesis of 1,3–disubstituted 1,2,3,4-tetrahydro-β-carbolines by carrying out Pictet-Spengler cyclization in an ionic liquid [bbim]BF_4.

Scheme 1



The Pictet-Spengler reaction

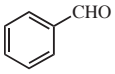
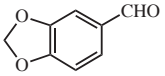
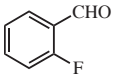
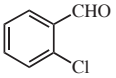
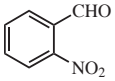
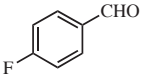
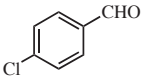
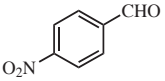
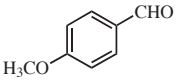
Results and Discussion.

We first examined the Pictet-Spengler condensation of *D*-tryptophan methyl ester **7** and benzaldehyde **8a** in different imidazolium based ionic liquids like [bbim]BF_4, [bbim]PF_6 and [bbim]Br in the presence of trifluoroacetic acid (TFA) as an acid catalyst. During the course of the screening of a variety of reaction conditions such as different ionic liquids, reaction temperature and reaction time, we found that [bbim]BF_4 was found to be superior in terms of yield, reaction time and easy isolation of products as compared with other ionic liquids. During further optimization, surprisingly, we found that the use of corrosive, hazardous TFA as a acid catalyst was in fact not necessary for the efficient Pictet-Spengler cyclization in ionic liquid [14].

Thus, In a typical experiment, treatment of *D*-tryptophan methyl ester **7** with benzaldehyde **8a** in ionic liquid [bbim]BF_4 at 100 °C for 2 h afforded the corresponding 1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline **9a** in 90% Yield (Scheme 1). The products were isolated as mixtures of diastereomers. The *cis* and *trans* isomers were separated by flash chromatography. The assignment of *cis*/*trans* stereochemistry for tetrahydro-β-carboline **9** was based on a detailed study of the ^1H and ^{13}C NMR spectroscopy and by comparison with the literature data, well established by Cook [15] *i.e*

Table 1

Pictet-spengler cyclization of **7** with various aromatic aldehydes **8 a-i**

	Aldehyde	Product	Reaction time (h)	Yield (%)	Diastereomeric ratio
1		**9a**	2	90	1: 0.9
2		**9b**	4	70	1: 0.8
3		**9c**	2	85	1: 0.7
4		**9d**	2	82	1: 1
5		**9e**	2.5	84	1: 0.6
6		**9f**	2	75	1: 0.7
7		**9g**	4	80	1: 1
8		**9h**	2	75	1: 0.6
9		**9i**	5	82	1: 0.9

[a] isolated and unoptimized yields.

the signals for C-1 and C-3 in the *trans* isomer appeared at higher field in the carbon spectrum than the analogous carbons of the corresponding *cis* isomer. For example, *trans* isomer of compound **9i** showed the signals of C-1 and C-3 at δ 55.3 and δ 54.4, while in *cis* isomer the corresponding signals are at δ 58.1 and δ 57.0 respectively. In addition, the NMR signals for the proton at C-1 is more shielded in the *cis* isomer and appeared at δ 5.19 and in the *trans* isomer it is at δ 5.34. These values are in full agreement with the reported NMR data for compound **9i** [8a].

After having optimized the reaction conditions for Pictet-Spengler cyclization in [bbim]BF_4, the potential of this methodology was extended to variety of substituted aromatic aldehydes and the results are summarized in Table 1. In all cases moderate to good yields were obtained. The identities of all the products were confirmed by ^1H NMR, ^{13}C NMR and mass spectral

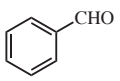
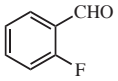
analyses. For the selected example **9b**, the C-1 and C-3 were unequivocally assigned by ^{1}H-^{13}C HSQC NMR experiment. It has been observed that the substitution pattern on the aromatic aldehydes seems to have little effect on the Pictet-Spengler reaction as the aromatic aldehydes carrying either electron-donating or electron-withdrawing groups afford comparable results. Moreover, in the present series of tetrahydro-β-carbolines **9**, the *cis* isomer is less polar than the *trans*, as indicated by TLC R_f values (silica, ethyl acetate/pet ether developing solvent). It is important to mention that, from the known literature results [8a], the Pictet-Spengler cyclization of racemic tryptophan methyl ester **7** with *p*-anisaldehyde **8i** catalyzed by TFA in molecular organic solvent, *e.g.* methylenechloride gave corresponding 1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline **9i** in 62% yield after stirring at room temperature for 4 days, in comparison to the 82% yield in entry 9 of Table 1.

