Supporting Information

Total synthesis, structure elucidation and expanded bioactivity of Icosalide A: Effect of lipophilicity and ester to amide substitution on its bioactivity

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All the amino acids required for solid-phase peptide synthesis, peptide coupling reagents (HCTU, HOAt), and 2-CTC resin were purchased from GL Biochem (Shanghai) Ltd. DIPEA, diethyl ether, and TIPS, D-Phenyl alanine, butanal, acetaldehyde, hexanal, octanal, cyclopropane aldehyde, decanal, dodecanal, DIC, DMAP, and $TiCl_4$ were obtained from Spectrochem. Piperidine, TFA, TFE, and NMP were purchased from Avra Laboratories. O-Benzylhydroxylamine, Pd/C purchased from sigma Aldrich. Dry DCM was purchased from Acros Organics. Pyridine was obtained from Finar. HPLC gradient grade acetonitrile was obtained from Thomas Baker.

Experimental Section

1.1. **Synthetic procedure for (*R*)-1-(4-benzyl-2-thioxothiazolidin-3-yl) ethan-1-one (15)**: Synthesis of *R*-chiral auxiliary was started by dissolving D-phenyl alanine (3 gm, 18.8 mmol, 1 eq.) in dry THF and thus formed suspension was cooled to 0 °C. To this cooled suspension, $LiAlH_4$ (1 gm, 26.91 mmol, 1.48 eq.) was added in portions over a duration of 10 minutes, and the reaction contents were heated to reflux overnight. Then the reaction mixture was cooled to 0 °C and quenched with slow addition of water for 10 minutes, followed by slow addition of 15% (aq) KOH for 30 min. The quenched mixture was diluted and extracted with ethyl acetate. The ethyl acetate extract was concentrated over rotavapor to afford D-phenylalaninol (2.7 gm, 99%) as a white viscous oil, which was further used without purification.

D-Phenylalaninol (2.7 gm, 19.2 mmol, 1 eq.) was dissolved in aqueous KOH (3 M, 100 mL). CS_2, (5.8 mL, 96 mmol, 5 eq.) was added, and the solution was heated to reflux overnight. The solution was extracted with CH_2Cl_2 (3*200 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography to afford (*R*)-4-benzylthiazolidine-2-thione (3.19 gm, 86%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.38 (2H, t, *J* =7.4 Hz), 7.32 (1H, t, *J* =7.4 Hz), 7.26 – 7.20 (2H, m), 4.49 (1H, p, *J* =7.2 Hz), 3.61 (1H, dd, *J* =11.3, 7.6 Hz), 3.35 (1H, dd, *J* =11.1, 6.8 Hz), 3.03 (2H, qd, *J* =13.6, 7.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.11, 135.98, 129.29, 129.16, 127.62, 65.20, 40.20, 38.35. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{10}H_{11}NS_2$ 210.0336, found 210.0366.

The above compound (2.3 g, 11 mmol, 1 eq.), DMAP (134 mg, 1.1 mmol, 0.1 eq.), and NEt_3 (2.3 mL, 16.5 mmol, 1.5 eq.) were dissolved in dry CH_2Cl_2 (100 mL) and cooled to 0 °C. To this reaction contents, AcCl (1.2 mL, 16.5 mmol, 1.5 eq.) was added dropwise, and the reaction was allowed to reach room temperature and stirred overnight. Then, the reaction was quenched with saturated NH_4Cl (100 mL), and the organic contents were extracted with Et_2O (1*50 mL) and EtOAc (2*50 mL). The combined organic phase was washed with water (50 mL) and brine (50 mL), dried over (Na_2SO_4), filtered, and concentrated to give the crude compound as a yellow solid. Recrystallization of this yellow solid from EtOH afforded the acetylated chiral auxiliary **15** bright yellow crystals (2.8 gm, 80%); $[\alpha]_D^{26}$ = -142.5 (c 0.5, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (2H, m), 7.34 – 7.27 (3H, m), 5.40 (1H, ddd, *J* = 10.8, 7.2, 3.8 Hz), 3.41 (1H, dd, *J* = 11.5, 7.2 Hz), 3.25 (1H, dd, *J* = 13.2, 3.8 Hz), 3.07 (1H, dd, *J* = 13.2, 10.5 Hz), 2.91 (1H, d, *J* = 11.4 Hz), 2.82 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.69, 170.84, 136.63, 129.57, 129.02, 127.34, 68.33, 36.80, 31.94, 27.18. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{12}H_{13}NOS_2$ 252.0439, found 252.0472.

The characterization data was in accordance with the previous report.[1]

1.2. **General procedure for aldol reaction**: 0.2 M solution of acetylated auxiliary 15 (1.7 eq.) in DCM was prepared. To this solution, $TiCl_4$ (1.8 eq.) and *i*-Pr_2NEt (1.8 eq.) were added dropwise, and the resulting suspension was cooled to -78 °C and stirred for 2 h. To this solution, a solution of the appropriate aldehyde (according to Scheme **1a**, 0.2 M in CH_2Cl_2, 1 eq.) was added dropwise. The mixture was stirred at -78 °C for 4 to 24 h depending on the reaction. After completion of the reaction, the reaction was quenched with saturated NH_4Cl (50 mL) and water (50 mL). The organic phase in CH_2Cl_2 was separated and washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to give a yellow crude material, which was further purified by column chromatography to obtain the compounds **16a-h** and **17a-h**.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxybutan-1-one (16a): Compound **15** was reacted with acetaldehyde according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16a** (1.2 g, 53%) as a yellow oil (major diastereomer); Rf 0.16 (pet ether : EtOAc, 4:1) 1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (2H, m), 7.36 – 7.28 (3H, m), 5.43 (1H, ddd, *J* = 10.8, 7.2, 4.1 Hz), 4.36 (1H, ddt, *J* = 10.2, 6.6, 3.2 Hz), 3.69 (1H, dd, *J* = 17.7, 2.5 Hz), 3.44 (1H, dd, *J* = 11.5, 7.2 Hz), 3.25 (1H, dd, *J* = 13.2, 4.0 Hz), 3.22 – 2.99 (2H, m), 2.93 (1H, d, *J* = 11.5 Hz), 1.31 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.56, 173.29, 136.53, 129.59, 129.10, 127.46, 68.42, 64.25, 47.44, 37.01, 32.20, 22.45. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_{17}NO_2S_2$ 296.0701, found 296.0703.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhexan-1-one (16b): Compound **15** was reacted with butanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16b** (1.1 g, 55%) as a yellow oil (major diastereomer); Rf 0.16 (Pet ether : EtOAc, 4:1) ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.20 (5H, m), 5.44 (1H, ddd, *J* = 10.7, 7.1, 4.0 Hz), 4.10 (1H, tdt, *J* = 7.4, 4.0, 2.4 Hz), 3.59 – 2.89 (7H, m), 1.66 – 1.36 (4H, m), 0.97 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.62, 174.03, 136.50, 129.58, 129.09, 127.43, 68.37, 68.33, 45.63, 38.88, 36.93, 32.16, 18.81, 14.14. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{21}NO_2S_2$ 324.1014, found 324.1104.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyoctan-1-one (16c): Compound **15** was reacted with hexanal according to general procedure **1.2** and subsequent flash

chromatography furnished title compound **16c** (2 g, 45%) as a yellow oil (major diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.05 (5H, m), 5.41 (1H, ddd, *J* = 10.9, 7.2, 4.0 Hz), 4.05 (1H, tt, *J* = 6.9, 3.4 Hz), 3.57 – 2.70 (6H, m), 1.65 – 1.16 (9H, m), 0.89 (3H, t, *J* = 6.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.62, 174.03, 136.52, 129.58, 129.09, 127.43, 68.63, 68.38, 45.64, 36.95, 36.76, 32.18, 31.89, 25.30, 22.74, 14.18. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{18}H_{25}NO_2S_2$ 352.1327, found 352.1360.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxydecan-1-one (16d): Compound **15** was reacted with octanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16d** (2.2 g, 51%) as a yellow oil (major diastereomer). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 – 7.29 (5H, m), 5.44 (1H, ddd, *J* = 10.8, 7.2, 4.1 Hz), 4.10 – 4.04 (1H, m), 3.48 (1H, dd, *J* = 17.5, 9.4 Hz), 3.43 (1H, ddd, *J* = 11.5, 7.3, 1.0 Hz), 3.36 (1H, dd, *J* = 17.5, 2.5 Hz), 3.25 (1H, dd, *J* = 13.3, 4.0 Hz), 3.12 (1H, d, *J* = 4.1 Hz), 3.07 (1H, dd, *J* = 13.3, 10.4 Hz), 2.93 (1H, d, *J* = 11.5 Hz), 1.55 – 1.43 (1H, m), 1.41 – 1.26 (11H, m), 0.90 (3H, t, *J* = 7.0 Hz). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{29}NO_2S_2$ 380.1640, found 380.1673.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxydodecan-1-one (16e): Compound **15** was reacted with decanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16e** (1g, 51%) as a yellow oil (major diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (2H, m), 7.33 – 7.25 (3H, m), 5.41 (1H, ddd, *J* = 10.8, 7.1, 4.0 Hz), 4.14 (1H, ddd, *J* = 14.3, 9.2, 5.9 Hz), 3.66 (1H, dd, *J* = 17.9, 2.4 Hz), 3.42 (1H, ddd, *J* = 11.5, 7.2, 1.0 Hz), 3.24 (1H, dd, *J* = 13.2, 4.0 Hz), 3.19 – 3.00 (2H, m), 2.91 (1H, d, *J* = 11.6 Hz), 2.72 (1H, d, *J* = 3.8 Hz), 1.66 – 1.47 (1H, m), 1.50 – 1.41 (1H, m), 1.29 (13H, q, *J* = 4.9 Hz), 0.88 (3H, t); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.55, 173.51, 136.55, 129.58, 129.09, 127.44, 68.47, 68.00, 46.06, 36.97, 36.51, 32.18, 32.03, 29.70, 29.46, 25.69, 22.82, 14.26. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{33}NO_2S_2$ 408.1953, found 408.1951.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxytetradecan-1-one (16f): Compound **15** was reacted with dodecanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16f** (0.5 g, 51%) as a yellow oil (major diastereomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.34 (2H, m), 7.34 – 7.28 (3H, m), 5.43 (1H, ddd, *J* = 10.7, 7.0, 3.9 Hz), 4.17 (1H, dddd, *J* = 9.9, 7.5, 4.7, 2.4 Hz), 3.68 (1H, dd, *J* = 17.9, 2.4 Hz), 3.44 (1H, dd, *J* = 11.6, 7.2 Hz), 3.26 (1H, dd, *J* = 13.2, 4.0 Hz), 3.15 (1H, dd, *J* = 17.7, 9.5 Hz), 3.08 (1H, dd, *J* = 13.2, 10.5 Hz), 2.93 (1H, d, *J* = 11.6 Hz), 2.37 (1H, t, *J* =

7.5 Hz), 1.74 – 1.19 (27H, m), 0.91 (4H, t, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.57, 173.53, 136.56, 129.59, 129.10, 127.45, 68.49, 68.05, 46.05, 36.99, 36.51, 34.05, 32.20, 32.06, 29.74, 29.58, 29.49, 29.39, 29.21, 25.70, 24.85, 22.83, 14.26. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{37}NO_2S_2$ 436.2266, found 436.2291.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-4-methylpentan-1-one (16g): Compound **15** was reacted with isobutyraldehyde according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16g** (1 g, 51%) as a yellow oil; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 – 7.35 (2H, m), 7.32 (3H, d, *J* = 7.4 Hz), 5.43 (1H, ddd, *J* = 10.8, 7.2, 4.0 Hz), 3.97 (1H, ddd, *J* = 10.2, 5.6, 2.0 Hz), 3.68 – 3.62 (1H, m), 3.43 (1H, dd, *J* = 11.5, 7.2 Hz), 3.26 (1H, dd, *J* = 13.2, 3.9 Hz), 3.19 (1H, dd, *J* = 17.6, 10.2 Hz), 3.08 (1H, dd, *J* = 13.2, 10.4 Hz), 2.93 (1H, d, *J* = 11.5 Hz), 1.85 – 1.76 (1H, m, *J* = 6.7 Hz), 1.00 (6H, dd, *J* = 15.0, 6.8 Hz); ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.62, 173.88, 136.57, 129.59, 129.09, 127.43, 72.60, 68.54, 43.33, 36.97, 33.30, 32.20, 18.64, 18.06. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{21}NO_2S_2$ 324.1014, found 324.1047.

(*R*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-cyclopropyl-3-hydroxypropan-1-one (16h): Compound **15** was reacted with cyclopropane aldehyde according to general procedure **1.2** and subsequent flash chromatography furnished title compound **16h** (0.5 g, 53%) as pale yellow liquid; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.34 (2H, t, *J* = 7.6 Hz), 7.29 (3H, d, *J* = 7.4 Hz), 5.39 (1H, ddd, *J* = 10.9, 7.1, 3.9 Hz), 3.71 (1H, dd, *J* = 17.4, 2.1 Hz), 3.47 (1H, td, *J* = 9.0, 2.3 Hz), 3.44 – 3.39 (1H, m), 3.41 – 3.35 (1H, m), 3.23 (1H, dd, *J* = 13.3, 4.0 Hz), 3.05 (1H, dd, *J* = 13.3, 10.4 Hz), 2.90 (1H, d, *J* = 11.5 Hz), 1.02 (1H, ddt, *J* = 13.1, 8.2, 4.2 Hz), 0.57 (2H, dqd, *J* = 27.0, 8.8, 4.5 Hz), 0.42 (1H, dq, *J* = 9.7, 5.0 Hz), 0.27 (1H, dq, *J* = 10.0, 5.0 Hz); ^{13}C NMR (500 MHz, $CDCl_3$): 3.35 (1H, td, *J* = 8.6, 3.5 Hz), 2.70 (2H, qd, *J* = 16.3, 6.3 Hz), 1.07 – 0.87 (2H, m), 0.58 (3H, dtt, *J* = 17.7, 9.0, 4.2 Hz), 0.42 (1H, dq, *J* = 8.7, 4.6 Hz), 0.27 (1H, dq, *J* = 10.0, 4.7 Hz); ^{13}C NMR (176 MHz, $CDCl_3$) δ 201.50, 173.07, 136.56, 129.57, 129.07, 127.41, 72.71, 68.56, 45.88, 45.58, 36.92, 32.22, 16.93. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{19}NO_2S_2$ 322.0857, found 322.0891.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxybutan-1-one (17a): Compound **15** was reacted with acetaldehyde according to general procedure **1.2** and subsequent flash chromatography furnished title compound **17a** as a yellow oil (minor diastereomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 5H), 5.43 (ddd, *J* = 10.8, 7.2, 4.1 Hz, 1H), 4.36 (dtt, *J* = 8.9, 6.3, 3.2 Hz, 1H), 3.69 (dd, *J* = 17.8, 2.5 Hz, 1H), 3.44 (dd, *J* = 11.5, 7.2 Hz, 1H), 3.34 – 3.03 (m, 3H), 2.93 (d, *J* = 11.9 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ 201.43, 173.15, 136.40, 129.46, 129.22, 128.97, 128.53, 128.48, 127.32, 126.82, 68.29, 64.10, 47.32, 36.87, 32.06, 22.32., 14.2. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{14}H_{17}NO_2S_2$ 296.0701, found 296.0703.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyhexan-1-one (17b): Compound **15** was reacted with butanal according to the general procedure **1.2** and subsequent flash chromatography furnished title compound **17b** as a yellow oil (minor diastereomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.31 (dd, *J* = 7.7, 5.6 Hz, 4H), 5.44 (ddd, *J* = 10.8, 7.1, 4.1 Hz, 1H), 4.08 (s, 1H), 3.48 (dd, *J* = 17.5, 9.4 Hz, 1H), 3.45 – 3.40 (m, 1H), 3.36 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.25 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.12 (s, 1H), 3.10 – 3.00 (m, 1H), 2.93 (d, *J* = 11.7 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.49 (s, 1H), 1.33 (s, 9H), 1.38 – 1.26 (m, 3H), 0.94 – 0.86 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.50, 173.91, 136.39, 129.46, 128.97, 127.31, 68.25, 68.21, 45.51, 38.76, 36.82, 32.05, 18.70, 14.03. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{16}H_{21}NO_2S_2$ 324.1014, found 324.1104.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxyoctan-1-one (17c): Compound **15** was reacted with hexanal according to the general procedure **1.2** and subsequent flash chromatography furnished title compound **17c** as a yellow oil (minor diastereomer)^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 6H), 5.43 (ddd, *J* = 10.6, 7.0, 3.8 Hz, 1H), 4.17 (t, *J* = 10.4 Hz, 1H), 3.72 – 3.60 (m, 1H), 3.40 (ddd, *J* = 27.2, 11.3, 6.9 Hz, 1H), 3.29 – 3.17 (m, 1H), 3.17 – 3.00 (m, 2H), 2.92 (d, *J* = 11.4 Hz, 1H), 1.61 (dt, *J* = 18.1, 6.6 Hz, 1H), 1.53 (dd, *J* = 11.2, 6.3 Hz, 1H), 1.52 – 1.37 (m, 1H), 1.41 – 1.30 (m, 5H), 0.92 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.44, 173.37, 136.42, 129.45, 129.25, 128.99, 128.95, 127.57, 127.30, 68.34, 67.89, 64.97, 45.92, 40.25, 38.42, 36.85, 36.36, 32.07, 31.74, 25.24, 22.61, 14.05. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{18}H_{25}NO_2S_2$ 352.1327, found 352.1360.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxydecan-1-one (17d): Compound **15** was reacted with octanal according to the general procedure **1.2** and subsequent flash chromatography furnished title compound **17d** as a pale-yellow oil (minor diastereomer); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.43 – 7.32 (m, 3H), 7.34 – 7.28 (m, 3H), 5.43 (ddd, *J* = 10.8, 7.1, 4.0 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.67 (dd, *J* = 17.8, 2.4 Hz, 1H), 3.43 (ddd, *J* = 11.5, 7.2, 1.1 Hz, 1H), 3.25 (dd, *J* = 13.3, 4.0 Hz, 1H), 3.15 (dd, *J* = 17.7, 9.5 Hz, 1H), 3.07 (dd, *J* = 13.3, 10.5 Hz, 1H), 2.92 (d, *J* = 11.5 Hz, 1H), 2.73 (d, *J* = 3.9 Hz, 1H), 1.64 – 1.56 (m, 1H), 1.55 – 1.44 (m, 2H), 1.49 (s, 1H), 1.36 – 1.25 (m, 7H), 0.91 (t, *J* = 7.0 Hz, 3H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{20}H_{29}NO_2S_2$ 380.1640, found 380.1673.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxydodecan-1-one (17e): Compound **15** was reacted with decanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **17e** as a yellow oil (minor diastereomer); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.33 – 7.28 (m, 3H), 5.44 (ddd, *J* = 10.8, 7.2, 4.1 Hz, 1H), 4.10 – 4.04 (m, 1H), 3.48 (dd, *J* = 17.5, 9.4 Hz, 1H), 3.43 (ddd, *J* = 11.5, 7.3, 1.0 Hz, 1H), 3.36 (dd, *J* = 17.5, 2.5 Hz, 1H), 3.25 (dd, *J* = 13.3, 4.0 Hz, 1H), 3.12 (d, *J* = 4.1 Hz, 1H), 3.07 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.93 (d, *J* = 11.5 Hz, 1H), 1.65 – 1.57 (m, 6H), 1.55 – 1.46 (m, 1H), 1.32 (s, 6H), 1.31 (ddt, *J* = 17.1, 11.9, 8.2 Hz, 6H), 0.90 (t, *J* = 7.0 Hz, 3H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{22}H_{33}NO_2S_2$ 408.1953, found 408.1951.

(*S*)-1-((*R*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxytetradecan-1-one (17f): Compound **15** was reacted with dodecanal according to general procedure **1.2** and subsequent flash chromatography furnished title compound **17f** as a yellow oil (minor diastereomer); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.4 Hz, 2H), 7.32 (s, 1H), 7.23 (d, *J* = 7.3 Hz, 3H), 4.49 (p, *J* = 7.2 Hz, 2H), 3.63 (dd, *J* = 11.1, 7.6 Hz, 2H), 3.39 – 3.22 (m, 2H), 3.12 – 2.97 (m, 4H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.65 (p, *J* = 7.5 Hz, 2H), 1.34 (dd, *J* = 27.0, 11.6 Hz, 5H), 1.31 (s, 5H), 1.28 (s, 10H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.43, 179.08, 173.39, 136.42, 129.45, 128.96, 127.31, 68.35, 67.91, 60.43, 45.91, 36.85, 36.37, 33.91, 32.06, 31.92, 29.67, 29.60, 29.44, 29.35, 29.25, 29.07, 25.56, 24.71, 22.70, 14.13. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{37}NO_2S_2$ 436.2266, found 436.2291.

Supplementary Table 1. Stereoselectivities observed in the above aldol reactions.

Aldehyde	**Compound**	***syn*:*anti***
Acetaldehyde	**16a**:**17a**	90:10
Butanal	**16b**:**17b**	88:12
Hexanal	**16c**:**17c**	95:5
Octanal	**16d**:**17d**	89:11
Decanal	**16e**:**17e**	93:7
Dodecanal	**16f**:**17f**	96:4
Isobutaraldehyde	**16g**:**17g**	98:2
Cyclopropanecarbaldehyde	**16h**:**17h**	97:3

1.3. **General procedure for the hydrolysis of aldol adducts**: To a 0.2 M solution of aldol adduct (**16a-h**, 1 eq.) in THF, 1 M aqueous LiOH (4 eq.) was added. The reaction mixture was stirred at room temperature for 3-4 h. After the reaction, THF was removed over rotavapor, and the aqueous phase was washed with EtOAc (2*100 mL), then acidified with 2 M HCl to 2-3 pH. The solution was extracted with EtOAc (3*100 mL), which was dried over Na_2SO_4, filtered, and concentrated to afford the corresponding beta hydroxy acid (**18a-h**).

(*R*)-3-hydroxyhexanoic acid (18b): Following the general procedure **1.3** hydrolysis of **16b** afforded the desired product **18b** with 95% yield as colourless oil; $[\alpha]_D^{25}$ = -12.2 (c 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 – 3.88 (1H, m), 2.57 – 2.22 (2H, m), 1.63 – 1.20 (4H, m), 0.85 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.34, 68.02, 42.10, 38.68, 18.55, 13.90. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_6H_{12}O_3$ 133.0786, found 133.0826; in agreement with previously reported data.[1]

(*R*)-3-hydroxyoctanoic acid (18c): Following the general procedure **1.3** hydrolysis of **16c** afforded the desired product **18c** with 96% yield as colourless oil; $[\alpha]_D^{25}$ = -4.45 (c 0.5, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (1H, tt, *J* = 8.0, 3.7 Hz), 2.64 – 2.38 (2H, m), 1.62 – 1.21 (8H, m), 0.89 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.11, 68.35, 41.48, 36.65, 31.77, 25.24, 22.66, 14.09. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_8H_{16}O_3$ 161.1099, found 161.1069; data in agreement with previously reported data.[1]

(*R*)-3-hydroxydecanoic acid (18d): Following the general procedure **1.3** hydrolysis of **16d** afforded the desired product **18d** with 91% yield as white sticky solid; $[\alpha]_D^{25}$ = -8.68 (c 0.5, CH_2Cl_2) ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.03 (1H, tdd, *J* = 8.1, 4.6, 3.0 Hz), 2.57 (1H, dd, *J* = 16.5, 3.0 Hz), 2.47 (1H, dd, *J* = 16.6, 9.1 Hz), 1.61 – 1.20 (13H, m), 0.88 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, CDCl3) δ 177.74, 68.28, 41.27, 36.61, 31.92, 29.57, 29.35, 25.59, 22.78, 14.22. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{10}H_{20}O_3$ 189.1412, found 189.1446

(*R*)-3-hydroxydodecanoic acid (18e): Following the general procedure **1.3** hydrolysis of **16e** afforded the desired product **18e** with 93% yield as white solid; $[\alpha]_D^{25}$ = -16.6 (c 0.5, CH_2Cl_2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (1H, tt, *J* = 8.3, 3.9 Hz), 2.60 (1H, dd, *J* = 16.6, 3.0 Hz), 2.50 (1H, dd, *J* = 16.6, 9.0 Hz), 1.63 – 1.42 (2H, m), 1.39 – 1.27 (13H, m), 0.90 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, CDCl3) δ 177.91, 68.20, 41.21, 36.63, 32.03, 29.69, 29.67, 29.62, 29.44, 25.59, 22.82, 14.25; in agreement with previously reported data.[3] HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{12}H_{24}O_3$ 216.1725, found 216.1759.

(*R*)-3-hydroxy-4-methylpentanoic acid (18g): Following the general procedure **1.3** hydrolysis of **16g** afforded the desired product **18g** with 95% yield as colourless oil; ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.82 (1H, ddd, *J* = 9.8, 5.7, 2.6 Hz), 2.56 (1H, dd, *J* = 16.3, 2.6 Hz), 2.48 (1H, dd, *J* = 16.3, 9.8 Hz), 1.79 – 1.70 (1H, m), 0.96 (3H, d, *J* = 6.8 Hz), 0.94 (3H, d, *J* = 6.8 Hz) ^{13}C NMR (176 MHz, $CDCl_3$) δ 178.33, 72.94, 38.46, 33.31, 18.46, 17.83; in agreement with previously reported data.[4] HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_6H_{12}O_3$ 133.0786, found 133.0756.

(*R*)-3-cyclopropyl-3-hydroxypropanoic acid (18h): Following the general procedure **1.3** hydrolysis of **16h** afforded the desired product **18h** with 88% yield as colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.35 (1H, td, *J* = 8.6, 3.5 Hz), 2.70 (2H, qd, *J* = 16.3, 6.3 Hz), 1.07 – 0.87 (2H, m), 0.58 (3H, dtt, *J* = 17.7, 9.0, 4.2 Hz), 0.42 (1H, dq, *J* = 8.7, 4.6 Hz), 0.27 (1H, dq, *J* = 10.0, 4.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.92, 72.99, 41.27, 29.83, 17.00. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_6H_{10}O_3$ 131.0630, found 131.0631.

1.4. **General procedure for the synthesis of β-amino acids (22c and 22d)**: Following the literature procedure required β-amino acids (**22c** and **22d**) were synthesized in four steps with an overall yield of 85%.[2]

1.41. **(*S*)-N-(benzyloxy)-3-hydroxydecanamide (19d)**: To a stirring mixture of β-hydroxy acid **17d** (1.1 gm, 5.8 mmol, 1 eq.) in THF-H_2O (4:1, 50 mL), $BnONH_2$×HCl (1.86 gm, 11.7 mmol, 2eq.) was added. The pH of the solution was adjusted to 4.5 with 1N NaOH, and then EDCI (1.3 gm, 8.7, 1.5 eq.) was added in one portion. The resulting solution was stirred at rt for 2 h while maintaining the pH at 4.5 with 1 M HCl by using a pH meter. After the completion of the reaction, THF was removed, and the residue was extracted with ethyl acetate (3*25 mL). The whole EtOAc organic layer was washed with 10% citric acid, 10 % $NaHCO_3$, dried over Na_2SO_4, and concentrated to afford **19d** (1.65 gm, 95%) as a white solid which was used further without purification.

The analogous compound **19c** was synthesized by following the same procedure.

1.42. **(*R*)-1-(benzyloxy)-4-heptylazetidin-2-one (20d)**: To a stirring cooled (0 °C) solution of *o*-benzylhydroxamate **19d** (1.65 gm g, 5.6 mmol) and PPh_3 (1.61 gm, 6.2 mmol) in dry THF (50 mL), DEAD (1.27 mL, 5.6 mmol) was added dropwise. The resulting solution was stirred for 4 h at room temperature. After evaporation of THF, the residue was purified by column chromatography (hexane/EtOAc, 5:1) to give the product **20d** as a colorless oil (1.2 g, 80%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (5H, ddt, *J* = 15.8, 7.2, 2.9 Hz), 5.03 – 4.93 (2H, m), 3.53 (1H, dtd, *J* = 7.6, 5.0, 2.4 Hz), 2.73 (1H, dd, *J* = 13.5, 5.1 Hz), 2.30 (1H, dd, *J* = 13.6, 2.4 Hz), 1.73 – 1.63 (1H, m), 1.43 – 1.24 (12H, m), 0.91 (3H, t, *J* = 7.0 Hz). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{17}H_{25}NO_2$ 276.1877, found 276.1891.

The analogous compound **20c** was synthesized by following the same procedure. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 – 7.35 (5H, m), 4.99 (1H, d, *J* = 11.1 Hz), 4.95 (1H, d, *J* = 11.2 Hz), 3.52 (1H, dtd, *J* = 7.5, 5.0, 2.4 Hz), 2.72 (1H, dd, *J* = 13.4, 5.1 Hz), 2.30 (1H, dd, *J* = 13.5, 2.5 Hz), 1.68 (1H, ddt, *J* = 14.2, 10.1, 5.2 Hz), 1.41 – 1.34 (1H, m), 1.34 – 1.20 (6H, m), 0.90 (3H, t, *J* = 7.2 Hz) ^{13}C NMR (176 MHz, $CDCl_3$) δ 135.53, 129.38, 129.02, 128.70, 78.30, 77.34, 77.16, 76.98, 58.23, 37.93, 32.50, 31.66, 25.27, 22.56, 14.05. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{19}H_{29}NO_2$ 304.2189, found 304.2168.

1.43. **(*R*)-3-((benzyloxy)amino) decanoic acid (21d)**: To a cooled (0 °C) solution of β-lactam **20d** (960 mg, 3.88 mmol, 1 eq.) in THF:MeOH (3:1, 8 mL), LiOH (149 mg, 4.6 mmol, 1.2 eq.) in water (2 mL) was added under stirring. The resulting solution was stirred at 0 °C until complete consumption of the starting material. Then the reaction solution was acidified to pH 2 with 4N HCl, and the organic solvents were evaporated. The residue was extracted with ethyl acetate (3*30 mL), and the combined organic layer was washed with brine (2*10 mL), dried over Na_2SO_4, and evaporated to give **21d** (1.02 gm, 98%).

The analogous compound **21c** was synthesized by following the same procedure.

1.44. **(*R*)-3-aminodecanoic acid (22d)**: A solution of **21d** (1.02 gm, 3.44 mmol) in MeOH (30 mL) was hydrogenated in the presence of 10% Pd/ C (100 mg) at atmospheric pressure. The reaction was monitored using TLC. After completion of the reaction, Pd/C was filtered off, and the solvent was evaporated to give **22d** as a white solid (650 mg, 99%).

The analogous compound **22c** was synthesized by following the same procedure.

1.5. **General procedure for the Fmoc protection of β-amino acids**: To a solution of (*R*)-3-β-amino acid (**22c** or **22d**) (540 mg, 2.88 mmol) in dioxane was added 10% (aq.) Na_2CO_3 (5 mL) and stirred at 0 °C for 10 min. Then the Fmoc-Cl (1.1 gm, 4.33 mmol) in dioxane (5 mL) was added to the stirring solution and further stirred for 2-3 hr at room temperature. After completion of the reaction, dioxane was evaporated on rotavapor and the aqueous layer was washed with diethyl ether. The pH of aq. layer brought up to 2-3 by 2 M HCl, and then the

residue was extracted with ethyl acetate (2*50), dried over Na_2SO_4, and evaporated to give corresponding Fmoc-protected (*R*)-3-β-amino acid.

(*R*)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino) octanoic acid (23c)

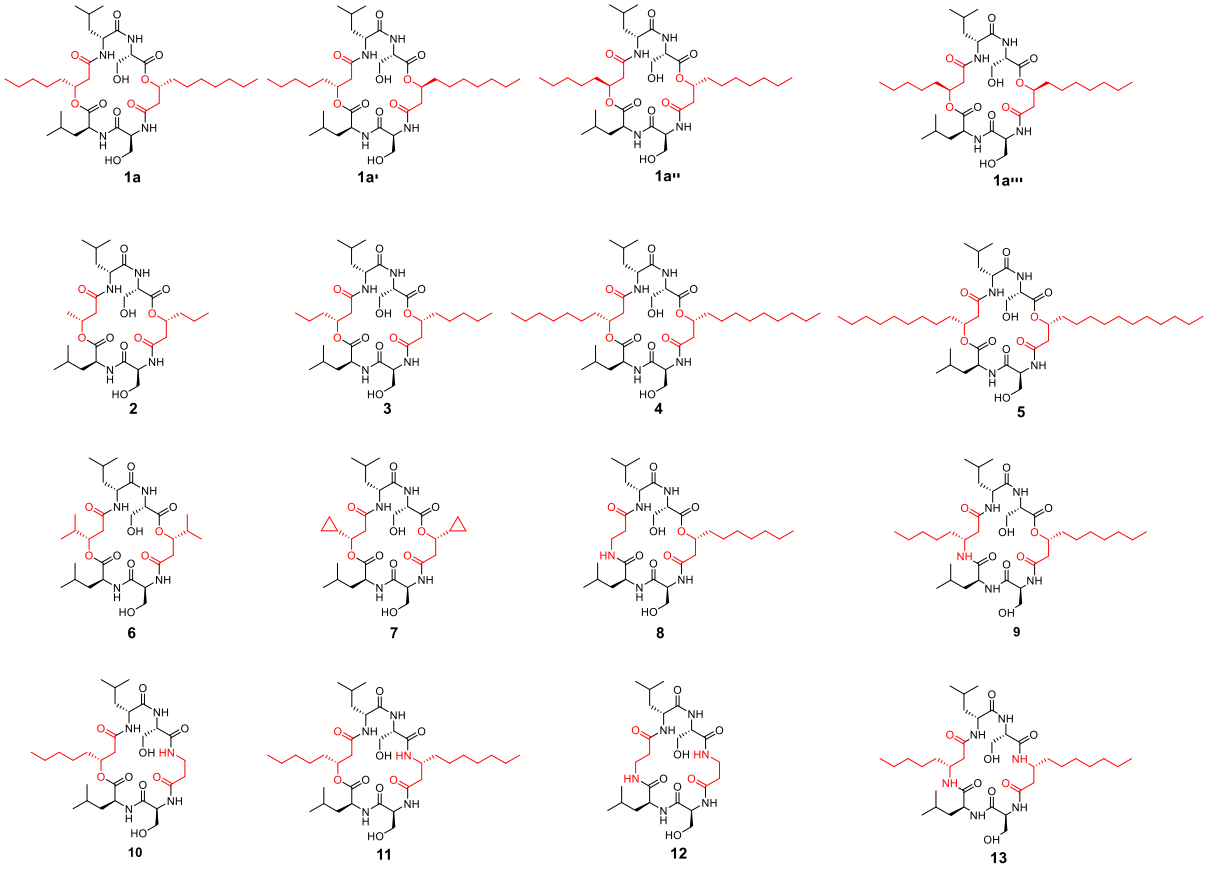
Following the general procedure **1.41** to **1.45,** five step afforded the desired product **23c** as white solid with overall yield of 85% ^{1}H NMR (700 MHz, CDCl3) δ 7.78 (2H, d, *J* = 7.6 Hz), 7.61 (2H, d, *J* = 7.5 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 7.33 (2H, t, *J* = 7.4 Hz), 5.19 (1H, d, *J* = 9.2 Hz), 4.52 (1H, s), 4.42 (2H, d, *J* = 7.2 Hz), 4.24 (1H, t, *J* = 7.0 Hz), 4.00 (1H, q, *J* = 7.7 Hz), 2.61 (2H, qd, *J* = 16.0, 5.4 Hz), 1.38 (1H, s), 1.38 – 1.25 (6H, m), 1.22 (1H, s), 0.90 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (176 MHz, CDCl3) 177.03, 156.11, 144.10, 144.02, 141.46, 127.81, 127.18, 125.23, 125.19, 120.11, 66.79, 48.18, 47.42, 39.06, 34.42, 31.59, 25.95, 22.65, 14.15. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{23}H_{27}NO_4$ 382.1940, found 382.1914.

(R)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)decanoic acid (23d)

Following the general procedure **1.41** to **1.45,** five steps afforded the desired product **23d** with overall yield of 82% ^{1}H NMR (700 MHz, CDCl3) δ 7.78 (2H, d, *J* = 7.6 Hz), 7.61 (2H, d, *J* = 7.4 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 7.33 (2H, t, *J* = 7.4 Hz), 5.16 (1H, d, *J* = 9.1 Hz), 4.42 (2H, dt, *J* = 14.2, 7.3 Hz), 4.24 (1H, t, *J* = 7.0 Hz), 3.99 (1H, q, *J* = 7.7 Hz), 2.62 (2H, qd, *J* = 16.3, 5.3 Hz), 1.57 (2H, h, *J* = 7.4 Hz), 1.40 – 1.18 (13H, m), 0.90 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (176 MHz, CDCl3) δ 176.69, 156.09, 144.10, 144.03, 141.47, 127.82, 127.19, 125.24, 125.19, 120.12, 66.79, 48.19, 47.43, 39.00, 34.48, 31.91, 29.40, 29.32, 26.30, 22.78, 14.23. HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{25}H_{31}NO_4$ 410.2253, found 410.2245.

1.6. **Solid phase peptide synthesis of Icosalide 1a and its analogues**: Synthesis of **1a-1a'''**, and **2-7** started with the loading of *R*-3-hydroxy acid or *S*-3-hydroxy acid (1.2 eq.) at residue position 6 (depending on the peptides sequence) (see Figure **1)** onto the 2-chloro trityl chloride resin (150 mg, 1.6 mmol/g, 0.24 mmol) in dry DCM and DIPEA (3 eq.) for 2 hrs. After loading the first hydroxy acid, capping of the resin's unreacted active sites was done by MeOH (0.5 mL) and DIPEA (30 uL) for 30 min. Then, on resin esterification of hydroxy acid to Fmoc-Leu was performed in the presence of DIC (2 eq.) and DMAP (0.2 eq.) in dry DCM for 1.5 hrs.[5] After completing the esterification, the resin was washed 3 times with DCM, 3 times with NMP, and then the Fmoc deprotection was done with 20% piperidine in DMF (2*10 min) followed by washing the resin 4 times with NMP. The peptide chain was elongated by coupling Fmoc-Ser(tBu)-OH, HCTU (2 eq.), HOAt (2 eq.), DIPEA (3 eq.) in NMP for 1.5 hrs following

which Fmoc deprotection was done with 20% piperidine in DMF (2*10 min) and washing the resin with NMP. Coupling of *R*-3-hydroxy acid or *S*-3-hydroxy acid (2 eq.) at residue position 5 (depending on the peptides sequence) (see Figure **1)** using HCTU (2 eq.), HOAt (2 eq.), DIPEA (3 eq.) in NMP was carried out for 1.5 hrs. Later, the resin was washed 3 times with NMP and 3 times with DCM. On resin esterification with Fmoc-Ser (tBu)-OH was done in the presence of DIC (2 eq.), DMAP (0.2 eq.) in dry DCM for 1.5 hrs. After esterification, Fmoc deprotection was done using 20% piperidine in DMF (2*10 min). Coupling of Fmoc-Leu in the presence of HCTU (2 eq.), HOAt (2 eq.), and DIPEA (2 eq.) in NMP was carried out for 2 hrs. The exact procedure described here was also followed for synthesizing linear peptides of **8**-**13**; however, the amide coupling protocol as mentioned above is employed whenever amide coupling was used instead of esterification because of substituting *R*-3-hydroxy acid with *R*-3-amino acid. After obtaining the complete linear sequence, Fmoc deprotection of the terminal residue was carried out with 20% piperidine in DMF (2*10 min), and then the resin was washed 4 times with NMP, 4 times with DCM. The linear hexapeptide was cleaved from the resin using TFE: Acetic acid: DCM (1:1:8) for 1.5 hrs (3*30 min). The filtrate was collected and concentrated by removing the excess acetic acid as an azeotrope using chloroform. The head to tail cyclization of these linear peptides was done using HCTU (2 eq.), HOAt (2 eq.), and DIPEA (5 eq.) in DMF. After overnight stirring, the reaction mixture was concentrated and dissolved in saturated sodium bicarbonate. The sidechain protected cyclic peptides of **1a-1a'''**, **2-13** were extracted from this solution with ethyl acetate and purified by column chromatography. Global deprotection of the *tert*-Butyl groups of the cyclic peptide was accomplished with 50% (TFA) in DCM. After complete deprotection of sidechain protecting groups, the reaction mixture was concentrated and purified by column chromatography to obtain peptides **1a**-**1a'''** and **2-13**.



Supplementary Figure 1. Icosalide **1a** and its analogues synthesized in this work.

Icosalide 1a: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (d, J = 4.6 Hz, 1H), 8.00 (d, J = 9.3 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 5.78 (s, 1H), 4.90 (ddq, J = 29.5, 8.8, 4.0 Hz, 2H), 4.48 (td, J = 8.4, 4.5 Hz, 1H), 4.42 – 4.32 (m, 2H), 3.92 (ddd, J = 17.1, 9.4, 3.7 Hz, 2H), 3.66 (dd, J = 10.8, 3.0 Hz, 1H), 3.56 (dd, J = 10.9, 4.5 Hz, 1H), 2.59 (dd, J = 13.9, 3.8 Hz, 1H), 2.51 (d, J = 2.0 Hz, 1H), 2.46 (d, J = 3.9 Hz, 1H), 2.25 (dd, J = 13.9, 3.6 Hz, 1H), 1.85 (s, 1H), 1.58 (dd, J = 13.9, 8.3 Hz, 4H), 1.53 – 1.06 (m, 19H), 0.92 (d, J = 5.6 Hz, 3H), 0.88 (d, J = 5.7 Hz, 3H), 0.83 (t, J = 8.1 Hz, 6H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{65}N_4O_{10}$ 713.4697, found 713.4695.

Icosalide 1a': ^{1}H NMR (700 MHz, DMSO-d_6) δ 8.37 (d, J = 6.0 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 5.10 (t, J = 5.6 Hz, 1H), 4.98 (tdd, J = 10.9, 5.6, 3.3 Hz, 2H), 4.89 (t, J = 5.5 Hz, 1H), 4.42 (td, J = 9.1, 5.3 Hz, 1H), 4.36 – 4.29 (m, 2H), 4.04 (td, J = 7.7, 6.1 Hz, 1H), 3.75 (dt, J = 10.7, 5.3 Hz, 1H), 3.59 (ddt, J = 31.0, 10.6, 5.2 Hz, 2H), 3.51 (ddd, J = 10.8, 7.1, 5.3 Hz, 1H), 2.50 – 2.45 (m, 2H), 2.40 – 2.31 (m, 2H), 1.67 (tt, J = 12.7, 6.5 Hz, 1H), 1.64 – 1.46 (m, 9H), 1.25 (q, 16H), 0.92 (d, J = 6.4 Hz, 3H), 0.90 –

0.80 (m, 15H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{65}N_4O_{10}$ 713.4702, found 713.4695.

Icosalide 1a'': ^{1}H NMR (400 MHz, DMSO) δ 8.27 (d, *J* = 7.1 Hz 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 5.57 (s, 1H), 5.02 (q, *J* = 5.7 Hz, 1H), 4.98 (s, 1H), 4.44 (dd, *J* = 8.3, 3.8 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.24 – 4.17 (m, 1H), 3.90 – 3.83 (m, 1H), 3.78 – 3.60 (m, 2H), 2.56 (d, *J* = 3.1 Hz, 1H), 2.28 (s, 1H), 2.21 (dd, *J* = 13.6, 5.3 Hz, 1H), 1.81 – 1.58 (m, 3H), 1.49 (dd, *J* = 18.8, 11.5 Hz, 8H), 1.23 (m, 4H), 1.19 (m, 13H), 1.00 – 0.67 (m, 24H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{65}N_4O_{10}$ 713.4620, found 713.4697.

