Extending the architecture of bolaamphiphilic disinfectants: An investigation of octenidine and isooctenidine analogs

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I. General Information

All reagents and solvents were purchased from Sigma-Aldrich, TCI Chemicals, Pharmco and ThermoFisher Scientific and were used without further purification. Reactions were run in heated mineral oil baths (**Isooct-0,5**, **Isooct-0,6**, **Isooct-0,8**, and **Isooct-0,10**) or in pie blocks (Chemglass) with reagent grade solvents and magnetic stirring. ^{1}H and ^{13}C NMR spectra were measured with a 400 MHz and 500 MHz JEOL spectrophotometer, and chemical shifts were reported on a δ-scale (ppm) downfield from TMS. Coupling constants were calculated in hertz (Hz) The solvents used for NMR spectroscopy were chloroform-d ($CDCl_3$) and methanol-d (CD_3OD), with chemical shifts internally referenced to the solvent peak of 7.26 ppm ($CDCl_3$ ^{1}H), 77.16 ppm ($CDCl_3$ ^{13}C), 3.31 ppm (CD_3OD ^{1}H), and 49.15 ppm (CD_3OD ^{13}C). Mass spectrometry data was acquired using an AB SCIEX 3200 Q-TRAP using electrospray ionization in positive mode.

II. Biological Assays

For all biological assays, laboratory strains of methicillin-susceptible *Staphylococcus aureus* MSSA (SH1000), *Enterococcus faecalis* (OG1RF), *Escherichia coli* (MC4100), *Pseudomonas*

aeruginosa (PAO1), *Acinetobacter baumannii* (ATCC 17978), *Klebsiella pneumoniae* (ATCC 4352), community-acquired methicillin-resistant *Staphylococcus aureus* CA-MRSA (USA300-0114), and hospital-acquired methicillin-resistant *Staphylococcus aureus* HA-MRSA (ATCC 33591) were grown with shaking at 37 ºC overnight from freezer stocks in 5 mL of the indicated media: SH1000, OG1RF, MC4100, USA300-0114, ATCC 17978, ATCC 4352, and PAO1 were grown in BD™ Mueller-Hinton broth (MHB), whereas ATCC 33591 was grown in BD™ tryptic soy broth (TSB). Optical density (OD) measurements were obtained using a BioTek Synergy H1 Hybrid plate reader (Santa Clara, CA).

III. Minimum Inhibitory Concentration (MIC)

Compounds were serially diluted two-fold from stock solutions (1.0 mM) to yield twelve 100 µL test concentrations, wherein the starting concentration of dimethyl sulfoxide (DMSO) was 2.5%. Overnight *S. aureus, E. faecalis, E. coli, P. aeruginosa*, *A. baumannii* (ATCC 17978), *K. pneumoniae*, USA300-0114 (CA-MRSA), and ATCC 33591 (HA-MRSA) cultures were diluted to ca. 10^6 CFU/mL in MHB or TSB and regrown to mid-exponential phase, as determined by optical density recorded at 600 nm (OD_{600}). All cultures were then diluted again to ca. 10^6 CFU/mL and 100 µL were inoculated into each well of a U-bottom 96-well plate containing 100 µL of compound solution. Plates were incubated statically at 37 ºC for 72 h upon which wells were evaluated visually for bacterial growth. The MIC was determined as the lowest concentration of compound resulting in no bacterial growth visible to the naked eye, based on the highest value in three independent experiments. Aqueous DMSO controls were conducted as appropriate for each compound.

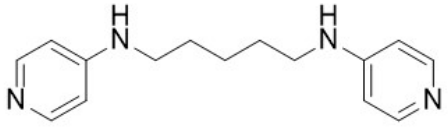
IV. Red Blood Cell (RBC) Lysis Assay ($Lysis_{20}$)

RBC lysis assays were performed on mechanically defibrinated sheep blood (Hemostat Labs: DSB030). An aliquot of 1.5 mL blood was placed into a microcentrifuge tube and centrifuged at 10,000 rpm for ten min. The supernatant was removed, and the cells were resuspended with 1 mL of phosphate-buffered saline (PBS). The suspension was centrifuged as described above, the supernatant was removed, and cells were resuspended 4 additional times in 1 mL PBS. The final cell suspension was diluted twenty-fold with PBS. Compounds were serially diluted with PBS two-fold from stock solutions (1.0 mM) to yield 100 µL of twelve test concentrations on a flat-bottom 96-well plate (Corning, 351172), wherein the starting concentration of DMSO was 2.5%. To each of the wells, 100 µL of the twenty-fold suspension dilution was then inoculated. The concentration of DMSO in the first well was 2.5%, resulting in DMSO-induced lysis at all concentrations >63 µM. TritonX (1% by volume) served as a positive control (100% lysis marker) and sterile PBS served as a negative control (0% lysis marker). Samples were then placed in an incubator at 37 ºC and shaken at 200 rpm. After 1 h, the samples were centrifuged at 2,000 rpm for ten min. The absorbance of the supernatant was measured with a UV spectrometer at a 540 nm wavelength. The concentration inducing 20% RBC lysis was then calculated for each compound based upon the absorbances of the TritonX and PBS controls. Aqueous DMSO controls were conducted as appropriate for each compound.[1-3]

1. ***Procedure adapted from:*** Peng, L.; DeSousa, J.; Su, Z.; Novak, B. M.; Nevzorov, A. A.; Garland, E. R.; Melander,C. *Chem. Comm.* **2011**, *47*, 4896-4898.
2. ***Optimized conditions are drawn from:*** Sæbø, I.P., Bjørås, M., Franzyk, H., Helgesen, E., Booth, J.A. Optimization of the hemolysis assay for the assessment of cytotoxicity. **2023**. *Int. J. Mol. Sci.*, *24*, 2914.
3. ***Commentary on suitability of RBC lysis as proxy for mammalian toxicity:*** Pagano, M., Faggio, C. The use of erythrocyte fragility to assess xenobiotic cytotoxicity. **2015** *Cell Bio. Funct.*, *33*, 351-355.

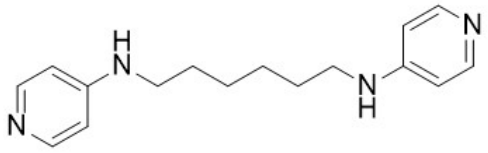
V. Synthetic Procedures

Preparation of Isooct-0,5



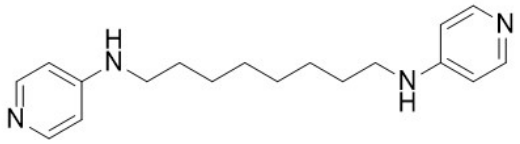
To a 40 mL reaction vial with a pressure relieving septum cap was added 4-chloropyridine hydrochloride (1.80 g, 12.0 mmol) and 1,5 diamino pentane bishydrochloride (0.845 g, 6.12 mmol). The mixture was vortexed for 30 seconds to thoroughly combine the powders. The vial was placed in an oil bath and heated to 227℃ for 5.5 hours and stirring began when the mixture had melted. The mixture was cooled to room temperature, then dissolved in boiling hot water. A solution of 15 mL saturated sodium bicarbonate and 40 mL distilled water was added, and the mixture was washed with 20 mL of dichloromethane. The aqueous layer was then brought to a pH of 12 using 6 M NaOH and was extracted dichloromethane (15 mL x 6), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure. A crude tan product was obtained (0.932 g) and was purified by trituration in 20 mL of 2:1 diethyl ether: hexanes. The product was isolated as a tan/yellow powdery solid (0.904 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.08 (m, 4H), 6.53 – 6.26 (m, 4H), 4.10 (s, 2H), 3.16 (td, J = 7.0, 5.6 Hz, 4H), 1.73 – 1.60 (m, 4H), 1.50 (d, J = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 155.0, 148.0, 41.8, 28.3, 24.2. Mass spectrum *m/z*: 257.4 ($[M+H]^+$; calculated for $[C_{15}H_{21}N_4]^+$: 257.2).

Preparation of Isooct-0,6



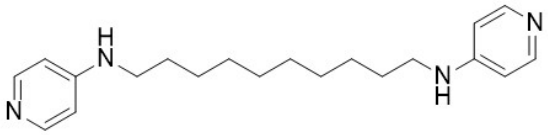
To a 40 mL reaction vial with a pressure relieving septum cap was added 4-chloropyridine hydrochloride (1.87 g, 12.5 mmol) and 1,6 diaminohexane bishydrochloride (0.977 g, 6.40 mmol). The mixture was vortexed for 30 seconds to thoroughly combine the powders. The vial was placed in an oil bath and heated to 227℃ for 5.5 hours and stirring began when the mixture had melted. The mixture was cooled to room temperature, then dissolved in boiling hot water. A solution of 15 mL saturated sodium bicarbonate and 40 mL distilled water was added, and the mixture was washed with 20 mL of dichloromethane. The aqueous layer was then brought to a pH of 12 using 6 M NaOH and was extracted using dichloromethane (15 mL x 10), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure. A crude pale-yellow product was obtained. An additional extraction with 30 mL of DCM was performed and the product was evaporated under reduced pressure and purified by trituration in 20 mL of 2:1 diethyl ether: hexanes. The product was isolated as a pale yellow powdery solid (0.663 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 4H), 6.43 – 6.37 (m, 4H), 4.09 (s, 2H), 3.14 (td, J = 7.1, 5.6 Hz, 4H), 1.66 – 1.58 (m, 4H), 1.50 – 1.35 (m, 4H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ 155.0, 148.0, 41.8, 28.5, 26.5. Mass spectrum *m/z*: 271.4 ($[M+H]^+$; calculated for $[C_{16}H_{23}N_4]^+$: 271.2).

Preparation of Isooct-0,8



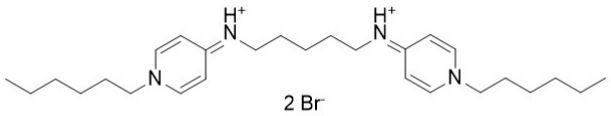
To a 40 mL reaction vial with a pressure relieving septum cap was added 4-chloropyridine hydrochloride (1.21 g, 8.03 mmol) and 1,8 diaminooctane (0.294 g, 2.03 mmol). The mixture was vortexed for 30 seconds to thoroughly combine the powders. The vial was placed in an oil bath and heated to 227°C for 5.5 hours and stirring began when the mixture had melted. The mixture was cooled to room temperature, then dissolved in boiling hot water. A solution of 10 mL saturated sodium bicarbonate and 25 mL distilled water was added, and the mixture was washed with 15 mL of dichloromethane. The aqueous layer was then brought to a pH of 12 using 6 M NaOH and was extracted using dichloromethane (10 mL x 5), dried with anhydrous $MgSO_4$, and evaporated under reduced pressure. A crude tan product was obtained (0.395 g) and was purified by trituration in 12 mL of 2:1 diethyl ether: hexanes. The product was isolated as a tan powdery solid (0.3419 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 7.88 (m, 4H), 6.47 – 6.25 (m, 4H), 4.09 (s, 2H), 3.12 (td, J = 7.1, 5.5 Hz, 4H), 1.60 (p, J = 7.2 Hz, 4H), 1.36 (d, J = 9.3 Hz, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.5, 150.0, 112.2, 107.5, 42.7, 29.3, 29.2, 27.0. Mass spectrum *m/z*: 299.4 ($[M+H]^+$; calculated for $[C_{18}H_{27}N_4]^+$: 299.2).

Preparation of Isooct-0,10



To a 40 mL reaction vial with a pressure relieving septum cap was added 4-chloropyridine hydrochloride (2.48 g, 16.5 mmol) and 1,10 diaminodecane (0.733 g, 4.25 mmol). The mixture was vortexed for 30 seconds to thoroughly combine the powders. The vial was placed in an oil bath and heated to 227°C for 5.5 hours and stirring began when the mixture had melted. The mixture was cooled to room temperature, then dissolved in boiling hot water. A solution of 20 mL saturated sodium bicarbonate and 50 mL distilled water was added, and the mixture was washed with 20 mL of dichloromethane, and its extracted products were discarded. The aqueous layer was then brought to a pH of 12 using 6 M NaOH and was extracted using dichloromethane (15 mL x 7), dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. A crude tan product was obtained (1.01 g) and was purified by trituration in 12 mL of 2:1 diethyl ether: hexanes. The product was isolated as a tan solid (1.01 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 4H), 6.44 – 6.39 (m, 4H), 4.19 (s, 2H), 3.12 (td, J = 7.1, 5.4 Hz, 4H), 1.60 (p, J = 7.1 Hz, 4H), 1.29 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 153.6, 150.8, 150.0, 112.2, 107.5, 42.7, 29.5, 29.4, 29.2, 27.1. Mass spectrum *m/z*: 327.4 ($[M+H]^+$; calculated for $[C_{20}H_{31}N_4]^+$: 327.3).

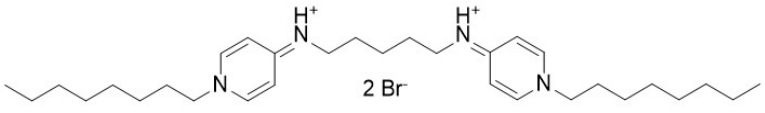
Preparation of Isooct-6,5



Note: compounds in the SI are drawn as the iminium resonance form, to highlight the differentiation of the pseudoaromatic protons

To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.101 g, 0.394 mmol), 1-bromohexane (110 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan and sticky crude material was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a tan flaky powder (0.243 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (t, *J* = 5.4 Hz, 2H), 8.07 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.69 (dd, *J* = 7.3, 2.8 Hz, 2H), 7.59 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.82 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.08 (t, *J* = 7.2 Hz, 4H), 3.34 (q, *J* = 5.9 Hz, 4H), 1.65 (d, *J* = 22.1 Hz, 6H), 1.29 (d, *J* = 4.4 Hz, 16H), 0.91 – 0.83 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.2, 139.8, 111.9, 106.0, 58.4, 42.8, 31.2, 31.1, 27.3, 25.8, 24.1, 22.5, 14.0. Mass spectrum *m/z*: 505.5 ([M-Br]$^{+}$; calculated for $[C_{27}H_{46}N_4Br]^{+}$: 505.3).

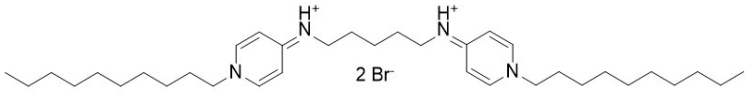
Preparation of Isooct-8, 5



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.103 g, 0.402 mmol), 1-bromooctane (139 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was

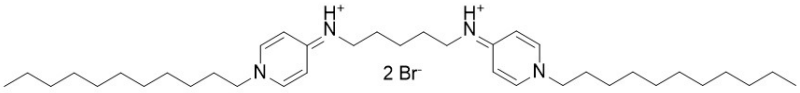
dried under reduced pressure, and a tan and sticky crude material was obtained. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a pale yellow semi-sticky powder (0.225 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 2H), 8.03 (dd, *J* = 18.8, 7.0 Hz, 2H), 7.70 (dd, *J* = 7.4, 2.8 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 6.81 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.07 (t, *J* = 7.2 Hz, 4H), 3.35 (q, *J* = 5.9 Hz, 4H), 1.84 – 1.74 (m, 6H), 1.25 (dd, *J* = 13.8, 8.9 Hz, 24H), 0.91 – 0.80 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.2, 139.7, 111.9, 106.0, 58.4, 42.8, 31.7, 31.23, 31.18, 29.09, 29.08, 27.3, 26.8, 24.1, 22.6, 22.5, 14.1, 14.0. Mass spectrum *m/z*: 561.5 ([M-Br]$^{+}$; calculated for $[C_{31}H_{54}N_4Br]^{+}$: 561.4).

Preparation of Isooct-10, 5



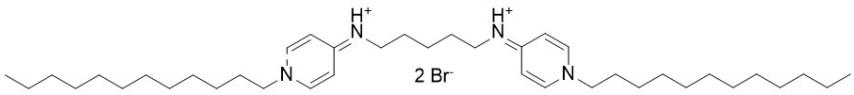
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.106 g, 0.413 mmol), 1-bromodecane (165 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a pale orange crude material was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a pale orange powder (0.260 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (t, *J* = 5.5 Hz, 2H), 8.04 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.70 (dd, *J* = 7.4, 2.9 Hz, 2H), 7.56 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.81 (dd, *J* = 7.4, 2.9 Hz, 2H), 4.07 (t, *J* = 7.3 Hz, 4H), 3.35 (q, *J* = 5.9 Hz, 4H), 1.85 – 1.75 (m, 6H), 1.27 – 1.16 (m, 32H), 0.90 – 0.81 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.2, 139.7, 111.9, 106.0, 58.4, 42.8, 31.9, 31.2, 29.5, 29.4, 29.3, 29.1, 27.3, 26.2, 24.1, 22.7, 14.2. Mass spectrum *m/z*: 617.6 ([M-Br]$^{+}$; calculated for $[C_{35}H_{62}N_4Br]^{+}$: 617.4).

Preparation of Isooct-11, 5



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.105 g, 0.410 mmol), 1-bromoundecane (179 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a pale-yellow crude material was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a pale-yellow powder (0.244 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (t, *J* = 5.5 Hz, 2H), 8.12 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.65 (qd, *J* = 7.4, 2.2 Hz, 4H), 6.83 (dd, J = 7.4, 2.6 Hz, 2H), 4.10 (t, *J* = 7.3 Hz, 4H), 3.34 (q, *J* = 5.9 Hz, 4H), 1.79 (dq, *J* = 13.5, 6.6 Hz, 6H), 1.26 (d, *J* = 21.9 Hz, 36H), 0.90 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.2, 139.7, 111.9, 106.0, 58.4, 42.8, 32.0, 31.2, 29.60, 29.57, 29.5, 29.3, 29.1, 27.3, 26.2, 24.1, 22.74, 14.2. Mass spectrum *m/z*: 645.6 ([M-Br]$^{+}$; calculated for $[C_{37}H_{66}N_4Br]^{+}$: 645.4).

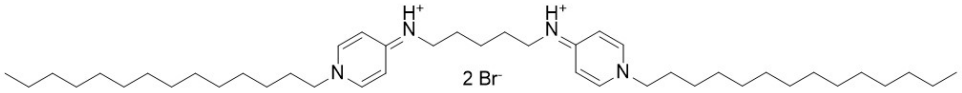
Preparation of Isooct-12,5



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.107 g, 0.417 mmol), 1-bromododecane (192 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified

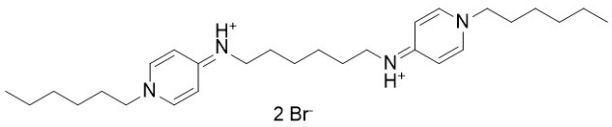
via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a pale yellow semi-sticky powder (0.216 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 2H), 8.07 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.69 (dd, *J* = 7.4, 2.8 Hz, 2H), 7.58 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.82 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.08 (t, *J* = 7.3 Hz, 4H), 3.34 (q, *J* = 5.9 Hz, 4H), 1.83 – 1.73 (m, 6H), 1.27 (d, *J* = 11.8 Hz, 40H), 0.90 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.4, 143.1, 139.6, 112.0, 106.0, 58.4, 42.8, 32.0, 31.2, 29.7, 29.6, 29.5, 29.4, 29.1, 27.2, 26.2, 24.1, 22.8, 14.2. Mass spectrum m/z: 675.6 ([M-Br]$^{+}$; calculated for $[C_{39}H_{70}N_4{}^{81}Br]^{+}$: 675.5).

Preparation of Isooct-14,5



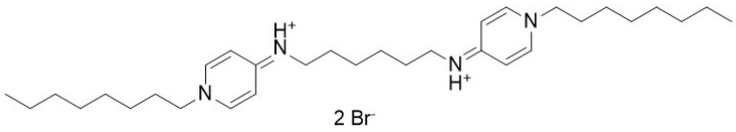
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,5** (0.103 g, 0.402 mmol), 1-bromotetradecane (238 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a white sticky crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a white flaky powder (0.319 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 2H), 8.06 (d, *J* = 7.4 Hz, 2H), 7.70 (dd, *J* = 7.4, 2.7 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 6.82 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.07 (t, *J* = 7.3 Hz, 4H), 3.36 – 3.30 (m, 4H), 1.78 (dd, *J* = 14.6, 7.1 Hz, 6H), 1.24 (d, *J* = 2.6 Hz, 48H), 0.90 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.2, 139.6, 112.0, 106.0, 58.4, 42.8, 32.0, 31.2, 29.8, 29.73, 29.72, 29.67, 29.62, 29.59, 29.5, 29.4, 29.1, 27.3, 26.2, 22.8, 14.21, 14.20. Mass spectrum m/z: 731.6 ([M-Br]$^{+}$; calculated for $[C_{43}H_{78}N_4Br]^{+}$: 731.0).

Preparation of Isooct-6,6



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.114 g, 0.423 mmol), 1-bromohexane (110 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan sticky crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a light tan flaky powder (0.240 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (t, *J* = 5.8 Hz, 2H), 8.02 – 7.96 (m, 2H), 7.72 (dd, *J* = 7.4, 2.9 Hz, 2H), 7.61 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.76 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.15 – 3.99 (m, 4H), 3.33 (dq, *J* = 11.1, 6.1 Hz, 4H), 1.84 – 1.69 (m, 8H), 1.32 – 1.25 (m, 16H), 0.90 – 0.81 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.1, 139.8, 111.9, 105.8, 58.4, 42.7, 31.2, 31.1, 27.6, 26.0, 25.8, 22.5, 14.0. Mass spectrum *m/z*: 519.4 ($[M\text{-}Br]^+$; calculated for $[C_{28}H_{48}N_4Br]^+$: 519.3).

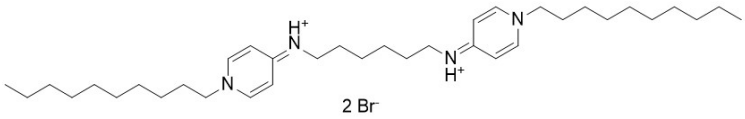
Preparation of Isooct-8,6



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.109 g, 0.403 mmol), 1-bromooctane (139 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via

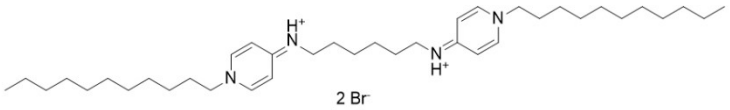
trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a light tan flaky powder (0.243 g, 91.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (t, *J* = 5.6 Hz, 2H), 8.05 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.67 (qd, *J* = 7.4, 2.2 Hz, 4H), 6.78 (dd, *J* = 7.5, 2.6 Hz, 2H), 4.10 (t, *J* = 7.3 Hz, 4H), 3.34 (q, *J* = 6.2 Hz, 4H), 1.76 (dd, *J* = 34.7, 7.2 Hz, 8H), 1.31 – 1.15 (m, 24H), 0.90 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 143.1, 139.8, 111.9, 105.8, 58.4, 42.7, 31.7, 31.2, 29.10, 29.09, 27.6, 26.2, 26.0, 22.7. Mass spectrum *m/z*: 575.6 ([M-Br]$^{+}$; calculated for $[C_{32}H_{56}N_4Br]^{+}$: 575.4).

Preparation of Isooct-10,6



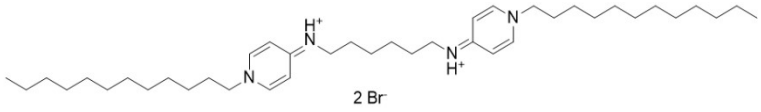
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.108 g, 0.399 mmol), 1-bromodecane (165 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a light tan semi-sticky crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a light tan flaky powder (0.275 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (t, *J* = 5.8 Hz, 2H), 8.05 – 7.97 (m, 2H), 7.72 (dd, *J* = 7.4, 2.8 Hz, 2H), 7.61 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.77 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.08 (t, *J* = 7.3 Hz, 4H), 3.34 (q, *J* = 6.3 Hz, 4H), 1.90 – 1.64 (m, 8H), 1.24 (s, 32H), 0.92 – 0.80 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 143.1, 139.8, 111.9, 105.8, 58.4, 42.7, 31.9, 31.2, 29.5, 29.31, 29.14, 29.13, 27.6, 26.2, 25.9, 22.7, 14.2. Mass spectrum *m/z*: 631.6 ([M-Br]$^{+}$; calculated for $[C_{36}H_{64}N_4Br]^{+}$: 631.4).

Preparation of Isooct-11,6



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.110 g, 0.407 mmol), 1-bromoundecane (179 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow sticky crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow semi-sticky powder (0.291 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (t, *J* = 5.7 Hz, 2H), 8.06 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.67 (qd, *J* = 7.4, 2.2 Hz, 4H), 6.78 (dd, *J* = 7.5, 2.6 Hz, 2H), 4.10 (t, *J* = 7.2 Hz, 4H), 3.34 (q, *J* = 6.3 Hz, 4H), 1.89 – 1.57 (m, 8H), 1.26 (d, *J* = 21.1 Hz, 36H), 0.86 (t, J = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.1, 139.8, 112.0, 105.9, 58.4, 42.7, 32.0, 31.2, 29.61, 29.57, 29.5, 29.4, 29.1, 27.5, 26.2, 25.9, 22.7, 14.2. Mass spectrum *m/z*: 659.6 ([M-Br]$^{+}$; calculated for $[C_{38}H_{68}N_4Br]^{+}$: 659.5).

