Supplementary Information

1-Benzylindoles as inhibitors of cytosolic phospholipase $A_2\alpha$: synthesis, biological activity, aqueous solubility, and cell permeability

Imke Meyer zu Vilsendorf,[a] Judith Einerhand,[a] Dennis Mulac,[b] Klaus Langer[b] and Matthias Lehr *[a]

[a] Institute of Pharmaceutical and Medicinal Chemistry, University of Münster, Corrensstrasse 48, 48149 Münster, Germany

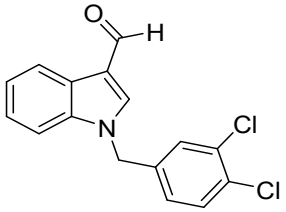
[b] Institute of Pharmaceutical Technology and Biopharmacy, University of Münster, Corrensstrasse 48, 48149 Münster, Germany

*Corresponding author, E-mail: lehrm@uni-muenster.de

Supplementary information content:

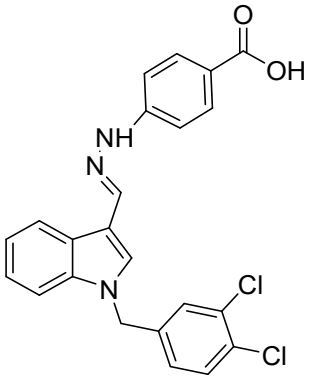
1. Synthetic procedures

1-(3,4-Dichlorobenzyl)indole-3-carbaldehyde (11)



A solution of indole-3-carbaldehyde (151 mg, 1.04 mmol) in dry DMF was treated with sodium hydride (60% dispersion in mineral oil) (94 mg, 2.35 mmol) under nitrogen atmosphere and cooling in an ice bath and stirred for 5 min. The ice bath was then removed and stirring continued for another 25 min at room temperature. After dropwise addition of a solution of 3,4-dichlorobenzyl bromide (500 mg, 2.08 mmol) in dry DMF, the mixture was stirred at room temperature for 3 h. After addition of water, the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) to yield **11** as a solid (252 mg, 80%). $C_{16}H_{11}Cl_2NO$ (304.2); mp 152 – 153 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.49 (s, 1H), 8.12 (dd, J = 6.8 and 1.2 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.31 – 7.29 (m, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 1H), 5.56 (s, 2H);
HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 304.0290, found: 304.0317.

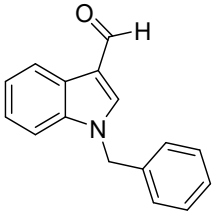
(*E*)-4-(2-{[1-(3,4-Dichlorobenzyl)indol-3-yl]methylene}hydrazineyl)benzoic acid (12)



A solution of **11** (120 mg, 0.39 mmol) and 4-hydrazinobenzoic acid (41 mg, 0.27 mmol) in dry ethanol (5 mL) was heated for 3 h under reflux. After cooling to room temperature, the mixture was concentrated to half its volume and then treated dropwise with ice-cooled water until the product precipitated. The solid was filtered off and dried *in vacuo* to give **12** (43 mg, 36%). $C_{23}H_{17}N_3O_2$ (438.3); mp 262 – 263 °C; purity (HPLC) 97%;

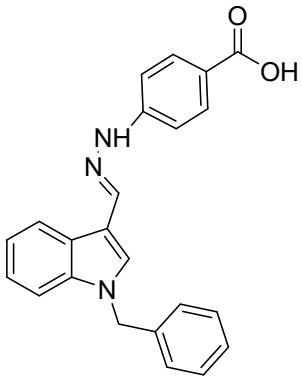
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 8.29 – 8.24 (m, 1H), 8.19 (s, 1H), 7.90 (s, 1H), 7.82 (d, J = 8.9 Hz, 2H), 7.58 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.25 – 7.21 (m, 2H), 7.21 – 7.17 (m, 1H), 7.06 (d, J = 8.8 Hz, 2H), 5.47 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.4, 149.3, 138.9, 136.7, 136.5, 131.32, 131.29, 131.19, 130.9, 130.2, 129.2, 127.5, 124.9, 122.9, 122.0, 120.9, 119.1, 112.4, 110.5, 48.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.0771, found: 438.0826.

1-Benzylindole-3-carbaldehyde (13)



The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from indole-3-carbaldehyde (500 mg, 3.44 mmol) and benzyl bromide (883 mg, 5.16 mmol) (reaction time: 1 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3), **13** was obtained as a solid (508 mg, 63%). $C_{16}H_{13}NO$ (235.3); mp 109 – 110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.46 (s, 1H), 8.14 – 8.10 (m, 1H), 7.60 – 7.57 (m, 1H), 7.37 – 7.22 (m, 7H), 5.54 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 236.1070, found: 236.1065.

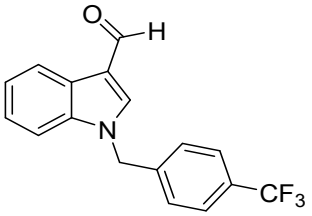
(*E*)-4-{2-[(1-Benzylindol-3-yl)methylene]hydrazineyl}benzoic acid (14)



Compound **13** (200 mg, 0.85 mmol) was reacted with 4-hydrazinobenzoic acid (87 mg, 0.57 mmol) according to the procedure described for the synthesis of **12** (reaction time: 3.5 h) to give **14** as a solid (152 mg, 72%). $C_{23}H_{19}N_3O_2$ (369.4); mp 215 – 216 °C; purity (HPLC) 96%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (brs, 1H), 10.44 (s, 1H), 8.28 – 8.23 (m, 1H), 8.19 (s, 1H), 7.88 (s, 1H), 7.82 (d, J = 8.9 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.33 – 7.20 (m, 7H), 7.06 (d, J = 8.7 Hz, 2H), 5.45 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.4, 149.3, 137.7, 136.9, 136.7, 131.5, 131.3, 128.6, 127.5, 127.1, 124.8,

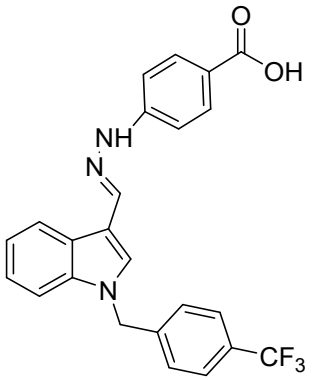
122.6, 121.9, 120.6, 119.0, 112.1, 110.6, 110.4, 49.2; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 370.1550, found: 370.1544.

1-[4-(Trifluoromethyl)benzyl]indole-3-carbaldehyde (15)



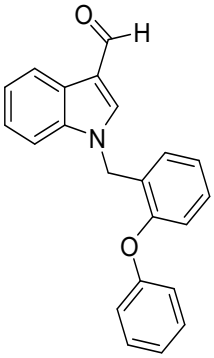
The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from indole-3-carbaldehyde (500 mg, 3.44 mmol) and 4-(trifluoromethyl)-benzyl bromide (1233 mg, 5.16 mmol) (reaction time: 1 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 6:4), **15** was obtained as a solid (574 mg, 55%). $C_{17}H_{12}F_3NO$ (303.3); mp 150 – 151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.50 (s, 1H), 8.15 – 8.11 (m, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.30 – 7.23 (m, 2H), 5.68 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 304.0944, found: 304.0954.

(*E*)-4-[2-({1-[4-(Trifluoromethyl)benzyl]indol-3-yl}methylene)hydrazineyl]benzoic acid (16)



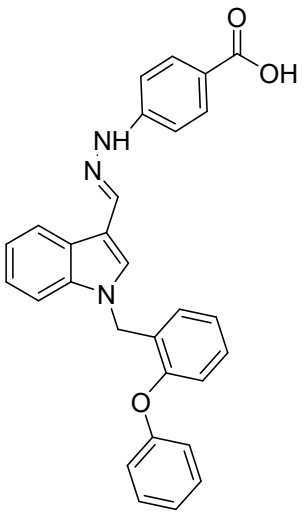
Compound **15** (140 mg, 0.46 mmol) was reacted with 4-hydrazinobenzoic acid (47 mg, 0.31 mmol) according to the procedure described for the synthesis of **12** (reaction time: 3.5 h) to give **16** as a solid (39 mg, 29%). $C_{24}H_{18}F_3N_3O_2$ (437.4); mp 242 – 243 °C; purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (brs, 1H), 10.47 (s, 1H), 8.30 – 8.26 (m, 1H), 8.20 (s, 1H), 7.91 (s, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.07 (d, J = 8.7 Hz, 2H), 5.58 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.4, 149.3, 142.6, 136.9, 136.5, 131.5, 131.3, 128.1, 127.67, 125.6, 124.9, 122.83, 122.77 (q, J = 270.9 Hz), 122.0, 120.8, 119.1, 112.4, 110.48, 110.47, 48.7; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.1424, found: 438.1448.

1-(2-Phenoxybenzyl)indole-3-carbaldehyde (17)



The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from indole-3-carbaldehyde (500 mg, 3.44 mmol) and 2-phenoxybenzyl chloride (1505 mg, 6.88 mmol) (reaction time: 17 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3), **17** was obtained as an oil (604 mg, 54%). $C_{22}H_{17}NO_2$ (327.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.46 (s, 1H), 8.13 – 8.10 (m, 1H), 7.59 – 7.56 (m, 1H), 7.39 – 7.35 (m, 2H), 7.35 – 7.33 (m, 1H), 7.30 – 7.24 (m, 2H), 7.13 (tt, *J* = 7.3 and 1.1 Hz, 1H), 7.04 – 7.02 (m, 1H), 7.02 (m, 1H), 6.98 – 6.94 (m, 2H), 6.88 (ddd, *J* = 8.1, 2.5 and 1.0 Hz, 1H), 5.55 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 328.1332, found: 328.1348.

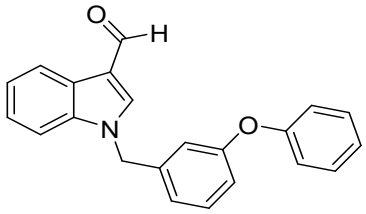
(*E*)-4-(2-{[1-(2-Phenoxybenzyl)indol-3-yl]methylene}hydrazineyl)benzoic acid (18)



Compound **17** (140 mg, 0.43 mmol) was reacted with 4-hydrazinobenzoic acid (44 mg, 0.29 mmol) according to the procedure described for the synthesis of **12** (reaction time: 3 h) to give **18** as a solid (101 mg, 76%). $C_{29}H_{23}N_3O_3$ (461.5); mp 230 – 231 °C; purity (HPLC) 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (brs, 1H), 10.45 (s, 1H), 8.28 – 8.24 (m, 1H), 8.18 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.53 – 7.48 (m, 1H), 7.39 – 7.34 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.15 – 7.10 (m, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.00 – 6.97 (m, 1H), 6.97 – 6.94 (m, 3H), 6.86 (ddd, *J* = 8.1,

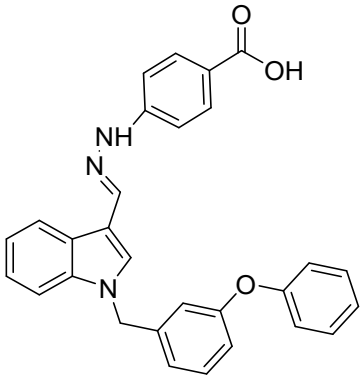
2.5 and 1.0 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.4, 156.8, 156.3, 149.3, 140.0, 136.9, 136.6, 131.5, 131.3, 130.3, 130.0, 124.8, 123.5, 122.7, 122.0, 121.9, 120.7, 119.0, 118.6, 117.4, 117.3, 112.2, 110.6, 110.4, 48.9; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 462.1812, found: 462.1891.

1-(3-Phenoxybenzyl)indole-3-carbaldehyde (19)



The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from indole-3-carbaldehyde (83 mg, 0.57 mmol) and 3-phenoxybenzyl bromide (300 mg, 1.14 mmol) (reaction time: 1.5 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3), **19** was obtained as an oil (129 mg, 69%). $C_{22}H_{17}NO_2$ (327.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.94 (s, 1H), 8.46 (s, 1H), 8.13 – 8.10 (m, 1H), 7.58 (dd, *J* = 7.5 and 1.4 Hz, 1H), 7.38 – 7.35 (m, 2H), 7.35 – 7.32 (m, 1H5), 7.30 – 7.27 (m, 1H), 7.27 – 7.24 (m, 1H), 7.13 (tt, *J* = 7.4 and 0.9 Hz, 1H), 7.04 – 7.02 (m, 1H), 7.01 – 7.02 (m, 1H), 6.98 – 6.95 (m, 2H), 6.88 (dd, *J* = 8.2 and 2.5 Hz, 1H), 5.55 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 328.1332, found: 328.1342.

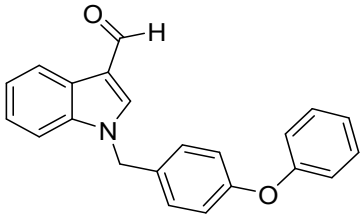
(*E*)-4-(2-{[1-(3-Phenoxybenzyl)indol-3-yl]methylene}hydrazineyl)benzoic acid (20)



Compound **19** (122 mg, 0.37 mmol) was reacted with 4-hydrazinobenzoic acid (38 mg, 0.25 mmol) according to the procedure described for the synthesis of **12** (reaction time: 2.5 h) to give **20** as a solid (86 mg, 75%). $C_{29}H_{23}N_3O_3$ (461.5); mp 227 – 228 °C; purity (HPLC) 97%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.17 (brs, 1H), 10.45 (s, 1H), 8.27 – 8.24 (m, 1H), 8.18 (s, 1H), 7.88 (s, 1H), 7.82 (d, *J* = 9.0 Hz, 2H), 7.52 – 7.49 (m, 1H), 7.38 – 7.34 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.20 (m, 2H), 7.13 (tt, *J* = 7.3 and 1.1 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.99 (dt, *J* = 7.9 and 1.2 Hz, 1H), 6.97 – 6.94 (m,

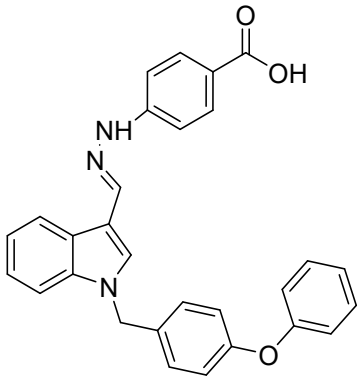
3H), 6.86 (ddd, J = 8.2, 2.5 and 1.0 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.4, 156.8, 156.3, 149.3, 140.1, 136.9, 136.6, 131.5, 131.3, 130.3, 130.0, 124.82, 123.6, 122.7, 122.1 121.9, 120.7, 119.0, 118.6, 117.41, 117.34, 112.2, 110.6, 110.5, 48.9; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 462.1812, found: 462.1856.

1-(4-Phenoxybenzyl)indole-3-carbaldehyde (21)



The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from indole-3-carbaldehyde (83 mg, 0.57 mmol) and 4-phenoxybenzyl bromide (300 mg, 1.14 mmol) (reaction time: 1 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2), **21** was obtained as an oil (150 mg, 80%). $C_{22}H_{17}NO_2$ (327.4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.34 – 8.31 (m, 1H), 7.72 (s, 1H), 7.38 – 7.36 (m, 1H), 7.36 – 7.32 (m, 4H), 7.18 – 7.15 (m, 2H), 7.13 (tt, J = 7.4 and 1.1 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.99 – 6.96 (m, 2H), 5.33 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 328.1332, found: 328.1329.

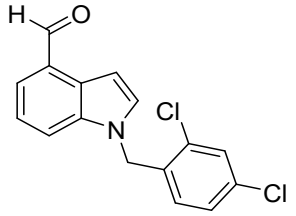
(*E*)-4-(2-{[1-(4-Phenoxybenzyl)indol-3-yl]methylene}hydrazineyl)benzoic acid (22)



Compound **21** (79 mg, 0.24 mmol) was reacted with 4-hydrazinobenzoic acid (24 mg, 0.16 mmol) according to the procedure described for the synthesis of **12** (reaction time: 3 h) to give **22** as a solid (32 mg, 44%). $C_{29}H_{23}N_3O_3$ (461.5); mp 240 – 241 °C; purity (HPLC) 96%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.17 (brs, 1H), 10.45 (s, 1H), 8.26 (dd, J = 6.9 and 2.2 Hz, 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.56 (dd, J = 6.9 and 1.6 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.32 – 7.29 (m, 2H), 7.26 – 7.19 (m, 2H), 7.12 (tt, J = 7.2 and 1.0 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.98 – 6.95 (m, 4H), 5.42 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.4, 156.5, 156.0, 149.3, 136.8, 136.6, 132.8, 131.36, 131.29, 130.0, 129.0, 124.8, 123.5, 122.7, 121.9, 120.7, 119.0,

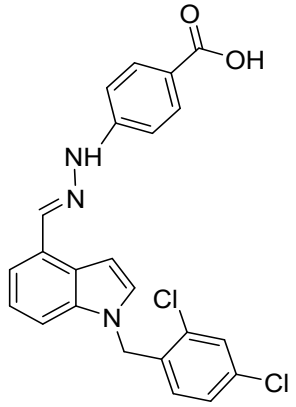
118.7, 118.6, 112.1, 110.6, 110.4, 48.6; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 462.1812, found: 462.1850.

1-(2,4-Dichlorobenzyl)indole-4-carbaldehyde (26)



Indole-4-carbaldehyde (100 mg, 0.69 mmol) and 2,4-dichlorobenzyl bromide (182 mg, 0.76 mmol) were stirred with potassium carbonate (191 mg, 1.38 mmol) in dry DMF (5 mL) at 80 °C for 3 h. The reaction was terminated by the addition of ice-cooled water. The resulting precipitate was filtered off, dried *in vacuo*, and purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to yield **26** (80 mg, 38%). $C_{16}H_{11}Cl_2NO$ (304.2); mp 96 – 97 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.81 (dt, J = 8.2 and 0.9 Hz, 1H), 7.72 (dd, J = 7.3 and 0.9 Hz, 1H), 7.70 (d, J = 3.1 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.35 (t, J = 8.2 and 7.2 Hz, 1H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1H), 7.19 (dd, J = 3.0 and 0.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.62 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 304.029, found: 304.0304.

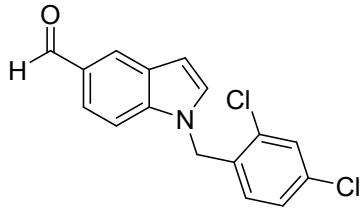
(*E*)-4-(2-{[1-(2,4-Dichlorobenzyl)indol-4-yl]methylene}hydrazineyl)benzoic acid (27)



Compound **26** (70 mg, 0.23 mmol) was reacted with 4-hydrazinobenzoic acid (23 mg, 0.15 mmol) according to the procedure described for the synthesis of **12** (reaction time: 2.5 h) to give **27** as a solid (44 mg, 66%). $C_{23}H_{17}Cl_2N_3O_2$ (438.3); mp 239 – 240 °C; purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.27 (brs, 1H), 10.81 (s, 1H), 8.24 (s, 1H), 7.85 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 3.1 Hz, 1H), 7.40 (dt, J = 8.2 and 0.9 Hz, 1H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1H), 7.25 (d, J = 6.7 Hz, 1H), 7.20 (dd, J = 3.1 and 0.8 Hz, 1H), 7.17 (t, J = 8.2 and 7.3 Hz, 1H), 7.13 (d, J = 8.4

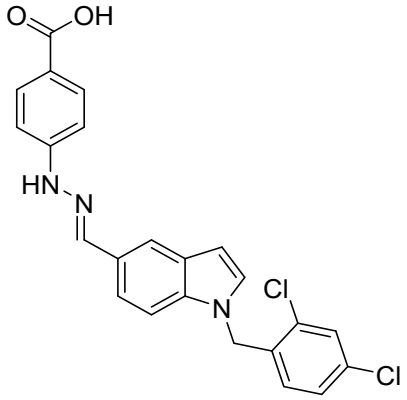
Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.57 (s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.3, 148.9, 140.7, 136.3, 134.7, 132.8, 132.6, 131.3, 130.3, 129.5, 128.9, 127.7, 127.0, 124.3, 121.5, 120.7, 120.1, 111.0, 110.8, 102.5, 46.6; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.0799, found: 438.0799.

1-(2,4-Dichlorobenzyl)indole-5-carbaldehyde (28)



Indole-5-carbaldehyde (300 mg, 2.07 mmol) was reacted with 2,4-dichlorobenzyl bromide (547 mg, 2.28 mmol) using the procedure described for the synthesis of **26** to afford **28** as a solid (265 mg, 42%). $C_{16}H_{11}Cl_2NO$ (304.2); mp 125 – 126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.09 – 8.04 (m, 1H), 7.78 – 7.74 (m, 2H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.59 (dd, *J* = 8.2 and 1.4 Hz, 1H), 7.34 (dd, *J* = 8.4 and 2.2 Hz, 1H), 6.69 (dd, *J* = 3.1 and 0.9 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 304.029, found: 304.0309.

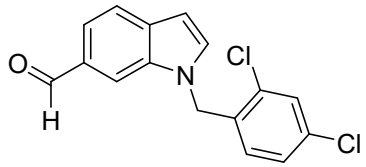
(*E*)-4-(2-{[1-(2,4-Dichlorobenzyl)indol-5-yl]methylene}hydrazineyl)benzoic acid (29)



Compound **28** (250 mg, 0.82 mmol) was reacted with 4-hydrazinobenzoic acid (108 mg, 0.71 mmol) according to the procedure described for the synthesis of **12** (reaction time: 2.5 h) to give **29** as a solid (194 mg, 62%). $C_{23}H_{17}Cl_2N_3O_2$ (438.3); mp 256 – 257 °C; purity (HPLC) 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (brs, 1H), 10.62 (s, 1H), 8.04 (s, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 2.2 Hz, 1H), 7.58 (dd, *J* = 8.7 and 1.6 Hz, 1H), 7.47 (d, *J* = 3.2 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.59 (dd, *J* = 3.1 and 0.8 Hz, 1H), 5.52 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 149.2, 140.8, 136.2, 134.6, 132.9, 132.7 131.2, 130.1, 129.6, 129.0, 128.4, 127.7,

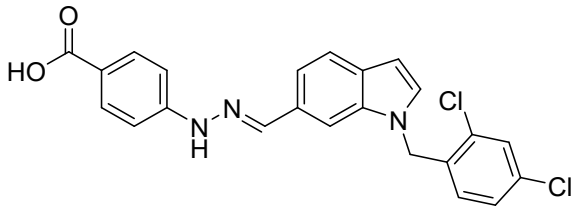
127.2, 119.68, 119.64, 119.55, 110.9, 110.5, 102.3, 46.6; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.0799, found: 438.0764.

1-(2,4-Dichlorobenzyl)indole-6-carbaldehyde (30)



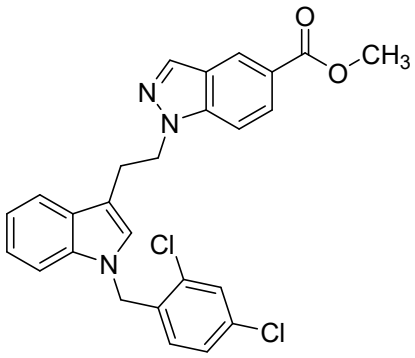
Indole-6-carbaldehyde (150 mg, 1.03 mmol) was reacted with 2,4-dichlorobenzyl bromide (271 mg, 1.13 mmol) using the procedure described for the synthesis of **26**. Purification by silica gel chromatography (cyclohexane to cyclohexane/ethyl acetate, 8:2) yielded **30** as a solid (149 mg, 47%). $C_{16}H_{11}Cl_2NO$ (304.2); mp 101 – 102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.23 (dd, *J* = 1.6 and 0.7 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.66 (dd, *J* = 8.6 and 1.6 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.34 (dd, *J* = 8.4 and 2.2 Hz, 1H), 6.78 (dd, *J* = 3.1 and 0.9 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.58 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 304.029, found: 304.0304.

(*E*)-4-(2-{[1-(2,4-Dichlorobenzyl)indol-6-yl]methylene}hydrazineyl)benzoic acid (31)



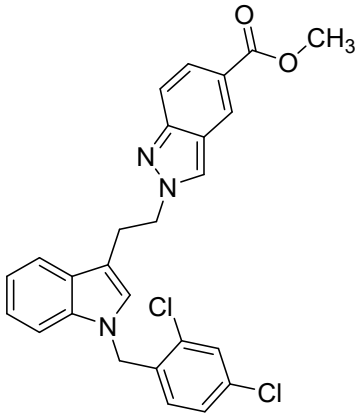
Compound **30** (140 mg, 0.46 mmol) was reacted with 4-hydrazinobenzoic acid (47 mg, 0.31 mmol) according to the procedure described for the synthesis of **12** (reaction time: 3 h) to give **31** as a solid (87 mg, 64%). $C_{23}H_{17}Cl_2N_3O_2$ (438.3); mp 230 – 231 °C; purity (HPLC) 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (brs, 1H), 10.66 (s, 1H), 7.99 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.65 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.35 (dd, *J* = 8.3 and 2.2 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.56 (dd, *J* = 3.2 and 0.8 Hz, 1H), 5.56 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.3, 149.0, 140.5, 136.0, 134.7, 132.9, 132.8, 131.2, 130.5, 129.8, 129.1, 129.0, 128.9, 127.8, 120.9, 119.9, 117.6, 111.0, 108.5, 102.0, 46.5; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.0799, found: 438.0778.

Methyl 1-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-1*H*-indazole-5-carboxylate (38)



A solution of methyl indazole-5-carboxylate (34 mg, 0.19 mmol) in dry DMF (2 mL) was treated with a suspension of sodium hydride (60% dispersion in mineral oil) (8 mg, 0.20 mmol) in dry DMF (1 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 5 min and at room temperature for 25 min. Then a solution of **34** (73 mg, 0.19 mmol) in dry DMF (1 mL) was added and stirring was continued at room temperature for 18 h. The reaction mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined organic phases were washed three times with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 82:18) to give **38** as an oil (49 mg, 54%) $C_{26}H_{21}Cl_2N_3O_2$ (478.4); mp 93 – 94 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (dd, J = 1.6 and 0.8 Hz, 1H), 8.24 (d, J = 0.9 Hz, 1H), 7.75 (dd, J = 8.9 and 1.6 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.44 (dt, J = 8.9 and 0.9 Hz, 1H), 7.24 (dt, J = 8.3 and 0.9 Hz, 1H), 7.11 – 7.00 (m, 3H), 6.95 (s, 1H), 6.21 (d, J = 8.3 Hz, 1H), 5.30 (s, 2H), 4.73 (t, J = 6.8 Hz, 2H), 3.86 (s, 3H), 3.30 (d, J = 6.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 478.1084, found: 478.1086.

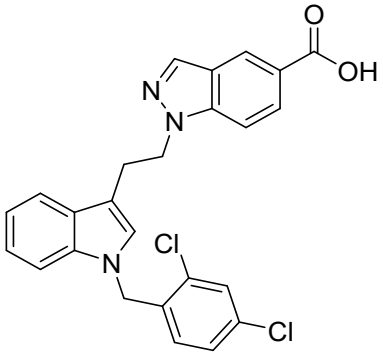
Methyl 2-{2-[1-(2,4-dichlorobenzyl)indole-3-yl]ethyl}-2*H*-indazole-5-carboxylate (39)



Compound **39** was isolated as another oily product (40 mg, 44%) during chromatography in the synthesis of **38**. $C_{26}H_{21}Cl_2N_3O_2$ (478.4); mp 102 – 103 °C; ^{1}H

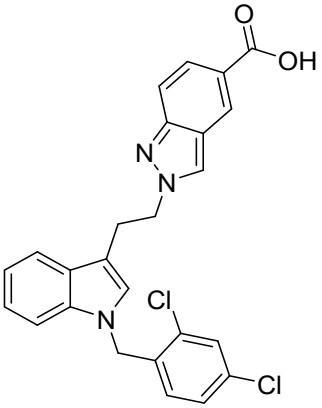
NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.41 (m, 2H), 7.73 (dd, *J* = 9.1 and 1.6 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.32 (dt, *J* = 8.3 and 0.9 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.04 (dd, *J* = 8.0 and 1.1 Hz, 1H), 6.97 (s, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.34 (s, 2H), 4.75 (t, *J* = 6.9 Hz, 2H), 3.85 (s, 3H), 3.40 (t, *J* = 6.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 478.1084, found: 478.1115.

1-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-1*H*-indazole-5-carboxylic acid (40)



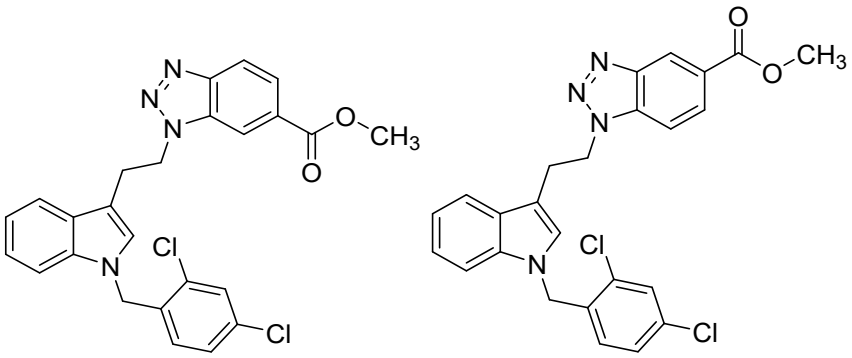
A solution of **38** (45 mg, 0.094 mmol) in a mixture of methanol (2 mL), 10% aqueous potassium hydroxide solution (1 mL), and THF (1 mL) was heated to 70 °C for 3 h with stirring. After adjustment to pH 1 with 10% aqueous hydrochloric acid, the mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and the solvent was removed *in vacuo*. Chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 7:3:0.1) gave **40** as an oil (40 mg, 92%). $C_{25}H_{19}Cl_2N_3O_2$ (464.3); mp 94 – 95 °C. purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.38 (dd, *J* = 1.6 and 0.8 Hz, 1H), 8.22 (d, *J* = 0.9 Hz, 1H), 7.77 (dd, *J* = 8.8 and 1.6 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.60 (dt, *J* = 7.8 and 1.0 Hz, 1H), 7.44 (dt, *J* = 8.9 and 0.9 Hz, 1H), 7.24 (dt, *J* = 8.2 and 0.9 Hz, 1H), 7.13 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.08 (td, *J* = 8.2 and 1.2 Hz, 1H), 7.04 (td, *J* = 7.9 and 1.1 Hz, 1H), 6.99 (s, 1H), 6.24 (d, *J* = 8.4 Hz, 1H), 5.32 (s, 2H), 4.72 (t, *J* = 6.9 Hz, 2H), 3.30 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.6, 141.0, 135.9, 134.59, 134.58, 132.6, 132.5, 129.2, 128.8, 127.6, 127.4, 127.0, 126.2, 123.9, 123.02, 123.01, 121.6, 119.1, 118.7, 111.1, 109.8, 109.3, 48.9, 46.1, 25.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 464.0927, found: 464.0967.

2-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-2*H*-indazole-5-carboxylic acid (41)



Compound **39** (40 mg, 0.084 mmol) was saponified in a similar manner as described for the synthesis of **40** to give **41** as a solid (36 mg, 93%). $C_{25}H_{19}Cl_2N_3O_2$ (464.3); mp 219 – 220 °C, purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.43 (d, J = 1.0 Hz, 1H), 8.39 – 8.38 (m, 1H), 7.73 (dd, J = 9.1 and 1.6 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.60 (d, J = 2.2 Hz, 1H), 7.32 (dt, J = 8.3 and 1.0 Hz, 1H), 7.15 (dd, J = 8.4 and 2.2 Hz, 1H), 7.11 (td, J = 8.2 and 1.2 Hz, 1H), 7.04 (td, J = 7.9 and 1.0 Hz, 1H), 7.02 (s, 1H), 6.39 (d, J = 8.4 Hz, 1H), 5.36 (s, 2H), 4.74 (t, J = 7.0 Hz, 2H), 3.40 (t, J = 7.0 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.8, 149.1, 136.1, 134.6, 132.7, 132.5, 129.4, 128.8, 127.50, 127.42, 127.0, 126.8, 125.1, 124.8, 123.5, 121.7, 120.5, 119.1, 118.8, 116.7, 110.8, 109.9, 53.5, 46.1, 26.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 464.0927, found: 464.0967.

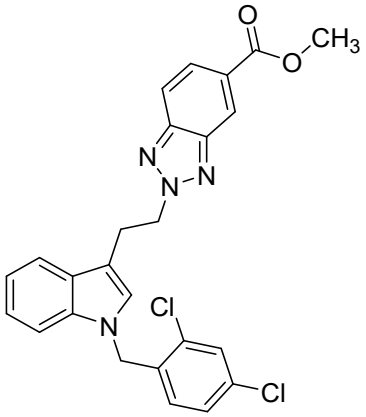
Methyl 1-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-1*H*-benzotriazole-5-carboxylate and methyl 1-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-1*H*-benzotriazole-6-carboxylate (42)



A solution of **34** (140 mg, 0.37 mmol) and methyl benzotriazole-5-carboxylate (66 mg, 0.37 mmol) in dry DMF (10 mL) was treated with anhydrous potassium carbonate (103 mg, 0.75 mmol) and stirred for 17 h at room temperature. After addition of water, the reaction mixture was exhaustively extracted with ethyl acetate, dried over sodium

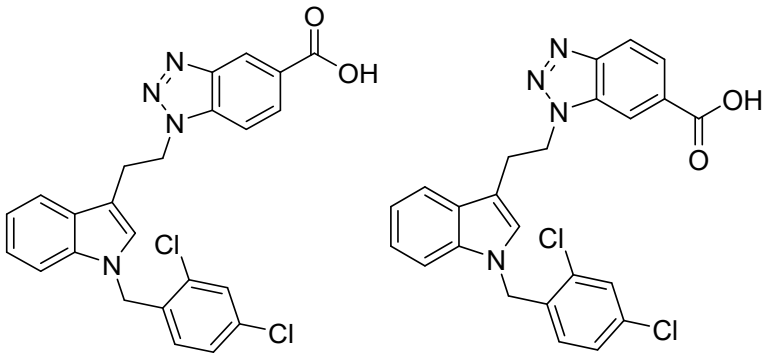
sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 83:17) to yield **42**, which was a mixture (6:4) of the 1*H*-indazole-5- and -6-carboxylic acid ester derivatives (44 mg, 25%). $C_{25}H_{20}Cl_2N_4O_2$ (479.4); ^{1}H NMR (600 MHz, DMSO-d_6) signals of benzotriazole-5-carboxylate: δ 8.55 (dd, *J* = 1.5 and 0.8 Hz, 1H), 7.92 (dd, *J* = 8.8 and 1.5 Hz, 1H), 7.68 (dd, *J* = 8.8 and 0.8 Hz, 1H), 7.61 – 7.60 (m, 1H), 7.58 (dt, *J* = 3.4 and 1.0 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.17 – 7.11 (m, 1H), 7.13 – 7.05 (m, 1H), 7.05 – 7.01 (m, 1H), 6.95 (s, 1H), 6.25 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 2H), 5.05 (t, *J* = 6.8 Hz, 2H), 3.90 (s, 3H), 3.43 – 3.38 (m, 2H); signals of benzotriazole-6-carboxylate: δ 8.13 (dd, *J* = 1.5 and 0.8 Hz, 0.7H), 8.06 (dd, *J* = 8.7 and 0.8 Hz, 0.7H), 7.85 (dd, *J* = 8.7 and 1.4 Hz, 0.7H), 7.61 – 7.60 (m, 0.7H), 7.56 (dt, *J* = 3.3 and 1.0 Hz, 0.7H), 7.29 – 7.24 (m, 0.7H), 7.17 – 7.11 (m, 0.7H), 7.13 – 7.05 (m, 0.7H), 7.05 – 7.01 (m, 0.7H), 6.97 (s, 0.7H), 6.29 (d, *J* = 8.4 Hz, 0.7H), 5.29 (s, 1.4H), 5.12 (t, *J* = 6.7 Hz, 1.4H), 3.90 (s, 2.1H), 3.84 (s, 2.1H), 3.43 – 3.38 (m, 1.4H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 479.1036, found: 479.1026.

Methyl 2-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-2*H*-benzotriazole-5-carboxylate (43)



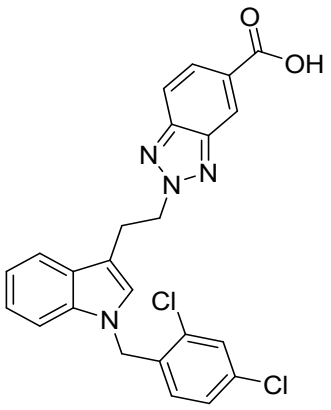
Compound **43** was isolated as another product (45 mg, 26%) during chromatography in the synthesis of **42**. $C_{25}H_{20}Cl_2N_4O_2$ (479.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.53 – 8.51 (m, 1H), 8.00 (dd, *J* = 9.0 and 0.9 Hz, 1H), 7.92 (dd, *J* = 8.9 and 1.5 Hz, 1H), 7.62 (dt, *J* = 7.8 and 1.0 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.12 – 7.08 (m, 2H), 7.06 – 7.01 (m, 1H), 6.96 (s, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 2H), 5.09 (t, *J* = 6.8 Hz, 2H), 3.91 (s, 3H), 3.54 (t, *J* = 6.8 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 479.1036, found: 479.1013.

1-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-1*H*-benzotriazole-5-carboxylic acid and 1-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-1*H*-benzotriazole-6-carboxylic acid (44)



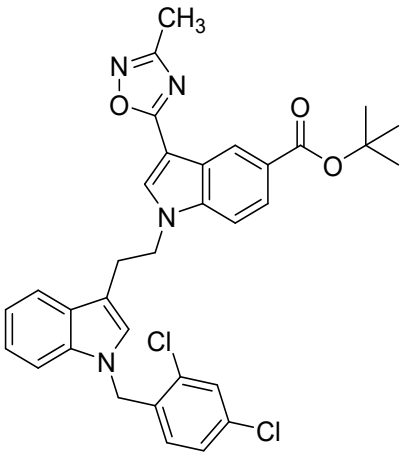
The isomeric mixture **42** (38 mg, 0.079 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give the isomeric mixture **44** (32 mg, 87%) in a ratio of 6:4 as a solid. $C_{24}H_{18}Cl_2N_4O_2$ (465.3); mp 94 – 95 °C; ^{1}H NMR (600 MHz, DMSO-d_6) signals of benzotriazole-6-carboxylic acid: δ 8.54 – 8.50 (m, 1H), 7.93 (dd, *J* = 8.7 and 1.4 Hz, 1H), 7.68 (dd, *J* = 8.7 and 0.8 Hz, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.57 (dt, *J* = 7.8 and 1.1 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.16 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.11 – 7.04 (m, 1H), 7.04 – 6.99 (m, 2H), 6.26 (d, *J* = 9.1 Hz, 1H), 5.31 (s, 2H), 5.05 (t, *J* = 6.8 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H); signals of benzotriazole-6-carboxylic acid: δ 8.27 – 8.26 (m, 0.7 H), 8.04 (dd, *J* = 8.7 and 0.8 Hz, 0.7H), 7.86 (dd, *J* = 8.7 and 1.4 Hz, 0.7H), 7.62 (d, *J* = 2.1 Hz, 0.7H), 7.53 (dt, *J* = 7.8 and 0.9 Hz, 0.7H), 7.28 – 7.22 (m, 0.7H), 7.18 (dd, *J* = 8.4 and 2.1 Hz, 0.7H), 7.11 – 7.04 (m, 0.7H), 7.04 – 6.99 (m, 0.7H), 6.98 (s, 0.7H), 6.30 (d, *J* = 9.1 Hz, 0.7H), 5.32 (s, 1.4H), 5.10 (t, *J* = 6.9 Hz, 1.4H), 3.41 (t, *J* = 6.8 Hz, 1.4H); ^{13}C NMR (151 MHz, DMSO-d_6) signals of benzotriazole-5-carboxylic acid: δ 167.0, 144.7, 136.0, 135.2, 134.6, 132.6, 132.5, 129.3, 128.8, 127.5, 127.4, 127.3, 127.2, 126.6, 121.7, 121.2, 119.1, 118.6, 110.6, 110.4, 109.9, 48.4, 46.1, 25.3; signals of benzotriazole-6-carboxylic acid: δ 167.0, 146.9, 136.0, 134.6, 132.8, 132.7, 132.6, 129.4, 129.3, 128.8, 127.44, 127.40, 127.18, 124.12, 121.70, 119.11, 119.0, 118.5, 113.0, 110.6, 109.8, 48.5, 46.1, 25.4; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 465.0880, found: 465.0876.

2-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-2*H*-benzotriazole-5-carboxylic acid (45)



Compound **43** (40 mg, 0.083 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give **45** as a solid (33 mg, 85%). $C_{24}H_{18}Cl_2N_4O_2$ (465.3); mp 177 – 178 °C; purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (t, J = 1.2 Hz, 1H), 7.96 (dd, J = 8.9 and 0.9 Hz, 1H), 7.91 (dd, J = 9.0 and 1.4 Hz, 1H), 7.62 (dt, J = 7.8 and 1.0 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.30 (dt, J = 8.2 and 1.0 Hz, 1H), 7.12 – 7.10 (m, 1H), 7.10 – 7.05 (m, 1H), 7.08 – 6.99 (m, 1H), 7.00 (s, 1H), 6.35 (d, J = 8.4 Hz, 1H), 5.32 (s, 2H), 5.08 (t, J = 6.9 Hz, 2H), 3.54 (t, J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.1, 145.4, 143.0, 136.0, 134.5, 132.7, 132.6, 129.4, 128.9, 128.8, 127.39, 127.34, 127.0, 126.0, 121.7, 120.6, 119.1, 118.6, 117.9, 110.3, 109.9, 56.9, 46.1, 25.4; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 465.0880, found: 465.0873.

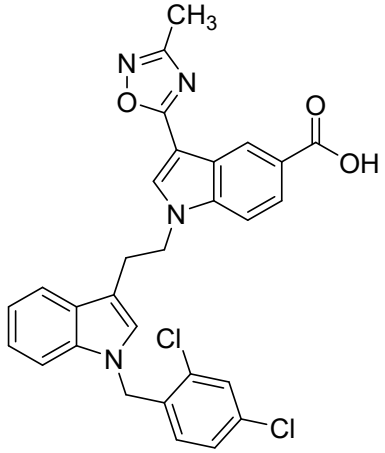
***tert*-Butyl 1-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-3-(3-methyl-1,2,4-oxadiazol-5-yl)indole-5-carboxylate (49)**



To a solution of *tert*-butyl 3-(3-methyl-1,2,4-oxadiazol-5-yl)indole-5-carboxylate (S. Bovens *et al.*, *J. Med. Chem.*, 2010, **53**, 8298) (40 mg, 0.13 mmol) in dry DMF (5 mL) was added cesium carbonate (65 mg, 0.20 mmol) and **34** (50 mg, 0.13 mmol). After

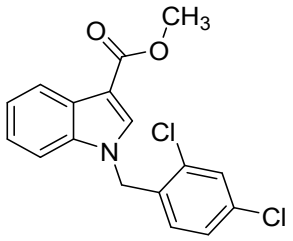
stirring at 50 °C for 16 h, the reaction mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Purification by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) afforded **49** as a solid (61 mg, 78%). $C_{33}H_{30}Cl_2N_4O_3$ (601.5); mp 75 – 76 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.69 (d, J = 1.6 Hz, 1H), 8.40 (s, 1H), 7.76 (dd, J = 8.7 and 1.7 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 7.12 – 7.06 (m, 1H), 7.07 – 7.02 (m, 1H), 7.00 (dd, J = 8.4 and 2.1 Hz, 1H), 6.98 (s, 1H), 6.19 (d, J = 8.1 Hz, 1H), 5.31 (s, 2H), 4.66 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H), 1.58 (s, 9H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 601.1768, found: 601.1787.

1-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-3-(3-methyl-1,2,4-oxadiazol-5-yl)indole-5-carboxylic acid (50)



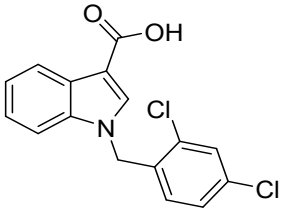
A solution of **49** (55 mg, 0.091 mmol) in dry dichloromethane (11 mL) was treated with trifluoroacetic acid (924 mg, 8.1 mmol) and stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to give **50** as a solid (42 mg, 84%). $C_{29}H_{22}Cl_2N_4O_3$ (545.4); mp 214 – 215 °C; purity (HPLC) 96%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.81 (brs, 1H), 8.74 (d, J = 2.1 Hz, 1H), 8.39 (s, 1H), 7.83 (dd, J = 8.7 and 1.7 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.59 (d, J = 2.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.06 – 7.03 (m, 2H), 7.03 (s, 1H), 6.27 (d, J = 8.3 Hz, 1H), 5.33 (s, 2H), 4.66 (t, J = 6.9 Hz, 2H), 3.31 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.7, 167.8, 167.0, 138.7, 136.0, 134.8, 134.6, 132.6, 132.5, 129.1, 128.8, 127.5, 127.3, 127.2, 124.27, 124.21, 123.8, 122.6, 121.7, 119.1, 118.8, 111.1, 110.7, 109.8, 100.0, 47.0, 46.1, 25.3, 11.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 545.1142, found: 545.1149.

Methyl 1-(2,4-dichlorobenzyl)indole-3-carboxylate (53)



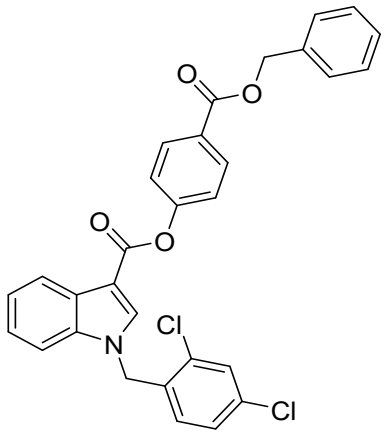
The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from methyl indole-3-carboxylate (500 mg, 2.85 mmol) and 2,4-dichlorobenzyl bromide (753 mg, 3.14 mmol) (reaction time: 30 min). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 9:1), **53** was obtained as a solid (880 mg, 92%). $C_{17}H_{13}Cl_2NO_2$ (334.2); mp 133 – 134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.08 – 8.02 (m, 1H), 7.71 (d, J = 2.1 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.35 (dd, J = 8.3 and 2.2 Hz, 1H), 7.27 – 7.21 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 5.60 (s, 2H), 3.81 (s, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 334.0396, found: 334.0373.

1-(2,4-Dichlorobenzyl)indole-3-carboxylic acid (54)



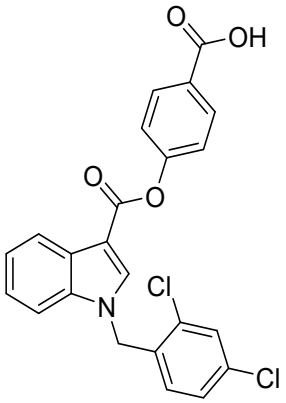
A solution of **53** (800 mg, 2.39 mmol) in a mixture of methanol (6 mL), 10% aqueous potassium hydroxide solution (3 mL), and THF (3 mL) was heated at 70 °C for 4 h with stirring. After cooling, the mixture was adjusted with 10% aqueous hydrochloric acid to pH 1. The formed precipitate was filtered off and dried under reduced pressure to give **54** (742 mg, 97%). $C_{16}H_{11}Cl_2NO_2$ (320.2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.07 – 8.03 (m, 1H), 7.71 (d, J = 2.1 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.36 (dd, J = 8.4 and 2.2 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 5.59 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 320.0240, found: 320.0255.

4-[(Benzyloxy)carbonyl]phenyl 1-(2,4-dichlorobenzyl)indole-3-carboxylate (55)



A solution of **54** (270 mg, 0.84 mmol) in dry dichloromethane (10 mL) was treated with dicyclohexylcarbodiimide (173 mg, 0.84 mmol), 4-dimethylaminopyridine (103 mg, 0.84 mmol), and benzyl 4-hydroxybenzoate (192 mg, 0.84 mmol) and stirred at room temperature for 21 h. The mixture was filtered and the filtrate was concentrated. The residue was diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed twice each with 5% acetic acid, 1 M sodium hydroxide solution, and water, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 85:15) to yield **55** as an oil (115 mg, 26%). $C_{30}H_{21}Cl_2NO_4$ (530.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.11 – 8.06 (m, 3H), 7.73 (d, J = 2.2 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.51 – 7.48 (m, 2H), 7.47 – 7.45 (m, 2H), 7.44 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 7.33 – 7.27 (m, 2H), 6.88 (d, J = 8.4 Hz, 1H), 5.67 (s, 2H), 5.38 (s, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 530.0920, found: 530.0975.

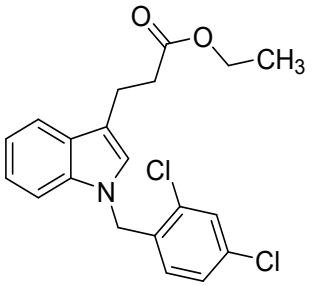
4-{[1-(2,4-Dichlorobenzyl)indol-3-carbonyl]oxy}benzoic acid (56)



Compound **55** (100 mg, 0.19 mmol) was dissolved in a mixture of ethyl acetate (2 mL) and ethanol (1 mL). After addition of Pd/C (30 mg, 10%), the mixture was stirred under

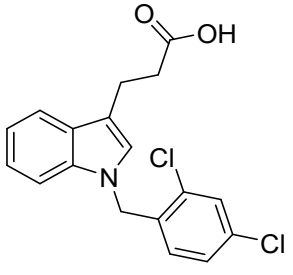
a hydrogen-filled balloon at room temperature for 5 h. The suspension was then diluted with ethyl acetate and filtered. The filtrate was concentrated to dryness under reduced pressure and the residue was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 7:3:0.1) to give **56** as a solid (42 mg, 51%). $C_{23}H_{15}Cl_2NO_4$ (440.3); mp 223 – 224 °C; purity (HPLC) 96%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.11 – 8.06 (m, 1H), 8.06 – 8.01 (m, 2H), 7.73 (d, J = 2.1 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.45 – 7.40 (m, 2H), 7.39 (dd, J = 8.4 and 2.2 Hz, 1H), 7.33 – 7.26 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H), 5.67 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 161.7, 154.1, 137.3, 136.5, 133.32, 133.28, 133.0, 130.9, 130.0, 129.2, 128.1, 127.9, 126.2, 123.3, 122.5, 122.3, 120.8, 111.4, 105.0, 47.2; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 440.0451, found: 440.0497.

Ethyl 3-[1-(2,4-dichlorobenzyl)indol-3-yl]propanoate (61)



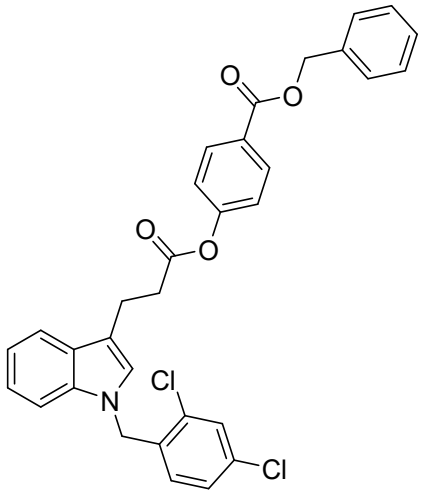
The synthesis was carried out in a similar manner as described for the preparation of **11**, starting from ethyl 3-(indol-3-yl)propionate (400 mg, 1.84 mmol) (M. Pedras *et al.*, *J. Agric. Food Chem.*, 2012, **60**, 7792) and 2,4-dichlorobenzyl bromide (485 mg, 2.02 mmol) (reaction time: 1.5 h). After chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 93:7), **61** was obtained as an oil (230 mg, 33%). $C_{20}H_{19}Cl_2NO_2$ (376.3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 2.2 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.35 – 7.29 (m, 2H), 7.20 (s, 1H), 7.11 (td, J = 8.2 and 1.3 Hz, 1H), 7.04 (td, J = 8.0 and 1.1 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.43 (s, 2H), 4.02 (q, J = 7.1 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 376.0866, found: 376.0876.

3-[1-(2,4-Dichlorobenzyl)indol-3-yl]propionic acid (62)



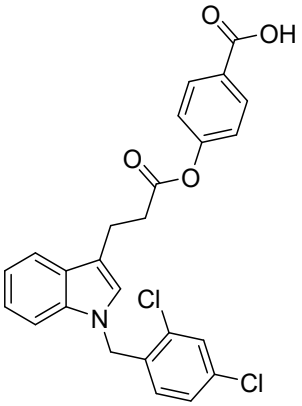
A solution of **61** (109 mg, 0.29 mmol) in methanol (4 mL) was treated with 5 M aqueous sodium hydroxide solution (2 mL) and stirred at 50 °C for 3 h. After adjusting pH to 1 with 10% aqueous hydrochloric acid solution, the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 8:2:0.1) to obtain **62** as a solid (95 mg, 94%). $C_{18}H_{15}Cl_2NO_2$ (348.2); mp 180 – 181 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 2.2 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.23 (s, 1H), 7.10 (td, J = 8.2 and 1.2 Hz, 1H), 7.04 (td, J = 8.1 and 1.1 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 5.43 (s, 2H), 2.94 (t, J = 8.0 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 348.0553, found: 348.0547.

Benzyl 4-({3-[1-(2,4-dichlorobenzyl)indol-3-yl]propanoyl}oxy)benzoate (63)



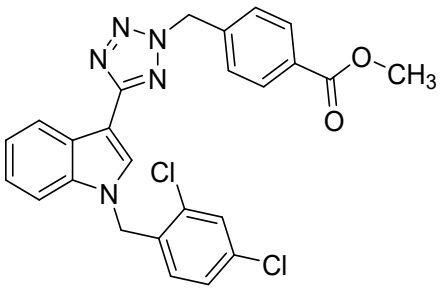
The synthesis was carried out analogously to the procedure described for the preparation of **55**, starting from **62** (87 mg, 0.25 mmol) and benzyl 4-hydroxybenzoate (57 mg, 0.25 mmol) (reaction time: 23 h). The crude product was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 9:1) to give **63** as an oil (75 mg, 54%). $C_{32}H_{25}Cl_2NO_4$ (558.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.98 (m, 2H), 7.67 – 7.62 (m, 2H), 7.49 – 7.45 (m, 2H), 7.43 – 7.35 (m, 4H), 7.30 (s, 1H), 7.24 (dd, J = 8.3 and 2.2 Hz, 1H), 7.19 – 7.16 (m, 2H), 7.13 (td, J = 8.3 and 1.3 Hz, 1H), 7.06 (td, J = 7.9 and 1.0 Hz, 1H), 6.62 (d, J = 8.3 Hz, 1H), 5.45 (s, 2H), 5.35 (s, 2H), 3.12 (t, J = 7.3 Hz, 2H), 3.00 (t, J = 7.0 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 558.1233, found: 558.1263.

4-({3-[1-(2,4-Dichlorobenzyl)indol-3-yl]propanoyl}oxy)benzoic acid (64)



A solution of **63** (70 mg, 0.13 mmol) in a mixture of ethyl acetate (2 mL) and ethanol (1 mL) was treated with Pd/C 10% (28 mg) and stirred under hydrogen atmosphere for 5 h at room temperature. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was concentrated to dryness *in vacuo* and the residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 7:3:0.1). The crude product was additionally purified by preparative RP-HPLC (acetonitrile/water/formic acid, 8:2:0.01) to give **64** as a solid (30 mg, 51%). $C_{25}H_{19}Cl_2NO_4$ (468.3); mp 146 – 147 °C; purity (HPLC) 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.95 – 7.93 (m, 2H), 7.67 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.31 (s, 1H), 7.26 (dd, J = 8.4 and 2.2 Hz, 1H), 7.15 – 7.12 (m, 3H), 7.06 (td, J = 7.9 and 1.0 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.46 (s, 2H), 3.11 (t, J = 7.4 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.1, 166.6, 153.8, 136.2, 134.8, 132.8, 132.7, 130.8, 129.7, 128.9, 128.6, 127.6, 127.4, 126.3, 121.9, 121.7, 119.0, 118.9, 113.4, 110.0, 46.3, 34.4, 20.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 467.0691, found: 468.0764.

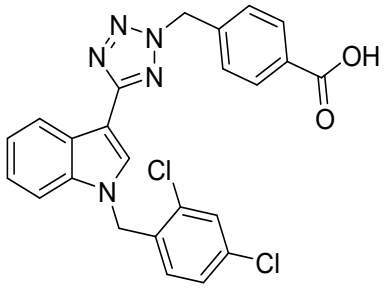
Methyl 4-({5-[1-(2,4-dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}methyl)benzoate (67)



A solution of **66** (85 mg, 0.25 mmol) in acetonitrile (5 mL) was treated with freshly ground anhydrous potassium carbonate (69 mg, 0.50 mmol). After addition of methyl 4-(bromomethyl)benzoate (64 mg, 0.28 mmol), the mixture was heated at reflux for 5 h. The reaction mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined organic phases were washed with water, and dried over sodium

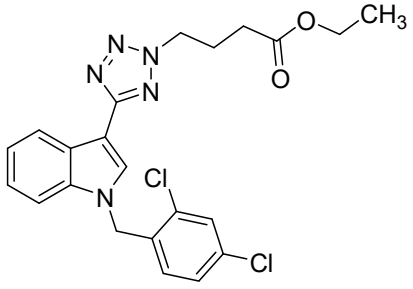
sulfate. The solvent was removed under reduced pressure and the residue chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) to give **67** as a solid (76 mg, 63%). $C_{25}H_{19}Cl_2N_5O_2$ (492.4); mp 148 – 149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.21 – 8.16 (m, 1H), 8.02 – 7.97 (m, 2H), 7.70 (d, J = 2.2 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.51 – 7.45 (m, 1H), 7.33 (dd, J = 8.4 and 2.2 Hz, 1H), 7.29 – 7.20 (m, 2H), 6.79 (d, J = 8.4 Hz, 1H), 6.11 (s, 2H), 5.62 (s, 2H), 3.85 (s, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 492.0989, found: 492.1021.

4-({5-[1-(2,4-Dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}methyl)benzoic acid (68)



Compound **67** (50 mg, 0.10 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 5 h) to give **68** as a solid (33 mg, 68%). $C_{24}H_{17}Cl_2N_5O_2$ (478.3); mp 227 – 228 °C; purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.21 – 8.17 (m, 1H), 8.00 – 7.94 (m, 2H), 7.70 (d, J = 2.2 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.33 (dd, J = 8.4 and 2.2 Hz, 1H), 7.28 – 7.21 (m, 2H), 6.78 (d, J = 8.4 Hz, 1H), 6.09 (s, 2H), 5.62 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8, 161.7, 139.0, 136.3, 134.0, 133.0, 132.8, 131.0, 129.8, 129.7, 129.0, 128.3, 127.8, 125.1, 122.8, 121.1, 120.7, 110.8, 102.7, 55.3, 46.8; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 478.0832, found: 478.0846.

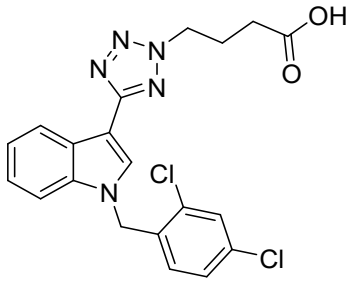
Ethyl 4-{5-[1-(2,4-dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}butanoate (69)



Compound **66** (91 mg, 0.26 mmol) was reacted with ethyl 4-bromobutanoate (57 mg, 0.29 mmol) according to the procedure described for the synthesis of **67**. Chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 75:25) gave **69** as an oil (43 mg, 35%). $C_{22}H_{21}Cl_2N_5O_2$ (458.3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 – 8.19 (m, 2H), 7.71 (d, J = 2.2 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.35 (dd, J = 8.4 and 2.2 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 5.63 (s, 2H), 4.77 (t, J = 6.9 Hz, 2H),

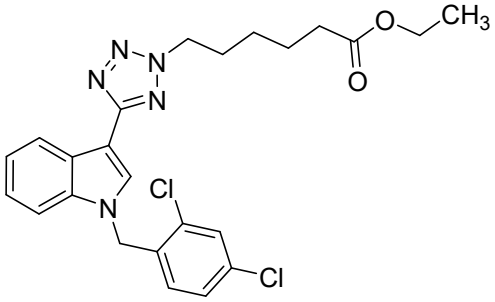
4.03 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.23 (p, *J* = 7.1 Hz, 2H), 1.18 – 1.13 (m, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1145, found: 458.1114.

4-{5-[1-(2,4-Dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}butyric acid (70)



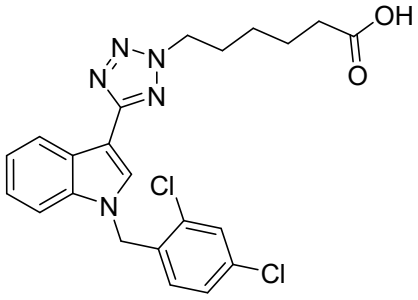
Compound **69** (38 mg, 0.83 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give **70** as a solid (27 mg, 76%). $C_{20}H_{17}Cl_2N_5O_2$ (430.3); mp 158 – 159 °C; purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 – 8.20 (m, 2H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.35 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.28 – 7.22 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.63 (s, 2H), 4.76 (t, *J* = 6.9 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.20 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.5, 161.3, 136.3, 134.0, 133.1, 132.9, 129.9, 129.6, 129.1, 127.8, 125.1, 122.8, 121.1, 120.8, 110.8, 103.0, 51.7, 46.8, 30.4, 24.4; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 430.0832, found: 430.0790.

Ethyl 6-{5-[1-(2,4-dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}hexanoate (73)



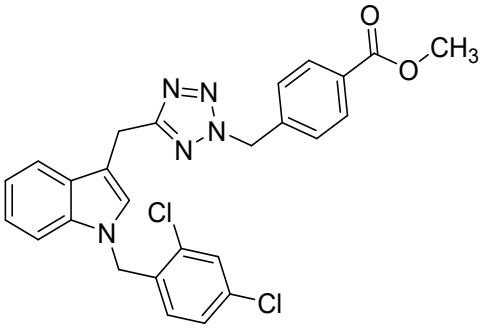
Compound **66** (590 mg, 1.71 mmol) was reacted with ethyl 6-bromohexanoate (460 mg, 2.06 mmol) according to the procedure described for the synthesis of **67** (reaction time: 3 h) to afford **73** as a solid **(**454 mg, 54%). $C_{24}H_{25}Cl_2N_5O_2$ (486.4); mp 118 – 119 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, *J* = 7.1 Hz, 3H), 1.26 – 1.38 (m, 2H), 1.58 (p, *J* = 7.4 Hz, 2H), 1.93 – 2.07 (m, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 4.72 (t, *J* = 6.9 Hz, 2H), 5.63 (s, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.28 (m, 2H), 7.35 (dd, *J* = 8.4 and 2.2 Hz, 1H5), 7.47 – 7.52 (m, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 8.19 – 8.24 (m, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 486.1458, found: 486.1457.

6-{5-[1-(2,4-Dichlorobenzyl)indol-3-yl]-2*H*-tetrazol-2-yl}hexanoic acid (74)



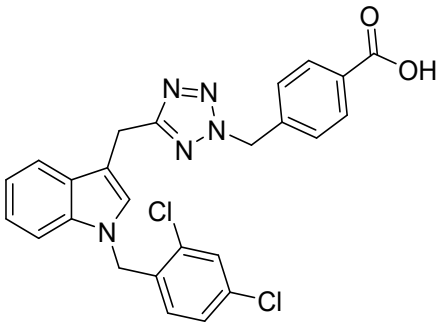
Compound **73** (440 mg, 0.90 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 2 h) to give **74** as a solid (382 mg, 92%). $C_{22}H_{21}Cl_2N_5O_2$ (458.3); mp 136 – 137 °C; purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.29 – 1.35 (m, 2H), 1.56 (p, J = 7.5 Hz, 2H), 1.96 – 2.02 (m, 2H), 2.21 (t, J = 7.4 Hz, 2H), 4.72 (t, J = 7.0 Hz, 2H), 5.63 (s, 2H), 6.80 (d, J = 8.4 Hz, 1H), 7.21 – 7.28 (m, 2H), 7.35 (dd, J = 8.4 and 2.2 Hz, 1H), 7.45 – 7.52 (m, 1H), 7.71 (d, J = 2.2 Hz, 1H), 8.19 – 8.26 (m, 2H), 12.02 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 23.8, 25.4, 28.5, 33.4, 46.8, 52.3, 103.0, 110.7, 120.8, 121.1, 122.8, 125.1, 127.8, 129.1, 129.5, 129.9, 132.8, 133.1, 134.0, 136.3, 161.2, 174.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1145, found: 458.1170.

Methyl 4-[(5-{[1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)methyl]benzoate (77)



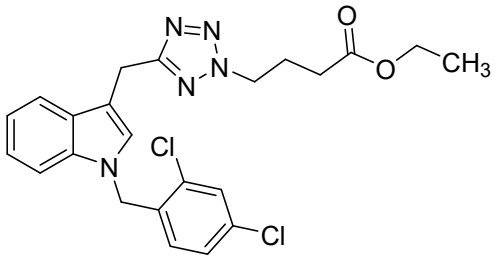
Compound **76** (100 mg, 0.28 mmol) was reacted with methyl 4-(bromomethyl)benzoate (71 mg, 0.31 mmol) according to the procedure described for the synthesis of **68** to yield **77** as a solid (46 mg, 33%). $C_{26}H_{21}Cl_2N_5O_2$ (506.4); mp 147 – 148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 – 7.93 (m, 2H), 7.67 (d, J = 2.1 Hz, 1H), 7.51 (dt, J = 7.9 and 1.0 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.35 (dt, J = 8.2 and 0.9 Hz, 1H), 7.31 (s, 1H), 7.29 (dd, J = 8.4 and 2.2 Hz, 1H), 7.11 (td, J = 8.2 and 1.2 Hz, 1H), 7.00 (td, J = 7.9 and 1.0 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.99 (s, 2H), 5.44 (s, 2H), 4.33 (s, 2H), 3.85 (s, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 506.1145, found: 506.1160.

4-[(5-{[1-(2,4-Dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)methyl]benzoic acid (78)



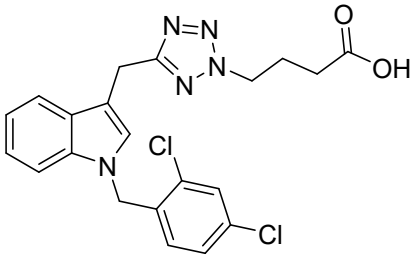
Compound **77** (40 mg, 0.079 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give **78** as a solid (29 mg, 75%). $C_{25}H_{19}Cl_2N_5O_2$ (492.4); mp 152 – 153 °C; purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.90 (m, 2H), 7.66 (d, J = 2.1 Hz, 1H), 7.51 (dt, J = 7.8 and 1.0 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.35 (dt, J = 8.3 and 0.9 Hz, 1H), 7.32 (s, 1H), 7.29 (dd, J = 8.4 and 2.2 Hz, 1H), 7.11 (td, J = 8.3 and 1.2 Hz, 1H), 7.00 (td, J = 7.9 and 1.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.97 (s, 2H), 5.44 (s, 2H), 4.33 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.9, 165.8, 138.8, 136.1, 134.6, 132.8, 132.7, 131.0, 129.75, 129.73, 128.9, 128.2, 127.6, 127.25, 127.23, 121.8, 119.1, 119.0, 110.1, 110.0, 55.2, 46.3, 21.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 492.0989, found: 492.0986.

Ethyl 4-(5-{[1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)butanoate (79)



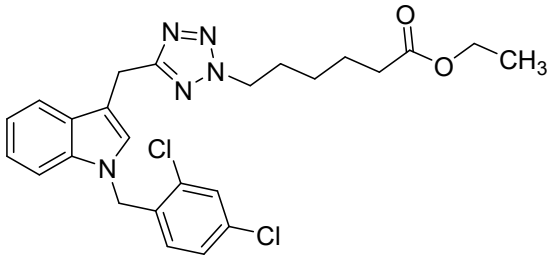
Compound **76** (100 mg, 0.28 mmol) was reacted with ethyl 4-bromobutanoate (60 mg, 0.31 mmol) according to the procedure described for the synthesis of **67** to yield **79** as an oil (62 mg, 47%). $C_{23}H_{23}Cl_2N_5O_2$ (472.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 2.2 Hz, 1H), 7.56 (dt, J = 7.9 and 1.0 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.11 (td, J = 8.3 and 1.2 Hz, 1H), 7.03 (td, J = 8.0 and 1.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 4.65 (t, J = 6.9 Hz, 2H), 4.32 (d, J = 0.9 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.12 (p, J = 7.2 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 472.1302, found: 472.1317.

4-(5-{[1-(2,4-Dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)butyric acid (80)



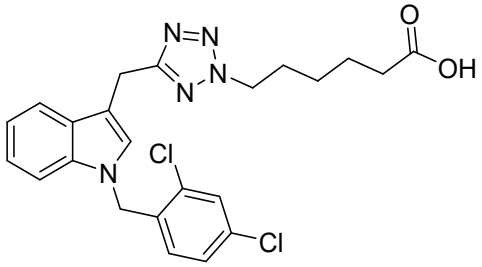
Compound **79** (55 mg, 0.12 mmol) was saponified in a similar manner as described for the synthesis of **40** to give **80** as an oil (40 mg, 77%). $C_{21}H_{19}Cl_2N_5O_2$ (444.3); purity (HPLC) 96%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 2.1 Hz, 1H), 7.55 (dt, J = 7.9 and 1.0 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.11 (td, J = 8.3 and 1.2 Hz, 1H), 7.03 (td, J = 7.9 and 1.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 4.64 (t, J = 7.0 Hz, 2H), 4.32 (d, J = 0.9 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.09 (p, J = 6.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 165.3, 136.1, 134.7, 132.8, 132.7, 129.8, 129.0, 127.7, 127.32, 127.25, 121.8, 119.2, 119.0, 110.3, 110.0, 51.6, 46.3, 30.2, 24.3, 21.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 444.0989, found: 444.1008.

