Supporting Information

**Design, Synthesis, Anti-proliferative Evaluation and Molecular Docking Studies of N-(3-hydroxyindole) appended β-carbolines/ tetrahydro-β-carbolines targeting Triple Negative and Non-Triple Negative Breast Cancer**

Bharvi Sharma\textsuperscript{a}, Sourav Taru Saha\textsuperscript{b}, Shanen Perumal\textsuperscript{b}, Liang Gu\textsuperscript{b}, Oluwakemi Ebenezer\textsuperscript{c}, Parvesh Singh\textsuperscript{c}, Mandeep Kaur\textsuperscript{b}, Vipan Kumar\textsuperscript{a}\textsuperscript{*}.

\textsuperscript{a}Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
\textsuperscript{b}School of Molecular and Cell Biology, University of the Witwatersrand, Private Bag 3, Wits, 2050 Johannesburg, South Africa
\textsuperscript{c}School of Chemistry and Physics, University of KwaZulu Natal, P/Bag X54001, Westville, Durban 4000, South Africa

\*Corresponding Author. Tel: +91 183 2258802-09*3320 (V.K.); Fax: +91 183 2258819-20, Email address: vipan.org@yahoo.com (V. Kumar)

**Table S1**: Physicochemical and ADMET properties of compound 8f, 9e, 9f, 9d, 10d.

| Properties                      | Predicted values |
|--------------------------------|------------------|
|                                | 8f   | 9e   | 9f   | 9d   | 10d  |
| **Absorption**                 |       |      |      |      |      |
| Water solubility               | -3.251| -3.069| -4.049| -4.107| -3.966|
| Caco2 permeability             | 1.36  | 0.881 | 0.862 | 0.877 | 0.780 |
| Intestinal absorption (human) | 96.149| 97.935| 96.824| 97.098| 96.984|
| P-glycoprotein substrate       | No    | Yes  | Yes  | Yes  | Yes  |
| P-glycoprotein I inhibitor     | Yes   | Yes  | Yes  | Yes  | Yes  |
| P-glycoprotein II inhibitor    | Yes   | No   | Yes  | Yes  | Yes  |
| **Metabolism**                 |       |      |      |      |      |
| CYP2C19                        | Yes   | No   | Yes  | Yes  | Yes  |
| inhibitor                     | Yes | No | No | No | No |
|------------------------------|-----|----|----|----|----|
| CYP2C9 inhibition            | Yes | No | No | No | No |
| CYP2D6 inhibition            | No  | No | No | No | No |
| CYP1A2 inhibition            | No  | No | No | No | No |
| CYP3A4 inhibition            | Yes | No | Yes| Yes| Yes|

**Excretion**

| Excretion                      | 0.419| 0.765| 0.830| 0.845| 0.867 |
|-------------------------------|------|------|------|------|------|
| Total Clearance                | 0.419| 0.765| 0.830| 0.845| 0.867 |
| Renal OCT2 substrate          | No   | No   | No   | No   | No   |

**Distribution**

| Distribution                     | -0.727| 0.319| 0.425| 0.541| 0.816 |
|---------------------------------|-------|------|------|------|------|
| VDss (human)                    | -0.727| 0.319| 0.425| 0.541| 0.816 |
| BBB permeability                | -0.337| -1.09| -1.104| -1.092| -1.051 |
| Fraction unbound (human)        | 0.276 | 0.345| 0.062| 0.042| 0.051 |
| CNS permeability                | -3.272| -2.903| -2.614| -2.461| -2.312 |

**Toxicity**

| Toxicity                      | 2.544 | 3.3  | 3.281 | 3.479 | 3.423 |
|-------------------------------|-------|------|-------|-------|-------|
| Oral Rat Acute Toxicity (LD50)| 2.544 | 3.3  | 3.281 | 3.479 | 3.423 |
| Hepatotoxicity                | Yes   | No   | Yes   | No   | No   |
| Skin Sensitisation            | No    | No   | No    | No   | No   |
| T. Pyriformis toxicity        | 0.285 | 0.285| 0.285| 0.285| 0.295 |
| Minnow toxicity               | -5.426| 2.16 | -0.418| -0.107| -0.15 |
| LogP                          | 4.90  | 2.79 | 4.19  | 4.03  | 4.03  |
| TPSA                          | 84.67 | 85.87| 85.87 | 85.87 | 85.87 |
| Num of HBA/HBD                | 6/1   | 6/2  | 6/2   | 5/2   | 5/2   |
| Molar refractivity            | 144.60| 123.77| 148.26| 153.83| 153.83|
Table S2: Binding Energy, Hydrogen Bonding Interactions and important residues involved in the active compounds docked on AKT receptor

| Ligand      | Binding energy( kcal/mol) | Interacting residue of 3OCB                        | Hydrogen Bonding interaction | Distance(A˚) |
|-------------|---------------------------|--------------------------------------------------|------------------------------|--------------|
| 8f          | -8.5                      | GLY159, GLU234, VAL164, ALA177, MET281, LEU156   | GLY159                       | 3.32         |
| 9d          | -8.9                      | VAL164, ALA177, MET281, LEU156, GLU278, PHE236, GLU234 | GLU234                       | 2.77         |
| 9e          | -8.6                      | ASN279, ASP292, LYS276, VAL164, ALA177, MET281   | ASP292                       | 2.51         |
| 9f          | -8.8                      | LYS276, VAL164, ALA177, MET281, GLU234, LEU156, PHE442 | GLU234, LEU156               | 3.75, 3.75   |
| 10d         | -8.7                      | ASN279, ASP292, LYS276, VAL164, ALA177, MET281, PHE161 | ASP292                       | 3.35         |
| Peganumine-A| -7.6                      | GLU234, ASP292, VAL164, LYS158, LYS158           | GLU234, LYS158               | 2.16, 2.32   |
| Tamoxifen   | -6.4                      | ALA230, VAL164, LYS179, PHE161                   | ALA230                       | 3.78         |
Synthetic procedure for synthesis of conjugates (8a-f)