Icosalide 1a''': ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (d, *J* = 8.3 Hz, 1H), 8.17 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 5.23 (d, *J* = 8.7 Hz, 1H), 5.07 (d, *J* = 60.4 Hz, 1H), 4.38 – 4.32 (m, 2H), 4.25 (s, 1H), 4.24 – 3.96 (m, 1H), 3.50 (t, *J* = 8.4 Hz, 3H), 2.61 (d, *J* = 3.6 Hz, 1H), 2.56 (s, 1H), 2.19 (dd, *J* = 13.4, 5.2 Hz, 1H), 1.58 (d, *J* = 8.6 Hz, 1H), 1.25 (m, 35H), 0.85 (m, 23H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{65}N_4O_{10}$ 713.4620, found 713.4694.

Icosalide analogue 2: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.31 (s, 1H), 7.91 (d, *J* = 9.3 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.37 (s, 1H), 5.17 (tq, *J* = 6.7, 3.3 Hz, 1H), 5.11 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.72 – 4.60 (m, 2H), 4.52 (dt, *J* = 8.8, 2.7 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.86 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.78 – 3.66 (m, 2H), 3.48 (s, 1H), 2.79 (d, *J* = 3.8 Hz, 1H), 2.64 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.26 (ddd, *J* = 13.4, 9.3, 3.6 Hz, 2H), 1.87 – 1.65 (m, 4H), 1.62 – 1.49 (m, 3H), 1.38 – 1.23 (m, 4H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.00 – 0.91 (m, 9H), 0.88 (t, *J* = 7.4 Hz, 3H).). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{28}H_{49}N_4O_{10}$ 601.3433, found 601.3443.

Icosalide analogue 3: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.00 (d, *J* = 7.1 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.37 (s, 1H), 7.24 (d, *J* = 9.4 Hz, 1H), 5.13 (ddd, *J* = 29.4, 10.3, 5.1 Hz, 2H), 4.65 – 4.54 (m, 2H), 4.49 (tt, *J* = 8.9, 4.5 Hz, 2H), 4.14 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.02 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.89 (dd, *J* = 11.3, 4.0 Hz, 1H), 3.80 (dd, *J* = 10.6, 2.8 Hz, 1H), 2.64 (dd, *J* = 13.9, 3.7 Hz, 1H), 2.33 – 2.23 (m, 2H), 1.98 (t, *J* = 10.3 Hz, 1H), 1.89 – 1.76 (m, 1H), 1.79 – 1.67 (m, 2H), 1.66 – 1.52 (m, 4H), 1.35 (dd, *J* = 14.8, 7.3 Hz, 2H), 1.28 (d, *J* = 14.0 Hz, 12H), 0.97 (d, *J* = 6.5 Hz, 4H), 0.96 – 0.83 (m, 18H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{32}H_{57}N_4O_{10}$ 657.4065, found 657.4069.

Icosalide analogue 4: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.33 (d, *J* = 4.9 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 5.06 (dq, *J* = 8.6, 4.1 Hz, 1H),

4.99 (dq, *J* = 11.9, 3.5 Hz, 1H), 4.68 (ddd, *J* = 8.6, 7.0, 5.3 Hz, 1H), 4.60 (ddd, *J* = 12.7, 9.4, 3.5 Hz, 1H), 4.49 (dt, *J* = 9.0, 2.7 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.85 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.73 (dd, *J* = 11.1, 5.3 Hz, 1H), 3.66 (dd, *J* = 11.1, 7.0 Hz, 1H), 2.76 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.62 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.27 (ddd, *J* = 13.8, 7.1, 3.3 Hz, 2H), 1.84 – 1.60 (m, 6H), 1.59 – 1.50 (m, 2H), 1.39 (s, 2H), 1.29 (d, *J* = 9.4 Hz, 23H), 1.02 (d, *J* = 6.1 Hz, 3H), 1.00 – 0.92 (m, 9H), 0.88 (td, *J* = 6.8, 4.2 Hz, 6H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{40}H_{73}N_4O_{10}$ 769.5323, found 769.5321.

Icosalide analogue 5: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.34 (d, *J* = 4.9 Hz, 1H), 7.94 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 5.06 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.67 (td, *J* = 7.7, 5.3 Hz, 1H), 4.61 (ddd, *J* = 12.7, 9.3, 3.5 Hz, 1H), 4.49 (dt, *J* = 9.0, 2.6 Hz, 1H), 4.19 (ddd, *J* = 28.0, 9.0, 3.7 Hz, 2H), 3.72 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.66 (dd, *J* = 11.1, 7.0 Hz, 1H), 2.28 (dd, *J* = 9.3, 3.4 Hz, 1H), 2.28 – 2.20 (m, 1H), 1.79 (td, *J* = 13.1, 3.6 Hz, 1H), 1.77 – 1.62 (m, 4H), 1.54 (tt, *J* = 11.1, 3.7 Hz, 2H), 1.39 (s, 2H), 1.29 (d, *J* = 6.5 Hz, 33H), 1.05 – 0.93 (m, 12H), 0.91 – 0.85 (m, 6H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{44}H_{81}N_4O_{10}$ 825.5946, found 825.5947.

Icosalide analogue 6: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.29 (d, *J* = 5.1 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 4.76 – 4.49 (m, 5H), 4.24 (td, *J* = 7.6, 5.1 Hz, 1H), 4.15 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.84 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.72 (dd, *J* = 11.1, 5.3 Hz, 1H), 3.66 (dd, *J* = 11.1, 6.9 Hz, 1H), 2.65 (dd, *J* = 14.2, 3.8 Hz, 1H), 2.52 (dd, *J* = 14.1, 3.9 Hz, 1H), 2.45 (ddd, *J* = 13.9, 9.6, 3.8 Hz, 2H), 1.96 (ddd, *J* = 10.2, 6.8, 3.7 Hz, 1H), 1.92 – 1.68 (m, 5H), 1.56 (ddd, *J* = 14.1, 10.7, 3.8 Hz, 1H), 1.05 – 0.87 (m, 21H), 0.84 (d, *J* = 6.5 Hz, 3H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{30}H_{53}N_4O_{10}$ 629.3739, found 629.3756.

Icosalide analogue 7: ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.27 (d, *J* = 5.1 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 4.67 (s, 1H), 4.67 – 4.58 (m, 1H), 4.53 (dt, *J* = 9.1, 2.9 Hz, 1H), 4.45 (dt, *J* = 8.3, 3.9 Hz, 1H), 4.26 (dtd, *J* = 12.9, 8.3, 4.5 Hz, 2H), 4.12 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.83 (dd, *J* = 10.5, 2.9 Hz, 1H), 3.75 – 3.63 (m, 2H), 2.76 (dd, *J* = 13.9, 4.0 Hz, 1H), 2.66 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.47 – 2.34 (m, 2H), 1.87 (dd, *J* = 13.8, 9.7 Hz, 1H), 1.76 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.70 (dd, *J* = 8.0, 5.9 Hz, 2H), 1.58 (ddd, *J* = 14.3, 10.6, 4.0 Hz, 1H), 1.12 (ddt, *J* = 12.8, 8.5, 4.6 Hz, 2H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.98 – 0.87 (m, 11H), 0.90 – 0.84 (m, 1H), 0.65 – 0.48 (m, 3H), 0.43 (dq, *J* = 8.4, 4.1 Hz, 1H), 0.42 – 0.32 (m, 2H), 0.29 (ddt, *J* = 18.8, 9.3, 5.1 Hz, 2H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{30}H_{49}N_4O_{10}$ 625.3436, found 625.3443.

Icosalide analogue 8: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14 (t, *J* = 7.9 Hz, 2H), 8.03 (d, *J* = 8.7 Hz, 1H), 7.77 (t, *J* = 6.1 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 5.20 (t, *J* = 5.2 Hz, 1H), 5.11 (d, *J* = 7.4 Hz, 1H), 4.90 – 4.82 (m, 1H), 4.49 (ddt, *J* = 15.1, 10.1, 4.6 Hz, 2H), 4.38 – 4.23 (m, 1H), 4.10 (q, *J* = 7.3 Hz, 1H), 3.67 (s, 0H), 3.63 – 3.57 (m, 2H), 3.19 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.46 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.37 – 2.25 (m, 3H), 1.68 (dt, *J* = 13.6, 6.7 Hz, 1H), 1.55 – 1.48 (m, 5H), 1.48 – 1.35 (m, 1H), 1.30 – 1.23 (m, 3H), 1.24 (s, 11H), 0.92 – 0.81 (m, 17H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{31}H_{56}N_5O_9$ 642.4059, found 642.4073.

Icosalide analogue 9: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.06 (d, *J* = 6.4 Hz, 1H), 7.82 – 7.73 (m, 3H), 7.46 (d, *J* = 8.1 Hz, 1H), 5.41 (s, 1H), 5.01 (s, 1H), 4.83 (s, 1H), 4.43 – 4.35 (m, 2H), 4.29 (s, 1H), 4.08 (dt, *J* = 10.4, 5.7 Hz, 1H), 3.79 (s, 2H), 3.63 (d, *J* = 9.2 Hz, 1H), 3.58 – 3.50 (m, 1H), 2.22 (ddd, *J* = 29.9, 13.6, 5.8 Hz, 2H), 1.70 (d, *J* = 6.7 Hz, 1H), 1.50 (s, 4H), 1.47 – 1.37 (m, 3H), 1.31 – 1.25 (m, 2H), 1.23 (s, 2H), 1.22 (s, 16H), 0.86 (ddt, *J* = 15.6, 13.6, 6.5 Hz, 20H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{66}N_5O_9$ 712.4846, found 712.4855.

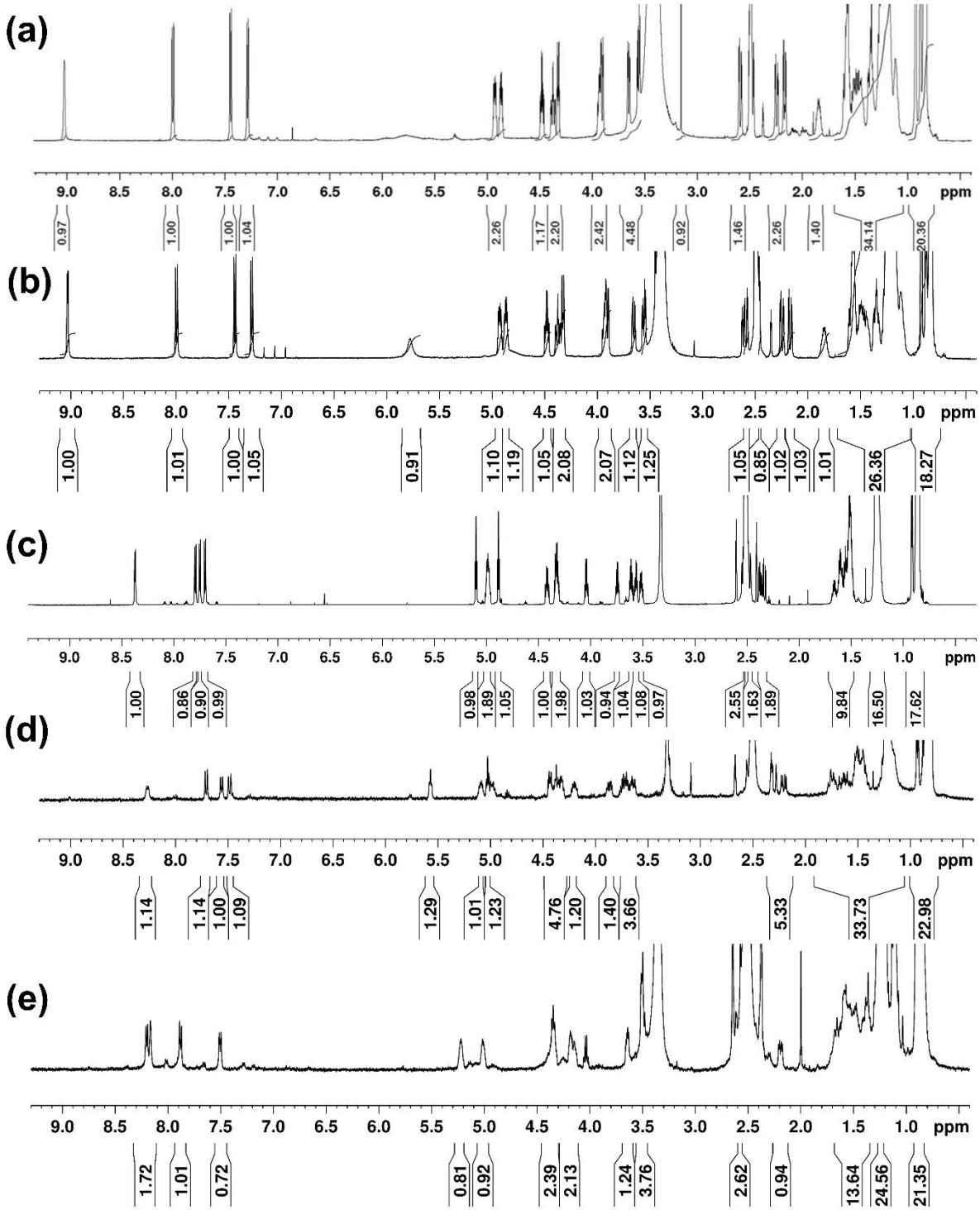
Icosalide analogue 10: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (d, *J* = 6.5 Hz, 1H), 7.69 (dd, *J* = 13.5, 8.2 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 8.4, 4.1 Hz, 1H), 4.99 (s, 1H), 4.37 (dtd, *J* = 30.9, 8.5, 4.4 Hz, 2H), 4.18 (dt, *J* = 8.9, 4.6 Hz, 1H), 4.12 (q, *J* = 7.3 Hz, 1H), 3.70 (dd, *J* = 10.8, 4.5 Hz, 2H), 3.63 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.57 – 3.50 (m, 2H), 2.94 (dd, *J* = 13.1, 9.6 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.13 – 2.06 (m, 1H), 1.71 (s, 1H), 1.65 – 1.48 (m, 4H), 1.53 (s, 4H), 1.28 – 1.19 (m, 9H), 0.94 – 0.80 (m, 16H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{29}H_{52}N_5O_9$ 614.3748, found 614.3760.

Icosalide analogue 11: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (d, *J* = 6.7 Hz, 1H), 7.48 (d, *J* = 9.2 Hz, 1H), 7.39 (dd, *J* = 12.0, 7.5 Hz, 2H), 7.00 (d, *J* = 9.6 Hz, 1H), 5.36 (t, *J* = 5.3 Hz, 1H), 4.96 (s, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.48 – 4.34 (m, 2H), 4.16 – 4.08 (m, 2H), 4.01 (s, 1H), 3.81 – 3.75 (m, 1H), 3.61 (dd, *J* = 10.7, 5.4 Hz, 2H), 2.58 (dd, *J* = 14.3, 3.7 Hz, 1H), 2.32 (s, 0H), 2.05 (dd, *J* = 12.7, 5.4 Hz, 1H), 1.81 – 1.75 (m, 1H), 1.70 – 1.60 (m, 2H), 1.53 (dt, *J* = 23.1, 8.3 Hz, 6H), 1.37 (d, *J* = 11.1 Hz, 1H), 1.24 (d, *J* = 9.0 Hz, 15H), 1.19 (s, 5H), 1.12 (s, 4H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.89 – 0.80 (m, 17H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{66}N_5O_9$ 712.4846, found 712.4855.

Icosalide analogue 12: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.83 – 7.72 (m, 4H), 4.92 (s, 2H), 4.27 (tt, *J* = 9.7, 5.2 Hz, 2H), 4.18 (td, *J* = 9.0, 5.1 Hz, 1H), 4.12 (q, *J* = 6.1 Hz, 1H), 3.57 (ddd, *J* = 28.5, 10.3, 5.5 Hz, 5H), 3.46 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.22 – 3.15 (m, 1H), 3.11 – 3.02 (m, 1H), 2.37 – 2.24 (m, 2H), 2.29 (s, 2H),

1.61 – 1.41 (m, 5H), 0.89 – 0.79 (m, 13H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{24}H_{43}N_6O_8$ 543.3134, found 543.3137.

Icosalide analogue 13: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (dd, *J* = 19.3, 7.4 Hz, 2H), 7.96 (dd, *J* = 11.0, 8.1 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 5.12 (t, *J* = 5.2 Hz, 1H), 4.80 (t, *J* = 5.5 Hz, 1H), 4.41 – 4.29 (m, 2H), 4.22 (dq, *J* = 14.3, 7.4 Hz, 2H), 4.13 (q, *J* = 5.9 Hz, 1H), 4.06 – 3.98 (m, 2H), 3.61 (dt, *J* = 10.9, 5.7 Hz, 1H), 3.56 (q, *J* = 5.3 Hz, 2H), 3.49 (d, *J* = 5.6 Hz, 1H), 3.27 (dd, *J* = 10.8, 5.5 Hz, 1H), 2.31 (dd, *J* = 15.3, 6.2 Hz, 1H), 2.27 (dd, *J* = 7.3, 3.9 Hz, 3H), 1.84 (s, 3H), 1.59 (d, *J* = 8.4 Hz, 3H), 1.45 (dq, *J* = 20.7, 7.7 Hz, 4H), 1.23 (s, 2H), 1.19 (s, 18H), 0.91 – 0.81 (m, 16H), 0.82 (d, *J* = 6.3 Hz, 4H). HRMS (ESI-TOF) m/z $[M+H]^+$ calculated for $C_{36}H_{67}N_6O_8$ 711.4993, found 711.5015.



Supplementary Figure 2. Comparison of the NMR spectra of **(a**) Icosalide **1a** isolated from cell culture,[6] (**b**) the synthesized Icosalide **1a** (3*R*6*R*), **(c)** Icosalide **1a′** (3*S*6*R*), (**d**) Icosalide **1a''** (3*R*6*S*), **(e)** Icosalide **1a'''** (3*S*6*S*). The data shows that the Icosalide **1a** has 3*R*6*R* configuration.

Supplementary Table 2. Comparison of the ^{1}H and ^{13}C chemical shift data of the synthesized Icosalide **1a** with that of the isolated peptide.

	Icosalide 1a (*Burkholderia gladioli HKI0739*)		**Icosalide 1a synthesized**	
Position	**^{13}C (ppm)**	**^{1}H (ppm)**	**^{13}C (ppm)**	**^{1}H (ppm)**
1-D-Leu				
C=O	173.0		173.2	
α	51.4	4.37; 1 H (m)	51.7	4.37; 1 H (td), (9.3)
β	40.6	1.58; 1 H (m)	40.5	1.58; 1 H (m)
		1.34; 1 H (m)		1.35; 1 H (m)
γ	24.3	1.57; 1 H (m)	24.3	1.84; 1 H (m)
γ-CH3	21.5	0.92; 3 H (d) (5.8)	21.5	0.92; 3 H (d), (5.8)
γ-CH3	22.4	0.88; 3 H (d) (5.9)	22.4	0.88; 3 H (d), (5.9)
NH		7.99; 1 H (d) (9.3)		7.99; 1 H (d), (9.3)
2-Ser				
C=O	170.4		170.5	
α	54.1	4.33; 1 H (dt), (8.8, 2.6)	54.1	4.33; 1 H (dt), (8.8, 2.6)
β	62.2	3.91; 1 H (dd), (10.4, 2.7))	62.5	3.91; 1 H (dd), (10.6, 2.7))
		3.65; 1 H (dd), (10.9, 3.1)		3.65; 1 H (dd), (10.6, 2.8)
NH		7.44; 1 H (d), (8.7)		7.44; 1 H (d), (8.7)
3-bHA2				
C=O	168.3		168.3	
2	40.4	2.47; 1 H (dd), (3.6)*	40.2	2.47; 1 H (dd), (3.6)
		2.17; 1 H (dd), (9.4, 3.7)		2.17; 1 H (dd), (9.4, 3.7)
3	71.5	4.93; 1 H (m)	71.5	4.93; 1 H (m)
4	31.8	1.34; 2 H (m)	31.8	1.34; 2 H (m)
5	25.3	1.11; 2 H (m)	25.3	1.11; 2 H (m)
6	28.9[c]	1.19; 2 H (m)	28.9[c]	1.19; 2 H (m)
7	28.7[c]	1.19; 2 H (m)	28.7[c]	1.19; 2 H (m)
8	30.7	1.19; 2 H (m)	30.7	1.19; 2 H (m)
9	21.8[a]	1.24; 2 H (m)	21.8[a]	1.24; 2 H (m)
10	13.7[b]	0.83; 3 H (m)	13.7[b]	0.83; 3 H (m)
4-Ser				
C=O	172.1		172.1	
α	54.6	4.48; 1 H (td), (8.5, 4.5)	54.9	4.48; 1 H (td), (8.5, 4.5)
β	61.7	3.56; 1 H (dd), (11.0, 4.6)	61.9	3.56; 1 H (dd), (11.0, 4.6)
		3.43; 1 H*		3.43; 1 H (dd), (11.0, 8.6)
NH		7.28; 1 H (d), (8.2)		7.28; 1 H (d) (8.2)
5-Leu				
C=O	172.1		172.1	
α	52.3	3.93; 1 H (m)	52.3	3.93; 1 H (dd)
β	38.7	1.57; 2 H (m)	38.33	1.57; 2 H (m)
γ	23.8	1.84; 2 H (m)	23.7	1.57; 1 H (m)
γ-CH3	23.5	0.84; 3 H (m)	23.5	0.84; 3 H (m)
γ-CH3	20.3	0.83; 3 H (m)	20.3	0.83; 3 H (m)
NH		9.03; 1 H (s)		9.03; 1 H (d) (4.3)

6-bHA1

C=O	168.1		168.1	
2	40.4	2.59; 1 H (dd), (13.9, 3.7) 2.25; 1 H (dd), (14.0, 4.0)	40.1	2.59; 1 H (dd), (13.9, 3.7) 2.25; 1 H (dd), (14.0, 4.0)
3	71.5	4.87; 1 H (m)	71.5	4.87; 1 H (m)
4	31.1	1.47; 2 H (m)	31.1	1.47; 2 H (m)
5	24.5	1.24; 2 H (m)	24.5	1.24; 2 H (m)
6	31.3	1.47; 2 H (m)	31.3	1.47; 2 H (m)
7	22.1	1.24; 2 H (m)	22.1	1.24; 2 H (m)
8	14.0	0.83; 3 H (m)	14.0	0.83; 3 H (m)

[a], [b], [c] interchangeable signals; * signal overlaid with solvent signal.

NMR Spectroscopic studies of Icosalide 1a: For NMR spectroscopic studies, 6 mg of Icosalide **1a** was dissolved in 0.5 mL of DMSO-d_6. 1D and 2D spectra were recorded at 298 K on Bruker 500 MHz NMR spectrometer equipped with BBO probe. ^{1}H-1D, DQF-COSY, TOCSY, ROESY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC NMR experiments were acquired. A mixing time of 300 ms was used for ROESY. The 2D NMR experiments were acquired with 320 (for DQF-COSY and TOCSY), 512 (for ROESY), 512 (for HSQC and HMBC) data points in F1 dimension, and 4k (for DQF-COSY, TOCSY, ROESY) and 1k (for HSQC and HMBC) data points in F2 dimension.

Temperature coefficient determination: For the determination of temperature coefficients of amide protons, ^{1}H NMR experiments were recorded at variable temperatures ranging from 300 K to 325 K with 5 K increments. The temperature coefficients were calculated according to $(\Delta\delta*1000)/\Delta T$, wherein $\Delta\delta$ and ΔT is the change in chemical shift of the amide NH and the change in sample temperature, respectively. In this study, three of the NHs in Icosalide **1a**, namely, 2-Ser-NH (-0.4), 4-Ser-NH (-1.6), and 1-D-Leu-NH (-2.8) exhibited low temperature coefficients, which indicate their involvement in hydrogen bonding and/or shielding from the solvent.

Supplementary Table 3. NMR Temperature co-efficients of amide protons in Icosalide **1a**

Name of the NH	Temp. coefficient (ppb/K)
1-D-Leu-NH	-2.8
2-Ser-NH	-0.4
4-Ser-NH	-1.6
5-Leu-NH	-6.8

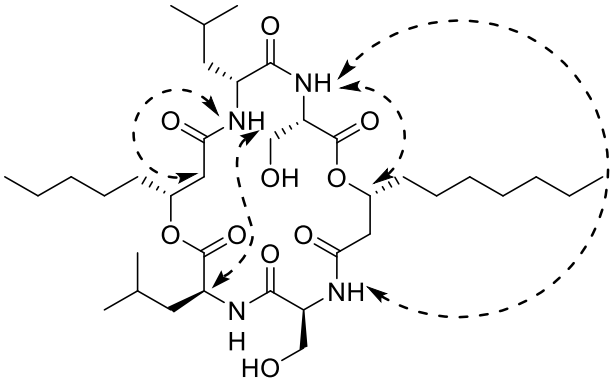
Structure calculation of Icosalide 1a: The inter-proton distances required for NMR-based structure calculation were derived from the cross-peak integrals of the ROESY experiment using SPARKY software. These integrated volumes of ROESY cross-peaks were converted to the corresponding inter-proton distances by the linear approximation method. These distances were used for the structural calculation by using Schrodinger Maestro macro model 13.1.

For the structure calculation, a minimized starting structure was obtained after a step-wise minimization process of an arbitrary structure by giving the inter-proton distance inputs one by one. The method used for energy minimization was SD (steepest descent) and dielectric constant of DMSO i.e., 47. Thus, obtained structure was saved and used as the starting template (beginning structure) for 'Molecular Dynamics Simulations' (MD). MD has been run on the structure at 300 K for 10 ns with simulation time step of 1 fs and by shaking all the bonds of the molecule.

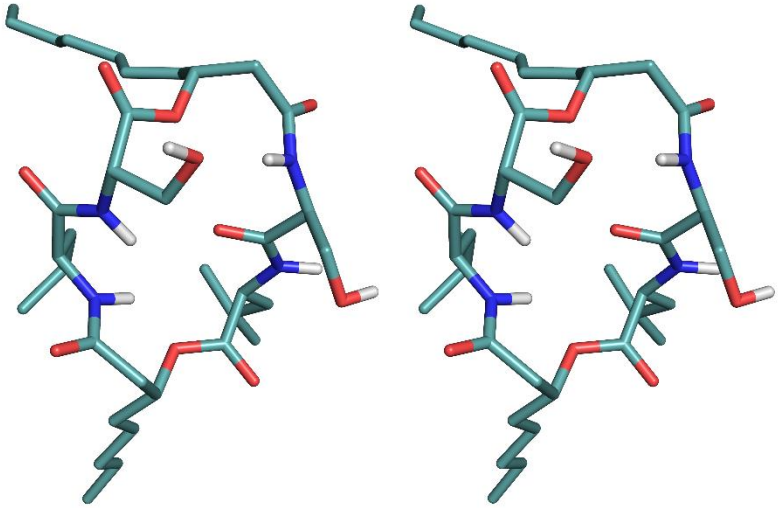
Supplementary Table 4. List of distance restraints that were used for structure calculation of Icosalide **1a**.

Residue	**Atom**	**Residue**	**Atom**	**d [Å]**	**d_{Low} [Å]**	**d_{up} [Å]**
1-D-Leu	NH	6-bHA1	Hα1	2.92	2.63	3.22
1-D-Leu	NH	6-bHA1	Hα2	2.92	2.63	3.22
1-D-Leu	NH	5-Leu	Hα	3.21	2.89	3.54
1-D-Leu	NH	1-D-Leu	Hα	3.12	2.81	3.43
6-bHA1	Hβ	5-Leu	Hα	3.99	3.59	4.39
6-bHA1	Hβ	6-bHA1	Hα1	2.42	2.18	2.66
6-bHA1	Hβ	6-bHA1	Hα2	2.51	2.26	2.76
5-Leu	NH	4-Ser	Hα	2.56	2.30	2.82
5-Leu	NH	5-Leu	Hα	3.24	2.92	3.57
4-Ser	NH	3-bHA2	Hα1	2.66	2.39	2.92
4-Ser	NH	3-bHA2	Hα2	2.66	2.39	2.92
4-Ser	NH	3-bHA2	Hβ	3.85	3.46	4.23
4-Ser	Hα	5-Leu	Hα	4.15	3.73	4.56
4-Ser	NH	4-Ser	Hα	3.02	2.72	3.33
3-bHA2	Hβ	2-Ser	Hα	4.18	3.76	4.60
2-Ser	NH	1-D-Leu	NH	3.14	2.82	3.45
2-Ser	NH	1-D-Leu	Hα	3.23	2.91	3.55
2-Ser	NH	4-Ser	NH	4.50	4.05	4.94
2-Ser	NH	2-Ser	Hα	2.89	2.60	3.18

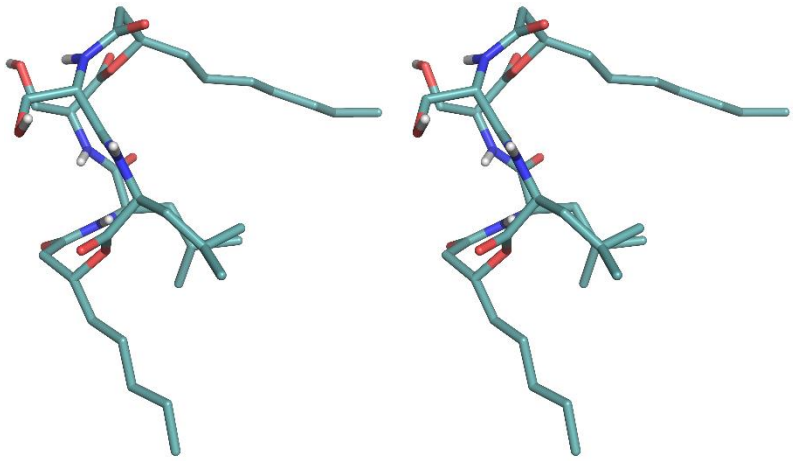
Hα1 and Hα2 of 6-bHA1, Hα1 and Hα2 of 3-bHA2 were considered as pseudo atoms.



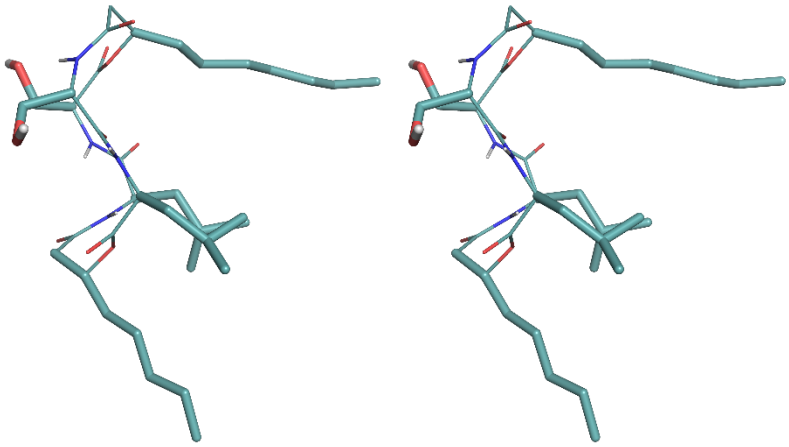
Supplementary Figure 3. Schematic representation of some of the key distant ROESY correlations observed for Icosalide **1a**.



Supplementary Figure 4. Stereoview (top view) of the NMR-derived conformation of Icosalide **1a**.

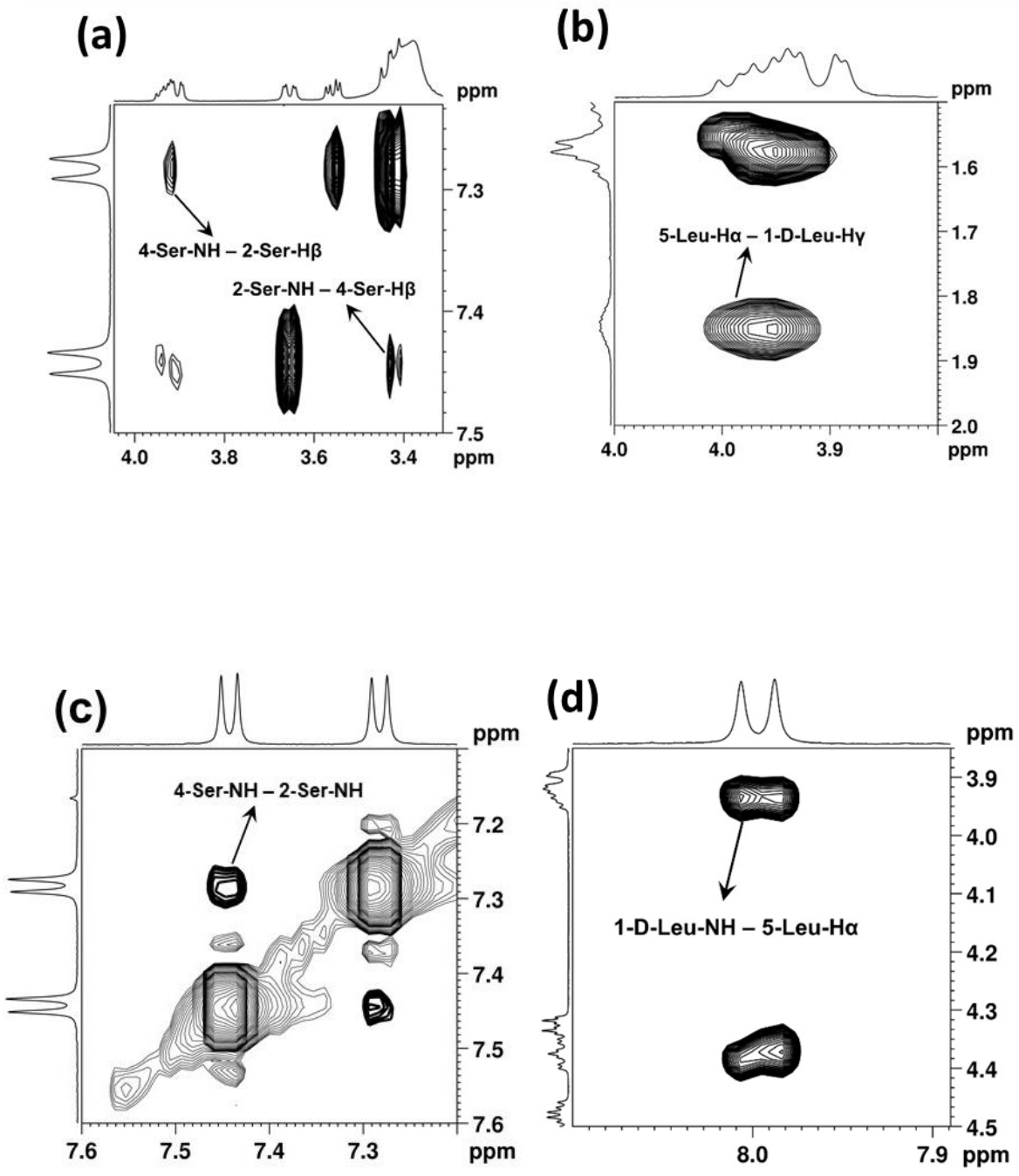


Supplementary Figure 5. Stereoview (side view) of the NMR-derived conformation of Icosalide **1a** showing the orientation of the nonpolar sidechains of Leucines and beta-hydroxy acids towards one face of the plane of the molecule and the polar sidechains of the Serine amino acids on the opposite face. Furthermore, the conformation displays the placement of the two Serine residues and the two Leucine residues facing each other in the macrocycle.



Supplementary Figure 6. Stereoview (side view) of the NMR-derived conformation of Icosalide **1a**. The molecule's backbone is shown as lines to highlight the orientation of the sidechains (shown as sticks).

The above structure and the facing of Serines and Leucines are well-supported by key ROE cross-peaks observed in the ROESY spectrum of Icosalide **1a**. ROESY spectra of Icosalide **1a** have shown cross-peaks between 4-Ser-NH to 2-Ser-Hβ protons and 2-Ser-NH to 4-Ser-Hβ protons, which support the orientation of Serine sidechains facing each other. Similarly, the ROESY cross peak between the 5-Leu-Hα proton to 1-D-Leu-Hγ proton supports the orientation of Leucines facing each other in the conformation.



Supplementary Figure 7. Expansions from the ROESY spectrum of Icosalide **1a** showing the cross-peaks between (**a**) 4-Ser-NH to 2-Ser-Hβ protons, and 2-Ser-NH to 4-Ser-Hβ (**b**) 5-Leu-Hα and 1-D-Leu-Hγ, in support of the Serine and Leucine sidechains facing each other (**c**) 2-Ser-NH and 4-Ser-NH, and (**d**) 1-D-Leu-NH and 5-Leu-Hα, in support of the inward orientation of Serine and Leucine NHs in the conformation of Icosalide **1a**.

Supplementary Table 5. The dihedral angles (φ, ψ) measured for all four amino acids from the NMR-derived structure of the Icosalide **1a**.

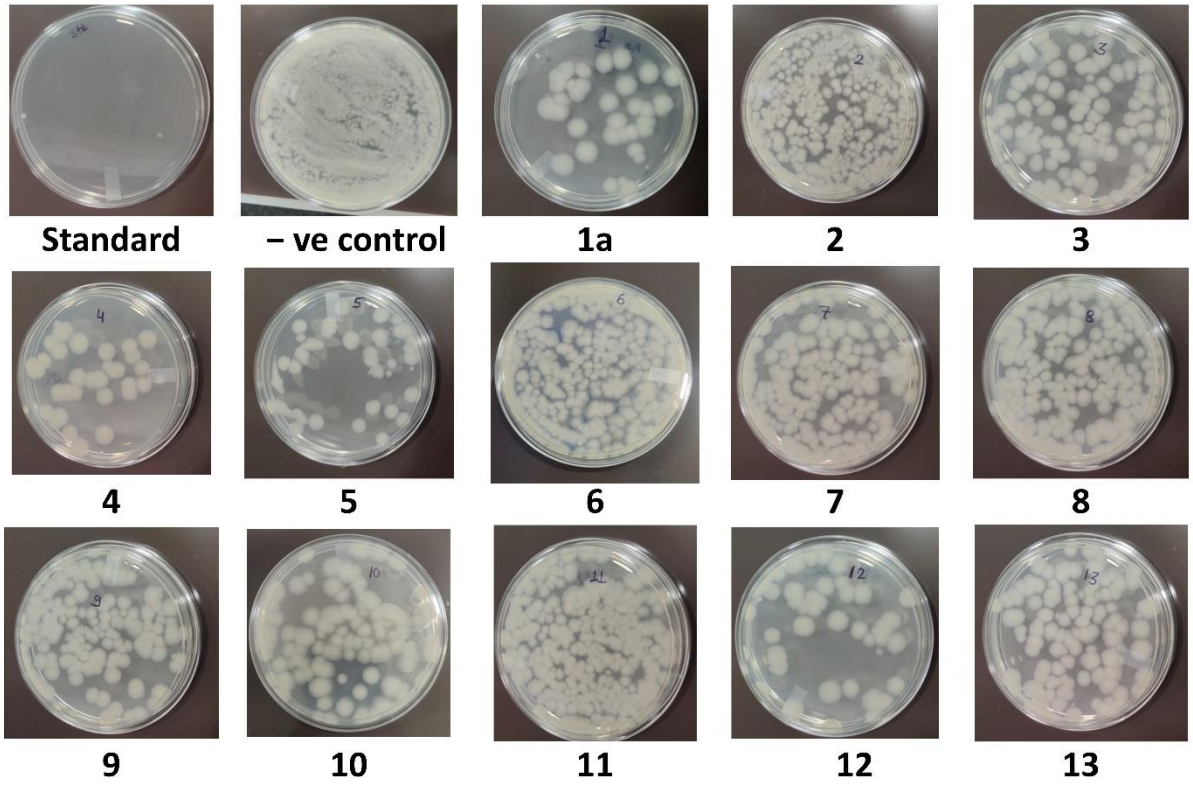
Amino acid	φ	ψ
1-D-Leu	77.8°	14.0°
2-Ser	-71.0°	-64.8°
4-Ser	-80.0°	145.3°
5-Leu	-77.1°	111.2°

Chemicals and media

Nutrient broth, nutrient agar (NA), dimethyl sulfoxide (DMSO), streptomycin sulphate (Hi Media, Mumbai, India), Resazurin (Sigma Aldrich, India). All icosalide compounds were dissolved in dimethyl sulfoxide (DMSO) and two-fold dilutions (50.0, 12.0, 6.0, 3.0, 1.6, 0.8, 0.4, 0.2, 0.1 and 0 µg/mL) were prepared. *Bacillus thuringiensis* NCIM-5467 and *Paenibacillus dendritiformis* used in this study were cultured in MGY+M9 and LB media, respectively. [6]

Time-kill test (time-kill curve)

The antibacterial activity of Icosalide and their analogues were determined using time -kill test method described by Clinical and Laboratory Standards Institute (CLSI).[7] A 50 µL *B. thuringenesis* suspension containing 0.1 OD was mixed in a tube with 50 µL of Icosalide compounds containing 50 µg/mL concentration then the mixture was incubated at 37 °C for 1 h. The standard antibiotic streptomycin was used as a positive control and a tube containing no compound was kept as negative control. The growth inhibition of *B. thuringenesis* was calculated relatively to the growth control by using agar plate count method and percentage inhibition was determined by calculating CFU count (CFU/mL).



