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Synthetic Studies Toward Inducamide C

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SUPPORTING INFORMATION

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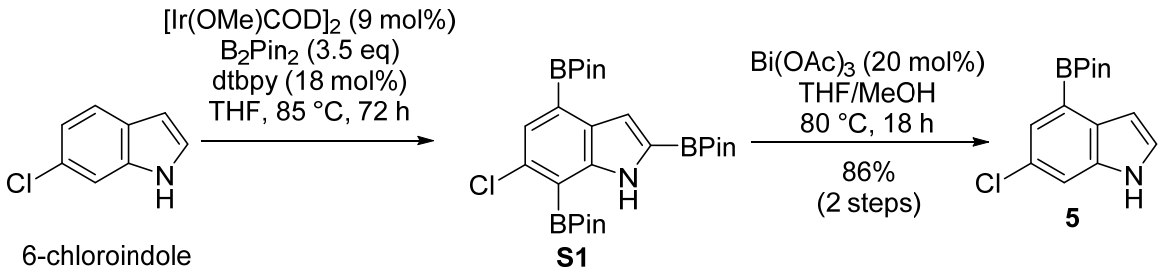
General Details

Unless otherwise noted, all reactions were performed under an atmosphere of dry nitrogen in oven-dried (100 °C) glassware. Commercially available starting materials and reagents were used as received unless otherwise noted. All the solvents used were dried by passage through a column of activated alumina under nitrogen using an LC Technology solvent purification system. Thin layer chromatography (TLC) was performed using F254 0.2 mm silica plates, followed by visualisation with UV irradiation at 254 nm, and staining with ethanolic vanillin or potassium permanganate solution. Flash column chromatography was performed using 63−100 μm silica gel. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded with an FT-IR spectrometer using a diamond ATR sampling accessory. NMR spectra were recorded at ambient temperature in $CDCl_3$, $(CD_3)_2SO$ or $(CD_3)_2CO$ solutions using a spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. All chemical shifts are reported in ppm on the δ scale and were measured relative to the protium solvent in which the sample was analysed: $CDCl_3$ (δ 7.26 ppm for ^1H NMR and δ 77.2 ppm for ^{13}C NMR), $(CD_3)_2SO$ (δ 2.50 ppm for ^1H NMR and δ 39.5 ppm for ^{13}C NMR) or $(CD_3)_2CO$ (δ 2.05 ppm for ^1H NMR and δ 29.8 ppm for ^{13}C NMR) with relative integral. Coupling constants, *J*, are reported in Hertz [Hz] where applicable. Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "q" (quartet), "m" (multiplet), "br" (broad or combination thereof). Where distinguishable from those due to a major isomer/diastereomer or rotamer, resonances due to the minor isomer, diastereomer and rotamer are denoted by an asterisk (*). High-resolution mass spectra were recorded on a microTOF QII (electrospray ionisation, ESI) mass spectrometer.

6-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-indole (5)

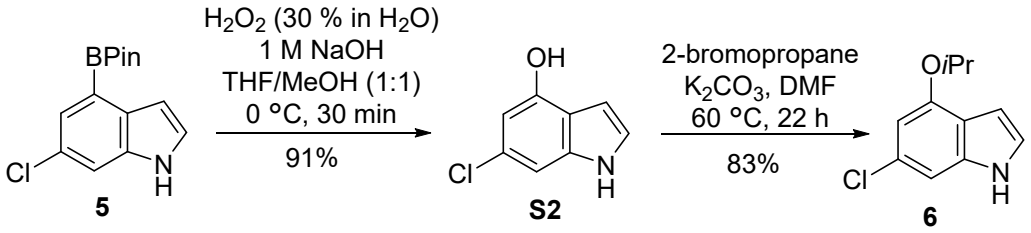


In a sealed tube, a solution of 6-chloroindole (200 mg, 1.32 mmol, 1 equiv.), bis(pinacolato)diboron (B_2Pin_2) (1.17 g, 4.62 mmol, 3.5 equiv.), $[Ir(OMe)COD]_2$ (79 mg, 0.12 mmol, 9 mol%) and 4,4-di-*tert*-butyl bipyridine (dtbpy) (64 mg, 0.24 mmol, 18 mol%) in THF (5 mL) was heated to 85 °C for 72 h. The resulting mixture was cooled to room temperature, quenched carefully with a few drops of methanol and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (9:1) to afford **S1** (608 mg, 1.15 mmol, 87%) as a colorless solid. M.p. 289.3 − 290.5 °C; HRMS [ESI, $(M + Na)^+$] found 552.2630, $[C_{26}H_{39}B_3{}^{35}ClNO_6 + Na]^+$ requires 552.2652; ν_{max}/cm^{-1} (neat): 3441, 2980, 1593, 1538, 1495, 1371, 1266, 1130, 972, 856, 700, 669; δ_H (400 MHz, $CDCl_3$) 9.63 (1 H, br, NH), 7.56 (1 H, s, ArH), 7.48 (1 H, d, *J* 2.2, ArH), 1.42 (12 H, s, 4 × Me), 1.36 (24 H, s, 8 × Me); δ_C (100 MHz, $CDCl_3$) 143.9 (C), 136.5 (C), 130.4 (C), 129.4 (CH), 115.2 (CH), 84.3 (2 × C of BPin), 84.2 (2 × C of BPin), 84.0 (2 × C of BPin), 25.21 (4 × Me of Bpin), 25.17 (4 × Me of BPin), 25.1 (4 × Me of BPin), 3 × C not observed.

In a sealed tube a solution of **S1** (608 mg, 1.15 mmol, 1 equiv.) and bismuth acetate (89 mg, 0.23 mmol, 20 mol%) in THF (2 mL) and methanol (5 mL) was heated at 80 °C for 18 h. The resulting mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether

(1:9) to afford the *title compound* (272 mg, 0.98 mmol, 85% over two steps) as a colorless solid. M.p. 138.7 − 141.3 °C; HRMS [ESI, $(M + Na)^+$] found 300.0928, $[C_{14}H_{17}B^{35}ClNO_2 + Na]^+$ requires 300.0936; ν_{max}/cm^{-1} (neat): 3438, 3324, 2979, 1599, 1575, 1371, 1134, 846, 780, 680; δ_H (400 MHz, $CDCl_3$) 8.13 (1 H, br, NH), 7.58 (1 H, d, *J* 1.9, CH), 7.45 (1 H, dd, *J* 1.9, 1.0, CH), 7.22 (1 H, dd, *J* 3.2, 2.4, CH), 6.99 (1 H, ddd, *J* 3.1, 2.1, 1.0, CH), 1.37 (12 H, s, 4 × Me); δ_C (100 MHz, $CDCl_3$) 135.9 (C), 131.4 (C), 128.1 (CH), 127.8 (C), 125.5 (CH), 113.8 (CH), 105.0 (CH), 84.0 (2 × C of Bpin), 25.2 (4 × Me of BPin), 1 × C not observed.

6-Chloro-4-isopropoxyindole (**6**)

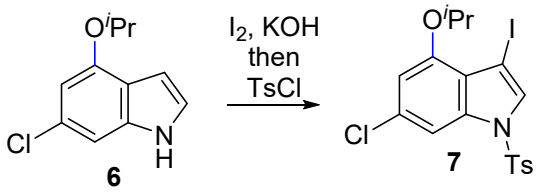


To a stirred solution of 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-indole (**5**) (200 mg, 0.72 mmol, 1 equiv.) in THF (3.0 mL) at 0 °C was added hydrogen peroxide (0.2 mL, 30% in H_2O) and sodium hydroxide (0.2 mL, 1 M). The resulting mixture was stirred at 0 °C for 10 min before being diluted with ethyl acetate (25 mL). The organic layer was separated, and the aqueous phase was further extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered and then concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:4) to afford **S2** (110 mg, 0.66 mmol, 91%) as a light brown solid. M.p. 113.2 − 116.4 °C; HRMS [ESI, $(M - H)^+$] found 166.0067, $[C_8H_6{}^{35}ClNO - H]^+$ requires 166.0065; ν_{max}/cm^{-1} (neat): 3510, 3329, 2920, 1624, 1581, 1456, 1405, 1353, 1248, 864, 762; δ_H (400 MHz,

$CDCl_3$) 8.14 (1 H, br, NH), 7.10 (1 H, dd, *J* 3.3, 2.4, ArH), 6.99 (1 H, dd, *J* 1.6, 1.0, ArH), 6.55 (1 H, ddd, *J* 3.3, 2.4, 1.0, ArH), 6.53 (1 H, d, *J* 1.5, ArH), 5.16 (1 H, br, OH); δ_C (100 MHz, $CDCl_3$) 149.3 (C), 137.7 (C), 128.4 (C), 123.7 (CH), 116.5 (C), 105.8 (CH), 104.6 (CH), 99.3 (CH).

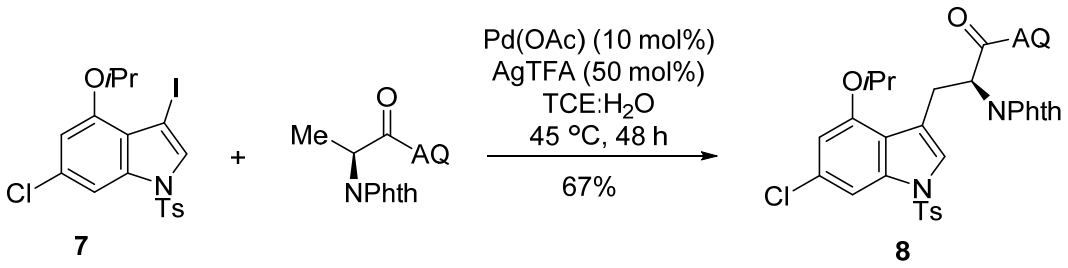
In a sealed tube, a solution of 6-chloro-4-hydroxyindole (**S2**) (110 mg, 0.66 mmol, 1 equiv.), potassium carbonate (274 mg, 1.98 mmol, 3 equiv.) and 2-bromopropane (0.12 mL, 1.32 mmol, 2 equiv.) in DMF (5 mL) was heated at 60 °C for 22 h. The resulting mixture was cooled to room temperature and poured into a saturated solution of ammonium chloride (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 30 mL), the combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:4) to afford the *title compound* (115 mg, 0.55 mmol, 83%) as a colorless solid. M.p. 69.7 − 70.9 °C; HRMS [ESI, $(M)^+$] found 209.0603, $[C_{11}H_{12}{}^{35}ClNO]^+$ requires 209.0602; ν_{max}/cm^{-1} (neat): 3402, 2984, 2933, 1610, 1576, 1498, 1396, 1359, 1288, 1137, 1081, 925, 821, 768, 681; δ_H (400 MHz, $CDCl_3$) 8.06 (1 H, br, NH), 7.06 (1 H, dd, *J* 3.2, 2.3, ArH), 6.98 (1 H, dd, *J* 1.5, 1.0, ArH), 6.59 (1 H, ddd, *J* 3.2, 2.3, 1.0, ArH), 6.51 (1 H, d, *J* 1.7, ArH), 4.65 (1 H, m, CH), 1.39 (6 H, d, *J* 6.0, 2 × Me); δ_C (100 MHz, $CDCl_3$) 152.0 (C), 137.3 (C), 128.5 (C), 123.0 (CH), 118.6 (C), 104.3 (CH), 104.0 (CH), 100.7 (CH), 70.8 (CH), 22.4 (2 × Me).

6-Chloro-3-iodo-4-isopropoxy-1-tosylindole (7)



To a stirred solution of 6-chloro-4-isopropoxyindole (**6**) (125 mg, 0.60 mmol, 1 equiv.) and freshly ground sodium hydroxide (72 mg, 1.79 mmol, 3.0 equiv.) in DMF (3 mL) was added a solution of iodine (167 mg, 0.66 mmol, 1.1 equiv.) in DMF (2 mL). The resulting mixture was stirred at room temperature for 30 min. Sodium hydroxide (72 mg, 1.79 mmol, 2.5 equiv.) was then again added, followed by addition *p*-toluensulfonyl chloride (341 mg, 1.79 mmol, 3.0 equiv.) and the resulting mixture was stirred at room temperature for 20 h before poured into sat. solution of sodium thiosulfate (5 mL) and then diluted with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate (4:1) to afford the *title compound* (265 mg, 0.54 mmol, 91%) as a white foam. M.p. 53.6 − 55.7 °C; HRMS [ESI, $(M + Na)^+$] found 511.9539, $[C_{18}H_{17}I^{35}ClNO_3S + Na]^+$ requires 511.9555; ν_{max}/cm^{-1} (neat): 3136, 2977, 2924, 2544, 2162, 1980, 1733, 1595, 1572, 1493, 1469, 1371, 1238, 1188, 997, 934, 899, 709, 664; δ_H (400 MHz, $CDCl_3$) 7.74 (2 H, m, 2 × ArH), 7.55 (1 H, d, *J* 1.6, ArH), 7.52 (1 H, s, ArH), 7.25 (2 H, m, 2 × ArH), 6.61 (1 H, d, *J* 1.3, ArH), 4.59 (1 H, hept, *J* 6.0, CH), 2.35 (3 H, s, Me), 1.38 (6 H, d, *J* 6.0, 2 × Me); δ_C (100 MHz, $CDCl_3$) 152.1 (C), 145.8 (C), 136.2 (C), 134.9 (C), 132.2 (C), 130.4 (2 × CH), 130.0 (CH), 127.2 (2 × CH), 119.3 (C), 107.7 (CH), 106.1 (CH), 71.7 (CH), 59.7 (CH), 22.1 (2 × Me), 21.9 (Me).

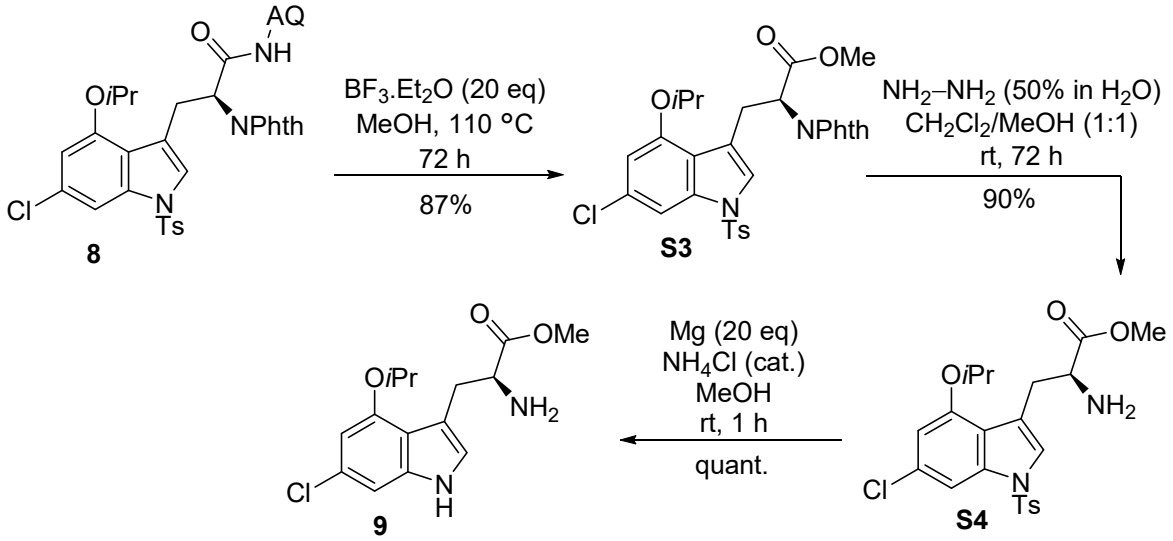
(*S*)-3-(6-Chloro-4-isopropoxy-1-tosylindol-3-yl)-2-(1,3-dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-propenamide (8)



A suspension of 6-chloro-3-iodo-4-isopropoxy-1-tosylindole (**7**) (100 mg, 0.20 mmol, 1.0 equiv.), *N*-phthaloyl-L-alanine-8-aminoquinoline amide[1] (77.5 mg, 0.22 mmol, 1.1 equiv.), palladium acetate (4.6 mg, 0.020 mmol, 10 mol%) and silver trifluoroacetate (22.5 mg, 0.10 mmol, 50 mol%) in 1,1,2,2-tetrachloroethane (1 mL) and water (2 mL) was stirred **vigorously** at 45 °C for 48 h then poured into a separation funnel containing aqueous sodium hydroxide solution (1 M, 5 mL), water (20 mL) and dichloromethane (25 mL). The organic layer was separated, and the aqueous layer was further extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with dichloromethane-ethyl acetate (99:1) to afford the *title compound* (97 mg, 0.14 mmol, 67%) as a colorless solid. M.p. 253.5 − 256.7 °C; $[\alpha]_D^{20}$ −62.5° (*c* 0.2, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 729.1551, $[C_{38}H_{31}{}^{35}ClN_4O_6S + Na]^+$ requires 729.1545; ν_{max}/cm^{-1} (neat): 3317, 3106, 2930, 2160, 1778, 1717, 1690, 1596, 1529, 1486, 1370, 1329, 1268, 1187, 951, 879, 793, 717, 668; δ_H (400 MHz, $CDCl_3$) 10.29 (1 H, s, NH), 8.72 (1 H, dd, *J* 5.1, 3.9, ArH), 8.61 (1 H, dd, *J* 4.2, 1.7, ArH), 8.12 (1 H, dd, *J* 8.3, 1.7, ArH), 7.82 (2 H, m, 2 × ArH), 7.74 (2 H, m, 2 × ArH), 7.51 (1 H, d, *J* 1.5, ArH), 7.48 (4 H, m, 4 × ArH), 7.39 (1 H, dd, *J* 8.3, 4.2, ArH), 7.22 (1 H, s, ArH), 6.89 (2 H, d, *J* 8.6, 2 × ArH), 6.64 (1 H, dd, *J* 1.5, ArH), 5.76 (1 H, dd, *J* 10.7, 5.8, ArH), 4.70 (1 H, m,

CH), 3.98 (1 H, dd, *J* 14.0, 5.8, CH_2), 3.91 (1 H, dd, *J* 14.0, 10.7, CH_2), 2.21 (3 H, s, Me), 1.49 (3 H, d, *J* 6.0, Me), 1.46 (3 H, d, *J* 6.0, Me); δ_C (100 MHz, $CDCl_3$) 168.2 (2 × CO), 166.6 (CO), 152.6 (C), 148.5 (CH), 145.0 (C), 138.7 (C), 138.6 (C), 137.1 (C), 136.5 (CH), 135.0 (C), 134.4 (2 × CH), 134.1 (C), 132.0 (2 × C), 131.8 (C), 129.9 (2 × CH), 128.1 (C), 127.5 (CH), 126.7 (2 × CH), 124.4 (CH), 123.8 (2 × CH), 122.2 (CH), 121.9 (CH), 119.1 (C), 118.0 (C), 117.0 (CH), 106.8 (CH), 106.5 (CH), 71.1 (CH), 55.9 (CH), 26.6 (CH_2), 22.2 (Me), 22.0 (Me), 21.7 (Me).

6-Chloro-4-isopropoxytryptophan methyl ester (9)



In a sealed tube, a solution of **8** (80 mg, 0.11 mmol, 1.0 equiv.) and boron trifluoride diethyl etherate (0.28 mL, 2.26 mmol, 20 equiv.) in methanol (3 mL) was heated at 110 °C for 72 h. The resulting mixture was cooled to room temperature, diluted with dichloromethane (15 mL), and quenched carefully with triethylamine (0.4 mL, 2.83 mmol, 25 equiv.) before being concentrated *in vacuo.* The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-petroleum ether (1:4) to afford **S3** (58 mg, 0.098 mmol, 87%) as a colorless solid. M.p. 182.3 − 183.8 °C; $[\alpha]_D^{21}$ -176.5° (*c* 0.5, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 617.1106, $[C_{30}H_{27}{}^{35}ClN_2O_7S + Na]^+$ requires 617.1120; ν_{max}/cm^{-1} (neat): 2962, 2922, 2159, 1976,

1745, 1716, 1597, 1559, 1469, 1386, 1259, 1176, 1100, 1018, 799, 720, 669; δ_H (400 MHz, acetone-d_6) 7.94 (2 H, m, 2 × ArH), 7.84 (2 H, m, 2 × ArH), 7.57 (2 H, m, 2 × ArH), 7.46 (1 H, d, *J* 1.5, ArH), 7.24 (1 H, d, *J* 1.0, ArH), 7.06 (2 H, m, 2 × ArH), 6.83 (1 H, d, *J* 1.5, ArH), 5.51 (1 H, dd, *J* 11.9, 4.1, CH), 4.88 (1 H, m, CH), 3.80 (1 H, dd, *J* 14.3, 4.1, CH_2), 3.77 (3 H, s, OMe), 3.62 (1 H, dd, *J* 14.3, 11.9, CH_2), 2.30 (3 H, s, Me), 1.47 (3 H, d, *J* 6.0, Me), 1.42 (3 H, d, *J* 6.0, Me); δ_C (100 MHz, acetone-d_6) 170.0 (CO), 168.1 (2 × CO), 153.7 (C), 146.5 (C), 137.7 (C), 135.7 (2 × CH), 135.5 (C), 132.5 (2 × C), 132.1 (C), 131.0 (2 × CH), 127.5 (2 × CH), 125.1 (CH), 124.4 (2 × CH), 120.1 (C), 119.1 (C), 107.6 (CH), 106.8 (CH), 71.7 (CH), 53.4 (CH), 53.2 (OMe), 26.8 (CH_2), 22.2 (Me), 22.0 (Me), 21.6 (Me).

