Electronic Supplementary Information

Iridium (III) Catalyzed Regioselective Amidation of Indoles at C4 –Position Using Weak Coordinating Groups

Veeranjeyulu Lanke, and Kandikere Ramaiah Prabhu*

Department of Organic Chemistry, Indian Institute of Science
Bangalore 560 012, Karnataka, India
Contents

1. General experimental ESI-3
2. NMR yield calculation ESI-3
3. Typical experimental procedure ESI-4
4. Deuterium incorporation experiment ESI-5
5. Preliminary DFT studies ESI-5
6. Characterization data ESI-7
7. Procedure for deprotection of tosyl group ESI-16
8. \(^1\text{H}\) and \(^{13}\text{C}\) NMR Spectra ESI-17
**Experimental Section:**

**General experimental**

NMR spectra were recorded on 400 MHZ spectrometer in CDCl₃, Tetramethylsilane (TMS; δ = 0.00 ppm) served as an internal standard for ¹H NMR. The corresponding residual non-deuterated solvent signal (CDCl₃; δ = 77.00 ppm) was used as internal standard for ¹³C NMR. IR spectra were measured using a FT/IR spectrometer. Mass spectra were measured using Q-Tof (ESI-HRMS) machine. Column chromatography was carried out on Silica gel 230-400 mesh (commercial suppliers) and thin-layer chromatography was carried out using SILICA GEL GF-254. Iridium catalyst has prepared based on reported procedure¹ and Silver catalysts are purchased from Alfa asera.

3-Formyl indole derivatives were prepared by Vilsmeier-Haack reaction according to a literature method.² and sulfonyl azides were synthesized from commercially available reagents.³ Other reagents and solvents were purchased from commercial supplier and used without further purification.

**NMR Yield calculation** – After work up, 0.5 equiv of terephthaldehyde was added into the round bottom flask containing the combined organic layers from the work up. Either an aliquot from the round bottom flask was taken, evaporated and then submitted for NMR, or the organic layer was completely evaporated and the residue was dissolved in an appropriate amount of solvent to submit for NMR.

---


1. Typical experimental procedure for C4-amidation.

To a pre-dried 8mL screw cap vial was added indole-3-carbaldehyde derivative (1, 0.3 mmol, 1 equiv), tosyl azide derivative (2, 0.36 mmol, 1.2 equiv), \([\text{IrCp}^*\text{Cl}_2]_2\) (5 mol %), AgNTf₂ (20 mol %) Li₂CO₃ (1 equiv) and AcOH (1 equiv) in open atmosphere in dichloroethane (2 mL). Then, the reaction mixture was stirred at 60 °C for 3-6 h (monitored by TLC). After the completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with 50% EtOAc/hexane (5 mL), passed through a short silica gel (100-200 mesh size) bed, and washed with 50% EtOAc/ hexane (20 mL x 3 times). The combined organic layer was concentrated under reduced pressure and the crude product was purified on a silica gel column using EtOAc/hexane mixture.
2. Deuterium incorporation studies:

To a pre-dried 8mL screw cap vial was added 1H-indole-3-carbaldehyde(1a)/ 2,2,2-trifluoro-1-(1H-indol-3-yl)ethanone(4a) (0.2mmol, 1 equiv), \([\text{IrCp}^*\text{Cl}_2]_2\) (5mol %), AgNTf$_2$ (20mol %), Li$_2$CO$_3$ (1 equiv) and CD$_3$CO$_2$D (2 mmol, 10 equiv) and dichloroethane (2 mL). The vial was placed in a pre-heated (60 °C) metal block. After 6h, the reaction mixture was cooled to room temperature, and diluted with diethyl ether and passed through a short silica gel (100-200 mesh size) bed, and repeatedly washed with diethyl ether (20 mL x 3 times). The combined organic layers were concentrated under reduced pressure and the crude product was submitted for NMR.

