# **Supporting Information**

# Design, synthesis *via* one-pot approach and molecular docking studies of novel pyrrolo[2,1-*a*]isoquinoline derivatives

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#### **EXPERIMENTAL SECTION**

#### 1. Materials and Methods

All the Pyrrolo[2,1-a]isoquinoline derivatives were prepared using isatins, 1,2,3,4tetrahydroisoquinoline and chalcones under reflux conditions for 10 h. All the starting materials, chemical reagents and solvents except the chalcones were obtained from commercial sellers and used as such without any further purification. The progress of the reaction was monitored by thin-layer chromatography (TLC) performed on silica gel 60 F254 precoated aluminium sheets. TLC was visualised by a 254 nm UV lamp and iodine staining. The reaction products were purified through silica gel (230–400 mesh) column chromatography using ethyl acetate/hexane as eluent in increasing polarity. Melting points were recorded using melting point equipment and are uncorrected. NMR spectra were recorded using 500 MHz for <sup>1</sup>H and 126 MHz for <sup>13</sup>C using CDCl<sub>3</sub> as a solvent. Tetramethylsilane (TMS) was used as internal standard (signal at 0 ppm) for <sup>1</sup>H chemical shifts measurements, and coupling constants (J) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer using positive electrospray ionisation (ESI<sup>+</sup>) for ion detection. The structural assignments of products were made by analysing their <sup>1</sup>H/<sup>13</sup>C NMR, HRMS spectra of a typical compound.

#### **Representative Procedure for the Synthesis of Chalcones:**

In a 50 mL round bottom flask, suitably substituted acetophenone (7.35 mmol) was dissolved in ethanol (10 mL). Then 6 mL of 10% NaOH solution was added to it and stirring the reaction mixture for 30 min at 0 °C. After that, substituted benzaldehydes were added to the reaction mixture and stirring was continued for 3-4 hrs. Next, the reaction mixture was concentrated under reduced pressure and extracted with ethyl acetate/water. The organic layer was dried over anhydrous sodium sulphate and concentrated in a vacuum to yield the crude product.

# **Representative Procedure for the Synthesis of Pyrrolo**[2,1-a]isoquinoline derivatives: In a 50 mL round bottom flask, substituted isatin (0.5 mmol) was dissolved in toluene (5 mL) followed by the addition of 1,2,3,4-tetrahydroisoquinoline (0.5 mmol) and the mixture was stirred at room temperature for half an hour. After that, substituted chalcones (0.5 mmol) was added to the reaction mixture and stirring was continued at reflux condition for 10 hrs. Next, the reaction mixture was concentrated under reduced pressure and extracted with ethyl

acetate/water. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to yield the crude product which was purified by column chromatography using ethyl acetate/n-hexane (3:17) as eluent.

## 2. Spectral Data:

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'pyrrolo[2,1-a]isoquinolin]-2-one (4a):



Prepared following the general procedure; pale yellow solid (0.204 g, 87%);  $R_f = 0.37$  (EtOAc/Hexane = 2/5); mp 205-206 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (s, 1H), 7.71 – 7.66 (m, 2H), 7.46 – 7.32 (m, 4H), 7.32 – 7.20 (m, 2H), 7.14 – 7.10 (m, 2H), 7.10 – 7.04 (m, 3H), 6.98 – 6.90 (m, 2H), 6.86 (m, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.46 (m, 1H), 5.21 (d, J = 10.1 Hz, 1H), 4.58 (d, J = 9.5 Hz, 1H), 4.34 (t, J = 9.8 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.72 – 2.66 (m, 1H), 2.63 – 2.56 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.69, 180.19, 141.86, 140.53, 137.91, 137.22, 134.49, 132.46, 129.02, 128.97, 128.94, 128.68, 127.91, 127.46, 127.31, 126.86, 126.67, 126.20, 125.39, 124.95, 122.95, 108.81, 70.86, 63.40, 63.26, 50.55, 42.22, 30.20; HRMS (ESI, Orbitrap) calcd for C<sub>32</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 471.2073, found = 471.2075.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4b):



Prepared following the general procedure; pale yellow solid (0.211 g, 87%);  $R_f = 0.37$  (EtOAc/Hexane = 2/5); mp 229-230 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 7.13

-7.09 (m, 3H), 7.08 - 7.04 (m, 2H), 6.97 - 6.97 (m, 2H), 6.84 - 6.82 (m, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.45 (d, J = 7.7 Hz, 1H), 5.17 (d, J = 10.1 Hz, 1H), 4.56 (d, J = 9.5 Hz, 1H), 4.30 (t, J = 9.8 Hz, 1H), 3.01 - 2.88 (m, 2H), 2.73 - 2.54 (m, 2H), 2.35 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.90, 180.48, 140.67, 138.86, 138.15, 137.37, 136.50, 134.61, 132.56, 129.76, 129.12, 128.91, 128.78, 128.02, 127.59, 127.50, 126.78, 126.29, 125.51, 125.10, 123.06, 108.97, 70.99, 63.44, 63.39, 50.31, 42.36, 30.33, 21.18; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 485.2229, found = 485.2241.

4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-2-oxo-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4c):



Prepared following the general procedure; white solid (0.223 g, 85%);  $R_f = 0.31$  (EtOAc/Hexane = 2/5); mp 217-218 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 – 7.79 (m, 2H), 7.73 – 7.68 (m, 2H), 7.58 (s, 1H), 7.15 – 7.07 (m, 2H), 7.07 – 7.01 (m, 2H), 6.98 – 6.93 (m, 3H), 6.90 – 6.81 (m, 3H), 6.54 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 7.7 Hz, 1H), 5.22 (d, J = 9.9 Hz, 1H), 4.46 (d, J = 9.5 Hz, 1H), 4.38 (t, J = 9.7 Hz, 1H), 3.67 (s, 3H), 3.00 – 2.89 (m, 2H), 2.73 – 2.56 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.27, 180.01, 159.42, 147.95, 140.78, 138.48, 137.35, 134.75, 133.02, 130.02, 129.51, 129.16, 127.08, 126.76, 126.72, 125.71, 124.76, 123.26, 120.10, 119.96, 118.98, 111.53, 111.07, 109.20, 71.03, 63.58, 63.51, 55.36, 50.76, 42.34, 30.27. (One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for C<sub>34</sub>H<sub>28</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup> = 526.2131, found = 526.2133.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-chlorophenyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4d):



Prepared following the general procedure; yellow solid (0.217 g, 86%);  $R_f = 0.39$  (EtOAc/Hexane = 2/5); mp 235-236 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (s, 1H), 7.65 – 7.60 (m, 2H), 7.42 – 7.34 (m, 4H), 7.30 – 7.24 (m, 1H), 7.14 – 7.10 (m, 3H), 7.09 – 7.03 (m, 2H), 6.99 – 6.92 (m, 2H), 6.87 – 6.84 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.46 (d, J = 7.6 Hz, 1H), 5.17 (d, J = 10.1 Hz, 1H), 4.50 (d, J = 9.4 Hz, 1H), 4.31 (t, J = 9.8 Hz, 1H), 3.00 – 2.87 (m, 2H), 2.73 – 2.54 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.53, 180.23, 140.55, 140.49, 137.59, 137.06, 134.49, 132.68, 132.63, 130.30, 129.15, 128.80, 127.99, 127.43, 127.09, 126.58, 126.36, 125.46, 124.78, 123.02, 108.94, 70.83, 63.29, 63.19, 49.93, 42.18, 30.15 (One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for  $C_{32}H_{26}N_2O_2Cl[M+H]^+ = 505.1683$ , found = 505.1684.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-2',5',6',10b'tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4e):



Prepared following the general procedure; white solid (0.229 g, 87%);  $R_f = 0.51$  (EtOAc/Hexane = 2/5); mp 181-182 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 7.12 – 7.05 (m, 3H), 7.04 – 6.99 (m, 1H), 6.94 – 6.85 (m, 3H), 6.72 (d, J = 7.8 Hz, 1H), 6.53 (dd, J = 8.0, 1.7 Hz, 2H), 5.87 (q, J = 1.4 Hz, 2H), 5.14 (d, J = 10.1 Hz, 2H), 4.44 (d, J = 9.4 Hz, 1H), 4.27 (t, J = 9.8 Hz, 1H), 2.93 (d, J = 8.0 Hz, 1H), 2.67 (d, J = 11.5 Hz, 1H), 2.64 – 2.54 (m, 2H), 2.34 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.58, 179.96, 151.17, 147.55, 140.42, 138.75, 138.03, 136.32, 134.46, 132.43, 129.60, 128.95, 128.75, 128.60, 127.45, 126.80, 126.11, 125.33, 124.96, 123.66, 122.96, 108.67, 107.34, 107.09, 101.48, 70.91, 63.26, 63.08, 50.41, 42.25, 30.21, 21.01; HRMS (ESI, Orbitrap) calcd for C<sub>34</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 529.2127, found = 529.2128.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-methoxyphenyl)-5-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4f):



Prepared following the general procedure; off white solid (0.213 g, 83%);  $R_f = 0.44$  (EtOAc/Hexane = 2/5); mp 156-157 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 – 7.56 (m, 2H), 7.42 – 7.34 (m, 3H), 7.29 – 7.21 (m, 2H), 7.13 – 7.08 (m, 2H), 7.08 – 7.03 (m, 1H), 6.94 – 6.90 (m, 3H), 6.86 (s, 1H), 6.75 – 6.70 (m, 2H), 6.30 (d, J = 7.8 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.50 (d, J = 9.5 Hz, 1H), 4.25 (t, J = 9.8 Hz, 1H), 3.80 (s, 3H), 3.02 – 2.86 (m, 2H), 2.72 – 2.53 (m, 2H), 2.16 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.97, 180.13, 158.41, 138.07, 138.03, 137.46, 134.48, 133.87, 132.42, 132.32, 129.88, 129.22, 128.64, 127.86, 127.42, 127.36, 127.25, 126.13, 125.34, 124.93, 114.31, 108.45, 70.79, 63.29, 55.13, 49.77, 42.24, 30.20, 20.80.(One peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for C<sub>34</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> = 515.2335, found = 515.2333.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-5-methyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4g):



Prepared following the general procedure; pale yellow solid (0.231 g, 85%);  $R_f = 0.44$  (EtOAc/Hexane = 2/5); mp 207-208 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.58 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.10 – 6.98 (m, 3H), 6.89 (td, J = 7.6, 7.0, 1.8 Hz, 3H), 6.79 (dd, J = 7.8, 1.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 6.41 (d, J = 7.9 Hz, 1H), 5.91 – 5.79 (m, 2H), 5.12 (d, J = 10.1 Hz, 1H), 4.42 (d, J = 9.4 Hz, 1H), 4.25 (t, J = 9.7 Hz, 1H), 3.01 – 2.86 (m, 2H), 2.74 – 2.53 (m, 2H), 2.33 (s, 3H), 2.18 (s, 3H). <sup>13</sup>C

NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.81, 180.31, 151.21, 147.65, 138.97, 138.22, 138.18, 136.41, 134.59, 132.68, 132.57, 129.71, 129.36, 128.88, 128.72, 127.58, 127.49, 126.22, 125.44, 125.08, 123.77, 108.58, 107.42, 107.21, 101.58, 71.13, 63.39, 63.21, 50.49, 42.41, 30.31, 21.14, 20.96; HRMS (ESI, Orbitrap) calcd for C<sub>35</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 543.2284, found = 543.2289.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(2-bromophenyl)-5-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4h):



Prepared following the general procedure; pale yellow solid (0.225 g, 80%);  $R_f = 0.31$  (EtOAc/Hexane = 2/5); mp 211-212 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.05 (d, J = 7.9 Hz, 1H), 7.63 (dd, J = 8.0, 1.3 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.29 – 7.24 (m, 1H), 7.13 (td, J = 7.9, 4.1 Hz, 4H), 7.07 (d, J = 7.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.93 (d, J = 1.8 Hz, 1H), 6.75 (dd, J = 8.0, 1.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 5.16 (d, J = 9.8 Hz, 1H), 5.01 (d, J = 11.2 Hz, 1H), 4.59 (s, 1H), 3.04 – 2.94 (m, 1H), 2.90 (td, J = 10.9, 3.7 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.18 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.32, 180.21, 160.16, 142.97, 138.06, 137.32, 137.29, 134.28, 133.42, 132.59, 132.40, 130.14, 129.37, 128.67, 128.33, 128.22, 127.92, 127.55, 127.51, 126.82, 126.28, 125.59, 124.62, 108.53, 70.99, 65.39, 63.07, 48.13, 42.31, 30.13, 20.79; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>BrN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 563.1334, found= 563.1335.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-nitro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4i):



Prepared following the general procedure; pale yellow solid (0.212 g, 80%);  $R_f = 0.37$  (EtOAc/Hexane = 2/5); mp 220-221 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> & DMSO-d<sub>6</sub>)  $\delta$  10.18 (br s, 1H), 7.89 (t, J = 5.9 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 7.29 (d, J = 10.7 Hz, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.17 – 7.09 (m, 3H), 7.07 (d, J = 7.3 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.16 (d, J = 10.2 Hz, 1H), 4.55 (d, J = 9.4 Hz, 1H), 4.32 (t, J = 9.7 Hz, 1H), 2.96 (q, J = 12.1, 9.0 Hz, 2H), 2.69 (d, J = 11.8 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub> & DMSO-d<sub>6</sub>)  $\delta$  196.20, 180.57, 147.83X2, 143.20, 138.32, 137.57, 137.04, 136.51, 134.10, 132.77, 129.66, 128.70, 128.62, 128.15, 127.35, 126.30, 125.84, 125.43, 124.83, 122.18, 108.97, 70.54, 63.32, 63.22, 50.11, 42.44, 30.05, 21.01; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>[M+H]<sup>+</sup> = 530.2080, found = 530.2064.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-fluoro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4j):



Prepared following the general procedure; pale yellow solid (0.211 g, 84%);  $R_f = 0.34$  (EtOAc/Hexane = 2/5); mp 255-256 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.90 (s, 1H), 7.59 – 7.51 (m, 2H), 7.45 – 7.38 (m, 2H), 7.30 – 7.25 (m, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.13 (t, J = 7.8 Hz, 2H), 7.10 – 7.04 (m, 2H), 6.93 (td, J = 7.4, 1.9 Hz, 1H), 6.82 (dd, J = 8.0, 2.6 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.66 (td, J = 8.7, 2.7 Hz, 1H), 6.39 (dd, J = 8.5, 4.1 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 4.55 (d, J = 9.5 Hz, 1H), 4.27 (t, J = 9.8 Hz, 1H), 3.02 – 2.84 (m, 2H), 2.69 (dd, J = 13.0, 7.6 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.34 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.62, 180.52, 160.25, 158.33, 138.61, 137.91, 137.30, 136.61, 136.59, 134.42, 132.75, 129.80, 129.47, 129.41, 128.86, 128.78, 128.16, 127.63, 126.38, 125.56, 125.05, 115.78, 115.59, 114.61, 114.41, 109.65, 109.59, 71.29, 71.27, 63.45, 63.39, 50.28, 42.45, 30.28, 21.15; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 503.2135, found = 503.2136.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-chloro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4k):



Prepared following the general procedure; white solid (0.215 g, 83%);  $R_f = 0.44$  (EtOAc/Hexane = 2/5); mp 138-139 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.80 – 7.74 (m, 2H), 7.65 (d, J = 2.2 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.37 – 7.32 (m, 2H), 7.24 (s, 1H), 7.20 (dd, J = 8.2, 2.2 Hz, 1H), 7.07 (t, J = 7.9 Hz, 3H), 7.04 – 6.96 (m, 3H), 6.82 (t, J = 7.5 Hz, 1H), 6.67 (dd, J = 7.7, 1.4 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H), 5.80 (d, J = 8.4 Hz, 1H), 5.19 (dd, J = 8.4, 6.7 Hz, 1H), 4.08 (d, J = 6.8 Hz, 1H), 3.25 – 3.15 (m, 1H), 2.78 (dd, J = 9.4, 3.2 Hz, 2H), 2.72 – 2.62 (m, 1H), 2.24 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  202.28, 177.21, 139.78, 138.80, 137.20, 135.90, 134.62, 132.72, 132.38, 130.46, 129.22, 129.12, 128.98, 128.47, 128.42, 128.36, 128.11, 125.74, 125.65, 125.16, 125.07, 110.24, 63.83, 60.44, 51.31, 43.03, 30.02, 29.59, 20.95; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 519.1839, found = 519.1845.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-bromo-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4l):



Prepared following the general procedure; pale yellow solid (0.228 g, 81%);  $R_f = 0.63$  (EtOAc/Hexane = 2/5); mp 155-156 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (s, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.7 Hz, 2H), 7.27 (d, J = 12.3 Hz, 1H), 7.22 – 7.18 (m, 3H), 7.15 (t, J = 7.6 Hz, 2H), 7.11 – 7.07 (m, 3H), 6.93 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.31 (d, J = 8.2 Hz, 1H), 5.14 (d, J = 10.1 Hz, 1H), 4.54 (d, J = 9.4 Hz, 1H), 4.27 (t, J = 9.8

Hz, 1H), 3.04 - 2.88 (m, 2H), 2.72 - 2.65 (m, 1H), 2.63 - 2.54 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.52, 179.59, 139.46, 138.44, 137.73, 137.35, 136.49, 134.24, 132.54, 131.85, 129.68, 128.73, 128.64, 128.04, 127.47, 126.26, 125.42, 124.90, 115.64, 110.20, 70.78, 63.41, 63.34, 50.05, 42.36, 30.13, 21.02. (Two peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>BrN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 563.1334, found = 563.1336.

(1'R,2'S,3R,10b'S)-2'-benzoyl-5-iodo-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4m):



Prepared following the general procedure; pale yellow solid (0.253 g 83%);  $R_f = 0.43$  (EtOAc/Hexane = 2/5); mp 175-176 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (br s, 1H), 7.77 – 7.72 (m, 2H), 7.54 (dd, J = 8.1, 1.8 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.14 (s, 1H), 7.05 (q, J = 6.9, 5.8 Hz, 3H), 6.98 (t, J = 9.5 Hz, 3H), 6.86 – 6.77 (m, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 8.1 Hz, 1H), 5.78 (d, J = 8.3 Hz, 1H), 5.18 (dd, J = 8.4, 6.7 Hz, 1H), 4.05 (d, J = 6.7 Hz, 1H), 3.19 (m, 1H), 2.76 (dd, J = 9.1, 2.7 Hz, 2H), 2.66 (d, J = 15.7 Hz, 1H), 2.23 (s, 3H).<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  202.55, 176.96, 141.15, 139.03, 138.25, 137.41, 136.14, 134.81, 133.66, 132.95, 132.56, 131.23, 129.36, 129.19, 128.69, 128.57, 128.30, 125.94, 125.84, 125.27, 111.43, 85.70, 64.05, 60.68, 51.37, 43.25, 30.21, 21.15; (one peak is missing due to over lap); HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>IN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 611.1195, found = 611.1198.

(1'R,2'S,3R,10b'S)-2'-benzoyl-7-fluoro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4n):



Prepared following the general procedure; pale yellow solid (0.176 g, 70%);  $R_f = 0.69$  (EtOAc/Hexane = 2/5); mp 197-198 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 (s, 1H), 7.57 – 7.54 (m, 2H), 7.41 – 7.37 (m, 2H), 7.32 – 7.28 (m, 1H), 7.19 (d, J = 7.8 Hz, 2H), 7.17 – 7.11 (m, 2H), 7.11 – 7.05 (m, 2H), 6.95 – 6.92 (m, 1H), 6.86 (dd, J = 7.5, 1.2 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.76 – 6.70 (m, 2H), 5.17 (d, J = 10.1 Hz, 1H), 4.56 (d, J = 9.5 Hz, 1H), 4.28 (t, J = 9.8 Hz, 1H), 3.01 – 2.88 (m, 2H), 2.74 – 2.64 (m, 1H), 2.63 – 2.55 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.45, 179.32, 146.95, 145.01, 138.48, 137.85, 137.12, 136.47, 134.33, 132.67, 130.16, 130.14, 129.67, 128.75, 128.63, 127.97, 127.74, 127.65, 127.38, 126.21, 125.42, 124.95, 123.47, 123.43, 122.29, 122.27, 115.95, 115.82, 71.12, 71.10, 63.50, 63.25, 50.15, 42.32, 30.15, 21.01; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 503.2135, found = 503.2130.

