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Structural modulation of membrane-intercalating conjugated oligoelectrolytes decouples outer membrane permeabilizing and antimicrobial activities

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Materials and Instrumentation

Solvents and reagents for the preparation of the MICOEs were purchased from Fisher Scientific, Alfa Aesar, Acros, Sigma Aldrich, and Tokyo Chemical Industry. *E. coli* total lipid extract was purchased from Avanti Polar Lipids. 2-Nitrophenyl β-D-galactopyranoside (ONPG) was purchased from Sigma-Aldrich. *Escherichia coli* ATCC 10798 (K12) was purchased from American Type Culture Collection (Manassas, VA). Inhibitor-free anhydrous solvents were prepared using packed alumina columns under argon in a solvent purification system. EMD Millipore Analytical Chromatography aluminum-backed plates (Silica gel 60 F254) were used for thin layer chromatography and separation was visualized with UV light (254/366 nm). Silicycle SiliaFlash P60 silica gel was used for normal-phase flash chromatography under positive air pressure. Reversed-phase column chromatography was conducted using a Biotage Isolera autocolumn with pre-packed C18 Biotage SNAP columns. Measurements for MIC, ONPG, and association studies were conducted on a Tecan M220 Infinite Pro. ^{1}H NMR (400 MHz, 500 MHz, 600 MHz) and ^{13}C NMR (101 MHz and 126 MHz) were measured on an actively shielded Agilent Technologies 400-MR DDR2 400 MHz, a Varian Unity Inova 500 MHz, or a Varian VNMRS 600 MHz spectrometer. Multiplicity of signals was described by s (singlet), d (doublet), t (triplet), and m (multiplet). Chemical shifts (δ in ppm) were referenced to residual solvent peaks of $CDCl_3$ (^{1}H NMR δ = 7.26 and ^{13}C NMR δ = 77.0) or DMSO-d_6 (^{1}H NMR δ = 2.50 and ^{13}C-NMR δ = 39.52). HRMS (m/z) measurements were performed on a Waters GCT Premier time-of-flight mass spectrometer.

Strain and Culture Conditions

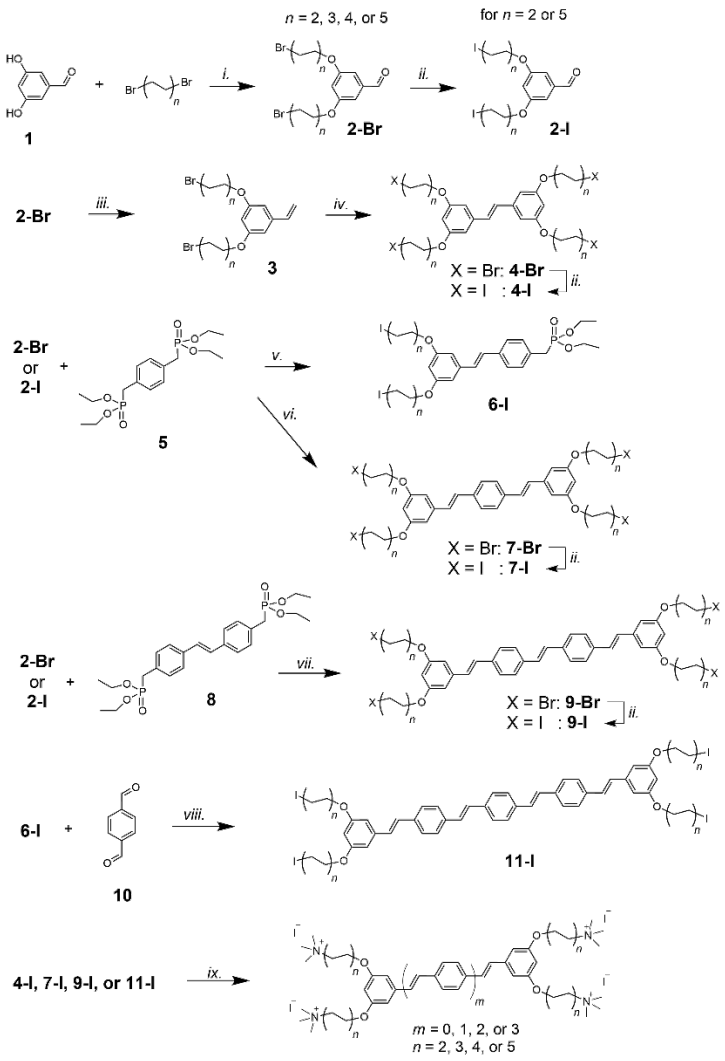
Escherichia coli K12 (ATCC 10798, American Type Culture Collection, VA) was grown under aerobic conditions in Luria-Bertani (LB) broth (10 g/L bactotryptone, 5 g/L yeast extract, 10 g/L NaCl) overnight at 37 °C with orbital shaking (250 rpm). Cell cultures for ONPG turnover assay

were supplemented with 2 g/L galactose for the induction of *lacZ*. Cells were collected by centrifugation and either resuspended in fresh Luria-Bertani broth (for MIC assay) or washed 2x with M9 minimal media (6.8 g/L Na_2HPO_4, 3 g/L KH_2PO_4, 1 g/L NH_4Cl, 0.5 g/L NaCl) before resuspending in M9 (for association and ONPG turnover assays).

Synthetic Procedures

The syntheses of the MICOEs in this study are summarized in Scheme S1, begin with the alkylation of 3,5-dihydroxybenzaldehyde (**1**) using α,ω-dibromoalkanes.[1-3] For the stilbenyl COEs, the dialkoxybenzaldehyde intermediates **2-Br** were converted to the analogous styrene derivatives **3** through a Wittig-type reaction. Following olefin metathesis to generate the stilbene fragment, the bromides **4-Br** were converted to iodides using the Finkelstein reaction to provide **4-I**. Quaternization with trimethylamine afforded the final charged compounds. For COEs containing cores with 3 or 4 phenylene rings, benzaldehyde intermediates **2-Br** or **2-I** were reacted with bis-diethoxymethylphosponate **5** or **8** respectively under standard Horner-Wadsworth-Emmons (HWE) conditions. As with the stilbenyl derivatives, the subsequent sequence of halogen exchange and quaternization reactions provided the final compounds. By altering the benzaldehyde/bisphosphonate ratio used for the synthesis of the 3-ring compounds, mono-diethoxymethylphosponate intermediates **6-I** were produced. A second HWE reaction with terephthaldehyde and quaternization afforded the 5-ring COEs.

The synthesis of COE2-2C-C6, COE2-3C-C6, COE2-4C-C6, and COE2-5C-C6 have been described in literature.[3, 4] Note that these structures were previously referred to as COE2-2C, COE2-3C, COE2-4C, and COE2-5C. COE2-3C-C4 was also previously reported.[5] Phosphonates **5** and **8** were made according to literature.[2]

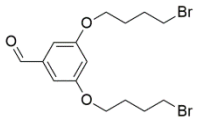


Scheme S1. Synthetic route for the preparation of MICOEs. Reagents and conditions: (*i*) K_2CO_3, acetone, reflux, 48h. (*ii*) NaI, acetone, reflux, 48h. (*iii*) $CH_3PPh3Br$, K_2CO_3, THF, reflux, overnight. (*iv*) Grubb's II, DCM, reflux, overnight. (*v*)–(*viii*) NaO*t*Bu, THF, 0 °C to RT, 6h. (*ix*) Trimethylamine/MeOH, THF, RT, 48h.

General Procedure for alkylations of 3,5-dihydroxybenzaldehyde:

3,5-dihydroxybenzaldehyde, the appropriate dibromoalkane (10 eq), and potassium carbonate (2.5 eq) were refluxed in acetone for two days under argon atmosphere. Following aqueous workup, products were purified by flash chromatography.

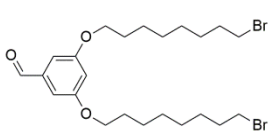
***3,5-bis((4-bromobutyl)oxy)benzaldehyde* (2-Br-a)**



3,5-dihydroxybenzaldehyde (800 mg, 1 eq), 1,4-dibromobutane (12.5 g, 10 eq), potassium carbonate (2 g, 2.5 eq), and acetone (40 mL) were added to a 100 mL flame-dried two-next flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for two days under inert atmosphere. After cooling to room temperature, the mixture was portioned between ethyl acetate and brine. The aqueous layer was removed and extracted three additional times with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to leave a slightly yellow oil (note: most of the excess 1,4-dibromobutane was removed during concentration). The pure product was obtained as a white solid (1.3 g, 56%) following flash chromatography (2 CV hexanes followed by 1:5 ethyl acetate/ hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.99 (d, *J* = 2.3 Hz, 2H), 6.69 – 6.67 (m, 1H), 4.03 (t, *J* = 6.1 Hz, 4H), 3.49 (t, *J* = 6.6 Hz, 4H), 2.10 – 2.04 (m, 4H), 1.99 – 1.93 (m, 4H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 191.81, 160.48, 138.39, 107.96, 107.68, 67.30, 33.21, 29.36, 27.74; **HRMS (ESI-TOF):** 462.9893 $[M+Na+CH_3OH]^+$

***3,5-bis((8-bromooctyl)oxy)benzaldehyde* (2-Br-c)**

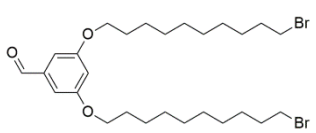


3,5-dihydroxybenzaldehyde (800 mg, 1 eq), 1,8-dibromooctane (15.8 g, 10 eq), potassium carbonate (2 g, 2.5 eq), and acetone (40 mL) were added to a 100 mL flame-dried two-next flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for two days under inert atmosphere. After

cooling to room temperature, the mixture was portioned between ethyl acetate and brine. The aqueous layer was removed and extracted three addition times with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to leave a clear oil. The pure product was obtained as a white solid (2 g, 67%) following flash chromatography (3 CV hexanes, 1 CV 1:20 ethyl acetate/ hexanes, 1:9 ethyl acetate/ hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.98 (d, *J* = 2.3 Hz, 2H), 6.69 (t, *J* = 2.3 Hz, 1H), 3.99 (t, *J* = 6.5 Hz, 4H), 3.41 (t, *J* = 6.8 Hz, 4H), 3.38 (d, *J* = 6.6 Hz, 4H), 1.93 – 1.83 (m, 4H), 1.84 – 1.74 (m, 4H), 1.52 – 1.40 (m, 8H), 1.43 – 1.29 (m, 8H); **^{13}C NMR (500 MHz, $CDCl_3$)** δ 192.02, 160.71, 138.31, 108.01, 107.58, 68.33, 33.91, 32.74, 29.11, 29.05, 28.64, 28.05, 25.88; **HRMS (ESI-TOF):** 543.0891 $[M+Na]^+$

***3,5-bis((10-bromodecyl)oxy)benzaldehyde* (2-Br-d)**



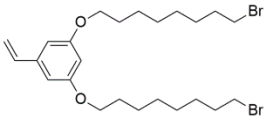
3,5-dihydroxybenzaldehyde (800 mg, 1 eq), 1,10-dibromodecane (17.4 g, 10 eq), potassium carbonate (2 g, 2.5 eq), and acetone (40 mL) were added to a 100 mL flame-dried two-next flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for two days under inert atmosphere. After cooling to room temperature, the mixture was portioned between ethyl acetate and brine. The aqueous layer was removed and extracted three additional times with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to leave a clear, viscous oil. Excess 1,10-dibromodecane was removed by vacuum distillation. The pure product was obtained as a white solid (2.2 g, 66%) following flash chromatography (1.5 CV hexanes, 1:25 ethyl acetate/ hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.98 (d, *J* = 2.3 Hz, 2H), 6.69 (t, *J* = 2.3 Hz, 1H), 3.99 (t, *J* = 6.5 Hz, 4H), 3.41 (t, *J* = 6.9 Hz, 4H), 1.90 – 1.74 (m, 8H), 1.50 – 1.29 (m, 24H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 192.22, 160.89, 138.45, 108.17, 107.73, 77.16, 68.55, 34.17, 32.96, 29.56, 29.49, 29.42, 29.26, 28.88, 28.30, 26.12.

General Procedure for Wittig Reaction:

Benzaldehyde derivatives **2-Br-c** and **2-Br-d** were converted to the analogous styrene derivatives **3c** and **3d** with the Wittig reagent methyl triphenylphosphonium bromide (1.1 eq) in the presence of potassium carbonate (1.1 eq). Reactions were refluxed in anhydrous THF overnight. Following aqueous workup, products were purified by flash chromatography.

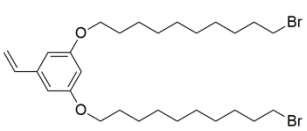
1,3-bis((8-bromooctyl)oxy)-5-vinylbenzene **(3c)**



2-Br-c (300 mg, 1.0 eq), methyl triphenylphosphonium bromide (227 mg, 1.1 eq), and potassium carbonate (88 mg, 1.1 eq) were added to a flame dried 15 mL round bottom flask equipped with a stir bar and reflux condenser. 7 mL of anhydrous THF was added via cannula. The reaction mixture was heated to reflux overnight under inert atmosphere. After cooling to room temperature, the reaction mixture was diluted with 25 mL of dichloromethane and transferred to a separatory funnel. The organic layer was extracted three times with brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The product was isolated as a white solid (220 mg, 73%) following flash chromatography (1:15 ethyl acetate/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 1H), 5.69 (d, *J* = 17.5 Hz, 1H), 5.21 (d, *J* = 10.8 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 4H), 3.39 (t, *J* = 6.8 Hz, 4H), 1.84 (p, *J* = 6.9 Hz, 4H), 1.75 (p, *J* = 6.7 Hz, 4H), 1.50 – 1.37 (m, 16H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.35, 139.47, 136.92, 114.11, 104.83, 100.96, 67.93, 33.97, 32.77, 29.21, 29.16, 28.68, 28.08, 25.95; **HRMS (ESI-TOF):** 519.1297 $[M+H]^+$

1,3-bis((10-bromodecyl)oxy)-5-vinylbenzene **(3d)**



2-Br-d (140 mg, 1.0 eq), methyl triphenylphosphonium bromide (96 mg, 1.1 eq), and potassium carbonate (37 mg, 1.1 eq) were added to a flame dried 10 mL round bottom flask equipped with a stir bar and reflux condenser. 5 mL of anhydrous

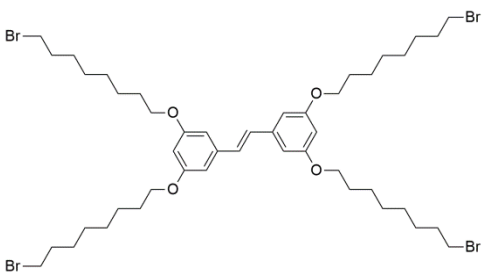
THF was added via cannula. The reaction mixture was heated to reflux overnight under inert atmosphere. After cooling to room temperature, the reaction mixture was diluted with 25 mL of dichloromethane and transferred to a separatory funnel. The organic layer was extracted three times with brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The product was isolated as a white solid (99 mg, 71%) following flash chromatography (1:15 ethyl acetate/hexane).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 2H), 6.38 (t, *J* = 2.2 Hz, 1H), 5.72 (dd, *J* = 17.5, 0.9 Hz, 1H), 5.23 (dd, *J* = 10.8, 0.8 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 4H), 3.41 (t, *J* = 6.9 Hz, 4H), 1.86 (p, *J* = 7.1 Hz, 4H), 1.77 (p, *J* = 7.1 Hz, 4H), 1.50 – 1.27 (m, 24H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.37, 139.44, 136.94, 114.08, 104.81, 100.97, 67.99, 34.02, 32.81, 29.42, 29.34, 29.30, 29.25, 28.73, 28.15, 26.02; **HRMS (ESI-TOF):** 575.1878 $[M+H]^+$

General Procedure for Metathesis Reactions:

Styrene derivatives **3c** and **3d** were converted to the analogous stilbene derivatives using Grubbs 2nd Generation (0.01 eq). Reactions were heated to 50°C in dry DCM under inert atmosphere for 16 hours. Products were purified by flash chromatography.

***(E)-1,2-bis(3,5-bis((8-bromooctyl)oxy)phenyl)ethene* (4-Br-c)**

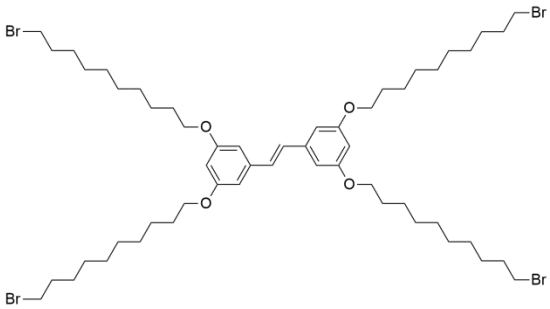


3c (125 mg, 1.0 eq) was added to a flame dried microwave tube equipped with a stir bar and septum. Grubbs Catalyst 2nd Generation (2 mg, 0.01 eq) was transferred to a small vial under inert atmosphere. 1 mL of dry DCM was added to the catalyst and the solution was transferred via syringe to the reaction vessel. The reaction mixture was heated to 50°C under inert atmosphere for 16 hours with most of the microwave tube above the oil to prevent the

reaction from drying out. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography (5:7 chloroform/hexane) to afford the product as a white solid (101 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 2H), 6.64 (d, *J* = 2.2 Hz, 4H), 6.39 (t, *J* = 2.2 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.42 (t, *J* = 6.8 Hz, 8H), 1.87 (p, *J* = 7.3 Hz, 8H), 1.79 (p, *J* = 6.6 Hz, 8H), 1.57 – 1.31 (m, 32H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.44, 139.08, 129.11, 105.14, 103.73, 100.97, 67.98, 33.97, 32.78, 29.23, 29.16, 28.68, 28.09, 25.97.

***(E)-1,2-bis(3,5-bis((10-bromodecyl)oxy)phenyl)ethene* (4-Br-d)**

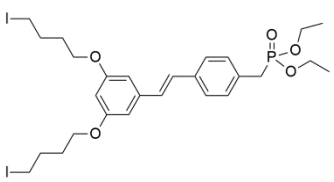


3d (85 mg, 1.0 eq) was added to a flame dried microwave tube equipped with a stir bar and septum. Grubbs Catalyst 2nd Generation (1.3 mg, 0.01 eq) was transferred to a small vial under inert atmosphere. 1 mL of dry DCM was added to the catalyst and the solution was transferred via syringe to the reaction vessel. The reaction mixture was heated to 50°C under inert atmosphere for 16 hours with most of the microwave tube above the oil to prevent the reaction from drying out. After cooling to room temperature, the reaction mixture was directly purified by flash chromatography (5:7 chloroform/hexane) to afford the product as a white solid (60 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 2H), 6.64 (d, *J* = 2.1 Hz, 4H), 6.39 (t, *J* = 2.2 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 8H), 3.41 (t, *J* = 6.9 Hz, 8H), 1.86 (p, *J* = 7.1 Hz, 8H), 1.79 (p, *J* = 7.6 Hz, 8H), 1.51 – 1.28 (m, 48H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.45, 139.07, 129.10, 105.12, 100.96, 68.03, 34.03, 32.82, 29.43, 29.35, 29.32, 29.28, 28.74, 28.15, 26.04.

Procedures for Horner-Wadsworth-Emmons Reactions for 5-ring Compounds:

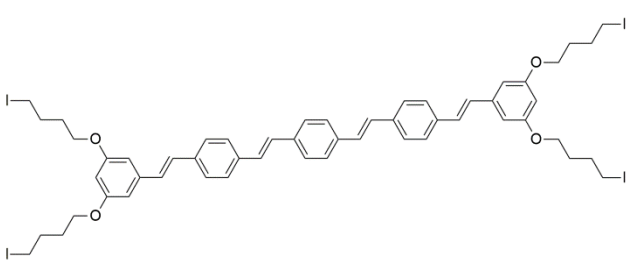
***(E)-diethyl 4-(3,5-bis(4-iodomobutoxy)styryl)benzylphosphonate* (6-I)**



2-I-a (300 mg, 1.1 eq) and anhydrous THF (4 mL) were added to a flame-dried 10 mL round bottom flask. **5** (216 mg, 1.05 eq) and anhydrous THF (4 mL) were added under inert atmosphere to a flame-*d*ried 25 mL round bottom flask equipped with a stir bar. The solution was cooled to 0°C and sodium *tert*-butoxide (52.2 mg, 1 eq) was added as a solution in anhydrous THF (5 mL). After 15 minutes, the solution of **2-I-a** was added in a single portion via syringe under inert atmosphere. The reaction was maintained at 0°C for 1 hour. The contents were portioned between water and DCM. The organic layer was removed and the aqueous layer was extracted with DCM an additional 3 times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The pure product (150 mg, 38%) was obtained as a yellowish oil following flash chromatography (9:1 DCM/ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.29 (dd, *J* = 8.2, 2.5 Hz, 2H), 7.10 – 6.94 (m, 2H), 6.64 (d, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 1H), 4.10 – 3.96 (m, 8H), 3.27 (t, *J* = 6.8 Hz, 4H), 3.16 (d, *J* = 21.8 Hz, 2H), 2.09 – 1.98 (m, 4H), 1.96 – 1.86 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.23, 139.34, 135.80, 135.77, 131.20, 131.12, 130.14, 130.09, 128.81, 128.79, 128.48, 128.46, 126.73, 126.71, 105.20, 100.90, 66.73, 62.21, 62.16, 30.18, 30.14, 16.43, 16.38, 6.42.

***1,4-bis((E)-4-((E)-3,5-bis(4-iodobutoxy)styryl)styryl)benzene* (9-I-a)**



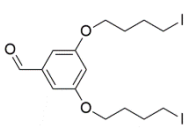
6-I (43 mg, 2.2 eq), terephthalaldehyde (3.6 mg, 1 eq), and anhydrous THF (3 mL) were added to a flame-*d*ried 10 mL round bottom flask equipped with a stir bar. The solution was cooled to 0°C under inert atmosphere. Sodium *tert*-butoxide (5.4 mg, 2.1 eq) was added as a solution in anhydrous THF (2 mL) via syringe slowly over 5 minutes. The reaction was maintained at 0°C for 1 hour and then partitioned between DCM and water. The organic layer was removed and the aqueous layer was extracted with DCM an additional 3 times. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The pure product (20 mg, 58%) was obtained as a bright yellow solid following flash chromatography (2:1 DCM/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.47 (m, 12H), 7.20 – 6.96 (m, 8H), 6.66 (d, *J* = 2.2 Hz, 4H), 6.37 (t, *J* = 2.2 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 8H), 3.28 (t, *J* = 6.8 Hz, 8H), 2.14 – 1.99 (m, 8H), 1.98 – 1.87 (m, 8H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.26, 139.39, 136.86, 136.74, 136.51, 128.83, 128.49, 128.25, 128.16, 126.95, 126.90, 126.88, 105.23, 100.95, 66.75, 30.19, 30.15, 6.41.

General Procedure for Halogen Exchange (Finkelstein reaction):

All final products were prepared directly from alkyl iodide intermediates via quaternization with trimethylamine but the conversion from alkyl bromide to iodide occurred at different stages depending on the particular MICOE. In all cases, alkyl bromides were converted to analogous iodides via refluxing for ~2 days in acetone in the presence of sodium iodide. Some compounds were directly used following aqueous workup while others were purified as described below.

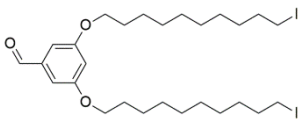
***3,5-bis((4-iodobutyl)oxy)benzaldehyde* (2-I-a)**



2-I-a (678 mg, 1 eq), sodium iodide (7.22 g, 25 eq), and acetone (15 mL) were combined in a 25 mL round bottom flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for 2 days under inert atmosphere. After cooling, the mixture was portioned between ethyl acetate and brine. The aqueous layer was discarded and the organic layer was extracted 2 additional times with brine, once with saturated sodium thiosulfate, and once with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. No further purification was necessary. (810 mg, 97%)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 1H), 7.05 (d, *J* = 2.3 Hz, 2H), 6.82 (t, *J* = 2.3 Hz, 2H), 4.06 (t, *J* = 6.3 Hz, 5H), 3.35 (t, *J* = 6.9 Hz, 5H), 1.93 (p, *J* = 6.9 Hz, 6H), 1.80 (p, *J* = 6.4 Hz, 6H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 191.82, 160.47, 138.37, 107.96, 107.68, 67.09, 30.06, 29.98, 6.11.

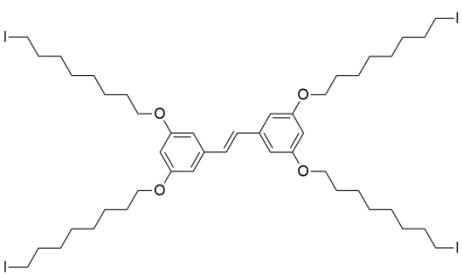
***3,5-bis((10-iododecyl)oxy)benzaldehyde* (2-I-c)**



2-I-c (650 mg, 1 eq), sodium iodide (4.7 g, 25 eq), and acetone (15 mL) were combined in a 25 mL round bottom flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for 2 days under inert atmosphere. After cooling, the mixture was portioned between ethyl acetate and brine. The aqueous layer was discarded and the organic layer was extracted 2 additional times with brine, once with saturated sodium thiosulfate, and three times with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. No further purification was necessary. (718 mg, 95%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 6.98 (d, *J* = 2.3 Hz, 2H), 6.69 (t, *J* = 2.3 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 4H), 3.19 (t, *J* = 7.0 Hz, 4H), 1.90 – 1.72 (m, 8H), 1.49 – 1.20 (m, 24H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 191.82, 160.48, 138.38, 107.95, 107.68, 67.30, 33.21, 30.45, 29.36, 29.25, 29.09, 28.48, 27.74, 25.95, 7.26.

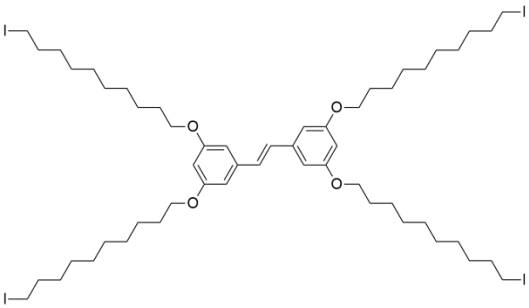
***(E)-1,2-bis(3,5-bis((8-iodooctyl)oxy)phenyl)ethene* (4-I-c)**



4-Br-c (47 mg, 1 eq), sodium iodide (105 mg, 15 eq), and acetone (1mL) were added to a microwave tube equipped with a stir bar. The vessel was placed in a 70°C oil bath such that headspace within the vessel remained above the oil level. The reaction was allowed to proceed for 2 days under inert atmosphere. After cooling to room temperature, the mixture was diluted in 10 mL of dichloromethane. The mixture was extracted once with saturated sodium thiosulfate and five times with water. The organic layer was then dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. No further purification was necessary. (50 mg, 89%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 2H), 6.63 (d, *J* = 2.2 Hz, 4H), 6.38 (t, *J* = 2.2 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 8H), 3.20 (t, *J* = 7.0 Hz, 8H), 1.86 – 1.74 (m, 16H), 1.48 – 1.31 (m, 32H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.59, 139.23, 129.26, 105.29, 101.11, 68.12, 33.64, 30.56, 29.38, 29.30, 28.61, 26.12, 7.43.

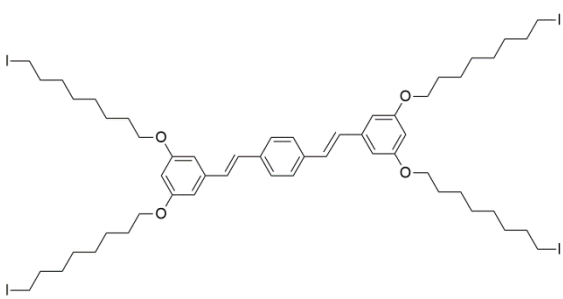
***(E)-1,2-bis(3,5-bis((10-iododecyl)oxy)phenyl)ethene* (4-I-d)**



4-Br-d (40 mg, 1 eq), sodium iodide (54 mg, 10 eq), and acetone (1mL) were added to a microwave tube equipped with a stir bar. The vessel was placed in a 70°C oil bath such that only the part containing the reaction mixture was submerged. The reaction was allowed to proceed for 2 days under inert atmosphere. After cooling to room temperature, the mixture was diluted in 10 mL of dichloromethane. The mixture was extracted once with saturated sodium thiosulfate and five times with water. The organic layer was then dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The resulting orange solid was passed through a silica plug with 1:8 ethyl acetate/hexane to afford the product as a white solid (42 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.66 (d, *J* = 2.2 Hz, 4H), 6.40 (t, *J* = 2.3 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 8H), 3.21 (t, *J* = 7.0 Hz, 8H), 1.88 – 1.77 (m, 16H), 1.53 – 1.45 (m, 8H), 1.44 – 1.34 (m, 40H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.47, 139.08, 129.11, 105.14, 100.98, 68.04, 33.54, 30.48, 29.44, 29.33, 29.31, 29.28, 28.51, 26.04, 7.29.

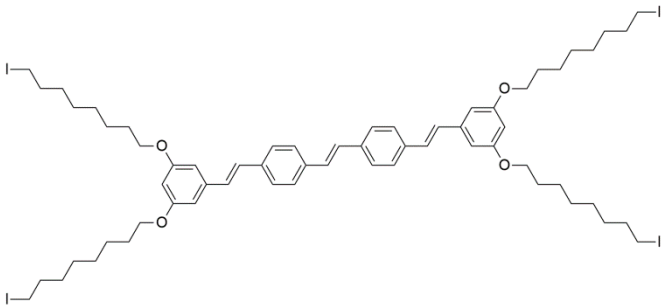
***1,4-bis((E)-3,5-bis((8-iodooctyl)oxy)styryl)benzene* (7-I-c)**



7-Br-c (400 mg, 1 eq), sodium iodide (1.35 g, 25 eq), and acetone (5 mL) were combined in a 10 mL round bottom flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for 2 days under inert atmosphere. After cooling to room temperature, the mixture was partitioned between dichloromethane and saturated sodium thiosulfate. The organic layer was discarded and the organic layer was extracted with water three times. The organic layer was then dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The resulting pinkish solid was passed through a silica plug with 1:8 ethyl acetate/hexane to afford the product as a white solid (420 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 4H), 7.10 – 7.01 (m, 4H), 6.66 (d, *J* = 2.1 Hz, 4H), 6.39 (t, *J* = 2.2 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.20 (t, *J* = 7.0 Hz, 8H), 1.88 – 1.74 (m, 16H), 1.52 – 1.32 (m, 32H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.60, 139.33, 136.76, 128.86, 128.71, 127.01, 105.27, 101.14, 68.14, 33.65, 30.56, 29.39, 29.30, 28.61, 26.13, 7.38.

