Supporting Information

Broad-spectrum Cyclopropane-based Inhibitors of Coronavirus 3C-like Proteases: Biochemical, Structural, and Virological Studies.

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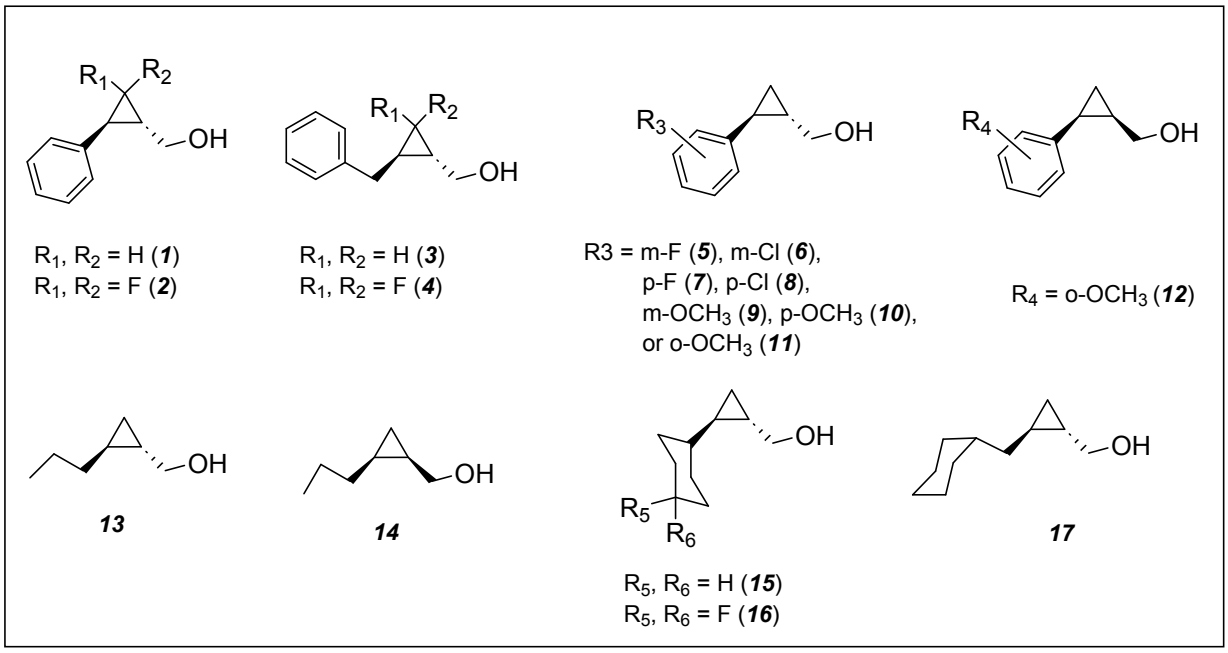
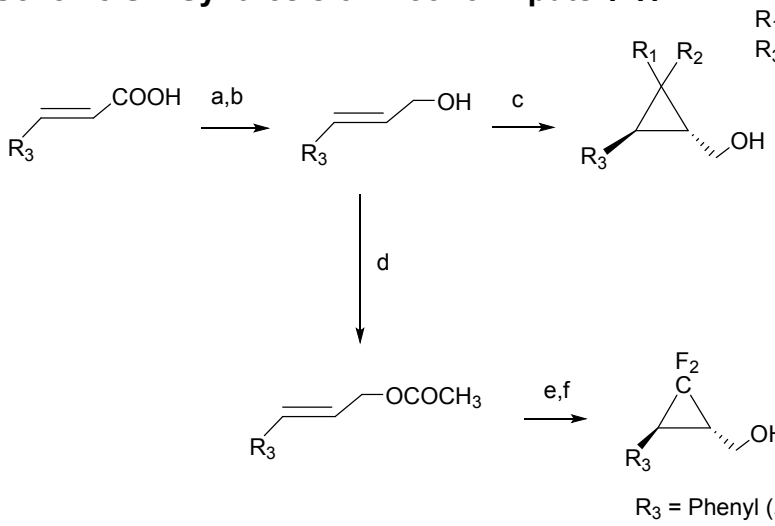


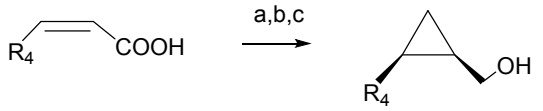
Figure S1. **Alcohol inputs *1-17***

Scheme S1. Synthesis of Alcohol Inputs *1-17*

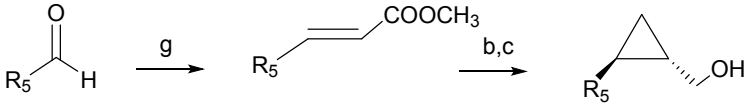


R_1=R_2=H,
R_3 = Phenyl (***1***), m-F phenyl (***5***),
m-Cl phenyl (***6***), p-F phenyl (***7***),
p-Cl phenyl (***8***), m-OCH_3 phenyl (***9***),
p-OCH_3 phenyl (***10***),
o-OCH_3 phenyl (***11***),
n-Propyl (***13***)

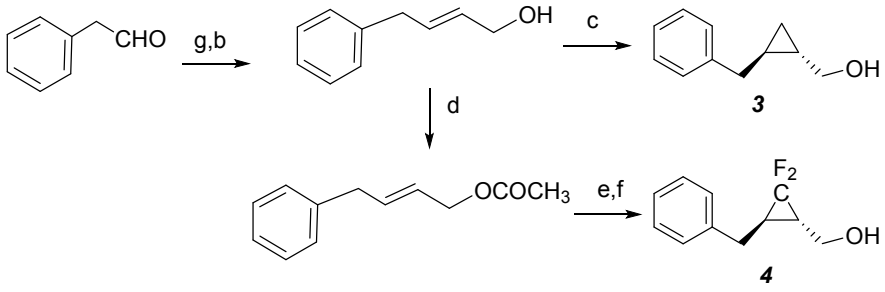
R_3 = Phenyl (***2***)



R_4 = o-OCH_3 phenyl (***12***), n-Propyl (***14***)

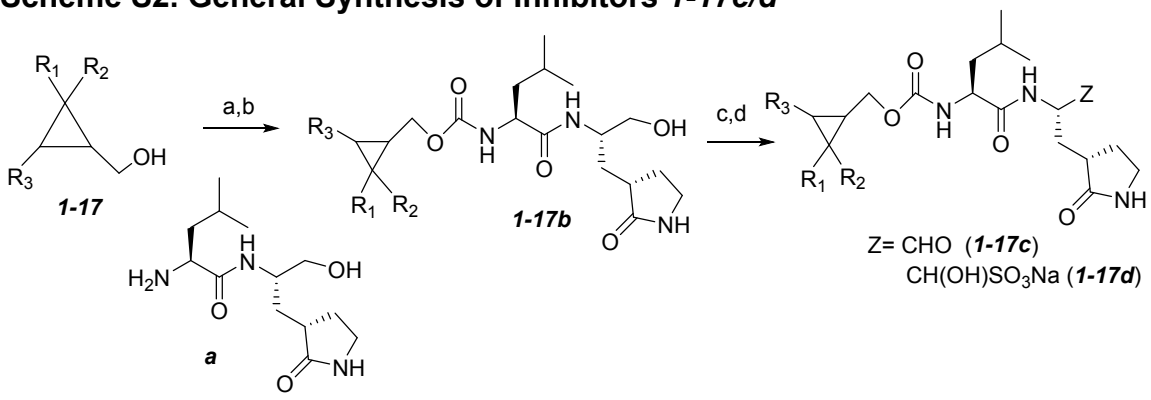


R_5 = Cyclohexyl (***15***),
4,4-difluorocyclohexyl (***16***),
1-Cyclohexanemethyl (***17***)



[a] CH_3I/Cs_2CO_3/ACN/reflux/2h,[b] DIBAL/DCM/ 0-5^{0}C/2h, [c] Et_2Zn/CH_2I_2/DCM/0-5^{0}C/30 min/then RT/overnight,
[d] $(CH_3CO)_2O$/TEA/4-DMAP/RT/overnight, [e] TFDA/NaF/Toluene/130-135^{0}C/2h, [f] $LiOH_{aq}$/THF/RT/3h,
[g] NaH/$(CH_3O)_2P(O)CH_2COOCH_3$ /DCM/RT/ovenight.

Scheme S2. General Synthesis of Inhibitors *1-17c/d*



[a] DSC/TEA/ACN/RT/4h,[b] ***a***/TEA/DCM/RT/3h, [c] DMP/DCM/15^{0}C/3h, [d] $NaHSO_3$/EtOAc/EtOH/50^{0}C/3h

Synthesis of compounds *1c/d-17c/d*

General information

Reagents and dry solvents were purchased from various chemical suppliers (Sigma-Aldrich, Acros Organics, Chem-Impex, TCI America, Oakwood chemical, Cambridge Isotopes, Alpha Aesar and Fisher) and were used as obtained. Silica gel (230-450 mesh) used for flash chromatography was purchased from Sorbent Technologies (Atlanta, GA). Normal phase chromatography was performed on a Teledyne ISCO CombiFlash system using RediSep normal phase silica cartridges (35-70 μm particle size range). Thin layer chromatography was performed using Analtech silica gel plates. Visualization was accomplished using UV light and/or iodine. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using Varian XL-400 spectrometer. The purity of the final compounds was found to be ≥ 95 %, as determined by absolute qNMR analysis using a Bruker AV III 500 NMR spectrometer equipped with a CPDUL CRYOprobe and CASE autosampler (the University of Kansas Nuclear Magnetic Resonance Laboratory). Dimethyl sulfone *Trace*CERT® was used as the internal calibrant. High resolution mass spectrometry (HRMS) was performed at the Wichita State University Mass Spectrometry lab using an Orbitrap Velos Pro mass spectrometer (ThermoFisher, Waltham, MA) equipped with an electrospray ion source.

Synthesis of alcohol inputs *1-17*

Preparation of α,β-unsaturated alcohols for *1, 2, 5-14* (Scheme S1). General procedure. Methyl iodide (5 eq) was added to a solution of α,β-unsaturated carboxylic acid (1 eq) and cesium carbonate (1.5 eq) in anhydrous acetonitrile (54 ml/g α,β-

unsaturated carboxylic acid), and refluxed for 2 h. The reaction mixture was cooled down to room temperature, filtered and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (40 ml/g α,β-unsaturated carboxylic acid) and washed with saturated aqueous $NaHCO_3$ (2 x 20 mL/ g carboxylic acid), followed by brine (20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to yield the α, β-unsaturated methyl ester which was used in the next step.

α, β-unsaturated methyl ester (1 eq) in DCM (4 ml/g α, β-unsaturated methyl ester) was cooled to -78 ^{0}C and diisobutyl aluminum hydride in toluene (1M, 2 eq) was added, followed by stirring for 1 h at -78 ^{0}C. The reaction mixture was neutralized by adding saturated ammonium chloride (2 ml/g α,β-unsaturated ester). When the reaction mixture reached room temperature, the solid was filtered off and washed with DCM. The filtrate was washed with brine (20 mL/g ester) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The resulting crude product was purified by flash chromatography (silica gel/ethyl acetate/hexane) to yield to yield the α, β-unsaturated alcohol.

Preparation of α,β-unsaturated alcohols for *3, 4, 15-17* (Scheme S1). General procedure. A solution of trimethyl phosphonoacetate (3 eq) in anhydrous DCM (40 ml/g trimethyl phosphonoacetate) was added dropwise to a solution of sodium hydride (90%, 2.5 eq) in anhydrous DCM (25 ml/g sodium hydride) and stirred for 0.5 h at room temperature. The appropriate aldehyde (1 eq) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled in ice and quenched by adding water dropwise. The organic layer was separated and washed with 5% aqueous hydrochloric acid (2 x 20 mL/g aldehyde), saturated aqueous $NaHCO_3$ (2 x 20 mL), followed by brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4,

filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography to yield the α, β-unsaturated ester.

α, β-unsaturated ester (1 eq) in DCM (4 ml/g α, β-unsaturated methyl ester) was cooled to -78 ^{0}C and diisobutyl aluminum hydride in toluene (1M, 2 eq) was added, followed by stirring for 1 h at -78 ^{0}C. The reaction mixture was neutralized by adding saturated ammonium chloride (2 ml/g ester). When the temperature of the solution reached room temperature, the solid was filtered off, washed with DCM, and the combined filtrates were washed with brine (20 mL/g ester) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The resulting crude product was purified by flash chromatography (silica gel/ethyl acetate/hexane) to yield the α, β-unsaturated alcohol.

General procedure for making cyclopropane alcohols (Simmons-Smith reaction). A solution of Et_2Zn in hexane (1M, 2 eq) and anhydrous dichloromethane (mL) were mixed and cooled to 0-5 ^{0}C. CH_2I_2 (or CD_2I_2) (4 eq) was added dropwise and stirred for 10 min, whereupon a white precipitate formed. ***Caution!*** The reaction was found to react violently upon addition of CH_2I_2 producing a higher pressure inside the round bottom flask. A solution of the α, β-unsaturated alcohol in DCM (20 ml/g alcohol) was added dropwise at 0-5 ^{0}C into above precipitate and the reaction mixture was stirred at RT overnight. The reaction mixture was quenched by adding saturated ammonium chloride (10 ml/g alcohol). The organic layer was separated. The aqueous layer was extracted with DCM (20 mL/g alcohol) and the combined organic layer was washed with brine (20 mL/g alcohol) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The resulting crude product was purified by flash chromatography (silica gel/ethyl acetate/hexane) to yield cyclopropane alcohols ***1,3, 5-17.***

General procedure for making *gem*-difluorocyclopropane alcohols *2* and *4*. To a solution of α, β-unsaturated alcohol (1 eq) in anhydrous DCM (2 ml/g α,β-unsaturated alcohol) was added TEA (1 eq) and acetic anhydride (1 eq), followed by 4-dimethylamino pyridine (4-DMAP) portion-wise and stirred overnight at room temperature. The reaction mixture was quenched by adding water dropwise. The organic layer was separated and washed with 5% aqueous hydrochloric acid (2 x 20 mL/g aldehyde), saturated aqueous $NaHCO_3$ (2 x 20 mL), followed by brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the α, β-unsaturated acetate ester.

Sodium fluoride (0.012 eq), α, β-unsaturated acetate ester (1 eq) and anhydrous toluene (1 eq) were added into a dry round bottom flask and heated up to 130±5 ^{0}C in an oil bath. Trimethylsilyl-2,2-difluoro-2-(fluorosulfonyl) acetate (1 eq) was added dropwise over 2h while heating. The reaction mixture was refluxed for 2 h and then cooled down to room temperature and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (40 ml/g α, β-unsaturated acetate ester) and washed with brine (20 mL/g α, β-unsaturated acetate ester). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography (silica gel/ethyl acetate/hexane) to yield the *gem*-difluorocyclopropane acetate ester.

Lithium hydroxide (4 eq) was added to a solution of *gem*-difluorocyclopropane acetate ester (1 eq) in THF (7 ml/g ester) and stirred at room temperature for 3 h. The reaction mixture was acidified using 5% hydrochloric acid and extracted into ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The

crude product was purified by flash chromatography to yield *the gem*-difluorocyclopropane acetate ester.

Synthesis of compounds *1c/d-17c/d*

Preparation of compounds *1b-17b* (Scheme S2). General procedure. To a solution of alcohol (1 eq) (Fig 2) in anhydrous acetonitrile (10 mL/g alcohol) was added N, N'-disuccinimidyl carbonate (1.2 eq) and TEA (3.0 eq) and the reaction mixture was stirred for 4h at room temperature. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (40 mL/g alcohol). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 20 mL/ g alcohol), followed by brine (20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the mixed carbonate which was used in the next step without further purification.

To a solution of Leu-Gln surrogate amino alcohol ***a*** (1.0 eq) in dry methylene chloride (10 mL/g of amino alcohol) was added TEA (1.5 eq) and the reaction mixture was stirred for 20 min at room temperature (solution 1). In a separate flask, the mixed carbonate was dissolved in dry methylene chloride (10 mL/g of carbonate) (solution 2). Solution 1 was added to solution 2 and the reaction mixture was stirred 3h at room temperature. Methylene chloride was added to the organic phase (40 mL/g of carbonate) and then washed with saturated aqueous $NaHCO_3$ (2 x 20 mL/ g alcohol), followed by brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resultant crude product was purified by flash chromatography (silica gel/hexane/ethyl acetate) to yield dipeptidyl alcohol ***b*** as a white solid.

Preparation of compounds *1c-17c* (Scheme S2). General procedure. To a solution of dipeptidyl alcohol ***b*** (1 eq) in anhydrous dichloromethane (300 mL/g dipeptidyl alcohol) kept at 0-5 ^{o}C under a N_2 atmosphere was added Dess-Martin periodinane reagent (3.0 eq) and the reaction mixture was stirred for 3 h at 15-20 ^{o}C. The organic phase was washed with 10% aq $Na_2S_2O_3$ (2 x 100 mL/g dipeptidyl alcohol), followed by saturated aqueous $NaHCO_3$ (2 x 100 mL/ g dipeptidyl alcohol), distilled water (2 x 100 mL/ g dipeptidyl alcohol), and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (silica gel/hexane/ethyl acetate) to yield aldehyde ***c*** as a white solid.

Preparation of compounds *1-17d* (Scheme S2). General procedure. To a solution of dipeptidyl aldehyde ***c*** (1 eq) in ethyl acetate (10 mL/g of dipeptidyl aldehyde) was added absolute ethanol (5 mL/g of dipeptidyl aldehyde) with stirring, followed by a solution of sodium bisulfite (1 eq) in water (1 mL/ g of dipeptidyl aldehyde). The reaction mixture was stirred for 3 h at 50 ^{o}C. The reaction mixture was allowed to cool to room temperature and then vacuum filtered. The solid was thoroughly washed with absolute ethanol and the filtrate was dried over anhydrous sodium sulfate, filtered, and concentrated to yield a white solid. The white solid was stirred with dry ethyl ether (3 x 10 mL/ g of dipeptidyl aldehyde), followed by careful removal of the solvent using a pipette and dried using a vacuum pump for 2 h to yield dipeptidyl bisulfite adduct ***d*** as a white solid.

Characterization of compounds *1c/d-17c/d*

((1S,2S)-2-phenylcyclopropyl) methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl) propan-2-yl)amino)pentan-2-yl)carbamate (***1c***). 1H NMR (400 MHz, dmso) δ 9.39 (dd, J = 6.3, 3.0 Hz, 1H), 8.46 (dd, J = 18.2, 7.4 Hz, 1H), 7.71 – 7.32 (m, 2H), 7.23 (t, J = 7.5 Hz, 2H), 7.18 – 7.10 (m, 1H), 7.07 (d, J = 7.5 Hz, 2H), 4.73 – 4.11 (m, 1H), 4.10 – 3.72 (m, 3H), 3.29 – 2.98 (m, 2H), 2.36 – 2.05 (m, 2H), 1.95 – 1.71 (m, 2H), 1.71 – 1.30 (m, 6H), 0.95 (d, J = 6.2 Hz, 2H), 0.91 – 0.78 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}N_3NaO_5$ 466.2318; Found 466.2297.

((1R,3R)-2,2-difluoro-3-phenylcyclopropyl) methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***2c***). Yield (90%). 1H NMR (400 MHz, cdcl3) δ 9.47 (s, 1H), 8.49 (dd, J = 15.0, 5.5 Hz, 1H), 7.38 – 7.15 (m, 5H), 5.98 (d, J = 13.7 Hz, 1H), 5.41 – 5.31 (m, 1H), 4.44 – 4.16 (m, 4H), 3.42 – 3.25 (m, 2H), 2.75 – 2.63 (m, 1H), 2.54 – 2.19 (m, 3H), 2.00 – 1.84 (m, 2H), 1.82 – 1.46 (m, 4H), 1.03 – 0.82 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{31}F_2N_3NaO_5$ 686.2829; Found 686.2793.

((1S,2R)-2-benzylcyclopropyl) methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***3c***). Yield (75%). 1H NMR (400 MHz, cdcl3) δ 9.53 (d, J = 33.7 Hz, 1H), 8.48 – 8.22 (m, 1H), 7.42 – 7.27 (m, 2H), 7.26 – 7.15 (m, 3H), 6.20 – 5.98 (m, 1H), 5.32 – 5.12 (m, 1H), 4.62 – 4.23 (m, 2H), 4.23 – 3.79 (m, 2H), 3.43 – 3.23 (m, 2H), 2.72 – 2.26 (m, 3H), 2.14 – 1.77 (m, 3H), 1.76 – 1.61 (m, 3H), 1.59 – 1.46 (m, 1H), 1.35 – 1.16 (m, 1H), 1.15 – 0.78 (m, 8H), 0.59 – 0.46 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{35}N_3NaO_5$ 480.2475; Found 480.2476.

((1S,3R)-3-benzyl-2,2-difluorocyclopropyl) methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***4c***). Yield (46%). 1H NMR (400 MHz, cdcl3) δ 9.53 (d, J = 38.5 Hz, 1H), 8.52 – 8.37 (m, 1H), 7.45 – 7.06 (m, 5H), 5.92 – 5.68 (m, 1H), 5.28 – 5.12 (m, 1H), 4.44 – 3.95 (m, 4H), 3.43 – 3.21 (m, 2H), 2.90 – 2.72 (m, 1H), 2.53 – 2.27 (m, 2H), 2.19 – 1.80 (m, 3H), 1.78 – 1.42 (m, 6H), 1.00 – 0.86 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{33}F_2N_3NaO_5$ 516.2286; Found 516.2269.

((1S,2S)-2-(3-fluorophenyl) cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***5c***). Yield (82%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 6.99 – 6.85 (m, 3H), 4.28 – 4.09 (m, 1H), 4.08 – 3.96 (m, 2H), 3.94 – 3.80 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.23 (m, 1H), 2.19 – 2.06 (m, 1H), 2.01 – 1.83 (m, 2H), 1.70 – 1.54 (m, 3H), 1.53 – 1.33 (m, 3H), 1.04 – 0.95 (m, 2H), 0.93 – 0.77 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{32}FN_3NaO_5$ 484.2224; Found 484.2216.

((1S,2S)-2-(3-chlorophenyl) cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***6c***). Yield (90%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.6 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.15 – 7.12 (m, 1H), 7.07 – 7.01 (m, 1H), 4.23 – 4.13 (m, 1H), 4.09 – 3.97 (m, 2H), 3.93 – 3.79 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.21 (m, 1H), 2.20 – 2.08 (m, 1H), 2.01 – 1.84 (m, 2H), 1.68 – 1.56 (m, 3H), 1.53 – 1.34 (m, 3H), 1.06 – 0.95 (m, 2H), 0.91 – 0.79 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{32}ClN_3NaO_5$ 500.1928; Found 500.1932.

((1S,2S)-2-(4-fluorophenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***7c***). Yield (86%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.15 – 7.01 (m, 4H), 4.23 – 4.14 (m, 1H), 4.09 – 3.94 (m, 2H), 3.93 – 3.82 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.20 (m, 1H), 2.18 – 2.08 (m, 1H), 1.96 – 1.82 (m, 2H), 1.70 – 1.53 (m, 3H), 1.51 – 1.29 (m, 3H), 0.98 – 0.79 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{32}FN_3NaO_5$ 484.2224; Found 484.2224.

((1S,2S)-2-(4-chlorophenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***8c***). Yield (81%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.7 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 4.26 – 4.12 (m, 1H), 4.11 – 3.96 (m, 2H), 3.93 – 3.82 (m, 1H), 3.22 – 3.03 (m, 2H), 2.37 – 2.21 (m, 1H), 2.19 – 2.04 (m, 1H), 2.01 – 1.83 (m, 2H), 1.63 (s, 3H), 1.52 – 1.35 (m, 3H), 1.05 – 0.92 (m, 2H), 0.89 – 0.78 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{32}ClN_3NaO_5$ 500.1928; Found 500.1927.

