CHAPTER-1

N-Bromosuccinimide promoted synthesis of β-carbolines and 3,4-dihydro-β-carbolines from tetrahydro-β-carbolines
Introduction:

Carbolines are nitrogen-containing heterocycles found in a plethora of natural products, alkaloids and drug candidates. This class of heterocycle contains an indole ring fused with pyridine ring system. Depending on the position of the N atom in the pyridine ring, carbolines are classified into α-carboline, β-carboline, γ-carboline and δ-carboline (Scheme-1.1). The important properties of these heterocycles makes them a suitable target for drug candidates to the organic and medicinal chemists around the globe. Among others, β-carboline alkaloids are enriched with diverse biological properties. β-Carboline alkaloids are present in leaves, barks and roots of several plants. Some β-carboline alkaloids such as Tryptoline and Pinoline are also present in the human body.

\[ \text{Scheme-1.1} \]

β-Carboline scaffolds are mainly divided into three types depending on the presence of unsaturation (Scheme-1.2). Fully aromatic member is called as β-carboline, whereas the partially or completely saturated forms are known as dihydro-β-carboline and tetrahydro-β-carboline respectively.

\[ \text{Scheme-1.2} \]

The first β-carboline alkaloid was isolated from Peganum harmala (Zygophyllaceae, Syrian rue) which is used as a traditional herbal drug.\(^{33}\) The seed extracts of Peganum harmala has been used for years to treat the alimentary tract cancers and malaria in northwest China.\(^{34}\) Among other β-carboline alkaloids Tryptoline, Pinoline, Tetrahydroharmine, Harmaline, Isoeudistomin U, Harmane, Harmine, Eudistomin U, Eudistomin O, Eudistomin T possess various biological properties (Scheme-1.3). They are potential MAO-A inhibitor, reuptake inhibitor and benzodiazepine receptor.
Numerous previous reports disclosed the presence of β-carboline ester in human urine and described their binding properties with benzodiazepine receptor.\textsuperscript{35-37} This class of heterocycle is having a broad spectrum of pharmacological properties including antianxiolytic, antihypnotic, anticonvulsant,\textsuperscript{38-39} antiparasiticidal,\textsuperscript{40} antiviral,\textsuperscript{41} antimicrobial\textsuperscript{42} and antifungal activities.\textsuperscript{43-44} They also acts as 5-HT\textsubscript{2A}, 5-HT\textsubscript{2C} receptors,\textsuperscript{45-47} and imidazoline receptor.\textsuperscript{48}

Recent research interest on various β-carboline heterocycle has been directed towards their potent antitumor activity. Several such investigations on the synthesis of structurally diverse β-carboline derivatives and their evaluation of antitumor activities reveal that β-carbolines are potent antitumor compounds. The activity of β-carboline derivatives is correlated to both the planarity of the molecule and the presence of the ring substituents.\textsuperscript{49-61} β-Carboline derivatives display their antitumor activity through multiple mechanisms, such as intercalating into DNA,\textsuperscript{62} inhibiting Topoisomerase I and II,\textsuperscript{63} CDK,\textsuperscript{64} and IKK (IkB kinase complex).\textsuperscript{65}

**Brief Literature review:**

Due to the immense importance of β-carboline heterocycle, there is a lot of advancement in the synthesis of such compounds. Oxidative dehydrogenation strategy has evolved one of the useful tool to access these heterocycles. Here in we are presenting few such recent and important methods reported in literature.
Cuny and Duval et al.\textsuperscript{66} reported the synthesis of substituted β-carboline from diketoindoles by using ammonium acetate in presence of acetic acid with excellent yield. The optimised protocol helps to access a wide variety of substitution at 1, 3 and 4 position of β-carboline skeleton. The reaction takes place at 60 °C with nice functional group tolerance (Scheme-1.4).

![Scheme-1.4](image)

Among others, Ivanov et al.\textsuperscript{67} reported the synthesis of 3,4-dihydro-β-carboline from different carboxylic acid and tryptamine in dichloromethane at ambient temperature (Scheme-1.5). The presence of strong polyphosphoric acid completes the reaction within two hours to furnish the final compounds in good yield. A wide variety of functional groups were well tolerated under the reaction condition.

![Scheme-1.5](image)

Huang and co-workers\textsuperscript{68} reported the synthesis of aromatic β-carboline from tetrahydro-β-carboline using ammonium persulfate in the presence of catalytic silver nitrate. This oxidative decarboxylation occurs in presence of 0.1 equivalent of silver nitrate at 80 °C in a mixture of 1:1 CH\textsubscript{3}CN and water. Depending on the substitution, the optimised condition was further utilised for the synthesis of isoquinoline and 3-deazapurines in good yield (Scheme-1.6).