(1'R,2'S,3R,10b'S)-2'-benzoyl-7-chloro-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'Hspiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (40):



Prepared following the general procedure; pale yellow solid (0.181 g, 70%); Rf = 0.51 (EtOAc/Hexane = 2/6); mp 233-234 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.57 – 7.52 (m, 2H), 7.51 (s, 1H), 7.40 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 7.20 (d, J = 7.8 Hz, 2H), 7.19 – 7.12 (m, 2H), 7.14 – 7.04 (m, 2H), 6.82 – 6.79 (m,3H), 6.81 (dd, J = 8.2, 7.4 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 5.16 (d, J = 10.1 Hz, 1H), 4.54 (d, J = 9.5 Hz, 1H), 4.27 (t, J = 9.8 Hz, 1H), 3.02 – 2.89 (m, 2H), 2.69 (d, J = 11.5 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.69, 179.37, 138.62, 138.29, 138.02, 137.24, 136.70, 134.52, 132.92, 129.88, 129.28, 128.95, 128.85, 128.14, 127.53, 126.44, 125.63, 125.14, 125.01, 123.92, 114.25, 99.98, 71.60, 66.74, 64.61, 55.13, 44.71, 32.13, 21.87; HRMS (ESI, Orbitrap) calcd for C<sub>33</sub>H<sub>28</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 519.1839, found = 519.1843.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1-methyl-1'-(naphthalen-2-yl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4p):



Prepared following the general procedure; pale yellow solid (0.213 g, 82%); Rf = 0.56 (EtOAc/Hexane = 2/6); mp 221-222 °C; <sup>1</sup>H NMR (500 MHz, Chloroform-d)  $\delta$  8.11 (s, 1H), 7.91 (d, J = 1.2 Hz, 2H), 7.89 – 7.86 (m, 1H), 7.85 – 7.82 (m, 1H), 7.50 – 7.42 (m, 2H), 7.27 – 7.21 (m, 3H), 7.11 (dd, J = 7.4, 1.3 Hz, 1H), 7.09 – 7.03 (m, 4H), 7.03 – 7.00 (m, 1H), 6.92 – 6.89 (m, 1H), 6.86 – 6.83 (m, 1H), 6.73 – 6.69 (m, 1H), 6.34 (d, J = 7.7 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 4.66 (d, J = 9.8 Hz, 1H), 4.48 (t, J = 9.9 Hz, 1H), 3.10 (s, 3H), 3.02 – 2.90 (m, 2H), 2.73 – 2.63 (m, 1H), 2.59 – 2.50 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.84, 178.61, 143.61, 139.40, 138.10, 137.33, 134.70, 133.75, 132.65, 132.46, 129.16, 128.93, 128.82, 128.15, 128.01, 127.79, 127.67, 127.45, 127.04, 126.86, 126.33, 126.21, 126.06, 125.70, 125.54, 125.14, 123.10, 107.23, 71.03, 64.02, 63.54, 50.72, 42.47, 30.30, 25.95; HRMS (ESI, Orbitrap) calcd for C<sub>37</sub>H<sub>231</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 535.2386, found = 535.2388.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(4-methoxyphenyl)-1-methyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4q):



Prepared following the general procedure; pale yellow solid (0.211 g, 82%); Rf = 0.58 (EtOAc/Hexane = 2/6); mp 229-230 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (d, J = 8.7 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.14 – 7.03 (m, 5H), 7.02 – 6.98 (m, 1H), 6.96 – 6.90 (m, 3H), 6.92 – 6.85 (m, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.32 (d, J = 7.7 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 4.52 (d, J = 9.7 Hz, 1H), 4.24 (t, J = 9.9 Hz, 1H), 3.81 (s, 3H), 3.07 (s, 3H), 2.92 (d, J = 7.7 Hz, 2H), 2.65 (d, J = 12.3 Hz, 1H), 2.52 – 2.47 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  197.01, 178.63, 158.55, 143.58, 138.24, 137.45, 134.71, 133.83, 132.39, 130.02, 129.07,

128.78, 127.77, 127.46, 127.12, 126.26, 126.15, 125.46, 125.04, 123.04, 114.43, 107.16, 70.87, 64.13, 63.59, 55.26, 49.83, 42.39, 30.32, 25.89; HRMS (ESI, Orbitrap) calcd for  $C_{34}H_{31}N_2O_3 [M+H]^+ = 515.1335$ , found = 515.2333.

4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-1-methyl-2-oxo-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4r):



Prepared following the general procedure; pale yellow solid (0.218 g 81%); Rf = 0.59 (EtOAc/Hexane = 2/6); mp 225-226 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.85 – 7.80 (m, 2H), 7.73 – 7.68 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.08 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.06 – 7.02 (m, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.85 – 6.80 (m, 2H), 6.73 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.42 – 6.36 (m, 1H), 5.23 (d, *J* = 10.0 Hz, 1H), 4.44 (d, *J* = 9.7 Hz, 1H), 4.34 (t, *J* = 9.8 Hz, 1H), 3.65 (s, 3H), 3.11 (s, 3H), 2.98 – 2.86 (m, 2H), 2.71 – 2.69 (m, 1H), 2.55 – 2.49 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.28, 178.32, 159.31, 147.82, 143.70, 138.44, 137.37, 134.76, 132.90, 129.98, 129.40, 129.10, 128.71 X 2, 126.66, 125.99, 125.59, 124.66, 123.15, 119.79, 119.68, 118.91, 111.41, 110.96, 107.44, 70.92, 64.28, 63.61, 55.26, 50.57, 42.32, 30.17, 25.98; HRMS (ESI, Orbitrap) calcd for C<sub>35</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup>=540.2287, found = 540.2289.

# (1'R,2'S,3R,10b'S)-2'-benzoyl-1-phenyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4s):



Prepared following the general procedure; pale yellow solid (0.210 g, 75%); Rf = 0.53 (EtOAc/Hexane = 2/6); mp 233-234 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.59 – 7.55 (m, 2H), 7.52 (dd, J = 8.3, 7.0 Hz, 2H), 7.44 – 7.38 (m, 3H), 7.33 – 7.22 (m, 3H), 7.19 – 7.15 (m, 3H), 7.15 – 7.11 (m, 2H), 7.11 – 7.05 (m, 2H), 6.97 – 6.90 (m, 3H), 6.76 (d, J = 7.8 Hz, 1H), 6.45

-6.37 (m, 1H), 5.22 (d, J = 10.1 Hz, 1H), 4.65 (d, J = 9.6 Hz, 1H), 4.33 (t, J = 9.9 Hz, 1H), 3.10 -2.90 (m, 2H), 2.77 -2.62 (m, 2H), 2.33 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$ 196.73, 177.91, 143.44, 138.74, 138.11, 137.53, 136.37, 134.47, 134.00, 132.43, 129.64, 129.47, 128.84, 128.81, 128.67, 128.01, 127.50, 126.72, 126.55, 126.18, 125.93, 125.38, 124.98, 123.43, 108.48, 70.64, 63.97, 63.54, 50.03, 42.18, 30.27, 21.02(One peak is missing due to overlap); HRMS (ESI, Orbitrap) calcd for C<sub>39</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 561.2542, found = 561.2540.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1'-(naphthalen-2-yl)-1-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4t):



Prepared following the general procedure; yellow solid (0.224 g, 75%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 211-212 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.11 (s, 1H), 7.94 – 7.88 (m, 2H), 7.87 – 7.82(m, 2H), 7.54 (t, J = 7.7 Hz, 2H), 7.50 – 7.42 (m, 3H), 7.40 (dd, J = 8.3, 1.5 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.22 – 7.17 (m, 1H), 7.15 – 7.08 (m, 4H), 6.98 – 6.93 (m, 2H), 6.88 – 6.84 (m, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.47 – 6.41 (m, 1H), 5.41 (d, J = 10.1 Hz, 1H), 4.77 (dd, J = 9.6, 1.3 Hz, 1H), 4.56 (t, J = 9.6 Hz, 1H), 3.10 (td, J = 10.7, 3.8 Hz, 1H), 3.01 (td, J = 13.8, 11.6, 6.7 Hz, 1H), 2.77 – 2.69 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.80, 178.04, 143.60, 139.47, 138.08, 137.55, 134.60, 134.10, 133.77, 132.66, 132.64, 129.64, 129.05, 129.00, 128.84 X 2, 128.20, 128.16, 128.12, 128.01, 127.67, 127.60, 126.81, 126.74, 126.70, 126.38, 126.07, 125.71, 125.58, 125.16, 123.62, 108.67, 70.88, 63.97, 63.56, 50.67, 42.37, 30.38; HRMS (ESI, Orbitrap) calcd for C<sub>42</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub> [M+H]+ = 597.2542, found =597.2548.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1-phenyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4u):



Prepared following the general procedure; yellow solid (0.227 g, 75%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 257-258 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (t, *J* = 8.0 Hz, 4H), 7.47 – 7.40 (m, 1H), 7.37 – 7.31 (m, 2H), 7.19 – 7.13 (m, 3H), 7.12 – 7.04 (m, 3H), 7.00 (td, *J* = 7.7, 1.4 Hz, 1H), 6.96 – 6.90 (m, 3H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.56 – 6.49 (m, 2H), 5.89 (dd, *J* = 9.5, 1.3 Hz, 2H), 5.21 (d, *J* = 10.1 Hz, 1H), 4.53 (d, *J* = 9.5 Hz, 1H), 4.32 (t, *J* = 9.8 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.74 – 2.65 (m, 2H), 2.33 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.48, 177.98, 151.21, 147.63, 143.48, 138.81, 138.13, 136.33, 134.46, 134.03, 132.53, 129.62, 129.53, 128.87, 128.79, 128.64, 128.08, 126.74, 126.59, 126.14, 126.05, 125.35, 124.97, 123.59, 123.47, 108.53, 107.45, 107.15, 101.55, 70.79, 63.73, 63.48, 50.17, 42.22, 30.26, 21.02; HRMS (ESI, Orbitrap) calcd for C<sub>40</sub>H<sub>33</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 605.2440, found = 605.2435.

4-((1'R,2'S,3R,10b'S)-2'-(3-methoxybenzoyl)-2-oxo-1-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-1'-yl)benzonitrile (4v):



Prepared following the general procedure; yellow solid (0.220 g, 73%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 207-208 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.85 – 7.80 (m, 2H), 7.71 – 7.66 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.47 – 7.41 (m, 1H), 7.32 – 7.28 (m, 2H), 7.16 – 7.10 (m, 3H), 7.07 (dd, *J* = 9.0, 7.6 Hz, 1H), 7.01 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 6.89 – 6.87 (m, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.49 – 6.44 (m, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 4.55 (d, *J* = 9.5 Hz, 1H), 4.41 (t, *J* = 9.8 Hz, 1H), 3.64 (s, 3H), 3.08 – 2.93 (m, 2H), 2.76 – 2.67

(m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.08, 177.66, 159.33, 147.75, 143.58, 138.54, 137.23, 134.54, 133.78, 132.82, 129.83, 129.51, 129.17, 129.04, 128.99, 128.20, 126.57, 126.35, 126.23, 125.98, 125.51, 124.56, 123.52, 119.80, 119.52, 118.76, 111.65, 110.89, 108.76, 70.69, 64.04, 63.55, 55.15, 50.37, 42.10, 30.12; HRMS (ESI, Orbitrap) calcd for  $C_{40}H_{32}N_3O_3 [M+H]^+ = 602.2444$  found = 602.2440.