9H-β-Carboline-3-carboxylic acid ethyl ester 7 (1mmol) was added to stirred suspension of NaH in anhydrous DMF (10 mL), resulting in formation of anionic solution. Isatin epoxide 3 (1mmol) was added dropwise to solution of 7 in dry DMF. The reaction mixture was heated at 60 °C for 6h. After completion of reaction as monitored by TLC, reaction was quenched by addition of water (20mL), followed by extraction with ethylacetate (3x30 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude mixture thus obtained was purified via column chromatography using ethyl acetate: hexane (70:20) mixture to yield 8a-f in good to excellent yields.

9-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8a)

Yield 84%; pale yellow solid; mp 195-198 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.44 (t, J = 7.1 Hz, 3H, -OCH₂CH₃); 2.05 (s, 1H, -NH(exchangeable with D₂O)); 3.11 (s, 3H, -NCH₃); 4.47 (q, J = 7.1 Hz, 2H, -OCH₂CH₃); 4.63 (d, J = 15.2 Hz, 1H, -NCH₂); 4.90 (d, J = 15.2 Hz, 1H, -NCH₂); 6.73-6.75 (m, 3H, Ar-H); 7.17-7.21 (m, 1H, Ar-H); 7.29 (t, J = 7.6 Hz, 1H, Ar-H); 7.43-7.51 (m, 2H, Ar-H); 8.11 (d, J = 7.8 Hz, 1H, Ar-H); 8.77 (s, 2H, Ar-H) ¹³C NMR (100 MHz, CDCl₃)δ 14.5, 26.5, 50.8, 61.7, 76.9, 108.8, 111.3, 117.4, 121.2, 121.4, 121.7, 123.4, 125.0, 127.5, 128.7, 128.8, 130.6, 133.1, 137.9, 138.8, 142.6, 142.9, 166.1, 176.6 HRMS calcd for C₂₄H₂₁N₃O₄ [M+1]+ 416.1566, found 416.1532.

9-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8b)

Yield 82%; pale yellow solid; mp 220-222 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.47 (t, J = 7.1 Hz, 3H, -OCH₂CH₃); 4.50 (q, J = 7.1 Hz, 2H, -OCH₂CH₃); 4.67 (d, J = 15.7 Hz, 1H, -NCH₂); 4.81 (d, J = 15.2 Hz, 1H, -CH₂Ph); 4.91 (d, J = 15.7 Hz, 1H, -NCH₂); 4.99 (d, J = 15.2 Hz, 1H, -CH₂Ph); 6.63 (d, J = 7.9 Hz, 1H, Ar-H); 6.82 (t, J = 7.5 Hz, 1H, Ar-H); 7.00-7.03 (m, 3H, Ar-
H); 7.12 (t, J = 7.65 Hz, 1H, Ar-H); 7.22 (s, 3H, Ar-H); 7.32-7.35 (m, 1H, Ar-H); 7.51 (s, 2H, Ar-H); 8.16 (d, J = 7.7 Hz, 1H, Ar-H); 8.80 (s, 1H, Ar-H); 8.86 (s, 1H, Ar-H) ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 44.0, 50.9, 61.6, 76.6, 109.8, 111.3, 114.0, 117.2, 121.2, 121.3, 121.7, 123.4, 124.0, 125.0, 127.0, 127.6, 128.8, 129.0, 130.6, 132.9, 134.8, 137.3, 138.6, 142.3, 142.6, 165.7, 176.5 HRMS calcd for C₃₀H₂₅N₃O₄ [M+1]⁺ 492.1879, found 492.1823.

9-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8c)

Yield 86%; pale white solid; mp 201-203 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.46 (t, J = 7.0 Hz, 3H, -OCH₂CH₃); 3.12 (s, 3H, -NCH₃); 3.65 (s, 1H, -OH (exchangeable with D₂O)); 4.49 (q, J = 7.0 Hz, 2H, -OCH₂CH₃); 4.71 (d, J = 15.3 Hz, 1H, -NCH₂); 6.68 (d, J = 8.3 Hz, 1H, Ar-H); 6.79 (s, 1H, Ar-H); 7.17 (d, J = 8.2 Hz, 1H, Ar-H); 7.32-7.37 (m, 2H, Ar-H); 7.53 (t, J = 7.7 Hz, 1H, Ar-H); 813 (d, J = 7.8 Hz, 1H, Ar-H); 8.77 (s, 1H, Ar-H); 9.05 (s, 1H, Ar-H) ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 26.6, 50.7, 61.8, 76.8, 109.6, 110.0, 117.3, 121.1, 121.3, 121.8, 123.4, 124.0, 125.7, 128.7, 129.0, 129.4, 130.1, 132.9, 138.6, 141.3, 142.6, 165.4, 176.1 HRMS calcd for C₂₄H₂₀ClN₃O₄ [M+1]⁺ 451.1113, found 451.1182.