**Preliminary DFT studies towards identification of probable reasons for regioselectivity**

1. Preferred orientation of the directing group

<table>
<thead>
<tr>
<th>G</th>
<th>$\Delta G_{C4} - \Delta G_{C2}$</th>
<th>$\Delta G_{C4-C2}^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_3$</td>
<td>-1.43</td>
<td>12.6</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>-0.97</td>
<td>11.2</td>
</tr>
<tr>
<td>H</td>
<td>-1.42</td>
<td>14.0</td>
</tr>
<tr>
<td>Ph</td>
<td>-1.70</td>
<td>8.24</td>
</tr>
<tr>
<td>OMe</td>
<td>-0.16</td>
<td>10.6</td>
</tr>
<tr>
<td>NHMe</td>
<td>+0.08</td>
<td>6.38</td>
</tr>
<tr>
<td>OH</td>
<td>-0.68</td>
<td>7.99</td>
</tr>
</tbody>
</table>

---

2. **Acidity of proton for C-H activation:**

*Børøsted acidity of the C–H bond*

Theoretically determined pKₐ values (in parentheses)

\[
\text{Ind} - \text{H} + \text{OAc} \rightleftharpoons \Delta G \rightarrow \text{Ind} - \text{HO}
\]

\[
\begin{align*}
\text{H} & \quad (58.4) \\
\text{H} & \quad (43.8) \\
\text{H} & \quad (55.8) \\
\text{H} & \quad (39.7)
\end{align*}
\]

C(2)–H bond is more acidic than C(4)–H bond.

3. **Strength of metallacycle:** Done with Ru(II) and Rh(III), expect same results with Iridium

*Strength of the forming C–Metal bond*

Theoretically determined BDE values (kcal/mol)

\[
\begin{align*}
\text{G} & \quad \text{O} \quad \text{O} \\
\text{Ind} & \quad \text{M} \quad \text{L} \\
\end{align*}
\]

\[
\begin{align*}
\text{C}(2) & \quad \text{M} \quad \text{bonds} \quad \text{are} \quad \text{more} \quad \text{stable} \\
\text{C}(4) & \quad \text{M} \quad \text{bonds}
\end{align*}
\]

\[
\begin{align*}
61 - 67 \text{ kcal/mol} & \quad \text{with Ru cat.} \\
59 - 60 \text{ kcal/mol} & \quad \text{with Rh cat.} \\
40 - 46 \text{ kcal/mol} & \quad \text{with Iridium}
\end{align*}
\]

4. **Partial charge calculations on various positions of indole**

*Partial charges on vicinal carbons*

\[
\begin{align*}
\text{H or CF}_3 & \quad -0.21 \\
\text{H} & \quad -0.07
\end{align*}
\]

Since, no result is a clear cut support for C4 functionalization vs C2 functionalization, further work is needed and is currently ongoing in our laboratory.
Characterization data for the products

1. N-(3-formyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3a)

![Structure 3a]

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, Yield - 86 mg, (90%); R<sub>f</sub> (40% EtOAc/Hexane) 0.3; IR (KBr, cm<sup>-1</sup>): 3266, 1620,1141; mp: 205 - 208 °C; <sup>1</sup>H NMR (400 MHz, DMSO-<i>d</i><sub>6</sub>) ppm 2.25 (s, 3 H) 7.11 - 7.21 (m, 2 H) 7.25 (d, <i>J</i>=7.33 Hz, 3 H) 7.62 (d, <i>J</i>=8.34 Hz, 2 H) 8.40 (d, <i>J</i>=3.03 Hz, 1 H) 9.61 (s, 1 H) 11.53 (s, 1 H) 12.48 (br. s., 1 H), <sup>13</sup>C NMR (100 MHz, DMSO-<i>d</i><sub>6</sub>) ppm 20.84, 108.23, 110.09, 115.79, 117.81, 125.04, 126.69, 129.63, 131.45, 136.36, 138.72, 142.19, 143.42, 186.78. HRESI-MS(<i>m/z</i>)–Calculated for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>SNa (M+Na): 337.0623, found (M+Na) 337.0628