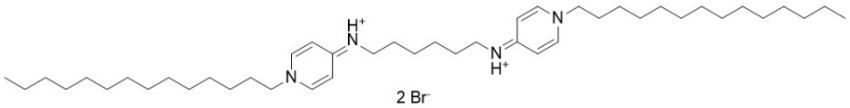
Preparation of Isooct-12,6



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.107 g, 0.396 mmol), 1-bromododecane (192 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes twice and a yellow flaky material (0.292

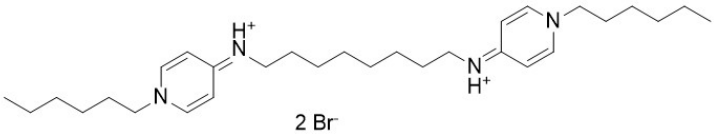
g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (t, *J* = 5.7 Hz, 2H), 8.07 – 7.97 (m, 2H), 7.69 (dd, *J* = 7.4, 2.8 Hz, 2H), 7.64 (dd, *J* = 7.4, 1.9 Hz, 2H), 6.78 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.09 (t, *J* = 7.3 Hz, 4H), 3.33 (p, *J* = 6.6 Hz, 4H), 1.77 (dt, *J* = 33.9, 6.3 Hz, 8H), 1.26 (d, *J* = 21.2 Hz, 40H), 0.91 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.0, 139.7, 112.0, 105.8, 58.4, 42.7, 32.0, 31.2, 29.66, 29.65, 29.6, 29.5, 29.4, 29.1, 27.5, 26.2, 25.9, 22.8, 14.2. Mass spectrum *m/z*: 687.6 ([M-Br]$^{+}$; calculated for $[C_{40}H_{72}N_4Br]^{+}$: 687.5).

Preparation of Isooct-14,6



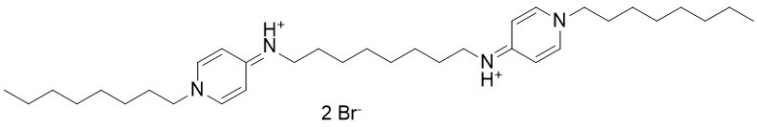
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,6** (0.108 g, 0.399 mmol), 1-bromotetradecane (238 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow powder (0.292 g) which was triturated again to produce a yellow flaky material (0.254 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (t, *J* = 5.8 Hz, 2H), 8.04 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.70 (dd, *J* = 7.4, 2.7 Hz, 2H), 7.64 (dd, *J* = 7.4, 1.8 Hz, 2H), 6.78 (dd, *J* = 7.5, 2.7 Hz, 2H), 4.09 (t, *J* = 7.2 Hz, 4H), 3.43 – 3.29 (m, 4H), 1.51 (m, 8H), 1.32 – 1.17 (m, 48H), 0.86 (t, *J* = 6.7 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.0, 139.7, 112.0, 105.9, 58.4, 42.7, 32.0, 31.1, 29.77, 29.76, 29.73, 29.72, 29.67, 29.6, 29.5, 29.4, 29.2, 27.5, 26.2, 25.9, 22.8, 14.2. Mass spectrum *m/z*: 743.7 ([M-Br]$^{+}$; calculated for $[C_{44}H_{80}N_4Br]^{+}$: 743.6).

Preparation of Isooct-6,8



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.139 g, 0.466 mmol), 1-bromohexane (110 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan sticky crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow powder (0.239 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (t, *J* = 5.5 Hz, 2H), 7.96 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.84 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.77 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.65 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.19 – 4.04 (m, 4H), 3.28 (q, *J* = 6.3 Hz, 4H), 1.88 – 1.67 (m, 12H), 1.39 – 1.23 (m, 16H), 0.90 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.1, 139.9, 111.9, 105.6, 58.3, 43.3, 31.2, 31.2, 28.4, 27.9, 26.4, 25.8, 22.5, 14.0. Mass spectrum *m/z*: 547.5 ([M-Br]$^{+}$; calculated for $[C_{30}H_{52}N_4Br]^{+}$: 547.3).

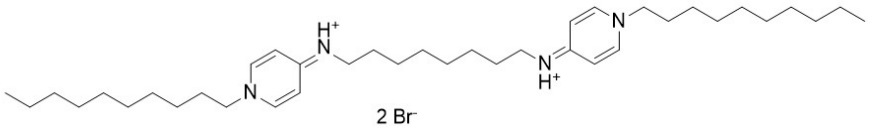
Preparation of Isooct-8, 8



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.130 g, 0.436 mmol), 1-bromooctane (153 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a tan powder (0.253 g, 88%). ^{1}H

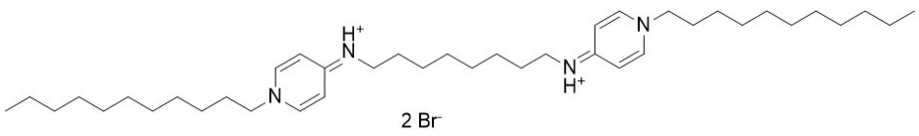
NMR (500 MHz, $CDCl_3$) δ 9.28 (t, *J* = 5.5 Hz, 2H), 8.07 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.81 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.72 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.68 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.14 (t, *J* = 7.2 Hz, 4H), 3.27 (q, *J* = 6.4 Hz, 4H), 1.66 (d, *J* = 20.9 Hz, 12H), 1.35 – 1.17 (m, 24H), 0.88 – 0.81 (m, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.3, 143.0, 139.9, 111.9, 105.6, 58.3, 43.3, 31.7, 31.2, 29.11, 29.10, 28.3, 27.8, 26.4, 26.2, 22.7, 14.1. Mass spectrum *m/z*: 603.6 ($[M\text{-}Br]^+$; calculated for $[C_{34}H_{60}N_4Br]^+$: 603.4).

Preparation of Isooct-10,8



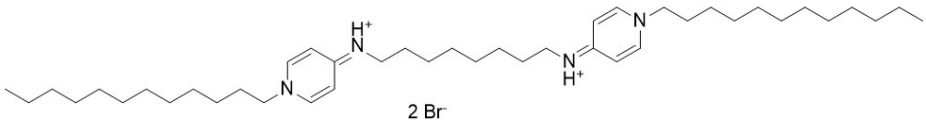
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.119 g, 0.399 mmol), 1-bromodecane (165 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a light tan powder (0.249 g, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.84 (dd, *J* = 7.6, 1.8 Hz, 2H), 7.78 (dd, *J* = 7.4, 2.7 Hz, 2H), 6.68 – 6.61 (m, 2H), 4.13 (t, *J* = 7.2 Hz, 4H), 3.29 (q, *J* = 6.2 Hz, 4H), 1.95 – 1.65 (m, 12H), 1.26 (d, *J* = 21.9 Hz, 32H), 0.90 – 0.82 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.3, 143.1, 139.9, 111.9, 105.6, 58.3, 43.3, 31.9, 31.2, 29.5, 29.5, 29.3, 29.2, 28.3, 27.8, 26.4, 26.2, 14.2. Mass spectrum *m/z*: 659.6 ($[M\text{-}Br]^+$; calculated for $[C_{38}H_{68}N_4Br]^+$: 659.5).

Preparation of Isooct-11,8



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.111 g, 0.372 mmol), 1-bromoundecane (179 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a dark yellow powder (0.270 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (t, J = 5.4 Hz, 2H), 7.92 (d, J = 7.3 Hz, 2H), 7.87 – 7.82 (m, 2H), 7.79 (dd, J = 7.4, 2.7 Hz, 2H), 6.64 (dd, J = 7.5, 2.7 Hz, 2H), 4.13 (t, J = 7.3 Hz, 4H), 3.29 (q, J = 6.2 Hz, 4H), 1.82 (s, 12H), 1.26 (d, J = 21.7 Hz, 36H), 0.86 (t, J = 6.8 Hz, 6H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3, 143.1, 139.9, 111.9, 105.6, 58.3, 43.3, 31.9, 31.2, 29.61, 29.57, 29.5, 29.4, 29.2, 28.4, 27.9, 26.4, 26.2, 22.7, 14.2. Mass spectrum *m/z*: 687.7 ([M-Br]$^{+}$; calculated for $[C_{40}H_{72}N_4Br]^{+}$ 687.5).

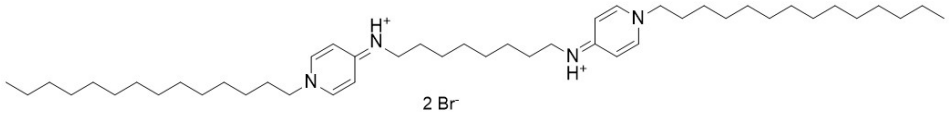
Preparation of Isooct-12,8



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.117 g, 0.392 mmol), 1-bromododecane (192 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a dark orange solid (0.277 g, 89%).

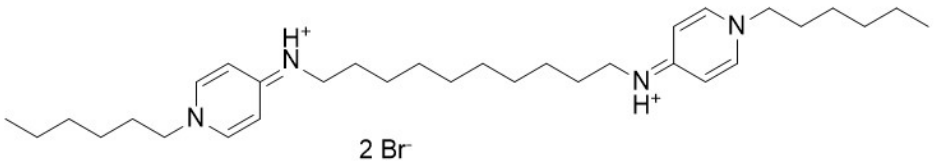
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.77 (dd, *J* = 7.5, 2.7 Hz, 2H), 6.65 (d, *J* = 7.5 Hz, 2H), 4.13 (t, *J* = 7.2 Hz, 4H), 3.28 (q, *J* = 6.2 Hz, 4H), 1.88 – 1.67 (m, 12H), 1.26 (d, *J* = 21.7 Hz, 40H), 0.86 (t, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 143.0, 139.9, 111.9, 105.6, 58.3, 43.3, 32.00, 31.2, 29.7, 29.6, 29.5, 29.4, 29.2, 28.3, 27.8, 26.3, 26.2, 14.2. Mass spectrum *m/z*: 715.7 ([M-Br]$^{+}$; calculated for $[C_{42}H_{76}N_4Br]^{+}$: 715.5).

Preparation of Isooct-14,8



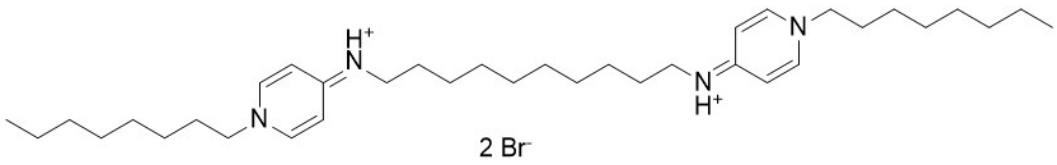
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,8** (0.113 g, 0.379 mmol), 1-bromotetradecane (238 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a tan solid (0.274 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 2H), 7.99 (d, *J* = 7.1 Hz, 2H), 7.83 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.75 (dd, *J* = 7.4, 2.6 Hz, 2H), 6.66 (dd, *J* = 7.5, 2.7 Hz, 2H), 4.13 (t, *J* = 7.2 Hz, 4H), 3.28 (q, *J* = 6.3 Hz, 4H), 1.77 (dt, *J* = 39.6, 7.5 Hz, 12H), 1.49 – 1.13 (m, 48H), 0.92 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 143.1, 139.9, 111.9, 105.6, 58.3, 43.3, 32.0, 31.2, 29.8, 29.72, 29.68, 29.6, 29.2, 28.3, 27.8, 26.4, 26.2, 22.8, 14.2. Mass spectrum *m/z*: 773.8 ([M-Br]$^{+}$; calculated for $[C_{46}H_{84}N_4{}^{81}Br]^{+}$: 773.6).

Preparation of Isooct-6,10



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,10** (0.140 g, 0.423 mmol), 1-bromohexane (123 μL, 0.880 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow sticky solid (0.182 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (t, *J* = 5.7 Hz, 2H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.86 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.72 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.62 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.14 (q, *J* = 7.9 Hz, 4H), 3.27 (q, *J* = 6.7 Hz, 4H), 1.82 – 1.72 (m, *J* = 7.3 Hz, 8H), 1.45 – 1.18 (m, 24H), 0.87 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 142.9, 140.0, 112.0, 105.3, 58.3, 43.3, 31.2, 28.6, 28.5, 28.0, 26.6, 25.8, 22.5, 14.0. Mass spectrum *m/z*: 575.6 ($[M\text{-}Br]^+$; calculated for $[C_{32}H_{56}N_4Br]^+$: 575.4).

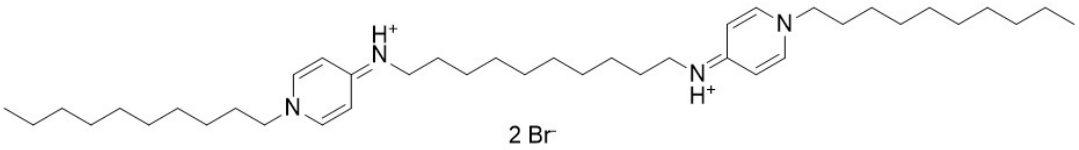
Preparation of Isooct-8,10



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,10** (0.117 g, 0.358 mmol), 1-bromooctane (152 μL, 0.880 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was

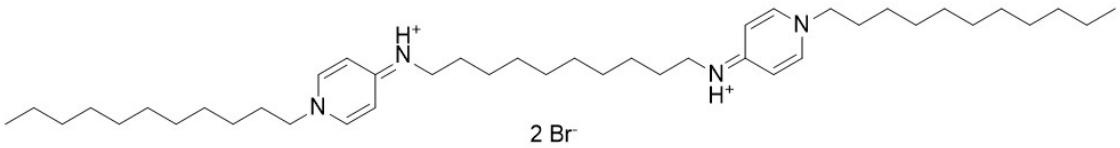
dried under reduced pressure, and a tan crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a tan powder (0.218 g, 85.7%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (t, *J* = 5.5 Hz, 2H), 7.94 (dd, *J* = 7.2, 1.9 Hz, 2H), 7.87 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.75 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.60 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.15 (t, *J* = 7.3 Hz, 4H), 3.27 (q, *J* = 6.6 Hz, 4H), 1.77 (dt, *J* = 49.3, 7.3 Hz, 8H), 1.27 (dd, *J* = 22.6, 8.6 Hz, 32H), 0.90 – 0.83 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2, 143.0, 139.9, 112.0, 105.4, 58.3, 43.3, 31.8, 31.2, 29.1, 28.7, 28.6, 28.0, 26.7, 26.2, 22.7, 14.2. Mass spectrum *m/z*: 631.6 ([M-Br]$^{+}$; calculated for $[C_{36}H_{64}N_4Br]^{+}$: 631.4).

Preparation of Isooct-10,10



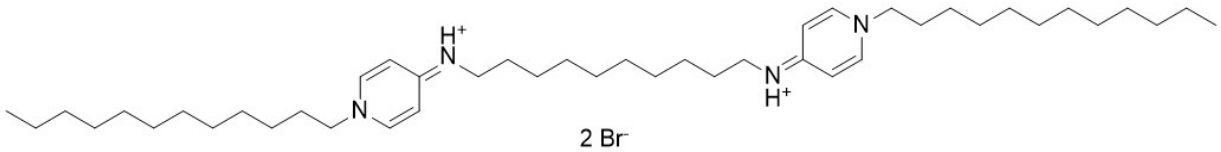
To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,10** (0.140 g, 0.420 mmol), 1-bromodecane (182 μL, 0.880 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow powder (0.184 g, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (t, *J* = 5.6 Hz, 2H), 8.09 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.82 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.68 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.63 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.16 (t, *J* = 7.3 Hz, 4H), 3.26 (q, *J* = 6.7 Hz, 4H), 1.95 – 1.58 (m, 8H), 1.30 – 1.24 (m, 40H), 0.85 (t, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 142.9, 139.9, 112.0, 105.4, 58.3, 43.3, 31.9, 31.2, 29.5, 29.5, 29.3, 29.2, 28.63, 28.56, 28.0, 26.6, 26.2, 14.2. Mass spectrum *m/z*: 687.6 ([M-Br]$^{+}$; calculated for $[C_{40}H_{72}N_4Br]^{+}$: 687.5).

Preparation of Isooct-11,10



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,10** (0.145 g, 0.444 mmol), 1-bromoundecane (196 µL, 0.880 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a yellow powder (0.259 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (t, *J* = 5.6 Hz, 2H), 7.97 (dd, *J* = 7.3, 1.9 Hz, 2H), 7.86 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.73 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.61 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.15 (t, *J* = 7.3 Hz, 4H), 3.27 (q, *J* = 6.6 Hz, 4H), 1.86 – 1.67 (m, 8H), 1.44 – 1.16 (m, 44H), 0.86 (t, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 142.9, 139.9, 112.0, 105.4, 58.3, 43.3, 32.0, 31.2, 29.62, 29.58, 29.5, 29.2, 28.6, 28.5, 28.0, 26.6, 26.2, 14.2. Mass spectrum *m/z*: 715.7 ([M-Br]$^{+}$; calculated for $[C_{42}H_{76}N_4Br]^{+}$: 715.5).

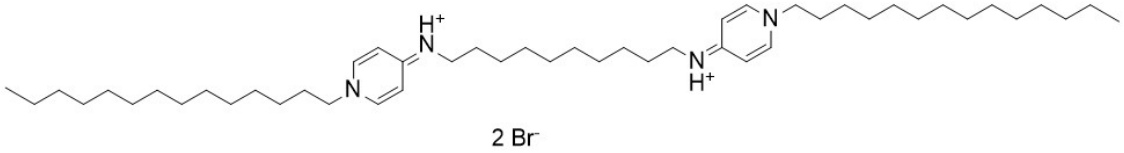
Preparation of Isooct-12,10



To a 20 mL reaction vial with a pressure relieving septum cap was added **Isooct-0,10** (0.127 g, 0.389 mmol), 1-bromododecane (192 µL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a tan crude powder was recovered. The product was purified via

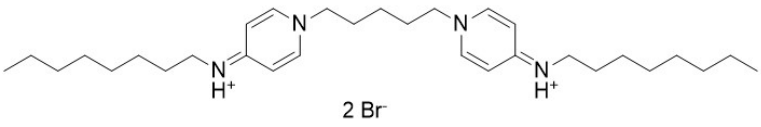
trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a tan semi-sticky solid (0.250 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (t, *J* = 5.7 Hz, 2H), 7.95 (dd, J = 7.4, 1.9 Hz, 2H), 7.86 (dd, J = 7.4, 1.9 Hz, 2H), 7.72 (dd, J = 7.4, 1.9 Hz, 2H), 6.60 (dd, J = 7.5, 2.8 Hz, 2H), 4.18 – 4.01 (m, 4H), 3.27 (q, J = 6.6 Hz, 4H), 1.82 – 1.41 (m, 8H), 1.30 – 1.15 (m, 48H), 0.90 – 0.82 (m, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 154.7, 140.3, 137.4, 109.5, 102.8, 55.8, 40.7, 29.4, 28.7, 27.1, 27.0, 26.94, 26.87, 26.6, 26.00, 25.94, 25.4, 24.1, 23.7, 20.23, 20.22, 11.7. Mass spectrum *m/z*: 745.7 ([M-Br]$^{+}$; calculated for $[C_{44}H_{80}N_4{}^{81}Br]^{+}$: 745.6).

Preparation of Isooct-14,10



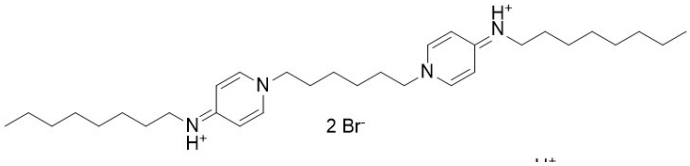
To a 20 mL reaction vial with a pressure relieving septum cap was **Isooct-0,10** (0.154 g, 0.472 mmol), 1-bromotetradecane (238 μL, 0.800 mmol), and acetonitrile (7 mL). The mixture was heated to 80 ℃ for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a yellow crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a pale-yellow powder (0.451. g, 108%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (t, *J* = 5.7 Hz, 2H), 7.94 – 7.85 (m, 4H), 7.75 (dd, *J* = 7.3, 2.7 Hz, 2H), 6.59 (dd, *J* = 7.3, 2.8 Hz, 2H), 4.14 (t, *J* = 7.3 Hz, 4H), 3.27 (q, *J* = 6.5 Hz, 4H), 1.73 (p, *J* = 6.9 Hz, 8H), 1.31 – 1.21 (m, 56H), 0.86 (t, *J* = 6.8 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 157.2, 143.0, 139.9, 112.0, 105.4, 58.3, 43.3, 32.0, 31.2, 29.8, 29.72, 29.68, 29.67, 29.60, 29.59, 29.5, 29.4, 29.2, 28.7, 28.6, 28.0, 26.7, 26.2, 22.8, 14.21, 14.20. Mass spectrum *m/z*: 801.8 ([M-Br]$^{+}$; calculated for $[C_{48}H_{88}N_4{}^{81}Br]^{+}$: 801.6).

Preparation of Oct-8,5



To a 20 mL reaction vial with a pressure relieving septum cap was added 4-(octylamino)-pyridine (0.164 g, 0.795 mmol), 1,5-dibromopentane (54.5 µL, 0.400 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a white crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a white product. The product was further purified via trituration with 18 mL of 2:1 ethyl ether: hexanes, producing a flaky white powder (0.249 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (t, *J* = 5.6 Hz, 2H), 8.43 (dd, *J* = 7.5, 1.8 Hz, 2H), 8.26 (d, *J* = 7.4 Hz, 2H), 7.48 (dd, *J* = 7.4, 2.8 Hz, 2H), 6.54 (dd, *J* = 7.4, 2.8 Hz, 2H), 4.35 (t, *J* = 7.2 Hz, 4H), 3.21 (q, *J* = 7.0 Hz, 4H), 2.03 (p, *J* = 7.3 Hz, 4H), 1.71 (p, *J* = 7.4 Hz, 4H), 1.49 – 1.31 (m, 2H), 1.29 – 1.15 (m, 20H), 0.89 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.0, 143.5, 141.1, 111.4, 105.2, 57.1, 43.4, 31.9, 30.1, 29.3, 28.4, 27.1, 22.7, 22.2, 14.2. Mass spectrum *m/z*: 561.5 ([M-Br]$^{+}$; calculated for $[C_{31}H_{54}N_4Br]^{+}$: 561.4).

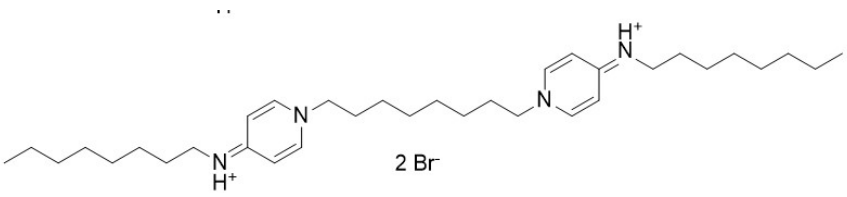
Preparation of Oct-8,6



To a 20 mL reaction vial with a pressure relieving septum cap was added 4-(octylamino)-pyridine (0.165 g, 0.800 mmol), 1,6-dibromohexane (61.5 µL, 0.400 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the

product was dried under reduced pressure, and a white crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a white product. The product was further purified via trituration with 18 mL of 2:1 ethyl ether: hexanes, producing a flaky white powder (0.244 g, 92.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (t, *J* = 5.6 Hz, 2H), 8.39 (d, *J* = 7.5 Hz, 2H), 8.13 (d, *J* = 7.4 Hz, 2H), 7.55 (dd, *J* = 7.3, 2.8 Hz, 2H), 6.60 – 6.52 (m, 2H), 4.38 (t, *J* = 7.2 Hz, 4H), 3.23 (q, *J* = 6.6 Hz, 4H), 1.87 – 1.67 (m, 8H), 1.25 (d, *J* = 9.2 Hz, 24H), 0.85 (t, *J* = 6.4 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.1, 143.3, 141.0, 111.5, 105.2, 57.2, 43.4, 31.87, 31.85, 30.5, 29.29, 29.28, 29.27, 28.3, 27.1, 24.6, 22.7, 14.2. Mass spectrum *m/z*: 575.6 ([M-Br]$^{+}$; calculated for [$C_{32}H_{56}N_4Br$]$^{+}$: 575.4).

Preparation of Oct-8,8



To a 20 mL reaction vial with a pressure relieving septum cap was added 4-(octylamino)-pyridine (0.163 g, 0.790 mmol), 1,8-dibromooctane (73.6 μL, 0.400 mmol), and acetonitrile (7 mL). The mixture was heated to 80 °C for 24 hours with stirring. After cooling to room temperature, the product was dried under reduced pressure, and a white crude powder was recovered. The product was purified via trituration with 12 mL of 1:5 ethyl acetate: hexanes, leading to a white product. The product was further purified via trituration with 18 mL of 2:1 ethyl ether: hexanes, producing a flaky white powder (0.251 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (t, *J* = 5.6 Hz, 2H), 8.23 (dd, *J* = 7.4, 1.9 Hz, 2H), 8.06 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.62 (dd, *J* =m 7.4, 1.9 Hz, 2H) 6.60 (dd, *J* = 7.5, 2.8 Hz, 2H), 4.27 (t, *J* = 7.0 Hz, 4H), 3.25 (td, *J* = 7.6, 5.7 Hz, 4H), 1.84 – 1.68 (m, *J* = 7.0 Hz, 8H), 1.33 – 1.16 (m, 28H), 0.89 – 0.82 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1,

143.1, 140.7, 111.6, 105.2, 57.9, 43.4, 31.9, 30.9, 29.3, 29.3, 28.3, 28.2, 27.2, 25.3, 22.7, 14.2. Mass spectrum *m/z*: 603.6 ($[M\text{-}Br]^+$; calculated for $[C_{34}H_{60}N_4Br]^+$: 603.4).

