Supplementary information

Structure-activity relationship expansion and microsomal stability assessment of the 2-morpholinobenzoic acid scaffold as antiproliferative phosphatidylcholine-specific phospholipase C inhibitors

Supplementary Information Part 1: Synthesis and stability experimental results

Shaun W. P. Rees[a], Tayla A. Rees[b,c], Emily K. Paulin[a], Olivia R. Arnerich[a,d], Euphemia Leung[c,e], Christopher S. Walker[b,c], David Barker[a,d]*, Lisa I. Pilkington[a,f]*

[a] School of Chemical Sciences, University of Auckland, Auckland 1010, New Zealand

[b] School of Biological Sciences, University of Auckland, Auckland 1010, New Zealand

[c] Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, Auckland 1010, New Zealand.

[d] The MacDiarmid Institute for Advanced Materials and Nanotechnology, Wellington, New Zealand

[e] Auckland Cancer Society Research Centre, University of Auckland, Grafton, Auckland 1023, New Zealand

[f] Te Pūnaha Matatini, Auckland 1142, New Zealand.

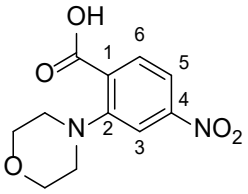
*Corresponding author. Email: d.barker@auckland.ac.nz (D.B), lisa.pilkington@auckland.ac.nz (L.I.P).

Table of Contents:

Synthetic procedures and characterisation data	S2
^{1}H and ^{13}C NMR spectra	S107
HPLC curves, tables and representative traces	S203
References	S208

Synthetic procedures and characterisation data

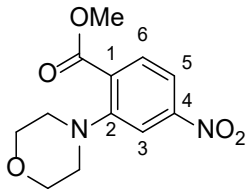
2-Morpholino-4-nitrobenzoic acid 6[1]



Morpholine (10.27 mL, 119.07 mmol) was added dropwise to a solution of 2-chloro-4-nitrobenzoic acid **5** (8.000 g, 39.69 mmol), K_2CO_3 (10.971 g, 79.38 mmol), copper (I) iodide (0.756 g, 3.97 mmol) and L-Proline (0.914 g, 7.94 mmol) in DMSO (50 mL) under a nitrogen atmosphere. The mixture was heated for 24 h at 130 °C, then cooled to room temperature and diluted with H_2O (100 mL). The solution was then adjusted to pH ~3 using 12 M HCl, forming a brown precipitate that was extracted using EtOAc (6 x 70 mL), the combined organic extracts were washed once with brine, dried with Na_2SO_4, and filtered. The resulting filtrate was concentrated in vacuo to afford a dark brown solid, which was recrystallized from EtOH to give the *title compound* **6** (7.385 g, 74%) as a light brown solid. M.p.: 195 – 198 °C (Lit.[1] 198 - 200 °C). R.f.: 0.14 (2:1, ethyl acetate/petroleum ether). IR: ν_{max} (film)/cm^{-1}; 3078 (OH), 2960 (CH aromatic), 2852 (CH alkane), 1691 (C=O acid), 1588 (C=C aromatic), 1520 (NO_2), 1458 (CH alkane), 1347 (NO_2), 1289 and 1265 (C-O ether), 1118 (C-N amine). δ_H (400 MHz; $CDCl_3$, Me_4Si) 3.14 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 4.00 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 8.26 (1H, dd, *J* = 2.0, 8.5 Hz, H-5), 8.32 (1H, d, *J* = 2.0 Hz, H-3) and 8.52 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; ($CDCl_3$) 53.9 (N(*C*H$_2$CH$_2$)$_2$O), 66.8 (N(CH$_2$*C*H$_2$)$_2$O), 118.4 (C-3), 122.5 (C-5), 130.5 (C-1), 134.2 (C-6), 151.2 (C-2), 151.4 (C-4) and 164.6 (C=O). *m/z* (ESI+): 275 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 275.0641, $C_{11}H_{12}N_2NaO_5$ requires 275.0638.

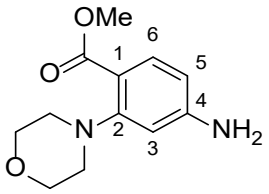
The ^{1}HNMR data was in accordance with literature values [1].

Methyl 2-morpholino-4-nitrobenzoate 7



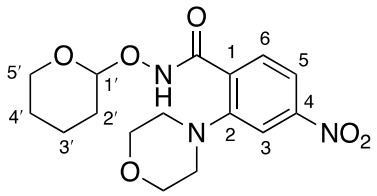
To a stirred solution of 2-morpholino-4-nitrobenzoic acid **6** (7.200 g, 28.55 mmol) in dry MeOH (75 mL) was added concentrated H_2SO_4 (0.720 mL, 13.43 mmol) dropwise, the mixture was then heated at 80 °C for 24 h. The solvent was then removed *in vacuo* and the resulting residue suspended in ice cold water (100 mL), then extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed 1 M NaOH (2 x 25 mL), water (25 mL) and brine (25 mL), then dried with Na_2SO_4 and filtered. The resulting filtrate was concentrated *in vacuo* to give a red/orange residue, which was purified by flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **7** (6.114 g, 80%) as a bright red viscous oil. R.f.: 0.54 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 2955 (CH aromatic), 2857 (CH alkane), 1725 (C=O ester), 1524 (NO_2), 1437 (C-H alkane), 1349 (NO_2), 1244 (C-O ester), 1116 (C-N amine). δ_H (400 MHz; $(CD_3)_2SO$) 3.06 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.71 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.86 (3H, s, OCH_3) and 7.77 – 7.80 (3H, m, H-3, H-5, H-6). δ_C (100 MHz; $(CD_3)_2SO$) 51.5 ($N(CH_2CH_2)_2O$), 52.6 (OCH_3), 66.0 ($N(CH_2CH_2)_2O$), 112.9 & 115.1 (C-3 & C-5), 128.9 (C-1), 132.0 (C-6), 149.9 & 151.7 (C-2 & C-4) and 166.9 (C=O). HRMS (ESI+): Found (MNa^+): 289.0794, $C_{12}H_{14}N_2NaO_5$ requires 289.0795.

Methyl 4-amino-2-morpholinobenzoate 8



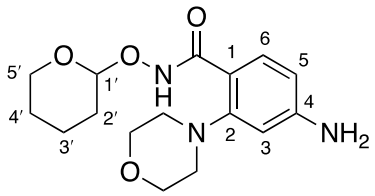
A mixture of methyl 2-morpholino-4-nitrobenzoate **7** (6.101 g, 22.91 mmol) and 10% Pd/C (10% w/w of **7**, 0.601 g) in EtOAc (60 mL) was stirred at room temperature for 24 h under an atmosphere of H_2. The mixture was filtered through a plug of Celite, and the subsequent filtrate was concentrated *in vacuo* to give the *title compound* **8** (4.787 g, 88%) as a white solid. m.p.: 139 – 141 °C. R.f.: 0.14 (2:1, petroleum ether/ethyl acetate). IR: vmax (film)/cm^{-1}; 3434 and 3352 (NH), 2945 (CH aromatic), 2865 (CH alkane), 1686 (C=O ester), 1628 and 1598 (C=C aromatic), 1430 and 1323 (CH alkane), 1242 and 1103 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.86 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 (3H, s, OCH_3), 3.70 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 5.80 (2H, br s, NH_2), 6.15 – 6.18 (2H, m, H-3, H-5) and 7.56 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$) 52.5 ($N(CH_2CH_2)_2O$), 50.8 (OCH_3), 66.3 ($N(CH_2CH_2)_2O$), 102.5 & 106.6 (C-3 & C-5), 108.6 (C-1), 134.2 (C-6), 153.7 & 155.2 (C-2 & C-4) and 166.0 (C=O). *m/z* (ESI+): 259 (MNa^+, 10%), 237 (MH^+, 15%) and 205 (100%). HRMS (ESI+): Found (MH^+): 237.1231, $C_{12}H_{17}N_2O_3$ requires 237.1234.

2-Morpholino-4-nitro-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide 13



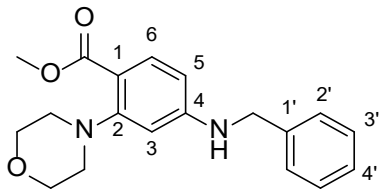
COMU (16.681 g, 38.95 mmol) in anhydrous DMF (20 mL) was added dropwise over 10 min to a stirred solution of 2-morpholino-4-nitrobenzoic acid **6** (7.557 g, 29.96 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (5.265 g, 44.94 mmol) and DIPEA (15.66 mL, 89.88 mmol) in anhydrous DMF (60 mL) under an atmosphere of nitrogen. The resulting mixture was allowed to stir for 65 hr at room temperature, then diluted with EtOAc (100 mL) and washed once with sat. $NaHCO_3$ then twice with brine. The organic layer was collected, dried with Na_2SO_4 and filtered, the filtrate was dried *in vacuo* and purified by flash chromatography (99.5:0.4:0.1, CH_2Cl_2/MeOH/NEt_3), affording the *title compound* **13** (8.816 g, 84%) as an orange solid. M.p.: 112 – 114 °C. R.f.: 0.43 (1:1, petroleum ether/ethyl acetate). IR: vmax (film)/cm^{-1}; 2964 (CH aromatic), 2861 (CH alkane), 1679 (C=O amide), 1586 (C=C aromatic), 1528 (N-O nitro), 1456 and 1351 (CH alkane), 1260 and 1108 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.55 (3H, br s, H-3'eq., H-4'ax., H-4'eq.), 1.72 (3H, br s, H-2'ax., H-2'eq., H-3'ax.), 3.08 (4H, m, N(C*H*$_2$CH$_2$)$_2$O), 3.52 (1H, d, *J* = 11.0 Hz, H-5'ax.), 3.71 (4H, m, N(CH$_2$C*H*$_2$)$_2$O), 4.05 (1H, t, *J* = 11.0 Hz, H-5'eq.), 5.04 (1H, br s, H-1'), 7.56 (1H, d, *J* = 8.0 Hz, H-6), 7.77 (1H, d, *J* = 2.5 Hz, H-3), 7.85 (1H, dd, *J* = 2.5, 8.0 Hz, H-5) and 11.66 (1H, s, N-H). δ_C (100 MHz; $(CD_3)_2SO$) 18.1 (C-3'), 24.7 (C-4'), 27.8 (C-2'), 51.2 (N(*C*H$_2$CH$_2$)$_2$O), 61.3 (C-5'), 66.0 (N(CH$_2$*C*H$_2$)$_2$O), 100.8 (C-1'), 112.9 (C-3), 116.0 (C-5), 131.0 (C-6), 133.0 (C-1), 149.1 (C-4), 151.0 (C-2) and 163.7 (C=O). *m/z* (ESI+): 344 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 344.1576, $C_{16}H_{23}N_3NaO_4$ requires 344.1581.

4-Amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide 14



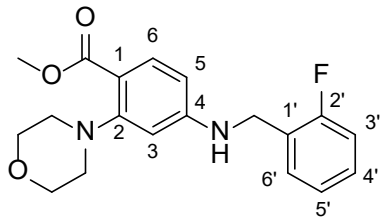
A solution of 2-morpholino-4-nitro-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **13** (8.00 g, 22.769 mmol) and 10% Pd/C (10% w/w of **13**, 0.800 g) in anhydrous MeOH (80 mL) was stirred at 0°C for 45 min. The mixture was filtered through a bed of Celite and the subsequent filtrate evaporated to give a crude green residue, which was purified by recrystallization from EtOH followed by flash chromatography (98:1.5:0.5, CH_2Cl_2/MeOH/NEt_3) to afford the *title compound* **14** (3.366 g, 46%) as a pale orange solid. M.p.: 207 – 209 °C. R.f.: 0.40 in ethyl acetate. IR: vmax (film)/cm^{-1}; 3445 and 3345 (N-H), 2941 (CH aromatic), 2839 (CH alkane), 1651 (C=O amide), 1596 (C=C aromatic), 1456 and 1338 (CH alkane), 1256 and 1108 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.55 (3H, br s, H-3'eq., H-4'ax., H-4'eq.), 1.71 (3H, br s, H-2'ax., H-2'eq., H-3'ax.), 2.82 (4H, m, N(C*H*$_2$CH_2)$_2$O), 3.58 (1H, d, *J* = 11.0 Hz, H-5'ax.), 3.72 – 3.80 (4H, m, N(CH_2C*H*$_2$)$_2$O), 3.96 – 4.01 (1H, m, H-5'eq.), 4.91 (1H, br s, H-1'), 5.70 (2H, br s, N-H), 6.36 (1H, dd, *J* = 1.5, 8.5 Hz, H-5), 6.43 (1H, d, *J* = 1.5 Hz, H-3), 7.52 (1H, d, *J* = 8.5 Hz, H-6) and 11.89 (1H, s, N-H). δ_C (100 MHz; $(CD_3)_2SO$) 18.4 (C-3'), 24.7 (C-4'), 27.8 (C-2'), 53.1 (N(*C*H$_2$CH$_2$)$_2$O), 61.5 (C-5'), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 101.1 (C-1'), 105.1 (C-3), 109.6 (C-5), 113.5 (C-1), 131.9 (C-6), 152.4 & 152.6 (C-2 & C-4) and 164.6 (C=O). *m/z* (ESI+): 374 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 379.1316, $C_{16}H_{21}N_3NaO_6$ requires 374.1323.

Methyl 4-(benzylamino)-2-morpholinobenzoate 10a



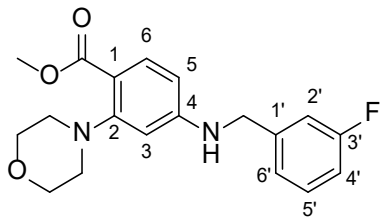
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.35 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 2-benzaldehyde **9a** (0.267 g, 2.52 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This intermediate was then dissolved in THF/MeOH (1:1, 6 mL) and $NaBH_4$ (0.224 g, 5.92 mmol) was added portion-wise and the mixture was stirred for 24 h. The resulting crude product was purified by flash chromatography (4:1, petroleum ether/ethyl acetate) to furnish the *title compound* **10a** (0.261 g, 54%) as a white solid. M.p.: 124 – 126 °C. R.f.: 0.46 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3319 (NH), 2963 and 2944 (CH aromatic), 2861 and 2809 (CH alkane), 1698 (C=O ester), 1601 and 1570 (C=C aromatic), 1424 (CH alkane), 1229 and 1105 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.84 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.66 – 3.69 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.31 (2H, d, *J* = 6.0 Hz, CH_2), 6.19 – 6.22 (2H, m, H-3, H-5), 6.94 (1H, t, *J* = 6.0 Hz, NH), 7.22 – 7.26 (1H, m, H-4'), 7.30 – 7.35 (4H, m, H-2', H-3') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.9 (CH_2), 50.8 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.4 (C-3), 104.9 (C-5), 108.8 (C-1), 126.8 (C-4'), 127.2 (C-2'), 128.3 (C-3'), 134.0 (C-6), 139.5 (C-1'), 152.9 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 349 (MNa^+, 40%) and 295 (100%). HRMS (ESI+): Found (MNa^+): 349.1521, $C_{19}H_{22}N_2NaO_3$ requires 349.1523.

Methyl 4-((2'-fluorobenzyl)amino)-2-morpholinobenzoate 10b



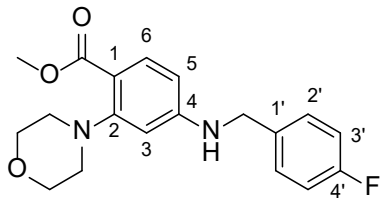
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.300 g, 1.27 mmol), 4Å molecular sieves (1.27 g) and 2-fluorobenzaldehyde **9b** (0.205 g, 1.65 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.144 g, 3.81 mmol) and stirred for 24 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10b** (0.293 g, 67%) as an off-white solid. M.p.: 113 – 115 °C. R.f.: 0.34 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3318 (NH), 2963 and 2944 (CH aromatic), 2860 and 2809 (CH alkane), 1694 (C=O ester), 1600 and 1574 (C=C aromatic), 1434 (CH alkane), 1233 (C-F), 1216 and 1105 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.86 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.70 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.36 (2H, d, *J* = 6.0 Hz, CH_2), 6.21 – 6.23 (2H, m, H-3, H-5), 6.90 (1H, t, *J* = 6.0 Hz, NH), 7.14 – 7.22 (2H, m, H-3', H-5'), 7.28 – 7.34 (1H, m, H-4'), 7.38 (1H, td, *J* = 1.5, 7.5 Hz, H-6') and 7.58 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 39.6 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.2 (C-3), 104.8 (C-5), 109.1 (C-1), 115.2 (d, $^2J_{F/C}$ = 21.4 Hz, C-3'), 124.4 (d, $^4J_{F/C}$ = 3.0 Hz, C-5'), 126.0 (d, $^2J_{F/C}$ = 14.7 Hz, C-1'), 129.0 (d, $^3J_{F/C}$ = 8.2 Hz, C-4'), 129.6 (d, $^3J_{F/C}$ = 4.5 Hz, C-6'), 134.1 (C-6), 152.7 (C-4), 154.9 (C-2), 160.3 (d, $^1J_{F/C}$ = 244.3 Hz, C-2') and 166.1 (C=O). *m/z* (ESI+): 367 (MNa^+, 50%) and 313 (100%). HRMS (ESI+): Found (MNa^+): 367.1426, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

Methyl 4-((3'-fluorobenzyl)amino)-2-morpholinobenzoate 10c



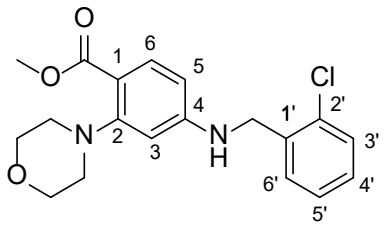
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 3-fluorobenzaldehyde **9c** (0.239 g, 1.93 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 24 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10c** (0.353 g, 69%) as an off-white solid. M.p.: 98 – 100 °C. R.f.: 0.31 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3312 (NH), 2947 (CH aromatic), 2857 (CH alkane), 1704 (C=O ester), 1603 and 1575 (C=C aromatic), 1442 (CH alkane), 1237 (C-F), 1221 and 1087 (C-O). δ_H (400 MHz; $(CD_3)_2SO$): 2.84 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.67 – 3.69 (7H, m, N(CH$_2$C*H*$_2$)$_2$O, OCH$_3$), 4.35 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.19 – 6.21 (2H, m, H-3, H-5), 6.98 (1H, t, *J* = 6.0 Hz, NH), 7.06 (1H, td, *J* = 2.5, 8.5 Hz, H-4'), 7.14 (1H, d, *J* = 10.0 Hz, H-2'), 7.19 (1H, d, *J* = 8.5 Hz, H-6'), 7.37 (1H, q, *J* = 7.5 Hz, H-5') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.3 (CH$_2$), 50.9 (OCH$_3$), 52.4 (N(*C*H$_2$CH$_2$)$_2$O), 66.3 (N(CH$_2$*C*H$_2$)$_2$O), 101.5 (C-3), 104.9 (C-5), 109.1 (C-1), 113.5 (d, $^2J_{F/C}$ = 21.8 Hz, C-4'), 113.8 (d, $^2J_{F/C}$ = 21.8 Hz, C-2'), 123.2 (d, $^4J_{F/C}$ = 2.4 Hz, C-6'), 130.3 (d, $^3J_{F/C}$ = 8.4 Hz, C-5'), 134.1 (C-6), 142.8 (d, $^3J_{F/C}$ = 7.0 Hz, C-1'), 152.7 (C-4), 154.8 (C-2), 162.3 (d, $^1J_{F/C}$ = 243.7 Hz, C-3') and 166.1 (C=O). *m/z* (ESI+): 367 (MNa$^+$, 35%) and 313 (100%). HRMS (ESI+): Found (MNa$^+$): 367.1427, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

Methyl 4-((4'-fluorobenzyl)amino)-2-morpholinobenzoate 10d



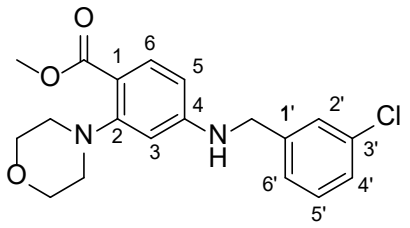
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 4-fluorobenzaldehyde **9d** (0.239 g, 1.93 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 24 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10d** (0.223 g, 44%) as an off white solid. M.p.: 132 – 134 °C. R.f.: 0.34 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3310 (NH), 2948 (CH aromatic), 2808 (CH alkane), 1706 (C=O ester), 1600 and 1575 (C=C aromatic), 1428 (CH alkane), 1235 (C-F), 1209 and 1085 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.84 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.66 – 3.69 (7H, m, N(CH$_2$C*H*$_2$)$_2$O, OCH$_3$), 4.30 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.17 – 6.21 (2H, m, H-3, H-5), 6.94 (1H, t, *J* = 6.0 Hz, NH), 7.15 (2H, t, *J* = 8.5 Hz, H-3'), 7.37 (2H, dd, *J* = 5.5, 8.5 Hz, H-2') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH$_2$), 50.9 (OCH$_3$), 52.4 (N(*C*H$_2$CH$_2$)$_2$O), 66.3 (N(CH$_2$*C*H$_2$)$_2$O), 101.4 (C-3), 104.9 (C-5), 109.0 (C-1), 115.0 (d, $^2J_{F/C}$ = 21.2 Hz, C-3'), 129.1 (d, $^3J_{F/C}$ = 8.1 Hz, C-2'), 134.0 (C-6), 135.7 (d, $^4J_{F/C}$ = 2.4 Hz, C-1'), 152.8 (C-4), 154.8 (C-2), 161.1 (d, $^1J_{F/C}$ = 242.0 Hz, C-4') and 166.1 (C=O). *m/z* (ESI+): 367 (MNa$^+$, 40%) and 313 (100%). HRMS (ESI+): Found (MNa$^+$): 367.1427, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

Methyl 4-((2'-chlorobenzyl)amino)-2-morpholinobenzoate 10e



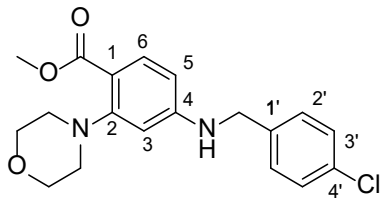
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 2-chlorobenzaldehyde **9e** (0.271 g, 1.93 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 22 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10e** (0.385 g, 72%) as an off white solid. M.p.: 100 – 102 °C. R.f.: 0.40 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3332 (NH), 2962 (CH aromatic), 2824 (CH alkane), 1694 (C=O ester), 1600 and 1566 (C=C aromatic), 1430 (CH alkane), 1205 and 1086 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.69 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.39 (2H, d, *J* = 6.0 Hz, CH_2), 6.16 – 6.19 (2H, m, H-3, H-5), 6.96 (1H, t, *J* = 6.0 Hz, NH), 7.26 – 7.33 (2H, m, H-4', H-5'), 7.38 (1H, dd, *J* = 2.5, 6.5 Hz, H-6'), 7.46 (1H, dd, *J* = 2.5, 6.5 Hz, H-3') and 7.58 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 43.7 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.4 (C-3), 104.7 (C-5), 109.2 (C-1), 127.2 (C-5'), 128.7 (C-4'), 129.1 (C-6'), 129.3 (C-3'), 132.2 (C-2'), 134.1 (C-6), 136.3 (C-1'), 152.6 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 385 ($^{37}ClMNa^+$, 15%), 383 ($^{35}ClMNa^+$, 50%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MNa^+): 385.1110, $C_{19}H_{21}{}^{37}ClN_2NaO_3$ requires 385.1110. Found (MNa^+): 383.1128, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 383.1133.

Methyl 4-((3'-chlorobenzyl)amino)-2-morpholinobenzoate 10f



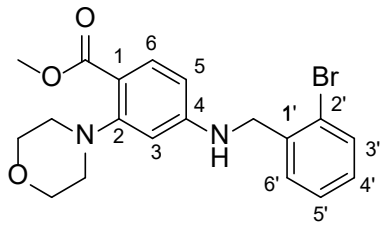
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 3-chlorobenzaldehyde **9f** (0.271 g, 1.93 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 24 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10f** (0.344 g, 64%) as an off-white solid. M.p.: 103 – 105 °C. R.f.: 0.38 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3331 (NH), 2962 (CH aromatic), 2824 (CH alkane), 1694 (C=O ester), 1600 and 1570 (C=C aromatic), 1430 (CH alkane), 1236 and 1086 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.69 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.33 (2H, d, *J* = 6.0 Hz, CH_2), 6.18 – 6.21 (2H, m, H-3, H-5), 6.99 (1H, t, *J* = 6.0 Hz, NH), 7.28 – 7.40 (4H, m, H-2', H-4', H-5', H-6') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.2 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.5 (C-3), 104.9 (C-5), 109.2 (C-1), 125.9 (C-6'), 126.7 (C-4'), 127.0 (C-2'), 130.2 (C-5'), 133.0 (C-6), 134.1 (C-3'), 142.4 (C-1'), 152.6 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 385 ($^{37}ClMNa^+$, 15%), 383 ($^{35}ClMNa^+$, 45%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MNa^+): 385.1116, $C_{19}H_{21}{}^{37}ClN_2NaO_3$ requires 383.1110. Found (MNa^+): 383.1136, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 383.1133.

Methyl 4-((4'-chlorobenzyl)amino)-2-morpholinobenzoate 10g



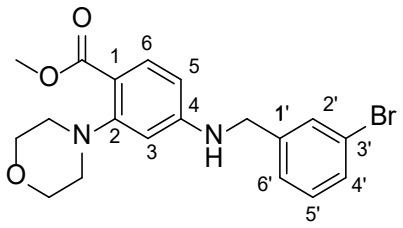
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 4-chlorobenzaldehyde **9g** (0.271 g, 1.93 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 22 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10g** (0.420 g, 79%) as an off-white solid. M.p.: 115 – 117 °C. R.f.: 0.38 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3332 (NH), 2962 (CH aromatic), 2823 (CH alkane), 1694 (C=O ester), 1599 and 1567 (C=C aromatic), 1430 (CH alkane), 1235 and 1086 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.84 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.66 – 3.69 (7H, m, N(CH$_2$C*H*$_2$)$_2$O, OCH_3), 4.31 (2H, d, *J* = 6.0 Hz, CH_2), 6.17 – 6.19 (2H, m, H-3, H-5), 6.97 (1H, t, *J* = 6.0 Hz, NH), 7.34 – 7.40 (4H, m, H-2', H-3') and 7.57 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH_2), 50.9 (OCH_3), 52.4 (N(*C*H$_2$CH$_2$)$_2$O), 66.3 (N(CH$_2$*C*H$_2$)$_2$O), 101.4 (C-3), 104.9 (C-5), 109.1 (C-1), 128.3 (C-3'), 129.0 (C-2'), 131.2 (C-4'), 134.1 (C-6), 138.7 (C-1'), 152.7 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 385 (^{37}ClMNa$^+$, 15%), 383 (^{35}ClMNa$^+$, 50%), 363 (^{37}ClMH$^+$, 45%), 361 (^{35}ClMH$^+$, 15%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MH$^+$): 363.1293, $C_{19}H_{22}{}^{37}ClN_2O_3$ requires 363.1291. Found (MH$^+$): 361.1312, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 361.1313.

Methyl 4-((2'-bromobenzyl)amino)-2-morpholinobenzoate 10h



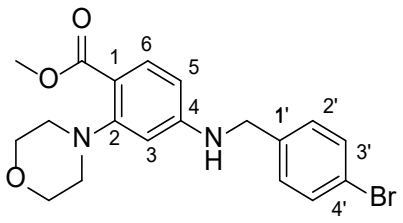
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 2-bromobenzaldehyde **9h** (0.355 g, 1.92 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 25 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10h** (0.367 g, 61%) as an off white solid. M.p.: 103 – 105 °C. R.f.: 0.50 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3338 (NH), 2961 (CH aromatic), 2849 (CH alkane), 1694 (C=O ester), 1602 and 1531 (C=C aromatic), 1427 (CH alkane), 1215 and 1104 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.66 – 3.69 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.36 (2H, d, *J* = 6.0 Hz, CH_2), 6.14 – 6.18 (2H, m, H-3, H-5), 6.98 (1H, t, *J* = 6.0 Hz, NH), 7.20 – 7.23 (1H, m, H-4'), 7.32 – 7.37 (2H, m, H-5', H-6'), 7.58 (1H, d, *J* = 8.5 Hz, H-6) and 7.63 (1H, d, *J* = 8.0 Hz, H-3'). δ_C (100 MHz; $(CD_3)_2SO$): 46.2 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.3 (C-3), 104.7 (C-5), 109.3 (C-1), 122.7 (C-2'), 127.8 (C-5'), 129.0 (C-4'), 129.1 (C-6'), 132.5 (C-3'), 134.1 (C-6'), 137.8 (C-1'), 152.6 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 429 ($^{81}BrMNa^+$, 50%), 427 ($^{79}ClMNa^+$, 50%), 407 ($^{81}BrMH^+$, 45%), 405 ($^{79}BrMH^+$, 45%), 375 (100%), 373 (100%). HRMS (ESI+): Found (MH^+): 407.0782, $C_{19}H_{22}{}^{81}BrN_2NaO_3$ requires 407.0790. Found (MH^+): 405.0799, $C_{19}H_{21}{}^{79}BrN_2NaO_3$ requires 405.0808.

Methyl 4-((3'-bromobenzyl)amino)-2-morpholinobenzoate 10i



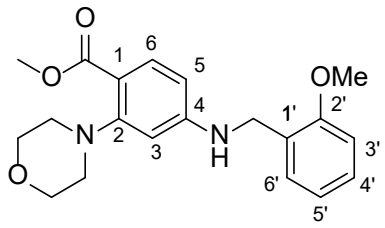
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 3-bromobenzaldehyde **9i** (0.355 g, 1.92 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 24 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10i** (0.336 g, 56%) as an off white solid. M.p.: 101 – 103 °C. R.f.: 0.50 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3316 (NH), 2955 (CH aromatic), 2832 (CH alkane), 1691 (C=O ester), 1602 and 1566 (C=C aromatic), 1426 (CH alkane), 1236 and 1105 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.69 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.33 (2H, d, *J* = 6.0 Hz, CH_2), 6.18 – 6.20 (2H, m, H-3, H-5), 6.98 (1H, t, *J* = 6.0 Hz, NH), 7.29 (1H, t, *J* = 8.0 Hz, H-5'), 7.35 (1H, d, *J* = 8.0 Hz, H-6'), 7.43 (1H, d, *J* = 8.0 Hz, H-4'), 7.56 (1H, br s, H-2') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.2 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.5 (C-3), 104.9 (C-5), 109.2 (C-1), 121.7 (C-3'), 126.3 (C-6'), 129.6 (C-4'), 129.9 (C-2'), 130.5 (C-5'), 134.1 (C-6), 142.7 (C-1'), 152.6 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 429 ($^{81}BrMNa^+$, 50%), 427 ($^{79}ClMNa^+$, 50%), 407 ($^{81}BrMH^+$, 50%), 405 ($^{79}BrMH^+$, 50%), 375 (100%), 373 (100%). HRMS (ESI+): Found (MH^+): 407.0782, $C_{19}H_{22}{}^{81}BrN_2NaO_3$ requires 407.0790. Found (MH^+): 405.0798, $C_{19}H_{21}{}^{79}BrN_2NaO_3$ requires 405.0808.

Methyl 4-((4'-bromobenzyl)amino)-2-morpholinobenzoate 10j



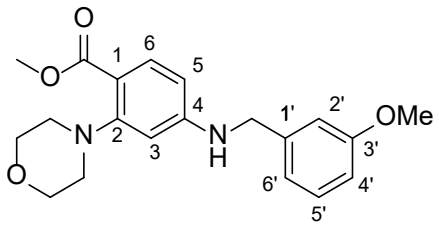
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.350 g, 1.48 mmol), 4Å molecular sieves (1.48 g) and 4-bromobenzaldehyde **9j** (0.355 g, 1.92 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.168 g, 4.44 mmol) and stirred for 18.5 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10j** (0.261 g, 44%) as an off white solid. M.p.: 114 – 116 °C. R.f.: 0.37 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3316 (NH), 2950 (CH aromatic), 2814 (CH alkane), 1698 (C=O ester), 1601 and 1567 (C=C aromatic), 1426 (CH alkane), 1207 and 1086 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.70 (7H, m, $N(CH_2CH_2)_2O$, OCH_3), 4.30 (2H, d, *J* = 6.0 Hz, CH_2), 6.16 – 6.19 (2H, m, H-3, H-5), 6.97 (1H, t, *J* = 6.0 Hz, NH), 7.30 (2H, d, *J* = 8.5 Hz, H-2'), 7.52 (2H, d, *J* = 8.5 Hz, H-3') and 7.57 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.2 (CH_2), 50.9 (OCH_3), 52.4 ($N(CH_2CH_2)_2O$), 66.3 ($N(CH_2CH_2)_2O$), 101.4 (C-3), 104.9 (C-5), 109.1 (C-1), 119.7 (C-4'), 129.4 (C-2'), 131.2 (C-3'), 134.1 (C-6), 139.1 (C-1'), 152.7 (C-4), 154.8 (C-2) and 166.1 (C=O). *m/z* (ESI+): 429 ($^{81}BrMNa^+$, 50%), 427 ($^{79}ClMNa^+$, 50%), 407 ($^{81}BrMH^+$, 50%), 405 ($^{79}BrMH^+$, 50%), 375 (100%), 373 (100%). HRMS (ESI+): Found (MH^+): 407.0788, $C_{19}H_{22}{}^{81}BrN_2NaO_3$ requires 407.0790. Found (MH^+): 405.0804, $C_{19}H_{21}{}^{79}BrN_2NaO_3$ requires 405.0808.

Methyl 4-((2'-methoxybenzyl)amino)-2-morpholinobenzoate 10k



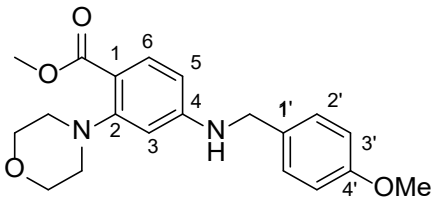
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.325 g, 1.38 mmol), 4Å molecular sieves (1.38 g) and 2-methoxybenzaldehyde **9k** (0.243 g, 1.79 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.156 g, 4.13 mmol) and stirred for 18.5 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10k** (0.410 g, 84%) as an off-white solid. M.p.: 108 – 110 °C. R.f.: 0.29 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3350 (NH), 2950 (CH aromatic), 2801 (CH alkane), 1694 (C=O ester), 1602 and 1568 (C=C aromatic), 1432 and 1426 (CH alkane), 1236, 1224 and 1105 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.66 (3H, s, CO_2CH_3), 3.69 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 3.83 (3H, s, 2'-OCH_3), 4.26 (2H, d, *J* = 6.0 Hz, CH_2), 6.16 (1H, dd, *J* = 2.5, 8.5 Hz, H-5), 6.20 (1H, d, *J* = 2.5 Hz, H-3), 6.78 (1H, t, *J* = 6.0 Hz, NH), 6.89 (1H, td, *J* = 1.0, 7.0 Hz, H-5'), 7.00 (1H, d, *J* = 8.0 Hz, H-3'), 7.21 – 7.26 (2H, m, H-4', H-6') and 7.57 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 40.6 (CH_2), 50.8 (CO_2*C*H$_3$), 52.4 (N(*C*H$_2$CH$_2$)$_2$O), 55.3 (3'-OCH_3) 66.3 (N(CH$_2$*C*H$_2$)$_2$O), 101.1 (C-3), 104.7 (C-5), 108.7 (C-1), 110.6 (C-3'), 120.2 (C-5'), 126.7 (C-1'), 128.1 (C-4', C-6'), 134.1 (C-6), 153.0 (C-4), 154.9 (C-2), 156.8 (C-2') and 166.1 (C=O). *m/z* (ESI+): 379 (MNa$^+$, 60%), 357 (MH$^+$, 35%) and 325 (100%). HRMS (ESI+): Found (MNa$^+$): 379.1616, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

Methyl 4-((3'-methoxybenzyl)amino)-2-morpholinobenzoate 10l



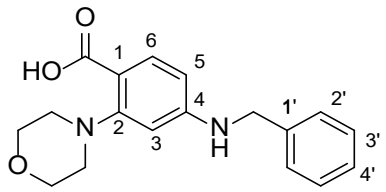
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.325 g, 1.38 mmol), 4Å molecular sieves (1.38 g) and 3-methoxybenzaldehyde **9l** (0.243 g, 1.79 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.156 g, 4.13 mmol) and stirred for 22 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10l** (0.290 g, 59%) as an off white solid. M.p.: 82 – 84 °C. R.f.: 0.28 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3347 (NH), 2949 (CH aromatic), 2836 (CH alkane), 1696 (C=O ester), 1600 and 1573 (C=C aromatic), 1432 (CH alkane), 1236 and 1105 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.67 – 3.70 (7H, m, $N(CH_2CH_2)_2O$, CO_2CH_3), 3.73 (3H, s, 3'-OCH_3), 4.29 (2H, d, *J* = 6.0 Hz, CH_2), 6.19 – 6.22 (2H, m, H-3, H-5), 6.91 – 6.94 (3H, m, NH, H-2', H-6'), 6.80 (1H, dd, *J* = 2.0, 8.0 Hz, H-4'), 7.24 (1H, t, *J* = 8.0 Hz, H-5') and 7.57 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.9 (CH_2), 50.8 (CO_2CH_3), 52.4 ($N(CH_2CH_2)_2O$), 54.9 (3'-OCH_3), 66.3 ($N(CH_2CH_2)_2O$), 101.4 (C-3), 104.9 (C-5), 108.9 (C-1), 112.1 (C-4'), 112.9 (C-2'), 119.4 (C-6'), 129.4 (C-5'), 134.0 (C-6), 141.2 (C-1'), 152.9 (C-4), 154.8 (C-2), 159.4 (C-3') and 166.1 (C=O). *m/z* (ESI+): 379 (MNa^+, 60%), 357 (MH^+, 20%) and 325 (100%). HRMS (ESI+): Found (MNa^+): 379.1625, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

Methyl 4-((4'-methoxybenzyl)amino)-2-morpholinobenzoate 10m



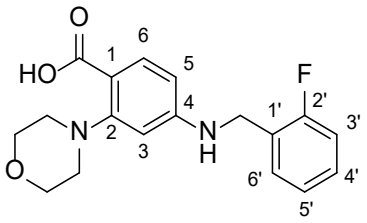
Following **General Procedure 4.2.1**, the reaction was carried out using methyl 4-amino-2-morpholinobenzoate **8** (0.248 g, 1.05 mmol), 4Å molecular sieves (1.05 g) and 4-methoxybenzaldehyde **9m** (0.185 g, 1.36 mmol) in CH_2Cl_2 (5 mL) to produce the desired imine intermediate as a yellow residue. This residue was redissolved in THF/MeOH (1:1, 6 mL), treated with $NaBH_4$ (0.119 g, 3.15 mmol) and stirred for 19.5 h. The crude product was purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title product* **10m** (0.186 g, 50%) as an off white solid. M.p.: 123 – 125 °C. R.f.: 0.28 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3369 (NH), 2956 (CH aromatic), 2852 and 2830 (CH alkane), 1656 (C=O ester), 1590 (C=C aromatic), 1437 and 1408 (CH alkane), 1238, 1201 and 1109 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.85 (4H, br s, N(C*H*$_2$CH$_2$)$_2$O), 3.66 – 3.72 (10H, m, N(CH$_2$C*H*$_2$)$_2$O, CO_2CH_3, 4'-OMe), 4.23 (2H, d, *J* = 5.0 Hz, CH_2), 6.19 – 6.21 (2H, m, H-3, H-5), 6.86 – 6.90 (3H, m, NH, H-3'), 7.26 (2H, d, *J* = 6.5 Hz, H-2') and 7.57 (1H, d, *J* = 7.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.4 (CH_2), 50.8 (CO_2CH_3), 52.4 (N(*C*H$_2$CH$_2$)$_2$O), 55.0 (3'-OCH_3), 66.3 (N(CH$_2$*C*H$_2$)$_2$O), 101.3 (C-3), 104.9 (C-5), 108.7 (C-1), 113.7 (C-3'), 128.5 (C-2'), 131.3 (C-1'), 134.0 (C-6), 152.9 (C-4), 154.8 (C-2), 158.2 (C-4') and 166.1 (C=O). *m/z* (ESI+): 379 (MNa^+, 55%), 357 (MH^+, 20%) and 325 (100%). HRMS (ESI+): Found (MNa^+): 379.1625, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

4-(Benzylamino)-2-morpholinobenzoic acid 11a



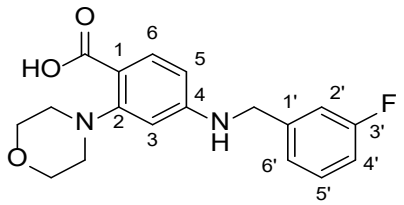
Following **General Procedure 4.2.2**, 1 M NaOH (3.83 mL, 3.83 mmol) was added to a solution of methyl 4-(benzylamino)-2-morpholinobenzoate **10a** (0.250 g, 0.766 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 23 h, affording the *title product* **11a** (0.181 g, 76%) as a fine white powder. M.p.: 184 – 186 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3368 (OH, NH), 2957 (CH aromatic), 2854 (CH alkane), 1656 (C=O carboxylic acid), 1593 and 1510 (C=C aromatic), 1452 and 1442 (CH alkane), 1262 and 1144 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.92 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.76 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.37 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.57 (1H, dd, *J* = 2.0, 8.0 Hz, H-5), 6.71 (1H, d, *J* = 2.0 Hz, H-3), 7.14 (1H, t, *J* = 6.0 Hz, NH), 7.23 – 7.27 (1H, m, H-4'), 7.32 – 7.38 (4H, m, H-2', H-3') and 7.72 (1H, d, *J* = 8.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.9 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.5 (C-5), 111.0 (C-1), 126.9 (C-4'), 127.4 (C-2'), 128.4 (C-3'), 132.9 (C-6), 139.2 (C-1'), 152.7 (C-2), 153.3 (C-4) and 166.5 (C=O). *m/z* (ESI+): 335 (MNa$^+$, 100%), 313 (10%). HRMS (ESI+): Found (MNa$^+$): 335.1366, $C_{18}H_{20}N_2NaO_3$ requires 335.1366.

4-((2'-Fluorobenzyl)amino)-2-morpholinobenzoic acid 11b



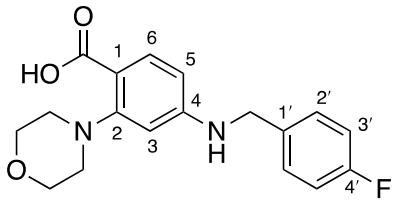
Following **General Procedure 4.2.2**, 1 M NaOH (3.63 mL, 3.63 mmol) was added to a solution of methyl 4-((2'-fluorobenzyl)amino)-2-morpholinobenzoate **10b** (0.250 g, 0.726 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 24 h, affording the *title product* **11b** (0.182 g, 76%) as a white powder. M.p.: 184 – 186 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3370 (OH, NH), 2961 (CH aromatic), 2853 (CH alkane), 1682 (C=O carboxylic acid), 1598 (C=C aromatic), 1488 and 1350 (CH alkane), 1259 (C-O ether), 1231 (C-F), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.94 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, m, N(CH$_2$C*H*$_2$)$_2$O), 4.41 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.59 (1H, dd, *J* = 2.5, 8.5 Hz, H-5), 6.74 (1H, d, *J* = 2.5 Hz, H-3), 7.08 (1H, t, *J* = 6.0 Hz, NH), 7.16 – 7.23 (2H, m, H-3', H-5'), 7.33 (1H, qd, *J* = 2.0, 7.5 Hz, H-4'), 7.41 (1H, td, *J* = 2.0, 7.5 Hz, H-6') and 7.73 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 39.8 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.7 (C-3), 110.4 (C-5), 111.2 (C-1), 115.2 (d, $^2J_{F/C}$ = 21.3 Hz, C-3'), 124.4 (d, $^4J_{F/C}$ = 3.2 Hz, C-5'), 125.7 (d, $^2J_{F/C}$ = 14.7 Hz, C-1'), 129.1 (d, $^3J_{F/C}$ = 8.1 Hz, C-4'), 129.7 (d, $^3J_{F/C}$ = 4.3 Hz, C-6'), 132.6 (C-6), 152.7 (C-2), 153.1 (C-4), 160.4 (d, $^1J_{F/C}$ = 244.3 Hz, C-2') and 166.5 (C=O). *m/z* (ESI+): 353 (MNa$^+$, 100%), 313 (10%). HRMS (ESI+): Found (MNa$^+$): 353.1273, $C_{18}H_{19}FN_2NaO_3$ requires 353.1272.

4-((3'-Fluorobenzyl)amino)-2-morpholinobenzoic acid 11c



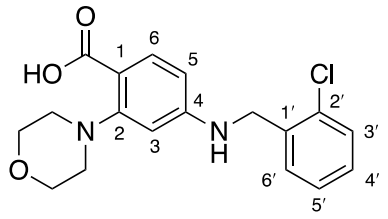
Following **General Procedure 4.2.2**, 1 M NaOH (4.30 mL, 4.30 mmol) was added to a solution of methyl 4-((3'-fluorobenzyl)amino)-2-morpholinobenzoate **10c** (0.296 g, 0.859 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 24 h, affording the *title product* **11c** (0.226 g, 80%) as a white powder. M.p.: 173 – 175 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3384 (OH, NH), 2961 (CH aromatic), 2853 (CH alkane), 1683 (C=O carboxylic acid), 1598 and 1586 (C=C aromatic), 1489 and 1350 (CH alkane), 1259 (C-O ether), 1231 (C-F), 1119 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.92 (4H, t, *J* = 4.5 Hz, N(CH_2CH_2)$_2$O), 3.76 (4H, t, *J* = 4.5 Hz, N(CH_2CH_2)$_2$O), 4.40 (2H, d, *J* = 6.0 Hz, CH_2), 6.56 (1H, dd, *J* = 2.0, 8.0 Hz, H-5), 6.71 (1H, d, *J* = 2.0 Hz, H-3), 7.07 (1H, td, *J* = 2.5, 8.5 Hz, H-4'), 7.17 – 7.22 (3H, m, N-H, H-2', H-6'), 7.39 (1H, q, *J* = 8.0 Hz, H-5') and 7.73 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.3 (CH_2), 52.8 (N(CH_2CH_2)$_2$O), 66.4 (N(CH_2CH_2)$_2$O), 104.9 (C-3), 110.6 (C-5), 111.3 (C-1), 113.6 (d, $^2J_{F/C}$ = 21.0 Hz, C-4'), 113.9 (d, $^2J_{F/C}$ = 21.4 Hz, C-2'), 123.3 (d, $^4J_{F/C}$ = 2.4 Hz, C-6'), 130.3 (d, $^3J_{F/C}$ = 8.4 Hz, C-5'), 132.6 (C-6), 142.5 (d, $^3J_{F/C}$ = 6.8 Hz, C-1'), 152.7 (C-2), 153.1 (C-4), 162.3 (d, $^1J_{F/C}$ = 243.5 Hz, C-3') and 166.5 (C=O). *m/z* (ESI+): 353 (MNa^+, 100%), 313 (10%). HRMS (ESI+): Found (MNa^+): 353.1274, $C_{18}H_{19}FN_2NaO_3$ requires 353.1272.

4-((4'-Fluorobenzyl)amino)-2-morpholinobenzoic acid 11d



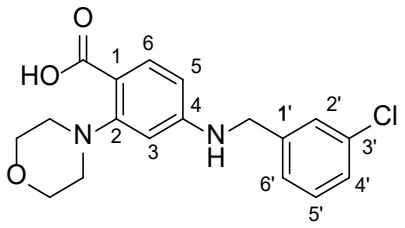
Following **General Procedure 4.2.2**, 1 M NaOH (2.18 mL, 2.18 mmol) was added to a solution of methyl 4-((4'-fluorobenzyl)amino)-2-morpholinobenzoate **10d** (0.150 g, 0.436 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 23 h, affording the *title product* **11d** (0.103 g, 72%) as a white powder. M.p.: 202 – 204 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3383 (OH, NH), 2961 (CH aromatic), 2854 (CH alkane), 1684 (C=O carboxylic acid), 1598 and 1586 (C=C aromatic), 1489 and 1350 (CH alkane), 1259 (C-O ether), 1231 (C-F), 1118 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.92 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.35 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.56 (1H, dd, *J* = 2.5, 8.5 Hz, H-5), 6.70 (1H, d, *J* = 2.5 Hz, H-3), 7.12 = 7.19 (3H, m, N-H, H-3'), 7.39 – 7.42 (2H, m, H-2') and 7.72 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.6 (C-5), 111.1 (C-1), 115.1 (d, $^2J_{F/C}$ = 21.3 Hz, C-3'), 129.3 (d, $^3J_{F/C}$ = 8.1 Hz, C-2'), 132.6 (C-6), 135.3 (d, $^4J_{F/C}$ = 2.7 Hz, C-1'), 152.7 (C-2), 153.2 (C-4), 161.2 (d, $^1J_{F/C}$ = 242.2 Hz, C-4') and 166.5 (C=O). *m/z* (ESI+): 353 (MNa$^+$, 100%), 313 (10%). HRMS (ESI+): Found (MNa$^+$): 353.1289, $C_{18}H_{19}FN_2NaO_3$ requires 353.1272.

4-((2'-Chlorobenzyl)amino)-2-morpholinobenzoic acid 11e



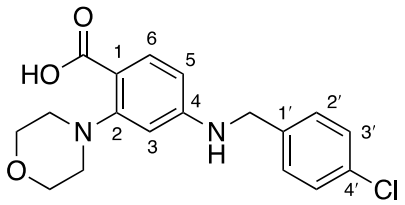
Following **General Procedure 4.2.2**, 1 M NaOH (3.46 mL, 3.46 mmol) was added to a solution of methyl 4-((2'-chlorobenzyl)amino)-2-morpholinobenzoate **10e** (0.250 g, 0.693 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 28 h, affording the *title product* **11e** (0.190 g, 79%) as a white powder. M.p.: 183 – 185 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3384 (OH, NH), 2961 (CH aromatic), 2853 (CH alkane), 1682 (C=O carboxylic acid), 1599 and 1586 (C=C aromatic), 1489 (CH alkane), 1259 and 1119 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, br s, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, m, N(CH$_2$C*H*$_2$)$_2$O), 4.44 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.55 (1H, d, *J* = 8.5 Hz, H-5), 6.72 (1H, s, H-3), 7.14 (1H, t, *J* = 6.0 Hz, NH), 7.30 – 7.32 (2H, m, H-4', H-5'), 7.39 – 7.41 (1H, m, H-6'), 7.47 – 7.49 (1H, m, H-3') and 7.74 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 43.8 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.8 (C-3), 110.3 (C-5), 111.3 (C-1), 127.3 (C-5'), 128.8 (C-4'), 129.2 (C-6'), 129.3 (C-3'), 132.5 (C-2'), 132.7 (C-6), 136.1 (C-1'), 152.7 (C-2), 153.1 (C-4) and 166.5 (C=O). *m/z* (ESI+): 371 (^{37}ClMNa$^+$, 30%), 369 (^{35}ClMNa$^+$, 100%) and 329 (10%). HRMS (ESI+): Found (MNa$^+$): 371.0961, $C_{18}H_{19}{}^{37}ClN_2NaO_3$ requires 371.0953. Found (MNa$^+$): 369.0980, $C_{18}H_{19}{}^{35}ClN_2NaO_3$ requires 369.0976.

4-((3'-Chlorobenzyl)amino)-2-morpholinobenzoic acid 11f



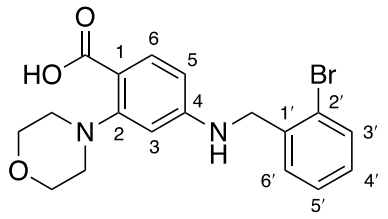
Following **General Procedure 4.2.2**, 1 M NaOH (3.13 mL, 3.13 mmol) was added to a solution of methyl 4-((3'-chlorobenzyl)amino)-2-morpholinobenzoate **10f** (0.226 g, 0.626 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 21 h, affording the *title product* **11f** (0.153 g, 71%) as a white powder. M.p.: 150 – 152 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3373 (OH, NH), 2961 (CH aromatic), 2853 (CH alkane), 1681 (C=O carboxylic acid), 1586 (C=C aromatic), 1489 (CH alkane), 1259 and 1118 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, br s, N(CH$_2$C*H*$_2$)$_2$O), 4.39 (2H, d, *J* = 5.0 Hz, CH$_2$), 6.56 (1H, dd, *J* = 2.0, 8.5 Hz, H-5), 6.72 (1H, d, *J* = 2.0 Hz, H-3), 7.19 (1H, t, *J* = 5.0 Hz, NH), 7.29 – 7.39 (3H, m, H-4', H-5', H-6'), 7.44 (1H, s, H-2') and 7.73 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.2 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 105.0 (C-3), 110.6 (C-5), 111.3 (C-1), 126.0 (C-6'), 126.8 (C-4'), 127.1 (C-2'), 130.3 (C-5'), 132.6 (C-6), 133.1 (C-3'), 142.1 (C-1'), 152.7 (C-2), 153.1 (C-4) and 166.5 (C=O). *m/z* (ESI+): 371 (^{37}ClMNa$^+$, 30%), 369 (^{35}ClMNa$^+$, 100%) and 329 (10%). HRMS (ESI+): Found (MNa$^+$): 371.0963, $C_{18}H_{19}{}^{37}ClN_2NaO_3$ requires 371.0953. Found (MNa$^+$): 369.0977, $C_{18}H_{19}{}^{35}ClN_2NaO_3$ requires 369.0976.

4-((4'-Chlorobenzyl)amino)-2-morpholinobenzoic acid 11g



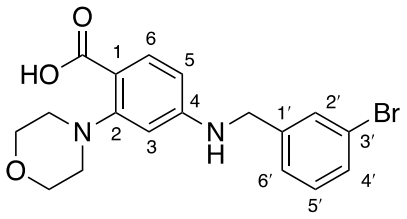
Following **General Procedure 4.2.2**, 1 M NaOH (3.44 mL, 3.44 mmol) was added to a solution of methyl 4-((4'-chlorobenzyl)amino)-2-morpholinobenzoate **10g** (0.248 g, 0.687 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 25 h, affording the *title product* **11g** (0.190 g, 80%) as a white powder. M.p.: 140 – 142 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3338 (OH, NH), 2850 (CH alkane), 1677 (C=O carboxylic acid), 1594 (C=C aromatic), 1491 (CH alkane), 1260 and 1120 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.37 (2H, br s, CH$_2$), 6.55 (1H, dd, *J* = 2.0, 8.5 Hz, H-5), 6.70 (1H, d, *J* = 2.0 Hz, H-3), 7.20 (1H, br s, NH), 7.37 – 7.42 (4H, m, H-2', H-3') and 7.72 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.6 (C-5), 111.1 (C-1), 128.3 (C-3'), 129.2 (C-2'), 131.4 (C-4'), 132.6 (C-6), 138.3 (C-1'), 152.6 (C-2), 153.2 (C-4) and 166.5 (C=O). *m/z* (ESI+): 371 (^{37}ClMNa$^+$, 30%), 369 (^{35}ClMNa$^+$, 100%) and 329 (10%). HRMS (ESI+): Found (MNa$^+$): 371.0965, $C_{18}H_{19}{}^{37}ClN_2NaO_3$ requires 371.0953. Found (MNa$^+$): 369.0976, $C_{18}H_{19}{}^{35}ClN_2NaO_3$ requires 369.0976.

4-((2'-Bromobenzyl)amino)-2-morpholinobenzoic acid 11h



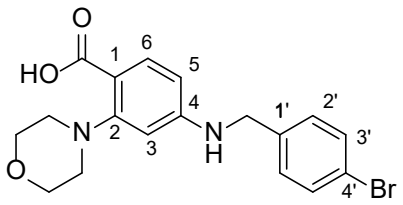
Following **General Procedure 4.2.2**, 1 M NaOH (2.5 mL, 2.47 mmol) was added to a solution of methyl 4-((2'-bromobenzyl)amino)-2-morpholinobenzoate **10h** (0.200 g, 0.493 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 18 h, affording the *title product* **11h** (0.163 g, 82%) as a white powder. M.p.: 184 – 186 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3364 (OH, NH), 2949 (CH aromatic), 2850 (CH alkane), 1679 (C=O carboxylic acid), 1598 (C=C aromatic), 1312, 1258 and 1126 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.41 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.54 (1H, dd, *J* = 2.0, 8.5 Hz, H-5), 6.70 (1H, d, *J* = 2.0 Hz, H-3), 7.14 (1H, *t*, *J* = 6.0 Hz, NH), 7.21 – 7.25 (1H, m, H-4'), 7.34 – 7.40 (2H, m, H-5', H-6'), 7.65 (1H, d, *J* = 8.0 Hz, H-3') and 7.74 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 46.3 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.8 (C-3), 110.3 (C-5), 111.4 (C-1), 122.8 (C-2'), 127.8 (C-5'), 129.1 (C-4'), 129.2 (C-6'), 132.6 (C-3'), 132.7 (C-6), 137.5 (C-1'), 152.7 (C-2), 153.0 (C-4) and 166.5 (C=O). *m/z* (ESI+): 415 (^{81}BrMNa$^+$, 100%), 413 (^{79}BrMNa$^+$, 100%). HRMS (ESI+): Found (MNa$^+$): 415.0448, $C_{18}H_{19}{}^{81}BrN_2NaO_3$ requires 415.0453. Found (MNa$^+$): 413.0468, $C_{18}H_{19}{}^{79}BrN_2NaO_3$ requires 413.0471.

4-((3'-Bromobenzyl)amino)-2-morpholinobenzoic acid 11i



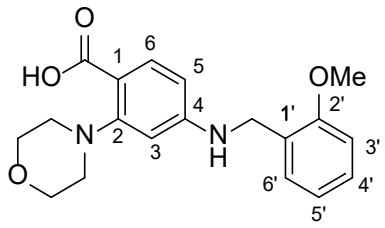
Following **General Procedure 4.2.2**, 1 M NaOH (3.26 mL, 3.26 mmol) was added to a solution of methyl 4-((3'-bromobenzyl)amino)-2-morpholinobenzoate **10i** (0.264 g, 0.651 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 20 h, affording the *title product* **11i** (0.179 g, 70%) as a white powder. M.p.: 171 – 173 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3363 (OH, NH), 2949 (CH aromatic), 2849 (CH alkane), 1678 (C=O carboxylic acid), 1598 (C=C aromatic), 1258 and 1126 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.39 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.56 (1H, d, *J* = 8.5 Hz, H-5), 6.72 (1H, s, H-3), 7.18 (1H, t, *J* = 6.0 Hz, NH), 7.30 (1H, t, *J* = 7.5 Hz, H-5'), 7.37 (1H, d, *J* = 7.5 Hz, H-6'), 7.44 (1H, d, *J* = 7.5 Hz, H-4'), 7.59 (1H, s, H-2') and 7.73 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 105.0 (C-3), 110.6 (C-5), 111.3 (C-1), 121.7 (C-3'), 126.4 (C-6'), 129.7 (C-4'), 130.1 (C-2'), 130.6 (C-5'), 132.6 (C-6), 142.3 (C-1'), 152.7 (C-2), 153.1 (C-4) and 166.5 (C=O). *m/z* (ESI+): 415 (^{81}BrMNa$^+$, 100%), 413 (^{79}BrMNa$^+$, 100%). HRMS (ESI+): Found (MNa$^+$): 415.0453, $C_{18}H_{19}{}^{81}BrN_2NaO_3$ requires 415.0453. Found (MNa$^+$): 413.0472, $C_{18}H_{19}{}^{79}BrN_2NaO_3$ requires 413.0471.

4-((4'-Bromobenzyl)amino)-2-morpholinobenzoic acid 11j



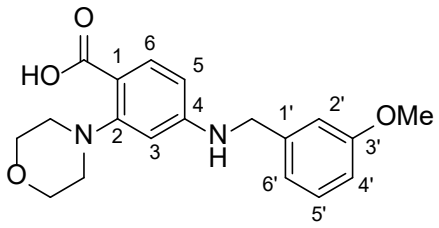
Following **General Procedure 4.2.2**, 1 M NaOH (2.53 mL, 2.53 mmol) was added to a solution of methyl 4-((4'-bromobenzyl)amino)-2-morpholinobenzoate **10j** (0.205 g, 0.506 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 23 h, affording the *title product* **11j** (0.133 g, 67%) as a white powder. M.p.: 125 – 127 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3361 (OH, NH), 2856 (CH alkane), 1678 (C=O carboxylic acid), 1599 (C=C aromatic), 1342 (CH alkane), 1257 and 1116 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.95 (4H, br s, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, br s, N(CH$_2$C*H*$_2$)$_2$O), 4.35 (2H, br s, CH$_2$), 6.55 (1H, d, *J* = 9.0 Hz, H-5), 6.71 (1H, s, H-3), 7.18 (1H, br s, NH), 7.33 (2H, d, *J* = 8.5 Hz, H-2'), 7.53 (2H, d, *J* = 8.5 Hz, H-3') and 7.72 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.1 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.6 (C-5), 111.1 (C-1), 119.9 (C-4'), 129.5 (C-2'), 131.2 (C-3'), 132.6 (C-6), 138.8 (C-1'), 152.5 (C-2), 153.1 (C-4) and 166.6 (C=O). *m/z* (ESI+): 415 (^{81}BrMNa$^+$, 100%), 413 (^{79}BrMNa$^+$, 100%). HRMS (ESI+): Found (MNa$^+$): 415.0450, $C_{18}H_{19}{}^{81}BrN_2NaO_3$ requires 415.0453. Found (MNa$^+$): 413.0474, $C_{18}H_{19}{}^{79}BrN_2NaO_3$ requires 413.0471.

4-((2'-Methoxybenzyl)amino)-2-morpholinobenzoic acid 11k



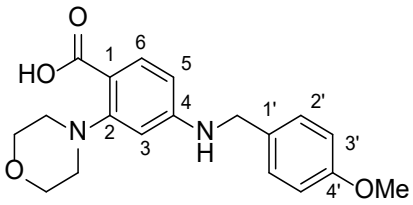
Following **General Procedure 4.2.2**, 1 M NaOH (3.44 mL, 3.44 mmol) was added to a solution of methyl 4-((2'-methoxybenzyl)amino)-2-morpholinobenzoate **10k** (0.245 g, 0.687 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 22 h, affording the *title product* **11k** (0.220 g, 94%) as a white powder. M.p.: 148 – 150 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3364 (OH, NH), 2849 (CH alkane), 1674 (C=O carboxylic acid), 1598 (C=C aromatic), 1342 (CH alkane), 1257 and 1125 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 3.85 (3H, s, 2'-OCH$_3$), 4.30 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.54 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.71 (1H, d, *J* = 2.5 Hz, H-3), 6.90 (1H, td, *J* = 7.5, 1.0 Hz, H-5'), 6.95 (1H, t, *J* = 6.0 Hz, NH), 7.02 (1H, dd, *J* = 7.5, 1.0 Hz, H-3'), 7.24 – 7.27 (2H, m, H-4', H-6') and 7.72 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 40.8 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 55.4 (2'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.7 (C-3), 110.2 (C-5), 110.7 (C-3'), 110.8 (C-1), 120.2 (C-5'), 126.3 (C-1'), 128.3 (C-4'), 128.3 (C-6'), 132.6 (C-6), 152.7 (C-2), 153.4 (C-4), 156.9 (C-2') and 166.5 (C=O). *m/z* (ESI+): 365 (MNa$^+$, 100%) and 325 (10%). HRMS (ESI+): Found (MNa$^+$): 365.1471, $C_{19}H_{22}N_2NaO_4$ requires 365.1472.

4-((3'-Methoxybenzyl)amino)-2-morpholinobenzoic acid 11l



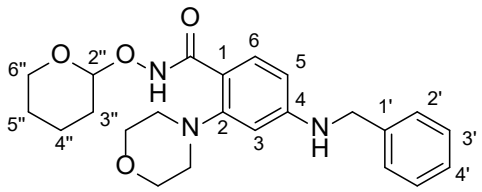
Following **General Procedure 4.2.2**, 1 M NaOH (2.25 mL, 2.25 mmol) was added to a solution of methyl 4-((3'-methoxybenzyl)amino)-2-morpholinobenzoate **10l** (0.160 g, 0.449 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 20 h, affording the *title product* **11l** (0.145 g, 95%) as a white powder. M.p.: 146 – 148 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3361 (OH, NH), 2857 (CH alkane), 1682 (C=O carboxylic acid), 1598, 1586 (C=C aromatic), 1488 (CH alkane), 1258 and 1119 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.78 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 3.73 (3H, s, 3'-OCH$_3$), 4.34 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.56 (1H, dd, *J* = 9.0, 2.5 Hz, H-5), 6.72 (1H, d, *J* = 2.5 Hz, H-3), 6.82 (1H, dd, *J* = 8.0, 2.0 Hz, H-4'), 6.93 – 6.95 (2H, m, H-2', H-6'), 7.12 (1H, t, *J* = 6.0 Hz, NH), 7.25 (1H, t, *J* = 8.0 Hz, H-5') and 7.72 (1H, d, *J* = 9.0 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.9 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 55.0 (3'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.0 (C-1), 110.6 (C-5), 112.2 (C-4'), 113.1 (C-2'), 119.5 (C-6'), 129.4 (C-5'), 132.6 (C-6), 140.9 (C-1'), 152.6 (C-2), 153.3 (C-4), 159.4 (C-3') and 166.5 (C=O). *m/z* (ESI+): 365 (MNa$^+$, 100%) and 325 (10%). HRMS (ESI+): Found (MNa$^+$): 365.1474, $C_{19}H_{22}N_2NaO_4$ requires 365.1472.

4-((4'-Methoxybenzyl)amino)-2-morpholinobenzoic acid 11m



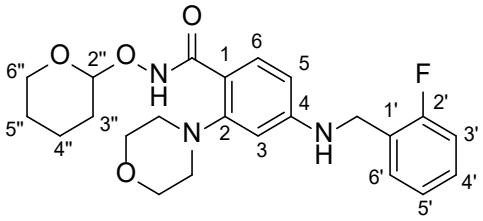
Following **General Procedure 4.2.2**, 1 M NaOH (1.88 mL, 1.88 mmol) was added to a solution of methyl 4-((4'-methoxybenzyl)amino)-2-morpholinobenzoate **10m** (0.134 g, 0.374 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 60 °C for 22.5 h, affording the *title product* **11m** (0.115 g, 89%) as a white powder. M.p.: 174 – 176 °C. R.f.: 0.1 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3360 (OH, NH), 2858 (CH alkane), 1681 (C=O carboxylic acid), 1599 (C=C aromatic), 1511 (CH alkane), 1249 and 1112 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.93 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.77 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 3.72 (3H, s, 4'-OCH$_3$), 4.28 (2H, d, *J* = 6.0 Hz, CH$_2$), 6.56 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.71 (1H, d, *J* = 2.5 Hz, H-3), 6.90 (2H, d, *J* = 9.0 Hz, H-3'), 7.05 (1H, t, *J* = 6.0 Hz, NH), 7.29 (2H, d, *J* = 9.0 Hz, H-2') and 7.72 (1H, d, *J* = 8.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 45.4 (CH$_2$), 52.8 (N(*C*H$_2$CH$_2$)$_2$O), 55.0 (4'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 104.9 (C-3), 110.5 (C-5), 110.9 (C-1), 113.8 (C-3'), 128.7 (C-2'), 130.9 (C-1'), 132.6 (C-6), 152.6 (C-2), 153.3 (C-4), 158.3 (C-4') and 166.5 (C=O). *m/z* (ESI+): 365 (MNa$^+$, 100%) and 325 (10%). HRMS (ESI+): Found (MNa$^+$): 365.1478, $C_{19}H_{22}N_2NaO_4$ requires 365.1472.

4-(Benzylamino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide 15a



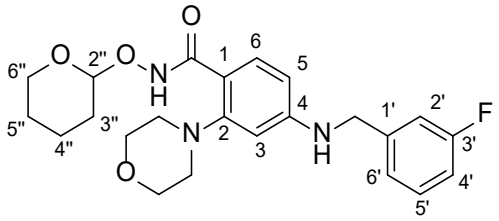
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.115 g, 0.358 mmol), benzaldehyde **9a** (0.190 g, 1.789 mmol) in EtOH (3 mL) for 18 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.079 g, 1.252 mmol) and stirred for 18 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15a** (0.097 g, 66%) as a light yellow solid. M.p.: 132 – 134 °C. R.f.: 0.49 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3359 (NH), 2858 (CH alkane), 1680 (C=O), 1599 and 1512 (C=C aromatic), 1459 and 1342 (CH alkane), 1250 and 1112 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.68 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.96 (3H, m, H-3''eq., H-3''ax., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.83 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.37 (2H, d, *J* = 5.0 Hz, $NHCH_2$), 4.49 (1H, t, *J* = 5.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.37 (1H, d, *J* = 2.5 Hz, H-3), 6.50 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.27 – 7.31 (1H, m, H-4'), 7.33 – 7.36 (4H, m, H-2', H-3'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.16 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 18.9 (C-4''), 25.2 (C-5''), 28.2 (C-3''), 47.9 ($NHCH_2$), 53.6 ($N(CH_2CH_2)_2O$), 62.5 (C-6''), 67.3 ($N(CH_2CH_2)_2O$), 102.4 (C-2''), 104.6 (C-3), 109.6 (C-5), 115.6 (C-1), 127.4 (C-2'), 127.6 (C-4'), 128.8 (C-3'), 133.4 (C-6), 138.3 (C-1'), 151.5 (C-4), 152.4 (C-2) and 165.1 (C=O). *m/z* (ESI+): 434 (MNa^+, 50%), 328 (40%) and 295 (100%). HRMS (ESI+): Found (MNa^+): 434.2045, $C_{24}H_{31}N_3NaO_5$ requires 434.2050.

4-((2'-Fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15b



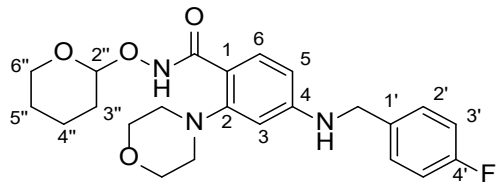
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 2-fluorobenzaldehyde **9b** (0.193 g, 1.556 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 21 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15b** (0.100 g, 75%) as a light-yellow solid. M.p.: 109 – 110 °C. R.f.: 0.40 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3359 (NH), 2858 (CH alkane), 1680 (C=O), 1599 and 1512 (C=C aromatic), 1459 and 1342 (CH alkane), 1250 and 1112 (C-O ether), 1027 (C-F). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.96 (3H, m, H-3''eq., H-3''ax., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.43 (2H, d, *J* = 5.0 Hz, $NHCH_2$), 4.49 (1H, t, *J* = 5.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.40 (1H, d, *J* = 2.5 Hz, H-3), 6.50 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.06 – 7.13 (2H, m, H-3', H-5'), 7.24 – 7.30 (1H, m, H-4'), 7.33 (1H, td, *J* = 7.5, 1.5 Hz, H-6'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.14 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 41.6 (d, $^3J_{F/C}$ = 4.3 Hz, $NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.7 (C-3), 109.8 (C-5), 115.6 (C-1), 115.9 (d, $^2J_{F/C}$ = 17.9 Hz, C-3'), 124.5 (d, $^4J_{F/C}$ = 3.4 Hz, C-5'), 125.4 (d, $^2J_{F/C}$ = 14.3 Hz, C-1''), 129.4 (d, $^3J_{F/C}$ = 8.1 Hz, C-4'), 129.6 (d, $^3J_{F/C}$ = 4.1 Hz, C-6'), 133.5 (C-6), 151.4 (C-4), 152.5 (C-2), 161.0 (d, $^1J_{F/C}$ = 245.8 Hz, C-2') and 165.2 (C=O). *m/z* (ESI+): 452 (MNa^+, 100%), 313 (60%). HRMS (ESI+): Found (MNa^+): 452.1958, $C_{23}H_{28}FN_3NaO_4$ requires 452.1956.

4-((3'-Fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15c



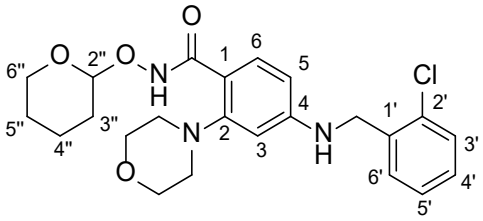
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 3-fluorobenzaldehyde **9c** (0.193 g, 1.556 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 23 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15c** (0.082 g, 61%) as a white solid. M.p.: 159 – 161 °C. R.f.: 0.43 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3360 (NH), 2858 (CH alkane), 1680 (C=O), 1599 and 1512 (C=C aromatic), 1460 and 1295 (CH alkane), 1250 and 1111 (C-O ether), 1027 (C-F). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.96 (3H, m, H-3''eq., H-3''ax., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.38 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.56 (1H, t, *J* = 5.5 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.36 (1H, d, *J* = 2.5 Hz, H-3), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.97 (1H, td, *J* = 8.5, 2.5 Hz, H-4'), 7.05 (1H, dt, *J* = 9.5, 2.0 Hz, H-2'), 7.12 (1H, d, *J* = 8.5 Hz, H-6'), 7.29 – 7.34 (1H, m, H-5'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.13 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.4 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.8 (C-3), 109.7 (C-5), 114.2 (d, $^2J_{F/C}$ = 21.8 Hz, C-2'), 114.6 (d, $^2J_{F/C}$ = 21.2 Hz, C-4'), 116.1 (C-1), 122.9 (d, $^2J_{F/C}$ = 2.6 Hz, C-6'), 130.5 (d, $^3J_{F/C}$ = 8.3 Hz, C-5'), 133.5 (C-6), 141.3 (d, $^3J_{F/C}$ = 6.9 Hz, C-1'), 151.4 (C-4), 152.5 (C-2), 163.3 (d, $^1J_{F/C}$ = 246.4 Hz, C-3') and 165.1 (C=O). *m/z* (ESI+): 452 (MNa^+, 100%), 313 (60%). HRMS (ESI+): Found (MNa^+): 452.1945, $C_{23}H_{28}FN_3NaO_4$ requires 452.1956.

4-((4'-Fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15d



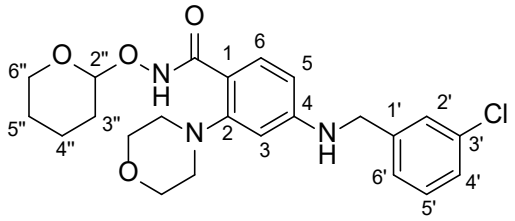
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 4-fluorobenzaldehyde **9d** (0.193 g, 1.556 mmol) in EtOH (3 mL) for 18 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 25 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15d** (0.090 g, 67%) as a light yellow solid. M.p.: 159 – 161 °C. R.f.: 0.41 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3360 (NH), 2858 (CH alkane), 1679 (C=O), 1599 and 1511 (C=C aromatic), 1456 and 1342 (CH alkane), 1250 and 1113 (C-O ether), 1026 (C-F). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.60 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.84 – 1.95 (3H, m, H-3''eq., H-3''ax., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.34 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.48 (1H, t, *J* = 5.5 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.36 (1H, d, *J* = 2.5 Hz, H-3), 6.48 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.04 (2H, tt, *J* = 8.5, 2.5 Hz, H-3'), 7.31 (2H, dd, *J* = 8.5, 2.5 Hz, H-2'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.14 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.3 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.7 (C-3), 109.7 (C-5), 115.8 (d, $^2J_{F/C}$ = 21.6 Hz, C-3'), 116.0 (C-1), 129.1 (d, $^3J_{F/C}$ = 8.1 Hz, C-2'), 133.5 (C-6), 134.1 (d, $^4J_{F/C}$ = 2.9 Hz, C-1'), 151.5 (C-4), 152.5 (C-2), 162.3 (d, $^1J_{F/C}$ = 246.1 Hz, C-4') and 165.2 (C=O). *m/z* (ESI+): 452 (MNa^+, 90%), 313 (100%). HRMS (ESI+): Found (MNa^+): 452.1959, $C_{23}H_{28}FN_3NaO_4$ requires 452.1956.

4-((2'-Chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15e



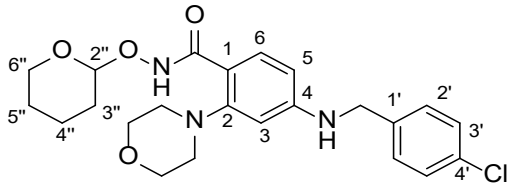
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 2-chlorobenzaldehyde **9e** (0.219 g, 1.556 mmol) in EtOH (3 mL) for 22.5 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 18 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15e** (0.085 g, 61%) as a white solid. M.p.: 154 – 156 °C. R.f.: 0.55 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3360 (NH), 2858 (CH alkane), 1679 (C=O), 1599 and 1511 (C=C aromatic), 1457 and 1339 (CH alkane), 1250 and 1112 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.68 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.94 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.85 – 3.93 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.08 (1H, m, H-6''eq.), 4.47 (2H, d, *J* = 6.0 Hz, $NHCH_2$), 4.61 (1H, t, *J* = 6.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.37 (1H, d, *J* = 2.0 Hz, H-3), 6.48 (1H, dd, *J* = 8.5, 2.0 Hz, H-5), 7.22 – 7.24 (2H, m, H-3', H-4'), 7.39 – 7.41 (1H, m, H-5'), 7.34 – 7.36 (1H, m, H-6'), 7.99 (1H, d, *J* = 8.5 Hz, H-6) and 12.13 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 45.5 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.7 (C-3), 109.8 (C-5), 116.0 (C-1), 127.1 (C-3'), 128.9 (C-6'), 129.2 (C-4'), 129.9 (C-5'), 133.5 (C-2'), 133.5 (C-6), 135.7 (C-1'), 151.4 (C-4), 152.5 (C-2) and 165.2 (C=O). *m/z* (ESI+): 470 ($^{37}ClMNa^+$, 30%), 468 ($^{35}ClMNa^+$, 100%), 331 (15%) and 329 (50%). HRMS (ESI+): Found (MNa^+): 470.1643, $C_{23}H_{28}{}^{37}ClN_3NaO_4$ requires 470.1641. Found (MNa^+): 468.1654, $C_{23}H_{28}{}^{35}ClN_3NaO_4$ requires 468.1661.