Ethyl 6-(5-{[1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)hexanoate (83)



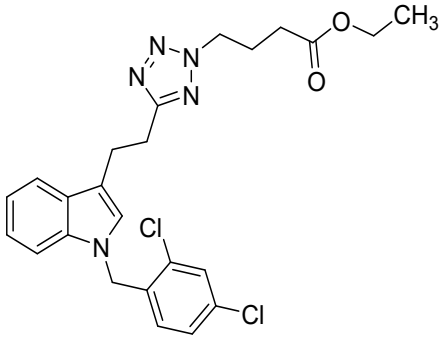
Compound **76** (129 mg, 0.36 mmol) was reacted with ethyl 6-bromohexanoate (89 mg, 0.40 mmol) according to the procedure described for the synthesis of **67** (reaction time: 6 h) to yield **83** as a solid (82 mg, 46%). $C_{25}H_{27}Cl_2N_5O_2$ (500.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, J = 2.1 Hz, 1H), 7.54 (dt, J = 7.9 and 1.1 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.11 (td, J = 8.2 and 1.2 Hz, 1H), 7.02 (td, J = 7.9 and 1.0 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 4.59 (t, J = 6.9 Hz, 2H), 4.32 (s, 2H), 4.01 (q, J = 7.1 Hz, 2H), 2.22 (t, J = 7.4 Hz, 2H), 1.87 (p, J = 7.0 Hz, 2H), 1.51 (p, J = 7.4 Hz, 2H), 1.12 – 1.26 (m, 5H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 500.1615, found: 500.1604.

6-(5-{[1-(2,4-Dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)hexanoic acid (84)



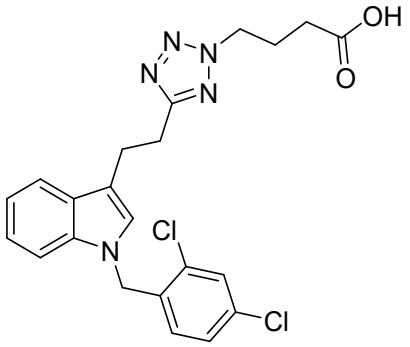
Compound **83** (70 mg, 0.14 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give **84** as a solid (48 mg, 73%). $C_{23}H_{23}Cl_2N_5O_2$ (472.4); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 2.1 Hz, 1H), 7.54 (dt, J = 7.9 and 1.0 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.11 (td, J = 8.2 and 1.2 Hz, 1H), 7.02 (td, J = 7.9 and 0.9 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 4.59 (t, J = 6.9 Hz, 2H), 4.32 (s, 2H), 2.15 (t, J = 7.4 Hz, 2H), 1.87 (p, J = 7.0 Hz, 2H), 1.49 (p, J = 7.5 Hz, 2H), 1.18 – 1.24 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.3, 165.2, 136.1, 134.7, 132.8, 132.7, 129.7, 129.0, 127.7, 127.3, 127.2, 121.8, 119.1, 119.0, 110.3, 110.0, 52.2, 46.3, 33.4, 28.4, 25.3, 23.8, 21.4; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 472.1302, found: 472.1317.

Ethyl 4-(5-{2-[1-(2,4-dichlorobenzyl)indol-3-yl]ethyl}-2*H*-tetrazol-2-yl)butanoate (89)



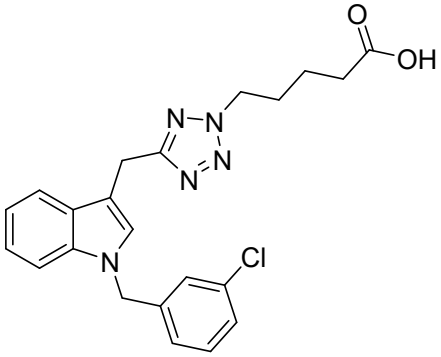
Compound **86** (113 mg, 0.30 mmol) was reacted with ethyl 4-bromobutanoate (64 mg, 0.33 mmol) according to the procedure described for the synthesis of **65**. Chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) gave **87** as an oil (78 mg, 53%). $C_{24}H_{25}Cl_2N_5O_2$ (486.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 2.1 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.33 – 7.27 (m, 2H), 7.18 (s, 1H), 7.09 (td, J = 8.2 and 1.3 Hz, 1H),7.02 (td, J = 7.9 and 1.1 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 4.62 (t, J = 6.9 Hz, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.23 – 3.13 (m, 4H), 2.29 (t, J = 7.3 Hz, 2H), 2.11 – 2.03 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 486.1458, found: 486.1437.

4-(5-{2-[1-(2,4-Dichlorobenzyl)indol-3-yl]ethyl}-2*H*-tetrazol-2-yl)butyric acid (90)



Compound **89** (70 mg, 0.14 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 4 h) to give **90** as an oil (63 mg, 96%). $C_{22}H_{21}Cl_2N_5O_2$ (458.3); purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J = 2.1 Hz, 1H), 7.53 (dt, J = 7.8 and 1.0 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.18 (s, 1H), 7.09 (td, J = 8.2 and 1.3 Hz, 1H), 7.03 (td, J = 8.0 and 1.1 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 3.23 – 3.11 (m, 4H), 2.22 (t, J = 7.3 Hz, 2H), 2.05 (p, J = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 165.7, 136.1, 134.8, 132.7, 132.6, 129.6, 128.9, 127.59, 127.52, 126.5, 121.6, 119.0, 118.7, 113.6, 109.9, 51.5, 46.2, 30.2, 25.8, 24.3, 23.2; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1145, found: 458.1115.

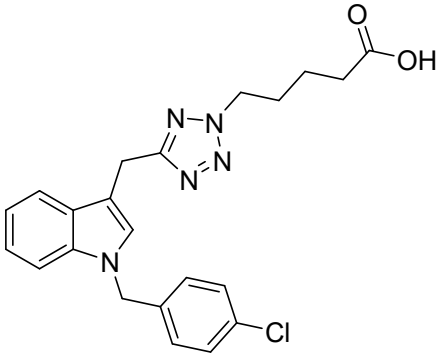
5-(5-{[1-(3-Chlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (96)



The procedure described for the preparation of **98** was applied to **94** (50 mg, 0.15 mmol) and 3-chlorobenzyl bromide (47 mg, 0.23 mmol) to give **96** as an oil (33 mg, 51%). $C_{22}H_{22}ClN_5O_2$ (423.9); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.52 (dt, J = 7.9 and 1.0 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.41 (s, 1H), 7.34 – 7.29 (m, 2H), 7.25 (t, J = 1.9 Hz, 1H), 7.13 (dt, J = 7.3 and 1.6 Hz, 1H), 7.10 (ddd, J = 8.2, 7.0 and 1.2 Hz, 1H), 7.00 (ddd, J = 7.9, 6.9 and 1.0 Hz, 1H), 5.39 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 4.32 (d, J = 0.9 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.50 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 140.9, 136.0, 133.1, 130.5, 127.35, 127.32, 127.2, 126.9, 125.7, 121.6, 118.97, 118.90, 110.07, 110.05, 52.1, 48.2,

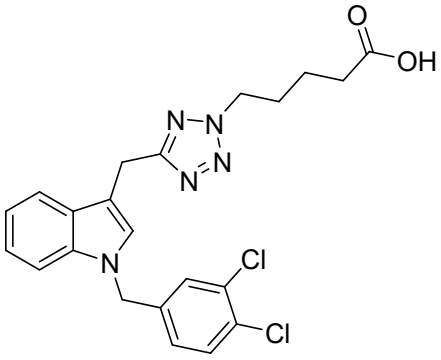
32.8, 28.2, 21.36, 21.34; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 424.1535, found: 424.1511.

5-(5-{[1-(4-Chlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (97)



The procedure described for the preparation of **98** was applied to **94** (50 mg, 0.15 mmol) and 4-chlorobenzyl bromide (47 mg, 0.23 mmol) to give **96** as an oil (29 mg, 45%). $C_{22}H_{22}ClN_5O_2$ (423.9); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (dt, *J* = 8.0 and 1.0 Hz, 1H), 7.40 (dt, *J* = 8.3 and 0.9 Hz, 1H), 7.38 – 7.34 (m, 3H), 7.21 – 7.18 (m, 2H), 7.09 (ddd, *J* = 8.2, 7.0 and 1.2 Hz, 1H), 7.00 (ddd, *J* = 8.0, 7.0 and 1.0 Hz, 1H), 5.37 (s, 2H), 4.62 (t, *J* = 6.9 Hz, 2H), 4.31 (d, *J* = 1.0 Hz, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.50 – 1.40 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 137.3, 136.0, 131.9, 128.9, 128.5, 127.4, 127.1, 121.5, 118.91, 118.87, 110.1, 109.9, 52.1, 48.2, 328, 28.2, 21.36, 21.34; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 424.1535, found: 424.1514.

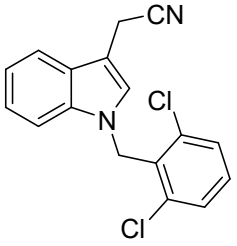
5-(5-{[1-(3,4-Dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (98)



Sodium hydride (60% dispersion in mineral oil) (12 mg, 0.30 mmol) was suspended in dry DMF under a nitrogen atmosphere in a heated glass flask and cooled in an ice bath. After the suspension was stirred for 5 min, a solution of **94** (50 mg, 0.15 mmol) in dry DMF was added and the mixture was stirred for another 5 min under ice cooling and for 30 min at room temperature. Then a solution of 3,4-dichlorobenzyl bromide (55 mg,

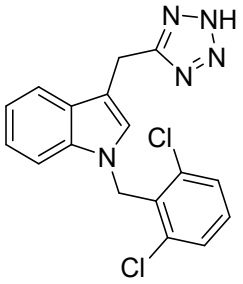
0.23 mmol) in dry DMF was added dropwise and stirring continued for 15 min at room temperature. The reaction mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined organic phases were washed three times with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was saponified and worked up in a similar manner as described for the synthesis of **40**. Chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) afforded **98** as an oil (40 mg, 57%). $C_{22}H_{21}Cl_2N_5O_2$ (458.3); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.56 (d, J = 8.3 Hz, 1H), 7.52 (dt, J = 7.9 and 1.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.44 – 7.42 (m, 1H), 7.41 (s, 1H), 7.14 – 7.09 (m, 2H), 7.01 (ddd, J = 7.9, 6.9 and 0.9 Hz, 1H), 5.39 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 4.31 (d, J = 1.0 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.49 – 1.42 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3), 139.5, 136.0, 131.1, 130.8, 130.0, 129.1, 127.40, 127.39, 127.1, 121.7, 119.1, 118.9, 110.2, 110.1, 52.1, 47.7, 32.8, 28.2, 21.36, 21.33; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1145, found: 458.1071.

2-[1-(2,6-Dichlorobenzyl)indol-3-yl]acetonitrile (99)



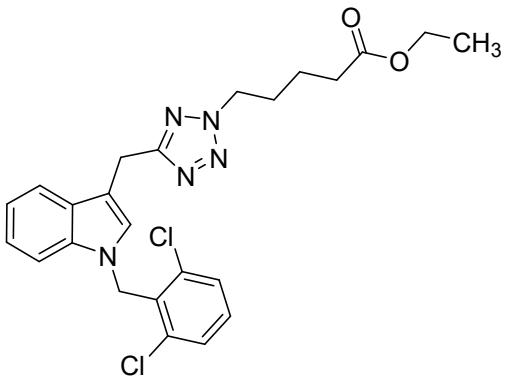
A solution of 2-(indol-3-yl)acetonitrile (400 mg, 2.56 mmol) in dry DMF (5 mL) was treated with sodium hydride (60% dispersion in mineral oil, 256 mg, 6.40 mmol) under nitrogen atmosphere and cooling at 0 °C. The mixture was stirred at room temperature for 30 min. Then a solution of 2,6-dichlorobenzyl bromide (677 mg, 2.82 mmol) in dry DMF (3 mL) was added and stirring was continued for another 30 min at room temperature. The reaction mixture was diluted with water (20 mL) and extracted exhaustively with ethyl acetate. The combined organic phases were washed three times with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate, 9:1) to give **99** as a solid (378 mg, 47%). $C_{17}H_{12}Cl_2N_2$ (315.2); mp 148 – 150 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.01 (d, J = 0.9 Hz, 2H), 5.55 (s, 2H), 7.01 (d, J = 1.0 Hz, 1H), 7.13 (ddd, J = 7.9, 7.0 and 0.9 Hz, 1H), 7.25 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 7.49 (dd, J = 8.6 and 7.7 Hz, 1H), 7.59 – 7.64 (m, 4H); HR-MS (APCI, DIP) *m/z* $[M+H]^+$ calc.: 315.0450, found: 315.0454.

1-(2,6-Dichlorobenzyl)- 3-[(tetrazol-5-yl)methyl]indole (100)



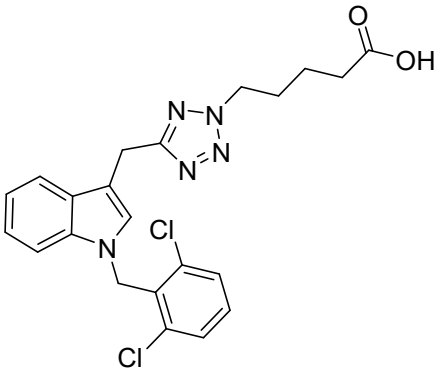
A mixture of **99** (365 mg, 1.16 mmol), trimethylsilyl azide (200 mg, 1.74 mmol), and tetrabutylammonium fluoride hydrate (152 mg) was heated at 140 °C for 5 min until all components were molten. The melt was then stirred at 125 °C for 6 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane/ethyl acetate/formic acid 5:5:0.1) to yield **100** as a solid (304 mg, 73%). $C_{17}H_{13}Cl_2N_5$ (358.2); mp 236 – 238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.32 (d, J = 0.9 Hz, 2H), 5.53 (s, 2H), 6.97 (s, 1H), 7.03 (ddd, J = 7.9, 7.0 and 1.0 Hz, 1H), 7.19 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 7.43 (dt, J = 7.9 and 1.0 Hz, 1H), 7.48 (dd, J = 8.8 and 7.4 Hz, 1H), 7.57 (d, J = 0.9 Hz, 1H), 7.58 – 7.62 (m, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 358.0621, found: 358.0622.

Ethyl 5-(5-{[1-(2,6-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (101)



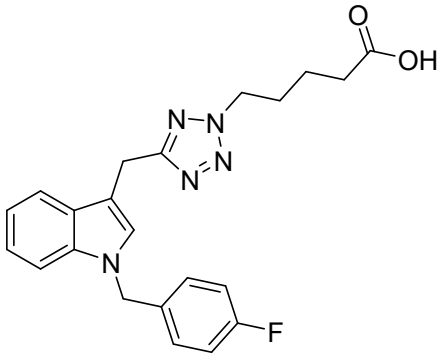
Compound **100** (140 mg, 0.39 mmol) was reacted with ethyl 5-bromopentanoate (96 mg, 0.43 mmol) according to the procedure described for the synthesis of **65** (reaction time: 3 h) to yield **101** as an oil (66 mg, 35%). $C_{24}H_{25}Cl_2N_5O_2$ (486.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.15 (t, J = 7.1 Hz, 3H), 1.46 (p, J = 7.6 Hz, 2H), 1.86 (p, J = 7.0 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.03 (q, J = 7.1 Hz, 2H), 4.25 (d, J = 0.9 Hz, 2H), 4.60 (t, J = 6.9 Hz, 2H), 5.51 (s, 2H), 6.94 (s, 1H), 7.01 (ddd, J = 8.0, 7.0 and 1.0 Hz, 1H), 7.17 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 7.44 – 7.50 (m, 2H), 7.56 (dt, J = 8.4 and 0.9 Hz, 1H), 7.59 (dd, J = 8.0 and 0.7 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 486.1458, found: 486.1387.

5-(5-{[1-(2,6-Dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (102)



Compound **101** (50 mg, 0.10 mmol) was saponified in a similar manner as described for the synthesis of **40** to give **102** as a solid (37 mg, 79%). $C_{22}H_{21}Cl_2N_5O_2$ (458.3); mp 149 – 150 °C; purity (HPLC) 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.44 (p, J = 7.7 Hz, 2H), 1.86 (p, J = 6.9 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 4.25 (d, J = 0.9 Hz, 2H), 4.59 (t, J = 6.9 Hz, 2H), 5.51 (s, 2H), 6.94 (s, 1H), 7.02 (ddd, J = 7.9, 7.0 and 0.9 Hz, 1H), 7.17 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 7.45 – 7.50 (m, 2H), 7.56 (dd, J = 8.3 and 0.9 Hz, 1H), 7.59 (d, J = 8.1 Hz, 2H), 12.08 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.25, 21.29, 28.2, 32.9, 44.6, 52.0, 109.9, 110.3, 118.9, 119.0, 121.7, 125.2, 127.0, 129.1, 131.2, 131.7, 135.9, 136.4, 165.2, 174.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1145, found: 458.1100.

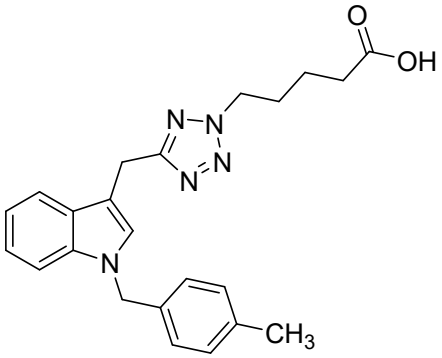
5-(5-{[1-(4-Fluorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (103)



The procedure described for the preparation of **98** was applied to **94** (50 mg, 0.15 mmol) and 4-fluorobenzyl bromide (43 mg, 0.23 mmol) to give **103** as a solid (40 mg, 64%). $C_{22}H_{22}FN_5O_2$ (407.4); mp 94 – 95 °C; purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (dt, J = 8.0 and 1.0 Hz, 1H), 7.43 (dt, J = 8.3 and 0.9 Hz, 1H), 7.38 (s, 1H), 7.27 – 7.23 (m, 2H), 7.15 – 7.11 (m, 2H), 7.09 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 6.99 (ddd, J = 7.8, 6.9 and 0.9 Hz, 1H), 5.35 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 4.30 (d, J = 0.9 Hz, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.49 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 161.4 (d, J = 242.9 Hz), 136.0,

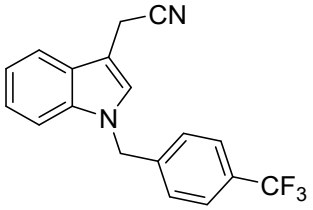
134.5 (d, *J* = 3.0 Hz), 129.2 (d, *J* = 8.2 Hz), 127.4, 127.1, 121.5, 118.87, 118.86, 115.3 (d, *J* = 21.9 Hz), 110.1, 109.9, 52.1, 48.1, 32.8, 28.2, 21.35, 21.34; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 408.1830, found: 408.1817.

5-(5-{[1-(4-Methylbenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (104)



The procedure described for the preparation of **98** was applied to **94** (50 mg, 0.15 mmol) and 4-methylbenzyl bromide (43 mg, 0.23 mmol) to give **104** as an oil (33 mg, 54%). $C_{23}H_{25}N_5O_2$ (403.5); purity (HPLC) 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.50 (dt, *J* = 7.9 and 1.0 Hz, 1H), 7.41 (dt, *J* = 8.2 and 0.9 Hz, 1H), 7.34 (s, 1H), 7.10 – 7.06 (m, 5H), 6.98 (ddd, *J* = 7.9, 6.9 and 1.0 Hz, 1H), 5.30 (s, 2H), 4.61 (t, *J* = 7.0 Hz, 2H), 4.30 (d, *J* = 1.0 Hz, 2H), 2.25 – 2.22 (m, 5H), 1.91 – 1.86 (m, 2H), 1.50 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 136.5, 136.0, 135.2, 129.0, 127.3, 127.16, 127.12, 121.4, 118.79, 118.75, 110.2, 109.6, 52.1, 48.7, 32.8, 28.2, 21.35, 21.34, 20.64; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 404.2081, found: 404.2101.

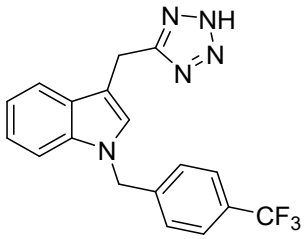
2-{1-[4-(Trifluoromethyl)benzyl]indol-3-yl}acetonitrile (105)



A solution of 2-(indol-3-yl)acetonitrile (700 mg, 4.48 mmol) in dry DMF (15 mL) was treated with anhydrous potassium carbonate (1238 mg, 8.96 mmol) and 4-(trifluoromethyl)benzyl bromide (1178 mg, 4.93 mmol). After stirring at 80 °C for 3 h, the mixture was diluted with water and extracted exhaustively with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 8:2) to obtain **105** as an oil (395 mg, 28%). $C_{18}H_{13}F_3N_2$ (314.3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 – 7.66 (m, 2H), 7.62 (dt, *J* = 7.8 and 0.8 Hz, 1H), 7.55 (s, 1H), 7.46 (dt, *J* = 8.2 and 0.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.17

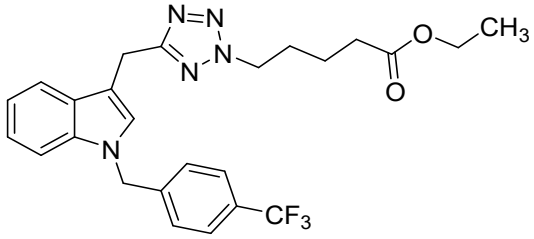
(td, *J* = 8.2 and 1.3 Hz, 1H), 7.10 (td, *J* = 8.0 and 1.1 Hz, 1H), 5.54 (s, 2H), 4.09 (d, *J* = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 315.1104, found: 315.1005.

3-[(Tetrazol-5-yl)methyl]-1-[4-(trifluoromethyl)benzyl]indole (106)



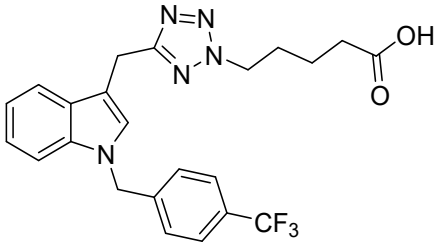
A mixture of **105** (385 mg, 1.22 mmol), trimethylsilyl azide (211 mg, 1.83 mmol), and tetrabutylammonium fluoride hydrate (160 mg) was stirred at 120 °C for 4 h. The resulting melt was cooled and purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 55:45:1) to afford **106** as a solid (346 mg, 79%). $C_{18}H_{14}F_3N_5$ (357.3); mp 192 – 193 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 – 7.65 (m, 2H), 7.47 (dt, *J* = 7.9 and 1.0 Hz, 1H), 7.43 (s, 1H), 7.40 (dt, *J* = 8.3 and 0.9 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.11 (td, *J* = 8.3 and 1.2 Hz, 1H), 7.02 (td, *J* = 8.0 and 1.0 Hz, 1H), 5.51 (s, 2H), 4.39 (d, *J* = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 358.1274, found: 358.1279.

Ethyl 5-[5-({1-[4-(trifluoromethyl)benzyl]indol-3-yl}methyl)-2*H*-tetrazol-2-yl]-pentanoate (107)



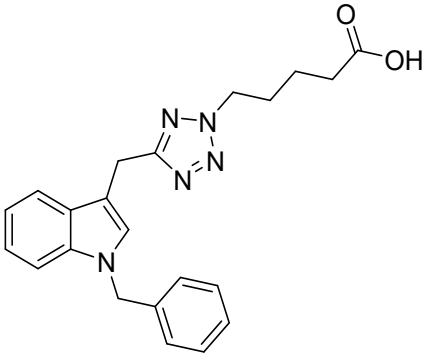
Compound **106** (167 mg, 0.47 mmol) was reacted with ethyl 5-bromopentanoate (109 mg, 0.52 mmol) according to the procedure described for the synthesis of **65** (reaction time: 3 h) to yield **107** as a solid (122 mg, 54%). $C_{25}H_{26}F_3N_5O_2$ (485.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.53 (dt, *J* = 7.9 and 1.0 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.10 (td, *J* = 8.3 and 1.2 Hz, 1H), 7.00 (td, *J* = 7.9 and 1.0 Hz, 1H), 5.49 (s, 2H), 4.62 (t, *J* = 6.9 Hz, 2H), 4.32 (d, *J* = 0.9 Hz, 2H)-, 4.02 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.49 – 1.41 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 486.2111, found: 486.2109.

5-[5-({1-[4-(Trifluoromethyl)benzyl]indol-3-yl}methyl)-2*H*-tetrazol-2-yl]pentanoic acid (108)



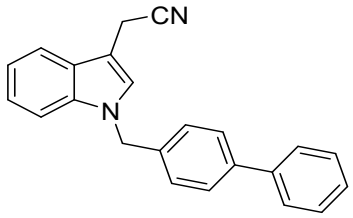
Compound **107** (100 mg, 0.21 mmol) was saponified in a similar manner as described for the synthesis of **40** to give **108** as an oil (88 mg, 93%). $C_{23}H_{22}F_3N_5O_2$ (457.5); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 8.2 Hz, 2H), 7.53 (dt, J = 7.9 and 1.0 Hz, 1H), 7.41 (s, 1H), 7.39 (dt, J = 8.5 and 0.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.10 (td, J = 8.3 and 1.2 Hz, 1H), 7.01 (td, J = 7.9 and 1.0 Hz, 1H), 5.49 (s, 2H), 4.62 (t, J = 7.0 Hz, 2H), 4.32 (d, J = 0.9 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.49 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.2, 143.2, 136.0, 127.8 (q, J = 31.6 Hz), 127.6, 127.4, 127.2, 126.0 (q, J = 271.9 Hz), 125.5 (q, J = 3.9 Hz), 121.6, 119.0, 118.9, 110.12, 110.04, 52.1, 48.4, 32.8, 28.2, 21.36, 21.35; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 458.1798, found: 458.180.

5-{5-[(1-Benzylindol-3-yl)methyl]-2*H*-tetrazol-2-yl}pentanoic acid (109)



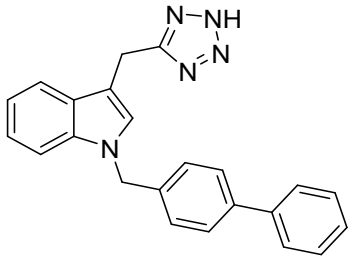
The procedure described for the preparation of **98** was applied to **94** (50 mg, 0.15 mmol) and benzyl bromide (39 mg, 0.23 mmol) to give **109** as an oil (38 mg, 64%). $C_{22}H_{23}N_5O_2$ (389.5); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.51 (dt, J = 8.0 and 1.0 Hz, 1H), 7.41 (dt, J = 8.2 and 0.9 Hz, 1H), 7.37 (s, 1H), 7.31 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 7.09 (ddd, J = 8.3, 7.0 and 1.2 Hz, 1H), 6.99 (ddd, J = 8.1, 7.0 and 1.0 Hz, 1H), 5.36 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 4.31 (d, J = 0.9 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.49 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 138.3, 136.1, 128.5, 127.32, 127.31, 127.2, 127.1, 121.4, 118.82, 118.81, 110.1, 109.7, 52.1, 48.9, 32.8, 28.2, 21.36, 21.35; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 390.1925, found: 390.1917.

2-[1-(4-Phenylbenzyl)indol-3-yl]acetonitrile (110)



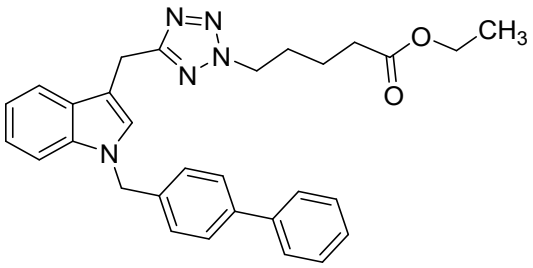
A solution of 2-(indol-3-yl)acetonitrile (500 mg, 3.20 mmol) in dry DMF (15 mL) was treated with anhydrous potassium carbonate (885 mg, 6.40 mmol) and 4-phenylbenzyl bromide (870 mg, 3.52 mmol) and stirred at 80 °C for 2 h. After dilution with water, the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 9:1) to afford **110** as an oil (281 mg, 27%). $C_{23}H_{18}N_2$ (322.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.63 – 7.58 (m, 5H), 7.56 – 7.52 (m, 2H), 7.46 – 7.41 (m, 2H), 7.36 – 7.33 (m, 1H), 7.32 – 7.28 (m, 2H), 7.18 (td, J = 8.2 and 1.2 Hz, 1H), 7.10 (td, J = 8.0 and 1.0 Hz, 1H), 5.46 (s, 2H), 4.09 (d, J = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 323.1543, found: 323.1542.

1-(4-Phenylbenzyl)-3-[(tetrazol-5-yl)methyl]indole (111)



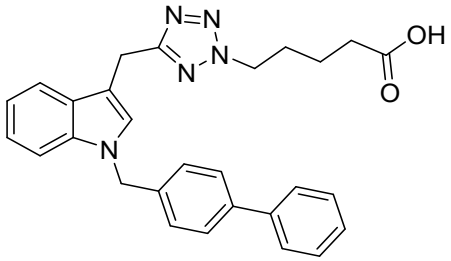
Compound **110** (168 mg, 0.52 mmol) was reacted with trimethylsilyl azide (90 mg, 0.78 mmol) according to the procedure described for the synthesis of **106** to give **111** as a solid (106 mg, 56%). $C_{23}H_{19}N_5$ (365.4); mp 215 – 216 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 – 7.57 (m, 4H), 7.49 – 7.41 (m, 5H), 7.37 – 7.28 (m, 3H), 7.12 (td, J = 8.2 and 1.1 Hz, 1H), 7.01 (td, J = 8.0 and 0.9 Hz, 1H), 5.43 (s, 2H), 4.39 (d, J = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 366.1713, found: 366.1725.

Ethyl 5-[5-{[1-(4-phenylbenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl]pentanoate (112)



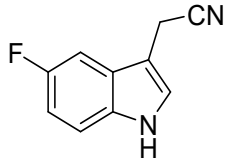
Compound **111** (98 mg, 0.27 mmol) was reacted with ethyl 5-bromopentanoate (63 mg, 0.30 mmol) according to the procedure described for the synthesis of **65** (reaction time: 4.5 h) to yield **112** as an oil (67 mg, 51%). $C_{30}H_{31}N_5O_2$ (493.6); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 – 7.56 (m, 4H), 7.52 (dt, J = 7.8 and 1.0 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.36 – 7.31 (m, 1H), 7.30 – 7.26 (m, 2H), 7.11 (td, J = 8.3 and 1.1 Hz, 1H), 7.00 (td, J = 7.9 and 1.0 Hz, 1H), 5.41 (s, 2H), 4.62 (t, J = 6.9 Hz, 2H), 4.32 (d, J = 0.9 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.49 (tt, J = 10.1 and 6.5 Hz, 2H), 1.16 (t, J = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 494.2551, found: 494.2517.

5-[5-{[1-(4-Phenylbenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl]pentanoic acid (113)



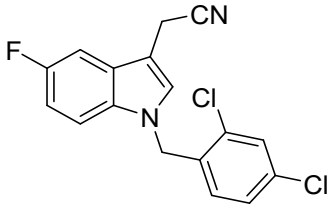
Compound **112** (60 mg, 0.12 mmol) was saponified in a similar manner as described for the synthesis of **40** (reaction time: 5 h) to give **113** as an oil (50 mg, 88%). $C_{28}H_{27}N_5O_2$ (465.6); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.62 – 7.57 (m, 4H), 7.52 (dt, J = 7.9 and 1.0 Hz, 1H), 7.46 (dt, J = 8.3 and 1.0 Hz, 1H), 7.45 – 7.40 (m, 3H), 7.36 – 7.32 (m, 1H), 7.30 – 7.26 (m, 2H), 7.11 (td, J = 8.1 and 1.1 Hz, 1H), 7.00 (td, J = 8.0 and 1.0 Hz, 1H), 5.41 (s, 2H), 4.62 (t, J = 7.0 Hz, 2H), 4.32 (s, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.49 – 1.42 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.3, 139.8, 139.3, 137.5, 136.1, 128.9, 127.7, 127.42, 127.35, 127.22, 126.9, 126.9, 121.5, 118.85, 118.84, 110.2, 109.8, 52.1, 48.6, 32.8, 28.2, 21.37, 21.36; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 466.2238, found: 466.2211.

2-(5-Fluoroindol-3-yl)acetonitrile (114)



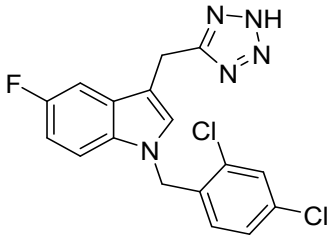
A solution of 5-fluoroindole-3-carbaldehyde (528 mg, 3.24 mmol) in methanol/formamide (1:1, 30 mL) was treated with sodium borohydride (157 mg, 4.15 mmol) and stirred at room temperature for 1 h. Potassium cyanide (2103 mg, 32.3 mmol) was then added, and the mixture was stirred at 100 °C for 1 h. After dilution with brine, the cooled reaction mixture was exhaustively extracted with ethyl acetate. The organic phases were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) to give **114** as a solid (480 mg, 85%). $C_{10}H_7FN_2$ (174.2); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.40 (dd, J = 8.7 and 4.6 Hz, 1H), 7.35 (dd, J = 9.9 and 2.6 Hz, 1H), 6.98 (td, J = 9.2 and 2.6 Hz, 1H), 4.02 (d, J = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 175.0666, found: 175.0664.

2-[1-(2,4-Dichlorobenzyl)-5-fluoroindol-3-yl]acetonitrile (115)



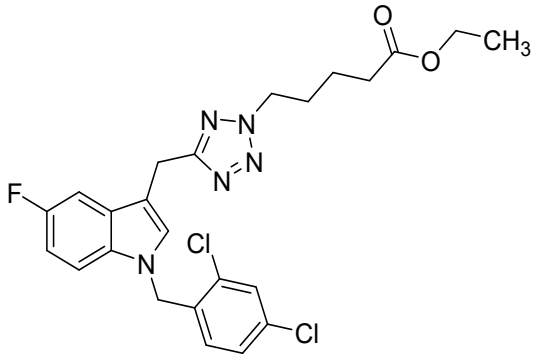
A solution of **114** (473 mg, 2.72 mmol) in dry DMF was treated with sodium hydride (60% dispersion in mineral oil) (218 mg, 5.45 mmol) under nitrogen atmosphere and cooling in an ice bath and stirred for 5 min. After stirring for another 25 min at room temperature, a solution of 2,4-dichlorobenzyl bromide (979 mg, 4.08 mmol) in dry DMF was added dropwise and stirring continued at room temperature for 20 min. Then the reaction mixture was diluted with water and extracted exhaustively with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 9:1) to yield **115** as a solid (398 mg, 44 %). $C_{17}H_{11}Cl_2FN_2$ (333.2); mp 144 – 145 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.69 (d, J = 2.2 Hz, 1H), 7.52 (s, 1H), 7.47 – 7.40 (m, 2H), 7.36 (dd, J = 8.4 and 2.2 Hz, 1H), 7.04 (td, J = 9.2 and 2.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.50 (s, 2H), 4.07 (d, J = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 333.0356, found: 333.0340.

1-(2,4-Dichlorobenzyl)- 5-fluoro-3-[(tetrazol-5-yl)methyl]indole (116)



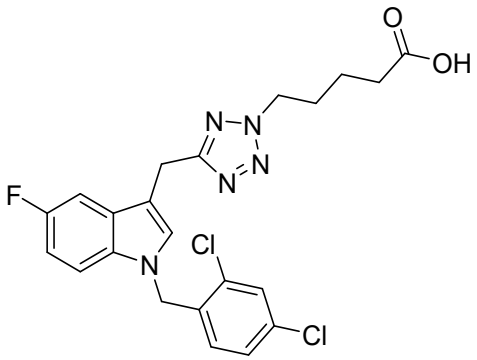
A mixture of **115** (389 mg, 1.17 mmol), trimethylsilyl azide (203 mg, 1.76 mmol), and tetrabutylammonium fluoride hydrate (154 mg) was stirred at 140 °C for 5 h. The resulting melt was cooled and purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 9:1:0.1) to afford **116** as a solid (262 mg, 60%). $C_{17}H_{12}Cl_2FN_5$ (376.2); mp 253 – 254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68 (d, J = 2.1 Hz, 1H), 7.41 (s, 1H), 7.38 (dd, J = 9.0 and 4.4 Hz, 1H), 7.34 (dd, J = 8.4 and 2.2 Hz, 1H), 7.30 (dd, J = 9.8 and 2.5 Hz, 1H), 6.98 (td, J = 9.2 and 2.6 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.47 (s, 2H), 4.35 (d, J = 0.9 Hz, 2H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 376.0527, found: 376.0524.

Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-5-fluoroindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoate (117)



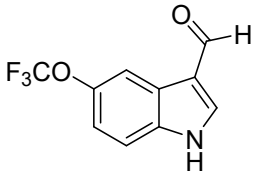
Compound **116** (188 mg, 0.50 mmol) was reacted with ethyl 5-bromopentanoate (105 mg, 0.50 mmol) according to the procedure described for the synthesis of **65** (reaction time: 3 h). Chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate, 75:25) gave **117** as an oil (113 mg, 45%). $C_{24}H_{24}Cl_2FN_5O_2$ (504.4); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.68 (d, J = 2.2 Hz, 1H), 7.40 (s, 1H), 7.38 (dd, J = 9.0 and 4.4 Hz, 1H), 7.36 – 7.28 (m, 2H), 6.96 (td, J = 9.2 and 2.6 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.46 (s, 2H), 4.63 (t, J = 6.9 Hz, 2H), 4.30 (d, J = 0.9 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.92 – 1.85 (m, 2H), 1.52 – 1.44 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 504.1364, found: 504.1339.

5-(5-{[1-(2,4-Dichlorobenzyl)-5-fluoroindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoic acid (118)



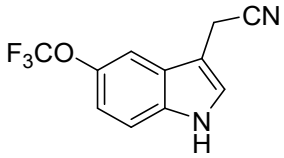
Compound **117** (100 mg, 0.20 mmol)) was saponified in a similar manner as described for the synthesis of **40** to give **118** as a solid (75 mg, 79%). $C_{22}H_{20}Cl_2FN_5O_2$ (476.3); purity (HPLC) 95%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.67 (d, J = 2.1 Hz, 1H), 7.41 – 7.29 (m, 4H), 6.96 (td, J = 9.2 and 2.5 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.45 (s, 2H), 4.62 (t, J = 7.0 Hz, 2H), 4.30 (s, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.50 – 1.41 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.1, 165.0, 155.9 (d, J = 252.1 Hz), 134.5, 132.89, 132.83, 132.76, 129.7, 129.2, 129.0, 127.7, 127.6 (d, J = 10.0 Hz), 111.2 (d, J = 9.8 Hz), 110.4 (d, J = 4.8 Hz), 109.9 (d, J = 26.0 Hz), 103.9 (d, J = 23.7 Hz), 52.1, 46.5, 32.7, 28.1, 21.3, 21.2; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 476.1051, found: 476.1025.

5-(Trifluoromethoxy)indole-3-carbaldehyde (129)



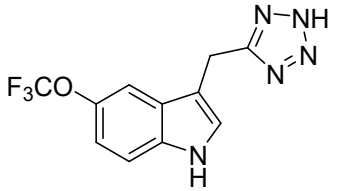
To a solution of 5-(trifluoromethoxy)indole (330 mg, 1.64 mmol) in dry DMF (5 mL) cooled to 0 °C, phosphorus oxychloride (280 mg, 1.80 mmol) was added dropwise. After the mixture was stirred for 1 h at 50 °C, saturated aqueous sodium bicarbonate solution (10 mL) was added and stirring continued at 60 °C for 20 min. The cooled reaction mixture was extracted exhaustively with ethyl acetate. The combined organic phases were washed twice with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* to afford **129** as a solid (360 mg, 96%). $C_{10}H_6F_3NO_2$ (229.2); mp 160 – 161 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.25 (ddd, J = 8.8, 2.5 and 1.0 Hz, 1H), 7.62 (dd, J = 8.8 and 0.6 Hz, 1H), 7.98 (dd, J = 2.7 and 1.3 Hz, 1H), 8.43 (s, 1H), 9.95 (s, 1H), 12.37 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 230.0423, found: 230.0425.

2-[5-(Trifluoromethoxy)indol-3-yl]acetonitrile (130)



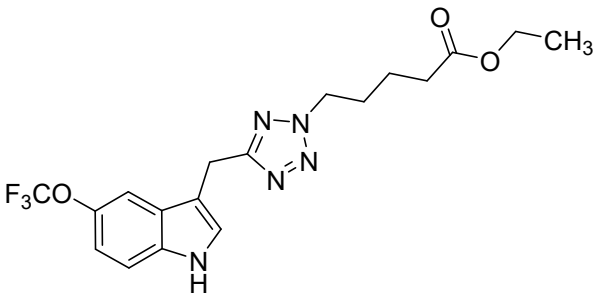
A solution of **129** (350 mg, 1.53 mmol) in methanol/formamide (1:1, 15 mL) was treated with sodium borohydride (70 mg, 1.85 mmol) and the mixture was stirred for 1 h at room temperature. After addition of potassium cyanide (996 mg, 15.3 mmol), the mixture was heated under reflux for 1 h. The cooled reaction mixture was diluted with ethyl acetate (20 mL). The organic phase was washed four times with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate 6:4) to afford **130** as a solid (292 mg, 80%). $C_{11}H_7F_3N_2O$ (240.2); mp 74 – 76 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.08 (d, J = 0.9 Hz, 2H), 7.11 (ddd, J = 8.8, 2.3 and 1.1 Hz, 1H), 7.47 – 7.51 (m, 2H), 7.59 (d, J = 2.0 Hz, 1H), 11.41 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 241.0583, found: 241.0479.

3-[Tetrazol-5-ylmethyl]-5-(trifluoromethoxy)indole (131)



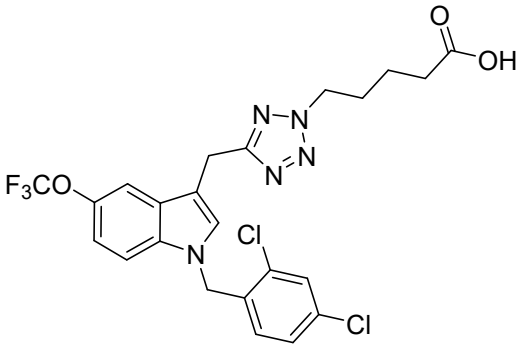
A mixture of **130** (288 mg, 1.20 mmol), trimethylsilyl azide (207 mg, 1.80 mmol), and tetrabutylammonium fluoride (157 mg) was heated for 7 h at 120 °C. The obtained melt was cooled and chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid 6:4:0.1) to afford **131** as a solid (248 mg, 73%). $C_{11}H_8F_3N_5O$ (283.2); mp 201 – 203 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.38 (d, J = 0.9 Hz, 2H), 7.03 – 7.09 (m, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.42 – 7.48 (m, 2H), 11.29 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 284.0754, found: 284.0724.

Ethyl 5-(5-{[5-(trifluoromethoxy)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (132)



A mixture of **131** (240 mg, 0.85 mmol), ethyl 5-bromopentanoate (213 mg, 1.02 mmol), anhydrous potassium carbonate (235 mg, 1.70 mmol), and acetonitrile (10 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL), washed three times with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) to give **132** as an oil (158 mg, 45%). $C_{18}H_{20}F_3N_5O_3$ (411.4); ^{1}H NMR (400 MHz, DMSO- d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.48 (p, J = 7.8 Hz, 2H), 1.88 (p, J = 7.3 Hz, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 4.31 (d, J = 0.9 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 7.04 (ddd, J = 8.8, 2.4 and 1.0 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.43 (dd, J = 8.8 and 0.5 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 11.21 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 412.1591, found: 412.1567.

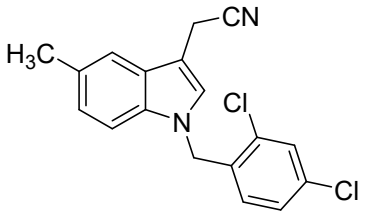
5-(5-{[1-(2,4-Dichlorobenzyl)-5-(trifluoromethoxy)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (133)



A solution of **132** (158 mg, 0.38 mmol) in dry DMF (5 mL) was slowly treated with sodium hydride (60% dispersion in mineral oil) (31 mg, 0.78 mmol) at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 30 min, a solution of 2,4-dichlorobenzyl bromide (120 mg, 0.50 mmol) in dry DMF (2 mL) was added in portions and stirring was continued at room temperature for another 2 h. The reaction mixture was diluted with water (20 mL) and exhaustively extracted with ethyl acetate. The combined organic phases were washed twice with brine, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was dissolved in methanol/THF (2:1, 6

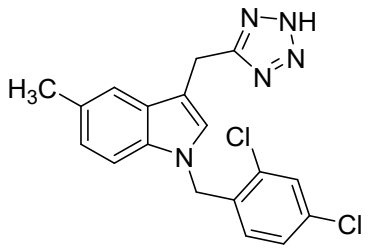
mL) and treated with 10% aqueous potassium hydroxide solution (2 mL). The mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was acidified with 3 M aqueous hydrochloric acid, diluted with ethyl acetate (15 mL), washed three times with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid 6:4:0.1) to give **133** as an oil (125 mg, 60%). $C_{23}H_{20}Cl_2F_3N_5O_3$ (542.3); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.46 (p, J = 7.7 Hz, 2H), 1.89 (p, J = 6.9 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 4.34 (d, J = 0.9 Hz, 2H), 4.62 (t, J = 7.0 Hz, 2H), 5.49 (s, 2H), 6.75 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 9.0 and 2.3 Hz, 1H), 7.35 (dd, J = 8.4 and 2.2 Hz, 1H), 7.46 – 7.50 (m, 2H), 7.55 (dd, J = 2.4 and 1.0 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.1, 21.3, 28.1, 32.7, 46.6, 52.1, 110.9, 111.3, 111.4, 115.4, 127.4, 127.8, 129.0, 129.5, 129.8, 132.8, 133.0, 134.3, 134.6, 141.9, 164.9, 174.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 542.0968, found: 542.0985.

2-[1-(2,4-Dichlorobenzyl)-5-methylindol-3-yl]acetonitrile (134)



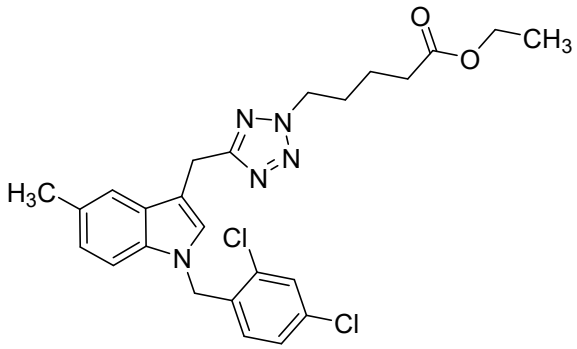
A solution of 2-(5-methylindol-3-yl)acetonitrile (F. Yamada *et al*., *Heterocycles*, 1998, **47**, 509) (355 mg, 2.09 mmol) in dry DMF (5 mL) was treated with sodium hydride (60% dispersion in mineral oil) (209 mg, 5.23 mmol) under nitrogen atmosphere and cooling at 0 °C. The mixture was stirred at room temperature for 30 min. Then a solution of 2,4-dichlorobenzyl bromide (653 mg, 2.72 mmol) in dry DMF (2 mL) was added and stirring was continued for another 2 h at room temperature. The reaction mixture was diluted with water and extracted exhaustively with ethyl acetate. The combined organic phases were washed three times with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate, 9:1) to give **134** as an oil (300 mg, 44%). $C_{18}H_{14}Cl_2N_2$ (329.2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.04 (d, J = 0.9 Hz, 2H), 5.45 (s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 7.00 (dd, J = 8.5 and 1.6 Hz, 1H), 7.29 (dd, J = 8.4 and 0.7 Hz, 1H), 7.34 (dd, J = 8.3 and 2.2 Hz, 1H), 7.39 (d, J = 0.9 Hz, 1H), 7.41 (dt, J = 1.7 and 0.8 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 329.0607, found: 329.0608.

1-(2,4-Dichlorobenzyl)-5-methyl-3-(tetrazol-5-ylmethyl)indole (135)



A mixture of **134** (279 mg, 0.85 mmol), trimethylsilyl azide (146 mg, 1.27 mmol), and tetrabutylammonium fluoride (111 mg) was heated at 120 °C for 8 h. The obtained melt was cooled and purified by chromatography on silica gel (cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to give **135** as a solid (163 mg, 52%). $C_{18}H_{15}Cl_2N_5$ (372.3); mp 191 – 192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 4.35 (d, J = 0.9 Hz, 2H), 5.43 (s, 2H), 6.67 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.5 and 1.6 Hz, 1H), 7.23 (dd, J = 8.3 and 0.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 372.0778, found: 372.0799.

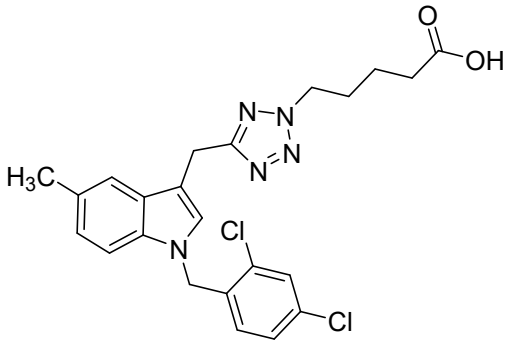
Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-5-methylindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoate (136)



A mixture of **135** (155 mg, 0.42 mmol), ethyl 5-bromopentanoate (132 mg, 0.63 mmol), anhydrous potassium carbonate (116 mg, 0.84 mmol), and acetonitrile (15 mL) was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), washed three times with water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate, 7:3) to give **136** as an oil (99 mg, 48%). $C_{25}H_{27}Cl_2N_5O_2$ (500.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.44 – 1.53 (m, 2H), 1.84 – 1.94 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H), 4.02 (q, J = 7.1 Hz, 2H), 4.28 (d, J = 0.9 Hz, 2H), 4.62 (t, J = 6.9 Hz, 2H), 5.41 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.93 (dd, J = 8.4 and 1.6 Hz, 1H), 7.22 (dd, J = 8.4 and 0.7 Hz,

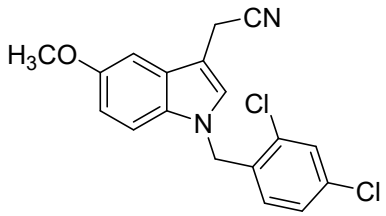
1H), 7.26 (d, *J* = 1.0 Hz, 1H), 7.29 – 7.34 (m, 2H), 7.66 (d, *J* = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 500.1615, found: 500.1629.

5-(5-{[1-(2,4-Dichlorobenzyl)-5-methylindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoic acid (137)



A solution of **136** (94 mg, 0.19 mmol) in methanol/THF (2:1, 9 mL) was treated with 10% aqueous potassium hydroxide solution (3 mL) and the mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was acidified with 3 M aqueous hydrochloric acid, diluted with ethyl acetate (20 mL), washed three times with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to give **137** as an oil (79 mg, 89%). $C_{23}H_{23}Cl_2N_5O_2$ (472.4); purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 – 1.51 (m, 2H), 1.85 – 1.94 (m, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 4.28 (d, *J* = 0.9 Hz, 2H), 4.62 (t, *J* = 7.0 Hz, 2H), 5.41 (s, 2H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.4 and 1.6 Hz, 1H), 7.22 (dd, *J* = 8.4 and 0.7 Hz, 1H), 7.26 (d, *J* = 1.0 Hz, 1H), 7.28 – 7.35 (m, 2H), 7.66 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.1, 21.3, 28.2, 32.8, 46.3, 52.0, 109.69, 109.74, 118.5, 123.3, 127.3, 127.5, 127.6, 127.8, 128.9, 129.6, 132.6, 132.7, 134.6, 134.8, 165.2, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 472.1302, found: 472.1269.

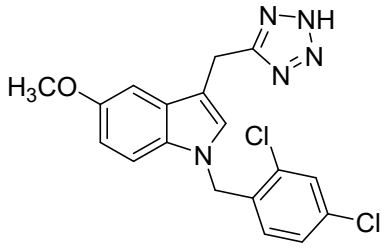
2-[1-(2,4-Dichlorobenzyl)-5-methoxyindol-3-yl]acetonitrile (138)



2-(5-Methoxyindol-3-yl)acetonitril (400 mg, 2.15 mmol) was reacted with 2,4-dichlorobenzyl bromide (669 mg, 2.79 mmol) according to the procedure described for the synthesis of **134** to obtain **138** as an oil (499 mg, 67%). $C_{18}H_{14}Cl_2N_2O$ (345.2); ^{1}H

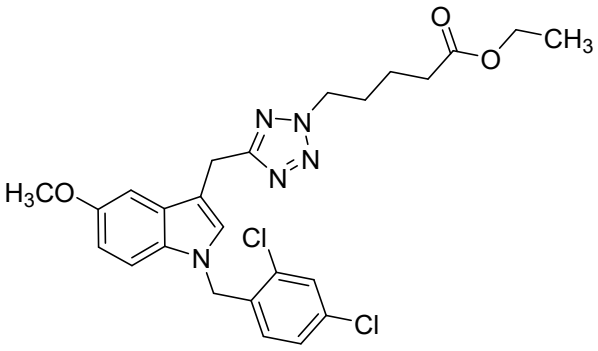
NMR (400 MHz, DMSO-d_6) δ 3.78 (s, 3H), 4.04 (d, J = 0.9 Hz, 2H), 5.45 (s, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.82 (ddd, J = 8.9, 2.5 and 0.4 Hz, 1H), 7.13 (dd, J = 2.4 and 0.5 Hz, 1H), 7.30 (dd, J = 9.0 and 0.6 Hz, 1H), 7.34 (dd, J = 8.3 and 2.2 Hz, 1H), 7.40 (s, 1H), 7.68 (d, J = 2.2 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 345.0556, found: 345.0576.

1-(2,4-Dichlorobenzyl)-5-methoxy-3-(tetrazol-5-ylmethyl)indole (139)



A mixture of **138** (483 mg, 1.40 mmol), trimethylsilyl azide (242 mg, 2.1 mmol), and tetrabutylammonium fluoride hydrate (183 mg) was heated at 120 °C for 5 h. The obtained melt was cooled and purified by chromatography on silica gel (cyclohexane/ethyl acetate/formic acid, 53:47:1) to give **139** as a solid (286 mg, 53%). $C_{18}H_{15}Cl_2N_5O$ (388.3); mp 203 – 204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.73 (s, 3H), 4.36 (d, J = 0.9 Hz, 2H), 5.42 (s, 2H), 6.68 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.8 and 2.4 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 8.9 and 0.5 Hz, 1H), 7.29 (s, 1H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 388.0727, found: 388.0763.

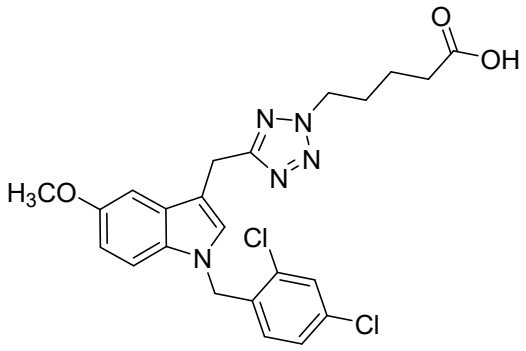
Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-5-methoxyindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoate (140)



Compound **139** (276 mg, 0.71 mmol) was reacted with ethyl 5-bromopentanoate (224 mg, 1.07 mmol) according to the procedure described for the synthesis of **136** (reaction time: 4.5 h) to yield **140** as an oil (180 mg, 49%). $C_{25}H_{27}Cl_2N_5O_3$ (516.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.42 – 1.54 (m, 2H), 1.83 – 1.95 (m,

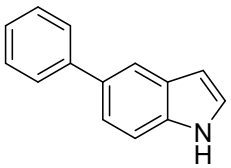
2H), 2.31 (t, *J* = 7.4 Hz, 2H), 3.73 (s, 3H), 4.01 (q, *J* = 7.1 Hz, 2H), 4.28 (d, *J* = 0.9 Hz, 2H), 4.63 (t, *J* = 6.9 Hz, 2H), 5.40 (s, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 6.4 and 2.5 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.24 (dd, *J* = 8.9 and 0.5 Hz, 1H), 7.26 (s, 1H), 7.32 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 516.1564, found: 516.1566.

5-(5-{[1-(2,4-Dichlorobenzyl)-5-methoxyindol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (141)



Compound **140** (173 mg, 0.34 mmol) was saponified as described for the synthesis of **137** to give **141** as an oil (129 mg, 79%). $C_{23}H_{23}Cl_2N_5O_3$ (488.4); purity (HPLC) > 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 – 1.51 (m, 2H), 1.85 – 1.94 (m, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 3.73 (s, 3H), 4.29 (d, *J* = 0.9 Hz, 2H), 4.62 (t, *J* = 7.0 Hz, 2H), 5.40 (s, 2H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.9 and 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.9 and 0.5 Hz, 1H), 7.27 (s, 1H), 7.32 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 12.05 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.32, 21.34, 28.2, 32.8, 46.4, 52.1, 55.3, 100.9, 109.9, 110.7, 111.7, 127.64, 127.73, 127.76, 128.9, 129.6, 131.3, 132.6, 132.8, 134.8, 153.5, 165.2, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 488.1251, found: 488.1253.

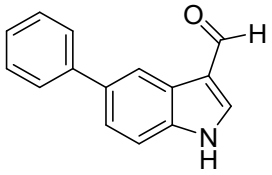
5-Phenylindole (142)



To a solution of 5-bromoindole (700 mg, 3.57 mmol) in toluene/ethanol (1:1, 8 mL) were added phenylboronic acid (871 mg, 7.15 mmol), sodium carbonate solution (1M, 10.7 mL), and tetrakis(triphenylphosphine)palladium(0) (46 mg, 0.040 mmol). The mixture was heated for 1 h under reflux. Subsequently, another portion of tetrakis-(triphenylphosphine)palladium(0) (46 mg, 0.040 mmol) in toluene/ethanol (1:1, 8 mL) was added and the mixture was heated for a further 4 h under reflux. After cooling to

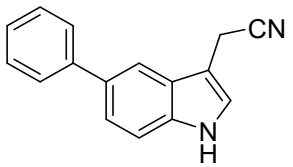
room temperature, the organic phase was separated and the aqueous phase was exhaustively extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate. After addition of some silica gel, the solvent was distilled off and the residue placed on a silica gel column. Elution with a gradient of 0-20% ethyl acetate in cyclohexane afforded **142** (442 mg, 64%) as an oil. $C_{14}H_{11}N$ (193.2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.47 – 6.50 (m, 1H), 7.26 – 7.31 (m, 1H), 7.36 – 7.49 (m, 5H), 7.64 – 7.67 (m, 2H), 7.81 (dt, J = 1.7 and 0.8 Hz, 1H), 11.13 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 194.0964, found: 194.0966.

5-Phenylindole-3-carbaldehyde (143)



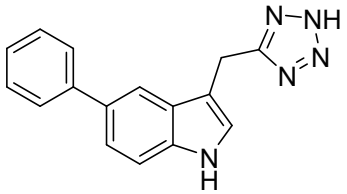
Compound **142** (440 mg, 2.28 mmol) was formylated according to the procedure described for the synthesis of **129** to yield **143** as a solid (455 mg, 90%). $C_{15}H_{11}NO$ (221.3); mp 257 – 258 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.31 – 7.38 (m, 1H), 7.44 – 7.51 (m, 2H), 7.56 (dd, *J* = 8.4 and 1.8 Hz, 1H), 7.60 (dd, *J* = 8.5 and 0.8 Hz, 1H), 7.63 – 7.70 (m, 2H), 8.30 – 8.36 (m, 2H), 9.97 (s, 1H), 12.20 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 222.0913, found: 222.0934.

2-(5-Phenylindol-3-yl)acetonitrile (144)



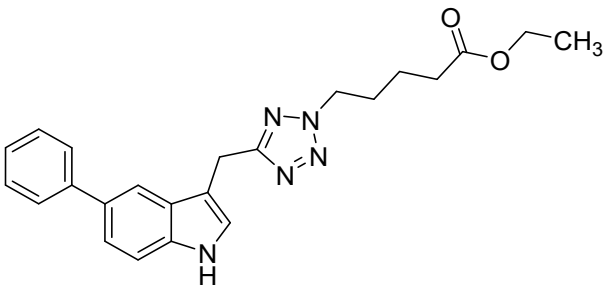
Compound **143** (450 mg, 2.03 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130** to give **144** as a solid (238 mg, 50%). $C_{16}H_{12}N_2$ (232.3); mp 101 – 102 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.10 (d, *J* = 0.9 Hz, 2H), 7.29 – 7.34 (m, 1H), 7.39 (dd, *J* = 2.1 and 1.1 Hz, 1H), 7.43 – 7.50 (m, 4H), 7.66 – 7.71 (m, 2H), 7.86 – 7.89 (m, 1H), 11.19 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 233.1073, found: 233.1062.

5-Phenyl-3-(tetrazol-5-ylmethyl)indole (145)



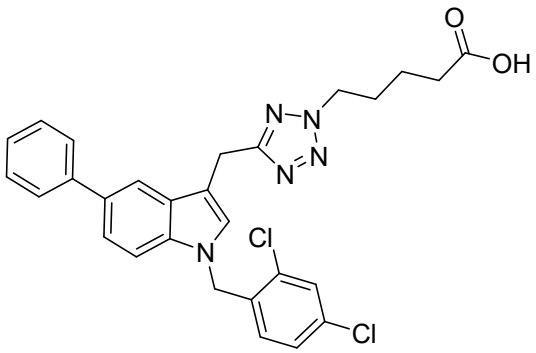
A mixture of **144** (230 mg, 0.99 mmol), trimethylsilyl azide (172, 1.49 mmol), and tetrabutylammonium fluoride hydrate (130 mg) was heated at 120 °C for 6 h. After addition of further trimethylsilyl azide (58 mg, 0.50 mmol), the heating was continued at 120 °C for 2 h. The resulting melt was cooled and purified by chromatography on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to give **145** as an oil (246 mg, 90%). $C_{16}H_{13}N_5$ (275.3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.43 (d, J = 0.9 Hz, 2H), 7.27 – 7.32 (m, 2H), 7.40 (dd, J = 8.5 and 1.7 Hz, 1H), 7.42 – 7.47 (m, 3H), 7.59 – 7.64 (m, 2H), 7.72 (dt, J = 1.6 and 0.7 Hz, 1H), 11.08 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 276.1244, found: 276.1232.

Ethyl 5-{5-[(5-phenylindol-3-yl)methyl]-2*H*-tetrazol-2-yl}pentanoate (146)



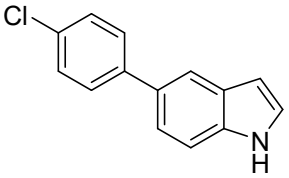
Compound **145** (235 mg, 0.85 mmol) was reacted with ethyl 5-bromopentanoate (232 mg, 1.11 mmol) according to the procedure described for the synthesis of **132** (reaction time: 2 h) to yield **146** as an oil (113 mg, 33%). $C_{23}H_{25}N_5O_2$ (403.5); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, J = 7.1 Hz, 3H), 1.42 – 1.50 (m, 2H), 1.83 – 1.91 (m, 2H), 2.25 (t, J = 7.4 Hz, 2H), 4.00 (q, J = 7.1 Hz, 2H), 4.35 (d, J = 0.9 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 7.27 (dd, J = 2.6 and 1.7 Hz, 1H), 7.28 – 7.32 (m, 1H), 7.38 (dd, J = 8.4 and 1.7 Hz, 1H), 7.40 – 7.46 (m, 3H), 7.59 – 7.64 (m, 2H), 7.77 (dt, J = 1.5 and 0.7 Hz, 1H), 10.99 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 404.2081, found: 404.2065.

5-(5-{[1-(2,4-Dichlorobenzyl)-5-phenylindol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (147)



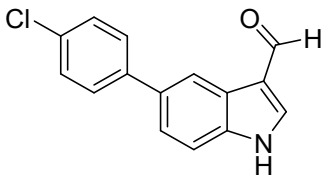
The synthesis was carried out starting from **146** (105 mg, 0.26 mmol) and 2,4-dichlorobenzyl bromide (74 mg, 0.31 mmol) analogous to the procedure described for the preparation of **133**. After silica gel chromatography, **147** was obtained as an oil (43 mg, 31%). $C_{28}H_{25}Cl_2N_5O_2$ (534.4); purity (HPLC) 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.45 (p, J = 7.4 Hz, 2H), 1.88 (p, J = 7.0 Hz, 2H), 2.20 (t, J = 7.4 Hz, 2H), 4.39 (d, J = 0.9 Hz, 2H), 4.62 (t, J = 7.0 Hz, 2H), 5.48 (s, 2H), 6.73 (d, J = 8.4 Hz, 1H), 7.28 – 7.32 (m, 1H), 7.35 (dd, J = 8.4 and 2.2 Hz, 1H), 7.36 (s, 1H), 7.42 – 7.46 (m, 4H), 7.63 (dt, J = 7.2 and 1.2 Hz, 2H), 7.68 (d, J = 2.2 Hz, 1H), 7.84 (t, J = 1.2 Hz, 1H), 12.06 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.27, 21.31, 28.16, 32.71, 46.40, 52.07, 110.4, 110.9, 117.2, 121.2, 126.4, 126.71, 127.72, 127.90, 127.99, 128.8, 129.0, 129.7, 131.8, 132.7, 132.9, 134.6, 135.7, 141.5, 165.2, 174.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 534.1458, found: 534.1387.

5-(4-Chlorophenyl)indole (148)



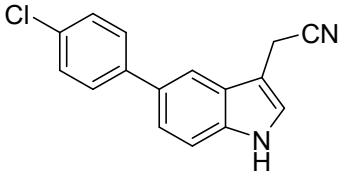
5-Bromoindole (721 mg, 3.68 mmol) was reacted with 4-chlorophenylboronic acid (1150 mg, 7.35 mmol) according to the procedure described for the synthesis of **142** to yield **148** as a solid (432 mg, 52%). $C_{14}H_{10}ClN$ (227.7); mp 93 – 94 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.49 (ddd, J = 2.8, 1.9 and 0.8 Hz, 1H), 7.37 – 7.39 (m, 2H), 7.46 – 7.48 (m, 3H), 7.67 – 7.69 (m,), 7.82 (dd, J = 1.9 and 0.8 Hz, 1H), 11.17 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 228.0575, found: 228.0560.

5-(4-Chlorophenyl)indole-3-carbaldehyde (149)



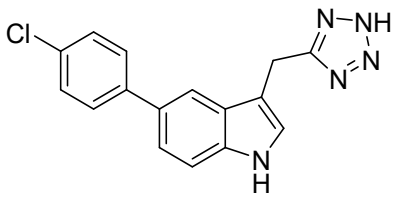
Compound **148** (418 mg, 1.84 mmol) was formylated according to the procedure described for the synthesis of **129** to yield **149** as a solid (445 mg, 95%). $C_{16}H_{12}ClNO_2$ (255.7); mp 216 – 218 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 – 7.54 (m, 2H), 7.56 (dd, J = 8.5 and 1.8 Hz, 1H), 7.61 (dd, J = 8.5 and 0.8 Hz, 1H), 7.67 – 7.72 (m, 2H), 8.33 – 8.35 (m, 2H), 9.97 (s, 1H), 12.22 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 256.0524, found: 256.0484.

2-[5-(4-Chlorophenyl)indol-3-yl]acetonitrile (150)



Compound **149** (437 mg, 1.71 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130**. After silica gel chromatography (cyclohexane to cyclohexane/ethyl acetate, 7:3) **150** was obtained as a solid (305 mg, 67%). $C_{16}H_{11}ClN_2$ (266.7); mp 131 – 132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.10 (d, J = 0.9 Hz, 2H), 7.40 (dt, J = 2.5 and 1.0 Hz, 1H), 7.45 (dd, J = 8.5 and 1.7 Hz, 1H), 7.48 (d, J = 0.8 Hz, 1H), 7.49 – 7.53 (m, 2H), 7.69 – 7.73 (m, 2H), 7.89 (dt, J = 1.6 and 0.7 Hz, 1H), 11.22 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 267.0684, found: 267.0680.

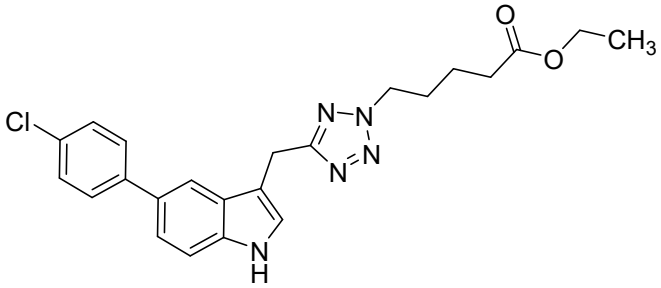
5-(4-Chlorophenyl)-3-(tetrazol-5-ylmethyl)indole (151)



A mixture of **150** (301 mg, 1.13 mmol), trimethylsilyl azide (195 mg, 1.69 mmol), and tetrabutylammonium fluoride hydrate (147 mg) was first heated at 140 °C for 5 min until all components were molten. The melt was then stirred at 120 °C for 3 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to

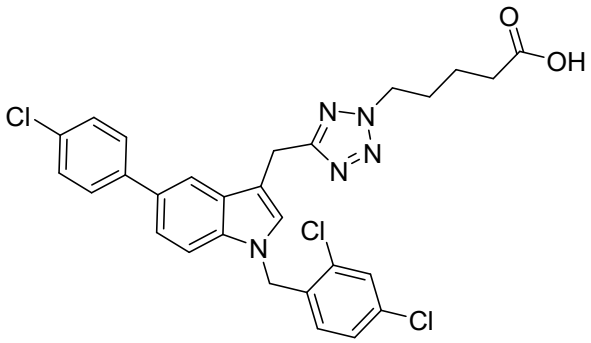
cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **151** as a solid (280 mg, 80%). $C_{16}H_{12}ClN_5$ (309.8); mp 223 – 225 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.42 (d, J = 0.9 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 8.5 and 1.8 Hz, 1H), 7.45 (dd, J = 8.5 and 0.7 Hz, 1H), 7.47 – 7.51 (m, 2H), 7.64 – 7.67 (m, 2H), 7.76 (dt, J = 1.7 and 0.7 Hz, 1H), 11.11 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 310.0854, found: 310.0832.

