Supporting Information

New Synthetic Approach to Paullones and Characterization of Their SIRT1 Inhibitory Activity†

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2-(5-Bromo-1H-indol-3-yl)acetonitrile 20b. General procedure for the synthesis of nitriles. Eschenmoser’s salt (222.0 mg, 1.2 mmol) was added to a solution of 5-bromoindole (196.1 mg, 1.0 mmol) in MeCN/AcOH (3.9 mL, 19:1) and the mixture was stirred at 25 °C. After 3 h, an additional portion of the Eschenmoser’s salt (18.5 mg, 0.1 mmol) was added and the mixture was stirred for 1 h. The reaction was treated with a 10% aqueous KOH solution until pH 9 and then extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated to provide a yellowish solid (313.5 mg) which was used in the next step without further purification. Methyl iodide (124.5 µL, 2.0 mmol) was added to a solution of the residue obtained above in EtOH (2.0 mL) and the mixture was stirred at 25 °C for 14 h. The solvent was evaporated and a solution of this residue in DMF (2.5 mL) was added a solution of NaCN (245.1 mg, 5.0 mmol) in water (0.5 mL) and the reaction was heated at 70 °C for 4 h. After cooling to 25 °C, the mixture was diluted with Et₂O, washed with water (5x) and dried (Na₂SO₄) and the solvent was evaporated. The residue was dried under high vacuum to give 20b as a yellow solid (162.5 mg, 69%). m.p.: 100-102 °C (ether). ¹H-NMR (400.13 MHz, CDCl₃): δ 8.29 (br, 1H, NH), 7.68 (d, J = 1.2 Hz, 1H, ArH), 7.30 (dd, J = 8.6, 1.7 Hz, 1H, ArH), 7.24 (d, J = 8.6 Hz, 1H, ArH), 7.20 (d, J = 1.4 Hz, 1H, ArH), 3.76 (s, 2H, CH₂) ppm. ¹³C-NMR (100.61 MHz, CDCl₃): δ 134.9 (s), 127.6 (s), 125.8 (d), 124.0 (d), 120.7 (d), 117.8 (s), 113.5 (s), 113.0 (d), 104.3 (s), 14.3 (t) ppm. HRMS (ESI⁺): calcd. for C₁₀H₇¹BrN₂Na ([M+Na]⁺), 258.9664; found, 258.9663. Calcld. for C₁₀H₇¹BrN₂Na ([M+Na]⁺), 258.9685; found, 258.9684. IR (NaCl): ν 3400-3300 (br, NH), 2904 (w, C-H), 2251 (m, C≡N), 1457 (s), 1419 (m), 1098 (m), 797 (s) cm⁻¹.

2-(6-Bromo-1H-indol-3-yl)acetonitrile 20c. Following the general procedure described above for the synthesis of indole acetonitriles, the reaction of 6-bromoindole 18c (80 mg, 0.41 mmol), Eschenmoser’s salt (90.6 mg, 0.49 mmol; 7.5 mg, 0.04 mmol) in MeCN/AcOH (1.6 mL, 19:1) and methyl iodide (51 µL, 0.82 mmol), EtOH (820 µL), DMF (1 mL), NaCN (100.5 mg, 2.05 mmol) and water (0.2 mL) afforded 20c as a yellow solid (56 mg, 58%).

2-(6-Bromo-1H-indol-3-yl)acetic acid 21c. Following the general procedure described above for the synthesis of carboxylic acids, the reaction of 2-(6-bromo-1H-
indol-3-yl)acetonitrile 20c (0.83 g, 3.53 mmol), MeOH (4.4 mL) and KOH (1.60 g, 28.56 mmol) in water (14.3 mL) afforded 21c acid as a white solid (0.67 g, 75%). m.p.: 164-166 °C (methanol). 1H-NMR (400.13 MHz, CD$_2$OD): δ 7.49 (d, J = 1.4 Hz, 1H, ArH), 7.43 (d, J = 8.4 Hz, 1H, ArH), 7.16 (s, 1H, ArH), 7.11 (dd, J = 8.4, 1.7 Hz, 1H, ArH), 3.70 (s, 2H, CH$_2$) ppm. 13C-NMR (100.61 MHz, CD$_3$OD): δ 172.6 (s), 136.0 (s), 127.1 (s), 125.6 (d), 123.0 (d), 121.1 (d), 115.9 (s), 115.1 (d), 109.5 (s), 31.8 (t) ppm. HRMS (ESI$^+$): calcd. for C$_{10}$H$_8$BrNNaO$_2$ ([M+Na]$^+$), 275.9631; found, 275.9630. IR: ν 3419 (w, NH), 2903 (w, C-H), 1701 (s, C=O), 1218 (s), 804 (s) cm$^{-1}$.