Supplementary Figure 8. Antibacterial activity of Icosalide against *B. thuringenesis.*

Antibacterial activity of Icosalide analogues by Dilution method[7]

A 96-well microtiter plate was used for the antimicrobial assay against *Bacillus thuringiensis* and *Paenibacillus dendritiformis*. [6] Briefly, 96 well microtiter plate was filled with 100 µL of MGY+M9 and LB medium used for the growth of *B. thuringiensis* and *P. dendritiformis*, respectively. A 100 µL of Icosalide (1 mg/mL) in DMSO was added into the first well containing 100 µL of respective medium. From this mixture, 100 µL was serially diluted to get the minimum concentration (0.4 µg/mL). Then 5 µL of overnight grown bacterial culture (0.1 OD600) was added, and plates were incubated at 90 rpm, 30 °C, for 18 hrs. After incubation period, the optical density (OD) was measured at 600 nm using multimode microplate reader (Bio-Rad, USA). The MIC of the compound was calculated using standard formula (Growth inhibition (%) = 100-At / Ac × 100

Supplementary Table 6. Effect of Icosalides on growth inhibition of *B. thuringiensis*

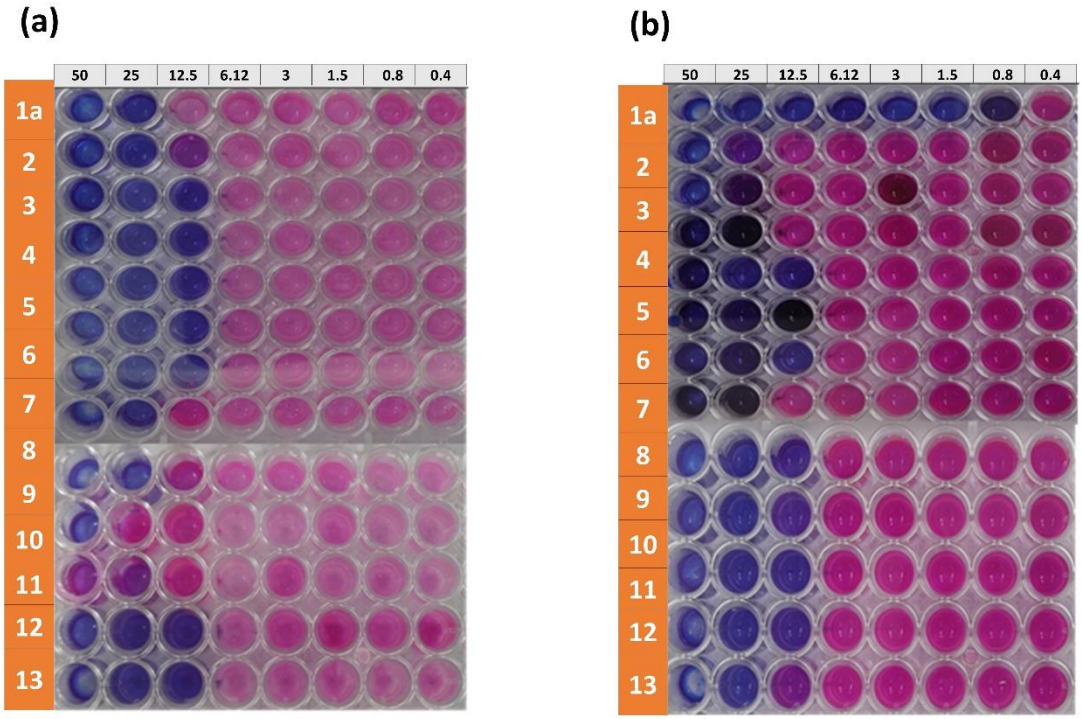
Conc. (µg/ml)	Peptide												
	1a	2	3	4	5	6	7	8	9	10	11	12	13
Growth Inhibition (%)													
50	68.31	89.90	84.35	80.71	81.16	84.79	84.65	84.32	87.93	82.92	82.10	79.68	88.71
25	67.04	86.99	83.61	76.03	78.17	84.11	83.97	71.40	85.52	79.73	75.45	78.23	85.27
12.5	39.35	85.35	81.70	64.78	75.14	83.39	77.97	52.31	82.41	78.31	40.34	72.34	83.82
6.25	3.29	3.70	8.21	9.29	2.14	14.58	0	0	0	0	0	15.69	23.99
3.12	0	0	4.73	2.56	0.05	0	0	0	0	0	0	0	18.23
1.5	0	0	0	0	0	0	0	0	0	0	0	0	6.04
0.8	0	0	0	0	0	0	0	0	0	0	0	0	0
0.4	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplementary Table 7. Effect of Icosalides on growth inhibition of *P. dendritiformis*

Conc. (µg/mL)	Peptides												
	1a	2	3	4	5	6	7	8	9	10	11	12	13
Growth Inhibition (%)													
50	82.72	82.77	79.65	85.76	75.28	81.58	87.53	77.61	84.77	80.64	78.95	79.80	82.26
25	82.70	80.59	76.74	73.63	68.68	81.07	80.19	70.14	82.99	79.69	76.70	76.25	80.65
12.5	82.66	40.41	16.27	46.51	67.77	80.55	73.84	11.91	80.71	77.75	74.26	74.29	71.66
6.25	82.01	0	2.64	0	0	0.52	0	0	0	0	0	0	0
3.12	81.14	0	0	0	0	0	0	0	0	0	0	0	0
1.5	72.27	0	0	0	0	0	0	0	0	0	0	0	0
0.8	70.21	0	0	0	0	0	0	0	0	0	0	0	0
0.4		0	0	0	0	0	0	0	0	0	0	0	0

Resazurin Assay

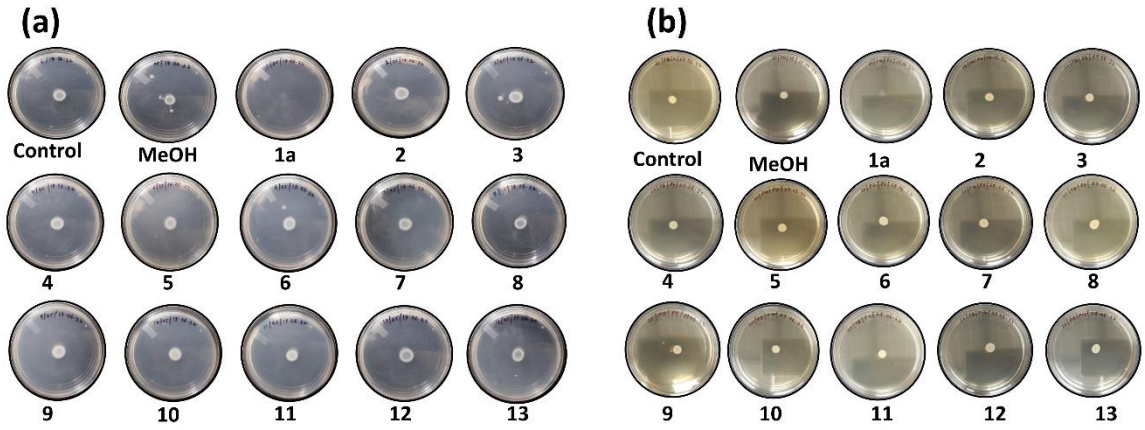
To determine the MIC endpoint, the resazurin was used as a growth indicator to differentiate the bacterial growth and inhibition. A 10 µL of resazurin containing 2 mg/mL concentration was added into each well in dark condition and incubated in dark for 2 h results in the color change to violet from pink indicated dead cells.



Supplementary Figure 9. **(a)** Antibacterial activity of Icosalide against *B. thuringenesis* **(b)** Antibacterial activity of Icosalide against *P. dendritiformis*

Swarming assay

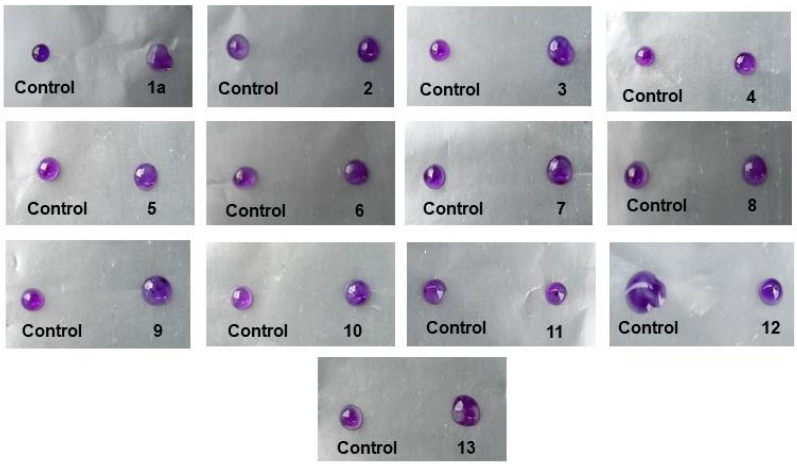
Novel Icosalide analogues were tested in a swarming assay against *B. thuringiensis* and *P. dendritiformis* (Dose et al., 2018). As previously mentioned, *B. thuringiensis and P. dendritiformis* were grown for 18 h in a MGY and LB media, and a 0.4 OD600 set. A 0.7% agar plate with 10 µL of culture was pipetted in the centre, and it was incubated at 30 °C for 48 hours. At the end of the incubation, the agar plates were photographed from a fixed height and the swarming area was calculated using zone sale (Hi Media, India)



Supplementary Figure 10. **(a)** Swarming inhibitory activities of Icosalides against *B. thuringiensis*, **(b)** swarming inhibitory activities of Icosalides against *P. dendritiformis*.

Drop-collapsing assay

The drop-collapsing assay was used to determine whether surfactants may destabilize liquid droplets (Jain et al. 1991). A single colony of *B. thuringiensis* cells was isolated and resuspended in a 10 µL water droplet. A 10 µL Icosalide droplet was placed on a hydrophobic surface with a 10 µL water droplet on top (Parafilm 'M' Laboratory). Crystal violet was added to the droplet (0.0025%) to help visualize the droplet crumbling. It had no effect on the droplet's form. Crystal violet, water, and *B. thuringiensis* were used to maintain the control.



Supplementary Figure 11. Drop-collapsing assay of Icosalides against *Bacillus thuringiensis*

Antitubercular activity of Icosalide analogues against active state of *Mycobacterium tuberculosis* H37Ra

Mycobacterium tuberculosis (ATCC 25177) H37 Ra RFP culture was grown in Dubos medium containing 10% glycerol with antibiotics hygromycin (50 µg/mL). Once OD600 reached 1 than 1% of the culture was inoculum in Dubos medium and aliquot in 96 black well plates as described in the earlier protocol. Novel red fluorescence protein based microplate assay for drug screening against dormant *Mycobacterium tuberculosis* by using paraffin.[8] The 2 fold serially dilution of Icosalide **1a** and its analogs were added in plate to reach final concentrations of 100, 50, 25, 12.5, 3.125, 1.5625, and 0.781 µg/mL for aerobic condition. 80 µL Paraffin oil was added in each well and incubated for 8 days. After incubation fluorescence was read at 587/610 nm using a multimode plate reader (Model Spectramax M5e, Molecular Devices, USA). Rifampicin and Isoniazid used as standard antituburcular drug. The data shown are representative of three independent experiments.

Anticancer activity of Icosalide and its analogues against HeLa and Thp1 cell lines

The anticancer activity was determined by MTT method, Cell sensitivity assays: the MTT assay.[9] Briefly, HeLa, Thp1 cells were seeded at 1 x 105/mL density in 96-well plate. An untreated group was kept as a positive control. Icosalide and their analogues were added at following concentrations (100, 50, 25, 12.5, and 6.25 µg/mL) in each triplicate well. After 48h of addition, MTT solution (5 mg/mL) was added to each well, and the cells were kept for another 4 h at 37°C in 5% CO_2 incubator. The formazan crystals formed were dissolved by addition of SDS-DMF. After 15 mins of incubation the amount of color formazan was determined by measuring optical density (OD) at 570 nm using a multimode plate reader.

The percentage viability was calculated as:

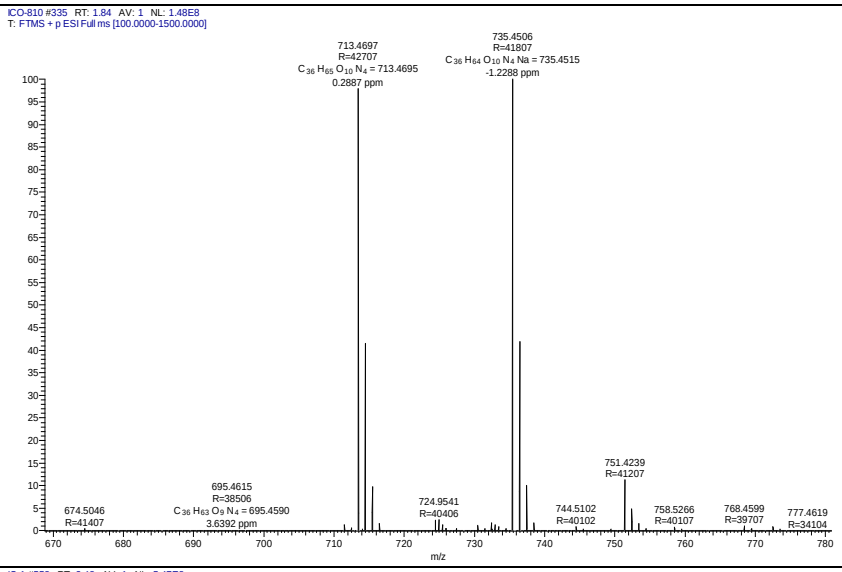
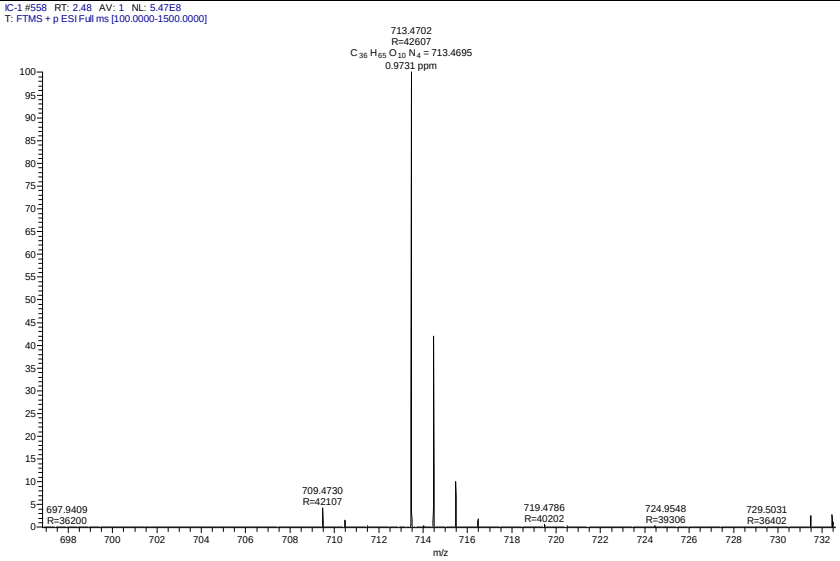
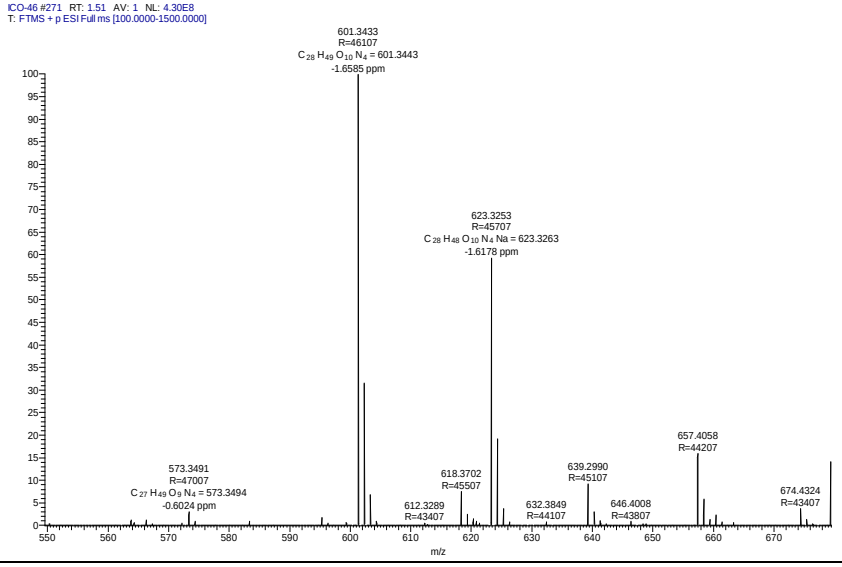
% Viability = (OD of treated Cells-OD of control/ OD of Control-OD of blank) x 100

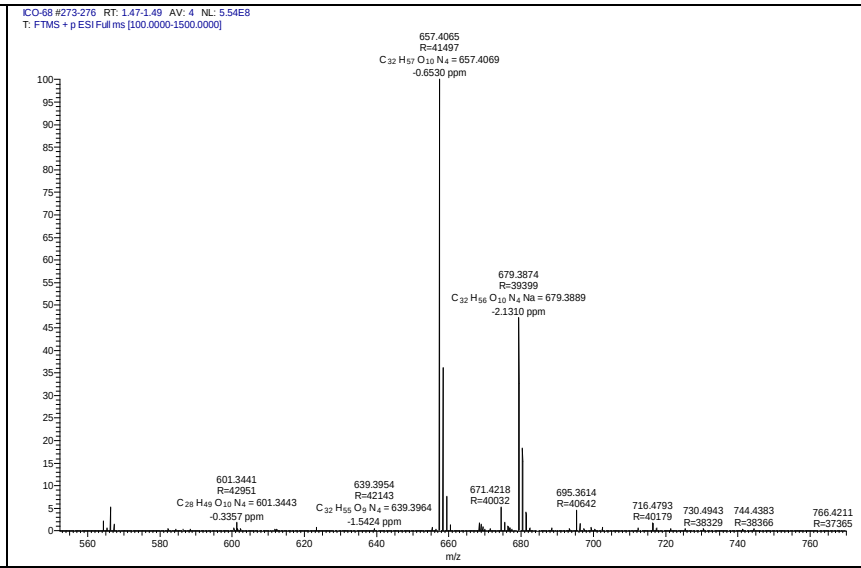
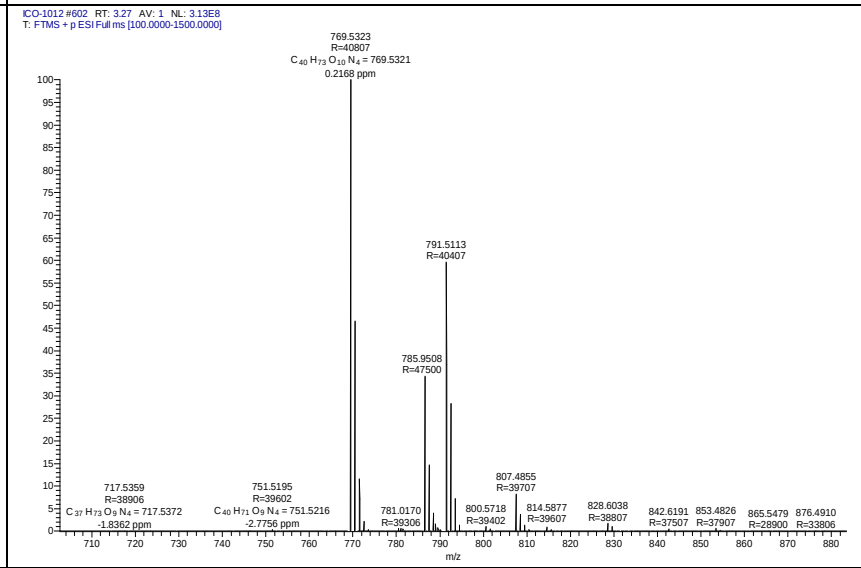
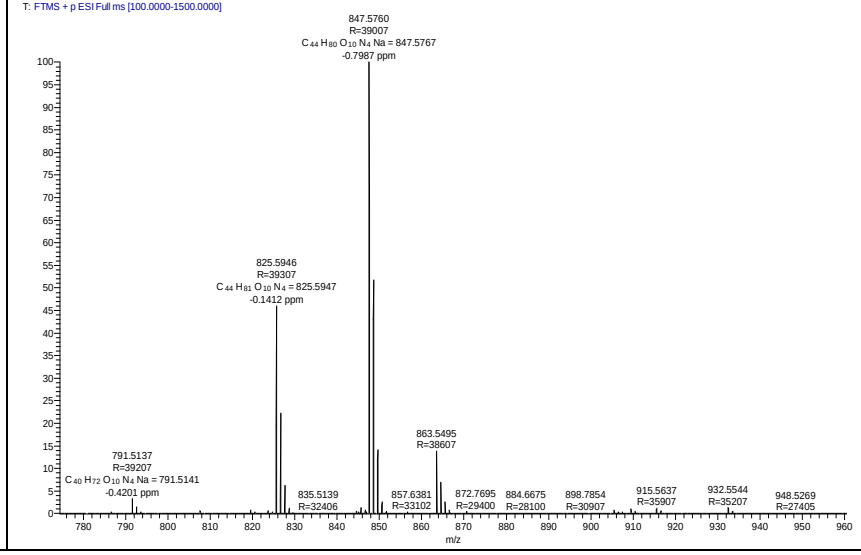
Supplementary Table 8. In vitro anti-cancer activity of Icosalide **1a** and its analogues against HeLa and ThP1 cell lines and antitubercular activity against *M. tuberculosis* H37RaRFP

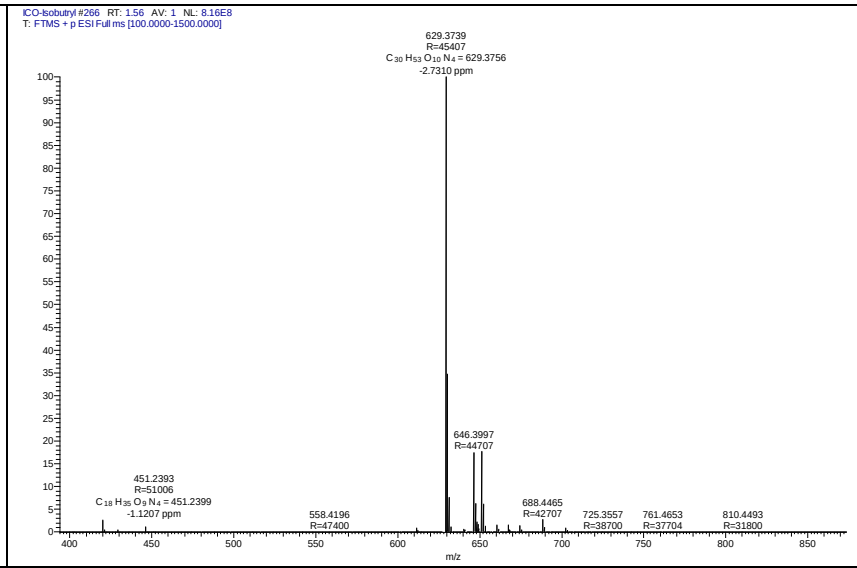
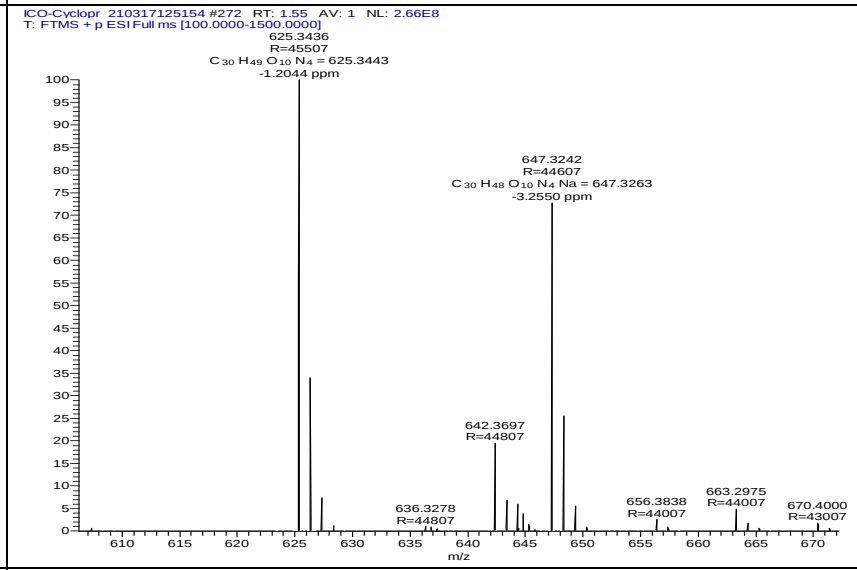
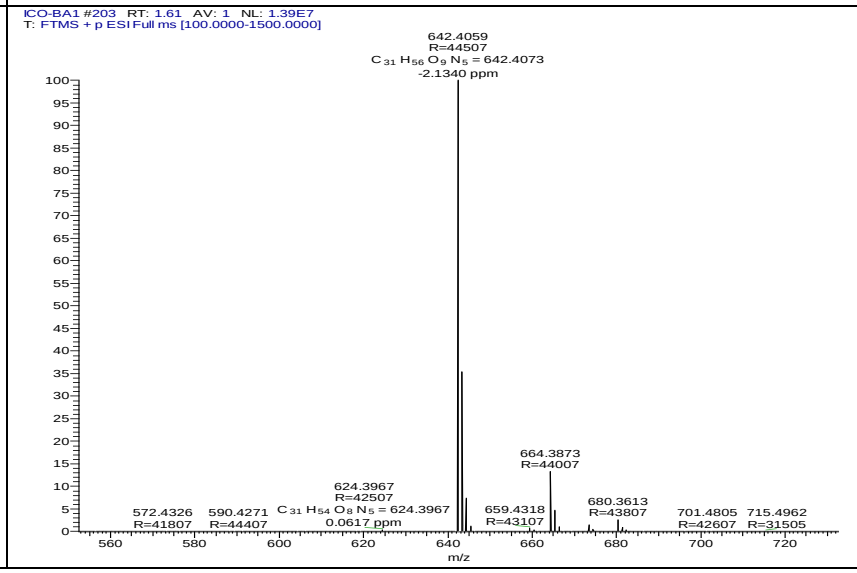
Peptide	**Anti-cancer activity**		**AntiTB activity (Active Stage *M. tb*)**
	HeLa IC_{50} (µg/mL)	ThP1 IC_{50} (µg/mL)	MIC_{90} (µg/mL)
1a	4.612**±0.389**	4.125**±1.271**	5.018**±0.254**
2	20.544**±2.705**	8.816**±4.106**	12.615**±2.149**
3	14.663**±2.003**	7.068**±2.443**	3.245**±0.194**
4	8.360**±0.627**	5.906**±0.414**	2.742**±0.163**
5	ND	ND	ND
6	14.867**±2.366**	13.31**±3.2837**	6.179**±0.277**
7	ND	ND	ND
8	20.093**±6.720**	3.881**±1.856**	8.835**±1.555**
9	23.407**±2.524**	24.028**±3.254**	25.95**±0.256**
10	24.141**±4.916**	34.257**±8.655**	5.109**±0.538**
11	16.481**±2.592**	6.374**±0.906**	3.288**±0.043**
12	8.854**±0.507**	13.353**±2.933**	4.779**±0.079**
13	21.015**±7.220**	15.590**±5.435**	5.408**±0.188**
Standard	Doxorubicin **50 ng/mL**	Doxorubicin **50 ng/mL**	Rifampicin **0.005±0.001** Isoniazid **0.047±0.021**

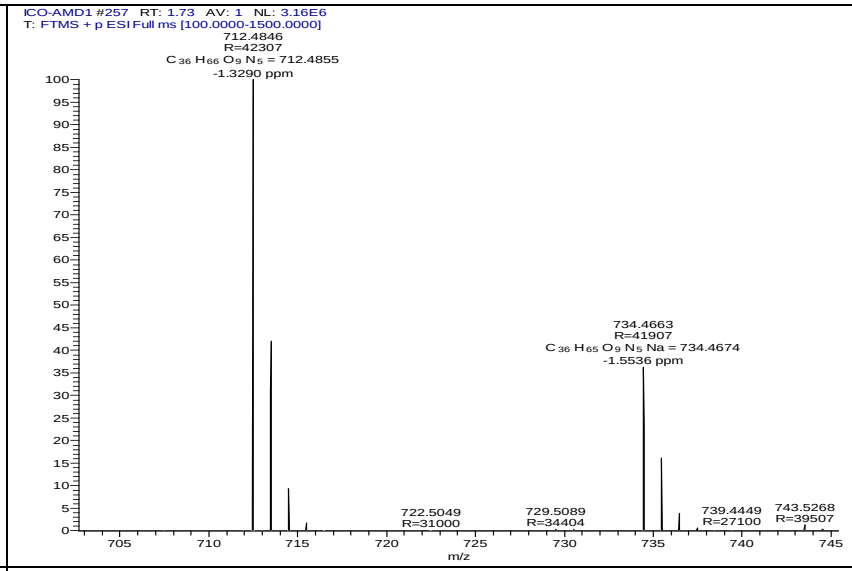
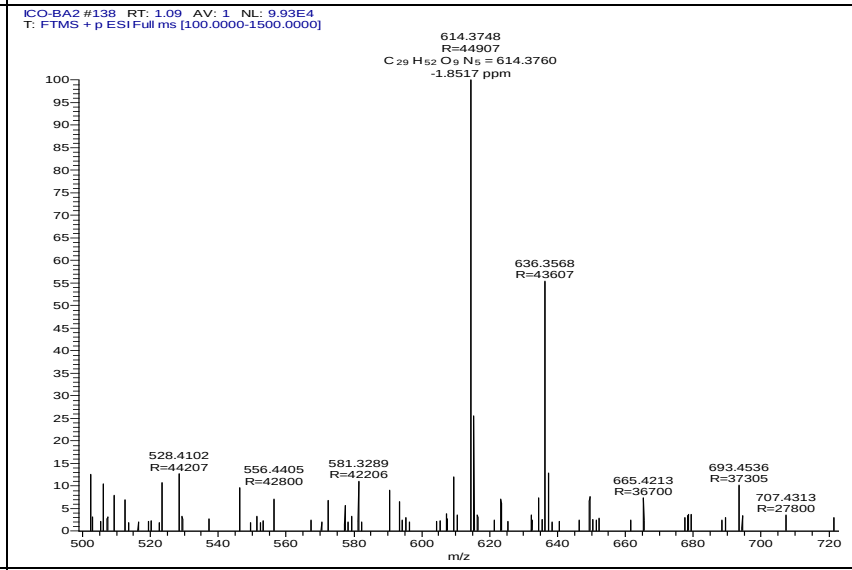
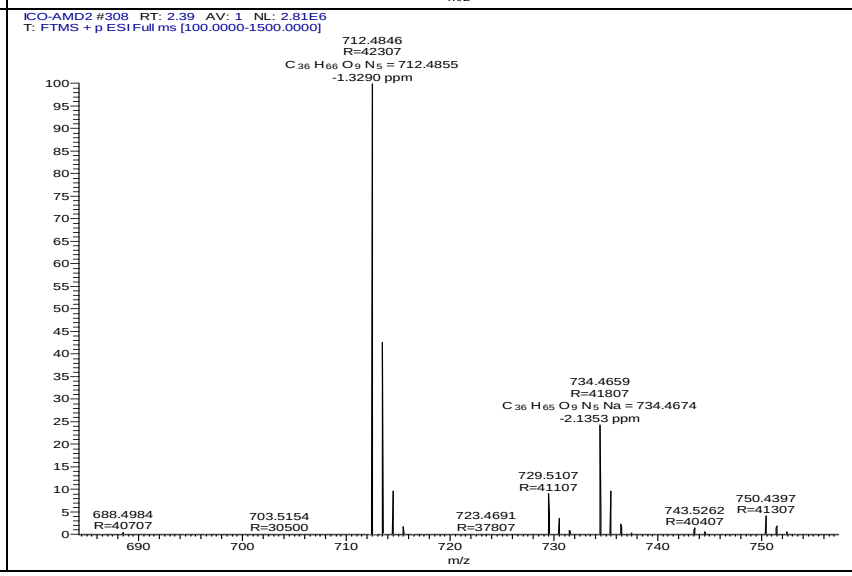
*ND-Not determined

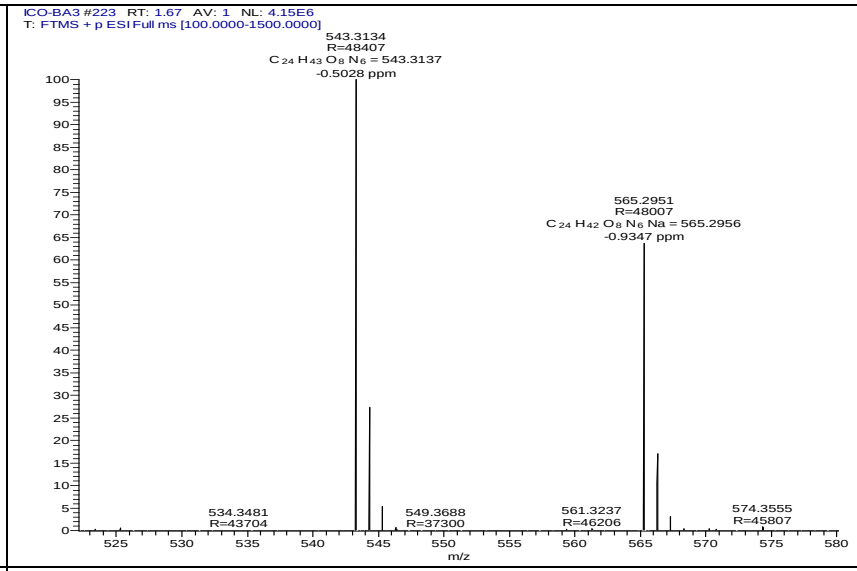
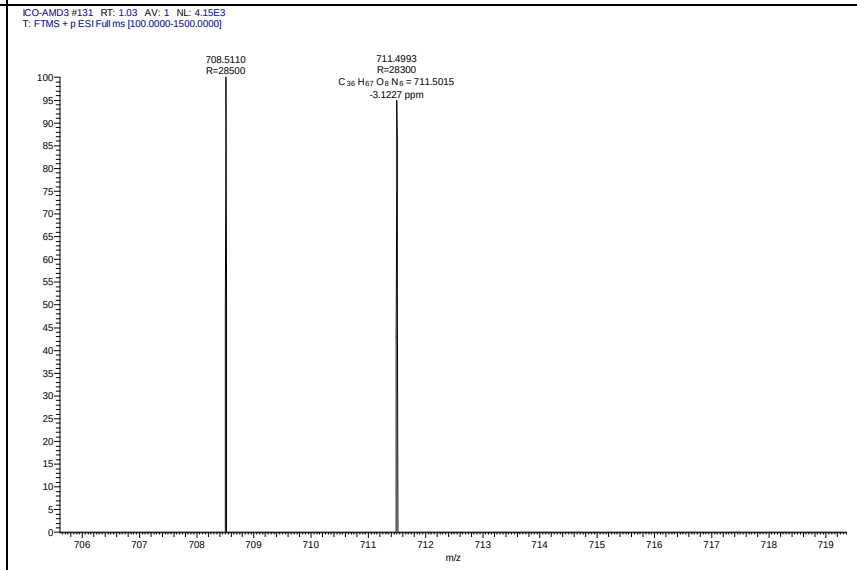
Supplementary Table 9. HRMS Data of peptides **1a** to **13**.

Peptide	Exact Mass	HRMS (M+1)	HRMS Data
Icosalide 1a	712	713	
Icosalide 1a′	712	713	
2	600	601	

3	656	657	
4	768	769	
5	824	825	

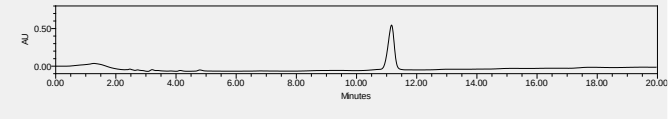
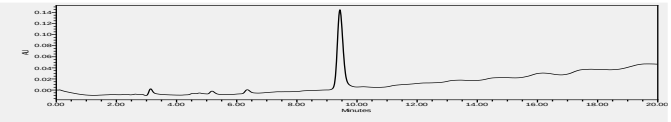
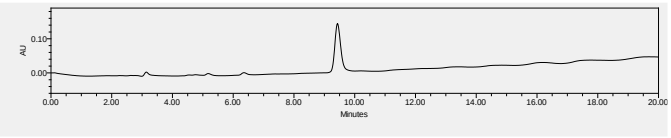
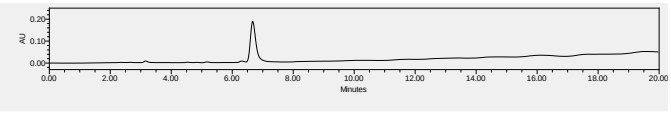
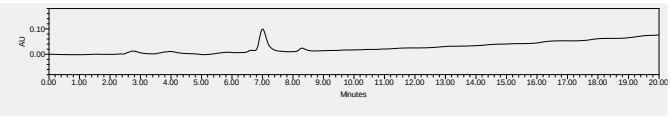
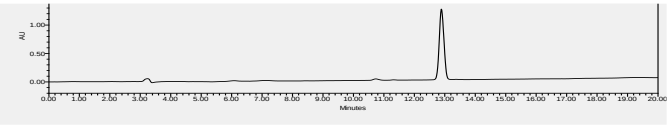
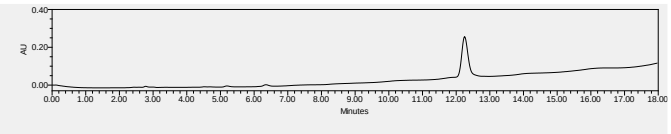
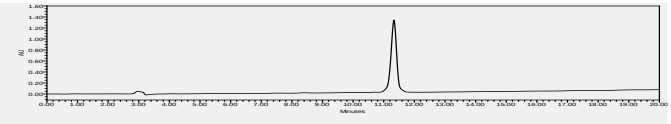
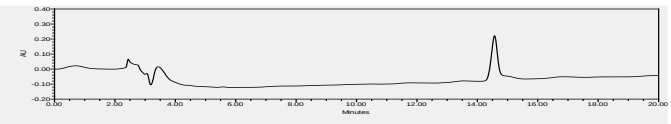
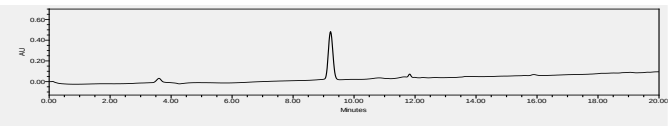
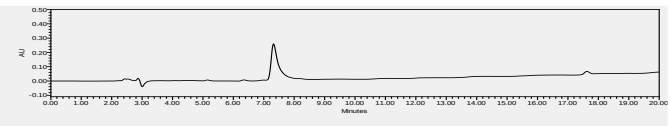
6	628	629	
7	624	625	
8	641	642	

9	711	712	
10	613	614	
11	711	712	

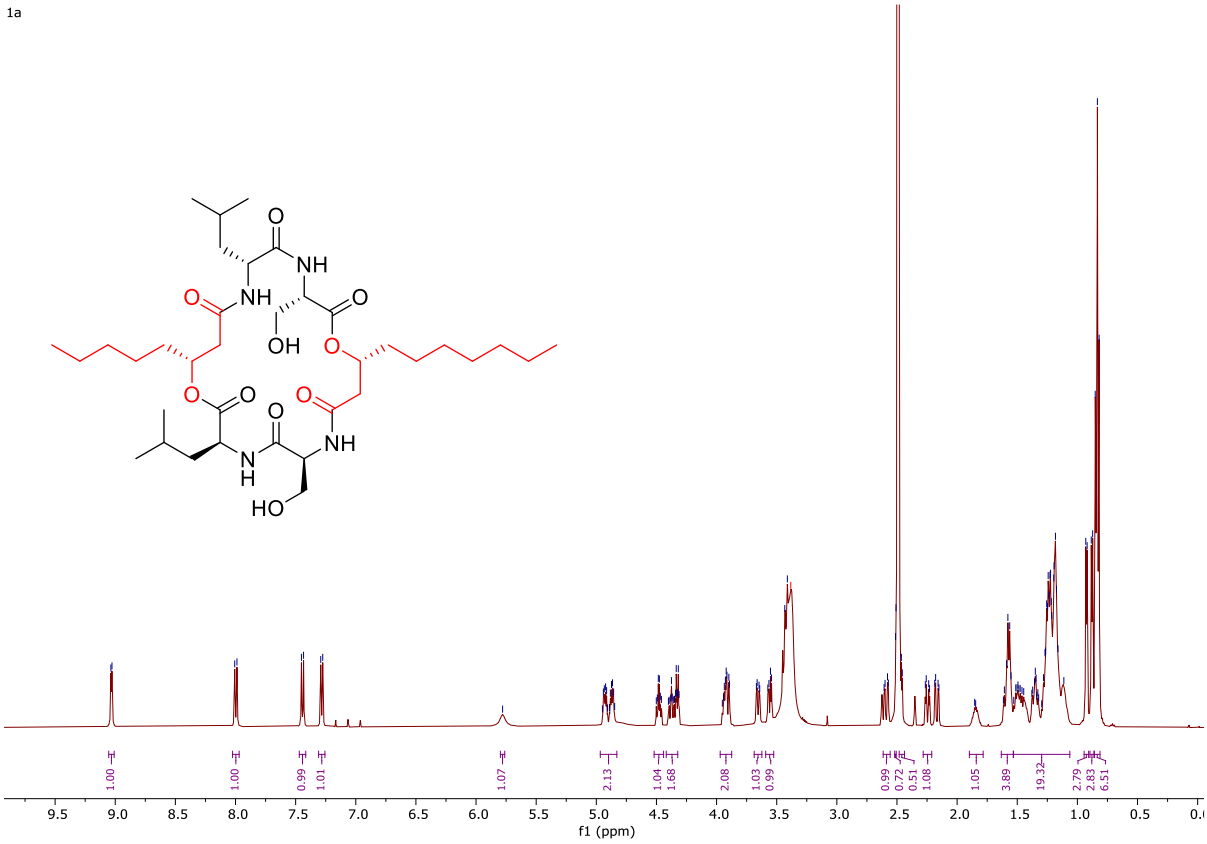
12	542	543	
13	710	711	

Analytical HPLC of peptides- The purity of all the peptides (except **4** and **5**, which, due to their high lipophilicity, could not be eluted from the column) was determined by analytical HPLC using YMC Pack ODS-A-HG C18 column with the dimensions S-10 µm, 12 nm, 250 mm * 4.6 mm I.D., on Waters HPLC 2545 Quaternary Gradient module with 2489 UV/Visible detector. A flow rate of 1 mL/min was used for the analytical run.