(1'R,2'S,3R,10b'S)-2'-benzoyl-1-benzyl-1'-(naphthalen-2-yl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4w):



Prepared following the general procedure; yellow solid (0.214 g, 70%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 226-227 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.13 – 8.10 (m, 1H), 7.96 – 7.90 (m, 2H), 7.88 (dd, J = 7.4, 1.9 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.52 – 7.41 (m, 2H), 7.36 – 7.32 (m, 1H), 7.32 – 7.30 (m, 3H), 7.30 (dd, J = 3.9, 1.6 Hz, 1H), 7.28 (d, J = 1.2 Hz, 1H), 7.26 (d, J = 1.4 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.12 (dd, J = 7.4, 1.4 Hz, 1H), 7.10 – 7.06 (m, 2H), 6.98 – 6.90 (m, 3H), 6.88 – 6.80 (m, 2H), 6.72 (dd, J = 7.8, 1.1 Hz, 1H), 6.38 – 6.33 (m, 1H), 5.42 (d, J = 10.1 Hz, 1H), 5.00 (d, J = 15.4 Hz, 1H), 4.74 – 4.61 (m, 2H), 4.54 (t, J = 9.8 Hz, 1H), 3.04 – 2.91 (m, 2H), 2.73 – 2.65 (m, 1H), 2.62 – 2.52 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.81, 178.45, 142.87, 139.41, 137.97, 137.18, 135.69, 134.47, 133.63, 132.53, 132.37, 128.96, 128.87, 128.79, 128.67, 128.00, 127.90, 127.80, 127.69, 127.56, 127.52, 127.40, 126.70, 126.38, 126.21, 125.95, 125.58, 125.44, 125.05, 122.99, 108.20, 70.68, 63.38, 63.28, 50.74, 43.76, 42.30, 30.23. HRMS (ESI, Orbitrap) calcd for C<sub>43</sub>H<sub>35</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> = 611.2699, found = 611.2695.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1-benzyl-1'-(p-tolyl)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinolin]-2-one (4x):



Prepared following the general procedure; yellow solid (0.218 g, 69%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 238-239 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 – 7.55 (m, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.29 (m, 3H), 7.27 (d, J = 17.1 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 7.12 – 7.03 (m, 2H), 6.95 – 6.88 (m, 2H), 6.88 – 6.82 (m, 2H), 6.76 – 6.73 (m, 2H), 6.32 (d, J = 7.9 Hz, 1H), 6.26 (d, J = 8.2 Hz, 1H), 5.86 (dd, J = 8.9, 1.3 Hz, 2H), 5.20 (d, J = 10.1 Hz, 1H), 4.99 (d, J = 15.5 Hz, 1H), 4.69 (d, J = 15.3 Hz, 1H), 4.46 (d, J = 9.4 Hz, 1H), 4.29 (t, J = 9.7 Hz, 1H), 2.96 – 2.90 (m, 2H), 2.68 (dd, J = 13.4, 7.5 Hz, 1H), 2.59 – 2.50 (m, 1H), 2.35 (s, 3H), 2.16 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.75, 178.38, 151.01, 147.58, 140.47, 138.95, 138.18, 136.30, 135.89, 134.46, 132.57, 132.51, 129.62, 129.12, 128.80, 128.74, 128.61, 127.63, 127.53, 127.11, 126.85, 126.11, 125.32, 124.98, 123.58, 107.90, 107.27, 106.85, 101.44, 70.75, 63.36, 63.28, 50.37, 43.75, 42.32, 30.22, 21.05, 20.81; HRMS (ESI, Orbitrap) calcd for C<sub>42</sub>H<sub>37</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 633.2753, found = 633.2752.

(1'R,2'S,3R,10b'S)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-5-(trifluoromethoxy)-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1a]isoquinolin]-2-one (4y):



Prepared following the general procedure; yellow solid (0.233 g, 76%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 234-235 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.02 (s, 1H), 7.53

(d, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 7.12 – 7.01 (m, 3H), 6.95 – 6.88 (m, 3H), 6.84 (dd, J = 8.4, 2.4 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.60 – 6.51 (m, 2H), 5.90 – 5.86 (m, 2H), 5.14 (d, J = 10.1 Hz, 1H), 4.42 (d, J = 9.3 Hz, 1H), 4.24 (t, J = 9.7 Hz, 1H), 2.94 – 2.94 (m, 2H), 2.68 (d, J = 11.7 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.34 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.35, 180.35, 151.28, 147.57, 144.07, 140.73, 138.67, 137.83, 136.25, 134.24, 131.97, 129.51, 128.96, 128.61, 128.54, 126.08, 125.21, 124.73, 123.63, 122.23, 121.24, 119.88, 119.20, 109.70, 107.10, 107.07, 101.49, 70.87, 63.18, 62.84, 50.15, 42.25, 30.05, 20.91; HRMS (ESI, Orbitrap) calcd for C35H<sub>28</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> = 613.1950, found = 613.1956.

(1'R,2'S,3R,8a'R)-2'-(benzo[d][1,3]dioxole-5-carbonyl)-1'-(p-tolyl)-2',5',6',7',8',8a'hexahydro-1'H-spiro[indoline-3,3'-indolizin]-2-one (5b):



Prepared following the general procedure; yellow solid (0.192 g, 80%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 195-196 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.44 (s, 1H), 7.41 – 7.36 (m, 2H), 7.11 (d, J = 7.9 Hz, 2H), 7.11 – 7.06 (m, 1H), 7.05 (dd, J = 8.2, 1.8 Hz, 1H), 6.99 (td, J = 7.6, 1.4 Hz, 1H), 6.93 – 6.83 (m, 2H), 6.53 (d, J = 8.1 Hz, 1H), 6.49 (d, J = 7.7 Hz, 1H), 5.87 (q, J = 1.4 Hz, 2H), 4.31 (d, J = 9.8 Hz, 1H), 3.82 (t, J = 9.9 Hz, 1H), 3.46 (td, J = 10.1, 2.5 Hz, 1H), 2.42 (td, J = 11.5, 11.0, 2.9 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.29 (s, 3H), 1.74 – 1.69 (m, 2H), 1.38 – 1.25 (m, 2H), 1.25 – 1.12 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  195.40, 180.25, 151.13, 147.52, 140.31, 137.09, 136.20, 132.49, 129.11, 128.65, 128.37, 127.99, 126.76, 123.65, 122.82, 108.49, 107.30, 107.07, 101.47, 72.33, 65.30, 60.82, 51.49, 45.56, 30.36, 25.54, 23.55, 20.94; HRMS (ESI, Orbitrap) calcd for C<sub>30</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup> = 481.2127 found = 481.2131

(3R,7'S,8'R,8a'S)-7'-(benzo[d][1,3]dioxole-5-carbonyl)-8'-(p-tolyl)-1',3',4',7',8',8a'hexahydrospiro[indoline-3,6'-pyrrolo[2,1-c][1,4]oxazin]-2-one (5c):



Prepared following the general procedure; yellow solid (0.188 g, 78%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 220-221 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.29 (br s, 1H), 7.41 – 7.35 (m, 2H), 7.13 – 7.08 (m, 3H), 7.07 – 6.99 (m, 2H), 6.95 – 6.87 (m, 2H), 6.58 (dd, J = 7.8, 2.0 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 5.85 (dt, J = 4.6, 1.4 Hz, 2H), 4.32 (d, J = 9.2 Hz, 1H), 3.97 – 3.88 (m, 2H), 3.84 (td, J = 10.0, 2.9 Hz, 1H), 3.76 (dd, J = 11.1, 3.1 Hz, 1H), 3.43 – 3.34 (m, 2H), 2.75 (td, J = 10.9, 3.4 Hz, 1H), 2.29 (s, 3H), 2.24 (dd, J = 10.9, 2.5 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  194.94, 179.99, 151.34, 147.62, 140.61, 136.63, 136.10, 132.26, 129.32, 129.08, 128.10, 126.91, 126.69, 123.72, 122.94, 108.99, 107.28, 107.17, 101.55, 72.18, 71.71, 66.42, 62.79, 60.98, 47.68, 45.67, 20.94; HRMS (ESI, Orbitrap) calcd for C<sub>29</sub>H<sub>27</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup> = 483.1920, found = 483.1914.

(1'R,2'S,3R,7a'R)-2'-benzoyl-1'-(2-bromophenyl)-1',2',5',6',7',7a'hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (5d):



Prepared following the general procedure; yellow solid (0.200 g, 82%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 235-236 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.09 (brs, 1H), 7.62 (dd, J = 21.0, 7.9 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 7.31 (m, 3H), 7.15 (m, 3H), 7.09 – 7.00 (m, 2H), 6.58 (m, 1H), 5.05 (d, J = 11.5 Hz, 1H), 4.65 (t, J = 10.7 Hz, 1H), 4.12 (m, 1H), 2.66 (m, 2H), 2.07 – 1.81 (m, 4H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  196.70, 180.74, 140.47, 138.86, 136.86, 133.21, 132.76, 129.39, 128.09, 128.03, 127.97, 127.75, 127.31, 125.67, 124.84,

122.49, 109.99, 73.55, 72.92, 64.19, 50.25, 48.24, 29.94, 27(one peak is missing due to overlap); HRMS (ESI, Orbitrap) calcd for  $C_{27}H_{24}BrN_2O_2$  [M+H]<sup>+</sup> =487.1021, found = 487.1023.

(1'R,2'S,3R,10b'S)-methyl 2-oxo-1'-phenyl-2',5',6',10b'-tetrahydro-1'H-spiro[indoline-3,3'-pyrrolo[2,1-a]isoquinoline]-2'-carboxylate (5e):



Prepared following the general procedure; white solid (0.174 g, 82%); Rf = 0.63 (EtOAc/Hexane = 2/6); mp 208-209 °C; <sup>1</sup>H NMR (400 MHz, Chloroform-d)  $\delta$  7.64 (dd, J = 7.4, 1.3 Hz, 1H), 7.30 (s, 1H), 7.26 – 7.19 (m, 2H), 7.17–7.11 (m, 6H), 7.10–7.06 (m, 3H), 6.64 (d, J = 7.6 Hz, 1H), 5.68 (d, J = 8.4 Hz, 1H), 4.22 (d, J = 6.3 Hz, 1H), 4.15 (dd, J = 8.4, 6.3 Hz, 1H), 3.46 (s, 3H), 3.11–3.03 (m, 1H), 2.71 (dd, J = 9.2, 3.1 Hz, 2H), 2.62 (dd, J = 15.8, 2.8 Hz, 1H). <sup>13</sup>C NMR (101 MHz, Chloroform-d)  $\delta$  177.72, 174.78, 141.56, 136.15, 135.86, 135.20, 129.45, 129.22, 128.62, 128.27, 127.51, 126.26, 125.41, 125.05, 123.20, 109.45, 76.06, 62.74, 58.96, 51.65, 50.82, 42.81, 30.25.(two peaks are missing due to overlap). HRMS (ESI, Orbitrap) calcd for C<sub>27</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> =425.1865, found = 425.1869.