Ethyl 5-(5-{[5-(4-chlorophenyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (152)



Compound **151** (270 mg, 0.87 mmol) was reacted with ethyl 5-bromopentanoate (217 mg, 1.04 mmol) according to the procedure described for the synthesis of **132** (reaction time: 3 h) to yield **152** as an oil (143 mg, 37%). $C_{23}H_{24}ClN_5O_2$ (437.9); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.2 Hz, 3H), 1.43 – 1.49 (m, 2H), 1.83 – 1.91 (m, 2H), 2.26 (t, J = 7.4 Hz, 2H), 4.00 (q, J = 7.1 Hz, 2H), 4.35 (d, J = 0.9 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 7.27 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.5 and 1.8 Hz, 1H), 7.43 (dd, J = 8.5 and 0.7 Hz, 1H), 7.46 – 7.50 (m, 2H), 7.63 – 7.66 (m, 2H), 7.79 (dt, J = 1.7 and 0.7 Hz, 1H), 11.02 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 438.1691, found: 438.1561.

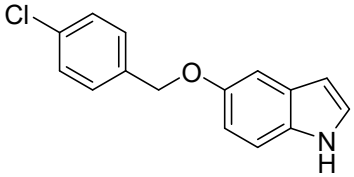
5-(5-{[5-(4-Chlorophenyl)-1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (153)



The synthesis was carried out starting from **152** (150 mg, 0.34 mmol) and 2,4-dichlorobenzyl bromide (98 mg, 0.41 mmol) analogous to the procedure described for the preparation of **133**. After silica gel chromatography, **153** was obtained as an oil (82 mg, 42%). $C_{28}H_{24}Cl_3N_5O_2$ (568.9); purity (HPLC) 97%; ^{1}H NMR (600 MHz, DMSO-

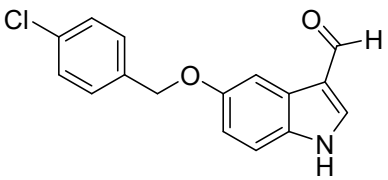
d$_6$) δ 1.41 – 1.47 (m, 2H), 1.85 – 1.91 (m, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 4.39 (d, *J* = 0.9 Hz, 2H), 4.62 (t, *J* = 7.0 Hz, 2H), 5.48 (s, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 7.34 (dt, *J* = 6.2 and 2.1 Hz, 1H), 7.37 (s, 1H), 7.41 – 7.46 (m, 2H), 7.47 – 7.51 (m, 2H), 7.64 – 7.68 (m, 2H), 7.68 (d, *J* = 2.2 Hz, 1H), 7.85 – 7.89 (m, 1H), 12.07 (s, 1H); ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 21.2, 21.3, 28.2, 32.7, 46.4, 52.1, 110.6, 111.0, 117.3, 121.0, 127.7, 127.9, 128.2, 128.4, 128.7, 129.0, 129.7, 130.4, 131.2, 132.7, 132.9, 134.6, 135.9, 140.3, 165.2, 174.0; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 568.1068, found: 568.1030.

5-[(4-Chlorobenzyl)oxy]indole (154)



A solution of 5-hydroxyindole (300 mg, 2.25 mmol), tetrabutylammonium bromide (364 mg, 1.13 mmol), and 4-chlorobenzyl bromide (510 mg, 2.48 mmol) in dichloromethane (15 mL) was treated with 20% aqueous sodium hydroxide solution (15 mL). The mixture was stirred at room temperature for 2 h. Then the organic phase was separated and the aqueous phase exhaustively extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate. After addition of some silica gel, the solvent was distilled off and the residue placed on a silica gel column. Elution with a gradient of 0-20% ethyl acetate in cyclohexane afforded **154** as a solid (485 mg, 84%). $C_{15}H_{12}ClNO$ (257.7); mp 126 – 128 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 5.08 (s, 2H), 6.31 (ddd, *J* = 2.9, 2.0 and 0.9 Hz, 1H), 6.79 (ddd, *J* = 8.7, 2.5 and 0.5 Hz, 1H), 7.10 (dt, *J* = 2.5 and 0.7 Hz, 1H), 7.26 – 7.30 (m, 2H), 7.42 – 7.46 (m, 2H), 7.47 – 7.51 (m, 2H), 10.91 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 258.0680, found: 258.0649.

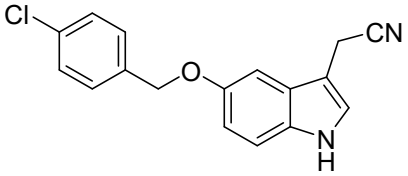
5-[(4-Chlorobenzyl)oxy]indole-3-carbaldehyde (155)



Compound **154** (420 mg, 1.63 mmol) was formylated according to the procedure described for the synthesis of **129** to yield **155** as a solid (460 mg, 99%). $C_{16}H_{12}ClNO_2$ (285.7); mp 187 – 189 °C; ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 5.13 (s, 2H), 6.97 (dd, *J* = 8.8 and 2.5 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.47 (m, 2H), 7.50 – 7.53 (m, 2H),

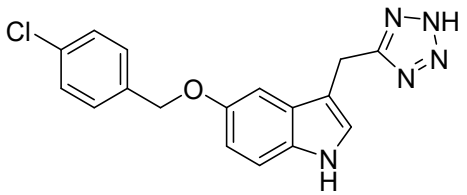
7.67 (d, *J* = 2.5 Hz, 1H), 8.22 (s, 1H), 9.89 (s, 1H), 12.03 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 286.0629, found: 286.0640.

2-{5-[(4-Chlorobenzyl)oxy]indol-3-yl}acetonitrile (156)



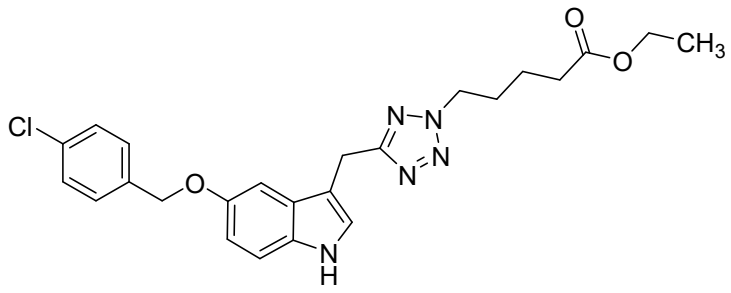
Compound **155** (451 mg, 1.58 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130** to give **156** as a solid (330 mg, 70%). $C_{17}H_{13}ClN_2O$ (296.8); mp 123 – 124 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.98 (d, *J* = 1.0 Hz, 2H), 5.10 (s, 2H), 6.86 (dd, *J* = 8.8 and 2.5 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.28 – 7.32 (m, 2H), 7.43 – 7.46 (m, 2H), 7.49 – 7.53 (m, 2H), 10.98 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 297.0789, found: 297.0776.

5-[(4-Chlorobenzyl)oxy]-3-(tetrazol-5-ylmethyl)indole (157)



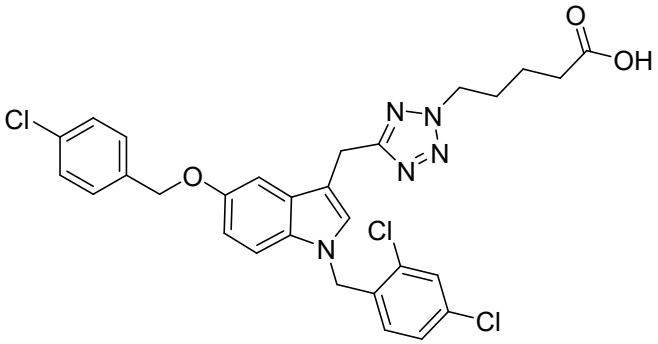
A mixture of **156** (310 mg, 1.05 mmol), trimethylsilyl azide (181 mg, 1.57 mmol), and tetrabutylammonium fluoride hydrate (136 mg) was heated at 120 °C for 4 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **157** as a solid (170 mg, 48%). $C_{17}H_{14}ClN_5O$ (339.8); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.32 (d, *J* = 0.8 Hz, 2H), 5.05 (s, 2H), 6.81 (dd, *J* = 8.7 and 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.26 (dd, *J* = 8.7 and 0.5 Hz, 1H), 7.41 – 7.45 (m, 2H), 7.46 – 7.50 (m, 2H), 10.86 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 340.0960, found: 340.0932.

Ethyl 5-[5-({5-[(4-chlorobenzyl)oxy]indol-3-yl}methyl)-2*H*-tetrazol-2-yl]pentanoate (158)



Compound **157** (170 mg, 0.50 mmol) was reacted with ethyl 5-bromopentanoate (125 mg, 0.60 mmol) according to the procedure described for the synthesis of **132** (reaction time: 3 h) to yield **158** as an oil (94 mg, 40%). $C_{24}H_{26}ClN_5O_3$ (468.0); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.45 – 1.54 (m, 2H), 1.84 – 1.94 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 4.24 (d, J = 0.9 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 5.05 (s, 2H), 6.80 (dd, J = 8.7 and 2.4 Hz, 1H), 7.09 (d, J = 2.5 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 8.8 and 0.5 Hz, 1H), 7.41 – 7.51 (m, 4H), 10.77 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 468.1797, found: 468.1727.

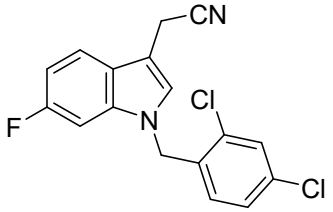
5-[5-({5-[(4-Chlorobenzyl)oxy]-1-(2,4-dichlorobenzyl)indol-3-yl}methyl)-2*H*-tetrazol-2-yl]pentanoic acid (159)



The synthesis was carried out starting from **158** (90 mg, 0.19 mmol) and 2,4-dichlorobenzyl bromide (55 mg, 0.23 mmol) analogous to the procedure described for the preparation of **133**. After silica gel chromatography, **159** was obtained as an oil (82 mg, 71%). $C_{29}H_{26}Cl_3N_5O_3$ (598.9); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.43 – 1.49 (m, 2H), 1.87 – 1.92 (m, 2H), 2.22 (t, J = 7.4 Hz, 2H), 4.27 (d, J = 0.8 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 5.07 (s, 2H), 5.40 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 8.8 and 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.28 (s, 1H), 7.32 (dd, J = 8.4 and 2.2 Hz, 1H), 7.41 – 7.46 (m, 2H), 7.46 – 7.51 (m, 2H), 7.66 (d, J = 2.2 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.3, 21.4, 28.2, 32.9, 46.4, 52.1, 69.0, 102.6, 109.9, 110.8, 112.2, 127.65, 127.73, 127.9, 128.3, 128.9, 129.4,

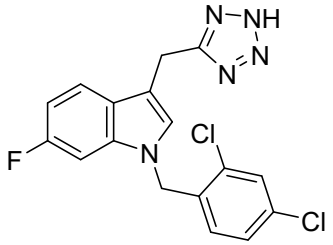
129.7, 131.5, 132.2, 132.6, 132.8, 134.8, 136.7, 152.4, 165.1, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 598.1174, found: 598.1175.

2-[1-(2,4-Dichlorobenzyl)-6-fluoroindol-3-yl]acetonitrile (160)



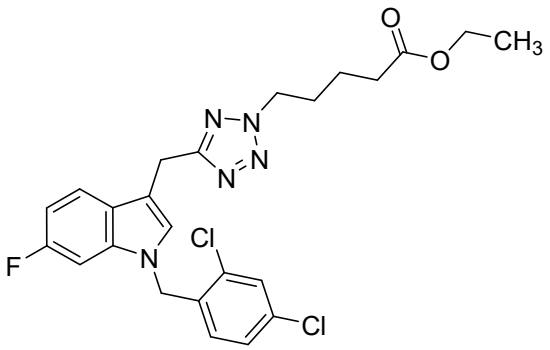
2-(6-Fluoroindol-3-yl)acetonitrile (481 mg, 2.76 mmol) was reacted with 2,4-dichlorobenzyl bromide (982 mg, 4.09 mmol) according to the procedure described for the synthesis of **134** (reaction time: 30 min) to obtain **160** as a solid (428 mg, 47%). $C_{17}H_{11}Cl_2FN$ (333.2); mp 105 – 106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (d, J = 0.9 Hz, 2H), 5.47 (s, 2H), 6.78 (d, J = 8.3 Hz, 1H), 7.00 (ddd, J = 9.7, 8.7 and 2.3 Hz, 1H), 7.34 – 7.39 (m, 2H), 7.42 (d, J = 1.0 Hz, 1H), 7.64 (dd, J = 8.6 and 5.4 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 333.0356, found: 333.0341.

1-(2,4-Dichlorobenzyl)-6-fluoro-3-(tetrazol-5-ylmethyl)indole (161)



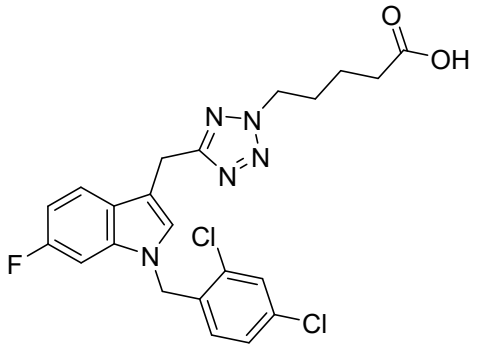
A mixture of **160** (370 mg, 1.11 mmol), trimethylsilyl azide (192 mg, 1.67 mmol), and tetrabutylammonium fluoride hydrate (146 mg) was heated at 120 °C for 4.5 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **161** as a solid (281 mg, 67%). $C_{17}H_{12}Cl_2FN_5$ (376.2); mp 245 – 246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.38 (d, J = 0.9 Hz, 2H), 5.44 (s, 2H), 6.76 (d, J = 8.3 Hz, 1H), 6.91 (ddd, J = 9.7, 8.7 and 2.3 Hz, 1H), 7.29 – 7.33 (m, 2H), 7.35 (dd, J = 8.3 and 2.2 Hz, 1H), 7.49 (dd, J = 8.7 and 5.4 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 376.0527, found: 376.0516.

Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-6-fluoroindol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (162)



Compound **161** (249 mg, 0.66 mmol) was reacted with ethyl 5-bromopentanoate (138 mg, 0.66 mmol) according to the procedure described for the synthesis of **136** (reaction time: 6.5 h) to yield **162** as an oil (165 mg, 49%). $C_{24}H_{24}Cl_2FN_5O_2$ (504.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.42 – 1.52 (m, 2H), 1.84 – 1.93 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.02 (q, J = 7.1 Hz, 2H), 4.31 (d, J = 1.0 Hz, 2H), 4.62 (t, J = 6.9 Hz, 2H), 5.42 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.89 (ddd, J = 9.7, 8.7 and 2.3 Hz, 1H), 7.27 – 7.31 (m, 2H), 7.35 (dd, J = 8.4 and 2.2 Hz, 1H), 7.54 (dd, J = 8.7 and 5.4 Hz, 1H), 7.68 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 504.1364, found: 504.1344.

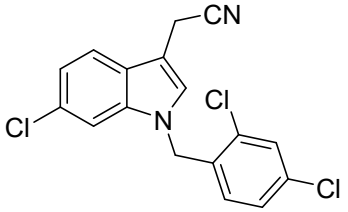
5-(5-{[1-(2,4-Dichlorobenzyl)-6-fluoroindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoic acid (163)



Compound **162** (114 mg, 0.23 mmol) was saponified as described for the synthesis of **137** to give **163** as an oil (83 mg, 77%). $C_{22}H_{20}Cl_2FN_5O_2$ (476.3); purity (HPLC) 98%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (p, J = 7.9 Hz, 2H), 1.89 (p, J = 7.4 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 4.31 (d, J = 1.0 Hz, 2H), 4.62 (t, J = 6.9 Hz, 2H), 5.42 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.89 (ddd, J = 9.7, 8.7 and 2.3 Hz, 1H), 7.25 – 7.32 (m, 2H), 7.35 (dd, J = 8.3 and 2.2 Hz, 1H), 7.53 (dd, J = 8.7 and 5.4 Hz, 1H), 7.67 (d, J = 2.1 Hz, 1H), 12.06 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 21.26, 21.32, 28.1, 32.8, 46.4, 52.1, 96.5 (d, J = 26.7 Hz), 107.6 (d, J = 24.6 Hz), 110.7, 120.2, 124.0, 127.65, 127.70, 129.0, 129.8, 132.87, 132.92, 134.4, 136.3 (d, J = 12.5 Hz), 158.1 (d, J = 233.8 Hz),

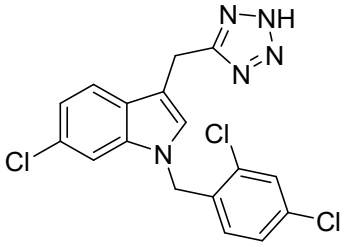
165.0, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 476.1051, found: 476.1050.

2-[6-Chloro-1-(2,4-dichlorobenzyl)indol-3-yl]acetonitrile (164)



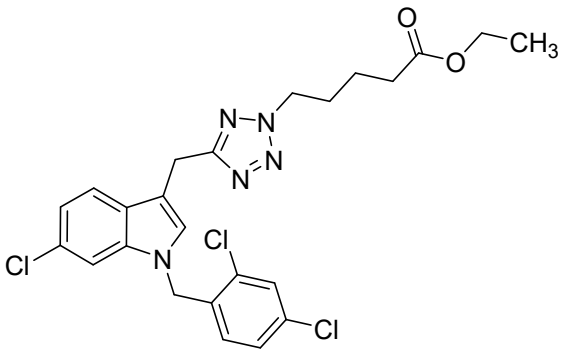
2-(6-Chloroindol-3-yl)acetonitrile (483 mg, 2.53 mmol) was reacted with 2,4-dichlorobenzyl bromide (990 mg, 4.13 mmol) according to the procedure described for the synthesis of **134** (reaction time: 30 min) to obtain **164** as a solid (540 mg, 61%). $C_{17}H_{11}Cl_3N_2$ (349.6); mp 129 – 130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.09 (d, J = 0.9 Hz, 2H), 5.50 (s, 2H), 6.75 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 8.5, 1.8 Hz and 1H), 7.37 (dd, J = 8.3 and 2.2 Hz, 1H), 7.45 (s, 1H), 7.63 (dd, J = 1.9 and 0.6 Hz, 1H), 7.65 (dd, J = 8.5 and 0.5 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 349.0061, found: 349.0038.

6-Chloro-1-(2,4-dichlorobenzyl)-3-(tetrazol-5-ylmethyl)indole (165)



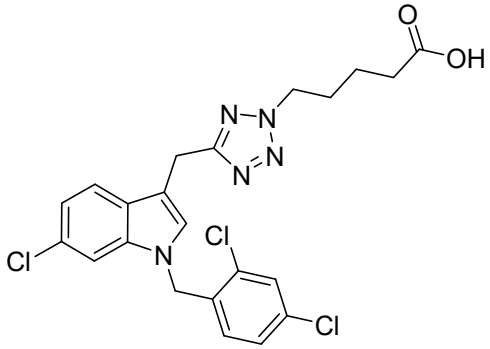
A mixture of **164** (482 mg, 1.38 mmol), trimethylsilyl azide (238 mg, 2.07 mmol), and tetrabutylammonium fluoride hydrate (180 mg) was heated at 135 °C for 7 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 5.5:4.5:0.1) to yield **165** as a solid (387 mg, 71%). $C_{17}H_{12}Cl_3N_5$ (392.7); mp 227 – 228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.39 (d, J = 0.9 Hz, 2H).5.48 (s, 2H), 6.73 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.5 and 1.9 Hz, 1H), 7.33 – 7.39 (m, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.55 – 7.58 (m, 1H), 7.69 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 392.0231, found: 392.0220.

Ethyl 5-(5-{[6-chloro-1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (166)



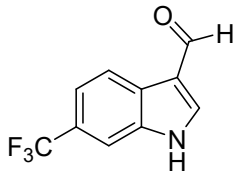
Compound **165** (353 mg, 0.90 mmol) was reacted with ethyl 5-bromopentanoate (282 mg, 1.35 mmol) according to the procedure described for the synthesis of **136** (reaction time: 4 h) to yield **166** as an oil (240 mg, 51%). $C_{24}H_{24}Cl_3N_5O_2$ (520.8); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.44 – 1.50 (m, 2H), 1.85 – 1.91 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.02 (q, J = 7.2 Hz, 2H), 4.31 (d, J = 0.9 Hz, 2H), 4.62 (t, J = 6.9 Hz, 2H), 5.46 (s, 2H), 6.67 (dd, J = 8.3 and 0.8 Hz, 1H), 7.05 (dd, J = 8.5 and 1.8 Hz, 1H), 7.33 – 7.36 (m, 2H), 7.54 – 7.56 (m, 2H), 7.68 (d, J = 2.2 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 520.1069, found: 520.1090.

5-(5-{[6-Chloro-1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (167)



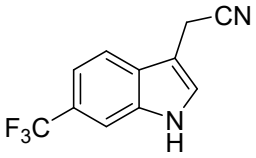
Compound **166** (212 mg, 0.41 mmol) was saponified as described for the synthesis of **137** to give **167** as a solid (180 mg, 90%). $C_{22}H_{20}Cl_3N_5O_2$ (492.8); mp 132 – 133 °C; purity (HPLC) > 99%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.41 – 1.49 (m, 2H), 1.85 – 1.91 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 4.31 (d, J = 1.0 Hz, 2H), 4.61 (t, J = 7.0 Hz, 2H), 5.46 (s, 2H), 6.69 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.5 and 1.8 Hz, 1H), 7.33 – 7.37 (m, 2H), 7.53 – 7.56 (m, 2H), 7.68 (d, J = 2.2 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.2, 21.3, 28.2, 32.8, 46.4, 52.1, 110.0, 110.8, 119.5, 120.5, 126.0, 126.8, 127.8, 128.2, 129.0, 129.7, 132.85, 132.94, 134.4, 136.7, 165.0, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 492.0756, found: 492.0764.

6-(Trifluoromethyl)indole-3-carbaldehyde (168)



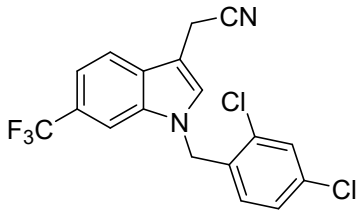
6-(Trifluoromethyl)indole (500 mg, 2.70 mmol) was formylated according to the procedure described for the synthesis of **129** to yield **168** as a solid (548 mg, 95%). $C_{10}H_6F_3NO$ (213.2); mp 236 – 238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (ddd, J = 8.3, 1.7 and 0.6 Hz, 1H), 7.86 (dt, J = 1.6 and 0.8 Hz, 1H), 8.28 (dt, J = 8.3 and 0.8 Hz, 1H), 8.51 (s, 1H), 10.00 (s, 1H), 12.45 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 214.0474, found: 214.0847.

2-[6-(Trifluoromethyl)indol-3-yl]acetonitrile (169)



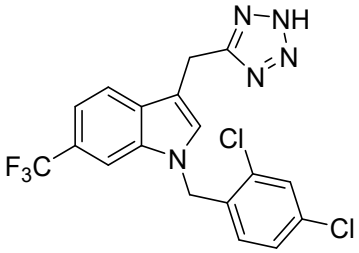
Compound **168** (529 mg, 2.48 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130**. After silica gel chromatography (cyclohexane to cyclohexane/ethyl acetate, 7:3), **169** was obtained as a solid (311 mg, 56%). $C_{11}H_7F_3N_2$ (224.2); mp 108 – 109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.11 (d, J = 0.9 Hz, 2H), 7.36 (ddd, J = 8.3, 1.7 and 0.6 Hz, 1H), 7.61 (s, 1H), 7.76 (t, J = 0.8 Hz, 1H), 7.80 (dt, J = 8.4 and 0.8 Hz, 1H), 11.56 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 225.0634, found: 225.0641.

2-[1-(2,4-Dichlorobenzyl)-6-(trifluoromethyl)indol-3-yl]acetonitrile (170)



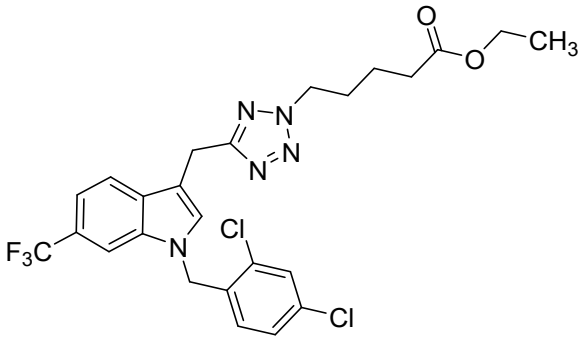
Compound **169** (305 mg, 1.36 mmol) was reacted with 2,4-dichlorobenzyl bromide (425 mg, 1.77 mmol) according to the procedure described for the synthesis of **134** (reaction time: 1.5 h) to obtain **170** as a solid (335 mg, 64%). $C_{18}H_{11}Cl_2F_3N_2$ (383.2); mp 169 – 170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.15 (d, J = 0.9 Hz, 2H), 5.63 (s, 2H), 6.77 (d, J = 8.4 Hz, 1H), 7.38 (dd, J = 8.4 and 2.2 Hz, 1H), 7.44 (dt, J = 7.1 and 1.3 Hz, 1H), 7.65 (s, 1H), 7.71 (d, J = 2.1 Hz, 1H), 7.86 (dt, J = 8.4 and 0.8 Hz, 1H), 7.97 (dt, J = 1.7 and 0.8 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 383.0324, found: 383.0347.

1-(2,4-Dichlorobenzyl)-3-(tetrazol-5-ylmethyl)-6-(trifluoromethyl)indole (171)



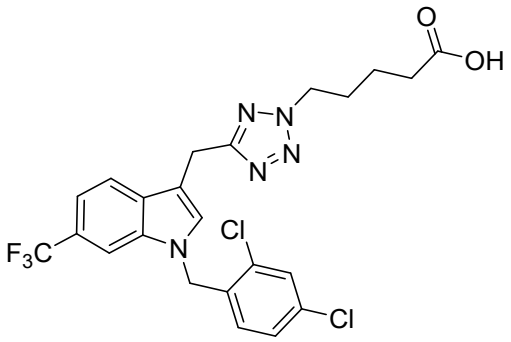
A mixture of **170** (320 mg, 0.84 mmol), trimethylsilyl azide (145 mg, 1.26 mmol), and tetrabutylammonium fluoride hydrate (110 mg) was heated at 150 °C for 5 min until all components were molten. The melt was then stirred at 125 °C for 5 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **171** as a solid (134 mg, 38%). $C_{18}H_{12}Cl_2F_3N_5$ (426.2); mp 240 – 241 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (d, J = 0.9 Hz, 2H), 5.60 (s, 2H), 6.75 (d, J = 8.4 Hz, 1H), 7.34 – 7.38 (m, 2H), 7.57 (s, 1H), 7.68 – 7.73 (m, 2H), 7.91 (dd, J = 1.7 and 0.9 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 426.0495, found: 426.0451.

Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-6-(trifluoromethyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoate (172)



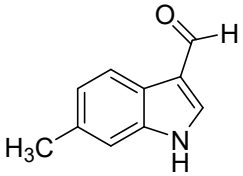
Compound **171** (120 mg, 0.28 mmol) was reacted with ethyl 5-bromopentanoate (88 mg, 0.42 mmol) according to the procedure described for the synthesis of **136** to yield **172** as an oil (65 mg, 42%). $C_{25}H_{24}Cl_2F_3N_5O_2$ (554.4); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (t, J = 7.1 Hz, 3H), 1.42 – 1.56 (m, 2H), 1.81 – 1.94 (m, 2H), 2.30 (t, J = 7.4 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 4.37 (d, J = 0.9 Hz, 2H), 4.62 (t, J = 6.9 Hz, 2H), 5.59 (s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 7.34 (m, 2H), 7.55 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.75 (dt, J = 8.4 and 0.7 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 554.1332, found: 554.1278.

5-(5-{[1-(2,4-Dichlorobenzyl)-6-(trifluoromethyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)pentanoic acid (173)



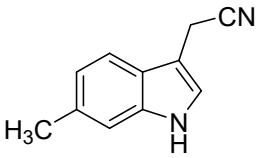
Compound **172** (49 mg, 0.088 mmol) was saponified as described for the synthesis of **137** to give **173** as a solid (40 mg, 86%). $C_{23}H_{20}Cl_2F_3N_5O_2$ (526.3); mp 126 – 128 °C; purity (HPLC) 98%; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.45 (p, J = 7.4 Hz, 2H), 1.89 (p, J = 7.7 Hz, 2H), 2.23 (t, J = 7.4 Hz, 2H), 4.37 (s, 2H), 4.61 (t, J = 7.0 Hz, 2H), 5.58 (s, 2H), 6.72 (d, J = 8.4 Hz, 1H), 7.33 (dd, J = 8.4 and 1.6 Hz, 1H), 7.36 (dd, J = 8.4 and 2.2 Hz, 1H), 7.55 (s, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 1.6 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.1, 21.3, 28.1, 32.8, 46.5, 52.1, 107.68 – 107.87, 111.0, 115.37 – 115.54, 119.9, 122.3 (q, J = 31.5 Hz), 125.3 (d, J = 273.0 Hz), 127.8, 129.1, 129.7, 130.5, 132.9, 133.0, 134.4, 135.2, 164.9, 174.1; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 526.1019, found: 526.1050.

6-Methylindole-3-carbaldehyde (174)



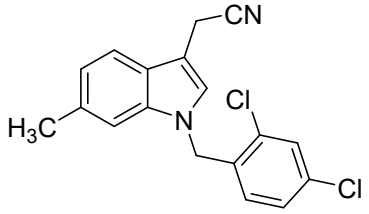
6-Methylindole (650 mg, 4.96 mmol) was formylated according to the procedure described for the synthesis of **129** to yield **174** as a solid (504 mg, 64%). $C_{10}H_9NO$ (159.2); mp 188 – 189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.41 (s, 3H), 7.04 (ddd, J = 8.1, 1.5 and 0.7 Hz, 1H), 7.29 (dt, J = 1.6 and 0.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 3.0 Hz, 1H), 9.89 (s, 1H), 11.98 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 160.0757, found: 160.0765.

2-(6-Methylindol-3-yl)acetonitrile (175)



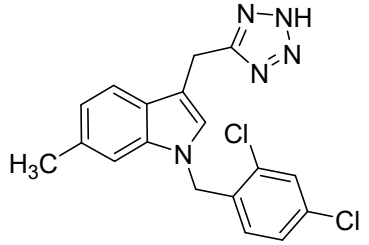
Compound **174** (480 mg, 3.02 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130** to give **175** as a solid (266 mg, 52%). $C_{11}H_{10}N_2$ (170.2); mp 122 – 123 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.39 (d, *J* = 0.7 Hz, 3H), 3.99 (d, *J* = 0.9 Hz, 2H), 6.89 (ddd, *J* = 8.1, 1.5 and 0.6 Hz, 1H), 7.18 (dt, *J* = 1.6 and 0.8 Hz, 1H), 7.24 (dt, *J* = 2.5 and 0.9 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 10.93 (s, 1H); HR-MS (APCI, direct probe) *m/z* [M+H]$^+$ calc.: 170.0917, found: 171.0910.

2-[1-(2,4-Dichlorobenzyl)-6-methylindol-3-yl]acetonitrile (176)



Compound **175** (258 mg, 1.52 mmol) was reacted with 2,4-dichlorobenzyl bromide (475 mg, 1.98 mmol) according to the procedure described for the synthesis of **134** to obtain **176** as an oil (300 mg, 60%). $C_{18}H_{14}Cl_2N_2$ (329.2); ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.37 (s, 3H), 4.05 (d, *J* = 0.9 Hz, 2H), 5.44 (s, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.96 (ddd, *J* = 8.1, 1.5 and 0.6 Hz, 1H), 7.21 (dt, *J* = 1.5 and 0.8 Hz, 1H), 7.32 – 7.37 (m, 2H), 7.51 (dd, *J* = 8.0 and 0.7 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* [M+H]$^+$ calc.: 329.0607, found: 329.0611.

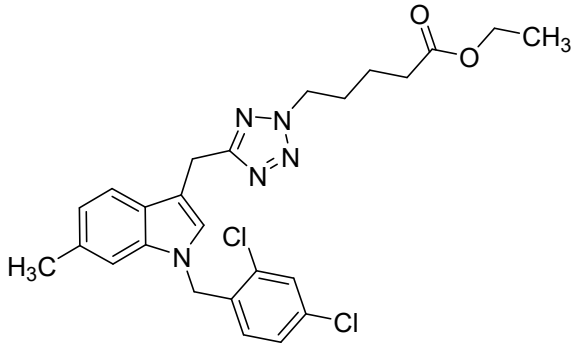
1-(2,4-Dichlorobenzyl)-6-methyl-3-(tetrazol-5-ylmethyl)indole (177)



A mixture of **176** (290 mg, 0.88 mmol), trimethylsilyl azide (152 mg, 1.32 mmol), and tetrabutylammonium fluoride hydrate (115 mg) was heated at 120 °C for 7 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **177** as a solid (40 mg, 12%). $C_{18}H_{15}Cl_2N_5$ (372.3); mp 179 – 180 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 2.35 (s, 3H), 4.33 (d, *J* = 0.9 Hz, 2H), 5.41 (s, 2H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.2 and 1.4

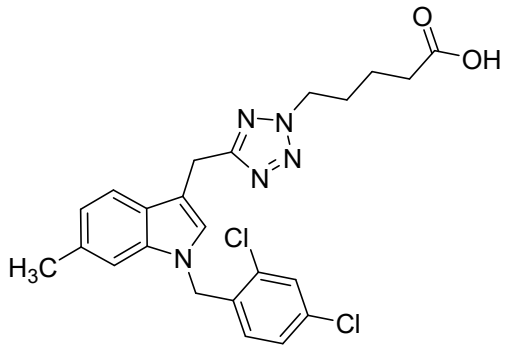
Hz, 1H), 7.15 (s, 1H), 7.23 (s, 1H), 7.32 (dd, *J* = 8.3 and 2.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 2.2 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 372.0778, found: 372.0786.

Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-6-methylindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoate (178)



Compound **176** (30 mg, 0.081 mmol) was reacted with ethyl 5-bromopentanoate (25 mg, 0.12 mmol) according to the procedure described for the synthesis of **136** reaction time: 4 h) to yield **178** as an oil (24 mg, 60%). $C_{25}H_{27}Cl_2N_5O_2$ (500.4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.61 – 1.70 (m, 2H), 1.99 – 2.08 (m, 2H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.41 (s, 3H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.36 (d, *J* = 0.9 Hz, 2H), 4.57 (t, *J* = 7.1 Hz, 2H), 5.28 (s, 2H), 6.48 – 6.51 (m, 1H), 6.93 – 6.98 (m, 2H), 7.01 (d, *J* = 1.0 Hz, 1H), 7.05 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.55 (dd, *J* = 8.1 and 0.8 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 500.1615, found: 500.1644.

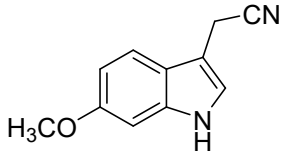
5-(5-{[1-(2,4-Dichlorobenzyl)-6-methylindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoic acid (179)



Compound **178** (19 mg, 0.038 mmol) was saponified as described for the synthesis of **137** to give **179** as an oil (15 mg, 84%). $C_{23}H_{23}Cl_2N_5O_2$ (472.4); purity (HPLC) 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 – 1.71 (m, 2H), 2.01 – 2.10 (m, 2H), 2.36 – 2.43 (m, 5H), 4.37 (d, *J* = 0.9 Hz, 2H), 4.57 (t, *J* = 7.0 Hz, 2H), 5.27 (s, 2H), 6.49 (dd, *J* = 8.4 and 0.8 Hz, 1H), 6.93 – 6.98 (m, 2H), 7.00 (s, 1H), 7.05 (dd, *J* = 8.3 and 2.1 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.54 (dd, *J* = 7.9 and 0.8 Hz, 1H); ^{13}C NMR (101 MHz,

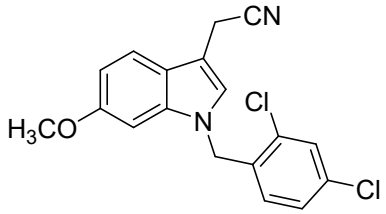
$CDCl_3$) δ 21.6, 22.0, 22.2, 28.6, 33.0, 47.1, 52.6, 109.6, 111.1, 119.2, 121.6, 125.7, 126.1, 127.7, 129.0, 129.4, 132.5, 133.96, 134.06, 137.1, 166.0, 177.8; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 472.1302, found: 472.1311.

2-(6-Methoxyindol-3-yl)acetonitrile (180)



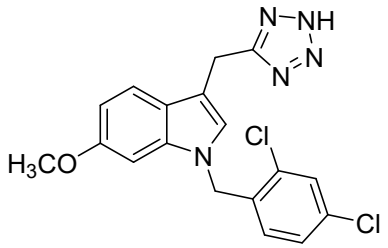
6-Methoxyindole-3-carbaldehyde (550 mg, 3.14 mmol) was treated with sodium borohydride and, subsequently, with potassium cyanide according to the procedure described for the preparation of **130** to give **180** as a solid (361 mg, 62%). $C_{11}H_{10}N_2O$ (186.2); mp 113 – 114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 3.98 (d, *J* = 1.0 Hz, 2H), 6.71 (dd, *J* = 8.6 and 2.3 Hz, 1H), 6.89 (dd, *J* = 2.3 and 0.6 Hz, 1H), 7.19 (dt, *J* = 2.5 and 1.0 Hz, 1H), 7.44 (dt, *J* = 8.6 and 0.6 Hz, 1H), 10.89 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 187.0866, found: 187.0830.

2-[1-(2,4-Dichlorobenzyl)-6-methoxyindol-3-yl]acetonitrile (181)



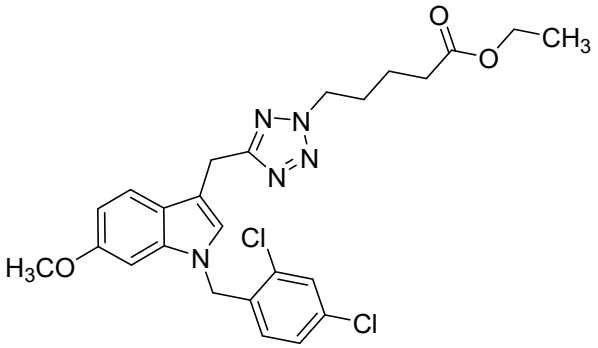
Compound **180** (291 mg, 1.56 mmol) was reacted with 2,4-dichlorobenzyl bromide (486 mg, 2.03 mmol) according to the procedure described for the synthesis of **134** (reaction time: 30 min) to obtain **181** as a solid (321 mg, 60%). $C_{18}H_{14}Cl_2N_2O$ (345.2); mp 132 – 133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.74 (s, 3H), 4.03 (d, *J* = 1.0 Hz, 2H), 5.44 (s, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.78 (dd, *J* = 8.7 and 2.2 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 7.27 (s, 1H), 7.36 (dd, *J* = 8.4 and 2.2 Hz, 1H), 7.50 (dd, *J* = 8.7 and 0.5 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 345.0556, found: 345.0486.

1-(2,4-Dichlorobenzyl)-6-methoxy-3-(tetrazol-5-ylmethyl)indole (182)



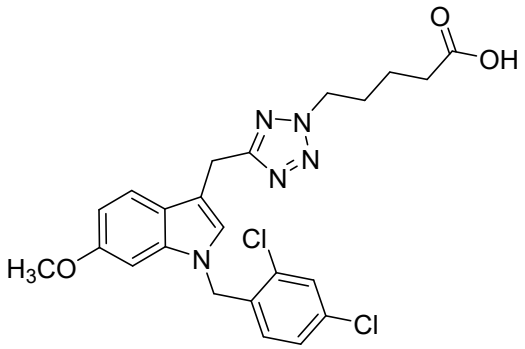
A mixture of **181** (313 mg, 0.91 mmol), trimethylsilyl azide (158 mg, 1.37 mmol), and tetrabutylammonium fluoride hydrate (120 mg) was heated at 130 °C for 8 h. After cooling, the reaction mixture was chromatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate/formic acid, 6:4:0.1) to yield **182** as an oil (42 mg, 12%). $C_{18}H_{15}Cl_2N_5O$ (388.3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.46 (d, J = 0.8 Hz, 2H), 5.29 (s, 2H), 6.57 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 5.2 and 3.1 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 6.99 (s, 1H), 7.09 (d, J = 2.1 Hz, 1H), 7.43 – 7.44 (m, 1H), 7.45 (d, J = 2.1 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 388.0727, found: 388.0755.

Ethyl 5-(5-{[1-(2,4-dichlorobenzyl)-6-methoxyindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoate (183)



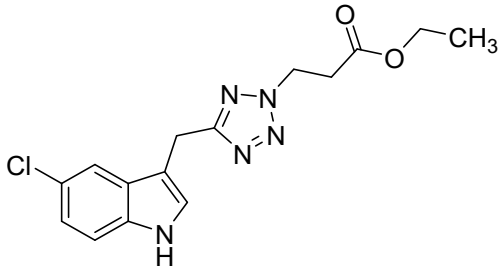
Compound **182** (30 mg, 0.077 mmol) was reacted with ethyl 5-bromopentanoate (25 mg, 0.12 mmol) according to the procedure described for the synthesis of **136** (reaction time: 4 h) to yield **183** as an oil (21 mg, 53%). $C_{25}H_{27}Cl_2N_5O_3$ (516.4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.63 – 1.68 (m, 2H), 2.01 – 2.07 (m, 2H), 2.33 (t, J = 7.3 Hz, 2H), 3.78 (s, 3H), 4.11 (q, J = 7.2 Hz, 2H), 4.35 (d, J = 1.0 Hz, 2H), 4.57 (t, J = 7.0 Hz, 2H), 5.26 (s, 2H), 6.54 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 6.79 (dd, J = 8.7 and 2.2 Hz, 1H), 6.97 (s, 1H), 7.07 (dd, J = 8.3 and 2.1 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 7.54 (dd, J = 8.7 and 0.5 Hz, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 516.1564, found: 516.1640.

5-(5-{[1-(2,4-Dichlorobenzyl)-6-methoxyindol-3-yl]methyl}-2*H*-tetrazol-2-yl)-pentanoic acid (184)



Compound **183** (17 mg, 0.033 mmol) was saponified as described for the synthesis of **137** to give **184** as an oil (15 mg, 93%). $C_{23}H_{23}Cl_2N_5O_3$ (488.4); purity (HPLC) > 99%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.61 – 1.70 (m, 2H), 2.01 – 2.10 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 3.78 (s, 3H), 4.35 (d, *J* = 1.0 Hz, 2H), 4.57 (t, *J* = 7.0 Hz, 2H), 5.25 (s, 2H), 6.54 (dd, *J* = 8.4 and 1.0 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.79 (dd, *J* = 8.7 and 2.2 Hz, 1H), 6.96 (d, *J* = 1.0 Hz, 1H), 7.06 (dd, *J* = 8.4 and 2.1 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.6, 22.2, 28.7, 33.1, 47.2, 52.6, 55.9, 93.4, 109.5, 111.3, 120.2, 122.3, 125.6, 127.7, 129.1, 129.4, 133.0, 133.8, 134.0, 137.5, 157.0, 165.9, 177.8; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 488.1251, found: 488.1277.

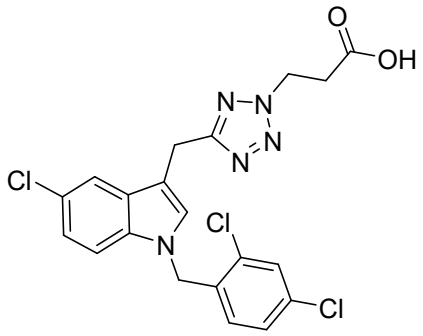
Ethyl 3-{5-[(5-chloroindol-3-yl)methyl]-2*H*-tetrazol-2-yl}propionate (185)



A mixture of **120** (330 mg, 1.41 mmol), potassium carbonate (390 mg, 2.82 mmol), ethyl 3-bromopropionate (255 mg, 1.41 mmol), and acetonitrile (10 mL) was heated under reflux for 8 h. The cooled reaction mixture was diluted with water (20 mL) and exhaustively extracted with ethyl acetate. The combined organic phases were washed three times with water, dried over magnesium sulphate, and concentrated *in vacuo*. The residue was chroatographed on silica gel (cyclohexane to cyclohexane/ethyl acetate 7:3) to give **185** as an oil (90 mg, 19%). $C_{15}H_{16}ClN_5O_2$ (333.8); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.08 (t, *J* = 7.1 Hz, 3H), 3.04 (t, *J* = 6.5 Hz, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 4.27 (d, *J* = 0.9 Hz, 2H), 4.81 (t, *J* = 6.6 Hz, 2H), 7.04 – 7.11 (m, 1H), 7.28 (d, *J* = 2.5

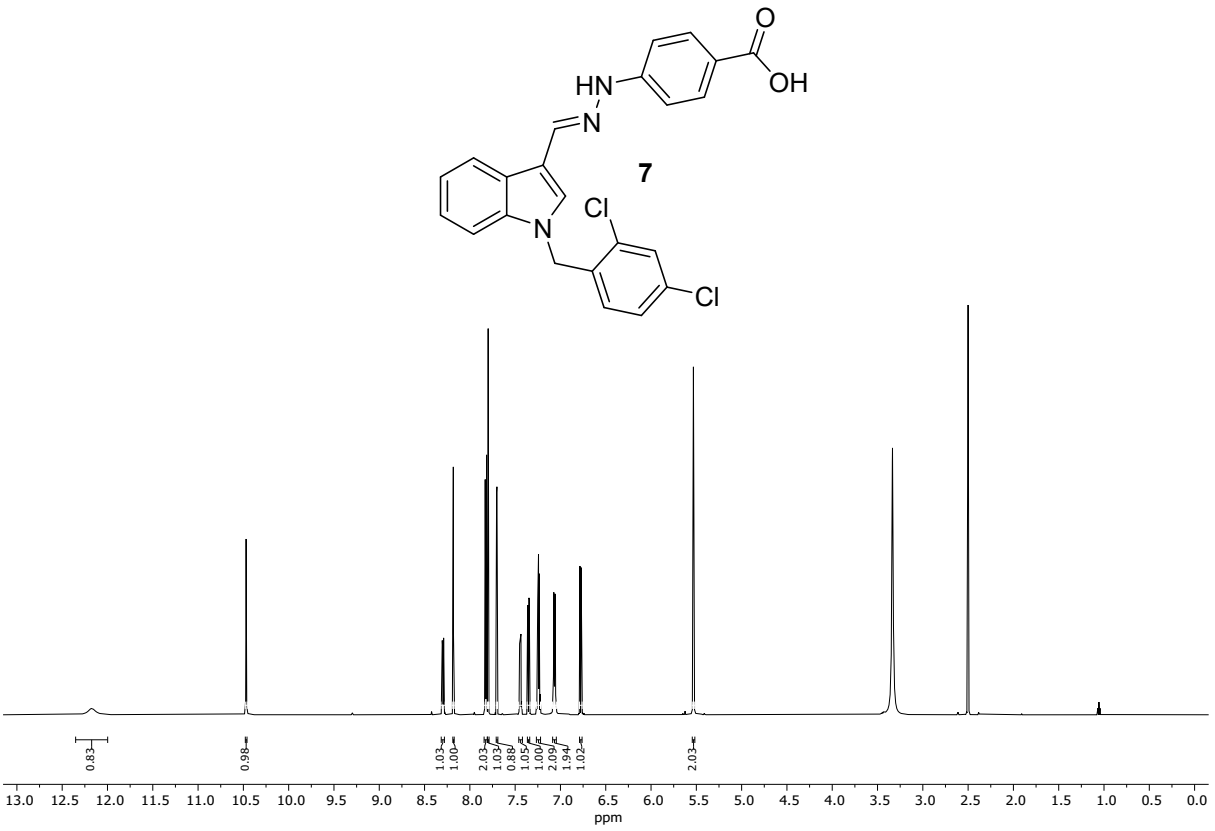
Hz, 1H), 7.36 (dd, *J* = 8.1 and 0.6 Hz, 1H), 7.55 (dd, *J* = 1.7 and 1.0 Hz, 1H), 11.12 (s, 1H); HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 334.1066, found: 334.1062.

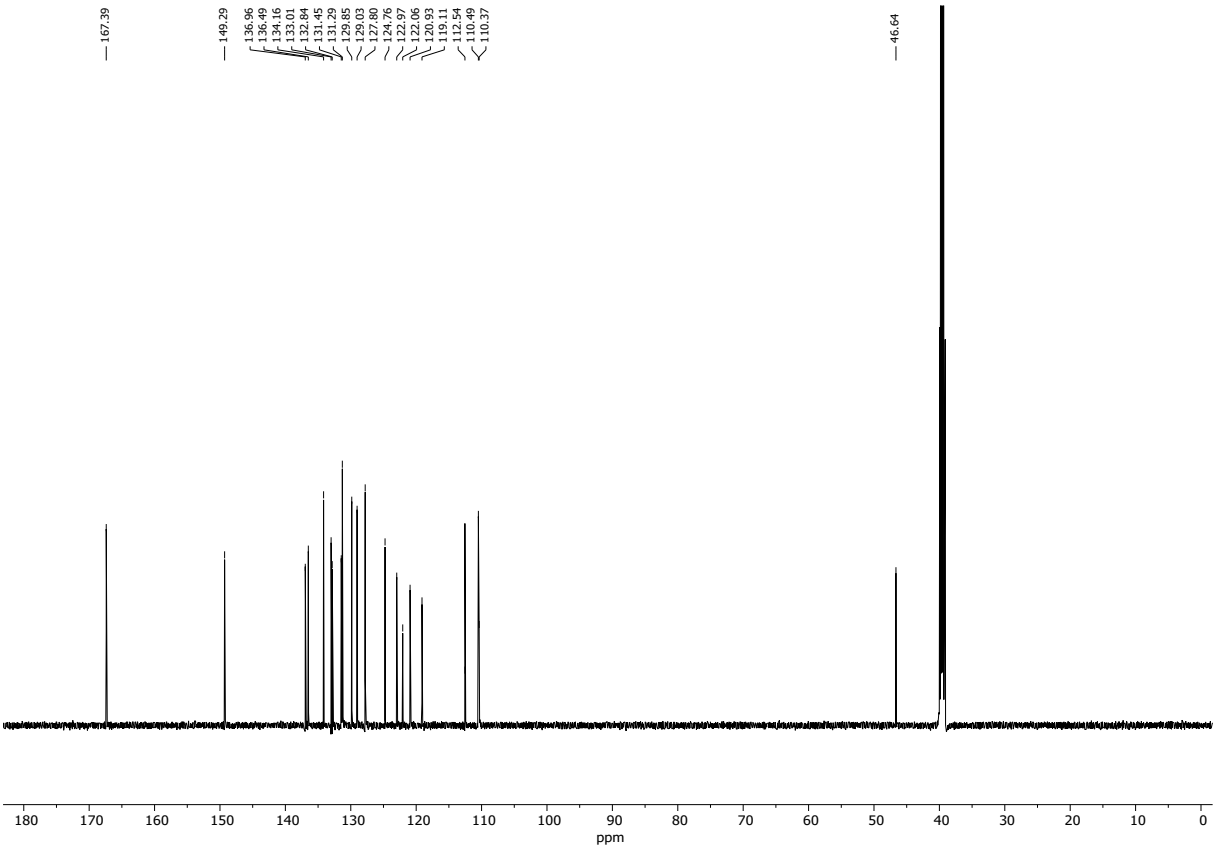
3-(5-{[5-Chloro-1-(2,4-dichlorobenzyl)indol-3-yl]methyl}-2*H*-tetrazol-2-yl)propionic acid (186)

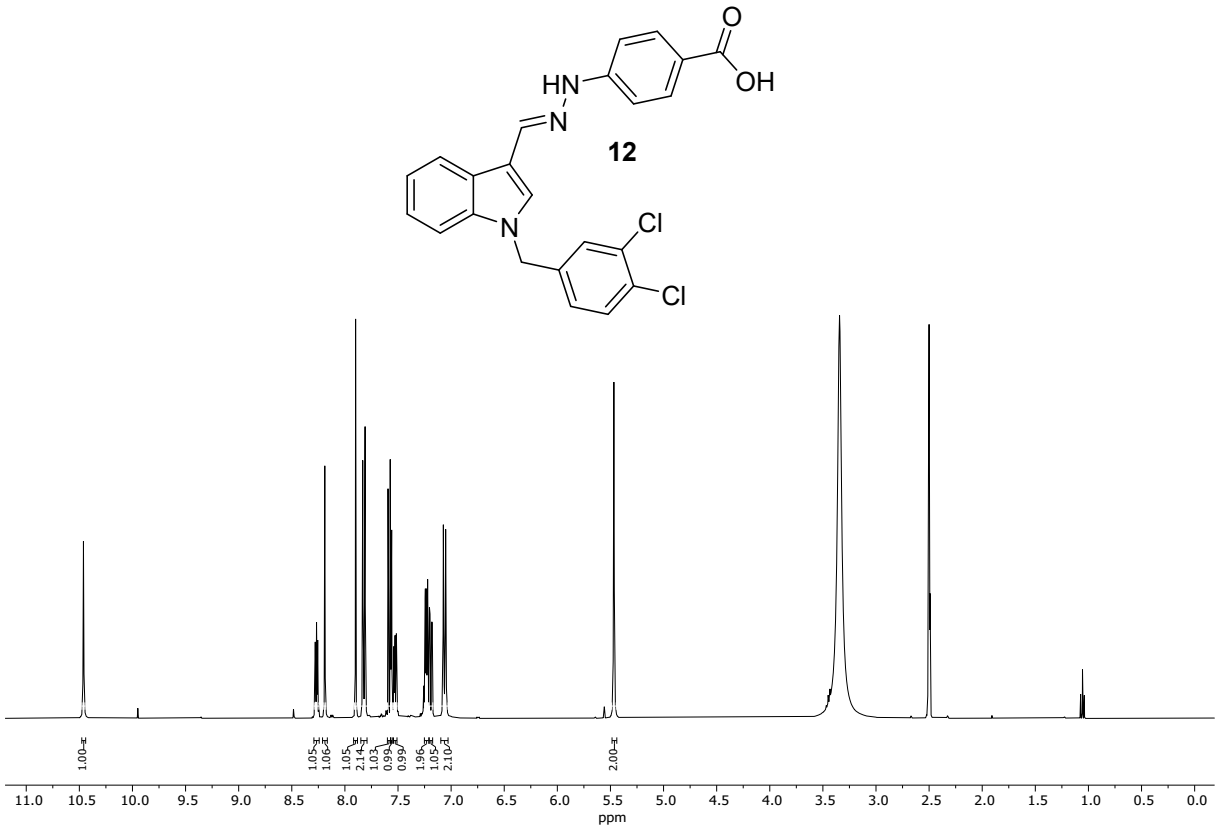


The synthesis was carried out starting from **185** (40 mg, 0.12 mmol) and 2,4-dichlorobenzyl bromide (34 mg, 0.14 mmol) in a similar manner as described for the preparation of **133**. After silica gel chromatography, **186** was obtained as an oil (27 mg, 48%). $C_{20}H_{16}Cl_3N_5O_2$ (464.7); purity (HPLC) 97%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.84 (t, *J* = 6.8 Hz, 2H), 4.29 (d, *J* = 0.9 Hz, 2H), 4.37 (t, *J* = 6.8 Hz, 2H), 5.82 (s, 2H), 7.08 (d, *J* = 8.3 Hz, 1H), 7.12 (s, 1H), 7.15 (dd, *J* = 8.7 and 2.0 Hz, 1H), 7.22 (dd, *J* = 8.7 and 0.6 Hz, 1H), 7.25 (dd, *J* = 8.3 and 2.1 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 2.0 and 0.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.1, 34.5, 41.8, 53.5, 110.1, 110.4, 119.0, 122.6, 125.5, 127.8, 128.0, 128.8, 129.89, 129.98, 131.2, 134.60, 134.68, 135.9, 166.1, 174.3; HR-MS (APCI, direct probe) *m/z* $[M+H]^+$ calc.: 464.0443, found: 464.0445.

2. ^{1}H NMR and ^{13}C NMR spectra of the target compounds



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1.06
1.05
2.14
1.03
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0.99
1.96
1.05
2.10
2.00
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 1.0 0.5 0.0
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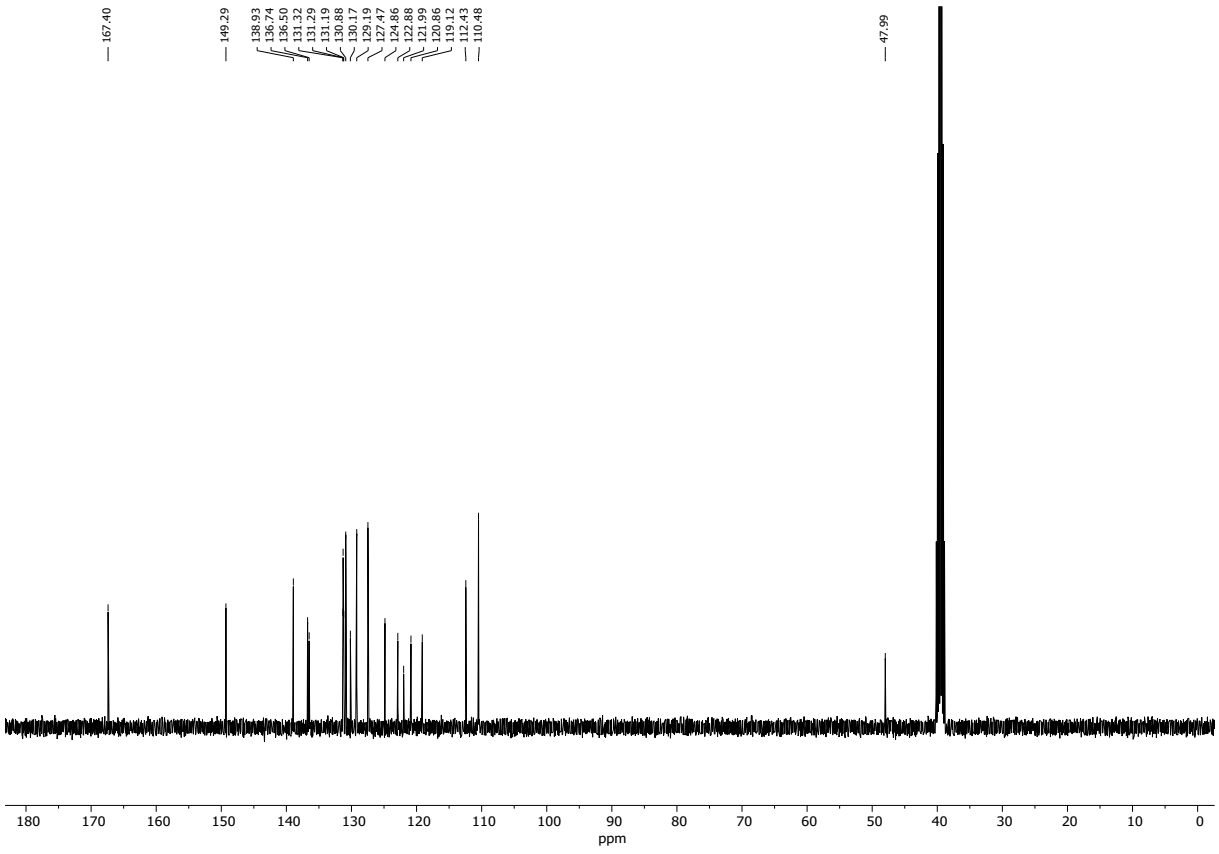
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131.29
131.19
130.88
130.17
129.19
127.47
124.86
122.88
121.99
120.86
119.12
112.43
110.48
47.99
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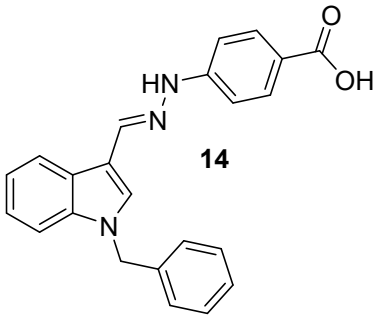
ppm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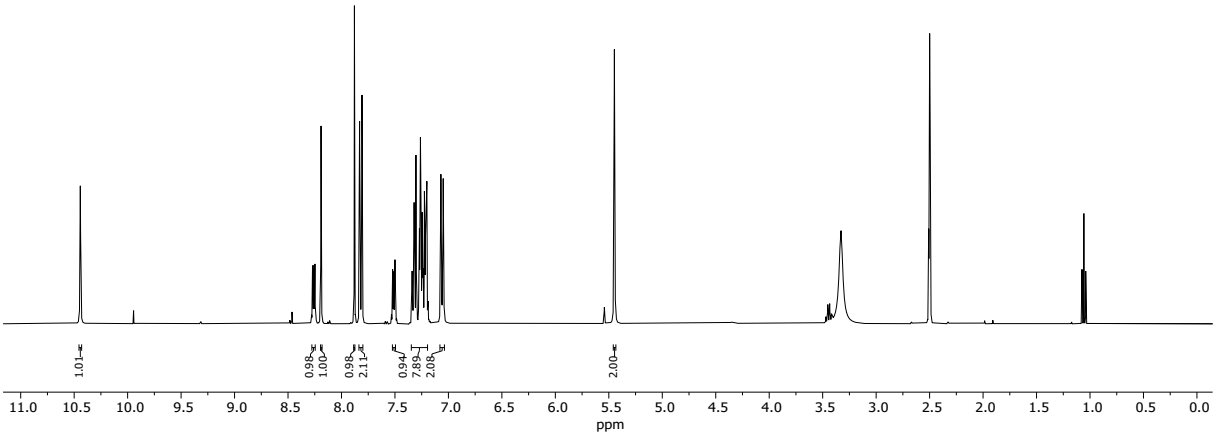
OH
N
N