The advantage of the use of ionic liquids as novel reaction media for this Pictet-Spengler cyclization is that these ionic liquids can be easily recovered and reused. Since the products were weakly soluble in the ionic phase, they were easily separated by simple extraction with ether. The remaining viscous ionic liquid was washed thoroughly with ether and reused successfully for selected compounds in Table 1 (entry 1 & 3) and obtained moderate to good yields in second and third runs (Table 2).

We have not made any attempt to study the mechanism of this acid catalyst free Pictet-Spengler cyclization in ionic liquid [bbim]BF_4. But the role of the ionic liquid may be postulated in terms of some Lewis/Brönsted acidity of the imidazolium cation, leading to its interaction with the carbonyl oxygen of the aldehyde group resulting in its increased polarization and thus promoting the reaction.

Table 2

Recyclability and reuse of [bbim]BF_4 for representative PS cyclization

Entry	Aldehyde	Product	Yield (%)a
1		**9a**	90 (1st run) 88 (2nd run) 86 (3rd run)
2		**9c**	85 (1st run) 82 (2nd run) 75 (3rd run)

[a] isolated and unoptimized yields.

Conclusion.

In conclusion, we described here rapid and environmentally benign synthesis of 1,3-disubstituted 1,2,3,4-tetrahydro–β-carbolines using the advantage of ionic liquid as a solvent and promoter. There is no need to add any acid catalyst. Shorter reaction time, easy work up, moderate to good isolated yield and reusability of ionic liquid makes this method simple for operation and useful in combinatorial chemistry to prepare vast array of tetrahydro-β-carbolines in short period.

EXPERIMENTAL

Melting points were measured using a Buchi B-540 apparatus and are uncorrected. NMR spectra were obtained with a Bruker AC-200 (200 MHz) spectrometer or a Bruker MSL 300 (300 MHz) or a Bruker DRX 500 (500 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained with Thermo Finnegan MSQ mass spectrometer. Column chromatography was performed using silica-gel (60-120 mesh) purchased from Qualigens and TLC was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ purchased from Merck. Ionic liquids [bbim]Br, [bbim]BF_4, [bbim]PF_6 were prepared as per reported method [16].

General Procedure for the Synthesis of 1,3-Disubstituted 1,2,3,4-tetrahydro- β –carbolines.

A mixture containing *D*-tryptophan methyl ester (2 mmol), an aromatic aldehyde (2 mmol) in [bbim] BF_4 (2 g) was heated at 100 °C for certain period of time (Table 1). After completion of the reaction (indicated by TLC), the reaction mixture was extracted with ether (3 X 5 ml). The organic layer was separated, washed with water, brine, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford crude 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines. The *cis* and *trans* isomers were separated by flash column chromatography over silica gel column using methylenechloride as an eluent.

Characterization Data of 1,3–Disubstituted 1, 2, 3, 4-tetrahydro-β-carbolines.

Methyl 1,2,3,4-tetrahydro-1-phenyl-9*H*-pyrido [3,4-*b*]indole-3-carboxylate **(9a)**.

cis Isomer: mp 184-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95-3.05 (m, 1H, C_4-H), 3.19-3.25 (m, 1H, C_4-H), 3.79 (s, 3H), 3.96 (dd, 1H, *J*=11.0, 4.5Hz, C_3-H), 5.22 (s, 1H, C_1-H), 7.11-7.54 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 140.7, 135.7, 133.9, 131.7, 128.7, 127.8, 127.7, 127.3, 125.9, 120.3, 117.9, 116.8, 110.49, 106.9, 57.6, 55.8, 51.1, 24.9; MS-ESI: 307.04 ($[M+1]^+$, 100%), 303.04 (41%), 204.04 (92%).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.66; H, 5.52; N, 9.24.

trans Isomer: mp 161-62 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.09-3.22 (m, 1H, C_4-H), 3.23-3.28 (m, 1H, C_4-H) 3.72 (s, 3H), 3.97-4.03 (m, 1H, C_3-H), 5.47 (s, 1H, C_1-H), 7.12-7.57 (m, 9H), 7.76 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 141.7, 136.3, 132.9, 132.7, 129.8, 128.5, 128.4, 128.1, 126.9, 121.9, 119.4, 118.1, 110.9, 108.4, 54.8, 52.2, 52.0, 24.6; MS-ESI: 307.04 ($[M+1]^+$, 100%), 204 (54%).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.72; H, 5.62; N, 9.44.

Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(9b)**.

cis Isomer: mp 92-93 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (ddd, 1H, *J* =15.0, 11.0, 2.2 Hz, C_4-H), 3.20 (ddd, 1H, *J* =14.9, 4.0, 1.4 Hz, C_4-H), 3.81 (s, 3H), 3.95 (dd, 1H, *J*=11.4, 4.4 Hz, C_3-H), 5.16 (s, 1H, C_1-H), 5.94 (s, 2H), 6.80-6.82 (m, 1H), 6.88 (d, 1H, *J*=8.1 Hz), 7.11-7.15 (m, 2H), 7.21-7.24 (m, 1H), 7.51-7.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 148.1, 147.7, 136.2, 136.2, 134.6, 127.1, 121.9, 121.9, 119.5, 118.1, 110.9, 108.7, 108.5, 108.2, 101.1, 58.3, 56.8, 52.1, 25.6; ^{1}H-^{13}C HSQC ($CDCl_3$) δ_H (δ_C) 5.16 (58.3, C_1), 3.95 (56.8, C_3); MS-ESI: :351 ([M+1]$^+$, 72%), 349 (69%), 204.05 (100%).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.52; H, 5.09; N, 8.22.

trans Isomer: mp 162-63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.13-3.17 (m, 1H, C_4-H), 3.27-3.31 (m, 1H, C_4-H), 3.72 (s, 3H), 3.99-4.02 (m, 1H, C_3-H), 5.41 (s, 1H, C_1-H), 5.92 (s, 2H), 6.75-6.76 (m, 3H), 7.12-7.20 (m, 2H), 7.23-7.25 (m, 1H), 7.53-7.54 (m, 1H), 7.66 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 148.0, 147.4, 136.2, 136.1, 133.3, 127.0, 121.9, 121.6, 119.4, 118.1, 110.9, 108.6, 108.3, 108.0, 101.1, 54.6, 52.4, 51.9, 24.6; ^{1}H-^{13}C HSQC ($CDCl_3$) δ_H (δ_C) 5.41 (54.6, C_1), 4.0 (52.4, C_3); MS-ESI: 351 ([M+1]$^+$, 100%), 349 (25%), 275 (25%), 204.05 (100%).

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.22; H, 4.92; N, 8.32.

1,2,3,4-Tetrahydro-1-(2-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate **(9c)**.

cis Isomer: mp 164-65 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01-3.08 (m,1H, C_4-H), 3.25 (dd, 1H, *J*=15.6, 4.6 Hz), 3.80 (s, 3H), 3.99-4.03 (m, 1H, C_3-H) 5.97 (s, 1H, C_1-H), 7.04-7.32 (m, 7H), 7.54 (d, 1H, *J* =7.4Hz), 7.83 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 136.1, 133.5, 129.9, 127.5, 127.3, 126.9, 124.8, 121.9, 119.5, 118.1, 115.8, 115.4, 110.9, 109.0, 56.7, 52.2, 50.8, 25.5; MS-ESI: 325.05 ([M+1]$^+$, 54%), 238 (100%).

Anal. Calcd. for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found: C, 70.64; H, 5.02; N, 8.02.

trans Isomer: mp 194-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.27-3.35 (m, 1H, C_4-H), 3.60 (dd, 1H, *J* = 15.6, 4.8 Hz, C_4-H), 3.75 (s, 3H), 4.21-4.25 (m, 1H, C_3-H), 6.32 (s, 1H, C_1-H), 7.05-7.21 (m, 6H), 7.34-7.38 (m, 1H), 7.52 (d, 1H, *J*=7.5Hz), 8.47 (br s,1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 135.2, 131.0, 128.8, 128.4, 128.0, 125.3, 122.5, 120.0, 117.4, 116.4, 114.4, 113.9, 110.01, 106.9, 50.4, 50.0, 46.9, 23.8**;** MS-ESI: 325.05 ([M+1]$^+$, 60%), 238 (100%).