**Methyl 2-(1H-indol-3-yl)acetate 22a. General procedure for the synthesis of methyl esters.** A solution of HCl in MeOH was prepared by adding SOCl$_2$ (1225 µL, 16.80 mmol) dropwise to anhydrous MeOH (35 mL) at 0 °C. This solution was added to a solution of 2-(1H-indol-3-yl)acetic acid 21a (2.6 g, 15.00 mmol) in MeOH (35 mL) at 0 °C. The mixture was allowed to reach 25 °C and stirred for 4 h. The resulting red solution was neutralized with solid NaHCO$_3$ and concentrated in vacuo. The residue was dissolved in EtOAc, washed with water and the aqueous layer was extracted with AcOEt (2x). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (silicagel, 80:20 hexane/AcOEt) to give 22a as a yellow oil (2.8 g, 99%). m.p.: 49-51 °C (hexane/ethyl acetate). 1H-NMR (400.13 MHz, CDCl$_3$): δ 8.11 (br, 1H, NH), 7.62 (d, J = 7.8 Hz, 1H, ArH), 7.34 (d, J = 8.0 Hz, 1H, ArH), 7.21 (t, J = 7.5 Hz, 1H, ArH), 7.2 – 7.1 (m, 2H, ArH), 3.79 (s, 2H, CH$_2$), 3.71 (s, 3H, CH$_3$) ppm. 13C-NMR (100.61 MHz, CDCl$_3$): δ 172.6 (s), 136.0 (s), 127.1 (s), 123.1 (d), 122.2 (d), 119.6 (d), 118.8 (d), 111.2 (d), 108.3 (s), 52.0 (q), 31.1 (t) ppm. HRMS (ESI$^+$): calcd. for C$_{11}$H$_{11}$NNaO$_2$ ([M+Na]$^+$), 212.0682; found, 212.0683. IR (NaCl): ν 3405 (br, NH), 3056 (w, C-H), 2950 (w, C-H), 2845 (w, C-H), 1720 (s, C=O), 1432 (m), 1160 (m), 1009 (m), 742 (s) cm$^{-1}$. UV (MeOH): λ$_{max}$ 280 nm.$^3$

**Methyl 2-(5-Bromo-1H-indol-3-yl)acetate 22b.** Following the general procedure described above for the synthesis of methyl esters, the reaction of 2-(5-bromo-1H-indol-3-yl)acetic acid 21b (1.0 g, 5.71 mmol) and SOCl$_2$ (466 µL, 6.39 mmol) in MeOH (26.2 mL) afforded, after purification by column chromatography (silicagel, from 85:15 to 70:30 hexane/AcOEt), 22b as a yellow solid (1.07 g, 99%). m.p.: 102-104 °C.
(hexane/ethyl acetate). \(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): \(\delta 8.17\) (br, 1H, NH), 7.72 (s, 1H, ArH), 7.26 (d, \(J = 9.3\) Hz, 1H, ArH), 7.19 (d, \(J = 8.6\) Hz, 1H, ArH), 7.12 (s, 1H, ArH), 3.72 (s, 2H, CH\(_2\)), 3.71 (s, 3H, CH\(_3\)) ppm. \(^{13}\)C-NMR (100.61 MHz, CDCl\(_3\)): \(\delta 172.3\) (s), 134.7 (s), 128.9 (s), 125.1 (d), 124.3 (d), 121.5 (d), 113.0 (s), 112.6 (d), 108.1 (s), 52.1 (q), 30.9 (t) ppm. HRMS (ESI\(^{+}\)): calcd for C\(_{11}\)H\(_{10}\)BrNNaO\(_2\), 291.9767; found, 291.9765. Calcd. for C\(_{11}\)H\(_{10}\)BrNNaO\(_2\) ([M+Na]\(^{+}\)), 289.9787; found 289.9785. IR (NaCl): \(\nu 3400-3300\) (br, NH), 2999 (w, C-H), 2930 (w, C-H), 2899 (w, C-H), 1726 (s, C=O), 1457 (m), 1167 (m), 795 (m) cm\(^{-1}\).

**Methyl 2-(6-Bromo-1H-indol-3-yl)acetate 22c.** Following the general procedure described above for the synthesis of methyl esters, the reaction of 2-(6-bromo-1H-indol-3-yl)acetic acid 21c (0.45 g, 1.77 mmol), SOCl\(_2\) (145 \(\mu\)L, 1.98 mmol) and MeOH (82 mL) afforded methyl 2-(6-bromo-1H-indol-3-yl)acetate 22c as an orange oil (0.38 g, 80%).