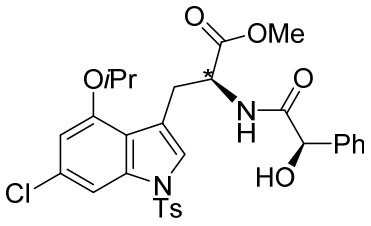
To a stirred solution of **S3** (58 mg, 0.098 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) and methanol (1.5 mL) was added hydrazine hydrate (19 μL, 0.294 mmol, 3 equiv., 50% in H_2O). The resulting mixture was stirred at room temperature for 72 h before being concentrated *in vacuo.* The resulting residue was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (19:1) to afford **S4** (41 mg, 0.088 mmol, 90%) as a colourless oil. $[\alpha]_D^{20}$ −15.3° (*c* 0.9, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 487.1049, $[C_{22}H_{25}{}^{35}ClN_2O_5S + Na]^+$ requires 487.1065; ν_{max}/cm^{-1} (neat): 3382, 3107, 2979, 2928, 1736, 1594, 1557, 1472, 1404, 1372, 1237, 1173, 1110, 1074, 1017, 962, 900, 836, 811, 702, 667; δ_H (400 MHz, acetone-d_6) 7.84 (2 H, m, 2 × ArH), 7.56 (1 H, d, *J* 1.6, ArH), 7.42 (2 H, m, 2 × ArH), 7.23 (1 H, t, *J* 0.8, ArH), 6.80 (1 H, d, *J* 1.6, ArH), 4.81 (1 H, m, CH), 4.48 (1 H, dd, *J* 8.6, 4.6, CH), 3.64 (3 H, s, OMe), 3.48 (1 H, dd, *J* 13.7, 4.6, CH_2), 3.00 (1 H, dd, *J* 13.7, 8.6, CH_2), 2.81 (2 H, d, *J* 13.7, NH_2), 2.39 (3 H, s, Me), 1.38 (3 H, d, *J* 1.9, Me), 1.36 (3 H, d, *J* 1.9, Me); δ_C (100 MHz, acetone-d_6) 172.8 (CO), 153.8 (C), 146.7 (C), 137.7 (C), 136.1 (C), 131.8 (C), 131.2 (2 × CH), 127.8 (2 × CH), 124.9 (CH),

120.5 (C), 120.2 (C), 107.5 (CH), 106.9 (CH), 71.5 (CH), 64.5 (CH), 52.0 (CH), 31.2 (CH_2), 22.12 (Me), 22.07 (Me), 21.5 (Me).

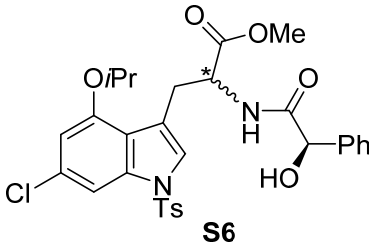
Magnesium powder (43 mg, 1.76 mmol, 20 equiv.) and ammonium chloride (1 drop) were added to methanol (5 mL) at room temperature. After hydrogen gas had evolved, a solution of **S4** (41 mg, 0.088 mmol, 1 equiv.) in methanol (1 mL) was added. The resulting mixture was stirred at room temperature for 1 h before quenched with a sat. solution of ammonium chloride (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers washed with sodium bicarbonate (sat. solution), brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the *title compound* (27 mg, 0.088 mmol, ~100%) as a colourless oil. The resulting residue was used for the next step without further purification. HRMS [ESI, $(M + H)^+$] found 311.1158, $[C_{15}H_{19}{}^{35}ClN_2O_3 + H]^+$ requires 311.1157; δ_H (400 MHz, $CDCl_3$) 7.99 (1 H, s, NH), 6.90 (1 H, d, *J* 1.5, ArH), 6.86 (1 H, d, *J* 2.3, ArH), 6.45 (1 H, d, *J* 1.5, ArH), 4.67 (1 H, m, CH), 3.90 (1 H, dd, *J* 9.3, 4.5, CH), 3.71 (3 H, s, OMe), 3.47 (1 H, dd, *J* 14.0, 4.5, CH_2), 2.79 (1 H, dd, *J* 14.0, 9.3, CH_2), 1.43 (6 H, d, *J* 5.6, 2 × Me).

Calculating the enantiomeric excess of the C(sp^3)-H arylation product

The enantiomeric excess of the tryptophan (-)-**S4** was calculated upon coupling with (*R*)-mandelic acid to give the amide **S5**. The crude ^{1}H NMR of **S5** spectrum was compared to that of the diastereomeric amides **S6** prepared from the racemic tryptophan (±)-**S4**.

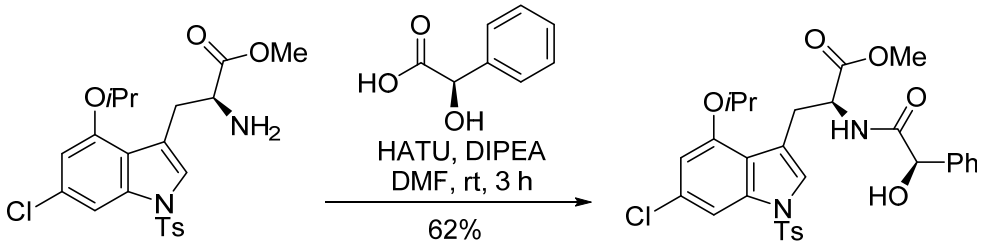


S5
from (-)-S4



S6
from (±)-S4

Methyl (*S*)-3-(6-chloro-4-isopropoxy-1-tosylindol-3-yl)-2-((*R*)-2-hydroxy-2 phenylacetamido)-propanoate (S5)



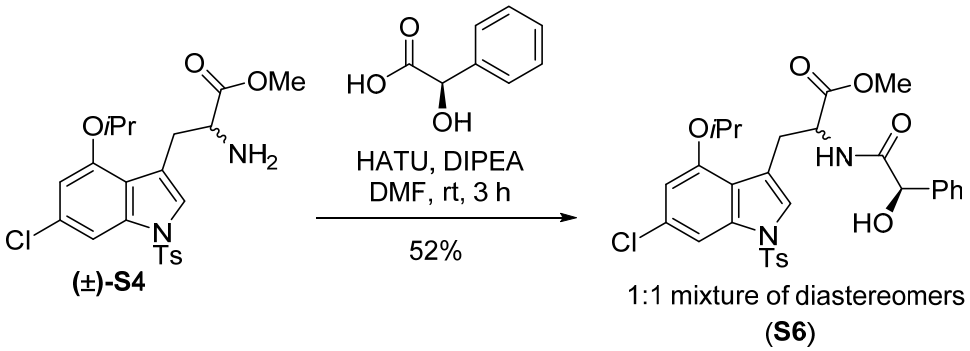
(–)-S4

enantioenriched
(**S5**)

To a stirred solution of (*R*)-mandelic acid (5.0 mg, 0.032 mmol, 1.0 equiv.) and HATU (15.0 mg, 0.034 mmol, 1.2 equiv.) in *N,N*-dimethylformamide (2 mL) was added *N,N*-diisopropylethylamine (16.0 μL, 0.092 mmol, 2.8 equiv.). After stirring for 10 min, a solution of tryptophan (-)-**S4** (15.0 mg, 0.032 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (3 mL) was added. The resulting mixture was stirred at room temperature for 30 min then poured onto water (25 mL). The aqueous phase was extracted with ethyl ether (3 × 25 mL) and the combined organic layers washed with water, brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (19:1) to afford the *title compound* (12 mg, 0.020 mmol, 62%), as a colourless solid. M.p. 54.6 − 57.3 °C; $[\alpha]_D^{20}$ −26.4° (*c* 0.5, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 621.1457, $[C_{30}H_{31}{}^{35}ClN_2O_7S + Na]^+$ requires 621.1433; ν_{max}/cm^{-1} (neat): 3388, 2924, 2852, 1742, 1662, 1596, 1558, 1520, 1473, 1405, 1365, 1239, 1173, 1115, 1089, 969, 901, 840, 813, 701, 667; δ_H (400 MHz, acetone-d_6) 7.85

(2 H, m, 2 × ArH), 7.79 (1 H, d, *J* 8.4, NH), 7.51 (2 H, d, *J* 1.6, 2 × ArH), 7.40 (4 H, m, 4 × ArH), 7.27 (3 H, m, 3 × ArH), 6.79 (1 H, d, *J* 1.6, ArH), 5.21 (1 H, d, *J* 4.5, OH), 4.87 (2 H, m, 2 × CH), 4.80 (1 H, m, CH), 3.63 (3 H, s, OMe), 3.47 (1 H, dd, *J* 14.0, 4.8, CH_2), 3.19 (1 H, dd, *J* 14.0, 10.4, CH_2), 2.37 (3 H, s, Me), 1.41 (3 H, d, *J* 6.0, Me), 1.38 (3 H, d, *J* 6.0, Me); δ_C (100 MHz, acetone-d_6) 172.9 (CO), 172.7 (CO), 153.8 (C), 146.7 (C), 141.2 (C), 137.7 (C), 135.9 (C), 131.8 (C), 131.2 (2 × CH), 129.0 (2 × CH), 128.6 (CH), 128.0 (2 × CH), 127.9 (2 × CH), 125.4 (CH), 120.4 (C), 119.3 (C), 107.5 (CH), 106.8 (CH), 74.9 (CH), 71.7 (CH), 53.5 (CH), 52.3 (CH), 29.4 (CH_2), 22.1 (Me), 22.0 (Me), 21.6 (Me).

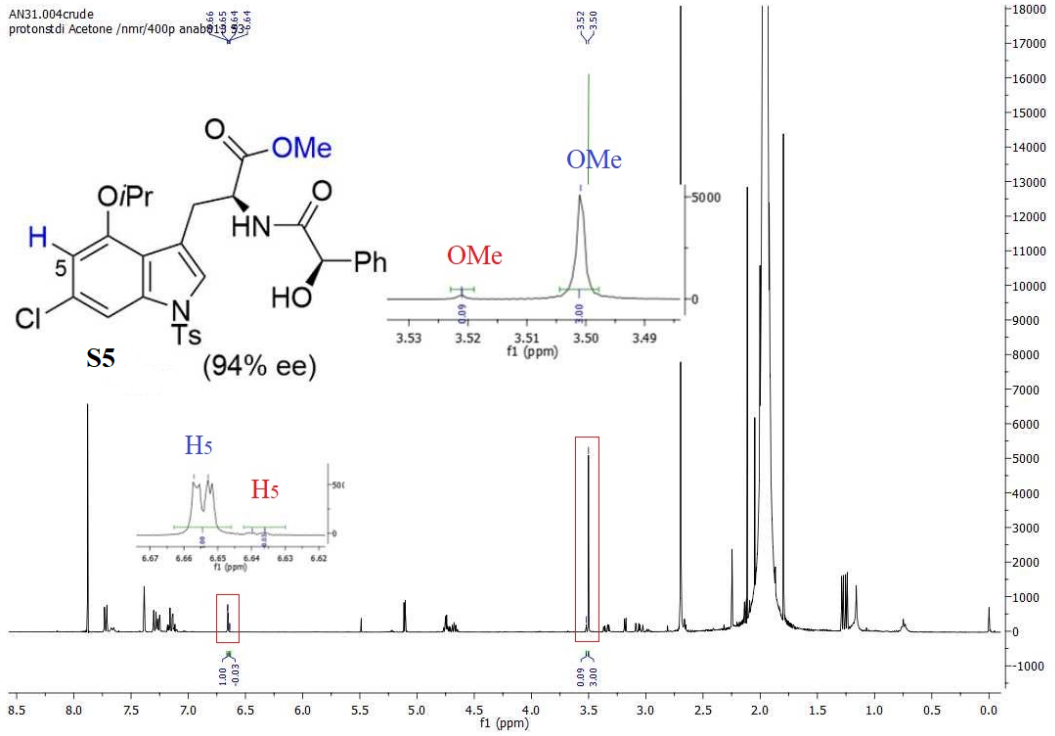
Methyl 3-(6-chloro-4-isopropoxy-1-tosylindol-3-yl)-2-((*R*)-2-hydroxy-2-phenylacetamido)-propanoate (S6)

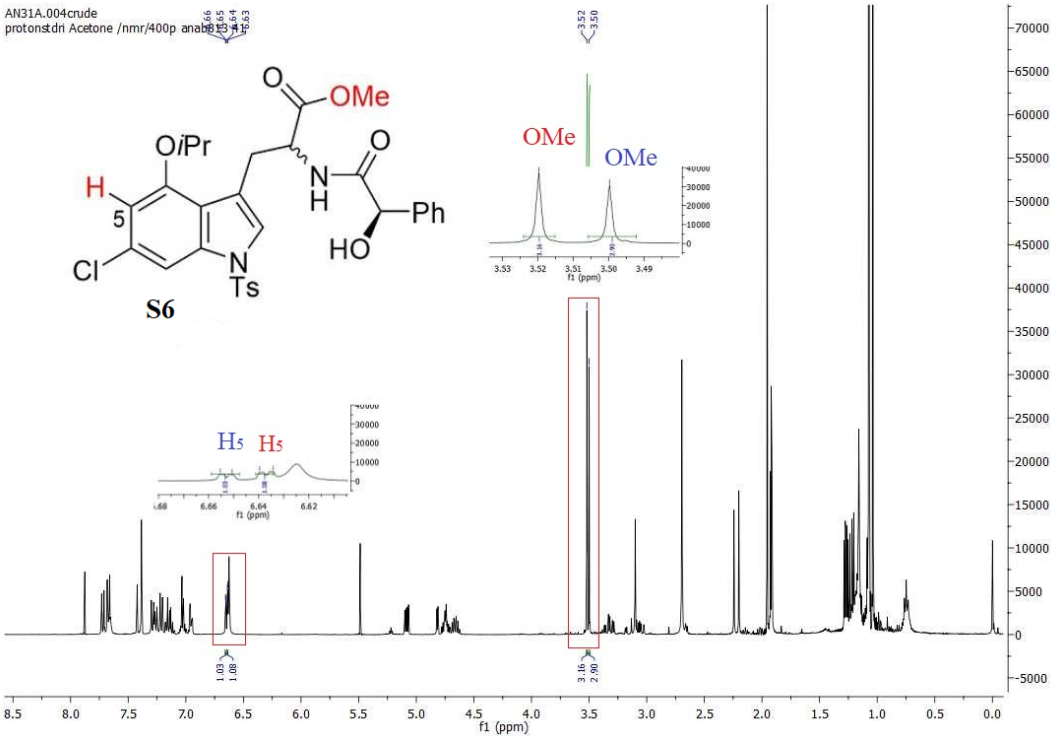


To a stirred solution of (*R*)-mandelic acid (6.5 mg, 0.043 mmol, 1.0 equiv.) and HATU (20 mg, 0.052 mmol, 1.2 equiv.) in *N,N*-dimethylformamide (2 mL) was added *N,N*-diisopropylethylamine (21 µL, 0.12 mmol, 2.8 equiv.). After stirring for 10 min, a solution of tryptophan (±)-**S4** (20 mg, 0.043 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (3 mL) was added. The resulting mixture was stirred at room temperature for 2 h then poured onto water (30 mL). The aqueous phase was extracted with ethyl ether (3 × 30 mL) and the combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was

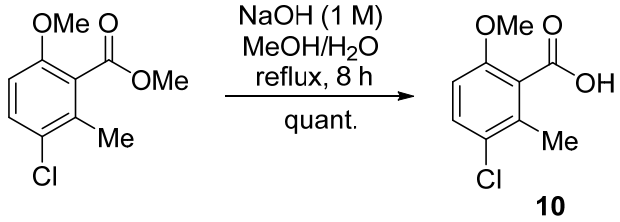
purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (19:1) to afford the *title compound* (13.5 mg, 0.022 mmol, 52%), as a colourless solid.

A comparison of the crude ^{1}H NMR spectra of amides **S5** and **S6** showed that the enantioenriched compound **S5** had an enantiomeric excess of 94 %



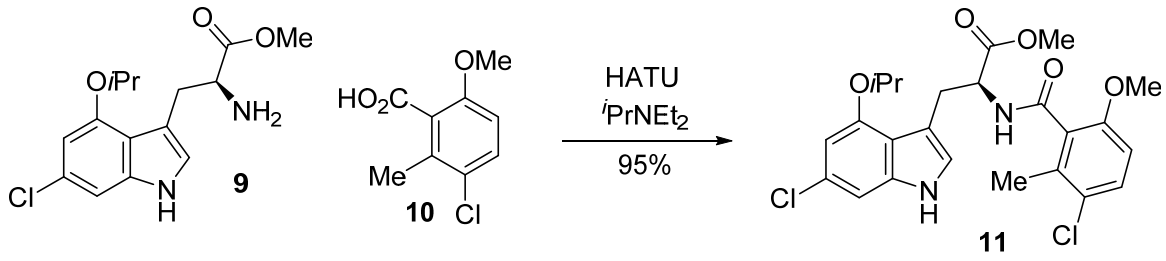


3-Chloro-6-methoxy-2-methylbenzoic acid (10)



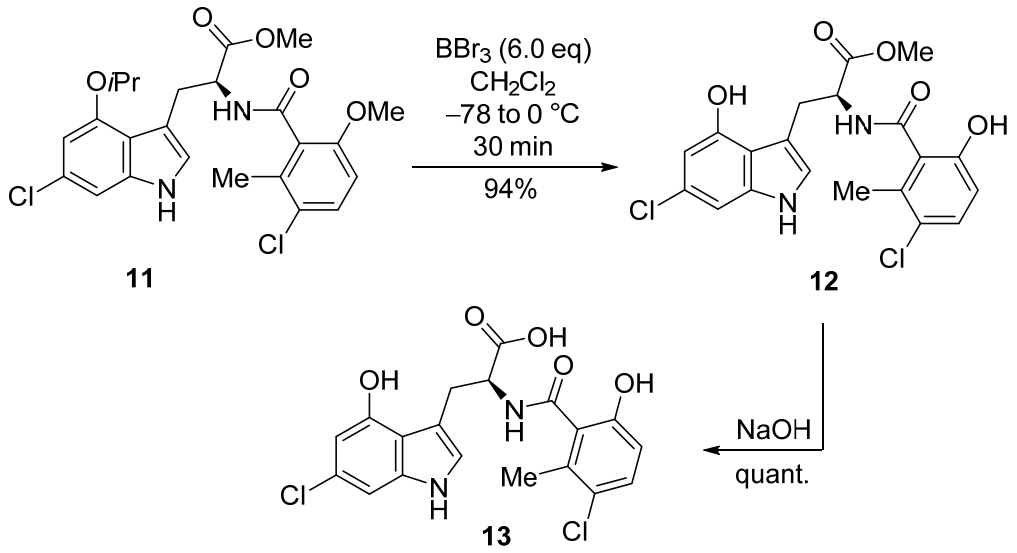
To a stirred solution of methyl-3-chloro-6-methoxy-2-methylbenzoate[2] (50 mg, 0.23 mmol, 1 equiv.) in methanol (3 mL) was added 1 M sodium hydroxide (3.03 mL, 3.029 mmol, 13 equiv.). The resulting mixture was heated at reflux for 8 h then cooled to room temperature. The reaction mixture was washed with ethyl acetate (10 mL) and the extracted organic layer discarded. The aqueous layer was acidified to pH 2 with 1 M HCl (10 mL) and extracted with ethyl ether (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the *title compound* (46 mg, 0.023 mmol, ~100%) as a colourless solid. M.p. 153.6 − 156.4 °C; HRMS [ESI, $(M + Na)^+$] found 223.0134, $[C_9H_9{}^{35}ClO_3 + Na]^+$ requires 223.0132; ν_{max}/cm^{-1} (neat): 2974, 2918, 2843, 1689, 1583, 1464, 1431, 1267, 1085, 899, 802, 657; δ_H (400 MHz, acetone-d_6) 7.39 (1 H, d, *J* 8.9, ArH), 6.96 (1 H, dd, *J* 8.9, ArH), 3.83 (3 H, s, OMe), 2.31 (3 H, s, Me), OH not observed; δ_C (100 MHz, acetone-d_6) 168.2 (CO), 155.9 (C), 133.9 (C), 131.0 (CH), 127.8 (C), 126.6 (C), 111.4 (CH), 56.6 (OMe), 17.3 (Me).