((1S,2S)-2-(3-methoxyphenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***9c***). Yield (91%). 1H NMR (400 MHz, dmso) δ 9.40 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.66 – 6.57 (m, 2H), 4.24 – 4.10 (m, 1H), 4.11 – 3.95 (m, 2H), 3.94 – 3.80 (m, 1H), 3.72 (s, 3H), 3.20 – 3.03 (m, 2H), 2.35 – 2.08 (m, 2H), 1.96 – 1.80 (m, 2H), 1.74 – 1.54 (m, 3H), 1.54 – 1.28 (m, 3H), 1.03 – 0.76 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{35}N_3NaO_6$ 496.2424; Found 496.2404.

((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***10c***). Yield (88%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 7.3 Hz, 2H), 6.81 (d, J = 6.9 Hz, 1H), 4.26 – 4.13 (m, 1H), 4.12 – 3.93 (m, 2H), 3.93 – 3.82 (m, 1H), 3.71 (s, 3H), 3.22 – 3.02 (m, 2H), 2.37 – 2.20 (m, 1H), 2.20 – 2.08 (m, 1H), 1.98 – 1.79 (m, 2H), 1.72 – 1.55 (m, 3H), 1.54 – 1.38 (m, 2H), 1.37 – 1.22 (m, 1H), 0.97 – 0.74 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{35}N_3NaO_6$ 496.2424; Found 496.2398.

((1S,2S)-2-(2-methoxyphenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***11c***). Yield (72%). 1H NMR (400 MHz, dmso) δ 9.39 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.17 – 7.08 (m, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 5.1 Hz, 2H), 4.31 – 4.12 (m, 1H), 4.11 – 4.01 (m, 1H), 4.00 – 3.88 (m, 2H), 3.79 (s, 3H), 3.19 – 3.01 (m, 2H), 2.35 – 2.21 (m, 1H), 2.18 – 2.01 (m, 2H), 1.96 – 1.81 (m, 1H), 1.72 – 1.54 (m, 3H), 1.52 – 1.31 (m, 3H), 0.96 – 0.73 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{35}N_3NaO_6$ 496.2424; Found 496.2404.

((1R,2S)-2-(2-methoxyphenyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***12c***). Yield (87%). 1H NMR (400 MHz, dmso) δ 9.38 (d, J = 1.7 Hz, 1H), 8.38 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.25 – 7.13 (m, 2H), 7.07 (t, J = 6.9 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.86 (t, J = 7.0 Hz, 1H), 4.23 – 4.10 (m, 1H), 4.03 – 3.91 (m, 1H), 3.80 (s, 3H), 3.77 – 3.67 (m, 1H), 3.32 – 3.24 (m, 1H), 3.21 – 3.00 (m, 2H), 2.34 – 2.03 (m, 3H), 1.95 – 1.80 (m, 1H), 1.70 – 1.53

(m, 3H), 1.52 – 1.34 (m, 3H), 1.04 – 0.78 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{35}N_3NaO_6$ 496.2424; Found 496.2406.

((1S,2S)-2-propylcyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***13c***). Yield (56%). 1H NMR (400 MHz, dmso) δ 9.40 (d, J = 1.0 Hz, 1H), 8.42 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.28 (d, J = 8.1 Hz, 1H), 4.23 – 4.12 (m, 1H), 4.09 – 3.96 (m, 1H), 3.88 – 3.65 (m, 2H), 3.21 – 3.04 (m, 2H), 2.32 – 2.19 (m, 1H), 2.19 – 2.06 (m, 1H), 1.95 – 1.83 (m, 1H), 1.70 – 1.59 (m, 2H), 1.53 – 1.38 (m, 2H), 1.34 (p, J = 7.3 Hz, 2H), 1.26 – 1.10 (m, 2H), 0.88 (td, J = 7.0, 4.3 Hz, 11H), 0.72 – 0.59 (m, 1H), 0.44 – 0.34 (m, 1H), 0.33 – 0.21 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{21}H_{36}N_3O_5$ 410.2655; Found 410.2636.

((1R,2S)-2-propylcyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***14c***). Yield (83%). 1H NMR (400 MHz, cdcl3) δ 9.54 (d, J = 28.9 Hz, 1H), 8.27 (d, J = 6.2 Hz, 1H), 6.41 (d, J = 41.1 Hz, 1H), 5.42 – 5.22 (m, 1H), 4.57 – 4.05 (m, 3H), 4.03 – 3.90 (m, 1H), 3.43 – 3.25 (m, 2H), 2.55 – 2.39 (m, 1H), 2.14 – 1.84 (m, 3H), 1.80 – 1.33 (m, 7H), 1.26 – 1.08 (m, 2H), 0.98 – 0.85 (m, 10H), 0.77 – 0.67 (m, 1H), 0.07 – -0.01 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{21}H_{35}N_3NaO_5$ 432.2475; Found 432.2474.

((1R,2S)-2-cyclohexylcyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***15c***). Yield (93%). 1H NMR (400 MHz, cdcl3) δ 9.50 (s, 1H), 8.28 (t, J = 6.3 Hz, 1H), 6.15 (s, 1H), 5.24 (d, J = 8.9 Hz, 1H), 4.41 – 4.23 (m, 2H), 4.12 – 3.70 (m, 2H), 3.41 – 3.30 (m, 2H), 2.52 – 2.35 (m, 2H), 2.07 – 1.81 (m, 3H), 1.77 – 1.52 (m, 8H), 1.19 – 0.83 (m, 12H), 0.61 – 0.44 (m, 2H), 0.43

– 0.31 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{39}N_3NaO_5$ 472.2788; Found 472.2780.

((1S,2S)-2-(cyclohexylmethyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***16c***). Yield (91%). 1H NMR (400 MHz, cdcl3) δ 9.50 (s, 1H), 8.32 – 8.20 (m, 1H), 6.30 (s, 1H), 5.27 (d, J = 8.8 Hz, 1H), 4.42 – 4.05 (m, 2H), 4.04 – 3.68 (m, 2H), 3.42 – 3.30 (m, 2H), 2.54 – 2.35 (m, 1H), 2.05 – 1.82 (m, 2H), 1.78 – 1.45 (m, 9H), 1.37 – 1.09 (m, 6H), 0.99 – 0.78 (m, 10H), 0.72 – 0.61 (m, 1H), 0.47 – 0.38 (m, 1H), 0.34 – 0.25 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{41}N_3NaO_5$ 486.2944; Found 486.2905.

((1S,2R)-2-(4,4-difluorocyclohexyl)cyclopropyl)methyl ((S)-4-methyl-1-oxo-1-(((S)-1-oxo-3-((S)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)pentan-2-yl)carbamate (***17c***). Yield (88%). 1H NMR (400 MHz, cdcl3) δ 9.49 (s, 1H), 8.42 – 8.30 (m, 1H), 6.01 (s, 1H), 5.27 – 5.17 (m, 1H), 4.37 – 4.27 (m, 1H), 4.07 – 3.68 (m, 1H), 3.43 – 3.32 (m, 2H), 2.51 – 2.38 (m, 1H), 2.12 – 1.35 (m, 16H), 0.98 (d, J = 5.8 Hz, 8H), 0.73 – 0.52 (m, 2H), 0.52 – 0.36 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{38}F_2N_3O_5$ 486.2779; Found 486.2926.

sodium (2S)-1-hydroxy-2-((S)-4-methyl-2-(((((1S,2S)-2-phenylcyclopropyl)methoxy)carbonyl)amino)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***1d***). ^{1}H NMR (400 MHz, dmso) δ 8.45 – 8.40 (m, 1H), 7.66 – 7.59 (m, 1H), 7.24 (t, *J* = 7.5 Hz, 3H), 7.17 – 7.09 (m, 1H), 7.09 – 7.00 (m, 2H), 5. 15 – 4.80 (m, 1H) 4.06 – 3.70 (m, 2H), 3.10 – 3.00 (m, 3H), 2.38 – 1.82 (m, 5H), 1.82 –1.34 (m, 6H), 0.99 – 0.92 (m, 2H), 0.92 – 0.79 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{34}N_3Na_2O_8S$ 570.1862; Found 570.1841.

sodium (2S)-2-((S)-2-(((((1R,3R)-2,2-difluoro-3-phenylcyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***2d***). Yield (88%). ^{1}H NMR (400 MHz, dmso) δ 7.71 – 7.39 (m, 3H), 7.38 – 7.19 (m, 5H), 5.50 (dd, *J* = 19.3, 6.2 Hz, 1H), 4.50 – 4.19 (m, 2H), 4.16 – 3.82 (m, 2H), 3.21 – 2.92 (m, 2H), 2.30 – 1.69 (m, 4H), 1.67 – 1.50 (m, 3H), 1.50 – 1.30 (m, 3H), 0.90 – 0.74 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{32}F_2N_3Na_2O_8S$ 768.2554; Found 768.3384.

sodium (2S)-2-((S)-2-(((((1S,2R)-2-benzylcyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***3d***). Yield (74%). ^{1}H NMR (400 MHz, dmso) δ 7.69 – 7.42 (m, 3H), 7.38 – 7.13 (m, 5H), 5.67 – 5.35 (m, 1H), 4.30 – 3.64 (m, 4H), 3.20 – 2.93 (m, 2H), 2.70 – 2.55 (m, 1H), 2.50 – 2.39 (m, 1H), 2.31 – 2.06 (m, 3H), 2.06 – 1.70 (m, 1H), 1.70 – 1.52 (m, 2H), 1.49 – 1.31 (m, 2H), 1.08 – 0.94 (m, 2H), 0.91 – 0.75 (m, 6H), 0.52 – 0.41 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{36}N_3Na_2O_8S$ 584.2019; Found 584.2019.

sodium (2S)-2-((S)-2-(((((1R,3S)-3-benzyl-2,2-difluorocyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***4d***). Yield (73%). ^{1}H NMR (400 MHz, dmso) δ 7.72 – 7.41 (m, 2H), 7.37 – 7.12 (m, 6H), 5.52 – 5.29 (m, 1H), 4.30 – 3.77 (m, 4H), 3.20 – 2.95 (m, 2H), 2.88 – 2.67 (m, 1H), 2.23 – 2.02 (m, 2H), 2.02 – 1.85 (m, 1H), 1.82 – 1.72 (m, 1H), 1.69 – 1.51 (m, 3H), 1.50 – 1.32 (m, 4H), 0.93 – 0.72 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{34}F_2N_3Na_2O_8S$ 620.1830; Found 620.1810.

sodium (2S)-2-((S)-2-(((((1S,2S)-2-(3-fluorophenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-

((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***5d***). Yield (56%). ^{1}H NMR (400 MHz, dmso) δ 7.68 – 7.43 (m, 2H), 7.43 – 7.31 (m, 1H), 7.28 – 7.22 (m, 1H), 6.98 – 6.86 (m, 3H), 5.54 – 5.31 (m, 1H), 4.07 – 3.77 (m, 4H), 3.20 – 2.95 (m, 2H), 2.23 – 2.04 (m, 2H), 2.02 – 1.84 (m, 2H), 1.70 – 1.50 (m, 3H), 1.50 – 1.33 (m, 3H), 1.05 – 0.94 (m, 2H), 0.90 – 0.74 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}FN_3Na_2O_8S$ 588.1768; Found 588.1774.

sodium (2S)-2-((S)-2-(((((1S,2S)-2-(3-chlorophenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***6d***). Yield (66%). ^{1}H NMR (400 MHz, dmso) δ 7.65 – 7.42 (m, 2H), 7.40 – 7.31 (m, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.11 (m, 2H), 7.10 – 6.99 (m, 1H), 5.45 – 5.21 (m, 1H), 4.12 – 3.81 (m, 4H), 3.21 – 2.97 (m, 2H), 2.33 – 2.04 (m, 2H), 2.03 – 1.77 (m, 2H), 1.74 – 1.50 (m, 3H), 1.49 – 1.31 (m, 3H), 1.03 – 0.95 (m, 2H), 0.91 – 0.77 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}ClN_3Na_2O_8S$ 604.1473; Found 604.1477.

sodium (2S)-2-((S)-2-(((((1S,2S)-2-(4-fluorophenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***7d***). Yield (35%). ^{1}H NMR (400 MHz, dmso) δ 7.65 – 7.43 (m, 2H), 7.36 (dd, *J* = 25.0, 7.9 Hz, 1H), 7.16 – 7.01 (m, 4H), 5.52 – 5.29 (m, 1H), 4.13 – 3.81 (m, 4H), 3.20 – 2.97 (m, 2H), 2.32 – 2.03 (m, 2H), 2.02 – 1.83 (m, 2H), 1.70 – 1.50 (m, 3H), 1.48 – 1.31 (m, 3H), 1.01 – 0.73 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}FN_3Na_2O_8S$ 588.1768; Found 588.1742.

sodium (2S)-2-((S)-2-(((((1S,2S)-2-(4-fluorophenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-

((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***8d***). Yield (70%). ^{1}H NMR (400 MHz, dmso) δ 7.64 – 7.50 (m, 2H), 7.48 – 7.38 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.06 (m, 2H), 5.44 – 5.31 (m, 1H), 4.10 – 3.80 (m, 4H), 3.18 – 2.92 (m, 2H), 2.24 – 2.04 (m, 2H), 2.01 – 1.80 (m, 2H), 1.72 – 1.49 (m, 3H), 1.48 – 1.31 (m, 3H), 1.02 – 0.90 (m, 2H), 0.88 – 0.74 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}FN_3Na_2O_8S$ 604.1473; Found 604.1481.

sodium (2S)-1-hydroxy-2-((S)-2-(((((1S,2S)-2-(3-methoxyphenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***9d***). Yield (86 %). ^{1}H NMR (400 MHz, dmso) δ 7.56 (dd, *J* = 19.6, 9.6 Hz, 1H), 7.45 (s, 1H), 7.34 (dd, *J* = 24.7, 8.3 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.73 – 6.61 (m, 3H), 5.45 – 5.25 (m, 1H), 4.13 – 3.80 (m, 4H), 3.72 (s, 3H), 3.21 – 2.95 (m, 2H), 2.26 – 2.03 (m, 2H), 2.01 – 1.84 (m, 2H), 1.70 – 1.50 (m, 3H), 1.49 – 1.33 (m, 3H), 1.00 – 0.92 (m, 2H), 0.89 – 0.77 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}FN_3Na_2O_8S$ 600.1968; Found 600.1939.

sodium (2S)-2-((S)-2-(((((1S,2S)-2-(4-fluorophenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***10d***). Yield (78%). ^{1}H NMR (400 MHz, dmso) δ 7.68 – 7.13 (m, 3H), 7.05 – 6.97 (m, 2H), 6.85 – 6.77 (m, 2H), 5.52 – 5.22 (m, 1H), 4.13 – 3.80 (m, 4H), 3.70 (s, 3H), 3.18 – 2.97 (m, 2H), 2.28 – 2.05 (m, 2H), 2.03 – 1.72 (m, 2H), 1.68 – 1.52 (m, 3H), 1.50 – 1.38 (m, 3H), 1.37 – 1.21 (m, 2H), 0.96 – 0.74 (m, 6H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{33}FN_3Na_2O_8S$ 600.1968 ; Found 600.1958.

sodium (2S)-1-hydroxy-2-((S)-4-methyl-2-(((((1S,2S)-2-(o-tolyl)cyclopropyl)methoxy)carbonyl)amino)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***11d***). Yield (83%). ^{1}H NMR (400 MHz, dmso) δ 7.65 – 7.48 (m, 1H), 7.45 (s, 1H), 7.39 – 7.25 (m, 1H), 7.15 – 7.08 (m, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.86 – 6.79 (m, 2H), 5.47 – 5.28 (m, 1H), 4.07 – 3.86 (m, 4H), 3.79 (s, 3H), 3.19 – 2.96 (m, 2H), 2.33 – 1.84 (m, 4H), 1.71 – 1.51 (m, 3H), 1.47 – 1.27 (m, 3H), 0.98 – 0.72 (m, 8H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{36}N_3Na_2O_8S$ 600.1968; Found 600.1946.

sodium (2S)-1-hydroxy-2-((S)-2-(((((1R,2S)-2-(2-methoxyphenyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***12d***). Yield (72%). ^{1}H NMR (400 MHz, dmso) δ 7.60 – 7.35 (m, 2H), 7.27 – 7.15 (m, 2H), 7.12 – 7.03 (m, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 5.45 – 5.27 (m, 1H), 4.06 – 3.86 (m, 2H), 3.81 (s, 3H), 3.76 – 3.66 (m, 2H), 3.18 – 2.97 (m, 2H), 2.27 – 1.95 (m, 4H), 1.68 – 1.31 (m, 6H), 1.01 – 0.93 (m, 1H), 0.92 – 0.73 (m, 7H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{36}N_3Na_2O_9S$ 600.1968; Found 600.1941.

sodium (2S)-1-hydroxy-2-((S)-4-methyl-2-(((((1S,2S)-2-propylcyclopropyl)methoxy)carbonyl)amino)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***13d***). Yield (83%). ^{1}H NMR (400 MHz, dmso) δ 7.57 (d, *J* = 9.1 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.24 (dd, *J* = 20.1, 8.0 Hz, 1H), 5.57 – 5.32 (m, 1H), 4.11 – 3.89 (m, 2H), 3.87 – 3.66 (m, 2H), 3.17 – 2.99 (m, 2H), 2.37 – 2.06 (m, 2H), 2.04 – 1.81 (m, 1H), 1.69 – 1.52 (m, 2H), 1.51 – 1.40 (m, 2H), 1.38 – 1.28 (m, 3H), 1.25 – 1.02 (m, 2H), 0.86 (dt, *J* = 11.3, 6.7 Hz, 10H), 0.71 – 0.57 (m, 1H), 0.44 – 0.34 (m, 1H), 0.31 –

0.22 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{21}H_{36}N_3Na_2O_8S$ 536.2019; Found 536.1994.

sodium (2S)-1-hydroxy-2-((S)-4-methyl-2-(((((1R,2S)-2-propylcyclopropyl)methoxy)carbonyl)amino)pentanamido)-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***14d***). Yield (49%). ^{1}H NMR (400 MHz, dmso) δ 7.54 (dd, *J* = 16.6, 8.8 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.33 – 7.22 (m, 1H), 5.55 – 5.31 (m, 1H), 4.10 – 3.80 (m, 4H), 3.22 – 2.99 (m, 2H), 2.32 – 2.07 (m, 2H), 2.05 – 1.84 (m, 1H), 1.74 – 1.51 (m, 3H), 1.50 – 1.30 (m, 5H), 1.28 – 1.16 (m, 1H), 1.14 – 1.00 (m, 1H), 0.93 – 0.76 (m, 10H), 0.70 – 0.59 (m, 1H), 0.07 – 0.01 (m, 1H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{21}H_{36}N_3Na_2O_8S$ 536.2019; Found 536.2017.

sodium (2S)-2-((S)-2-(((((1R,2S)-2-cyclohexylcyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***15d***). Yield (72%). ^{1}H NMR (400 MHz, dmso) δ 7.67 – 7.56 (m, 1H), 7.53 – 7.44 (m, 1H), 7.27 – 7.10 (m, 1H), 5.47 (d, *J* = 53.4 Hz, 1H), 4.12 – 3.54 (m, 4H), 3.24 – 2.96 (m, 2H), 2.37 – 2.06 (m, 2H), 2.05 – 1.84 (m, 1H), 1.82 – 1.50 (m, 11H), 1.47 – 1.28 (m, 2H), 1.25 – 0.95 (m, 3H), 0.89 – 0.74 (m, 6H), 0.68 – 0.45 (m, 2H), 0.39 – 0.26 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{40}N_3Na_2O_8S$ 576.2332; Found 576.2311.

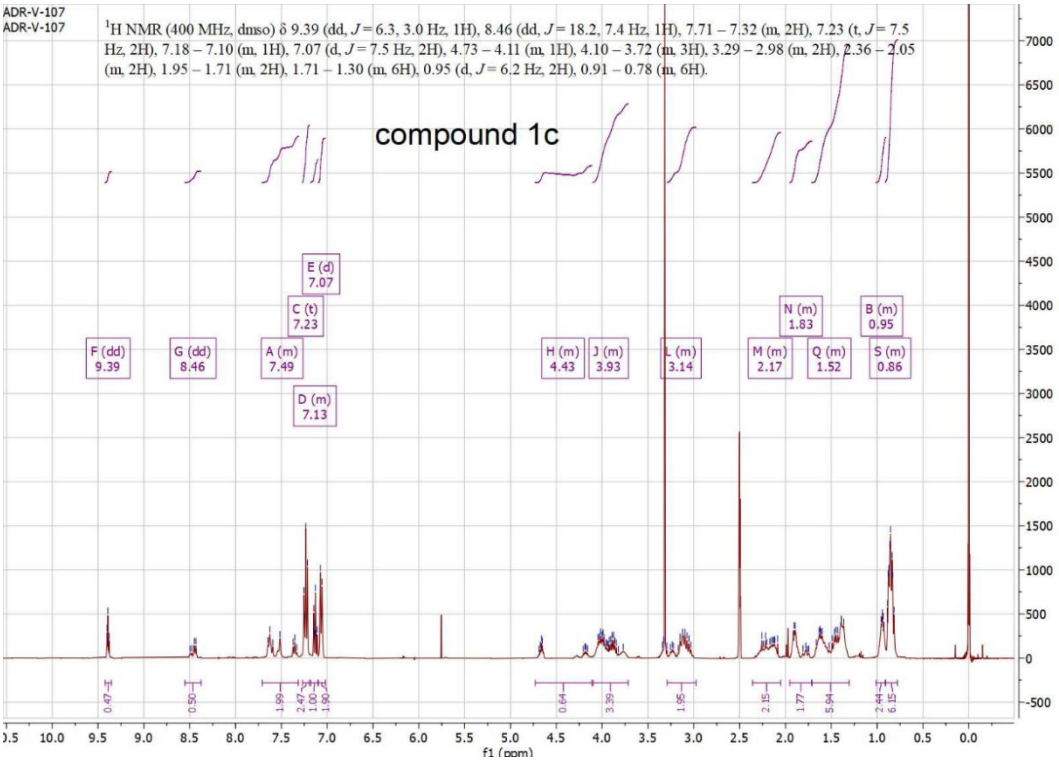
sodium (2S)-2-((S)-2-(((((1S,2S)-2-(cyclohexylmethyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***16d***). Yield (48%). ^{1}H NMR (400 MHz, dmso) δ 7.78 – 7.55 (m, 1H), 7.54 – 7.44 (m, 1H), 7.33 – 7.14 (m, 1H), 5.55 – 5.32 (m, 1H), 4.13 – 3.57 (m, 4H), 3.25 – 2.94 (m, 2H), 2.41 – 2.05 (m, 2H), 2.04 – 1.86 (m, 1H), 1.85 – 1.53 (m, 6H), 1.50 – 1.40 (m, 2H), 1.38 – 1.00 (m, 4H), 0.98 – 0.74 (m, 8H),

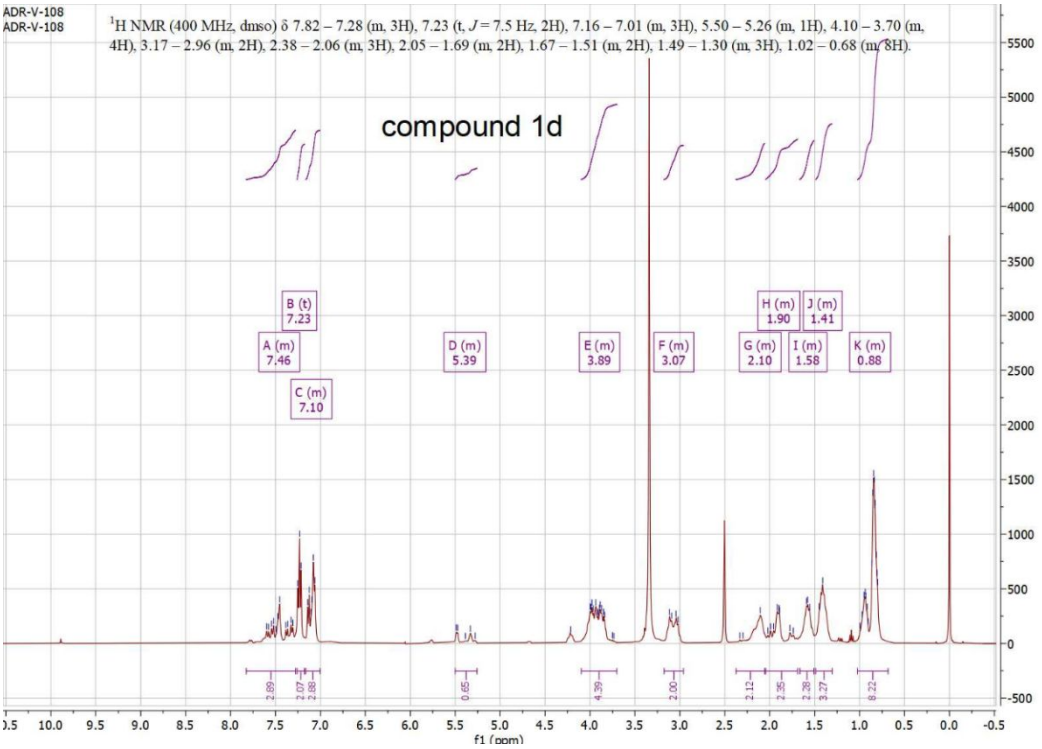
0.72 – 0.57 (m, 2H), 0.49 – 0.34 (m, 2H), 0.33 – 0.17 (m, 2H), 0.08 – 0.00 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{25}H_{42}N_3Na_2O_8S$ 590.2488; Found 590.2433.

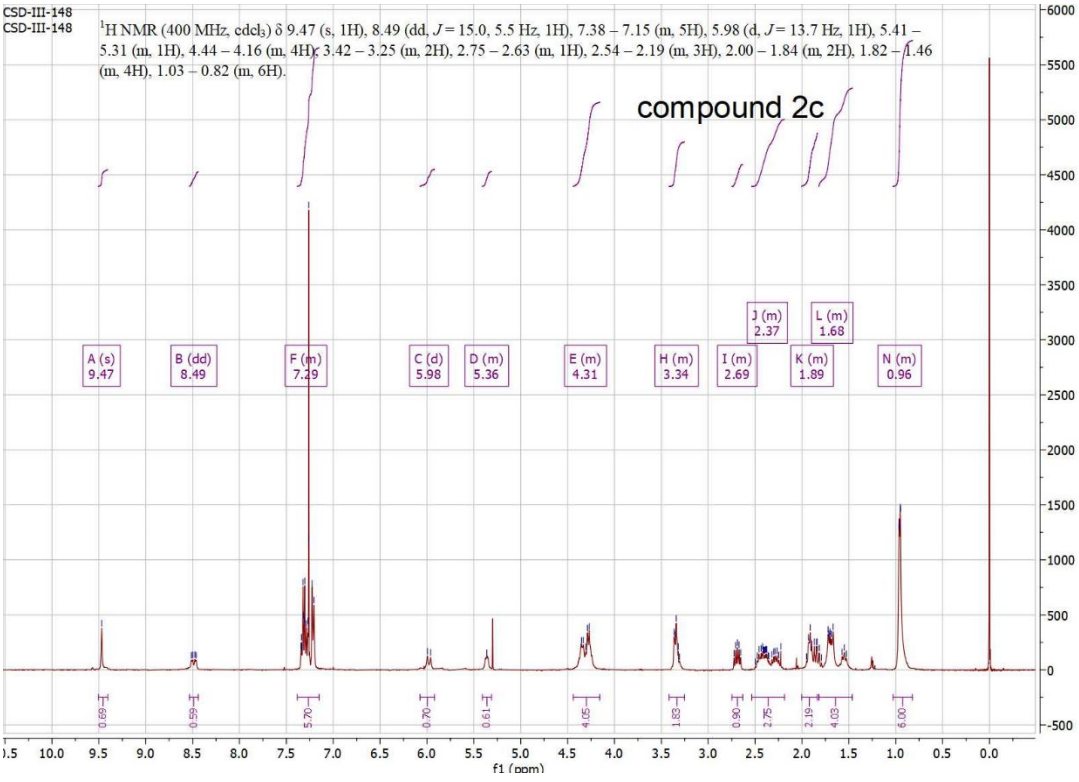
sodium (2S)-2-((S)-2-((((((1S,2R)-2-(4,4-difluorocyclohexyl)cyclopropyl)methoxy)carbonyl)amino)-4-methylpentanamido)-1-hydroxy-3-((S)-2-oxopyrrolidin-3-yl)propane-1-sulfonate (***17d***). Yield (58%). ^{1}H NMR (400 MHz, dmso) δ 7.72 – 7.40 (m, 2H), 7.36 – 7.16 (m, 1H), 5.33 (d, *J* = 47.5 Hz, 1H), 4.09 – 3.62 (m, 4H), 3.21 – 2.99 (m, 2H), 2.33 – 2.06 (m, 2H), 2.03 – 1.88 (m, 2H), 1.87 – 1.53 (m, 8H), 1.50 – 1.38 (m, 2H), 1.37 – 1.18 (m, 2H), 1.16 – 0.99 (m, 1H), 0.96 – 0.79 (m, 6H), 0.79 – 0.68 (m, 1H), 0.66 – 0.49 (m, 1H), 0.49 – 0.30 (m, 2H). HRMS m/z: $[M+Na]^+$ Calculated for $C_{24}H_{38}F_2N_3Na_2O_8S$ 612.2143; Found 612.2123.

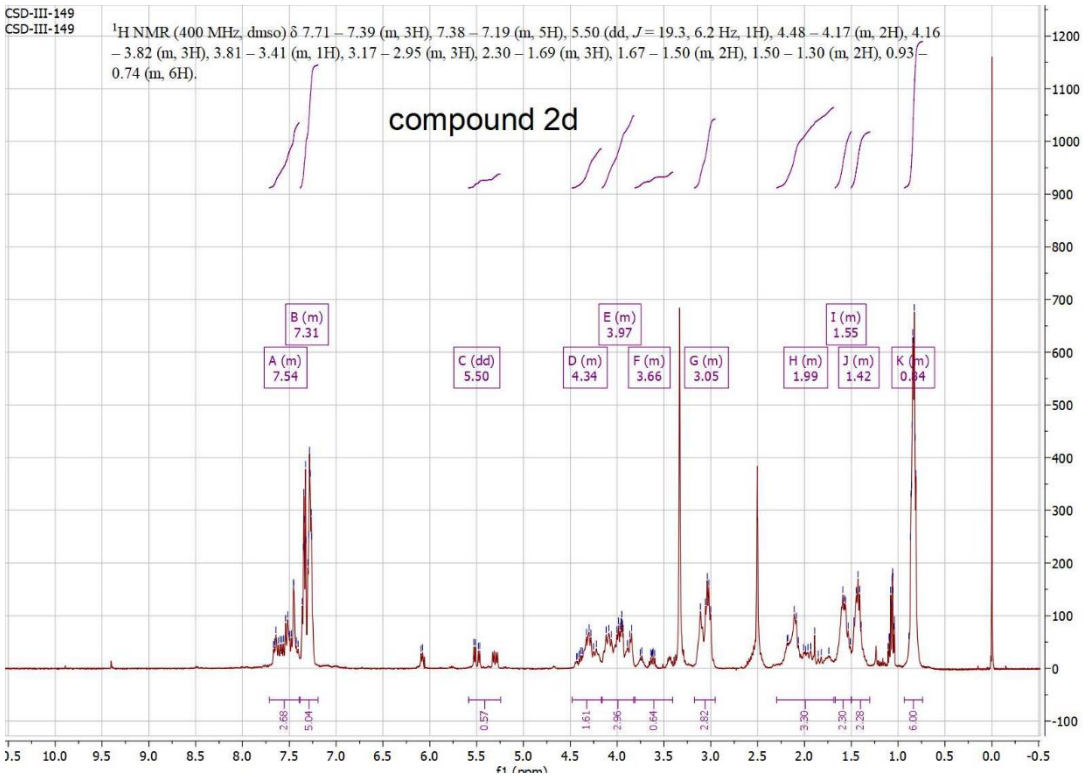
^{1}H-NMR of compounds 1-17c/d

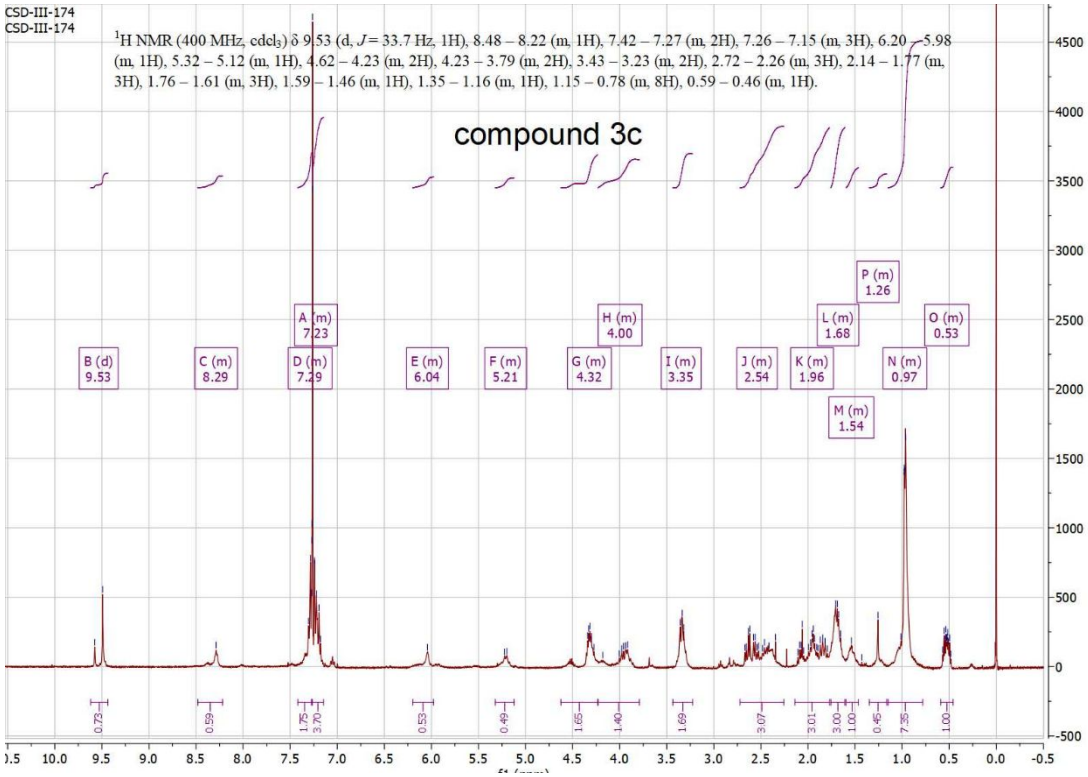
Peaks corresponding to residual solvents (H_2O, DCM, DMSO, $CHCl_3$) have not been integrated in below spectrums.

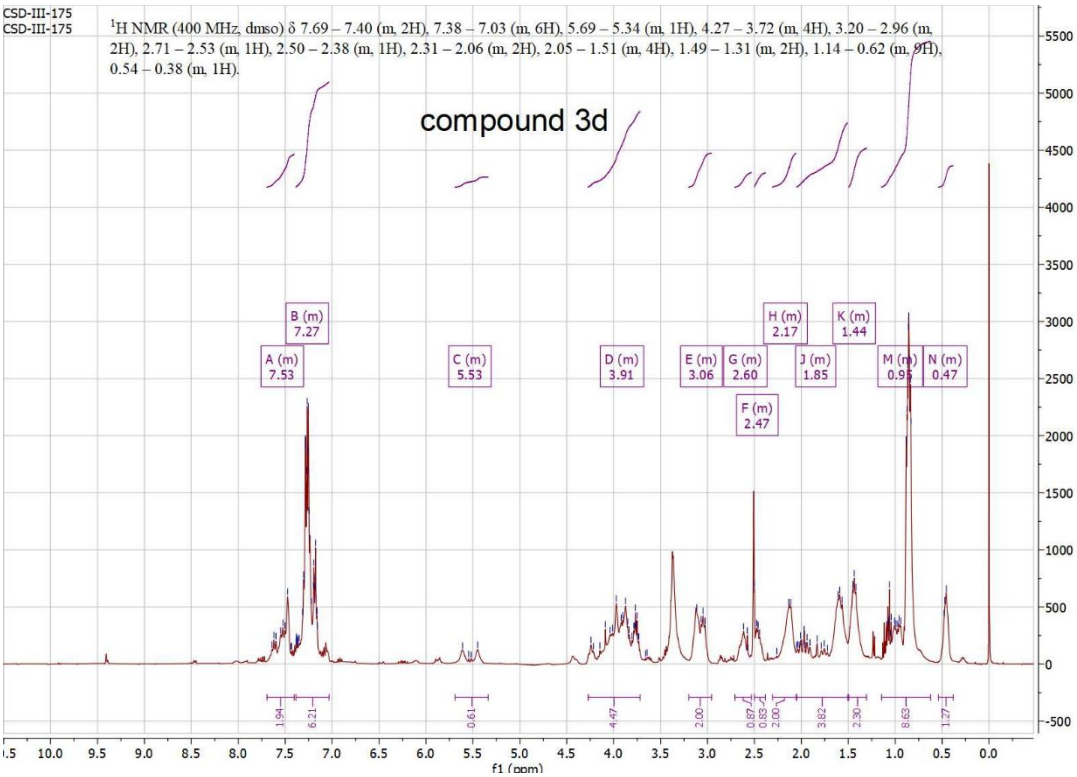


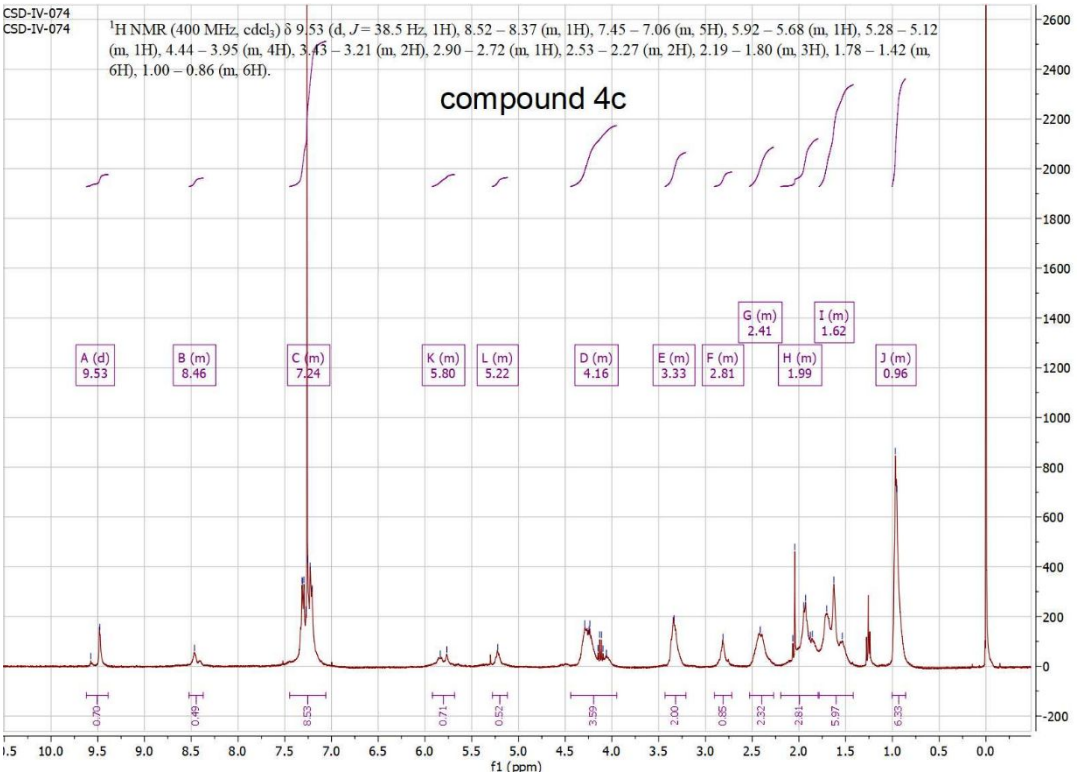

ADR-V-108
ADR-V-108
^{1}H NMR (400 MHz, dmso) δ 7.82 – 7.28 (m, 3H), 7.23 (t, J = 7.5 Hz, 2H), 7.16 – 7.01 (m, 3H), 5.50 – 5.26 (m, 1H), 4.10 – 3.70 (m, 4H), 3.17 – 2.96 (m, 2H), 2.38 – 2.06 (m, 3H), 2.05 – 1.69 (m, 2H), 1.67 – 1.51 (m, 2H), 1.49 – 1.30 (m, 3H), 1.02 – 0.68 (m, 8H).
compound 1d
B (t) 7.23
A (m) 7.46
C (m) 7.10
D (m) 5.39
E (m) 3.89
F (m) 3.07
H (m) 1.90
J (m) 1.41
G (m) 2.10
I (m) 1.58
K (m) 0.88
f1 (ppm)

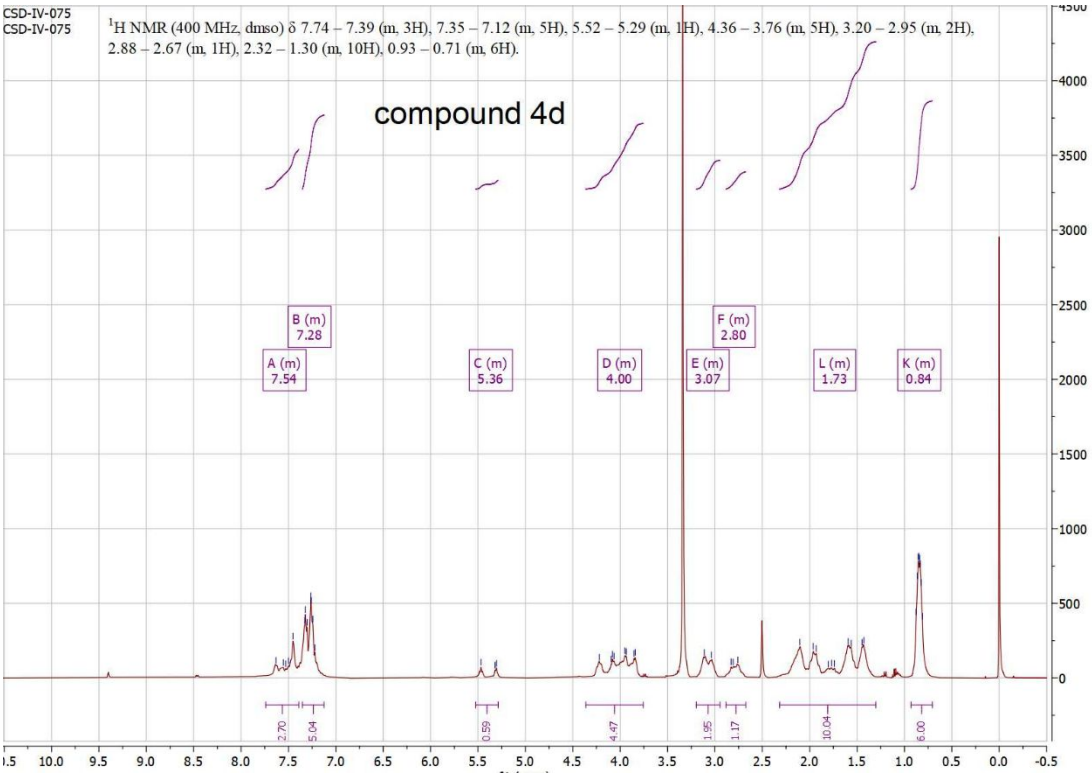

CSD-III-148
CSD-III-148
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.47 (s, 1H), 8.49 (dd, J = 15.0, 5.5 Hz, 1H), 7.38 – 7.15 (m, 5H), 5.98 (d, J = 13.7 Hz, 1H), 5.41 – 5.31 (m, 1H), 4.44 – 4.16 (m, 4H), 3.42 – 3.25 (m, 2H), 2.75 – 2.63 (m, 1H), 2.54 – 2.19 (m, 3H), 2.00 – 1.84 (m, 2H), 1.82 – 1.46 (m, 4H), 1.03 – 0.82 (m, 6H).
compound 2c
A (s) 9.47
B (dd) 8.49
F (m) 7.29
C (d) 5.98
D (m) 5.36
E (m) 4.31
H (m) 3.34
I (m) 2.69
J (m) 2.37
K (m) 1.89
L (m) 1.68
N (m) 0.96
f1 (ppm)

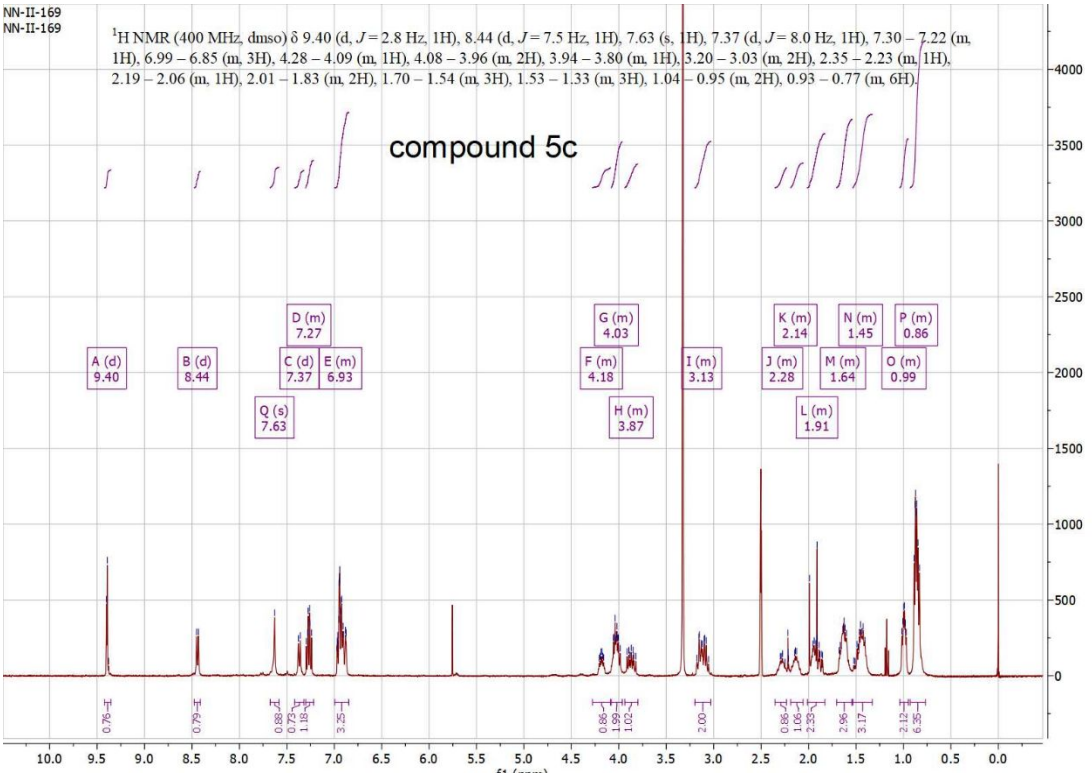

CSD-III-149
CSD-III-149
^{1}H NMR (400 MHz, dmso) δ 7.71 – 7.39 (m, 3H), 7.38 – 7.19 (m, 5H), 5.50 (dd, J = 19.3, 6.2 Hz, 1H), 4.48 – 4.17 (m, 2H), 4.16 – 3.82 (m, 3H), 3.81 – 3.41 (m, 1H), 3.17 – 2.95 (m, 3H), 2.30 – 1.69 (m, 3H), 1.67 – 1.50 (m, 2H), 1.50 – 1.30 (m, 2H), 0.93 – 0.74 (m, 6H).
compound 2d
B (m) 7.31
A (m) 7.54
C (dd) 5.50
E (m) 3.97
D (m) 4.34
F (m) 3.66
G (m) 3.05
I (m) 1.55
H (m) 1.99
J (m) 1.42
K (m) 0.84

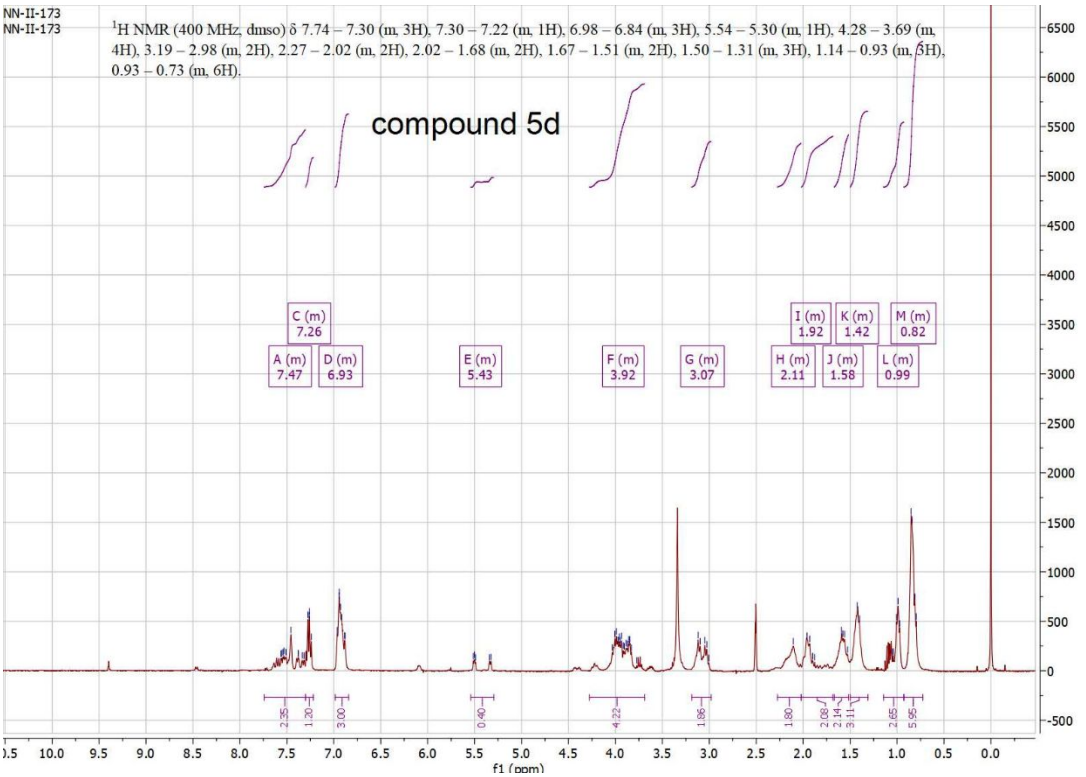

CSD-III-174
CSD-III-174
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.53 (d, J = 33.7 Hz, 1H), 8.48 – 8.22 (m, 1H), 7.42 – 7.27 (m, 2H), 7.26 – 7.15 (m, 3H), 6.20 – 5.98 (m, 1H), 5.32 – 5.12 (m, 1H), 4.62 – 4.23 (m, 2H), 4.23 – 3.79 (m, 2H), 3.43 – 3.23 (m, 2H), 2.72 – 2.26 (m, 3H), 2.14 – 1.77 (m, 3H), 1.76 – 1.61 (m, 3H), 1.59 – 1.46 (m, 1H), 1.35 – 1.16 (m, 1H), 1.15 – 0.78 (m, 8H), 0.59 – 0.46 (m, 1H).
compound 3c
B (d) 9.53
C (m) 8.29
A (m) 7.23
D (m) 7.29
E (m) 6.04
F (m) 5.21
H (m) 4.00
G (m) 4.32
I (m) 3.35
J (m) 2.54
K (m) 1.96
P (m) 1.26
L (m) 1.68
O (m) 0.53
N (m) 0.97
M (m) 1.54

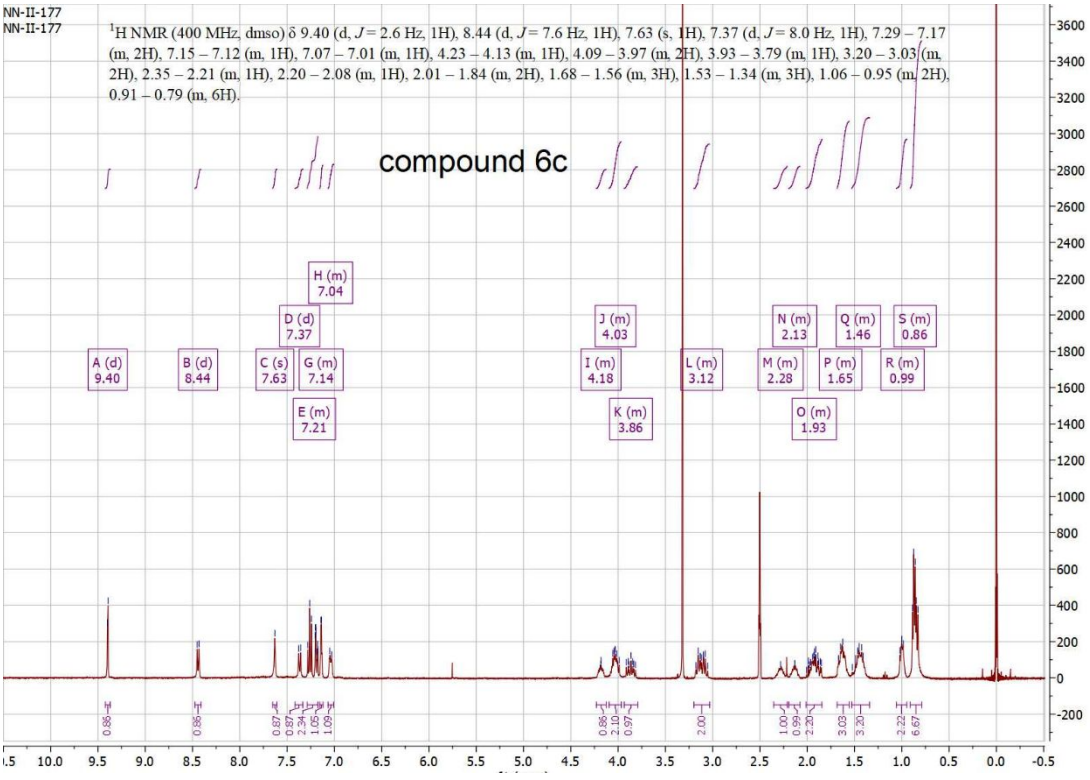

CSD-III-175
CSD-III-175
^{1}H NMR (400 MHz, dmso) δ 7.69 – 7.40 (m, 2H), 7.38 – 7.03 (m, 6H), 5.69 – 5.34 (m, 1H), 4.27 – 3.72 (m, 4H), 3.20 – 2.96 (m, 2H), 2.71 – 2.53 (m, 1H), 2.50 – 2.38 (m, 1H), 2.31 – 2.06 (m, 2H), 2.05 – 1.51 (m, 4H), 1.49 – 1.31 (m, 2H), 1.14 – 0.62 (m, 9H), 0.54 – 0.38 (m, 1H).
compound 3d
A (m) 7.53
B (m) 7.27
C (m) 5.53
D (m) 3.91
E (m) 3.06
G (m) 2.60
F (m) 2.47
J (m) 1.85
H (m) 2.17
K (m) 1.44
M (m) 0.95
N (m) 0.47
f1 (ppm)

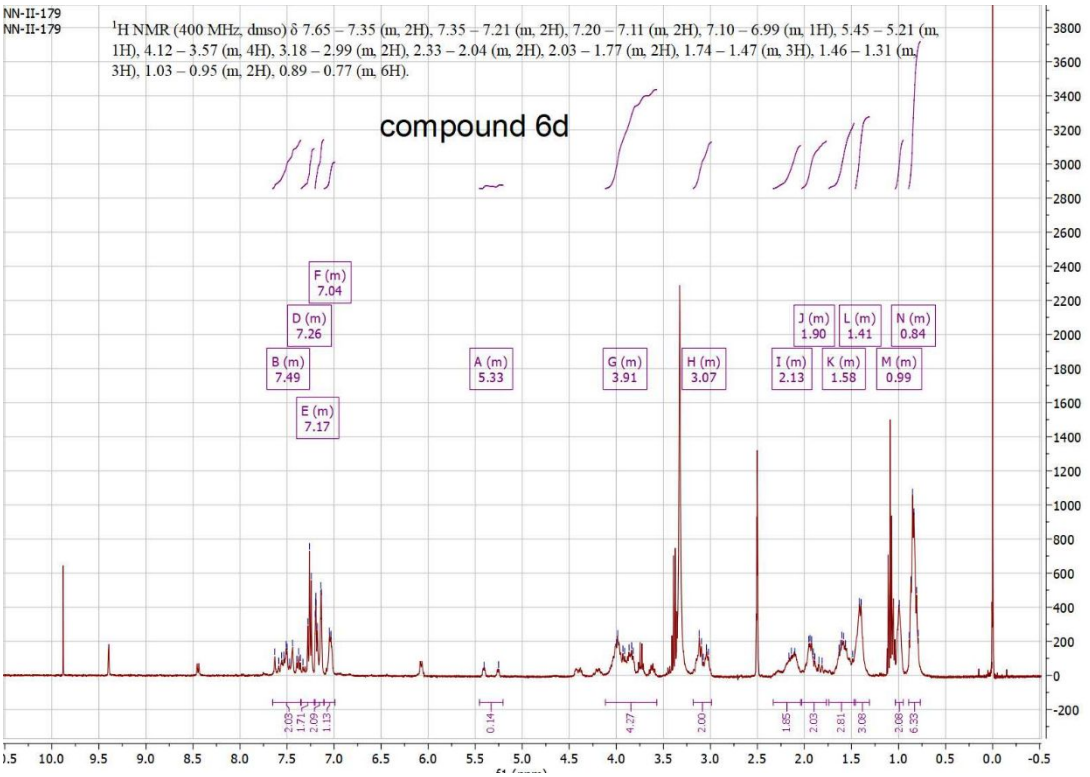

CSD-IV-074
CSD-IV-074
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.53 (d, J = 38.5 Hz, 1H), 8.52 – 8.37 (m, 1H), 7.45 – 7.06 (m, 5H), 5.92 – 5.68 (m, 1H), 5.28 – 5.12 (m, 1H), 4.44 – 3.95 (m, 4H), 3.43 – 3.21 (m, 2H), 2.90 – 2.72 (m, 1H), 2.53 – 2.27 (m, 2H), 2.19 – 1.80 (m, 3H), 1.78 – 1.42 (m, 6H), 1.00 – 0.86 (m, 6H).
compound 4c
A (d) 9.53
B (m) 8.46
C (m) 7.24
K (m) 5.80
L (m) 5.22
D (m) 4.16
E (m) 3.33
F (m) 2.81
G (m) 2.41
H (m) 1.99
I (m) 1.62
J (m) 0.96
f1 (ppm)

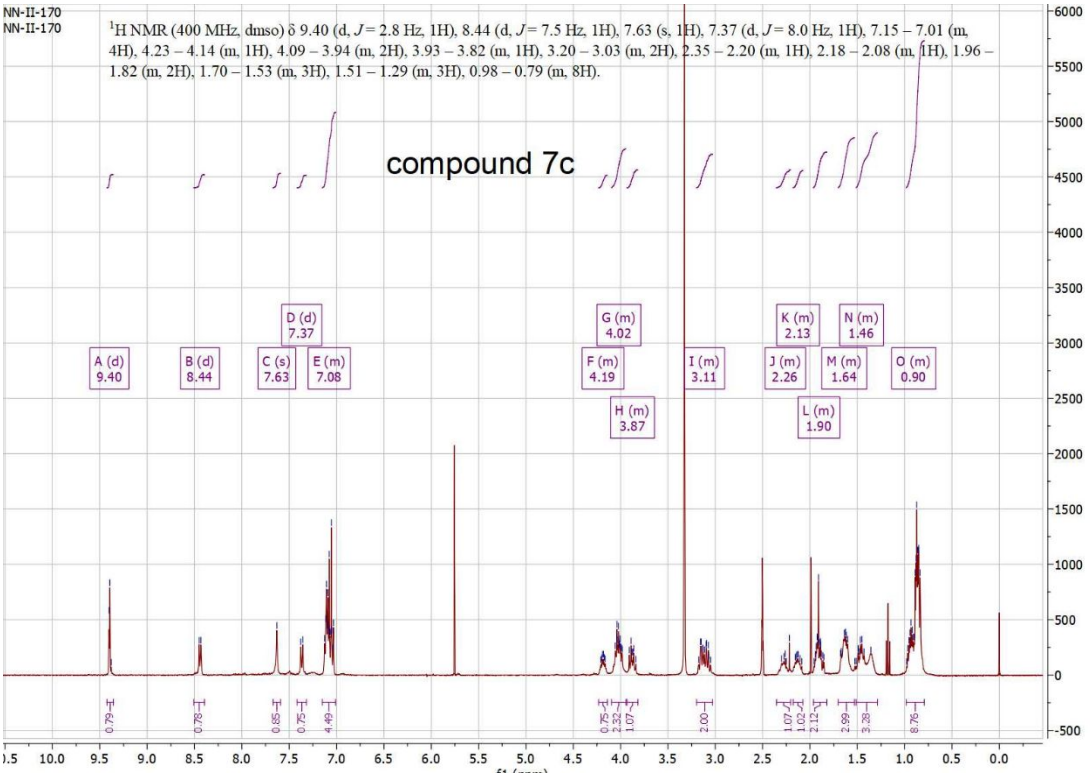

CSD-IV-075
CSD-IV-075
^{1}H NMR (400 MHz, dmso) δ 7.74 – 7.39 (m, 3H), 7.35 – 7.12 (m, 5H), 5.52 – 5.29 (m, 1H), 4.36 – 3.76 (m, 5H), 3.20 – 2.95 (m, 2H), 2.88 – 2.67 (m, 1H), 2.32 – 1.30 (m, 10H), 0.93 – 0.71 (m, 6H).
compound 4d
B (m) 7.28
A (m) 7.54
C (m) 5.36
D (m) 4.00
F (m) 2.80
E (m) 3.07
L (m) 1.73
K (m) 0.84

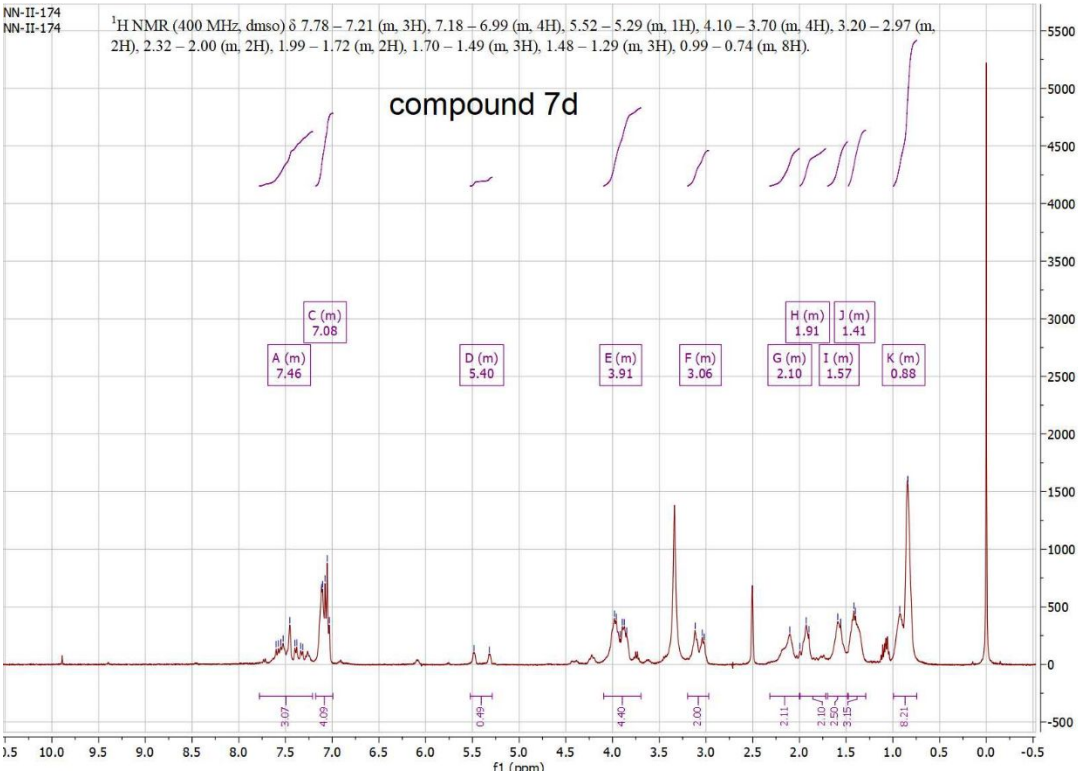

NN-II-169
NN-II-169
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 6.99 – 6.85 (m, 3H), 4.28 – 4.09 (m, 1H), 4.08 – 3.96 (m, 2H), 3.94 – 3.80 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.23 (m, 1H), 2.19 – 2.06 (m, 1H), 2.01 – 1.83 (m, 2H), 1.70 – 1.54 (m, 3H), 1.53 – 1.33 (m, 3H), 1.04 – 0.95 (m, 2H), 0.93 – 0.77 (m, 6H).
compound 5c
A (d) 9.40
B (d) 8.44
D (m) 7.27
C (d) 7.37
E (m) 6.93
Q (s) 7.63
G (m) 4.03
F (m) 4.18
H (m) 3.87
I (m) 3.13
K (m) 2.14
J (m) 2.28
L (m) 1.91
N (m) 1.45
M (m) 1.64
P (m) 0.86
O (m) 0.99

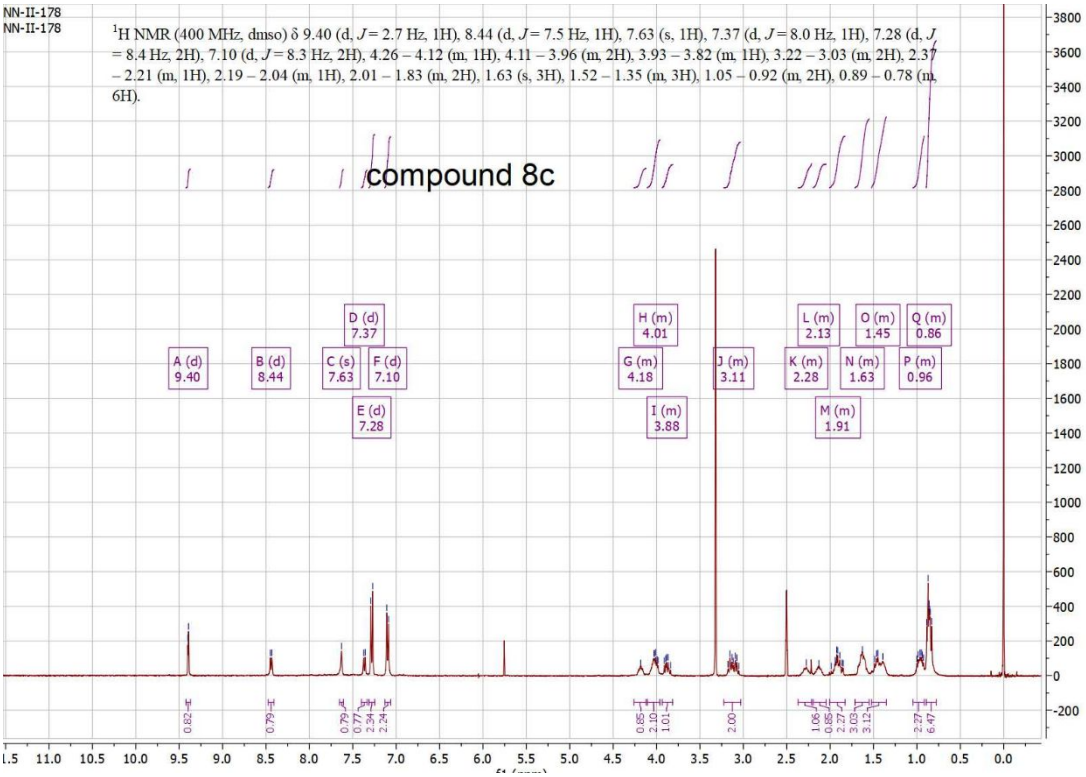

NN-II-173
NN-II-173
^{1}H NMR (400 MHz, dmso) δ 7.74 – 7.30 (m, 3H), 7.30 – 7.22 (m, 1H), 6.98 – 6.84 (m, 3H), 5.54 – 5.30 (m, 1H), 4.28 – 3.69 (m, 4H), 3.19 – 2.98 (m, 2H), 2.27 – 2.02 (m, 2H), 2.02 – 1.68 (m, 2H), 1.67 – 1.51 (m, 2H), 1.50 – 1.31 (m, 3H), 1.14 – 0.93 (m, 3H), 0.93 – 0.73 (m, 6H).
compound 5d
C (m) 7.26
A (m) 7.47
D (m) 6.93
E (m) 5.43
F (m) 3.92
G (m) 3.07
I (m) 1.92
K (m) 1.42
M (m) 0.82
H (m) 2.11
J (m) 1.58
L (m) 0.99
f1 (ppm)

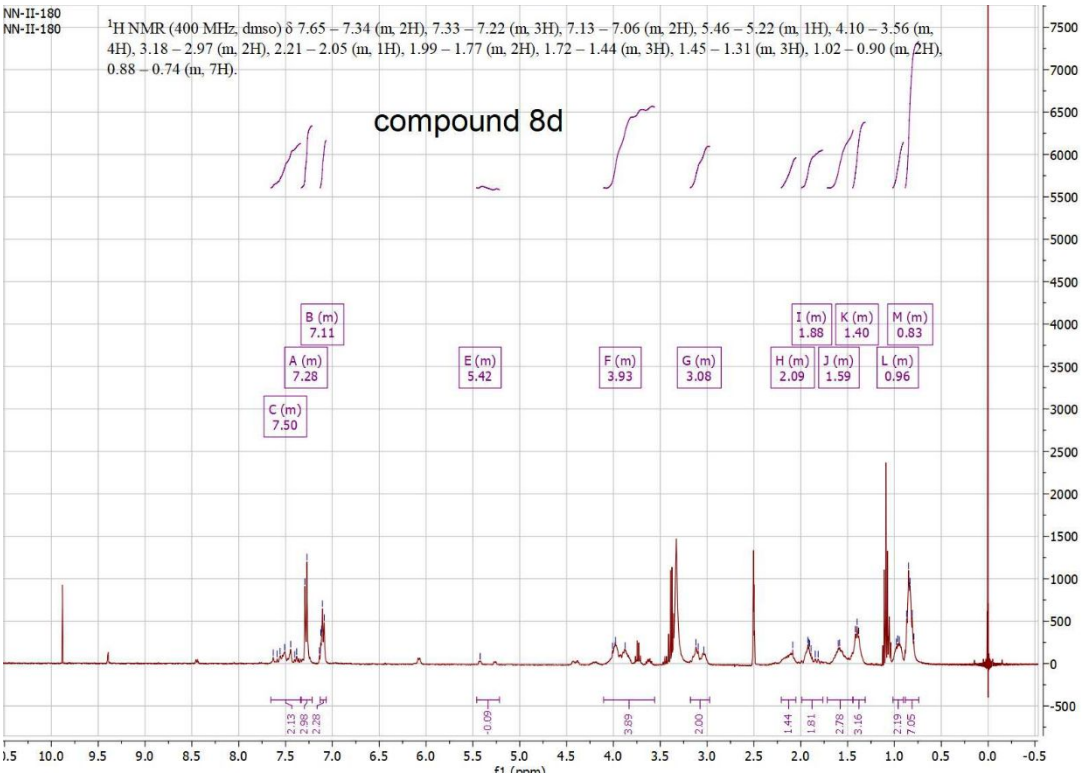

NN-II-177
NN-II-177
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.6 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.15 – 7.12 (m, 1H), 7.07 – 7.01 (m, 1H), 4.23 – 4.13 (m, 1H), 4.09 – 3.97 (m, 2H), 3.93 – 3.79 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.21 (m, 1H), 2.20 – 2.08 (m, 1H), 2.01 – 1.84 (m, 2H), 1.68 – 1.56 (m, 3H), 1.53 – 1.34 (m, 3H), 1.06 – 0.95 (m, 2H), 0.91 – 0.79 (m, 6H).
compound 6c
H (m) 7.04
D (d) 7.37
A (d) 9.40
B (d) 8.44
C (s) 7.63
G (m) 7.14
E (m) 7.21
J (m) 4.03
I (m) 4.18
K (m) 3.86
L (m) 3.12
N (m) 2.13
Q (m) 1.46
S (m) 0.86
M (m) 2.28
P (m) 1.65
R (m) 0.99
O (m) 1.93

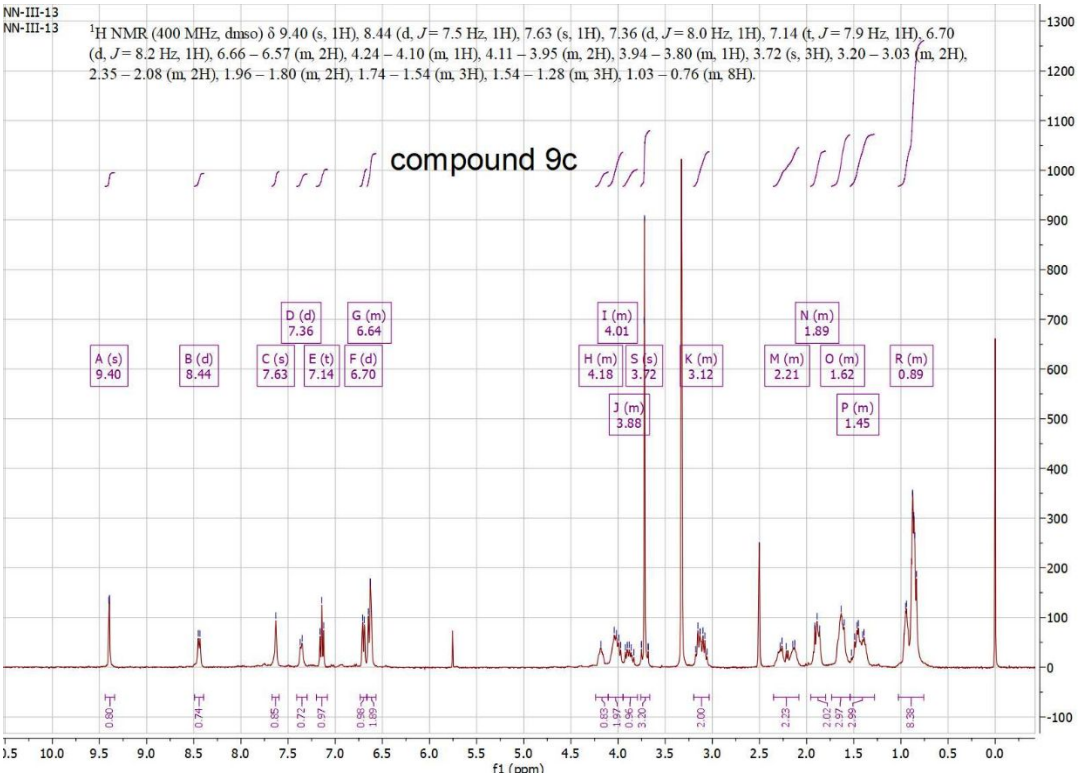

NN-II-179
NN-II-179
^{1}H NMR (400 MHz, dmso) δ 7.65 – 7.35 (m, 2H), 7.35 – 7.21 (m, 2H), 7.20 – 7.11 (m, 2H), 7.10 – 6.99 (m, 1H), 5.45 – 5.21 (m, 1H), 4.12 – 3.57 (m, 4H), 3.18 – 2.99 (m, 2H), 2.33 – 2.04 (m, 2H), 2.03 – 1.77 (m, 2H), 1.74 – 1.47 (m, 3H), 1.46 – 1.31 (m, 3H), 1.03 – 0.95 (m, 2H), 0.89 – 0.77 (m, 6H).
compound 6d
F (m) 7.04
D (m) 7.26
B (m) 7.49
E (m) 7.17
A (m) 5.33
G (m) 3.91
H (m) 3.07
J (m) 1.90
L (m) 1.41
N (m) 0.84
I (m) 2.13
K (m) 1.58
M (m) 0.99

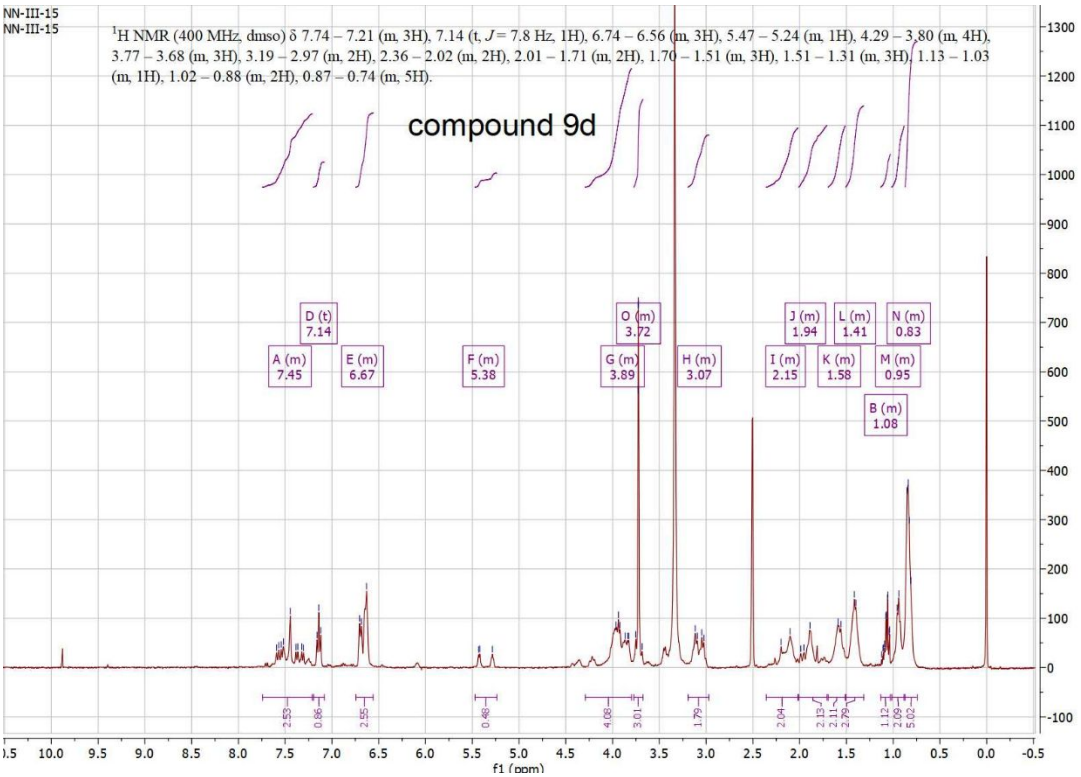

NN-II-170
NN-II-170
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.8 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.15 – 7.01 (m, 4H), 4.23 – 4.14 (m, 1H), 4.09 – 3.94 (m, 2H), 3.93 – 3.82 (m, 1H), 3.20 – 3.03 (m, 2H), 2.35 – 2.20 (m, 1H), 2.18 – 2.08 (m, 1H), 1.96 – 1.82 (m, 2H), 1.70 – 1.53 (m, 3H), 1.51 – 1.29 (m, 3H), 0.98 – 0.79 (m, 8H).
compound 7c
A (d) 9.40
B (d) 8.44
D (d) 7.37
C (s) 7.63
E (m) 7.08
G (m) 4.02
F (m) 4.19
H (m) 3.87
I (m) 3.11
K (m) 2.13
N (m) 1.46
J (m) 2.26
M (m) 1.64
O (m) 0.90
L (m) 1.90

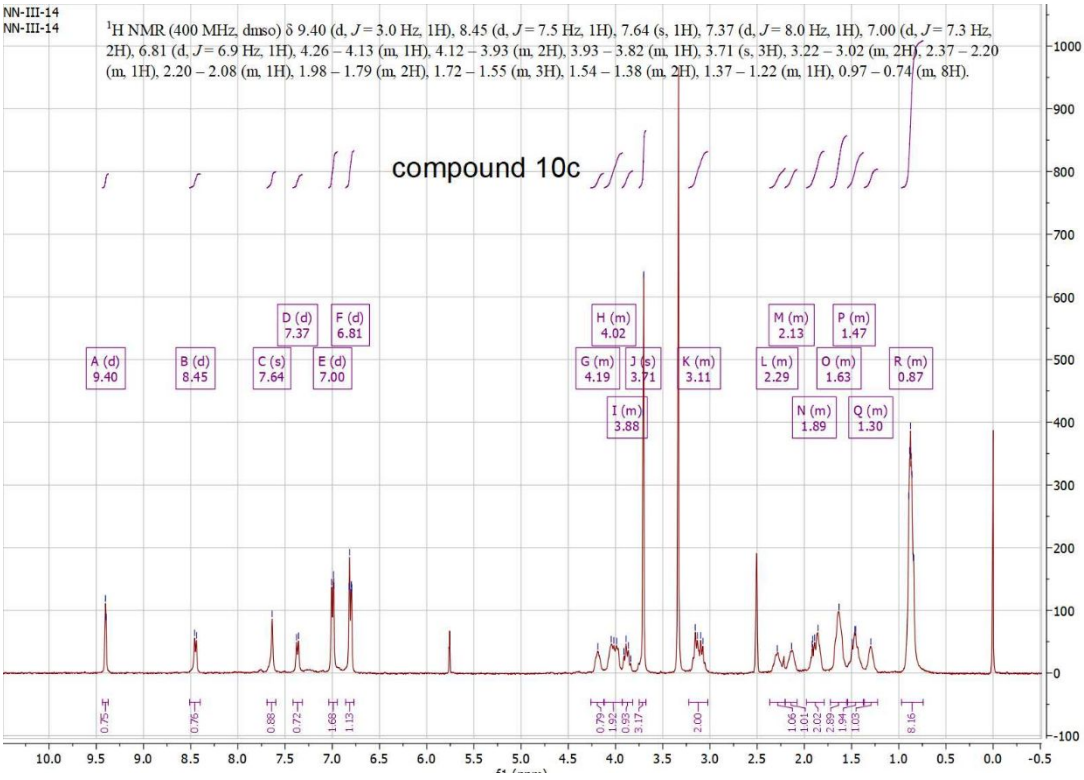

NN-II-174
NN-II-174
^{1}H NMR (400 MHz, dmso) δ 7.78 – 7.21 (m, 3H), 7.18 – 6.99 (m, 4H), 5.52 – 5.29 (m, 1H), 4.10 – 3.70 (m, 4H), 3.20 – 2.97 (m, 2H), 2.32 – 2.00 (m, 2H), 1.99 – 1.72 (m, 2H), 1.70 – 1.49 (m, 3H), 1.48 – 1.29 (m, 3H), 0.99 – 0.74 (m, 8H).
compound 7d
A (m) 7.46
C (m) 7.08
D (m) 5.40
E (m) 3.91
F (m) 3.06
G (m) 2.10
I (m) 1.57
H (m) 1.91
J (m) 1.41
K (m) 0.88
f1 (ppm)

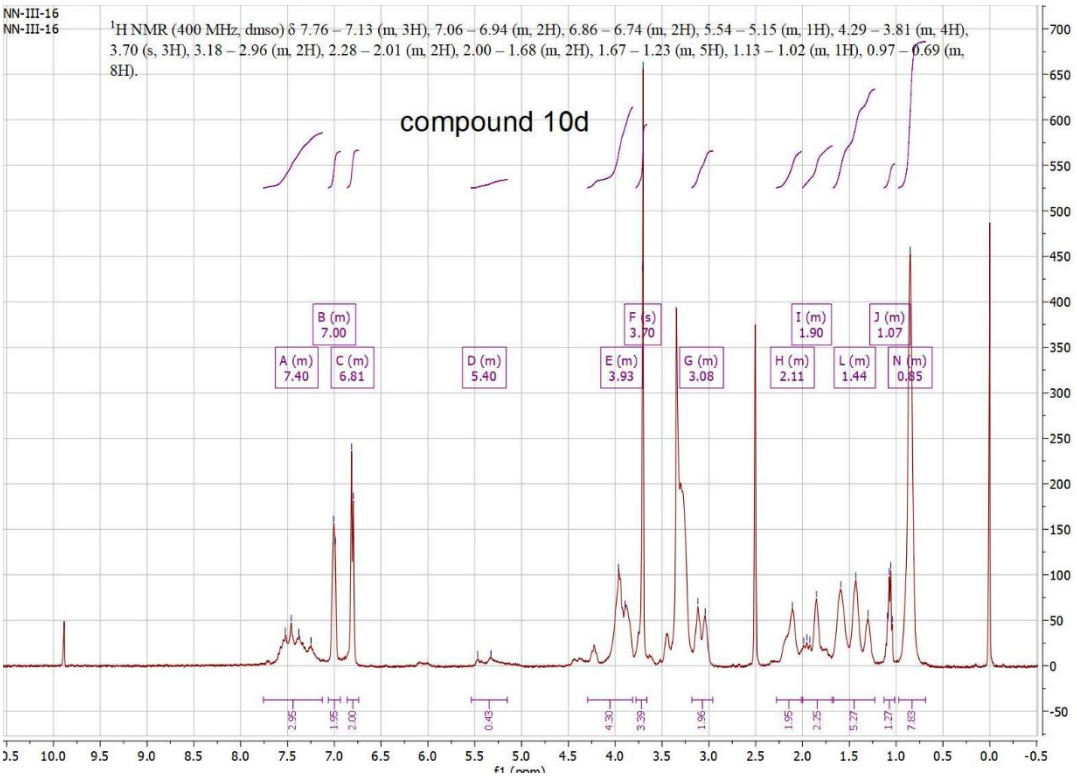

NN-II-178
NN-II-178
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 2.7 Hz, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 4.26 – 4.12 (m, 1H), 4.11 – 3.96 (m, 2H), 3.93 – 3.82 (m, 1H), 3.22 – 3.03 (m, 2H), 2.37 – 2.21 (m, 1H), 2.19 – 2.04 (m, 1H), 2.01 – 1.83 (m, 2H), 1.63 (s, 3H), 1.52 – 1.35 (m, 3H), 1.05 – 0.92 (m, 2H), 0.89 – 0.78 (m, 6H).
compound 8c
A (d) 9.40
B (d) 8.44
C (s) 7.63
D (d) 7.37
E (d) 7.28
F (d) 7.10
G (m) 4.18
H (m) 4.01
I (m) 3.88
J (m) 3.11
K (m) 2.28
L (m) 2.13
M (m) 1.91
N (m) 1.63
O (m) 1.45
P (m) 0.96
Q (m) 0.86

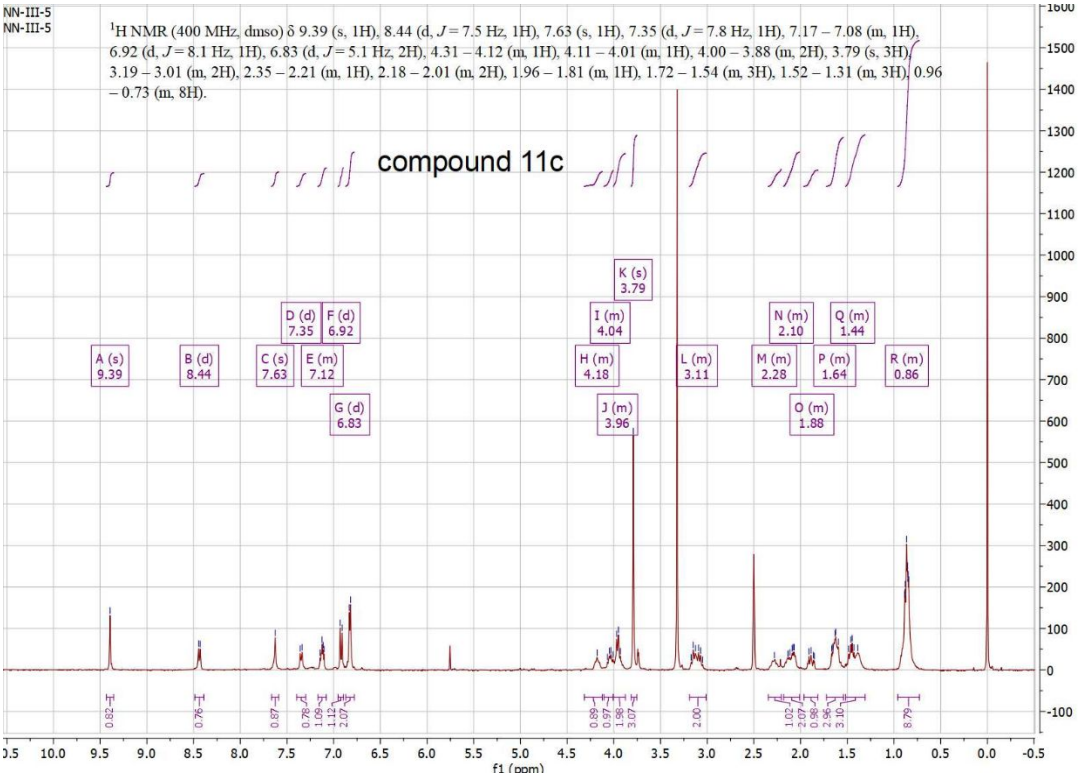

NN-II-180
NN-II-180
¹H NMR (400 MHz, dmso) δ 7.65 – 7.34 (m, 2H), 7.33 – 7.22 (m, 3H), 7.13 – 7.06 (m, 2H), 5.46 – 5.22 (m, 1H), 4.10 – 3.56 (m, 4H), 3.18 – 2.97 (m, 2H), 2.21 – 2.05 (m, 1H), 1.99 – 1.77 (m, 2H), 1.72 – 1.44 (m, 3H), 1.45 – 1.31 (m, 3H), 1.02 – 0.90 (m, 2H), 0.88 – 0.74 (m, 7H).
compound 8d
B (m) 7.11
A (m) 7.28
C (m) 7.50
E (m) 5.42
F (m) 3.93
G (m) 3.08
I (m) 1.88
K (m) 1.40
M (m) 0.83
H (m) 2.09
J (m) 1.59
L (m) 0.96
f1 (ppm)

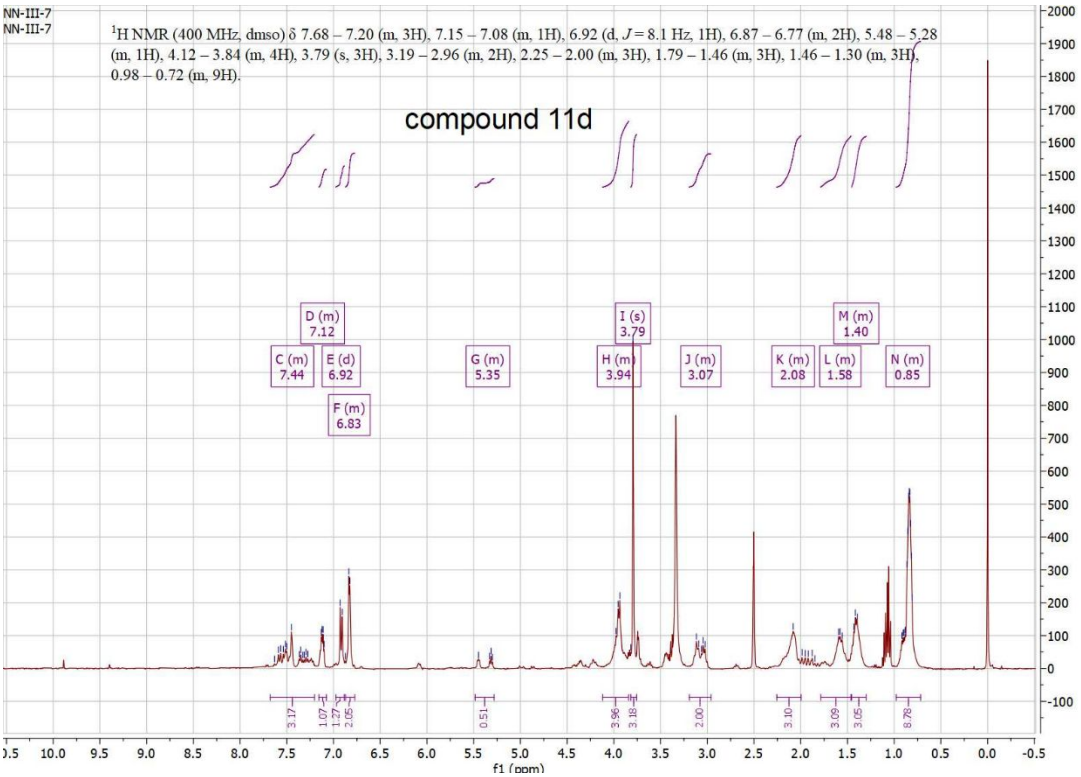

NN-III-13
NN-III-13
¹H NMR (400 MHz, dmso) δ 9.40 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 6.66 – 6.57 (m, 2H), 4.24 – 4.10 (m, 1H), 4.11 – 3.95 (m, 2H), 3.94 – 3.80 (m, 1H), 3.72 (s, 3H), 3.20 – 3.03 (m, 2H), 2.35 – 2.08 (m, 2H), 1.96 – 1.80 (m, 2H), 1.74 – 1.54 (m, 3H), 1.54 – 1.28 (m, 3H), 1.03 – 0.76 (m, 8H).
compound 9c
A (s) 9.40
B (d) 8.44
C (s) 7.63
D (d) 7.36
E (t) 7.14
F (d) 6.70
G (m) 6.64
H (m) 4.18
I (m) 4.01
J (m) 3.88
S (s) 3.72
K (m) 3.12
M (m) 2.21
N (m) 1.89
O (m) 1.62
P (m) 1.45
R (m) 0.89
f1 (ppm)

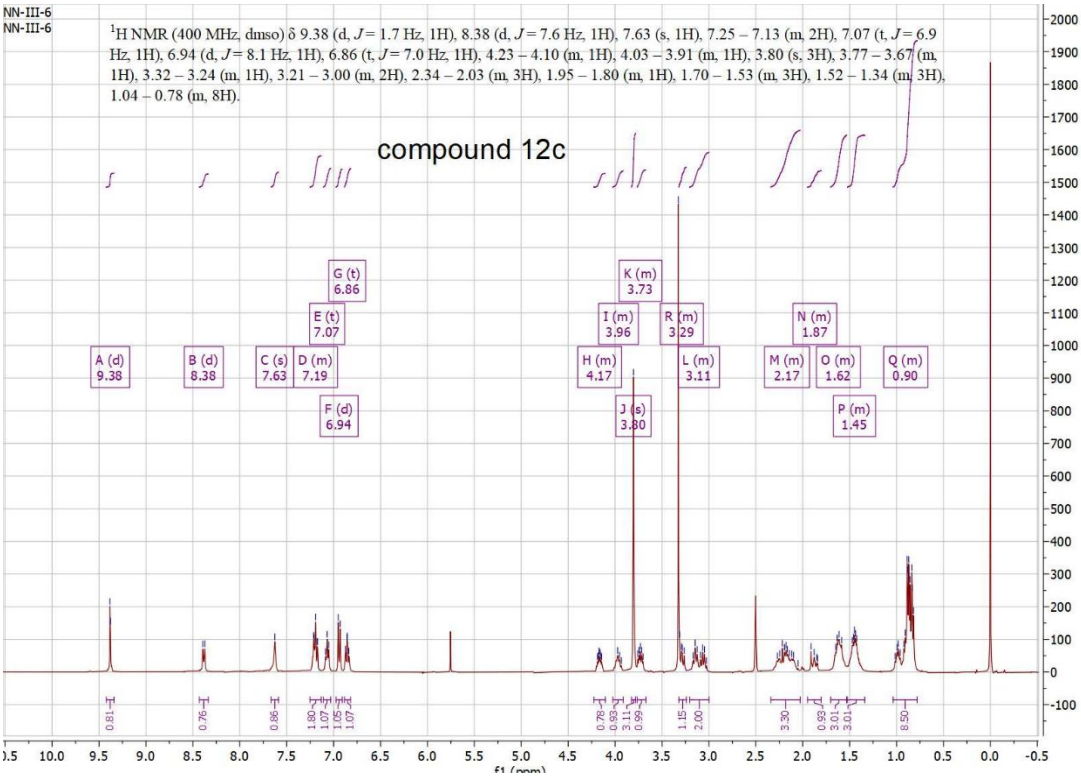

NN-III-15
NN-III-15
^{1}H NMR (400 MHz, dmso) δ 7.74 – 7.21 (m, 3H), 7.14 (t, J = 7.8 Hz, 1H), 6.74 – 6.56 (m, 3H), 5.47 – 5.24 (m, 1H), 4.29 – 3.80 (m, 4H), 3.77 – 3.68 (m, 3H), 3.19 – 2.97 (m, 2H), 2.36 – 2.02 (m, 2H), 2.01 – 1.71 (m, 2H), 1.70 – 1.51 (m, 3H), 1.51 – 1.31 (m, 3H), 1.13 – 1.03 (m, 1H), 1.02 – 0.88 (m, 2H), 0.87 – 0.74 (m, 5H).
compound 9d
D (t) 7.14
A (m) 7.45
E (m) 6.67
F (m) 5.38
O (m) 3.72
G (m) 3.89
H (m) 3.07
J (m) 1.94
L (m) 1.41
N (m) 0.83
I (m) 2.15
K (m) 1.58
M (m) 0.95
B (m) 1.08
f1 (ppm)

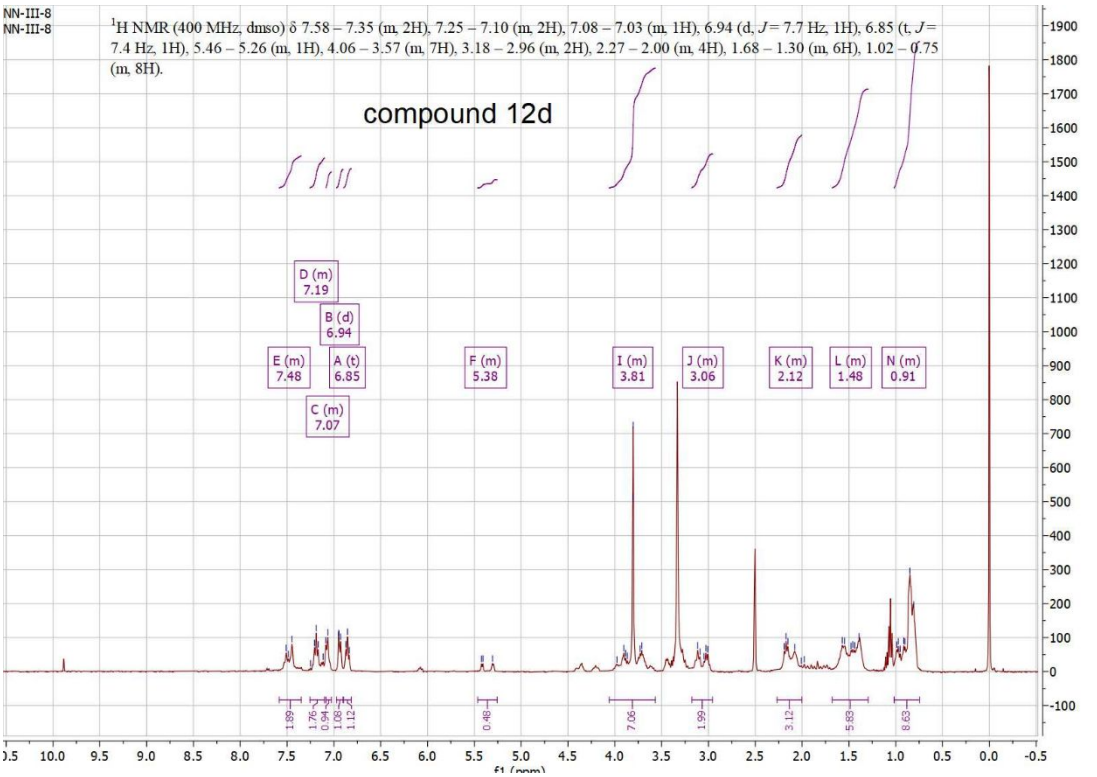

NN-III-14
NN-III-14
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 7.64 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 7.3 Hz, 2H), 6.81 (d, J = 6.9 Hz, 1H), 4.26 – 4.13 (m, 1H), 4.12 – 3.93 (m, 2H), 3.93 – 3.82 (m, 1H), 3.71 (s, 3H), 3.22 – 3.02 (m, 2H), 2.37 – 2.20 (m, 1H), 2.20 – 2.08 (m, 1H), 1.98 – 1.79 (m, 2H), 1.72 – 1.55 (m, 3H), 1.54 – 1.38 (m, 2H), 1.37 – 1.22 (m, 1H), 0.97 – 0.74 (m, 8H).
compound 10c
A (d) 9.40
B (d) 8.45
C (s) 7.64
D (d) 7.37
E (d) 7.00
F (d) 6.81
G (m) 4.19
H (m) 4.02
I (m) 3.88
J (s) 3.71
K (m) 3.11
L (m) 2.29
M (m) 2.13
N (m) 1.89
O (m) 1.63
P (m) 1.47
Q (m) 1.30
R (m) 0.87

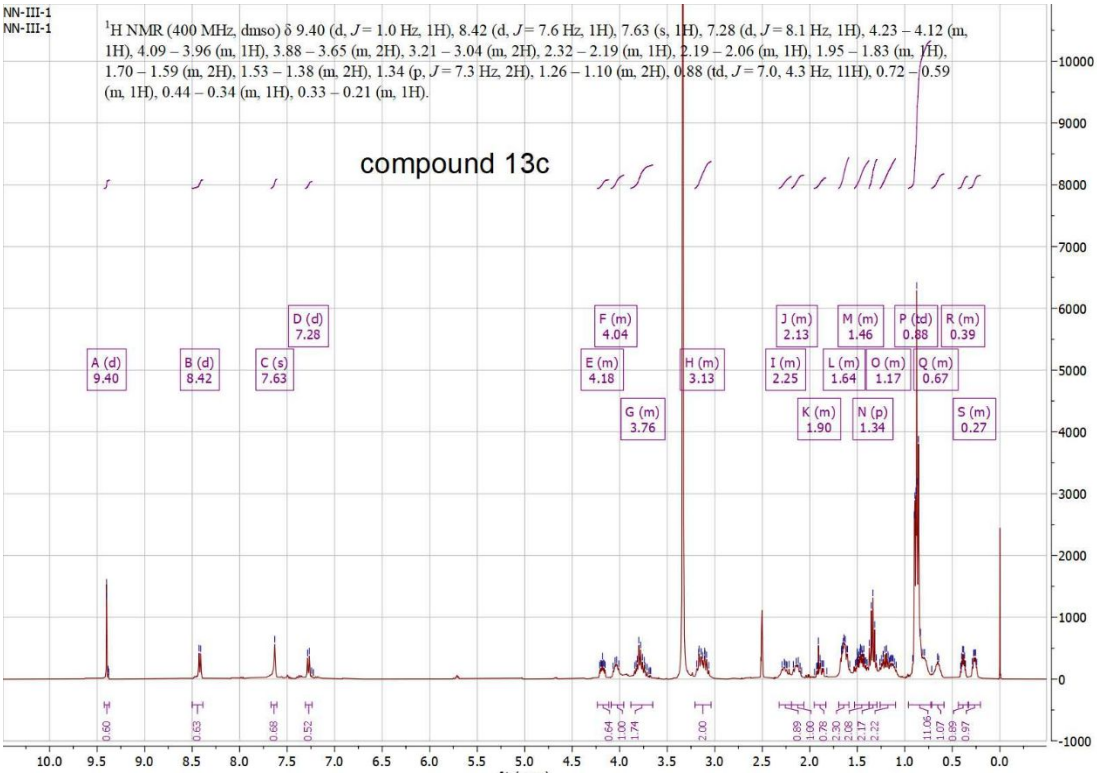

NN-III-16
NN-III-16
^{1}H NMR (400 MHz, dmso) δ 7.76 – 7.13 (m, 3H), 7.06 – 6.94 (m, 2H), 6.86 – 6.74 (m, 2H), 5.54 – 5.15 (m, 1H), 4.29 – 3.81 (m, 4H), 3.70 (s, 3H), 3.18 – 2.96 (m, 2H), 2.28 – 2.01 (m, 2H), 2.00 – 1.68 (m, 2H), 1.67 – 1.23 (m, 5H), 1.13 – 1.02 (m, 1H), 0.97 – 0.69 (m, 8H).
compound 10d
B (m) 7.00
A (m) 7.40
C (m) 6.81
D (m) 5.40
F (s) 3.70
E (m) 3.93
G (m) 3.08
I (m) 1.90
H (m) 2.11
L (m) 1.44
J (m) 1.07
N (m) 0.85
f1 (ppm)

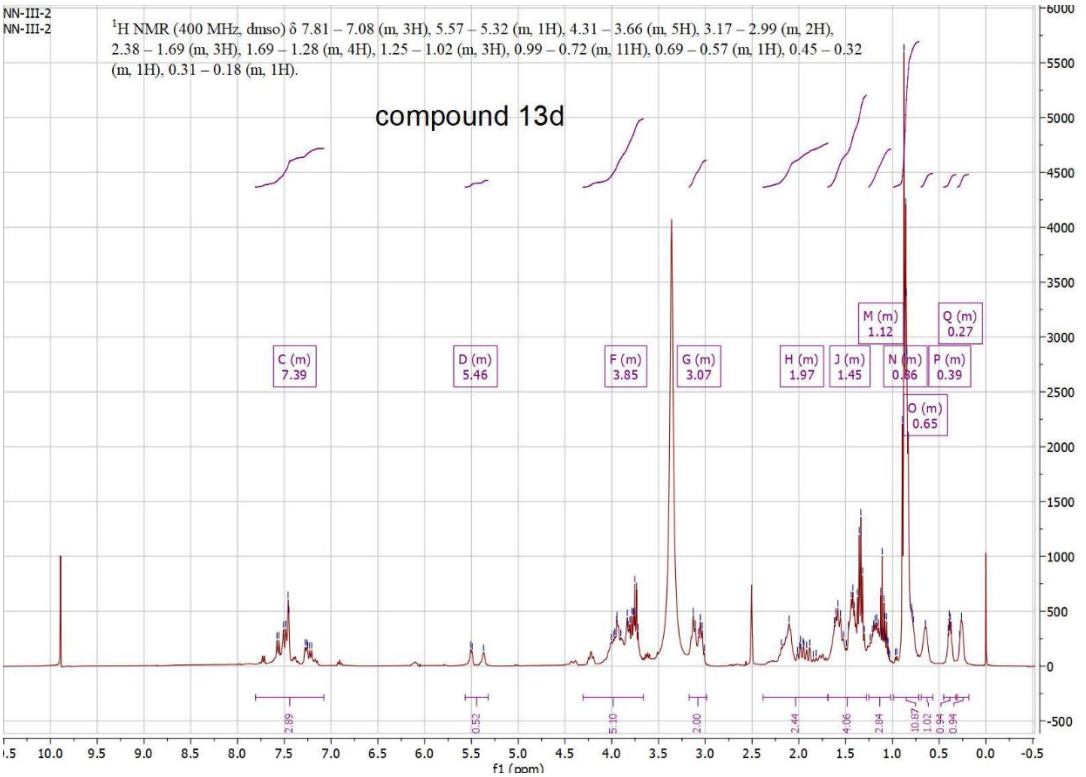

NN-III-5
NN-III-5
^{1}H NMR (400 MHz, dmso) δ 9.39 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.17 – 7.08 (m, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 5.1 Hz, 2H), 4.31 – 4.12 (m, 1H), 4.11 – 4.01 (m, 1H), 4.00 – 3.88 (m, 2H), 3.79 (s, 3H), 3.19 – 3.01 (m, 2H), 2.35 – 2.21 (m, 1H), 2.18 – 2.01 (m, 2H), 1.96 – 1.81 (m, 1H), 1.72 – 1.54 (m, 3H), 1.52 – 1.31 (m, 3H), 0.96 – 0.73 (m, 8H).
compound 11c
A (s) 9.39
B (d) 8.44
C (s) 7.63
D (d) 7.35
E (m) 7.12
F (d) 6.92
G (d) 6.83
H (m) 4.18
I (m) 4.04
J (m) 3.96
K (s) 3.79
L (m) 3.11
M (m) 2.28
N (m) 2.10
O (m) 1.88
P (m) 1.64
Q (m) 1.44
R (m) 0.86
f1 (ppm)

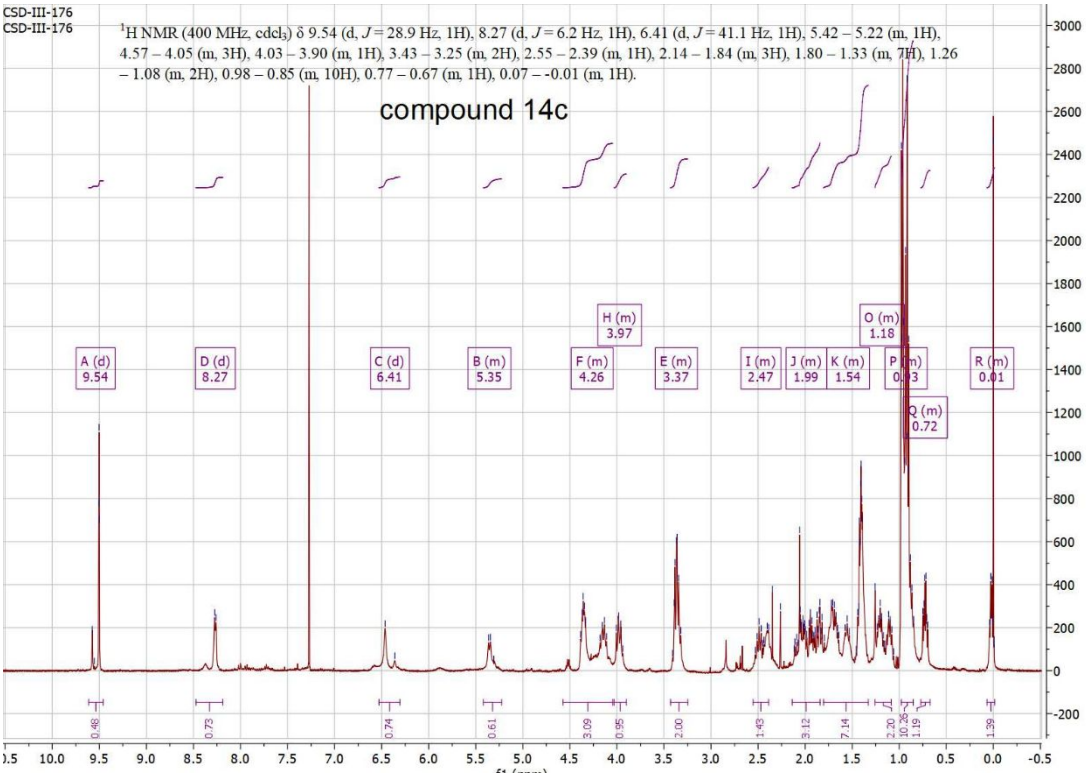

NN-III-7
NN-III-7
^{1}H NMR (400 MHz, dmso) δ 7.68 – 7.20 (m, 3H), 7.15 – 7.08 (m, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.87 – 6.77 (m, 2H), 5.48 – 5.28 (m, 1H), 4.12 – 3.84 (m, 4H), 3.79 (s, 3H), 3.19 – 2.96 (m, 2H), 2.25 – 2.00 (m, 3H), 1.79 – 1.46 (m, 3H), 1.46 – 1.30 (m, 3H), 0.98 – 0.72 (m, 9H).
compound 11d
D (m) 7.12
C (m) 7.44
E (d) 6.92
F (m) 6.83
G (m) 5.35
I (s) 3.79
H (m) 3.94
J (m) 3.07
K (m) 2.08
L (m) 1.58
M (m) 1.40
N (m) 0.85
f1 (ppm)

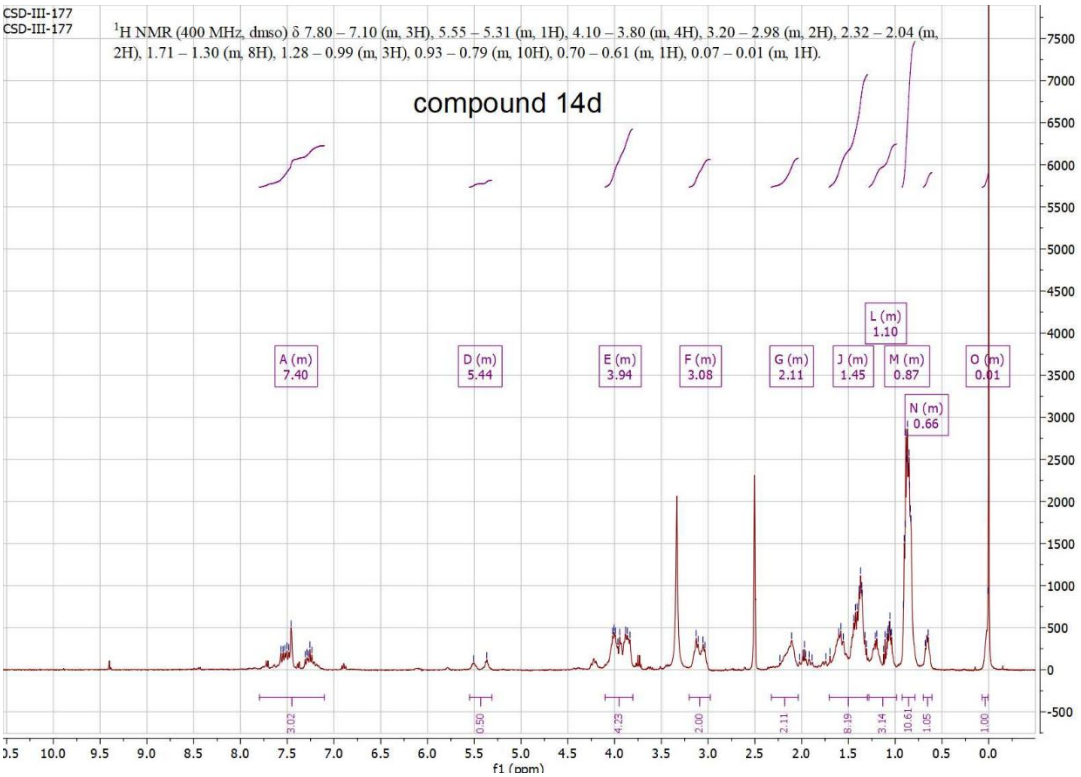

NN-III-6
NN-III-6
^{1}H NMR (400 MHz, dmso) δ 9.38 (d, J = 1.7 Hz, 1H), 8.38 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.25 – 7.13 (m, 2H), 7.07 (t, J = 6.9 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.86 (t, J = 7.0 Hz, 1H), 4.23 – 4.10 (m, 1H), 4.03 – 3.91 (m, 1H), 3.80 (s, 3H), 3.77 – 3.67 (m, 1H), 3.32 – 3.24 (m, 1H), 3.21 – 3.00 (m, 2H), 2.34 – 2.03 (m, 3H), 1.95 – 1.80 (m, 1H), 1.70 – 1.53 (m, 3H), 1.52 – 1.34 (m, 3H), 1.04 – 0.78 (m, 8H).
compound 12c
A (d) 9.38
B (d) 8.38
C (s) 7.63
D (m) 7.19
E (t) 7.07
F (d) 6.94
G (t) 6.86
H (m) 4.17
I (m) 3.96
J (s) 3.80
K (m) 3.73
L (m) 3.11
M (m) 2.17
N (m) 1.87
O (m) 1.62
P (m) 1.45
Q (m) 0.90
R (m) 3.29
f1 (ppm)

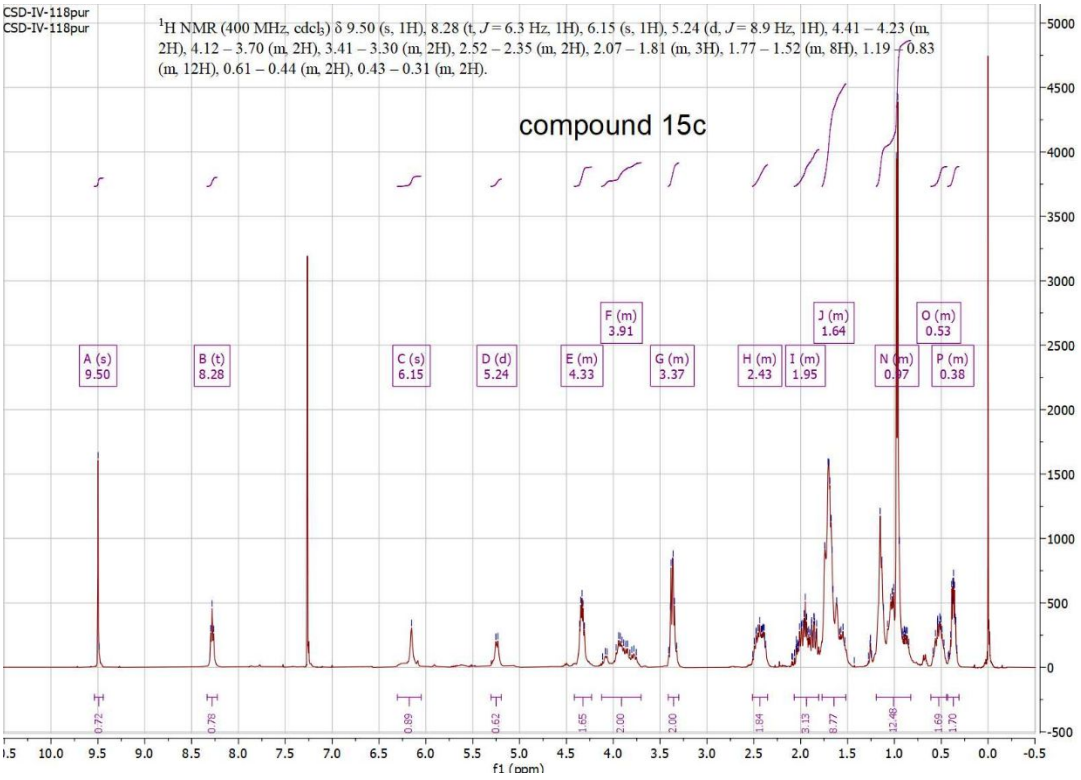

NN-III-8
NN-III-8
^{1}H NMR (400 MHz, dmso) δ 7.58 – 7.35 (m, 2H), 7.25 – 7.10 (m, 2H), 7.08 – 7.03 (m, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.85 (t, J = 7.4 Hz, 1H), 5.46 – 5.26 (m, 1H), 4.06 – 3.57 (m, 7H), 3.18 – 2.96 (m, 2H), 2.27 – 2.00 (m, 4H), 1.68 – 1.30 (m, 6H), 1.02 – 0.75 (m, 8H).
compound 12d
D (m) 7.19
B (d) 6.94
E (m) 7.48
A (t) 6.85
C (m) 7.07
F (m) 5.38
I (m) 3.81
J (m) 3.06
K (m) 2.12
L (m) 1.48
N (m) 0.91
f1 (ppm)

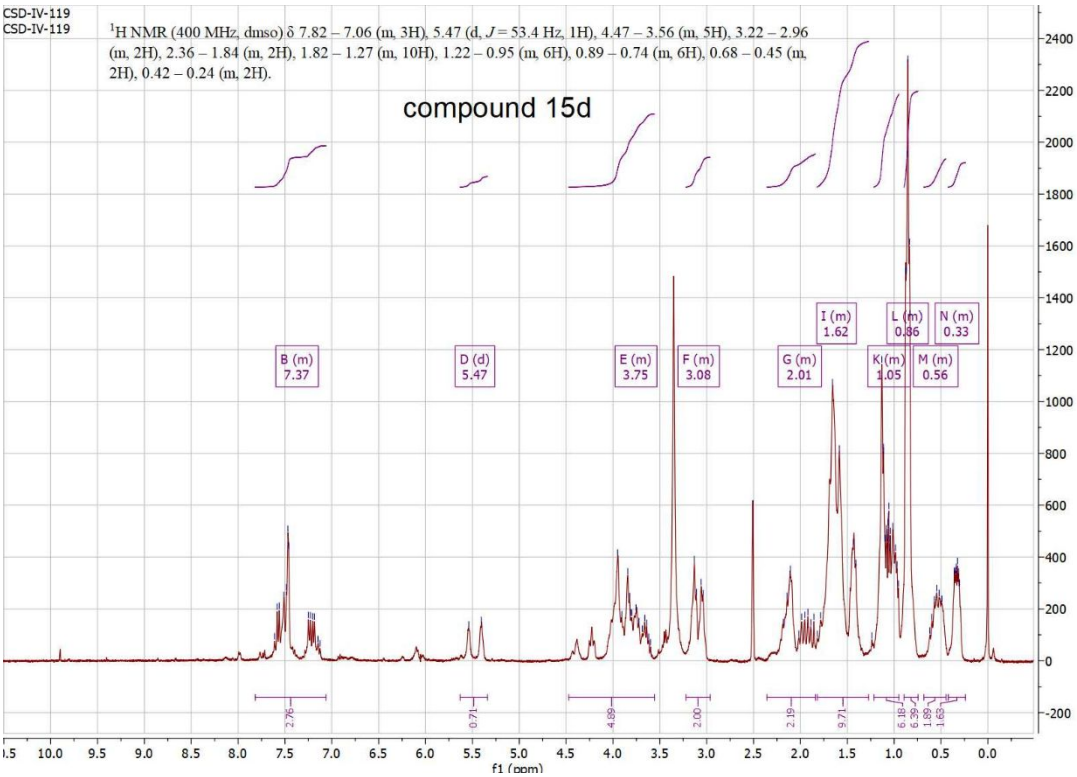

NN-III-1
NN-III-1
^{1}H NMR (400 MHz, dmso) δ 9.40 (d, J = 1.0 Hz, 1H), 8.42 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.28 (d, J = 8.1 Hz, 1H), 4.23 – 4.12 (m, 1H), 4.09 – 3.96 (m, 1H), 3.88 – 3.65 (m, 2H), 3.21 – 3.04 (m, 2H), 2.32 – 2.19 (m, 1H), 2.19 – 2.06 (m, 1H), 1.95 – 1.83 (m, 1H), 1.70 – 1.59 (m, 2H), 1.53 – 1.38 (m, 2H), 1.34 (p, J = 7.3 Hz, 2H), 1.26 – 1.10 (m, 2H), 0.88 (td, J = 7.0, 4.3 Hz, 11H), 0.72 – 0.59 (m, 1H), 0.44 – 0.34 (m, 1H), 0.33 – 0.21 (m, 1H).
compound 13c
A (d) 9.40
B (d) 8.42
C (s) 7.63
D (d) 7.28
F (m) 4.04
E (m) 4.18
G (m) 3.76
H (m) 3.13
J (m) 2.13
I (m) 2.25
K (m) 1.90
M (m) 1.46
L (m) 1.64
N (p) 1.34
P (td) 0.88
O (m) 1.17
R (m) 0.39
Q (m) 0.67
S (m) 0.27

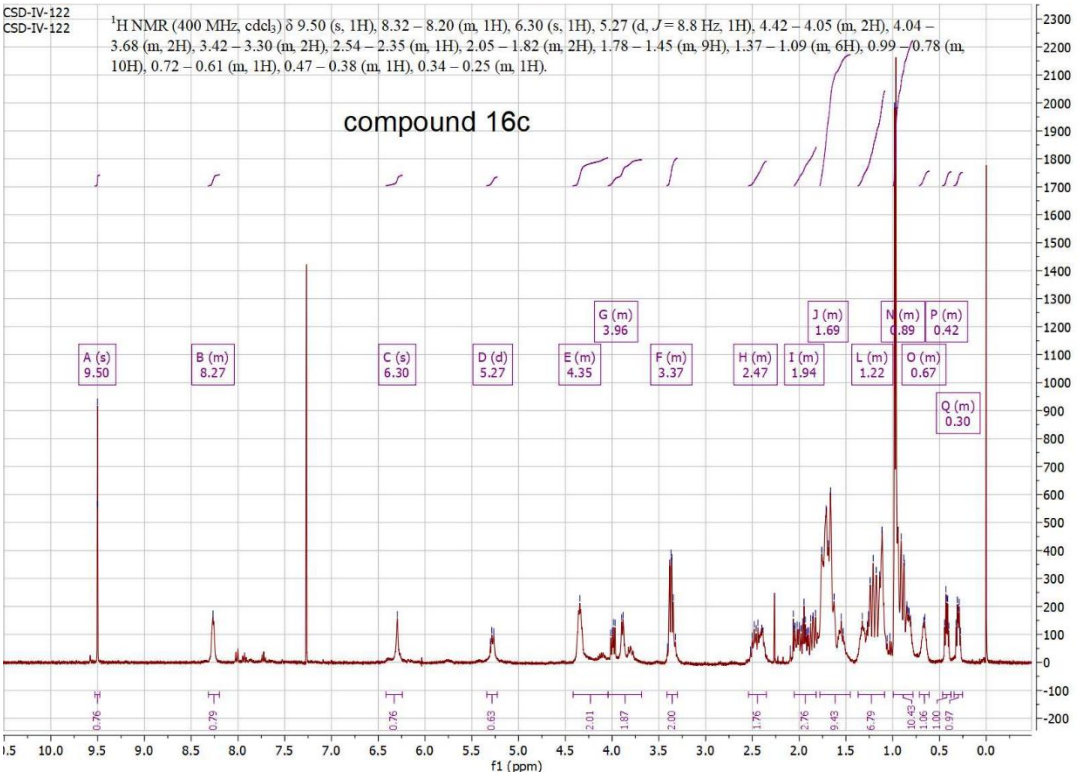

NN-III-2
NN-III-2
^{1}H NMR (400 MHz, dmso) δ 7.81 – 7.08 (m, 3H), 5.57 – 5.32 (m, 1H), 4.31 – 3.66 (m, 5H), 3.17 – 2.99 (m, 2H), 2.38 – 1.69 (m, 3H), 1.69 – 1.28 (m, 4H), 1.25 – 1.02 (m, 3H), 0.99 – 0.72 (m, 11H), 0.69 – 0.57 (m, 1H), 0.45 – 0.32 (m, 1H), 0.31 – 0.18 (m, 1H).
compound 13d
C (m) 7.39
D (m) 5.46
F (m) 3.85
G (m) 3.07
H (m) 1.97
J (m) 1.45
N (m) 0.86
P (m) 0.39
M (m) 1.12
Q (m) 0.27
O (m) 0.65
f1 (ppm)

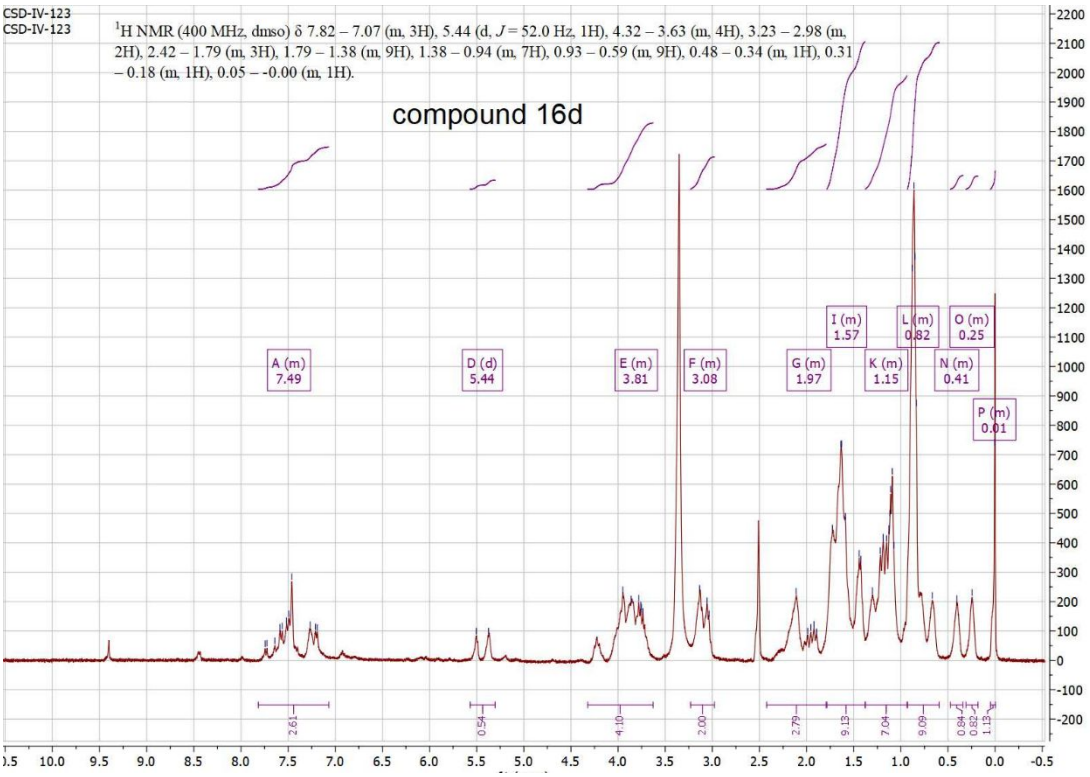

CSD-III-176
CSD-III-176
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.54 (d, J = 28.9 Hz, 1H), 8.27 (d, J = 6.2 Hz, 1H), 6.41 (d, J = 41.1 Hz, 1H), 5.42 – 5.22 (m, 1H), 4.57 – 4.05 (m, 3H), 4.03 – 3.90 (m, 1H), 3.43 – 3.25 (m, 2H), 2.55 – 2.39 (m, 1H), 2.14 – 1.84 (m, 3H), 1.80 – 1.33 (m, 7H), 1.26 – 1.08 (m, 2H), 0.98 – 0.85 (m, 10H), 0.77 – 0.67 (m, 1H), 0.07 – -0.01 (m, 1H).
compound 14c
A (d) 9.54
D (d) 8.27
C (d) 6.41
B (m) 5.35
F (m) 4.26
H (m) 3.97
E (m) 3.37
I (m) 2.47
J (m) 1.99
K (m) 1.54
R (m) 0.01
O (m) 1.18
Q (m) 0.72

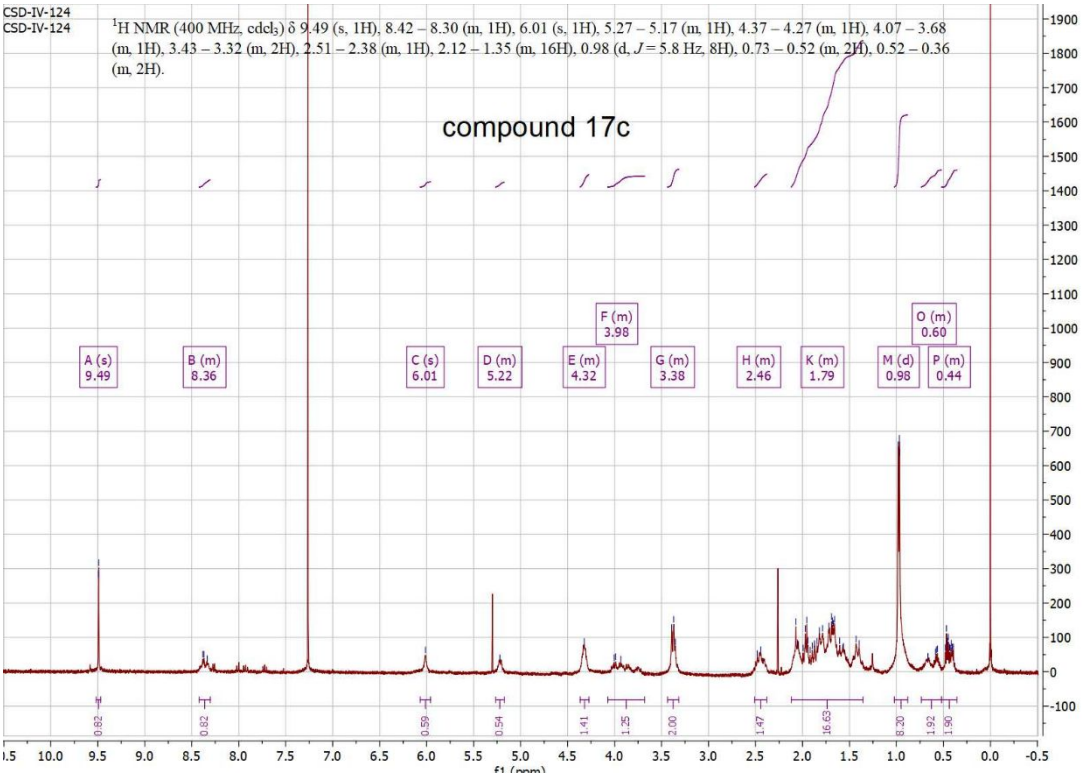

CSD-III-177
CSD-III-177
^{1}H NMR (400 MHz, dmso) δ 7.80 – 7.10 (m, 3H), 5.55 – 5.31 (m, 1H), 4.10 – 3.80 (m, 4H), 3.20 – 2.98 (m, 2H), 2.32 – 2.04 (m, 2H), 1.71 – 1.30 (m, 8H), 1.28 – 0.99 (m, 3H), 0.93 – 0.79 (m, 10H), 0.70 – 0.61 (m, 1H), 0.07 – 0.01 (m, 1H).
compound 14d
A (m) 7.40
D (m) 5.44
E (m) 3.94
F (m) 3.08
G (m) 2.11
J (m) 1.45
L (m) 1.10
M (m) 0.87
N (m) 0.66
O (m) 0.01
f1 (ppm)

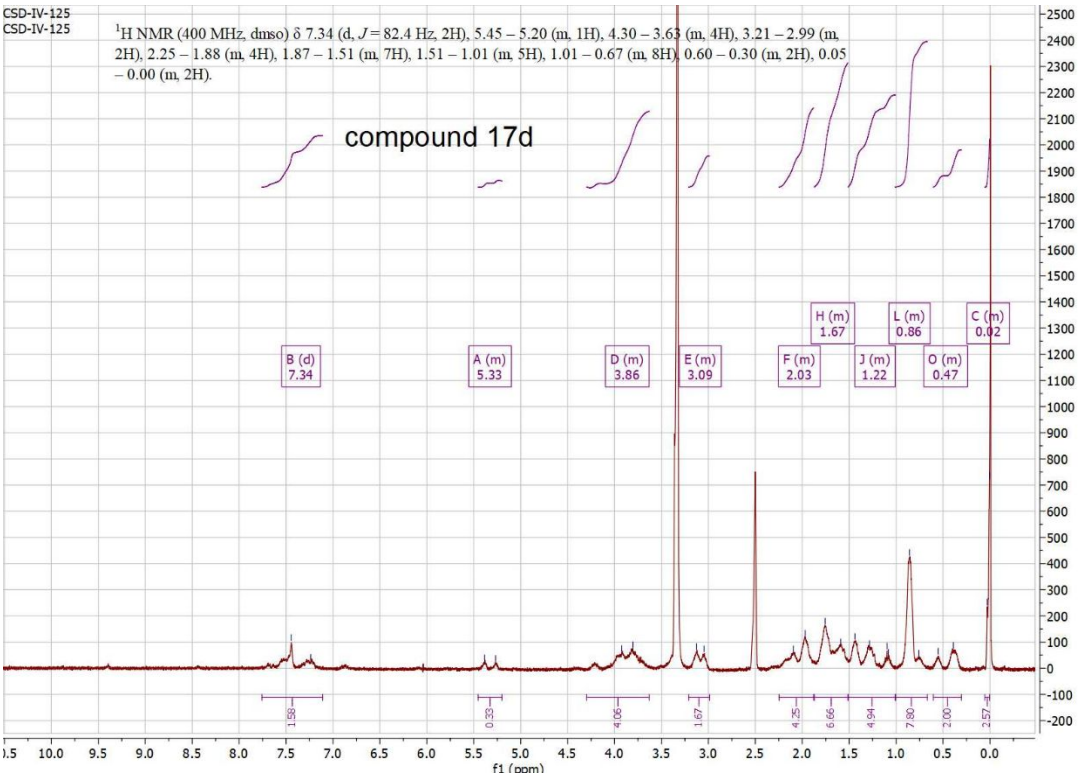

CSD-IV-118pur
CSD-IV-118pur
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.50 (s, 1H), 8.28 (t, J = 6.3 Hz, 1H), 6.15 (s, 1H), 5.24 (d, J = 8.9 Hz, 1H), 4.41 – 4.23 (m, 2H), 4.12 – 3.70 (m, 2H), 3.41 – 3.30 (m, 2H), 2.52 – 2.35 (m, 2H), 2.07 – 1.81 (m, 3H), 1.77 – 1.52 (m, 8H), 1.19 – 0.83 (m, 12H), 0.61 – 0.44 (m, 2H), 0.43 – 0.31 (m, 2H).
compound 15c
A (s) 9.50
B (t) 8.28
C (s) 6.15
D (d) 5.24
E (m) 4.33
F (m) 3.91
G (m) 3.37
H (m) 2.43
I (m) 1.95
J (m) 1.64
N (m) 0.97
O (m) 0.53
P (m) 0.38
f1 (ppm)


CSD-IV-119
CSD-IV-119
^{1}H NMR (400 MHz, dmso) δ 7.82 – 7.06 (m, 3H), 5.47 (d, J = 53.4 Hz, 1H), 4.47 – 3.56 (m, 5H), 3.22 – 2.96 (m, 2H), 2.36 – 1.84 (m, 2H), 1.82 – 1.27 (m, 10H), 1.22 – 0.95 (m, 6H), 0.89 – 0.74 (m, 6H), 0.68 – 0.45 (m, 2H), 0.42 – 0.24 (m, 2H).
compound 15d
B (m) 7.37
D (d) 5.47
E (m) 3.75
F (m) 3.08
G (m) 2.01
I (m) 1.62
K (m) 1.05
L (m) 0.86
M (m) 0.56
N (m) 0.33
f1 (ppm)


CSD-IV-122
CSD-IV-122
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.50 (s, 1H), 8.32 – 8.20 (m, 1H), 6.30 (s, 1H), 5.27 (d, J = 8.8 Hz, 1H), 4.42 – 4.05 (m, 2H), 4.04 – 3.68 (m, 2H), 3.42 – 3.30 (m, 2H), 2.54 – 2.35 (m, 1H), 2.05 – 1.82 (m, 2H), 1.78 – 1.45 (m, 9H), 1.37 – 1.09 (m, 6H), 0.99 – 0.78 (m, 10H), 0.72 – 0.61 (m, 1H), 0.47 – 0.38 (m, 1H), 0.34 – 0.25 (m, 1H).
compound 16c
A (s) 9.50
B (m) 8.27
C (s) 6.30
D (d) 5.27
E (m) 4.35
F (m) 3.37
G (m) 3.96
H (m) 2.47
I (m) 1.94
J (m) 1.69
L (m) 1.22
N (m) 0.89
O (m) 0.67
P (m) 0.42
Q (m) 0.30
f1 (ppm)


CSD-IV-123
CSD-IV-123
^{1}H NMR (400 MHz, dmso) δ 7.82 – 7.07 (m, 3H), 5.44 (d, J = 52.0 Hz, 1H), 4.32 – 3.63 (m, 4H), 3.23 – 2.98 (m, 2H), 2.42 – 1.79 (m, 3H), 1.79 – 1.38 (m, 9H), 1.38 – 0.94 (m, 7H), 0.93 – 0.59 (m, 9H), 0.48 – 0.34 (m, 1H), 0.31 – 0.18 (m, 1H), 0.05 – -0.00 (m, 1H).
compound 16d
A (m) 7.49
D (d) 5.44
E (m) 3.81
F (m) 3.08
G (m) 1.97
I (m) 1.57
K (m) 1.15
L (m) 0.82
N (m) 0.41
O (m) 0.25
P (m) 0.01


CSD-IV-124
CSD-IV-124
^{1}H NMR (400 MHz, cdcl$_3$) δ 9.49 (s, 1H), 8.42 – 8.30 (m, 1H), 6.01 (s, 1H), 5.27 – 5.17 (m, 1H), 4.37 – 4.27 (m, 1H), 4.07 – 3.68 (m, 1H), 3.43 – 3.32 (m, 2H), 2.51 – 2.38 (m, 1H), 2.12 – 1.35 (m, 16H), 0.98 (d, J = 5.8 Hz, 8H), 0.73 – 0.52 (m, 2H), 0.52 – 0.36 (m, 2H).
compound 17c
A (s) 9.49
B (m) 8.36
C (s) 6.01
D (m) 5.22
E (m) 4.32
F (m) 3.98
G (m) 3.38
H (m) 2.46
K (m) 1.79
M (d) 0.98
O (m) 0.60
P (m) 0.44


CSD-IV-125
CSD-IV-125
^{1}H NMR (400 MHz, dmso) δ 7.34 (d, J = 82.4 Hz, 2H), 5.45 – 5.20 (m, 1H), 4.30 – 3.63 (m, 4H), 3.21 – 2.99 (m, 2H), 2.25 – 1.88 (m, 4H), 1.87 – 1.51 (m, 7H), 1.51 – 1.01 (m, 5H), 1.01 – 0.67 (m, 8H), 0.60 – 0.30 (m, 2H), 0.05 – 0.00 (m, 2H).
compound 17d
B (d) 7.34
A (m) 5.33
D (m) 3.86
E (m) 3.09
F (m) 2.03
J (m) 1.22
O (m) 0.47
H (m) 1.67
L (m) 0.86
C (m) 0.02
f1 (ppm)

Determination of purity of compounds *1c/d-17c/d*

Sample preparation. Compounds (***1c/d-17c/d***) were weighed into glass vials using an analytical balance (Mettler Toledo XS105) with 0.01 mg accuracy (specific quantities are listed in the table). A stock solution of dimethyl sulfone (*Trace*CERT®, 99.82 ±0.18%, lot BCBZ3940, traceability: NIST SRM 84L) in DMSO-d_6 (with 1% v/v TMS) was prepared. A concentration of stock solution was prepared for ***1c-17c, 1d-5d*** and ***14d-17d*** at 2.00 mg/600 µL and for ***6d-13d*** was 4.00 mg/600 µL. A 600 µL aliquot of stock solution was added into each vial and capped with a lid. The vials were vortex mixed for two minutes to ensure compounds dissolved completely. The content in the vials were quantitatively transferred to 5 mm standard NMR tubes. The tubes were capped, wrapped with PTFE tape, followed by paraffin tape.