![Scheme-1.6](image)
Scheme-1.6

Although dehydrogenation using different oxidant have been much explored for the synthesis of β-carboline, there is still scope for further improvement in this reaction, in a bid to achieve good selectivity and tolerance to a wide spectrum of functional groups. From the synthetic point of view, an easy and mild approach is desirable for academic as well as industrial purposes to access both dihydro and the aromatic β-carbolines at low temperature. Keeping this in mind, we developed a new room temperature protocol employing N-bromosuccinamide for oxidative dehydrogenation of tetrahydro-β-carboline to dihydro and aromatic β-carboline (Scheme-1.7).

![Scheme-1.7]

**Present Work:**

**1.1. Result and discussion:**

In our continuous effort in search of novel and mild oxidising agent for oxidative dehydrogenation reaction of β-carboline, we have performed a thorough literature search on the NBS as a brominating and oxidizing agent. NBS is an effective brominating agent and used in Wohl-Ziegler reaction widely. NBS is useful in α-bromination of 1,3-dicarbonyl compounds. It also used in oxidative ring contraction strategy. The oxidising property of NBS was also useful for the synthesis of α-amino ketones from commercially available secondary alcohols and amines. Furthermore N-alkoxamides produces the corresponding carboxylic esters in the presence of NBS via oxidative homocoupling. After close scrutiny of all the reports, we believe NBS can be potentially applied as an oxidant for oxidative dehydrogenation of tetrahydro-β-carboline.

Initially, to optimise the reaction for the synthesis of 3,4-dihydro-β-carboline, 1-phenyl-tetrahydro-β-carboline (Ia) was chosen as the model substrate (Table-1.1, Scheme-1.8). The reactions were conducted in wide range of solvents such as methanol, acetonitrile (ACN), tetrahydrofuran (THF) and toluene. At higher temperature NBS facilitates aromatic ring
bromination. Consequently the reaction temperature was maintained between 0 °C to rt. The average time taken for complete consumption of 1a ranged from 4 to 6 hours at room temperature. The product conversion was monitored by LCMS. Starting with 0.5 equivalent of N-bromosuccinimide (NBS), the dihydro-β-carboline derivative 2a was obtained in all the solvents all be in moderate yield (Table-1.1, entry 1-4). Later with the increase in the amounts of NBS from 0.5 equivalent to 1 equivalent in the reaction led to a considerable improvement in the yield of 2a. The best result was obtained when the reaction was conducted in toluene and acetonitrile which provided 84% and 82% of the desired product respectively. Finally, a slight increase in NBS to 1.1 equivalent in toluene further improved the yield to nearly 95%. Based on these observations it was concluded that 1.1 equivalent of NBS in toluene at 0 °C to room temperature is the optimal condition for the synthesis of 3,4-dihydro-β-carbolines (Table-1.1, entry-9).

\[\text{Scheme-1.8}\]

**Table-1.1: Optimization of the synthesis of 3,4-dihydro-β-carbolines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>NBS (equiv.)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>LCMS Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>THF</td>
<td>4</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>Toluene</td>
<td>4</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>CH₃CN</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>Methanol</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>THF</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Toluene</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>CH₃CN</td>
<td>6</td>
<td>3</td>
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<tr>
<td>8</td>
<td>1</td>
<td>Methanol</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>Toluene</td>
<td>6</td>
<td>ND</td>
</tr>
</tbody>
</table>

The reactions were monitored by LCMS, NBS: N-Bromosuccinimide
THF-Tetrahydrofuran, ND-Not detected
To assure the generic nature of the optimised protocol substituted tetrahydro-β-carbolines with varied functionality such as trifluoromethyl, methyl, methoxy, chloro, fluoro were subjected to oxidative dehydrogenation. Best yield was obtained with strong electron donating substituents such as 3,5-dimethyl, 4-methoxy and 3-methyl-4-methoxy on the aromatic ring. Compound 2k with three electron donating methoxy group was obtained in 61% yield with significant amount of ring brominated side product. The presence of multiple electron withdrawing group reduces the yield of the dihydro-β-carboline significantly. A variety of 3,4-dihydro-β-carbolines (2a-2n) were synthesised in moderate to excellent yield (59% to 95%). The only aliphatic variant 2f was obtained in 72% yield (Scheme-1.9). All the reactions were conducted in 1 mmol scale and simple purification by column chromatography with silica gel afforded the desired products.

Scheme-1.9
Next, we examined the scope of our protocol to access aromatic β-carboline. Initially, compound 1a was treated with 3-4 equivalents of NBS at elevated reaction temperature which provided ring brominated product of 2a. Consequently, we have changed our model substrate to 1p, the tryptophan analogue of compound 1a. We envisioned that introduction of an ester moiety at the α-position of nitrogen will increase the acidity of the α-proton and will facilitate the complete aromatisation. Accordingly, treatment of 1p with two equivalent of NBS in toluene at 0 °C to room temperature furnished the aromatic β-carboline 3a in 85% yield (Scheme-1.10). This methodology afforded a diverse range of aromatic β-carboline esters (3a-3g) from their appropriate precursors in moderate to excellent yields (Scheme-1.10) however, this methodology is limited to the tetrahydro-β-carboline containing an ester group.