# 3. Crystallographic data of product 4q

#### Sample preparation and crystal structure determination of 5f

The pure compound 4q as obtained from column chromatography was crystallised from ethanol solvent.

X-ray data for the compounds 4q was collected at room temperature on a Bruker D8 QUEST instrument with an IµS Mo microsource ( $\lambda = 0.7107$  A) and a PHOTON-100 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 3 software suite programs [1]. The structure was solved using the intrinsic phasing method [2] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. All C bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H =

0.93-0.97 Å and  $U_{iso}(H) = 1.5U_{eq}(C)$  for methyl H or  $1.2U_{eq}(C)$  for other H atoms]. The methyl groups were allowed to rotate but not to tip. The ethanol solvate of **4q** could not be resolved due to extensive disorder, and their assumed presence was removed from the overall scattering by the PLATON SQUEEZE procedure. The N bound H atoms of **4q** were located in a difference density map and refined isotropically.

Crystal Data for **4q**:  $C_{34}H_{30}N_2O_3$  (*M*=514.60 g/mol): monoclinic, space group P2<sub>1</sub>/c (no. 14), *a* = 9.56320(10) Å, *b* = 17.8067(3) Å, *c* = 16.1958(3) Å, *β* = 103.4627(6)°, *V* = 2682.18(7) Å<sup>3</sup>, *Z* = 4, *T* = 294.15 K, µ(MoKα) = 0.081 mm<sup>-1</sup>, *Dcalc* = 1.274 g/cm<sup>3</sup>, 24289 reflections measured (4.574°  $\leq 2\Theta \leq 52.496°$ ), 5392 unique ( $R_{int} = 0.0552$ ,  $R_{sigma} = 0.0474$ ) which were used in all calculations. The final  $R_1$  was 0.0549 (I > 2 $\sigma$ (I)) and  $wR_2$  was 0.1500 (all data).

CCDC 1983982 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: <a href="mailto:deposit@ccdc.cam.ac.uk">deposit@ccdc.cam.ac.uk</a>].



Figure S1: X-ray crystal structure of 5q Thermal ellipsoids are drown at 30% probability

# checkCIF/PLATON report

Structure factors have been supplied for datablock(s) KA904\_0m

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

# Datablock: KA904\_0m

Bond precision:	C-C = 0.003	1 A		Wavelen	gth=0.71073	
Cell:	a=9.5632(1) alpha=90	b=1 bet	L7.8067	(3) 1627(6)	c=16.1958(3) gamma=90	
Temperature:	294 K					
	Calculated			Report	ed	
Volume	2682.18(7)			2682.1	8(7)	
Space group	P 21/c		P 21/c			
Hall group	-P 2ybc			-P 2yb	C	
Moiety formula	C34 H30 N2 O	3	C34 H30 N2 O3			
Sum formula	C34 H30 N2 O	3	C34 H30 N2 O3			
Mr	514.60			514.60		
Dx,g cm-3	1.274		1.274			
Z	4			4		
Mu (mm-1)	0.081			0.081		
F000	1088.0	1088.0				
F000'	1088.46					
h,k,lmax	11,22,20			11,22,	20	
Nref	5399			5392		
Tmin, Tmax	0.979,0.990		0.565,0.746			
Tmin'	0.979					
Correction method= # Reported T Limits: Tmin=0.565 Tmax=0.746 AbsCorr = MULTI-SCAN						
Data completeness= 0.999			Theta(max) = 26.248			
R(reflections) = 0.0549( 4055) wR2(reflections) = 0.1500( 5392)						
S = 1.057	Nj	par= 3	78			

The following ALERTS were generated. Each ALERT has the format test-name\_ALERT\_alert-type\_alert-level.

Click on the hyperlinks for more details of the test.

#### Alert level C

PLAT220\_ALERT\_2\_C NonSolvent Resd 1 CUeq(max) / Ueq(min) Range3.1 RatioPLAT241\_ALERT\_2\_C HighMainMol Ueq as Compared to Neighbors ofC18 CheckPLAT241\_ALERT\_2\_C HighMainMol Ueq as Compared to Neighbors ofC29 CheckPLAT241\_ALERT\_2\_C HighMainMol Ueq as Compared to Neighbors ofC31 CheckPLAT241\_ALERT\_2\_C HighMainMol Ueq as Compared to Neighbors ofC31 CheckPLAT241\_ALERT\_2\_C HighMainMol Ueq as Compared to Neighbors ofC31 CheckPLAT911\_ALERT\_3\_C Missing FCF Refl Between Thmin & STh/L=0.6003 Report

### Alert level G

PLAT171_ALERT_4_G The CIF-Embedded .res File Contains EADP Records	1 Report
PLAT230_ALERT_2_G Hirshfeld Test Diff for C29C30 .	10.7 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for C29C30D .	10.0 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for C30C31 .	19.7 s.u.
PLAT230_ALERT_2_G Hirshfeld Test Diff for C31C30D .	7.0 s.u.
PLAT301_ALERT_3_G Main Residue Disorder	8% Note
PLAT413_ALERT_2_G Short Inter XH3 XHn H24H33D .	2.09 Ang.
1-x,1-y,1-z =	3_666 Check
PLAT432_ALERT_2_G Short Inter XY Contact C6C33D	3.18 Ang.
1-x,-1/2+y,3/2-z =	2_646 Check
PLAT793_ALERT_4_G Model has Chirality at C1 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G Model has Chirality at C9 (Centro SPGR)	S Verify
PLAT793_ALERT_4_G Model has Chirality at C10 (Centro SPGR)	R Verify
PLAT793_ALERT_4_G Model has Chirality at C11 (Centro SPGR)	S Verify
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .	Please Do !
<pre>PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).</pre>	2 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600	2 Note
PLAT913_ALERT_3_G Missing # of Very Strong Reflections in FCF	1 Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.	4 Info
PLAT992_ALERT_5_G Repd & Actual _reflns_number_gt Values Differ by	1 Check

0 ALERT level A = Most likely a serious problem - resolve or explain 0 ALERT level B = A potentially serious problem, consider carefully 5 ALERT level C = Check. Ensure it is not caused by an omission or oversight 18 ALERT level G = General information/check it is not something unexpected 1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data 11 ALERT type 2 Indicator that the structure model may be wrong or deficient 4 ALERT type 3 Indicator that the structure quality may be low 6 ALERT type 4 Improvement, methodology, query or suggestion 1 ALERT type 5 Informative message, check



#### Data blockshelxl\_sq - ellipsoid plot

# 4. Copies of NMR Spectra



Figure S3: <sup>13</sup>C NMR of compound 4a (126 MHz, CDCl<sub>3</sub>)



Figure S5: <sup>13</sup>C NMR of compound 4b (126 MHz, CDCl<sub>3</sub>)



Figure S7: <sup>13</sup>C NMR of compound 4c (126 MHz, CDCl<sub>3</sub>)



**Figure S9:** <sup>13</sup>C NMR of compound **4d** (126 MHz, CDCl<sub>3</sub>)



Figure S11: <sup>13</sup>C NMR of compound 4e (126 MHz, CDCl<sub>3</sub>)



Figure S13: <sup>13</sup>C NMR of compound 4f (126 MHz, CDCl<sub>3</sub>)



Figure S15: <sup>13</sup>C NMR of compound 4g (126 MHz, CDCl<sub>3</sub>)



Figure S17: <sup>13</sup>C NMR of compound 4h (126 MHz, CDCl<sub>3</sub>)



Figure 19: <sup>13</sup>C NMR of compound 4i (126 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>)







Figure S23: <sup>13</sup>C NMR of compound 4k (126 MHz, CDCl<sub>3</sub>)



Figure S25: <sup>13</sup>C NMR of compound 4l (126 MHz, CDCl<sub>3</sub>)




Figure S29: <sup>13</sup>C NMR of compound 4n (126 MHz, CDCl<sub>3</sub>)



Figure S31: <sup>13</sup>C NMR of compound 40 (126 MHz, CDCl<sub>3</sub>)



Figure S33: <sup>13</sup>C NMR of compound 4p (126 MHz, CDCl<sub>3</sub>)





Figure S37: <sup>13</sup>C NMR of compound 4r (126 MHz, CDCl<sub>3</sub>)



Figure S39: <sup>13</sup>C NMR of compound 4s (126 MHz, CDCl<sub>3</sub>)



Figure S41: <sup>13</sup>C NMR of compound 4t (126 MHz, CDCl<sub>3</sub>)



Figure S43: <sup>13</sup>C NMR of compound 4u (126 MHz, CDCl<sub>3</sub>)



Figure S45: <sup>13</sup>C NMR of compound 4v (126 MHz, CDCl<sub>3</sub>)



Figure S47: <sup>13</sup>C NMR of compound 4w (126 MHz, CDCl<sub>3</sub>)



Figure S49: <sup>13</sup>C NMR of compound 4x (126 MHz, CDCl<sub>3</sub>)



Figure S51: <sup>13</sup>C NMR of compound 4y (126 MHz, CDCl<sub>3</sub>)



Figure S53: <sup>13</sup>C NMR of compound 5b (126 MHz, CDCl<sub>3</sub>)



Figure S55: <sup>13</sup>C NMR of compound 5c (126 MHz, CDCl<sub>3</sub>)



Figure S57: <sup>13</sup>C NMR of compound 5d (126 MHz, CDCl<sub>3</sub>)



Figure S59: <sup>13</sup>C NMR of compound 5d (126 MHz, CDCl<sub>3</sub>)