***(E)-1,2-bis(4-((E)-3,5-bis((8-iodooctyl)oxy)styryl)phenyl)ethene* (9-I-c)**

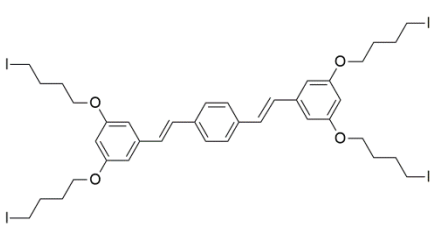


9-Br-c (220 mg, 1 eq), sodium iodide (680 mg, 25 eq), and acetone (5 mL) were combined in a 10 mL round bottom flask equipped with a stir bar and fitted with a reflux condenser. The mixture was refluxed for 2 days under inert atmosphere. After cooling to room temperature, the mixture was partitioned between dichloromethane and saturated sodium thiosulfate. The organic layer was discarded and the organic layer was extracted an additional time with saturated sodium thiosulfate and with water three times. The organic layer was then dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. No further purification was necessary to obtain the pure product as a white solid (420 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.2 Hz, 8H), 7.12 (s, 2H), 7.11 – 7.01 (m, 4H), 6.66 (d, *J* = 2.0 Hz, 4H), 6.41 – 6.37 (m, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.20 (t, *J* = 6.9 Hz, 8H), 1.82 (dq, *J* = 25.4, 7.2 Hz, 16H), 1.51 – 1.32 (m, 32H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.46, 139.20, 136.73, 136.58, 128.70, 128.57, 128.15, 126.91, 126.86, 105.12, 100.99, 68.00, 33.53, 30.46, 29.28, 29.20, 28.50, 26.01, 7.34.

General Procedure for Horner-Wadsworth-Emmons Reactions for 3-ring and 4-ring Compounds:

***1,4-bis((E)-3,5-bis(4-iodobutoxy)styryl)benzene* (7-I-a)**

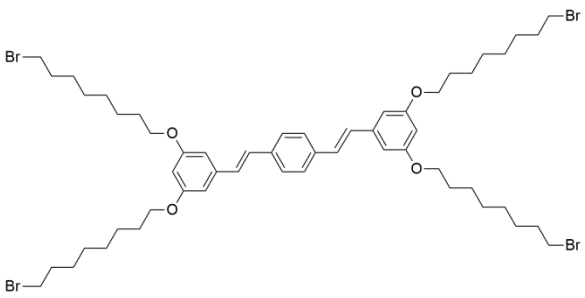


2-I-a (200 mg, 1 eq) and anhydrous THF (1 mL) were added to a flame-dried 2 Dr vial under inert atmosphere. **5** (79 mg, 0.525 eq) and anhydrous THF (2 mL) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under

inert atmosphere. This mixture was cooled to 0°C before adding sodium *tert*-butoxide (38 mg, 1 eq) as a solution in anhydrous THF (2 mL). The temperature was maintained at 0°C for 15 minutes, at which point the solution of **2-I-a** was added slowly via syringe. After an additional 2 hours at 0°C, the mixture was portioned between dichloromethane and water. The organic layer was collected and the aqueous layer was extracted with an additional portion of dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The pure product was obtained as a white solid (148 mg, 69%) by flash chromatography (2:5 DCM/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.45 (m, 4H), 7.11 – 6.98 (m, 4H), 6.66 (d, *J* = 2.2 Hz, 4H), 6.37 (t, *J* = 2.2 Hz, 2H), 4.02 (t, *J* = 6.1 Hz, 8H), 3.28 (t, *J* = 6.9 Hz, 9H), 2.10 – 2.01 (m, 8H), 1.95 – 1.87 (m, 9H); **^{13}C NMR (126 MHz, $CDCl_3$)** δ 160.25, 139.36, 136.61, 128.79, 128.56, 126.93, 105.24, 100.96, 66.75, 30.19, 30.15, 6.44.

***1,4-bis((E)-3,5-bis((8-bromooctyl)oxy)styryl)benzene* (7-Br-c)**

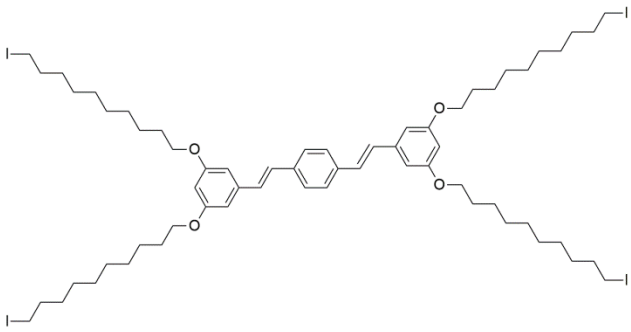


2-Br-c (500 mg, 2 eq) and **5** (191 mg, 1.05 eq) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar. Anhydrous THF (2 mL) was added via syringe under inert atmosphere. The mixture was cooled to 0°C. In a separate flame-dried flask, a solution of sodium *tert*-butoxide (97 mg, 2.1 eq) was prepared in anhydrous THF (3 mL). The entirety of the sodium *tert*-butoxide solution was added to the reaction flask via syringe slowly. The mixture was left in the ice bath and allowed to warm to room temperature overnight. The contents were partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer was extracted with three additional portions of dichloromethane. The organic layers were combined, back-extracted with an additional portion of water, dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The pure product

was obtained as a white solid (415 mg, 78%) following flash chromatography (1:8 ethyl acetate/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 4H), 7.10 – 7.00 (m, 4H), 6.66 (d, *J* = 1.9 Hz, 4H), 6.39 (t, *J* = 2.2 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.42 (t, *J* = 6.8 Hz, 8H), 1.87 (p, *J* = 7.0 Hz, 8H), 1.79 (d, *J* = 6.9 Hz, 8H), 1.52 – 1.33 (m, 32H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.46, 139.19, 136.62, 128.71, 128.55, 126.87, 105.12, 100.99, 67.99, 33.98, 32.80, 29.26, 29.19, 28.70, 28.11, 25.99.

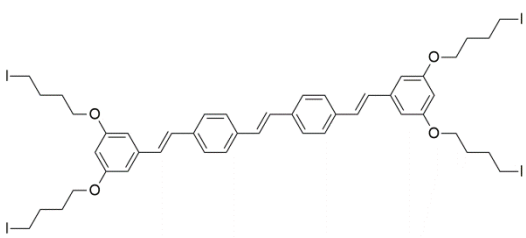
***1,4-bis((E)-3,5-bis((10-iododecyl)oxy)styryl)benzene* (7-I-d)**



2-I-d (200 mg, 1 eq) and anhydrous THF (1 mL) were added to a flame-dried 2 Dr vial under inert atmosphere. **5** (52 mg, 0.525 eq) and anhydrous THF (2 mL) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under inert atmosphere. This mixture was cooled to 0°C before adding sodium *tert*-butoxide (31 mg, 1.05 eq) as a solution in anhydrous THF (2 mL). The temperature was maintained at 0°C for 15 minutes, at which point the solution of **2-I-d** was added slowly via syringe. After an additional 2 hours at 0°C, the mixture was portioned between dichloromethane and water. The organic layer was collected and the aqueous layer was extracted with an additional portion of dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The pure product was obtained as a white solid (154 mg, 74%) by flash chromatography (1:9 ethyl acetate/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 4H), 7.08 – 7.02 (m, 4H), 6.66 (s, 4H), 6.39 (s, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.19 (t, *J* = 7.0 Hz, 8H), 1.86 – 1.75 (m, 16H), 1.50 – 1.25 (m, 48H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.48, 139.17, 136.62, 128.73, 128.54, 126.85, 105.11, 101.00, 68.05, 33.54, 30.47, 29.43, 29.32, 29.30, 29.27, 28.50, 26.03, 7.26.

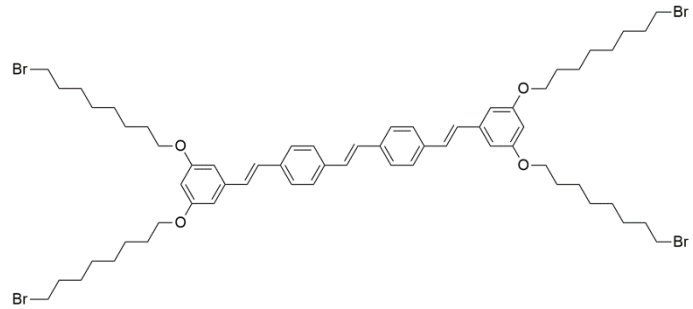
***(E)-1,2-bis(4-((E)-3,5-bis(4-iodobutoxy)styryl)phenyl)ethene* (9-I-a)**



2-I-a (100 mg, 1 eq) and anhydrous THF (1 mL) were added to a flame-dried 2 Dr vial under inert atmosphere. **8** (62 mg, 0.525 eq) and anhydrous THF (2 mL) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under inert atmosphere. This mixture was cooled to 0°C before adding sodium *tert*-butoxide (24 mg, 1 eq) as a solution in anhydrous THF (2 mL). The temperature was maintained at 0°C for 15 minutes, at which point the solution of **2-I-a** was added slowly via syringe. After an additional 4 hours at 0°C, the mixture was portioned between dichloromethane and water. The organic layer was collected and the aqueous layer was extracted with an additional portion of dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The pure product was obtained as a bright yellow solid (95 mg, 66%) by flash chromatography (1 CV hexanes, 1:8 ethyl acetate/hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 8H), 7.13 (s, 2H), 7.11 – 7.01 (m, 4H), 6.66 (s, 4H), 6.37 (s, 2H), 4.02 (t, *J* = 6.1 Hz, 4H), 3.28 (t, *J* = 6.9 Hz, 4H), 2.10 – 1.99 (m, 4H), 1.95 – 1.89 (m, 4H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.24, 141.61, 136.82, 136.52, 128.81, 128.49, 128.21, 126.92, 126.86, 105.24, 101.86, 66.74, 30.18, 30.13, 6.35.

***(E)-1,2-bis(4-((E)-3,5-bis((8-bromooctyl)oxy)styryl)phenyl)ethene* (9-Br-c)**



2-Br-c (500 mg, 2 eq) and **8** (252 mg, 1.05 eq) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar. Anhydrous THF (2 mL) was added via syringe under inert atmosphere. The mixture was cooled to 0°C. In a separate flame-dried flask, a solution of sodium

tert-butoxide (97 mg, 2.1 eq) was prepared in anhydrous THF (3 mL). The entirety of the sodium *tert*-butoxide solution was added to the reaction flask via syringe slowly. The mixture was left in the ice bath and allowed to warm to room temperature overnight. The contents were partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer was extracted with three additional portions of dichloromethane. The organic layers were combined, back-extracted with an additional portion of water, dried over Na_2SO_4, filtered, and concentrated via rotary evaporation. The pure product was obtained as a white solid (419 mg, 72%) following flash chromatography (2 CV 1:10 ethyl acetate/hexanes, 1:5:5 ethyl acetate/hexanes/DCM).

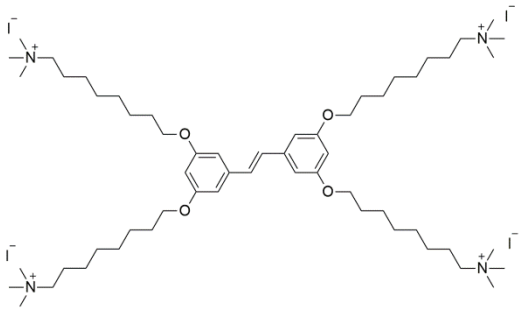
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (s, 8H), 7.15 – 6.99 (m, 6H), 6.67 (d, *J* = 2.2 Hz, 4H), 6.40 (t, *J* = 2.2 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 8H), 3.42 (t, *J* = 6.8 Hz, 8H), 1.87 (p, *J* = 6.9 Hz, 8H), 1.80 (p, *J* = 6.6 Hz, 8H), 1.53 – 1.34 (m, 32H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 160.48, 139.21, 136.74, 136.58, 128.70, 128.56, 128.14, 126.92, 126.88, 105.14, 101.01, 68.00, 34.04, 32.83, 29.31, 29.24, 28.74, 28.15, 26.03.

General Procedure for Quaternization Reactions:

Final target compounds were prepared by quaternization of alkyl iodide intermediates with trimethylamine. In all cases, intermediates were dissolved in anhydrous tetrahydrofuran and trimethylamine (20 eq) was added as a 3.2 M solution in methanol. All reactions were allowed to proceed for 2 days at room temperature under inert atmosphere in sealed 1 Dr vials. During the course of the reaction, methanol was added whenever insoluble material was observed (dropwise until solids dissolved). Following the reaction, mixtures were transferred to 50 mL centrifuge tubes and 10-20 mL of diethyl ether was added to precipitate the final target compounds. Suspensions were centrifuge and the supernatant decanted. The solids were dissolved in methanol and again precipitated with diethyl ether, centrifuged, and decanted. The centrifuge tubes were placed within glass containers and left under vacuum overnight. Solids were then dissolved in water, filtered

through 0.45 μM PTFE syringe filters, and lyophilized to provide the final products as fluffy solids (white in the case of 2- and 3-ring structures (m = 0 and 1) and bright yellow in the case of 4- and 5-ring structures (m = 2 and 3)). All reactions were quantitative.

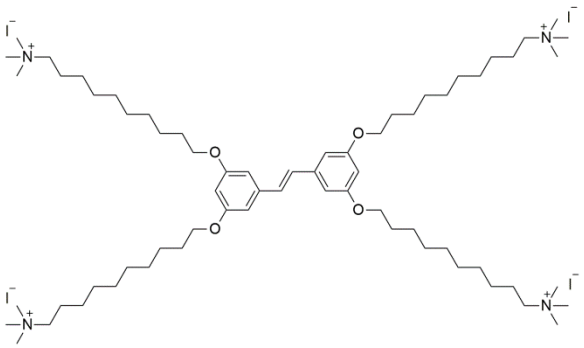
(E)-8,8',8'',8'''-((ethene-1,2-diylbis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethyloctan-1-aminium) iodide (**COE2-2C-C8**)



From **4-I-c**

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.16 (s, 2H), 6.73 (d, *J* = 2.2 Hz, 4H), 6.37 (t, *J* = 2.3 Hz, 2H), 3.96 (t, *J* = 6.4 Hz, 8H), 3.26 (ddd, *J* = 10.7, 6.2, 2.3 Hz, 8H), 3.03 (s, 36H), 1.75 – 1.62 (m, 16H), 1.45 – 1.24 (m, 32H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 160.48, 139.38, 129.31, 105.39, 101.15, 67.94, 65.75, 52.61, 29.20, 29.06, 28.95, 26.20, 25.94, 22.49; **HRMS (ESI-TOF):** 589.3229 $[M-2I]^{2+}$

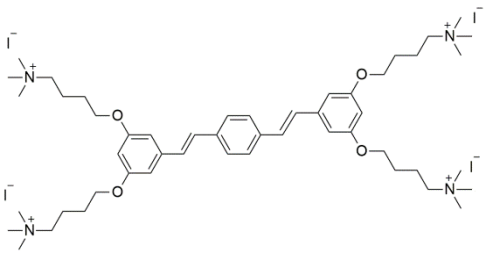
(E)-10,10',10'',10'''-((ethene-1,2-diylbis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethyldecan-1-aminium) iodide **(COE2-2C-C10)**



From **4-I-d**

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.17 (s, 2H), 6.74 (d, *J* = 2.1 Hz, 4H), 6.37 (t, *J* = 2.2 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 8H), 3.30 – 3.24 (m, 8H), 3.04 (s, 36H), 1.75 – 1.62 (m, 16H), 1.46 – 1.38 (m, 8H), 1.37 – 1.24 (m, 40H); **^{13}C NMR (151 MHz, DMSO-d_6)** δ 160.49, 139.40, 129.32, 105.42, 101.19, 67.96, 65.77, 52.63, 29.39, 29.25, 29.23, 28.96, 26.21, 26.02, 22.50; **HRMS (ESI-TOF):** 645.3853 $[M-2I]^{2+}$

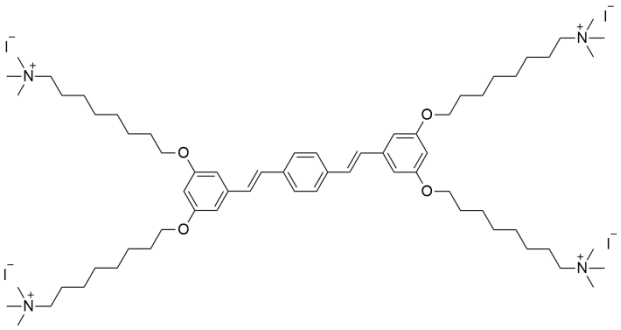
***4,4',4'',4'''-((((1E,1'E)-1,4-phenylenebis(ethene-2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethylbutan-1-aminium) iodide* (COE2-3C-C4)**



From **7-I-a**

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.60 (s, 4H), 7.25 (dd, *J* = 36.5, 15.9 Hz, 4H), 6.81 (s, 4H), 6.44 (s, 2H), 4.05 (t, *J* = 6.2 Hz, 8H), 3.43 – 3.37 (m, 8H), 3.10 – 3.04 (m, 32H), 1.90 – 1.79 (m, 8H), 1.74 (p, *J* = 6.8 Hz, 8H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 160.27, 139.60, 136.82, 129.03, 128.81, 127.38, 105.66, 101.43, 67.32, 65.47, 52.72, 26.08, 19.69; **HRMS (ESI-TOF):** 528.2205 $[M-2I]^{2+}$

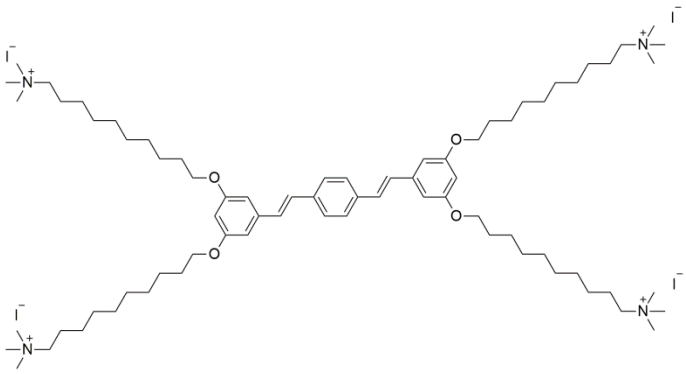
***8,8',8'',8'''-((((1E,1'E)-1,4-phenylenebis(ethene-2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy)) tetrakis(N,N,N-trimethyloctan-1-aminium) iodide* (COE2-3C-C8)**



From **7-I-c**

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.60 (s, 4H), 7.33 – 7.14 (m, 4H), 6.77 (s, 4H), 6.39 (s, 2H), 3.99 (s, 8H), 3.35 – 3.22 (m, 8H), 3.04 (s, 36H), 1.80 – 1.59 (m, 16H), 1.51 – 1.20 (m, 32H); **^{13}C NMR (151 MHz, DMSO-d_6)** δ 160.35, 139.50, 136.60, 128.94, 128.65, 127.41, 105.35, 101.25, 68.20, 66.30, 52.80, 28.79, 28.74, 28.62, 25.81, 25.64, 22.41; **HRMS (ESI-TOF):** 640.3478 $[M-2I]^{2+}$

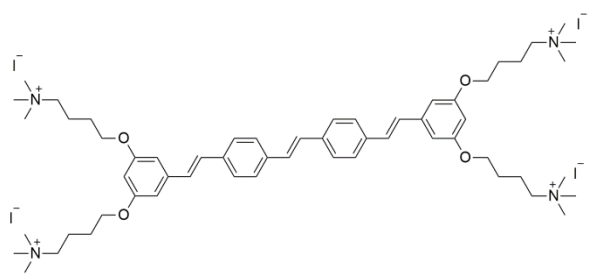
***10,10',10'',10'''-((((1E,1'E)-1,4-phenylenebis(ethene-2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethyldecan-1-aminium) iodide* (COE2-3C-C10)**



From **7-I-d**

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.60 (s, 4H), 7.23 (dd, *J* = 32.2, 16.3 Hz, 4H), 6.75 (s, 4H), 6.37 (s, 2H), 3.97 (t, *J* = 6.3 Hz, 8H), 3.31 – 3.15 (m, 8H), 3.03 (s, 36H), 1.90 – 1.54 (m, 16H), 1.49 – 1.37 (m, 8H), 1.34 – 1.20 (m, 40H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 160.49, 139.48, 136.82, 128.88, 127.33, 105.39, 101.13, 67.96, 65.80, 52.64, 39.88, 29.38, 29.24, 29.22, 29.19, 28.94, 26.17, 26.01, 22.50; **HRMS (ESI-TOF):** 696.4102 $[M-2I]^{2+}$

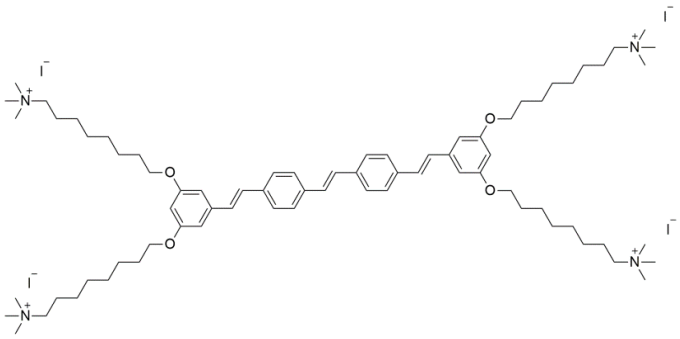
***4,4',4'',4'''-((((1E,1'E)-((E)-ethene-1,2-diylbis(4,1-phenylene))bis(ethene-2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethylbutan-1-aminium) iodide* (COE2-4C-C4)**



From **9-I-a**

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.63 (q, *J* = 8.3 Hz, 8H), 7.32 – 7.20 (m, 8H), 6.82 (s, 4H), 6.45 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 8H), 3.41 – 3.37 (m, 8H), 3.08 (s, 36H), 1.90 – 1.83 (m, 8H), 1.79 – 1.73 (m, 8H); **^{13}C NMR (126 MHz, DMSO-d_6)** δ 160.29, 139.63, 137.04, 136.74, 129.08, 128.79, 128.50, 127.38, 105.63, 105.00, 101.44, 67.28, 65.47, 52.70, 40.30, 40.13, 39.96, 39.80, 39.63, 26.11, 19.70; **HRMS (ESI-TOF):** 579.2454 $[M+H]^+$

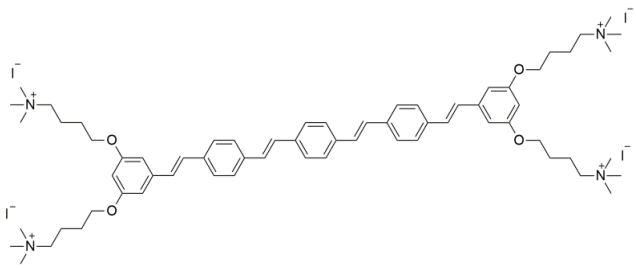
***8,8',8'',8'''-((((1E,1'E)-((E)-ethene-1,2-diylbis(4,1-phenylene))bis(ethene-2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethyloctan-1-aminium) iodide* (COE2-4C-C8)**



From **9-I-c**

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.66 – 7.59 (m, 8H), 7.36 – 7.16 (m, 6H), 6.77 (s, 4H), 6.39 (s, 2H), 3.99 (t, *J* = 6.5 Hz, 8H), 3.28 (dd, *J* = 10.7, 6.4 Hz, 8H), 3.04 (s, 36H), 1.75 – 1.65 (m, 16H), 1.48 – 1.25 (m, 32H); **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 160.51, 139.52, 136.97, 136.80, 128.90, 128.46, 127.34, 105.39, 101.16, 67.93, 65.76, 52.61, 39.98, 29.18, 29.03, 28.94, 26.19, 25.94, 22.49; **HRMS (ESI-TOF):** 691.3712 $[M-2I]^{2+}$

***4,4',4'',4'''-((((1E,1'E)-(((1E,1'E)-1,4-phenylenebis(ethene-2,1-diyl))bis(4,1phenylene))bis(ethene -2,1-diyl))bis(benzene-5,3,1-triyl))tetrakis(oxy))tetrakis(N,N,N-trimethylbutan-1-aminium) iodide* (COE2-5C-C4)**



From **11-I-a**

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.67 – 7.59 (m, 12H), 7.33 – 7.17 (m, 8H), 6.82 (d, *J* = 2.1 Hz, 4H), 6.45 (t, *J* = 2.1 Hz, 2H), 4.07 (t, *J* = 6.1 Hz, 8H), 3.45 – 3.36 (m, 8H), 3.09 (s, 36H), 1.92 – 1.83 (m, 8H), 1.81 – 1.72 (m, 8H); **^{13}C NMR (126 MHz, DMSO-*d*$_6$)** δ 160.30, 139.66, 137.09, 136.96, 136.72, 129.11, 128.57, 128.45, 127.39, 105.64, 101.46, 67.29, 65.48, 52.71, 40.50, 40.33, 40.17, 40.00, 39.83, 39.66, 39.50, 26.13, 19.72; **HRMS (ESI-TOF):** 630.2702 $[M-2I]^{2+}$

Minimum Inhibitory Concentration

Following overnight growth, collection, and resuspension in fresh LB, cells were diluted to 1 OD_{600}. Stock bacteria solutions were prepared by further 1:1000 dilution in LB. For MICOEs with sufficient solubility, stock solutions of 5.12 mM were prepared in 150 mM PBS before further diluting in LB to a final concentration of 1.024 mM. For MICOEs with lower solubility (both 5-ring compounds (*m* = 3), and all with C8 or C10 chains (*n* = 4 or 5)), stock solutions were prepared directly in LB at 1.024 mM. 100 µL of 1.024 mM stock MICOE solutions were transferred to the first column of 96-well plates (in triplicate), and serially diluted across the next nine columns in LB (50 µL each well, concentrations from 2 µM to 1024 µM). The 11^{th} column received 50 µL of LB, and the 12^{th} column 100 µL of LB (LB sterility control). 50 µL of the bacteria stock was added to columns 1 through 11 to give final MICOE concentrations from 1 µM to 512 µM. Plates were incubated overnight at 37 °C with orbital shaking (250 rpm). Optical density at 600 nm was measured on a Tecan plate reader. MIC was determined as the lowest concentration to give OD < 0.1 $OD_{control}$ after subtracting blank.

Association Assay

Following overnight growth, collection, washing and resuspension in M9, cells were diluted to 2 OD_{600}. COE stock solutions of 60 and 120 µM were made in M9. 100 µL of stock cell solution was mixed with 100 µL of stock MICOE solution in 1 mL microcentrifuge tubes (triplicate) to give final concentrations of 1 OD_{600} cells and 30 or 60 µM MICOE. After 30-minute incubation at room temperature, all samples were centrifuged and 100 µL of supernatants were removed to a 96-well plate. MICOE remaining in the supernatant was quantified by optical absorption (310 nm for 2-ring compounds (*m* = 0), 365 nm for 3-ring compounds (*m* = 1), 385 nm for 4-ring compounds (*m* = 2), and 400 nm for 5-ring compounds (*m* = 3)) on a Tecan plate reader. Calibration curves were made by measuring COE solutions in M9 from 5 µM to 60 µM. Cell-associated MICOE was

calculated by subtracting the supernatant concentration (calculated from the calibration curve) from the original concentration in the cell/MICOE mixture.

EPR Experiments

E. coli total lipid extract and 1 mol% 16-SASL (Aldrich) were dissolved in chloroform (approximately 10 mg in a 2 Dr. vial) before drying by rotary evaporation. Resulting lipid films were further dried under vacuum overnight. Lipids were resuspended in 150 mM PBS at 10 mg/mL. Liposomes were formed by sequential extrusion through 200 nm and 100 nm filters and diluted to ~2 mM. Liposome solutions were mixed 1:1 by volume with 20 μM MICOE solutions. Samples were prepared in quartz capillary tubes (Vitrotubes^{TM} 0.60 mm ID x 0.84 mm OD), sealed with Leica Critoseal CRITOSEAL®, and placed in 3 mm EPR tubes. EPR spectra were processed in MATLAB R2016b (academic license). Order parameter (S) was calculated as follows:

$$S = 0.5407(T_{\parallel} - T_{\perp})/a_o$$

$$a_o = (T_{\parallel} - 2T_{\perp})/3$$

where $T_{\parallel}$ and $T_{\perp}$ are tensor components along and perpendicular to the long axis of the molecule, respectively. $T_{\parallel}$ and $T_{\perp}$ were extracted directly from EPR spectra as shown in Figure S1.[6, 7] Percent change in order parameter (%ΔS) was calculated for each MICOE relative to untreated vesicles (Figure S2).

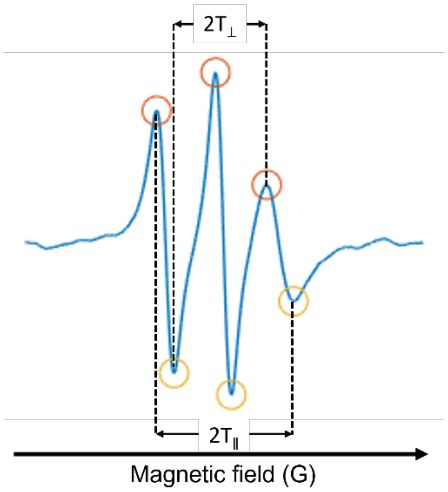


Fig. S1 Parameters $T_{\parallel}$ and $T_{\perp}$ were obtained from peak-to-peak widths in EPR spectra.

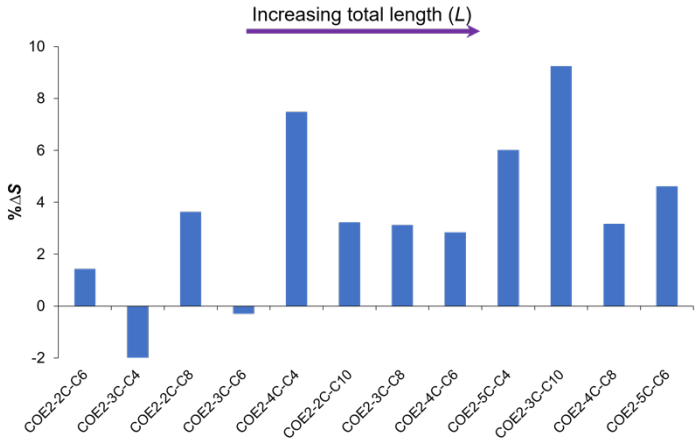


Fig. S2 Percent change in order parameter (%Δ*S*) by each COE. The COEs are ranked in ascending total length of the molecule (*L*).

ONPG Assay

Following overnight growth of *E. coli* K12 (including induction of *lacZ*), cells were washed and resuspended in M9 at 2x OD_{600} = 1.0 and left for 1 hour. Cell and MICOE solutions were mixed 1:1 by volume and left for 30 minutes at room temperature. The final concentration of MICOEs

was 10 μM. Cells were centrifuged and the supernatant was removed before resuspending to a final OD_{600} = 0.6 in M9. 200 μL of cell solutions were transferred to a 96-well plate (in triplicate). 100 μL of 3.9 mM ONPG was added to each well and turnover measurements were initiated immediately by recording absorption at 420 nm. Turnover rate was measured as the slope of the line in the linear regime.

Due to the low antimicrobial activity and high membrane permeabilizing activity of COE2-2C-C10, a comparison of membrane permeabilization of *E. coli* K12 using ONPG assay was made with Triton X-100 (Figure S3a). Triton X-100 was found to be most effective at 0.2% v/v.[8] Treatment with Triton X-100 afforded an ONPG turnover rate twice that of the untreated control. In comparison, the addition of 40 μM COE2-2C-C10 resulted in an ONPG turnover rate ten times that of the control (Figure S3b). The significant permeabilizing ability of this compound at concentrations significantly below its measured MIC (256 μM) is a testament that membrane permeabilizing activity from antimicrobial activity of MICOEs are not intrinsically coupled.

