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Supporting Information

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Benzoylurea Oligomers: Synthetic Foldamers That Mimic Extended α-helices

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Part I: General Experimental Section

General Methods. All chemicals were obtained from Sigma/Aldrich, Fluka and TCI America unless otherwise noted. All air and/or moisture sensitive reactions were carried out under a positive pressure of nitrogen in flame-dried glassware. Solvents tetrahydrofuran (THF) and dimethylformamide (DMF) were obtained from commercial sources and dried on an Innovative Technology SPS-400 dry solvent system. Column chromatography was performed using silica gel (230-400 mesh) from Solvent technologies. Proton ^{1}H-NMR data were recorded at 500 MHz on a Bruker Advance DPX-500 spectrometer at room temperature. ^{1}H chemical shifts are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or internal tetramethylsilane (TMS, δ 0.00 ppm). ^{13}C-NMR data were recorded at 125 MHz on a Bruker Advance DPX-500 spectrometer at room temperature. ^{13}C chemical shifts are reported relative to the central line of $CDCl_3$ (77.0 ppm) in ppm. All high-resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign on a Micromass Q-Tof Ultima quadrupole time of flight mass spectrometer. Analysis and purification by revere phase HPLC (*rp*HPLC) were performed using either a Waters 2487 dual λ UV detector (214 nm) with a Waters 1525EF binary pump using a Phenomenex Luna 5μ C18(2) 250 x 21 mm column run at 20 mL/minute using gradient mixtures of water with 0.1% trifluoroacetic acid (TFA) (A) and 10:1 acetonitrile:water (B) with 0.1% TFA.

Part II: Crystallographic Data

CCDC 644652, CCDC 644653, and CCDC 644654 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Part III. Synthesis of Benzoylurea Oligomers

1. Synthesis of amide subunit (**6**):

Step 1: *Bis-benzyl protection*
To a stirred solution of methyl-4-amino-3-methyl benzoate (2.00 g, 12.1 mmol) in DMF (20 mL) was added benzyl bromide (4.31 mL, 36.3 mmol) and DIPEA (6.33 mL, 36.3 mmol). The solution was refluxed overnight and concentrated. The residue was diluted with water, extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4 and concentrated. Column chromatography [Hexanes/EtOAc (80:20)] on silica gel afforded the bis-benzyl protected product as a colorless oil in 97% yield. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 3.71 (s, 3H), 4.02 (s, 4H), 6.75 (d, 1H, J = 8.4 Hz), 7.06-7.10 (m, 6H), 7.13-7.16 (m, 4H), 7.60 (dd, 1H, J = 8.4, 2.0 Hz), 7.78 (d, 1H, J = 2.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.9, 51.6, 55.9, 121.5, 124.1, 127.0, 127.7, 128.2, 128.3, 132.4, 132.7, 137.6, 154.3, 167.0. HRMS(ESI) calcd for $C_{23}H_{24}NO_2$ [$(M+H)^+$]: 346.1807, found 346.1823.

Step 2: *Hydrolysis of methyl ester*
Hydrolysis of the methyl ester was effected by the addition of a solution of LiOH (0.69 g, 29.0 mmol) in water (3mL) to a stirred solution of the bis-benzyl protected methyl ester (2.01g, 5.82 mmol) in THF (9 mL). The reaction was refluxed for 2 hrs, acidified with HCl and extracted with chloroform (3 x 15 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resulting white solid was used subsequently without further purification. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 4.04 (s, 4H), 6.76 (d, 1H, J = 8.4 Hz), 7.06-7.10 (m, 6H), 7.13-7.16 (m, 4H), 7.66 (d, 1H, J = 8.4 Hz), 7.84 (s, 1H), 11.35 (br s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 19.1, 55.6, 121.4, 123.1, 127.1, 128.3, 128.4, 128.6, 132.3, 133.5, 137.6, 155.3, 172.5. HRMS(ESI) calcd for $C_{22}H_{21}NO_2$ [$(M+H)^+$]: 332.1651, found 332.1664.

Step 3: *Amide bond formation*
To a stirred solution of the respective benzoic acid derivative (2.66 g, 8.03 mmol) in THF (20 mL), were added EDCI (1.69 g, 8.83 mmol), DMAP (0.10 g, 0.82 mmol) and isobutylamine (0.89 mL, 8.83 mmol). The resulting mixture was stirred at room temperature for 10 hr. After stirring, the reaction was poured into water and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated. Column chromatography [Hexanes/EtOAc (70:30)] on silica gel afforded the amide product as a white solid in 90% yield. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78 (d, 6H, J = 6.7 Hz), 1.71 (sp, 1H, J = 6.7 Hz), 2.33 (s, 3H), 3.06 (t, 2H, , J = 6.5 Hz), 3.96 (s, 4H), 6.22 (t, 1H, J = 5.8 Hz), 6.72 (d, 1H, J = 8.3 Hz), 7.04-7.12 (m, 10H), 7.28 (dd, 1H, J = 8.3, 2.0 Hz), 7.50 (d, 1H, J = 2.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.8, 20.1, 28.5, 47.1, 56.2, 121.6, 124.7, 126.9, 128.1, 128.3, 129.1, 130.1, 133.0, 137.8, 152.6, 167.4. HRMS(ESI) calcd for $C_{26}H_{31}N_2O$ [$(M+H)^+$]: 387.2436, found 387.2446.

2. General procedures for the synthesis of benzoylurea oligomers**:

Procedure A: *Formation of isocyanate*
A solution of $NaHCO_3$ (0.84 mmol) in water (3 mL) was added to a solution of aniline derivative (0.42 mmol) and triphosgene (0.13 mmol) in CH_2Cl_2 (3 mL). The solution was stirred vigorously at room temperature for 30 min. The reaction mixture was poured into water and extracted with CH_2Cl_2 (2 x 4 mL), dried over Na_2SO_4, and concentrated. The crude residue was dried under vacuum for 2 hr and used without further purification.

Procedure B: *Reaction of isocyanate and amide subunits*
A flame-dried flask was charged with amide (0.42 mmol) and capped with a septum. Dry THF (3 mL) was added under N_2 and the solution was cooled to –78 ˚C. LiHMDS (1.0 M in THF, 0.84 mmol) was added dropwise and the resulting mixture was allowed to stir for at –78 ˚C for 5 min.

In a separate flask, the crude isocyanate was dissolved in dry THF (5 mL) under N_2. The resulting solution was subsequently added dropwise to the amide/LiHMDS solution described above via syringe at –78 ˚C. The resulting solution was allowed to stir for 30 min, warmed to room temperature, and quenched with aqueous NH_4Cl. The solution was then extracted with ether (2 x 5 mL), dried over Na_2SO_4, and concentrated. Column chromatography [Hexanes/EtOAc (80:20)] on silica gel afforded the corresponding benzoylurea .

Procedure C: *Boc-protection of the benzoylureas*
To a stirred solution of the respective benzoylurea (0.40 mmol) in THF (10 mL), was added di-*tert*-butyldicarbonate (0.81 mmol) and DMAP (0.04 mmol) respectively. The reaction mixture was allowed to stir at room temperature for 30 min. The solution was concentrated and purified by column chromatography [Hexanes/EtOAc (80:20)] on silica gel to afford the protected benzoylurea. The Boc-protected intermediates were characterized by ^{1}H-NMR and HRMS, spectral information not included.

Procedure D: *Hydrogenolysis*
A suspension containing the corresponding benzoylurea (0.20 mmol) and Pd/C (10% Pd, 20 mg) in a 1:1 MeOH/EtOAc mixture (10 mL) was purged with hydrogen, then stirred under a balloon of hydrogen. The suspension was stirred for 4 hrs, filtered through a pad of celite, and washed thoroughly with EtOAc. Column chromatography [Hexanes/EtOAc (70:30)] on silica gel afforded the corresponding benzoylurea.

Procedure E: *Boc-deprotection*
The respective benzoylurea (0.39 mmol) was dissolved in a 1:1 CH_2Cl_2/TFA mixture (10 mL) and allowed to stir at room temperature for 1 hr. The solution was concentrated and purified by column chromatography [Hexanes/EtOAc (80:20)] to yield the unprotected benzoylureas.

**Note: Final compounds were further purified by preparative reverse-phase HPLC and lyophilized to afford the corresponding benzoylureas. Preparative HPLC purifications were performed using a linear gradient from 50% B to 100% B with changing solvent composition over 50 minutes for all the bis-benzyl protected benzoylureas and a linear gradient from 10% B to 100% B with changing solvent composition over 40 minutes for the free amine benzoylurea derivatives. Product fractions were lyophilized to dryness.

3. Characterization of New Compounds

9a: To a stirred solution of *m*-toluic acid (0.51 g, 3.75 mmol) in CH_2Cl_2 (10 mL), were added EDCI (0.79 g, 4.1 mmol), methyl amine (2.0 M in THF, 7.50 mmol) and DMAP (0.05 g, 0.37 mmol). The resulting mixture was stirred at room temperature for 10 hr. After stirring, the reaction was poured into water and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated. Column chromatography [Hexanes/EtOAc (60:40)] on silica gel afforded the amide product as a white solid in 49% yield.

A flame-dried flask was charged with the above amide (0.21 g, 1.41 mmol) and capped with a septum. Dry THF (3 mL) was added under N_2 and the solution was cooled to –78 ˚C. LiHMDS (1.0 M in THF, 2.82 mmol) was added dropwise and the resulting mixture was allowed to stir for at –78 ˚C for 5 min. In a separate flask, the *o*-tolyl isocyanate (0.37 g, 2.82 mmol) was dissolved in dry THF (5 mL) under N_2. The resulting solution was subsequently added dropwise to the amide/LiHMDS solution described above via syringe at –78 ˚C. The resulting solution was allowed to stir for 30 min, warmed to room temperature, and quenched with aqueous NH_4Cl. The solution was then extracted with ether (2 x 5 mL), dried over Na_2SO_4, and concentrated. Column chromatography [Hexanes/EtOAc (80:20)] on silica gel afforded the corresponding benzoylurea **2a**. Yield: 88%. ^{1}H-NMR (500 MHz, C_6D_6): δ 1.69 (s, 3H), 2.01 (s, 3H), 2.61 (s, 3H), 6.57-6.66 (m, 5H), 6.72 (d, 1H, J = 7.3 Hz), 6.87-6.92 (m, 1H), 8.43 (d, 1H, J = 8.1 Hz), 11.41 (s, 1H); (125 MHz, C_6D_6): δ 18.3, 21.1, 35.5, 121.3, 124.0, 127.2, 127.5, 127.6, 128.4, 130.6, 131.3, 136.5, 137.5, 138.4, 152.5, 175.1.

9b: The same procedure was followed for the synthesis of **3**, except that methylamine (2.0 M in THF) was used in Step 3: *Amide bond formation*.