9-(1-Benzyl-5-chloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8d)

Yield 85%; pale white solid; mp 205-208 °C; ¹H NMR (500 MHz, CDCl₃) δ 1.43 (t, J = 7.1 Hz, 3H, -OCH₂CH₃); 4.52 (q, J = 7.1 Hz, 2H, -OCH₂CH₃); 4.71 (d, J = 15.8 Hz, 1H, -NCH₂); 4.83 (d, J = 15.2 Hz, 1H, -CH₂Ph); 4.96 (d, J = 15.7 Hz, 1H, -NCH₂); 4.98 (d, J = 15.2 Hz, 1H, -CH₂Ph); 6.68 (d, J = 7.9 Hz, 1H, Ar-H); 6.83 (t, J = 7.5 Hz, 1H, Ar-H); 7.04-7.07 (m, 2H, Ar-H); 7.15 (t, J = 7.65 Hz, 1H, Ar-H); 7.23 (s, 3H, Ar-H); 7.34-7.36 (m, 1H, Ar-H); 7.54 (s, 2H, Ar-H); 8.17 (d, J = 7.7 Hz, 1H, Ar-H); 8.83 (s, 1H, Ar-H); 8.87 (s, 1H, Ar-H) ¹³C NMR (125 MHz, CDCl₃) δ 14.4, 26.6, 50.7, 61.8, 76.8, 109.6, 110.0, 117.3, 121.1, 121.3, 121.8, 123.4, 124.0, 125.7, 128.7, 129.0, 129.4, 130.1, 132.9, 138.6, 141.3, 142.6, 165.4, 176.1 HRMS calcd for C₂₄H₂₀ClN₃O₄ [M+1]⁺ 451.1113, found 451.1182.
MHz, CDCl$_3$) $\delta$ 14.6, 44.3, 50.8, 61.6, 76.5, 110.2, 111.7, 114.5, 117.3, 121.3, 121.8, 121.4, 123.5, 124.1, 125.2, 127.1, 127.5, 127.4, 128.5, 129.1, 130.7, 132.3, 134.5, 137.8, 138.7, 142.2, 142.8, 165.8, 176.8 HRMS calcd for C$_{30}$H$_{24}$ClN$_3$O$_4$ [M+1]$^+$ 526.1489, found 526.1432.

9-(5-Fluoro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8e)

Yield 83%; light brown solid; mp 188-190 °C; 1H NMR (500 MHz, CDCl$_3$) $\delta$ 1.44 (t, $J = 7.1$ Hz, 3H, -OCH$_2$CH$_3$); 3.14 (s, 3H, -NCH$_3$); 4.49 (q, $J = 7.1$ Hz, 2H, -OCH$_2$CH$_3$); 4.72 (d, $J = 15.4$ Hz, 1H, -NCH$_2$); 4.97 (d, $J = 15.3$ Hz, 1H, -NCH$_2$); 6.67 (d, $J = 8.3$ Hz, 1H, Ar-H); 6.80 (s, 1H, Ar-H); 7.16 (d, $J = 8.1$ Hz, 1H, Ar-H); 7.34-7.38 (m, 2H, Ar-H); 7.54 ( t, $J = 7.8$ Hz, 1H, Ar-H); 8.13 (d, $J = 7.6$ Hz, 1H, Ar-H); 8.78 (s, 1H, Ar-H); 9.07 (s, 1H, Ar-H) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.7, 26.8, 50.9, 61.7, 76.7, 109.4, 110.2 (d, $J_{CF} = 34.3$ Hz), 113.4 (d, $J_{CF} = 89.0$ Hz), 117.8(d, $J_{CF} = 95.7$ Hz), 121.0, 121.4, 121.8, 124.1, 125.6, 128.8, 129.1, 129.3, 130.2, 132.6, 138.7, 141.2, 142.7, 165.3, 176.2 HRMS calcd for C$_{24}$H$_{20}$ClN$_3$O$_4$ [M+1]$^+$ 451.1113, found 451.1182.

9-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8f)

Yield 80%; light brown solid; mp 195-198 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.43 (t, $J = 7.4$ Hz, 3H, -OCH$_2$CH$_3$); 4.44 (q, $J = 6.95$ Hz, 2H, -OCH$_2$CH$_3$); 4.62 (d, $J = 15.7$ Hz, 1H, -NCH$_2$); 4.78 (d, $J = 15.2$ Hz, 1H, -CH$_2$Ph); 4.86 (d, $J = 15.7$ Hz, 1H, -NCH$_2$); 4.98 (d, $J = 15.2$ Hz, 1H, -CH$_2$Ph); 6.50-6.52 (m, 1H, Ar-H); 6.72-6.79 (m, 2H, Ar-H); 6.97-6.98 (m, 2H, Ar-H); 7.18-7.28 (m, 3H, Ar-H); 7.30 (m, 1H, Ar-H); 7.40-7.41 (m, 1H, Ar-H); 7.46-7.49 (m, 1H, Ar-H); 8.12 (d, $J = 7.8$ Hz, 1H, Ar-H); 8.73 (s, 1H, Ar-H); 8.92 (s, 1H, Ar-H) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.4, 44.1, 50.9, 61.6, 76.9, 110.5 (d, $J_{CF} = 31.2$ Hz), 113.3 (d, $J_{CF} = 99.6$ Hz), 116.6 (d, $J_{CF} = 93.7$ Hz), 117.2, 121.2, 121.7, 126.9, 127.8, 128.8, 128.8, 128.9, 129.7, 129.8, 132.9,
134.6, 137.5, 138.1, 138.6, 142.4, 158.2, 160.1, 165.7, 176.6 HRMS calcd for C_{30}H_{24}FN_{3}O_{4} [M+1]^+ 510.1784, found 510.1714.

**Synthetic procedure for synthesis of conjugates 9a-f and 10a-f**

To a well stirred solution of spiro-epoxy isatin3 (1mmol) in dry carbinol, 2,3,4,9-Tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester 6 was added and the reaction mixture was stirred for 48 h. Upon completion of reaction, as monitored by TLC, solvent was removed under reduced pressure. The reaction mixture was extracted with chloroform and washed well with water (2x50 mL). Combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The reaction mixture was purified via column chromatography using ethylacetate:hexane (40:60) to yield target compounds 9a-f and 10a-f in appreciable yields. The target compounds, thus obtained, are racemic and are not enantiopure.