4-((3'-Chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15f



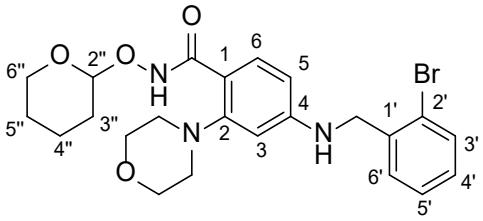
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 3-chlorobenzaldehyde **9f** (0.219 g, 1.556 mmol) in EtOH (3 mL) for 22.5 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 18 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15f** (0.070 g, 50%) as a white solid. M.p.: 162 – 164 °C. R.f.: 0.54 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3321 (NH), 2948 (CH aromatic), 2847 (CH alkane), 1640 (C=O), 1596 (C=C aromatic), 1457 and 1338 (CH alkane), 1250 and 1113 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.67 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.82 – 1.96 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.08 (1H, m, H-6''eq.), 4.36 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.58 (1H, t, *J* = 5.5 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.36 (1H, d, *J* = 2.5 Hz, H-3), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.20 – 7.28 (3H, m, H-4', H-5', H-6'), 7.34 (1H, s, H-2'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.13 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.2 (C-3''), 47.4 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.9 (C-3), 109.7 (C-5), 116.1 (C-1), 125.5 (C-6'), 127.5 (C-2'), 127.8 (C-4'), 130.1 (C-5'), 133.5 (C-6), 134.8 (C-3'), 140.7 (C-1'), 151.3 (C-4), 152.5 (C-2) and 165.1 (C=O). *m/z* (ESI+): 470 ($^{37}ClMNa^+$, 30%), 468 ($^{35}ClMNa^+$, 100%), 331 (10%) and 329 (30%). HRMS (ESI+): Found (MNa^+): 470.1652, $C_{23}H_{28}{}^{37}ClN_3NaO_4$ requires 470.1641. Found (MNa^+): 468.1663, $C_{23}H_{28}{}^{35}ClN_3NaO_4$ requires 468.1661.

4-((4'-Chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15g



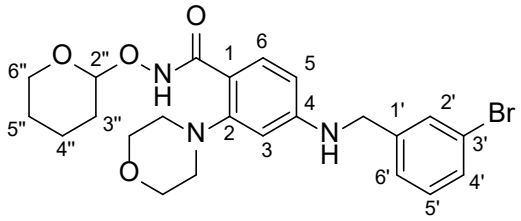
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.150 g, 0.467 mmol), 4-chlorobenzaldehyde **9g** (0.328 g, 2.334 mmol) in EtOH (3 mL) for 17 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.103 g, 1.634 mmol) and stirred for 18 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15g** (0.104 g, 50%) as a cream white solid. M.p.: 150 – 152 °C. R.f.: 0.54 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3308 (NH), 2949 (CH aromatic), 2844 (CH alkane), 1640 (C=O), 1599 (C=C aromatic), 1456 and 1338 (CH alkane), 1250 and 1110 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.60 – 1.68 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.84 – 1.95 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.85 – 3.93 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.08 (1H, m, H-6''eq.), 4.35 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.49 (1H, t, *J* = 6.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.35 (1H, d, *J* = 2.5 Hz, H-3), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.27 (2H, d, *J* = 8.5 Hz, H-2'), 7.32 (2H, d, *J* = 8.5 Hz, H-3'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.13 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.3 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.8 (C-3), 109.7 (C-5), 116.1 (C-1), 128.8 (C-2'), 129.1 (C-3'), 133.5 (C-4'), 133.5 (C-6), 137.0 (C-1'), 151.4 (C-4), 152.5 (C-2), 165.1 (C=O). *m/z* (ESI+): 470 ($^{37}ClMNa^+$, 30%), 468 ($^{35}ClMNa^+$, 100%), 362 (20%), 360 (60%), 331 (10%) and 329 (30%). HRMS (ESI+): Found (MNa^+): 470.1641, $C_{23}H_{28}{}^{37}ClN_3NaO_4$ requires 470.1641. Found (MNa^+): 468.1653, $C_{23}H_{28}{}^{35}ClN_3NaO_4$ requires 468.1661.

4-((2'-Bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15h



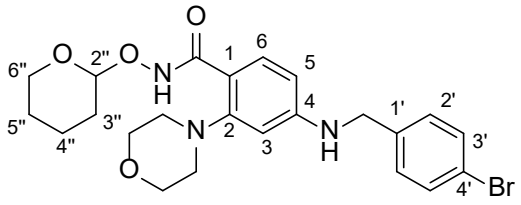
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 2-bromobenzaldehyde **9h** (0.288 g, 1.556 mmol) in EtOH (3 mL) for 23 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 24 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15h** (0.100 g, 65%) as a white solid. M.p.: 159 – 161 °C. R.f.: 0.46 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3320 (NH), 2948 (CH aromatic), 2844 (CH alkane), 1640 (C=O), 1598 (C=C aromatic), 1456 and 1337 (CH alkane), 1261 and 1109 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.82 – 1.92 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, N(CH_2CH_2)$_2$O), 3.65 – 3.70 (1H, m, H-6''ax.), 3.85 – 3.94 (4H, m, N(CH_2CH_2)$_2$O), 4.03 – 4.08 (1H, m, H-6''eq.), 4.45 (2H, d, *J* = 5.5 Hz, NHCH_2), 4.63 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.36 (1H, d, *J* = 2.5 Hz, H-3), 6.48 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.16 (1H, td, *J* = 7.5, 1.5 Hz, H-4'), 7.27 (1H, td, *J* = 7.5, 1.5 Hz, H-5'), 7.35 (1H, dd, *J* = 7.5, 1.5 Hz, H-6'), 7.59 (1H, dd, *J* = 7.5, 1.5 Hz, H-3'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.13 (1H, s, N*H*OTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 48.0 ($NHCH_2$), 53.7 (N(CH_2CH_2)$_2$O), 62.6 (C-6''), 67.4 (N(CH_2CH_2)$_2$O), 102.5 (C-2''), 104.8 (C-3), 109.8 (C-5), 116.0 (C-1), 123.5 (C-2'), 127.8 (C-5'), 129.2 (C-6'), 129.3 (C-4'), 133.2 (C-3'), 133.5 (C-6), 137.3 (C-1'), 151.3 (C-4), 152.5 (C-2) and 165.2 (C=O). *m/z* (ESI+): 514 (^{81}BrMNa^+, 100%) and 512 (^{79}BrMNa^+, 100%). HRMS (ESI+): Found (MNa^+): 514.1135, $C_{23}H_{28}{}^{81}BrN_3NaO_4$ requires 514.1138. Found (MNa^+): 512.1149, $C_{23}H_{28}{}^{79}BrN_3NaO_4$ requires 512.1155.

4-((3'-Bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15i



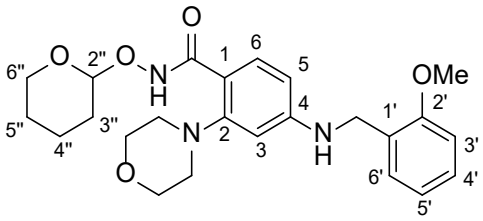
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 3-bromobenzaldehyde **9i** (0.288 g, 1.556 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 23 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15i** (0.093 g, 61%) as a light-yellow solid. M.p.: 152 – 154 °C. R.f.: 0.44 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3320 (NH), 2947 (CH aromatic), 2844 (CH alkane), 1641 (C=O), 1599 (C=C aromatic), 1456 and 1337 (CH alkane), 1249 and 1110 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.60 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.96 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.35 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.52 (1H, t, *J* = 6.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.36 (1H, d, *J* = 2.5 Hz, H-3), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.22 (1H, t, *J* = 7.5 Hz, H-5'), 7.27 (1H, d, *J* = 7.5 Hz, H-6'), 7.42 (1H, dt, *J* = 7.5, 1.5 Hz, H-4'), 7.50 (1H, br s, H-2'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.12 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.4 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.9 (C-3), 109.7 (C-5), 116.1 (C-1), 123.0 (C-3'), 126.0 (C-6'), 130.5 (C-5'), 130.5 (C-2'), 130.8 (C-4'), 133.5 (C-6), 140.9 (C-1'), 151.3 (C-4), 152.5 (C-2) and 165.1 (C=O). *m/z* (ESI+): 514 ($^{81}BrMNa^+$, 100%), 512 ($^{79}BrMNa^+$, 100%) and 360 (40%). HRMS (ESI+): Found (MNa^+): 514.1145, $C_{23}H_{28}{}^{81}BrN_3NaO_4$ requires 514.1138. Found (MNa^+): 512.1156, $C_{23}H_{28}{}^{79}BrN_3NaO_4$ requires 512.1155.

4-((4'-Bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15j



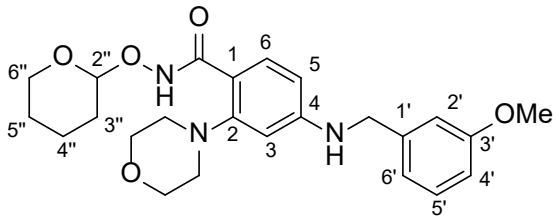
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 4-bromobenzaldehyde **9j** (0.288 g, 1.556 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 24 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15j** (0.141 g, 92%) as a white solid. M.p.: 150 – 152 °C. R.f.: 0.46 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3319 (NH), 2948 (CH aromatic), 2845 (CH alkane), 1642 (C=O), 1600 (C=C aromatic), 1456 and 1335 (CH alkane), 1251 and 1111 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.82 – 1.96 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.91 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.08 (1H, m, H-6''eq.), 4.33 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.51 (1H, t, *J* = 6.0 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.35 (1H, d, *J* = 2.5 Hz, H-3), 6.47 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 7.22 (2H, d, *J* = 8.5 Hz, H-2'), 7.47 (1H, dt, *J* = 8.5, 2.0 Hz, H-3'), 7.99 (1H, d, *J* = 8.5 Hz, H-6) and 12.12 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.3 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.8 (C-3), 109.7 (C-5), 116.1 (C-1), 121.5 (C-4'), 129.1 (C-2'), 132.0 (C-3'), 133.5 (C-6), 137.5 (C-1'), 151.4 (C-4), 152.5 (C-2) and 165.1 (C=O). *m/z* (ESI+): 514 ($^{81}BrMNa^+$, 100%) and 512 ($^{79}BrMNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 514.1140, $C_{23}H_{28}{}^{81}BrN_3NaO_4$ requires 514.1138. Found (MNa^+): 512.1150, $C_{23}H_{28}{}^{79}BrN_3NaO_4$ requires 512.1155.

4-((2'-Methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15k



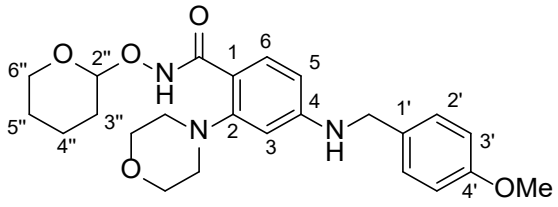
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.100 g, 0.311 mmol), 2-methoxybenzaldehyde **9k** (0.212 g, 1.556 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.068 g, 1.089 mmol) and stirred for 20 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15k** (0.110 g, 80%) as a light yellow solid. M.p.: 162 – 164 °C. R.f.: 0.46 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3314 (NH), 2947 (CH aromatic), 2844 (CH alkane), 1642 (C=O), 1599 (C=C aromatic), 1457 and 1340 (CH alkane), 1244 and 1108 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.69 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.83 – 1.96 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.93 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.84 – 3.94 (7H, m, $N(CH_2CH_2)_2O$, 2'-OCH_3), 4.03 – 4.09 (1H, m, H-6''eq.), 4.36 (2H, d, *J* = 5.5 Hz, $NHCH_2$), 4.54 (1H, t, *J* = 5.5 Hz, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.40 (1H, d, *J* = 2.5 Hz, H-3), 6.50 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.89 – 6.93 (2H, m, H-3', H-5'), 7.25 – 7.28 (2H, m, H-4', H-6'), 7.99 (1H, d, *J* = 8.5 Hz, H-6) and 12.19 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 43.1 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 55.5 (2'-OCH_3), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.8 (C-3), 109.9 (C-5), 110.6 (C-3'), 115.4 (C-1), 120.7 (C-5'), 126.4 (C-1'), 128.9 (C-4'), 129.1 (C-6'), 133.4 (C-6), 152.0 (C-4), 152.4 (C-2), 157.5 (C-2') and 165.3 (C=O). *m/z* (ESI+): 464 (MNa^+, 100%) and 360 (25%). HRMS (ESI+): Found (MNa^+): 464.2154, $C_{24}H_{31}N_3NaO_5$ requires 464.2156.

4-((3'-Methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15l



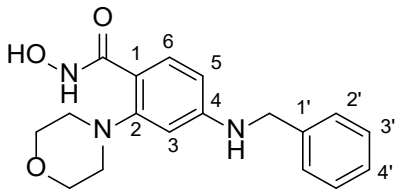
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.125 g, 0.389 mmol), 3-methoxybenzaldehyde **9l** (0.265 g, 1.945 mmol) in EtOH (3 mL) for 24 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.086 g, 1.362 mmol) and stirred for 21 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15l** (0.102 g, 59%) as a light yellow solid. M.p.: 128 – 130 °C. R.f.: 0.43 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3319 (NH), 2946 (CH aromatic), 2843 (CH alkane), 1641 (C=O), 1595 (C=C aromatic), 1457 and 1333 (CH alkane), 1264, 1249 and 1109 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.59 – 1.70 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.84 – 1.95 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.80 (3H, s, 3'-OCH_3), 3.85 – 3.93 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.09 (1H, m, H-6''eq.), 4.34 (2H, d, *J* = 4.5 Hz, $NHCH_2$), 4.50 (1H, br s, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.38 (1H, d, *J* = 2.5 Hz, H-3), 6.49 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.83 (1H, dd, *J* = 8.0, 2.5 Hz, H-4'), 6.88 (1H, br s, H-2'), 6.92 (1H, d, *J* = 8.0 Hz, H-6'), 7.27 (1H, t, *J* = 8.0 Hz, H-5'), 7.99 (1H, d, *J* = 8.5 Hz, H-6) and 12.16 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.9 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 55.4 (3'-OCH_3), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.8 (C-3), 109.7 (C-5), 113.0 (C-4'), 113.2 (C-2'), 115.7 (C-1), 119.7 (C-6'), 130.0 (C-5'), 133.5 (C-6), 140.1 (C-1'), 151.7 (C-4), 152.5 (C-2), 160.1 (C-3') and 165.2 (C=O). *m/z* (ESI+): 464 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 464.2142, $C_{24}H_{31}N_3NaO_5$ requires 464.2156.

4-((4'-Methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy) benzamide 15m



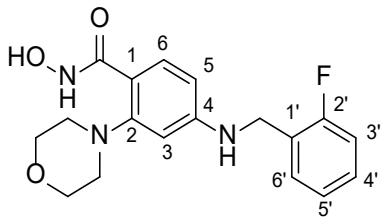
Following **General Procedure 4.2.3**, the reaction was carried out using 4-amino-2-morpholino-*N*-((tetrahydro-2*H*-pyran-2-yl)oxy)benzamide **14** (0.125 g, 0.389 mmol), 4-methoxybenzaldehyde **9m** (0.265 g, 1.945 mmol) in EtOH (3 mL) for 23 h, to afford the imine intermediate. The imine was dissolved in THF/MeOH (1:1, 5 mL), combined with $NaBH_3CN$ (0.086 g, 1.362 mmol) and stirred for 22.5 h. The crude product was then purified with flash chromatography (2:1, petroleum ether/ethyl acetate) affording the *title compound* **15m** (0.111 g, 65%) as a yellow solid. M.p.: 124 – 126 °C. R.f.: 0.46 (1:4 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3278 (NH), 2948 (CH aromatic), 2835 (CH alkane), 1650 (C=O), 1597 (C=C aromatic), 1513, 1451 and 1338 (CH alkane), 1250 and 1109 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.60 – 1.68 (3H, m, H-4''eq., H-5''ax., H-5''eq.), 1.84 – 1.96 (3H, m, H-3''ax., H-3''eq., H-4''ax.), 2.92 (4H, t, *J* = 4.5 Hz, $N(CH_2CH_2)_2O$), 3.65 – 3.70 (1H, m, H-6''ax.), 3.81 (3H, s, 4'-OCH_3), 3.87 – 3.93 (4H, m, $N(CH_2CH_2)_2O$), 4.03 – 4.08 (1H, m, H-6''eq.), 4.29 (2H, br s, $NHCH_2$), 4.39 (1H, br s, $NHCH_2$), 5.02 (1H, t, *J* = 3.0 Hz, H-2''), 6.37 (1H, d, *J* = 2.5 Hz, H-3), 6.49 (1H, dd, *J* = 8.5, 2.5 Hz, H-5), 6.89 (2H, d, *J* = 8.5 Hz, H-3'), 7.26 (2H, d, *J* = 8.5 Hz, H-2'), 8.00 (1H, d, *J* = 8.5 Hz, H-6) and 12.17 (1H, s, NHOTHP). δ_C (100 MHz; $CDCl_3$): 19.0 (C-4''), 25.3 (C-5''), 28.3 (C-3''), 47.4 ($NHCH_2$), 53.7 ($N(CH_2CH_2)_2O$), 55.5 (4'-OCH_3), 62.6 (C-6''), 67.4 ($N(CH_2CH_2)_2O$), 102.5 (C-2''), 104.7 (C-3), 109.7 (C-5), 114.3 (C-3'), 115.6 (C-1), 128.9 (C-2'), 130.4 (C-1'), 133.5 (C-6), 151.7 (C-4), 152.5 (C-2), 159.2 (C-4') and 165.3 (C=O). *m/z* (ESI+): 464 (MNa^+, 100%) and 360 (30%). HRMS (ESI+): Found (MNa^+): 464.2149, $C_{24}H_{31}N_3NaO_5$ requires 464.2156.

4-(Benzylamino)-*N*-hydroxy-2-morpholinobenzamide 12a



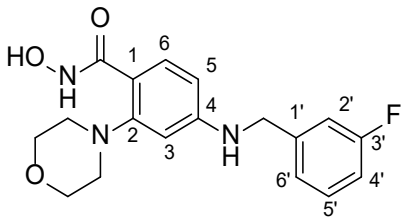
Following **General Procedure 4.2.4**, the reaction was conducted using 4-(benzylamino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15a** (0.025 g, 0.061 mmol) and 2 M HCl (0.02 mL, 0.031 mmol) in THF/MeOH (1:1, 4 mL) for 17 hr. The *title compound* **12a** was afforded as a brown solid (0.017 g, 89%). M.p.: 159 – 161 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3301 (NH), 3086 (OH), 2967 (CH aromatic), 2851 (CH alkane), 1634 (C=O), 1594 (C=C aromatic), 1453 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.79 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.30 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.74 (1H, br s, N*H*CH$_2$), 6.31 (1H, d, *J* = 8.5 Hz, H-5), 6.36 (1H, s, H-3), 7.23 (1H, t, *J* = 6.5 Hz, H-4'), 7.30 – 7.40 (5H, m, H-6, H-2', H-3'), 8.84 (1H, s, N*H*OH) and 10.91 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 46.1 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.8 (C-5), 114.2 (C-1), 126.7 (C-4'), 127.2 (C-2'), 128.3 (C-3'), 131.5 (C-6), 139.7 (C-1'), 151.5 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 350 (MNa$^+$, 50%) and 295 (100%). HRMS (ESI+): Found (MNa$^+$): 350.1473, $C_{18}H_{21}N_3NaO_3$ requires 350.1475.

4-((2'-Fluorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12b



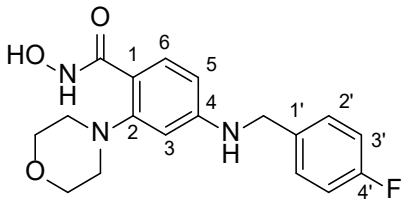
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((2'-fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15b** (0.050 g, 0.116 mmol) and 2 M HCl (0.03 mL, 0.058 mmol) in THF/MeOH (1:1, 4 mL) for 16 hr. The *title compound* **12b** was afforded as a cream white solid (0.028 g, 70%). M.p.: 158 – 160 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3305 (NH), 3076 (OH), 2964 (CH aromatic), 2847 (CH alkane), 1634 (C=O), 1597 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether), 1021 (C-F). δ_H (400 MHz; $(CD_3)_2SO$) 2.81 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.72 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.34 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.33 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.38 (1H, d, *J* = 1.5 Hz, H-3), 6.68 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 7.14 – 7.21 (2H, m, H-3', H-5'), 7.30 (1H, q, *J* = 7.5 Hz, H-4'), 7.37 – 7.41 (2H, m, H-6, H-6'), 8.85 (1H, s, N*H*OH) and 10.91 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 39.8 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 102.9 (C-3), 106.6 (C-5), 114.5 (C-1), 115.2 (d, $^2J_{F/C}$ = 21.2 Hz, C-3'), 124.3 (d, $^4J_{F/C}$ = 3.2 Hz, C-5'), 126.2 (d, $^2J_{F/C}$ = 14.9 Hz, C-1'), 128.9 (d, $^3J_{F/C}$ = 8.0 Hz, C-4'), 129.6 (d, $^3J_{F/C}$ = 4.7 Hz, C-6'), 131.5 (C-6), 151.2 (C-4), 151.9 (C-2), 160.3 (d, $^1J_{F/C}$ = 243.4 Hz, C-2') and 165.5 (C=O). *m/z* (ESI+): 368 (MNa$^+$, 80%), 360 (40%) and 313 (100%). HRMS (ESI+): Found (MNa$^+$): 368.1374, $C_{18}H_{20}FN_3NaO_3$ requires 368.1381.

4-((3'-Fluorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12c



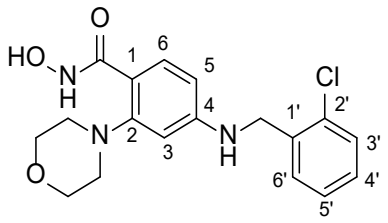
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((3'-fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15c** (0.050 g, 0.116 mmol) and 2 M HCl (0.03 mL, 0.058 mmol) in THF/MeOH (1:1, 4 mL) for 16 hr. The *title compound* **12c** was afforded as a light green solid (0.034 g, 85%). M.p.: 160 – 162 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3303 (NH), 3079 (OH), 2966 (CH aromatic), 2848 (CH alkane), 1634 (C=O), 1597 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether), 1021 (C-F). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.33 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.30 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.35 (1H, d, *J* = 1.5 Hz, H-3), 6.78 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 7.05 (1H, td, *J* = 8.5, 2.0 Hz, H-4'), 7.15 (1H, d, *J* = 7.5 Hz, H-2'), 7.20 (1H, d, *J* = 7.5 Hz, H-6'), 7.34 – 7.39 (2H, m, H-6, H-5'), 8.85 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.5 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.7 (C-5), 114.5 (C-1), 113.5 (d, $^2J_{F/C}$ = 20.9 Hz, C-4'), 113.7 (d, $^2J_{F/C}$ = 21.3 Hz, C-2'), 123.2 (d, $^4J_{F/C}$ = 2.5 Hz, C-6'), 130.3 (d, $^3J_{F/C}$ = 8.1 Hz, C-5'), 131.5 (C-6), 143.1 (d, $^3J_{F/C}$ = 6.7 Hz, C-1'), 151.2 (C-4), 151.8 (C-2), 162.3 (d, $^1J_{F/C}$ = 243.4 Hz, C-3') and 165.5 (C=O). *m/z* (ESI+): 368 (MNa$^+$, 80%), 360 (75%) and 313 (100%). HRMS (ESI+): Found (MNa$^+$): 368.1379, $C_{18}H_{20}FN_3NaO_3$ requires 368.1381.

4-((4'-Fluorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12d



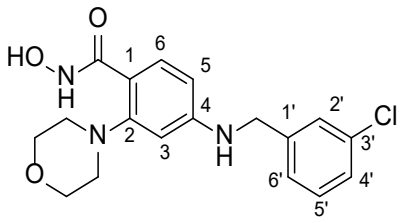
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((4'-fluorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15d** (0.050 g, 0.116 mmol) and 2 M HCl (0.03 mL, 0.058 mmol) in THF/MeOH (1:1, 4 mL) for 26 h. The *title compound* **12d** was afforded as a brown solid (0.036 g, 90%). M.p.: 191 – 193 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3303 (NH), 3083 (OH), 2965 (CH aromatic), 2850 (CH alkane), 1634 (C=O), 1597 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether), 1020 (C-F). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, br s, N(C*H*$_2$CH$_2$)$_2$O), 3.72 (4H, br s, N(CH$_2$C*H*$_2$)$_2$O), 4.29 (2H, d, *J* = 3.5 Hz, NHC*H*$_2$), 6.31 (1H, d, *J* = 8.5 Hz, H-5), 6.34 (1H, br s, H-3), 6.74 (1H, br s, N*H*CH$_2$), 7.15 (2H, t, *J* = 8.5 Hz, H-3'), 7.36 – 7.40 (3H, m, H-6, H-2'), 8.85 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.3 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.8 (C-5), 114.3 (C-1), 115.0 (d, $^2J_{F/C}$ = 21.2 Hz, C-3'), 129.1 (d, $^3J_{F/C}$ = 8.0 Hz, C-2'), 131.5 (C-6), 135.9 (d, $^4J_{F/C}$ = 2.7 Hz, C-1'), 151.3 (C-4), 151.8 (C-2), 161.1 (d, $^1J_{F/C}$ = 241.9 Hz, C-4') and 165.5 (C=O). *m/z* (ESI+): 368 (MNa$^+$, 90%), 360 (30%) and 313 (100%). HRMS (ESI+): Found (MNa$^+$): 368.1377, $C_{18}H_{20}FN_3NaO_3$ requires 368.1381.

4-((2'-Chlorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12e



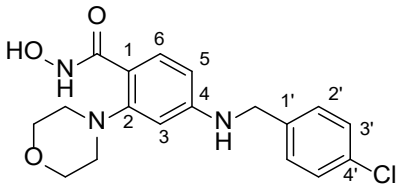
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((2'-chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15e** (0.050 g, 0.112 mmol) and 2 M HCl (0.03 mL, 0.056 mmol) in THF/MeOH (1:1, 4 mL) for 23 h. The *title compound* **12e** was afforded as a reddish-brown solid (0.028 g, 69%). M.p.: 165 – 167 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3298 (NH), 3078 (OH), 2850 (CH alkane), 1634 (C=O), 1598 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.81 (4H, br s, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, br s, N(CH$_2$C*H*$_2$)$_2$O), 4.37 (2H, d, *J* = 3.5 Hz, NHC*H*$_2$), 6.27 (1H, d, *J* = 8.5 Hz, H-5), 6.35 (1H, s, H-3), 6.75 (1H, s, N*H*CH$_2$), 7.27 – 7.32 (2H, m, H-4', H-5'), 7.38 – 7.47 (3H, m, H-6, H-3', H-6'), 8.86 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 43.8 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 102.9 (C-3), 106.5 (C-5), 114.6 (C-1), 127.2 (C-5'), 128.6 (C-6'), 129.0 (C-4'), 129.3 (C-3'), 131.6 (C-6), 132.3 (C-2'), 136.5 (C-1'), 151.2 (C-4), 151.9 (C-2) and 165.5 (C=O). *m/z* (ESI+): 386 (^{37}ClMNa$^+$, 25%), 384 (^{35}ClMNa$^+$, 75%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MNa$^+$): 386.1064, $C_{18}H_{20}{}^{37}ClN_3NaO_3$ requires 386.1062. Found (MNa$^+$): 384.1082, $C_{18}H_{20}{}^{35}ClN_3NaO_3$ requires 384.1085.

4-((3'-Chlorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12f



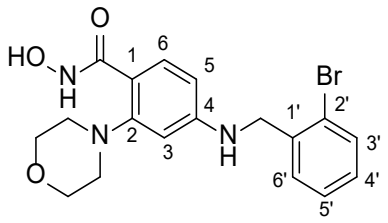
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((3'-chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15f** (0.040 g, 0.090 mmol) and 2 M HCl (0.02 mL, 0.045 mmol) in THF/MeOH (1:1, 4 mL) for 25 h. The *title compound* **12f** was afforded as a brown solid (0.020 g, 61%). M.p.: 165 – 167 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3306 (NH), 3078 (OH), 2850 (CH alkane), 1634 (C=O), 1596 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.32 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.30 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.35 (1H, s, H-3), 6.79 (1H, t, *J* = 5.5 Hz, N*H*CH$_2$), 7.28 – 7.41 (5H, m, H-6, H-2', H-4', H-5', H-6'), 8.86 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.4 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.7 (C-5), 114.6 (C-1), 125.9 (C-6'), 126.7 (C-4'), 127.0 (C-2'), 130.2 (C-5'), 131.5 (C-6), 133.0 (C-3'), 142.7 (C-1'), 151.2 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 386 (^{37}ClMNa$^+$, 30%), 384 (^{35}ClMNa$^+$, 90%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MNa$^+$): 386.1068, $C_{18}H_{20}{}^{37}ClN_3NaO_3$ requires 386.1062. Found (MNa$^+$): 384.1089, $C_{18}H_{20}{}^{35}ClN_3NaO_3$ requires 384.1085.

4-((4'-Chlorobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12g



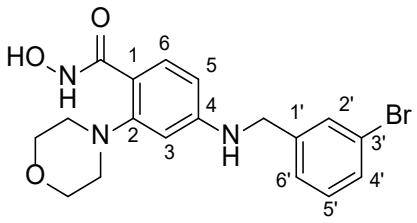
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((4'-chlorobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15g** (0.045 g, 0.101 mmol) and 2 M HCl (0.02 mL, 0.050 mmol) in THF/MeOH (1:1, 4 mL) for 24 h. The *title compound* **12g** was afforded as a light brown solid (0.021 g, 58%). M.p.: 162 – 164 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3305 (NH), 3084 (OH), 2847 (CH alkane), 1634 (C=O), 1596 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.30 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.28 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.34 (1H, d, *J* = 1.5 Hz, H-3), 6.78 (1H, t, *J* = 5.5 Hz, N*H*CH$_2$), 7.35 – 7.39 (5H, m, H-6, H-2', H-3'), 8.86 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.3 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.7 (C-5), 114.4 (C-1), 128.3 (C-3'), 129.0 (C-2'), 131.2 (C-4'), 131.5 (C-6), 138.9 (C-1'), 151.3 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 386 (^{37}ClMNa$^+$, 30%), 384 (^{35}ClMNa$^+$, 90%), 331 (30%) and 329 (100%). HRMS (ESI+): Found (MNa$^+$): 386.1061, $C_{18}H_{20}{}^{37}ClN_3NaO_3$ requires 386.1062. Found (MNa$^+$): 384.1082, $C_{18}H_{20}{}^{35}ClN_3NaO_3$ requires 384.1085.

4-((2'-Bromobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12h



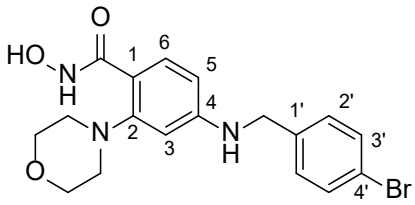
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((2'-bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15h** (0.050 g, 0.102 mmol) and 2 M HCl (0.02 mL, 0.05 mmol) in THF/MeOH (1:1, 4 mL) for 25 h. The *title compound* **12h** was afforded as a brown solid (0.021 g, 51%). M.p.: 103 – 105 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3304 (NH), 3076 (OH), 2966 (CH aromatic), 2848 (CH alkane), 1634 (C=O), 1597 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.34 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.25 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.33 (1H, s, H-3), 6.78 (1H, br s, N*H*CH$_2$), 7.19 – 7.23 (1H, m, H-4'), 7.32 – 7.40 (3H, m, H-6, H-5', H-6'), 7.63 (1H, d, *J* = 8.0 Hz, H-3'), 8.87 (1H, s, N*H*OH) and 10.89 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 46.4 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 102.9 (C-3), 106.4 (C-5), 114.7 (C-1), 122.7 (C-2'), 127.8 (C-5'), 129.0 (C-4'), 129.1 (C-6'), 131.6 (C-6), 132.5 (C-3'), 138.0 (C-1'), 151.1 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 430 (^{81}BrMNa$^+$, 90%), 428 (^{79}BrMNa$^+$, 90%), 375 (100%) and 373 (100%). HRMS (ESI+): Found (MNa$^+$): 430.0564, $C_{18}H_{20}{}^{81}BrN_3NaO_3$ requires 430.0562. Found (MNa$^+$): 428.0582, $C_{18}H_{20}{}^{79}BrN_3NaO_3$ requires 428.0580.

4-((3'-Bromobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12i



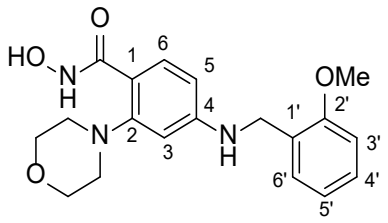
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((3'-bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15i** (0.050 g, 0.102 mmol) and 2 M HCl (0.02 mL, 0.05 mmol) in THF/MeOH (1:1, 4 mL) for 23 h. The *title compound* **12i** was afforded as a dark green solid (0.033 g, 80%). M.p.: 173 – 175 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3299 (NH), 3086 (OH), 2846 (CH alkane), 1634 (C=O), 1598 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.0 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.0 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.32 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.30 (1H, d, *J* = 8.5 Hz, H-5), 6.35 (1H, s, H-3), 6.79 (1H, br s, N*H*CH$_2$), 7.29 (1H, t, *J* = 7.5 Hz, H-5'), 7.35 – 7.39 (2H, m, H-6, H-6'), 7.42 (1H, d, *J* = 7.5 Hz, H-4'), 7.55 (1H, s, H-2'), 8.86 (1H, s, N*H*OH) and 10.90 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.4 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.8 (C-5), 114.6 (C-1), 121.7 (C-3'), 126.3 (C-6'), 129.6 (C-2'), 129.9 (C-4'), 130.5 (C-5'), 131.5 (C-6), 142.9 (C-1'), 151.2 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 430 (^{81}BrMNa$^+$, 90%), 428 (^{79}BrMNa$^+$, 90%), 375 (100%) and 373 (100%). HRMS (ESI+): Found (MNa$^+$): 430.0561, $C_{18}H_{20}{}^{81}BrN_3NaO_3$ requires 430.0562. Found (MNa$^+$): 428.0583, $C_{18}H_{20}{}^{79}BrN_3NaO_3$ requires 428.0580.

4-((4'-Bromobenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12j



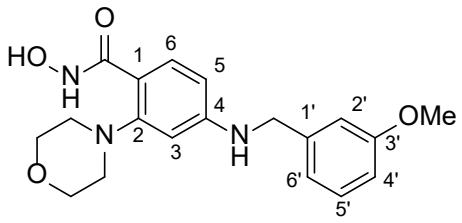
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((4'-bromobenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15j** (0.060 g, 0.122 mmol) and 2 M HCl (0.03 mL, 0.061 mmol) in THF/MeOH (1:1, 4 mL) for 20 h. The *title compound* **12j** was afforded as a brown solid (0.025 g, 50%). M.p.: 174 – 176 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3301 (NH), 3078 (OH), 2851 (CH alkane), 1634 (C=O), 1596 and 1485 (C=C aromatic), 1456 (CH alkane), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.0 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 (4H, t, *J* = 4.0 Hz, N(CH$_2$C*H*$_2$)$_2$O), 4.28 (2H, d, *J* = 5.0 Hz, NHC*H*$_2$), 6.28 (1H, d, *J* = 8.5 Hz, H-5), 6.33 (1H, s, H-3), 6.78 (1H, br s, N*H*CH$_2$), 7.30 (2H, d, *J* = 8.0 Hz, H-2'), 7.38 (1H, d, *J* = 8.5 Hz, H-6), 7.51 (2H, d, *J* = 8.0 Hz, H-3'), 8.86 (1H, s, N*H*OH) and 10.89 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.3 (NH*C*H$_2$), 52.6 (N(*C*H$_2$CH$_2$)$_2$O), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.7 (C-5), 114.5 (C-1), 119.7 (C-4'), 129.4 (C-2'), 131.2 (C-3'), 131.5 (C-6), 139.4 (C-1'), 151.2 (C-4), 151.8 (C-2) and 165.5 (C=O). *m/z* (ESI+): 430 (^{81}BrMNa$^+$, 100%), 428 (^{79}BrMNa$^+$, 100%), 375 (80%) and 373 (80%). HRMS (ESI+): Found (MNa$^+$): 430.0560, $C_{18}H_{20}{}^{81}BrN_3NaO_3$ requires 430.0562. Found (MNa$^+$): 428.0581, $C_{18}H_{20}{}^{79}BrN_3NaO_3$ requires 428.0580.

4-((2'-Methoxybenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12k



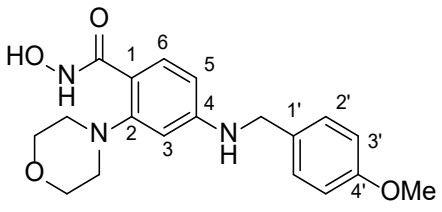
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((2'-methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15k** (0.050 g, 0.113 mmol) and 2 M HCl (0.03 mL, 0.057 mmol) in THF/MeOH (1:1, 4 mL) for 26 h. The *title compound* **12k** was afforded as a brown solid (0.035 g, 88%). M.p.: 84 – 86 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3307 (NH), 3078 (OH), 2847 (CH alkane), 1634 (C=O), 1596 and 1486 (C=C aromatic), 1456 (CH alkane), 1244 and 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.72 (4H, t, *J* = 4.5 Hz, N(CH$_2$C*H*$_2$)$_2$O), 3.84 (3H, s, 2'-OCH$_3$), 4.24 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.27 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.37 (1H, s, H-3), 6.57 (1H, t, *J* = 5.5 Hz, N*H*CH$_2$), 6.89 (1H, t, *J* = 7.5 Hz, H-5'), 7.00 (1H, d, *J* = 8.5 Hz, H-3'), 7.21 – 7.25 (2H, m, H-4', H-6'), 7.39 (1H, d, *J* = 8.5 Hz, H-6), 8.85 (1H, s, N*H*OH) and 10.92 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 40.7 (NH*C*H$_2$), 52.7 (N(*C*H$_2$CH$_2$)$_2$O), 55.4 (2'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 102.8 (C-3), 106.6 (C-5), 114.1 (C-1), 110.6 (C-3'), 120.2 (C-5'), 126.9 (C-1'), 128.1 (C-4' and C-6'), 131.6 (C-6), 151.6 (C-4), 151.8 (C-2), 156.8 (C-2') and 165.6 (C=O). *m/z* (ESI+): 380 (MNa$^+$, 90%) and 325 (100%). HRMS (ESI+): Found (MNa$^+$): 380.1573, $C_{19}H_{23}N_3NaO_4$ requires 380.1581.

4-((3'-Methoxybenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12l



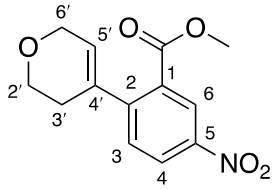
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((3'-methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15l** (0.050 g, 0.113 mmol) and 2 M HCl (0.03 mL, 0.057 mmol) in THF/MeOH (1:1, 4 mL) for 23 h. The *title compound* **12l** was afforded as a light brown solid (0.030 g, 75%). M.p.: 170 – 172 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3358 (NH), 3088 (OH), 2844 (CH alkane), 1628 (C=O), 1587 and 1489 (C=C aromatic), 1455 (CH alkane), 1266 and 1112 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 – 3.72 (7H, m, N(CH$_2$C*H*$_2$)$_2$O, 3'-OCH$_3$), 4.27 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.31 (1H, d, *J* = 8.5 Hz, H-5), 6.36 (1H, s, H-3), 6.73 (1H, br s, N*H*CH$_2$), 6.80 (1H, dd, *J* = 8.0, 1.5 Hz, H-4'), 6.92 – 6.93 (2H, m, H-2', H-6'), 7.23 (1H, t, *J* = 8.0 Hz, H-5'), 7.39 (1H, d, *J* = 8.5 Hz, H-6), 8.86 (1H, s, N*H*OH) and 10.91 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 46.1 (NH*C*H$_2$), 52.7 (N(*C*H$_2$CH$_2$)$_2$O), 55.0 (3'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.8 (C-5), 114.3 (C-1), 112.0 (C-4'), 112.9 (C-2'), 119.4 (C-6'), 129.4 (C-5'), 131.5 (C-6), 141.5 (C-1'), 151.5 (C-4), 151.8 (C-2), 159.4 (C-3') and 165.6 (C=O). *m/z* (ESI+): 380 (MNa$^+$, 90%) and 325 (100%). HRMS (ESI+): Found (MNa$^+$): 380.1576, $C_{19}H_{23}N_3NaO_4$ requires 380.1581.

4-((4'-Methoxybenzyl)amino)-*N*-hydroxy-2-morpholinobenzamide 12m



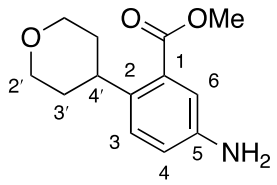
Following **General Procedure 4.2.4**, the reaction was conducted using 4-((4'-methoxybenzyl)amino)-2-morpholino-*N*-((tetrahydro-2H-pyran-2''-yl)oxy)benzamide **15m** (0.050 g, 0.113 mmol) and 2 M HCl (0.03 mL, 0.057 mmol) in THF/MeOH (1:1, 4 mL) for 23 h. The *title compound* **12m** was afforded as a cream solid (0.031 g, 78%). M.p.: 174 – 176 °C. R.f.: 0.1 (1:3 petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3358 (NH), 3079 (OH), 2846 (CH alkane), 1629 (C=O), 1587 and 1490 (C=C aromatic), 1455 (CH alkane), 1267 and 1112 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 2.80 (4H, t, *J* = 4.5 Hz, N(C*H*$_2$CH$_2$)$_2$O), 3.71 – 3.73 (7H, m, N(CH$_2$C*H*$_2$)$_2$O, 4'-OCH$_3$), 4.21 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.31 (1H, dd, *J* = 8.5, 1.5 Hz, H-5), 6.36 (1H, d, *J* = 1.5 Hz, H-3), 6.65 (1H, d, *J* = 5.5 Hz, N*H*CH$_2$), 6.88 (2H, d, *J* = 8.5 Hz, H-3'), 7.27 (2H, d, *J* = 8.5 Hz, H-2'), 7.39 (1H, d, *J* = 8.5 Hz, H-6), 8.85 (1H, s, N*H*OH) and 10.92 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 45.5 (NH*C*H$_2$), 52.7 (N(*C*H$_2$CH$_2$)$_2$O), 55.0 (4'-OCH$_3$), 66.4 (N(CH$_2$*C*H$_2$)$_2$O), 103.1 (C-3), 106.8 (C-5), 113.7 (C-3'), 128.5 (C-2'), 114.1 (C-1), 131.5 (C-6 and C-1'), 151.5 (C-4), 151.8 (C-2), 158.2 (C-4') and 165.6 (C=O). *m/z* (ESI+): 380 (MNa$^+$, 100%) and 325 (90%). HRMS (ESI+): Found (MNa$^+$): 380.1582, $C_{19}H_{23}N_3NaO_4$ requires 380.1581.

Methyl 2-(3',6'-dihydro-2*H*-pyran-4'-yl)-5-nitrobenzoate 17



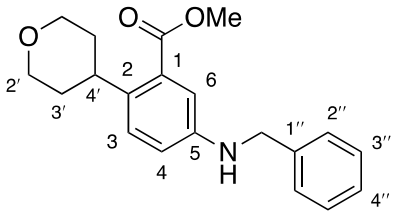
A stirred mixture of methyl 2-chloro-5-nitrobenzoate **16** (5.132 g, 23.80 mmol), 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester (7.341 g, 34.94 mmol), $Pd(dppf)Cl_2$ (1.768 g, 2.42 mmol) and K_2CO_3 (4.316 g, 30.23 mmol) in 1,4-dioxane/H_2O (5:1, 72 mL) was heated at 60°C for 22 h under an atmosphere of nitrogen. The reaction mixture was then partitioned between a biphasic mixture of EtOAc/H_2O, the organic layer was collected and aqueous layer further extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H_2O (25 mL), brine (25 mL), then dried with Na_2SO_4 and filtered. The filtrate was evaporated *in vacuo* and purified by flash chromatography (4:1, petroleum ether/ethyl acetate) to afford the *title compound* **17** (5.455 g, 86%) as a white crystalline solid. M.p.: 83 – 85 °C. R.f.: 0.29 (4:1, petroleum ether/ethyl acetate). IR: vmax (film)/cm^{-1}; 2991 and 2950 (CH aromatic), 2873 and 2823 (CH alkane), 1734 (C=O ester), 1602 and 1513 (C=C aromatic), 1435 and 1348 (CH alkane), 1249 and 1115 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.34 – 2.38 (2H, m, H-3'), 3.93 – 3.96 (5H, m, H-2', OCH_3), 4.29 – 4.32 (2H, m, H-6'), 5.67 – 5.69 (1H, m, H-5'), 7.42 (1H, d, *J* = 8.5 Hz, H-3), 8.31 (1H, dd, *J* = 8.5, 2.5 Hz, H-4) and 8.69 (1H, d, *J* = 2.5 Hz, H-6). δ_C (100 MHz; $(CD_3)_2SO$): 29.7 (C-3'), 52.9 (OCH_3), 64.4 (C-2'), 65.6 (C-6'), 125.2 (C-5'), 125.6 (C-6), 126.4 (C-4), 130.9 (C-1), 131.0 (C-3), 135.9 (C-4'), 146.9 (C-5), 150.1 (C-2) and 166.1 (C=O). *m/z* (ESI+): 286 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 286.0686, $C_{13}H_{13}NNaO_5$ requires 286.0686.

Methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 18



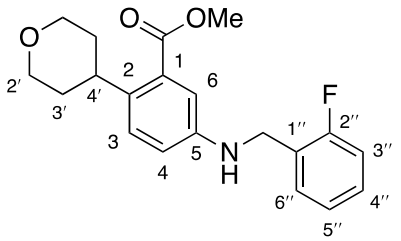
A solution of methyl 2-(3',6'-dihydro-2*H*-pyran-4'-yl)-5-nitrobenzoate **17** (5.400 g, 20.51 mmol) and 10% Pd/C (10% w/w of **17**, 0.540 g) in EtOAc (20 mL) was stirred at room temperature for 48 h under an atmosphere of H_2. The reaction mixture was then filtered through a plug of Celite and filtrate evaporated *in vacuo* to afford the *title compound* **18** (4.624 g, 96%) as a yellow solid. M.p.: 110 – 112 °C. R.f.: 0.37 (2:1, petroleum ether/ethyl acetate). IR: vmax (film)/cm^{-1}; 3439 and 3354 (NH aniline), 2957 and 2920 (CH aromatic), 2843 (CH alkane), 1701 (C=O ester), 1610 and 1505 (C=C aromatic), 1430 and 1323 (CH alkane), 1231 and 1068 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.54 – 1.66 (4H, m, H-3'), 3.21 – 3.29 (1H, m, H-4'), 3.33 – 3.39 (2H, m, H-2a'), 3.78 (3H, s, OCH_3), 3.89 – 3.92 (2H, m, H-2b'), 5.15 (2H, br s, NH_2), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.90 (1H, d, *J* = 2.5 Hz, H-6) and 7.08 (1H, d, *J* = 8.5 Hz, H-3). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.2 (C-4'), 51.7 (OCH_3), 67.7 (C-2'), 114.4 (C-6), 117.4 (C-4), 127.3 (C-3), 130.0 (C-1), 132.8 (C-2), 146.5 (C-5) and 168.4 (C=O).
m/z (ESI+): 258 (MNa^+, 100%), 236 (MH^+, 85%). HRMS (ESI+): Found (MH^+): 236.1281, $C_{13}H_{18}NO_3$ requires 236.1281.

Methyl 5-(benzylamino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19a



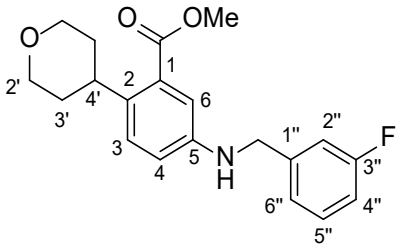
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.20 g, 0.850 mmol) and benzaldehyde **9a** (0.108 g, 1.02 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.161 g, 4.25 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19a** (0.251 g, 91%) as a white solid. M.p.: 134 – 136 °C. R.f.: 0.60 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3301 (NH), 2950 (CH aromatic), 2854 (CH alkane), 1714 (C=O ester), 1612 and 1571 (C=C aromatic), 1504 and 1449 (CH alkane), 1278, 1215 and 1080 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.53 – 1.66 (4H, m, H-3'), 3.18 – 3.25 (1H, m, H-4'), 3.35 (2H, td, *J* = 2.5, 11.5 Hz, H-2a'), 3.78 (3H, s, OCH_3), 3.88 – 3.91 (2H, m, H-2b'), 4.26 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.39 (1H, t, *J* = 6.0 Hz, NH), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.92 (1H, d, *J* = 2.5 Hz, H-6), 7.11 (1H, d, *J* = 8.5 Hz, H-3), 7.19 – 7.24 (1H, m, H-4'') and 7.29 – 7.36 (4H, m, H-2'', H-3''). δ_C (100 MHz; $(CD_3)_2SO$): 33.8 (C-3'), 36.3 (C-4'), 46.3 ($NHCH_2$), 51.8 (OCH_3), 67.7 (C-2'), 113.0 (C-6), 115.4 (C-4), 126.6 (C-4''), 127.1 (C-2''), 127.4 (C-3), 128.3 (C-3''), 130.2 (C-1), 132.8 (C-2), 140.0 (C-1''), 146.5 (C-5) and 168.4 (C=O). *m/z* (ESI+): 348 (MNa^+, 100%), 326 (MH^+, 25%). HRMS (ESI+): Found (MNa^+): 348.1561, $C_{20}H_{23}NNaO_3$ requires 348.1570.

Methyl 5-((2''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19b



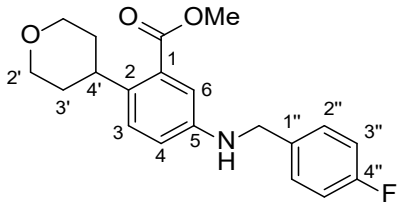
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 2-fluorobenzaldehyde **9b** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19b** (0.448 g, 88%) as a white solid. M.p.: 135 – 137 °C. R.f.: 0.60 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3306 (NH), 2950 (CH aromatic), 2845 (CH alkane), 1713 (C=O ester), 1612 and 1572 (C=C aromatic), 1491 and 1454 (CH alkane), 1233 and 1068 (C-O ether) and 1208 (C-F). δ_H (400 MHz; $(CD_3)_2SO$): 1.54 – 1.66 (4H, m, H-3'), 3.18 – 3.26 (1H, m, H-4'), 3.33 – 3.39 (2H, m, H-2a'), 3.78 (3H, s, OCH_3), 3.88 – 3.92 (2H, m, H-2b'), 4.30 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.35 (1H, t, *J* = 6.0 Hz, NH), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.93 (1H, d, *J* = 2.5 Hz, H-6), 7.13 – 7.20 (3H, m, H-3, H-3'', H-5'), 7.26 – 7.32 (1H, m, H-4'') and 7.38 (1H, td, *J* = 1.5, 7.5 Hz, H-6'). δ_C (100 MHz; $(CD_3)_2SO$): 33.8 (C-3'), 36.3 (C-4'), 39.7 ($NHCH_2$), 51.8 (OCH_3), 67.7 (C-2'), 112.9 (C-6), 115.1 (d, $^2J_{F/C}$ = 21.3 Hz, C-3''), 115.3 (C-4), 124.3 (d, $^4J_{F/C}$ = 3.1 Hz, C-5''), 126.5 (d, $^2J_{F/C}$ = 14.5 Hz, C-1''), 127.5 (C-3), 128.7 (d, $^3J_{F/C}$ = 8.1 Hz, C-4''), 129.3 (d, $^3J_{F/C}$ = 4.7 Hz, C-6''), 130.3 (C-1), 133.0 (C-2), 146.2 (C-5), 160.3 (d, $^1J_{F/C}$ = 243.9 Hz, C-2'') and 168.4 (C=O). *m/z* (ESI+): 366 (MNa^+, 100%), 344 (MH^+, 25%). HRMS (ESI+): Found (MNa^+): 366.1477, $C_{20}H_{22}FNNaO_3$ requires 366.1476.

Methyl 5-((3''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19c



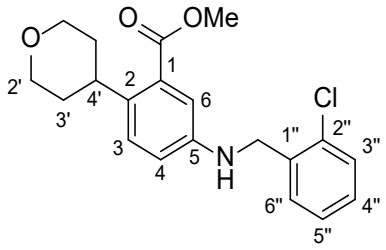
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 3-fluorobenzaldehyde **9c** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 21 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19c** (0.467 g, 91%) as a white solid. M.p.: 120 – 122 °C. R.f.: 0.57 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3304 (NH), 2950 (CH aromatic), 2848 (CH alkane), 1714 (C=O ester), 1612 and 1572 (C=C aromatic), 1490 and 1438 (CH alkane), 1233 and 1068 (C-O ether) and 1209 (C-F). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.50 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.5, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.12 (1H, br s, N-H), 4.34 (2H, br s, NHCH_2), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.96 (1H, td, *J* = 1.5, 8.5 Hz, H-4''), 7.04 – 7.08 (2H, m, H-6, H-2''), 7.13 (1H, d, *J* = 7.5 Hz, H-6''), 7.18 (1H, d, *J* = 8.5 Hz, H-3) and 7.27 – 7.33 (1H, m, H-5''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.9 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.3 (d, $^2J_{F/C}$ = 21.4 Hz, C-2''), 114.3 (C-6), 114.4 (d, $^2J_{F/C}$ = 20.8 Hz, C-4''), 116.6 (C-4), 122.9 (d, $^4J_{F/C}$ = 2.7 Hz, C-6''), 128.0 (C-3), 130.3 (d, $^3J_{F/C}$ = 8.2 Hz, C-5''), 130.6 (C-1), 135.9 (C-2), 142.0 (d, $^3J_{F/C}$ = 6.9 Hz, C-1''), 145.8 (C-5), 163.3 (d, $^1J_{F/C}$ = 246.1 Hz, C-3'') and 168.8 (C=O). *m/z* (ESI+): 366 (MNa^+, 100%), 344 (MH^+, 20%). HRMS (ESI+): Found (MNa^+): 366.1472, $C_{20}H_{22}FNNaO_3$ requires 366.1476.

Methyl 5-((4''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19d



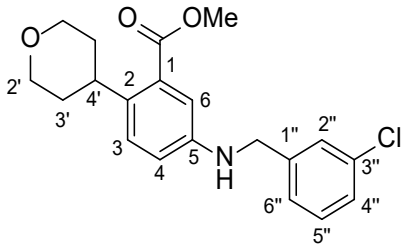
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 4-fluorobenzaldehyde **9d** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 2.5 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19d** (0.440 g, 86%) as a white solid. M.p.: 150 – 152 °C. R.f.: 0.54 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3308 (NH), 2950 (CH aromatic), 2846 (CH alkane), 1713 (C=O ester), 1612 and 1572 (C=C aromatic), 1491 and 1438 (CH alkane), 1234 and 1068 (C-O ether) and 1208 (C-F). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.50 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.03 – 4.06 (3H, m, H-2b', N-H), 4.30 (2H, br s, NHC*H*$_2$), 6.73 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.00 – 7.05 (3H, m, H-6, H-3''), 7.18 (1H, d, *J* = 8.5 Hz, H-3) and 7.30 – 7.34 (2H, m, H-2''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.8 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.2 (C-6), 115.7 (d, $^2J_{F/C}$ = 21.4 Hz, C-3''), 116.6 (C-4), 128.0 (C-3), 129.2 (d, $^3J_{F/C}$ = 8.0 Hz, C-2''), 130.6 (C-1), 134.9 (d, $^4J_{F/C}$ = 2.9 Hz, C-1''), 145.9 (C-5), 162.3 (d, $^1J_{F/C}$ = 245.2 Hz, C-4'') and 168.8 (C=O). *m/z* (ESI+): 366 (MNa^+, 100%), 344 (MH^+, 15%). HRMS (ESI+): Found (MNa^+): 366.1470, $C_{20}H_{22}FNNaO_3$ requires 366.1476.

Methyl 5-((2''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19e



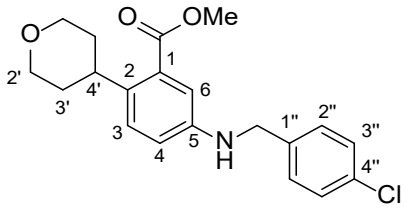
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 2-chlorobenzaldehyde **9e** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 20 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19e** (0.466 g, 87%) as a white solid. M.p.: 123 – 125 °C. R.f.: 0.57 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3317 (NH), 2947 and 2920 (CH aromatic), 2843 (CH alkane), 1708 (C=O ester), 1611 and 1571 (C=C aromatic), 1517 and 1436 (CH alkane), 1233 and 1056 (C-O ether) and 753 (C-Cl). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.49 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.19 (1H, br s, N-H), 4.43 (2H, d, *J* = 5.0 Hz, $NHCH_2$), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.06 (1H, d, *J* = 2.5 Hz, H-6), 7.18 (1H, d, *J* = 8.5 Hz, H-3), 7.20 – 7.24 (2H, m, H-3'', H-4'') and 7.37 – 7.40 (2H, m, H-5'', H-6''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 46.1 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.4 (C-6), 116.5 (C-4), 127.1 (C-3''), 128.0 (C-3), 128.7 (C-4''), 129.2 (C-6''), 129.8 (C-5''), 130.6 (C-1), 133.5 (C-2''), 135.8 (C-2), 136.4 (C-1''), 145.7 (C-5) and 168.8 (C=O). *m/z* (ESI+): 384 ($^{37}MNa^+$, 30%), 382 ($^{35}MNa^+$, 100%), 362 ($^{37}MH^+$, 5%) and 360 ($^{35}MH^+$, 20%). HRMS (ESI+): Found (MNa^+): 384.1164, $C_{20}H_{22}{}^{37}ClNNaO_3$ requires 384.1158. Found (MNa^+): 382.1177, $C_{20}H_{22}{}^{35}ClNNaO_3$ requires 382.1180.

Methyl 5-((3''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19f



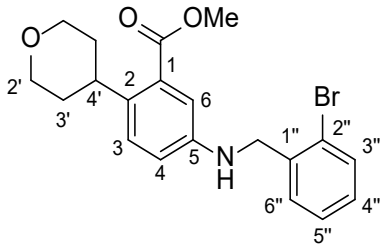
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 3-chlorobenzaldehyde **9f** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 21.5 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19f** (0.485 g, 90%) as a white solid. M.p.: 87 – 89 °C. R.f.: 0.57 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3317 (NH), 2947 and 2919 (CH aromatic), 2843 (CH alkane), 1709 (C=O ester), 1611 and 1573 (C=C aromatic), 1517 and 1437 (CH alkane), 1250, 1232 and 1069 (C-O ether) and 754 (C-Cl). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.49 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.11 (1H, br s, N-H), 4.32 (2H, d, *J* = 3.5 Hz, NHCH_2), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.04 (1H, d, *J* = 2.5 Hz, H-6), 7.18 (1H, d, *J* = 8.5 Hz, H-3), 7.22 – 7.29 (3H, m, H-4'', H-5'', H-6'') and 7.35 (1H, br s, H-2''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.9 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.3 (C-6), 116.6 (C-4), 125.6 (C-6''), 127.6 (C-4''), 127.7 (C-2''), 128.0 (C-3), 130.1 (C-5''), 130.6 (C-1), 134.7 (C-3''), 136.0 (C-2), 141.4 (C-1''), 145.7 (C-5) and 168.8 (C=O). *m/z* (ESI+): 384 ($^{37}MNa^+$, 30%) and 382 ($^{35}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 384.1172, $C_{20}H_{22}{}^{37}ClNNaO_3$ requires 384.1158. Found (MNa^+): 382.1175, $C_{20}H_{22}{}^{35}ClNNaO_3$ requires 382.1180.

Methyl 5-((4''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19g



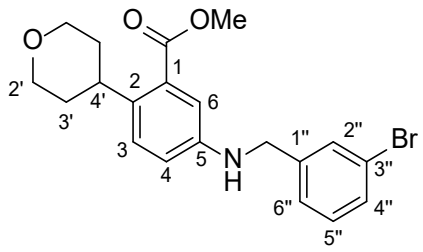
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 4-chlorobenzaldehyde **9g** (0.22 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3.5 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19g**(0.413 g, 77%) as a white solid. M.p.: 151 – 153 °C. R.f.: 0.51 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3319 (NH), 2950 and 2907 (CH aromatic), 2845 (CH alkane), 1706 (C=O ester), 1615 and 1575 (C=C aromatic), 1519 and 1438 (CH alkane), 1234 and 1080 (C-O ether) and 810 (C-Cl). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.69 – 1.81 (4H, m, H-3'), 3.42 – 3.49 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.08 (1H, br s, N-H), 4.31 (2H, br s, NHCH_2), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 2.5 Hz, H-6), 7.18 (1H, d, *J* = 8.5 Hz, H-3) and 7.27 (4H, m, H-2'', H-3''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.7 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.2 (C-6), 116.6 (C-4), 128.0 (C-3), 128.8 (C-3''), 129.0 (C-2''), 130.6 (C-1), 133.2 (C-4''), 135.9 (C-2), 137.7 (C-1''), 145.8 (C-5) and 168.8 (C=O). *m/z* (ESI+): 384 ($^{37}MNa^+$, 30%) and 382 ($^{35}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 384.1169, $C_{20}H_{22}{}^{37}ClNNaO_3$ requires 384.1158. Found (MNa^+): 382.1176, $C_{20}H_{22}{}^{35}ClNNaO_3$ requires 382.1180.

Methyl 5-((2''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19h



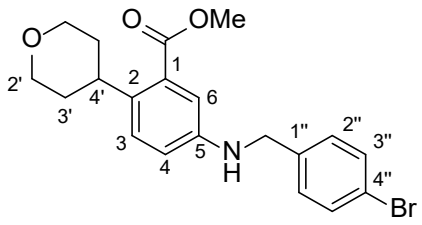
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.35 g, 1.49 mmol) and 2-bromobenzaldehyde **9h** (0.331 g, 1.79 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.282 g, 7.45 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3.5 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19h** (0.481 g, 80%) as a white solid. M.p.: 108 – 110 °C. R.f.: 0.54 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3307 (NH), 2945 and 2913 (CH aromatic), 2852 (CH alkane), 1711 (C=O ester), 1612 and 1571 (C=C aromatic), 1519 and 1436 (CH alkane), 1251, 1234 and 1069 (C-O ether) and 662 (C-Br). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.69 – 1.81 (4H, m, H-3'), 3.41 – 3.51 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.21 (1H, br s, N-H), 4.40 (2H, d, *J* = 5.0 Hz, NHCH_2), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.06 (1H, d, *J* = 2.5 Hz, H-6), 7.14 (1H, td, *J* = 7.5, 1.5 Hz, H-4''), 7.18 (1H, d, *J* = 8.5 Hz, H-3), 7.27 (1H, td, *J* = 1.0, 7.5 Hz, H-5''), 7.38 (1H, dd, *J* = 1.5, 7.5 Hz, H-6'') and 7.57 (1H, dd, *J* = 1.0, 7.5 Hz, H-3''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 48.5 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.4 (C-6), 116.6 (C-4), 123.5 (C-2''), 127.8 (C-5''), 128.0 (C-3), 129.0 (C-4''), 129.4 (C-6''), 130.6 (C-1), 133.0 (C-3''), 135.8 (C-2), 138.0 (C-1''), 145.7 (C-5) and 168.8 (C=O). *m/z* (ESI+): 428 ($^{81}MNa^+$, 100%) and 426 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 428.0657, $C_{20}H_{22}{}^{81}BrNNaO_3$ requires 428.0657. Found (MNa^+): 426.0673, $C_{20}H_{22}{}^{79}BrNNaO_3$ requires 426.0675.

Methyl 5-((3''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19i



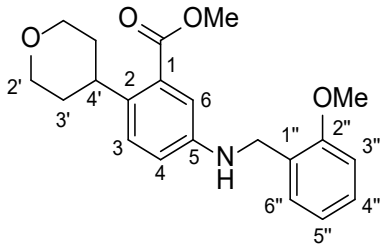
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.22 g, 0.94 mmol) and 3-bromobenzaldehyde **9i** (0.208 g, 1.12 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.177 g, 4.68 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3.5 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19i** (0.360 g, 95%) as a white solid. M.p.: 82 – 84 °C. R.f.: 0.55 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3294 (NH), 2949 (CH aromatic), 2850 (CH alkane), 1715 (C=O ester), 1611 and 1572 (C=C aromatic), 1515 and 1436 (CH alkane), 1224 and 1069 (C-O ether) and 669 (C-Br). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.69 – 1.81 (4H, m, H-3'), 3.42 – 3.49 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.03 – 4.07 (2H, m, H-2b'), 4.11 (1H, br s, N-H), 4.31 (2H, s, NHCH_2), 6.72 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.05 (1H, d, *J* = 2.5 Hz, H-6), 7.17 – 7.23 (2H, m, H-3, H-5''), 7.28 (1H, d, *J* = 8.0 Hz, H-6''), 7.41 (1H, d, *J* = 8.0 Hz, H-4'') and 7.52 (1H, s, H-2''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.9 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.3 (C-6), 116.6 (C-4), 122.9 (C-3''), 126.0 (C-6''), 128.0 (C-3), 130.4 (C-5''), 130.5 (C-4''), 130.5 (C-1), 130.6 (C-2''), 136.0 (C-2), 141.7 (C-1''), 145.7 (C-5) and 168.8 (C=O). *m/z* (ESI+): 428 ($^{81}MNa^+$, 100%) and 426 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 428.0659, $C_{20}H_{22}{}^{81}BrNNaO_3$ requires 428.0657. Found (MNa^+): 426.0670, $C_{20}H_{22}{}^{79}BrNNaO_3$ requires 426.0675.

Methyl 5-((4''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19j



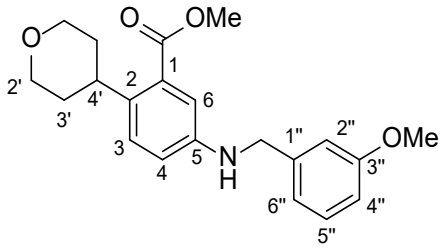
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.22 g, 0.94 mmol) and 4-bromobenzaldehyde **9j** (0.208 g, 1.12 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.177 g, 4.68 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 19 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19j** (0.336 g, 89%) as a white solid. M.p.: 160 – 162 °C. R.f.: 0.51 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3322 (NH), 2948 (CH aromatic), 2840 (CH alkane), 1706 (C=O ester), 1615 and 1573 (C=C aromatic), 1518 and 1438 (CH alkane), 1254, 1233 and 1071 (C-O ether) and 623 (C-Br). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.69 – 1.81 (4H, m, H-3'), 3.41 – 3.51 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.08 (1H, br s, N-H), 4.29 (2H, s, NHCH_2), 6.71 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 2.5 Hz, H-6), 7.18 (1H, d, *J* = 8.5 Hz, H-3), 7.23 (2H, d, *J* = 8.5 Hz, H-2'') and 7.46 (2H, d, *J* = 8.5 Hz, H-3''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 47.8 ($NHCH_2$), 52.1 (OCH_3), 68.8 (C-2'), 114.3 (C-6), 116.6 (C-4), 121.2 (C-4''), 128.0 (C-3), 129.2 (C-2''), 130.6 (C-1), 131.9 (C-3''), 135.9 (C-2), 138.3 (C-1''), 145.7 (C-5) and 168.8 (C=O). *m/z* (ESI+): 428 ($^{81}MNa^+$, 100%) and 426 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 428.0662, $C_{20}H_{22}{}^{81}BrNNaO_3$ requires 428.0657. Found (MNa^+): 426.0674, $C_{20}H_{22}{}^{79}BrNNaO_3$ requires 426.0675.

Methyl 5-((2''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19k



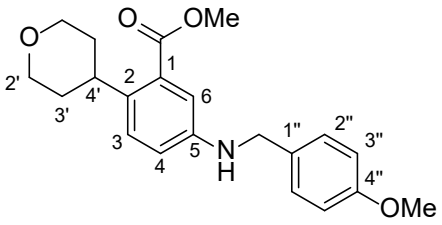
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.219 g, 0.94 mmol) and 2-methoxybenzaldehyde **9k** (0.153 g, 1.12 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.177 g, 4.68 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19k** (0.293 g, 88%) as a white solid. M.p.: 114 – 116 °C. R.f.: 0.46 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3330 (NH), 2954 and 2908 (CH aromatic), 2857 (CH alkane), 1703 (C=O ester), 1613 and 1570 (C=C aromatic), 1511, 1458 and 1432 (CH alkane), 1278, 1235, 1069 and 1021 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.69 – 1.81 (4H, m, H-3'), 3.41 – 3.49 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.86 (3H, s, 2''-OCH_3), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (2H, m, H-2b'), 4.16 (1H, br s, N-H), 4.33 (2H, s, NHCH_2), 6.76 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.88 – 6.93 (2H, m, H-3'', H-5''), 7.08 (1H, d, *J* = 2.5 Hz, H-6), 7.17 (1H, d, *J* = 8.5 Hz, H-3) and 7.23 – 7.30 (2H, m, H-4'', H-6''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 43.7 ($NHCH_2$), 52.1 (OCH_3), 55.5 (2''-OCH_3), 68.8 (C-2'), 110.5 (C-3''), 114.4 (C-6), 116.8 (C-4), 120.7 (C-5''), 127.1 (C-1''), 127.9 (C-3), 128.6 (C-4''), 129.2 (C-6''), 130.4 (C-1), 135.4 (C-2), 146.4 (C-5), 157.6 (C-2'') and 169.0 (C=O). *m/z* (ESI+): 378 (MNa^+, 100%) and 356 (MH^+, 15%). HRMS (ESI+): Found (MNa^+): 378.1683, $C_{21}H_{25}NNaO_4$ requires 378.1676.

Methyl 5-((3''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19l



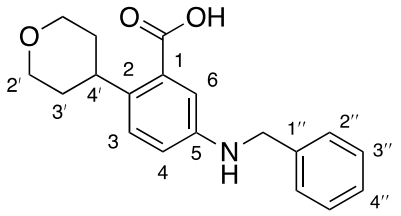
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.216 g, 0.92 mmol) and 3-methoxybenzaldehyde **9l** (0.150 g, 1.10 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.174 g, 4.59 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19l** (0.283 g, 87%) as a white solid. M.p.: 76 – 78 °C. R.f.: 0.50 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3288 (NH), 2947 (CH aromatic), 2836 (CH alkane), 1709 (C=O ester), 1609 and 1582 (C=C aromatic), 1517, 1487 and 1434 (CH alkane), 1279, 1233, 1149 and 1070 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.50 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.79 (3H, s, 3''-OCH_3), 3.87 (3H, s, OCH_3), 4.02 – 4.06 (3H, m, H-2b', N-H), 4.30 (2H, br s, NHCH_2), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.82 (1H, dd, *J* = 8.0, 2.5 Hz, H-4''), 6.91 (1H, br s, H-2''), 6.94 (1H, d, *J* = 8.0 Hz, H-6''), 7.06 (1H, d, *J* = 2.5 Hz, H-6), 7.17 (1H, d, *J* = 8.5 Hz, H-3) and 7.26 (1H, t, *J* = 8.0 Hz, H-5''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.8 (C-4'), 48.4 ($NHCH_2$), 52.1 (OCH_3), 55.3 (3''-OCH_3), 68.8 (C-2'), 112.8 (C-4''), 113.2 (C-2''), 114.2 (C-6), 116.6 (C-4), 119.9 (C-6''), 127.9 (C-3), 129.8 (C-5''), 130.5 (C-1), 135.7 (C-2), 140.9 (C-1), 146.1 (C-5), 160.1 (C-3'') and 168.9 (C=O). *m/z* (ESI+): 378 (MNa^+, 100%) and 356 (MH^+, 15%). HRMS (ESI+): Found (MNa^+): 378.1672, $C_{21}H_{25}NNaO_4$ requires 378.1676.

Methyl 5-((4''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate 19m



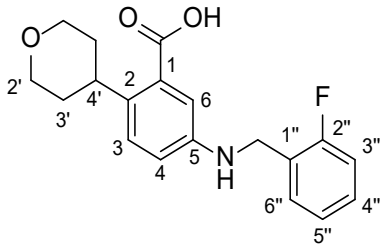
Following **General Procedure 4.2.5**, the reaction was carried out using methyl 5-amino-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **18** (0.212 g, 0.90 mmol) and 4-methoxybenzaldehyde **9m** (0.150 g, 1.10 mmol) in anhydrous EtOH (5 mL) to afford the imine intermediate as a white solid. The imine was then combined with $NaBH_4$ (0.170 g, 4.51 mmol) and stirred in THF/MeOH (1:1, 6 mL) for 3 h, until completion. The crude product was then purified using flash chromatography (4:1, petroleum ether/ethyl acetate) to give the *title compound* **19m** (0.290 g, 91%) as a white solid. M.p.: 113 – 115 °C. R.f.: 0.43 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3396 (NH), 2949 (CH aromatic), 2852 (CH alkane), 1718 (C=O ester), 1610 and 1569 (C=C aromatic), 1509, 1471 and 1436 (CH alkane), 1277, 1218 and 1080 (C-O ether). δ_H (400 MHz; $CDCl_3$, Me_4Si): 1.70 – 1.81 (4H, m, H-3'), 3.42 – 3.50 (1H, m, H-4'), 3.54 (2H, td, *J* = 11.0, 3.0 Hz, H-2a'), 3.80 (3H, s, 4''-OCH_3), 3.87 (3H, s, OCH_3), 3.98 (1H, br s, N-H), 4.03 – 4.07 (2H, m, H-2b'), 4.25 (2H, br s, NHCH_2), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.88 (2H, d, *J* = 8.5 Hz, H-3''), 7.06 (1H, d, *J* = 2.5 Hz, H-6), 7.18 (1H, d, *J* = 8.5 Hz, H-3) and 7.27 (2H, d, *J* = 8.5 Hz, H-2''). δ_C (100 MHz; $CDCl_3$): 34.3 (C-3'), 36.9 (C-4'), 48.0 ($NHCH_2$), 52.1 (OCH_3), 55.4 (4''-OCH_3), 68.8 (C-2'), 114.1 (C-6), 114.2 (C-3''), 116.6 (C-4), 127.9 (C-3), 129.0 (C-2''), 130.5 (C-1), 131.2 (C-1''), 135.6 (C-2), 146.2 (C-5), 159.1 (C-4'') and 168.9 (C=O). *m/z* (ESI+): 378 (MNa^+, 100%) and 356 (MH^+, 15%). HRMS (ESI+): Found (MNa^+): 378.1675, $C_{21}H_{25}NNaO_4$ requires 378.1676.

5-(Benzylamino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20a



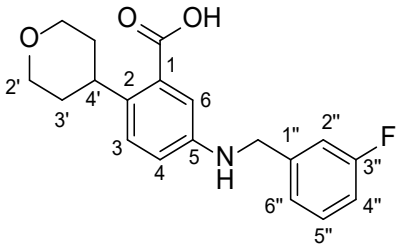
Following **General Procedure 4.2.6**, 1 M NaOH (1.5 mL, 1.536 mmol) was added to a solution of methyl 5-(benzylamino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19a** (0.125 g, 0.384 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20a** (0.110 g, 92%) as a white powder. M.p.: 134 – 136 °C. R.f.: 0.11 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3319 (OH, NH), 2946 (CH aromatic), 2856 (CH alkane), 1687 (C=O carboxylic acid), 1612 and 1570 (C=C aromatic), 1497 and 1418 (CH alkane), 1288, 1232 and 1126 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.32 – 3.37 (3H, m, H-2a', H-4'), 3.88 – 3.92 (2H, m, H-2b'), 4.26 (2H, br s, NHCH_2), 6.33 (1H, br s, NH), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.90 (1H, d, *J* = 2.5 Hz, H-6), 7.08 (1H, d, *J* = 8.5 Hz, H-3), 7.21 (1H, t, *J* = 7.0 Hz, H-4''), 7.29 – 7.35 (4H, m, H-2'', H-3'') and 12.63 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 46.4 ($NHCH_2$), 67.7 (C-2'), 113.0 (C-6), 115.0 (C-4), 126.6 (C-4''), 127.1 (C-2''), 127.2 (C-3), 128.3 (C-3''), 131.6 (C-1), 132.6 (C-2), 140.1 (C-1''), 146.4 (C-5) and 169.9 (C=O). *m/z* (ESI+): 334 (MNa^+, 100%), 316 (MH^+, 30%). HRMS (ESI+): Found (MNa^+): 334.1417, $C_{19}H_{21}NNaO_3$ requires 334.1414.

5-((2''-Fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20b



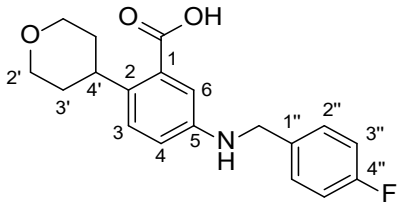
Following **General Procedure 4.2.6**, 1 M NaOH (4.4 mL, 4.36 mmol) was added to a solution of methyl 5-((2''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19b** (0.375 g, 1.09 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2.5 h, affording the *title compound* **20b** (0.311 g, 87%) as a fine white powder. M.p.: 120 – 122 °C. R.f.: 0.15 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3310 (OH, NH), 2960 (CH aromatic), 2854 (CH alkane), 1678 (C=O carboxylic acid), 1610 and 1574 (C=C aromatic), 1494 and 1401 (CH alkane), 1285 and 1232 (C-O ether), 1082 (C-F). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.29 – 3.37 (3H, m, H-2a', H-4'), 3.90 (2H, dd, *J* = 10.5, 3.0 Hz, H-2b'), 4.30 (2H, d, *J* = 5.0 Hz, NHC*H*$_2$), 6.30 (1H, t, *J* = 5.5 Hz, NH), 6.69 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.91 (1H, d, *J* = 2.5 Hz, H-6), 7.10 (1H, d, *J* = 8.5 Hz, H-3), 7.13 – 7.20 (2H, m, H-3'', H-5''), 7.29 (1H, m, H-4''), 7.38 (1H, td, *J* = 7.5, 1.5 Hz, H-6'') and 12.63 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 40.1 ($NHCH_2$), 67.7 (C-2'), 112.9 (C-6), 114.8 (C-4), 115.1 (d, $^2J_{F/C}$ = 21.3 Hz, C-3''), 124.3 (d, $^4J_{F/C}$ = 3.1 Hz, C-5''), 126.6 (d, $^2J_{F/C}$ = 14.6 Hz, C-1''), 127.3 (C-3), 128.7 (d, $^3J_{F/C}$ = 8.0 Hz, C-4''), 129.3 (d, $^3J_{F/C}$ = 4.5 Hz, C-6''), 131.7 (C-1), 132.9 (C-2), 146.1 (C-5), 160.3 (d, $^1J_{F/C}$ = 243.7 Hz, C-2'') and 169.8 (C=O). *m/z* (ESI+): 352 (MNa^+, 100%) and 330 (MH^+, 30%). HRMS (ESI+): Found (MNa^+): 352.1313, $C_{19}H_{20}FNNaO_3$ requires 352.1319.