2. N-(6-bromo-3-formyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3b)

![Structure 3b]

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, Yield - 108 mg, (92%); R<sub>f</sub> (40% EtOAc/Hexane) 0.3; IR (KBr, cm<sup>-1</sup>): 3126, 1635, 1193; mp: 260 - 262 °C; <sup>1</sup>H NMR (400 MHz, DMSO-<i>d</i><sub>6</sub>) ppm 2.27 (s, 3 H) 7.24 - 7.38 (m, 4 H) 7.64 (d, <i>J</i>=8.24 Hz, 2 H) 8.43 (d, <i>J</i>=3.05 Hz, 1 H) 9.62 (s, 1 H) 11.67 (s, 1 H) 12.56 (br. s., 1 H); <sup>13</sup>C NMR (100 MHz, DMSO-<i>d</i><sub>6</sub>) ppm 20.90, 110.89, 112.48, 114.90, 117.14, 117.83
3. N-(6-chloro-3-formyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3c)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, **Yield** - 88 mg, (84%); **Rf** (40% EtOAc/Hexane) 0.3; **IR** (KBr, cm⁻¹): 3221, 1712, 1127; **mp**: 255 - 258 °C; **¹H NMR** (400 MHz, DMSO-d₆) ppm 2.22 (s, 3 H) 7.12 - 7.33 (m, 4 H) 7.57 (d, J=8.10 Hz, 2 H) 8.24 (d, J=3.2 Hz, 1 H) 9.60 (s, 1 H) 11.71 (s, 1 H) 12.49 (br. s., 1 H); **¹³C NMR** (100 MHz, DMSO-d₆) ppm 20.85, 52.34, 110.09, 110.25, 117.74, 117.75, 126.00, 129.23, 132.62, 136.07, 140.15, 142.47, 144.07, 187.92; **HRESI-MS (m/z)**–Calculated for C₁₆H₁₃ClN₂O₃Sn (M+Na): 414.9728, found (M+Na) 414.9729

4. Methyl 3-formyl-4-((4-methylphenyl)sulfonamido)-1H-indole-6-carboxylate (3d)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 5:5) to obtain the product as a yellow solid, **Yield** - 86 mg, (77%); **Rf** (50% EtOAc/Hexane) 0.2; **IR** (KBr, cm⁻¹): 3190, 1620, 1141; **mp**: 253 - 255 °C; **¹H NMR** (400 MHz, DMSO-d₆) ppm 2.23 (s, 3 H) 3.87 (s, 3 H) 7.26 (m, J=8.08 Hz, 2 H) 7.61 (m, J=8.08 Hz, 2 H) 7.78 (d, J=1.26 Hz, 1 H) 7.88 (d, J=1.26 Hz, 1 H) 8.58 (d, J=3.03 Hz, 1 H) 9.67 (s, 1 H) 11.55 (s, 1 H) 12.77 (br. s., 1 H); **¹³C NMR** (100 MHz, DMSO-d₆) ppm 20.86, 52.34, 110.09, 110.25, 117.74, 119.35, 126.18, 126.65, 129.78
5. N-(3-formyl-5-methoxy-1H-indol-4-yl)-4-methylbenzenesulfonamide (3e)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 5:5) to obtain the product as a yellow solid, **Yield** - 53 mg, (48%); **R<sub>f</sub>** (50% EtOAc/Hexane) 0.2; **IR** (KBr, cm<sup>-1</sup>): 3214, 1625, 1209; **mp**: **232 - 234 °C**; **<sup>1</sup>H NMR** (400 MHz, DMSO-<sup>d<sub>6</sub></sup>) ppm 2.26 (s, 3 H) 3.38 (s, 3 H) 6.96 (m, <i>J</i>=8.4 Hz, 1 H) 7.30 (d, <i>J</i>=8.3 Hz, 3 H) 7.56 (d, <i>J</i>=8.0 Hz, 2 H) 8.28 (d, <i>J</i>=3.1 Hz, 1 H) 9.90 (s, 1 H) 10.2 (s, 1 H) 12.28 (br. s., 1 H); **<sup>13</sup>C NMR** (100 MHz, DMSO-<sup>d<sub>6</sub></sup>) ppm 21.42, 56.40, 111.23, 111.36, 118.33, 118.86, 122.58, 126.99, 129.28, 133.47, 139.30, 142.70, 149.36, 186.34.; **HRESI-MS**(m/z)–Calculated for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S Na (M+Na): 367.3747, found (M+Na) 367.3742

