

**Supplementary Material for:**  
**Patterned Recognition of Amines and Ammonium Ions by a Stimuli-Responsive Foldamer-Based Hexameric Oligophenol Host**

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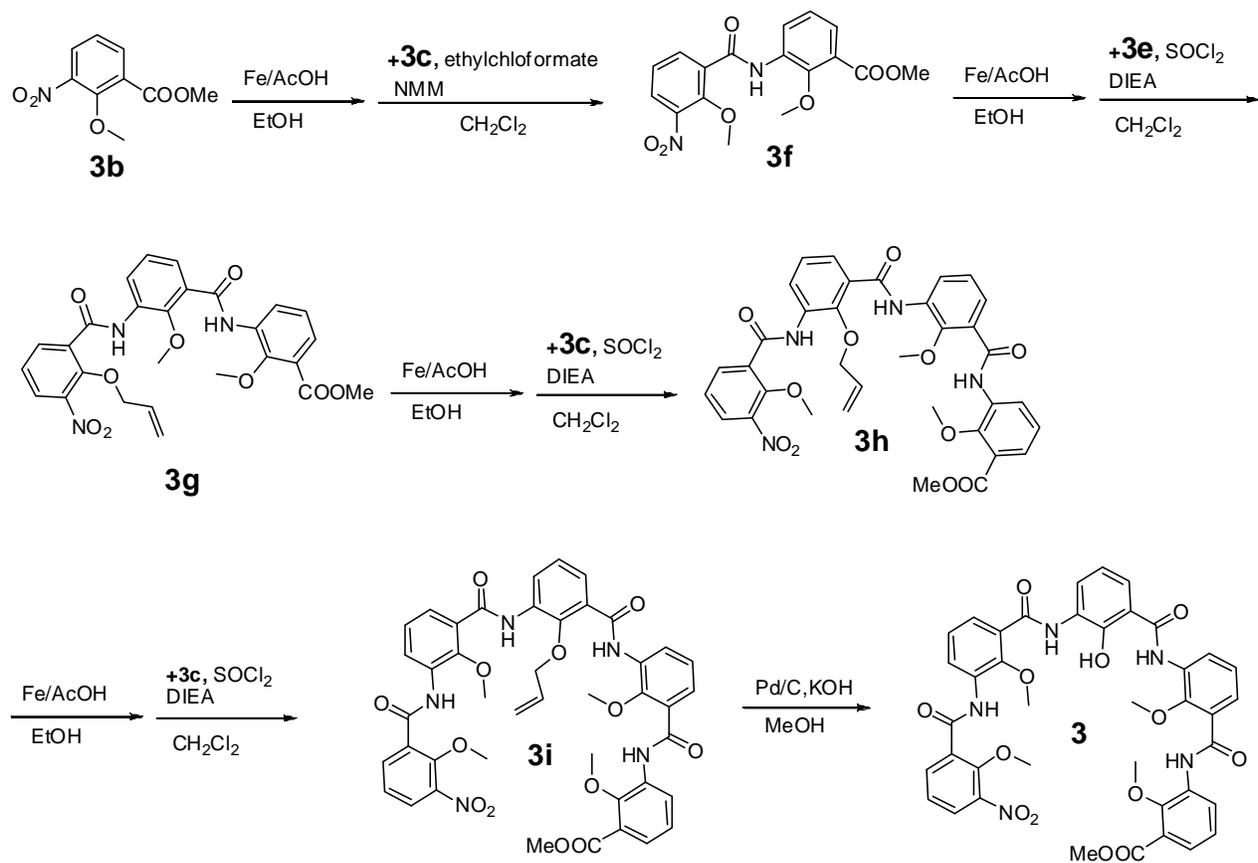
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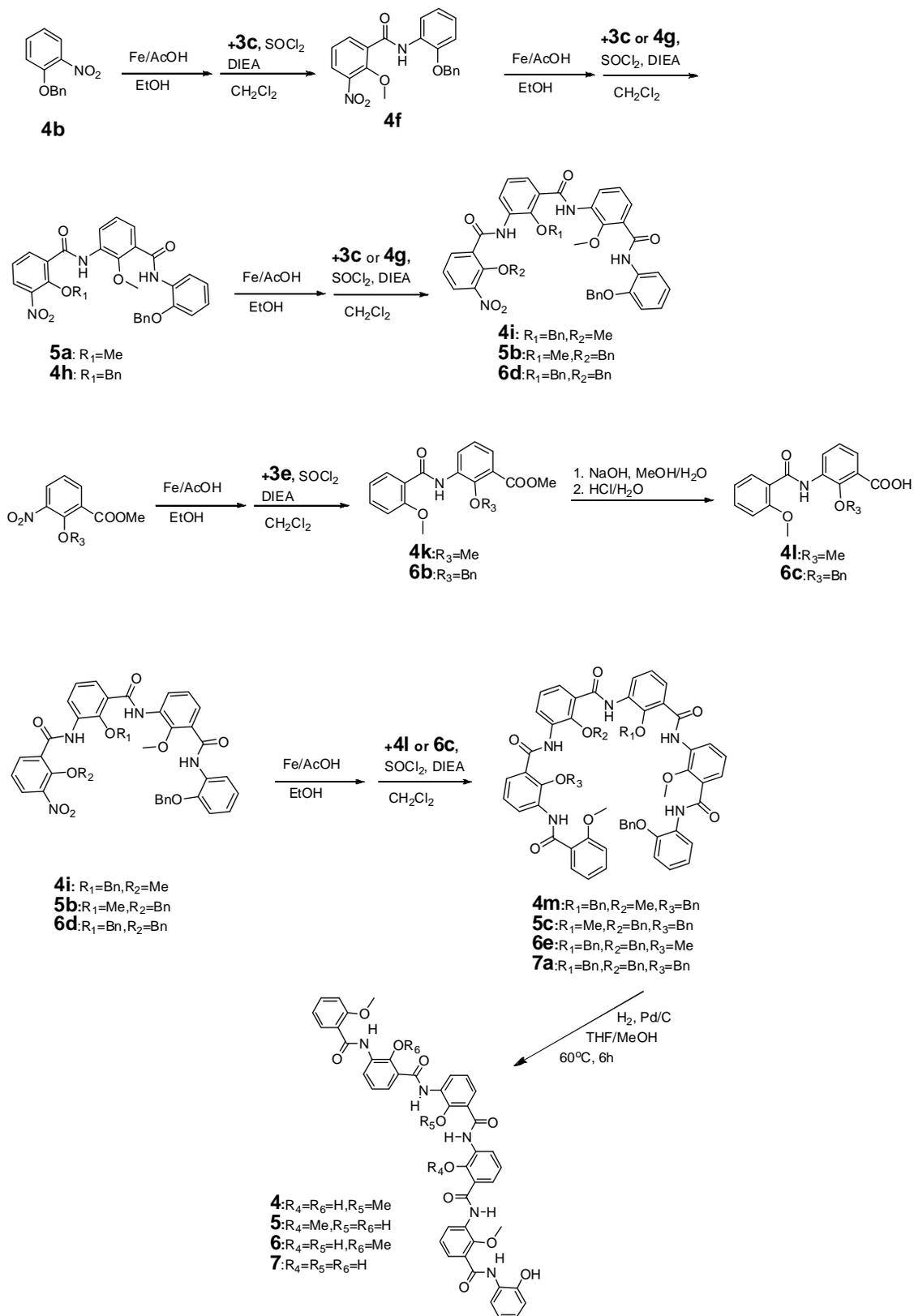
## 1. General Remarks

All the reagents were obtained from commercial suppliers and used as received unless otherwise noted. Aqueous solutions were prepared from distilled water. The organic solutions from all liquid extractions were dried over anhydrous  $\text{Na}_2\text{SO}_4$  for a minimum of 15 minutes before filtration. Reactions were monitored by thin-layer chromatography (TLC) on silica gel precoated glass plates (0.25 mm thickness, 60F-254, E. Merck). Flash column chromatography was performed using pre-coated 0.2 mm silica plates from Selecto Scientific. Chemical yields refer to pure isolated substances. Mass spectra were obtained using the Instrumentation includes Finnigan MAT95XL-T and Micromass VG7035.  $^1\text{H}$  NMR spectra were recorded on Bruker ACF-300 (300 MHz) or AVF500 spectrometers (500 MHz). The solvent signal of  $\text{CDCl}_3$  was referenced at  $\delta = 7.26$ . Coupling constants ( $J$  values) are reported in Hertz (Hz).  $^1\text{H}$  NMR data are recorded in the order: chemical shift value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons that gave rise to the signal and coupling constant, where applicable.  $^{13}\text{C}$  spectra are proton-decoupled and recorded on Bruker ACF300 (300 MHz) and ACF500 spectrometers (500 MHz). The solvent,  $\text{CDCl}_3$ , was referenced at  $\delta = 77$  ppm and  $\text{DMSO-d}_6$  was referenced at  $\delta = 39.5$ .  $\text{CDCl}_3$  (99.8%-Deuterated) and  $\text{DMSO-d}_6$  (99.8%-Deuterated) was purchased from Aldrich and used without further purification. UV-vis absorption and fluorescence spectra were recorded on a Shimadzu UV-1700 spectrometer and a RF-5301 fluorometer respectively.

## 2. Scheme S1a. Synthetic Route that Affords Pentamer **3**.

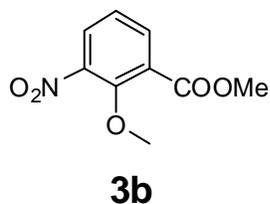


## 2. Scheme S1b. Synthetic Route that Affords Hexamers 4, 5, 6 and 7



### 3. Experimental Procedures and Compound Characterizations

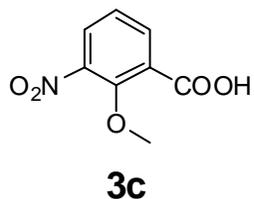
#### Methyl 2-methoxy-3-nitrobenzoate (**3b**)



Compound **3a** (6.00 g, 30.4 mmol) was dissolved in DMF (125mL) to which anhydrous  $K_2CO_3$  (15.6 g, 112.9 mmol) and iodomethane (6.98 mL, 112 mmol) were added. The mixture was heated at 70 °C for 4 hours. The reaction mixture was then filtered and the solvent was removed in *vacuo*.

The residue was dissolved in  $CH_2Cl_2$  (100 mL), washed with water ( $2 \times 50$  mL), and dried over anhydrous  $Na_2SO_4$ . Removal of  $CH_2Cl_2$  gave a pure light yellow solid **3a**. Yield: 6.41g, 82%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.01 (dd, 1H,  $J = 7.9, 1.8$ ), 7.90 (dd, 1H,  $J = 8.1, 1.8$ ), 7.26 (m, 1H), 3.99 (s, 3H), 3.95 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  164.4, 152.9, 145.17, 135.3, 128.0, 127.1, 123.5, 63.9, 52.4. HRMS-EI: calculated for  $[M]^+$  ( $C_9H_9NO_5$ ):  $m/z$  211.0481, found:  $m/z$  211.0480.

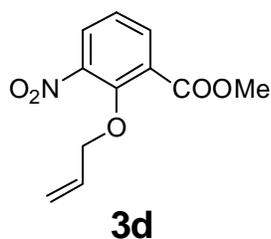
#### 2-methoxy-3-nitrobenzoic acid (**3c**)



Compound **3b** (4.00 g, 19.0 mmol) was dissolved in hot methanol (10 mL) to which 1M NaOH (40 mL, 40 mmol) was added. The mixture was heated under reflux for 2 hours and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl (80 mL) until the pH

was at least 1. The precipitated crude product was collected by filtration, which was recrystallized from hot methanol to give a pure white solid **3c**. Yield: 3.45 g, 92.0%,  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  8.28 (dd, 1H,  $J = 7.9, 1.8$ ), 8.03 (dd, 1H,  $J = 8.1, 1.8$ ), 7.36 (t, 1H,  $J = 7.9$ ), 4.08 (s, 3H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  164.9, 151.9, 144.5, 134.7, 127.3, 126.8, 122.8, 63.1.

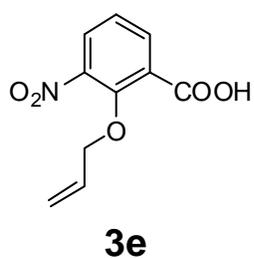
### Methyl 2-(allyloxy)-3-nitrobenzoate (**3d**)



Compound **3a** (6.00 g, 30.4 mmol) was dissolved in DMF (125mL) to which anhydrous  $K_2CO_3$  (8.4 g, 60.8 mmol) and allyl bromide (3.12 mL, 36 mmol) were added. The mixture was heated at 70 °C for 4 hours. The reaction mixture was then filtered and the solvent was removed in *vacuo*.

The residue was dissolved in  $CH_2Cl_2$  (100 mL), washed with water (2 x 50 mL), and dried over anhydrous  $Na_2SO_4$ . Removal of  $CH_2Cl_2$  gave a pure light yellow solid **3d**. Yield: 5.85g, 81%;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.03 (dd,  $J = 7.9, 1.8$  Hz, 1H), 7.91 (dd,  $J = 8.1, 1.8$  Hz, 1H), 7.28 (t,  $J = 8.0$  Hz, 1H), 6.08 (ddt,  $J = 16.4, 10.4, 6.0$  Hz, 1H), 5.39 (dq,  $J = 17.2, 1.4$  Hz, 1H), 5.30 (dd,  $J = 10.4, 1.2$  Hz, 1H), 4.66 – 4.65 (m, 1H), 4.65 – 4.63 (m, 1H), 3.95 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  164.9, 151.7, 145.8, 135.5, 132.5, 128.4, 127.9, 123.9, 119.3, 77.7, 52.8. HRMS-ESI: calculated for  $[M+Na]^+$  ( $C_{11}H_{11}NO_5Na$ ):  $m/z$  260.0535, found:  $m/z$  260.0539.

### 2-(allyloxy)-3-nitrobenzoic acid (**3e**)

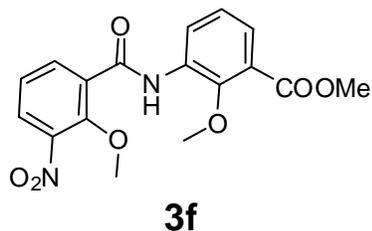


Compound **3d** (5.0 g, 21.0 mmol) was dissolved in hot methanol (10 mL) to which 1M NaOH (42 mL, 42 mmol) was added. The mixture was heated under reflux for 2 hours and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl (80 mL) until the pH

was at least 1. The precipitated crude product was collected by filtration, which was recrystallized from hot methanol to give a pure white solid **3e**. Yield: 4.10 g, 87.0%.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  8.28 (dd,  $J = 7.9, 1.6$  Hz, 1H), 8.03 (dd,  $J = 8.1, 1.7$  Hz, 1H), 7.37 (t,  $J = 8.0$  Hz, 1H), 6.10 (ddt,  $J = 16.7, 10.3, 6.3$  Hz, 1H), 5.43 (dd,  $J = 17.2, 1.2$  Hz, 1H), 5.36 (d,  $J = 10.3$  Hz, 1H), 4.71 (s, 1H), 4.70 (s, 1H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  168.4, 152.3, 145.6,

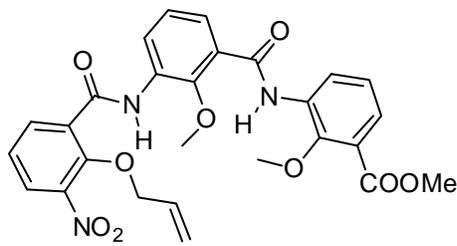
136.7, 131.9, 129.8, 126.1, 124.3, 120.6, 78.3. HRMS-ESI: calculated for  $[M]^-$  ( $C_{10}H_8NO_5$ ):  $m/z$  222.0402, found:  $m/z$  222.0398.

### Methyl 2-methoxy-3- (2-methoxy-3-nitrobenzamido)benzoate (**3f**)



To a solution of **3b** (3.16 g, 15 mmol) and iron (3.36 g, 60 mmol) in EtOH (100 mL) was added acetate acid (15 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $CH_2Cl_2$  and washed with water and Brine. The organic layer was dried over  $Na_2SO_4$ . Remove of  $CH_2Cl_2$  gave the amine product used for the next step reaction without purification. Acid **3c** (3.00 g, 15.2 mmol) was dissolved in  $CH_2Cl_2$  (30 mL) to which 4- methylmorpholine, NMM (2.2mL, 17.9mmol) and ethyl chloroformate (1.96 mL, 16.4 mmol) was added at 0 °C. The reaction mixture was stirred for at least 15 min then a solution of methyl 3-amino-2-methoxybenzoate dissolved in  $CH_2Cl_2$  (30 mL) was added. The reaction mixture was allowed to stir continuously for 6 hours at room temperature. The reaction mixture was washed with 1M  $KHSO_4$ , followed by saturated  $NaHCO_3$  and saturated  $NaCl$ . Drying over  $Na_2SO_4$  and removal of solvent in *vacuo* gave the crude product, which was recrystallized from methanol to give the pure product **3f** as a white solid. Yield: 3.49 g, 71%;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  10.37 (s, 1H), 8.80 (dd, 1H,  $J = 8.2, 1.6$ ), 8.45 (dd, 1H,  $J = 7.9, 1.8$ ), 7.99 (dd, 1H,  $J = 8.1, 1.8$ ), 7.63 (dd, 1H,  $J = 7.9, 1.6$ ), 7.41 (t, 1H,  $J = 8.1$ ), 7.24 (t, 1H,  $J = 8.1$ ), 4.10 (s, 3H), 3.95 (s, 6H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  165.9, 161.3, 151.5, 149.4, 136.5, 132.7, 128.8, 126.6, 124.6, 123.5, 64.5, 62.6. HRMS-ESI: calculated for  $[M+Na]^+$  ( $C_{17}H_{16}N_2O_7Na$ ):  $m/z$  383.0850, found:  $m/z$  383.0856.

### Methyl 3-(3-(2-(allyloxy)-3-nitrobenzamido)-2-methoxybenzamido)-2-methoxybenzoate (**3g**)

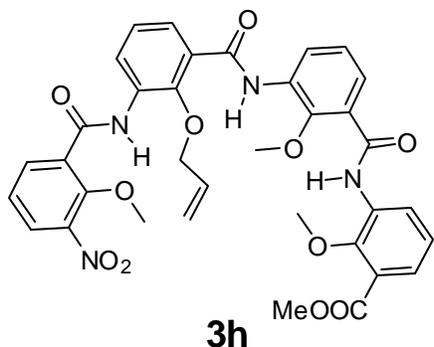


**3g**

To a solution of **3f** (5.00 g, 13.9 mmol) and iron (3.11 g, 55.6 mmol) in EtOH (100 mL) was added acetate acid (14 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the

solvent gave the amine product used for the next step reaction without purification. A solution of 2-(allyloxy)-3-nitrobenzoic acid **3e** (3.70 g, 16.7 mmol) in SOCl<sub>2</sub> (10.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine product and DIEA (4.75 mL, 28 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **3g** as a white solid. Yield: 5.50 g, 74%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.20 (s, 1H), 10.04 (s, 1H), 8.84 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.75 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.42 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.01 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.08 (ddt, *J* = 16.8, 10.3, 6.4 Hz, 1H), 5.36 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 3.95 (s, 6H), 3.93 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 165.9, 162.8, 161.7, 149.6, 149.3, 147.4, 144.8, 136.3, 133.1, 131.8, 131.1, 130.0, 128.8, 126.9, 126.7, 126.2, 125.7, 125.1, 124.9, 124.6, 124.4, 123.5, 121.8, 78.6, 63.1, 62.5, 52.3. HRMS-ESI: calculated for [M+Na]<sup>+</sup> (C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>9</sub>Na): *m/z* 558.1488, found: *m/z* 558.1494.

**Methyl 3-(3-(2-(allyloxy)-3-(2-methoxy-3-nitrobenzamido)benzamido)-2-methoxybenzamido)-2-methoxybenzoate (3h)**

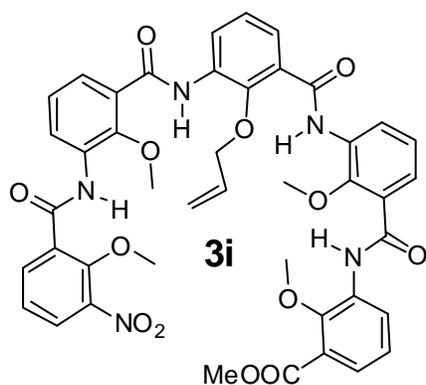


To a solution of **3g** (4.00 g, 7.47 mmol) and iron (1.67 g, 30.0 mmol) in EtOH (100 mL) was added acetate acid (7.50 mL). The reaction was heated at 60 °C for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine.

The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave the amine product used for the next step reaction without purification. A solution of 2-methoxy-3-nitrobenzoic acid (**3c**) (1.77 g, 9.0 mmol) in SOCl<sub>2</sub> (5.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine product and DIEA (3.0 mL, 18 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **3h** as a white solid. Yield: 4.04 g, 79%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.21 (s, 1H, amide proton), 10.09 (s, 1H, amide proton), 9.84 (s, 1H, amide proton), 8.84 (d, *J* = 8.2 Hz, 1H, aromatic proton), 8.78 (t, *J* = 7.1 Hz, 2H, aromatic proton), 8.42 (dd, *J* = 7.9, 1.5 Hz, 1H, aromatic proton), 8.03 (dd, *J* = 8.0, 1.7 Hz, 1H, aromatic proton), 7.92 – 7.87 (m, 2H, aromatic proton), 7.61 (dd, *J* = 7.9, 1.4 Hz, 1H, aromatic proton), 7.45 (t, *J* = 8.0 Hz, 1H, aromatic proton), 7.39 (t, *J* = 6.5 Hz, 1H, aromatic proton), 7.36 (t, *J* = 6.5 Hz, 1H, aromatic proton), 7.22 (t, *J* = 8.0 Hz, 1H, aromatic proton), 6.10 (ddt, *J* = 16.7, 10.3, 6.3 Hz, 1H, allyl proton), 5.33 (dd, *J* = 17.1, 0.9 Hz, 1H, allyl proton), 5.27 (d, *J* = 10.3 Hz, 1H, allyl proton), 4.55 (d, *J* = 6.3 Hz, 2H, methylene proton), 4.10 (s, 3H, methoxyl or methyl ester protons), 3.95 (s, 3H, methoxyl or methyl ester protons), 3.94 (s,

3H, methoxyl or methyl ester protons), 3.93 (s, 3H, methoxyl or methyl ester protons).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.9, 163.2, 162.9, 161.5, 151.3, 149.3, 147.2, 145.7, 144.4, 136.4, 133.1, 132.3, 132.1, 131.1, 129.3, 128.9, 127.5, 126.7, 126.6, 126.5, 126.2, 125.9, 125.8, 125.1, 124.9, 124.9, 124.7, 124.4, 123.4, 121.5, 77.3, 64.4, 63.0, 62.4, 52.4. HRMS-ESI: calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{35}\text{H}_{32}\text{N}_4\text{O}_{11}\text{Na}$ ):  $m/z$  707.1965, found:  $m/z$  707.1968.

