Supporting Information

Ligand-controlled product selectivity in palladium-catalyzed domino post-Ugi construction of (spiro)polyheterocycles


[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium
[b] Biomolecular Architecture, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium

† Both authors equally contributed.

Corresponding authors: usahrma81@gmail.com; erik.vandereycken@chem.kuleuven.be

List of Contents

General experimental method ............................................................................................................ S2
General procedure and data for Ugi products ............................................................................... S3-S8
General procedure and data for spirocyclic oxindoles .............................................................. S9-S19
General procedure and data for benzofuro-isoquinoline carboxamides ................................. S20-S23
Crystallographic data for compound 2p, 2n and 3a ................................................................. S24-S26
Copies of 1H and 13C NMR spectra .......................................................................................... S27-S87

S1
General Experimental Methods

NMR spectra were recorded on a 300 MHz or a 600 MHz instrument using CDCl₃ and DMSO-d₆ as solvent unless and otherwise stated. The ¹H and ¹³C chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The notation bs is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). For the Mass spectrometry, ion source temperature was 150-250°C. High-resolution EI or ESI-mass spectra were performed with a resolution of 10,000. Thin layer chromatography was carried out using plates coated with 70-230 mesh silica gels. Commercially available reagents were used without additional purification, unless otherwise stated. Sealed tubes were dried in oven for overnight and cooled at room temperature prior to use.

Table S1: Starting materials for Ugi reaction

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>Amines</th>
<th>Acids</th>
<th>Isonitriles</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="A1" /></td>
<td><img src="image" alt="B1" /></td>
<td><img src="image" alt="C1" /></td>
<td><img src="image" alt="D1" /></td>
</tr>
<tr>
<td><img src="image" alt="A2" /></td>
<td><img src="image" alt="B2" /></td>
<td><img src="image" alt="C2" /></td>
<td><img src="image" alt="D2" /></td>
</tr>
<tr>
<td><img src="image" alt="A3" /></td>
<td><img src="image" alt="B3" /></td>
<td><img src="image" alt="C3" /></td>
<td><img src="image" alt="D3" /></td>
</tr>
<tr>
<td><img src="image" alt="A4" /></td>
<td><img src="image" alt="B4" /></td>
<td><img src="image" alt="C4" /></td>
<td><img src="image" alt="D4" /></td>
</tr>
<tr>
<td><img src="image" alt="A5" /></td>
<td><img src="image" alt="B5" /></td>
<td><img src="image" alt="C5" /></td>
<td><img src="image" alt="D5" /></td>
</tr>
</tbody>
</table>
General procedure for syntheses of Ugi products (1a-r and 4a-f)

To a solution of aldehyde (A1-A7; 200 mg) in methanol (3 mL) were added successively Na₂SO₄ (0.3 g), amine (B1-B5; 1.2 equiv), acid (C1-C2; 1.2 equiv) and isonitrile (D1-D5; 1.2 equiv) in a screw capped vial equipped with a magnetic stir bar. The reaction mixture was stirred at room temperature for 24-48 h in closed vial. After completion of the reaction, the mixture was diluted with dichloromethane (100 mL) and extracted with water (50 mL). Organic layer was washed with brine (50 mL), dried over magnesium sulfate and evaporated under reduced pressure to obtained residue which was subjected to silica gel column chromatography (10-30 % EtOAc in heptane) to afford the desired product 1a-r and 4a-f.

Ugi products appear as mixture of two rotamers, so ¹H and ¹³C NMR spectra are not very characteristic. Only representative data for one compound is given.

2-acetyl-N-(1-(2-bromophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methoxybenzyl)benzamide (1a)

Offwhite solid, Yield 80%, Melting point: 151-152°C. ¹H NMR (300 MHz, CDCl₃) δ 7.86-7.83 (m, 1H), 7.74-7.66 (m, 1H), 7.56-7.33 (m, 5H), 7.17-7.11 (m, 1H), 6.92-6.86 (m, 2H), 6.80-6.61 (m, 3H), 5.76 (s, 0.71H), 4.98 (s, 0.30H), 4.42-4.19 (m, 2H), 3.78-3.73 (m, 3H), 2.73-2.64 (m, 3H), 1.38-1.17 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 173.2, 172.1, 167.5, 165.4, 158.9, 158.6, 136.6, 136.4, 135.6, 135.4, 134.9, 134.2, 132.8, 132.6, 130.0, 129.9, 129.7, 129.5, 129.3, 129.2, 129.1, 128.9, 128.0, 127.9, 127.7, 127.4, 127.2, 127.0, 125.8, 123.7, 122.4, 113.7, 113.5, 68.7, 64.7, 55.3, 55.2, 52.9, 51.7, 51.5, 48.5, 45.7, 28.8, 28.2, 28.0, 27.6. HRMS (EI) calculated for C₂₄H₂₇BrN₂O₅ 550.1467, found 451.0823(M-100).

Table S2. Ugi products 1a-r and 4a-f.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>2-acetyl-N-(1-(2-bromophenyl)-2-(butylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1b)</td>
</tr>
</tbody>
</table>

Offwhite solid, Yield 55%, Melting point: 52-54°C. HRMS (EI) calculated for C₃₀H₃₃BrN₂O₅ 580.1573, found 580.1574.
2-acetyl-N-(1-(2-bromophenyl)-2-( tert -butylamino)-2-oxoethyl)-N-butyllbenzamide (1c)

Yellow solid, Yield 36%, Melting point: 89-90 °C.
HRMS (EI) calculated for C\textsubscript{25}H\textsubscript{31}BrN\textsubscript{2}O\textsubscript{3} 486.1518, found 386.0772(M-100).

2-acetyl-N-(1-(6-bromobenzo[d][1,3]dioxol-5-yl)-2-(butylamino)-2-oxoethyl)-N-(4-methoxybenzyl)benzamide (1d)

Brown oil, Yield 44%.
HRMS (EI) calculated for C\textsubscript{30}H\textsubscript{31}BrN\textsubscript{2}O\textsubscript{6} 594.1365, found 515.2246(M-Br).

2-acetyl-N-(1-(6-bromobenzo[d][1,3]dioxol-5-yl)-2-(cyclohexylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1e)

Yellow solid, Yield 64%, Melting point: 69-71 °C.
HRMS (EI) calculated for C\textsubscript{33}H\textsubscript{35}BrN\textsubscript{2}O\textsubscript{7} 650.1628, found 571.2533(M-Br).

2-acetyl-N-(1-(2-bromo-4,5-dimethoxyphenyl)-2-( tert -butylamino)-2-oxoethyl)-N-(4-methylbenzyl)benzamide (1f)

Yellow oil, Yield 82%.
HRMS (EI) for C\textsubscript{31}H\textsubscript{35}BrN\textsubscript{2}O\textsubscript{5} calculated 594.1729, found 594.1758.

2-acetyl-N-benzyl-N-(1-(2-bromo-4,5-dimethoxyphenyl)-2-( tert -butylamino)-2-oxoethyl)benzamide (1g)

Yellow solid, Yield 83%, Melting point: 58-60°C.
HRMS (EI) calculated for C\textsubscript{30}H\textsubscript{33}BrN\textsubscript{2}O\textsubscript{5} 580.1573, found 501.2400(M-Br).
2-acetyl-N-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1h)

Offwhite solid, Yield 80%, Melting point: 66-68°C.
**HRMS (EI)** calculated for C$_{32}$H$_{37}$BrN$_2$O$_7$ 640.1784, found 640.1799.

2-acetyl-N-(1-(2-bromo-5-methoxyphenyl)-2-(cyclohexylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1i)

White solid, Yield 67%, Melting point: 152-154°C.
**HRMS (EI)** calculated for C$_{33}$H$_{37}$BrN$_2$O$_6$ 636.1835, found 557.2626(M-Br).

2-acetyl-N-(1-(2-bromo-5-chlorophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methoxybenzyl)benzamide (1j)

White solid, Yield 79%, Melting point: 134-136°C.
**HRMS (EI)** calculated for C$_{30}$H$_{33}$BrN$_2$O$_5$ 580.1573, found 501.2378(M-Br).

2-acetyl-N-(1-(2-bromo-5-chlorophenyl)-2-(butylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1k)

Offwhite solid, Yield 71%, Melting point: 77-78°C.
**HRMS (EI)** calculated for C$_{30}$H$_{32}$BrClN$_2$O$_5$ 614.1183, found 515.0469(M-Br).