General procedures A, B and D were followed starting from aniline methyl-4-amino-3-methyl benzoate (0.51 g, 3.09 mmol) and amide (1.06 g, 3.08 mmol). Product was isolated as a white fluffy. Yield: 91%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.31 (s, 3H), 3.31 (s, 3H), 3.81 (s, 3H), 3.99 (br s, -NH_2), 6.59 (d, 1H, J = 8.2 Hz), 7.22 (d, 1H, J = 8.1 Hz), 7.26 (s, 1H), 7.80 (s, 1H), 7.83 (d, 1H, J = 8.6 Hz), 8.24 (d, 1H, J = 8.6 Hz), 11.53 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.2, 18.1, 36.6, 51.8, 113.6, 119.6, 121.5, 124.0, 124.7, 126.9, 127.6, 128.5, 130.8, 131.6, 141.1, 148.3, 153.0, 166.9, 175.6.

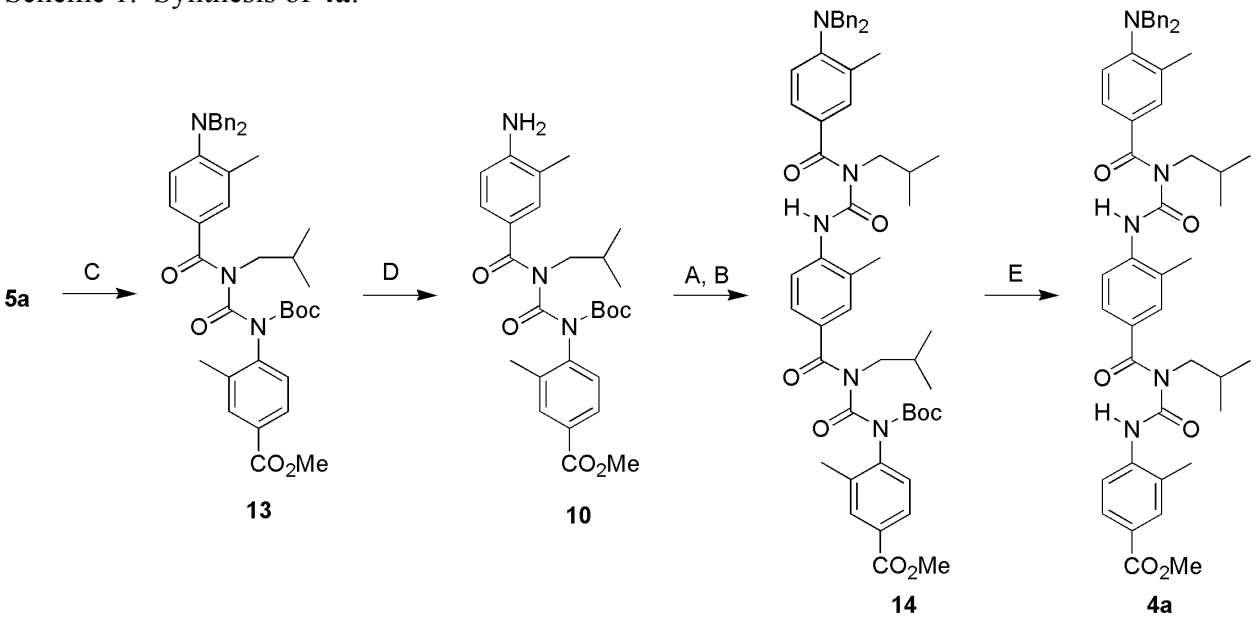
9c: General procedures A and B were followed starting from the aniline 3-(4-Amino-3-isobutyl-phenyl)-acrylic acid benzyl ester (50.3 mg, 0.16 mmol) and amide 2-isobutyl-4-[(naphthalen-1-ylmethyl)-carbamoyl]-phenoxy acetic acid benzyl ester (38.9 mg, 0.08 mmol). Column chromatography [Hexanes/EtOAc (80:20)] on silica gel afforded the corresponding benzoylurea in 46% yield. The resulting benzoylurea was subjected to hydrogenolysis following procedure D. Product was isolated as a white fluffy solid. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.63 (d, 6H, J = 6.6 Hz), 0.93 (d, 6H, J = 6.6 Hz), 1.51 (sp, 1H, J = 6.7 Hz), 1.86 (sp, 1H, J = 6.7 Hz), 2.30 (d, 2H, J = 7.1 Hz), 2.489 (d, 2H, J = 7.2 Hz), 2.66 (t, 2H, J = 7.5 Hz), 2.90 (t, 2H, J = 7.5 Hz), 4.60 (s, 2H), 5.55 (s, 2H), 6.58 (d, 1H, J = 8.7 Hz), 6.66 (br. s, 2H), 6.99 (s, 1H), 7.03 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.20 (m, 1H), 7.33 (dd, 1H, J_1 = 8.4 Hz, J_2 = 2.1 Hz), 7.35-7.37 (m, 1H), 7.40-7.46 (m, 3H), 7.72 (d, 1H, J = 8.2 Hz), 7.75 (d, 1H, J = 8.1 Hz), 7.83-7.85 (m, 2H), 11.05 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.2, 22.4, 28.4 29.0, 30.0,

35.5, 38.8, 41.0, 48.4, 64.6, 110.7, 122.3, 123.1, 123.2, 125.3, 125.8, 126.2, 126.3, 126.5, 127.8, 128.4, 128.8, 129.6, 130.3, 130.7, 131.1, 132.8, 133.2, 133.7, 133.9, 136.2, 153.1, 157.7, 173.3, 175.4, 178.7, 178.8.

5a: General procedures A and B were followed starting from aniline methyl-4-amino-3-methyl benzoate (1.01 g, 6.05 mmol) and amide **3** (2.34 g, 6.05 mmol). Product was isolated as a white fluffy solid. Yield: 95%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.63 (d, 6H, *J* = 6.7 Hz), 1.79 (sp, 1H, *J* = 6.7 Hz), 2.22 (s, 3H), 2.37 (s, 3H), 3.63 (d, 2H, *J* = 7.0 Hz), 3.73 (s, 3H), 4.01 (s, 4H), 6.76 (d, 2H, *J* = 8.3 Hz), 7.04-7.09 (m, 8H), 7.12-7.14 (m, 3H), 7.24 (s, 1H), 7.74 (s, 1H), 7.77 (d, 1H, *J* = 8.6 Hz), 8.20 (d, 1H, *J* = 8.6 Hz), 11.33 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.0, 18.8, 19.7, 28.5, 51.7, 54.3, 56.1, 119.6, 122.0, 124.8, 125.5, 126.8, 127.1, 128.1, 128.4, 128.4, 129.6, 130.5, 131.5, 133.5, 137.4, 140.9, 152.1, 152.6, 166.7, 176.3. HRMS(ESI) calcd for $C_{36}H_{40}N_3O_4$ [$(M+H)^+$]: 578.3019, found 578.3016.

5b: General procedure D was followed starting from **5a**. Product was isolated as a white fluffy solid. Yield: 91%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78 (d, 6H, *J* = 6.7 Hz), 1.96 (sp, 1H, *J* = 6.8 Hz), 2.28 (s, 3H), 2.36 (s, 3H), 3.78 (d, 2H, *J* = 7.1 Hz), 3.90 (s, 3H), 6.93 (d, 1H, *J* = 8.1 Hz), 7.30 (d, 1H, *J* = 8.1 Hz), 7.35 (s, 1H), 7.49 (br s, -NH_2), 7.87 (s, 1H), 7.89 (d, 1H, *J* = 8.8 Hz), 8.21 (d, 1H, *J* = 8.5 Hz), 11.30 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.1, 18.0, 19.7, 28.6, 52.1, 55.0, 117.0, 120.2, 125.0, 125.2, 127.4, 127.5, 128.1, 128.6, 130.8, 131.7, 140.8, 143.1, 152.6, 167.4, 176.1. HRMS(ESI) calcd for $C_{22}H_{28}N_3O_4$ [$(M+H)^+$]: 398.2080, found 398.2087.

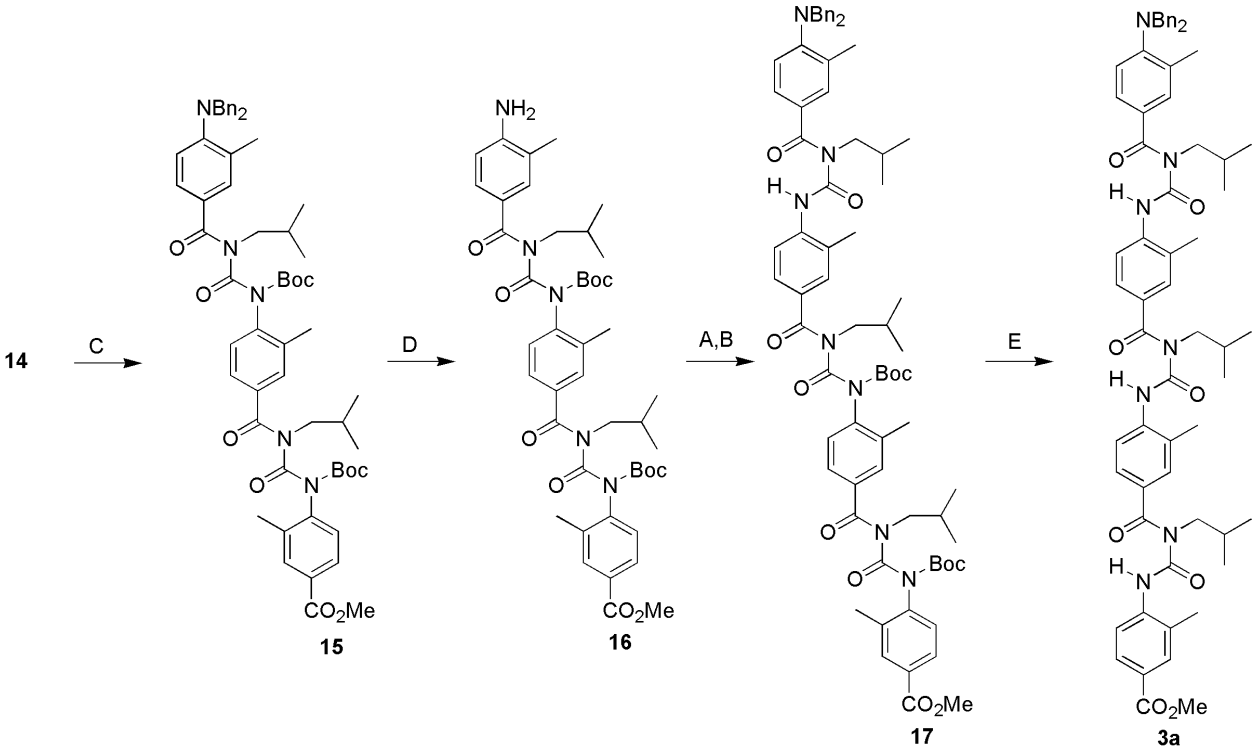
Scheme 1. Synthesis of **4a**.