5-((3''-Fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20c



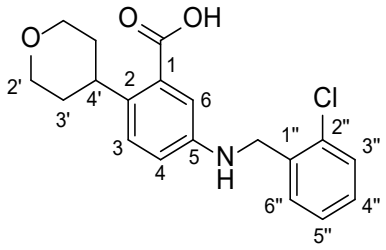
Following **General Procedure 4.2.6**, 1 M NaOH (4.7 mL, 4.66 mmol) was added to a solution of methyl 5-((3''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19c** (0.400 g, 1.17 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 3 h, affording the *title compound* **20c** (0.360 g, 94%) as a white powder. M.p.: 124 – 126 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3326 (OH, NH), 2946 (CH aromatic), 2855 (CH alkane), 1688 (C=O carboxylic acid), 1611 and 1570 (C=C aromatic), 1487 and 1417 (CH alkane), 1287, 1232 and 1127 (C-O ether), 1084 (C-F). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.29 – 3.37 (3H, m, H-2a', H-4'), 3.88 – 3.92 (2H, m, H-2b'), 4.29 (2H, br s, NHCH_2), 6.39 (1H, br s, NH), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.90 (1H, d, *J* = 2.5 Hz, H-6), 7.09 (1H, d, *J* = 8.5 Hz, H-3), 7.03 (1H, td, *J* = 8.0, 2.5 Hz, H-4''), 7.15 (1H, d, *J* = 10.0 Hz, H-2''), 7.18 (1H, d, *J* = 8.0 Hz, H-6''), 7.33 – 7.38 (1H, m, H-5'') and 12.63 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.8 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 113.4 (d, $^2J_{F/C}$ = 21.0 Hz, C-4''), 113.6 (d, $^2J_{F/C}$ = 21.0 Hz, C-2''), 115.0 (C-4), 123.0 (d, $^4J_{F/C}$ = 2.0 Hz, C-6''), 127.3 (C-3), 130.2 (d, $^3J_{F/C}$ = 8.2 Hz, C-5''), 131.6 (C-1), 132.8 (C-2), 143.5 (d, $^3J_{F/C}$ = 6.6 Hz, C-1''), 146.1 (C-5), 162.3 (d, $^1J_{F/C}$ = 243.3 Hz, C-3'') and 169.8 (C=O). *m/z* (ESI+): 352 (MNa^+, 100%) and 330 (MH^+, 30%). HRMS (ESI+): Found (MNa^+): 352.1311, $C_{19}H_{20}FNNaO_3$ requires 352.1319.

5-((4''-Fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20d



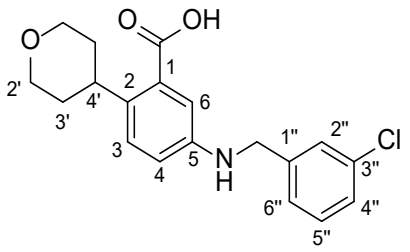
Following **General Procedure 4.2.6**, 1 M NaOH (4.3 mL, 4.34 mmol) was added to a solution of methyl 5-((4''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19d** (0.373 g, 1.086 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 3 h, affording the *title compound* **20d** (0.352 g, 98%) as a white powder. M.p.: 152 – 154 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3317 (OH, NH), 2946 (CH aromatic), 2856 (CH alkane), 1688 (C=O carboxylic acid), 1611 and 1569 (C=C aromatic), 1506 and 1416 (CH alkane), 1288 and 1232 (C-O ether), 1084 (C-F). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.29 – 3.37 (3H, m, H-2a', H-4'), 3.90 (2H, dd, *J* = 10.0, 3.0 Hz, H-2b'), 4.24 (2H, br s, NHCH_2), 6.34 (1H, br s, NH), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.89 (1H, d, *J* = 2.5 Hz, H-6), 7.09 (1H, d, *J* = 8.5 Hz, H-3), 7.13 (2H, t, *J* = 9.0 Hz, H-3''), 7.35 – 7.39 (2H, m, H-2'') and 12.62 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.6 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 114.9 (d, $^2J_{F/C}$ = 20.9 Hz, C-3''), 115.0 (C-4), 127.2 (C-3), 128.9 (d, $^3J_{F/C}$ = 8.0 Hz, C-2''), 131.6 (C-1), 132.7 (C-2), 136.2 (d, $^4J_{F/C}$ = 2.7 Hz, C-1''), 146.2 (C-5), 161.1 (d, $^1J_{F/C}$ = 241.7 Hz, C-4'') and 169.8 (C=O). *m/z* (ESI+): 352 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 352.1323, $C_{19}H_{20}FNNaO_3$ requires 352.1319.

5-((2''-Chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20e



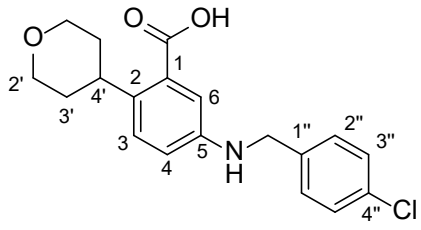
Following **General Procedure 4.2.6**, 1 M NaOH (4.38 mL, 4.38 mmol) was added to a solution of methyl 5-((2''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19e** (0.394 g, 1.094 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2.5 h, affording the *title compound* **20e** (0.350 g, 92%) as a white powder. M.p.: 160 – 162 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3396 and 3382 (OH, NH), 2951 (CH aromatic), 2847 (CH alkane), 1687 (C=O carboxylic acid), 1613 and 1572 (C=C aromatic), 1501 and 1427 (CH alkane), 1320 and 1240 (C-O ether), 753 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.29 – 3.37 (3H, m, H-2a', H-4'), 3.90 (2H, d, *J* = 10.0 Hz, H-2b'), 4.32 (2H, d, *J* = 5.0 Hz, NHC*H*$_2$), 6.38 (1H, t, *J* = 5.0 Hz, NH), 6.64 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.88 (1H, d, *J* = 2.5 Hz, H-6), 7.11 (1H, d, *J* = 8.5 Hz, H-3), 7.25 – 7.32 (2H, m, H-4'', H-5''), 7.39 (1H, dd, *J* = 7.0, 2.5 Hz, H-6''), 7.45 (1H, dd, *J* = 7.0, 2.5 Hz, H-3'') and 12.64 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 44.1 ($NHCH_2$), 67.7 (C-2'), 112.9 (C-6), 114.8 (C-4), 127.2 (C-5''), 127.4 (C-3), 128.5 (C-4''), 128.7 (C-6''), 129.2 (C-3''), 131.7 (C-1), 132.2 (C-2''), 132.9 (C-2), 138.6 (C-1''), 146.0 (C-5) and 169.8 (C=O). *m/z* (ESI+): 370 ($^{37}MNa^+$, 30%) and 368 ($^{35}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 370.1021, $C_{19}H_{20}{}^{37}ClNNaO_3$ requires 370.1001. Found (MNa^+): 368.1023, $C_{19}H_{20}{}^{35}ClNNaO_3$ requires 368.1024.

5-((3''-Chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20f



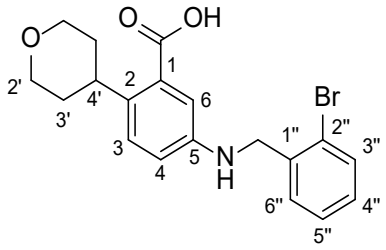
Following **General Procedure 4.2.6**, 1 M NaOH (4.64 mL, 4.64 mmol) was added to a solution of methyl 5-((3''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19f** (0.417 g, 1.159 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20f** (0.373 g, 93%) as a light yellow powder. M.p.: 138 – 140 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3374 (OH, NH), 2958 (CH aromatic), 2850 (CH alkane), 1683 (C=O carboxylic acid), 1613 and 1575 (C=C aromatic), 1506 and 1424 (CH alkane), 1305 and 1242 (C-O ether), 755 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.32 – 3.37 (3H, m, H-2a', H-4'), 3.90 (2H, d, *J* = 10.0 Hz, H-2b'), 4.28 (2H, d, *J* = 3.5 Hz, NHCH_2), 6.40 (1H, br s, NH), 6.66 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.89 (1H, d, *J* = 2.5 Hz, H-6), 7.09 (1H, d, *J* = 8.5 Hz, H-3), 7.26 – 7.37 (3H, m, H-4'', H-5'', H-6''), 7.40 (1H, br s, H-2'') and 12.64 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.7 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 115.0 (C-4), 125.7 (C-6''), 126.6 (C-4''), 126.8 (C-2''), 127.3 (C-3), 130.2 (C-5''), 131.7 (C-1), 133.1 (C-3''), 138.2 (C-2), 143.0 (C-1''), 146.1 (C-5) and 169.8 (C=O). *m/z* (ESI+): 370 ($^{37}MNa^+$, 30%) and 368 ($^{35}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 370.1037, $C_{19}H_{20}{}^{37}ClNNaO_3$ requires 370.1001. Found (MNa^+): 368.1035, $C_{19}H_{20}{}^{35}ClNNaO_3$ requires 368.1024.

5-((4''-Chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20g



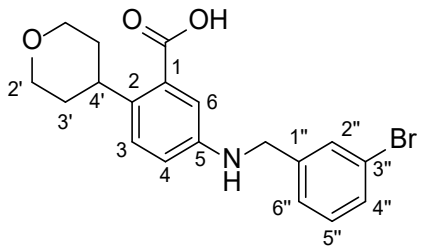
Following **General Procedure 4.2.6**, 1 M NaOH (3.81 mL, 3.81 mmol) was added to a solution of methyl 5-((4''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19g**(0.343 g, 0.953 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 3 h, affording the *title compound* **20g** (0.280 g, 85%) as a white powder. M.p.: 178 – 180 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3317 (OH, NH), 2940 (CH aromatic), 2844 (CH alkane), 1676 (C=O carboxylic acid), 1611 and 1574 (C=C aromatic), 1507 and 1491 (CH alkane), 1290, 1233 and 1125 (C-O ether), 810 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.29 – 3.37 (3H, m, H-2a', H-4'), 3.89 (2H, dd, *J* = 10.5, 2.5 Hz, H-2b'), 4.26 (2H, br s, NHCH_2), 6.38 (1H, br s, NH), 6.65 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.88 (1H, d, *J* = 2.5 Hz, H-6), 7.08 (1H, d, *J* = 8.5 Hz, H-3), 7.34 – 7.39 (4H, m, H-2'', H-3'') and 12.62 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.6 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 115.0 (C-4), 127.2 (C-3), 128.2 (C-3''), 128.9 (C-2''), 131.1 (C-4''), 131.6 (C-1), 132.8 (C-2), 139.2 (C-1''), 146.1 (C-5) and 169.8 (C=O). *m/z* (ESI+): 370 ($^{37}MNa^+$, 30%) and 368 ($^{35}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 370.1049, $C_{19}H_{20}{}^{37}ClNNaO_3$ requires 370.1001. Found (MNa^+): 368.1036, $C_{19}H_{20}{}^{35}ClNNaO_3$ requires 368.1024.

5-((2''-Bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20h



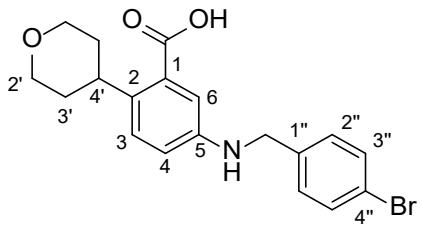
Following **General Procedure 4.2.6**, 1 M NaOH (4.08 mL, 4.08 mmol) was added to a solution of methyl 5-((2''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19h** (0.412 g, 1.019 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 3 h, affording the *title compound* **20h** (0.377 g, 95%) as a white powder. M.p.: 108 – 110 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3322 (OH, NH), 2933 (CH aromatic), 2850 (CH alkane), 1684 (C=O carboxylic acid), 1612 and 1577 (C=C aromatic), 1508 and 1469 (CH alkane), 1291 and 1237 (C-O ether), 660 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.66 (4H, m, H-3'), 3.31 – 3.38 (3H, m, H-2a', H-4'), 3.90 (2H, dd, *J* = 10.5, 3.0 Hz, H-2b'), 4.28 (2H, d, *J* = 5.5 Hz, NHC*H*$_2$), 6.41 (1H, t, *J* = 5.5 Hz, NH), 6.62 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.87 (1H, d, *J* = 2.5 Hz, H-6), 7.11 (1H, d, *J* = 8.5 Hz, H-3), 7.20 (1H, td, *J* = 7.5, 2.0 Hz, H-4''), 7.33 (1H, td, *J* = 7.5, 1.0 Hz, H-5''), 7.37 (1H, dd, *J* = 7.5, 2.0 Hz, H-6''), 7.62 (1H, dd, *J* = 7.5, 1.0 Hz, H-3'') and 12.64 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.8 (C-3'), 36.1 (C-4'), 46.8 ($NHCH_2$), 67.7 (C-2'), 112.9 (C-6), 114.8 (C-4), 122.6 (C-2''), 127.4 (C-3), 127.8 (C-5''), 128.8 (C-4''), 128.8 (C-6''), 131.7 (C-1), 132.5 (C-3''), 132.9 (C-2), 138.3 (C-1''), 146.0 (C-5) and 169.8 (C=O). *m/z* (ESI+): 414 ($^{81}MNa^+$, 100%) and 412 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 414.0518, $C_{19}H_{20}{}^{81}BrNNaO_3$ requires 414.0500. Found (MNa^+): 412.0528, $C_{19}H_{20}{}^{79}BrNNaO_3$ requires 412.0519.

5-((3''-Bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20i



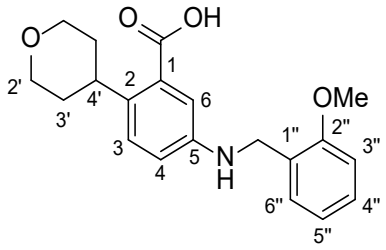
Following **General Procedure 4.2.6**, 1 M NaOH (2.89 mL, 2.89 mmol) was added to a solution of methyl 5-((3''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19i** (0.292 g, 0.722 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 3.5 h, affording the *title compound* **20i** (0.280 g, 99%) as a white solid. M.p.: 156 – 158 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3311 (OH, NH), 2958 (CH aromatic), 2837 (CH alkane), 1679 (C=O carboxylic acid), 1611 and 1576 (C=C aromatic), 1515 and 1466 (CH alkane), 1300 and 1235 (C-O ether), 669 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.32 – 3.37 (3H, m, H-2a', H-4'), 3.90 (2H, dd, *J* = 10.5, 3.0 Hz, H-2b'), 4.27 (2H, d, *J* = 4.5 Hz, NHC*H*$_2$), 6.40 (1H, br s, NH), 6.66 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.89 (1H, d, *J* = 2.5 Hz, H-6), 7.09 (1H, d, *J* = 8.5 Hz, H-3), 7.28 (1H, t, *J* = 7.5 Hz, H-5''), 7.35 (1H, d, *J* = 7.5 Hz, H-6''), 7.41 (1H, d, *J* = 7.5 Hz, H-4''), 7.54 (1H, br s, H-2'') and 12.63 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.7 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 115.0 (C-4), 121.8 (C-3''), 126.1 (C-6''), 127.3 (C-3), 129.5 (C-2''), 129.7 (C-4''), 130.5 (C-5''), 131.6 (C-1), 132.8 (C-2), 143.3 (C-1''), 146.0 (C-5) and 169.8 (C=O). *m/z* (ESI+): 414 ($^{81}MNa^+$, 100%) and 412 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 414.0498, $C_{19}H_{20}{}^{81}BrNNaO_3$ requires 414.0500. Found (MNa^+): 412.0517, $C_{19}H_{20}{}^{79}BrNNaO_3$ requires 412.0519.

5-((4''-Bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20j



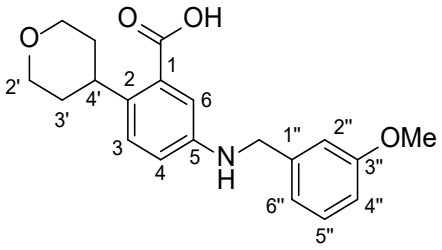
Following **General Procedure 4.2.6**, 1 M NaOH (2.78 mL, 2.78 mmol) was added to a solution of methyl 5-((4''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19j** (0.280 g, 0.695 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20j** (0.242 g, 89%) as a white solid. M.p.: 186 – 188 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3312 (OH, NH), 2958 (CH aromatic), 2837 (CH alkane), 1678 (C=O carboxylic acid), 1611 and 1576 (C=C aromatic), 1512 and 1413 (CH alkane), 1321 and 1235 (C-O ether), 669 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 3.31 – 3.36 (3H, m, H-2a', H-4'), 3.89 (2H, d, *J* = 10.5 Hz, H-2b'), 4.24 (2H, br s, NHC*H*$_2$), 6.38 (1H, br s, NH), 6.64 (1H, dd, *J* = 8.5, 2.0 Hz, H-4), 6.88 (1H, d, *J* = 2.0 Hz, H-6), 7.08 (1H, d, *J* = 8.5 Hz, H-3), 7.29 (2H, d, *J* = 8.0 Hz, H-2''), 7.50 (2H, d, *J* = 8.0 Hz, H-3'') and 12.63 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.7 ($NHCH_2$), 67.7 (C-2'), 113.1 (C-6), 115.0 (C-4), 119.5 (C-4''), 127.2 (C-3), 129.2 (C-2''), 131.2 (C-3''), 131.6 (C-1), 132.8 (C-2), 139.7 (C-1''), 146.1 (C-5) and 169.8 (C=O). *m/z* (ESI+): 414 ($^{81}MNa^+$, 100%) and 412 ($^{79}MNa^+$, 100%). HRMS (ESI+): Found (MNa^+): 414.0518, $C_{19}H_{20}{}^{81}BrNNaO_3$ requires 414.0500. Found (MNa^+): 412.0525, $C_{19}H_{20}{}^{79}BrNNaO_3$ requires 412.0519.

5-((2''-Methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20k



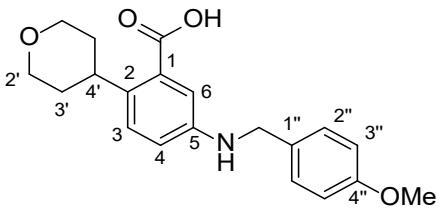
Following **General Procedure 4.2.6**, 1 M NaOH (2.70 mL, 2.70 mmol) was added to a solution of methyl 5-((2''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19k** (0.240 g, 0.675 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20k** (0.216 g, 94%) as a yellow powder. M.p.: 137 – 139 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3330 (OH, NH), 2959 (CH aromatic), 2838 (CH alkane), 1682 (C=O carboxylic acid), 1611 and 1574 (C=C aromatic), 1498 and 1402 (CH alkane), 1318, 1288 and 1240 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.66 (4H, m, H-3'), 3.31 – 3.37 (3H, m, H-2a', H-4'), 3.83 (3H, s, 2'-OCH_3), 3.90 (2H, d, *J* = 10.5 Hz, H-2b'), 4.21 (2H, br s, NHCH_2), 6.13 (1H, br s, NH), 6.63 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.85 – 6.89 (2H, m, H-6, H-5''), 6.99 (1H, d, *J* = 8.0 Hz, H-3''), 7.07 (1H, d, *J* = 8.5 Hz, H-3) and 7.19 – 7.23 (2H, m, H-4'', H-6''). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 41.1 ($NHCH_2$), 55.3 (2''-OCH_3), 67.8 (C-2'), 110.5 (C-3''), 112.7 (C-6), 114.8 (C-4), 120.1 (C-5''), 127.1 (C-3), 127.2 (C-1''), 127.7 (C-4''), 127.8 (C-6''), 132.0 (C-1), 132.4 (C-2), 146.4 (C-5), 156.8 (C-2'') and 170.0 (C=O). *m/z* (ESI+): 364 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 364.1507, $C_{20}H_{23}NNaO_4$ requires 364.1519.

5-((3''-Methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20l



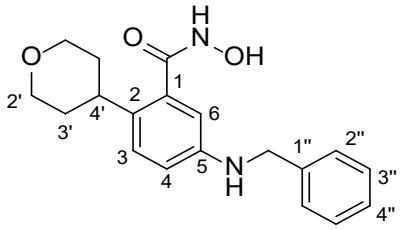
Following **General Procedure 4.2.6**, 1 M NaOH (2.70 mL, 2.70 mmol) was added to a solution of methyl 5-((3''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19l** (0.217 g, 0.611 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20l** (0.205 g, 99%) as a fine white powder. M.p.: 168 – 170 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3380 (OH, NH), 2930 (CH aromatic), 2845 (CH alkane), 1675 (C=O carboxylic acid), 1599 and 1570 (C=C aromatic), 1510, 1467 and 1404 (CH alkane), 1324, 1258 and 1235 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.66 (4H, m, H-3'), 3.32 – 3.37 (3H, m, H-2a', H-4'), 3.72 (3H, s, 3'-OCH_3), 3.90 (2H, dd, *J* = 10.5, 3.0 Hz, H-2b'), 4.22 (2H, d, *J* = 3.5 Hz, NHCH_2), 6.32 (1H, br s, NH), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.77 – 6.79 (1H, m, H-4''), 6.90 – 6.92 (3H, m, H-2'', H-6'' and H-6), 7.08 (1H, d, *J* = 8.5 Hz, H-3), 7.22 (1H, t, *J* = 8.0 Hz, H-5'') and 12.61 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 46.3 ($NHCH_2$), 54.9 (3''-OCH_3), 67.7 (C-2'), 111.9 (C-4''), 112.8 (C-2''), 113.1 (C-6), 115.0 (C-4), 119.2 (C-6''), 127.2 (C-3), 129.3 (C-5''), 131.6 (C-1), 132.6 (C-2), 141.9 (C-1''), 146.4 (C-5), 159.3 (C-3'') and 169.9 (C=O). *m/z* (ESI+): 364 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 364.1516, $C_{20}H_{23}NNaO_4$ requires 364.1519.

5-((4''-Methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid 20m



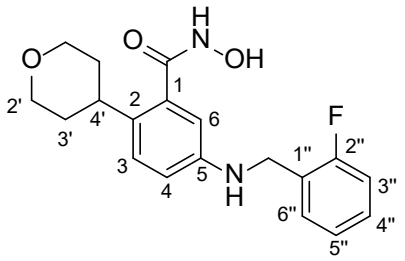
Following **General Procedure 4.2.6**, 1 M NaOH (2.70 mL, 2.70 mmol) was added to a solution of methyl 5-((4''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoate **19m** (0.240 g, 0.675 mmol) in THF/MeOH (1:1, 5 mL), the reaction was stirred at 80 °C for 2 h, affording the *title compound* **20m** (0.208 g, 90%) as a fine white powder. M.p.: 183 – 185 °C. R.f.: 0.10 (2:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3303 (OH, NH), 2950 (CH aromatic), 2833 (CH alkane), 1675 (C=O carboxylic acid), 1610 and 1575 (C=C aromatic), 1510, 1465 and 1412 (CH alkane), 1322, 1285 and 1235 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.66 (4H, m, H-3'), 3.31 – 3.37 (3H, m, H-2a', H-4'), 3.71 (3H, s, 4'-OCH_3), 3.90 (2H, dd, *J* = 10.5, 3.0 Hz, H-2b'), 4.17 (2H, s, NHCH_2), 6.24 (1H, br s, NH), 6.67 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.86 – 6.89 (3H, m, H-6, H-3''), 7.07 (1H, d, *J* = 8.5 Hz, H-3), 7.26 (2H, d, *J* = 8.5 Hz, H-2'') and 12.61 (1H, br s, CO_2H). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.1 (C-4'), 45.8 ($NHCH_2$), 55.0 (4''-OMe), 67.7 (C-2'), 113.0 (C-6), 113.7 (C-3''), 115.0 (C-4), 127.1 (C-3), 128.3 (C-2''), 131.6 (C-1), 131.8 (C-1''), 132.5 (C-2), 146.4 (C-5), 158.1 (C-4'') and 169.9 (C=O). *m/z* (ESI+): 364 (MNa^+, 100%). HRMS (ESI+): Found (MNa^+): 364.1520, $C_{20}H_{23}NNaO_4$ requires 364.1519.

5-(Benzylamino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21a



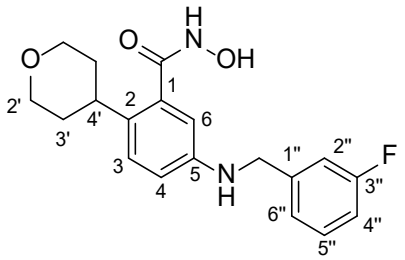
The reaction was carried out following **General Procedure 4.2.7**, using 5-(benzylamino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20a** (0.135 g, 0.434 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.076 g, 0.651 mmol), COMU (0.242 g, 0.564 mmol) and DIPEA (0.168 g, 1.302 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography (98.75:0.75:0.5, CH_2Cl_2/MeOH/NEt_3) to give the amide intermediate, which was used immediately in the following step. The amide intermediate was dissolved in THF/MeOH (1:1, 3 mL) and treated with 2 M HCl (0.05 mL, 0.091 mmol) for 21 h. The *title product* **21a** was given as a pink solid (0.054 g, 70%). M.p.: 164 – 166 °C. R.f.: 0.07 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3397 (NH), 3206 (OH), 2940 and 2913 (CH aromatic), 2842 (CH alkane), 1650 (C=O hydroxamic acid), 1610 and 1580 (C=C aromatic), 1493, 1335 and 1120 (CH alkane), 1075 and 1013 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.87 (1H, m, H-4'), 3.27 – 3.33 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.25 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.30 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 6.44 (1H, d, *J* = 2.5 Hz, H-6), 6.58 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.22 (1H, t, *J* = 6.5 Hz, H-4''), 7.29 – 7.35 (4H, m, H-2'', H-3''), 8.95 (1H, d, *J* = 1.5 Hz, N*H*OH) and 10.70 (1H, d, *J* = 1.5 Hz, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 46.4 (NH*C*H_2), 33.9 (C-3'), 36.3 (C-4'), 67.6 (C-2'), 111.3 (C-6), 113.1 (C-4), 126.8 (C-3), 126.6 (C-4''), 127.0 (C-2''), 128.3 (C-3''), 130.8 (C-2), 134.9 (C-1), 140.2 (C-1''), 146.3 (C-5) and 166.8 (C=O). *m/z* (ESI+): 349 (MNa^+, 100%) and 327 (MH^+, 75%). HRMS (ESI+): Found (MH^+): 327.1692, $C_{19}H_{23}N_2O_3$ requires 327.1703.

5-((2''-Fluorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21b



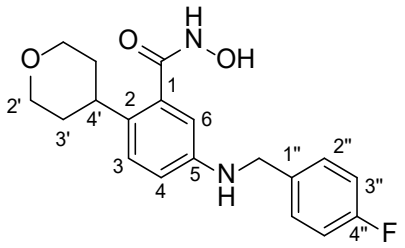
The reaction was carried out following **General Procedure 4.2.7**, the reaction was carried out using 5-((2''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20b** (0.200 g, 0.582 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.102 g, 0.736 mmol), COMU (0.324 g, 0.757 mmol) and DIPEA (0.226 g, 1.746 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was immediately dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.09 mL, 0.185 mmol) for 21 h. The *title product* **21b** was given as a light pink solid (0.110 g, 78%). M.p.: 167 – 169 °C. R.f.: 0.06 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3344 (NH), 3162 (OH), 2934 (CH aromatic), 2837 (CH alkane), 1638 (C=O hydroxamic acid), 1611 and 1586 (C=C aromatic), 1490, 1340 and 1123 (CH alkane), 1229 (C-F), 1082 and 1020 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.56 – 1.65 (4H, m, H-3'), 2.82 – 2.90 (1H, m, H-4'), 3.27 – 3.34 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.29 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.26 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.45 (1H, d, *J* = 2.5 Hz, H-6), 6.60 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.05 (1H, d, *J* = 8.5 Hz, H-3), 7.13 – 7.20 (2H, m, H-3'', H-5''), 7.26 – 7.32 (1H, m, H-4''), 7.38 (1H, td, *J* = 7.5, 1.5 Hz, H-6''), 8.96 (1H, s, N*H*OH) and 10.71 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 33.9 (C-3'), 36.4 (C-4'), 40.0 (NH*C*H$_2$), 67.7 (C-2'), 111.2 (C-6), 113.0 (C-4), 115.1 (d, $^2J_{F/C}$ = 21.2 Hz, C-3''), 124.3 (d, $^4J_{F/C}$ = 3.1 Hz, C-5''), 126.6 (d, $^2J_{F/C}$ = 14.7 Hz, C-1''), 126.9 (C-3), 128.7 (d, $^3J_{F/C}$ = 8.0 Hz, C-4''), 129.3 (d, $^3J_{F/C}$ = 4.5 Hz, C-6''), 131.0 (C-2), 135.0 (C-1), 146.1 (C-5), 160.3 (d, $^1J_{F/C}$ = 243.9 Hz, C-2'') and 166.8 (C=O). *m/z* (ESI+): 367 (MNa$^+$, 100%) and 345 (MH$^+$, 75%). HRMS (ESI+): Found (MNa$^+$): 367.1430, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

5-((3''-Fluorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21c



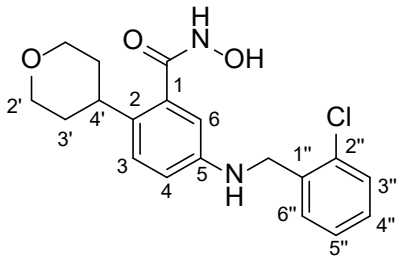
The reaction was carried out following **General Procedure 4.2.7**, the reaction was carried out using 5-((3''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20c** (0.285 g, 0.830 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.146 g, 1.250 mmol), COMU (0.462 g, 1.079 mmol) and DIPEA (0.322 g, 2.490 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.16 mL, 0.320 mmol) for 23 h. The *title product* **21c** was given as a light pink solid (0.192 g, 85%). M.p.: 169 – 171 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3336 (NH), 3274 (OH), 2842 (CH alkane), 1651 (C=O hydroxamic acid), 1611 and 1591 (C=C aromatic), 1489, 1337 and 1116 (CH alkane), 1260 (C-F), 1067 and 1019 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.56 – 1.64 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.30 (2H, td, *J* = 10.5, 3.0 Hz, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.28 (2H, s, NHC*H*$_2$), 6.37 (1H, br s, N*H*CH$_2$), 6.43 (1H, d, *J* = 2.5 Hz, H-6), 6.57 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.01 – 7.06 (2H, m, H-3, H-4''), 7.14 (1H, d, *J* = 10.0 Hz, H-2''), 7.19 (1H, d, *J* = 7.5 Hz, H-6''), 7.33 – 7.39 (1H, m, H-5''), 8.96 (1H, s, N*H*OH) and 10.70 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 33.9 (C-3'), 36.4 (C-4'), 45.9 (NH*C*H$_2$), 67.7 (C-2'), 111.4 (C-6), 113.2 (C-4), 113.4 (d, $^2J_{F/C}$ = 16.2 Hz, C-4''), 113.6 (d, $^2J_{F/C}$ = 16.5 Hz, C-2''), 123.0 (d, $^4J_{F/C}$ = 1.9 Hz, C-6''), 126.8 (C-3), 130.2 (d, $^3J_{F/C}$ = 8.0 Hz, C-5''), 131.0 (C-2), 135.0 (C-1), 143.6 (d, $^3J_{F/C}$ = 6.7 Hz, C-1''), 146.1 (C-5), 162.4 (d, $^1J_{F/C}$ = 243.2 Hz, C-3'') and 166.8 (C=O). *m/z* (ESI+): 367 (MNa$^+$, 100%) and 345 (MH$^+$, 60%). HRMS (ESI+): Found (MNa$^+$): 367.1436, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

5-((4''-Fluorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21d



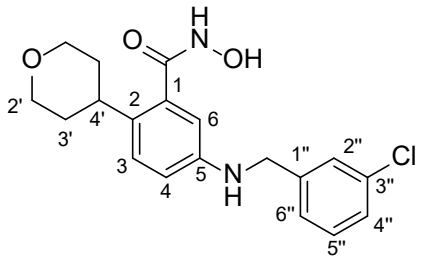
The reaction was carried out following **General Procedure 4.2.7**, using 5-((4''-fluorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20d** (0.277 g, 0.807 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.142 g, 1.210 mmol), COMU (0.449 g, 1.049 mmol) and DIPEA (0.313 g, 2.421 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was immediately dissolved in MeOH/THF (1:1, 3 mL) and treated using 2 M HCl (0.16 mL, 0.327 mmol) for 24 h. The *title product* **21d** was given as a light pink solid (0.193 g, 85%). M.p.: 190 – 192 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3348 (NH), 3186 (OH), 2857 (CH alkane), 1639 (C=O hydroxamic acid), 1611 (C=C aromatic), 1506, 1341 and 1122 (CH alkane), 1242 (C-F), 1083 and 1013 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$) 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.27 – 3.31 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.23 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.31 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.43 (1H, d, *J* = 2.5 Hz, H-6), 6.57 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.14 (2H, tt, *J* = 9.0, 2.5 Hz, H-3''), 7.37 (2H, dd, *J* = 9.0, 6.0 Hz, H-2''), 8.96 (1H, d, *J* = 1.5 Hz, N*H*OH) and 10.70 (1H, d, *J* = 1.5 Hz, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$) 33.9 (C-3'), 36.3 (C-4'), 45.7 (NH*C*H$_2$), 67.7 (C-2'), 111.4 (C-6), 113.2 (C-4), 115.0 (d, $^2J_{F/C}$ = 21.1 Hz, C-3''), 126.8 (C-3), 128.9 (d, $^3J_{F/C}$ = 8.0 Hz, C-2''), 130.9 (C-2), 135.0 (C-1), 136.3 (d, $^4J_{F/C}$ = 2.7 Hz, C-1''), 146.1 (C-5), 161.1 (d, $^1J_{F/C}$ = 241.8 Hz, C-4'') and 166.8 (C=O). *m/z* (ESI+): 367 (MNa$^+$, 100%) and 345 (MH$^+$, 30%). HRMS (ESI+): Found (MNa$^+$): 367.1427, $C_{19}H_{21}FN_2NaO_3$ requires 367.1428.

5-((2''-Chlorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21e



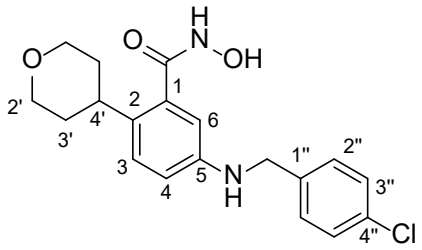
The reaction was carried out following **General Procedure 4.2.7**, using 5-((2''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20e** (0.280 g, 0.807 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.142 g, 1.215 mmol), COMU (0.451 g, 1.053 mmol) and DIPEA (0.314 g, 2.429 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was dissolved in MeOH/THF (1:1, 3 mL) and hydrolysed using 2 M HCl (0.16 mL, 0.315 mmol) for 22.5 h. The *title product* **21e** was given as a light pink solid (0.183 g, 79%). M.p.: 150 – 152 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3348 (NH), 3187 (OH), 2857 (CH alkane), 1639 (C=O hydroxamic acid), 1611 (C=C aromatic), 1506, 1341 and 1122 (CH alkane), 1082 and 1014 (C-O ether), 820 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 2.82 – 2.90 (1H, m, H-4'), 3.27 – 3.34 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.32 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.34 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.42 (1H, d, *J* = 2.5 Hz, H-6), 6.55 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.06 (1H, d, *J* = 8.5 Hz, H-3), 7.25 – 7.32 (2H, m, H-4'', H-5''), 7.39 (1H, dd, *J* = 7.0, 2.5 Hz, H-6''), 7.44 – 7.46 (1H, m, H-3''), 8.95 (1H, d, *J* = 1.5 Hz, N*H*OH) and 10.71 (1H, d, *J* = 1.5 Hz, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.4 (C-4'), 44.2 (NHCH$_2$), 67.6 (C-2'), 111.1 (C-6), 113.0 (C-4), 126.9 (C-5''), 127.2 (C-3), 128.5 (C-4''), 128.7 (C-6''), 129.2 (C-3''), 131.1 (C-2), 132.2 (C-2''), 135.0 (C-1), 136.9 (C-1''), 146.0 (C-5) and 166.7 (C=O). *m/z* (ESI+): 385 (^{37}MNa$^+$, 30%), 383 (^{35}MNa$^+$, 100%), 363 (^{37}MH$^+$, 10%) and 361 (^{35}MH$^+$, 30%). HRMS (ESI+): Found (MNa$^+$): 385.1137, $C_{19}H_{21}{}^{37}ClN_2NaO_3$ requires 385.1110. Found (MNa$^+$): 383.1133, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 383.1133.

5-((3''-Chlorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21f



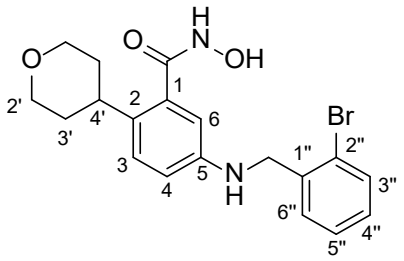
The reaction was carried out following **General Procedure 4.2.7**, using 5-((3''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20f** (0.300 g, 0.868 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.153 g, 1.302 mmol), COMU (0.483 g, 1.128 mmol) and DIPEA (0.337 g, 2.604 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was then dissolved in MeOH/THF (1:1, 3 mL) and hydrolysed using 2 M HCl (0.16 mL, 0.314 mmol) for 20 h. The *title product* **21f** was given as a light pink solid (0.200 g, 84%). M.p.: 173 – 175 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3334 (NH), 3236 (OH), 2849 (CH alkane), 1653 (C=O hydroxamic acid), 1611 and 1578 (C=C aromatic), 1509, 1472, 1337 and 1116 (CH alkane), 1078 and 1013 (C-O ether), 811 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.28 – 3.31 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.27 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.38 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.43 (1H, d, *J* = 2.5 Hz, H-6), 6.57 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.04 (1H, d, *J* = 8.5 Hz, H-3), 7.26 – 7.37 (3H, m, H-4'', H-5'', H-6''), 7.39 (1H, br s, H-2''), 8.96 (1H, d, *J* = 1.5 Hz, N*H*OH) and 10.71 (1H, d, *J* = 1.5 Hz, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.4 (C-4'), 45.8 (NHCH$_2$), 67.6 (C-2'), 111.4 (C-6), 113.1 (C-4), 125.7 (C-6''), 126.6 (C-4''), 126.7 (C-2''), 126.9 (C-3), 130.2 (C-5''), 131.0 (C-2), 133.1 (C-3''), 135.0 (C-1), 143.2 (C-1''), 146.0 (C-5) and 166.7 (C=O). *m/z* (ESI+): 385 (^{37}MNa$^+$, 30%), 383 (^{35}MNa$^+$, 100%), 363 (^{37}MH$^+$, 10%) and 361 (^{35}MH$^+$, 30%). HRMS (ESI+): Found (MNa$^+$): 385.1136, $C_{19}H_{21}{}^{37}ClN_2NaO_3$ requires 385.1110. Found (MNa$^+$): 383.1137, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 383.1133.

5-((4''-Chlorobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21g



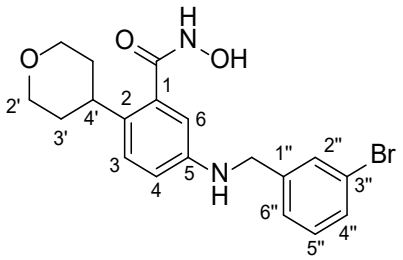
The reaction was carried out following **General Procedure 4.2.7**, using 5-((4''-chlorobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20g** (0.210 g, 0.607 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.107 g, 0.911 mmol), COMU (0.338 g, 0.789 mmol) and DIPEA (0.235 g, 1.821 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.10 mL, 0.203 mmol) for 23 h. The *title product* **21g** was given as a light pink solid (0.092 g, 57%). M.p.: 194 – 196 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3339 (NH), 3162 (OH), 2925 (CH aromatic), 2855 (CH alkane), 1635 (C=O hydroxamic acid), 1612 (C=C aromatic), 1513, 1488, 1324 and 1121 (CH alkane), 1082 and 1013 (C-O ether), 804 (C-Cl). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.27 – 3.31 (2H, m, H-2' a), 3.88 (2H, d, *J* = 10.5 Hz, H-2'b), 4.24 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.36 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.42 (1H, d, *J* = 2.5 Hz, H-6), 6.55 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.34 – 7.39 (4H, m, H-2'', H-3''), 8.96 (1H, d, *J* = 1.5 Hz, N*H*OH) and 10.70 (1H, d, *J* = 1.5 Hz, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.3 (C-4'), 45.7 (NHCH$_2$), 67.7 (C-2'), 111.4 (C-6), 113.2 (C-4), 126.8 (C-3), 128.3 (C-3''), 128.8 (C-2''), 130.9 (C-2), 131.1 (C-4''), 135.0 (C-1), 139.4 (C-1''), 146.1 (C-5) and 166.8 (C=O). *m/z* (ESI+): 385 (^{37}MNa$^+$, 30%), 383 (^{35}MNa$^+$, 100%), 363 (^{37}MH$^+$, 10%) and 361 (^{35}MH$^+$, 30%). HRMS (ESI+): Found (MNa$^+$): 383.1216, $C_{19}H_{21}{}^{35}ClN_2NaO_3$ requires 383.1133. Found (MH$^+$): 361.1329, $C_{19}H_{22}{}^{35}ClN_2O_3$ requires 361.1319.

5-((2''-Bromobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21h



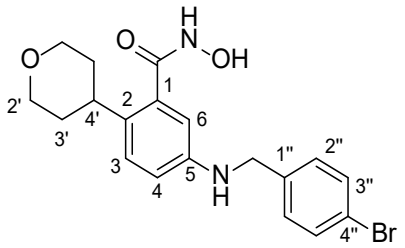
The reaction was carried out following **General Procedure 4.2.7**, using 5-((2''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20h** (0.300 g, 0.769 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.130 g, 1.110 mmol), COMU (0.412 g, 0.963 mmol) and DIPEA (0.287 g, 2.221 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. Next this intermediate was dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.14 mL, 0.286 mmol) for 24 h. The *title product* **21h** was given as a light pink solid (0.180 g, 77%). M.p.: 172 – 174 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3350 (NH), 3187 (OH), 3046 and 2908 (CH aromatic), 2833 (CH alkane), 1643 (C=O hydroxamic acid), 1609 (C=C aromatic), 1512, 1323 and 1122 (CH alkane), 1083 and 1020 (C-O ether), 542 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.56 – 1.65 (4H, m, H-3'), 2.82 – 2.90 (1H, m, H-4'), 3.27 – 3.34 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.27 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.37 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.41 (1H, d, *J* = 2.5 Hz, H-6), 6.53 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.06 (1H, d, *J* = 8.5 Hz, H-3), 7.20 (1H, td, *J* = 8.0, 2.0 Hz, H-4''), 7.32 – 7.38 (2H, m, H-5'', H-6''), 7.62 (1H, dd, *J* = 8.0, 1.0 Hz, H-3''), 8.96 (1H, d, *J* = 1.0 Hz, N*H*OH) and 10.73 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.4 (C-4'), 46.8 (NHCH$_2$), 67.7 (C-2'), 111.2 (C-6), 113.0 (C-4), 122.5 (C-2''), 127.0 (C-3), 127.8 (C-5''), 128.8 (C-4''), 128.8 (C-6''), 131.2 (C-2), 132.5 (C-3''), 135.1 (C-1), 138.4 (C-1''), 145.9 (C-5) and 166.7 (C=O). *m/z* (ESI+): 429 (^{81}MNa$^+$, 100%), 427 (^{79}MNa$^+$, 100%), 407 (^{81}MH$^+$, 40%) and 405 (^{79}MH$^+$, 40%). HRMS (ESI+): Found (MNa$^+$): 407.0786, $C_{19}H_{22}{}^{81}BrN_2O_3$ requires 407.0790. Found (MNa$^+$): 405.0804, $C_{19}H_{22}{}^{79}BrN_2O_3$ requires 405.0808.

5-((3''-Bromobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21i



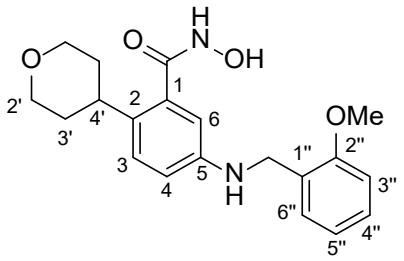
The reaction was carried out following **General Procedure 4.2.7**, using 5-((3''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20i** (0.205 g, 0.525 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.093 g, 0.788 mmol), COMU (0.293 g, 0.683 mmol) and DIPEA (0.204 g, 1.575 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the intermediate as a white crystalline solid. Next, this intermediate was dissolved in MeOH/THF (1:1, 3 mL) and hydrolysed using 2 M HCl (0.09 mL, 0.184 mmol) for 26 h. The *title product* **21i** was given as a light pink solid (0.122 g, 81%). M.p.: 172 – 174 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3329 (NH), 3247 (OH), 2900 (CH aromatic), 2849 (CH alkane), 1653 (C=O hydroxamic acid), 1610 (C=C aromatic), 1508, 1320 and 1116 (CH alkane), 1067 and 1012 (C-O ether), 523 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.64 (4H, m, H-3'), 2.82 – 2.89 (1H, m, H-4'), 3.27 – 3.33 (2H, m, H-2' a), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.26 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.37 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.43 (1H, d, *J* = 2.5 Hz, H-6), 6.57 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.04 (1H, d, *J* = 8.5 Hz, H-3), 7.28 (1H, t, *J* = 7.5 Hz, H-5''), 7.35 (1H, d, *J* = 7.5 Hz, H-6''), 7.41 (1H, d, *J* = 7.5 Hz, H-4''), 7.53 (1H, br s, H-2''), 8.97 (1H, s, N*H*OH) and 10.71 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.4 (C-4'), 45.7 (NHCH$_2$), 67.7 (C-2'), 111.4 (C-6), 113.1 (C-4), 121.8 (C-3''), 126.1 (C-6''), 126.9 (C-3), 129.5 (C-2''), 129.6 (C-4''), 130.5 (C-5''), 131.0 (C-2), 135.0 (C-1), 143.4 (C-1''), 146.0 (C-5) and 166.7 (C=O). *m/z* (ESI+): 429 (^{81}MNa$^+$, 100%), 427 (^{79}MNa$^+$, 100%), 407 (^{81}MH$^+$, 50%) and 405 (^{79}MH$^+$, 50%). HRMS (ESI+): Found (MNa$^+$): 429.0612, $C_{19}H_{21}{}^{81}BrN_2NaO_3$ requires 429.0609. Found (MNa$^+$): 427.0618, $C_{19}H_{21}{}^{79}BrN_2NaO_3$ requires 427.0628.

5-((4''-Bromobenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21j



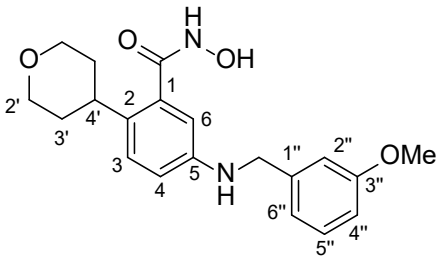
The reaction was carried out following **General Procedure 4.2.7**, using 5-((4''-bromobenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20j** (0.190 g, 0.487 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.086 g, 0.730 mmol), COMU (0.271 g, 0.633 mmol) and DIPEA (0.189 g, 1.460 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was then dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.09 mL, 0.184 mmol) for 24 h. The *title product* **21j** was given as a cream coloured solid (0.098 g, 65%). M.p.: 191 – 193 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3327 (NH), 3223 (OH), 2849 (CH alkane), 1652 (C=O hydroxamic acid), 1611 (C=C aromatic), 1510, 1470, 1321 and 1116 (CH alkane), 1067 and 1011 (C-O ether), 517 (C-Br). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.88 (1H, m, H-4'), 3.27 – 3.30 (2H, m, H-2' a), 3.88 (2H, d, *J* = 10.5 Hz, H-2'b), 4.23 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.35 (1H, t, *J* = 6.0 Hz, N*H*CH$_2$), 6.41 (1H, d, *J* = 2.5 Hz, H-6), 6.55 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.29 (2H, d, *J* = 8.5 Hz, H-2''), 7.51 (2H, d, *J* = H-3''), 8.96 (1H, d, *J* = 1.0 Hz, N*H*OH) and 10.70 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.3 (C-4'), 45.7 (NHCH$_2$), 67.7 (C-2'), 111.4 (C-6), 113.2 (C-4), 119.5 (C-4''), 126.8 (C-3), 129.2 (C-2''), 131.0 (C-2), 131.2 (C-3''), 135.0 (C-1), 139.8 (C-1), 146.1 (C-5) and 166.8 (C=O). *m/z* (ESI+): 429 (^{81}MNa$^+$, 100%), 427 (^{79}MNa$^+$, 100%), 407 (^{81}MH$^+$, 50%) and 405 (^{79}MH$^+$, 50%). HRMS (ESI+): Found (MNa$^+$): 407.0790, $C_{19}H_{22}{}^{81}BrN_2O_3$ requires 407.0790. Found (MNa$^+$): 405.0805, $C_{19}H_{22}{}^{79}BrN_2O_3$ requires 405.0808.

5-((2''-Methoxybenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21k



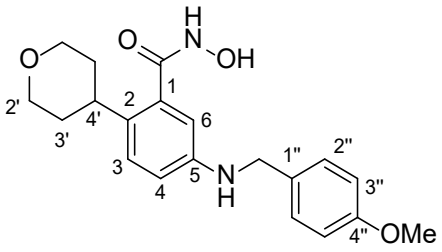
The reaction was carried out following **General Procedure 4.2.7**, using 5-((2''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20k** (0.160 g, 0.469 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.082 g, 0.703 mmol), COMU (0.261 g, 0.610 mmol) and DIPEA (0.182 g, 1.406 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was then dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.07 mL, 0.137 mmol) for 28 h. The *title product* **21k** was given as a yellow solid (0.060 g, 58%). M.p.: 158 – 160 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3406 (NH), 3206 (OH), 2918 (CH aromatic), 2850 (CH alkane), 1649 (C=O hydroxamic acid), 1609 (C=C aromatic), 1492, 1462, 1239 and 1120 (CH alkane), 1074, 1026 and 1013 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.61 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.27 – 3.33 (2H, m, H-2' a), 3.83 (3H, s, 2''-OCH_3), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.20 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.11 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 6.41 (1H, d, *J* = 2.5 Hz, H-6), 6.55 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.88 (1H, t, *J* = 7.5 Hz, H-5''), 6.99 (1H, d, *J* = 8.0 Hz, H-3''), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.20 – 7.23 (2H, m, H-4'', H-6''), 8.94 (1H, s, N*H*OH) and 10.70 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.3 (C-4'), 41.2 ($NHCH_2$), 55.3 (2''-OCH_3), 67.7 (C-2'), 110.5 (C-3''), 111.1 (C-6), 113.1 (C-4), 120.1 (C-5''), 126.8 (C-3), 127.3 (C-1''), 127.6 (C-6''), 127.8 (C-4''), 130.6 (C-2), 134.9 (C-1), 146.4 (C-5), 156.8 (C-2'') and 166.8 (C=O). *m/z* (ESI+): 401 (MNa^+, 25%) and 379 (MH^+, 100%). HRMS (ESI+): Found (MH^+): 379.1623, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

5-((3''-Methoxybenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21l



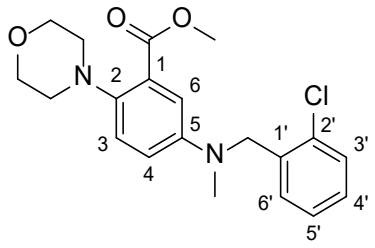
The reaction was carried out following **General Procedure 4.2.7**, using 5-((3''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20l** (0.160 g, 0.469 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.082 g, 0.703 mmol), COMU (0.261 g, 0.610 mmol) and DIPEA (0.182 g, 1.406 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the desired intermediate as a white crystalline solid. This intermediate was dissolved in MeOH/THF (1:1, 3 mL) and treated with 2 M HCl (0.07 mL, 0.137 mmol) for 22 h. The *title product* **21l** was given as a light pink solid (0.092 g, 85%). M.p.: 155 – 157 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3331 (NH), 3272 (OH), 2920 (CH aromatic), 2843 (CH alkane), 1650 (C=O hydroxamic acid), 1612 and 1509 (C=C aromatic), 1491, 1476, 1261 and 1166 (CH alkane), 1067, 1043 and 1013 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.64 (4H, m, H-3'), 2.81 – 2.89 (1H, m, H-4'), 3.27 – 3.31 (2H, m, H-2' a), 3.72 (3H, s, 3''-OCH_3), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.22 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 6.29 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 6.44 (1H, d, *J* = 2.5 Hz, H-6), 6.58 (1H, dd, *J* = 8.5, 2.5 Hz, H-4), 6.77 – 6.80 (1H, m, H-4''), 6.90 – 6.92 (2H, m, H-2'', H-6''), 7.03 (1H, d, *J* = 8.5 Hz, H-3), 7.23 (1H, t, *J* = 8.0 Hz, H-5''), 8.96 (1H, s, N*H*OH) and 10.71 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.4 (C-4'), 46.4 ($NHCH_2$), 54.9 (3''-OCH_3), 67.7 (C-2'), 111.4 (C-6), 111.8 (C-4''), 112.8 (C-2''), 113.2 (C-4), 119.2 (C-6''), 126.8 (C-3), 129.4 (C-5''), 130.8 (C-2), 134.9 (C-1), 142.0 (C-1''), 146.3 (C-5), 159.4 (C-3'') and 166.8 (C=O). *m/z* (ESI+): 401 (MNa^+, 30%) and 379 (MH^+, 100%). HRMS (ESI+): Found (MH^+): 379.1618, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

5-((4''-Methoxybenzyl)amino)-*N*-hydroxy-2-(tetrahydro-2H-pyran-4'-yl)benzamide 21m



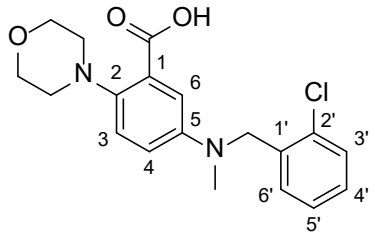
The reaction was carried out following **General Procedure 4.2.7**, using 5-((4''-methoxybenzyl)amino)-2-(tetrahydro-2*H*-pyran-4'-yl)benzoic acid **20m** (0.165 g, 0.483 mmol), *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (0.085 g, 0.725 mmol), COMU (0.269 g, 0.628 mmol) and DIPEA (0.187 g, 1.450 mmol) in dry DMF (6 mL) for 2 days. The crude product was purified by flash chromatography on amino-silica (4:1, petroleum ether/ethyl acetate) to give the amide intermediate as a white crystalline solid. This intermediate was the hydrolysed using 2 M HCl (0.08 mL, 0.159 mmol) for 22 h. The *title product* **21m** was given as a light yellow solid (0.102 g, 86%). M.p.: 185 – 187 °C. R.f.: 0.08 (1:1, petroleum ether/ethyl acetate). IR: ν_{max} (film)/cm^{-1}; 3327 (NH), 3256 (OH), 2930 (CH aromatic), 2843 (CH alkane), 1651 (C=O hydroxamic acid), 1601 (C=C aromatic), 1491, 1464, 1236 and 1166 (CH alkane), 1068 and 1013 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 1.55 – 1.61 (4H, m, H-3'), 2.85 (1H, br s, H-4'), 3.27 – 3.30 (2H, m, H-2' a), 3.72 (3H, s, 4''-OCH_3), 3.89 (2H, d, *J* = 10.5 Hz, H-2'b), 4.16 (2H, d, *J* = 6.0 Hz, NHCH_2), 6.21 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 6.43 (1H, d, *J* = 2.0 Hz, H-6), 6.58 (1H, dd, *J* = 8.5, 2.0 Hz, H-4), 6.88 (2H, d, *J* = 8.5 Hz, H-3''), 7.02 (1H, d, *J* = 8.5 Hz, H-3), 7.25 (2H, d, *J* = 8.5 Hz, H-2''), 8.95 (1H, s, N*H*OH) and 10.70 (1H, s, NHO*H*). δ_C (100 MHz; $(CD_3)_2SO$): 33.9 (C-3'), 36.3 (C-4'), 45.9 ($NHCH_2$), 55.0 (4''-OCH_3), 67.7 (C-2'), 111.3 (C-6), 113.2 (C-4), 113.7 (C-3''), 126.7 (C-3), 128.3 (C-2''), 130.7 (C-2), 131.9 (C-1''), 134.9 (C-1), 146.4 (C-5), 158.1 (C-4'') and 166.8 (C=O). *m/z* (ESI+): 401 (MNa^+, 25%) and 379 (MH^+, 100%). HRMS (ESI+): Found (MH^+): 379.1625, $C_{20}H_{24}N_2NaO_4$ requires 379.1628.

Methyl 5-((2-chlorobenzyl)(methyl)amino)-2-morpholinobenzoate 23



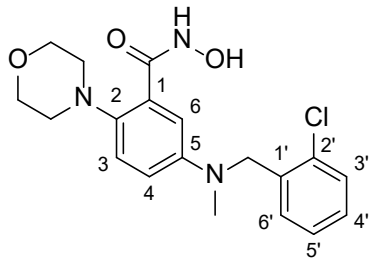
Iodomethane (0.42 mL, 0.944 g, 6.651 mmol) was added dropwise to methyl 5-((2-chlorobenzyl) amino)-2-morpholinobenzoate **22** (0.600 g, 1.663 mmol) and K_2CO_3 (0.460 g, 3.326 mmol) in MeCN (30 mL) and the resulting mixture was allowed to stir for 18 h at 80 °C, under an atmosphere of nitrogen. Following this, the reaction was cooled to r.t. and H_2O (30 mL) was added and stirred for 15 min, the mixture was then extracted with ethyl acetate (3 x 25 mL) and combined organic extracts washed with sat. aq. $Na_2S_2O_3$ (15 mL) and brine (20 mL). The resulting organic solution was dried with Na_2SO_4, concentrated *in vacuo,* and subsequently purified by flash chromatography (4:1 ethyl acetate/iso-hexane) to afford the *title compound* **23** (0.500 g, 80%) as a light-yellow amorphous solid. R.f.: 0.66 (2:1, ethyl acetate/iso-hexane). IR: vmax (film)/cm^{-1}; 2974 (CH aromatic), 2866 and 2809 (CH alkane), 1702 (C=O ester), 1615 and 1505 (C=C aromatic), 1295 (C-N amine), 1111 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.79 (4H, t, *J* = 4.3 Hz, $N(C\underline{H}_2CH_2)_2O$), 3.02 (3H, s, N-Me), 3.64 (4H, t, *J* = 4.3 Hz, $N(CH_2C\underline{H}_2)_2O$), 3.76 (3H, s, CO_2Me), 4.56 (2H, s, N(Me)-$C\underline{H}_2$), 6.75 (1H, dd, *J* = 9.0, 3.0 Hz, H-4), 6.84 (1H, d, *J* = 3.0 Hz, H-6), 7.05 (1H, d, *J* = 9.0 Hz, H-3), 7.08 – 7.10 (1H, m, H-6'), 7.27 – 7.31 (2H, m, H-4', H-5') and 7.46 – 7.49 (1H, m, H-3'). δ_C (100 MHz; $(CD_3)_2SO$): 38.7 (N-Me), 51.8 (CO_2Me), 53.1 ($N(\underline{C}H_2CH_2)_2O$), 53.7 (N(Me)-$\underline{C}H_2$), 66.6 ($N(CH_2\underline{C}H_2)_2O$), 112.5 (C-6), 115.4 (C-4), 121.4 (C-3), 127.3 (C-4'), 127.9 (C-6'), 128.0 (C-1), 128.5 (C-5'), 129.5 (C-3'), 132.0 (C-2'), 135.6 (C-1'), 141.2 (C-2), 144.7 (C-5) and 168.3 (C=O). HRMS (ESI+): Found (MH^+): 377.1427, $C_{20}H_{24}{}^{37}ClN_2O_3$ requires 377.1441. Found (MH^+): 375.1458, $C_{20}H_{24}{}^{35}ClN_2O_3$ requires 375.1470.

5-((2-Chlorobenzyl)(methyl)amino)-2-morpholinobenzoic acid 24



1M NaOH (6.7 mL, 6.669 mmol) was added dropwise to methyl 5-((2-chlorobenzyl)(methyl)amino)-2-morpholinobenzoate **23** (0.500 g, 1.334 mmol) in THF/MeOH (1:1, 14 mL) and stirred for 1.5 h at 80 °C. The reaction mixture was then partitioned between 1 M NaOH (20 mL) and EtOAc (20 mL) and the aqueous layer was collected and acidified to pH 4 with 2 M HCl, affording a white precipitate. The suspension was then extracted with ethyl acetate (3 x 25 mL) and the combined organic layers washed with brine (20 mL) and dried with Na_2SO_4. The filtrate was evaporated *in vacuo* to afford the *title compound* **24** (0.458 g, 96%) as an off-white amorphous solid, no further purification was required. R.f.: 0.05 (1:1, ethyl acetate/iso-hexane). IR: vmax (film)/cm^{-1}; 3173 (OH acid), 2961 (CH aromatic), 2840 (CH alkane), 1708 (C=O acid), 1603 and 1498 (C=C aromatic), 1221 (C-N amine), 1115 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 3.00 (4H, t, *J* = 4.5 Hz, N(C<u>*H*</u>$_2$CH$_2$)$_2$O), 3.12 (3H, s, N-Me), 3.78 (4H, t, *J* = 4.5 Hz, N(CH$_2$C<u>*H*</u>$_2$)$_2$O), 4.64 (2H, s, N(Me)-C<u>*H*</u>$_2$), 6.88 (1H, dd, *J* = 8.9, 3.2 Hz, H-4), 7.04 – 7.07 (1H, m, H-6'), 7.25 – 7.32 (3H, m, H-6, H-4', H-5), 7.49 – 7.51 (1H, m, H-3') and 7.55 (1H, d, *J* = 8.9 Hz, H-3). δ_C (100 MHz; $(CD_3)_2SO$): 38.7 (N-Me), 52.9 (N(<u>*C*</u>H$_2$CH$_2$)$_2$O), 53.5 (N(Me)-<u>*C*</u>H$_2$), 66.4 (N(CH$_2$<u>*C*</u>H$_2$)$_2$O), 112.2 (C-6), 116.5 (C-4), 124.3 (C-3), 125.3 (C-1), 127.4 (C-4'), 127.6 (C-6'), 128.6 (C-5'), 129.6 (C-3'), 132.0 (C-2'), 135.1 (C-1'), 138.7 (C-2), 147.4 (C-5) and 166.8 (C=O). HRMS (ESI+): Found (MH^+): 363.1271, $C_{19}H_{22}{}^{37}ClN_2O_3$ requires 363.1284. Found (MH^+): 361.1303, $C_{19}H_{22}{}^{35}ClN_2O_3$ requires 361.1314.

5-((2-Chlorobenzyl)(methyl)amino)-*N*-hydroxy-2-morpholinobenzamide 25



A solution of *O*-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.073 g, 0.627 mmol) in DMF (2 mL) was added dropwise to 5-((2-chlorobenzyl)(methyl)amino)-2-morpholinobenzoic acid **24** (0.150 g, 0.418 mmol), COMU (0.233 g, 0.543 mmol) and DIPEA (0.22 mL, 0.162 g, 1.254 mmol) in DMF (3 mL) and allowed to stir for 2 d at room temperature. Following this, the reaction mixture was diluted with EtOAc (35 mL) and washed with H_2O (2 x 20 mL), sat. aq. $NaHCO_3$ (15 mL), brine (15 mL) and then dried with Na_2SO_4. The resulting crude residue was purified by flash chromatography (4:1, ethyl acetate/iso-hexane), to afford the desired amide intermediate, which was immediately used in the next step. The amide intermediate (0.120 g, 0.262 mmol) was dissolved in THF/MeOH (1:1, 5 mL), 2 M HCl (0.065 mL, 0.131 mmol) was added dropwise, and the subsequent mixture was allowed to stir for 24 h at room temperature. The reaction mixture was partitioned between 1 M NaOH (20 mL) and Et_2O (20 mL) and the aqueous layer was collected and acidified to pH 4 with 2 M HCl, affording a white precipitate. The suspension was then extracted with ethyl acetate (3 x 20 mL) and the combined organic layers washed with brine (15 mL) and dried with Na_2SO_4. The filtrate was evaporated *in vacuo* to afford the *title compound* **25** (0.080 g, 52% over two steps) as a grey amorphous solid, no further purification was required. R.f.: 0.1 (1:2, petroleum ether/iso-hexane). IR: vmax (film)/cm^{-1}; 3177 (N-H and OH hydroxamic acid), 2960 (CH aromatic), 2840 (CH alkane), 1648 (C=O hydroxamic acid), 1596 (C=C aromatic), 1115 (C-O ether). δ_H (400 MHz; $(CD_3)_2SO$): 2.80 (4H, br s, N(C<u>*H*</u>$_2$CH$_2$)$_2$O), 3.06 (3H, s, N-Me), 3.70 (4H, br s, N(CH$_2$C<u>*H*</u>$_2$)$_2$O), 4.58 (2H, s, N(Me)-C<u>*H*</u>$_2$), 6.71 (1H, br s, H-4), 6.96 (1H, s, H-6), 7.10 (2H, app br d, *J* = 13.3 Hz, H-3 and H-6'), 7.28 (2H, br s, H-4', H-5'), 7.48 (1H, br s, H-3'), 9.04 (1H, br s, N<u>*H*</u>OH) and 11.49 (1H, s, NHO<u>*H*</u>). δ_C (100 MHz; $(CD_3)_2SO$): 38.7 (N-Me), 53.1 (N(<u>*C*</u>H$_2$CH$_2$)$_2$O), 53.7 (N(Me)-<u>*C*</u>H$_2$), 66.6 (N(CH$_2$<u>*C*</u>H$_2$)$_2$O), 112.5 (C-6), 114.3 (C-4), 121.8 (C-3), 127.3 (C-4'), 127.8 (C-6'), 128.5 (C-5'), 128.9 (C-1), 129.5 (C-3'), 132.0 (C-2'), 135.6 (C-1'), 139.8 (C-2), 145.6 (C-5) and 164.7 (C=O). HRMS (ESI+): Found (MH^+): 378.1380, $C_{19}H_{23}{}^{37}ClN_3O_3$ requires 378.1393. Found (MH^+): 376.1414, $C_{19}H_{23}{}^{35}ClN_3O_3$ requires 376.1423.

^{1}H and ^{13}C NMR spectra

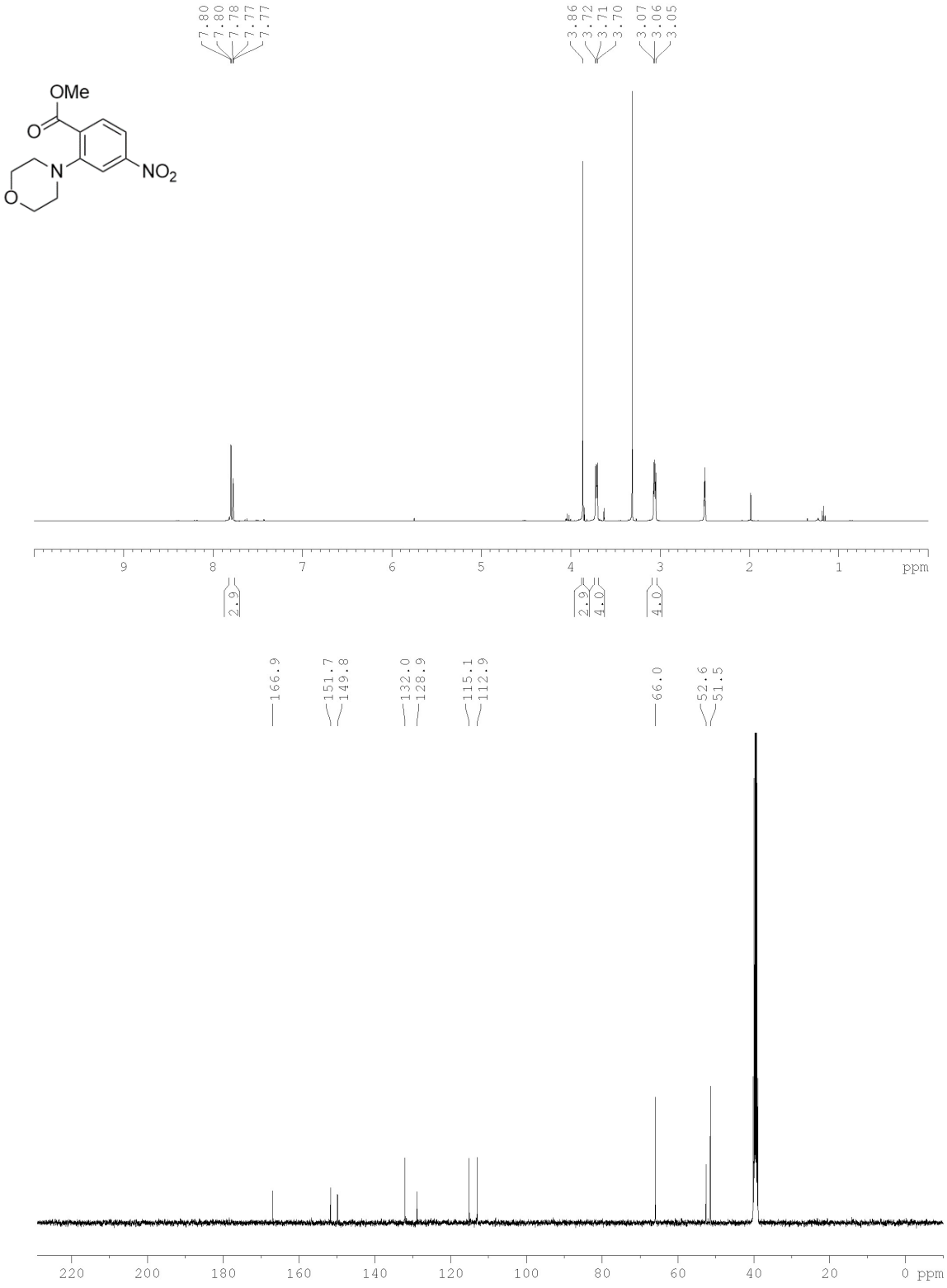


Figure S1. ^{1}H NMR and ^{13}C NMR spectra of **7**.

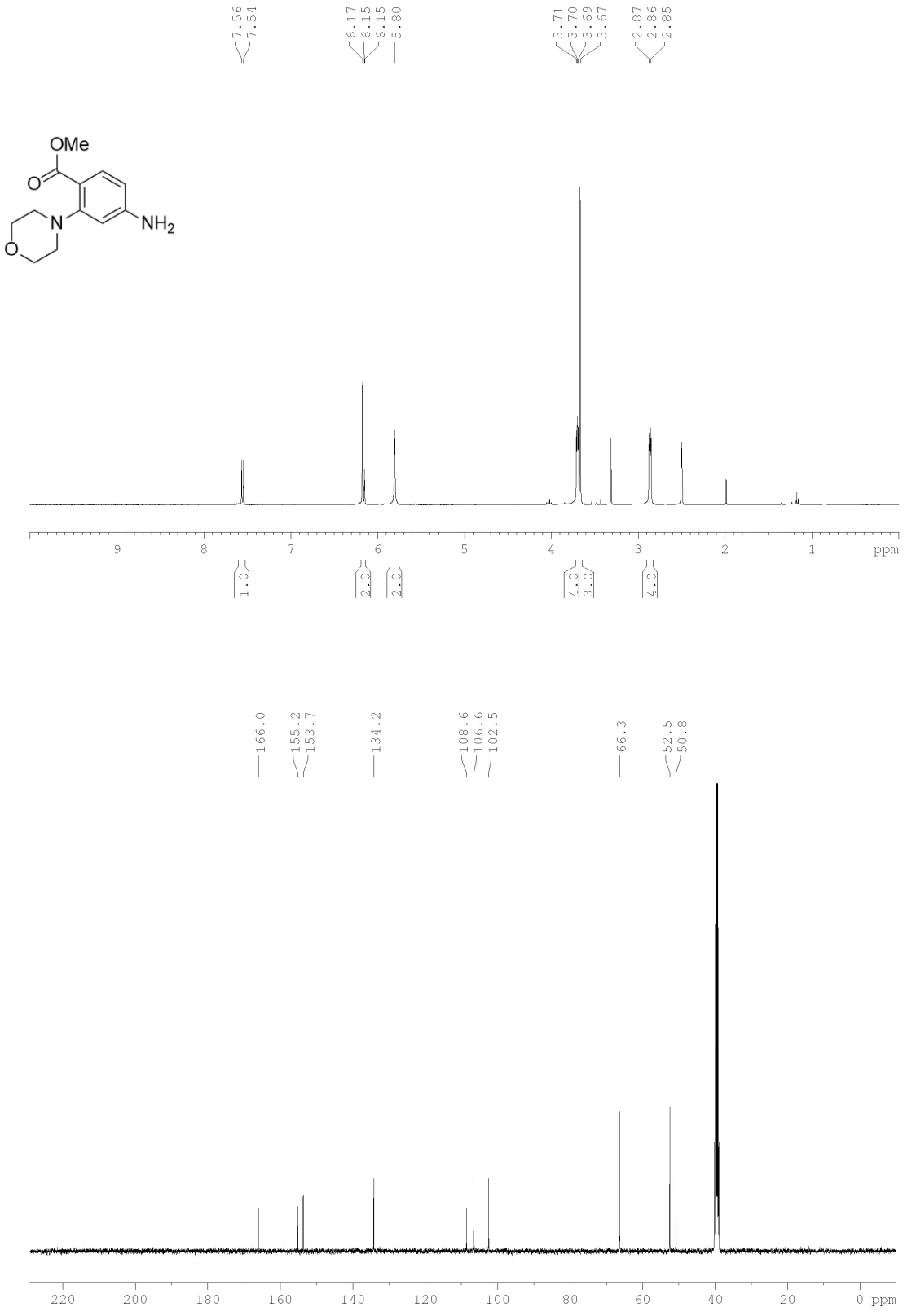


Figure S2. ^{1}H NMR and ^{13}C NMR spectra of **8**.

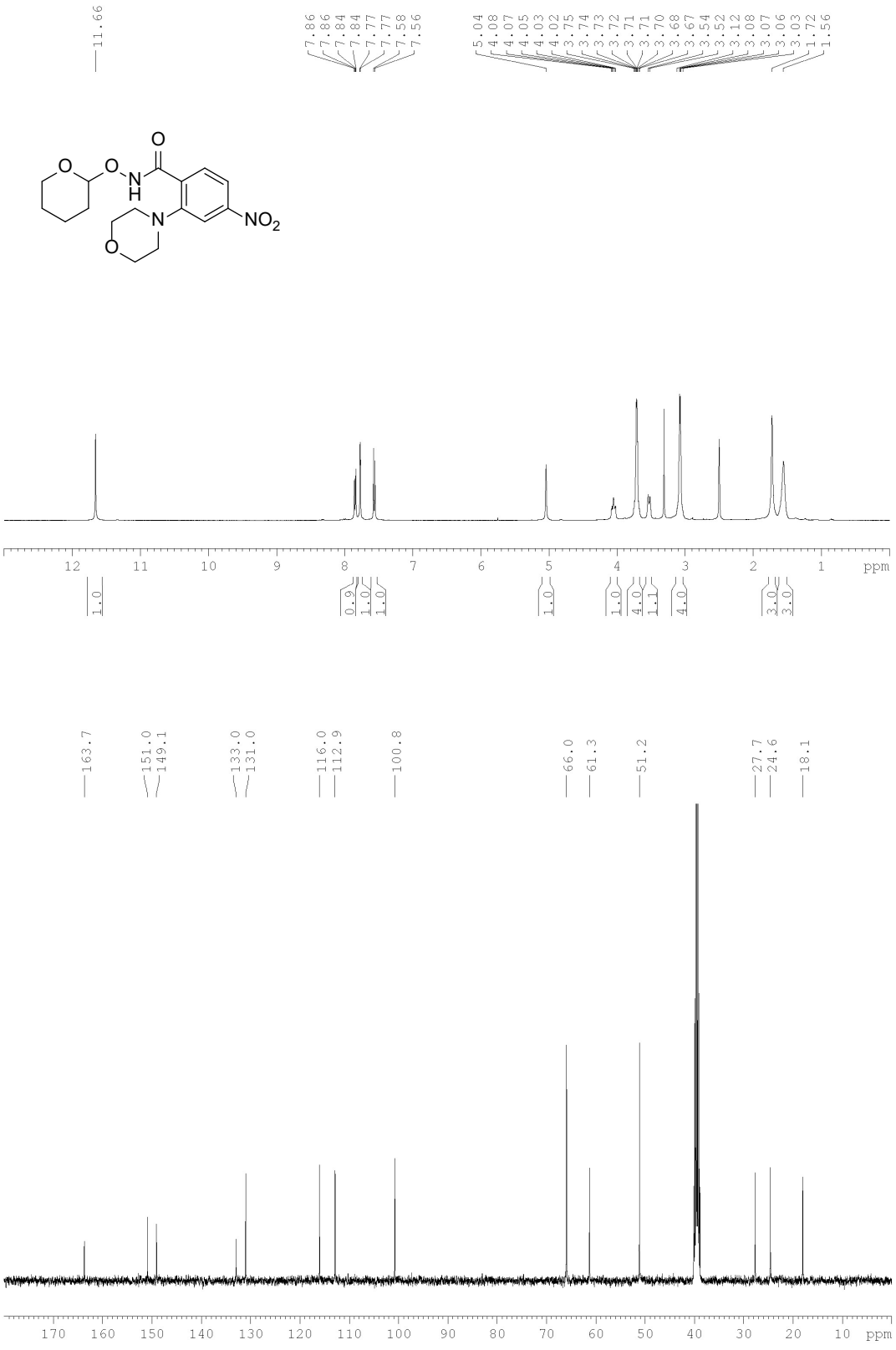


Figure S3. ^{1}H NMR and ^{13}C NMR spectra of **13**.