**Methyl 3-(3-(2-(allyloxy)-3-(2-methoxy-3-(2-methoxy-3-nitrobenzamido) benzamido) benzamido)-2-methoxybenzamido)-2-methoxybenzoate (3i)**

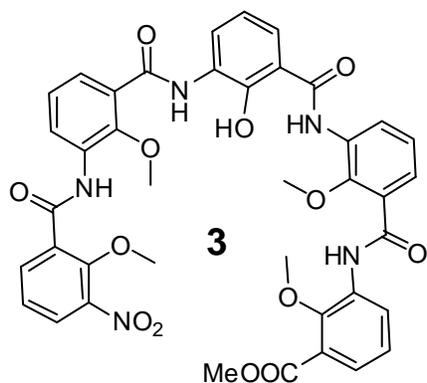


To a solution of **3h** (3.00 g, 4.40 mmol) and iron (1.00 g, 17.60 mmol) in EtOH (80 mL) was added acetate acid (4.40 mL). The reaction was heated at 60 °C for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $\text{CH}_2\text{Cl}_2$  and washed with water and Brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the

solvent gave the amine product used for the next step reaction without purification. A solution of 2-methoxy-3-nitrobenzoic acid (**3c**) (1.04 g, 5.30 mmol) in  $\text{SOCl}_2$  (5.0 mL) was heated at reflux for 2 hours. After removal of the  $\text{SOCl}_2$ , the amine product and DIEA (1.8 mL, 10.6 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat.  $\text{NaHCO}_3$  and Brine, the organic layer was dried over  $\text{Na}_2\text{SO}_4$ . The residue was recrystallized from methanol to give the pure product **3i** as a white solid. Yield: 2.67 g, 73%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.23 (s, 1H, amide proton), 10.22 (s, 1H, amide proton), 9.86 (s, 1H, amide proton), 9.79 (s, 1H, amide proton), 8.83 (m, 4H, aromatic proton), 8.49 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.05 (d,  $J = 8.0$  Hz, 1H, aromatic proton), 7.93 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 7.92 – 7.86 (m, 2H, aromatic proton), 7.63 (d,

$J = 7.9$  Hz, 1H, aromatic proton), 7.47 (t,  $J = 8.0$  Hz, 1H, aromatic proton), 7.40 (dt,  $J = 12.6, 8.0$  Hz, 3H, aromatic proton), 7.24 (t,  $J = 8.0$  Hz, 1H, aromatic proton), 6.15 (ddt,  $J = 16.6, 10.4, 6.1$  Hz, 1H, allyl proton), 5.39 (d,  $J = 17.1$  Hz, 1H, allyl proton), 5.30 (d,  $J = 10.3$  Hz, 1H, allyl proton), 4.61 (d,  $J = 6.1$  Hz, 2H, methylene proton), 4.15 (s, 3H, methoxyl or methyl ester protons), 4.03 (s, 3H, methoxyl or methyl ester protons), 3.95 (s, 3H, methoxyl or methyl ester protons), 3.92 (s, 3H, methoxyl or methyl ester protons), 3.90 (s, 3H, methoxyl or methyl ester protons).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.8, 163.5, 163.3, 163.0, 161.5, 151.6, 149.5, 147.5, 147.3, 145.8, 144.4, 136.8, 133.2, 132.6, 132.2, 132.2, 131.7, 129.3, 129.1, 127.6, 127.0, 126.7, 126.7, 126.6, 126.4, 126.3, 126.0, 125.9, 125.8, 125.2, 125.1, 125.1, 124.9, 124.9, 124.6, 123.5, 120.8, 64.6, 63.3, 63.1, 62.5, 52.3. HRMS-ESI: calculated for  $[\text{M-H}]^-$  ( $\text{C}_{43}\text{H}_{38}\text{N}_5\text{O}_{13}$ ):  $m/z$  832.2544, found:  $m/z$  832.2500.

**Methyl 3-(3-(2-hydroxy-3-(2-methoxy-3-(2-methoxy-3-nitrobenzamido) benzamido) benzamido)-2-methoxybenzamido)-2-methoxybenzoate (3)**

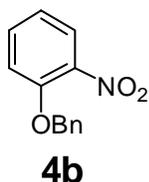


To a solution of **3i** (0.083 g, 0.1mmol) in MeOH (10 ml), Pd/C (0.008 g, 10%) and KOH (0.011g, 2mmol) were added. The reaction was allowed to proceed for 24 hours. The reaction mixture was then filtered and the solvent was removed in *vacuo*. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL), washed with 1M HCl (2 x 5 mL), and dried over

anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of  $\text{CH}_2\text{Cl}_2$  gave a pure product **3** as light yellow solid. Yield: 0.06 g, 75%.  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  15.09 (s, 1H, amide proton), 11.05 (s, 1H, amide proton), 10.53 (s, 1H, amide proton), 10.51 (s, 1H, amide proton), 8.84 (dd,  $J = 8.1, 1.6$  Hz, 1H, aromatic proton), 8.62 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.30 (dd,  $J = 7.4, 1.9$  Hz, 1H,

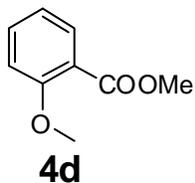
aromatic proton), 8.23 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.07 (d,  $J = 8.0$  Hz, 1H, aromatic proton), 8.00 (d,  $J = 7.7$  Hz, 1H, aromatic proton), 7.86 (dd,  $J = 7.8, 1.4$  Hz, 1H, aromatic proton), 7.58 (dd,  $J = 7.8, 1.4$  Hz, 1H, aromatic proton), 7.55 – 7.52 (m, 1H, aromatic proton), 7.52 – 7.50 (m, 1H, aromatic proton), 7.46 (t,  $J = 7.9$  Hz, 1H, aromatic proton), 7.35 (t,  $J = 7.9$  Hz, 1H, aromatic proton), 7.27 (dt,  $J = 14.8, 8.0$  Hz, 2H, aromatic proton), 6.17 (t,  $J = 7.7$  Hz, 1H, aromatic proton), 4.02 (s, 3H, methoxyl or methyl ester protons), 4.00 (s, 3H, methoxyl or methyl ester protons), 3.99 (s, 3H, methoxyl or methyl ester protons), 3.84 (s, 3H, methoxyl or methyl ester protons), 3.81 (s, 3H, methoxyl or methyl ester protons).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  167.7, 166.0, 164.1, 163.9, 163.8, 161.4, 150.5, 150.2, 149.8, 148.0, 144.3, 135.4, 134.5, 133.3, 132.5, 132.1, 131.9, 128.6, 128.6, 127.4, 127.3, 127.1, 126.8, 126.1, 125.4, 125.2, 124.9, 124.7, 124.6, 124.4, 124.3, 123.3, 119.9, 116.4, 107.9, 64.0, 62.8, 62.7, 62.4, 52.6. HRMS-ESI: calculated for  $[\text{M-H}]^-$  ( $\text{C}_{40}\text{H}_{34}\text{N}_5\text{O}_{13}$ ):  $m/z$  792.2231, found:  $m/z$  792.2151.

### 1-(benzyloxy)-2-nitrobenzene (**4b**)



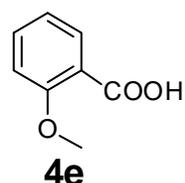
Compound **4a** (7.00 g, 50.4 mmol) was dissolved in DMF (150mL) to which anhydrous  $\text{K}_2\text{CO}_3$  (17.4 g, 126 mmol) and benzyl bromide (7.19 mL, 60.5 mmol) were added. The mixture was heated at 70 °C for 4 hours. The reaction mixture was then filtered and the solvent was removed in *vacuo*. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL), washed with water (2 x 50 mL), and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of  $\text{CH}_2\text{Cl}_2$  gave a pure light yellow solid **4b**. Yield: 9.8g, 85%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.87 (d,  $J = 9.6$  Hz, 1H), 7.51 (dd,  $J = 17.4, 8.4$  Hz, 3H), 7.42 (t,  $J = 7.5$  Hz, 2H), 7.36 (t,  $J = 7.3$  Hz, 1H), 7.15 (d,  $J = 8.4$  Hz, 1H), 7.05 (t,  $J = 7.7$  Hz, 1H), 5.25 (s, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.9, 140.2, 135.6, 134.1, 128.7, 128.2, 127.0, 125.6, 120.6, 115.2, 71.1.

### Methyl 2-methoxybenzoate (**4d**)



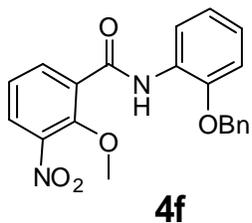
Compound **4c** (7.00 g, 50.7 mmol) was dissolved in DMF (100mL) to which anhydrous  $K_2CO_3$  (14 g, 101.4 mmol) and iodomethane (3.78 mL, 60.8 mmol) were added. The mixture was heated at 70 °C for 4 hours. The reaction mixture was then filtered and the solvent was removed in *vacuo*. The residue was dissolved in  $CH_2Cl_2$  (100 mL), washed with water (2 x 50 mL), and dried over anhydrous  $Na_2SO_4$ . Removal of  $CH_2Cl_2$  gave a pure light yellow solid. **1b**. Yield: 6.20g, 74%.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.78 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.78 (dd,  $J = 7.8, 1.6$  Hz, 1H), 7.52 – 7.37 (m, 1H), 7.04 – 6.89 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  166.7, 159.1, 133.5, 131.6, 120.1, 112.1, 56.0, 52.0. HRMS-EI: calculated for [M] ( $C_9H_{10}O_3$ ): m/z 166.0630, found: m/z 166.0631.

### 2-methoxybenzoic acid (**4e**)



Compound **4d** (5.00 g, 30.0 mmol) was dissolved in hot methanol (10 mL) to which 1M NaOH (60 mL, 60 mmol) was added. The mixture was heated under reflux for 2 hours and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl until the pH was at least 1. The precipitated crude product was collected by filtration, which was recrystallized from hot methanol to give a pure white solid **4e**. Yield: 4.30g, 94%.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  10.79 (s, 1H), 8.19 (d,  $J = 7.8$  Hz, 1H), 7.58 (t,  $J = 7.9$  Hz, 1H), 7.15 (t,  $J = 7.6$  Hz, 1H), 7.07 (d,  $J = 8.4$  Hz, 1H), 4.08 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  157.9, 135.0, 133.8, 122.2, 117.5, 111.5, 56.6. MS-ESI: calculated for  $[M-H]^-$  ( $C_8H_7O_3$ ): m/z 151.0, found: m/z 151.0.

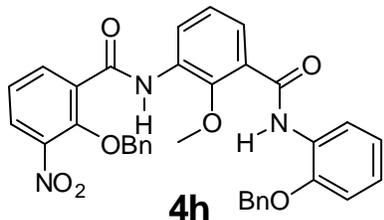
### *N*-(2-(benzyloxy)phenyl)-2-methoxy-3-nitrobenzamide (**4f**)



To a solution of **4b** (8.00 g, 34.9 mmol) and iron (7.82g, 140.0 mmol) in EtOH (400 mL) was added acetate acid (35 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of 2-methoxy-3-nitrobenzoic acid (**3c**) (8.27g, 42mmol) in SOCl<sub>2</sub> (20.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine product and DIEA (14.2 mL, 84 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (120 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **4f** as a white solid. Yield: 10.69g, 81%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.29 (s, 1H), 8.60 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.44 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.53 – 7.30 (m, 6H), 7.15 – 6.96 (m, 3H), 5.16 (s, 2H), 3.63 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 160.9, 151.5, 147.8, 144.3, 136.5, 136.0, 129.4, 128.8, 128.6, 128.4, 128.0, 127.9, 124.5, 124.4, 121.5, 120.7, 111.4, 71.0, 63.8. HRMS-ESI: calculated for [M-H]<sup>-</sup> (C<sub>21</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>): *m/z* 377.1137, found: *m/z* 377.1143.

## 2-(benzyloxy)-N-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenyl)-3-nitrobenzamide

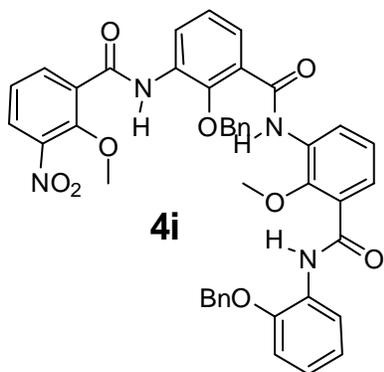
(4h)



To a solution of **4f** (5.00 g, 13.2 mmol) and iron (2.96 g, 52.9 mmol) in EtOH (100 mL) was added acetate acid (13 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and

washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of 2-(benzyloxy)-3-nitrobenzoic acid (**4g**) (4.32 g, 15.8 mmol) in SOCl<sub>2</sub> (8.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine and DIEA (5.4 mL, 31.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **4h** as a white solid. Yield: 5.34 g, 78%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.08 (s, 1H), 9.46 (s, 1H), 8.72 – 8.57 (m, 2H), 8.33 (dd, *J* = 7.9, 1.8 Hz, 1H), 8.06 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.27 (m, 6H), 7.23 – 7.01 (m, 8H), 5.12 (s, 2H), 5.08 (s, 2H), 3.17 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 162.3, 161.6, 149.4, 147.8, 147.3, 145.0, 136.1, 135.9, 133.8, 131.4, 130.9, 129.6, 129.2, 128.7, 128.6, 128.5, 128.4, 128.0, 127.0, 126.4, 125.3, 124.2, 124.0, 121.4, 120.9, 111.0, 80.5, 77.4, 77.0, 76.6, 70.8, 62.2. HRMS-ESI: calculated for [M+Na]<sup>+</sup> (C<sub>35</sub>H<sub>29</sub>N<sub>3</sub>O<sub>7</sub>Na): m/z 726.1903, found: m/z 626.1908.

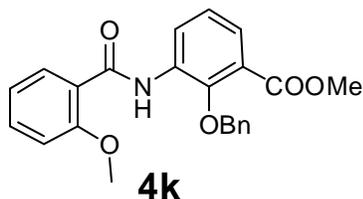
**2-(benzyloxy)-N-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenyl)-3-(2-methoxy-3-nitrobenzamido)benzamide (4i)**



To a solution of **4h** (4.00 g, 6.6 mmol) and iron (1.48 g, 26.5 mmol) in EtOH (100 mL) was added acetate acid (7 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of 2-methoxy-3-nitrobenzoic acid (**3c**) (1.56 g, 8.0 mmol) in SOCl<sub>2</sub> (20.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine and DIEA (2.7 mL, 16 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **4i** as a white solid. Yield: 4.32 g, 72%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.03 (s, 1H, amide proton), 9.92 (s, 1H, amide proton), 9.32 (s, 1H, amide proton), 8.79 (d, *J* = 8.0 Hz, 1H, aromatic proton), 8.71 (d, *J* = 7.9 Hz, 1H, aromatic proton), 8.60 (d, *J* = 6.9 Hz, 1H, aromatic proton), 8.32 (d, *J* = 7.7 Hz, 1H, aromatic proton), 7.99 (d, *J* = 7.7 Hz, 1H, aromatic proton), 7.89 (d, *J* = 7.7 Hz, 1H, aromatic proton), 7.79 (d, *J* = 7.6 Hz, 1H, aromatic proton), 7.45 – 7.28 (m, 5H, aromatic proton), 7.21 (m, 4H, aromatic proton), 7.12 – 7.01 (m, 6H, aromatic proton), 6.97 (d, *J* = 7.2 Hz, 1H, aromatic proton), 5.14 (s, 2H, methylene proton), 5.00 (s, 2H, methylene proton), 3.82 (s, 3H, methoxyl proton), 3.47 (s, 3H, methoxyl proton). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 163.6, 162.6, 161.4, 151.1, 147.6, 147.2, 145.8, 144.4, 136.4, 136.2, 134.3, 132.5, 131.9, 129.4, 129.2, 128.6, 128.6, 128.5, 128.4, 128.2,

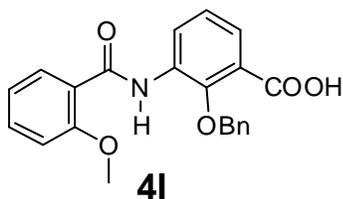
128.1, 127.4, 126.9, 126.5, 126.2, 125.8, 125.4, 124.9, 124.3, 124.2, 124.1, 121.6, 120.8, 111.6, 79.3, 70.7, 64.1, 62.4. HRMS-ESI: calculated for  $[M+Na]^+$  ( $C_{43}H_{36}N_4O_9Na$ ):  $m/z$  775.2380, found:  $m/z$  775.2374.

### Methyl 2-(benzyloxy)-3-(2-methoxybenzamido) benzoate (**4k**)



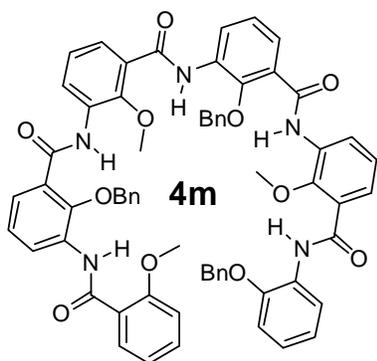
To a solution of methyl 2-(benzyloxy)-3-nitrobenzoate (**4j**) (2.87 g, 10.0 mmol) and iron (2.24 g, 40.0 mmol) in EtOH (100 mL) was added acetate acid (10 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $CH_2Cl_2$  and washed with water and Brine. The organic layer was dried over  $Na_2SO_4$ . Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of 2-methoxybenzoic acid (**4e**) (1.82 g, 12.0 mmol) in  $SOCl_2$  (10.0 mL) was heated at reflux for 2 hours. After removal of the  $SOCl_2$ , the amine and DIEA (0.92 mL, 24 mmol) in dry  $CH_2Cl_2$  (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat.  $NaHCO_3$  and Brine, the organic layer was dried over  $Na_2SO_4$ . The residue was recrystallized from methanol to give the pure product **4k** as a white solid. Yield: 2.97 g, 76%.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  10.66 (s, 1H), 8.84 (dd,  $J = 8.2, 1.4$  Hz, 1H), 8.29 (dd,  $J = 7.8, 1.7$  Hz, 1H), 7.63 (dd,  $J = 7.9, 1.5$  Hz, 1H), 7.50 – 7.43 (m, 3H), 7.34 – 7.27 (m, 3H), 7.23 (t,  $J = 8.0$  Hz, 1H), 7.10 (t,  $J = 7.5$  Hz, 1H), 6.87 (d,  $J = 8.3$  Hz, 1H), 4.99 (s, 2H), 3.91 (s, 3H), 3.38 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  166.0, 163.3, 157.3, 148.2, 136.7, 133.8, 133.3, 132.4, 128.3, 128.2, 125.8, 125.3, 124.4, 123.7, 121.2, 121.2, 111.2, 76.8, 55.2, 52.2. HRMS-ESI: calculated for  $[M+Na]^+$  ( $C_{23}H_{21}NO_5Na$ ):  $m/z$  414.1312, found:  $m/z$  414.1296.

### 2-(benzyloxy)-3-(2-methoxybenzamido) benzoic acid (**4l**)



Compound **4k** (3.90 g, 10.0 mmol) was dissolved in hot methanol (10 mL) to which 1M NaOH (20 mL, 20 mmol) was added. The mixture was heated under reflux for 2 hours and then quenched with water (100 mL). The aqueous layer was neutralized by addition of 1M HCl until the pH was at least 1. The precipitated crude product was collected by filtration, which was recrystallized from hot methanol to give a pure white solid **4l**. Yield: 3.13g, 83%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.59 (s, 1H), 8.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.32 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.44 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.31 (dd, *J* = 9.8, 4.9 Hz, 4H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 5.04 (s, 2H), 3.49 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 169.5, 163.6, 157.4, 148.8, 136.1, 133.7, 133.6, 132.6, 128.8, 128.6, 128.5, 126.9, 126.8, 124.9, 122.7, 121.4, 121.2, 111.3, 77.5, 55.4. HRMS-ESI: calculated for [M+Na]<sup>+</sup> (C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub>Na): *m/z* 400.1161, found: *m/z* 400.1151.

### 2-(benzyloxy)-3-(3-(2-(benzyloxy)-3-(2-methoxybenzamido)benzamido)-2-methoxybenzamido)-N-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenyl)benzamide (**4m**)

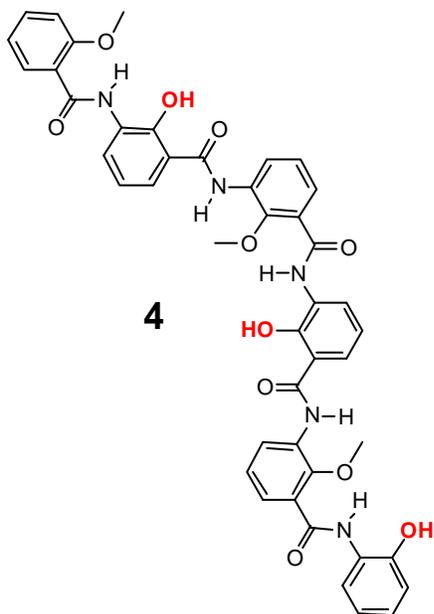


To a solution of **4i** (1.00 g, 1.3 mmol) and iron (0.30 g, 5.2 mmol) in EtOH (20 mL) was added acetate acid (1.3 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of **4l** (0.75 g, 2.0 mmol) in SOCl<sub>2</sub> (5.0 mL) was heated at reflux

for 2 hours. After removal of the SOCl<sub>2</sub>, the amine product and DIEA (0.68 mL, 4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by column chromatography to give **4m** as a white solid. Yield: 1.04 g, 73%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.33 (s, 1H, amide proton), 9.94 (s, 1H, amide proton), 9.73 (s, 1H, amide proton), 9.28 (s, 1H, amide proton), 9.08 (s, 1H, amide proton), 8.84 (d, *J* = 7.9 Hz, 1H, aromatic proton), 8.79 (d, *J* = 8.0 Hz, 1H, aromatic proton), 8.70 (d, *J* = 7.8 Hz, 1H, aromatic proton), 8.66 (d, *J* = 7.8 Hz, 1H, aromatic proton), 8.58 (d, *J* = 7.0 Hz, 1H, aromatic proton), 8.28 (d, *J* = 7.4 Hz, 1H, aromatic proton), 7.85 (d, *J* = 7.6 Hz, 1H, aromatic proton), 7.79 – 7.70 (m, 3H, aromatic proton), 7.48 (t, *J* = 7.4 Hz, 1H, aromatic proton), 7.43 – 7.29 (m, 4H, aromatic proton), 7.24 (s, 1H, aromatic proton), 7.20 – 6.91 (m, 18H, aromatic proton), 6.86 (d, *J* = 8.2 Hz, 1H, aromatic proton), 4.99 (s, 4H, methylene proton), 4.95 (s, 2H, methylene proton), 3.61 (s, 3H, methoxyl proton), 3.49 (s, 3H, methoxyl proton), 3.36 (s, 3H, methoxyl proton). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 163.9, 163.8, 163.5, 163.3, 162.5, 157.1, 147.5, 147.1, 147.1, 146.1, 145.7, 136.2, 134.8, 134.8, 134.6, 133.6, 133.1, 132.7, 132.6, 132.0, 131.8, 129.0, 129.0, 129.0, 128.5, 128.5, 128.3, 128.1, 128.1, 127.5, 126.8, 126.7, 126.4, 126.0, 125.7, 125.7, 125.6, 125.5, 125.5, 125.4, 124.9, 124.4, 124.2, 124.1, 121.7, 121.6, 121.4, 120.6, 111.4, 111.4, 78.7, 78.4, 70.6, 62.6, 62.3, 55.6. HRMS-ESI: calculated for [M+Na]<sup>+</sup> (C<sub>65</sub>H<sub>55</sub>N<sub>5</sub>O<sub>11</sub>Na): *m/z* 1104.3796, found: *m/z* 1104.3779.