2-acetyl-N-(1-(2-bromo-5-chlorophenyl)-2-(butylamino)-2-oxoethyl)-N-(4-methoxybenzyl)benzamide (1l)

White solid, Yield 49%, Melting point: 96-97°C.
**HRMS (EI)** calculated for C$_{29}$H$_{30}$BrClN$_2$O$_4$ 584.1077, found 439.0605(M-147).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
<th>Yield</th>
<th>Melting Point</th>
<th>HRMS (EI) Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-acetyl-N-(1-(2-bromo-5-fluorophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methoxybenzyl)benzamide (1m)</td>
<td>White solid</td>
<td>51%</td>
<td>147-149°C</td>
<td>C20H30BrFN2O4 (M-100) 568.1373</td>
<td>469.0722</td>
</tr>
<tr>
<td>2-acetyl-N-(1-(2-bromo-5-fluorophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methylbenzyl)benzamide (1n)</td>
<td>White solid</td>
<td>39%</td>
<td>131-132°C</td>
<td>C20H30BrFN2O3 (M-147) 552.1424</td>
<td>405.0989</td>
</tr>
<tr>
<td>2-acetyl-N-(1-(2-bromo-5-fluorophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)benzamide (1o)</td>
<td>Yellow solid</td>
<td>81%</td>
<td>61-62°C</td>
<td>C29H32BrFN2O5 598.1479</td>
<td>598.1465</td>
</tr>
<tr>
<td>2-acetyl-N-(1-(2-bromo-6-fluorophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methylbenzyl)benzamide (1p)</td>
<td>White solid</td>
<td>78%</td>
<td>140-141°C</td>
<td>C29H30BrFN2O3 (M-100) 552.1424</td>
<td>452.9835</td>
</tr>
<tr>
<td>2-acetyl-N-(1-(2-bromo-5-fluorophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-N-(4-methoxybenzyl)benzamide (1q)</td>
<td>Yellow solid</td>
<td>66%</td>
<td>50-52°C</td>
<td>C33H39BrFN2O4 ([M+H]+) 625.2072</td>
<td>625.2075</td>
</tr>
<tr>
<td>Compound</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-(1-(2-bromophenyl)-2-(tert-butlamino)-2-oxoethyl)-N-(4-methoxybenzyl)-4-oxopentanamide (4a)</td>
<td>Colorless oil, Yield 84%. HRMS (EI) calculated for C₂₅H₃₁BrN₂O₄ 502.1467, found 403.1027(M-100).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-(1-(6-bromobenzo[d][1,3]dioxol-5-yl)-2-(tert-butlamino)-2-oxoethyl)-N-(4-methylbenzyl)-4-oxopentanamide (4b)</td>
<td>White solid, Yield 48%, Melting point: 186-188°C. HRMS (EI) calculated for C₂₆H₃₂BrN₂O₅ 530.1416, found 430.0648(M-100).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-(1-(2-bromo-5-fluorophenyl)-2-(cyclohexylamino)-2-oxoethyl)-N-(4-methylbenzyl)-4-oxopentanamide (4c)</td>
<td>White solid, Yield 48%, Melting point: 165-166°C. HRMS (EI) calculated for C₂₇H₃₂BrFN₂O₅ 530.1580, found 431.1139(M-100).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(butylamino)-2-oxoethyl)-N-(3,4-dimethoxybenzyl)-4-oxopentanamide (4d)</td>
<td>Yellow oil, Yield 76%. HRMS (EI) calculated for C₂₈H₃₇BrN₂O₇ 592.1784, found 493.1322(M-100).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
$N$-(2-(benzylamino)-1-(2-bromo-5-fluorophenyl)-2-oxoethyl)-$N$-(4-methoxybenzyl)-4-oxopentanamide (4e)

![Chemical structure](image.png)

Offwhite solid, Yield 66\%, Melting point: 141-143$^\circ$C.  
**HRMS** (EI) calculated for $C_{28}H_{28}BrFN_2O_4$ 554.1216, found 456.9801(M-100).

$N$-(1-(2-bromo-5-fluorophenyl)-2-oxo-2-((2,4,4-trimethylpentan-2-yl)amino)ethyl)-$N$-(4-methoxybenzyl)-4-oxopentanamide (4f)

![Chemical structure](image.png)

Colorless oil solid, Yield 76\%.  
**HRMS** (ESI) calculated for $C_{29}H_{39}BrFN_2O_4$ ([M+H]$^+$) 577.2072, found 577.2061.
General procedure for the synthesis of spirocyclic oxindoles via Buchwald-Hartwig/Aldol reaction sequence

To a dry screw capped glass vial Pd(OAc)₂ (5 mol%), Xantphos (7.5 mol%), Cs₂CO₃ (2 equiv.) were loaded along with dry toluene (2 mL). Ugi product 1a-p and 4a-f (0.2 mmol) was added. The reaction vial was evacuated, backfilled with nitrogen (4 cycles) and was stirred at 120°C for 24 hours. After completion, the reaction mixture was cooled, directly loaded over a silica gel column and chromatographed (10-30% EtOAc in heptane) to afford compounds 2a-p and 5a-f. The structures of the compounds were confirmed by NMR and HRMS data.

Table S2: Effect of different conditions on domino cyclization

<table>
<thead>
<tr>
<th>Pd(OAc)₂</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Cs₂CO₃</th>
<th>Yield % 2a/3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>-</td>
<td>Toluene (2 mL)</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
<tr>
<td>b)</td>
<td>-</td>
<td>Toluene (2 mL)</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
<tr>
<td>c)</td>
<td>5 mol%</td>
<td>Toluene (2 mL)</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
<tr>
<td>d)</td>
<td>-</td>
<td>Toluene:MeOH₈</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
<tr>
<td>e)</td>
<td>5 mol%</td>
<td>Toluene:MeOH₈</td>
<td>2 equiv</td>
<td>77/22</td>
</tr>
<tr>
<td>f)</td>
<td>5 mol%</td>
<td>Toluene:MeOH₈</td>
<td>2 equiv</td>
<td>traces/72</td>
</tr>
<tr>
<td>g)</td>
<td>-</td>
<td>Toluene:MeOH₈</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
<tr>
<td>h)</td>
<td>5 mol%</td>
<td>Toluene:MeOH₈</td>
<td>2 equiv</td>
<td>0/0</td>
</tr>
</tbody>
</table>

₈ 1.95 mL: 0.05 mL; b dr = 64:36

Scheme 1
Characterization data for spiro-oxindoles (2a-p and 5a-f)

1-(tert-butyl)-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-
1',2(2'H,4'H)-dione (2a)

White solid, Yield 97% (dr: 75:25), Melting point: 180-182°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.11-8.08 (m, 0.75H), 7.96 (d, \(J = 6.8\) Hz, 0.25H), 7.66-7.33 (m, 5H), 7.23-7.17 (m, 1H), 7.11-7.06 (m, 1H), 6.62-6.42 (m, 4H), 6.02 (s, 0.75H), 5.68 (s, 0.25H), 5.40-5.23 (m, 1H), 3.95-3.87 (m, 1H), 3.63 (s, 4H), 1.23 (s, 6.6H), 1.22 (s, 3H), 1.14 (s, 2.4H). \(^{13}\)C NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 175.0, 174.0, 165.3, 165.0 158.3, 145.9, 144.5, 144.4, 140.6, 131.9, 131.7, 129.8, 129.6, 129.3, 128.6, 128.4(2), 128.2, 128.1, 127.9, 127.7, 127.2, 126.8, 126.5, 124.6, 124.3, 123.9, 123.8(2), 120.2, 119.9, 113.1, 113.0, 112.8, 74.1, 71.6, 71.2, 71.1, 56.7, 56.2, 54.9(2), 46.1, 45.6, 45.2, 29.0, 28.3, 28.2 21.78, 20.5. HRMS (EI) calculated for C\(_{29}\)H\(_{30}\)N\(_2\)O\(_4\) 470.2206, found 470.2212.

1-butyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-
1',2(2'H,4'H)-dione (2b)

Yellow solid, Yield 68% (dr: 66:34), Melting point: 175-177°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.15-7.96 (m, 1H), 7.63-7.30 (m, 5H), 7.20 -7.02 (m, 2H), 6.86-6.82 (m, 1H), 6.63-6.59 (m, 1H), 6.22-6.19 (m, 0.68H), 6.13 (s, 0.66H), 6.00 (s, 0.31H), 5.72 (s, 0.34H), 5.32-5.14 (m, 1H), 4.02-3.92 (m, 1H), 3.70-3.68 (m, 3H), 3.49-3.47 (m, 3H), 3.23-3.12 (m, 1H), 3.02-2.92 (m, 1H), 1.25-0.99 (m, 7H), 0.90 -0.59 (m, 3H). \(^{13}\)C NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 174.3, 173.2, 164.7, 147.8, 147.7, 145.3, 144.0, 132.0, 131.86, 129.79, 128.59, 128.01, 127.71, 127.36, 126.68, 124.26, 123.80, 123.64, 121.46, 120.69, 120.6, 120.5, 120.0, 111.8, 111.0, 108.5, 108.4, 74.2, 73.6, 71.6, 71.3, 55.4, 55.3, 54.9, 46.3, 28.7, 19.5, 19.3, 13.4. HRMS (EI) calculated for C\(_{30}\)H\(_{32}\)N\(_2\)O\(_5\) 500.2311, found 500.2328.

