Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

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

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2-(5-Bromo-1*H*-indol-3-yl)acetonitrile 20b.[1] **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 ºC. 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 (Na_2SO_4) 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 ºC 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 ºC, the mixture was diluted with Et_2O, washed with water (5x) and dried (Na_2SO_4) 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 ºC (ether). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 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, CH_2) ppm. **^{13}C-NMR** (100.61 MHz, $CDCl_3$): 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 $C_{10}H_7{}^{81}BrN_2Na$ ($[M+Na]^+$), 258.9664; found, 258.9663. Calcd. for $C_{10}H_7{}^{79}BrN_2Na$ ($[M+Na]^+$), 256.9685; found, 256.9684. **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-1*H*-indol-3-yl)acetonitrile 20c.[2] 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-1*H*-indol-3-yl)acetic acid 21c.[2] Following the general procedure described above for the synthesis of carboxylic acids, the reaction of 2-(6-bromo-1*H*-

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 ºC (methanol). **^{1}H-NMR** (400.13 MHz, CD_3OD): 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. **^{13}C-NMR** (100.61 MHz, CD_3OD): δ 176.2 (s), 138.9 (s), 127.7 (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 $C_{10}H_8{}^{79}BrNNaO_2$ ($[M+Na]^+$), 275.9631; found, 275.9630. **IR**: ν 3419 (w, NH), 2903 (w, C-H), 1701 (s, C=O), 1218 (s), 804 (s) cm^{-1}.

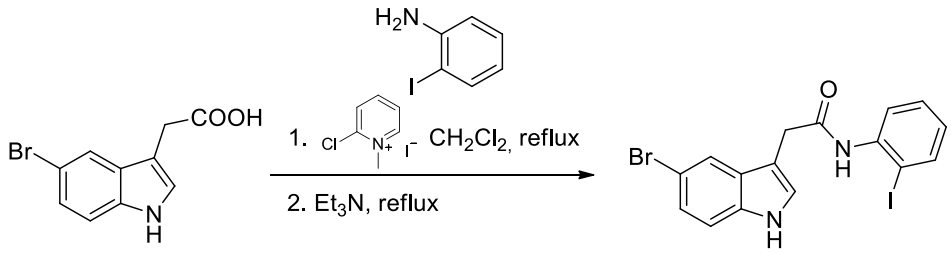
Methyl 2-(1*H*-indol-3-yl)acetate 22a. General procedure for the synthesis of methyl esters. A solution of HCl in MeOH was prepared by adding $SOCl_2$ (1225 μL, 16.80 mmol) dropwise to anhydrous MeOH (35 mL) at 0 °C. This solution was added to a solution of 2-(1*H*-indol-3-yl)acetic acid **21a** (2.6 g, 15.00 mmol) in MeOH (35 mL) at 0 °C. The mixture was allowed to reach 25 ºC 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_2SO_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 ºC (hexane/ethyl acetate). **^{1}H-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. **^{13}C-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-1*H*-indol-3-yl)acetate 22b.[4] Following the general procedure described above for the synthesis of methyl esters, the reaction of 2-(5-bromo-1*H*-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 ºC

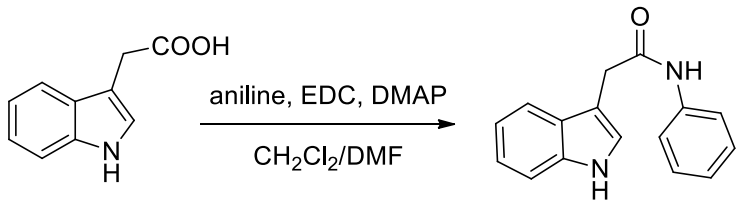
(hexane/ethyl acetate). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.17 (br, 1H, NH), 7.72 (s, 1H, ArH), 7.26 (d, *J* = 9.3 Hz, 1H, ArH), 7.19 (d, *J* = 8.6 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 3.72 (s, 2H, CH_2), 3.71 (s, 3H, CH_3) ppm. **^{13}C-NMR** (100.61 MHz, $CDCl_3$): δ 172.3 (s), 134.7 (s), 128.9 (s), 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 $C_{11}H_{10}{}^{81}BrNNaO_2$, 291.9767; found, 291.9765. Calcd. for $C_{11}H_{10}{}^{79}BrNNaO_2$ ($[M+Na]^+$), 289.9787; found 289.9785. **IR** (NaCl): ν 3400-3300 (br, NH), 2999 (w, C-H), 2950 (w, C-H), 1726 (s, C=O), 1457 (m), 1167 (m), 795 (m) cm^{-1}.

Methyl 2-(6-Bromo-1*H*-indol-3-yl)acetate 22c.[5] Following the general procedure described above for the synthesis of methyl esters, the reaction of 2-(6-bromo-1*H*-indol-3-yl)acetic acid **21c** (0.45 g, 1.77 mmol), $SOCl_2$ (145 μL, 1.98 mmol) and MeOH (8.2 mL) afforded methyl 2-(6-bromo-1*H*-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 $(Boc)_2O$ (0.70 g, 3.20 mmol) in anhydrous THF (3.5 mL) was refluxed for 89 h. H_2O was added and the mixture was extracted with AcOEt (3x). The combined organic layers were washed with brine, dried (Na_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{11}H_{14}INNaO_2$ ($[M+Na]^+$), 341.9961; found, 341.9958. **IR** (NaCl): ν 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}.[6]

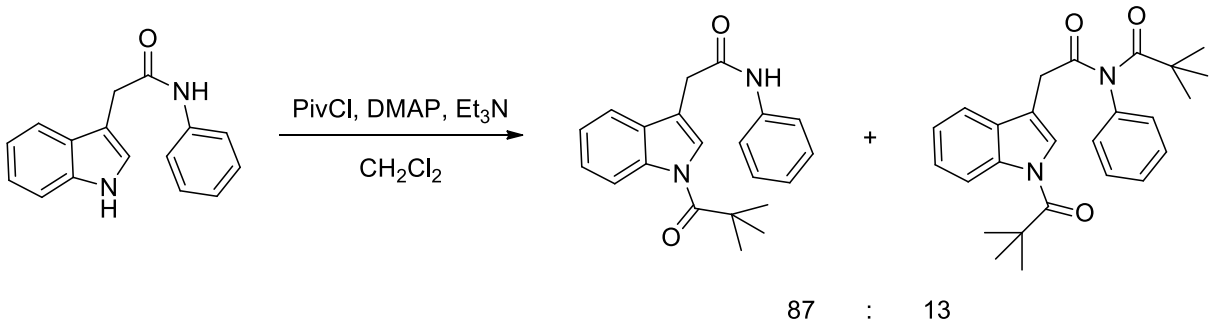


2-(5-Bromo-1*H*-indol-3-yl)-*N*-(2-iodophenyl)acetamide. General procedure for the synthesis of amides. To a solution of 2-(5-bromo-1*H*-indol-3-yl)acetic acid (54.9 mg, 0.216 mmol) in CH_2Cl_2 (1.1 mL) was added 2-chloro-1-methyl-pyridinium iodide (66.2 mg, 0.259 mmol) and 2-iodoaniline (260.3 mg, 1.188 mmol). The mixture was heated at reflux for 1 h, and then, after cooling down, Et_3N (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 CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_4) 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-1*H*-indol-3-yl)-*N*-(2-iodophenyl)acetamide as a light brown solid (70.6 mg, 72%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 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, CH_2) ppm.



2-(1*H*-Indol-3-yl)-*N*-phenylacetamide. To a solution of 2-(1*H*-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 Na_2CO_3, a 1M aqueous solution of HCl and brine, and dried (Na_2SO_4), 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-(1*H*-indol-3-yl)-*N*-phenylacetamide as a white solid (476.1 mg, 95%). **^{1}H-NMR** (400.13 MHz, DMSO-d_6): 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): δ 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^+): calcd. for $C_{16}H_{14}N_2NaO$ ($[M+Na]^+$), 273.0998; found, 273.0996. **IR** (NaCl): ν 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}.



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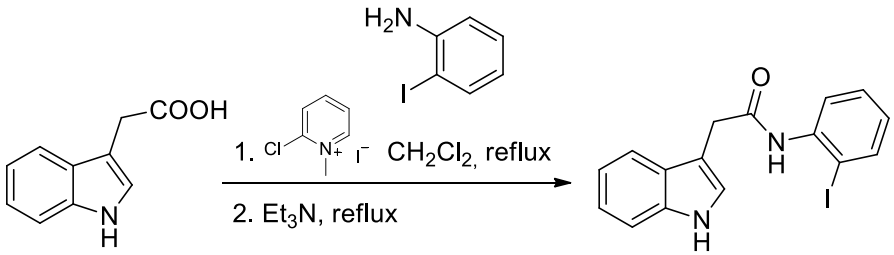
***N*-Phenyl-2-(1-pivaloyl-1*H*-indol-3-yl)acetamide and *N*-Phenyl-*N*-pivaloyl-*N*-[2-(1-pivaloyl-1*H*-indol-3-yl)acetyl]amide. General procedure for the synthesis of pivaloyl-indoles.** To a solution of 2-(1*H*-indol-3-yl)-*N*-phenylacetamide (0.1 g, 0.4 mmol) and DMAP (4.9 mg, 0.04 mmol) in CH_2Cl_2 (1.0 mL), triethylamine (82.4 μL, 0.59 mmol) was added. After cooling down to 0 ºC, pivaloyl chloride (59 μL, 0.48 mmol) was added slowly and the mixture was stirred for 10 min. The reaction was warmed up to 25 ºC and stirred for 24 h. Then, CH_2Cl_2 was evaporated and the residue was partitioned between Et_2O and a saturated aqueous solution of NH_4Cl. The layers were separated and the organic layer was washed with brine (1x). The aqueous layers were extracted with Et_2O (2x), the combined organic layers were dried (Na_2SO_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-1*H*-indol-3-yl)acetamide (71.6 mg, 54%) and *N*-phenyl-*N*-pivaloyl-*N*-[2-(1-pivaloyl-1*H*-indol-3-yl)acetyl]amide (10.6 mg, 6%). Major product: **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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),

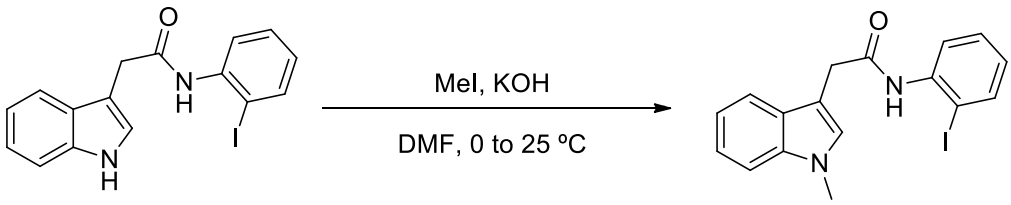
124.0 (d), 120.1 (d, 2x), 118.3 (d), 117.7 (d), 114.1 (s), 41.3 (s), 34.2 (t), 28.7 (q, 3x) ppm. **HRMS** (ESI^+): calcd. for $C_{21}H_{22}N_2NaO_2$ ($[M+Na]^+$), 357.1574; found, 357.1570. Minor product: **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 8.51 (d, *J* = 8.2, 1H, ArH), 7.71 (s, 1H, ArH), 7.5 – 7.3 (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 x CH_3), 1.06 (s, 9H, 3 x CH_3) ppm. **HRMS** (ESI^+): calcd. for $C_{26}H_{30}N_2NaO_3$ ($[M+Na]^+$), 441.2149; found, 441.2144.

Methyl 2-(1-Pivaloyl-1*H*-indol-3-yl)acetate. Following the general procedure described above for the synthesis of pivaloilindoles, the reaction of methyl 2-(1*H*-indol-3-yl)acetate (94.6 mg, 0.5 mmol), DMAP (6.1 mg, 0.05 mmol), Et_3N (103.1 μL, 0.74 mmol), pivaloyl chloride (73.8 μL, 0.6 mmol) in CH_2Cl_2 (0.9 mL) afforded, after purification by column chromatography (silicagel, 85:15 hexane/AcOEt), methyl 2-(1-pivaloyl-1*H*-indol-3-yl)acetate as a white solid (122.3 mg, 90%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 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 x 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 $C_{16}H_{19}NNaO_3$ ($[M+Na]^+$), 296.1263; found, 296.1255.

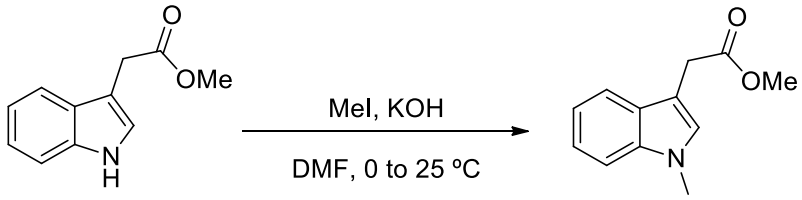


2-(1*H*-Indol-3-yl)-*N*-(2-iodophenyl)acetamide. Following the general procedure described above for the synthesis of amides, the reaction of 2-(1*H*-indol-3-yl)acetic acid (0.35 g, 2.00 mmol), 2-chloro-1-methyl-pyridinium iodide (0.61 g, 2.40 mmol), 2-iodoaniline (2.41 g, 11.00 mmol) and Et_3N (0.56 mL, 4.00 mmol) in CH_2Cl_2 (10.0 mL) afforded, after purification by column chromatography (silicagel, from 80:20 to 70:30 hexane/AcOEt), 2-(1*H*-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 –

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): δ 169.8 (s), 139.3 (s), 138.8 (d), 136.1 (s), 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 $C_{16}H_{13}IN_2NaO$ ($[M+Na]^+$), 398.9965; found, 398.9961.

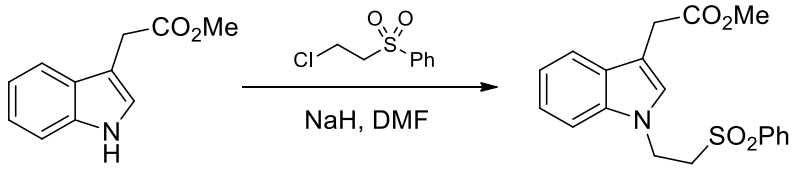


***N*-(2-iodophenyl)-2-(*N*-methyl-1*H*-indol-3-yl)acetamide.** To a solution of 2-(1*H*-indol-3-yl)-*N*-(2-iodophenyl)acetamide (100.0 mg, 0.266 mmol) in DMF (1.0 mL) at 0 ºC was added finely powdered KOH (22.4 mg, 0.399 mmol) and the mixture was stirred for 10 min at this temperature. Then, MeI (18.2 μL, 0.292 mmol) was added slowly and the reaction was stirred at 0 ºC for 15 h. The mixture was diluted with H_2O and extracted with AcOEt (5x). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silicagel, from 70:30 to 50:50 hexane/AcOEt) to afford *N*-(2-iodophenyl)-2-(*N*-methyl-1*H*-indol-3-yl)acetamide as a white foam (47.3 mg, 46%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 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.

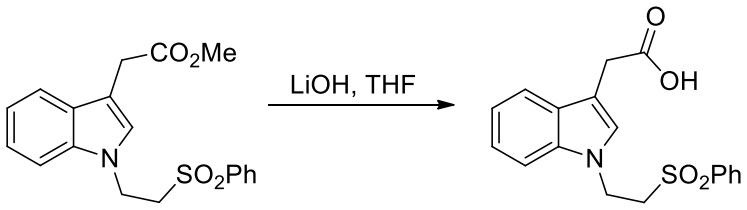


Methyl 2-(*N*-methyl-1*H*-indol-3-yl)acetate. Following the general procedure described above for the methylation of indole, the reaction of methyl 2-(1*H*-indol-3-yl)acetate (189.2 mg, 1.00 mmol), powdered KOH (84.2 mg, 1.50 mmol) and MeI (68.5 μL, 1.10 mmol) in DMF (3.6 mL) afforded, after purification by column

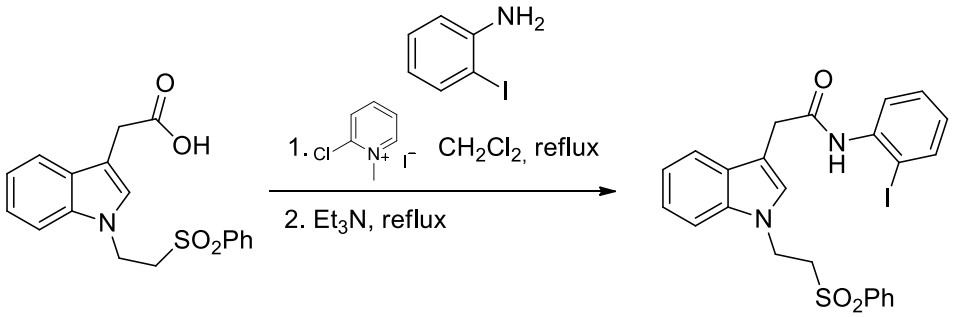
chromatography (30% hexane/AcOEt), methyl 2-(*N*-methyl-1*H*-indol-3-yl)acetate as a colorless oil (180.7 mg, 89%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 7.65 (d, *J* = 7.9 Hz, 1H, ArH), 7.34 (d, *J* = 8.2 Hz, 1H, ArH), 7.3-7.2 (m, 1H, ArH), 7.2-7.1 (m, 1H, ArH), 7.08 (s, 1H, ArH), 3.82 (s, 2H, CH_2), 3.78 (s, 3H, CH_3), 3.74 (s, 3H, CH_3) ppm. **^{13}C-NMR** (100.61 MHz, $CDCl_3$): δ 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]-1*H*-indol-3-yl]acetate. A solution of methyl 2-(1*H*-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_2O, washed with H_2O (2x) and the combined aqueous layers were extracted with Et_2O (2x) and AcOEt (2x). The combined organic layers were washed with brine (1x) and dried (Na_2SO_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]-1*H*-indol-3-yl]acetate as a yellow solid (94.6 mg, 99%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{19}H_{20}NO_4S$ ($[M+H]^+$), 358.1108; found, 358.1105. **IR** (NaCl): ν 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}.

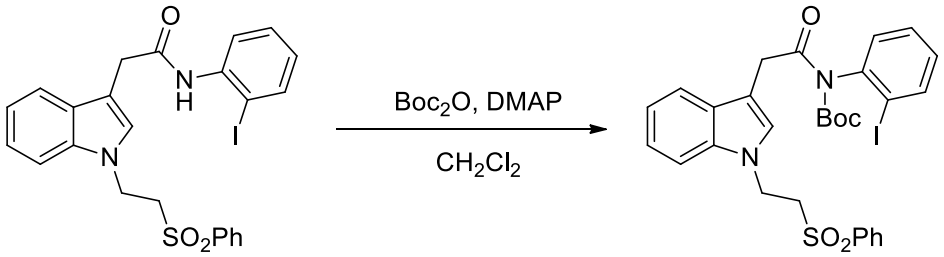


2-[1-[2-(Phenylsulfonyl)ethyl]-1*H*-indol-3-yl]acetic acid. To a solution of methyl 2-[1-[2-(phenylsulfonyl)ethyl]-1*H*-indol-3-yl]acetate (60.0 mg, 0.17 mmol) in THF (1.6 mL) was added a solution of LiOH (8.8 mg, 0.21 mmol) in H_2O (0.2 mL). The mixture was stirred at 25 ºC for 3 h. The solvent was evaporated, the residue was dissolved in H_2O 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_2SO_4) and the solvent was evaporated, to afford 2-[1-(2-[phenylsulfonyl)ethyl]-1*H*-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, $CDCl_3$): δ 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]-1*H*-indol-3-yl]acetamide.** Following the general procedure described above for the synthesis of amides, the reaction of 2-[1-[2-(phenylsulfonyl)ethyl]-1*H*-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_3N (165.4 μL, 1.19 mmol) in CH_2Cl_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]-1*H*-indol-3-yl]acetamide as a brown solid (0.23 g, 71%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{24}H_{22}IN_2O_3S$ ($[M+H]^+$), 545.0390; found, 545.0378.



***tert*-Butyl (2-Iodophenyl[2-[1-(2-(phenylsulfonyl)ethyl)-1*H*-indol-3-yl]acetyl]carbamate.** To a solution of *N*-(2-iodophenyl)-2-[1-[2-(phenylsulfonyl)ethyl]-1*H*-indol-3-yl]acetamide (228.1 mg, 0.42 mmol) in CH_2Cl_2 (6.4 mL) was added Boc_2O (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_2O was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried (Na_2SO_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)-1*H*-indol-3-yl]acetyl]carbamate as a white foam (243.1 mg, 90%). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{29}H_{29}IN_2NaO_5S$ ($[M+Na]^+$), 667.0734; found, 667.0713.

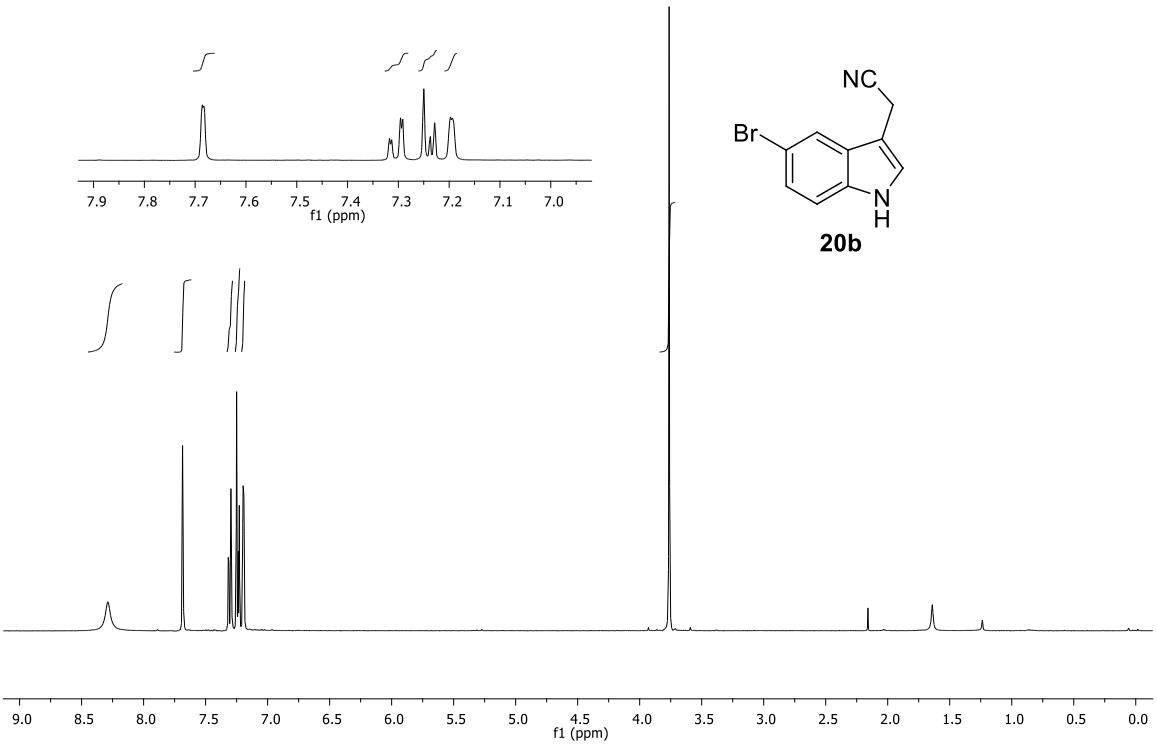
Methyl 2-(2-Bromo-1*H*-indol-3-yl)acetate 24a.[7] To a suspension of methyl 2-(1*H*-indol-3-yl)acetate **22a** (60.0 mg, 0.32 mmol, 1 equiv.) in CCl_4 (2.1 mL), was added

benzoyl 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 ºC 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). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 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, CH_2), 3.70 (s, 3H, CH_3) ppm. **^{13}C-NMR** (100.61 MHz, $CDCl_3$): 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^+): calcd. for $C_{11}H_{10}{}^{81}BrNNaO_2$ ($[M+Na]^+$), 291.9767; found, 291.9765. Calcd. for $C_{11}H_{10}{}^{79}BrNNaO_2$ ($[M+Na]^+$), 289.9787; found 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), 1434 (s), 1336 (s), 1167 (m), 742 (s) cm^{-1}. **UV** (MeOH): λ_{max} 281 nm.