<table>
<thead>
<tr>
<th>3a, 85%</th>
<th>3b, 72%</th>
<th>3c, 65%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="3a" /></td>
<td><img src="image" alt="3b" /></td>
<td><img src="image" alt="3c" /></td>
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</table>

<table>
<thead>
<tr>
<th>3d, 88%</th>
<th>3e, 72%</th>
<th>3f, 94%</th>
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<table>
<thead>
<tr>
<th>3g, 82%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="3g" /></td>
</tr>
</tbody>
</table>

**Scheme-1.10**

To demonstrate the mechanism LCMS monitoring of the reaction of 1p indicated the formation of the intermediate 2o which was then oxidized to 3a (Scheme-1.11). To confirm the formation of 2o, it was isolated, purified and characterized by 1H and 13C NMR. The appearance of multiplet proton near 4.5 ppm and disappearance of singlet of the starting material near 5.5 ppm in 1H spectra and in 13C spectra new peak of 159.5 ppm confirms the formation of the compound 2o. Additionally, 1p was further reacted with 1.1 equivalent of NBS to generate 2o.
1.2. Conclusion:

In conclusion, we have developed an efficient strategy for the synthesis of aromatic-β-carbolines and 3,4-dihydro-β-carboline through an efficient oxidative dehydrogenation of the corresponding tetrahydro-β-carbolines under mild conditions at room temperature. This strategy used NBS as an oxidant for oxidative dehydrogenation reactions to provide the desired compounds in moderate to excellent yields. This mild strategy provided a practical approach to access these classes of heterocycles that can be applied effectively in generating combinatorial libraries for structure activity relationship studies.

1.3. Experimental Section:

All reagents were purchased from Sigma Aldrich, Acros, Alfa Aesar or Spectrochem. Purifications of reaction products were carried out by column chromatography using Chem Lab silica gel (230-400 mesh). $^1$H NMR and $^{13}$C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a JEOL JNM-ECX500 at 500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiple (m). The Mass Spectrometry analysis was done on the 6540 UHD Accurate-Mass Q-TOF LC/MS system (Agilent Technologies) equipped with Agilent 1290 LC system. Tetrahydro-β-carbolines were prepared from tryptamine or L-tryptophan methyl ester and aldehydes used
without further purification. Please note the yields of the final products 2a-n and 3a-g are based on the amount of tryptamine and L-tryptophan methyl ester used in the reaction.

General procedure for the synthesis of 3,4-dihydro-β-carbolines (2a-n):

Tryptamine (160 mg, 1 mmol) and appropriate aldehyde (1 mmol) was dissolved in 10 mL of dichloromethane and 0.5 mL of TFA was added. Resulting mixture was stirred in presence of 4Å mol. sieves at rt. Once TLC indicates complete consumption of the starting material, the solution was filtered through celite. Organic solution was quenched, extracted and the solvent evaporated to obtain the crude tetrahydro-β-carbolines 1a-n, which were used without further purification. N-Bromosuccinimide (1.1 equiv.) was added to a solution of resulting tetrahydro-β-carbolines in 10 mL of toluene at 0 °C and gradually warmed to room temperature and stirred for nearly 6 hours. Once TLC confirms the total consumption of the starting tetrahydro-β-carboline, the reaction was quenched with water. The aqueous layer was extracted twice with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous magnesium sulphate and was evaporated to provide the crude compound which was purified by column chromatography using ethyl acetate in hexane as eluent to afford the desired 3,4-dihydro-β-carbolines (2a-n).

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

Following the general procedure crude 1a (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2a in 234 mg (yield 95%) as a white solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 11.12 (s, 1H); 7.77-7.75 (m, 2H); 7.62 (d, $J = 8.25$ Hz, 1H); 7.54-7.51 (m, 3H); 7.43 (d, $J = 8.25$, 1H), 7.22-7.18 (m, 1H); 7.65 (t, $J = 7.55$ Hz, 1H); 3.89 (t, $J = 8.25$ Hz, 2H); 2.86 (t, $J = 8.25$ Hz, 2H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 162.3, 158.5, 137.5, 136.9, 129.7, 128.4, 127.9, 127.4, 124.7, 123.6, 119.5, 116.3, 112.7, 48.3, 18.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{15}$N$_2$: 247.1229, found-247.1249.
1-(3-(trifluoromethyl) phenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2b):

Following the general procedure crude 1b (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 3-trifluoromethyl benzaldehyde (174 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in 10 mL toluene provided the desired compound 2b in 229 mg (yield 73%) as an off white solid. 1H NMR (500 MHz; DMSO-d$_6$): 11.25 (s, 1H); 8.05 (d, $J = 8.25$ Hz, 2H); 7.90 (d, $J = 7.6$ Hz, 1H); 7.77 (t, $J = 7.55$ Hz, 1H); 7.63 (d, $J = 8.25$ Hz, 1H); 7.44 (d, $J = 8.25$ Hz, 1H); 7.23 (t, $J = 8.25$ Hz, 1H); 7.09 (t, $J = 7.55$ Hz, 1H); 3.92 (t, $J = 8.25$ Hz, 2H); 2.89 (t, $J = 8.25$ Hz, 2H). 13C NMR (125 MHz; DMSO-d$_6$): 157.5, 138.3, 137.0, 132.0, 129.7 (q), 127.1, 126.3, 125.2, 124.7, 124.3, 123.9, 123.0, 119.7, 119.6, 116.9, 112.7, 48.4, 18.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{14}$F$_3$N$_2$-315.1104, found-315.1115.