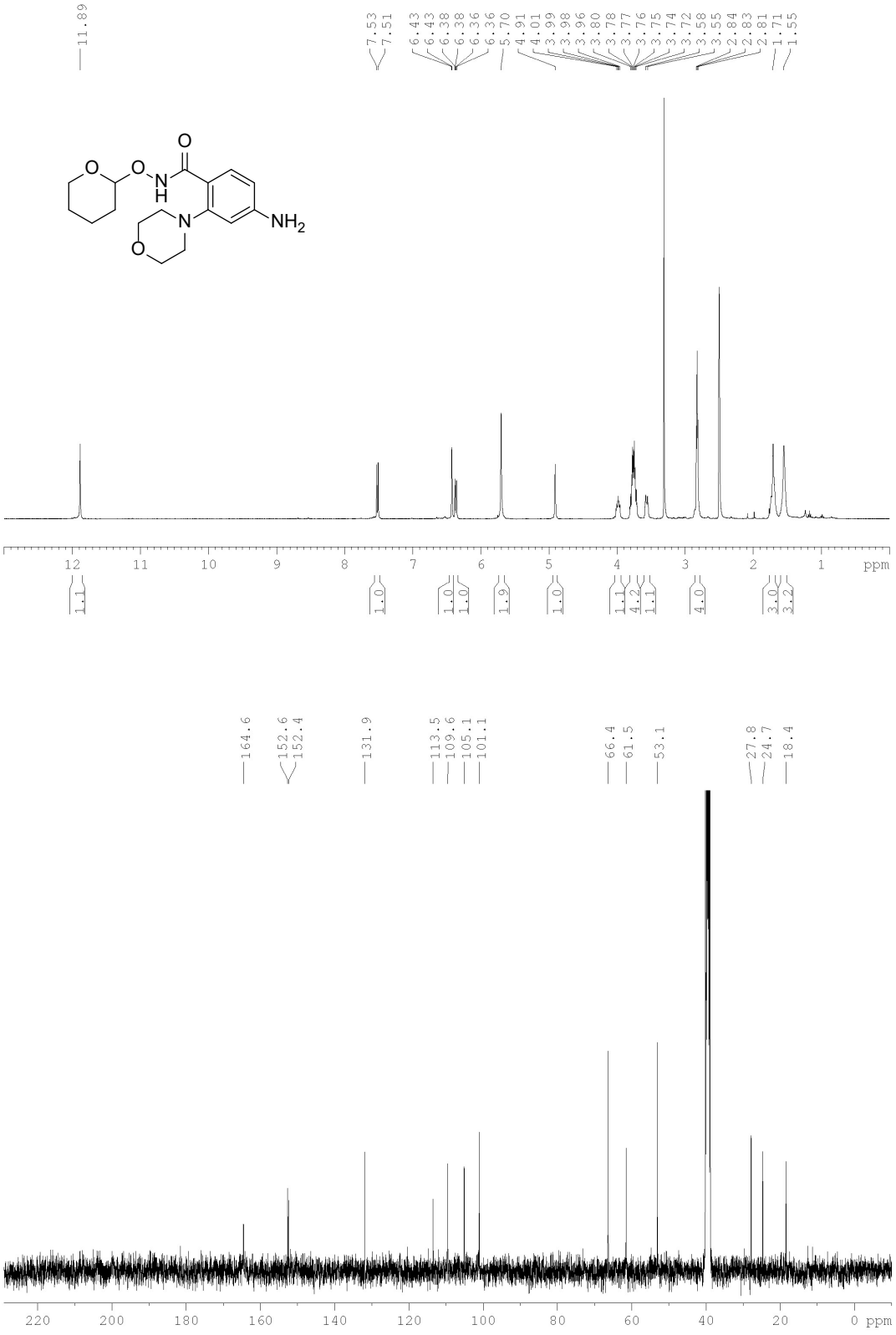


Figure S4. ^{1}H NMR and ^{13}C NMR spectra of **14**.

^{1}H and ^{13}C NMR spectra for 1,2,4-series analogues **10a-m, 11a-m, 12a-m**

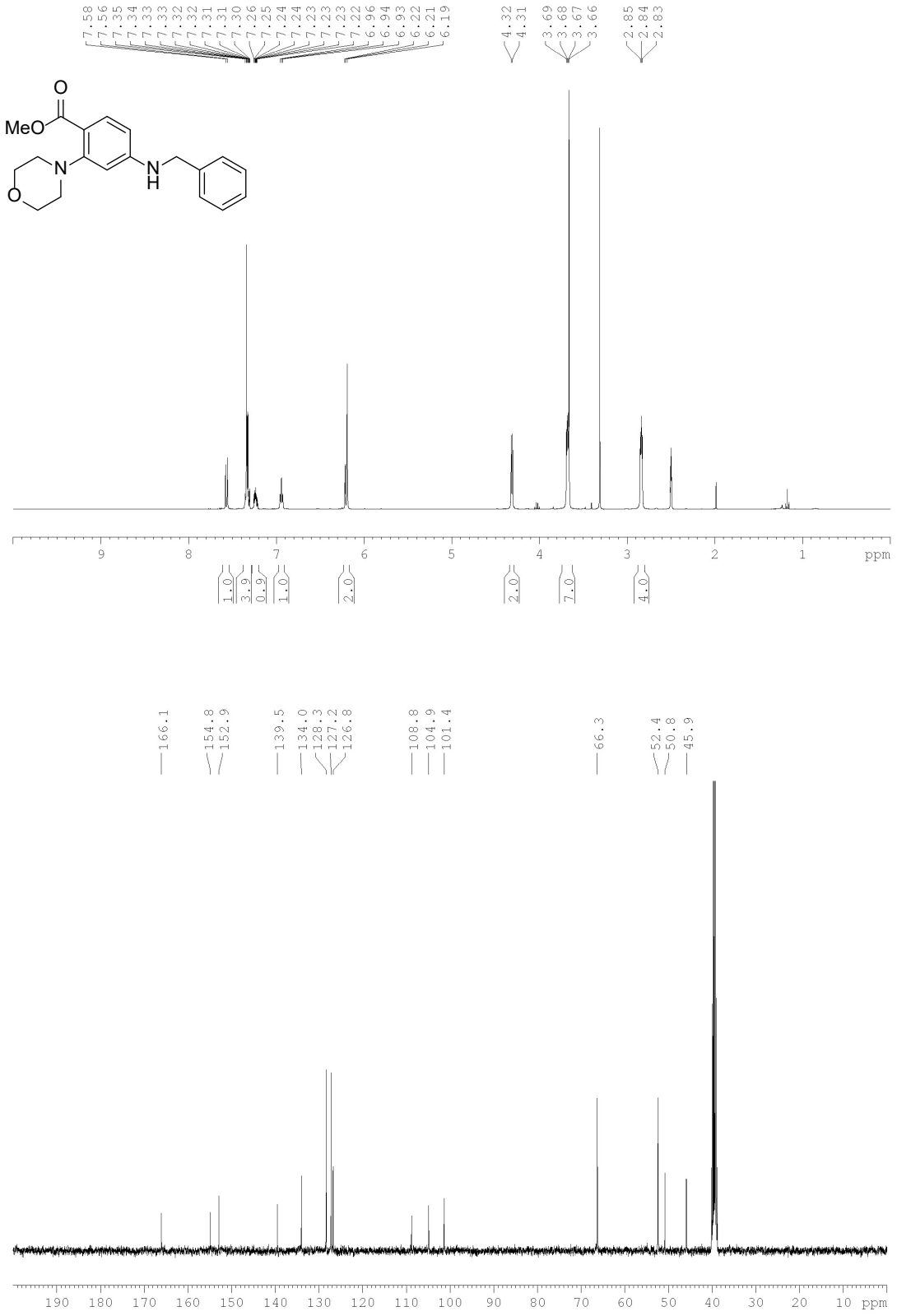


Figure S5. ^{1}H NMR and ^{13}C NMR spectra of **10a**.

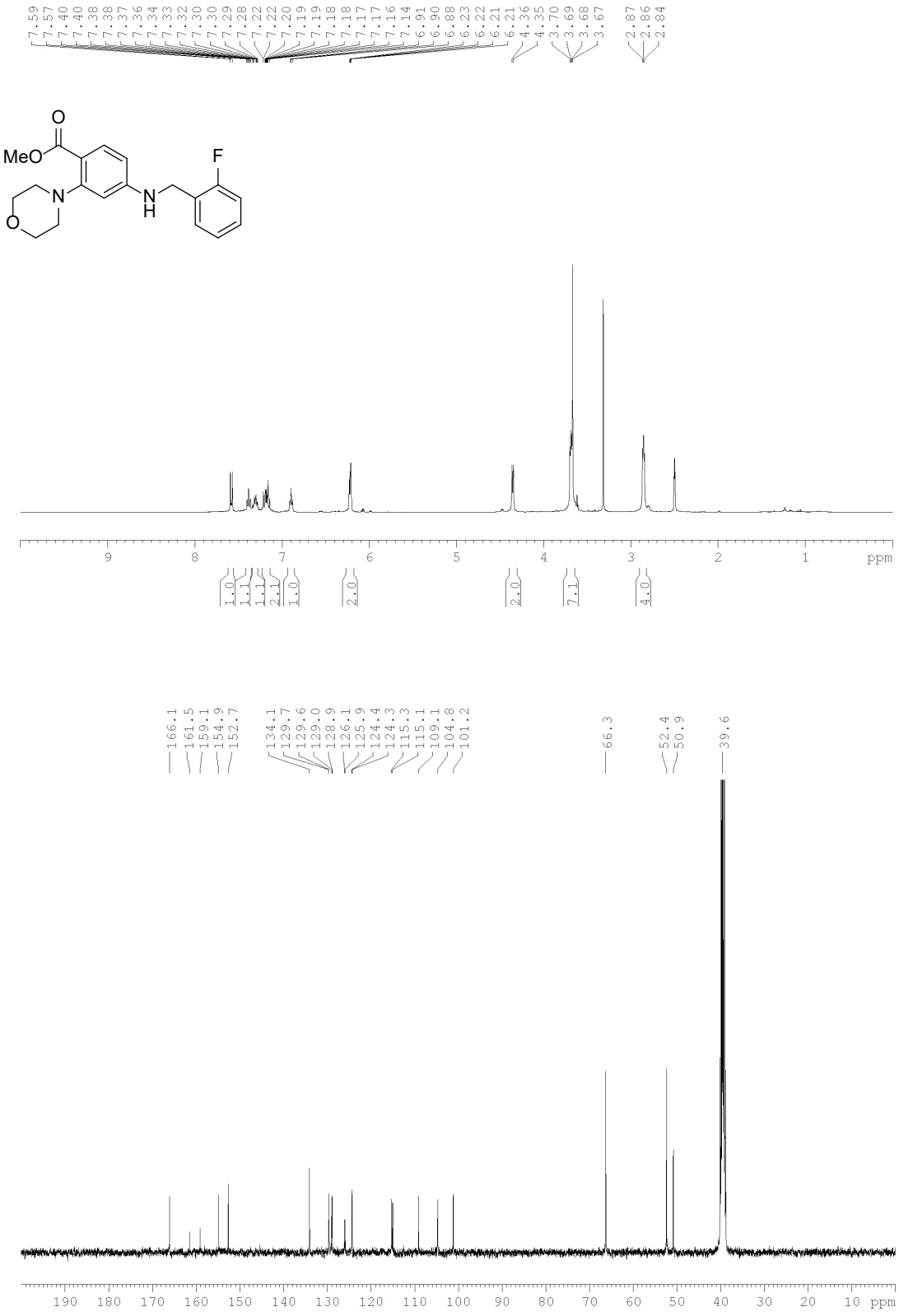


Figure S6. ^{1}H NMR and ^{13}C NMR spectra of **10b**.

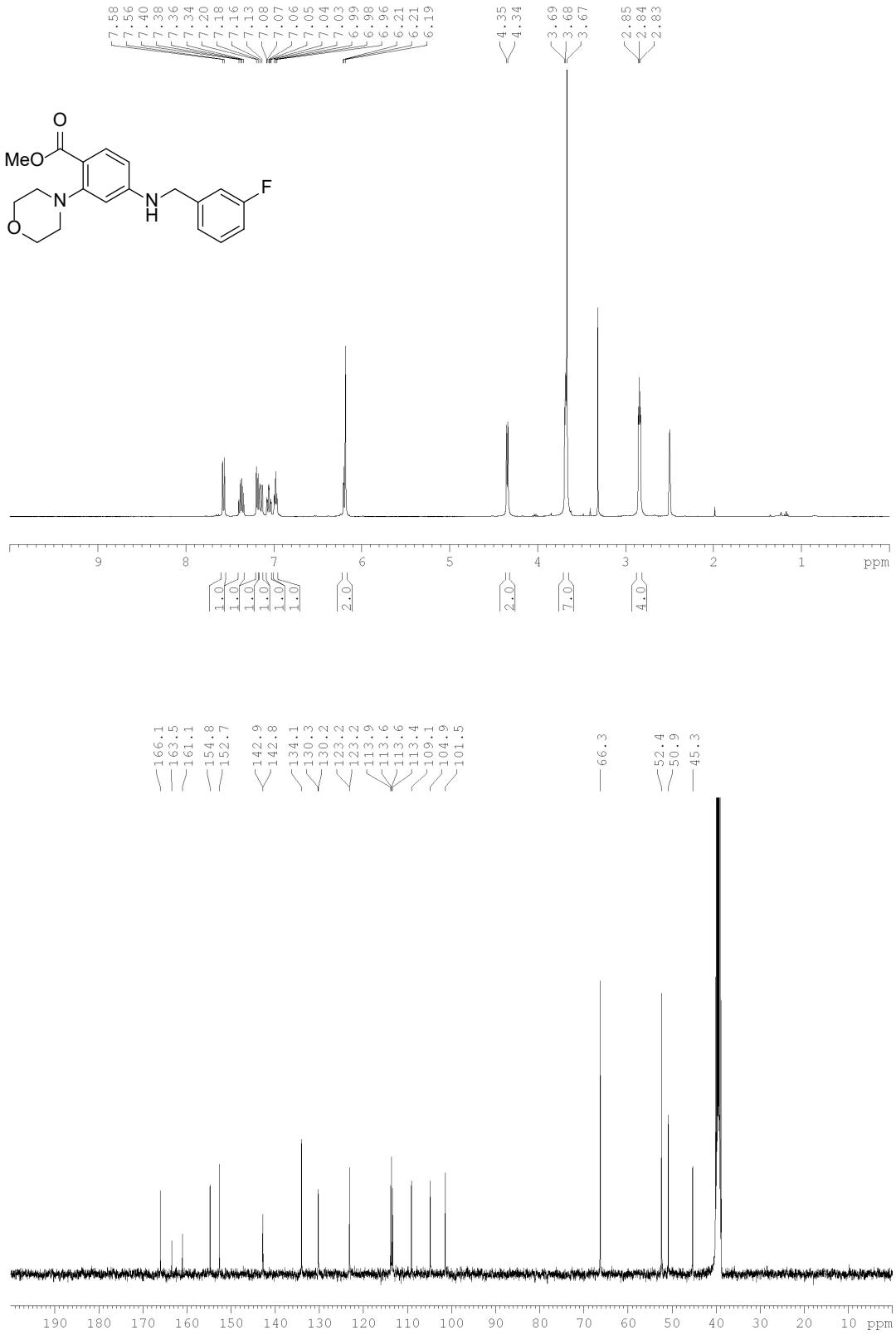


Figure S7. ^{1}H NMR and ^{13}C NMR spectra of **10c**.

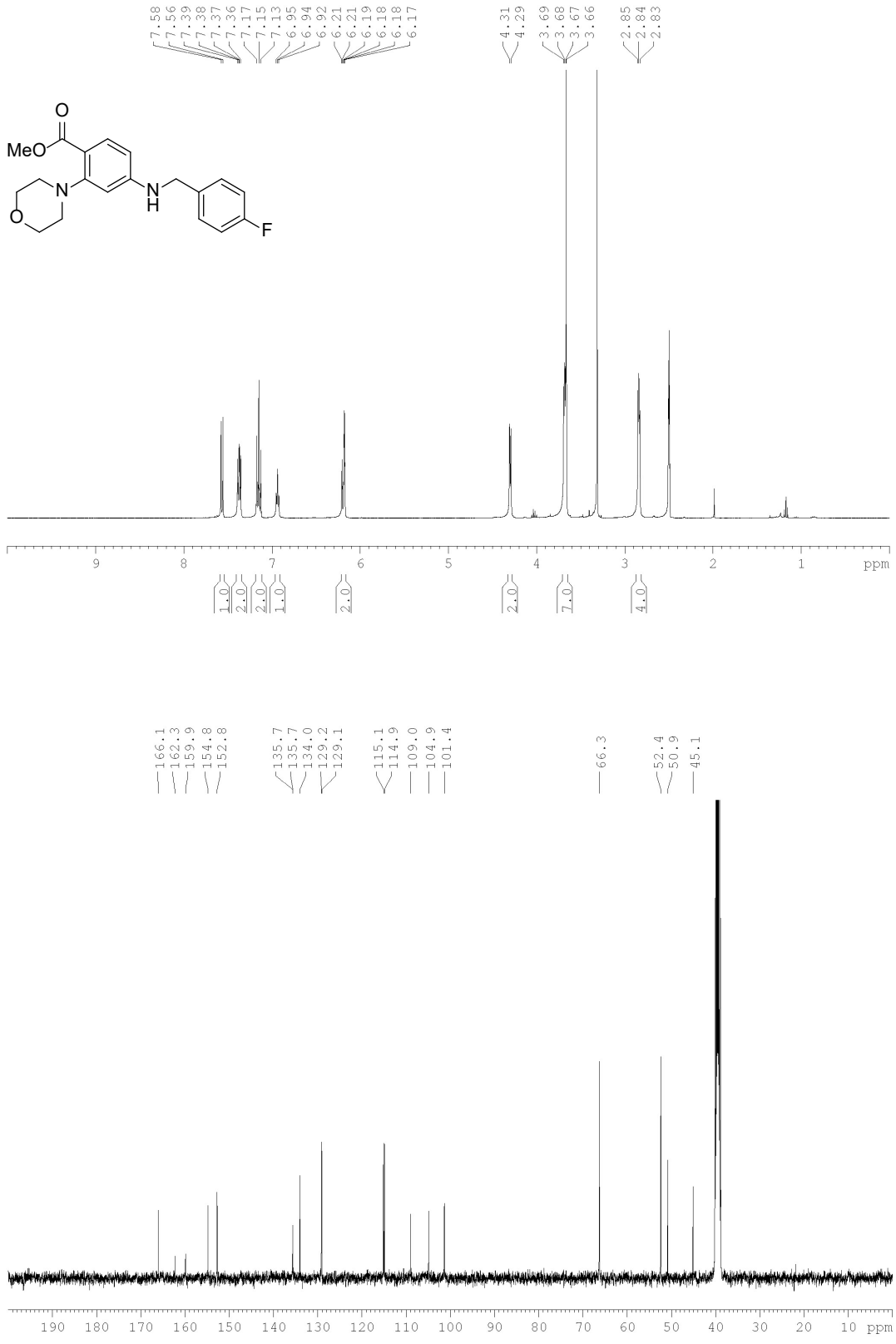


Figure S8. ^{1}H NMR and ^{13}C NMR spectra of **10d**.

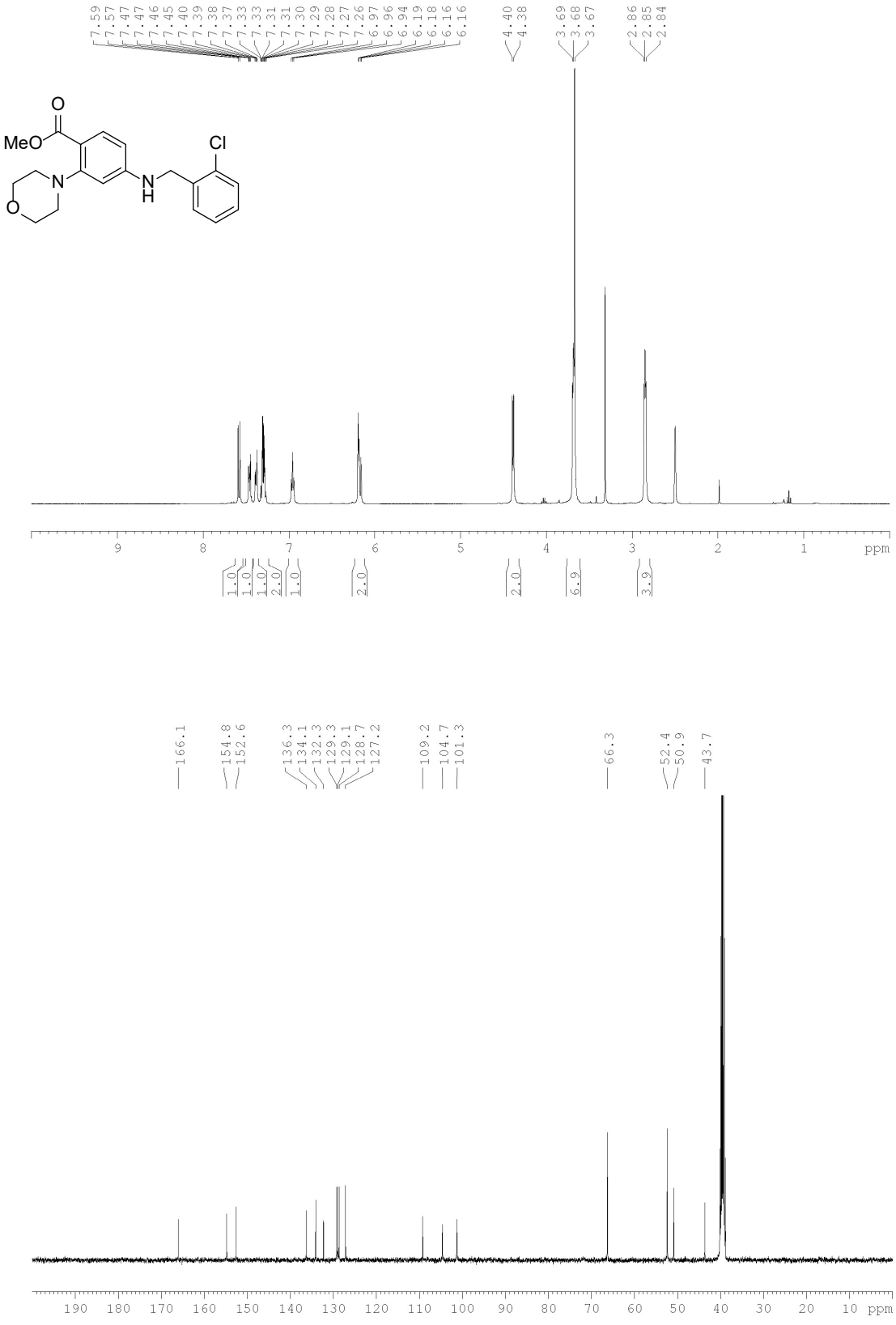


Figure S9. ^{1}H NMR and ^{13}C NMR spectra of **10e**.

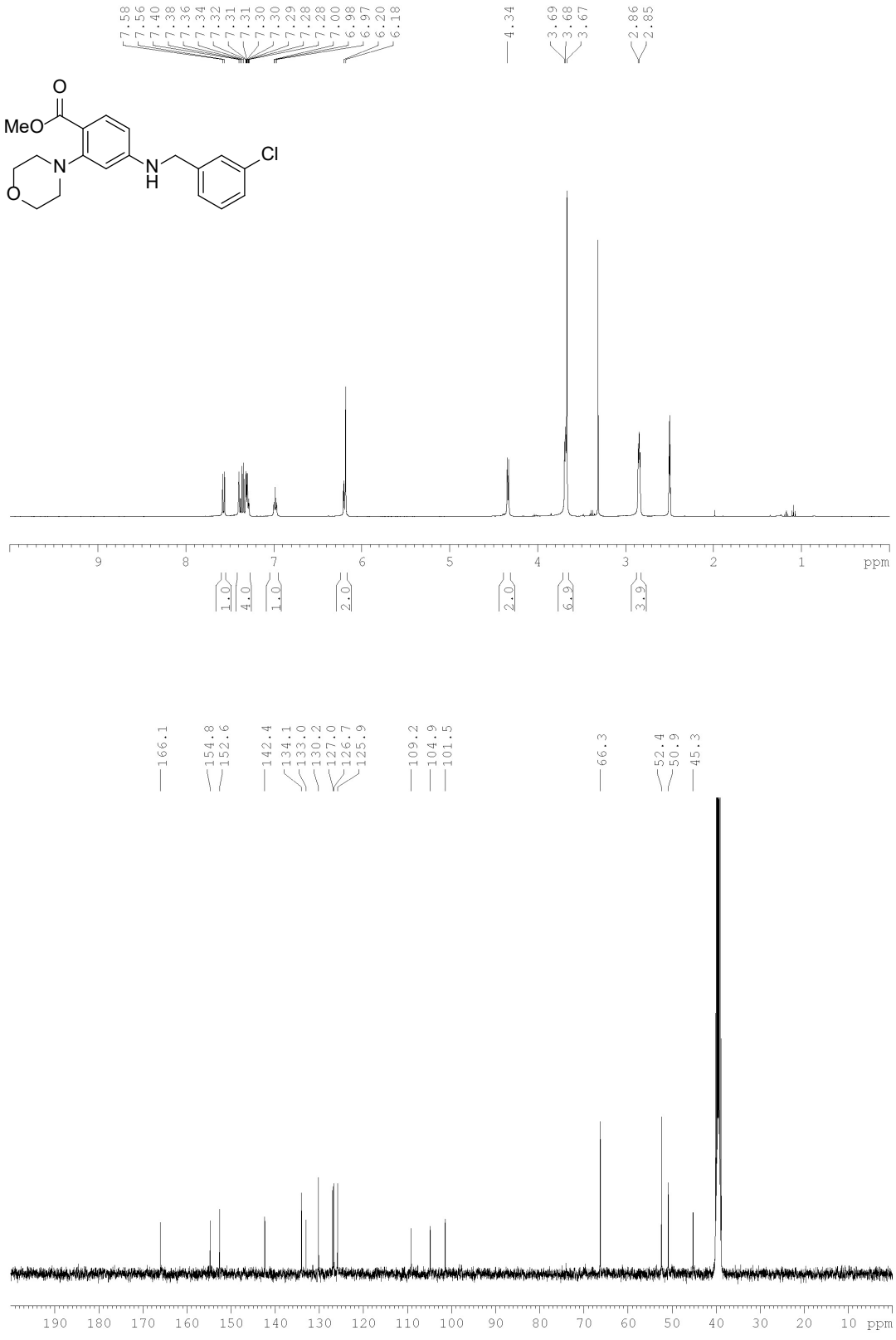


Figure S10. ^{1}H NMR and ^{13}C NMR spectra of **10f**.

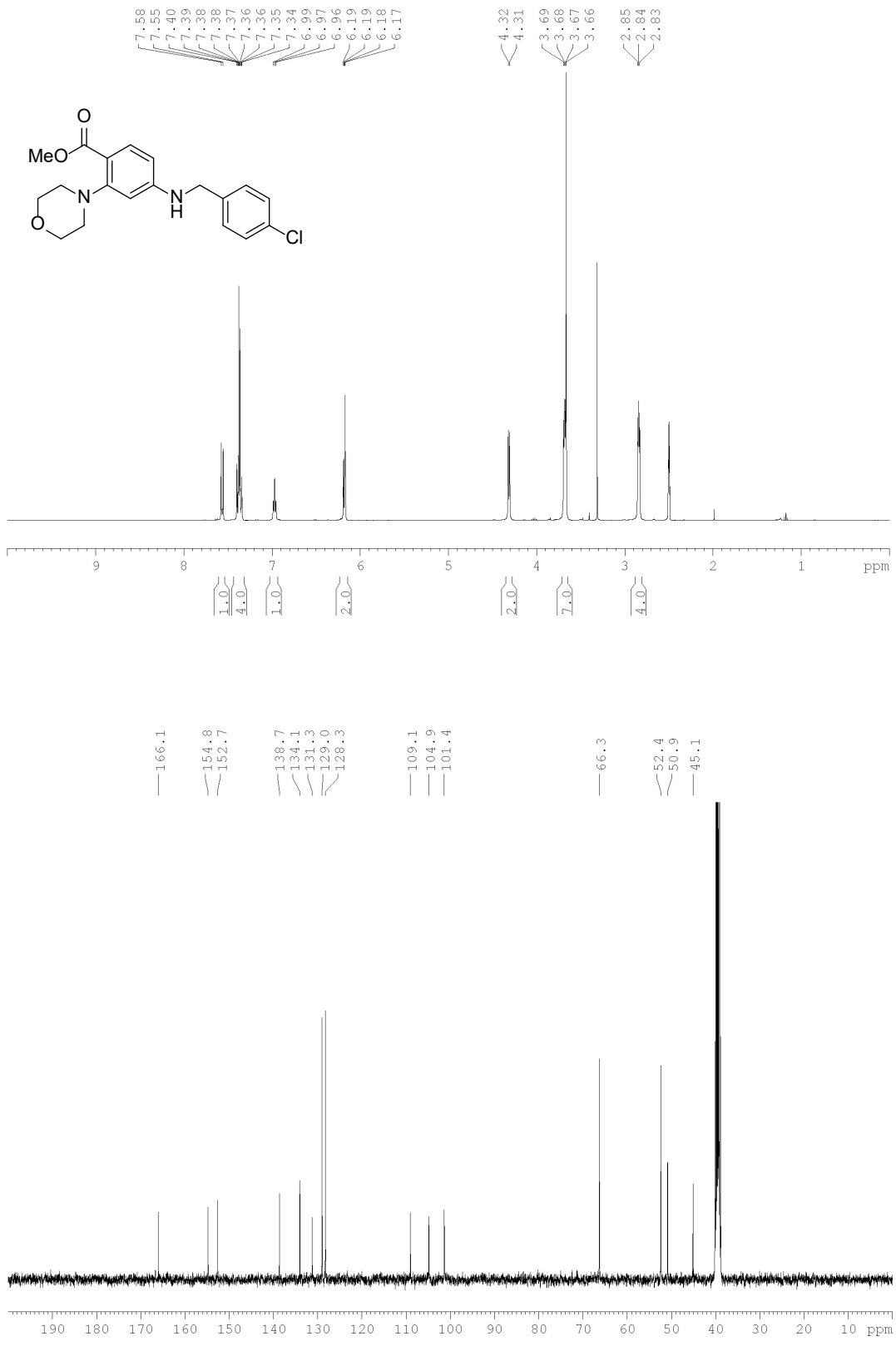


Figure S11. ^{1}H NMR and ^{13}C NMR spectra of **10g**.

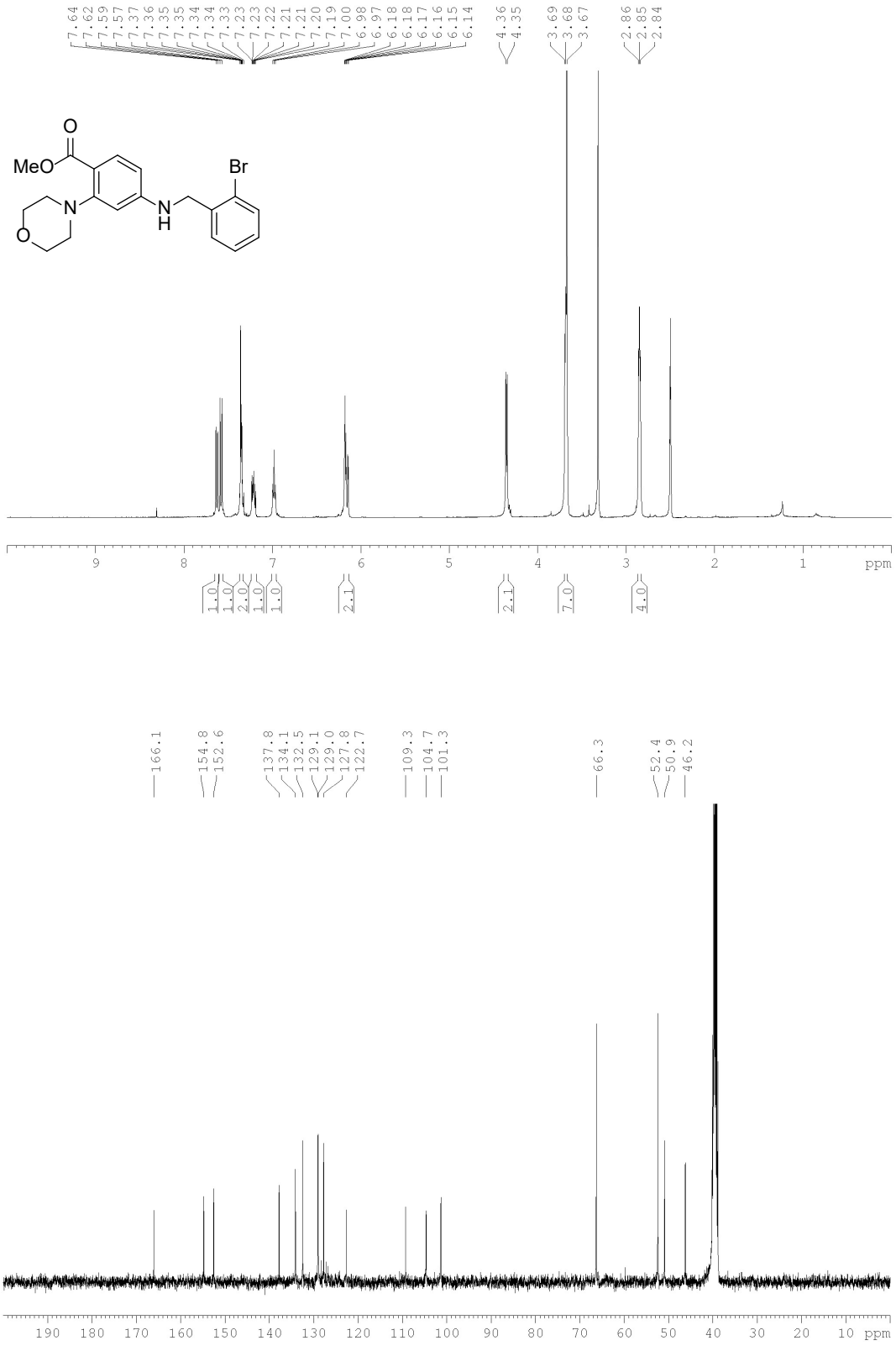


Figure S12. ^{1}H NMR and ^{13}C NMR spectra of **10h**.

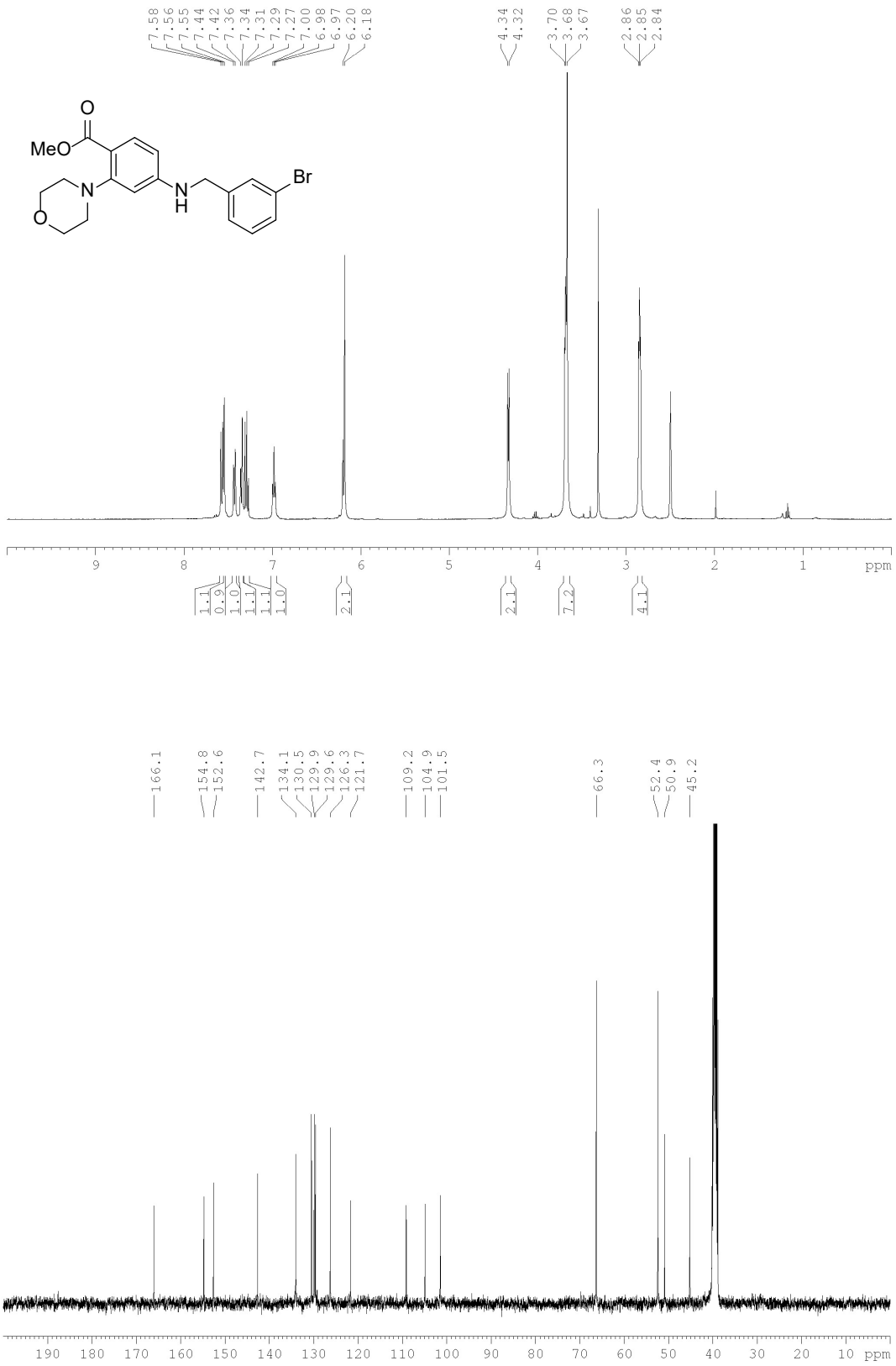


Figure S13. ^{1}H NMR and ^{13}C NMR spectra of **10i**.

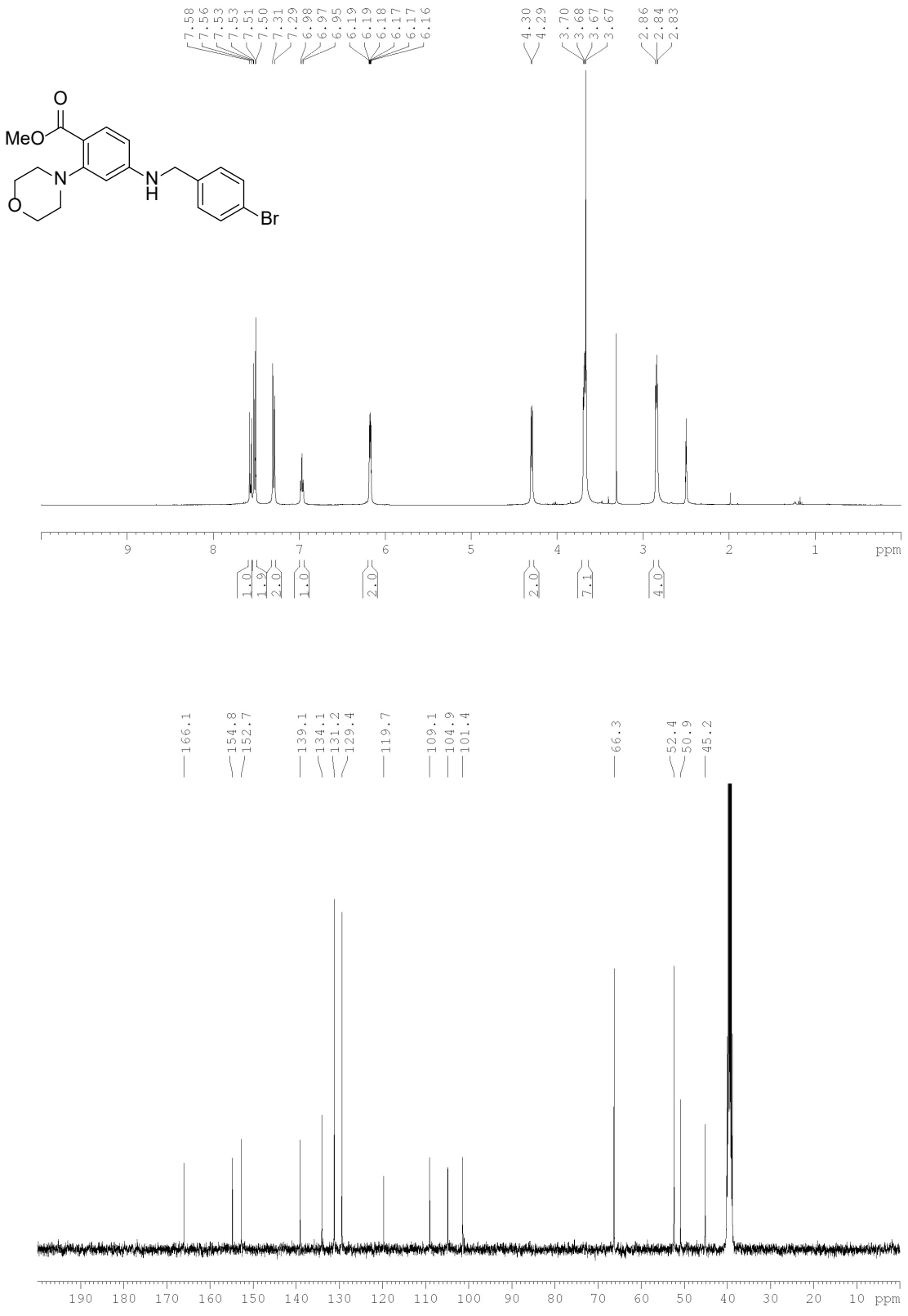


Figure S14. ^{1}H NMR and ^{13}C NMR spectra of **10j**.

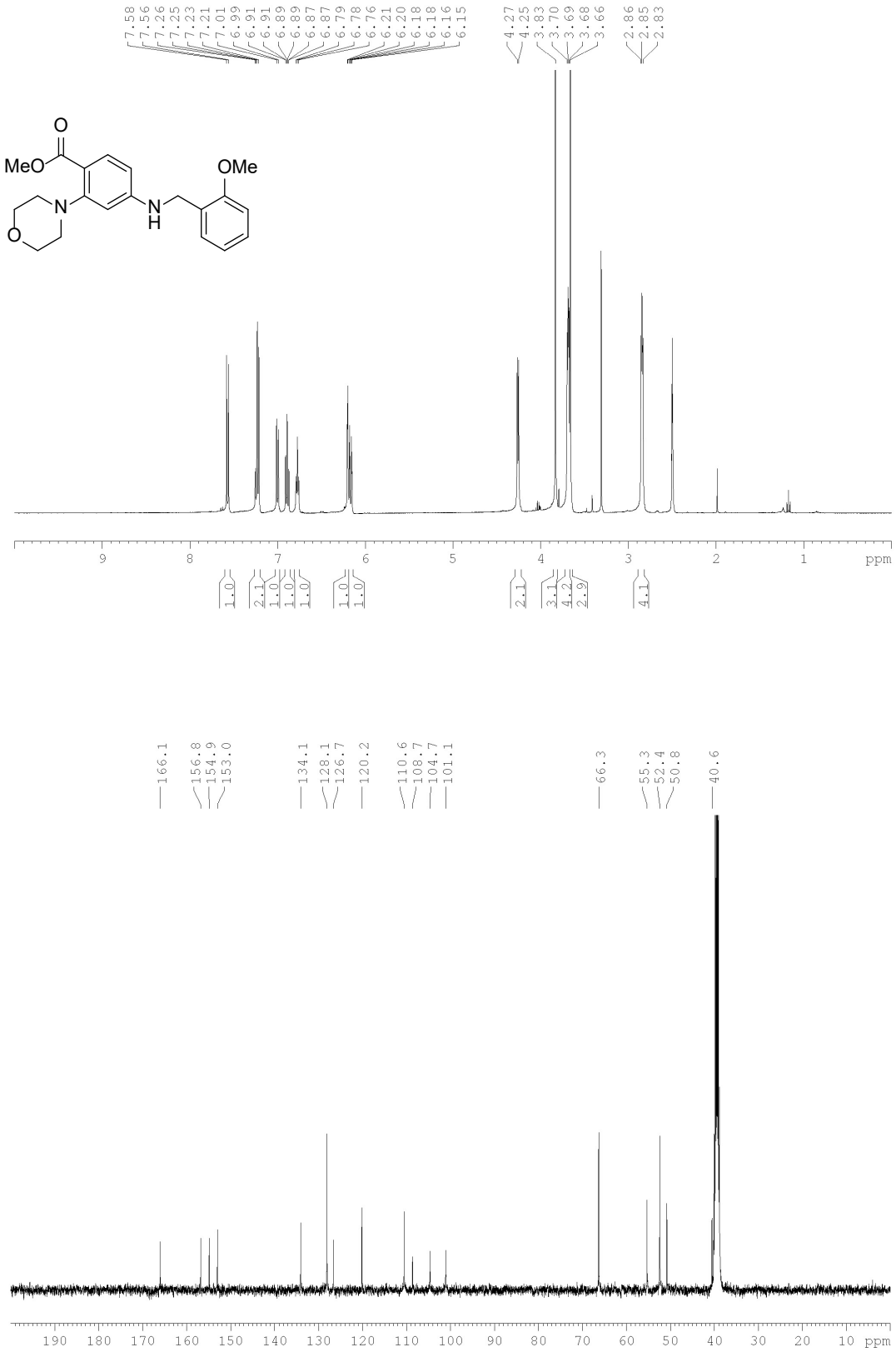


Figure S15. ^{1}H NMR and ^{13}C NMR spectra of **10k**.

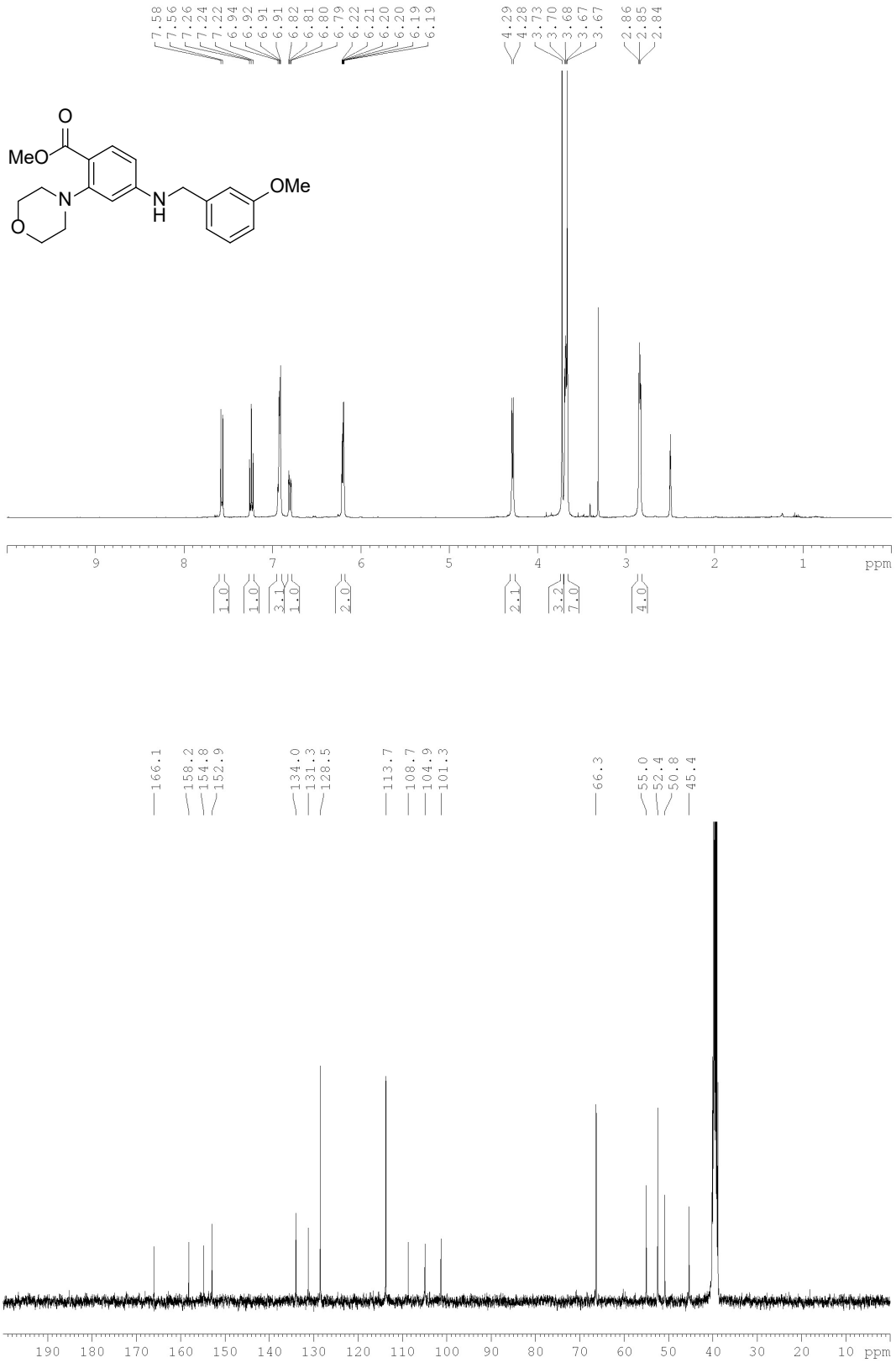


Figure S16. ^{1}H NMR and ^{13}C NMR spectra of **10l**.

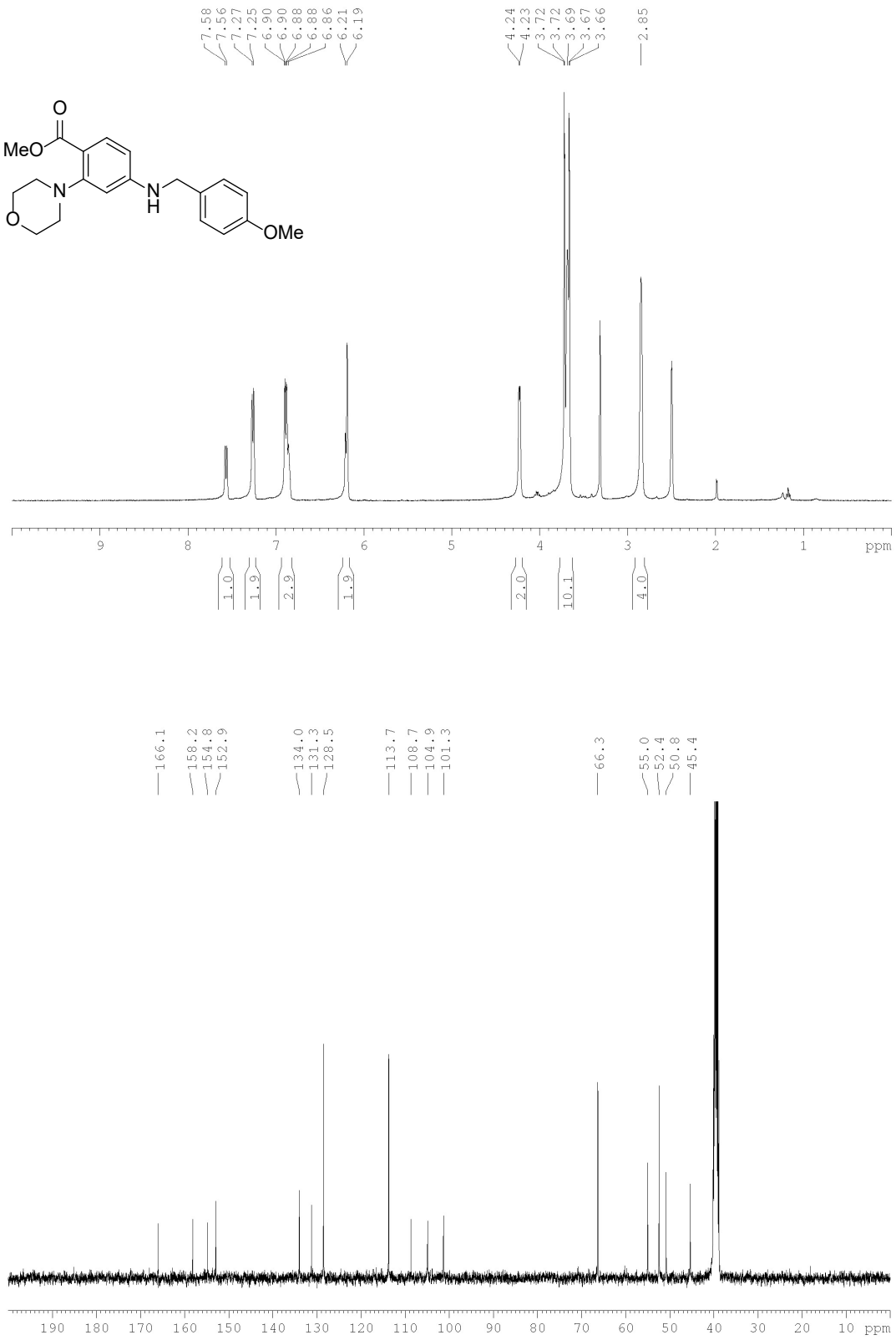


Figure S17. ^{1}H NMR and ^{13}C NMR spectra of **10m**.

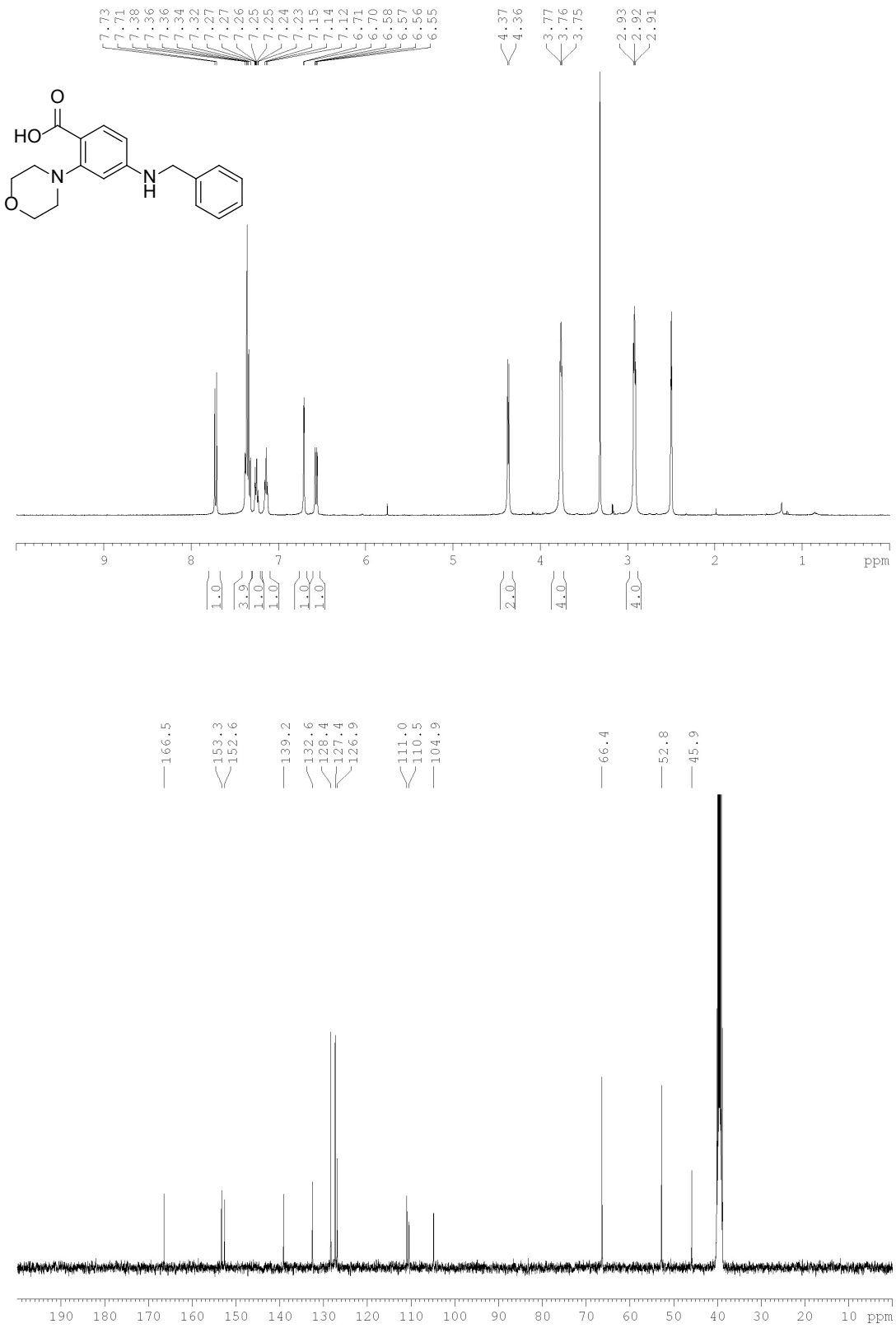


Figure S18. ^{1}H NMR and ^{13}C NMR spectra of **11a**.

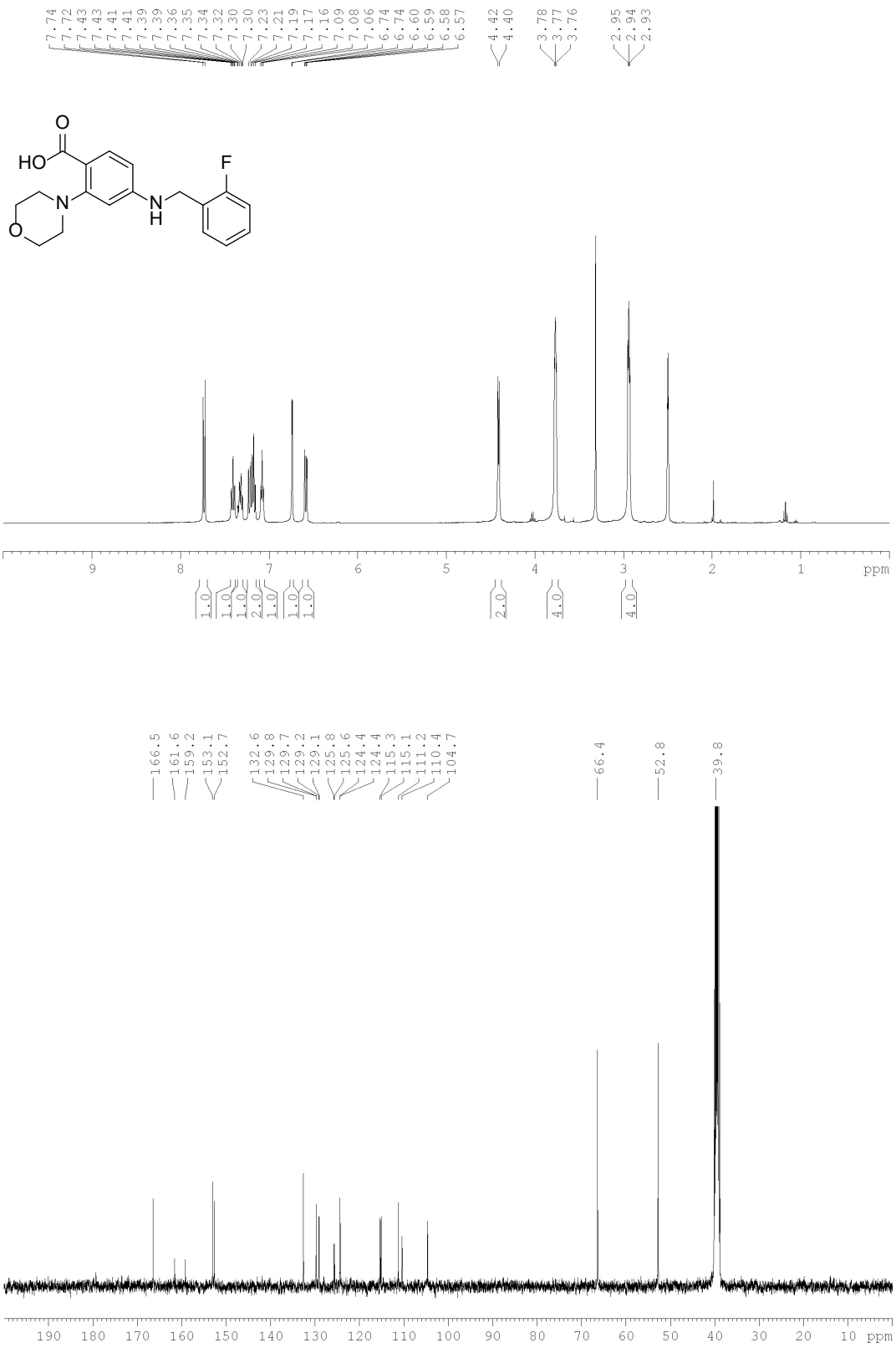


Figure S19. ^{1}H NMR and ^{13}C NMR spectra of **11b**.

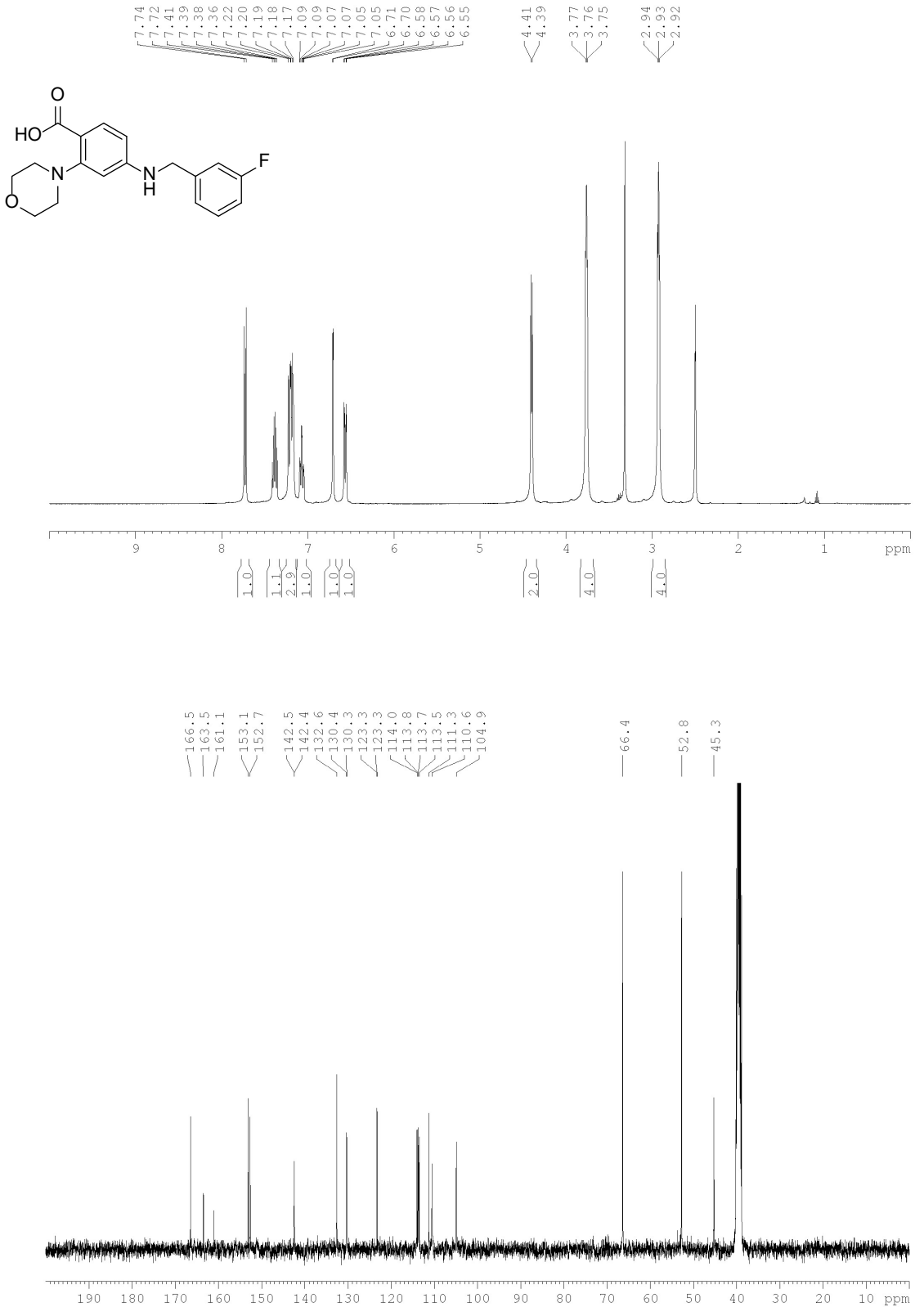


Figure S20. ^{1}H NMR and ^{13}C NMR spectra of **11c**.

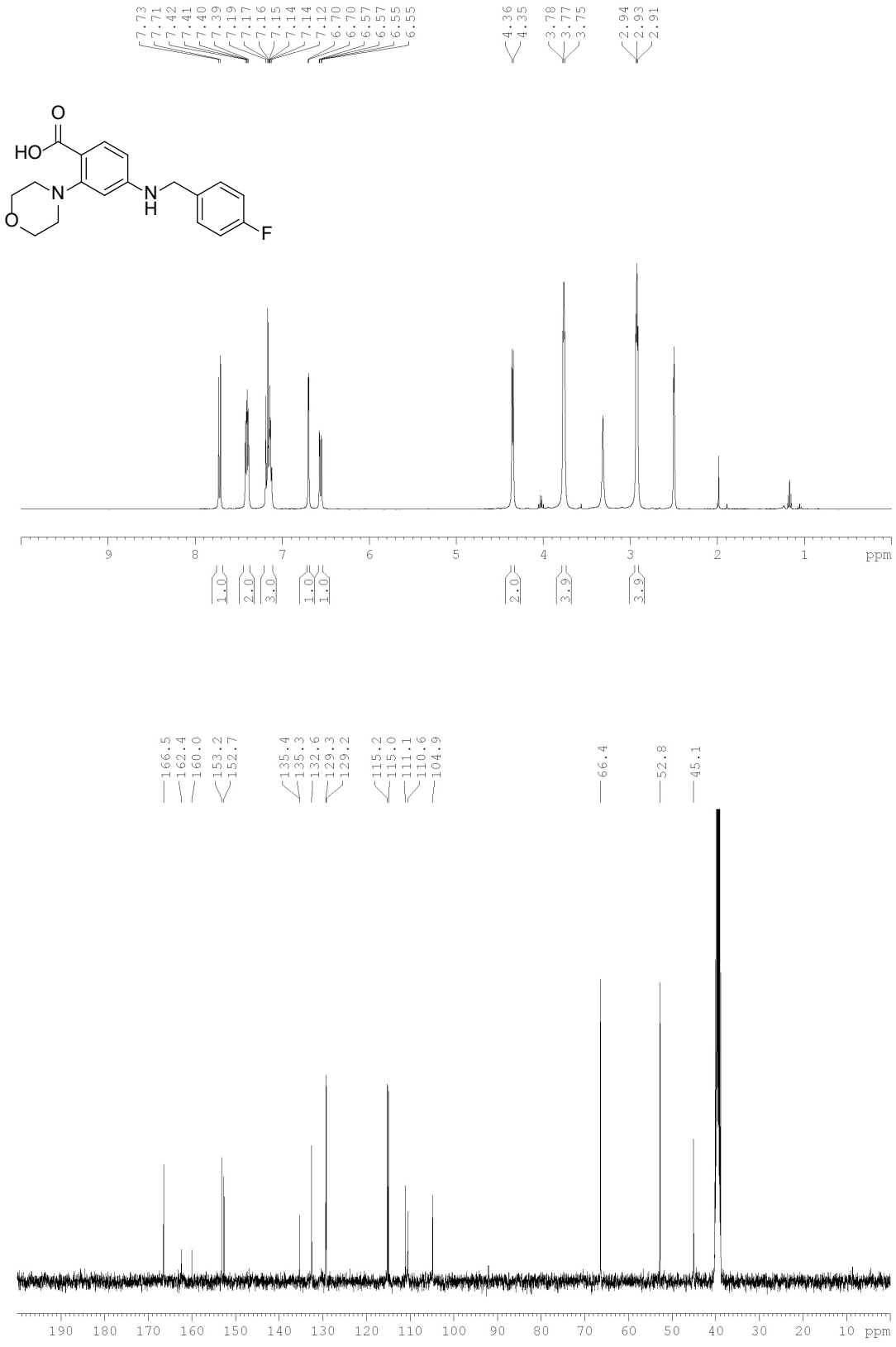


Figure S21. ^{1}H NMR and ^{13}C NMR spectra of **11d**.

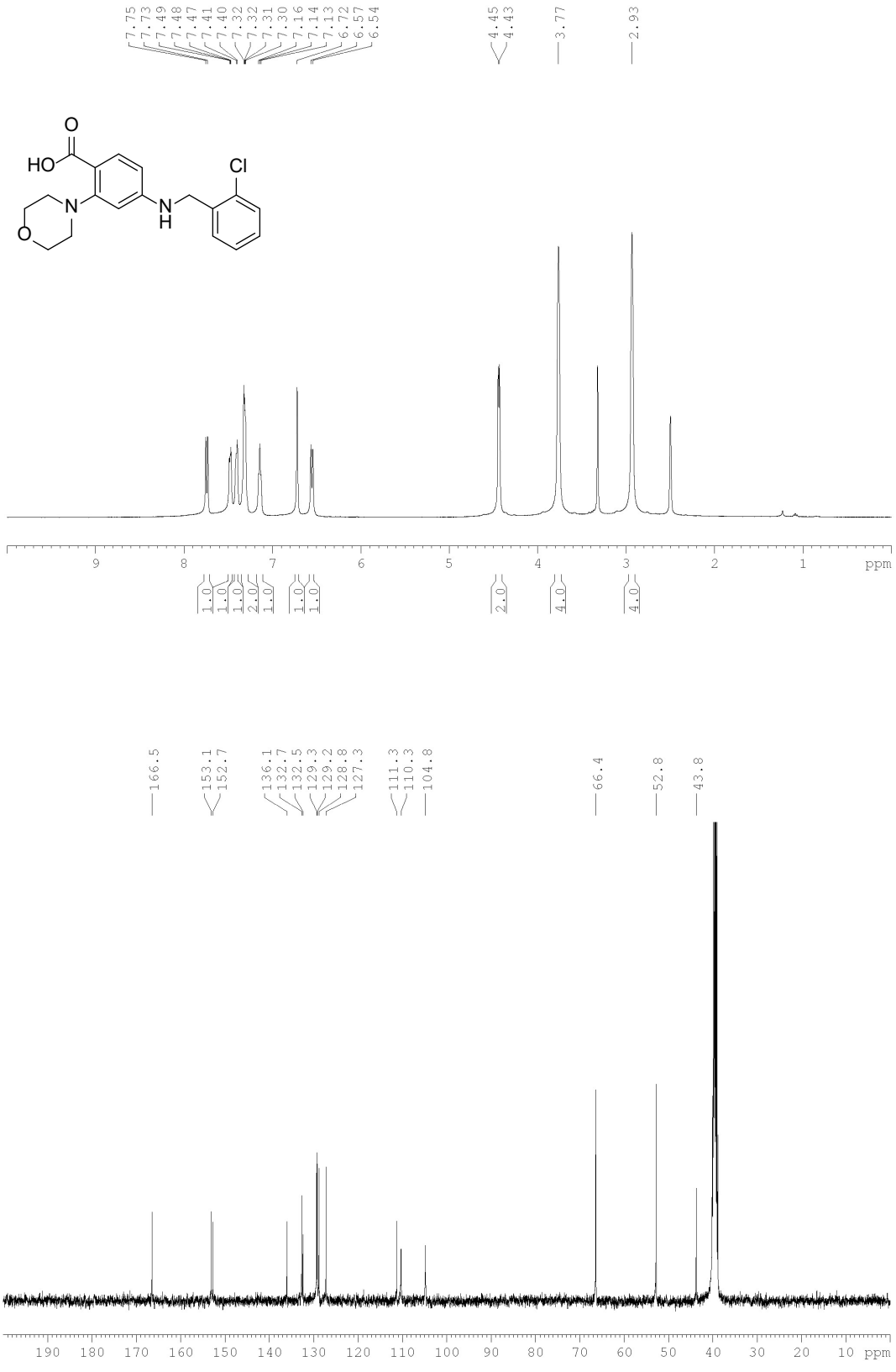


Figure S22. ^{1}H NMR and ^{13}C NMR spectra of **11e**.

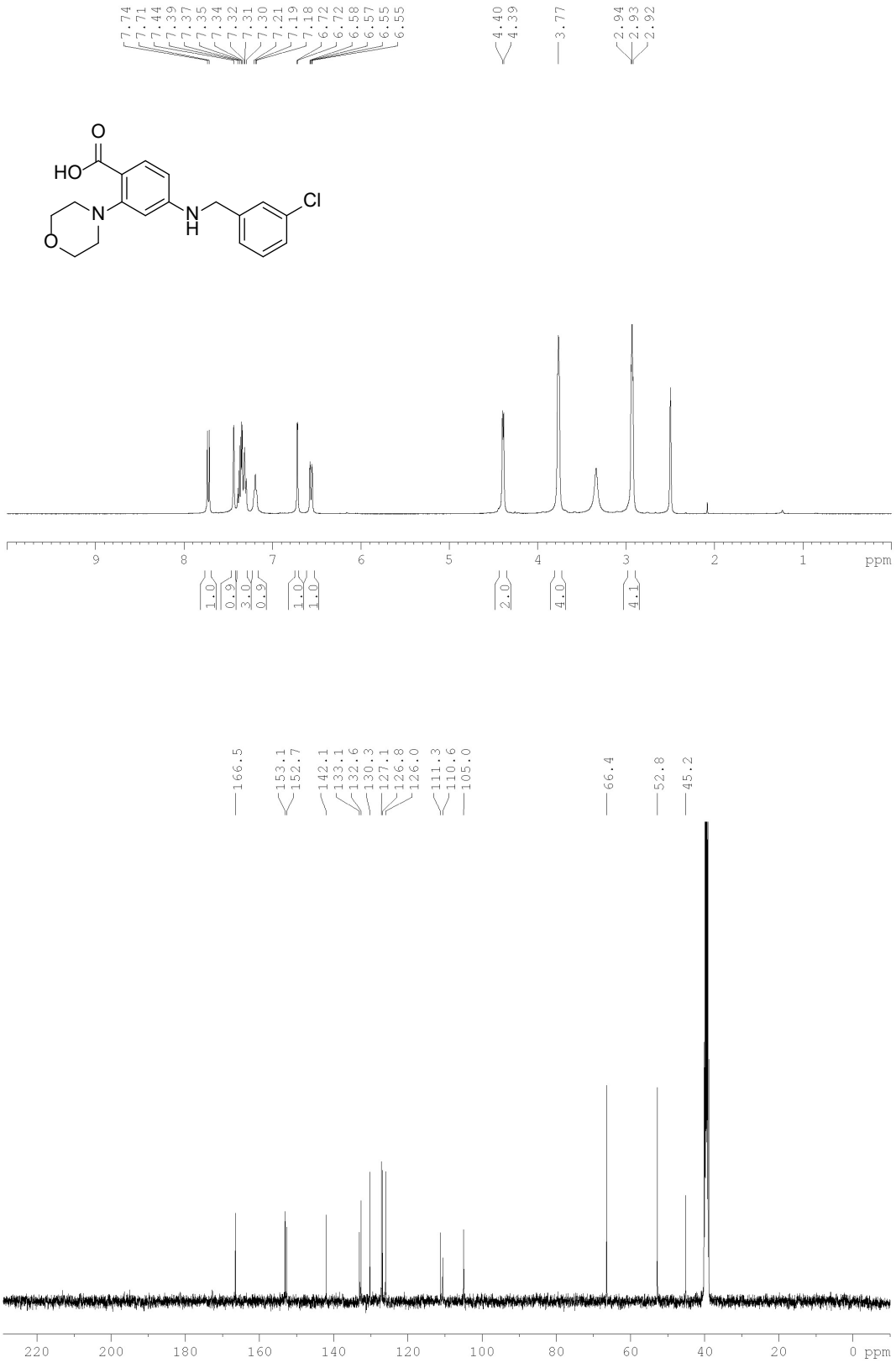


Figure S23. ^{1}H NMR and ^{13}C NMR spectra of **11f**.

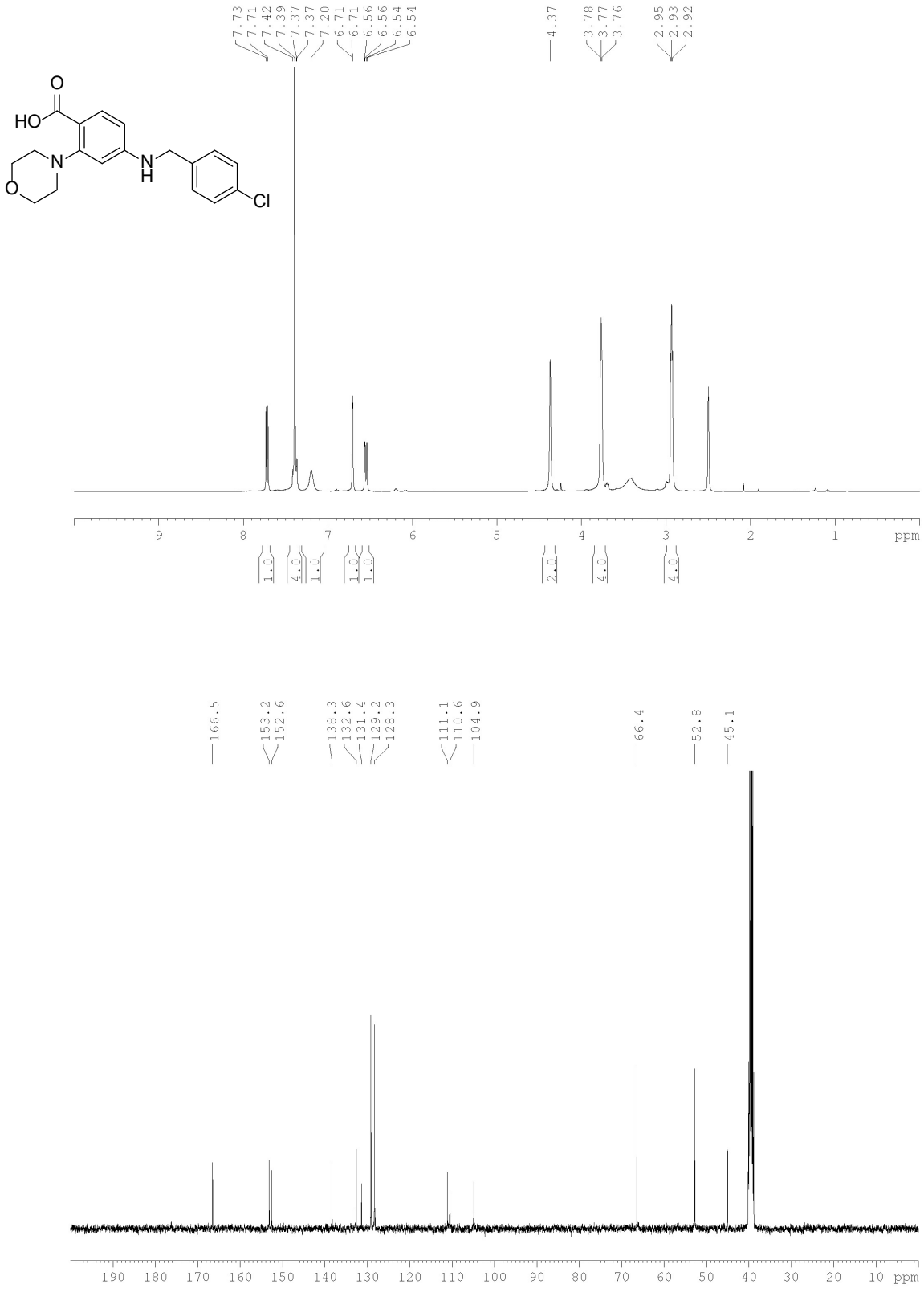


Figure S24. ^{1}H NMR and ^{13}C NMR spectra of **11g**.