Methyl-(*S*)-3-(6-chloro-4-isopropoxyindol-3-yl)-2-(3-chloro-6-methoxy-2-methylbenzamido)-propanoate (11)



To a stirred solution of 3-chloro-6-methoxy-2-methylbenzoic acid (**10**)[2] (53 mg, 0.27 mmol, 1.5 equiv.) and HATU (121 mg, 0.32 mmol, 1.8 equiv.) in *N,N*-dimethylformamide (3 mL) was added *N,N*-diisopropylethylamine (56 µL, 0.32 mmol, 1.8 equiv.). After stirring for 10 min, a solution of the crude tryptophan **9** (55 mg, 0.18 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (3 mL) was added. The resulting mixture was stirred at room temperature for 30 min before poured into water (25 mL). The aqueous phase was extracted with ethyl ether (3 × 25 mL); the combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with dichloromethane-methanol (19:1) to give the *title compound* (83 mg, 0.17 mmol, 95%) as a colourless solid. M.p. 95.3 − 99.6 °C; $[\alpha]_D^{23}$ +62.3° (*c* 0.4, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 515.1100, $[C_{24}H_{26}{}^{35}Cl_2N_2O_5 + Na]^+$ requires 515.1111; ν_{max}/cm^{-1} (neat): 3311, 2920, 2850, 1743, 1647, 1578, 1495, 1434, 1365, 1266, 1211, 1081, 928, 883, 803, 729, 661; δ_H (400 MHz, acetone-d_6) 10.20 (1 H, s, NH), 7.62 (1 H, d, *J* 7.3, NH), 7.29 (1 H, d, *J* 8.8, ArH), 7.15 (1 H, d, *J* 2.4, ArH), 7.02 (1 H, d, *J* 1.6, ArH), 6.81 (1 H, d, *J* 8.8, ArH), 6.50 (1 H, d, *J* 1.6, ArH), 4.91 (1 H, ddd, *J* 10.4, 7.3, 5.0, CH), 4.74 (1 H, hept, *J* 6.0, CH), 3.72 (3 H, s, OMe), 3.52 (3 H, s, OMe), 3.48 (1 H, dd, *J* 14.0, 5.0, CH_2), 3.20 (1 H, dd, *J* 14.0, 10.4, CH_2), 2.10 (3 H, s, Me), 1.42 (3 H, d, *J* 6.0, Me), 1.33 (3 H, d, *J* 6.0, Me); δ_C (100 MHz, acetone-d_6) 173.4 (CO), 166.9 (CO), 156.0 (C), 153.4 (C), 139.4 (C), 135.1 (C), 130.5 (CH), 130.2 (C), 128.2 (C), 126.6 (C), 124.6 (CH), 117.8 (C), 112.0 (C), 111.1 (CH), 105.3 (CH), 102.9 (CH), 71.0 (CH), 56.1 (OMe), 55.6 (CH), 52.1 (OMe), 29.4 (CH_2), 22.3 (Me), 22.1 (Me), 16.8 (Me).

(*S*)-3-(6-Chloro-4-hydroxyindol-3-yl)-2-(3-chloro-6-hydroxy-2-methylbenzamido)propanoic acid (13)

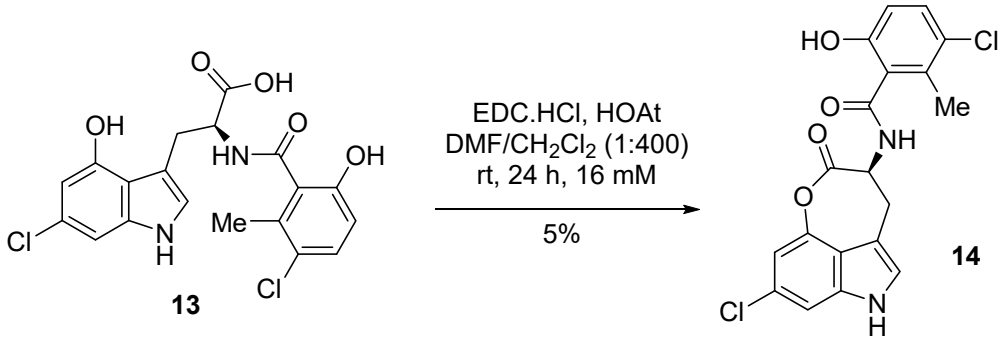


To a stirred solution of **11** (25 mg, 0.051 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 °C was slowly added boron tribromide (0.3 mL, 0.31 mmol, 6.0 equiv., 1 M in dichloromethane). The resulting mixture was stirred at the same temperature for 30 min, then warmed to 0 °C before quenched with 1 M HCl (10 mL) and diluted with dichloromethane (25 mL). The organic layer was separated, and the aqueous phase was further extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **12** (21 mg, 0.048 mmol, ~94%) as a colourless solid that was used in the subsequent step without further purification.

To a stirred solution of crude **12** (20 mg, 0.046 mmol, 1.0 equiv.) in methanol (5 mL) was added 1 M sodium hydroxide (0.18 mL, 0.18 mmol, 4.0 equiv.). The resulting mixture was stirred at room temperature for 2 h before being concentrated *in vacuo*. The resulting residue was dissolved in water (5 mL) and basified to pH 9 with sodium bicarbonate (sat. solution). The aqueous layer

was washed with ethyl acetate (5 mL), and the organic layer was discarded. The aqueous layer was then acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the *title compound* (~20 mg, 0.046 mmol, ~100%), as a brown oil and used for the next step without further purification. HRMS [ESI, $(M - H)^+$] found 421.0353, $[C_{19}H_{16}{}^{35}Cl_2N_2O_5 - H]^+$ requires 421.0364; δ_H (400 MHz, DMSO-d_6) 10.75 (1 H, s, NH), 8.38 (1 H, d, *J* 7.0, NH), 7.17 (1 H, d, *J* 8.7, CH), 7.0 (1 H, d, *J* 2.3, ArH), 6.80 (1 H, d, *J* 1.7, ArH), 6.66 (1 H, dd, *J* 8.7, ArH), 6.31 (1 H, d, *J* 1.7, ArH), 4.64 (1 H, dd, *J* 9.9, 4.4, CH), 3.38 (1 H, dd, *J* 14.5, 4.4, CH_2), 3.06 (1 H, dd, *J* 14.5, 9.9, CH_2), 1.98 (3 H, s, Me), 3 × OH not observed.

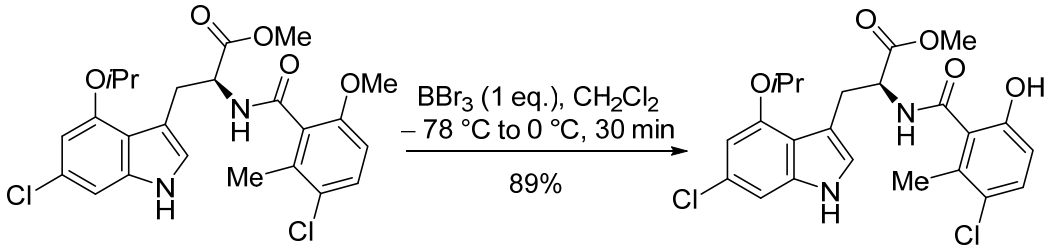
(*S*)-3-Chloro-*N*-(8-chloro-2-oxo-2,3,4,6-tetrahydrooxepino[4,3,2-*cd*]indol-3-yl)-6-hydroxy-2-methylbenzamide (14)



To a stirred solution of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride salt (EDC.HCl) (8 mg, 0.041 mmol, 1.5 equiv.) and 1-hydroxy-7-azabenzotriazole (HOAt) (6 mg, 0.041 mmol, 1.5 equiv.) in dichloromethane (25 mL) was added a solution of crude **13** (12 mg, 0.027 mmol, 1 equiv.) in dichloromethane (25 mL), over a period of 30 min. The resulting mixture was stirred at room temperature for 24 h before washed with brine (sat. solution), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified by quickly passing through

a glass pipette filled with silica gel eluting with dichloromethane-acetone (9:1) to afford the *title compound* (0.5 mg, 0.0012 mmol, 5%) as an unstable colorless solid. HRMS [ESI, $(M - H)^+$] found 403.0259, $[C_{19}H_{14}{}^{35}Cl_2N_2O_4 - H]^+$ requires 403.0259; δ_H (400 MHz, DMSO-d_6) 11.42 (1 H, s, NH), 9.72 (1 H, s, OH), 9.12 (1 H, s, NH), 7.37 (1 H, d, *J* 2.3, ArH), 7.29 (1 H, d, *J* 1.6, ArH), 7.23 (1 H, d, *J* 8.7, ArH), 6.87 (1 H, d, *J* 1.6, ArH), 6.71 (1 H, d, *J* 8.8, ArH), 4.68 (1 H, ddd, *J* 9.3, 6.1, 4.4, CH), 3.19 (2 H, dd, *J* 9.3, 4.4, CH_2), 2.21 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 169.5 (CO), 166.4 (CO), 152.9 (C), 137.9 (C), 133.4 (C), 129.4 (CH), 126.9 (C), 126.0 (C), 125.2 (C), 123.6 (CH), 123.0 (C), 115.0 (C), 114.6 (CH), 108.3 (C), 107.8 (CH), 107.2 (CH), 54.5 (CH), 26.9 (CH_2), 16.5 (Me). The NMR spectroscopic data had to be collected within 1 h of the final purification due to stability issues

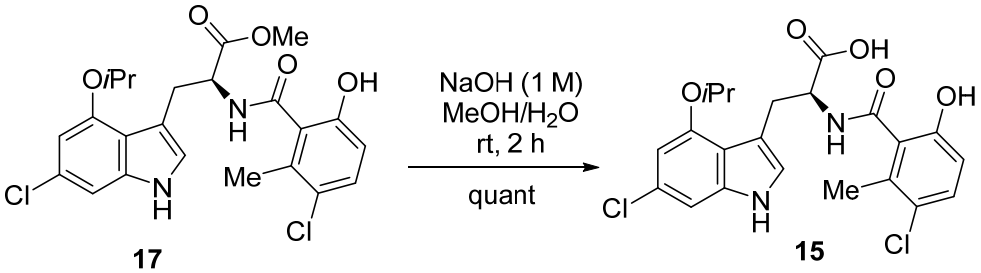
Methyl (*S*)-3-(6-chloro-4-isopropoxyindol-3-yl)-2-(3-chloro-6-hydroxy-2-methylbenzamido) -propanoate (17)



To a stirred solution of **11** (76 mg, 0.15 mmol, 1.0 equiv.) in dichloromethane (5 mL) at –78 °C was slowly added boron tribromide (0.15 mL, 0.15 mmol, 1.0 equiv., 1 M in dichloromethane) and stirred at the same temperature for 30 min. The resulting mixture was then warmed to 0 °C before quenched with 1 M HCl (10 mL) and diluted with dichloromethane (35 mL). The organic layer was separated, and the aqueous phase was further extracted with dichloromethane (3 × 35 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered,

and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel eluting with dichloromethane-methanol (95:5) to afford the *title compound* (65 mg, 0.14 mmol, 89%) as a colourless solid. M.p. 163.8 − 166.2 °C; $[\alpha]_D^{24}$ +20.8° (*c* 0.5, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 501.0956, $[C_{23}H_{24}{}^{35}Cl_2N_2O_5 + Na]^+$ requires 501.0954; ν_{max}/cm^{-1} (neat): 3313, 2963, 2924, 2851, 1730, 1638, 1579, 1541, 1493, 1436, 1364, 1326, 1291, 1258, 1211, 1136, 1081, 1031, 926, 883, 805, 662; δ_H (400 MHz, acetone-d_6) 10.16 (1 H, s, NH), 8.70 (1 H, s, OH), 7.76 (1 H, d, *J* 7.2, NH), 7.21 (1 H, d, *J* 8.7, ArH), 7.15 (1 H, d, *J* 2.3, ArH), 7.00 (1 H, d, *J* 1.7, ArH), 6.72 (1 H, d, *J* 8.7, ArH), 6.52 (1 H, d, *J* 1.7, ArH), 5.01 (1 H, ddd, *J* 9.1, 7.3, 5.0, CH), 4.78 (1 H, hept, *J* 6.0, CH), 3.73 (3 H, s, OMe), 3.55 (1 H, dd, *J* 14.1, 5.1, CH_2), 3.23 (1 H, dd, *J* 14.1, 9.1, CH_2), 2.09 (3 H, s, Me), 1.42 (3 H, d, *J* 6.0, Me), 1.39 (3 H, d, *J* 6.0, Me); δ_C (100 MHz, acetone-d_6) 173.7 (CO), 168.2 (CO), 155.1 (C), 153.4 (C), 139.5 (C), 135.0 (C), 131.4 (CH), 128.3 (C), 126.2 (C), 125.6 (C), 124.7 (CH), 117.7 (C), 116.0 (CH), 111.8 (C), 105.4 (CH), 103.0 (CH), 71.0 (CH), 55.9 (CH), 52.3 (OMe), 29.3 (CH_2), 22.3 (Me), 22.2 (Me), 17.6 (Me).

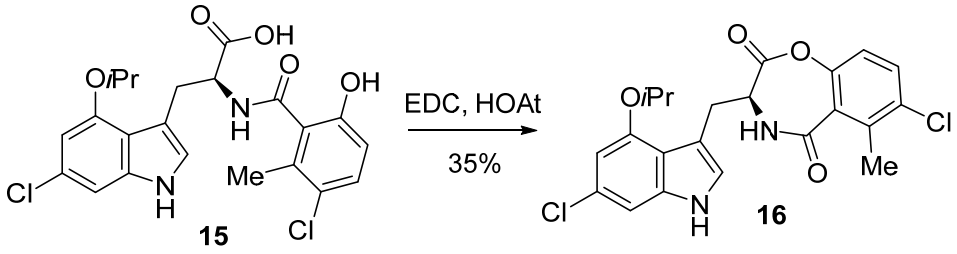
(*S*)-3-(6-Chloro-4-isopropoxyindol-3-yl)-2-(3-chloro-6-hydroxy-2-methylbenzamido)-propanoic acid (15)



To a stirred solution of **17** (65 mg, 0.14 mmol, 1.0 equiv.) in methanol (5 mL) was added 1 M sodium hydroxide (0.56 mL, 0.56 mmol, 4.0 equiv.). The resulting mixture was stirred at room temperature for 2 h before concentrated *in vacuo*. The resulting residue was dissolved in water (5

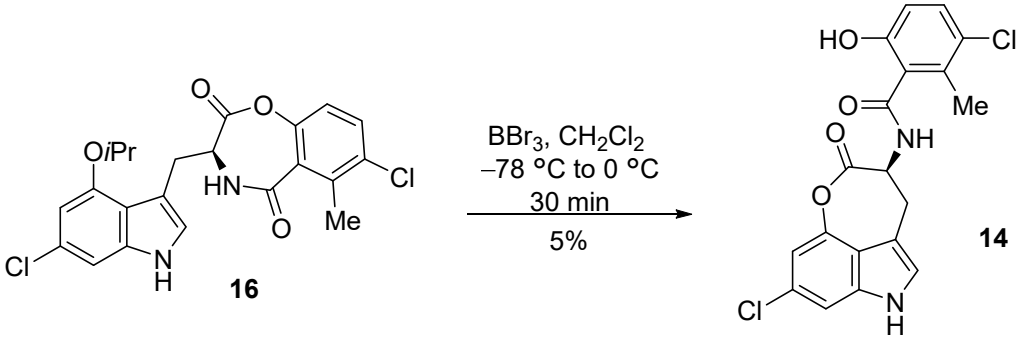
mL), basified to pH 9 with sodium bicarbonate (sat. solution), washed with ethyl acetate (5 mL), and the organic layer discarded. The aqueous layer was then acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the *title compound* (64 mg, 0.14 mmol, 100%), as a brown oil and used for the next step without further purification. $[\alpha]_D^{24}$ −16.4° (*c* 0.2, MeOH); HRMS [ESI, $(M - H)^+$] found 463.0845, $[C_{22}H_{22}{}^{35}Cl_2N_2O_5 - H]^+$ requires 463.0833; ν_{max}/cm^{-1} (neat): 3302, 2976, 2925, 2854, 1703, 1635, 1607, 1580, 1539, 1439, 1361, 1291, 1228, 1112, 1086, 1035, 931, 878, 820; δ_H (400 MHz, acetone-d_6) 10.19 (1 H, s, NH), 8.79 (1 H, s, OH), 7.76 (1 H, d, *J* 7.4, NH), 7.21 (1 H, d, *J* 8.7, ArH), 7.18 (1 H, d, *J* 2.2, ArH), 7.01 (1 H, d, *J* 1.4, ArH), 6.73 (1 H, d, *J* 8.7, ArH), 6.51 (1 H, d, *J* 1.5, ArH), 5.04 (1 H, dd, *J* 10.5, 7.4, 4.5, CH), 4.77 (1 H, hept, *J* 6.0, CH), 3.66 (1 H, dd, *J* 14.2, 4.5, CH_2), 3.26 (1 H, dd, *J* 14.2, 10.5, CH_2), 2.07 (3 H, s, Me), 1.43 (3 H, d, *J* 6.0, Me), 1.39 (3 H, d, *J* 6.0, Me); 1 × OH not observed; δ_C (100 MHz, acetone-d_6) 174.3 (CO), 168.4 (C), 155.1 (C), 153.4 (C), 139.4 (C), 131.5 (CH), 126.3 (C), 125.5 (C), 124.8 (CH), 117.7 (C), 116.1 (CH), 112.0 (C), 105.4 (CH), 103.0 (CH), 71.1 (C), 55.7 (CH), 29.1 (CH_2), 22.2 (Me), 22.3 (Me), 17.6 (Me), 1 × C not observed.

_O_-Isopropylinducamide C (16)



To a stirred solution of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride salt (EDC.HCl) (10 mg, 0.052 mmol, 1.5 equiv.) and 1-hydroxy-7-azabenzotriazole (HOAt) (7.0 mg, 0.052 mmol, 1.5 equiv.) in dichloromethane (25 mL) was added crude **15** (16 mg, 0.034 mmol, 1 equiv.) in dichloromethane (25 mL), over a period of 30 min. The resulting mixture was stirred at room temperature for 24 h, washed with sodium bicarbonate (sat. solution), brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by quickly passing through a glass pipette filled with silica gel eluting with dichloromethane-acetone (9:1) to afford the *title compound* (5 mg, 0.011 mmol, 35%) as a unstable colorless solid. M.p. 213.6 − 215.8 °C; $[\alpha]_D^{24}$ +6.75° (*c* 0.5, $CHCl_3$); HRMS [ESI, $(M + Na)^+$] found 469.0696, $[C_{22}H_{20}{}^{35}Cl_2N_2O_4 + Na]^+$ requires 469.0692; ν_{max}/cm^{-1} (neat): 3315, 2975, 2928, 2853, 1783, 1668, 1615, 1582, 1494, 1439, 1366, 1257, 1230, 1206, 1115, 1083, 1032, 928, 883, 824, 791, 733, 664; δ_H (400 MHz, DMSO-d_6) 10.97 (1 H, s, NH), 9.17 (1 H, d, *J* 6.9, NH), 7.64 (1 H, d, *J* 8.8, ArH), 7.17 (1 H, d, *J* 8.8, ArH), 7.09 (1 H, dd, *J* 2.3, ArH), 6.92 (1 H, d, *J* 1.6, ArH), 6.37 (1 H, d, *J* 1.5, ArH), 4.58 (1 H, hept, *J* 6.0, CH), 4.35 (1 H, dd, *J* 7.1, 6.8, CH), 3.30 (1 H, dd, *J* 14.3, 6.8, CH_2), 3.12 (1 H, dd, *J* 14.3, 7.1, CH_2), 2.38 (3 H, s, Me) 1.00 (3 H, dd, *J* 6.0, Me), 0.95 (3 H, dd, *J* 6.0, Me); δ_C (100 MHz, DMSO-d_6) 168.2 (CO), 165.5 (CO), 151.3 (C), 148.1 (C), 137.7 (C), 136.5 (C), 132.4 (C), 132.0 (CH), 126.3 (C), 126.2 (C), 124.6 (CH), 119.7 (CH), 115.8 (C), 108.7 (C), 104.3 (CH), 101.5 (CH), 68.7 (CH), 52.4 (CH), 25.6 (CH_2), 21.3 (Me), 21.0 (Me), 17.7 (Me). The product was deployed in the subsequent step within one hour.