1-(tert-butyl)-2'-butyl-4'-hydroxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-
dione (2c)

White solid, Yield 74% (dr: 65:35), Melting point: 116-117°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.99 (dd, \(J = 7.9, 1.4\) Hz, 0.65H), 7.86 (dd, \(J = 7.7, 1.0\) Hz, 0.35H), 7.57-7.26 (m, 6H), 7.12-7.02 (m, 1H), 5.95 (s, 0.65H), 5.74 (s, 0.35H), 3.69-3.51 (m, 1H), 2.96-2.88 (m, 1H), 1.59-1.56 (m, 9H), 1.50 (s, 1H), 1.26 (s, 2H), 1.19-0.83 (m, 4H), 0.61 (m, 3H). \(^{13}\)C NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 176.0, 174.7, 164.8, 164.4, 145.3, 144.2, 144.0, 141.1, 131.8, 131.7, 129.4, 1281, 127.7, 127.5, 126.9, 126.8, 126.6, 126.3, 125.7, 124.6, 124.1, 123.7, 121.2, 120.5, 113.4, 113.1, 99.5, 73.8, 72.1, 71.9, 71.2, 57.3, 56.8, 43.6, 29.4, 29.2, 28.43, 28.4, 21.5, 19.5, 19.5, 13.4. HRMS (EI) calculated for C\(_{25}\)H\(_{30}\)N\(_2\)O\(_3\) 406.2256, found 406.2231.
5-butyl-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'H-spiro[[1,3]dioxolo[4,5-f]indole-7,3'-isoquinoline]-1',6(2'H,4'H,5H)-dione (2d)

Offwhite solid, Yield 89% (dr: 67:33), Melting point: 135-137°C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.08 (d, $J = 7.7$ Hz, 6H), 7.95 (d, $J = 7.2$ Hz, 3H), 7.62 -7.33 (m, 3H), 7.13 (s, 0.33H), 6.87 (s, 0.37H), 6.72-6.65 (m, 6H), 6.09-6.01 (m, 2.67H), 5.62 (s, 0.33H), 5.22-5.02 (m, 1H), 4.07-3.97 (m, 1H), 3.69-3.55 (m, 3H), 3.11-2.96 (m, 2H), 1.26-0.91 (m, 7H), 0.79-0.73 (m, 3H). $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ 174.5, 173.4, 165.1, 164.7, 158.2, 148.3, 144.6, 141.8, 141.5, 140.3, 138.9, 132.0, 131.8, 129.5, 129.3, 128.6, 128.4, 128.1, 127.7, 127.3, 126.6, 124.3, 123.8, 114.6, 113.0, 113.0, 109.3, 101.1, 99.5, 92.5, 92.3, 73.6, 71.9, 71.7, 71.0, 54.9, 54.9, 46.0, 45.5, 28.9, 28.4, 19.4, 19.3, 13.5(2). HRMS (EI) calculated for C$_{30}$H$_{30}$N$_{2}$O$_{6}$ 514.2104, found 514.2119.

5-cyclohexyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-4'-methyl-1'H-spiro[[1,3]dioxolo[4,5-f]indole-7,3'-isoquinoline]-1',6(2'H,4'H,5H)-dione (2e)

Offwhite solid, Yield 96% (dr: 68:32), Melting point: 77-79°C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.13- 8.05 (m, 0.68H), 7.96 (d, $J = 7.7$ Hz, 0.32H), 7.87-7.28 (m, 3H), 7.18-6.80 (s, 1H), 6.70-6.59 (m, 1H), 6.36-5.97 (m, 3.70H), 5.58 (s, 0.50H), 5.43-4.89 (m, 1H), 4.06-3.95 (m, 1H), 3.66-3.47 (m, 6H), 1.74-1.48 (m, 5H), 1.18-0.82 (m, 8H). $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ 174.5(2), 165.2, 164.9, 148.9, 148.3, 148.2, 148.0, 147.9(2), 146.9, 144.5, 141.4, 141.1, 140.8, 139.9, 138.6, 131.9, 131.7, 130.9, 129.2, 128.8, 128.3, 127.6, 127.3, 126.8, 126.6, 124.3, 123.9, 120.7, 120.4, 118.4, 116.4, 115.9, 114.8, 112.2, 112.0, 111.5, 111.4, 109.4, 101.2, 93.4, 93.1, 86.2, 78.3, 73.9, 71.7, 71.3, 71.1, 55.4, 55.4, 55.0, 54.9, 51.8, 46.1, 45.6, 28.1, 27.9, 27.7, 25.3, 25.2, 24.8, 24.5, 22.2, 20.4. HRMS (EI) calculated for C$_{33}$H$_{34}$N$_{2}$O$_{7}$ 570.2366, found 570.2376.

(3S,4'S)-1-(tert-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-2'-(4-methylbenzyl)-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H-dione (2f)

Offwhite solid, Yield 24%, Melting point: 192-194°C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.07 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.59-7.40 (m, 3H), 7.00 (s, 1H), 6.92 (d, $J = 7.9$ Hz, 2H), 6.76 (s, 1H), 6.68 (d, $J = 7.9$ Hz, 2H), 5.90 (s, 1H), 4.76 (d, $J = 14.0$ Hz, 1H), 4.24 (d, $J = 15.0$ Hz, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 2.19 (s, 3H), 1.31 (s, 9H), 1.17 (s, 3H). $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ 174.4, 165.1, 149.4, 143.0, 140.8, 138.4, 135.7, 134.3, 131.7, 128.4, 128.2, 127.8, 127.5, 127.2, 124.3, 115.8, 113.6, 98.9, 72.2, 71.2, 56.8, 56.0, 55.8, 46.5, 28.4, 20.6.
HRMS (EI) calculated for C_{31}H_{34}N_{2}O_{5} 514.2468, found 514.2468.

(3S,4'R)-1-(tert-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-2'-(4-methylbenzyl)-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2f')

Brown oil, Yield 18%; \( ^1H \text{NMR (300 MHz, DMSO-d}_{6} ) \) \( \delta \) 7.94 (dd, \( J = 7.7, 1.0 \text{ Hz, 1H}), 7.57-7.44 (m, 2H), 7.37 (td, \( J = 7.5, 1.4 \text{ Hz, 1H}), 6.92 (d, \( J = 7.8 \text{ Hz, 2H}), 6.87 (s, 1H), 6.74 (s, 1H), 6.61 (d, \( J = 8.0 \text{ Hz, 2H}), 5.60 (s, 1H), 4.75 (d, \( J = 15.2 \text{ Hz, 1H}), 4.28 (d, \( J = 15.2 \text{ Hz, 1H}), 3.82 (s, 3H), 3.56 (s, 3H), 2.19 (s, 3H), 1.56 (s, 3H), 1.30 (s, 9H). \( ^{13}C \text{NMR (300 MHz, DMSO-d}_{6} ) \) \( \delta \) 175.4, 165.5, 149.5, 144.6, 142.6, 139.9, 135.8, 134.1, 131.9, 128.2, 127.9, 126.7, 126.4, 123.8, 114.8, 113.3, 99.3, 74.0, 72.1, 56.3, 56.0, 54.9, 46.4, 28.6, 20.6. HRMS (EI) calculated for C_{31}H_{34}N_{2}O_{5} 514.2468, found 514.2441.

(6aS,11aS)-N-(tert-butyl)-8,9-dimethoxy-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3f)

White solid, Yield 25%, Melting point: 196-198°C. \( ^1H \text{NMR (300 MHz, DMSO-d}_{6} ) \) \( \delta \) 8.10 (dd, \( J = 7.7, 1.4 \text{ Hz, 1H}), 7.85 (d, \( J = 7.4 \text{ Hz, 1H}), 7.69 (td, \( J = 7.6, 1.5 \text{ Hz, 1H}), 7.63-7.54 (m, 1H), 7.08 (s, 1H), 6.91 (s, 1H), 6.82 (d, \( J = 7.9 \text{ Hz, 2H}), 6.66 (s, 1H), 6.59 (d, \( J = 8.0 \text{ Hz, 2H}), 4.98 (d, \( J = 16.2 \text{ Hz, 1H}), 4.22 (d, \( J = 16.2 \text{ Hz, 1H}), 3.70 (s, 3H), 3.48 (s, 3H), 2.13 (s, 3H), 1.76 (s, 3H), 1.28 (s, 9H). \( ^{13}C \text{NMR (75 MHz, DMSO-d}_{6} ) \) \( \delta \) 165.7, 162.6, 154.9, 151.7, 143.5, 135.0, 134.9, 134.6, 132.3, 129.3, 128.0, 127.4, 127.0, 126.5, 125.7, 114.8, 113.1, 96.1, 85.9, 78.62, 56.8, 55.9, 51.9, 47.0, 27.8, 21.9, 20.5. HRMS (EI) calculated for C_{31}H_{34}N_{2}O_{5} 514.2468, found 514.2505.

