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ARTICLE

$PhI(OAc)_2$-Mediated one-pot oxidative decarboxylation and aromatization of tetrahydro-β-carbolines: synthesis of norharmane, harmane, eudistomin U and eudistomin I

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Iodobenzene diacetate was employed as a mild and efficient reagent for one-pot oxidative decarboxylation of tetrahydro-β-carboline acids and dehydrogenation of tetrahydro-β-carbolines to access the corresponding aromatic β-carbolines. To the best of our knowledge this is the first synthesis of β-carbolines via a one-pot oxidative decarboxylation at ambeint temperature. The utility of this protocol has been demonstrated in the synthesis of β-carboline alkaloids norharmane (**2o**), harmane (**2p**), eudistomin U (**9**) and eudistomin I (**12**).

Introduction

Natural products constitute an important source of chemical leads in the drug discovery program worldwide. Majority of the drugs that are presently in clinical use are derived from natural product scaffolds.[1] The aromatic β-carboline skeleton is a common structural motif found in a wide variety of biologically active natural and synthetic compounds.[2] β-Carboline derivatives are known to exhibit diverse biological properties such as antitumor,[3] antimalarial,[4] anti-HIV[5] and antibacterial[6] activities. Additionally, detailed investigations on certain β-carboline derivatives have revealed thier excellent binding affinities towards 5-hydroxy serotonin receptors,[7] monoamine oxidase[8] and benzodiazepine receptors[9] in the central nervous system. Moreover, compounds bearing this ring system have also been used as versatile synthetic intermediates in the construction of pharmaceutically important molecules.[10]

In view of their biological importance, development of newer practical methods for the synthesis of this scaffold is of considerable interest. In general, Pictet–Spengler reaction followed by oxidative decarboxylation and dehydrogenation reactions are the most widely followed methods to access β-carbolines. Oxidative decarboxylation reactions are genrally sluggish and are typically carried out at high temperatures using reagents such as $K_2Cr_2O_7$[11] in acetic acid, persulfate in the presence of catalytic silver[12] or copper salts.[13] On the other hand, dehydrogenation of the tetrahydro-β-carboline carboxylate genrally requires exposure to large excess of oxidants like SeO_2[14], MnO_2[15], sulfur[3d,16], palladium on carbon[17] for long periods of time. Other reagents like chloranil[18] and DDQ[19] are also effective in the dehydrogenation reaction, but the yields are often very low. Recently, gold (III)-catalyzed cycloisomerisation, palladium catalyzed cross-coupling and iminoannulation reactions have been reported for the construction of β-carbolines.[20] However, most of the methods discussed above require expensive and toxic transition metal reagents and harsh reaction conditions. They cannot be deemed as environment-friendly and therefore development of ecofriendly and cost effective protocols under milder conditions assumes importance.

In recent years, the use of hypervalent iodine based reagents as alternative to toxic heavy metal oxidants has gained popularity.[21] Reagents such as Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX) have been used for the dehydrogenation of tetrahydro-β-carbolines.[22] Based on these observations and in continuation our efforts to develop greener and practical synthetic routes for compounds of pharmaceutical relevance, we attempted the synthesis of β-carbolines using iodobenzene diacetate under mild reaction conditions. In the following passages, we disclose a one-pot oxidative decarboxylation and aromatization of tetrahydro-β-carbolines mediated by the hypervalent iodine reagent, iodobenzene diacetate. Additionally, this method has been employed for the synthesis of β-carboline alkaloids such as norharmane (**2o**), harmane (**2p**) eudistomin U (**9**) and eudistomin I (**12**) in high yields.

Results and discussion

Initially, as a test reaction, we investigated the effect of iodobenzene diacetate on the tetrahydro β-carboline acid **1a** in various solvents at ambient temperature. The β-carboline

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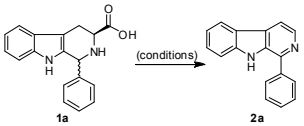
derivative **2a** was readily fomed in all the conditions explored. The use of equimolar amounts of iodobenzene diacetate in acetonitrile afforded 32% yield of **2a** (entry 1, Table 1). Increasing the amount of iodobenzene diacetate to 2 mmol led to a huge improvement of the yield as well as reduction of the reaction time (68%, entry 2, Table 1). Further increase in the stoichiometric ratio of the reagent showed no effect on the yield as well as time (entry 3, Table 1). Screening of various solvents such as DMF, DMSO, DCM and 1,4-dioxane (entries 4-7, Table 1) revealed that the use of DMF afforded the best yield (82%, entry 7, Table 1) for the reaction. Additionally, carrying out the reaction under oxygen atmosphere with varying mmols of the reagent led to similar results with respect to the reaction times and yields (entries 8-9, Table 1). Based on these observations it can be concluded that oxygen has no effect on oxidative decarboxylation process. Thus, the optimal reaction conditions involved the use of iodobenzene diaceate (2 mmol) in DMF at ambient temperature for 1h (entry 7, Table 1). It was evident that a facile and convenient method for one-pot oxidative decarboxylation of tetrahydro-β-carboline acids leading to the formation of β-carbolines at room temperature was developed and to the best of our knowledge this was the first successful case of this transformation being carried out under such mild conditions.

Table 1. Optimization studies of the iodobenzene diacetate mediated one-pot oxidative decarboxylation on tetrahydro-β-carboline acids[a]

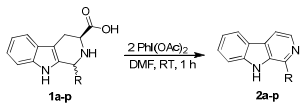


Entry	$PhI(OAc)_2$ (mmol)	Solvent	Time (h)	Yield (%)[b]
1	1	acetonitrile	12	32[c]
2	2	acetonitrile	3	68
3	3	acetonitrile	3	68
4	2	DMSO	2	74
5	2	DCM	8	71
6	2	1,4-dioxane	4	73
7	2	DMF	1	82
8	2	DMF	1	82[d]
9	1	DMF	1	44[d]

*[a]Reactions were performed using **1a** (1 mmol) and iodobenzene diacetate (1-3 mmol) at rt. [b]Isolated yields. [c]Product accompanied by 40% of starting material. [d]Isolated yield in presence of oxygen.*

With the optimal reaction conditions in hand, the scope and generality of oxidative decarboxylation were examined by employing various substituted tetrahydro-β-carboline acids as reaction substrates and the results are depicted in Table 2. A wide array of aliphatic, aromatic and heteroaromatic substituents at position-1 of tetrahydro-β-carboline acids are tolerated in the reaction. Interestingly, better yields of the products were obtained from substrates possessing aromatic and heteroaromatic substituents compared to those with aliphatic substituents (entries 15 and 16, Table 2). It was also apparent that the electronic nature of the substituents has some effect on the product yields. The substrates bearing electron-rich groups (entries 2-5, Table 2) afforded products in higher yields than those bearing electron-deficient groups (entries 6 and 7, Table 2). Importantly, two naturally occurring β-carbolines, norharmane (**2o**) and harmane (**2p**), were synthesized using this protocol in good yields (entries 15 and 16, Table 2).

Table 2. Synthesis of β-carbolines (**2a-p**) from tetrahydro-β-carboline acids (**1a-p**) by using iodobenzene diacatate[a]

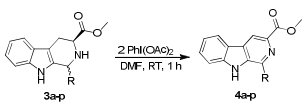


Entry	Substrate	R	product	Yield (%)[b]
1	**1a**	C_6H_5	**2a**	82
2	**1b**	4-OMe-C_6H_4	**2b**	88
3	**1c**	3,4,5-$(OMe)_3$-C_6H_3	**2c**	90
4	**1d**	2-OMe-C_6H_4	**2d**	81
5	**1e**	4-Me-C_6H_4	**2e**	85
6	**1f**	4-O_2N-C_6H_4	**2f**	76
7	**1g**	4-CN-C_6H_4	**2g**	78
8	**1h**	4-F-C_6H_4	**2h**	79
9	**1i**	3-F-C_6H_4	**2i**	80
10	**1j**	4-OH-3-OMe-C_6H_3	**2j**	80
11	**1k**	3-OH-C_6H_4	**2k**	76
12	**1l**	3,4-methylenedioxy-C_6H_3	**2l**	89
13	**1m**	3-pyridyl	**2m**	90
14	**1n**	1-naphthyl	**2n**	80
15	**1o**	H	norharmane(**2o**)	77
16	**1p**	CH_3	harmane(**2p**)	76

[a]Reactions were performed using tetrahydro-β-carboline acid (1 mmol) and iodobenzene diacetate (2 mmol) for 1 h at rt in DMF. [b]Isolated yield.

The facile nature of the decarboxylative oxidation prompted us to examine the effect of iodobenzene diacetate on the related acid derivatives, viz. the tetrahydro-β-carboline esters (**3a-p**). Interestingly, the reaction resulted in the formation of the corresponding aromatic β-carbolines in very good yields, with the ester functionality intact (Table 3).