VI. NMR Spectroscopic Data: ^{1}H and ^{13}C NMR

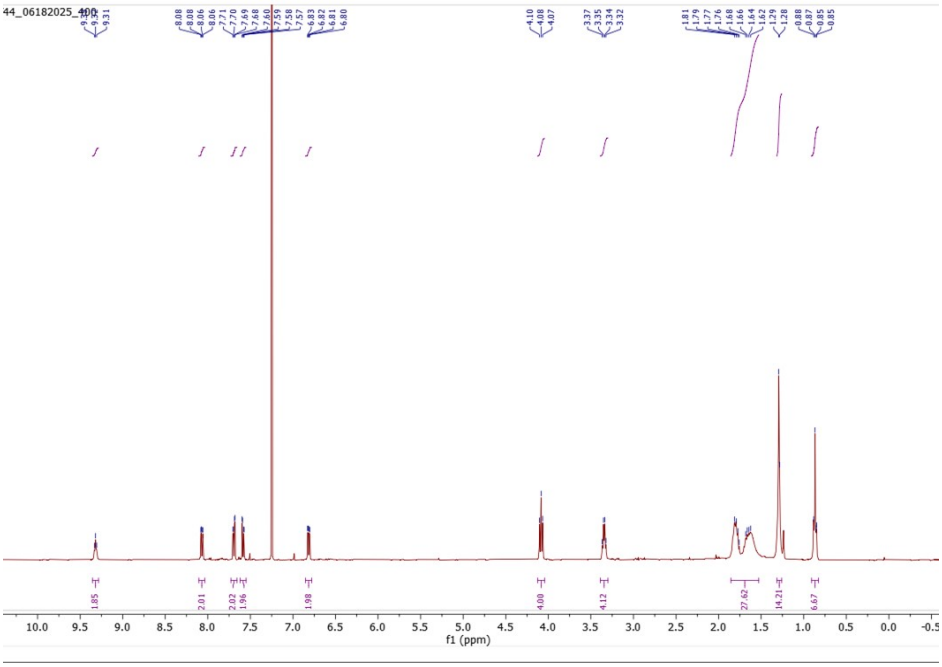


Figure S1: ^{1}H NMR (400 MHz) of **Isooct-6,5** in $CDCl_3$

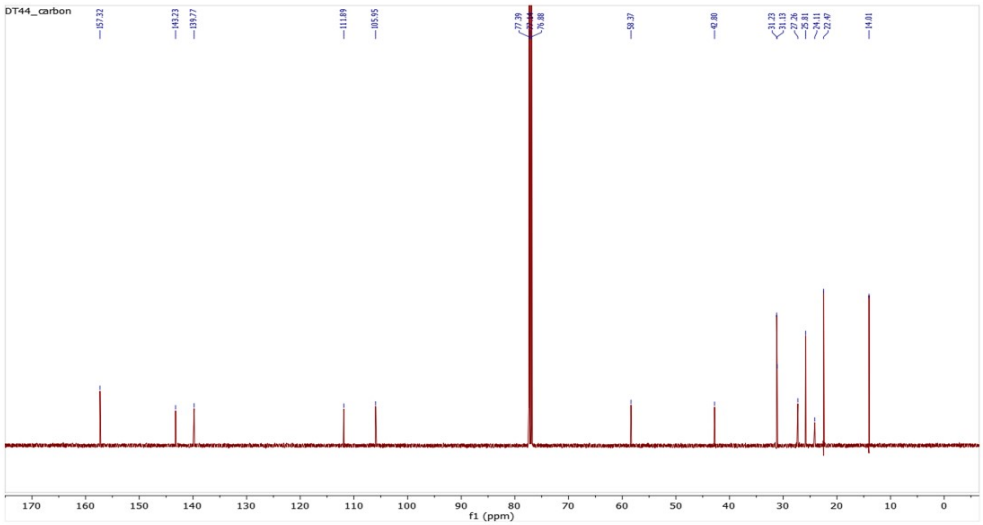
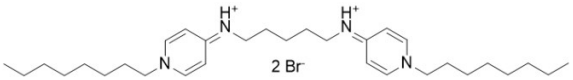