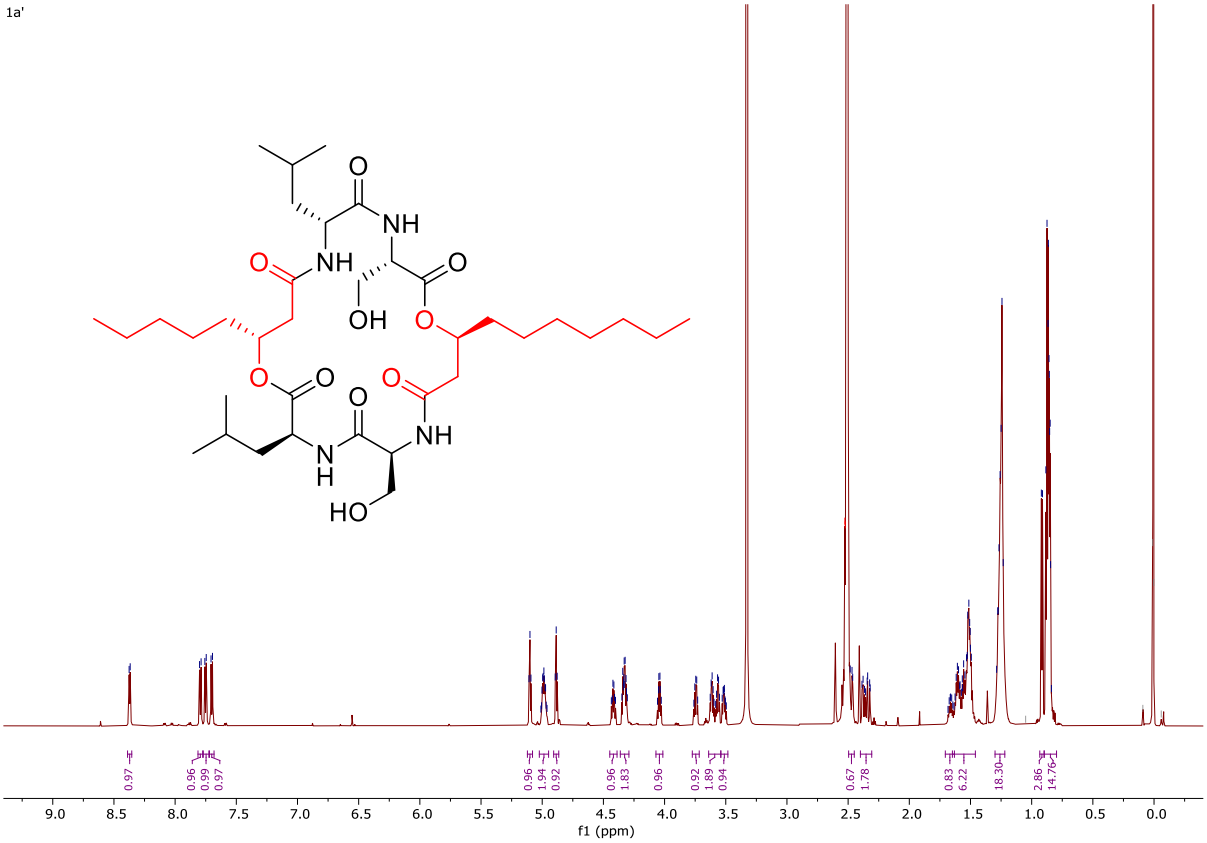
Supplementary Table 10. Analytical HPLC methods and retention times for the purified peptides. (ACN- Acetonitrile)

Peptide	HPLC Gradient	HPLC Chromatogram
Icosalide 1a	70% to 90% ACN in 20 min	
2	60% to 90% ACN in 20 min	
3	60% to 90% ACN in 20 min	
6	60% to 90% ACN in 20 min	
7	50% to 90% ACN in 20 min	
8	40% to 90% ACN in 20 min	
9	60% to 90% ACN in 18 min	
10	40% to 90% ACN in 20 min	
11	60% to 90% ACN in 20 min	
12	20% to 90% ACN in 20 min	
13	60% to 90% ACN in 20 min	

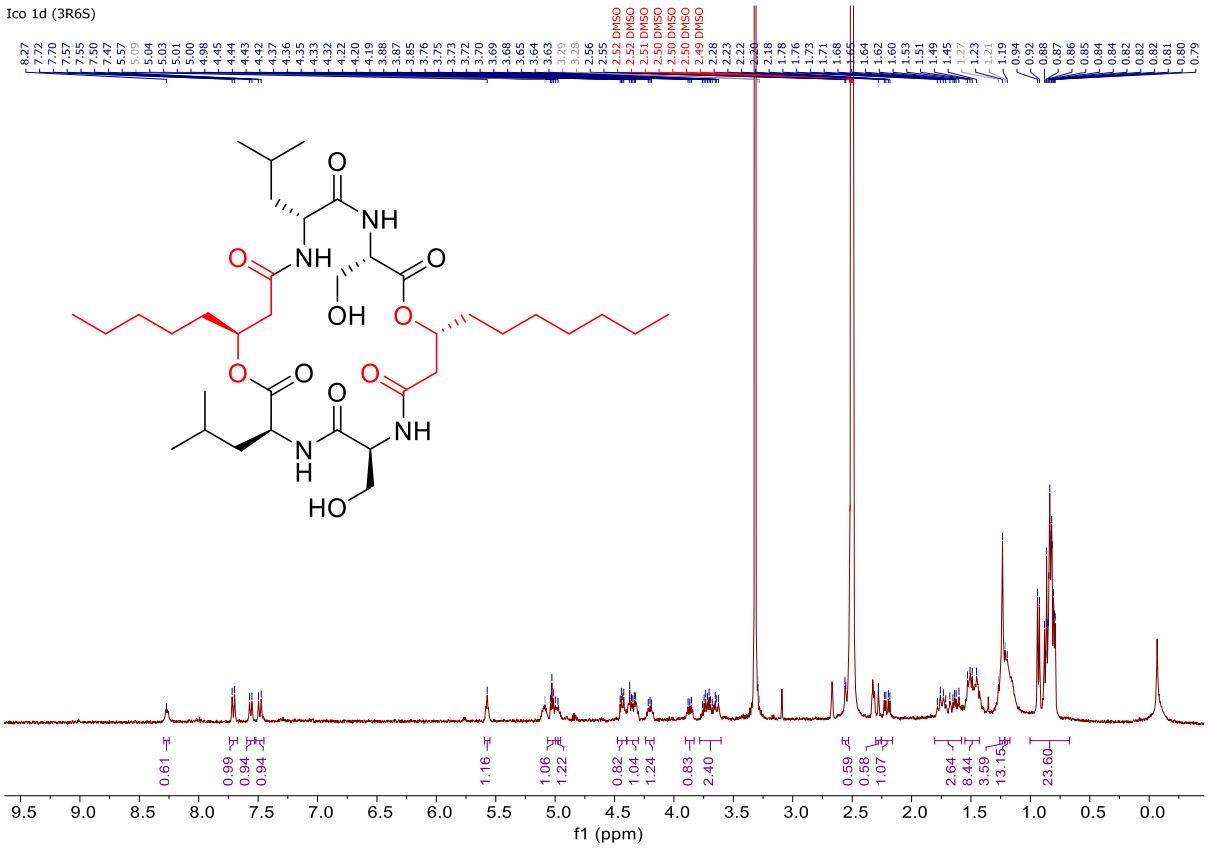
Supplementary Figure 12. ^{1}H NMR of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



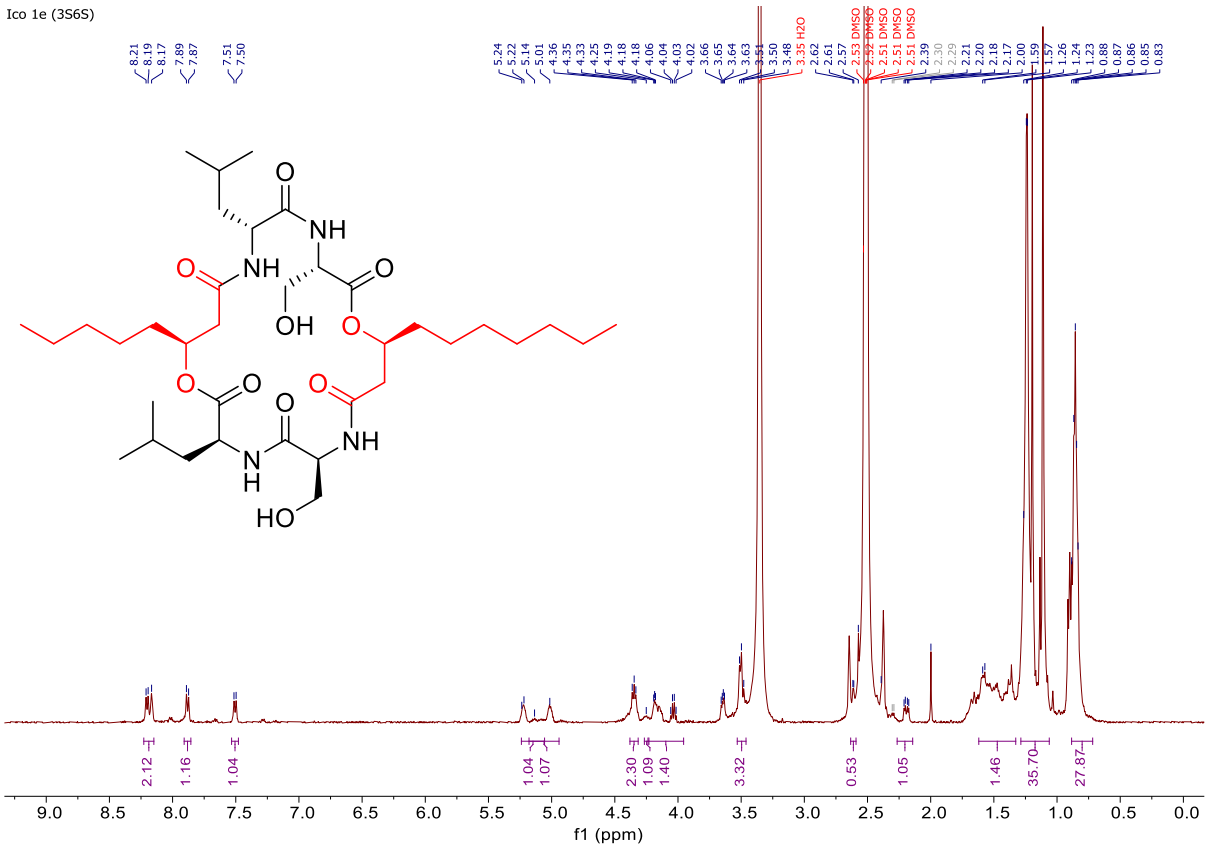
Supplementary Figure 13. ^{1}H NMR of Icosalide **1a'** on 700 MHz at 298 K in DMSO-d_6.



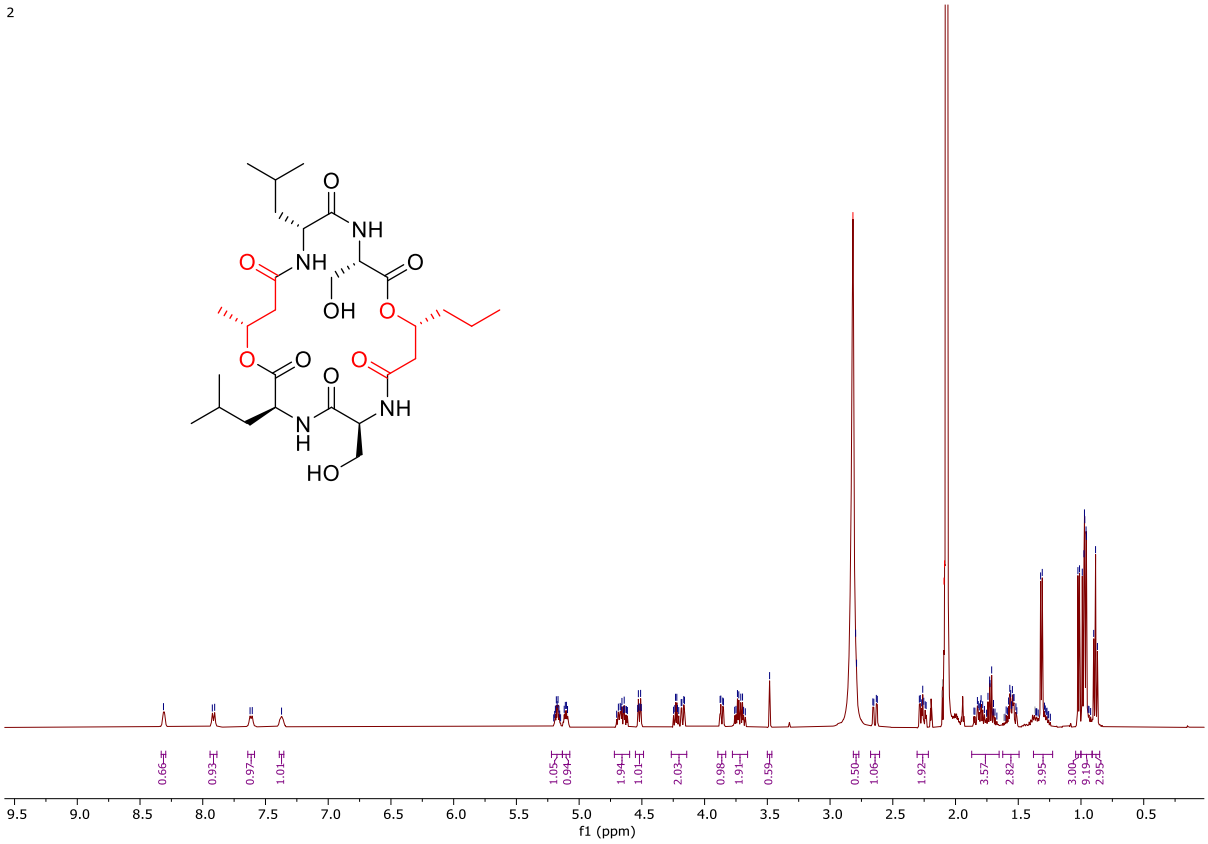
Supplementary Figure 14. ^{1}H NMR of Icosalide **1a''** on 700 MHz at 298 K in DMSO-d_6.



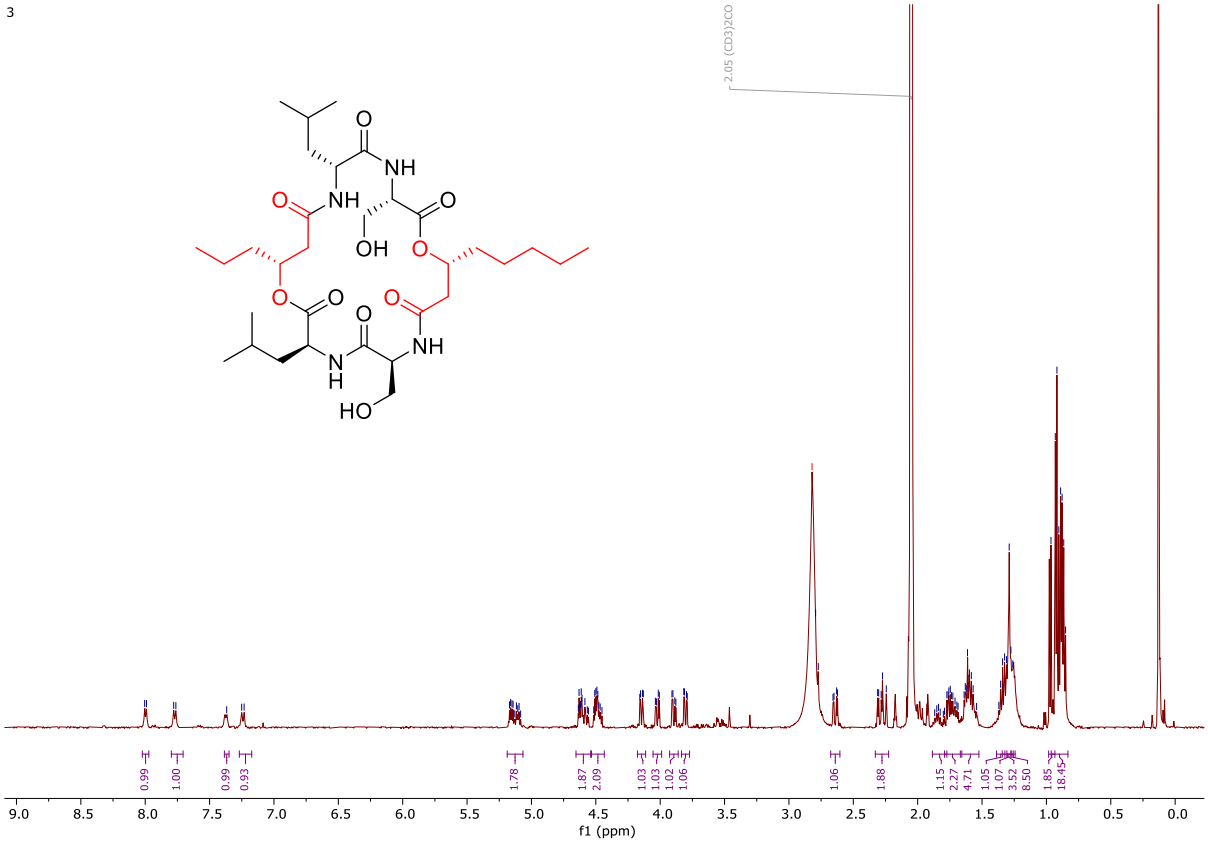
Supplementary Figure 15. ^{1}H NMR of Icosalide **1a'''** on 700 MHz at 298 K in DMSO-d_6.



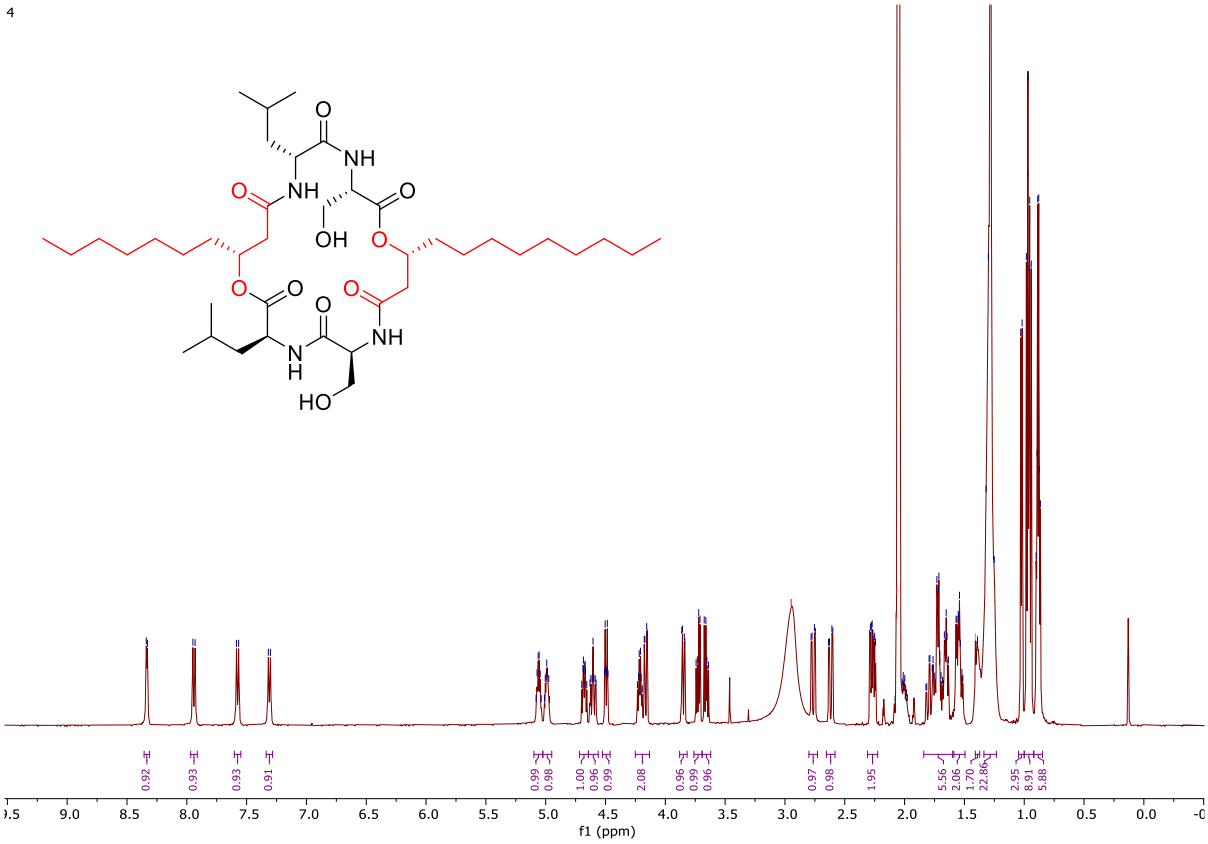
Supplementary Figure 16. ^{1}H NMR of **2** on 500 MHz at 298 K in Acetone-d_6.



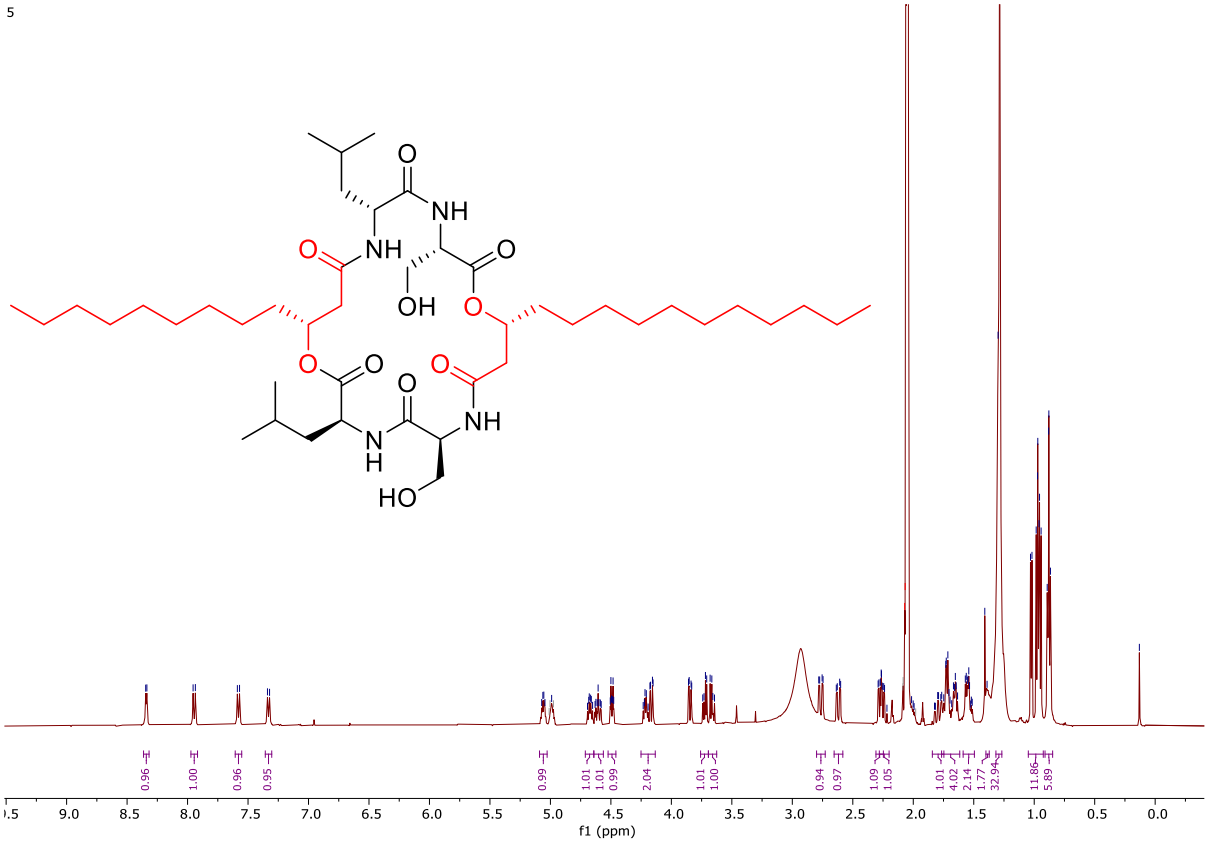
Supplementary Figure 17. ^{1}H NMR of **3** on 500 MHz at 298 K in Acetone-d_6.



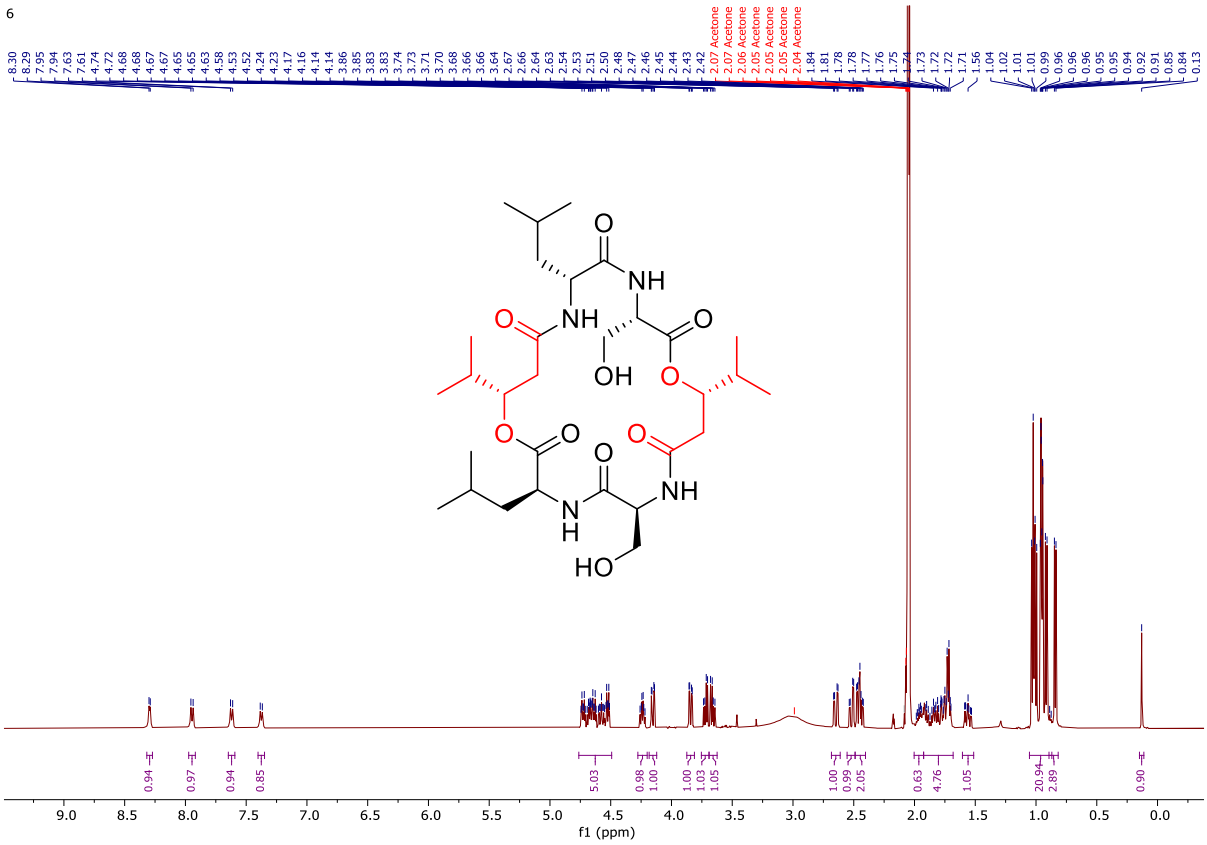
Supplementary Figure 18. ^{1}H NMR of **4** on 500 MHz at 298 K in Acetone-d_6.



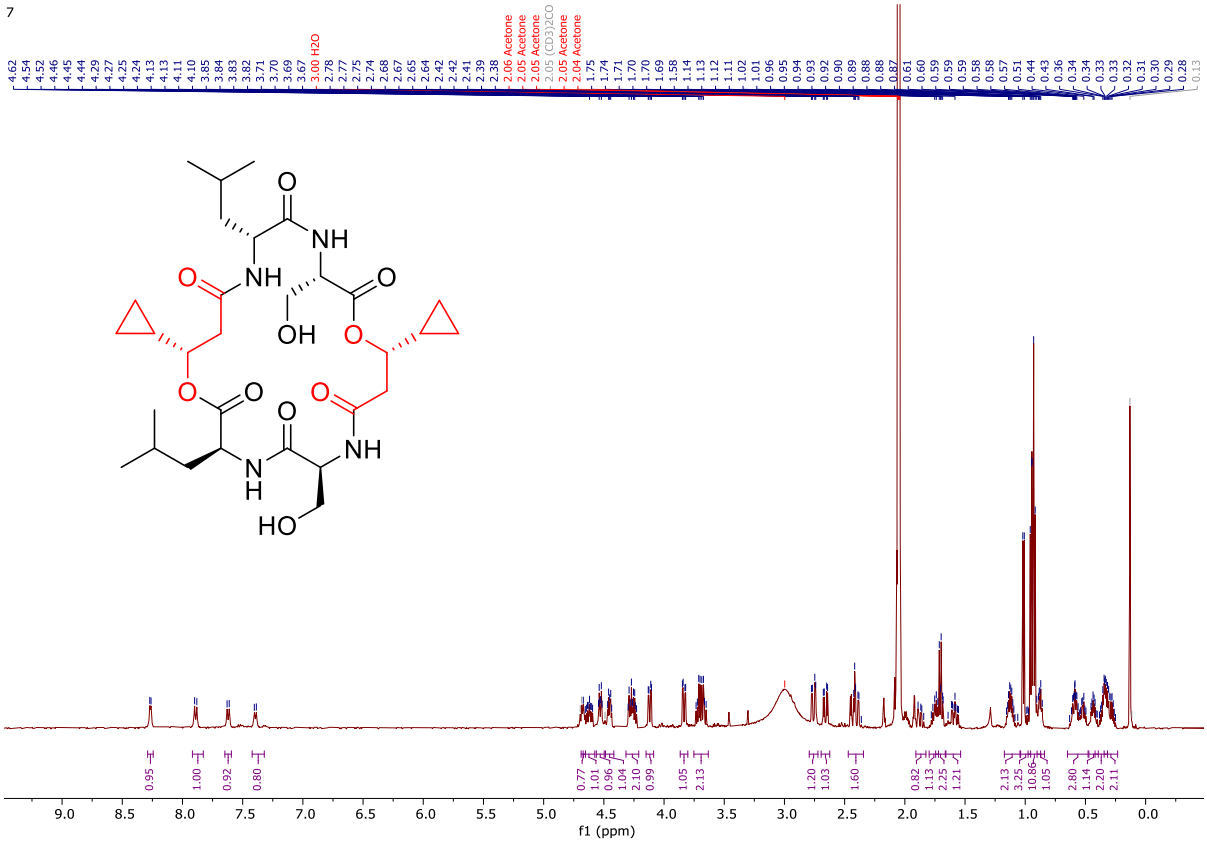
Supplementary Figure 19. ^{1}H NMR of **5** on 500 MHz at 298 K in Acetone-d_6.



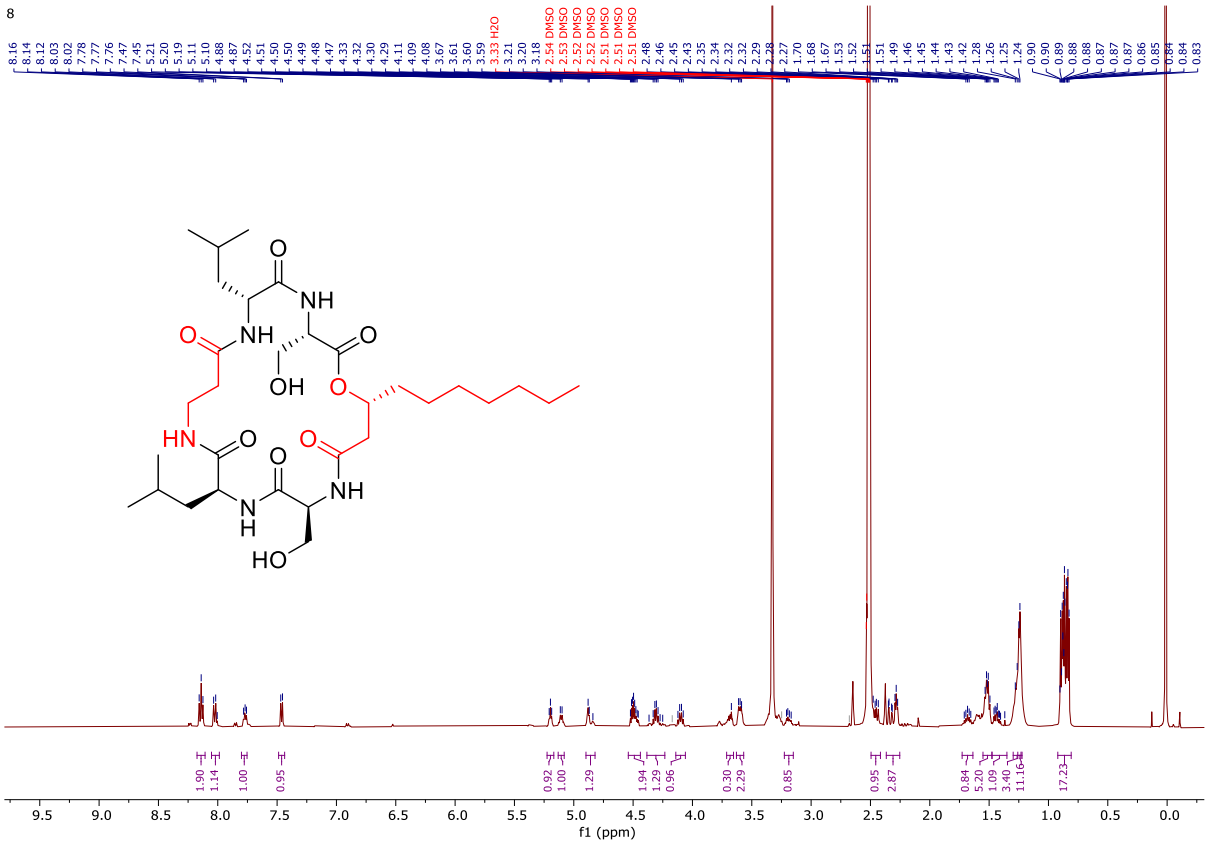
Supplementary Figure 20. ^{1}H NMR of **6** on 500 MHz at 298 K in Acetone-d_6.



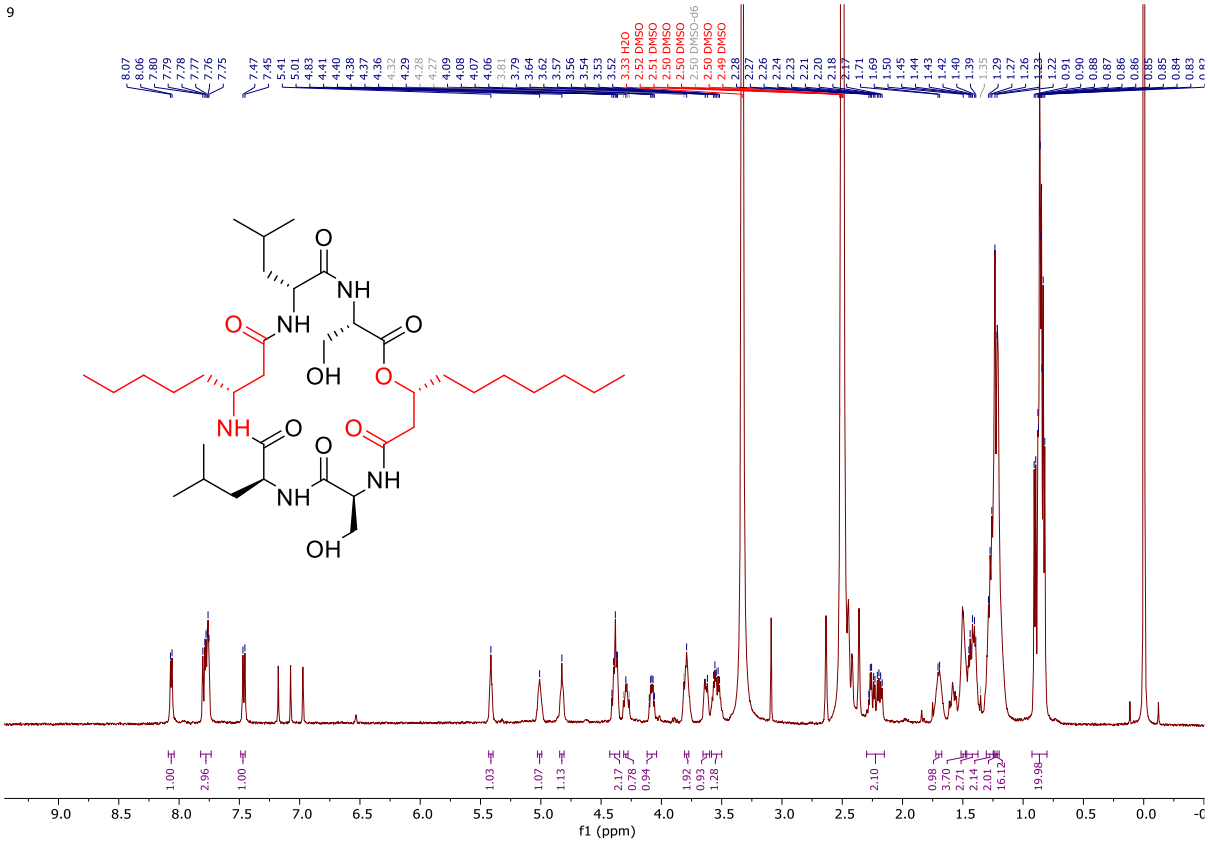
Supplementary Figure 21. ^{1}H NMR of **7** on 500 MHz at 298 K in Acetone-d_6.



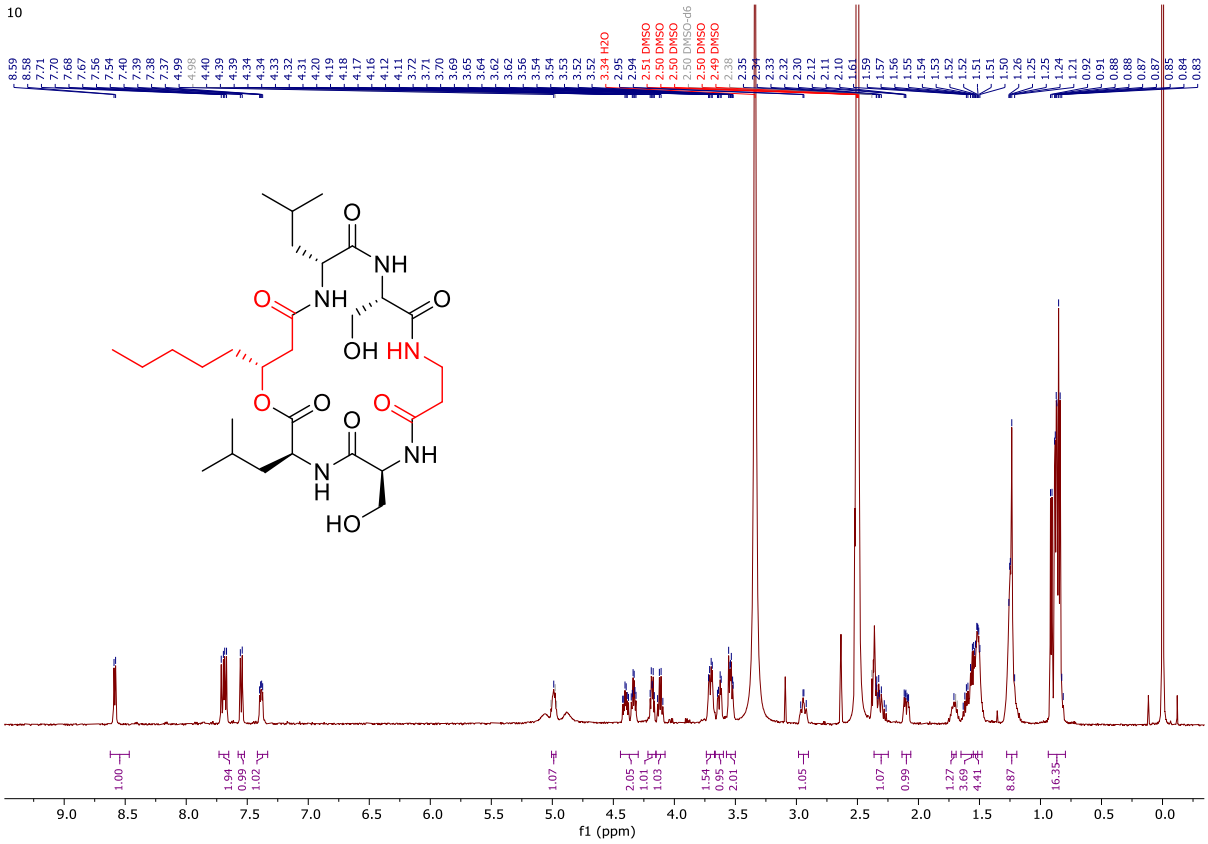
Supplementary Figure 22. ^{1}H NMR of **8** on 500 MHz at 298 K in DMSO-d_6.



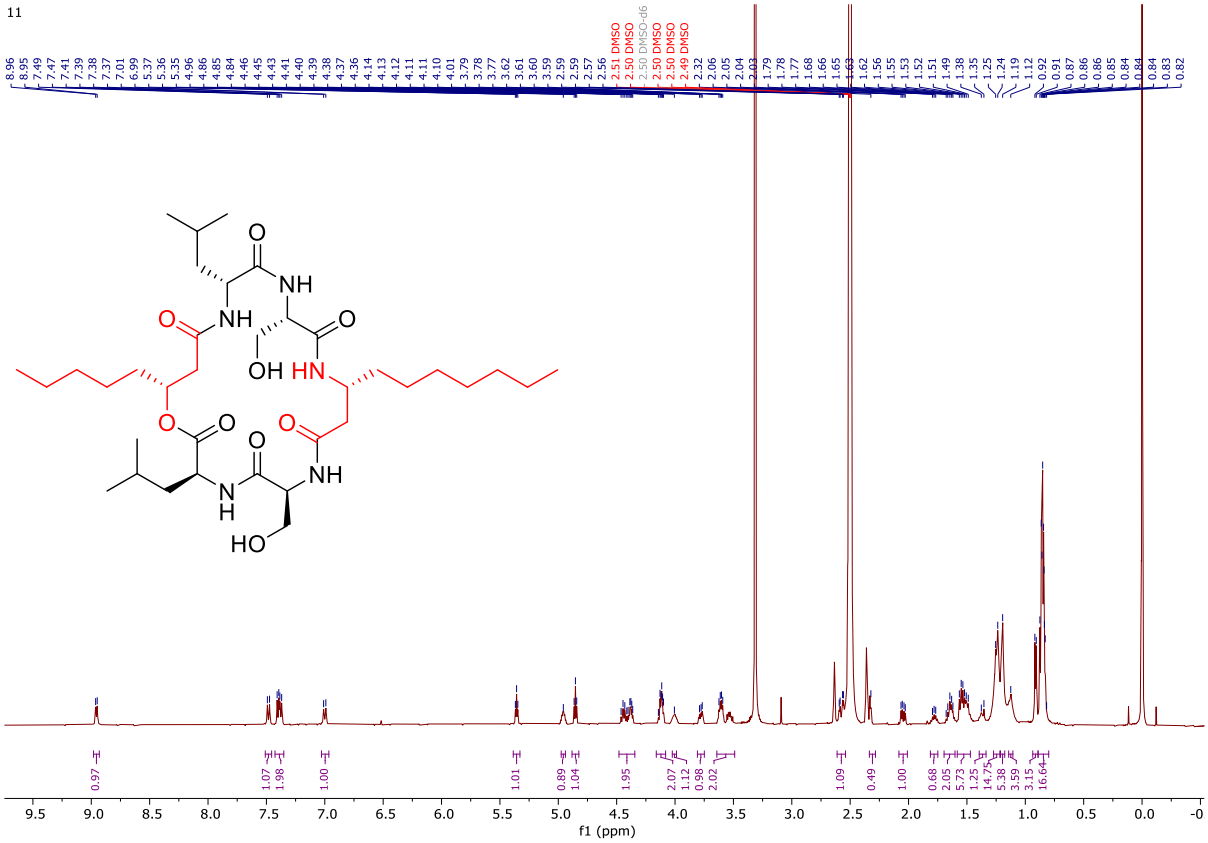
Supplementary Figure 23. ^{1}H NMR of **9** on 500 MHz at 298 K in DMSO-d_6.