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

Following the general procedure crude 1c (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 3,5-dimethylbenzaldehyde (134 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2c in 240 mg (yield 88%) as a white solid. 1H NMR (500 MHz; DMSO-d$_6$): 11.14 (s, 1H); 7.61 (d, $J = 7.55$ Hz, 1H); 7.44 (d, $J = 8.25$ Hz, 1H); 7.36 (s, 2H); 7.20 (t, $J = 7.55$ Hz, 1H); 7.16 (s, 1H); 7.07 (t, $J = 8.25$ Hz, 1H); 3.87 (t, $J = 8.2$ Hz, 2H); 2.86 (t, $J = 8.2$ Hz, 2H); 2.35 (s, 6H). 13C NMR (125 MHz; DMSO-d$_6$): 158.9, 137.4, 137.1, 137.0, 131.1, 127.5, 125.8, 124.7, 123.7, 119.5, 116.5, 112.8, 48.0, 21.0, 21.0, 18.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{19}$N$_2$-275.1543, found-275.1553.
1-(p-tolyl)-4,9-dihydro-3\textit{H}-pyrido[3,4-\textit{b}]indole (2d):

Following the general procedure crude 1d (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 4-methylbenzaldehyde (120 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2d in 161 mg (yield 62%) as a white solid. $^1$H NMR (500 MHZ; DMSO-d$_6$): 11.11 (s, 1H); 7.66 (d, $J = 8.25$ Hz, 2H); 7.61 (d, $J = 7.55$ Hz, 1H); 7.43 (d, $J = 8.2$ Hz, 1H); 7.33 (d, $J = 8.25$ Hz, 2H); 7.21-7.19 (m, 1H); 7.07 (t, $J = 7.55$ Hz, 1H); 3.87 (t, $J = 8.2$ Hz, 2H); 2.85 (t, $J = 8.20$ Hz, 2H); 2.39 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 158.4, 139.3, 136.9, 134.7, 129.0, 127.9, 127.6, 124.8, 123.6, 119.5, 119.5, 116.3, 112.7, 48.2, 21.1, 18.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{17}$N$_2$-261.1386, found- 261.1395.

1-(o-tolyl)-4,9-dihydro-3\textit{H}-pyrido[3,4-\textit{b}]indole (2e):

Following the general procedure crude 1e (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 2-methylbenzaldehyde (120 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2e in 195 mg (yield 75%) as a colourless solid. $^1$H NMR (500 MHZ; DMSO-d$_6$): 10.81 (s, 1H); 7.60 (d, $J = 7.55$ Hz, 1H); 7.38-7.37 (m, 1H); 7.38-7.29 (m, 5H); 7.16 (t, $J = 8.25$ Hz, 1H); 7.05 (t, $J = 8.25$ Hz, 1H); 3.93 (t, $J = 8.25$ Hz, 2H); 2.90 (t, $J = 8.25$ Hz, 2H); 2.56 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 160.1, 137.6, 137.0, 135.6, 130.4, 128.6, 128.5, 128.4, 125.7, 124.8, 123.6, 119.5, 115.0, 112.7, 48.3, 19.2, 18.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{17}$N$_2$-261.1386, found- 261.1399.
1-heptyl-4,9-dihydro-3H-pyrido[3,4-b]indole (2f):

Following the general procedure crude 1f (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and octanal (128.2 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene provided the desired compound 2f in 192 mg (yield 72%) as a yellow solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 10.79 (s, 1H); 7.47 (d, $J = 5$ Hz, 1H); 7.27-7.24 (m, 1H); 7.05-7.03 (m, 1H); 6.91 (d, $J = 5$ Hz, 1H); 3.59-3.46 (m, 2H); 2.45-2.30 (m, 2H); 1.22-1.12 (m, 12H). 13C NMR (125 MHz; DMSO-d$_6$): 172.5, 142.7, 129.4, 128.4, 123.7, 122.6, 110.3, 56.0, 43.4, 34.7, 31.4, 27.5, 26.1, 22.4, 21.5, 14.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{18}$H$_{25}$N$_2$: 269.1202, found-269.1210.