Compound code	***1c***	***2c***	***3c***	***4c***	***5c***	***6c***	***7c***	***8c***	***9c***
Weight(mg)	12.40	13.19	11.26	10.50	11.76	12.97	11.70	13.40	12.50

Compound code	***10c***	***11c***	***12c***	***13c***	***14c***	***15c***	***16c***	***17c***
Weight(mg)	11.71	12.80	12.08	9.01	11.77	12.44	9.80	10.86

Compound code	***1d***	***2d***	***3d***	***4d***	***5d***	***6d***	***7d***	***8d***	***9d***
Weight(mg)	13.13	11.18	14.08	11.18	11.95	11.98	12.47	12.53	11.85

Compound code	***10d***	***11d***	***12d***	***13d***	***14d***	***15d***	***16d***	***17d***
Weight(mg)	13.77	13.32	14.19	14.97	14.67	13.94	11.72	9.81

Acquisition. The instrument and controlled parameters used during the acquisition are listed below.

NMR instrument	: Bruker AV III 500
Probe	: CPDUL CRYOprobe CP BBO 500S2
Preacquisition delay (DE)	: 10 μs
Pulse program	: Single pulse, zg with 90^0 pulse
Sample temperature	: 25.0 ± 0.1 ^{0}C
Data points acquired (TD)	: 64 K
Dummy scans (DS)	: 4
Pulse width (PW):	: 90^0

Relaxation delay (D1=T_1x5)	: 12 s
Acquisition time (AQ)	: 2.1845 s (set by TD)
Spectral window (SW)	: 30 ppm
Transmitter offset	: 7.5 ppm
Number of scans	: 32
360^0 Pulse	: 51.079 μs
90^0 Pulse	: 12.769 μs
Automatic tuning and automatic matching were performed. Automatic locking and automatic shimming were performed.	

Post-acquisition processing

Apodization	: LB = 0.1 Hz
Zero-filling	: 256 K
Phasing	: Manual phase correction
Baseline correction	: Polynomial fit, 5^{th} order

Quantitative measurement of integrals. TMS was set at 0.0000 ppm. The integral values and range (ppm) of all signals used for quantification have been documented below. The integral of the internal calibrant resonance signal (dimethyl sulfone) is in *Italic*.

Code	***1c***		***2c***		***3c***		***4c***	
Integral	7.15 .. 7.10	27601.65	7.38 .. 7.32	56224.79	7.43 .. 7.09	171597.05	3.20 .. 3.02	49658.31
	7.09 .. 7.02	55534.37	7.31 .. 7.23	84120.20	3.20 .. 3.01	53109.98	*3.01 .. 2.98*	*166111.04*
	3.19 .. 3.01	53790.64	3.19 .. 3.01	74113.90	*3.01 .. 2.98*	*165393.47*	0.93 .. 0.76	162350.10
	3.01 .. 2.99	*134221.44*	*3.00 .. 2.99*	*136770.50*	1.06 .. 0.92	37663.64		
	1.00 .. 0.90	56632.74	0.92 .. 0.79	165155.96	0.92 .. 0.76	173979.53		
	0.90 .. 0.76	171059.26			0.51 .. 0.40	33147.32		
Avg.	28047.59		29201.14		31299.83		26501.05	

Code	***5c***		***6c***		***7c***		***8c***	
Integral	7.30 .. 7.23	39512.15	7.29 .. 7.23	39227.19	7.14 .. 7.01	125503.11	7.31 .. 7.26	65771.14
	6.99 .. 6.84	89627.98	7.22 .. 7.17	31990.27	*3.01 .. 2.99*	*162118.90*	7.13 .. 7.06	62643.44
	3.20 .. 3.02	54910.15	7.16 .. 7.12	32509.44	0.99 .. 0.77	251341.77	3.20 .. 3.02	58559.03
	3.00 .. 2.99	*152052.33*	7.07 .. 7.00	33841.56			*3.01 .. 2.98*	*152578.87*
	1.04 .. 0.95	57632.52	3.20 .. 3.02	62493.98			1.05 .. 0.91	64872.28
	0.92 .. 0.78	173592.17	*3.01 .. 2.99*	*162817.09*			0.91 .. 0.74	190084.58
			1.05 .. 0.94	65759.92				
			0.91 .. 0.77	197330.68				
Avg.	29662.5		33082.36		31403.7		31947.6	

Code	***9c***		***10c***		***11c***		***12c***	
Integral	7.18 .. 7.11	31862.83	7.04 .. 6.94	57334.04	7.16 .. 7.09	33197.60	7.25 .. 7.16	44541.58
	6.73 .. 6.58	95583.23	6.84 .. 6.76	57974.81	6.95 .. 6.89	35414.47	7.09 .. 7.04	28746.73
	3.74 .. 3.69	98004.31	3.71 .. 3.69	82761.22	6.86 .. 6.78	63855.40	6.97 .. 6.91	29074.14
	3.19 .. 3.04	66066.20	3.19 .. 3.04	53981.74	3.82 .. 3.77	93258.08	6.89 .. 6.81	30665.39
	3.01 .. 2.98	*161741.07*	*3.01 .. 2.98*	*153721.86*	3.20 .. 3.02	65634.73	3.83 .. 3.77	87161.54
			0.97 .. 0.77	229313.02	*3.01 .. 2.98*	*161301.27*	*3.01 .. 2.97*	*156484.15*
					0.97 .. 0.73	271185.37	1.05 .. 0.70	236886.60
Avg.	32390.73		28315.58		33090.92		30471.73	

Code	***13c***		***14c***		***15c***		***16c***	
Integral	3.21 .. 3.03	50735.30	3.21 .. 3.02	68684.05	3.20 .. 3.05	64008.81	3.20 .. 3.05	46845.05
	3.01 .. 2.98	*153813.18*	*3.00 .. 2.99*	*160715.41*	*3.01 .. 2.98*	*143266.72*	*3.01 .. 2.98*	*152562.35*
	0.70 .. 0.59	27616.61	0.93 .. 0.77	377425.44	2.34 .. 2.23	28453.87	0.70 .. 0.61	26374.78
	0.42 .. 0.35	23538.75	0.70 .. 0.61	37506.23	2.18 .. 2.09	30133.96	0.43 .. 0.35	23693.53
	0.30 .. 0.22	24152.70			0.64 .. 0.44	63974.68	0.28 .. 0.19	23580.00
					0.41 .. 0.26	55750.75		
Avg.	25208.67		34543.98		30290.26		24098.67	

Code	***17c***
Integral	3.20 .. 3.04 55776.64 *3.01 .. 2.97 164506.63* 0.98 .. 0.67 233475.40 0.62 .. 0.51 23305.10 0.45 .. 0.30 46823.96
Avg.	27644.7

Code	***1d***	***2d***	***3d***	***4d***
Integral	7.27 .. 7.20 58128.34 7.18 .. 7.02 76365.05 *3.01 .. 2.97 148877.68* 1.02 .. 0.90 53973.14 0.89 .. 0.75 159588.58	7.38 .. 7.23 119977.09 *3.00 .. 2.98 163499.22* 0.90 .. 0.76 140604.97	7.33 .. 7.15 147249.89 *3.00 .. 2.98 152606.91* 0.91 .. 0.77 166997.61 0.51 .. 0.41 32025.85	*3.01 .. 2.97 162671.85* 0.93 .. 0.74 141224.94
Avg.	26773.47	23689.28	28856.11	23537.49

Code	***5d***	***6d***	***7d***	***8d***
Integral	7.30 .. 7.23 32364.19 6.98 .. 6.85 81015.99 *3.01 .. 2.98 162112.51* 1.03 .. 0.95 51182.52 0.90 .. 0.75 158157.98	7.29 .. 7.23 31557.31 7.21 .. 7.00 72165.85 *3.01 .. 2.98 160598.11* 1.03 .. 0.95 47085.52 0.90 .. 0.75 144654.41	7.31 .. 7.25 50398.24 7.15 .. 7.06 45621.89 *3.00 .. 2.98 268957.15* 1.03 .. 0.91 46140.94 0.90 .. 0.77 135347.83	7.30 .. 7.25 49587.72 7.13 .. 7.07 42647.81 *3.00 .. 2.99 266588.84* 1.02 .. 0.91 45294.24 0.88 .. 0.77 132164.18
Avg.	26893.39	24621.92	23125.74	22474.50

Code	***9d***	***10d***	***11d***	***12d***
Integral	7.17 .. 7.10 18767.60 6.73 .. 6.60 56852.66 3.74 .. 3.70 57949.80 *3.01 .. 2.97 257392.13* 1.01 .. 0.76 167755.45	7.04 .. 6.97 48649.37 6.84 .. 6.78 49996.91 3.71 .. 3.69 73315.25 *3.01 .. 2.98 267459.75* 0.95 .. 0.78 203613.72	7.16 .. 7.09 24220.69 6.94 .. 6.90 24577.07 6.86 .. 6.79 44966.77 3.81 .. 3.77 68358.79 *3.01 .. 2.98 267098.83* 0.98 .. 0.73 198351.82	7.22 .. 7.17 29529.03 7.10 .. 7.04 27367.66 6.96 .. 6.91 26002.00 6.89 .. 6.82 26127.23 3.82 .. 3.79 86009.97 *3.02 .. 2.97 280486.35* 1.02 .. 0.75 210298.68
Avg.	20088.37	25038.35	24031.68	27022.3

Code	***13d***	***14d***	***15d***	***16d***
Integral	3.17 .. 3.09 19710.27 3.08 .. 3.01 17432.69 *3.01 .. 2.96 160845.93* 0.70 .. 0.59 19638.02 0.43 .. 0.34 17103.57 0.31 .. 0.20 18140.96	3.18 .. 3.09 27082.74 3.09 .. 3.01 21616.39 *3.01 .. 2.97 228007.38* 0.94 .. 0.77 248988.14 0.71 .. 0.59 24195.02	3.18 .. 3.09 31948.57 3.09 .. 3.01 26635.23 *3.01 .. 2.98 162246.78* 0.91 .. 0.77 197240.35	3.19 .. 3.09 30718.38 3.08 .. 3.01 21982.97 *3.01 .. 2.98 154122.65* 0.70 .. 0.60 24975.16 0.46 .. 0.35 23409.90 0.28 .. 0.19 22935.89
Avg.	18405.1	24760.2	31978.02	24804.46

Code	***17d***	
Integral	3.17 .. 3.09	25788.16
	3.08 .. 3.02	21650.05
	3.01 .. 2.99	*160256.81*
	0.89 .. 0.81	157335.03
	0.79 .. 0.70	20322.52
	0.61 .. 0.50	19325.96
	0.45 .. 0.32	39028.50
Avg.	20246.44	

Calculation of purity

$$P\ [\%] = \frac{n_{IC} \,.\, Int_t \,.\, MW_t \,.\, m_{IC}}{n_t \,.\, Int_{IC} \,.\, MW_{IC} \,.\, m_s} \,.\, P_{IC}$$

- P – purity of the target analyte, %
- P_{IC} – purity of the internal calibrant, %
- n_{IC} – number of protons that give rise to Int_{IC}
- n_t – number of protons that give rise to Int_t
- Int_{IC} – integral of the internal calibrant resonance signal
- Int_t – integral of the target analyte resonance signal
- MW_{IC} – molecular weight of the internal calibrant
- MW_t – molecular weight of the target analyte
- m_{IC} – weight of the internal calibrant
- m_s – weight of the target analyte

Purity of c-series compounds

Compound code	Purity (%)
1c	95.1
2c	98.8
3c	97.9
4c	95.4
5c	97.4
6c	95.3
7c	97.2
8c	95.0
9c	96.5

Compound code	Purity (%)
10c	94.8
11c	96.6
12c	97.1
13c	94.8
14c	95.2
15c	97.2
16c	95.1
17c	95.6

Purity of d-series compounds

Compound code	Purity (%)
1d	95.4
2d	96.2
3d	96.0
4d	98.4
5d	99.9
6d	94.8
7d	99.3
8d	99.7
9d	96.8

Compound code	Purity (%)
10d	99.9
11d	99.3
12d	99.8
13d	99.9
14d	96.8
15d	99.6
16d	99.2
17d	96.6

Table S1. Crystallographic data for MERS 3CLpro.

Compound Code	***13c***	***14d***	***15d***	***16d***	***17d***
PDB Code	**7TQ7**	**7TQ8**	**8CZT**	**8DGY**	**8CZV**
Data Collection					
Unit-cell parameters (Å, °)	*a*=101.44	*a*=100.73	*a*=101.62	*a*=100.44 *b*=57.31	*a*=101.47
	b=57.94	*b*=57.61	*b*=56.94	*c*=49.68 β=112.2	*b*=57.45
	c=49.85	*c*=49.74	*c*=49.83		*c*=49.86
	β=112.4	β=112.2	β=112.4		β=112.5
Space group	*C*2	*C*2	*C*2	*C*2	*C*2
Resolution (Å)[1]	49.29-1.70 (1.73-1.70)	49.01-1.65 (1.68-1.65)	48.69-2.10 (2.15-2.10)	48.79-2.70 (2.77-2.70)	48.99-1.95 (2.00-1.95)
Wavelength (Å)	1.0000	1.0000	0.9795	0.9795	0.9795
Temperature (K)	100	100	100	100	100
Observed reflections	101,432	162,225	50,621	25,372	68,418
Unique reflections	29,349	31,177	14,941	6,987	19,245
$\langle I/\sigma(I)\rangle$[1]	11.3 (1.8)	10.1 (2.5)	10.6 (2.9)	7.0 (2.2)	9.8 (1.8)
Completeness (%)[1]	99.6 (97.3)	98.2 (94.0)	96.5 (99.5)	95.7 (99.9)	99.5 (99.7)
Multiplicity[1]	3.5 (3.1)	5.2 (4.4)	3.4 (3.4)	3.6 (3.8)	3.5 (3.6)
R_{merge} (%)[1, 2]	6.0 (66.9)	8.5 (77.7)	6.6 (35.9)	14.1 (69.1)	8.9 (66.1)
R_{meas} (%)[1, 4]	7.1 (80.9)	9.5 (88.3)	8.4 (43.2)	16.5 (80.2)	9.9 (72.8)
R_{pim} (%)[1, 4]	3.8 (45.1)	4.2 (41.0)	4.3 (22.8)	8.6 (40.4)	5.5 (40.5)
$CC_{1/2}$ [1, 5]	0.998 (0.718)	0.997 (0.716)	0.998 (0.933)	0.994 (0.800)	0.997 (0.840)
Refinement					
Resolution (Å) [1]	46.10-1.70	46.05-1.65	48.69-2.10	46.49-2.70	48.99-1.95
Reflections (working/test)[1]	27,890/1,448	29,587/1,566	14,231/688	6,636/330	18,350/968
R_{factor} / R_{free} (%)[1,3]	15.9/19.0	15.9/19.1	20.0/26.2	21.2/25.8	18.4/24.1
No. of atoms (Protein/Ligand/Water)	2,280/58/205	2,281/58/226	2,270/32/53	2,269/33/-	2,269/68/85
Model Quality					
R.m.s deviations					
Bond lengths (Å)	0.011	0.009	0.002	0.003	0.007
Bond angles (°)	1.003	1.044	0.488	0.557	0.865
Average *B*-factor (Å^2)					
All Atoms	26.0	25.8	40.4	48.2	35.2
Protein	25.3	24.9	40.5	48.1	35.3
Ligand	25.1	25.2	37.7	52.3	35.5

Water	33.7	34.3	38.4	-	33.1
Coordinate error(maximum likelihood) (Å)	0.17	0.17	0.24	0.31	0.26
Ramachandran Plot					
Most favored (%)	99.7	99.0	98.3	95.3	98.3
Additionally allowed (%)	0.3	1.0	1.7	4.7	1.7

1) Values in parenthesis are for the highest resolution shell.
2) $R_{merge} = \Sigma_{hkl}\Sigma_i |I_i(hkl) - \langle I(hkl)\rangle| / \Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the intensity measured for the *i*th reflection and $\langle I(hkl)\rangle$ is the average intensity of all reflections with indices hkl.

3) $R_{factor} = \Sigma_{hkl} ||F_{obs}(hkl)| - |F_{calc}(hkl)|| / \Sigma_{hkl} |F_{obs}(hkl)|$; Rfree is calculated in an identical manner using 5% of randomly selected reflections that were not included in the refinement.

4) R_{meas} = redundancy-independent (multiplicity-weighted) R_{merge} [74]. R_{pim} = precision-indicating (multiplicity-weighted) R_{merge} [75,76].
5) $CC_{1/2}$ is the correlation coefficient of the mean intensities between two random half-sets of data [77,78].

Table S2. Crystallographic data for SARS-CoV-2 3CLpro.

Compound Code	***1c***	***5c***	***6c***	***10d***	***13d***	***15d***	***17d***
PDB Code	**7TQ2**	**7TQ3**	**7TQ4**	**7TQ5**	**7TQ6**	**8CZW**	**8CZX**
Data Collection							
Unit-cell parameters (Å, °)	*a*=45.59, *b*=54.61, *c*=114.32, *β*=101.0	*a*=54.25 *b*=98.85 *c*=58.58 *β*=107.6	*a*=113.88 *b*=53.87 *c*=45.62 *β*=101.6	*a*=55.38 *b*=98.44 *c*=59.28 *β*=108.3	*a*=55.26 *b*=98.72 *c*=58.92 *β*=108.2	*a*=55.17 *b*=98.53 *c*=59.14 *β*=108.0	*a*=54.86 *b*=98.50 *c*=58.68 *β*=107.7
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P2_1$
Resolution (Å)[1]	49.11-2.30 (2.38-2.30)	48.61-2.00 (2.05-2.00)	48.51-2.45 (2.55-2.45)	48.86-1.65 (1.68-1.65)	48.69-1.55 (1.58-1.55)	46.31-1.70 (1.73-1.70)	48.63-1.65 (1.68-1.65)
Wavelength (Å)	1.0000	1.0000	1.0000	1.0000	1.0000	0.9795	0.9795
Temperature (K)	100	100	100	100	100	100	100
Observed reflections	86,865	138,606	35,501	250,742	300,837	231,847	254,941
Unique reflections	24,770	40,112	10,065	72,411	86,805	65,228	58,790
$\langle I/\sigma(I)\rangle$[1]	7.3 (2.2)	12.2 (1.9)	8.5 (1.8)	11.2 (1.6)	13.2 (1.8)	11.2 (1.9)	11.5 (1.6)
Completeness (%)[1]	99.9 (99.8)	98.9 (99.7)	99.7 (100)	99.9 (100)	99.9 (99.9)	98.8 (99.3)	98.3 (97.5)
Multiplicity[1]	3.5 (3.6)	3.5 (3.6)	3.5 (3.6)	3.5 (3.4)	3.5 (3.5)	3.6 (3.6)	3.6 (3.8)
R_{merge} (%)[1, 2]	11.2 (60.9)	5.9 (76.9)	9.8 (64.3)	5.4 (74.9)	4.2 (71.2)	5.6 (73.9)	3.9 (62.6)
R_{meas} (%)[1, 4]	13.3 (71.5)	7.0 (90.5)	11.6 (75.6)	6.3 (89.3)	4.9 (84.3)	6.5 (86.7)	4.6 (72.8)
R_{pim} (%)[1, 4]	7.0 (37.2)	3.7 (47.3)	6.2 (39.5)	3.3 (48.1)	2.6 (44.7)	3.4 (44.8)	2.4 (36.8)
$CC_{1/2}$ [1, 5]	0.994 (0.771)	0.999 (0.753)	0.996 (0.866)	0.998 (0.668)	0.998 (0.732)	0.998 (0.700)	0.999 (0.802)
Refinement							
Resolution (Å) [1]	38.79-2.30	37.01-2.00	34.40-2.45	46.37-1.65	35.96-1.55	28.77-1.70	33.46-1.65
Reflections (working/test)[1]	23,533/1,198	37,986/1,900	9,537/507	68,809/3,546	82,418/4,328	62,016/3,164	66,582/3,422
R_{factor} / R_{free} (%)[1,3]	18.1/26.3	18.2/24.7	21.3/29.6	17.9/21.7	18.5/21.6	17.8/21.6	17.8/22.0
No. of atoms (Protein/Ligand/ Water)	4,407/64/127	4,389/132/ 205	2,135/33/30	4,511/120/352	4,503/102/338	4,555/118/426	4,617/116/407
Model Quality							
R.m.s deviations							
Bond lengths (Å)	0.009	0.010	0.005	0.010	0.009	0.007	0.007

Bond angles (°)	0.936	1.032	0.565	1.031	0.972	0.926	0.877
Average *B*-factor (Å^2)							
All Atoms	36.2	37.8	53.9	31.7	30.5	32.4	31.3
Protein	36.4	37.5	54.2	31.1	30.0	31.8	30.6
Ligand	36.5	45.7	44.0	33.1	28.9	33.3	31.9
Water	32.3	37.8	43.1	38.1	37.3	38.5	39.0
Coordinate error(maximum likelihood) (Å)	0.36	0.27	0.36	0.23	0.20	0.20	0.19
Ramachandran Plot							
Most favored (%)	96.8	94.7	95.1	97.5	98.0	97.7	98.5
Additionally allowed (%)	2.9	5.0	4.5	2.4	2.0	2.3	1.5

1) Values in parenthesis are for the highest resolution shell.
2) $R_{merge} = \Sigma_{hkl}\Sigma_i |I_i(hkl) - \langle I(hkl)\rangle| / \Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the intensity measured for the *i*th reflection and $\langle I(hkl)\rangle$ is the average intensity of all reflections with indices hkl.
3) $R_{factor} = \Sigma_{hkl} ||F_{obs}(hkl)| - |F_{calc}(hkl)|| / \Sigma_{hkl} |F_{obs}(hkl)|$; Rfree is calculated in an identical manner using 5% of randomly selected reflections that were not included in the refinement.
4) R_{meas} = redundancy-independent (multiplicity-weighted) R_{merge} [74]. R_{pim} = precision-indicating (multiplicity-weighted) R_{merge} [75,76].
5) $CC_{1/2}$ is the correlation coefficient of the mean intensities between two random half-sets of data [77,78].