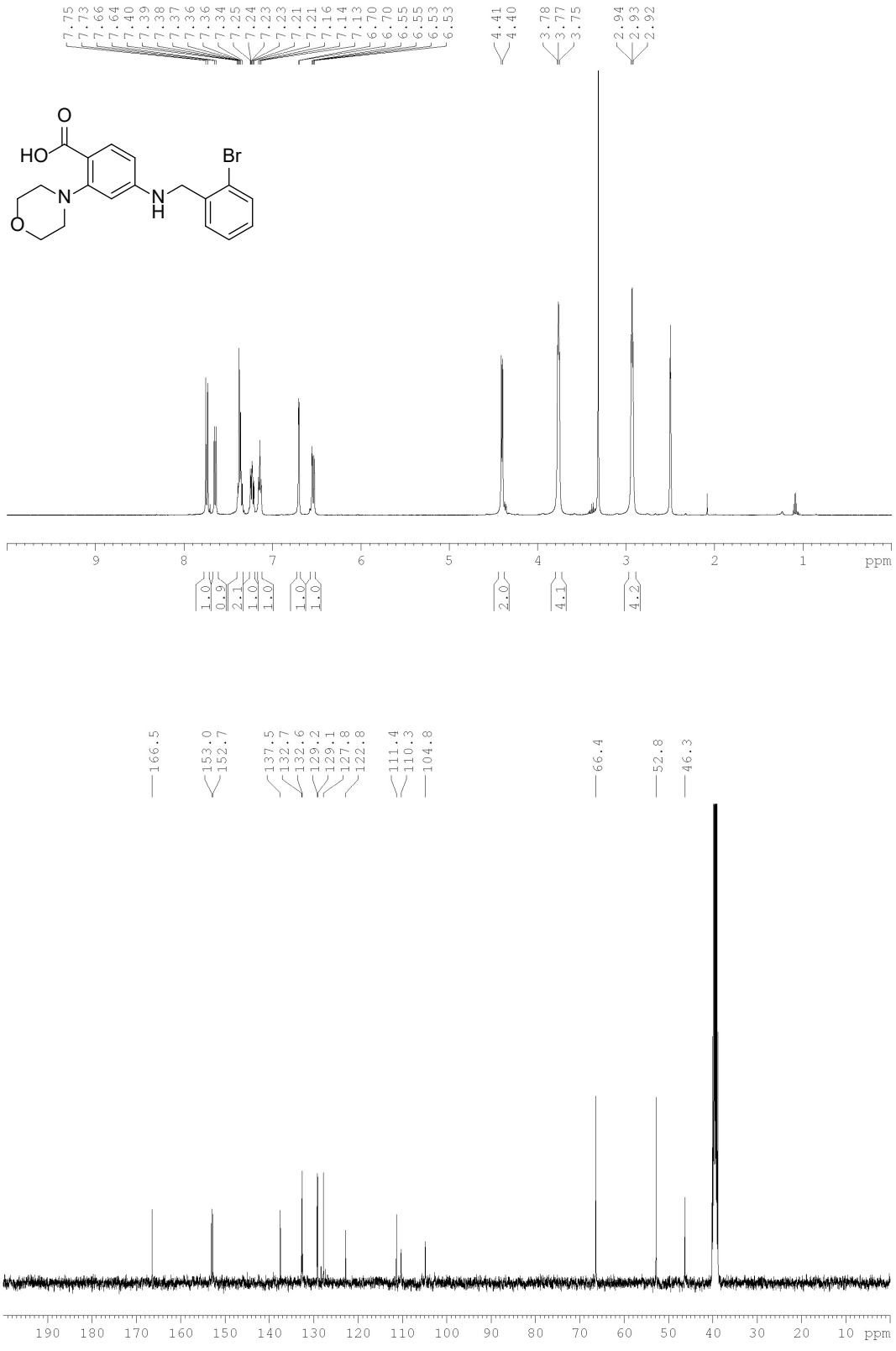


Figure S25. ^{1}H NMR and ^{13}C NMR spectra of **11h**.

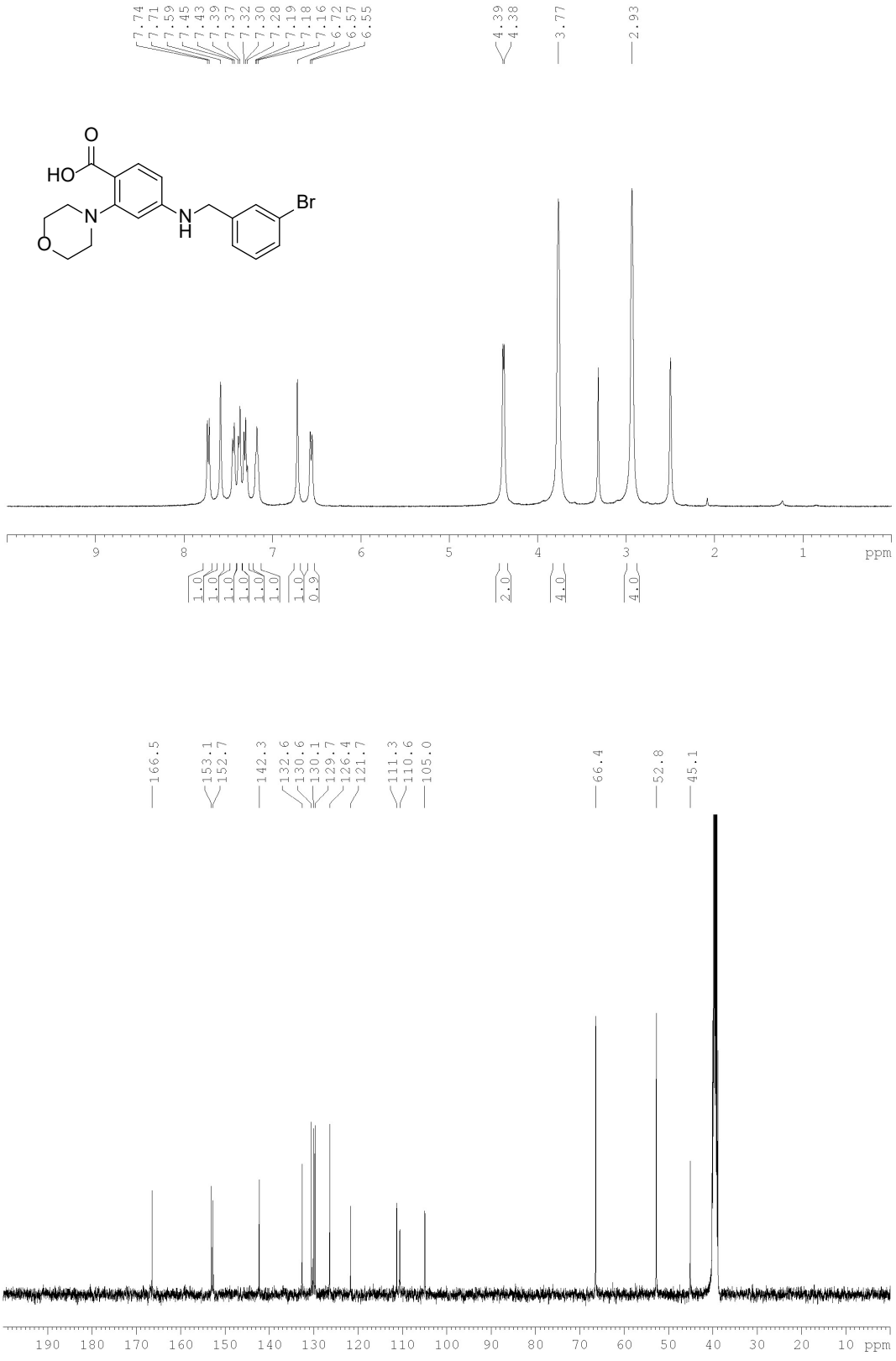


Figure S26. ^{1}H NMR and ^{13}C NMR spectra of **11i**.

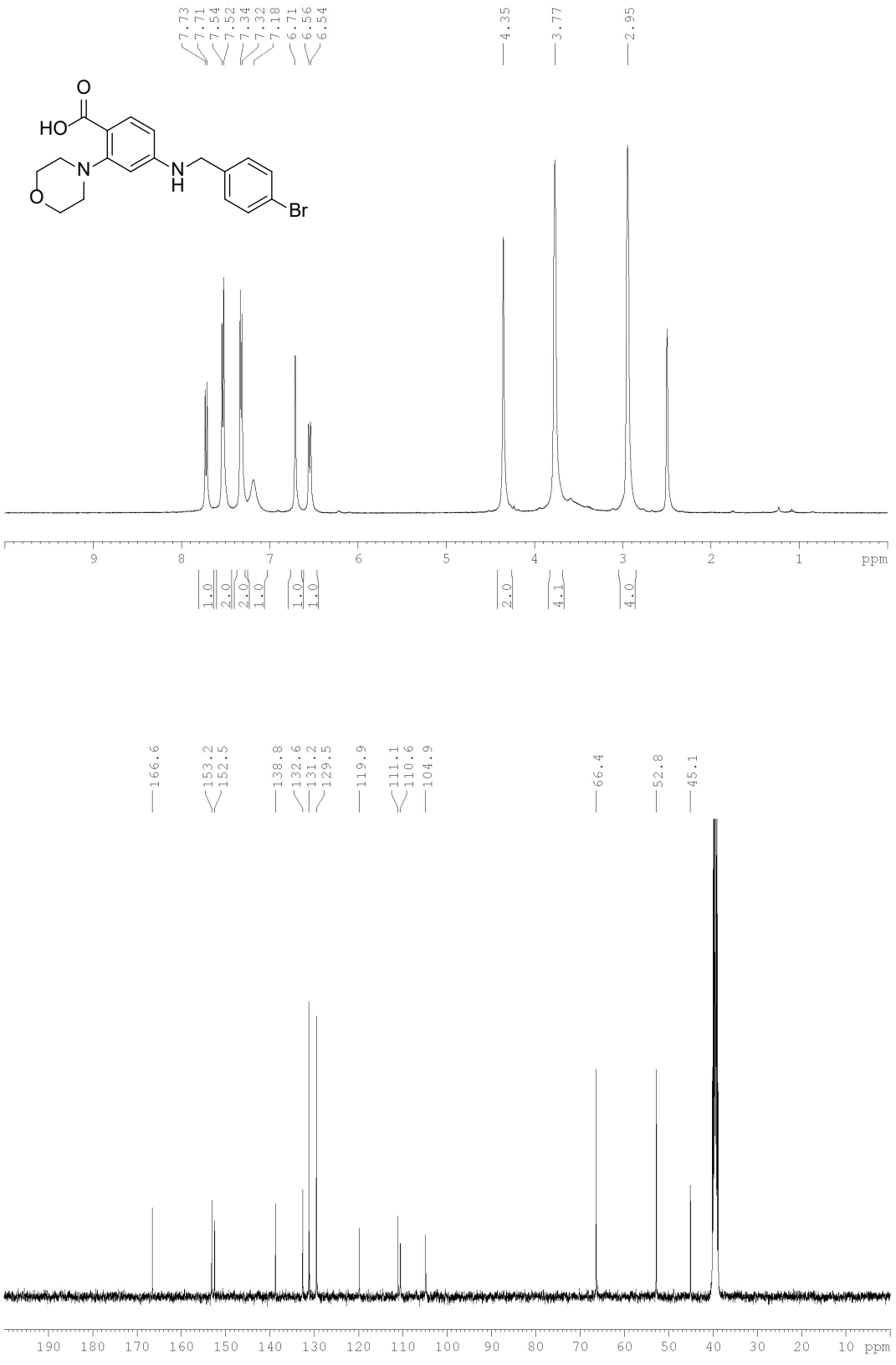


Figure S27. ^{1}H NMR and ^{13}C NMR spectra of **11j**.

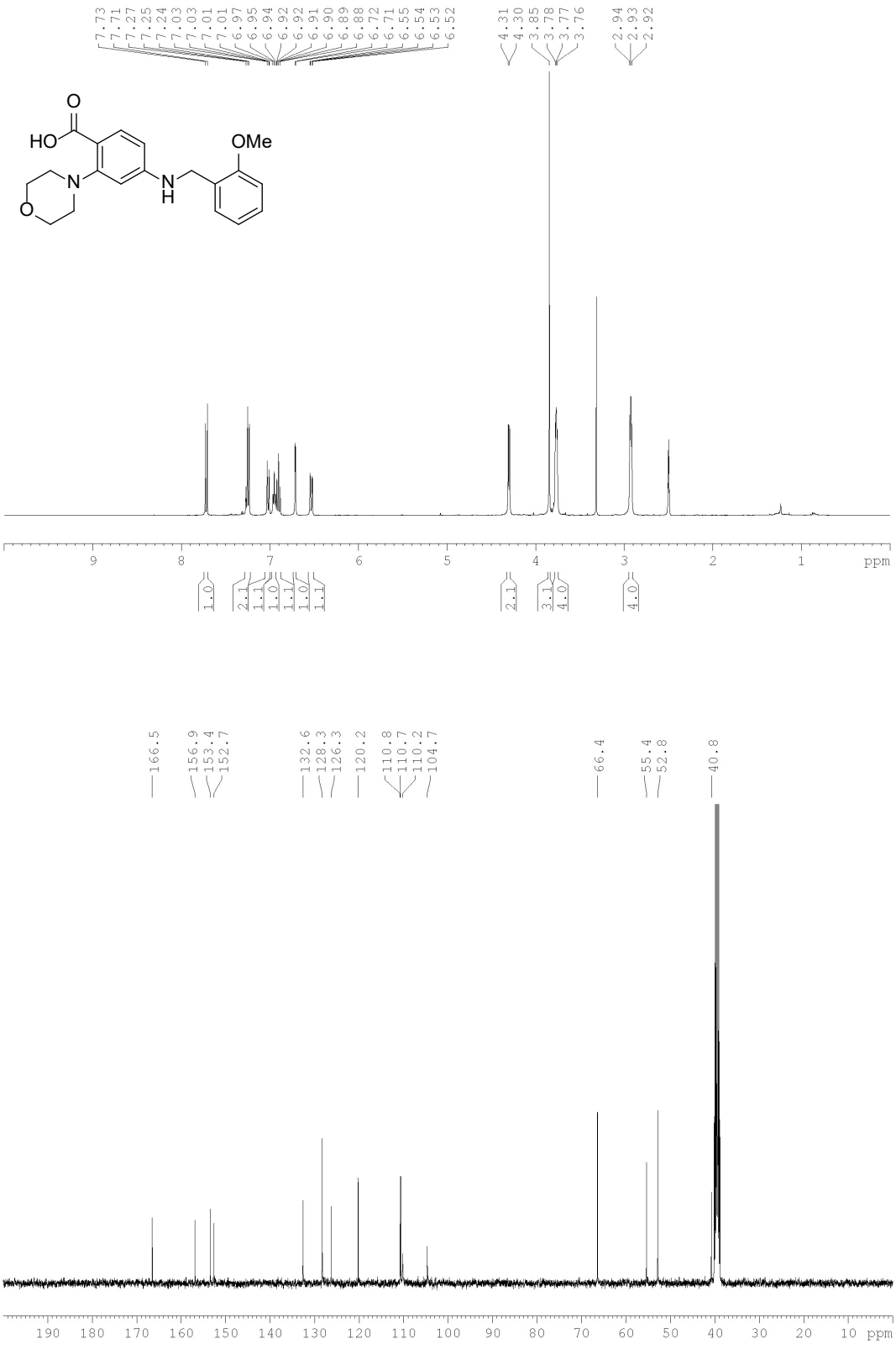


Figure S28. ^{1}H NMR and ^{13}C NMR spectra of **11k**.

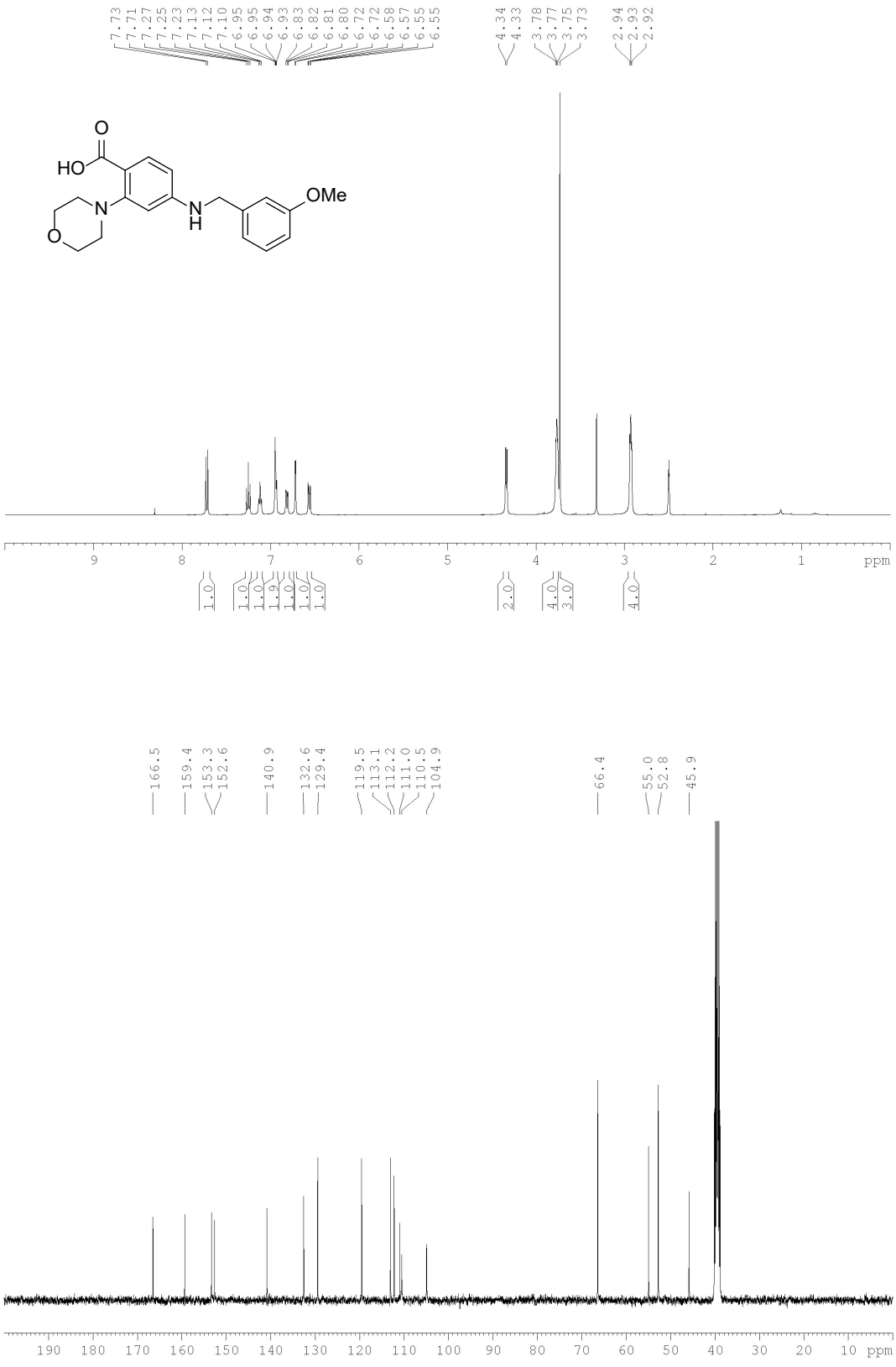


Figure S29. ^{1}H NMR and ^{13}C NMR spectra of **11l**.

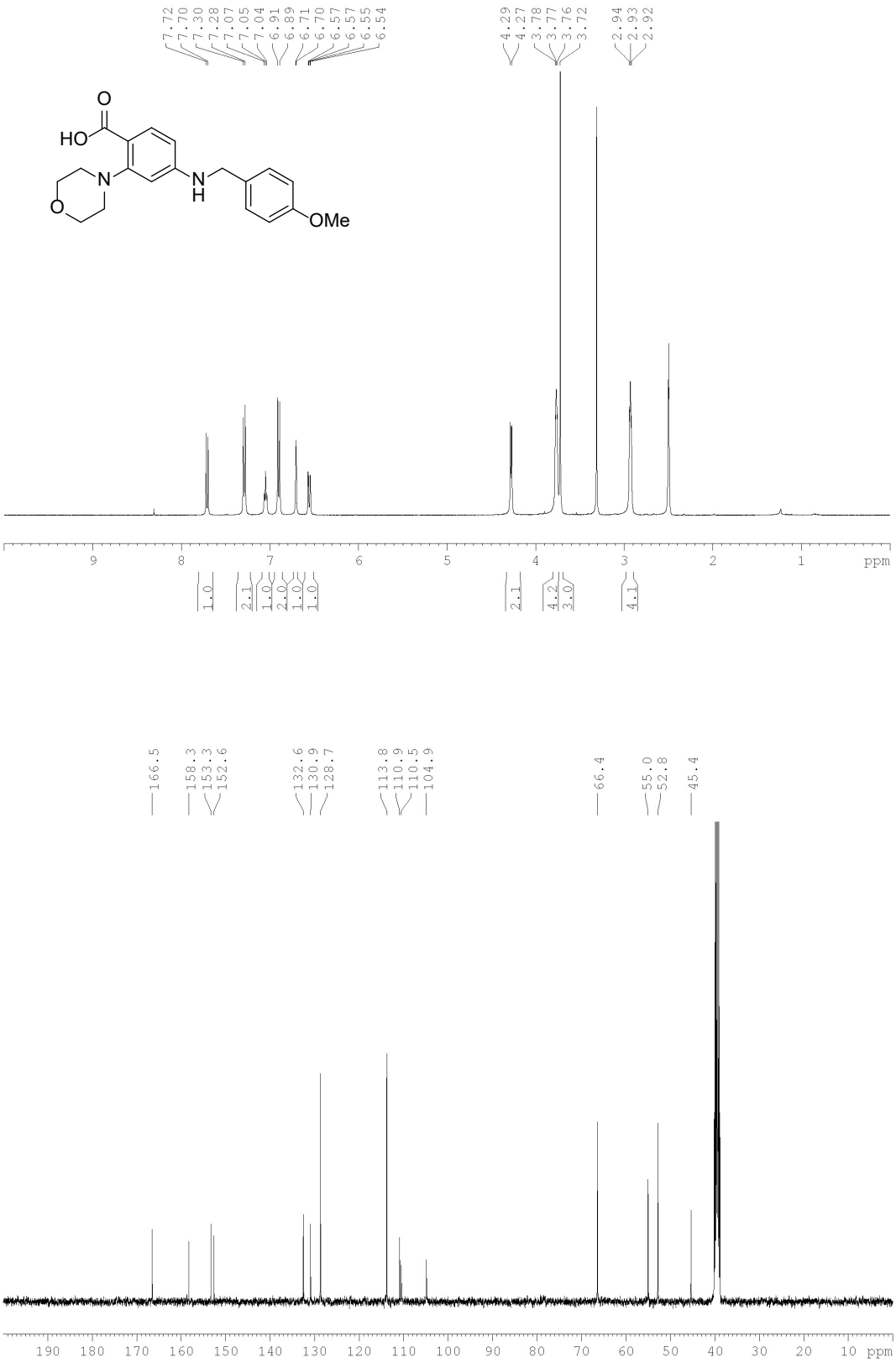


Figure S30. ^{1}H NMR and ^{13}C NMR spectra of **11m**.

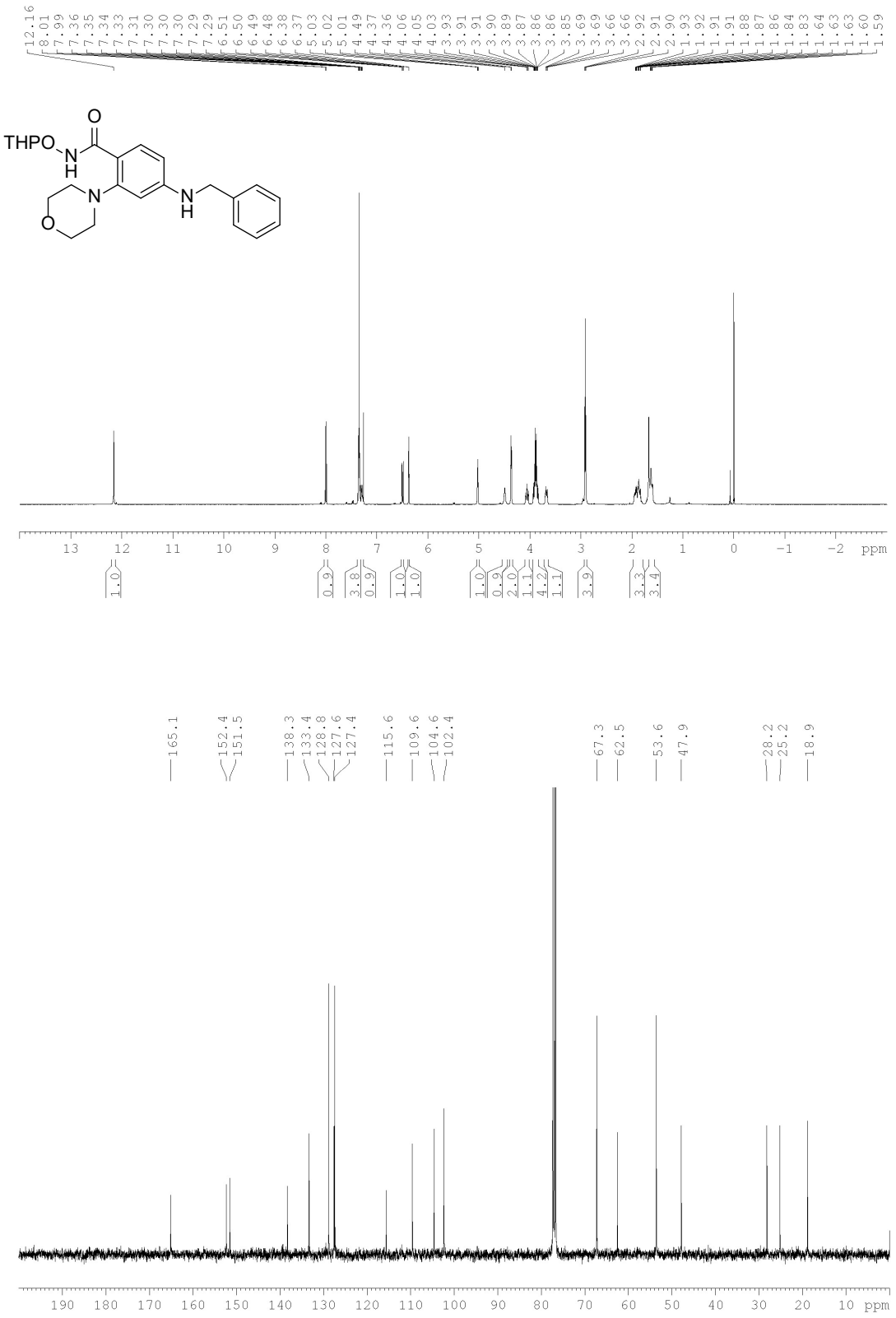


Figure S31. ^{1}H NMR and ^{13}C NMR spectra of **15a**.

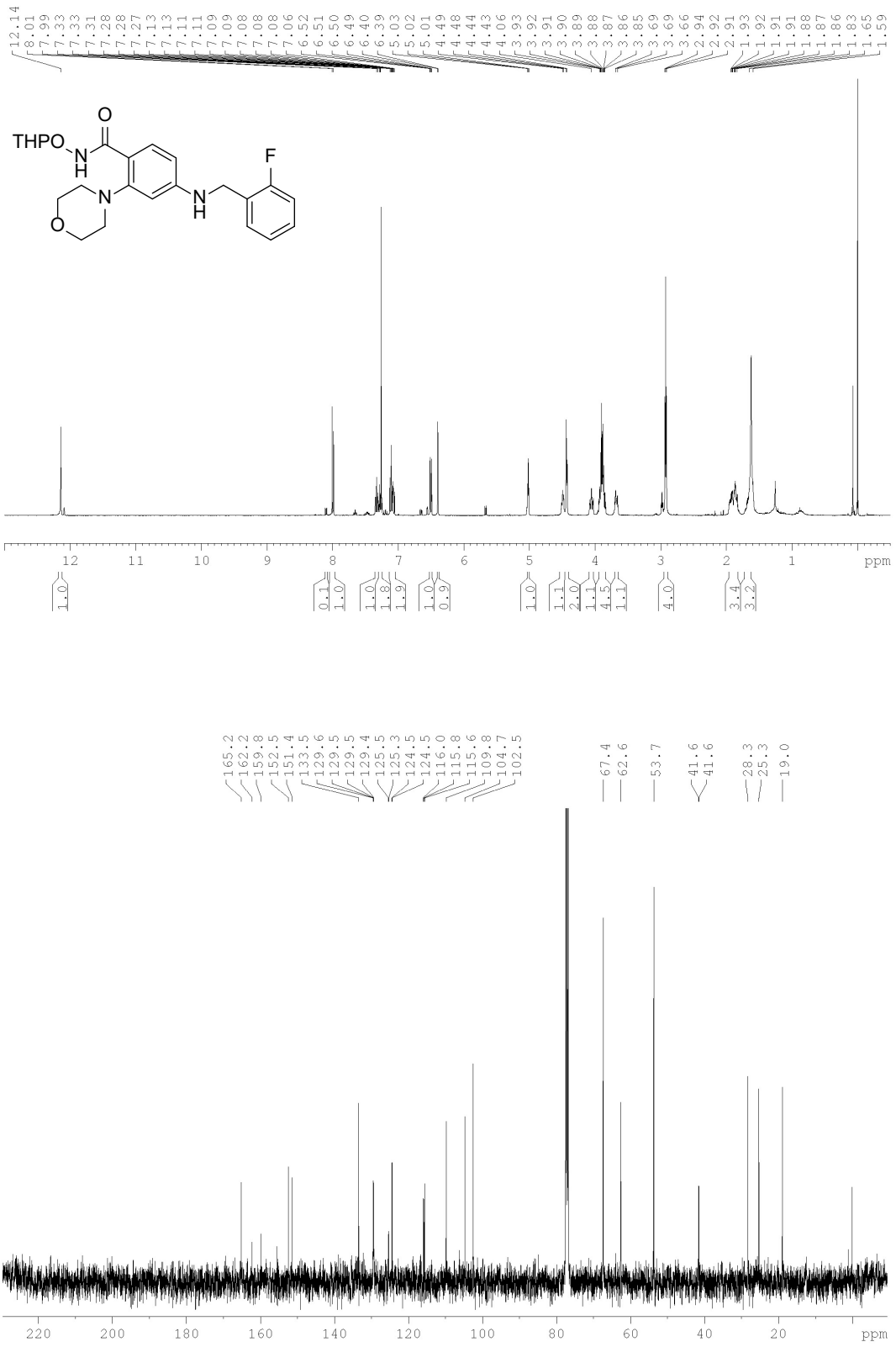


Figure S32. ^{1}H NMR and ^{13}C NMR spectra of **15b**.

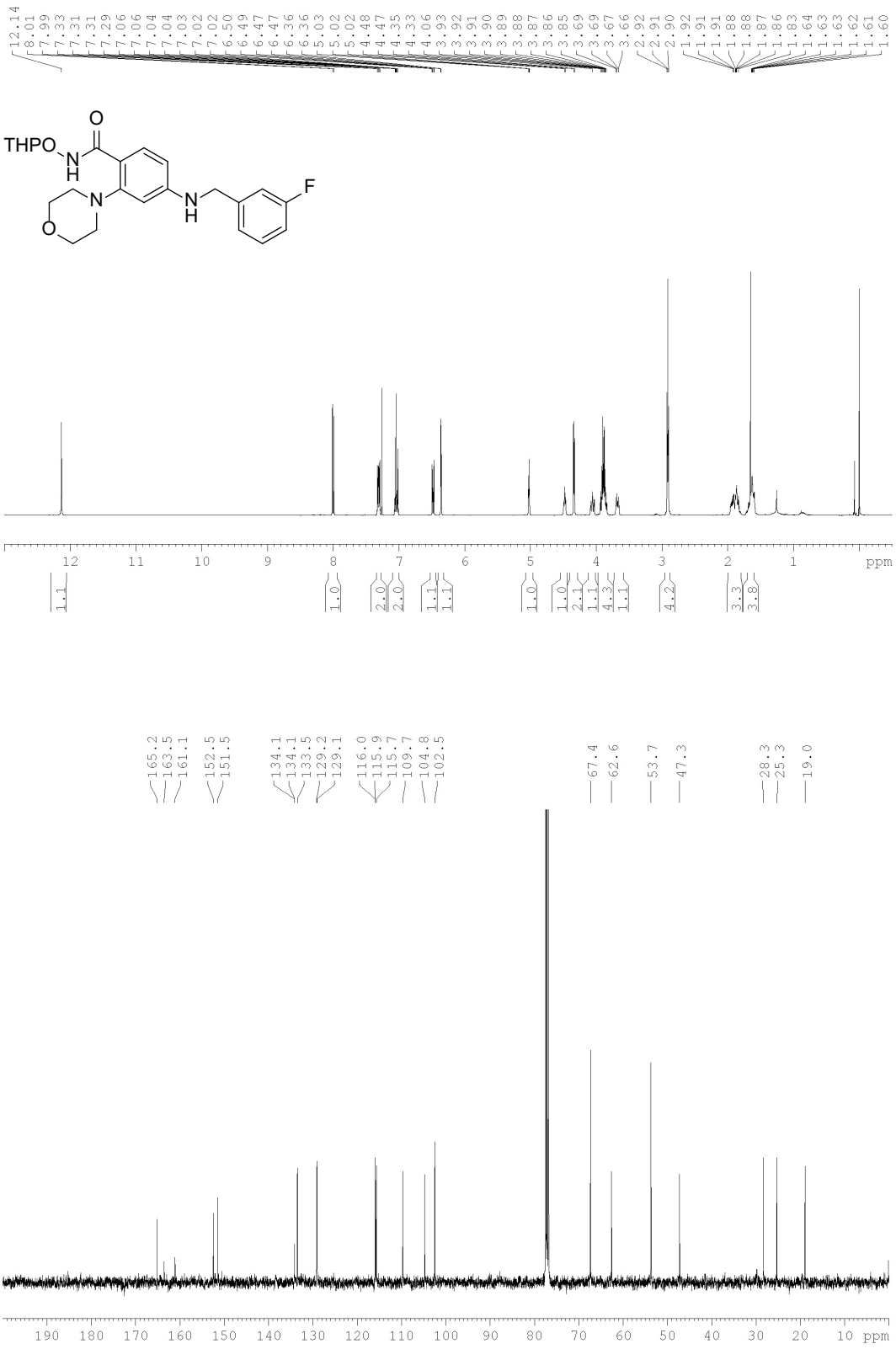


Figure S33. ^{1}H NMR and ^{13}C NMR spectra of **15c**.

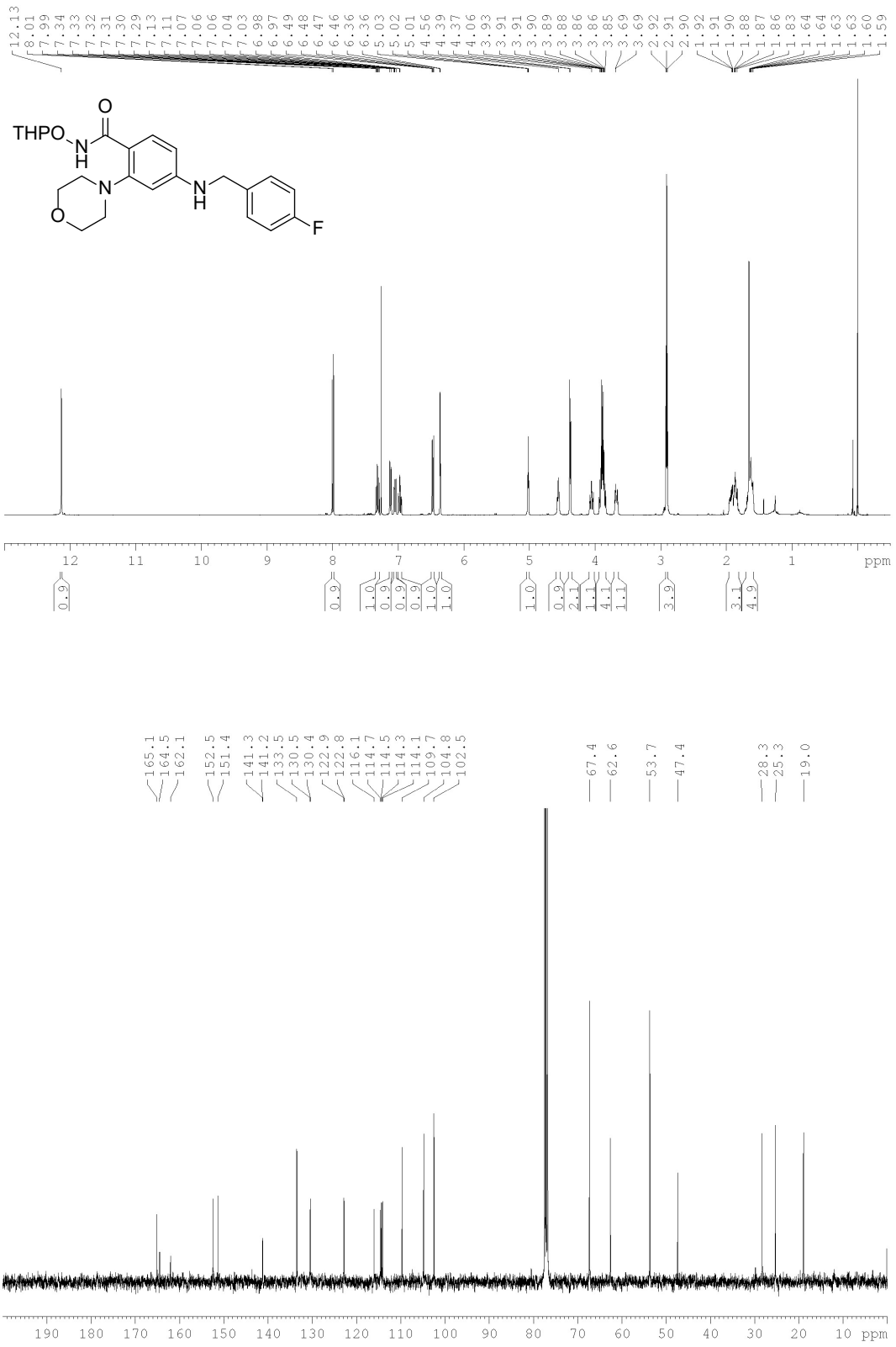


Figure S34. ^{1}H NMR and ^{13}C NMR spectra of **15d**.

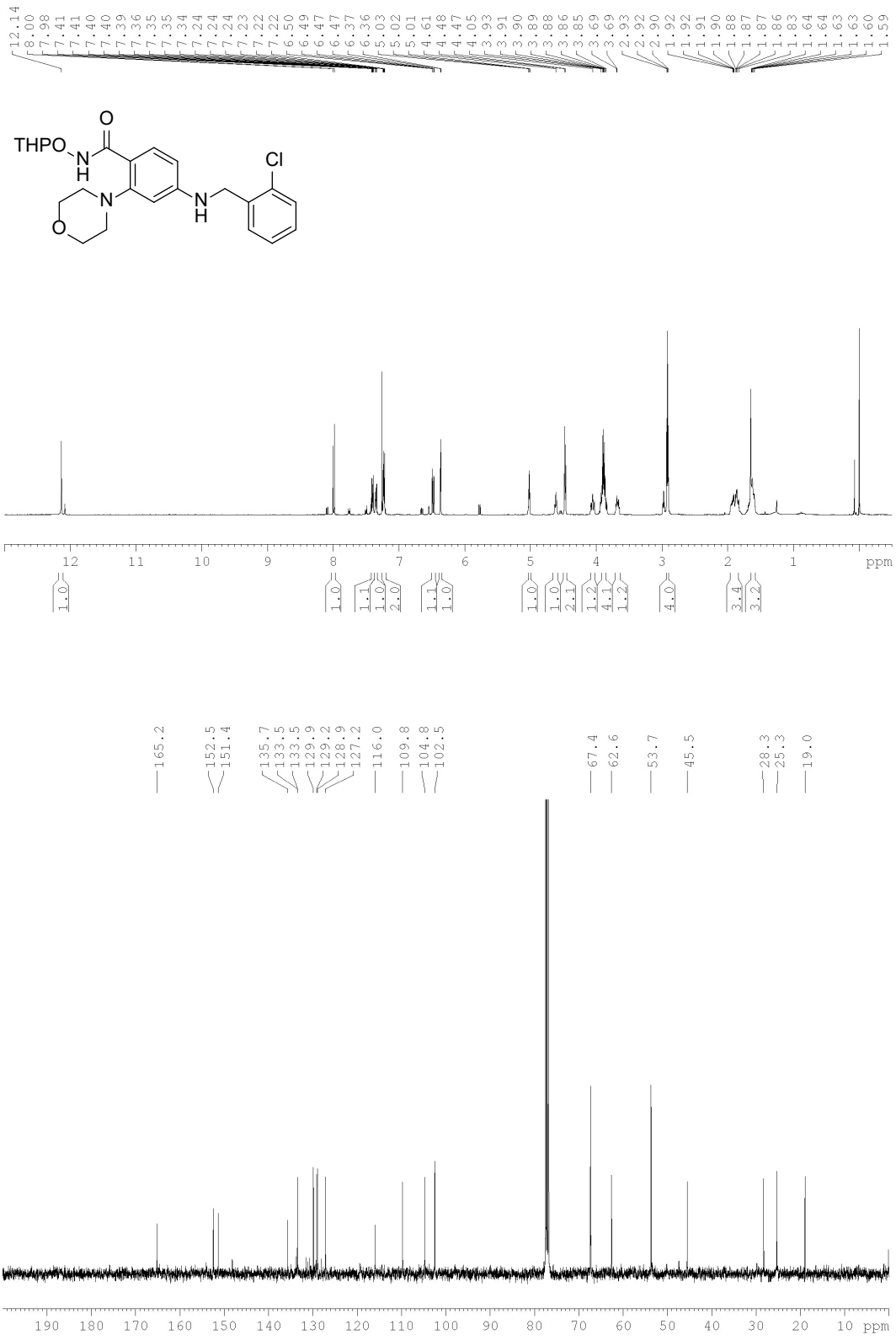


Figure S35. ^{1}H NMR and ^{13}C NMR spectra of **15e**.

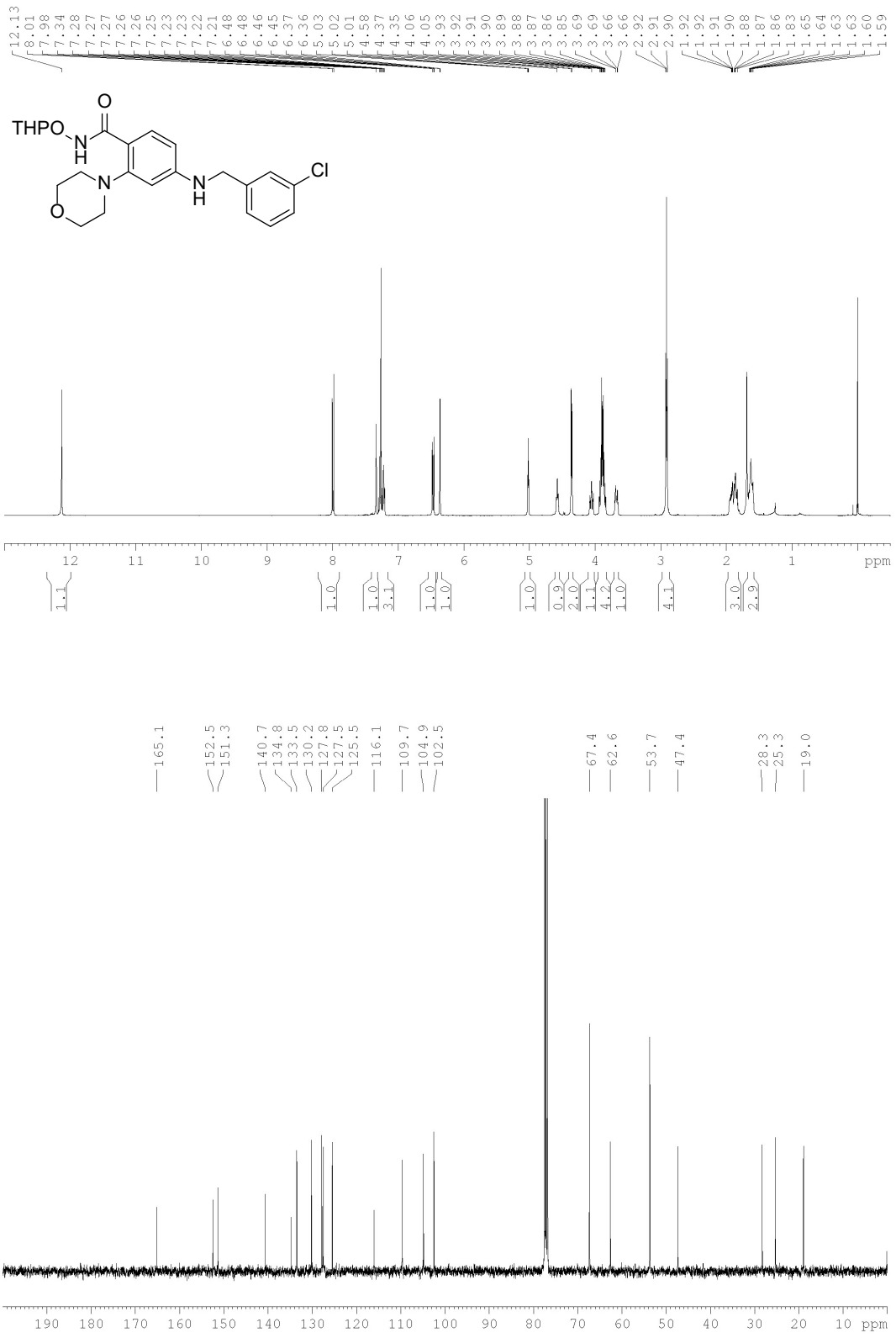


Figure S36. ^{1}H NMR and ^{13}C NMR spectra of **15f**.

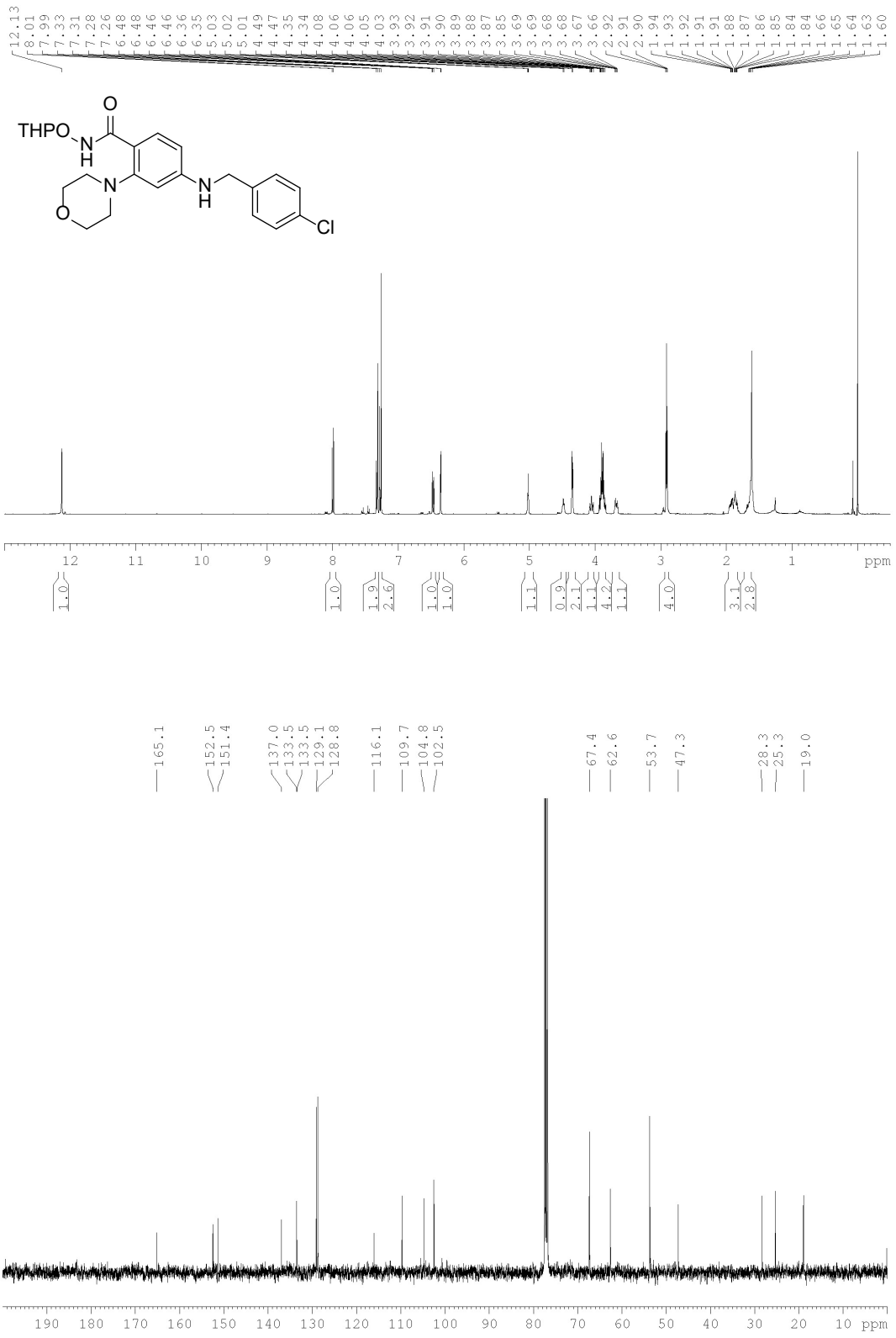


Figure S37. ^{1}H NMR and ^{13}C NMR spectra of **15g**.

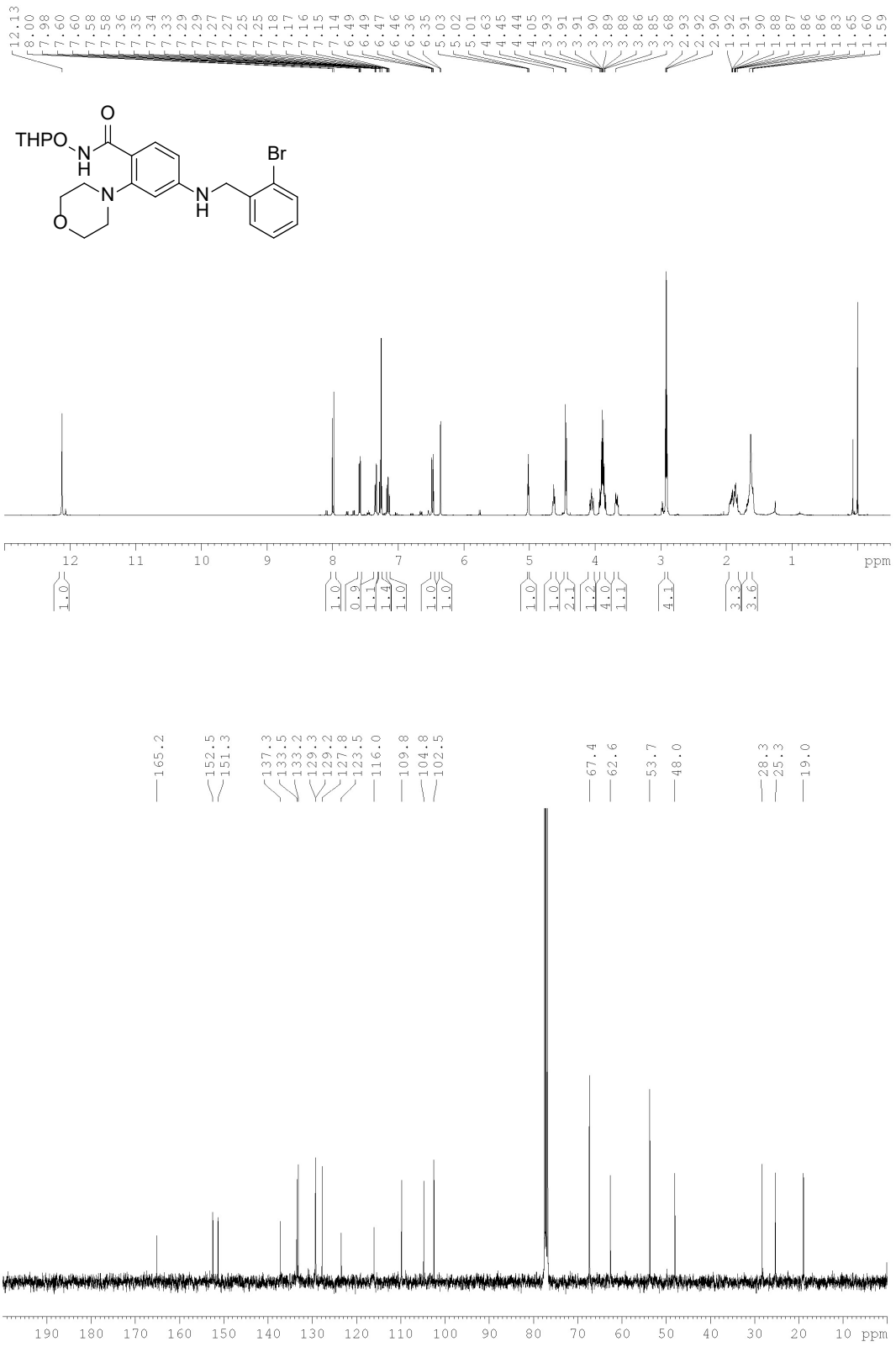


Figure S38. ^{1}H NMR and ^{13}C NMR spectra of **15h**.

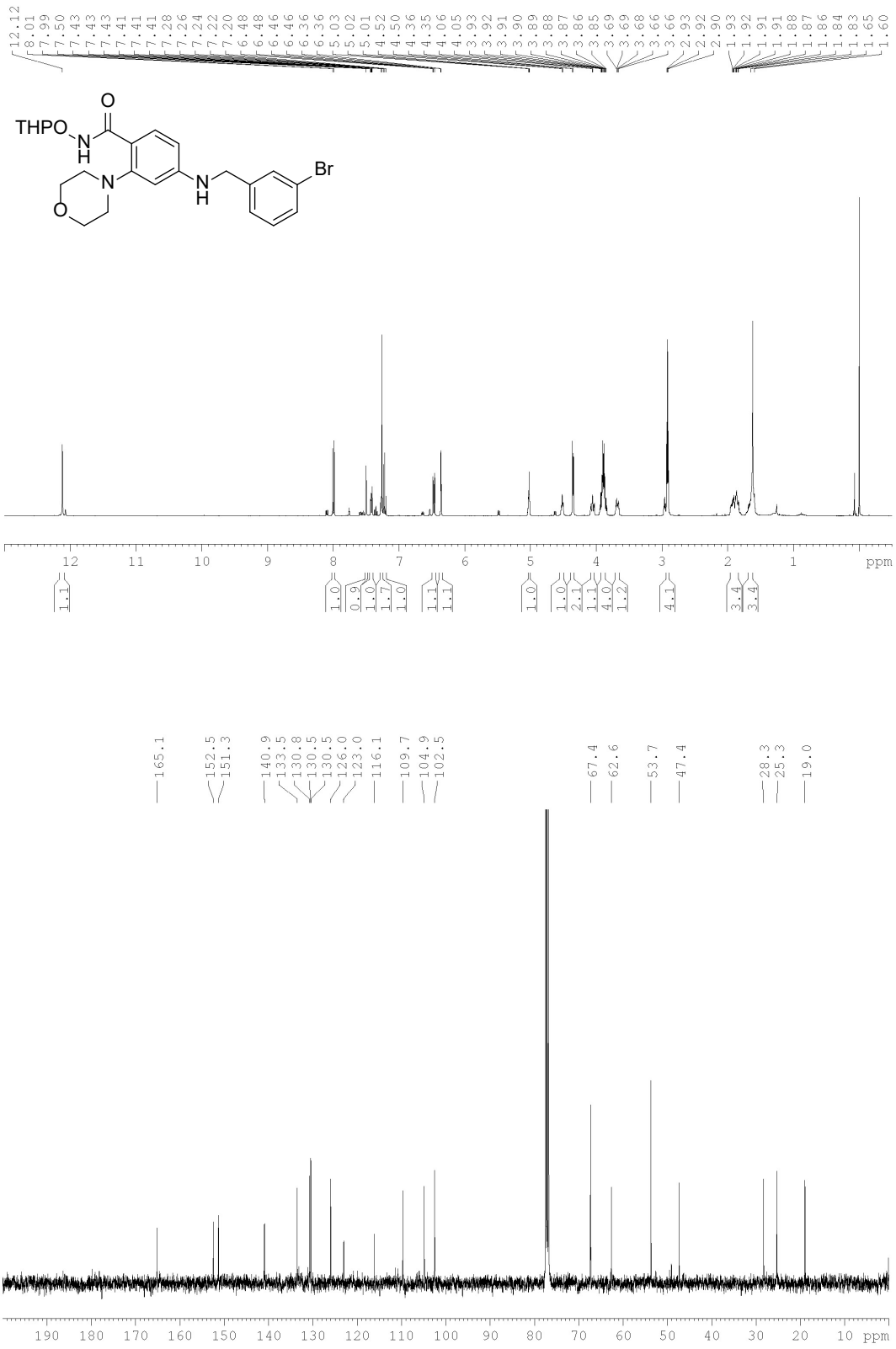


Figure S39. ^{1}H NMR and ^{13}C NMR spectra of **15i**.

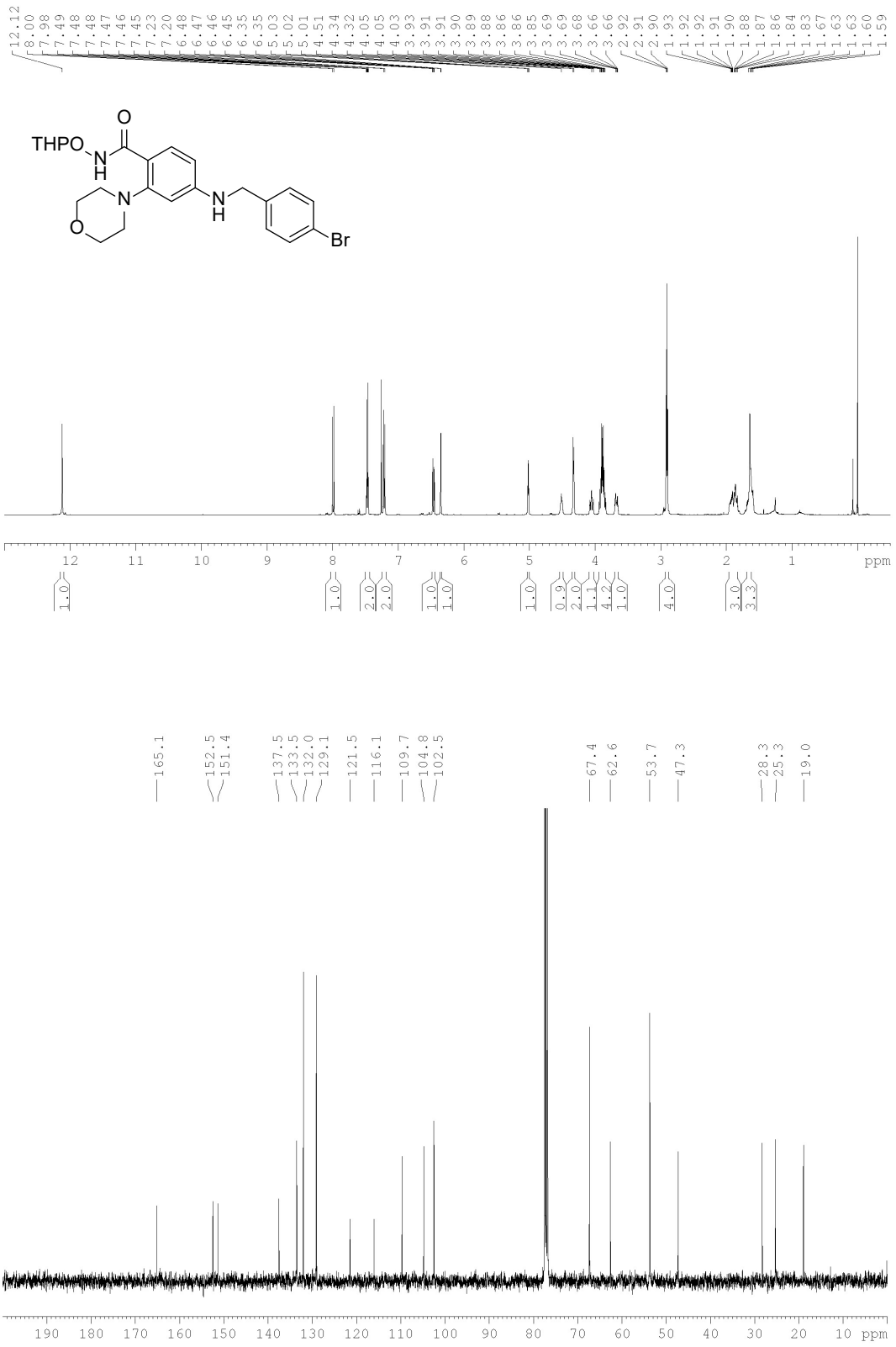


Figure S40. ^{1}H NMR and ^{13}C NMR spectra of **15j**.

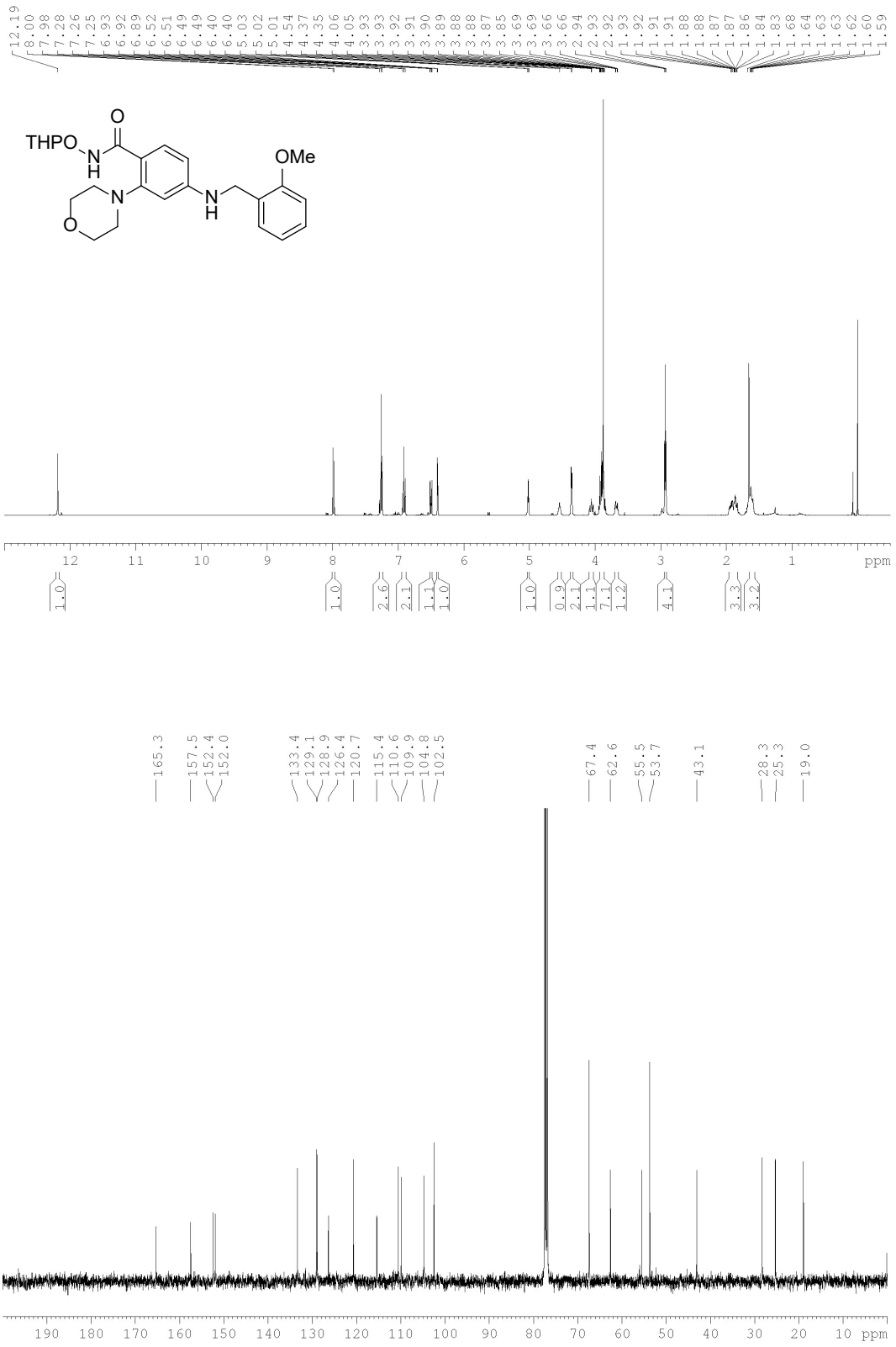


Figure S41. ^{1}H NMR and ^{13}C NMR spectra of **15k**.

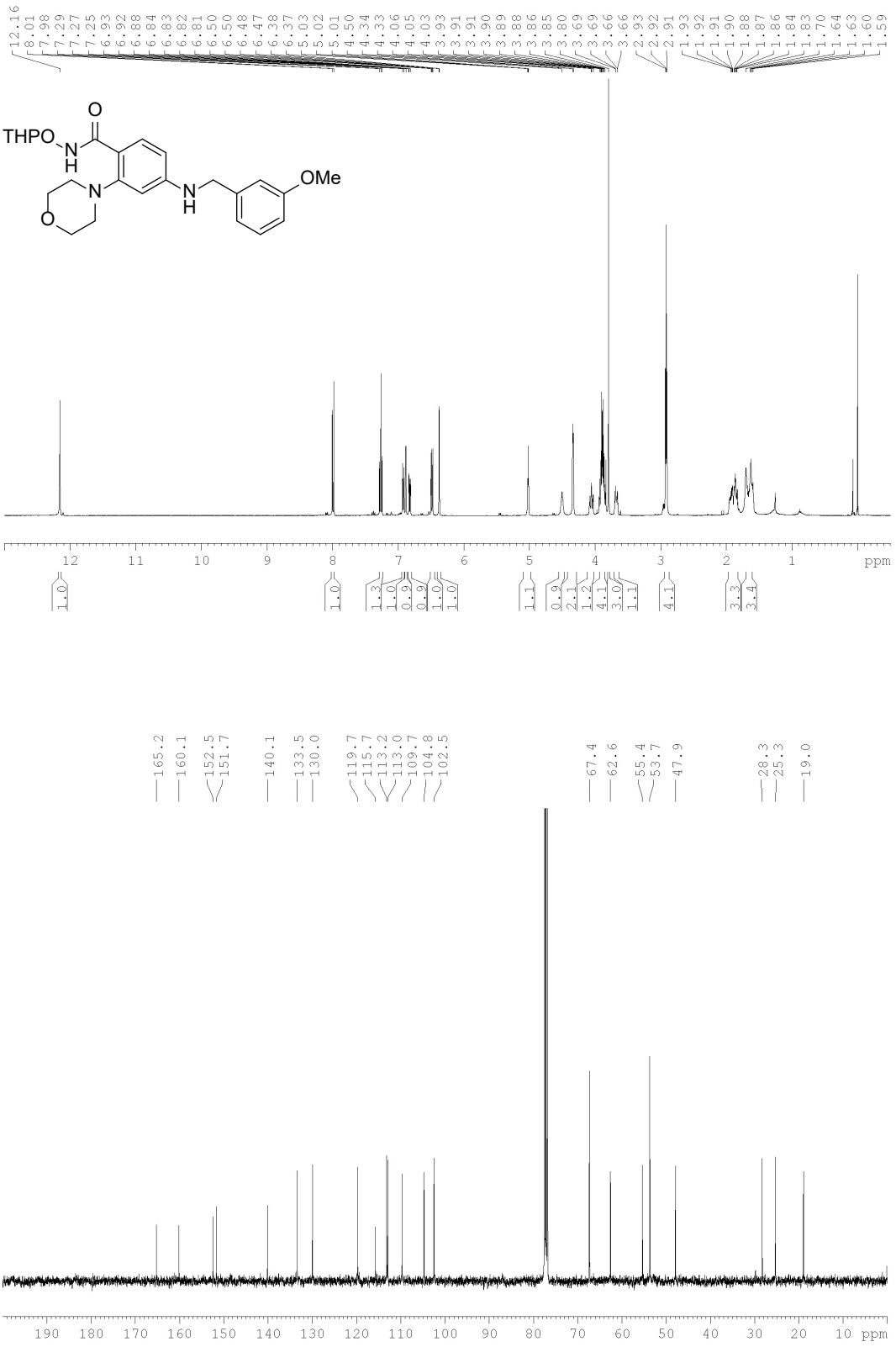


Figure S42. ^{1}H NMR and ^{13}C NMR spectra of **15l**.

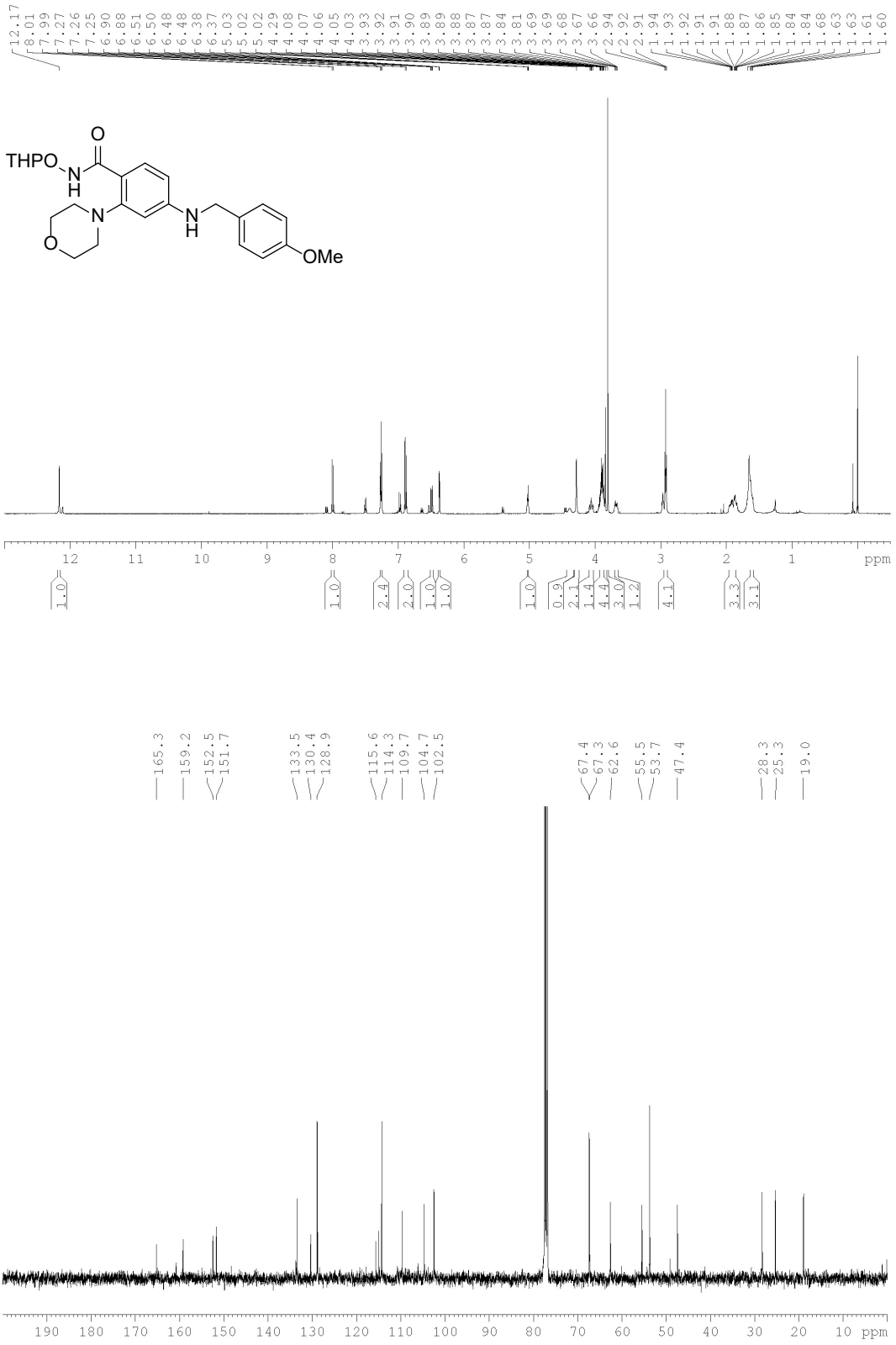


Figure S43. ^{1}H NMR and ^{13}C NMR spectra of **15m**.

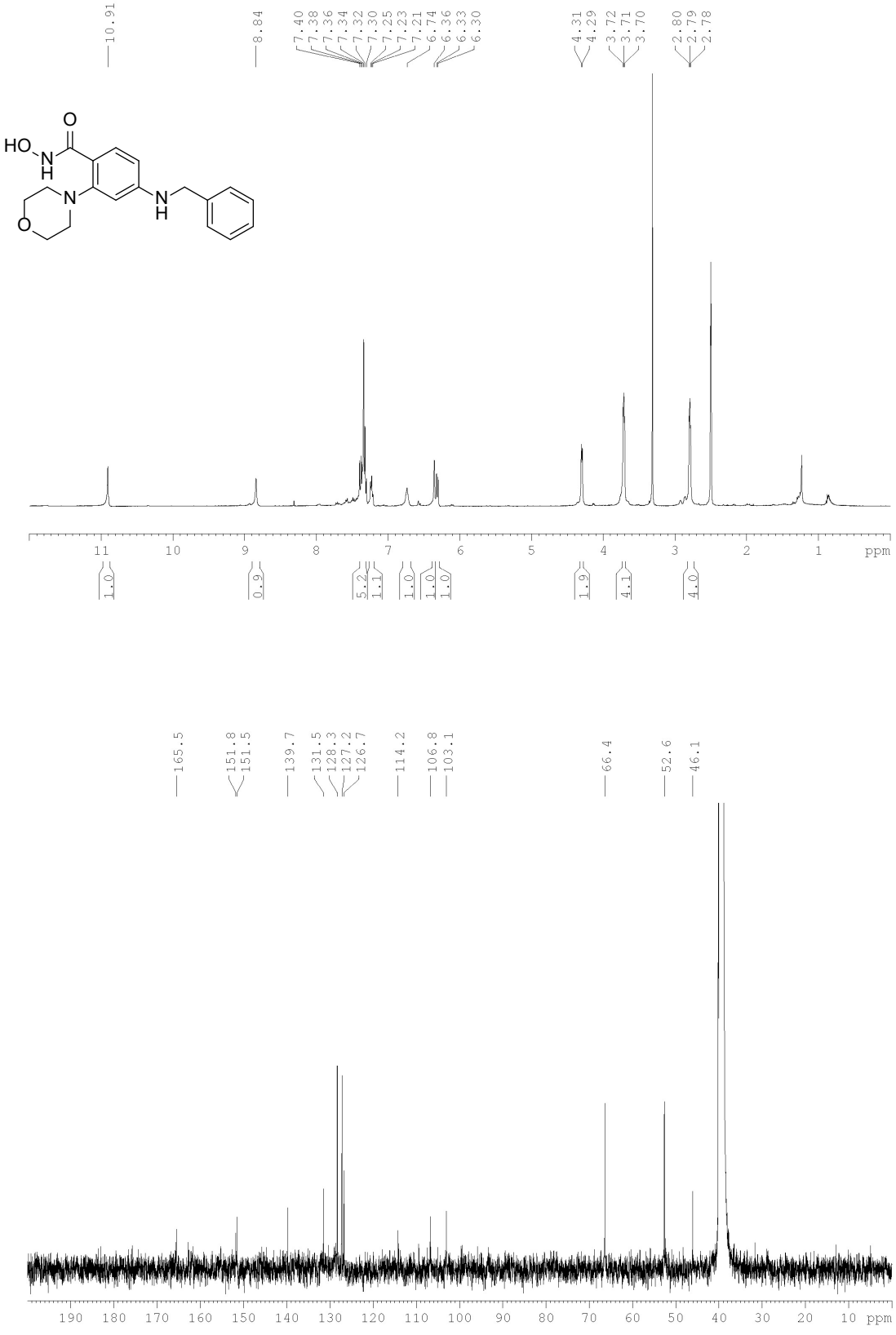


Figure S44. ^{1}H NMR and ^{13}C NMR spectra of **12a**.