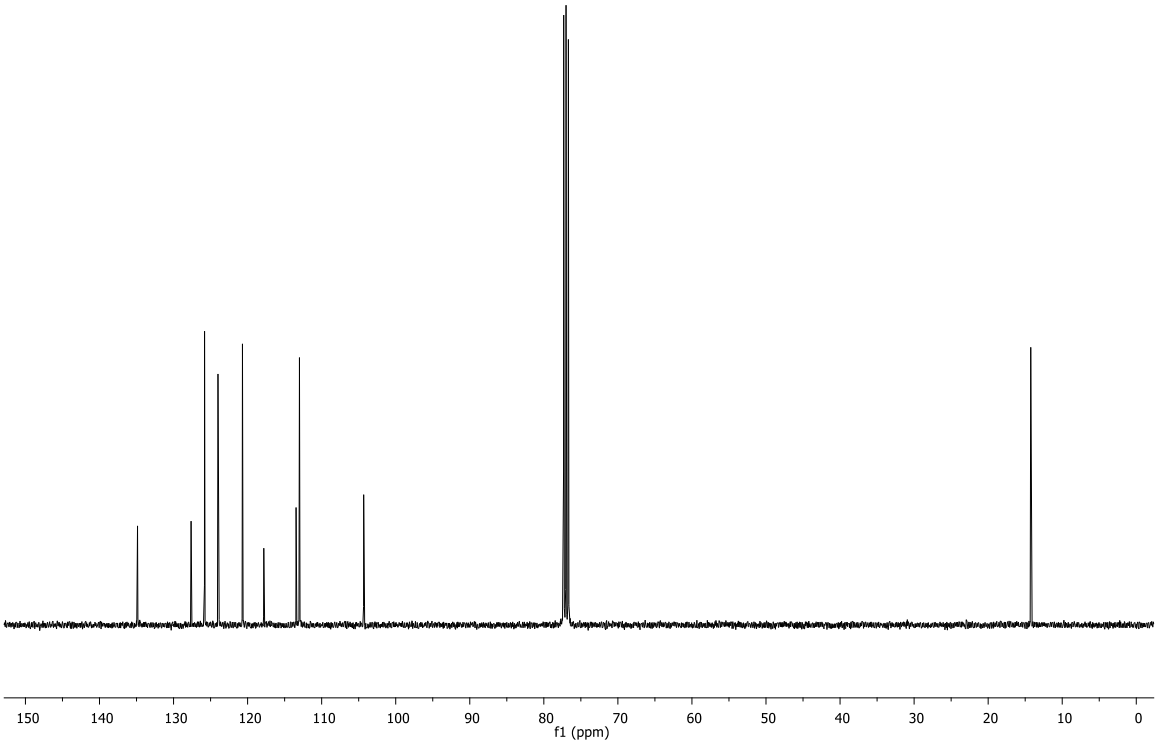
Methyl 2-(2-Iodo-1*H*-indol-3-yl)acetate 25a.[8] **General procedure for the iodination of indoles in C2 position.** To a solution of methyl 2-(1*H*-indol-3-yl)acetate **22a** (0.91 g, 4.82 mmol, 1 equiv.) and AgOTf (1.48 g, 5.78 mmol, 1.2 equiv.) in THF (28.3 mL) was added dropwise a solution of iodine (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 $Na_2S_2O_3$ was added and the mixture was extracted with EtOAc (2x). The combined organic layers were washed with brine (1x) and dried (Na_2SO_4) 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). **^{1}H-NMR** (400.13 MHz, $CDCl_3$): 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, CH_2), 3.72 (s, 3H, CH_3) ppm. **^{13}C-NMR** (100.61 MHz, $CDCl_3$): 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^+): calcd. for $C_{11}H_{10}INNaO_2$ ($[M+Na]^+$), 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-1*H*-indol-3-yl)acetonitrile 20b

^{1}H-NMR (400.13 MHz, $CDCl_3$)

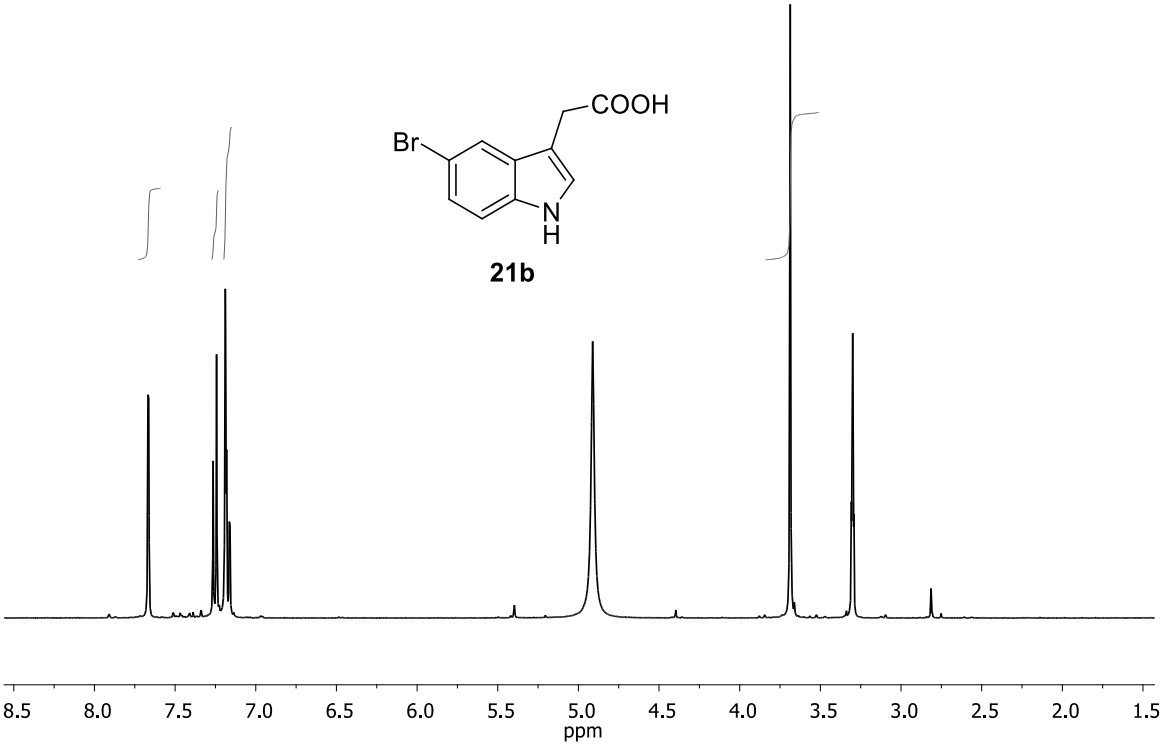


^{13}C-NMR (100.61 MHz, $CDCl_3$)

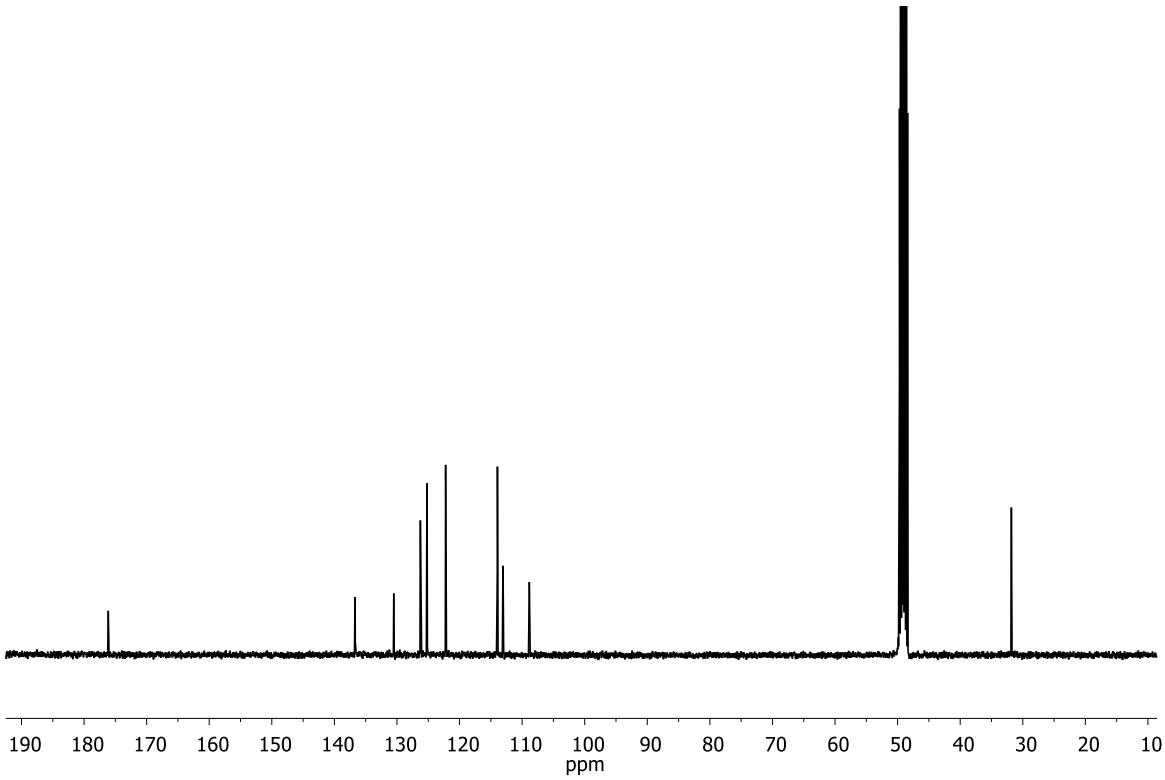


2-(5-Bromo-1*H*-indol-3-yl)acetic acid 21b

^{1}H-NMR (400.13 MHz, CD_3OD)

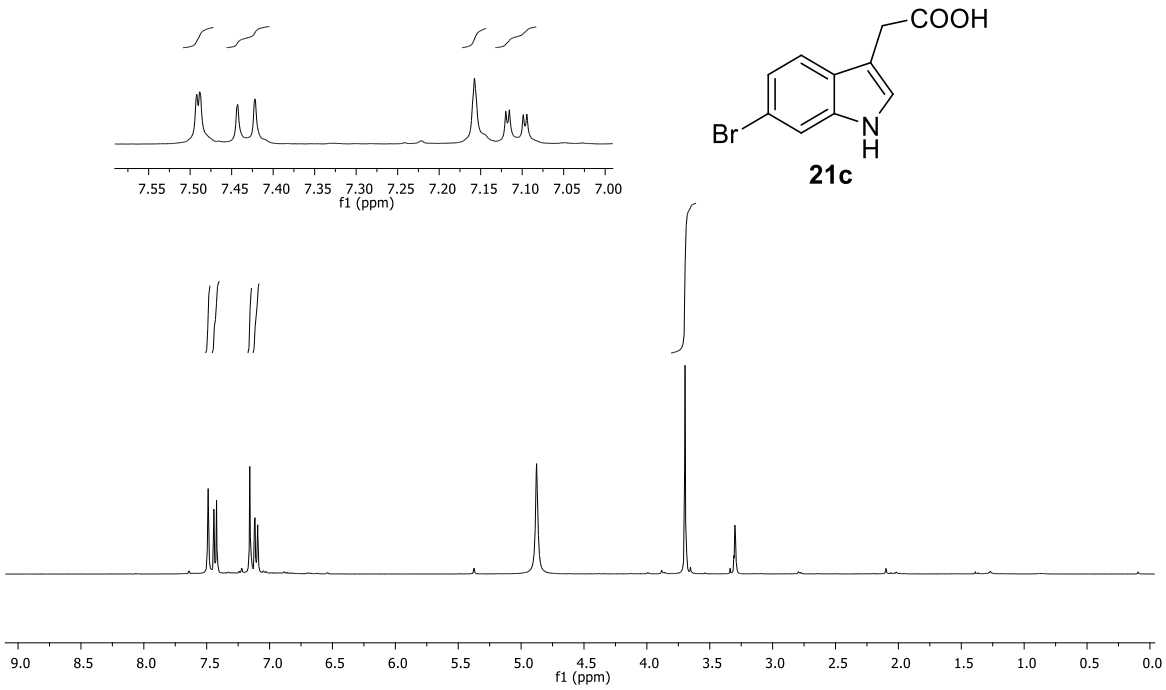


^{13}C-NMR (100.61 MHz, CD_3OD)

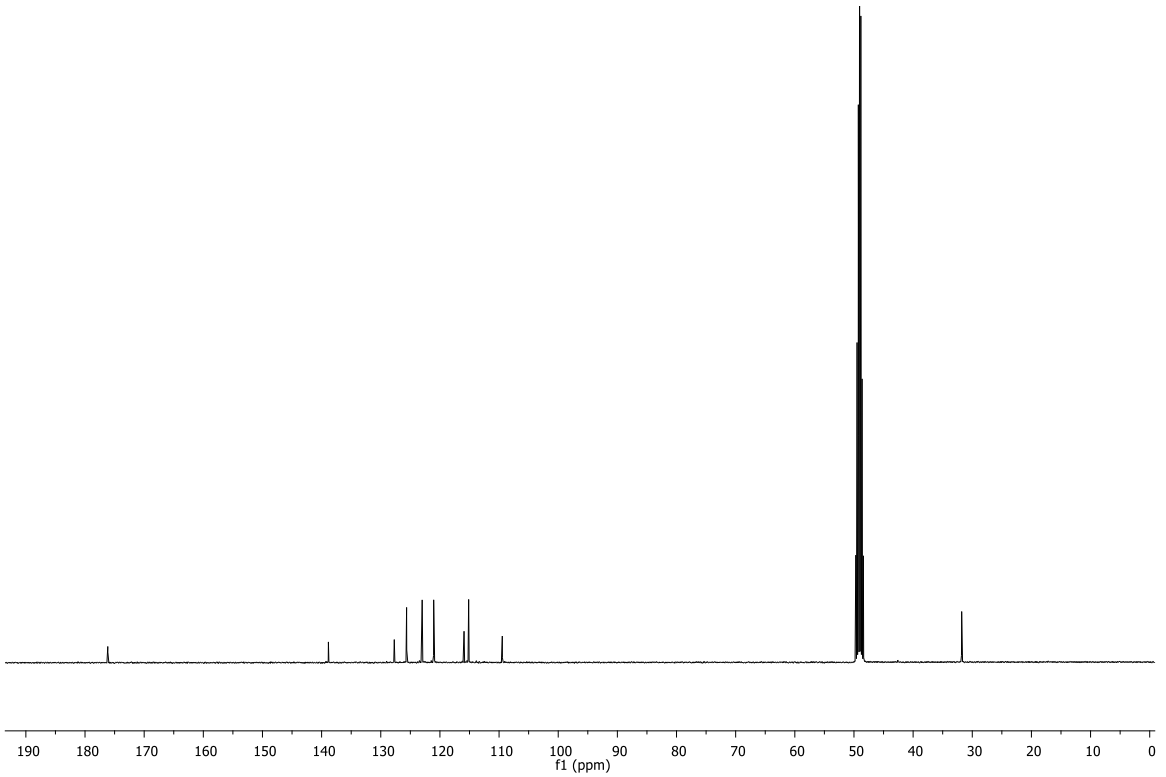


2-(6-Bromo-1*H*-indol-3-yl)acetic acid 21c

^{1}H-NMR (400.13 MHz, CD_3OD)

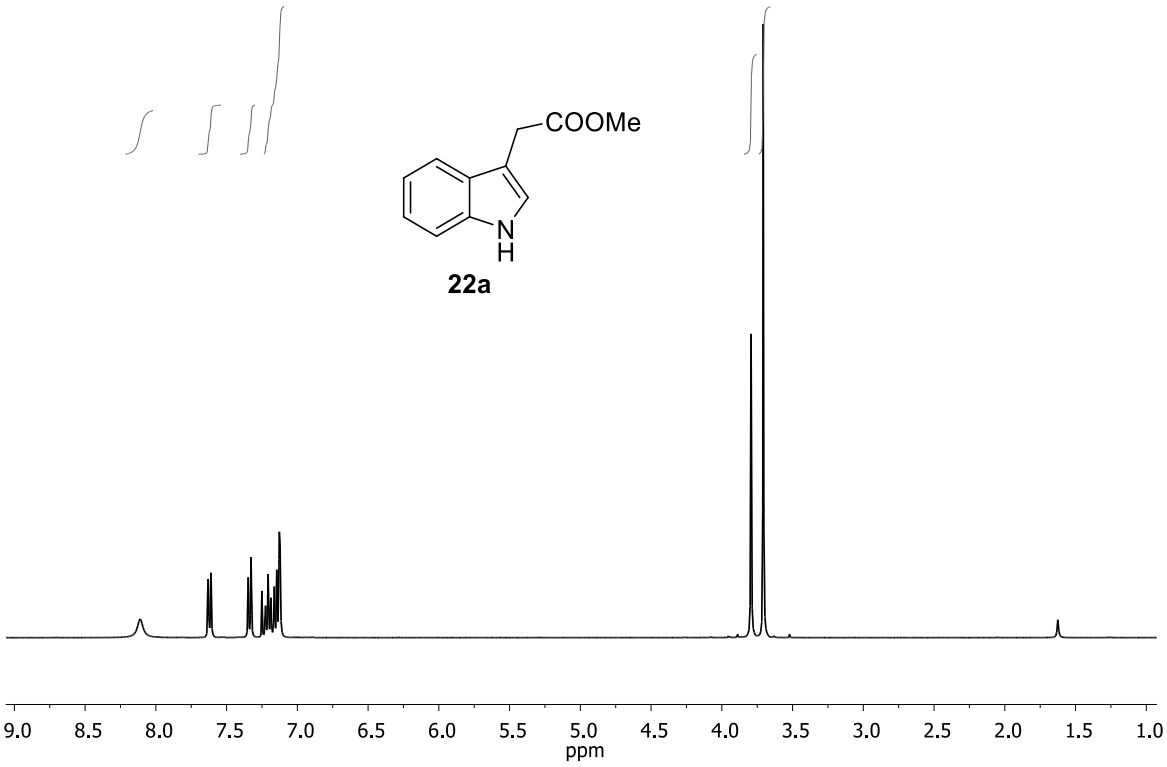


^{13}C-NMR (100.61 MHz, CD_3OD)



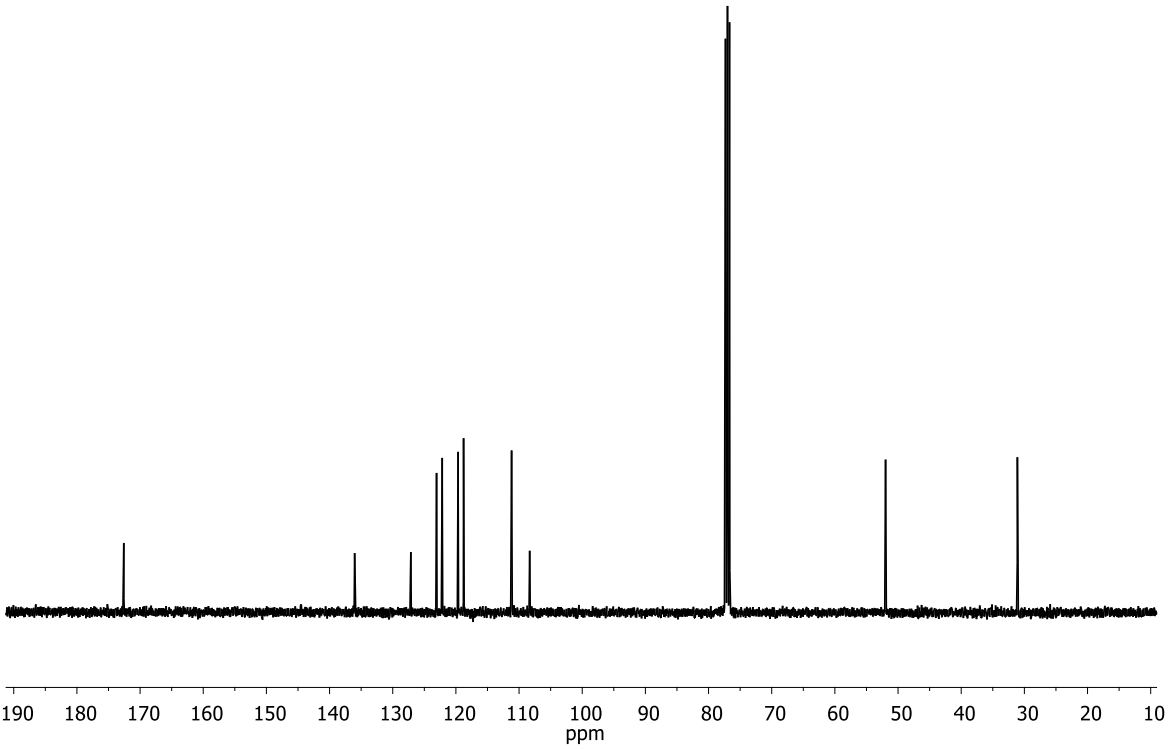
Methyl 2-(1*H*-indol-3-yl)acetate 22a

^{1}H-NMR (400.13 MHz, $CDCl_3$)



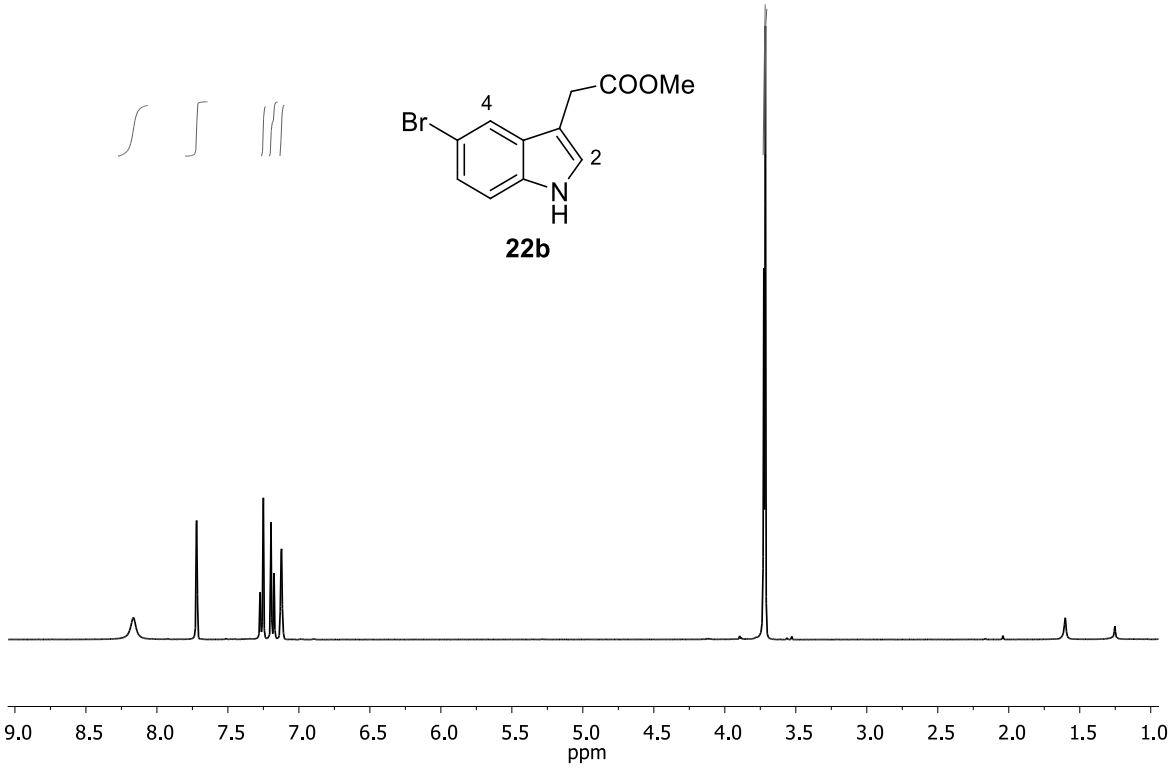
22a

^{13}C-NMR (100.61 MHz, $CDCl_3$)

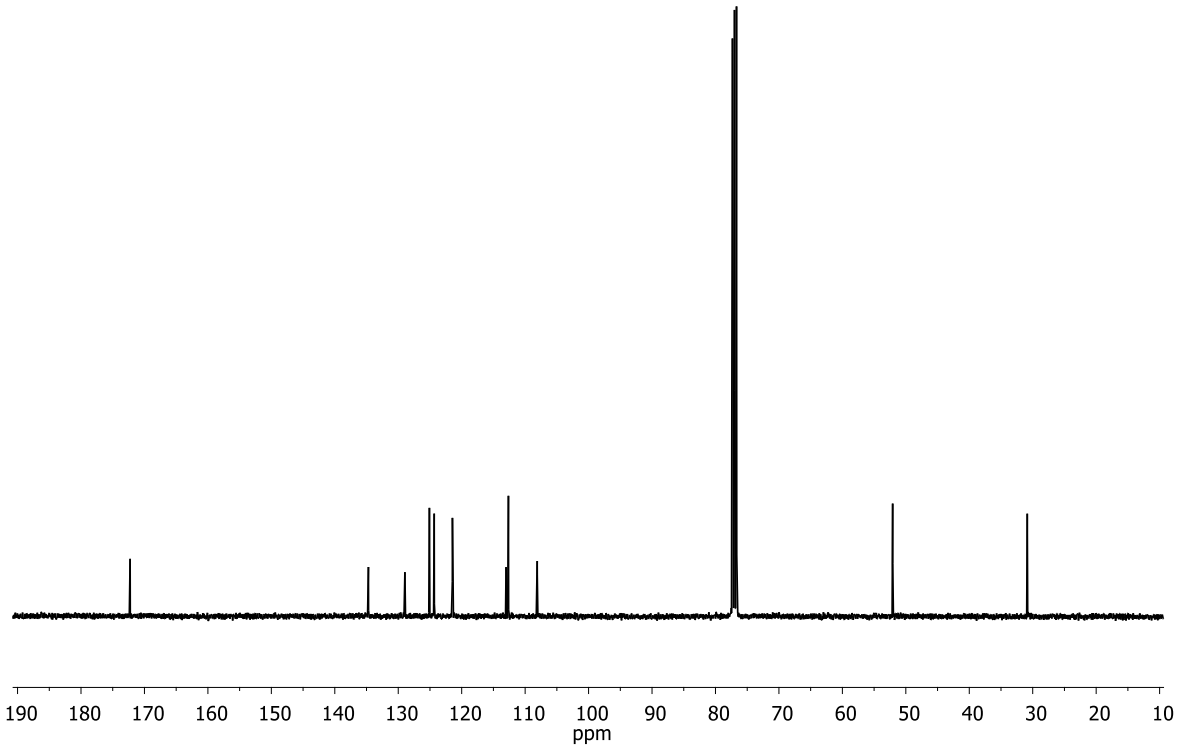


Methyl 2-(5-Bromo-1*H*-indol-3-yl)acetate 22b

^{1}H-NMR (400.13 MHz, $CDCl_3$)

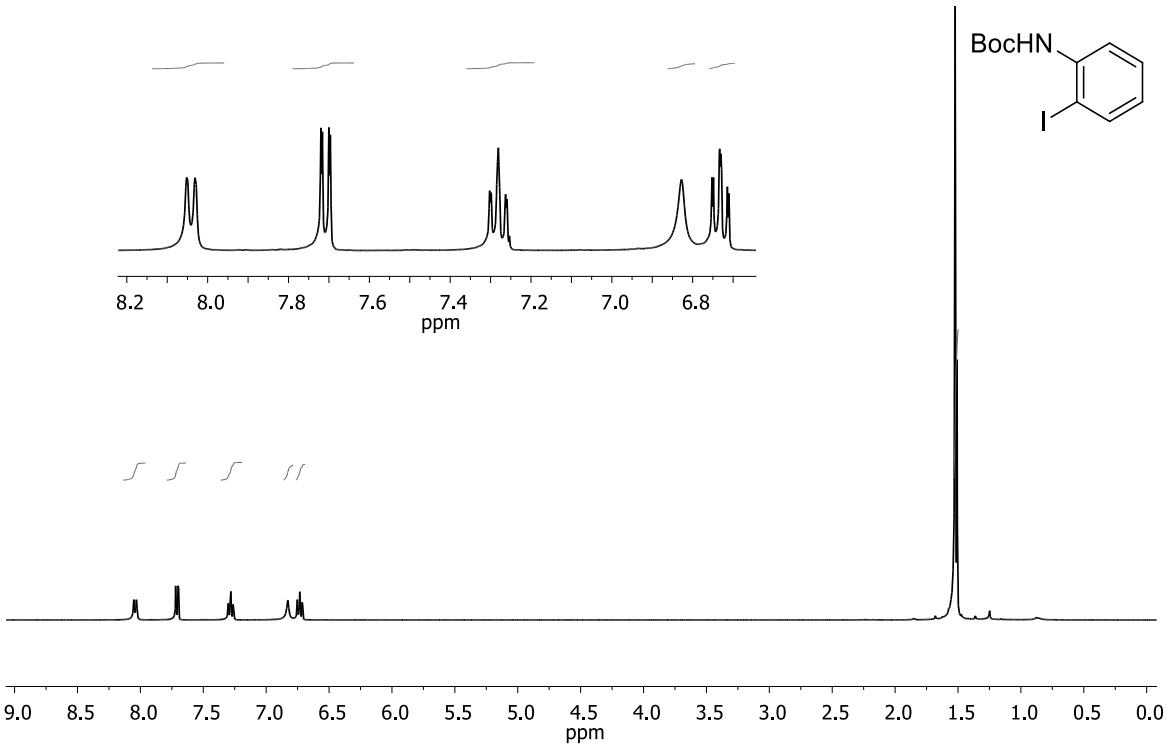


^{13}C-NMR (100.61 MHz, $CDCl_3$)

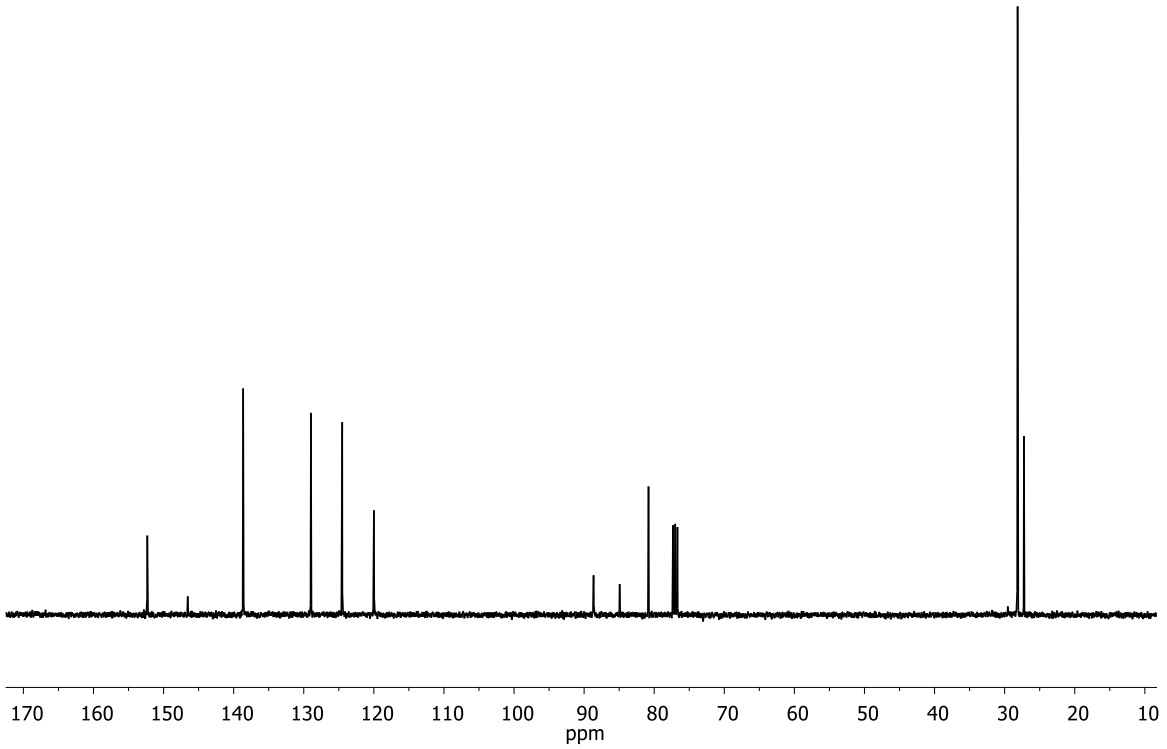


tert-Butyl (2-Iodophenyl)carbamate

^{1}H-NMR (400.13 MHz, $CDCl_3$)