**2-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9a)**

Yield 42%; light brown powder; mp 145-147 ºC. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.23 (t, \(J = 7.1\) Hz, 3H, H-1); 3.05 (d, \(J = 15.6\) Hz, 1H, each H-4); 3.14 (s, 3H, -NCH\(_3\)); 3.15-3.23 (m, 3H, H-4+H-6); 3.90 (t, \(J = 5.3\) Hz, 1H, H-3); 4.03-4.18 (m, 3H, H-2+H-5); 4.35 (d, \(J = 15.3\) Hz, 1H, H-5); 6.69 (d, \(J = 8.1\) Hz, 1H, Ar-H); 7.04-7.15 (m, 2H, Ar-H); 7.21-7.23 (m, 2H, Ar-H); 7.25-7.27 (m, 1H, Ar-H); 7.34-7.38 (m, 1H, Ar-H); 7.45 (d, \(J = 7.5\) Hz, 1H, Ar-H); 7.91 (s, 1H, -NH (exchangeable with D\(_2\)O)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 14.1, 23.7, 26.5, 32.0, 48.5, 61.2, 62.3, 76.2, 106.4, 109.3, 110.9, 117.8, 119.3, 121.6, 124.8, 126.9, 128.7, 129.3, 131.4, 131.5, 136.7, 142.4, 172.7, 178.5 HRMS calcd for C_{24}H_{25}N_{3}O_{4} [M+1]^+ 420.1879, found 420.1861.

**2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9b)**
Yield 47%; light yellow powder; mp 151-152 °C. 1H NMR (500 MHz, CDCl₃) δ: 1.22 (t, J = 7.1 Hz, 3H, H-1); 3.07 (dd, J = 15.4 Hz, 5.8 Hz, 1H, each H-4); 3.17-3.21 (dd, J = 15.4, J = 2.9 Hz, 1H, each H-4); 3.33-3.45 (dd, J = 45.3, J = 14.5 Hz, 2H, H-6); 3.94-3.97 (m, 2H, H-3+H-5); 4.03-4.17 (m, 2H, H-2); 4.29 (d, J = 15.1 Hz, 1H, H-5); 4.68 (d, J = 15.9 Hz, 1H, H-7); 5.06 (d, J = 15.9 Hz, 1H, H-7); 6.60 (d, J = 7.6 Hz, 1H, Ar-H); 7.05-7.10 (m, 3H, Ar-H); 7.12-7.15 (m, 2H, Ar-H); 7.16-7.26 (m, 5H, Ar-H); 7.44-7.51 (m, 2H, Ar-H); 7.90 (s, 1H, -NH (exchangeable with D₂O)).

13C NMR (125 MHz, CDCl₃) δ: 14.2, 23.7, 32.0, 43.7, 48.3, 61.0, 62.4, 75.5, 105.9, 109.6, 109.9, 117.9, 119.3, 121.5, 123.2, 124.2, 126.9, 127.0, 127.6, 128.8, 129.9, 130.2, 131.7, 135.3, 136.1, 143.0, 172.9, 178.7 HRMS calcd for C₃₀H₂₉N₃O₄ [M+1]+ 496.2192, found 496.2161.

2-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9c)

Yield 45%; pale white powder; mp 140-142 °C. 1H NMR (400 MHz, CDCl₃) δ: 1.20 (t, J = 7.1 Hz, 3H, H-1); 3.04-3.09 (dd, J = 15.6 Hz, J = 5.8 Hz, 1H, each H-4); 3.12 (s, 3H, -NCH₃); 3.13-3.25 (m, 3H, H-4+H-6); 3.88 (t, J = 5.2Hz, 1H, H-3); 4.02-4.17 (m, 3H, H-2+H-5); 4.31 (d, J = 15.3 Hz, 1H, H-5); 6.67 (d, J = 8.2 Hz, 1H, Ar-H); 7.03-7.13 (m, 2H, Ar-H); 7.23-7.24 (m, 1H, Ar-H); 7.25-7.26 (m, 1H, Ar-H); 7.36-7.37 (m, 1H, Ar-H); 7.44 (d, J = 7.3 Hz, 1H, Ar-H); 7.90 (s, 1H, -NH (exchangeable with D₂O)).

13C NMR (100 MHz, CDCl₃) δ: 14.1, 23.6, 26.4, 33.9, 48.7, 61.1, 62.4, 74.9, 106.0, 109.4, 110.8, 117.9, 119.4, 121.6, 124.7, 126.9, 128.6, 129.7, 131.5, 131.9, 136.0, 142.3, 172.6, 178.3 HRMS calcd for C₂₄H₂₉ClN₃O₄ [M+1]+ 454.1489, found 454.1453.

2-(1-Benzyl-5-chloro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9d)

Yield 46%; light yellow powder; mp 155-158 °C. 1H NMR (500 MHz, CDCl₃) δ: 1.23 (t, J = 7.1 Hz, 3H, H-1); 3.08 (dd, J = 15.6 Hz, J = 5.9 Hz, 1H, each H-4); 3.21 (dd, J = 15.5 Hz, J = 3.5 Hz, 1H, each H-4); 3.33-3.45 (dd, J = 45.3, J = 14.5 Hz, 2H, H-6); 3.94-3.97 (m, 2H, H-3+H-5); 4.03-4.17 (m, 2H, H-2); 4.29 (d, J = 15.1 Hz, 1H, H-5); 4.68 (d, J = 15.9 Hz, 1H, H-7); 5.06 (d, J = 15.9 Hz, 1H, H-7); 6.60 (d, J = 7.6 Hz, 1H, Ar-H); 7.05-7.10 (m, 3H, Ar-H); 7.12-7.15 (m, 2H, Ar-H); 7.16-7.26 (m, 5H, Ar-H); 7.44-7.51 (m, 2H, Ar-H); 7.90 (s, 1H, -NH (exchangeable with D₂O)).