1-(3-fluorophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2g):

Following the general procedure crude 1g (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 3-fluorobenzaldehyde (124 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2g in 200 mg (yield 75%) as a white solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 11.18 (s, 1H); 7.63-7.56 (m, 3H); 7.53-7.51 (m, 1H) ; 7.43 (d, $J = 8.25$ Hz, 1H); 7.38-7.37 (m, 1H); 7.23-7.20 (m, 1H); 7.09-7.06 (m, 1H); 3.91 (t, $J = 8.25$ Hz, 2H); 2.87 (t, $J = 8.25$ Hz, 2H). 13C NMR (125 MHz; DMSO-d$_6$): 163.1, 137.0, 130.6, 130.5, 127.1, 124.7, 124.2, 123.9, 119.6, 119.6, 116.7, 116.6, 114.9, 114.8, 112.8, 43.3, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{17}$H$_{14}$FN$_2$: 265.1136, found-265.1149.

1-(2,4-bis(trifluoromethyl)phenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2h):
Following the general procedure crude 1h (334 mg) (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 2,4-bis(trifluoromethyl)benzaldehyde (242 mg, 1 mmol), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2h in 225 mg (yield 59%) as a grey solid. \(^1\)H NMR (500 MHz; DMSO-d\(_6\)): 12.65 (s, 1H); 9.09 (s, 1H); 8.55-8.48 (m, 1H); 8.31 (s, 1H); 8.03 (d, \(J = 8.25\) Hz, 1H); 7.95-7.66 (m, 3H); 3.36 (s, 4H). \(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)): 144.2, 140.8, 139.1, 131.8, 130.7, 130.4, 129.6, 129.4, 129.0, 126.5, 126.3, 124.3, 123.8, 123.2, 123.1, 122.2, 121.2, 119.3, 89.9. HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C\(_{19}\)H\(_{13}\)F\(_6\)N\(_2\) -383.0977, found-383.1001.

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

\[
\begin{align*}
\text{Following the general procedure crude 1i (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 3-methoxybenzaldehyde (136 mg, 1 mmol)), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2i in 180 mg (yield 65%) as a white solid.} \\
\text{\(^1\)H NMR (500 MHz; DMSO-d\(_6\)): 11.15 (s, 1H); 7.61 (d, \(J = 7.6\) Hz, 1H); 7.46-7.42 (m, 2H); 7.34 (d, \(J = 7.6\) Hz, 1H); 7.29-7.28 (m, 1H); 7.22-7.19 (m, 1H); 3.89 (t, \(J = 8.25\) Hz, 2H); 3.82 (s, 3H); 2.87 (t, \(J = 8.25\) Hz, 2H).} \\
\text{\(^{13}\)C NMR (125 MHz; DMSO-d\(_6\)): 159.2, 138.7, 137.0, 129.6, 127.4, 124.7, 123.7, 120.4, 119.6, 119.5, 116.5, 115.8, 112.8, 112.8, 55.1, 48.2, 21.1. HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C\(_{18}\)H\(_{17}\)NO-277.1335, found-277.1356.}
\end{align*}
\]

1-(4-methoxyphenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2j):

\[
\begin{align*}
\text{Following the general procedure crude 1j (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 4-methoxybenzaldehyde (136 mg, 1 mmol)), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2j in 230 mg (yield 83%) as off white solid.} \\
\text{\(^1\)H NMR (500 MHz; DMSO-d\(_6\)): 11.12 (s, 1H); 7.73 (d, \(J = 8.25\) Hz, 2H);}
\end{align*}
\]
7.61 (d, \( J = 8.25 \) Hz, 1H); 7.43 (d, \( J = 8.25 \) Hz, 1H); 7.20 (t, \( J = 7.6 \) Hz, 1H); 7.08 (d, \( J = 8.25 \) Hz, 3H); 3.83 (m, 5H); 2.84 (t, \( J = 8.25 \) Hz, 2H).  \( ^{13} \)C NMR (125 MHz; DMSO-d\(_6\)): 160.5, 157.9, 136.8, 129.9, 129.5, 127.5, 124.8, 123.6, 119.5, 119.4, 116.4, 113.8, 112.7, 53.3, 48.0, 21.1. HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O-277.1335, found-277.1345.

1-(2,4,5-trimethoxyphenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2k):

Following the general procedure crude 1k (which was synthesized \textit{via} general protocol from tryptamine (160 mg, 1 mmol) and 2,4,5-trimethoxybenzaldehyde (196 mg, 1 mmol), with TFA and NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2k in 205 mg (yield 61%) as a light brown solid. \( ^{1} \)H NMR (500 MHz; DMSO-d\(_6\)): 10.71 (s, 1H); 7.55 (d, \( J = 7.55 \) Hz, 1H); 7.36 (d, \( J = 8.25 \) Hz, 1H); 7.16-7.12 (m, 1H); 7.02-7.00 (t, \( J = 8.25 \) Hz, 1H); 6.93 (s, 1H); 6.82 (s, 1H); 3.88 (m, 5H); 3.72 (s, 3H); 3.70 (s, 3H); 2.85 (t, \( J = 8.9 \) Hz, 2H). \( ^{13} \)C NMR (125 MHz; DMSO-d\(_6\)): 158.1, 151.7, 150.1, 142.6, 136.5, 128.2, 124.6,123.2, 119.3, 119.1, 118.3, 113.8, 113.7, 113.5, 98.2, 56.1, 56.1, 55.8, 48.4, 18.8. HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{20}\)H\(_{21}\)N\(_2\)O\(_3\)-337.1547, found 337.1564.