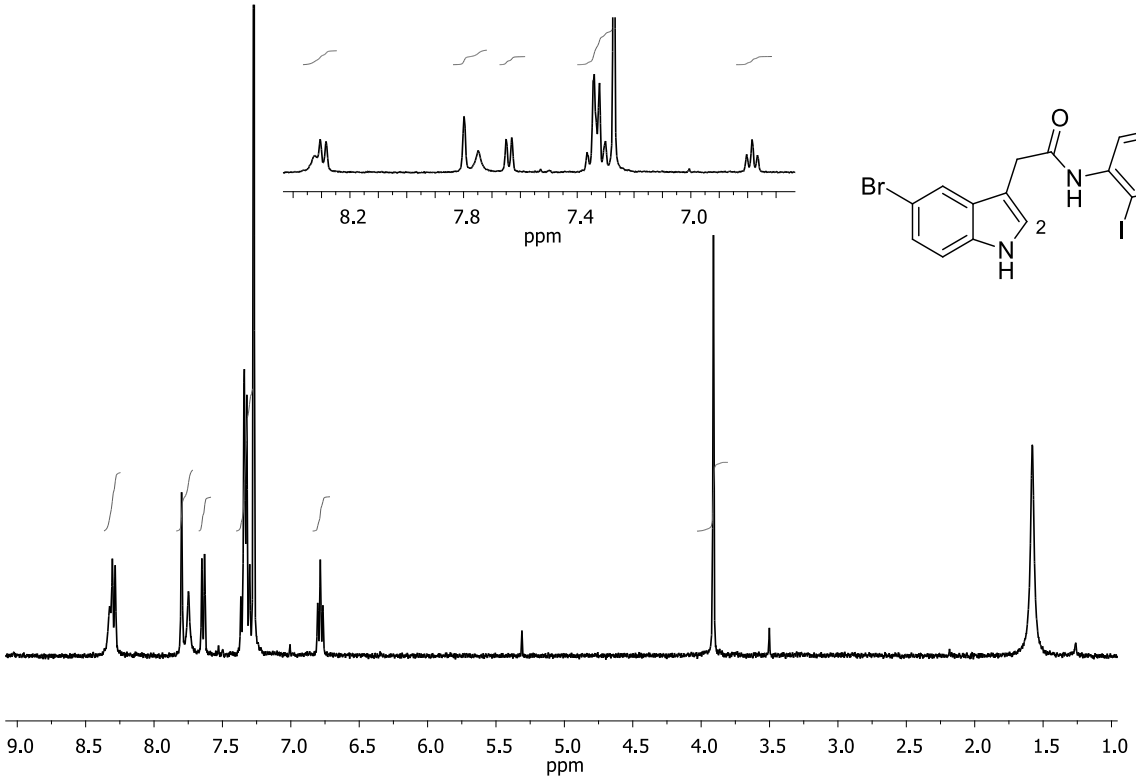


^{13}C-NMR (100.61 MHz, $CDCl_3$)



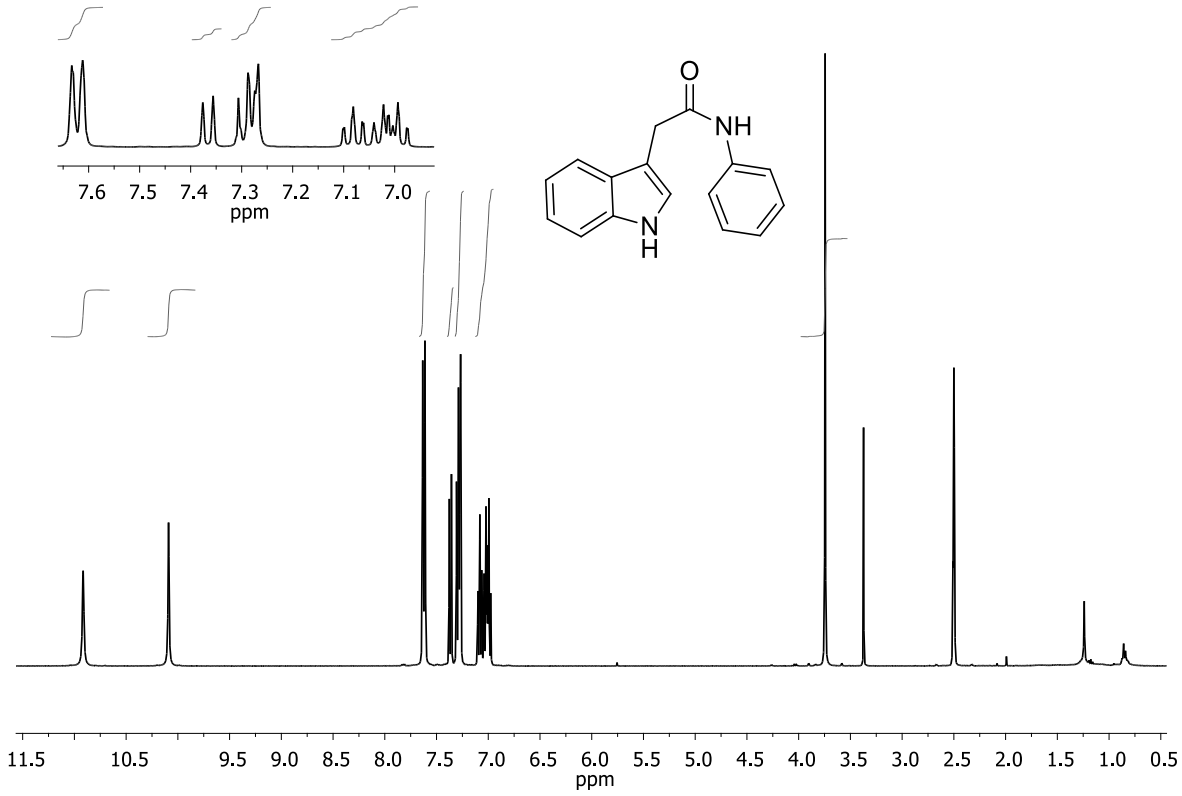
2-(5-Bromo-1*H*-indol-3-yl)-*N*-(2-iodophenyl)acetamide

^{1}H-NMR (400.13 MHz, $CDCl_3$)

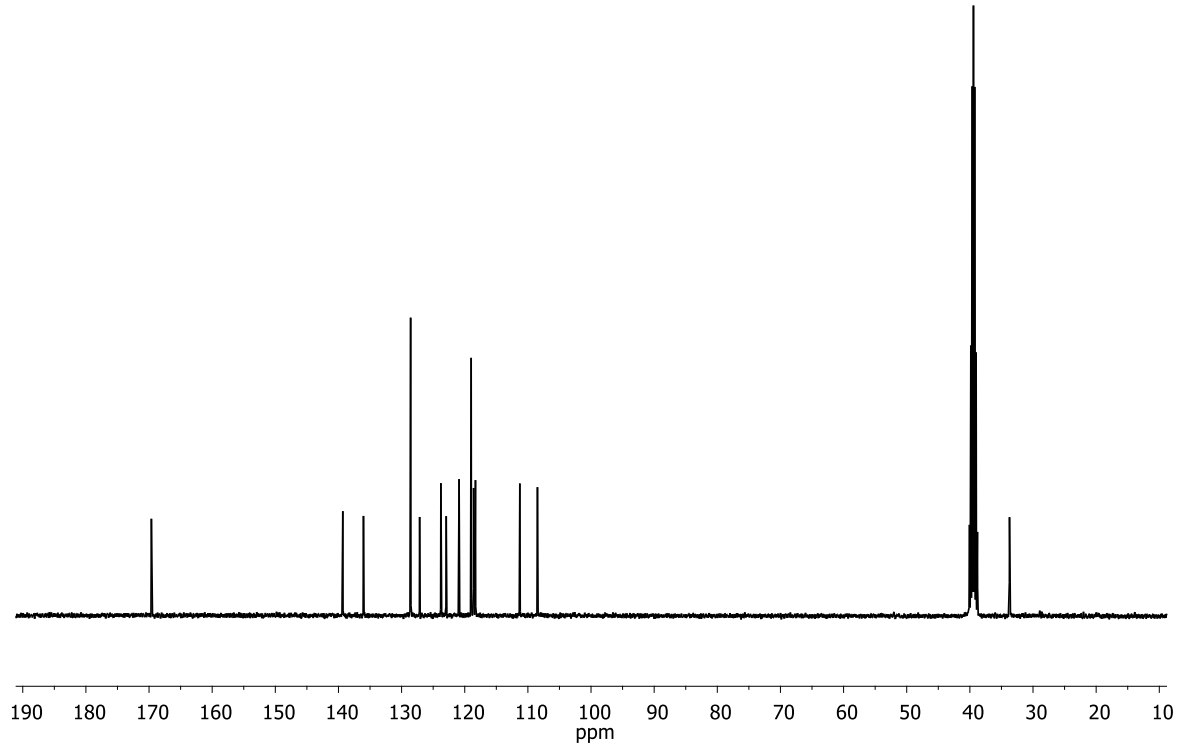


2-(1*H*-Indol-3-yl)-*N*-phenylacetamide

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

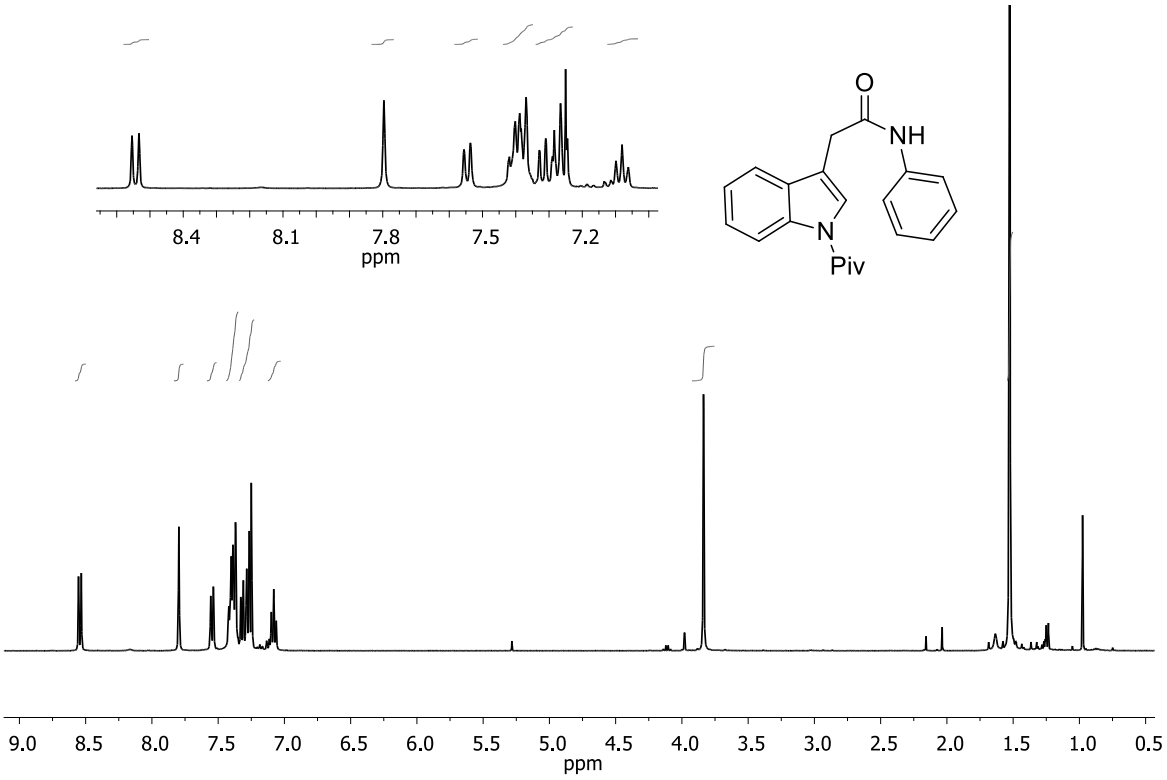


^{13}C-NMR (100.61 MHz, DMSO-d_6)

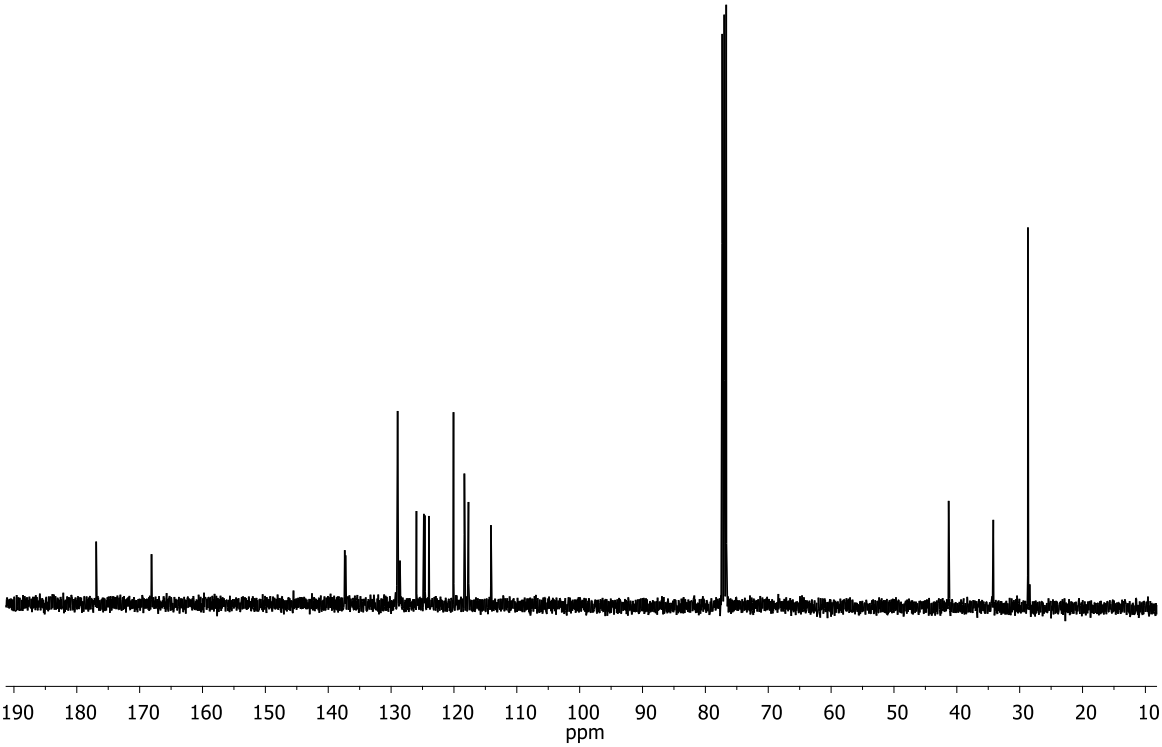


_N_-Phenyl-2-(1-pivaloyl-1_H_-indol-3-yl)acetamide

^{1}H-NMR (400.13 MHz, $CDCl_3$)

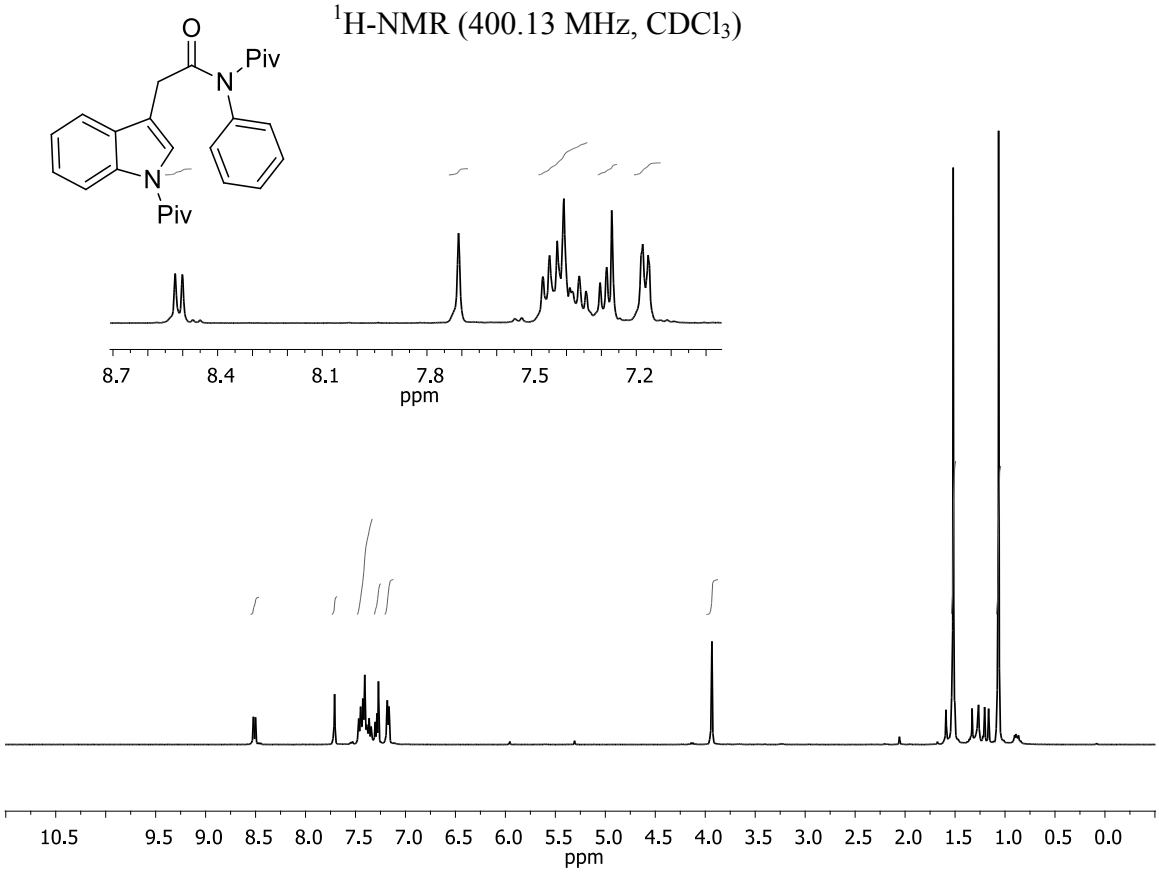


^{13}C-NMR (100.61 MHz, $CDCl_3$)



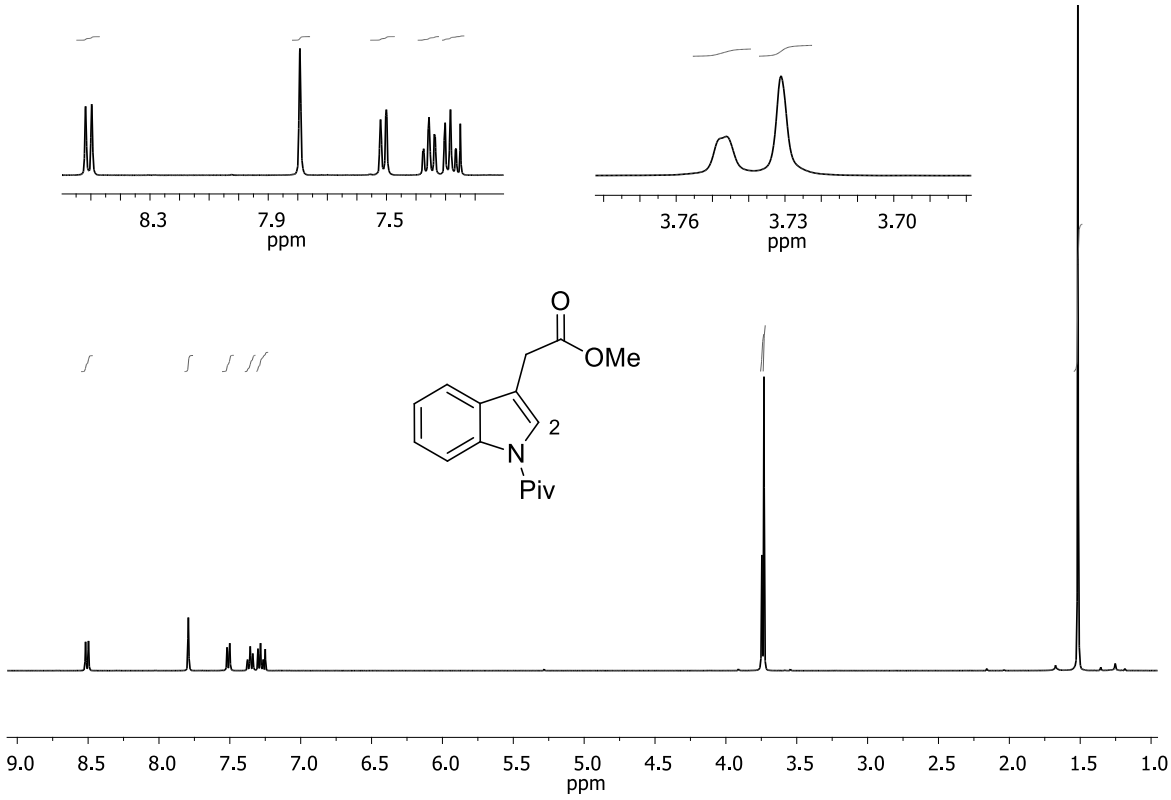
_N_-Phenyl-_N_-[2-(1-pivaloyl-1_H_-indol-3-yl)acetyl]pivalamide

^{1}H-NMR (400.13 MHz, $CDCl_3$)

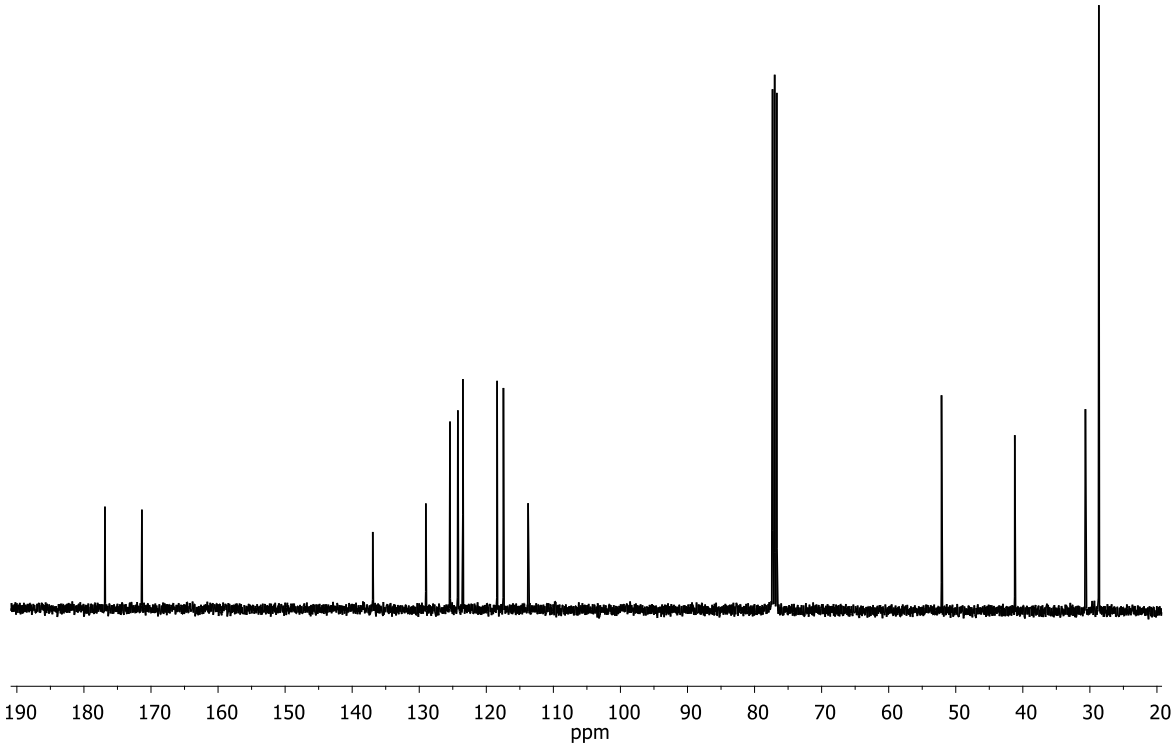


Methyl 2-(1-Pivaloyl-1*H*-indol-3-yl)acetate

^{1}H-NMR (400.13 MHz, $CDCl_3$)

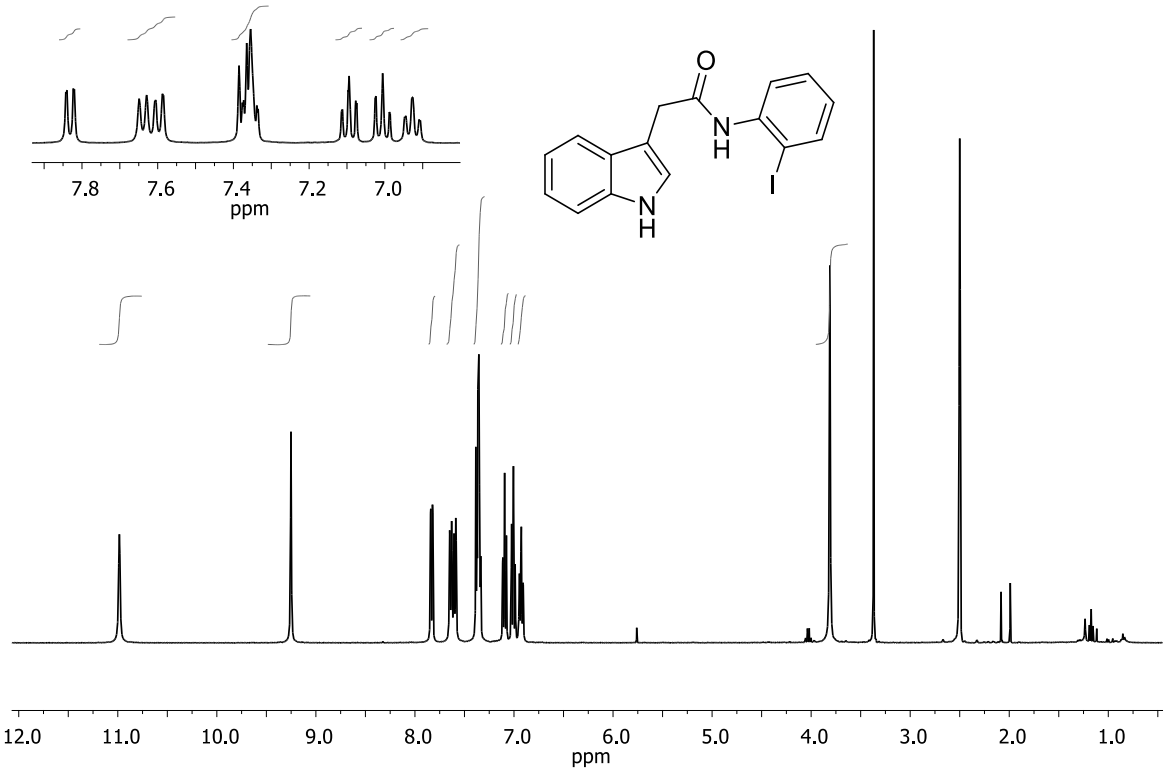


^{13}C-NMR (100.61 MHz, $CDCl_3$)