5. N-(3-formyl-2-methyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3g)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, **Yield** - 87 mg, (88%); **R<sub>f</sub>** (40% EtOAc/Hexane) 0.2; **IR** (KBr, cm<sup>-1</sup>): 3310, 1670, 1121; **mp**: **256 - 258 °C**; **<sup>1</sup>H NMR** (400 MHz, DMSO-<sup>d<sub>6</sub></sup>) ppm 2.24 (s, 3 H) 2.65 (s, 3 H) 6.99 - 7.04 (m, 1 H) 7.10 (t, <i>J</i>=7.96 Hz, 1 H) 7.18 - 7.27 (m, 3 H) 7.62 (d, <i>J</i>=8.08 Hz, 2 H) 9.69 (s, 1 H) 11.96 (s, 1 H) 12.37 (br. s., 1 H); **<sup>13</sup>C NMR** (100 MHz, DMSO-<sup>d<sub>6</sub></sup>) ppm 11.64, 20.85
6. 10. N-(3-formyl-1H-indol-4-yl)methanesulfonamide (3h)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a light yellow solid, Yield - 41mg, (57%); R\textsubscript{f} (40% EtOAc/Hexane) 0.2; IR (KBr, cm\textsuperscript{-1}): 3251, 1617, 1113; mp: 175 - 177 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) ppm 3.02 (s, 3 H) 7.20 - 7.32 (m, 3 H) 8.47 (d, \textit{J}=3.28 Hz, 1 H) 9.65 (s, 1 H) 11.05 (s, 1 H) 12.56 (br. s., 1 H); \textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6) ppm 39.06 ,108.01 ,109.71 ,115.59 ,118.08 ,125.27 ,132.17 ,138.96 ,142.13 ,186.64.; HRESI-MS\textit{(m/z)}--Calculated for C\textsubscript{17}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}SNa (M+Na): 351.0779, found (M+Na) 351.0777.

7. N-(3-formyl-1H-indol-4-yl)benzenesulfonamide (3i)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, Yield - 63mg, (70%); R\textsubscript{f} (40% EtOAc/Hexane) 0.2; IR (KBr, cm\textsuperscript{-1}): 3162, 1634, 1155; mp: 203 - 205 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6) ppm 7.11 - 7.19 (m, 2 H) 7.24 (d, \textit{J}=7.21 Hz, 1 H) 7.43 (t, \textit{J}=7.21 Hz, 2 H) 7.55 (t, \textit{J}=7.34 Hz, 1H) 7.71 (d, \textit{J}=8.2 Hz, 1H) 8.40 (d,
J = 3.03 Hz, 1 H) 9.60 (s, 1 H) 11.56 (s, 1 H) 12.48 (br. s., 1 H), 13C NMR (100 MHz, DMSO-d6) ppm 108.23, 110.09, 115.79, 117.81, 125.04, 126.69, 129.63, 131.45, 136.36, 138.72, 142.19, 143.42, 186.78. HRESI-MS (m/z) – Calculated for C13H12N2O3NSNa (M+Na): 323.0466, found (M+Na) 323.0467.