Table 3. Synthesis of aromatized β-carboline methyl esters (**4a-p**) from tetrahydro-β-carboline methyl ester (**3a-p**) by using iodobenzene diacetate[a]



Entry	Substrate	R	product	Yield (%)[b]
1	**3a**	C_6H_5	**4a**	88
2	**3b**	4-OMe-C_6H_4	**4b**	93
3	**3c**	3,4,5-$(OMe)_3$-C_6H_3	**4c**	95
4	**3d**	2-OMe-C_6H_4	**4d**	88
5	**3e**	4-Me-C_6H_4	**4e**	90
6	**3f**	4-O_2N-C_6H_4	**4f**	80

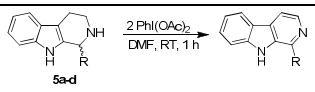
7	**3g**	4-CN-C_6H_4	**4g**	83
8	**3h**	4-CF_3-C_6H_4	**4h**	85
9	**3i**	4-F-C_6H_4	**4i**	86
10	**3j**	3-F-C_6H_4	**4j**	87
11	**3k**	3-OH-C_6H_4	**4k**	83
12	**3l**	3,4-methylenedioxy-C_6H_3	**4l**	92
13	**3m**	3-pyridyl	**4m**	90
14	**3n**	*N*-acetyl-3-indolyl	**4n**	85
15	**3o**	H	**4o**	82
16	**3p**	CH_3	**4p**	80

[a]*Reactions were performed using tetrahydro-β-carboline ester (1 mmol) and iodobenzene diacetate (2 mmol) for 1 h at rt in DMF.* [b]*Isolated yield.*

A series of substituents were found to be well tolerated and the yields were generally excellent for β-carboline esters with electron-donating groups (entries 2-5, Table 3) than the ones with electron-withdrawing groups (entries 6-8, Table 3). Moreover, heteroaryl (entries 13 and 14, Table 3) and aliphatic (entries 15 and 16, Table 3) substrates also reacted well to furnish the corresponding products.

This protocol is applicable for the dehydrogenation of tetrahydro-β-carbolines without any functionality at position-3. Here, the corresponding β-carbolines are formed in excellent yields as evident from the entries 1-4, Table 4. It is important to note that previously this transformation has been achieved using DDQ in very low yields.[19c]

Table 4. Synthesis of β-carbolines from tetrahydro-β-carbolines (**5a-d**) by using iodobenzene diacetate[a]

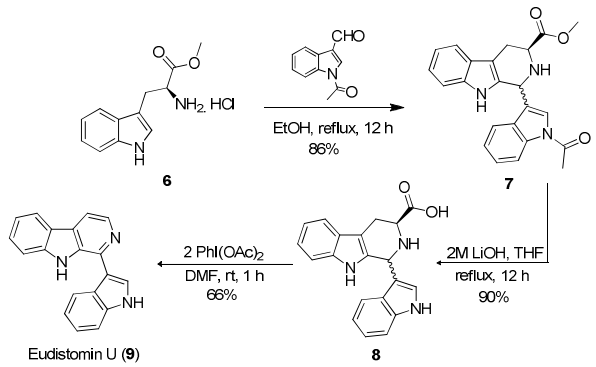


Entry	Substrate	R	product	Yield (%)[b]
1	**5a**	C_6H_4	**2a**	85
2	**5b**	4-OMe-C_6H_4	**2b**	90
3	**5c**	4-O_2N-C_6H_4	**2f**	80
4	**5d**	CH_3	harmane (**2p**)	84

[a]*Reactions were performed using tetrahydro-β-carboline (1 mmol) and iodobenzenediacetate (2 mmol) for 1 h at rt in DMF.* [b]*Isolated yield.*

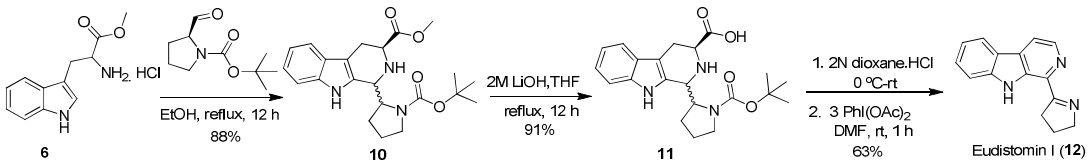
In view of the above findings, this method appeared suitable for the total syntheses of marine β-carboline alkaloids eudistomin U (**9**) and eudistominI (**12**). Eudistomin U (**9**) was isolated from the marine ascidian *lissoclinum fragile* and is reported to possess antimicrobial and anticancer activities with strong DNA binding ability.[23] Eudistomin I **(12),** on the other hand, was isolated from Caribbean tunicate *Eudistoma olivaceum* and showed strong antiviral and antimicrobial activities.[24] Eudistomin U (**9**) has been synthesised six times[22,25] and eudistomin I (**12**) thrice.[26] However, most of these syntheses employed expensive metal catalysts, drastic conditions or required prolonged reaction times to construct the core skeleton. In view of these issues, we attempted the syntheses of these natural products from commercially available starting materials in three linear steps. In the event, too shorter and more efficient syntheses of these natural products were developed and the details are described in the following passages.

The synthesis of eudistomin U (**9**) started with tryptophan methyl ester (**6**), which underwent a Pictet-Spengler condensation with *N*-acetyl indole-3-carboxaldehyde to provide the corresponding tetrahydro-β-carboline ester **7** as diastereomeric mixture (86% yield). Saponification of ester **7** was accompanied by the loss of *N*-acetyl group to provide the carboxylic acid **8**. The latter, on exposure to iodobenzene diacetate, underwent ready oxidative decarboxylation to afford eudistomin U (**9**) in 66% yield.



Scheme 1. Total synthesis of eudistomin U (**9**) via iodobenzene diacetate-mediated oxidative decarboxylation.

Synthesis of eudistomin I (**12**) began with the acid catalyzed Pictet-Spengler condensation of tryptophan methyl ester **6** with tert-butyl 2-formyl pyrrolidine-1-carboxylate to give the corresponding tetrahydro-β-carboline **10** as a diastereomeric mixture (88% yield). Further, saponification of **10** followed by deprotection of the Boc group with 2N HCl in dioxane, afforded the corresponding hydrochloride salt, which under the optimized conditions of oxidative decarboxylation, furnished eudistomin I **12** in 63% yield (Scheme 3). Here, it is important to note that iodobenzene diacetate mediates three distinct chemical transformations (decarboxylation, aromatization and dehydrogenation of the pyrrolidine ring) in a single, one-pot operation.



Scheme 2. Total synthesis of eudistomin I (**12**) via iodobenzene diacetate-mediated oxidative decarboxylation.

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Conclusions

In summary, we have developed a practical and highly efficient protocol for the synthesis of aromatic β-carbolines through a one-pot oxidative decarboxylation of the corresponding tetrahydro-β-carboline precursors at ambient temperature. The method employs a mild oxidant, iodobenzene diacetate, providing high yields of the desired products and could serve as an alternative to the traditional methods employing harsh metal-based reagents. In addition, this protocol could be useful in instances when forcing conditions must be avoided. The method provides easy access to biologically active β-carboline derivatives like norharmane (**2o**) and harmane (**2p**). Moreover, efficient total syntheses of marine β-carboline alkaloids eudistomin U (**9**) and eudistomin I (**12**) from commercially available starting materials were carried out by employing this protocol in just three linear steps. In view of its efficiency and operational simplicity, this method may be expected to find commercial applications in the synthesis of β-carboline derivatives of pharmaceutical as well as industrial importance.

Acknowledgements

The authors, Y.T, M.S and V.S acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi (India) for the financial support under the 12th Five Year Plan project "Affordable Cancer Therapeutics (ACT)" (CSC0301). This project was also supported by King Saud University, Deanship of Scientific Research, Research Chair.

Experimental Section

General Information

The reagent, chemicals and solvents were either purchased from commercial Suppliers or prepared and purified by standard techniques. Thin layer chromatography (TLC) was performed using pre-coated silica gel 60 F254 MERCK. TLC plates were visualized by exposure to UV light or iodine vapors and aqueous solution of ninhydrin. Column chromatography was performed using indicated solvent system on Merck flash silica gel with 60–120 mesh size. ^{1}H and ^{13}C NMR spectra were recorded with 300 and 500 MHz NMR instruments with tertramethylsilane (TMS) as an internal standard. Infrared spectra were recorded using a FT-IR spectrophotometer and values reported in cm^{-1}. Mass spectra were recorded by 45 electro spray ionization mass spectrometry (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on ESI-QTOF mass spectrometer. Melting points were determined on an Electro thermal melting point apparatus and are uncorrected.

General experimental procedure for the synthesis of β-carbolines (2a-p) via one-pot oxidative decarboxylation of tetrahydro-β-carboline acids (1a-p)

To a stirred solution of tetrahydro-β-carboline acids **1a-p** (1 mmol) in DMF was added iodobenzene diacetate (2 mmol) and the resulting mixture was stirred for 1h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by silica-gel column chromatography using ethyl acetate-hexane as eluent in increasing polarity to afford the desired β-carbolines **2a-p**.