4a: General procedures C, D, A, B, and E were followed starting from **5** (1.00g, 1.74 mmol). Product was isolated as a white fluffy solid. Yield (after 5 steps): 62%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.67 (d, 6H, *J* = 6.7 Hz), 0.68 (d, 6H, *J* = 6.7 Hz), 1.81 (sp, 1H, *J* = 6.8 Hz), 1.87 (sp, 1H, *J* = 6.8 Hz), 2.29 (s, 6H), 2.32 (s, 3H), 3.63 (d, 1H, *J* = 6.8 Hz), 3.70 (d, 1H, *J* = 6.8 Hz), 3.79 (s, 3H), 4.20 (s, 4H), 6.91 (d, 1H, *J* = 8.3 Hz), 7.11-7.18 (m, 11H), 7.22 (s, 1H), 7.28-7.30 (m, 2H), 7.78 (s, 1H), 7.81 (d, 1H, *J* = 8.7 Hz), 8.20 (d, 1H, *J* = 8.6 Hz), 8.23 (d, 1H, *J* = 8.3 Hz), 11.36 (s, 1H), 11.38 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.1, 18.2, 18.8, 19.7, 19.8, 28.5, 28.6, 51.9, 54.5, 54.7, 57.2, 119.9, 120.2, 122.2, 125.0, 125.6, 126.4, 127.2, 127.6, 127.8, 128.3, 128.5, 128.8, 129.7, 130.5, 130.6, 130.6, 131.6, 133.9, 136.2, 139.5, 140.9, 150.6, 152.2, 152.3, 167.0, 176.1, 176.2. HRMS(ESI) calcd for $C_{49}H_{56}N_5O_6$ [$(M+H)^+$]: 810.4231, 810.4223.

4b: General procedure D and E were followed starting from **14**. Product was isolated as a white fluffy solid. Yield: 83%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79 (d, 3H, *J* = 6.7 Hz), 0.80 (d, 3H, *J* = 6.7 Hz), 1.94-2.01 (m, 2H), 2.23 (s, 3H), 2.39 (s, 6H), 3.80 (d, 2H, *J* = 6.6 Hz), 3.84 (d, 2H, *J* = 7.1 Hz), 3.91 (s, 3H), 5.42 (br s, -NH_2), 6.75 (d, 1H, *J* = 8.1 Hz), 7.29 (d, 1H, *J* = 8.1 Hz), 7.34 (s, 1H), 7.39-7.41 (m, 2H), 7.89 (s, 1H), 7.91 (d, 1H, *J* = 8.1 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.30 (s, 1H, *J* = 8.3 Hz), 11.36 (s, 1H), 11.46 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.2, 18.1, 18.2, 19.8, 28.5, 28.6, 52.1, 54.8, 55.3, 114.6, 120.2, 120.4, 122.5, 125.1, 125.2, 126.4, 127.5, 127.8, 128.0, 128.6, 129.7, 130.4, 130.9, 131.7, 139.6, 140.9, 147.1, 152.5, 152.9, 167.3, 176.2, 176.6. HRMS(ESI) calcd for $C35H_{44}N_5O_6$ [$(M+H)^+$]: 630.3292, found 630.3298.

Scheme 2: Synthesis of **3a**.

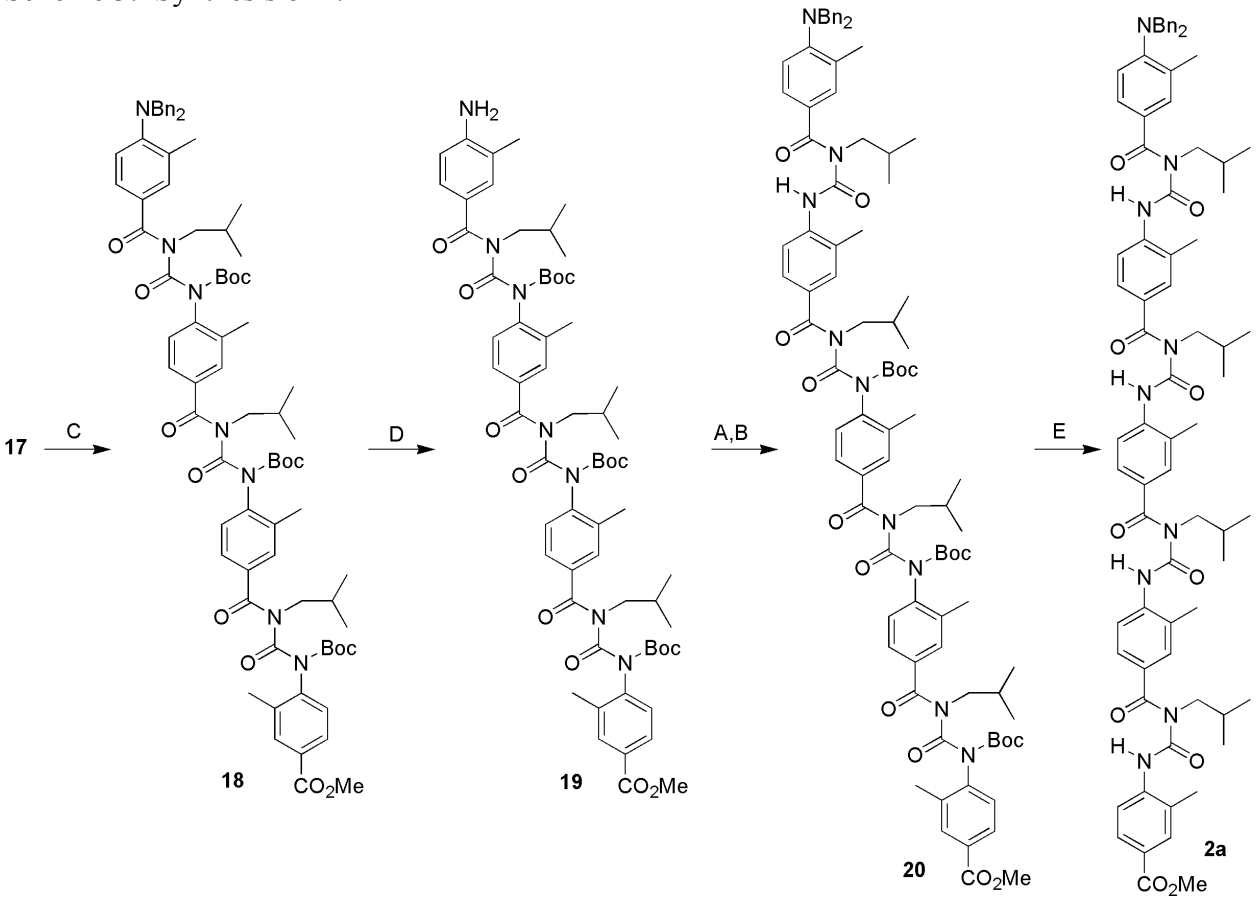


3a: General procedures C, D, A, B, and E were followed starting from **14** (Scheme 2, 0.54 g, 0.59 mmol). Product was isolated as a white fluffy solid. Yield (after 5 steps): 58%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.68 (d, 6H, *J* = 7.0 Hz), 0.70 (d, 6H, *J* = 6.8 Hz), 0.71 (d, 6H, *J* = 7.0 Hz), 1.81-1.91 (m, 3H), 2.31 (s, 6H), 2.32 (s, 3H), 2.39 (s, 3H), 3.67 (d, 2H, *J* = 6.6 Hz), 3.70-3.74 (br m, 4H), 3.81 (s, 1H), 4.14 (s, 4H), 6.86 (d, 1H, *J* = 8.3 Hz), 7.12-7.20 (m, 11H), 7.26 (s, 1H), 7.23-7.32 (m, 4H), 7.80 (s, 1H), 7.82 (d, 1H, *J* = 8.7 Hz), 8.22 (d, 2H, *J* = 8.5 Hz), 8.26 (d, 2H, *J* = 8.2 Hz), 11.39 (s, 1H), 11.43 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.2, 18.3, 18.4, 18.9, 19.8, 18.9, 28.5, 28.6, 28.7, 29.7, 52.0, 54.5, 54.7, 56.7, 56.7, 119.9, 120.1, 120.2, 122.2, 124.9, 125.6, 126.4, 127.1, 127.4, 127.4, 127.8, 127.9, 128.3, 128.6, 128.7, 128.7, 129.7, 130.4, 130.5, 130.7, 131.7, 133.8, 136.8, 136.9, 136.9, 139.6, 139.7, 141.0, 152.3, 152.3, 152.4, 167.0, 176.1, 176.2, 176.4. HRMS(ESI) calcd for $C_{62}H_{72}N_7O_8$ [$(M+H)^+$]: 1042.5442, found 1042.5419.

3b: General procedures D and E were followed starting from **17** (Scheme 2). Product was isolated as a white fluffy solid. Yield: 83%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.78-0.81 (m, 18H), 1.95-2.02 (m, 3H), 2.21 (s, 3H), 2.40 (s, 6H), 2.42 (s, 3H), 3.80-3.82 (m, 4H), 3.85 (d, *J* = 7.1 Hz), 3.90 (s, 3H), 4.44 (br s, -NH_2), 6.69 (d, 1H, *J* = 8.2 Hz), 7.26-7.28 (m, 1H), 7.31 (s, 1H), 7.39 (s, 3H), 7.41 (s, 1H), 7.89 (s, 1H), 7.91 (d, 1H, *J* = 8.6 Hz), 8.30 (d, 1H, *J* = 8.6 Hz), 8.35 (d, 2H, *J* = 8.2 Hz), 11.41 (s, 1H), 11.48 (s, 1H), 11.52 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.2, 18.1, 18.2, 18.3, 19.8(0), 19.8(3), 28.6(0), 28.6(1), 29.7, 52.0, 54.7, 54.8, 55.3, 114.0, 120.0, 120.1, 120.2, 121.8, 124.5, 125.0, 126.3, 126.4, 127.2, 127.8(1),

127.8(3), 127.9, 128.6, 129.7 (2 Carbons), 130.2, 130.5, 130.9, 131.7, 139.6, 139.8, 141.0, 148.0, 152.3, 152.4, 152.8, 167.1, 176.2, 176.3, 176.7. HRMS(ESI) calcd for $C_{48}H_{60}N_7O_8$ [$(M+H)^+$]: 862.4503, found 862.4502.

Scheme 3: Synthesis of **2**.