8. N-(3-formyl-1H-indol-4-yl)-4-(trifluoromethyl)benzenesulfonamide (3j)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230–400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a light yellow solid, Yield - 75 mg, (67%); Rf (40% EtOAc/Hexane) 0.2; IR (KBr, cm⁻¹): 3266, 1674, 1145; mp: 209 - 211 °C; 1H NMR (400 MHz, DMSO-d6) ppm 7.18 – 7.23 (m, 2 H) 7.27 (dd, J = 6.19, 2.40 Hz, 1 H) 7.85 (d, J = 8.34 Hz, 2 H) 7.94 (d, J = 8.34 Hz, 2 H) 8.42 (d, J = 3.03 Hz, 1 H) 9.60 (s, 1 H) 11.79 (s, 1 H) 12.54 (br. s., 1 H); 13C NMR (100 MHz, DMSO-d6) ppm 108.87 , 110.52 , 116.05, 117.68, 123.23 (d, J = 271 Hz) 125.16, 126.50, (d, J = 4 Hz) 127.70, 130.74, 132.72 (d, J = 33 Hz) 138.78, 142.39, 143.02, 187.00.; HRESI-MS (m/z) – Calculated for C16H11F3N2O3SNa (M+Na): 391.0340, found (M+Na) 391.0339

9. N-(1-benzyl-3-formyl-1H-indol-4-yl)4-methylbenzenesulfonamide (3k)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230–400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a yellow solid, Yield - 100 mg, (82%); Rf (40% EtOAc/Hexane) 0.4; IR (KBr, cm⁻¹): 3217,
1632, 1181; mp: 165 – 167 °C; $^1$H NMR (400 MHz, CHLOROFORM-d) ppm 2.29 (s, 3 H) 5.27 (s, 2 H) 6.94 (d, $J$=8.24 Hz, 1 H) 7.08 - 7.20 (m, 5 H) 7.31 - 7.37 (m, 3 H) 7.44 (d, $J$=7.93 Hz, 1 H) 7.63 (s, 1 H) 7.73 (d, $J$=7.93 Hz, 2 H) 9.47 (s, 1 H) 11.35 (s, 1 H); $^{13}$C NMR (100 MHz, CHLOROFORM-d) ppm 21.42, 51.14, 105.71, 111.41, 116.81, 118.25, 125.72, 127.22, 127.37, 128.59, 129.16, 129.30, 132.49, 134.49, 137.13, 139.13, 141.39, 143.13, 185.00.; HRESI-MS (m/z) – Calculated for C$_{23}$H$_{20}$N$_2$O$_3$SNa (M+Na): 427.1092, found (M+Na) 427.1090.

10. Tert-butyl 3-formyl-4-((4-methylphenyl)sulfonamido)-1H-indole-1-carboxylate (3l)

![3l](image)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 7:3) to obtain the product as a light brown solid, Yield - 84mg, (67%); R$_f$ (40% EtOAc/Hexane) 0.4; IR (KBr, cm$^{-1}$): 3174, 1672, 1099; mp: 132 - 135 °C; $^1$H NMR (400 MHz, CHLOROFORM-d) ppm 1.68 (s, 9 H) 2.30 (s, 3 H) 7.12 (m, $J$=7.83 Hz, 2 H) 7.31 (t, $J$=8.21 Hz, 1 H) 7.57 (d, $J$=8.08 Hz, 1 H) 7.70 (m, $J$=8.34 Hz, 2 H) 7.81 (d, $J$=8.34 Hz, 1 H) 8.22 (s, 1 H) 9.68 (s, 1 H) 10.91 (s, 1 H); $^{13}$C NMR (100 MHz, CHLOROFORM-d) ppm 21.42, 27.95, 86.60, 110.55, 113.88, 117.06, 121.33, 127.18, 127.52, 129.36, 132.49, 136.81, 137.41, 140.01, 143.34, 147.98, 186.61.; HRESI-MS (m/z) – Calculated for C$_{21}$H$_{22}$N$_2$O$_5$SNa (M+Na): 437.1147, found (M+Na) 437.1150.