13C NMR (125 MHz, CDCl₃) δ: 14.2, 23.7, 32.0, 43.7, 48.3, 61.0, 62.4, 75.5, 105.9, 109.6, 109.9, 117.9, 119.3, 121.5, 123.2, 124.2, 126.9, 127.0, 127.6, 128.8, 129.9, 130.2, 131.7, 135.3, 136.1, 143.0, 172.9, 178.7 HRMS calcd for C₂₄H₂₉ClN₃O₄ [M+1]+ 454.1489, found 454.1453.
Hz, 1H, each H-4); 3.37 (dd, \( J = 45.6 \) Hz, \( J = 14.5 \) Hz, 2H, H-6); 3.95-3.99 (m, 2H, H-3+H-5); 4.06-4.19 (m, 2H, H-2); 4.32 (d, \( J = 15.1 \) Hz, 1H, H-5); 4.69 (d, \( J = 15.9 \) Hz, 1H, H-7); 5.04 (d, \( J = 15.9 \) Hz, 1H, H-7); 6.51 (dd, \( J = 8.5 \) Hz, \( J = 4.0 \) Hz, 1H, Ar-H); 6.86-6.90 (m, 1H, Ar-H); 7.07-7.22 (m, 8H, Ar-H); 7.28 (s, 1H, Ar-H); 7.48 (d, \( J = 7.6 \) Hz, 1H, Ar-H); 7.84 (s, 1H, -NH(exchangeable with D\(_2\)O))

13C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 14.1, 22.7, 33.8, 43.8, 48.4, 60.9, 62.4, 75.4, 106.0, 110.2, 110.7, 112.4, 114.0, 115.9, 117.8, 119.4, 121.6, 126.8, 127.7, 128.8, 131.3, 131.9, 134.9, 136.1, 138.8, 157.2, 178.5 HRMS calcd for C\(_{30}\)H\(_{28}\)ClN\(_3\)O\(_4\) [M+1]+ 530.1802, found 530.1829.

2-(5-Fluoro-3-hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9e)

Yield 42%; pale white powder; mp 120-122 °C

1H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.23 (t, \( J = 7.1 \) Hz, 3H, H-1); 3.07-3.09 (dd, \( J = 15.7 \) Hz, \( J = 6.1 \) Hz, 1H, each H-4); 3.15 (s, 3H, -NCH\(_3\)); 3.15-3.22 (m, 3H, H-4+H-6); 3.89 (t, \( J = 5.2 \) Hz, 1H, H-3); 4.04-4.15 (m, 3H, H-2+H-5); 4.34 (d, \( J = 15.4 \) Hz, 1H, H-5); 6.69 (d, \( J = 8.3 \) Hz, 1H, Ar-H); 7.05-7.17 (m, 2H, Ar-H); 7.25-7.27 (m, 1H, Ar-H); 7.37-7.39 (m, 1H, Ar-H); 7.45 (d, \( J = 7.3 \) Hz, 1H, Ar-H); 7.91 (s, 1H, -NH (exchangeable with D\(_2\)O))

13C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 14.3, 23.7, 26.7, 33.7, 48.4, 61.1, 62.4, 76.4, 106.2, 109.3, 110.4 (d, \( J_{CF} = 32.4 \) Hz), 117.9 (d, \( J_{CF} = 93.4 \) Hz), 119.4, 121.6, 121.9, 126.9, 127.6, 129.7, 131.5, 131.9, 136.1, 158.2, 172.6, 178.3 HRMS calcd for C\(_{24}\)H\(_{24}\)FN\(_3\)O\(_4\) [M+1]+ 514.2097, found 514.2073.

2-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9f)

Yield 44%; pale yellow powder; mp 153-158 °C

1H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.20 (t, \( J = 7.1 \) Hz, 3H, H-1); 3.05 (dd, \( J = 15.7 \) Hz, \( J = 6.04 \) Hz, 1H, each H-4); 3.17 (dd, \( J = 15.7 \) Hz, \( J = 4.0 \) Hz, 1H, each H-4); 3.32 (dd, \( J = 35.0 \) Hz, \( J = 14.4 \) Hz, 2H, each H-6); 3.92-3.97 (m, 2H, H-3+H-5); 4.02-4.17 (m, 2H, H-2); 4.29 (d, \( J = 15.1 \) Hz, 1H, H-5); 4.66 (d, \( J = 15.9 \) Hz, 1H, H-7);
5.01 (d, J = 15.9 Hz, 1H, H-7); 6.48 (dd, J = 8.8 Hz, J = 4.5 Hz, 1H, Ar-H); 6.82-6.87 (m, 1H, Ar-H); 7.06-7.17 (m, 8H, Ar-H); 7.24-7.26 (m, 2H, Ar-H+CDCl<sub>3</sub>); 7.44 (d, J = 7.6 Hz, 1H, Ar-H); 7.73 (s, 1H, -NH (exchangeable with D<sub>2</sub>O))

13C NMR (100 MHz, CDCl<sub>3</sub>) δ: 14.2, 23.6, 33.9, 43.8, 48.4, 61.0, 62.4, 75.4, 106.1, 110.2 (d, J<sub>CF</sub> = 30.6Hz), 110.8, 112.2 (d, J<sub>CF</sub> = 100Hz), 114.1, 116.0 (d, J<sub>CF</sub> = 93.6 Hz), 117.9, 119.5, 121.7, 126.9, 127.0, 127.7, 128.8, 131.3, 135.0, 136.1, 138.9, 158.3, 172.7, 178.5. HRMS calcd for C<sub>30</sub>H<sub>28</sub>FN<sub>3</sub>O<sub>4</sub>[M+1]⁺ 514.2097, found 514.2073.