**2-hydroxy-3-(3-(2-hydroxy-3-(2-methoxybenzamido) benzamido)-2-methoxybenzamido)-N-(3-(2-hydroxyphenylcarbamoyl)-2-methoxyphenyl) benzamide (4)**

Compound **4m** (0.50 g, 0.05 mmol) was going through hydrogenolysis at 40 °C in 12 ml THF and 4 ml MeOH using Pd/C (1.0 g, 200%) as catalyst for 3 hours. The reaction mixture was then

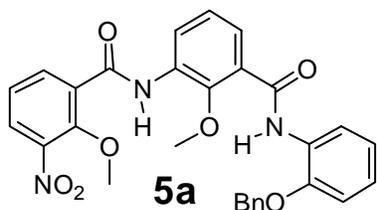


filtered and the residue was washed with DMF. DMF was removed under *vacuo* to give the solid.  $\text{CHCl}_3$  was added to the solid and stirred for 1 hour then filter to give product **4** as white solid. Yield: 0.29 g, 80%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3/\text{DMSO-}d_6 = 1:1$ )  $\delta$  13.07 (s, 1H, hydroxyl proton), 13.03 (s, 1H, hydroxyl proton), 10.71 (s, 3H, amide or hydroxyl proton), 10.64 (s, 1H, amide or hydroxyl proton), 10.45 (s, 1H, amide or hydroxyl proton), 10.15 (s, 1H, amide or hydroxyl proton), 8.58 (d,  $J = 7.8$  Hz, 1H,

aromatic proton), 8.54 (d,  $J = 7.5$  Hz, 1H, aromatic proton), 8.32 (d,  $J = 7.8$  Hz, 1H, aromatic proton), 8.09 (d,  $J = 7.5$  Hz, 1H, aromatic proton), 7.92 (m, 6H, aromatic proton), 7.58 (d,  $J = 6.7$  Hz, 1H, aromatic proton), 7.39 (m, 2H, aromatic proton), 7.27 (d,  $J = 8.1$  Hz, 1H, aromatic proton), 7.15 (t,  $J = 7.1$  Hz, 1H, aromatic proton), 7.06 (m, 2H, aromatic proton), 6.94 (d,  $J = 10.7$  Hz, 2H, aromatic proton), 6.84 (d,  $J = 6.5$  Hz, 1H, aromatic proton), 4.06 (s, 3H, methoxyl proton), 3.93 (s, 3H, methoxyl proton), 3.89 (s, 3H, methoxyl proton).  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-}d_6$ )  $\delta$  168.7, 168.7, 162.7, 162.5, 161.6, 157.2, 152.2, 152.2, 150.8, 150.3, 146.6, 133.6, 131.3, 131.2, 131.0, 130.5, 130.4, 128.7, 128.6, 128.3, 127.9, 126.9, 126.8, 126.8, 124.7, 124.4, 124.0, 123.9, 122.8, 122.3, 121.0, 121.0, 120.2, 119.1, 118.8, 114.9, 114.8, 114.6, 112.5, 62.1, 62.0, 56.4. HRMS-ESI: calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{44}\text{H}_{37}\text{N}_5\text{O}_{11}\text{Na}$ ):  $m/z$  834.2387, found:  $m/z$  834.2404.

#### **N-(2-(benzyloxy)phenyl)-2-methoxy-3-(2-methoxy-3-nitrobenzamido)benzamide (5a)**

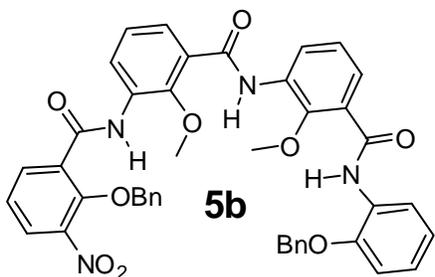
To a solution of **4f** (3.78 g, 10.0 mmol) and iron (2.24 g, 40.0 mmol) in EtOH (100 mL) was added acetate acid (10 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was



evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution

of **3c** (2.36 g, 12.0 mmol) in SOCl<sub>2</sub> (10.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine and DIEA (4.0 mL, 24 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **5a** as a white solid. Yield: 4.16g, 79%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.09 (s, 1H), 9.93 (s, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.66 (d, *J* = 7.6 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 3H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.13 – 7.01 (m, 3H), 5.13 (s, 2H), 3.91 (s, 3H), 3.58 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 162.2, 161.1, 150.9, 147.7, 147.1, 144.4, 136.3, 135.9, 131.6, 129.2, 128.7, 128.5, 128.0, 127.9, 126.8, 126.6, 125.3, 124.9, 124.2, 123.9, 121.3, 120.7, 111.1, 70.8, 64.4, 62.6. HRMS-ESI: calculated for [M-H]<sup>-</sup> (C<sub>29</sub>H<sub>24</sub>N<sub>3</sub>O<sub>7</sub>): *m/z* 526.1693, found: *m/z* 526.1604.

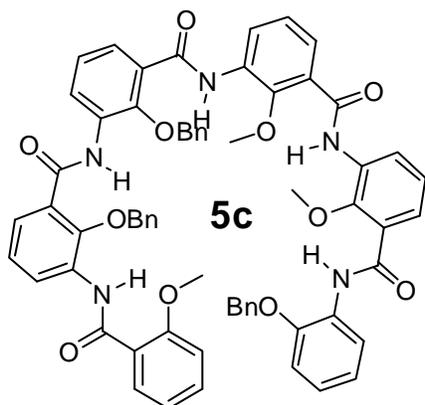
### 2-(benzyloxy)-N-(3-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenylcarbamoyl)-2-methoxyphenyl)-3-nitrobenzamide (5b)



To a solution of **5a** (2.63 g, 5.0 mmol) and iron (1.12 g, 20.0 mmol) in EtOH (50 mL) was added acetate acid (5 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub>

and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of **4g** (1.64 g, 6.0 mmol) in SOCl<sub>2</sub> (20.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine and DIEA (2.0 mL, 12 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **5b** as a white solid. Yield: 2.74g, 73%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.96 (s, 1H, amide proton), 9.64 (s, 1H, amide proton), 9.54 (s, 1H, amide proton), 8.74 – 8.68 (m, 2H, aromatic proton), 8.62 (dd, *J* = 7.6, 1.8 Hz, 1H, aromatic proton), 8.37 (dd, *J* = 7.8, 1.7 Hz, 1H, aromatic proton), 8.06 (dd, *J* = 8.0, 1.7 Hz, 1H, aromatic proton), 7.88 (ddd, *J* = 12.6, 7.9, 1.5 Hz, 2H, aromatic proton), 7.48 (t, *J* = 7.9 Hz, 1H, aromatic proton), 7.38 (t, *J* = 7.7 Hz, 4H, aromatic proton), 7.31 (t, *J* = 8.0 Hz, 1H, aromatic proton), 7.27-7.25 (m, 2H, aromatic proton), 7.21 (t, *J* = 7.7 Hz, 2H, aromatic proton), 7.16 (dd, *J* = 5.7, 4.1 Hz, 2H, aromatic proton), 7.11 – 6.92 (m, 4H, aromatic proton), 5.16 (s, 2H, methylene proton), 5.13 (s, 2H, methylene proton), 3.56 (s, 3H, methoxyl proton), 3.40 (s, 3H, methoxyl proton). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 162.9, 162.7, 161.9, 149.5, 147.7, 147.2, 147.2, 144.9, 136.3, 136.3, 136.2, 134.0, 131.9, 131.5, 131.0, 129.4, 129.3, 128.7, 128.5, 128.1, 128.0, 127.7, 126.9, 126.9, 126.6, 126.5, 125.6, 125.4, 125.4, 124.8, 124.5, 124.1, 121.6, 120.9, 111.5, 80.3, 70.8, 62.7, 62.6. HRMS-ESI: calculated for [M-H]<sup>-</sup> (C<sub>43</sub>H<sub>35</sub>N<sub>4</sub>O<sub>9</sub>): *m/z* 751.2482, found: *m/z* 751.2383.

**2-(benzyloxy)-3-(2-(benzyloxy)-3-(2-methoxybenzamido)benzamido)-N-(3-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenylcarbamoyl)-2-methoxyphenyl)benzamide**  
**(5c)**

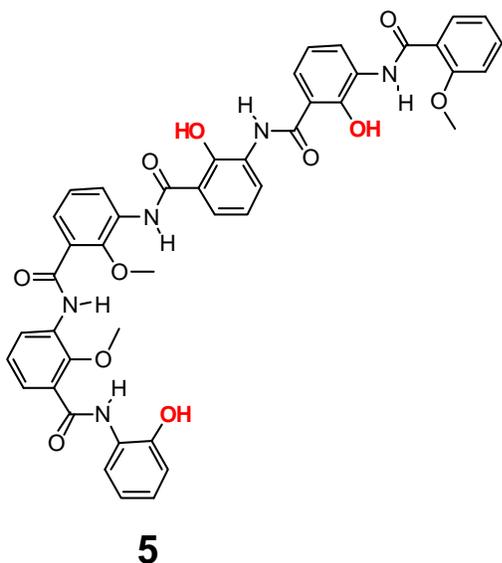


To a solution of **5b** (1.50 g, 2.0 mmol) and iron (0.45 g, 8.0 mmol) in EtOH (40 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the

amine product used for the next step reaction without purification. A solution of **4l** (1.13 g, 3.0 mmol) in SOCl<sub>2</sub> (5.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, the amine product and DIEA (1.0 mL, 6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **5c** as a white solid. Yield, 1.47g, 68%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.36 (s, 1H, amide proton), 9.84 (s, 1H, amide proton), 9.59 (s, 1H, amide proton), 9.53 (s, 1H, amide proton), 9.32 (s, 1H, amide proton), 8.78 (dd, *J* = 8.1, 1.4 Hz, 2H, aromatic proton), 8.75 – 8.67 (m, 2H, aromatic proton), 8.57 (dd, *J* = 7.8, 1.7 Hz, 1H, aromatic proton), 8.30 (dd, *J* = 7.8, 1.7 Hz, 1H, aromatic proton), 7.88 (dd, *J* = 7.8, 1.4 Hz, 1H, aromatic proton), 7.83 (d, *J* = 7.9 Hz, 2H, aromatic proton), 7.56 (dd, *J* = 7.8, 1.5 Hz, 1H, aromatic proton), 7.51 – 7.45 (m, 1H, aromatic proton), 7.40 (dt, *J* = 12.2, 8.0 Hz, 2H, aromatic proton), 7.30 (td, *J* = 8.0, 4.3 Hz, 2H, aromatic proton), 7.25 (s, 1H, aromatic proton), 7.21 – 6.97 (m, 17H, aromatic proton), 6.94 (dd, *J* = 7.8, 1.3 Hz, 1H, aromatic proton), 6.88 (d, *J* = 8.3 Hz, 1H, aromatic proton), 4.97 (s, 2H, methylene

proton), 4.92 (s, 2H, methylene proton), 4.90 (s, 2H, methylene proton), 3.58 (s, 3H, methoxyl proton), 3.53 (s, 3H, methoxyl proton), 3.42 (s, 3H, methoxyl proton).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 163.7, 163.5, 163.3, 162.7, 157.2, 147.6, 147.3, 147.2, 146.1, 145.9, 136.2, 135.1, 134.8, 133.8, 133.1, 132.6, 132.5, 132.1, 129.1, 128.9, 128.7, 128.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 127.0, 126.8, 126.3, 126.2, 126.1, 125.9, 125.7, 125.6, 125.5, 125.2, 125.2, 125.1, 125.0, 124.5, 124.2, 121.7, 121.6, 121.3, 120.8, 111.6, 111.5, 78.8, 78.2, 70.8, 65.9, 62.7, 62.6, 55.6. HRMS-ESI: calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{65}\text{H}_{54}\text{N}_5\text{O}_{11}\text{Na}$ ):  $m/z$  1104.3796, found:  $m/z$  1104.3831.

**2-hydroxy-3-(2-hydroxy-3-(2-methoxybenzamido)benzamido)-N-(3-(3-(2-hydroxyphenylcarbamoyl)-2-methoxyphenylcarbamoyl)-2-methoxyphenyl)benzamide (5)**

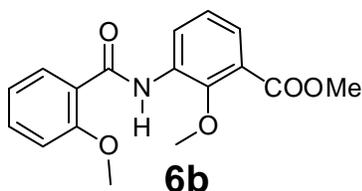


Compound **5c** (0.50 g, 0.05 mmol) was going through hydrogenolysis at 40 °C in 12 ml THF and 4 ml MeOH using Pd/C (1.0 g, 200%) as catalyst for 3 hours. The reaction mixture was then filtered and the solid was washed with DMF. DMF was removed in *vacuo* to give the solid.  $\text{CHCl}_3$  was added to the solid and stirred for 1 hour then filter to give product **5** as white solid. Yield, 29mg, 72%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  13.25 (s, 1H, hydroxyl proton), 12.11 (s, 1H, hydroxyl proton), 11.03 (s, 1H, amide or hydroxyl proton), 10.75 (s, 1H, amide or hydroxyl proton), 10.52 (s, 1H, amide or hydroxyl proton), 10.37 (s, 1H, amide or hydroxyl proton), 10.22 (s, 1H, amide or hydroxyl proton), 10.16 (s, 1H, amide or hydroxyl proton), 8.62 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.39 (d,  $J = 7.8$  Hz, 1H, aromatic proton), 8.33 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.24 (d,  $J = 7.9$  Hz, 1H,

$\text{CDCl}_3$ )  $\delta$  13.25 (s, 1H, hydroxyl proton), 12.11 (s, 1H, hydroxyl proton), 11.03 (s, 1H, amide or hydroxyl proton), 10.75 (s, 1H, amide or hydroxyl proton), 10.52 (s, 1H, amide or hydroxyl proton), 10.37 (s, 1H, amide or hydroxyl proton), 10.22 (s, 1H, amide or hydroxyl proton), 10.16 (s, 1H, amide or hydroxyl proton), 8.62 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.39 (d,  $J = 7.8$  Hz, 1H, aromatic proton), 8.33 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.24 (d,  $J = 7.9$  Hz, 1H,

aromatic proton), 8.11 (t,  $J = 6.4$  Hz, 2H, aromatic proton), 7.91 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 7.78 – 7.67 (m, 3H, aromatic proton), 7.59 (t,  $J = 7.8$  Hz, 1H, aromatic proton), 7.36 (q,  $J = 8.1$  Hz, 2H, aromatic proton), 7.27 (d,  $J = 8.4$  Hz, 1H, aromatic proton), 7.14 (dt,  $J = 20.4$ , 7.7 Hz, 2H, aromatic proton), 7.04 (t,  $J = 8.0$  Hz, 1H, aromatic proton), 6.95 (dt,  $J = 14.4$ , 7.4 Hz, 2H, aromatic proton), 6.84 (t,  $J = 7.4$  Hz, 1H, aromatic proton), 4.06 (s, 3H, methoxyl proton), 3.97 (s, 3H, methoxyl proton), 3.93 (s, 3H, methoxyl proton).  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  169.2, 165.7, 163.8, 162.6, 162.3, 157.2, 152.9, 149.4, 148.8, 146.9, 133.7, 131.9, 131.5, 131.3, 128.3, 128.1, 127.8, 127.2, 126.9, 126.5, 126.1, 126.0, 125.7, 124.5, 124.4, 124.3, 123.5, 122.3, 121.1, 121.0, 120.7, 119.2, 118.9, 118.4, 118.3, 114.9, 114.7, 112.6, 62.6, 62.4, 56.5, 39.7, 39.5, 39.3. HRMS-ESI: calculated for  $[\text{M-H}]^-$  ( $\text{C}_{43}\text{H}_{36}\text{N}_5\text{O}_{11}$ ):  $m/z$  810.2490, found:  $m/z$  810.2427.

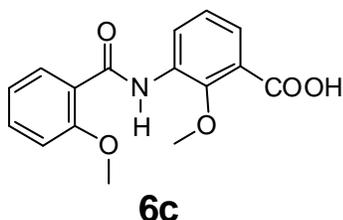
### Methyl 2-methoxy-3-(2-methoxybenzamido)benzoate (**6b**)



To a solution of **6a** (2.11 g, 10.0 mmol) and iron (2.24 g, 40.0 mmol) in EtOH (100 mL) was added acetate acid (10 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $\text{CH}_2\text{Cl}_2$  and washed with water and Brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of **4e** (1.82 g, 12.0 mmol) in  $\text{SOCl}_2$  (10.0 mL) was heated at reflux for 2 hours. After removal of the  $\text{SOCl}_2$ , the amine and DIEA (4.1 mL, 24 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (60 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat.  $\text{NaHCO}_3$  and Brine, the organic layer was dried over  $\text{Na}_2\text{SO}_4$ . The residue was recrystallized from methanol to give the pure product **6b** as a white solid. Yield: 2.42 g, 77%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.75 (s, 1H), 8.84 (dd,  $J = 8.2$ , 1.6 Hz, 1H), 8.33 (dd,  $J = 7.8$ , 1.8 Hz, 1H), 7.58

(dd,  $J = 7.9, 1.7$  Hz, 1H), 7.52 (ddd,  $J = 8.4, 7.3, 1.8$  Hz, 1H), 7.21 (t,  $J = 8.0$  Hz, 1H), 7.18 – 7.13 (m, 1H), 7.07 (d,  $J = 8.3$  Hz, 1H), 4.11 (s, 3H), 3.95 (s, 3H), 3.95 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 163.3, 157.4, 149.4, 133.7, 133.4, 132.6, 125.6, 125.0, 124.4, 123.5, 121.6, 111.6, 105.0, 62.1, 56.1, 52.2. HRMS-ESI: calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{17}\text{H}_{17}\text{NO}_5\text{Na}$ ):  $m/z$  338.0999, found:  $m/z$  338.1012.

### 2-methoxy-3-(2-methoxybenzamido)benzoic acid (**6c**)



Compound **6b** (1.58 g, 5.0 mmol) was dissolved in hot methanol (5 mL) to which 1M NaOH (10 mL, 10 mmol) was added. The mixture was heated under reflux for 2 hours and then quenched with water. The aqueous layer was neutralized by addition of 1M HCl

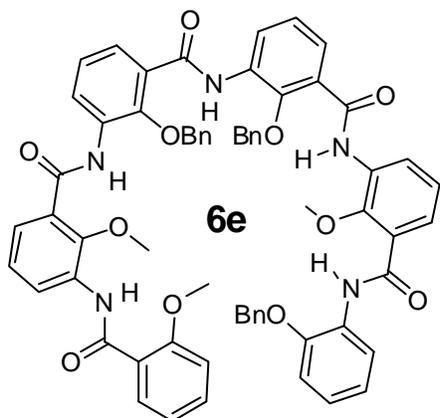
until the pH was at least 1. The precipitated crude product was collected by filtration, which was recrystallized from hot methanol to give a pure white solid **6c**. Yield, 1.31g, 87%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.66 (s, 1H), 8.87 (d,  $J = 8.2$  Hz, 1H), 8.34 (dd,  $J = 7.8, 1.8$  Hz, 1H), 7.80 (d,  $J = 7.9$  Hz, 1H), 7.60 – 7.47 (m, 1H), 7.29 (t,  $J = 8.1$  Hz, 1H), 7.17 (t,  $J = 7.6$  Hz, 1H), 7.08 (d,  $J = 8.3$  Hz, 1H), 4.13 (s, 3H), 4.01 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.4, 157.4, 133.7, 132.7, 126.8, 126.7, 126.7, 125.2, 125.2, 122.0, 121.9, 121.8, 121.4, 111.6, 62.5, 56.14. HRMS-ESI: calculated for  $[\text{M}-\text{H}]^-$  ( $\text{C}_{16}\text{H}_{14}\text{NO}_5$ ):  $m/z$  300.0872, found:  $m/z$  300.0881.