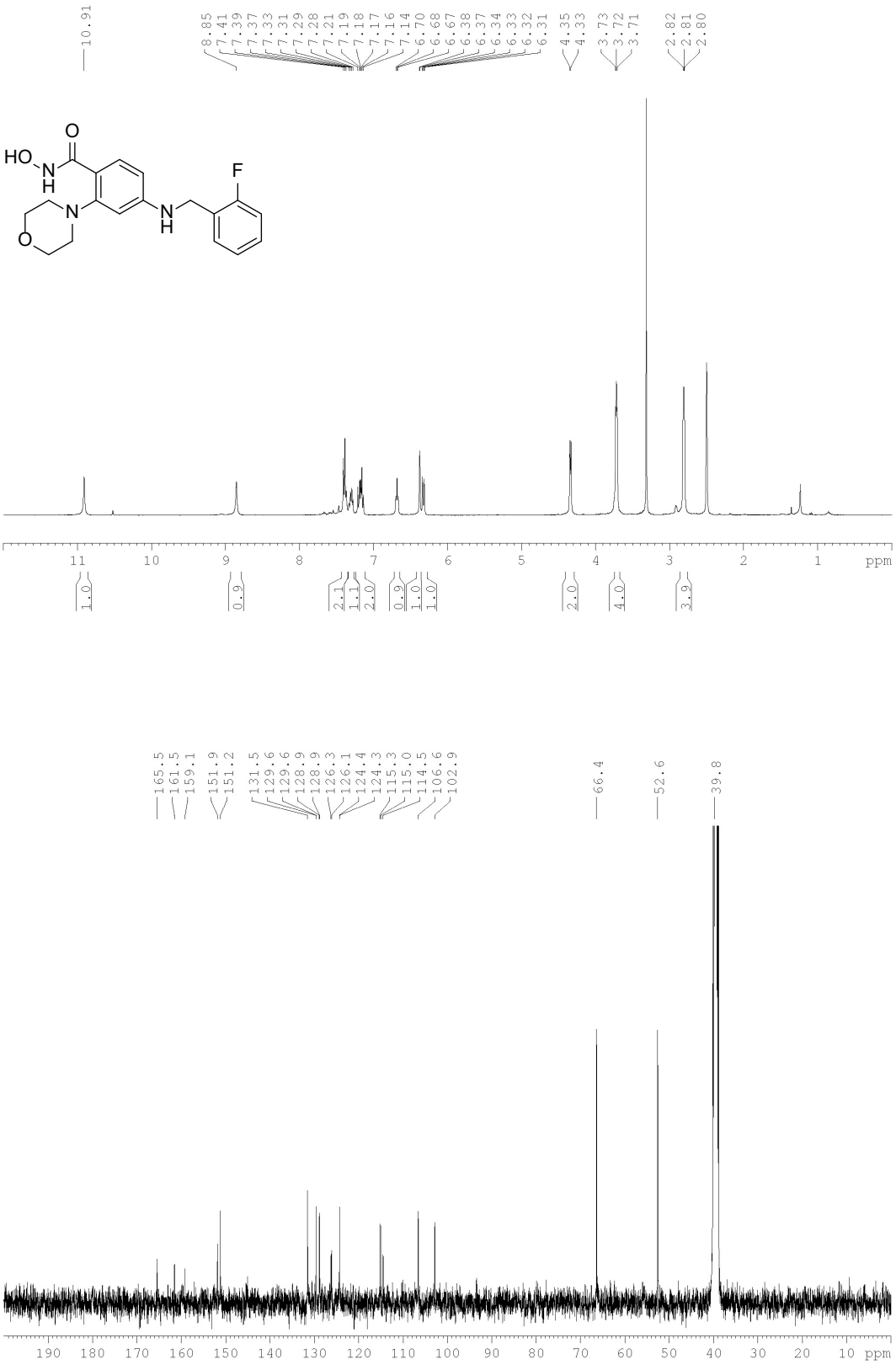


Figure S45. ^{1}H NMR and ^{13}C NMR spectra of **12b**.

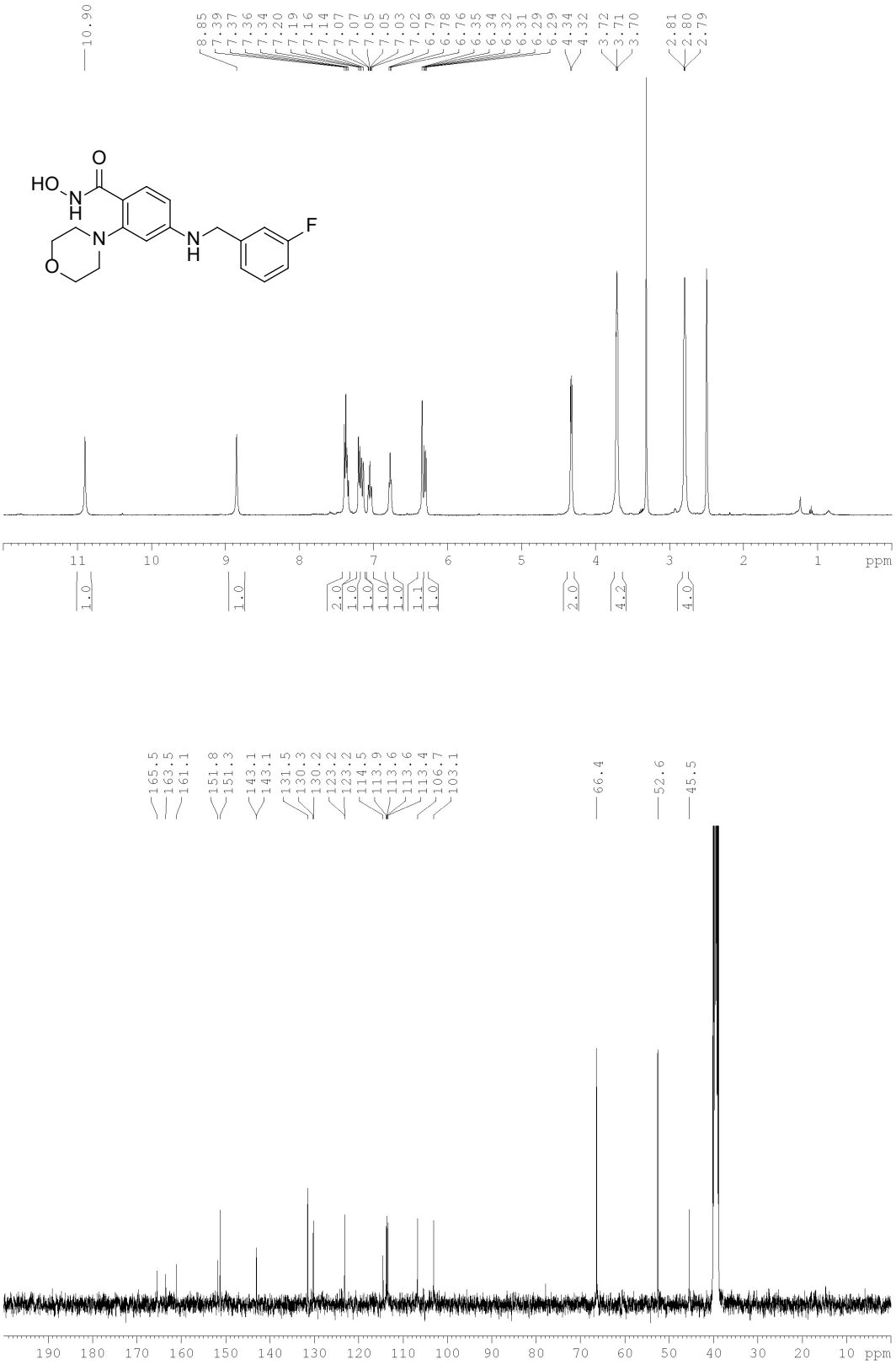


Figure S46. ^{1}H NMR and ^{13}C NMR spectra of **12c**.

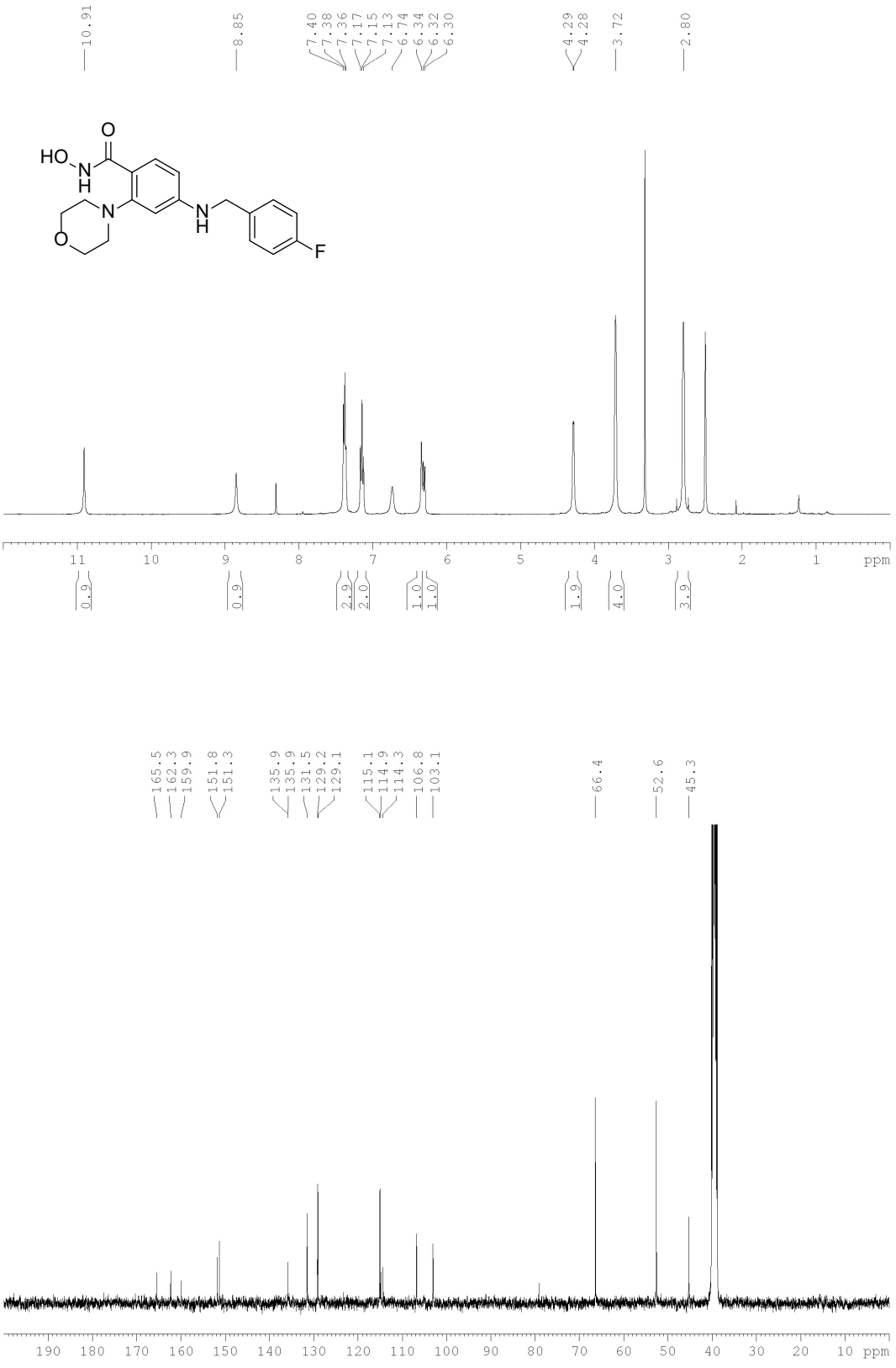


Figure S47. ^{1}H NMR and ^{13}C NMR spectra of **12d**.

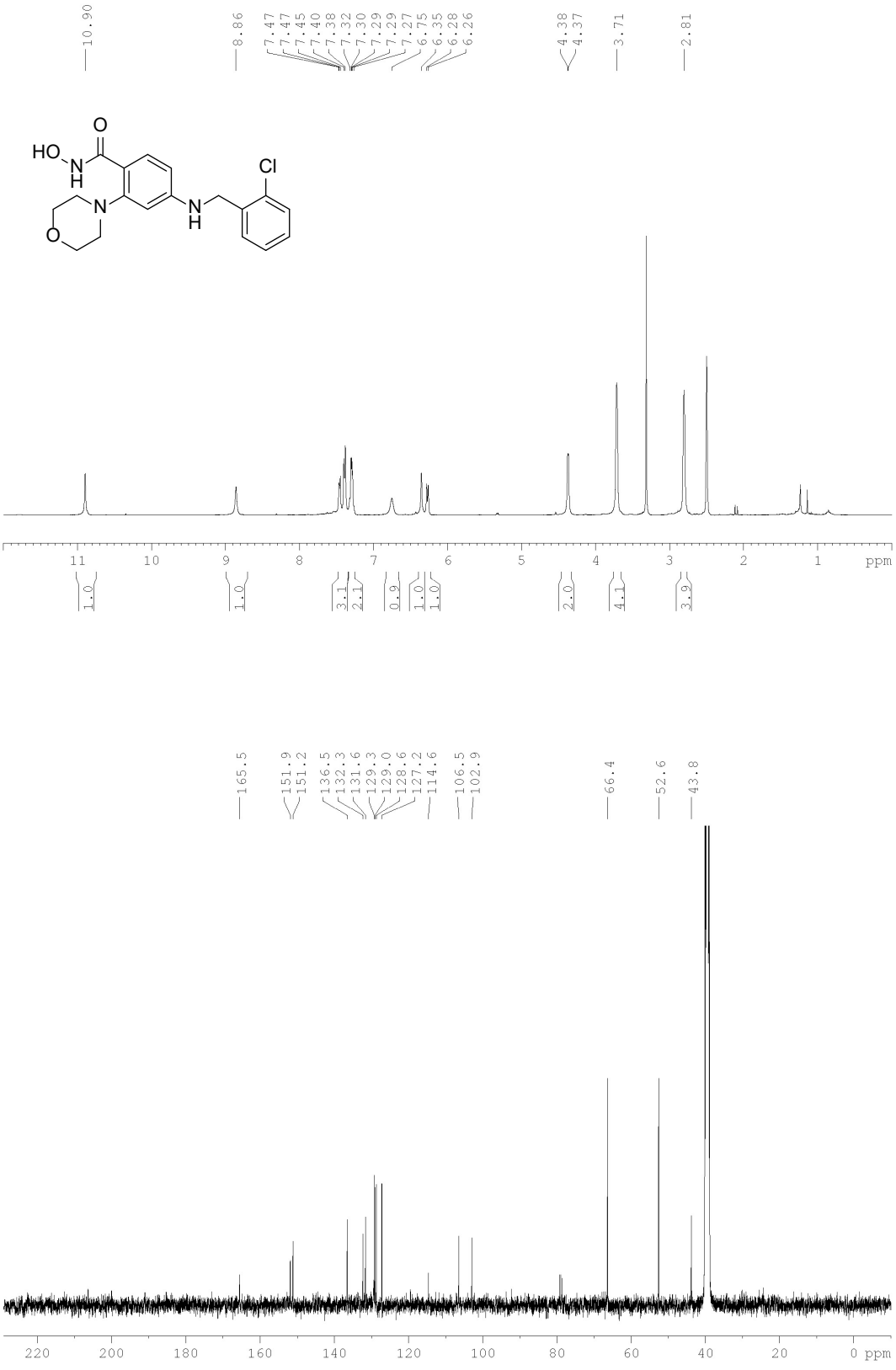


Figure S48. ^{1}H NMR and ^{13}C NMR spectra of **12e**.

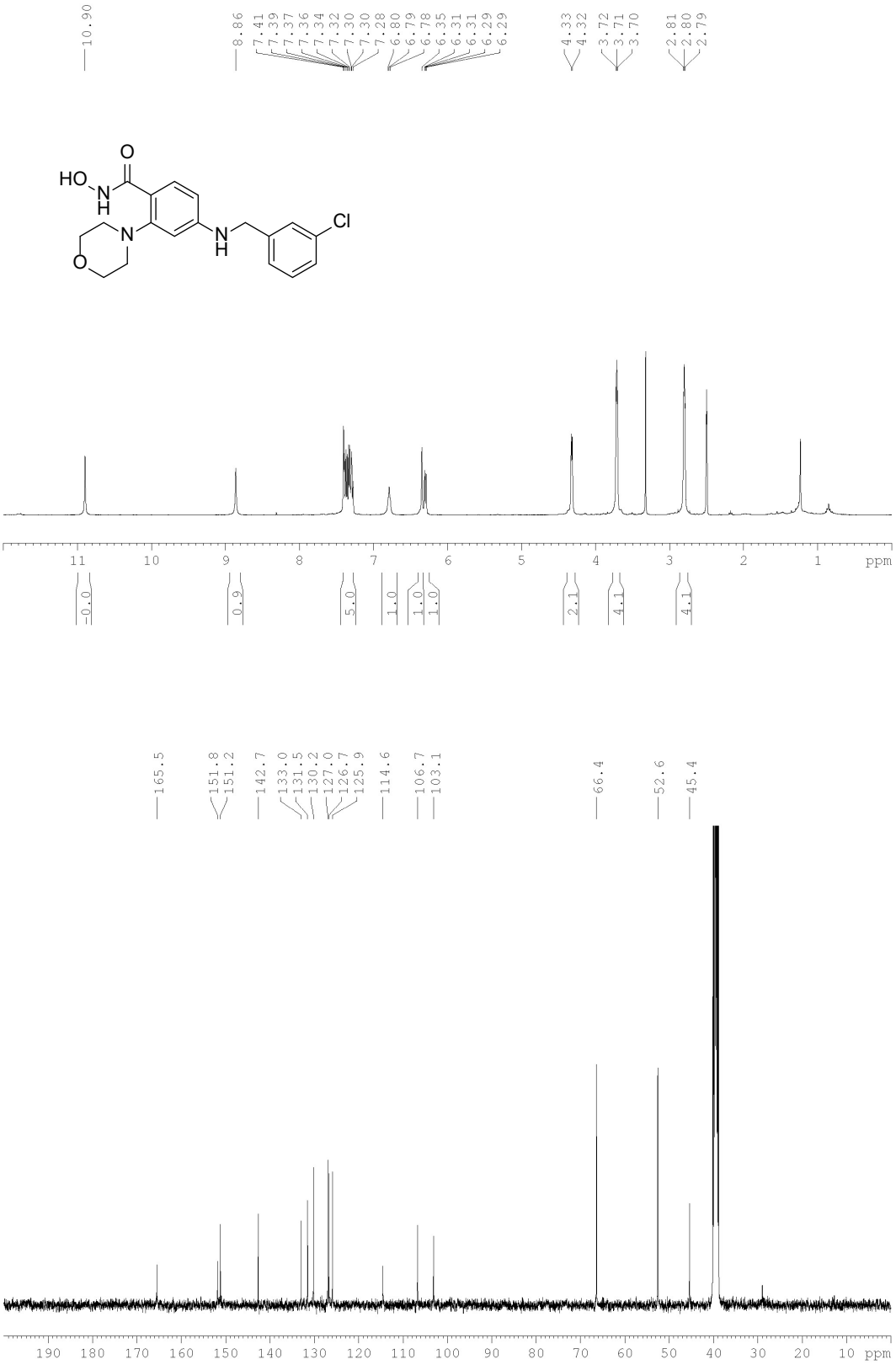


Figure S49. ^{1}H NMR and ^{13}C NMR spectra of **12f**

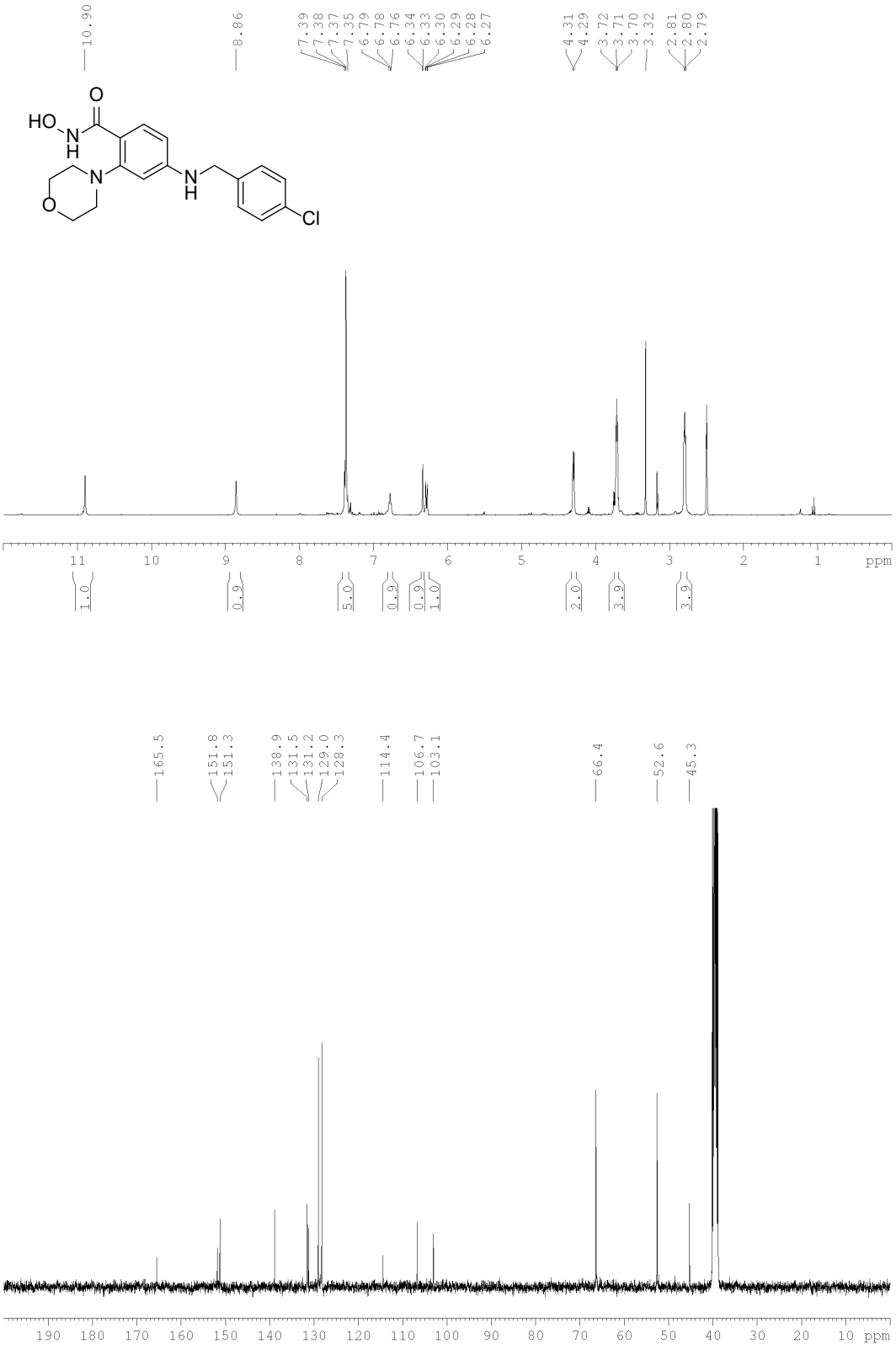


Figure S50. ^{1}H NMR and ^{13}C NMR spectra of **12g**.

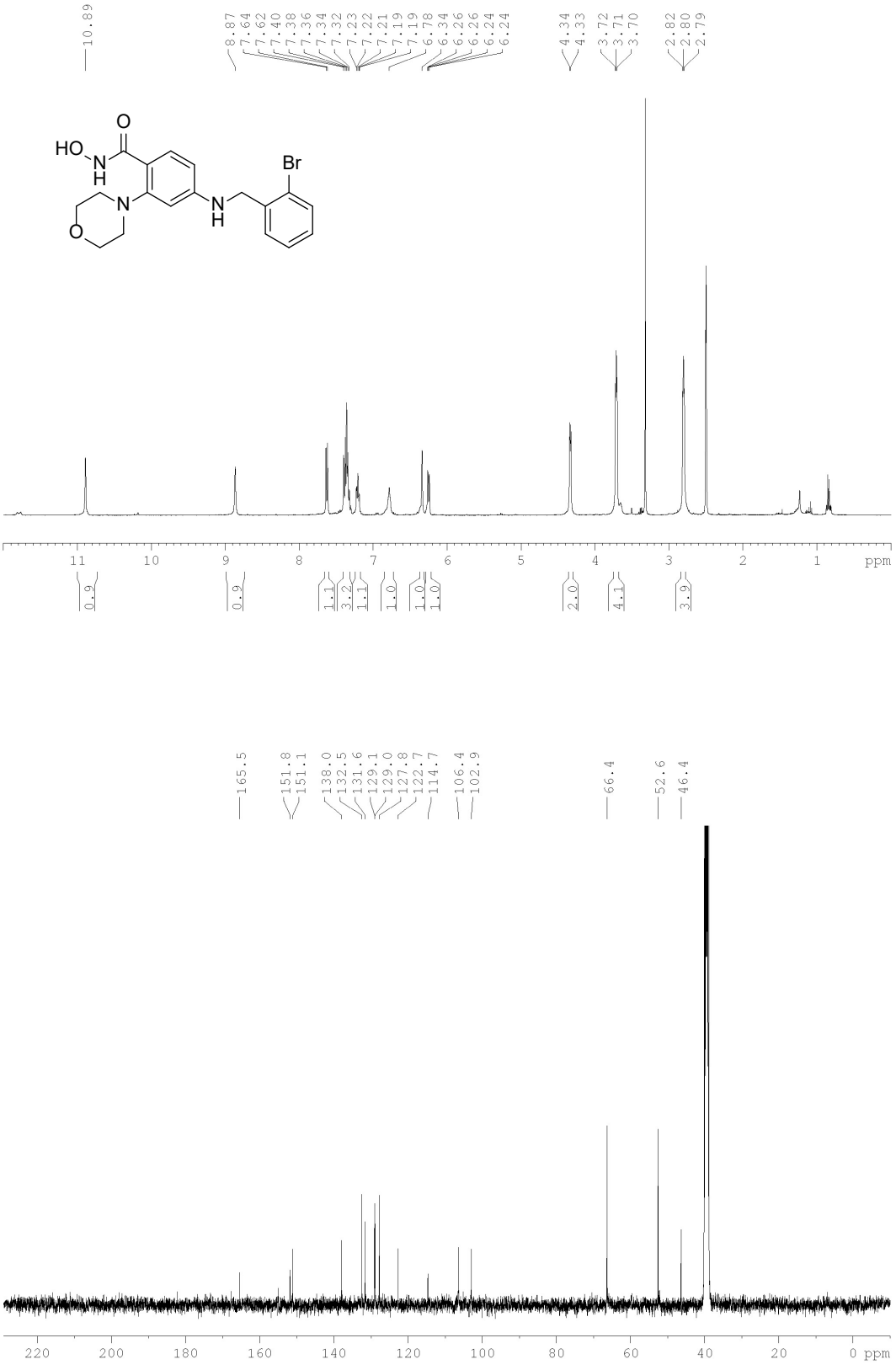


Figure S51. ^{1}H NMR and ^{13}C NMR spectra of **12h**.

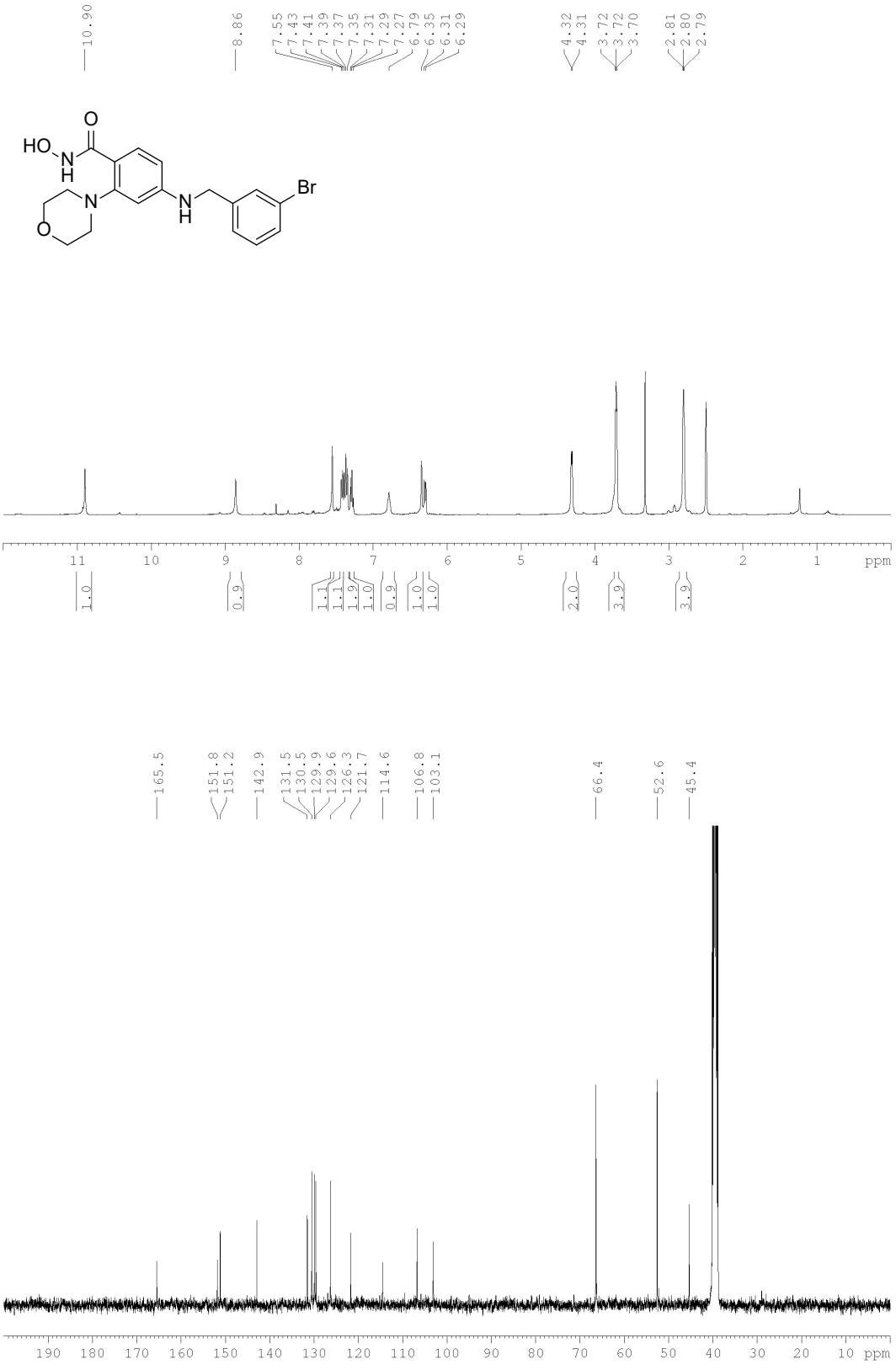


Figure S52. ^{1}H NMR and ^{13}C NMR spectra of **12i**.

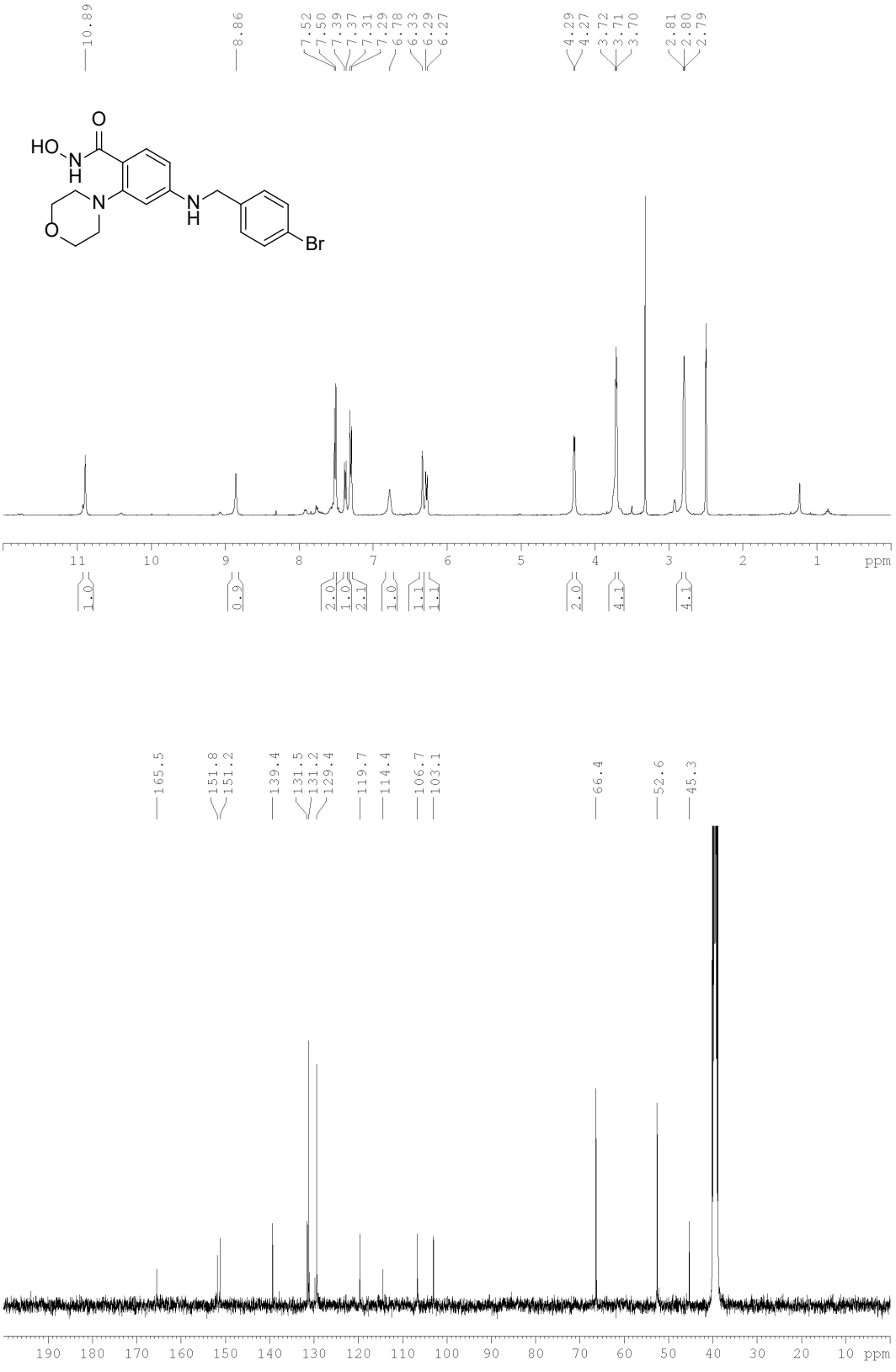


Figure S53. ^{1}H NMR and ^{13}C NMR spectra of **12j**.

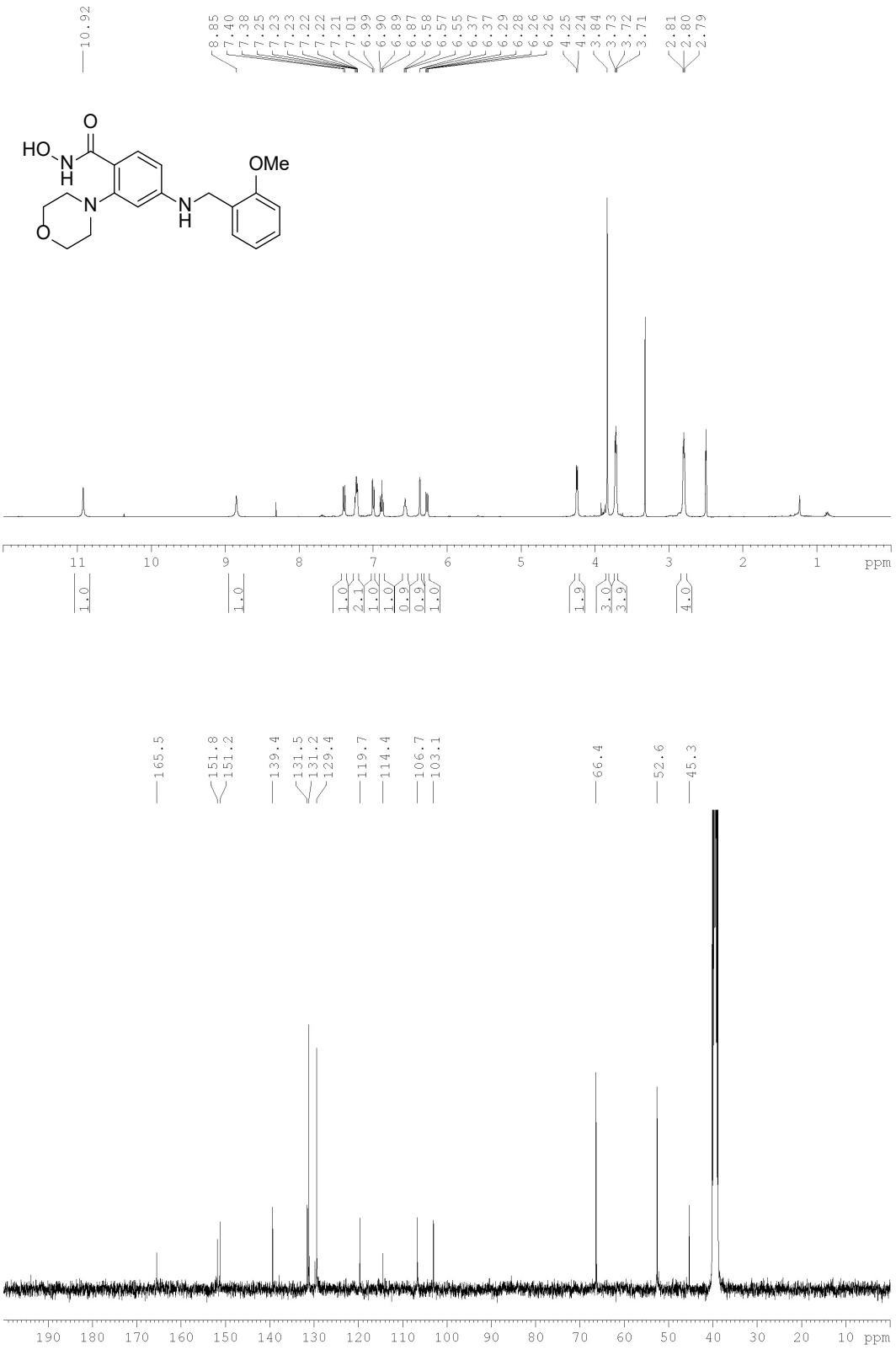


Figure S54. ^{1}H NMR and ^{13}C NMR spectra of **12k**.

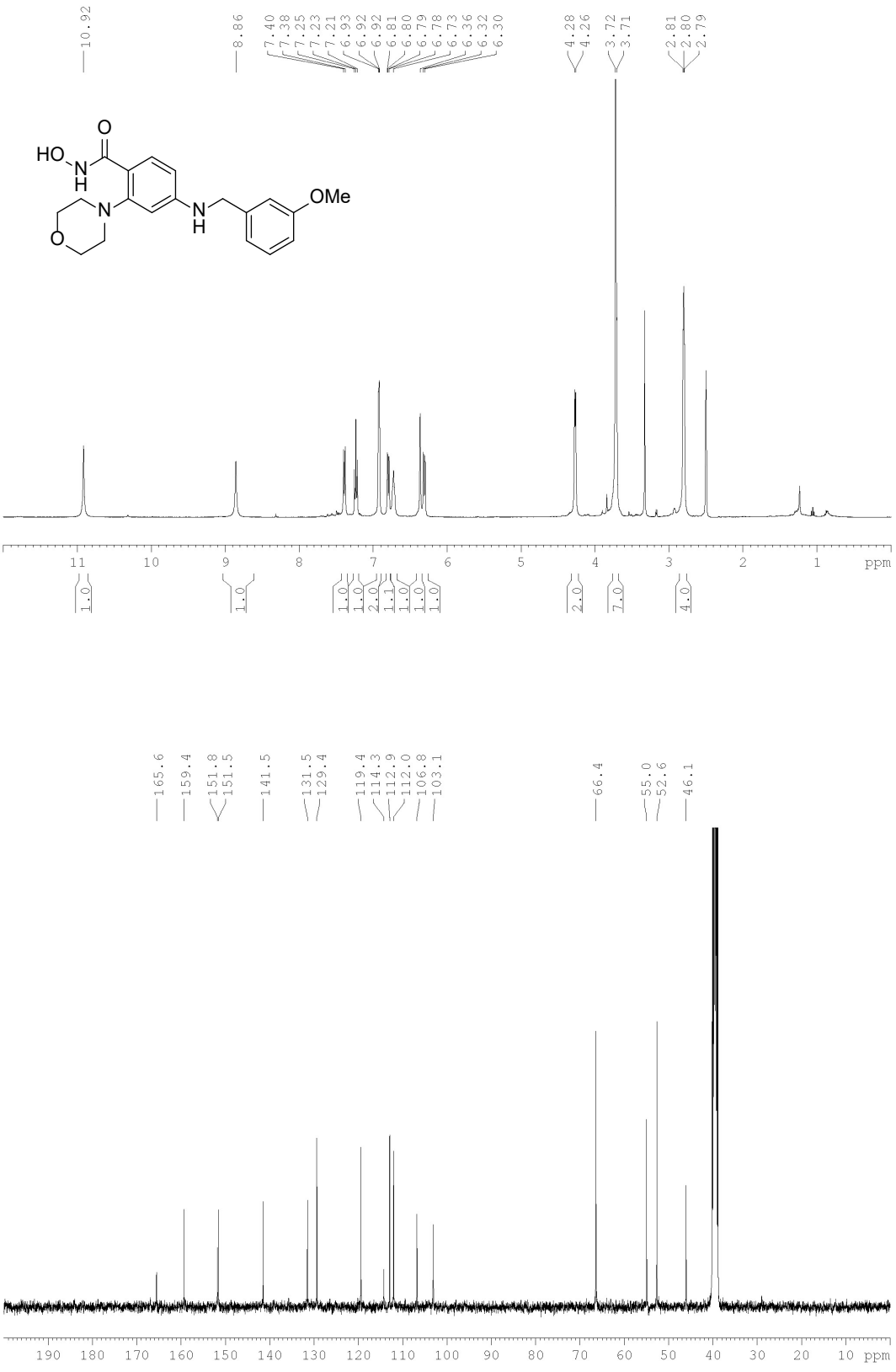


Figure S55. ^{1}H NMR and ^{13}C NMR spectra of **12l**.

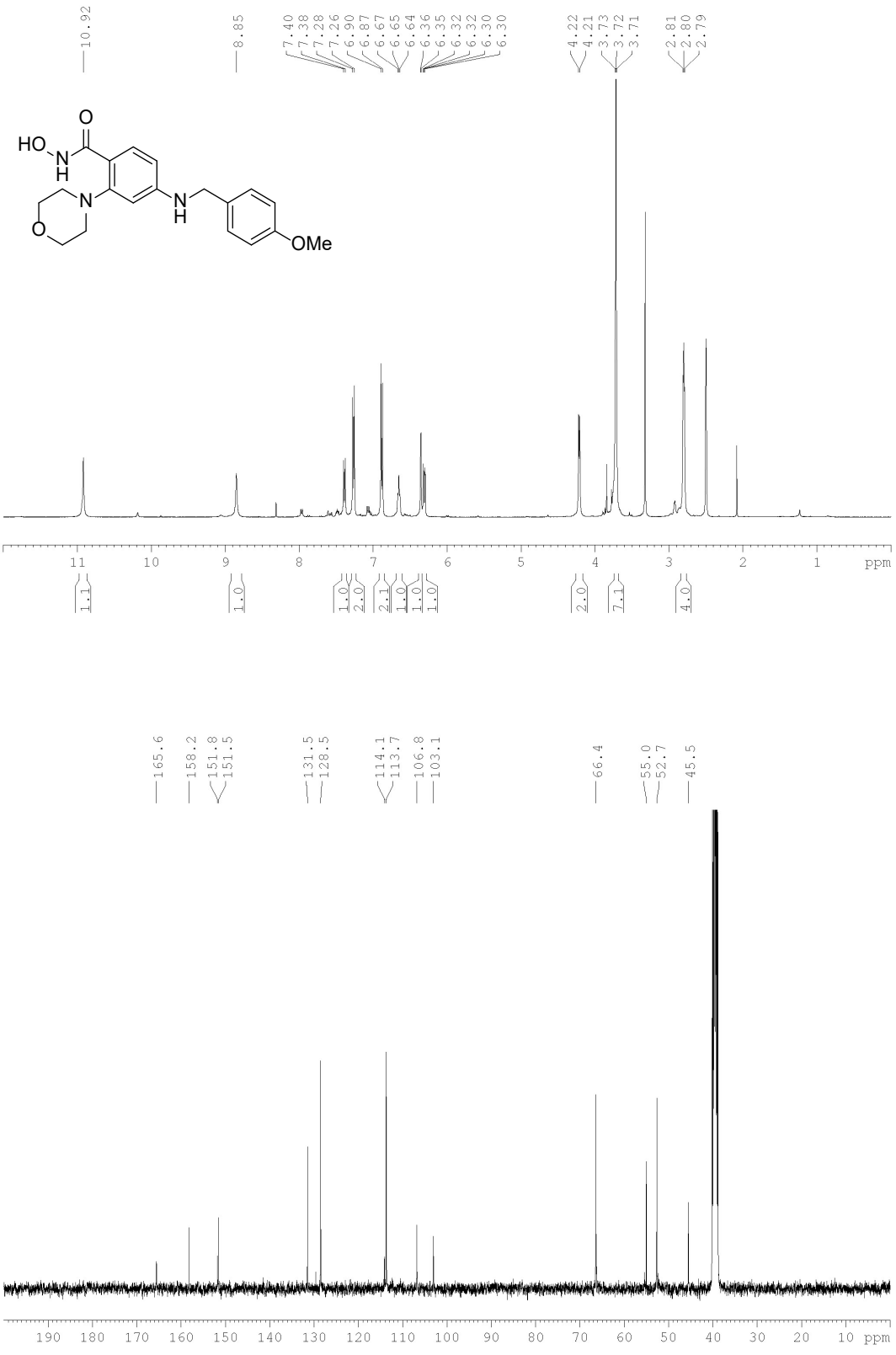


Figure S56. ^{1}H NMR and ^{13}C NMR spectra of **12m**.

^{1}H and ^{13}C NMR spectra for THP-series intermediates **17** and **18**

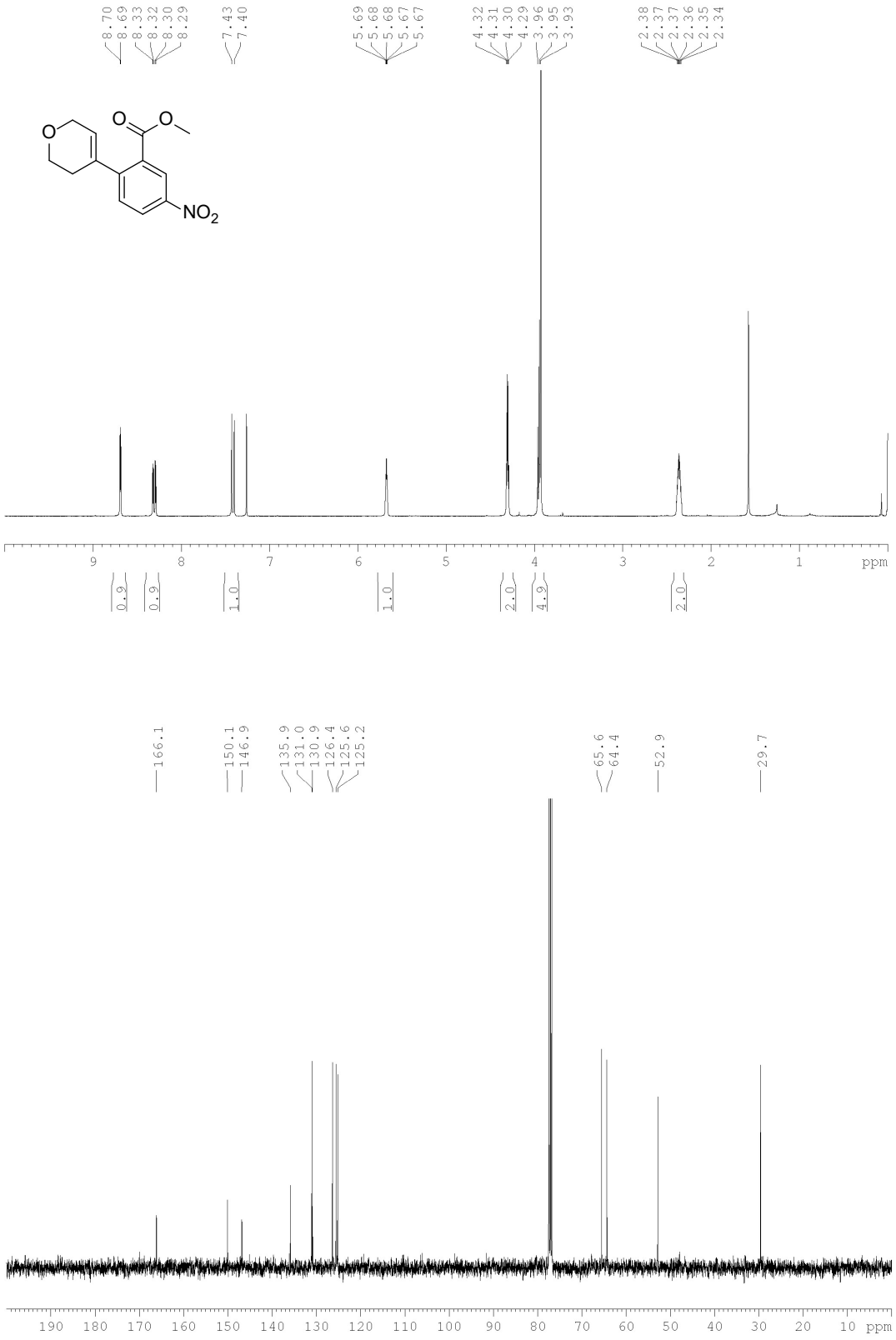


Figure S57. ^{1}H NMR and ^{13}C NMR spectra of **17**.

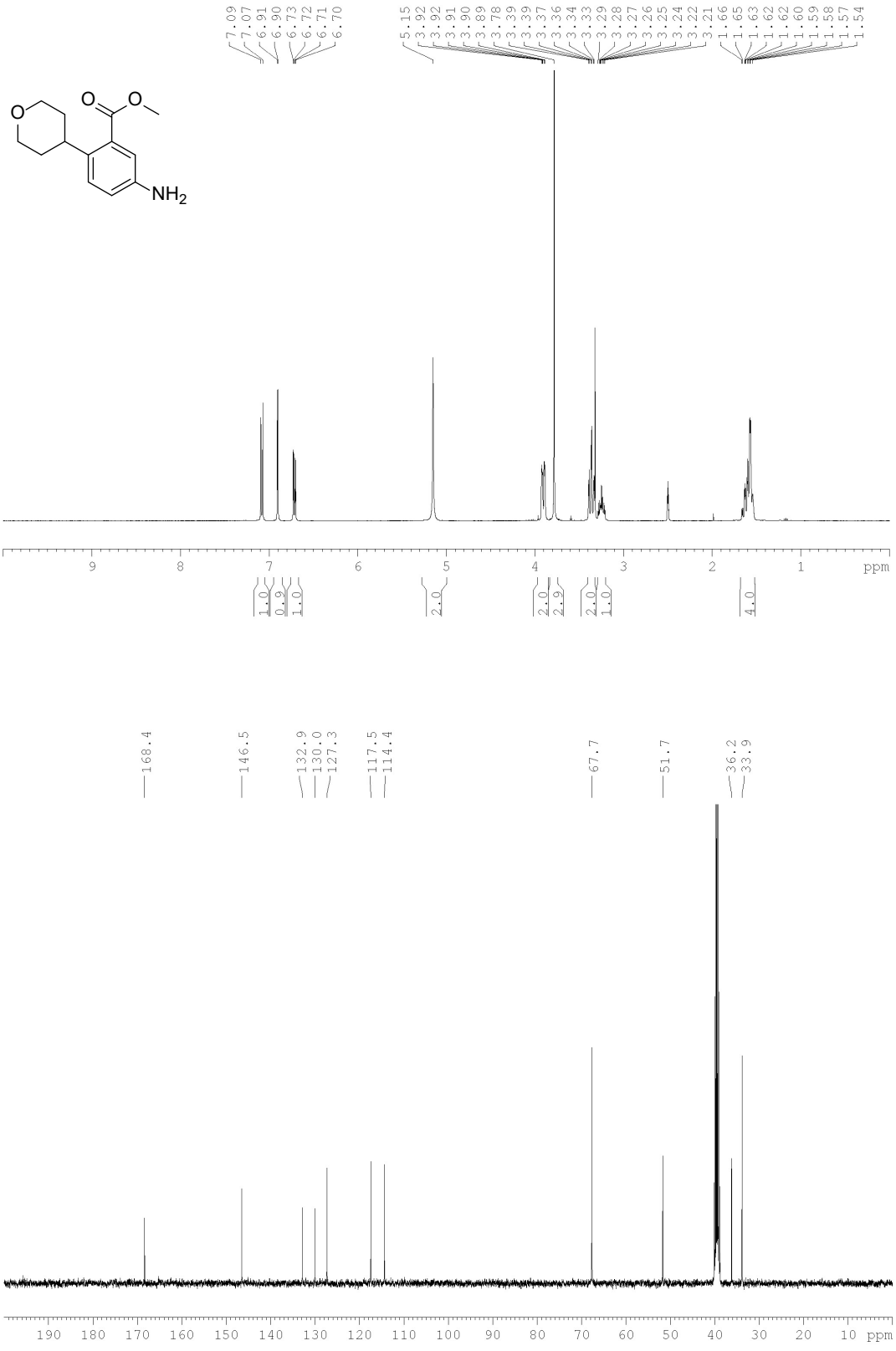


Figure S58. ^{1}H NMR and ^{13}C NMR spectra of **18**.

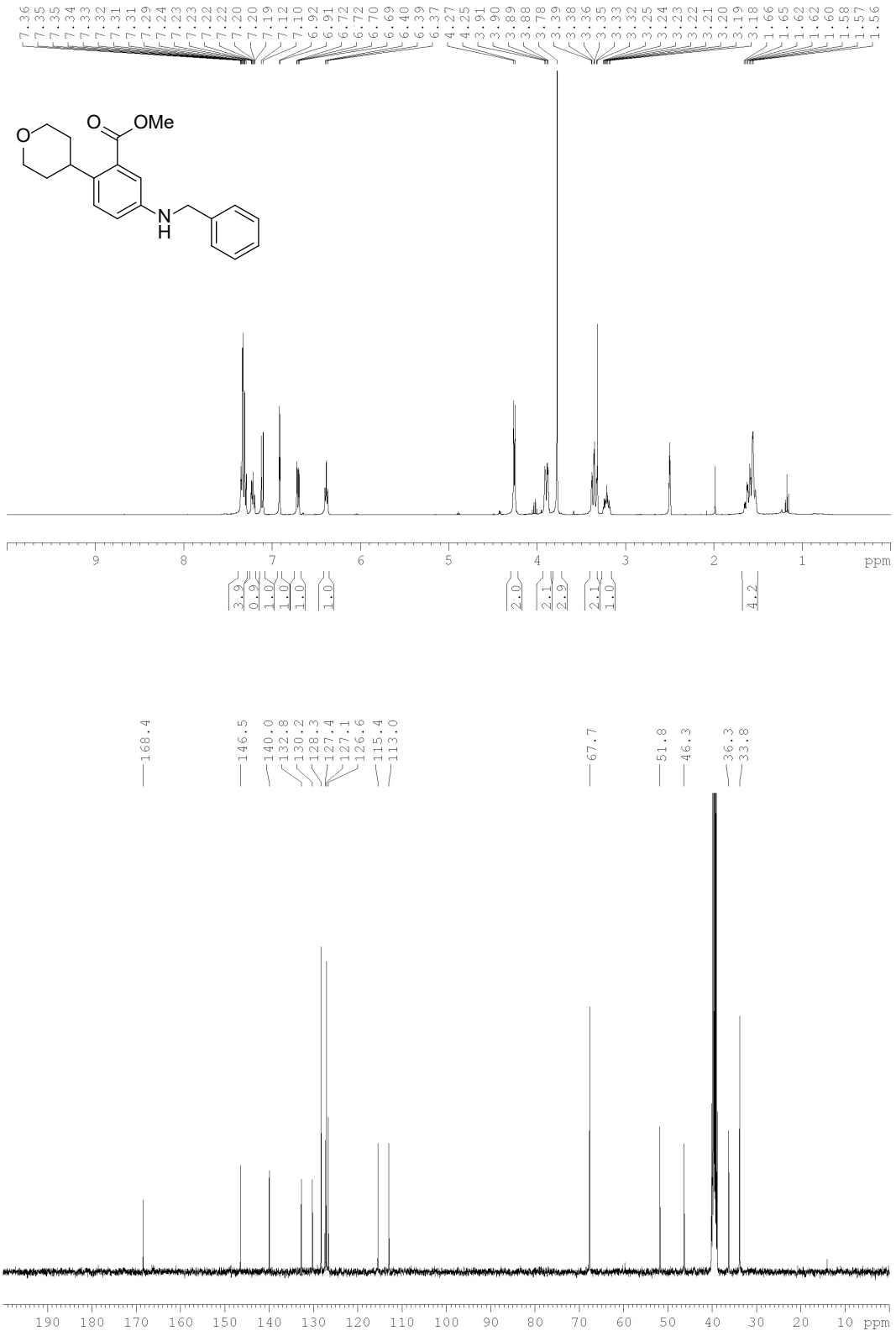


Figure S59. ^{1}H NMR and ^{13}C NMR spectra of **19a**.

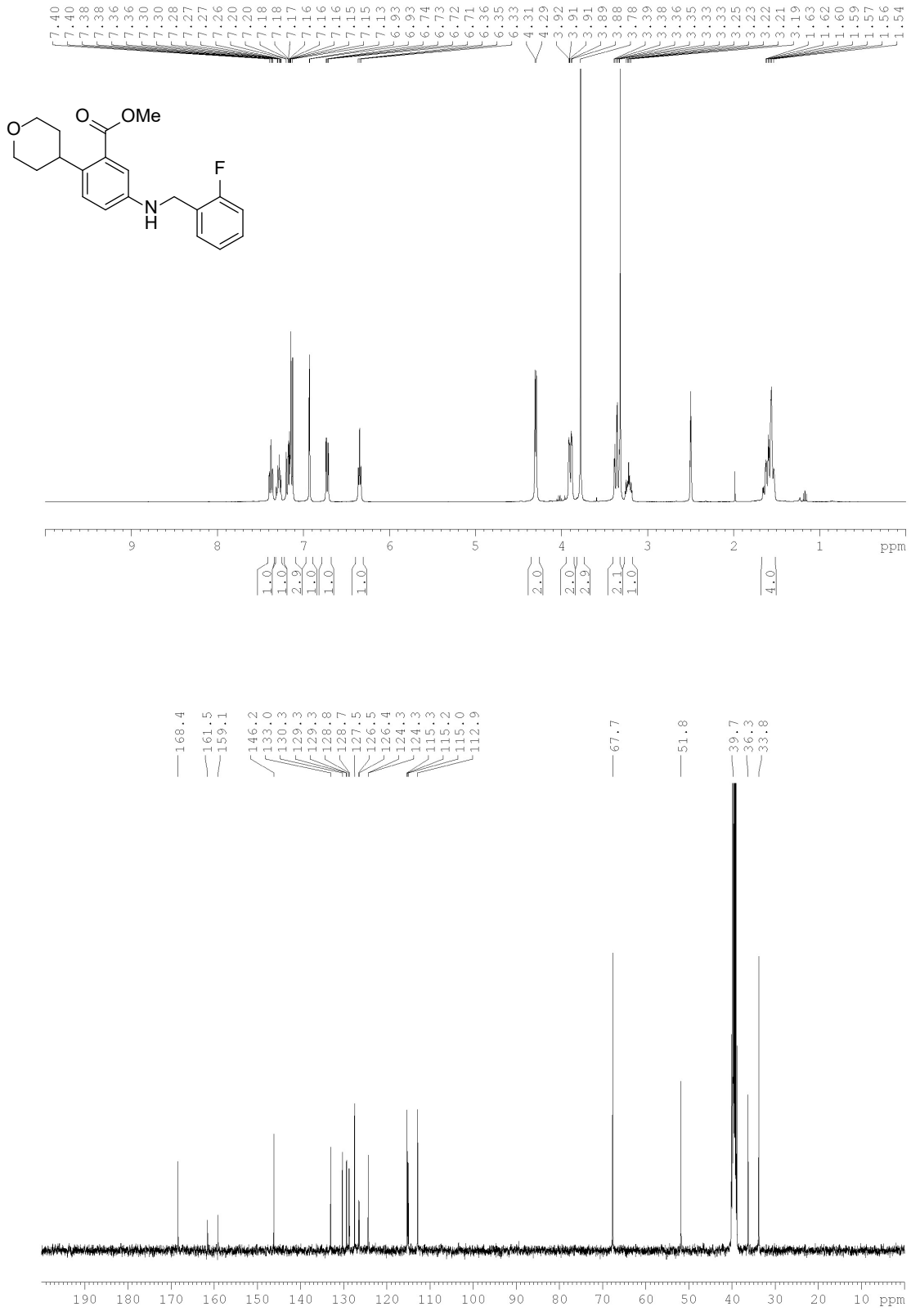


Figure S60. ^{1}H NMR and ^{13}C NMR spectra of **19b**.

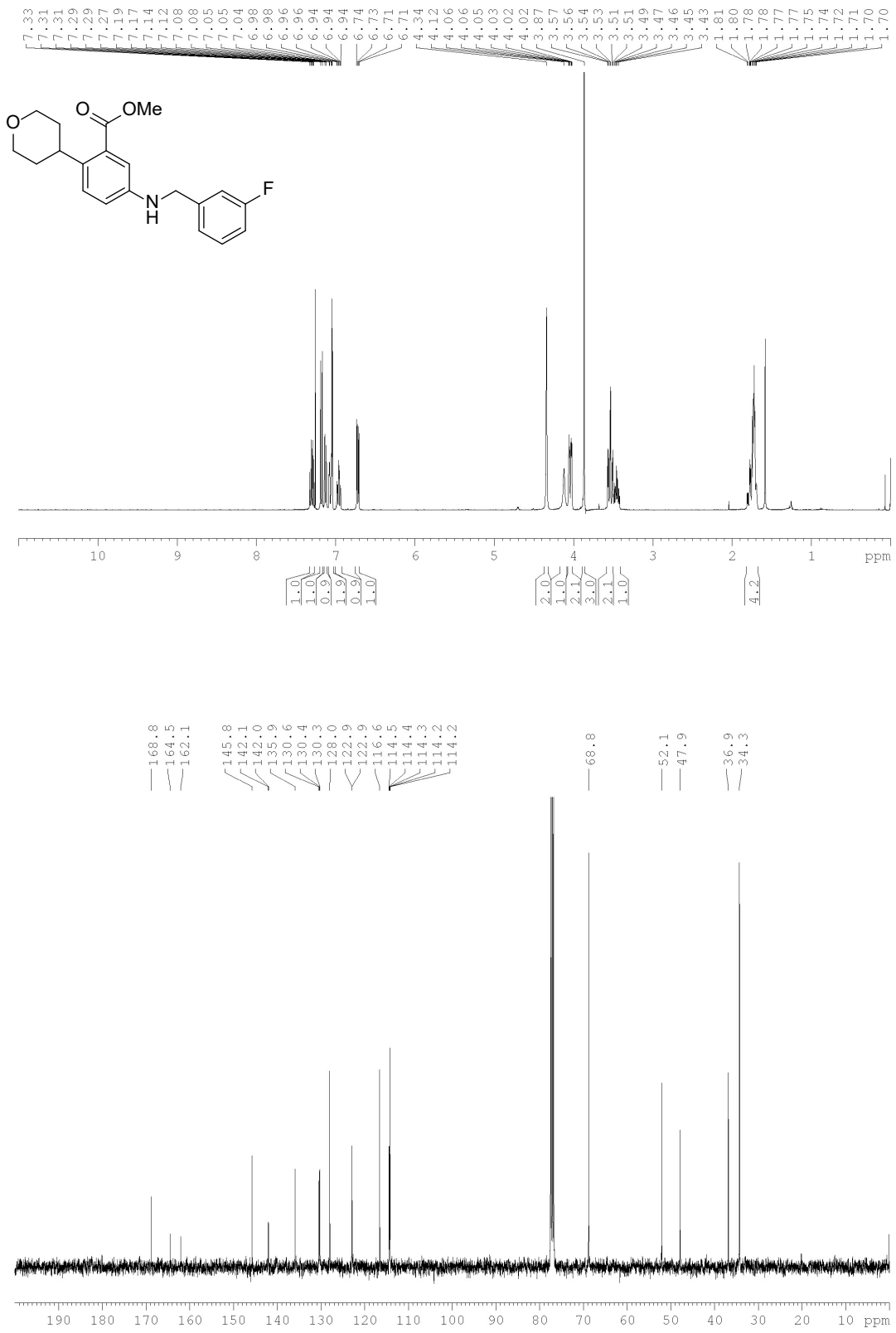


Figure S61. ^{1}H NMR and ^{13}C NMR spectra of **19c**.

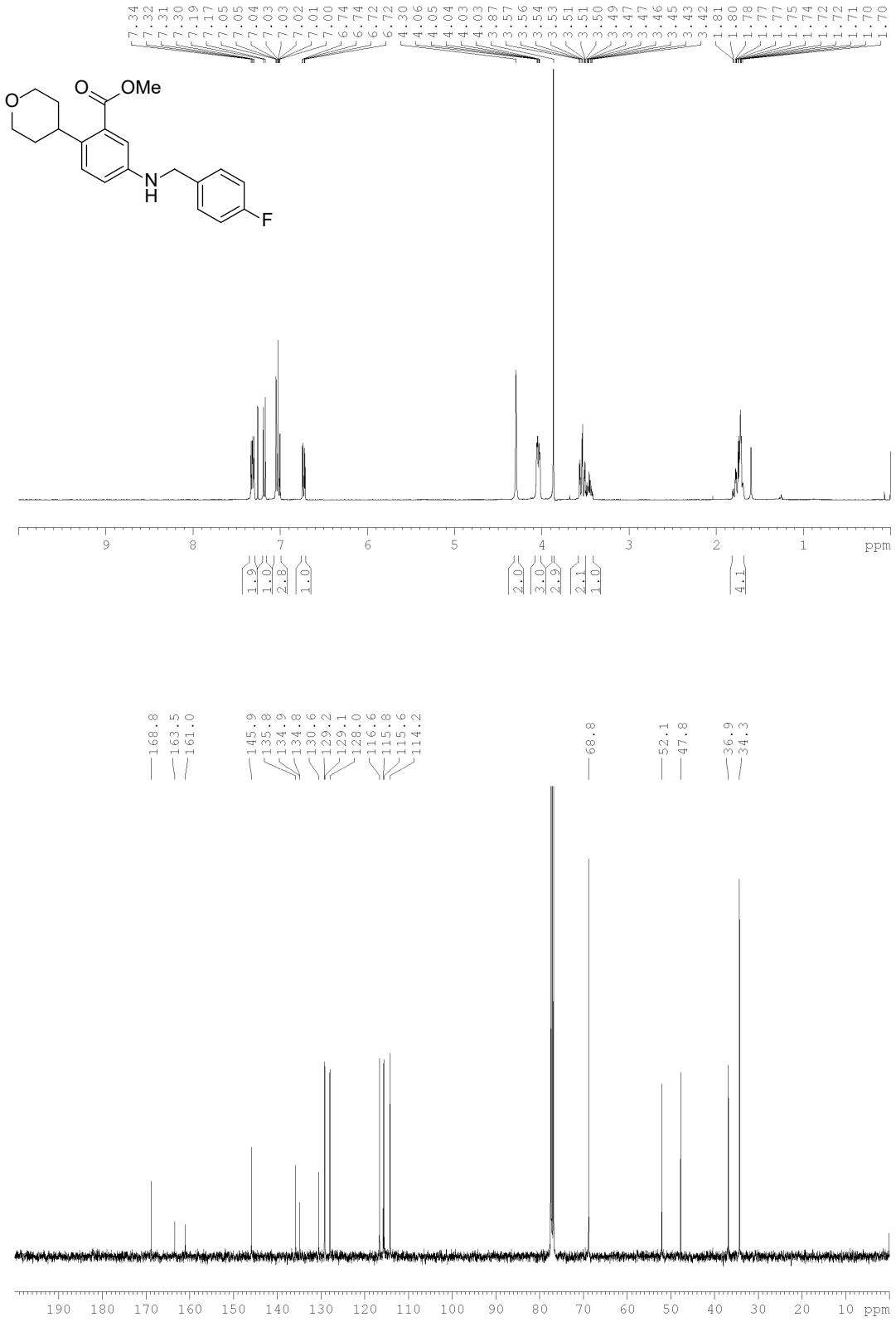


Figure S62. ^{1}H NMR and ^{13}C NMR spectra of **19d**.

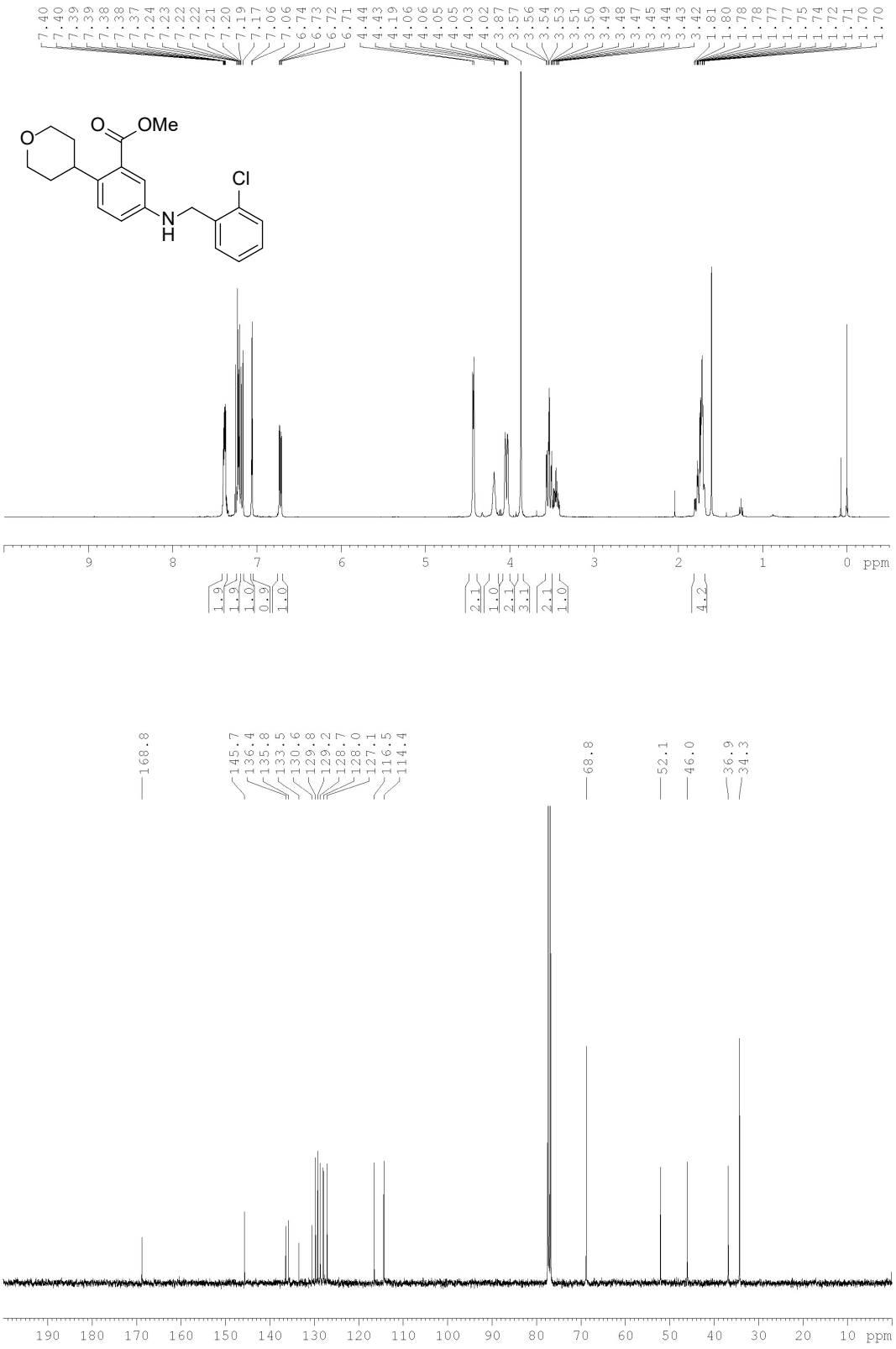


Figure S63. ^{1}H NMR and ^{13}C NMR spectra of **19e**.

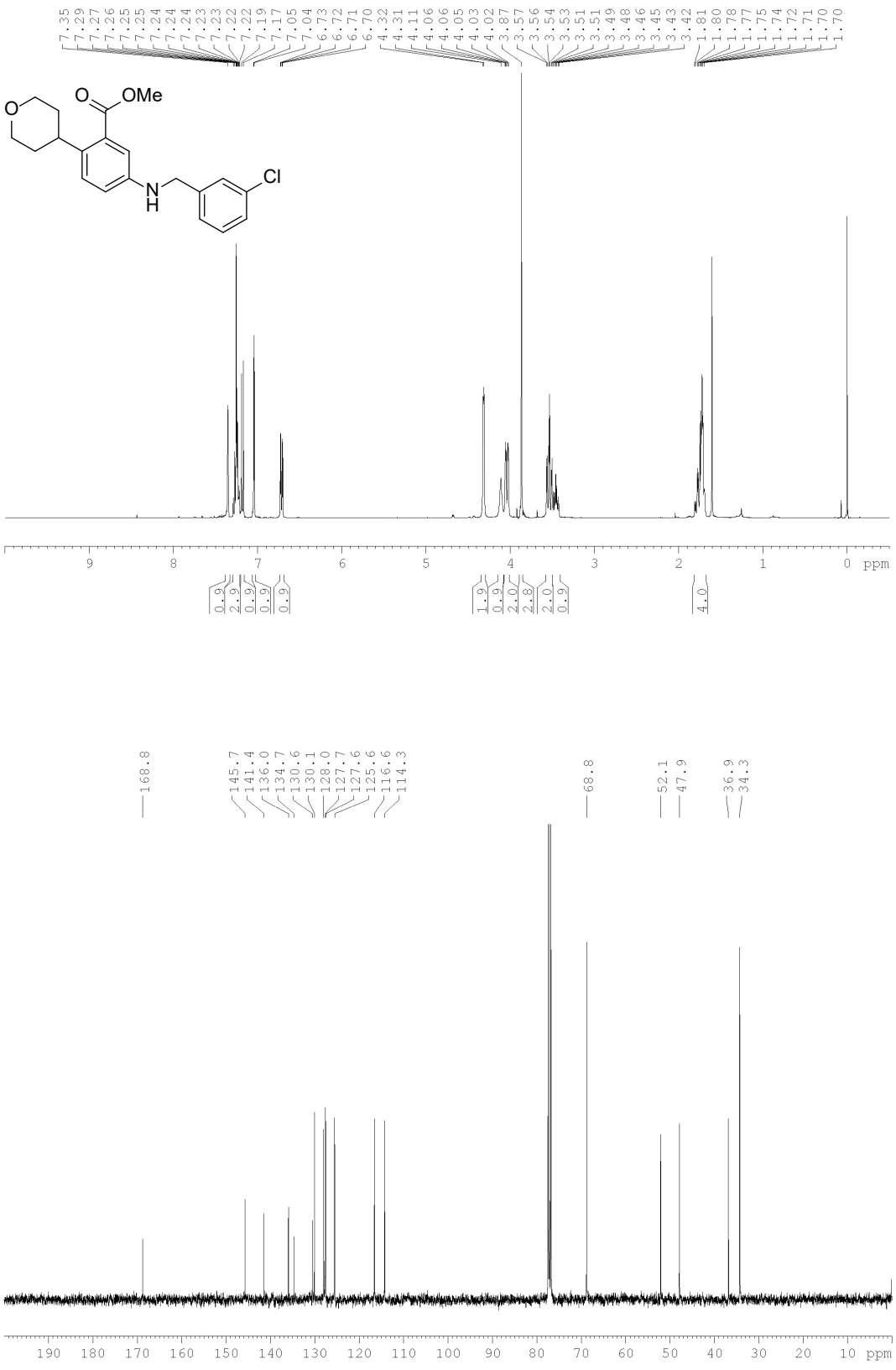


Figure S64. ^{1}H NMR and ^{13}C NMR spectra of **19f**.

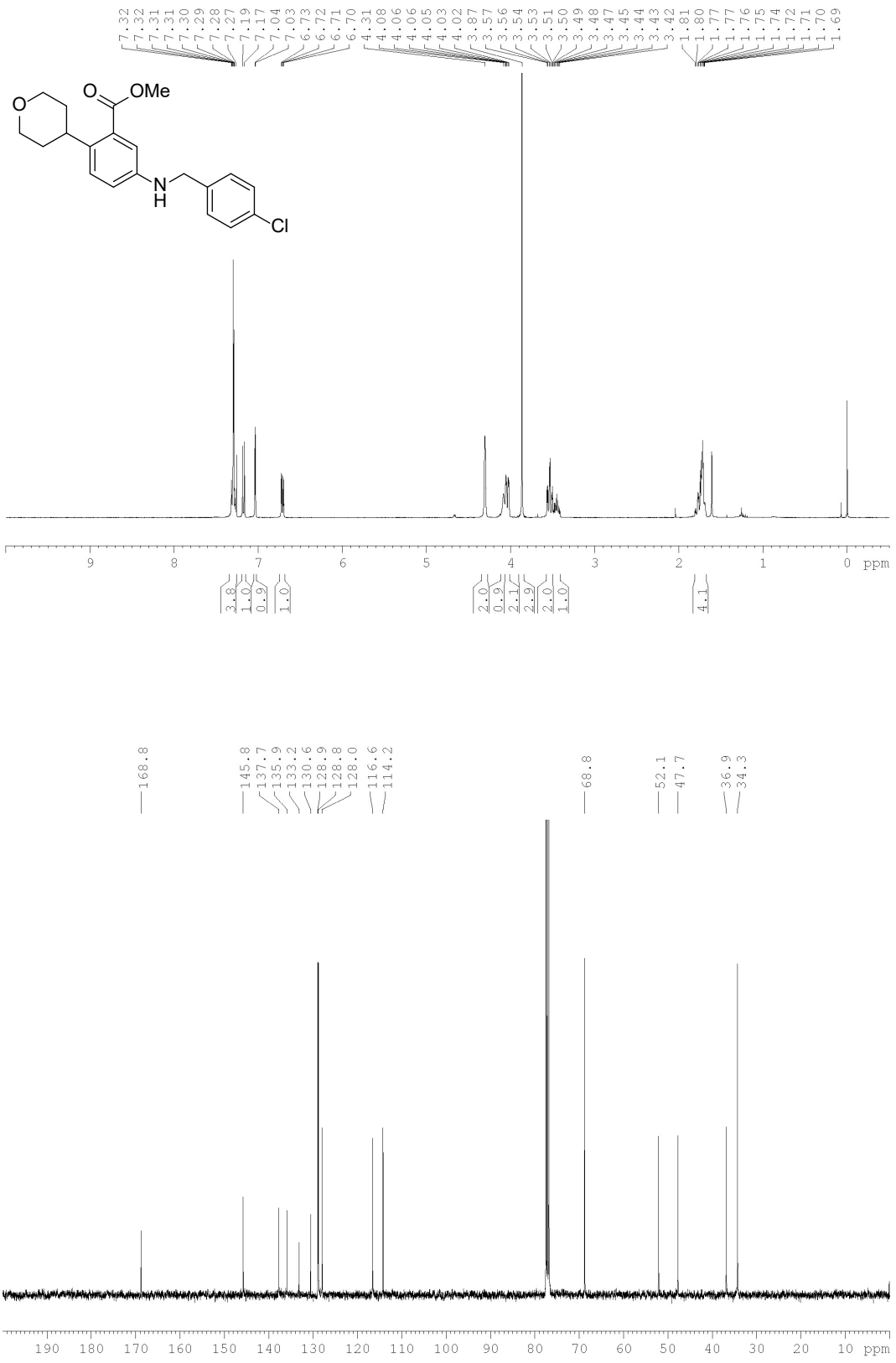


Figure S65. ^{1}H NMR and ^{13}C NMR spectra of **19g**.

