Small molecule inhibitors of Gli transcriptional factors of the Hedgehog Signalling Pathway

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   h. Compound characterisation, 1H, 13C NMR and IR spectra.
**Biology**

Dual Luciferase Reporter Assay results for Tryptophan derivatives (Table 1)

![Graph 1](image1.png)

Figure S1. The relative total Gli protein expression in Shh LIGHT 2 cells after treatment with 100 nM SAG and subsequent treatment with 10 μM 4, 11-17. Sonidegib at 100 nM was used as the positive control. * P < 0.05, **P < 0.001, *** P < 0.0001 compared to SAG treatment. All experiments were performed in triplicate.

![Graph 2](image2.png)

Figure S2. The suppression of Gli protein expression in 100nM SAG-activated Shh LIGHT2 cells by L- and D-Tryptophan analogues 14 and 14a at 10 μM, respectively. Sonidegib (100 nM) was used as the positive control. All experiments were performed in triplicate. **P < 0.001, ***P < 0.0001 compared to SAG treatment.

**SHH Light II cells**  
*(24hr treatment with Recombinant SHH)*

![Western Blot Analysis](image3.png)

Figure S3. Western blotting analysis identifying the presence of Gli1 in adult mouse testes, but its absence on treatment (red box); (B) presence of Ptc1 (treated and untreated); and (C) presence of Sufu (treated and untreated).
Reverse phase and chiral separation of L– and D–Tryptophan derivatives

Figure S4. The HPLC chromatograms (A) reverse phase HPLC analysis of a mixture of 14 and 14a; (B) chiral column HPLC analysis of 14 prepared from L-Tryptophan; (C) chiral column HPLC analysis of 14a prepared from D-Tryptophan; (D) chiral column HPLC analysis of a mixture of 14 and 14a.
Amide rotamer of benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives

Figure S5. A) $^1$H NMR (A) and (B) $^{13}$C NMR spectra of analogue 5 highlighting the presence of duplicative peaks.
Figure S6. Variable-temperature NMR experiment with analogue 5 at 30, 35, 40, 45, and 50 °C. Arrows indicated the splitting (red arrows) merging into individual peaks (black arrows) when increasing the temperatures from 30 to 50 °C. Displayed is the aliphatic region of the $^1$H NMR in DMSO-$d_6$.

**1D selective NOSEY NMR Experiment**

Figure S7. 1D selective NOSEY and $^1$H NMR spectra of analogue 5. The irradiation at the peak at 6.04 ppm results in two peaks at the same phase at 6.04 and 5.96 ppm which correspond to $H_A$ and $H_B$, respectively. Other peaks are not visible.
Figure S8. Chiral HPLC analysis of amide rotamer analogue 5.

Figure S9. The relative total Gli protein expression in Shh LIGHT 2 cells after treatment with 100 nM SAG and subsequent treatment with 10 µM 7 (A) and 23-28 (B). Sonidegib at 100 nM was used as the positive control. * P < .05, **P < .001, *** P < .0001 compared to SAG treatment. All treatments were performed in triplicate.

Figure S9. IC₅₀ curves for analogues 27 and 28.
### Compound Characterization

**Synthesis of L-tryptophan derivatives (4, 11–17)**

Table S1. Isolated yields, $^1$H NMR featuring the ABX systems and the diastereotopic protons, and base cations in HRMS [M+H]$^+$ of L-Tryptophan derivatives (4, 11–17). *Reagents and conditions: (i) 1.5 eq. HATU, 3eq. DIPEA (Table 1)*

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>$^1$H NMR Proton-X (ppm)</th>
<th>Diastereotopic protons (ppm)</th>
<th>HRMS [M+H]$^+$ (m/z)</th>
</tr>
</thead>
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<td><img src="image" alt="R" /></td>
<td><img src="image" alt="R'" /></td>
<td>18</td>
<td>(dd*, $J_{AB} = 22.8$, $J_{AC} = 14.4$, $J_{a} = 7.2$ Hz, 2H)</td>
<td>4.59</td>
<td>(dd, $J = 14.4$, 8.1 Hz, 1H)</td>
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<td><img src="image" alt="R" /></td>
<td><img src="image" alt="R'" /></td>
<td>22</td>
<td>(dd, $J_{AB} = 22.3$, $J_{AC} = 14.4$, $J_{a} = 7.1$ Hz, 2H)</td>
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<td>(dd, $J = 14.4$, 7.9 Hz, 1H)</td>
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<td><img src="image" alt="R" /></td>
<td><img src="image" alt="R'" /></td>
<td>18</td>
<td>(dd, $J_{AB} = 22.8$, $J_{AC} = 14.4$, $J_{a} = 7.3$ Hz, 2H)</td>
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<td>(dd, $J = 14.4$, 8.2 Hz, 1H)</td>
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<td><img src="image" alt="R" /></td>
<td><img src="image" alt="R'" /></td>
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<td>(dd, $J_{AB} = 28.6$, $J_{AC} = 14.6$, $J_{a} = 5.2$ Hz, 2H)</td>
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<td><img src="image" alt="R'" /></td>
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<td>(dd, $J_{AC} = 36.4$, $J_{a} = 5.2$ Hz, 2H)</td>
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<td>(dd, $J = 9.3$, 5.2 Hz, 1H)</td>
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<td><img src="image" alt="R'" /></td>
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<td>(dd, $J = 9.3$, 4.8 Hz, 1H)</td>
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<td><img src="image" alt="R'" /></td>
<td>39</td>
<td>3.22 – 3.07 (m, 2H) overlapping</td>
<td>4.81</td>
<td>(dd, $J = 8.6$, 6.0 Hz, 1H)</td>
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</table>
Synthesis of benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives

**Table S2.** Isolated yields, and base cations in HRMS [M+H]+ of benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives 5, 20-29.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>Isolated yields (%)</th>
<th>HRMS (ES') m/z [M+H]⁺</th>
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<td><img src="structure29.png" alt="Structure" /></td>
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<td>438.1812</td>
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Table S3. Percentage inhibition of Gli protein expression in 100 nM SAG-activated Shh LIGHT2 cells by L-Tryptophan analogues 4 and 11-17 at 10 μM compound concentration and cLogP values.