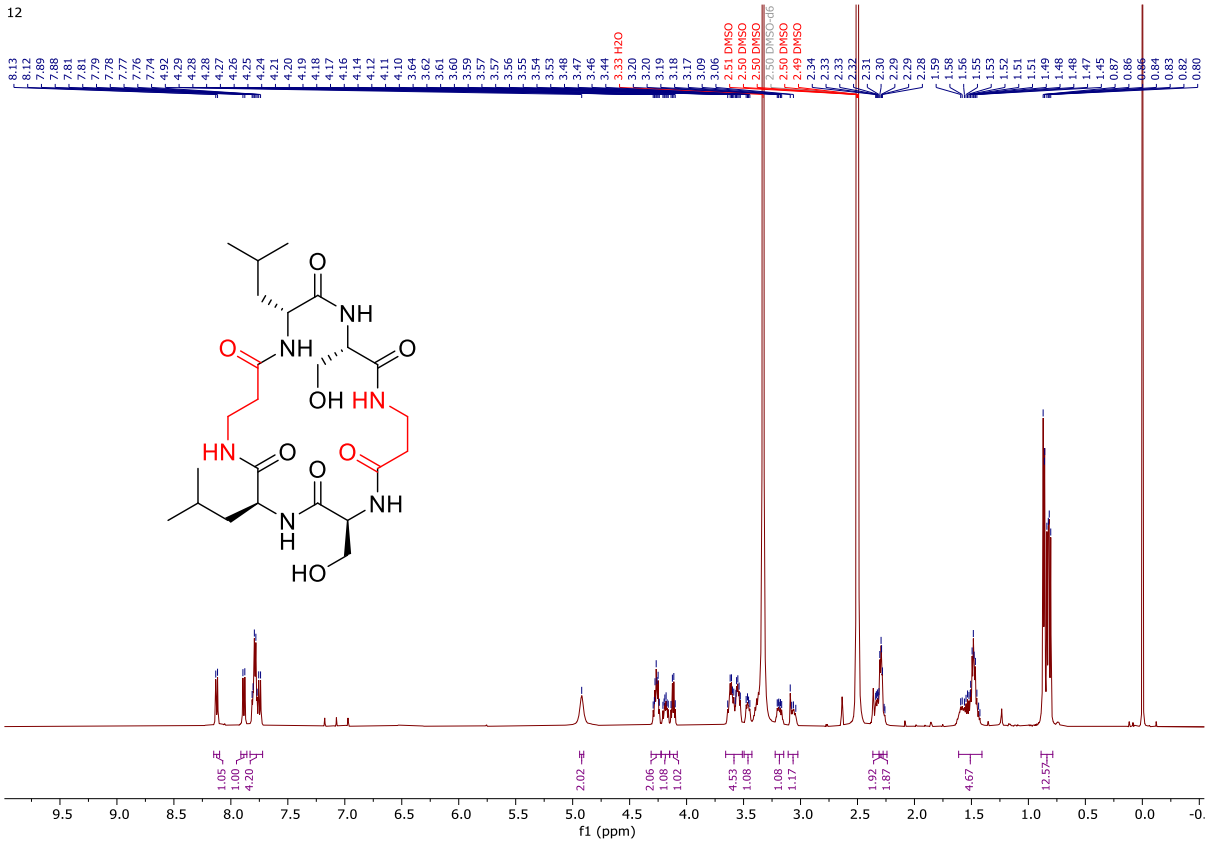
Supplementary Figure 24. ^{1}H NMR of **10** on 500 MHz at 298 K in DMSO-d_6.



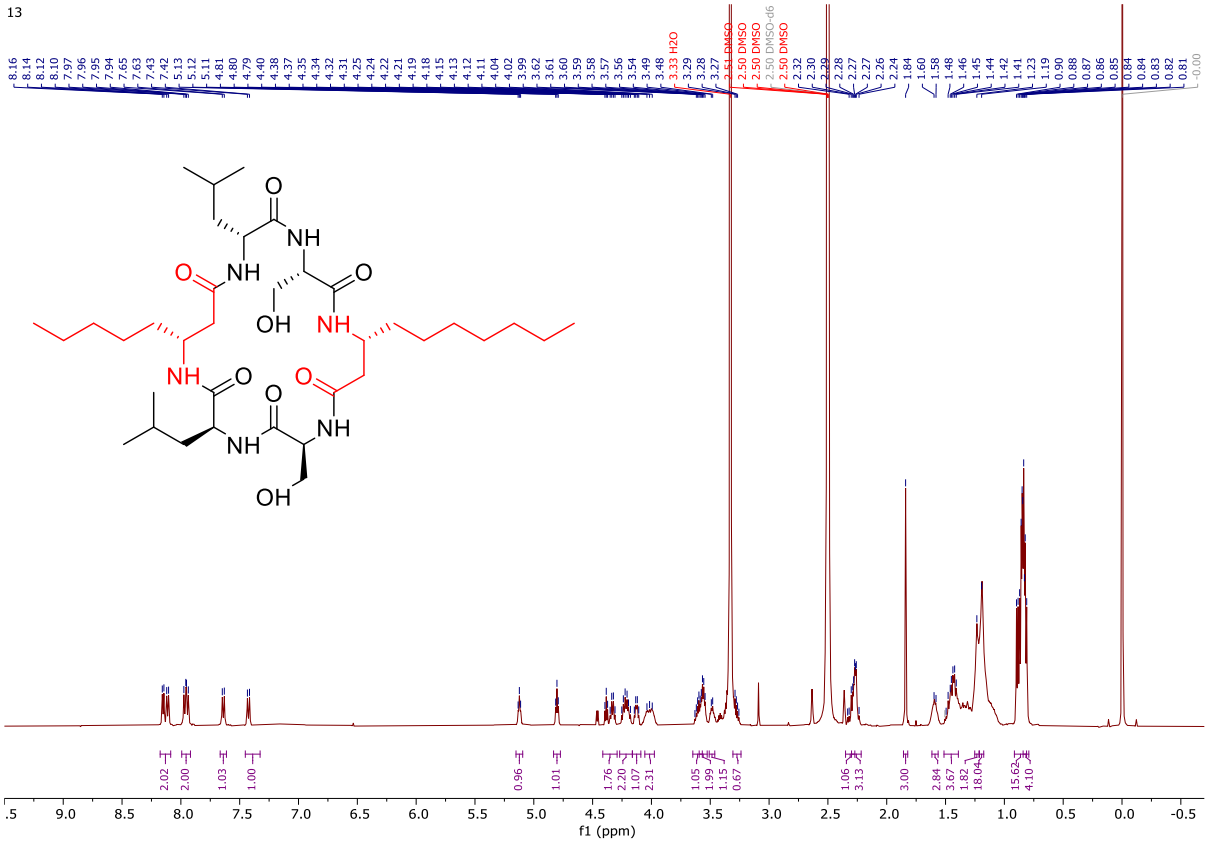
Supplementary Figure 25. ^{1}H NMR of **11** on 500 MHz at 298 K in DMSO-d_6.



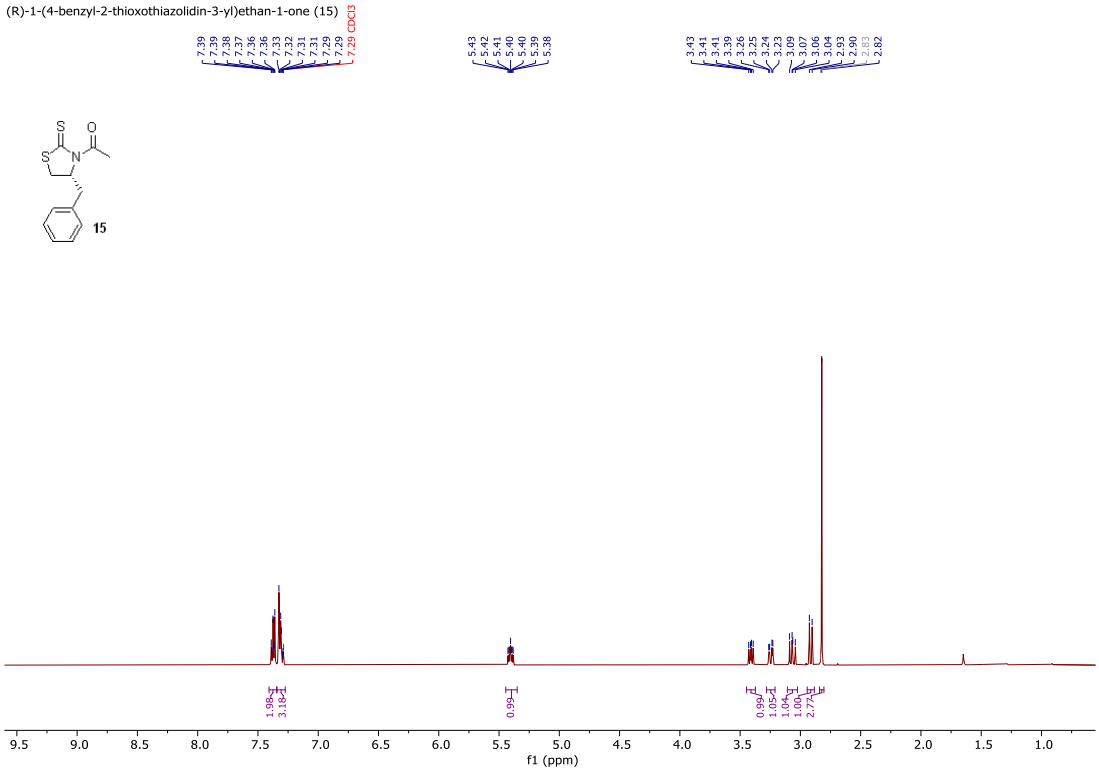
Supplementary Figure 26. ^{1}H NMR of **12** on 500 MHz at 298 K in DMSO-d_6.



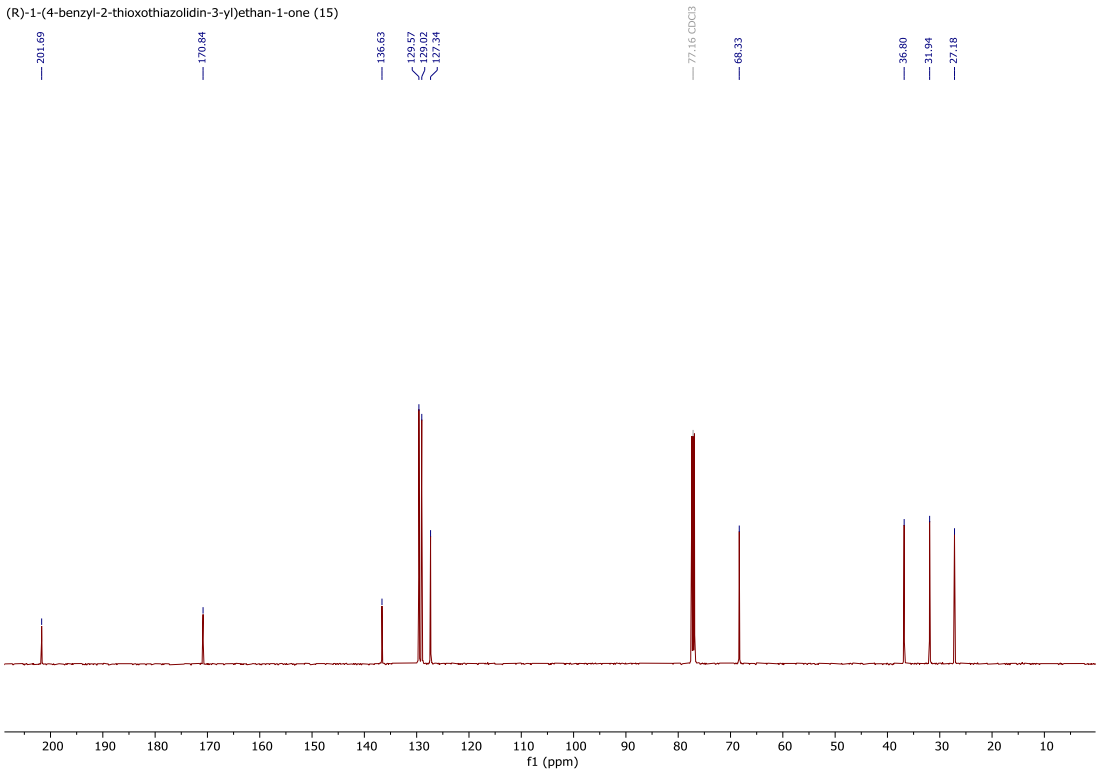
Supplementary Figure 27. ^{1}H NMR of **13** on 500 MHz at 298 K in DMSO-d_6.



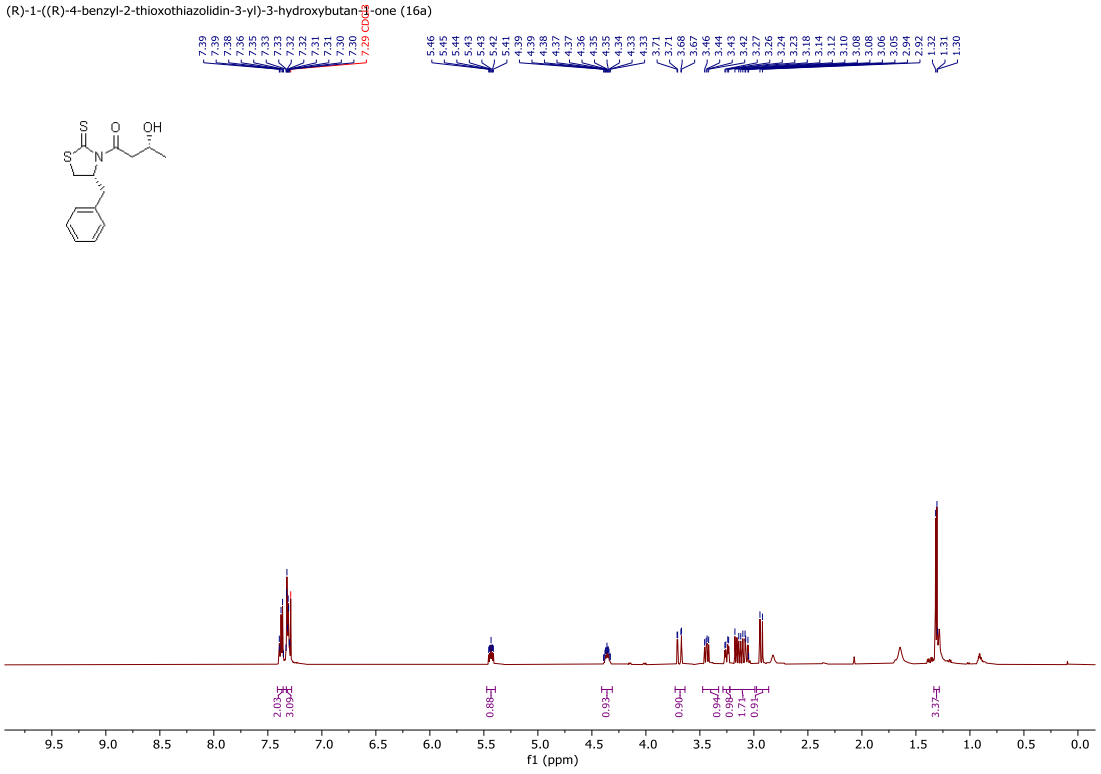
Supplementary Figure 28. ^{1}H NMR of ***R*-chiral auxillary (15)** on 500 MHz at 298 K in $CDCl_3$.



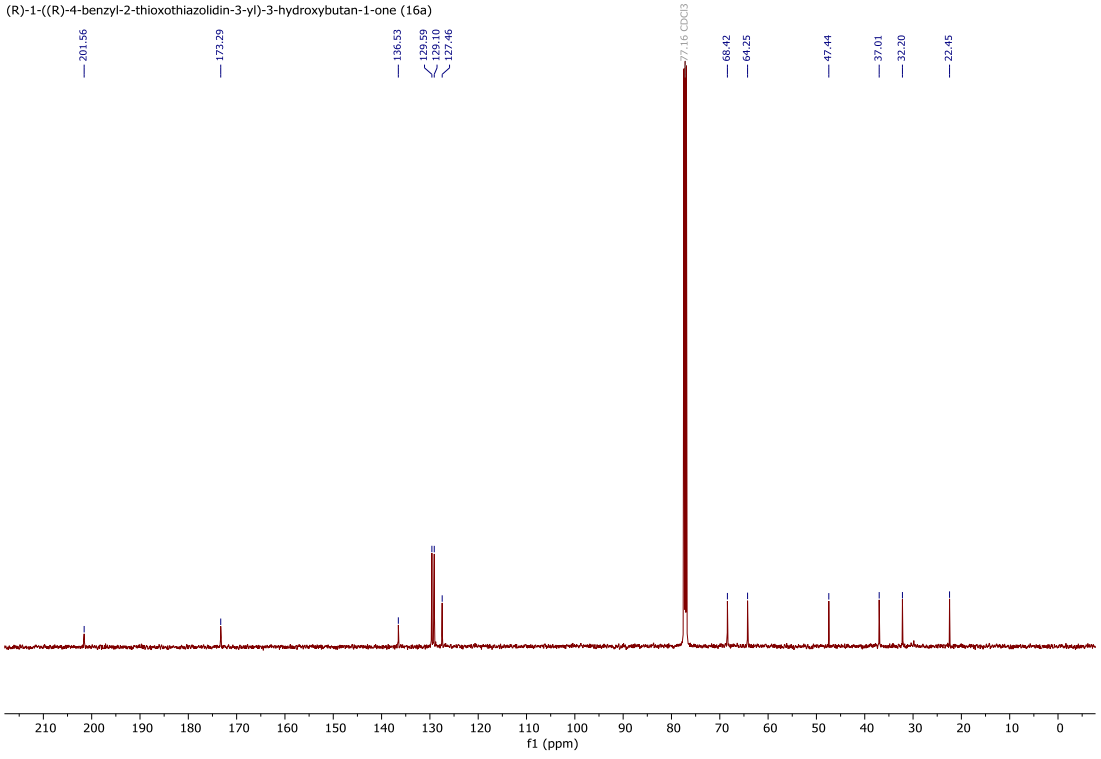
Supplementary Figure 29. ^{13}C NMR of ***R*-chiral auxillary (15)** on 125 MHz at 298 K in $CDCl_3$.



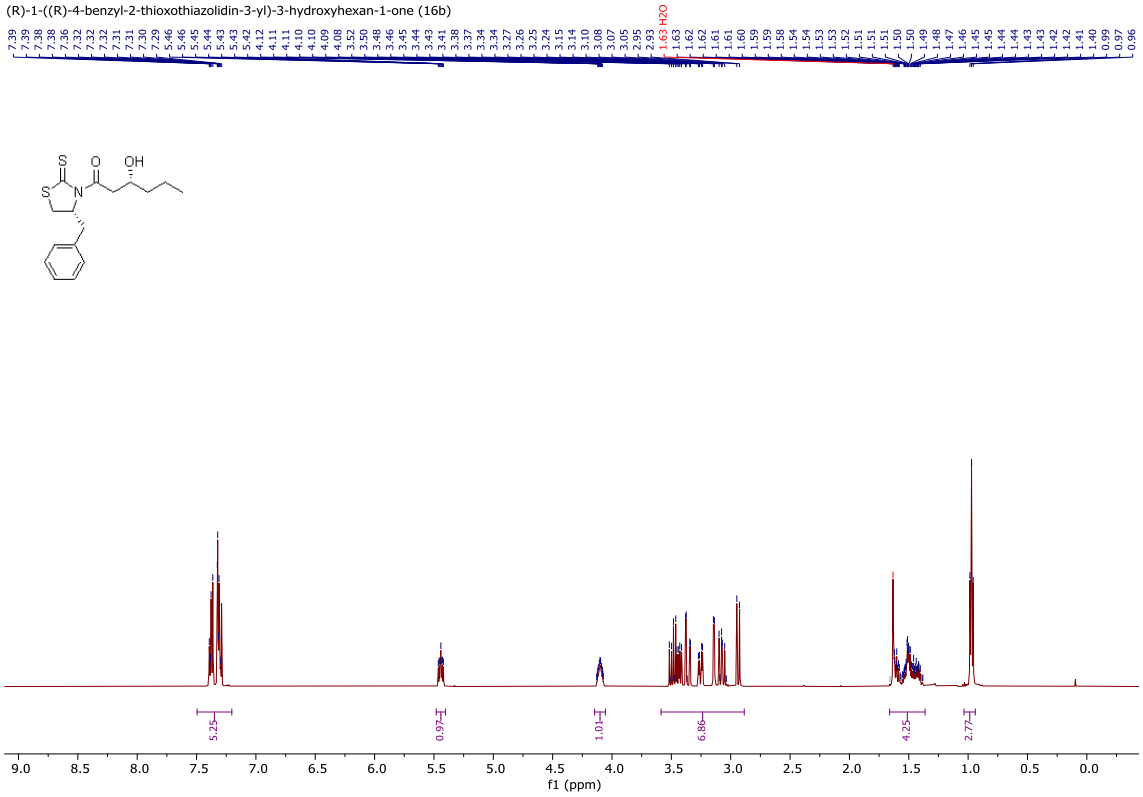
Supplementary Figure 30. ^{1}H NMR of **16a** on 500 MHz at 298 K in $CDCl_3$.



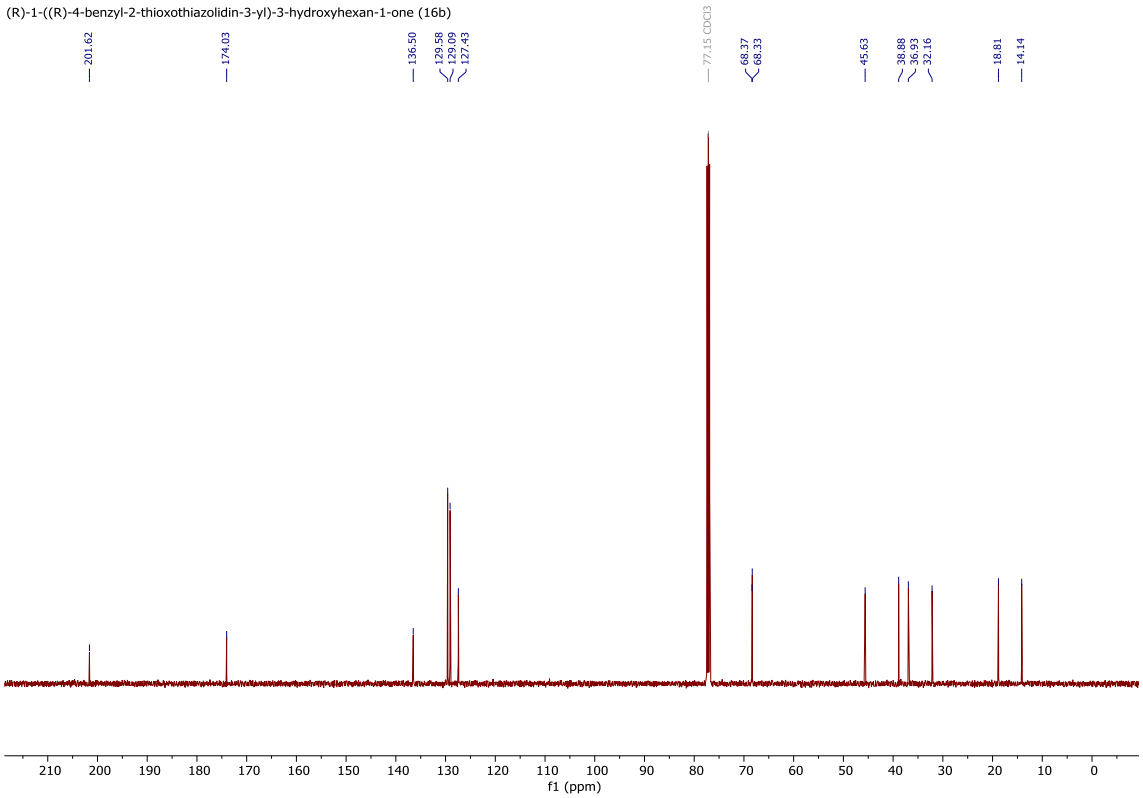
Supplementary Figure 31. ^{13}C NMR of **16a** on 125 MHz at 298 K in $CDCl_3$.



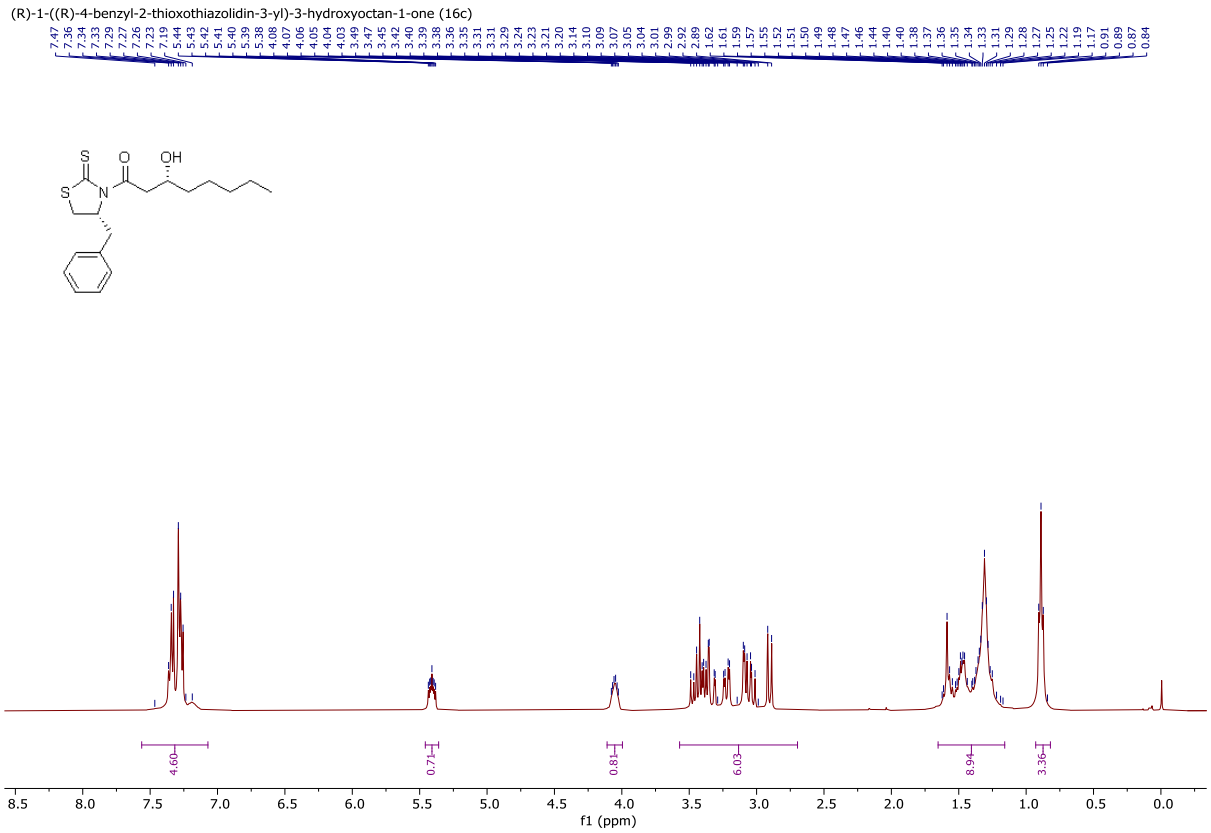
Supplementary Figure 32. ^{1}H NMR of **16b** on 500 MHz at 298 K in $CDCl_3$.



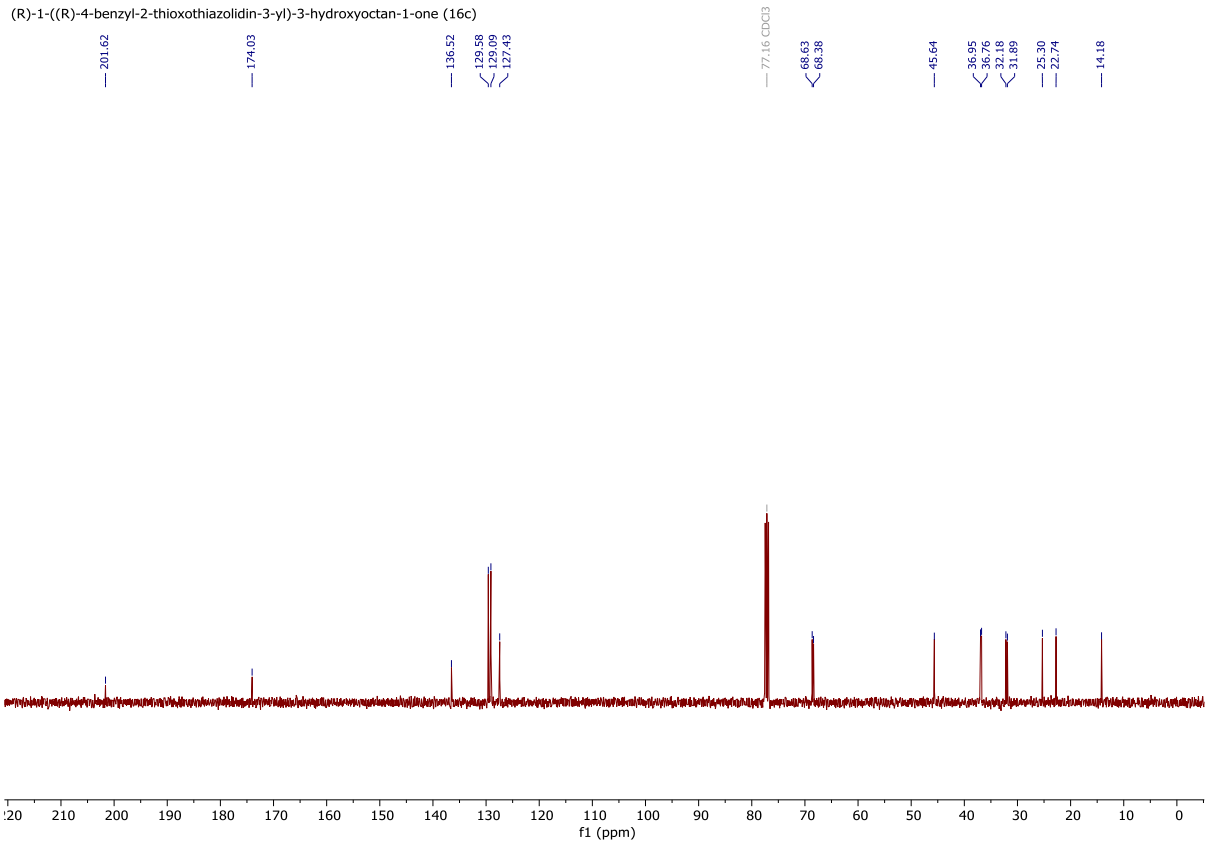
Supplementary Figure 33. ^{13}C NMR of **16b** on 125 MHz at 298 K in $CDCl_3$.



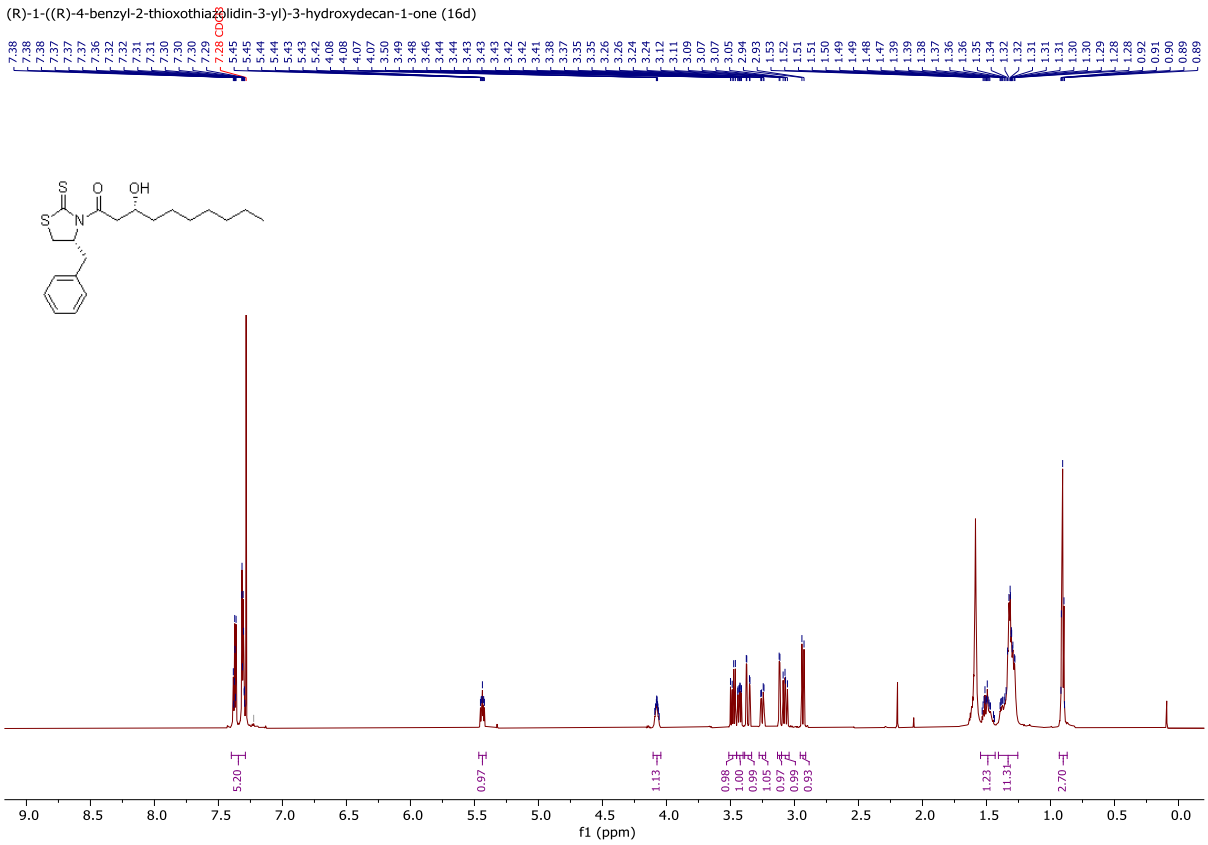
Supplementary Figure 34. ^{1}H NMR of **16c** on 400 MHz at 298 K in $CDCl_3$.



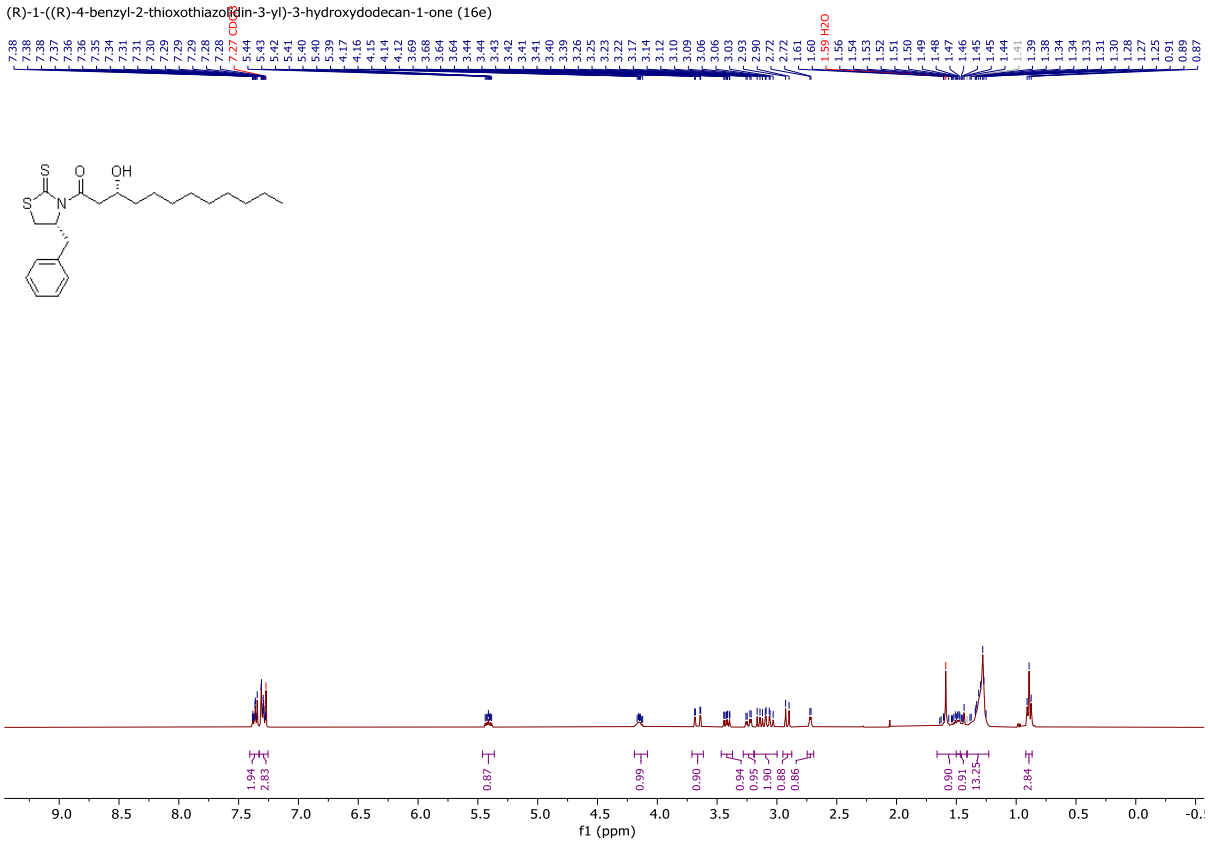
Supplementary Figure 35. ^{13}C NMR of **16c** on 100 MHz at 298 K in $CDCl_3$.



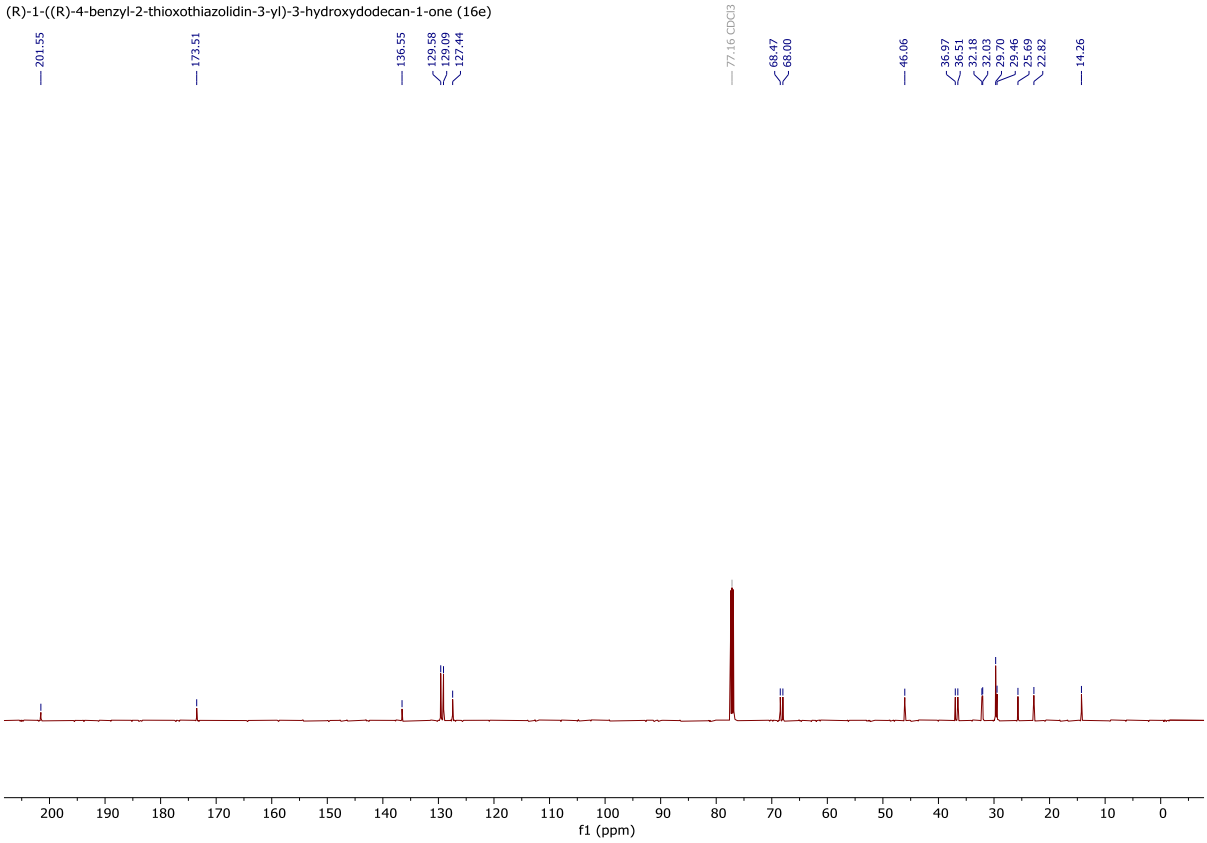
Supplementary Figure 36. ^{1}H NMR of **16d** on 400 MHz at 298 K in $CDCl_3$.