Figure S2: ^{13}C NMR (500 MHz) of **Isooct-6,5** in $CDCl_3$



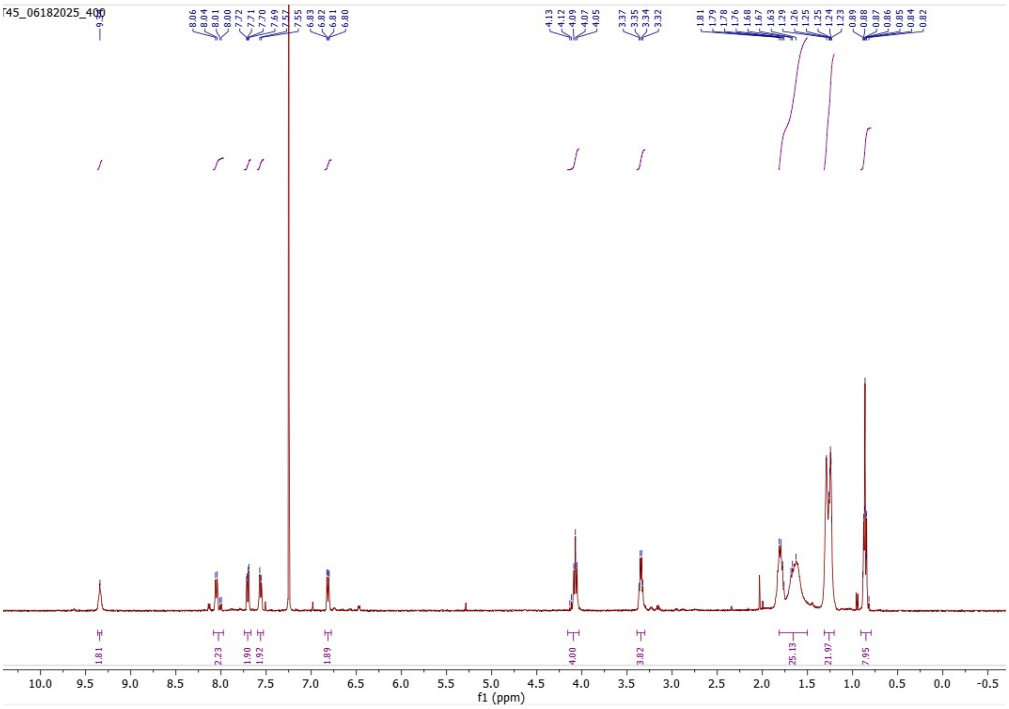


Figure S3: ^{1}H NMR (400 MHz) of **Isooct-8,5** in $CDCl_3$

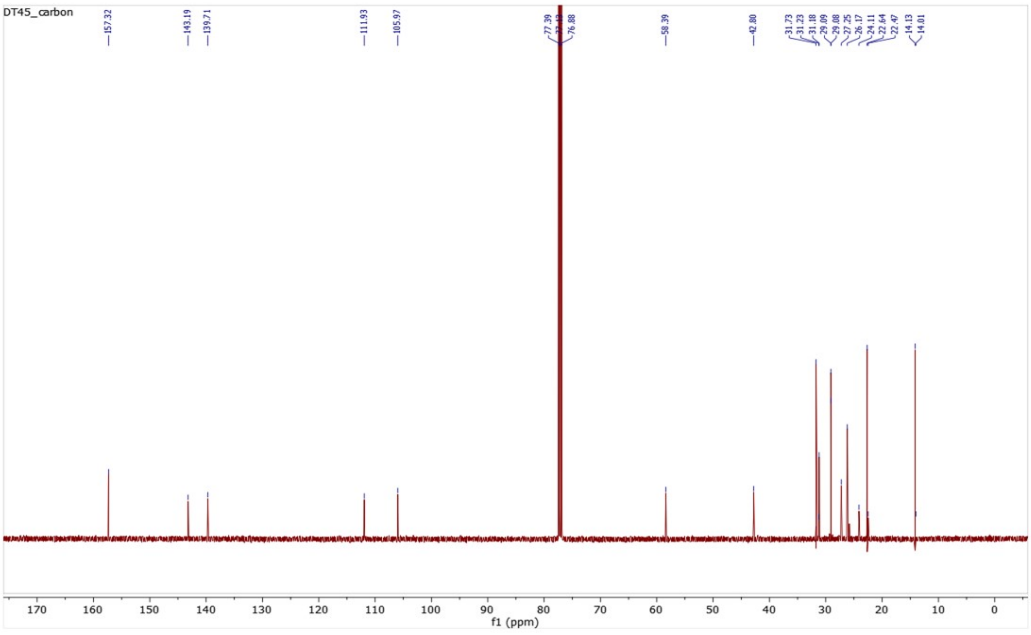


Figure S4: ^{13}C NMR (500 MHz) of **Isooct-8,5** in $CDCl_3$

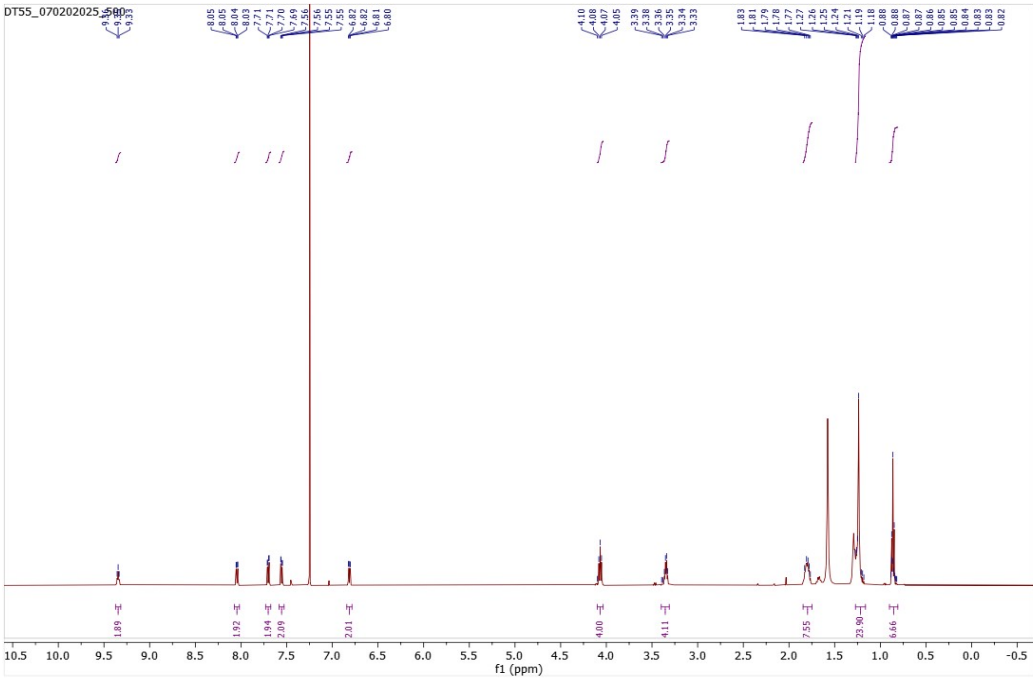


Figure S5: ^{1}H NMR (500 MHz) of **Isooct-10,5** in $CDCl_3$

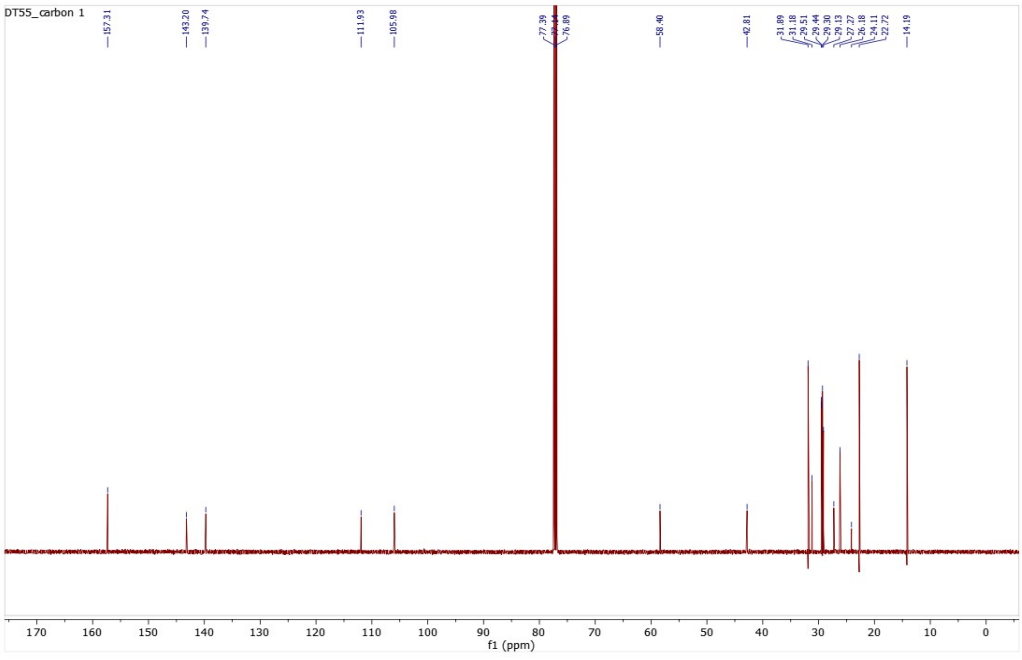


Figure S6: ^{13}C NMR (500 MHz) of **Isooct-10,5** in $CDCl_3$

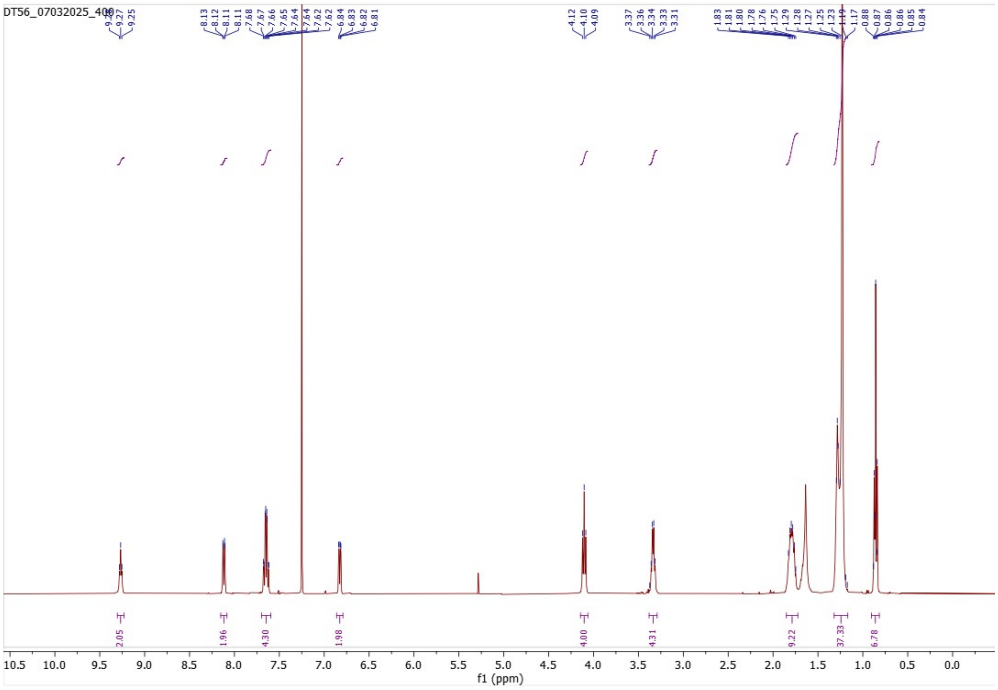


Figure S7: ^{1}H NMR (400 MHz) **of Isooct-11,5** in $CDCl_3$

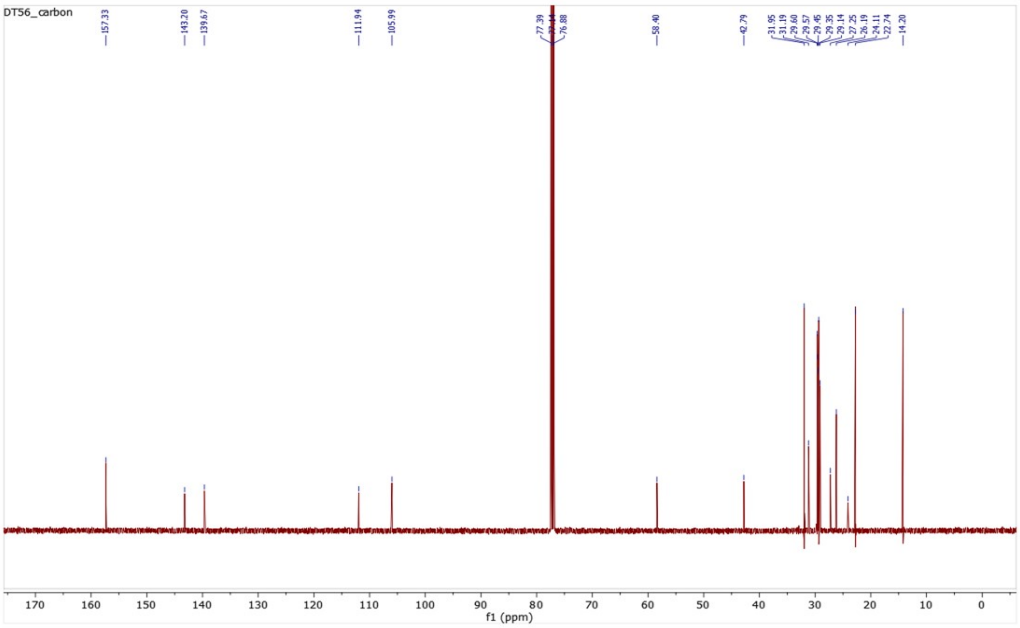


Figure S8: ^{13}C NMR (500 MHz) of **Isooct-11,5** in $CDCl_3$

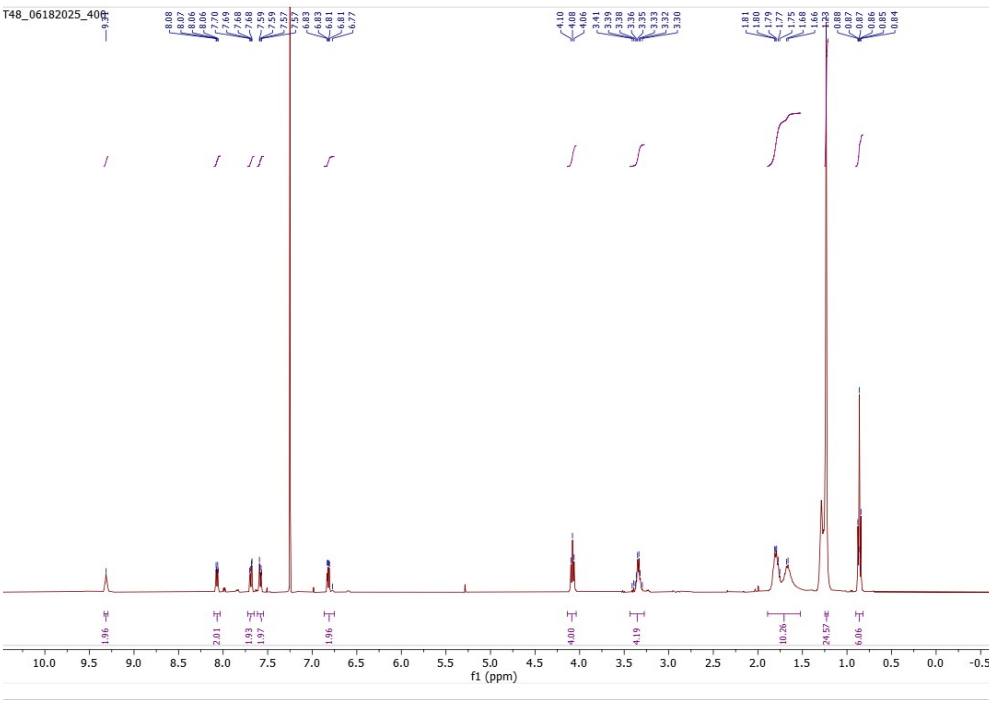


Figure S9: ^{1}H NMR (400 MHz) of **Isooct-12,5** in $CDCl_3$

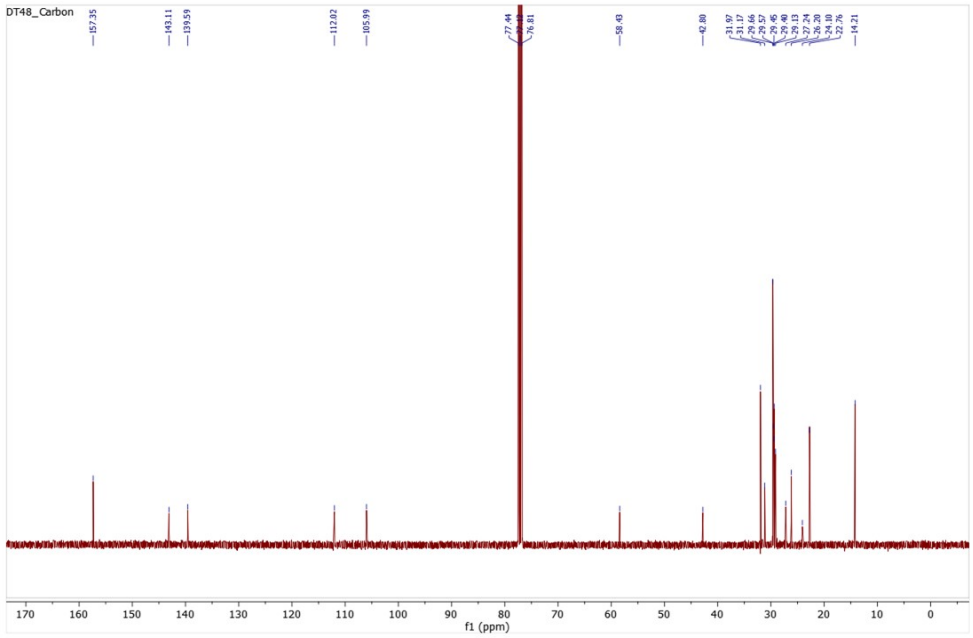


Figure S10: ^{13}C NMR (400 MHz) of **Isooct-12,5** in $CDCl_3$

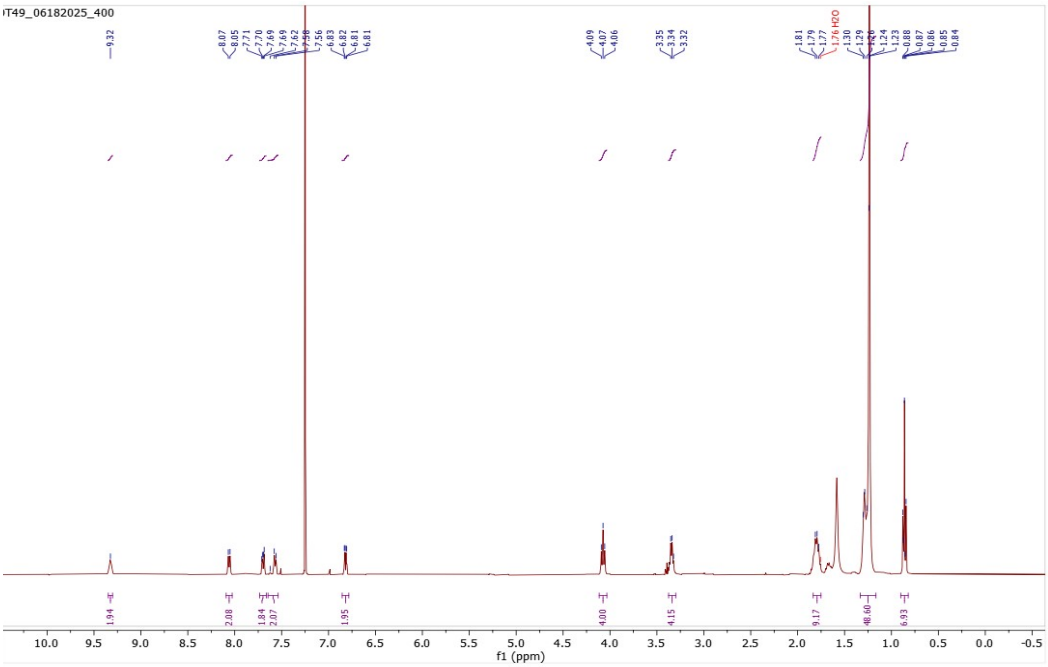


Figure S11: ^{1}H NMR (400 MHz) of **Isooct-14,5** in $CDCl_3$

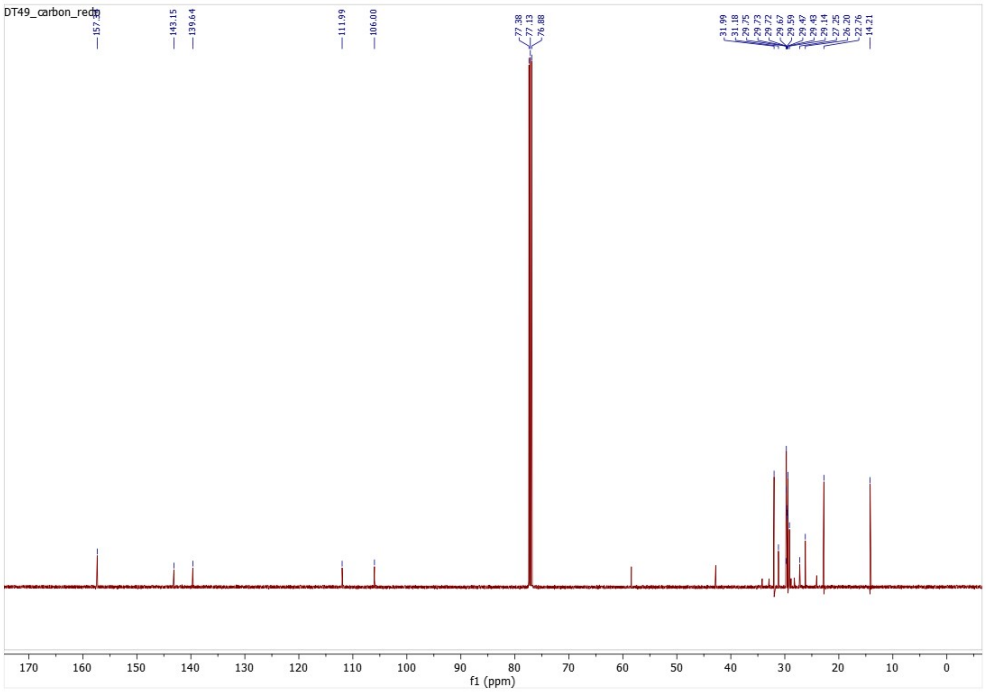


Figure S12: ^{13}C NMR (500 MHz) of **Isooct-14,5** in $CDCl_3$

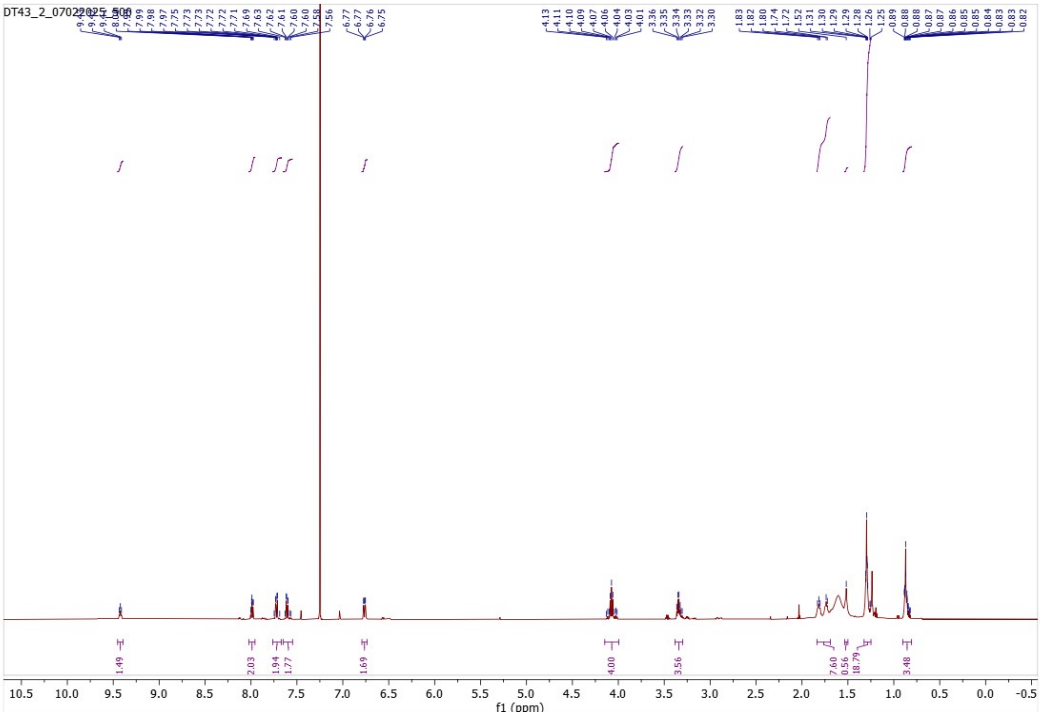


Figure S13: ^{1}H NMR (500 MHz) **of Isooct-6,6** in $CDCl_3$

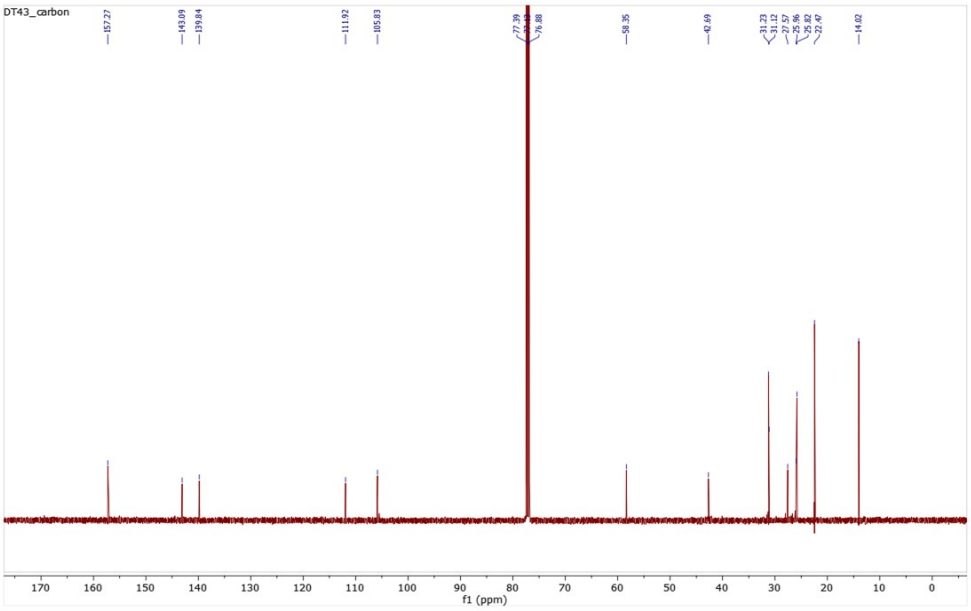


Figure S14: ^{13}C NMR (500 MHz) of **Isooct-6,6** in $CDCl_3$

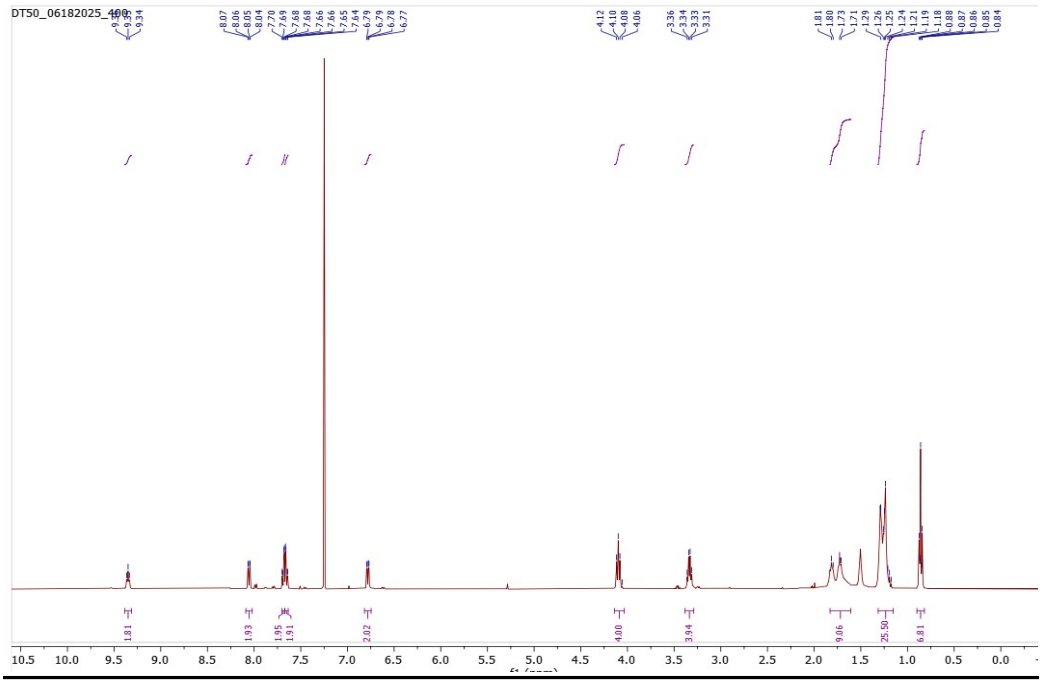


Figure S15: ^{1}H NMR (400 MHz) of **Isooct-8,6** in $CDCl_3$

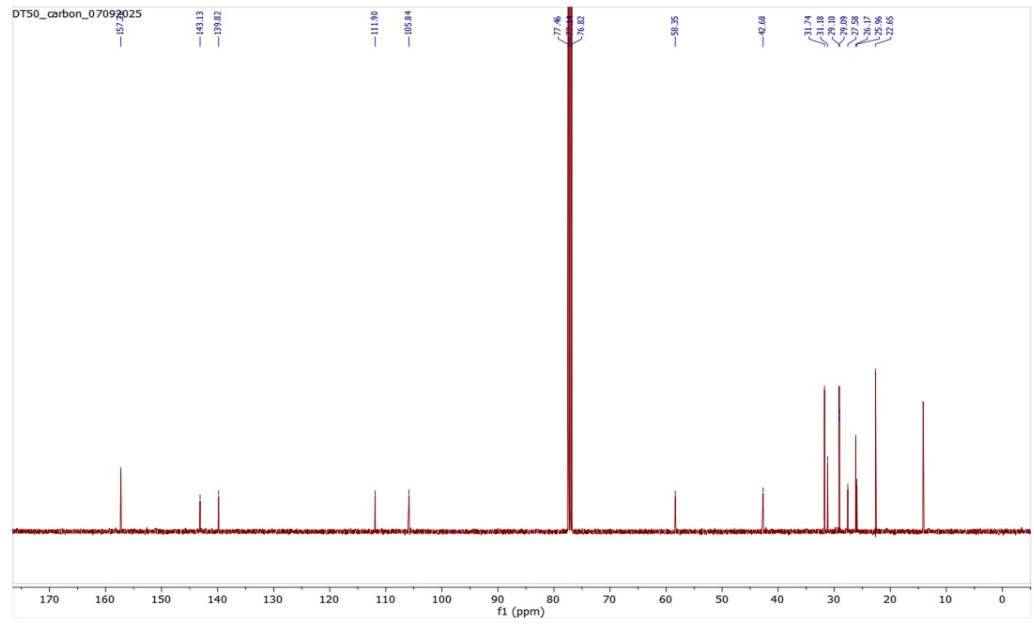


Figure S16: ^{13}C NMR (400 MHz) of **Isooct-8,6** in $CDCl_3$

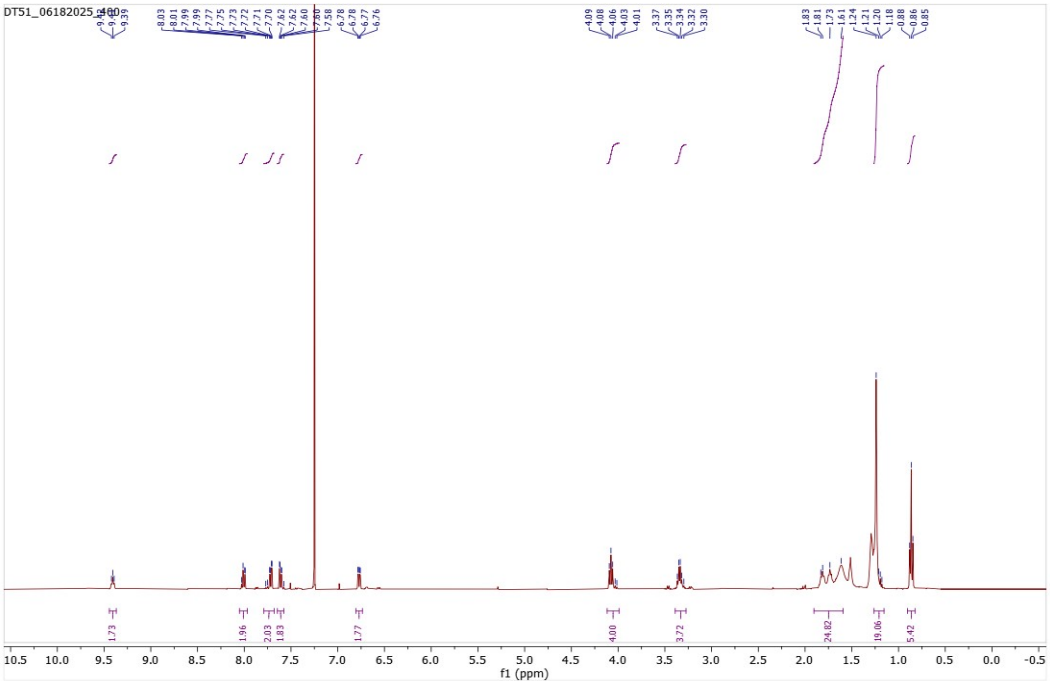


Figure S17: ^{1}H NMR (400 MHz) of **Isooct-10,6** in $CDCl_3$

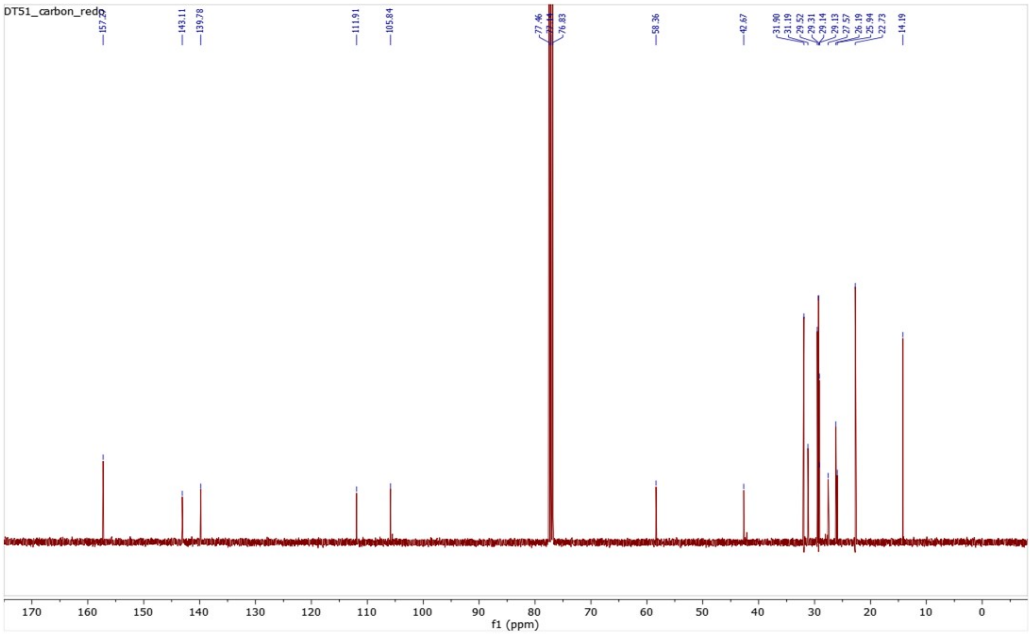
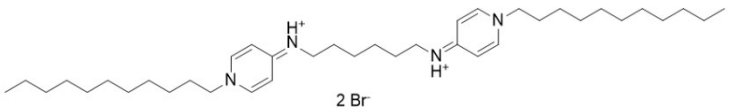


Figure S18: ^{13}C NMR (400 MHz) of **Isooct-10,6** in $CDCl_3$



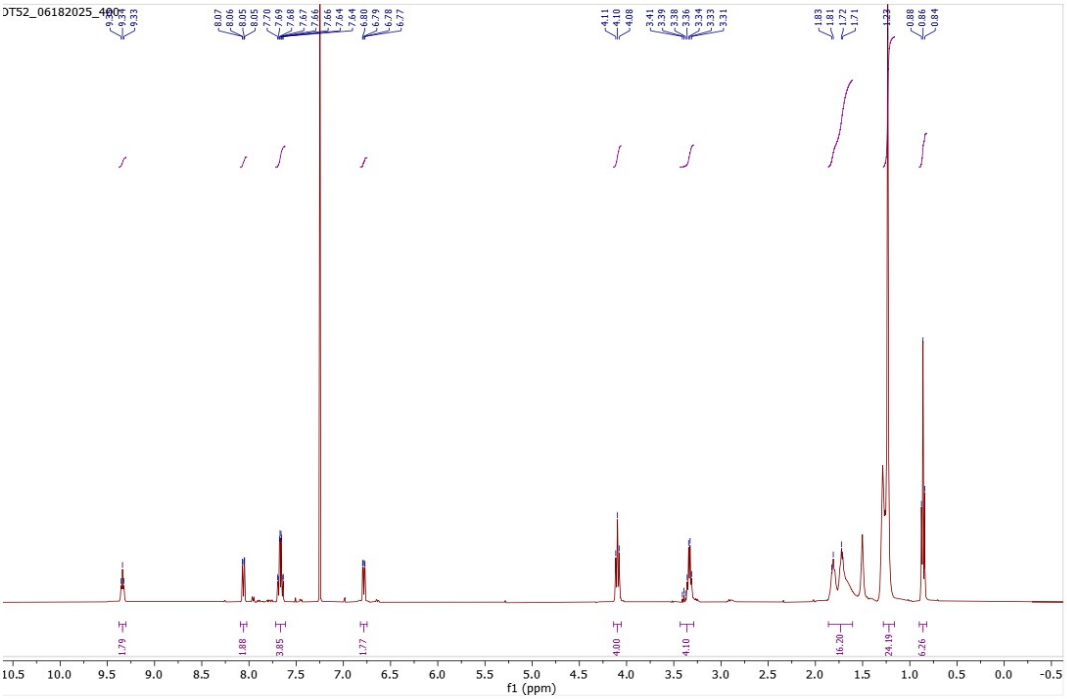


Figure S19: ^{1}H NMR (400 MHz) of **Isooct-11,6** in $CDCl_3$

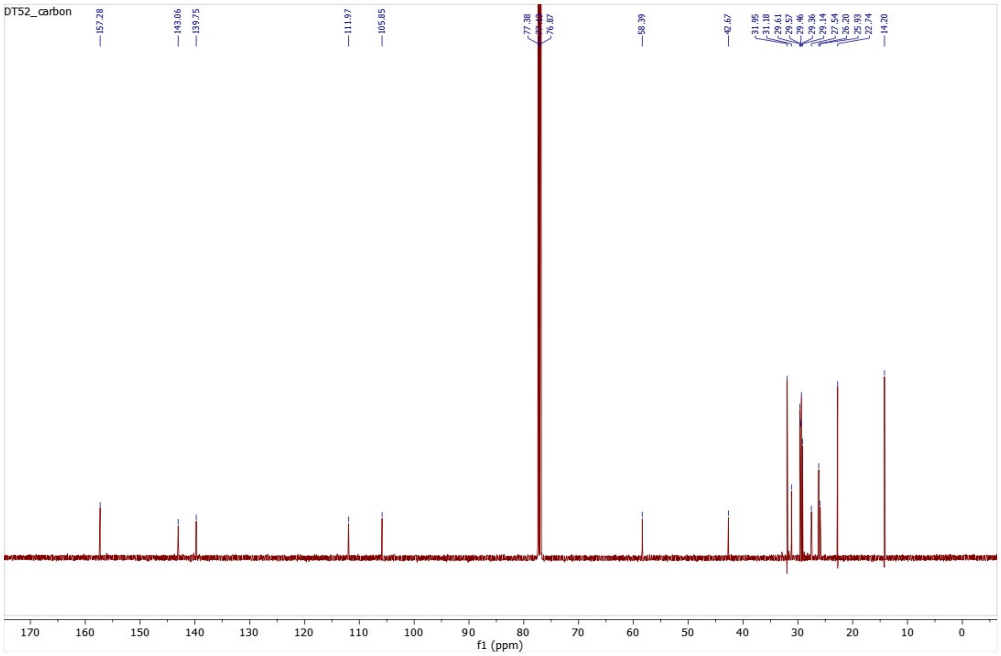


Figure S20: ^{13}C NMR (500 MHz) of **Isooct-11,6** in $CDCl_3$

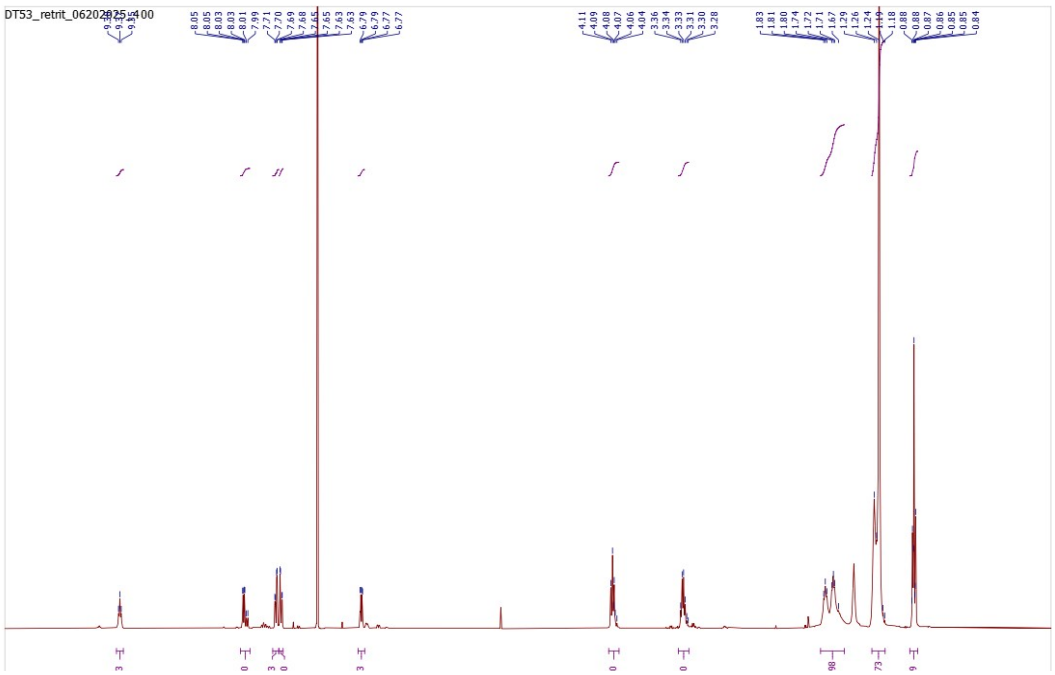


Figure S21: ^{1}H NMR (400 MHz) of **Isooct-12,6** in $CDCl_3$

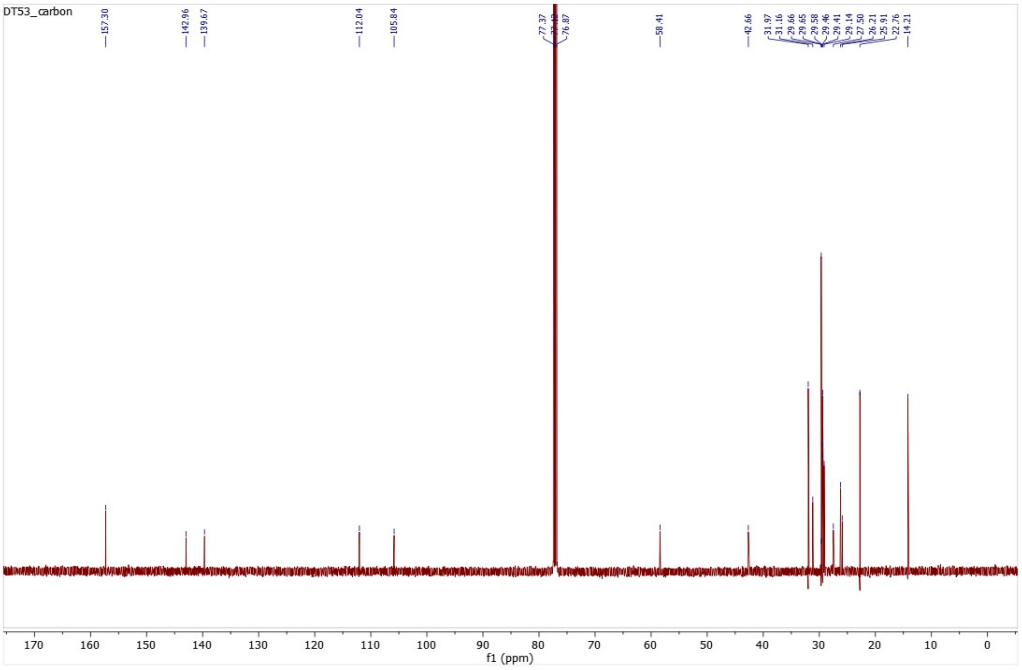


Figure S22: ^{13}C NMR (500MHz) of **Isooct-12,6** in $CDCl_3$

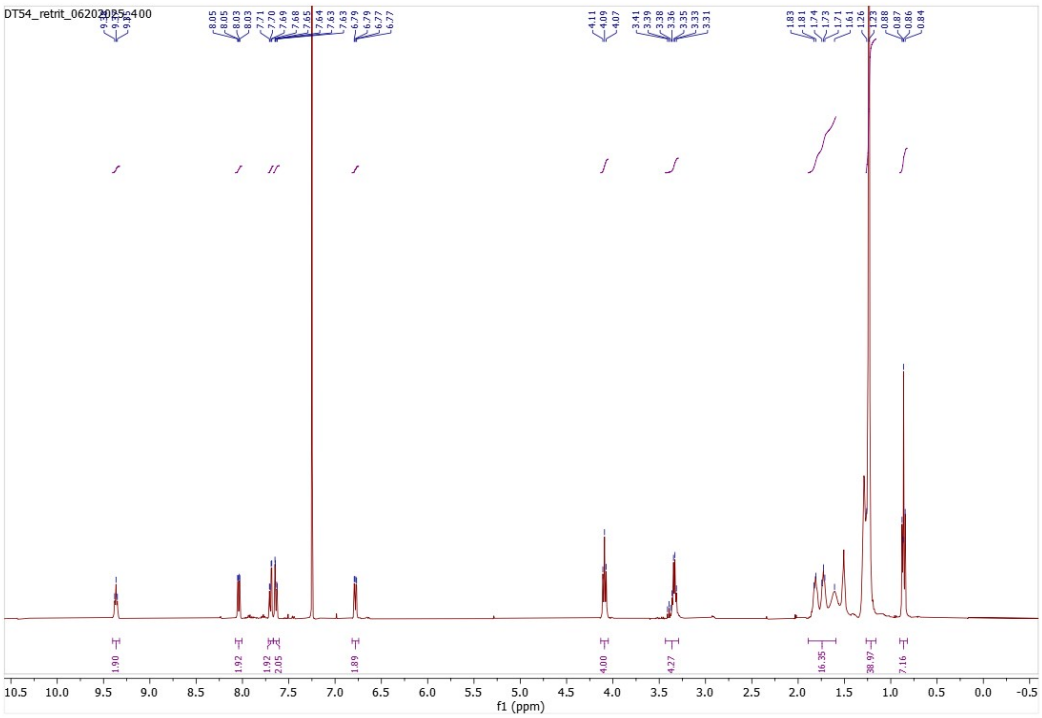


Figure S23: ^{1}H NMR (400 MHz) of **Isooct-14,6** in $CDCl_3$

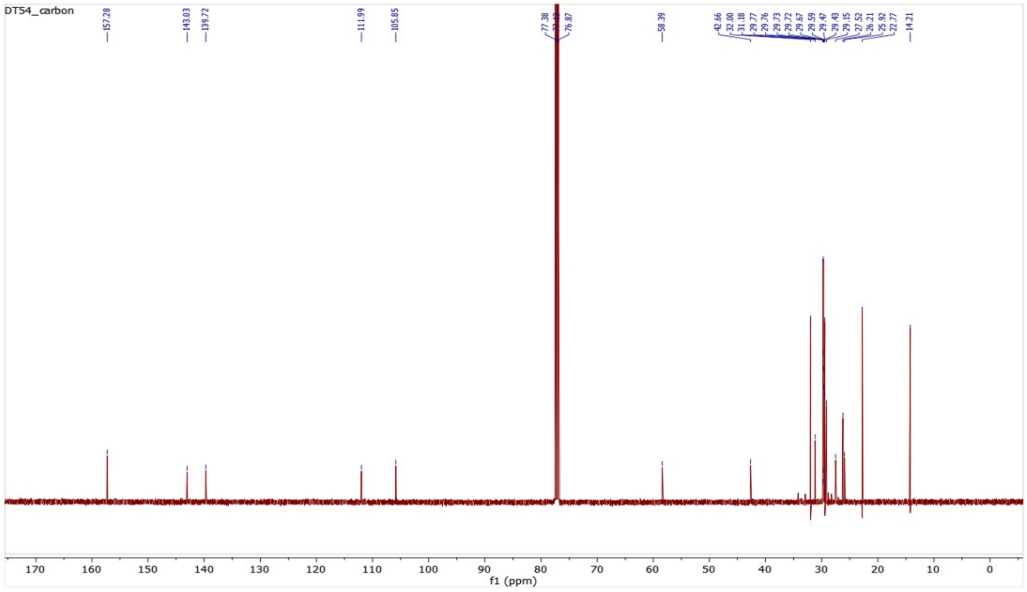


Figure S24: ^{13}C NMR (500 MHz) of **Isooct-14,6** in $CDCl_3$

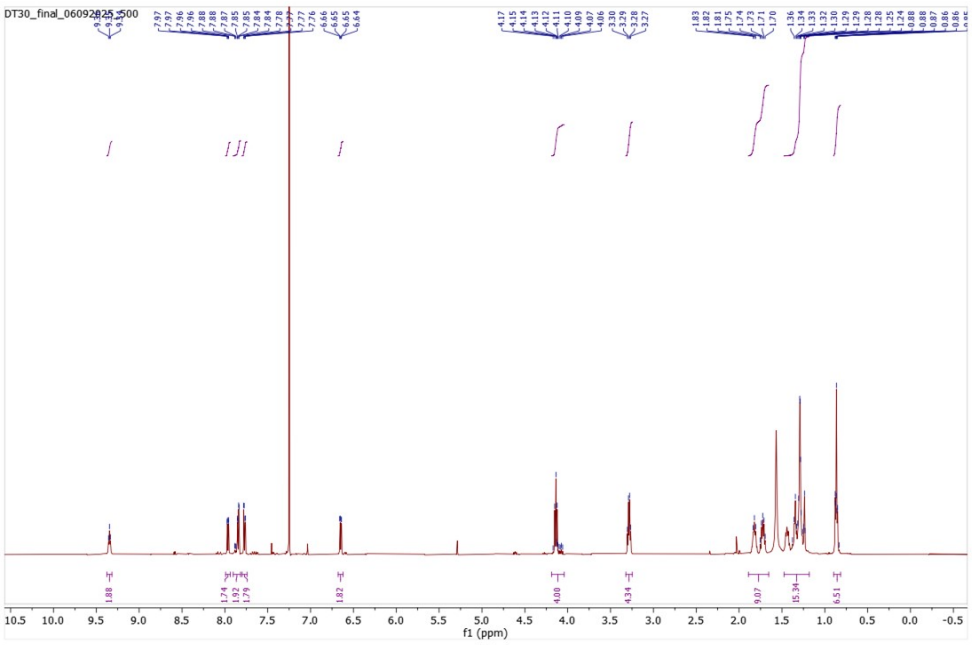


Figure S25: ^{1}H NMR (500 MHz) of **Isooct-6,8** in $CDCl_3$

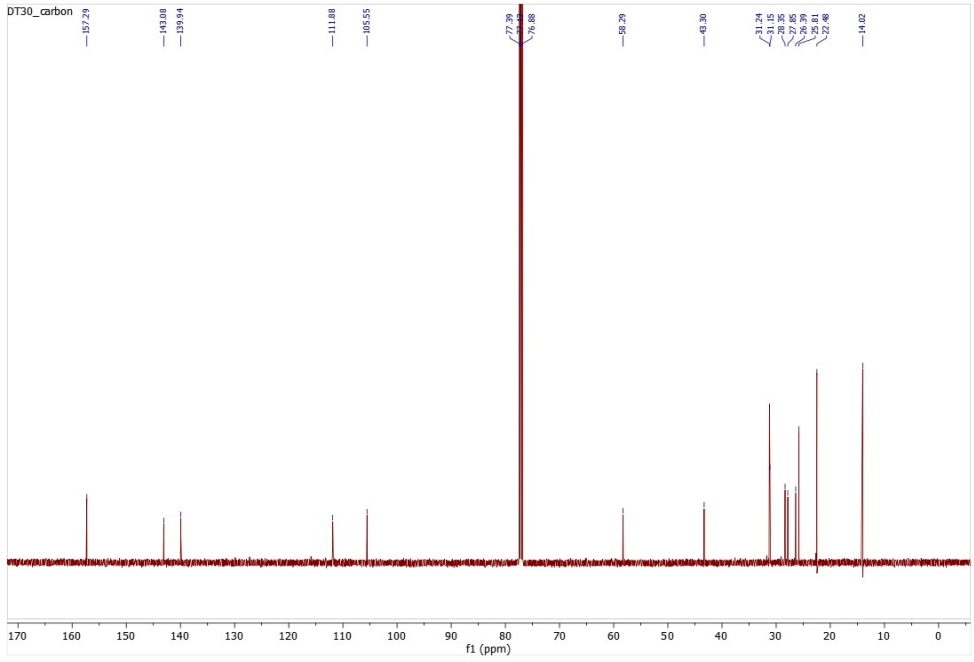


Figure S26: ^{13}C NMR (500 MHz) of **Isooct-6,8** in $CDCl_3$

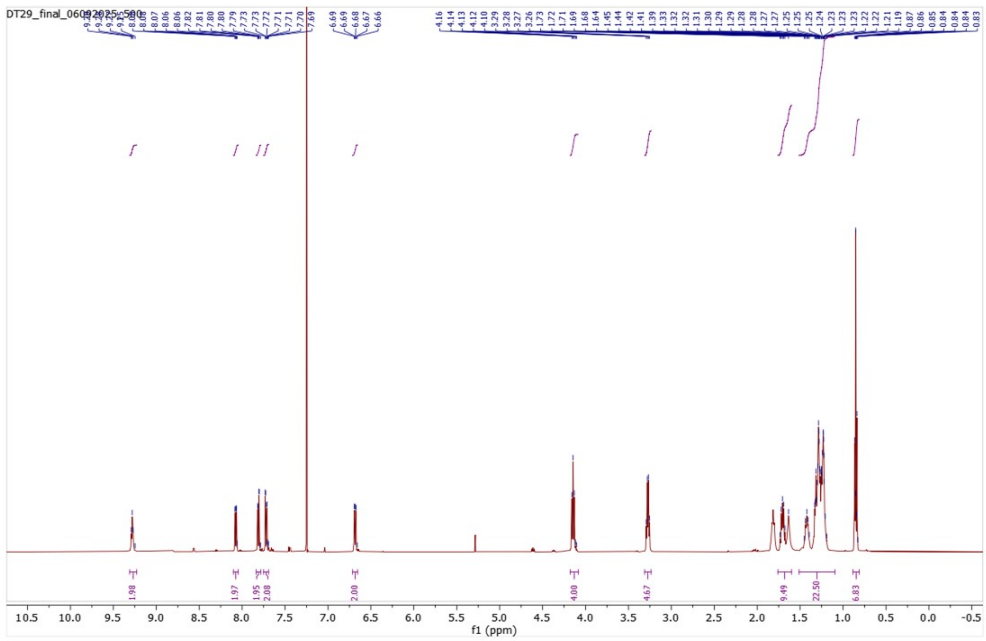


Figure S27: ^{1}H NMR (500 MHz) of **Isooct-8,8** in $CDCl_3$

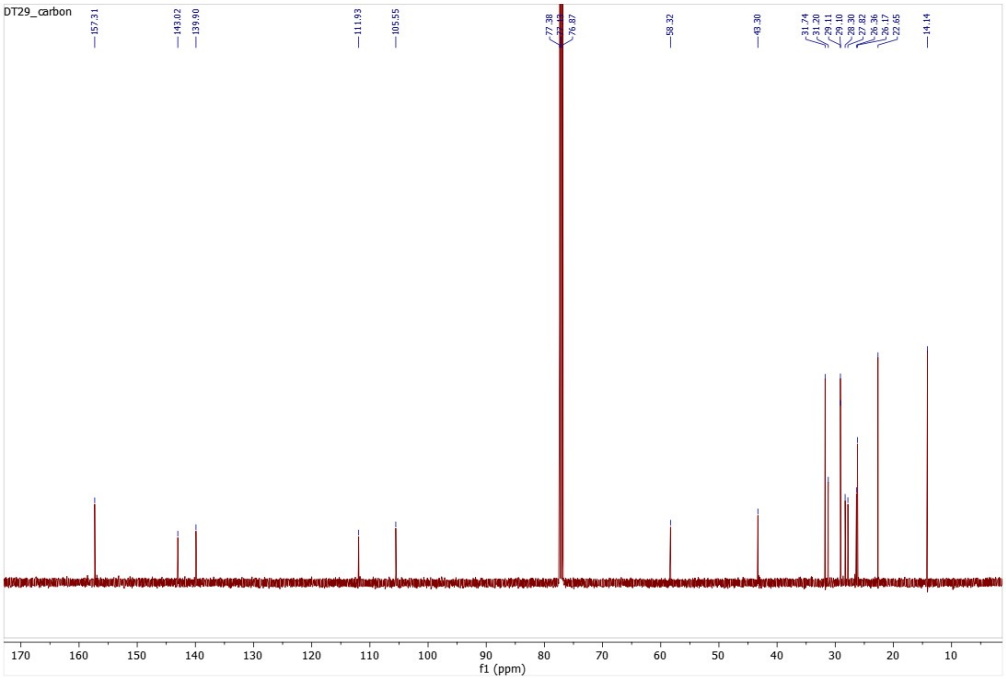


Figure S28: ^{13}C NMR (500 MHZ) of **Isooct-8,8** in $CDCl_3$

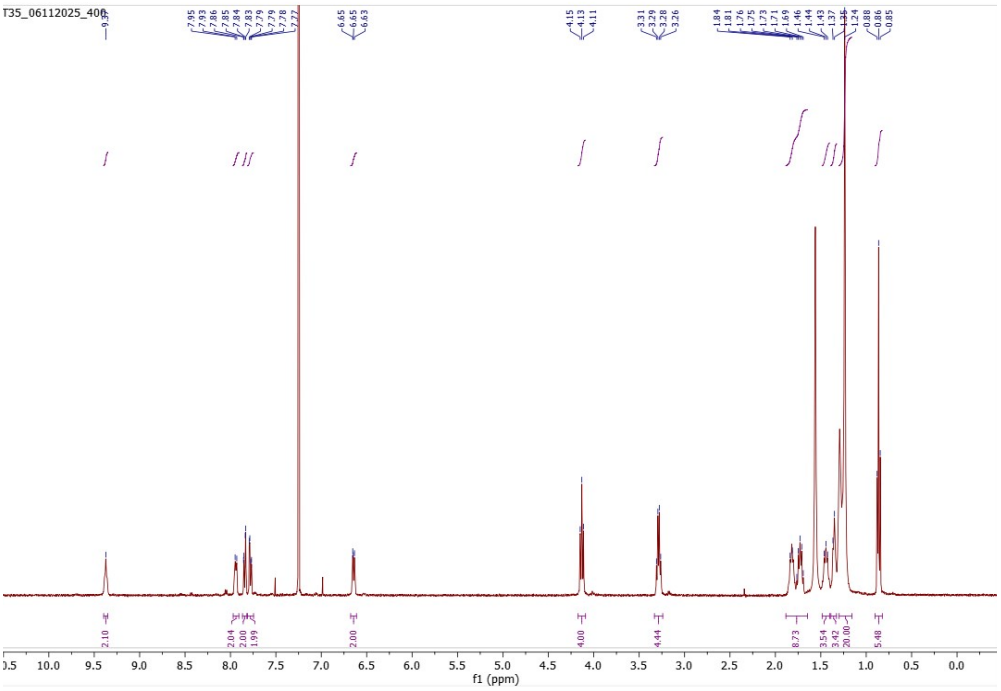


Figure S29: ^{1}H NMR (400 MHz) of **Isooct-10,8** in $CDCl_3$

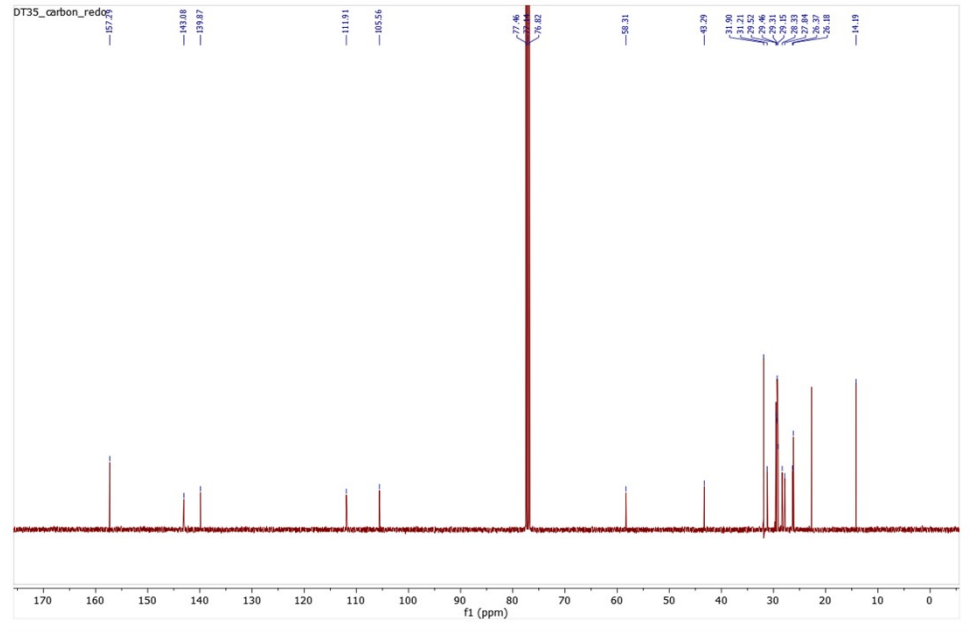


Figure S30: ^{13}C NMR (400 MHz) of **Isooct-10,8** in $CDCl_3$

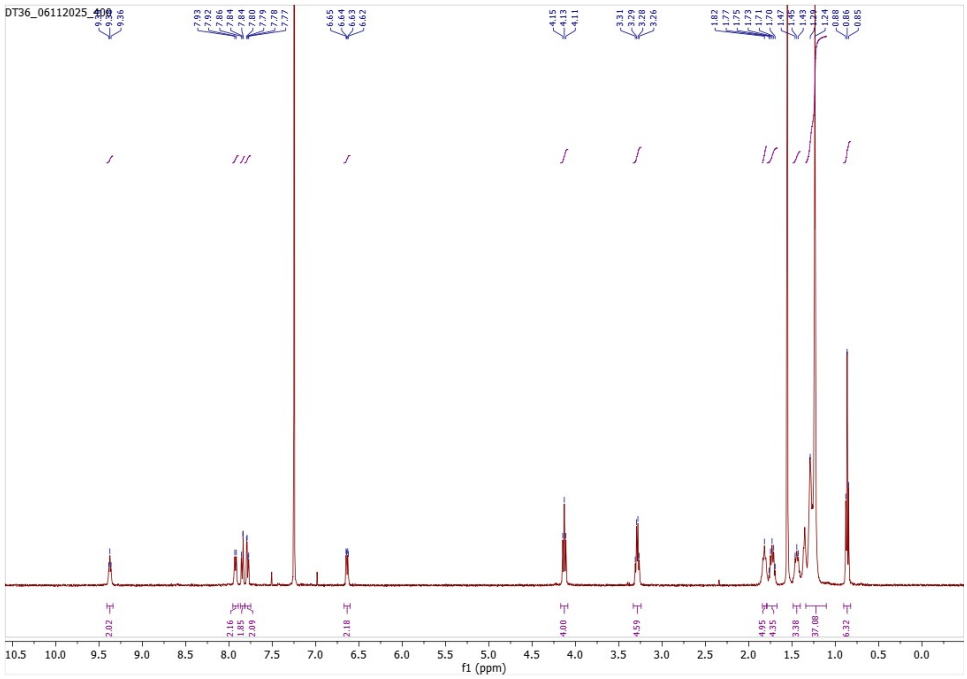


Figure S31: ^{1}H NMR (400 MHz) of **Isooct-11,8** in $CDCl_3$

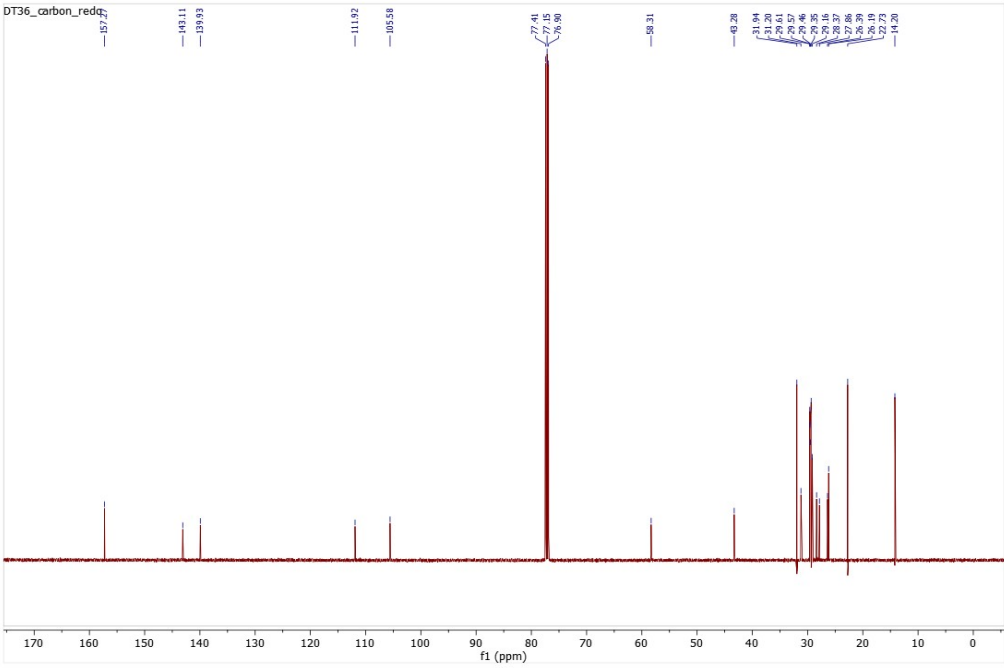


Figure S32: ^{13}C NMR (500 MHz) of **Isooct-11,8** in $CDCl_3$

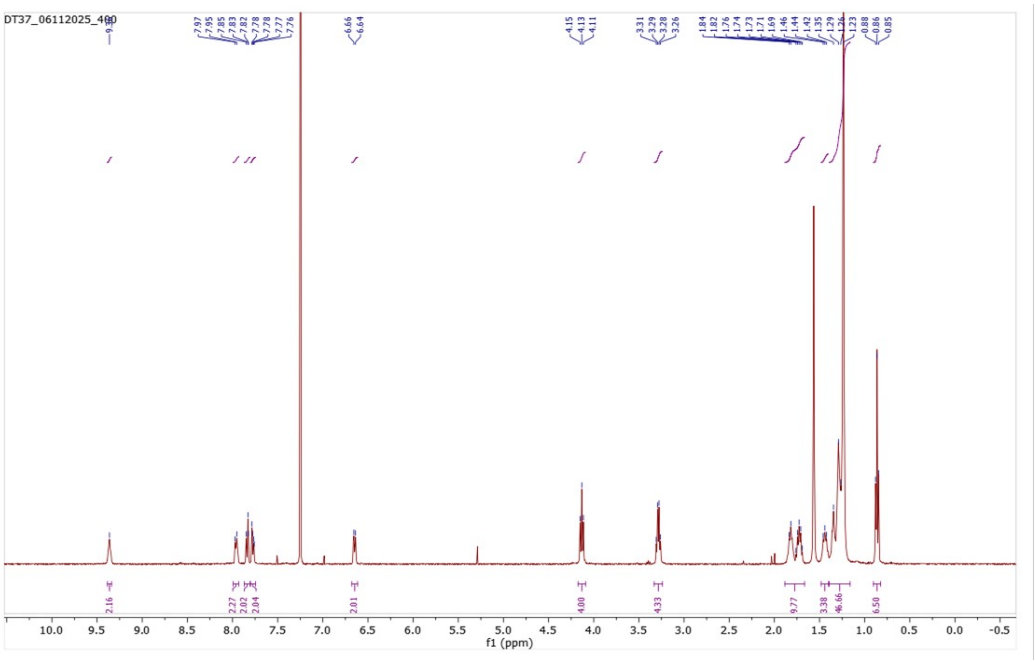