<table>
<thead>
<tr>
<th>Rᵢ</th>
<th>Inhibition (%)ᵃ</th>
<th>cLogP</th>
<th>Rᵢ</th>
<th>Inhibition (%)ᵃ</th>
<th>cLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>66</td>
<td>4.84</td>
<td>14 [14a; D-isomer]</td>
<td>86 [99]</td>
<td>2.72</td>
</tr>
<tr>
<td>11</td>
<td>83</td>
<td>4.84</td>
<td>15</td>
<td>71</td>
<td>4.77</td>
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<tr>
<td>12</td>
<td>-38</td>
<td>4.84</td>
<td>16</td>
<td>-105</td>
<td>4.99</td>
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<tr>
<td>13</td>
<td>64</td>
<td>4.28</td>
<td>17</td>
<td>26</td>
<td>4.46</td>
</tr>
</tbody>
</table>

*Inhibition calculated as Gli signal (SAG) – Gli Signal (SAG+Compound).

Table S4. Percentage inhibition of Gli expression in 100 nM SAG-activated Shh LIGHT2 cells by benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives analogues 5 and 20-26 at 10 μM compound concentration and cLogP values.

<table>
<thead>
<tr>
<th>Rᵢ</th>
<th>Inhibition (%)ᵃ</th>
<th>cLogP</th>
<th>Rᵢ</th>
<th>Inhibition (%)ᵃ</th>
<th>cLogP</th>
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<td>89</td>
<td>5.23</td>
<td>23</td>
<td>102</td>
<td>4.73</td>
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<td>20</td>
<td>111</td>
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<td>92</td>
<td>4.12</td>
<td>25</td>
<td>108</td>
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<td>22</td>
<td>84</td>
<td>3.55</td>
<td>26</td>
<td>-16</td>
<td>2.68</td>
</tr>
</tbody>
</table>
Table S3. Percentage inhibition of Gli protein expression in 100 nM SAG-activated Shh LIGHT2 cells by L-Tryptophan analogues 4 and 11-17 at 10 μM compound concentration.

<table>
<thead>
<tr>
<th>R₁</th>
<th>Inhibition (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cLogP</th>
<th>R₁</th>
<th>Inhibition (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
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<td>4.84</td>
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<td>86 [99]</td>
<td>2.72</td>
</tr>
<tr>
<td>11</td>
<td>83</td>
<td>4.84</td>
<td>15</td>
<td>71</td>
<td>4.77</td>
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<td>12</td>
<td>-38</td>
<td>4.84</td>
<td>16</td>
<td>-105</td>
<td>4.99</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>4.28</td>
<td>17</td>
<td>26</td>
<td>4.46</td>
</tr>
</tbody>
</table>

<sup>a</sup>Inhibition calculated as Gli signal (SAG) – Gli Signal (SAG+Compound).

Table S4. Percentage inhibition of Gli expression in 100 nM SAG-activated Shh LIGHT2 cells by benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amine derivatives analogues 5 and 20-26 at 10 μM compound concentration.

<table>
<thead>
<tr>
<th>R₁</th>
<th>Inhibition (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cLogP</th>
<th>R₁</th>
<th>Inhibition (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>cLogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>89</td>
<td>5.23</td>
<td>23</td>
<td>102</td>
<td>4.73</td>
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<tr>
<td>20</td>
<td>111</td>
<td>3.18</td>
<td>24</td>
<td>67</td>
<td>5.29</td>
</tr>
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<td>21</td>
<td>92</td>
<td>4.12</td>
<td>25</td>
<td>108</td>
<td>5.44</td>
</tr>
<tr>
<td>22</td>
<td>84</td>
<td>3.55</td>
<td>26</td>
<td>-16</td>
<td>2.68</td>
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### Table S5. Primer sequences used in qPCR assay.

<table>
<thead>
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<th>Human gene</th>
<th>Forward Sequence (5’-3’)</th>
<th>Reverse Sequence (5’-3’)</th>
<th>Annealing Temp (°C)</th>
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</thead>
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<tr>
<td>Gli₂</td>
<td>ATCTCTTGCCACCATTCAT</td>
<td>GGACAGAATGAGGCTCGTAA</td>
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<tr>
<td>Smo</td>
<td>CTGCCACTTCTACGACTTCT</td>
<td>GGCCTGACATAGCAGCATAGT</td>
<td>56</td>
</tr>
<tr>
<td>SuFu</td>
<td>GACCCCTTGGACTATGTTAG</td>
<td>CTagATGATGCGAGTCAGTCGTC</td>
<td>55</td>
</tr>
<tr>
<td>Ptch₁</td>
<td>CCCTCACGTCATCCAGCAAT</td>
<td>AACACCCTACTACCCGCTGC</td>
<td>58</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mouse gene</th>
<th>Forward Sequence (5’-3’)</th>
<th>Reverse Sequence (5’-3’)</th>
<th>Annealing Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gli₂</td>
<td>TCCAGTCAATGGTCTGTCC</td>
<td>TGGCTCAGCATCGTCACCTTC</td>
<td>60</td>
</tr>
<tr>
<td>Gli₃</td>
<td>GGCCTGTACCATTATGATCC</td>
<td>CTGAGGCTGCAGTGAGTAGA</td>
<td>60</td>
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<tr>
<td>Shh</td>
<td>TGCTTTGTAAACCCTGGCTT</td>
<td>CGCTGCTAGGTGCACTTTTA</td>
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<tr>
<td>Smo</td>
<td>GAACCTCAATCGCTACCCTGT</td>
<td>ATCTGCTCGGCAAAATCTG</td>
<td>60</td>
</tr>
<tr>
<td>SuFu</td>
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<td>CTagATGATGCGAGTCAGTCGTC</td>
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<tr>
<td>Ptch₁</td>
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<td>GGTCTGAAGTAGGCTGCTGG</td>
<td>55</td>
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</tbody>
</table>