1-Phenyl-9*H*-pyrido[3,4-*b*]indole (2a):

Yellow solid: 68 mg (82% yield); R_f = 0.51 (ethyl acetate/n-hexane, 3:7), mp: 242–244 °C (Ref[28]: 241–242 °C); IR (KBr): 3448, 3057, 2954, 2874, 1621, 1559, 1495, 1447, 1414, 1319, 1232, 1061, 736, 696, 615 cm^{-1}; ^{1}H NMR (300 MHz, DMSO–d_6) δ: 11.52 (s, 1H), 8.46 (d, *J* = 5.3 Hz, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 8.12 (d, *J* = 5.3 Hz, 1H), 8.04 (d, *J* = 7.0 Hz, 2H), 7.68–7.49 (m, 5H), 7.27 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 142.1, 141.0, 138.4, 138.3, 132.9, 129.1, 128.7, 128.4, 128.3, 128.1, 121.5, 120.7, 119.4, 113.8, 112.4; MS (ESI): *m/z* 245 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{17}H_{13}N_2$: 245.10732; found: 245.10627 [M + H]$^+$.

1-(4-Methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole (2b):

White solid: 75 mg (88% yield); R_f = 0.55 (ethyl acetate/n-hexane, 1:1), mp: 156–159 °C (Ref[28]: 156–159 °C); IR (KBr): 3053, 2952, 2850, 1735, 1608, 1563, 1512, 1496, 1465, 1321, 1248, 1174, 1039, 821, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.94–7.88 (m, 3H), 7.55 (t, *J* = 7.1Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.0 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 158.7, 141.6, 140.5, 137.2, 132.2, 130.2, 128.7, 128.3, 126.8, 120.2, 118.4, 113.0, 112.0, 111.3, 54.2; MS (ESI): *m/z* 275 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{15}ON_2$: 275.11789; found: 275.11665 [M + H]$^+$.

1-(3,4,5-Trimethoxyphenyl)-9*H*-pyrido[3,4-*b*]indole (2c):

White solid: 78 mg (90% yield); R_f = 0.36 (ethyl acetate/n-hexane, 4:6), mp: 168–171 °C (Ref[29]: 241–242 °C); IR (KBr): 3310, 3058, 2937, 1624, 1584, 1503, 1455, 1404, 1346, 1232, 1127, 1004, 747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.77 (s, 1H), 8.54 (d, *J* = 5.2 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 5.2 Hz, 1H), 7.59–7.52 (m, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.13 (s, 2H), 3.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.5, 143.1, 140.5, 139.0, 138.3, 134.1, 133.5, 129.8, 128.4, 121.7, 121.8, 120.1, 113.7, 111.7, 105.7, 60.8, 56.1; MS (ESI): *m/z* 335 [M + H]$^+$; HRMS (ESI):

m/z: calcd for $C_{20}H_{19}O_3N_2$: 335.13902; found: 335.13750 [M + H]$^+$.

1-(2-Methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole (2d):

White solid: 69 mg (81% yield); R_f = 0.42 (ethyl acetate/n-hexane, 4:6), mp: 172–174 °C; IR (KBr): 3424, 3058, 2934, 1625, 1496, 1456, 1421, 1320, 1240, 1023, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.59 (d, *J* = 5.2 Hz, 1H), 8.51 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 5.2 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H),7.54 (t, *J* = 7.6 Hz, 1H), 7.51–7.46 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.5, 141.1, 140.4, 139.2, 134.8, 132.4, 130.3, 129.3, 128.2, 127.7, 121.9, 121.8, 121.7, 119.9, 113.7, 112.2, 111.5, 56.4; MS (ESI): *m/z* 275 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{15}ON_2$: 275.11789; found: 275.11679 [M + H]$^+$.

1-(p-Tolyl)-9*H*-pyrido[3,4-*b*]indole (2e):

White solid: 71 mg (85% yield); R_f = 0.45 (ethyl acetate/n-hexane, 3:7), mp: 191–193 °C (Ref[30]: 190.3–191.6 °C); IR (KBr): 3643, 3057, 2975, 2875, 1623, 1562, 1495, 1423, 1319, 1069, 820, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.24 (s, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.90 (t, *J* = 5.5 Hz, 3H), 7.59 (d, *J* = 8.2 Hz, 1H),7.45 (t, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J*= 7.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 142.2, 140.8, 137.8, 135.4, 135.4, 132.9, 128.9, 128.0, 127.5, 120.8, 120.6, 119.0, 112.9, 112.0, 20.8; MS (ESI): *m/z* 259 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{15}N_2$: 259.12298; found: 259.12192 [M + H]$^+$.

1-(4-Nitrophenyl)-9*H*-pyrido[3,4-*b*]indole (2f):

Yellow solid: 65 mg (76% yield); R_f = 0.49 (ethyl acetate/n-hexane, 3:7), mp: 244–246 °C (Ref[31]: 241–242 °C); IR (KBr): 3367, 3055, 1623, 1597, 1506, 1346, 1316, 1223, 1100, 854, 784, 553 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.07 (s, 1H), 8.56 (d, *J* = 5.3 Hz, 1H), 8.42 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 7.9 Hz, 1H), 8.03 (d, *J* = 5.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 146.5, 144.2, 140.7, 138.9, 137,9, 133.0, 129.6, 128.7, 127.7, 122.9, 120.6, 120.2, 119.1, 114.1, 111.6; MS (ESI): *m/z* 290 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{17}H_{12}O_2N_3$: 290.09240; found: 290.09110 [M + H]$^+$.

4-(9*H*-Pyrido[3,4-*b*]indol-1-yl)benzonitrile (2g):

White solid: 66 mg (78% yield); R_f = 0.42 (ethyl acetate/n-hexane, 3:7), mp: 230–232 °C; IR (KBr): 3404, 3058, 2220, 1624, 1602, 1563, 1454, 1399, 1322, 1225, 1138, 833, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.12 (s, 1H), 8.53 (d, *J* = 5.3 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 2H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 5.5 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 142.5, 140.7, 139.5, 138.0, 133.0, 131.6, 129.6, 128.6, 127.8, 120.7, 120.4, 119.2, 118.1, 113.9, 111.6, 110.7; MS (ESI): *m/z* 270 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{12}N_3$: 270.10257; found: 270.10141 [M + H]$^+$.

1-(4-Fluorophenyl)-9*H*-pyrido[3,4-*b*]indole (2h):

White solid: 66 mg (79% yield); R_f = 0.53 (ethyl acetate/n-hexane, 3:7), mp: 206–207 °C (Ref[30]: 203–205 °C); IR (KBr): 3447, 3122, 3062, 2874, 1623, 1605, 1507, 1461, 1425, 1319, 1234, 1153, 1066, 854, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.11 (s, 1H), 8.47 (d, *J* = 5.3 Hz, 1H), 8.14 (d, *J* = 7.7 Hz, 1H), 8.06 (dd, *J* = 5.5, 8.5 Hz, 2H), 7.95 (d, *J* = 5.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.33–7.22 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 163.2 and 160.0 (d, *J* = 247.6 Hz), 140.4 (d, *J* = 21.4 Hz), 137.3, 133.9 (d, *J* = 2.2Hz), 132.3, 129.4, 129.3, 128.6, 127.0, 120.2, 122.1, 118.5, 114.4 (d, *J* = 21.0 Hz), 112.5, 111.3; MS (ESI): *m/z* 263 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{17}H_{12}N_2F$: 263.09790; found: 263.09668 [M + H]$^+$.

1-(3-Fluorophenyl)-9*H*-pyrido[3,4-*b*]indole (2i):

White solid: 67 mg (80% yield); R_f = 0.51 (ethyl acetate/n-hexane, 3:7), mp: 183–184 °C; IR (KBr): 3132, 3065, 1868, 1726, 1619, 1588, 1494, 1448, 1411, 1318, 1231, 1200, 1066, 881, 790, 737, 617, 555 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.35 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.11 (d, *J* = 7.9Hz, 1H), 7.96 (t, *J* = 4.7 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H),7.73 (d, *J* = 10.0 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 6.2 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 7.5, 14.7 Hz, 2H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 163.8 and 160.6 (d, *J* = 244.8 Hz), 140.9, 140.4, 137.8, 132.8, 129.8 (d, *J* = 8.2 Hz), 129.3, 127.7, 123.8, 120.8, 120.5, 119.1, 114.9 (d, *J* = 14.3 Hz), 114.6 (d, *J* = 13.2 Hz), 113.6, 111.9; MS (ESI): *m/z* 263 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{17}H_{12}N_2F$: 263.09790; found: 263.09777 [M + H]$^+$.

2-Methoxy-4-(9*H*-pyrido[3,4-*b*]indol-1-yl)phenol (2j):

White solid: 68 mg (80% yield); R_f = 0.46 (ethyl acetate/n-hexane, 4:6), mp: 261–264 °C (Ref[32]: 260–262 °C); IR (KBr): 3357, 3059, 2928, 1626, 1523, 1446, 1325, 12233, 1027, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.24 (s, 1H), 9.05 (s, 1H), 8.41 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 5.3 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H),7.57 (d, *J* = 1.7 Hz, 1H), 7.53–7.46 (m, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 3.99 (s, 3H), peaks at 11.35, 9.29, 7.97, 7.60 and 4.02 are due to rotamours; ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 147.4, 147.0, 142.2, 140.8, 137.7, 132.6, 129.5, 128.6, 127.4, 121.3, 120.9, 120.7, 119.0, 115.2, 112.6, 112.1, 111.9, 55.3, small peaks at 140.9, 127.6, 113.1, 110.2 and 55.8 are due to rotamers; MS (ESI): *m/z* 291 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{15}O_2N_2$: 291.11280; found: 291.11153 [M + H]$^+$.