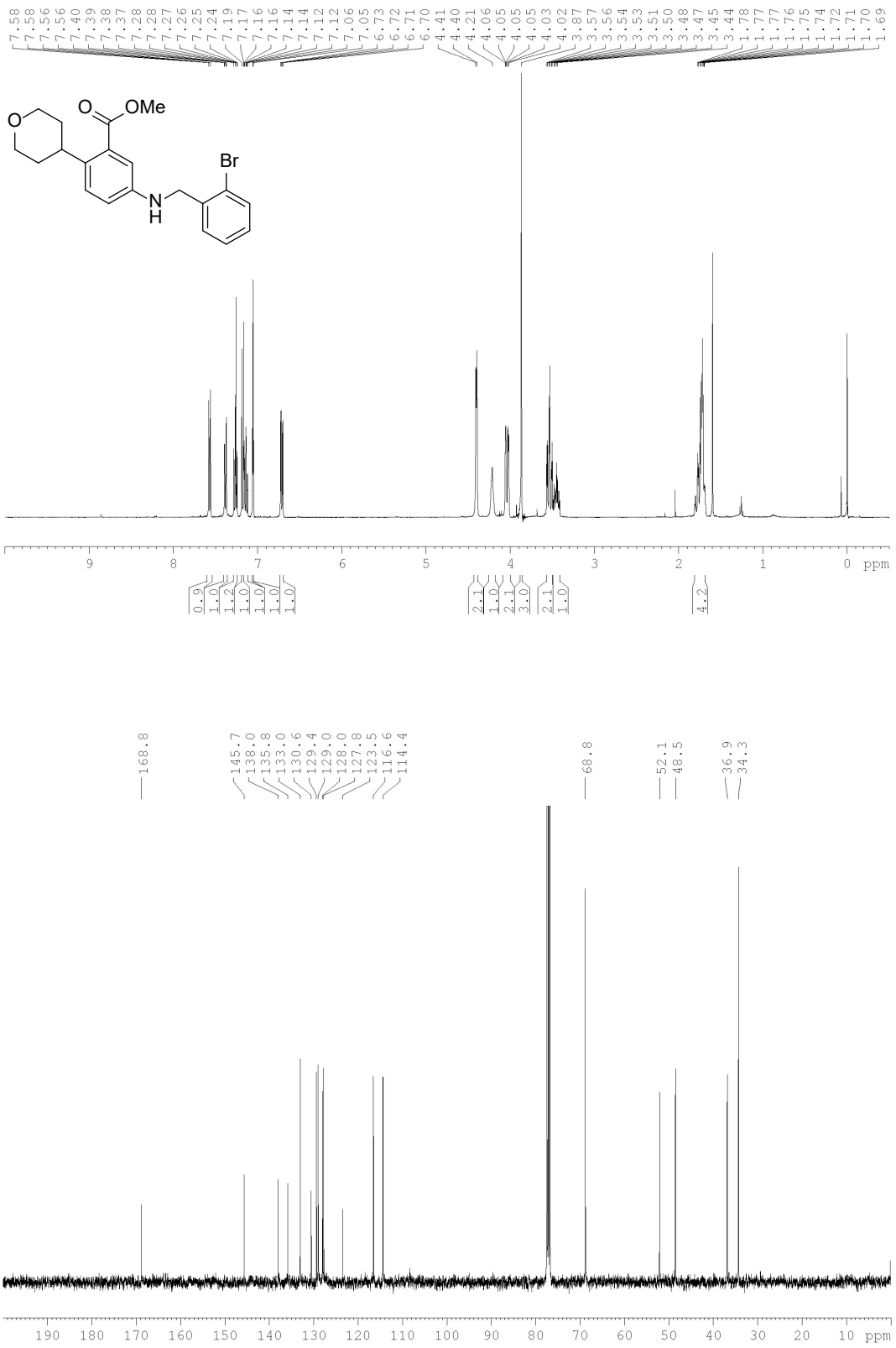


Figure S66. ^{1}H NMR and ^{13}C NMR spectra of **19h**.

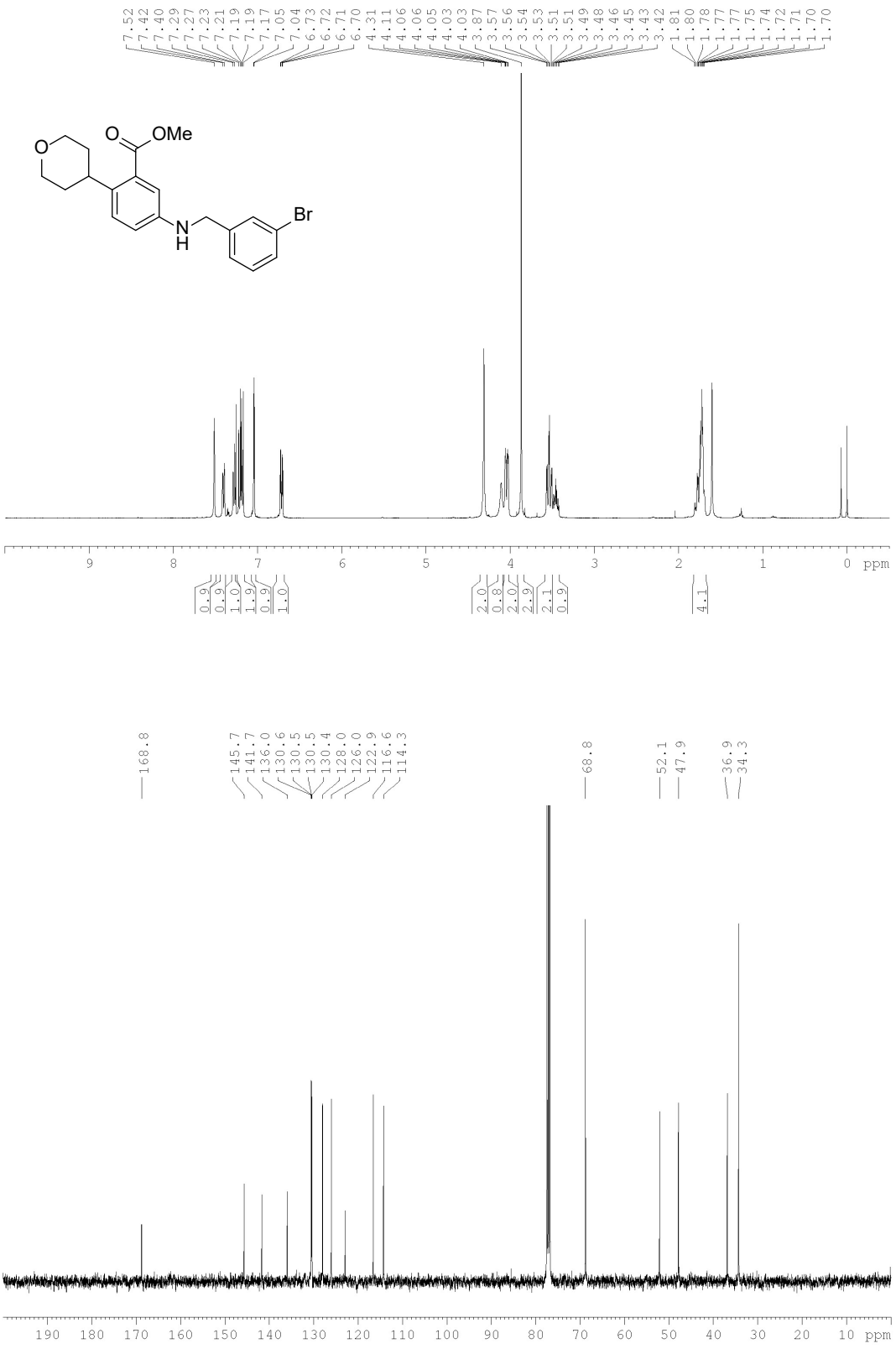


Figure S67. ^{1}H NMR and ^{13}C NMR spectra of **19i**.

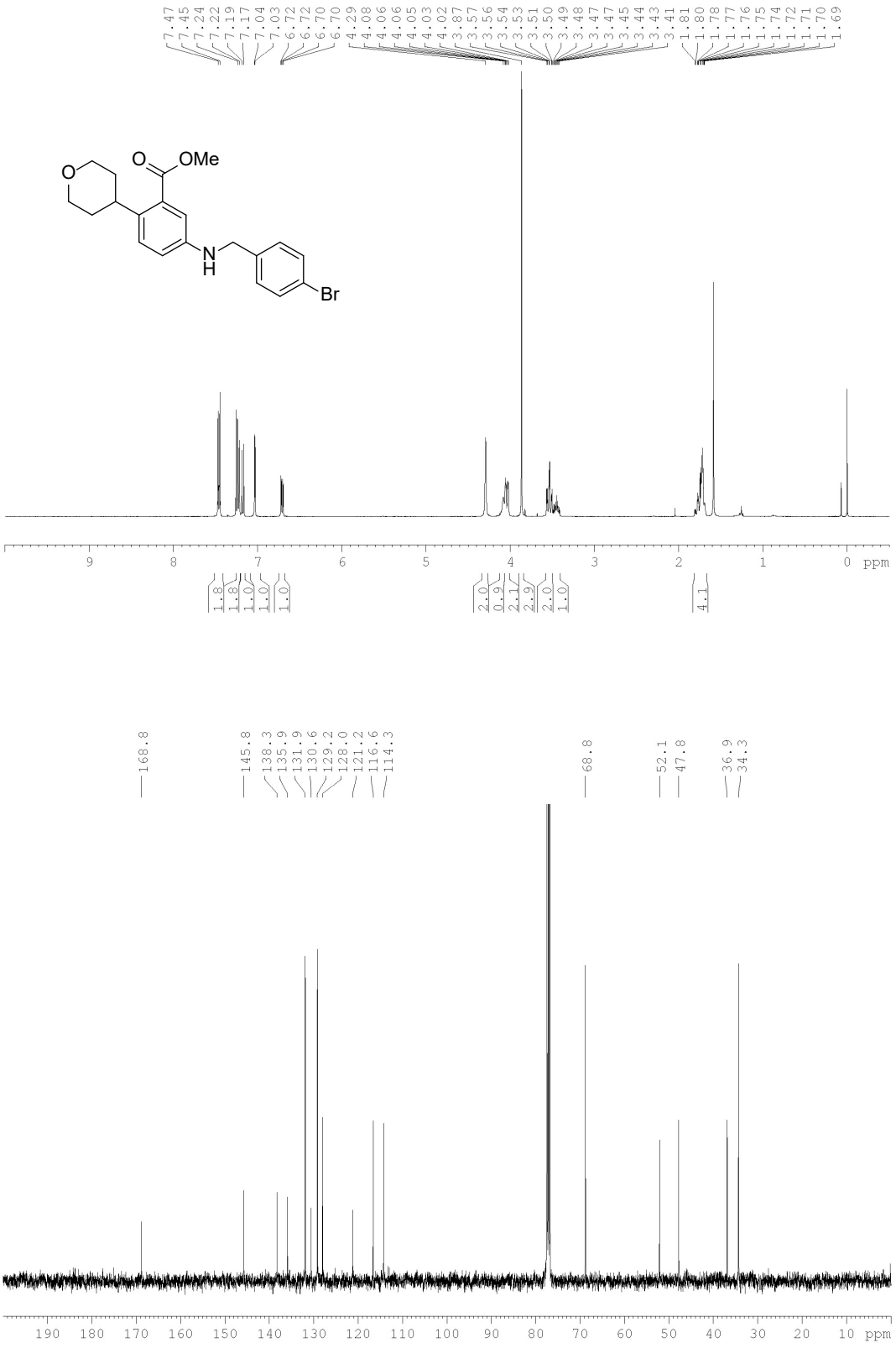


Figure S68. ^{1}H NMR and ^{13}C NMR spectra of **19j**.

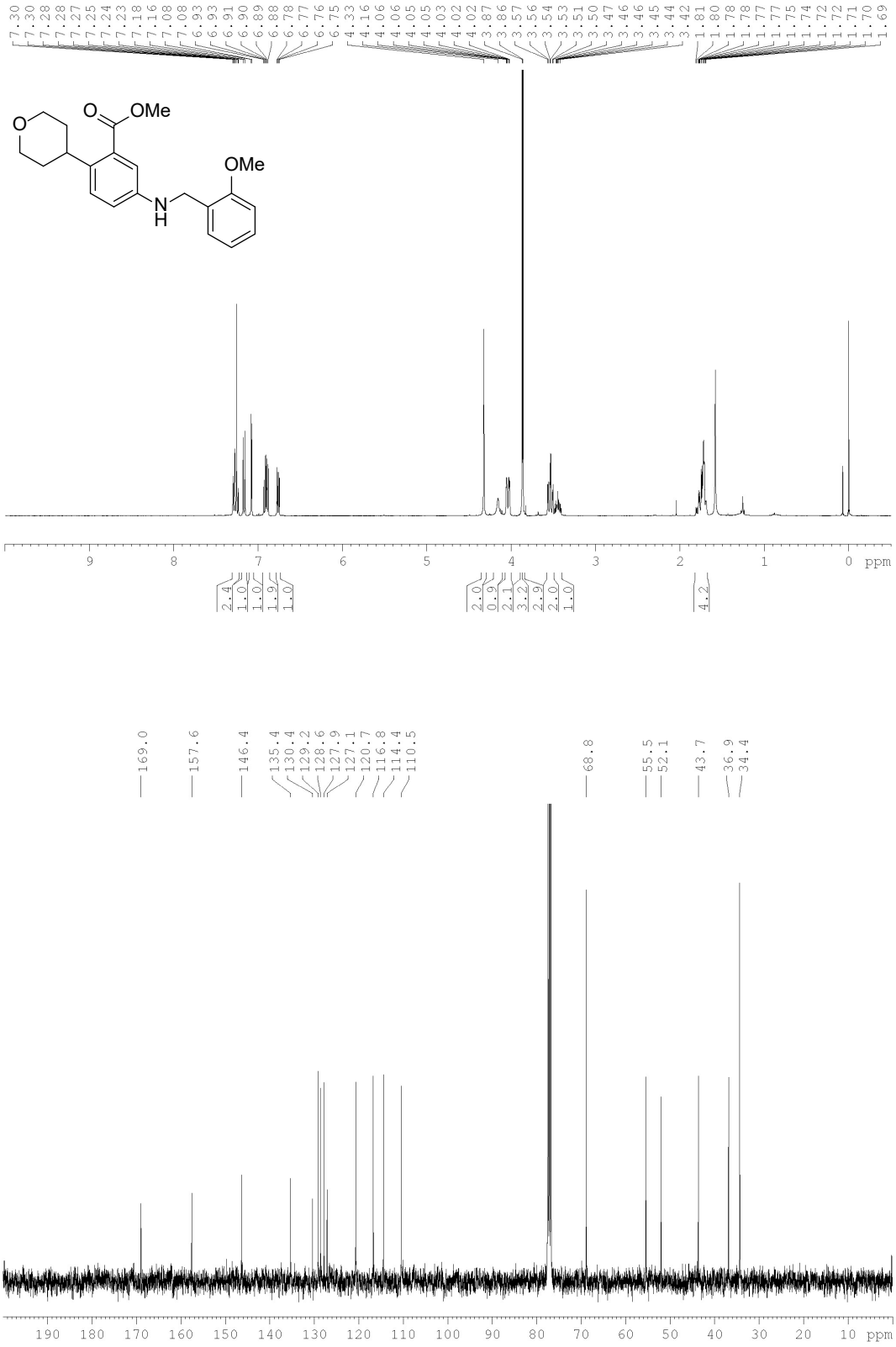


Figure S69. ^{1}H NMR and ^{13}C NMR spectra of **19k**.

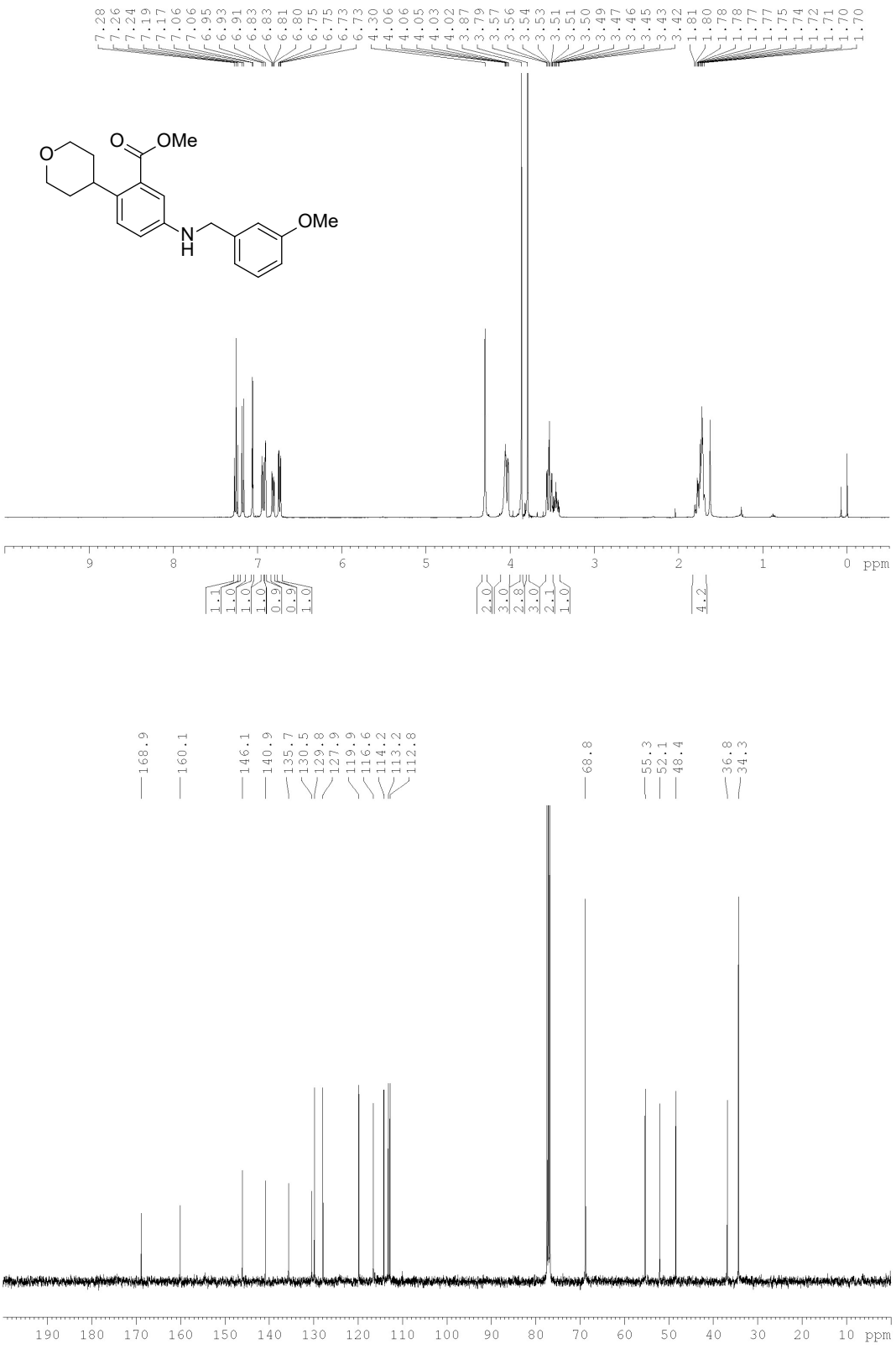


Figure S70. ^{1}H NMR and ^{13}C NMR spectra of **19l**.

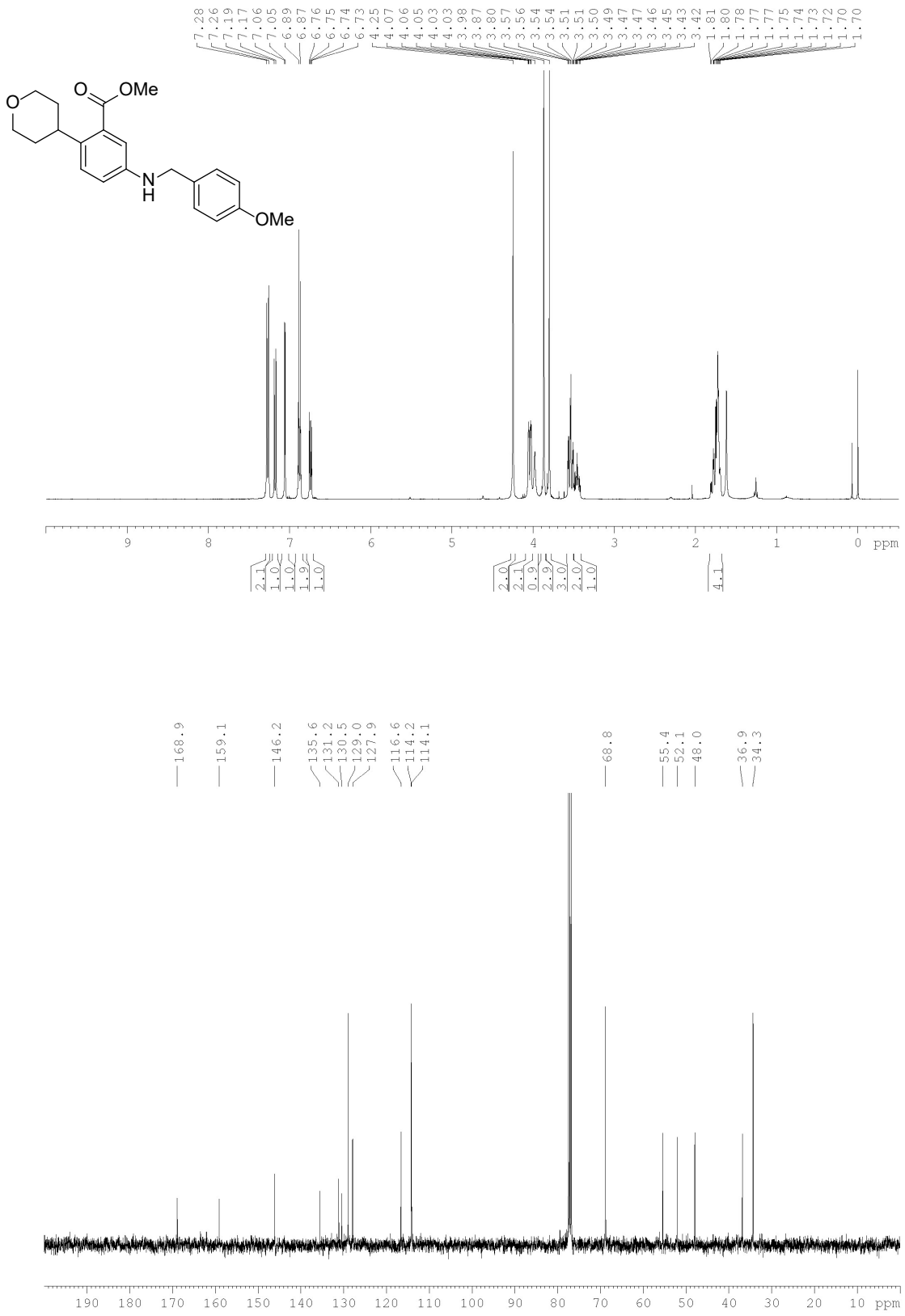


Figure S71. ^{1}H NMR and ^{13}C NMR spectra of **19m**.

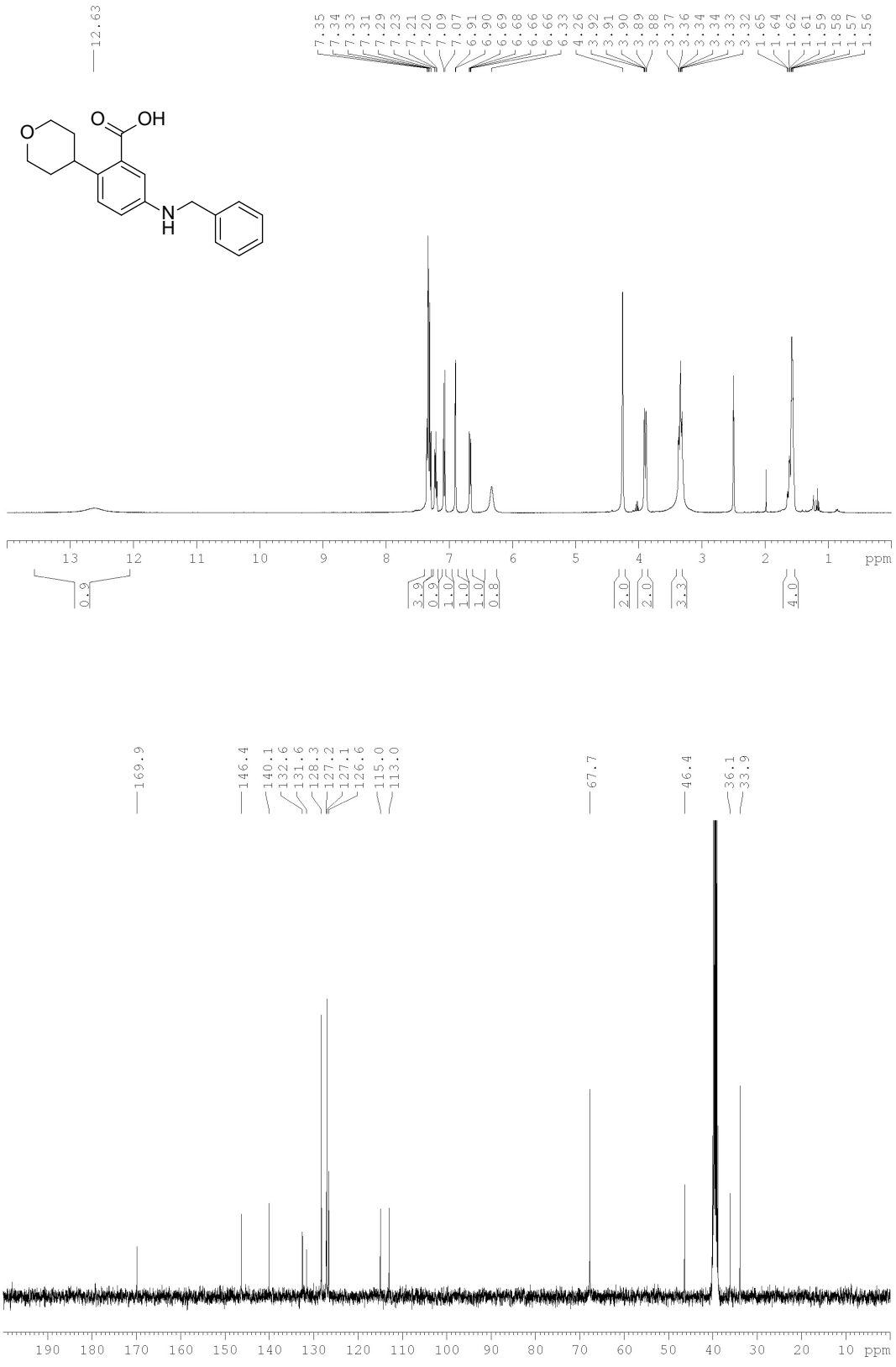


Figure S72. ^{1}H NMR and ^{13}C NMR spectra of **20a**.

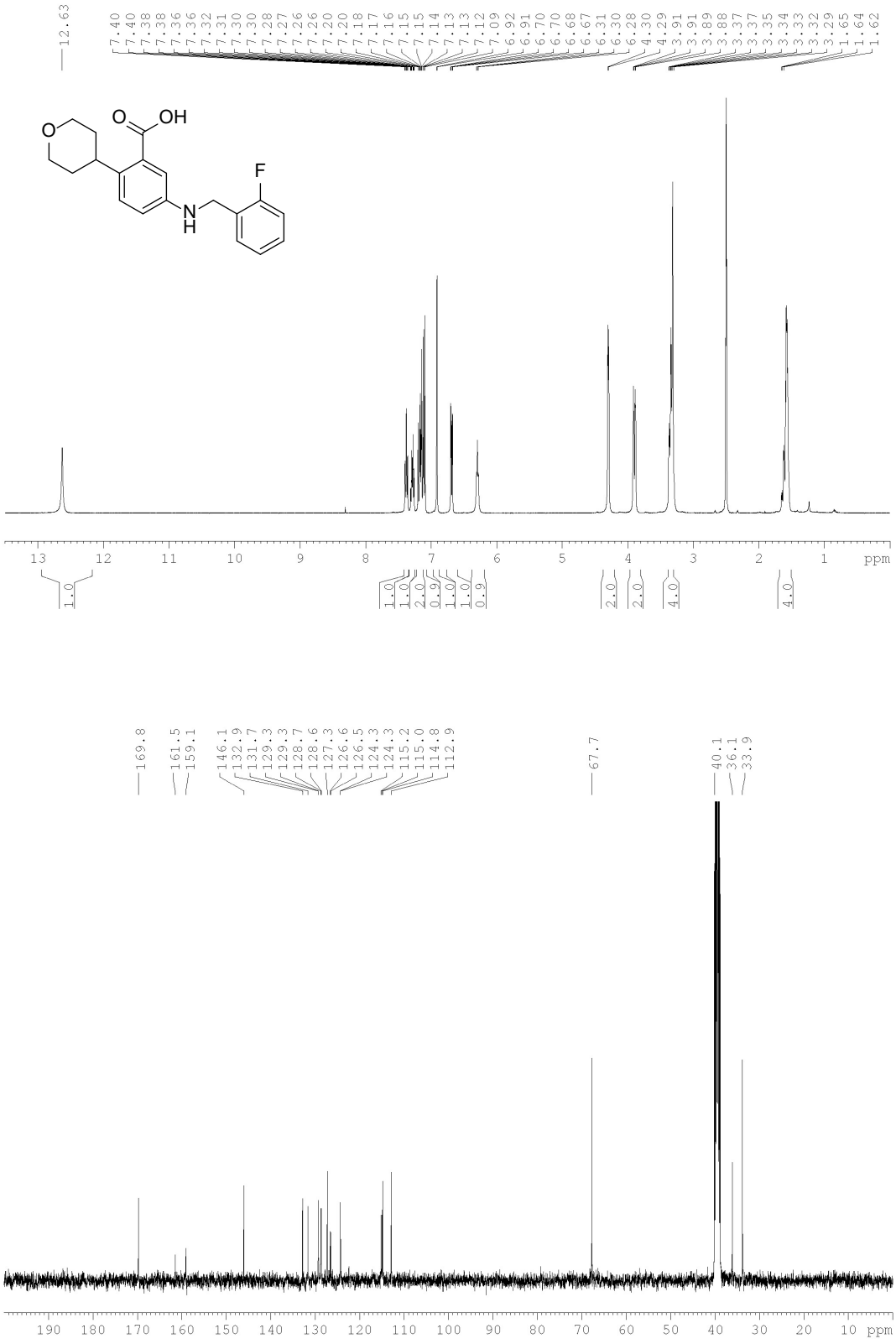


Figure S73. ^{1}H NMR and ^{13}C NMR spectra of **20b**.

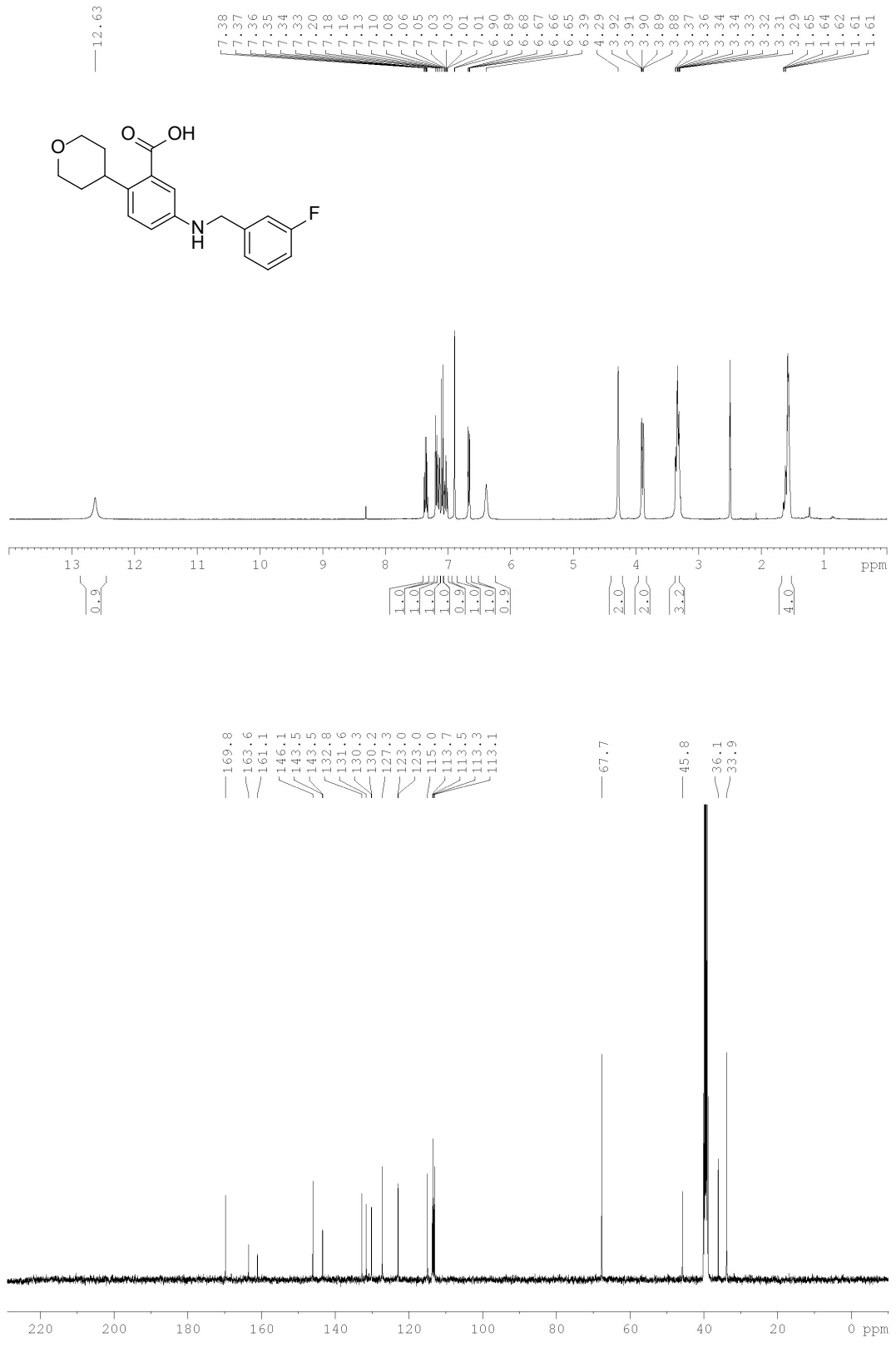


Figure S74. ^{1}H NMR and ^{13}C NMR spectra of **20c**.

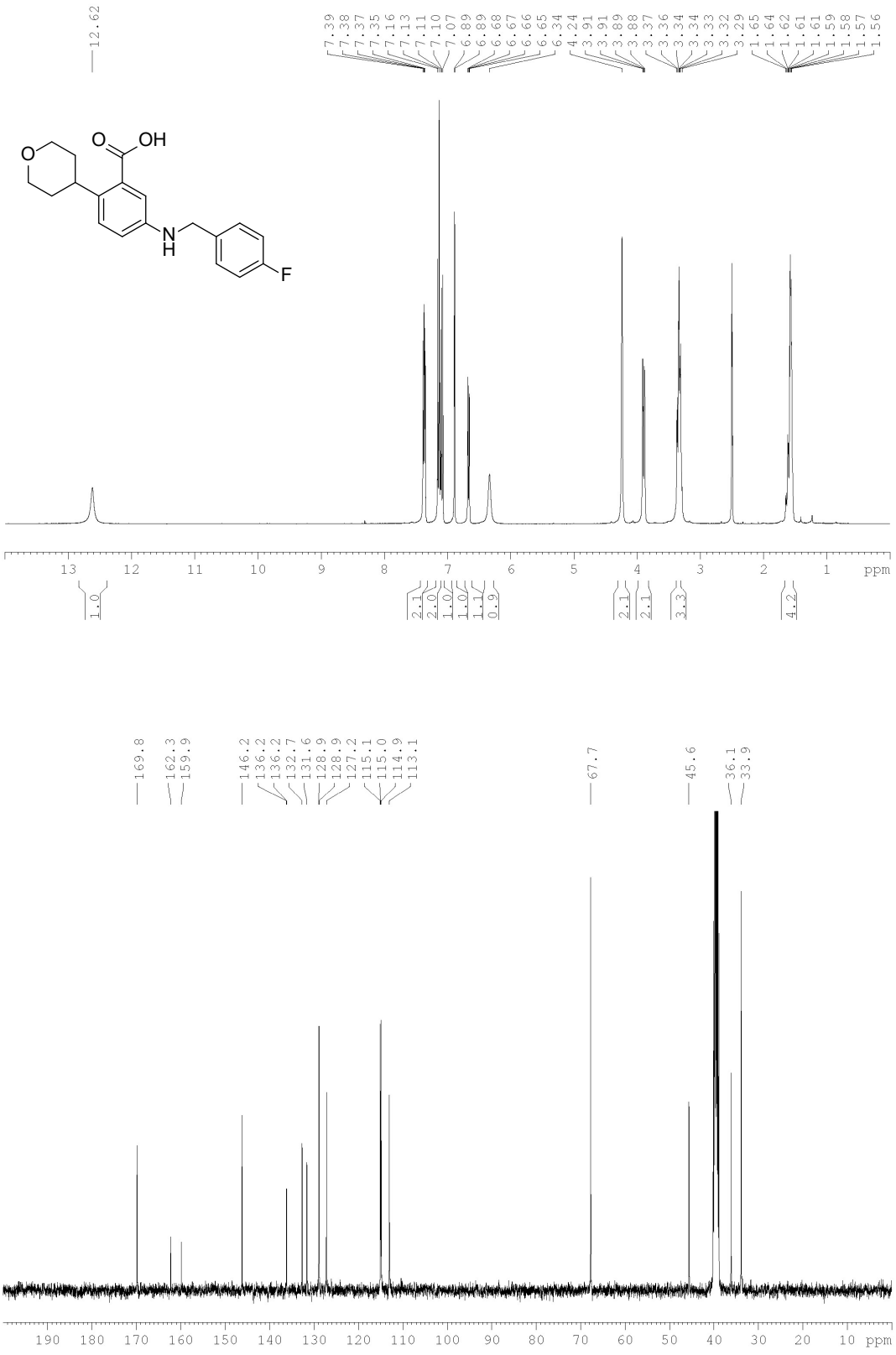


Figure S75. ^{1}H NMR and ^{13}C NMR spectra of **20d**.

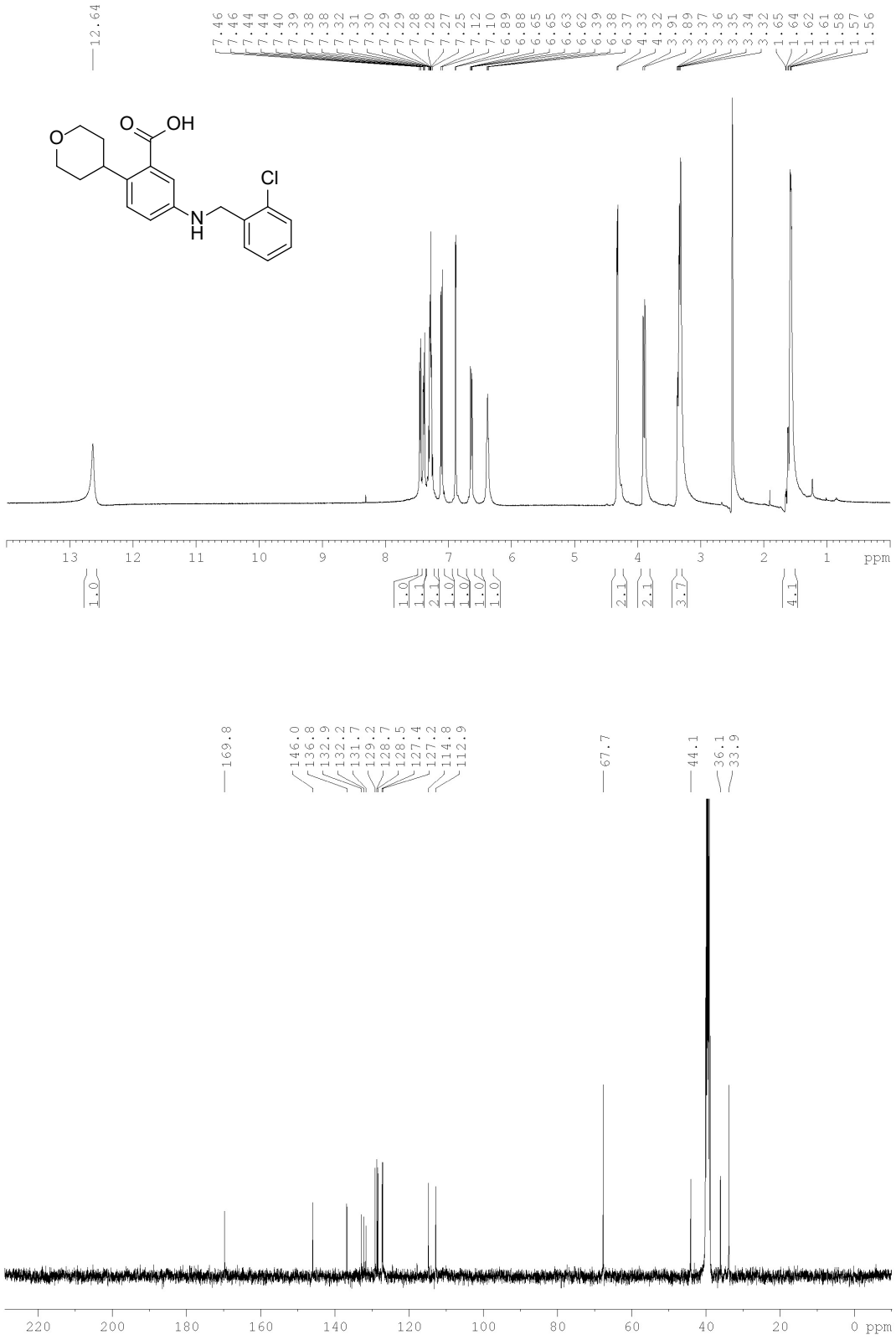


Figure S76. ^{1}H NMR and ^{13}C NMR spectra of **20e**.

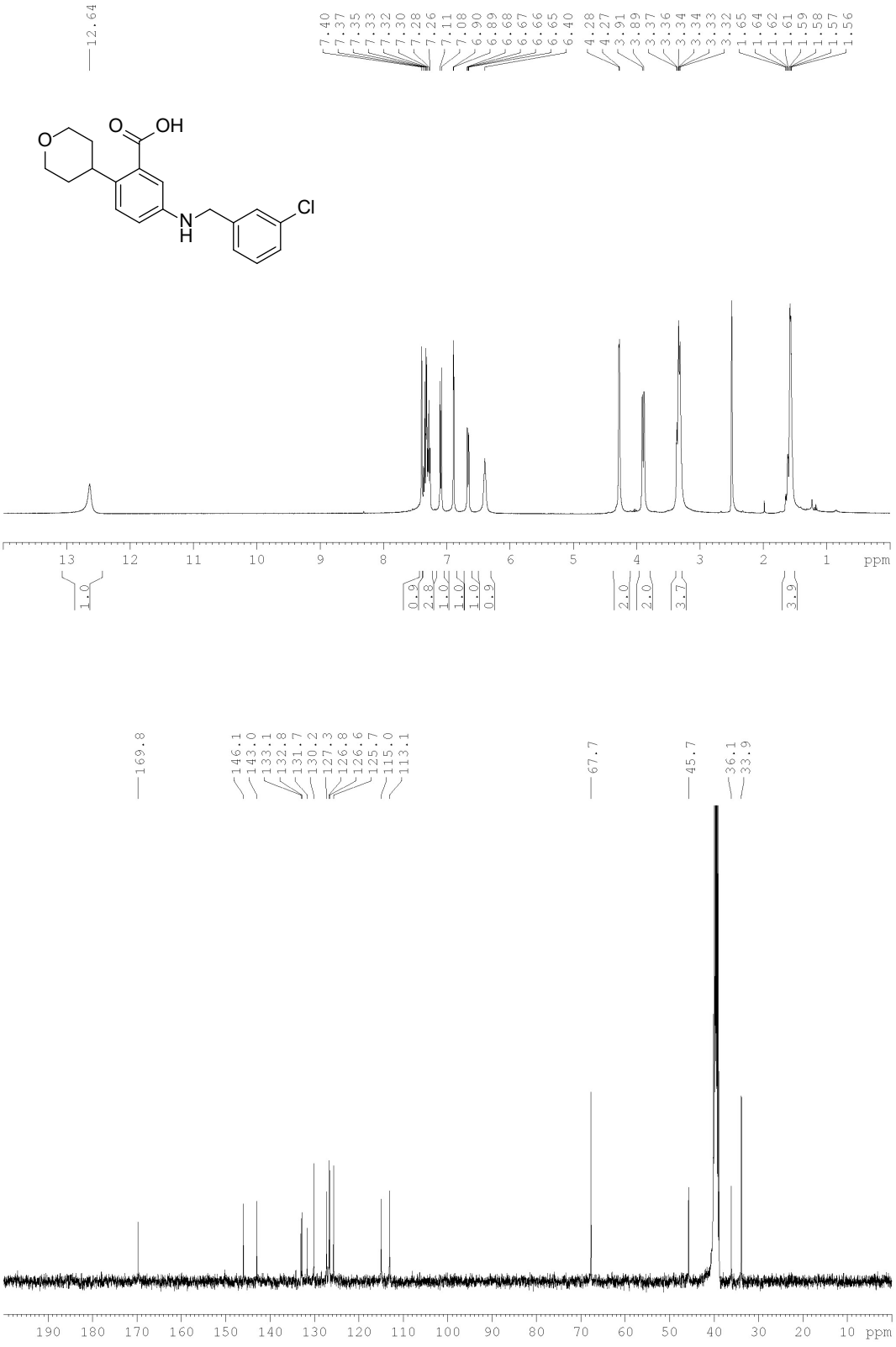


Figure S77. ^{1}H NMR and ^{13}C NMR spectra of **20f**.

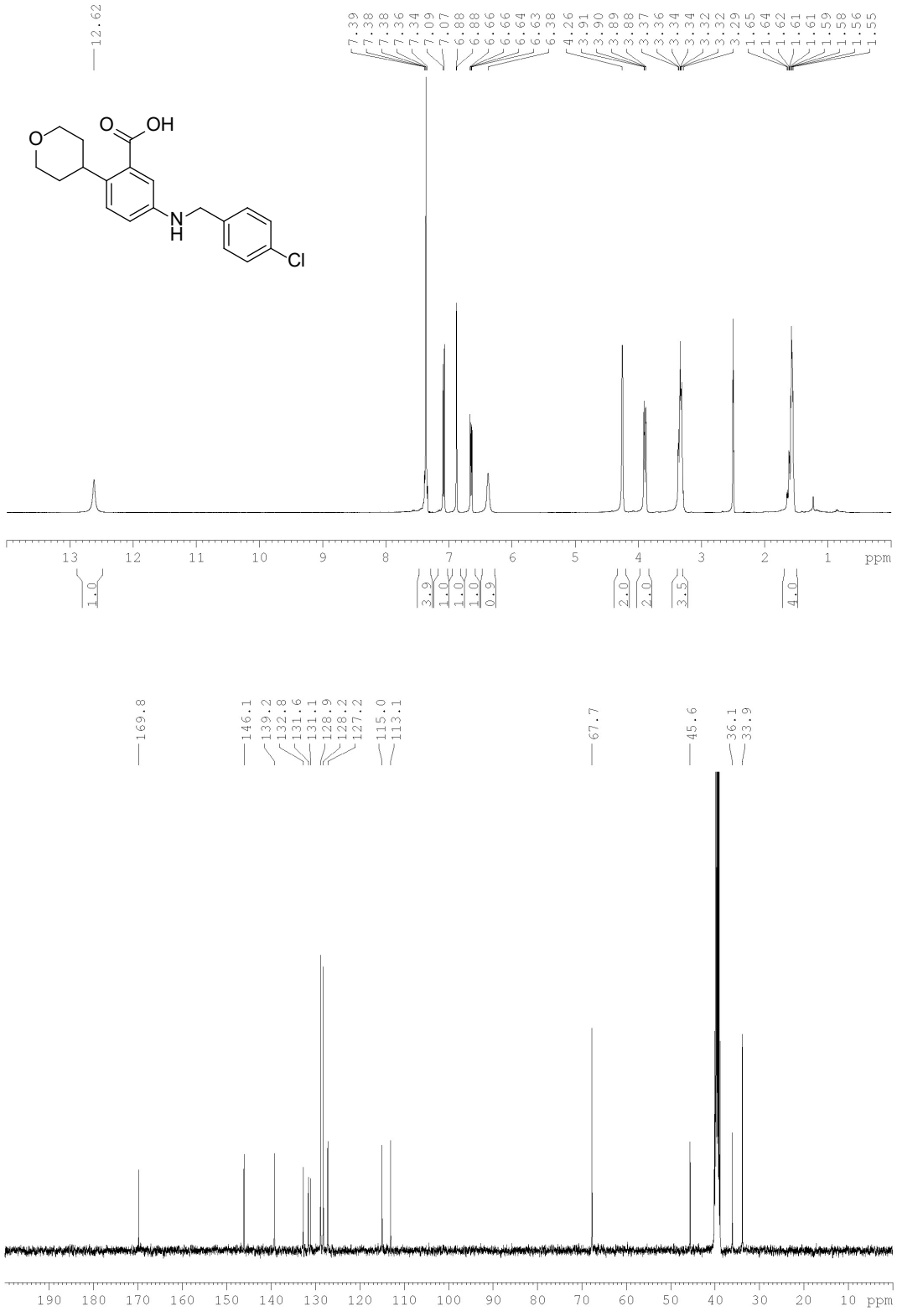


Figure S78. ^{1}H NMR and ^{13}C NMR spectra of **20g**

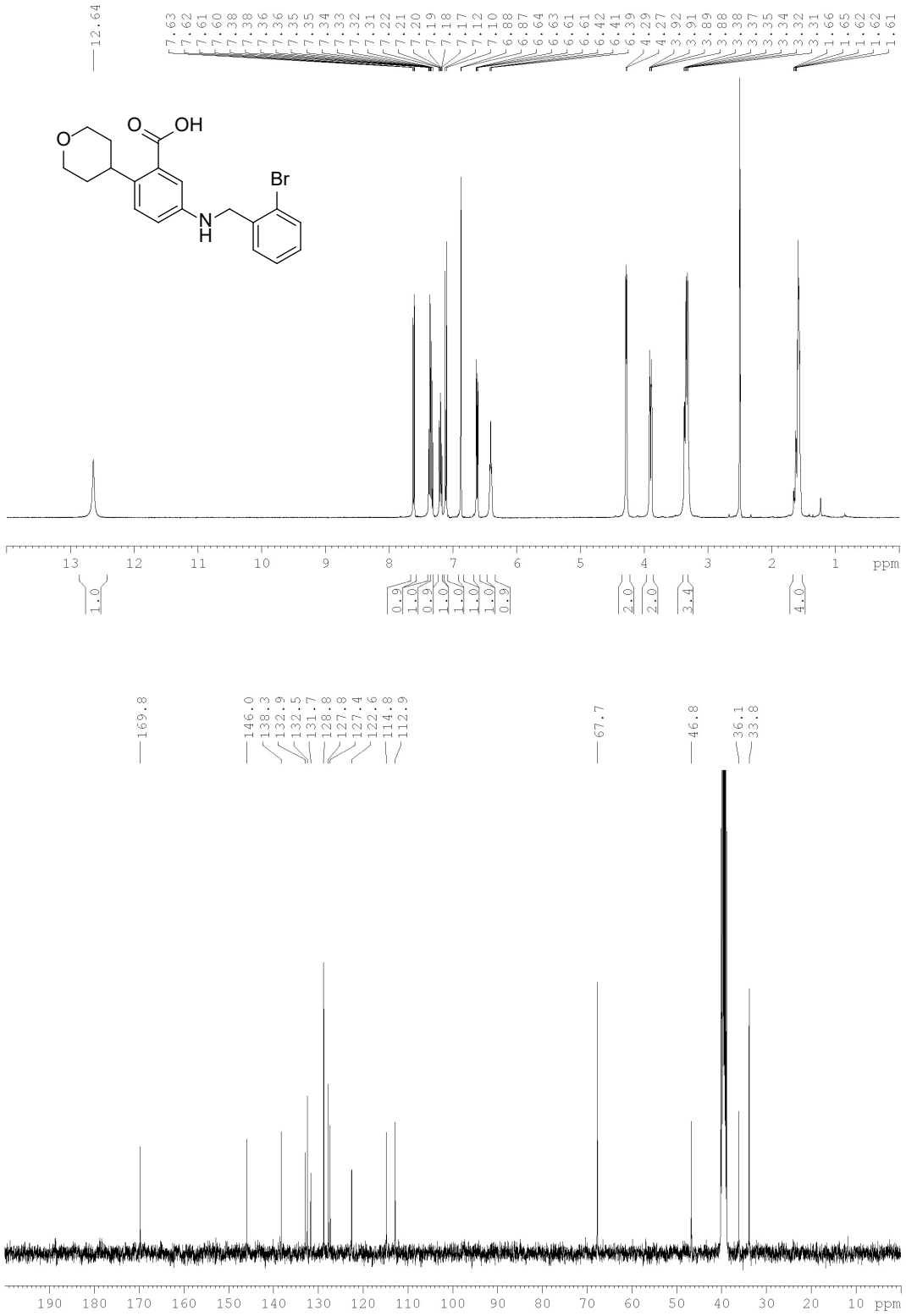


Figure S79.[1]H NMR and [13]C NMR spectra of **20h**

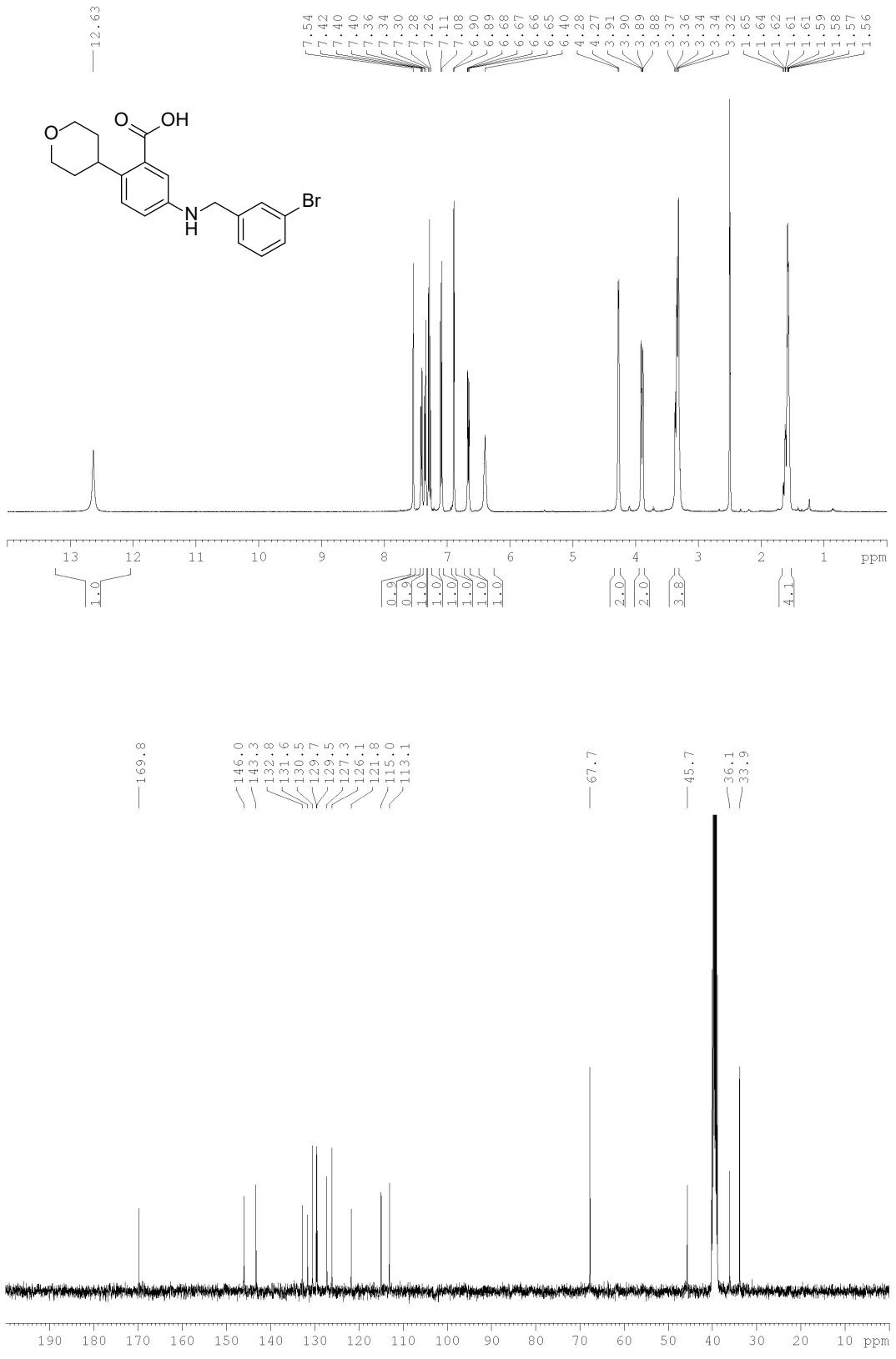


Figure S80. ^{1}H NMR and ^{13}C NMR spectra of **20i**.

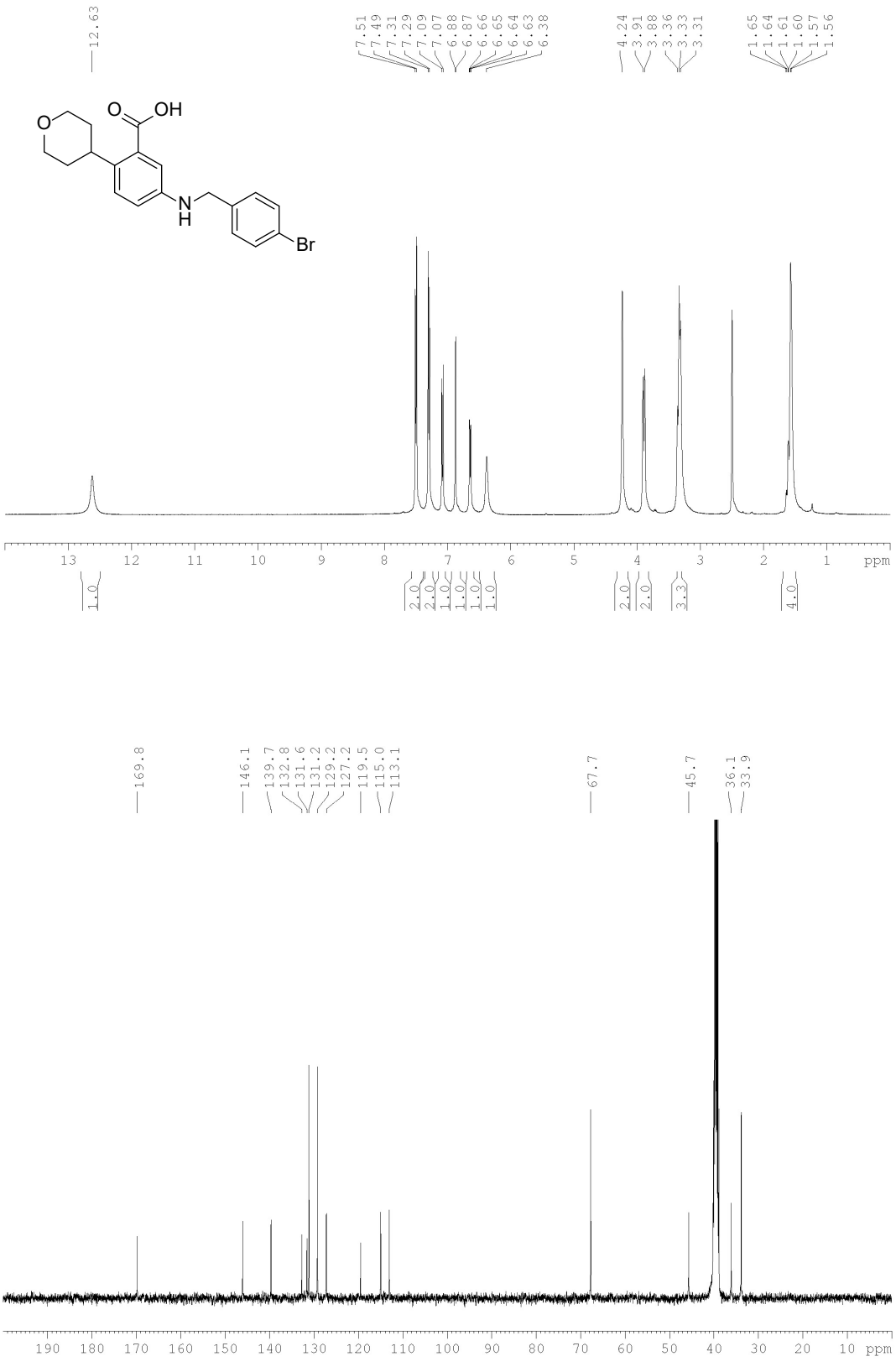


Figure S81. ^{1}H NMR and ^{13}C NMR spectra of **20j**.

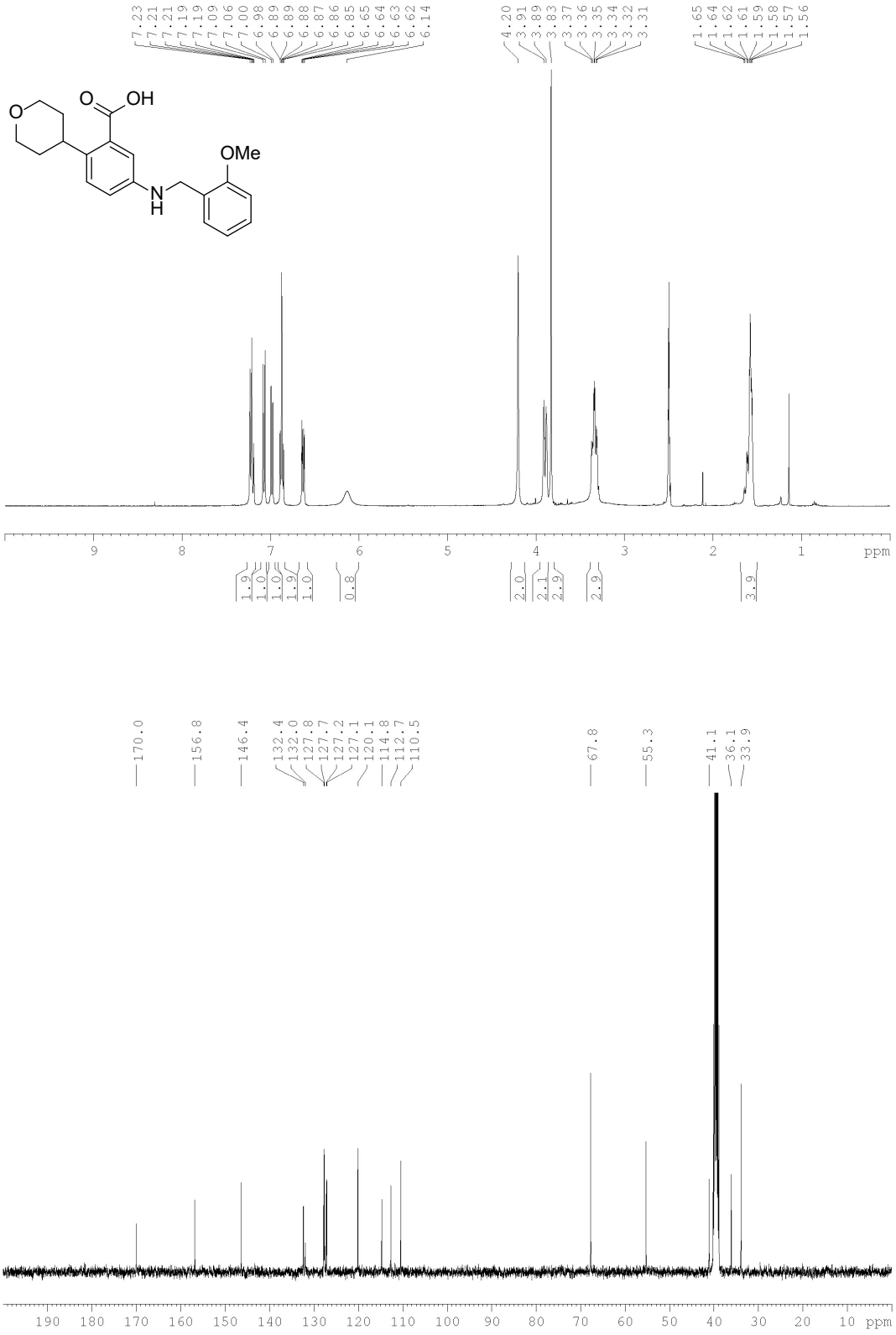


Figure S82. ^{1}H NMR and ^{13}C NMR spectra of **20k**.

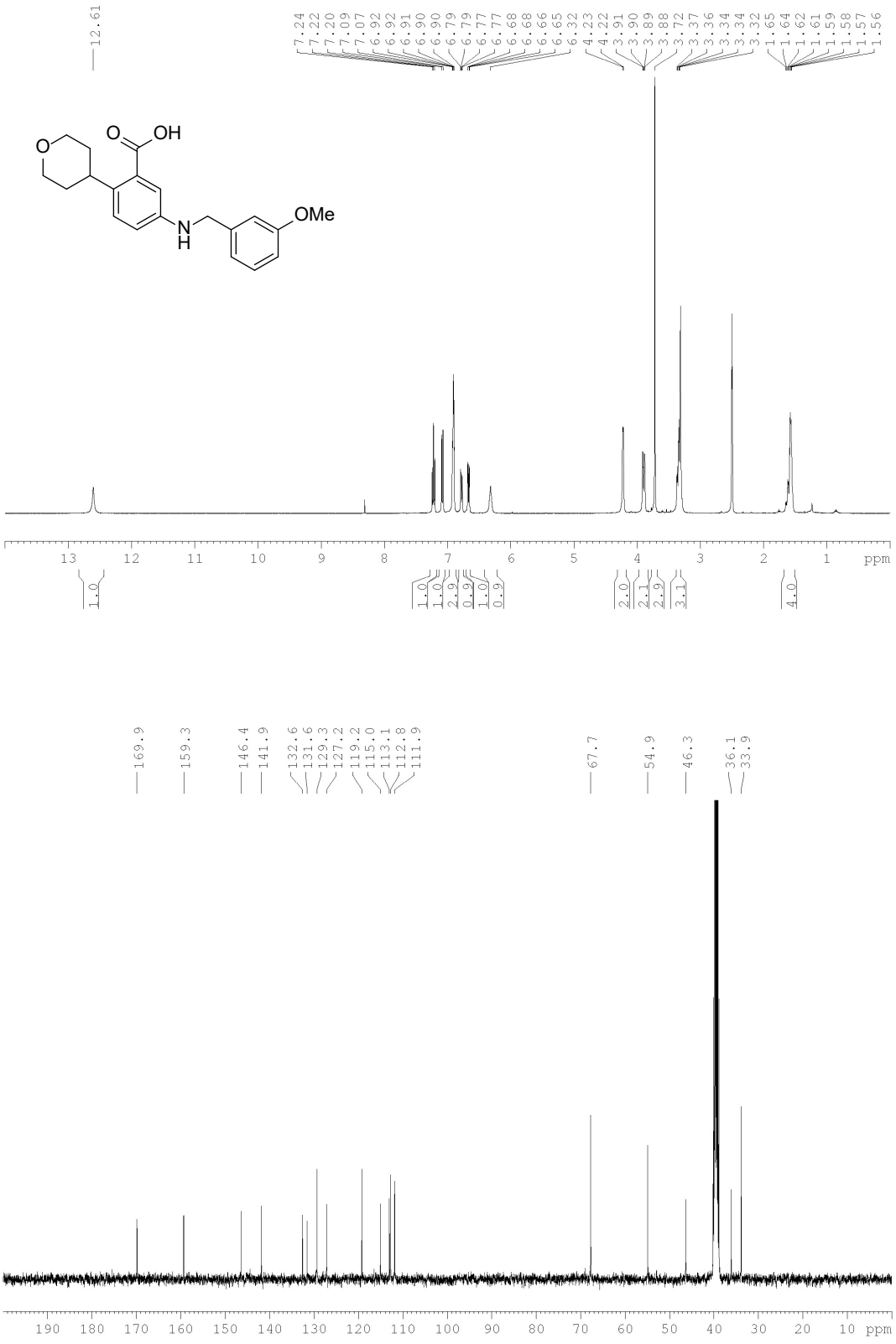


Figure S83. ^{1}H NMR and ^{13}C NMR spectra of **20l**.

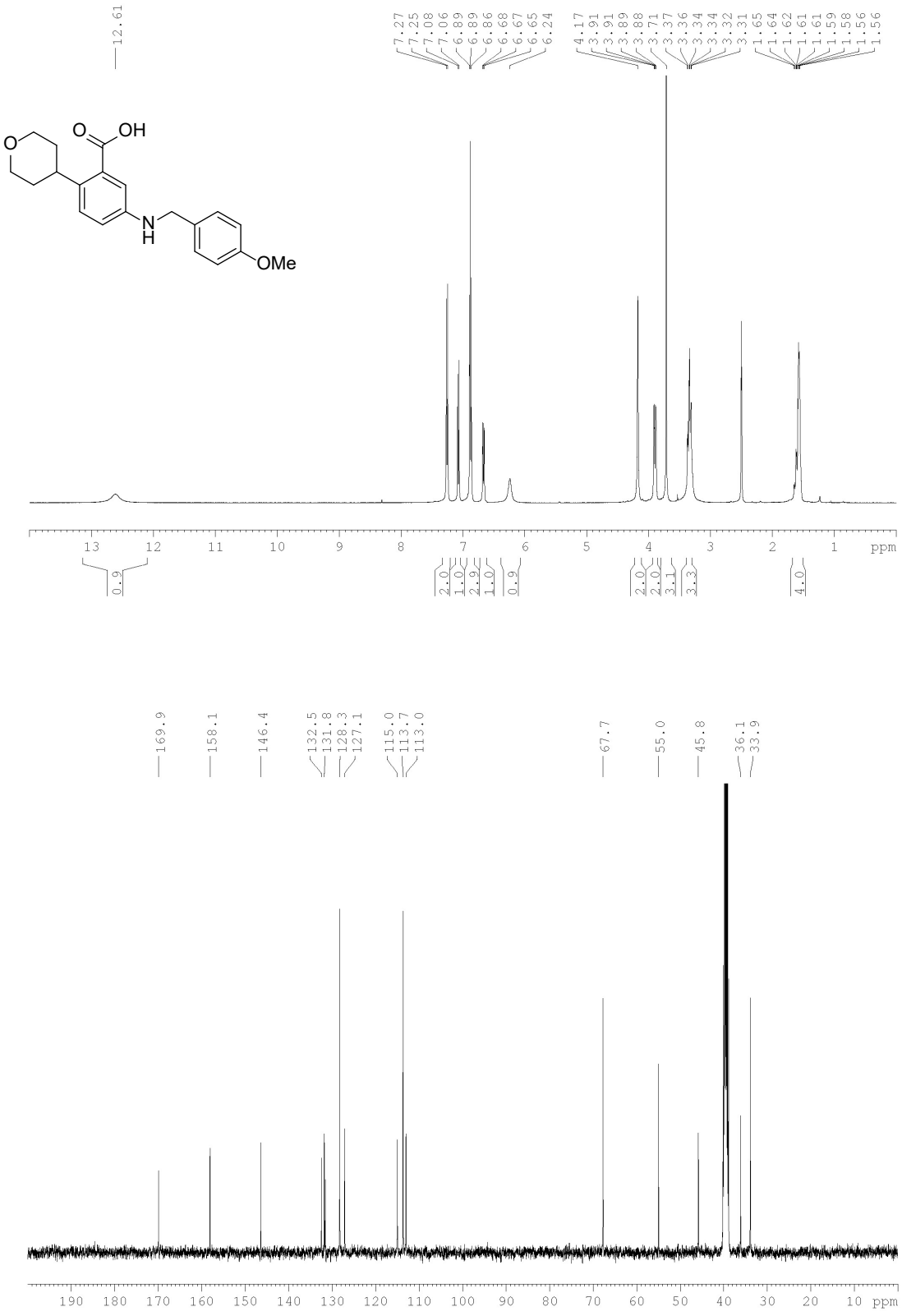


Figure S84. ^{1}H NMR and ^{13}C NMR spectra of **20m**.

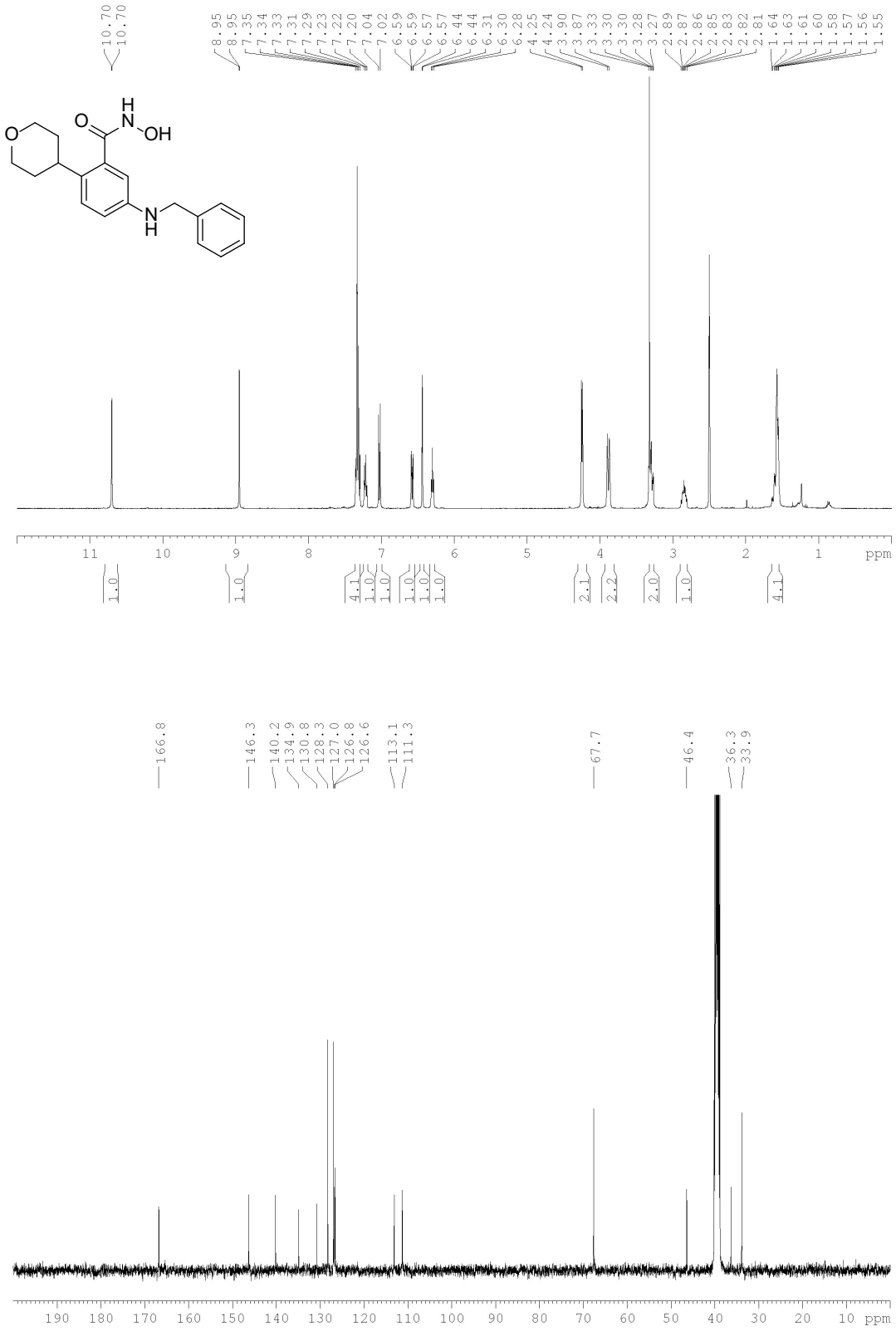


Figure S85. ^{1}H NMR and ^{13}C NMR spectra of **21a**.