**N-(4-Chlorobenzyl)-2-[2-(3,4-dichlorophenyl)-acetylamino]-3-(1H-indol-3-yl)-propionamide (4)**

Yield: 182 mg, 35%. MP 208 – 209 °C;
IR: νmax/cm⁻¹ 3410 (NH), 3277 (NH), 3068 (CH), 1636 (CON);
¹H NMR (400 MHz, DMSO-d₆) δ 10.84 (s, 1H), 8.56 (s, J = 5.9 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.16 – 7.02 (m, 5H), 6.97 (t, J = 7.1 Hz, 1H), 4.59 (dd, J = 14.4, 8.1 Hz, 1H), 4.24 (qd, J = 15.6, 5.9 Hz, 2H), 3.47 (s, 2H), 3.05 (dd, J₆₋₇ = 22.8, J₇₋₈ = 14.4, J₈₋₉ = 7.2 Hz, 2H);
¹³C NMR (101 MHz, DMSO-d₆) δ 191.9, 169.6, 138.7, 138.6, 136.8, 131.6, 131.5, 131.0, 130.6, 129.7, 129.4, 129.2 (Cₓ2), 128.5 (Cₓ2), 127.7, 124.2, 121.4, 119.0, 118.7, 111.8, 110.4, 54.2, 41.8, 41.2, 28.5;
RP-HPLC Alltima™ C18 5 μm 150 μm x 4.6 mm, 10–100% B in 15 min, Rₜ = 14.31 min, 100%;
LRMS (ESI⁺) m/z: 513, 514 [M+H]⁺, 95%. HRMS (ESI⁺) for C₂₉H₂₃Cl₂N₉O₃S, calculated 514.0850, found 514.08498.
N-(4-Chlorobenzyl)-2-[2-(2,4-dichlorophenyl)-acetylamino]-3-(1H-indol-3-yl)-propionamide (II)

Yield: 55 mg, 24%. MP 207-208 °C;
IR: νmax/cm⁻¹ 3410 (NH), 3280 (NH), 3065 (CH), 1642 (CON);

¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (s, 1H), 8.54 (t, J = 5.9 Hz, 1H), 8.40 (d, J = 8 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.33 – 7.2 3H), 7.12 (ddd, J = 22.2, 12.5, 7.8 Hz, 5H), 6.98 (t, J = 7.4 Hz, 1H), 4.63 (dd, J = 14.3, 8 1H), 4.25 (qd, J = 15.5, 5.9 Hz, 2H), 3.60 (s, 2H), 3.07 (ddd, J₆= 22.9, J₇= 14.4, J₈= 7.2 Hz, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 171.9, 168.9, 138.8, 136.6, 135.0, 133.9, 133.3, 132.3, 131.6, 129.3 (Cx2), 128.5 (Cx2) 127.7, 127.4, 124.2, 121.3, 119.0, 118.7, 111.7, 110.4, 54.2, 41.8, 31.0, 28.5;
RP-HPLC Alltima™ C18 5 µm 150 mm x 4.6 mm, 10–100% B in 15 min, Rᵣ =14.38 min, 99.2%;
LRMS (APCI⁺) m/z 513, 514 [M+H]+ 50%. HRMS (ES⁺) for C₂₅H₁₂Cl₃N₃O₂, calculated 514.0850, 514.0850.
N-(4-Chlorobenzyl)-2-[2-(2,6-dichlorophenyl)-acetylamino]-3-(1H-indol-3-yl)-propionamide (14)

Yield: 80 mg, 40%. MP 265-256 °C;
IR: νmax/cm⁻¹ 3410 (NH), 3292 (NH), 3252 (NH), 1641 (CON);

¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (s, 1H), 8.49 (t, J = 6.0 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.1 Hz, 1H), 7.28 (ddd, J = 8.6, 4.7, 2.5 Hz, 3H), 7.13 (d, J = 2.2 Hz, 1H), 7.11 - 7.03 (m, 3H), 7.00 - 6.94 (m, 1H), 4.60 (dd, J = 14.4, 7.9 Hz, 1H), 4.24 (qd, J = 15.5, 5.9 Hz, 2H), 3.84 (q, J = 16.3 Hz, 2H), 3.07 (ddd, Jₓₓ = 22.3, Jₓᵧ = 14.4, Jᵧᵧ = 7.1 Hz, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 171.9, 167.8, 138.7, 136.5, 136.0 (Cx2), 133.1, 131.6, 129.6, 129.2 (Cx2), 128.5 (Cx2), 127.8, 124.1, 121.3, 118.9, 118.7, 111.7, 110.4, 54.3, 41.8, 37.9, 28.6;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10-100% B in 15 min, Rt = 6.54 min, 100%;
LRMS (ESI⁺) m/z 513, 514 [M+H]⁺ 95%. HRMS (ESI⁺) for C₂₅H₂₂Cl₂N₂O₅, calculated 514.0850, found 514.08496.
N-(4-Chlorobenzyl)-2-[2-(4-chlorophenyl)acetylamino]-3-(1H-indol-3-yl)propionamide (13)

Yield: 60 mg, 32%. MP 205.2-206.3 °C;
IR: νmax/cm⁻¹ 3410 (NH), 3292 (NH), 3061 (CH), 1635 (CON);

¹H NMR (400 MHz, DMSO-d₆) δ 10.84 (s, 1H), 8.55 (t, J = 5.9 Hz, 1H), 8.38 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.32 – 7.21 (m, 4H), 7.16 – 7.01 (m, 1H), 6.90 (m, 1H), 4.59 (td, J = 14.4, 8.2 Hz, 1H), 4.23 (qd, J = 15.5, 5.9 Hz, 2H), 3.44 (dd, J = 19.8, 14.4 Hz, 2H), 3.05 (ddd, Jₓₓ = 22.8, Jₓᵧ = 14.4, Jᵧᵧ = 7.3 Hz, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 172.0, 170.0, 138.7, 136.6, 135.8, 131.6, 131.4, 131.3 (Cₓ₂), 129.2 (Cₓ₂), 128.4 (Cₓ₂), 127.7, 124.2, 121.4, 119.0, 118.7, 111.7, 110.4, 54.1, 41.8, 41.7, 28.5;