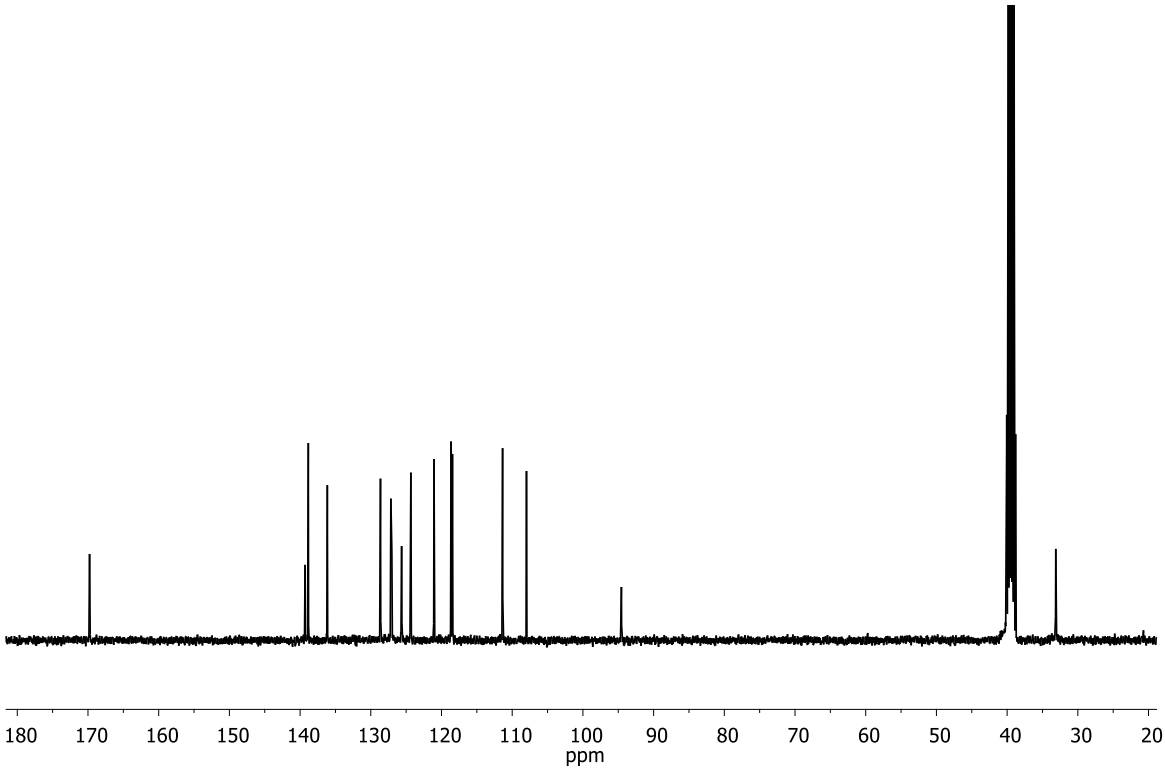


2-(1*H*-Indol-3-yl)-*N*-(2-iodophenyl)acetamide

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

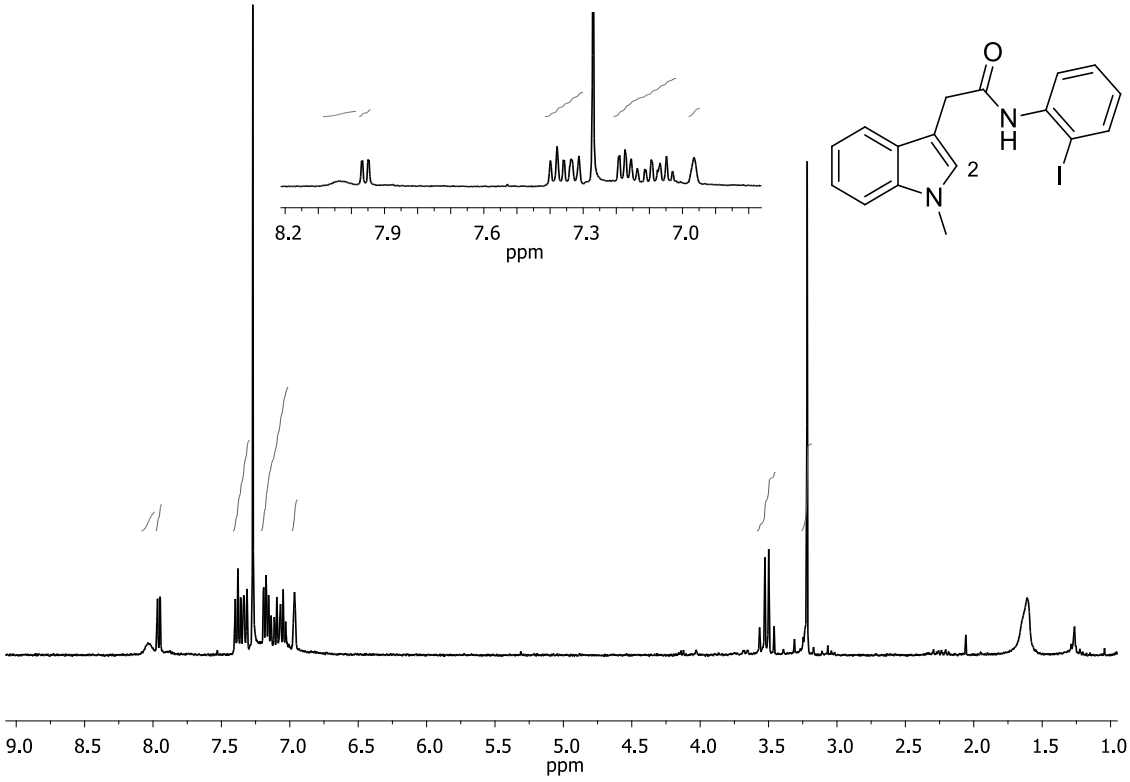


^{13}C-NMR (100.61 MHz, DMSO-d_6)



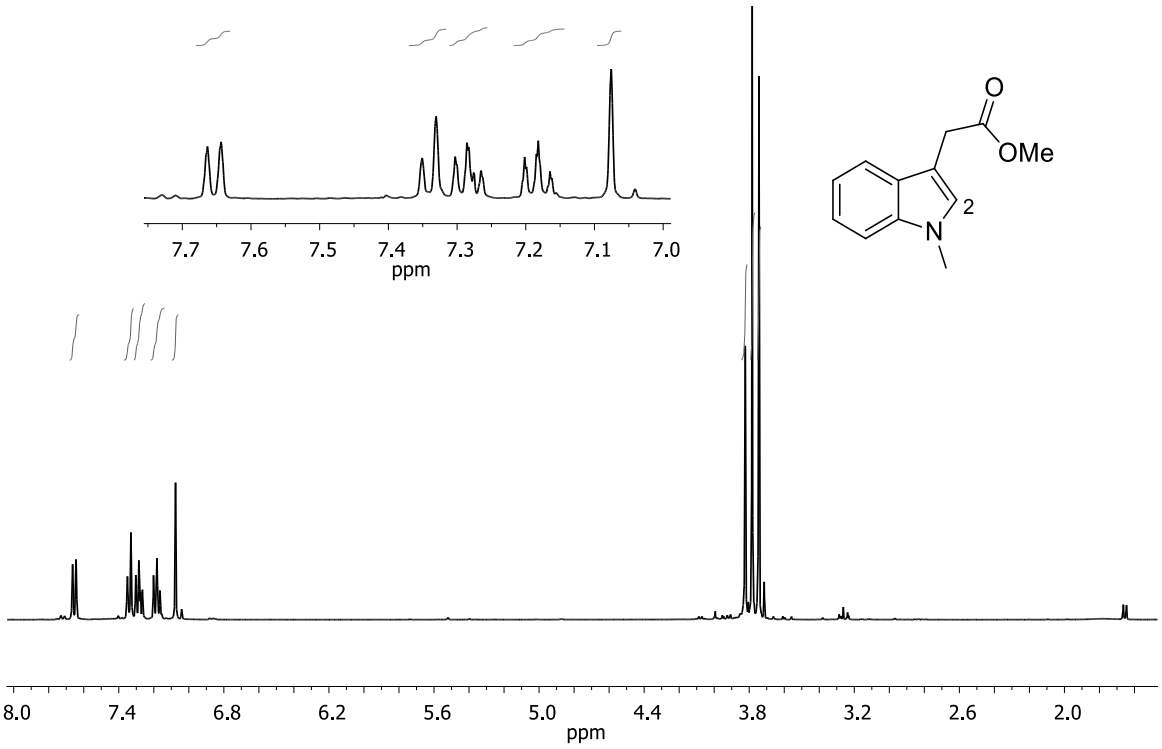
_N_-(2-iodophenyl)-2-(_N_-methyl-1_H_-indol-3-yl)acetamide

^{1}H-NMR (400.13 MHz, $CDCl_3$)

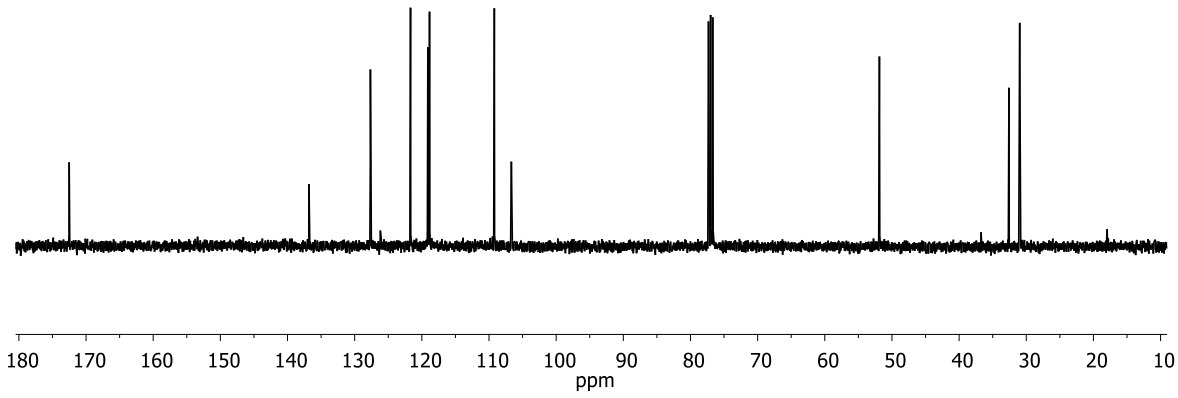


Methyl 2-(*N*-methyl-1*H*-indol-3-yl)acetate

^{1}H-NMR (400.13 MHz, $CDCl_3$)

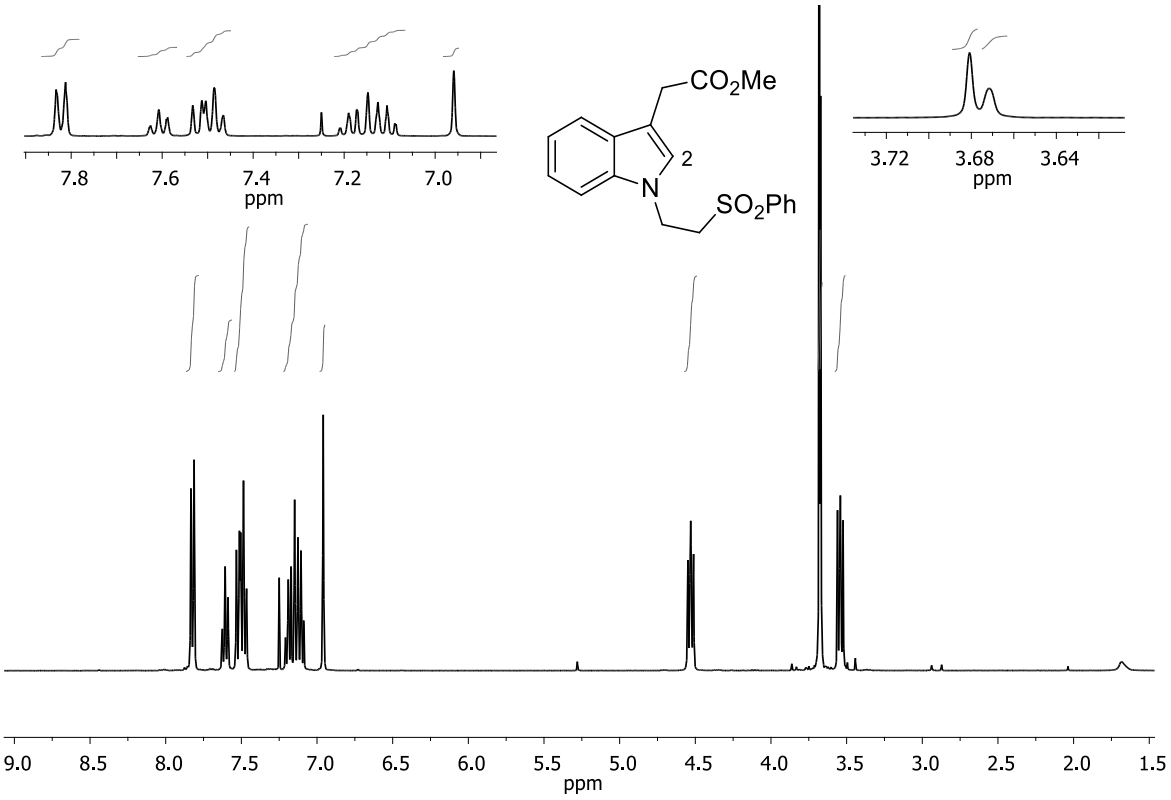


^{13}C-NMR (100.61 MHz, $CDCl_3$)

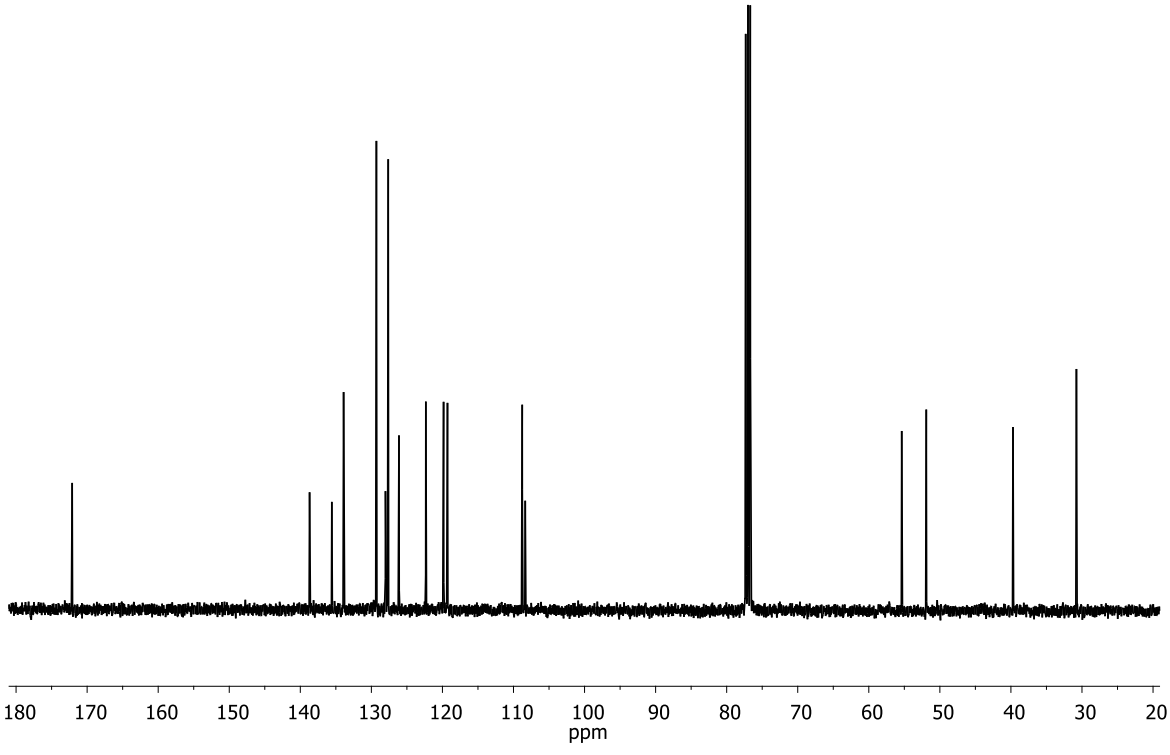


Methyl 2-{1-[2-(phenylsulfonyl)ethyl]-1*H*-indol-3-yl}acetate

^{1}H-NMR (400.13 MHz, $CDCl_3$)

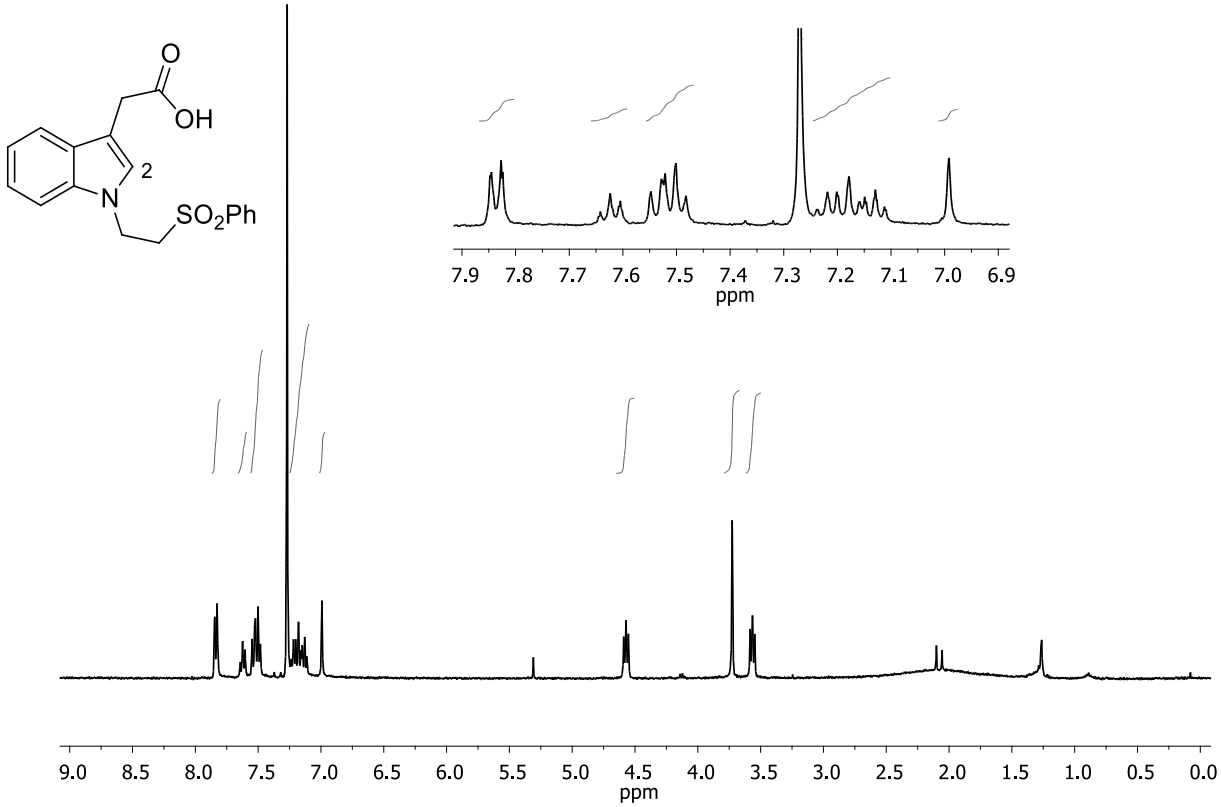


^{13}C-NMR (100.61 MHz, $CDCl_3$)



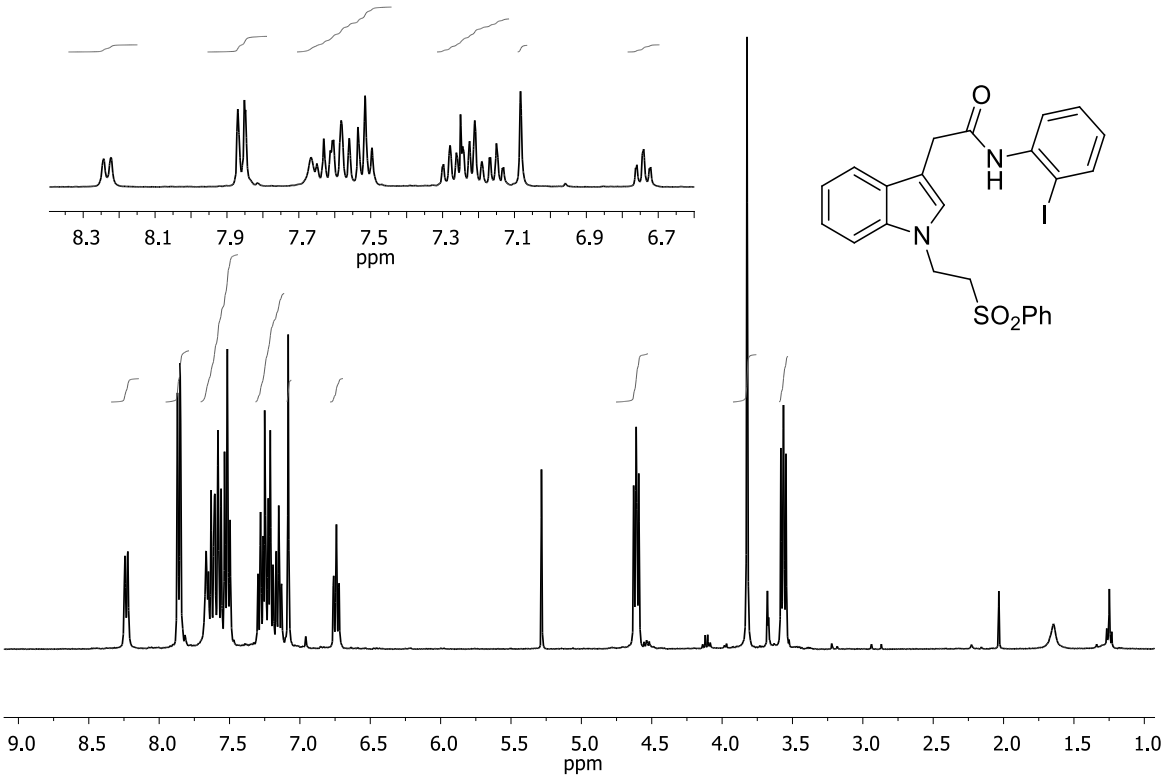
2-{1-[2-(Phenylsulfonyl)ethyl]-1*H*-indol-3-yl}acetic acid

^{1}H-NMR (400.13 MHz, $CDCl_3$)

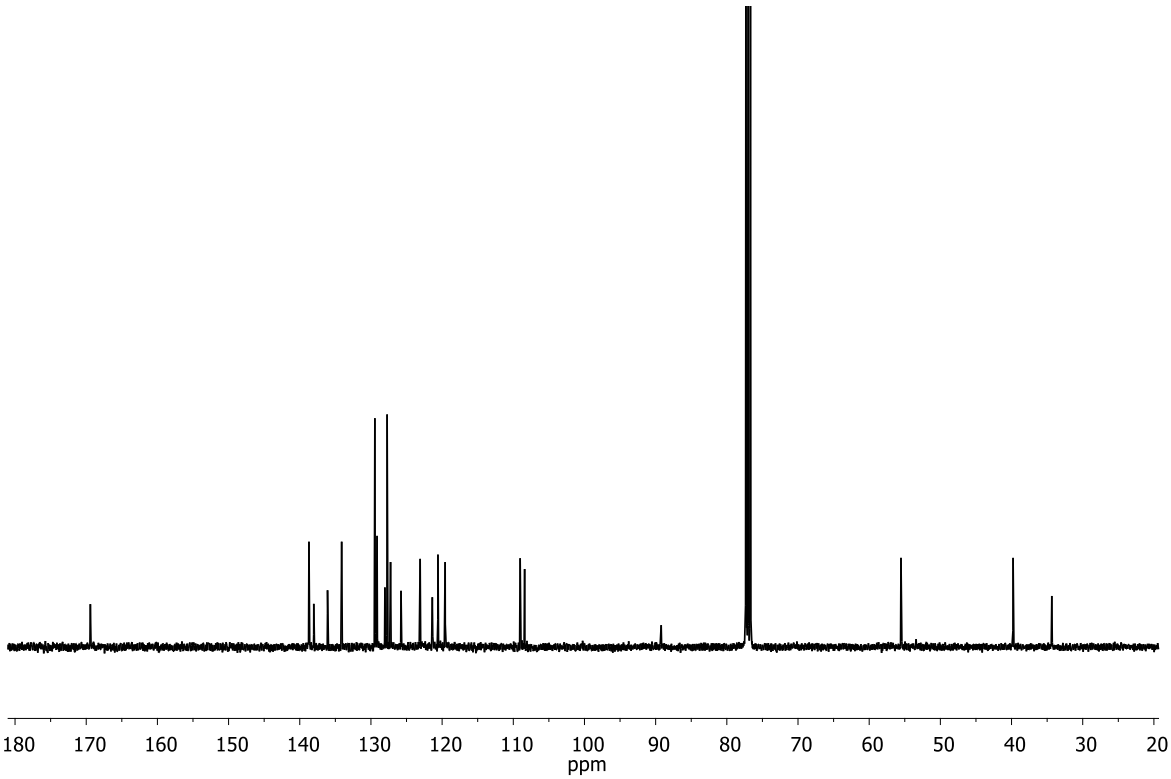


_N_-(2-iodophenyl)-2-{1-[2-(phenylsulfonyl)ethyl]-1_H_-indol-3-yl}acetamide

^{1}H-NMR (400.13 MHz, $CDCl_3$)

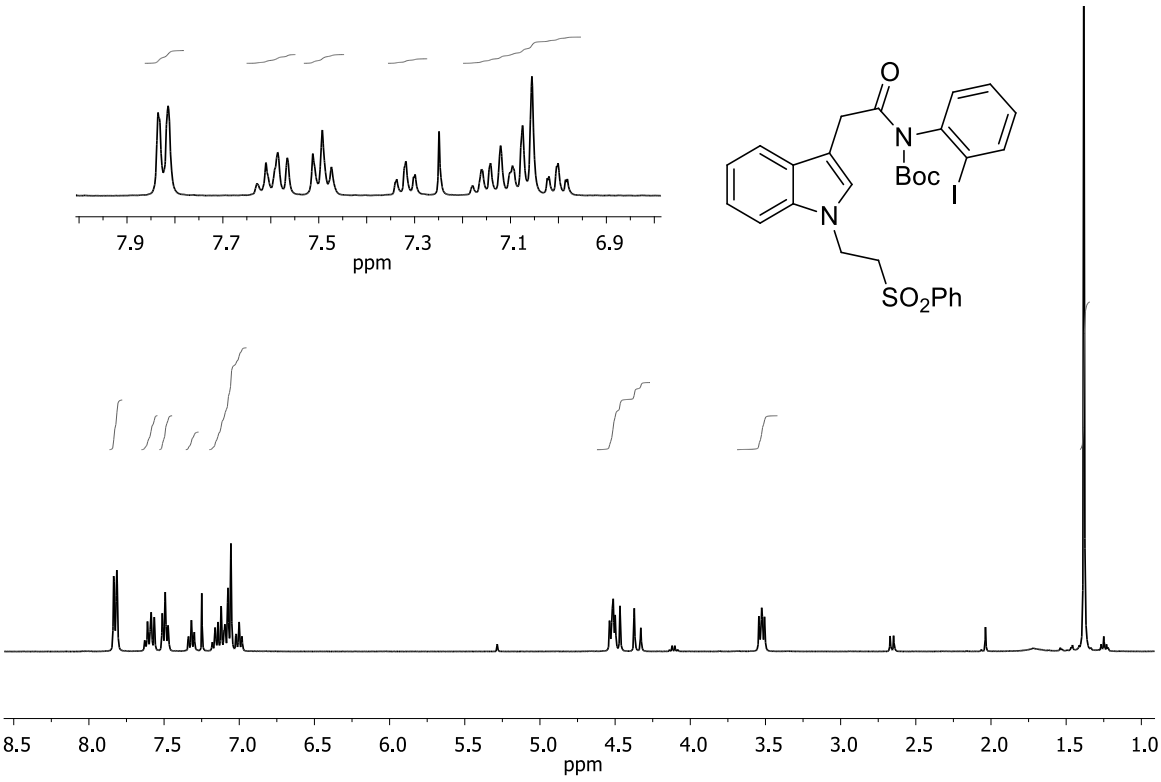


^{13}C-NMR (100.61 MHz, $CDCl_3$)