**tert-Butyl (2-Iodophenyl)carbamate.** A solution of 2-iodoaniline (0.44 g, 2.00 mmol) and (Boc)\(_2\)O (0.70 g, 3.20 mmol) in anhydrous THF (3.5 mL) was refluxed for 89 h. H\(_2\)O was added and the mixture was extracted with AcOEt (3x). The combined organic layers were washed with brine, dried (Na\(_2\)SO\(_4\)), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 98:2 to 95:5 hexane/AcOEt) to afford tert-butyl (2-iodophenyl)carbamate as a yellow oil (0.49 g, 76%). \(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): \(\delta 8.04\) (d, \(J = 8.2\) Hz, 1H, ArH), 7.71 (dd, \(J = 7.9, 1.4\) Hz, 1H, ArH), 7.28 (td, \(J = 7.7, 1.3\) Hz, 1H, ArH), 6.83 (br, 1H, NH), 6.73 (td, \(J = 7.8, 1.5\) Hz, 1H, ArH), 1.52 (s, 9H, 3xCH\(_3\)) ppm. \(^{13}\)C-NMR (100.61 MHz, CDCl\(_3\)): \(\delta 152.3\) (s), 146.6 (s), 138.6 (d), 129.0 (d), 124.5 (d), 120.0 (d), 88.6 (s), 84.9 (s, minor rotamer), 80.8 (s, major rotamer), 28.1 (q, 3x, major rotamer), 27.2 (q, 3x, minor rotamer) ppm. HRMS (ESI\(^{+}\)): calcd. for C\(_{11}\)H\(_{14}\)IINaO\(_2\) ([M+Na]\(^{+}\)), 341.9961; found, 341.9958. IR (NaCl): \(\nu 3394\) (br, NH), 3064 (w, C-H), 2979 (w, C-H), 2930 (w, C-H), 1734 (s, C=O), 1517 (s), 1155 (s) cm\(^{-1}\).
2-(5-Bromo-1H-indol-3-yl)-N-(2-iodophenyl)acetamide. General procedure for the synthesis of amides. To a solution of 2-(5-bromo-1H-indol-3-yl)acetic acid (54.9 mg, 0.216 mmol) in CH₂Cl₂ (1.1 mL) was added 2-chloro-1-methyl-pyridinium iodide (66.2 mg, 0.259 mmol) and 2-iodoaniline (260.3 mg, 1.188 mmol). The mixture was heated at reflux for 1 h, and then, after cooling down, Et₃N (60.2 µL, 0.432 mmol) was added, and the mixture was heated at reflux for an additional 22 h. The reaction was cooled down and poured into water, and the mixture was extracted with CH₂Cl₂ (3x). The combined organic layers were dried (Na₂SO₄) and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 80:20 to 50:50 hexane/AcOEt) to afford 2-(5-bromo-1H-indol-3-yl)-N-(2-iodophenyl)acetamide as a light brown solid (70.6 mg, 72%). ¹H-NMR (400.13 MHz, CDCl₃): δ 8.32 (br, 1H, NH indole), 8.29 (d, J = 8.2 Hz, 1H, ArH), 7.80 (s, 1H, ArH), 7.75 (br, 1H, NH amide), 7.64 (d, J = 7.9 Hz, 1H, ArH), 7.4-7.3 (m, 4H, ArH), 6.78 (t, J = 7.7 Hz, 1H, ArH), 3.91 (s, 2H, CH₂) ppm.

2-(1H-Indol-3-yl)-N-phenylacetamide. To a solution of 2-(1H-indol-3-yl)acetic acid (350.4 mg, 2.0 mmol) and aniline (218.7 µL, 2.4 mmol) in DMF (0.5 mL) at 0 ºC were added DMAP (48.9 mg, 0.4 mmol) and EDC (421.8 mg, 2.2 mmol) and the mixture was stirred for 23 h at 25 ºC. The reaction was washed with a saturated aqueous solution of Na₂CO₃, a 1M aqueous solution of HCl and brine, and dried (Na₂SO₄), and the solvent was evaporated. The residue was purified by column chromatography (silica gel, from 70:30 to 50:50 hexane/AcOEt) to afford 2-(1H-indol-3-yl)-N-phenylacetamide as a white solid (476.1 mg, 95%). ¹H-NMR (400.13 MHz, DMSO-d₆): δ 10.92 (br, 1H, NH indole), 10.09 (br, 1H, NH amide), 7.7-7.6 (m, 3H, ArH), 7.37 (d, J = 8.1 Hz, 1H,
ArH), 7.3-7.2 (m, 3H, ArH), 7.1-7.0 (td, \(J = 7.5, 1.2\) Hz, 1H, ArH), 7.0-6.9 (m, 2H, ArH), 3.74 (s, 2H, CH\(_2\)) ppm. \(^{13}\)C-NMR (100.61 MHz, DMSO-d\(_6\)): \(\delta\) 169.6 (s), 139.3 (s), 136.0 (s), 128.6 (d, 2x), 127.1 (s), 123.8 (d), 122.9 (d), 120.9 (d), 119.0 (d), 118.6 (d, 2x), 118.3 (d), 111.3 (d), 108.5 (s), 33.7 (t) ppm. HRMS (ESI\(^+\)): calc. for C\(_{16}\)H\(_{14}\)N\(_2\)O (\([\text{M+Na}]^+\)), 273.0998; found, 273.0996. IR (NaCl): \(\nu\) 3376 (br, NH), 3298 (br, NH), 3058 (w, C-H), 2923 (w, C-H), 1661 (s, C=O), 1598 (s), 1524 (s), 1442 (s), 741 (s) cm\(^{-1}\).