Figure S33: ^{1}H NMR (400 MHz) of **Isooct-12,8** in $CDCl_3$

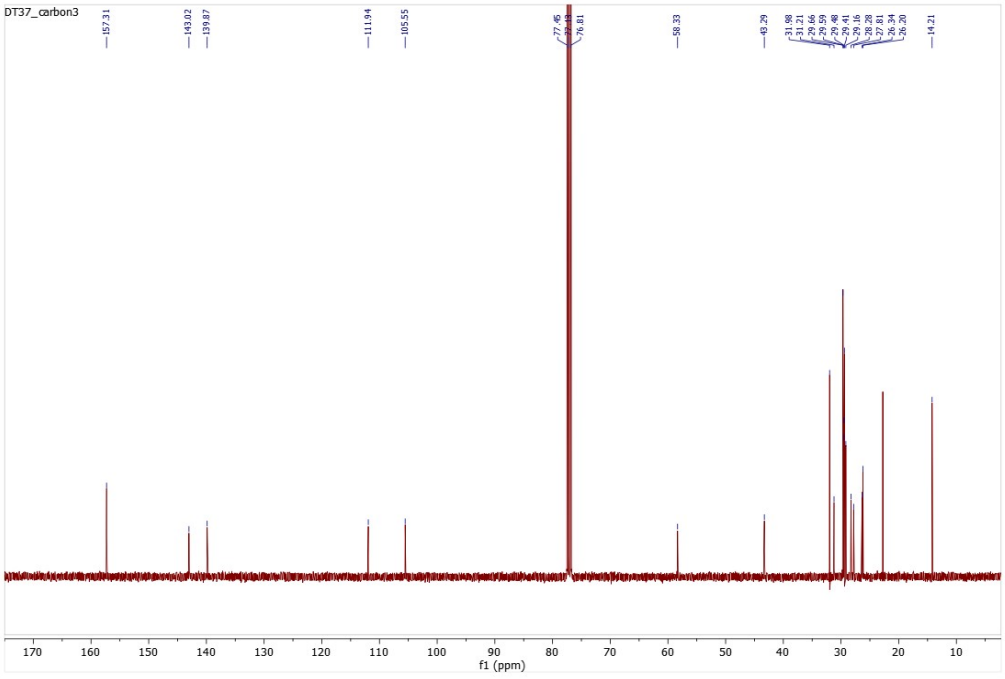


Figure S34: ^{13}C NMR (400 MHz) of **Isooct-12,8** in $CDCl_3$

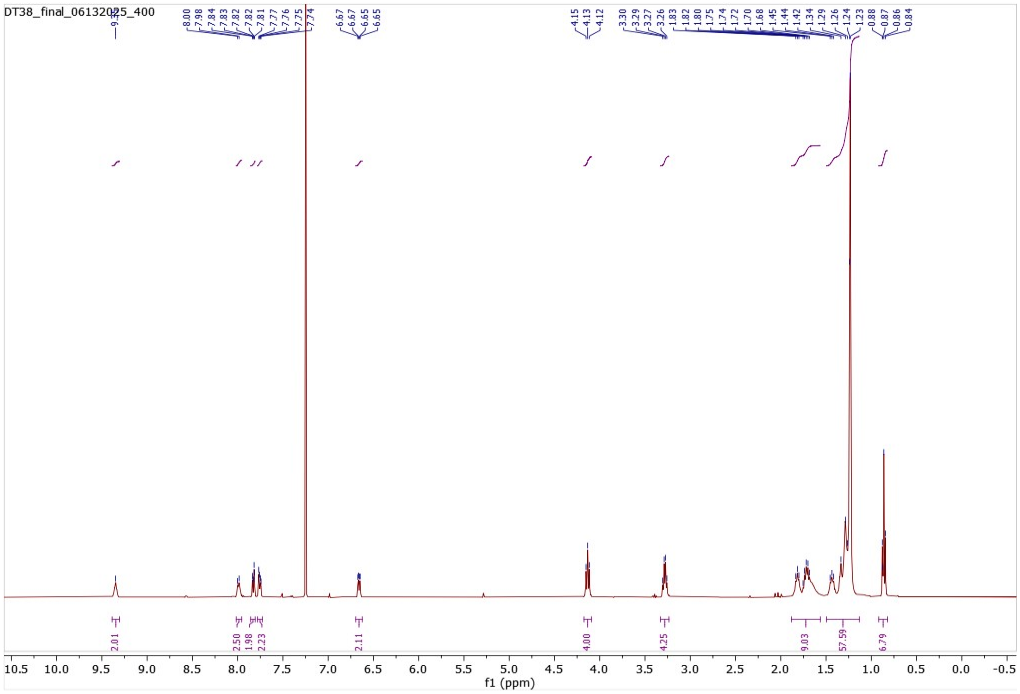


Figure S35: ^{1}H NMR (400 MHz) of **Isooct-14,8** in $CDCl_3$

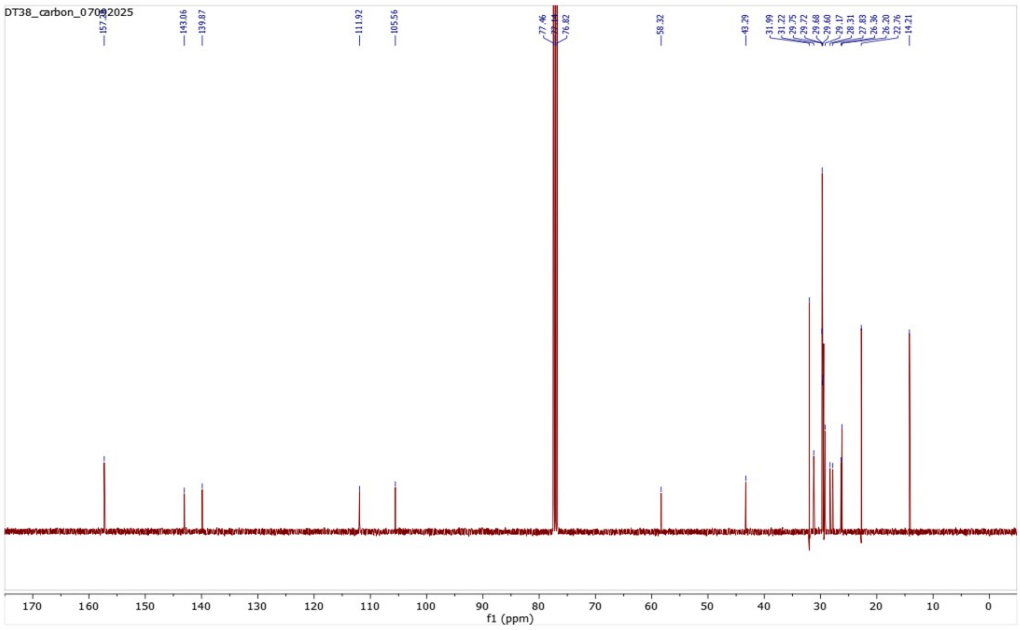


Figure S36: ^{13}C NMR (400 MHz) of **Isooct-14,8** in $CDCl_3$

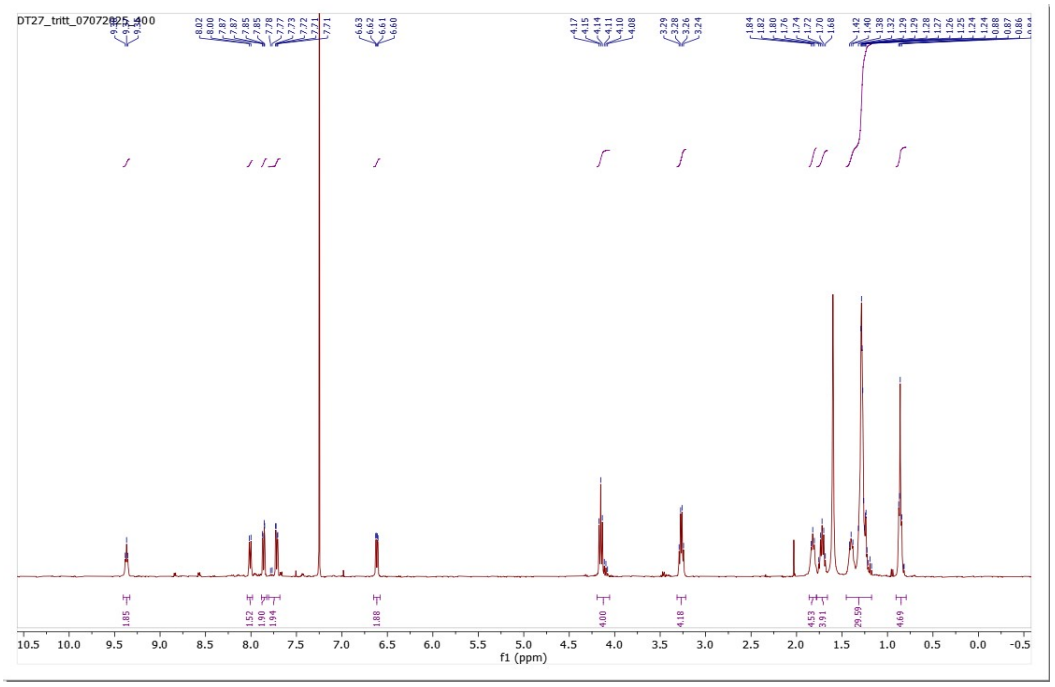


Figure S37: ^{1}H NMR (400 MHz) **Isooct-6,10** in $CDCl_3$

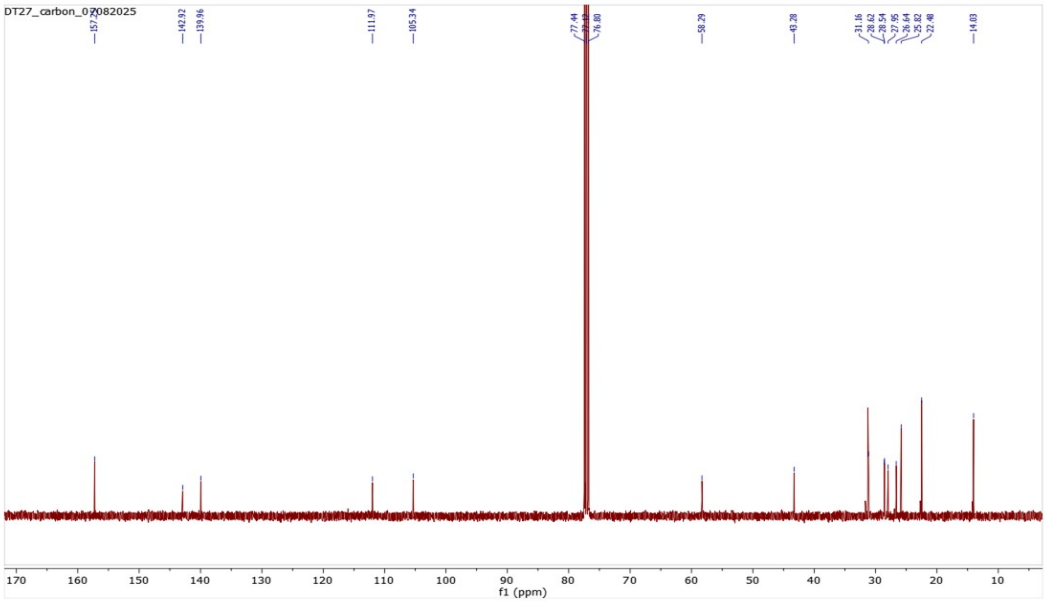
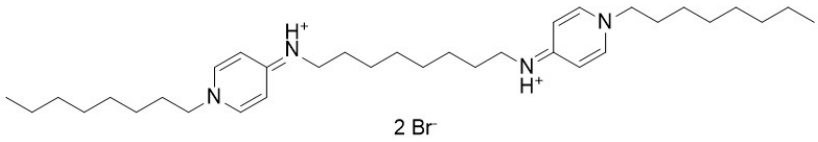


Figure S38: ^{13}C NMR (400 MHz) of **Isooct-6,10** in $CDCl_3$



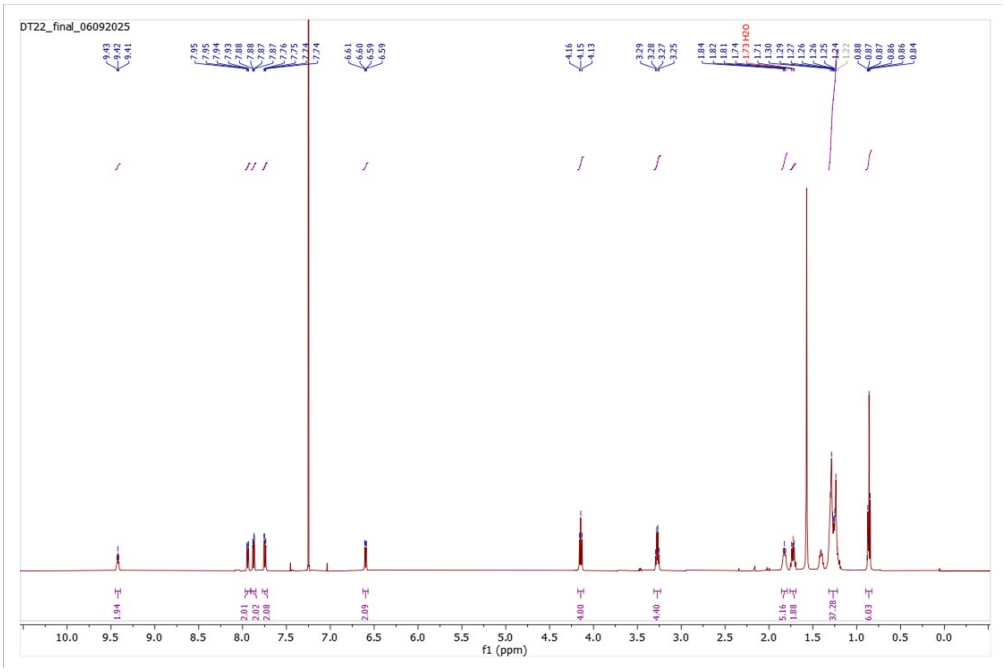


Figure S39: ^{1}H NMR (500 MHz) of **Isooct-8,10** in $CDCl_3$

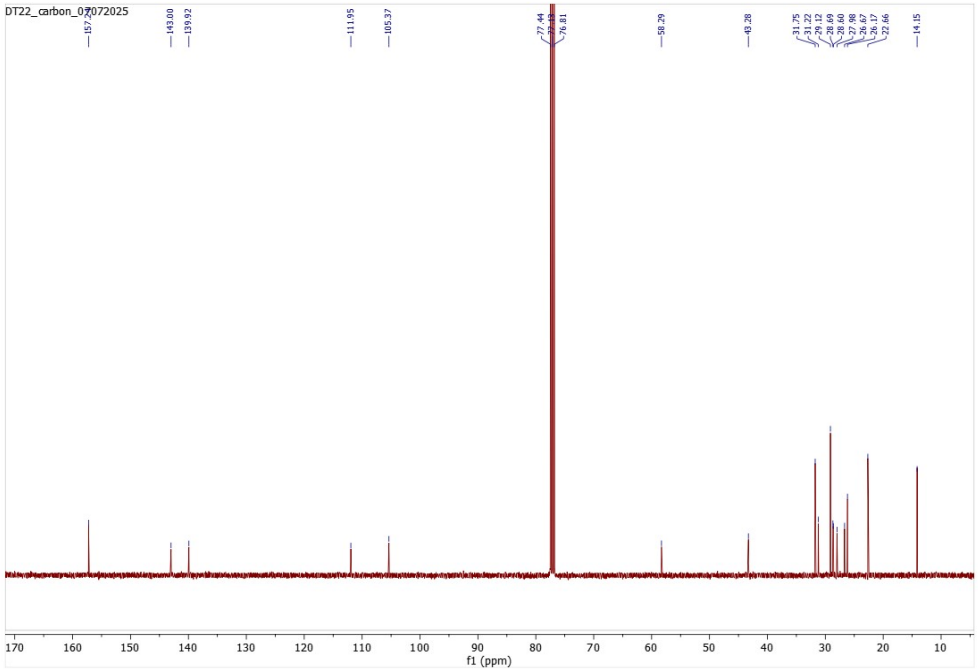
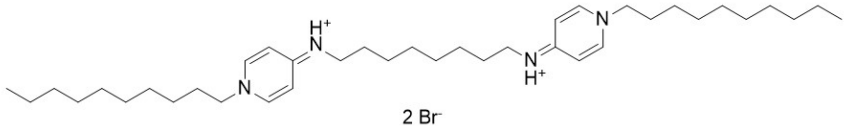


Figure S40: ^{13}C NMR (400 MHz) of **Isooct-8,10** in $CDCl_3$



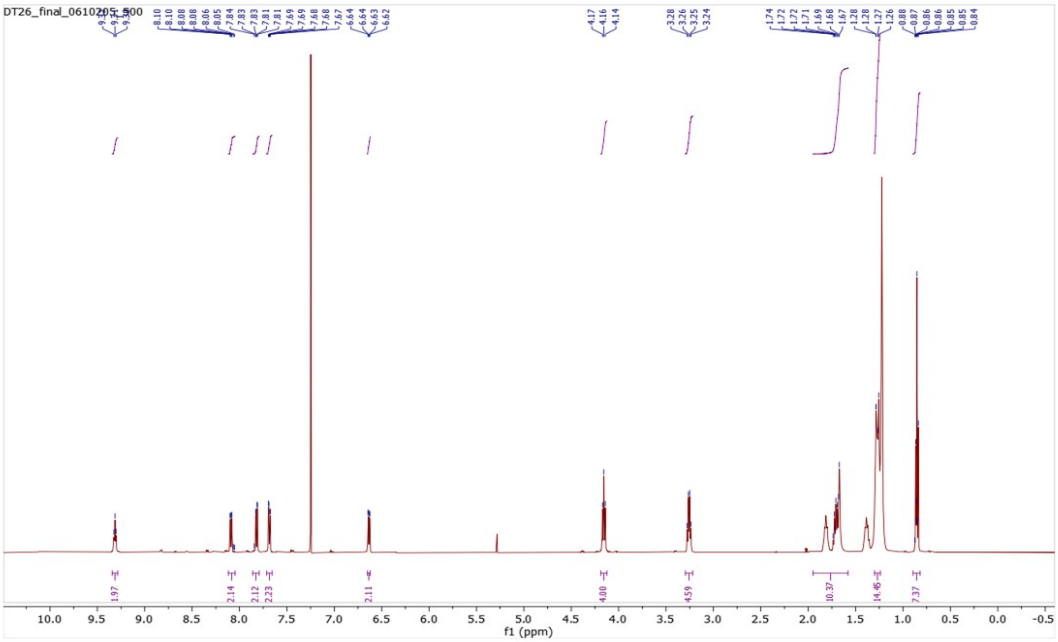


Figure S41: ^{1}H NMR (500 MHz) of **Isooct-10,10** in $CDCl_3$

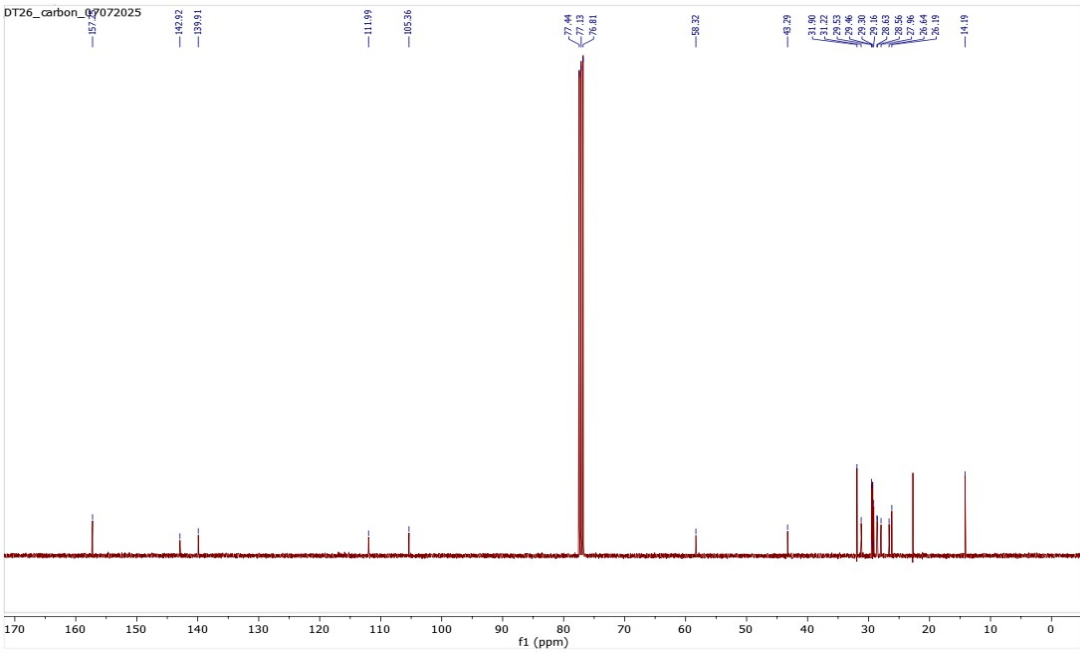


Figure S42: ^{13}C NMR (400 MHz) of **Isooct-10,10** in $CDCl_3$

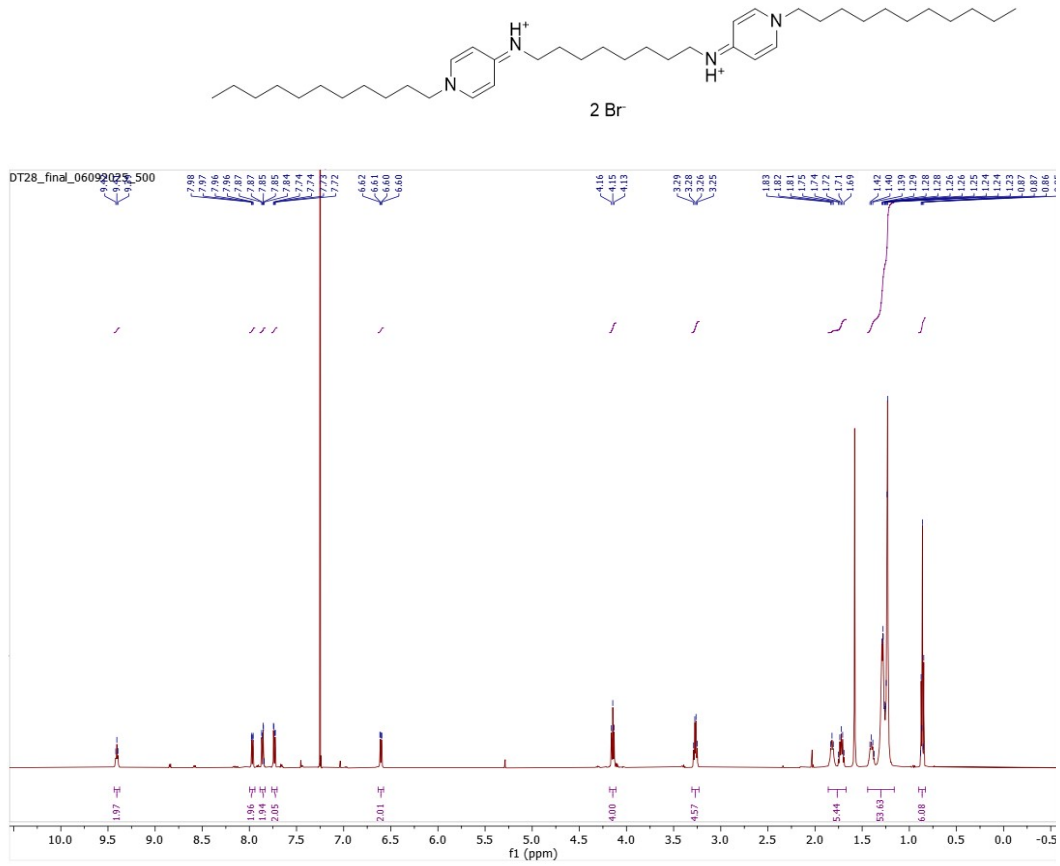


Figure S43: ^{1}H NMR (500 MHz) of **Isooct-11,10** in $CDCl_3$

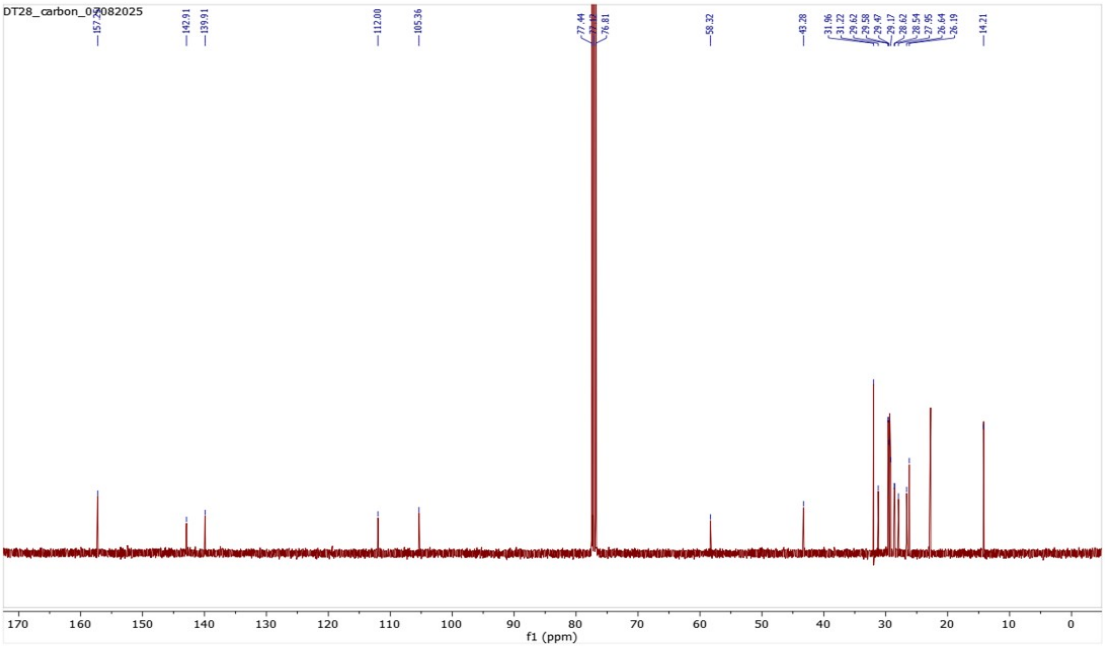
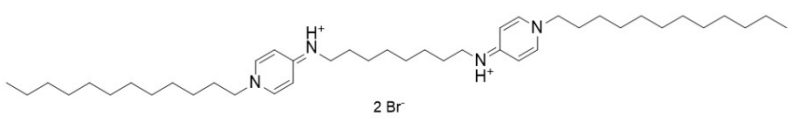


Figure S44: ^{13}C NMR (400 MHz) of **Isooct-11,10** in $CDCl_3$



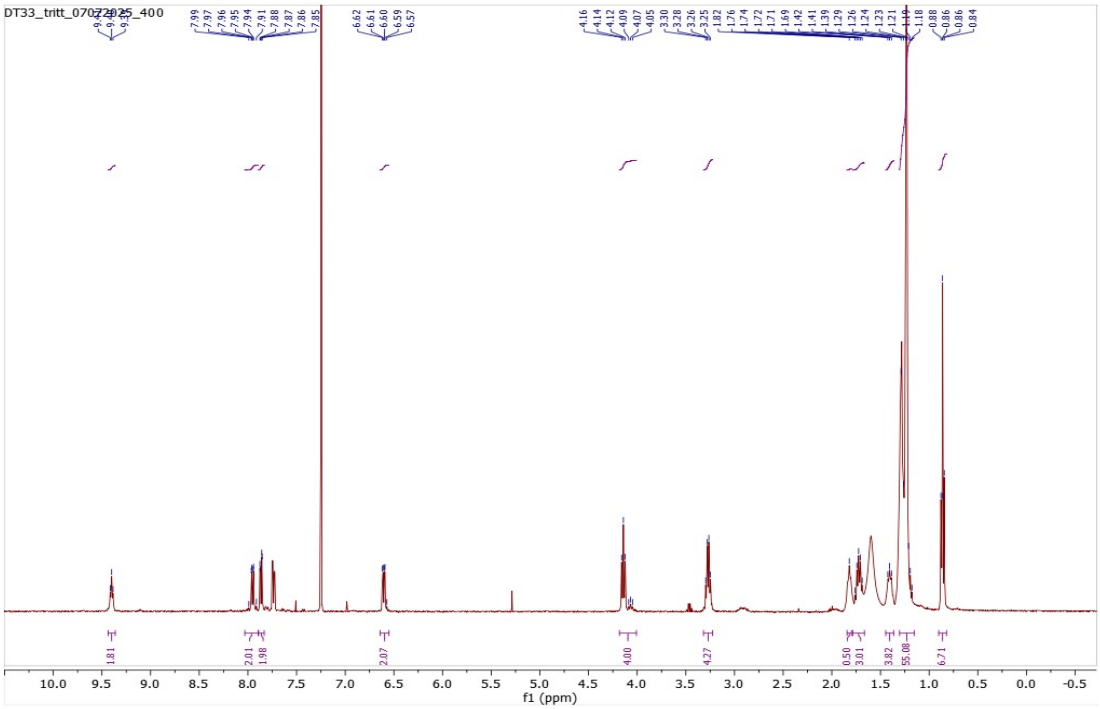


Figure S45: ^{1}H NMR (400 MHz) of **Isooct-12,10** in $CDCl_3$

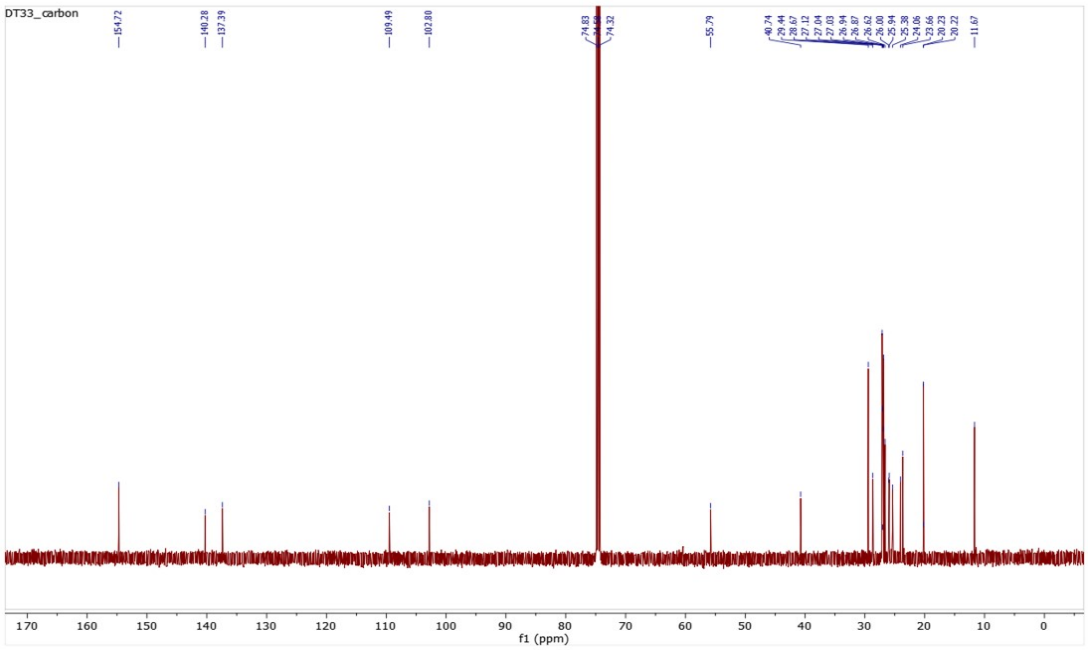
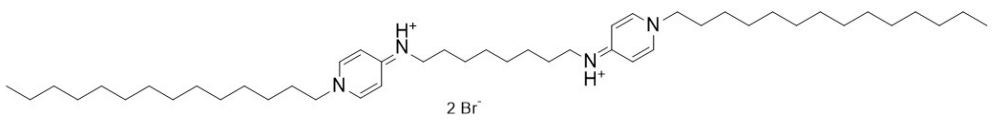


Figure S46: ^{13}C NMR (500 MHz) of **Isooct-12,10** in $CDCl_3$



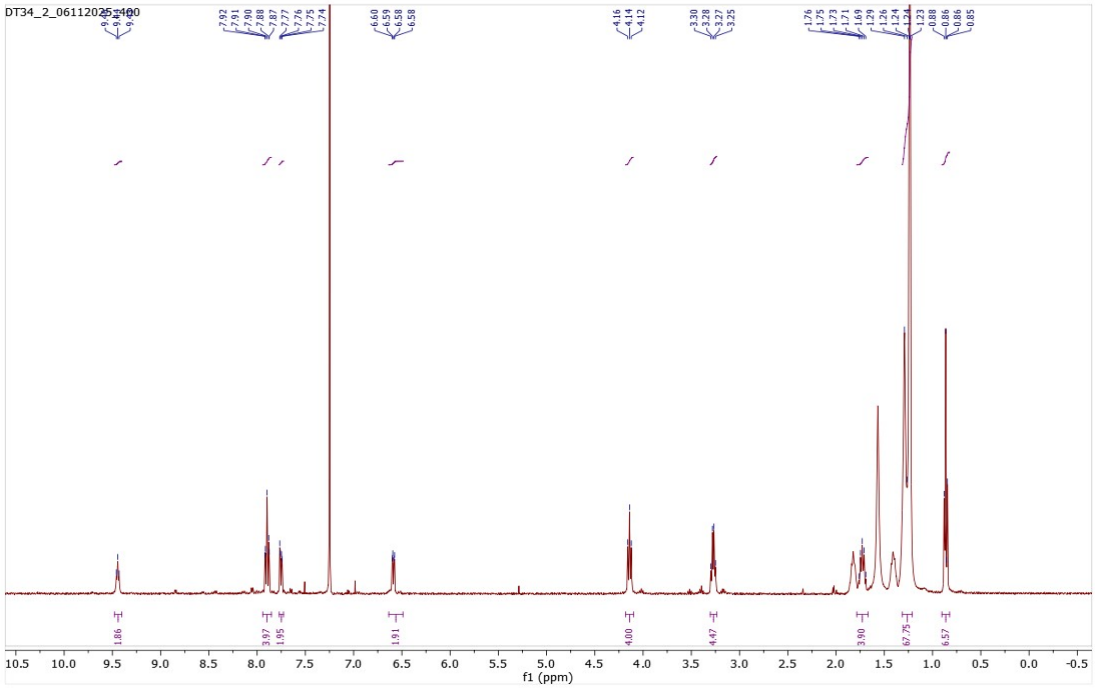


Figure S47: ^{1}H NMR (400 MHz) of **Isooct-14,10** in $CDCl_3$

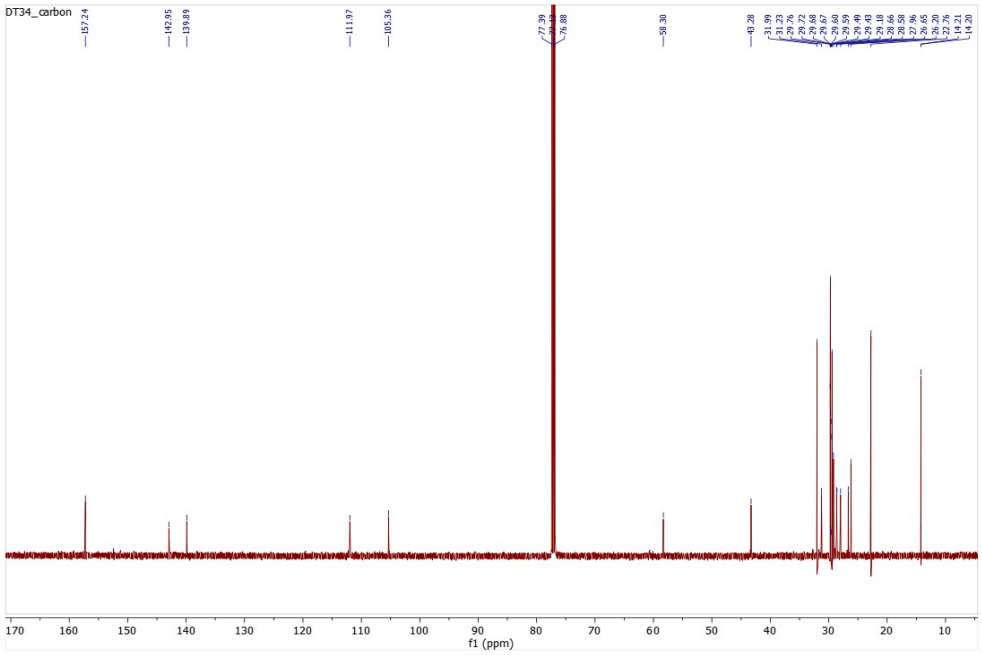


Figure S48: ^{13}C NMR (500 MHz) of **Isooct-14,10** in $CDCl_3$

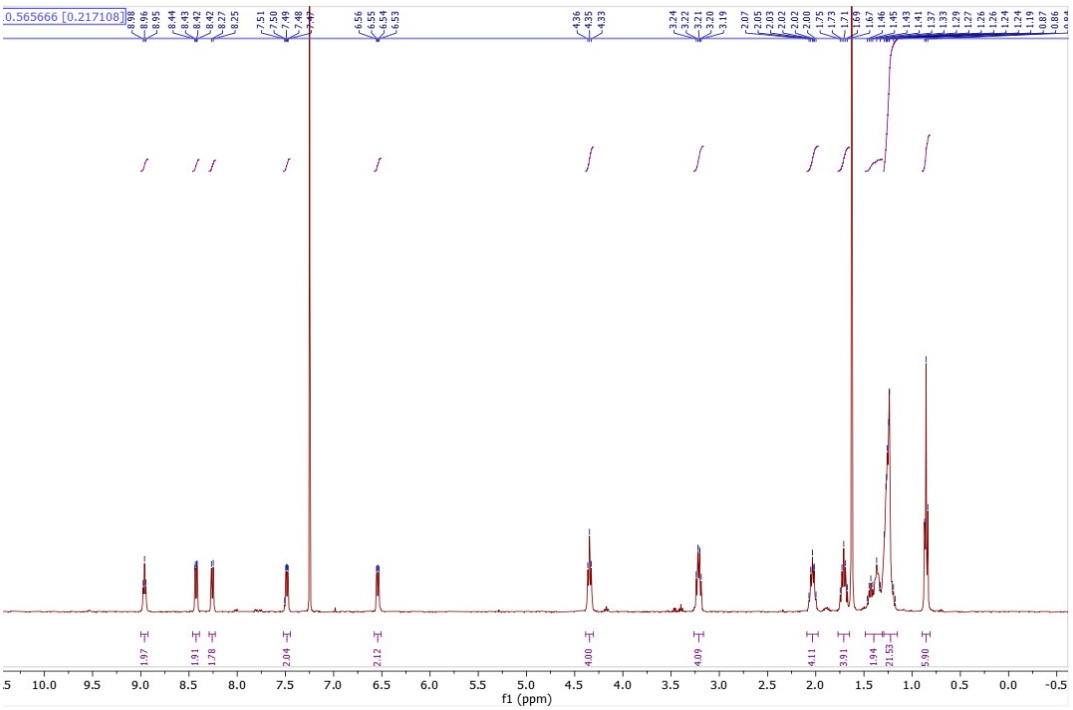


Figure S49: ^{1}H NMR (400 MHz) of **Oct-8,5** in $CDCl_3$

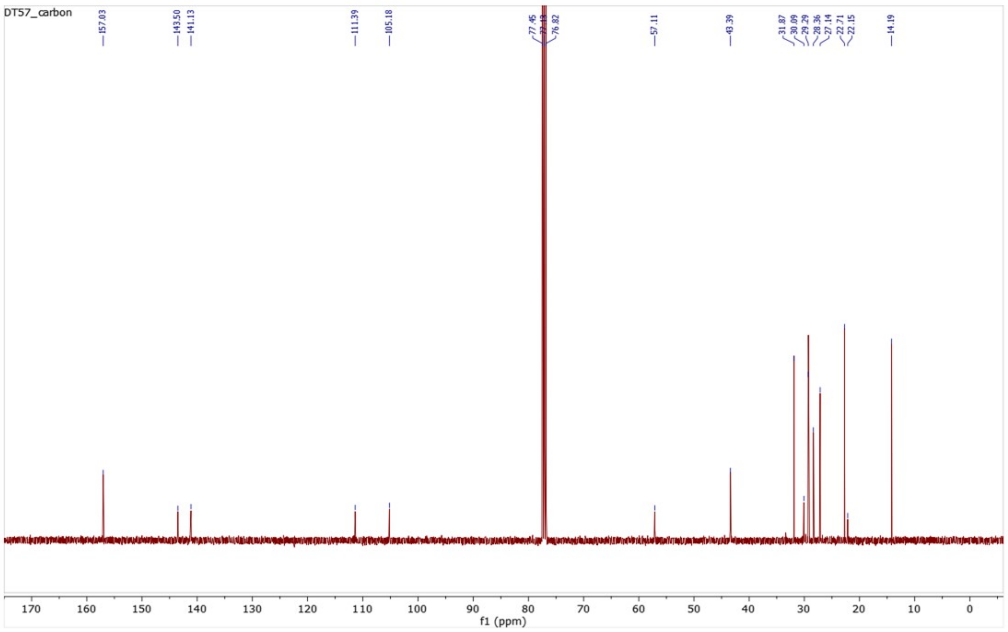


Figure S50: ^{13}C NMR (400 MHz) of **Oct-8,5** in $CDCl_3$

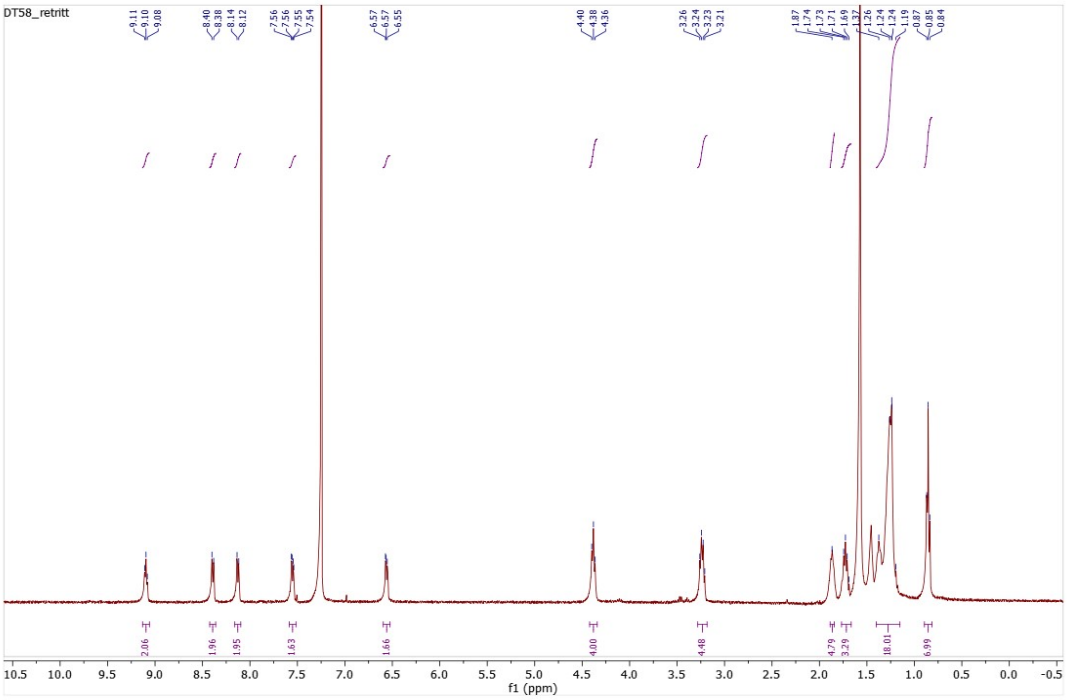


Figure S51: ^{1}H NMR (400 MHz) of **Oct-8,6** in $CDCl_3$

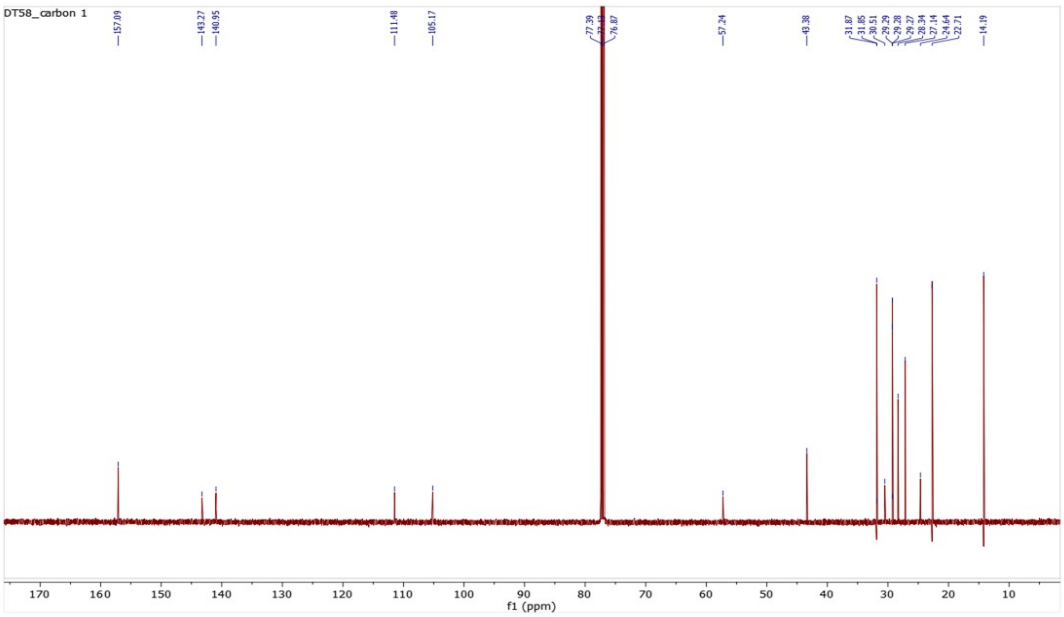


Figure S52: ^{13}C NMR (500 MHZ) of **Oct-8,6** in $CDCl_3$

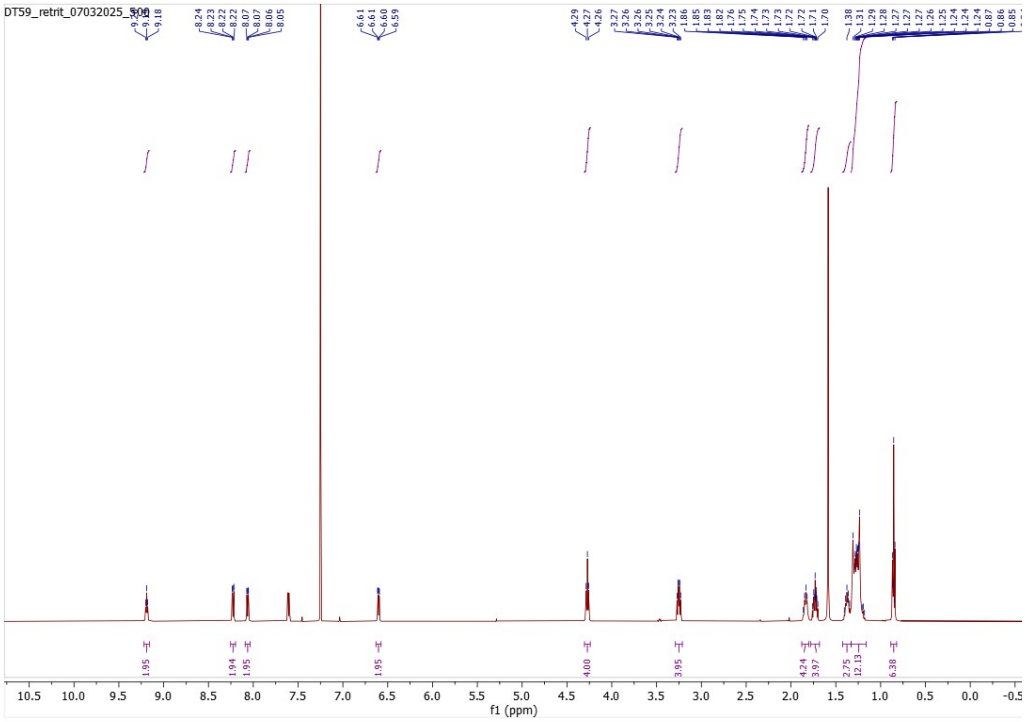


Figure S53: ^{1}H NMR (400 MHz) of **Oct-8,8** in $CDCl_3$

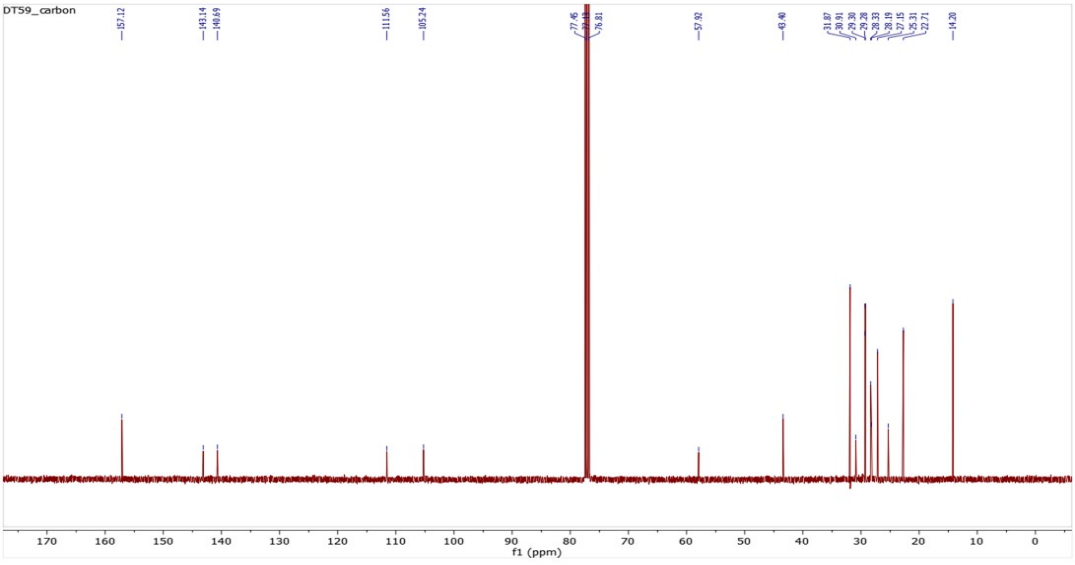


Figure S54: ^{13}C NMR (400 MHz) of **Oct-8,8** in $CDCl_3$

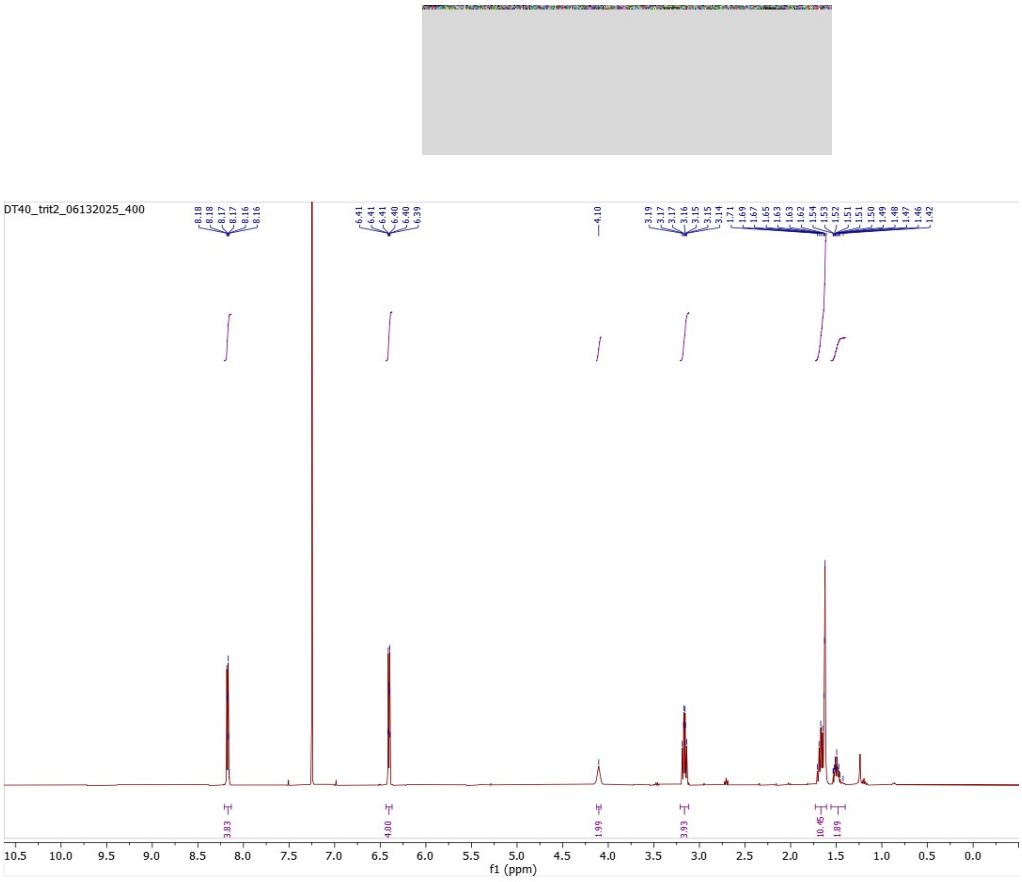


Figure S55: ^{1}H NMR (400 MHz) of **Isooct-0,5** In $CDCl_3$

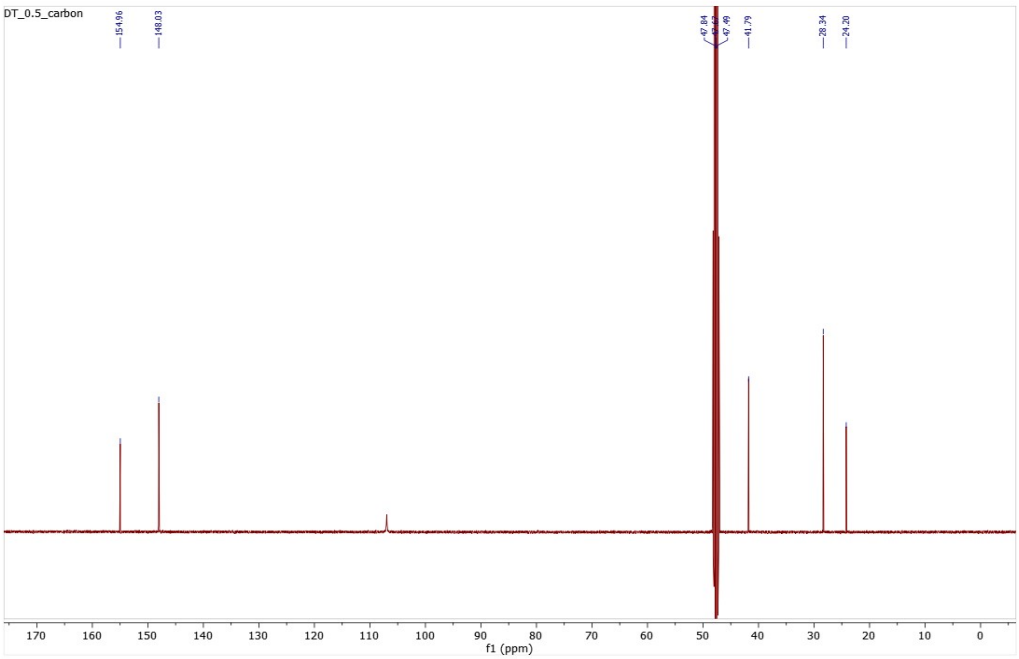


Figure S56: ^{13}C NMR (500 MHz) of **Isooct-0,5** in CD_3OD

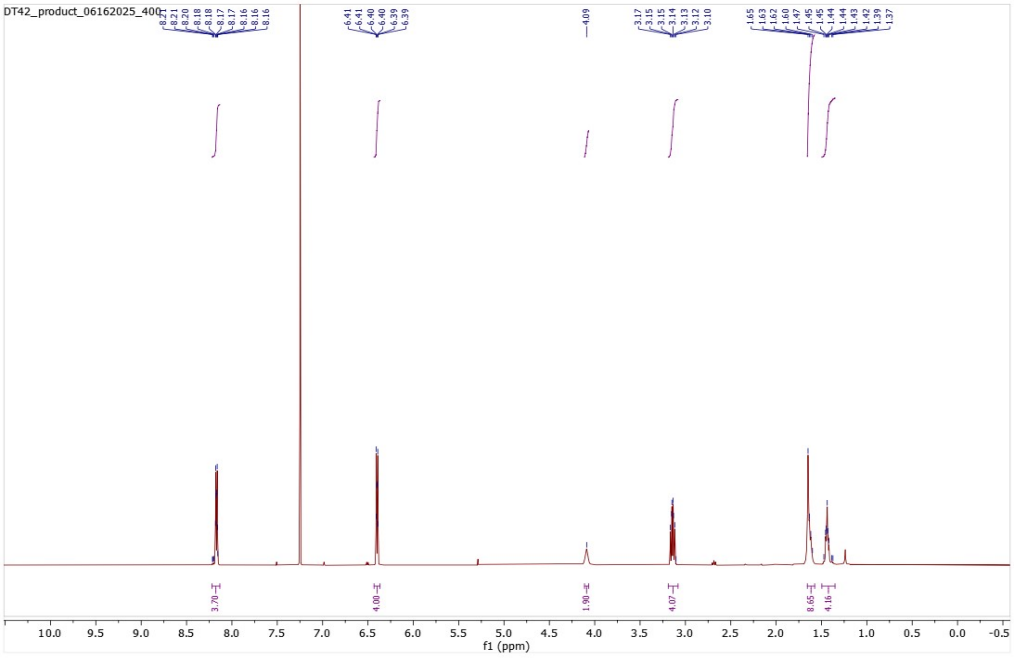


Figure S57: ^{1}H NMR (400 MHz) of **Isooct-0,6** in $CDCl_3$

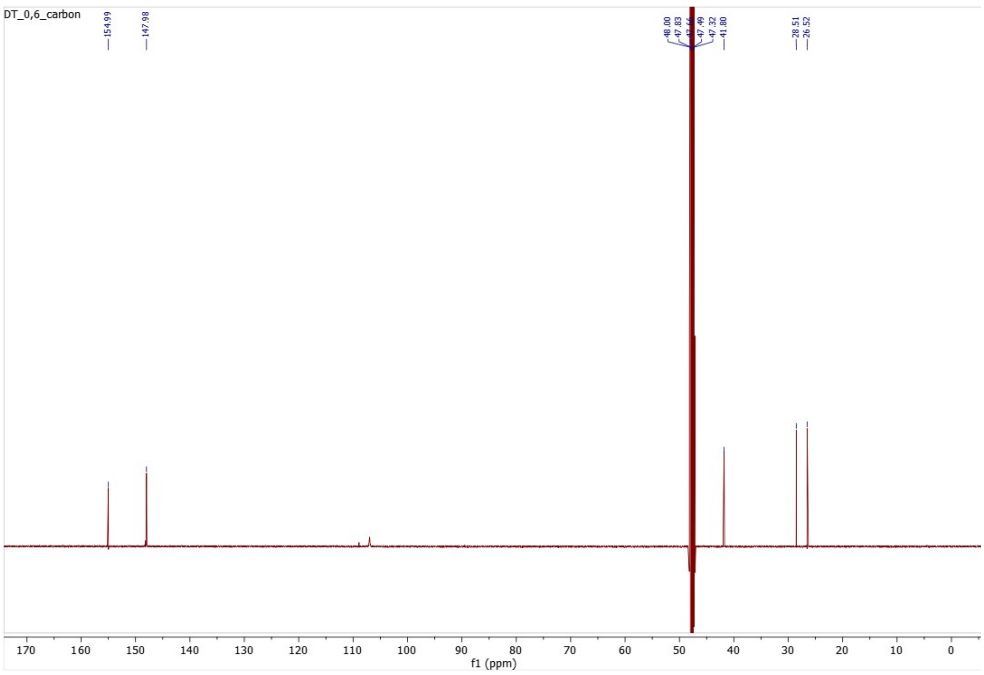


Figure S58: ^{13}C NMR (500 MHz) of **Isooct-0,6** in CD_3OD

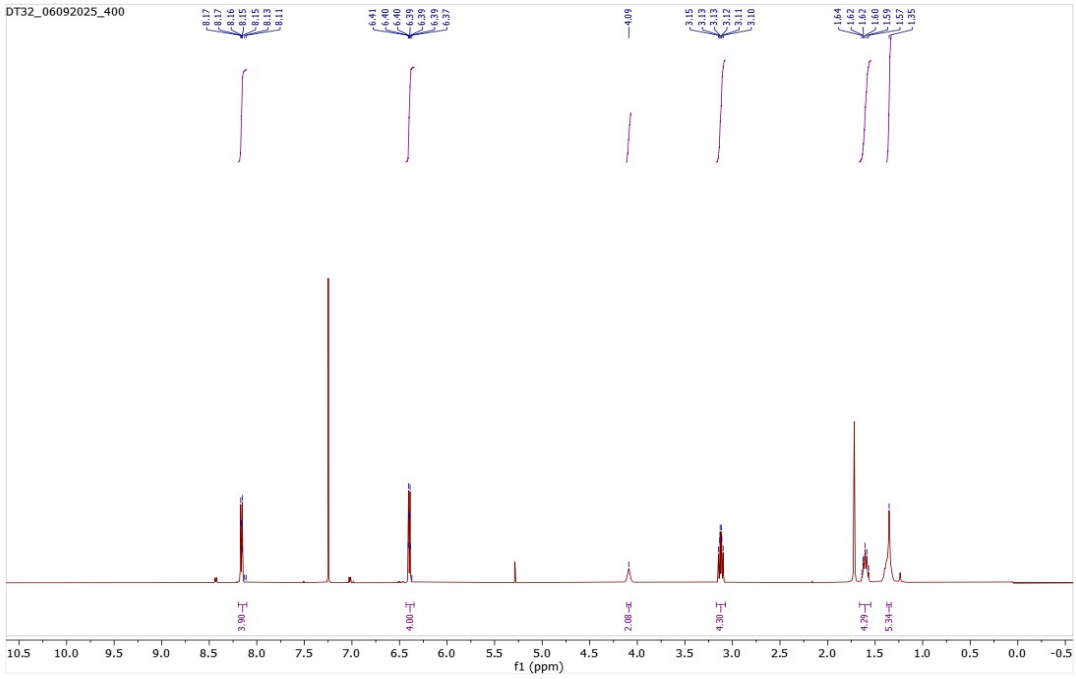


Figure S59: ^{1}H NMR of **Isooct-0,8** in $CDCl_3$

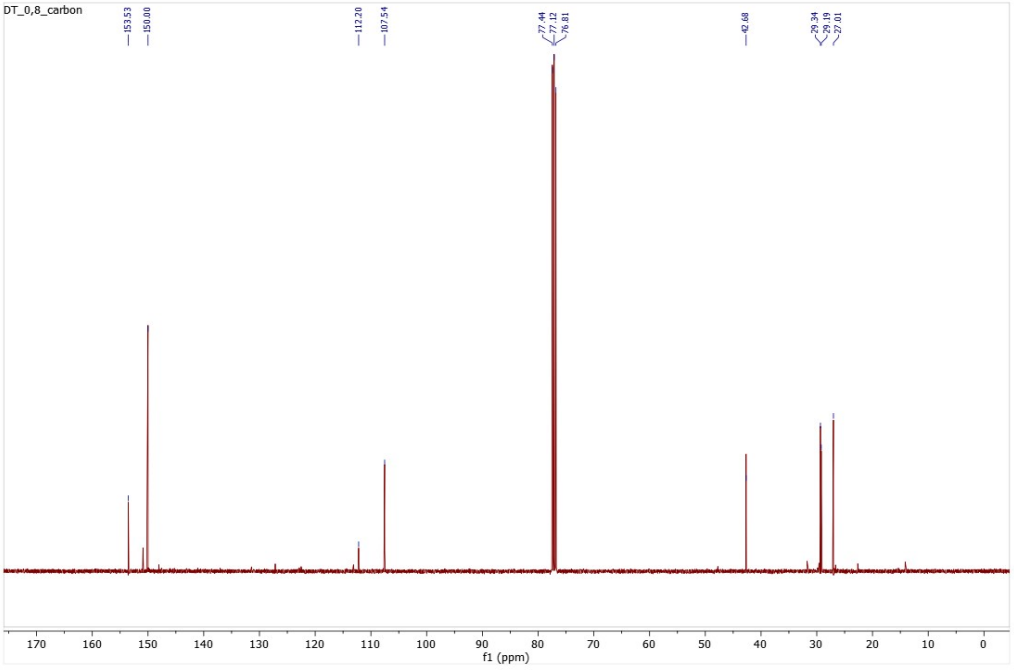


Figure S60: ^{13}C NMR (400 MHz) of **Isooct-0,8** in $CDCl_3$

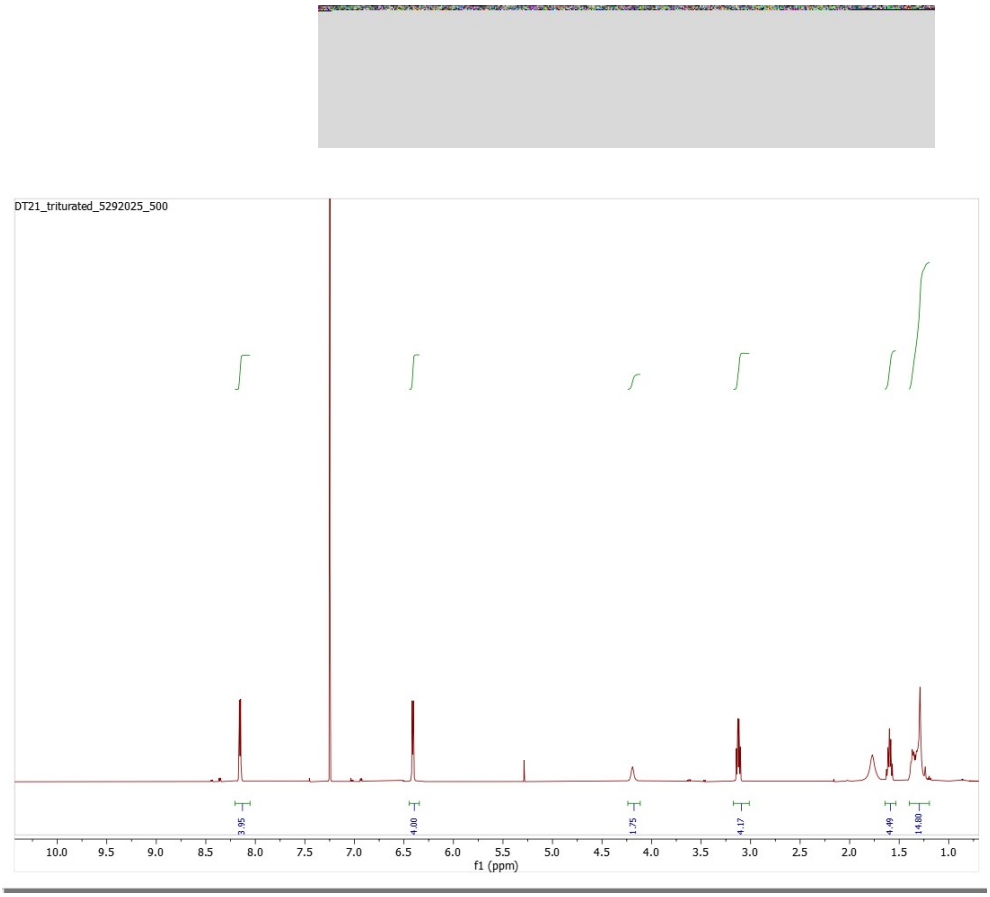


Figure S61: ^{1}H (500 MHz) NMR of **Isooct-0,10** in $CDCl_3$

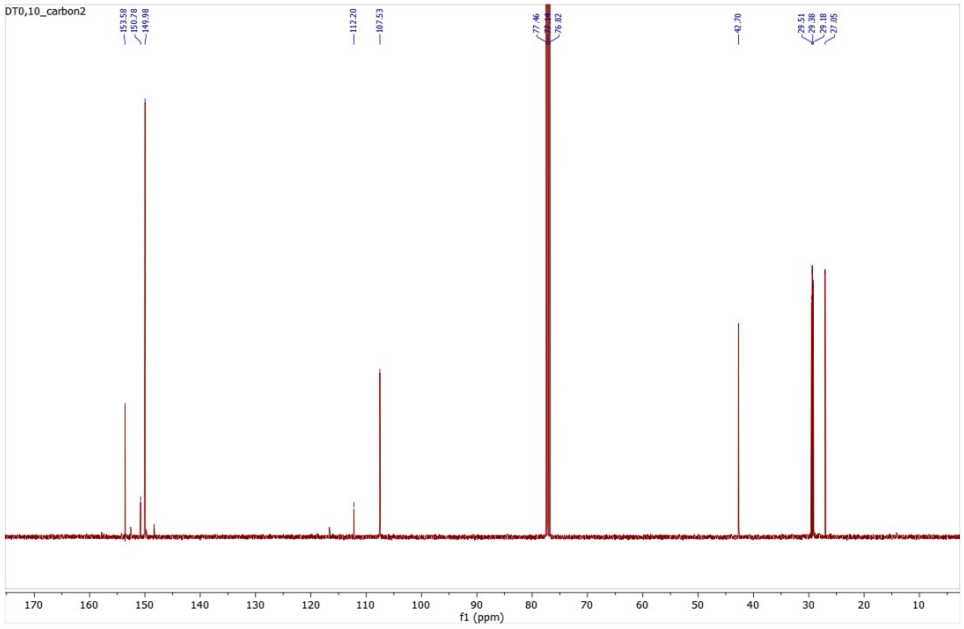


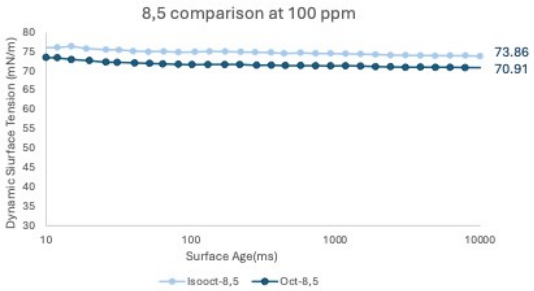
Figure S62: ^{13}C NMR (400 MHz) of **Isooct-0,10** in $CDCl_3$

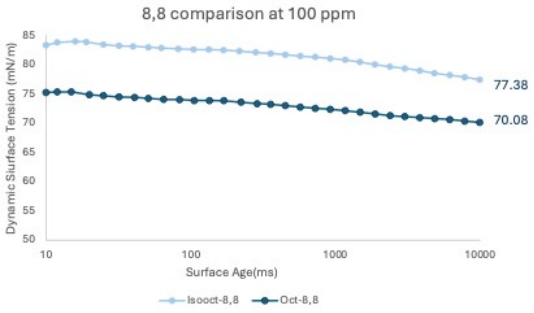
VII. Dynamic Surface Tension Measurements

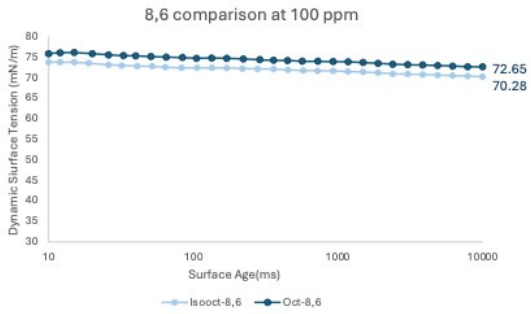
The solutions were prepared at three concentrations: 100 ppm, 300 ppm and 1000 ppm. The 1000 ppm stock solution was prepared by dissolving 30 mg of each compound in 30 mL of deionized water. Lower concentration solutions were prepared by serial dilution from the 1000 ppm stock solution. The 300 ppm and 100 ppm solutions were prepared by combining 6 mL and 2 mL of the 1000 ppm stock solution