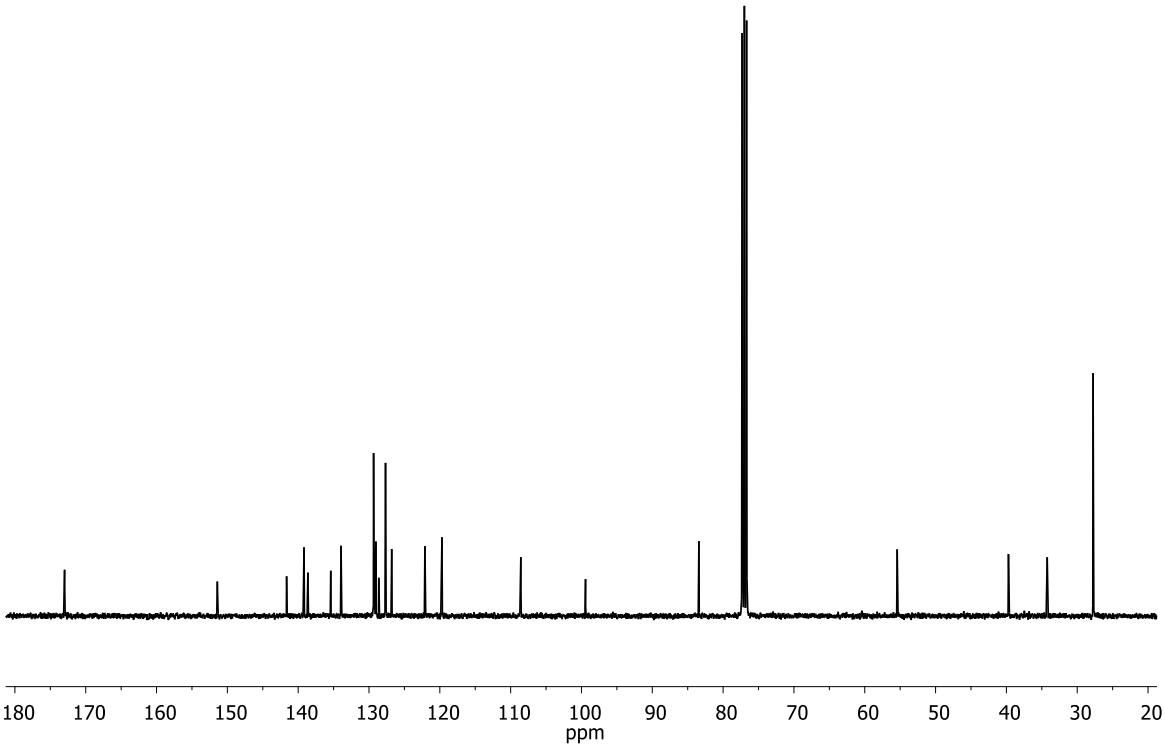


tert-Butyl (2-Iodophenyl{2-[1-(2-(phenylsulfonyl)ethyl)-1*H*-indol-3-yl]acetyl}carbamate

^{1}H-NMR (400.13 MHz, $CDCl_3$)

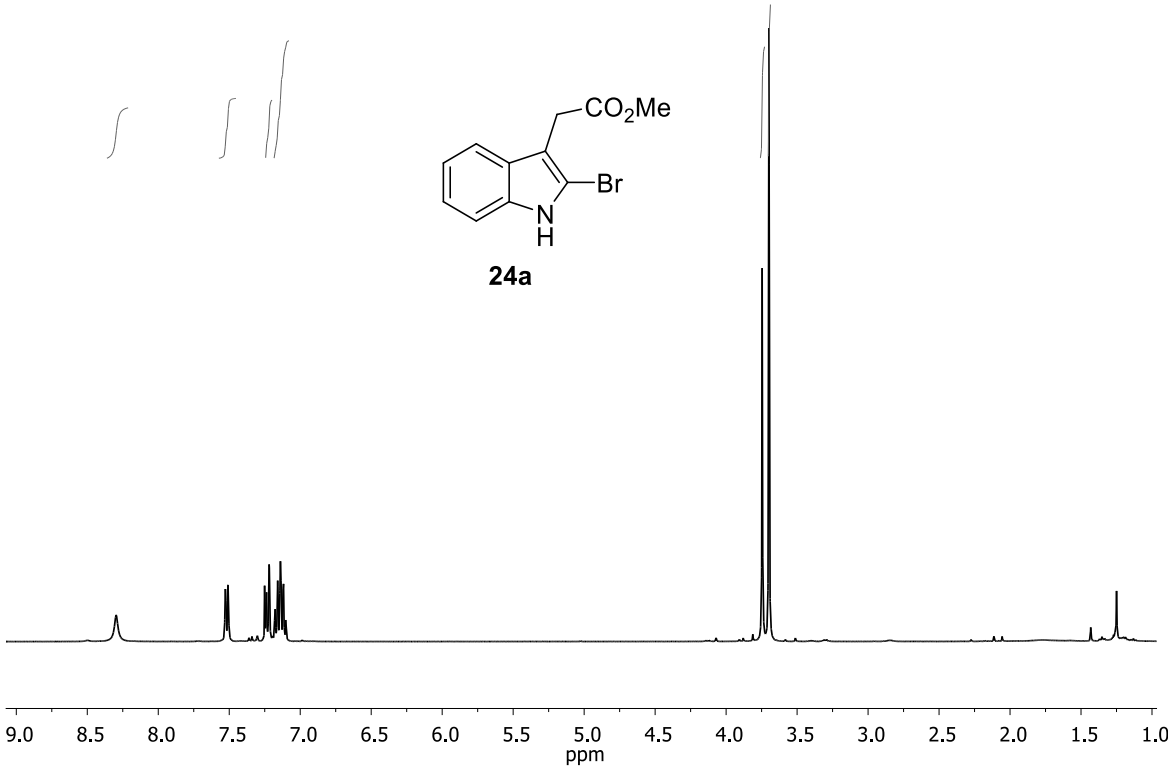


^{13}C-NMR (100.61 MHz, $CDCl_3$)



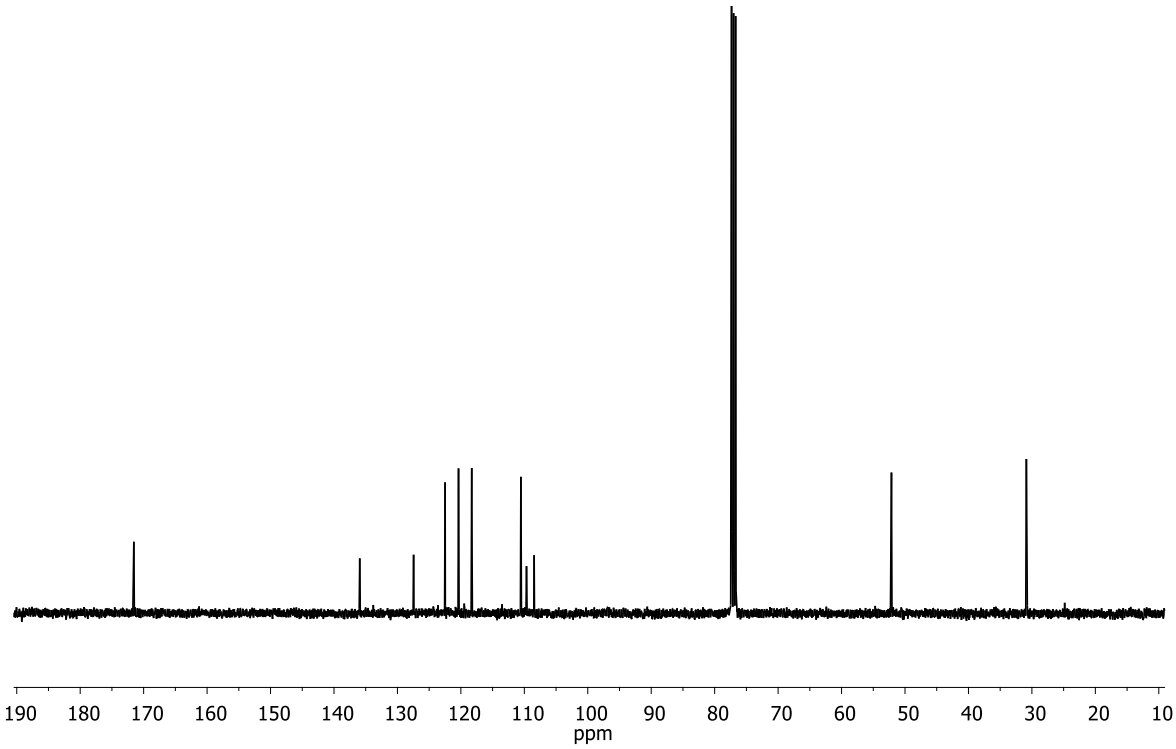
Methyl 2-(2-Bromo-1*H*-indol-3-yl)acetate 24a

^{1}H-NMR (400.13 MHz, $CDCl_3$)



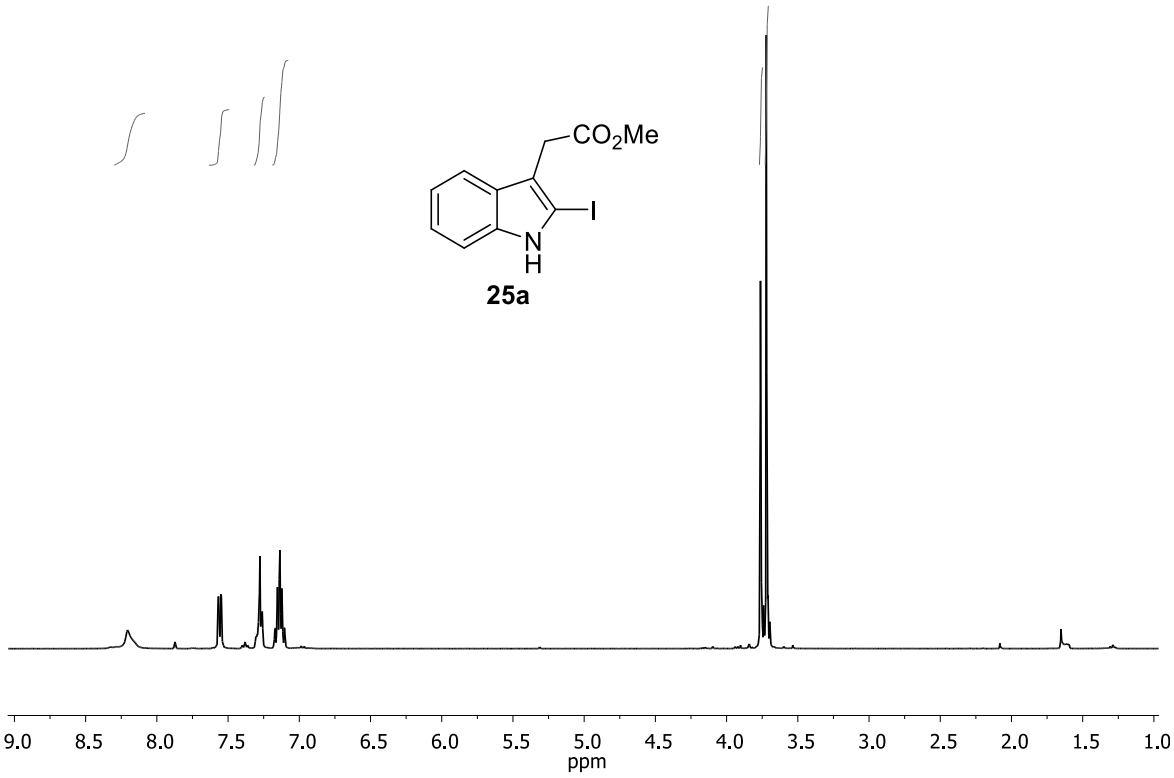
24a

^{13}C-NMR (100.61 MHz, $CDCl_3$)

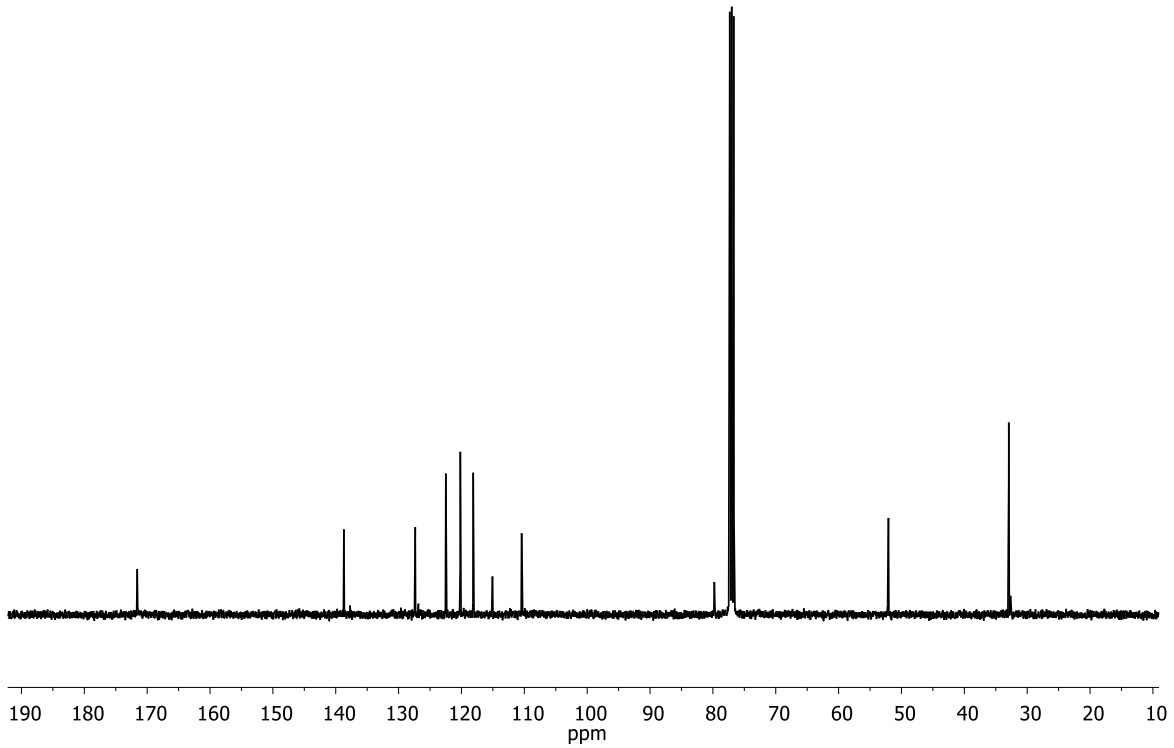


Methyl 2-(2-Iodo-1*H*-indol-3-yl)acetate 25a

^{1}H-NMR (400.13 MHz, $CDCl_3$)

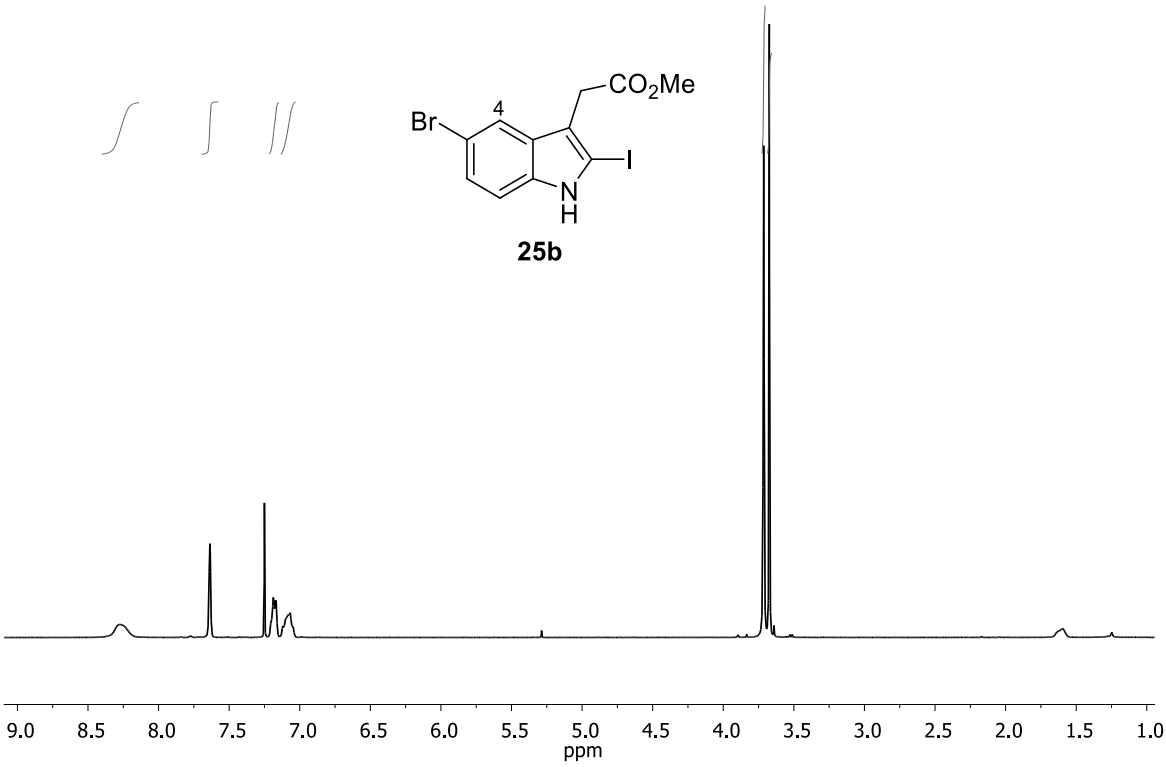


^{13}C-NMR (100.61 MHz, $CDCl_3$)

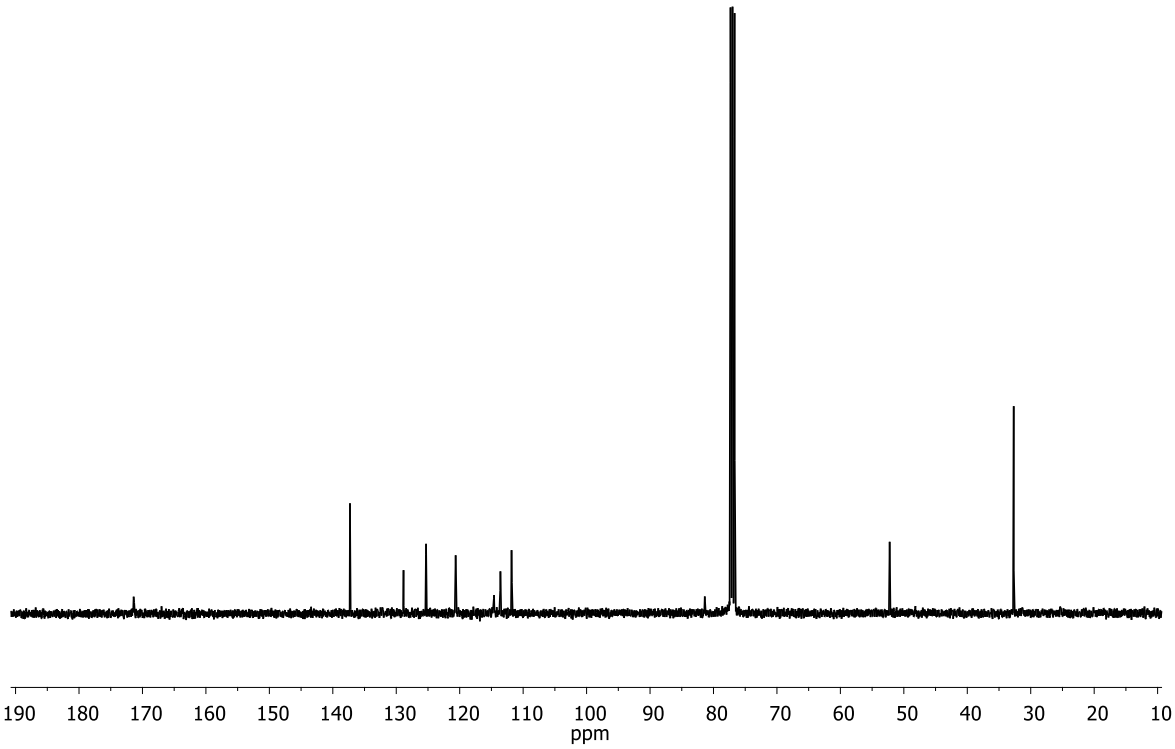


Methyl 2-(5-Bromo-2-iodo-1*H*-indol-3-yl)acetate 25b

^{1}H-NMR (400.13 MHz, $CDCl_3$)

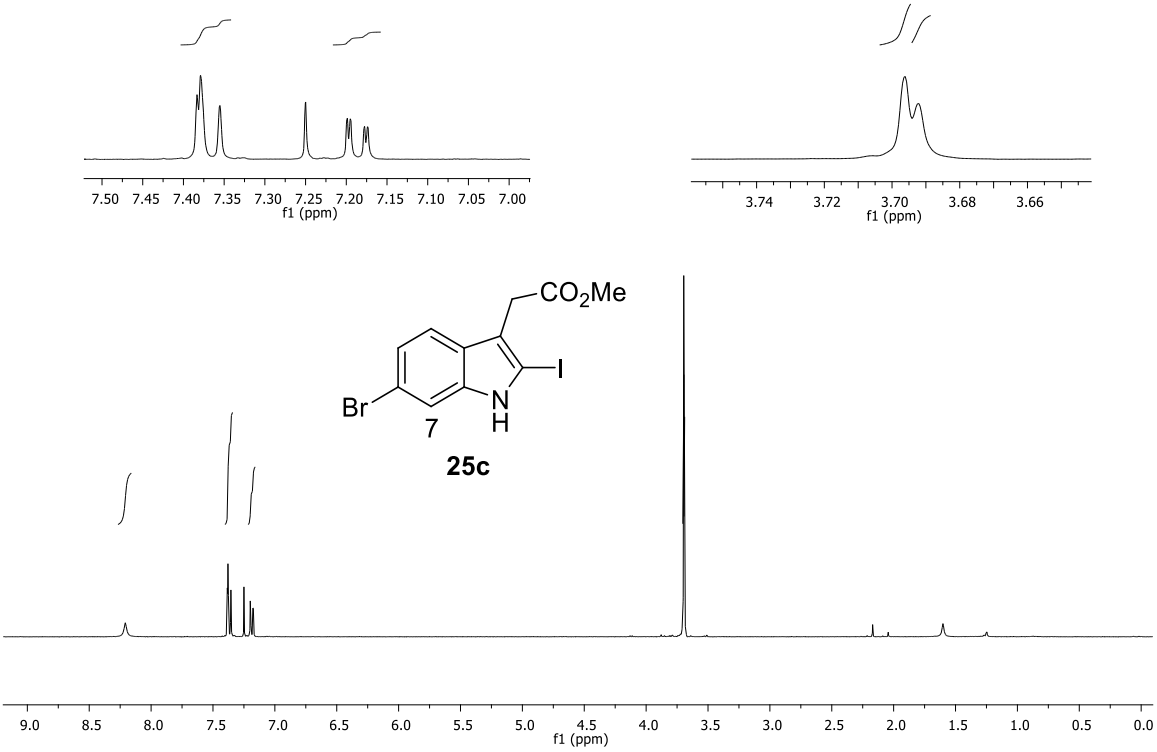


^{13}C-NMR (100.61 MHz, $CDCl_3$)

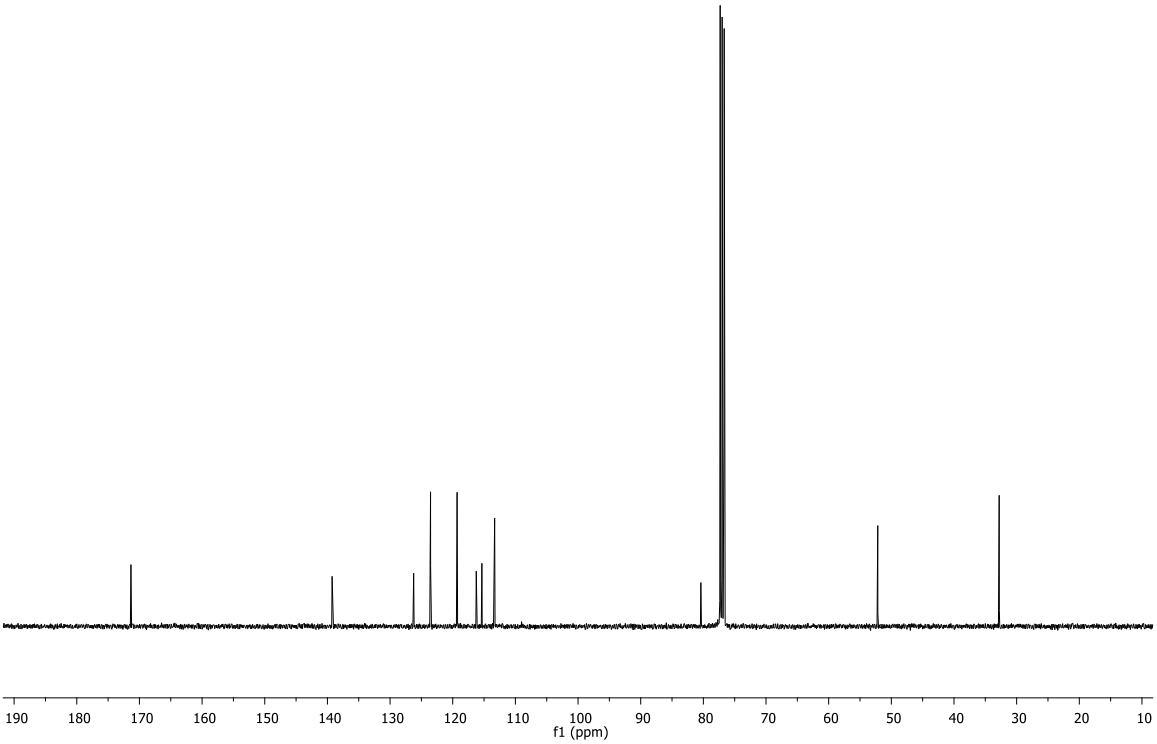


Methyl 2-(6-Bromo-2-iodo-1*H*-indol-3-yl)acetate 25c

^{1}H-NMR (400.13 MHz, $CDCl_3$)

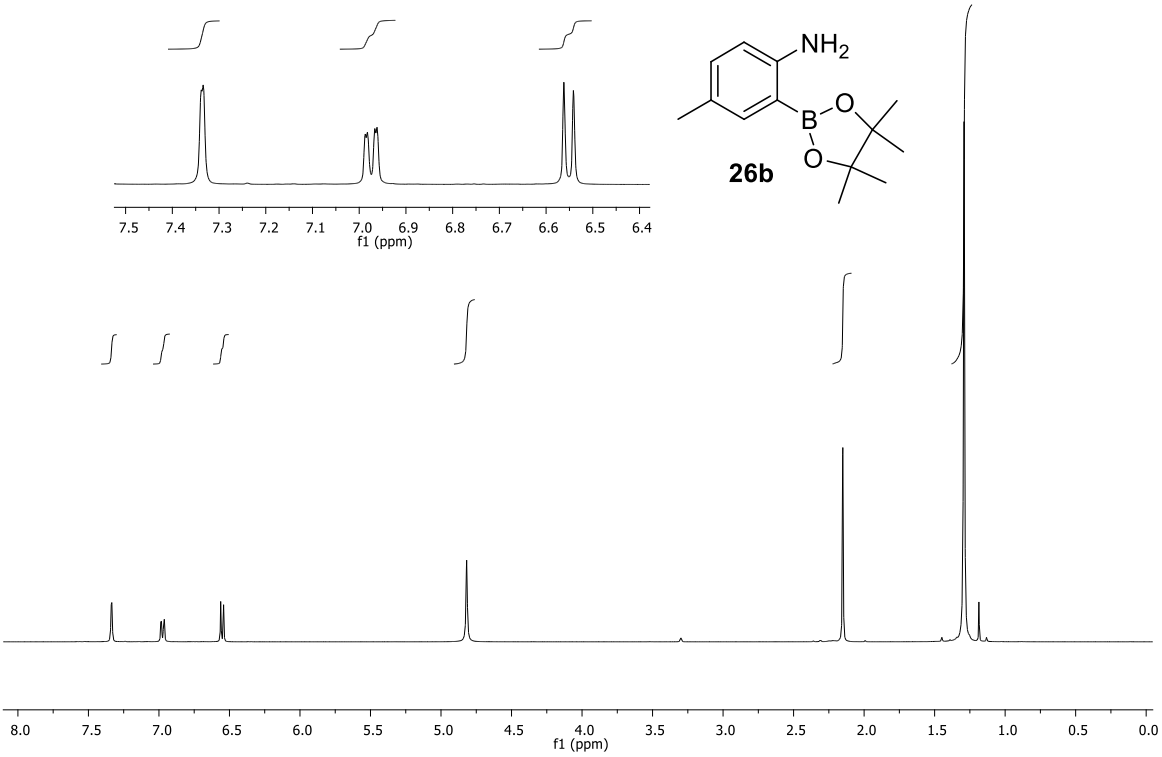


^{13}C-NMR (100.61 MHz, $CDCl_3$)