11. N-(3-formyl-1-tosyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3m)

![3m](image)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 7:3) to obtain the product as
a light brown solid, **Yield** - 90mg, (64%); **Rf** (30% EtOAc/Hexane) 0.3; **IR** (KBr, cm⁻¹): 3214, 1635, 1134; **mp**: **171 - 173** °C; ¹H NMR (400 MHz, CHLOROFORM-d) ppm 2.30 (s, 3 H) 2.38 (s, 3 H) 7.12 (m, J=8.34 Hz, 2 H) 7.30 (d, J=8.59 Hz, 3 H) 7.55 (d, J=8.34 Hz, 1 H) 7.52 (d, J=8.08 Hz, 1 H) 7.69 (m, J=8.08 Hz, 2 H) 7.82 (d, J=8.34 Hz, 2 H) 8.25 (s, 1 H) 9.70 (s, 1 H) 10.84 (s, 1 H); ¹³C NMR (100 MHz, CHLOROFORM-d) ppm 21.42 ,21.66 ,108.27 ,113.70 ,117.10 ,122.04 ,127.17 ,127.39 ,127.74 ,129.42 ,130.44 ,132.96 ,133.54 ,136.49 ,136.68 ,139.47 ,143.54 ,146.72 ,186.40.; **HRESI-MS**(m/z)—Calculated for C₂₃H₂₀N₂O₅S₂Na (M+Na): 491.0711, found (M+Na) 491.0712.

12. N-(1-allyl-3-formyl-1H-indol-4-yl)-4-methylbenzenesulfonamide (3n)

![Chemical Structure](image)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc,7:3) to obtain the product as a light brown solid, **Yield** - 36mg, (34%); **Rf** (30% EtOAc/Hexane) 0.3; **IR** (KBr, cm⁻¹): 3194, 1671, 1177; **mp**: **140 - 143** °C; ¹H NMR (400 MHz, CHLOROFORM-d) ppm 2.29 (s, 3 H) 5.16 (dd, J=16.93, 0.76 Hz, 1 H) 5.33 (dd, J=10.36, 0.76 Hz, 1 H) 5.91 - 6.02 (m, 1 H) 6.96 (d, J=8.34 Hz, 1 H) 7.13 (d, J=8.34 Hz, 2 H) 7.21 (t, J=8.08 Hz, 1 H) 7.46 (d, J=7.83 Hz, 1 H) 7.68 (s, 1 H) 7.75 (d, J=8.08 Hz, 2 H) 9.52 (s, 1 H) 11.34 (s, 1 H); ¹³C NMR (100 MHz, CHLOROFORM-d) ppm 21.43 ,49.74 ,105.59 ,111.46 ,116.79 ,118.21 ,119.67 ,125.66 ,127.25 ,129.31 ,130.99,138.95 ,141.09 ,143.11 ,184.94.; **HRESI-MS**(m/z)—Calculated for C₁₉H₁₈N₂O₃SNa (M+Na): 377.0936, found (M+Na) 377.0933.
13. 4-methyl-N-(3-(2,2,2-trifluoroacetyl)-1H-indol-4-yl)benzenesulfonamide (4aa)

![Chemical Structure](4aa)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 6:4) to obtain the product as a light brown solid, Yield - 69mg, (60%); Rf (40% EtOAc/Hexane) 0.3; IR (KBr, cm⁻¹): 3184, 1677, 1191; mp: 215 - 218 °C; ¹H NMR (400 MHz, DMSO-d₆) ppm 2.25 (s, 3 H) 7.19 - 7.36 (m, 5 H) 7.55 (d, J=8.24 Hz, 2 H) 8.56 (d, J=1.53 Hz, 1 H) 10.86 (s, 1 H) 13.09 (br. s., 1 H); ¹³C NMR (100 MHz, DMSO-d₆) ppm 20.84, 109.02, 109.36, 113.14, 115.99, 117.87 (d, J= 200 MHz), 125.98, 126.75, 129.60, 131.34, 135.88, 138.61, 141.13, 143.66, 175.19 (d, J= 34 MHz); HRESI-MS (m/z) – Calculated for C₁₇H₁₃F₃N₂O₃SNa (M+Na): 405.0497, found (M+Na) 405.0500.