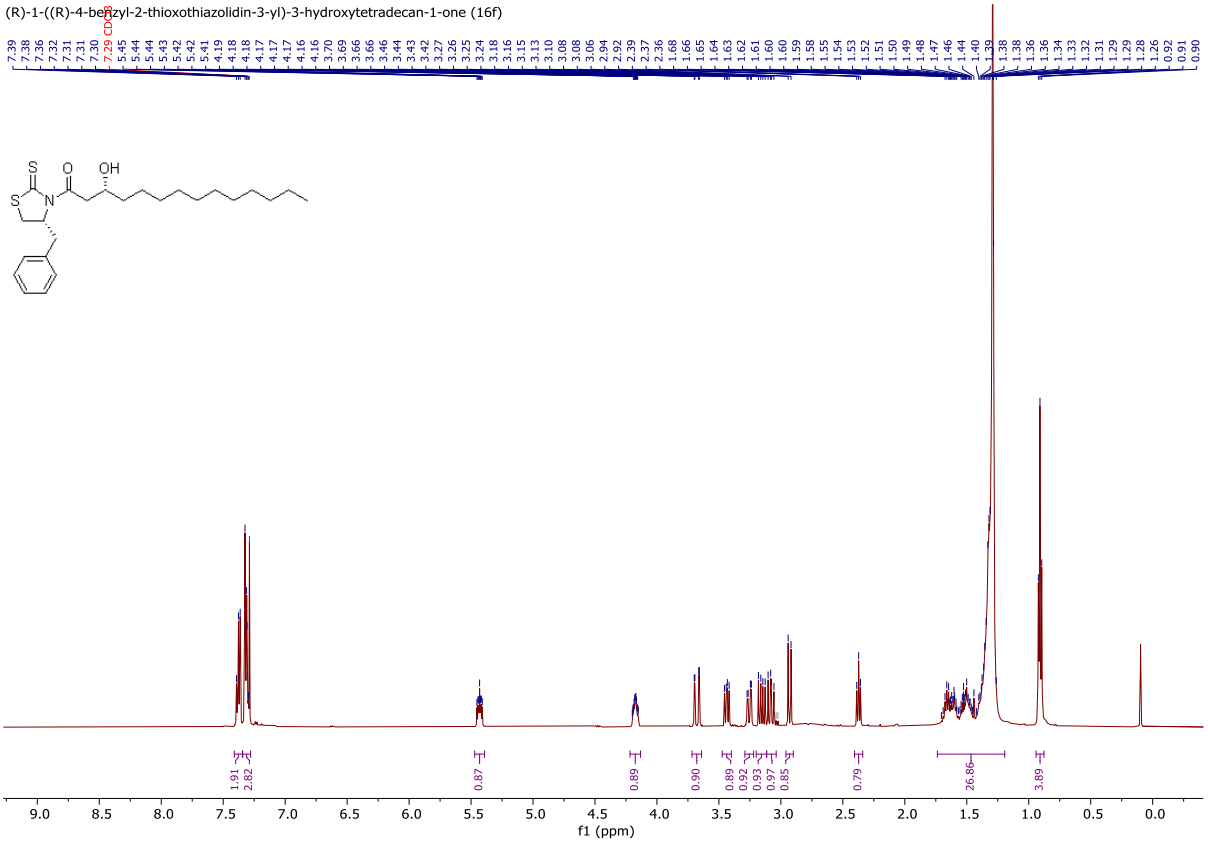
Supplementary Figure 37. ^{1}H NMR of **16e** on 400 MHz at 298 K in $CDCl_3$



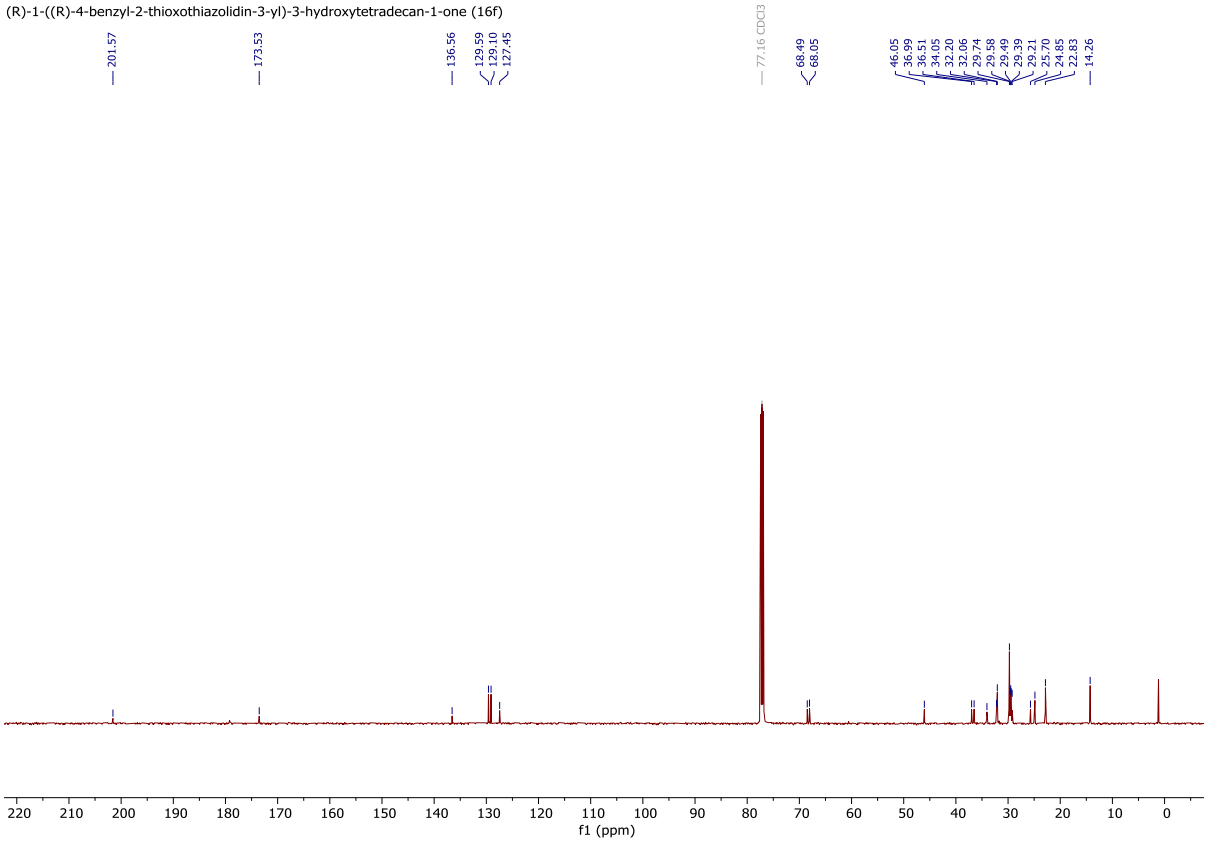
Supplementary Figure 38. ^{13}C NMR of **16e** on 100 MHz at 298 K in $CDCl_3$



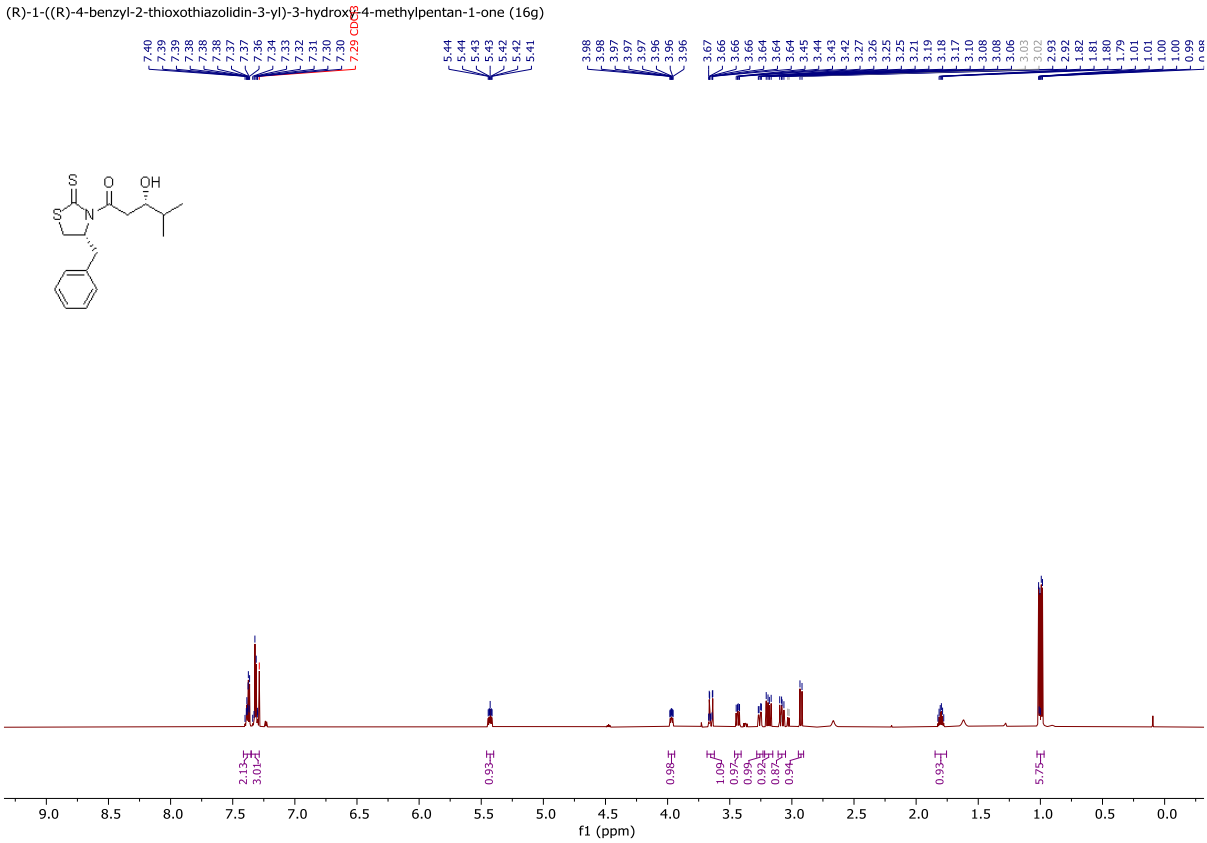
Supplementary Figure 39. ^{1}H NMR of **16f** on 500 MHz at 298 K in $CDCl_3$.



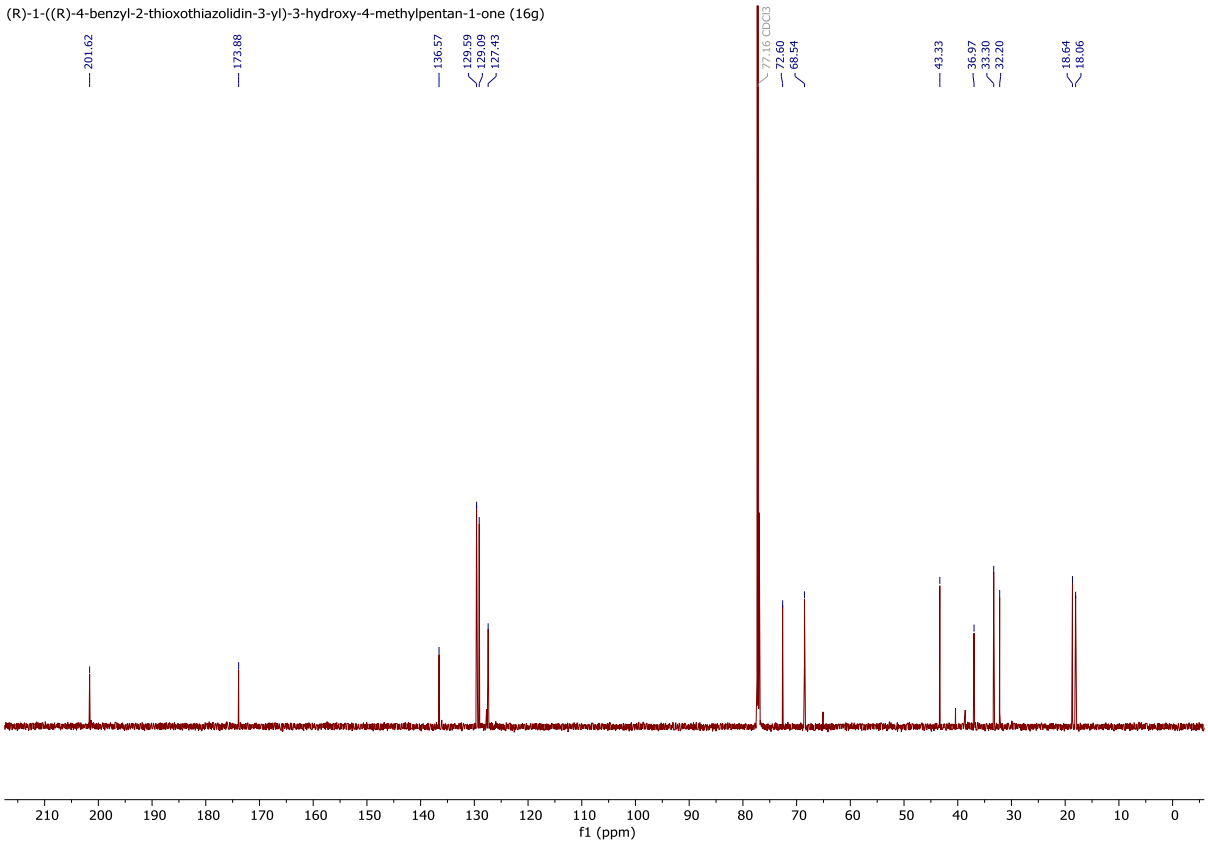
Supplementary Figure 40. ^{13}C NMR of **16f** on 125 MHz at 298 K in $CDCl_3$.



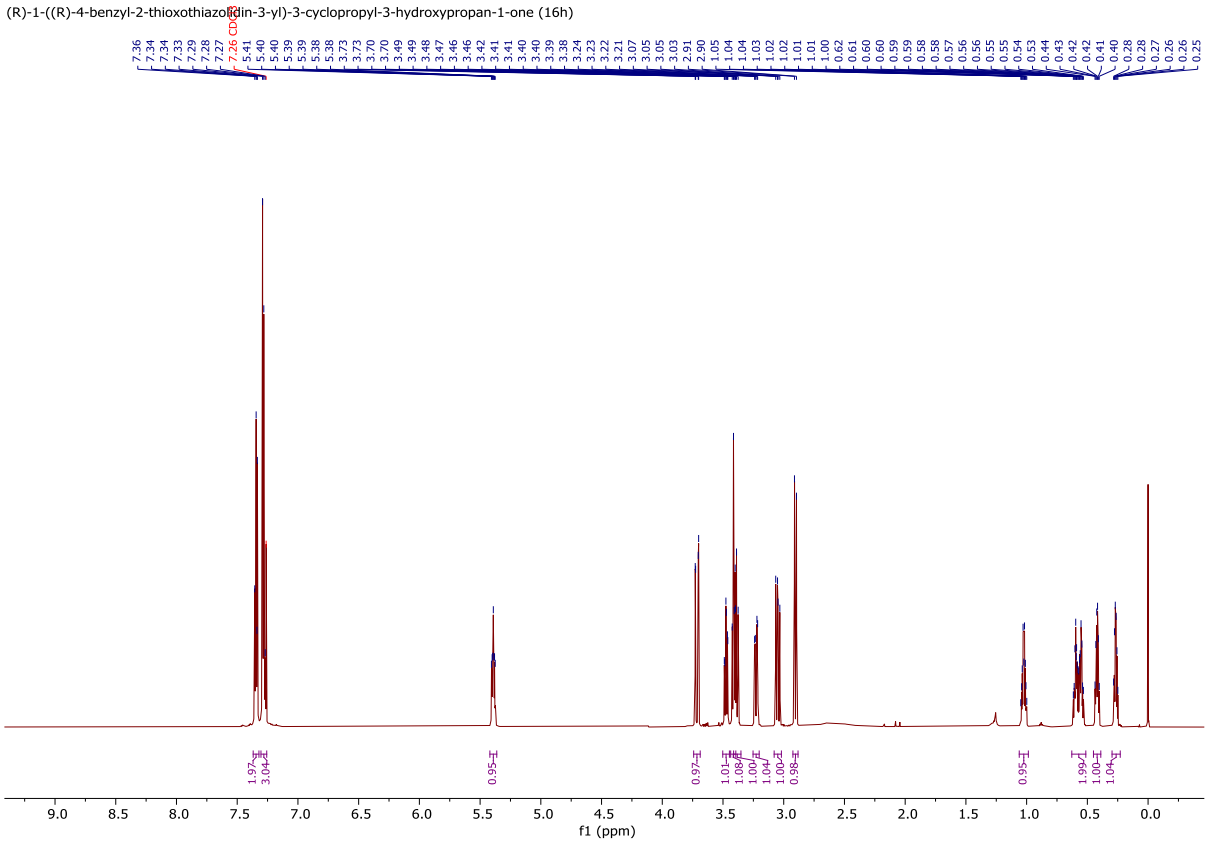
Supplementary Figure 41. ^{1}H NMR of **16g** on 700 MHz at 298 K in $CDCl_3$.



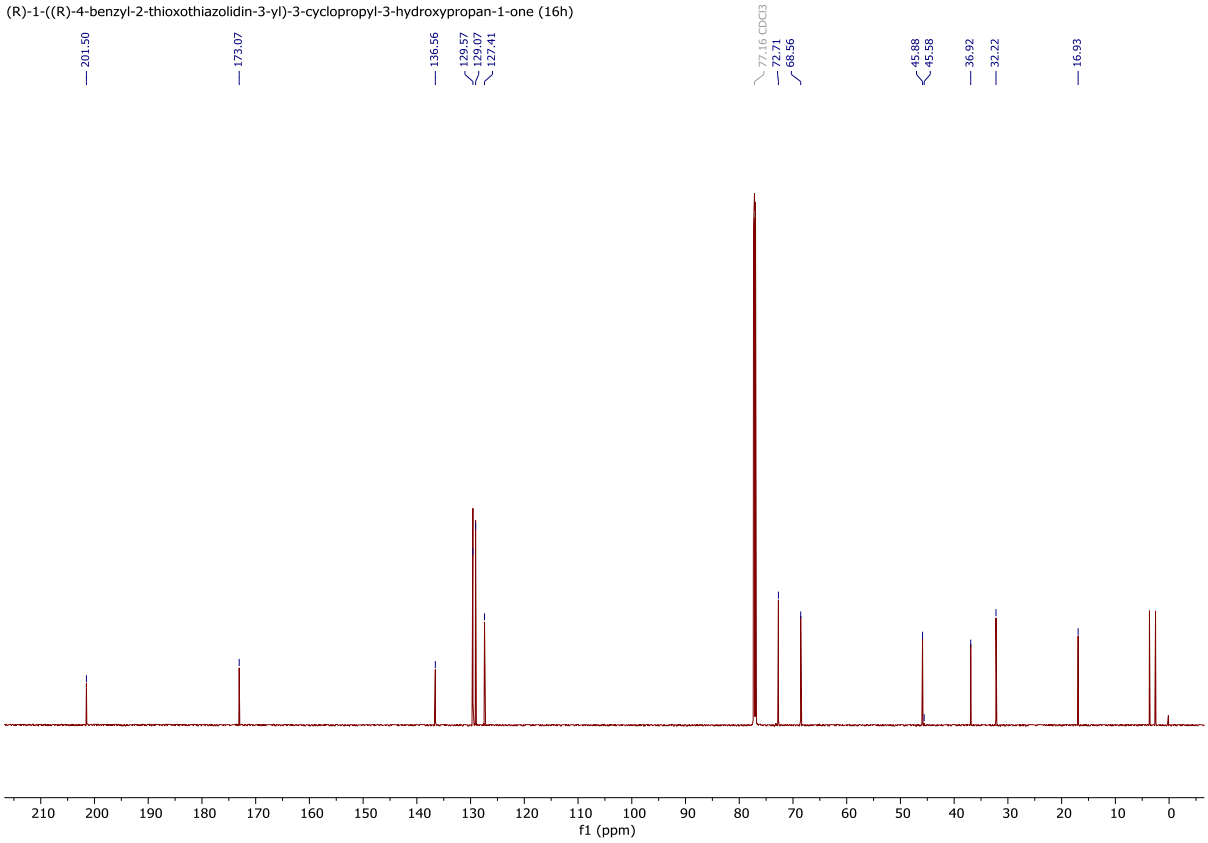
Supplementary Figure 42. ^{13}C NMR of **16g** on 175 MHz at 298 K in $CDCl_3$.



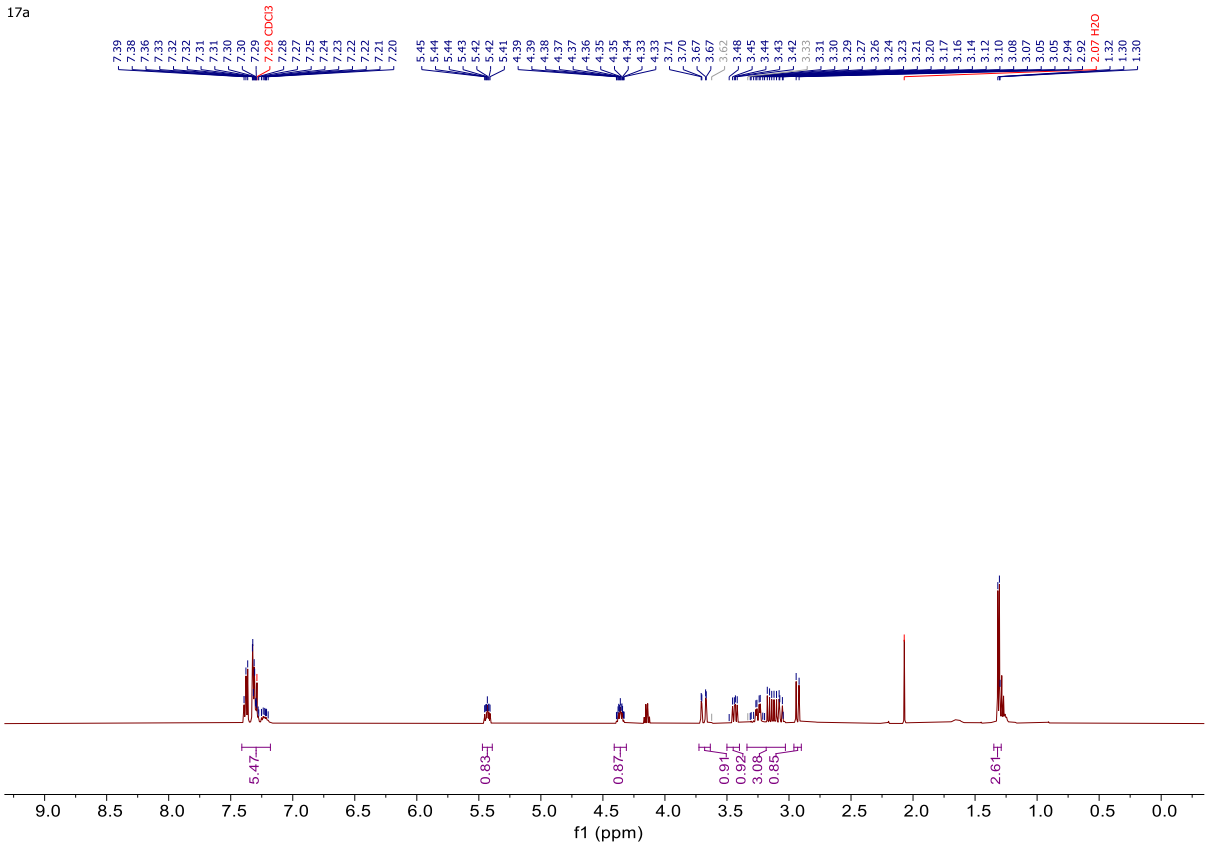
Supplementary Figure 43. ^{1}H NMR of **16h** on 700 MHz at 298 K in $CDCl_3$.



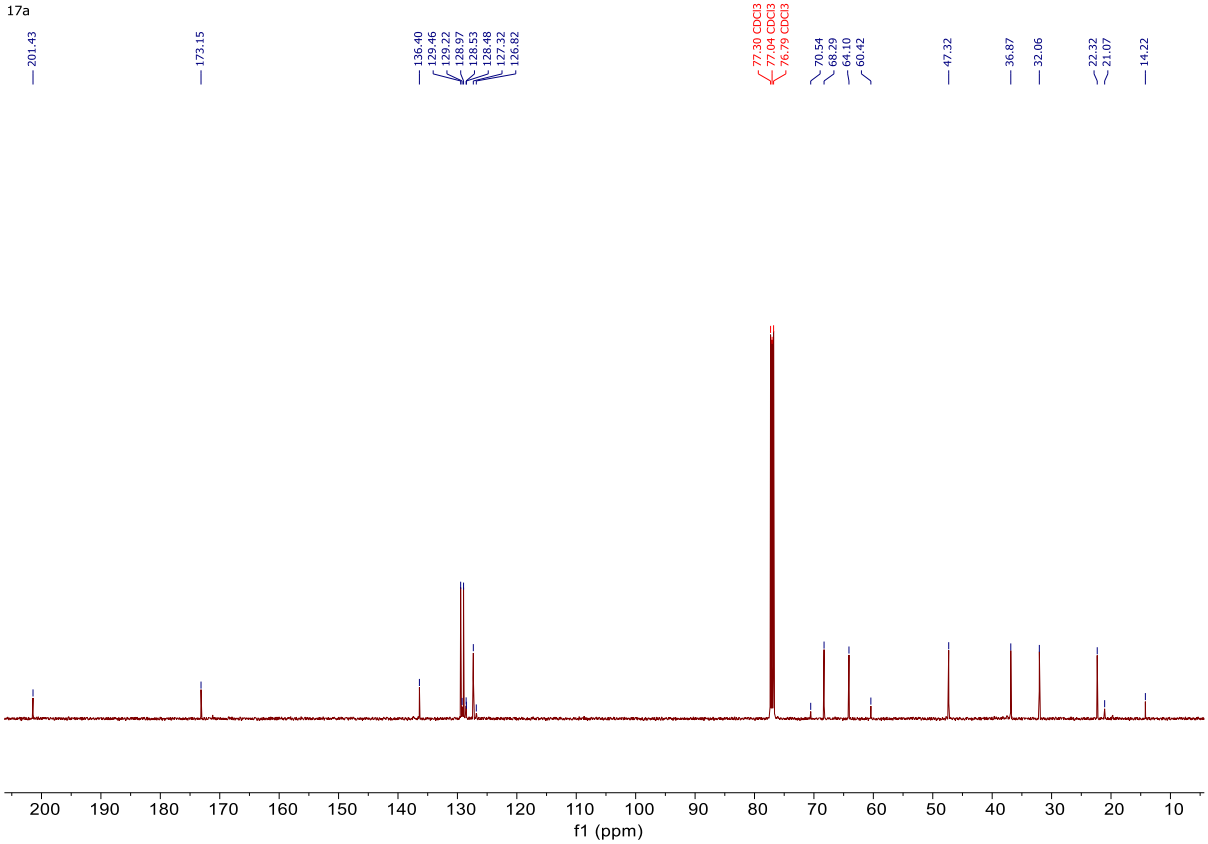
Supplementary Figure 44. ^{13}C NMR of **16h** on 175 MHz at 298 K in $CDCl_3$.



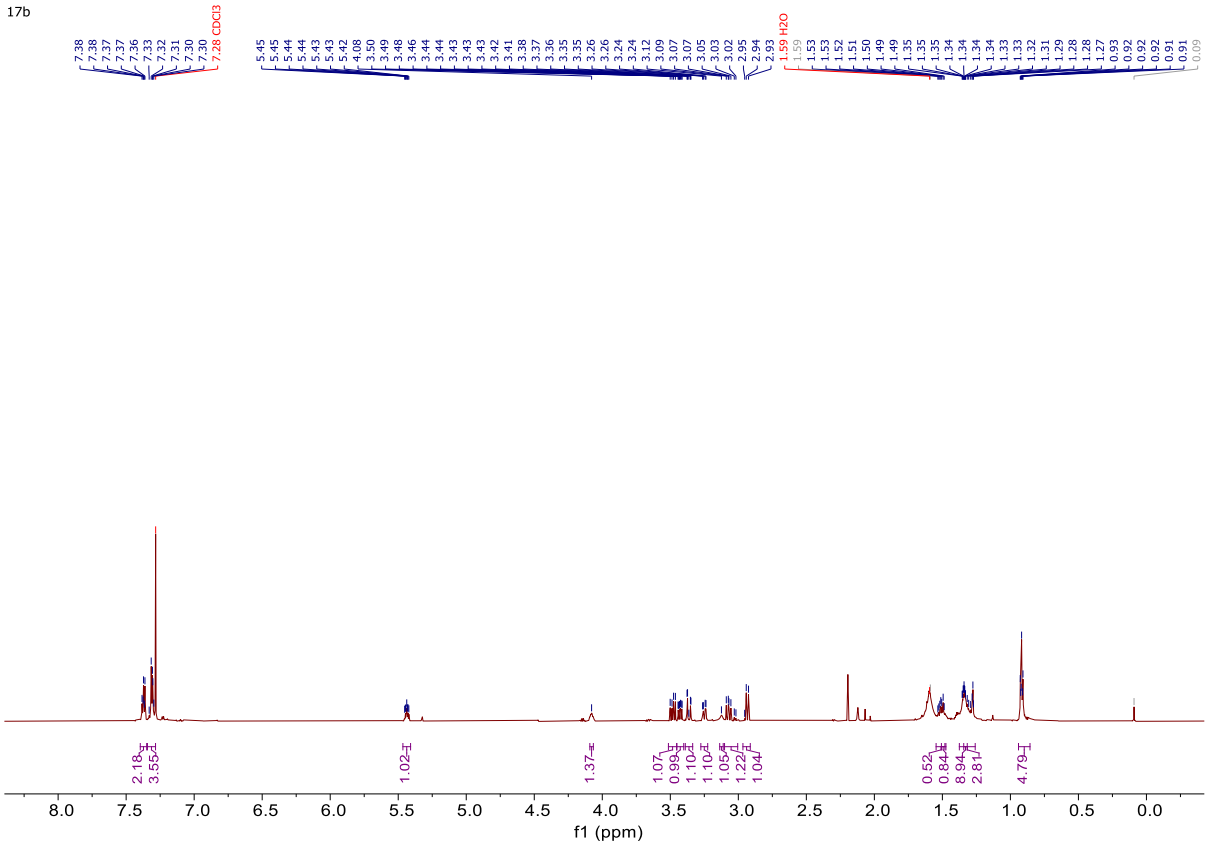
Supplementary Figure 45. ^{1}H NMR of **17a** on 500 MHz at 298 K in $CDCl_3$.



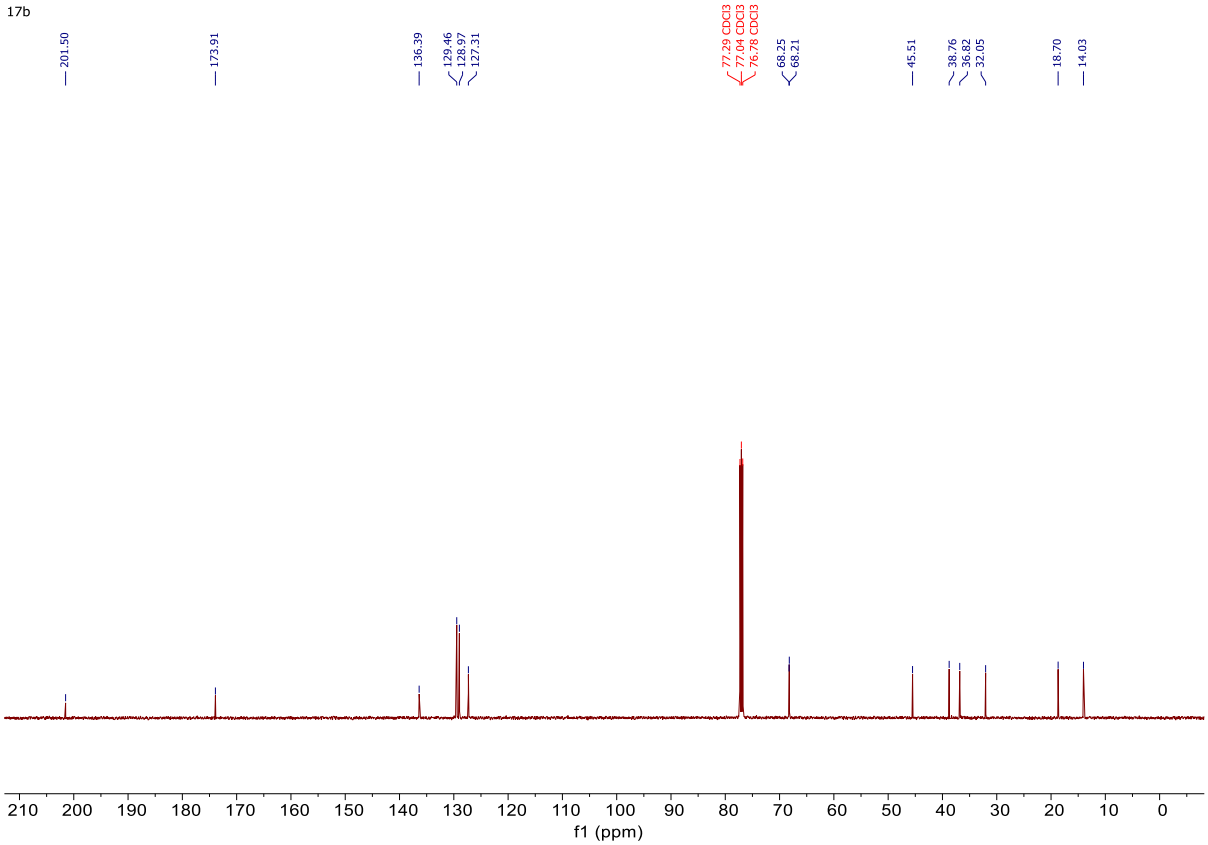
Supplementary Figure 46. ^{13}C NMR of **17a** on 500 MHz at 298 K in $CDCl_3$.



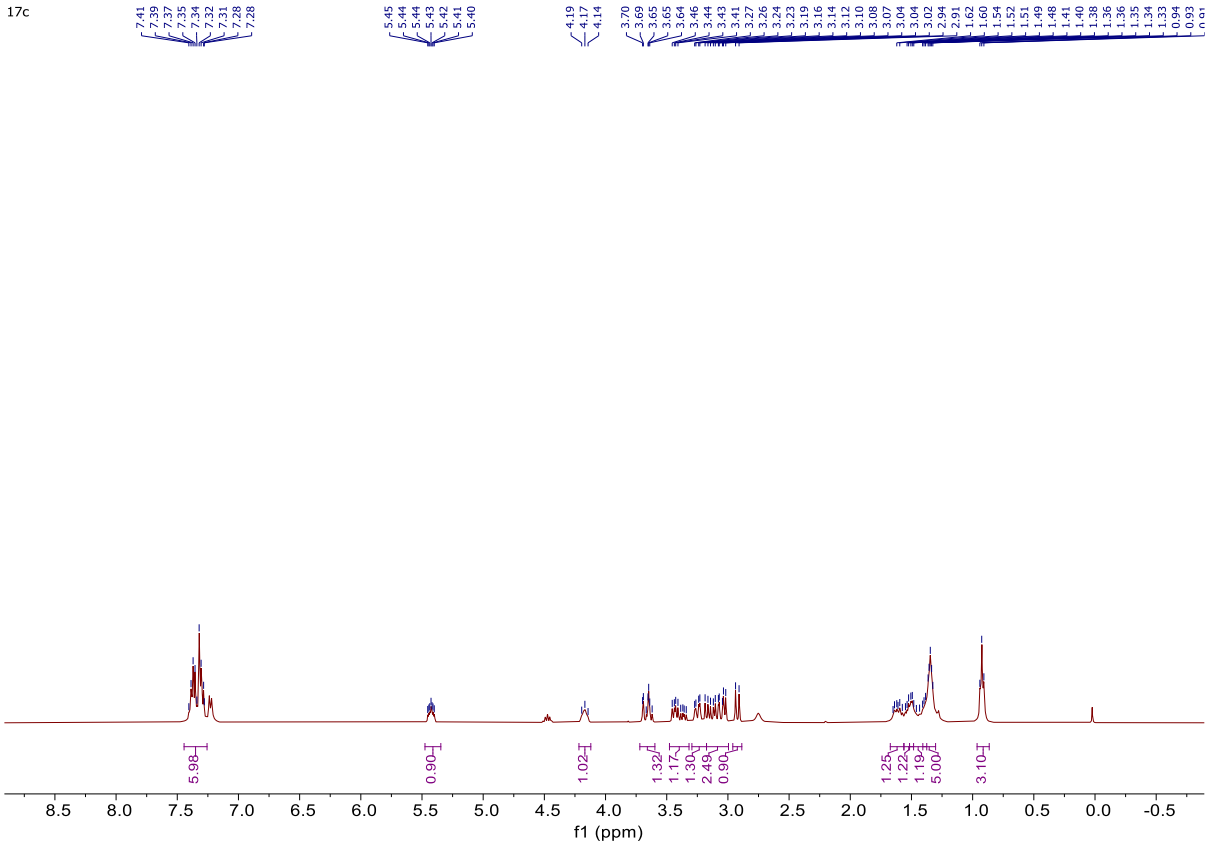
Supplementary Figure 47. ^{1}H NMR of **17b** on 500 MHz at 298 K in $CDCl_3$.



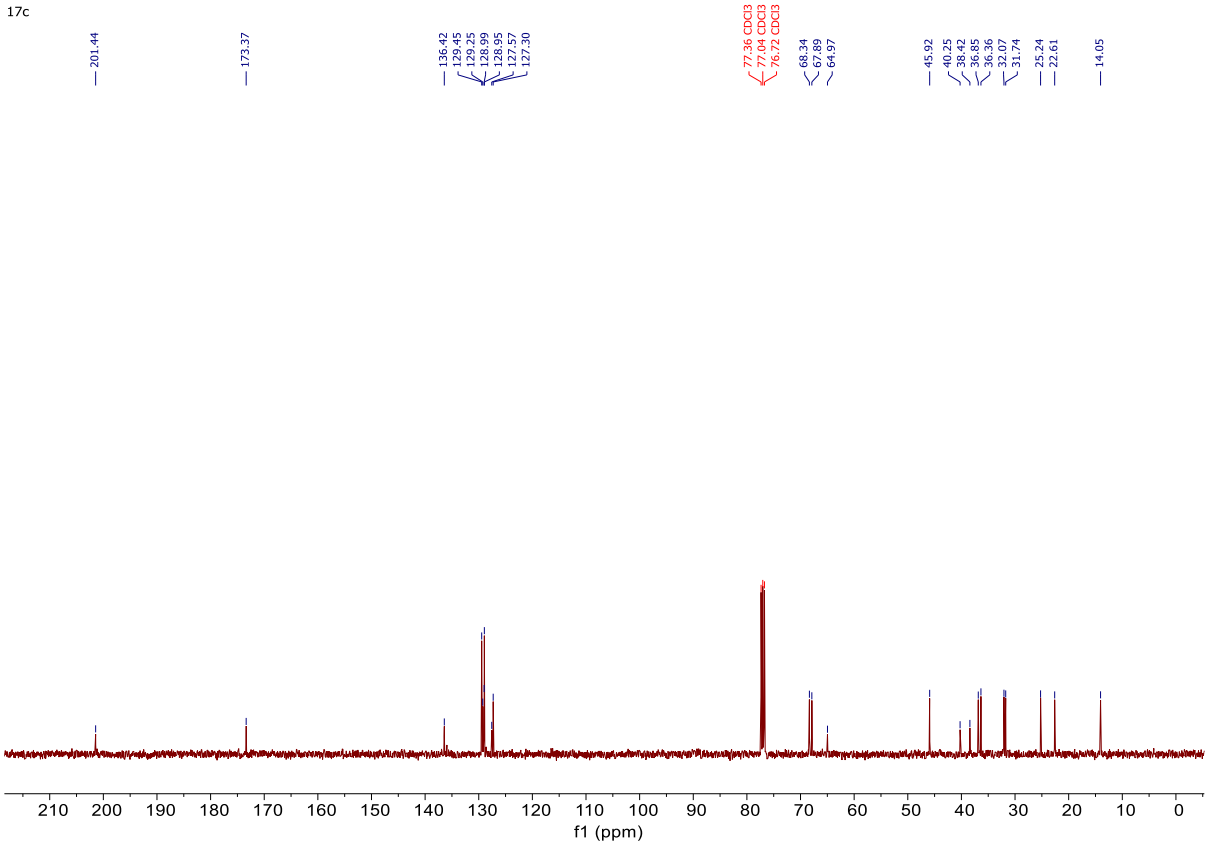
Supplementary Figure 48. ^{13}C NMR of **17b** on 500 MHz at 298 K in $CDCl_3$.



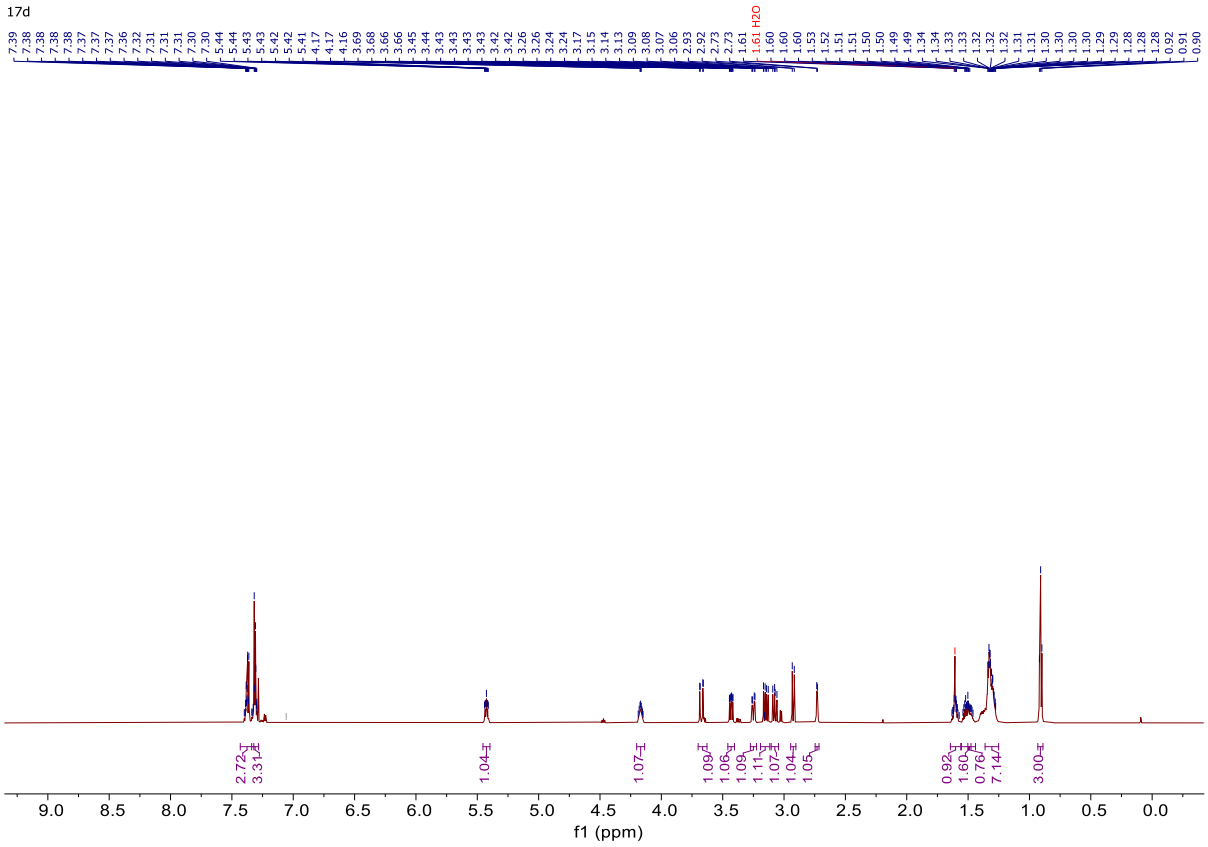
Supplementary Figure 49. ^{1}H NMR of **17c** on 500 MHz at 298 K in $CDCl_3$.



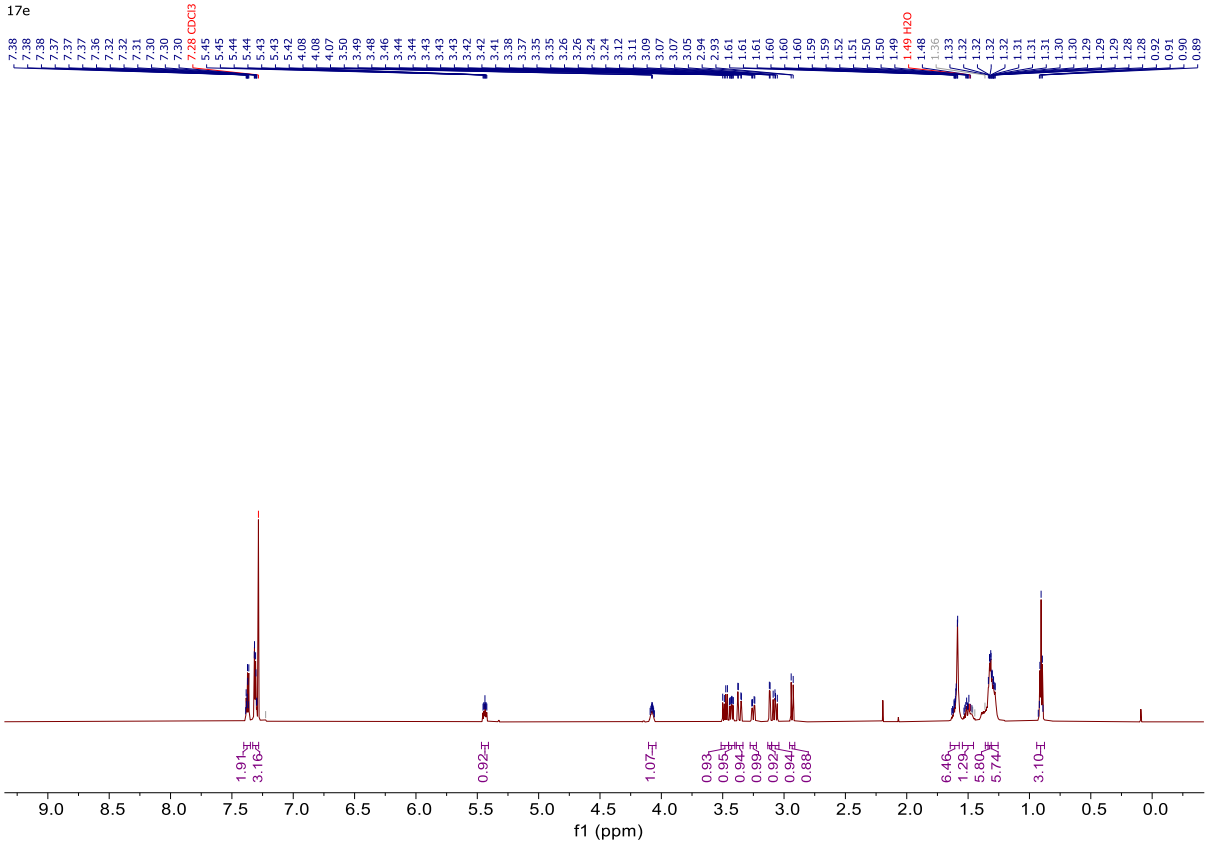
Supplementary Figure 50. ^{13}C NMR of **17c** on 500 MHz at 298 K in $CDCl_3$.