2a: General procedures C, D, A, B, and E were followed starting from **17** (Scheme 3, 0.20 g, 0.24 mmol). Product was isolated as a white fluffy solid. Yield (after 5 steps): 60%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.77-0.81 (m, 24H), 1.94-2.00 (m, 4H), 2.40 (s, 6H), 2.42 (s, 6H), 2.52 (s, 3H), 3.77-3.83 (m, 8H), 3.90 (s, 3H), 4.17 (s, 4H), 6.91 (d, 1H, J = 8.3 Hz), 7.19-7.24 (m, 6H), 7.27-7.30 (m, 4H), 7.39-7.41 (m, 8H), 7.89 (s, 1H), 7.91 (d, 1H, J = 8.7 Hz), 8.33 (d, 1H, J = 8.6 Hz), 8.36-8.38 (m, 3H), 11.49 (s, 1H), 11.53 (s, 1H), 11.54 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.6, 18.6, 18.7(0), 18.7(1), 19.4, 20.2, 20.3, 29.0(3), 29.0(4), 29.0(5), 30.1, 52.3, 55.0, 55.1, 55.2, 56.7, 120.3, 120.6(0), 120.6(2), 122.6, 125.4, 126.0, 126.8, 127.5, 127.6, 128.2, 128.2, 128.3, 128.7, 128.9,129.0, 130.1(0), 130.1(2), 130.8(0), 130.8(2), 130.9, 131.1, 132.1, 134.1, 137.9, 140.0, 140.1, 140.2, 141.4, 152.7, 152.8(0), 152.8(4), 153.3, 167.4, 176.6(0), 176.6(4), 176.6(5), 177.0. HRMS(ESI) calcd for $C_{75}H_{88}N_9O_{10}$ [$(M+H)^+$]: 1274.6654, found 1274.6656.

2b: General procedures D and E were followed starting from **20** (Scheme 3). Product was isolated as a white fluffy solid. Yield: 80%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.79-0.81 (m, 24H), 1.94-2.02 (m, 4H), 2.21 (s, 3H), 2.40 (s, 6H), 2.42 (s, 6H), 3.03 (br s, -NH_2), 3.80-3.82 (m, 6H), 3.85 (d, 2H, J = 7.2 Hz), 3.90 (s, 3H), 6.69 (d, 1H, J = 8.2 Hz), 7.26-7.28 (m, 1H), 7.31 (s, 1H), 7.39-7.41 (m, 6H), 7.89 (s, 1H), 7.92 (d, 1H, J = 8.6 Hz), 8.31 (d, 1H, J = 8.6 Hz), 8.34-8.36 (m, 3H), 11.41 (s, 1H), 11.47 (s, 1H), 11.51 (s, 1H), 11.52 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.2, 18.2, 18.3(0), 18.3(1), 19.8(2), 19.8(4), 28.6, 52.0, 54.7, 54.8, 54.9, 55.3, 113.9, 119.9, 120.1, 120.3, 121.8, 124.6, 125.0, 126.4, 127.2, 127.8, 127.9(0), 127.9(4), 128.6, 129.7, 130.2, 130.4, 130.5, 131.0, 131.7, 139.6, 139.7, 139.9, 141.0, 148.1, 152.3, 152.4(1), 152.4(3), 152.8, 167.0, 176.2, 176.3(0), 176.3(1), 176.7. HRMS(ESI) calcd for $C_{59}H_{77}N_9O_{10}Na$ [$(M+Na)^+$]: 1094.5691, found 1094.5698.

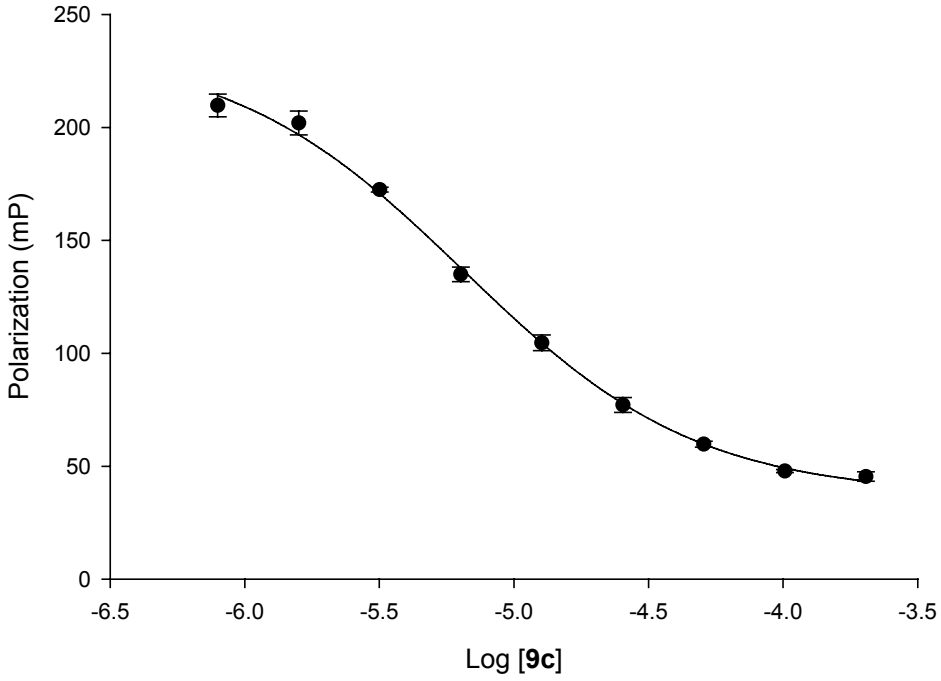
Part IV: ^{1}H NMR Procedures for Concentration and VT Experiments

Dilution ^{1}H-NMR Experiment: Three solutions of **9a** in $CDCl_3$ with varying concentrations of 0.5, 0.05, and 0.005 M were prepared. The ^{1}H-NMR spectrum of each solution was taken, and referenced to the solvent peak. The benzoylurea proton was monitored. The proton resonance did not show a concentration dependence suggesting that **9a** is intramolecularly hydrogen bonded.

Variable Temperature ^{1}H-NMR Experiment: A 0.005 M solution of **9a** in d_6-DMSO was prepared. ^{1}H-NMR measurements were made in the range of 298-368 K. The first measurement was made at the lowest temperature and then the temperature was increased in 10 K increments. All the spectra obtained were referenced to the solvent peak and the ppm change of the benzoylurea peak was monitored. The change in chemical shift was plotted versus the change in temperature and the data was fitted to a linear equation using EXCEL (2000, Microsoft Corporation).

Part V: Fluorescence Polarization Competition Assay

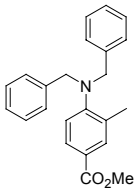
A previously reported fluorescence polarization (FP) assay[1] from our laboratory[2] was used to evaluate the effectiveness of benzoylurea derivative **9c** (where X=-OCH_2CO_2H, Y=-$(CH_2)_2CO_2H$, R^1=R^3= -*i*Bu, and R^2= -CH_2-2-naphthyl) to inhibit the Bcl-x_L/Bak protein-protein interaction. Below is the FP data obtained from an experiment performed in triplicate, showing that the benzoylurea derivative effectively displaces Flu-Bak. The polarization value (mP) was plotted against a log scale of the inhibitor concentration. The data were fit to a non-linear one-site competition equation using SigmaPlot 2004 (Windows Version 9.01) to obtain the inhibition constant value (K_i). Benzoylurea **9c** was found to have a K_i value of 2.4 ± 0.3 μM.

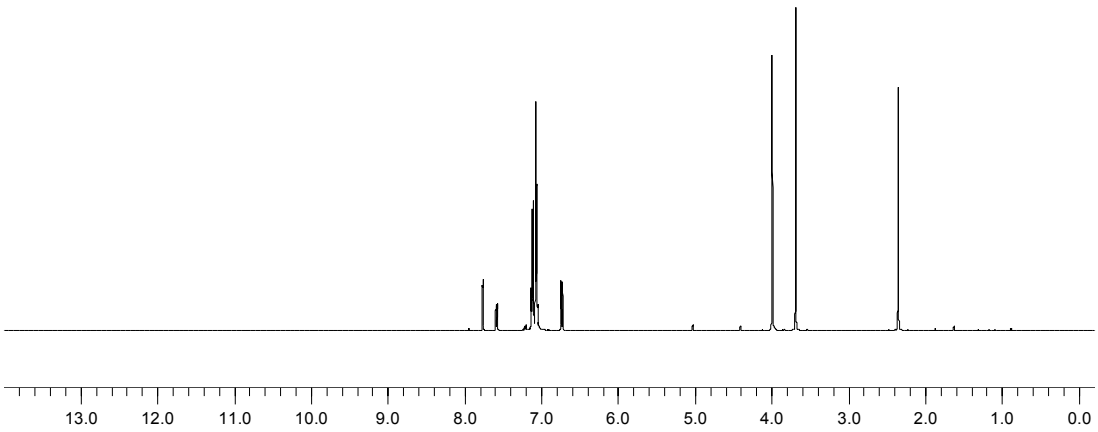


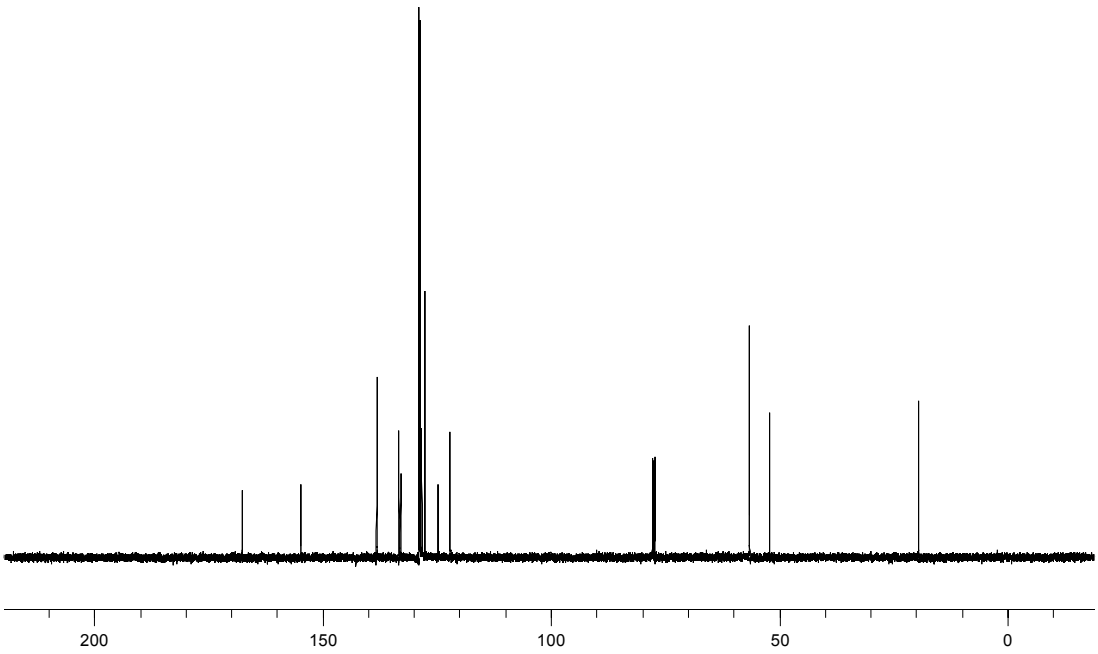
References for Part III:

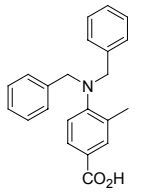
1. Wang, J. L.; Liu, D. X.; Zhang, Z. J.; Shan, S. M.; Han, X. B.; Srinivasula, S. M.; Croce, C. M.; Alnemri, E. S.; Huang, Z. W. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 7124-7129.
2. Yin, H.; Lee, G. I.; Park, H. S.; Payne, G. A.; Rodriguez, J. M.; Sebti, S. M.; Hamilton, A. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 2704-2707

Part VI: ^{1}H NMR and ^{13}C NMR Spectra of Prepared Compounds





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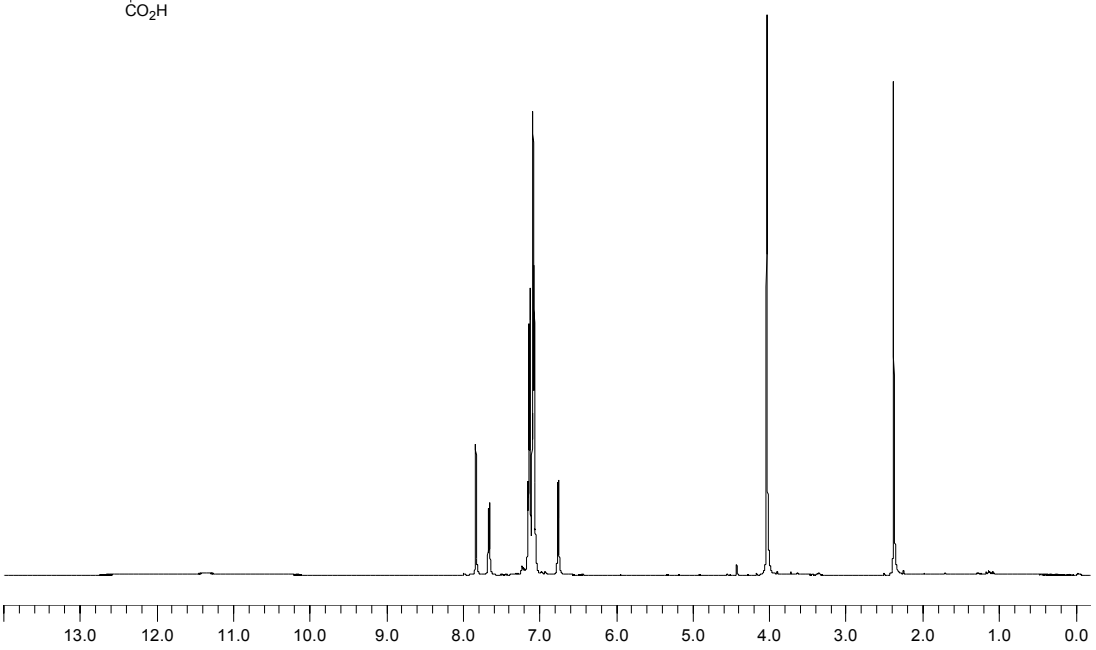
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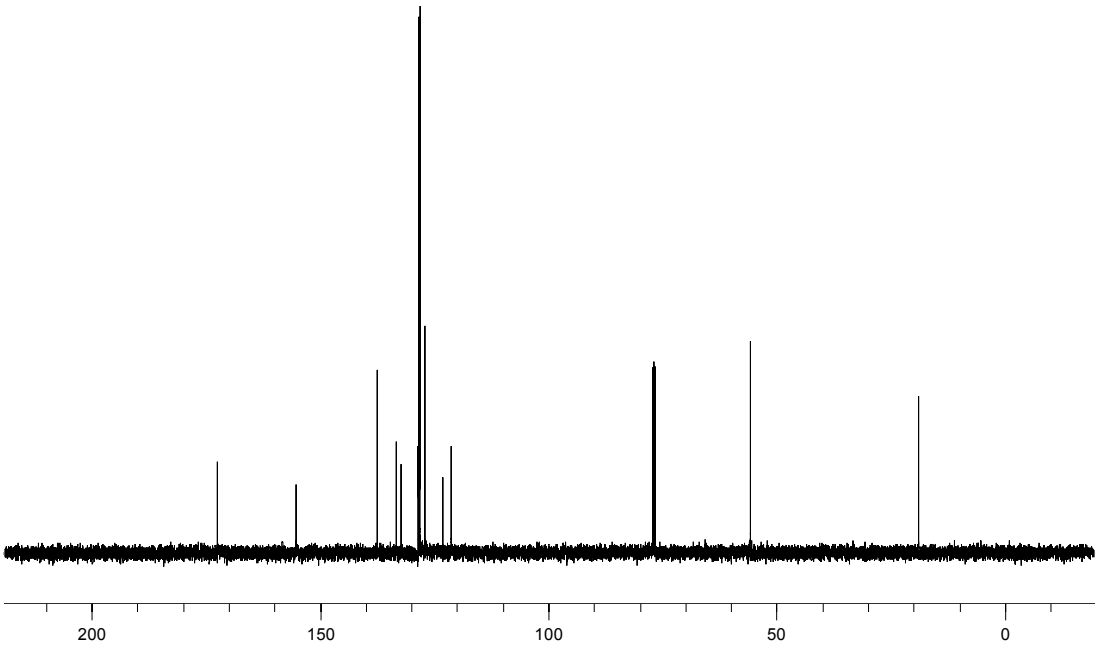
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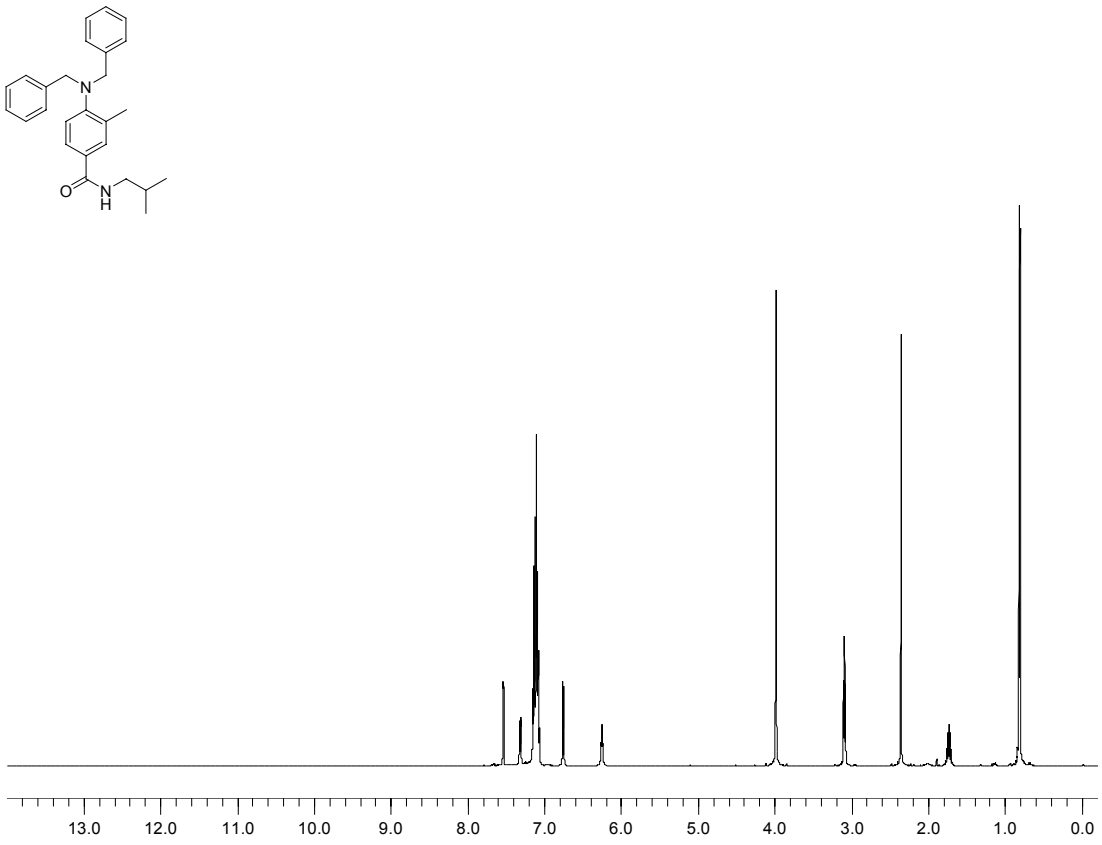
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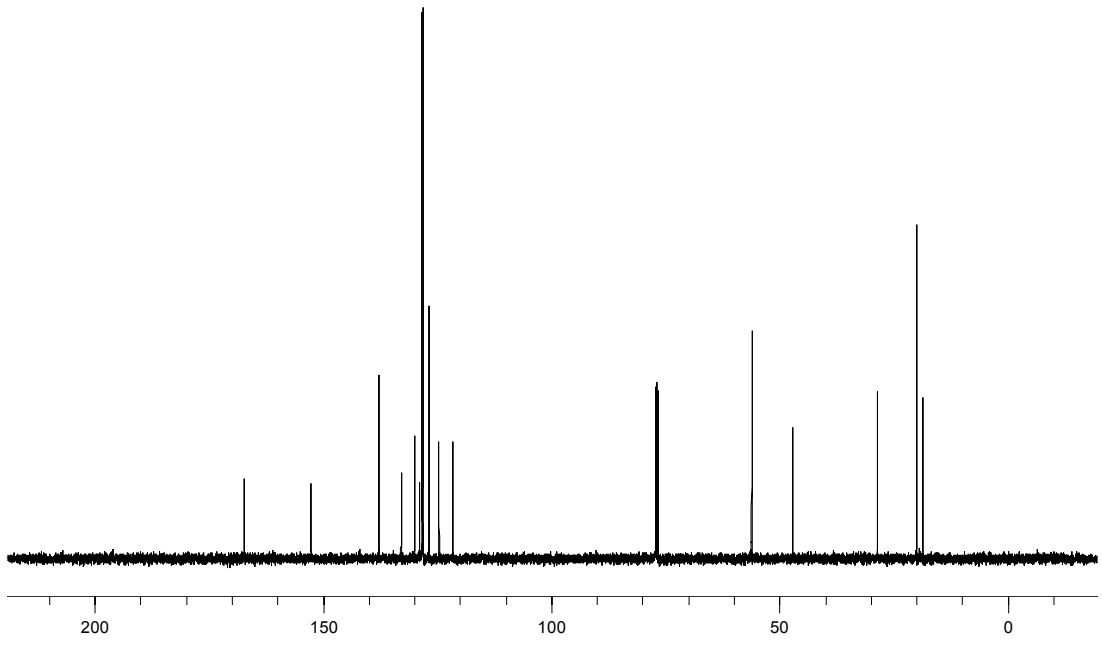
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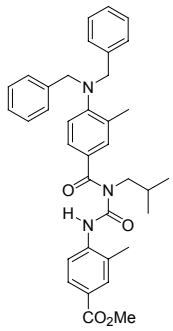
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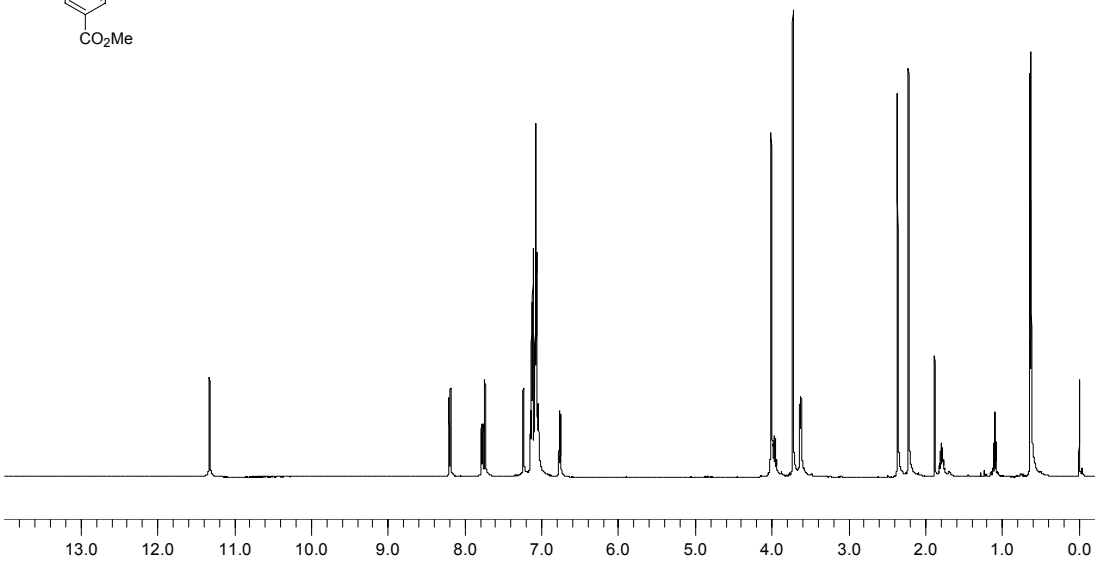