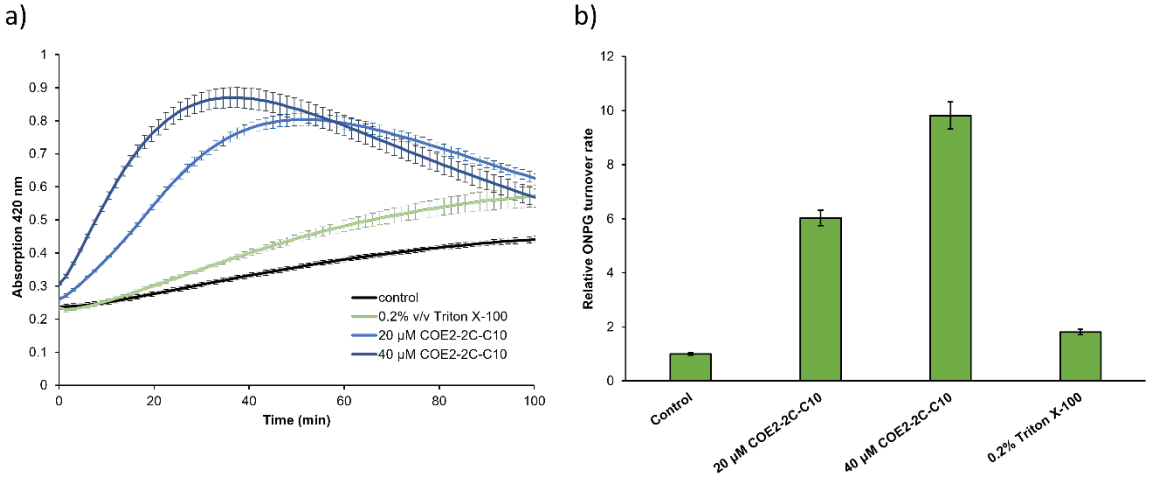


Fig. S3 a) Level of *o*-nitrophenol from ONPG hydrolysis by 1 OD_{600} of *E. coli* treated with Triton X-100 or COE2-2C-C10 as a function of time. b) The relative ONPG turnover rates of *E. coli* treated with Triton X-100 or COE2-2C-C10 compared to untreated control (relative rate = 1).

To rule out the possibility that MICOEs affect the activity of β-galactosidase, we performed a control experiment with cell lysates of untreated and MICOE-treated *E. coli* K12. COE2-3C-C6 was selected as a representative MICOE for this experiment. Briefly, *E. coli* K12 samples were prepared in M9 at the final OD_{600} of 0.6 according to the protocol described above. Cell samples were lysed using an ultrasonication probe in an ice bath. Resulting cell lysates were further diluted in M9 to yield samples for 100%, 50%, 25%, and 12.5% lysate. 100 µL of cell lysates (or its dilutions) were transferred to each well in a 96-well plate. 100 µL of 3.9 mM ONPG was added to each well. ONPG turnover was immediately monitored by recording absorption at 420 nm. The experiment was repeated with three biological replicates. According to Figure S4, there was no noticeable change in ONPG turnover activity between untreated and COE2-3C-C6-treated groups which indicates that MICOEs do not interfere with the activity of β-galactosidase.

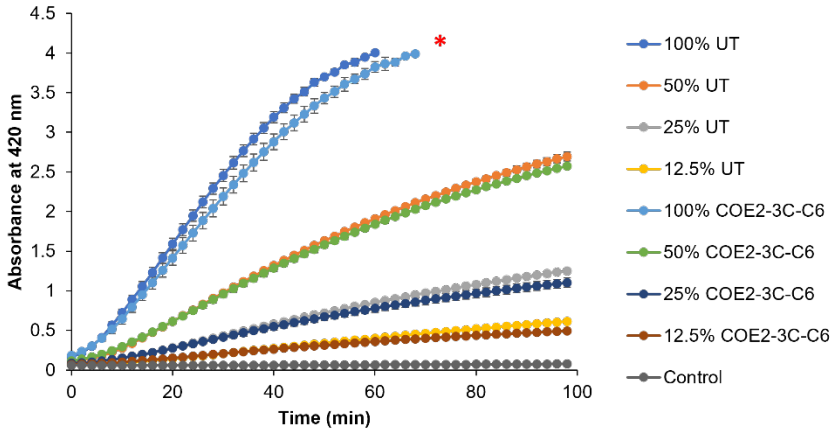


Fig. S4 ONPG turnover by cell lysates (100%, 50%, 25%, and 12.5% lysates) of untreated *E. coli* K12 (UT) and COE2-3C-C6-treated *E. coli* K12. An asterisk indicates that absorption at 420 nm exceeded the limit of the instrument.

Correlation and Significance

Pearson correlation (r) and significance (p) values were calculated in MATLAB 2016b by using the *corrcoef* function in the form of [r,p] = corrcoef(matrix) where "*matrix*" was derived from a table of structural parameters and experimental data arranged in columns (each compound filling one row). The first column was the length as measured between the two furthest ammonium nitrogens (total length, *L*). The second and third columns were the core length (*m* = 0–3) and the pendant chain length (*n* = 2–5), respectively. For association assay, the percent associated when stained with 60 μM MICOE/OD_{600} was used to calculate correlation with the structural parameters. For MIC, the MIC value was used. For membrane permeability assay, the relative ONPG turnover rate compared to untreated cells was used. The MATLAB function returns two matrices, the first for r and the second for p. Target values for each output occur at the position with column # = (column # of dependent variable in *matrix*) and row # = (column # of each structural parameter in *matrix*).

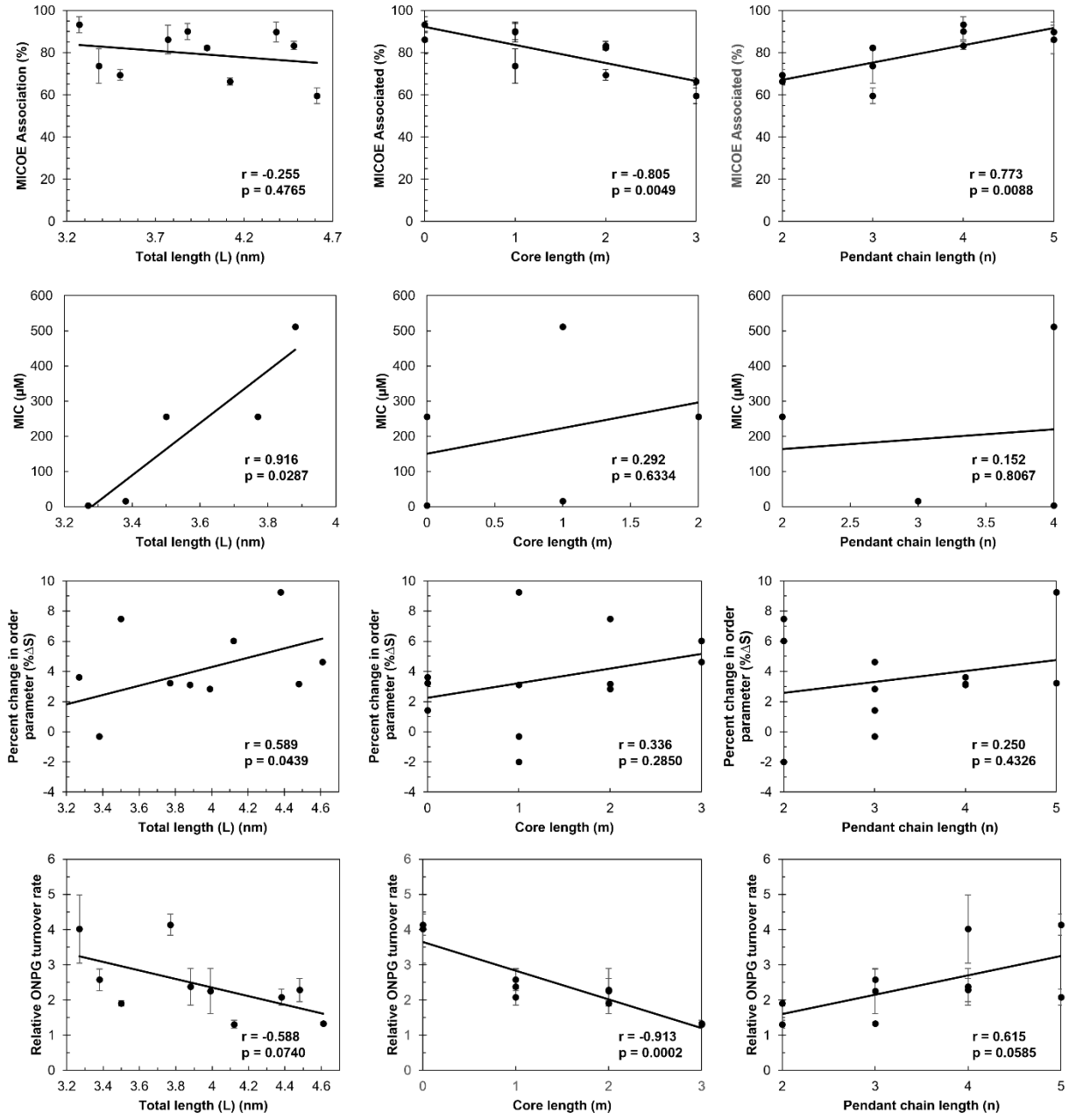
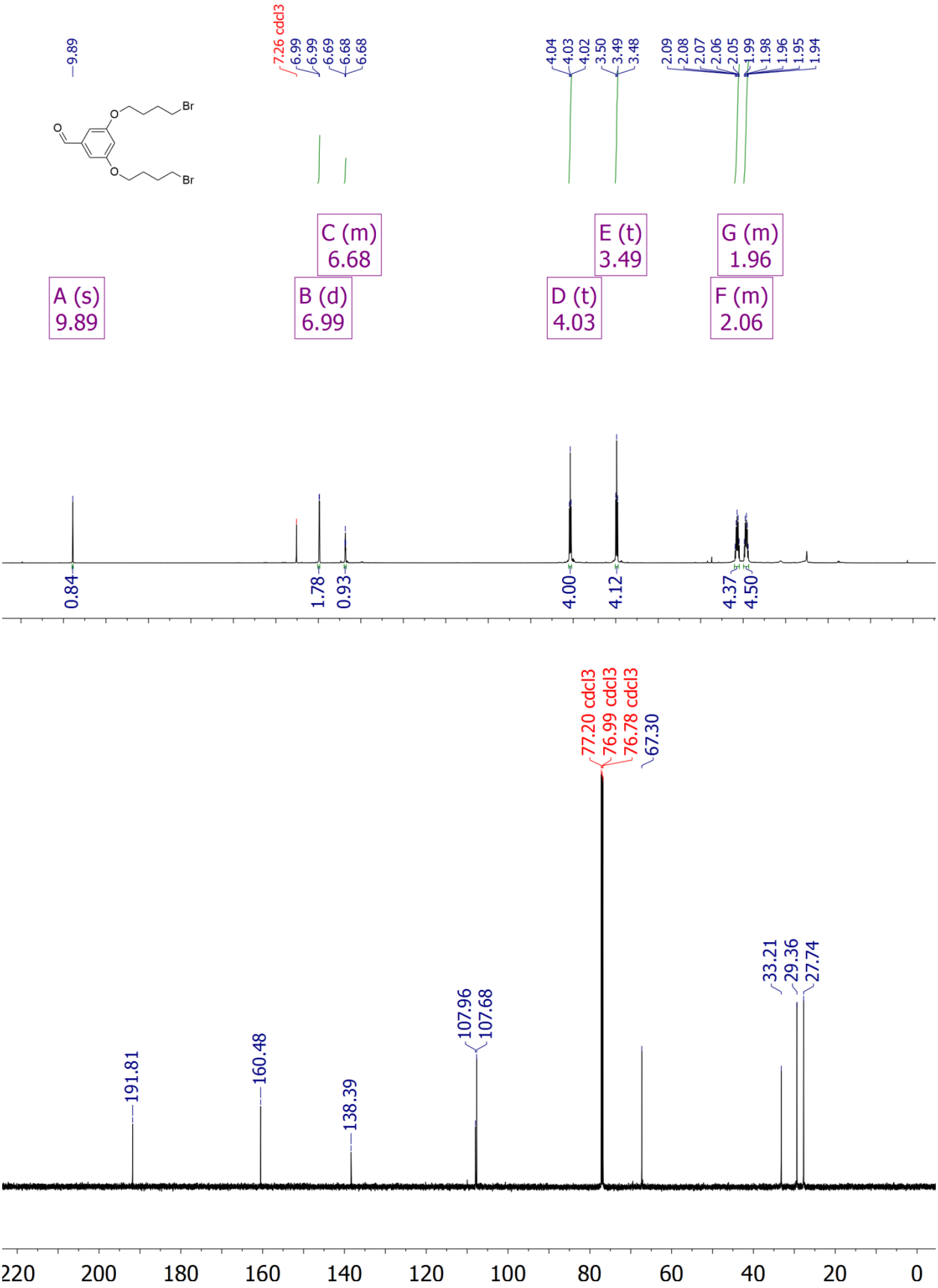
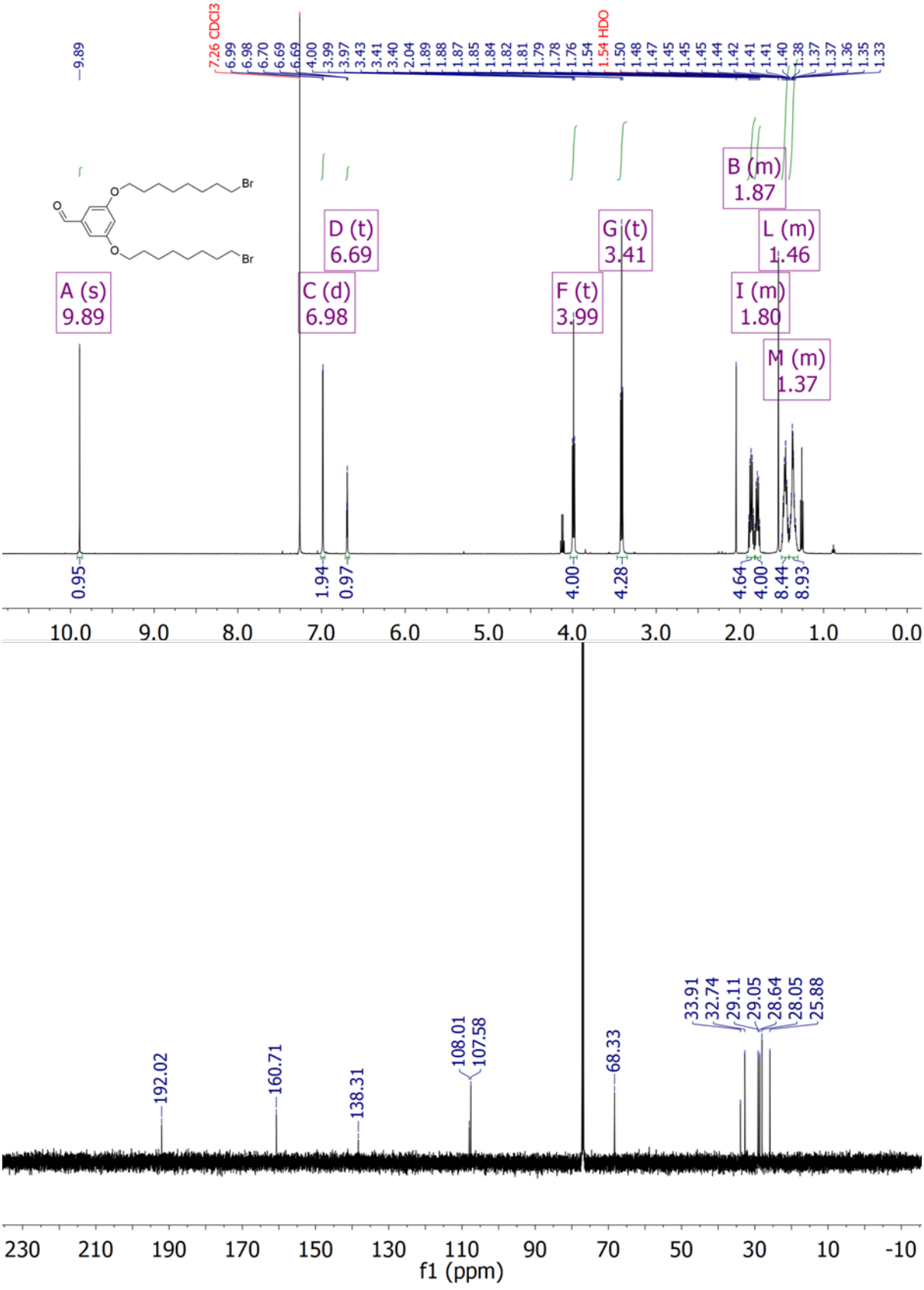


Fig. S5 Plots showing correlations (r) and significance of correlations (p) between effects of MICOEs on bacterial systems (membrane association, MIC, changes in lipid order parameter, and ONPG turnover rate versus molecular features of MICOEs (total length (*L*), core length (*m*), and pendant chain length (*n*)). $p < 0.05$ denotes a significant correlation.