14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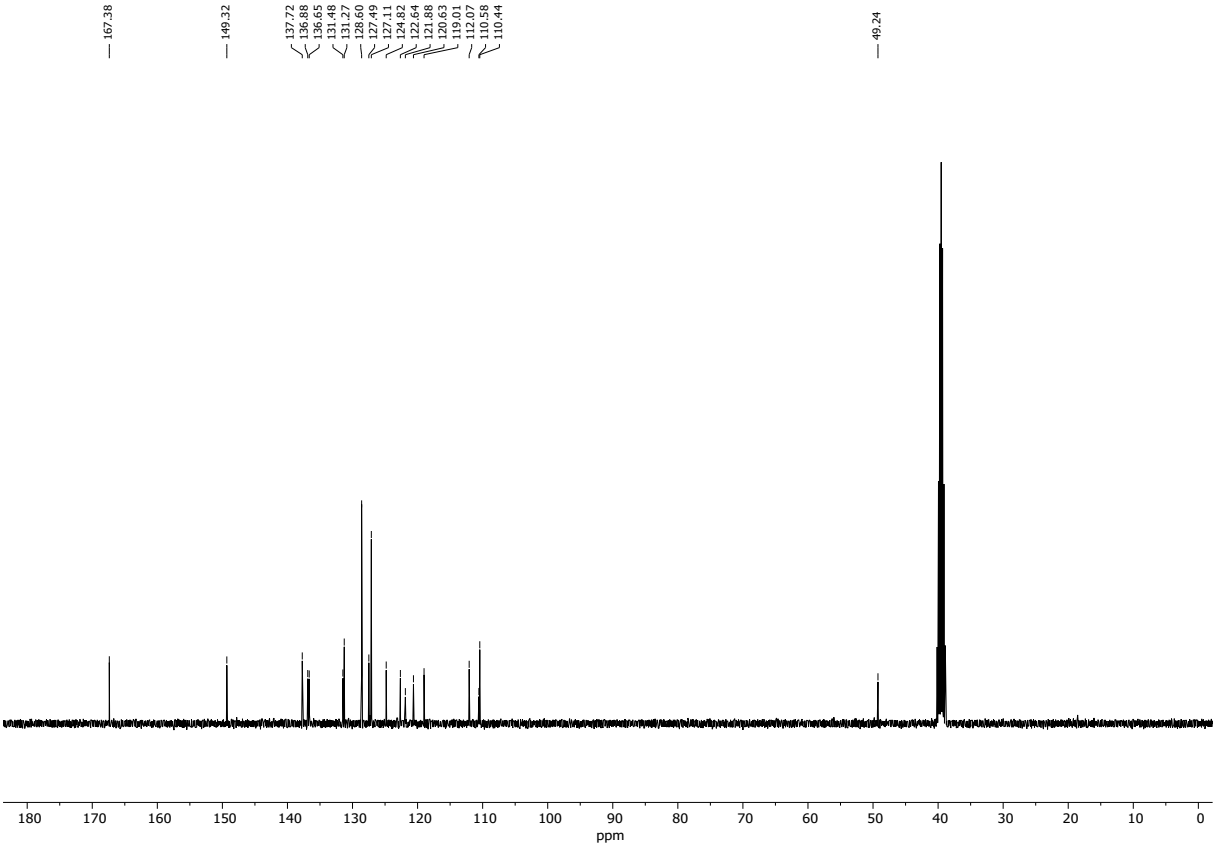
0.98
1.00
0.98
2.11
0.94
7.89
2.08
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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136.65
131.48
131.27
128.60
127.49
127.11
124.82
122.64
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119.01
112.07
110.58
110.44
49.24
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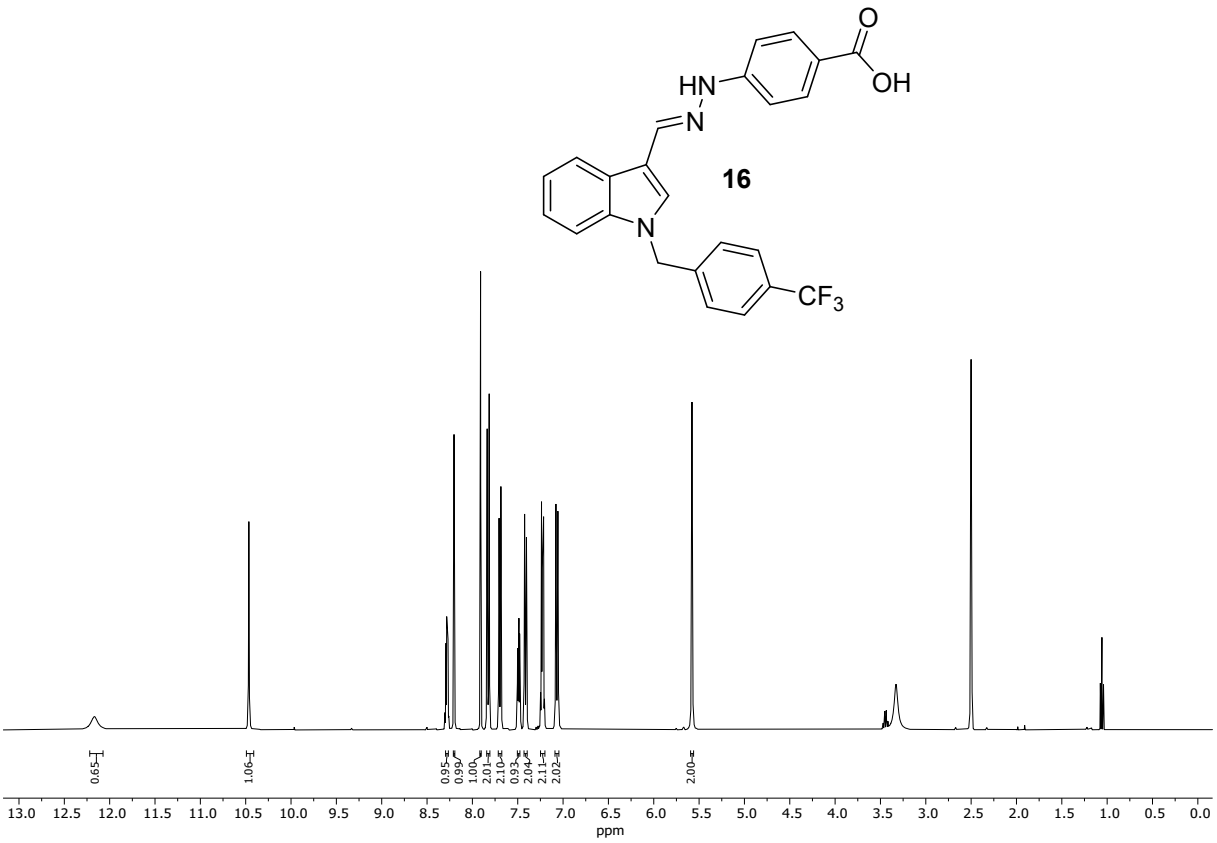
ppm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2.04
2.11
2.02
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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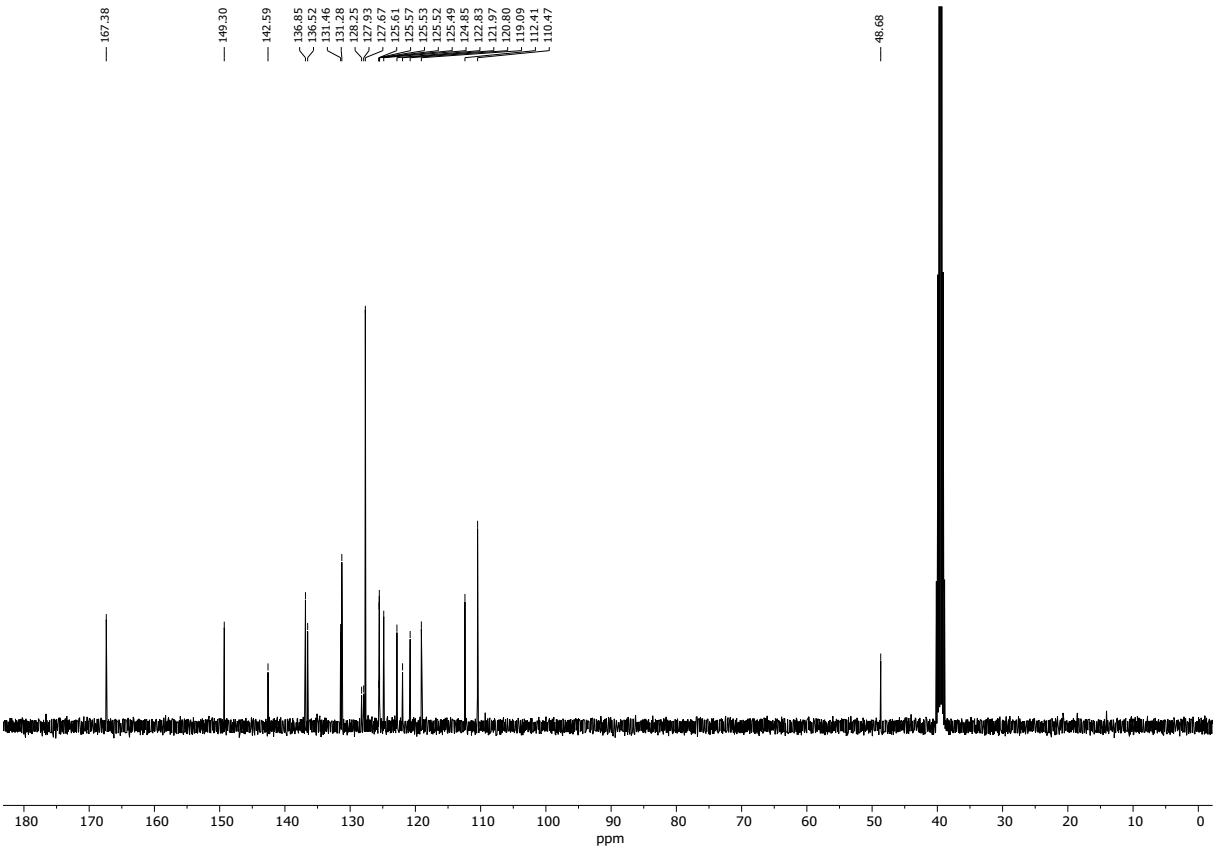
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125.53
125.52
125.49
124.85
122.83
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120.80
119.09
112.41
110.47
48.68
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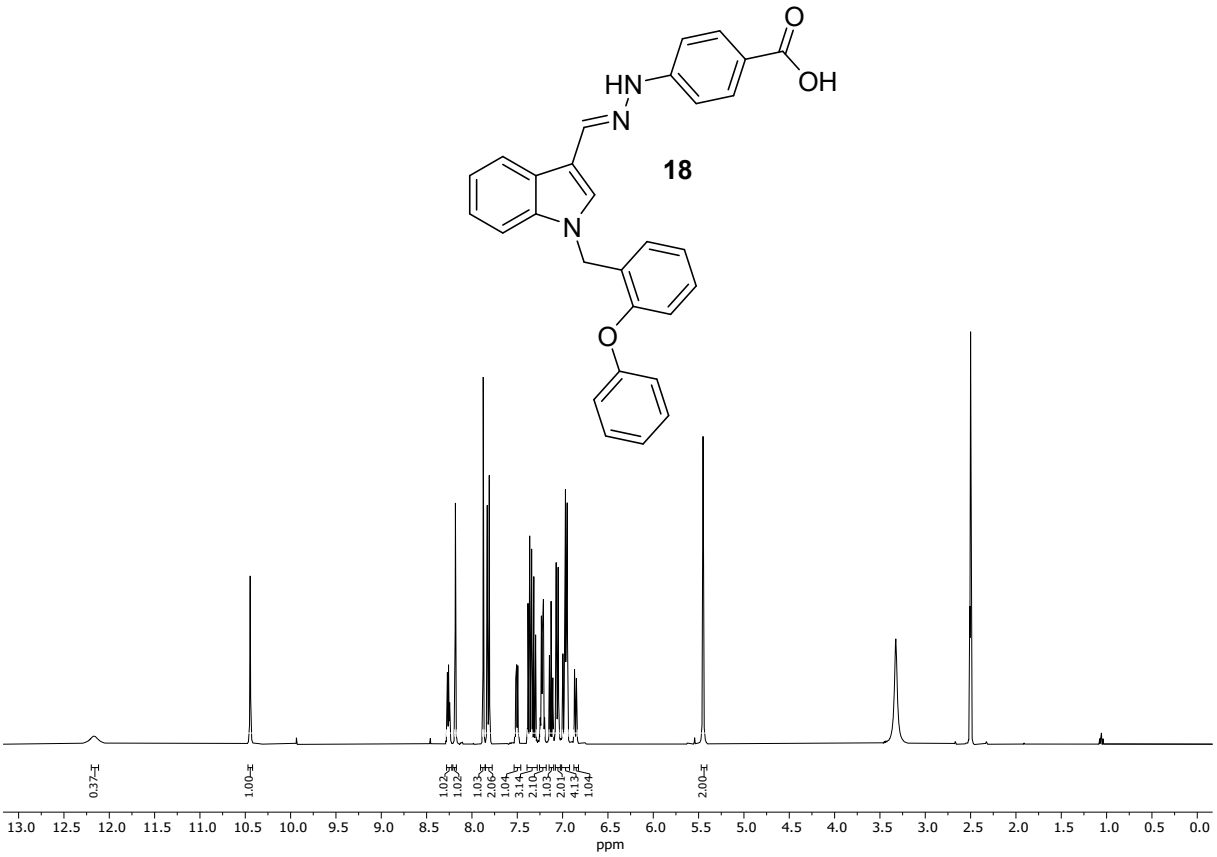
ppm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1.02
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2.01
4.13
1.04
2.00
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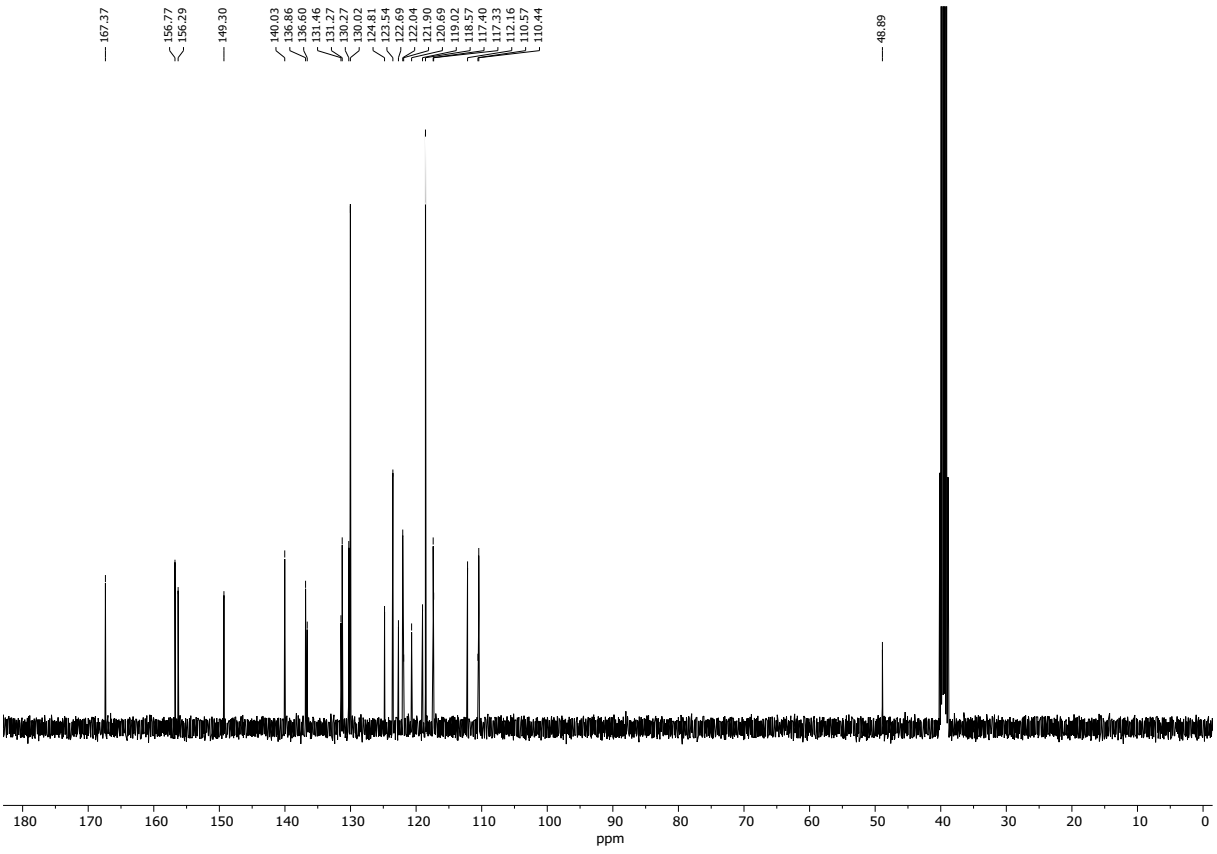
ppm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136.86
136.60
131.46
131.27
130.27
130.02
124.81
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122.04
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119.02
118.57
117.40
117.33
112.16
110.57
110.44
48.89
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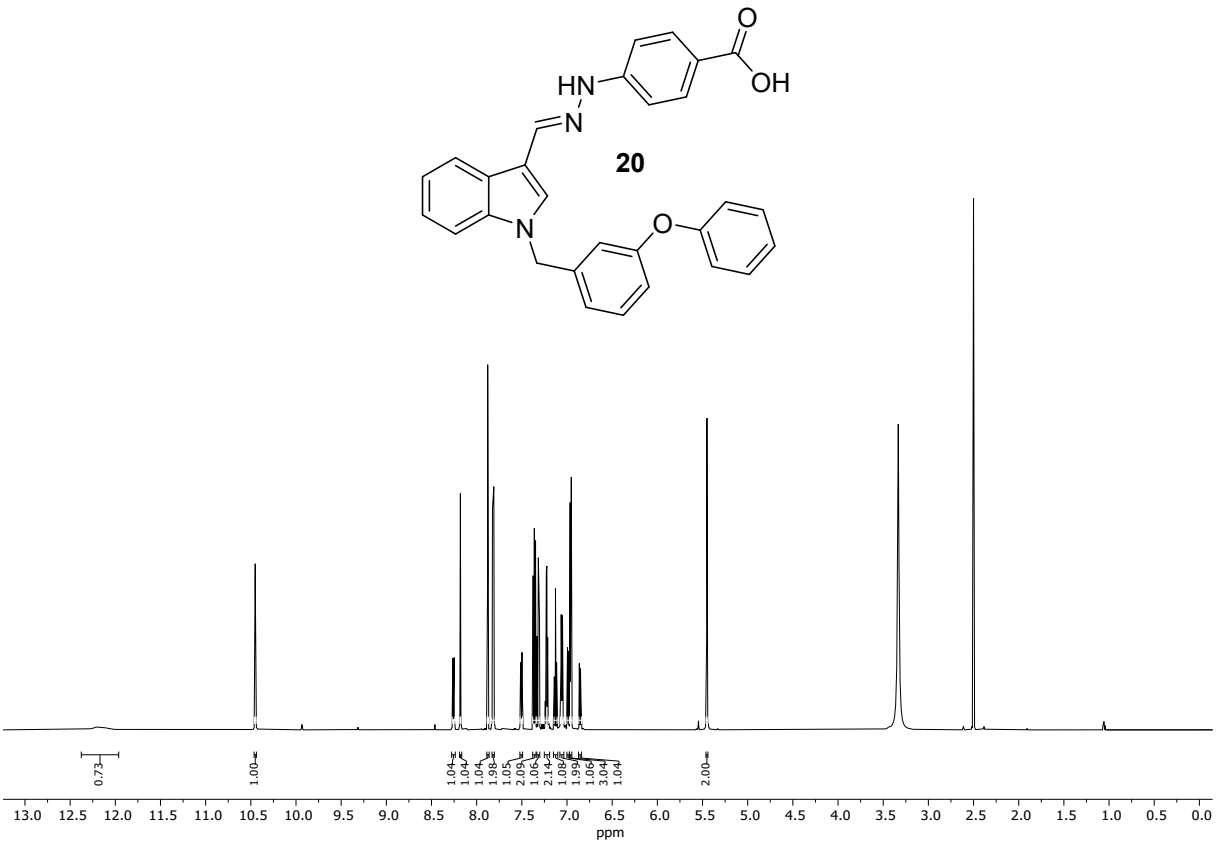
ppm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2.00
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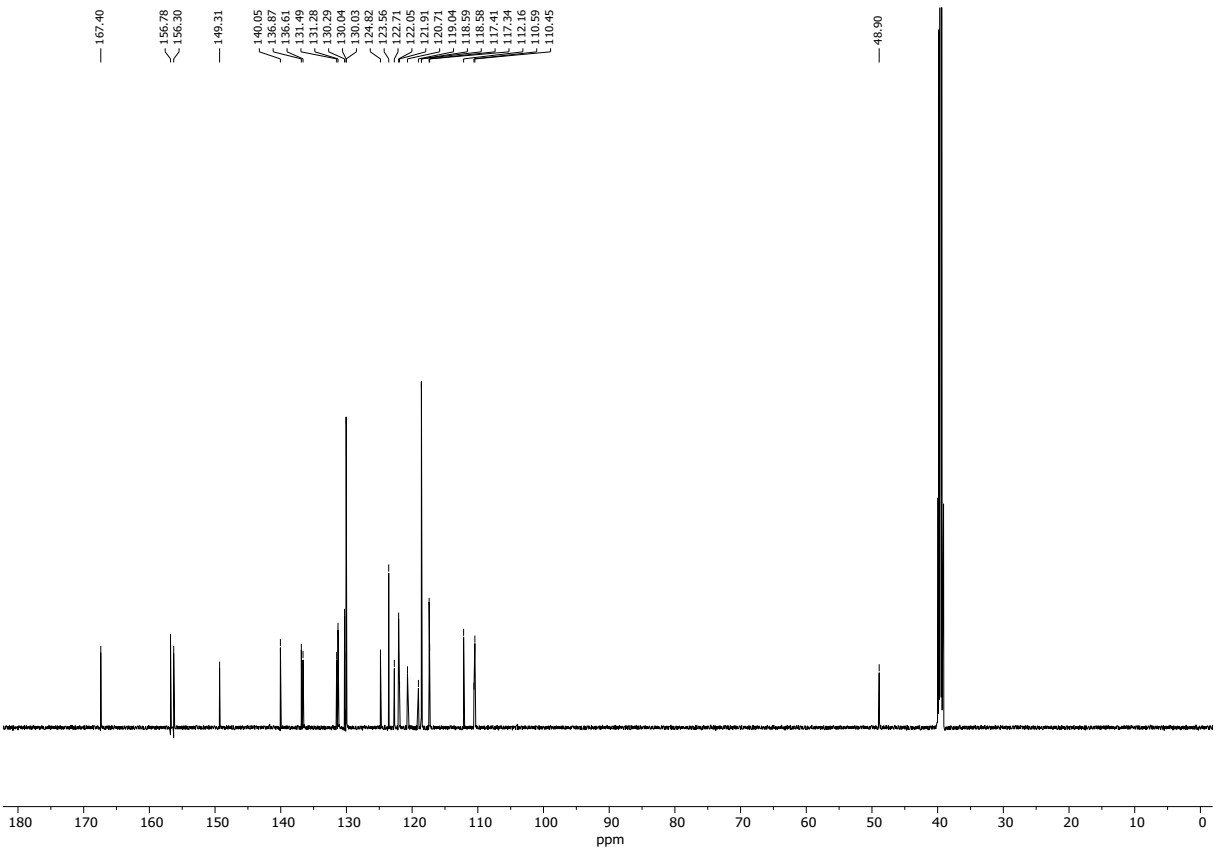
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122.71
122.05
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120.71
119.04
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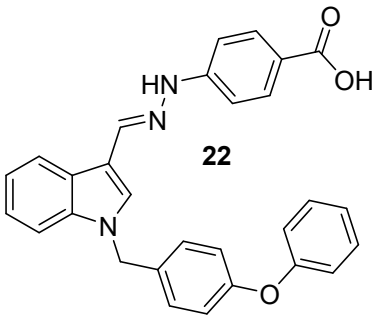
ppm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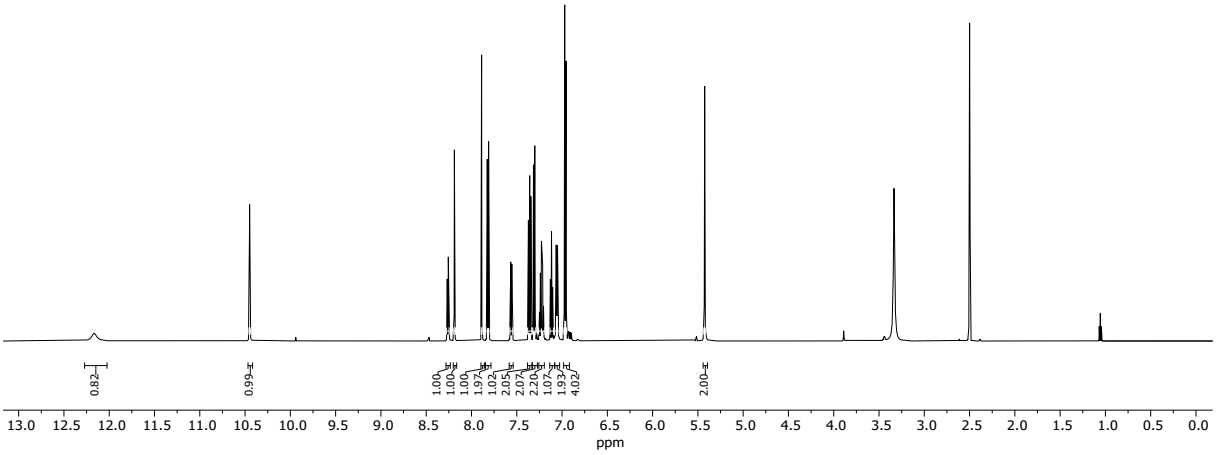
O

22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1.97
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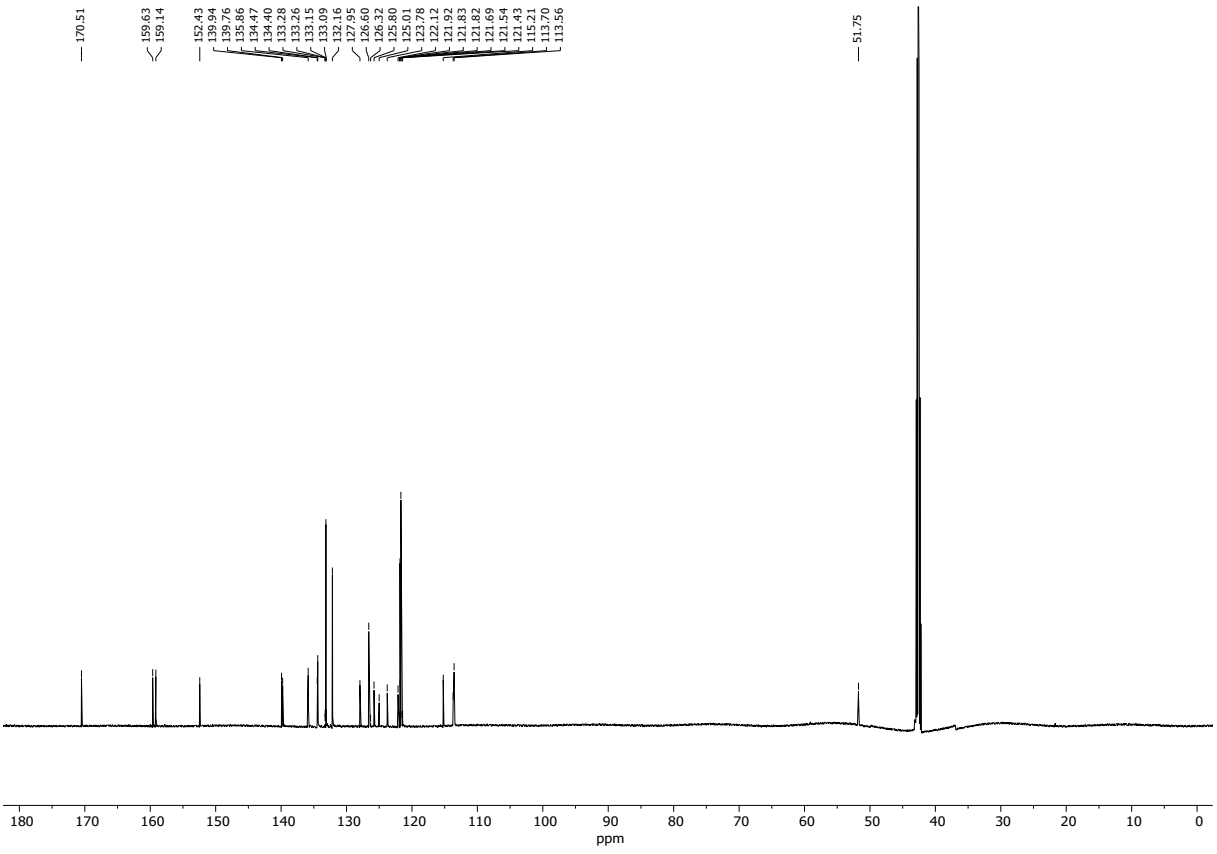
2.20
1.07
1.93
4.02
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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121.82
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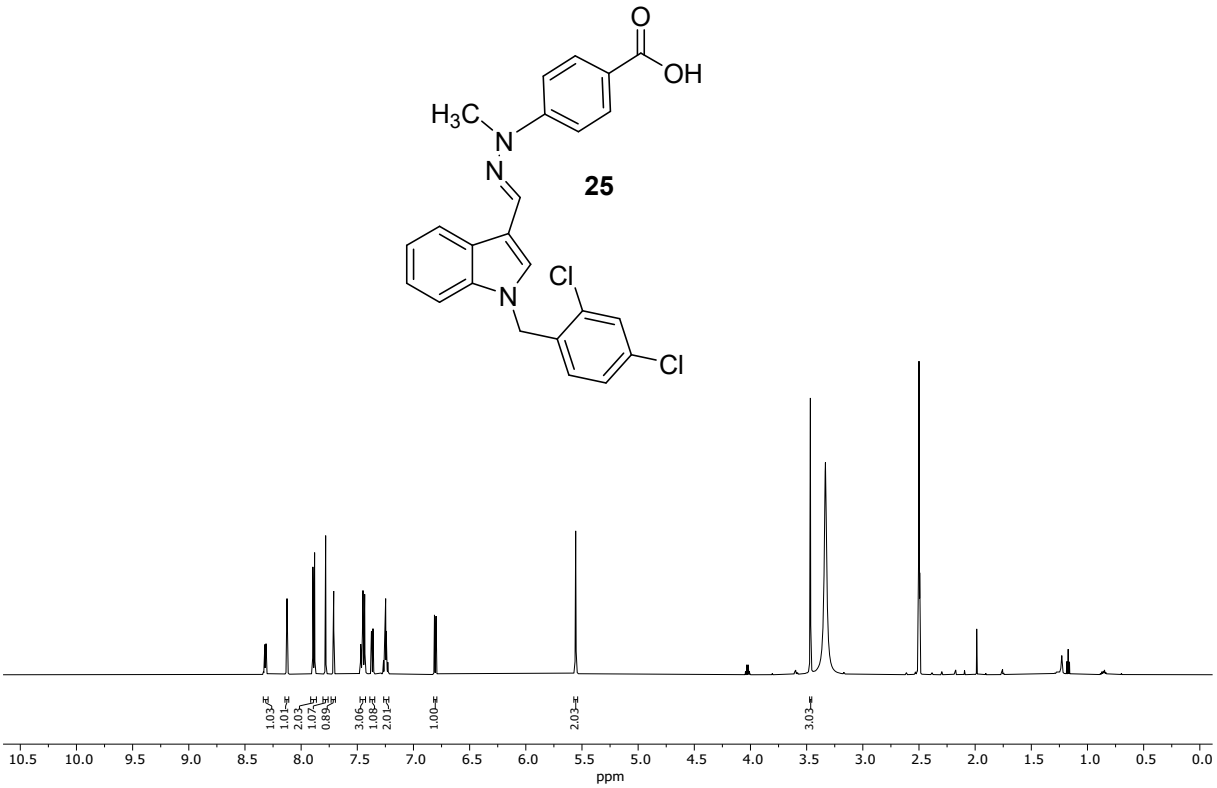
ppm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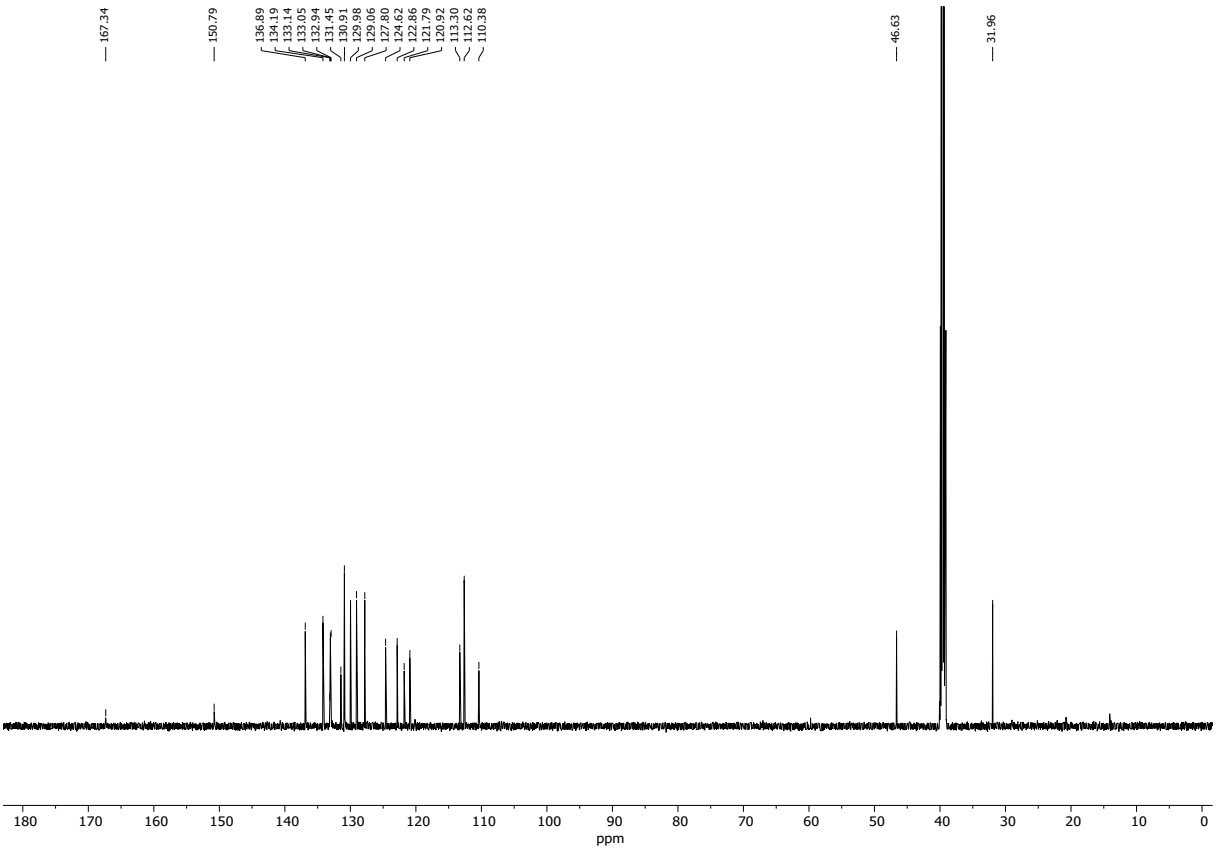
3.06
1.08
2.01
1.00
2.03
3.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm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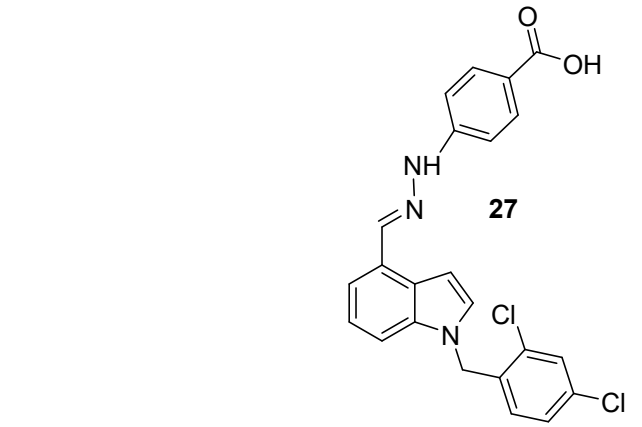
ppm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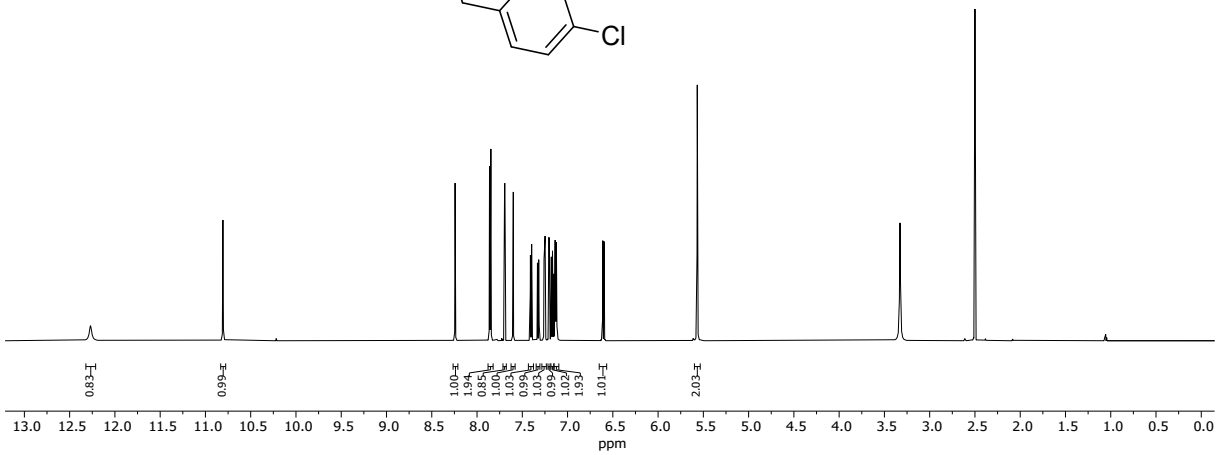
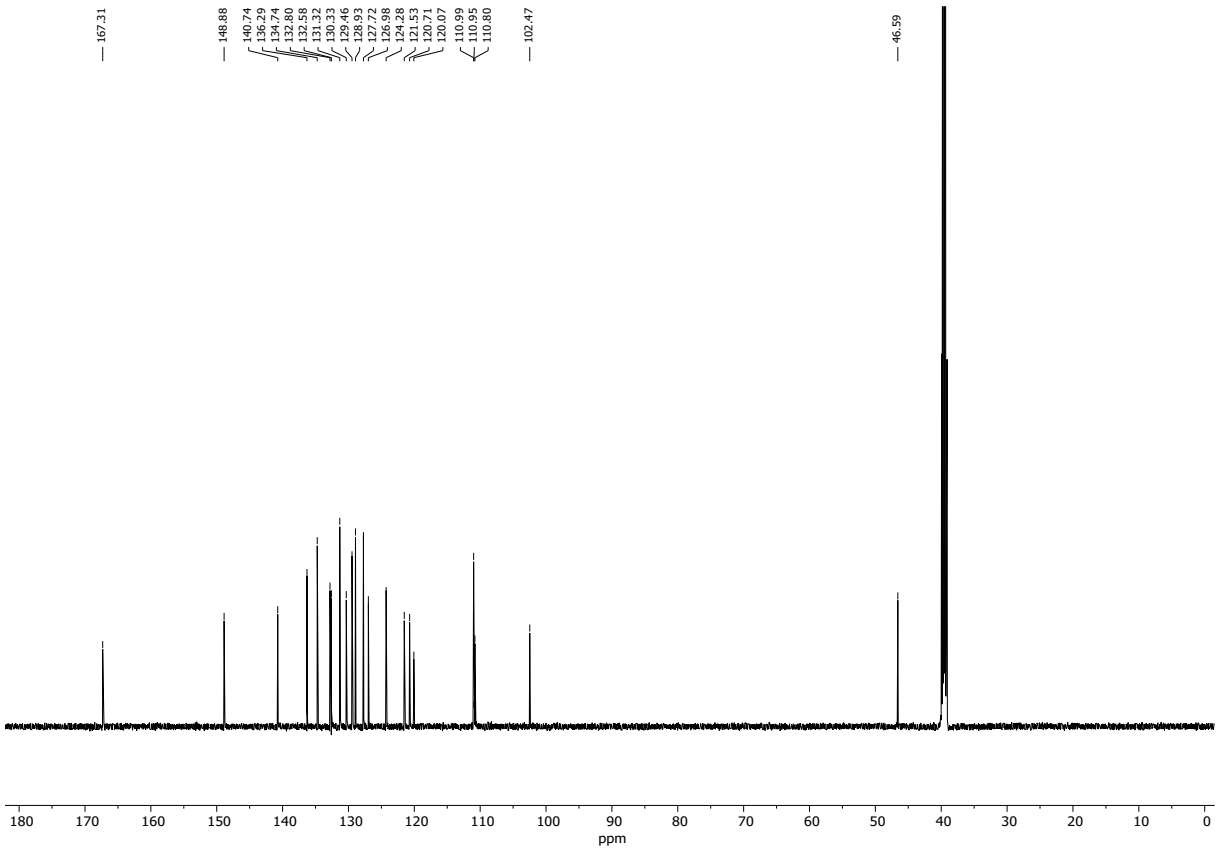
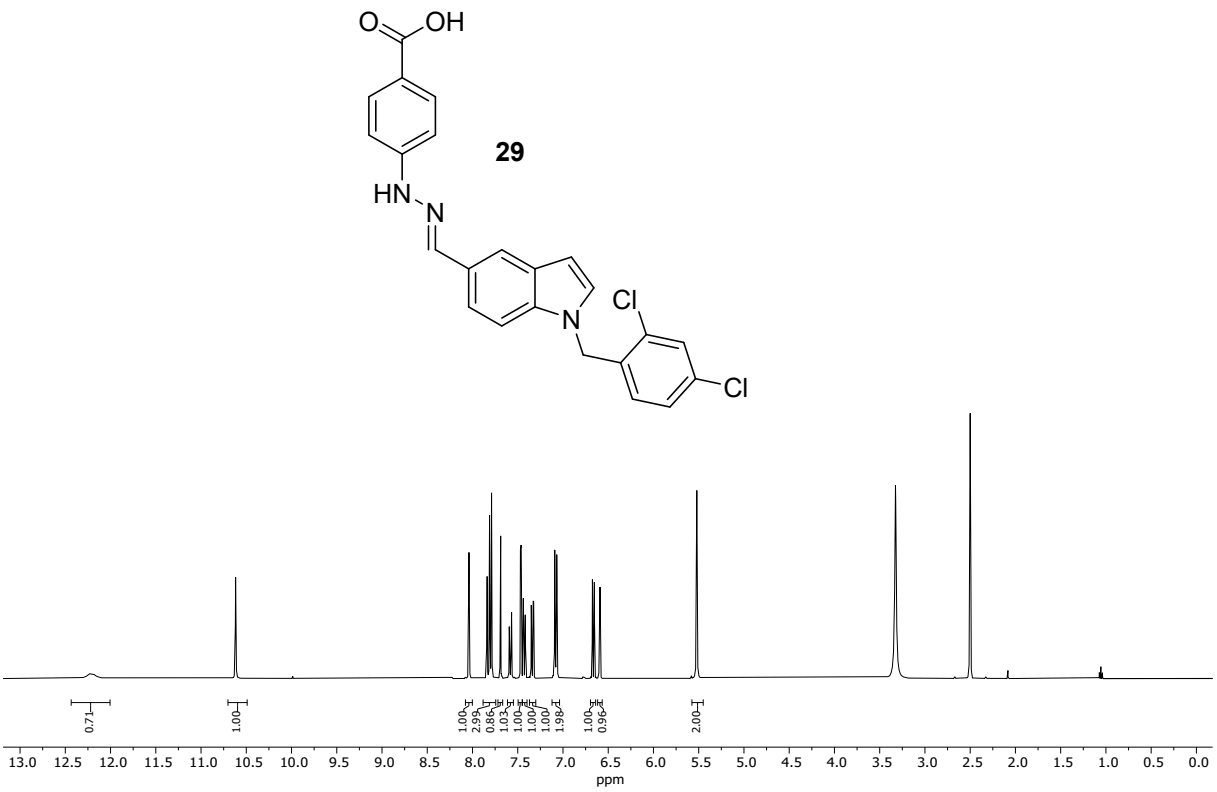
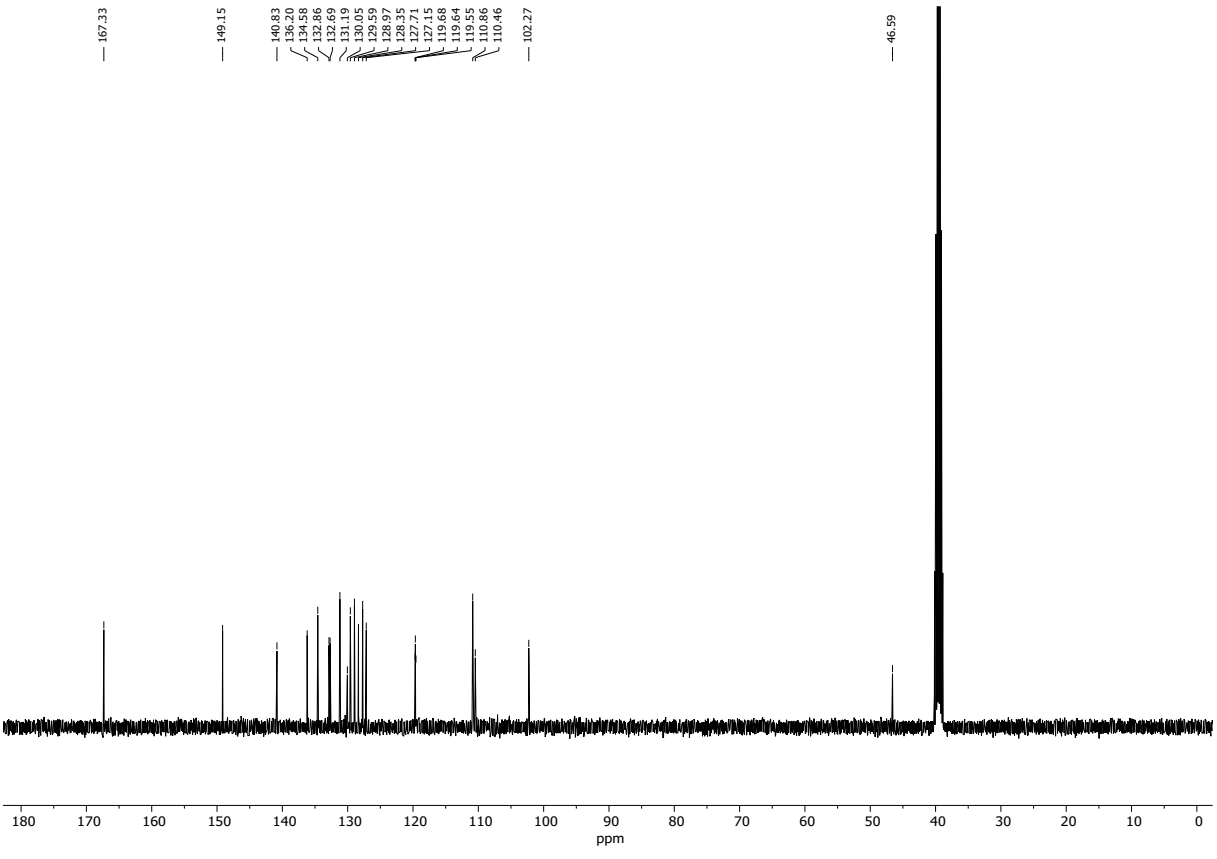
NH
N
Cl
N
Cl

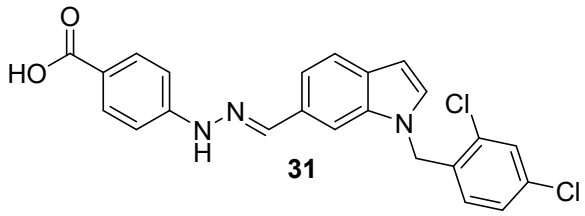
27


0.83
0.99
1.00
1.94
0.85
1.00
1.03
0.99
1.03
0.99
1.02
1.93
1.01
2.03
13.0 12.5 12.0 11.5 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 1.0 0.5 0.0
ppm

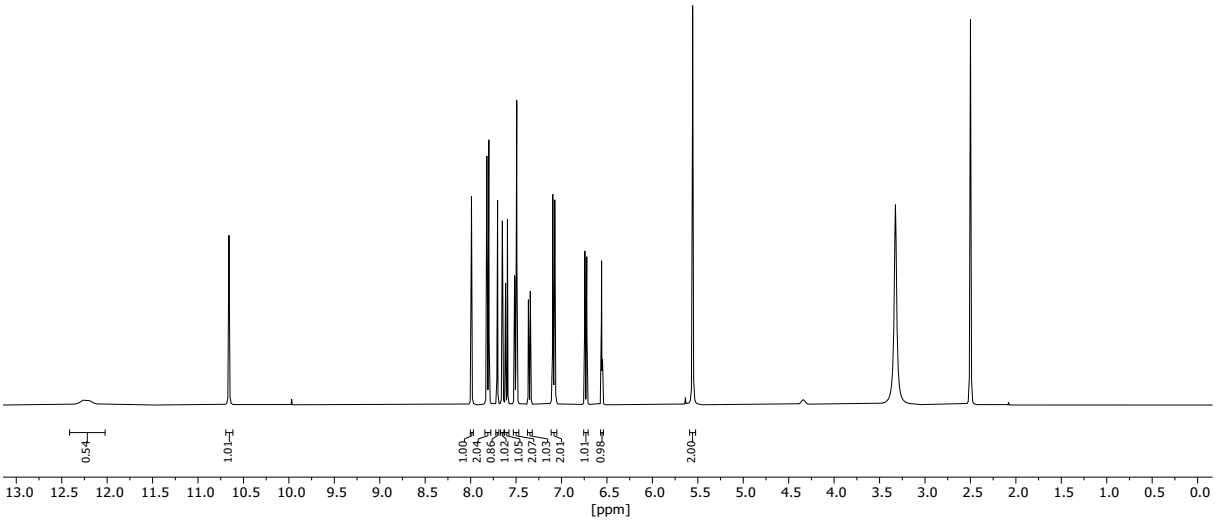

167.31
148.88
140.74
136.29
134.74
132.80
132.58
131.32
130.33
129.46
128.93
127.72
126.98
124.28
121.53
120.71
120.07
110.99
110.95
110.80
102.47
46.59
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

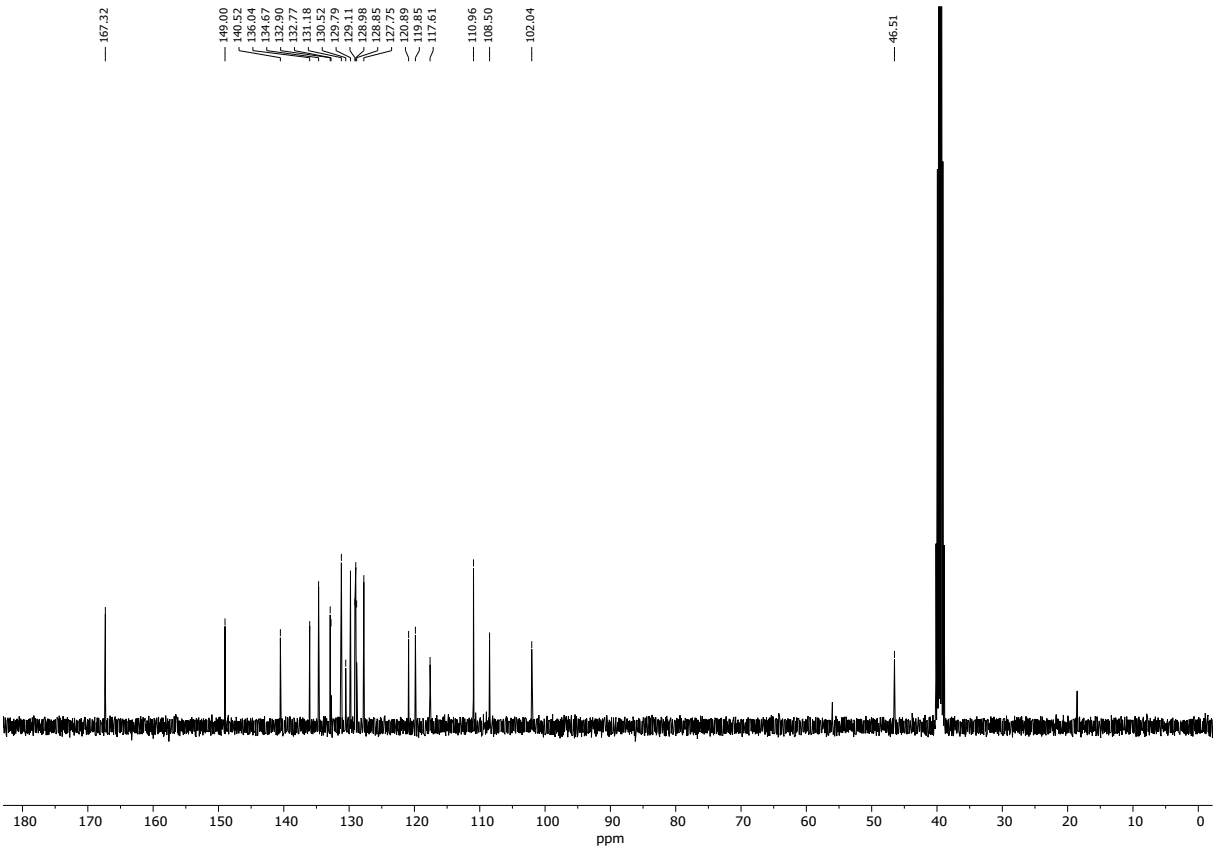

O
OH
29
HN
N
N
Cl
Cl
0.71
1.00
1.00
2.99
0.86
1.03
1.00
1.00
1.00
1.98
1.00
0.96
2.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

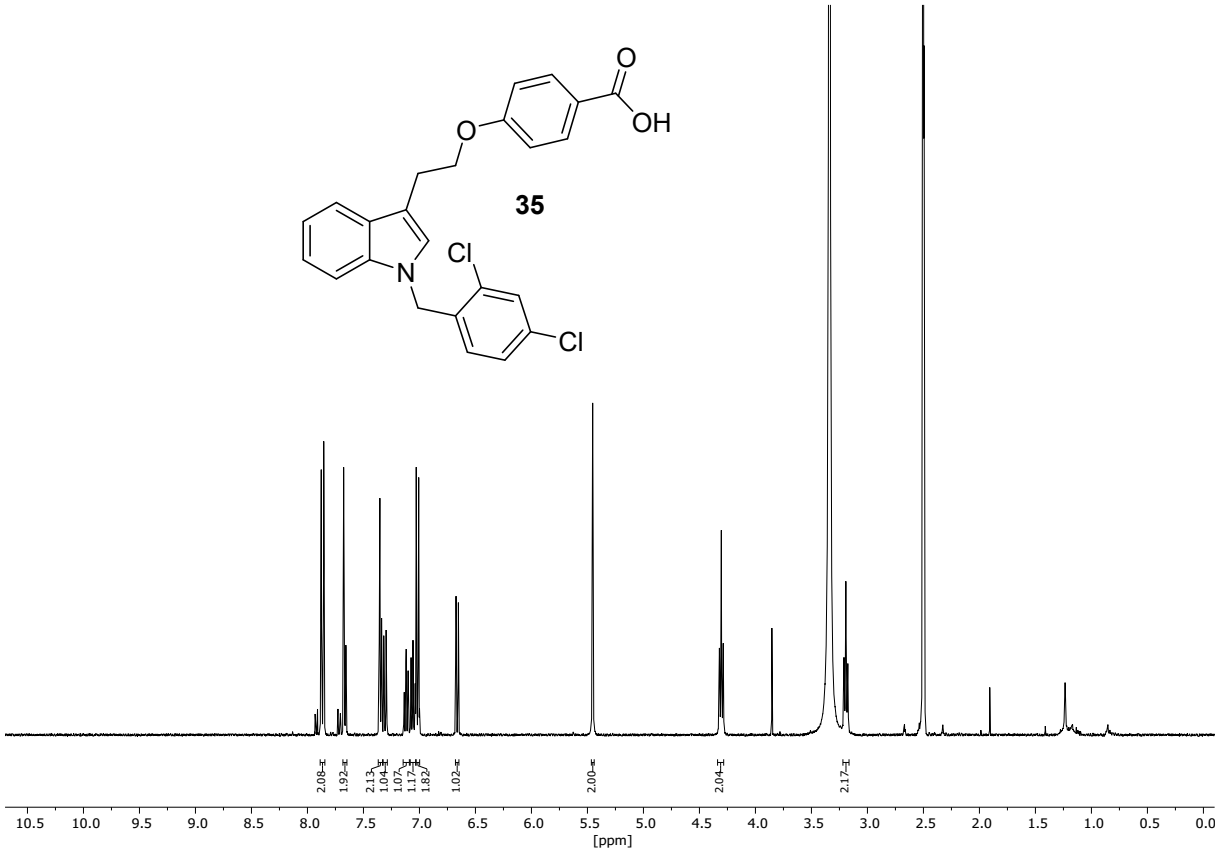

167.33
149.15
140.83
136.20
134.58
132.86
132.69
131.19
130.05
129.59
128.97
128.35
127.71
127.15
119.68
119.64
119.55
110.86
110.46
102.27
46.59
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

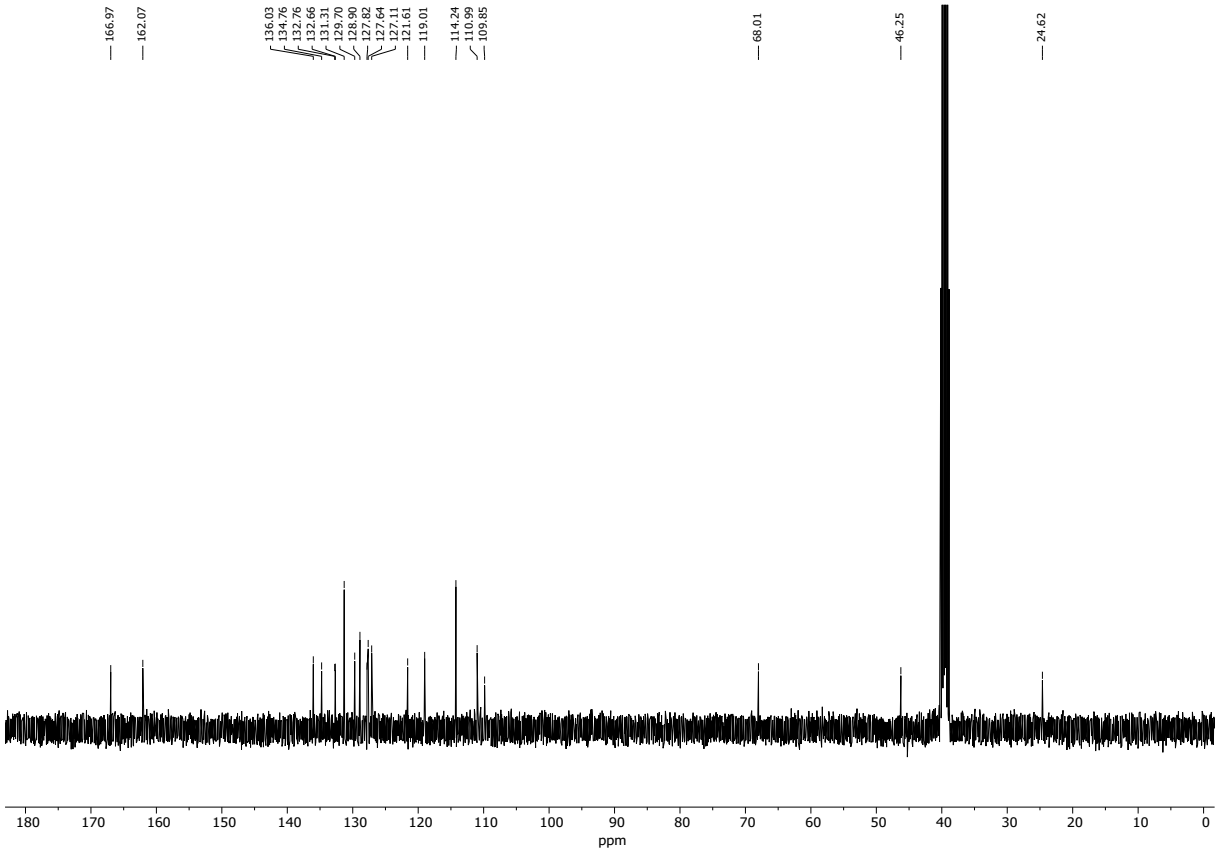

O
HO
N
N
H
Cl
N
Cl

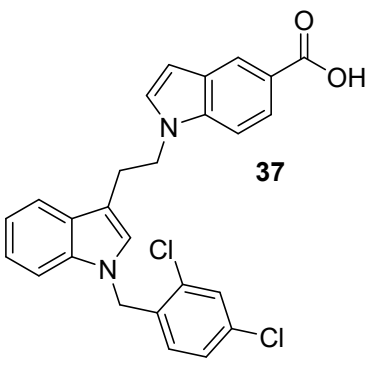
31


0.54
1.01
1.00
2.04
0.86
1.02
1.05
2.07
1.03
2.01
1.01
0.98
2.00
13.0 12.5 12.0 11.5 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 1.0 0.5 0.0
[ppm]


167.32
149.00
140.52
136.04
134.67
132.90
132.77
131.18
130.52
129.79
129.11
128.98
128.85
127.75
120.89
119.85
117.61
110.96
108.50
102.04
46.51
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

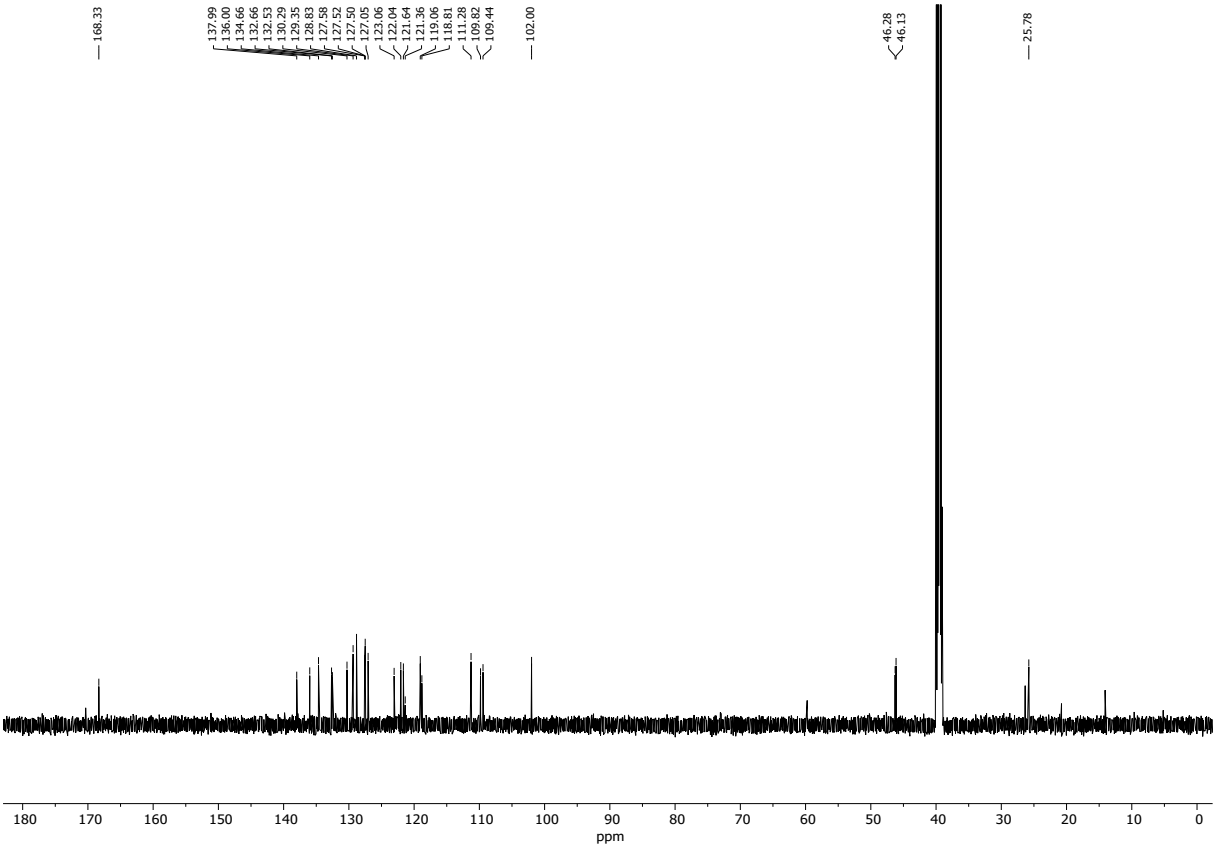

O
OH
O
35
Cl
N
Cl
2.08
1.92
2.13
1.04
1.07
1.17
1.82
1.02
2.00
2.04
2.17
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

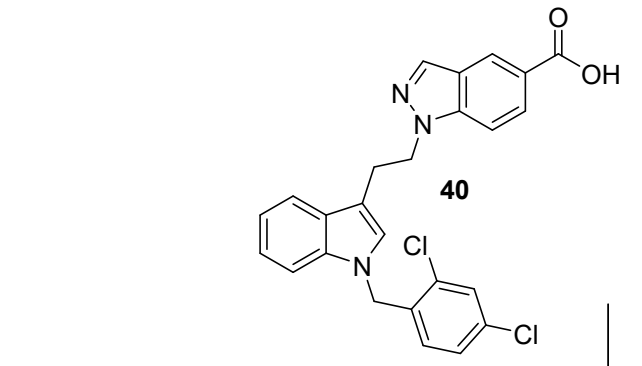

166.97
162.07
136.03
134.76
132.76
132.66
131.31
129.70
128.90
127.82
127.64
127.11
121.61
119.01
114.24
110.99
109.85
68.01
46.25
24.62
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
Cl
N
Cl

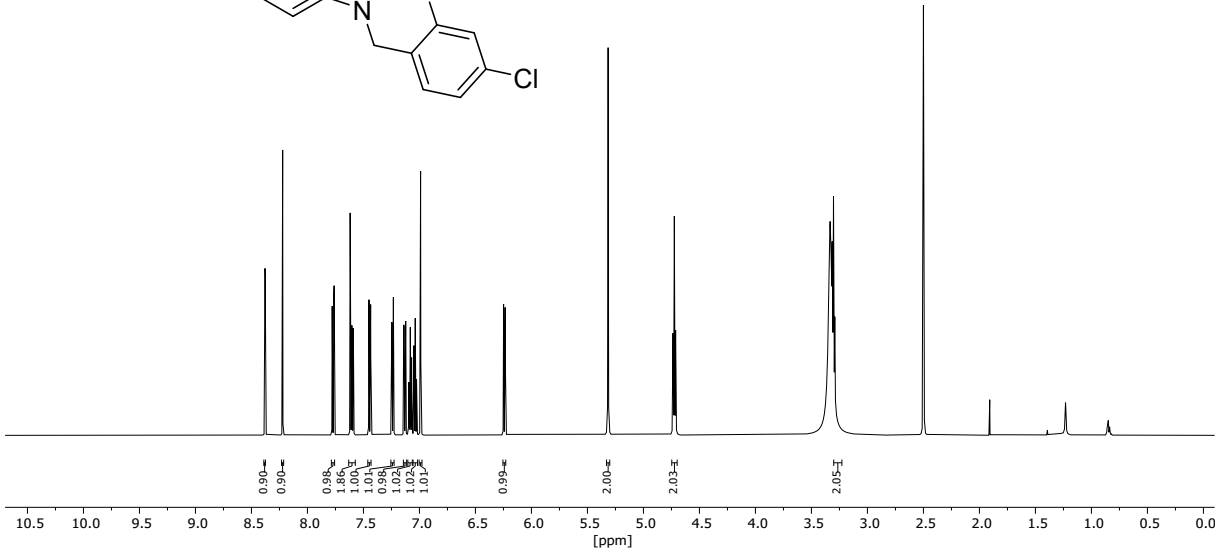
37

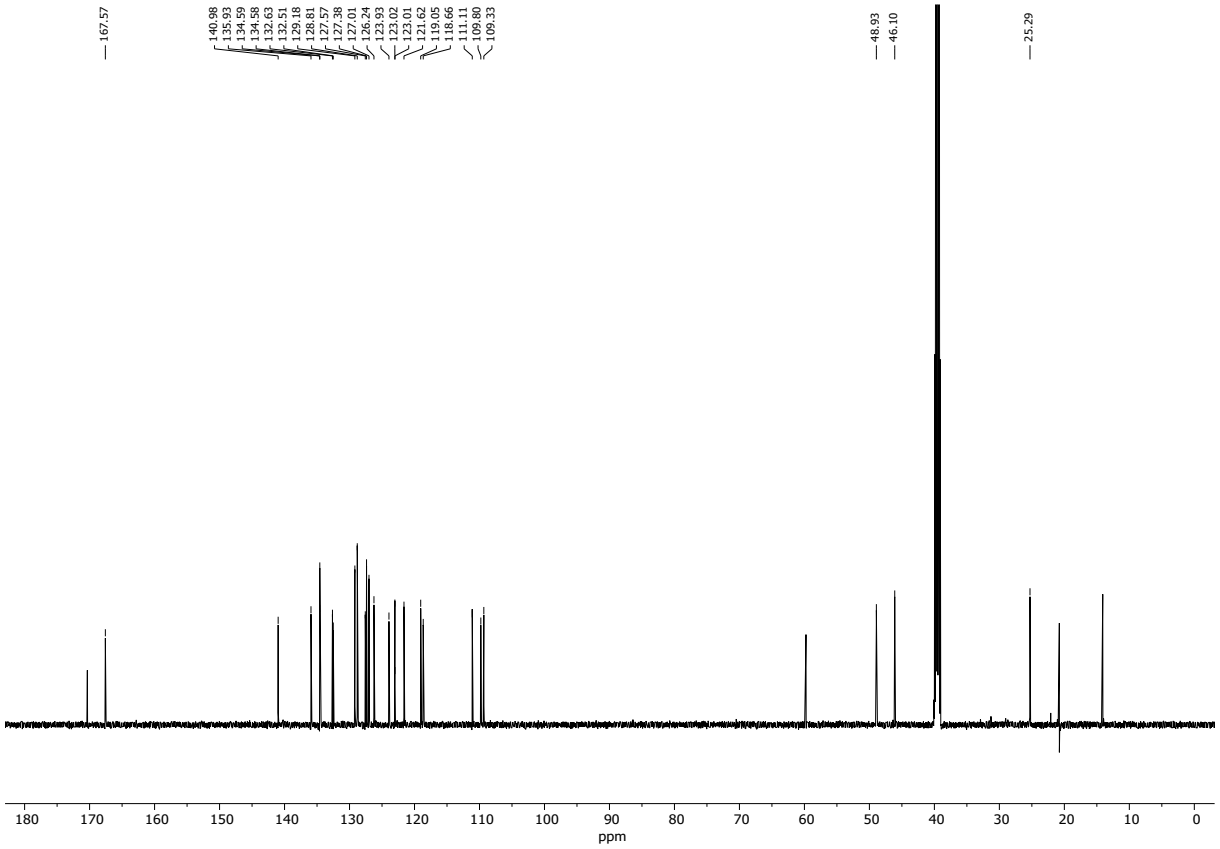
0.93
2.90
1.01
0.97
1.03
1.09
1.07
2.00
0.99
0.98
2.00
2.05
2.10
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

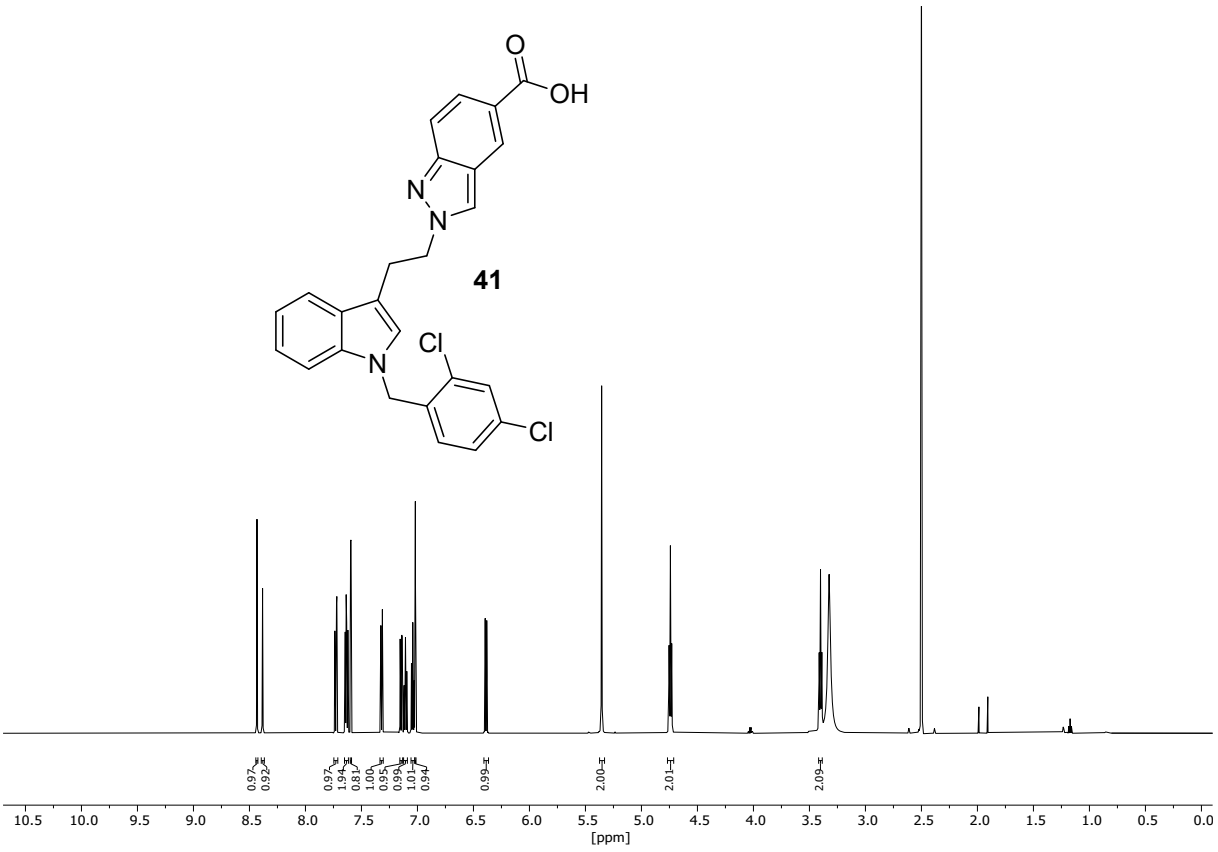

168.33
137.99
136.00
134.66
132.66
132.53
130.29
129.35
128.83
127.58
127.52
127.50
127.05
123.06
122.04
121.64
121.36
119.06
118.81
111.28
109.82
109.44
102.00
46.28
46.13
25.78
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

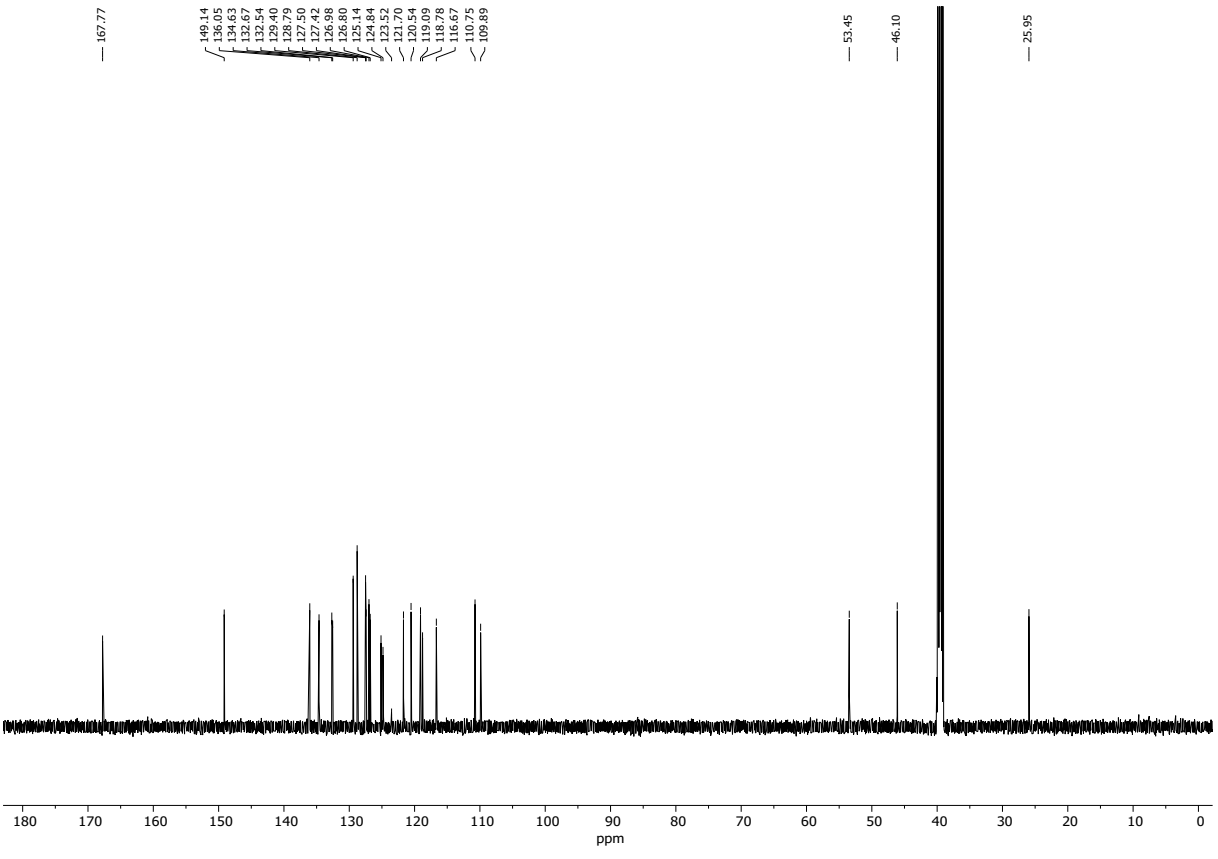

O
OH
N
N
Cl
N
Cl

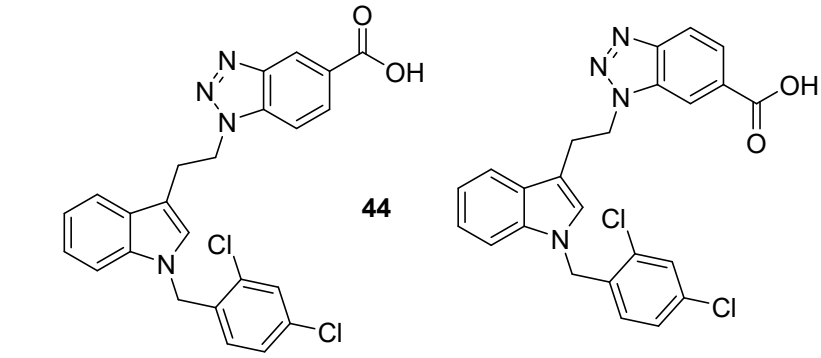
40


0.90
0.90
0.98
1.86
1.00
1.01
0.98
1.02
1.02
1.01
0.99
2.00
2.03
2.05
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 1.0 0.5 0.0
[ppm]