1-(2-fluoro-4-methoxyphenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2l):

Following the general procedure crude 1l (which was synthesized \textit{via} general protocol from tryptamine (160 mg, 1 mmol) and 2-fluoro-4-methoxybenzaldehyde (154 mg, 1 mmol)), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2l in 209 mg (yield 71%) as a white solid. \( ^{1} \)H NMR (500 MHz; DMSO-d\(_6\)): 11.07 (s, 1H); 7.59 (d, \( J = 8.25 \) Hz, 1H); 7.48 (t, \( J = 8.93 \) Hz, 1H); 7.37 (d, \( J = 8.25 \) Hz, 1H); 7.20-7.16 (m, 1H); 7.05 (t, \( J = 6.85 \) Hz, 1H); 6.98-6.95 (m, 1H); 6.92-6.90 (m, 1H); 3.90 (t, \( J = 8.25 \) Hz, 2H); 3.84 (s, 3H); 2.87 (t, \( J = 8.25 \), 2H). \( ^{13} \)C NMR (125 MHz; DMSO-d\(_6\)): 161.6, 159.7, 155.3, 136.8, 131.4, 119.1, 118.3, 113.8, 113.7, 113.5, 98.2, 56.1, 56.1, 55.8, 48.4, 18.8. HRMS (ESI-TOF) m/z: [M + H]\(^+\) Calcd for C\(_{21}\)H\(_{22}\)F\(_2\)N\(_2\)O\(_3\)-337.1547, found 337.1564.
128.3, 124.6, 123.7, 119.6, 119.4, 118.0, 114.9, 112.5, 110.6, 101.9, 55.8, 48.5, 18.7. HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C_{18}H_{16}FN_2O-295.1241, found-295.1263.

1-(4-methoxy-3-methylphenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2m):

Following the general procedure crude 1m (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 3-methyl-4-methoxybenzaldehyde (150 mg, 1 mmol)), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2m in 258 mg (yield 89%) as a colourless gummy solid. ^1^H NMR (500 MHz; DMSO-d_6): 11.12 (s, 1H); 7.60 (t, J = 8.2 Hz, 3H); 7.44 (d, J = 8.25 Hz, 1H); 7.20 (t, J = 7.55 Hz, 1H); 7.07 (t, J = 8.2 Hz, 2H); 3.90-3.81 (m, 5H); 2.84 (t, J = 8.2 Hz, 2H); 2.23 (s, 3H). ^1^C NMR (125 MHz; DMSO-d_6): 158.7, 158.1, 136.8, 130.1, 129.3, 127.6, 127.2, 125.5, 124.8, 123.5, 119.5, 119.4, 116.3, 112.7, 109.9, 55.4, 47.9, 18.9, 16.2. HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C_{19}H_{19}N_2O-291.1492, found-291.1510.

1-(2,3,5-trichlorophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (2n):

Following the general procedure crude 1n (which was synthesized via general protocol from tryptamine (160 mg, 1 mmol) and 2,3,5-trichlorobenzaldehyde (209 mg, 1mmol)), with NBS (196 mg, 1.1 mmol) in toluene (10 mL) provided the desired compound 2n in 226 mg (yield 65%) as a white solid. ^1^H NMR (500 MHz; DMSO-d_6): 11.05 (s, 1H); 8.01 (d, J = 2.05 Hz, 1H); 7.61-7.56 (m, 2H); 7.33 (d, J= 8.25 Hz, 1H); 7.20 (t, J = 6.85 Hz, 1H); 7.06 (t, J = 6.85 Hz, 1H); 3.96 (t, J = 8.2 Hz, 2H); 2.92 (t, J = 8.9 Hz, 2H). ^1^C NMR (125 MHz; DMSO-d_6): 156.8, 140.1, 136.9, 133.2, 132.4, 130.3, 129.2, 128.9, 127.5, 124.7, 124.0, 119.7, 119.6, 115.2, 112.4, 48.7, 18.7. HRMS (ESI-TOF) m/z: [M + H]^+ Calcd for C_{17}H_{12}Cl_3N_2-349.0061, found-349.0091.
General procedure for the synthesis of 2o:

L-Tryptophan methyl ester (218 mg, 1 mmol) and benzaldehyde (1 mmol) was dissolved in 10 mL of dichloromethane and 0.5 mL of TFA was added. Resulting mixture was stirred in presence of 4Å mol. sieves at rt. Once TLC indicates complete consumption of the starting material, the solution was filtered through celite. Organic solution was quenched, extracted and the solvent evaporated to obtain the crude tetrahydro-β-carbolines 1p, which were used without further purification. N-Bromosuccinimide (NBS) (1.1 equiv.) was added to a solution of resulting tetrahydro-β-carbolines in 10 mL of toluene at 0 °C and gradually warmed to room temperature and stirred for nearly 6 hours. Once TLC confirms the total consumption of the tetrahydro-β-carbolines, the reaction was quenched with water. The aqueous layer was extracted twice with ethyl acetate. The organic extracts were combined and washed with brine, dried over anhydrous magnesium sulphate and was evaporate to provide the crude compound. It was purified by column chromatography using ethyl acetate in hexane as eluent to afford the 2o in 112 mg (37% yield). 1H NMR (500 MHz; DMSO-d6): 11.29 (s, 1H); 7.80-7.68 (m, 2H); 7.67-7.66 (m, 1H); 7.60-7.54 (m, 3H); 7.45 (t, J = 6.85 Hz, 1H); 7.28-7.26 (m, 1H); 7.25-7.22 (m, 1H); 7.11 (t, J = 4.85 Hz, 1H); 4.61-4.59 (m, 1H); 3.75 (s, 3H); 3.28-3.24 (m, 1H); 3.07-3.01 (m, 1H). 13C NMR (125 MHz; DMSO-d6): 159.5, 137.8, 137.3, 130.6, 129.2, 129.1, 128.9, 128.7, 127.7, 125.1, 124.6, 120.2, 120.2, 115.9, 113.3, 61.6, 52.4, 22.0. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C19H17N2O2-305.1284, found-305.1269.

General procedure for the synthesis of aromatic β-carbolines 3a-3g:

L-Tryptophan methyl ester (218 mg, 1 mmol) and appropriate aldehyde was dissolved in 10 mL of dichloromethane and 0.5 mL of TFA was added. Resulting mixture was stirred in presence of 4Å mol. sieves at rt. Once TLC indicates complete consumption of the starting material, the solution was filtered through celite. Organic solution was quenched, extracted and the solvent evaporated to obtain the crude tetrahydro-β-carbolines 1p-v, which were used without further purification. N-Bromosuccinimide (2.0 equiv.) was added to a solution of resulting tetrahydro-β-carbolines in 10 mL of toluene at 0 °C and gradually warmed to room
temperature and stirred for nearly 5 hours. Once TLC confirms the total consumption of the tetrahydro-β-carbolines, the reaction was quenched with water. The aqueous layer was extracted twice with ethyl acetate. The organic extracts were combined and washed with brine, dried over anhydrous magnesium sulphate and was evaporate to provide the crude compound. It was purified by column chromatography using ethyl acetate in hexane as eluent to afford the desired aromatic β-carbolines 3a-g.

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

Following the general procedure crude 1p (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and benzaldehyde (105 mg, 1mmol)), with NBS (356 mg, 2 mmol) in toluene (10 mL) provided the desired compound 3a in 256 mg (yield 85%) as off white solid. 1H NMR (500 MHz; DMSO-d6): 11.95 (s, 1H); 8.93 (s, 1H); 8.44 (d, J = 7.55 Hz, 1H); 8.03-8.01 (m, 2H); 7.70-7.57 (m, 5H); 7.34 (t, J = 7.55 Hz, 2H); 3.93 (s, 3H). 13C NMR (125 MHz; DMSO-d6): 166.1, 142.1, 141.4, 137.5, 136.6, 134.5, 129.1, 129.0, 128.8, 128.7, 128.6, 122.0, 121.1, 120.4, 116.7, 112.8, 52.0. HRMS (ESI-TOF) m/z: [M + H]+ Calcd for C19H15N2O2-303.1123, found-303.1121.

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

Following the general procedure crude 1q (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and 3-fluorobenzaldehyde (124 mg, 1mmol)), with NBS (356 mg, 2 mmol) in toluene provided the desired compound 3b in 230 mg (yield 72%) as grey solid. 1H NMR (500 MHz; DMSO-d6): 12.01 (s, 1H); 8.96 (s, 1H); 8.44 (d, J = 8.25 Hz, 1H); 7.87 (d, J = 7.55 Hz, 1H), 7.80 (d, J = 9.65 Hz, 1H), 7.70 (t, J = 8.25 Hz, 2H); 7.63 (t, J = 6.9 Hz, 1H); 7.43-7.39 (m, 1H),
7.35 (t, J = 7.6 Hz, 1H), 3.94 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 165.9, 141.5, 140.5, 139.7, 136.6, 134.5, 130.9, 129.5, 128.8, 124.8, 122.1, 121.0, 120.5, 117.1, 115.7, 115.4, 115.2, 112.7, 52.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{19}$H$_{14}$FN$_2$O$_2$: 321.1034, found-321.1049.

Methyl 1-(2,6-difluorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (3c):

Following the general procedure crude 1r (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and 2,6-difluorobenzaldehyde (142 mg, 1mmol)), with NBS (356 mg, 2.0 mmol) in toluene (10 mL) provided the desired compound 3c in 219 mg (yield 65%) as colorless solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 12.04 (s, 1H); 9.04 (s, 1H); 8.47 (d, J = 7.55 Hz, 1H); 7.72 (t, J = 7.6 Hz, 1H), 7.62-7.59 (m, 2H), 7.39-7.33 (m, 3H ), 3.91 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 165.7, 161.3, 159.3, 141.2, 136.5, 131.8, 129.1, 128.6, 122.4, 120.6, 117.8, 112.4, 112.1, 52.1. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{19}$H$_{13}$F$_2$N$_2$O$_2$: 339.0940, found-339.0920.