(3S,4'S)-2'-benzyl-1-(tert-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2g)

Offwhite solid, Yield 36%, Melting point: 194-196°C. \( ^1H \text{NMR (300 MHz, DMSO-d}_{6} ) \) \( \delta \) 8.07 (dd, \( J = 7.9, 1.4 \text{ Hz, 1H}), 7.56-7.44 (m, 3H), 7.17-7.08 (m, 3H), 6.98 (s, 1H), 6.86 (dd, \( J = 6.2, 2.9 \text{ Hz, 2H}), 6.78 (s, 1H), 5.93 (s, 1H), 4.67 (d, \( J = 15.2 \text{ Hz, 1H}), 4.36 (d, \( J = 15.2 \text{ Hz, 1H}), 3.82 (s, 3H), 3.49 (s, 3H), 1.33 (s, 9H), 1.19 (s, 3H). \( ^{13}C \text{NMR (300 MHz, DMSO-d}_{6} ) \) \( \delta \) 174.4, 165.1, 149.4, 143.0, 140.9, 138.4, 137.6, 131.7, 128.3, 127.7, 127.6, 127.1, 126.6, 124.3, 115.8, 113.5, 98.9, 72.4, 71.1, 56.9, 56.0, 55.8, 46.9, 28.5, 20.6. HRMS (EI) calculated for C_{30}H_{32}N_{2}O_{5} 500.2311, found 500.2293.
(3S,4'R)-2'-benzyl-1-(tert-butyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2g)

Offwhite solid, Yield 13%, Melting point: 52-53°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.94 (dd, \(J = 7.7, 1.0\) Hz, 1H), 7.58 - 7.44 (m, 2H), 7.38 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.20 - 7.10 (m, 3H), 6.84 (s, 1H), 6.79 - 6.75 (m, 3H), 5.63 (s, 1H), 4.68 (d, \(J = 15.2\) Hz, 1H), 4.38 (d, \(J = 15.2\) Hz, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 1.57 (s, 3H), 1.32 (s, 9H). \(^13\)C NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 175.4, 165.6, 149.5, 144.6(2), 139.8, 137.4, 132.0, 127.8, 127.7, 126.6, 126.4, 123.9, 114.8, 113.2, 99.3, 74.0, 72.3, 56.4, 56.0, 46.9, 28.7. HRMS (EI) calculated for C\(_{30}\)H\(_{32}\)N\(_2\)O\(_5\) 500.2311, found 500.2348.

(6a\(\$\),11a\(\$\))-6-benzyl-N-(tert-butyl)-8,9-dimethoxy-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3g)

Offwhite solid, Yield 22%, Melting point: 235-237°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.11 (dd, \(J = 7.7, 1.3\) Hz, 1H), 7.86 (d, \(J = 7.5\) Hz, 1H), 7.70 (td, \(J = 7.6, 1.4\) Hz, 1H), 7.60 (t, \(J = 7.1\) Hz, 1H), 7.05 (s, 1H), 7.00 (dd, \(J = 5.1, 1.7\) Hz, 3H), 6.93 (s, 1H), 6.71 (d, \(J = 3.5\) Hz, 2H), 6.64 (s, 1H), 5.09 (d, \(J = 16.5\) Hz, 1H), 4.24 (d, \(J = 16.5\) Hz, 1H), 3.68 (s, 3H), 3.44 (s, 3H), 1.76 (s, 3H), 1.29 (s, 9H). \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 165.6, 162.6, 154.9, 151.7, 143.4, 138.0, 134.9, 132.4, 129.3, 127.5, 127.4, 127.0, 126.6, 125.7, 125.5, 114.6, 113.1, 96.0, 85.8, 78.6, 56.8, 55.8, 51.8, 47.1, 27.8, 21.8. HRMS (EI) calculated for C\(_{30}\)H\(_{32}\)N\(_2\)O\(_5\) 500.2312, found 500.2305.

1-(tert-butyl)-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-5,6-dimethoxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2h)

Offwhite solid, Yield 58% (dr: 78:22), Melting point: 198-200°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.09 (d, \(J = 7.4\) Hz, 2H), 7.96 (d, \(J = 7.6\) Hz, 1H), 7.58-7.33 (m, 3H), 7.20-7.03 (m, 1H), 6.77-6.60 (m, 2H), 6.38-6.13 (m, 2H), 5.93 (s, 0.78H), 5.59 (s, 0.22H), 5.13-4.91 (m, 1H), 4.20-3.94 (m, 1H), 3.82 (s, 3H), 3.77-3.58 (m, 6H), 3.54-3.52 (m, 3H), 1.29-1.27 (m, 9H), 1.21-1.14 (m, 3H). \(^13\)C NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 175.4, 174.4, 165.5, 165.4, 165.1, 149.4, 147.9, 147.8, 144.6, 143.1, 142.7, 140.8, 140.0, 138.5, 131.9, 131.6, 129.4, 129.0, 128.5(2), 127.2, 126.8, 126.5, 124.3, 123.9, 120.6, 120.3, 115.7, 114.8, 113.8(2), 111.4, 99.2, 98.9, 74.1, 71.9, 71.7, 71.2, 56.7, 56.4, 56.2, 56.0, 56.0, 55.5, 55.4, 54.9, 54.8, 46.2, 46.0, 28.6, 28.5, 20.4. HRMS (EI) calculated for C\(_{32}\)H\(_{36}\)N\(_2\)O\(_7\) 560.2523, found 560.2548.
(6aS,11aS)-N-(tert-butyl)-6-(3,4-dimethoxybenzyl)-8,9-dimethoxy-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3h)

Offwhite solid, Yield 19%, Melting point: 124-126°C. \[^1\text{H} \text{NMR (300 MHz, DMSO-d}_6\) \delta 8.10 (dd, \(J = 7.7, 1.4 \text{ Hz, 1H}), 7.85 (d, \(J = 7.3 \text{ Hz, 1H}), 7.69 (td, \(J = 7.6, 1.5 \text{ Hz, 1H}), 7.59 (td, \(J = 7.6, 1.0 \text{ Hz, 1H}), 7.14 (s, 1H), 6.94 (s, 1H), 6.69 (s, 1H), 6.63 (d, \(J = 8.3 \text{ Hz, 1H}), 6.36 (dd, \(J = 8.3, 1.8 \text{ Hz, 1H}), 6.12 (d, \(J = 1.8 \text{ Hz, 1H}), 4.93 (d, \(J = 15.9 \text{ Hz, 1H}), 4.19 (d, \(J = 15.9 \text{ Hz, 1H}), 3.70 (s, 3H), 3.61 (s, 3H), 3.53 (s, 3H), 3.44 (s, 3H), 1.76 (s, 3H), 1.29 (s, 9H). \[^{13}\text{C} \text{NMR (75 MHz, DMSO-d}_6\) \delta 165.5, 162.7, 154.9, 151.7, 148.0, 146.9, 143.5, 134.8, 132.3, 130.6, 129.3, 127.4, 127.1, 126.6, 118.4, 114.0, 113.2, 111.2, 109.7, 96.1, 85.9, 78.7, 56.8, 55.8, 55.5, 54.9, 51.86, 46.9, 27.8, 21.8.

HRMS (EI) calculated for C32H36N2O7 560.2523, found 560.2511.

1-cyclohexyl-2'-(3,4-dimethoxybenzyl)-4'-hydroxy-5-methoxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2i)

Offwhite solid, Yield 95% (dr: 73:27), Melting point: 161-163°C. \[^1\text{H} \text{NMR (300 MHz, DMSO-d}_6\) \delta 8.09 (dd, \(J = 7.5, 1.5 \text{ Hz, 0.73H}), 7.97 (dd, \(J = 7.6, 1.1 \text{ Hz, 0.27H}), 7.59-7.35 (m, 3H), 7.15-6.78 (m, 3H), 6.67-6.62 (m, 1H), 6.32-6.05 (m, 2H), 6.02 (s, 0.73H), 5.64 (s, 0.27H), 5.20-4.91 (m, 1H), 4.10-4.07 (m, 1H), 3.78-3.43 (m, 9H), 1.72-1.64 (m, 5H), 1.24-0.89 (m, 8H). \[^{13}\text{C} \text{NMR (300 MHz, DMSO-d}_6\) \delta 173.8, 172.7, 166.1, 165.2, 164.8, 154.0, 153.6, 147.9, 147.9, 140.9, 136.9, 131.9, 131.7, 129.1, 128.8, 128.3, 127.7, 127.3, 126.8, 126.6, 125.7, 124.8, 124.2, 123.8, 120.7, 120.4, 115.6, 115.4, 114.3, 114.0, 112.2, 112.0, 111.4, 110.2, 109.8, 73.8, 71.8, 71.4, 71.0, 55.6, 55.4, 55.4, 55.0, 54.9, 51.5, 51.3, 46.2, 28.0, 27.8, 25.2, 24.6, 20.6. HRMS (EI) calculated for C33H36N2O6 556.2573, found 556.2608.

1-(tert-butyl)-4'-hydroxy-5-methoxy-2'-((4-methoxybenzyl)-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2j)

Offwhite solid, Yield 76% (dr: 86:14), Melting point: 192-194°C. \[^1\text{H} \text{NMR (300 MHz, DMSO-d}_6\) \delta 8.09 (d, \(J = 7.6 \text{ Hz, 1H}), 7.96 (d, \(J = 7.3 \text{ Hz, 1H}), 7.60-7.35 (m, 3H), 7.16-7.10 (m, 1H), 7.04-7.01 (m, 1H), 6.93-6.90 (m, 1H), 6.63-6.57 (m, 4H), 5.98 (s, 0.86H), 5.65 (s, 0.14H), 5.09-5.04 (m, 1H), 4.019-4.04 (m, 1H), 3.72-3.69 (m, 3H), 3.64 (s, 3H), 1.27-1.24 (m, 9H), 1.17 (s, 3H). \[^{13}\text{C} \text{NMR (300 MHz, DMSO-d}_6\) \delta 173.6, 165.0, 158.3, 153.5, 140.8, 137.7, 131.7, 129.4, 128.7, 128.3, 127.5, 127.2, 126.0, 124.3, 115.4, 113.8, 113.2, 113.1, 74.0, 72.0, 71.0, 56.6, 56.1, 55.4, 55.3, 54.9, 45.8, 28.3, 28.2, 20.6. HRMS (EI) calculated for C30H32N2O5 500.2311, found 500.2345.