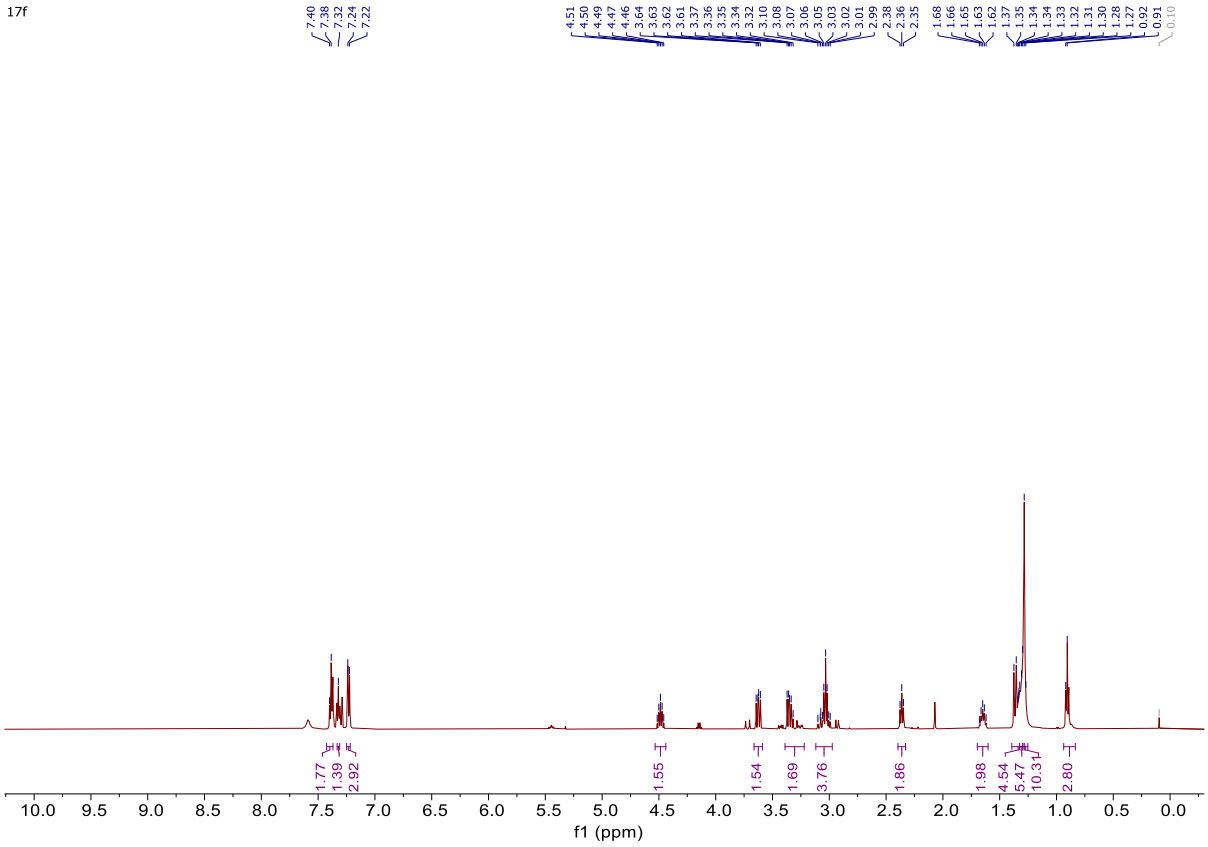
Supplementary Figure 51. ^{1}H NMR of **17d** on 500 MHz at 298 K in $CDCl_3$.



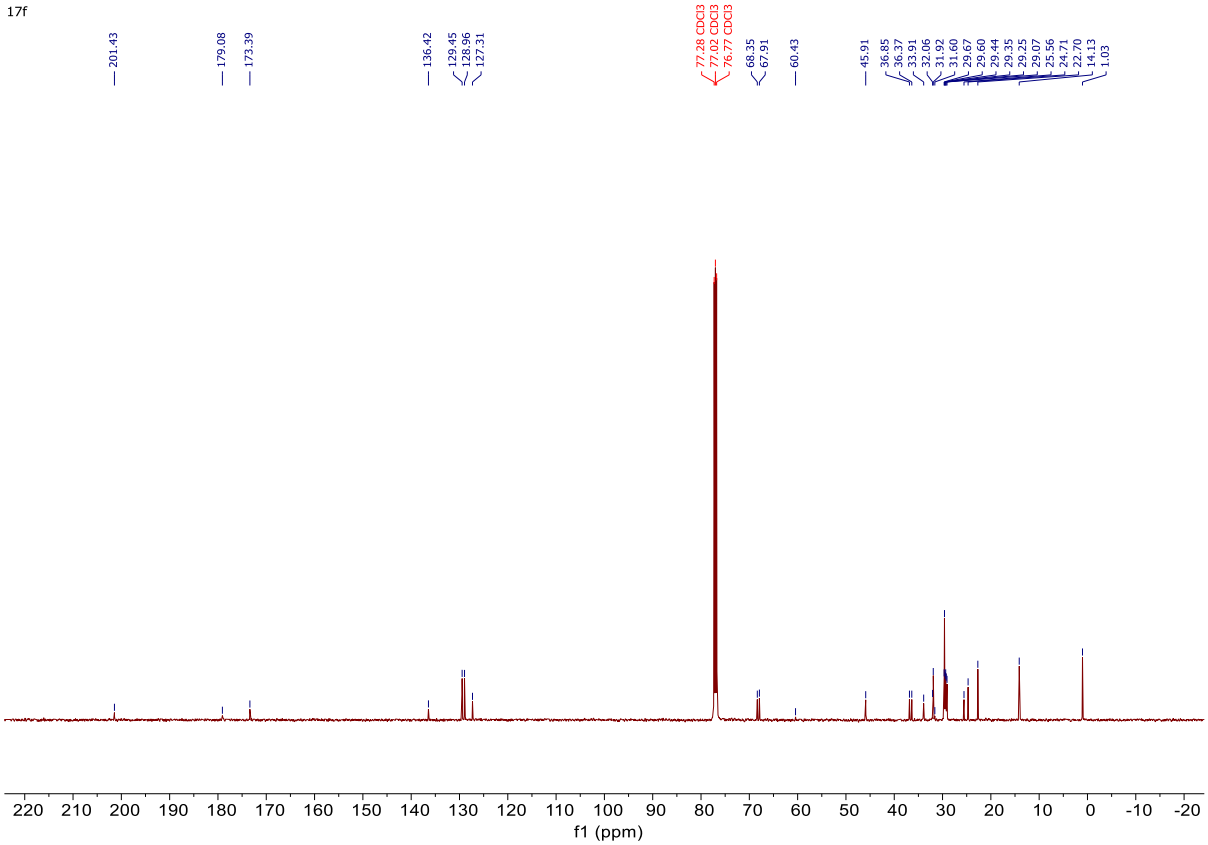
Supplementary Figure 52. ^{1}H NMR of **17e** on 500 MHz at 298 K in $CDCl_3$.



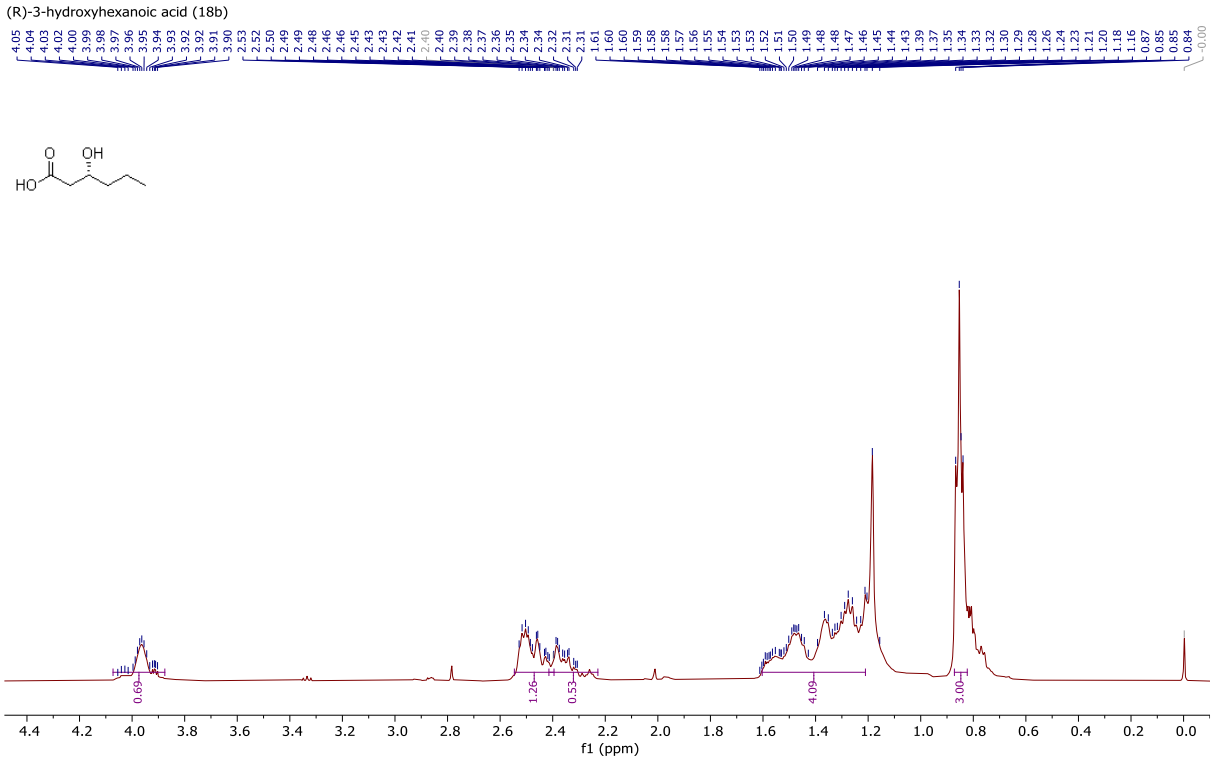
Supplementary Figure 53. ^{1}H NMR of **17f** on 500 MHz at 298 K in $CDCl_3$.



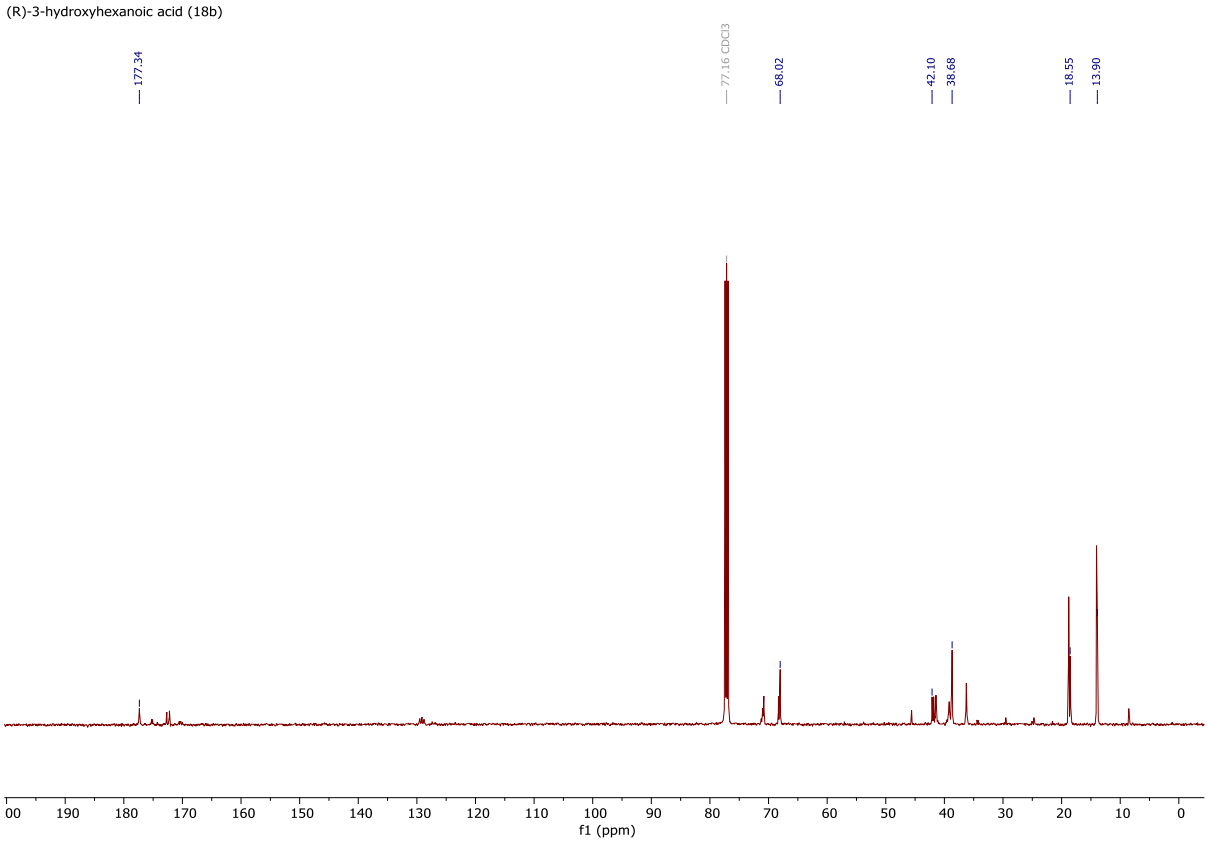
Supplementary Figure 54. ^{13}C NMR of **17f** on 125 MHz at 298 K in $CDCl_3$.



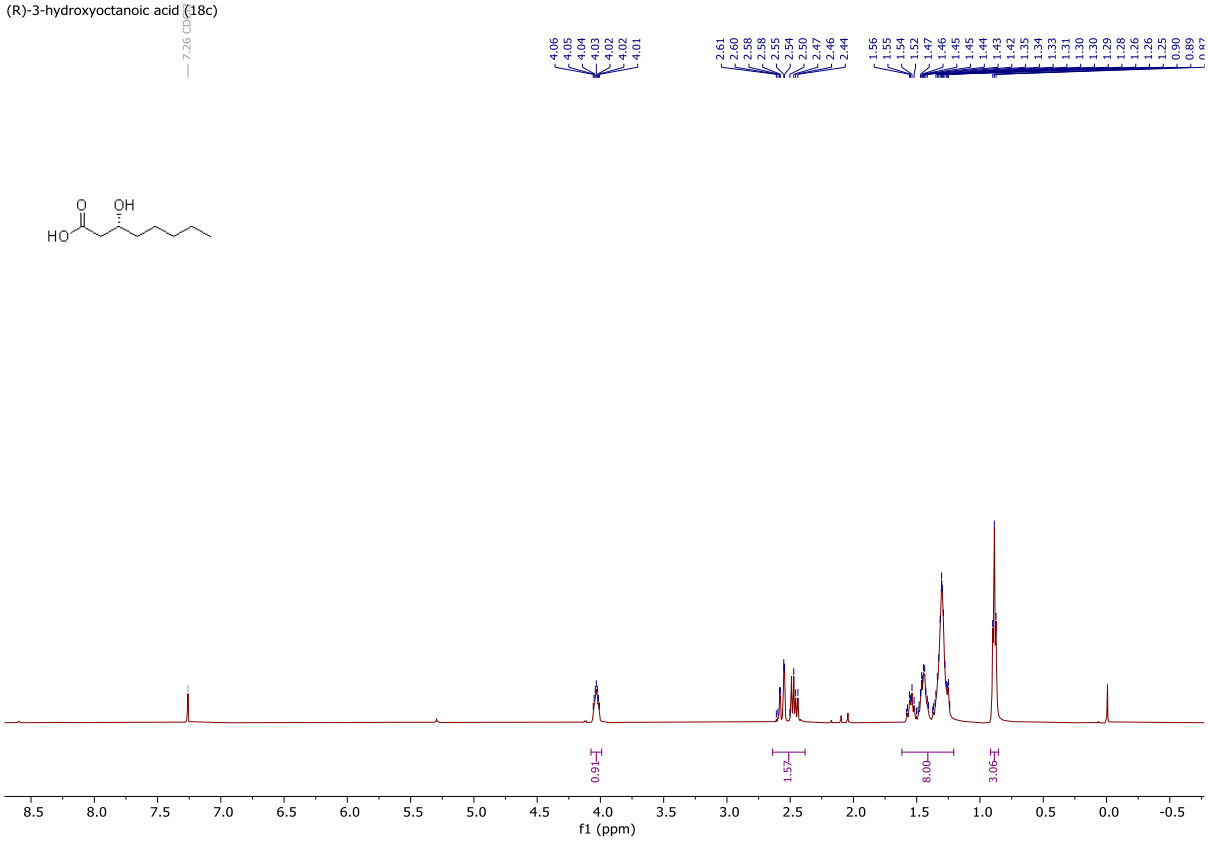
Supplementary Figure 55. ^{1}H NMR of **18b** on 500 MHz at 298 K in $CDCl_3$.



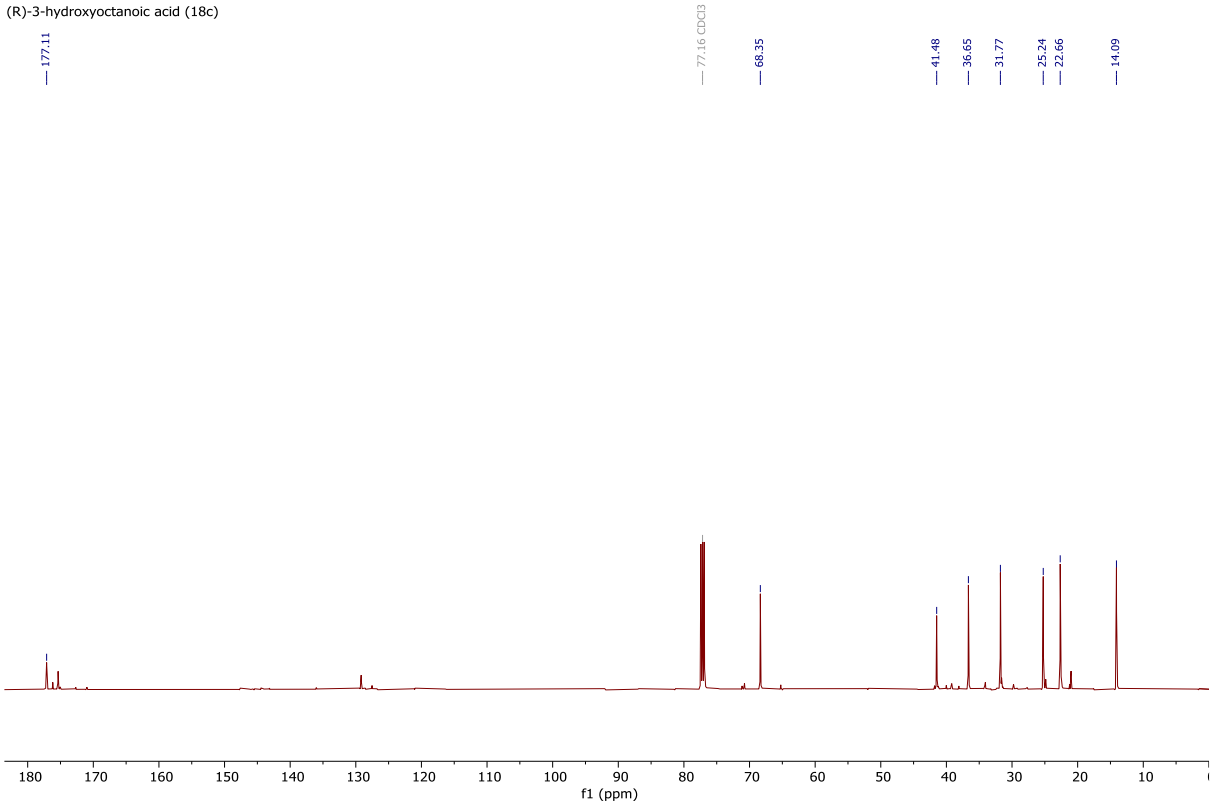
Supplementary Figure 56. ^{13}C NMR of **18b** on 125 MHz at 298 K in $CDCl_3$.



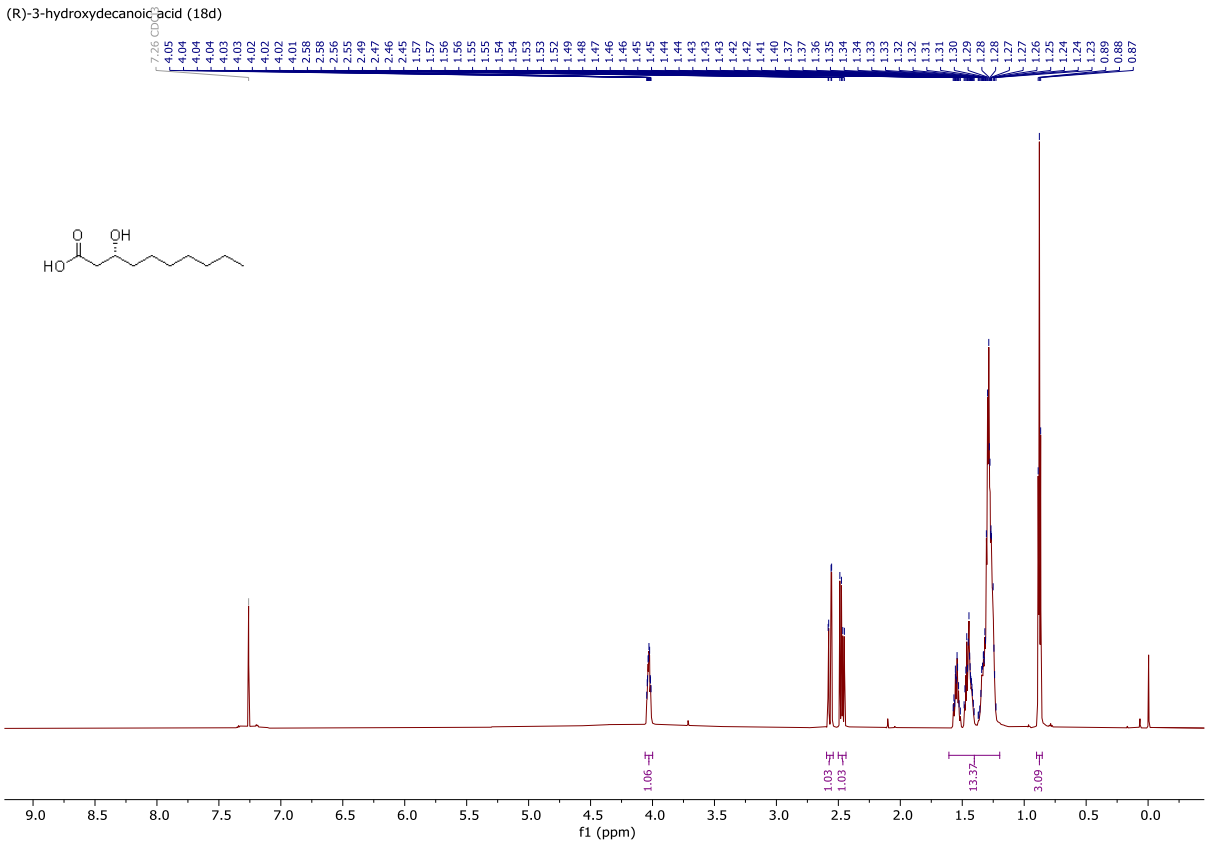
Supplementary Figure 57. ^{1}H NMR of **18c** on 500 MHz at 298 K in $CDCl_3$.



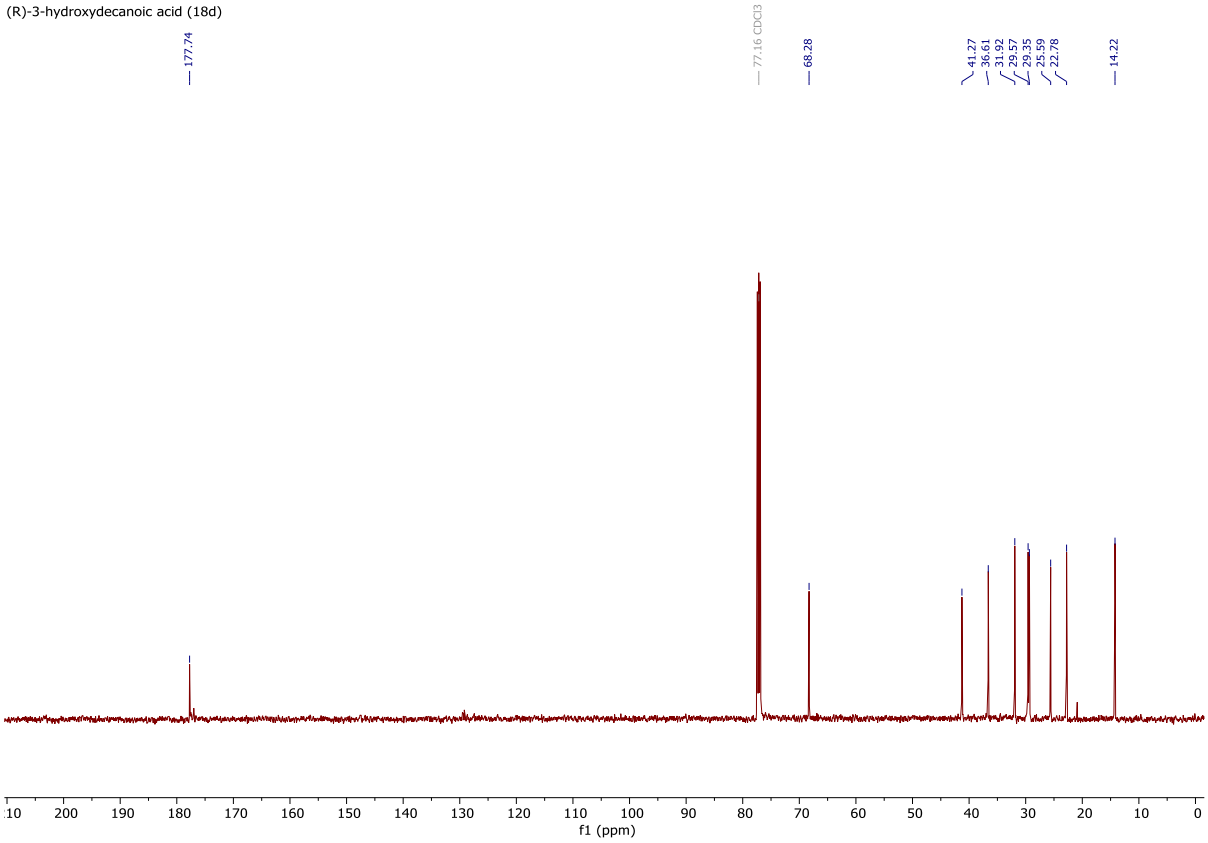
Supplementary Figure 58. ^{1}H NMR of **18c** on 125 MHz at 298 K in $CDCl_3$.



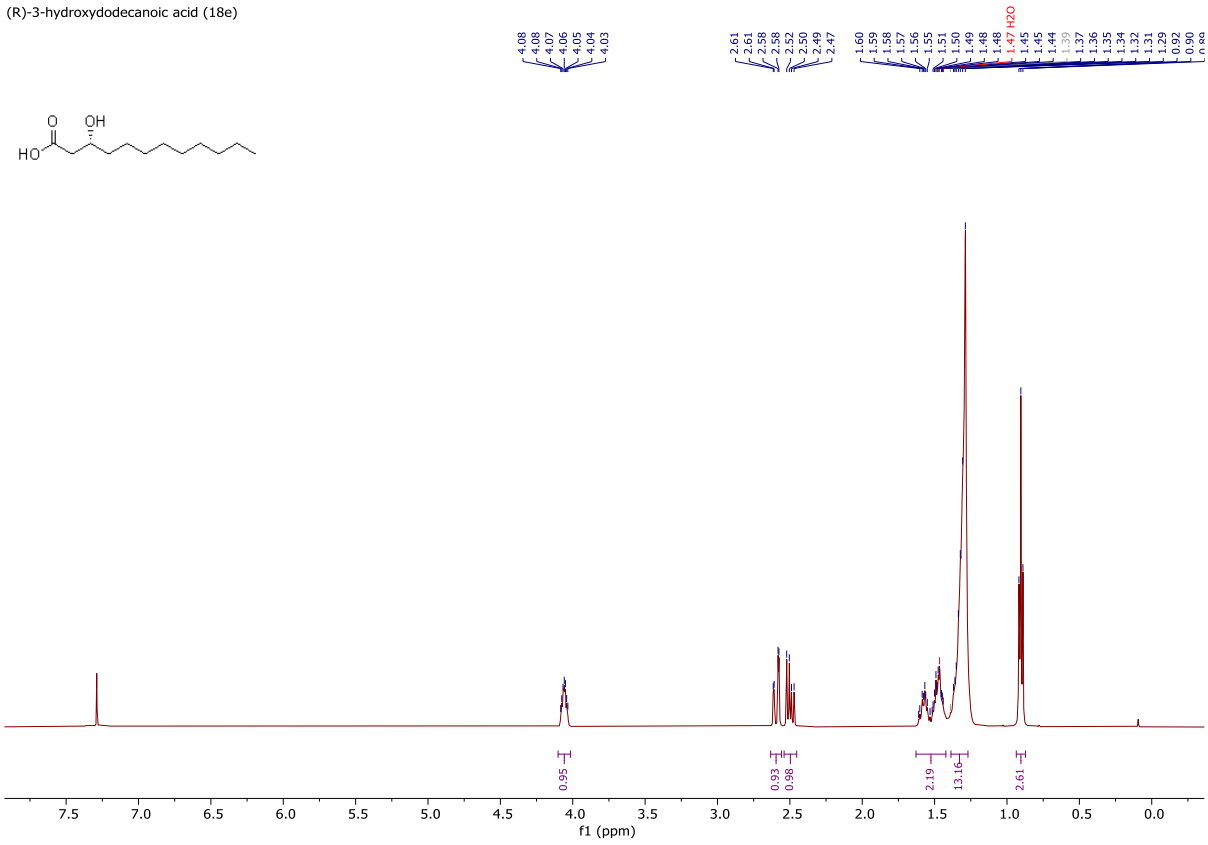
Supplementary Figure 59. ^{1}H NMR of **18d** on 700 MHz at 298 K in $CDCl_3$.



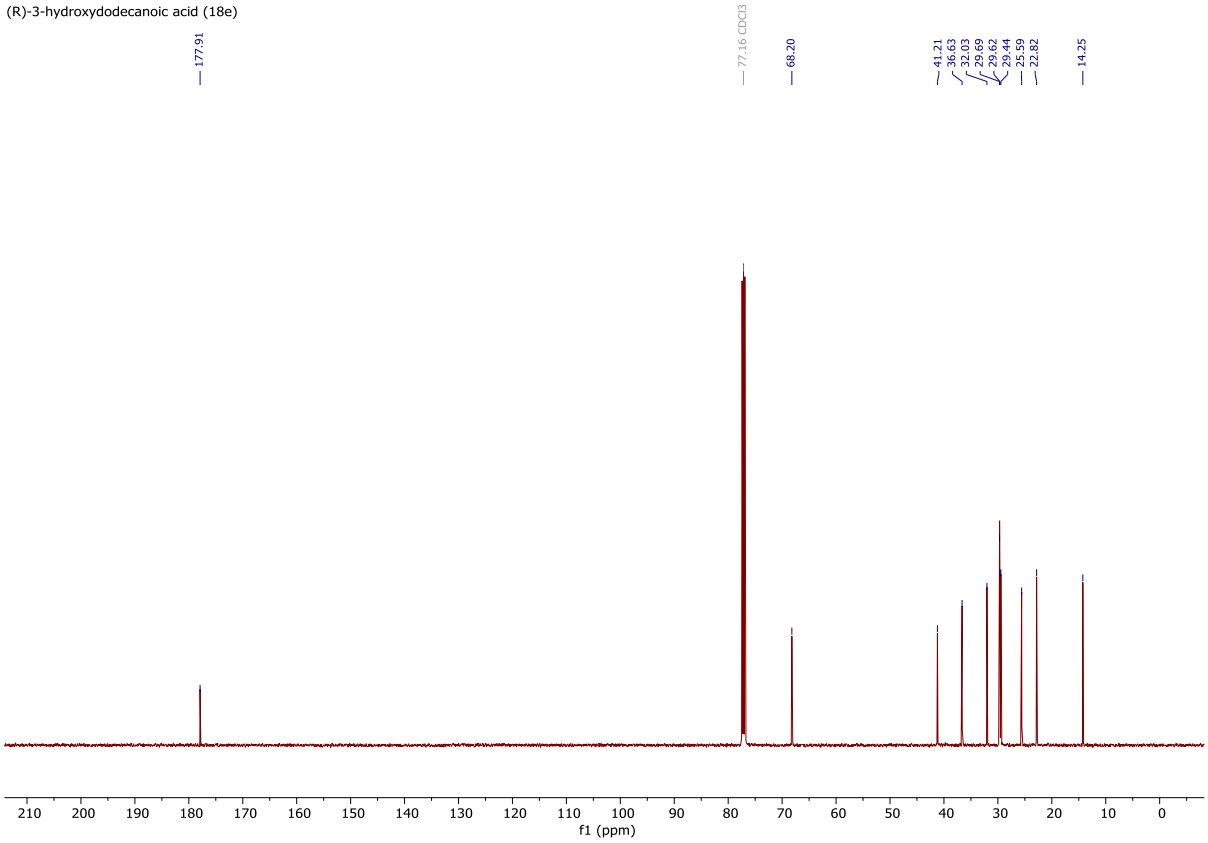
Supplementary Figure 60. ^{13}C NMR of **18d** on 175 MHz at 298 K in $CDCl_3$.



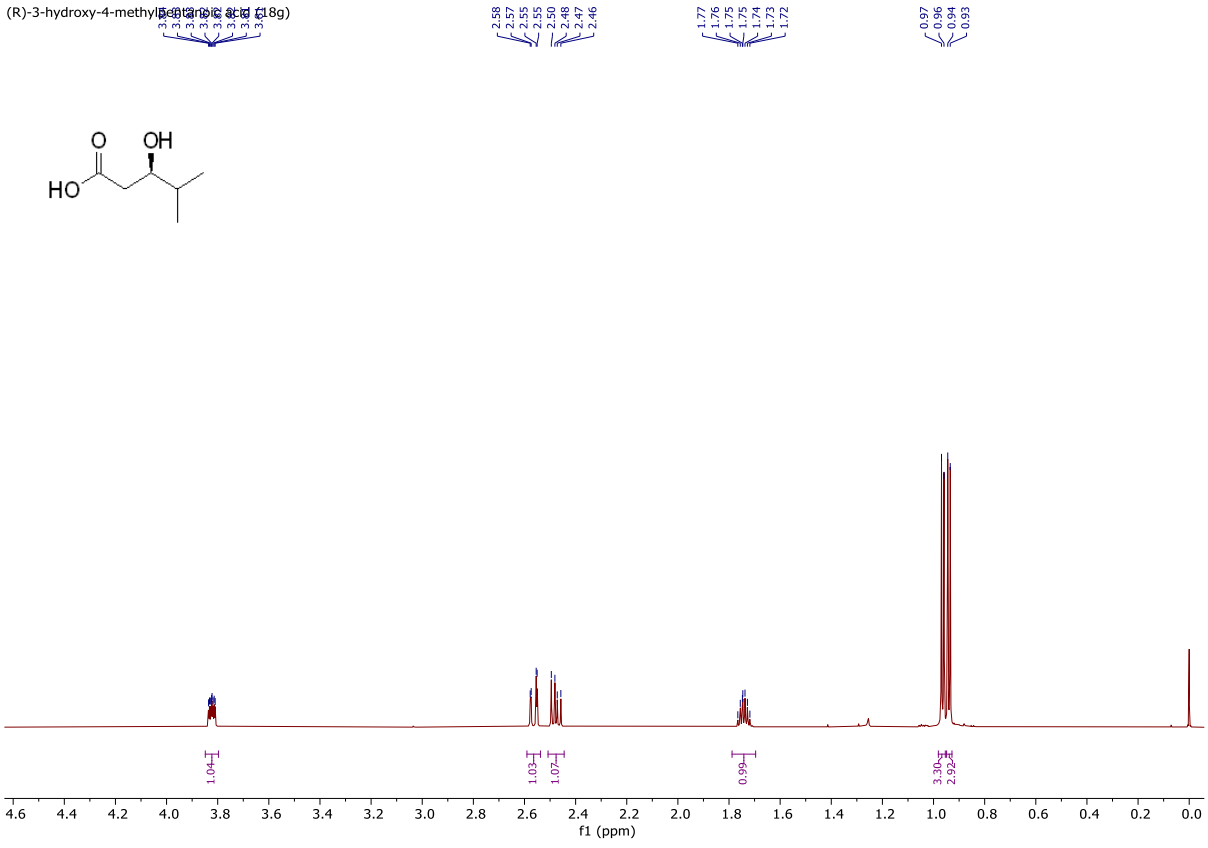
Supplementary Figure 61. ^{1}H NMR of **18e** on 500 MHz at 298 K in $CDCl_3$.



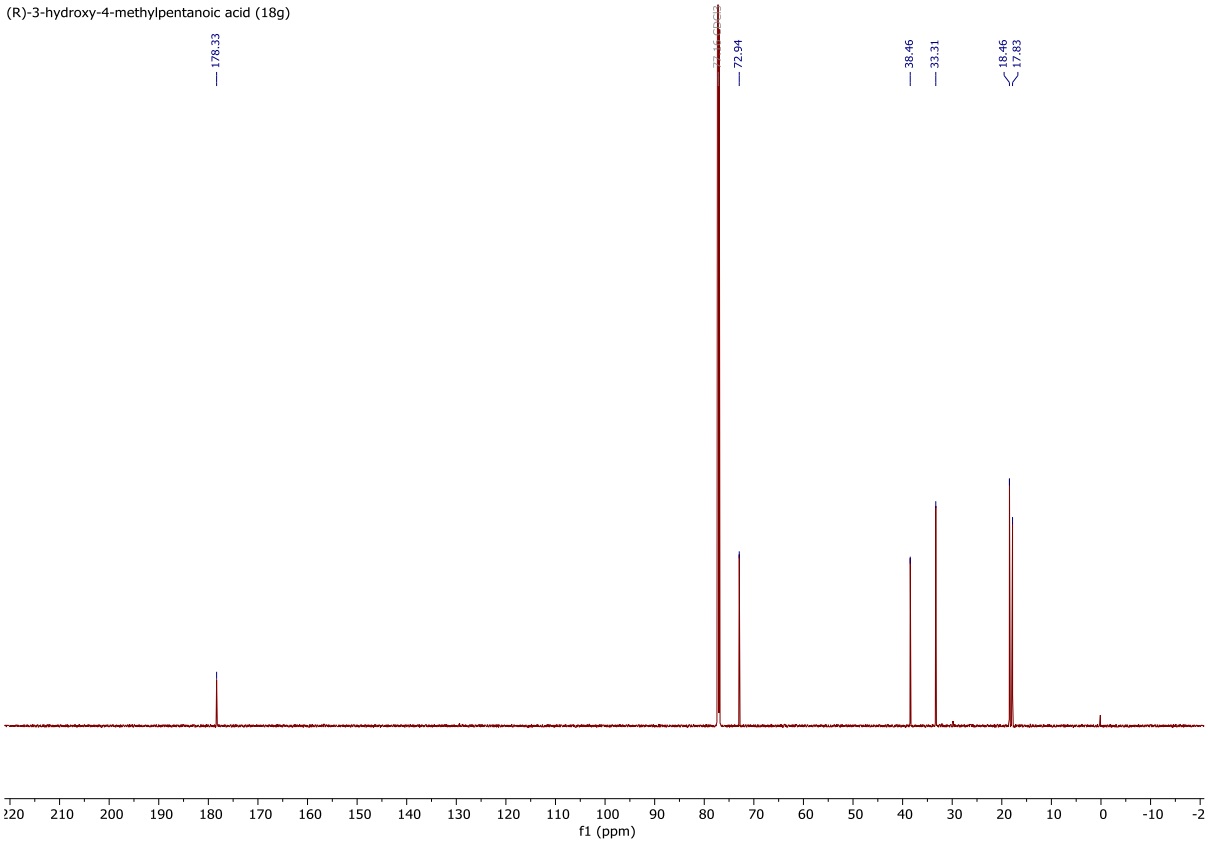
Supplementary Figure 62. ^{13}C NMR of **18e** on 125 MHz at 298 K in $CDCl_3$.



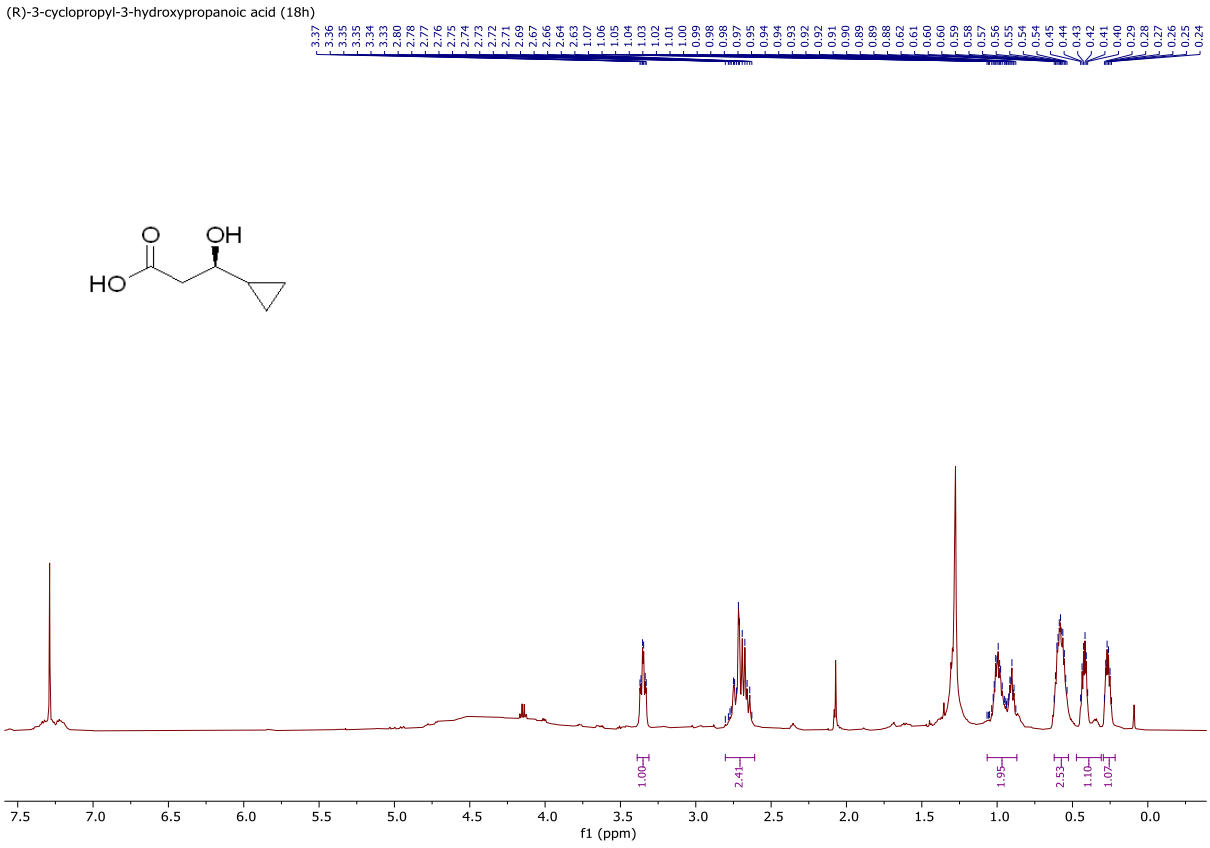
Supplementary Figure 63. ^{13}C NMR of **18g** on 700 MHz at 298 K in $CDCl_3$.