# 5. Copies of HRMS Spectra



Figure S60: HRMS of Compound 4a



Figure S61: HRMS of Compound 4b

E elemental Composition	
File Edit View Process Help	
Single Mass Analysis         Tolennex = 100 cm0 a / 10E; min = -1.5, max = 50.0         Element prediction: Off         Number of isotope pasks used for FIFT = 3         Monoiadopic Mass. Even Electron Ions         1209 formula(e) evaluated with 257 results within limits (all results (up to 1000) for each mass)	E E
Mass Calc. Mass mDa PPM DBE Formula i+FIT i+FIT Norm Fit Conf % C H N O	*
526.2133 526.2131 0.2 0.4 22.5 C34 H28 N3 0.3 5762 6.602 0.14 34 28 3 3	
Sabe_Lide         -0.3         -0.6         4.5         C.1.1         1.6         1.4           Sabe_Lide         -0.3         -0.6         1.5         CB (+0.4)         CB (-1.4)         1.4         1.4           Sabe_Lide         -0.3         -0.6         1.5         CB (+0.4)         CB (-1.4)         1.4         1.5           Sabe_Lide         -1.4         2.1         1.05         CB (+0.4)         Sabe_Lide         2.4         1.5         4.6           Sabe_Lide         -1.6         -3.0         -5.5         CE (+0.4)         FO (-1.4)         1.8         2.8         1.1         8           Sabe_Lide         -1.6         -3.0         -5.5         CE (+0.4)         FO (-1.4)         5.90         2.2         5         1.0	-
17102019_341_6127 RAM23_17702019_06145(3.735),MI2 (#30000.0.565.828.0.00.L8 1)	TOF MS ES+
100 528.2133	1.92e+007
9- 527 2187 526 1541 528 2246 528 2246 52	
0 123.0891.339.9834.204.0834 204.0834 312.3678 20002 992.8634 1048.4280 1136.72229.152.2837.684.5976 104.2837.6847.6837.6847.6837.6847.6837.6847.6837.6847.6837.6847.6847.6847.6847.6847.6847.6847.684	11 1198.2471 m/z
1 50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000 1050 1100 1150	1200
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Figure S62: HRMS of Compound 4c



Figure S63: HRMS of Compound 4d

Element	al Composition	April 1					_	_			_								- 0 -×
File Edit	View Process	Help																	
		M	X																
Tolerance	= 100.0 mDa	/ DBE:	min = -1.6	5, max =	= 50.0														i i i i i i i i i i i i i i i i i i i
Element	prediction: Off	und for	: EIT = 2																-
Monoisote	pic Mass, Even	Electron lo	ins																1
1223 form	nula(e) evaluated	d with 261 i	results with	hin limits	s (all results (up to 1000	) for each ma	ss)												
Elements	Used:																		*
Mass	Calc. Mass	mDa I	PPM D	BE For	irmula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	0							^
529.2128	529.2127 529.2132	-0.4	0.2 2 -0.8 3	15 C3	24 H29 N2 04	603.8	6.493	0.15	34	29	2	4							
	529.2132	-0.4	-0.8 1	4.5 CI	19 H25 N14 O5	601.6	4.280	1.38	19	25	14	5							
	529.2119	0.9 1	1.7 9	15 CI	18 H29 N10 O9	602.5	5.197	0.55	18	29	10	9							
17102019	341 6125	-10	2.0 2.			00110	0.750	0.42			-								
RAM-21_1	7102019_002 1	44 (3.709)	AM2 (Ar, 30	000.0,55	56.27,0.00,LS 1)														1: TOF MS ES+
100									529	2128									4.05e+007
1																			
%-																			
1																			
										500.04	0.0								
										530.21	88								
600			0.00	1054	263 1182 005 5705			7.5704	529.1533	531.2	256							4000.00	
0 0.2	117.065	1 202	2.0472	1204	285.5785	357.6811 3	98.1718 46	51.5/91 5	01.2195	-532	2328	613.0776 660.3073	723.3980 /40	5.7715 8	31.9971 88	1.5912	966.1235_983.5730	1057.4580	1188.8877
50	100	150	200		250 300	350	400	450	500	550	)	600 650	700 750	800	850	900	950 1000	1050 1100	1150
For Help, pr	ress F1			- Ind		-							_	_		-	-		2.25 014
1	e			Gel	A 📐			100										- 13 N - 6	10/17/2019

Figure S64: HRMS of Compound 4e

S Ele	emental	Composition	and the second s	-			-													10.10			0 ×
File	Edit	View Proces	ss Help																				
		86 8	M	X																			
Sin Tole Eler	gle Ma rance = nent pre	ass Analys = 100.0 mDa ediction: Off	/ DBE	: min = -	1.5, m	ax = 50.0																	Î
Mon 1273	oisotopi 3 formul	ic Mass, Ever la(e) evaluate	n Electron ed with 24	Ions 7 results v	3 within li	imits (all results (up to '	1000) for each m	ass)															]
Lien	iteritis O	Colo Marco	D.	0044	DOC	Commute	1.07	I FIT MANY	I TA COULE			AL I	0	-									*
515.2	333	515.2335	-0.2	-0.4	20.5	C34 H31 N2 O3	518.9	5.661	0.35	34	31	2	3										
		515.2340	-0.7	-1.4	13.5	C19 H27 N14 O4	519.0	5.765	0.31	19	27	14	4										
		515.2326	0.7	1.4	8.5	C18 H31 N10 08	519.8	6.519	0.15	18	31	10	8										
2000	2010.2	515.2353	-2.0	-3.9	7.5	C22 H35 N4 O10	519.1	5.858	0.29	22	35	4	10										
RAM-	07_280	82019_010	144 (3.709	9) AM2 (Ar,	30000.	0,556.47,0.00,LS 1)				515.233	3											1:1	OF MS ES+ 5.33e+007
96-																							
										51	5.2403												
											10457												
	10	6 0680				277.1340		454.90	513.2	241 21	1.2457						771 9410809 903	3	980 6	404	1074 2529		
0		132	.0791	217.087	70_234	278.1384	350.2008 39	5.4308 404.84	487.24	2	18.252	2 59	91.10	669.297	2 74	0.2149		885.8143	958.2703 500.0	1051.4752	1400	143.4502,11	63.6882 m/z
For He	eln nres	100 :s F1	150	20	0	250 300	350	400	450 5	00	550		60	00 650	700	/50	800	850 900	950 100	0 1050	1100	1150	1200
	op, pres	6	-	-	1						-			1	-		_					-	1:55 PM
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Figure S65: HRMS of Compound 4f

Elemental	Composition	Sec.											
File Edit V	liew Process	Help											
	6	M 🔲	$\times$										
Single Ma Tolerance = Element pre Number of is Monoisotopi 1335 formula Elements Us	ass Analysis 100.0 mDa ediction: Off sotope peaks c Mass, Even a(e) evaluated sed:	S USED FOR THE S USED	r i-FIT = 3 lons results wit	5, max = 50.0 thin limits (all res	ults (up to 100	0) for each m	ass)						· · · · ·
Mare	Cale Mare	mDa	DDM D	PE Earmula		i.crt	i.ETT Norm	Et Conf %		u l	NIO		-
543.2289	543.2289	0.0	0.0 1	4.5 C20 H27 I	N14 O5	618.9	6.749	0.12	20	27	14 5	5	â
	543.2289	0.0	0.0 3	3.5 C22 H39	015	619.1	6.978	0.09	22	39	15	15	
	543.2297	-0.8	-1.5 2	6.5 C36 H27 I	N6	617.1	4.938	0.72	36	27	6		
	543.2302 543.2275	-1.3	-2.4 8	3.5 C23 H35 I 9.5 C19 H31 I	N4 011 N10 09	618.5 619.3	6.429	0.16 0.07	23	35 31	4 11 10 9	11 9	-
17092019_33	31_5944								-			-	_
RAM-18_170	92019_019 15	50 (3.862)	) AM2 (Ar, 30	0000.0,556.40,0.	00,LS 1)					543.22	9	1: TOF MS ES 5.65e+0*	;+ 07
- - - - -				277	1345					54	4.2357	1357	
					278.1389				541.2	185	6.2530	2530	
0 1	17.0587.132.0	150	217.0901	234.1189	360	35.376.03	400	460	F00			623.1025 778.5222 804.6100 7 898.6149 967.5474 1026.7826 1108.5129 7 10.5103	٧z
For Help, press	5 F1	130	200	200	300	300	400	400	500	55		000 000 700 700 000 000 900 900 900 1000 10	_
<b>@</b> (	ê 🔋		2	A		1	28					📼 🔯 🖏 🚳 👘 扰 🐠 358 PM	

Figure S66: HRMS of Compound 4g

File         Bit Were         The State State           Single State Analysis         State         <	Eleme	ntal Composition	-	10.00				_											Sec. 1								0 ×
■ Note (model)         ■ Note (model)           Totacces 100 mm2 / UBE         Totacces 100 mm2 /	File Edi	t View Proces	ss Help																								
Endpd Base Analysis         Tube:         Statuse: 14.06 and 10.00 min.         Status: 14.00 min.         Status			M D	$ \times $																							
Term         Curr, May         Del         Fermion         Fer Card S.         C         I         N         D         D           201307         20130         2013	Single Tolerand Elemen Number Monoiso 4456 for Elemen	Mass Analys ce = 100.0 mDa t prediction: Off of isotope peal topic Mass, Ever mula(e) evaluate ts Used:	ks used f n Electror ed with 63	E: min = - for i-FIT = h lons 36 results v	1.5, ma 3 within lin	tox = 50.0 mits (all results (up to 1000	)) for each ma	iss)																			Ē
SA139         SA1         SA139         SA1         SA139         SA139 <thsa19< th="">         SA139         <thsa19< <="" td=""><td>Mare</td><td>Calc Mare</td><td>mDa</td><td>PPM</td><td>DRE</td><td>Formula</td><td></td><td>i.FIT</td><td>i-FIT Norn</td><td>Eit Con</td><td>195 0</td><td>Н</td><td>N</td><td>0</td><td>Br</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></thsa19<></thsa19<>	Mare	Calc Mare	mDa	PPM	DRE	Formula		i.FIT	i-FIT Norn	Eit Con	195 0	Н	N	0	Br												
Skillster         Skillster <t< td=""><td>563.1335</td><td>563.1334</td><td>0.1</td><td>0.2</td><td>10.5</td><td>C17 H23 N8 O14</td><td></td><td>631.5</td><td>23.327</td><td>0.00</td><td>17</td><td>23</td><td>8</td><td>14</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	563.1335	563.1334	0.1	0.2	10.5	C17 H23 N8 O14		631.5	23.327	0.00	17	23	8	14													
93139       0.4       0.7       13       CENAN MAR OF P       002       223       7.33       14       1       1         93139       0.4       0.7       13       CENAN MAR OF P       13       CENAN MAR OF P       13       CENAN MAR OF P       14       15       13       15       15       15       15       15       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       15       13       13       15       13       13       15       13       15       13       15       13       15		563.1334	0.1	0.2	20.5	C33 H28 N2 O2 Br		619.5	11.320	0.00	33	28	2	2	1												
5513131 04 07 05 05 04 11 20 05 04 10 06 02 0520 120 00 03 00 03 0 00 03 0 00 03 0 00 03 0 00 0		563.1339	-0.4	-0.7	13.5	C18 H24 N14 O3 Br C20 H36 O13 Br		610.7	2.613	7.33	18	24	14	3	1												
S93129         0.6         11         285         CDP HIS 25         0.00         30         15         10         3           10000019_3027 14         CASH 12, 00000 0565 31.0.00 LS 1); Cm (146; 151)         1.70F HIS 25         1.338+00         1.338+00         1.338+00           100         563 1335         563 1335         1.338+00         1.338+00         1.338+00           100         563 1335         563 1335         1.338+00         1.338+00         1.338+00           100         563 1335         563 1335         563 1335         1.338+00         1.338+00           100         563 1373         563 1373         563 1373         563 1373         563 1372           115.0488_332.0786         217.70801_2.204 1182         277.1340_2.93.1277         346 2483         425 2276         483 1275         561 1262         567 4455         511.022         567 4455         511.022         567 4455         511.022         567 4455         511.022         567 4455         511.022         567 4455         511.022         571.455         511.022         571.455         511.022         571.455         511.022         571.455         511.022         571.455         511.022         571.455         511.022         571.455         571.555         560		563.1331	0.4	0.7	0.5	C20 H41 N2 O6 Br2		623.0	14.901	0.00	20	41	2	6	2												
000000019 207 14 ( 2 011) AU2 (A30000 0.555 3 1.0 00 LS 1); Cm (145 151) 100 553 135 553 135 551 1		563.1329	0.6	1.1	28.5	C30 H15 N10 O3		631.8	23.656	0.00	30	15	10	3													*
565.1773 115.0488,132.0766 217.9001.234 1188 277.1340 293.1277 345.2483 425.2270 483.2125 551.1455 531.5007 957.4427.955.5227 788.591 0115.75684 1127.3169 (1150.2782 1184.31) 50 100 150 200 220 300 350 400 450 550 550 550 700 750 850 850 900 850 1000 1050 1100 1150 1200	0209201 RAM-12_	9_321_5776 02092019_027	148 (3.81	1) AM2 (Ar,	30000.0	0,556.31,0.00,LS 1); Cm (1-	45:151)					563.133	5													1:	TOF MS ES+ 1.36e+008
For Help, press F1	%	115.0488,132 100 pres FJ	2.0786	217.090	01,234 0	1188 277 1340 293 1277 250 300	346.2483 350	425	2270	483,2125 500	563.07 561.1	56 113 252 560	6.1373 77.1465 600	631.	5057 553 650	4627 605 5 700	227 1	788.5819	<u>8115755</u> 800	837.5984 850	900	950	1000	1050	1127.315 <u>8</u> 1100	1150.2782 1150	1180.4319 1200 m/z
		e		D	Carl.	A 🐫																			I 🔝 🐢 🚳	1 🗤 🌒	3:40 PM