2-(3-Hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (10a)

Yield 32%; light brown solid; mp 92-94 °C; 1H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.13 (t, J = 7.1 Hz, 3H, H-1); 2.92 (d, J = 15.2 Hz, 1H, each H-4); 3.02 (d, J = 15.1 Hz, 1H, each H-4); 3.09 (s, 3H, -NCH<sub>3</sub>); 3.12-3.16 (dd, J = 15.1 Hz, J = 3.4 Hz, 1H, H-5); 3.43 (d, J = 15.1 Hz, 1H, each H-5); 3.91-3.93 (m, 1H, H-3); 3.97-4.09 (m, 3H, H-2+H-6); 4.25 (d, J = 15.1 Hz, 1H, H-6); 6.73 (d, J = 8.5 Hz, 1H, Ar-H); 7.03-7.14 (m, 3H, Ar-H); 7.29-7.32 (m, 2H, Ar-H); 7.43-7.48 (m, 2H, Ar-H); 7.79 (s, 1H, -NH(exchangeable with D<sub>2</sub>O)) 13C NMR (100 MHz, CDCl<sub>3</sub>) δ: 14.3, 23.7, 26.3, 49.1, 61.2, 61.3, 62.5, 75.4, 106.7, 109.4, 110.9, 118.1, 119.6, 121.8, 124.5, 127.1, 128.6, 129.6, 131.2, 131.7, 136.2, 142.3, 172.9, 177.6 HRMS calcd for C<sub>24</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>[M+1]⁺ 454.1489, found 454.1453, HRMS calcd for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub>[M+1]⁺ 420.1879, found 420.1861.

2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (10b)

Yield31%; light yellow solid; mp 104-106 °C, 1H NMR (500 MHz, CDCl<sub>3</sub>) δ: 1.16 (t, J = 7.1 Hz, 3H, H-1); 2.50 (dd, J = 15.2 Hz, J = 6.5 Hz, 1H, each H-4); 3.00 (d, J = 15.2 Hz, 1H, each H-4); 3.48-3.65 (m, 4H, H-3+H6+H-5); 3.97-4.08 (m, 2H, H-2); 4.38 (d, J = 14.7 Hz, 1H, H-6); 4.48 (d, J = 16.1 Hz, 1H, H-7); 5.20 (d, J = 16.1 Hz, 1H, H-7); 6.61 (d, J = 7.8 Hz, 1H, Ar-H); 6.70 (t, J = 7.6 Hz, 2H, Ar-H); 6.91 (t, J = 7.4 Hz, 1H, Ar-H); 7.06-7.14 (m, 5H, Ar-H); 7.21-
7.24 (m, 2H, Ar-H); 7.40 (d, \( J = 7.6 \) Hz, 1H, Ar-H); 7.49 (d, \( J = 7.1 \) Hz, 1H, Ar-H); 8.11 (s, 1H, -NH (exchangeable with D2O)) ¹³C NMR (125 MHz, CDCl3) \( \delta \): 14.2, 24.6, 43.9, 47.8, 60.7, 60.8, 62.5, 76.3, 105.8, 109.7, 110.9, 117.8, 119.1, 121.3, 123.2, 124.1, 126.6, 127.1, 127.4, 128.5, 129.8, 130.0, 132.1, 135.0, 143.6, 179.2 calcd for C₃₀H₂₉N₃O₄ [M+1]⁺ 496.2192, found 496.2161.

2-(5-Chloro-3-hydroxymethyl-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-\( \beta \)-carboline-3-carboxylic acid ethyl ester (10c):

Yield 32%, pale white solid, mp 88-90 °C ¹H NMR (400 MHz, CDCl₃) \( \delta \): 1.17 (t, \( J = 7.1 \) Hz, 3H, H-1); 2.92-2.97 (dd, \( J = 15.4 \) Hz, 5.9 Hz, 1H, each H-4); 3.06 (d, \( J = 14.8 \) Hz, 1H, each H-4); 3.10 (s, 3H, -NCH₃); 3.12-3.17 (dd, \( J = 15.4 \) Hz, \( J = 3.04 \) Hz, 1H, H-5); 3.39 (d, \( J = 14.7 \) Hz, 1H, each H-5); 3.91-3.92 (m, 1H, H-3); 3.99-4.14 (m, 3H, H-2+H-6); 4.25 (d, \( J = 15.0 \) Hz, 1H, H-6); 6.71 (d, \( J = 8.3 \) Hz, 1H, Ar-H); 7.04-7.13 (m, 2H, Ar-H); 7.27-7.30 (m, 2H, Ar-H); 7.42-7.46 (m, 2H, Ar-H); 7.81 (s, 1H, -NH(exchangeable with D₂O)) ¹³C NMR (100 MHz, CDCl₃) \( \delta \): 14.2, 23.8, 26.4, 49.0, 61.0, 61.3, 62.4, 75.3, 106.6, 109.4, 110.8, 119.5, 121.7, 124.9, 127.0, 128.5, 129.7, 131.1, 131.6, 136.1, 158.2, 172.8, 177.8 HRMS calcd for C₂₄H₂₄ClN₃O₄ [M+1]⁺ 454.1489, found 454.1453.