S14
(6aS,11aS)-N-(tert-butyl)-8-methoxy-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3j)

Offwhite solid, Yield 23%, Melting point: 146-126°C. $^1$H NMR (300 MHz, DMSO-d$_6$) δ 8.10 (dd, J = 7.7, 1.4 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.69 (td, J = 7.6, 1.5 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.16 (d, J = 1.9 Hz, 1H), 6.95 (s, 1H), 6.85-6.78 (m, 2H), 6.63-6.52 (m, 4H), 4.91 (d, J = 15.9 Hz, 1H), 4.21 (d, J = 15.9 Hz, 1H), 3.61 (s, 3H), 3.59 (s, 3H), 1.76 (s, 3H), 1.27 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 165.1, 162.8, 157.4, 153.9, 153.8, 134.8, 132.4, 129.9, 129.4, 127.4, 127.1, 126.5, 125.9, 116.4, 114.4, 112.9, 110.7, 85.8, 78.5, 55.9, 54.9, 51.9, 46.8, 27.8, 21.5. HRMS (EI) calculated for C$_{30}$H$_{32}$N$_2$O$_5$ 500.2311, found 500.2339.

1-(tert-butyl)-5-chloro-2′-(3,4-dimethoxybenzyl)-4′-hydroxy-4′-methyl-1′H-spiro[indoline-3,3′-isoquinoline]-1′,2′(2′H,4′H)-dione (2k)

White solid, Yield 63% (dr: 81:19), Melting point: 180-181°C. $^1$H NMR (300 MHz, DMSO-d$_6$) δ 8.12 (dd, J = 7.4, 1.3 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.76-7.36 (m, 6H), 7.23-7.15 (m, 1H), 7.03 – 6.86 (m, 1H), 6.66-6.61 (m, 1H), 6.45 (s, 0.30H), 6.24-6.23 (m, 0.70H), 6.20-6.18(m, 0.82H), 6.15 (s, 0.81H), 6.10-6.07 (m, 0.20H), 5.75 (s, 0.19H), 5.36-3.96 (m, 2H), 3.72-3.62 (m, 6H), 1.25 (s, 7H), 1.21 (s, 1H), 1.16 (s, 2H), 1.01 (s, 2H). $^{13}$C NMR (300 MHz, DMSO-d$_6$) δ 174.8, 173.7, 168.5, 168.0, 165.2, 164.8, 148.7, 148.1, 148.0(2), 147.9, 144.6, 144.1, 143.3, 140.4, 132.2, 132.0, 131.9, 130.6, 130.0, 128.9, 128.6, 128.5, 128.1, 127.8, 127.3, 126.8, 126.7, 126.6 126.0, 125.2, 124.4, 123.8, 123.1, 121.3, 120.9, 120.6, 120.4, 114.1, 112.2, 111.9, 111.7, 111.3, 111.2, 74.2, 71.6, 71.4, 71.2, 69.7, 57.1, 56.5, 55.5, 55.4(2), 54.9, 50.6, 46.1, 43.5, 28.2, 28.0, 27.8, 22.0, 20.6. HRMS (EI) calculated for C$_{30}$H$_{31}$ClN$_2$O$_5$ 534.1921, found 534.1908. [The corresponding benzofuro-isoquinoline carboxamide is obtained in an isolated yield of 19% as byproduct].

1-butyl-5-chloro-4′-hydroxy-2′-(4-methoxybenzyl)-4′-methyl-1′H-spiro[indoline-3,3′-isoquinoline]-1′,2′(2′H,4′H)-dione (2l)

Offwhite solid, Yield 71% (dr: 77:23), Melting point: 202-204°C. $^1$H NMR (600 MHz, DMSO-d$_6$) δ 8.11 (d, J = 7.7 Hz, 0.78H), 7.98 (d, J = 7.7 Hz, 0.22H), 7.64-7.13 (m, 6H), 6.97-6.79 (m, 1H), 6.68-6.48 (m, 4H), 6.17 (s, 0.77H), 5.79 (s, 0.23H), 5.17-4.86 (m, 1H), 4.20-4.03 (m, 1H), 3.67-3.62 (m, 2H), 3.26-2.86 (m, 2H), 1.47-0.94 (m, 7H), 0.90 -0.68 (m, 3H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 174.0, 172.8, 165.0, 164.6, 158.3(2), 144.3, 142.8, 132.1, 129.6, 129.5, 129.3, 128.1, 128.0, 127.9, 127.8, 127.4, 126.7, 125.6, 125.3, 124.9, 124.3, 113.1, 110.0, 73.6, 71.8, 71.7, 71.0, 54.9, 46.1, 28.7, 19.4, 13.5. HRMS (EI) calculated for
C$_{29}$H$_{29}$ClN$_2$O$_4$ 504.1816, found 504.1823.

(3S,4'S)-1-( tert-butyl)-5-fluoro-4'-hydroxy-2'-(4-methoxybenzyl)-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2m)

White solid, Yield 58% (dr: 97:3), Melting point: 210-212°C. $^1$H NMR (600 MHz, DMSO-d$_6$) $\delta$ 8.11 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.62-7.52 (m, 1H), 7.60-7.46 (M, 2H), 7.24-7.17 (m, 3H), 6.68-6.58 (m, 4H), 6.10 (s, 1H), 5.70 (s, 1H), 5.16 (d, $J = 13.6$ Hz, 1H), 4.04 (d, $J = 13.6$ Hz, 1H), 3.65 (s, 3H), 1.26 (s, 9H), 1.17 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 173.8, 164.8, 158.4, 155.2, 140.7, 140.6, 140.5, 131.9, 129.5, 128.3, 127.8, 126.7, 126.6, 124.4, 116.0, 116.0, 115.4, 113.7, 113.6, 113.2, 71.7, 71.1, 56.9, 55.0, 54.9, 45.7, 28.1, 20.6. HRMS (EI) calculated for C$_{29}$H$_{29}$FN$_2$O$_4$ 488.2111, found 488.2097. [The corresponding benzofuro-isoquinoline carboxamide 3m is obtained in an isolated yield of 23% as byproduct]

(3S,4'S)-1-( tert-butyl)-5-fluoro-4'-hydroxy-4'-methyl-2'-(4-methylbenzyl)-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2n)

White solid, Yield 67% (dr: 92:8), Melting point: 216-218°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.10 (d, $J = 7.7$ Hz, 0.92H), 7.96 (d, $J = 7.7$ Hz, 0.08H), 7.59 -7.40 (m, 3H), 7.29-7.12 (m, 3H), 6.90-6.86 (m, 2H), 6.11-6.41 (m, 2H), 6.11 (s, 0.92H), 5.72 (s, 0.08H), 5.28-5.13 (m, 1H), 4.15-3.95 (m, 1H), 2.17 (s, 3H), 1.24 (s, 8.3H), 1.20 (s,0.7H), 1.16 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 173.8, 164.8, 158.4, 155.2, 140.6, 140.5, 136.0, 133.6, 133.5, 131.9, 128.4, 128.3, 128.1, 127.7, 127.3, 126.6, 126.5, 124.4, 116.0, 115.7, 115.4, 113.7, 113.6, 74.1, 71.8, 71.1, 56.9, 56.4, 46.2, 28.0, 20.6. HRMS (EI) calculated for C$_{29}$H$_{29}$FN$_2$O$_3$ 472.2162, found 472.2148. [The corresponding benzofuro-isoquinoline carboxamide 3n is obtained in an isolated yield of 23% as byproduct]

1-( tert-butyl)-2'-(3,4-dimethoxybenzyl)-5-fluoro-4'-hydroxy-4'-methyl-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2o)

White solid, Yield 62% (dr: 65:35), Melting point: 160-161°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.12 (d, $J = 6.8$ Hz, 0.65H), 7.98 (d, $J = 7.3$ Hz, 0.35H), 7.66-7.20 (m, 6H), 6.65-6.60 (m, 1H), 6.23-6.12 (m, 2.65H), 5.71 (s, 0.35H), 5.44-5.26 (m, 1H), 4.00-3.92 (m, 1H), 3.63-3.53 (m, 6H), 1.36-0.94 (m, 12H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 173.8, 165.2, 164.9, 158.4, 147.9, 147.8, 144.2, 142.0, 140.7, 140.4, 132.0, 131.8, 128.5, 128.2, 128.1, 127.8, 127.3, 126.7, 126.7, 126.6, 124.4, 123.8, 120.9, 120.6, 116.0, 115.8, 115.6, 115.5, 115.3, 115.1, 113.6, 113.5, 112.2, 112.0, 111.3, 111.1, 74.2, 71.7, 71.4, 71.2, 56.9, 56.3, 55.4(2), 54.9, 46.0(2), 30.7, 28.2, 28.1, 20.4. HRMS (EI) calculated
for C$_{30}$H$_{31}$FN$_2$O$_5$ 518.2217, found 518.2249. [The corresponding benzofuro-isoquinoline carboxamide is obtained in an isolated yield of 25% as byproduct]

(3S,4'S)-1-(tert-buty1)-4-fluoro-4'-hydroxy-4'-methyl-2'-((4-methylbenzyl)-1'H-spiro[indoline-3,3'-isoquinoline]-1',2(2'H,4'H)-dione (2p)

White solid, Yield 88% (dr: 98:2), Melting point: 197-199 ºC. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.12 (d, $J$ = 7.3 Hz, 1H), 7.58-7.34 (m, 4H), 7.05 (d, $J$ = 8.2 Hz, 1H), 6.94 (t, $J$ = 8.8 Hz, 1H), 6.84 (d, $J$ = 7.9 Hz, 2H), 6.53 (d, $J$ = 7.9 Hz, 2H), 6.13 (s, 1H), 5.67 (d, $J$ = 15.0 Hz, 1H), 3.71 (d, $J$ = 15.0 Hz, 1H), 2.15 (s, 3H), 1.21 (s, 3H), 1.19 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 173.5, 164.5, 160.9, 157.6, 146.3, 146.2, 140.5, 136.3, 133.1, 131.7, 131.4, 131.3, 128.7, 128.3, 128.2, 127.5, 127.3, 124.5, 115.6, 111.4, 110.0, 109.7, 109.436, 73.8(2), 72.3, 57.1, 46.7, 28.0, 21.2, 20.6. HRMS (EI) calculated for C$_{29}$H$_{29}$FN$_2$O$_3$ 472.2162, found 472.2122.