### 2-(benzyloxy)-N-(2-(benzyloxy)-3-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenylcarbamoyl)phenyl)-3-nitrobenzamide (**6d**)

To a solution of **4h** (3.02 g, 5.0 mmol) and iron (1.12 g, 20.0 mmol) in EtOH (50 mL) was added acetate acid (5 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $\text{CH}_2\text{Cl}_2$  and washed with water and Brine. The



**2-(benzyloxy)-3-(2-(benzyloxy)-3-(2-methoxy-3-(2-methoxybenzamido)benzamido)benzamido)-N-(3-(2-(benzyloxy)phenylcarbonyl)-2-methoxyphenyl)benzamide (6e)**



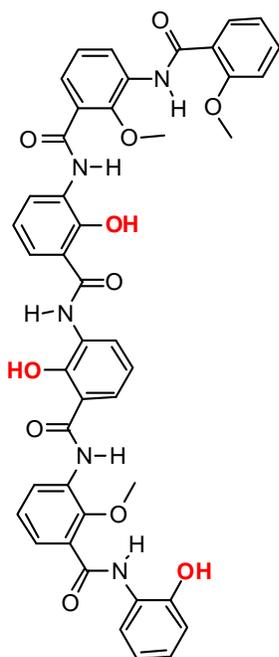
To a solution of **6d** (1.66 g, 2.0 mmol) and iron (0.45 g, 8.0 mmol) in EtOH (50 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with CH<sub>2</sub>Cl<sub>2</sub> and washed with water and Brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent gave the amine product used for the next step reaction without

purification. A solution of acid **6c** (0.9g, 3 mmol) in SOCl<sub>2</sub> (5.0 mL) was heated at reflux for 2 hours. After removal of the SOCl<sub>2</sub>, amine DIEA (1.0 mL, 6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was recrystallized from methanol to give the pure product **6d** as a white solid. Yield, 1.38g, 64%.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.40 (s, 1H, amide proton), 9.86 (s, 1H, amide proton), 9.65 (s, 1H, amide proton), 9.24 (s, 1H, amide proton), 9.16 (s, 1H, amide proton), 8.82 (d, *J* = 8.1 Hz, 2H, aromatic proton), 8.77 (d, *J* = 8.1 Hz, 1H, aromatic proton), 8.65 (d, *J* = 7.1 Hz, 1H, aromatic proton), 8.58 (dd, *J* = 7.5, 2.0 Hz, 1H, aromatic proton), 8.33 (dd, *J* = 7.8, 1.7 Hz, 1H, aromatic proton), 7.84 (dd, *J* = 7.9, 1.4 Hz, 1H, aromatic proton), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1H, aromatic proton), 7.69 (dd, *J* = 7.8, 1.4 Hz, 1H, aromatic proton), 7.64 (dd, *J* = 7.8, 1.5 Hz, 1H, aromatic proton), 7.53 – 7.48 (m, 1H, aromatic proton), 7.35 (ddt, *J* = 30.8, 11.0, 8.0 Hz, 4H, aromatic proton), 7.25 – 6.91 (m, 20H, aromatic proton), 5.00 (s, 2H, methylene proton), 4.97 (s,

2H, methylene proton), 4.79 (s, 2H, methylene proton), 3.77 (s, 3H, methoxyl proton), 3.68 (s, 3H, methoxyl proton), 3.36 (s, 3H, methoxyl proton).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.9, 163.6, 163.5, 163.4, 162.6, 157.2, 147.6, 147.2, 147.0, 145.8, 145.6, 136.2, 134.8, 133.7, 132.9, 132.8, 132.7, 132.5, 131.8, 130.8, 129.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 127.6, 126.9, 126.7, 126.4, 125.8, 125.75, 125.7, 125.6, 125.5, 125.4, 125.3, 125.1, 124.5, 124.4, 124.3, 124.1, 121.9, 121.6, 121.5, 120.8, 111.6, 111.5, 78.9, 78.7, 70.7, 62.4, 62.3, 55.9. HRMS-ESI: calculated for  $[\text{M}+\text{Na}]^+$  ( $\text{C}_{65}\text{H}_{55}\text{N}_5\text{O}_{11}\text{Na}$ ):  $m/z$  1104.3790, found:  $m/z$  1104.3805.

**2-hydroxy-3-(2-hydroxy-3-(2-methoxy-3-(2-methoxybenzamido)benzamido)benzamido)-N-(3-(2-hydroxyphenylcarbamoyl)-2-methoxyphenyl)benzamide (6)**

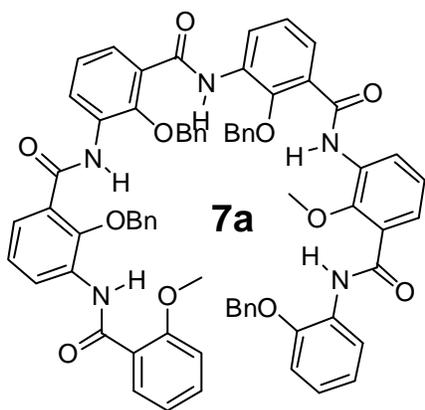


**6**

Compound **6e** (0.05 g, 0.05 mmol) was going through hydrogenolysis at 40 °C in 12 ml THF and 4 ml MeOH using Pd/C (0.10 g, 200%) as catalyst for 6 hours. The reaction mixture was then filtered and the solid was washed with DMF. DMF was removed in *vacuo* to give the solid.  $\text{CHCl}_3$  was added to the solid and stirred for 1 hour then filter to give product **6** as white solid. Yield, 28mg, 70%.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3/\text{DMSO}-d_6 = 1:1$ )  $\delta$  12.76 (s, 1H, hydroxyl proton), 12.16 (s, 1H, hydroxyl proton), 10.53 (s, 1H, amide or hydroxyl proton), 10.34 (s, 1H, amide or hydroxyl proton), 10.28 (s, 1H, amide or hydroxyl proton), 10.11 (s, 1H, amide or hydroxyl proton), 9.72 (s, 1H, amide or hydroxyl proton), 9.37 (s, 1H, amide or hydroxyl proton), 8.67 (d,  $J = 6.8$  Hz, 1H, aromatic proton), 8.57 (d,  $J = 7.9$  Hz, 1H, aromatic proton), 8.25 (d,  $J = 8.0$  Hz, 1H, aromatic proton), 8.21 – 8.16 (m, 2H, aromatic proton), 8.03 (d,  $J = 7.7$  Hz, 1H, aromatic proton), 7.95

(d,  $J = 8.0$  Hz, 1H, , aromatic proton), 7.85 (d,  $J = 9.3$  Hz, 1H, , aromatic proton), 7.74 (d,  $J = 7.9$  Hz, 1H, , aromatic proton), 7.69 (d,  $J = 8.1$  Hz, 1H, , aromatic proton), 7.50 (t,  $J = 7.8$  Hz, 1H, , aromatic proton), 7.25 (td,  $J = 8.0, 5.2$  Hz, 2H, , aromatic proton), 7.13 – 7.07 (m, 2H, , aromatic proton), 7.01 (t,  $J = 8.0$  Hz, 1H, , aromatic proton), 6.97 (t,  $J = 8.1$  Hz, 1H, , aromatic proton), 6.88 (dt,  $J = 7.1, 3.5$  Hz, 2H, , aromatic proton), 6.81 – 6.77 (m, 1H, , aromatic proton), 4.11 (s, 3H, methoxyl proton), 3.98 (s, 3H, methoxyl proton), 3.94 (s, 3H, methoxyl proton).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3/\text{DMSO}-d_6 = 1:1$ )  $\delta$  169.8, 166.2, 164.3, 163.1, 162.8, 157.7, 153.4, 151.1, 149.9, 149.3, 147.4, 134.2, 132.4, 132.2, 132.0, 131.8, 128.7, 128.6, 128.4, 127.7, 127.4, 127.1, 126.7, 126.5, 126.1, 125.1, 125.0, 124.8, 124.1, 122.8, 121.7, 121.5, 121.2, 119.7, 119.6, 118.9, 115.4, 115.2, 113.1, 63.1, 62.9, 57.0. HRMS-ESI: calculated for  $[\text{M}-\text{H}]^-$  ( $\text{C}_{44}\text{H}_{36}\text{N}_5\text{O}_{11}$ ):  $m/z$  810.2417, found:  $m/z$  810.2414.

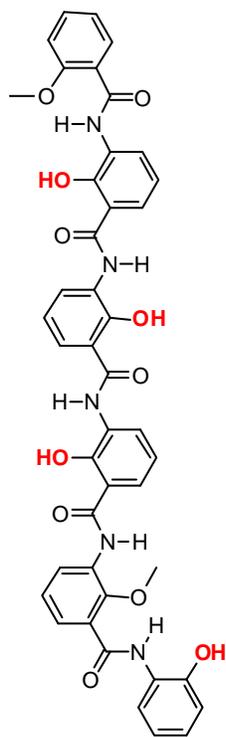
**2-(benzyloxy)-3-(2-(benzyloxy)-3-(2-(benzyloxy)-3-(2-methoxybenzamido)benzamido)benzamido)-N-(3-(2-(benzyloxy)phenylcarbamoyl)-2-methoxyphenyl)benzamide (7a)**



To a solution of **6d** (1.66 g, 2.0 mmol) and iron (0.45 g, 8.0 mmol) in EtOH (50 mL) was added acetate acid (2 mL). The reaction was refluxed for 2 hours. After cooling, the solvent was evaporated and the residue was dissolved with  $\text{CH}_2\text{Cl}_2$  and washed with water and Brine. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent gave the amine product used for the next step reaction without purification. A solution of acid **4l** (1.13g, 3 mmol) in  $\text{SOCl}_2$  (5.0 mL) was heated at reflux for 2 hours. After removal of the  $\text{SOCl}_2$ , amine and

DIEA (1.0 mL, 6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added to the residue. The reaction was allowed to proceed for overnight. After washing with HCl solution, aqueous sat. NaHCO<sub>3</sub> and Brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by column chromatography to give the pure product **7a** as a white solid. Yield, 1.20g, 52%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.33 (s, 1H, amide proton), 9.87 (s, 1H, amide proton), 9.30 (s, 1H, amide proton), 9.17 (s, 1H, amide proton), 9.03 (s, 1H, amide proton), 8.79 (dd, *J* = 8.2, 1.4 Hz, 1H, aromatic proton), 8.75 (d, *J* = 8.1 Hz, 1H, aromatic proton), 8.68 (d, *J* = 7.0 Hz, 1H, aromatic proton), 8.63 (d, *J* = 7.1 Hz, 1H, aromatic proton), 8.57 (dd, *J* = 7.3, 2.2 Hz, 1H, aromatic proton), 8.29 (dd, *J* = 7.8, 1.7 Hz, 1H, aromatic proton), 7.84 (dd, *J* = 7.9, 1.4 Hz, 1H, aromatic proton), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1H, aromatic proton), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H, aromatic proton), 7.52 – 7.46 (m, 2H, aromatic proton), 7.40 (t, *J* = 8.0 Hz, 1H, aromatic proton), 7.35 (t, *J* = 8.0 Hz, 1H, aromatic proton), 7.30 (td, *J* = 8.0, 2.2 Hz, 2H, aromatic proton), 7.23 – 6.90 (m, 24H, aromatic proton), 6.86 (d, *J* = 8.3 Hz, 1H, aromatic proton), 4.96 (s, 2H, methylene proton), 4.91 (s, 2H, methylene proton), 4.83 (s, 2H, methylene proton), 4.81 (s, 2H, methylene proton), 3.37 (s, 3H, methoxyl proton), 3.35 (s, 3H, methoxyl proton). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.0, 163.8, 163.7, 163.5, 162.7, 157.2, 147.6, 147.2, 146.0, 145.8, 145.7, 136.2, 135.0, 134.8, 134.6, 133.6, 133.2, 132.6, 132.6, 132.5, 131.9, 129.0, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 126.9, 126.4, 125.9, 125.7, 125.6, 125.6, 125.5, 125.3, 125.0, 124.9, 124.7, 124.5, 124.3, 124.1, 121.7, 121.6, 121.5, 120.8, 111.6, 111.4, 78.7, 78.6, 78.2, 70.7, 62.3, 55.6. HRMS-ESI: calculated for [M+Na]<sup>+</sup> (C<sub>71</sub>H<sub>59</sub>N<sub>5</sub>O<sub>11</sub> Na): *m/z* 1180.4109, found: *m/z* 1180.4074.

**2-hydroxy-3-(2-hydroxy-3-(2-hydroxy-3-(2-methoxybenzamido)benzamido)benzamido)-N-(3-(2-hydroxyphenylcarbamoyl)-2-methoxyphenyl)benzamide (7)**



**7**

Compound **7a** (0.046 g, 0.04 mmol) was going through hydrogenolysis at 40°C in 12 ml THF and 4 ml MeOH using Pd/C (0.10 g, 200%) as catalyst for 6 hours. The reaction mixture was then filtered and the solid was washed with DMF. Solvent was removed under *vacuo* to give the solid. CHCl<sub>3</sub> was added to the solid and stirred for 1 hour then filtered to give product **7** as white solid. Yield, 23 mg, 72%. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 13.20 (s, 1H, hydroxyl proton), 12.61 (s, 1H, hydroxyl proton), 12.38 (s, 1H, hydroxyl proton), 10.87 (s, 1H, amide proton), 10.75 (s, 1H, amide proton), 10.71 (s, 1H, amide proton), 10.41 (s, 1H, amide proton), 10.37 (s, 1H, amide proton), 10.13 (s, 1H, hydroxyl proton), 8.58 (d, *J* = 8.0 Hz, 1H, aromatic proton), 8.30 (d, *J* = 8.1 Hz, 1H, aromatic proton), 8.16 – 8.01 (m, 5H, aromatic proton), 7.88 (dd, *J* = 10.1, 4.0 Hz, 2H, aromatic proton), 7.75 (d, *J* = 7.7 Hz, 1H, aromatic

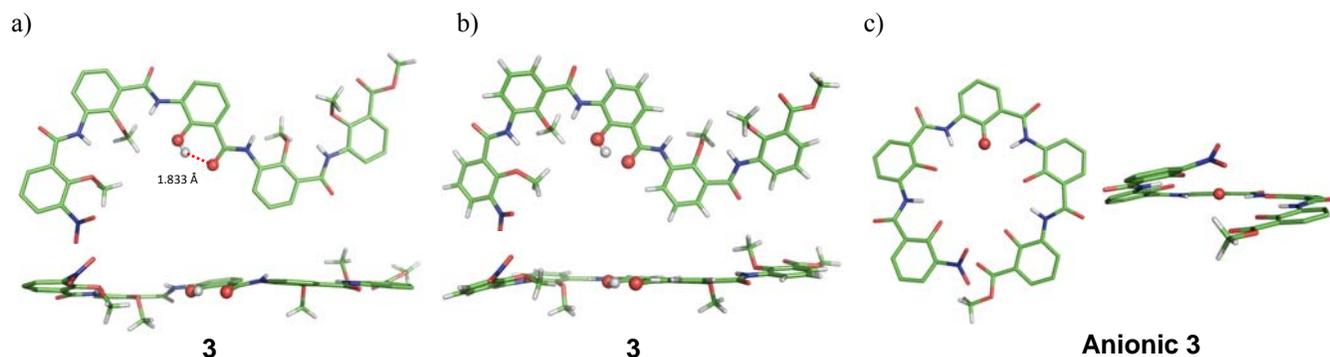
proton), 7.60 (dd, *J* = 11.2, 4.4 Hz, 1H, aromatic proton), 7.37 (t, *J* = 7.9 Hz, 1H, aromatic proton), 7.29 (d, *J* = 8.4 Hz, 1H, aromatic proton), 7.16 (t, *J* = 7.5 Hz, 1H, aromatic proton), 7.09 (q, *J* = 8.2 Hz, 2H, aromatic proton), 7.03 (t, *J* = 8.1 Hz, 1H, aromatic proton), 6.95 (ddd, *J* = 15.4, 8.0, 4.0 Hz, 2H, aromatic proton), 6.84 (t, *J* = 7.6 Hz, 1H, aromatic proton), 4.06 (s, 3H, methoxyl proton), 3.90 (s, 3H, methoxyl proton). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>) δ 169.4, 167.6, 167.3, 163.2, 162.4, 157.8, 153.9, 152.5, 151.3, 150.8, 147.2, 134.2, 131.8, 131.6, 129.6, 129.3, 128.7, 128.2, 127.8, 127.5, 127.3, 127.2, 126.1, 126.0, 125.1, 124.6, 124.2, 122.9, 121.6, 121.6, 120.9, 119.72, 119.51, 119.1, 119.0, 118.2, 117.2, 115.5, 115.3, 113.2, 62.7, 57.0. HRMS-ESI: calculated for [M-H]<sup>-</sup> (C<sub>43</sub>H<sub>34</sub>N<sub>5</sub>O<sub>11</sub>): *m/z* 796.2260, found: *m/z* 796.2255.

## 4. X-Ray Crystallography Data Sheet for Pentamer 3

**Table S1.** Crystal data and structure refinement for **Pentamer 3**.

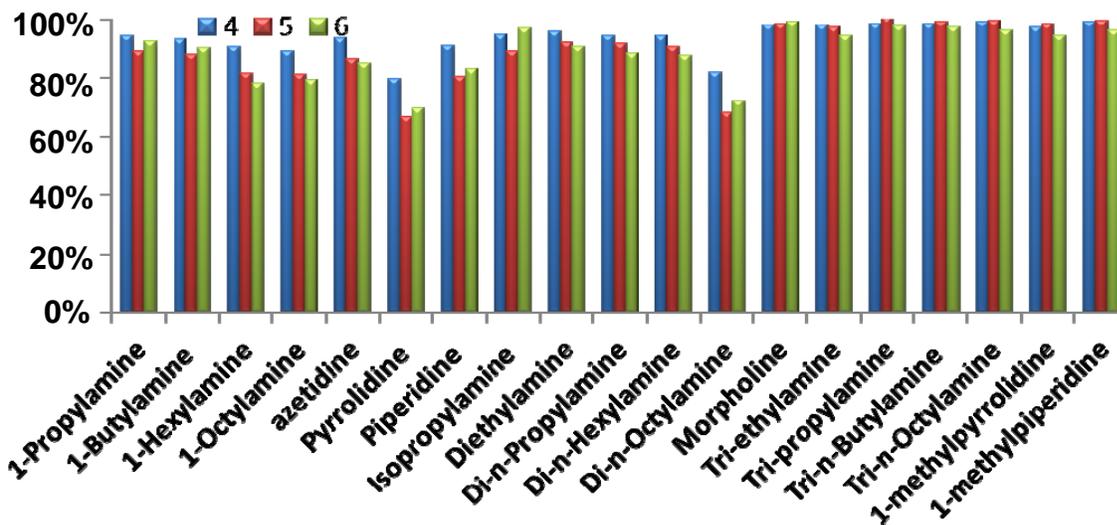
<b>CCDC No:</b>	<b>915672</b>	
Identification code	8253	
Empirical formula	$C_{42}H_{37}C_{16}N_5O_{13}$	
Formula weight	1032.47	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.4427(8) Å	a = 90°.
	b = 21.5076(12) Å	b = 109.8110(10)°.
	c = 15.8649(8) Å	g = 90°.
Volume	4636.4(4) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.479 Mg/m <sup>3</sup>	
Absorption coefficient	0.440 mm <sup>-1</sup>	
F(000)	2120	
Crystal size	0.56 x 0.22 x 0.08 mm <sup>3</sup>	
Theta range for data collection	1.50 to 25.00°.	
Index ranges	-16<=h<=17, -25<=k<=25, -18<=l<=18	
Reflections collected	26736	
Independent reflections	8163 [R(int) = 0.0476]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Sadabs, (Sheldrick 2001)	
Max. and min. transmission	0.9657 and 0.7909	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	8163 / 24 / 632	
Goodness-of-fit on F <sup>2</sup>	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0708, wR2 = 0.2032	
R indices (all data)	R1 = 0.0951, wR2 = 0.2233	
Largest diff. peak and hole	0.708 and -0.731 e.Å <sup>-3</sup>	

## 5. Figure S1.



**Figure S1.** (a) Top and side views of crystal structure of pentamer **3**, demonstrating the ability of hydroxyl group in red ball to form an alternative H-bonding pattern identical to that in **1** in Figure 1. (b) Top and side views of *ab initio* calculated structure of **3**, illustrating a good planarity around the hydroxyl region and slightly more distorted backbones by methoxy groups. (c) Top and side views of *ab initio* calculated structure of anionic **3** that becomes helically folded upon deprotonating the central hydroxyl group (O-atom in red ball). The computations were carried out at the B3LYP/6-31G level.

## 6. Figure S2.



**Figure S2.** Fluorescence quenching extents of **4-6** by 8 equivalents of amines of various types. The fluorescence spectra/data were obtained at 10  $\mu$ M in THF containing 1% DMSO at room temperature with an excitation wavelength at 351 nm. DMPC = Dimethylaminopropylchloride.

## 7. Table S1 and General Description of *Ab Initio* Molecular Modeling

All the calculations were carried out by utilizing the Gaussian 09<sup>1</sup> program package. The geometry optimizations were performed at the density functional theory (DFT) level, and the Becke's three parameter hybrid functional with the Lee-Yang-Parr correlation functional (B3LYP)<sup>2</sup> method was employed to do the calculations. The 6-31G<sup>3</sup> basic from the Gaussian basis set library has been used in all the calculations. The harmonic vibrational frequencies and zero-point energy corrections were calculated at the same level of theory. Single point energy were obtained at the B3LYP level in conjunction with the 6-311+G (2d, p) basis set with the use of the above optimized geometries, i.e., B3LYP/6-311+G(2d,p)//B3LYP/6-31G.