Figure S67: HRMS of Compound 4h



Figure S68: HRMS of Compound 4i



Figure S69: HRMS of Compound 4j



Figure S70: HRMS of Compound 4k



Figure S71: HRMS of Compound 41

S Elemen	ntal Compositio	n					and the second se										1000	- 0 <u>- ×</u>
File Edi	t View Proce	ess Help																
	666	M	$\times$															
Single Tolerand Element Number Monoiso 2610 for	Mass Analys ce = 100.0 mD t prediction: Of of isotope pea topic Mass, Eve mula(e) evaluat	sis la / DBE ff aks used fo en Electron ted with 507	i min = - r i-FIT = : lons 7 results v	1.5, ma 3 within lin	ax = 50.0 mits (all results (up to 1000	)) for each mass)												Ξ
Element	ts Used:																	
Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT i-F	FIT Norm   Fit Conf 9	6 C	н	N	0 1							
611.1198	611.1200	-0.2	-0.3	13.5	C18 H24 N14 O3 I	506.1 4.3	378 1.25	18	24	14	3 1							1
	611.1201	-0.3	-0.5	2.5	C20 H36 O13 I	507.6 5.8	348 0.29	20	36	12	13 1							
	611.1195	0.3	0.5	20.5	C33 H28 N2 O2 I	507.7 5.5	946 0.26	33	28	2	2 1							
	611.1203	-0.5	1.3	22.5	C33 H23 O12	509.2 7.3	507 0.05 393 0.06	34	23	4	8							
28082019 RAM-09-2	9_319_5706	08 143 (3 6	84) AM2 (A	Ar 3000	0.0 556 30 0.00 ( \$ 1)													1: TOF MS ES+
100-										6	11.1198							3.81e+00
96-																		
0	87.3666	163.0495	217.0	830 2	263.1154 297.0801	389.0142 388.8923 390.020	18 485 2294	19.1858 520.19	108 6	611.054	612.12	43 693.3704 713.0252	745 5086 779 1932		914.5523	1024.3962	1054.1830	1130.3394 <sup>1154.3132</sup> m
50	100	150	20	0	250 300	350 400	450 50		550	60	00	650 700	750 800	850	900 950	1000	1050 1	100 1150 1200
For Help, p	press F1	<u> </u>	<b>7</b>	- da		202		25					_	-			-	🖶 🛞 📆 🌒 1:53 PM
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Figure S73: HRMS of Compound 4n



Figure S74: HRMS of Compound 40



Figure S75: HRMS of Compound 4p



Figure S76: HRMS of Compound 4q



Figure S77: HRMS of Compound 4r

Section Elemental Composition	
File Edit View Process Help	
Single Mass Analysis Tolerance = 100.0 mDa / DBE: min = -1.5, max Element prediction: Off	x = 50.0
Monoisotopic Mass, Even Electron Ions 1372 formula(e) evaluated with 259 results within lim	itis (all results (up to 1000) for each mass)
Elements Used:	
Mass Calc. Mass mDa PPM DBE	Formula i+FIT   i-FIT Norm   Fit Conf %   C   H   N   0
561.2540 561.2542 -0.2 -0.4 24.5 561.2534 0.6 1.1 12.5	C39 H33 N2 O2 7112 6650 0.13 59 53 2 2 C31 H33 N0 07 7093 4 741 0.87 23 33 10 7
561.2547 -0.7 -1.2 17.5	C24 H29 N14 O3 708.9 4341 1.30 24 29 14 3
561.2547 -0.7 -1.2 6.5	C26 H41 O13 710.1 554 0.39 26 41 13
561.2520 2.0 3.6 7.5	C1 197 N02 D14 7153 000 11 57 12 14
26082019_016	
RAM-08-2_26082019_021 125 (3.218) AM2 (Ar, 30000	0.555 28,0.00LS 1); Cm (110.132) 1: TOF MS ES+ 5 5 18-00
100	01.290
-	
%-	
	562 2585
	561.1915 563.2656
115.0507,132.0780 180.0798 217.0	1887 311.1588 339.1504_354.1903 445.1938_459.2174 559.2436 569.2436 693.3409 721.3354 744.3219 839.3536 887.6115 1097.4689 1121.5406 1143.5112
50 100 150 200	250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000 1050 1100 1150 1200
For Help, press F1	
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Figure S78: HRMS of Compound 4s

Elementa	al Composition	1		-																							X
File Edit	View Proce	ss Help																									
	86 6	M	$\times$																								
Single M Tolerance Element p Monoisoto	Aass Analys = 100.0 mD; prediction: Off pic Mass, Eve	n Electron lo	min = -1. Ins	5, max =	= 50.0																						
Flements I	lisod	ed with 209	esuits wi	unninnis	aniesuita	(up to 100	io) ioi eau	,ii iiidəs	•]																		
C: 0-100	H: 0-6	0	N: 0-15		0:0-15																						
Mass	Calc. Mass	mDa	PPM 0	DBE For	rmula			CH	H N	0																	
597.2548	597.2547 597.2547 597.2552	0.1 0.1 -0.4	0.2 2	0.5 C2 9.5 C2 2.5 C1	7 H29 N14 9 H41 O13 4 H37 N12	03		27 2 29 4 14 3	9 14 1 7 12	13 14																	
	597,2542	-1.3	.0 2	4.5 (3)	0 H37 N4 I	02		42 3 30 3	3 <u>2</u> 7 4	9	 																
	597.2534	1.4	2.3 1	5.5 C2	6 H33 N10	07		26 3	3 10	7																	•
31102019_ RAM-24_31	349_6245 1102019_015	167 (4.302)																								1: TO	OF MS ES+
100													591.25	0													
-																											
													59	3.2554													
												597. 595.2	1948 2461														
											535.	2507															
50	100	150	200		250	300	350		100	450	 500	550	600		50	700	750	800		50	900	950	1000	1050	1100	1150	m/z
For Help, pre	ess F1	100	2.50										000					000	0					1050		1100	
	<u> </u>			<b>.</b>	Δ			÷.,			10.0	-		1						100				B	S = 0	10 (t) 4	:04 PM

Figure S79: HRMS of Compound 4t

Elemental Composition	
File Edit View Process Help	
Ince on LX	
Single Mass Analysis Tolerance = 100.0 mDa / DBE: min = -1.5, max = 50.0	
Element prediction: Off	
Monoisotopic Mass, Even Electron ions 1306 formula(e) evaluated with 272 results within limits (all results (up to 1000) for each mass)	
Elements Used:	
C: 0-100 H: 0-60 N: 0-15 O: 0-15	
Mass Calc. Mass mDa PPM DBE Formula C H N O	A
605.2430 605.2432 -0.2 -0.3 13.5 C24 H33 N10 O9 24 33 10 9 605.2440 -1.0 -1.7 25.5 C40 H33 N2 O4 40 33 2 4	
605.2419 1.1 1.8 8.5 C23 H37 N6 O13 23 37 6 13	
605.2445 -1.5 -2.5 7.5 C27 H41 015 27 41 15	
17102019_341_6126	4. TAE NO E0.
100- 605.2	430 9.69e+006
	306.2402
005 000	
605.1820.	
0-4 50 100 150 200 250 300 350 400 450 500 550 600	650 700 750 800 850 900 950 1000 1050 1100 1150 1200
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Figure S80: HRMS of Compound 4u



Figure S81: HRMS of Compound 4v

Element	al Composition	And and Address of the			_	_	_			_					- 10										
File Edit	View Process	s Help																							
	re s	M																							
Tolerance	= 100.0 mDa	/ DBE: min	= -1.5, n	nax = 50.0																					Â
Element p	prediction: Off																								
Number o	f isotope peaks	s used for i-FII	= 3																						
1303 form	ula(e) evaluater	d with 268 resu	Its within	limits (all results	(up to 1000) for	each m	ass)																		
Elements	Used:																								-
Mass	Calc. Mass	mDa PPM	DBE	Formula		i-FIT	i-FIT Norm	Fit Conf %	C	н	N	0													•
611.2695	611.2699	-0.4 -0.7	27.5	C43 H35 N2	02	601.8	5.818	0.30	43	35	2	2													
	611.2704	-0.9 -1.5	20.5	C28 H31 N14	03	600.7	4.727	0.89	28	31	14	3													
	611.2704	-0.9 -1.5	9.5	C30 H43 O13	~	601.1	5.130	0.59	30	43		13													
	611.2709 611.2677	-1.4 -2.3 1.8 2.9	2.5	C15 H39 N12 C26 H39 N6	014	603.3 601.1	7.326	0.07	15 26	39	12	14													-
26112019	361_6480																								
RAM-32_26	112019_020 1	77 (4.557) AM2	(Ar,30000	0.0,556.27,0.00,L	.S 1); Cm (175:18	33)							611 2605												1: TOF MS ES+ 8 80e+007
100													011.2000												
%-																									
													612.273	2											
												611.2	004												
												609.2	613.278	13											
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Figure S82: HRMS of Compound 4w