NMR Spectra


9.89
7.26 cdcl3
6.99
6.99
6.69
6.68
6.68
4.04
4.03
4.02
3.50
3.49
3.48
2.09
2.08
2.07
2.06
2.05
1.99
1.98
1.96
1.95
1.94
Br
Br
A (s)
9.89
B (d)
6.99
C (m)
6.68
D (t)
4.03
E (t)
3.49
F (m)
2.06
G (m)
1.96
0.84
1.78
0.93
4.00
4.12
4.37
4.50
77.20 cdcl3
76.99 cdcl3
76.78 cdcl3
67.30
191.81
160.48
138.39
107.96
107.68
33.21
29.36
27.74
220
200
180
160
140
120
100
80
60
40
20
0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1.54 HDO
A (s)
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C (d)
6.98
D (t)
6.69
F (t)
3.99
G (t)
3.41
B (m)
1.87
I (m)
1.80
L (m)
1.46
M (m)
1.37
0.95
1.94
0.97
4.00
4.28
4.64
4.00
8.44
8.93
f1 (ppm)
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108.01
107.58
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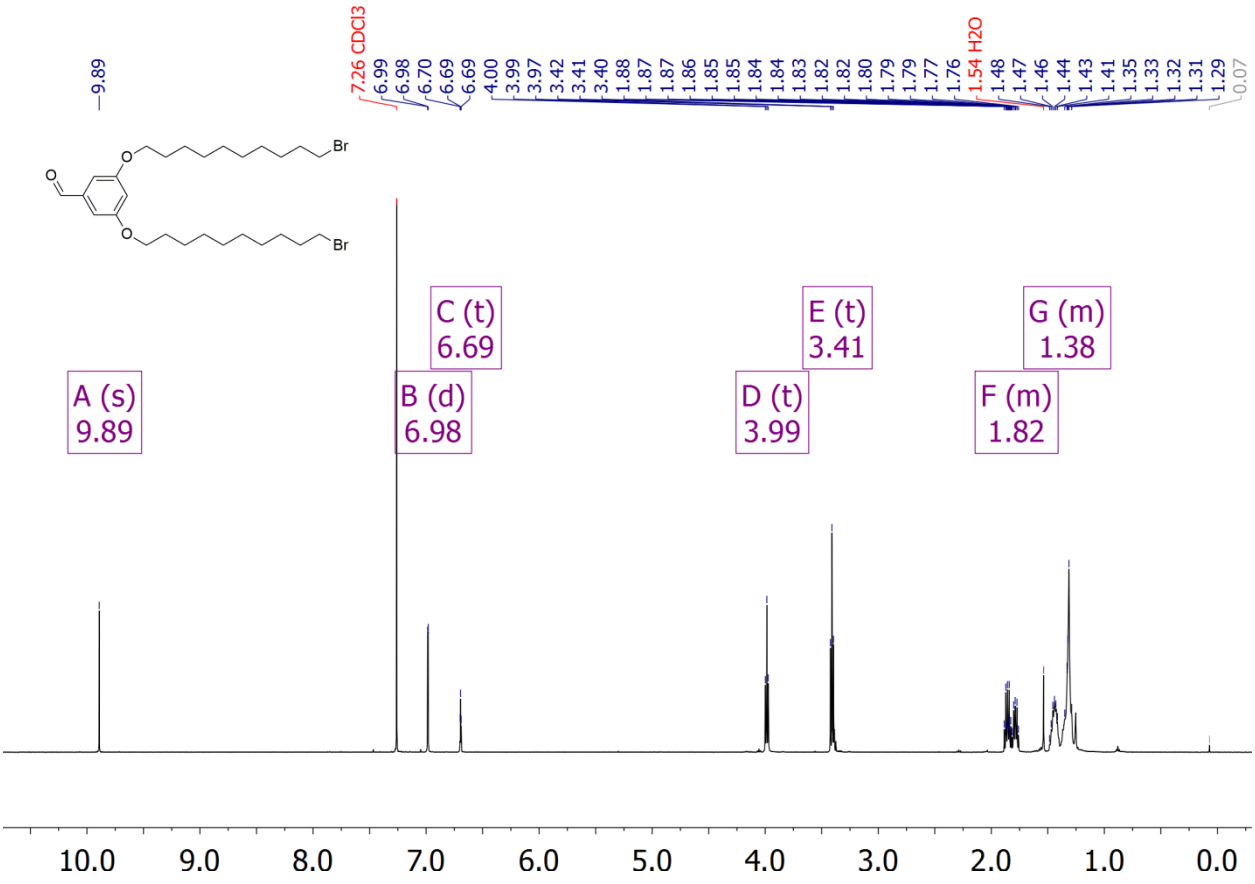
32.74
29.11
29.05
28.64
28.05
25.88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6.98
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6.69
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3.40
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1.87
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1.86
1.85
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1.84
1.84
1.83
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1.77
1.76
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1.48
1.47
1.46
1.44
1.43
1.41
1.35
1.33
1.32
1.31
1.29
0.07
O
O
Br
O
Br
A (s)
9.89
B (d)
6.98
C (t)
6.69
D (t)
3.99
E (t)
3.41
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G (m)
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7.0
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4.0
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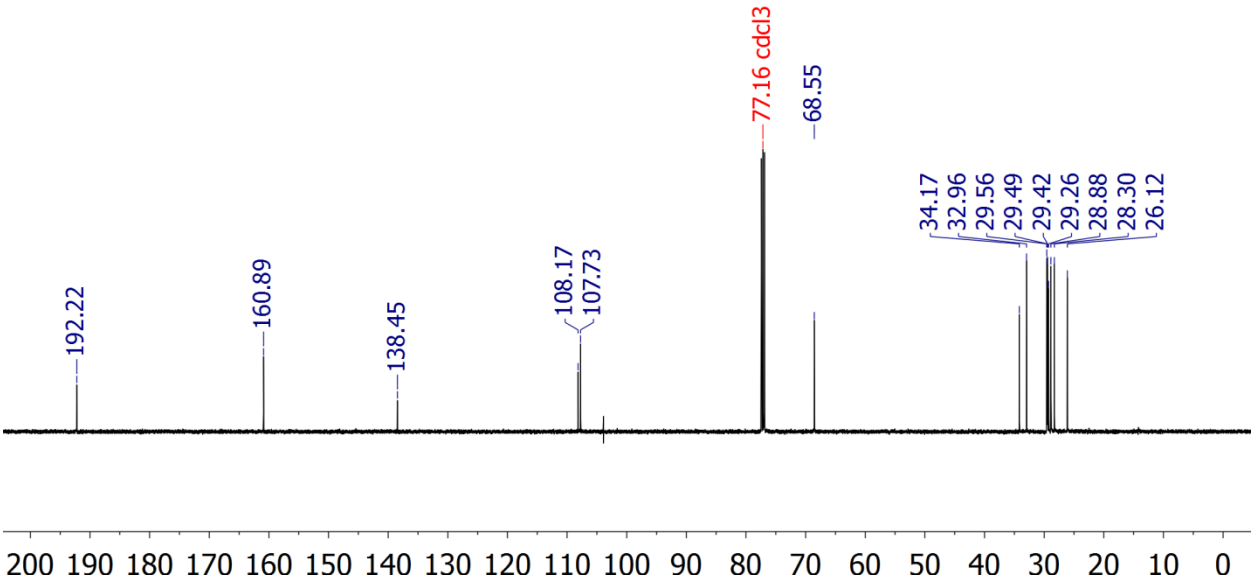
2.0
1.0
0.0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107.73
77.16 cdcl3
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34.17
32.96
29.56
29.49
29.42
29.26
28.88
28.30
26.12
200
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180
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150
140
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80
70
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30
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10
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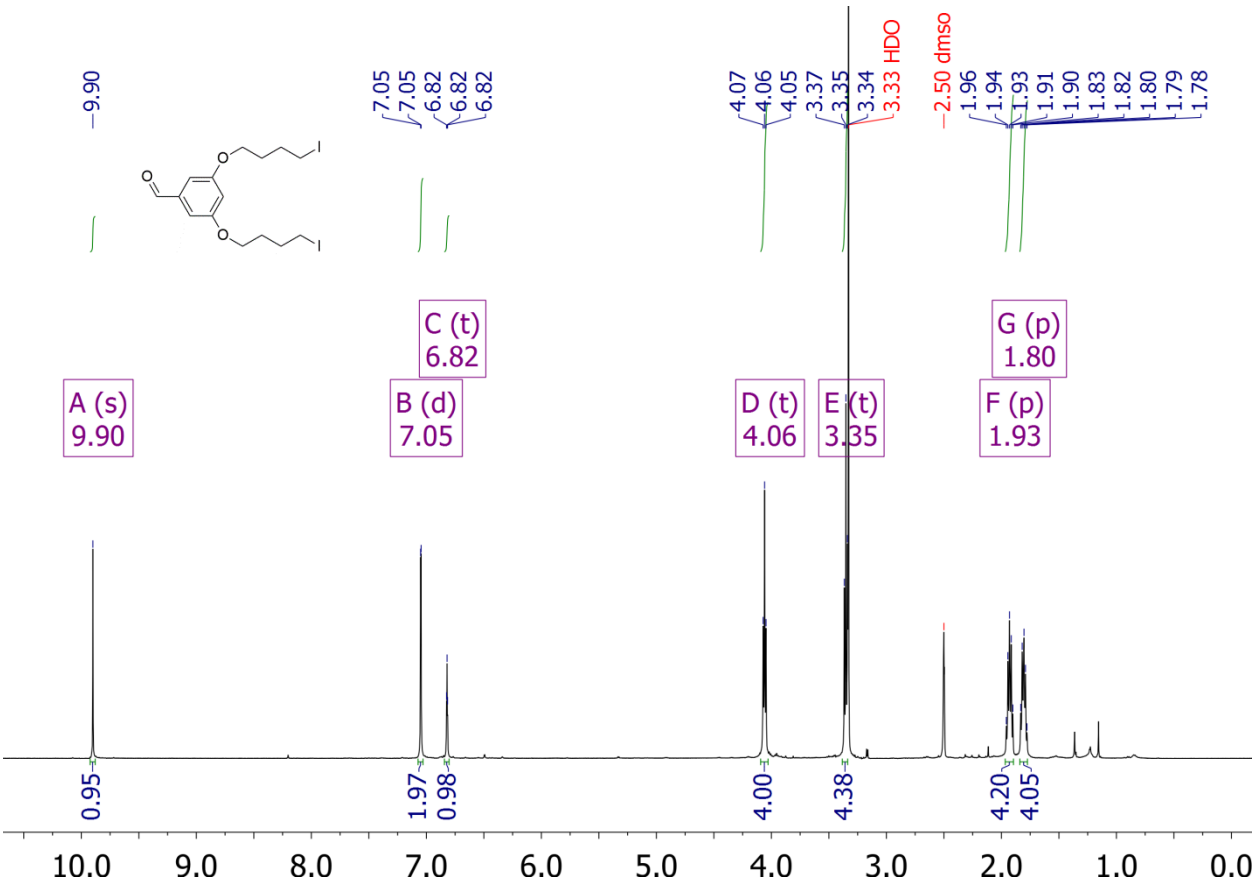
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7.05
6.82
6.82
6.82
4.07
4.06
4.05
3.37
3.35
3.34
3.33 HDO
2.50 dmso
1.96
1.94
1.93
1.91
1.90
1.83
1.82
1.80
1.79
1.78
A (s) 9.90
B (d) 7.05
C (t) 6.82
D (t) 4.06
E (t) 3.35
F (p) 1.93
G (p) 1.80
0.95
1.97
0.98
4.00
4.38
4.20
4.05
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9.0
8.0
7.0
6.0
5.0
4.0
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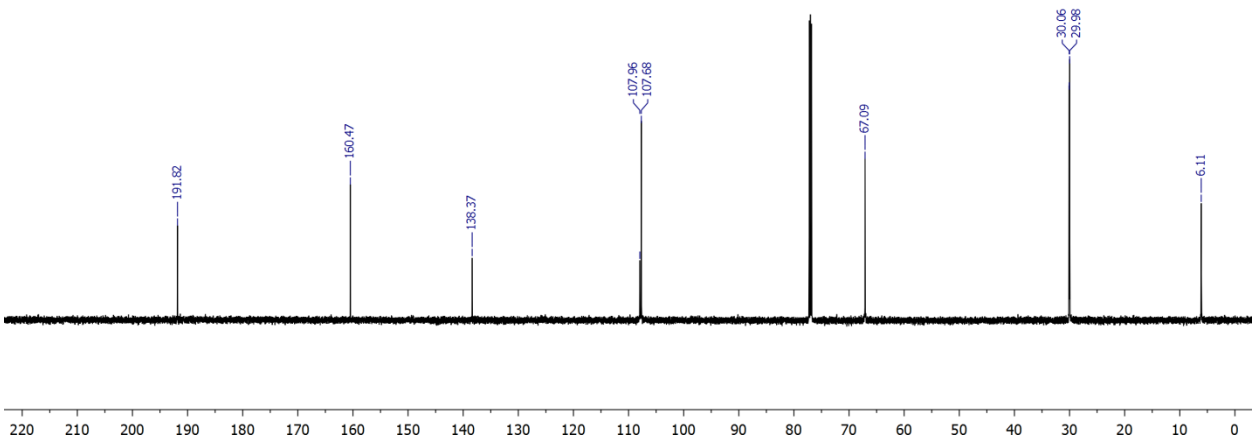
2.0
1.0
0.0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107.96
107.68
67.09
30.06
29.98
6.11
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70
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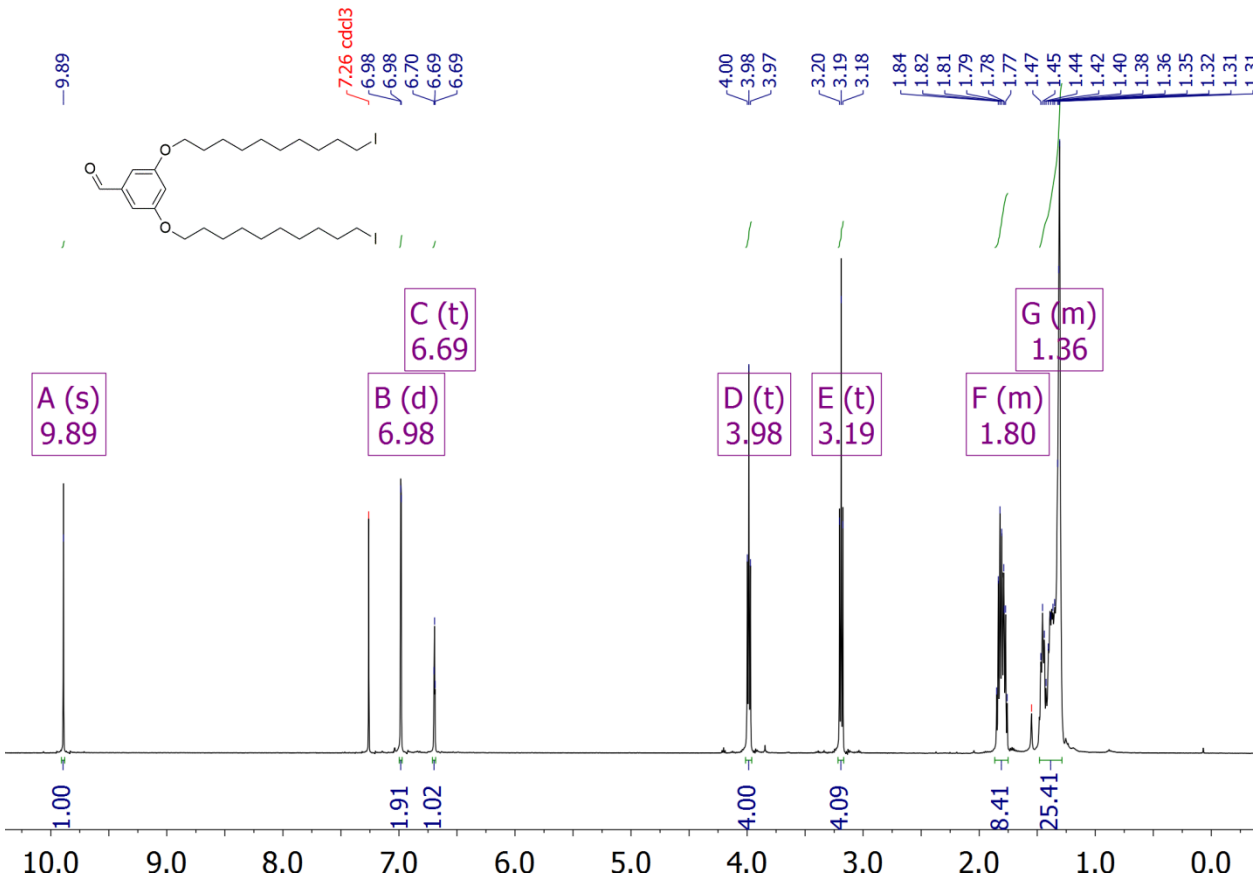
30
20
10
0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6.98
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6.69
4.00
3.98
3.97
3.20
3.19
3.18
1.84
1.82
1.81
1.79
1.78
1.77
1.47
1.45
1.44
1.42
1.40
1.38
1.36
1.35
1.32
1.31
A (s)
9.89
B (d)
6.98
C (t)
6.69
D (t)
3.98
E (t)
3.19
F (m)
1.80
G (m)
1.36
1.00
1.91
1.02
4.00
4.09
8.41
25.41