Anal. Calcd. for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found: C, 70.14; H, 5.56; N, 8.82.

Methyl 1,2,3,4-tetrahydro-1-(2-chlorophenyl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate **(9d)**.

cis Isomer: mp 170-01 °C**;** ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.03 (ddd, 1H, *J*=14.2, 11.2, 2.5 Hz, C_4-H), 3.24 (ddd, 1H, *J*=15.0, 4.0, 1.7 Hz, C_4-H), 3.81 (s, 3H), 4.01 (dd, 1H, *J*=11.4, 4.1 Hz, C_3-H), 5.84 (s, 1H, C_1-H), 7.10-7.16 (m, 2H), 7.21-7.29 (m, 3H), 7.42 (d, 1H, *J*=7.7Hz), 7.45 (d, 1H, *J*=7.7Hz), 7.54 (d,1H, *J*=7.7Hz), 7.59 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 138.6, 136.2, 133.7, 130.4, 129.7, 129.5, 127.6, 127.0, 122.0, 119.6, 118.2, 110.9, 109.2, 56.7, 54.5, 52.1, 25.5; MS-ESI: 341.05 ([M+1]$^+$, 100%), 339.05 (31%), 254 (37%).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.62; H, 5.12; N, 8.34.

trans Isomer: mp 201-02 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.07-3.12 (m, 1H, C_4-H), 3.27(dd, 1H, *J*=15.3, 4.8 Hz, C_4-H), 3.73 (s, 3H), 3.85-3.88 (m, 1H, C_3-H), 5.90 (s, 1H, C_1-H), 6.94 (dd, 1H, *J*=7.7, 1.8 Hz), 7.10-7.16 (m, 2H), 7.18 (d, 1H, *J*=7.1 Hz), 7.21-7.26 (m, 2H), 7.45 (d, 1H, *J*=8 Hz), 7.56 (d, 1H, *J* = 7.7 Hz), 7.74 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 138.0, 134.8, 131.7, 130.8, 128.5, 127.9, 127.3, 125.0, 119.5, 116.9, 115.9, 109.6, 106.5, 50.0, 49.8, 23.4; MS-ESI**:** 341.05 ([M+1]$^+$, 100%), 339.05 (24%), 254 (39%).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.34; H, 4.88; N, 8.26.

Methyl 1,2,3,4-tetrahydro-1-(2-nitrophenyl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate **(9e)**.

cis Isomer: mp 177-78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.11(ddd, 1H, *J*=14.2, 11.01, 2.4 Hz, C_4-H), 3.27 (dd, 1H, *J*=15.1, 4.2 Hz, C_4-H), 3.82 (s, 3H), 3.98 (dd, 1H, *J*=11.2, 3.9 Hz, C_3-H), 5.72 (s, 1H, C_1-H), 7.11-7.17 (m, 2H), 7.24 (d, 1H, *J*=7.7Hz), 7.45 (dd, 1H, *J*= 7.7, 1.5Hz), 7.52-7.62 (m, 2H), 7.71 (dd, 1H, *J*=7.9, 1.4Hz), 7.86 (d, 1H, *J*=8.2Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 148.9, 135.7, 135.3, 132.4, 132.2, 130.5, 127.5, 125.41, 122.7, 120.3, 117.8, 116.7, 110.2, 107.5, 55.3, 52.0, 50.9; MS-ESI: 352.05 ([M+1]$^+$, 55%), 341 (100%).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.81; H, 4.62; N, 12.34.

trans Isomer: mp 158-59 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.11-3.15 (m, 1H, C_4-H), 3.26 (dd, 1H, *J*=15.3, 4.1Hz, C_4-H), 3.68 (s, 3H), 3.90-3.93 (m, 1H, C_3-H), 5.89 (s, 1H, C_1-H), 7.10-7.16 (m, 2H), 7.21-7.23 (m, 1H), 7.38-7.45 (m, 2H), 7.54 (d, 1H, *J*=7.4Hz), 7.88 (d, 1H, *J*=7.4Hz), 8.03 (d, 1H, *J*=6.8Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 150.3, 137.3, 136.9, 133.6, 132.1, 131.7, 129.3, 127.3, 125.1, 122.9, 120.2, 118.9, 111.7, 110.0, 53.3, 52.8, 50.5, 25.1; MS-ESI: 352.52 ([M+1]$^+$, 100%), 341.52 (20%).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.12; H, 4.56; N, 11.94.