2-(1-Benzyl-5-chloro-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-\( \beta \)-carboline-3-carboxylic acid ethyl ester (10d)

Yield 32%, pale white solid, mp 82-84 °C ¹H NMR (400 MHz, CDCl₃) \( \delta \): 1.17 (t, \( J = 7.1 \) Hz, 3H, H-1); 2.57 (dd, \( J = 15.3 \) Hz, \( J = 6.0 \) Hz, 1H, each H-4); 3.04 (d, \( J = 15.2 \) Hz, 1H, H-4); 3.47 (d, \( J = 14.5 \) Hz, 1H, H-5); 3.55-3.68 (m, 2H, H-3+H-5); 3.96-4.11 (m, 3H, H-2+H-6); 4.35 (d, \( J = 14.9 \) Hz, 1H, each H-6); 4.49 (d, \( J = 16.1 \) Hz, 1H, H-7); 5.19 (d, \( J = 16.1 \) Hz, 1H, H-7); 6.51 (dd, \( J = 8.7 \) Hz, \( J = 4.3 \) Hz, 1H, Ar-H); 6.73 (t, \( J = 7.8 \) Hz, 2H, Ar-H); 6.83-6.94 (m, 2H, Ar-H); 7.04-7.15 (m, 4H, Ar-H); 7.21-7.25 (m, 2H, Ar-H); 7.39 (d, \( J = 7.5 \) Hz, 1H, Ar-H); 7.98 (s, 1H, -NH
(exchangeable with D$_2$O)) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 14.2, 24.5, 44.3, 48.7, 60.7, 60.8, 62.3, 76.4, 106.3, 110.9, 112.4, 116.4, 117.9, 119.2, 121.6, 126.5, 127.2, 127.7, 128.3, 131.4, 134.6, 136.5, 139.5, 158.2, 160.6, 172.8, 178.4 HRMS calcd for C$_{30}$H$_{28}$ClN$_3$O$_4$ [M+1]$^+$ 530.1802, found 530.1829.

2-(5-Fluoro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10e)

Yield 34%, pale white solid, mp 81-80 °C $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.16 (t, $J = 7.1$ Hz, 3H, H-1); 2.95-2.97 (dd, $J = 15.3$ Hz, 5.7 Hz, 1H, each H-4); 3.07 (d, $J = 15.1$ Hz, 1H, each H-4); 3.14 (s, 3H, -NCH$_3$); 3.14-3.18 (dd, $J = 15.3$ Hz, $J = 3.1$ Hz, 1H, H-5); 3.41 (d, $J = 14.9$ Hz, 1H, each H-5); 3.92-3.95 (m, 1H, H-3); 3.99-4.13 (m, 3H, H-2+H-6); 4.24 (d, $J = 15.2$ Hz, 1H, H-6); 6.72 (d, $J = 8.5$ Hz, 1H, Ar-H); 7.05-7.14 (m, 2H, Ar-H); 7.28-7.31 (m, 2H, Ar-H); 7.43-7.47 (m, 2H, Ar-H); 7.83 (s, 1H, -NH (exchangeable with D$_2$O)) 13C NMR (100 MHz, CDCl$_3$) $\delta$: 14.1, 23.8, 26.4, 49.5, 61.1, 61.3, 62.4, 75.3, 106.6, 109.4, 110.5 (d, $J_{CF} = 32.2$), 118.0 (d, $J_{CF} = 92.2$ Hz), 119.5, 121.3, 121.9, 127.0, 128.5, 129.7, 131.3, 131.6, 136.4, 158.2, 172.3, 177.4 HRMS calcd for C$_{24}$H$_{24}$FN$_3$O$_4$ [M+1]$^+$ 514.2097, found 514.2073.

2-(1-Benzyl-5-fluoro-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10f)

Yield 32%, pale white solid, mp 118-120 °C $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.15 (t, $J = 7.1$ Hz, 3H, H-1); 2.55 (dd, $J = 15.3$ Hz, $J = 6.0$ Hz, 1H, each H-4); 3.02 (d, $J = 14.5$ Hz, 1H, H-5); 3.42 (d, $J = 14.5$ Hz, 1H, H-5); 3.53-3.61 (m, 2H, H-3+H-4); 3.95-4.10 (m, 3H, H-2+H-6); 4.34 (d, $J = 14.8$ Hz, 1H, each H-6); 4.46 (d, $J = 16.1$ Hz, 1H, H-7); 5.14 (d, $J = 16.0$ Hz, 1H, H-7); 6.49 (dd, $J = 8.5$ Hz, $J = 4.0$ Hz, 1H, Ar-H); 6.72 (t, $J = 7.6$ Hz, 2H, Ar-H); 6.82-6.93 (m, 2H, Ar-H); 7.02-7.13 (m, 4H, Ar-H); 7.20-7.23 (m, 2H, Ar-H); 7.38 (d, $J = 7.4$ Hz, 1H, Ar-H); 7.97 (s, 1H, -NH (exchangeable with D$_2$O)) 13C NMR (125 MHz, CDCl$_3$) $\delta$: 14.2, 24.4, 44.1, 48.0, 60.9, 60.9,
62.5, 76.3, 106.1, 110.3 (d, $J_{CF} = 31.2$ Hz), 110.8, 112.2 (d, $J_{CF} = 98.6$ ), 115.9 (d, $J_{CF} = 93.8$), 117.8, 119.3, 121.5, 126.6, 127.1, 127.6, 128.7, 131.7, 134.7, 136.1, 139.4, 158.2, 160.7, 172.8, 178.6 HRMS calcd for C$_{30}$H$_{28}$FN$_3$O$_4$ [M+1]$^+$ 514.2097, found 514.2073.