3-(9*H*-Pyrido[3,4-*b*]indol-1-yl)phenol (2k):

Pale yellow solid: 64 mg (76% yield); R_f = 0.52 (ethyl acetate/n-hexane, 7:3), mp: 215–216 °C; IR (KBr): 3260, 3055, 2600, 1711, 1624, 1597, 1455, 1427, 1322, 1244, 853, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 10.88 (s, 1H), 9.21 (bs, 1H), 8.47 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 5.1 Hz, 1H), 7.61 (d, *J* = 3.0 Hz, 1H), 7.55–7.44 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 157.0, 142.1, 140.4, 139.0, 137.4, 132.7, 129.0, 128.6, 127.2, 120.4, 120.3, 118.6, 115.0, 114.8, 112.7, 111.5; MS (ESI): *m/z* 261 [M + H]$^+$; HRMS (ESI): *m/z*: calcd for $C_{17}H_{13}ON_2$: 261.10224; found: 261.10197 [M + H]$^+$.

1-(Benzo[*d*][1,3]dioxol-5-yl)-9*H*-pyrido[3,4-*b*]indole (2l):

White solid: 76 mg (89% yield); R_f = 0.40 (ethyl acetate/n-hexane, 3:7), mp: 169–170 °C (Ref[28]: 171–172 °C); IR (KBr): 3113, 3054, 2956, 2883, 1625, 1563, 1501, 1471, 1244, 1038, 934, 810, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.14 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 5.1 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.61–7.47 (m, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.09 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 146.6, 146.5, 141.0, 140.0, 136.9, 131.9, 131.5, 128.1, 126.7, 121.1, 120.0, 119.8, 118.2, 112.0, 111.1, 107.6,

107.1, 99.9; MS (ESI): *m/z* 289 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{13}O_2N_2$: 289.09715; found: 289.09561 $[M + H]^+$.

1-(Pyridin-3-yl)-9*H*-pyrido[3,4-*b*]indole (2m):

White solid: 75 mg (90% yield); R_f = 0.48 (ethyl acetate), mp: 205–208 °C; IR (KBr): 3207, 3154, 3055, 2980, 2891, 1624, 1567, 1428, 1405, 1320, 1229, 1139, 1025, 823, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO−d_6) δ: 11.08 (s, 1H), 9.32 (s, 1H), 8.69 (dd, *J* = 1.1, 4.5 Hz, 1H), 8.55(d, *J* = 5.3 Hz, 1H), 8.38 (d, *J* = 7.9 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 5.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.58−7.49 (m, 2H), 7.29 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO−d_6) δ: 149.3, 148.9, 141.1, 139.3, 138.5, 135.8, 134.0, 133.2, 129.3, 128.3, 123.8, 121.6, 120.6, 119.6, 114.4, 112.3; MS (ESI): *m/z* 246 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{16}H_{12}N_3$: 246.10257; found: 246.10124 $[M+H]^+$.

1-(Naphthalen-1-yl)-9*H*-pyrido[3,4-*b*]indole (2n):

Off white solid: 69 mg (80% yield); R_f = 0.50 (ethyl acetate/n-hexane, 3:7), mp: 178–180 °C; IR (KBr): 3448, 3052, 2940, 2654, 2759, 2675, 1623, 1562, 1502, 1453, 1421, 1322, 1239, 1067, 777, 749, 622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO−d_6) δ: 10.79 (s, 1H),8.47 (d, *J* = 5.3 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 5.5 Hz, 1H), 7.95 (d, *J* = 5.5 Hz, 1H), 7.85–7.76 (m, 1H), 7.72–7.67 (m, 2H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.45−7.40 (m, 2H), 7.34 (t, *J* = 8.1 Hz, 1H), 7.21−7.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ: 142.4, 140.8, 137.6, 135.4, 134.6, 133.4, 131.1, 128.5, 128.3, 127.8, 127.6, 127.1, 125.9, 125.6, 125.4, 125.2, 121.0, 120.7, 119.0, 113.4, 111.9; MS (ESI): *m/z* 295 $[M + H]^+$. HRMS (ESI): *m/z*: calcd for $C_{21}H_{14}N_2$: 295. 12298; found: 295.12249 $[M + H]^+$.

Norharmane (2o):

Yellow solid: 60 mg (77% yield); R_f = 0.43 (ethyl acetate), mp:193–196 °C (Ref[32]: 196 °C); IR (KBr): 3450, 3045, 2931, 2853, 2736, 2655, 1626, 1447, 1327, 1241, 737 cm^{-1}; ^1H NMR (500 MHz, DMSO−d_6) δ: 11.63 (s, 1H), 8.91 (s, 1H), 8.34 (d, *J* = 5.2Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 8.10 (d, *J* = 5.0 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO−d_6) δ; 140.4, 138.0, 135.9, 133.9, 128.0, 127.3, 121.7, 120.5, 119.1, 114.6, 111.8; MS (ESI): *m/z* 169 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{11}H_9N_2$: 169.07602; found: 169.07576 $[M + H]^+$.

Harmane (2p):

Off white solid: 60 mg (76% yield); R_f = 0.51 (ethyl acetate), mp: 229–231 °C (Ref[28]: 235–236 °C); IR (KBr): 3129, 3065, 2957, 2884, 2783, 1626, 1565, 1505, 1449, 1324, 1255, 819, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO−d_6) δ: 10.78 (s, 1H), 8.29 (d, *J* = 4.7 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 4.7 Hz, 1H), 7.63–7.47 (m, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ: 141.7, 140.3, 136.8, 134.3, 127.4, 126.9, 121.1, 120.8, 118.2, 112.2, 111.6, 20.0; MS (ESI): *m/z* 183 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{12}H_{11}N_2$: 183.09167; found: 183.09165 $[M + H]^+$.

General experimental procedure for the synthesis of β-carboline esters (4a-p) via dehydrogenation of tetrahydro-β-carboline esters (3a-p)

To a stirred solution of tetrahydro-β-carboline esters **3a-p** in DMF was added iodobenzene diacetate (2 equiv) and the resulting solution was stirred at room temperature for 1h. After consumption of starting material (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue obtained was purified by silica-gel column chromatography using ethyl acetate-hexane as eluent in increasing polarity to afford the desired β-carbolines esters **4a-p**.

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

White solid: 87 mg (88% yield); R_f = 0.50 (ethyl acetate/n-hexane, 4:6), mp: 257–259 °C (Ref[28]: 256–257 °C); IR (KBr): 3315, 3002, 2947, 1720, 1622, 1350, 1251, 1214, 1098, 739, 542 cm^{-1}; ^{1}HNMR (300 MHz, DMSO−d_6) δ: 8.92 (s, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 7.0 Hz, 2H), 7.73−7.54 (m, 5H), 7.33 (t, *J* = 7.7 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ: 165.8, 141.9, 141.3, 137.4, 136.4, 134.4, 128.9, 128.5, 128.4, 128.2, 121.4, 121.3, 120.9, 120.0, 116.3, 112.5, 51.7; MS (ESI): *m/z* 303 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{15}O_2N_2$: 303.11280; found: 303.11159 $[M + H]^+$.

Methyl 1-(4-methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4b):

White solid: 92 mg (93% yield); R_f = 0.49 (ethyl acetate/n-hexane, 4:6), mp: 228–231 °C (Ref[28]: 228–230 °C); IR (KBr): 3249, 2946, 2833, 1712, 1610, 1508, 1431, 1351, 1248, 1106, 1029, 833, 744, 577 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO−d_6) δ:11.65 (s, 1H), 8.79 (s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.55 (t, *J* = 7.1 Hz, 1H),7.31 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 3.99 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ: 164.9, 158.5, 140.1, 135.2, 133.3, 128.8, 128.5, 127.6, 126.8, 119.9, 119.8, 118.8, 114.6, 112.5, 111.3, 53.7, 50.6; MS (ESI): *m/z* 333 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{17}O_3N_2$: 333.12337; found: 333.12194 $[M + H]^+$.