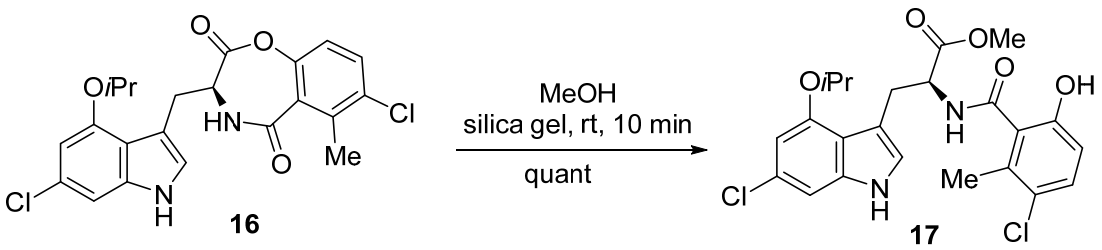
Boron tribromide-mediated deisopropylation of *O*-isopropylinducamide C (16)



To a stirred solution of *O*-isopropylinducamide C (**16**) (14 mg, 0.031 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 ºC was slowly added boron tribromide (95 µL, 0.095 mmol, 3.0 equiv., 1 M in dichloromethane). The resulting mixture was warmed to 0 °C, stirred for 30 min, then quenched with water (10 mL) and diluted with dichloromethane (15 mL). The organic layer was separated, and the aqueous phase was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by quickly passing through a glass pipette filled with silica gel eluting with dichloromethane-acetone (9:1) to afford **14** (0.5 mg, 0.0012 mmol, 5%) as a colourless solid. Spectroscopic data as described previously (see page 18).

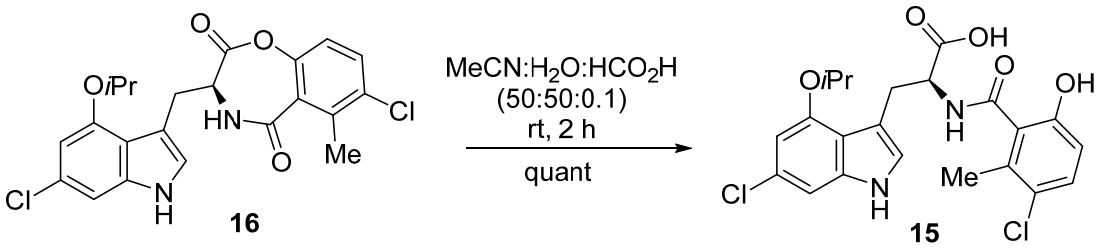
Benzoxazepine stability studies

Methanolysis of *O*-isopropylinducamide C (**16**)



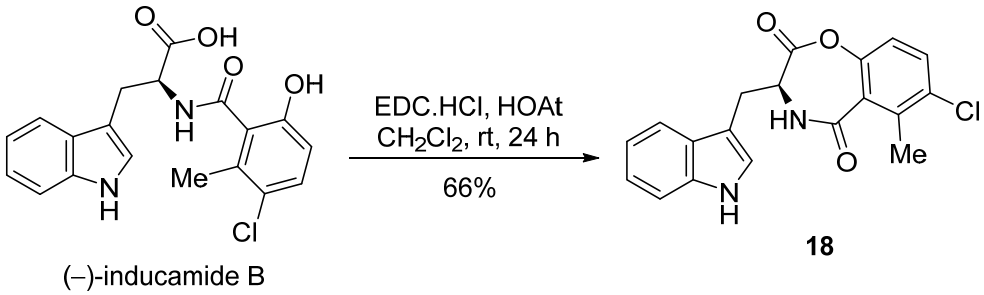
To a stirred solution of *O*-isopropylinducamide C (**16**) (1.0 mg, 0.0023 mmol, 1.0 equiv.) in methanol (1.0 mL) was added silica gel (20 mg). The resulting mixture was stirred at room temperature for 10 min then filtered. The silica was washed with methanol (1.0 mL) and the filtrate concentrated *in vacuo* to afford **17** (1.0 mg, 0.0023 mmol, ~100%) as a colorless solid. Spectroscopic data as described previously (see page 18).

Acid-mediated hydrolysis of *O*-isopropylinducamide C (**16**)



A solution of *O*-isopropylinducamide C (**16**) (5 mg, 0.011 mmol, 1.0 equiv.) in acetonitrile-water-formic acid (2 mL, 50:50:0.1) was stirred at room temperature for 2 h. The resulting mixture was concentrated *in vacuo* to afford **15** (5.0 mg, 0.011 mmol, ~100%) as a brown oil. Spectroscopic data as described previously (see page 19).

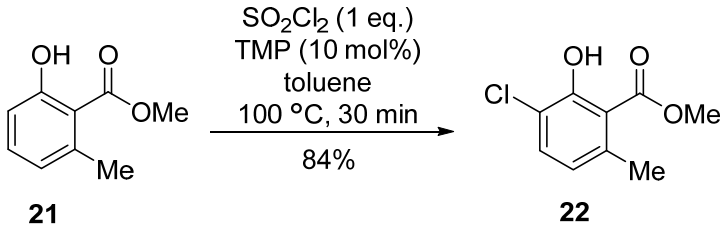
(*S*)-3-((Indol-3-yl)Methyl)-7-chloro-6-methyl-3,4-dihydrobenzo[*f*][1,4]oxazepine-2,5-dione (18)



To a stirred solution of *N*-ethyl-*N'*-3-(dimethylaminopropyl)carbodiimide hydrochloride salt (EDC.HCl) (25 mg, 0.13 mmol, 1.2 equiv.) and 1-hydroxy-7-azabenzotriazole (HOAt) (17.5 mg,

0.13 mmol, 1.2 equiv.) in dichloromethane (25 mL) was added a solution of (−)-inducamide B[2] (40 mg, 0.11 mmol, 1 equiv.) in dichloromethane (25 mL), over a period of 30 min. The resulting mixture was stirred at room temperature for 24 h then washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by quickly passing through the glass pipette filled with silica gel eluting with dichloromethane-acetone (9:1) to afford the *title compound* (25 mg, 0.070 mmol, 66%) as a colorless solid. M.p. 64.3 − 66.6 °C; $[\alpha]_D^{24}$ +5.9° (*c* 1.0, $CHCl_3$); HRMS [ESI, (M + Na)$^+$] found 377.0650, [$C_{19}H_{15}{}^{35}ClN_2O_3$ + Na]$^+$ requires 377.0663; ν_{max}/cm^{-1} (neat): 3321, 3076, 2962, 2924, 1777, 1705, 1661, 1590, 1456, 1438, 1354, 1259, 1228, 1098, 1067, 1029, 913, 792, 739, 685; δ_H (400 MHz, DMSO-d_6) 10.85 (1 H, s, NH), 9.03 (1 H, d, *J* 7.1, NH), 7.63 (1 H, d, *J* 8.8, ArH), 7.55 (1 H, d, *J* 7.9, ArH), 7.32 (1 H, d, *J* 8.1, ArH), 7.22 (1 H, d, *J* 2.3, ArH), 7.16 (1 H, d, *J* 8.8, ArH), 7.03 (1 H, ddd, *J* 8.1, 7.0, ArH), 6.92 (1 H, ddd, *J* 7.9, 7.0, ArH), 4.27 (1 H, ddd, *J* 9.5, 7.1, 4.9, CH), 3.25 (1 H, dd, *J* 15.0, 4.9, CH_2), 3.12 (1 H, dd, *J* 15.0, 9.5, CH_2), 2.33 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 168.9 (CO), 165.8 (CO), 148.5 (C), 136.3 (C), 135.9 (C), 132.1 (CH), 131.5 (C), 127.0 (C), 126.4 (C), 124.3 (CH), 121.0 (CH), 120.0 (CH), 118.4 (CH), 118.3 (CH), 111.4 (CH), 108.8 (C), 51.7 (CH), 23.6 (CH_2), 17.6 (Me).

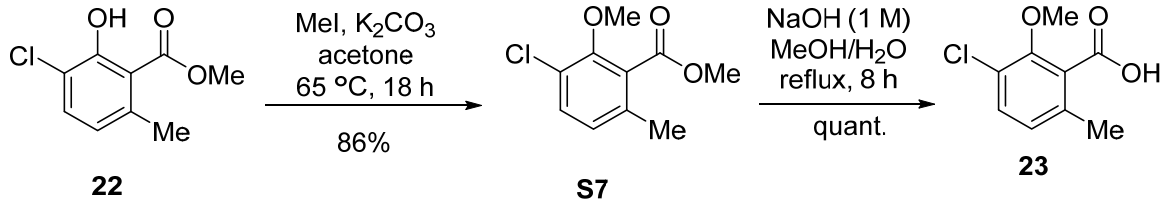
Methyl 3-chloro-2-hydroxy-6-methylbenzoate (22)



To a stirred solution of methyl 6-hydroxy-2-methyl benzoate (**21**)[3] (50 mg, 0.30 mmol, 1 equiv.) and 2,2,6,6-tetramethylpiperidine (5.5 µL, 0.030 mmol, 10 mol%) in toluene (10 mL) at 100 °C

was added SO_2Cl_2 (24 µL, 0.301 mmol, 1.0 equiv.) dropwise. The resulting mixture was heated at the same temperature for 30 min, then cooled to room temperature and concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (25 mL), washed with water, brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel eluting with diethyl ether-petroleum ether (1:9) to afford the *title compound* (51 mg, 0.25 mmol, 84%) as a pale-yellow solid. M.p. 29.1 − 30.7 °C; HRMS [ESI, $(M + Na)^+$] found 223.0126, $[C_9H_9{}^{35}ClO_3 + Na]^+$ requires 223.0132; ν_{max}/cm^{-1} (neat): 2957, 2850, 1662, 1600, 1567, 1411, 1345, 1297, 1253, 1196, 1151, 1122, 1057, 1034, 979, 958, 858, 789, 760; δ_H (400 MHz, $CDCl_3$) 11.81 (1 H, s, OH), 7.36 (1 H, d, *J* 8.1, ArH), 6.66 (1 H, d, *J* 8.1, ArH), 3.97 (3 H, s, OMe), 2.50 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 172.1 (CO), 158.4 (C), 140.2 (C), 134.4 (CH), 123.1 (CH), 120.2 (C), 113.8 (C), 52.8 (OMe), 24.0 (Me).

3-Chloro-2-methoxy-6-methylbenzoic acid (23)



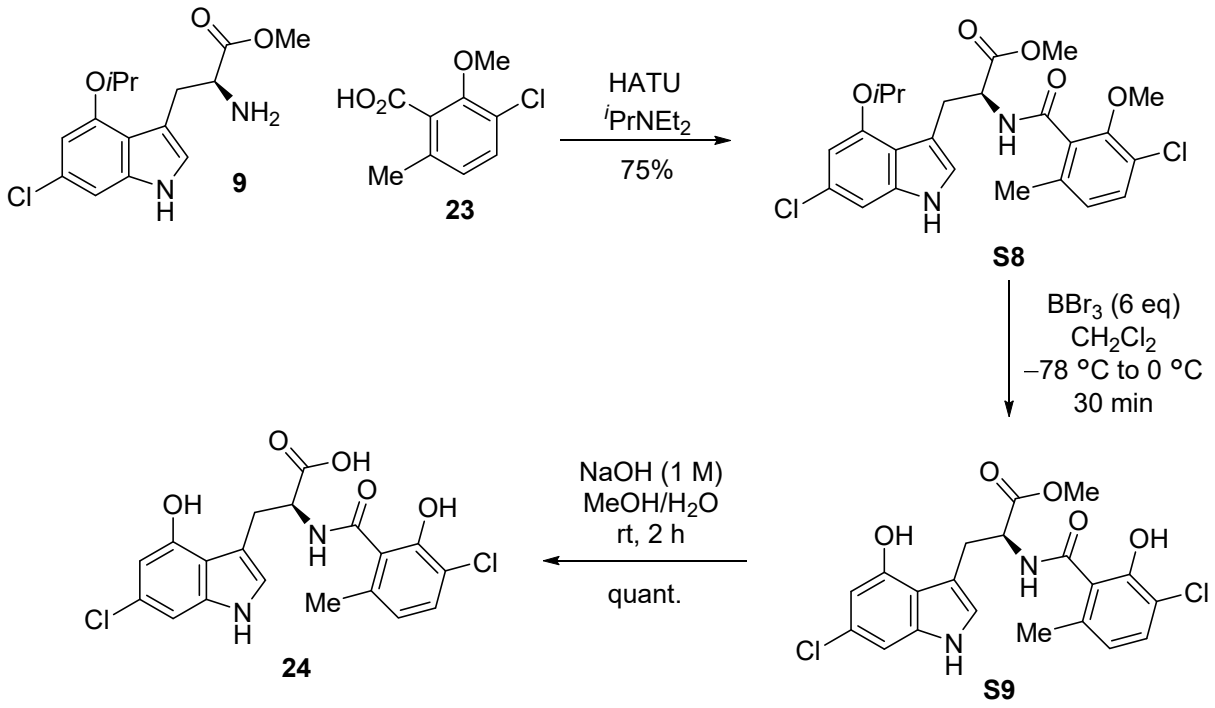
22 **S7** **23**

In a sealed tube, a solution of methyl 3-chloro-2-hydroxy-6-methyl benzoate (**22**) (50 mg, 0.25 mmol, 1 equiv.), potassium carbonate (103 mg, 0.75 mmol, 3.0 equiv.) and iodomethane (19 µL, 0.299 mmol, 1.2 equiv.) in acetone (10 mL) was heated at 65 °C for 18 h. The resulting mixture was cooled to room temperature before concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (20 mL) and washed with water (25 mL). The organic layer was separated, and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered and concentrated *in*

vacuo. The resulting residue was purified by flash column chromatography on silica gel eluting with diethyl ether-petroleum ether (1:9) to afford **S7** (46 mg, 0.22 mmol, 86%) as a colourless oil. HRMS [ESI, $(M + Na)^+$] found 237.0296, $[C_{10}H_{11}{}^{35}ClO_3 + Na]^+$ requires 237.0289; ν_{max}/cm^{-1} (neat): 2948, 1733, 1574, 1467, 1433, 1403, 1269, 1220, 1147, 1107, 1061, 999, 968, 922, 854, 810, 736; δ_H (400 MHz, $CDCl_3$) 7.27 (1 H, d, *J* 8.2, ArH), 6.88 (1 H, d, *J* 8.2, ArH), 3.91 (3 H, s, OMe), 3.87 (3 H, s, OMe), 2.25 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 167.9 (CO), 153.2 (C), 135.5 (C), 131.4 (CH), 130.5 (C), 126.8 (CH), 125.3 (C), 62.2 (OMe), 52.6 (OMe), 19.2 (Me).

To a stirred solution of methyl-3-chloro-2-methoxy-6-methylbenzoate (**S7**) (46 mg, 0.22 mmol, 1 equiv.) in methanol (2 mL) was added 1 M sodium hydroxide (2.86 mL, 2.86 mmol, 13 equiv.). The resulting mixture was heated to reflux for 8 h, then cooled to room temperature before washed with ethyl acetate (10 mL) and the extracted organic layer was discarded. The aqueous layer was acidified with to pH 2 with 1 M HCl (5 mL) and extracted with ethyl ether (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the *title compound* (44 mg, 0.22 mmol, ~100%) as a colourless solid. M.p. 51.2 − 52.7 °C; HRMS [ESI, $(M + Na)^+$] found 223.0127, $[C_9H_9{}^{35}ClO_3 + Na]^+$ requires 223.0132; ν_{max}/cm^{-1} (neat): 2955, 2924, 1687, 1587, 1569, 1467, 1414, 1383, 1287, 1268, 1223, 1153, 1121, 1060, 1000, 920, 896, 855, 794, 739, 721; δ_H (400 MHz, $CDCl_3$) 7.33 (1 H, d, *J* 8.2, ArH), 6.95 (1 H, d, *J* 8.2, ArH), 3.94 (3 H, s, OMe), 2.40 (3 H, s, Me), OH not observed; δ_C (100 MHz, $CDCl_3$) 153.7 (C), 136.8 (C), 132.2 (CH), 127.4 (CH), 125.6 (C), 62.5 (OMe), 19.9 (Me), 2 × C not observed.

(*S*)-2-(3-Chloro-2-hydroxy-6-methylbenzamido)-3-(6-chloro-4-hydroxyindol-3-yl)propanoic acid (24)



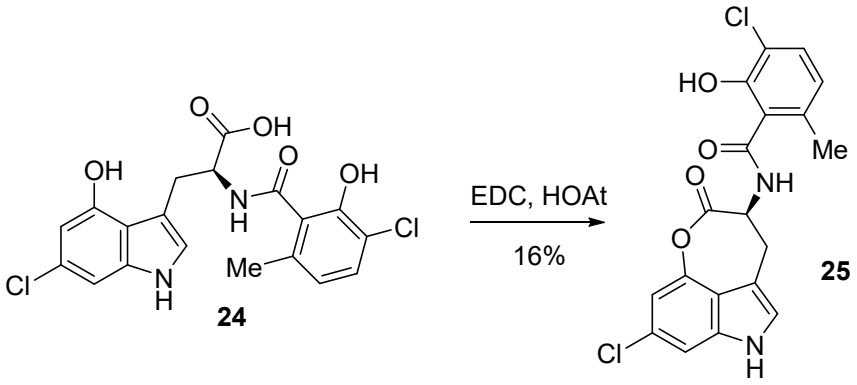
To a stirred solution of 3-chloro-2-methoxy-6-methyl benzoic acid (**23**) (52 mg, 0.26 mmol, 1.2 equiv.) and HATU (148 mg, 0.39 mmol, 1.8 equiv.) in *N,N*-dimethylformamide (2.5 mL) was added *N,N*-diisopropylethylamine (68 µL, 0.39 mmol, 1.8 equiv.). After stirring for 5 min, a solution of tryptophan **9** (67 mg, 0.22 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (3 mL) was added. The resulting mixture was stirred at room temperature for 30 min before poured into water (25 mL). The aqueous phase was extracted with ethyl ether (3 × 25 mL). The combined organic layers were washed with water, brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford the **S8** (80 mg, 0.16 mmol, 75%), as a colourless solid that was used in the next step without further purification.

To a solution of **S8** (30 mg, 0.061 mmol, 1.0 equiv.) in dichloromethane (5 mL) at −78 °C was slowly added boron tribromide (365 µL, 0.36 mmol, 6.0 equiv., 1 M in dichloromethane). The resulting mixture was warmed to 0 °C, stirred for 30 min before quenched with 1 M HCl (10 mL) and diluted with dichloromethane (10 mL). The organic layer was separated, and the aqueous phase was further extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **S9** (27 mg, 0.061 mmol, ~100%), as a colourless solid that was used in the next step without further purification.

To a stirred solution of **S9** (27 mg, 0.061 mmol, 1.0 equiv.) in methanol (5 mL) was added 1 M sodium hydroxide (0.61 mL, 0.61 mmol, 10.0 equiv.) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in water (10 mL), washed with ethyl acetate (10 mL), and the organic phase was discarded. The aqueous phase was then acidified to pH 2 with 1 M HCl and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by C18 reverse-phase column chromatography using aqueous formic acid (0.1%) in a gradient of 0% to 50% in acetonitrile to afford the *title compound* (26 mg, 0.061 mmol, ~100%) as a colourless solid. M.p. 39.1 − 40.9 °C; $[\alpha]_D^{21}$ −10.0° (*c* 0.5, MeOH); HRMS [ESI, $(M + Na)^+$] found 445.0320, $[C_{19}H_{16}{}^{35}Cl_2N_2O_5 + Na]^+$ requires 445.0328; ν_{max}/cm^{-1} (neat): 3240, 2924, 1710, 1622, 1587, 1539, 1456, 1416, 1358, 1323, 1242, 1202, 1133, 1045, 1021, 988, 887, 810, 761; δ_H (400 MHz, acetone-d_6) 10.19 (1 H, s, NH), 7.99 (1 H, d, *J* 6.0, NH), 7.22 (1 H, d, *J* 8.2, ArH), 7.16 (1 H, s, ArH), 6.91 (1 H, d, *J* 1.6, ArH), 6.65 (1 H, d, *J* 8.2, ArH), 6.46 (1 H, d, *J* 1.6, ArH), 4.99 (1 H, ddd, *J* 9.9, 6.0,

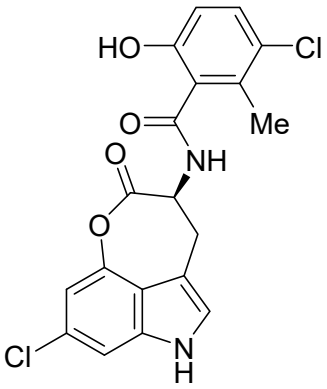
5.0, CH), 3.67 (1 H, dd, *J* 14.5, 5.0, CH_2), 3.37 (1 H, dd, *J* 14.5, 9.9, CH_2), 2.15 (3 H, s, Me); 3 × OH not observed; δ_C (100 MHz, acetone-d_6) 175.4 (CO), 169.2 (CO), 153.1 (C), 152.7 (C), 139.8 (C), 136.3 (C), 131.5 (CH), 127.9 (C), 124.2 (CH), 124.3 (C), 123.0 (CH), 119.3 (C), 116.8 (C), 111.8 (C), 105.2 (CH), 104.4 (CH), 56.3 (CH), 28.6 (CH_2), 19.9 (Me).