**Table S1.** Relative stabilities of various anionic isomers<sup>a</sup> derived from **7**.<sup>b</sup>

Mono-anionic isomers with one phenolate anion (kcal/mol)					
<b>7<sub>a</sub></b>	<b>7<sub>b</sub></b>	<b>7<sub>c</sub></b>	<b>7<sub>d</sub></b>		
5.39	1.92	<b>0.00</b>	18.99		
Di-anionic isomers with two phenolate anions (kcal/mol)					
<b>7<sub>ab</sub></b>	<b>7<sub>bc</sub></b>	<b>7<sub>ac</sub></b>	<b>7<sub>ad</sub></b>	<b>7<sub>bd</sub></b>	<b>7<sub>cd</sub></b>
13.84	7.64	<b>0.00</b>	16.67	14.51	15.66
Tri-anionic isomers with three phenolate anions (kcal/mol)					
		<b>7<sub>abc</sub></b>	<b>7<sub>abd</sub></b>	<b>7<sub>acd</sub></b>	<b>7<sub>bcd</sub></b>
		<b>0.00</b>	11.77	5.50	13.37

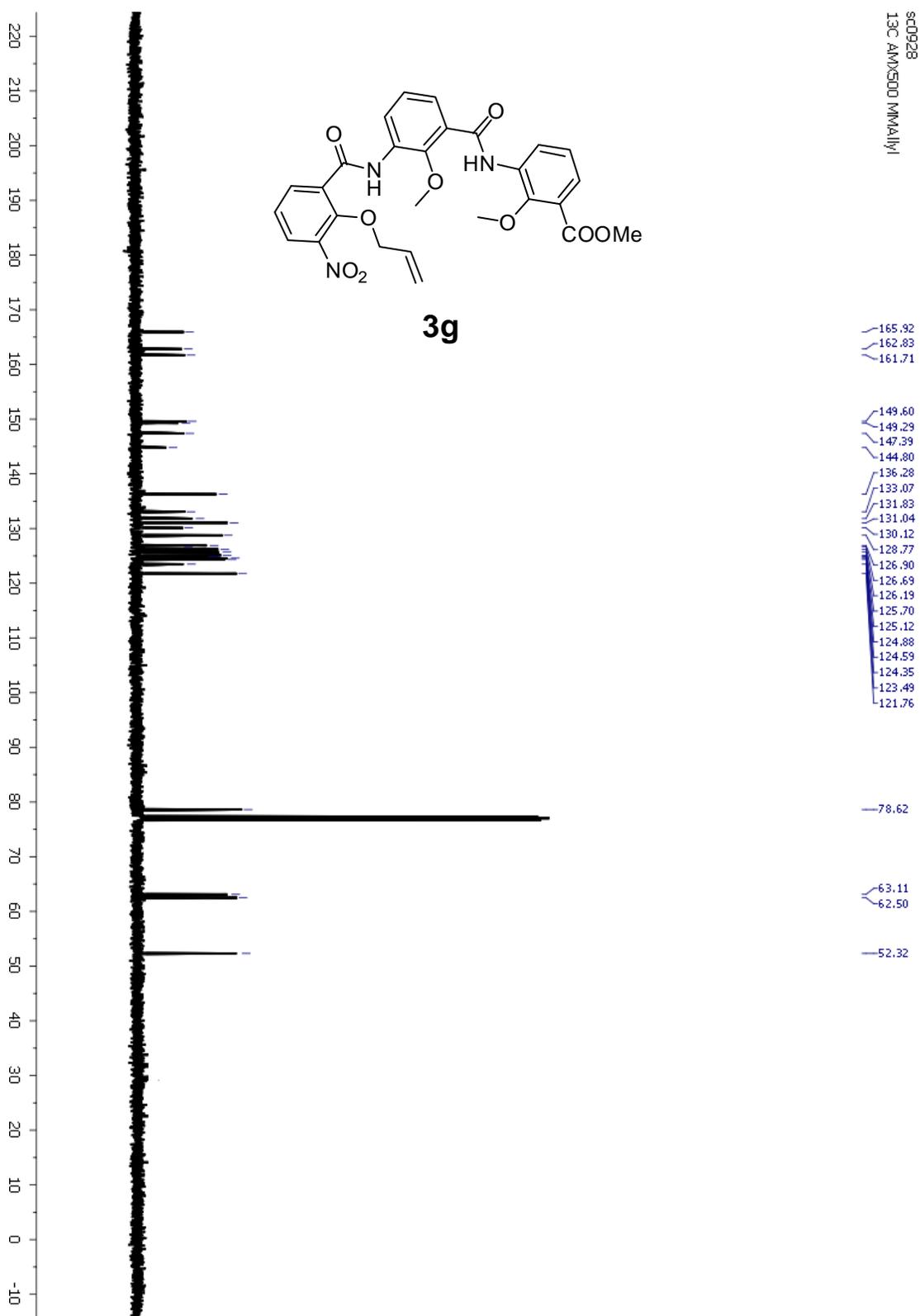
<sup>a</sup> Anionic oligomers are generated by using strong organic base TBAOH. <sup>b</sup> Geometrically optimized at the B3LYP/6-31G level with single point energy calculated at the B3LYP/6-311+G(2d,p) level using THF as the explicit solvent.

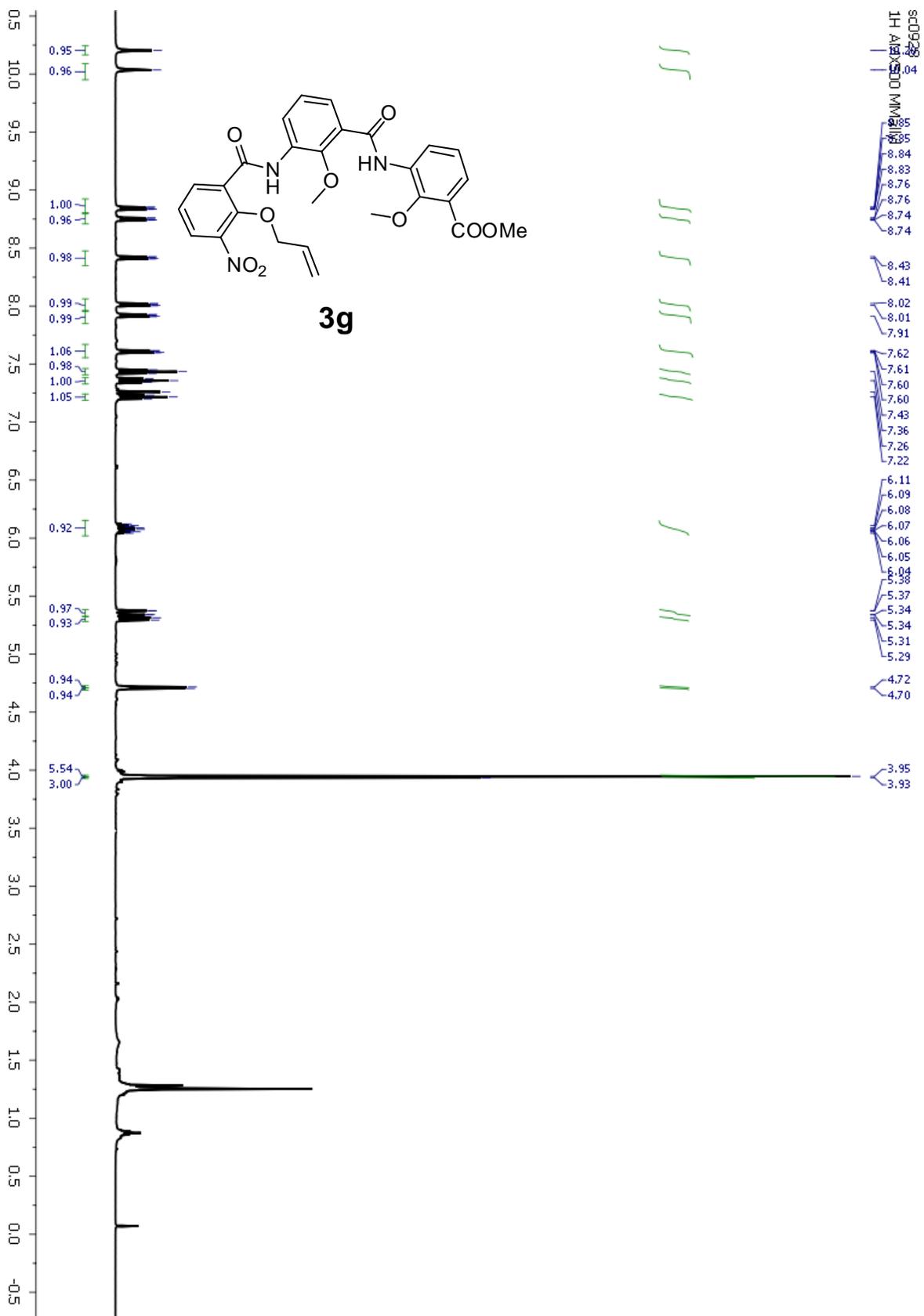
<sup>1</sup> Frisch, M. J.; et al. *Gaussian 09*; Gaussian, Inc.: Wallingford CT, 2009.

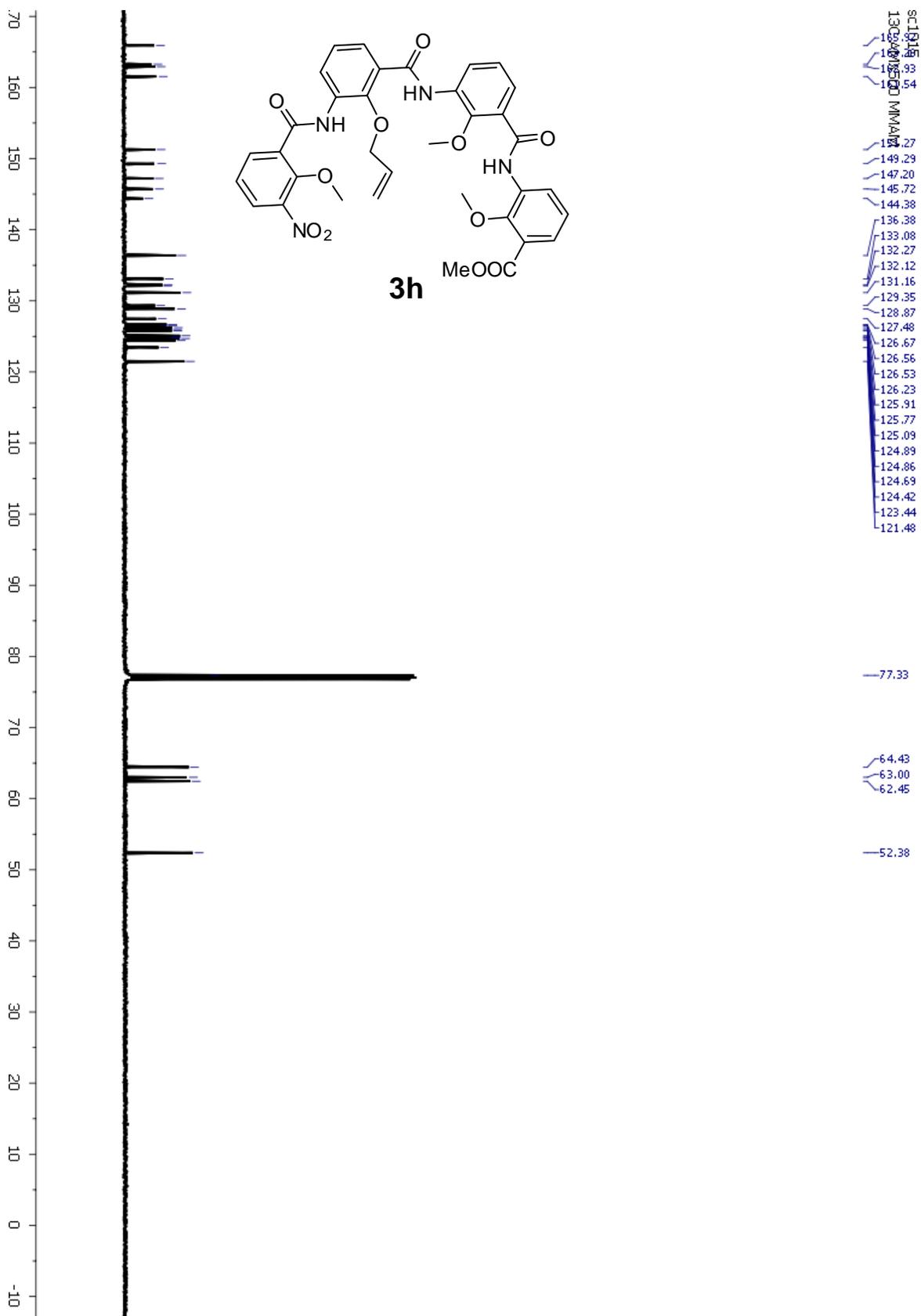
<sup>2</sup> Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648.

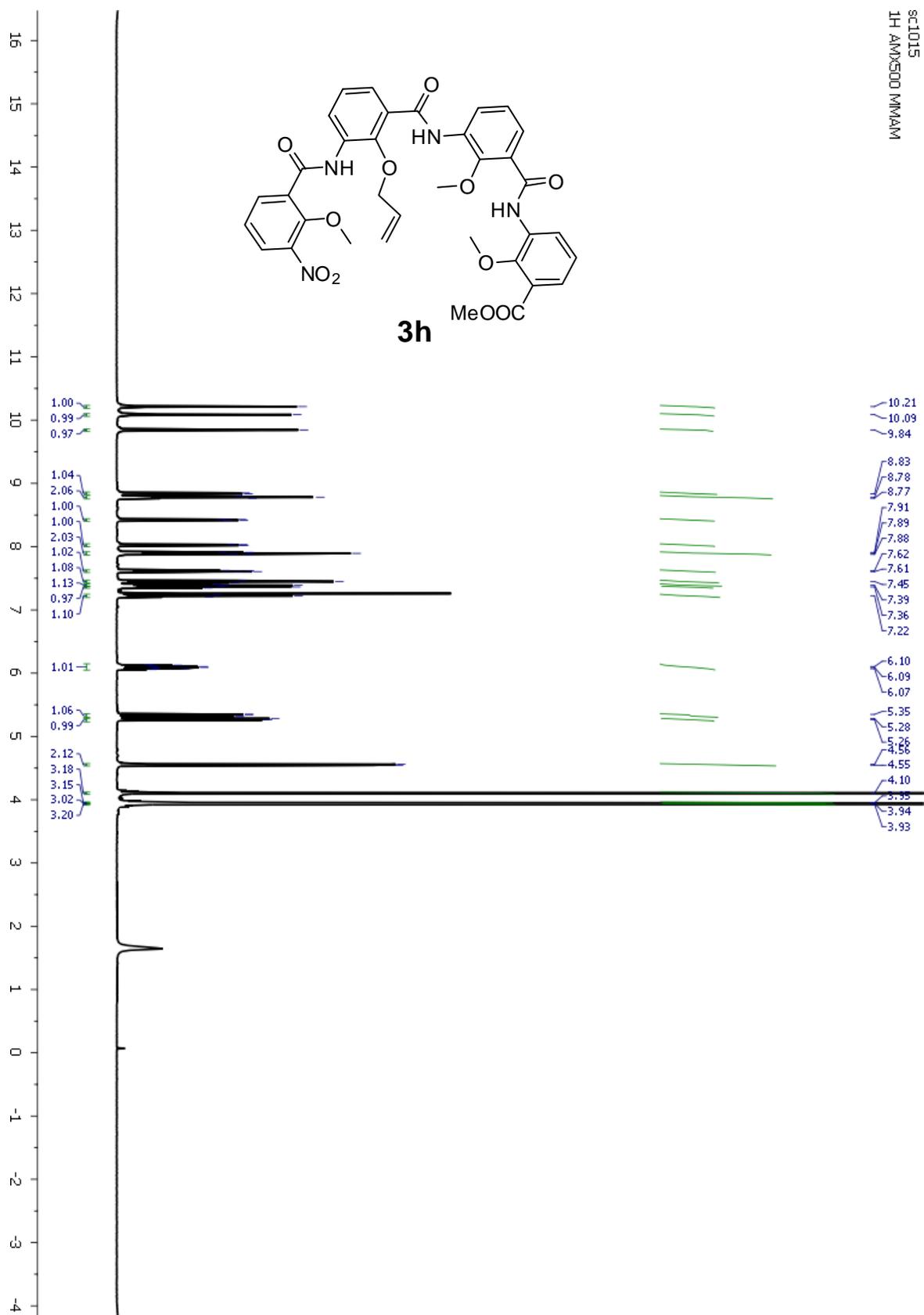
<sup>3</sup> Petersson, G. A.; Al-Laham, M. A. *J. Chem. Phys.* **1991**, 94, 6081; Petersson, G. A.; Bennett, A.; Tensfeldt, T. G.; Al-Laham, M. A.; Shirley, W. A.; Mantzaris, J. *J. Chem. Phys.* **1988**, 89, 2193.

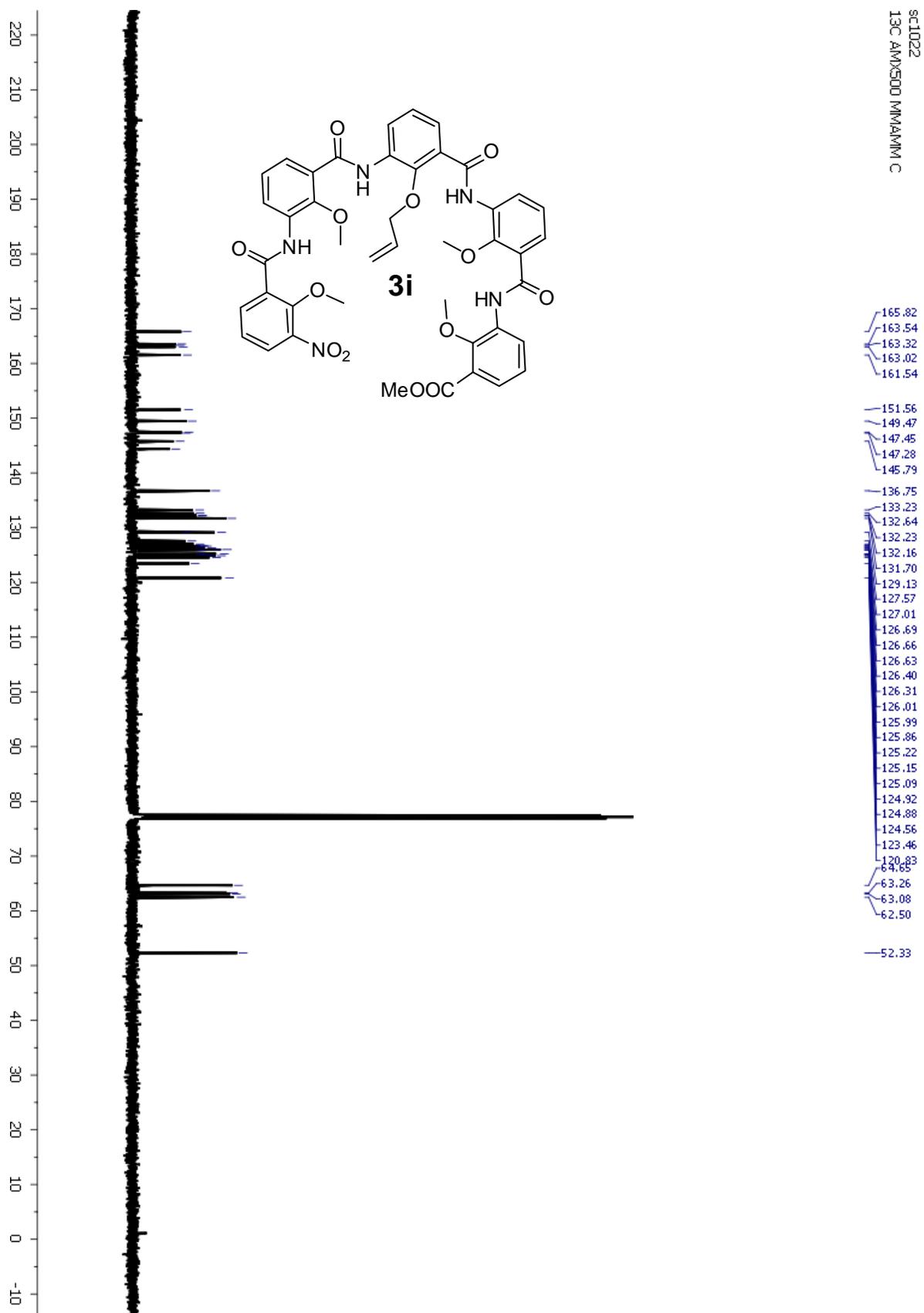
## 8. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra

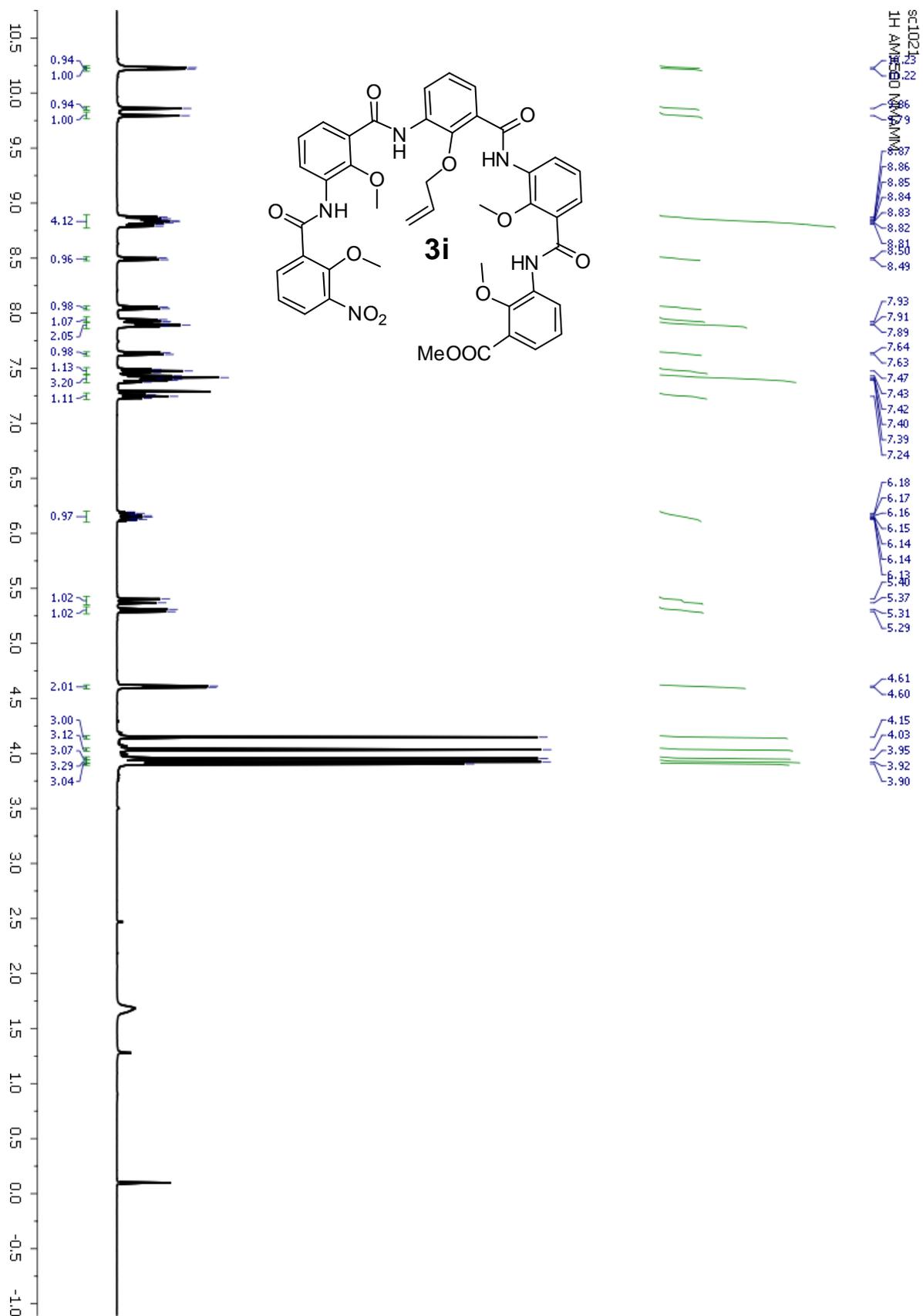


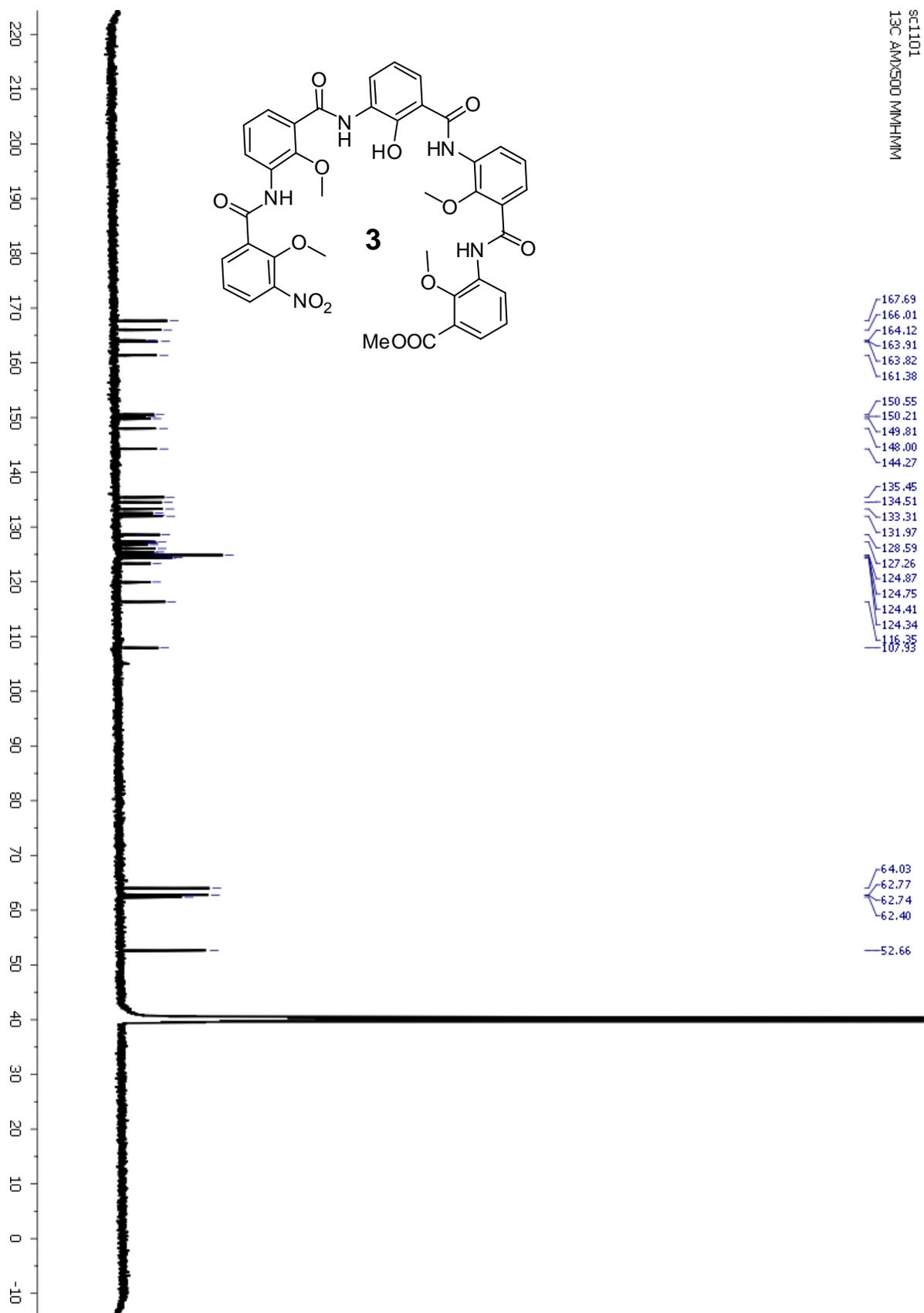


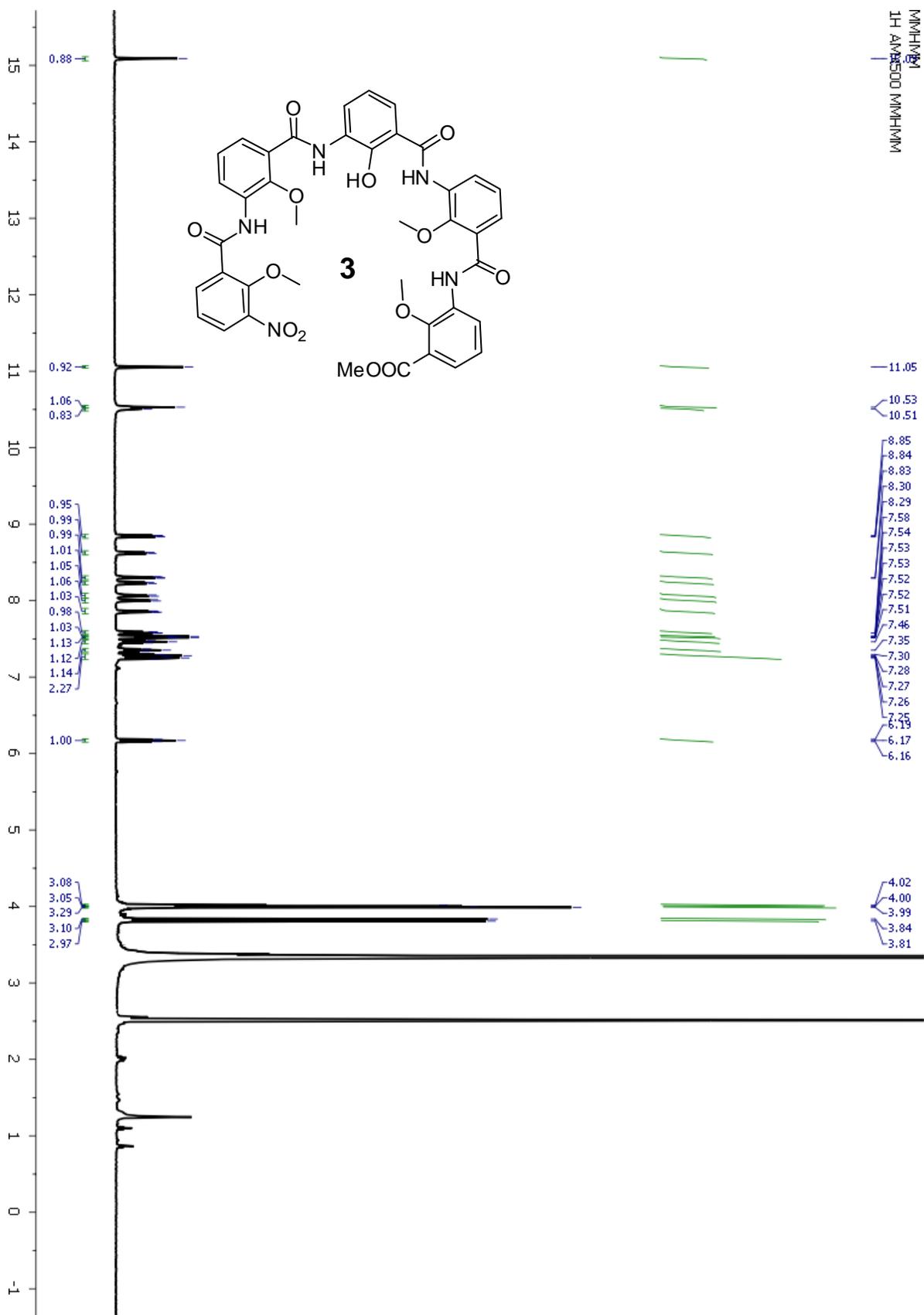


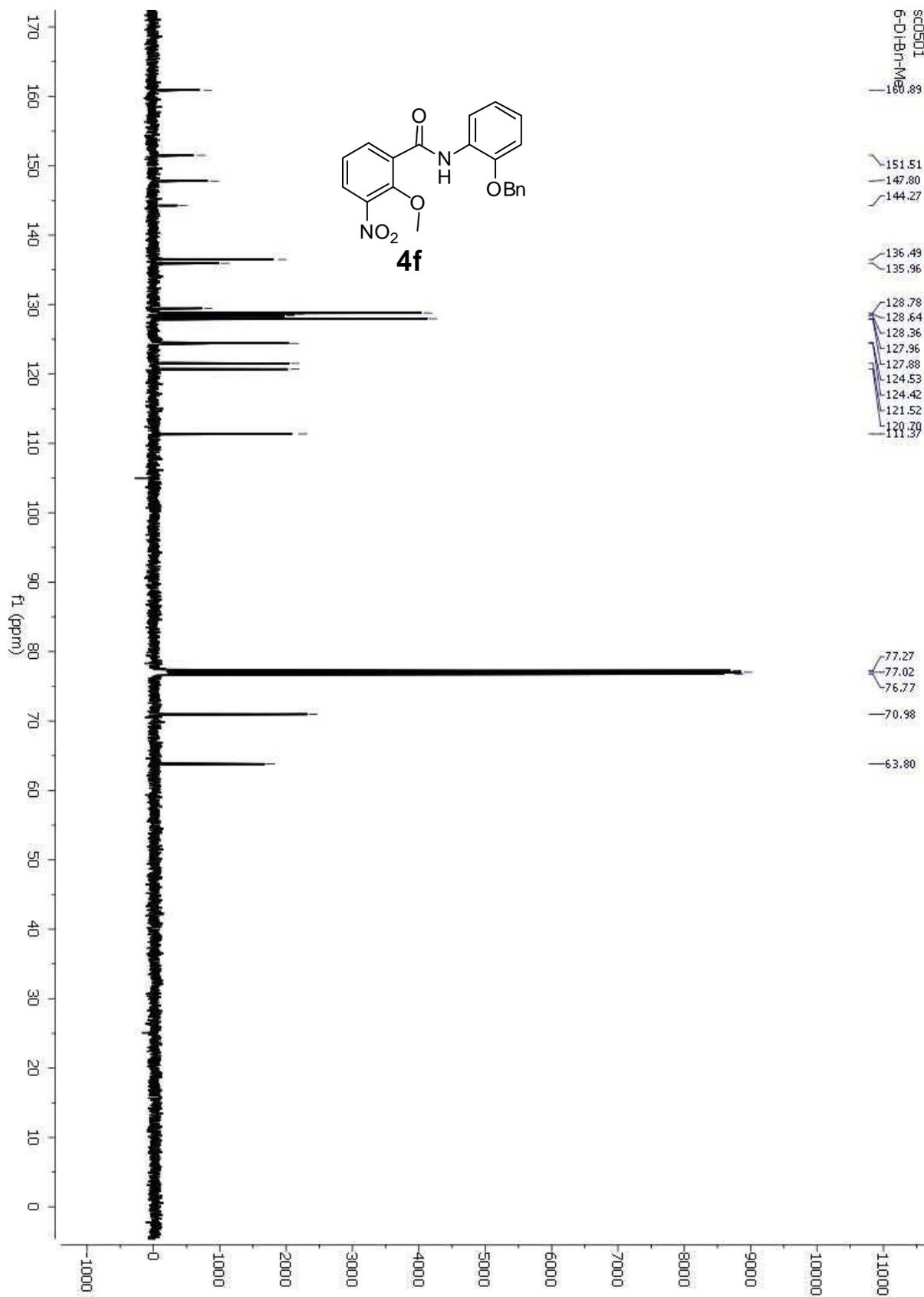


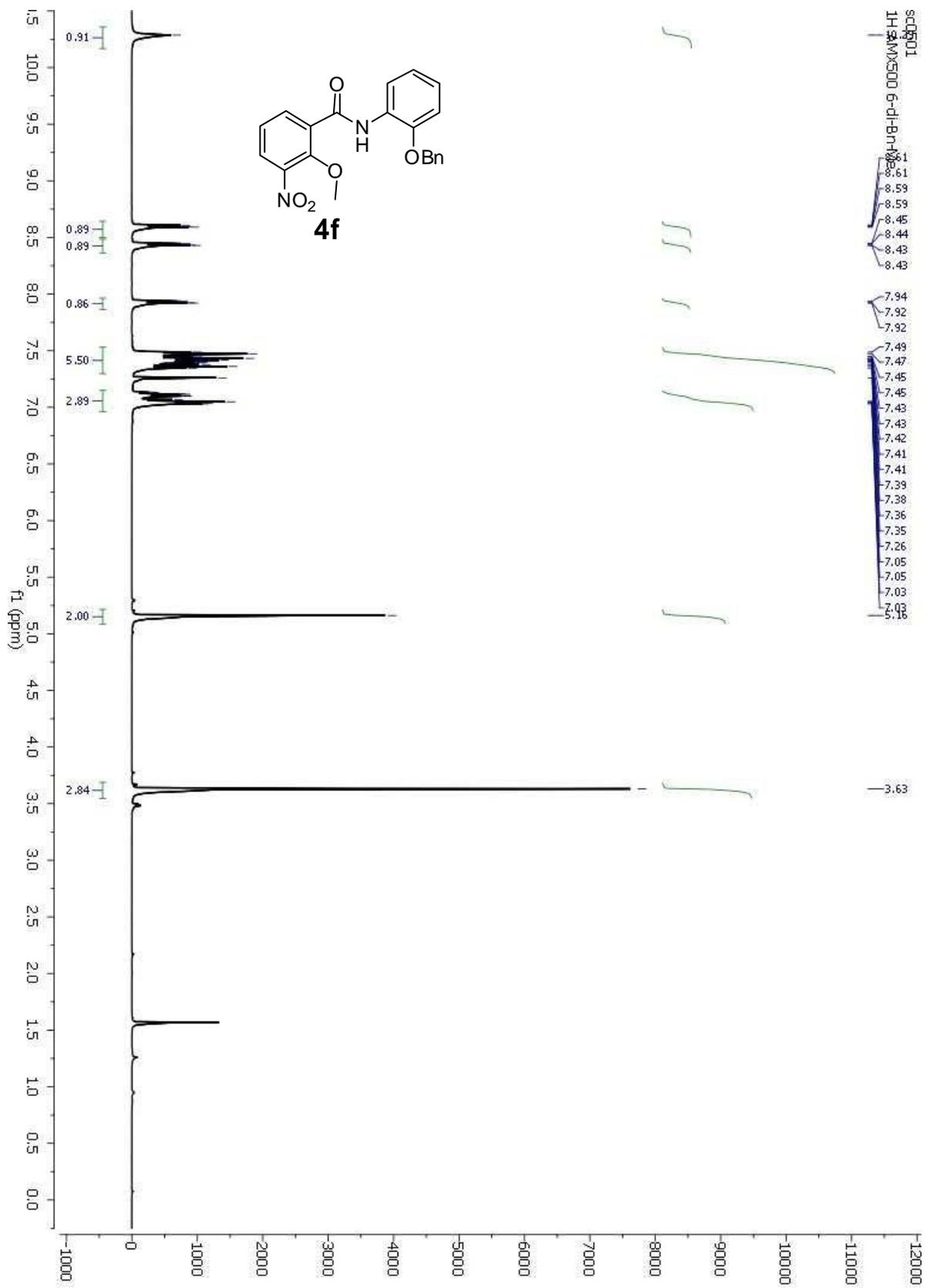


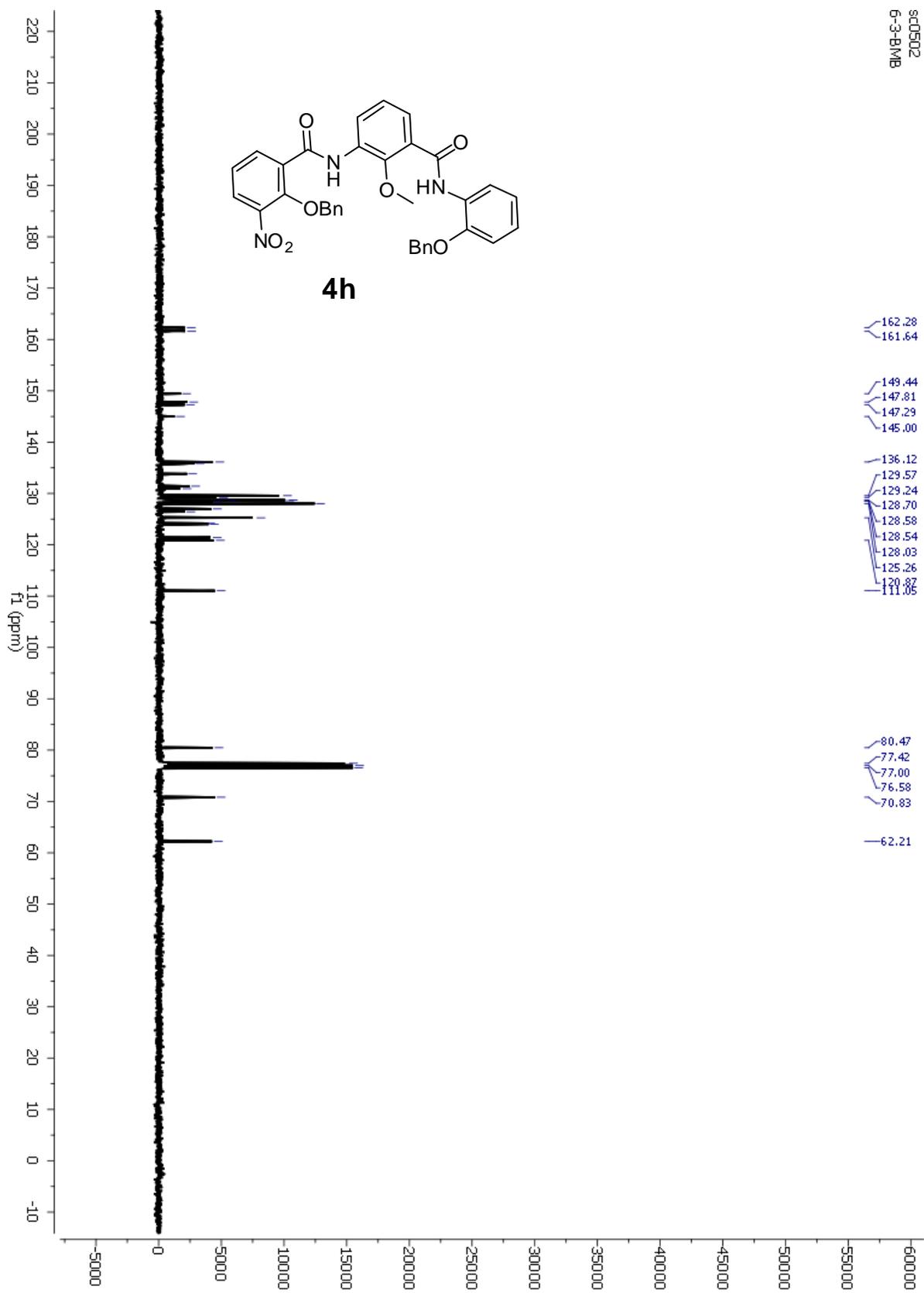


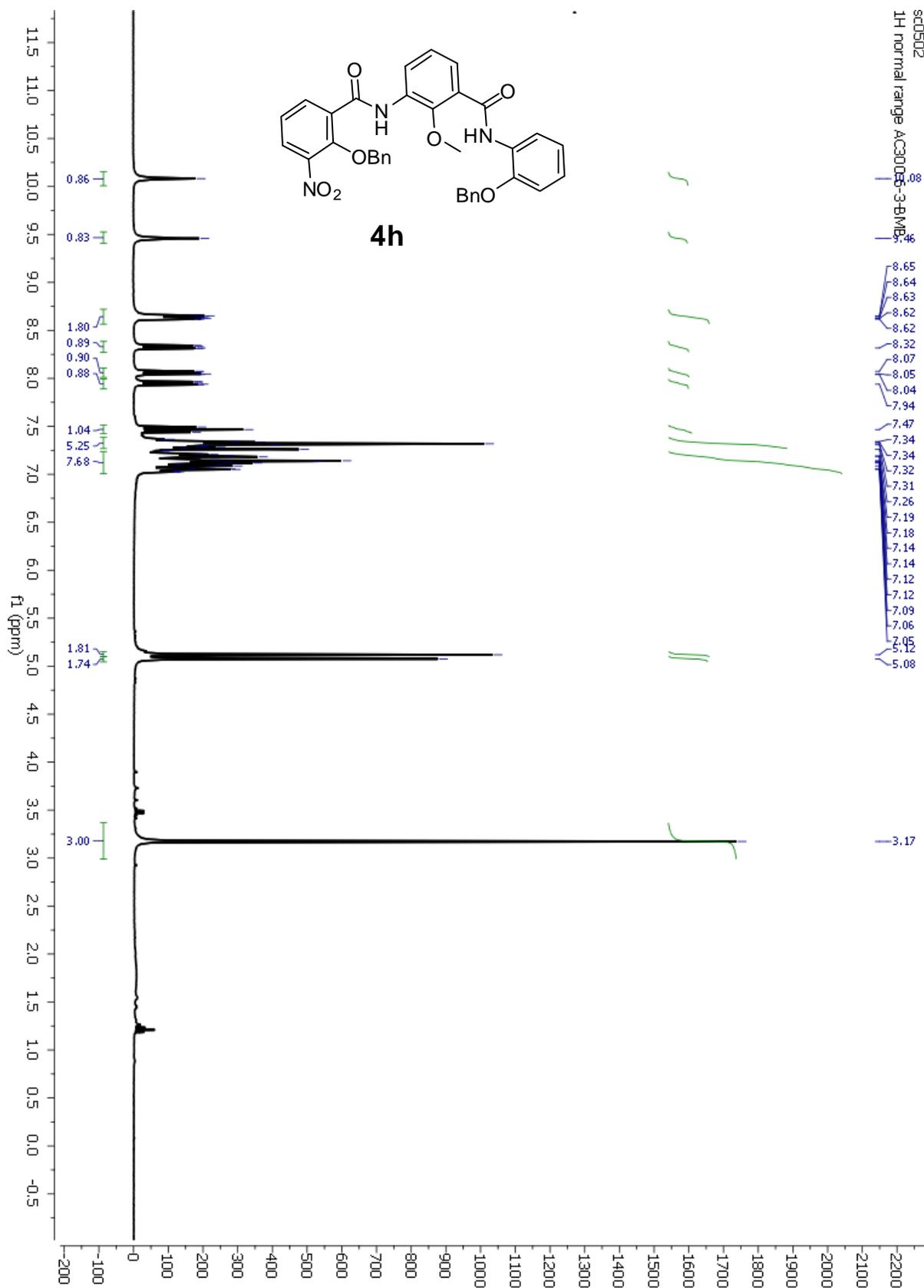


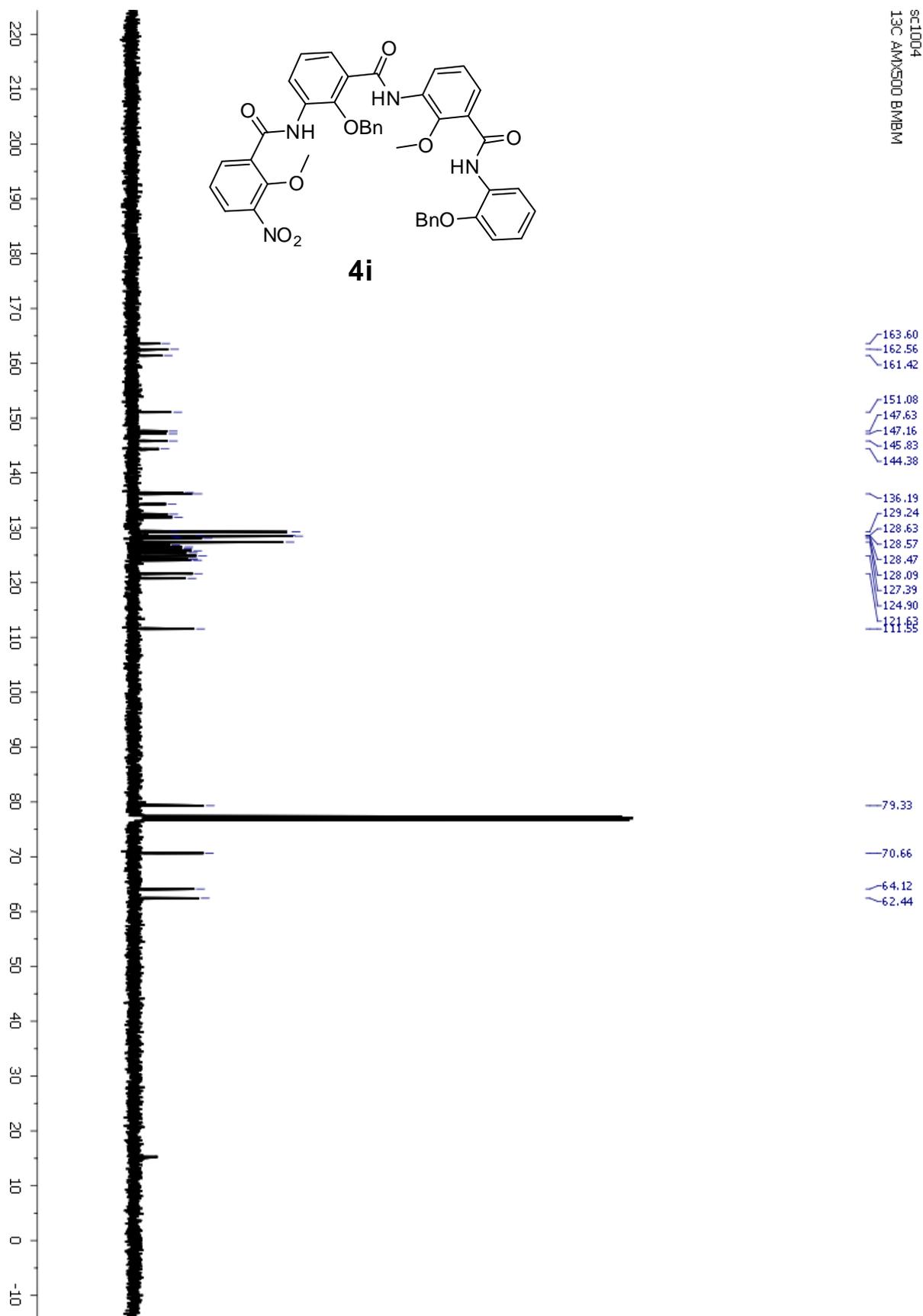


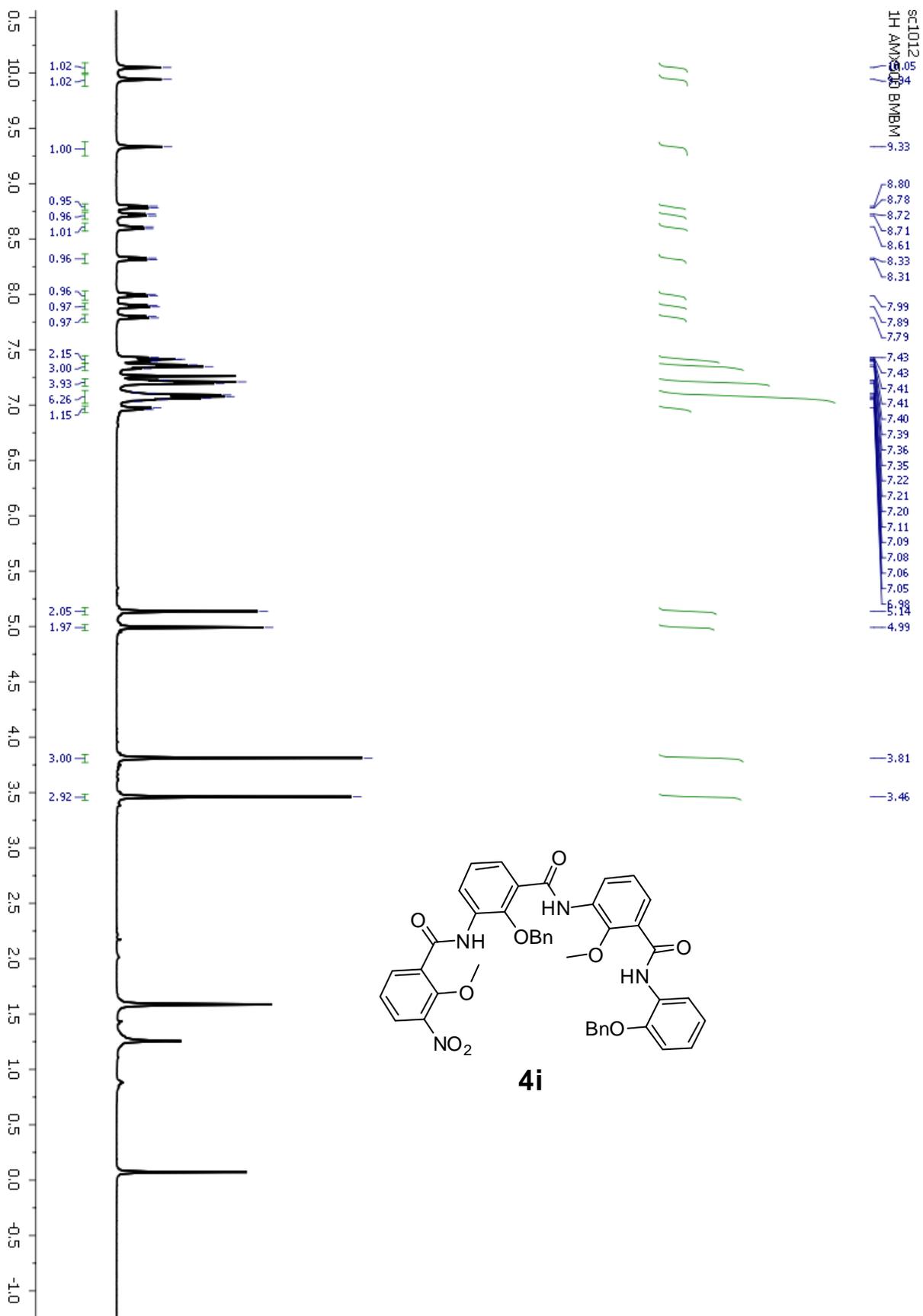


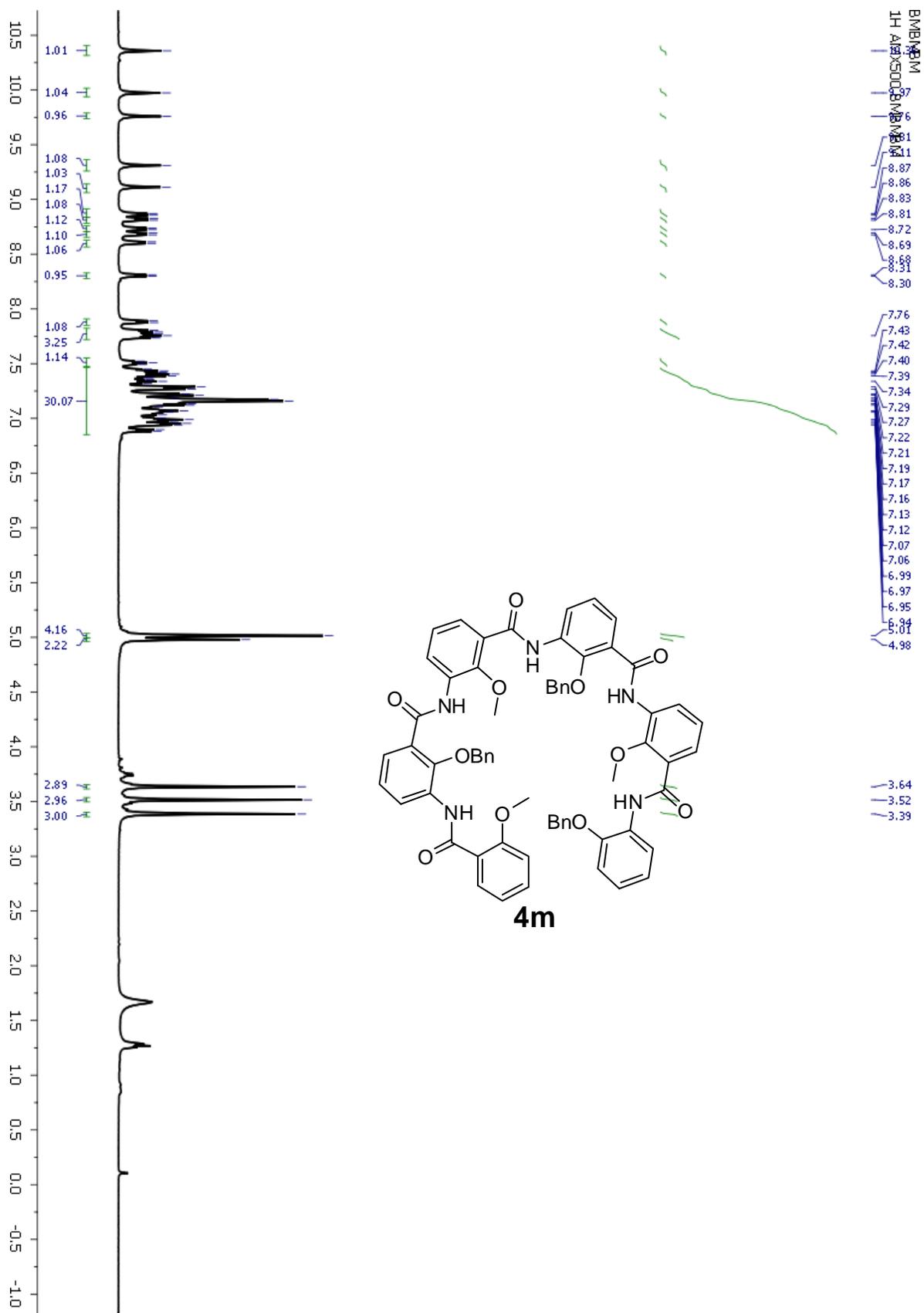




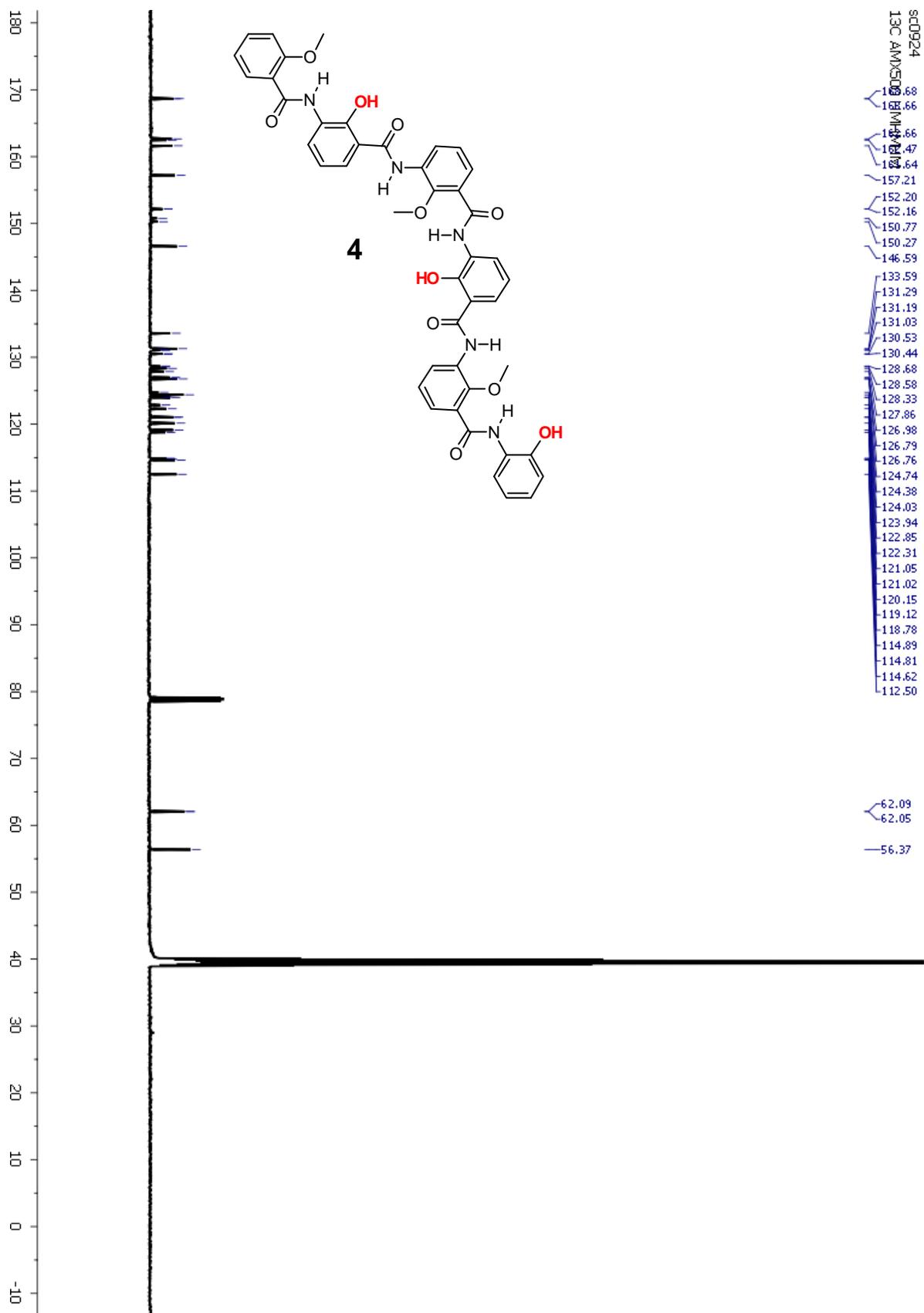


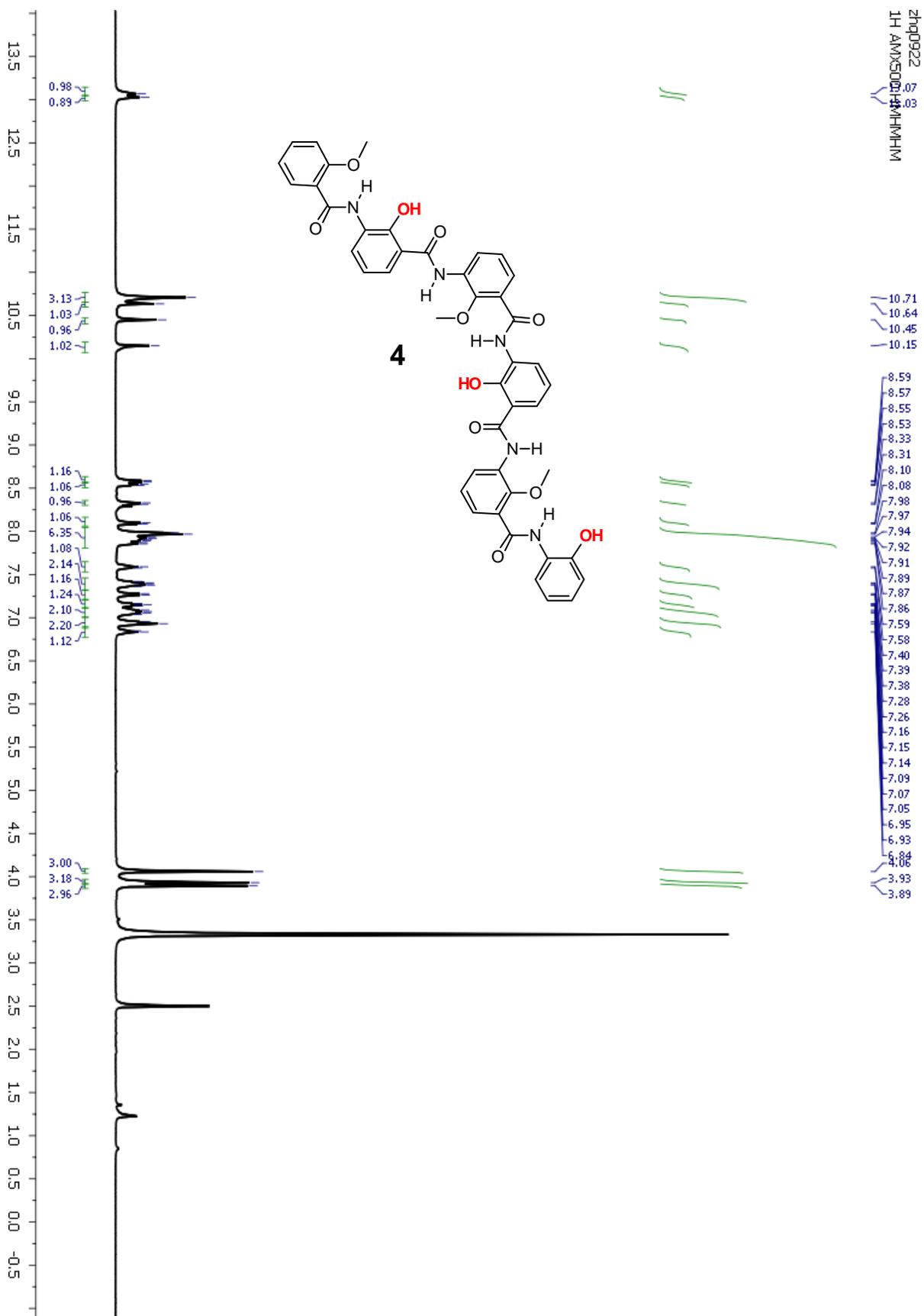


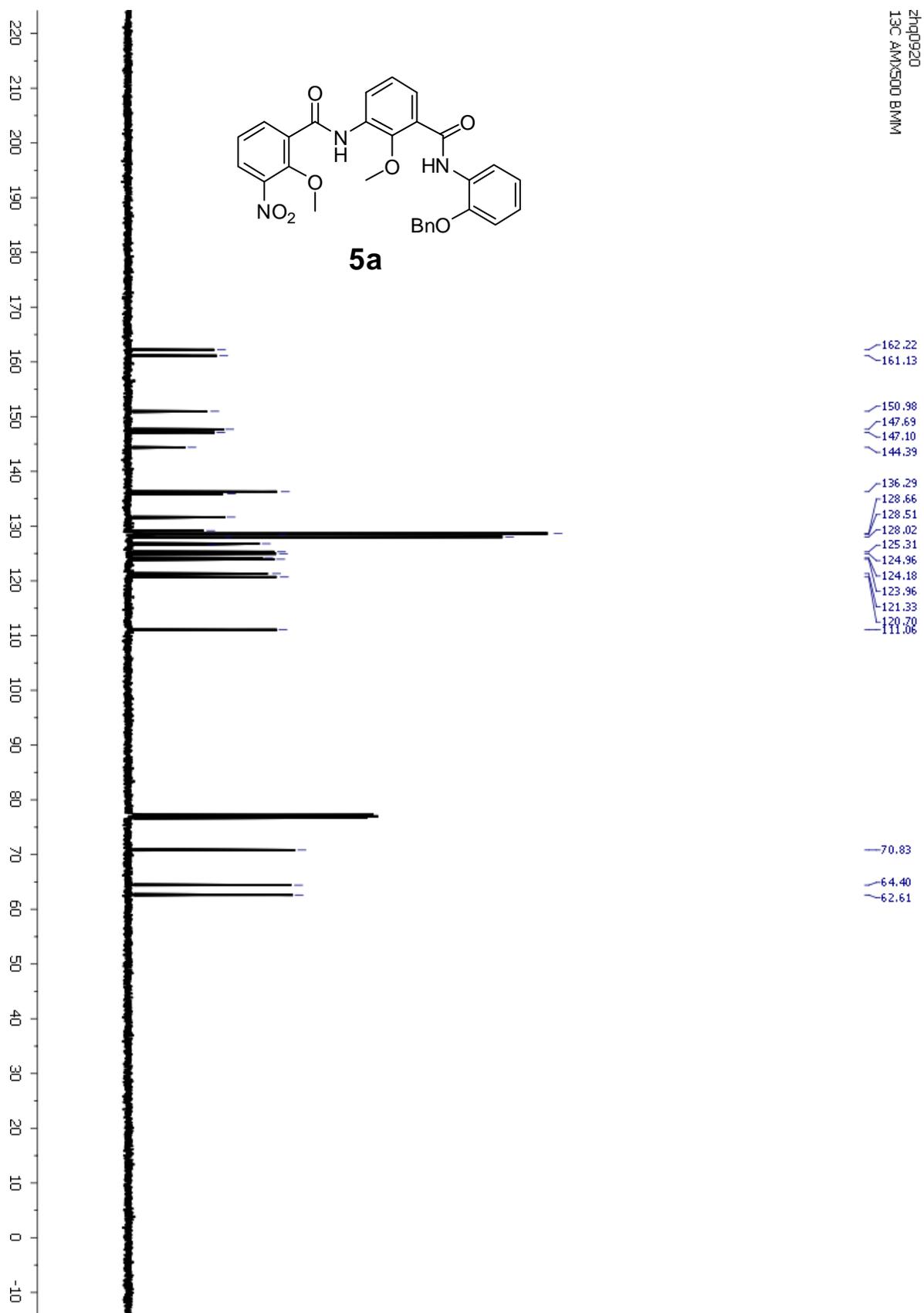


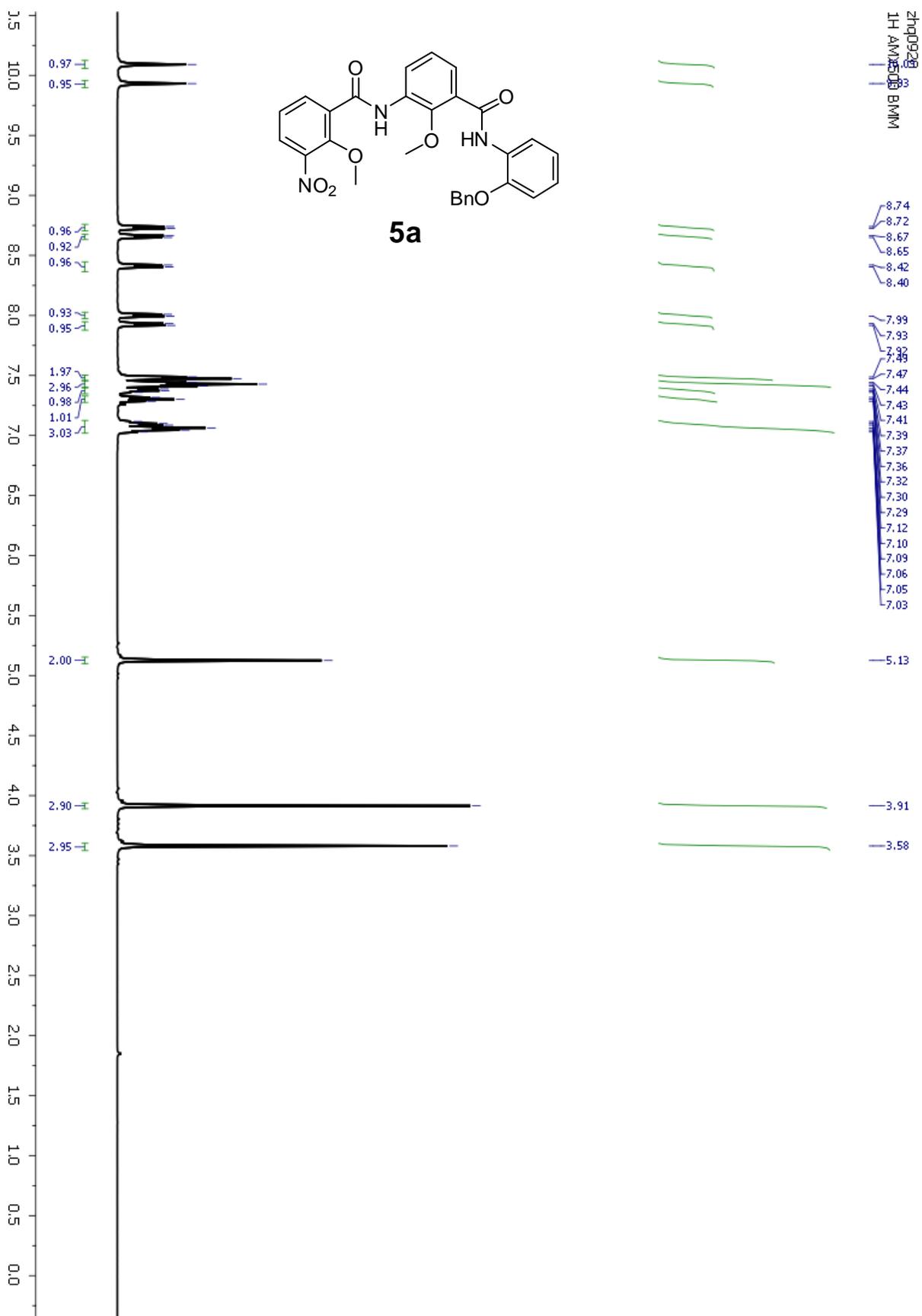


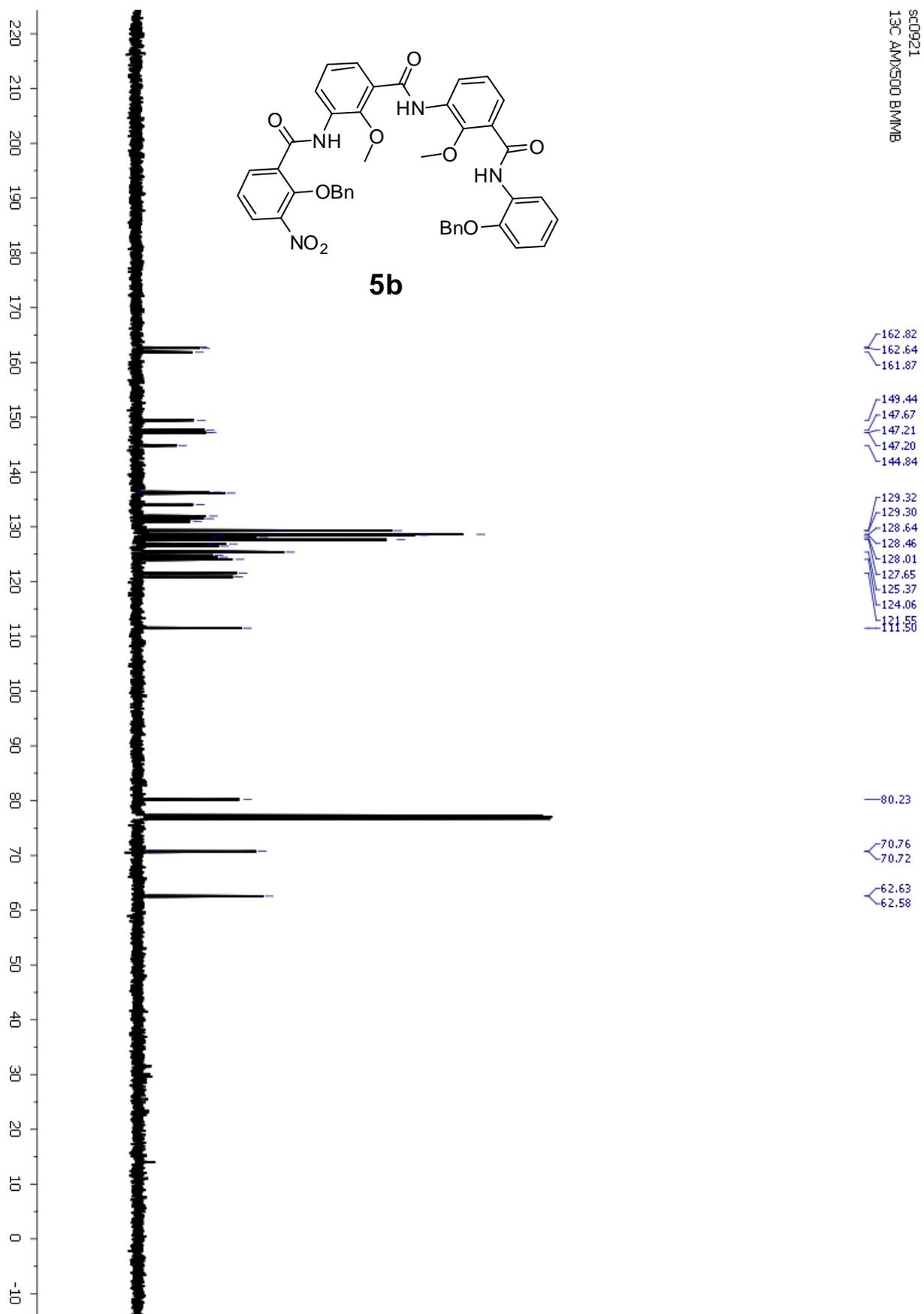


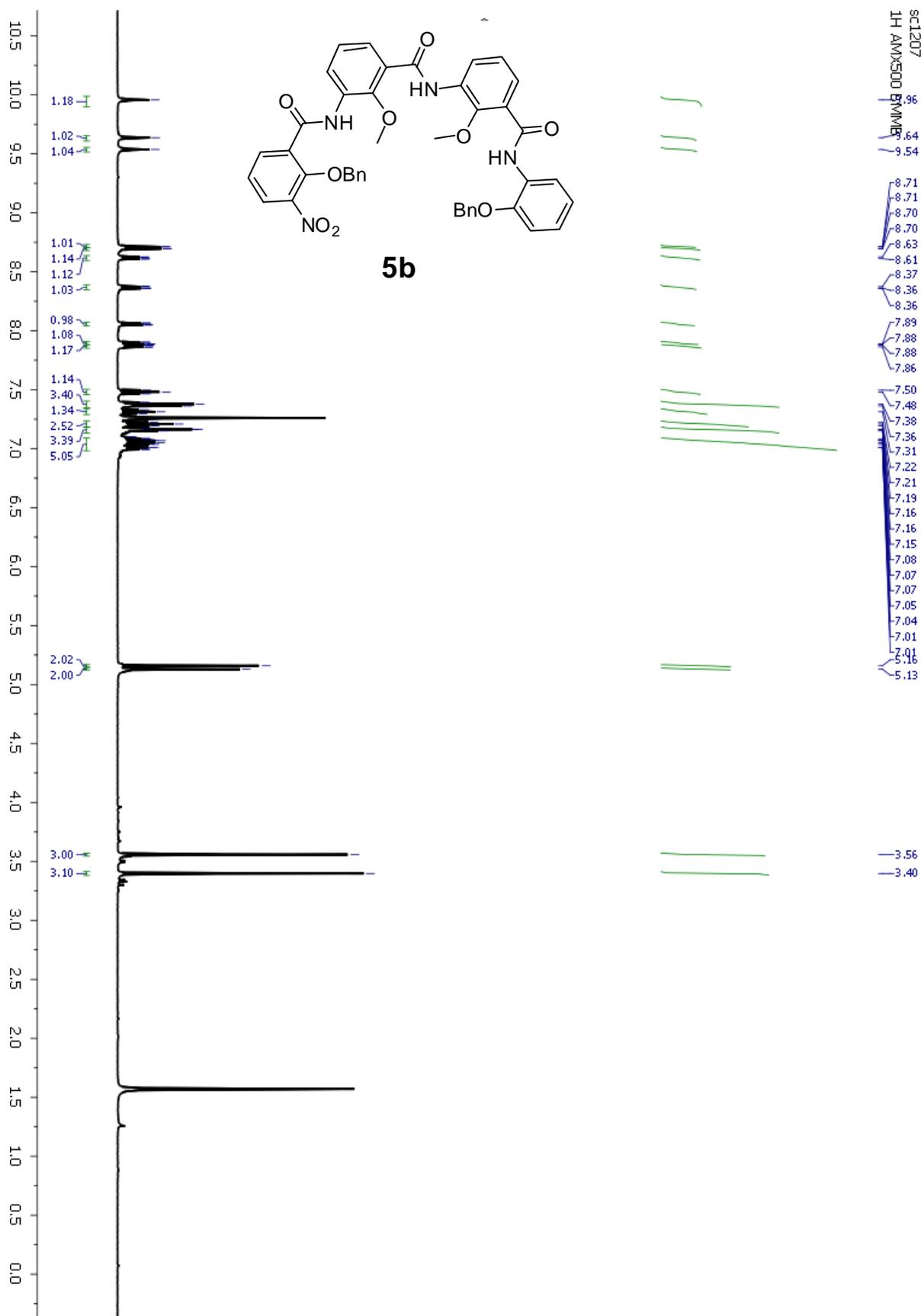


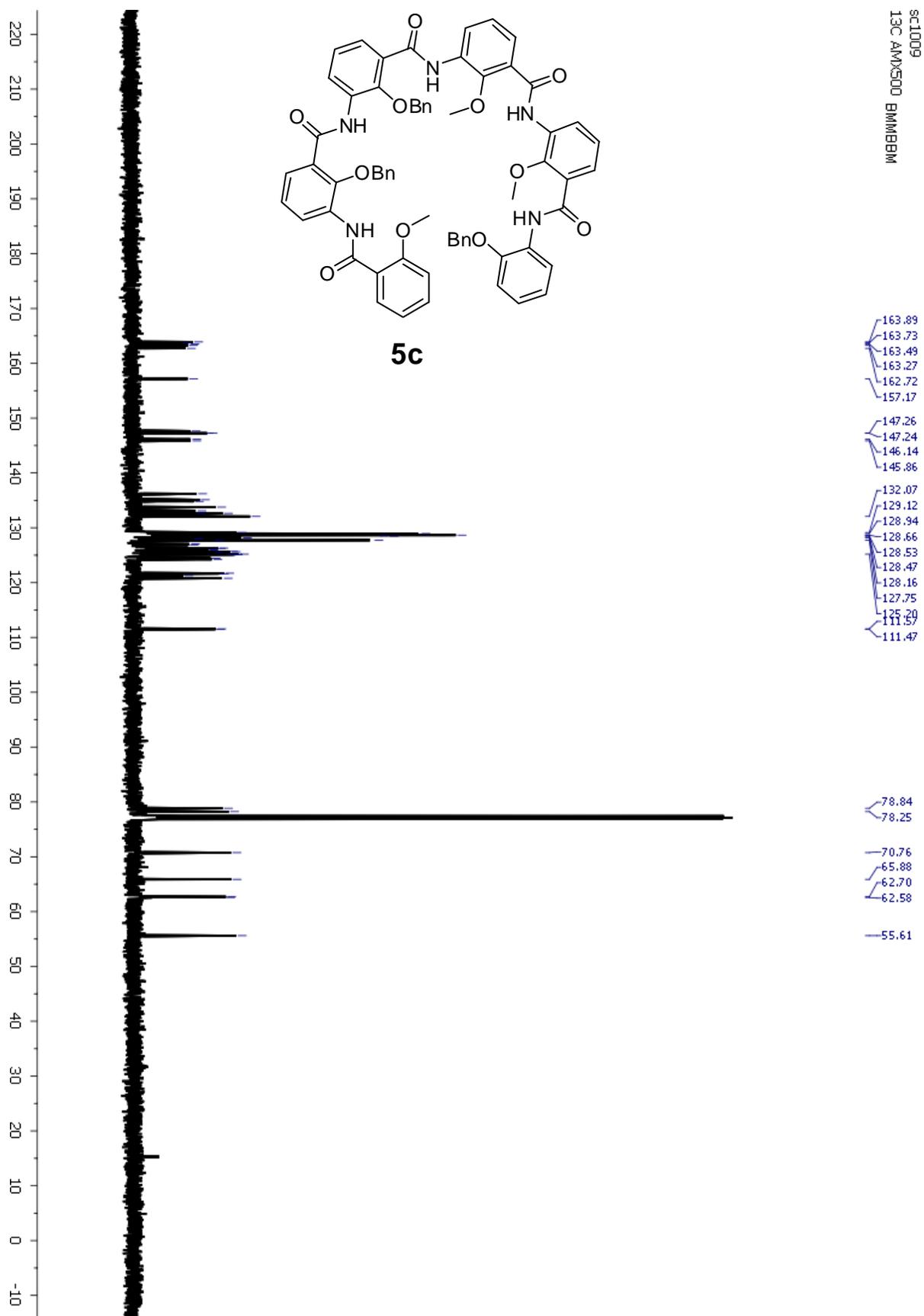


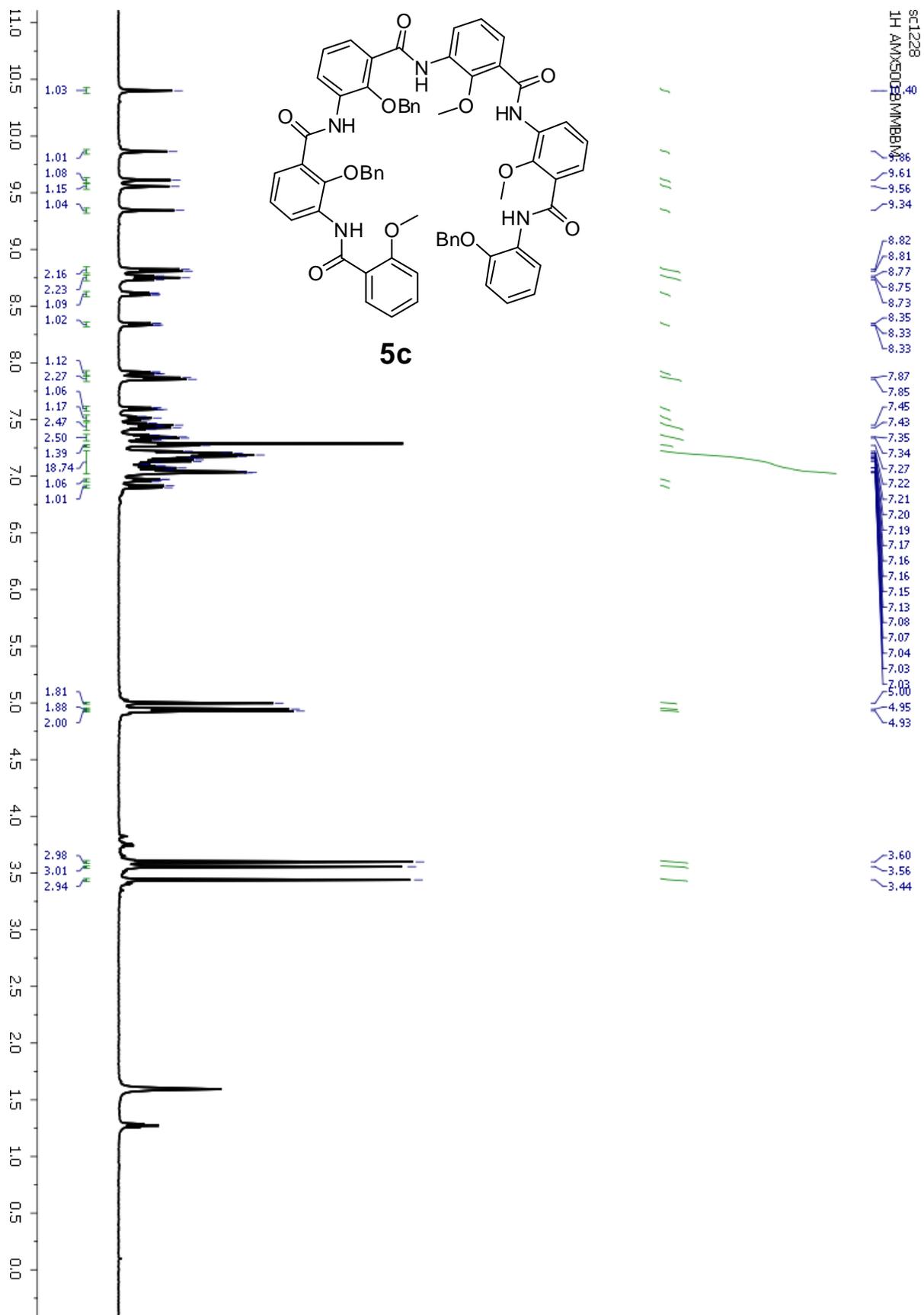


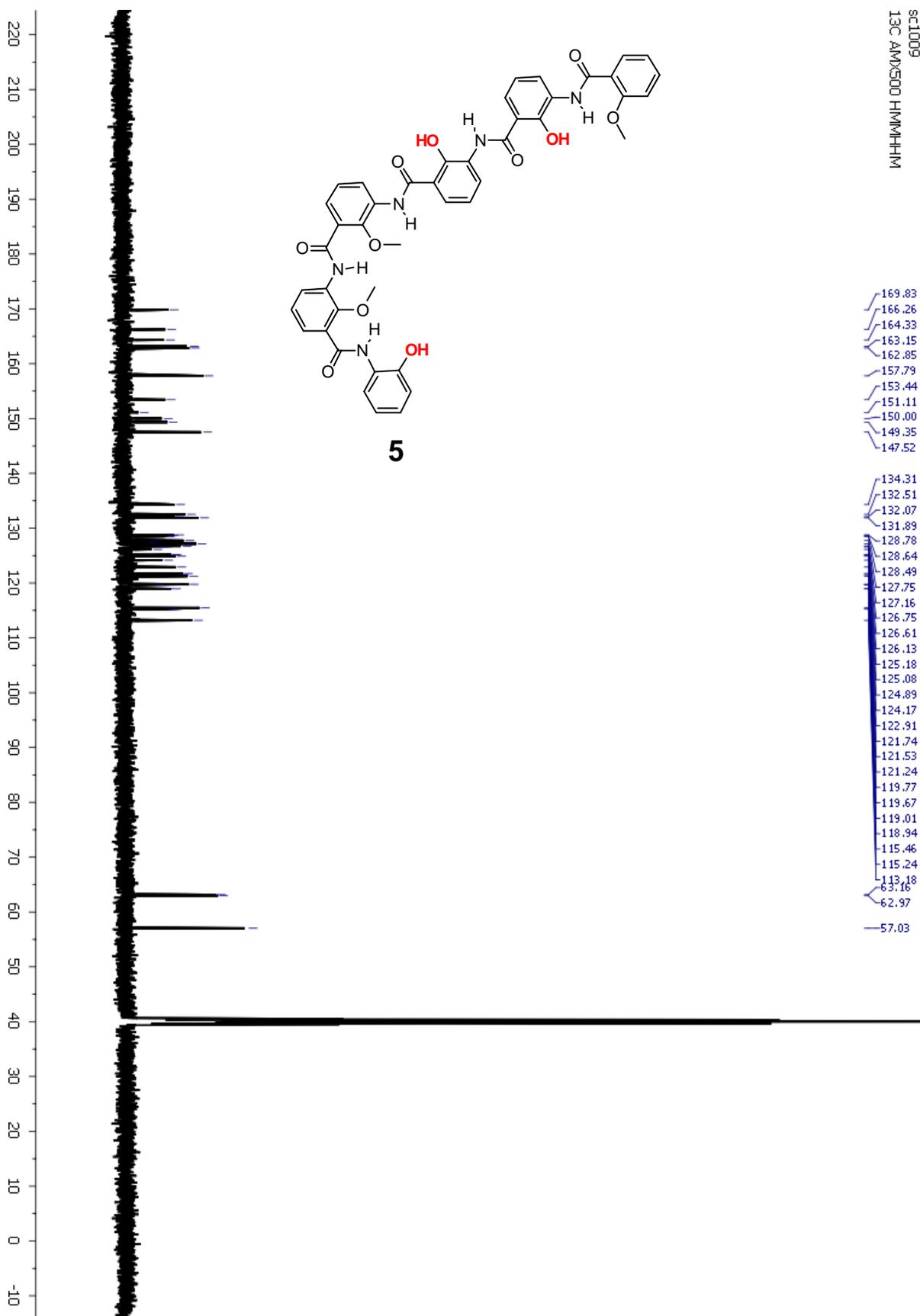












SC1009  
13C AMX500 HMHMHM

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57.03