**N-Phenyl-2-(1-pivaloyl-1H-indol-3-yl)acetamide and N-Phenyl-N-pivaloyl-N-[2-(1-pivaloyl-1H-indol-3-yl)acetyl]amide.** General procedure for the synthesis of pivaloyl-indoles. To a solution of 2-(1H-indol-3-yl)-N-phenylacetamide (0.1 g, 0.4 mmol) and DMAP (4.9 mg, 0.04 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL), triethylamine (82.4 \(\mu\)L, 0.59 mmol) was added. After cooling down to 0 °C, pivaloyl chloride (59 \(\mu\)L, 0.48 mmol) was added slowly and the mixture was stirred for 10 min. The reaction was warmed up to 25 °C and stirred for 24 h. Then, CH\(_2\)Cl\(_2\) was evaporated and the residue was partitioned between Et\(_2\)O and a saturated aqueous solution of NH\(_4\)Cl. The layers were separated and the organic layer was washed with brine (1x). The aqueous layers were extracted with Et\(_2\)O (2x), the combined organic layers were dried (Na\(_2\)SO\(_4\)) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, from 85:15 to 70:30 hexane/AcOEt), to afford N-phenyl-2-(1-pivaloyl-1H-indol-3-yl)acetamide (71.6 mg, 54%) and N-phenyl-N-pivaloyl-N-[2-(1-pivaloyl-1H-indol-3-yl)acetyl]amide (10.6 mg, 6%). **Major product:** \(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): \(\delta\) 8.54 (d, \(J = 8.4\) Hz, 1H, ArH), 7.80 (s, 1H, NH), 7.55 (d, \(J = 7.7\) Hz, 1H, ArH), 7.4 – 7.3 (m, 4H, ArH), 7.3-7.2 (m, 3H, ArH), 7.08 (t, \(J = 7.4\) Hz, 1H, ArH), 3.84 (s, 2H, CH\(_2\)), 1.52 (s, 9H, 3 x CH\(_3\)) ppm. \(^{13}\)C-NMR (100.61 MHz, CDCl\(_3\)): \(\delta\) 176.9 (s), 168.1 (s), 137.4 (s), 137.2 (s), 129.1 (d, 2x), 128.6 (s), 126.0 (d), 124.8 (d), 124.6 (d), 124.3 (d), 123.1 (d), 122.7 (s), 120.7 (d), 119.6 (d), 118.4 (s), 111.3 (s), 108.5 (s), 33.7 (t) ppm.
124.0 (d), 120.1 (d, 2x), 118.3 (d), 117.7 (d), 114.1 (s), 41.3 (s), 34.2 (t), 28.7 (q, 3x) ppm. HRMS (ESI\(^+\)):\ calcd. for C\(_{21}\)H\(_{22}\)N\(_2\)O\(_2\) ([M+Na]\(^+\)), 357.1574; found, 357.1570.

**Minor product:** \(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): δ 8.51 (d, \(J = 8.2\) Hz, 1H, ArH), 7.71 (s, 1H, ArH), 7.5 - 7.3 (m, 4H, ArH), 7.3 - 7.2 (m, 2H, ArH), 7.17 (d, \(J = 6.2\) Hz, 2H, ArH), 3.93 (s, 2H, CH\(_2\)), 1.52 (s, 9H, 3\(\times\)CH\(_3\)), 1.06 (s, 9H, 3\(\times\)CH\(_3\)) ppm. HRMS (ESI\(^+\)):\ calcd. for C\(_{26}\)H\(_{30}\)N\(_2\)O\(_3\) ([M+Na]\(^+\)), 441.2149; found, 441.2144.

**Methyl 2-(1-Pivaloyl-1H-indol-3-yl)acetate.** Following the general procedure described above for the synthesis of pivaloilindoles, the reaction of methyl 2-(1H-indol-3-yl)acetate (94.6 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol), Et\(_3\)N (103.1 \(\mu\)L, 0.74 mmol), pivaloyl chloride (73.8 \(\mu\)L, 0.6 mmol) in CH\(_2\)Cl\(_2\) (0.9 mL) afforded, after purification by column chromatography (silicagel, 85:15 hexane/AcOEt), methyl 2-(1-pivaloyl-1H-indol-3-yl)acetate as a white solid (122.3 mg, 90%).

\(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): δ 8.51 (d, \(J = 8.2\) Hz, 1H, ArH), 7.79 (s, 1H, ArH), 7.51 (d, \(J = 7.7\) Hz, 1H, ArH), 7.4-7.3 (m, 1H, ArH), 7.28 (td, \(J = 7.6, 0.9\) Hz, 1H, ArH), 3.75 (s, 2H, CH\(_2\)), 3.73 (s, 3H, CH\(_3\)), 1.52 (s, 9H, 3\(\times\)CH\(_3\)) ppm. \(^{13}\)C-NMR (100.61 MHz, CDCl\(_3\)): δ 176.9 (s), 171.3 (s), 136.9 (s), 129.0 (s), 125.4 (d), 124.2 (d), 123.5 (d), 118.4 (d), 117.4 (d), 113.8 (s), 52.1 (q), 41.2 (s), 30.7 (t), 28.7 (q, 3x) ppm. HRMS (ESI\(^+\)):\ calcd. for C\(_{16}\)H\(_{19}\)N\(_2\)NaO\(_3\) ([M+Na]\(^+\)), 296.1263; found, 296.1255.

**2-(1H-Indol-3-yl)-N-(2-iodophenyl)acetamide.** Following the general procedure described above for the synthesis of amides, the reaction of 2-(1H-indol-3-yl)acetic acid (0.35 g, 2.00 mmol), 2-chloro-1-methyl-pyridinium iodide (0.61 g, 2.40 mmol), 2-idoaniline (2.41 g, 11.00 mmol) and Et\(_3\)N (0.56 mL, 4.00 mmol) in CH\(_2\)Cl\(_2\) (10.0 mL) afforded, after purification by column chromatography (silicagel, from 80:20 to 70:30 hexane/AcOEt), 2-(1H-indol-3-yl)-N-(2-iodophenyl)acetamide as a brown solid (0.62 g, 82%).