167.57
140.98
135.93
134.59
134.58
132.63
132.51
129.18
128.81
127.57
127.38
127.01
126.24
123.93
123.02
123.01
121.62
119.05
118.66
111.11
109.80
109.33
48.93
46.10
25.29
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

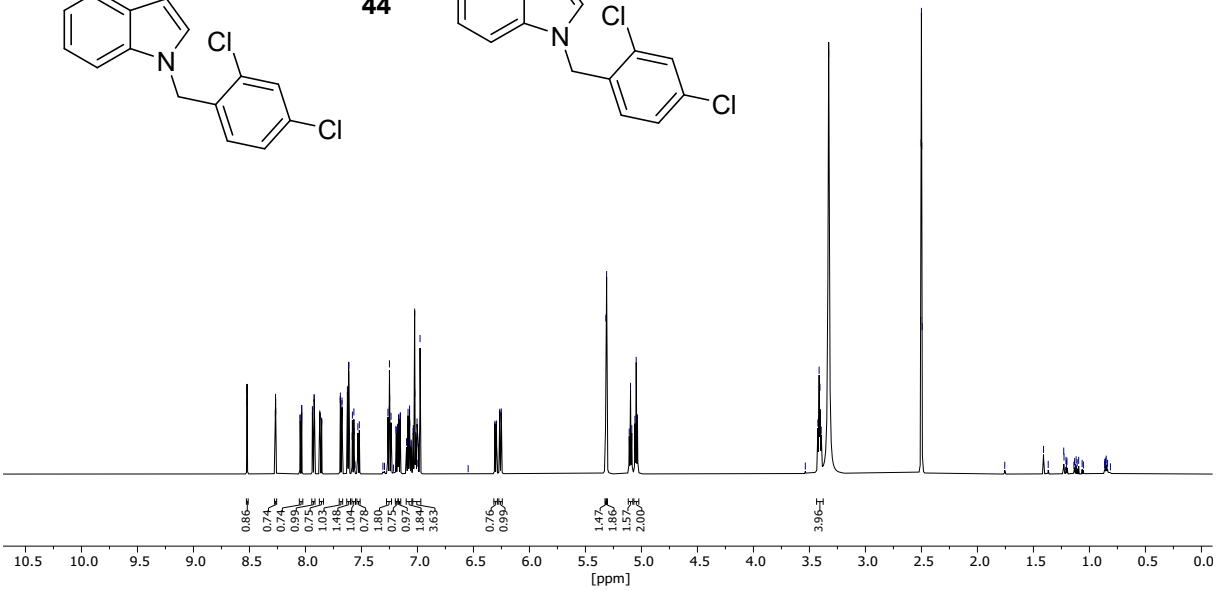

O
OH
N
N
41
Cl
N
Cl
0.97
0.92
0.97
1.94
0.81
1.00
0.95
0.99
1.01
0.94
0.99
2.00
2.01
2.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

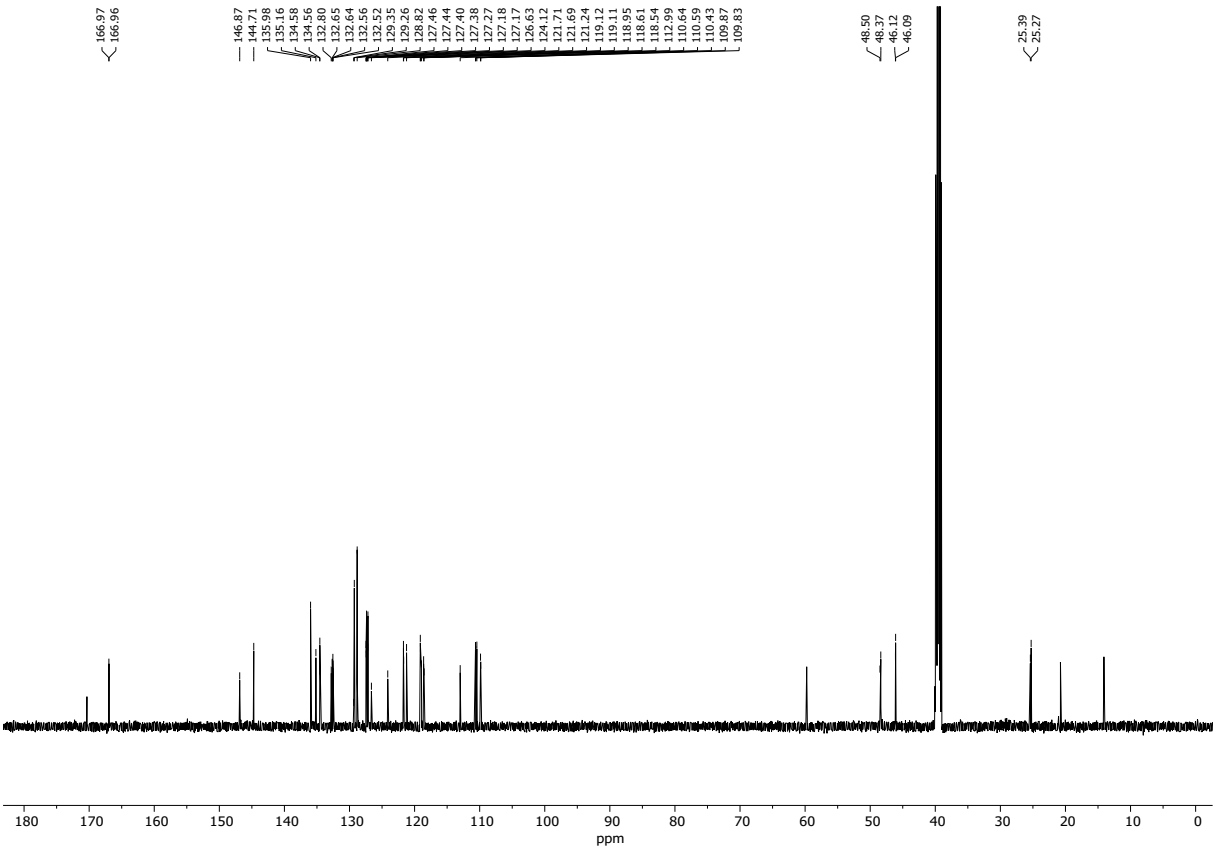

167.77
149.14
136.05
134.63
132.67
132.54
129.40
128.79
127.50
127.42
126.98
126.80
125.14
124.84
123.52
121.70
120.54
119.09
118.78
116.67
110.75
109.89
53.45
46.10
25.95
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

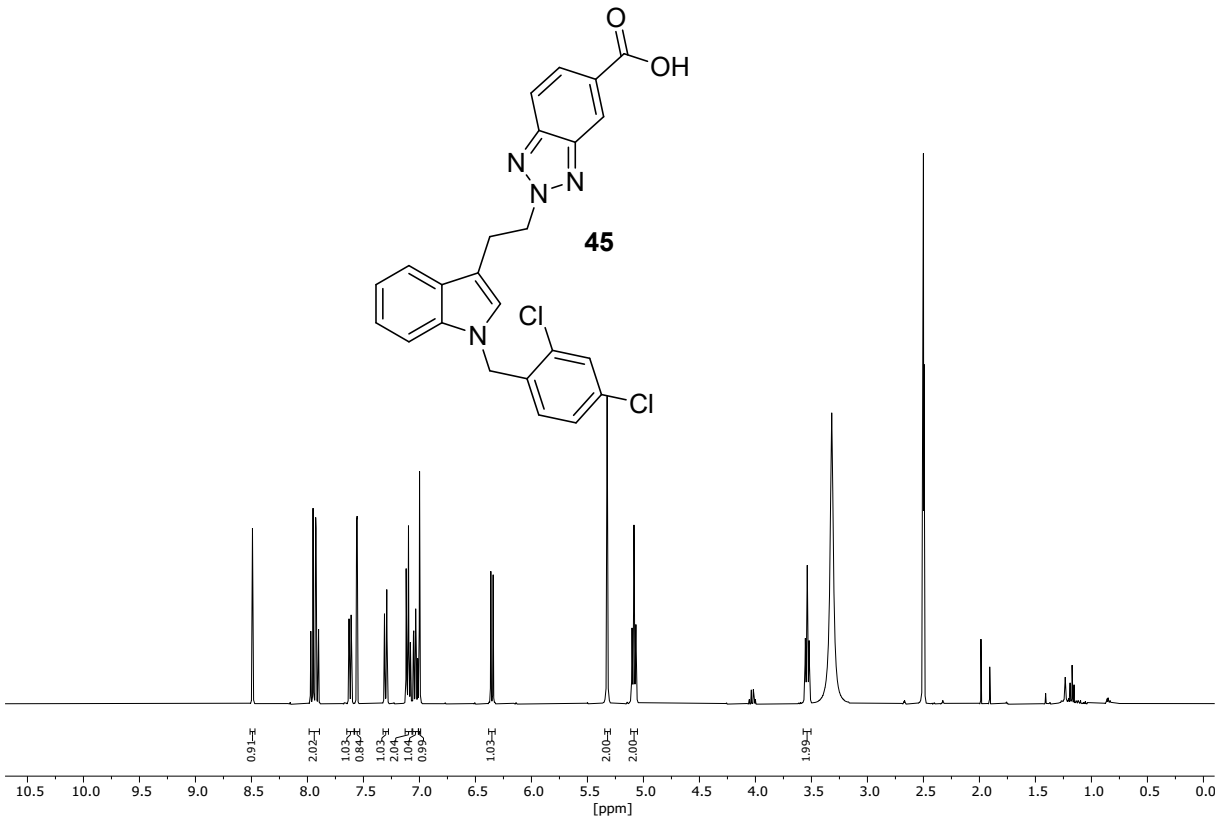

O
OH
N
N
N
Cl
N
Cl

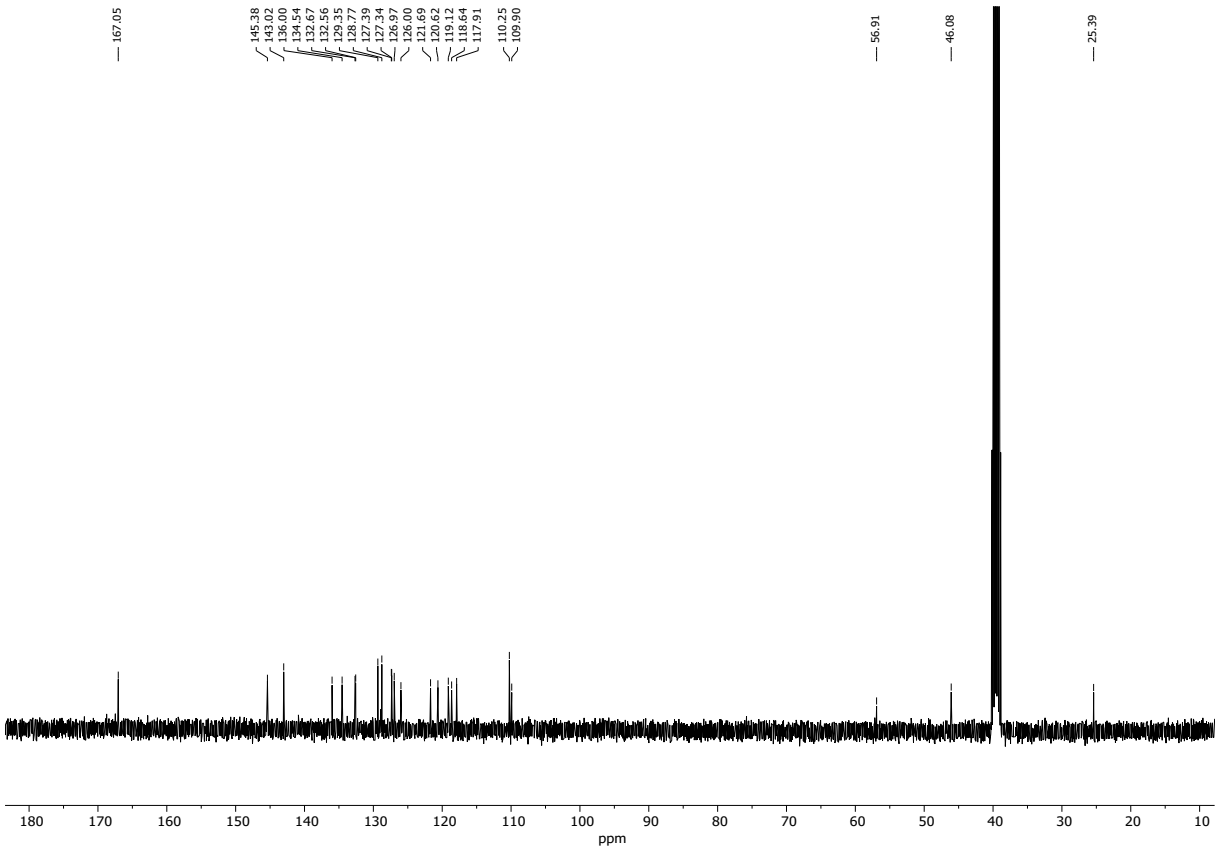
44

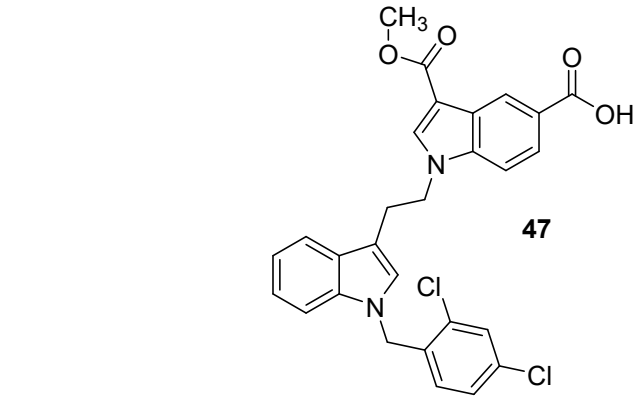
N
N
N
OH
O
Cl
N
Cl


0.86
0.74
0.74
0.99
0.75
1.03
1.48
1.04
0.78
1.86
0.75
0.97
1.84
3.63
0.76
0.99
1.47
1.86
1.57
2.00
3.96
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 1.0 0.5 0.0
[ppm]

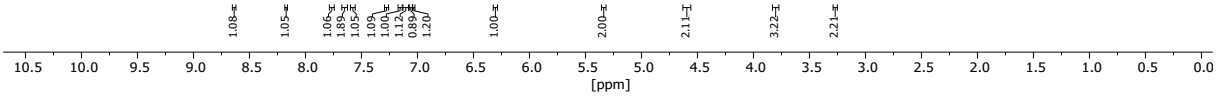

166.97
166.96
146.87
144.71
135.98
135.16
134.58
134.56
132.80
132.65
132.64
132.56
132.52
129.35
129.26
129.02
127.46
127.44
127.40
127.38
127.27
127.18
127.17
126.63
124.12
121.71
121.69
121.24
119.12
119.11
118.95
118.61
118.54
112.99
110.64
110.59
110.43
109.87
109.83
48.50
48.37
46.12
46.09
25.39
25.27
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
45
Cl
N
Cl
0.91
2.02
1.03
0.84
1.03
2.04
1.04
0.99
1.03
2.00
2.00
1.99
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 1.0 0.5 0.0
[ppm]


167.05
145.38
143.02
136.00
134.54
132.67
132.56
129.35
128.77
127.39
127.34
126.97
126.00
121.69
120.62
119.12
118.64
117.91
110.25
109.90
56.91
46.08
25.39
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm

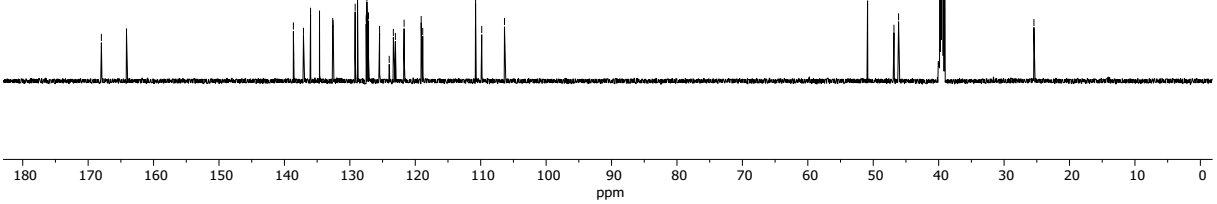

CH3
O
O
O
OH
N
Cl
N
Cl

47

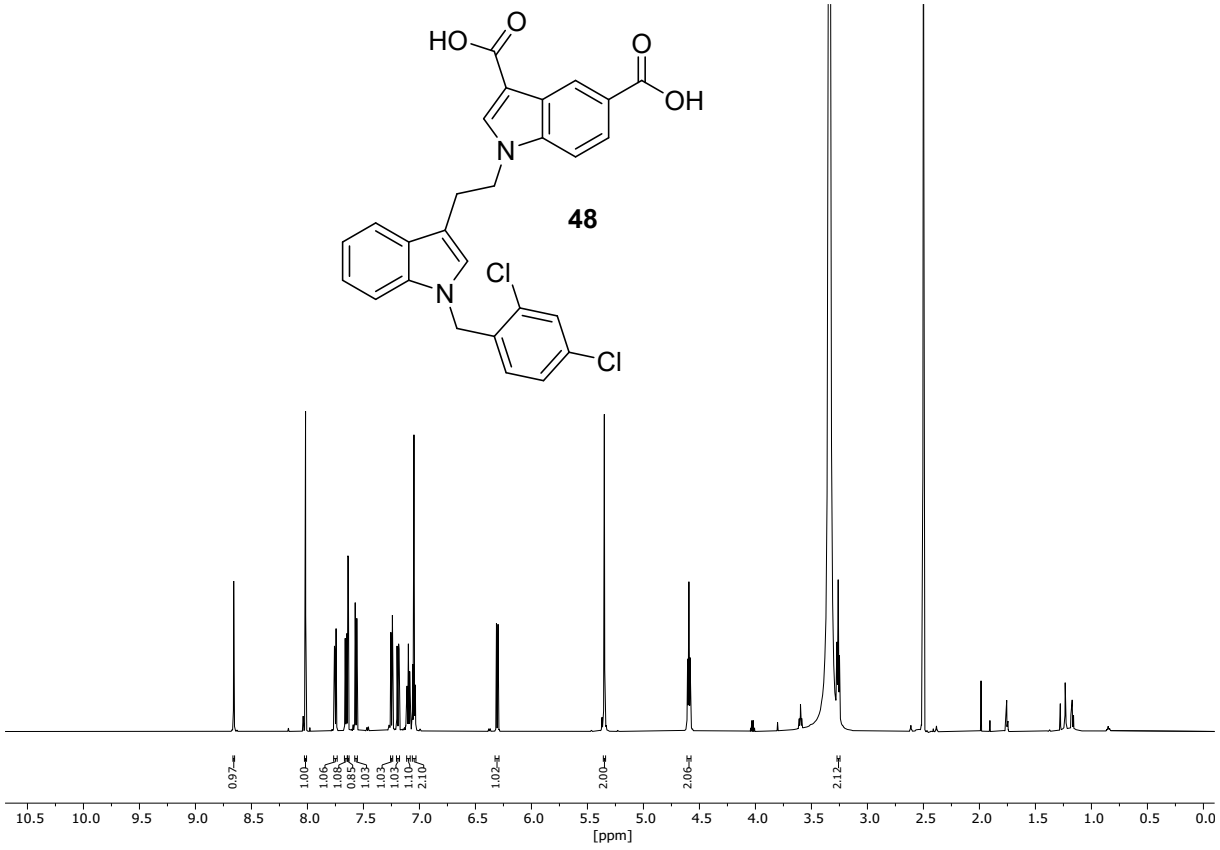

1.08
1.05
1.06
1.89
1.05
1.00
1.12
0.89
1.20
1.00
2.00
2.11
3.22
2.21

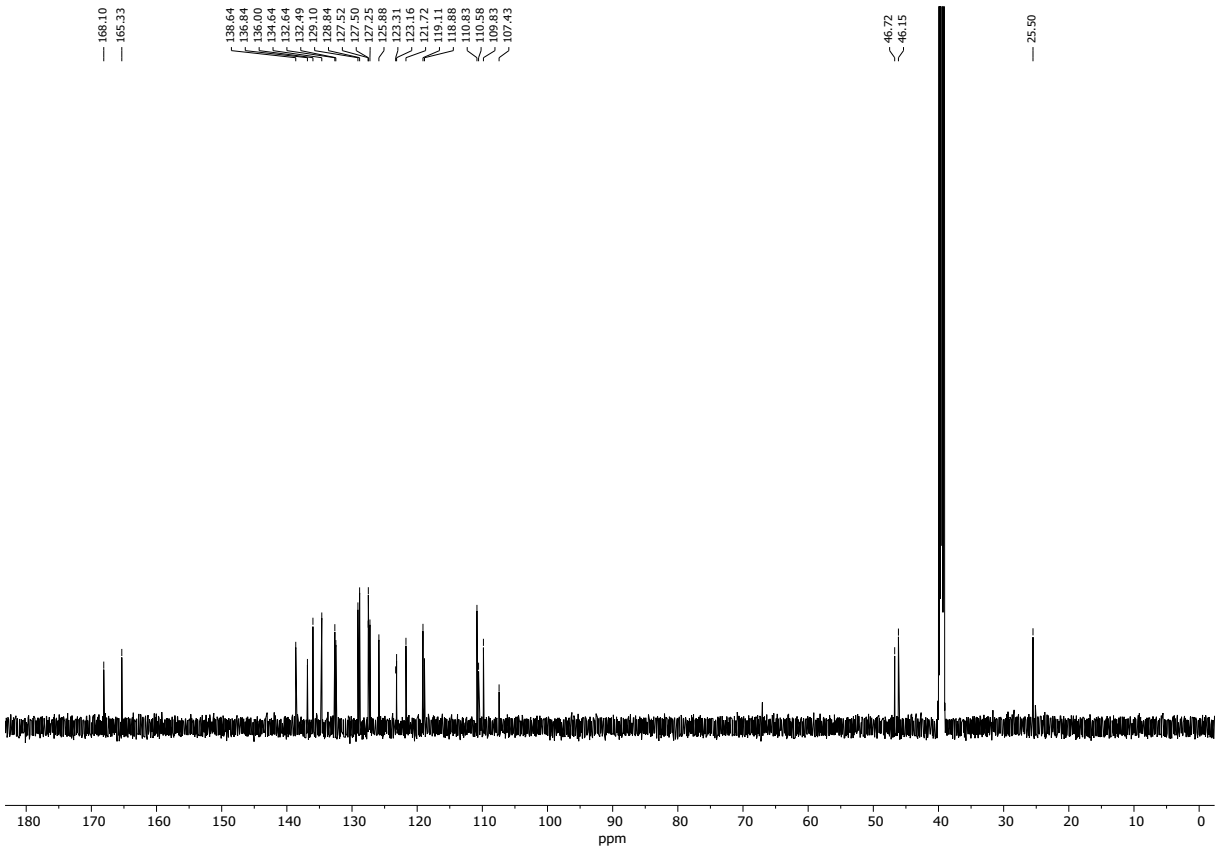
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
[ppm]

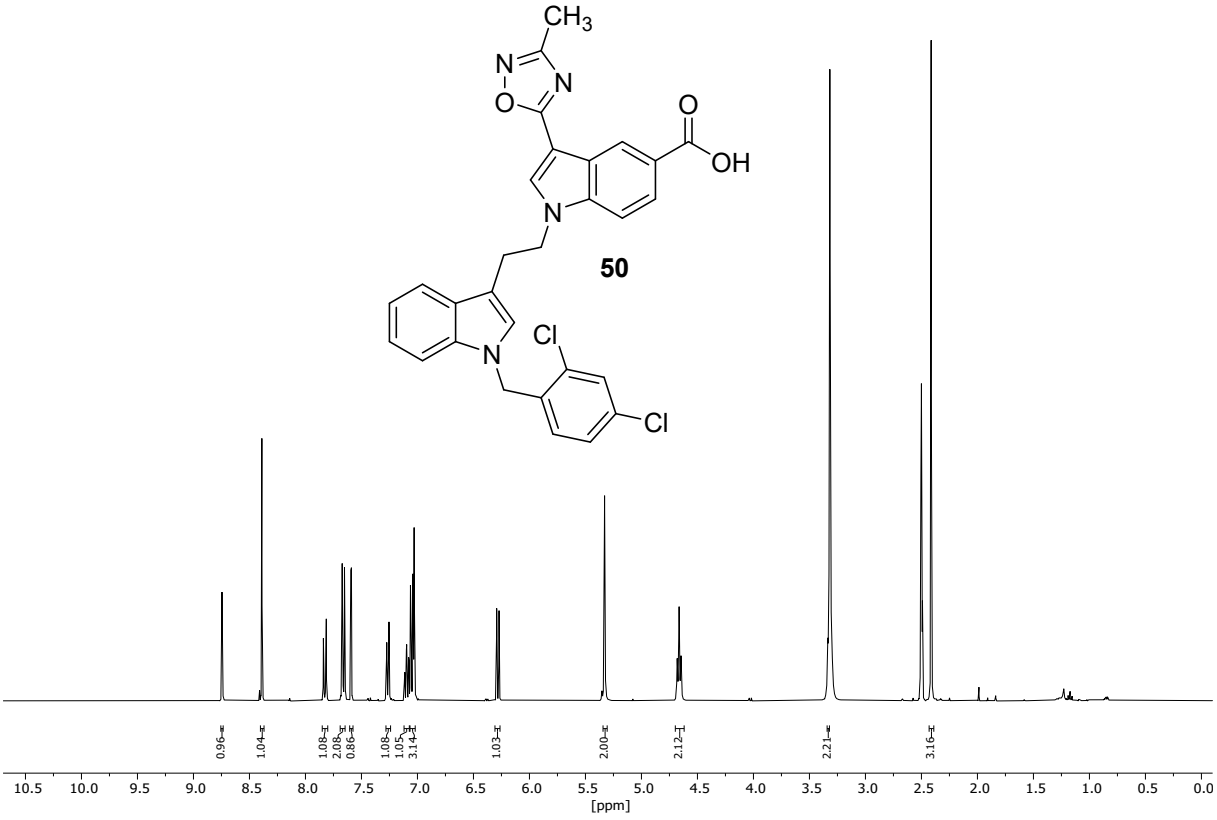

167.98
164.14
138.63
137.09
136.00
134.64
132.62
132.55
129.19
128.83
127.50
127.40
127.15
125.45
123.98
123.35
123.04
121.71
119.10
118.86
110.80
110.78
109.84
106.36
50.86
46.83
46.13
25.44

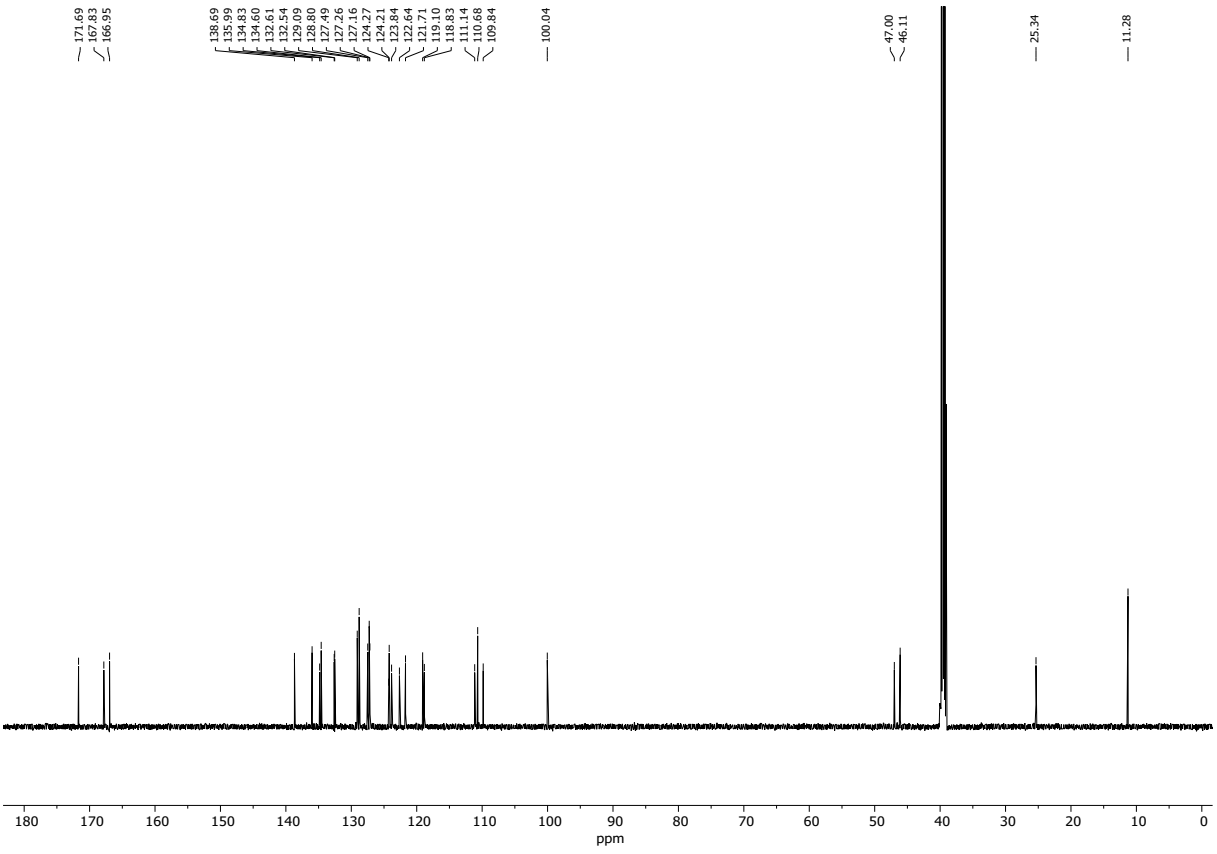


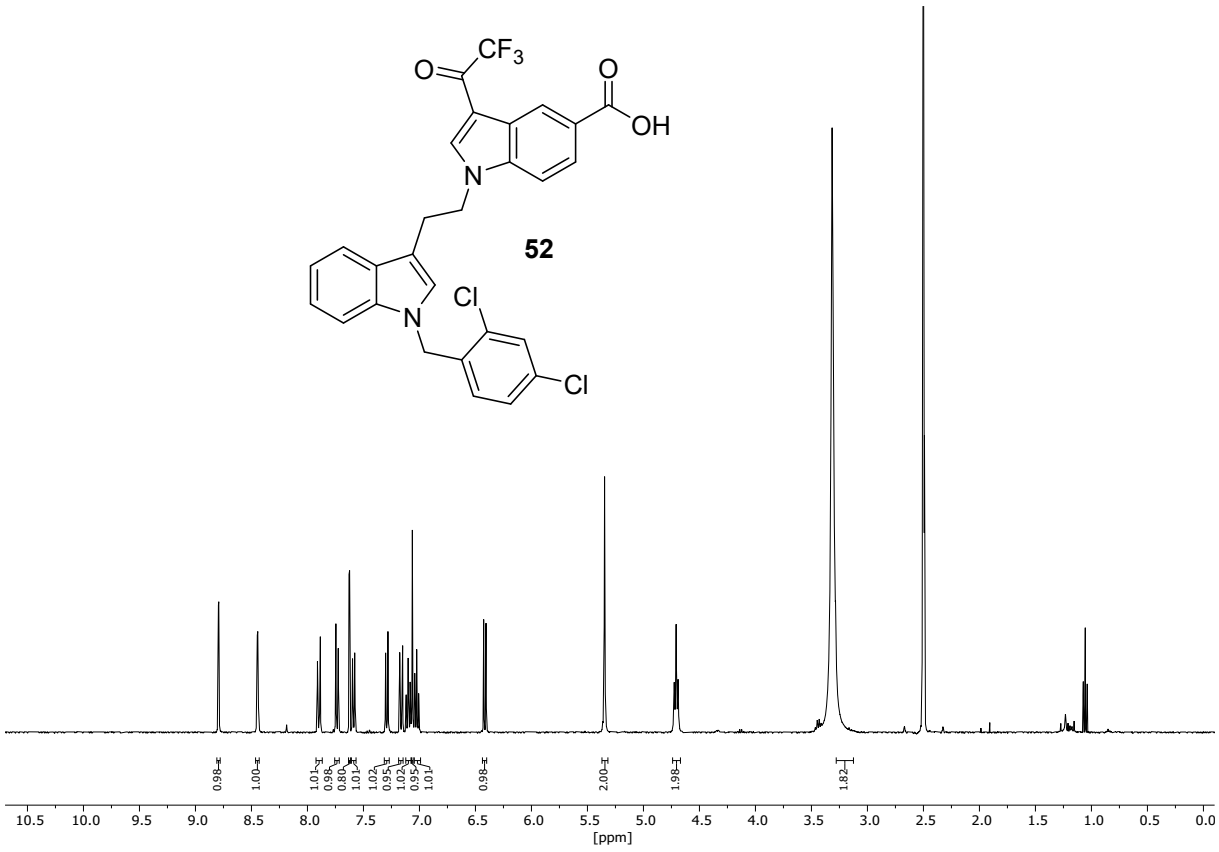
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

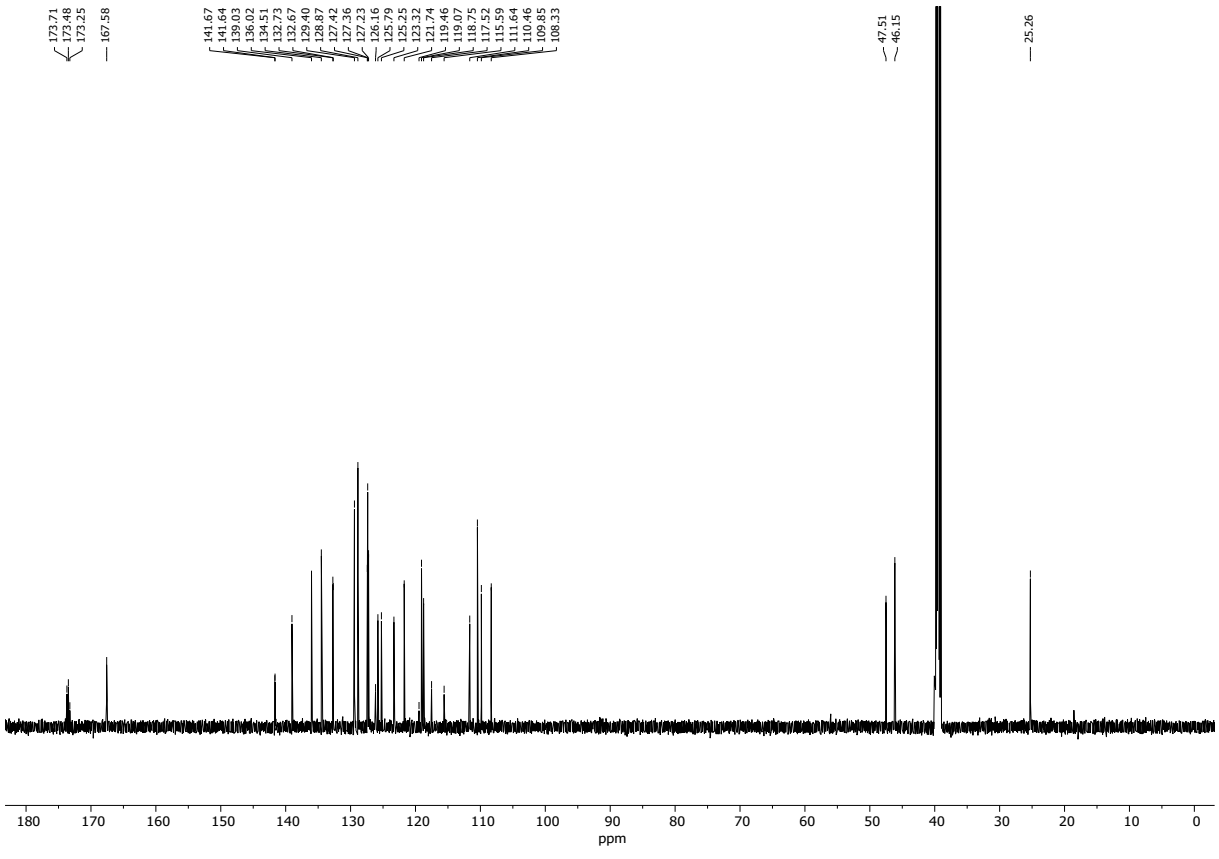

HO
O
O
OH
N
Cl
N
Cl
48
0.97
1.00
1.06
1.08
0.85
1.03
1.03
1.03
1.10
2.10
1.02
2.00
2.06
2.12
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

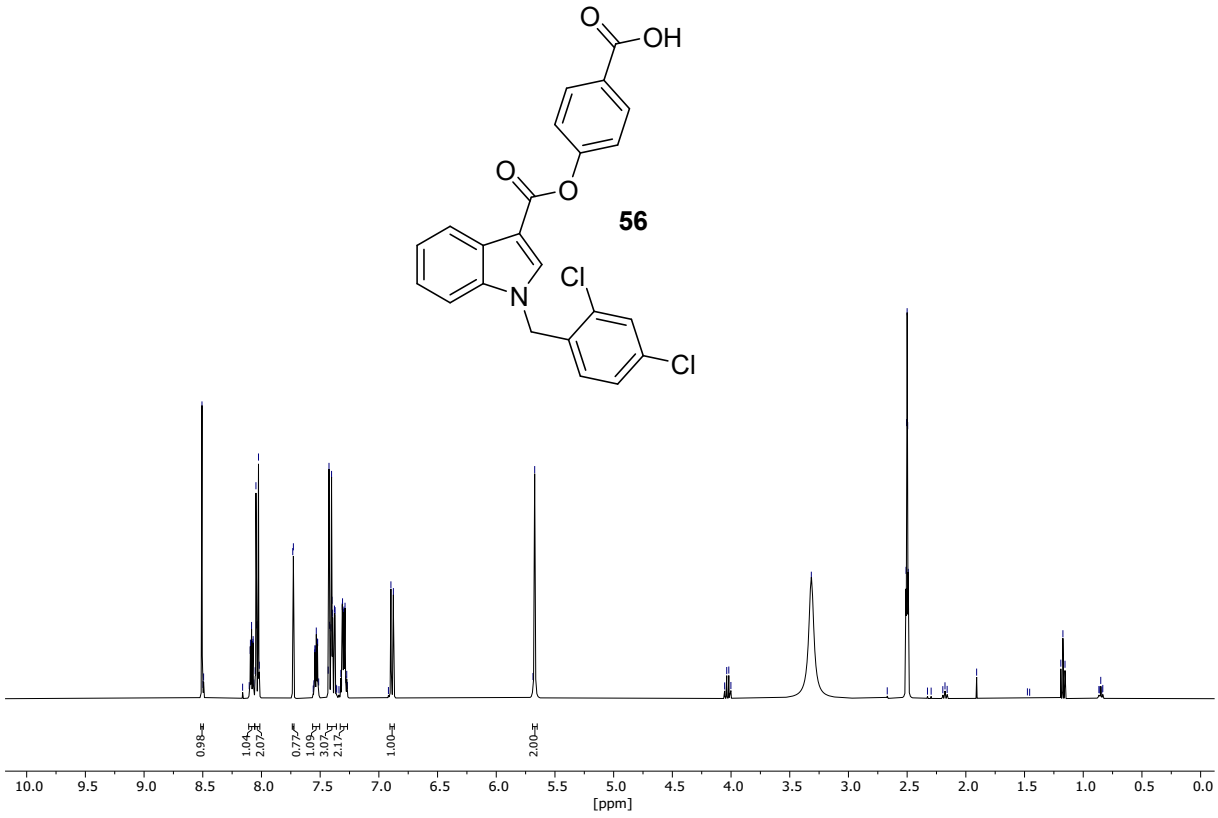

168.10
165.33
138.64
136.84
136.00
134.64
132.64
132.49
129.10
128.84
127.52
127.50
127.25
125.88
123.31
123.16
121.72
119.11
118.88
110.83
110.58
109.83
107.43
46.72
46.15
25.50
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

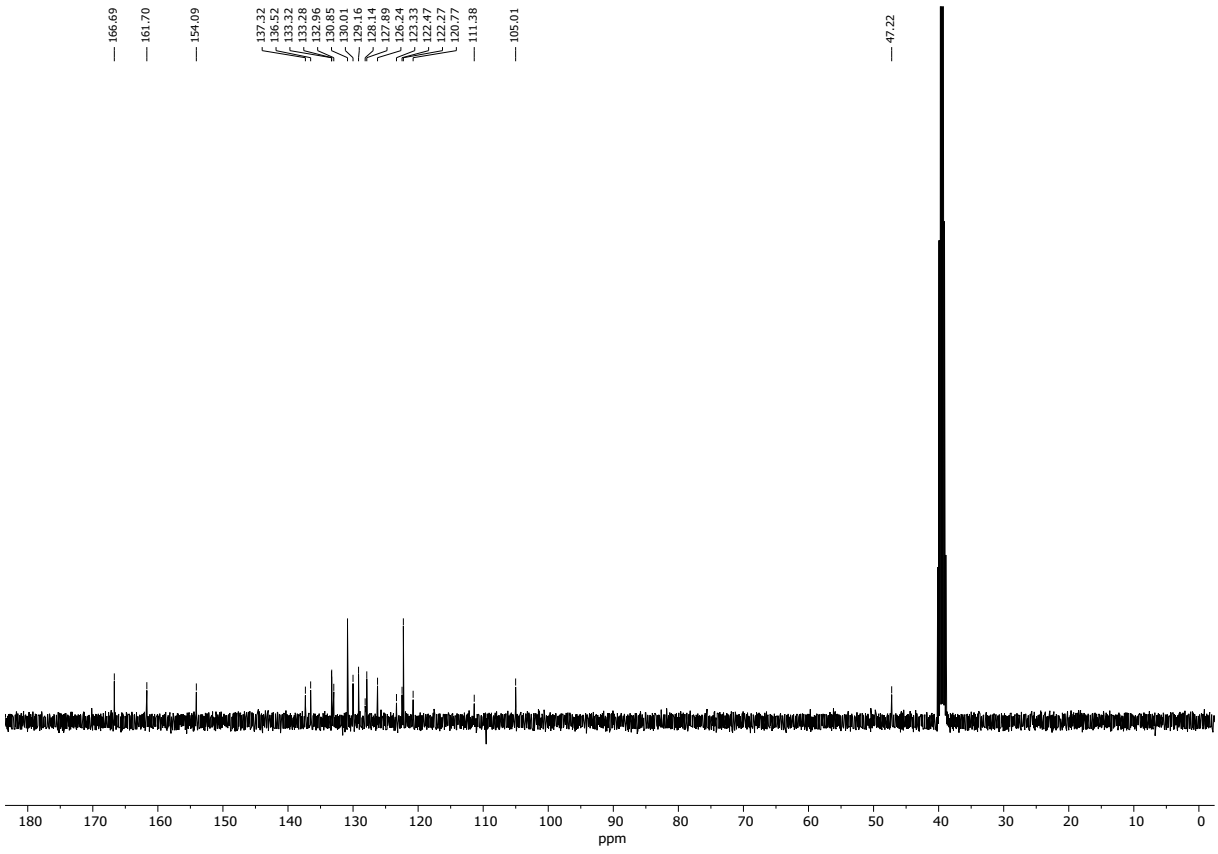

CH3
N
N
O
O
OH
N
50
N
Cl
Cl
0.96
1.04
1.08
2.08
0.86
1.08
1.05
3.14
1.03
2.00
2.12
2.21
3.16
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

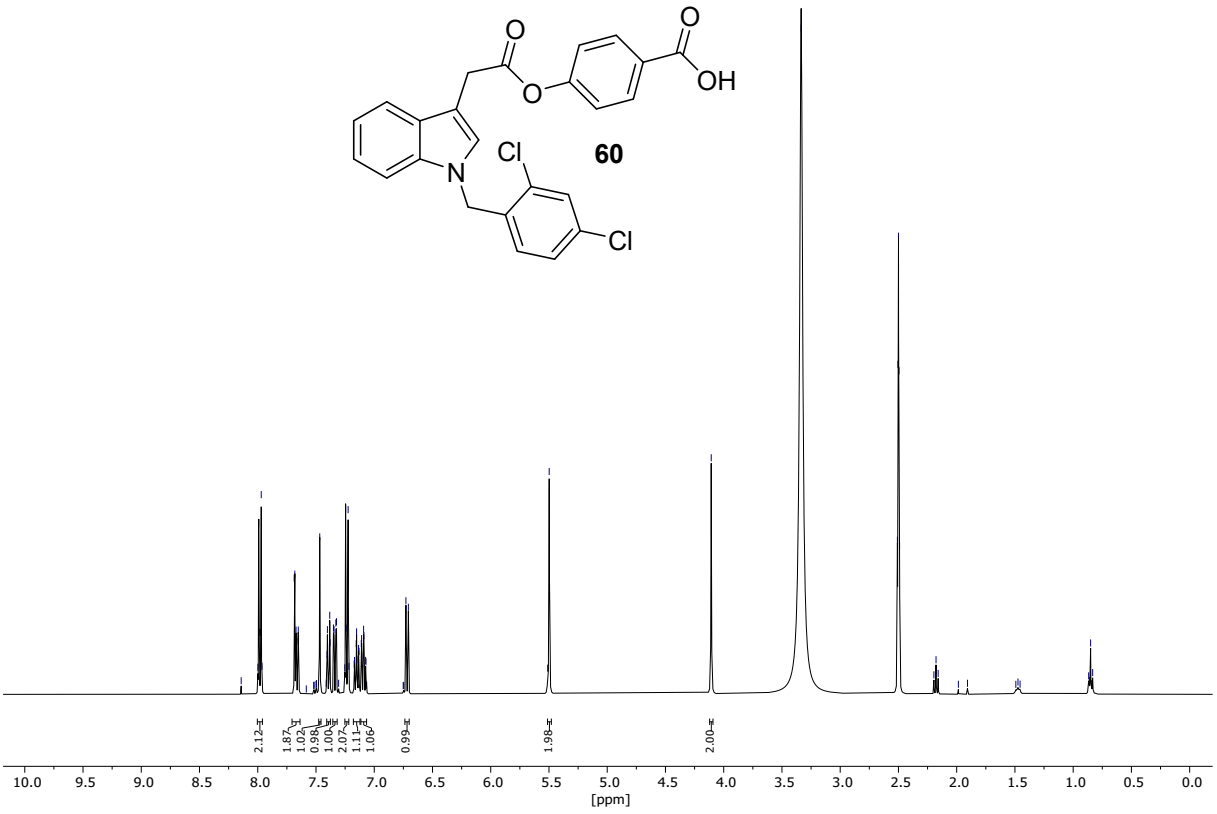

171.69
167.83
166.95
138.69
135.99
134.83
134.60
132.61
132.54
129.09
128.80
127.49
127.26
127.16
124.27
124.21
123.84
122.64
121.71
119.10
118.83
111.14
110.68
109.84
100.04
47.00
46.11
25.34
11.28
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

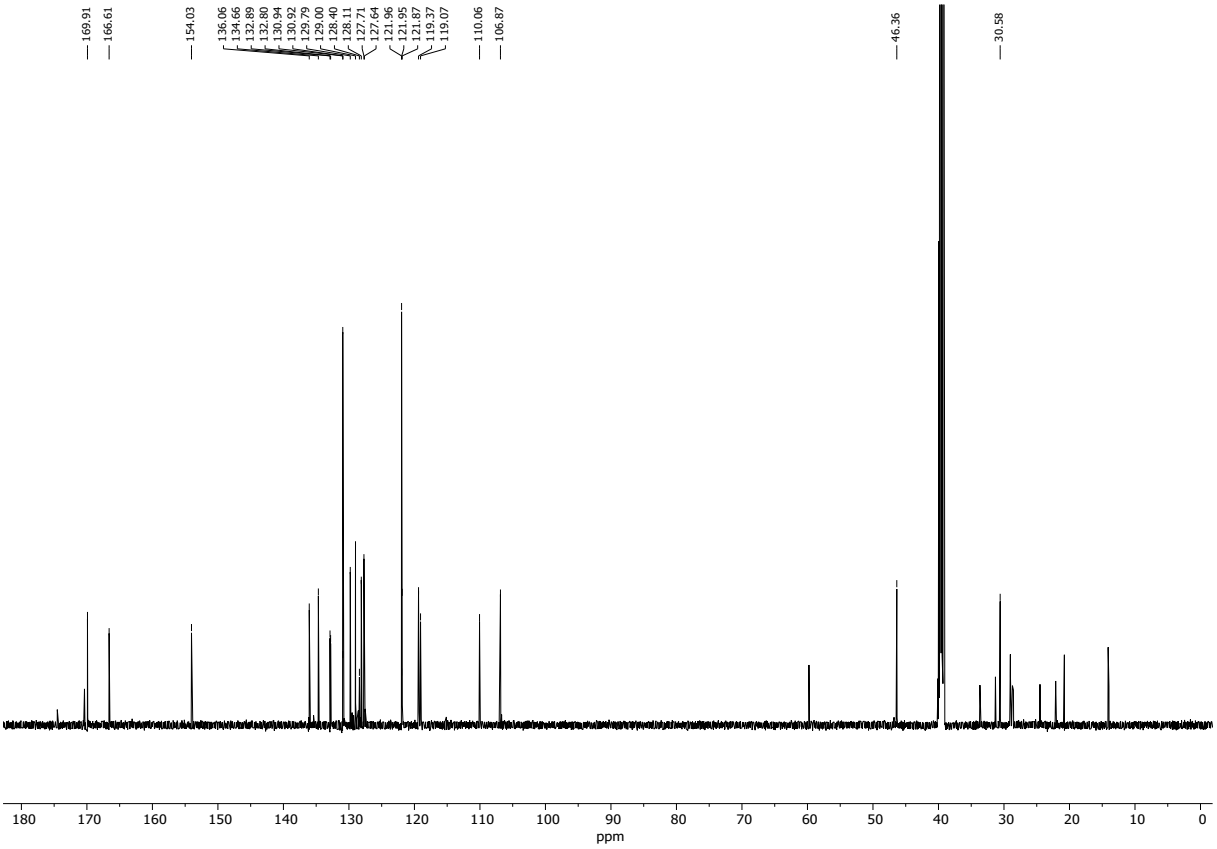

CF3
O
O
OH
N
Cl
N
Cl
Cl
52
0.98
1.00
1.01
0.98
0.80
1.01
1.02
0.95
1.02
0.95
1.01
0.98
2.00
1.98
1.82
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

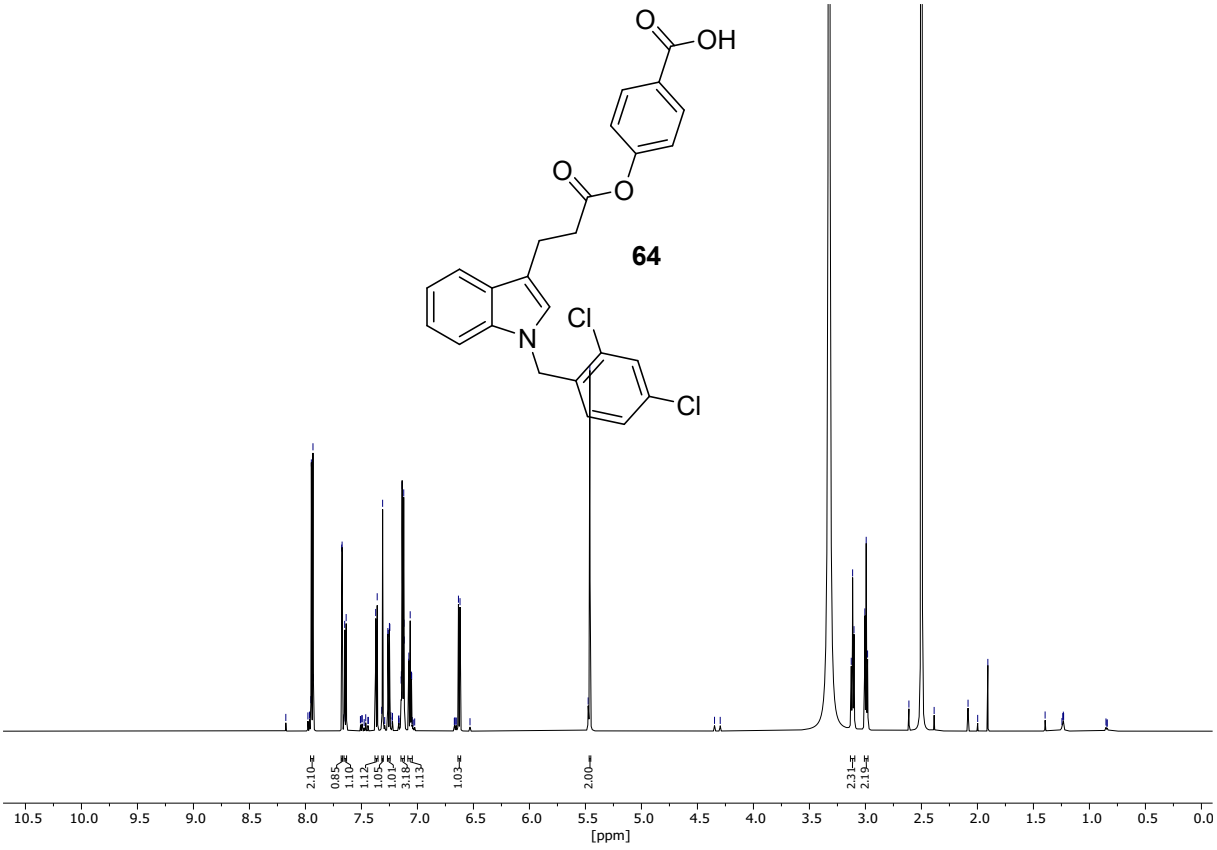

173.71
173.48
173.25
167.58
141.67
141.64
139.03
136.02
134.51
132.73
132.67
129.40
128.87
127.42
127.36
127.23
126.16
125.79
125.25
123.32
121.74
119.46
119.07
118.75
117.52
115.59
111.64
110.46
109.85
108.33
47.51
46.15
25.26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

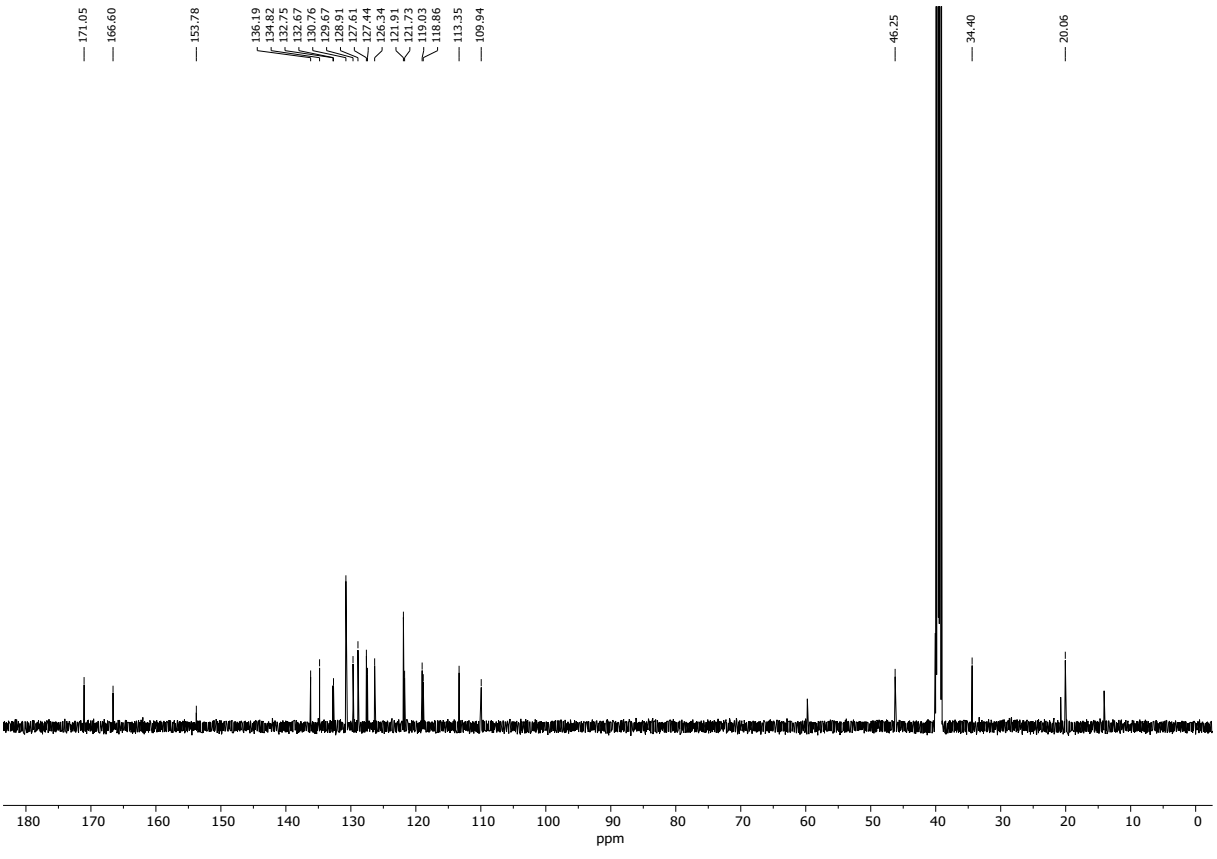

O
OH
O
O
56
N
Cl
Cl
0.98
1.04
2.07
0.77
1.09
3.07
2.17
1.00
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

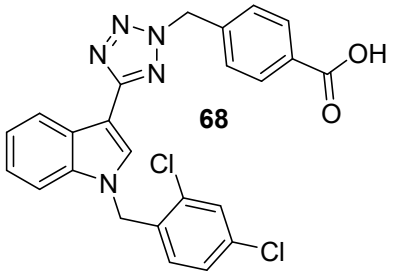

166.69
161.70
154.09
137.32
136.52
133.32
133.28
132.96
130.85
130.01
129.16
128.14
127.89
126.24
123.33
122.47
122.27
120.77
111.38
105.01
47.22
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
O
OH
O
Cl
N
Cl
60
2.12
1.87
1.02
0.98
1.00
2.07
1.11
1.06
0.99
1.98
2.00
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 1.0 0.5 0.0
[ppm]

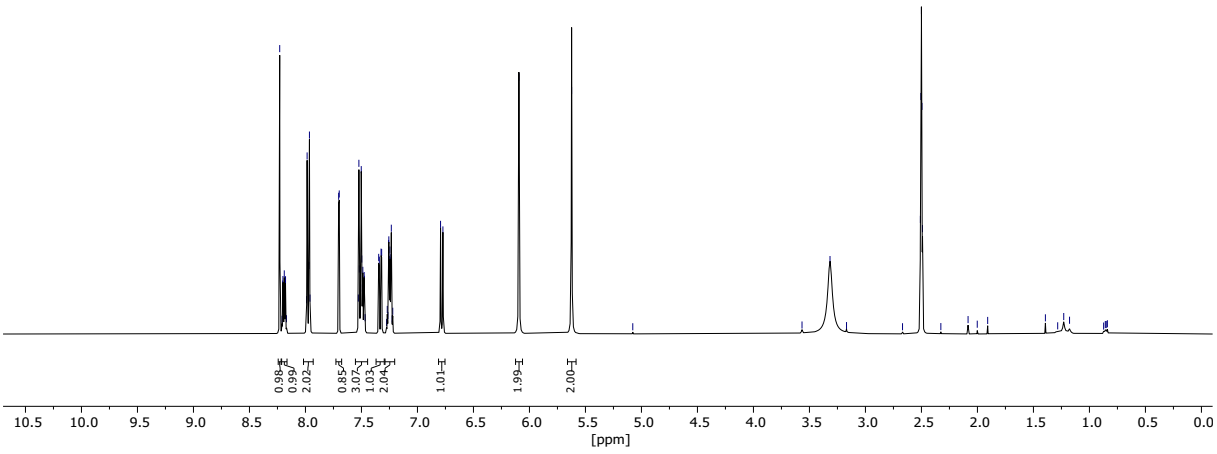

169.91
166.61
154.03
136.06
134.66
132.89
132.80
130.94
130.92
129.79
129.00
128.40
128.11
127.71
127.64
121.96
121.95
121.87
119.37
119.07
110.06
106.87
46.36
30.58
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

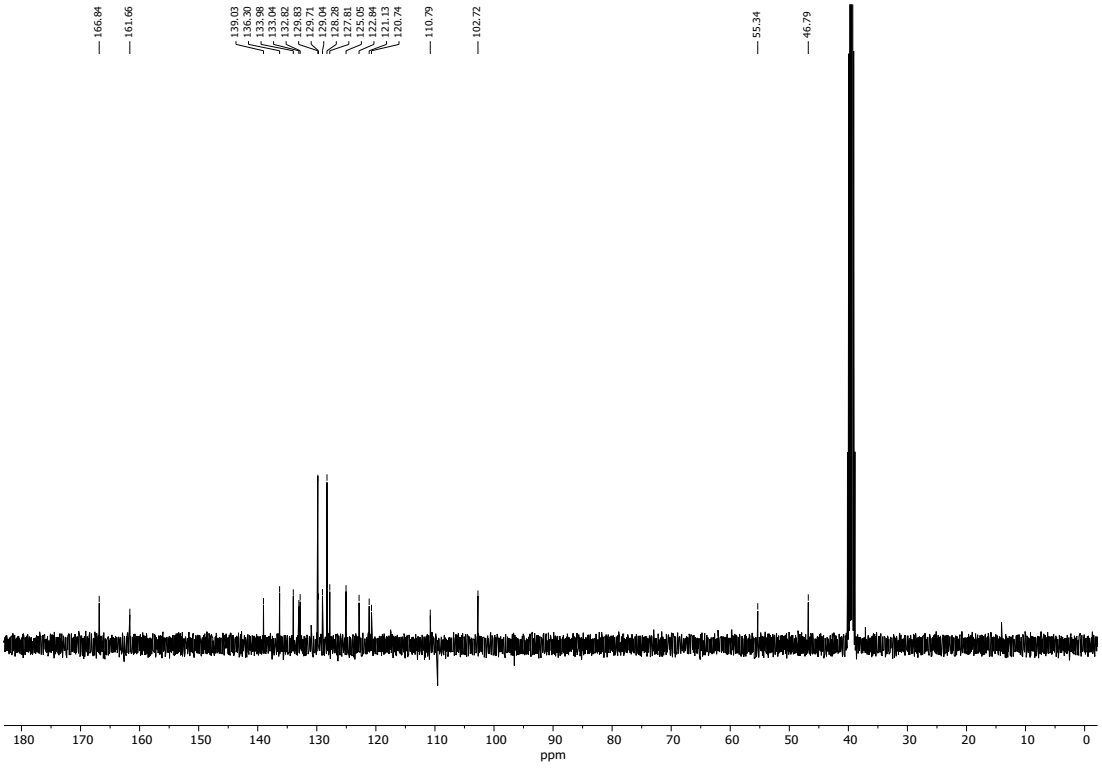

O
OH
O
O
64
N
Cl
Cl
2.10
0.85
1.10
1.12
1.05
1.01
3.18
1.13
1.03
2.00
2.31
2.19
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

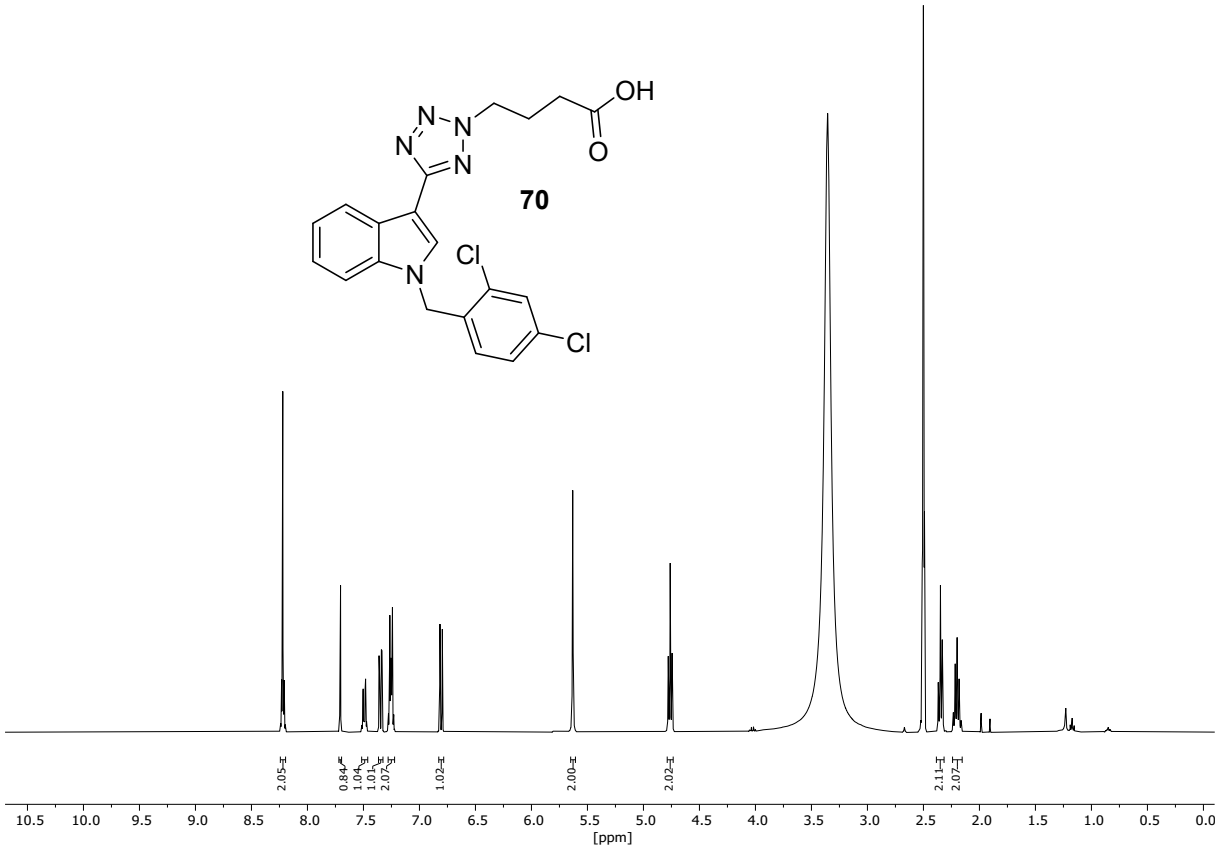

171.05
166.60
153.78
136.19
134.82
132.75
132.67
130.76
129.67
128.91
127.61
127.44
126.34
121.91
121.73
119.03
118.86
113.35
109.94
46.25
34.40
20.06
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

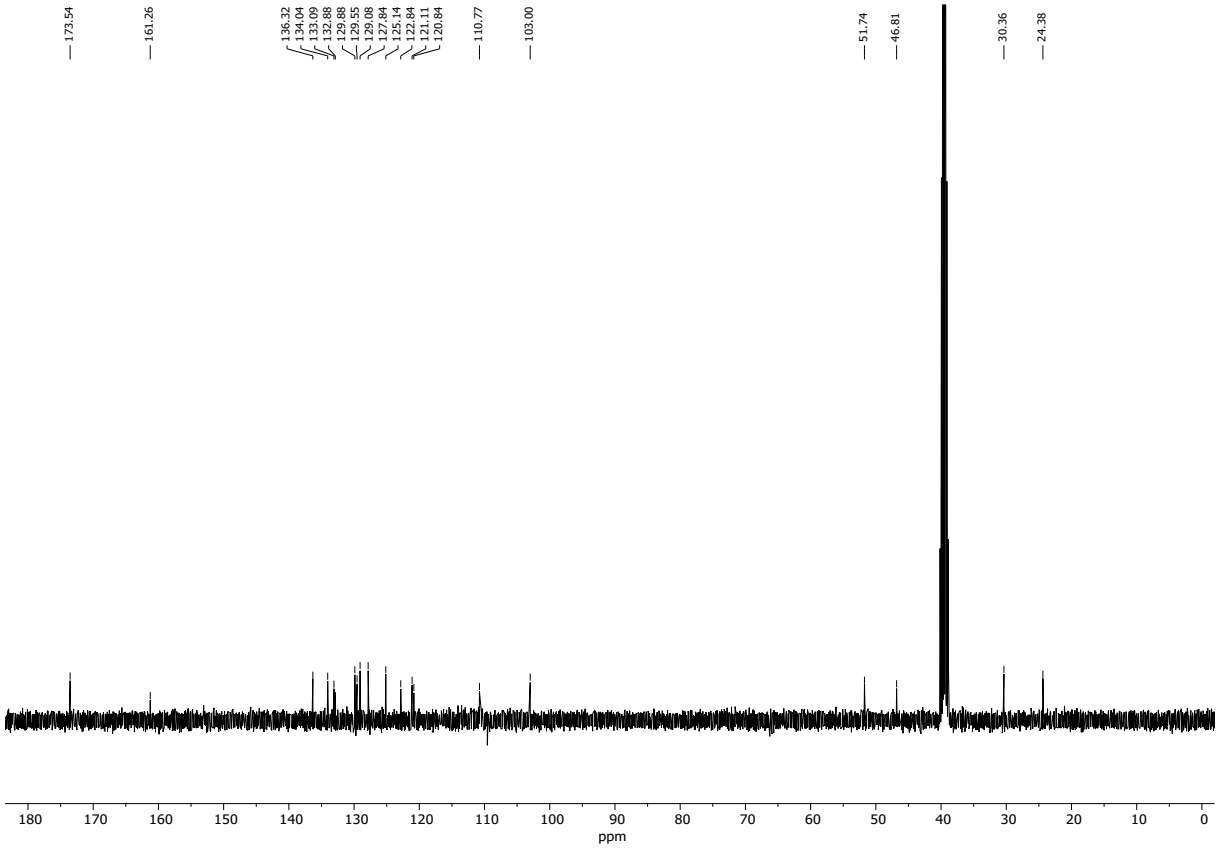

N
N
N
N
OH
O
Cl
N
Cl

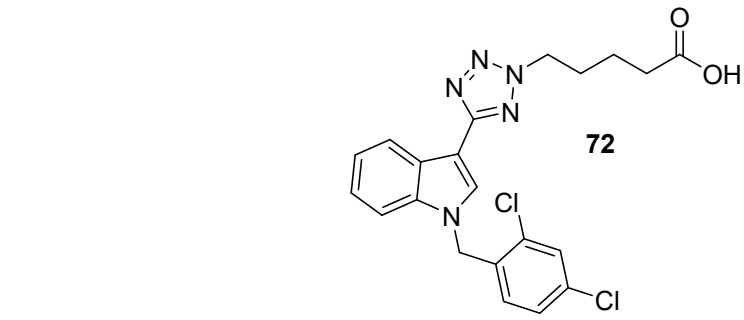
68


0.98
0.99
2.02
0.85
3.07
1.03
2.04
1.01
1.99
2.00
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 1.0 0.5 0.0
[ppm]