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9.0
8.0
7.0
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4.0
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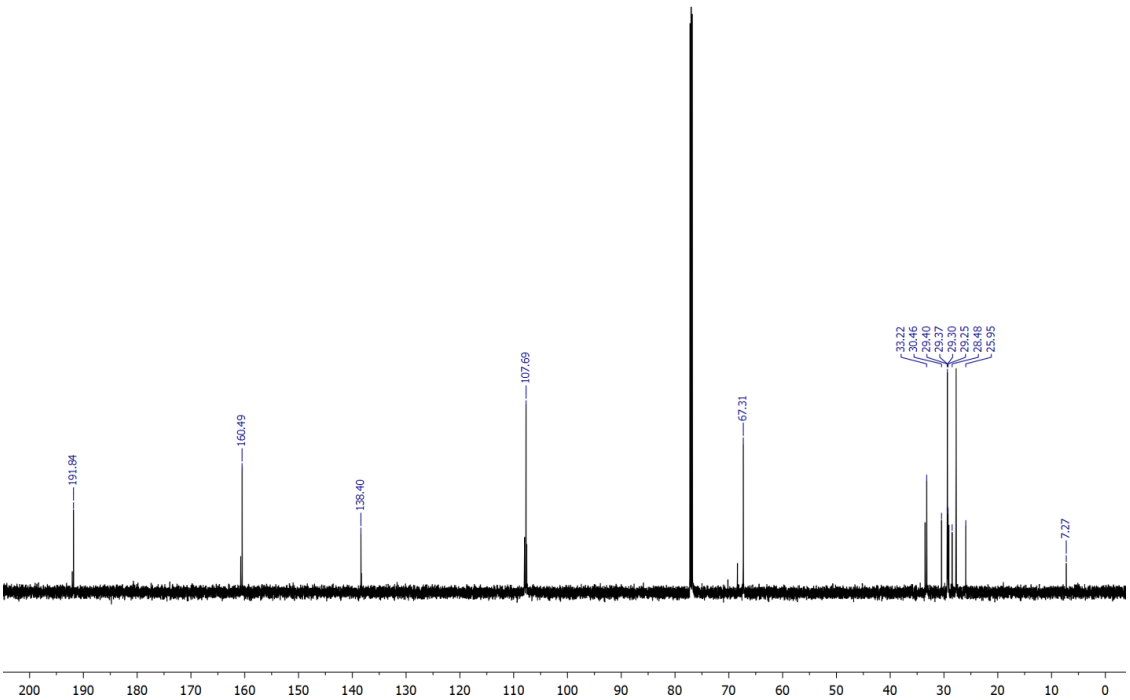
2.0
1.0
0.0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70
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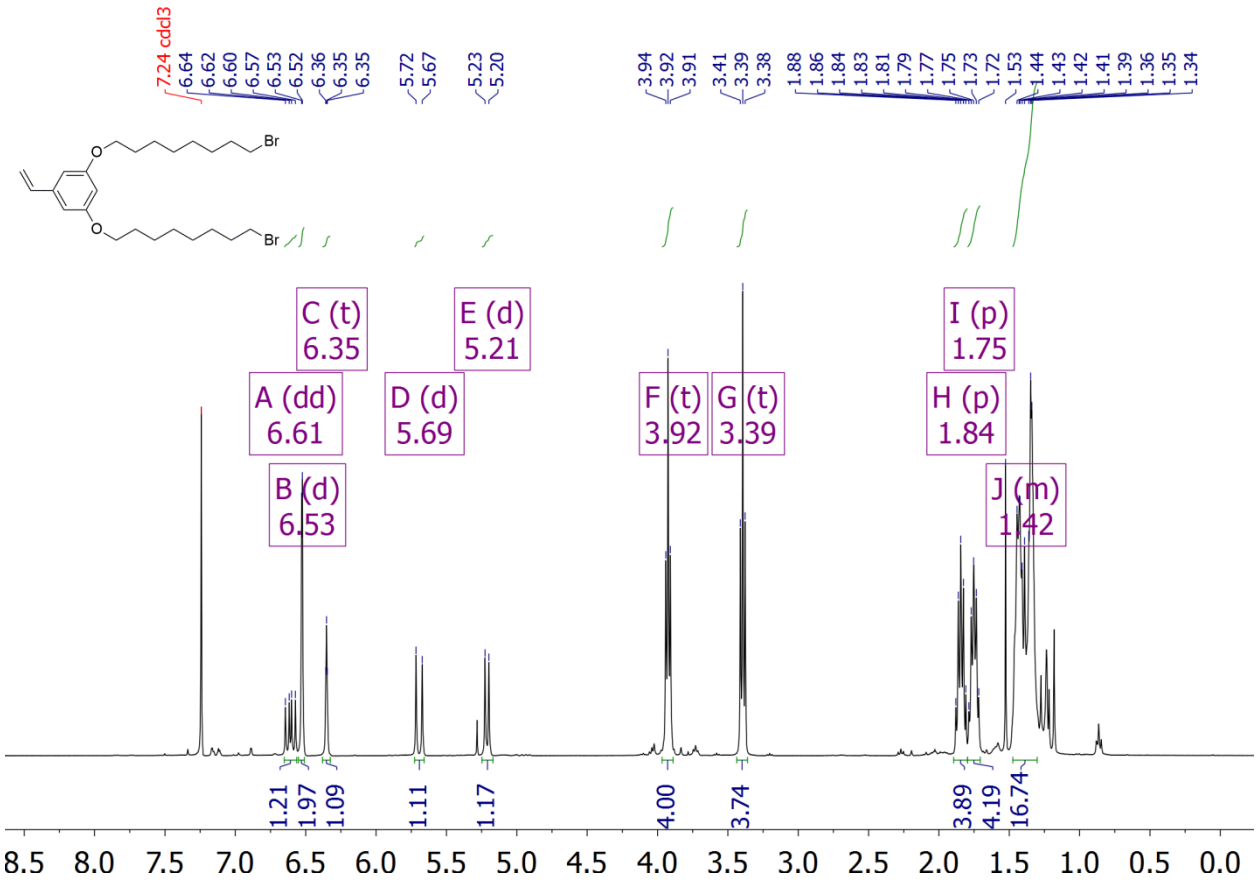
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5.23
5.20
3.94
3.92
3.91
3.41
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3.38
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1.86
1.84
1.83
1.81
1.79
1.77
1.75
1.73
1.72
1.53
1.44
1.43
1.42
1.41
1.39
1.36
1.35
1.34
Br
Br
C (t)
6.35
E (d)
5.21
I (p)
1.75
A (dd)
6.61
D (d)
5.69
F (t)
3.92
G (t)
3.39
H (p)
1.84
B (d)
6.53
J (m)
1.42
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1.09
1.11
1.17
4.00
3.74
3.89
4.19
16.74
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8.0
7.5
7.0
6.5
6.0
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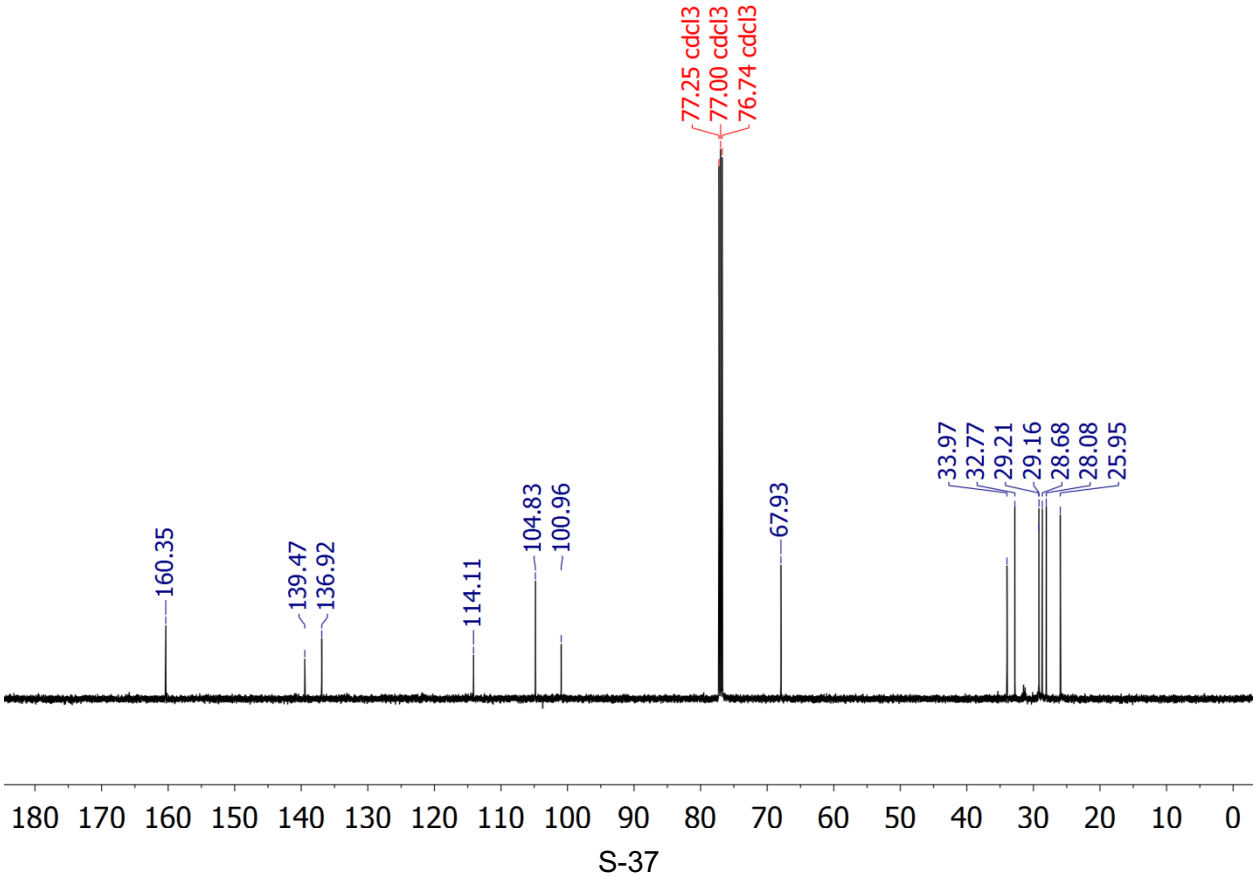
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104.83
100.96
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33.97
32.77
29.21
29.16
28.68
28.08
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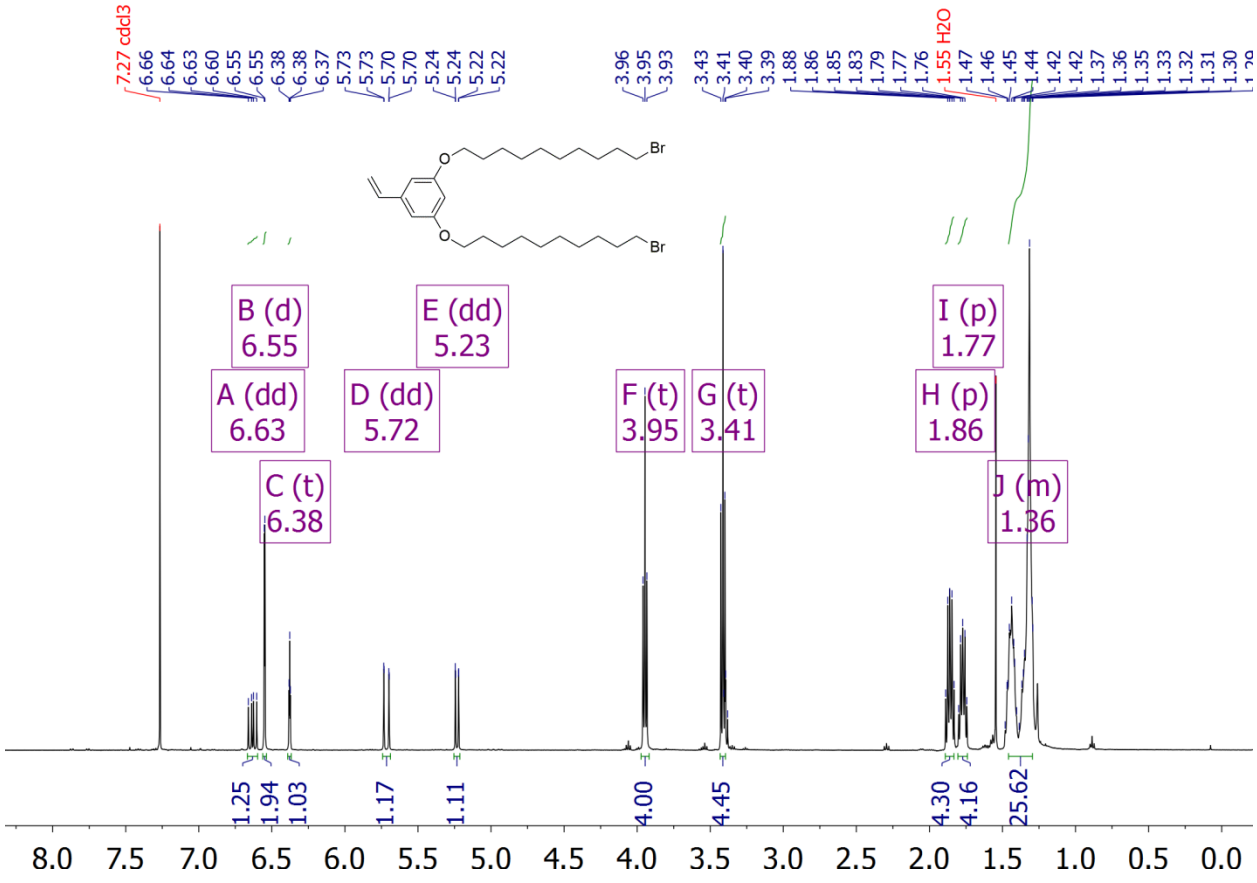
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5.70
5.24
5.24
5.22
5.22
3.96
3.95
3.93
3.43
3.41
3.40
3.39
1.88
1.86
1.85
1.83
1.79
1.77
1.76
1.55 H2O
1.47
1.46
1.45
1.44
1.42
1.42
1.37
1.36
1.35
1.33
1.32
1.31
1.30
Br
Br
B (d) 6.55
E (dd) 5.23
I (p) 1.77
A (dd) 6.63
D (dd) 5.72
F (t) 3.95
G (t) 3.41
H (p) 1.86
C (t) 6.38
J (m) 1.36
1.25
1.94
1.03
1.17
1.11
4.00
4.45
4.30
4.16
25.62
8.0
7.5
7.0
6.5
6.0
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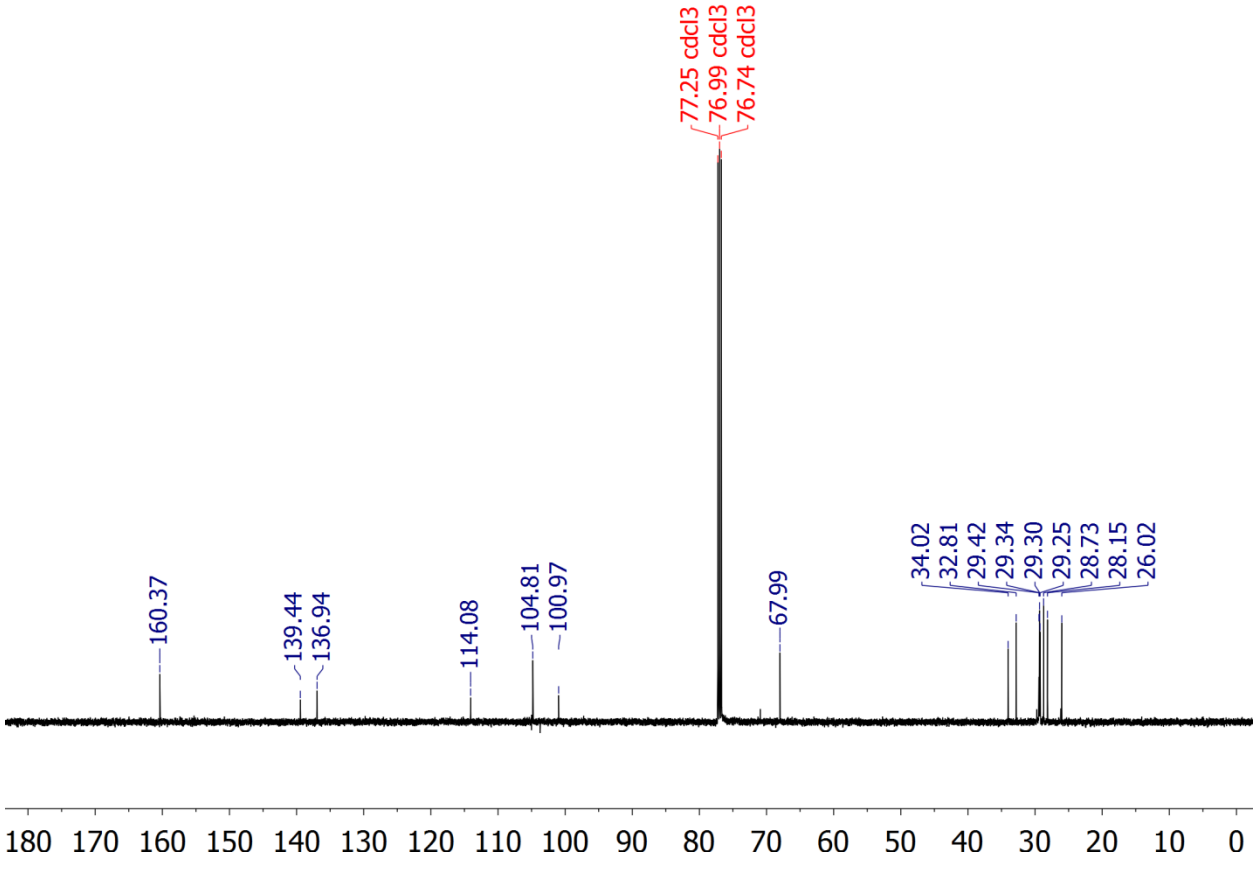
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34.02
32.81
29.42
29.34
29.30
29.25
28.73
28.15
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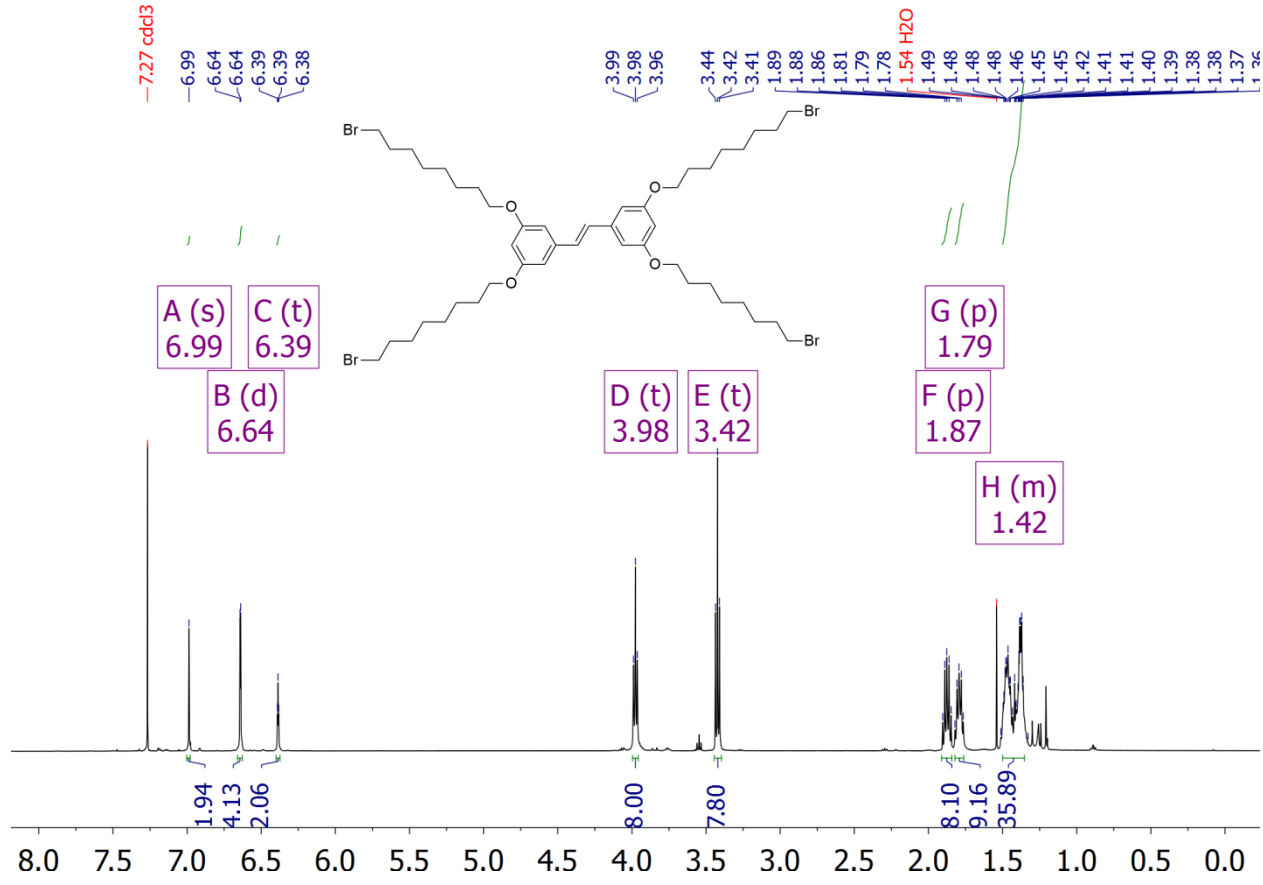
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6.64
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3.98
3.96
3.44
3.42
3.41
1.89
1.88
1.86
1.81
1.79
1.78
1.54 H2O
1.49
1.48
1.48
1.48
1.46
1.45
1.45
1.42
1.41
1.41
1.40
1.39
1.38
1.38
1.37
Br
Br
Br
Br
A (s) 6.99
C (t) 6.39
B (d) 6.64
D (t) 3.98
E (t) 3.42
G (p) 1.79
F (p) 1.87
H (m) 1.42
1.94
4.13
2.06
8.00
7.80
8.10
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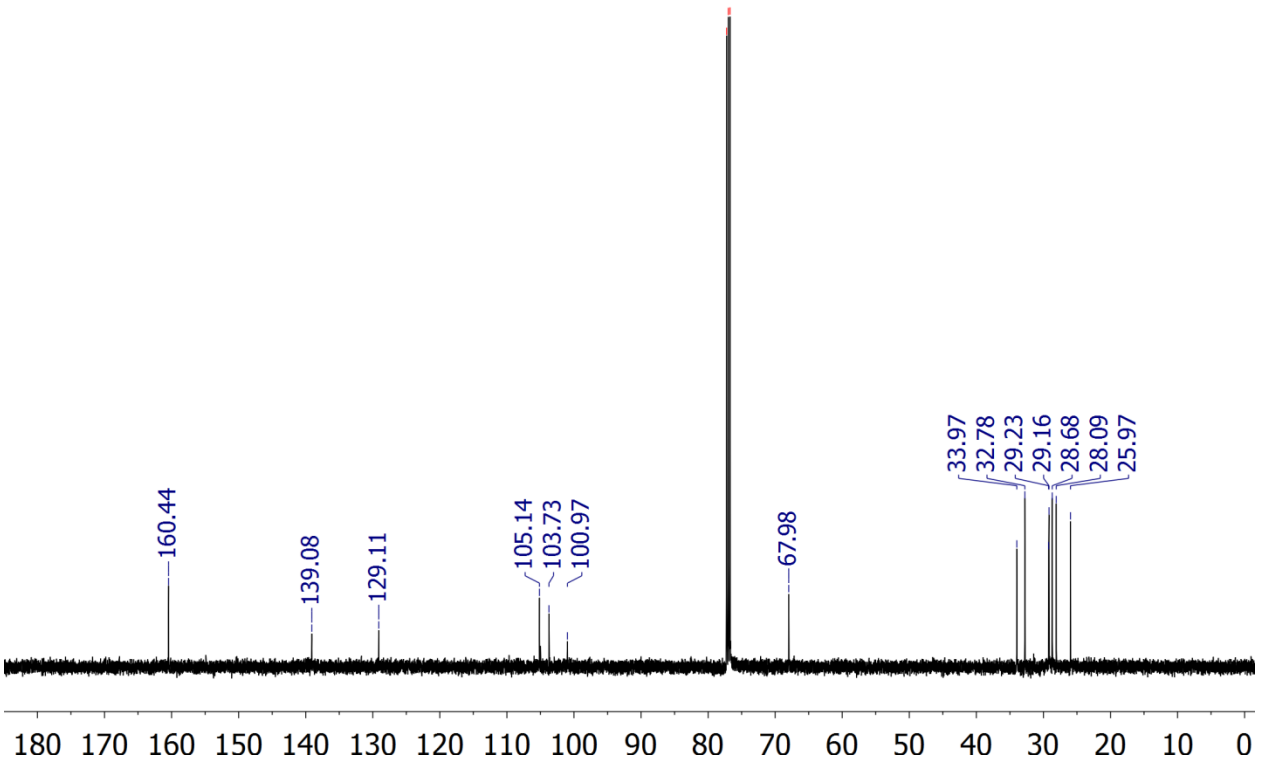
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129.11
105.14
103.73
100.97
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28.68
28.09
25.97
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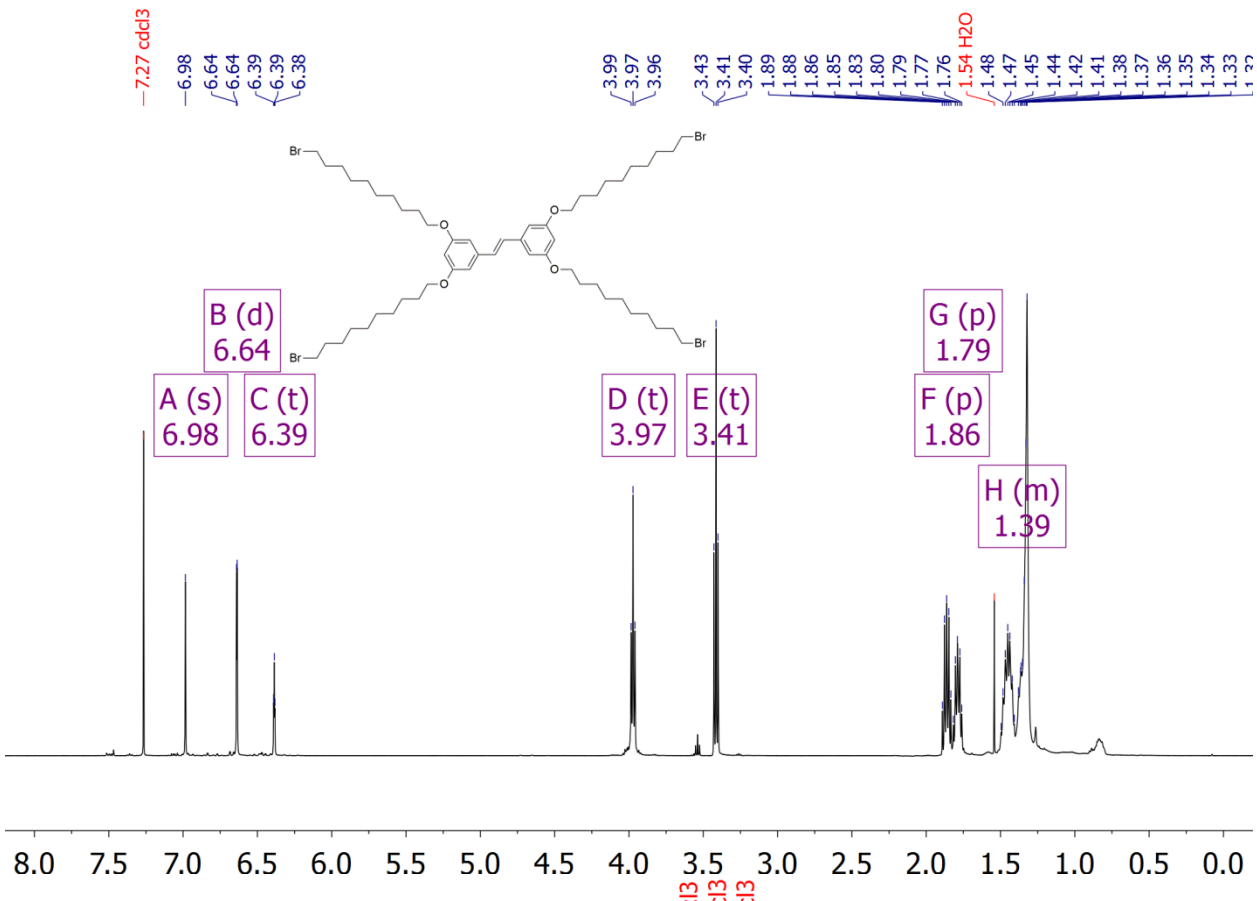
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3.43
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3.40
1.89
1.88
1.86
1.85
1.83
1.80
1.79
1.77
1.76
1.54 H2O
1.48
1.47
1.45
1.44
1.42
1.41
1.38
1.37
1.36
1.35
1.34
1.33
Br
Br
Br
Br
O
O
O
O
B (d)
6.64
A (s)
6.98
C (t)
6.39
D (t)
3.97
E (t)
3.41
G (p)
1.79
F (p)
1.86
H (m)
1.39
8.0
7.5
7.0
6.5
6.0
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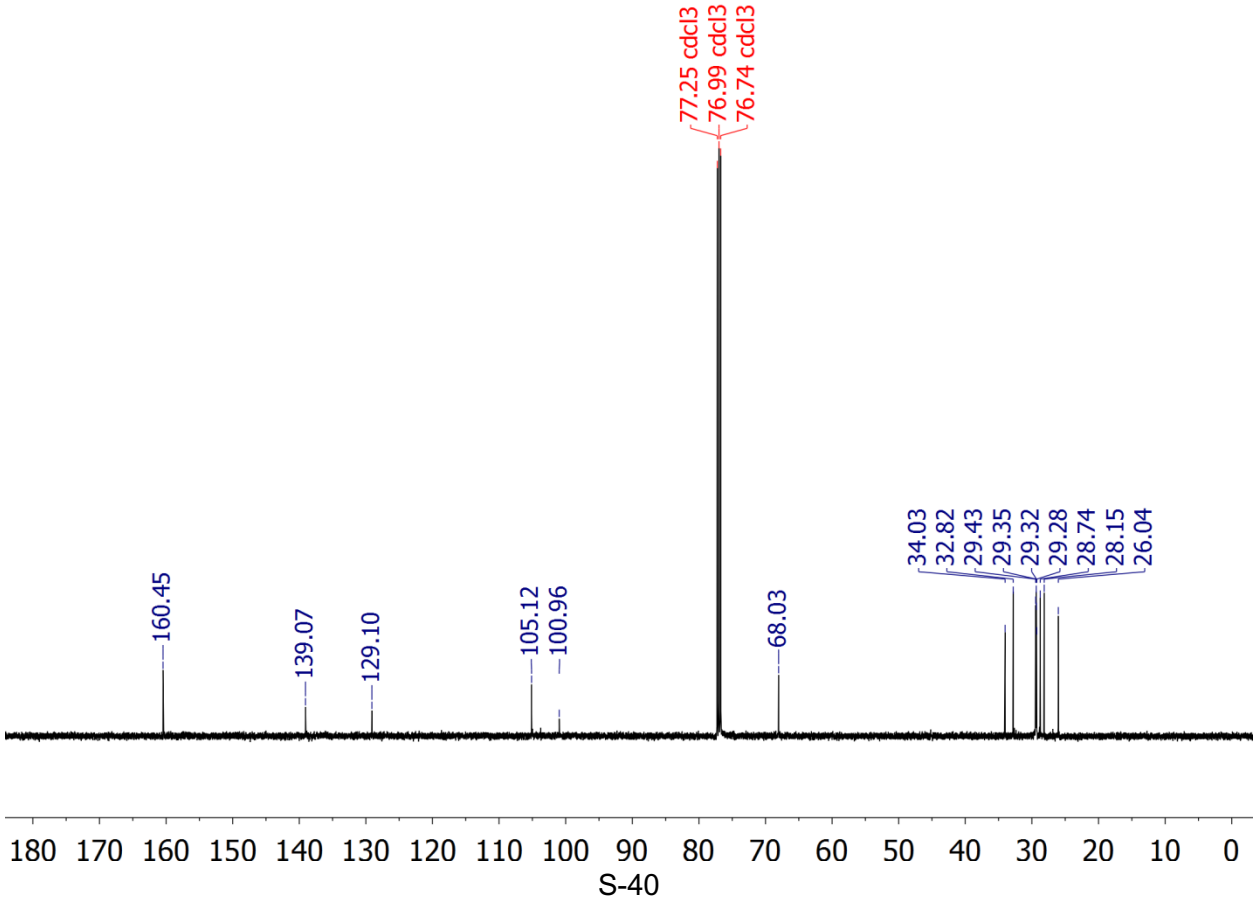
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76.74 cdcl3
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105.12
100.96
68.03
34.03
32.82
29.43
29.35
29.32
29.28
28.74
28.15
26.04