\(^1\)H-NMR (400.13 MHz, DMSO-\(d_6\)): δ 10.98 (s, 1H, NH indole), 9.25 (s, 1H, NH amide), 7.83 (dd, \(J = 7.9, 1.1\) Hz, 1H, ArH), 7.62 (td, \(J = 7.8, 1.9\) Hz, 2H, ArH), 7.4 –

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7.3 (m, 3H, ArH), 7.1 - 7.0 (m, 1H, ArH), 7.0 – 6.9 (m, 1H, ArH), 6.93 (td, \(J = 7.6, 1.2\) Hz, 1H, ArH), 3.81 (s, 2H, CH\(_2\)) ppm. \(^{13}\)C-NMR (100.61 MHz, DMSO-\(d_6\)): \(\delta\) 169.8 (s), 139.3 (s), 138.8 (d), 128.6 (d), 127.2 (s), 127.0 (d), 125.6 (d), 124.3 (d), 121.1 (d), 118.6 (d), 118.4 (d), 111.4 (d), 108.0 (s), 94.6 (s), 33.1 (t) ppm.

HRMS (ESI\(^+\)): calcd. for C\(_{16}\)H\(_{13}\)IN\(_2\)NaO ([M+Na]\(^+\)), 398.9965; found, 398.9961.

\(\text{N-(2-iodophenyl)-2-(N-methyl-1H-indol-3-yl)acetamide.}\) To a solution of 2-(1H-indol-3-yl)-N-(2-iodophenyl)acetamide (100.0 mg, 0.266 mmol) in DMF (1.0 mL) at 0 ºC was added finely powdered KOH (22.4 mg, 0.399 mmol) and the mixture was stirred for 10 min at this temperature. Then, MeI (18.2 \(\mu\)L, 0.292 mmol) was added slowly and the reaction was stirred at 0 ºC for 15 h. The mixture was diluted with H\(_2\)O and extracted with AcOEt (5x). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, from 70:30 to 50:50 hexane/AcOEt) to afford \(\text{N-(2-iodophenyl)-2-(N-methyl-1H-indol-3-yl)acetamide}\) as a white foam (47.3 mg, 46%). \(^1\)H-NMR (400.13 MHz, CDCl\(_3\)): \(\delta\) 8.04 (br, 1H, NH), 7.96 (d, \(J = 6.7\) Hz, 1H, ArH), 7.4 – 7.3 (m, 3H, ArH), 7.2 – 7.1 (m, 2H, ArH), 7.1 - 7.0 (m, 2H, ArH), 6.97 (s, 1H, H2), 3.55 (d, \(J = 15.7\) Hz, 1H, CH\(_2\)), 3.48 (d, \(J = 15.7\) Hz, 1H, CH\(_2\)), 3.22 (s, 3H, CH\(_3\)) ppm.

\(\text{Methyl 2-(N-methyl-1H-indol-3-yl)acetate.}\) Following the general procedure described above for the methylation of indole, the reaction of methyl 2-(1H-indol-3-yl)acetate (189.2 mg, 1.00 mmol), powdered KOH (84.2 mg, 1.50 mmol) and MeI (68.5 \(\mu\)L, 1.10 mmol) in DMF (3.6 mL) afforded, after purification by column
chromatography (30% hexane/AcOEt), methyl 2-((N-methyl-1H-indol-3-yl)acetate as a colorless oil (180.7 mg, 89%). $^1$H-NMR (400.13 MHz, CDCl$_3$): 7.65 (d, $J = 7.9$ Hz, 1H, ArH), 7.34 (d, $J = 8.2$ Hz, 1H, ArH), 7.3-7.2 (m, 1H, ArH), 7.2-7.1 (m, 1H, ArH), 7.08 (s, 1H, ArH), 3.82 (s, 2H, CH$_2$), 3.78 (s, 3H, CH$_3$), 3.74 (s, 3H, CH$_3$) ppm.

$^{13}$C-NMR (100.61 MHz, CDCl$_3$): $\delta$ 172.5 (s), 136.8 (s), 127.7 (d), 127.6 (s), 121.7 (d), 119.1 (d), 118.9 (d), 109.2 (d), 106.7 (s), 51.9 (q), 32.6 (q), 31.0 (t) ppm. HRMS (ESI$^+$): calcd. for C$_{12}$H$_{13}$NNaO$_2$ ([M+Na$^+$]), 226.0839; found, 226.0838.

Methyl 2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetate. A solution of methyl 2-(1H-indol-3-yl)acetate (63.4 mg, 0.33 mmol) in DMF (1.2 mL) was added slowly to a stirred solution of NaH (11.3 mg, 60% in oil, 0.28 mmol) in DMF (1.0 mL). The mixture was stirred at 25 ºC for 10 min and then 2-phenylsulfonylethyl chloride (57.6 mg, 0.28 mmol) in DMF (1.5 mL) was added and stirring was maintained for 5h. The reaction mixture was diluted with Et$_2$O, washed with H$_2$O (2x) and the combined aqueous layers were extracted with Et$_2$O (2x) and AcOEt (2x). The combined organic layers were washed with brine (1x) and dried (Na$_2$SO$_4$) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, 70:30 hexane/AcOEt) to afford methyl 2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetate as a yellow solid (94.6 mg, 99%). $^1$H-NMR (400.13 MHz, CDCl$_3$): $\delta$ 7.82 (d, $J = 8.3$ Hz, 2H, ArH), 7.7-7.6 (m, 1H, ArH), 7.5 - 7.4 (m, 3H, ArH), 7.2 - 7.1 (m, 3H, ArH), 6.96 (s, 1H, ArH), 4.53 (t, $J = 7.4$ Hz, 2H, CH$_2$), 3.68 (s, 3H, CH$_3$), 3.67 (s, 2H, CH$_2$), 3.54 (t, $J = 7.4$ Hz, 2H, CH$_2$) ppm. $^{13}$C-NMR (100.61 MHz, CDCl$_3$): $\delta$ 172.1 (s), 138.7 (s), 135.6 (s), 133.9 (d), 129.3 (d, 2x), 128.0 (s), 127.6 (d, 2x), 126.1 (d), 122.3 (d), 119.8 (d), 119.3 (d), 108.8 (d), 108.3 (s), 55.4 (t), 51.9 (q), 39.7 (t), 30.8 (t) ppm. HRMS (ESI$^+$): calcd. for C$_{19}$H$_{20}$NO$_4$S ([M+H$^+$]), 358.1108; found, 358.1105. IR (NaCl): $\nu$ 3058 (w, C-H), 3026 (w, C-H), 2951 (w, C-H), 1736 (s, C=O), 1468 (m), 1312 (s), 1146 (s), 742 (s) cm$^{-1}$. 