RP-HPLC Altima™ C18 5μm 150 mm x 4.6 mm, 10–100% B in 15 min, R₁ = 13.69 min, 100%;
LRMS (ESI⁺) m/z 479, 480 [M+H]⁺, 100%; HRMS (ESI⁺) for C₂₅H₂₁Cl₂N₂O₂, calculated 480.1240, found 480.12396.
1H-Indole-2-carboxylic acid [1-(4-chlorobenzylcarbamoyl)-2-[(1H-indol-3-yl)-ethyl]-amide (14, L-isomer)

Yield: 97 mg, 50%. MP 229.5-230.7 °C;
IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) 3422 (NH), 3381 (NH), 3316 (NH), 1630 (CON);
\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 11.53 (s, 1H), 10.80 (s, 1H), 8.70 (t, \( J = 6.0 \) Hz, 1H), 8.57 (d, \( J = 8.1 \) Hz, 1H), 7.71 (d, \( J = 7.8 \) Hz, 1H), 7.62 (d, \( J = 8.0 \) Hz, 1H), 7.41 (d, \( J = 8.2 \) Hz, 1H), 7.33 (dd, \( J = 7.7, 5.5 \) Hz, 3H), 7.25 - 7.14 (m, 5H), 7.09 - 6.96 (m, 3H), 4.80 (ddd, \( J = 9.2, 8.4, 5.2 \) Hz, 1H), 4.31 (dd, \( J = 15.96, 6.0 \) Hz, 2H), 3.24 (ddd, \( J_{AX} = 28.6 \) Hz, \( J_{AX} = 14.56 \) Hz, \( J_{AB} = 5.2 \) Hz, 2H);
\(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \( \delta \) 172.3, 161.5, 138.9, 136.9, 136.5, 131.7, 129.3 (Cx2), 128.6 (Cx2), 127.7, 127.5, 124.3, 123.8, 122.0, 121.4, 120.2, 119.0, 118.7, 112.7, 111.8, 110.8, 103.8, 54.5, 41.9, 28.2;
RP-HPLC Alltima™ C18 5 \( \mu \)m 150 mm x 4.6 mm, 10–100% B in 15 min, \( t_r = 13.35 \) min, 100%;
LRMS (APCI\(^+\)) m/z 470, 471 [M+1H]\(^+\), 90%; HRMS (ES\(^+\)) for \( C_{27}H_{35}ClN_4O_2 \) calculated 471.1582, found 471.1582.
**1H-Indole-2-carboxylic acid [1-(4-chlorobenzylcarbamoyl)-2-(1H-indol-3-yl)-ethyl]-amide (14a, D-isomer)**

Yield: 156 mg, 48%. MP 227-227.5 °C;

IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) 3420 (NH), 3382 (NH), 3325 (NH), 1630 (CONH), 1656 (CON), 737 (CH-aromatics);

\(^{1}\text{H}\) NMR (400 MHz, DMSO-\(d_6\)) \& 11.53 (s, 1H), 10.81 (d, \( J = 1.6 \) Hz, 1H), 8.71 (t, \( J = 6.0 \) Hz, 1H), 8.58 (d, \( J = 8.1 \) Hz, 1H), 7.72 (d, \( J = 7.8 \) Hz, 1H), 7.63 (d, \( J = 8.0 \) Hz, 1H), 7.45 - 7.39 (m, 1H), 7.37 - 7.30 (m, 3H), 7.26 - 7.14 (m, 5H), 7.11 - 6.95 (m, 3H), 4.82 (ddd, \( J = 9.2, 8.4, 5.2 \) Hz, 1H), 4.32 (dd, \( J = 16.4, 6.0 \) Hz, 2H), 3.23 (ddd, \( J_{AX} = 28.8 \) Hz, \( J_{BX} = 14.4 \) Hz, \( J_{AB} = 9.2 \) Hz, 2H);

\(^{13}\text{C}\) NMR (101 MHz, DMSO-\(d_6\)) \& 172.3, 161.5, 138.9, 136.9, 136.6, 131.8, 131.7, 129.3 (2C), 128.6 (2C), 127.7, 127.5, 124.3, 123.8, 122.0, 121.4, 120.2, 119.0, 118.7, 112.7, 111.8, 110.8, 103.9, 54.5, 42.0, 28.2;

RP-HPLC Altima™ C18 5 \( \mu \)m 150 mm x 4.6 mm, 10-100% B in 15 min, \( R_t = 6.44 \) min, 100%;

LRMS (ESI\(^{+}\)) m/z 470, 470 [M+H]\(^{+}\), 80%. HRMS (ESI\(^+\)) for C\(_{22}\)H\(_{20}\)ClN\(_3\)O\(_2\) calculated 471.1582, found 471.1584.
Naphthalene-1-carboxylic acid [1-(4-chlorobenzylcarbamoyl)-2-[(3H-indol-3-yl)-ethyl]amide (15)

Yield: 57 mg, 41%. MP 165.7-166.5 °C;

IR: v_{max}/cm^{-1} 3398 (NH), 3268 (bp NH), 3049 (CH), 1627 (CON), 739 (CH-aromatics);

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 10.89 (s, 1H), 8.73–8.67 (m, 2H) (overlapping two NH amides), 8.02 – 7.86 (m, 3H), 7.74 (d, \(J = 7.8\) Hz, 1H), 7.57 – 7.47 (m, 3H), 7.47 – 7.32 (m, 4H), 7.27 (d, \(J = 8.5\) Hz, 3H), 7.11 (dd, \(J = 11.1, 3.9\) Hz, 1H), 7.02 (dd, \(J = 11.0, 3.9\) Hz, 1H), 4.93 (dt, \(J = 9.3, 5.2\) Hz, 1H), 4.37 (ddd, \(J = 16.0, 6.0\) Hz, 2H), 3.23 (ddd, \(J_{\text{AX}} = 36.4, J_{\text{EX}} = 14.4, J_{\text{AX}} = 5.2\) Hz, 2H);

\(^{13}\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 172.3, 169.0, 139.0, 136.7, 135.0, 133.5, 131.7, 130.2 (Cx2), 129.4(Cx2), 128.6 (Cx3), 127.8, 126.9, 126.6, 126.0, 125.8, 125.3, 124.4, 121.4, 119.1, 118.7, 111.8, 110.7, 54.8, 42.0, 28.1;