Methyl 1,2,3,4-tetrahydro-1-(4-fluorophenyl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate **(9f)**.

cis Isomer: mp 151-52 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.0 (ddd, 1H, *J*=14.6, 11.0, 2.4 Hz, C_4-H), 3.22 (dd, 1H, *J*=15.1, 4.1Hz, C_4-H), 3.81 (s, 3H), 3.97 (dd, 1H, *J*=11.2, 4.2 Hz, C_3-H), 5.24 (s, 1H, C_1-H), 7.03-7.07 (m, 2H), 7.10-7.17 (m, 2H), 7.20 (d, 1H, *J*=7.7Hz), 7.34-7.37 (m, 2H), 7.42 (s,1H) 7.55 (d, 1H *J*=7.7Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 136.6, 135.5, 133.6, 129.2, 125.5, 120.0, 117.6, 116.4, 114.1, 113.8, 110.1, 106.4, 55.4, 55.4, 50.6, 24.5; MS-ESI: 325.03 ([M+1]$^+$, 71%), 323.03 (31%), 238.04 (100%).

Anal. Calcd. for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found: C, 70.42; H, 5.31; N, 8.22.

trans Isomer: mp 161-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11-3.18 (m, 1H, C_4-H), 3.25-3.31 (m, 1H, C_4-H), 3.73 (s, 3H), 3.96 (dd, 1H, *J*=11.4, 4.0 Hz, C_3-H), 5.41(s, 1H, C_1-H), 6.99-7.05 (m, 2H), 7.14-7.18 (m, 2H), 7.23-7.28 (m, 2H), 7.56 (dd, 1H, *J*=9Hz), 7.64 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 137.9, 136.3, 133.0, 130.0, 127.0, 122.1, 119.6, 118.2, 115.6, 115.3, 110.9, 108.4, 54.2, 52.5, 52.0, 24.6; MS-ESI: 325.04 ([M+1]$^+$, 89%), 323.05 (21%), 238.04 (100%).

Anal. Calcd. for $C_{19}H_{17}FN_2O_2$: C, 70.36; H, 5.28; N, 8.64. Found: C, 70.18; H, 5.35; N, 8.44.

Methyl 1,2,3,4-tetrahydro-1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate **(9g)**.

cis Isomer: mp 136-37 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (m, 1H, C_4-H), 3.23 (br d, 1H, *J*=14.8 Hz, C_4-H), 3.81 (s, 3H), 3.94 (ddd, 1H, , *J*=11.4, 4.1, 1.4 Hz, C_3-H), 5.22 (s, 1H, C_1-H), 7.10-7.16 (m, 2H), 7.21(d, 1H, *J*=7.5Hz), 7.30-7.35 (m, 4H), 7.53 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 140.2, 136.5, 134.3, 133.3, 130.0, 128.4, 126.5, 121.1, 118.7, 117.5, 111.1, 107.7, 57.6, 56.5, 51.8, 25.5; MS-ESI: 341.04 ([M+1]$^+$, 100%), 339 (95%), 204.05 (78%).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 66.59; H, 4.82; N, 8.12.

trans Isomer: mp 205-06 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10-3.15 (m, 1H, C_4-H), 3.26 (dd, 1H, *J*=15.4, 5.1Hz, C_4-H), 3.71 (s, 3H), 3.92-3.94 (m, 1H, C_3-H), 5.38 (s, 1H, C_1-H), 7.11-7.18 (m, 2H), 7.20-7.24 (m, 3H), 7.30 (d, 1H, *J*=8.2Hz), 7.55 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 140.5, 135.4, 132.2, 131.92, 128.8, 127.2, 125.6, 120.2, 117.7, 116.7, 110.2, 106.3, 53.0, 51.0, 50.7, 23.8; MS-ESI: 341.04 ([M+1]$^+$, 43%), 339 (20%), 204.05 (100%).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.96; H, 5.03; N, 8.22. Found: C, 67.14; H, 4.84; N, 8.43.