![Chemical Structure](image)
2-[1-[2-(Phenylsulfonyl)ethyl]-1H-indol-3-yl]acetic acid. To a solution of methyl 2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetate (60.0 mg, 0.17 mmol) in THF (1.6 mL) was added a solution of LiOH (8.8 mg, 0.21 mmol) in H$_2$O (0.2 mL). The mixture was stirred at 25 ºC for 3 h. The solvent was evaporated, the residue was dissolved in H$_2$O and a 1M aqueous solution of HCl was added until pH 1. The aqueous layer was extracted with AcOEt (3x), the combined organic layers were dried (Na$_2$SO$_4$) and the solvent was evaporated, to afford 2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetic acid as a pink solid (57.5 mg, 99%), which was used in the following reaction without further purification. $^1$H-NMR (400.13 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J = 7.2$ Hz, 2H, ArH), 7.61 (t, $J = 7.6$ Hz, 1H, ArH), 7.5 – 7.4 (m, 3H, ArH), 7.2 – 7.1 (m, 3H, ArH), 6.99 (s, 1H, ArH), 4.57 (m, 2H, CH$_2$), 3.73 (s, 2H, CH$_2$), 3.56 (m, 2H, CH$_2$) ppm.

N-(2-iodophenyl)-2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetamide.

Following the general procedure described above for the synthesis of amides, the reaction of 2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetic acid (0.20 g, 0.59 mmol), 2-chloro-1-methyl-pyridinium iodide (0.18 g, 0.71 mmol), 2-iodoaniline (0.71 g, 3.26 mmol) and Et$_3$N (165.4 $\mu$L, 1.19 mmol) in CH$_2$Cl$_2$ (3.0 mL) afforded, after purification by column chromatography (silicagel, from 80:20 to 50:50 hexane/AcOEt), N-(2-iodophenyl)-2-[1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetamide as a brown solid (0.23 g, 71%). $^1$H-NMR (400.13 MHz, CDCl$_3$): $\delta$ 8.23 (d, $J = 8.2$ Hz, 1H, ArH), 7.86 (d, $J = 7.7$ Hz, 2H, ArH), 7.7 – 7.5 (m, 6H, NH + ArH), 7.3 – 7.1 (m, 4H, ArH),
7.08 (s, 1H, ArH), 6.74 (t, $J = 7.6$ Hz, 1H, ArH), 4.61 (t, $J = 7.3$ Hz, 2H, CH$_2$), 3.82 (s, 2H, CH$_2$), 3.56 (t, $J = 7.3$ Hz, 2H, CH$_2$) ppm. $^{13}$C-NMR (100.61 MHz, CDCl$_3$): $\delta$ 169.4 (s), 138.7 (d), 138.0 (s), 136.1 (s), 134.1 (d), 129.4 (d), 129.1 (d, 2x), 128.0 (s), 127.7 (d, 2x), 127.2 (d), 125.8 (d), 123.1 (d), 121.4 (d), 120.6 (d), 119.6 (d), 109.0 (d), 108.4 (s, 2x), 89.2 (s), 55.5 (t), 39.8 (t), 34.3 (t) ppm. HRMS (ESI$^+$): calcd. for C$_{24}$H$_{22}$IN$_2$O$_3$S ([M+H$^+$]), 545.0390; found, 545.0378.

** tert-Butyl (2-Iodophenyl[2-1-(2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetyl)carbamate.** To a solution of N-(2-iodophenyl)-2-[1-(2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetamide (228.1 mg, 0.42 mmol) in CH$_2$Cl$_2$ (6.4 mL) was added Boc$_2$O (182.9 mg, 0.84 mmol) and DMAP (5.1 mg, 0.04 mmol). The mixture was stirred at 25 ºC for 5.5 h, and then H$_2$O was added. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3x). The combined organic layers were dried (Na$_2$SO$_4$) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, from 80:20 to 70:30 hexane/ACOEt), to afford tert-butyl (2-iodophenyl[2-1-(2-(phenylsulfonyl)ethyl]-1H-indol-3-yl]acetyl)carbamate as a white foam (243.1 mg, 90%). $^{1}$H-NMR (400.13 MHz, CDCl$_3$): $\delta$ 7.82 (ap. d, $J = 8.3$ Hz, 3H, ArH), 7.6 – 7.5 (m, 2H, ArH), 7.49 (t, $J = 7.7$ Hz, 2H, ArH), 7.32 (t, $J = 7.6$ Hz, 1H, ArH), 7.2 – 7.0 (m, 5H, ArH), 7.1-7.0 (m, 1H, ArH), 4.52 (t, $J = 7.4$ Hz, 2H, CH$_2$), 4.50 (d, $J = 17.4$ Hz, 1H, CH$_2$), 4.35 (d, $J = 17.4$ Hz, 1H, CH$_2$), 3.53 (t, $J = 7.4$ Hz, 2H, CH$_2$), 1.38 (s, 9H, 3 x CH$_3$) ppm. $^{13}$C-NMR (100.61 MHz, CDCl$_3$): $\delta$ 173.0 (s), 151.4 (s), 141.6 (s), 139.2 (d), 138.6 (s), 135.4 (s), 133.9 (d), 129.4 (d), 129.3 (d), 129.2 (d, 2x), 129.0 (d), 128.6 (s), 127.7 (d, 2x), 126.8 (d), 122.1 (d), 119.7 (d), 119.6 (d), 108.6 (s), 108.5 (d), 99.4 (s), 83.4 (s), 55.4 (t), 39.7 (t), 34.2 (t), 27.8 (q, 3x) ppm. HRMS (ESI$^+$): calcd. for C$_{29}$H$_{29}$IN$_2$NaO$_5$S ([M+Na$^+$]), 667.0734; found, 667.0713.

**Methyl 2-(2-Bromo-1H-indol-3-yl)acetate 24a.** To a suspension of methyl 2-(1H-indol-3-yl)acetate 22a (60.0 mg, 0.32 mmol, 1 equiv.) in CCl$_4$ (2.1 mL), was added
benzyol peroxide (7.7 mg, 0.032 mmol, 0.1 equiv.) and N-bromosuccinimide (56.4 mg, 0.32 mmol, 1 equiv.) and the mixture was stirred at 25 °C for 2 h. The solvent was evaporated and the residue was purified by column chromatography (silicagel, from 90:10 to 80:20 hexane/AcOEt) to afford 24a as a light yellow oil (66.1 mg, 78%). **m.p.:** 58-61 ºC (hexane/ethyl acetate). 1H-NMR (400.13 MHz, CDCl₃): δ 8.30 (br, 1H, NH), 7.52 (d, J = 7.5 Hz, 1H, ArH), 7.23 (d, J = 7.5 Hz, 1H, ArH), 7.2-7.1 (m, 2H, ArH), 3.75 (s, 2H, CH₃), 3.70 (s, 3H, CH₃) ppm. 13C-NMR (100.61 MHz, CDCl₃): δ 171.5 (s), 135.9 (s), 127.4 (s), 122.5 (d), 120.4 (d), 118.3 (d), 110.5 (d), 109.7 (s), 108.5 (s), 52.1 (q), 30.9 (t) ppm. HRMS (ESI⁺): calc. for C₁₁H₁₀BrNNaO₂ ([M+Na]⁺), 291.9767; found, 291.9765. Calcd. for C₁₁H₁₀BrNNaO₂ ([M+Na]⁺), 289.9785. IR (NaCl): ν 3334 (br, NH), 3058 (w, C-H), 3000 (w, C-H), 2951 (w, C-H), 2918 (w, C-H), 2847 (w, C-H), 1727 (s, C=O), 1450 (s), 1343 (s), 1336 (s), 1167 (m), 742 (s) cm⁻¹. UV (MeOH): λ_max 281 nm.

**Methyl 2-(2-Iodo-1H-indol-3-yl)acetate 25a.** General procedure for the iodination of indoles in C2 position. To a solution of methyl 2-(1H-indol-3-yl)acetate 22a (0.91 g, 4.82 mmol, 1 equiv.) and AgOTf (1.48 g, 5.78 mmol, 1.2 equiv.) in THF (28.3 mL) was added dropwise a solution of iodine (1.22 g, 4.82 mmol, 1 equiv.) in THF (12.0 mL). After stirring for 10 min, an additional portion of AgOTf (123.7 mg, 0.48 mmol, 0.1 equiv.) was added and the mixture was stirred for a further 30 min. A saturated aqueous solution of Na₂S₂O₅ was added and the mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine (1x) and dried (Na₂SO₄) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, from 95:5 to 50:50 hexane/EtOAc) to afford methyl 25a as a light brown solid (1.30 g, 86%). **m.p.:** 79-81 ºC (hexane/EtOAc). 1H-NMR (400.13 MHz, CDCl₃): δ 8.21 (br, 1H, NH), 7.56 (d, J = 6.8 Hz, 1H, ArH), 7.3 – 7.2 (m, 1H, ArH), 7.2 – 7.1 (m, 2H, ArH), 3.76 (s, 2H, CH₂), 3.72 (s, 3H, CH₃) ppm. 13C-NMR (100.61 MHz, CDCl₃): δ 171.6 (s), 138.7 (s), 127.3 (s), 122.5 (d), 120.2 (d), 118.1 (d), 115.1 (s), 110.4 (d), 79.8 (s), 52.1 (q), 32.9 (t) ppm. HRMS (ESI⁺): calc. for C₁₁H₁₀INaO₂ ([M+Na]⁺), 337.9648; found, 337.9644. IR (NaCl): ν 3330 (br, NH), 2948 (w, C-H), 1718 (s, C=O), 1433 (m), 1334 (m), 742 (s) cm⁻¹. UV (MeOH): λ_max 223, 283 nm.
2-(5-Bromo-1H-indol-3-yl)acetonitrile 20b

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
2-(5-Bromo-1H-indol-3-yl)acetic acid 21b

$^1$H-NMR (400.13 MHz, CD$_3$OD)

$^{13}$C-NMR (100.61 MHz, CD$_3$OD)
2-(6-Bromo-1H-indol-3-yl)acetic acid 21c

$^1$H-NMR (400.13 MHz, CD$_3$OD)

$^{13}$C-NMR (100.61 MHz, CD$_3$OD)
Methyl 2-(1H-indol-3-yl)acetate 22a

$^{1}H$-NMR (400.13 MHz, CDCl$_3$)

$^{13}C$-NMR (100.61 MHz, CDCl$_3$)
Methyl 2-(5-Bromo-1H-indol-3-yl)acetate 22b

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
**tert-Butyl (2-Iodophenyl)carbamate**

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^1$C-NMR (100.61 MHz, CDCl$_3$)
2-(5-Bromo-1H-indol-3-yl)-N-(2-iodophenyl)acetamide

$^1$H-NMR (400.13 MHz, CDCl$_3$)
2-(1H-Indol-3-yl)-N-phenylacetamide

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
N-Phenyl-2-(1-pivaloyl-1H-indol-3-yl)acetamide

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
$N$-Phenyl-$N$-[2-(1-pivaloyl-1$H$-indol-3-yl)acetyl]pivalamide

$^1$H-NMR (400.13 MHz, CDCl$_3$)
Methyl 2-(1-Pivaloyl-1H-indol-3-yl)acetate

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
2-(1H-Indol-3-yl)-N-(2-iodophenyl)acetamide

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
N-(2-iodophenyl)-2-(N-methyl-1H-indol-3-yl)acetamide

$^1$H-NMR (400.13 MHz, CDCl$_3$)
Methyl 2-(N-methyl-1H-indol-3-yl)acetate

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
Methyl 2-\{1-[2-(phenylsulfonyl)ethyl]-1H-indol-3-yl\}acetate

$^{1}H$-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
2-{1-[2-(Phenylsulfonyl)ethyl]-1H-indol-3-yl} acetic acid

$^1$H-NMR (400.13 MHz, CDCl$_3$)
$N$-(2-iodophenyl)-2-{1-[2-(phenylsulfonyl)ethyl]-1$H$-indol-3-yl}acetamide

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
**tert-Butyl (2-Iodophenyl[2-[1-(2-(phenylsulfonyl)ethyl)-1H-indol-3-yl]acetyl]carbamate**

**$^1$H-NMR (400.13 MHz, CDCl$_3$)**

![1H-NMR spectrum](image)

**$^{13}$C-NMR (100.61 MHz, CDCl$_3$)**

![13C-NMR spectrum](image)
Methyl 2-(2-Bromo-1H-indol-3-yl)acetate 24a

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
Methyl 2-(2-Iodo-1H-indol-3-yl)acetate 25a

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
Methyl 2-(5-Bromo-2-iodo-1H-indol-3-yl)acetate 25b

$^{1}$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
Methyl 2-(6-Bromo-2-iodo-1H-indol-3-yl)acetate 25c

$^1$H-NMR (400.13 MHz, CDCl$_3$)

$^{13}$C-NMR (100.61 MHz, CDCl$_3$)
4-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 26b

$^{1}$H-NMR (400.13 MHz, CD$_3$OD)

$^{13}$C-NMR (100.61 MHz, CD$_3$OD)
Methyl 4-amino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 26c

$^1$H-NMR (400.13 MHz, DMSO-$d_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-$d_6$)
2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline 26d

$^1$H-NMR (400.13 MHz, CD$_3$OD)

$^{13}$C-NMR (100.61 MHz, CD$_3$OD)
7,12-Dihydroindolo[3,2-d]benzazepin-6(5H)-one 28aa

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
9-Bromo-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one 28ba

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
10-Bromo-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one 28ca

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
2-Methyl-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one 28ab

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
9-Bromo-2-methyl-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one 28bb

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
10-Bromo-2-methyl-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one 28cb

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
Methyl 6-oxo-5,6,7,12-tetrahydroindolo[3,2-d]benzazepin-2-carboxylate 28ac

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
Methyl 9-bromo-6-oxo-5,6,7,12-tetrahydroindolo[3,2-d]benzazepin-2-carboxylate 28bc

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
Methyl 10-bromo-6-oxo-5,6,7,12-tetrahydroindolo[3,2-d]benzazepin-2-carboxylate

28cc

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
2-(Trifluoromethyl)-7,12-dihydroindolo[3,2-\(d\)]benzazepin-6-(5\(H\))-one 28ad

\(^1\)H-NMR (400.13 MHz, DMSO-\(d_6\))

\(^{13}\)C-NMR (100.61 MHz, DMSO-\(d_6\))
9-Bromo-2-(trifluoromethyl)-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one

28bd

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
10-Bromo-2-(trifluoromethyl)-7,12-dihydroindolo[3,2-d]benzazepin-6-(5H)-one  

28cd

$^1$H-NMR (400.13 MHz, DMSO-d$_6$)

$^{13}$C-NMR (100.61 MHz, DMSO-d$_6$)
REFERENCES