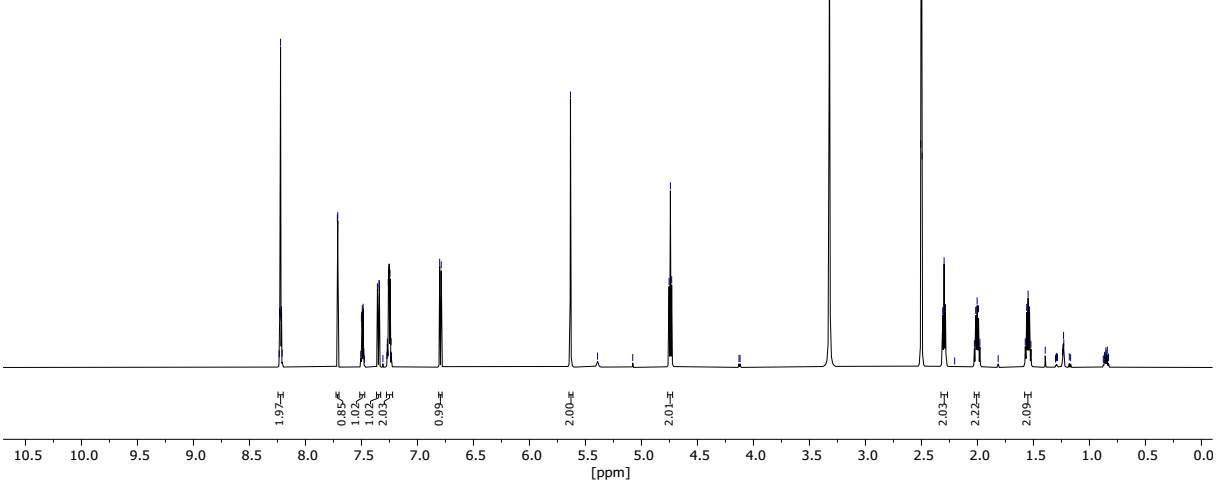

166.84
161.66
139.03
136.30
133.98
133.04
132.82
129.83
129.71
129.04
128.28
127.81
125.05
122.84
121.13
120.74
110.79
102.72
55.34
46.79
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

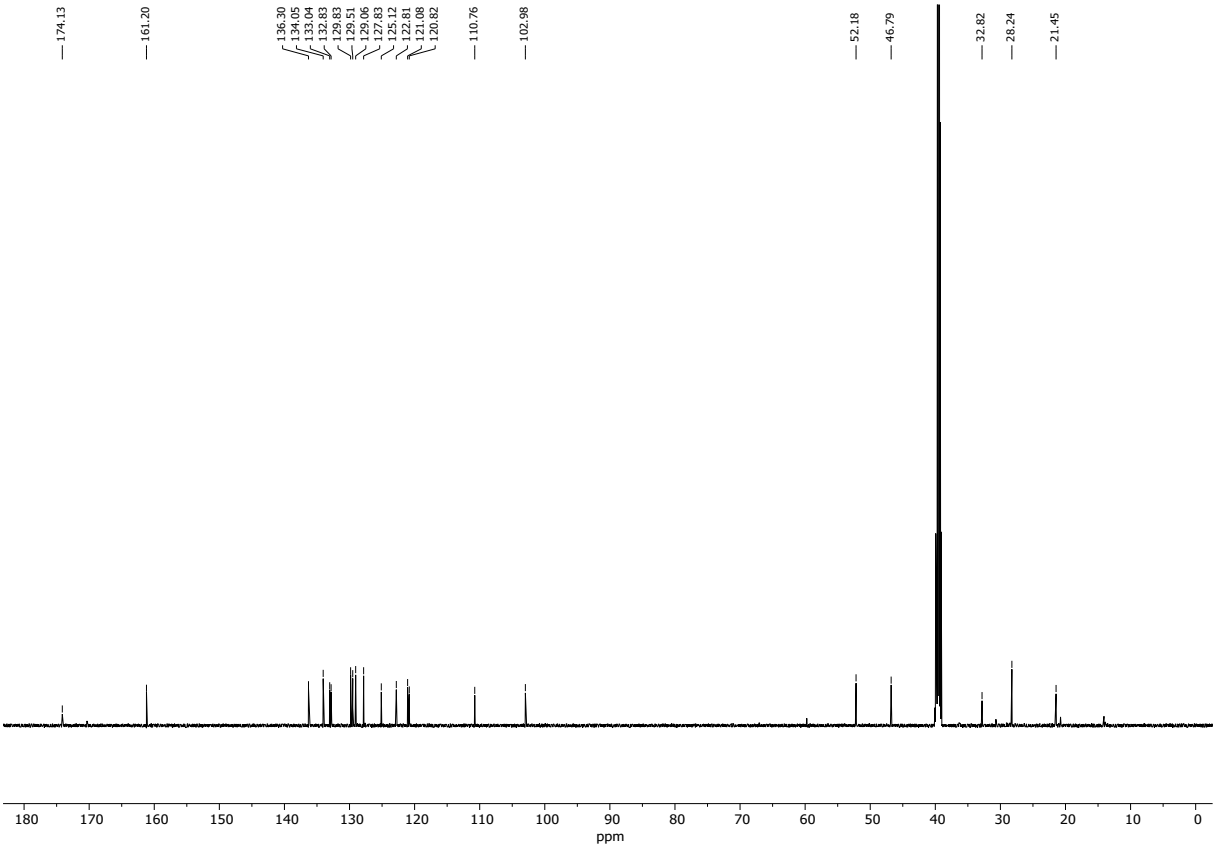

OH
O
N
N
N
N
Cl
N
Cl
70
2.05
0.84
1.04
1.01
2.07
1.02
2.00
2.02
2.11
2.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

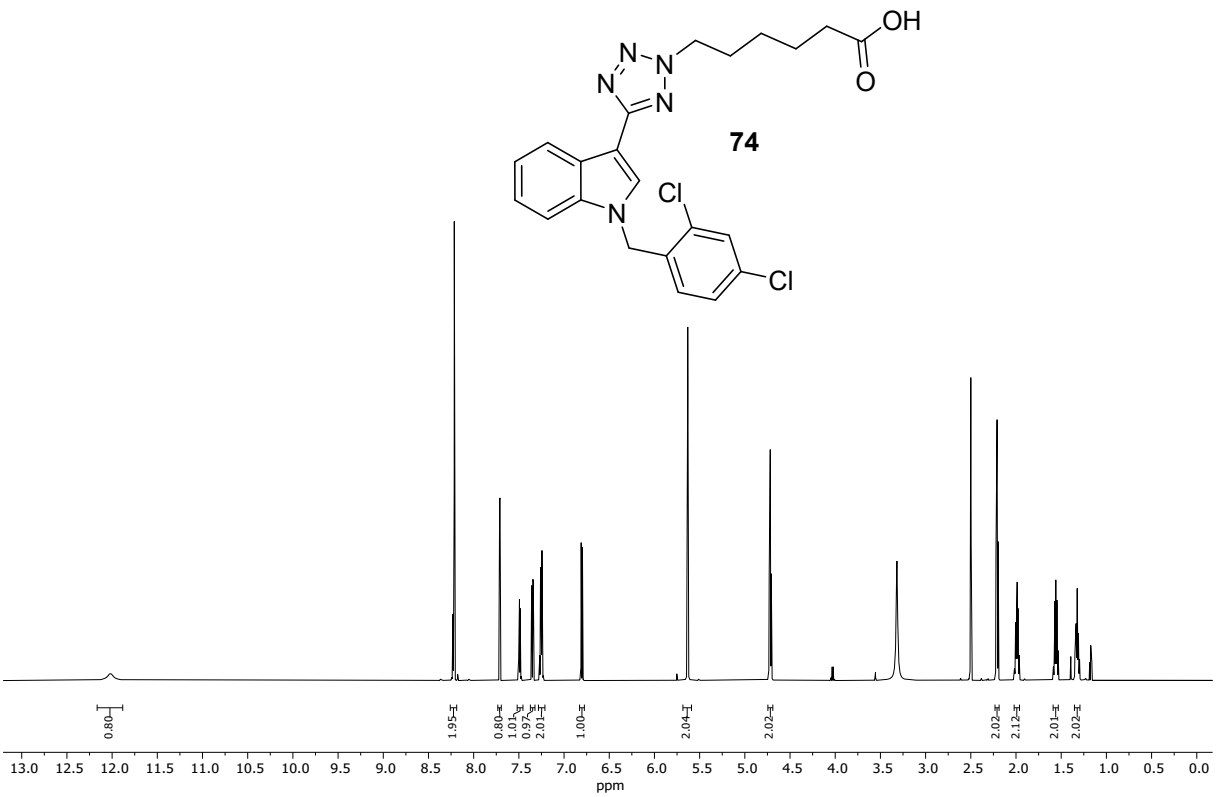

173.54
161.26
136.32
134.04
133.09
132.88
129.88
129.55
129.08
127.84
125.14
122.84
121.11
120.84
110.77
103.00
51.74
46.81
30.36
24.38
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

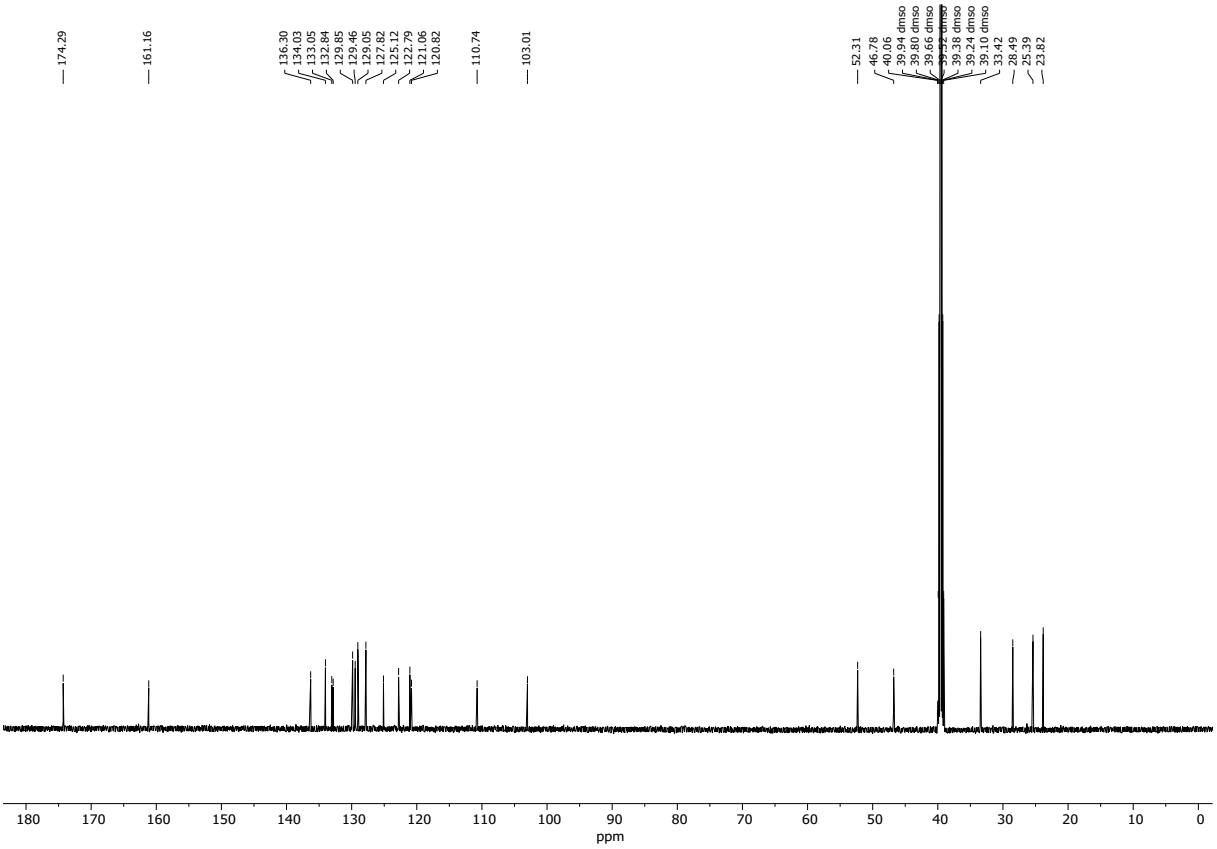

O
OH
N
N
N
N
Cl
Cl

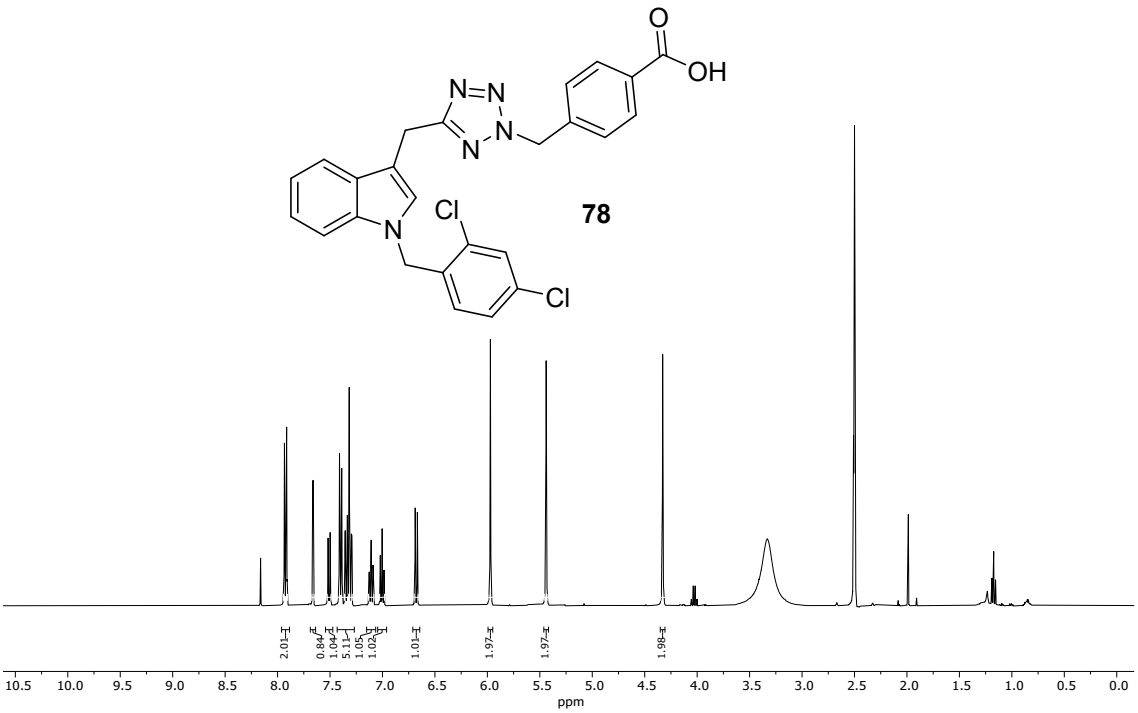
72


1.97
0.85
1.02
1.02
2.03
0.99
2.00
2.01
2.03
2.22
2.09
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 1.0 0.5 0.0
[ppm]

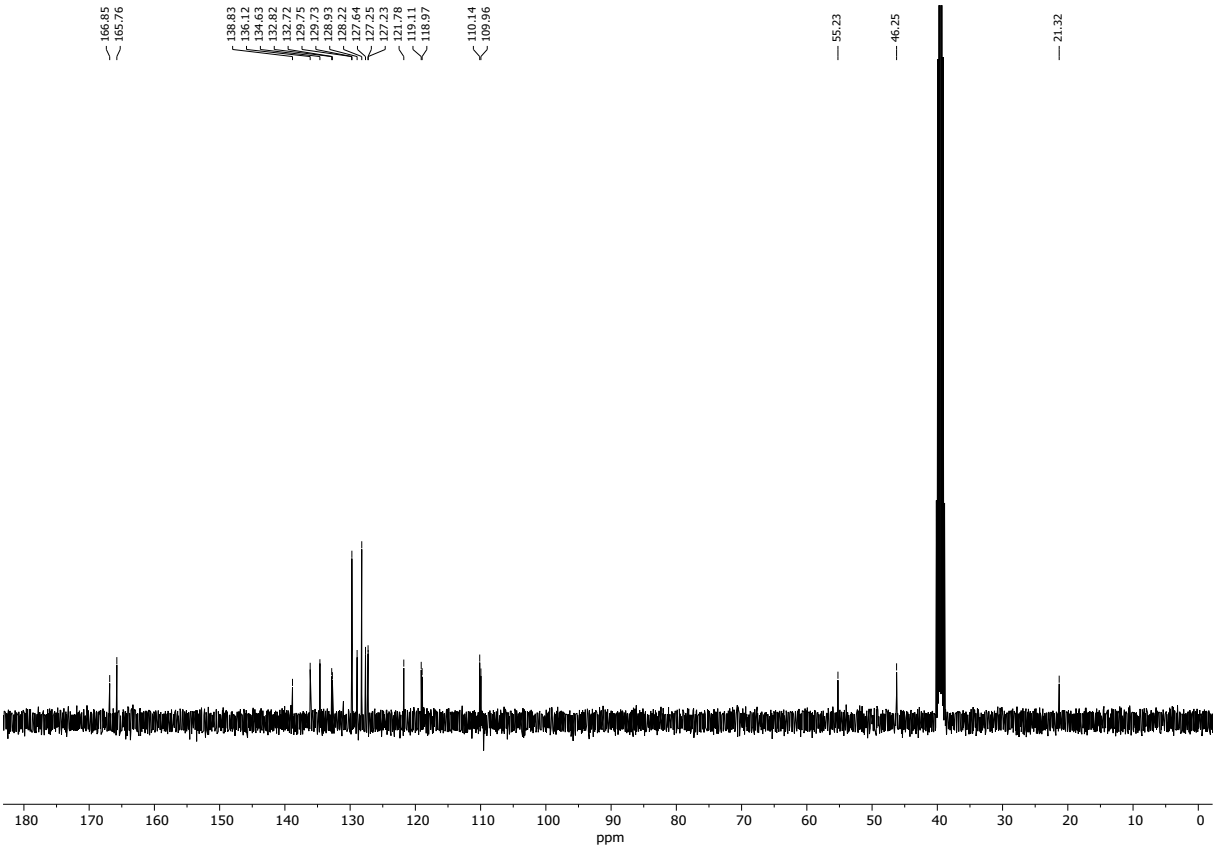

174.13
161.20
136.30
134.05
133.04
132.83
129.83
129.51
129.06
127.83
125.12
122.81
121.08
120.82
110.76
102.98
52.18
46.79
32.82
28.24
21.45
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

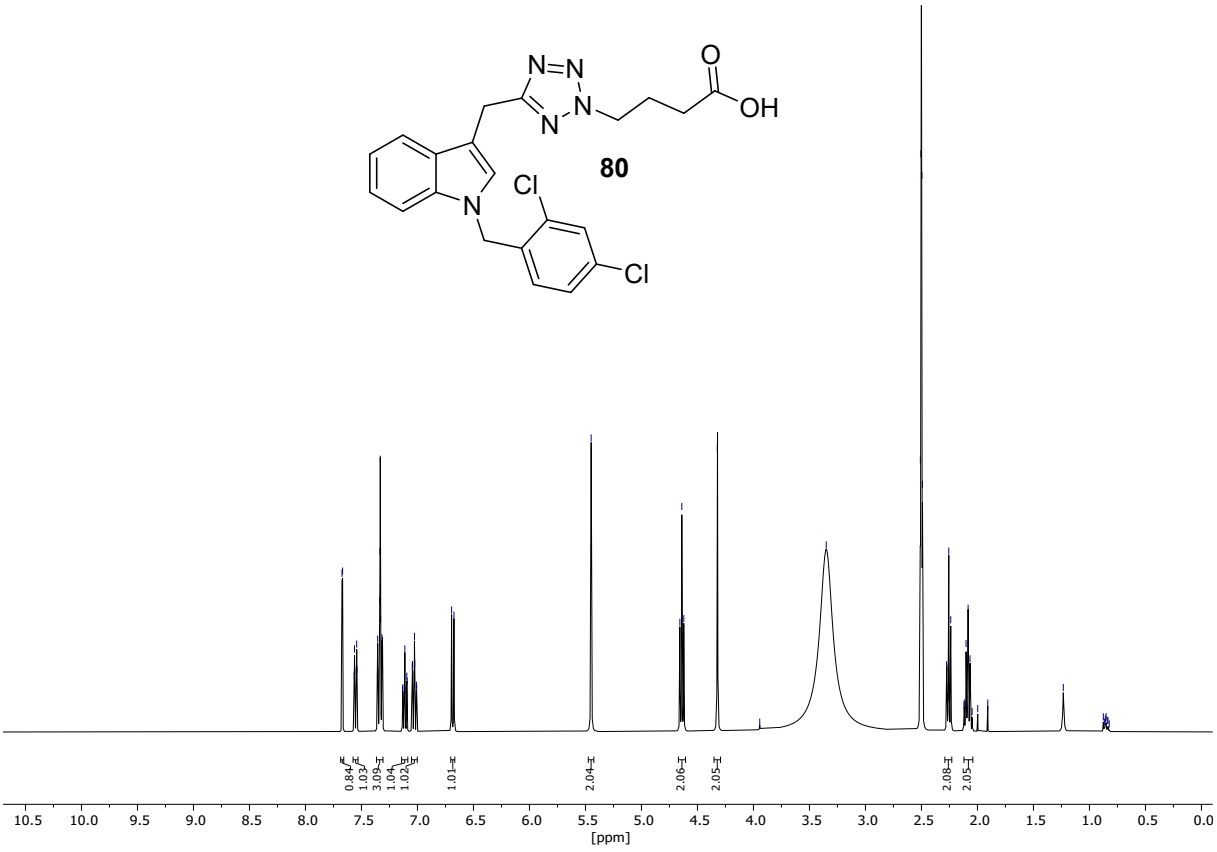

OH
O
N
N
N
N
Cl
N
Cl
74
0.80
1.95
0.80
1.01
0.97
2.01
1.00
2.04
2.02
2.02
2.12
2.01
2.02
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

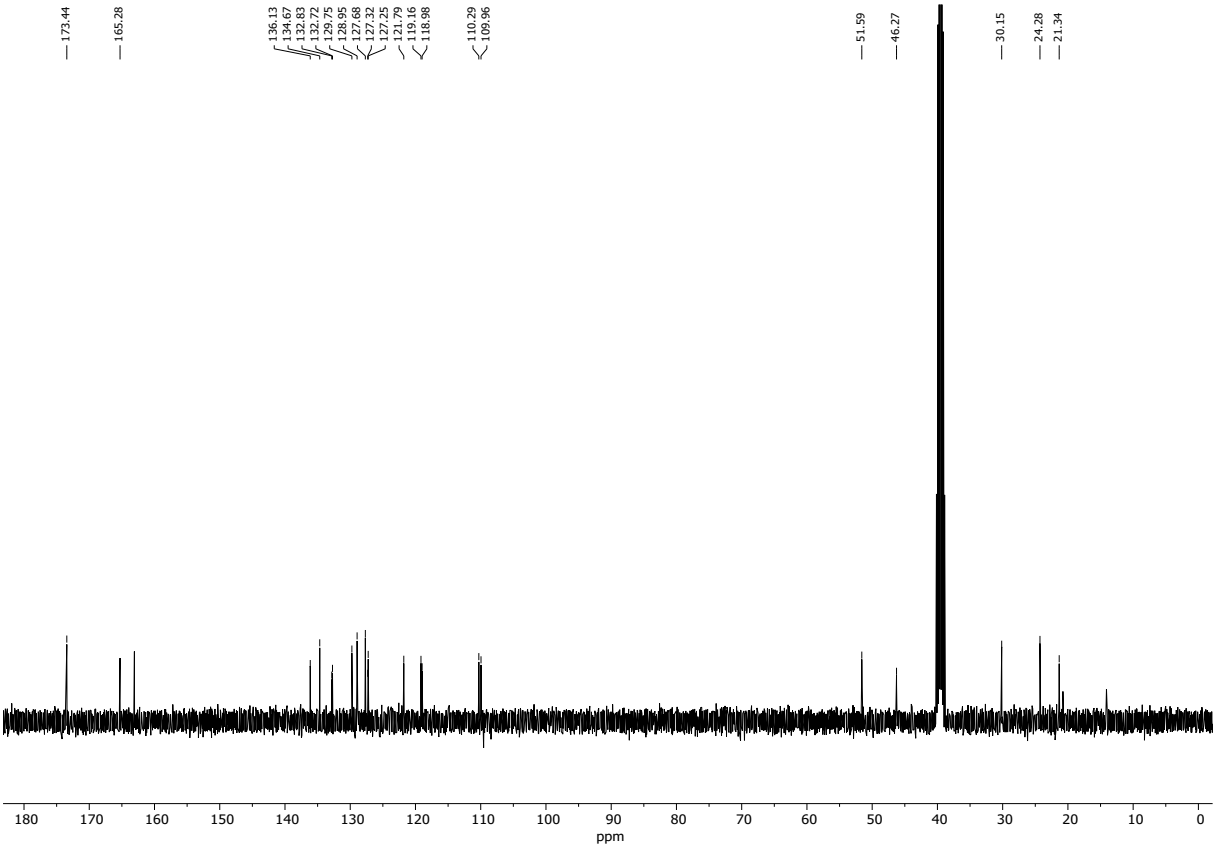

174.29
161.16
136.30
134.03
133.05
132.84
129.85
129.46
129.05
127.82
125.12
122.79
121.06
120.82
110.74
103.01
52.31
46.78
40.06
39.94 dmso
39.80 dmso
39.66 dmso
39.52 dmso
39.38 dmso
39.24 dmso
39.10 dmso
33.42
28.49
25.39
23.82
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

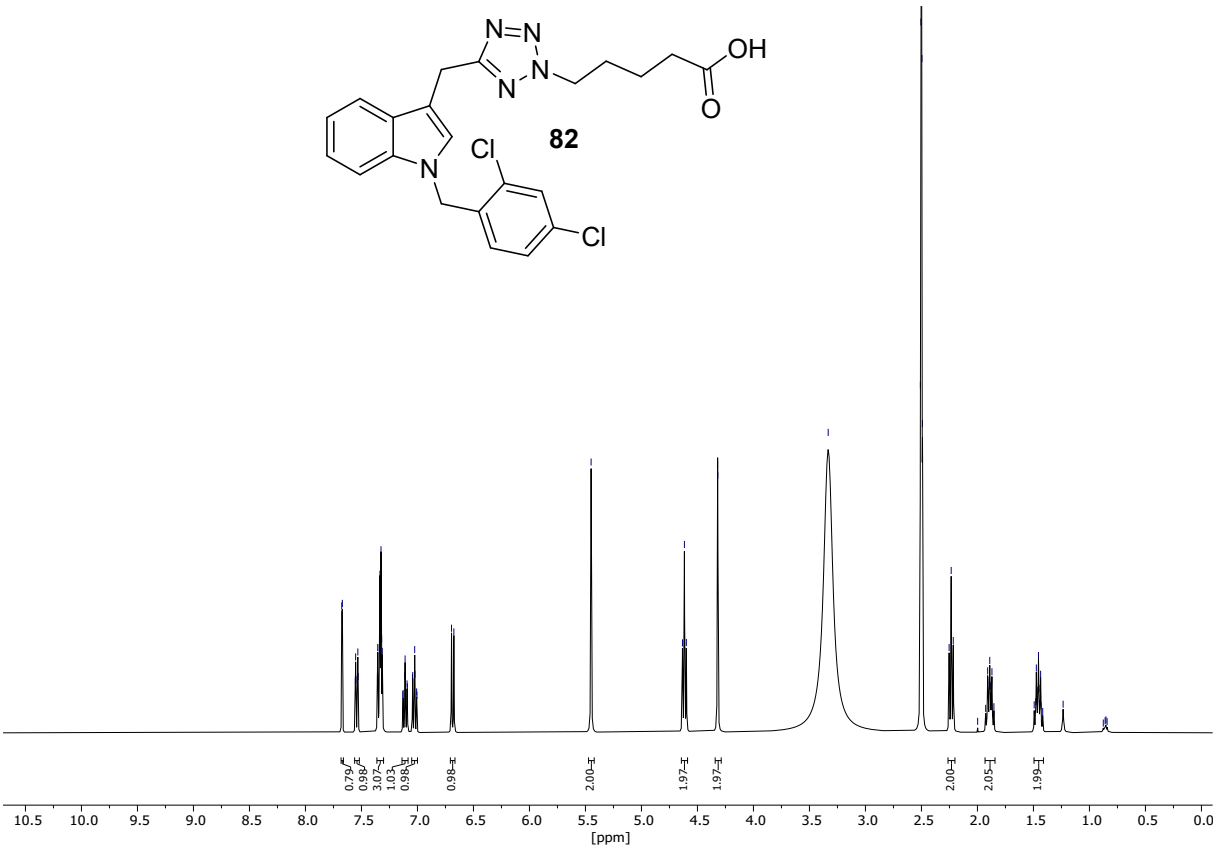

O
OH
N=N
N
N
Cl
N
Cl
78

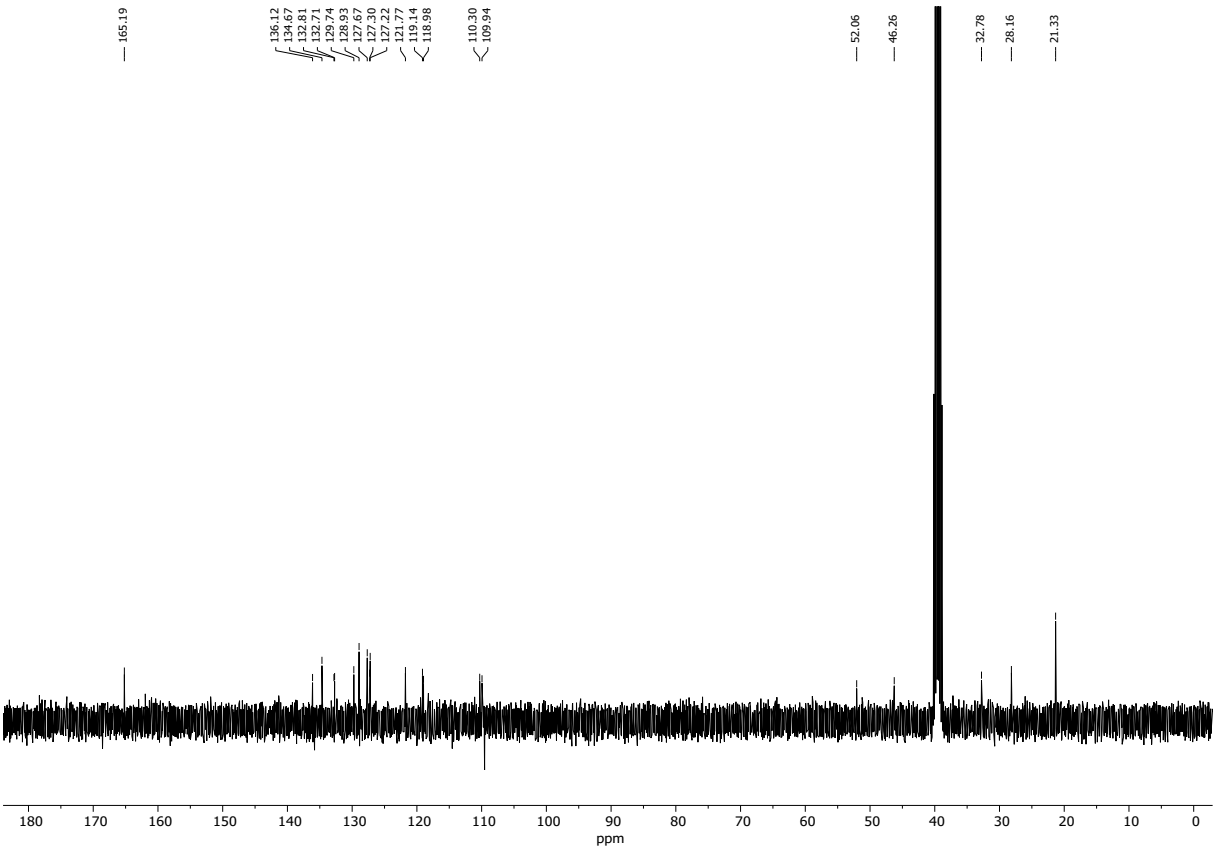
2.01
0.84
1.04
5.11
1.05
1.02
1.01
1.97
1.97
1.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

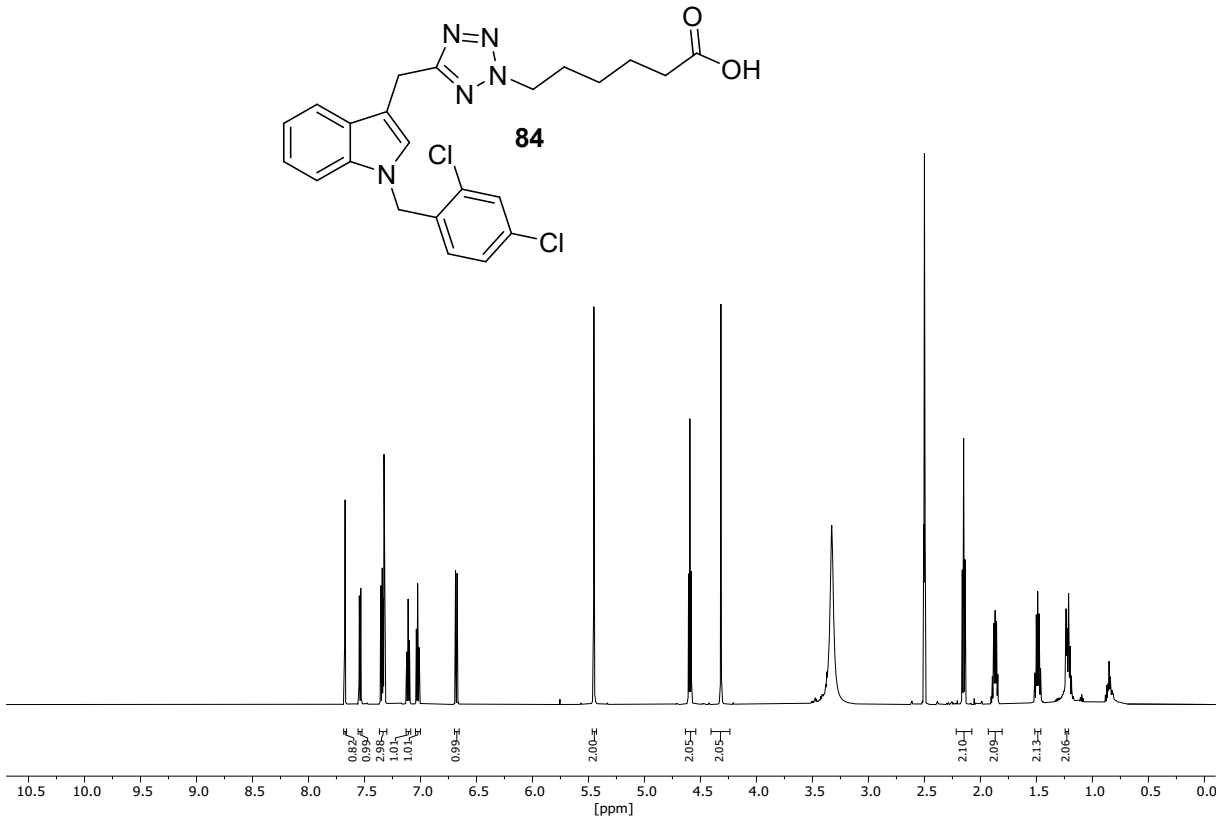

166.85
165.76
138.83
136.12
134.63
132.82
132.72
129.75
129.73
128.93
128.22
127.64
127.25
127.23
121.78
119.11
118.97
110.14
109.96
55.23
46.25
21.32
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


N=N
N
N
O
OH
Cl
N
Cl
80
0.84
1.03
3.09
1.04
1.02
1.01
2.04
2.06
2.05
2.08
2.05
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 1.0 0.5 0.0
[ppm]

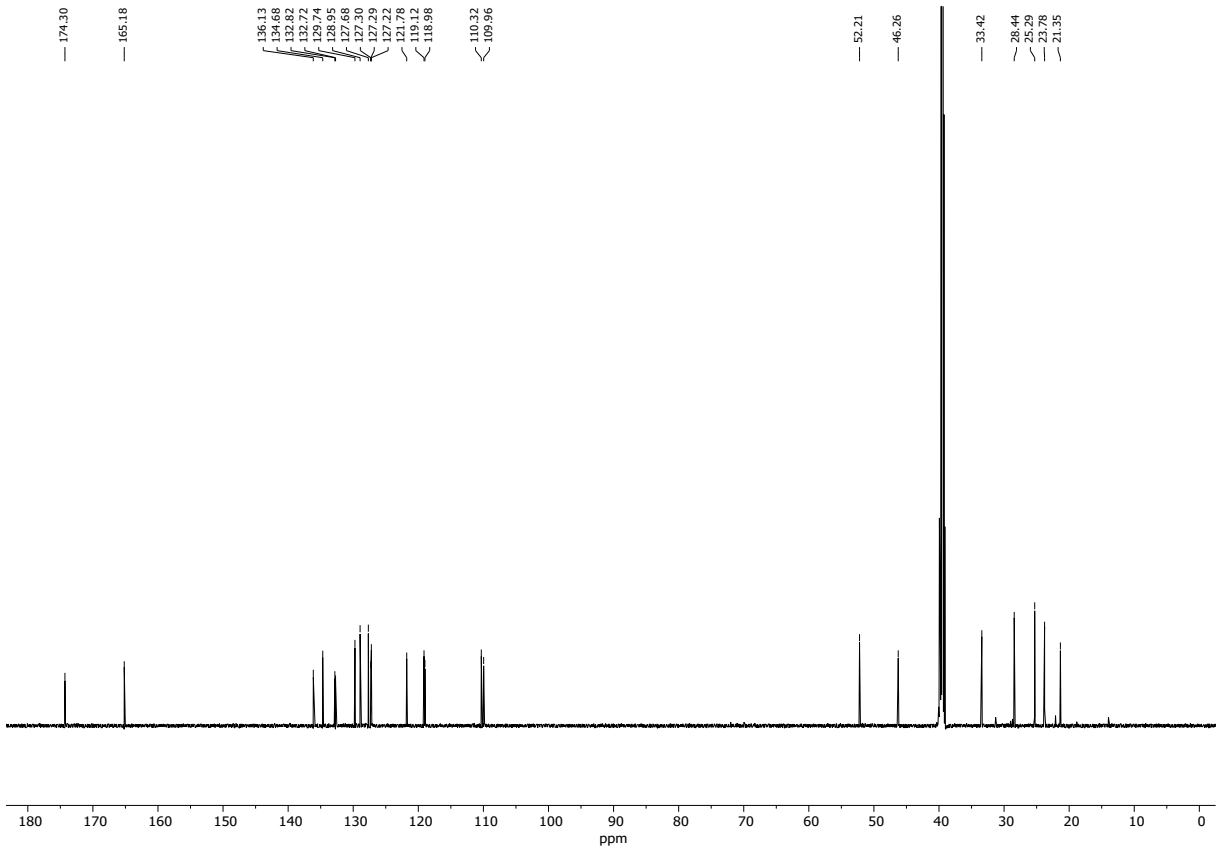

173.44
165.28
136.13
134.67
132.83
132.72
129.75
128.95
127.68
127.32
127.25
121.79
119.16
118.98
110.29
109.96
51.59
46.27
30.15
24.28
21.34
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

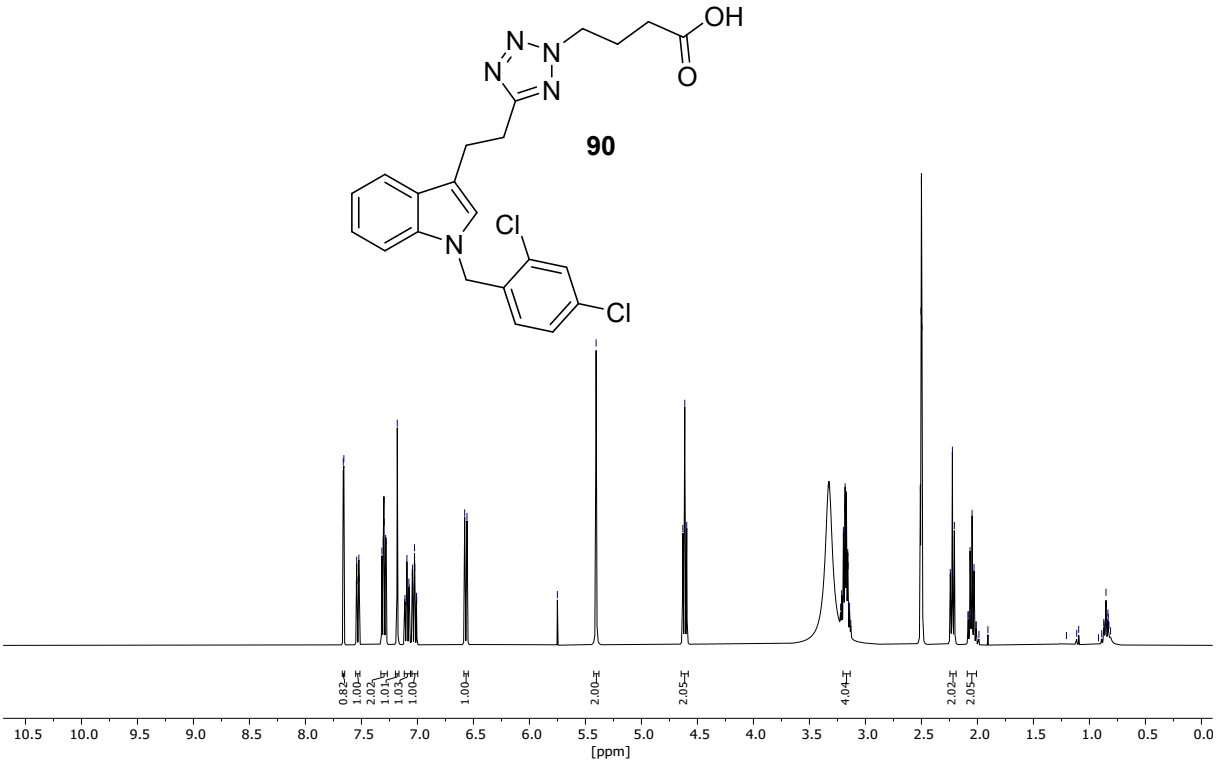

N=N
N
N
OH
O
Cl
N
Cl
82
0.79
0.98
3.07
1.03
0.98
0.98
2.00
1.97
1.97
2.00
2.05
1.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

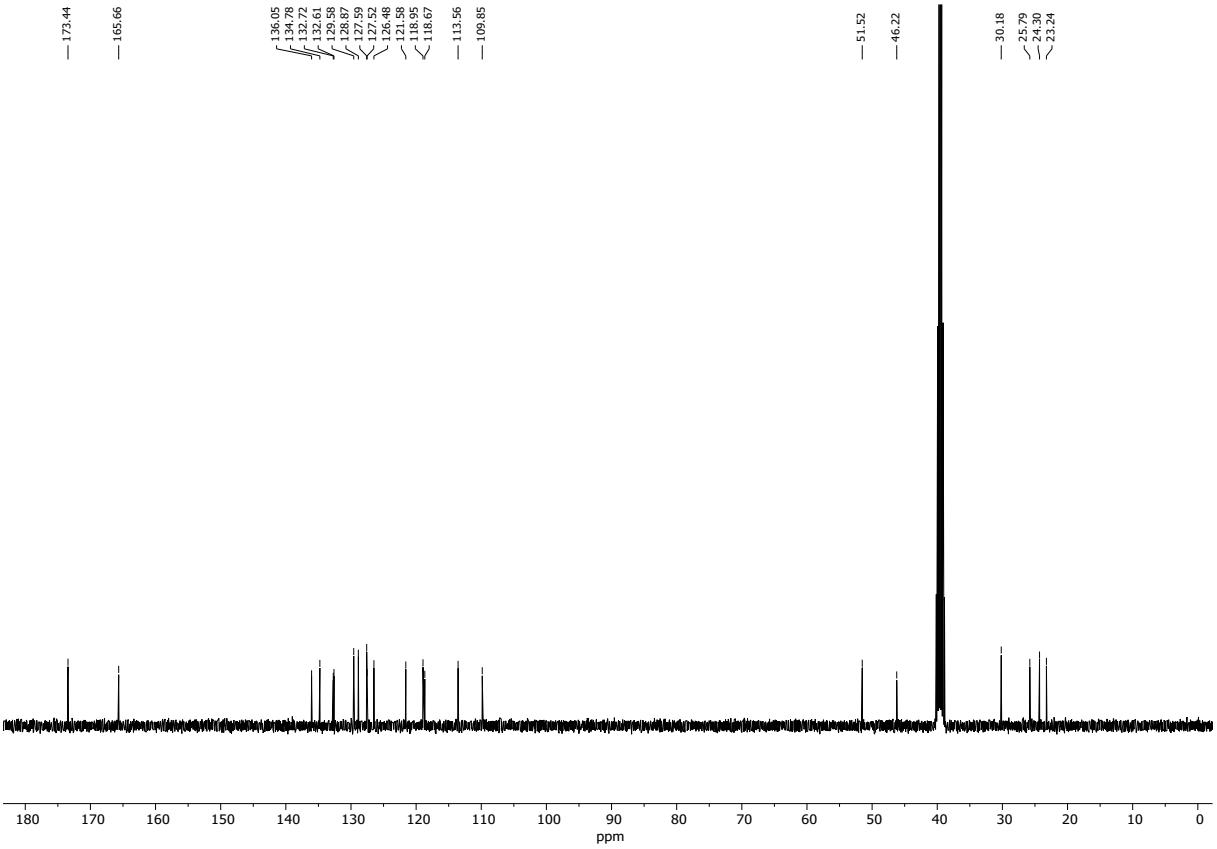

165.19
136.12
134.67
132.81
132.71
129.74
128.93
127.67
127.30
127.22
121.77
119.14
118.98
110.30
109.94
52.06
46.26
32.78
28.16
21.33
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

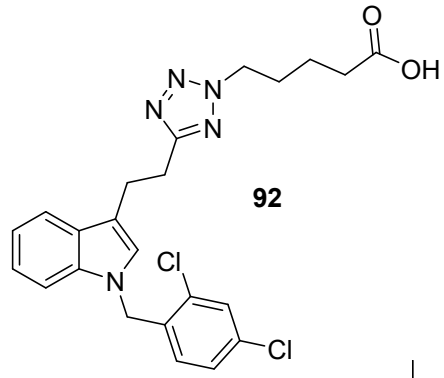

N=N
N
N
O
OH
Cl
N
Cl
0.82
0.99
2.98
1.01
1.01
0.99
2.00
2.05
2.05
2.10
2.09
2.13
2.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

84

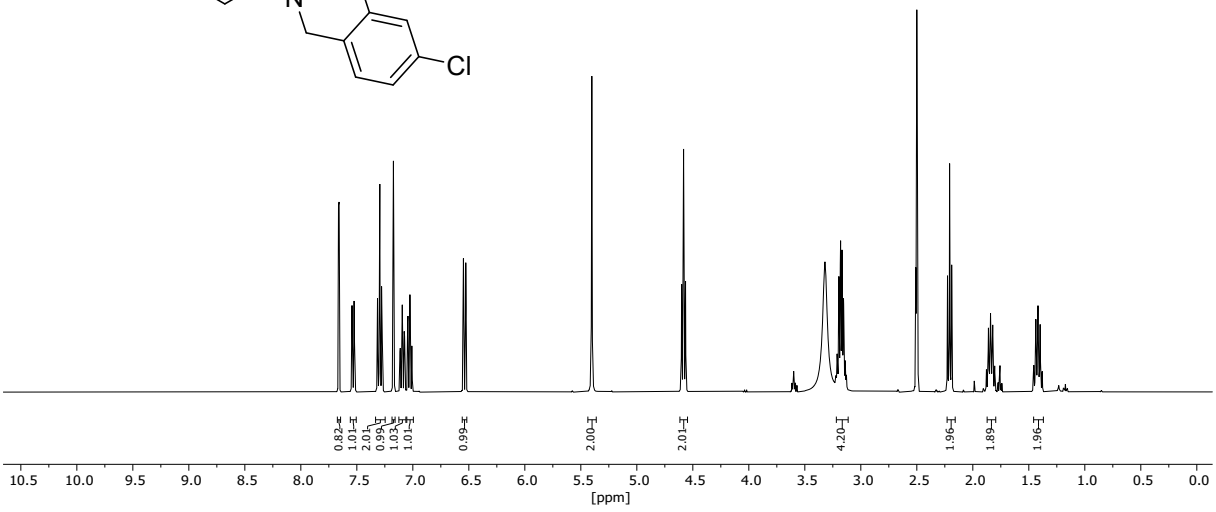

174.30
165.18
136.13
134.68
132.82
132.72
129.74
128.95
127.68
127.30
127.29
127.22
121.78
119.12
118.98
110.32
109.96
52.21
46.26
33.42
28.44
25.29
23.78
21.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

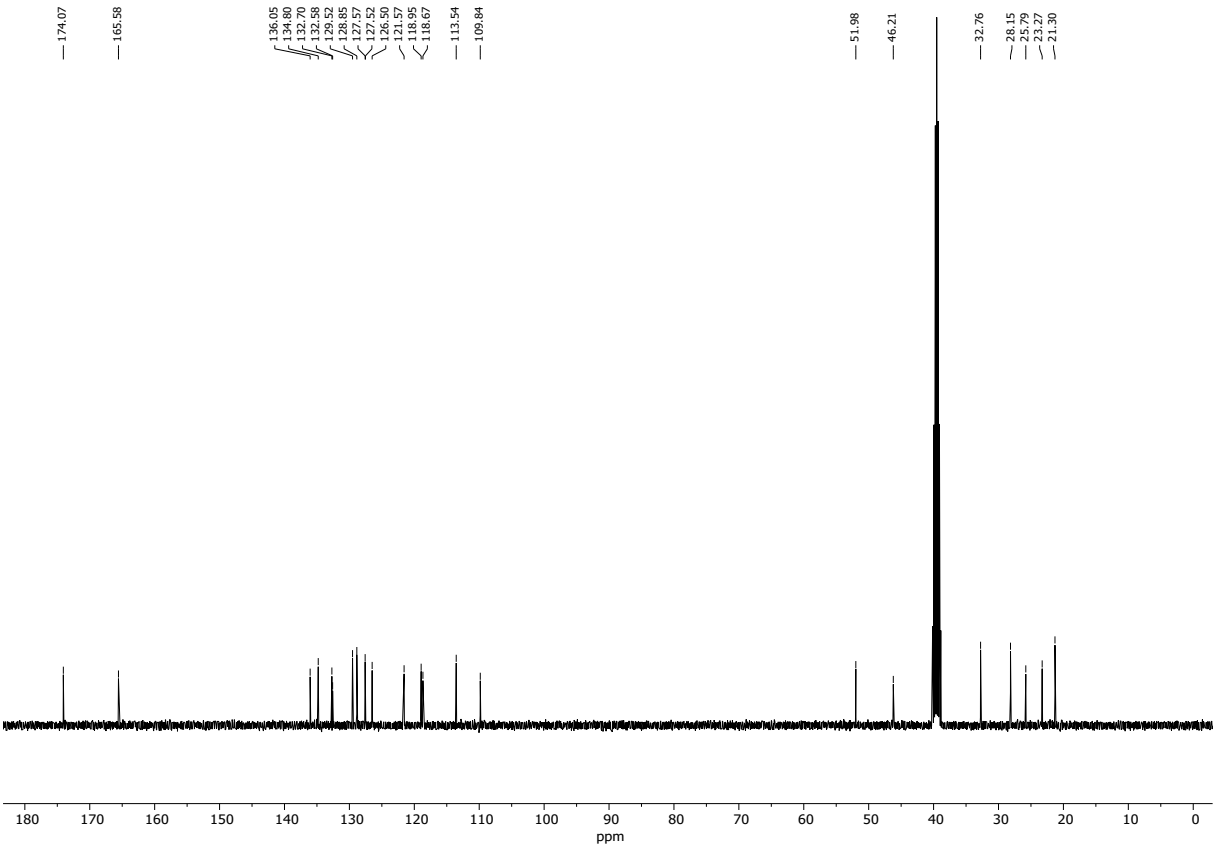

OH
O
N
N
N
N
Cl
N
Cl
90
0.82
1.00
2.02
1.01
1.03
1.00
1.00
2.00
2.05
4.04
2.02
2.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

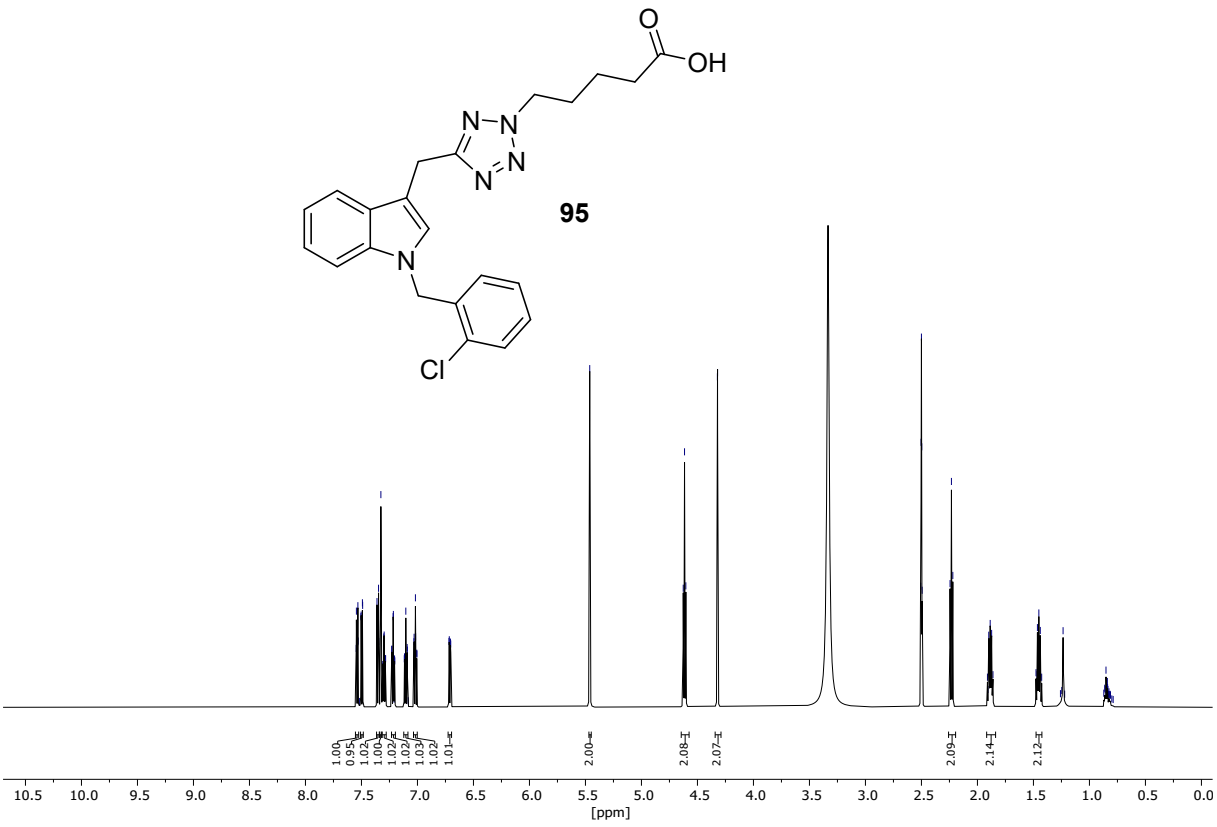

173.44
165.66
136.05
134.78
132.72
132.61
129.58
128.87
127.59
127.52
126.48
121.58
118.95
118.67
113.56
109.85
51.52
46.22
30.18
25.79
24.30
23.24
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

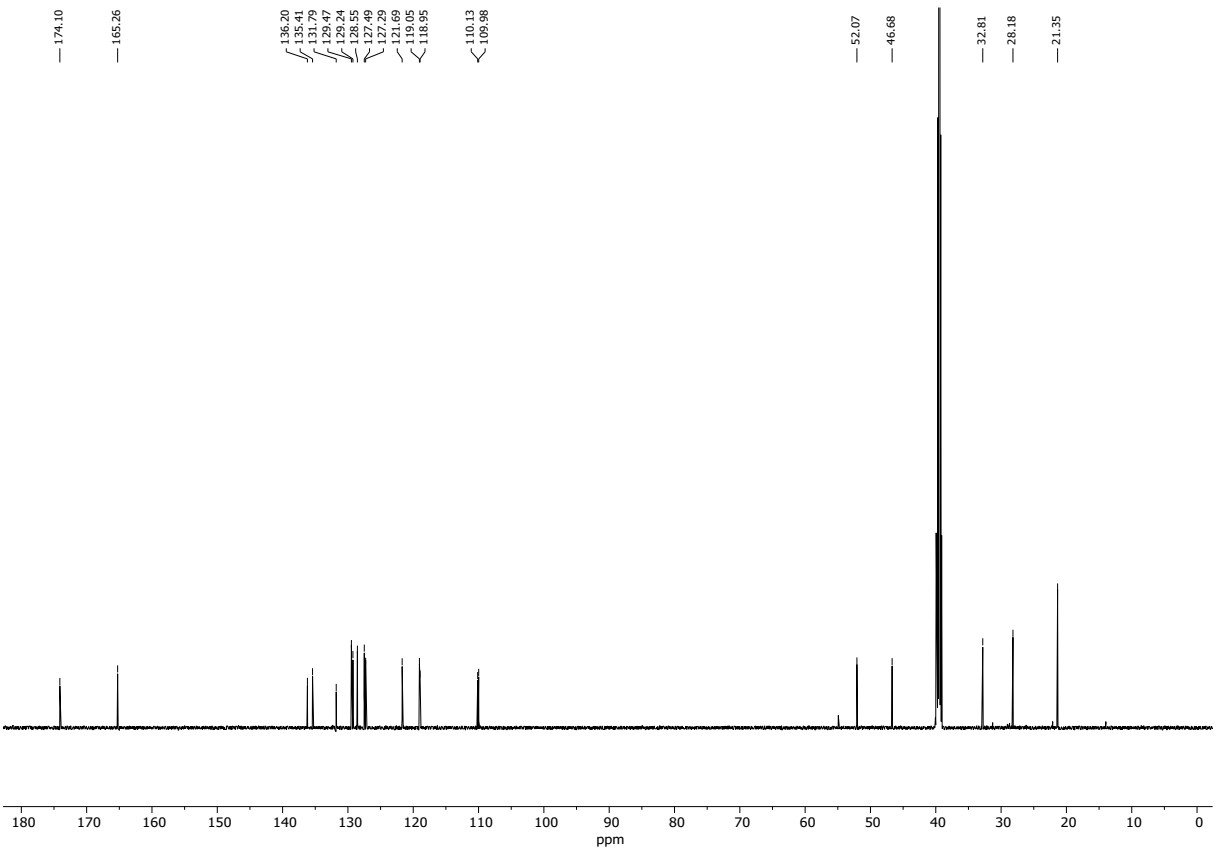

O
OH
N
N
N
N
N
Cl
Cl

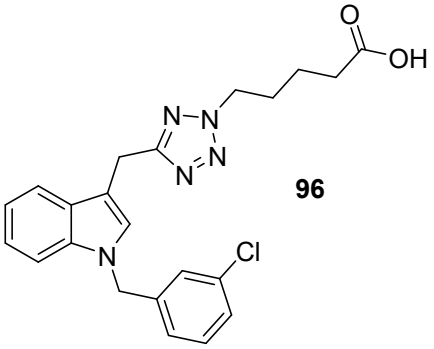
92


0.82
1.01
2.01
0.95
1.03
1.01
0.99
2.00
2.01
4.20
1.96
1.89
1.96
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 1.0 0.5 0.0
[ppm]

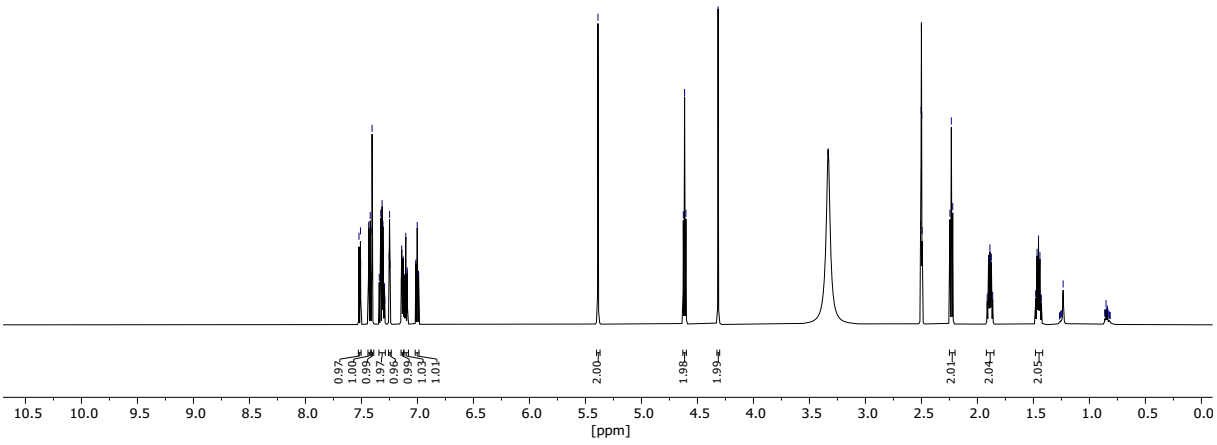

174.07
165.58
136.05
134.80
132.70
132.58
129.52
128.85
127.57
127.52
126.50
121.57
118.95
118.67
113.54
109.84
51.98
46.21
32.76
28.15
25.79
23.27
21.30
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

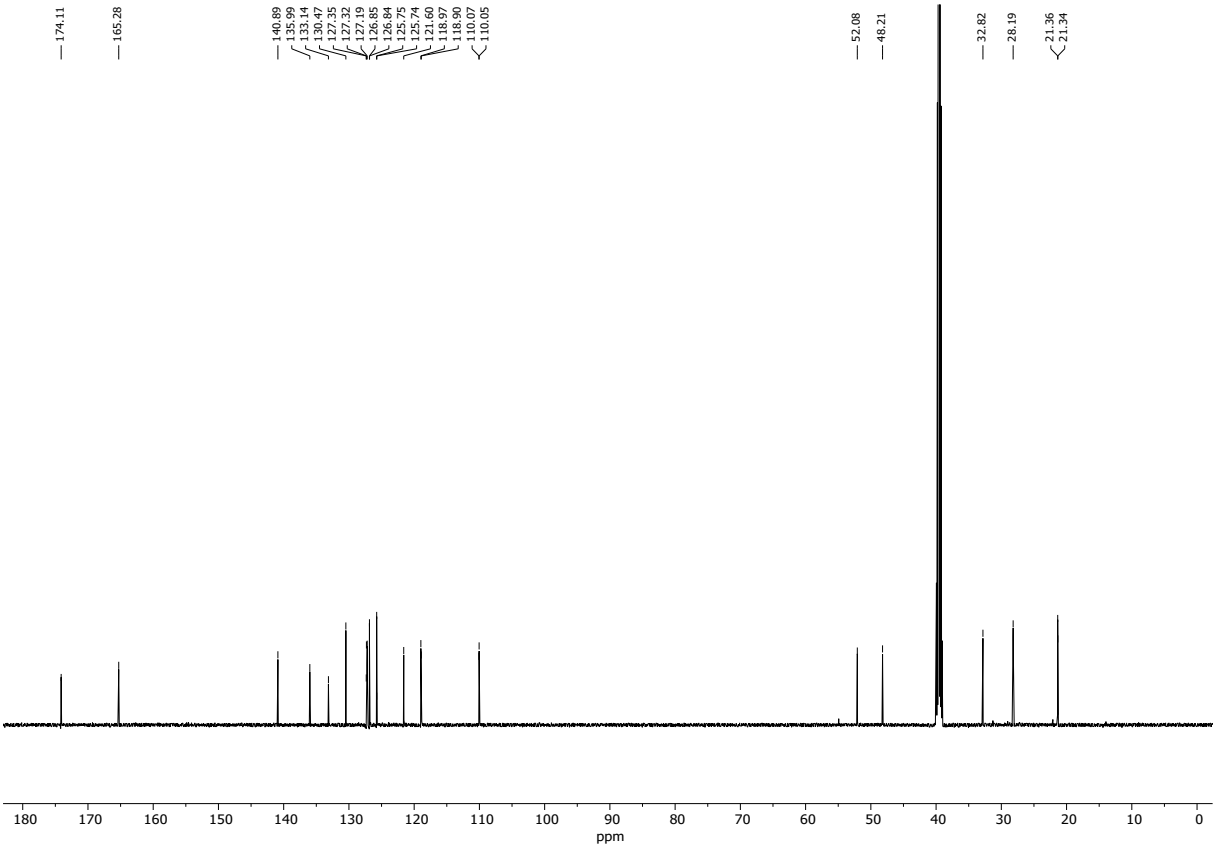

O
OH
N
N
N
N
N
Cl
95
1.00
0.95
1.02
1.00
1.02
1.02
1.03
1.02
1.01
2.00
2.08
2.07
2.09
2.14
2.12
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

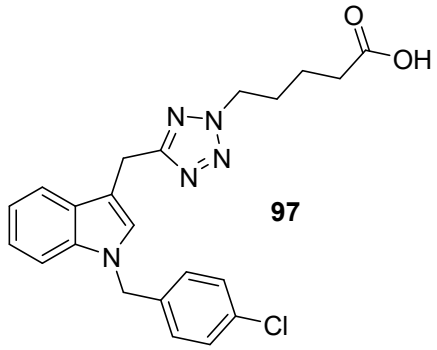

174.10
165.26
136.20
135.41
131.79
129.47
129.24
128.55
127.49
127.29
121.69
119.05
118.95
110.13
109.98
52.07
46.68
32.81
28.18
21.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
Cl

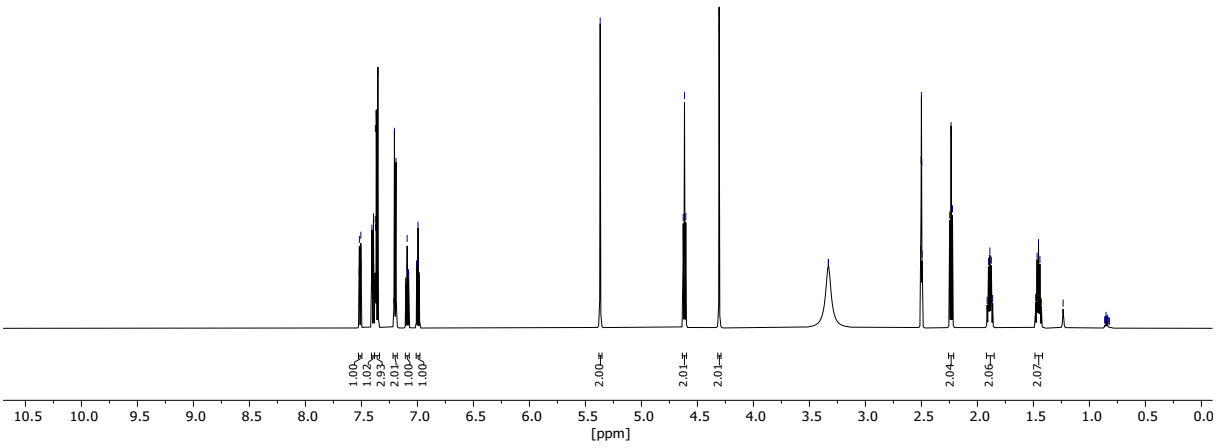
96

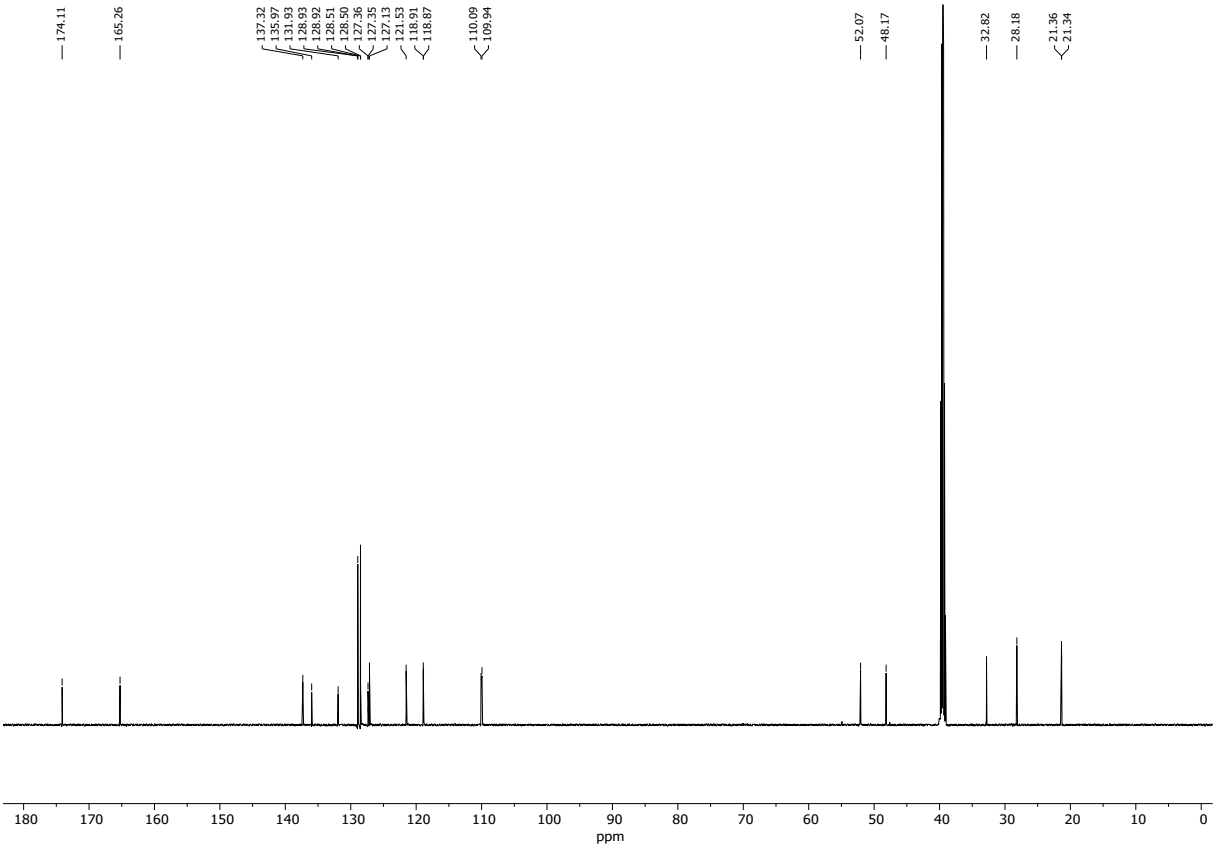

0.97
1.00
0.99
1.97
0.96
0.99
1.03
1.01
2.00
1.98
1.99
2.01
2.04
2.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