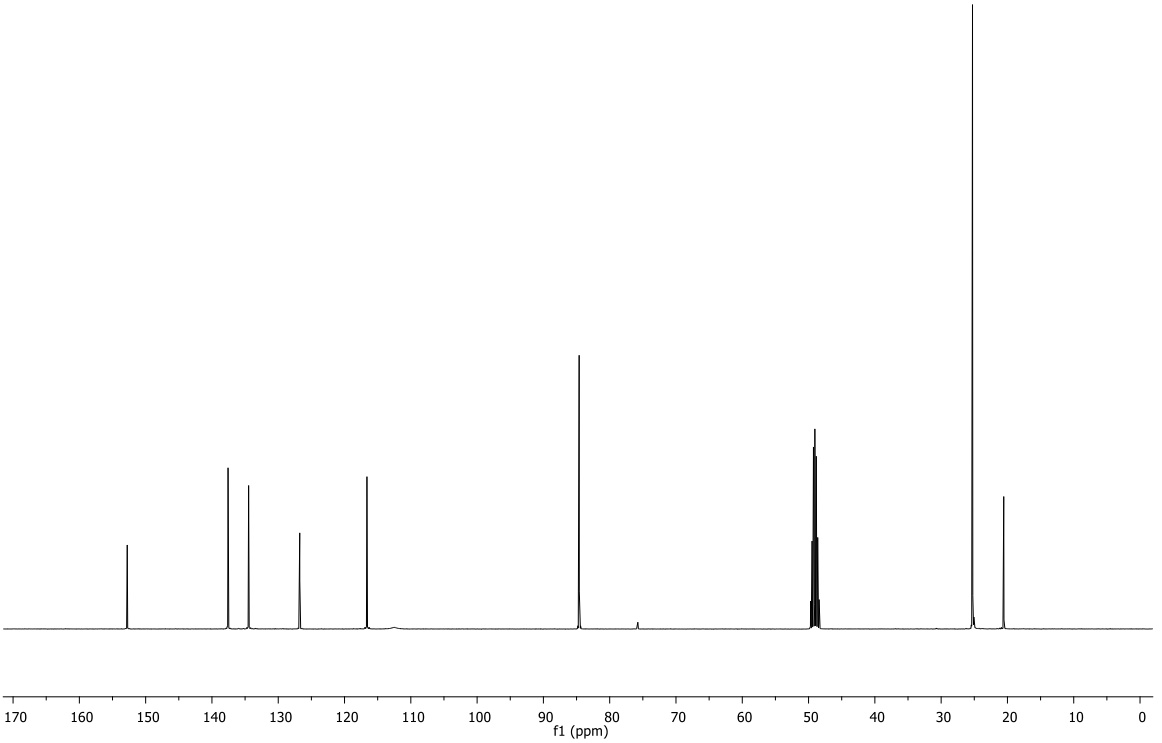


4-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 26b

^{1}H-NMR (400.13 MHz, CD_3OD)

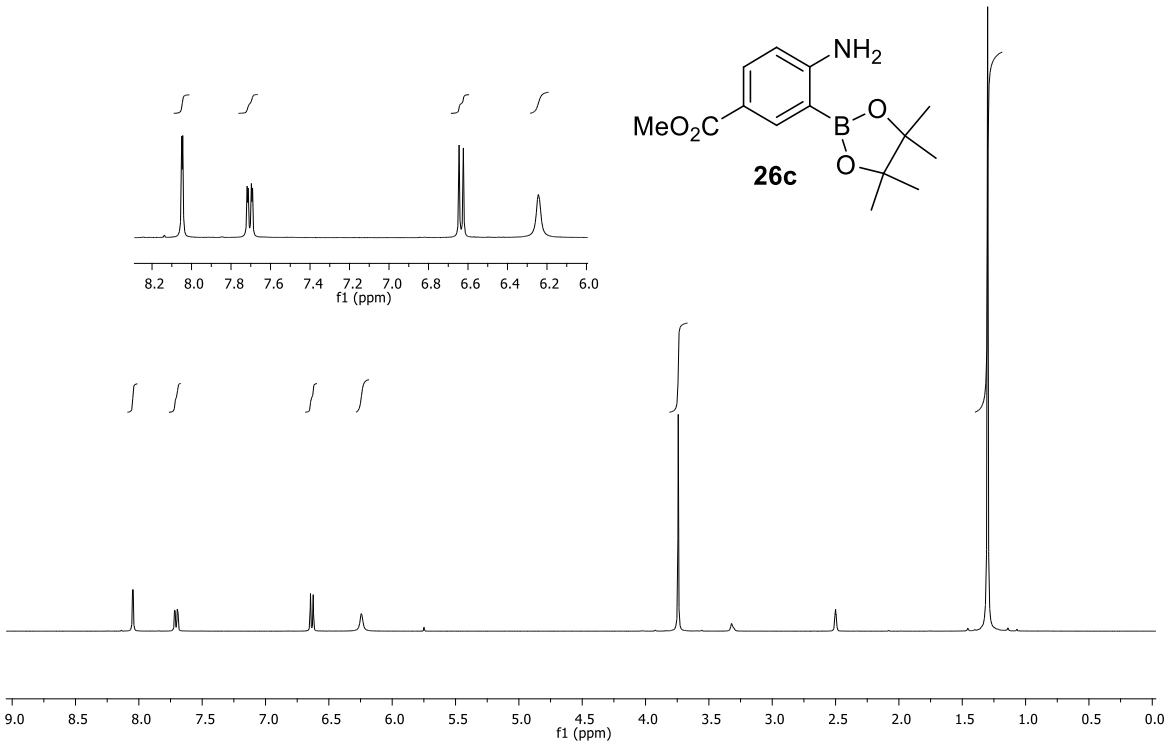


^{13}C-NMR (100.61 MHz, CD_3OD)

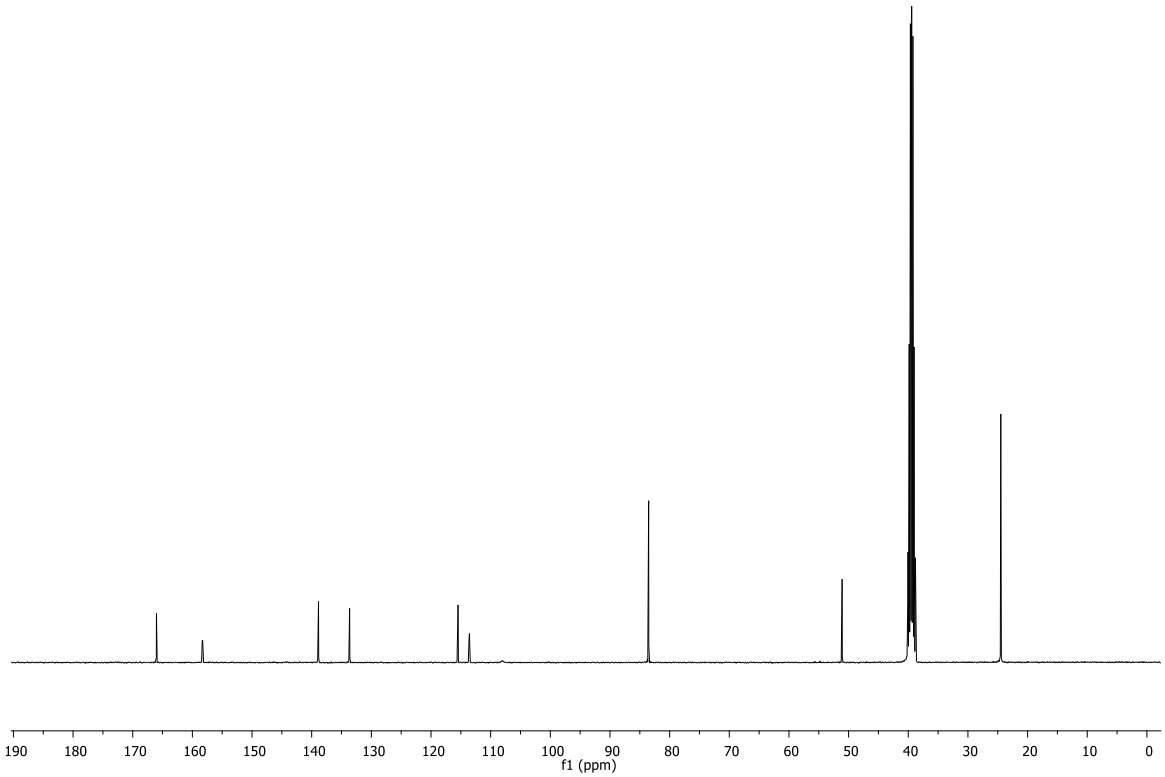


Methyl 4-amino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 26c

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

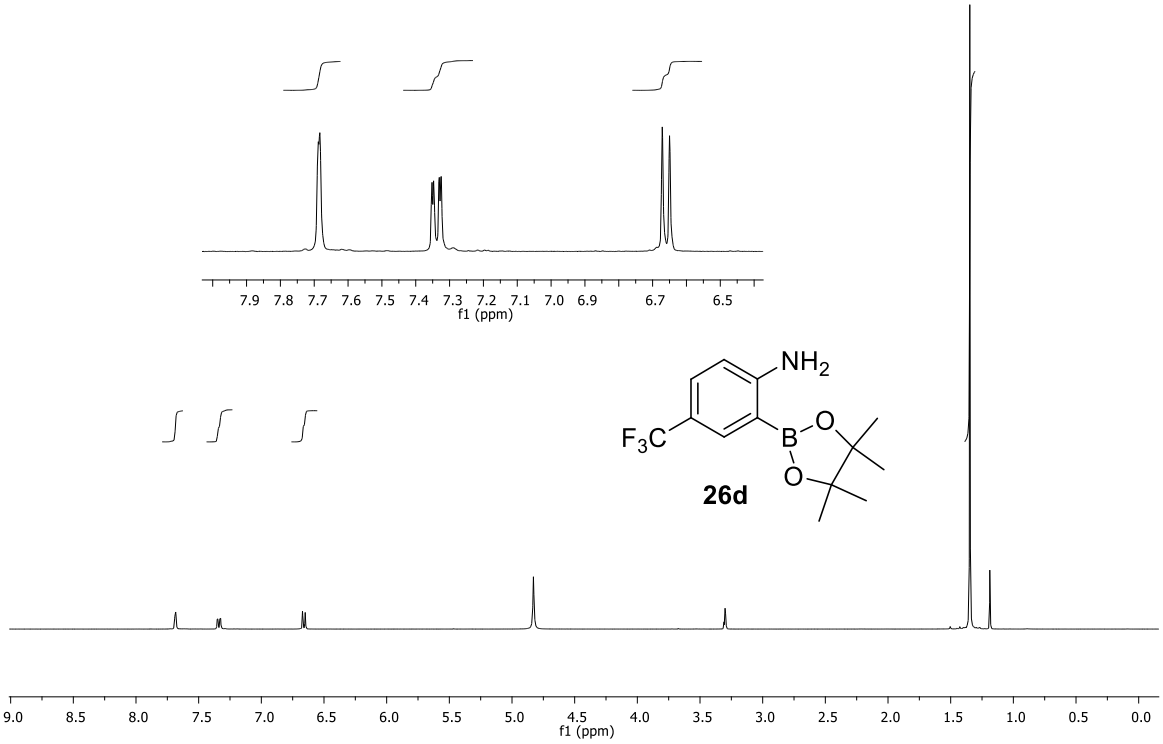


^{13}C-NMR (100.61 MHz, DMSO-d_6)

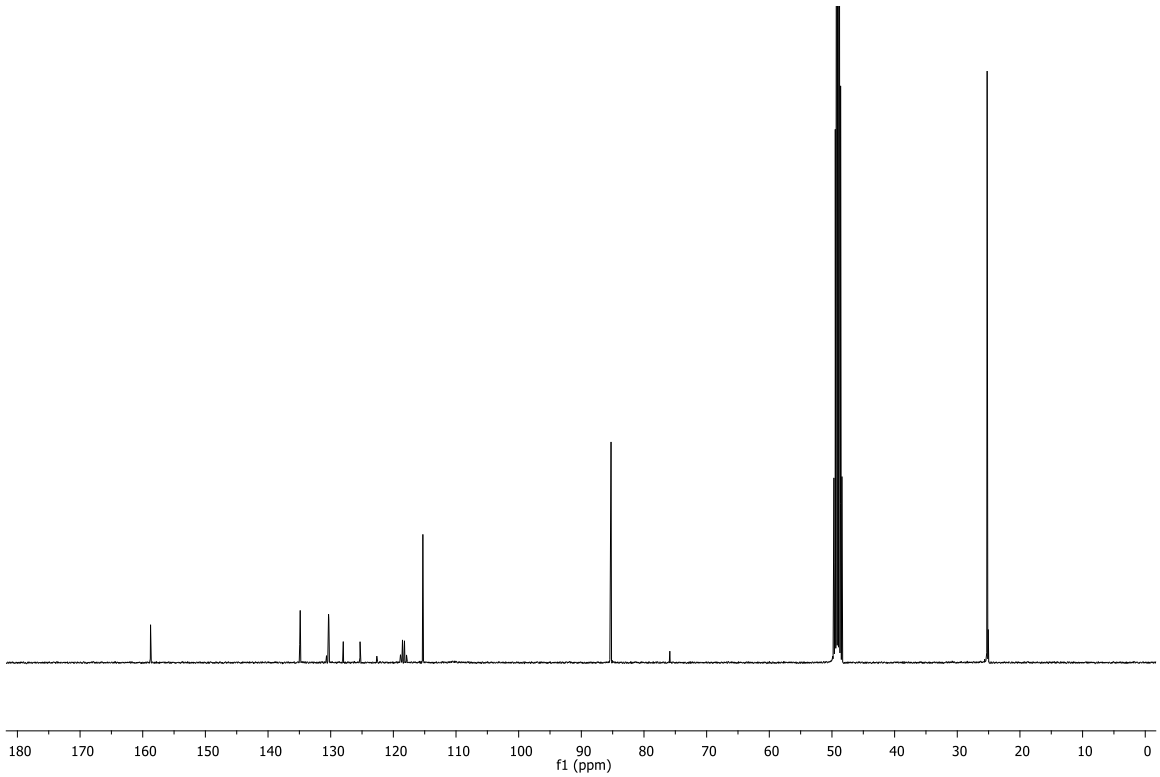


2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline 26d

^{1}H-NMR (400.13 MHz, CD_3OD)

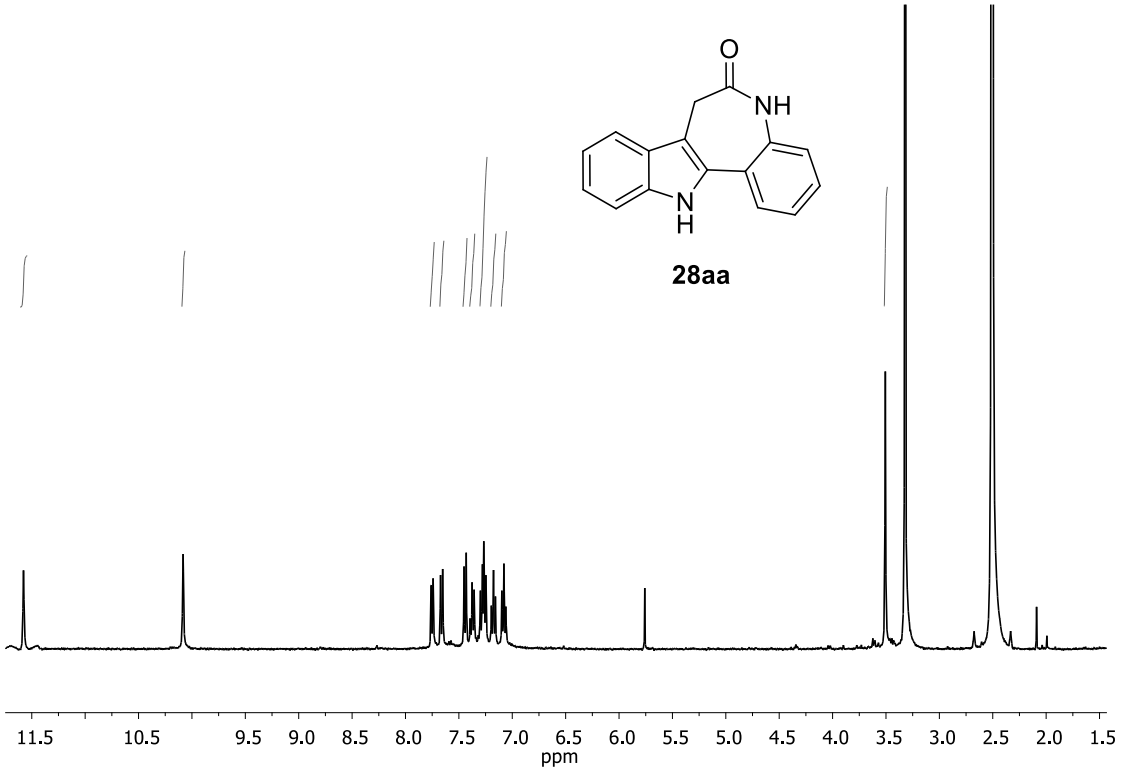


^{13}C-NMR (100.61 MHz, CD_3OD)

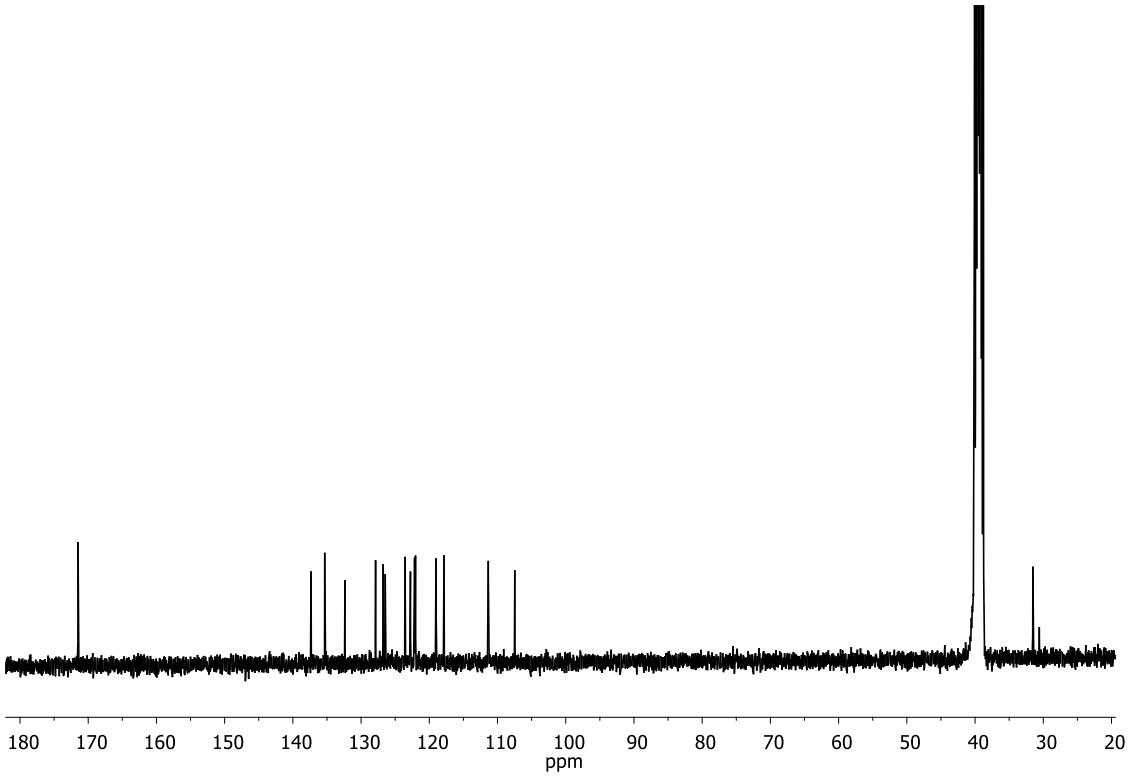


7,12-Dihydroindolo[3,2-*d*]benzazepin-6(5*H*)-one 28aa

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

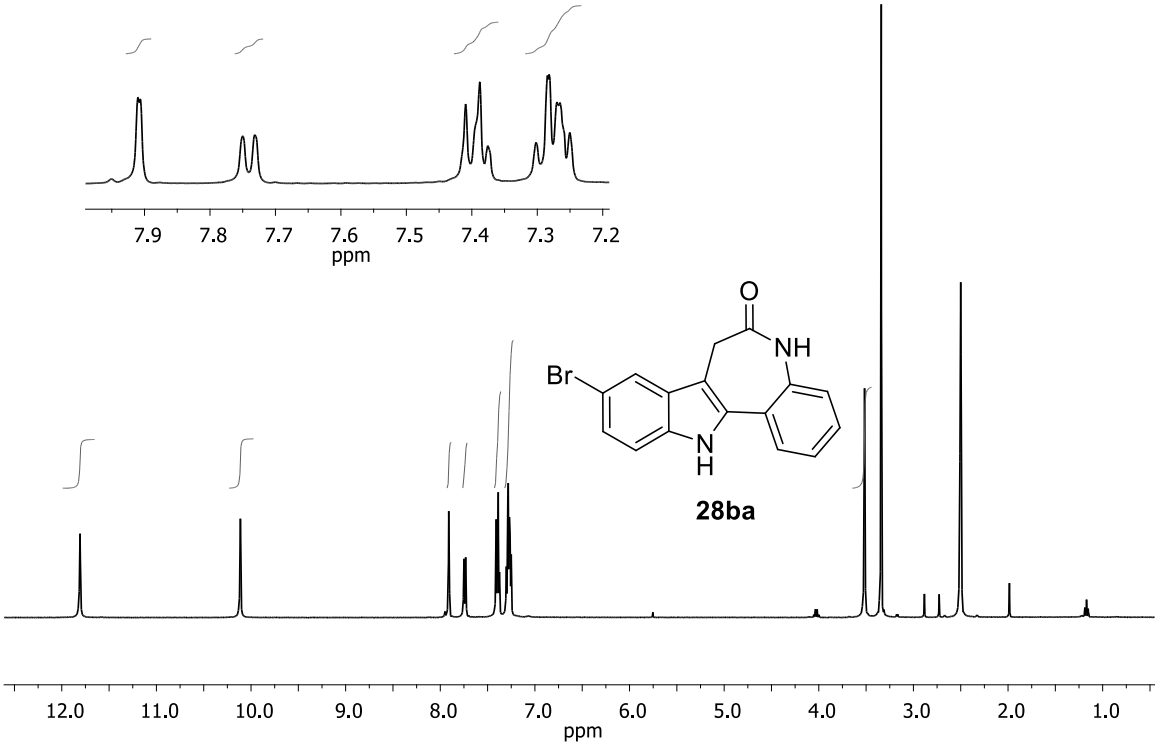


^{13}C-NMR (100.61 MHz, DMSO-d_6)

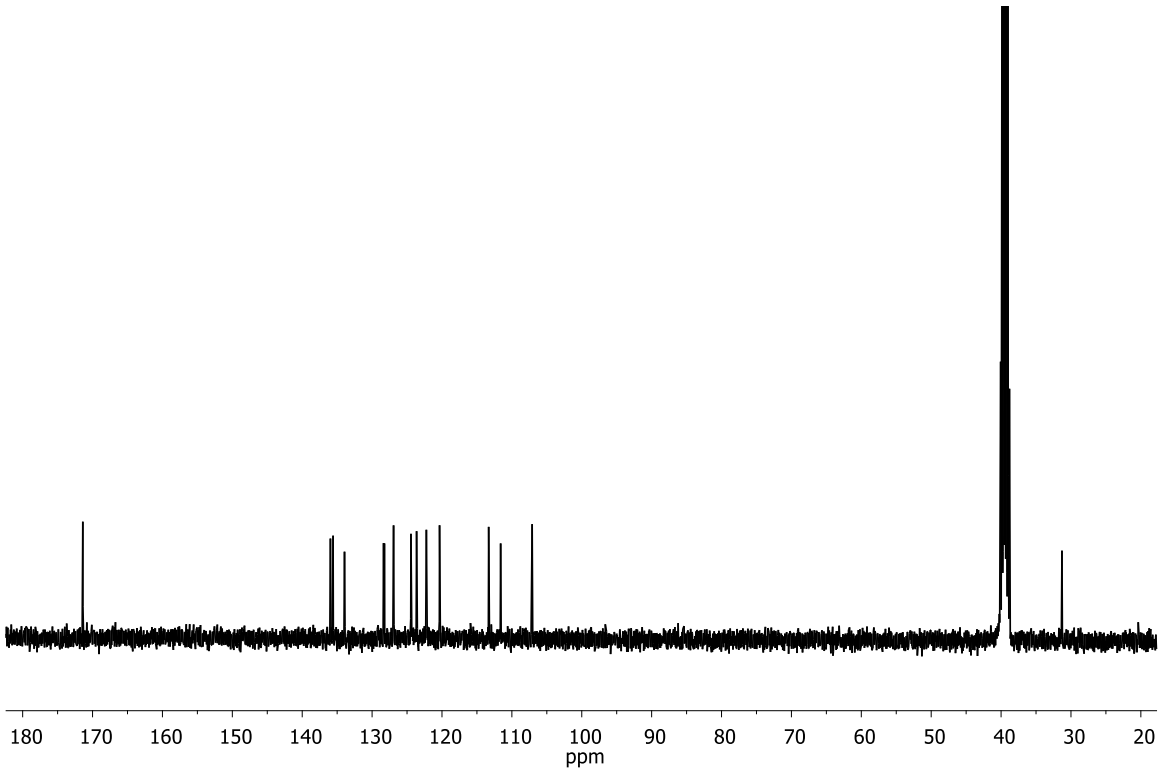


9-Bromo-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28ba

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

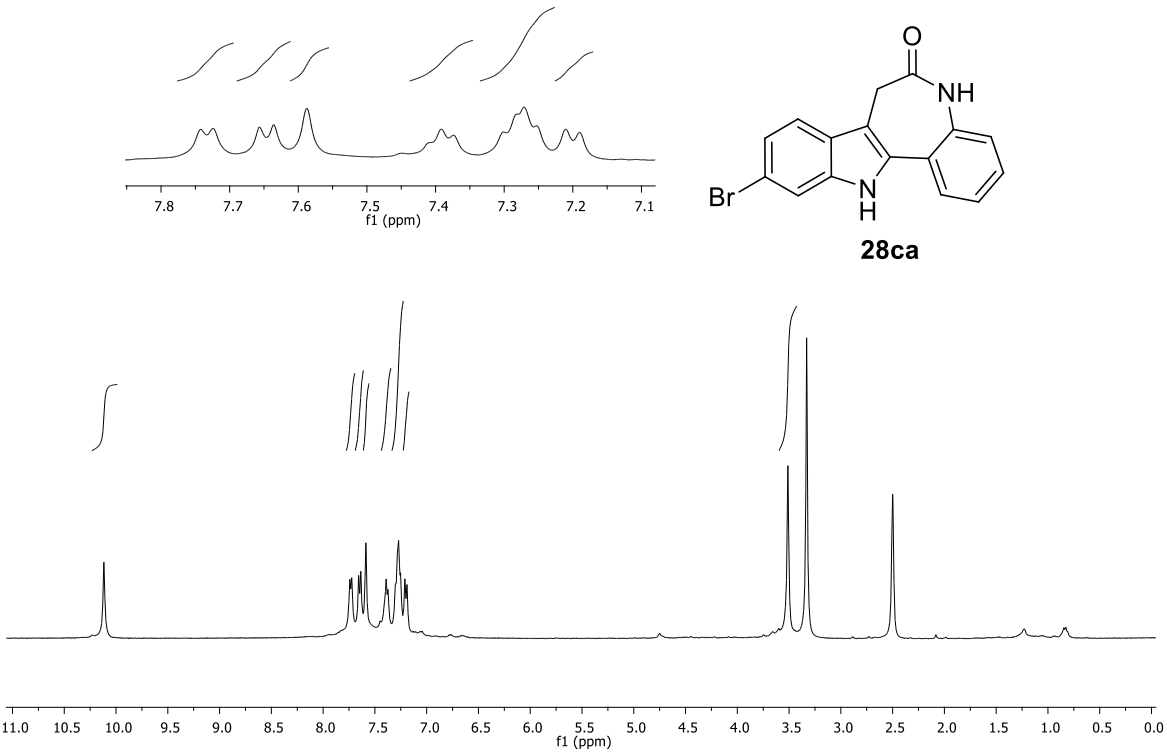


^{13}C-NMR (100.61 MHz, DMSO-d_6)

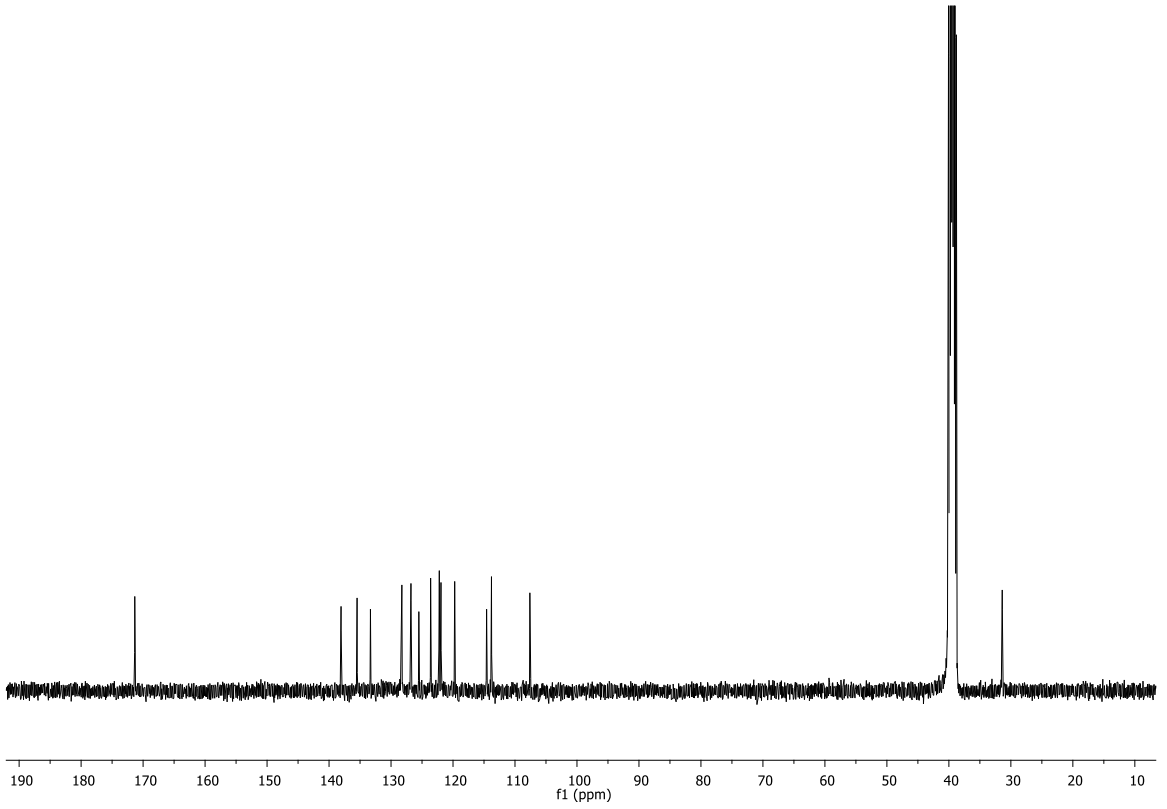


10-Bromo-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28ca

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

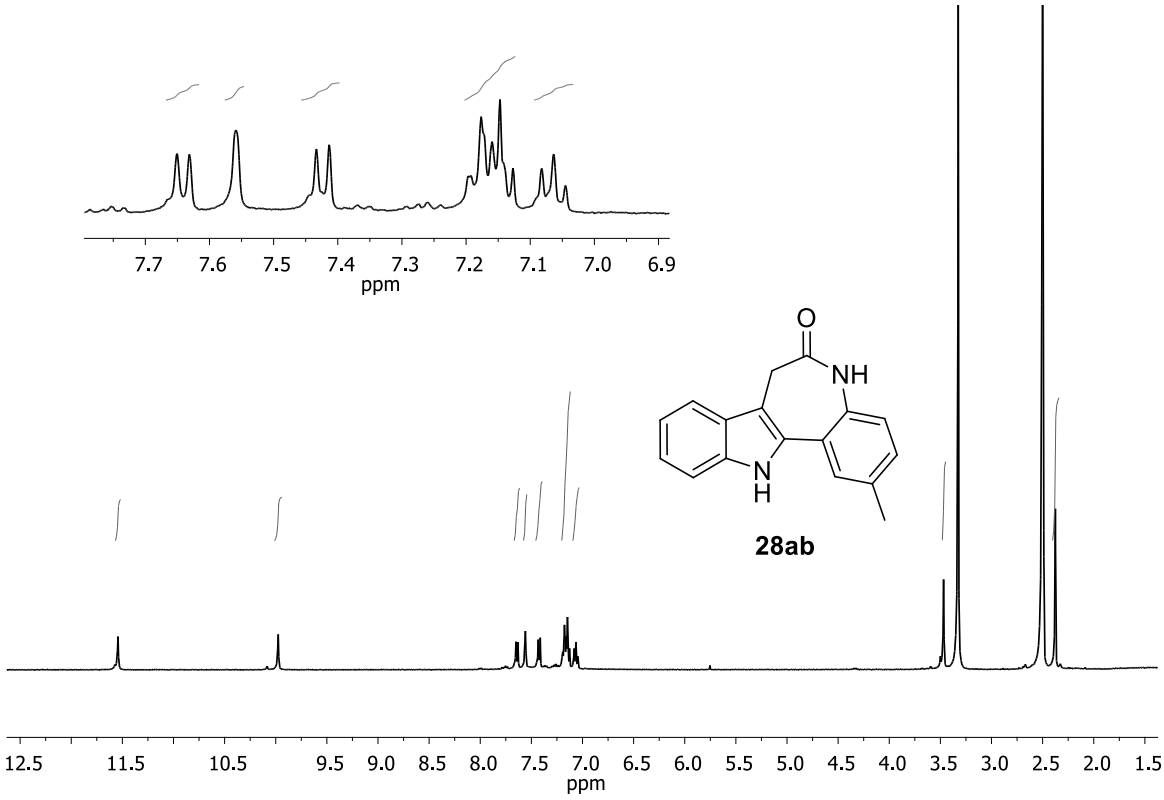


^{13}C-NMR (100.61 MHz, DMSO-d$_6$)

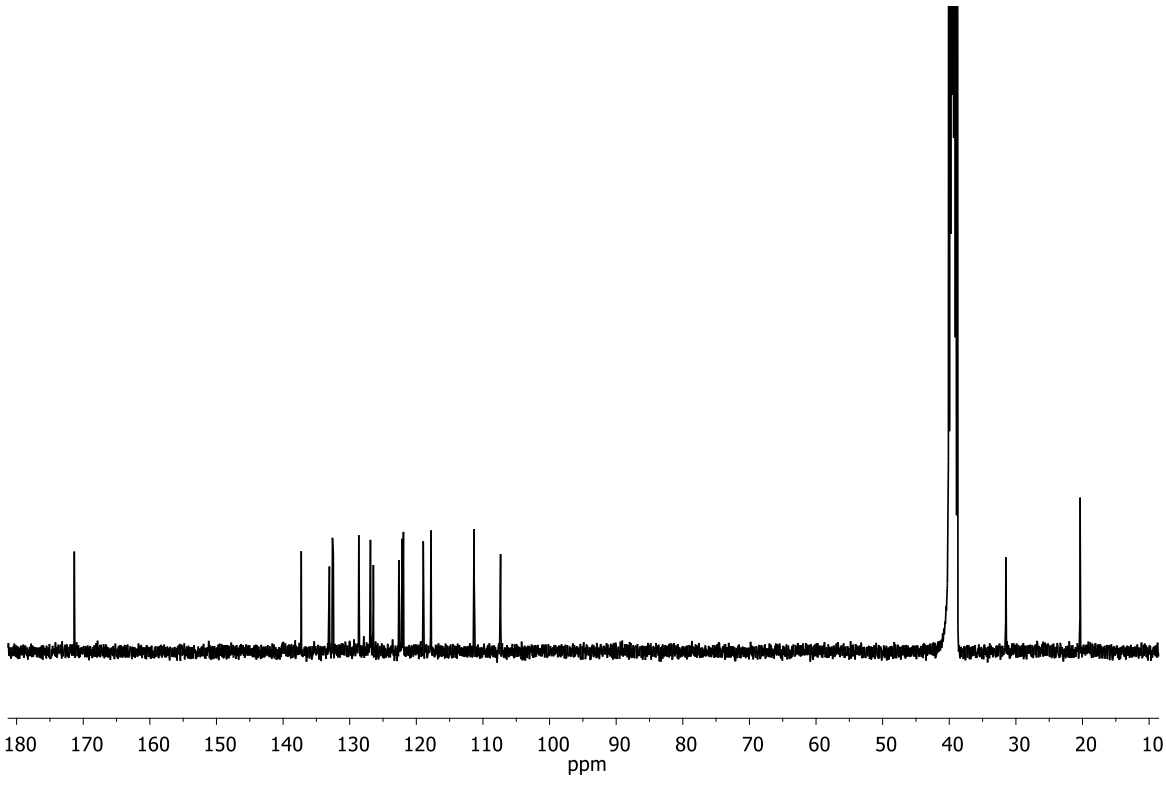


2-Methyl-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28ab

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

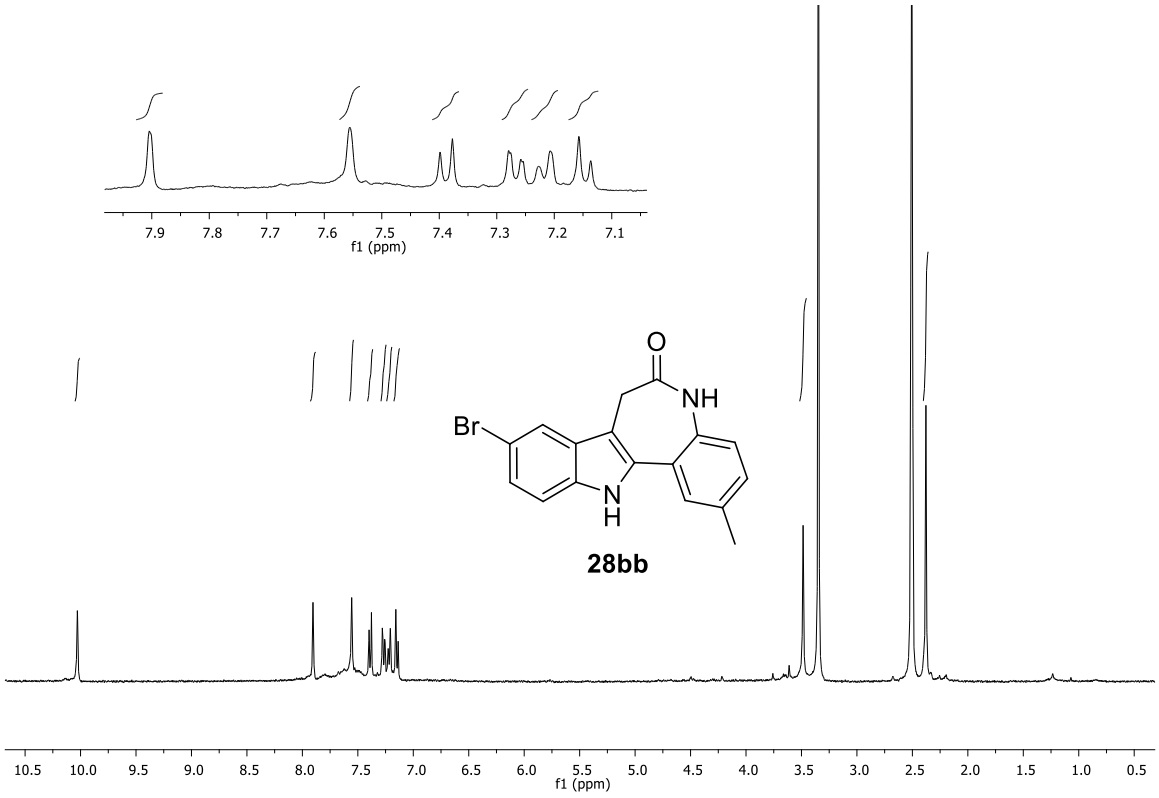


^{13}C-NMR (100.61 MHz, DMSO-d$_6$)

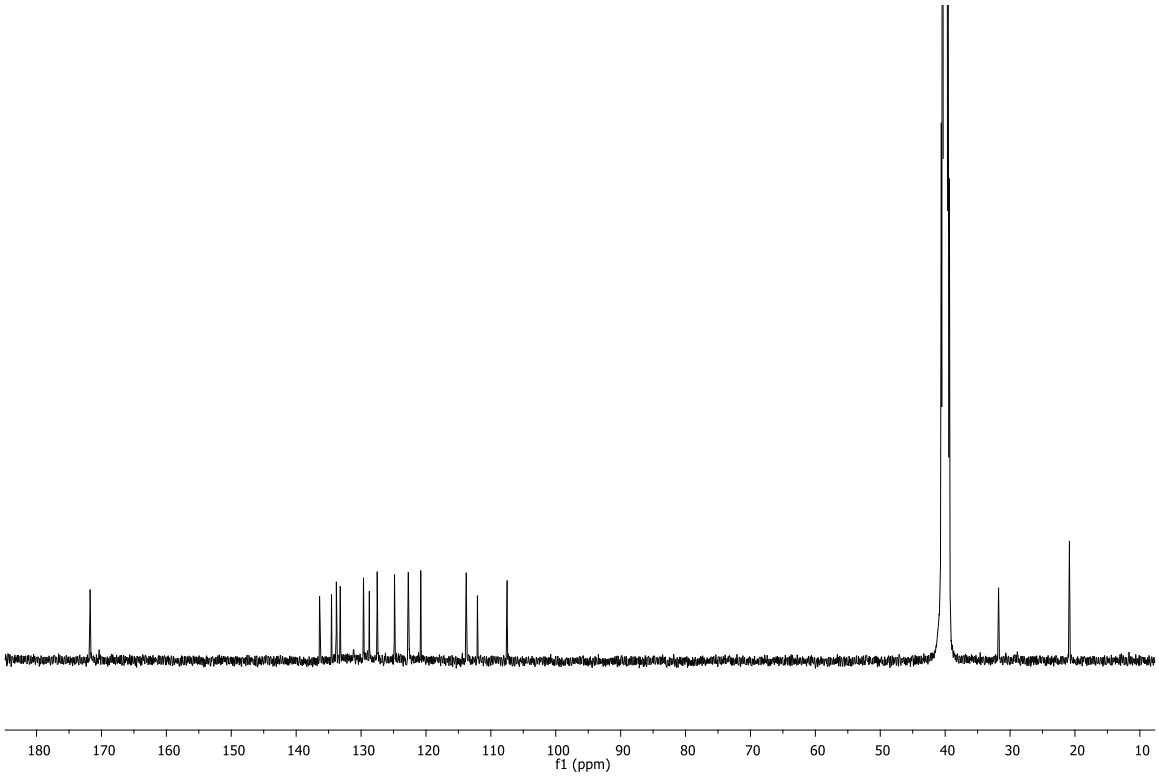


9-Bromo-2-methyl-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28bb

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

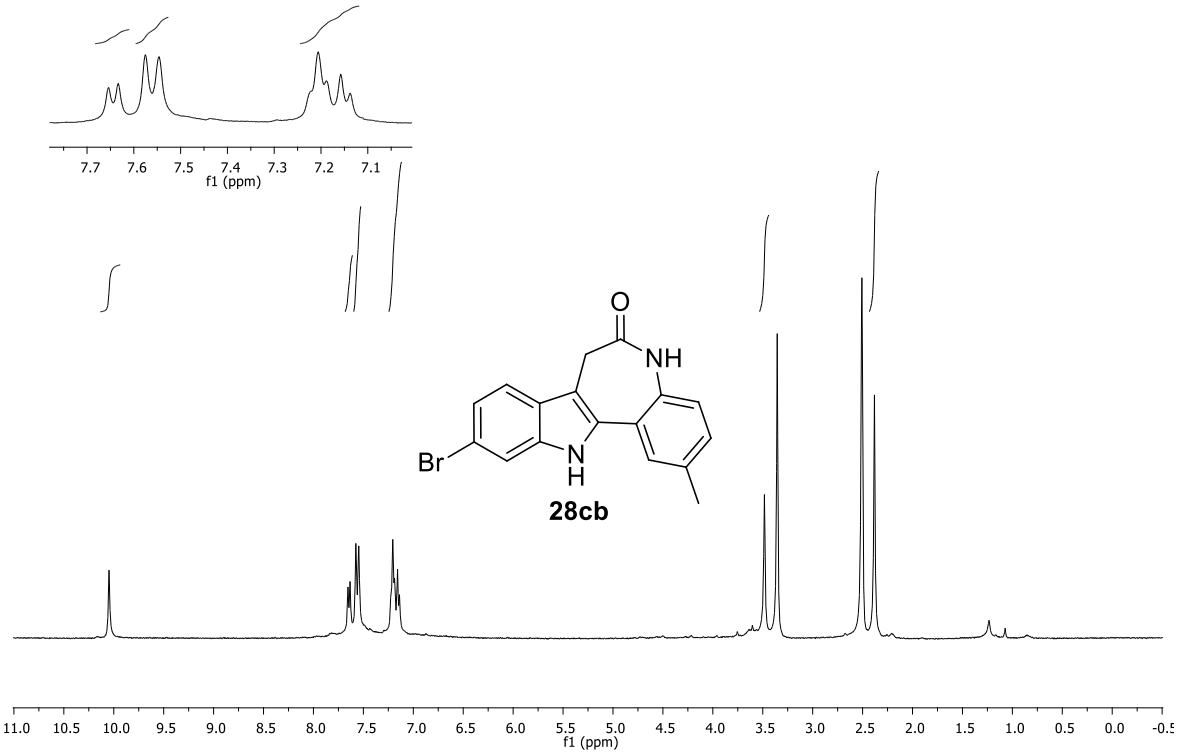


^{13}C-NMR (100.61 MHz, DMSO-d_6)

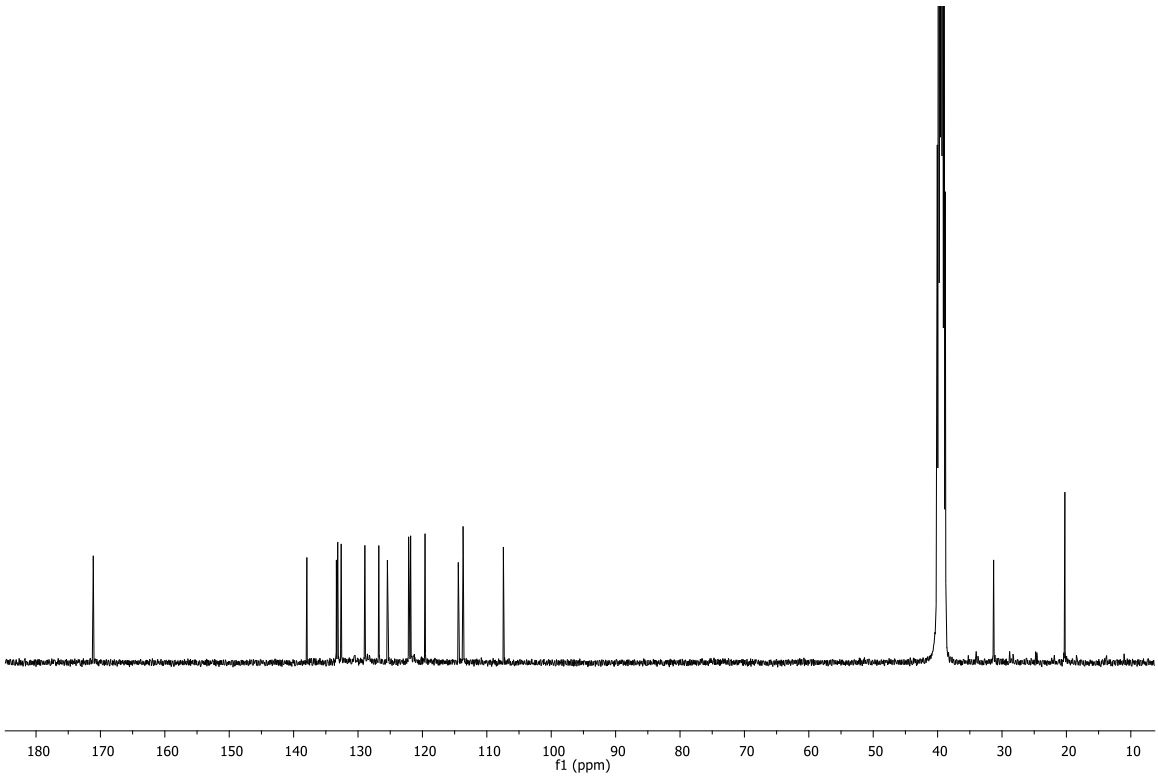


10-Bromo-2-methyl-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28cb

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

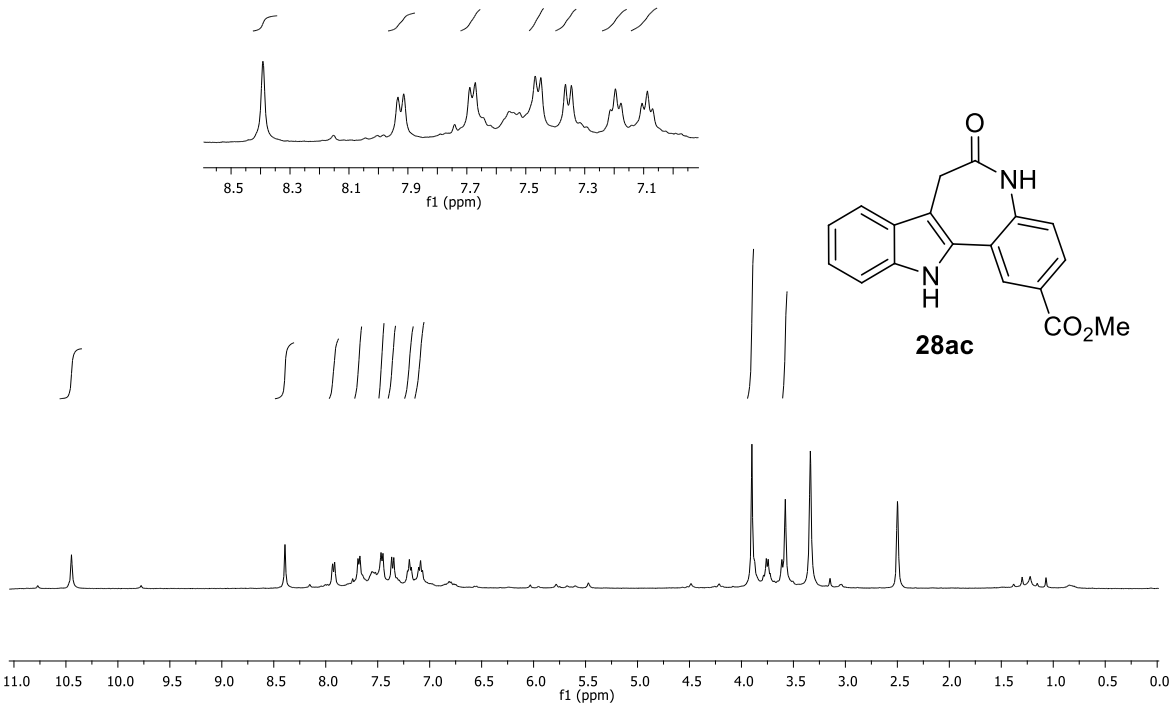


^{13}C-NMR (100.61 MHz, DMSO-d_6)

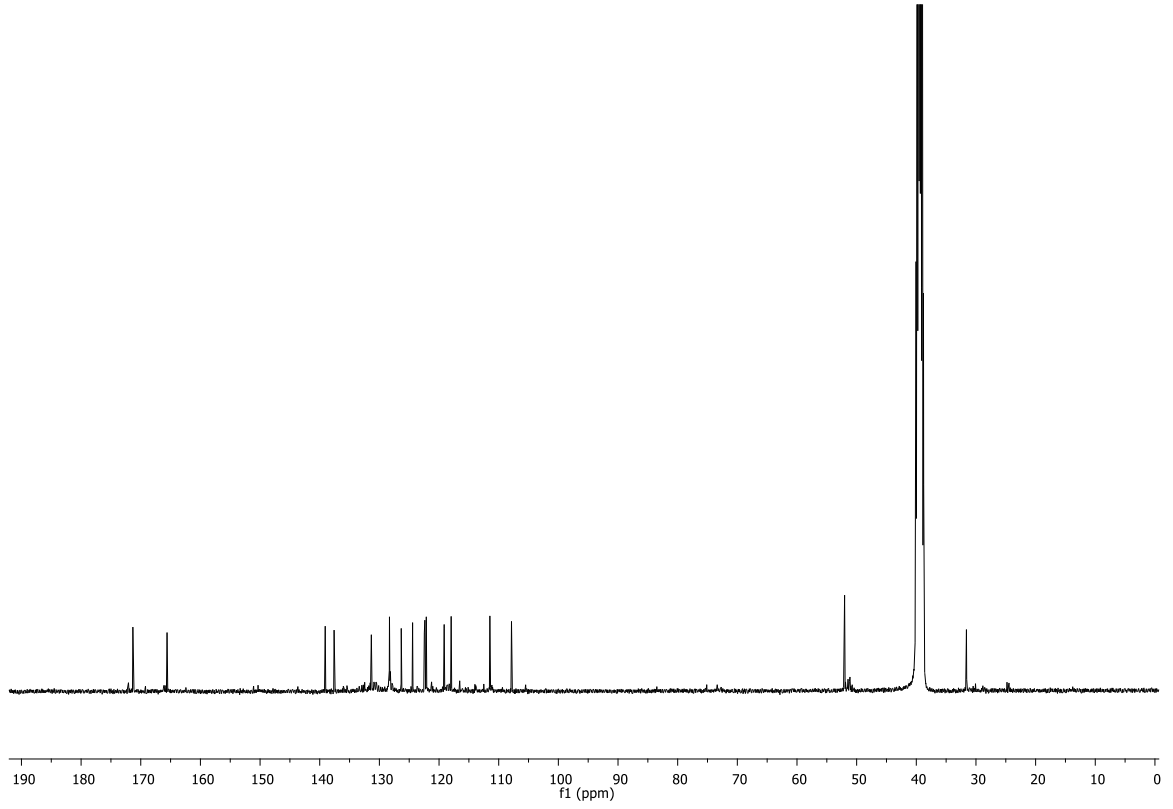


Methyl 6-oxo-5,6,7,12-tetrahydroindolo[3,2-*d*]benzazepin-2-carboxylate 28ac

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

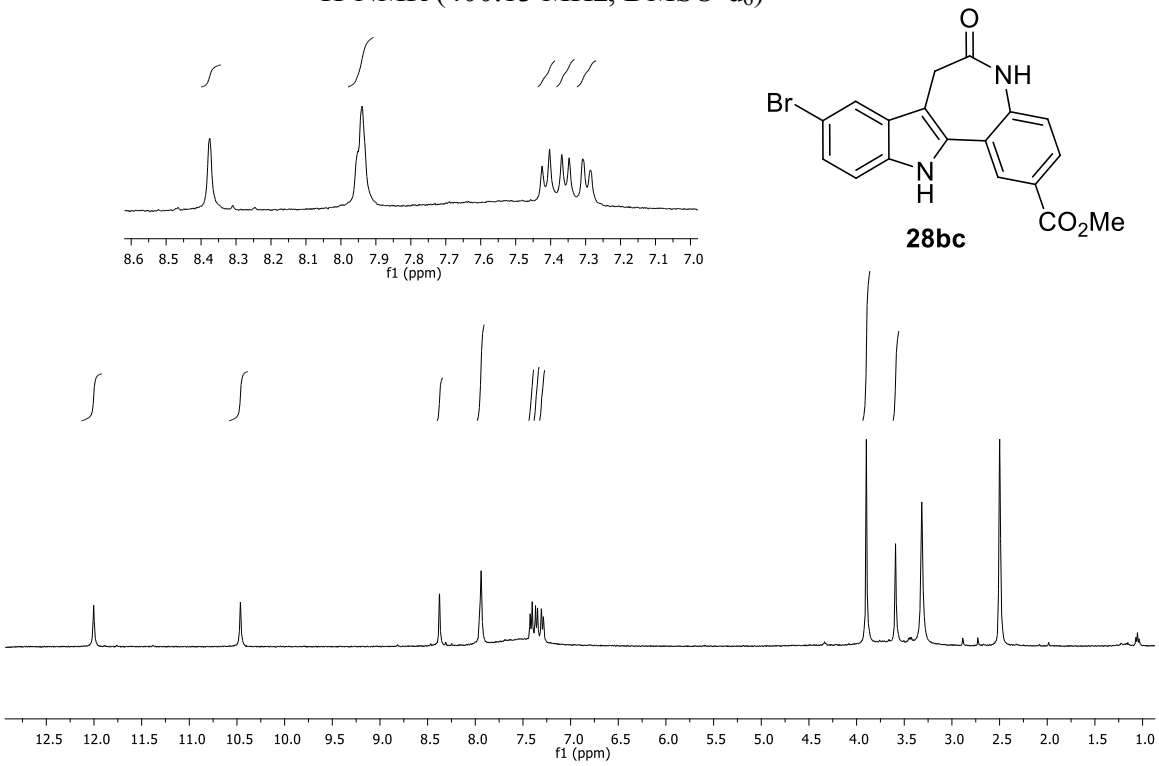


^{13}C-NMR (100.61 MHz, DMSO-d_6)