(*S*)-3-Chloro-*N*-(8-chloro-2-oxo-2,3,4,6-tetrahydrooxepino[4,3,2-*cd*]indol-3-yl)-2-hydroxy-6-methylbenzamide (25)

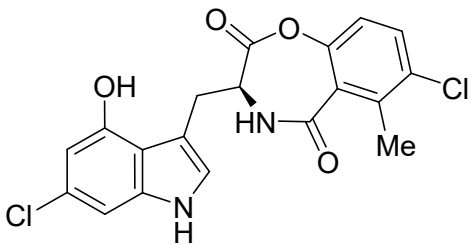


To a stirred solution of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride salt (EDC.HCl) (15 mg, 0.080 mmol, 2.0 equiv.) and 1-hydroxy-7-azabenzotriazole (HOAt) (11 mg, 0.080 mmol, 2.0 equiv.) in dichloromethane (25 mL) was added a solution of **24** (17 mg, 0.040 mmol, 1 equiv.) in dichloromethane (25 mL) and *N,N*-dimethylformamide (0.2 mL), over a period of 30 min. The resulting mixture was stirred at room temperature for 24 h before poured into water (30 mL). The organic layer was separated, and the aqueous phase was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were washed with brine (sat. solution), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by quickly passing through a glass pipette filled with silica eluting with dichloromethane-acetone (9:1), to afford the *title compound* (2.5 mg, 0.0062 mmol, 16%) as a yellow solid. M.p. 42.3 − 44.8 °C; $[\alpha]_D^{24}$ +5.9° (*c* 0.2, $CHCl_3$); HRMS [ESI, $(M - H)^+$] found 403.0259, $[C_{19}H_{14}{}^{35}Cl_2N_2O_4 - H]^+$

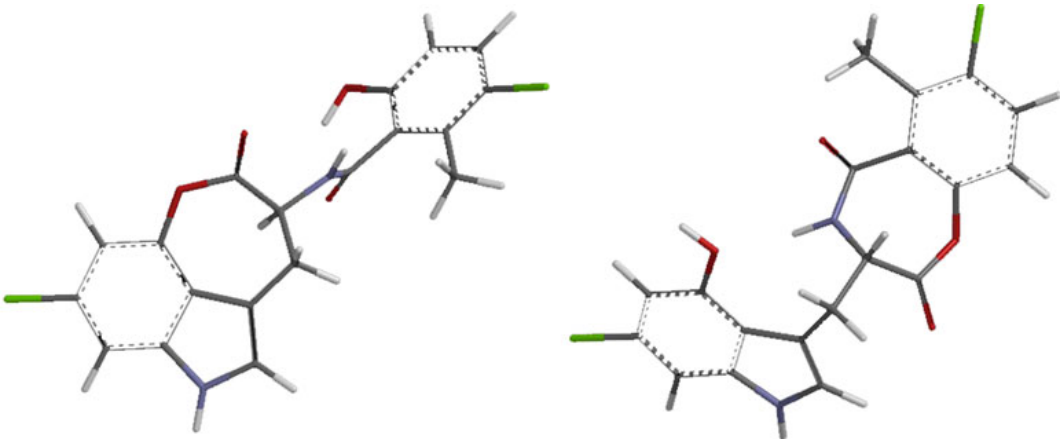
requires 403.0259; ν_{max}/cm^{-1} (neat): 3263, 2922, 2852, 1744, 1630, 1541, 1451, 1415, 1363, 1322, 1300, 1240, 1198, 1150, 1065, 1045, 1024, 989, 887; δ_H (400 MHz, DMSO-d_6) 11.43 (1 H, s, NH), 9.41 (1 H, s, OH), 9.19 (1 H, d, *J* 6.1, NH), 7.38 (1 H, d, *J* 2.1, ArH), 7.29 (1 H, d, *J* 1.6, ArH), 7.26 (1 H, d, *J* 8.1, ArH), 6.87 (1 H, d, *J* 1.6, ArH), 6.72 (1 H, d, *J* 8.1, ArH), 4.73 (1 H, ddd, *J* 10.5, 6.1, 3.1, CH), 3.23 (1 H, dd, *J* 15.7, 3.1, CH_2), 3.16 (1 H, dd, *J* 15.7, 10.5, CH_2), 2.19 (3 H, s, Me); δ_C (100 MHz, DMSO-d_6) 169.5 (CO), 166.3 (CO), 149.2 (C), 143.8 (C), 137.9 (C), 135.1 (C), 129.3 (CH), 127.2 (C), 126.0 (C), 123.5 (CH), 121.8 (CH), 118.1 (C), 115.1 (C), 108.3 (C), 107.8 (CH), 107.3 (CH), 54.5 (CH), 26.9 (CH_2), 18.4 (Me).



Oxepanoindole 14



proposed
(–)-inducamide C
benzoxazepine 3



Relative energies

without solvent	0	+4.6 (kcal/mol)
in toluene	0	+6.5 (kcal/mol)

Scheme S1: *Ab initio* Hartree-Fock point energy (6-31+G* basis set) calculations for inducamide C (**3**) and oxepanoindole **14**.

References

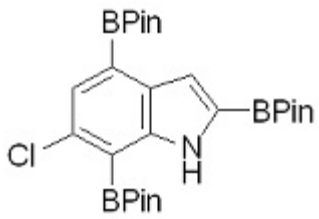
1) Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y. *Chem. Sci.* **2014**, 5, 3952-3957.

2) Scott, L. M.; Sperry, J. *J. Nat. Prod.* **2016,** *79*, 519-522.

3) Mandal, S. K.; Roy, S. C. *Tetrahedron* **2008,** *64*, 11050-11057.

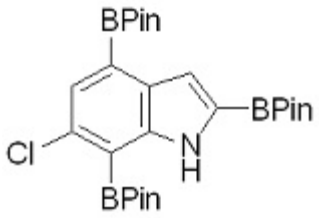
AN14.01H
protonstdi CDCl3 /nmr/400p anab813 35

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.56 (s, 1H), 7.48 (d, J = 2.2 Hz, 1H), 1.42 (s, 1H), 1.36 (s, 1H).



S1

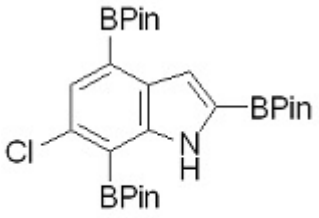
AN14.01C
carbonstdi CDCl3 /nmr/400p anab813 45



S1

143.90
136.45
130.40
129.39
115.17
84.28
84.19
84.04
77.23
25.21
25.17
25.06

f1 (ppm)



S1

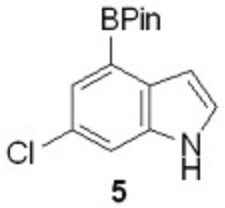
AN14.01HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 45

f2 (ppm)

f1 (ppm)

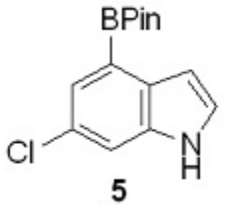
AN15.01H
protonstdi CDCl3 /nmr/400p anab813 34

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 1.9, 1.0 Hz, 1H), 7.22 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.99 (ddd, *J* = 3.1, 2.1, 1.0 Hz, 1H), 1.37 (s, 1H).

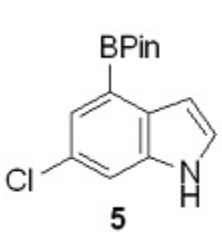


5

AN15.01C
carbonstdi CDCl3 /nmr/400p anab813 34



5

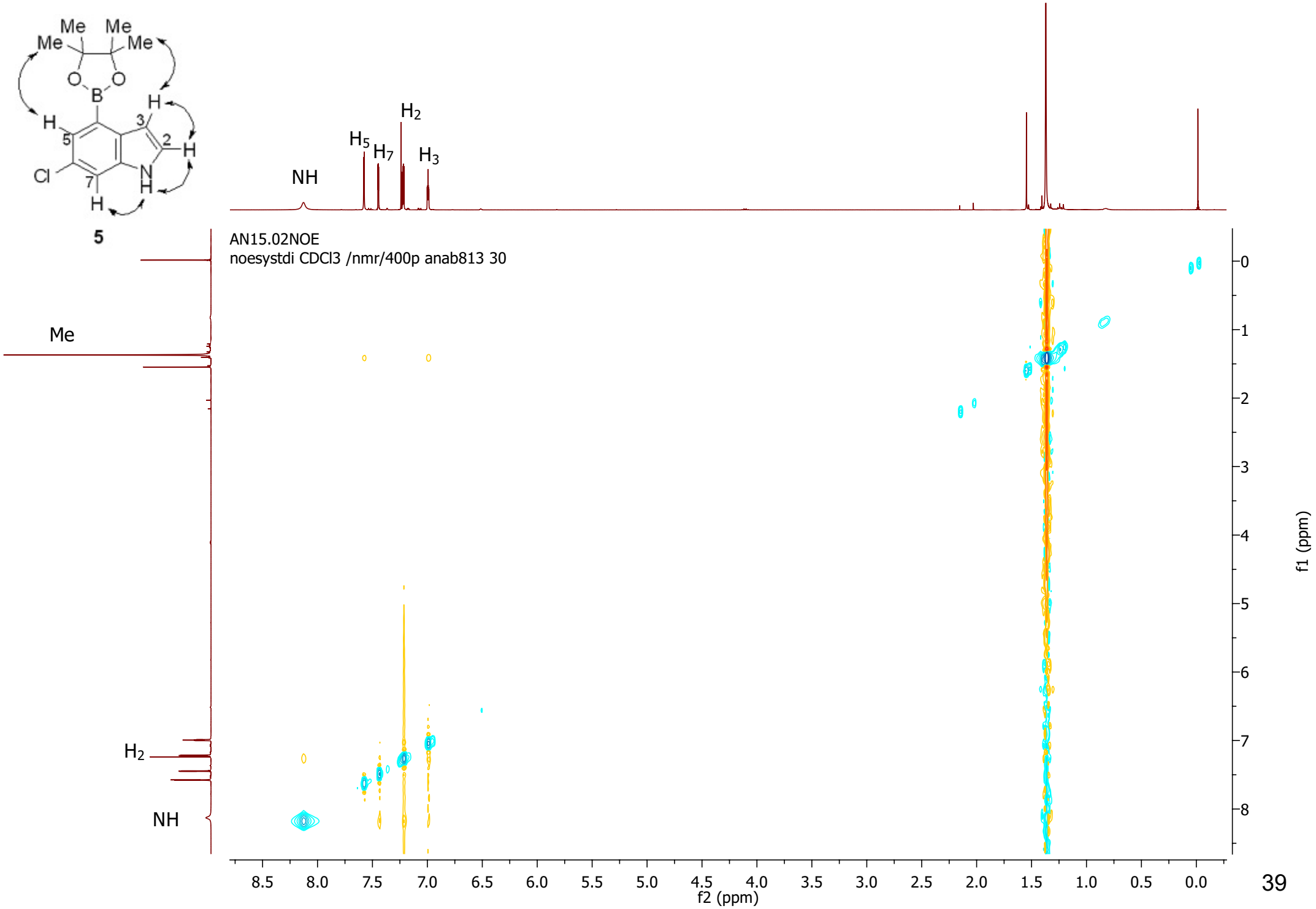


5

AN15.01HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 34

f2 (ppm)

f1 (ppm)


Me
Me
Me
Me
O
O
B
H
H
3
5
2
H
Cl
7
N
H
H
5
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H5
H7
H2
H3
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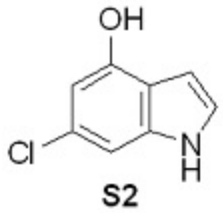
noesystdi CDCl3 /nmr/400p anab813 30
Me
H2
NH
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

5

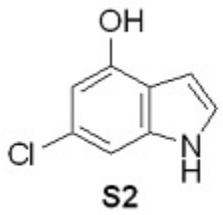
AN21.01
protonstdri CDCl3 /nmr/400p anab813 10

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.10 (dd, *J* = 3.3, 2.4 Hz, 1H), 6.99 (dd, *J* = 1.5, 1.0 Hz, 1H), 6.55 (ddd, *J* = 3.2, 2.2, 1.0 Hz, 1H), 6.53 (d, *J* = 1.6 Hz, 1H), 5.16 (s, 1H).

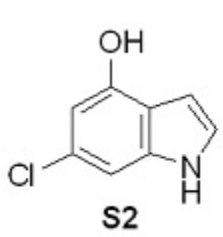


S2

AN21.0C
carbonstdi CDCl3 /nmr/400p anab813 10



S2



S2

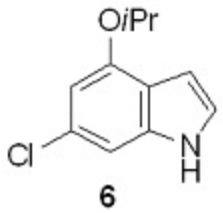
AN21.0HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 10

f2 (ppm)

f1 (ppm)

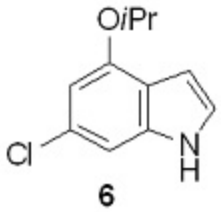
AN22.61H
protonstdri CDCl3 /nmr/400p anab813 50

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.06 (dd, *J* = 3.2, 2.3 Hz, 1H), 6.98 (dd, *J* = 1.5, 1.0 Hz, 1H), 6.59 (ddd, *J* = 3.2, 2.2, 0.9 Hz, 1H), 6.51 (dd, *J* = 1.7, 0.4 Hz, 1H), 4.72 – 4.59 (m, 1H), 1.39 (d, *J* = 6.0 Hz, 6H).

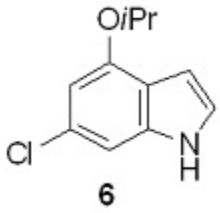


6

AN22.01C
carbonstdi CDCl3 /nmr/400p anab813 44



6



6

AN22.61HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 50

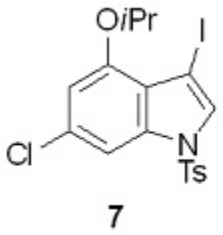
f2 (ppm)

f1 (ppm)

AN23.100H
protonstdi CDCl3 /nmr/400p anab813 26

7.24

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 1H), 7.55 (d, *J* = 1.6 Hz, 1H), 7.52 (s, 1H), 7.27 – 7.24 (m, 1H), 6.61 (d, *J* = 1.3 Hz, 1H), 4.59 (dh, *J* = 6.0, Hz, 1H), 2.35 (s, 1H), 1.38 (d, *J* = 6.0 Hz, 1H).



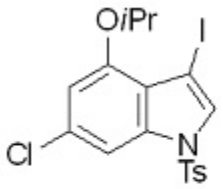
7

F (s) 7.52
H (m) 7.74
E (m) 7.25
D (d) 6.61
C (dh) 4.59
B (s) 2.35
A (d) 1.38
G (d) 7.55

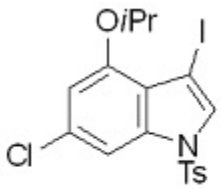
2.21 1.02 0.90 2.01 1.18 1.16 3.05 6.07

f1 (ppm)

AN23.100C
carbonstdi CDCl3 /nmr/400p anab813 26



7



7

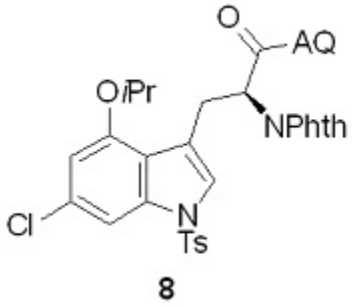
AN23.100HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 26

f2 (ppm)

f1 (ppm)

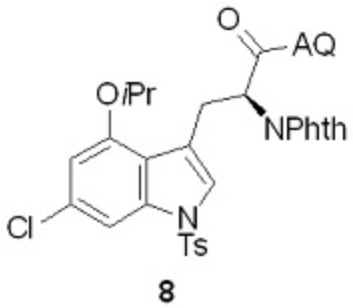
AN26.110H
protonstdri CDCl3 /nmr/400p anab813 12

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.75 – 8.69 (m, 1H), 8.61 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.76 – 7.71 (m, 2H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.50 – 7.44 (m, 4H), 7.39 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (s, 1H), 6.89 (dd, *J* = 8.5, 0.6 Hz, 2H), 6.64 (dd, *J* = 1.5, 0.5 Hz, 1H), 5.76 (dd, *J* = 10.7, 5.8 Hz, 1H), 4.76 – 4.66 (m, 1H), 3.98 (ddd, *J* = 13.9, 5.8, 1.0 Hz, 1H), 3.91 (dd, *J* = 14.0, 10.7 Hz, 1H), 2.21 (s, 3H), 1.49 (d, *J* = 6.1 Hz, 3H), 1.46 (d, *J* = 6.0 Hz, 3H).

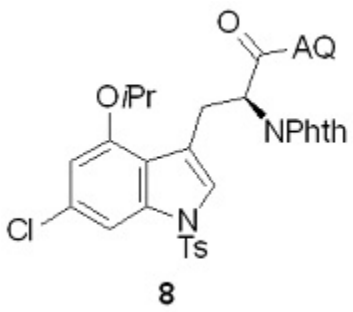


8

AN26.111C
carbonstdi CDCl3 /nmr/400pa...ab813 12



8



8

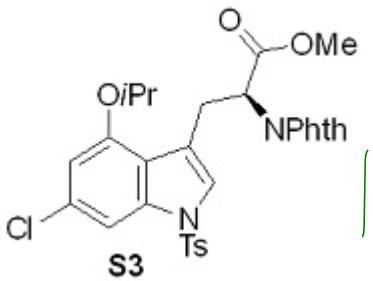
AN26.001HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 40

f2 (ppm)

f1 (ppm)

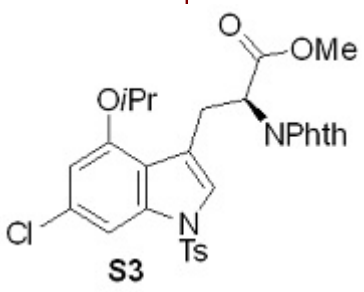
AN27.27H
protonstdi Acetone /nmr/400p anab813 5

^{1}H NMR (400 MHz, Acetone) δ 7.97 – 7.91 (m, 2H), 7.86 – 7.81 (m, 2H), 7.59 – 7.55 (m, 2H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.24 (d, *J* = 1.0 Hz, 1H), 7.08 – 7.05 (m, 2H), 6.83 (d, *J* = 1.5 Hz, 1H), 5.51 (dd, *J* = 11.9, 4.1 Hz, 1H), 4.94 – 4.83 (m, 1H), 3.80 (dd, *J* = 14.3, 4.1 Hz, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 14.3, 11.9 Hz, 1H), 2.30 (s, 3H), 1.47 (d, *J* = 6.0 Hz, 3H), 1.42 (d, *J* = 6.0 Hz, 3H).