Methyl 1-(3,4,5-trimethoxyphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4c):

Off white solid: 94 mg (95% yield); R_f = 0.47 (ethyl acetate/n-hexane, 1:1), mp: 227–229 °C (Ref[28]: 228–230 °C); IR (KBr): 3605, 3262, 2963, 2942, 2830, 1710, 1625, 1588, 1502, 1461, 1431, 1394, 1358, 1330, 1253, 1129, 1008, 842, 745, 631 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$ + DMSO−d_6) δ: 11.52 (s, 1H), 8.75 (s, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.1 Hz, 1H), 7.15 (s, 2H), 3.95 (s, 3H), 3.90 (s, 6H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ: 165.8, 152.7, 142.2, 141.2, 137.8, 136.2, 134.5, 132.9, 128.7, 128.0, 121.1, 120.9, 119.9, 116.1, 112.4, 105.5, 59.9, 55.5, 51.7; MS (ESI): *m/z* 393 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{22}H_{21}O_5N_2$: 393.14450; found: 393.14320 $[M + H]^+$.

methyl 1-(2-methoxyphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4d):

White solid: 87 mg (88% yield); R_f = 0.42 (ethyl acetate/n-hexane, 4:6), mp: 208–210 °C; IR (KBr): 3251, 3056, 2947, 2837, 1730, 1711, 1624, 1459, 1434, 1239, 1222, 1120, 1027, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.91 (d, *J* = 0.4 Hz, 1H), 8.75 (bs, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.79 (dd, *J* = 1.8, 7.6 Hz, 1H), 7.60−7.56 (m, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.50−7.46 (m, 1H), 7.37−7.34 (m, 1H), 7.20−7.17 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 4.05 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 156.6, 141.0, 140.5, 137.6, 136.3, 132.6, 130.5, 128.9, 128.6,

127.0, 121.8, 121.7, 120.6, 116.8, 112.0, 111.8, 56.3, 52.5; MS (ESI): *m/z* 333 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{17}O_3N_2$: 333.12337; found: 333.12278 $[M + H]^+$.

Methyl 1-(p-tolyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4e):

Yellow solid: 89 mg (90% yield); R_f = 0.51 (ethyl acetate/n-hexane, 3:7), mp: 192–194 °C; IR (KBr): 3640, 3325, 3028, 2946, 1716, 1621, 1457, 1433, 1350, 1258, 1218, 1109, 1047, 819, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO–d_6) δ: 8.90 (s, 1H), 8.42 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 3.93 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 166.0, 142.1, 141.4, 138.4, 136.5, 134.6, 134.4, 129.3,129.0, 128.5, 128.4, 121.9, 121.1, 120.3, 116.4, 112.7, 52.0, 20.9; MS (ESI): *m/z* 317 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{17}O_2N_2$: 317.12845; found: 317.12788 $[M + H]^+$.

Methyl 1-(4-nitrophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4f):

Yellow solid: 79 mg (83% yield); R_f = 0.33 (ethyl acetate/n-hexane, 3:7), mp: 265–266 °C (Ref[22]: 260 °C); IR (KBr): 3262, 2952, 1733, 1519, 1433, 1350, 1246, 1109, 1046, 854,741 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 9.00 (s, 1H), 8.47 (d, *J* = 8.7 Hz, 3H), 8.29 (d, *J* = 8.9 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.7, 147.4, 143.5, 141.5, 139.3, 139.8, 1345.7, 129.8, 129.0, 123.8, 122.1, 120.9, 120.6, 117.5, 112.6, 52.1; MS (ESI): *m/z* 348 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{14}O_4N_3$: 348.09788; found: 348.09769 $[M + H]^+$.

Methyl 1-(4-cyanophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4g):

White solid: 82 mg (85% yield); R_f = 0.55 (ethyl acetate/n-hexane, 3:7), mp: 324–327 °C; IR (KBr): 3250, 2952, 2227, 1726, 1500, 1386, 1253, 1104, 1045, 846, 754, 550 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 8.98 (s, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 2H), 8.11 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.8, 141.7, 141.5, 139.8, 136.7, 134.6, 132.6, 129.7, 129.4, 128.9, 122.1, 120.9, 120.6, 118.7, 117.4, 112.7, 111.3, 52.1; MS (ESI): *m/z* 328 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{14}O_2N_3$: 328.10805; found: 328.10760 $[M + H]^+$.

Methyl 1-(4-(trifluoromethyl)phenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4h):

White solid: 84 mg (85% yield); R_f = 0.55 (ethyl acetate/n-hexane, 3:7), mp: 306–310°C; IR (KBr): 3258, 2951, 1707, 1623, 1565, 1499, 1436, 1354, 1322, 1253, 1173, 1117, 1066, 846, 738, 575 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 8.80 (s, 1H), 8.13 (t, *J* = 7.4 Hz, 3H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.8, 141.5, 141.3, 140.3, 136.7, 134.7, 129.4 (q, *J* = 8.8, 17.6 Hz), 128.9, 128.8, 125.6, 125.5, 122.4, 122.1, 121.0, 120.5, 117.3, 112.6, 52.0; MS (ESI): *m/z* 371 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{14}O_2N_2F_3$: 371.10019; found: 371.09935 $[M + H]^+$.

Methyl 1-(4-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4i):

White solid: 85 mg (86% yield); R_f = 0.54 (ethyl acetate/n-hexane, 3:7), mp: 275–278 °C (Ref[34]: 203–205 °C); IR (KBr): 3314, 2955, 1719, 1623, 1509, 1435, 1387, 1351, 1252, 1221, 1101, 1045, 847, 750, 541 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ + DMSO–d_6) δ: 8.87 (s, 1H), 8.83 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 5.3, 8.7 Hz, 2H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 8.7 Hz, 2H), 4.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 165.7, 164.0 and 160.7 (d, *J* = 247.0 Hz), 141.3, 140.8, 136.4, 134.3, 133.7 (d, *J* = 2.7 Hz), 130.5, (d, *J* = 8.2 Hz), 129.0, 128.2, 121.4, 120.9, 120.0, 116.3, 115.4 and 115.1 (d, *J* = 21.4 Hz), 112.4, 51.7; MS (ESI): *m/z* 321 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{14}O_2N_2F$: 321.10338; found: 321.10298 $[M + H]^+$.

Methyl 1-(3-fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4j):

White solid: 86 mg (87% yield); R_f = 0.52 (ethyl acetate/n-hexane, 3:7), mp: 255–257 °C; IR (KBr): 3316, 3213, 3063, 1723, 1453, 1351, 1289, 1252, 1225, 1104, 746, 543 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 11.15 (s, 1H), 8.96 (s, 0.6H), 8.44 (d, *J* = 7.9 Hz, 0.7H), 7.87 (t, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 10.2 Hz, 1H), 7.74–7.67 (m, 2H), 7.66–7.59 (m, 1H), 7.46–7.31 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.8, 163.8 and 160.6 (d, *J* = 243.7 Hz), 149.8, 141.4, 136.5, 134.4, 130.7(d, *J* = 8.2 Hz),129.4, 128.8, 124.8, 124.7 (d, *J* = 2.2 Hz), 122.0, 121.7, 121.0, 117.0, 115.7 (d, *J* = 20.9 Hz),115.2(d, *J* = 22.2 Hz), 112.7, 52.0; MS (ESI): *m/z* 321 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{14}O_2N_2F$: 321.10338; found: 321.10298 $[M + H]^+$.

Methyl 1-(3-hydroxyphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4k):

Off white solid: 82 mg (83% yield); R_f = 0.32 (ethyl acetate/n-hexane, 1:1), mp: 234–235 °C; IR (KBr): 3448, 3289, 2953, 1690, 1599, 1563, 1440, 1356, 1329, 1264, 1113, 1047, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ : 8.54 (bs, 1H), 8.81 (s, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.46–7.32 (m, 3H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ; 165.7, 157.4, 142.2, 141.2, 138.5, 136.1, 134.4, 129.5, 128.9, 128.0, 121.1, 121.0, 120.0, 119.0, 116.1, 115.7, 115.3, 112.5, 51.6; MS (ESI): *m/z* 319 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{19}H_{15}O_3N_2$: 319.10772; found: 319.10674$[M + H]^+$.

Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4l):

White solid: 91 mg (92% yield); R_f = 0.48 (ethyl acetate/n-hexane, 4:6), mp: 294–296 °C (Ref[28]: 292–293 °C); IR (KBr): 3337, 2988, 2947, 2903, 1712, 1623, 1499, 1446, 1353, 1283, 1251, 1176, 1039, 747, 529 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 8.89 (s, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 7.70 (d, *J*= 8.3 Hz, 1H), 7.61 (d, *J* = 7.1 Hz, .0.9H), 7.58–7.51 (m, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 0.9H), 6.17 (s, 1.8H), 3.93 (s, 3H) peaks at 7.45, 7.10, 6.14 are due to 10% minor rotamer; ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.9, 147.9, 147.5, 141.6, 141.3, 136.4, 134.2, 131.5, 129.0, 128.5, 122.7, 121.9, 121.1, 120.3, 116.3, 112.7, 108.7, 108.5, 101.4, 52.0; MS (ESI): *m/z* 347 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{15}O_4N_2$: 347.10263; found: 347.10194 $[M + H]^+$.

Methyl 1-(pyridin-3-yl)-9*H*-pyrido [3, 4-*b*] indole-3-carboxylate (4m):

White solid: 88 mg (90% yield); R_f = 0.32 (ethyl acetate), mp: 233–236 °C (Ref[22]: 234–236 °C); IR (KBr): 3207, 3097, 3062, 2946, 2839, 1728, 1710, 1626, 1565, 1500, 1433, 1356, 1262,

1218, 1107, 1032, 741, 712, 620 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 9.21 (s, 1H), 8.98 (s, 1H), 8.77 (d, *J* = 3.8 Hz, 1H), 8.46 (d, *J* = 7.9 Hz, 1H), 8.42–8.36 (m, 1H), 7.73–7.60 (m, 3H), 7.35 (t, *J* = 7.7 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO–d_6) δ: 165.6, 149.4, 149.0, 141.4, 139.0, 136.6, 135.9, 134.6, 133.2, 129.2, 128.4, 123.5, 121.5, 120.8, 120.2, 116.8, 112.5, 51.8; MS (ESI): *m/z* 304 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{18}H_{14}O_2N_3$: 304.10805; found: 304.10700 $[M + H]^+$.

Methyl 1-(1-acetyl-1*H*-indol-3-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4n):

Yellow solid: 84 mg (85% yield); R_f = 0.36 (ethyl acetate/n-hexane, 4:6), mp: 199–201 °C (Ref[22]: 192–194 °C); IR (KBr): 3281, 2949, 1711, 1624, 1569, 1451, 1333, 1302, 1251, 1218, 1108, 1002, 744, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO–d_6) δ: 11.64 (s, 1H), 8.83 (s, 1H), 8.60 (dd, *J* = 3.0, 6.6 Hz, 1H), 8.52 (dd, *J* = 2.1, 6.2, Hz, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.46–7.33 (m, 3H), 4.05 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 169.9, 165.9, 141.1, 137.0, 136.2, 135.2, 134.3, 128.9, 128.8, 128.6, 127.1, 125.3, 123.9, 122.7, 121.9, 121.3, 120.5, 117.6, 116.0, 115.7, 112.6, 52.1, 24.1; MS (ESI): *m/z* 384 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{23}H_{18}O_3N_3$: 384.13427; found: 384.13417 $[M + H]^+$.

Methyl 9*H*-pyrido [3, 4-*b*] indole-3-carboxylate (4o):

White solid: 80 mg (82% yield); R_f = 0.41 (ethyl acetate), mp: 247–249 °C (Ref[22]: 242–244 °C) ; IR (KBr): 3245, 2944, 1716, 1501, 1434, 1343, 1301, 1248, 1101, 729 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 8.95 (d, *J* = 10.2 Hz, 2H), 8.41 (d, *J* = 7.9Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 165.9, 140.9, 137.3, 136.3, 133.7, 128.6, 127.4, 122.2, 120.8, 120.1, 117.6, 112.3, 51.9; MS (ESI): *m/z* 227 $[M + H]^+$. HRMS (ESI): *m/z*: calcd for $C_{13}H_{11}N_2O_2$: 227.08260; found: 227.08124 $[M + H]^+$.

Methyl 1-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4p):

White solid: 78 mg (80% yield); R_f = 0.42 (ethyl acetate/n-hexane, 9:1), mp: 243–244 °C (Ref[28]: 242–243 °C); IR (KBr): 3329, 3041, 2948, 1716, 1500, 1434, 1256, 1010, 784, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.23 (s, 1H), 8.80 (s, 1H), 8.17 (d, *J* = 7.5 Hz, 1H), 7.57 (s, 2H),7.41–7.30 (m, 1H), 4.03 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 166.1, 142.1, 140.6, 136.1, 135.8, 128.3, 126.7, 122.0, 121.2, 120.1, 115.9, 112.2, 51.8, 20.3; MS (ESI): *m/z* 241 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}O_2N_2$: 241.09715; found: 241.09615 $[M + H]^+$.

Synthesis of Eudistomin U:

Methyl 1-(1-acetyl-1*H*-indol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (7):

A stirred solution of L-tryptophan methyl ester hydrochloride **6** (1g, 3.93 mmol) and *N*-acetyl indole-3-carboxaldehyde (736 mg, 3.93 mmol) in ethanol was refluxed for 12 h. Ethanol was removed, basified with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (4:6 ethyl acetate/n-hexane) to afford diastereomeric mixture tetrahydro-β-carboline **7** (1.3g, 86% yield) as a yellow solid; R_f = 0.50 (ethyl acetate/n-hexane, 7:3), mp: 237–239 °C; IR (KBr): 3394, 3214, 3088, 2906, 2552, 2462, 1748, 1704, 1455, 1375, 1328, 1224, 1135, 1002, 743, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, *J* = 8.1 Hz, 1H), 8.00 (s, 0.2H), 7.65 (s, 0.7H), 7.61–7.54 (m, 1H), 7.52 (s, 1H), 7.40–7.33 (m, 2H), 7.24–7.18 (m, 2H), 7.18–7.11 (m, 2H), 7.56 (s, 0.2H), 5.58 (t, *J* = 1.8 Hz, 0.8H), 4.07–4.00 (m, 1H), 3.82 (s, 2.4H), 3.72 (s, 0.6H), 3.32–3.26 (m, 1H), 3.10–3.01 (m, 1H), 2.50 (s, 2.4H), 2.41 (s, 0.6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.1, 173.1, 168.7, 168.6, 136.3, 136.2, 136.0, 133.6, 132.4, 128.9, 128.7, 127.0, 126.9, 125.8, 125.7, 124.3, 124.1, 123.0, 122.5, 122.0, 121.7, 120.2, 119.7, 119.5, 118.3, 118.2, 116.8, 111.1, 108.3, 108.0, 56.9, 53.2, 52.3, 52.1, 50.5, 46.9, 29.7, 25.6, 24.5, 23.7; MS (ESI): *m/z* 388 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{23}H_{22}O_3N_3$: 388.16557; found: 388.16572 $[M + H]^+$.

1-(1*H*-Indol-3-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (8):

A stirred mixture of tetrahydro-β-carboline 12 (500mg, 1.29 mmol) and 2M LiOH•H_2O (5 ml) in THF (5ml) was heated at reflux for 12 h. The reaction mixture was cooled to rt, THF was removed under reduced pressure and the reaction mixture was acidified (pH 7) by drop wise addition of 5N HCl. The resultant precipitate was collected by filtration, washed with ice cold water and dried well to provide pure carboxylic acid **8** (384 mg, 90% yield) as a yellow solid: R_f = 0.39 (methanol/dichloromethane, 4:6), mp: 250–253 °C; IR (KBr): 3176, 2475, 1628, 1453, 1382, 1310, 1236, 1155, 1099, 738, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ: 11.35 (s, 0.2H), 10.82 (s, 1H), 10.51 (s, 0.1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.11–6.97 (m, 3H), 6.89 (t, *J* = 7.7 Hz, 1H), 5.99 (s, 0.8H), 5.80 (s, 0.2H),3.73 (q, *J* = 5.5, 7.5 Hz, 1H), 3.21 (dd, *J* = 5.3, 15.7 Hz, 1H), 3.05 (dd, *J* = 7.9, 15.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO–d_6) δ: 171.2, 170.7, 136.4, 136.3, 136.2, 131.0, 127.2, 126.2, 126.1, 121.3, 121.2, 121.0, 119.1, 118.7, 118.6, 118.0, 117.8, 111.8, 111.2, 110.2, 110.0, 107.4, 106.8, 57.7, 53.4,, 50.2, 47.7, 23.7, 23.1; MS (ESI): *m/z* 332 $[M + H]^+$; HRMS (ESI): *m/z*: calcd for $C_{20}H_{18}O_2N_3$: 332.13935; found: 332.13866 $[M + H]^+$.

Eudistomin U (9):

To a stirred solution of acid **8** (100mg, 0. 30 mmol) in DMF was added iodobenzene diacetate (195 mg 0.60 mmol) and the resulting mixture was stirred at room temperature for 1h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated. The residue obtained was purified by silica gel chromatography (9:1 ethyl acetate/methanol) to afford the eudistomin U (**3**, 56 mg, 66% yield) as a pale yellow solid: R_f = 0.51 (ethyl acetate/n-hexane, 9:1), mp: 232–234 °C (Ref[25d]: 235–236 °C); IR (KBr): 3433, 3058, 2922, 1625, 1567, 1453, 1325, 1237, 743 cm^{-1}; ^1HNMR (500 MHz, DMSO–d_6) δ: 11.72 (s, 1H), 11.31 (s, 1H), 8.56 (d, *J* = 7.9 Hz, 1H), 8.45 (d, *J* = 5.2Hz, 1H), 8.30 (d, *J* = 2.7 Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 5.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO–d_6) δ: 159.5, 159.2, 156.7, 155.3, 150.3, 146.9, 146.5, 145.0, 144.8, 141.1, 140.8, 140.1, 140.0, 138.6, 138.2, 132.0, 131.2, 130.4, 130.3; MS (ESI): *m/z* 284 $[M + H]^+$; HRMS

(ESI): *m/z*: calcd for C_{19} H_{14} N_3: 284.11822; found: 284.11692 [M + H]$^+$.