Methyl 1,2,3,4-tetrahydro-1-(4-nitrophenyl)-9*H*-pyrido[3,4-*b*]-indole-3-carboxylate **(9h)**.

cis Isomer: mp 171-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (m, 1H, C_4-H), 3.23 (br d, 1H, *J*=14.8 Hz, C_4-H), 3.81 (s, 3H), 3.94 (ddd, 1H, *J*=11.4, 4.1, 1.4 Hz, C_3-H), 5.36 (s, 1H, C_1-H), 7.05-7.11 (m, 2H), 7.24 (d, 1H, *J*=7.8 Hz), 7.51 (d, 1H, *J*=7.8 Hz), 7.59 (dd, 2H, *J*=8.8, 1.7 Hz), 8.16 (dd, 2H, *J*=8.8, 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 149.0, 147.0, 136.4, 133.4, 129.5, 126.1, 123.0, 120.9, 118.5, 117.4, 110.9, 107.3, 57.2, 55.9, 51.6, 25.0; MS-ESI: 352.03 ([M+1]$^+$, 100%), 348.03 (25%), 265.04 (34%).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.86; H, 4.82; N, 12.33.

trans Isomer: mp 202-03 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (m, 1H, C_4-H), 3.23-3.29 (dd, 1H, *J*=11.32, 4.14 Hz, C_4-H), 3.73 (s, 3H), 3.85-3.90 (m, 1H, C_3-H) 5.52 (s, 1H, C_1-H) 7.09-7.20 (m, 2H), 7.31 (dd, 1H, *J*=7.8, 2.2 Hz), 7.50-7.57 (m, 3H), 8.17 (dd, 2H, *J*=8.6, 2.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 149.2, 146.0, 135.4, 131.4, 128.2, 125.5, 122.1, 120.3, 117.73, 116.7, 110.2, 106.3, 52.8, 51.0, 50.7, 23.7; MS-ESI**:** 352.04 ([M+1]$^+$, 60%), 265.04 (76%). 246.05 (100%).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.12; H, 4.95; N, 12.05.

Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9*H*-pyrido [3,4-*b*]indole-3-carboxylate **(9i)**.

cis Isomer: mp 138-39 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (ddd, 1H, *J*=14.42, 11.1, 2.5 Hz, C_4-H), 3.20 (dd, 1H, *J*=15.2, 4.3 Hz, C_4-H), 3.81 (s, 6H), 3.97 (dd, 1H, *J*=11.2, 4.1Hz, C_3-H), 5.19 (s, 1H, C_1-H), 6.89 (d, 2H, *J*=8.5 Hz), 7.09-7.15 (m, 2H), 7.21 (d, 1H, *J*=7.2Hz), 7.29 (d, 2H, *J*=8.5 Hz), 7.46 (br s, 1H), 7.53 (d, 1H, *J*=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 159.8, 136.2, 135.1, 132.9, 129.7, 127.2, 121.9, 119.6, 118.1, 114.3, 110.9, 108.8, 58.1, 57.0, 55.3, 52.1, 25.8; MS-ESI: 337.04 ([M+1]$^+$, 100%), 204.05 (19%).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.01; H, 6.15; N, 8.36.

trans Isomer: mp 193-94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (dd, 1H, *J*=14.60, 6.0 Hz, C_4-H), 3.24 (dd, 1H, *J*=15.42, 4.5 Hz, C_4-H), 3.77 (s, 3H), 3.85 (s, 3H), 3.92-3.97 (m, 1H, C_3-H), 5.34 (s, 1H, C_1-H), 6.84 (d, 2H, *J*=8.5 Hz), 7.09-7.22 (m, 5H), 7.54 (d, 1H, *J*=7.2Hz), 7.29 (d, 2H, *J*=8.5 Hz), 7.53 (d, 1H, *J*=7.2 Hz), 7.68 (br s, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 159.6, 136.3, 134.1, 133.6, 129.6, 127.1, 121.9, 119.5, 118.2, 114.1, 110.9, 108.3, 55.3, 54.4, 52.6, 52.0, 24.6; MS-ESI: 337.04 ([M+1]$^+$, 100%), 204.05 (34%), 181.05 (75%).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.73; H, 5.62; N, 8.12.

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