Figure S83: HRMS of Compound 4x



Figure S84: HRMS of Compound 4y



Figure S85: HRMS of Compound 5b

S Elemen	ntal Compositio	n					_		_					- C							
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Element	t prediction: Of	1																			
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483.1914	483.1912	0.2	0.4	5.5	C13 H27 N10 O10	514.9	6.280	0.19	13	27	10	10									
	483,1920	-0.5	-1.2	10.5	C14 H23 N14 06	514.5	5.843	0.44	14	21	14	5									
	483.1898	1.6	3.3	0.5	C12 H31 N6 O14	515.7	6.998	0.09	12	31	6	14									
	483.1933	-1.9	-3.9	22.5	C30 H23 N6 O	514.7	6.021	0.24	30	23	6	1									-
2212201	9 371 6650	6-4	4.5	10.5	025 1125 140 05	51555	5.424	0.00		20		, ,									100
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Figure S86: HRMS of Compound 5c

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Mass	Calc. Mass	mDa	PPM	DBE	Formula		i-FIT	i-FIT Norm	Fit Conf %	C	н	N	0	Br												
487.1023	487.1021	0.2	0.4	6.5	C11 H19 N8 O14		716.6	22.717	0.00	11	19	8	14	-												
	487.1021 487.1026 487.1026 487.1029 487.1016	-0.3 -0.3 -0.6 0.7	-0.6 -0.6 -1.2 1.4	9.5 -1.5 18.5 24.5	C12 H20 N14 03 C12 H20 N14 03 C14 H32 013 Br C27 H19 09 C24 H11 N10 03	Br	701.9 701.4 716.9 716.8	8.061 7.600 23.083 22.950	0.03 0.05 0.00 0.00	12 14 27 24	20 32 19 11	14 10	2 3 13 9 3	1 1												
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Figure S87: HRMS of Compound 5d



Figure S88: HRMS of Compound 5e

### 6. Docking Studies

The docking analysis was developed by Auto Dock Tools (ADT) (Sanner, 1999) version 1.5.6 and Auto dock version 4.2.5.1 programs; (Auto dock, Auto grid, Copyright-1989-2012) from the Scripps Research Institute <u>http://www.scripps.edu/mb/olson/doc/autodock</u>. All the ssynthesised Compounds were docked to target protein complex 4OHU with the protein molecule considered as a rigid body and the ligand as flexible. The search was carried out with the Lamarckian Genetic Algorithm; (Morris et al., 1998) populations of 150 individuals with a mutation rate of 0.02 evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed, and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The output was exported to ADT and Biovia-Discovery Studio for visual inspection of the binding modes and interactions of the compounds with amino acid residues in the active sites.

The docking simulations in the active sites of ACP reductase InhA, is one of the essential enzymes involved in the type II fatty acid biosynthesis pathway of M. tuberculosis (PDB: 4OHU), was performed by the Auto Dock Tools (ADT) version 1.5.6 and Auto dock version 4.2.5.1 programmes.

#### **Compound 4a**



**Figure S89(a-b):** Molecular docking results of **4a** with ACP reductase (4OHU): (S**89a**) 3D Docking pose of **4a** with the receptor (S**89b**) 2D Docking pose of **4a** with the receptor



### **Compound 4b**





Figure S90(a-b): Molecular docking results of 4b with ACP reductase (4OHU): (S90a) 3D Docking pose of 4b with the receptor (S90b) 2D Docking pose of 4b with the receptor

## **Compound 4c**







Figure S91(a-b): Molecular docking results of 4c with ACP reductase (40HU): (S91a) 3D Docking pose of 4c with the receptor (S91b) 2D Docking pose of 4c with the receptor

## **Compound 4d**

(S92a)

(S92b)



**Figure S92(a-b):** Molecular docking results of **4d** with ACP reductase (4OHU): **(S92a)** 3D Docking pose of **4d** with the receptor **(S92b)**2D Docking pose of **4d** with the receptor

## **Compound 4e**

(S93a)

(S93b)



**Figure S93(a-b):** Molecular docking results of **4e** with ACP reductase (4OHU): **(S93a)** 3D Docking pose of **4e** with the receptor **(S93b)** 2D Docking pose of **4e** with the receptor

# **Compound 4f**

(S94a)

(S94b)



**Figure S94(a-b):** Molecular docking results of **4f** with ACP reductase (4OHU): **(S94a)** 3D Docking pose of **4f** with the receptor **(S94b)** 2D Docking pose of **4f** with the receptor

## **Compound 4g**



**Figure S95(a-b):** Molecular docking results of **4g** with ACP reductase (40HU): **(S95a)** 3D Docking pose of **4g** with the receptor **(S95b)** 2D Docking pose of **4g** with the receptor
# **Compound 4h**



Figure S96(a-b): Molecular docking results of 4h with ACP reductase (4OHU): (S96a) 3D Docking pose of 4h with the receptor (S96b) 2D Docking pose of 4h with the receptor

# **Compound 4i**



**Figure S97(a-b):** Molecular docking results of **4i** with ACP reductase (4OHU): **(S97a)** 3D Docking pose of **4i** with the receptor **(S97b)** 2D Docking pose of **4i** with the receptor

# **Compound 4j**



Figure S98(a-b): Molecular docking results of 4j with ACP reductase (4OHU): (S98a) 3D Docking pose of 4j with the receptor (S98b) 2D Docking pose of 4j with the receptor

# **Compound 4k**



Figure S99(a-b): Molecular docking results of 4k with ACP reductase (40HU): (S99a) 3D Docking pose of 4k with the receptor (S99b) 2D Docking pose of 4k with the receptor

### **Compound 41**

(S100a)

(S100b)



**Figure S100(a-b):** Molecular docking results of **4** with ACP reductase (4OHU): **(S100a)** 3D Docking pose of **4** with the receptor **(S100b)** 2D Docking pose of **4** with the receptor



**Figure S101(a-b):** Molecular docking results of **4m** with ACP reductase (4OHU): **(S101a)** 3D Docking pose of **4m** with the receptor **(S101b)** 2D Docking pose of **4m** with the receptor

# **Compound 4m**

#### **Compound 4n**

(S102a)

(S102b)



Figure S102(a-b): Molecular docking results of 4n with ACP reductase (4OHU): (S102a) 3D Docking pose of 4n with the receptor (S102b) 2D Docking pose of 4n with the receptor

#### **Compound 4o**

(S103a)

#### (S103b)



Figure S103(a-b): Molecular docking results of 40 with ACP reductase (4OHU): (S103a) 3D Docking pose of 40 with the receptor (S103b) 2D Docking pose of 40 with the receptor

### **Compound 4p**



**Figure S104(a-b):** Molecular docking results of **4p**with ACP reductase (4OHU): (**S104a**) 3D Docking pose of **4p** with the receptor (**S104b**) 2D Docking pose of **4p** with the receptor

#### **Compound 4q**

(S105a)

(S105b)



Figure S105(a-b): Molecular docking results of 4q with ACP reductase (4OHU): (S105a) 3D Docking pose of 4q with the receptor (S105b) 2D Docking pose of 4q with the receptor

# **Compound 4r**

(S106a)

(S106b)



**Figure S106(a-b):** Molecular docking results of **4r** with ACP reductase (4OHU): (**S106a**) 3D Docking pose of **4r** with the receptor (**S106b**) 2D Docking pose of **4r** with the receptor

#### **Compound 4s**

(S107a)

(S107b)



Figure S107(a-b): Molecular docking results of 4s with ACP reductase (4OHU): (S107a) 3D Docking pose of 4s with the receptor (S107b) 2D Docking pose of 4s with the receptor

### **Compound 4t**

(S108a)

(S108b)



Figure S108(a-b): Molecular docking results of 4t with ACP reductase (4OHU): (S108a) 3D Docking pose of 4t with the receptor (S108b) 2D Docking pose of 4t with the receptor

#### **Compound 4u**



Figure S109(a-b): Molecular docking results of 4u with ACP reductase (4OHU): (S109a) 3D Docking pose of 4u with the receptor (S109b) 2D Docking pose of 4u with the receptor

#### **Compound 4v**



**Figure S110(a-b):** Molecular docking results of **4v** with ACP reductase (4OHU): (**S110a**) 3D Docking pose of **4v** with the receptor (**S110b**) 2D Docking pose of **4v** with the receptor

#### **Compound 4w**



(S111b)



**Figure S111(a-b):** Molecular docking results of **4w** with ACP reductase (4OHU): (**S111a**) 3D Docking pose of **4w** with the receptor (**S111b**) 2D Docking pose of **4w** with the receptor

# **Compound 4x**

(S112a)

(S112b)



**Figure S112(a-b):** Molecular docking results of **4x** with ACP reductase (4OHU): (**S112a**) 3D Docking pose of **4x** with the receptor (**S112b**) 2D Docking pose of **4x** with the receptor

#### **Compound 4y**

(S113a)

(S113b)



**Figure S113(a-b):** Molecular docking results of **4y** with ACP reductase (4OHU): (**S113a**) 3D Docking pose of **4y** with the receptor (**S113b**) 2D Docking pose of **4y** with the receptor

# **Compound 5b**



**Figure S114(a-b):** Molecular docking results of **5b** with ACP reductase (4OHU): (**S114a**) 3D Docking pose of **5b** with the receptor (**S114b**) 2D Docking pose of **5b** with the receptor

# **Compound 5c**

(S115a)

(S115b)



**Figure S115(a-b):** Molecular docking results of **5c** with ACP reductase (4OHU): (**S115a**) 3D Docking pose of **5c** with the receptor (**S115b**) 2D Docking pose of **5c** with the receptor

#### **Compound 5d**

(S116a)

(S116b)



Figure S116(a-b): Molecular docking results of 5d with ACP reductase (4OHU): (S116a) 3D Docking pose of 5d with the receptor (S116b) 2D Docking pose of 5d with the receptor

# Validation (Rifampicin)



**Figure S117(a-b):** Molecular docking results of **Rifampicin** with ACP reductase (4OHU): (**S117a**) 3D Docking pose of the **drug** with the receptor (**S117b**) 2D Docking pose of **drug** with the receptor