Synthesis of Eudistomin I:

Methyl 1-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (10):

A stirred solution of L-tryptophan methyl ester hydrochloride salt **6** (1g, 3.93 mmol) and (S)-tert-butyl-2-formylpyrrolidine-1-carboxylate (783 mg, 3.93 mmol) in ethanol was heated at reflux for 12 h. After cooling to rt, the ethanol was removed and basified with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (3:7 ethyl acetate/n-hexane) to afford the tetrahydro-β-carboline **10** (1.33 mg, 88% yield) as a diastereomeric mixture, Pale yellow solid; R_f = 0.48 (ethyl acetate/n-hexane, 1:1), mp: 100–102 °C; IR (KBr): 3345, 2971, 1738, 1675, 1453, 1398, 1165, 1116, 1012, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (m, 0.5H), 7.52−7.47 (m, 1H), 7.36−7.29 (m, 1H), 7.19−7.13 (m, 1H), 7.13−7.08 (m, 1H), 4.93 (s, 0.6H), 4.88 (s, 0.4H), 4.07−3.97 (s, 1H), 3.82 (s, 1.3H), 3.76−3.72 (s, 0.5H), 3.68 (s, 1.7H), 3.66−3.58 (m, 0.5H), 3.48−3.39 (m, 0.5H), 3.27−3.19 (m, 0.5H), 3.18−3.04 (m, 1.6H), 2.87−2.76 (m, 0.4H), 2.08−1.96 (m, 1H), 1.74−1.58 (m, 4H), 1.54 (s, 4.7H), 1.53 (s, 1.3H), 1.50 (bs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.3, 155.8, 155.7, 136.4, 136.1, 131.6, 126.9, 126.6, 121.7, 119.5, 119.3, 117.8, 117.8, 110.8, 110.4, 108.9, 80.4, 79.9, 79.6, 62.7, 61.4, 60.8, 56.2, 55.8, 54.2, 53.9, 53.5, 52.2, 52.1, 52.0, 51.9, 51.2, 48.4, 47.9, 28.5, 28.4, 27.5, 25.5, 24.6, 23.8; MS (ESI): *m/z* 400 [M + H]$^+$. HRMS (ESI): *m/z*: calcd for C_{22} H_{30} O_4 N_3: 400.22308; found: 400.22348 [M + H]$^+$.

1-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (11):

A stirred mixture of tetrahydro-β-carboline **10** (500mg) and 2M LiOH•H_2O (5ml) in THF (5ml) was heated at reflux for 12 h. The reaction mixture was cooled to rt, THF was removed under reduced pressure and the reaction mixture was acidified (pH 5) by drop wise addition of 5N HCl. The resultant precipitate was collected by filtration and washed with H_2O to provide pure carboxylic acid **11** (439 mg, 91% yield) as a white solid. R_f = 0.52 (methanol/dichloromethane, 2:8), mp: 248–250 °C; IR (KBr): 3424, 3059, 2978, 1629, 1610, 1455, 1395, 1367, 1258, 1164, 1109, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO−d_6) δ: 10.78–10.51 (m, 0.4H), 10.30 (s, 0.5H), 7.39−7.22 (m, 2H), 7.05−6.87 (m, 2H), 4.86−4.66 (m, 1H), 4.44 (s, 1H), 4.13 (q, *J* = 5.9, 11.3 Hz,1H), 4.06−3.84 (m, 1H), 3.63−3.38 (m, 2H), 3.15−2.98 (m, 1H), 2.91−2.79 (m, 0.5H), 2.74−2.63 (m, 0.6H), 1.98−1.55 (m, 4H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, DMSO−d_6) δ: 173.7, 136.3, 136.2, 135.5, 131.9, 126.4, 126.2, 120.7, 120.5, 118.3, 117.4, 111.3, 110.9, 107.8, 107.6, 78.7, 78.6, 60.4, 60.3, 59.3, 55.5, 52.3, 46.5, 28.1, 28.0, 27.9, 24.3, 23.0; MS (ESI): *m/z* 386 [M + H]$^+$. HRMS (ESI): *m/z*: calcd for $C_{21}H_{28}O_4$ N_3: 386.20743; found: 386.20800 [M + H]$^+$.

Eudistomin I (12):

The *N*-Boc tetrahydro-β-carboline acid **11** (100 mg, 0.25 mmol) were dissolved in 1,4-dioxane (1 mL) and was added 2N HCl in 1,4-dioxane (1ml) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The residue obtained was washed with diethylether, dried anddissolved in DMF was added iodobenzene diacetate (166mg, 0.51mmol) and the resulting mixture was stirred for 1h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by silica gel chromatography (2:8 ethylactate/n-hexane) to afford the eudistomin I (**12**, 38 mg, 63% yield) as a pale yellow solid: R_f = 0.43 (ethyl acetate/n-hexane, 3:7), mp: 153–155 °C (Ref[26a]: 153–155 °C); IR (KBr): 3355, 3047, 2918, 2855, 1627, 1608, 1490, 1452, 1430, 1345, 1319, 1285, 1256, 1135, 1034, 977, 751, 603, 551 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.85 (s, 1H), 8.51 (d, *J* = 5.0 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 5.2 Hz, 1H), 7.60−7.55 (m, 2H), 7.33−7.28 (m, 1H), 4.31−4.26 (m, 2H), 3.36−3.31 (m, 2H), 2.13−2.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.8, 140.7, 138.1, 135.8, 135.3, 129.5, 128.5, 121.8, 121.8, 120.0, 116.1, 111.9, 62.2, 34.9, 21.8; MS (ESI): *m/z* 236 [M + H]$^+$. HRMS (ESI): *m/z*: calcd for $C_{15}H_{14}N_3$: 236.11822 found: 236.11774 [M + H]$^+$.

References

1. (*a*) D. J Newman, G. M. Cragg *J. Nat. Prod.*2007, **70**, 461; (*b*) M. S. Butler, *J. Nat. Prod.,* 2004, **67**, 2141; (*c*) M. S. Butler, *Nat. Prod. Rep*., 2005, **22,** 162; (*d*) M. S. Butler, A. A. Robertson, M. A. Cooper, *Nat. Prod. Rep.,* 2014, ***31***, 1612.
2. (*a*) R. Cao, W. Peng, Z. Wang, A. Xu, *Curr. Med. Chem.,* 2007, 14, 479; (*b*) B. E. Love, *Org. Prep. Proced. Int.,* 1996, **28**, 3; (*c*) W. D. Inman, B W. M ray, N. C. Gassner, R. S. Lokey, K. Tenney, Y. Y. Shen, K. Tendyke, T. Suh, P. Crews, *J. Nat. Prod.,* 2010, **73**, 255.
3. (*a*) M. A. Rashid, K. R. Gustafson, M. R. Boyd, *J. Nat. Prod.,* 2001, **64**, 1454; (*b*) H. Guan, H. Chen, W. Peng, Y. Ma, R. Cao, X. Liu, A. Xu, *Eur. J. Med. Chem.,* 2006, **41**, 1167; (*c*) M. R. Prinsep, J. W. Blunt, M. H. G. Munro, *J. Nat. Prod.,* 1991, **54**, 1068. (*d*) A. Kamal, V. Srinivasulu, V. L. Nayak, M. Sathish, N. Shankaraiah, C. Bagul, N.V. Reddy. N. Rangaraj, N. Nagesh, *Chem.Med.Chem.*, 2014, **9**, 2084.
4. (*a*) A. G. Shilabin, N. Kasanah, B. L. Tekwani, M. T. Hamann, *J. Nat. Prod.,* 2008, **71**, 1218; (*b*) J. D. Winkler, A. T. Londregan, M. T. Hamann, *Org. Lett.,* 2006, **8**, 2591; (*c*) Y. Boursereau, I. Coldham, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 5841.
5. (*a*) J. G. Tang, Y. H. Wang, R. R. Wang, Z. J. Dong, L. M. Yang, Y. T. Zheng, J. K. Liu, *Chem. Biodiversity.,* 2008, ***5***, 447; (*b*) Y. H. Wang, J. G. Tang, R. R. Wang, L. M. Yang, Z. J. Dong, L. Du, X. Shen, J. K. Liu, Y. T. Zheng, *Biochem. Biophys. Res. Commun.,* 2007, **355**, 1091; (*c*) X. Yu, W. Lin, J. Li, M. Yang, *Bioorg. Med. Chem. Lett.,* 2004, **14**, 3127.
6. (*a*) H. J. Shin, H. S. Lee, D. S. Lee, *J. Microbiol. Biotechnol.,* 2010, **20**, 501; (*b*) R. B Volk, F. H. Furkert, *Microbiol Res.,* 2006, **161**, 180.
7. (*a*) B. Grella, M. Teitler, C. Smith, K. Herrick-Davis, R. A. Glennon, *Bioorg. Med. Chem. Lett*., 2003, *13*, 4421; (*b*) J. E. Audia, D. A. Evrard, G. R. Murdoch, J. J. Droste, J. S. Nissen, K. W. Schenck, P. Fludzinski, V. L. Lucaites, D. L. Nelson, M. L. Cohen, *J. Med. Chem*., 1996, **39**, 2773; (*c*) B. Grella, M. Dukat, R. Young, M. Teitler, K. Herrick-Davis, C. B. Gauthierr, R. A. Glennon, *Drug Alcohol Depend.,* 1998, **50**, 99; (*d*) R. A. Glennon, M. Dukat, B. Grella, S. S. Hong, L. Costantino, M.