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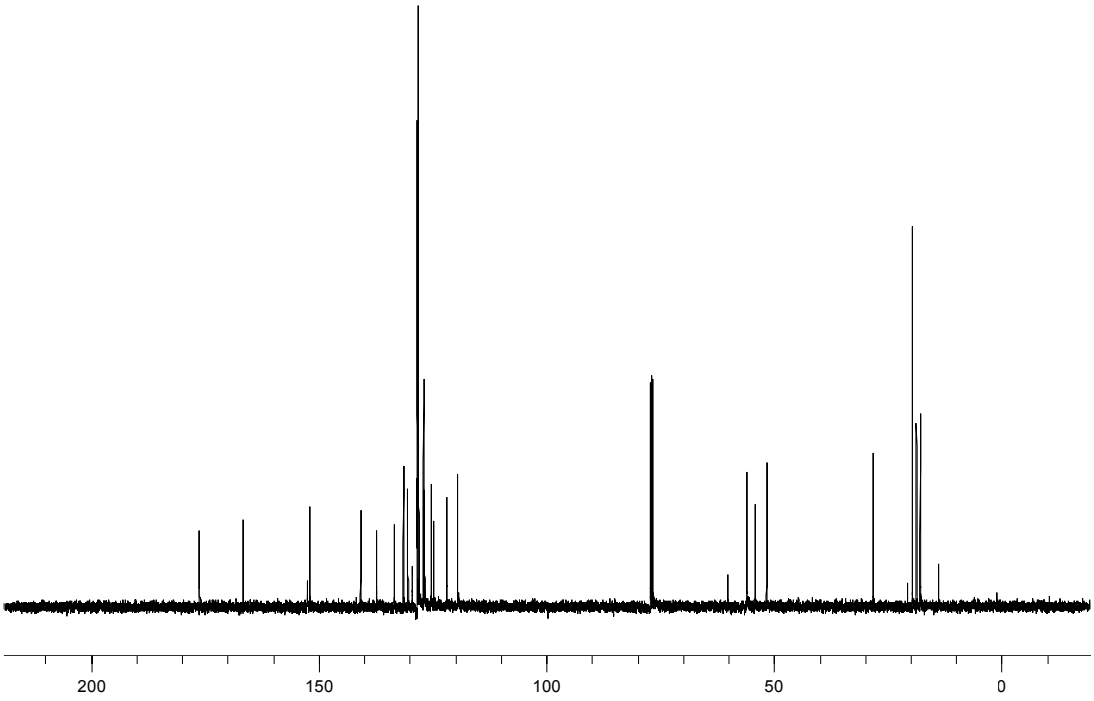
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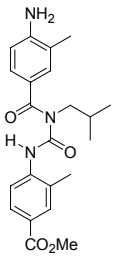
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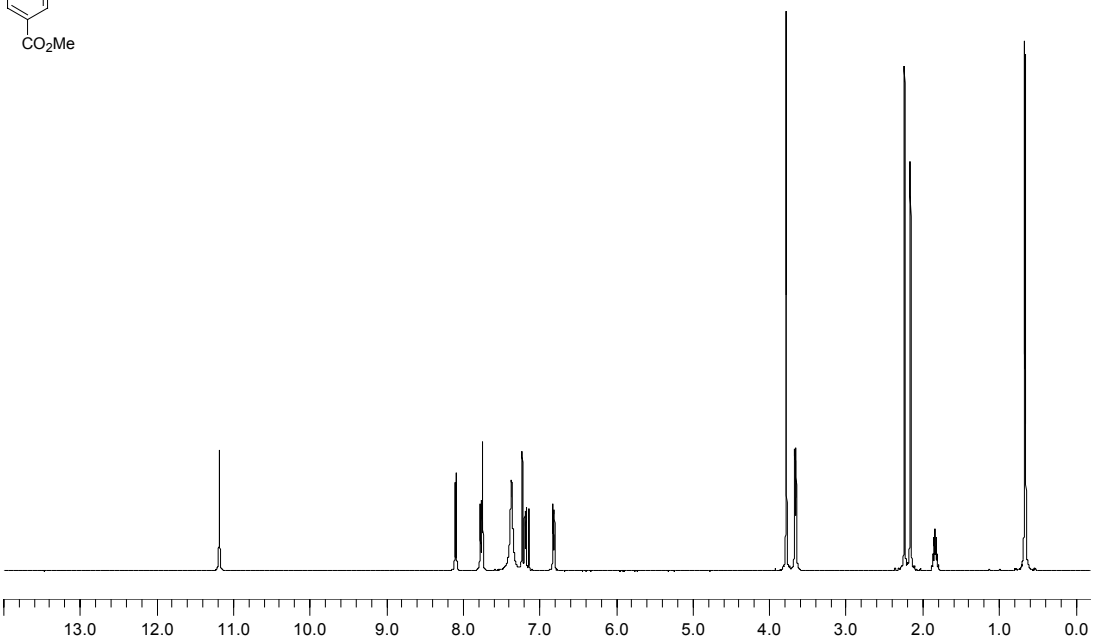
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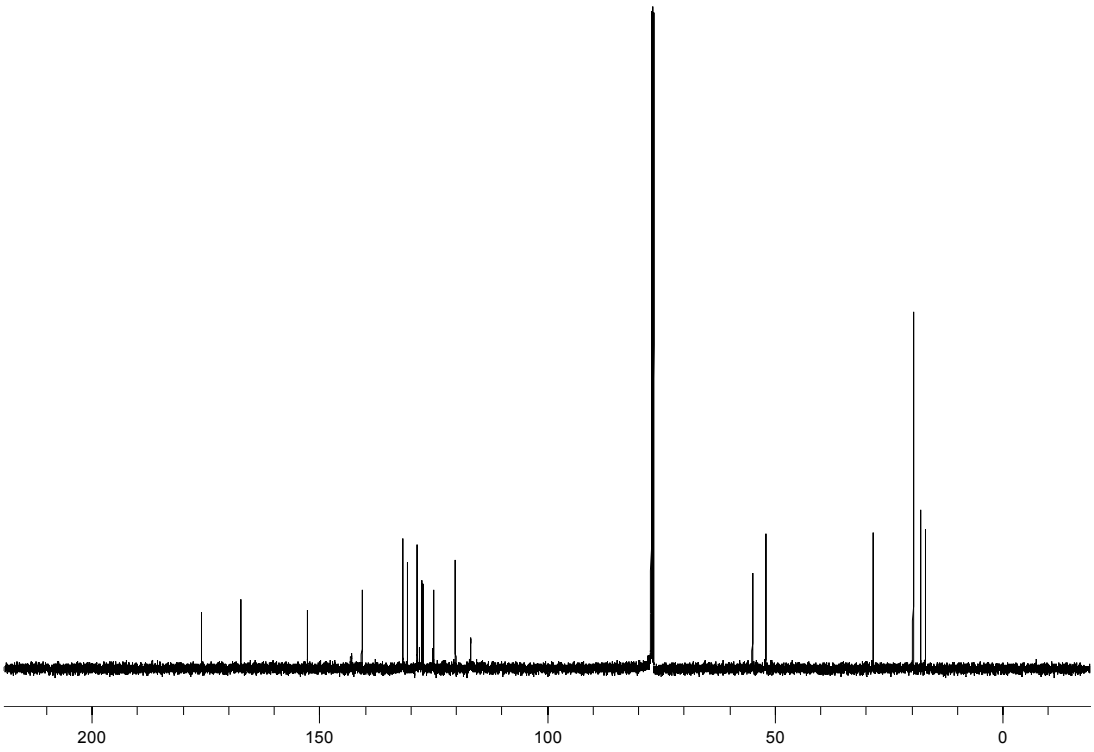
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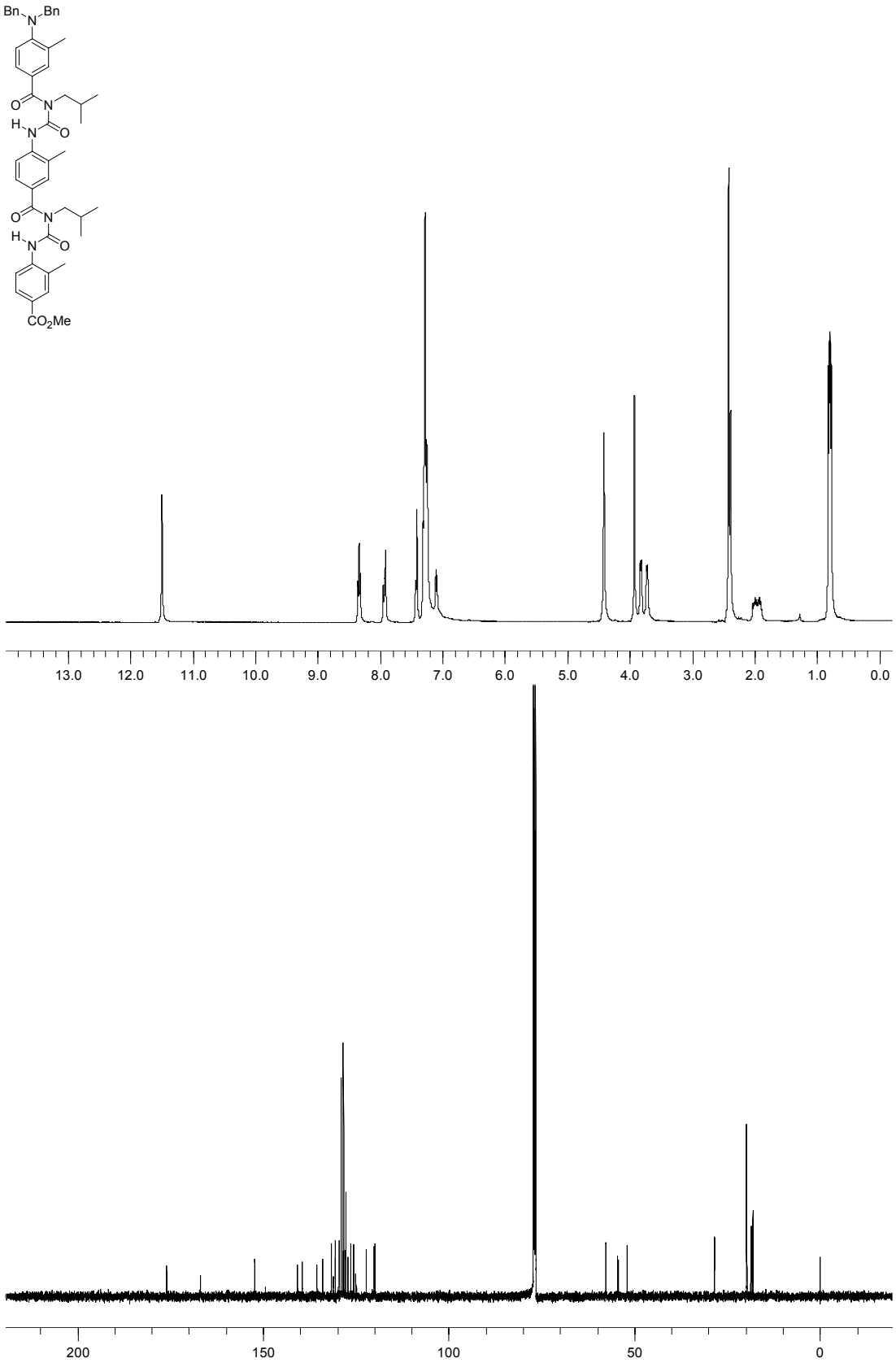