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150
140
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110
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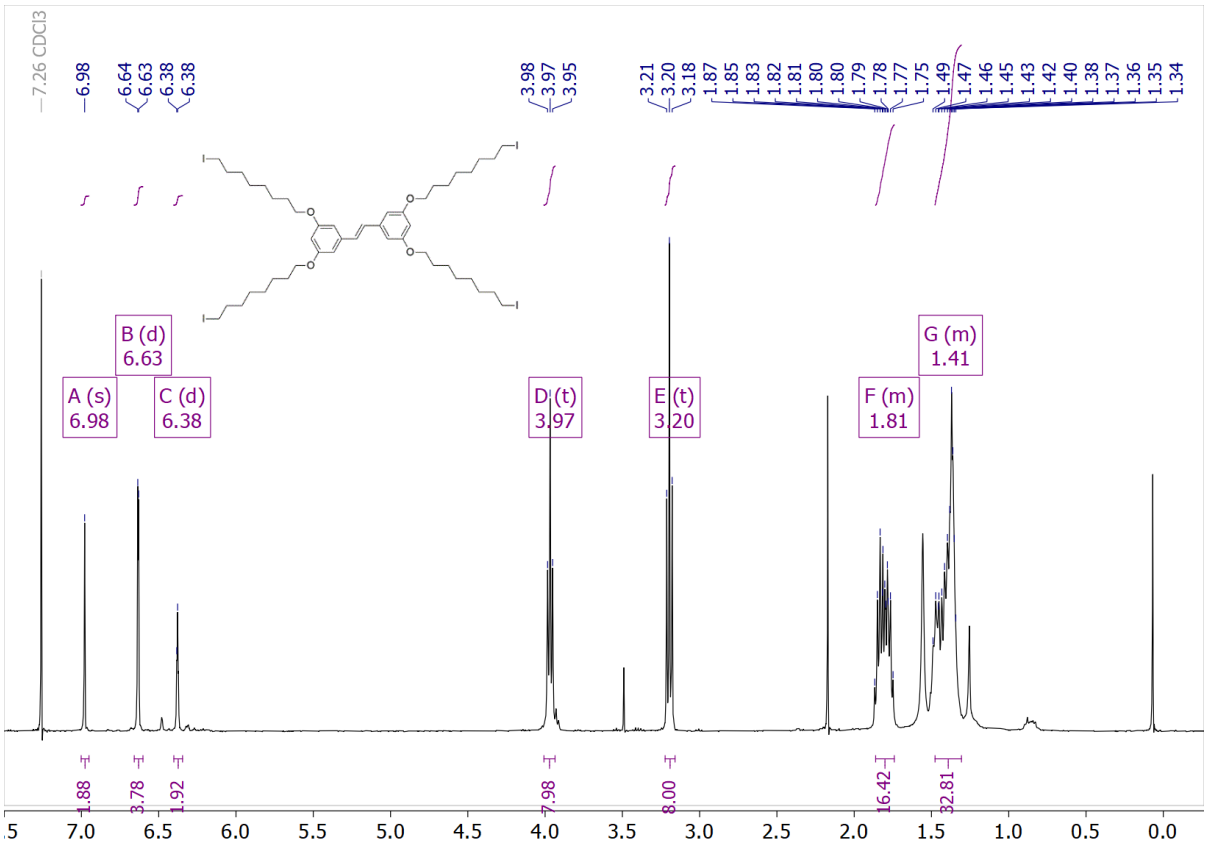
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3.95
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3.18
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1.85
1.83
1.82
1.81
1.80
1.80
1.79
1.78
1.77
1.75
1.49
1.47
1.46
1.45
1.43
1.42
1.40
1.38
1.37
1.36
1.35
1.34
A (s) 6.98
B (d) 6.63
C (d) 6.38
D (t) 3.97
E (t) 3.20
F (m) 1.81
G (m) 1.41
1.88
3.78
1.92
7.98
8.00
16.42
32.81
7.0
6.5
6.0
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4.0
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3.0
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2.0
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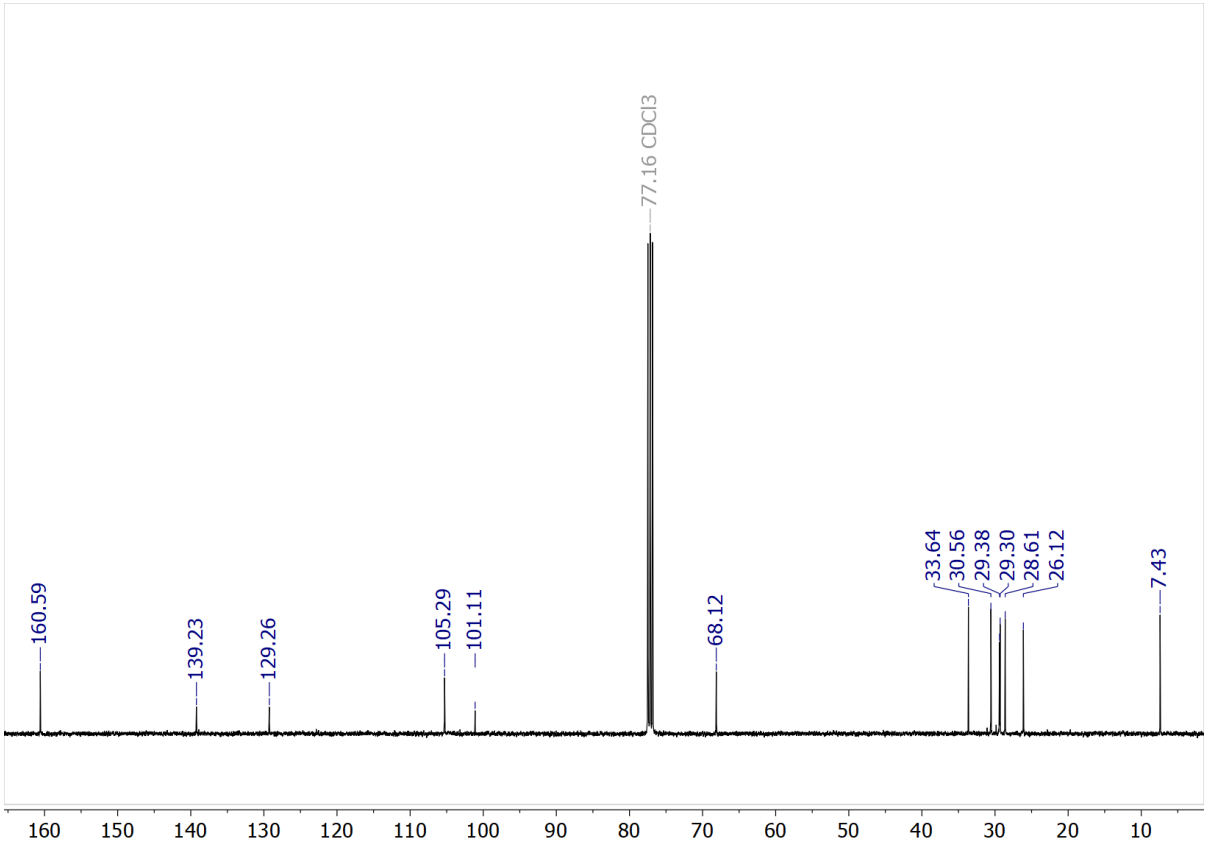
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150
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80
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40
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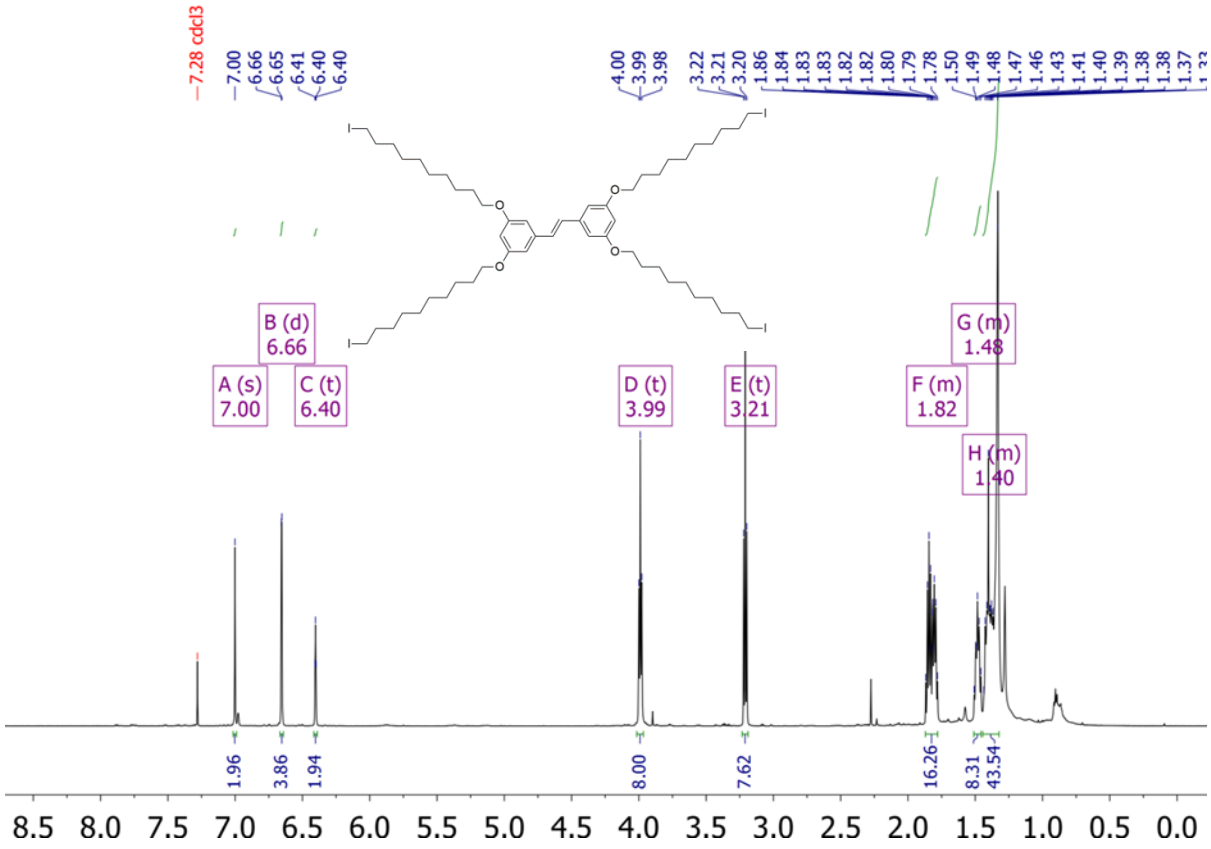
20
10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4.00
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3.20
1.86
1.84
1.83
1.83
1.82
1.82
1.80
1.79
1.78
1.50
1.49
1.48
1.47
1.46
1.43
1.41
1.40
1.39
1.38
1.38
1.37
A (s) 7.00
B (d) 6.66
C (t) 6.40
D (t) 3.99
E (t) 3.21
F (m) 1.82
G (m) 1.48
H (m) 1.40
1.96
3.86
1.94
8.00
7.62
16.26
8.31
43.54
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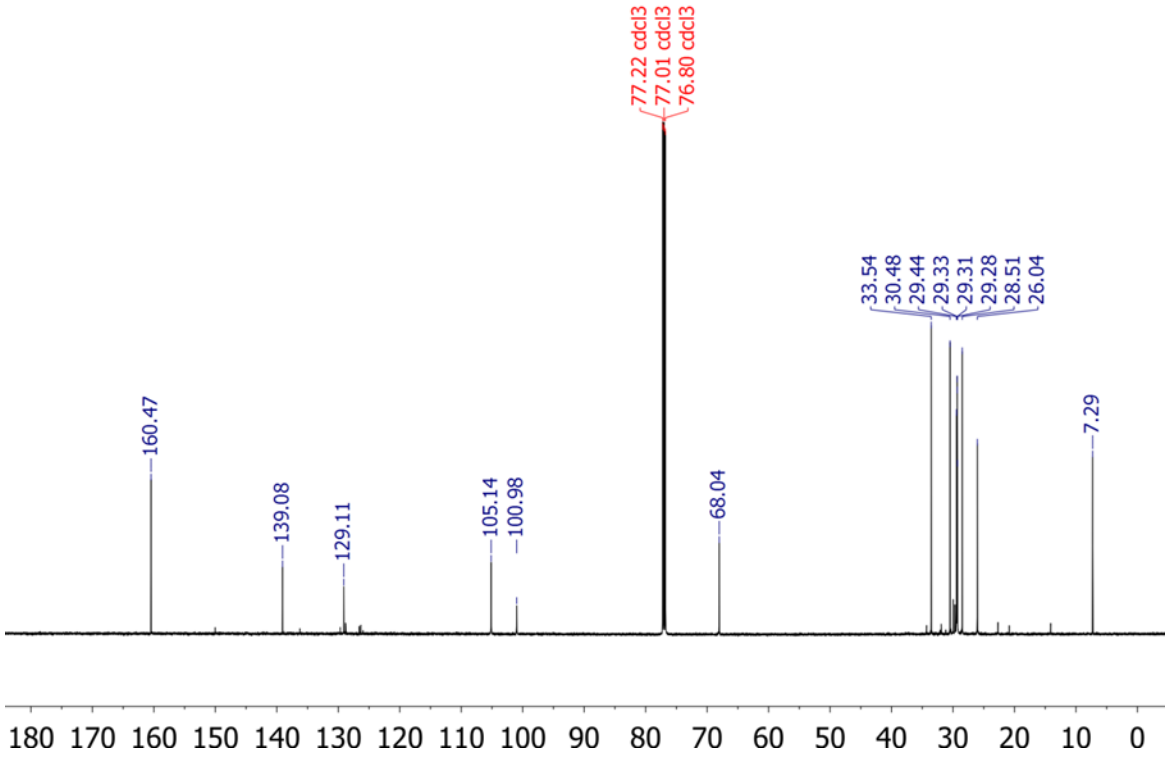
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28.51
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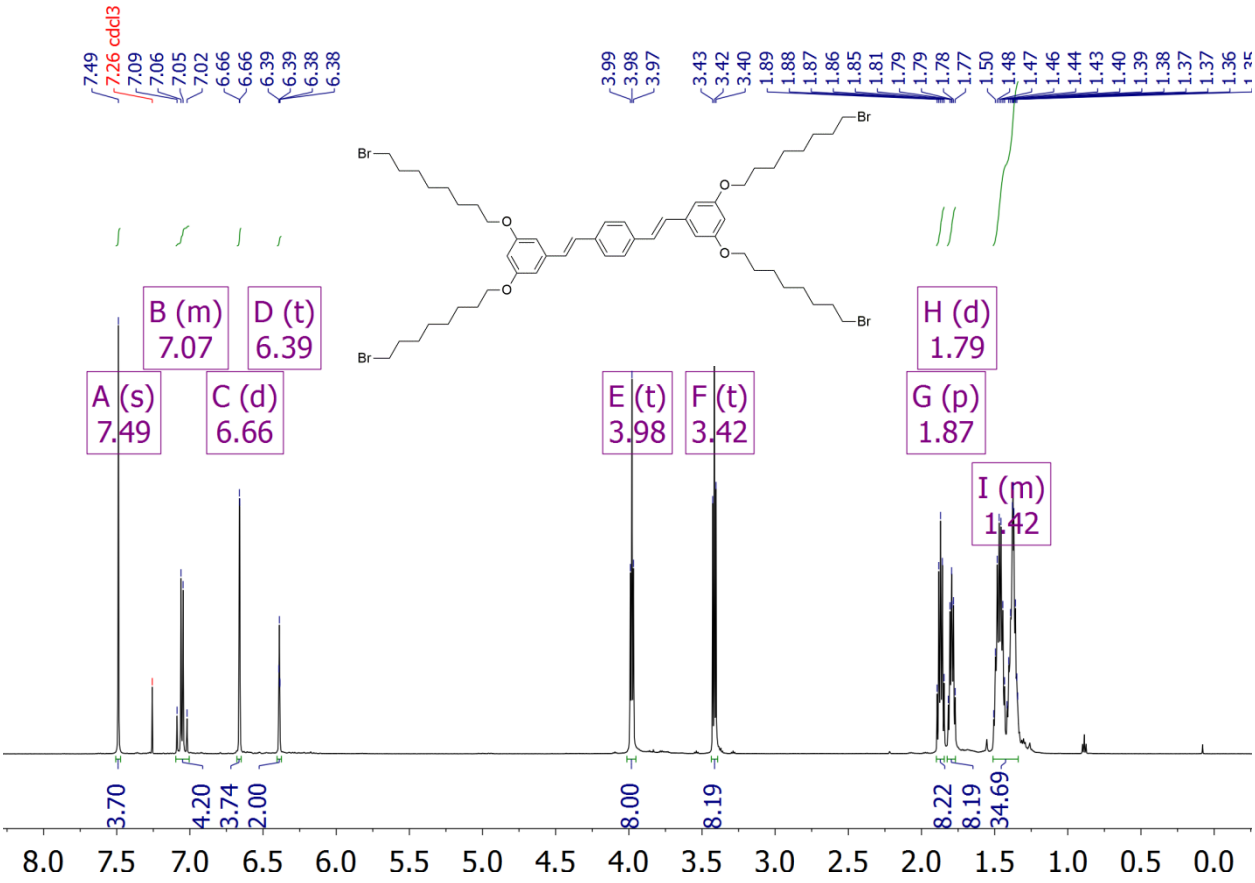
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7.05
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6.66
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6.39
6.38
6.38
3.99
3.98
3.97
3.43
3.42
3.40
1.89
1.88
1.87
1.86
1.85
1.81
1.79
1.79
1.78
1.77
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1.47
1.46
1.44
1.43
1.40
1.39
1.38
1.37
1.37
1.36
Br
Br
Br
Br
A (s) 7.49
B (m) 7.07
C (d) 6.66
D (t) 6.39
E (t) 3.98
F (t) 3.42
G (p) 1.87
H (d) 1.79
I (m) 1.42
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3.74
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8.00
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8.22
8.19
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7.0
6.5
6.0
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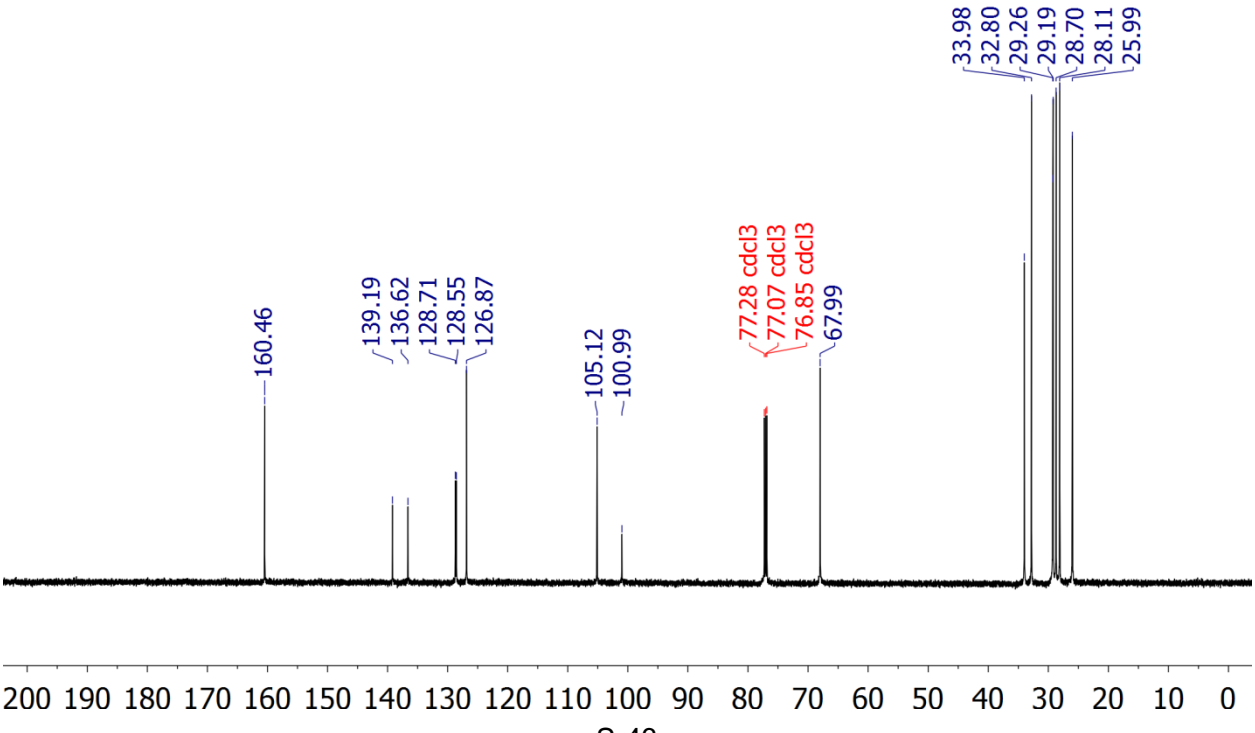
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77.07 cdcl3
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33.98
32.80
29.26
29.19
28.70
28.11
25.99
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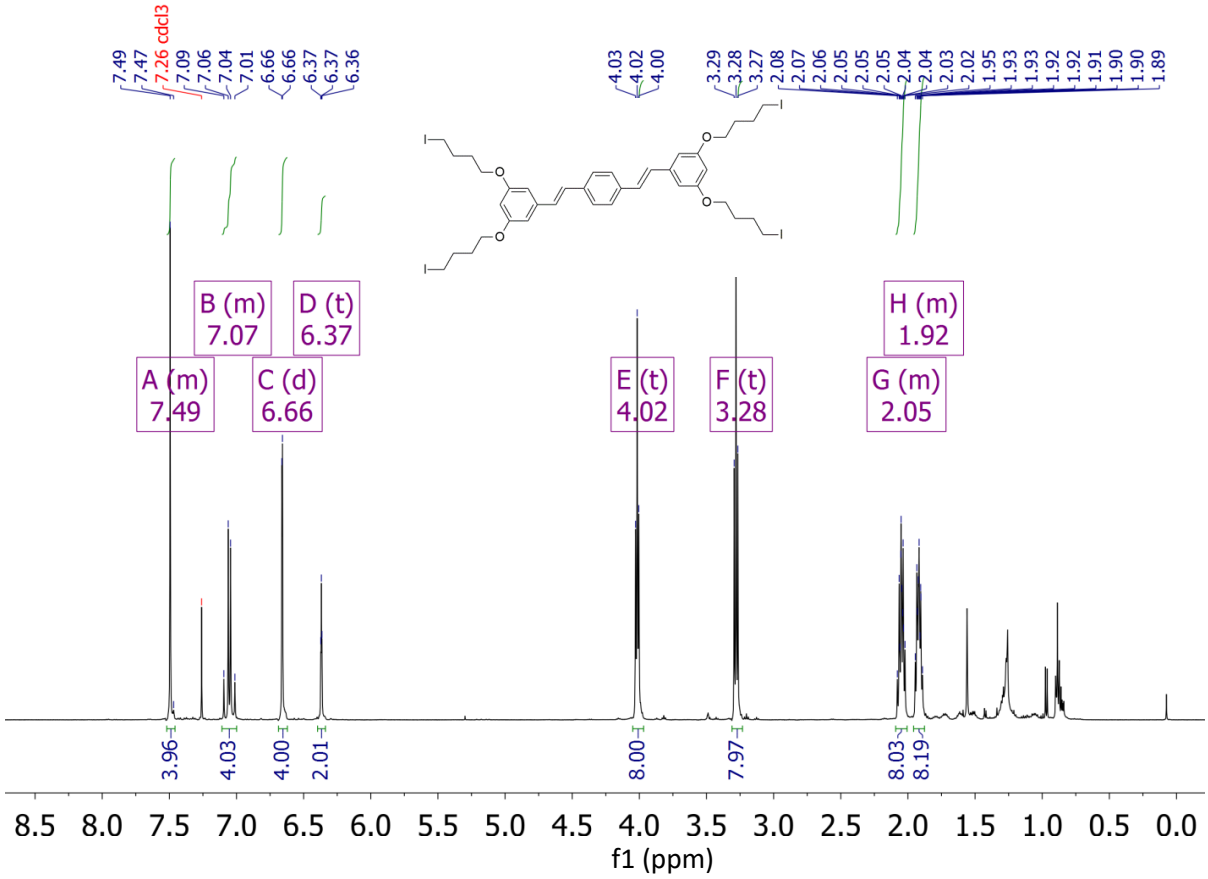
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6.66
6.66
6.37
6.37
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4.02
4.00
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3.28
3.27
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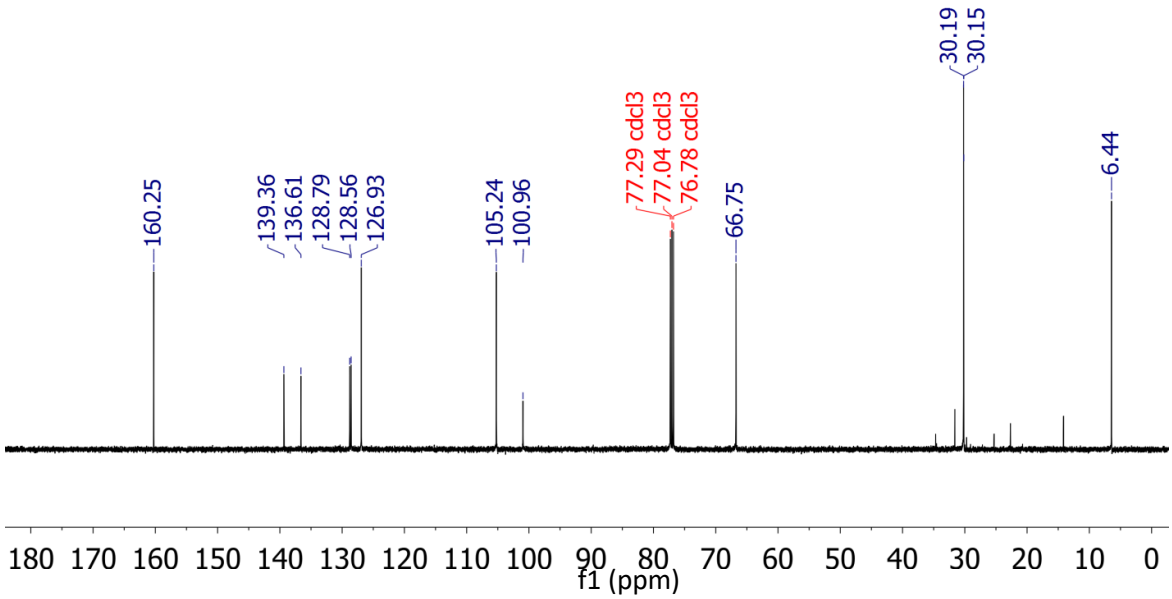
2.07
2.06
2.05
2.05
2.05
2.04
2.04
2.03
2.02
1.95
1.93
1.93
1.92
1.92
1.91
1.90
1.90
1.89
A (m) 7.49
B (m) 7.07
C (d) 6.66
D (t) 6.37
E (t) 4.02
F (t) 3.28
G (m) 2.05
H (m) 1.92
3.96
4.03
4.00
2.01
8.00
7.97
8.03
8.19