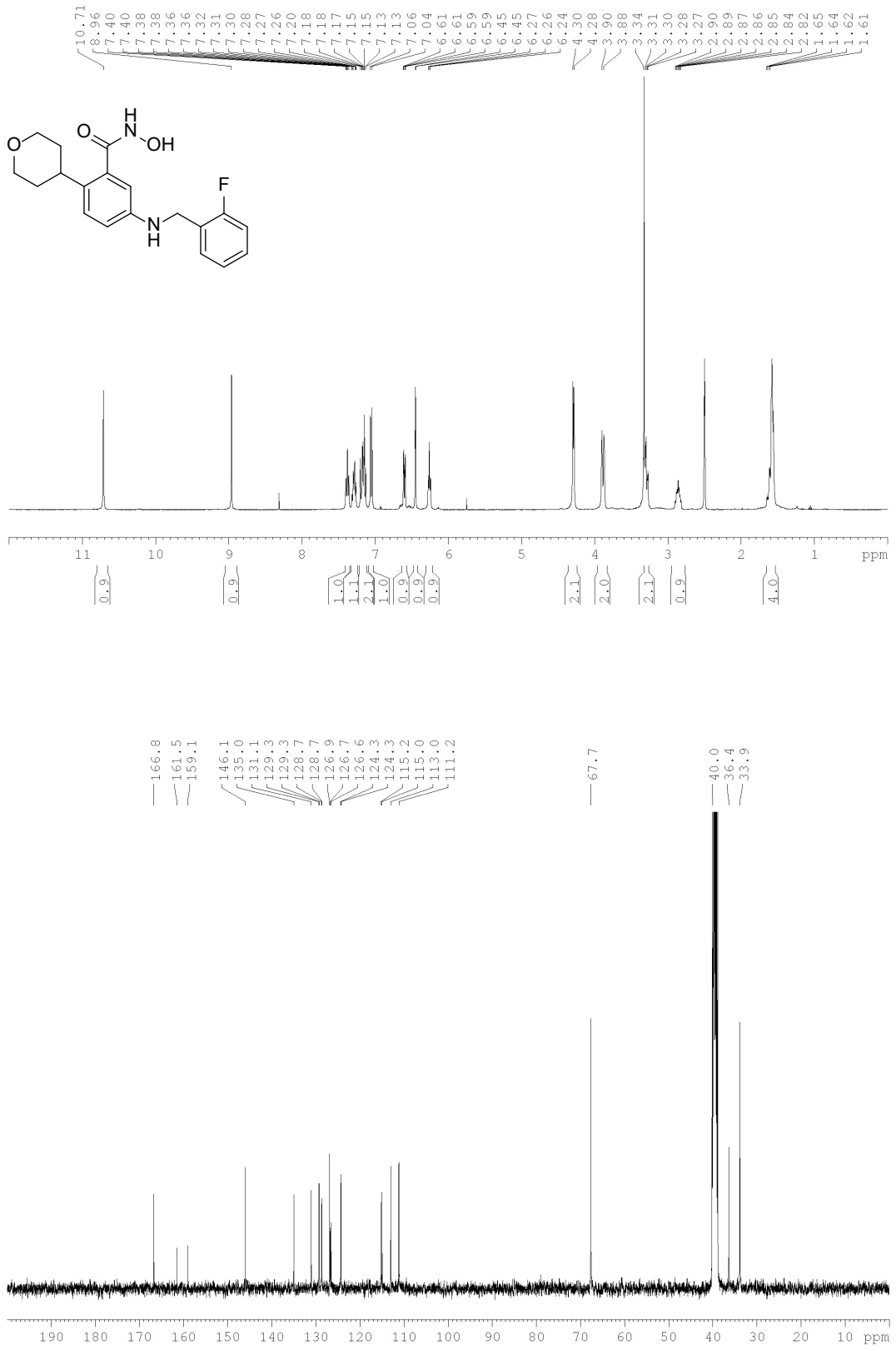


Figure S86. ^{1}H NMR and ^{13}C NMR spectra of **21b**.

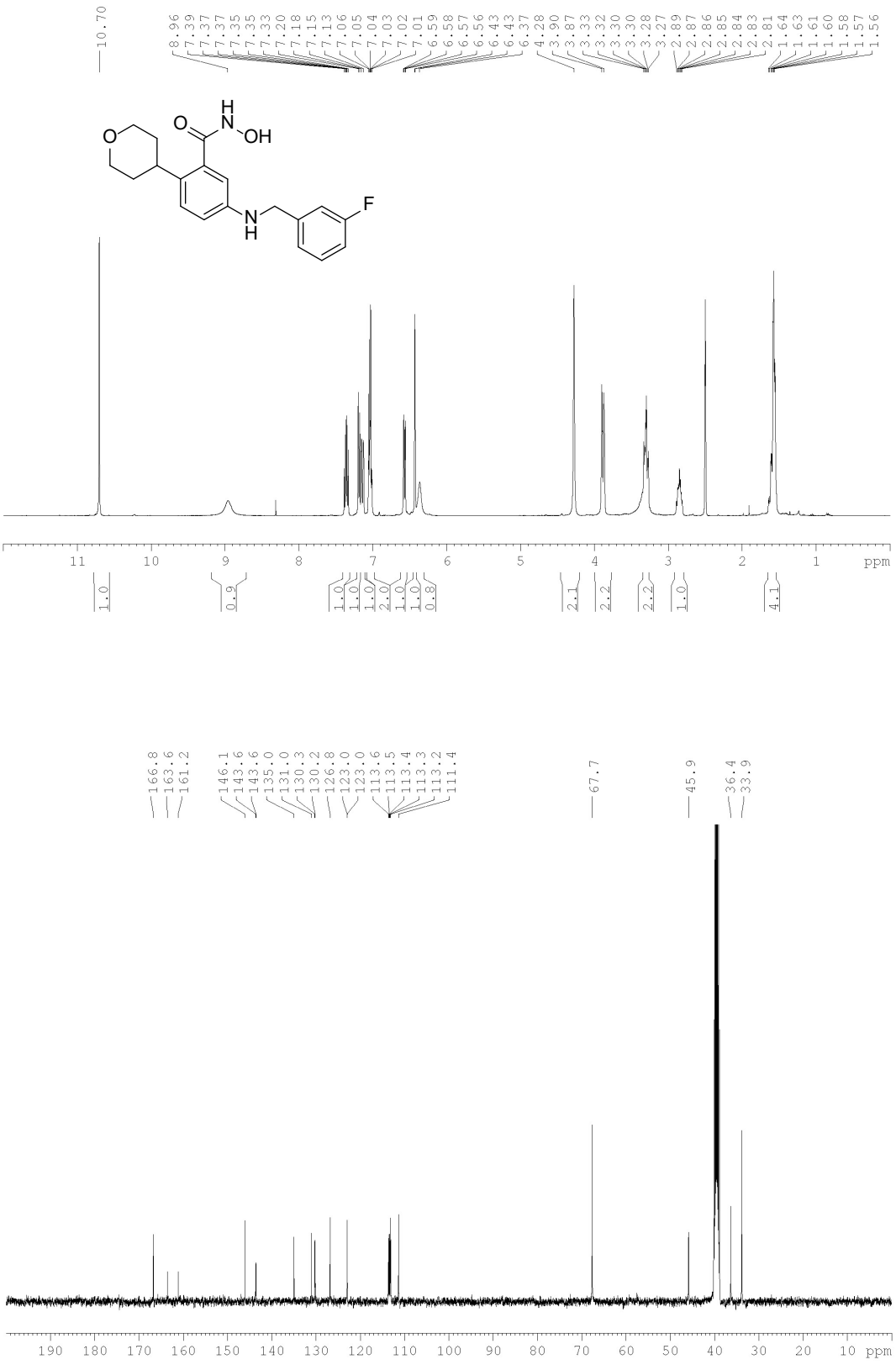


Figure S87. ^{1}H NMR and ^{13}C NMR spectra of **21c**.

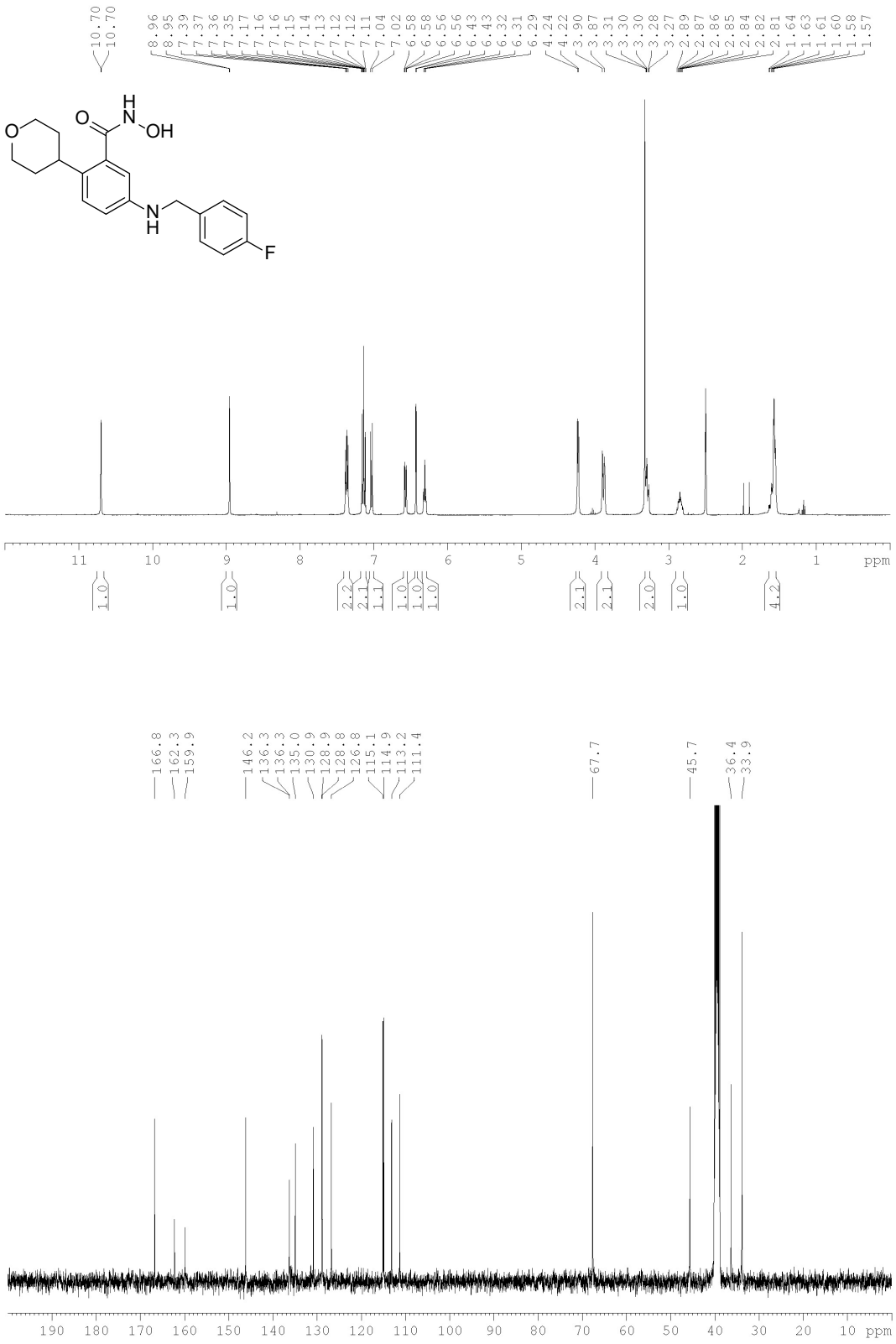


Figure S88. ^{1}H NMR and ^{13}C NMR spectra of **21d**.

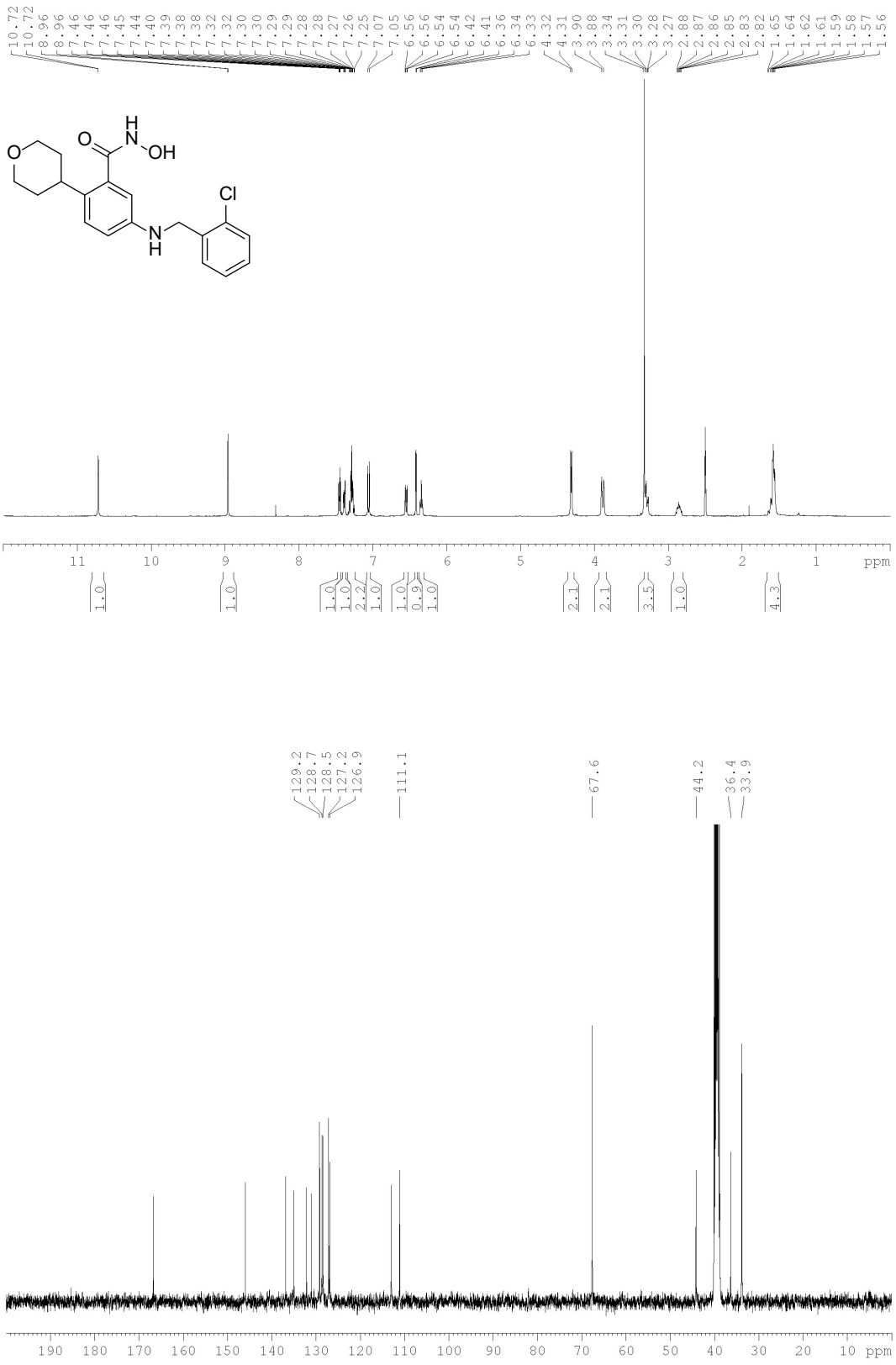


Figure S89. ^{1}H NMR and ^{13}C NMR spectra of **21e**.

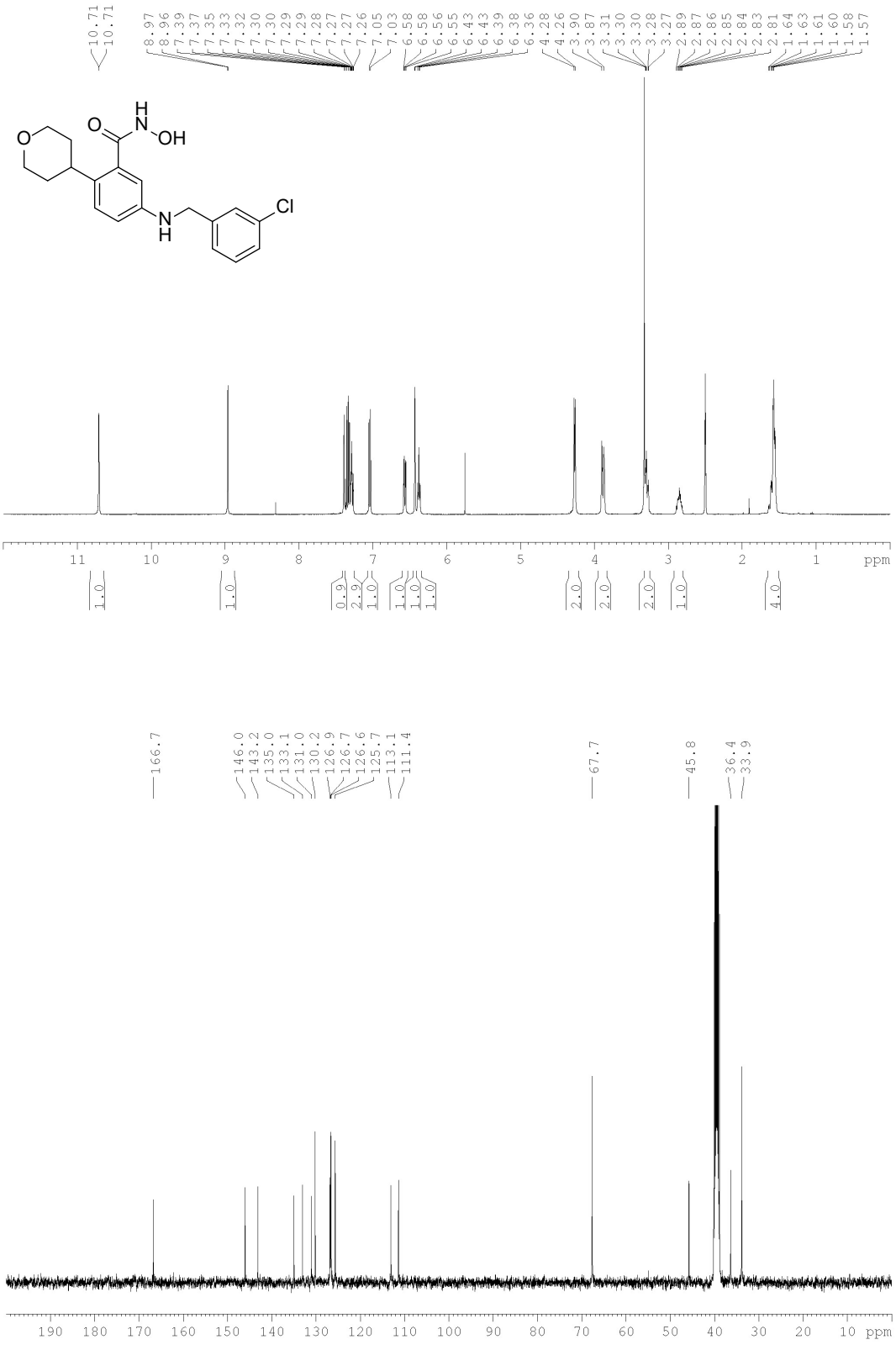


Figure S90. ^{1}H NMR and ^{13}C NMR spectra of **21f**.

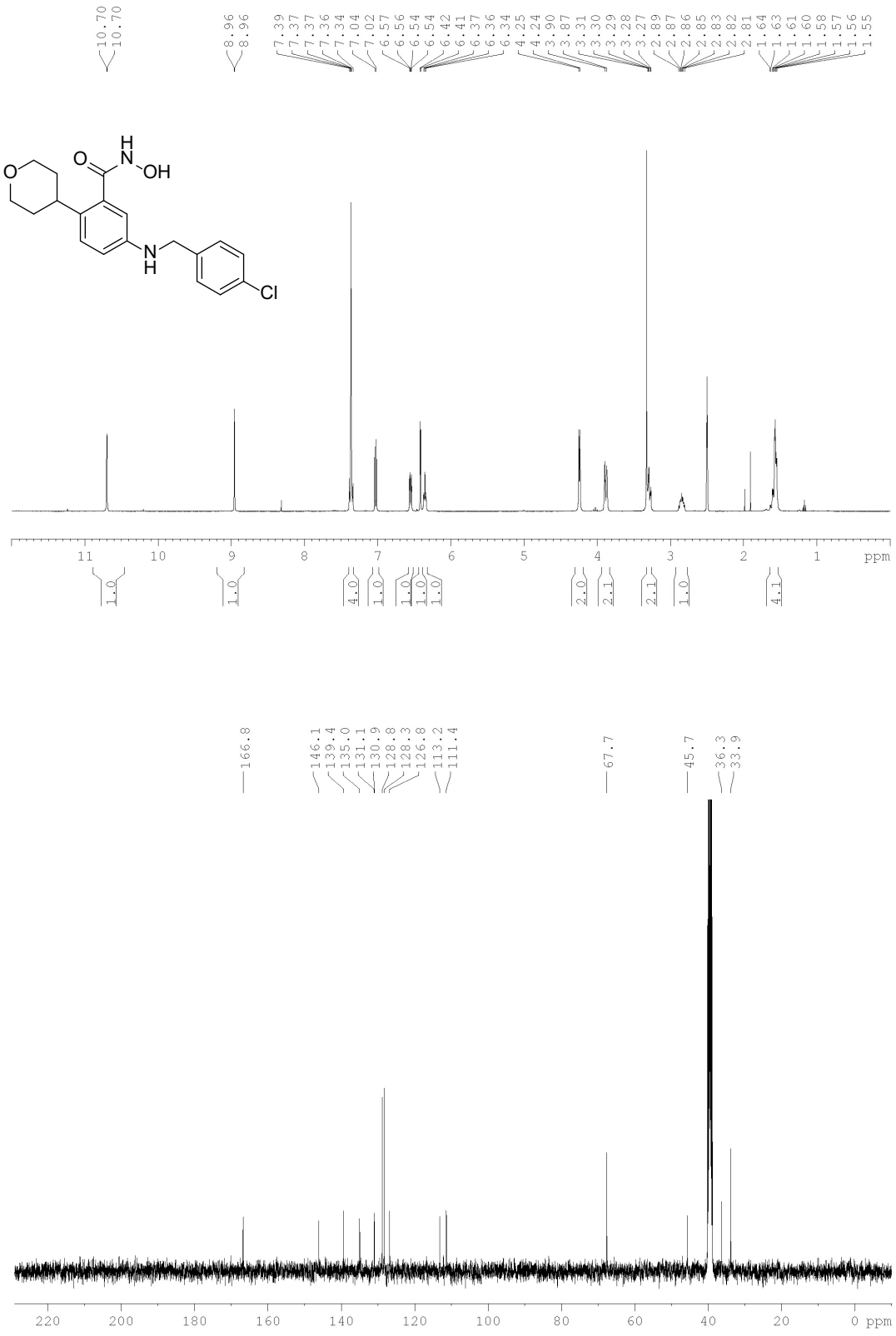


Figure S91. ^{1}H NMR and ^{13}C NMR spectra of **21g**.

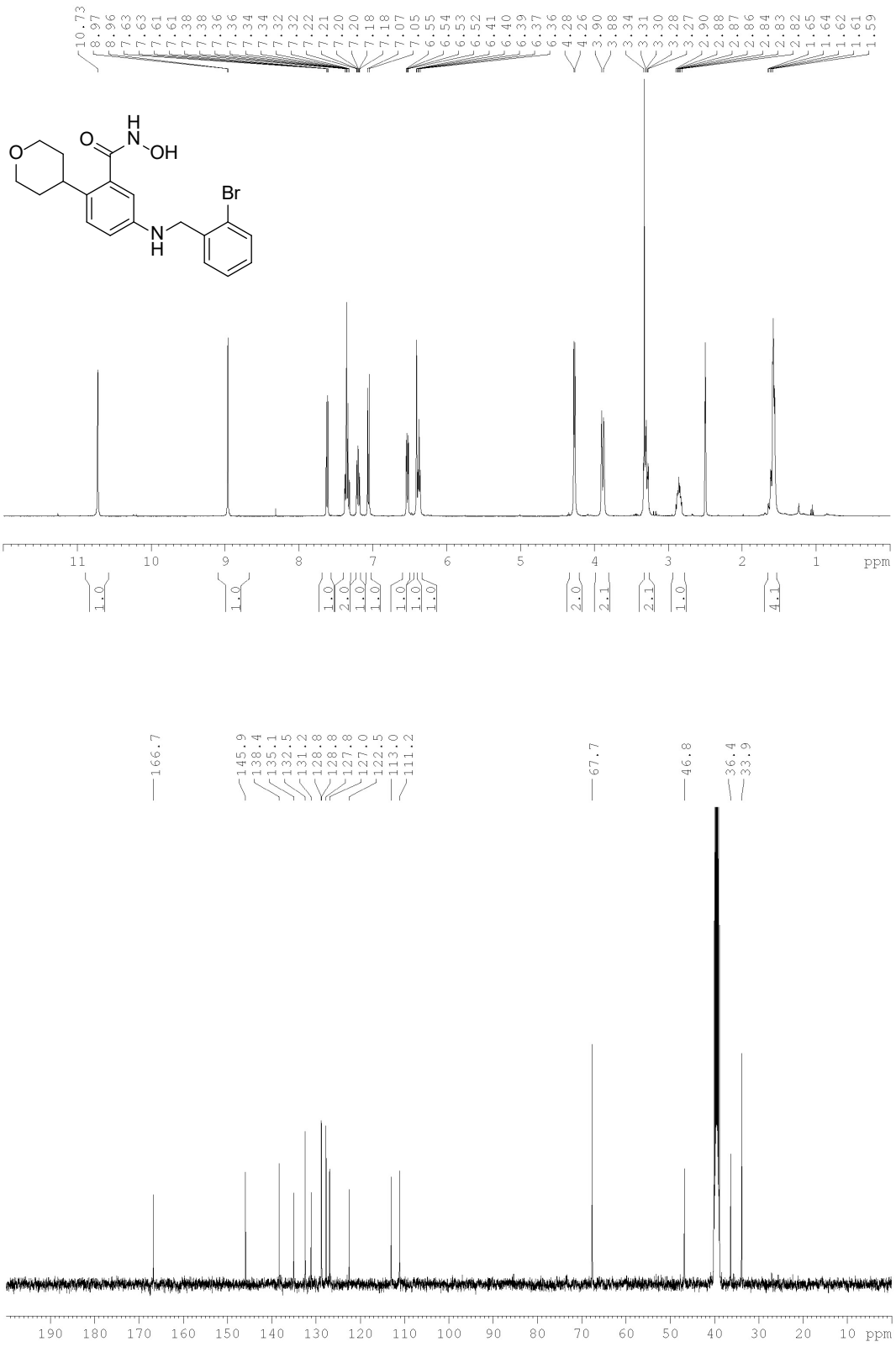


Figure S92. ^{1}H NMR and ^{13}C NMR spectra of **21h**.

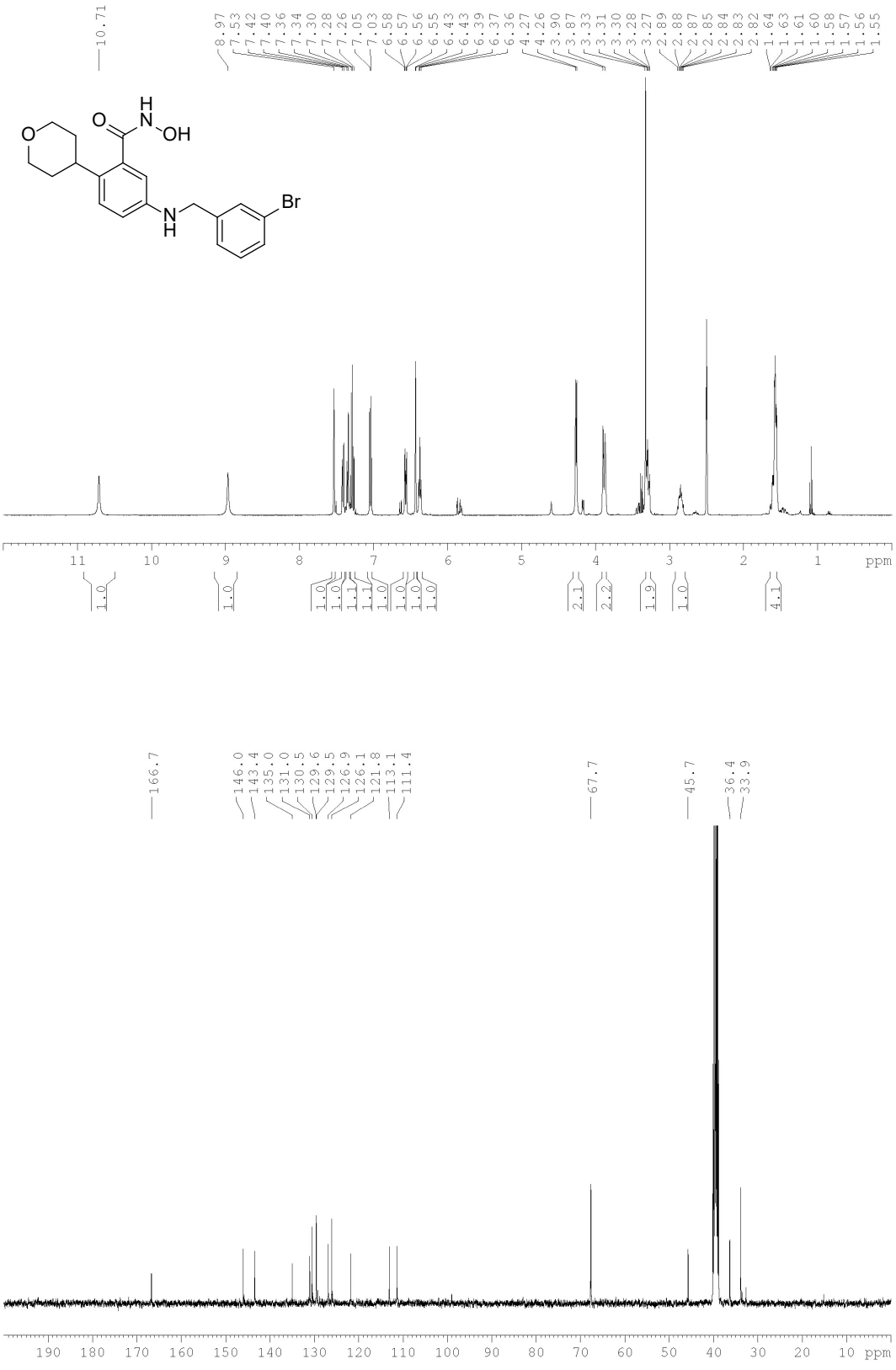


Figure S93. ^{1}H NMR and ^{13}C NMR spectra of **21i**.

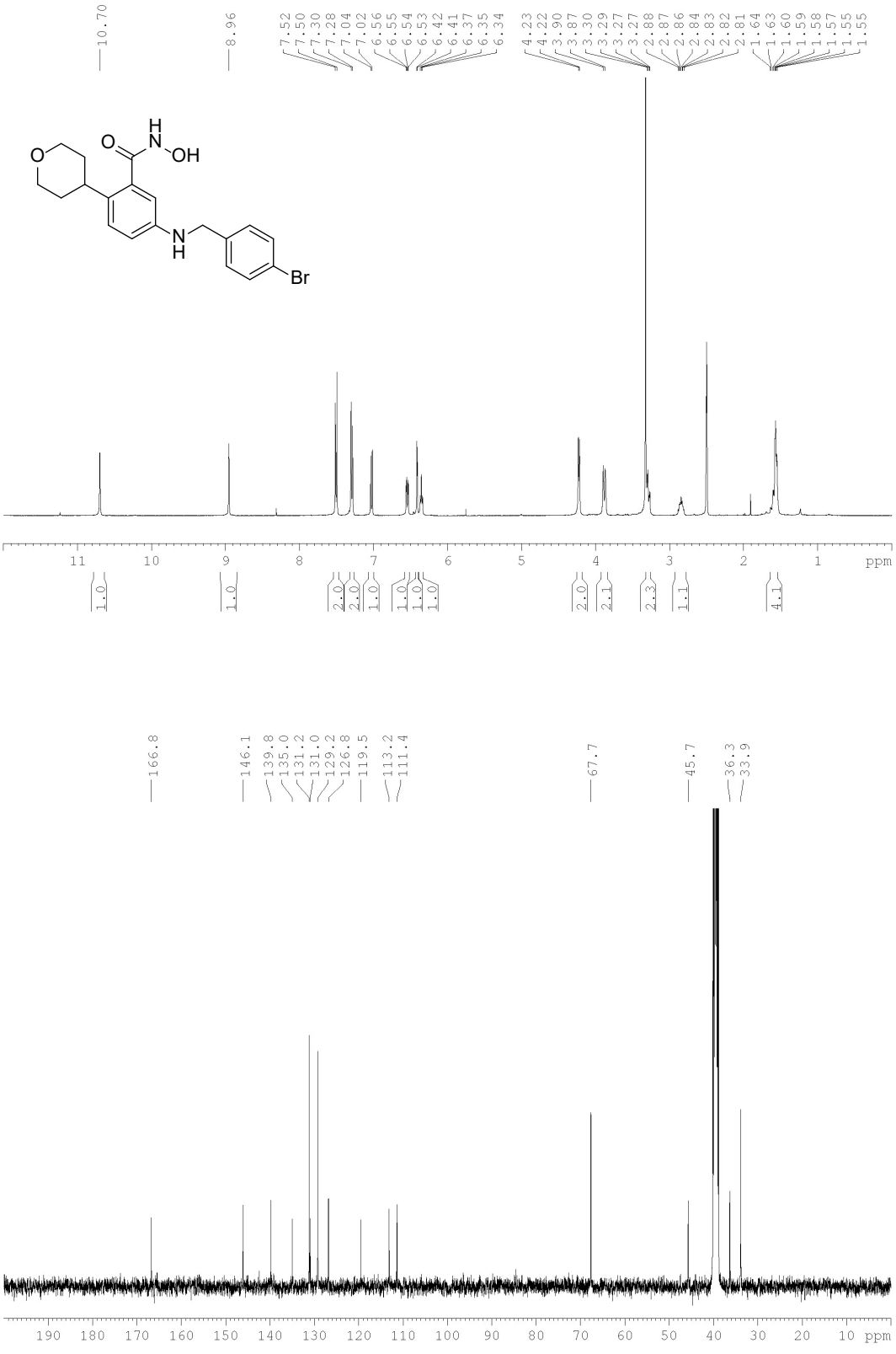


Figure S94. ^{1}H NMR and ^{13}C NMR spectra of **21j**.

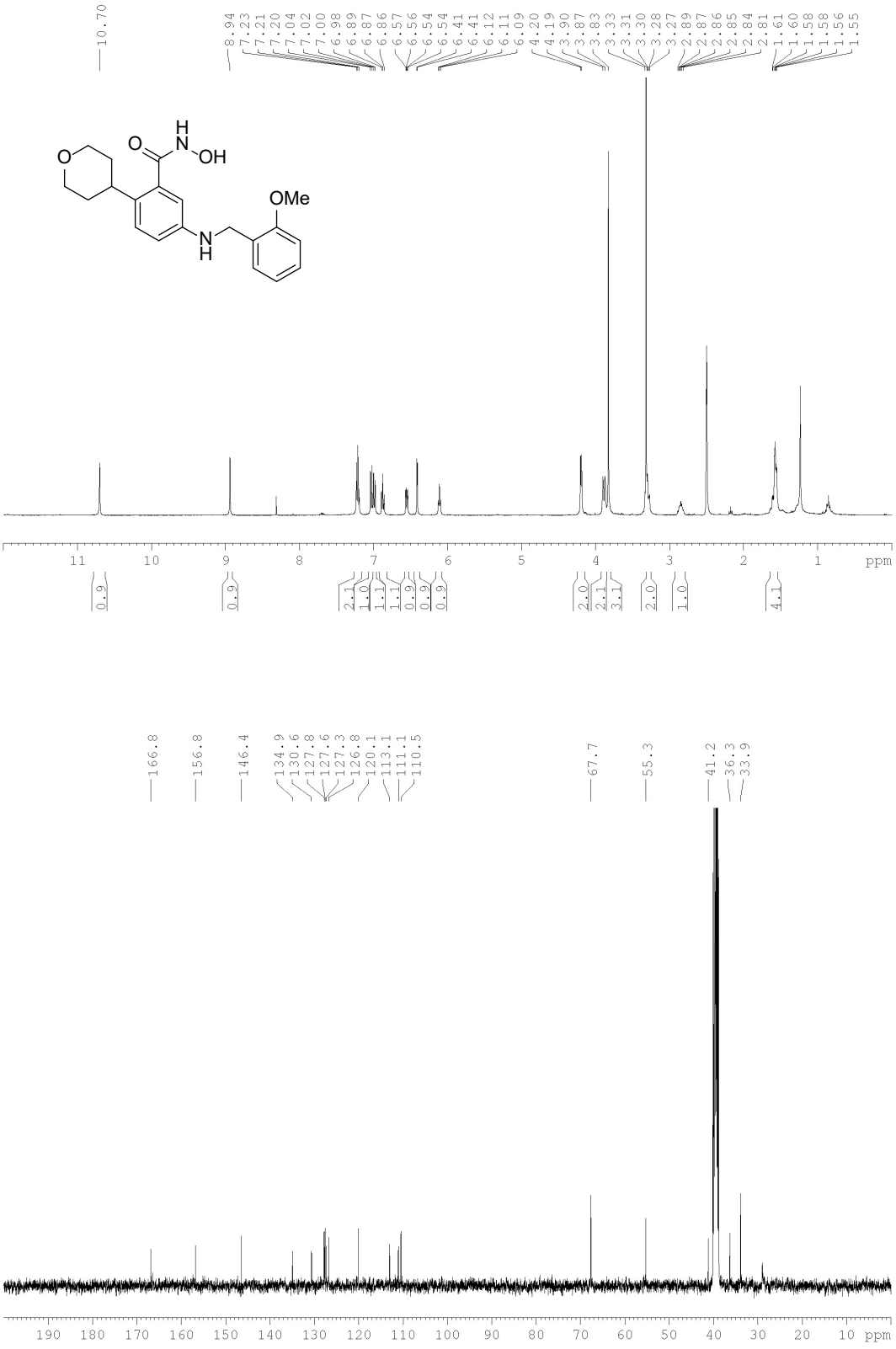


Figure S95. ^{1}H NMR and ^{13}C NMR spectra of **21k**.

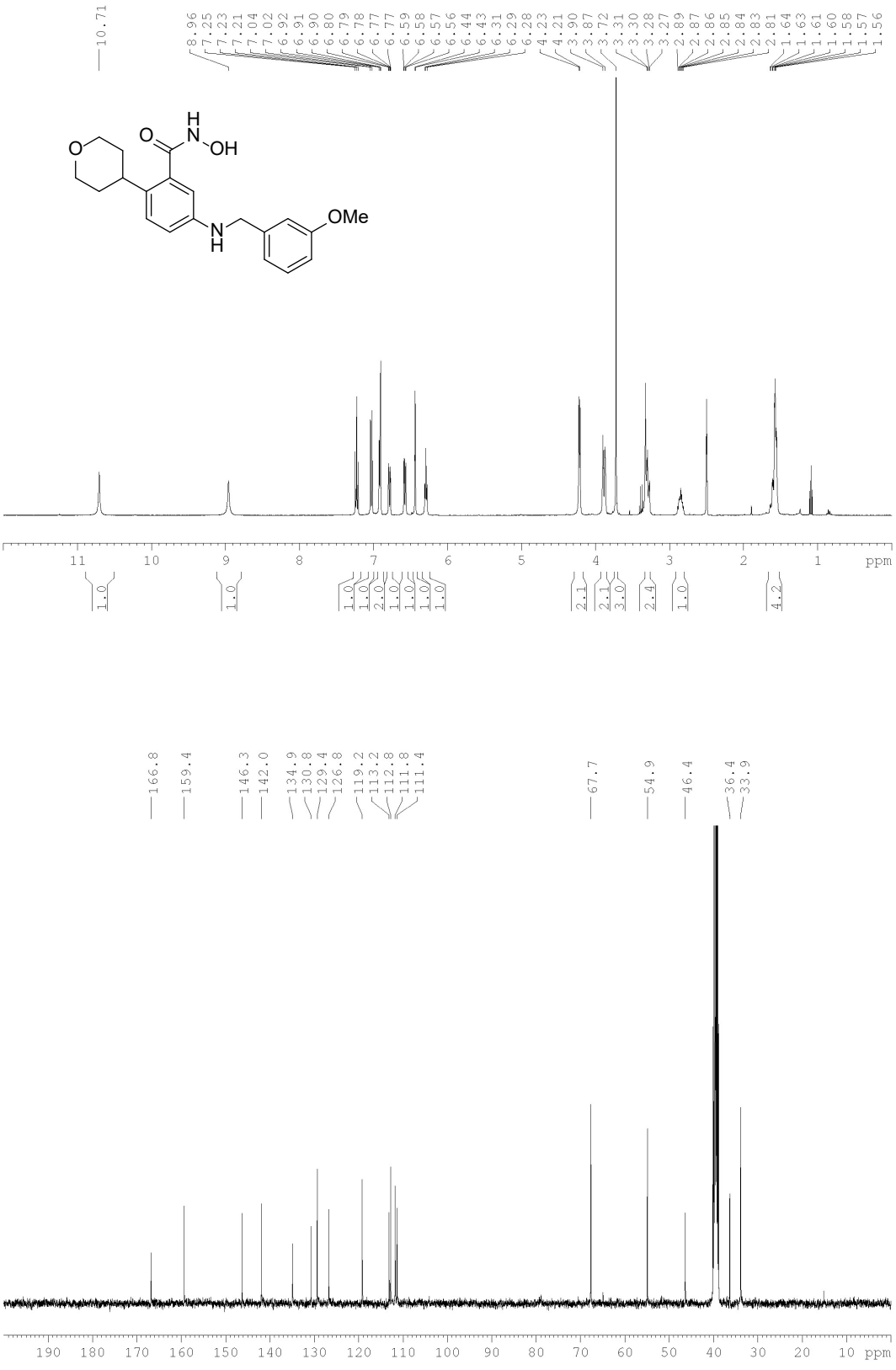


Figure S96. ^{1}H NMR and ^{13}C NMR spectra of **21l**.

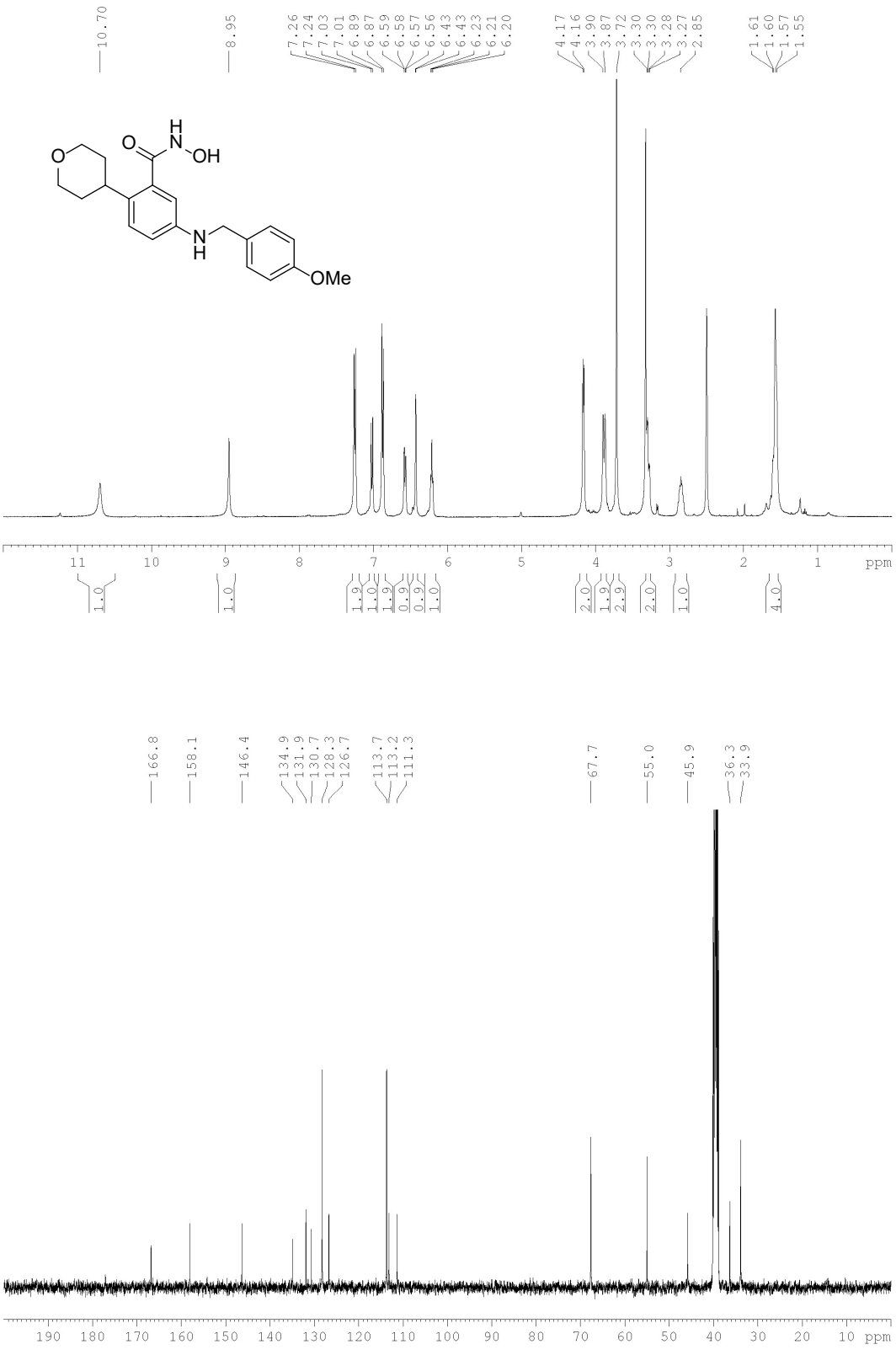


Figure S97. ^{1}H NMR and ^{13}C NMR spectra of **21m**.

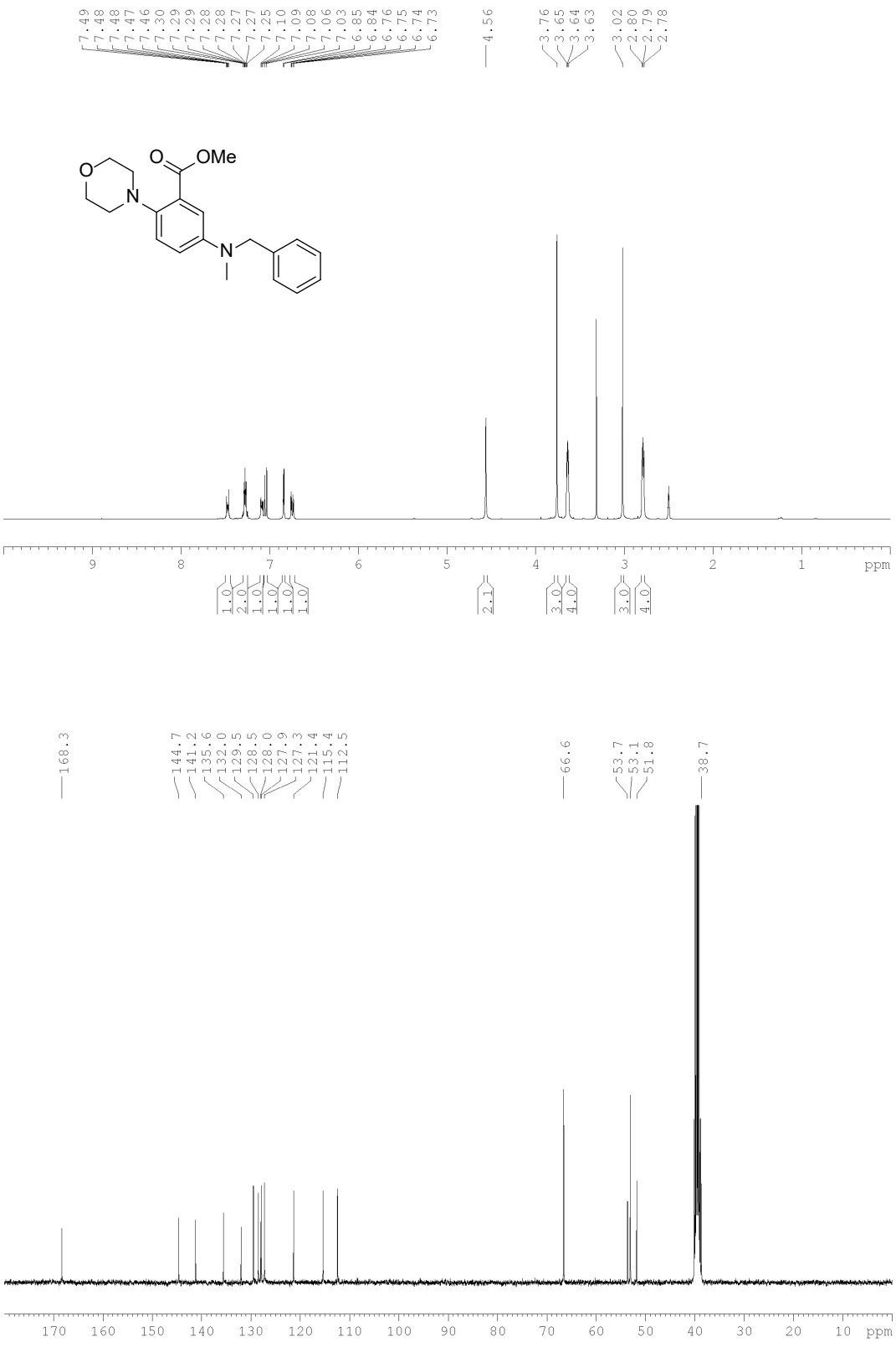


Figure S98. ^{1}H NMR and ^{13}C NMR spectra of **23**.

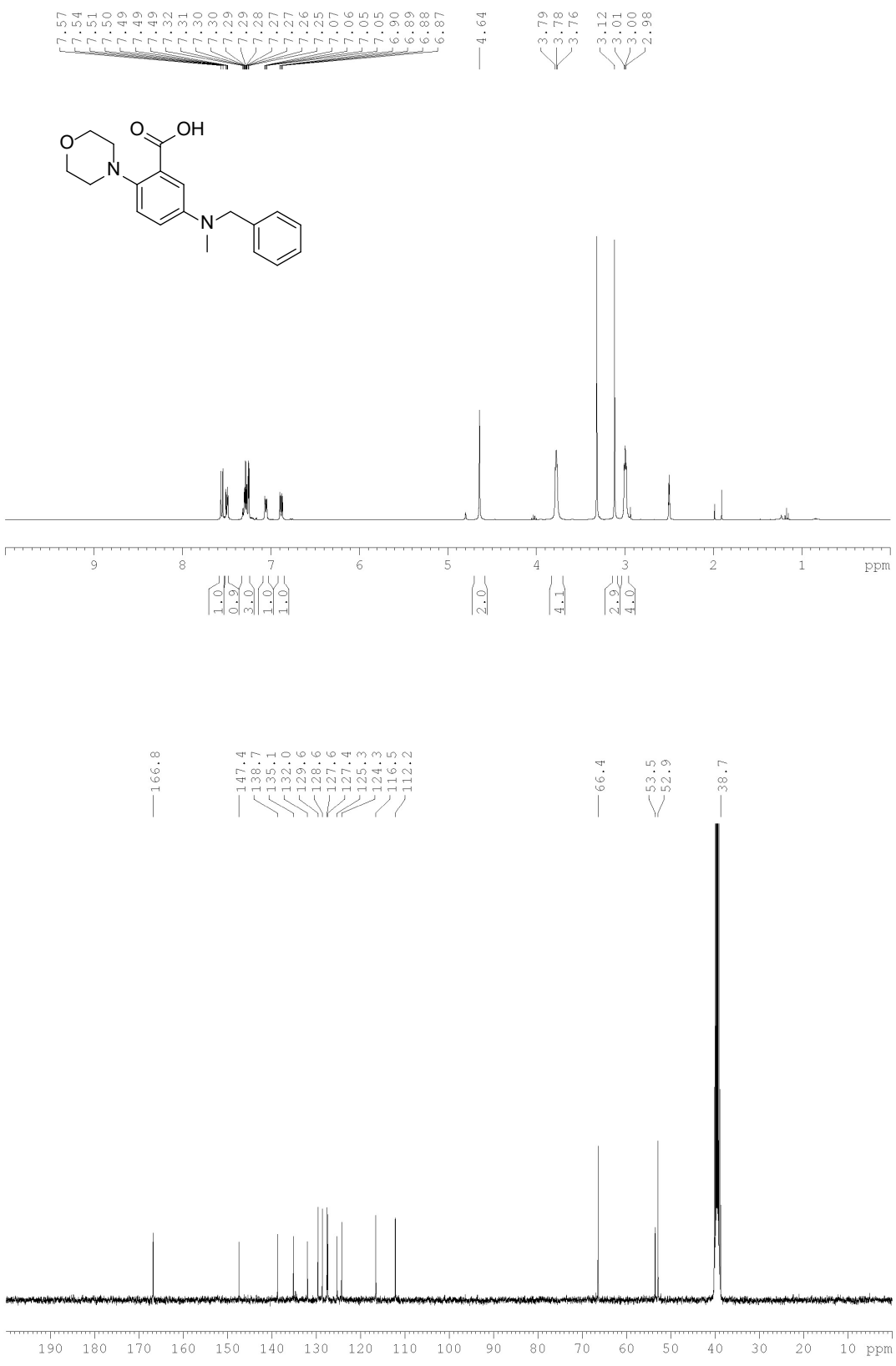


Figure S99. ^{1}H NMR and ^{13}C NMR spectra of **24**.

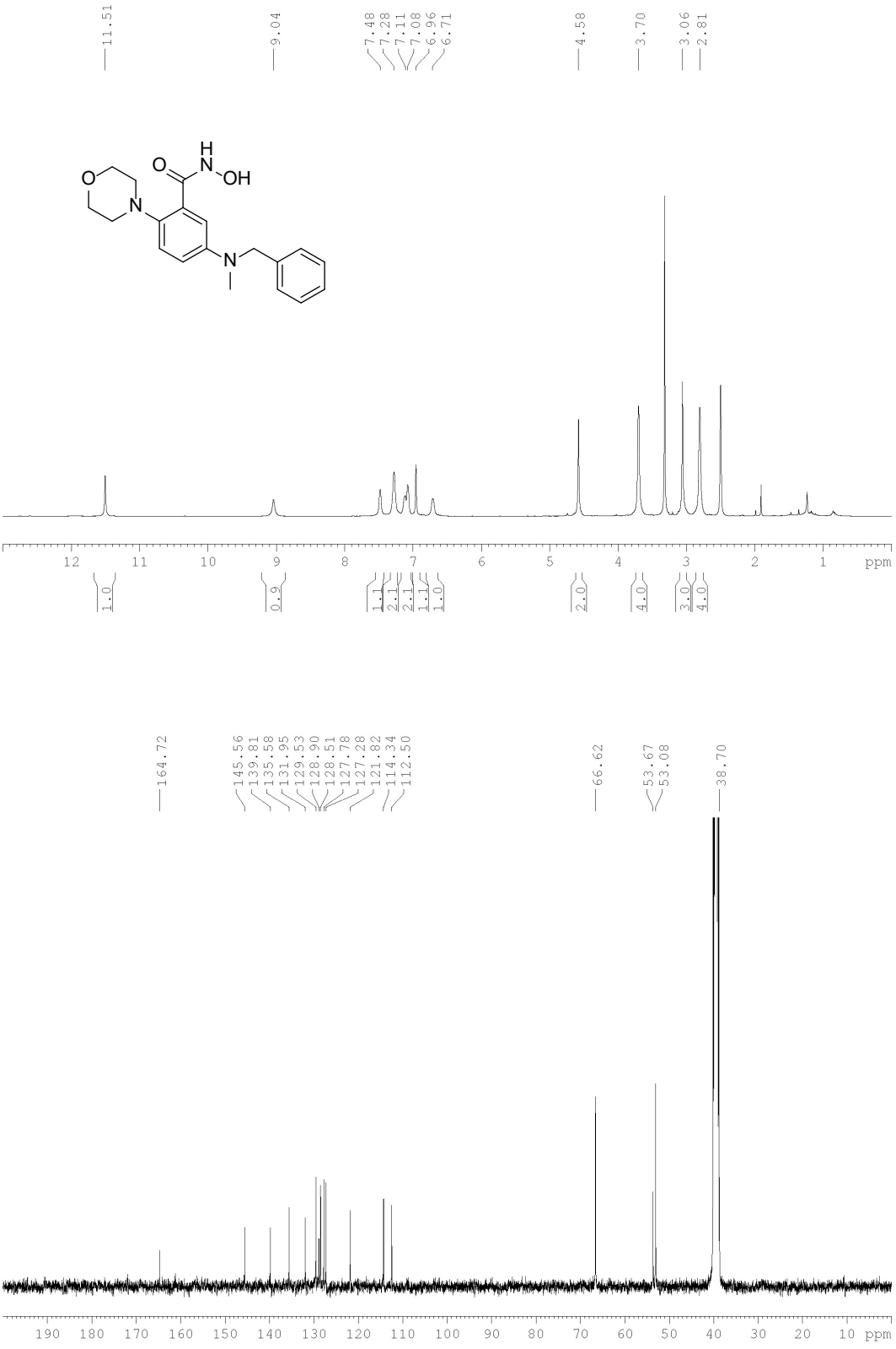


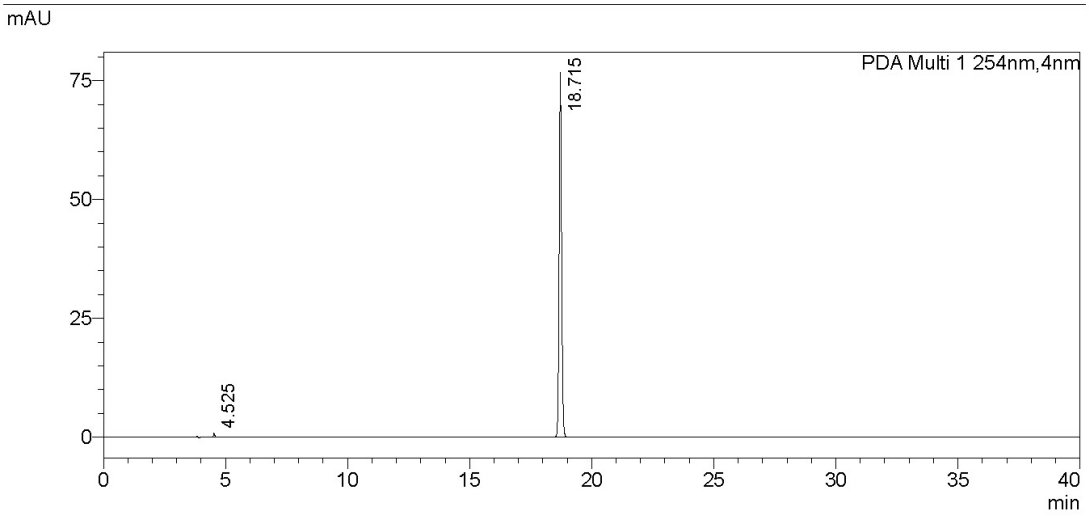
Figure S100. ^{1}H NMR and ^{13}C NMR spectra of **25**.

HPLC curves, tables and representative traces

Figure S101. Curve demonstrating mobile phase B (MeCN) proportion over the 40 min HPLC method used for purity and microsomal degradation analysis.

Table S1. Retention times and λ_{max} wavelengths for compounds assessed for microsomal stability. * = positive control.

Compound class	**Retention Time (min)**	**λ_{max} (nm)**
1,2,5 morpholinobenzoic acid (**1a**)	18.715	265
N-Me morpholinobenzoic acid (**24**)	21.665	271
1,2,4 morpholinobenzoic acid (**11e**)	19.856	299
1,2,5 tetrahydropyranyl benzoic acid (**20e**)	24.280	257
7-Ethoxycoumarin*	21.317	323

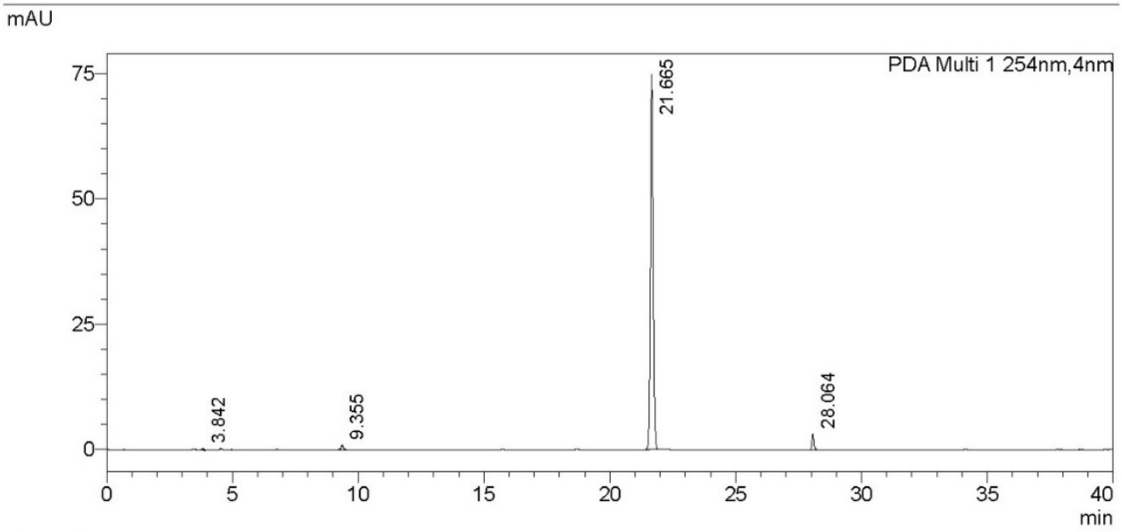


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	4.525	2997	780	0.531	0.531
2	18.715	561734	76730	99.469	99.469
Total		564732	77510		100.000

Figure S102. HPLC trace of **1a** at 254nm.

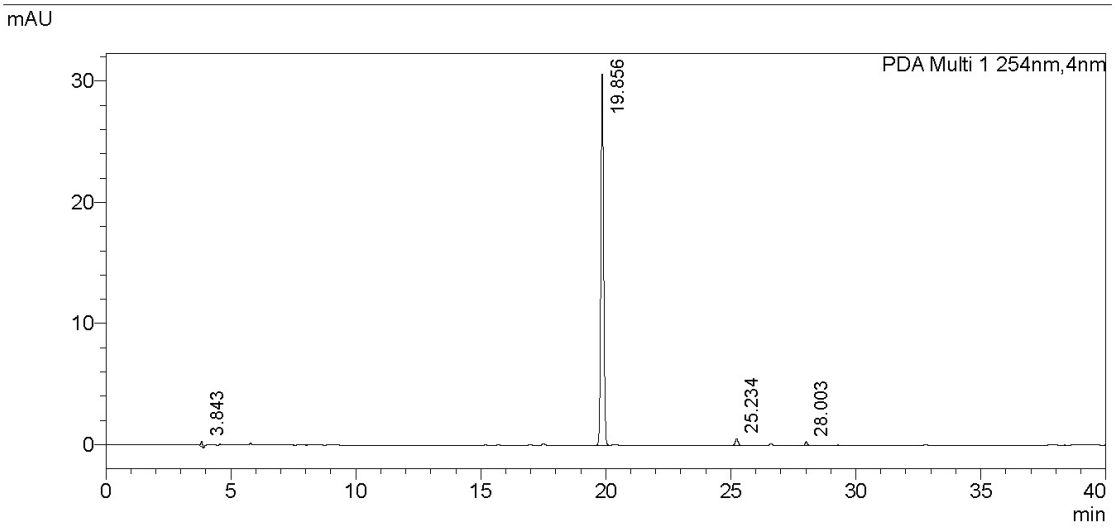


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	3.842	1724	379	0.000	0.280
2	9.355	6129	974	0.000	0.995
3	21.665	589108	74801	0.000	95.649
4	28.064	18946	3235	0.000	3.076
Total		615908	79389		100.000

Figure S103. HPLC trace of **24** at 254nm.

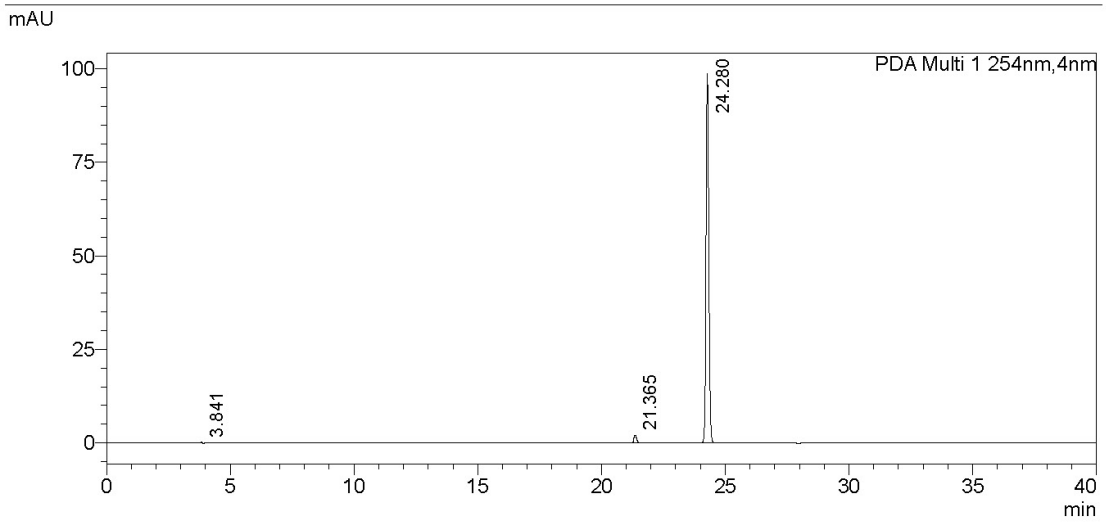


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	3.843	2104	462	0.892	0.892
2	19.856	227812	30634	96.572	96.572
3	25.234	4375	559	1.855	1.855
4	28.003	1607	302	0.681	0.681
Total		235898	31956		100.000

Figure S104. HPLC trace of **11e** at 254nm.

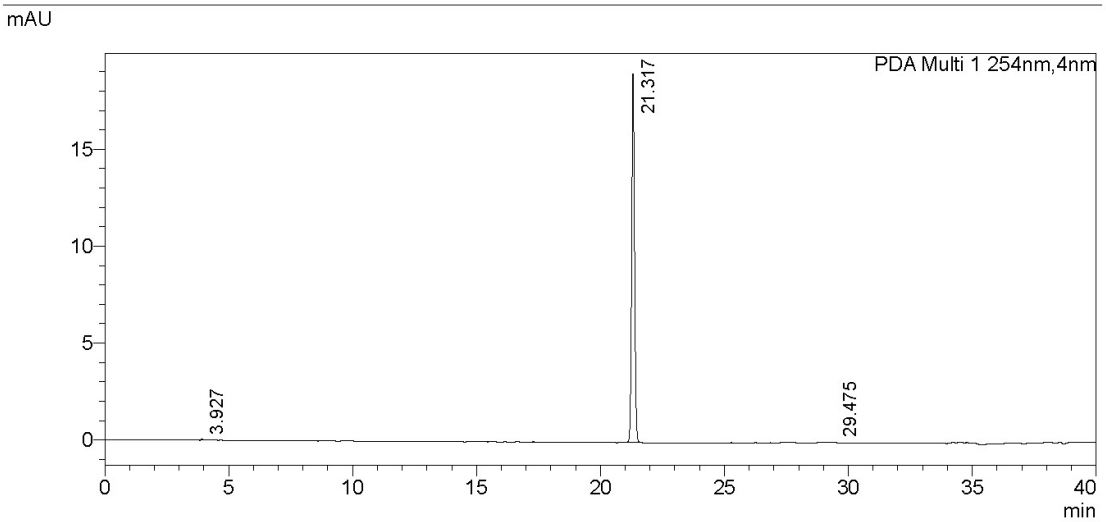


<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	3.841	1017	245	0.131	0.131
2	21.365	16111	2105	2.076	2.076
3	24.280	759070	98766	97.793	97.793
Total		776197	101115		100.000

Figure S105. HPLC trace of **20e** at 254nm.



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Area%
1	3.927	114	30	0.000	0.072
2	21.317	158165	19028	0.000	99.856
3	29.475	114	32	0.000	0.072
Total		158393	19090		100.000

Figure S106. HPLC trace of 7-ethoxycoumarin at 254nm.

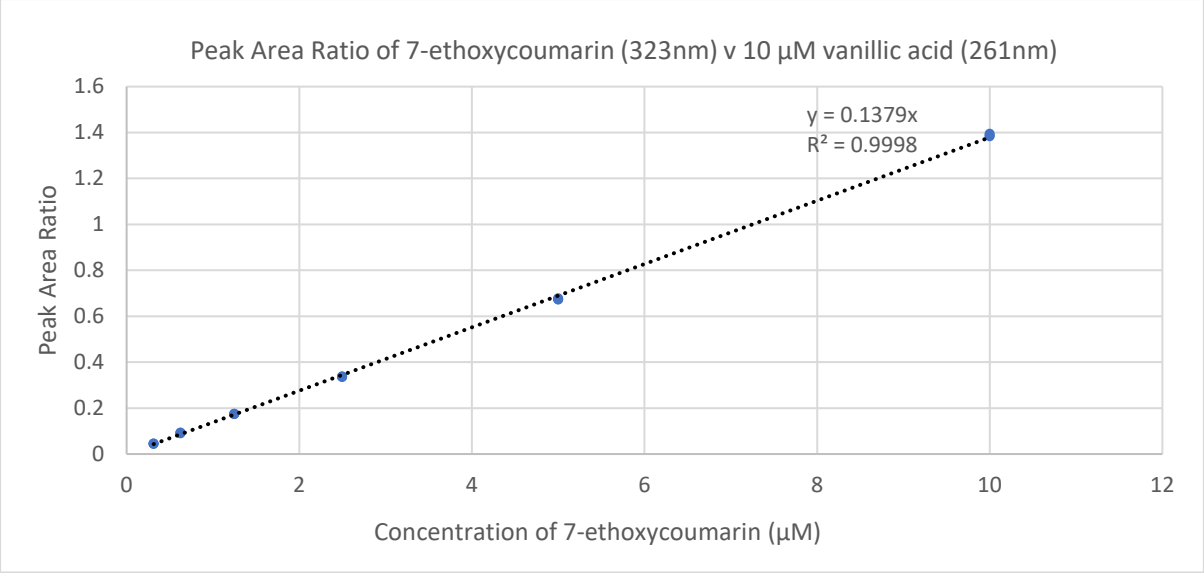


Figure S107. Standard curve of 7-ethoxycoumarin; positive control.

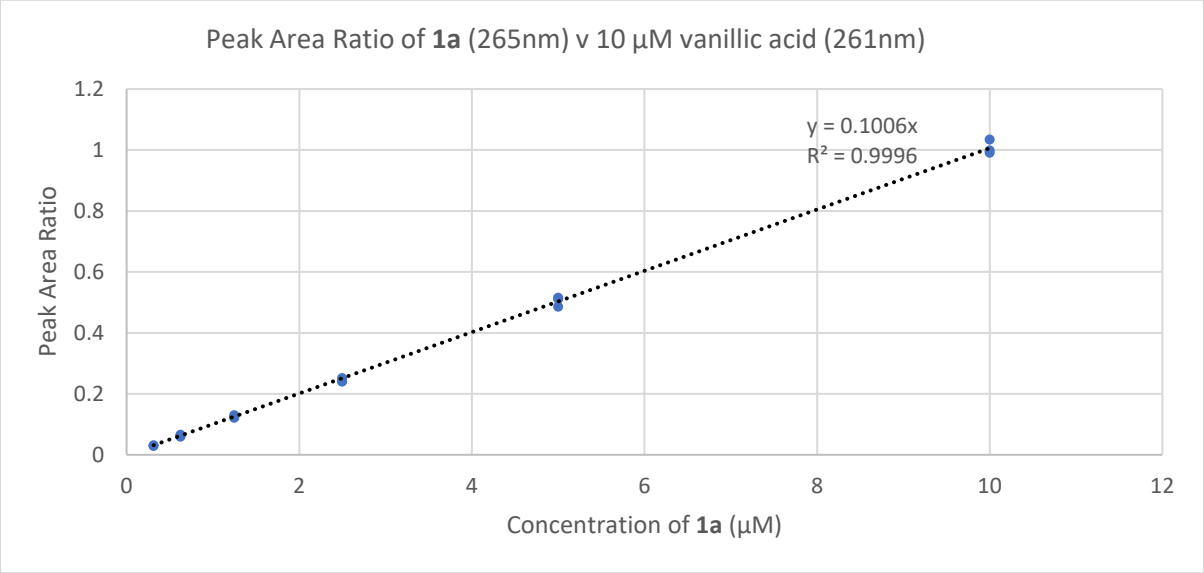


Figure S108. Standard curve of **1a**.

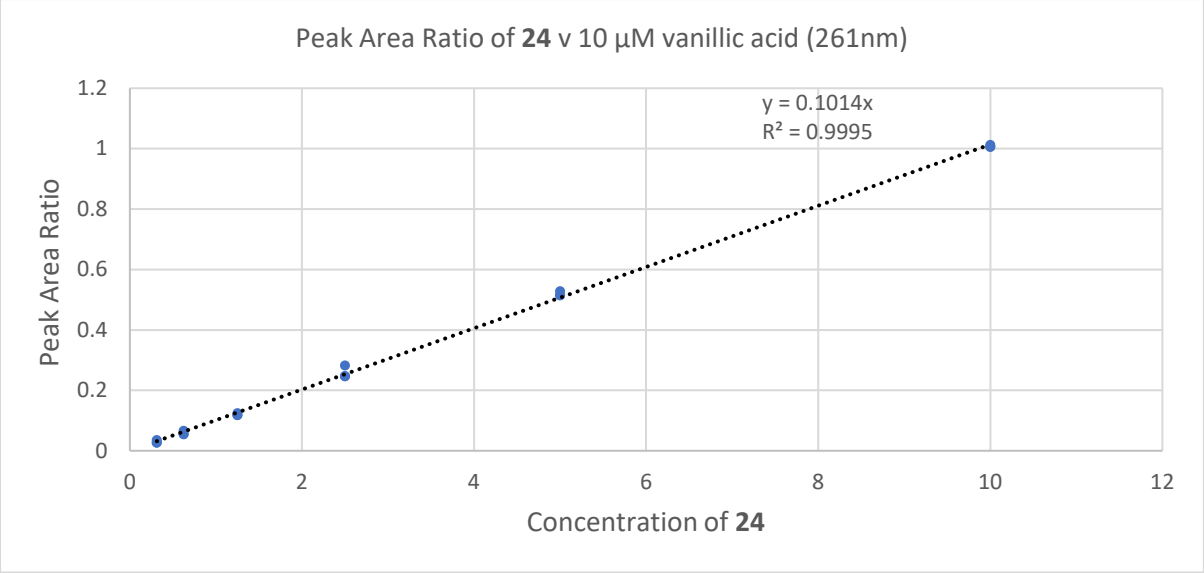


Figure S109. Standard curve of **24**.

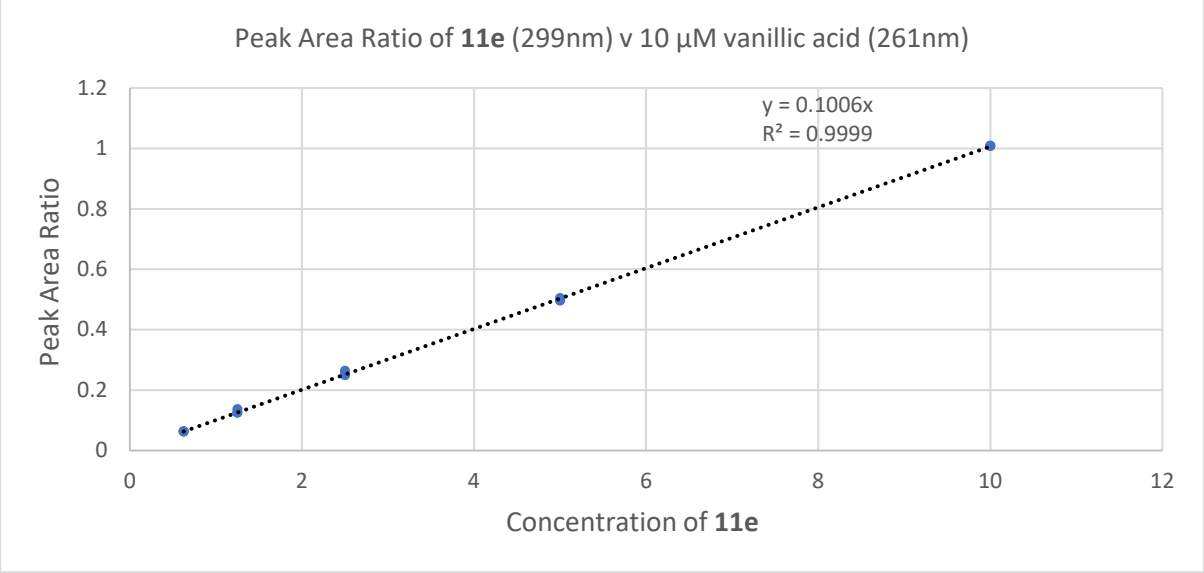


Figure S110. Standard curve of **11e**.

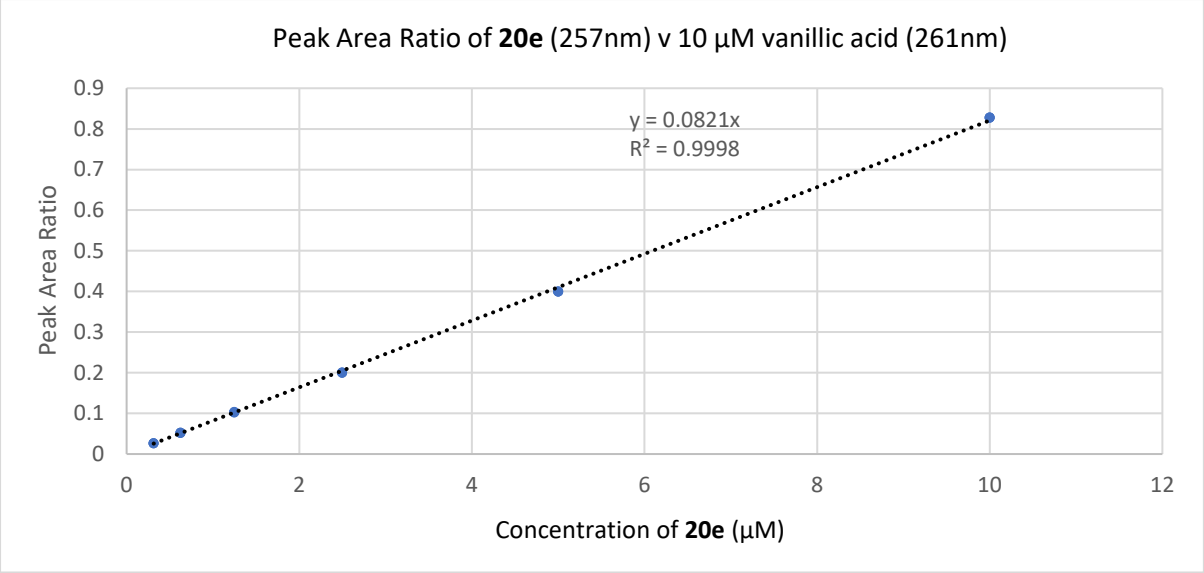


Figure S111. Standard curve of **20e**.

References:

[1] Docampo, M. L.; Pellón, R. F.; Estevez-Braun, A.; Ravelo, A. G. Ultrasound-Promoted Reaction of 2-Chlorobenzoic Acids and Aliphatic Amines. *Eur. J. Org. Chem.* **2007**, *2007* (24), 4111–4115. https://doi.org/10.1002/ejoc.200700281.