Methyl 1-(2,4,5-trimethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate (3d):

Following the general procedure crude 1s (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and 2,4,5-trimethoxybenzaldehyde (197 mg, 1mmol)), with NBS (356 mg, 2 mmol) in toluene (10 mL) provided the desired compound 3d in 345 mg (yield 88%) as white solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 11.42 (s, 1H); 8.88 (s, 1H); 8.38 (d, J = 8.25 Hz, 1H); 7.60 (d, J = 8.2 Hz, 1H); 7.56 (t, J = 6.9 Hz, 1H), 7.29 (t, J = 7.55 Hz, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.74 (s, 6H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 166.2, 151.6, 150.6, 142.7, 141.4, 141.0, 136.2, 136.0, 128.4, 127.4, 121.9, 121.0, 120.0, 117.5, 116.4, 115.3,
Methyl 1-heptyl-9H-pyrido[3,4-b]indole-3-carboxylate (3e):

Following the general procedure crude 1t (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and octanal (128 mg, 1mmol), with and NBS (356 mg, 2 mmol) in toluene (10 mL) provided the desired compound 3e in 234 mg (yield 72%) as light yellow solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 12.02 (s, 1H); 8.78 (s, 1H); 8.36 (d, $J = 5$ Hz, 1H); 7.66 (d, $J = 7.6$ Hz, 1H), 7.60-7.57 (m, 2H), 7.29 (t, $J = 8.25$ Hz, 1H), 3.90 (s, 3H), 3.14 (t, $J = 10$ Hz, 2H); 1.82-1.76 (m, 2H); 1.40-1.25 (m, 4H), 1.24-1.22 (m, 4H), 0.83 (t, $J = 5$ Hz, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 166.6, 146.5, 141.2, 136.5, 136.1, 128.8, 127.5, 122.4, 121.8, 120.5, 116.3, 112.7, 52.3, 34.1, 31.7, 29.5, 29.1, 28.8, 22.5, 14.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{21}$H$_{22}$O$_2$-325.1911, found-325.1931.

Methyl 1-(quinolin-2-yl)-9H-pyrido[3,4-b]indole-3-carboxylate (3f):

Following the general procedure crude 1u (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and quinolone-2-carbaldehyde (157 mg, 1mmol)), with NBS (356 mg, 2 mmol) in toluene (10 mL) provided the desired compound 3f in 332 mg (yield 94%) as yellow solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 12.42-12.35 (m, 1H); 9.13-9.07 (m, 1H); 8.85-8.81 (m, 1H); 8.77-8.73 (m, 1H), 8.61 (d, $J = 7.55$ Hz, 1H), 8.49 (d, $J = 7.55$ Hz, 1H), 8.08 (t, $J = 6.85$ Hz, 1H), 8.00 (d, $J = 8.25$ Hz, 1H), 7.92 (t, $J = 6.85$ Hz, 1H), 7.80 (dd, $J = 1.35$ Hz, 1H), 7.72-7.67 (m, 1H), 7.38 (t, $J = 7.55$ Hz, 1H), 3.99 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 165.8, 156.2, 147.1, 141.5, 140.2, 137.1, 136.3, 131.4, 129.8, 129.0, 127.8, 127.5, 127.3, 124.8, 122.1, 120.7, 118.8, 118.5, 115.6, 113.5, 112.8, 52.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{20}$H$_{25}$N$_2$O$_2$-325.1911, found-325.1931.
Methyl 1-methyl-9H-pyrido[3,4-b]indole-3-carboxylate (3g):

Following the general procedure crude 1v (prepared from L-tryptophan methyl ester (218 mg, 1 mmol) and acetaldehyde (44 mg, 1mmol)), with NBS (356 mg, 2 mmol) in toluene (10 mL) provided the desired compound 3g in 197 mg (yield 82%) as yellow solid. $^1$H NMR (500 MHz; DMSO-d$_6$): 12.06 (s, 1H); 8.78 (s, 1H); 8.36 (d, $J = 10$ Hz, 1H); 7.66 (d, $J = 10$ Hz, 1H); 7.61-7.58 (m, 1H); 7.32-7.29 (m, 1H); 3.90 (s, 3H), 2.82 (s, 3H). $^{13}$C NMR (125 MHz; DMSO-d$_6$): 166.6, 142.6, 141.1, 136.6, 136.3, 128.8, 127.2, 122.5, 121.8, 120.6, 116.4, 112.7, 52.3, 20.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for C$_{14}$H$_{13}$N$_2$O$_2$ 241.0972 Found-241.0986.
$^1$H and $^{13}$C Spectra of the Compounds Discussed in Chapter-1:
Compound-2-1H

Compound-2-13C

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