RP-HPLC Alliita\textsuperscript{TM} C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 13.62 min, 99.1%;

LRMS (APCI\textsuperscript{+}) m/z 481, 482 [M+H\textsuperscript{+}], 90%. 1H RIMS (ES\textsuperscript{+}) for C\textsubscript{24}H\textsubscript{22}ClN\textsubscript{3}O\textsubscript{2}, calculated 482.1630, found 482.1630.
4-Benzoyl-N-[1-(4-chlorobenzylcarbamoyl)-2-(1H-indol-3-yl)-ethyl]-benzamide (16)

Yield: 120 mg, 45%. MP 202 – 202.5 °C;

IR: νₘᵋₑₑ cm⁻¹ 3440 (NH), 3304 (NH), 1662 (CO), 1632 (CON), 743 (CH-aromatics);

¹H NMR (400 MHz, DMSO-d₆) δ 10.80 (s, 1H), 8.80 (d, J = 8.0 Hz, 1H), 8.68 (t, J = 4.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.81 – 7.66 (m, 6H), 7.58 (t, J = 7.6 Hz, 2H), 7.33 (dd 8.2, 3.5 Hz, 3H), 7.21 (dd, J = 9.2, 5.3 Hz, 3H), 7.03 (dt, J = 30.0, 7.0 Hz, 2H), 4.81 (td, J = 4.4 Hz, 1H), 4.37 – 4.23 (m, 2H), 3.25 (ddd, Jₓₓ = 45 Hz, Jₓᵧ = 14.9 Hz, Jᵧᵧ = 4.8 Hz, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 195.9, 172.1, 166.0, 139.7, 138.9, 137.8, 137.1, 136.6, 133.5, 131.7, 130.2 (t 129.8 (Cx2), 129.3 (Cx2), 129.1 (Cx2), 128.6 (Cx2), 128.2 (Cx2), 127.7, 124.2, 121.4, 119.0, 118.7, 111.8, 110.8, 42.0, 28.0;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rₜ = 14.14 min, 100%;

LRMS (APCI⁺) m/z 535, 536 [M+H]⁺, 20%. HRMS (ES⁺), for C₃₇H₂₉ClN₃O₅, calculated 536.1735, found 536.1735.
N-[1-((4-Chlorobenzylocarbamoyl)-2-(1H-indol-3-yl)-ethyl]-3,3-trifluoro-2-methoxy-2-phenyl-propionamide (17)

Yield: 171 mg, 71%, MP 171 – 172 °C;

IR: νmax/cm⁻¹ 3310 (bp, NH), 2925 (CH), 1657(CON), 741 (CH-aromatics);

¹H NMR (400 MHz, DMSO-d₆) δ 10.82 (s, 1H), 8.70 (t, J = 5.9 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.30 – 7.18 (m, 4H), 7.13 – 7.01 (m, 3H), 7.01 – 6.90 (m, 2H), 4.81 (t, J = 8.6, 6.0 Hz, 1H), 4.32 (qd, J = 15.4, 5.8 Hz, 2H), 3.27 (s, 3H), 3.22 – 3.07 (m, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 171.4, 165.6, 138.6, 136.6, 132.8, 131.8, 129.8, 129.4 (Cx4), 128.7 (Cx2), 128.6 (Cx4), 127.8, 124.4, 121.4, 119.0, 118.7, 111.7, 109.9, 84.4, 84.2, 83.9, 83.7, 55.2, 53.8, 42.0, 28.1. Note: CF₃ splitting at 84.0 (q, J = 25.2 Hz) and presented in italics;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rf = 14.53 min, 100%

LRMS (APCI⁺) m/z 543, 544 [M+ H]⁺, 50%. HRMS (ES⁺) for C₂₅H₂₂ClF₃N₅O₂, calculated 543.1646, found 544.16105
**N-(1,3-Benzodioxol-4-ylmethyl)-N-[2-(1H-indol-3-yl)ethyl]-napthalene carboxamide (18)**

Yield: 110 mg, 67%, MP 199 – 200°C;

IR: νmax/cm⁻¹ 3215 (NH), 1608 (CON), 743 (CH-aromatics);

*Proton and carbon spectra displays an atropoisomeric property of compound 5, with the approximate ratio 1:0.66 calculated based on the proton benzodioxole CH₂ peaks at 6.05 and 5.97 ppm, respectively.*

1H NMR (400 MHz, DMSO-d₆) δ 10.91 (s, 0.67H), 10.71 (s, 1H), 8.07 – 7.89 (m, 3.33H), 7.75 – 7.64 (m, 1H), 7.64 – 7.44 (m, 7H), 7.42 – 7.16 (m, 3.3H), 7.14 – 7.06 (m, 1.67H), 7.06 – 6.78 (m, 5.33H), 6.71 – 6.56 (m, 2.33H), 6.39 (d, J = 7.9 Hz, 1H), 6.05 (s, 2H), 5.97 (s, 1.33H), 5.01 – 4.70 (m, 2H), 4.26 – 4.02 (m, 2H), 3.43 (d, J = 20.9 Hz, 0.67H), 3.26 – 2.98 (m, 3.33H), 2.91 – 2.66 (m, 2H);

13C NMR (101 MHz, DMSO-d₆) δ 170.4, 170.0, 148.0, 148.0, 147.1, 147.0, 136.8, 136.4, 135.1, 135.0, 133.5 133.4, 132.3, 130.7, 129.5, 129.2, 129.0, 128.9, 128.9, 128.7, 127.5, 127.1, 126.9, 125.8, 125.0, 124.7, 124.1, 123.6, 123.3, 122.1, 121.5, 121.3, 121.1, 118.9, 118.8, 118.5, 118.0, 111.9, 111.8, 111.7, 110.7, 109.1, 108.8, 108.7, 108.1, 101.5, 51.8, 49.2, 47.1, 44.5, 24.9, 23.1;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 18.06 min, 100%