14. 4-methyl-N-(1-methyl-3-(2,2,2-trifluoroacetyl)-1H-indol-4-yl)benzenesulfonamide (4ba)

![Chemical Structure](4ba)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 7:3) to obtain the product as a light yellow solid, Yield - 47mg, (40%); Rf (40% EtOAc/Hexane) 0.4; IR (KBr, cm⁻¹): 3196, 1680, 1133; mp: 161 - 163 °C; ¹H NMR (400 MHz, DMSO-d₆) ppm 2.24 (s, 3 H) 3.88 (s, 3 H) 7.23 (m, J=7.83 Hz, 2 H) 7.31 - 7.41 (m, 3 H) 7.57 (m, J=8.08 Hz, 2 H) 8.64 (s, 1 H) 10.99 (s, 1 H); ¹³C NMR (101 MHz, DMSO-d₆) ppm 20.89, 34.23, 107.85, 113.29, 118.85-115.98 (m), 125.66, 126.08, 126.81, 129.71, 131.52, 135.89, 139.36, 143.79, 144.48 (d, J= 4 MHz), 174.64
(d, J= 34 MHz); \textbf{HRESI-MS}(m/z)–Calculated for C_{18}H_{13}F_{3}N_{2}O_{3}SNa (M+Na): 419.0653, found (M+Na) 419.0655.

15. Methyl 1-methyl-4-((4-methylphenyl)sulfonamido)-1H-indole-3-carboxylate (5aa)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 7:3) to obtain the product as a brown solid, \textbf{Yield} - 70mg, (65%); \textbf{R_{f}} (40% EtOAc/Hexane) 0.4; \textbf{IR} (KBr, cm^{-1}) : 3111, 1735, 1152; \textit{mp: 160 - 163 °C}; \textbf{^1H NMR} (400 MHz, CHLOROFORM-d) ppm 2.30 (s, 3 H) 3.74 (s, 3 H) 3.91 (s, 3 H) 6.96 (d, J=8.34 Hz, 1 H) 7.10 - 7.21 (m, 3 H) 7.40 (d, J=8.08 Hz, 1 H) 7.68 (s, 1 H) 7.77 (d, J=8.34 Hz, 2 H) 11.63 (s, 1 H); \textbf{C NMR} (100 MHz, CHLOROFORM-d) ppm 21.43 ,33.68 ,52.13 ,105.22 ,105.56 ,110.72 ,117.20 ,124.24 ,127.30 ,129.26 ,131.93 ,136.11 ,137.16 ,138.58 ,143.02 ,167.24 ; \textbf{HRESI-MS}(m/z)–Calculated for C_{18}H_{18}N_{2}O_{4}SNa (M+Na): 381.0885, found (M+Na) 381.0691.

16. Ethyl 1-methyl-4-((4-methylphenyl)sulfonamido)-1H-indole-3-carboxylate (5ba)

Prepared according to the general procedure. Crude reaction mixture was purified on flash column using silica (230-400) with a suitable eluent (Hexane/EtOAc, 7:3) to obtain the product as a brown solid, \textbf{Yield} - 77mg, (69%); \textbf{R_{f}} (40% EtOAc/Hexane) 0.4; \textbf{IR} (KBr, cm^{-1}) : 3219, 1715, 1141; \textit{mp: 164 - 166 °C}; \textbf{^1H NMR} (400 MHz, CHLOROFORM-d) ppm 1.39 (t, J=7.07 Hz, 3 H) 2.29 (s, 3 H) 3.72 (s, 3 H) 4.38 (q, J=7.07 Hz, 2 H) 6.95 (d, J=8.34 Hz, 1 H) 7.08 - 7.18 (m, 3 H)
H) 7.40 (d, $J=7.83$ Hz, 1 H) 7.69 (s, 1 H) 7.75 (d, $J=8.08$ Hz, 2 H) 11.70 (s, 1 H); $^{13}$C NMR (100 MHz, CHLOROFORM-$d$) ppm 14.37 ,21.37 ,33.59 ,60.94 ,105.28 ,110.71 ,117.24 ,124.06 ,126.34 ,127.21 ,129.21 ,131.78 ,136.13 ,137.07 ,138.52 ,142.98 ,166.84.; HRESI-MS ($m/z$)--Calculated for $C_{19}H_{20}N_{2}O_{4}SNa$ (M+Na): 395.1041, found (M+Na) 395.1042.

**Experimental section for deprotection of tosyl group**

The C4-amidated product, 3aa (0.5 mmol) was added to the cold conc H$_2$SO$_4$ (1 mL) at 0 °C. The mixture was stirred at rt for 2 h. Upon completion, the reaction mixture was quenched with NaHCO$_3$ solution and the resulting mixture was extracted with EtOAc(3 x 20mL). The organic layers were collected, dried over Na$_2$SO$_4$, and concentrated in vacuum to give 4-amino-1H-indole-3-carbaldehyde as a 52% yield.

**17. 4-amino-1H-indole-3-carbaldehyde**

![Structure of 4-amino-1H-indole-3-carbaldehyde](image)

Yield - 42mg, (52%); $R_f$ (40% EtOAc/Hexane) 0.3; IR (KBr, cm$^{-1}$): 3302, 1732, 1209;

$^1$H NMR (400 MHz, DMSO-$d_6$) ppm 6.25 (br. s., 2 H) 6.26 - 6.30 (m, 1 H) 6.55 - 6.62 (m, 1 H) 6.92 (t, $J=7.83$ Hz, 1 H) 8.14 (d, $J=3.28$ Hz, 1 H) 9.58 (s, 1 H) 11.98 (br. s., 1 H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) ppm 99.45 ,105.04 ,111.84 ,119.79 ,125.41 ,139.36 ,140.08 ,143.10 ,184.82 (s, 1 C); HRESI-MS ($m/z$)--Calculated for $C_9H_8N_2ONa$ (M+Na): 183.0534, found (M+Na) 183.0537.
LVR-08104B

100 MHz, $^{13}$C NMR (DMSO)

![NMR spectrum with peaks labeled]
LVR-Am
LVR-Am

100 MHz, $^{13}$C NMR (DMSO)
LVR-08127B

400 MHz, $^1$H NMR (DMSO)
LVR-08111B
LVR-08118B

100 MHz, $^{13}$C NMR (DMSO)
LVR-08118C

400 MHz, $^1$H NMR(DMSO)
LVR-08105C

400 MHz, $^1$H NMR (CDCl$_3$)
LVR-08105C
LVR-08102A

$^{13}$C NMR (DMSO)
LVR-08151A

100 MHz, $^{13}$C NMR (DMSO)
LVR-08152A

100 MHz, $^{13}$C NMR (CDCl$_3$)
LVR-NH2

400 MHz, $^1$H NMR (DMSO)
LVR-NH2

100 MHz, $^{13}$C NMR (DMSO)
Deuterium Incorporation studies:
Internal Standard – terephthaldehyde (0.5 equiv)
Starting Material – 4a
Deuterating agent – CD3COOD
C-4 deuteration – 55%
C-2 deuteration – 00%

overall yield, 94%
Deuterium Incorporation studies:
Internal Standard – terephthaldehyde (0.5 equiv)
Starting Material – 1a
Deuterating agent – CD3COOD
C-4 deuteration – 56%
C-2 deuteration – 00%

overall yield, 70%