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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77.04 cdcl3
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30.15
6.44
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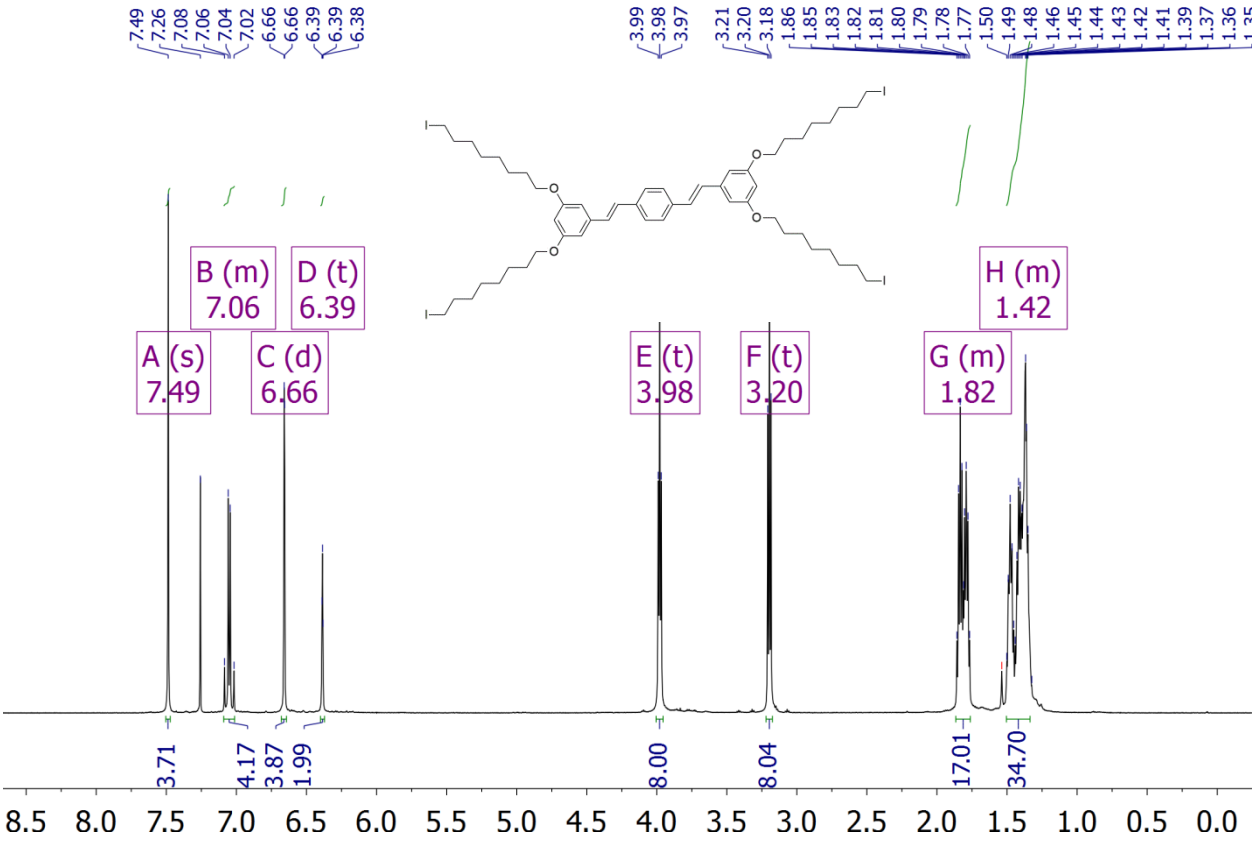
f1 (ppm)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6.39
6.38
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3.97
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3.20
3.18
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1.85
1.83
1.82
1.81
1.80
1.79
1.78
1.77
1.50
1.49
1.48
1.46
1.45
1.44
1.43
1.42
1.41
1.39
1.37
1.36
A (s) 7.49
B (m) 7.06
C (d) 6.66
D (t) 6.39
E (t) 3.98
F (t) 3.20
G (m) 1.82
H (m) 1.42
3.71
4.17
3.87
1.99
8.00
8.04
17.01
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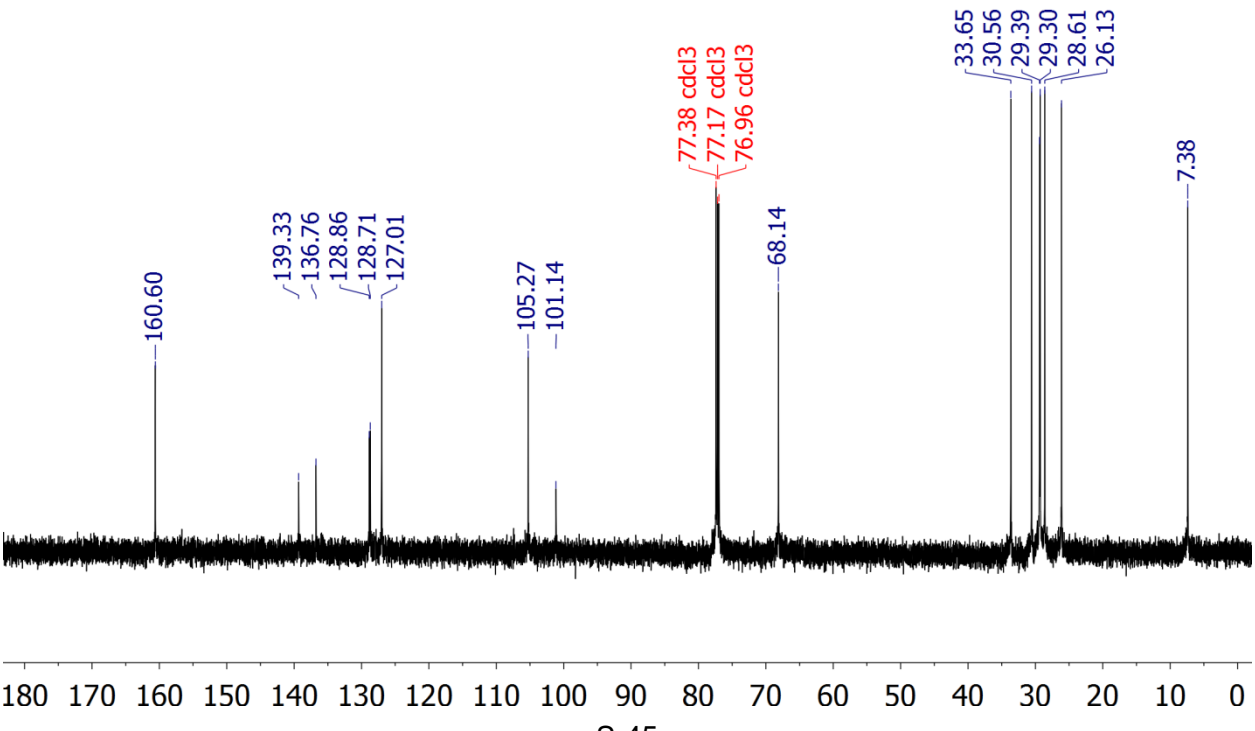
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76.96 cdcl3
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28.61
26.13
7.38
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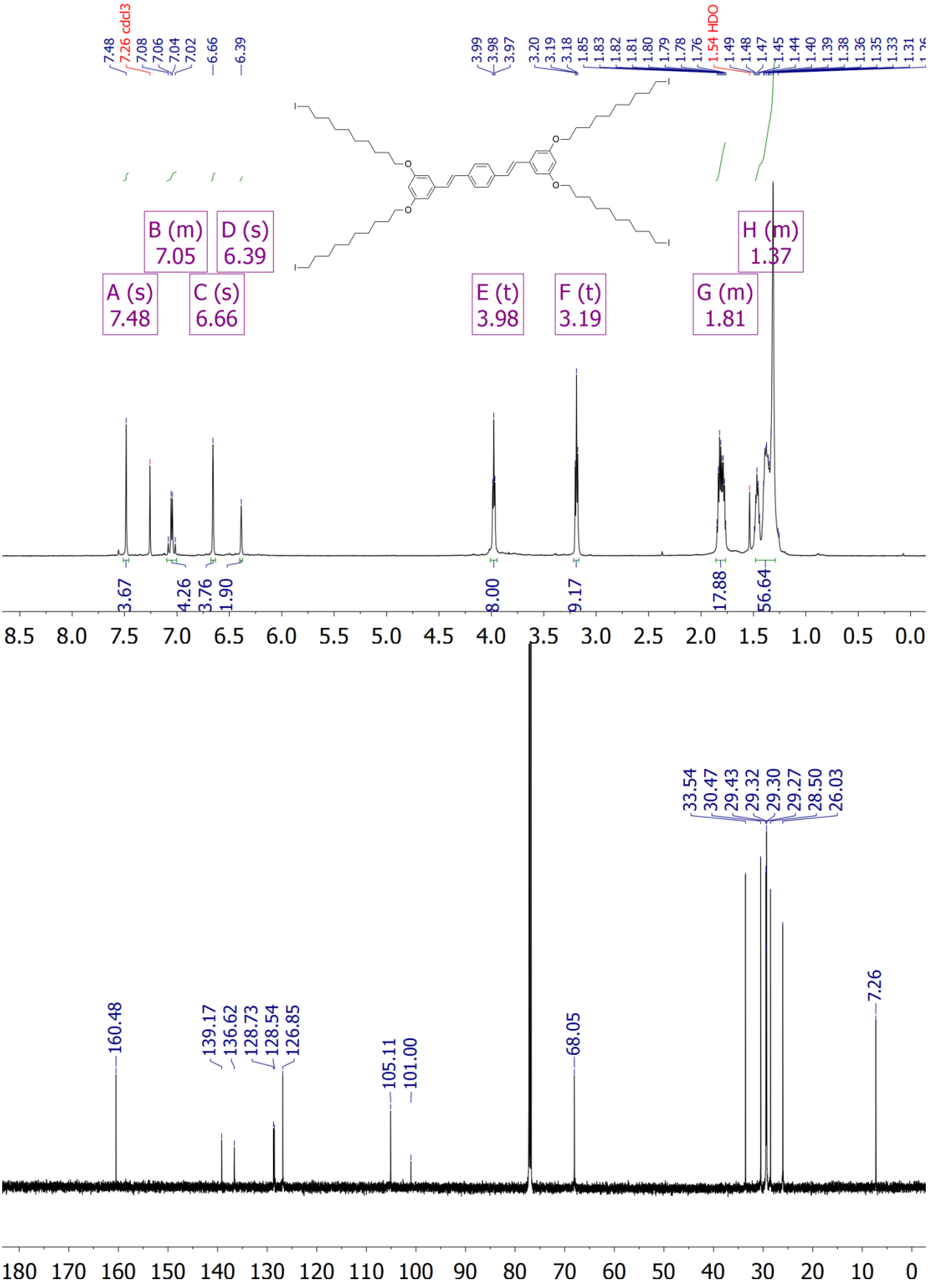
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7.02
6.66
6.39
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3.98
3.97
3.20
3.19
3.18
1.85
1.83
1.82
1.81
1.80
1.79
1.78
1.76
1.54 HDO
1.49
1.48
1.47
1.45
1.44
1.40
1.39
1.38
1.36
1.35
1.33
1.31
B (m) 7.05
D (s) 6.39
H (m) 1.37
A (s) 7.48
C (s) 6.66
E (t) 3.98
F (t) 3.19
G (m) 1.81
3.67
4.26
3.76
1.90
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9.17
17.88
56.64
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
160.48
139.17
136.62
128.73
128.54
126.85
105.11
101.00
68.05
33.54
30.47
29.43
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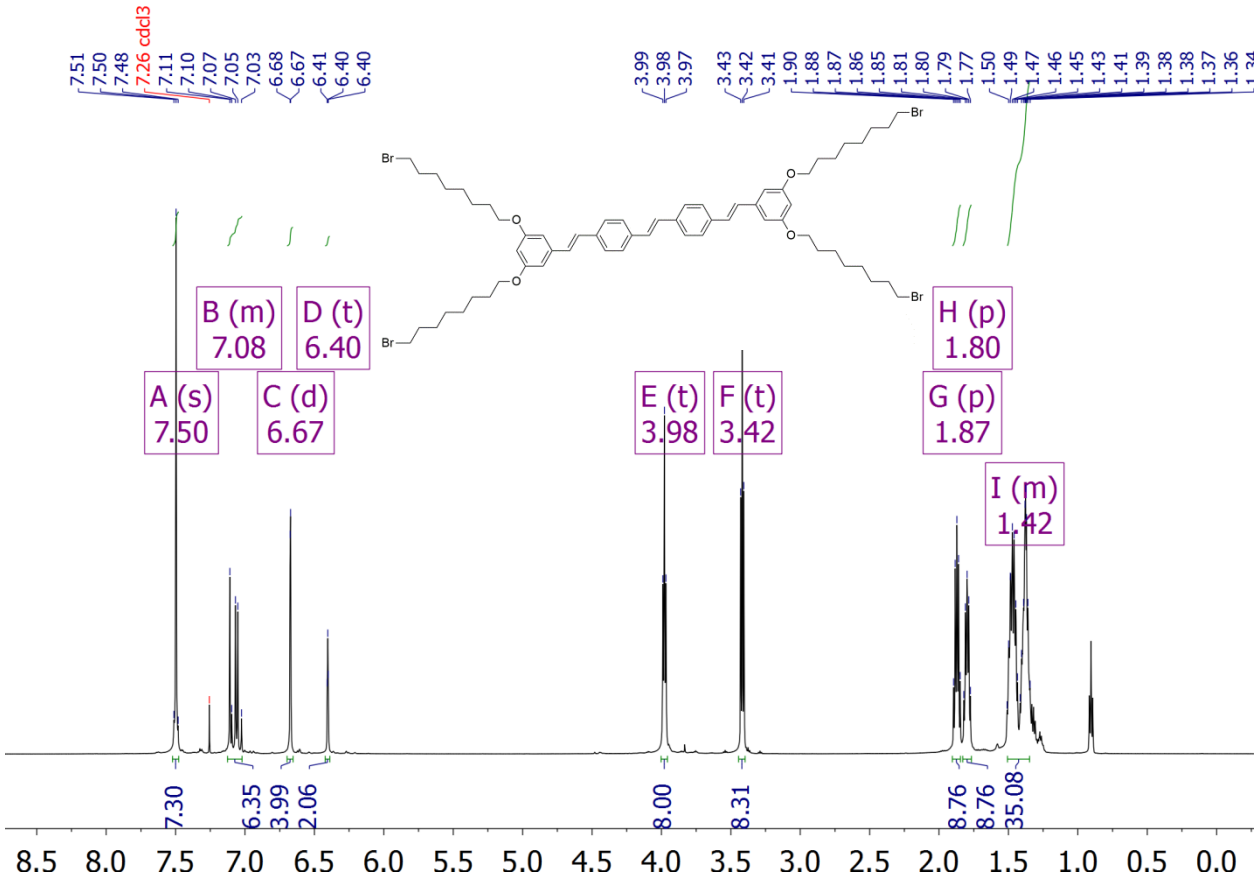
29.30
29.27
28.50
26.03
7.26
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.08
C (d)
6.67
D (t)
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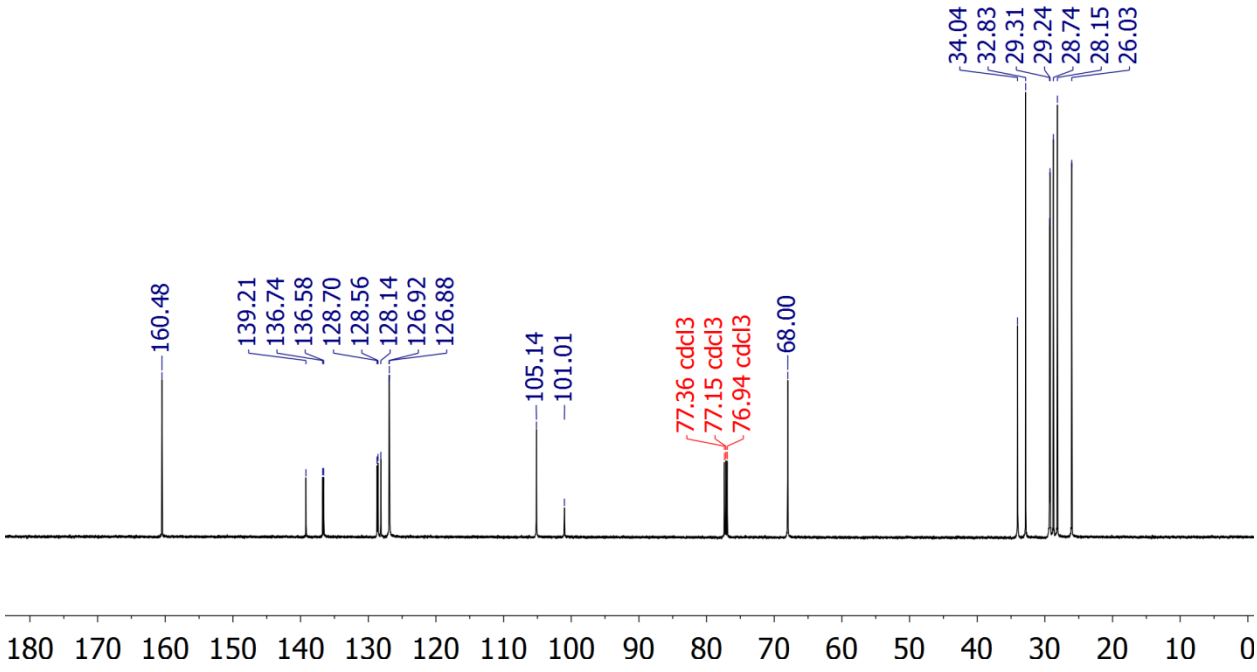
E (t)
3.98
F (t)
3.42
G (p)
1.87
H (p)
1.80
I (m)
1.42
Br
Br
Br
Br
O
O
O
O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101.01
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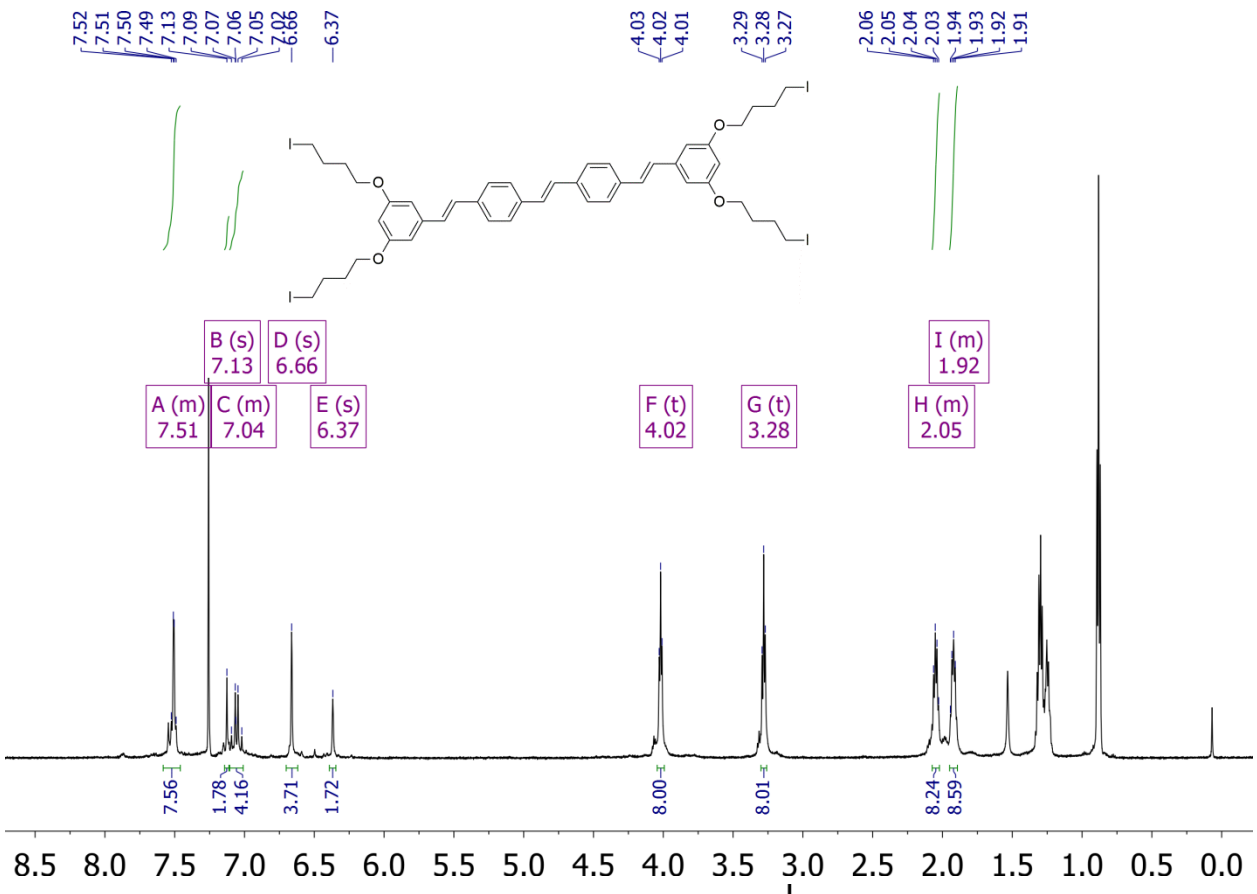
26.03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G (t) 3.28
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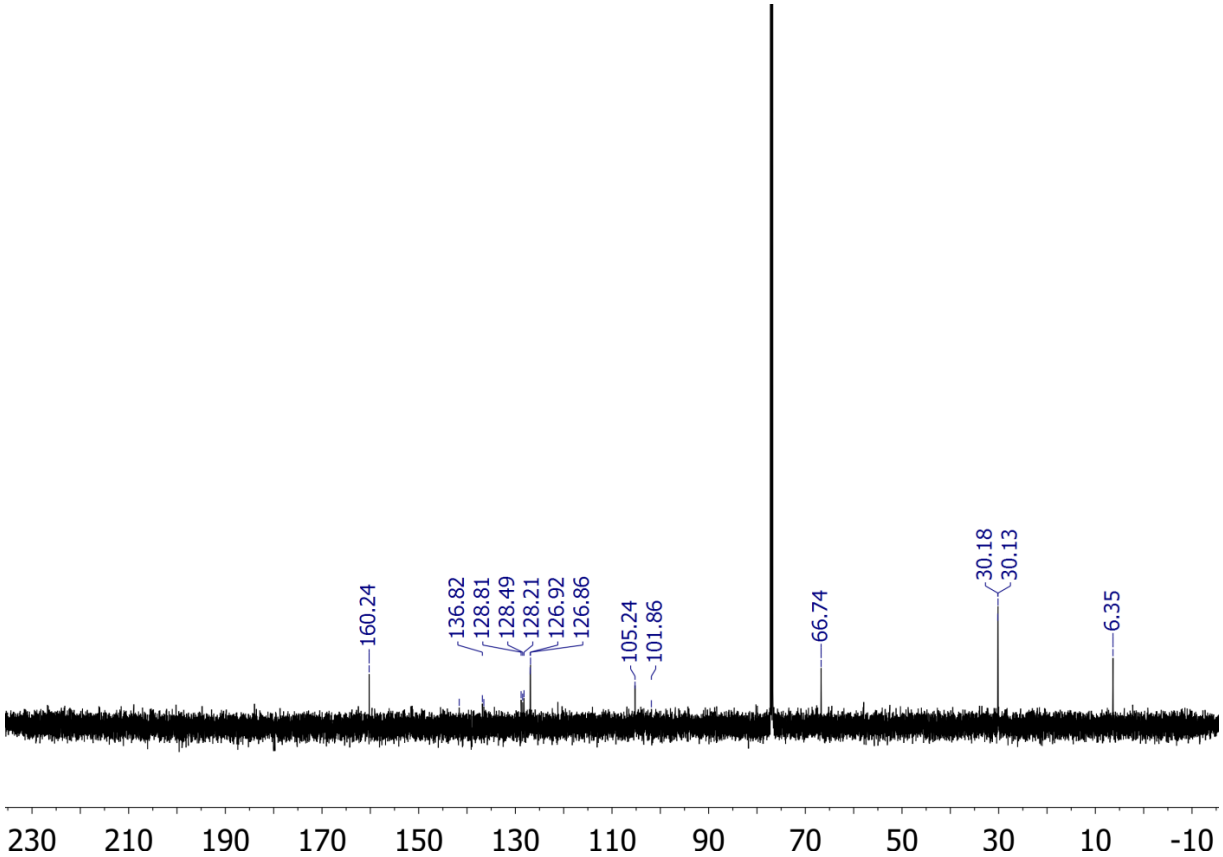
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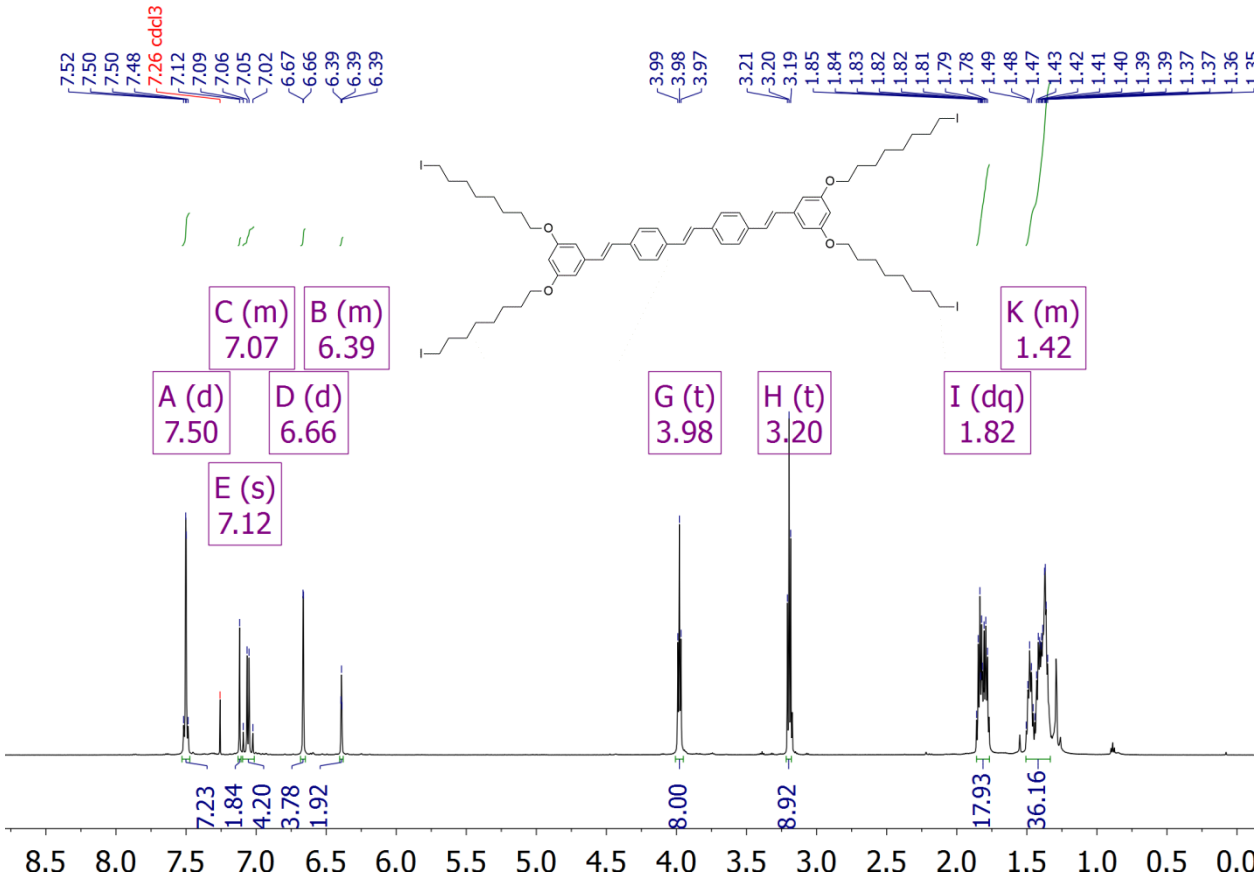
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C (m) 7.07
D (d) 6.66
E (s) 7.12
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K (m) 1.42
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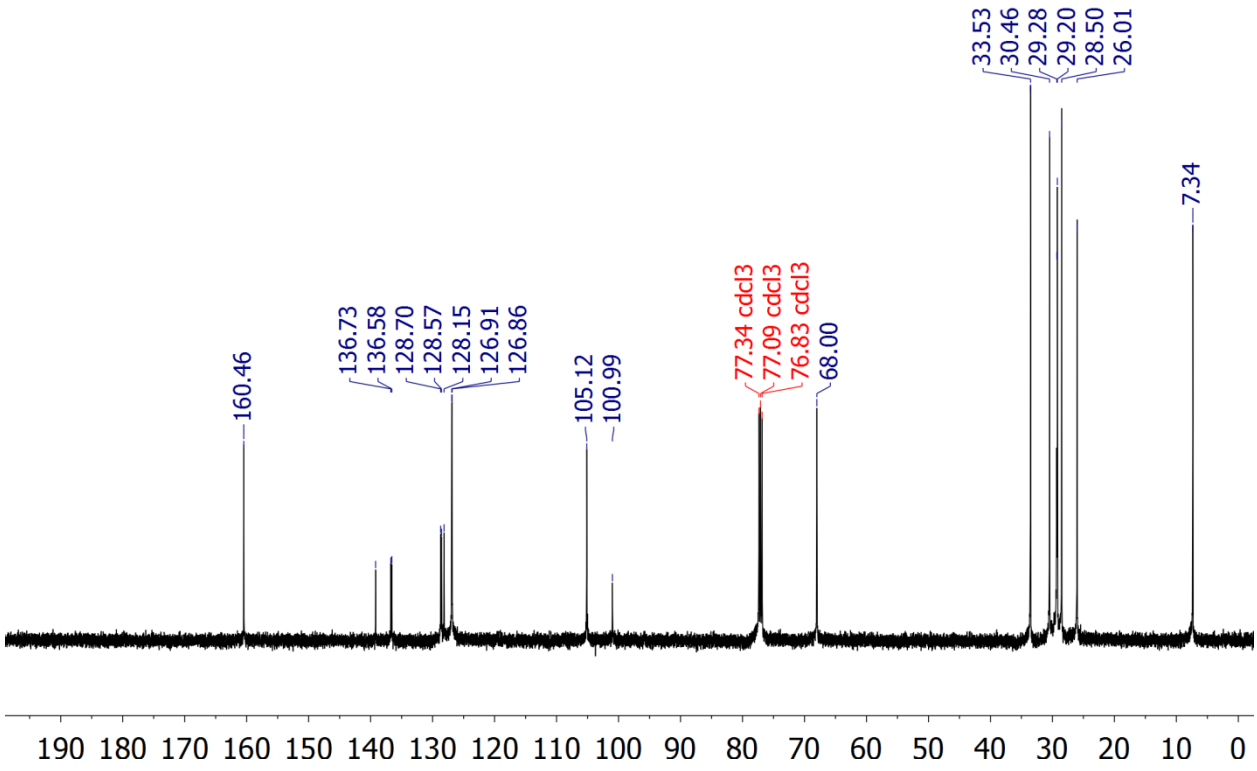
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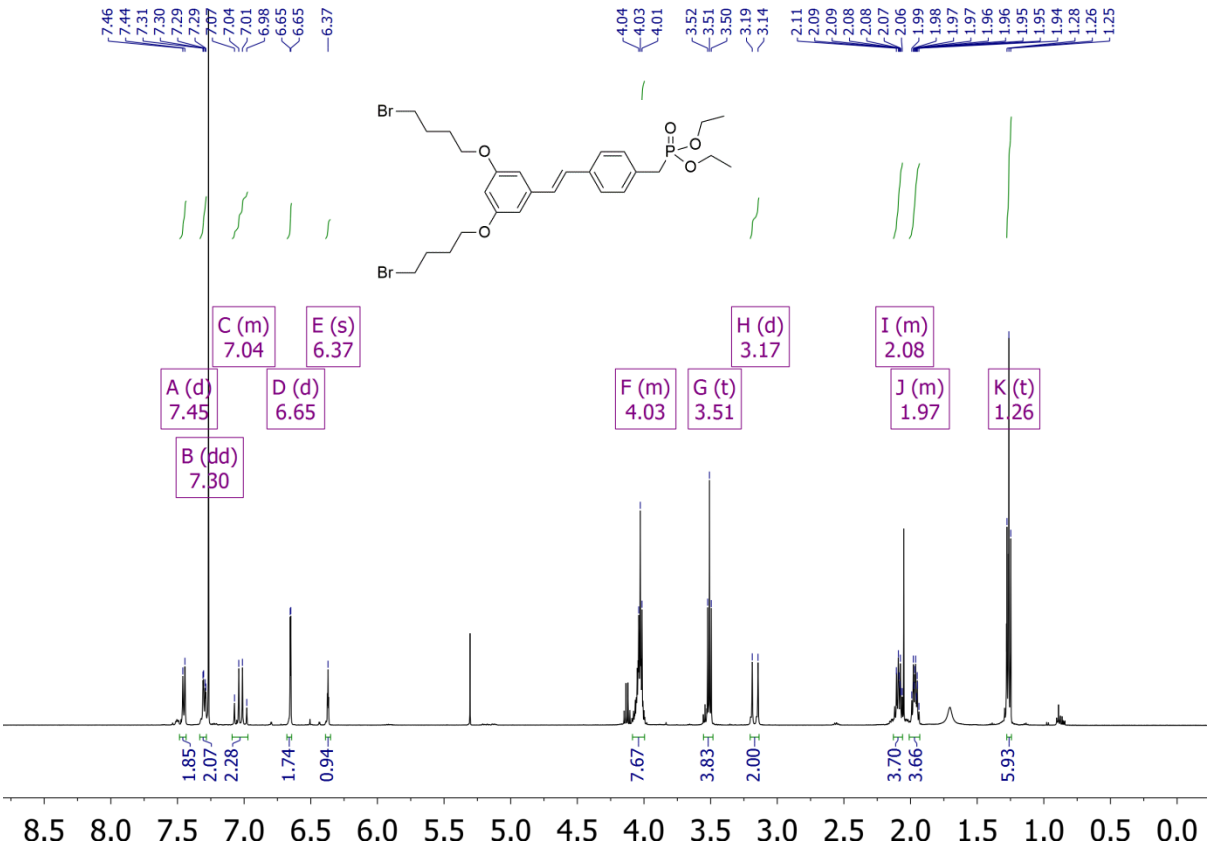
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Br
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P
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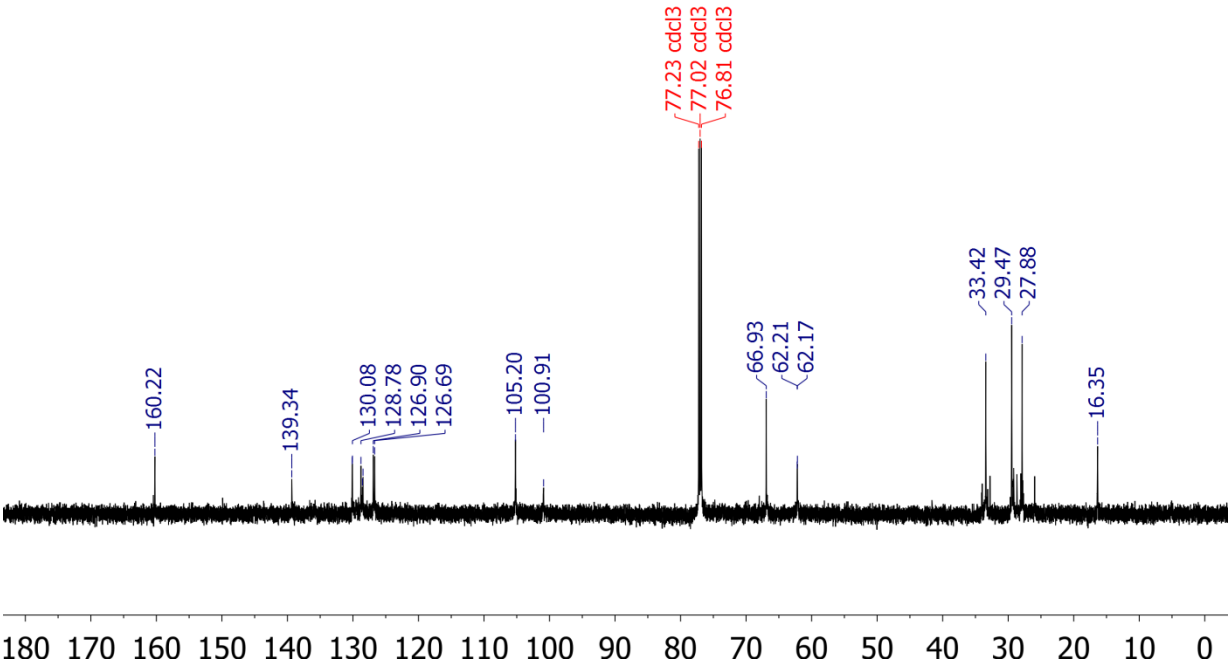
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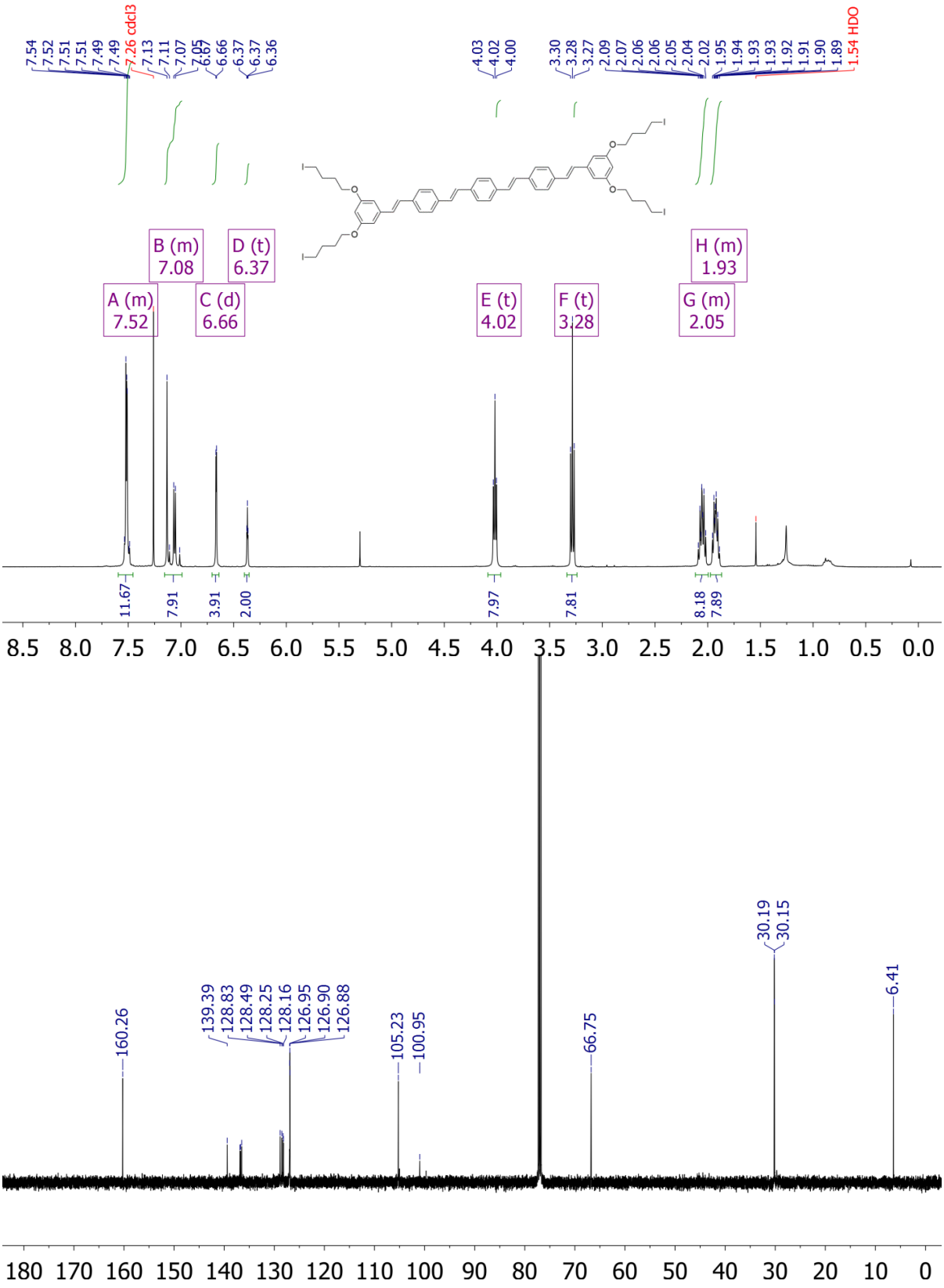
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B (m) 7.08
C (d) 6.66
D (t) 6.37
E (t) 4.02
F (t) 3.28
G (m) 2.05
H (m) 1.93
11.67
7.91
3.91
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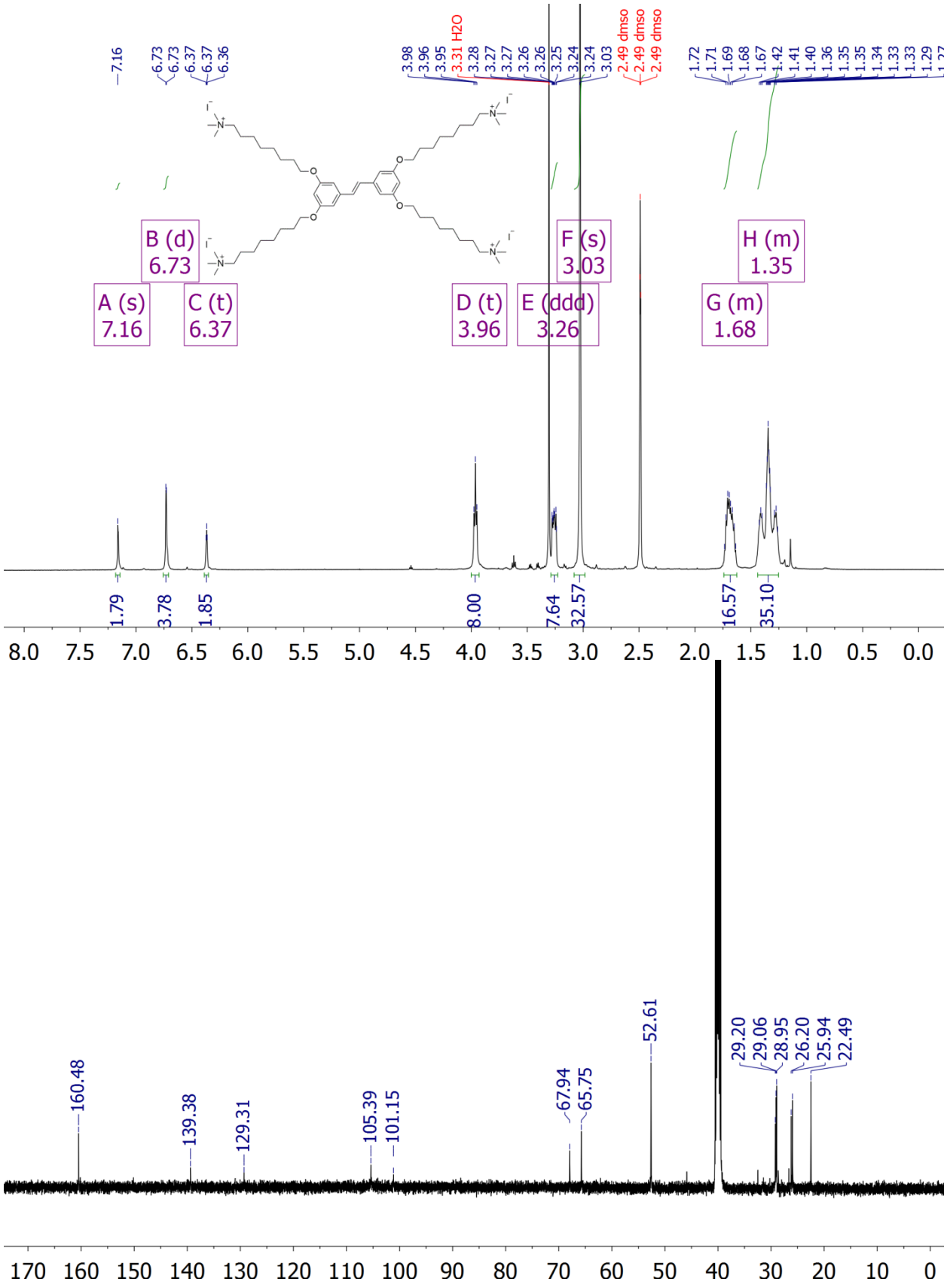
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3.25
3.24
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2.49 dmso