LRMS (APCI⁺) m/z 448, 449 [M+1H]+, 100%. HRMS (ES⁺) for C₂₃H₂₅N₂O₅, calculated 449.1860, found 449.1859.
N-(2-(1H-Indol-3-yl)ethyl)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-indole-2-carboxamide (20)

Yield: 140 mg, 67%. MP 198-199 °C;

IR: νmax/cm⁻¹ 3440 (NH), 3274 (NH), 1620 (CON);

¹H NMR (400 MHz, DMSO-d₆) δ 11.72 (s, 1H), 10.86 (s, 1H), 7.72 – 7.29 (m, 4H), 7.20 (dd, J = 9.2, 4.8 Hz, 2H), 7.13 – 6.58 (m, 7H), 6.01 (s, 2H), 4.81 (bs, 2H), 3.76 (bs, 2H), 3.09 (s, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 163.7, 148.1, 147.0, 136.7, 136.4, 131.9, 130.5, 127.5, 123.8, 123.3, 121.9, 121.5, 120.2, 118.8, 118.7, 112.5, 111.9, 111.2, 108.8, 107.7, 103.7, 101.5, 52.4, 48.6, 47.7, 24.7, 23.3;

RP-HPLC Alltima™ C18 5 µm 150 mm x 4.6 mm, 10-100% B in 15 min, Rt = 14.68 min, 100%;

LRMS (APCI⁺) m/z 437, 438 [M+1], 70%. HRMS (ES⁺) for C₂₁H₂₁N₅O₅, calculated 438.18122, found 439.18110.
**Benzo[b]thiophene-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amide (21)**

Yield: 118 mg, 53%. MP 166 – 167 °C;

IR: vmax/cm⁻¹ 3331 (NH), 1627 (CON);

¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (s, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H), 7.70 – 6.64 (m, 11H), 6.02 (s, 2H), 4.73 (s, 2H), 3.65 (s, 2H), 3.12 – 2.91 (m, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 164.5, 148.1, 147.0, 139.7, 139.1, 137.7, 136.6, 131.5, 127.5, 126.3, 125.3 (Cₓ2), 125.2, 123.5, 122.9, 121.5 (Cₓ2), 118.7 (Cₓ2), 118.6, 111.9, 110.9, 108.8, 101.5, 49.6, 48.4, 24.7;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 14.97 min, 100%;

LRMS (APCI⁺) m/z 454, 455 [M+H]⁺, 100%. HRMS (ES⁺) for C₂₇H₂₇N₂O₃S, calculated 455.14239, found 455.14231.
Benzofuran-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-[2-([1H-indol-3-yl]-ethyl]-amide (22)

Yield: 156 mg, 63%. MP 173 – 173.6 °C;

IR: ν_{max}/cm\(^{-1}\) 3316 (NH), 1627 (CON), 737 (CH-aromatic);

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) δ 10.83 (s, 1H), 7.72 (d, \(J = 5.8\) Hz, 1H), 7.62 (d, \(J = 8.3\) Hz, 1H), 7.58 – 7.26 (m, 5H), 7.19 – 6.71 (m, 6H), 6.01 (s, 2H), 4.72 (s, 2H), 3.91 – 3.51 (m, 2H), 3.05 (s, 2H);

\(^13\)C NMR (101 MHz, DMSO-\(d_6\)) δ 154.4, 149.3, 148.0, 147.0, 136.7, 131.7, 129.0, 127.4, 127.2, 126.9, 124.1, 123.6, 122.9, 122.0, 121.4, 118.7, 118.5, 112.2, 111.9, 111.1, 109.0, 108.8, 101.5, 48.7, 48.8, 25.1;

RP-HPLC Alltima\textsuperscript{TM} C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 7.12 min, 100%;
LRMS (APCI\textsuperscript{+/-}) m/z 438, 439 \([M+H]^+\), 100%. HRMS (ES\textsuperscript{+}) for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_4\), calculated 439.16523, found 439.16523.
N-Benzo[1,3]dioxol-5-ylmethyl-4-chloro-N-(2-(1H-indol-3-yl)-ethyl]benzamide (23)

Yield: 90 mg, 58%. MP 132-133 °C;
IR: νmax/cm⁻¹ 3203 (NH), 1626 (CON), 1500 (C=C aromatic), 1251 (C-N), 747 (C-H aromatic);
This is a mixture of atropoisomers of compound 23 with the ratio approximately 2.0 : 1.2 calculated on the CH₂ splitting peaks at 2.93 and 2.84 ppm of the proton NMR.

¹H NMR calculated separately for splitting peaks (400 MHz, DMSO-δ6) δ 10.89 (s, 2H), 10.79 (s, 1H), 7.50 (t, J = 6.8 Hz, 3H), 7.40-7.26 (m, 9H), 7.23 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 1.9 Hz, 2H), 7.12-6.91 (m, 11H), 6.90-6.82 (m, 3H), 6.82 - 6.62 (m, 6H), 6.03-5.94 (m, 6H), 4.57-4.46 (m, 6H), 3.59 - 3.43 (m, 10H), 2.93 (t, J = 7.2 Hz, 4H), 2.89 - 2.78 (m, 2H);

¹³C NMR calculated separately for splitting peaks (101 MHz, DMSO-δ6) δ 170.1 and 170.0 (1C), 147.6 and 147.4 (1C), 146.5 and 146.3 (1C), 136.2 (1C), 135.1 and 135.0 (1C), 132.1, 131.3 and 131.2 (2C), 131.1 and 130.9 (1C), 128.1 and 127.9 (2C), 127.1 and 127.0 (1C), 123.4, 122.7, 121.2 and 121.1 (1C), 120.9 and 120.2 (1C), 118.5 and 118.3 (1C), 118.2 and 118.1 (1C), 111.5 and 111.4 (1C), 110.9, 108.3 and 108.1 (1C), 107.4, 101.0 and 100.9 (1C), 50.8 and 47.1 (1C), 47.5 and 46.4 (1C), 38.9 and 38.5(1C), 23.8 and 23.0 (1C);

RP-HPLC Alliimta™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 14.76 min, 100%;
LRMS m/z APCI (+) 446, 447 [M+H]^+ 100%; HRMS (ES^+) calculated for C_{36}H_{23}ClN_{2}O_{3} 446.1397, fo 447.1467.
Selective NOSEY at 5.99 ppm

This is a mixture of atropoisomers of compound 24 with the ratio approximately 2:0: calculated on the CH₂ splitting peaks at 5.99 and 6.02 ppm of the proton NMR.