1-3-hydroxymethyl-3-methoxy-1,3dihydro-indol-2-one (11)

![Chemical structure image]

White solid, yield 89%, mp = 99-102 °C, $^1$H NMR (400MHz, CDCl$_3$) δ: 3.11 (s, 3H, -OCH$_3$), 3.90 ( dd, $J = 11.4$ Hz, 15.4 Hz, 2 H, -CH$_2$OH), 4.91 (s, 2H, -CH$_2$Ph), 6.73 ( d, $J = 7.8$ Hz, 1H, Indole H-7), 7.07 (t, $J = 7.36$ Hz, 1H, H-5), 7.21-7.31 (m, 6H, Ar-H), 7.37 (d, $J = 7.16$ Hz, 1H, Indole H-4)$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 43.6, 53.3, 66.7, 82.5, 109.6, 123.2, 124.90, 124.98 127.1, 127.7, 128.8, 130.2, 135.3, 143.3, 175.0 HRMS calcd for C$_{17}$H$_{17}$NO$_3$ [M+1]$^+$ 284.1242, found 284.1225.
Scanned $^1$H and $^{13}$C NMR spectra of representative compounds

Figure S1: $^1$H NMR of 9-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8a)
Figure S2: $^{13}$C NMR of 9-(3-Hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8a)
Figure S3: $^1$H NMR of 9-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8b)
Figure S4: $^{13}$C NMR of 9-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8b)
Figure S5: $^1$H NMR of 9-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8c)
Figure S6: $^{13}$C NMR of 9-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8c)
Figure S7: $^1$H NMR of 9-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-β-carboline-3-carboxylic acid ethyl ester (8f)
Figure S8: $^{13}$C NMR of 9-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-9H-$\beta$-carboline-3-carboxylic acid ethyl ester (8f)
Figure S9: $^1$H NMR of major isomer of 2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9b)
Figure S10: $^{13}$C NMR of major isomer of 2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9b)
Figure S11: Expansion of $^{13}$C NMR of 2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9b)

Figure S12: DEPT of 2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9b)
Figure S13: Expansion of DEPT of 2-(1-Benzyl-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-\(\beta\)-carboline-3-carboxylic acid ethyl ester (9b)

Figure S14: 1H NMR of 2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-\(\beta\)-carboline-3-carboxylic acid ethyl ester (10b)
Figure S15: $^{13}$C NMR of major isomer of 2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10b)
Figure S16: Expansion of $^{13}$C NMR of 2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10b)

Figure S17: DEPT of 2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10b)
Figure S18: Expansion of DEPT of 2-(1-Benzyl-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (10b)
Figure S19: $^1$H NMR of major isomer of 2-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9f)

Figure S20: $^{13}$C NMR of major isomer of 2-(1-Benzyl-5-fluoro-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (9f)
Figure S21: $^1$H NMR of major isomer of 2-(1-Benzyl-5-fluoro-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10f)
Figure S22: $^{13}$C NMR of major isomer of 2-(1-Benzyl-5-fluoro-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10f)

Figure S23: Expansion of $^{13}$C NMR of 2-(1-Benzyl-5-fluoro-3-hydroxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-2,3,4,9-tetrahydro-1H-$\beta$-carboline-3-carboxylic acid ethyl ester (10f)
Figure S24: $^1$H NMR of major isomer of 2-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9c)
Figure S25: $^{13}$C NMR of major isomer of 2-(5-Chloro-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-ylmethyl)-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylic acid ethyl ester (9c)
Figure S26: $^1$H NMR of 1-3-hydroxymethyl-3-methoxy-1,3dihydro-indol-2-one (11)
Figure S27: $^{13}$C NMR of 1,2-hydroxymethyl-3-methoxy-1,3-dihydro-indol-2-one (11):
Figure S28 Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 8a, 8b, and 8c. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed $P < 0.0001 (***)$ significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed $P < 0.005 (**)$ significance for MCF-7 cells and $P < 0.0001 (***)$ significance for MDA-MB 231 cells across all compounds. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where $^* p \leq 0.05$, $^{**} p \leq 0.01$ and $^{***} p \leq 0.001$ show significant difference.
Figure S29 Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 8a, 8b, and 8c. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed P < 0.0001 (*** ) significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed P < 0.005 (** ) significance for MCF-7 cells and P < 0.01 (*) significance for MDA-MB 231 cells for compound 8d. This was different for compounds 8e and 8f, where the Bartlett’s test for equal variance showed P < 0.0001 (*** ) for both MCF-7 and MDA-MB 231 cells. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where *p ≤ 0.05, **p ≤ 0.01 and ***p ≤ 0.001 show significant difference.
Figure S30 Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 9a, 9b, and 9c. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed P < 0.0001 (***). significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed P < 0.0001 (***). significance for both MCF-7 and MDA-MB 231 cells across all compounds. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where *p ≤ 0.05, **p ≤ 0.01 and ***p ≤ 0.001 show significant difference.
Figure S31 Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 9a, 9b, and 9c. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed P < 0.0001 (***), significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed P < 0.0001 (***), significance for both MCF-7 and MDA-MB 231 cells across all compounds. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where *p ≤ 0.05, **p ≤ 0.01 and ***p ≤ 0.001 show significant difference.
Figure S32 Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 9d, 10d, and 9e. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed P < 0.0001 (***') significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed P < 0.0001 (***') significance for both MCF-7 and MDA-MB 231 cells across all compounds. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where *p ≤ 0.05, **p ≤ 0.01 and ***p ≤ 0.001 show significant difference.
**Figure S33** Graph comparing the percentage cell death of MCF-7 and MDA-MB 231 cells at selected concentrations of test compounds 10e, 9f, and 10f. 40 µM Plumbagin was used as a positive control. Data are mean ± standard deviation S.D. (n=6). A one-way ANOVA analysis showed P < 0.0001 (***), significance for both MCF7 and MDA-MB-231. Furthermore, the Bartlett’s test for equal variance showed P < 0.0001 (***), significance for both MCF-7 and MDA-MB 231 cells across all compounds. Post hoc analysis (Dunnett’s multiple comparison test) was performed to compare significance of treated samples to the untreated samples, where *p ≤ 0.05, **p ≤ 0.01 and ***p ≤ 0.001 show significant difference.