Teitler, C. Smith, C. Egan, K. Davis, M. V. Mattson, *Drug Alcohol Depend.*, 2000, **60**, 121.
8. Q. Wu, R. Cao, M. Feng, X. Guan, C. Ma, J. Liu, H. Song, W. Peng, *Medicinal Chemistry.,* 2009, **44**, 533.
9. (*a*) T. J. Hagen, P. Skolnick, J. M. Cook, *J. Med. Chem.,* 1987, **30**, 750; (*b*) T. J. Hagen, F. Guzman, C. Schultz, J. M. Cook, P. Skolnick, H. E. Shannon, *Heterocycles.,* 1986, **10**, 2845; (*c*) W. E. Muller, K. J. Fehske, H. O. Borbe, U. Wollert, C. Nanz, H. Rommelspacher, *Pharmacol. Biochem. Behav*., 1981, **14**, 693; (*d*) S. P. Hollinshead, M. L. Trudell, P. Skolnick, J. M. Cook*, J. Med. Chem.,* 1990, **33**, 1062.
10. (*a*) V. G.erniest, X. Wang, N. D. Kimpe, A. Padwa, *J. Org. Chem.,* 2010, **75**, 424; (*b*) I. T. Raheem, P. S. Thiara, P E. A. eterson, E. N. J acobsen, *J. Am. Chem. Soc.,* 2007, **129**, 13404; (*c*) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.,* 2005, **44**, 6700.
11. (*a*) G. Zhang, R. Cao, L. Guo, Q. Ma, W. Fan, X. Chen, J. Li, G. Shao, L. Qiu, Z. Ren, *Eur. J. Med. Chem.,* 2013, **65**, 21; (*b*) Y. Song, J. Wang, S. F. Teng, D. Kesuma, Y. Deng, J. Duan, J. H. Wang, R .Z. Qi, M. M. Sim, *Bioorg. Med. Chem. Lett.,* 2002, **12**, 1129.
12. W. Huang, J. Li, L. Ou, *Synthetic Commun.,* 2007, **37**, 2137.
13. R. Meesala, M. N. Mordi, S. M. Mansor, *Synlett.,* 2014, **25**, 120.
14. (*a*) F. Gatta, D. J. Misiti, *Heterocycl. Chem.,* 1987, **24**, 1183; (b) M. Cain, O. Campos, F. Guzman, J. M. Cook*, J. Am. Chem. Soc.,* 1983, **105**, 907; (*c*) O. Campos, M. DiPierro, M. Cain, R. Mantei, A. Gawish, J. M. Cook, *Heterocycles.,* 1980, **14**, 975.
15. (*a*) W. Yin, P. V. V. Srirama Sarma, J. Ma, D. Han, J. L. Chen, J. M. Cook, *Tetrahedron Lett.*, 2005, 46, 6363; (*b*) S. B. Dantale, B.C.G. Soderberg, *Tetrahedron*., 2003, **59**, 5507.
16. (*a*) M. Cain, R. W. Weber, F. Guzman, J. M. Cook, S. A. Barker, K. C. Rice, J. N. Crawley, S. M. Paul, P. Skolnick, *J. Med. Chem.,* 1982, **25**, 108; (*b*) I. J. W. Still, J. McNulty, *Heterocycles.,* 1989, **29**, 2057; (*c*) W. Qifeng, C. Rihui, F. Manxiu, G. Xiangdong, M. Chunming, L. Jinbing, S. Huacan, P. Wenlie, *Eur. J. Med. Chem.,* 2009, **44**, 533.
17. (*a*) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, J. M. Cook, *J. Org. Chem.,* 1979, **44**, 535; (*b*) S. Hibino, O. Miko, I. Masataka, S. Kohichi, I. Takashi, *Heterocycles.,* 1985, **23**, 261; (*c*) R. T. Coutts, R. G. Micetich, G. B. Baker, A. Benderly, T. Dewhurst, T. W. Hall, A. R. Locock, J. Pyrozko, *Heterocycles.,* 1984, **22**, 131.
18. (*a*) K. P. Lippke, W. G. Schunack, W. Wenning, W. E. Muller, *J. Med. Chem.* 1983, **26**, 4993; (*b*) H. R. Snyder, C. H. Hansch, L. Katz, S. M. Parmerter, E. C. Spaeth, *J. Am. Chem. Soc.* 1948, **70**, 219.
19. C. Yeun-Mun, M. C. Hamann*, Heterocycles.* 2007, **71**, 245; (*b*) J. Kobayashi, J. Cheng, T. Ohta, S. Nozoe, Y. Ohizumi, T. Sasaki, *J. Org. Chem.,* 1990, **55**, 3666; (*c*) W.O. Foye, X. Wang, W. Hongfu, *Med. Chem. Res.,* 1997, **7**, 180.
20. (*a*) S. Ding, Z. Shi, N. Jiao, *Org. Lett.* 2010, **12**, 1540; (*b*) Z. Shi, Y. Cui, N. Jiao, *Org. Lett*., 2010, **12**, 2908; (*c*) H. Zhang, R. C. Larock, *J. Org. Chem*., 2002, **67**, 7048; (*d*) S. Chiba, Y. J. Xu, Y.F. Wang, *J. Am. Chem. Soc.,* 2009, **131**, 12886; (*e*) G. Verniest, D. England, N. De Kimpe, A. Padwa, *Tetrahedron.,* 2010, **66**, 1496.
21. (*a*) R. D. Richardson, T. Wirth, *Angew. Chem., Int. Ed.,* 2006, **45**, 4402; (*b*) V. V. Zhdankin, P. J. Stang, *Chem. Rev*., 2008, **108**, 5299; (*c*) E. A. Merritt, B. Olofsson, *Angew.Chem. Int. Ed.,* 2009, **48**, 9052; (*d*) H. Liang, M. A. Ciufolini, *Angew.Chem., Int. Ed.,* 2011, **50**, 11849; (*e*) M. Uyanik, K. Ishihara, *Chem.Cat.Chem*., 2012, 4, 177; (*f*) R. Samanta, A. P. Antonchick, *Synlett*., 2012, **23**, 809; (*g*) M. Brown, U. Farid, T. Wirth, *Synlett.,* 2013, **24**, 424; (*h*) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem.,* 2013, **26**, 5769; (*i*) A. Kamal, N. V. S. Reddy, B. Prasad*, Tetrahedron Lett*., 2014, **55**, 3972
22. J. D. Panarese, S. P. Waters, *Org. Lett*., 2010, **12**, 4086.
23. Badre, A. Boulanger, E. Abou-Mansour, B. Banaigs, G. Combaut, C. Francisco, *J. Nat. Prod.,* 1994, **57**, 528.
24. (*a*) J. Kobayashi, G. C. Harbour, J. Gilmore, K. L. Rinehart*, J. Am. Chem*. Sot., 1984, ***106***, 1524; (*b*) J. B. Hudson, H. Saboune, Z. Abramowski, G. H. Towers, K. L. Rinehart, *Photochem Photobiol.,* 1988, **47**, 377.
25. (*a*) P. Molina, P. M. Fresneda, S. García-Zafra, *Tetrahedron Lett.,* 1995, **36**, 3581; (*b*) P. Rocca, F. Marsais, A. Godard, G. Queguiner, L. Adams, B. Alo, *Tetrahedron Lett.,* 1995, **36**, 7085; (*c*) F. Nissen, V. Richard, C. Alayrac, B. Witulski, *Chem. Commun.,* 2011, **47**, 6656; (*d*) A. D. Yamaguchi, D. Mandal, J. Yamaguchi, K. Itami, *Chem. Lett.,* 2011, **40**, 555; (*e*) C. M. Roggero, J. M. Giulietti, S. P. Mulcahy, *Bioorg. Med. Chem. Lett.,* 2014, **24**, 3549.
26. (*a*) K. L. Rinehart, J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield, F. Lafargue. *J. Am. Chem soc.,* 1987, **109**, 3378; (*b*) T. Hino, Z. Lai, H. Seki, R. Hara, T. Kuramochi, M. Nakagawa, *Chem.pharm.bull.,* 1989, **37**, 2596; (*c*) H. Harry, Wasserman, T. A. Kelly, *Tetrahedron Lett.,* 1989, **30**, 7117.
27. (*a*) L. H. Du, Y. G. Wang, *Synthesis.,* 2007, **5**, 675; (*b*) A. Boto, I. Romero-Estudillo, *Org. Lett.,* 2011, **13**, 3426; (*c*) Y. Chi, W. X. Zhang, Z. Xi, *Org. Lett.,* 2014, **16**, 6274.
28. D. Jing, S. Xiao-Xin, Y. Jing-Jing, X. Jing, Z, Qiang, X. Sen, *Eur. J. Org. Chem.,* 2010, **36**, 6987.
29. Q. Wu, R. Cao, M. Feng, C. Ma, J. Liu, H. Song, W. Peng, *Eur. J .Med. Chem.,* 2009, **44**, 533.
30. Kulakarni, A. Mohammed, B. Toeroek, X. Huang, Tetrahedron Lett., 2009, **50**, 1791.
31. Lomakin, *J. Gen. Chem.* 1969, **39**, 1851.
32. S. Li, B. Yang, Q. Zhang, J. Zhang, J. Wang, W. Wu, *Nat. Prod. Commun.,* 2010, **5**, 1591.
33. P. S. Parameswaran, C. G. Naik, V .R. Hegde, *J. Nat. Prod.,* 1997, **60**, 802.
34. F. Gatta, D. Misiti, *J. Heterocyclic. Chem.,* 1987, **24**, 1183.

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