**N-Benzof[1,3]dioxol-5-ylmethyl-2,6-dichloro-N-[(1H-indol-3-yl)-ethyl]-benzamide (24)**

Yield: 100mg, 65%. MP 157-158 °C;
IR: ν max/cm⁻¹ 3280 (NH), 2937 (CH), 1626 (CON), 739 (CH- aromatics);

¹H NMR (400 MHz, DMSO-d₆) δ 10.90 (s, 1H), 10.80 (s, 0.7H), 7.59 - 7.25 (m, 8.3H), 7.21 (d, 2.2 Hz, 1H), 7.10 (s, 0.3H), 7.07 (dd, J = 15.0, 8.0 Hz, 2H), 7.03 - 6.91 (m, 2.3H), 6.88 (d, J = 7.7 Hz, 1.7H), 6.86 - 6.75 (m, 2.7H), 6.02 (s, 1.3H), 5.99 (s, 2H), 4.61 (s, 1.3H), 4.53 (s, 2H), 4.04 (s, 1.3H), 3.87 (s, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.58 - 3.44 (m, 1.3H), 3.04 (t, J = 7.1 Hz, 2H), 2.97 - 2.80 (m, 1.3H);
$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 168.2, 168.0, 148.1, 147.9, 147.0, 146.8, 136.8, 136.7, 135.9, 135.9, 135.9, 133.6, 132.5, 131.8, 129.6, 129.5, 128.5, 128.4, 127.6, 127.5, 124.0, 123.2, 121.5, 121.4, 120.5, 118.9, 118.7, 118.5, 112.0, 111.8, 111.1, 108.9, 108.6, 107.8, 101.5, 101.4, 51.1, 47.9, 47.7, 47.5, 36.7, 35.9, 24.2, 23.6;
RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 18.81 min, 100%;
LRMS (ESI$^+$) m/z 481, 481[M]$^+$, 100%. HRMS (ESI$^+$) for C$_{26}$H$_{22}$Cl$_2$N$_2$O$_3$, calculated 480.1007, found 481.1080.
N-Benz[1,3]dioxol-5-ylmethyl-4-benzoyl-N-[2-(1H-indol-3-yl)-ethyl]-benzamide (25)

Yield: 77 mg, 40%. MP 181.2-181.7 °C;
IR: ν_{max}/cm^{-1} 3191 (NH), 2990 (CH), 1643 (CON), 742 (CH-aromatic);

This is a mixture of atropoisomers of compound 25 with the ratio approximately 2.0 : 0.9 calculated on the CH₂ splitting peaks at 4.75 and 6.02 ppm of the proton NMR.

¹H NMR (400 MHz, DMSO-d₆) δ 10.83 (d, J = 10.1 Hz, 1H), 7.85 – 7.66 (m, 5H), 7.58 (dt, J = 18.2, 8.8 Hz, 6.5H), 7.41 – 7.17 (m, 4H), 7.11 – 6.85 (m, 7.5H), 6.84 – 6.56 (m, 2H), 6.01 (d, J = 13.2 Hz, 3H), 4.75 (s, 2H), 4.32 (s, 1H), 3.60 (d, J = 7.1 Hz, 1H), 3.36 – 3.30 (overlapped by water) (m, 2.5H), 3.03 (d, J = 7.1 Hz, 1H), 2.88 (t, J = 7.1 Hz, 2H);

¹³C NMR (101 MHz, DMSO-d₆) δ 195.6, 170.6, 148.0, 146.9, 140.9, 137.4, 137.2, 136.6, 133.4, 132.0, 130.1, 130.0, 129.1, 127.4, 127.1, 126.8, 123.7, 121.8, 121.4, 118.7, 118.6, 118.1, 111.9, 110.8, 108.8, 108.7, 101.4, 52.4, 49.1, 46.9, 45.5, 24.2, 23.1;

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt =17.71 min, 100%

LRMS (APCI+/−) m/z 502, 503 [M+1], 100%. HRMS (ES) for C₂₃H₂₃N₂O₄, calculated 503.19653, found 503.19636.
5-Methylpyrazine-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amide (26)

Yield: 47 mg, 22%. MP 132 – 133 °C;
IR: $\nu_{\text{max}}$/cm$^{-1}$ 3316 (NH), 1632 (CON), 1632 (CON), 739 (CH-aromatic);

This is a mixture of atropoisomers of compound 26 with the ratio approximately 2 : 1 calculated on the CH$_2$ splitting peaks at 4.71 and 4.46 ppm of the proton NMR. $^1$H NMR is reported as displayed on spectra. All peaks in $^{13}$C NMR are reported.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.83 (s, 0.5H), 10.77 (s, 1H), 8.75 (d, $J = 1.2$ Hz, 0.5H), 8.56 (s, 0.5H), 8.34 (s, 1H), 8.19 (d, $J = 1.3$ Hz, 1H), 7.52 (d, $J = 7.8$ Hz, 0.5H), 7.34 (d, $J = 8.1$ Hz, 0.7H), 7.25 (d, $J = 8.1$ Hz, 1.2H), 7.16 (d, $J = 2.0$ Hz, 0.7H), 7.11 – 7.02 (m, 1.8H), 7.02 – 6.79 (m, 8H), 6.75 (d, $J = 7.9$ Hz, 0.5H), 6.01 (s, 2H), 5.99 (s, 0.8H), 4.71 (s, 2H), 4.46 (s, 1H), 3.60 (dt, $J = 15.8$, 7.5 Hz, 3.2H), 2.92 (dt, $J = 13.8$, 7.5 Hz, 3.2H), 2.54 (s, 1.8H), 2.41 (s, 3.2);

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 167.2, 166.8, 155.0, 154.2, 147.9, 147.4, 147.1, 147.0, 146.9, 143.7, 143.2, 143.0, 142.0, 136.7, 136.6, 131.9, 131.3, 127.6, 127.1, 123.6, 123.3, 121.8, 121.6, 121.5, 121.3, 118.7, 118.5, 118.1, 111.9, 111.7, 110.9, 108.8, 108.7, 108.6, 108.5, 101.5, 101.4, 52.0, 48.6, 47.8, 46.192, 24.4, 23.1, 21.7, 21.5;

RP-HPLC Alltima™ C18 5 µm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 12.40 min, 100%;
LRMS (APCI±) m/z 414, 415 [M+H]⁺, 100%. HRMS (ES⁺) for C₂₄H₂₂N₂O₃, calculated 415.17647, fc 415.17611.
5-Methoxy-1H-indole-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)ethyl]-amide (27)

Yield: 149 mg, 62%. MP 202-202.5 °C;
IR: \( \nu_{\text{max}} \text{ cm}^{-1} \) 3439 (NH), 3258 (NH), 1612 (CON), 1450 (C-C ring), 738 (C-H ring);
\(^1\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 11.57 (s, 1H), 10.86 (s, 1H), 7.68-7.26 (m, 3H), 7.19 (s, 1H), 7.13 – 6.48 (m, 8H), 6.01 (s, 2H), 4.81 (s, 2H), 3.73 (s, 5H), 3.08 (s, 2H);
\(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 163.6, 154.2, 148.1, 146.9, 136.7, 132.0, 131.6, 130.1, 127.8, 127.6, 123.3, 121.5 (Cx2), 118.8 (Cx2), 115.0, 113.4, 111.9, 108.8, 103.5 (Cx2), 102.2, 101.5, 65.4, 55.7, 48.5, 48.1, 23.6;
RP-HPLC Altima™ C18 5 µm 150 mm x 4.6 mm, 10–100% B in 15 min, \( R_f = 6.92 \text{ min}, 100\% \);
LRMS (ESI\(^+\)) m/z 467, 467 [M\(^+\)], 100%; HRMS (ESI\(^+\)) for C\(_{29}\)H\(_{32}\)N\(_5\)O\(_4\), calculated 468.19178, found 468.19186.
5-Chloro-1H-indole-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-[2-(1H-indol-3-yl)-ethyl]-amide (28)

Yield: 170 mg, 64%. MP 194–194.5 °C;
IR: \( \nu_{\text{max}}/\text{cm}^{-1} \) 3433 (NH), 3265(NH), 1612 (CON), 739 (CH-aromatics);

\(^1\)H NMR (400 MHz, DMSO-d6) \( \delta \) 11.93 (s, 1H), 10.87 (s, 1H), 7.73 – 7.26 (m, 4H), 7.25 – 7.13 (m, 2H), 7.08 (t, \( J = 7.5 \text{ Hz} \), 1H), 7.02 – 6.60 (m, 5H), 6.02 (s, 2H), 4.79 (br.s, 2H), 3.74 (br.s, 2H), 3.08 (s, 2H);

\(^13\)C NMR (101 MHz, DMSO-d6) \( \delta \) 163.4, 148.1, 147.0, 136.7, 134.8, 132.1, 128.5, 127.5, 124.7, 123.9 (C2), 123.4, 121.5, 121.4, 121.0, 118.8 (C2), 118.7, 114.1, 111.9, 108.8, 103.2 (C2), 101.5, 52.4, 48.9, 48.6, 47.6, 24.7, 23.4;

*Note: 52.38 and 48.39 are the splitting of 1 C (Ar-CH\(_2\)-N-); 48.91 and 47.58 are the splitting of (CH\(_2\)-CH\(_2\)-N-), and 24.68, 23.41 are the splitting of (CH\(_2\)-CH\(_2\)-N-).

UPLC: Mobile phase B = 100% H\(_2\)O with 0.1% formic acid; Mobile phase B = 90% ACN : 10% H\(_2\)O and 0.1%
formic acid. RP-HPLC Agilent Zorbax SB-C18 1.8 \( \mu \)m, 50 mm x 2.1 mm, isocratic 80% mobile phase B at 0.6 mL/min in 8 minutes, Rt = 5.05 min, 100%;

LRMS (ESI) \( m/z \) 471, 470 [M-H]\(^+\), 100%; \( m/z \) 471, 472 [M+H]\(^+\), 100%. HRMS (ES\(^+\)) for C\(_{27}\)H\(_{22}\)ClN\(_3\)O\(_5\), calculated 472.1423, found 472.1422.
1-(1H-indol-3-yl)ethyl)-N-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-indole-5-carboxamide (29)

Yield: 158 mg, 67%. MP 162.5-163 °C;

IR: $v_{\text{max}}$/cm$^{-1}$ 3638 (NH), 3227 (NH), 1614(CON), 740 (CH-aromatic);

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.29 (s, 1H), 10.78 (s, 1H), 7.61 (s, 1H), 7.51 – 7.39 (2H), 7.56 – 6.38 (m, 9H), 6.47 (s, 1H), 6.01 (s, 2H), 4.87 – 4.29 (m, 2H), 3.65 – 3.45 (m, 2H), 3 – 2.70 (m, 2H);

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 186.0, 172.8, 148.0, 146.9, 136.6, 136.5, 127.8, 127.5, 127.0, 123.3, 123.4, 119.1, 118.6, 111.8, 111.7, 108.7, 102.2, 101.4, 49.1, 47.3, 45.6, 24.6, 23.4; *Note: Signs of atropoisomers of the CH$_2$ in which 47.3 is the splitting of 1 C (Ar-CH$_2$-N); 49.1 and 45.6 are the splitting of (CH$_2$-CH$_2$-N); 24.6 and 23.4 are the splitting of (CH$_3$-CH$_3$-N);

RP-HPLC Alltima™ C18 5 μm 150 mm x 4.6 mm, 10–100% B in 15 min, Rt = 6.48 min, 96%

LRMS (ESi+) m/z 437, 437 [M$^+$], 70%. HRMS (ESi+) for C$_{27}$H$_{33}$N$_3$O$_3$, calculated 438.18122, found 438.18122.