(2'S,3'S)-1-(tert-buty1)-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (5a)

Colorless oil, Yield 65% (dr > 95:5), $^1$H NMR (75 MHz, DMSO-d$_6$) $\delta$ 7.37-7.26 (m, 3H), 6.98-6.93 (m, 3H), 6.72-6.50 (m, 4H), 5.25 (s, 1H), 4.46 (d, $J$ = 15.0 Hz, 1H), 3.80 (d, $J$ = 15.0 Hz, 1H), 2.84-2.32 (m, 3H), 1.41 (s, 9H), 0.72 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ 175.4, 171.0, 158.1, 143.8, 129.2, 129.1, 128.9, 128.3, 123.5, 120.8, 113.0, 112.8, 72.8, 69.7, 57.0, 54.9, 46.0, 29.1, 28.3, 24.0. HRMS (EI) calculated for C$_{25}$H$_{30}$N$_2$O$_4$ 422.2206, found 422.2178.

(2'S,3'S)-5-(tert-buty1)-3'-hydroxy-3'-methyl-1'-(4-methylbenzyl)spiro[[1,3]dioxolo[4,5-f]indole-7,2'-piperidine]-6,6'(5H)-dione (5b)

Offwhite solid, Yield 55% (dr > 95:5), Melting point: 182-184 ºC. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.03 (s, 1H), 6.92 (d, $J$ = 7.8 Hz, 2H), 6.76 (s, 1H), 6.66 (d, $J$ = 7.9 Hz, 2H), 5.97 (d, $J$ = 6.6 Hz, 2H), 5.24 (s, 1H), 4.19 (d, $J$ = 15.1 Hz, 1H), 4.02 (d, $J$ = 15.1 Hz, 1H), 2.84-2.64 (m, 1H), 2.60-2.54 (m, 1H), 2.42-2.35 (m, 1H), 2.20 (s, 3H), 1.65-1.54 (m, 1H), 1.41 (s, 9H), 0.75 (s, 3H). $^{13}$C NMR (300 MHz, DMSO-d$_6$): $\delta$ 175.5, 171.0, 147.5, 141.2, 138.0, 135.4, 134.7, 128.1, 127.6, 117.4, 109.2, 101.0, 96.2, 73.0, 69.8, 57.1, 46.5, 29.1, 28.4, 24.0, 20.60. HRMS (EI) calculated for C$_{26}$H$_{30}$N$_2$O$_5$ 450.2155, found 450.2137.
(2'S,3'S)-1-cyclohexyl-5-fluoro-3'-hydroxy-3'-methyl-1'-(4-methylbenzyl)spiro[indoline-3,2'-piperidine]-2,6'-dione (5c)

Offwhite solid, Yield 74% (dr > 95:5), Melting point: 58-60°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.19-7.09 (m, 2H), 6.96 (dd, $J = 8.6, 2.3$ Hz, 1H), 6.90 (d, $J = 7.8$ Hz, 2H), 6.60 (d, $J = 7.9$ Hz, 2H), 5.41 (s, 1H), 4.17 (d, $J = 15.3$ Hz, 1H), 4.01 (d, $J = 15.3$ Hz, 1H), 3.87-3.80 (m, 1H), 2.80-2.73 (m, 1H), 2.67-2.58 (m, 1H), 2.50-2.40 (m, 1H), 2.19 (s, 3H), 2.13-2.04 (m, 1H), 1.96-1.69 (m, 5H), 1.31-1.13 (m, 5H), 0.70 (s, 3H). $^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$ 174.3, 170.8, 158.8, 155.7, 139.0, 135.6, 134.5, 128.1, 127.3, 126.6, 126.5, 116.4, 116.1, 115.8, 115.5, 110.3, 110.2, 73.0, 69.4, 52.0, 46.7, 29.2, 28.1, 28.0, 27.9, 25.2, 24.7, 23.9, 20.5. HRMS (EI) calculated for C$_{27}$H$_{31}$FN$_2$O$_3$ 450.2319, found 450.2309.

(2'S,3'S)-1-butyl-1'-(3,4-dimethoxy benzyl)-3'-hydroxy-5,6-dimethoxy-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (5d)

Offwhite solid, Yield 82% (dr > 95:5), Melting point: 54-56°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 6.80 (s, 1H), 6.72-6.69 (m, 2H), 6.33 (dd, $J = 8.2, 1.8$ Hz, 1H), 6.26 (d, $J = 1.8$ Hz, 1H), 5.27 (s, 1H), 4.19 (d, $J = 15.1$ Hz, 1H), 3.88 (d, $J = 15.1$ Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 3.57 (s, 3H), 3.47 (s, 3H), 3.44-3.37 (m, 2H), 2.84-2.69 (m, 2H), 2.45-2.38 (m, 1H), 1.61-1.55 (m, 1H), 1.42-1.35 (m, 2H), 1.29-1.24 (m, 3H), 0.87 (t, $J = 7.2$ Hz, 3H), 0.71 (s, 3H). $^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$ 174.9, 170.8, 150.2, 147.8, 147.4, 143.4, 137.3, 130.4, 119.7, 115.3, 113.7, 111.6, 111.2, 94.5, 73.2, 69.4, 56.0, 55.6, 55.5, 55.0, 46.6, 29.2, 28.3, 24.1, 19.6, 13.6. HRMS (EI) calculated for C$_{28}$H$_{36}$N$_2$O$_7$ 512.2523, found 512.2527.

(2'S,3'S)-1-benzyl-5-fluoro-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methylspiro[indoline-3,2'-piperidine]-2,6'-dione (5e)

Offwhite solid, Yield 81% (dr = 92:8), Melting point: 154-155°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.31-7.28 (m, 5H), 7.14 (t, $J = 7.9$ Hz, 1H), 6.99-6.94 (m, 2H), 6.71-6.60 (m, 2H), 5.47 (s, 1H), 4.68 (d, $J = 15.4$ Hz, 1H), 4.55 (d, $J = 15.3$ Hz, 1H), 4.15 (d, $J = 15.3$ Hz, 1H), 3.95 (d, $J = 15.2$ Hz, 1H), 3.69 (s, 3H), 2.81-2.75 (m, 1H), 2.67-2.63 (m, 1H), 2.60-2.43 (m, 1H), 1.67-1.62 (m, 1H), 0.68 (s, 3H). $^{13}$C NMR (300 MHz, DMSO-d$_6$) $\delta$ 174.6, 170.5, 157.8, 138.9, 135.9, 135.7, 129.2, 128.6, 128.4, 127.6, 127.4, 126.2, 115.8, 113.0, 112.8, 109.6, 73.4, 73.1, 69.5, 69.3, 55.0, 54.8, 46.3, 43.2, 29.2, 28.0, 23.8. HRMS (EI) calculated for C$_{28}$H$_{37}$FN$_2$O$_4$ 474.1955, found 474.1950.
(2'S,3'S)-5-fluoro-3'-hydroxy-1'-(4-methoxybenzyl)-3'-methyl-1-(2,4,4-trimethylpentan-2-yl)spiro[indoline-3,2'-piperidine]-2,6'-dione (5f)

Offwhite solid, Yield 50% \( (dr = 95:5) \), Melting point: 117-119°C. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \( \delta \) 7.37 (dd, \( J = 9.0, 4.3 \) Hz, 1H), 7.08 (td, \( J = 9.0, 3.0 \) Hz, 1H), 6.79 (dd, \( J = 8.6, 2.9 \) Hz, 1H), 6.70 (s, 4H), 5.37 (s, 1H), 4.43 (d, \( J = 15.2 \) Hz, 1H), 3.68 (s, 3H), 3.41 (d, \( J = 15.2 \) Hz, 1H), 2.84 – 2.72 (m, 1H), 2.70–2.64 (m, 1H), 2.43– 2.37 (m, 1H), 1.98-1.93 (m, 1H), 1.73 (s, 3H), 1.61-1.56 (m, 2H), 1.56 (s, 3H), 0.96 (s, 9H), 0.81 (s, 3H). \(^{13}\)C NMR (300 MHz, DMSO-\(d_6\)) \( \delta \) 176.0, 171.1, 158.4, 157.9, 155.2, 140.1, 140.0, 130.1, 128.0, 127.3, 127.2, 116.1, 115.7, 115.3, 115.0, 114.4, 114.3, 113.1, 74.2, 69.8, 61.5, 54.9, 50.0, 47.4, 31.2, 31.0, 29.8, 29.3, 29.1, 28.1, 24.3. HRMS (EI) calculated for \( C_{29}H_{37}FN_{2}O_{4} \) 496.2737, found 496.2724.
General procedure for the synthesis of benzofuro-isoquinoline carboxamides

To a dry screw capped glass vial Pd(OAc)$_2$ (5 mol%), BINAP (7.5 mol%), Cs$_2$CO$_3$ (2 equiv.) were loaded along with the mixture of toluene and MeOH (1.95 mL:0.05 mL). Ugi product 1a-p and 4a-f (0.2 mmol) was added. The reaction vial was evacuated, backfilled with nitrogen (4 cycles) and was stirred at 120°C for 24 hours. After completion, the reaction mixture was cooled, directly loaded over a silica gel column and chromatographed (10-30 % EtOAc in heptane) to afford compounds 3. The structures of the compounds were confirmed by NMR and HRMS data.