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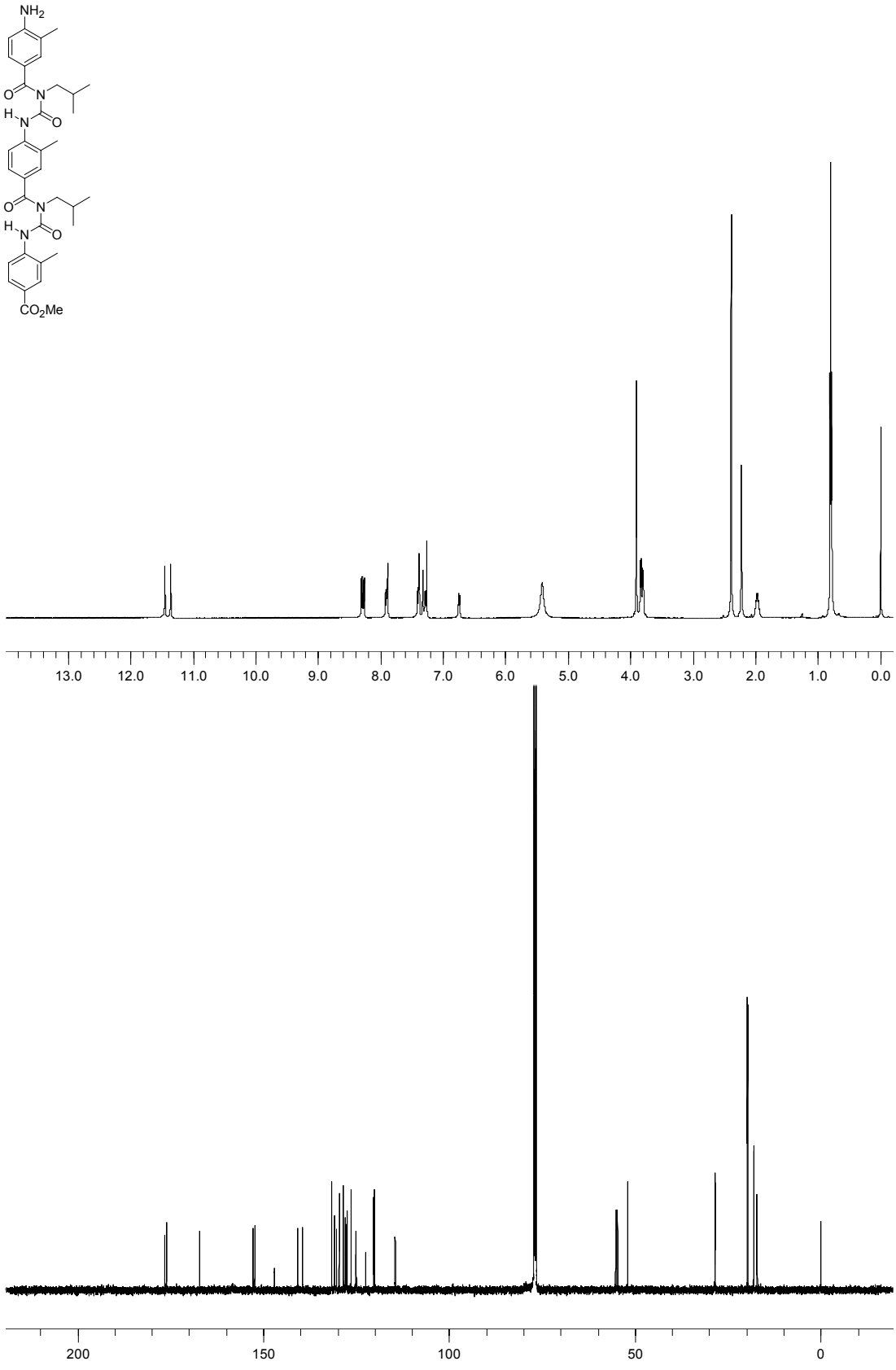
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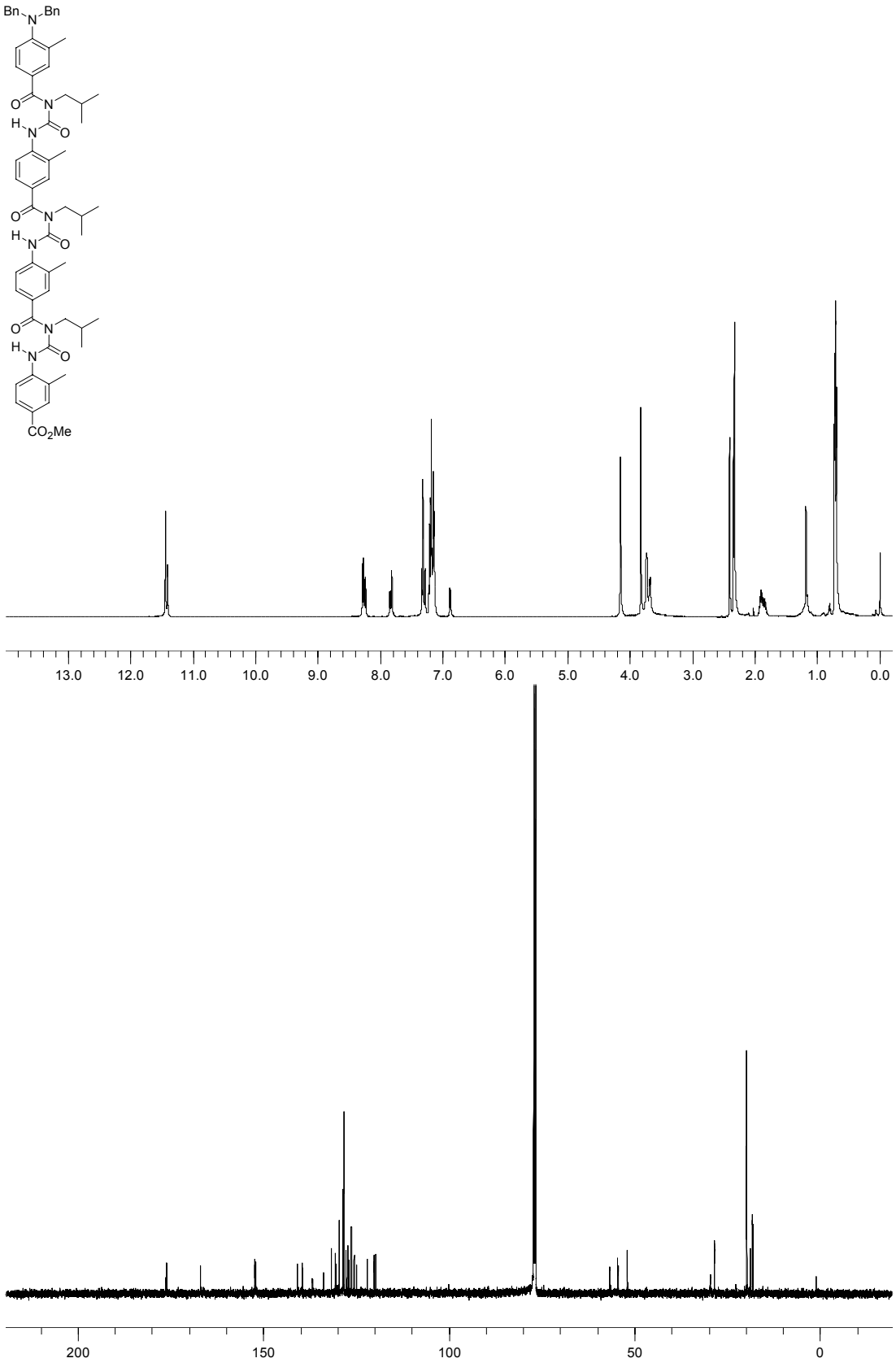
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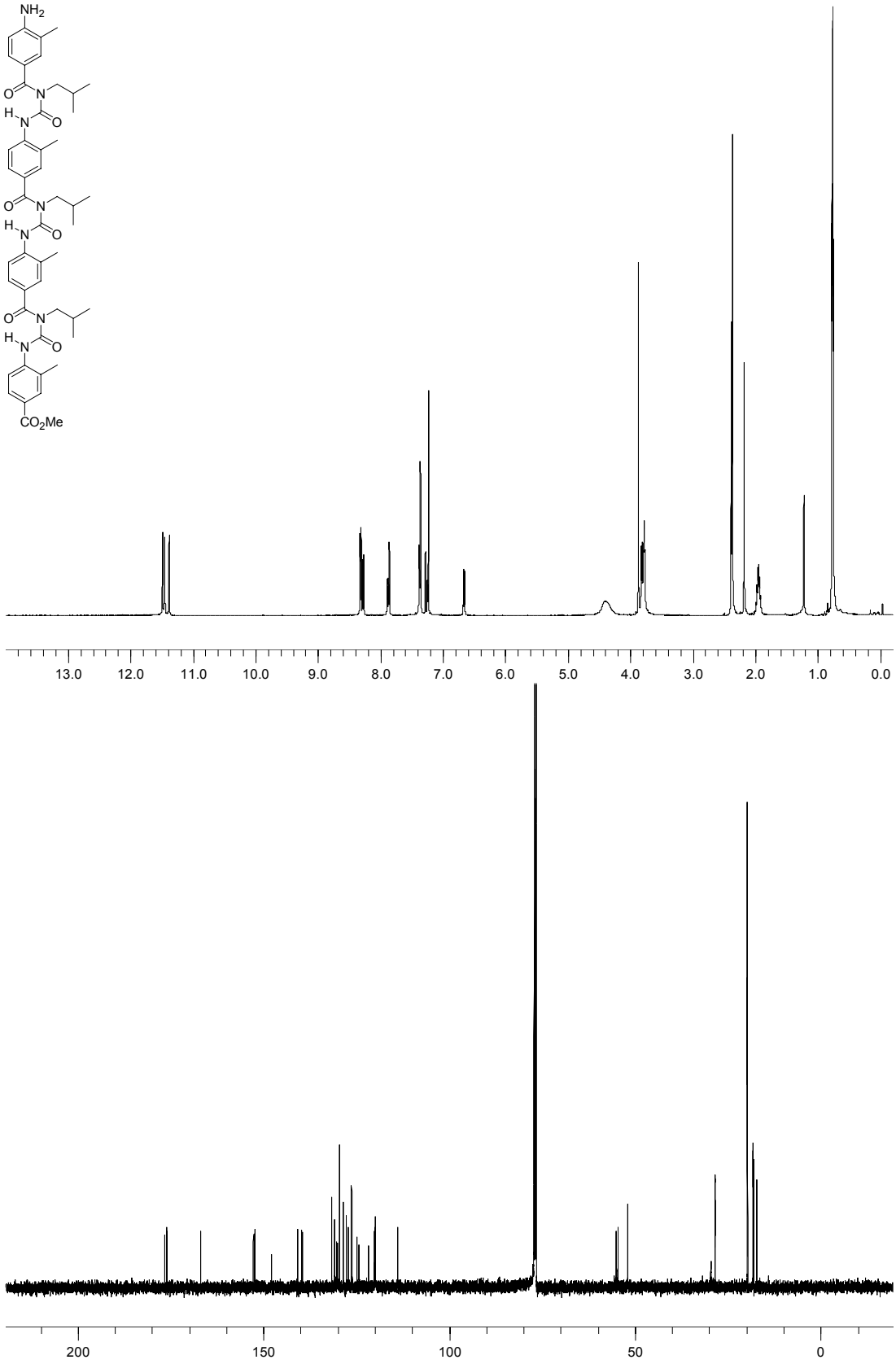
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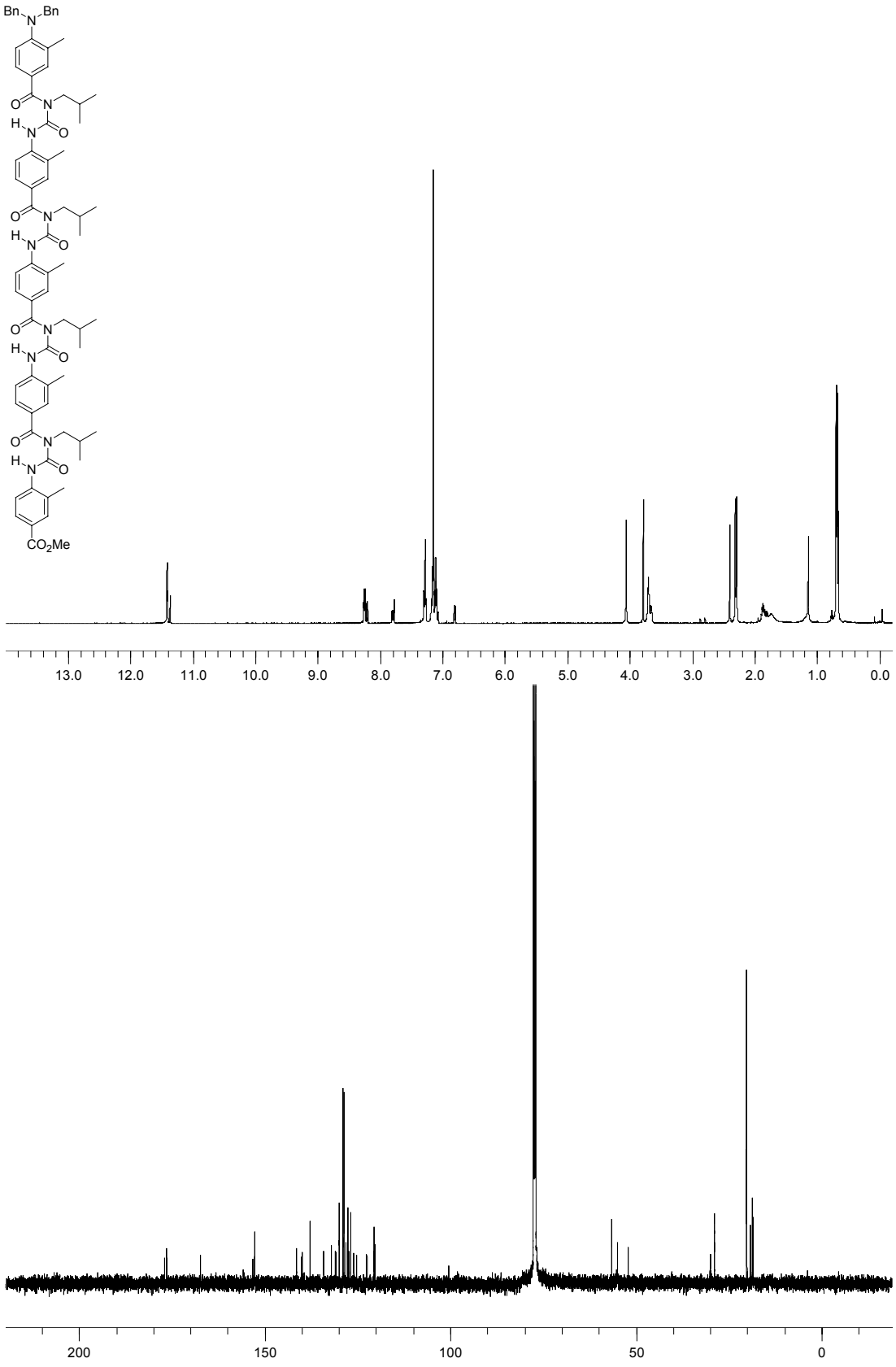
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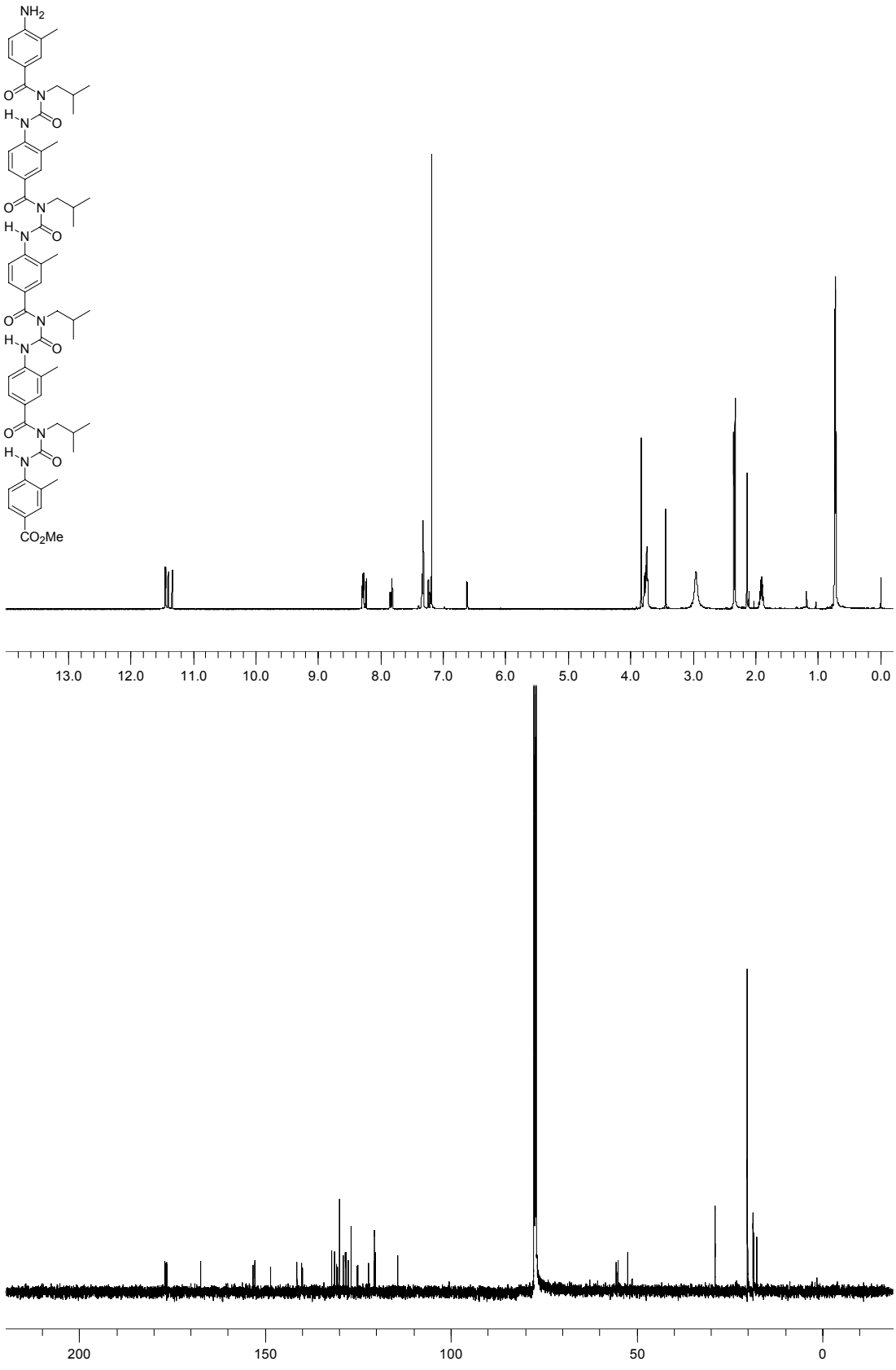
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