S3

AN27.27C
carbonstdi Acetone /nmr/400p anab813 5

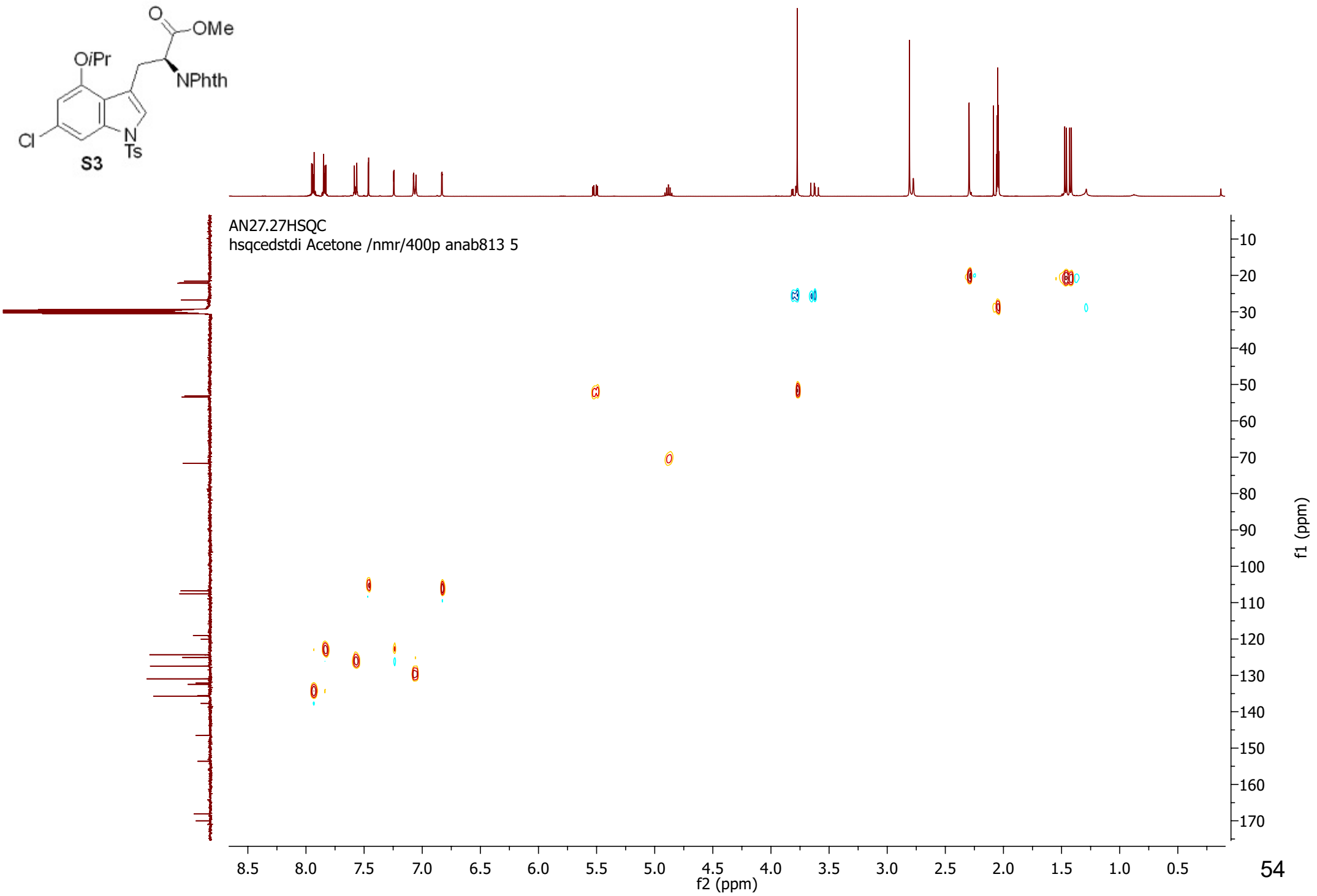


S3

170.02
168.11
153.65
146.48
137.69
135.72
135.53
132.46
132.10
130.95
127.45
125.06
124.35
120.06
119.05
107.57
106.78
71.70
53.42
53.17
29.92
26.76
22.18
22.03
21.56

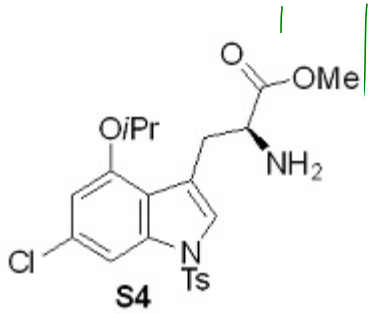
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OMe
OiPr
NPhth
Cl
N
Ts
S3
AN27.27HSQC
hsqcedstdi Acetone /nmr/400p anab813 5
f2 (ppm)
f1 (ppm)

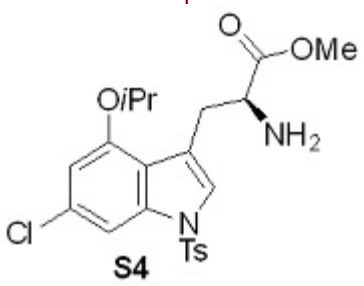
AN33A.11H
protonstdi Acetone /nmr/400p anab813 4

^{1}H NMR (400 MHz, Acetone) δ 7.86 – 7.82 (m, 2H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.23 (t, *J* = 0.8 Hz, 1H), 6.80 (dd, *J* = 1.6, 0.5 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.48 (dd, J = 8.6, 4.6 1H), 3.64 (s, 3H), 3.48 (dd, *J* = 13.7, 4.6, Hz, 1H), 3.00 (dd, *J* = 13.7, 8.6, Hz, 1H), 2.81 (d, J = 13.7 Hz, 2H), 2.39 (s, 3H), 1.38 (d, *J* = 1.9 Hz, 4H), 1.36 (d, *J* = 1.9 Hz, 3H).



S4

AN33A.11C
carbonstdi Acetone /nmr/400p anab813 4

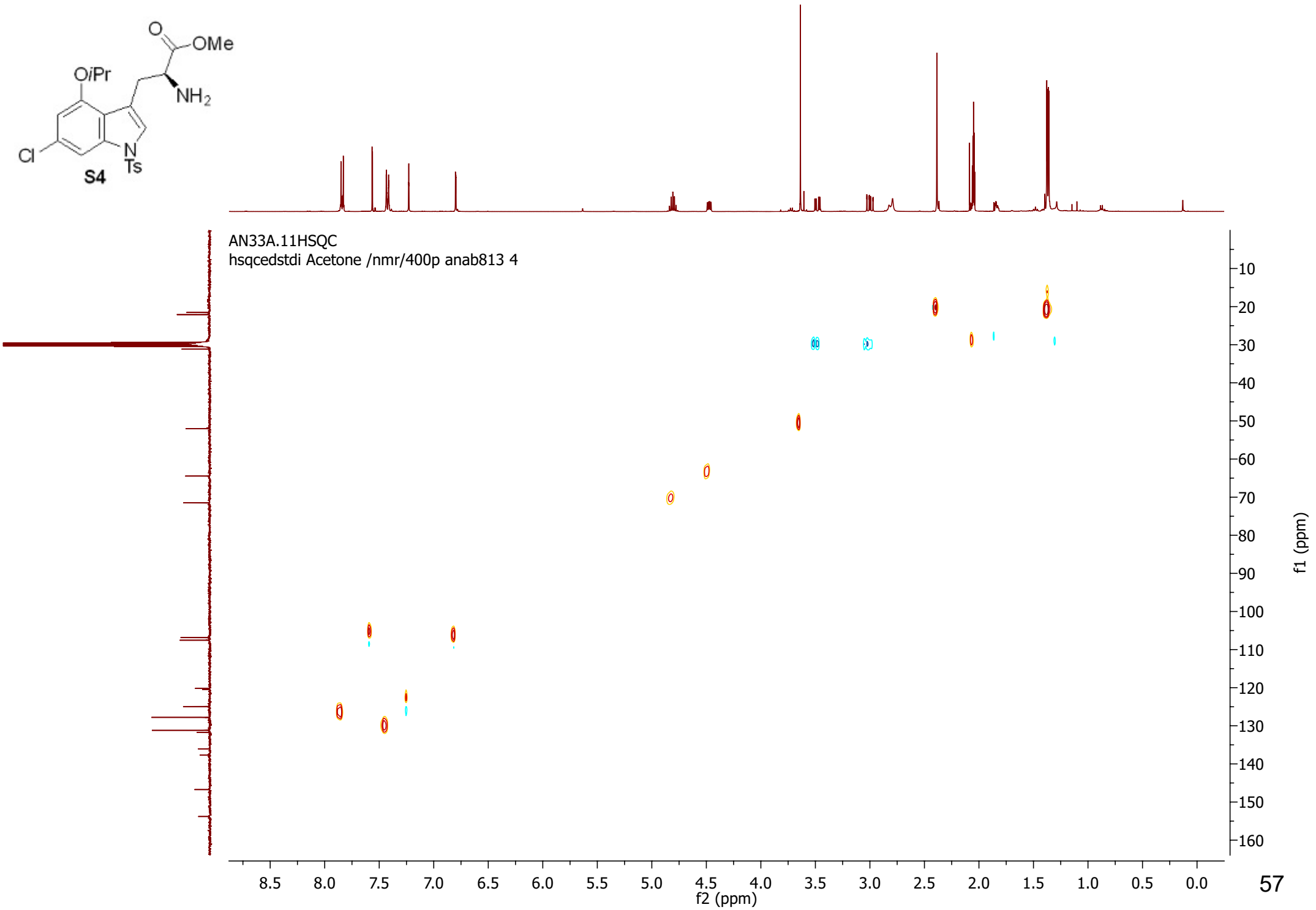


S4

172.81
153.81
146.74
137.68
136.05
131.76
131.18
127.79
124.94
120.47
120.20
107.54
106.87
71.51
64.47
52.01
31.15
29.92
22.12
22.07
21.54

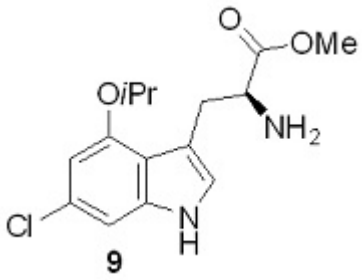
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OMe
OiPr
NH2
Cl
N
Ts
S4
AN33A.11HSQC
hsqcedstdi Acetone /nmr/400p anab813 4
f1 (ppm)
f2 (ppm)

AN33.6H
protonstdri CDCl3 /nmr/400p anab813 27

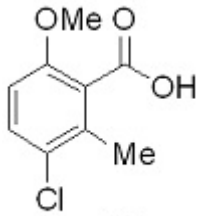
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.90 (d, J = 1.5 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.45 (dd, J = 1.5, 0.6 Hz, 1H), 4.72 – 4.62 (m, 1H), 3.90 (dd, J = 9.3, 4.5 Hz, 1H), 3.71 (s, 3H), 3.47 (dd, J = 14.0, 4.5 Hz, 1H), 2.79 (dd, J = 14.0, 9.3 Hz, 1H), 1.41 (d, J = 5.6 Hz, 4H).



9

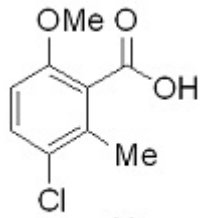
AN47.01H
protonstdri Acetone /nmr/400p anab813 38

^{1}H NMR (400 MHz, Acetone) δ 7.39 (d, J = 8.9 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 3.83 (s, 3H), 2.31 (s, 3H).



10

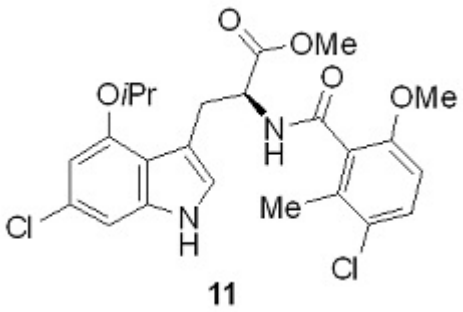
AN47.01C
carbonstdri Acetone /nmr/400p anab813 38



10

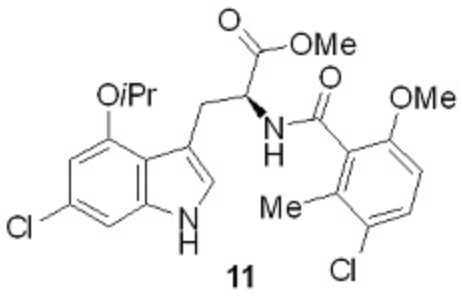
AN36.902H
protonstdri Acetone /nmr/400p anab813 7

^{1}H NMR (400 MHz, Acetone) δ 10.19 (s, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.50 (dd, *J* = 1.6, 0.5 Hz, 1H), 4.90 (ddd, *J* = 10.5, 7.3, 5.0 Hz, 1H), 4.80 – 4.69 (m, 1H), 3.72 (s, 1H), 3.48 (ddd, *J* = 14.1, 5.0, 0.7 Hz, 1H), 3.20 (ddd, *J* = 14.1, 10.5, 0.6 Hz, 1H), 2.10 (s, 1H), 1.43 (d, *J* = 6.0 Hz, 1H), 1.33 (d, *J* = 6.0 Hz, 1H).

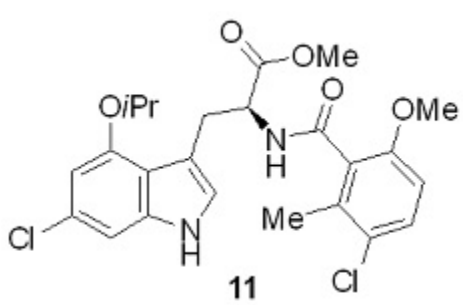


11

AN36.901C
carbonstdi Acetone /nmr/400p anab813 53



11



11

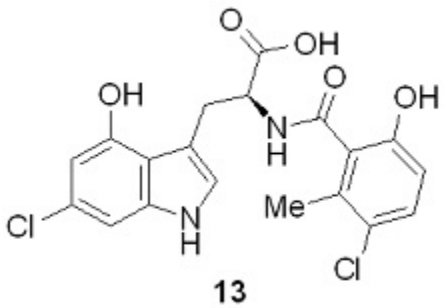
AN36.901HSQC
hsqcedstdi Acetone /nmr/400p anab813 53

f2 (ppm)

f1 (ppm)

AN38.005
protonstdri DMSO /nmr/400p anab813 18

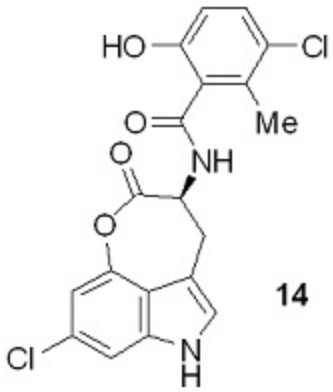
^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 8.38 (d, *J* = 7.0 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.31 (d, *J* = 1.7 Hz, 1H), 6.31 (d, *J* = 1.7 Hz, 1H), 4.64 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.38 (d, *J* = 14.5, 4.4 Hz, 1H), 3.06 (dd, *J* = 14.5, 9.9 Hz, 1H), 1.98 (s, 3H).



13

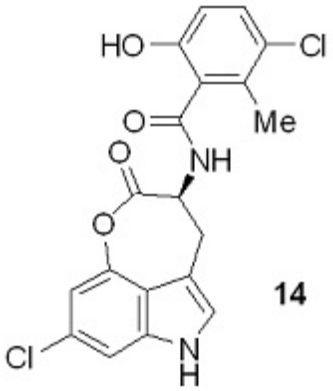
AN39B.005H
protonstdri DMSO /nmr/400p anab813 8

^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 9.72 (s, 1H), 9.12 (d, *J* = 6.1 Hz, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.68 (ddd, *J* = 9.3, 6.1, 4.4 Hz, 1H), 3.19 (dd, *J* = 9.3, 4.4 Hz, 2H), 2.21 (s, 3H).



14

AN39B.003C
carbonstdi DMSO /nmr/400p anab813 35

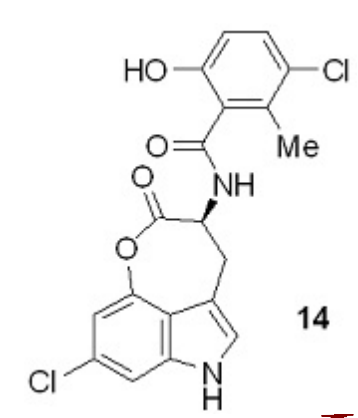


14

169.45
166.35
152.92
137.88
133.36
129.41
126.90
126.03
125.17
123.56
123.03
115.01
114.61
108.26
107.78
107.24
54.46
39.51
26.88
16.52

30000
25000
20000
15000
10000
5000
0

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

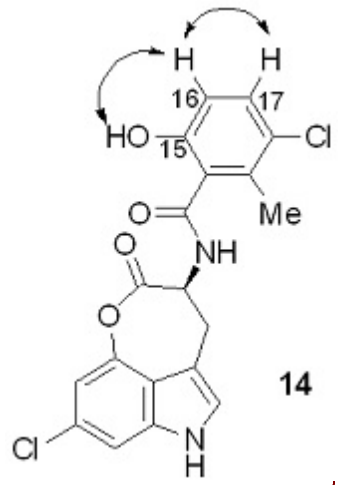


14

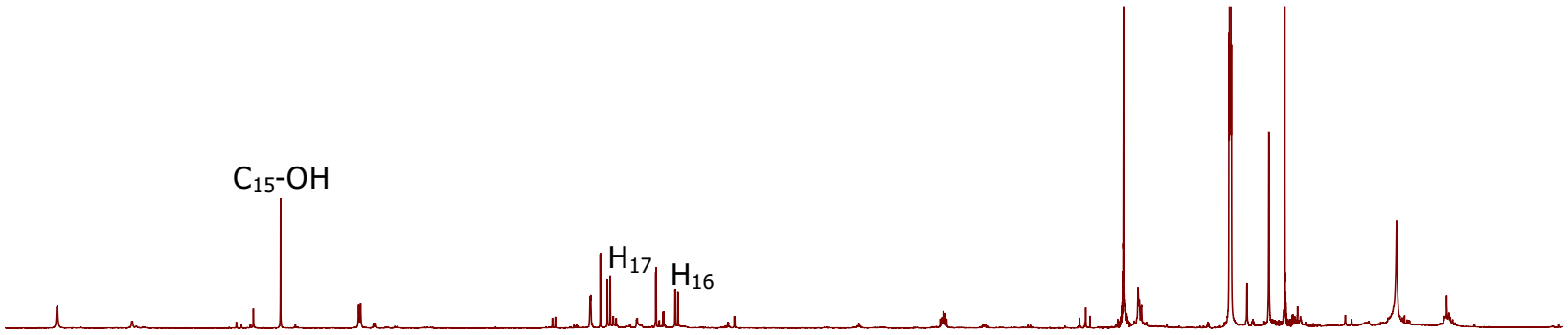
AN39B.007HSQC
hsqcedstdi DMSO /nmr/400p anab813 8

f2 (ppm)

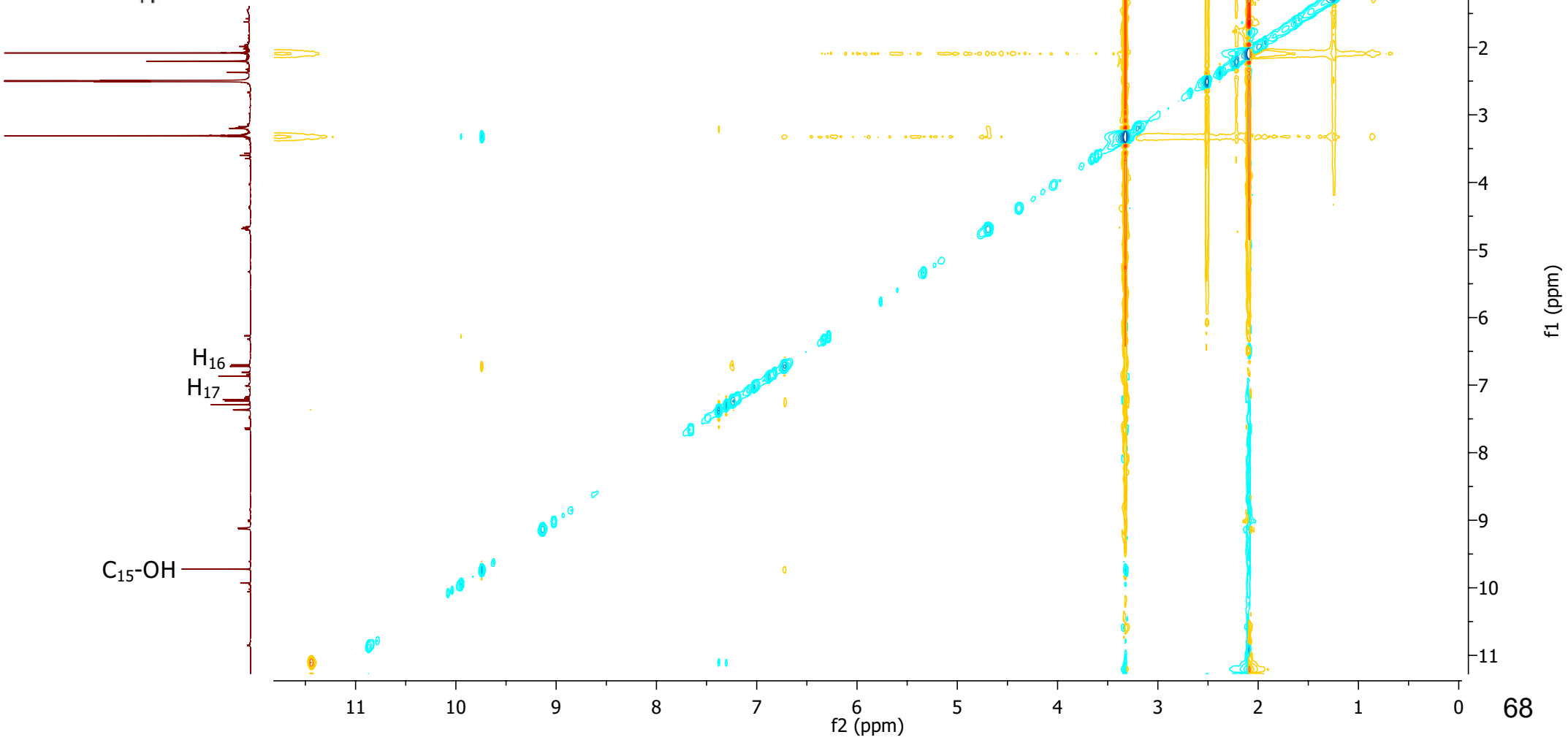
f1 (ppm)



14

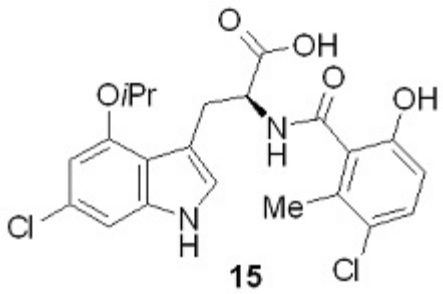


AN39B.07NOE
noesystdi DMSO /nmr/400p anab813 19



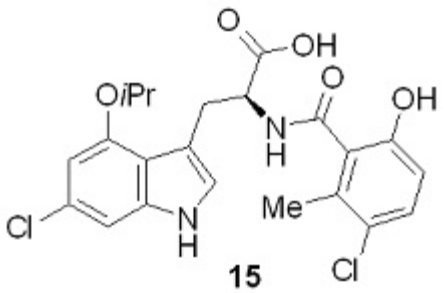
AN39B.005H
protonstdri Acetone /nmr/400p anab813 20

^{1}H NMR (400 MHz, Acetone) δ 10.19 (s, 1H), 8.79 (s, 1H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 1.4 Hz, 1H), 6.73 (d, *J* = 8.7,Hz, 1H), 6.51 (d, *J* = 1.5 Hz, 1H), 5.04 (ddd, *J* = 10.5, 7.4, 4.5 Hz, 1H), 4.77 (hpt, *J* = 6.0 Hz, 1H), 3.66 (dd, *J* = 14.2, 4.5 Hz, 1H), 3.26 (dd, *J* = 14.2, 10.5 Hz, 1H), 2.07 (s, 3H), 1.43 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H).