Characterization data for benzofuro-isoquinoline carboxamides (3a-i)

(6aS,11aS)-N-(tert-butyl)-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3a)

White solid, Yield 72%, Melting point: 194-196°C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.74 (dd, $J$ = 7.8, 0.9 Hz, 1H), 7.65 (td, $J$ = 7.6, 1.5 Hz, 1H), 7.56 (td, $J$ = 7.5, 1.3 Hz, 1H), 7.46 (d, $J$ = 7.6 Hz, 1H), 7.27-7.21 (m, 1H), 6.91-6.85 (m, 2H), 6.80-6.77 (m, 2H), 6.64-6.61 (m, 2H), 5.77 (s, 1H), 4.88 (d, $J$= 15.6 Hz, 1H), 4.48 (d, $J$= 15.6, 1H), 3.68 (s, 3H), 1.79 (s, 3H), 1.21 (s, 9H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.7, 163.0, 159.9, 158.2, 134.7, 132.8, 131.0, 129.9, 129.4, 128.9, 127.8, 127.7, 127.1, 126.0, 125.9, 121.4, 113.5, 111.5, 86.3, 78.6, 55.2, 52.2, 47.8, 28.3. HRMS (EI) calculated for C$_{29}$H$_{30}$N$_2$O$_4$ 470.2206, found 470.2214.

(6aS,11aS)-N-(tert-butyl)-6-butyl-11a-methyl-5-oxo-5,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3c)

Offwhite solid, Yield 63%, Melting point: 97-99 °C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.31 (d, $J$ = 7.7 Hz, 1H), 7.72-7.53 (m, 4H), 7.32 (t, $J$ = 7.8 Hz, 1H), 7.04 (t, $J$ = 7.5 Hz, 1H), 6.88 (d, $J$ = 8.1 Hz, 1H), 5.67 (s, 1H), 3.73-3.63 (m, 1H), 3.20-3.11 (m, 1H), 1.76 (s, 3H), 1.68-1.48 (m, 2H), 1.27 (s, 9H), 1.24-1.13 (m, 1H), 0.81 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.0, 162.0, 159.7, 134.67, 132.7, 130.8, 129.9, 128.6, 127.4, 127.2, 126.2, 126.0, 121.2, 111.4, 86.0, 78.1, 52.1, 45.8, 29.6, 28.3, 21.6, 20.3, 13.7. HRMS (ESI) calculated for C$_{25}$H$_{31}$N$_2$O$_3$ ([M+H]$^+$) 407.2329, found 407.2338.
(6aS,11aS)-N-(tert-butyl)-8-chloro-6-(3,4-dimethoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3k)

White solid, Yield 65%. Melting point: 53-55°C. 1H NMR (600 MHz, DMSO-d6) δ 8.12 (d, J = 7.7 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.71 (dd, J = 10.9, 4.4 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.22 (dd, J = 8.5, 2.2 Hz, 1H), 7.10 (s, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 6.27 (d, J = 8.3 Hz, 1H), 6.23 (s, 1H), 5.01 (d, J = 16.0 Hz, 1H), 4.09 (d, J = 16.0 Hz, 1H), 3.61 (s, 3H), 3.51 (m, 1H), 1.79 (s, 3H), 1.29 (s, 9H). 13C NMR (600 MHz, DMSO-d6) δ 164.7, 162.8, 158.5, 148.1, 146.9, 134.2, 132.5, 130.4, 129.6, 128.9, 127.6, 127.4, 127.0, 126.6, 124.7, 118.0, 111.7, 111.4, 109.7, 78.3, 55.5, 55.1, 52.1, 47.0, 27.8. HRMS (EI) calculated for C30H31ClN2O5 534.1921, found 534.1958.

(6aS,11aS)-N-(tert-butyl)-8-fluoro-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3m)

White solid, Yield 54%. Melting point: 146-148°C. 1H NMR (600 MHz, DMSO-d6) δ 7.87 (d, J = 7.8 Hz, 1H), 7.70 (td, J = 7.7, 1.3 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.55 (dd, J = 8.5, 2.7 Hz, 1H), 7.06-7.02 (m, 2H), 6.89 (dd, J = 8.7, 4.2 Hz, 1H), 6.58 (s, 4H), 4.97 (d, J = 16.0 Hz, 1H), 4.13 (d, J = 16.0 Hz, 1H), 3.61 (s, 3H), 1.79 (s, 3H), 1.28 (s, 9H). 13C NMR (600 MHz, DMSO-d6) δ 164.8, 162.8, 157.4, 155.9, 155.2, 134.4, 132.5, 129.8, 129.5, 127.5, 127.0, 126.8, 126.7, 126.6, 117.2, 116.9, 116.1, 115.8, 112.9, 111.1, 110.9, 86.4, 78.4, 52.07, 46.8, 27.8, 21.4. HRMS (EI) calculated for C29H29FN2O4 488.2111, found 488.2116.

(6aS,11aS)-N-(tert-butyl)-8-fluoro-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3n)

White solid, Yield 69%. Melting point: 177-178°C. 1H NMR (300 MHz, DMSO-d6) δ 8.10 (dd, J = 7.7, 1.3 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.71 (td, J = 7.6, 1.4 Hz, 1H), 7.61 (t, J = 7.1 Hz, 1H), 7.54 (dd, J = 8.6, 2.6 Hz, 1H), 7.06 (s, 1H), 7.04-6.99 (m, 1H), 6.93-6.86 (m, 1H), 6.82 (d, J = 7.9 Hz, 2H), 6.54 (d, J = 8.0 Hz, 2H), 5.00 (d, J = 16.2 Hz, 1H), 4.15 (d, J = 16.2 Hz, 1H), 2.13 (s, 3H), 1.79 (s, 3H), 1.29 (s, 9H). 13C NMR (75 MHz, DMSO-d6) δ 164.8, 162.7, 158.3, 155.9, 155.2, 134.9, 134.7, 134.5, 132.5, 129.5, 128.0, 127.5, 126.9, 126.7, 126.6, 125.5, 117.2, 116.9, 116.1, 115.7, 111.0, 110.9, 86.4, 78.4, 52.1, 47.1, 27.8, 21.5, 20.5. HRMS (EI) calculated for C29H29FN2O3 472.2162, found 472.2155.
(6aS,11aS)-N-(tert-butyl)-6-(3,4-dimethoxybenzyl)-8-fluoro-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3o)

White solid, Yield 81%, Melting point: 161-162°C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.11 (dd, $J = 7.7$, 1.2 Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.71 (td, $J = 7.6$, 1.3 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.63-7.57 (m, 2H), 7.10-7.03 (m, 2H), 6.93-6.89 (m, 1H), 6.60 (d, $J = 8.3$ Hz, 1H), 6.26-6.21(m, 2H), 4.97 (d, $J = 16.0$ Hz, 1H), 4.12 (d, $J = 16.0$ Hz, 1H), 3.61 (s, 3H), 3.48 (s, 3H), 1.79 (s, 3H), 1.29 (s, 9H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 164.8, 162.8, 158.4, 156.0, 155.2, 148.0, 146.9, 134.4, 132.5, 130.5, 129.6, 127.5, 127.0, 126.8, 126.7, 126.6, 118.0, 117.3, 116.9, 116.3, 115.9, 111.3, 111.1, 111.0, 109.7, 86.4, 78.4, 55.5, 55.1, 52.1, 47.1, 27.8, 21.5. HRMS (EI) calculated for C$_{39}$H$_{35}$FN$_{2}$O$_{5}$ 518.2217, found 518.2187.