with 14 mL and 18 mL deionized water, respectively. All volumetric transfers were performed using pipettes to ensure accuracy. For compounds with limited solubility at room temperature, dissolution was facilitated using a water bath maintained at 60C. Once complete dissolution was achieved, solutions were allowed to equilibrate to room temperature (20C) prior to measurement.

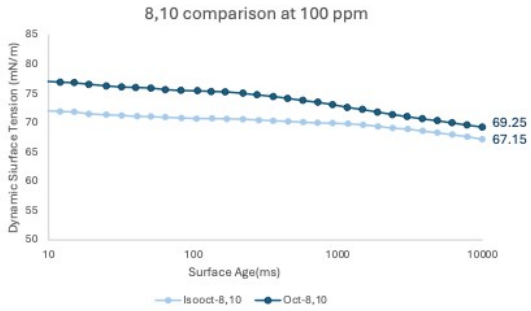
Dynamic surface tension measurements were conducted using a Kruss bubble pressure tensiometer. All measurements were performed at room temperature using 20 mL beakers. The tensiometer recorded surface tension as a function of surface age. Following the data collection, the measured surface tension values were exported and imported into Microsoft Excel for analysis. Graphs of surface tension versus surface age were generated for each compound at three concentrations and presented in the Supporting Information.

At 100 ppm

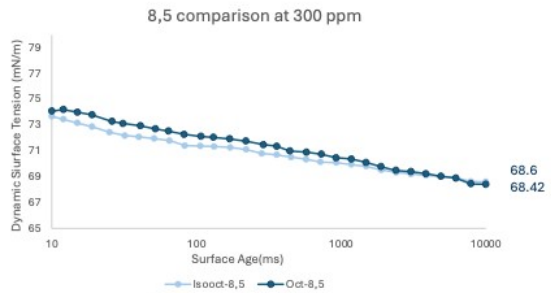


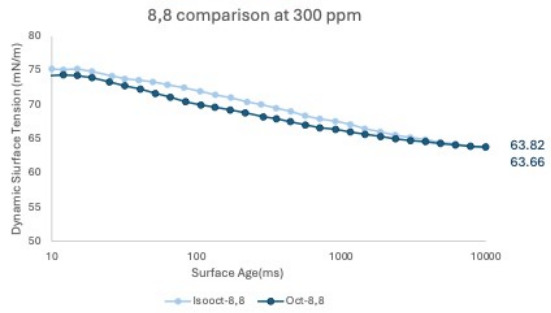


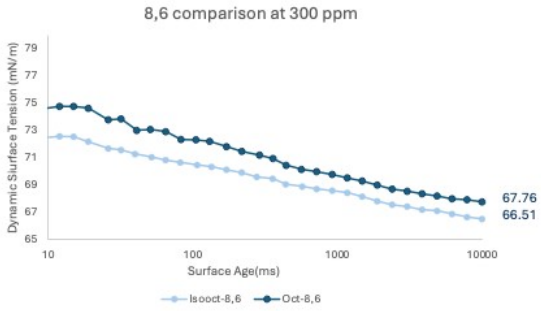


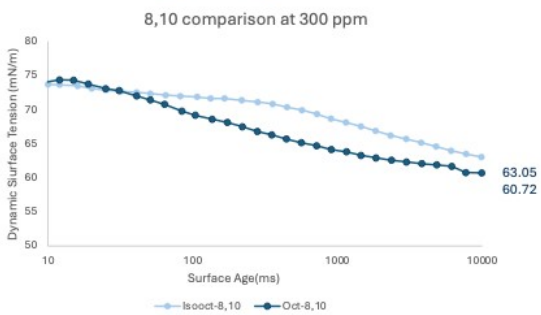


At 300 ppm

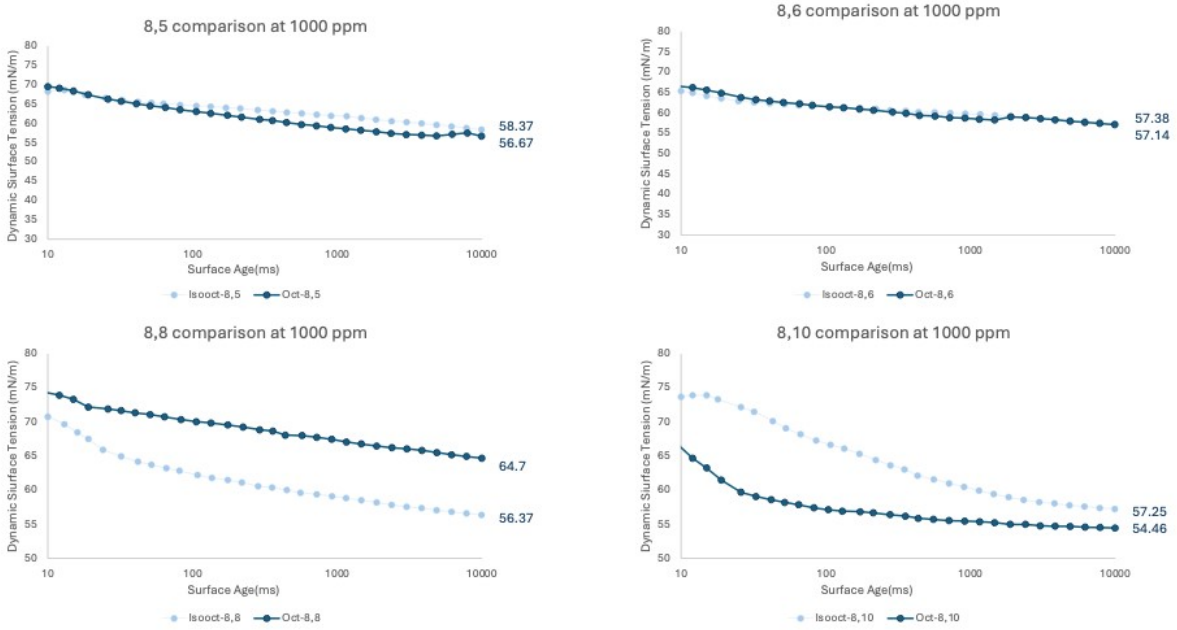








At 1000 ppm



VIII. Solubility Measurements

Octenidine dihydrochloride (15.5, 18.1, 19.6, 22.0, 22.6, 24.6, 26.3, 30.3 and 37.0 mg/mL) and isooctenidine dihydrochloride (18.0, 21.4 and 24.4 mg/mL) samples were each dissolved in 1.0 mL of deionized water by heating in a water bath at 70 °C with continuous magnetic stirring for 15 minutes. Samples were then removed from the water bath and allowed to cool to room temperature; cloudiness was assessed visually after 24h. Representative photographs are shown below.

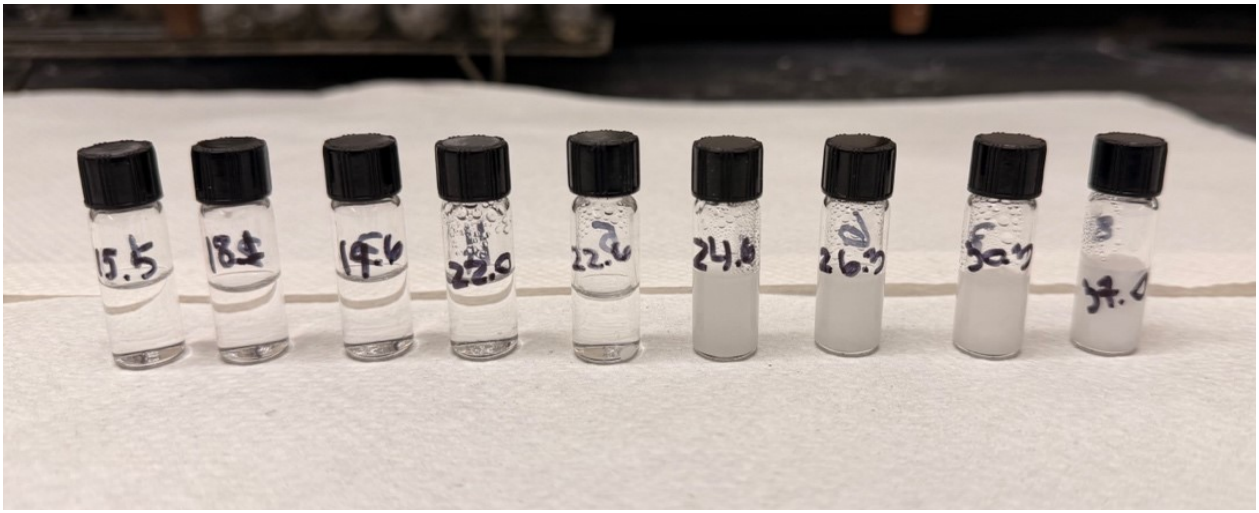


Figure S64: Aqueous solubility assessment of octenidine dihydrochloride (15.5 – 37.0 mg in 1.0 mL deionized water) after heating then 24 hours at room temperature. The highest concentration at which octenidine dihydrochloride remained soluble was 22.6 mg/mL.

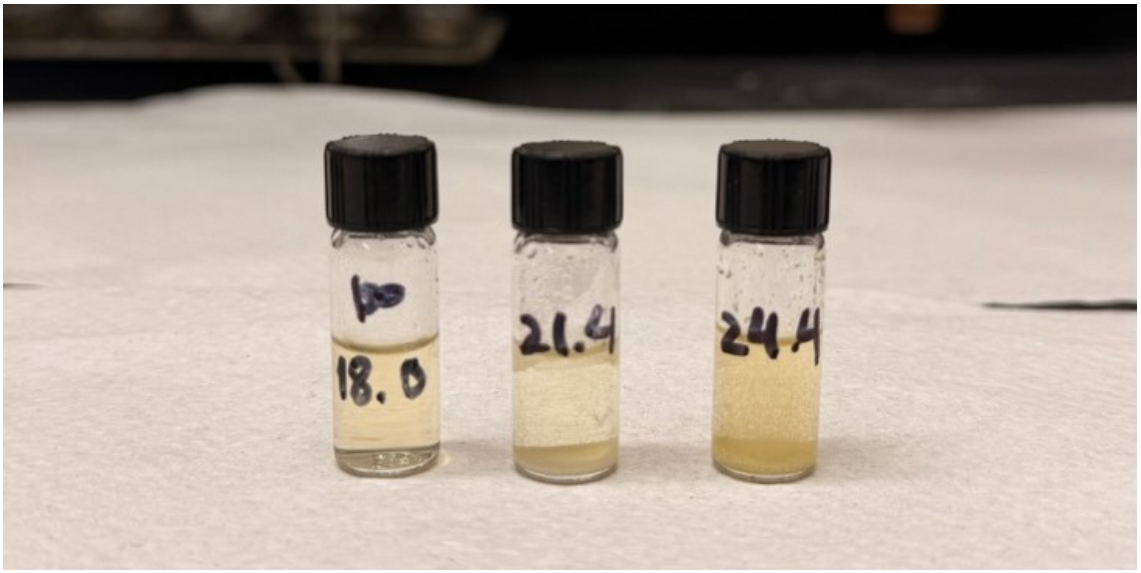


Figure S65: Aqueous solubility assessment of isooctenidine dihydrochloride (18.0 – 24.4 mg in 1.0 mL deionized water) after heating then 24 hours at room temperature. The highest concentration at which isooctenidine dihydrochloride remained soluble was 18.0 mg/mL.