2.49 dmso
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B (d) 6.73
C (t) 6.37
D (t) 3.96
E (ddd) 3.26
F (s) 3.03
G (m) 1.68
H (m) 1.35
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3.78
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105.39
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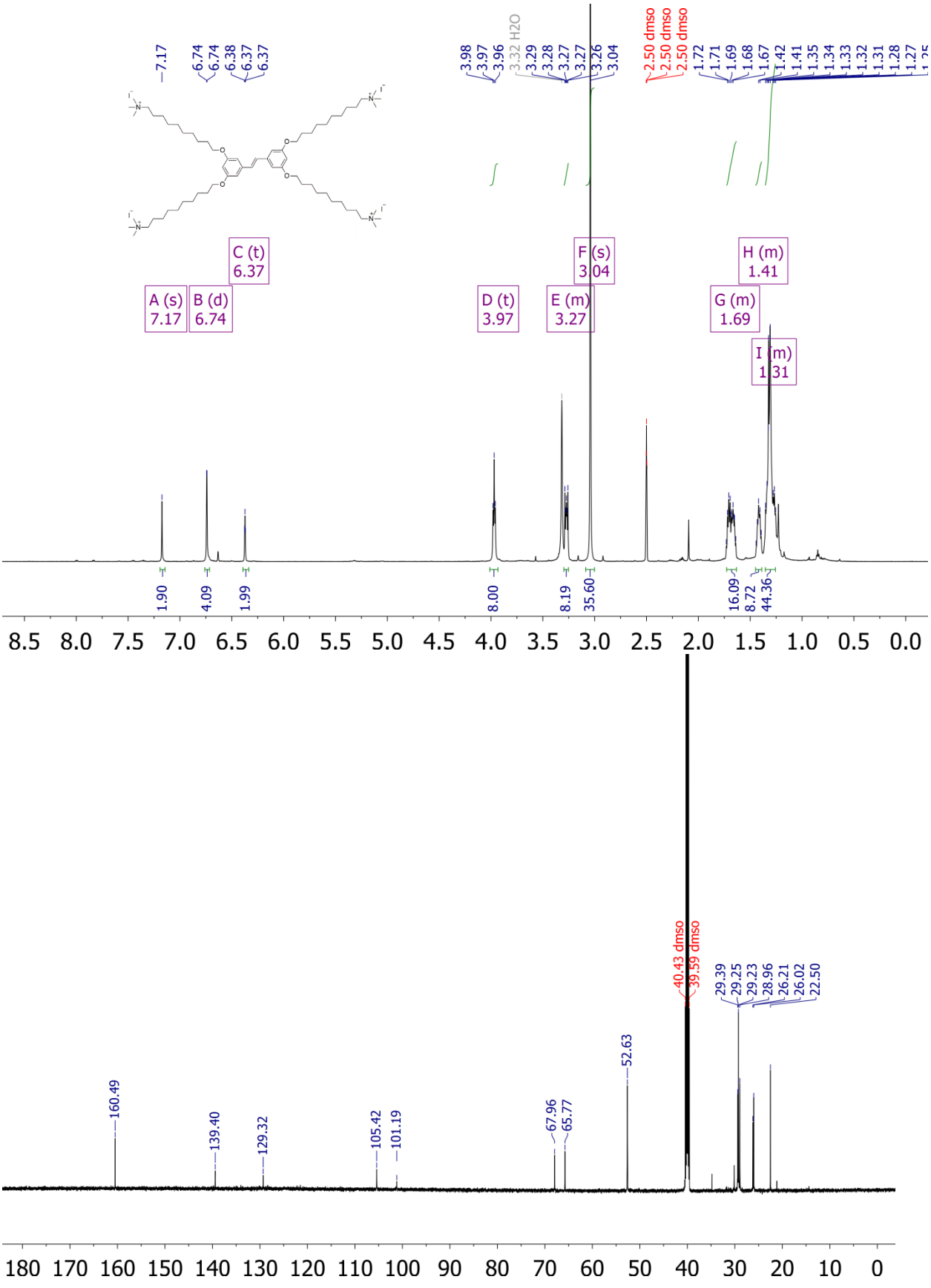
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2.50 dmso
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A (s) 7.17
B (d) 6.74
C (t) 6.37
D (t) 3.97
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F (s) 3.04
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H (m) 1.41
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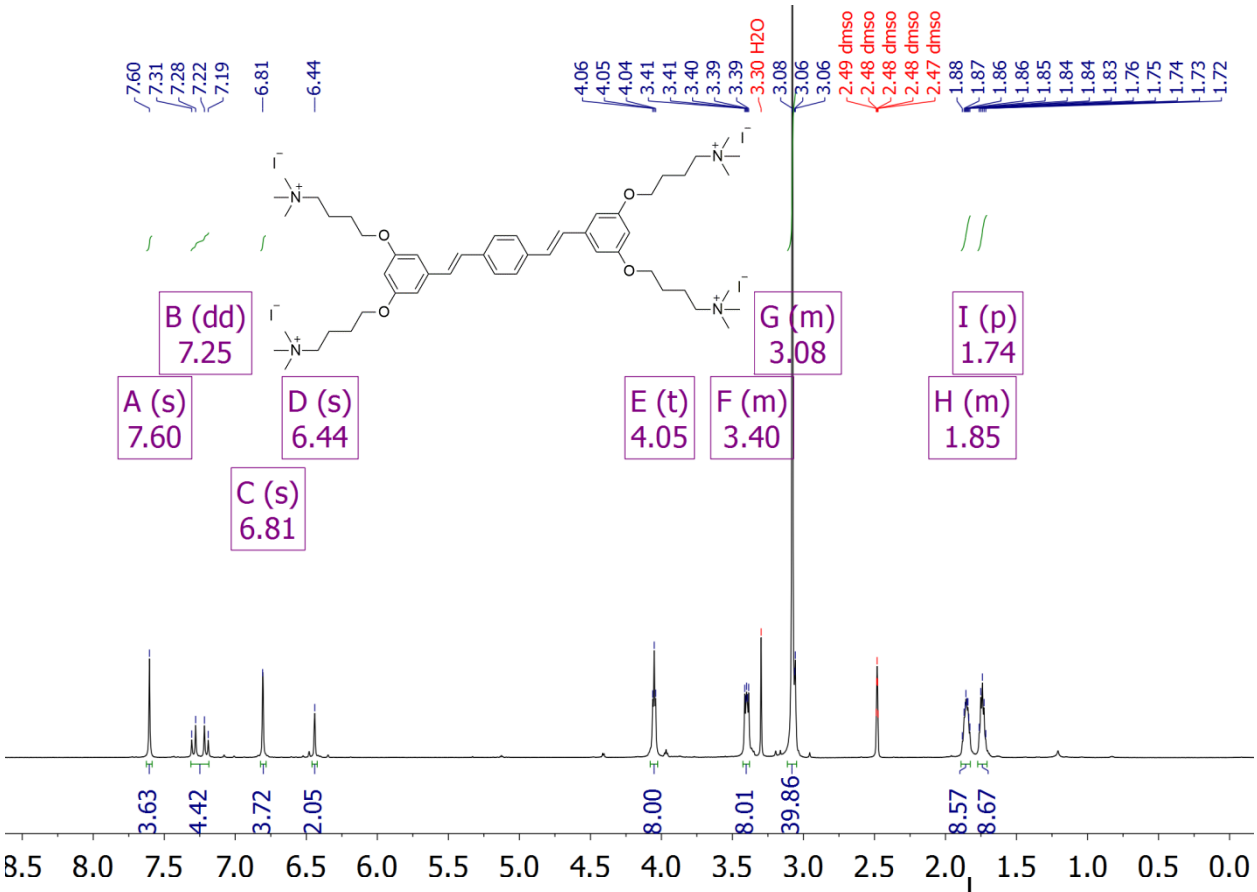
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2.48 dmso
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1.72
B (dd) 7.25
A (s) 7.60
D (s) 6.44
C (s) 6.81
E (t) 4.05
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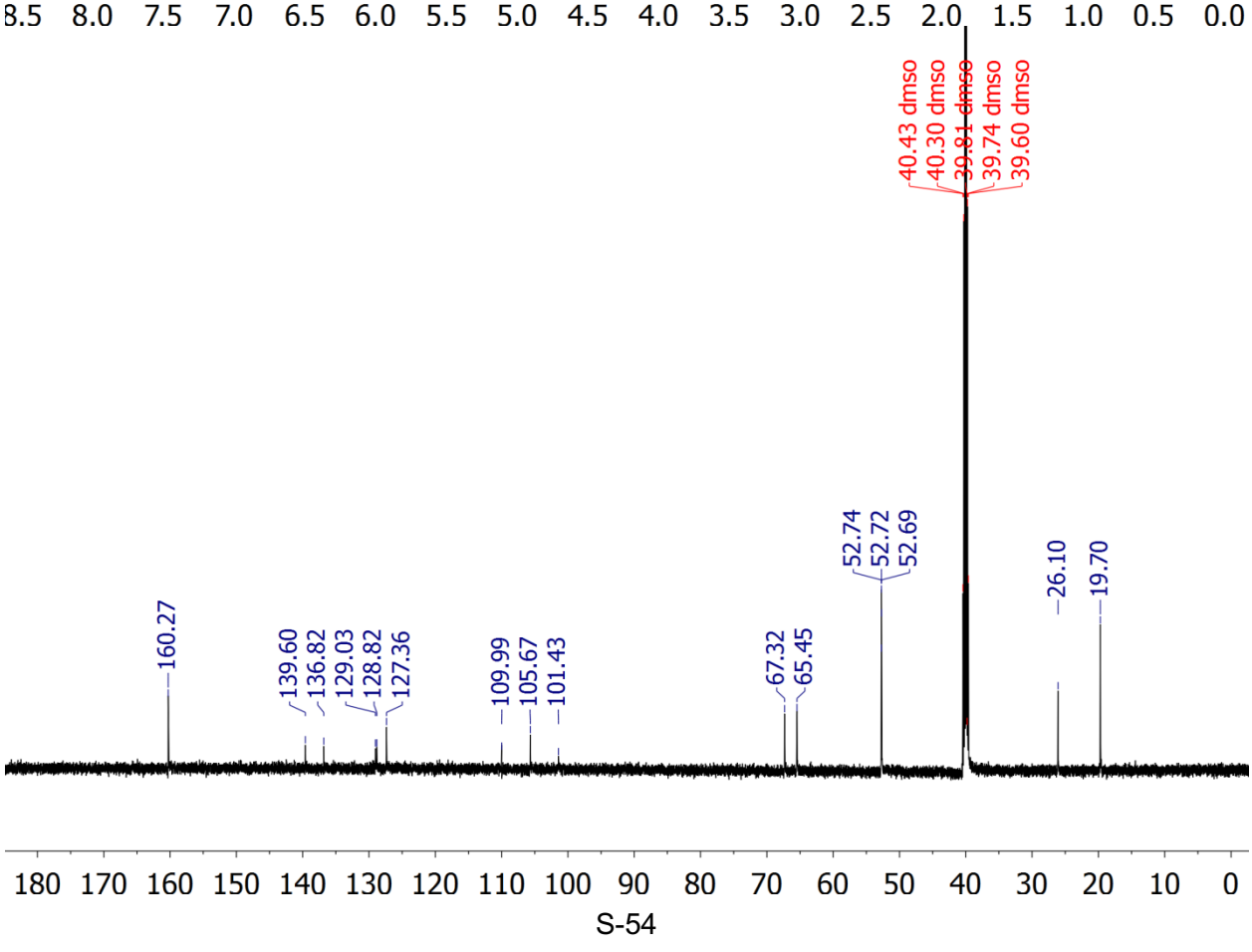
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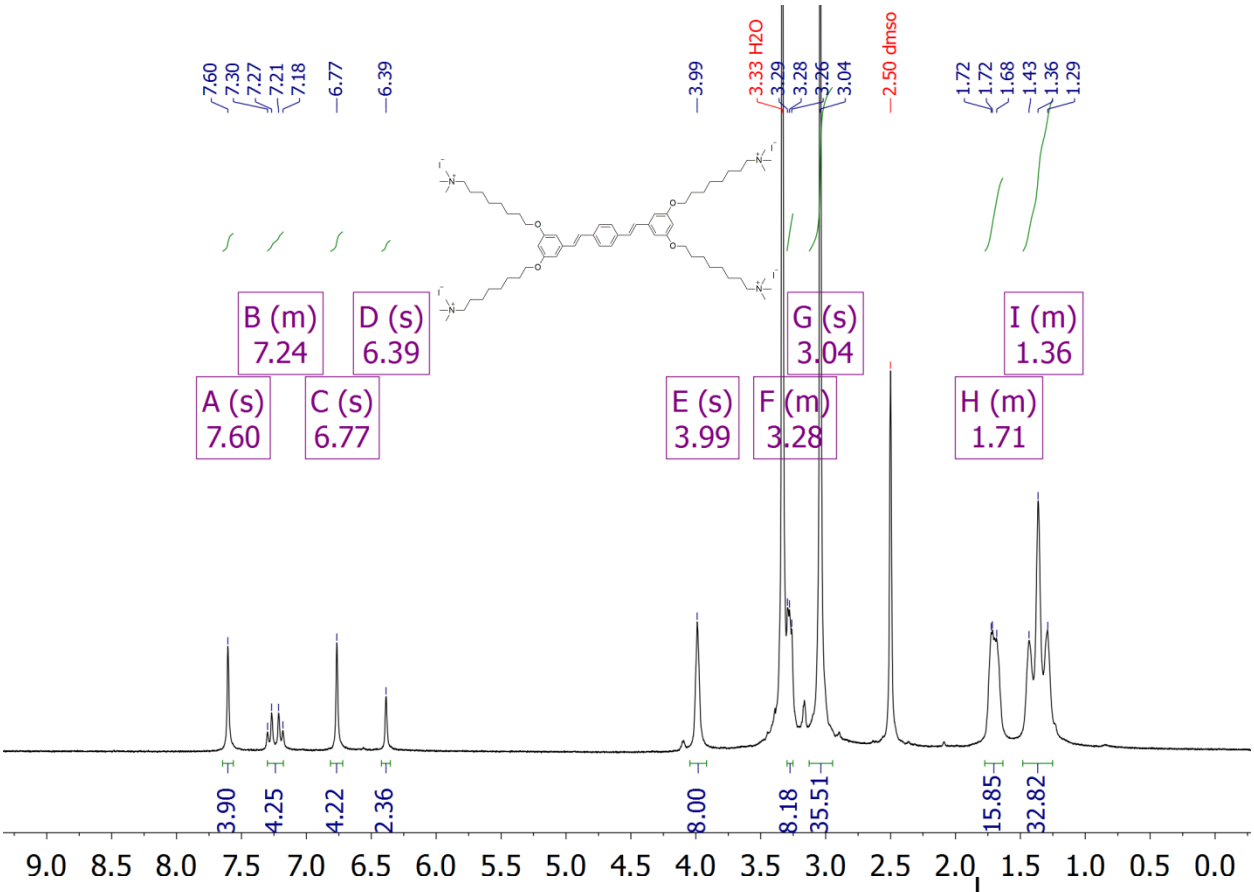
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3.04
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1.72
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1.29
B (m) 7.24
D (s) 6.39
G (s) 3.04
I (m) 1.36
A (s) 7.60
C (s) 6.77
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F (m) 3.28
H (m) 1.71
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4.25
4.22
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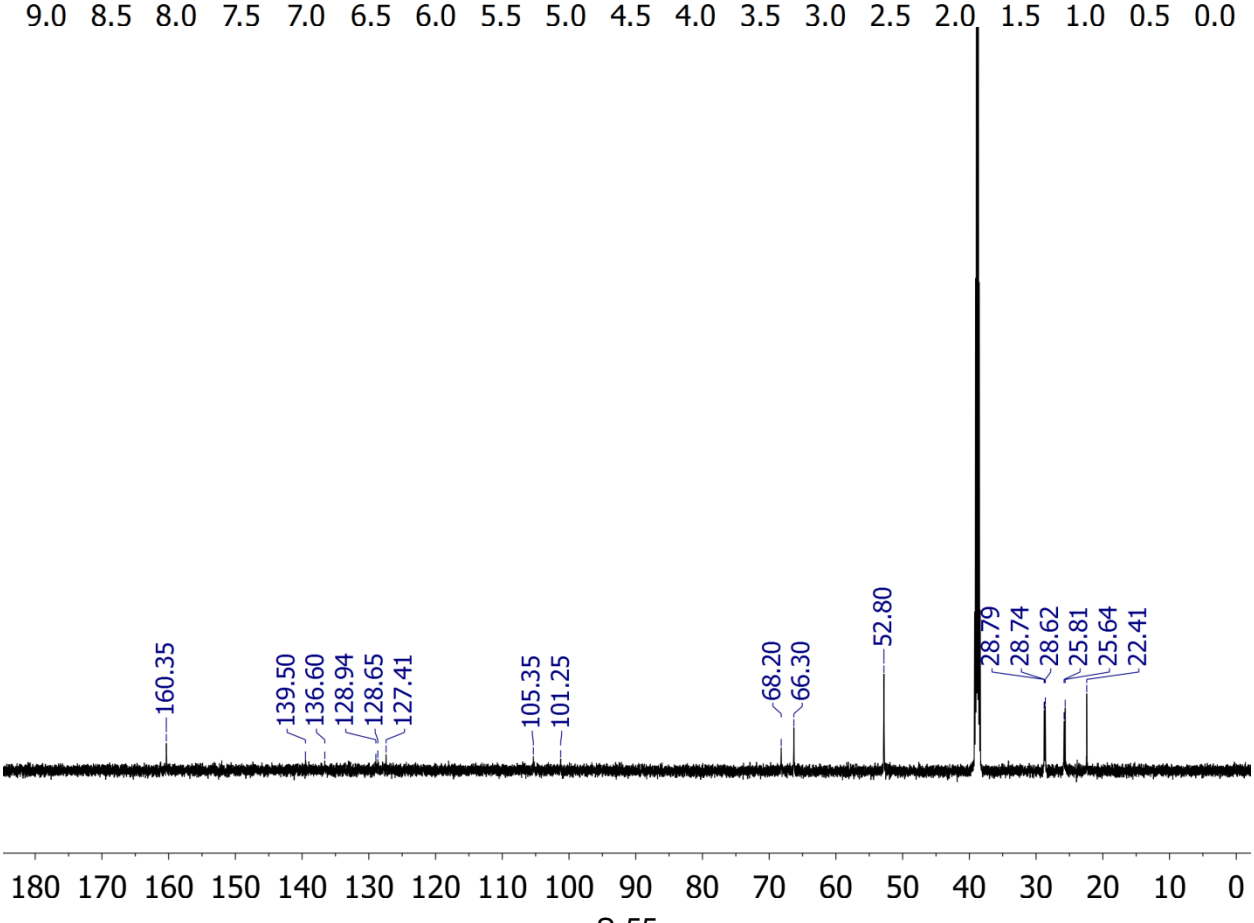
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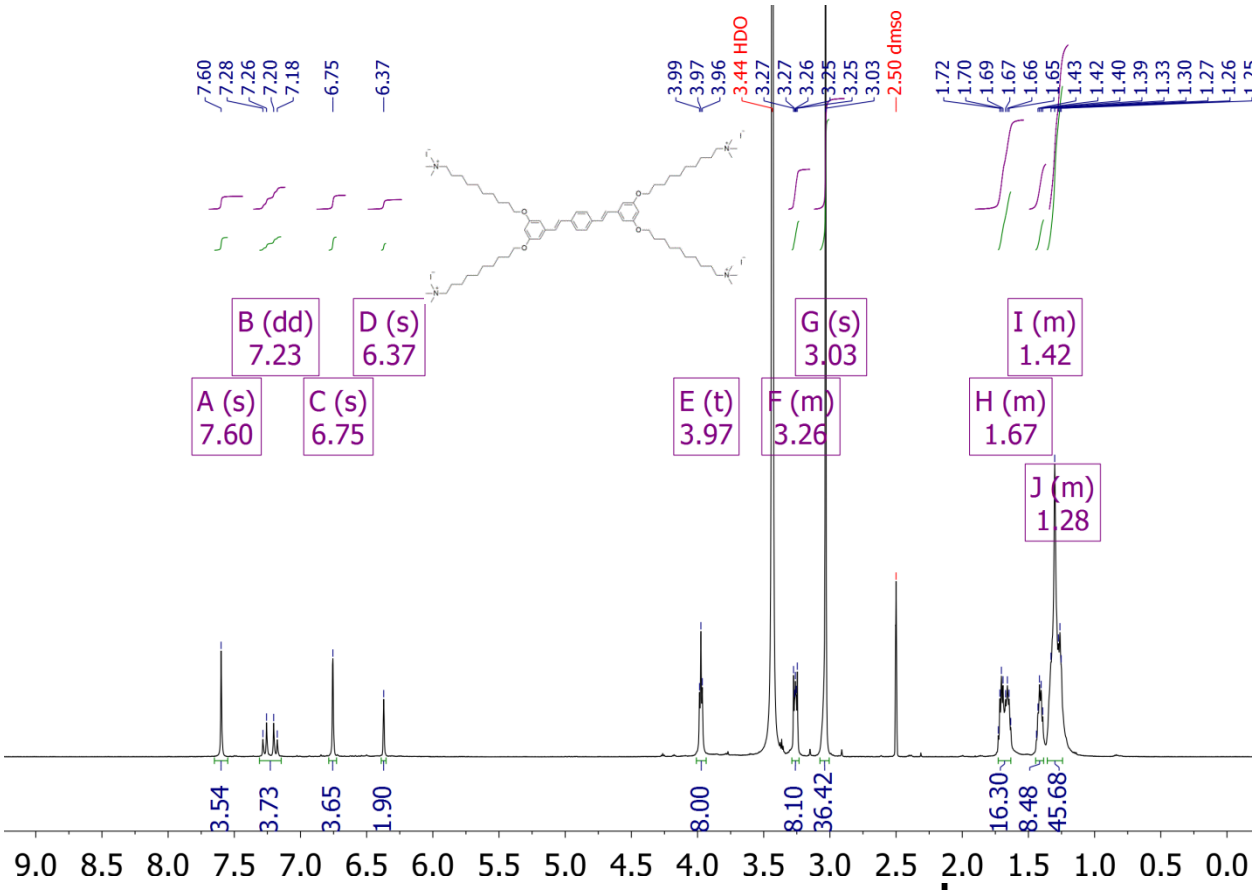
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3.27
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3.03
2.50 dmso
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1.26
B (dd) 7.23
D (s) 6.37
G (s) 3.03
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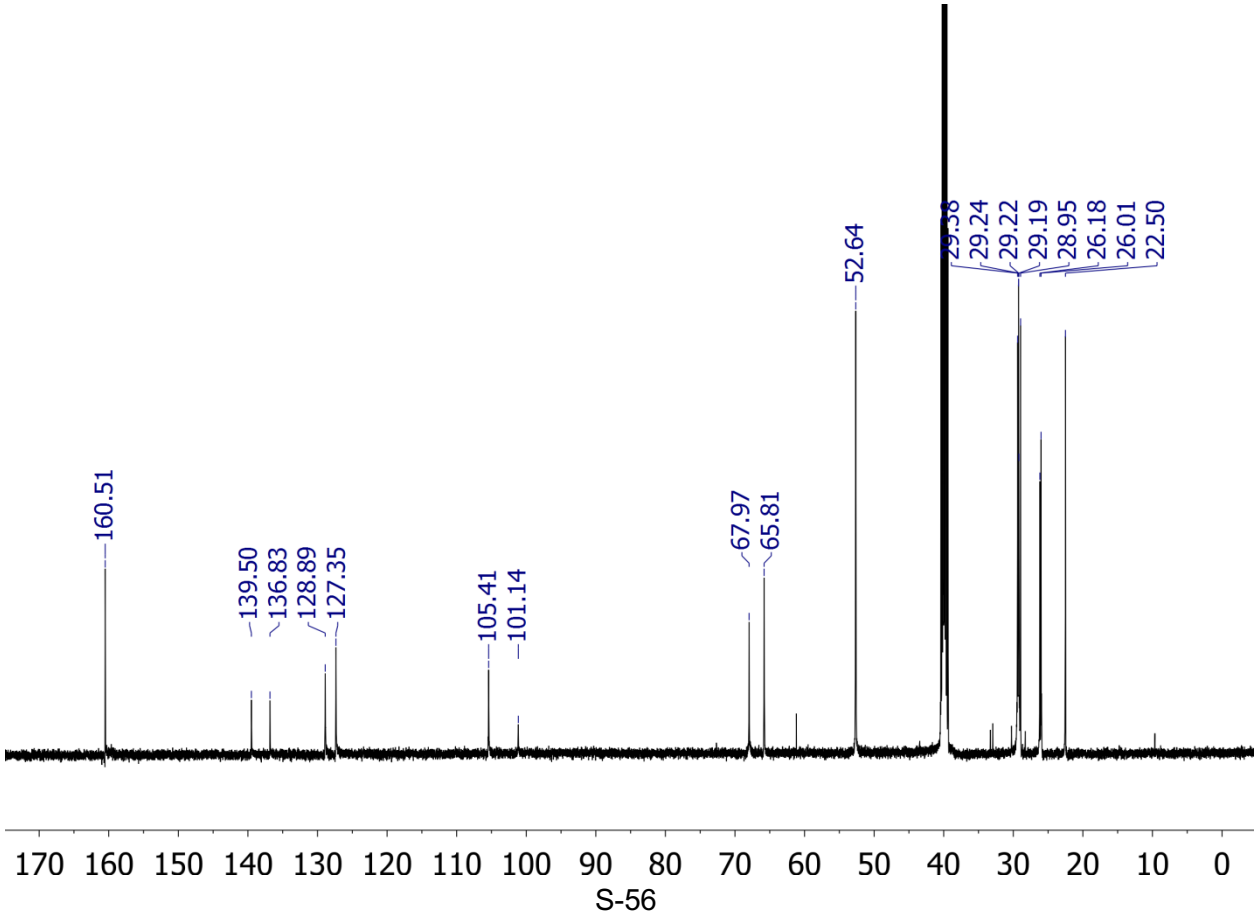
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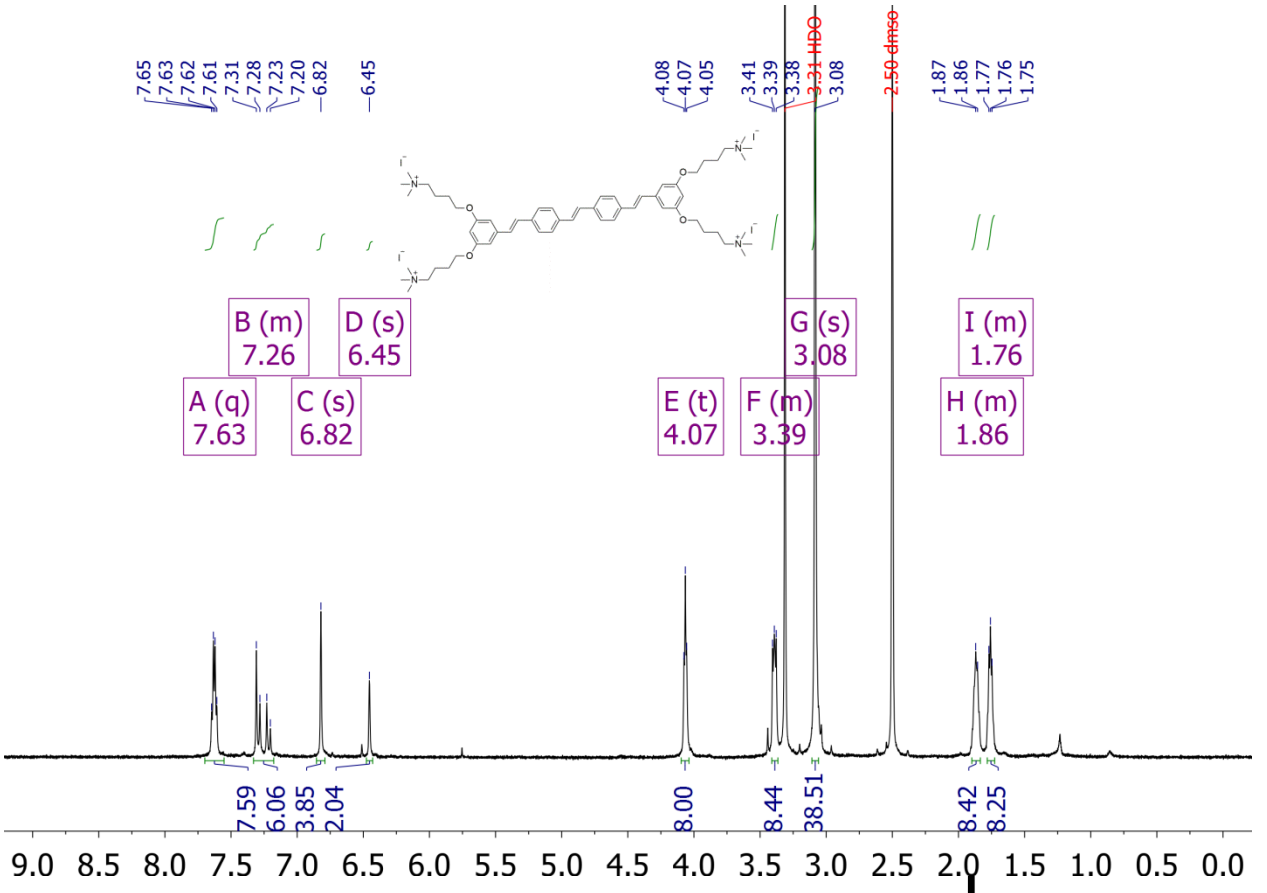
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B (m)
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D (s)
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H (m)
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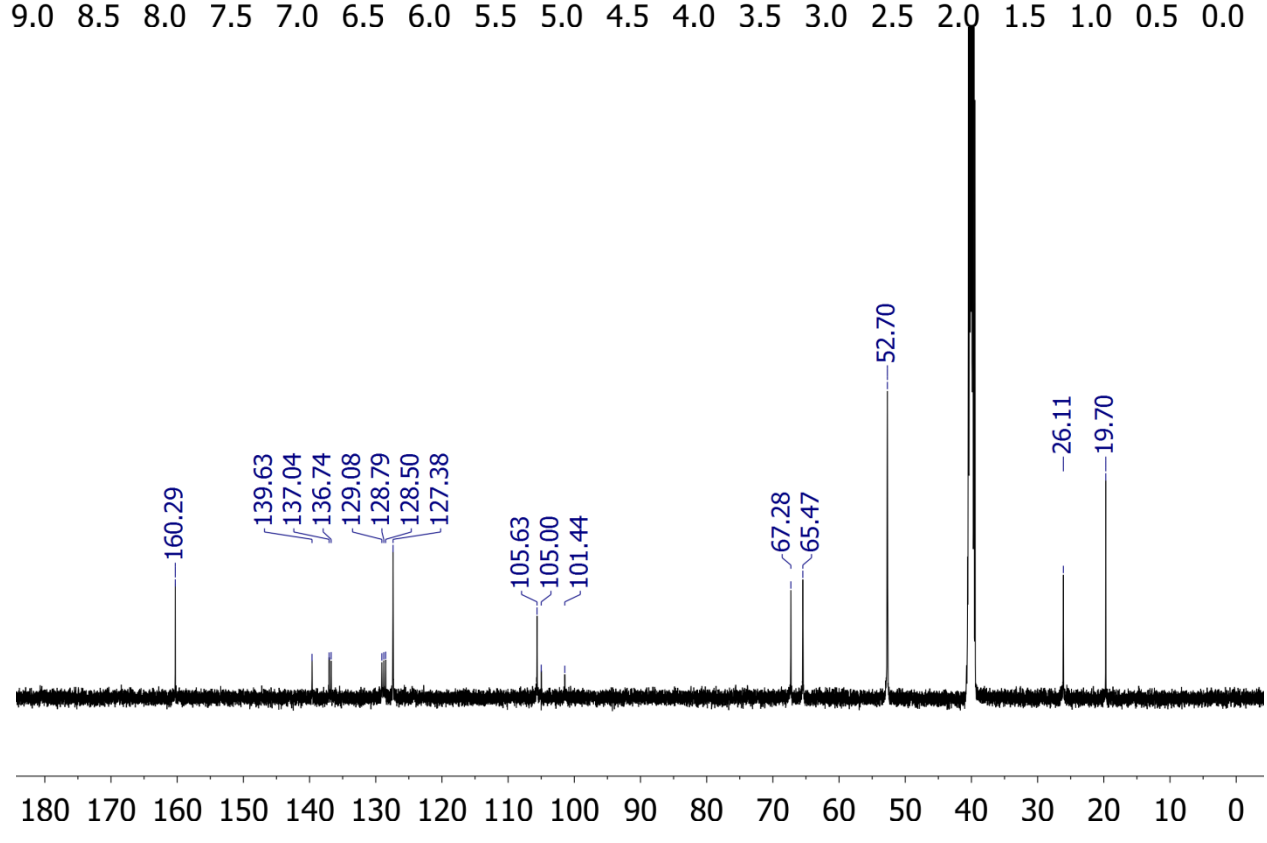
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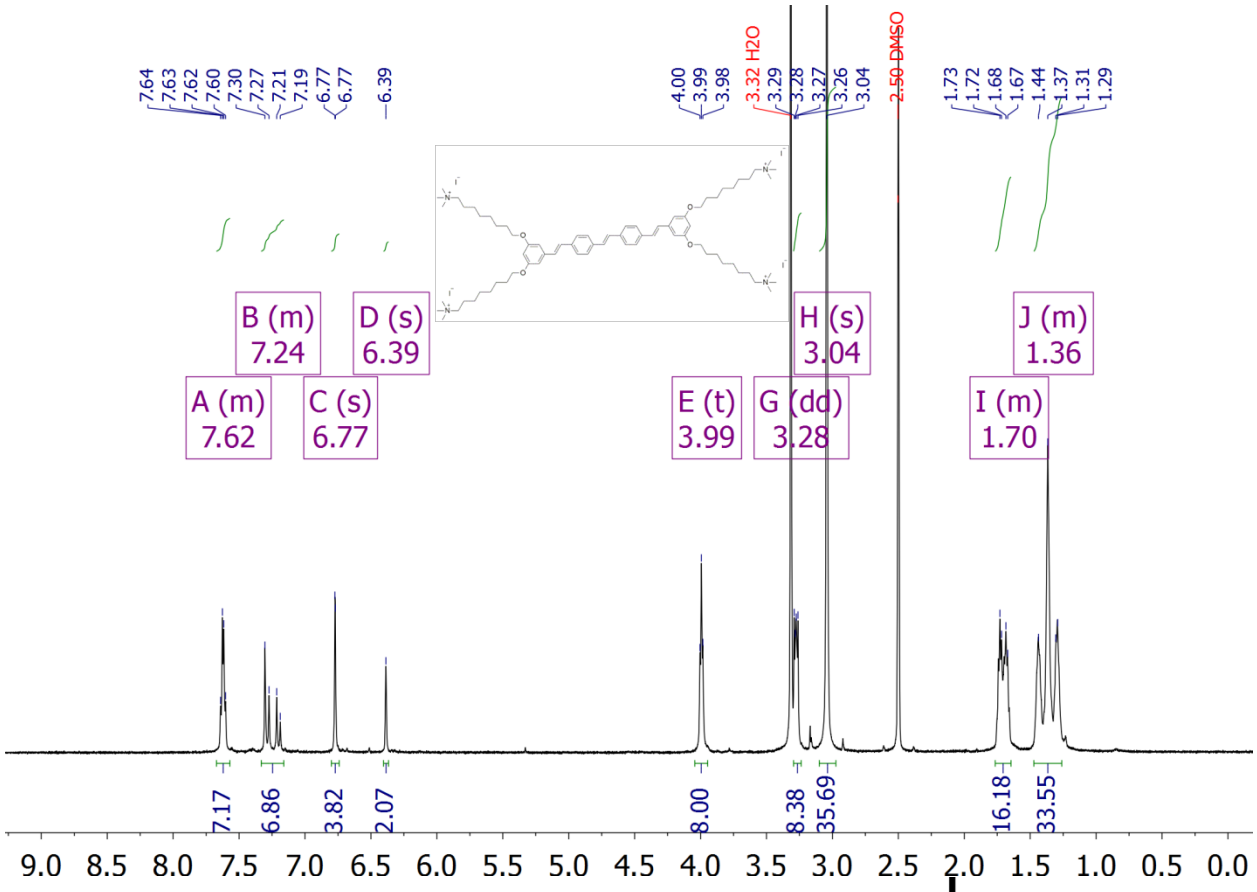
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H (s)
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J (m)
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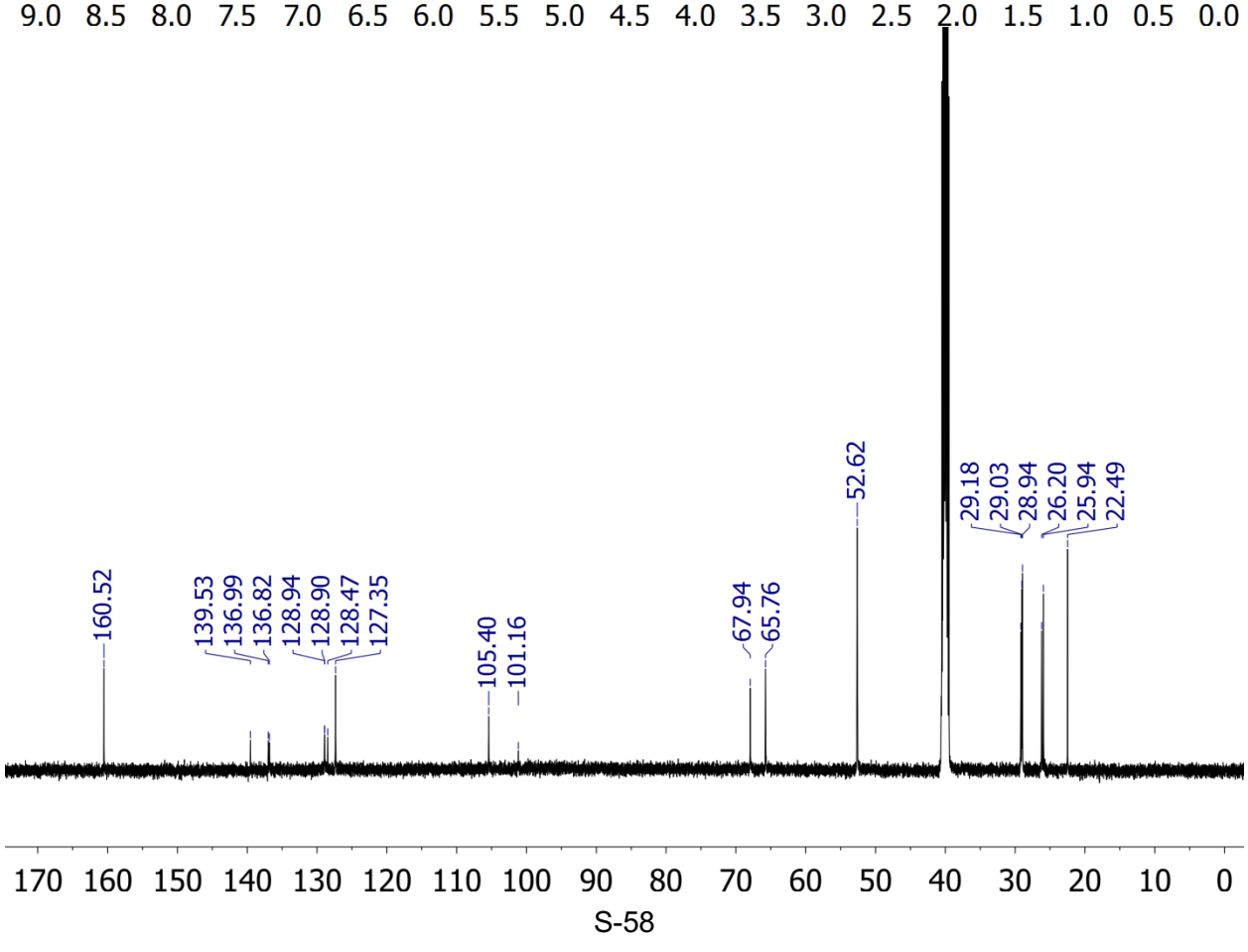
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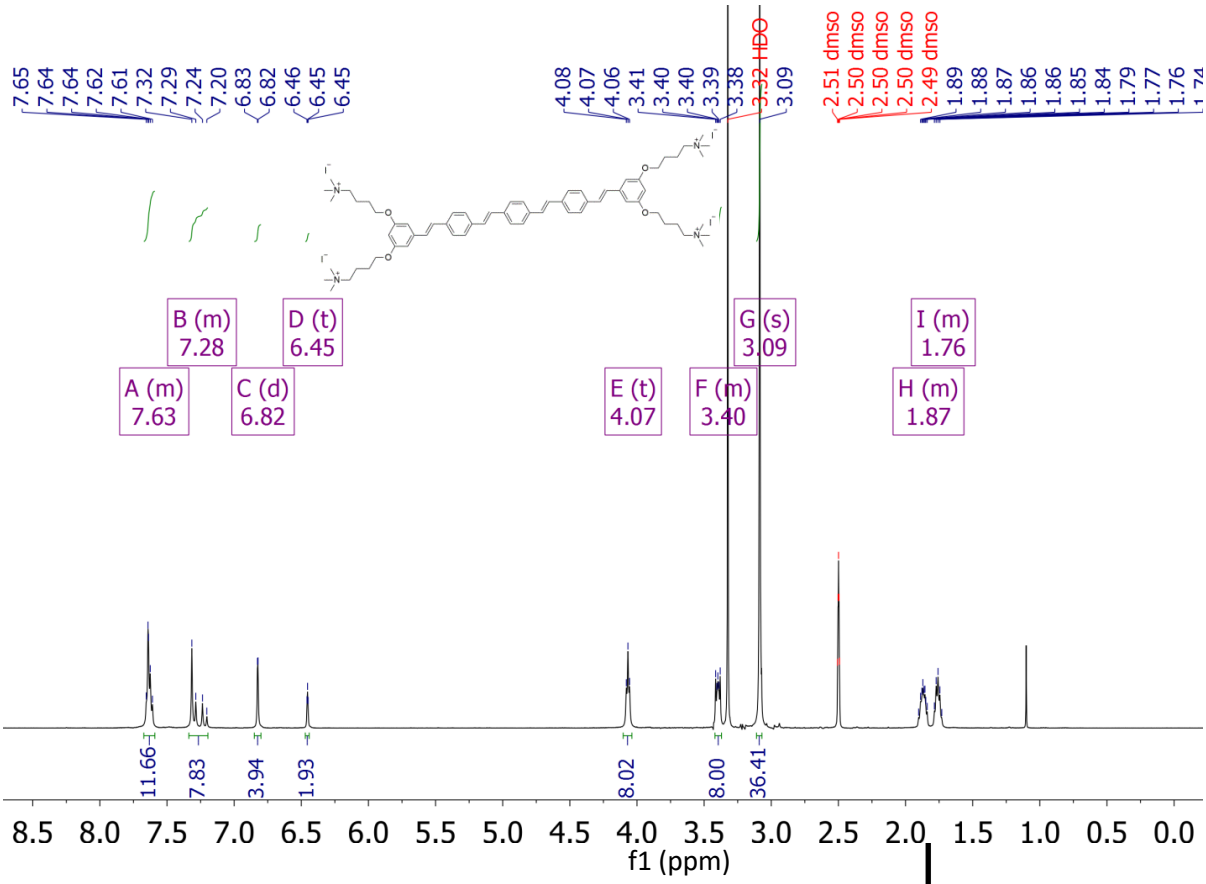
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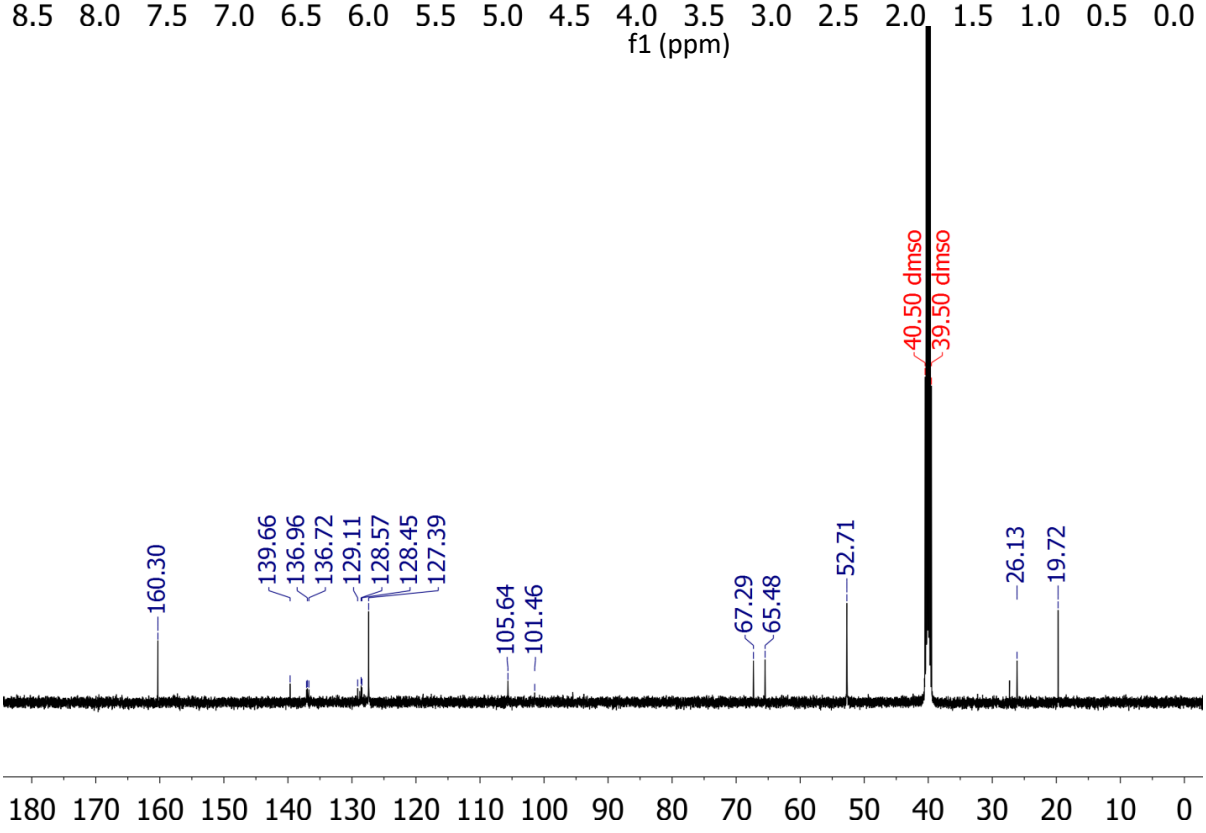
4.08 4.07 4.06 3.41 3.40 3.40 3.39 3.38 3.32 HDO 3.09
2.51 dmso 2.50 dmso 2.50 dmso 2.49 dmso 1.89 1.88 1.87 1.86 1.86 1.85 1.84 1.79 1.77 1.76
B (m) 7.28
D (t) 6.45
G (s) 3.09
I (m) 1.76
A (m) 7.63
C (d) 6.82
E (t) 4.07
F (m) 3.40
H (m) 1.87
11.66
7.83
3.94
1.93
8.02
8.00
36.41
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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65.48
52.71
26.13
19.72
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

References

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