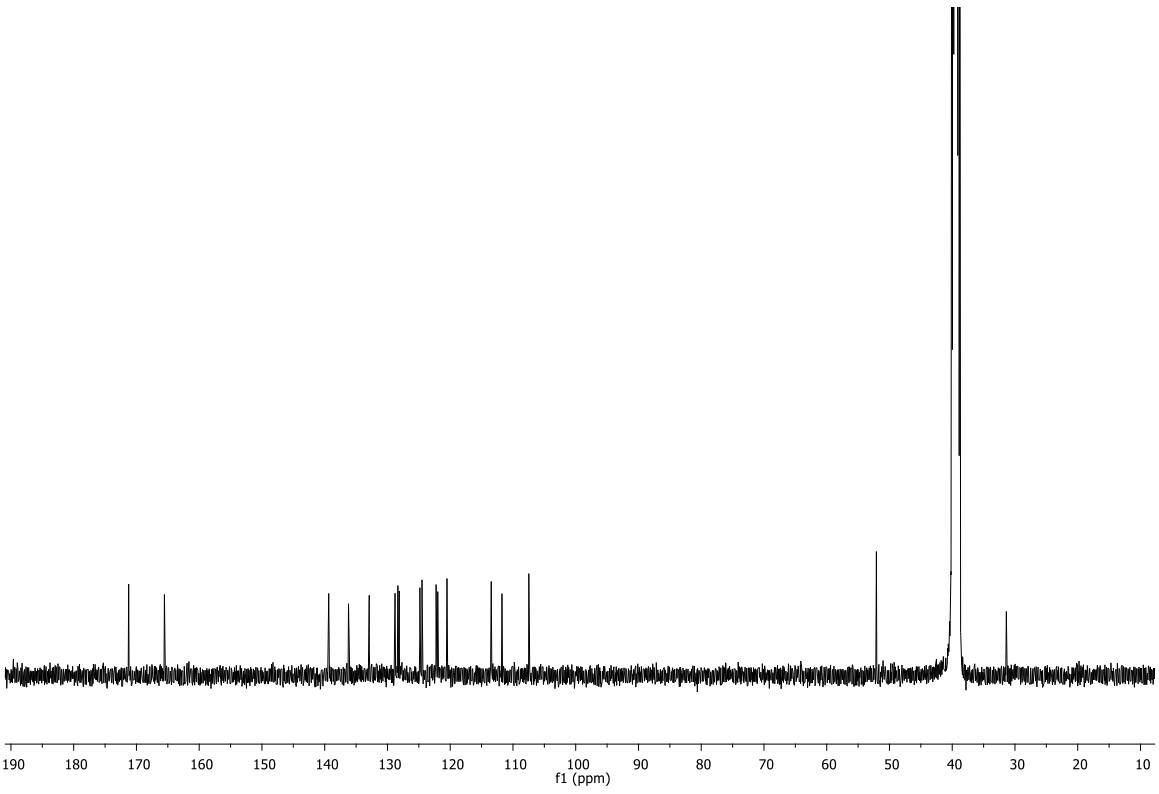


Methyl 9-bromo-6-oxo-5,6,7,12-tetrahydroindolo[3,2-*d*]benzazepin-2-carboxylate 28bc

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

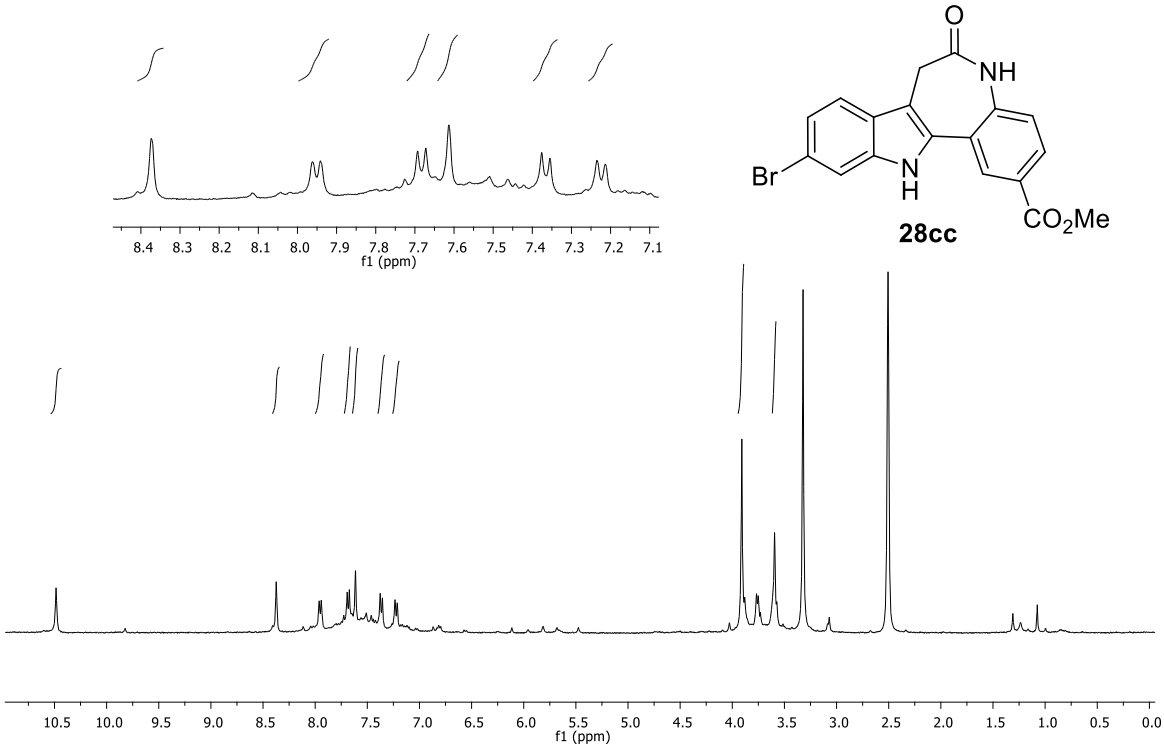


^{13}C-NMR (100.61 MHz, DMSO-d_6)

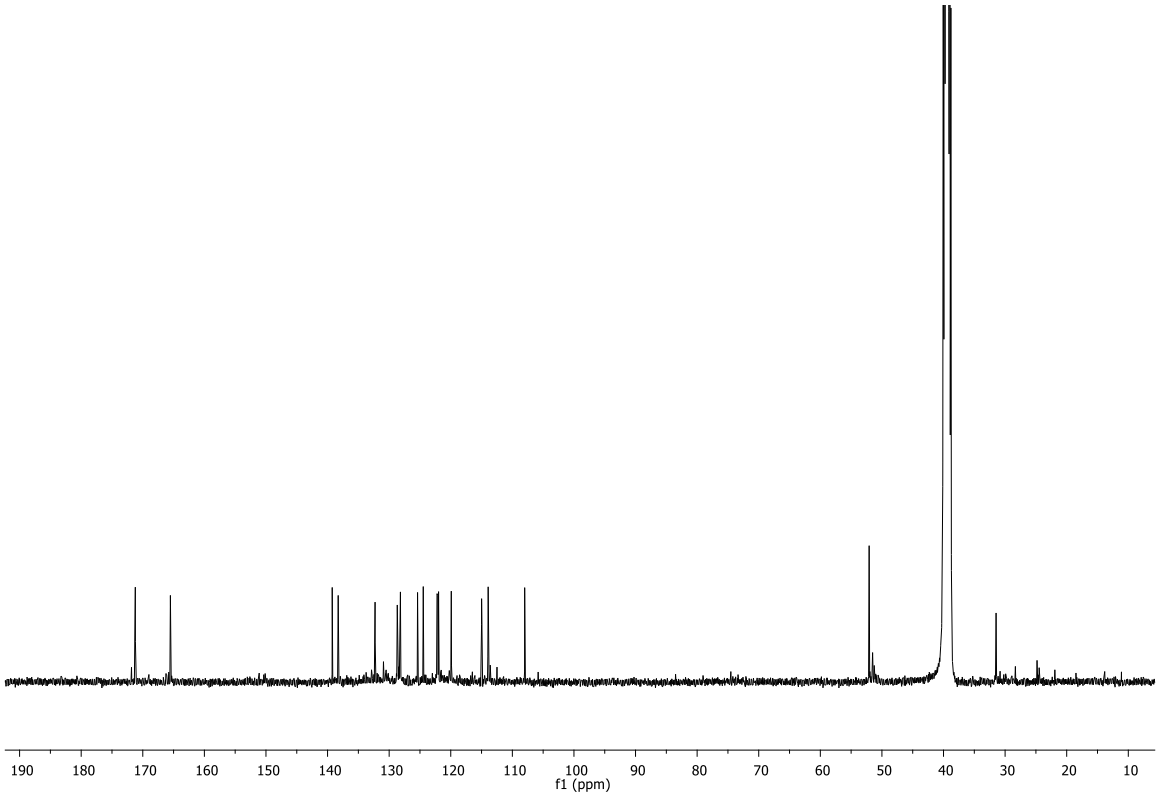


Methyl 10-bromo-6-oxo-5,6,7,12-tetrahydroindolo[3,2-*d*]benzazepin-2-carboxylate 28cc

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

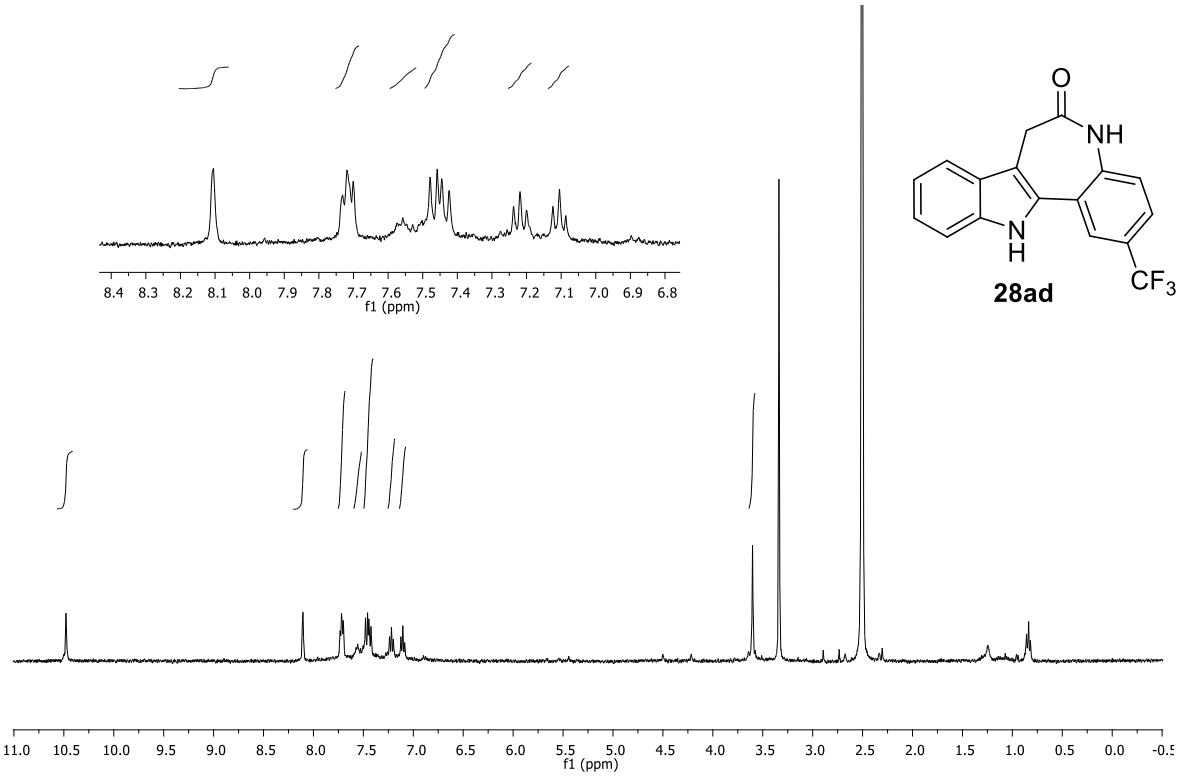


^{13}C-NMR (100.61 MHz, DMSO-d_6)

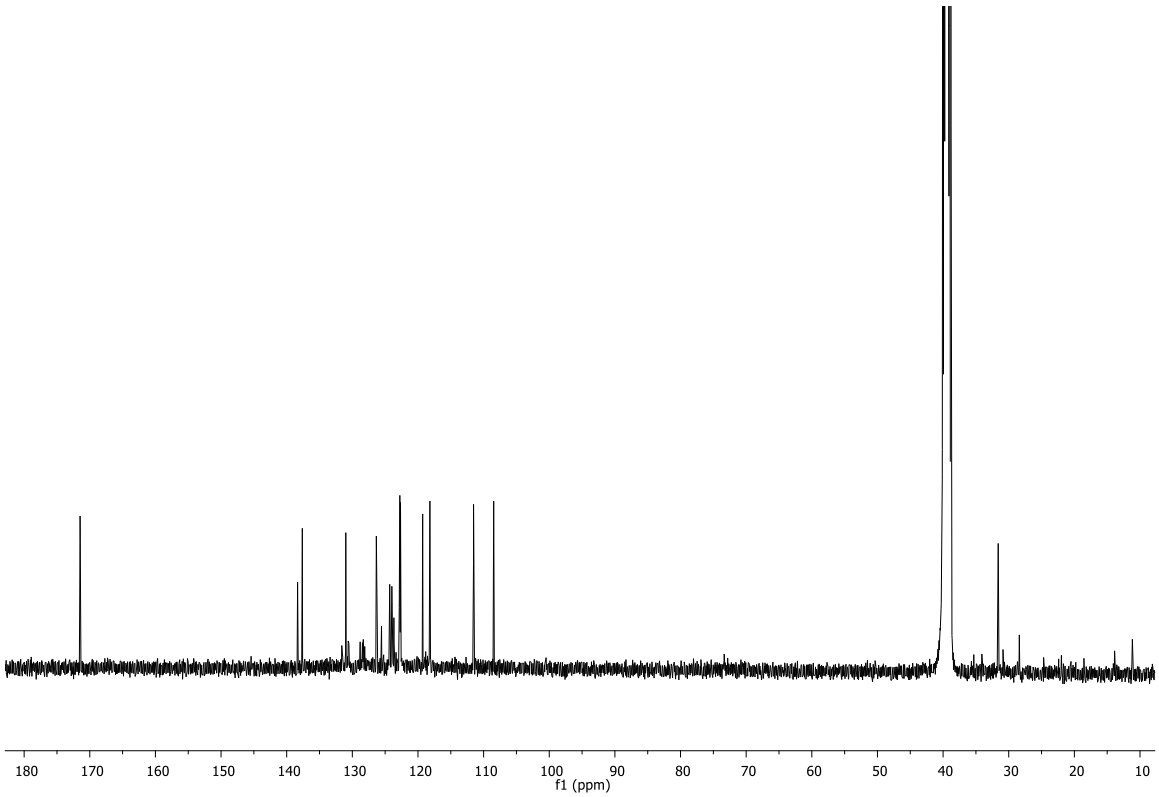


2-(Trifluoromethyl)-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one 28ad

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



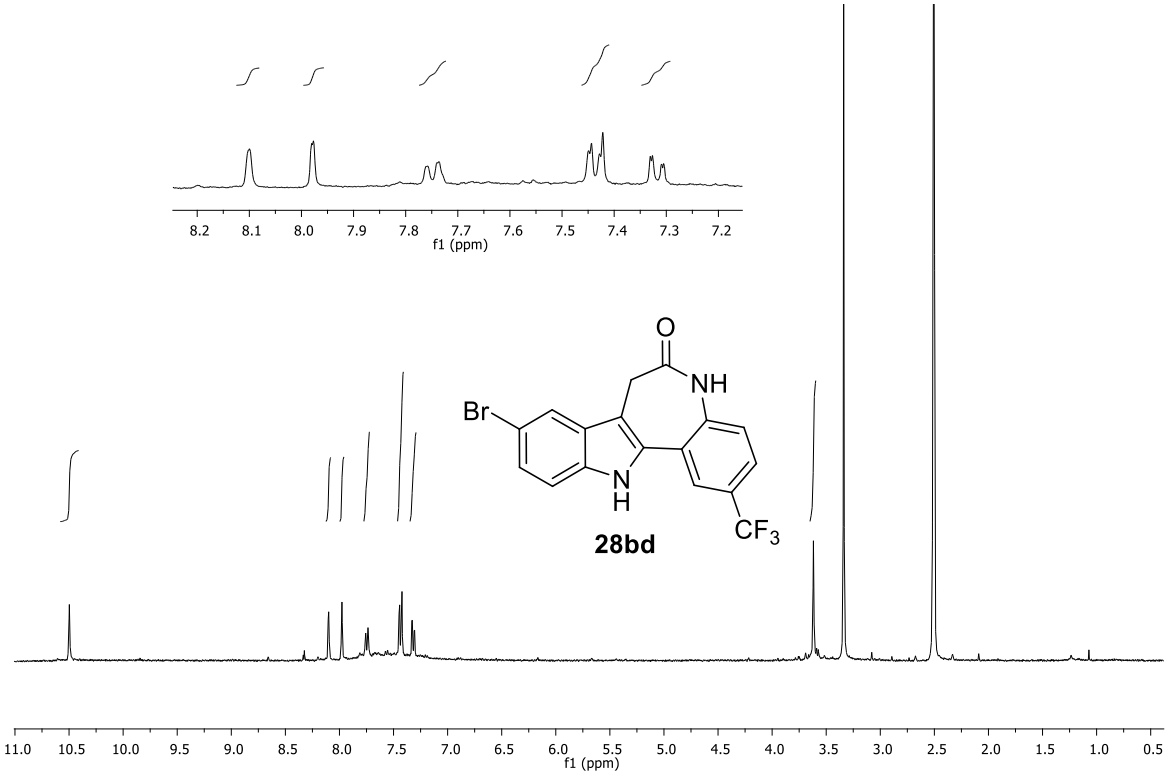
^{13}C-NMR (100.61 MHz, DMSO-d$_6$)



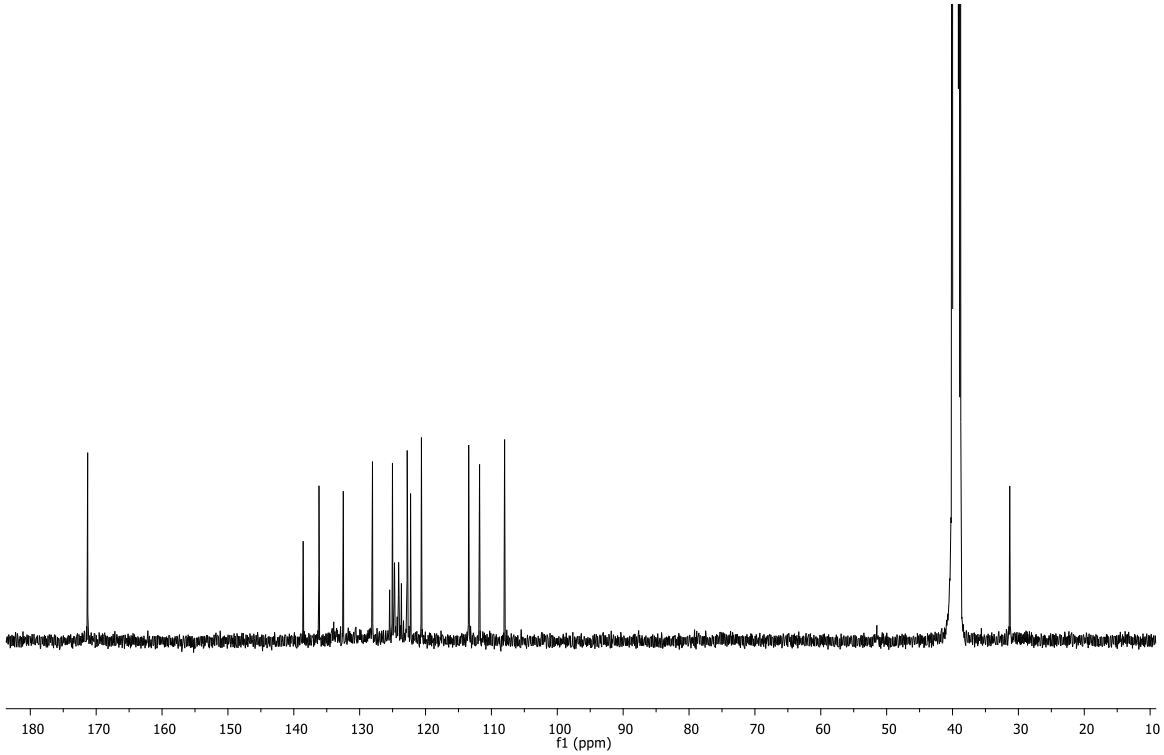
9-Bromo-2-(trifluoromethyl)-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one

28bd

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



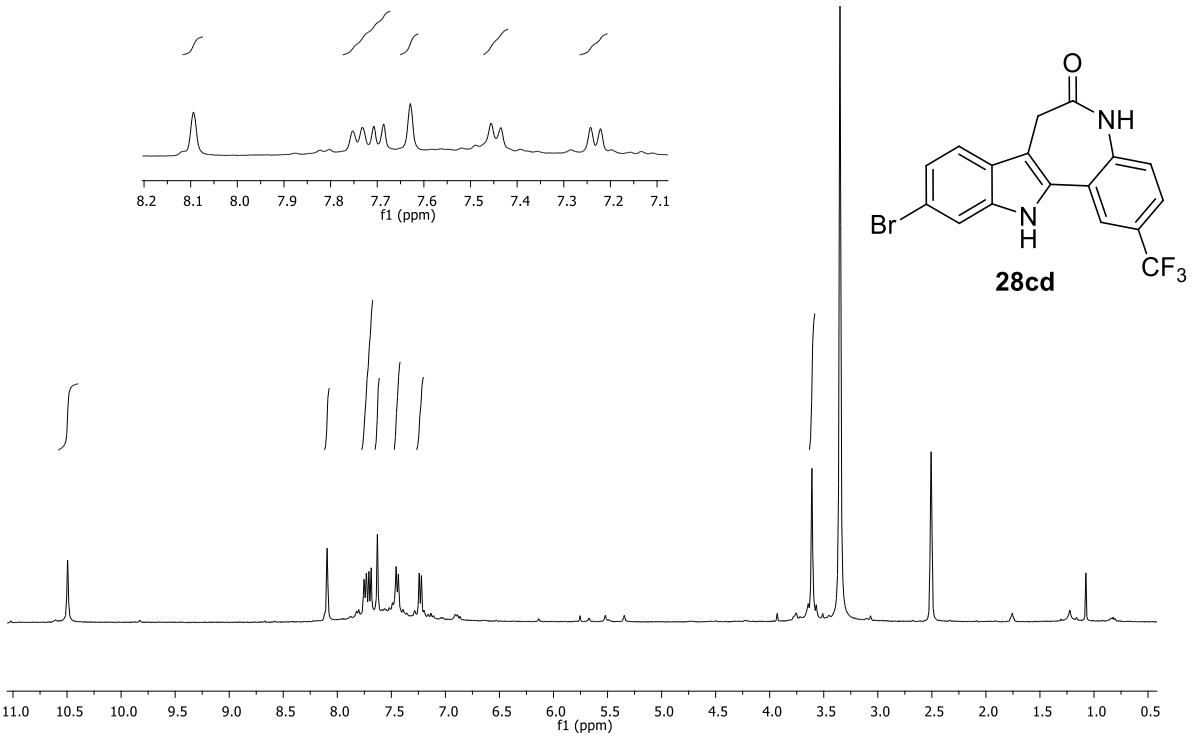
^{13}C-NMR (100.61 MHz, DMSO-d_6)



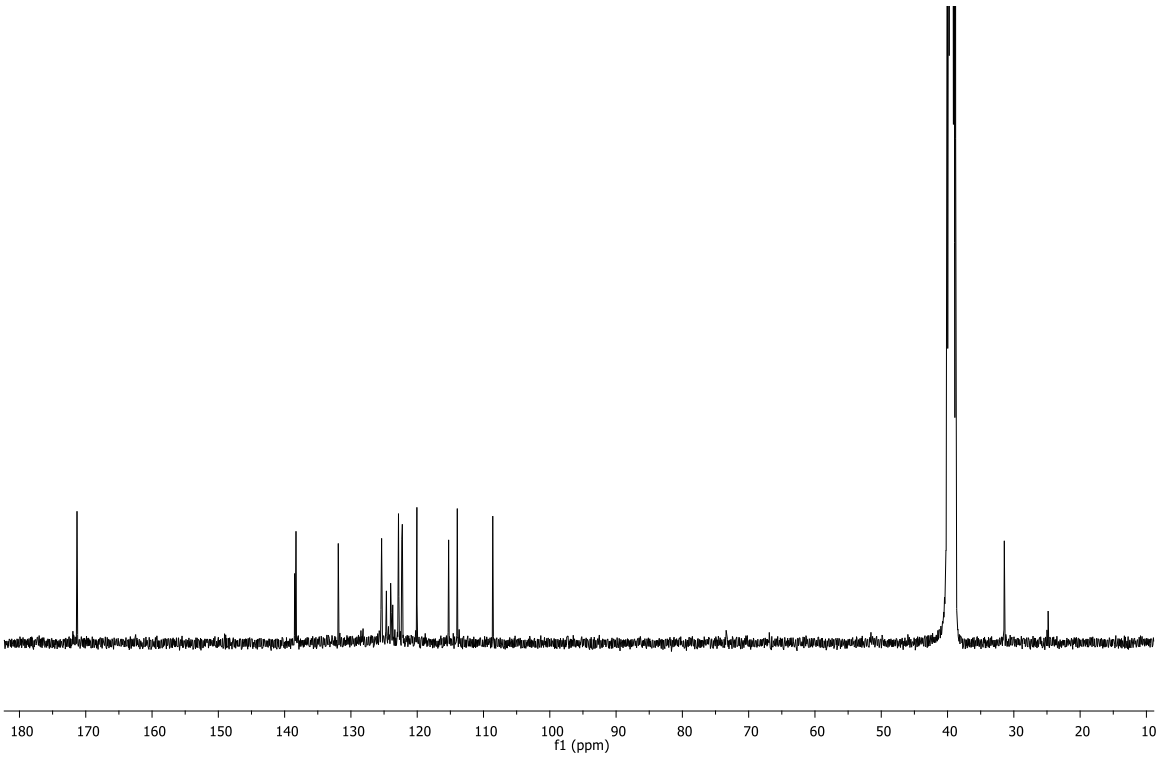
10-Bromo-2-(trifluoromethyl)-7,12-dihydroindolo[3,2-*d*]benzazepin-6-(5*H*)-one

28cd

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



^{13}C-NMR (100.61 MHz, DMSO-d_6)



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