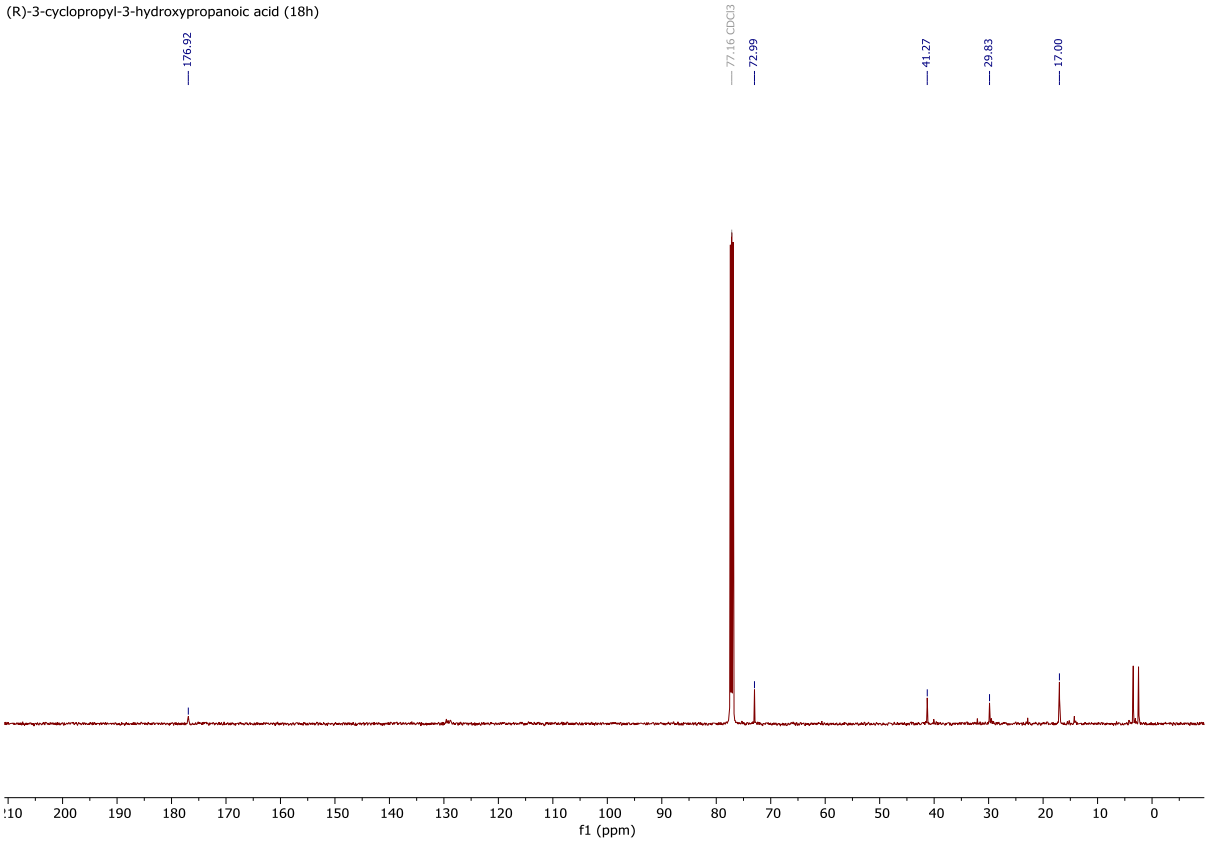
Supplementary Figure 64. ^{13}C NMR of **18g** on 125 MHz at 298 K in $CDCl_3$.



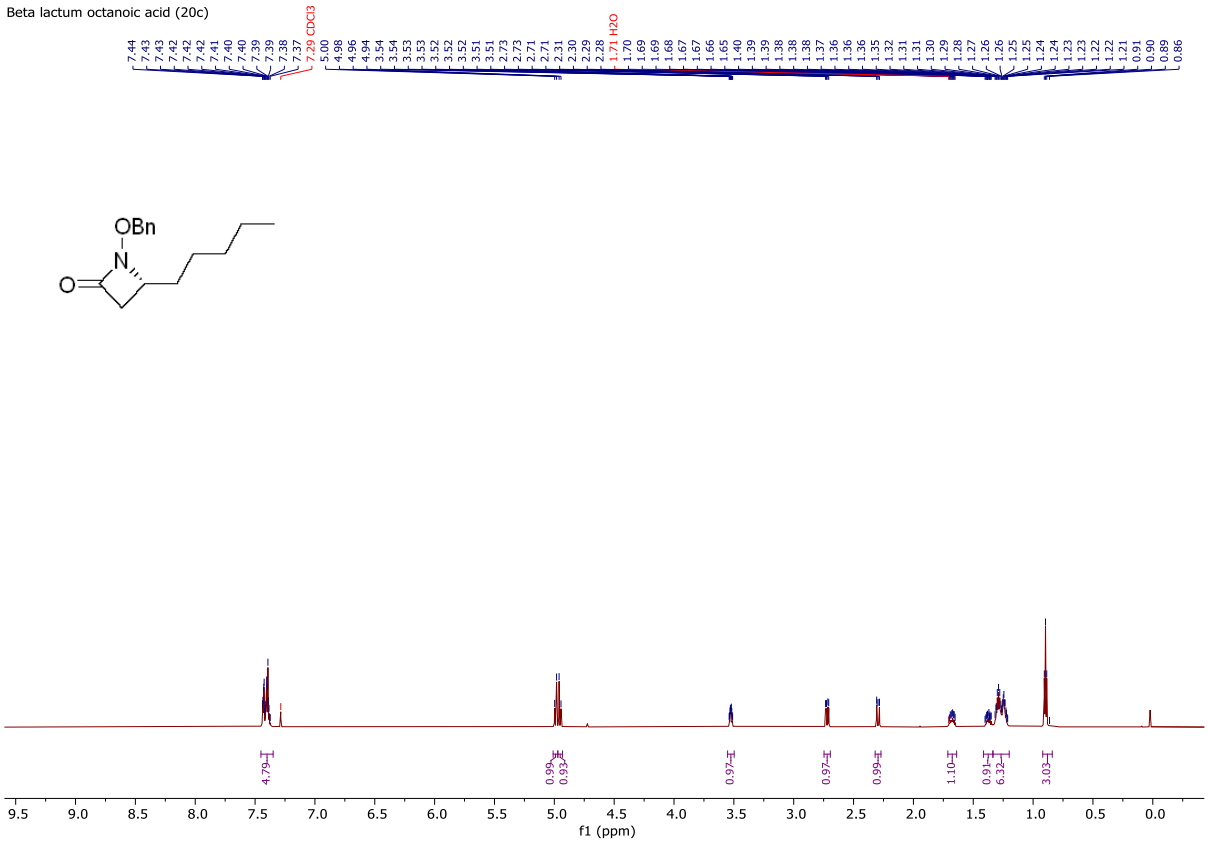
Supplementary Figure 65. ^{1}H NMR of **18h** on 500 MHz at 298 K in $CDCl_3$.



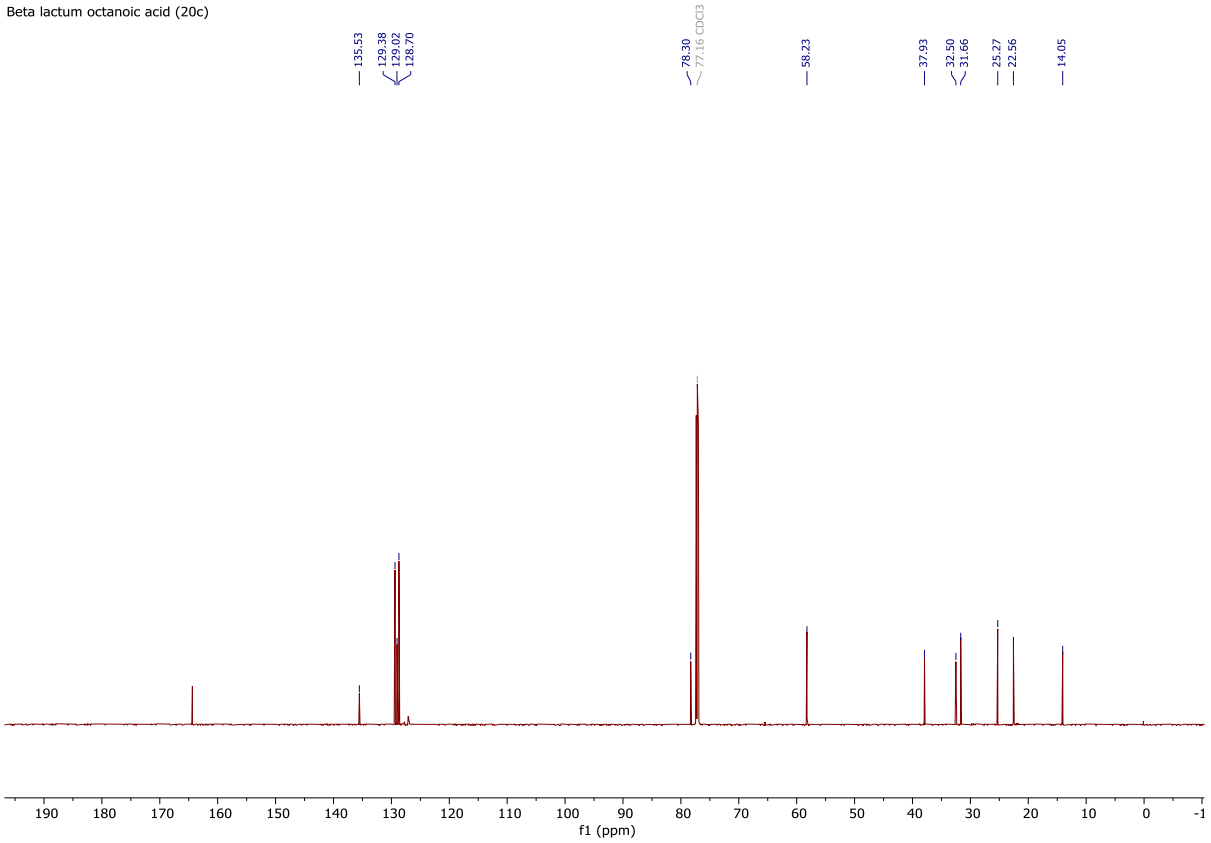
Supplementary Figure 66. ^{13}C NMR of **18h** on 125 MHz at 298 K in $CDCl_3$.



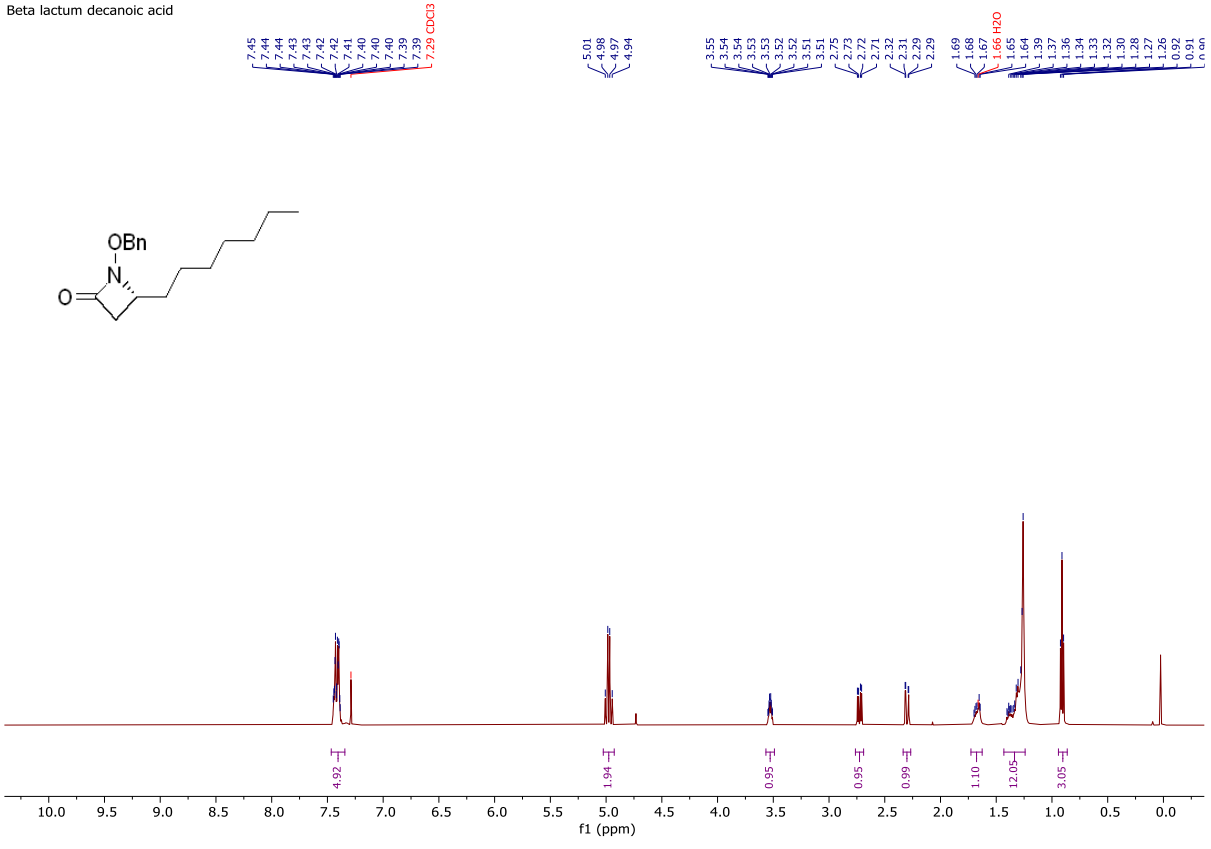
Supplementary Figure 67. ^{1}H NMR of **20c** on 700 MHz at 298 K in $CDCl_3$.



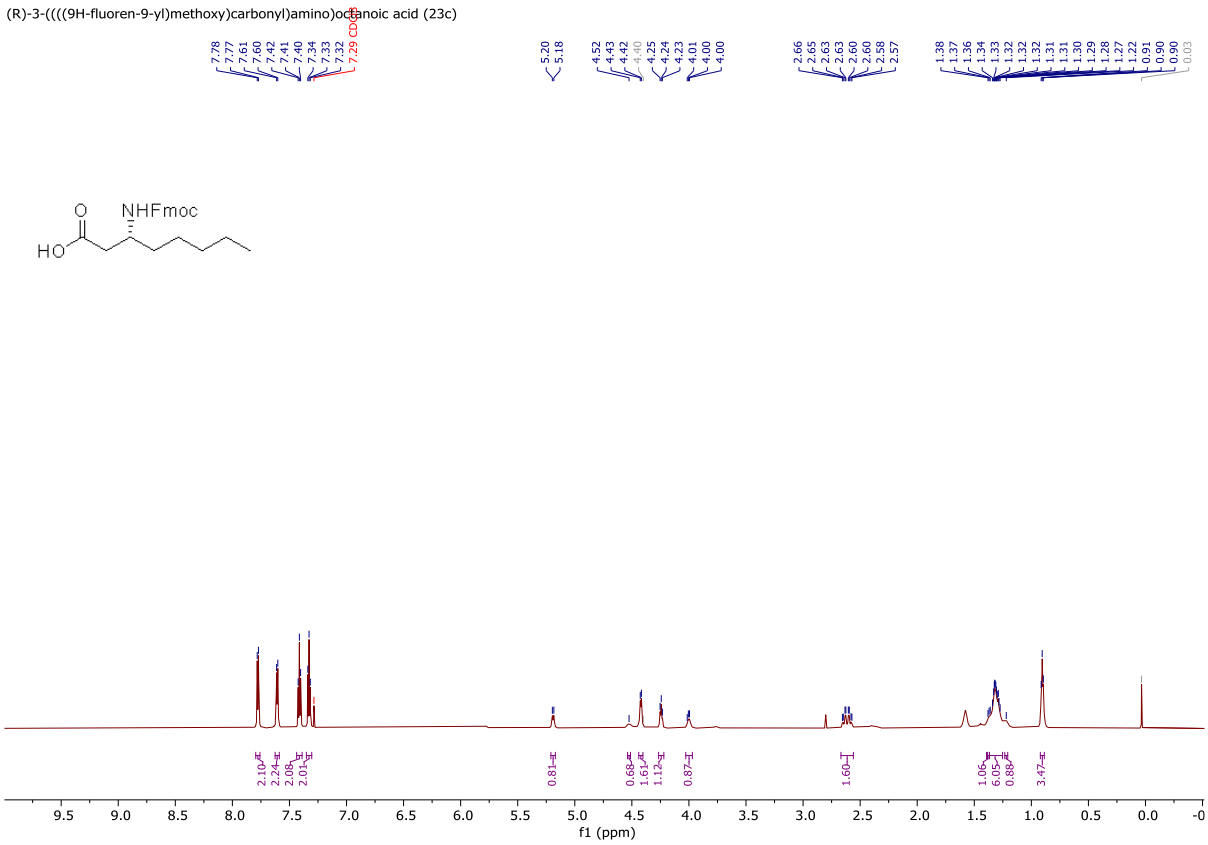
Supplementary Figure 68. ^{1}H NMR of **20c** on 175 MHz at 298 K in $CDCl_3$.



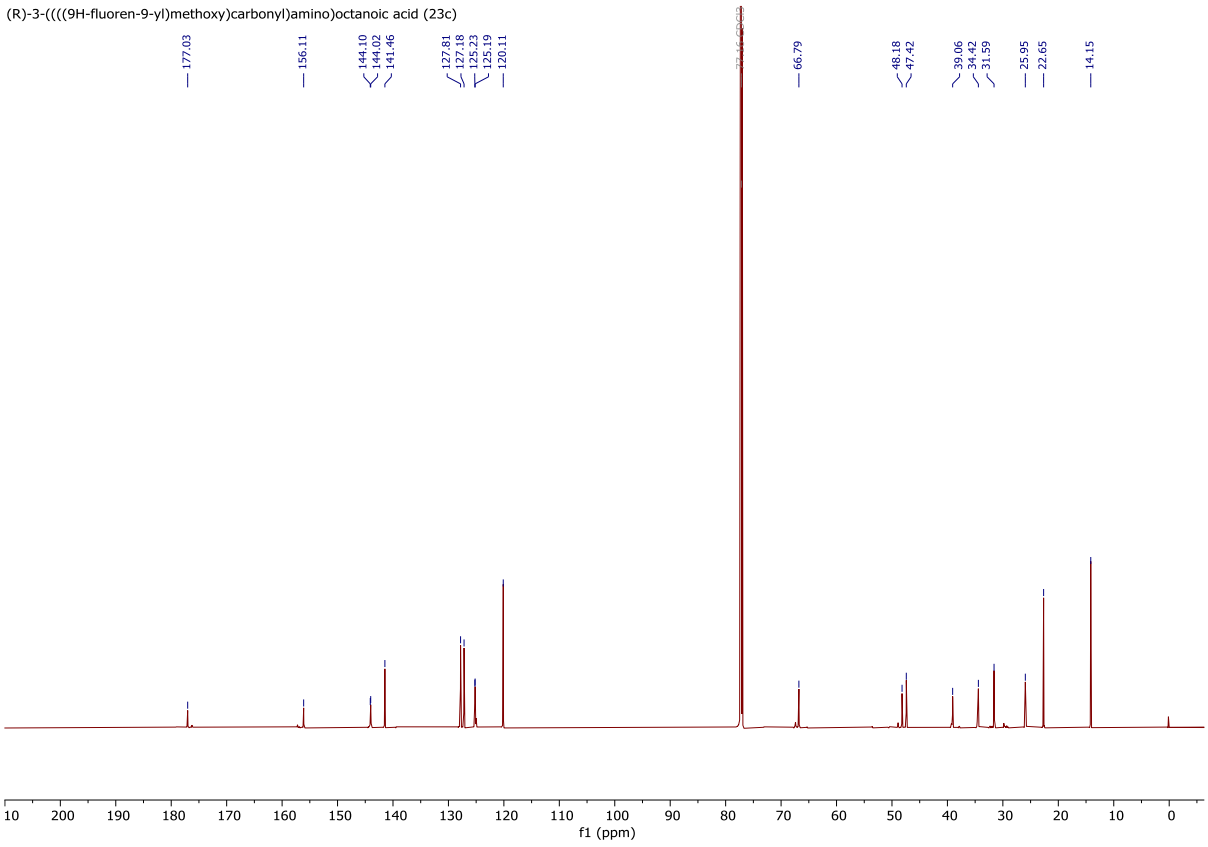
Supplementary Figure 69. ^{1}H NMR of **20d** on 500 MHz at 298 K in $CDCl_3$.



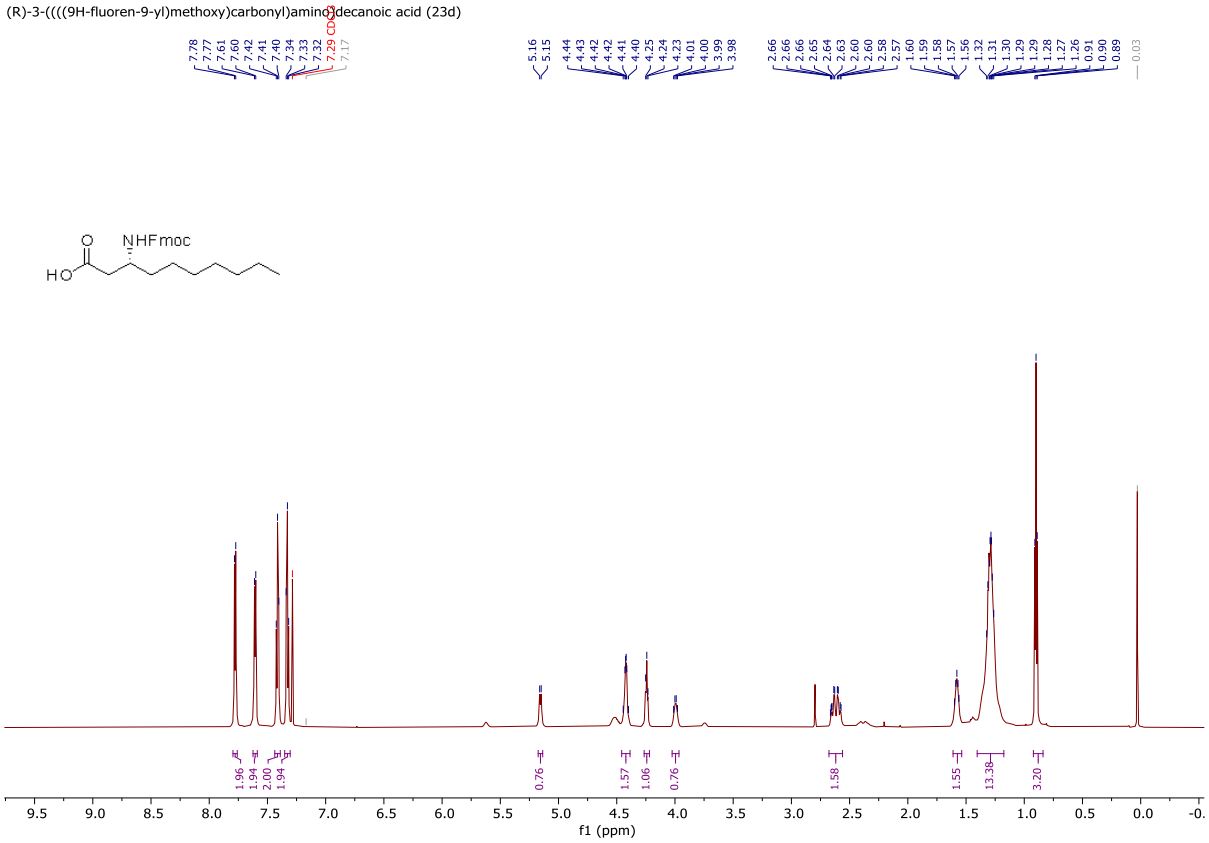
Supplementary Figure 70. ^{1}H NMR of **23c** on 500 MHz at 298 K in $CDCl_3$.



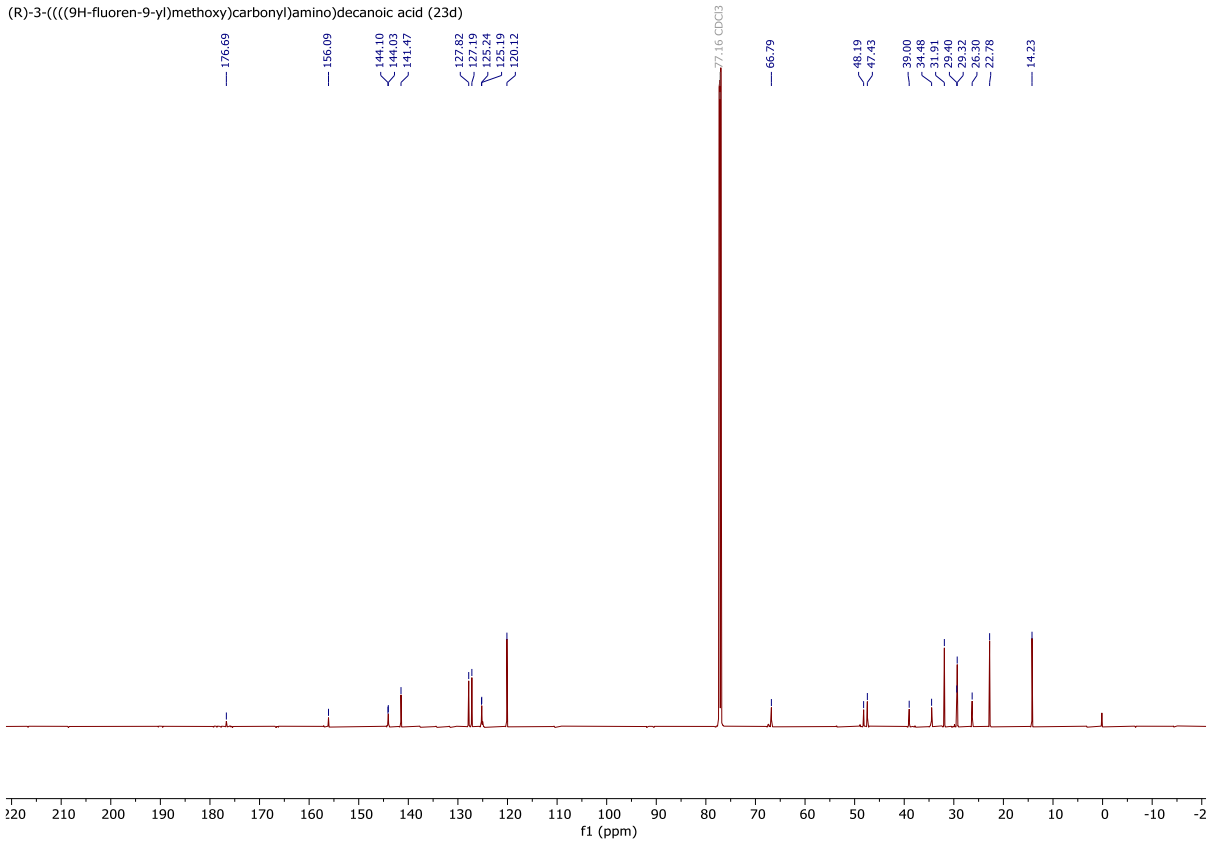
Supplementary Figure 71. ^{13}C NMR of **23c** on 125 MHz at 298 K in $CDCl_3$.



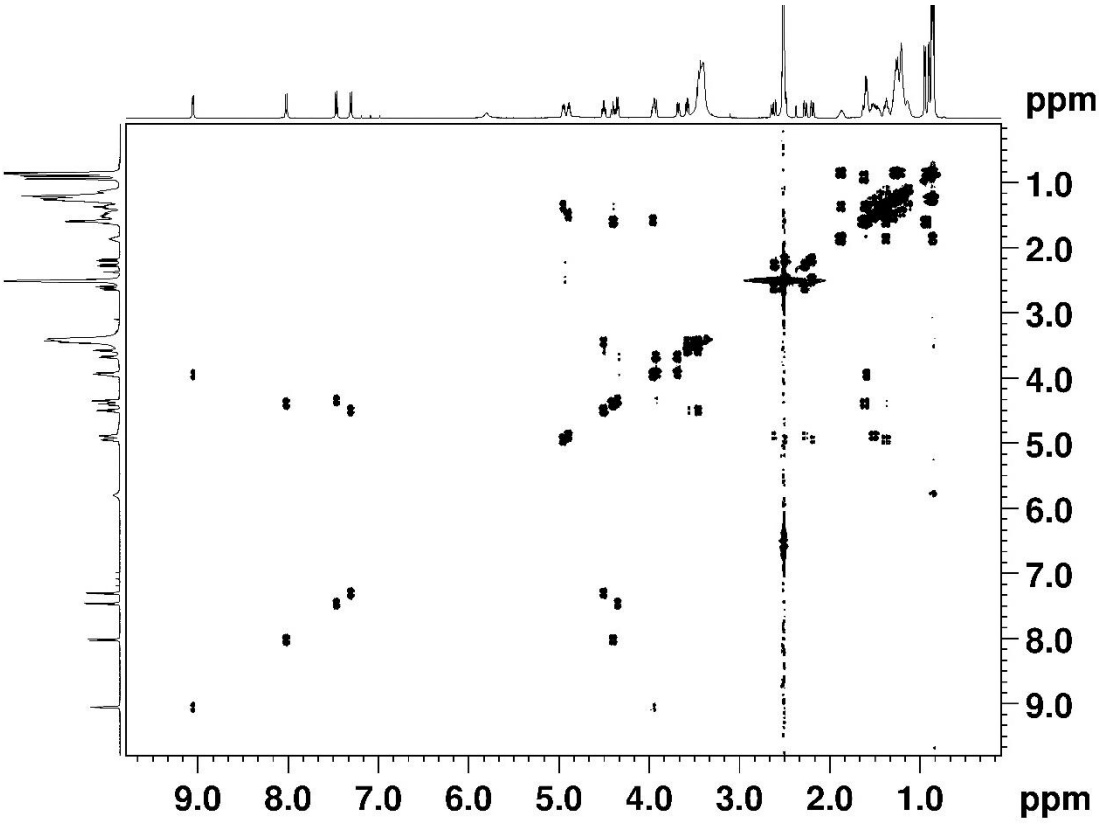
Supplementary Figure 72. ^{1}H NMR of **23d** on 700 MHz at 298 K in $CDCl_3$.



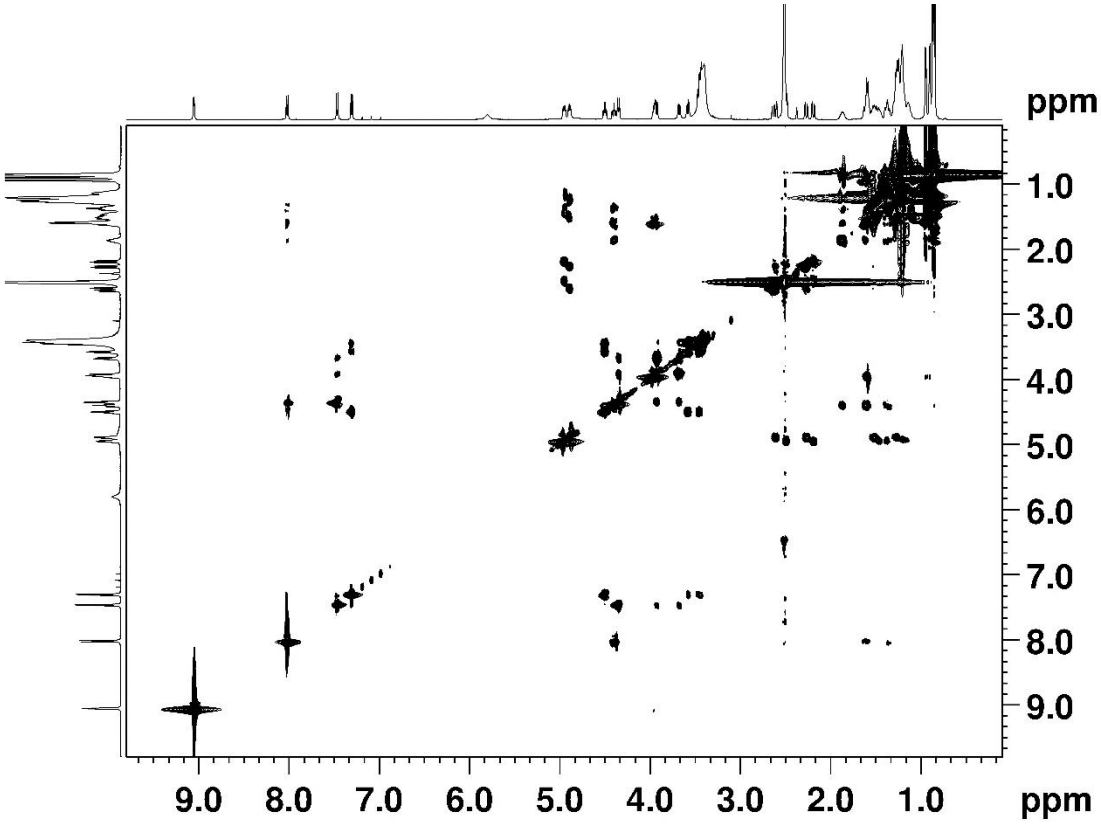
Supplementary Figure 73. ^{13}C NMR of **23d** on 175 MHz at 298 K in $CDCl_3$.



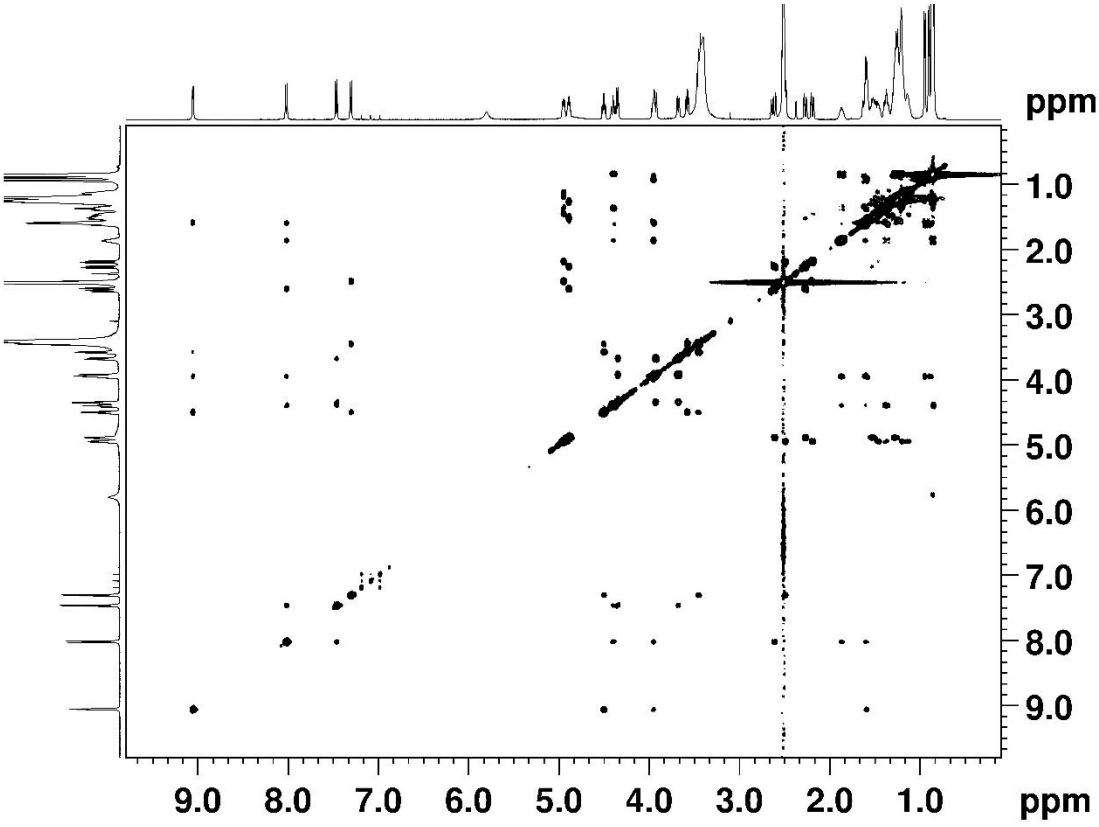
Supplementary Figure 74. DQF-COSY spectrum of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



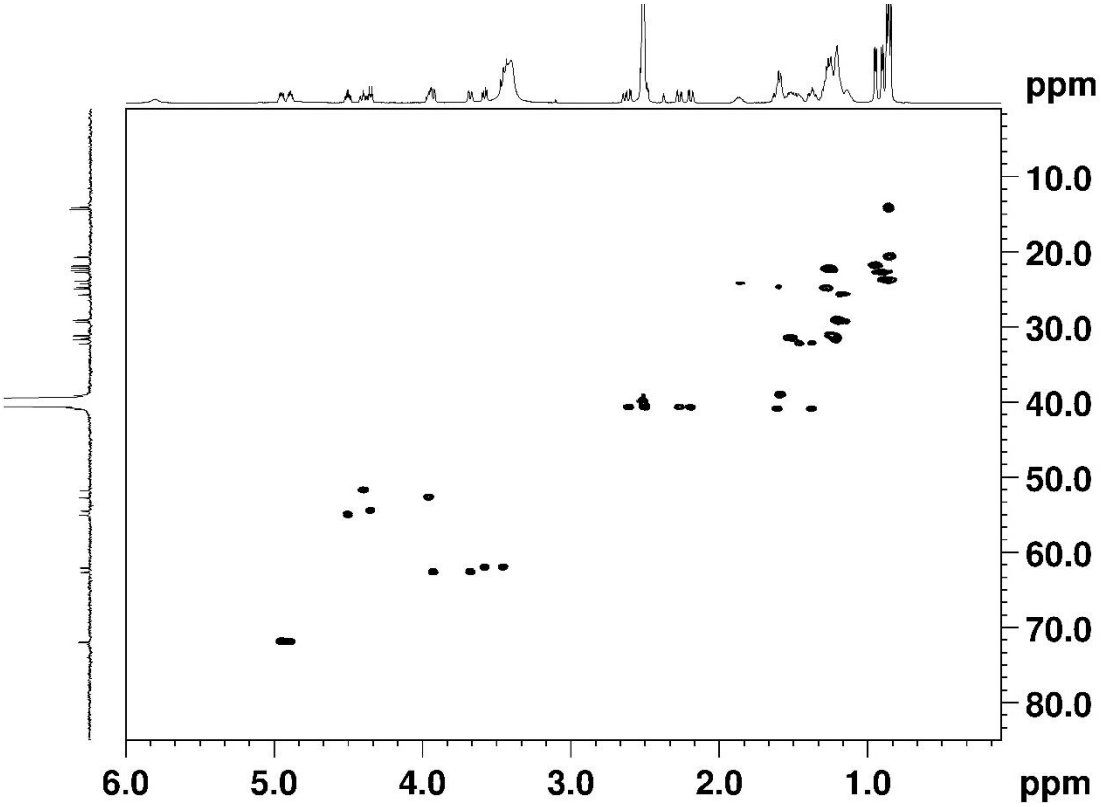
Supplementary Figure 75. TOCSY spectrum of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



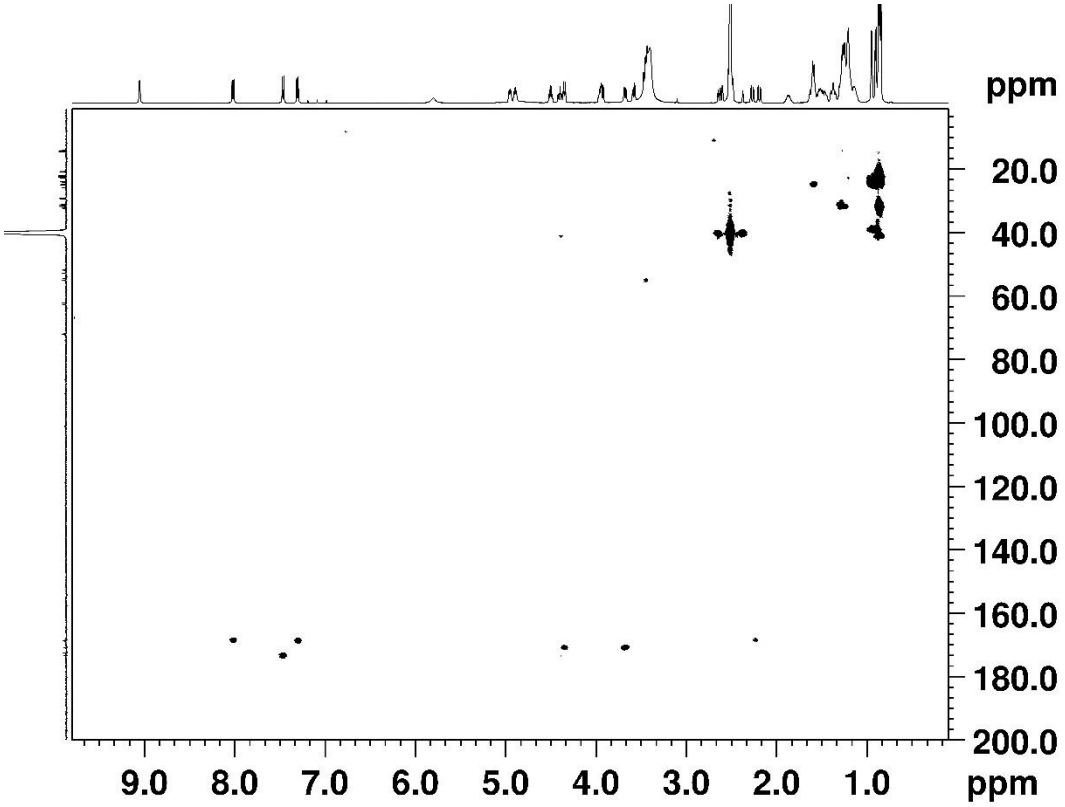
Supplementary Figure 76. ROESY spectrum of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



Supplementary Figure 77. HSQC spectrum of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



Supplementary Figure 78. HMBC spectrum of Icosalide **1a** on 500 MHz at 298 K in DMSO-d_6.



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