15

AN39B.005C
carbonstdi Acetone /nmr/400p anab813 13

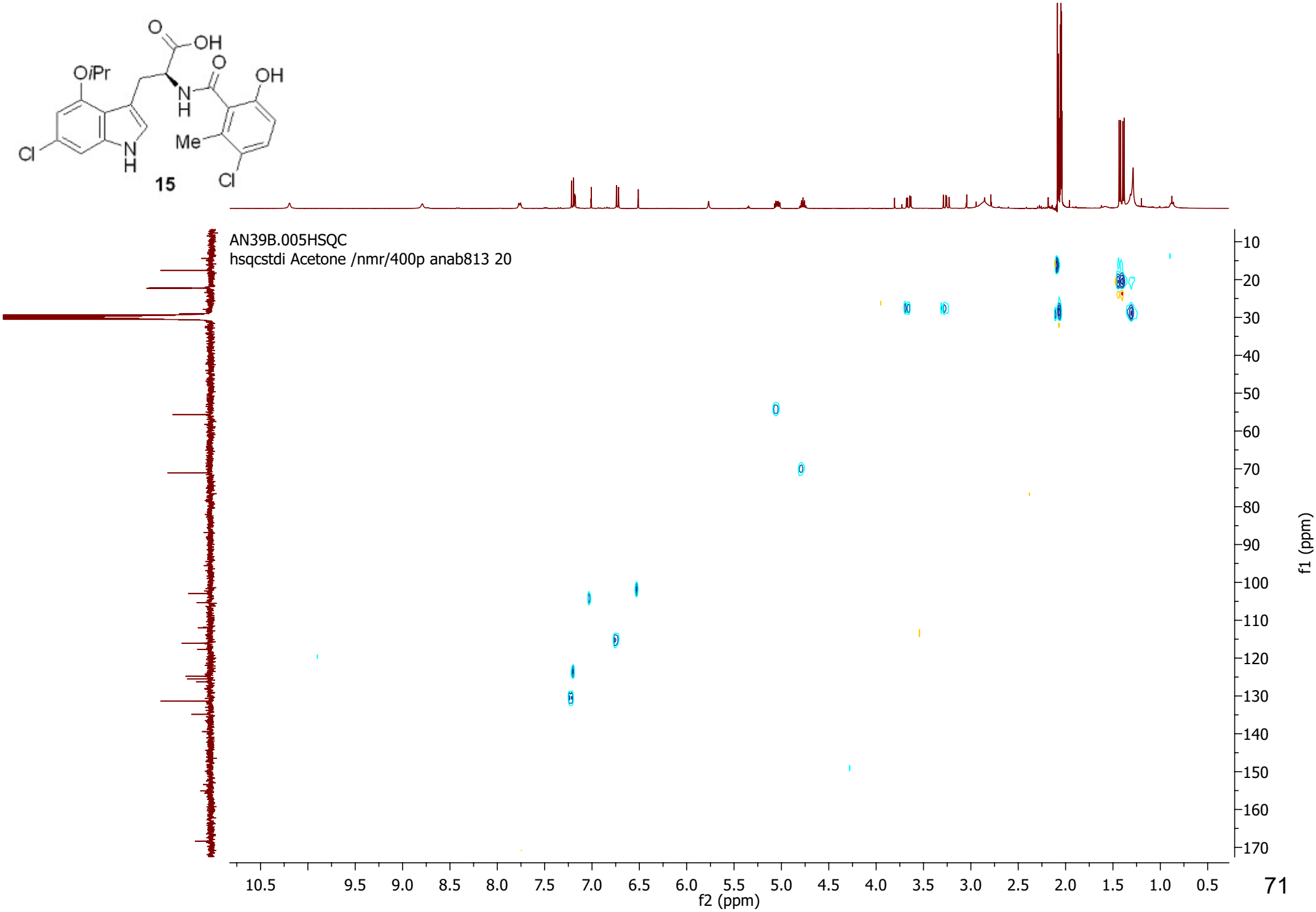


15

174.26
168.35
155.10
153.39
139.40
134.85
131.38
126.25
125.48
124.78
117.73
116.07
111.97
105.36
102.97
71.05
55.70
29.06
22.28
22.22
17.56

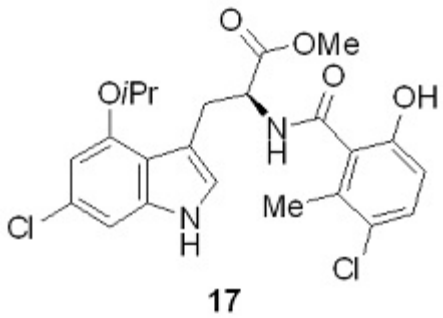
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
OH
OiPr
O
OH
N
H
Me
Cl
N
H
Cl
15
AN39B.005HSQC
hsqcstdi Acetone /nmr/400p anab813 20
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)

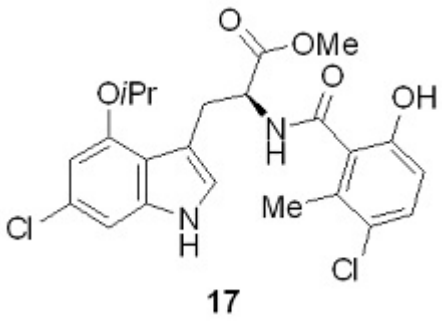
AN37A.901H
protonstdri Acetone /nmr/400p anab813 57

^{1}H NMR (400 MHz, Acetone) δ 10.16 (s, 1H), 8.70 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.00 (d, *J* = 1.6 Hz, 1H), 6.72 (dd, *J* = 8.7, 0.4 Hz, 1H), 6.52 (dd, *J* = 1.7, 0.4 Hz, 1H), 5.01 (ddd, *J* = 9.1, 7.2, 5.1 Hz, 1H), 4.83 – 4.74 (m, 1H), 3.73 (s, 3H), 3.55 (ddd, *J* = 14.1, 5.1, 0.7 Hz, 1H), 3.23 (dd, *J* = 14.1, 9.1 Hz, 1H), 2.09 (s, 3H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H).

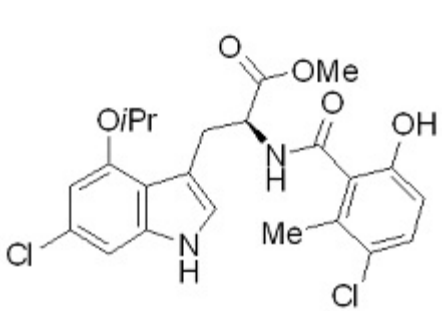


17

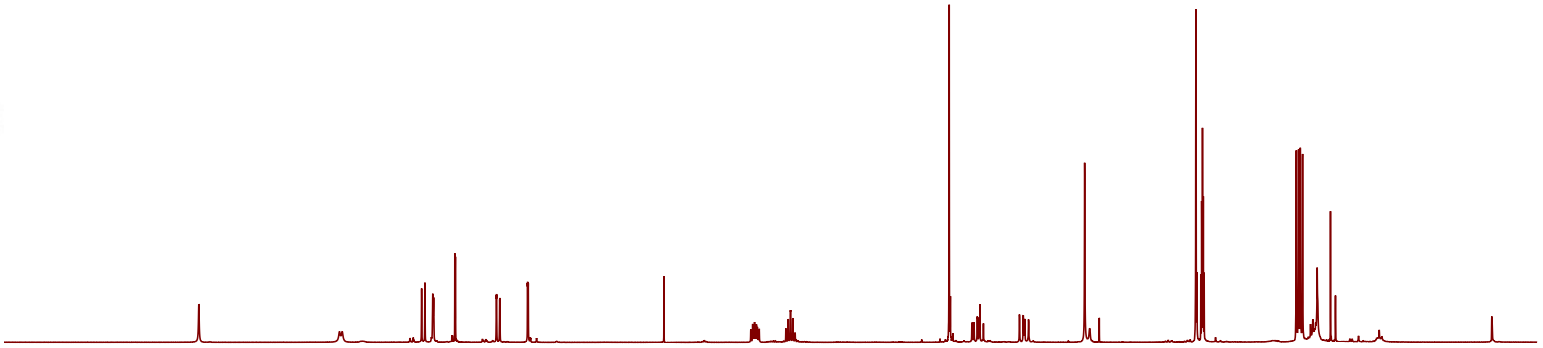
AN37A.901C
carbonstdi Acetone /nmr/400p anab813 57

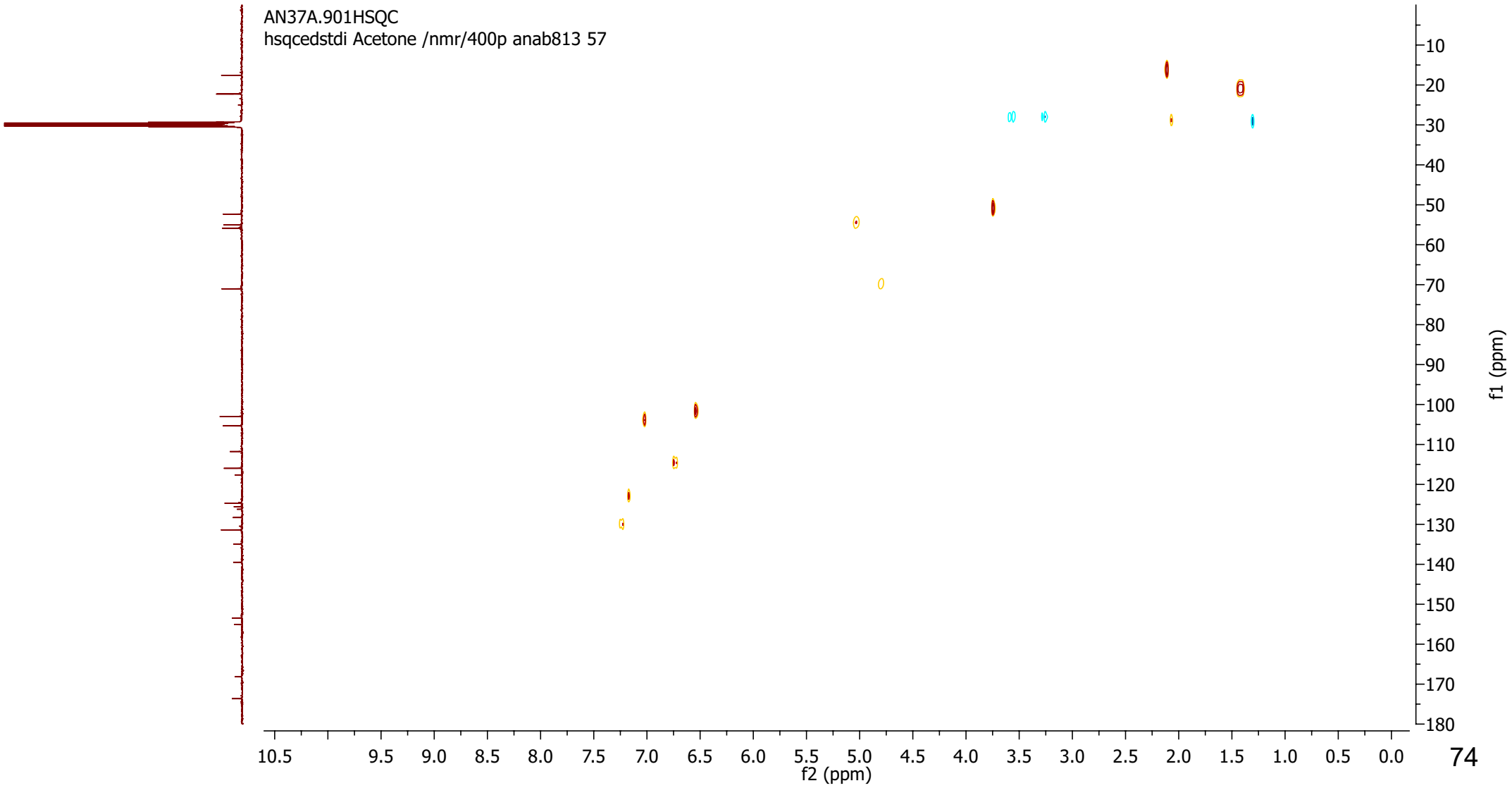


17


O
OMe
O
OiPr
OH
N
H
Me
Cl
N
H
Cl

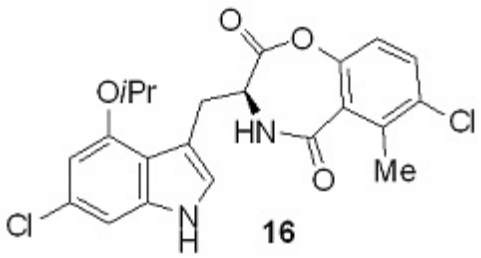
17



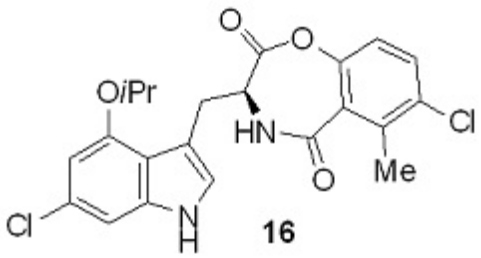

AN37A.901HSQC
hsqcedstdi Acetone /nmr/400p anab813 57
f1 (ppm)
f2 (ppm)
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

AN39A.941H
protonstdi DMSO /nmr/400p anab813 11

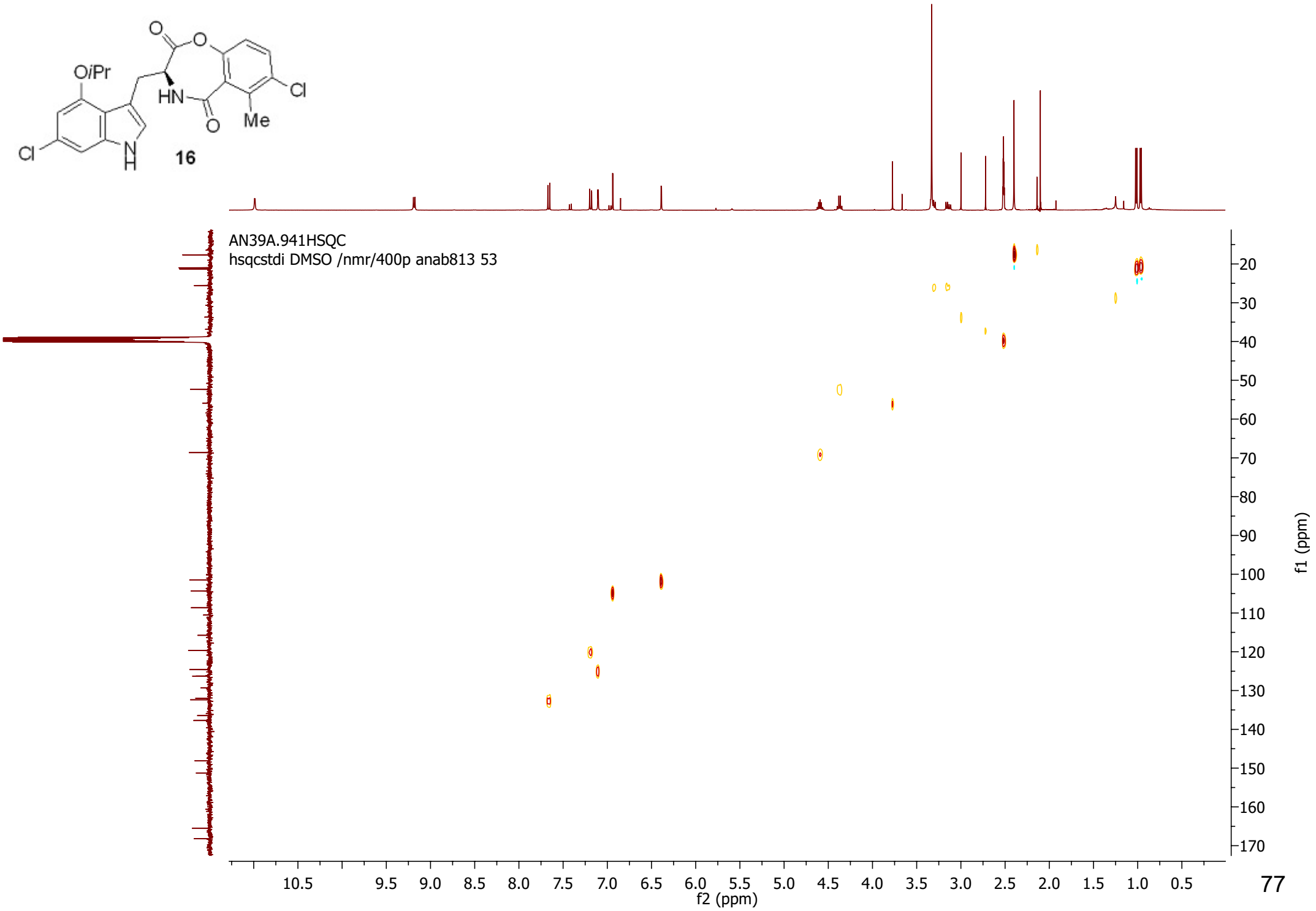
^{1}H NMR (400 MHz, DMSO) δ 10.97 (d, *J* = 1.9 Hz, 1H), 9.17 (d, *J* = 6.9 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.8, Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.92 (d, *J* = 1.6 Hz, 1H), 6.37 (d, *J* = 1.5 Hz, 1H), 4.58 (hept, *J* = 6.9 Hz, 1H), 4.35 (dd, *J* = 7.1, 6.8 Hz, 1H), 3.30 (dd, *J* = 14.3, 6.8 Hz, 1H), 3.12 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.38 (s, 3H), 1.00 (d, *J* = 6.0 Hz, 3H), 0.95 (d, *J* = 6 Hz, 3H).



AN39A.941C
carbonstdi DMSO /nmr/400p anab813 53

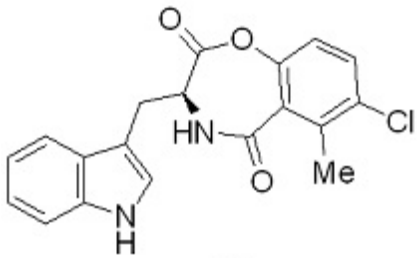


16


OiPr
HN
Cl
Me
Cl
16
AN39A.941HSQC
hsqcstdi DMSO /nmr/400p anab813 53
f2 (ppm)
f1 (ppm)

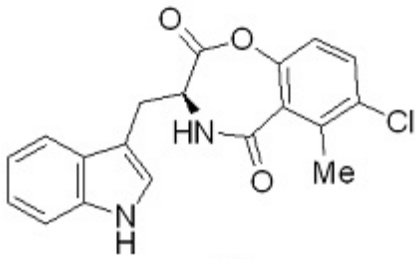
AN39.906H
protonstdri DMSO /nmr/400p anab813 29

^{1}H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.03 (d, *J* = 7.1 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 8.8, Hz, 1H), 7.03 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.92 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 4.27 (ddd, *J* = 9.5, 7.1, 4.9 Hz, 1H), 3.25 (dd, *J* = 15.0, 4.9 Hz, 1H), 3.12 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.33 (s, 3H).

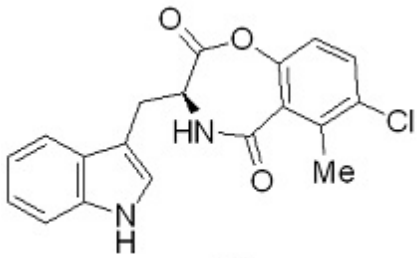


18

AN39.906C
carbonstdi DMSO /nmr/400p anab813 29



18



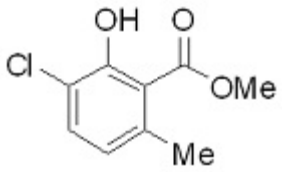
18

AN39.906HSQC
hsqcedstdi DMSO /nmr/400p anab813 29

f2 (ppm)
f1 (ppm)

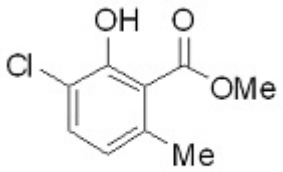
AN44A.02H
protonstdri CDCl3 /nmr/400p anab813 6

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 3.97 (s, 3H), 2.50 (s, 3H).

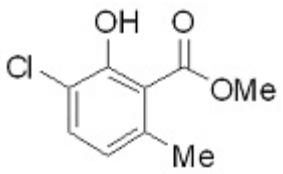


22

AN44A.02C
carbonstdi CDCl3 /nmr/400p anab813 6



22

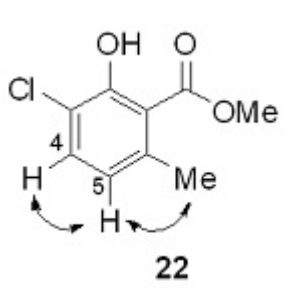


22

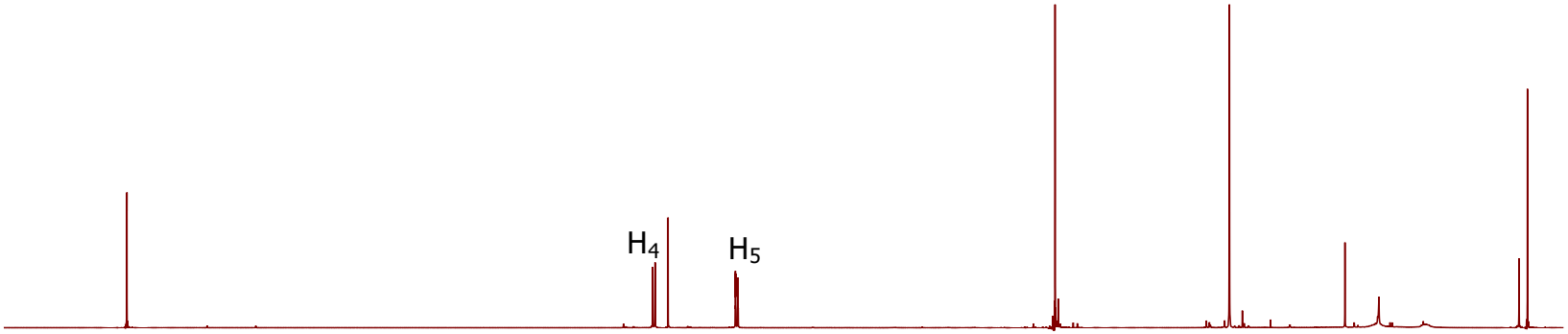
AN44A.02HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 6

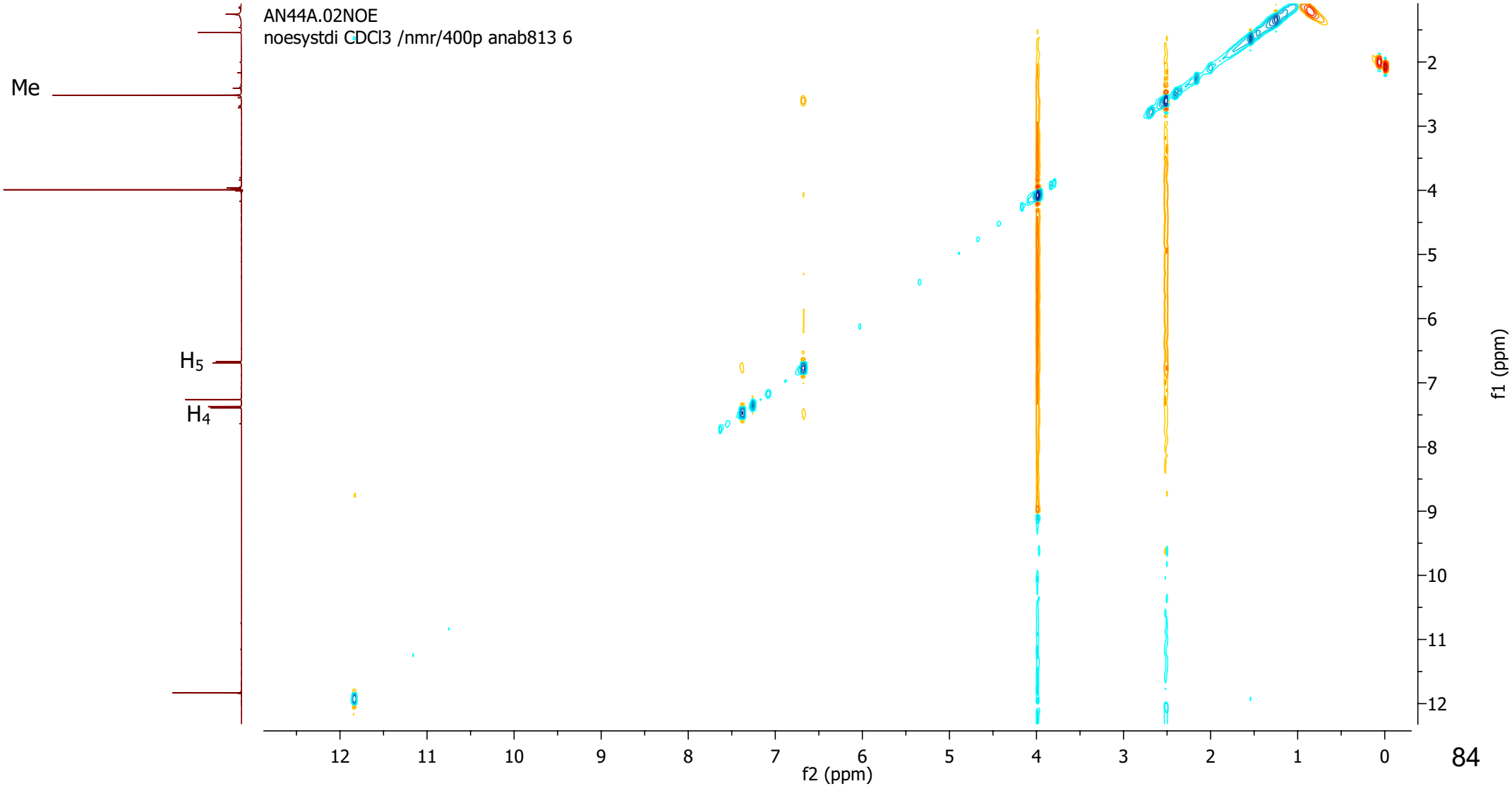
f2 (ppm)

f1 (ppm)


OH
O
Cl
OMe
4
H
5
Me
H

22

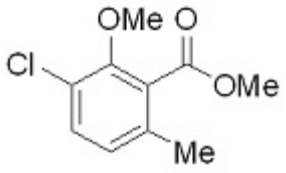

H4
H5


AN44A.02NOE
noesystdi CDCl3 /nmr/400p anab813 6
Me
H5
H4
12
11
10
9
8
7
6
5
4
3
2
1
0
f2 (ppm)
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)

AN48.01H
protonstdi CDCl3 /nmr/400p anab813 29

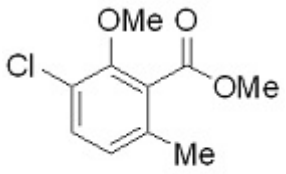
7.24

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.25 (s, 3H).

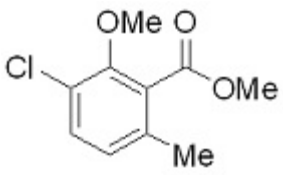


S7

AN48.01C
carbonstdi CDCl3 /nmr/400p anab813 29



S7



S7

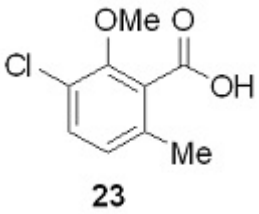
AN48.01HSQC
hsqcedstdi CDCl3 /nmr/400p anab813 29

f2 (ppm)

f1 (ppm)

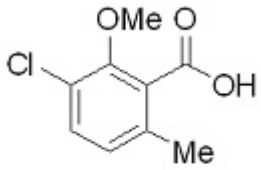
AN47A.01H
protonstdri CDCl3 /nmr/400p anab813 56

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 3.94 (s, 3H), 2.40 (s, 3H).

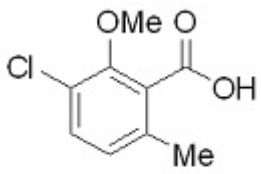


23

AN47A.01C
carbonstdi CDCl3 /nmr/400p anab813 56



23



23

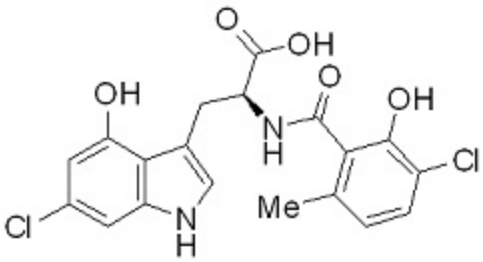
AN47A.01HSQC
hsqcstdi CDCl3 /nmr/400p anab813 56

f2 (ppm)

f1 (ppm)

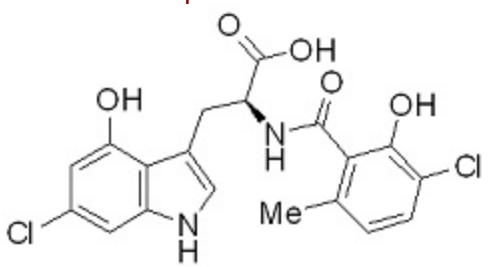
AN382.5H
protonstdri Acetone /nmr/400p anab813 55

^{1}H NMR (400 MHz, Acetone) δ 10.19 (s, 1H), 7.99 (d, *J* = 6.0 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.16 (s, 1H), 6.91 (d, *J* = 1.5 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 4.99 (ddd, *J* = 9.9, 6.0, 5.0 Hz, 1H), 3.67 (dd, *J* = 14.5, 5.0 Hz, 1H), 3.37 (dd, *J* = 14.5, 9.9 Hz, 1H), 2.15 (s, 3H).

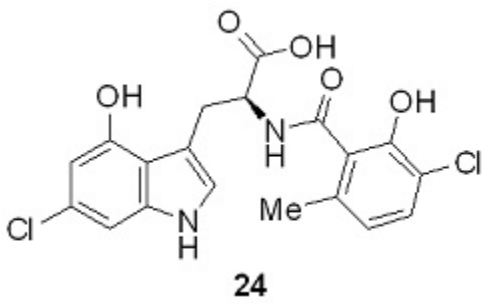


24

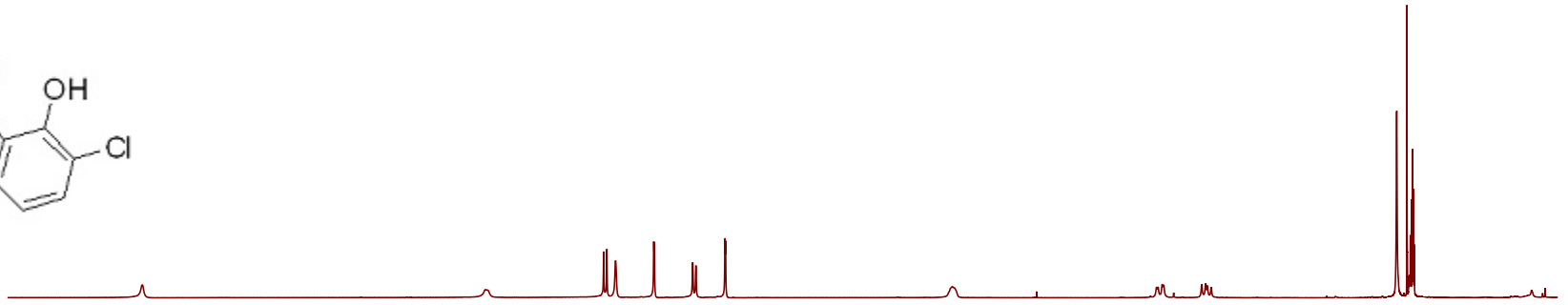
AN38A.5C
carbonstdi Acetone /nmr/400p anab813 24



24



24



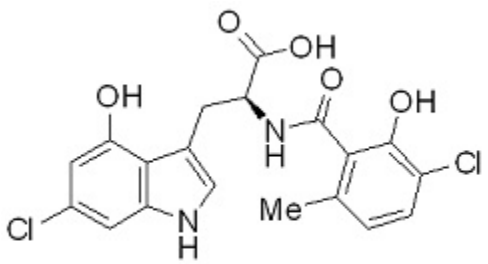
AN38A.5HSQC
hsqcedstdi Acetone /nmr/400p anab813 54

f1 (ppm)

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5

f2 (ppm)



24

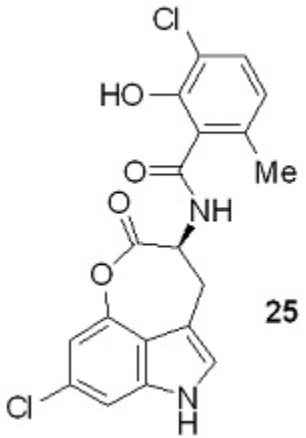
AN38A.5NOE
noesystdi Acetone /nmr/400p anab813 54

f2 (ppm)

f1 (ppm)

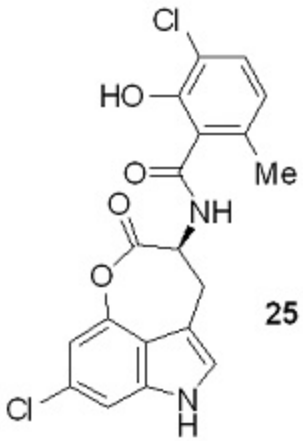
AN39A2.1509H
protonstdri DMSO /nmr/400p anab813 49

^{1}H NMR (400 MHz, DMSO) δ 11.43 (d, J = 1.9 Hz, 1H), 9.41 (s, 1H), 9.19 (d, J = 6.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 1.6 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 4.73 (ddd, J = 10.5, 6.1, 3.1 Hz, 1H), 3.23 (dd, J = 15.9, 3.1 Hz, 1H), 3.16 (dd, J = 15.7, 10.5 Hz, 1H), 2.19 (s, 1H).

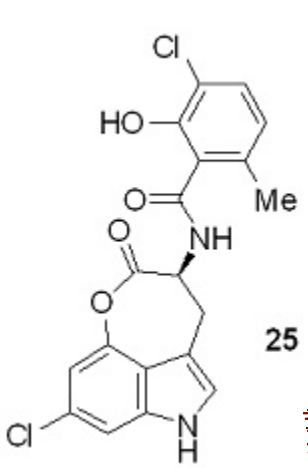


25

AN39A2.1509C
carbonstdi DMSO /nmr/400p anab813 49



25

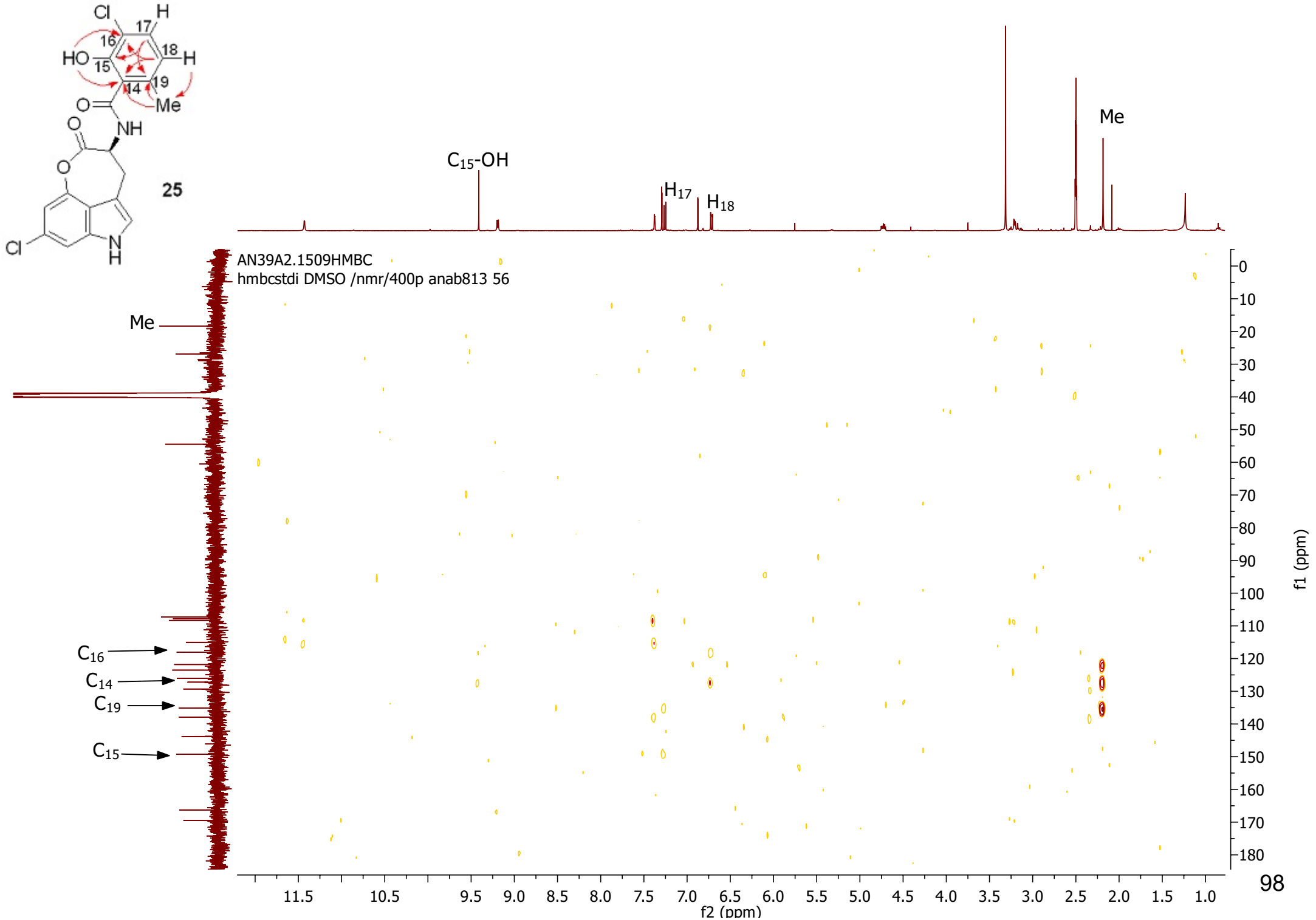


25

AN39A2.1509HSQC
hsqcedstdi DMSO /nmr/400p anab813 56

f2 (ppm)

f1 (ppm)


Cl
H
17
16
18
HO
15
H
14
19
Me
O
NH
O
O
25
Cl
N
H
C15-OH
H17
H18
Me
AN39A2.1509HMBC
hmbcstdi DMSO /nmr/400p anab813 56
Me
C16
C14
C19
C15
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180