(6aS,11aS)-N-(tert-butyl)-7-fluoro-11a-methyl-6-(4-methylbenzyl)-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3p)

White solid, Yield 83%, Melting point: 168-169°C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.37 (dd, $J = 7.7$, 1.4 Hz, 1H), 7.73 (dd, $J = 7.8$, 1.1 Hz, 1H), 7.66 (td, $J = 7.5$, 1.6 Hz, 1H), 7.58 (td, $J = 7.5$, 1.4 Hz, 1H), 7.09 (td, $J = 8.2$, 5.7 Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 2H), 6.73 (d, $J = 8.0$ Hz, 2H), 6.62 (dd, $J = 8.1$, 0.7 Hz, 1H), 6.46-6.32 (m, 1H), 5.88 (s, 1H), 5.22 (d, $J = 16.2$ Hz, 1H), 4.32 (d, $J = 16.2$ Hz, 1H), 2.17 (s, 3H), 1.83 (s, 3H), 1.27 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.6, 162.9, 161.6, 161.5, 160.5, 157.2, 135.7, 134.2, 133.9, 132.9, 132.6, 132.5, 130.1, 129.1, 128.6, 127.0, 126.0, 125.6, 113.7, 113.5, 109.3, 109.0, 107.4, 107.4, 86.9, 79.6, 79.5, 52.4, 48.5, 48.4, 28.3, 21.5, 21.0. HRMS (ESI) calculated for C$_{29}$H$_{30}$FN$_{2}$O$_{3}$ ([M+H]$^+$) 473.2235, found 473.2238.

(6aS,11aS)-8-fluoro-6-(4-methoxybenzyl)-11a-methyl-5-oxo-N-(2,4,4-trimethylpentan-2-yl)-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3q)

White solid, Yield 64%, Melting point: 143-145°C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J = 7.5$ Hz, 1H), 7.75 (d, $J = 6.9$ Hz, 1H), 7.68 (t, $J = 7.4$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.14 (dd, $J = 8.0$, 2.6 Hz, 1H), 6.86-6.80 (m, 3H), 6.74-6.70 (m, 1H), 6.64 (d, $J = 8.7$ Hz, 1H), 5.73 (s, 1H), 5.06 (d, $J = 15.6$ Hz, 1H), 4.36 (d, $J = 15.6$ Hz, 1H), 3.70 (s, 3H), 1.82 (s, 3H), 1.41 (s, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 0.78 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.4, 165.0, 162.4, 158.6, 158.2, 155.7, 155.6, 134.8, 133.2, 130.1, 129.1, 129.0, 128.0, 127.5, 127.3, 127.2, 127.0, 126.6, 126.1, 117.1, 116.8, 116.0, 115.7, 113.6, 111.4, 111.3, 86.7, 78.7, 56.5, 55.2, 54.0, 48.1, 31.4, 31.3, 27.9, 27.2, 21.3, 14.1. HRMS (ESI) calculated for C$_{33}$H$_{38}$FN$_{2}$O$_{4}$ ([M+H]$^+$) 545.2810, found 545.2801.
(6αS,11αS)-N-(adamantan-1-yl)-6-(4-methoxybenzyl)-11a-methyl-5-oxo-5,6,6a,11a-tetrahydrobenzofuro[3,2-c]isoquinoline-6a-carboxamide (3r)

White solid, Yield 75%, Melting point: 230-231°C. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.33 (d, $J = 7.6$ Hz, 1H), 7.74 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.0$ Hz, 1H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 6.91-6.84 (m, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 6.62 (d, $J = 8.6$ Hz, 2H), 5.66 (s, 1H), 4.90 (d, $J = 15.5$ Hz, 1H), 4.48 (d, $J = 15.5$ Hz, 1H), 3.69 (s, 3H), 2.02 (s, 3H), 1.88-1.54 (m, 16H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.3, 163.0, 159.9, 158.2, 134.6, 132.7, 131.0, 129.8, 129.4, 128.9, 127.8, 127.7, 127.1, 126.0, 125.8, 121.4, 113.5, 111.5, 86.2, 78.6, 55.2, 52.8, 47.79, 41.1, 36.1, 29.2, 22.0. HRMS (ESI) calculated for C$_{35}$H$_{37}$N$_2$O$_4$ ([M+H]$^+$) 549.2748, found 549.2756.
Crystallographic data for compound 2p, 2n and 3a

Single crystals of 2p, 2n and 3a suitable for X-ray diffraction were obtained by slow evaporation from acetonitrile at room temperature. X-ray intensity data were collected at 100K on an Agilent Supernova diffractometer, equipped with an Atlas CCD detector, using Mo Kα radiation (λ = 0.71073 Å). The images were interpreted and integrated with the CrysAlisPro software from Rigaku Oxford Diffraction.[1] Using Olex2,[2] the structures were solved with the ShelXS[3] structure solution program using Direct Methods and refined with the ShelXL[3] refinement package using full-matrix least squares minimization on F². Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors were fixed at 1.2 times Ueq of the parent atoms (1.5 for methyl groups). Respectively, CCDC 1435833, 1435835 and 1435834 contain the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystallographic data

2p C₃₁H₇₂FN₃O₃, M = 513.60 g mol⁻¹, monoclinic, P2₁/c (no. 14), a = 9.0851(3) Å, b = 16.6480(5) Å, c = 17.5220(5) Å, β = 98.553(3)°, V = 2620.71(14) Å³, T = 100.01(10) K, Z = 4, ρcalcd = 1.302 g cm⁻³, μ(Mo Kα) = 0.089 mm⁻¹, F(000) = 1088, crystal size 0.2 x 0.2 x 0.1 mm³, 5353 reflections measured, 4678 unique which were used in all calculations. The final wR₂ was 0.1096 (all data) and R₁ was 0.0475 (>2sigma(I)).

3a C₂₉H₃₈N₂O₄, M = 470.55 g mol⁻¹, monoclinic, P2₁/c (no. 14), a = 15.2680(8) Å, b = 11.6042(4) Å, c = 15.6622(8) Å, β = 115.596(7)°, V = 2502.6(2) Å³, T = 100.00(10) K, Z = 4, ρcalcd = 1.249 g cm⁻³, μ(Mo Kα) = 0.083 mm⁻¹, F(000) = 1000, crystal size 0.2 x 0.2 x 0.1 mm³, 5115 reflections measured, 4350 unique which were used in all calculations. The final wR₂ was 0.1053 (all data) and R₁ was 0.0420 (>2sigma(I)).

2n C₃₁H₇₂FN₃O₃, M = 513.60 g mol⁻¹, monoclinic, P2₁/c (no. 14), a = 9.0977(4) Å, b = 16.6165(7) Å, c = 17.6000(8) Å, β = 96.066(4)°, V = 2645.7(2) Å³, T = 100.01(10) K, Z = 4, ρcalcd = 1.289 g cm⁻³, μ(Mo Kα) = 0.088 mm⁻¹, F(000) = 1088, crystal size 0.2 x 0.2 x 0.1 mm³, 5412 reflections measured, 4584 unique which were used in all calculations. The final wR₂ was 0.1047 (all data) and R₁ was 0.0421 (>2sigma(I)).
Figure 1 Asymmetric unit of 2p. Thermal ellipsoids are drawn at 50% probability level.

Figure 2 Asymmetric unit of 2n. Thermal ellipsoids are drawn at 50% probability level.
**Figure 3** Asymmetric unit of 3a. Thermal ellipsoids are drawn at 50% probability level.

**References**:  
$^1$H and $^{13}$C NMR spectra of compound 1a (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1b (300 MHz, CDCl₃)
$^{1}$H and $^{13}$C NMR spectra of compound 1c (300 MHz, CDCl$_3$)
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compound 1d (300 MHz, CDCl$_3$)
$^{1}$H and $^{13}$C NMR spectra of compound 1e (300 MHz, CDCl$_3$)
\(^1\text{H} \text{ and } ^{13}\text{C} \text{ NMR spectra of compound 1f (300 MHz, CDCl}_3\text{)}\)
$^1$H and $^{13}$C NMR spectra of compound 1g (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1h (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1i (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1j (300 MHz, CDCl$_3$)
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra of compound 1k (300 MHz, CDCl$_3$)
$^{1}H$ and $^{13}C$ NMR spectra of compound 11 (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1m (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1n (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 10 (300 MHz, CDCl$_3$)
$^{1}H$ and $^{13}C$ NMR spectra of compound 1p (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1q (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 1r (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 2a (300 MHz, DMSO-$d_6$)
$^{1}\text{H}$ and $^{13}\text{C}$ NMR spectra of compound 2b (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2c (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2d (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2e (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2f (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2f' (300 MHz, DMSO-$d_6$)
$^{1}$H and $^{13}$C NMR spectra of compound 3f (300 MHz, DMSO-d$_6$)
$^1$H and $^{13}$C NMR spectra of compound 2g (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound $2g'$ (300 MHz, DMSO-$d_6$) Z
$^1$H and $^{13}$C NMR spectra of compound 3g (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2h (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound $3\text{h}$ (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2i (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2j (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3j (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2k (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2l (600 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2m (600 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2n (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 2o (300 MHz, DMSO-$d_6$)
$^{1}$H and $^{13}$C NMR spectra of compound 2p (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3a (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 3c (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 3k (600 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3m (600 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3n (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3o (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 3p (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 3q (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 3r (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4a (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4b (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4c (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4d (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4e (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 4f (300 MHz, CDCl$_3$)
$^1$H and $^{13}$C NMR spectra of compound 5a (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 5b (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 5c (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 5d (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 5e (300 MHz, DMSO-$d_6$)
$^1$H and $^{13}$C NMR spectra of compound 5f (300 MHz, DMSO-$d_6$)