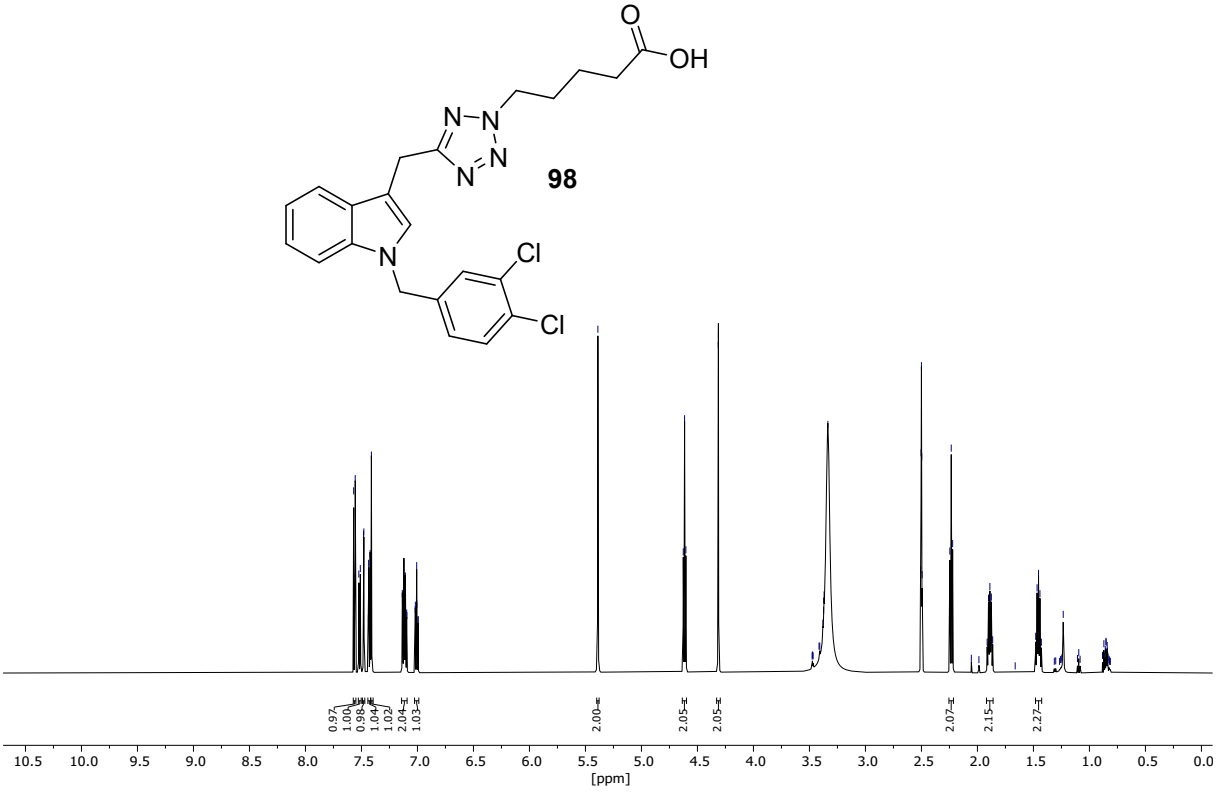

174.11
165.28
140.89
135.99
133.14
130.47
127.35
127.32
127.19
126.85
126.84
125.75
125.74
121.60
118.97
118.90
110.07
110.05
52.08
48.21
32.82
28.19
21.36
21.34
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

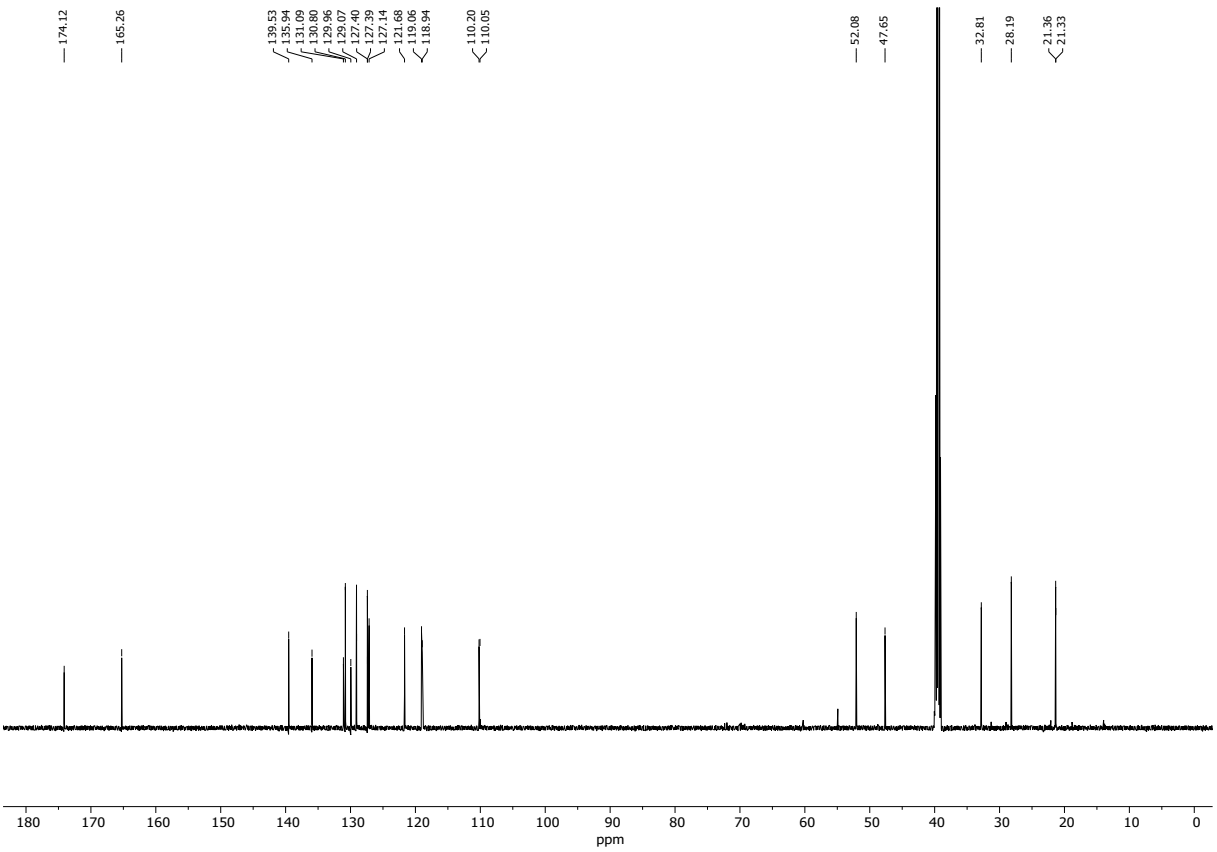

O
OH
N
N
N
N
N
Cl

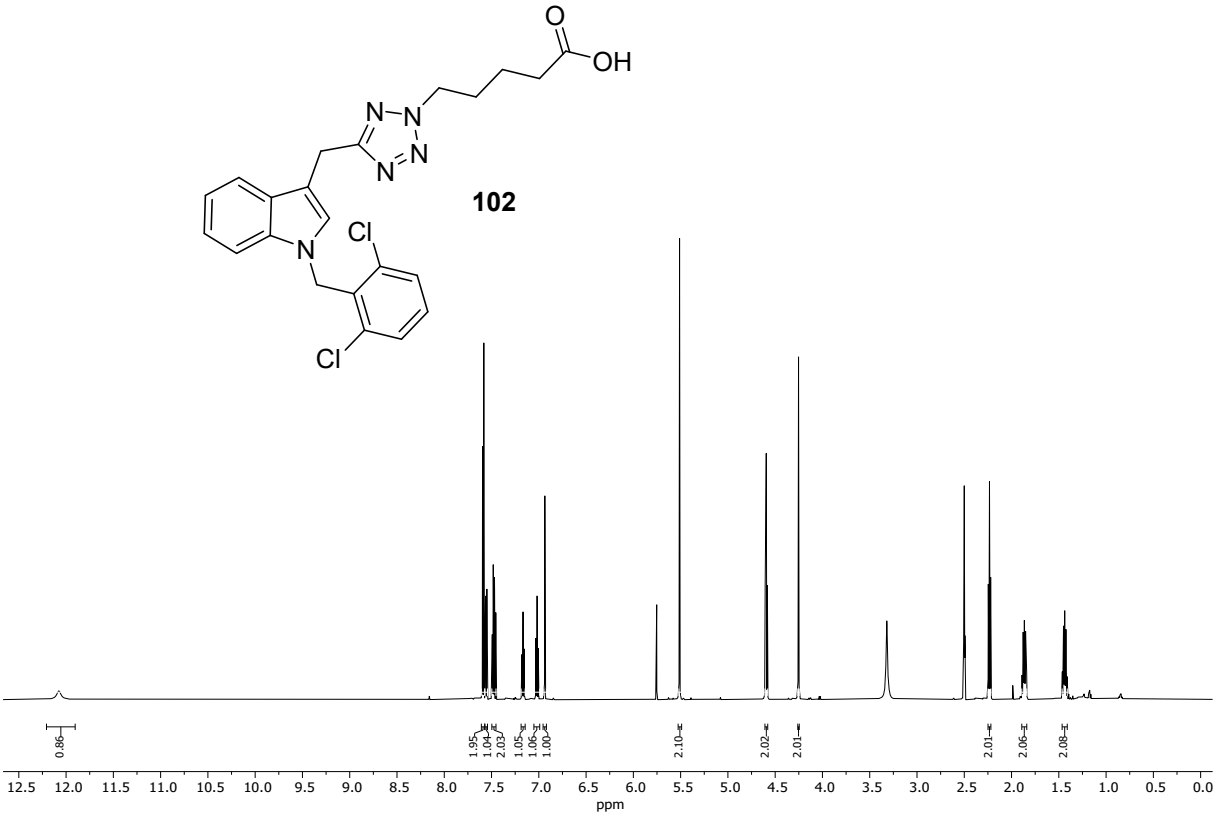
97


1.00
1.02
2.93
2.01
1.00
1.00
2.00
2.01
2.01
2.04
2.06
2.07
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 1.0 0.5 0.0
[ppm]

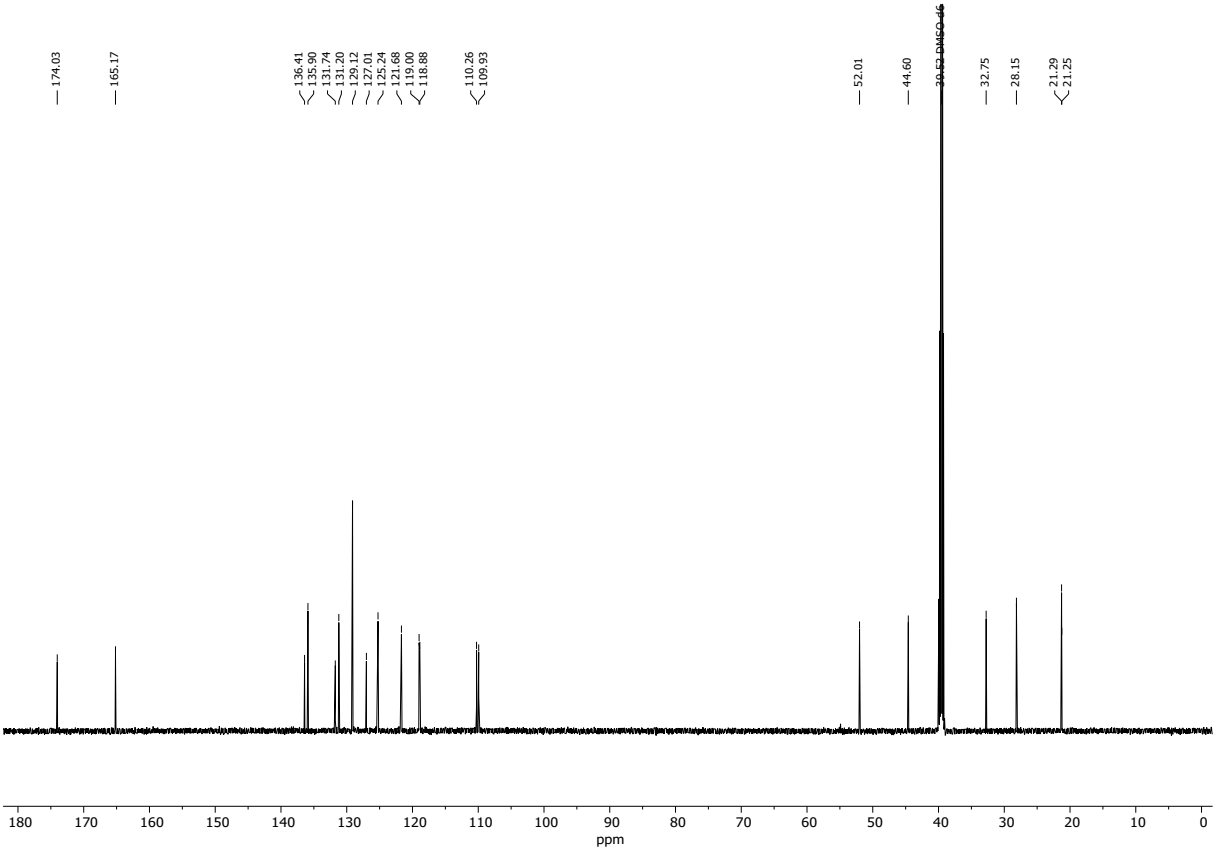

174.11
165.26
137.32
135.97
131.93
128.93
128.92
128.51
128.50
127.36
127.35
127.13
121.53
118.91
118.87
110.09
109.94
52.07
48.17
32.82
28.18
21.36
21.34
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

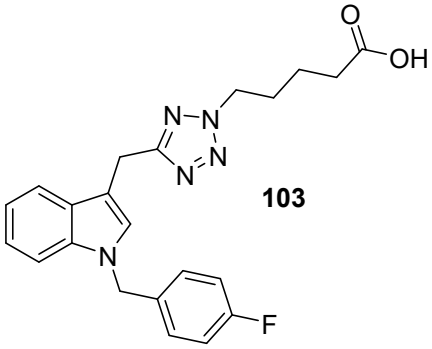

O
OH
N
N
N
N
98
N
Cl
Cl
0.97
1.00
0.98
1.04
1.02
2.04
1.03
2.00
2.05
2.05
2.07
2.15
2.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]


174.12
165.26
139.53
135.94
131.09
130.80
129.96
129.07
127.40
127.39
127.14
121.68
119.06
118.94
110.20
110.05
52.08
47.65
32.81
28.19
21.36
21.33
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

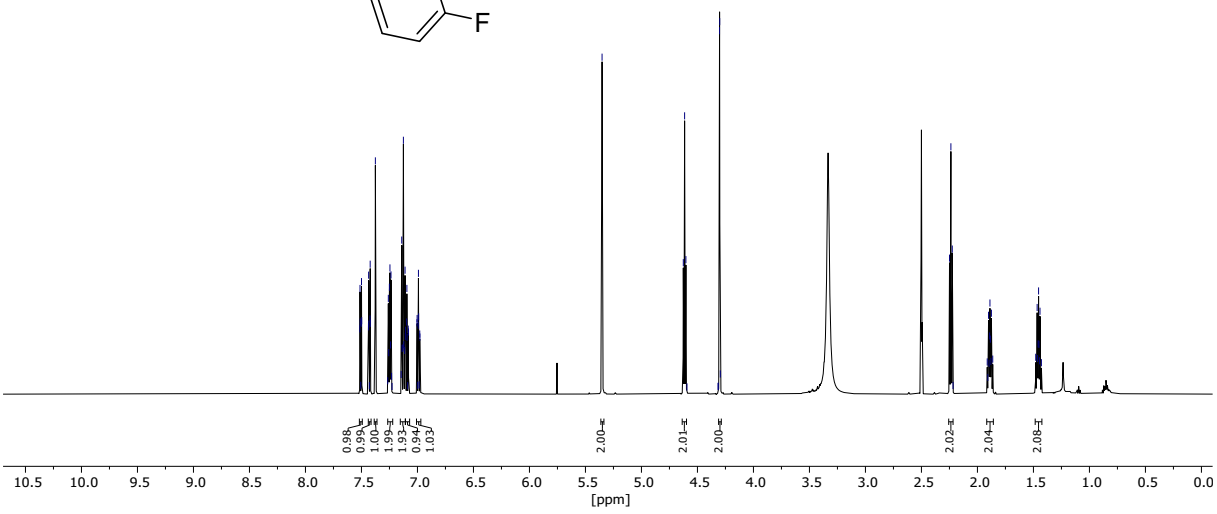

O
OH
N
N
N
N
Cl
N
Cl
0.86
1.95
1.04
2.03
1.05
1.06
1.00
2.10
2.02
2.01
2.01
2.06
2.08
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

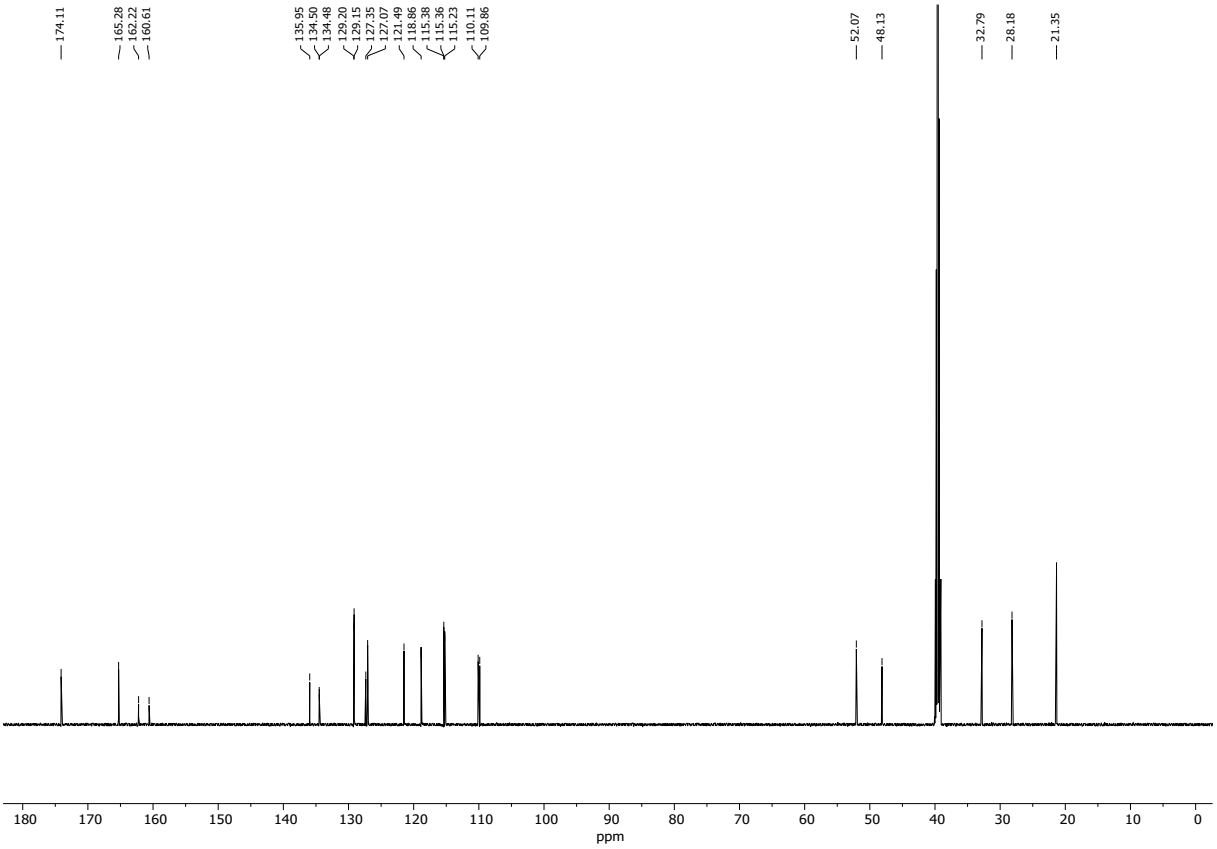
102

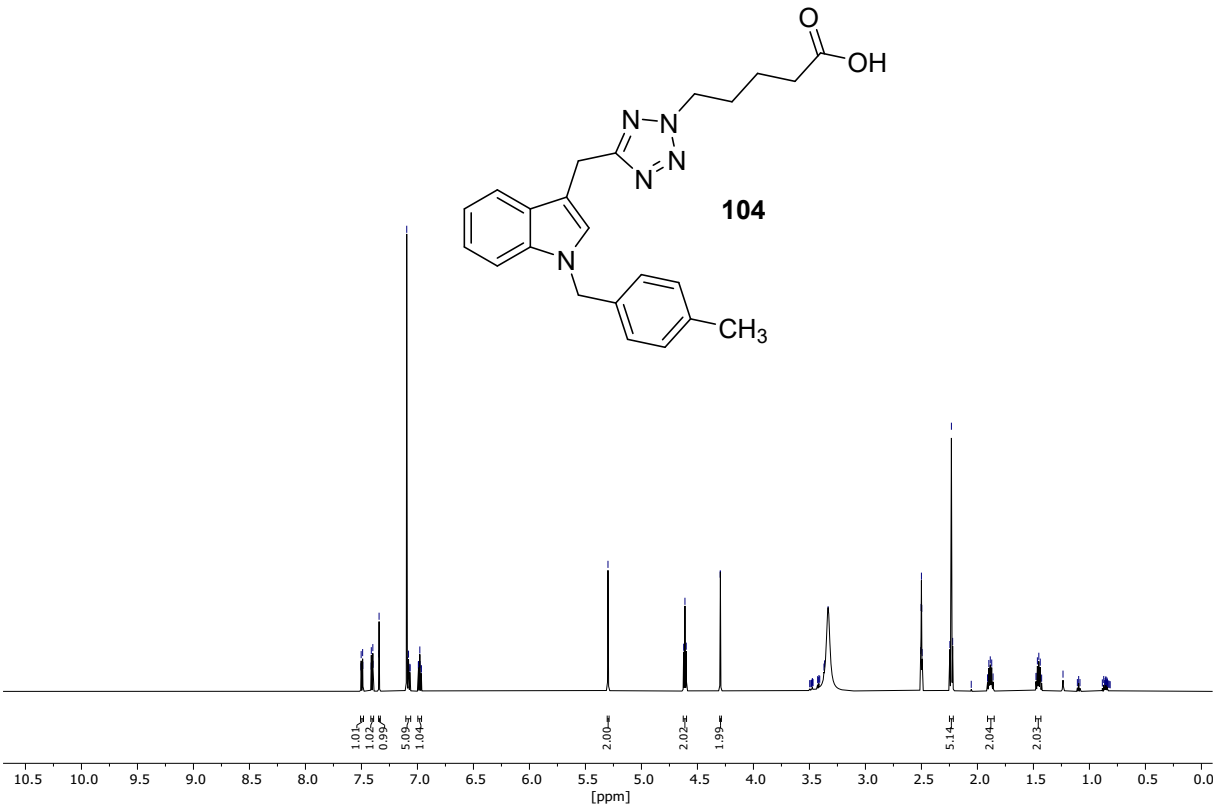

174.03
165.17
136.41
135.90
131.74
131.20
129.12
127.01
125.24
121.68
119.00
118.88
110.26
109.93
52.01
44.60
39.83 DMSO-d6
32.75
28.15
21.29
21.25
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

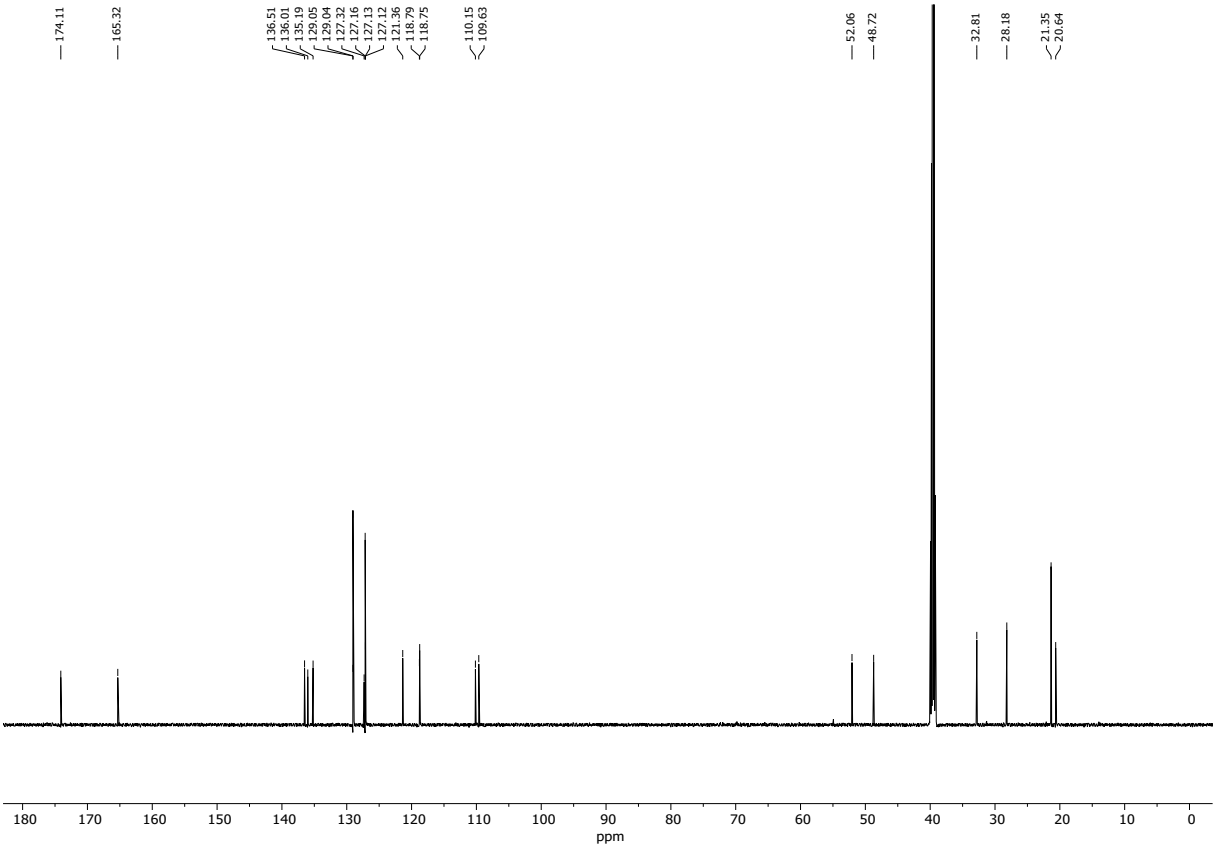

O
OH
N
N
N
N
N
F

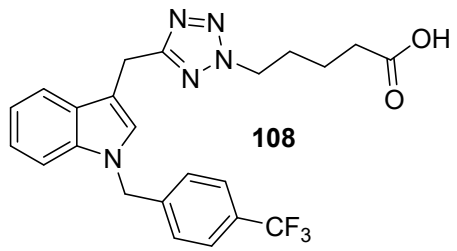
103


0.98
0.99
1.00
1.99
1.93
0.94
1.03
2.00
2.01
2.00
2.02
2.04
2.08
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 1.0 0.5 0.0
[ppm]

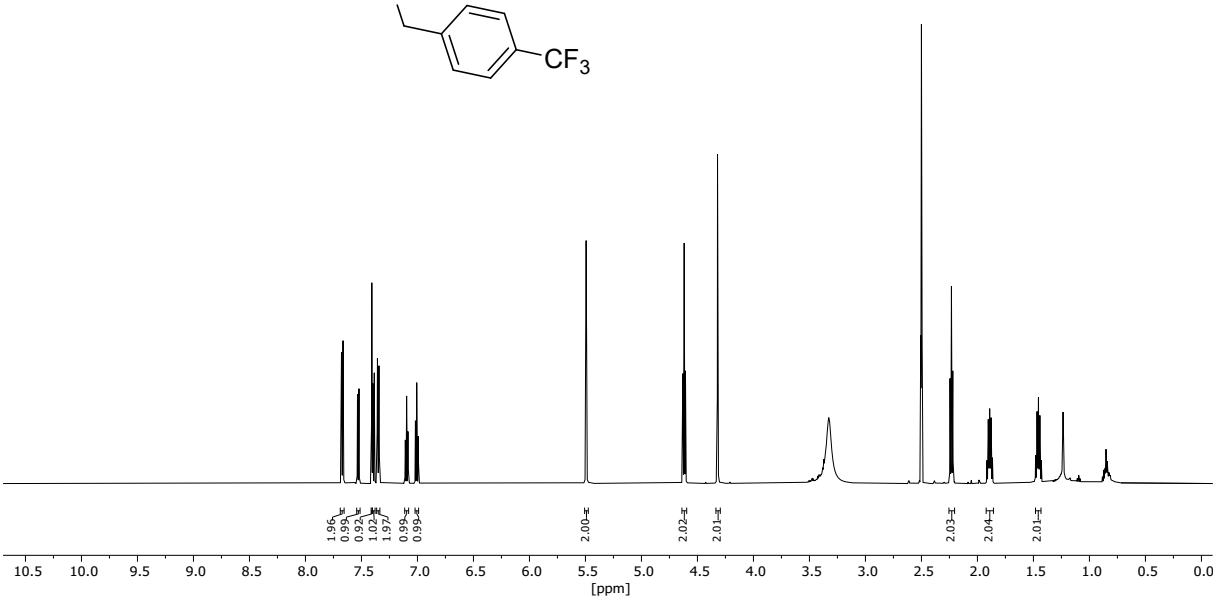

174.11
165.28
162.22
160.61
135.95
134.50
134.48
129.20
129.15
127.35
127.07
121.49
118.86
115.38
115.36
115.23
110.11
109.86
52.07
48.13
32.79
28.18
21.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

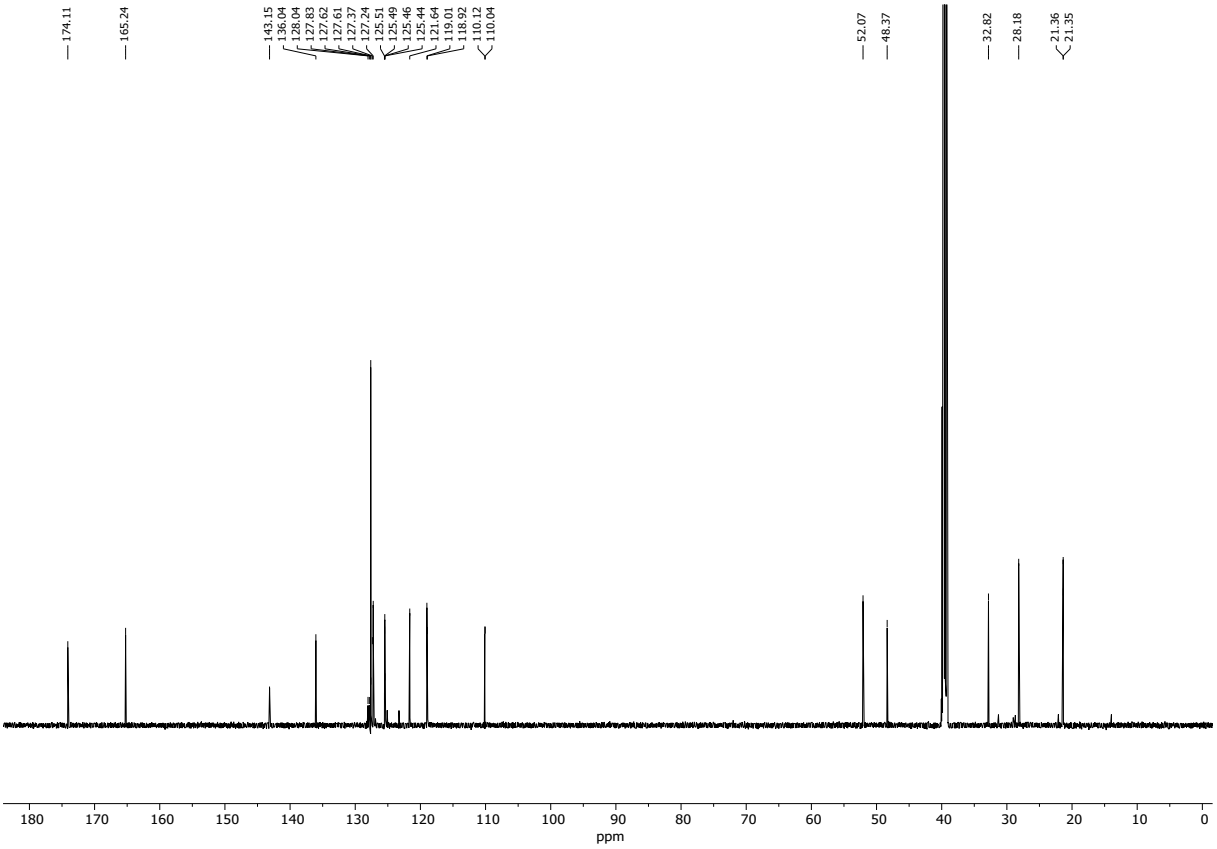

O
OH
N
N
N
N
104
N
CH3
1.01
1.02
0.99
5.09
1.04
2.00
2.02
1.99
5.14
2.04
2.03
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

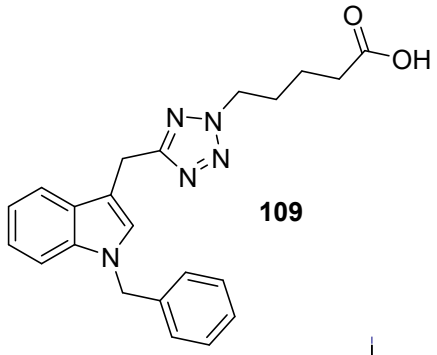

174.11
165.32
136.51
136.01
135.19
129.05
129.04
127.32
127.16
127.13
127.12
121.36
118.79
118.75
110.15
109.63
52.06
48.72
32.81
28.18
21.35
20.64
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


N=N
N
N
OH
O
N
CF3

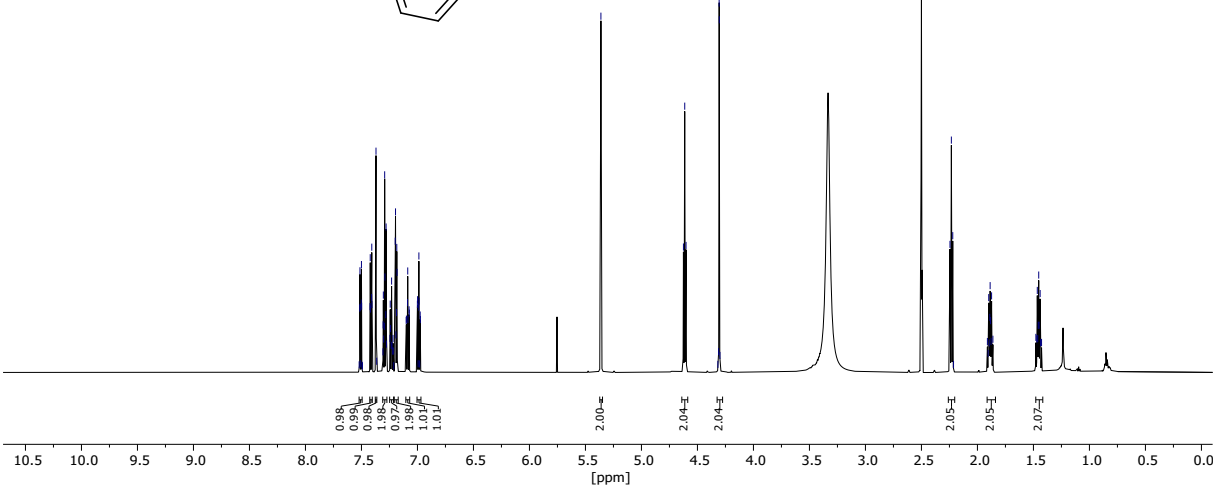
108

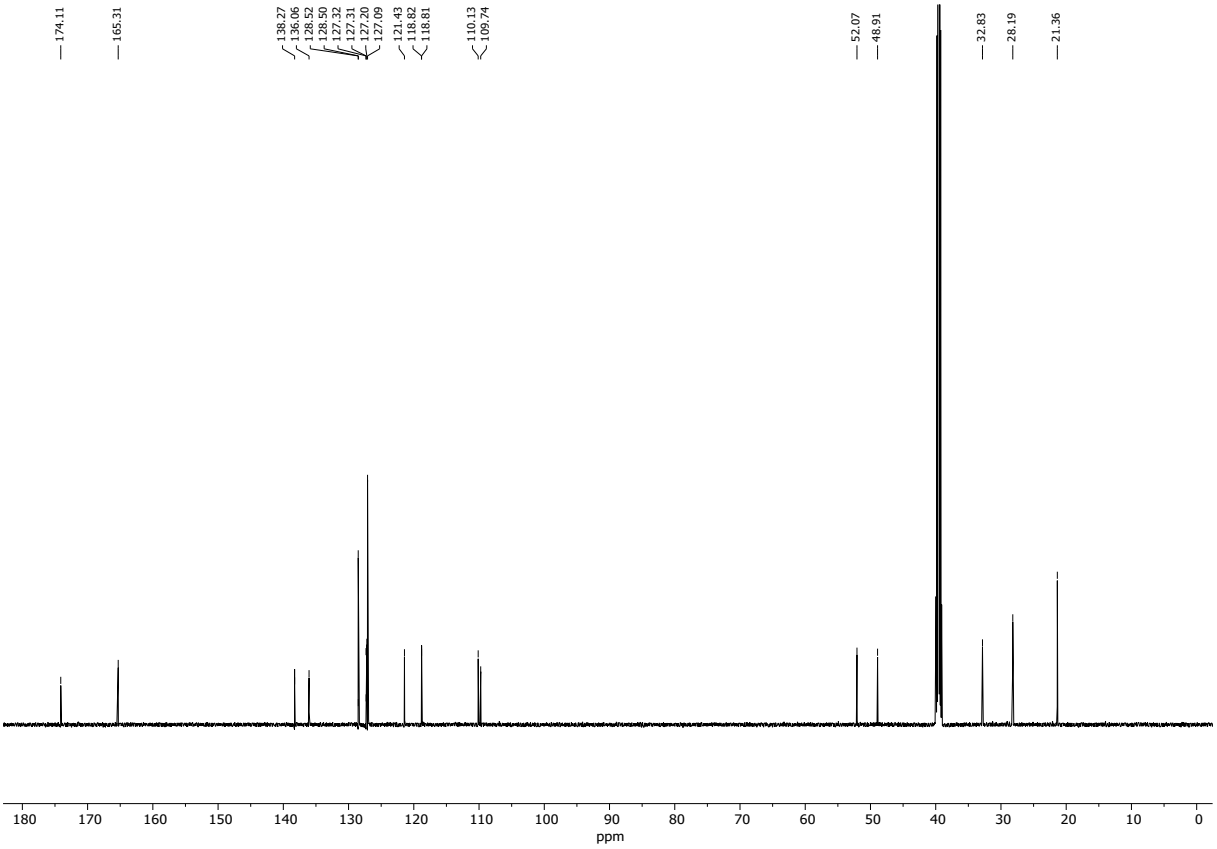

1.96
0.99
0.92
1.02
1.97
0.99
0.99
2.00
2.02
2.01
2.03
2.04
2.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

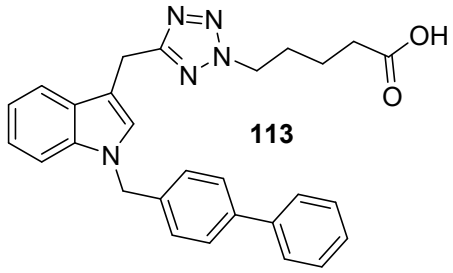

174.11
165.24
143.15
136.04
128.04
127.83
127.62
127.61
127.37
127.24
125.51
125.49
125.46
125.44
121.64
119.01
118.92
110.12
110.04
52.07
48.37
32.82
28.18
21.36
21.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
N

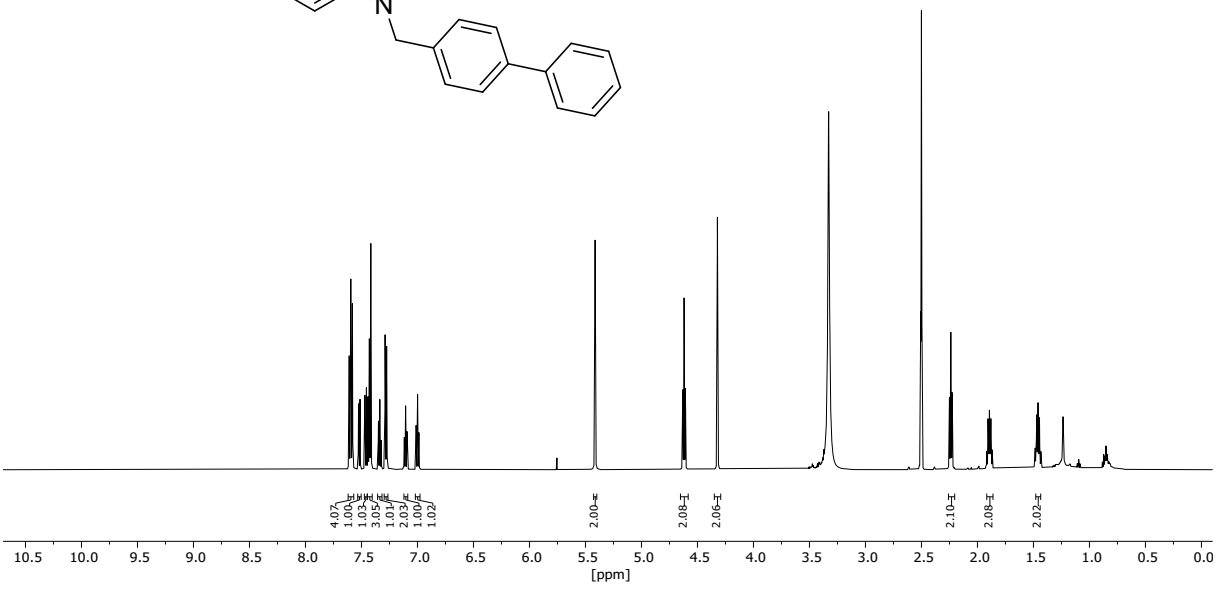
109

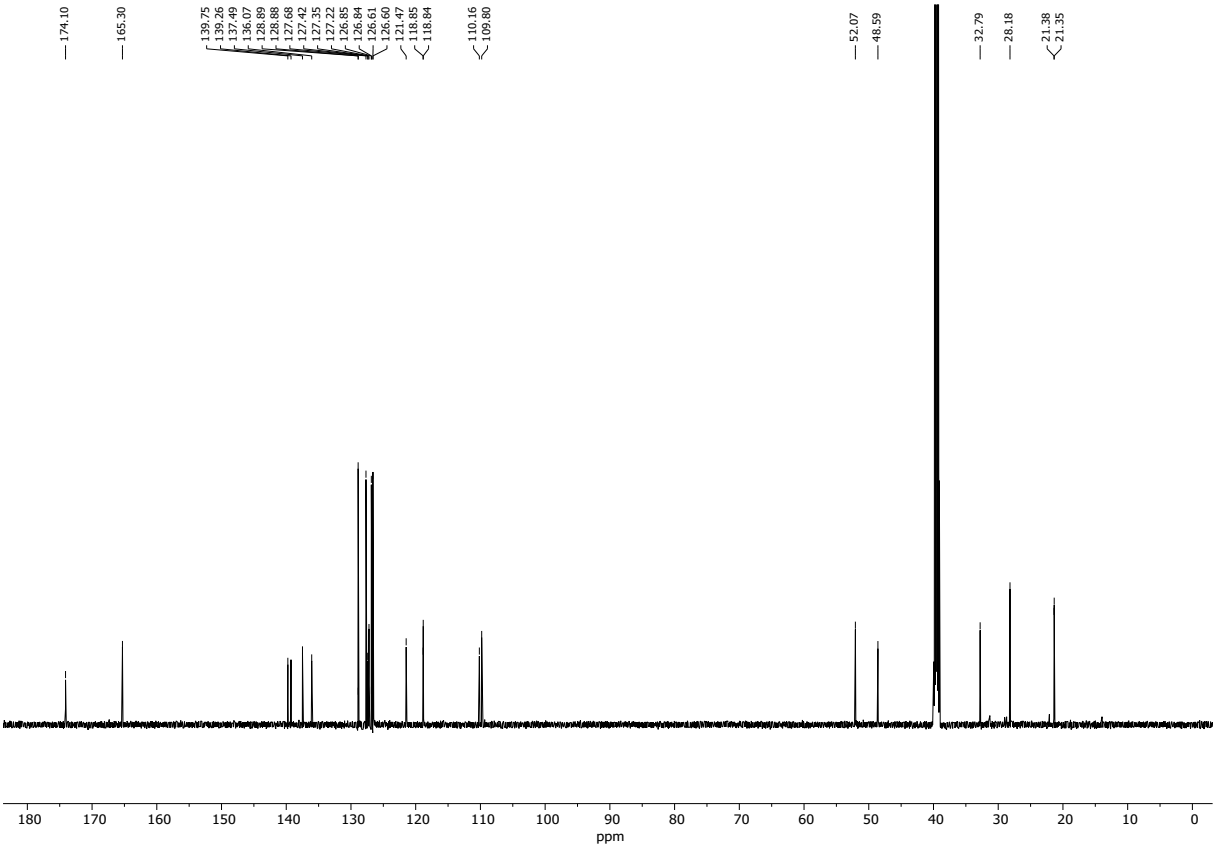

0.98
0.99
0.98
1.98
0.97
1.98
1.01
1.01
2.00
2.04
2.04
2.05
2.05
2.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

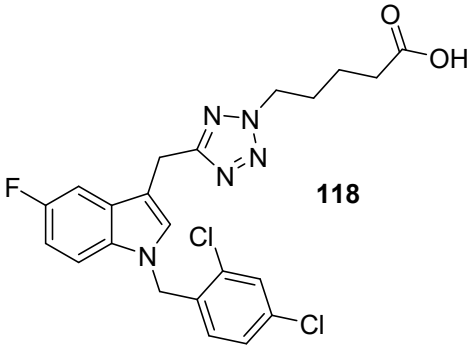

174.11
165.31
138.27
136.06
128.52
128.50
127.32
127.31
127.20
127.09
121.43
118.82
118.81
110.13
109.74
52.07
48.91
32.83
28.19
21.36
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


N=N
N
N
OH
O
N

113

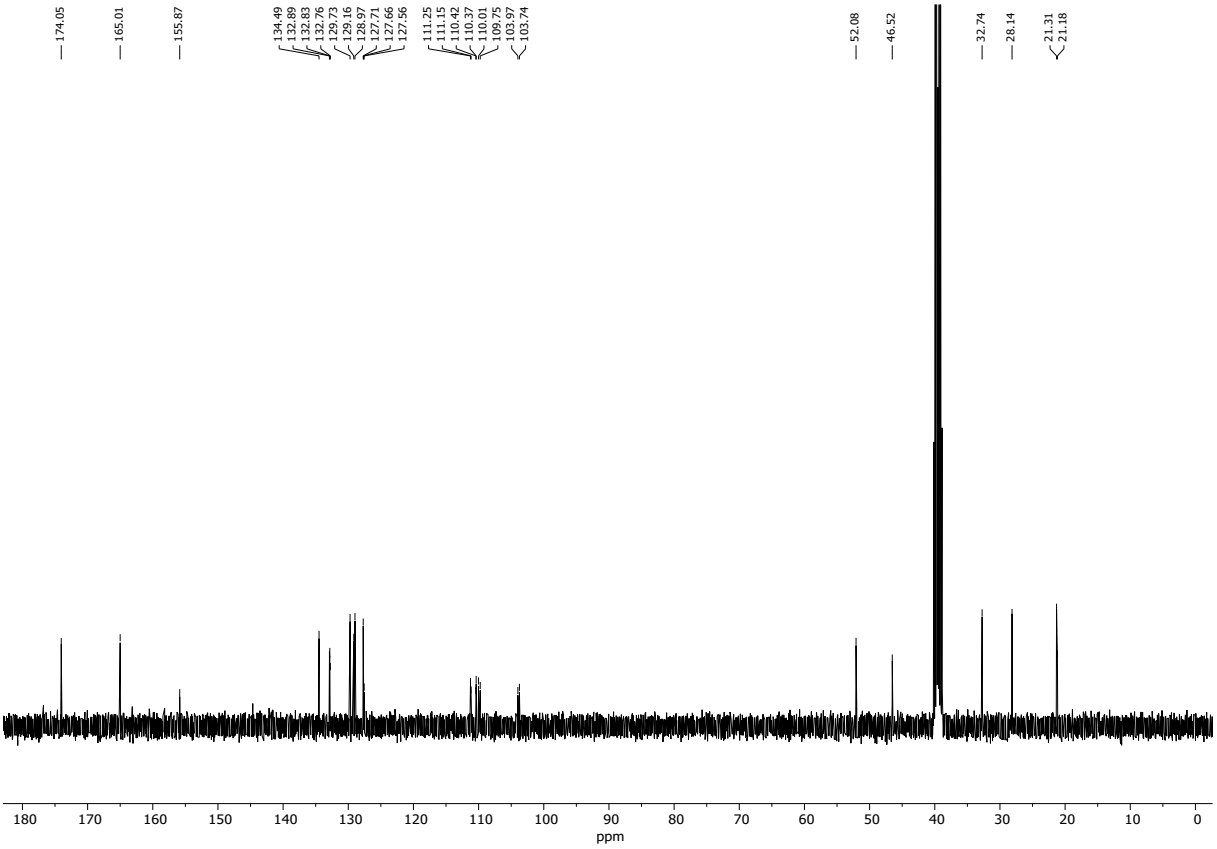

4.07
1.00
1.03
3.05
1.01
2.03
1.00
1.02
2.00
2.08
2.06
2.10
2.08
2.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

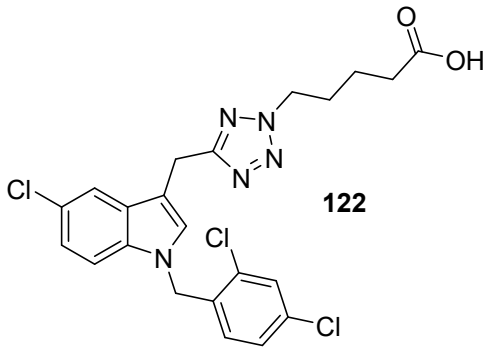

174.10
165.30
139.75
139.26
137.49
136.07
128.89
128.88
127.68
127.42
127.35
127.22
126.85
126.84
126.61
126.60
121.47
118.85
118.84
110.16
109.80
52.07
48.59
32.79
28.18
21.38
21.35
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
F
Cl
N
Cl

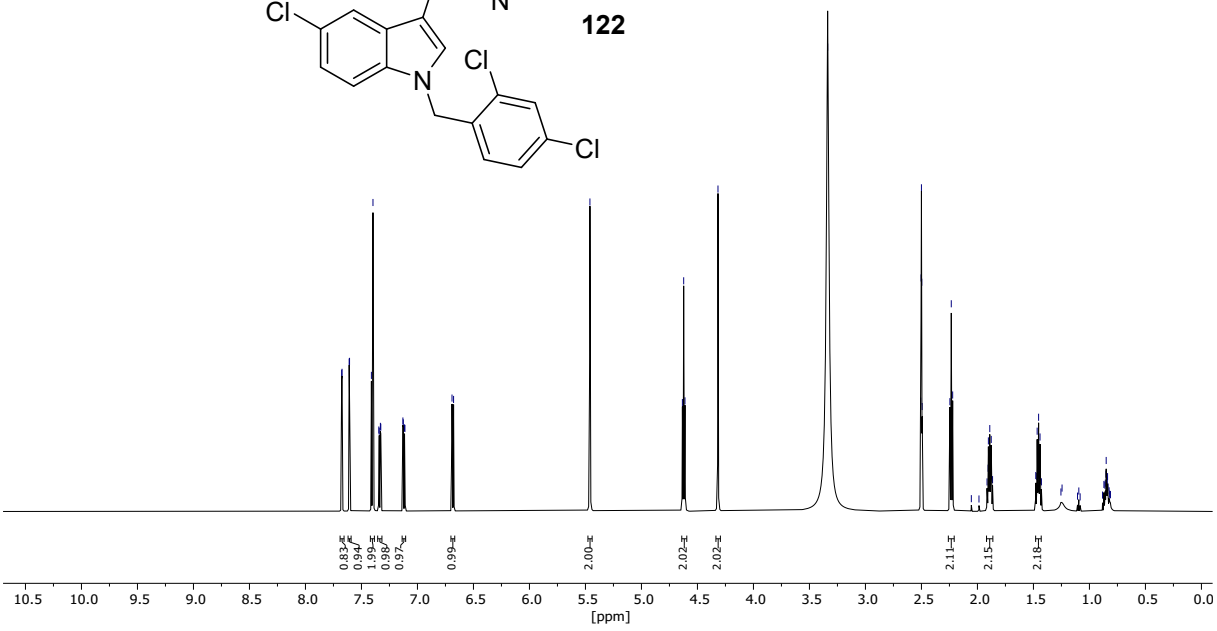
118

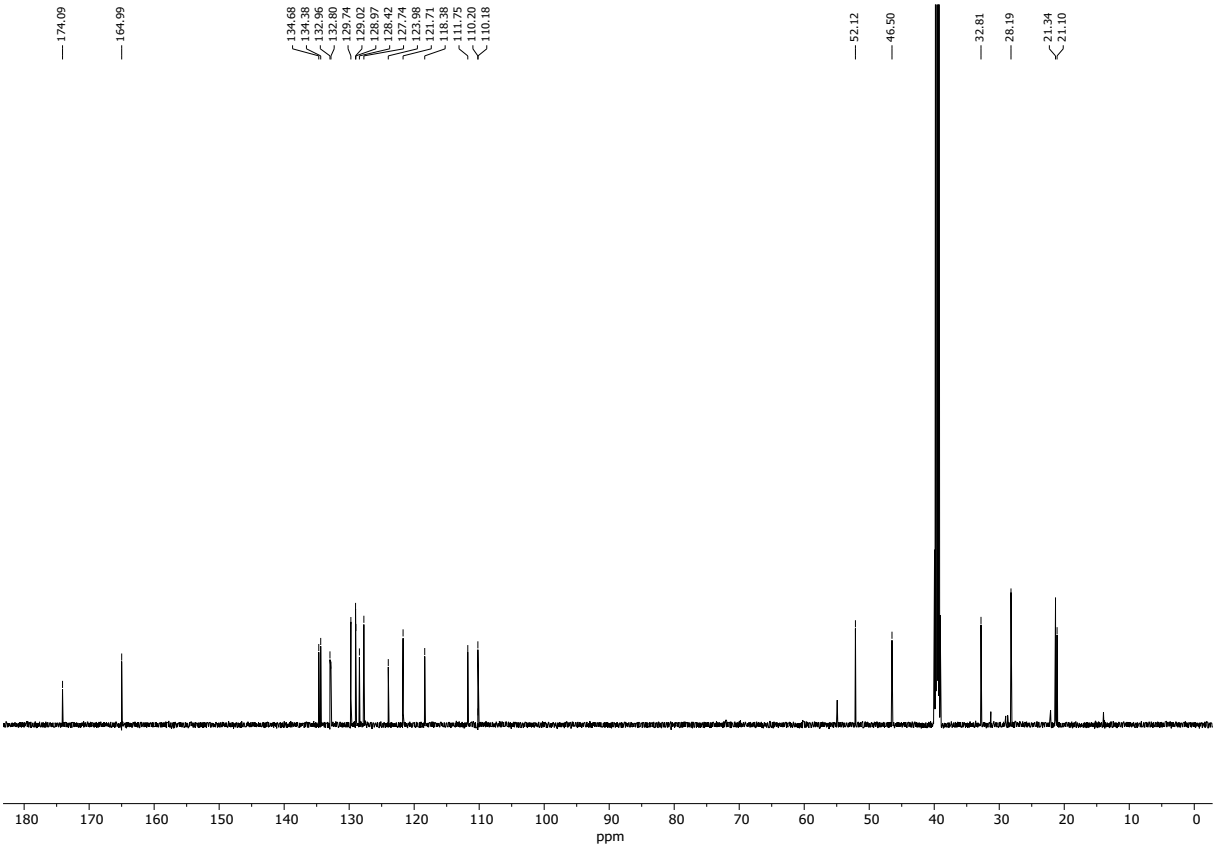
0.85
0.97
1.05
2.03
1.07
1.04
2.00
2.01
2.06
2.07
2.08
2.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

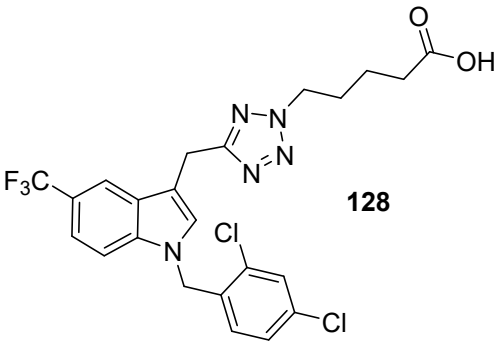

174.05
165.01
155.87
134.49
132.89
132.83
132.76
129.73
129.16
128.97
127.71
127.66
127.56
111.25
111.15
110.42
110.37
110.01
109.75
103.97
103.74
52.08
46.52
32.74
28.14
21.31
21.18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
Cl
Cl
N
Cl

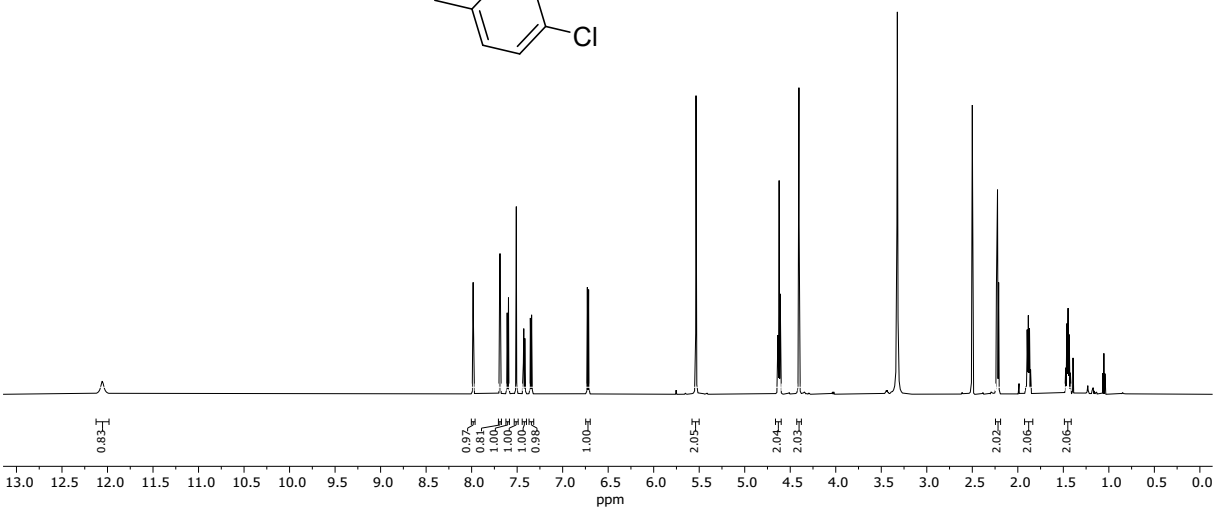
122

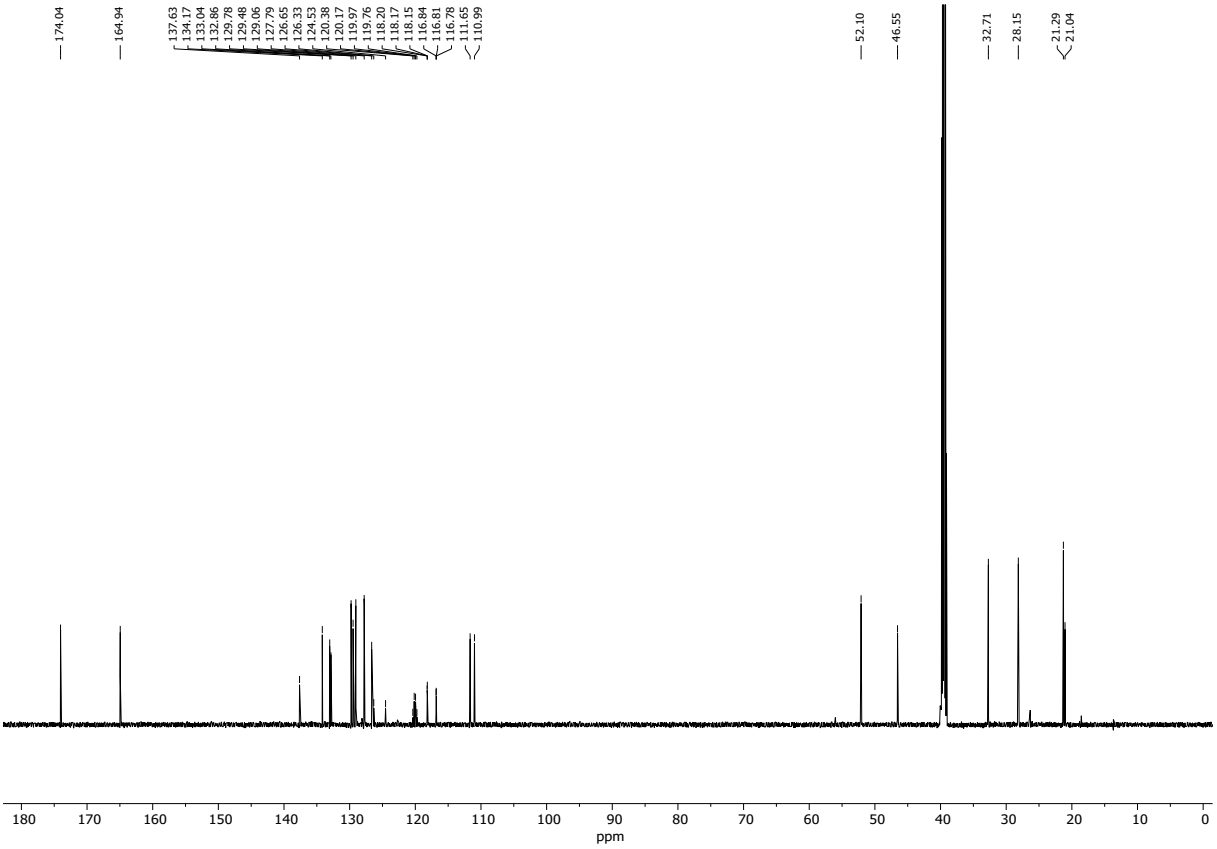

0.83
0.94
1.99
0.98
0.97
0.99
2.00
2.02
2.02
2.11
2.15
2.18
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
[ppm]

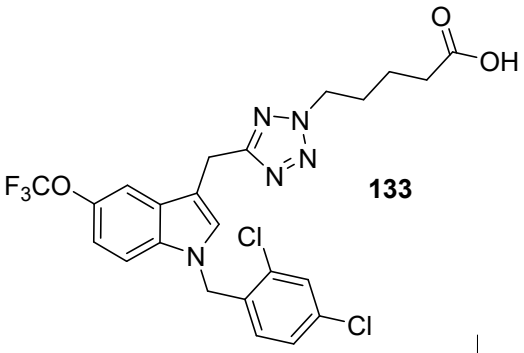

174.09
164.99
134.68
134.38
132.96
132.80
129.74
129.02
128.97
128.42
127.74
123.98
121.71
118.38
111.75
110.20
110.18
52.12
46.50
32.81
28.19
21.34
21.10
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
F3C
Cl
N
Cl

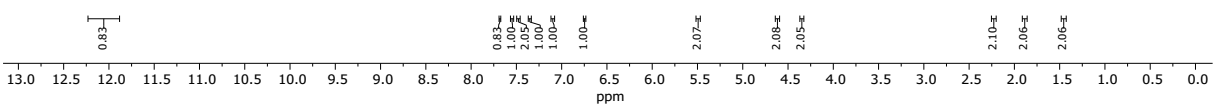
128

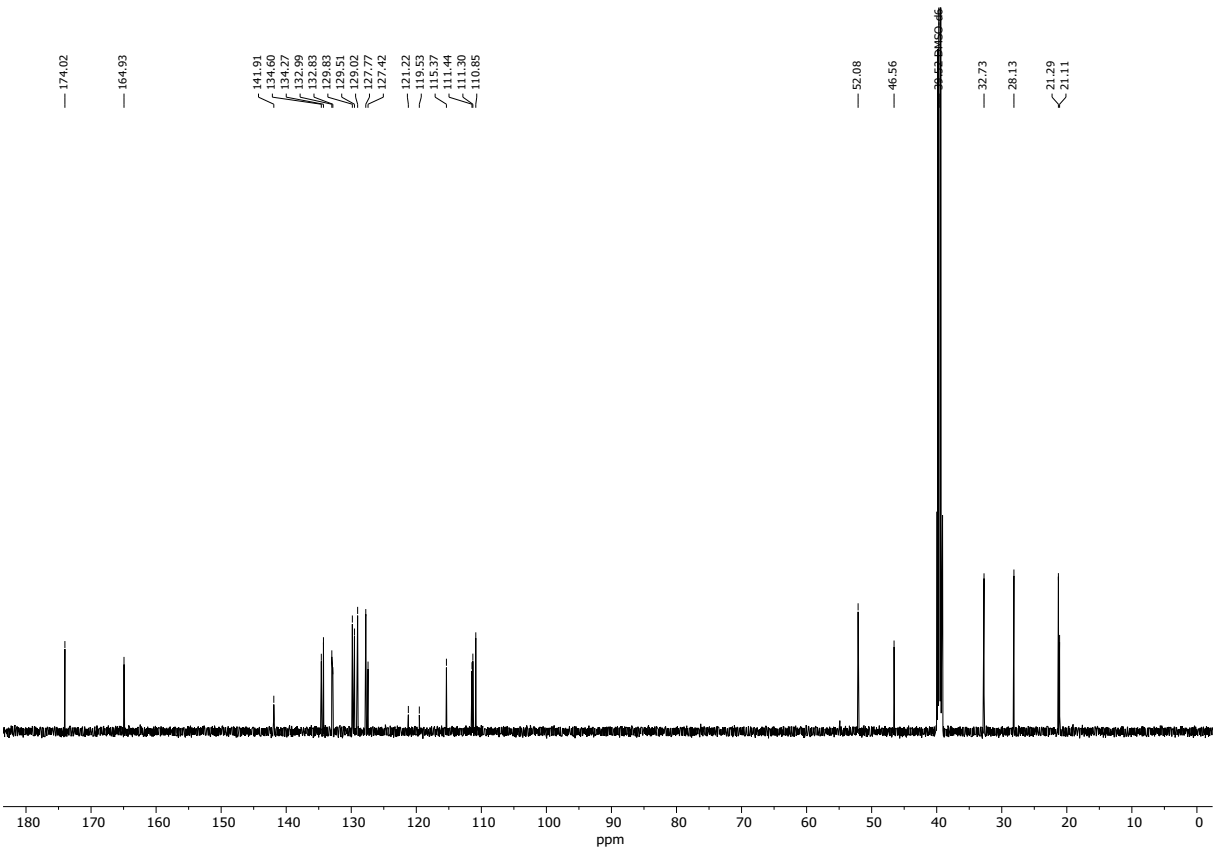

0.83
0.97
0.81
1.00
1.00
1.00
0.98
1.00
2.05
2.04
2.03
2.02
2.06
2.06
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

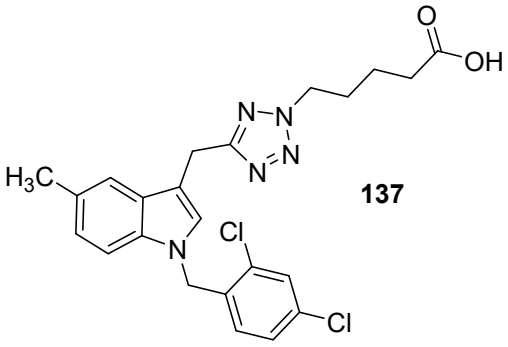

174.04
164.94
137.63
134.17
133.04
132.86
129.78
129.48
129.06
127.79
126.65
126.33
124.53
120.38
120.17
119.97
119.76
118.20
118.17
118.15
116.84
116.81
116.78
111.65
110.99
52.10
46.55
32.71
28.15
21.29
21.04
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
F3CO
Cl
N
Cl

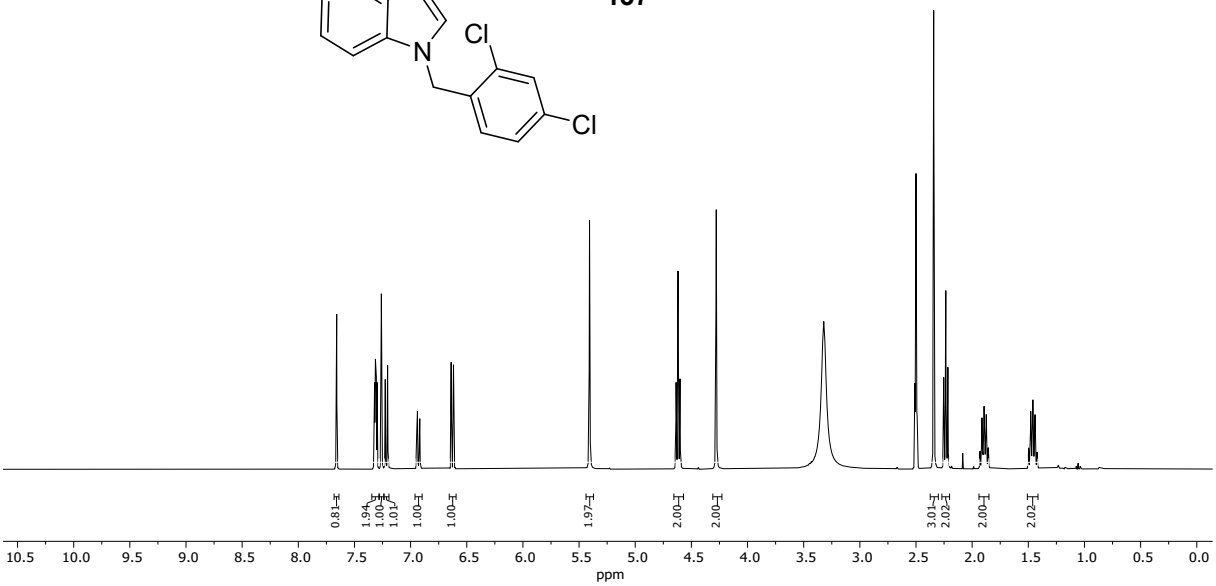
133

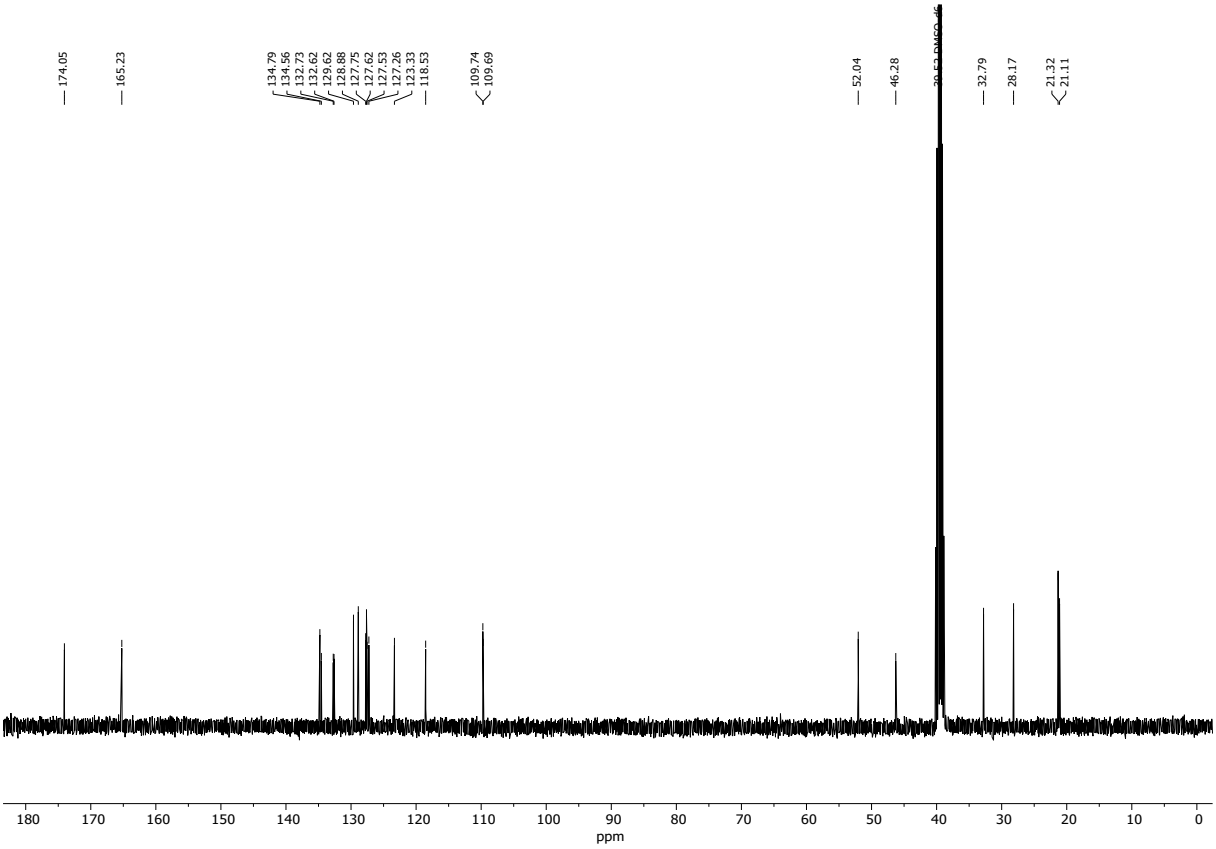

0.83
0.83
1.00
2.05
1.00
1.00
1.00
2.07
2.08
2.05
2.10
2.06
2.06
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

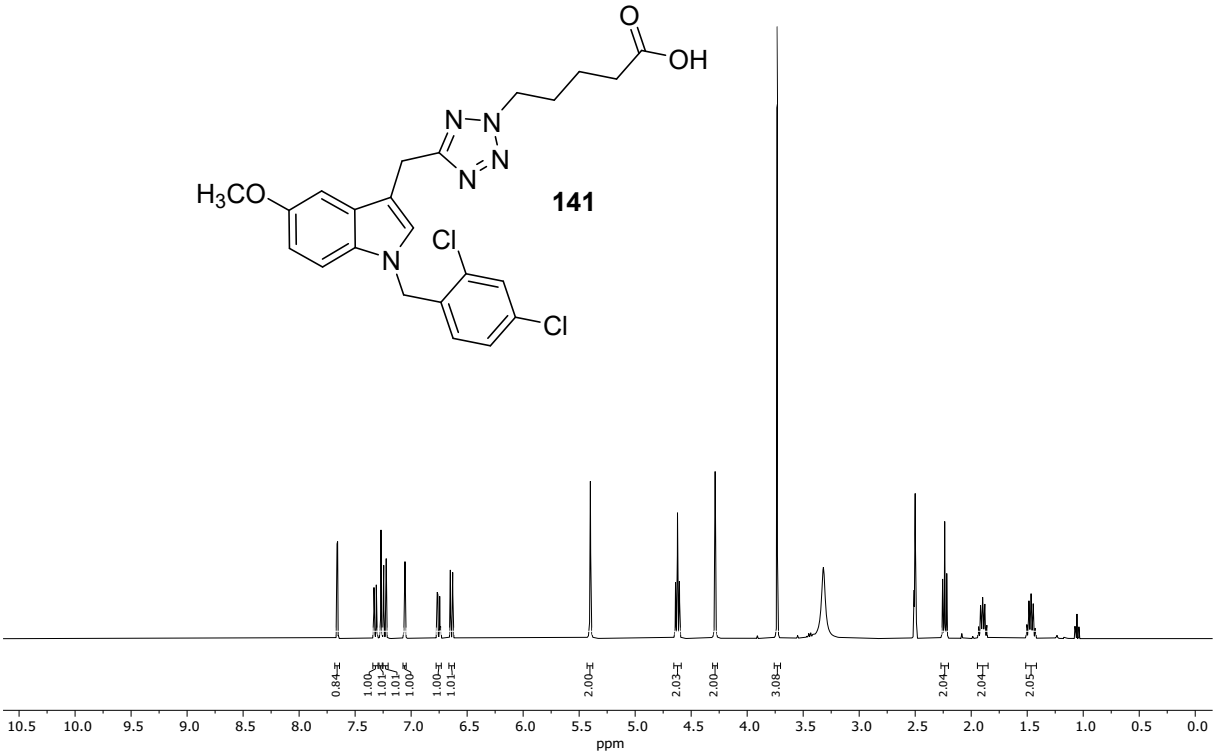

174.02
164.93
141.91
134.60
134.27
132.99
132.83
129.83
129.51
129.02
127.77
127.42
121.22
119.53
115.37
111.44
111.30
110.85
52.08
46.56
39.53 DMSO-d6
32.73
28.13
21.29
21.11
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

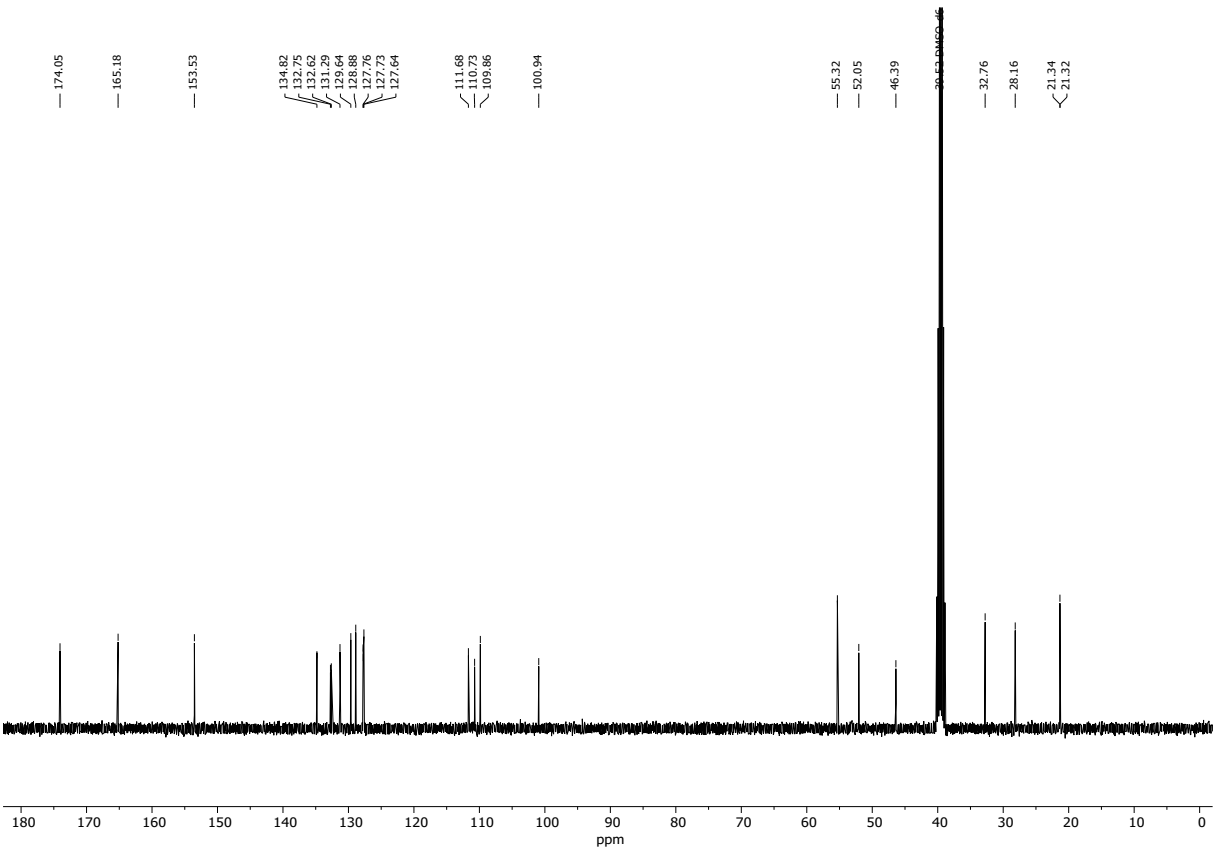

O
OH
N
N
N
N
H_3C
Cl
N
Cl

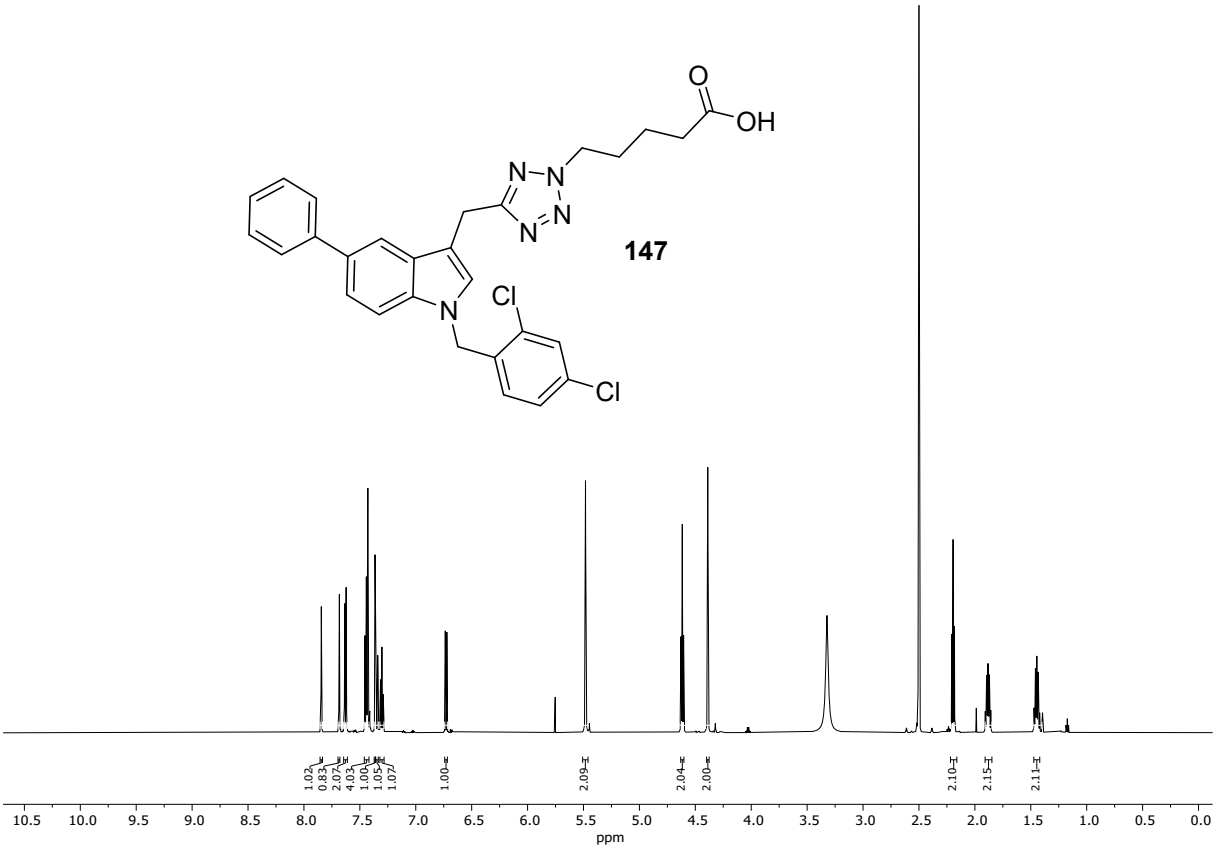
137

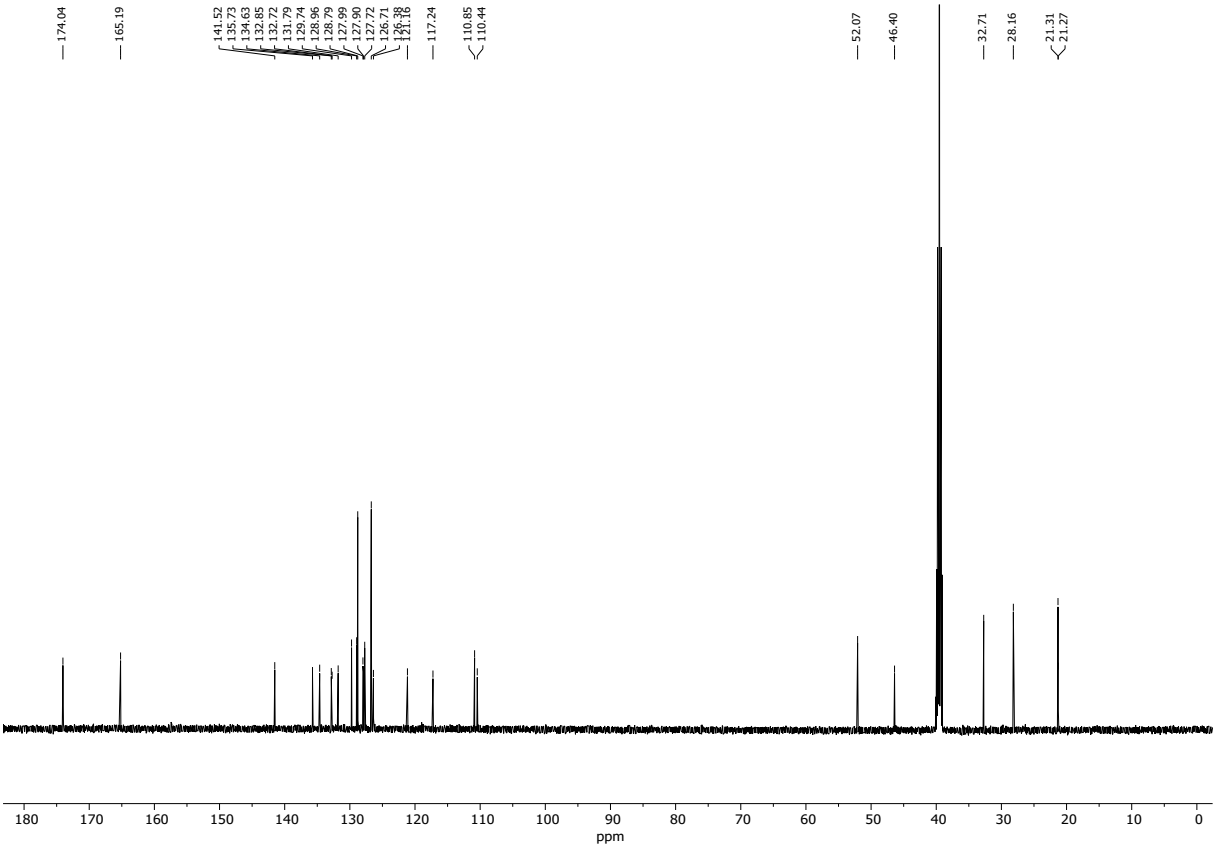

0.81
1.94
1.00
1.01
1.00
1.00
1.97
2.00
2.00
3.01
2.02
2.00
2.02
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

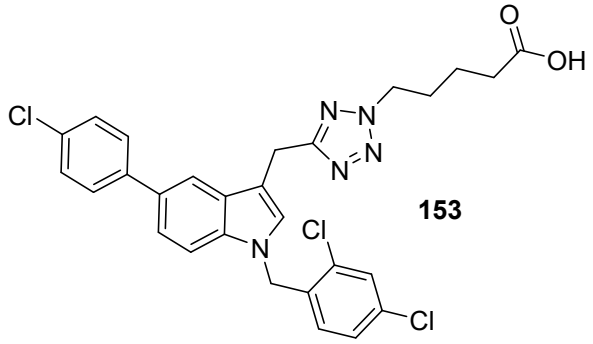

174.05
165.23
134.79
134.56
132.73
132.62
129.62
128.88
127.75
127.62
127.53
127.26
123.33
118.53
109.74
109.69
52.04
46.28
32.79
28.17
21.32
21.11
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
H3CO
141
Cl
N
Cl
0.84
1.00
1.01
1.01
1.00
1.00
1.01
2.00
2.03
2.00
3.08
2.04
2.04
2.05
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 1.0 0.5 0.0
ppm

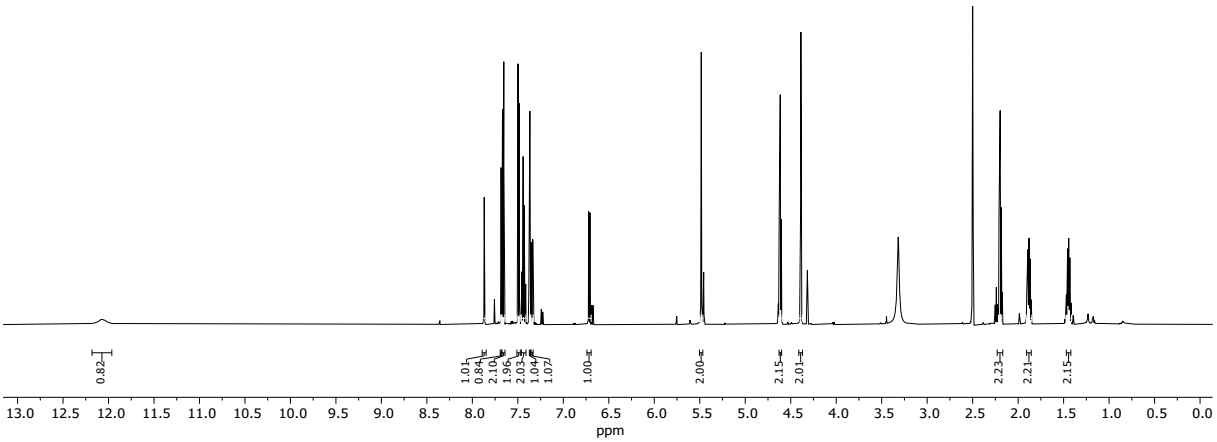

174.05
165.18
153.53
134.82
132.75
132.62
131.29
129.64
128.88
127.76
127.73
127.64
111.68
110.73
109.86
100.94
55.32
52.05
46.39
32.76
28.16
21.34
21.32
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

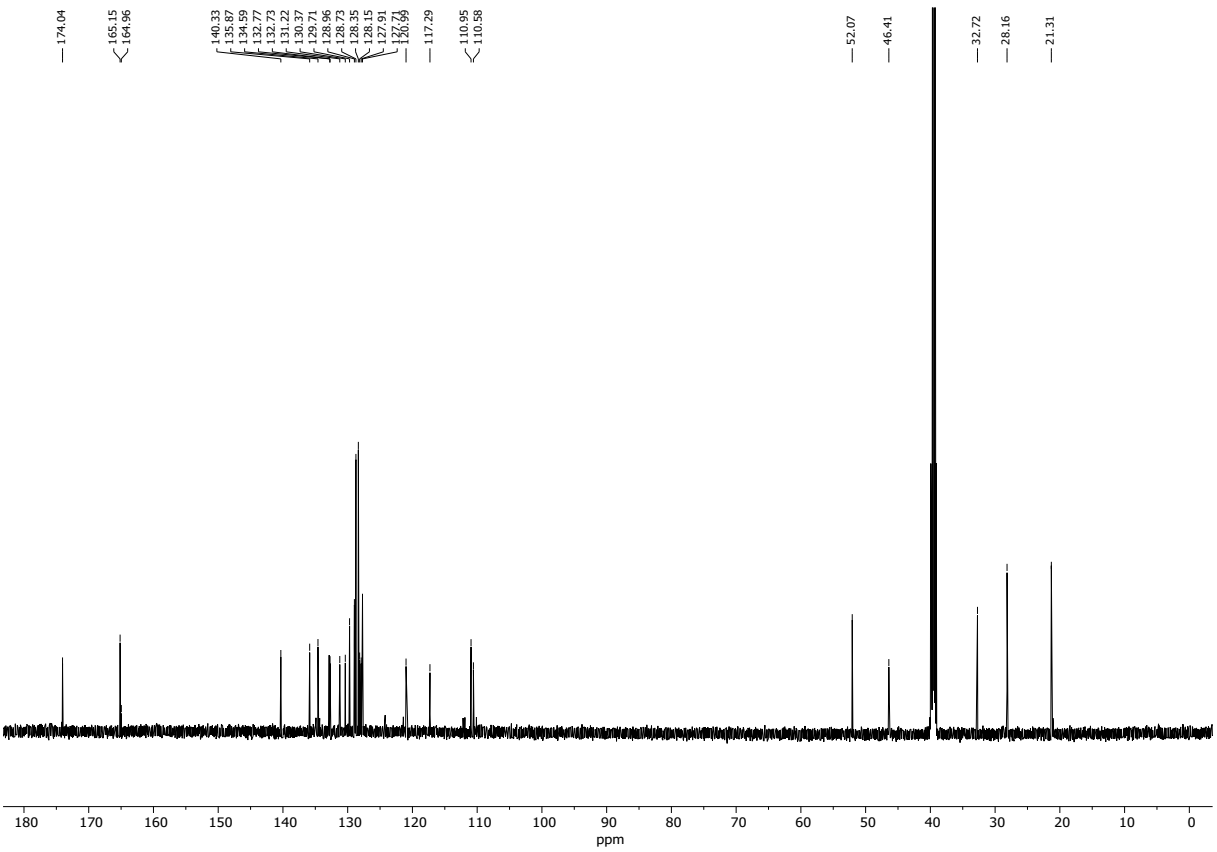

O
OH
N
N
N
N
147
N
Cl
Cl
1.02
0.83
2.07
4.03
1.00
1.05
1.07
1.00
2.09
2.04
2.00
2.10
2.15
2.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


174.04
165.19
141.52
135.73
134.63
132.85
132.72
131.79
129.74
128.96
128.79
127.99
127.90
127.72
126.71
126.38
126.32
121.18
117.24
110.85
110.44
52.07
46.40
32.71
28.16
21.31
21.27
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


O
OH
N
N
N
N
Cl
Cl
N
Cl

153


0.82
1.01
0.84
2.10
1.96
2.03
1.04
1.07
1.00
2.00
2.15
2.01
2.23
2.21
2.15
13.0 12.5 12.0 11.5 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 1.0 0.5 0.0
ppm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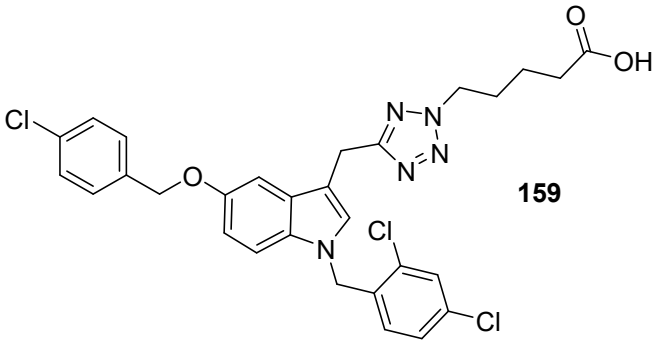
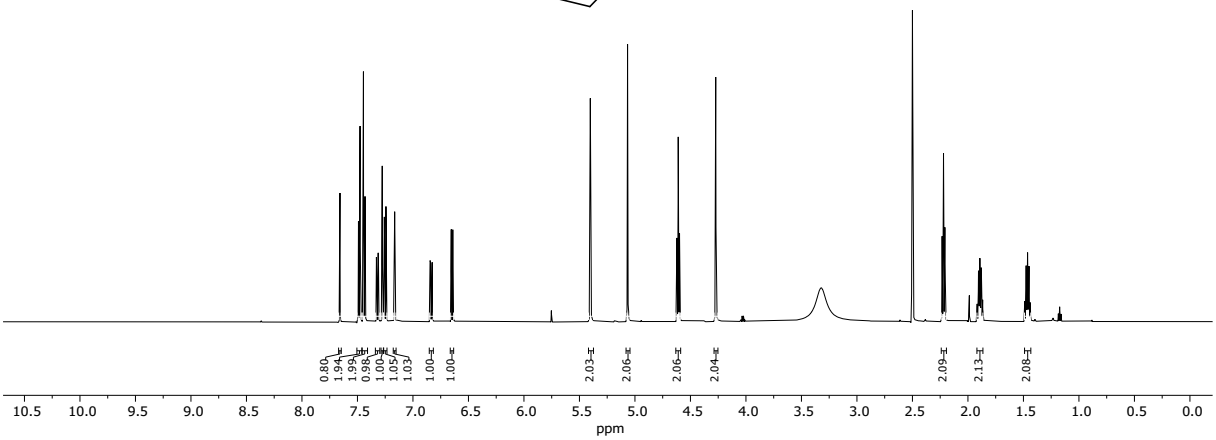
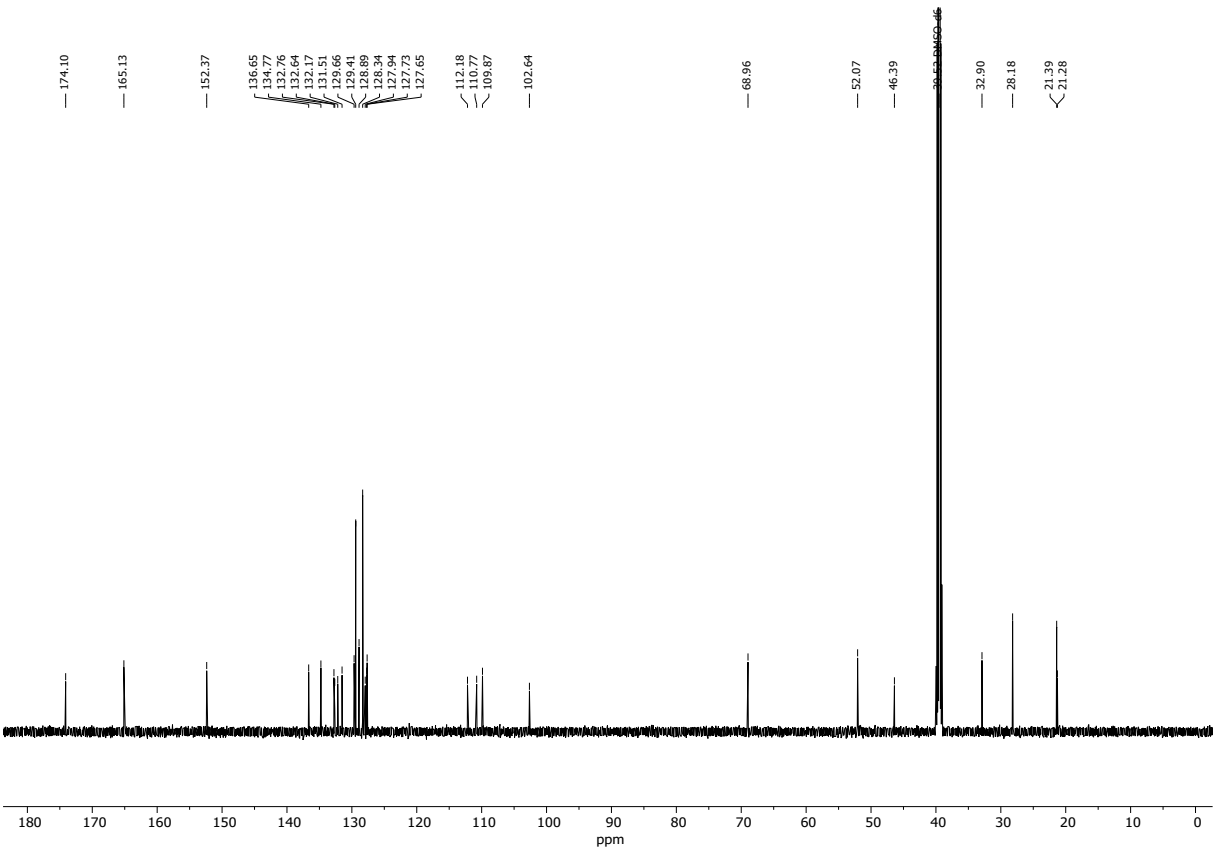
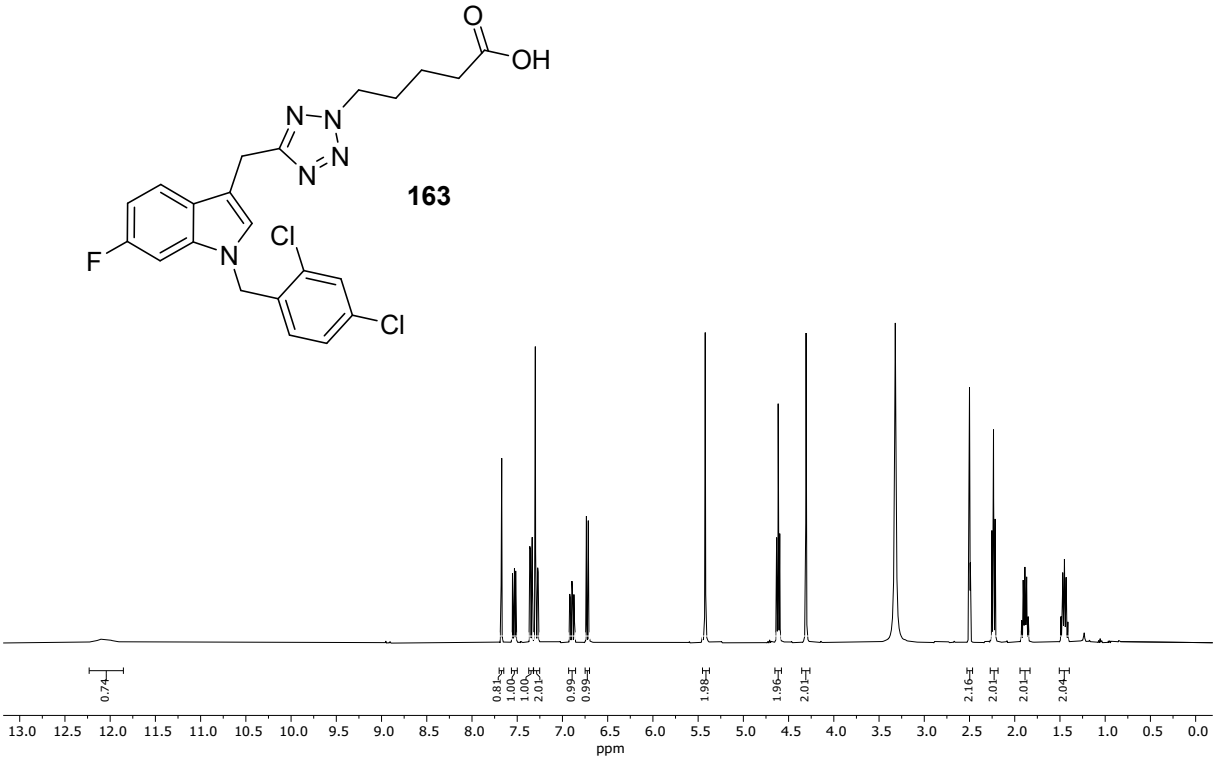
165.15
164.96
140.33
135.87
134.59
132.77
132.73
131.22
130.37
129.71
128.96
128.73
128.35
128.15
127.91
127.71
127.64
120.99
117.29
110.95
110.58
52.07
46.41
32.72
28.16
21.31
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

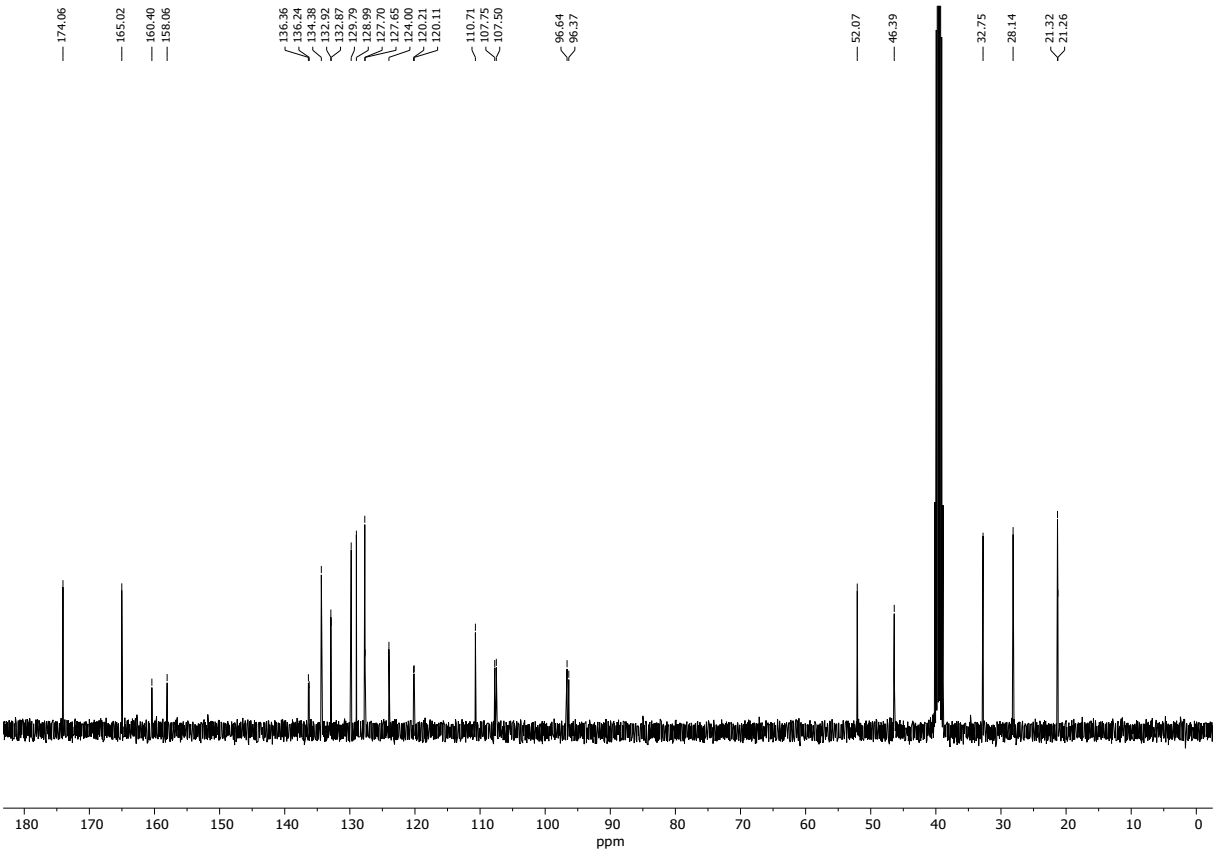

O
OH
Cl
N
N
N
N
O
Cl
N
Cl

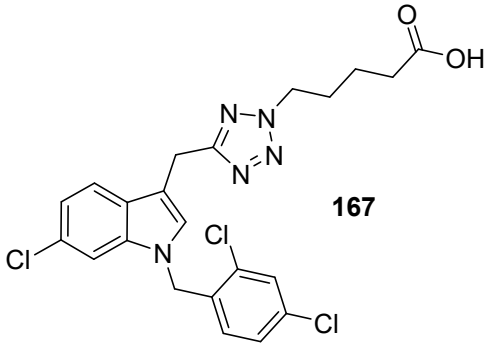
159


0.80
1.94
1.99
0.98
1.00
1.05
1.03
1.00
1.00
2.03
2.06
2.06
2.04
2.09
2.13
2.08
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 1.0 0.5 0.0
ppm

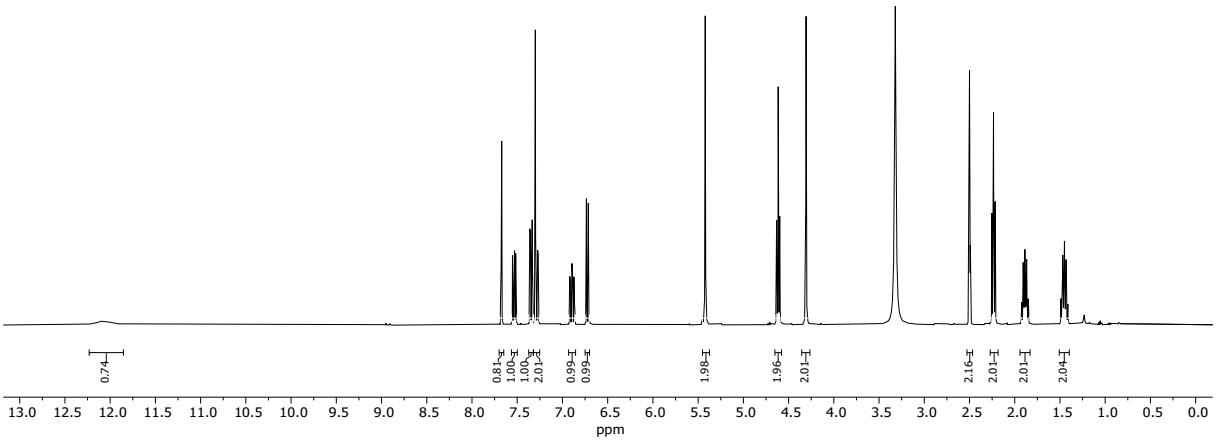

174.10
165.13
152.37
136.65
134.77
132.76
132.64
132.17
131.51
129.66
129.41
128.89
128.34
127.94
127.73
127.65
112.18
110.77
109.87
102.64
68.96
52.07
46.39
32.90
28.18
21.39
21.28
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

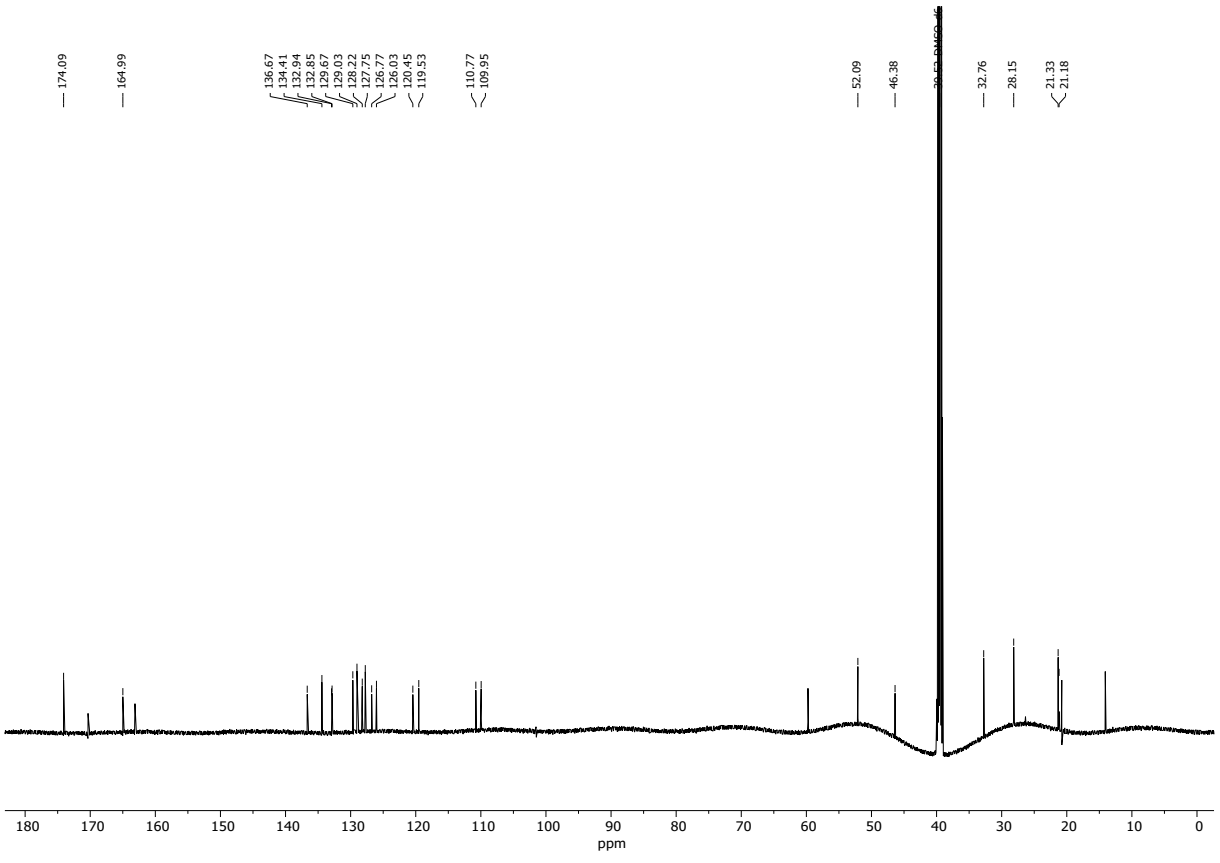

O
OH
N
N
N
N
163
F
N
Cl
Cl
0.74
0.81
1.00
1.00
2.01
0.99
0.99
1.98
1.96
2.01
2.16
2.01
2.01
2.04
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

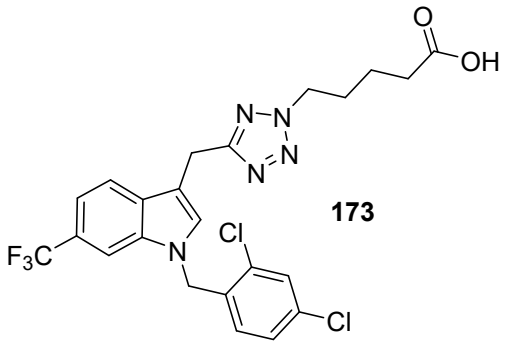

174.06
165.02
160.40
158.06
136.36
136.24
134.38
132.92
132.87
129.79
128.99
127.70
127.65
124.00
120.21
120.11
110.71
107.75
107.50
96.64
96.37
52.07
46.39
32.75
28.14
21.32
21.26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
Cl
N
Cl
Cl

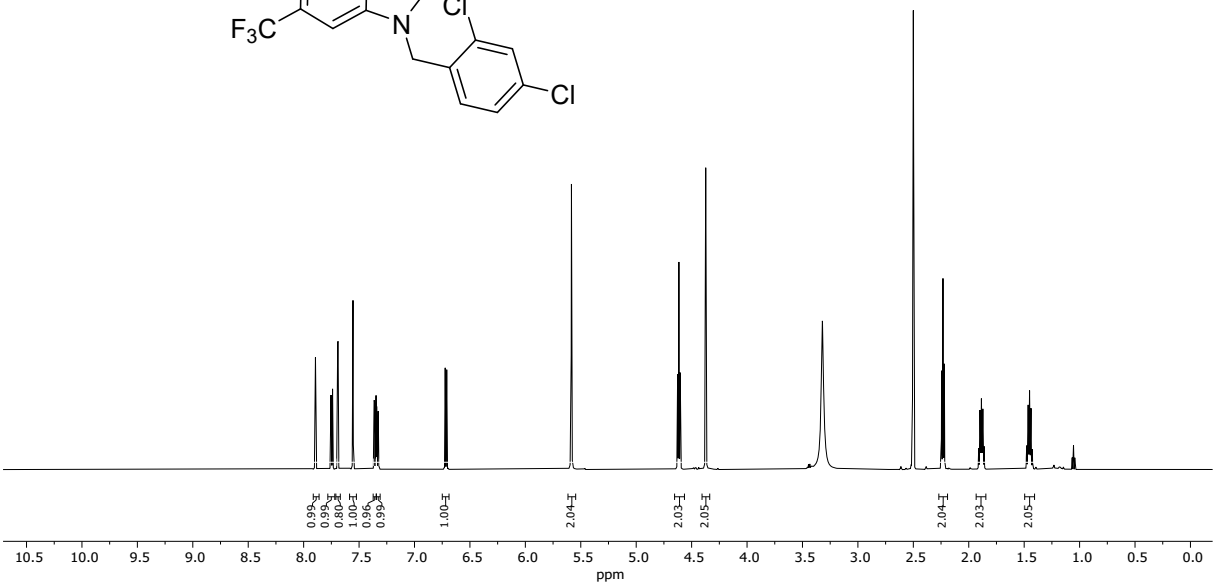
167

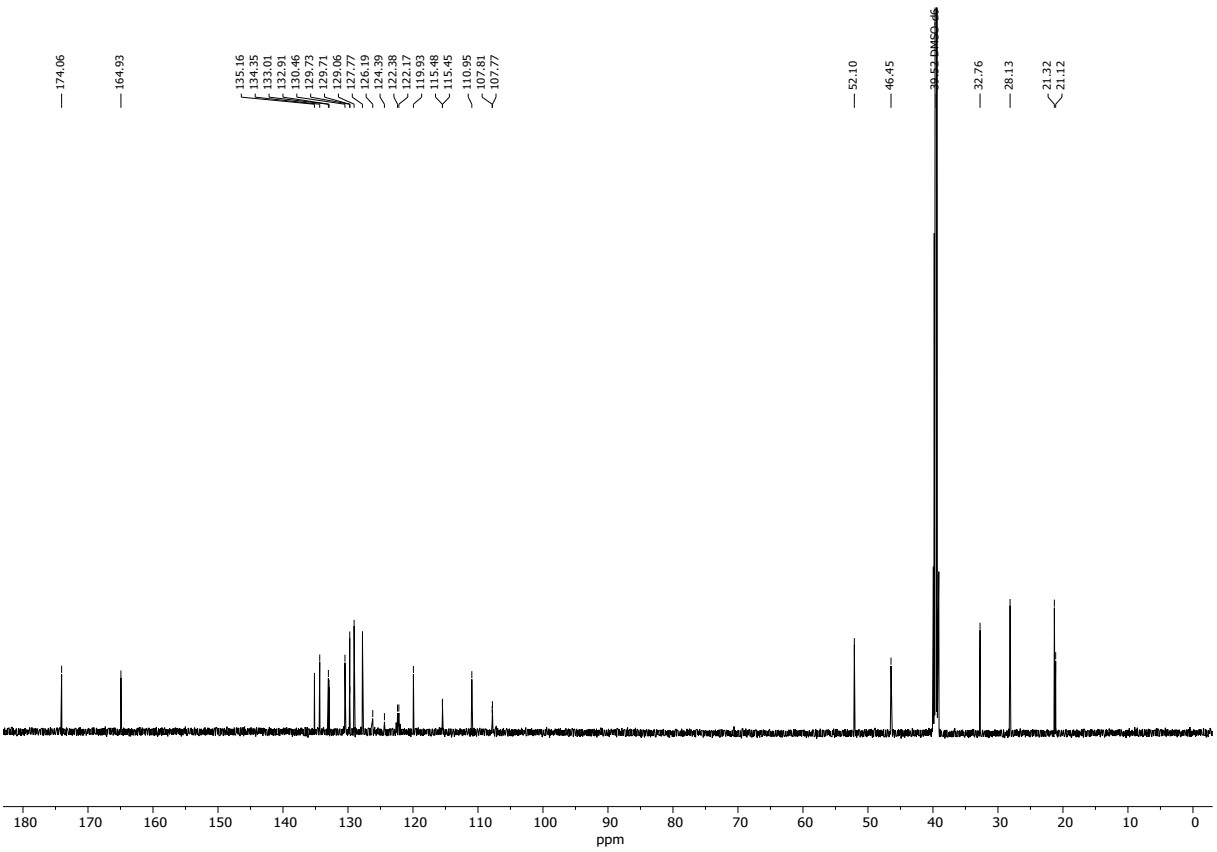

0.74
0.81
1.00
1.00
2.01
0.99
0.99
1.98
1.96
2.01
2.16
2.01
2.01
2.04
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

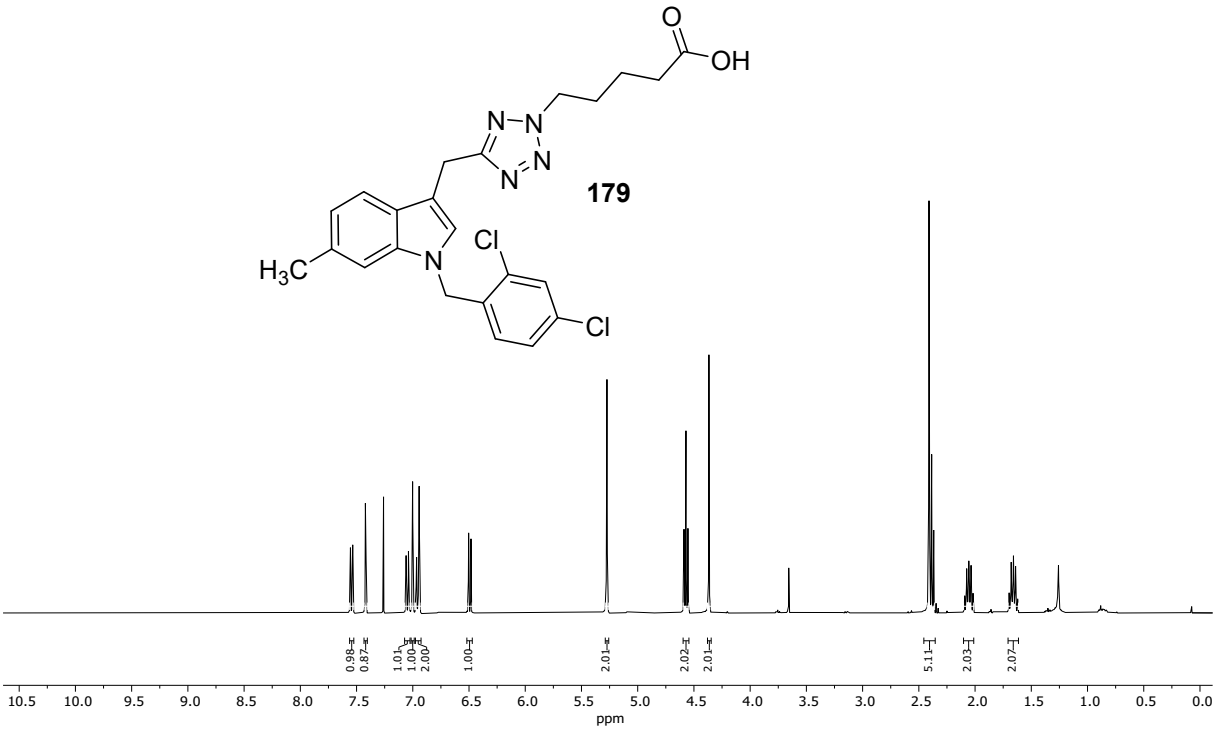

174.09
164.99
136.67
134.41
132.94
132.85
129.67
129.03
128.22
127.75
126.77
126.03
120.45
119.53
110.77
109.95
52.09
46.38
32.76
28.15
21.33
21.18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

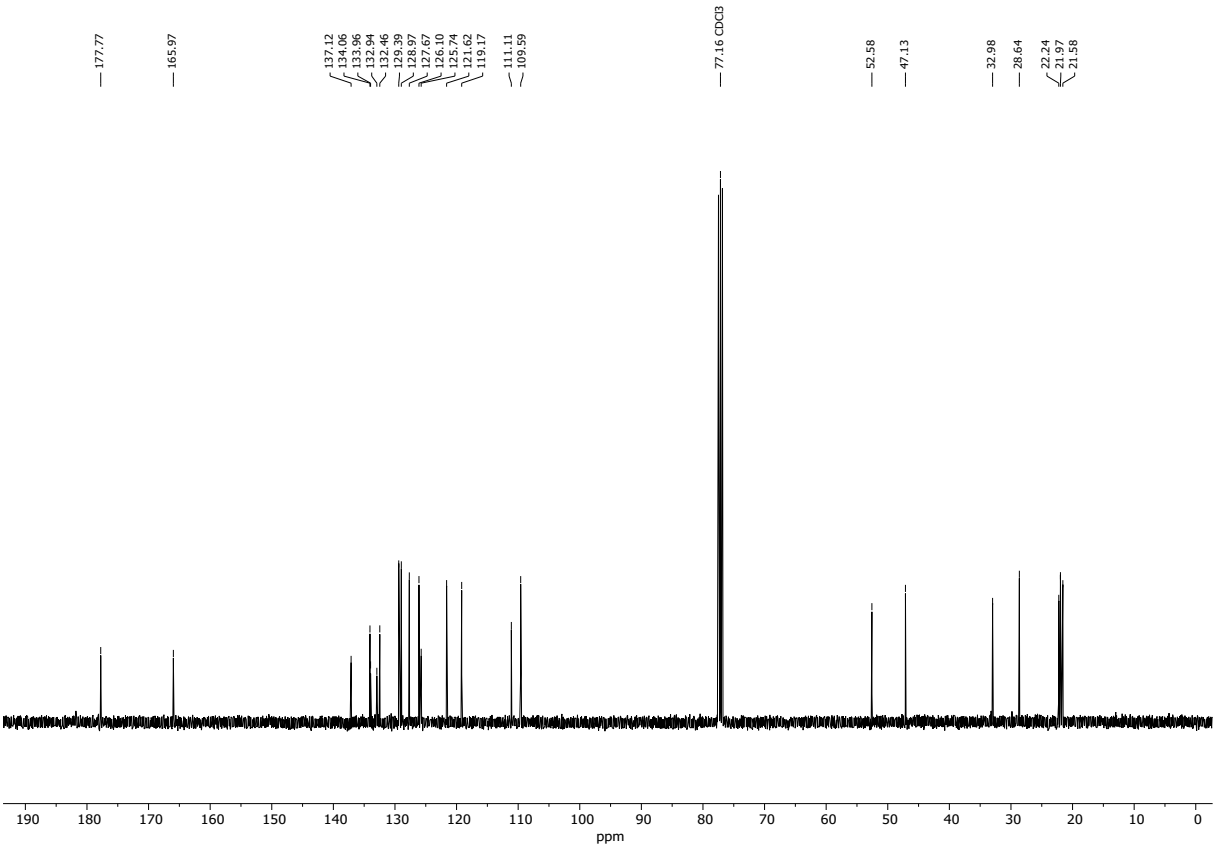

O
OH
N
N
N
N
F3C
Cl
N
Cl

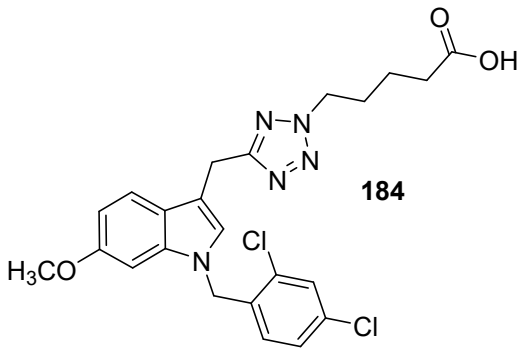
173

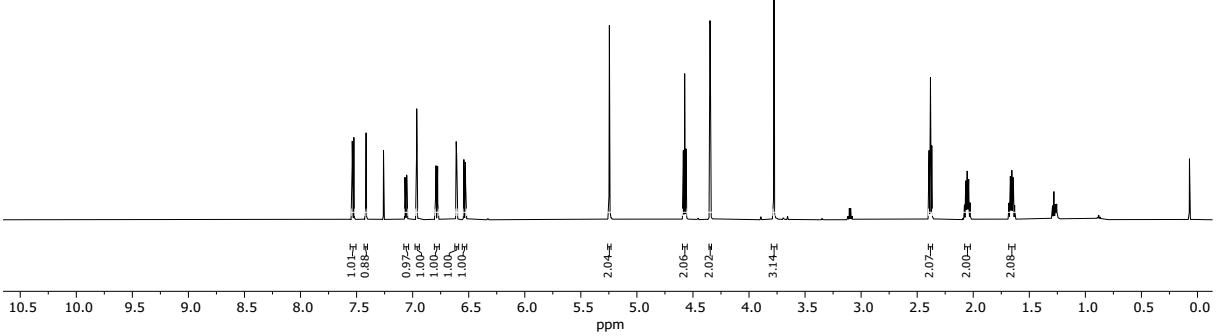

0.99
0.99
0.80
1.00
0.96
0.99
1.00
2.04
2.03
2.05
2.04
2.03
2.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

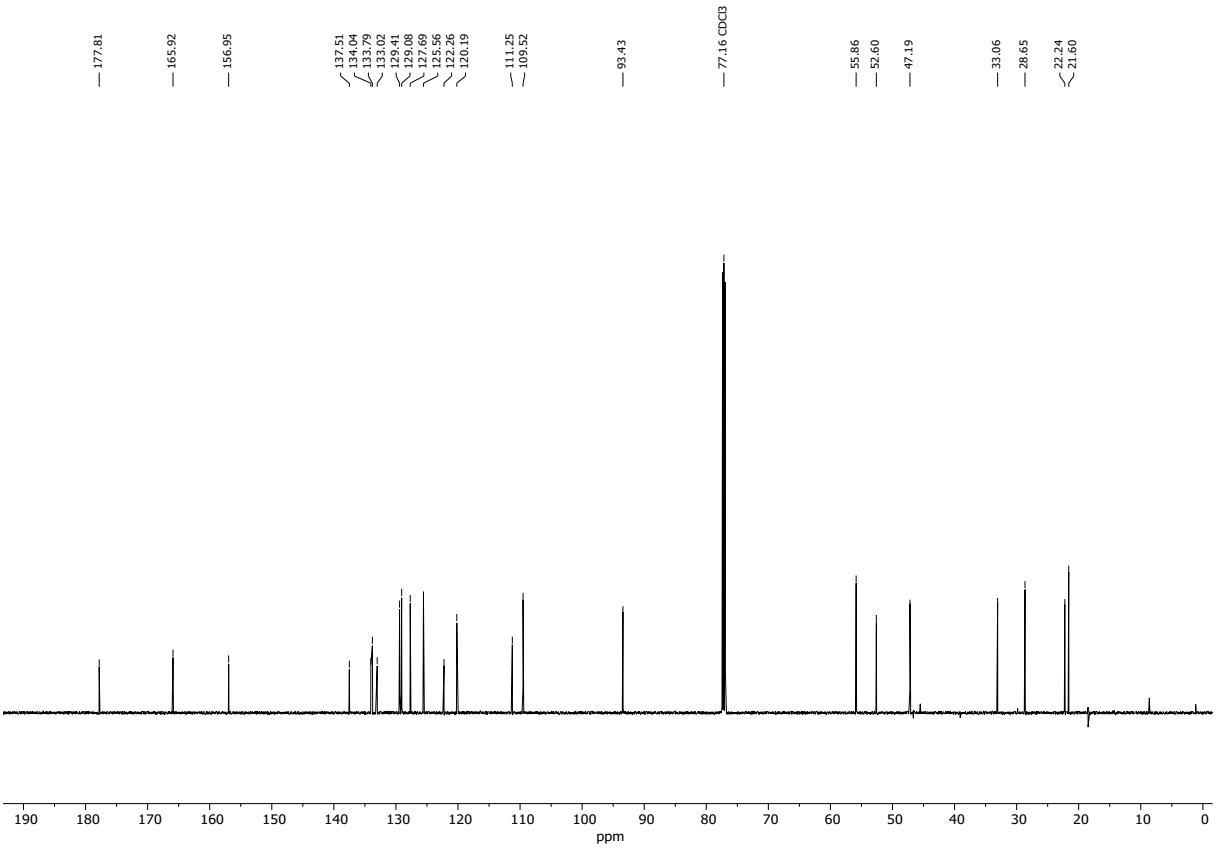

174.06
164.93
135.16
134.35
133.01
132.91
130.46
129.73
129.71
129.06
127.77
126.19
124.39
122.38
122.17
119.93
115.48
115.45
110.95
107.81
107.77
52.10
46.45
39.52 DMSO-d6
32.76
28.13
21.32
21.12
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

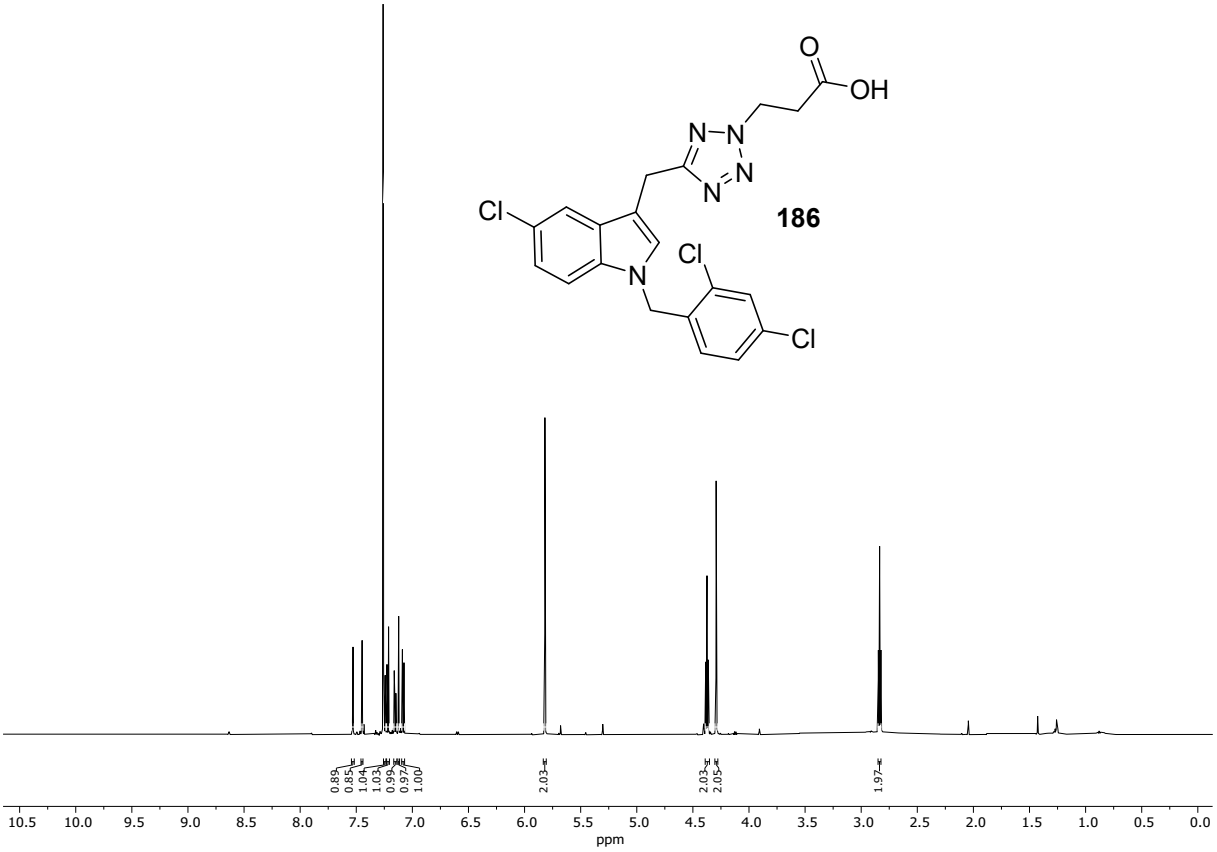

O
OH
N
N
N
N
179
Cl
H3C
N
Cl
0.98
0.87
1.01
1.00
2.00
1.00
2.01
2.02
2.01
5.11
2.03
2.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

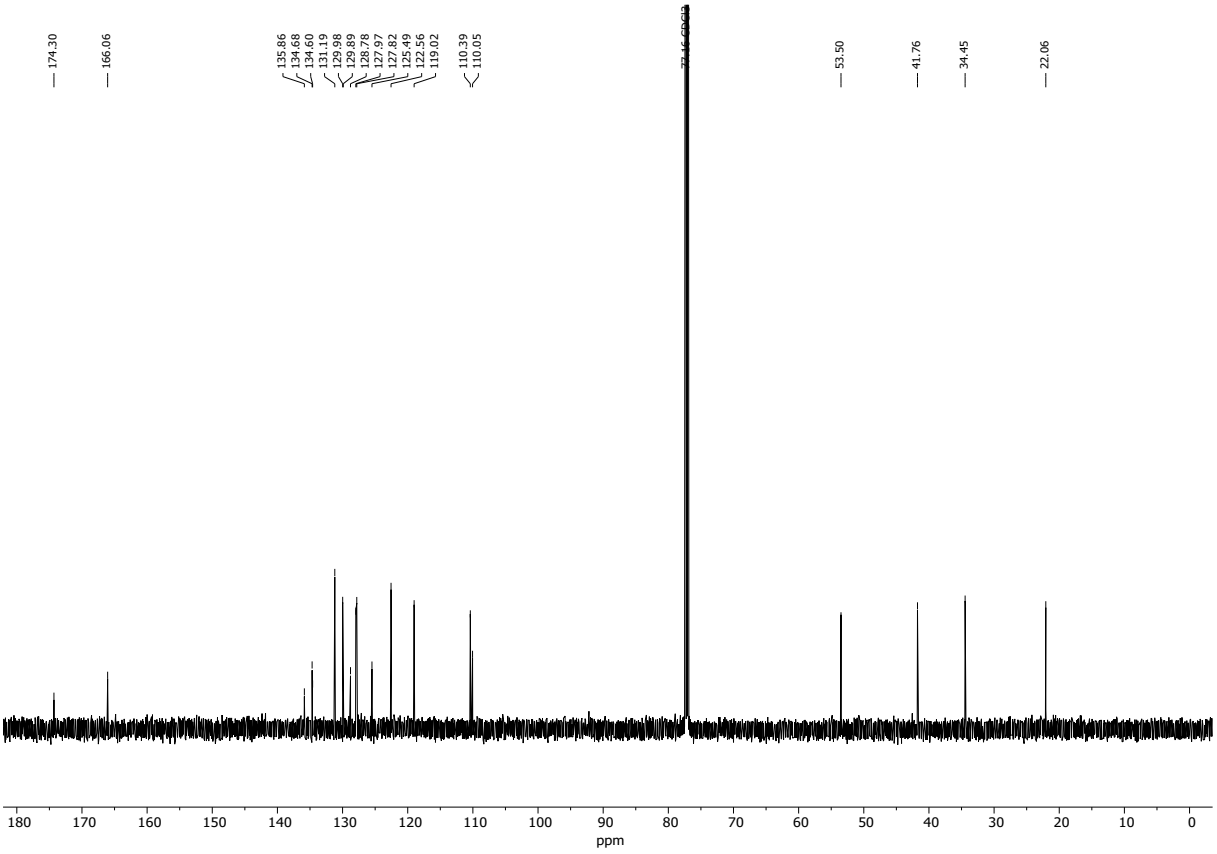

177.77
165.97
137.12
134.06
133.96
132.94
132.46
129.39
128.97
127.67
126.10
125.74
121.62
119.17
111.11
109.59
77.16 CDCl3
52.58
47.13
32.98
28.64
22.24
21.97
21.58
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
184
Cl
H3CO
N
Cl


1.01
0.88
0.97
1.00
1.00
1.00
2.04
2.06
2.02
3.14
2.07
2.00
2.08
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 1.0 0.5 0.0
ppm


177.81
165.92
156.95
137.51
134.04
133.79
133.02
129.41
129.08
127.69
125.56
122.26
120.19
111.25
109.52
93.43
77.16 CDCl3
55.86
52.60
47.19
33.06
28.65
22.24
21.60
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


O
OH
N
N
N
N
Cl
Cl
N
Cl
186
0.89
0.85
1.04
1.01
0.99
0.97
1.00
2.03
2.03
2.05
1.97
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 1.0 0.5 0.0
ppm


174.30
166.06
135.86
134.68
134.60
131.19
129.98
129.89
128.78
127.97
127.82
125.49
122.56
119.02
110.39
110.05
77.16
53.50
41.76
34.45
22.06
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm