Norbornane-based Cationic Antimicrobial Peptidomimetics Targeting the Bacterial Membrane

Shane M. Hickey,[a]* Trent D. Ashton,[b,c] Gareth Boer,[d] Christie A. Bader,[a] Michael Thomas,[e] Alysha G. Elliott,[f] Carsten Schmuck,[g] Heidi Y. Yu,[h] Jian Li,[h] Roger L. Nation,[h] Matthew A. Cooper,[f] Sally E. Plush,[a] Douglas A. Brooks,[a] and Frederick M. Pfeffer[d]*

[a]*Cancer Research Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, 5000, Australia.*

[b]*The Walter and Eliza Hall Institute of Medical Research, Parkville, 3052, Australia,*

[c]*Department of Medical Biology, The University of Melbourne, Parkville 3010, Australia*

[d]*Centre for Chemistry and Biotechnology, School of Life and Environmental Sciences, Deakin University, Waurn Ponds, Victoria, 3216, Australia,*

[e]*Research School of Chemistry, The Australian National University, Acton, ACT, 2601, Australia,*

[f]*Institute for Molecular Bioscience, The University of Queensland, Brisbane, Queensland, 4072, Australia,*

[g]*Institute for Organic Chemistry, University of Duisburg-Essen, 45117 Essen, Germany, and,*

[h]*Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Science, Royal Parade, Parkville, Victoria, 3052, Australia.*

Email: Shane.Hickey@unisa.edu.au, fred.pfeffer@deakin.edu.au

CONTENTS

Experimental

General

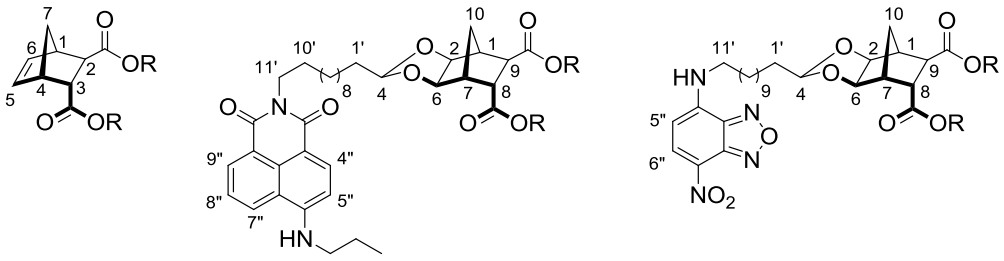
Chemicals were purchased from commercial sources and used without further purification. Anhydrous DMF and THF were obtained using the Pure Solv solvent drying system (Innovative Technology, Inc., Amesbury, MA, USA). Solvents were degassed and passed through two drying chambers of alumina and stored and collected under a positive pressure of nitrogen gas. Anhydrous CH_2Cl_2 was obtained by drying over freshly activated 3 Å molecular sieves.

All microwave reactions were conducted using a CEM Discover S-Class Explorer 48 Microwave Reactor, operating on a frequency of 50/60 Hz and continuous irradiation power from 0–300 W. All reactions were performed in sealed reaction vessels.

All melting points were obtained using Stuart Scientific SMP3 melting point apparatus and are uncorrected. All ^{1}H and ^{13}C NMR spectra were collected on either a JEOL JNM-GX 270 MHz FT-NMR spectrometer, a JEOL JNM-ECP 400 MHz FT-NMR spectrometer, or a BRUKER ADVANCE III 500 MHz FT-NMR spectrometer where indicated. All NMR experiments were performed at 25 °C. All 2D NMR experiments were performed on a BRUKER ADVANCE 500 MHz FT-NMR spectrometer and can be provided upon request. Samples were dissolved in $CDCl_3$, DMSO-d_6 or CD_3OD where specified with the residual solvent peak used as the internal reference – $CDCl_3$; 7.26 (^{1}H) and 77.0 (^{13}C), DMSO-d_6; 2.50 (^{1}H) and 39.52 (^{13}C), CD_3OD; 3.31 (^{1}H) and 49.0 (^{13}C).[1] Proton spectra are reported as chemical shift (ppm) δ (integral, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet and m = multiplet), coupling constant (Hz), assignment). Carbon spectra are reported as chemical shift δ (ppm).

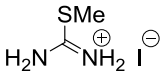
High resolution mass spectral data was collected on an Agilent Technologies 6520 QTOF mass spectrometer (LC-1200 series) under the following conditions: gas temperature (300 °C), nitrogen drying gas (10.0 L min^{-1}), capillary voltage (3500 V), fragmentor (140 V), and nebuliser (45 psi) in a 80% MeCN in H_2O solvent system. Analyte solutions were prepared in HPLC grade methanol (conc. ~ 1 mg mL^{-1}).

All norbornane-based compounds are named using the von-Baeyer system of nomenclature.[2] All other parts of the structure are named following the IUPAC guidelines. Numbering of norbornane protons follows the general structures shown below. Protons on the bridge carbon are labelled either *syn* (*s*) or *anti* (*a*) in regards to the priority functional group.



2-Methylisothiouronium iodide (37)[3]

[CAS Reg. No. 14257-47-7]



A mixture of thiourea (10.0 g, 0.13 mol), iodomethane (8.2 mL, 0.13 mol) and MeOH (100 mL) was heated at 65 °C for 90 min. The MeOH was removed *in vacuo* and the resulting yellow solid was transferred to a sintered glass funnel and washed with Et_2O (5 × 50 mL) to afford the title compound (28.2 g, 99%) as an amorphous white powder.

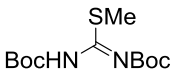
m.p. 116–118 °C (lit. 117 °C).[4]

^{1}H NMR (270 MHz, DMSO-d_6) δ 8.89 (4H, br s, NH_2), 2.56 (3H, s, CH_3).

^{13}C NMR (67.5 MHz, DMSO-d_6) δ 171.1, 13.3.

***N,N′*-Bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (3)**[3]

[CAS Reg. No. 107819-90-9]



To a stirring solution of 2-methylisothiouronium iodide **37** (9.82 g, 45.0 mmol) in sat. $NaHCO_3$ (50 mL) and CH_2Cl_2 (105 mL) was added Boc_2O (19.67 g, 90.1 mmol) using CH_2Cl_2 (3 × 25 mL). After 48 h the reaction mixture was transferred to a separatory funnel, the organic phase was isolated and the aqueous phase was extracted using CH_2Cl_2 (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude solid was stirred in EtOH/H_2O (1:9, 100 mL) for 1 h before the mixture was cooled to 0 °C and the solid was collected by vacuum filtration. Washing with EtOH/H_2O (1:9, 50 mL) gives the title compound (12.3 g, 94%) as a white powder.

m.p. 122–124 °C (lit. 127 °C).[5]

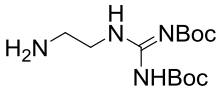
^{1}H NMR (270 MHz, $CDCl_3$) δ 11.61 (1H, br s, NH), 2.40 (3H, s, CH_3), 1.53 (9H, br s, *t*-Bu), 1.51 (9H, br s, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 160.9, 150.9, 83.4, 81.1, 28.2, 14.6.

HRMS (ESI, *m/z*) for $C_{12}H_{22}N_2O_4S$ $[M + Na]^+$ calc. 313.1193; found 313.1186.

2-[2,3-Bis(*tert*-butoxycarbonyl)guanidino]ethylamine (22)[6]

[CAS Reg. No. 203258-44-0]



A solution of Boc-protected methylisothiourea **3** (20.4 g, 70.3 mmol) in CH_2Cl_2 (110 mL) was added in one portion to a stirred solution of 1,2-ethylenediamine (11.7 mL, 176 mmol) in CH_2Cl_2 (150 mL). The reaction was stirred at 21 °C for 90 min. The reaction mixture was transferred to a separatory funnel and washed with H_2O (2 × 80 mL), brine (80 mL), then dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* at ambient temperature to afford the title compound (20.7 g, 97%) as a white powder.

m.p. 96–100 °C.

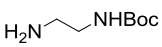
^{1}H NMR (270 MHz, $CDCl_3$) δ 11.51 (1H, br s, NH), 8.67 (1H, br s, NH), 3.49 (2H, app. q, *J* = 5.5 Hz, CH_2), 2.90 (2H, t, *J* = 6.2 Hz, CH_2), 1.51 (9H, br s, *t*-Bu), 1.50 (9H, br s, *t*-Bu).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 163.7, 156.5, 153.3, 83.2, 79.4, 43.5, 41.1, 28.4, 28.2.

HRMS (ESI, *m/z*) for $C_{13}H_{26}N_4O_4$ $[M + H]^+$ calc. 303.2027; found 303.2032.

2-(*tert*-Butoxycarbonylamino)ethylamine (38)[7]

[CAS Reg. No. 57260-73-8]



A solution of Boc_2O (8.35 g, 38.3 mmol) in THF (75 mL) was added dropwise, over approximately 30 min, to a stirred solution of ethylenediamine (EDA, 8.4 mL, 125 mmol) in THF (25 mL). The reaction was stirred for 4 h after which time the mixture was filtered and the solvent was then removed *in vacuo* to give the desired product (5.65 g, 92%) as a viscous oil.

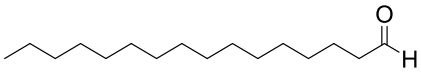
^{1}H NMR (270 MHz, $CDCl_3$) δ 4.83 (1H, br s, NH), 3.15 (2H, app. q, *J* = 6.0 Hz, NH_2CH_2), 2.78 (2H, t, *J* = 6.0 Hz, CH_2NH), 1.43 (9H, s, *t*-Bu), 1.16 (2H, br s, NH_2).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 156.3, 43.4, 41.8, 40.7, 28.4.

HRMS (ESI, *m/z*) for $C_7H_{16}N_2O_2$ $[M + H]^+$ calc. 161.1285; found 161.1290.

Hexadecanal (39)[8]

[CAS Reg. No. 629-80-1]



To the stirring solution of DMSO (700 μL, 10.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added oxalyl chloride (550 μL, 6.0 mmol) under an inert atmosphere. After 20 min, 1-hexadecanol (486 mg, 2.0 mmol) in CH_2Cl_2 (6 mL) was added and the reaction was stirred for 5.5 h at −41 °C. The reaction was quenched with Et_3N (3 mL, 21.5 mmol) and slowly warmed to ambient temperature over 30 min. The reaction mixture was washed with sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with 2M HCl (2 × 20 mL), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a yellow solid (445 mg, 92%).

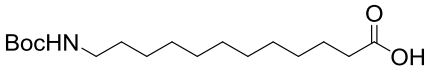
m.p. 36–38 °C (lit. 33.0–35.0 °C).[9]

^{1}H NMR (270 MHz, $CDCl_3$) δ 9.76 (1H, t, *J* = 1.9 Hz, CHO), 2.41 (2H, dt, *J* = 7.4, 1.9 Hz, CH_2), 1.62 (2H, app. t, *J* = 7.4 Hz, CH_2), 1.30–1.25 (24H, m, 12 × CH_2), 0.87 (3H, t, *J* = 6.4 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 44.1, 32.1, 29.8 (6 × C), 29.7, 29.6, 29.5, 29.3, 22.8, 22.2, 14.2.

***N*-(*tert*-Butoxycarbonyl)-12-aminododecanoic acid (40)**[10]

[CAS Reg. No. 18934-81-1]



A 250 mL round-bottom flask was charged with 12-aminododecanoic acid (6.00 g, 27.86 mmol), Boc_2O (6.08 g, 27.86 mmol), Et_3N (4.7 mL, 33.62 mmol) and MeOH (90 mL) and stirred at 60 °C for 16 h. The colourless solution was concentrated under reduced pressure and the residue was dissolved in EtOAc (150 mL). The organic phase was washed with 0.25 M HCl (2 × 40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (7.47 g, 85%) as a white solid.

m.p. 85–86 °C (lit. 83.5–84.5 °C).[11]

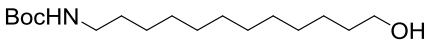
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (1H, br s, NH), 3.10–3.09 (2H, m, NHCH_2), 2.33 (2H, t, *J* = 7.5 Hz, C$H_2$$CO_2$H), 1.62 (2H, app. quin, *J* = 7.5 Hz, CH_2), 1.48–1.44 (11H, m, *t*-Bu, CH_2), 1.34–1.26 (14H, m, 7 × CH_2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 156.2, 79.2, 40.8, 34.1, 30.2, 29.6, 29.54, 29.46, 29.4, 29.3, 29.1, 28.6, 26.9, 24.8.

HRMS (ESI, *m/z*) for $C_{17}H_{33}NO_4$ $[M + Na]^+$ calc. 338.2302; found 338.2309.

***N*-(*tert*-Butoxycarbonyl)-12-aminododecan-1-ol (14)**[10]

[CAS Reg. No. 67341-03-1]



To a stirring solution of carboxylic acid **40** (7.33 g, 23.25 mmol) and anhydrous THF (110 mL) at 0 °C under an inert atmosphere, was added Red-Al® (18 mL, 59.97 mmol) dropwise over 25 min. The reaction was warmed to ambient temperature and stirring was maintained for 1 h before the reaction was cooled on ice and slowly quenched with sat. Na_2SO_3 (30 mL). The precipitate was removed using vacuum filtration and the filtrate was concentrated under reduced pressure before being diluted with EtOAc (100 mL). The organic phase was washed with H_2O (2 × 40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (5.31 g, 76%) as a white solid.

m.p. 82–83 °C.

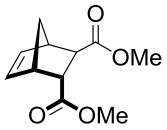
^{1}H NMR (270 MHz, $CDCl_3$) δ 4.48 (1H, br s, NH), 3.63 (2H, t, *J* = 6.6 Hz, C*H*$_2$CO$_2$H), 3.09 (2H, t, *J* = 7.0 Hz, NHC*H*$_2$), 1.56–1.26 (29H, m, 10 × CH_2, *t*-Bu).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 79.2, 63.2, 40.8, 32.9, 30.2, 29.70, 29.66 (3 × C), 29.5, 29.4, 28.6, 26.9, 25.9.

HRMS (ESI, *m/z*) for $C_{17}H_{35}NO_3$ $[M + Na]^+$ calc. 324.2509; found 324.2504.

Dimethyl bicyclo[2.2.1]hept-5-ene-3-*endo*-2-*exo*-dicarboxylate (41)

[CAS Reg. No. 3014-58-2]



Method A[12]

To the stirring solution of dimethyl fumarate (65.3 g, 0.453 mol) in THF (200 mL), was added freshly prepared cyclopentadiene (40 mL, 0.476 mol), and the reaction was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure to give the title compound (95.2 g, 99%) as a colourless oil.

Method B[13, 14]

A 35 mL MW vial was charged with dicyclopentadiene (2.0 mL, 15.0 mmol), dimethyl fumarate (2.88 g, 20.0 mmol) and hydroquinone (100 mg, 0.90 mmol), and heated using microwave irradiation to 150 °C for 2 h. The resulting orange oil was purified by flash column chromatography (10% EtOAc in pet. spirits) to give a clear oil (4.14 g, 98%).

R_f = 0.32 (10% EtOAc in pet. spirits).

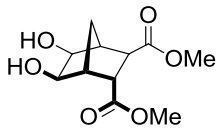
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (1H, dd, *J* = 5.6, 3.1 Hz, H5), 6.06 (1H, dd, *J* = 5.6, 2.8 Hz, H6), 3.71 (3H, s, Me), 3.64 (3H, s, Me), 3.37 (1H, app. t, *J* = 5.6 Hz, H3), 3.25 (1H, br s, H1), 3.12 (1H, br s, H4), 2.68 (1H, dd, *J* = 3.1, 1.2 Hz, H2), 1.61 (1H, d, *J* = 8.8 Hz, H7*a*), 1.45 (1H, dd, *J* = 8.8, 1.7 Hz, H7*s*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 174.0, 137.7, 135.3, 51.9, 51.7, 47.7, 47.5, 47.2, 46.9, 45.5.

HRMS (ESI, *m/z*) for $C_{11}H_{14}O_4$ $[M + Na]^+$ calc. 233.0784; found 233.0785.

Dimethyl 5,6-*exo*-dihydroxybicyclo[2.2.1]heptane-3-*endo*-2-*exo*-dicarboxylate (17)

[CAS Reg. No. 1228039-59-5]



Method A[15]

The dimethyl ester **41** (3.05 g, 14.5 mmol) and NMO·H_2O (1.87 g, 16.0 mmol) were dissolved in a solution of H_2O/acetone (1:4, 36 mL) to which OsO_4 (4% in H_2O, 730 µL, 0.40 mol%) was added. The reaction was stirred for 3 d and then quenched with sat. $NaHSO_3$ (30 mL). The suspension was extracted with EtOAc (4 × 25 mL), and the combined organic phase was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound (3.34 g, 94%) as a white solid.

Method B[16]

A solution of $KMnO_4$ (405 mg, 2.56 mmol), K_2CO_3 (212 mg, 1.54 mmol) in H_2O (6.0 mL) was added dropwise to a stirring solution of dimethyl ester **41** (270 mg, 1.28 mmol), *t*-BuOH (4.7 mL) and H_2O (1.2 mL) at 0 °C. The reaction was stirred for a further 25 min before consumption of starting material was observed by TLC analysis. The reaction mix was quenched with sat. $NaHSO_3$ (25 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound (181 mg, 58%) as a white solid.

m.p. 90–92 °C (lit. 81–84 °C).[15]

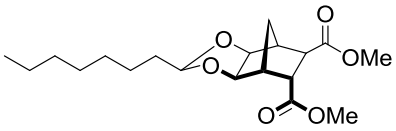
^{1}H NMR (270 MHz, $CDCl_3$) δ 3.85 (1H, br s, H5), 3.77–3.71 (1H, m, H6), 3.64 (3H, s, Me), 3.62 (3H, s, Me), 3.11 (1H, app. t, *J* = 5.1 Hz, H3), 2.63 (1H, d, *J* = 4.9 Hz, H2), 2.46 (1H, dd, *J* = 4.5, 1.2 Hz, H4), 2.40 (1H, br s, H1), 1.78 (1H, dd, *J* = 11.0, 1.2 Hz, H7*a*), 1.33 (1H, d, *J* = 11.0 Hz, H7*s*).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.2, 173.2, 73.3, 70.2, 52.5, 52.3, 48.2, 46.4, 46.2, 44.8, 31.8.

HRMS (ESI, *m/z*) for $C_{11}H_{16}O_6$ $[M + Na]^+$ calc. 267.0839; found 267.0836.

Dimethyl 4-heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylate (42)[17]

[CAS Reg. No. 1233074-95-7]



To a stirring suspension of diol **17** (3.50 g, 14.34 mmol), *p*-TSA (140 mg, 0.72 mmol), $MgSO_4$ (1.73 g, 14.34 mmol) and PhMe (24 mL) was added octanal (3.4 mL, 21.5 mmol) and the reaction was heated for 3 h at 120 °C. Solid $MgSO_4$ was removed by filtration and the filtrate was diluted with EtOAc (50 mL), washed with H_2O (2 × 15 mL), brine (15 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude material which was purified using column chromatography (10% EtOAc in pet. spirits) to afford the title compound (4.66 g, 92%) as a light yellow viscous oil.

R_f = 0.26 (10% EtOAc in pet. spirits).

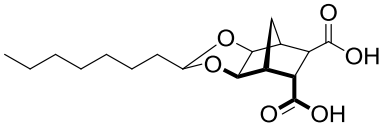
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (1H, t, *J* = 4.9 Hz, H4), 3.98 (1H, d, *J* = 5.6 Hz, H2), 3.85 (1H, d, *J* = 5.6 Hz, H6), 3.66 (6H, s, 2 × Me), 3.18 (1H, app. t, *J* = 4.7 Hz, H8), 2.67 (1H, d, *J* = 4.7 Hz, H9), 2.60 (2H, br s, H1, H7), 1.73 (1H, d, *J* = 10.8 Hz, H10*a*), 1.59–1.56 (2H, m, CHCH_2), 1.36–1.19 (11H, m, 5 × CH_2, H10*s*), 0.82 (3H, t, *J* = 6.6 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 173.0, 104.2, 81.2, 78.7, 52.1, 51.9, 45.0, 44.8, 43.4, 43.0, 32.5, 31.5, 31.3, 29.2, 28.9, 23.9, 22.3, 13.7.

HRMS (ESI, *m/z*) for $C_{19}H_{30}O_6$ $[M + Na]^+$ calc. 377.1935; found 377.1924.

4-Heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylic acid (43)[17]

[CAS Reg. No. 1233074-96-8]



To the stirred solution of the ester **42** (1.00 g, 2.82 mmol) in THF (12 mL), 2M NaOH (6 mL) was added and the reaction was stirred for 16 h at ambient temperature. The reaction was concentrated under reduced pressure and all organic-soluble impurities were extracted with CH_2Cl_2 (2 × 10 mL). The aqueous solution was acidified with sat. KH_2PO_4 (pH = 5), extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$) and filtered to give a white waxy solid (795 mg, 86%).

m.p. 141–143 °C (lit. 153.0–154.0 °C).[15]

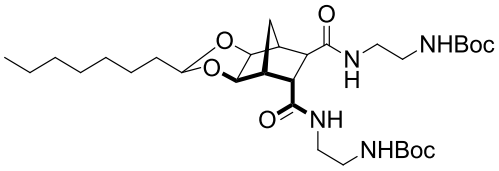
^{1}H NMR (270 MHz, DMSO-d_6) δ 4.62 (1H, t, *J* = 4.7 Hz, H4), 3.97 (2H, d, *J* = 5.6 Hz, H2), 3.88 (1H, d, *J* = 5.6 Hz, H6), 3.00 (1H, dd, *J* = 5.2, 0.6 Hz, H8), 2.45 (1H, br s, H7), 2.54 (1H, br s, H1), 2.40 (1H, d, *J* = 5.2 Hz, H9), 1.61–1.50 (3H, m, CHC*H*$_2$, H10*a*), 1.33–1.19 (11H, m, 5 × CH_2, H10*s*), 0.85 (3H, t, *J* = 6.4 Hz, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.6, 173.3, 103.2, 80.7, 78.2, 45.0, 44.4, 43.3, 42.6, 32.3, 31.2 (2 × C), 28.9, 28.6, 23.7, 22.1, 14.0.

HRMS (ESI, *m/z*) for $C_{17}H_{26}O_6$ $[M + Na]^+$ calc. 349.1622; found 349.1627.

8-*endo*-9-*exo*-Di[2′-(2″,3″-bis-*tert*-butoxycarbonylamino)ethylcarbamoyl]-4-heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane (44)[17]

[CAS Reg. No. 1774366-82-3]



A MW vial was charged with diacid **43** (333 mg, 1.02 mmol), EDCI (590 mg, 3.06 mmol), HOBt (14 mg, 0.1 mmol) and anhydrous $CHCl_3$ (2.1 mL) and was stirred at ambient temperature for 30 min. Amine **50** (490 mg, 3.06 mmol) was then added and the reaction was irradiated for 30 min at 50 °C. The resulting homogenous clear liquid was diluted with $CHCl_3$ (15 mL), washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a white solid that was purified by flash column chromatography (50–70% EtOAc in pet. spirits) to give the title compound (357 mg, 57%) as a white solid.

R_f = 0.21 (70% EtOAc in pet. spirits).

m.p. 122–123 °C.

^{1}H NMR (270 MHz, $CDCl_3$) δ 6.89 (1H, br s, NH), 6.86 (1H, br s, NH), 5.08–5.01 (2H, m, 2 × NH), 4.64 (1H, t, *J* = 4.8 Hz, H4), 4.13 (1H, d, *J* = 5.7 Hz, H6), 3.96 (1H, d, *J* = 5.7 Hz, H2), 3.41–3.26 (8H, m, 4 × NHC*H*$_2$), 2.92 (1H, app. t, *J* = 5.1 Hz, H8), 2.57–2.53 (2H, m, H7, H9), 2.43 (1H, d, *J* = 5.0 Hz,

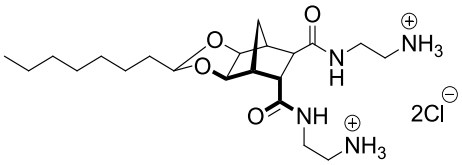
H1), 1.80 (1H, d, *J* = 10.3 Hz, H10*a*), 1.65–1.57 (3H, m, CHCH_2, H10*s*), 1.44–1.25 (28H, m, 5 × CH_2, 2 × *t*-Bu), 0.87 (3H, t, *J* = 6.9 Hz, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.3, 172.5, 157.1, 156.8, 104.2, 81.6, 80.0, 79.8, 78.8, 47.8, 44.7, 44.5, 43.4 (2 × C), 41.2, 40.6, 40.4, 33.0, 32.6, 31.9, 29.8, 29.6, 29.3, 28.5, 24.4, 22.8, 14.2.

HRMS (ESI, *m/z*) for $C_{31}H_{54}N_4O_8$ $[M + H]^+$ calc. 611.4014; found 611.4031.

4-Heptyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxamidoethylamine hydrogen chloride (5)[15]

[CAS Reg. No. 1233074-99-1]



To a stirring solution of Boc-protected amine **44** (650 mg, 1.06 mmol) and MeOH (10.6 mL) was added dropwise AcCl (760 μL, 10.6 mmol), and the reaction was stirred for 24 h at ambient temperature. The reaction was concentrated *in vacuo* and co-evaporated with MeOH (2 × 0.5 mL), to afford the title compound (510 mg, 99%) as a white solid.

m.p. 242–243 °C.

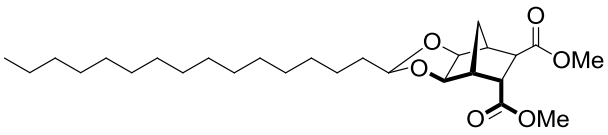
^{1}H NMR (270 MHz, CD_3OD) δ 4.66 (1H, t, *J* = 4.7 Hz, H4), 4.04 (1H, d, *J* = 5.6 Hz, H2), 4.00 (1H, d, *J* = 5.6 Hz, H6), 3.53–3.35 (4H, m, 2 × NHCH_2), 3.23 (1H, app. t, *J* = 4.9 Hz, H8), 3.10–3.03 (4H, m, 2 × NHCH_2), 2.65–2.62 (2H, m, H1, H7), 2.51 (1H, br s, H9), 1.75 (1H, d, *J* = 9.8 Hz, H10*a*), 1.64–1.56 (2H, m, CHCH_2), 1.48–1.29 (11H, m, 5 × CH_2, H10*s*), 0.90 (3H, t, *J* = 6.5 Hz, CH_3).

^{13}C NMR (67.5 MHz, CD_3OD) δ 177.0, 175.1, 105.1, 82.8, 80.0, 47.3, 47.1, 45.1, 44.9, 40.8, 38.5, 38.4, 33.9, 32.9, 32.7, 30.6, 30.3, 28.2, 25.2, 23.7, 14.4.

HRMS (ESI, *m/z*) for $C_{21}H_{38}N_4O_4$ $[M + 2H]^{2+}$ calc. 206.1519; found 206.1528.

Dimethyl 4-pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylate (45)[17]

[CAS Reg. No. 1774366-94-7]



To a stirring suspension of diol **17** (403 mg, 2.0 mmol), *p*-TSA (18 mg, 0.139 mmol), $MgSO_4$ (210 mg, 1.31 mmol) and PhMe (5 mL) was added hexadecanal **39** (805 mg, 3.0 mmol) and the reaction was heated for 16 h at 110 °C. Solid $MgSO_4$ was removed by filtration and the filtrate was diluted with EtOAc (30 mL), washed with H_2O (2 × 25 mL), brine (25 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the crude material which was purified by column chromatography (5% EtOAc in pet. spirits) to afford the title compound (505 mg, 65%) as a white solid.

R_f = 0.10 (50% EtOAc in pet. spirits).

m.p. 71–74 °C.

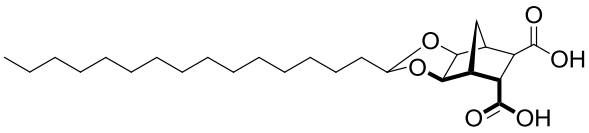
^{1}H NMR (270 MHz, $CDCl_3$) δ 4.65 (1H, t, *J* = 4.8 Hz, H4), 4.03 (1H, d, *J* = 5.4 Hz, H2), 3.90 (1H, d, *J* = 5.4 Hz, H6), 3.70 (6H, s, 2 × Me), 3.22 (1H, app. t, *J* = 4.9 Hz, H8), 2.72 (1H, d, *J* = 4.9 Hz, H9), 2.66–2.64 (2H, m, H1, H7), 1.78 (1H, dd, *J* = 10.7, 1.4 Hz, H10*a*), 1.66–1.59 (2H, m, CHCH_2), 1.41–1.25 (27H, m, 13 × CH_2, H10*s*), 0.88 (3H, t, *J* = 6.4 Hz, CH_3).

^{13}C NMR (67.5 MHz, $CDCl_3$) δ 174.1, 172.9, 104.4, 81.4, 78.9, 52.5, 52.3, 45.4, 45.2, 43.8, 43.4, 32.9, 32.1, 31.8, 29.8 (6 × C), 29.7 (2 × C), 29.6, 29.5, 24.4, 22.8, 14.3.

HRMS (ESI, *m/z*) for $C_{27}H_{46}O_6$ $[M + H]^+$ calc. 467.3367; found 467.3378.

4-Pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxylic acid (46)[17]

[CAS Reg. No. 1233075-00-7]



To the stirred solution of the ester **45** (258 mg, 0.56 mmol) in THF (2.3 mL), 2M NaOH (1.1 mL) was added and the reaction was stirred for 16 h at ambient temperature. The reaction was concentrated under reduced pressure and all organic-soluble impurities were extracted with CH_2Cl_2 (2 × 10 mL). The aqueous solution was acidified with sat. KH_2PO_4 (pH = 5), extracted with EtOAc (4 × 25 mL), dried ($MgSO_4$) and filtered to give a white waxy solid (198 mg, 86%).

m.p. 127–134 °C (lit. 125.0–127.0 °C).[15]

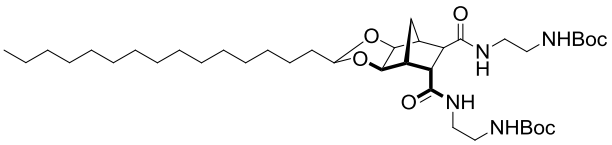
^{1}H NMR (270 MHz, DMSO-d_6) δ 4.62 (1H, t, *J* = 4.7 Hz, H4), 3.96 (1H, d, *J* = 5.6 Hz, H2), 3.89 (1H, d, *J* = 5.6 Hz, H6), 3.00 (1H, app. t, *J* = 5.0 Hz, H8), 2.53 (1H, br s, H1), 2.45 (1H, br s, H7), 2.40 (1H, d, *J* = 5.0 Hz, H9), 1.62–1.49 (3H, m, CHCH_2, H10*a*), 1.23–1.18 (27H, m, 13 × CH_2, H10*s*), 0.85 (3H, t, *J* = 6.2 Hz, CH_3).

^{13}C NMR (100 MHz DMSO-d_6) δ 174.6, 173.3, 103.2, 80.7, 78.2, 45.0, 44.4, 43.6, 43.3, 32.3, 31.3, 31.2, 29.0 (7 × C), 28.9 (2 × C), 28.7, 23.6, 22.1, 13.9.

HRMS (ESI, *m/z*) for $C_{25}H_{42}O_6$ [M + Na]$^+$ calc. 461.2874; found 461.2882.

8-*endo*-9-*exo*-Di[2′-(2″,3″-bis-*tert*-butoxycarbonylamino)ethylcarbamoyl]-4-pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane (47)[17]

[CAS Reg. No. 1774366-99-2]



A MW vial was charged with diacid **46** (350 mg, 0.798 mmol), EDCI (640 mg, 3.34 mmol), HOBt (12 mg, 0.089 mmol) and anhydrous $CHCl_3$ (13 mL) and stirred at ambient temperature for 30 min. Amine **38** (387 mg, 2.42 mmol) was then added and the reaction was irradiated for 30 min at 50 °C. The resulting homogenous clear solution was diluted with $CHCl_3$ (15 mL), washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a white solid that was purified using flash column chromatography (50–70% EtOAc in pet. spirits) to give the title compound (303 mg, 52%) as a colourless oil.

R_f = 0.07 (70% EtOAc in pet. spirits).

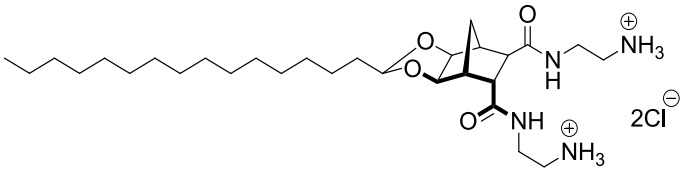
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (1H, br s, NH), 6.69 (1H, br s, NH), 5.08–5.01 (2H, m, 2 × NH), 4.64 (1H, t, *J* = 4.9 Hz, H4), 4.13 (1H, d, *J* = 5.2 Hz, H6), 3.96 (1H, d, *J* = 5.2 Hz, H2), 3.43–3.22 (8H, m, 4 × NHC*H*$_2$), 2.91 (1H, app. t, *J* = 5.3 Hz, H8), 2.57 (1H, br s, H1), 2.54 (1H, d, *J* = 3.7 Hz, H7), 2.42 (1H, d, *J* = 5.3 Hz, H9), 1.81 (1H, d, *J* = 9.8 Hz, H10*a*), 1.64–1.59 (2H, m, CHC*H*$_2$), 1.44–1.43 (18H, m, 2 × *t*-Bu), 1.39–1.24 (27H, m, 13 × CH_2, H10*s*), 0.87 (3H, t, *J* = 6.9 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 172.5, 157.1, 156.8, 104.2, 81.6, 80.0, 79.8, 78.7, 47.8, 44.6, 44.5, 43.4, 41.1, 40.6, 40.5, 34.0, 33.0, 32.6, 32.1, 29.84 (2 × C), 29.81 (2 × C), 29.80 (2 × C), 29.72, 29.69, 29.67, 29.5, 28.55, 28.53, 24.4, 22.8, 14.3.

HRMS (ESI, *m/z*) for $C_{39}H_{70}N_4O_8$ [M + H]$^+$ calc. 723.5266; found 723.5263.

4-Pentadecyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]decane-8-*endo*-9-*exo*-dicarboxamidoethylamine hydrogen chloride (8)[17]

[CAS Reg. No. 1774367-02-0]



To a stirring solution of Boc-protected amine **47** (76 mg, 0.11 mmol) and MeOH (1.1 mL) was added dropwise AcCl (80 µL, 1.1 mmol), and the reaction was stirred for 24 h at ambient temperature. The reaction was concentrated *in vacuo* and co-evaporated with MeOH (2 × 0.5 mL), to afford the title compound (58 mg, 94%) as a white solid.

m.p. 156–200 °C (slow decomposition).

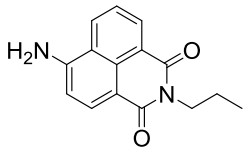
^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.33 (1H, t, *J* = 5.5 Hz, NH), 8.23 (1H, t, *J* = 5.4 Hz, NH), 7.96 (6H, br s, 2 × NH_3), 4.59 (1H, t, *J* = 4.7 Hz, H4), 3.91 (1H, d, *J* = 5.6 Hz, H2), 3.86 (1H, d, *J* = 5.6 Hz, H6), 3.32–3.19 (4H, m, 2 × NHC*H*$_2$), 3.10 (1H, app. t, *J* = 4.7 Hz, H8), 2.86–2.81 (4H, m, 2 × NHC*H*$_2$), 2.60 (1H, d, *J* = 4.7 Hz, H9), 2.51–2.49 (1H, m, H7), 2.41 (1H, br s, H1), 1.53–1.49 (3H, m, CHC*H*$_2$, H10*a*), 1.31–1.23 (27H, m, 13 × CH_2, H10*s*), 0.85 (3H, t, *J* = 7.1 Hz, CH_3).

^{13}C NMR (125 MHz, DMSO-*d*$_6$) δ 173.5, 171.5, 102.9, 81.0, 78.2, 46.1, 44.5, 43.1, 42.8, 38.5, 38.4, 36.8, 36.7, 32.4, 31.3, 31.1, 29.1 (3 × C), 29.04 (3 × C), 28.99 (3 × C), 28.7, 23.8, 22.1, 14.0.

HRMS (ESI, *m/z*) for $C_{29}H_{54}N_4O_4$ $[M + 2H]^{2+}$ calc. 262.2145; found 262.2150.

6-Amino-2-propyl-1*H*-benz[*de*]isoquinoline-1,3-(2*H*)-dione (35)[18]

[CAS Reg. No. 94860-68-1]



A stirring solution of *tert*-Butyl (1,3-dioxo-2-propyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)carbamate[19] (106 mg, 0.299 mmol) in CH_2Cl_2 (2.7 mL) was treated with TFA (300 µL, 3.918 mmol, 13.1 equiv.) and the homogeneous yellow solution stirred at ambient temperature for 18 h. After this time an orange precipitate had formed. The solvent was removed under reduced pressure to give a powder that was reconstituted in H_2O (*ca*. 3 mL) and the pH was adjusted to 8 using sat. $NaHCO_3$. The resulting solid was collected using vacuum filtration, washing with H_2O gives the title compound (72 mg, 95%) as a light orange powder.

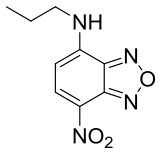
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 7.4, 0.7, 1H), 8.42 (d, *J* = 8.1, 1H), 8.10 (dd, *J* = 8.3, 0.7, 1H), 7.66 (dd, *J* = 8.3, 7.4, 1H), 6.89 (d, *J* = 8.1, 1H), 4.14–4.11 (m, 2H), 1.75 (app. sext, J_{app} = 7.5, 2H), 1.01 (t, *J* = 7.5, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 164.1, 148.9, 133.7, 131.5, 129.8, 126.7, 125.0, 123.2, 120.1, 112.3, 109.6, 41.7, 21.4, 11.5.

Data is in accordance with the literature.[18]

4-Propylamino-7-nitrobenzo-2-oxa-1,3-diazole (36)[20]

[CAS Reg. No. 54517-98-5]



To the stirring solution of 4-chloro-7-nitrobenzofuran (196 mg, 0.982 mmol) in MeOH (9.8 mL) was added propylamine (80 µL, 0.982 mmol) and Et_3N (210 µL, 1.51 mmol). Stirring was maintained at ambient temperature for 24 h before the reaction mixture was concentrated under reduced pressure. The crude material was diluted in EtOAc (20 mL) and washed with 0.1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the title compound (204 mg, 94%) as a dark green oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (1H, d, *J* = 8.7 Hz, ArH), 6.31 (1H, br s, NH), 6.18 (1H, d, *J* = 8.7 Hz, ArH), 3.49–3.46 (2H, m, NHCH_2), 1.89–1.82 (2H, m, CH_2CH$_3$), 1.10 (3H, t, *J* = 7.4 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 144.1, 144.0, 136.7, 124.0, 98.7, 45.8, 22.0, 11.6.

HRMS (ESI, *m/z*) for $C_9H_{10}N_4O_3$ $[M + H]^+$ calc. 223.0826; found 223.0823.

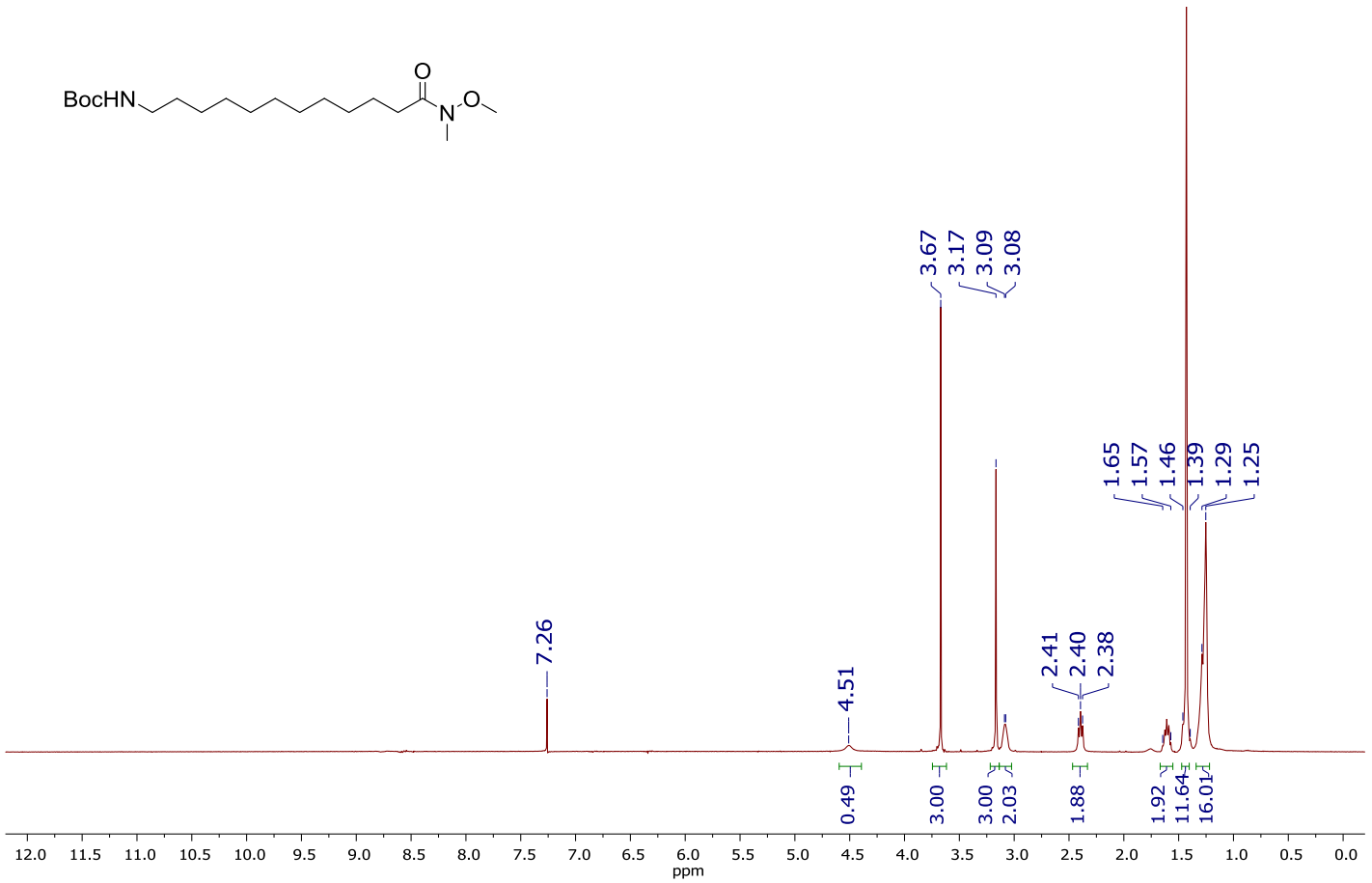


Figure S1: ^{1}H NMR spectrum of **15** in $CDCl_3$.

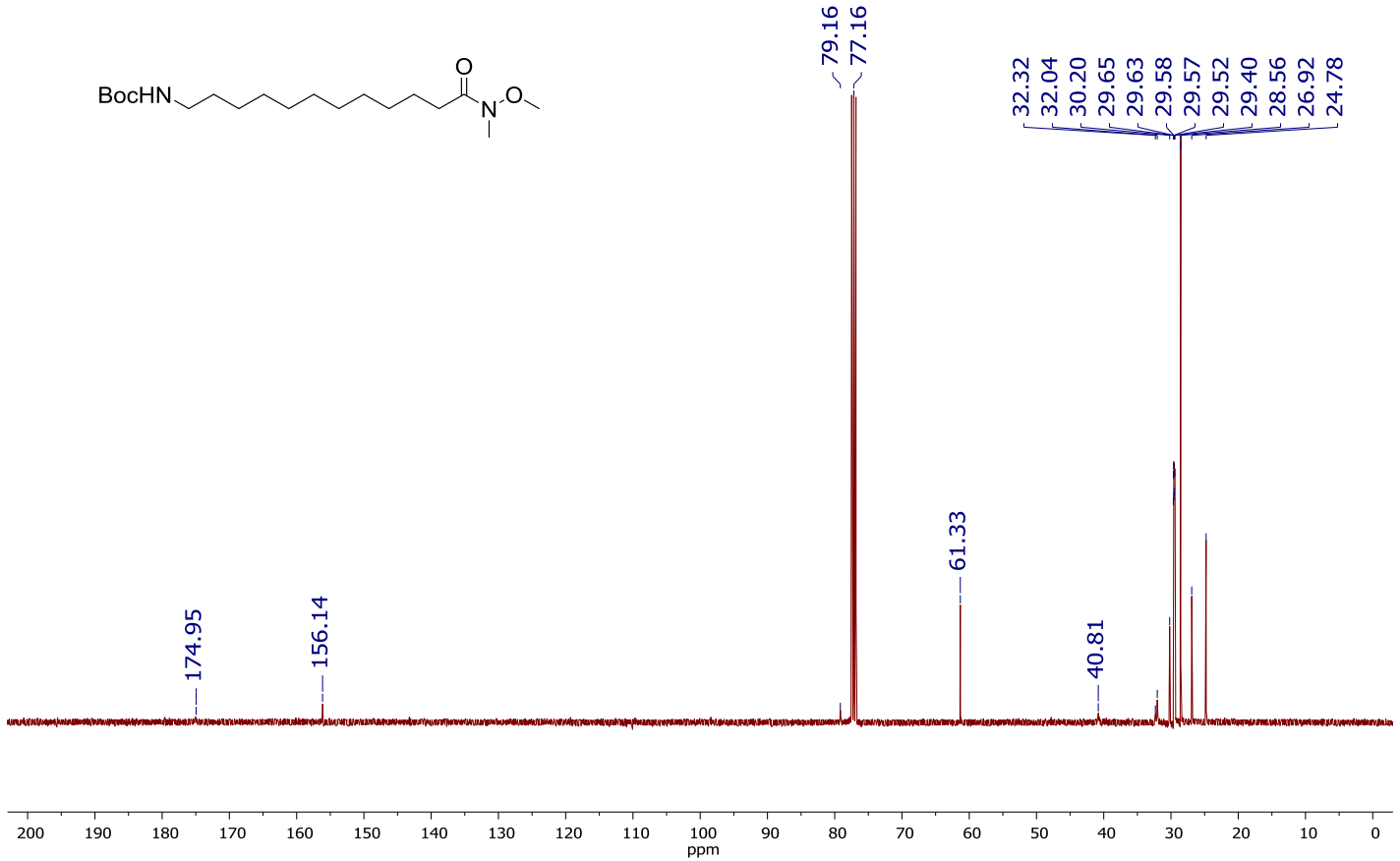


Figure S2: ^{13}C NMR spectrum of **15** in $CDCl_3$.

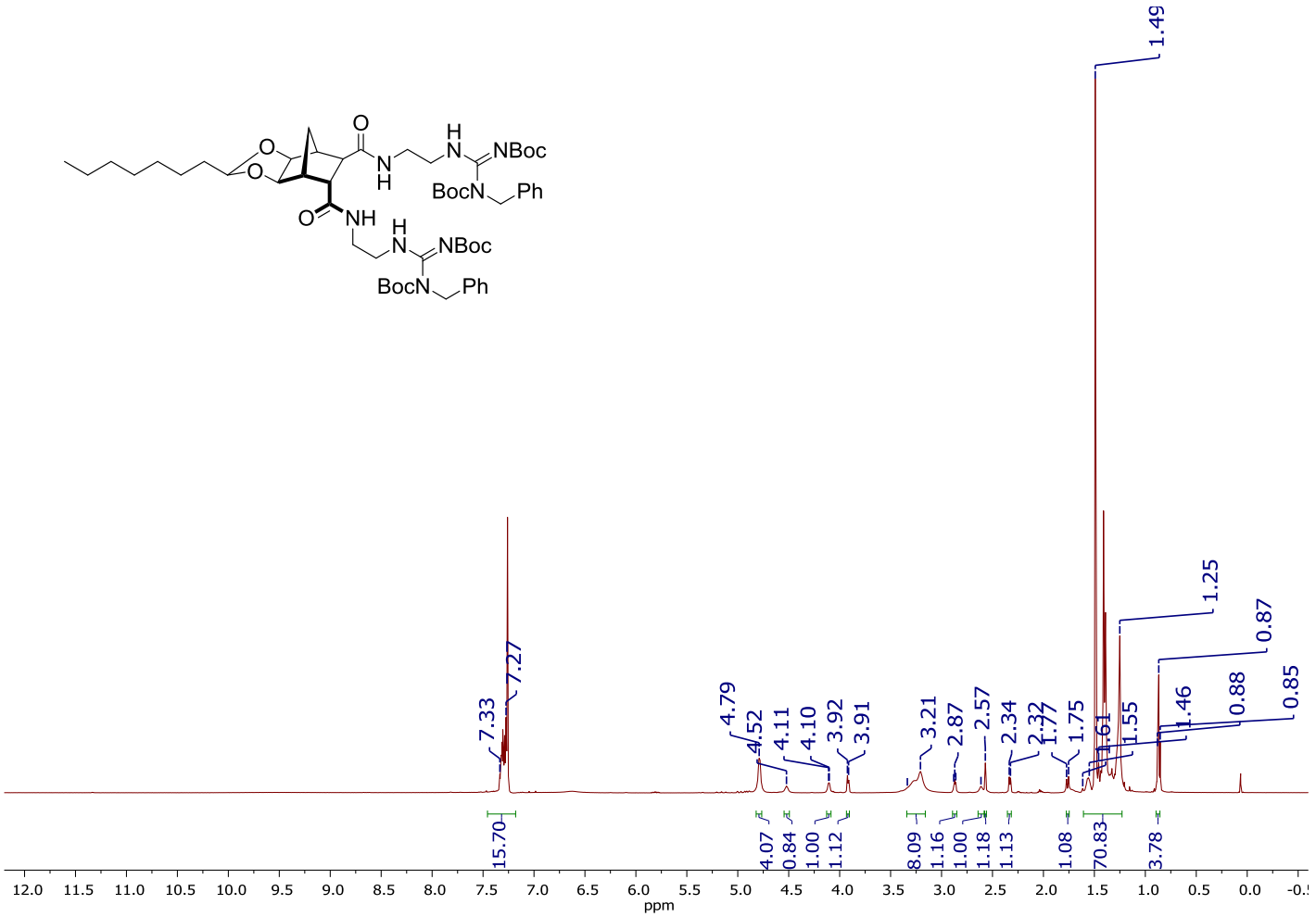


Figure S3: ^{1}H NMR spectrum of **6** in $CDCl_3$.

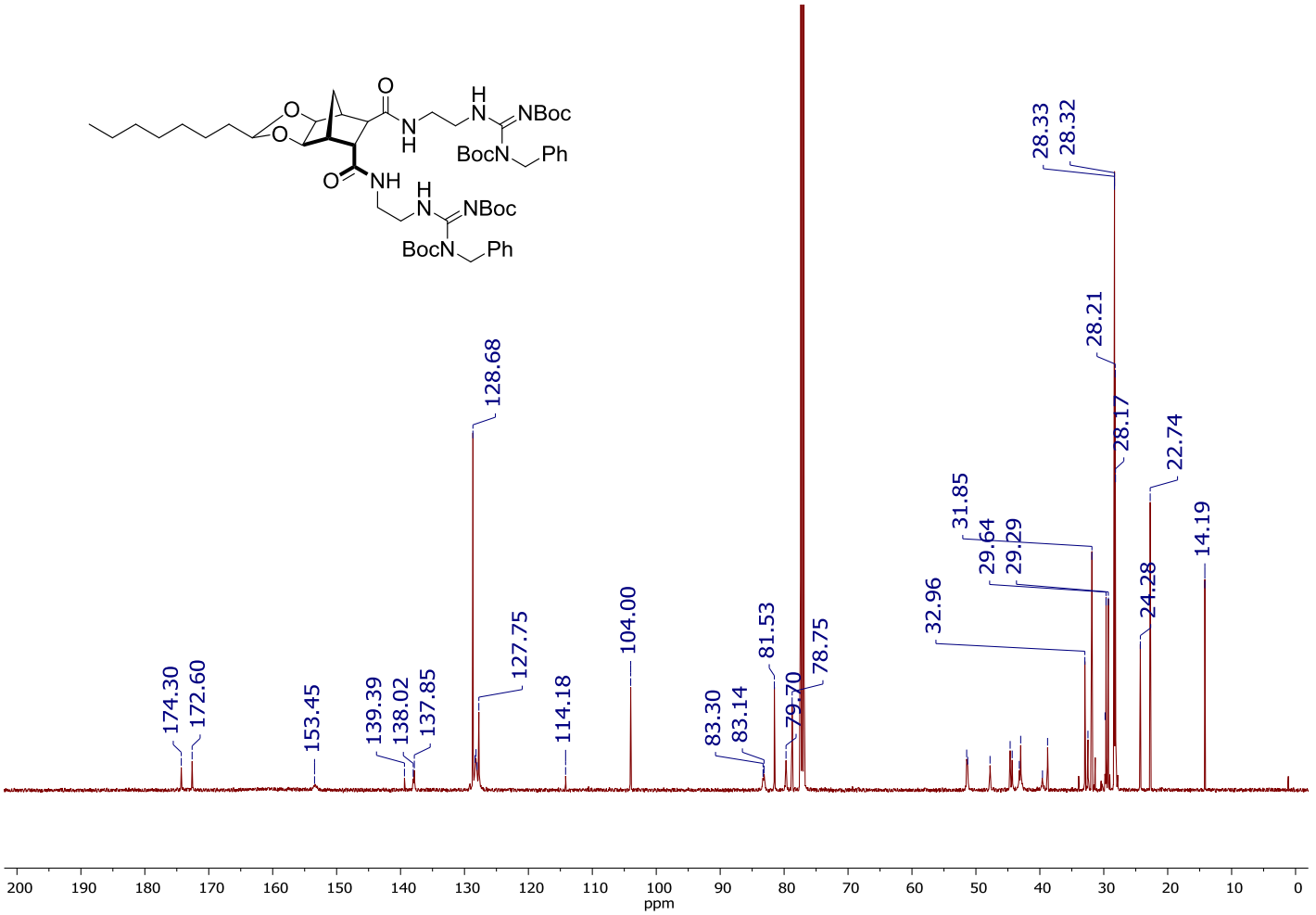


Figure S4: ^{13}C NMR spectrum of **6** in $CDCl_3$.

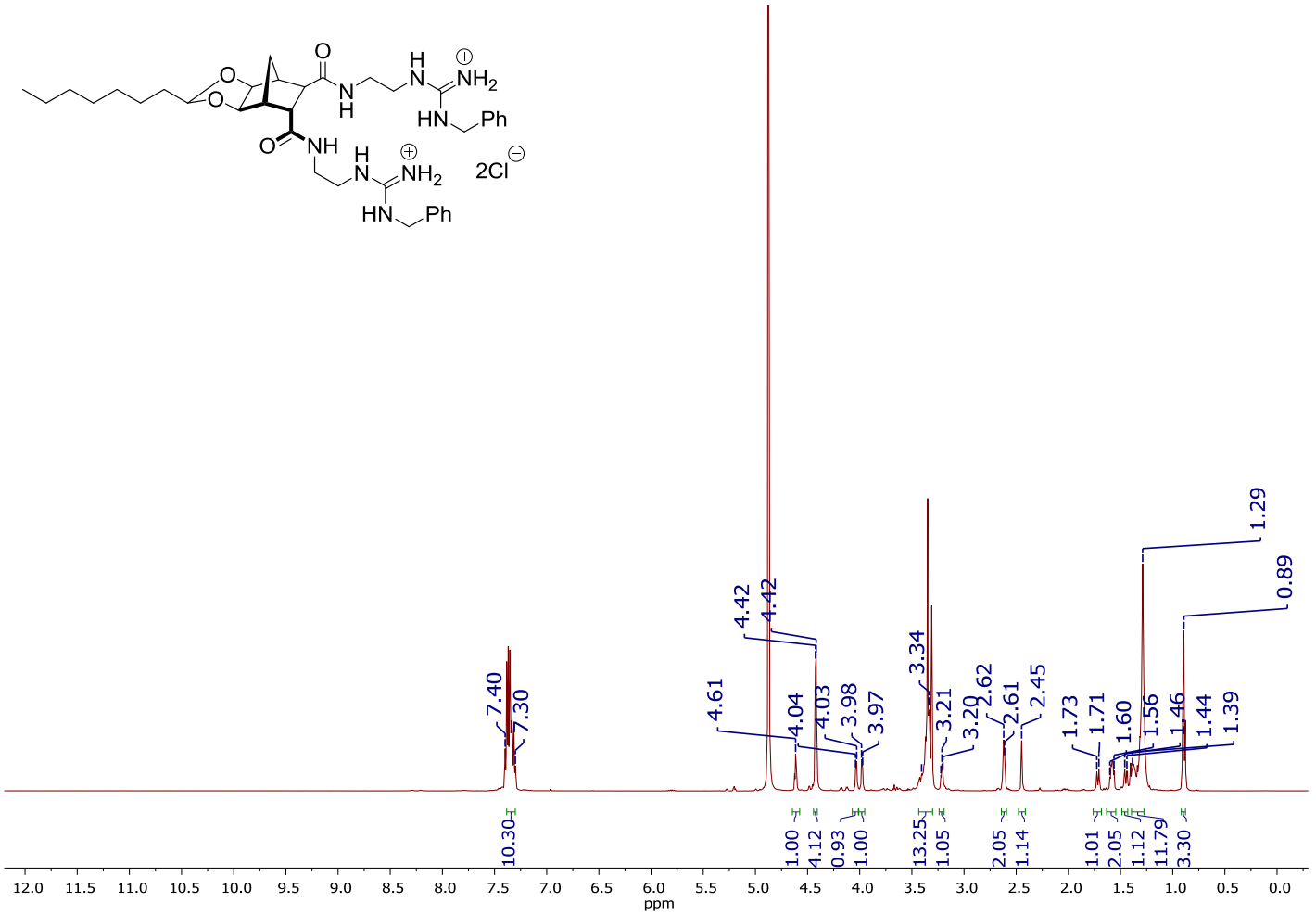


Figure S5: ^{1}H NMR spectrum of **7** in CD_3OD.

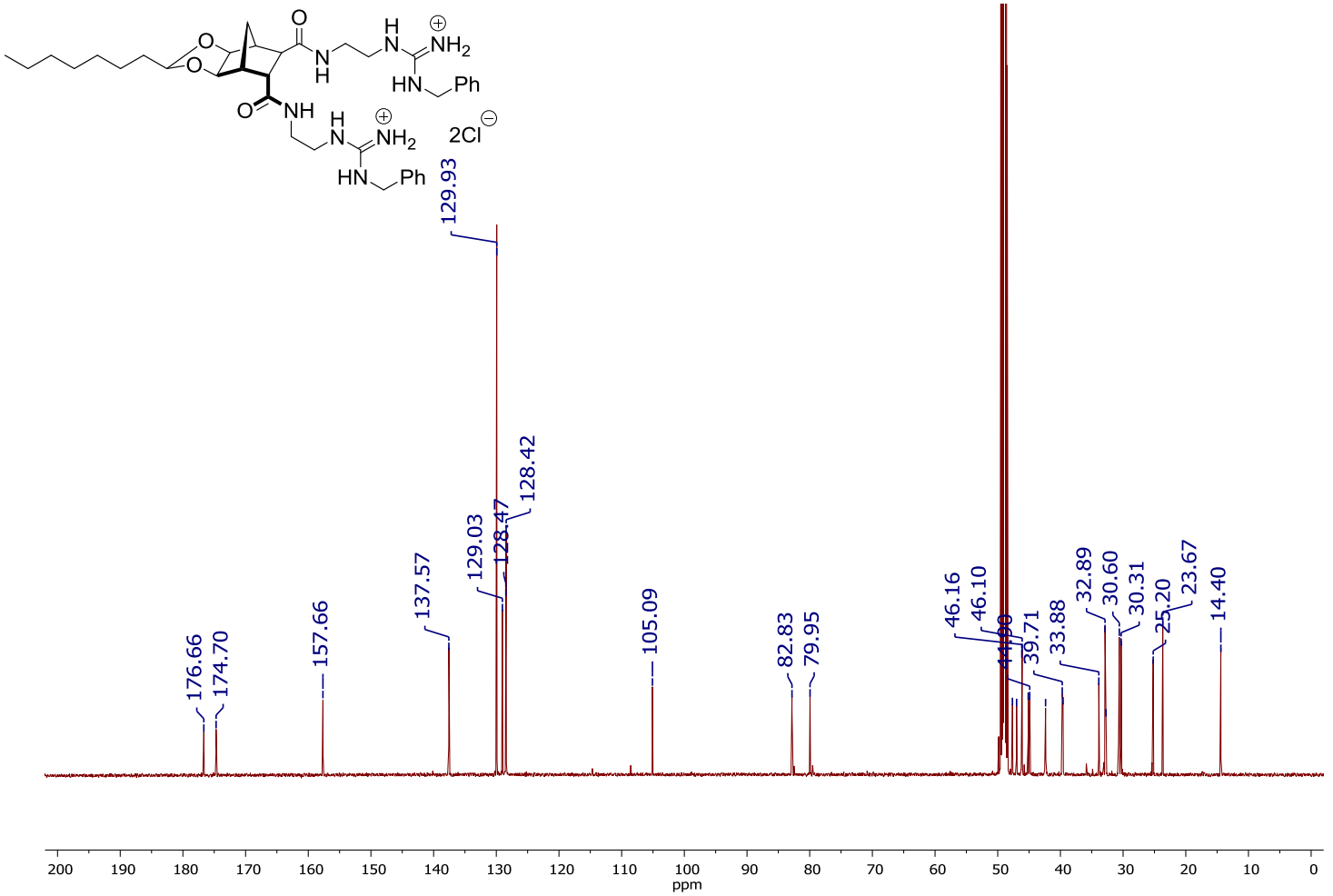


Figure S6: ^{13}C NMR spectrum of **7** in CD_3OD.

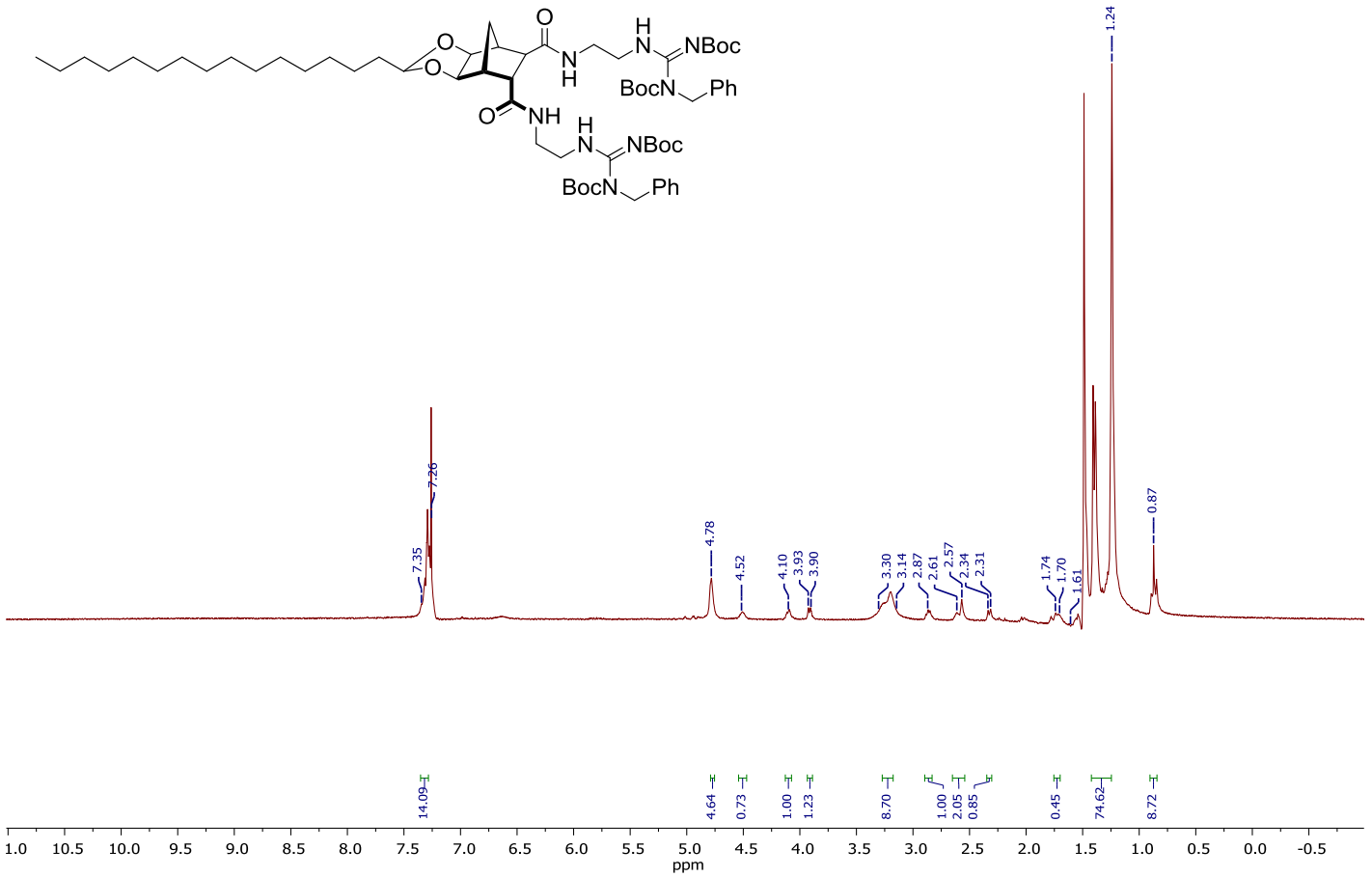


Figure S7: ^{1}H NMR spectrum of **9** in $CDCl_3$.

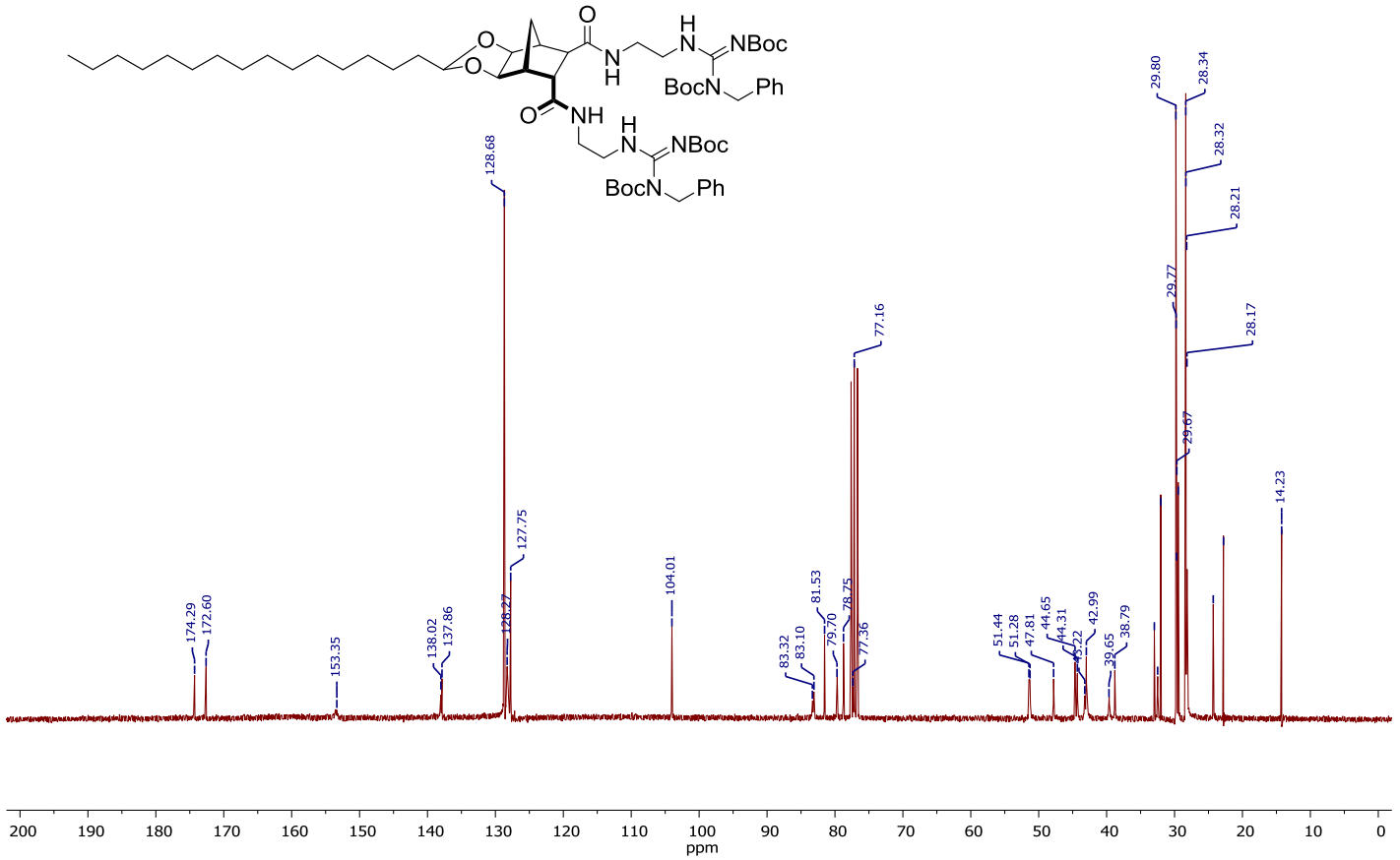


Figure S8: ^{13}C NMR spectrum of **9** in $CDCl_3$.

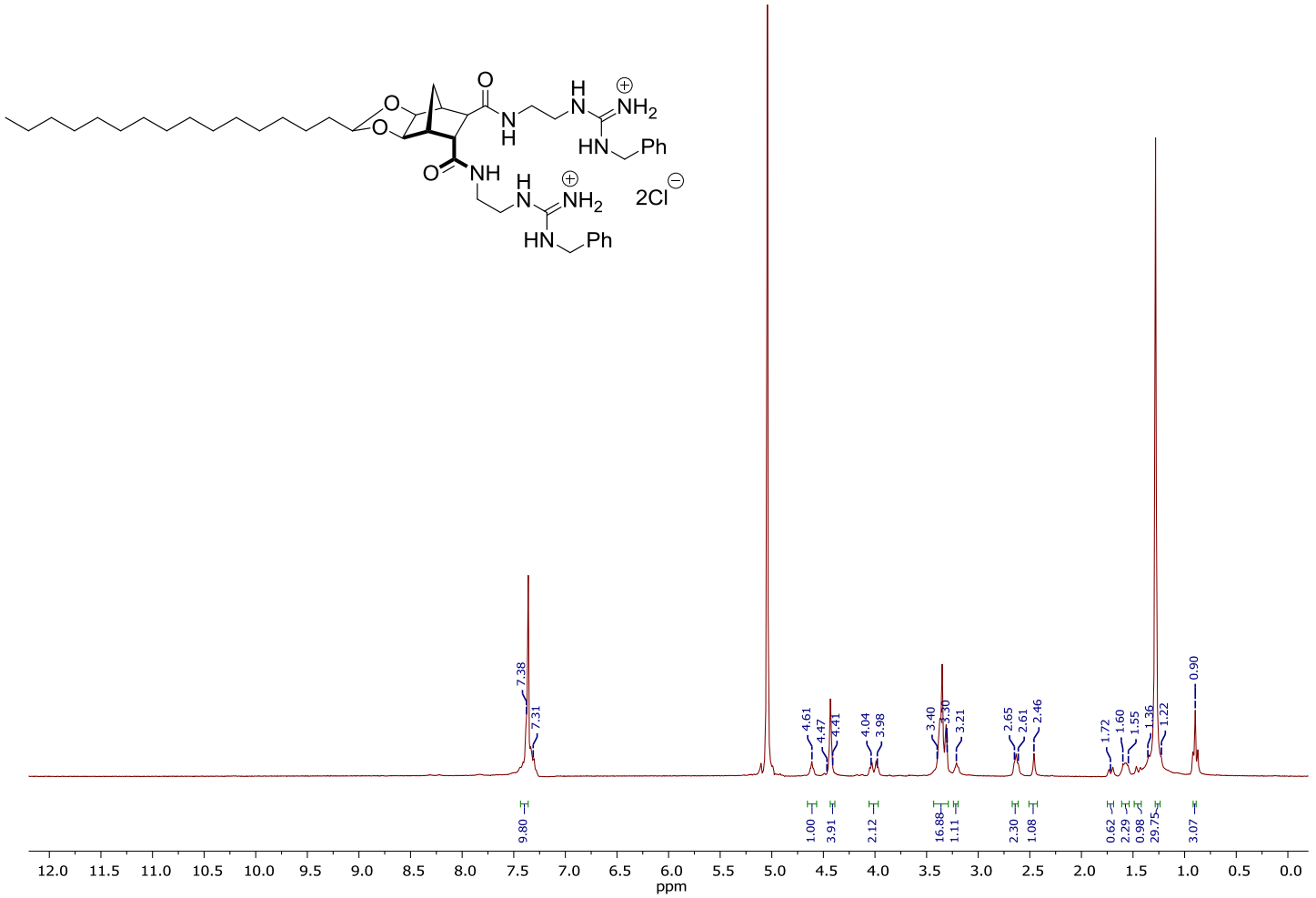


Figure S9: ^{1}H NMR spectrum of **10** in CD_3OD.

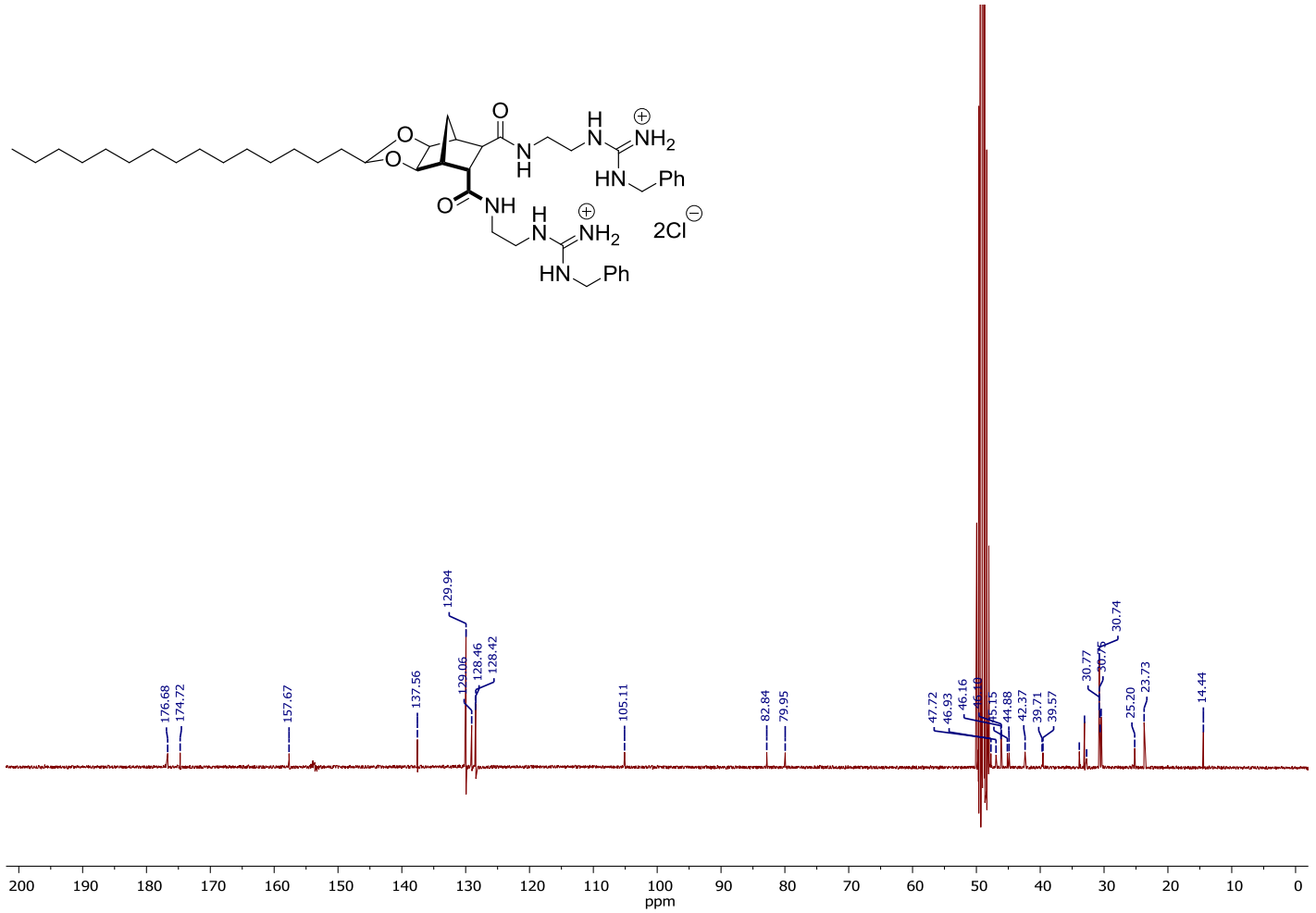


Figure S10: ^{13}C NMR spectrum of **10** in CD_3OD.

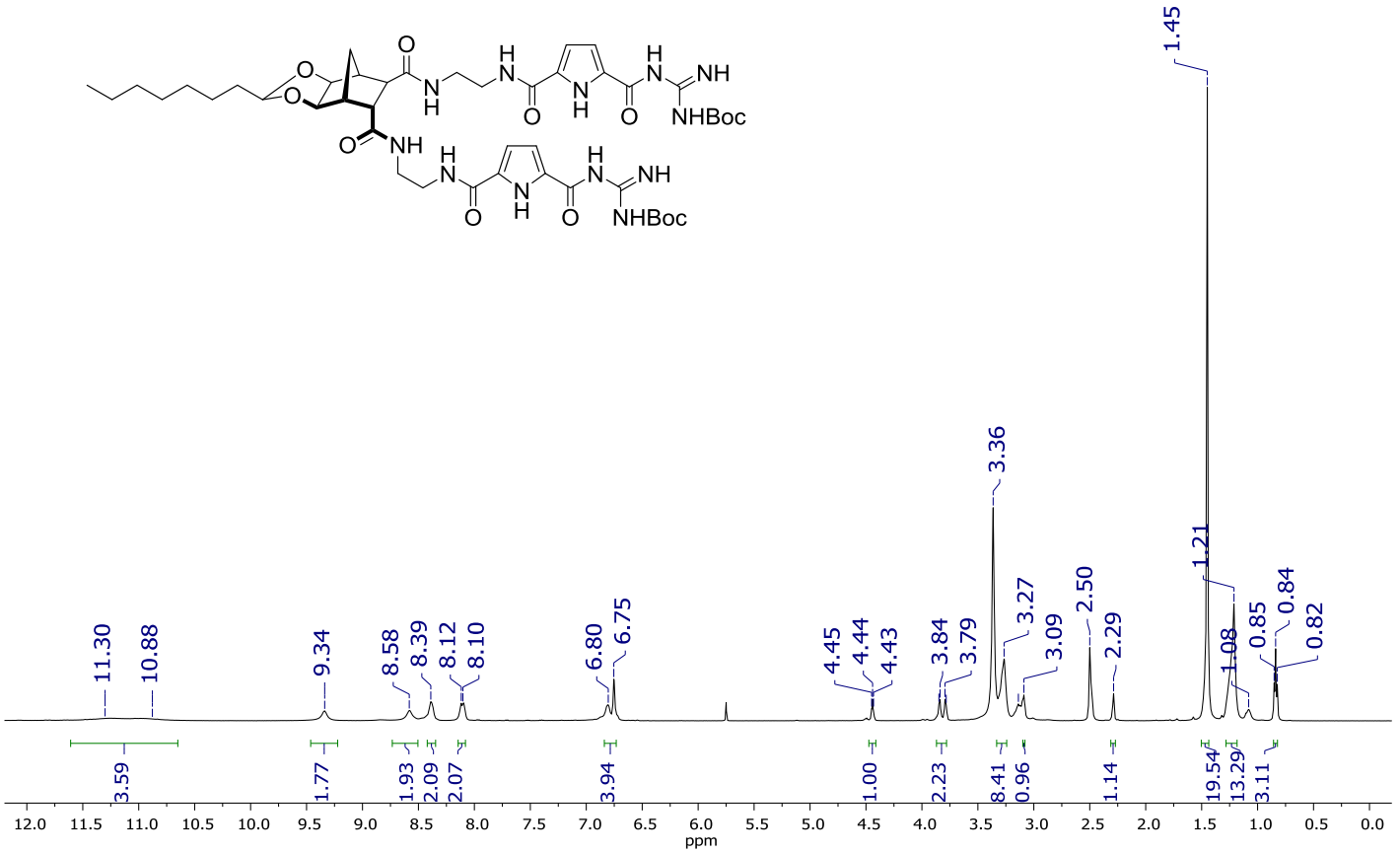


Figure S11: ^{1}H NMR spectrum of **12** in DMSO-*d*$_6$.

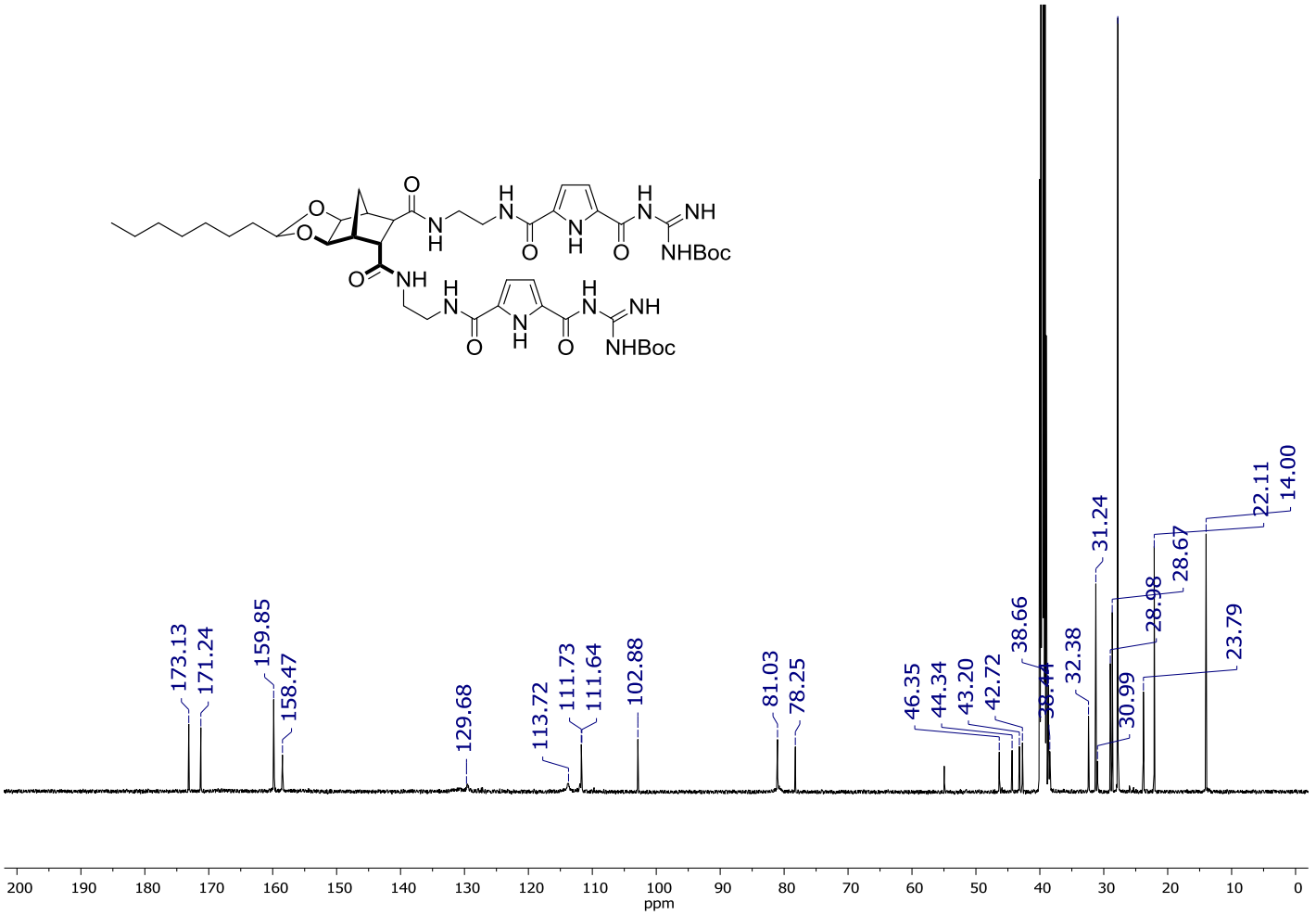


Figure S12: ^{13}C NMR spectrum of **12** in DMSO-d_6.

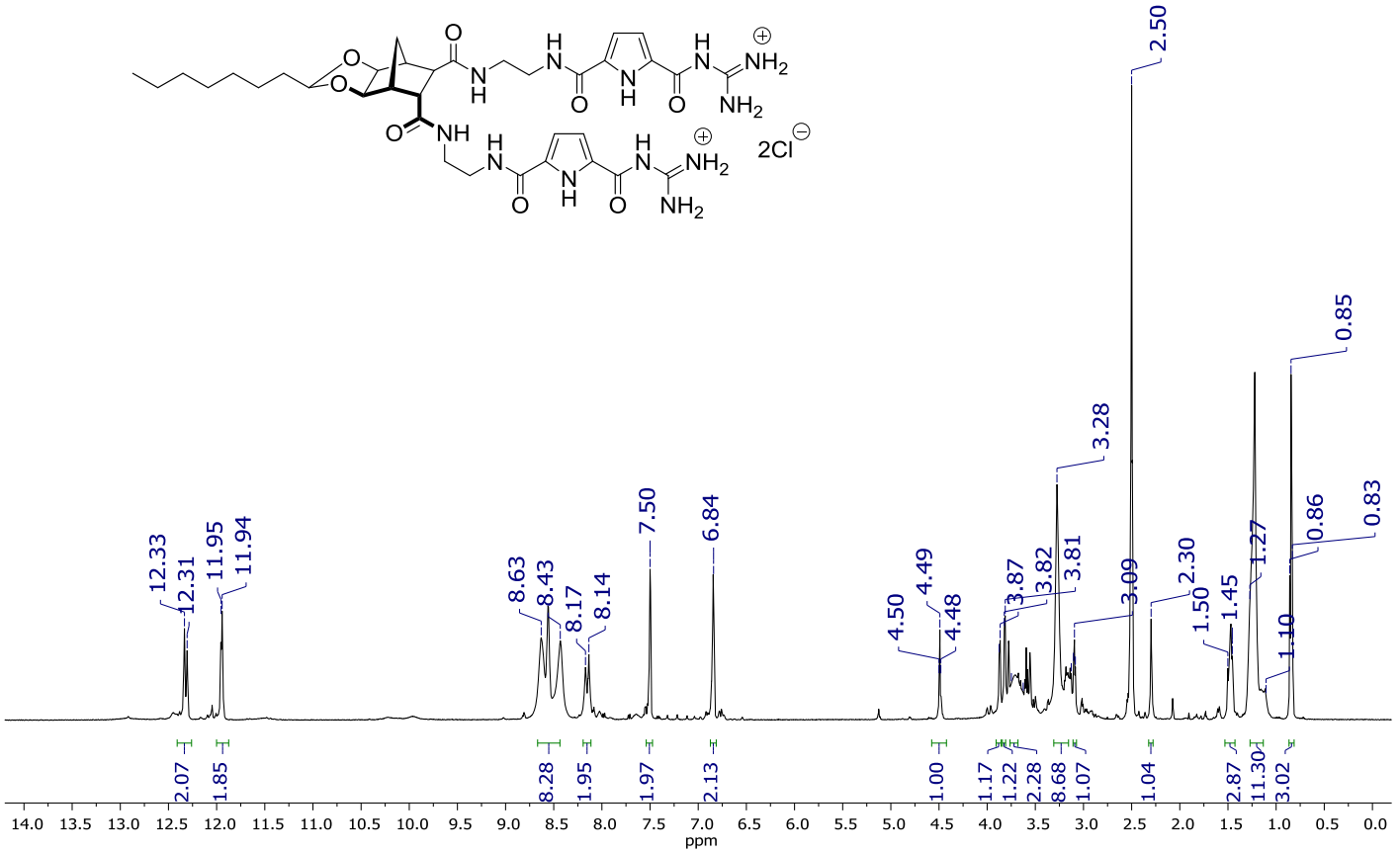


Figure S13: ^{1}H NMR spectrum of **13** in DMSO-d_6.

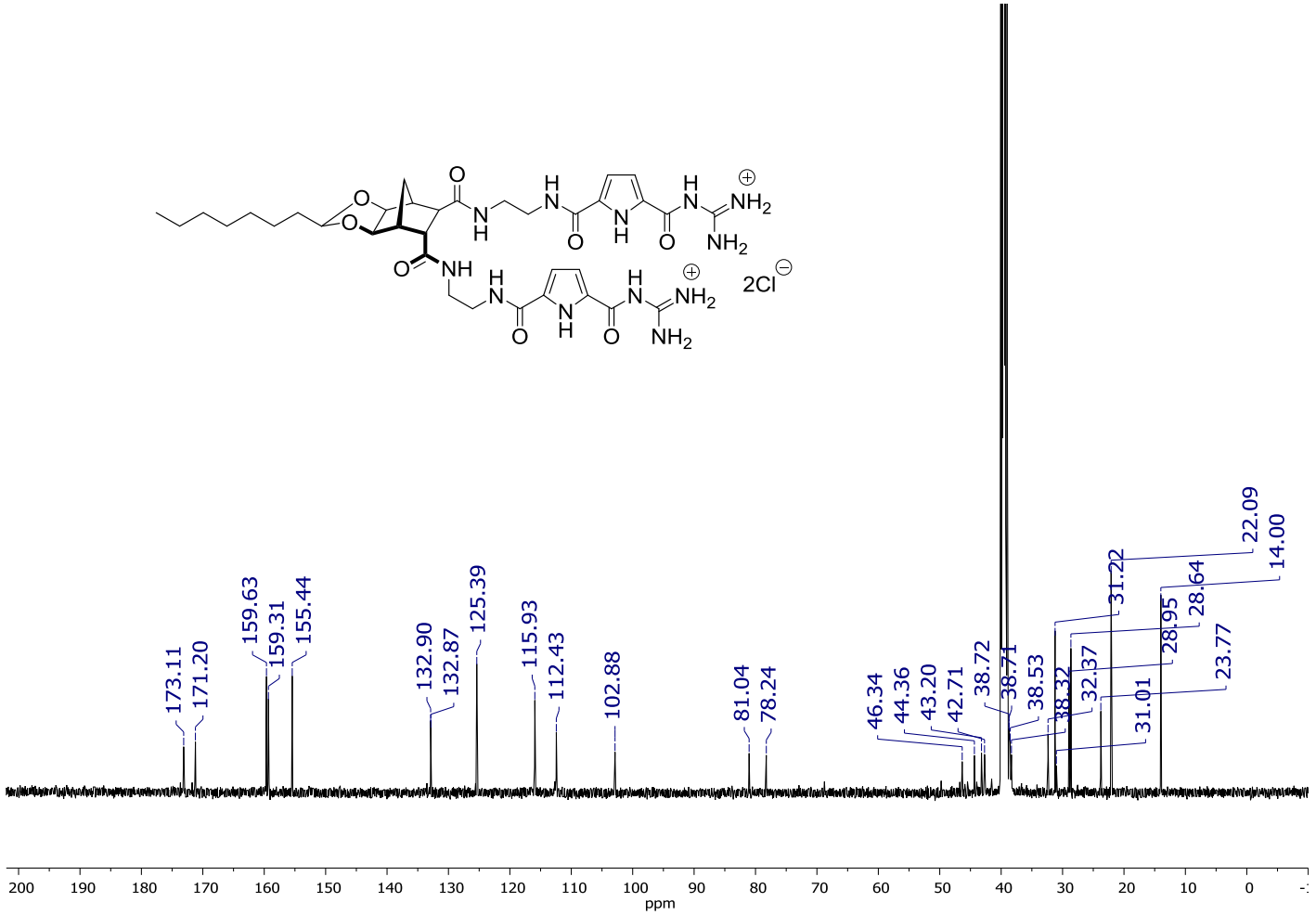


Figure S14: ^{13}C NMR spectrum of **13** in DMSO-d_6.

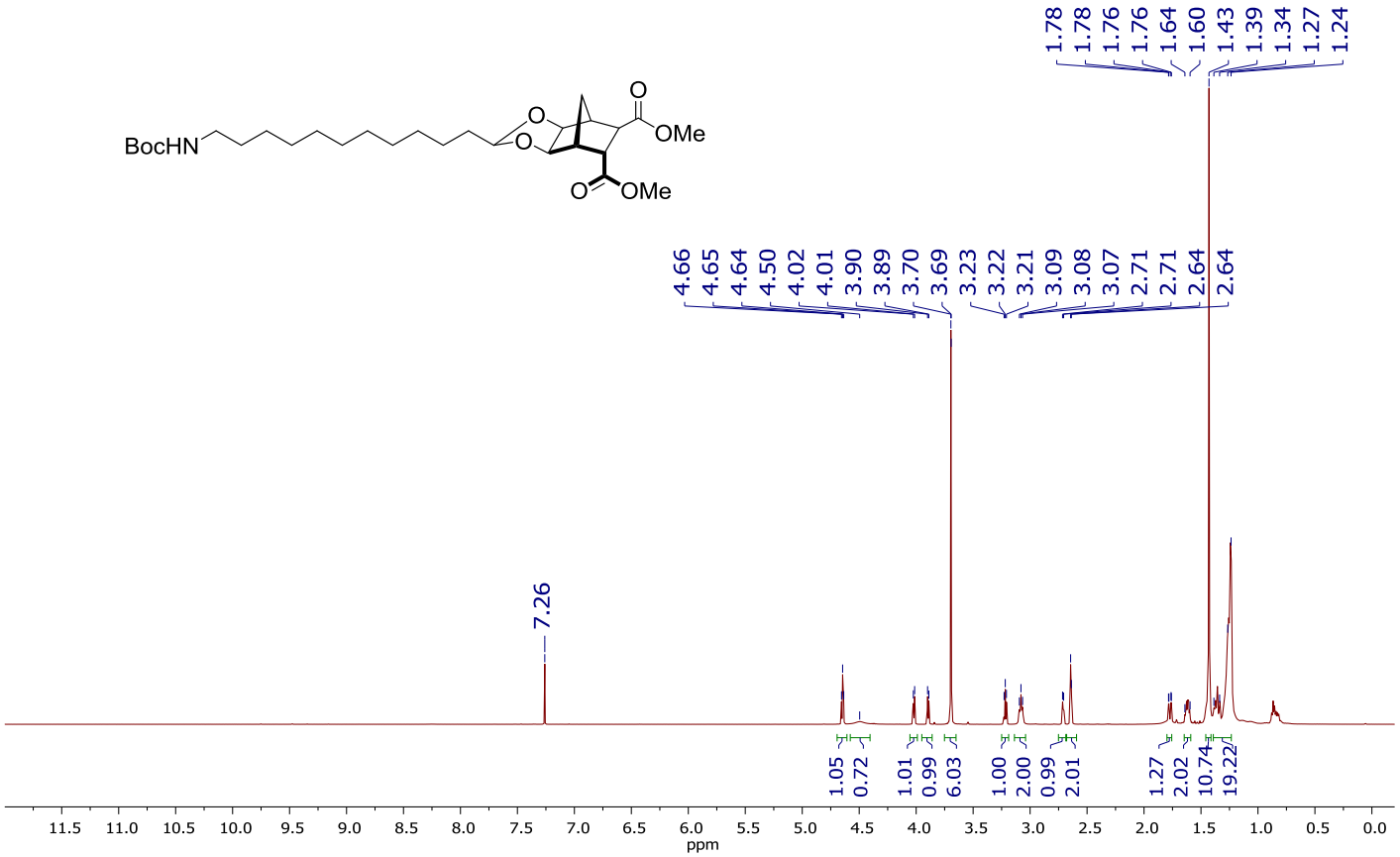


Figure S15: ^{1}H NMR spectrum of **18** in $CDCl_3$.

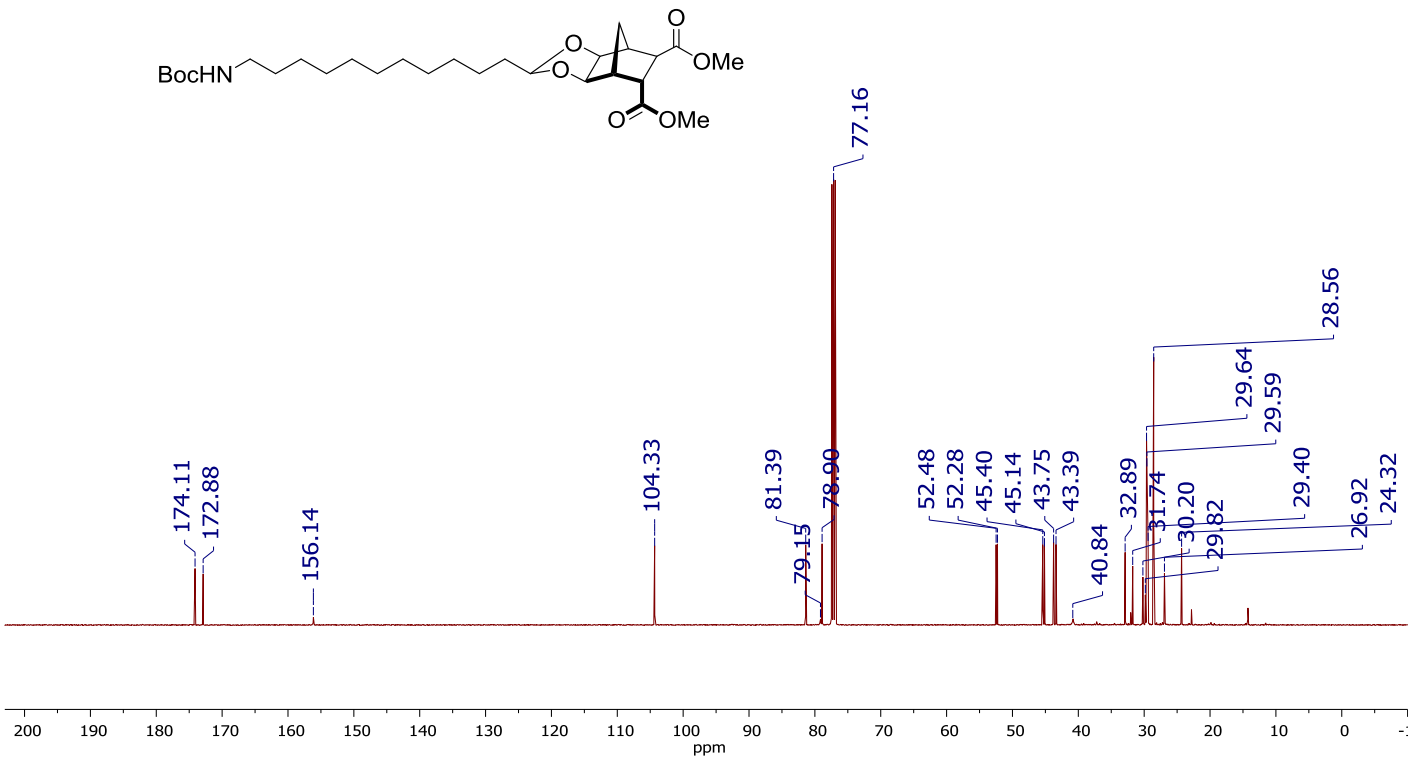


Figure S16: ^{13}C NMR spectrum of **18** in $CDCl_3$.

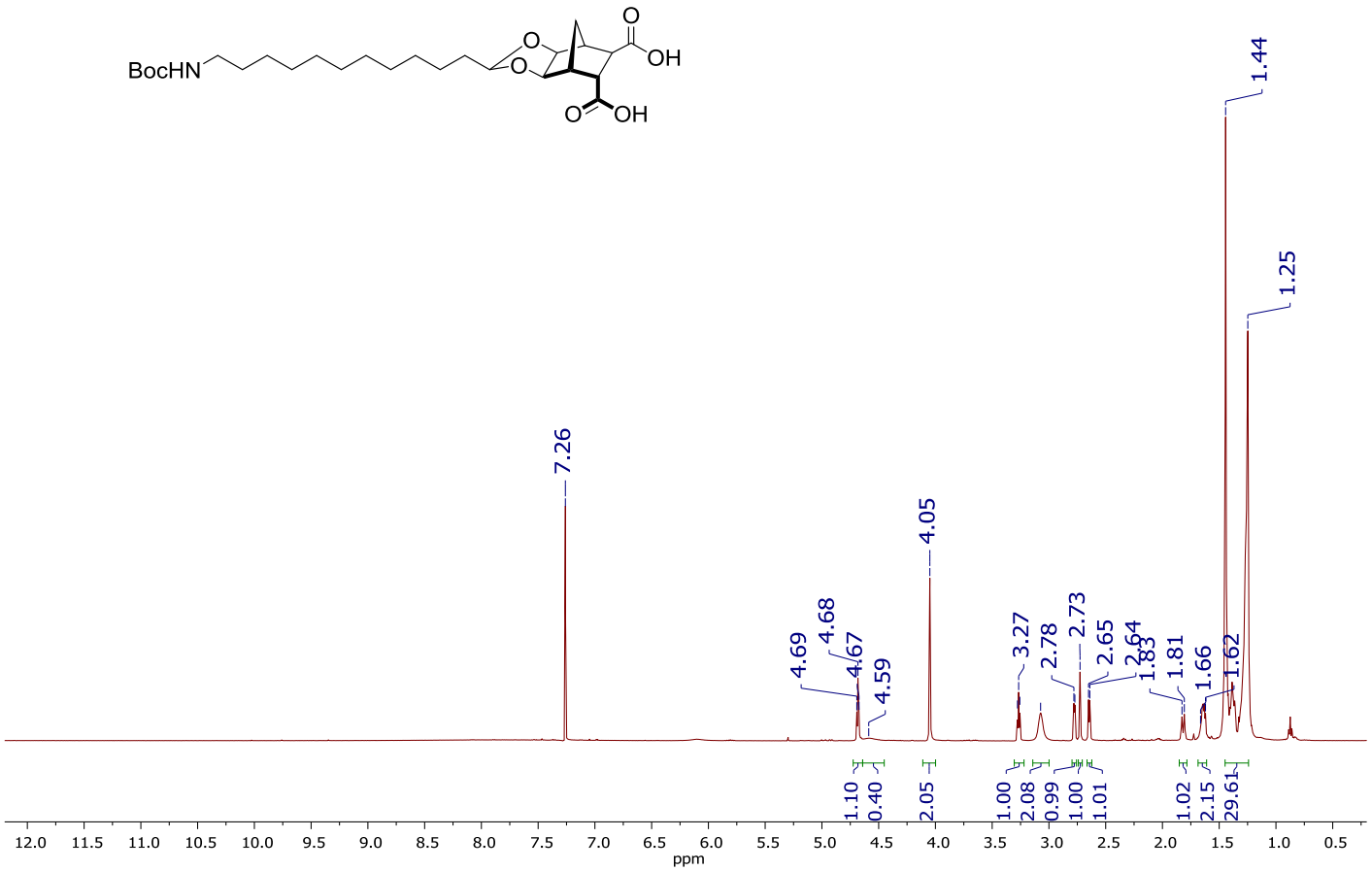


Figure S17: ^{1}H NMR spectrum of **19** in $CDCl_3$.

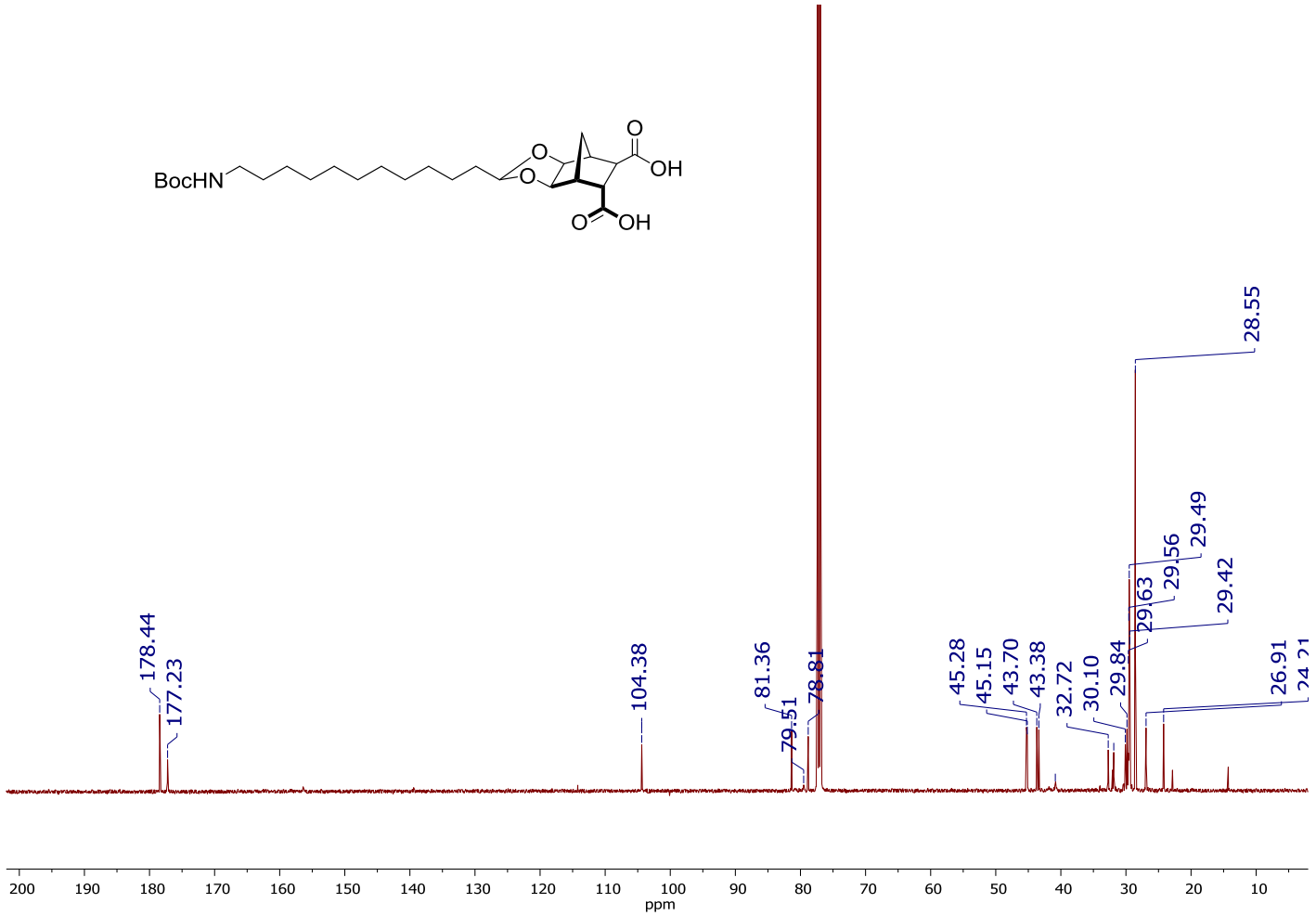


Figure S18: ^{13}C NMR spectrum of **19** in $CDCl_3$.

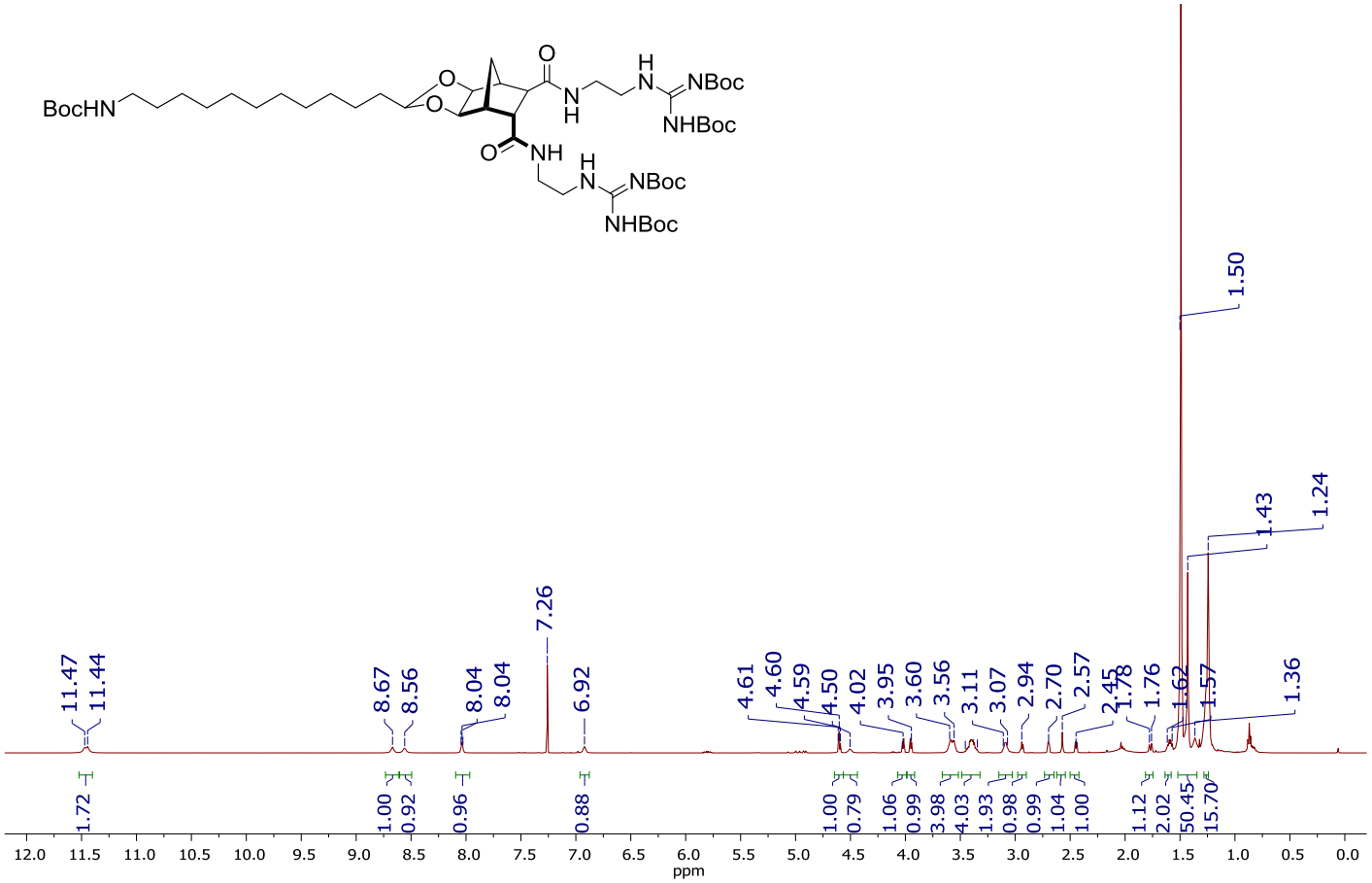


Figure S19: ^{1}H NMR spectrum of **20** in $CDCl_3$

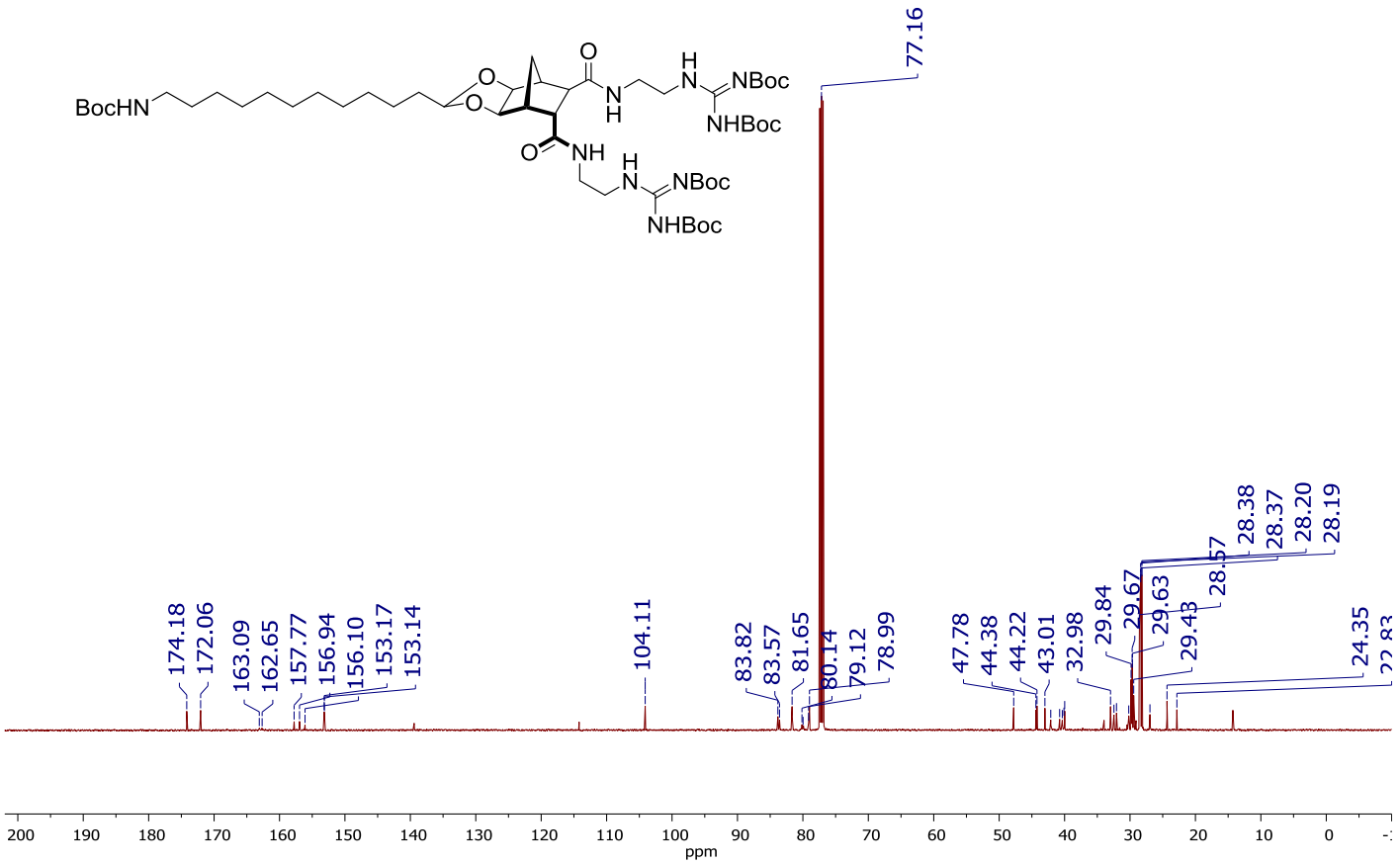


Figure S20: ^{13}C NMR spectrum of **20** in $CDCl_3$

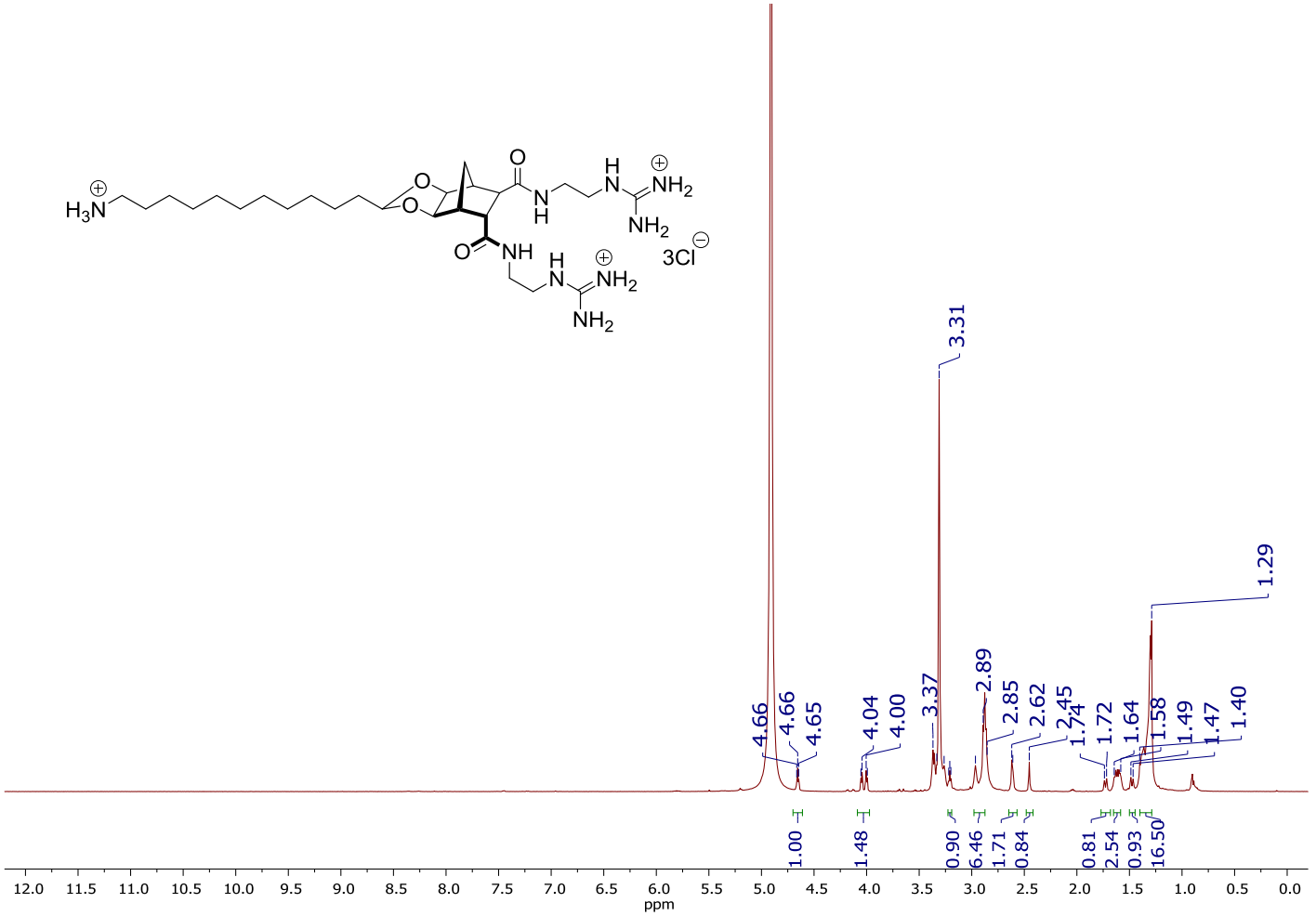


Figure S21: ^{1}H NMR spectrum of **21** in CD_3OD.

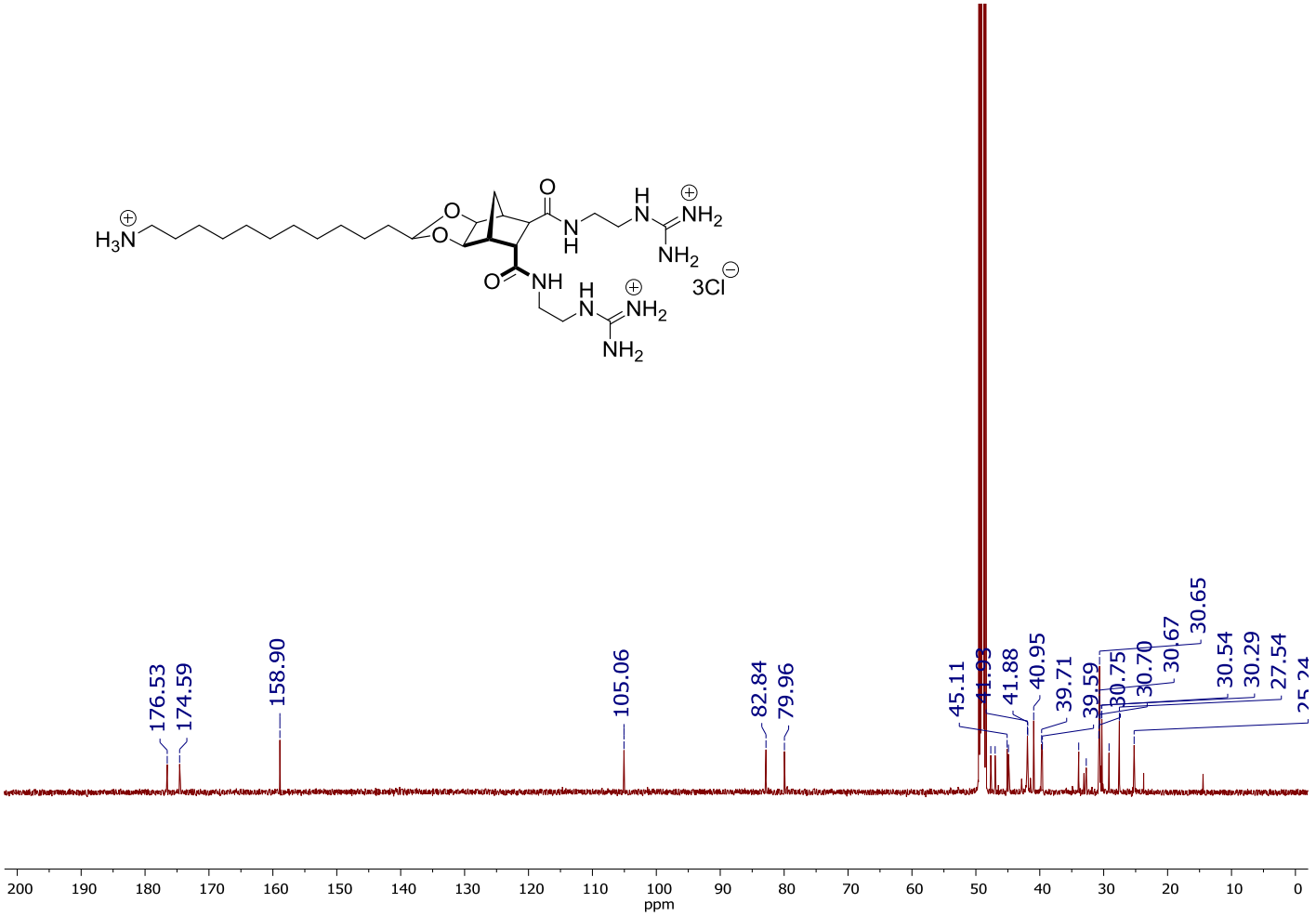


Figure S22: ^{13}C NMR spectrum of **21** in CD_3OD.

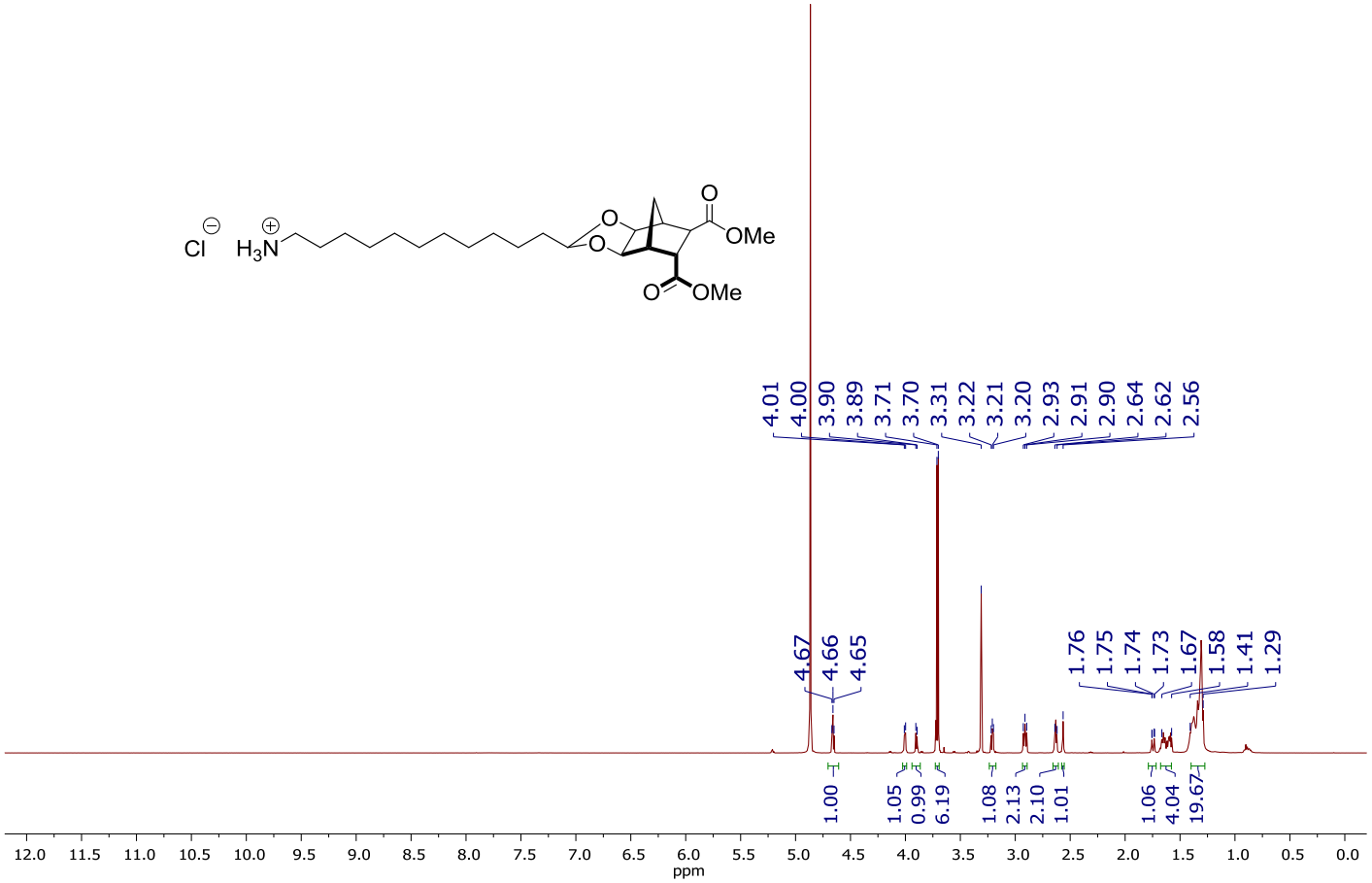


Figure S23: ^{1}H NMR spectrum of **23** in CD_3OD.

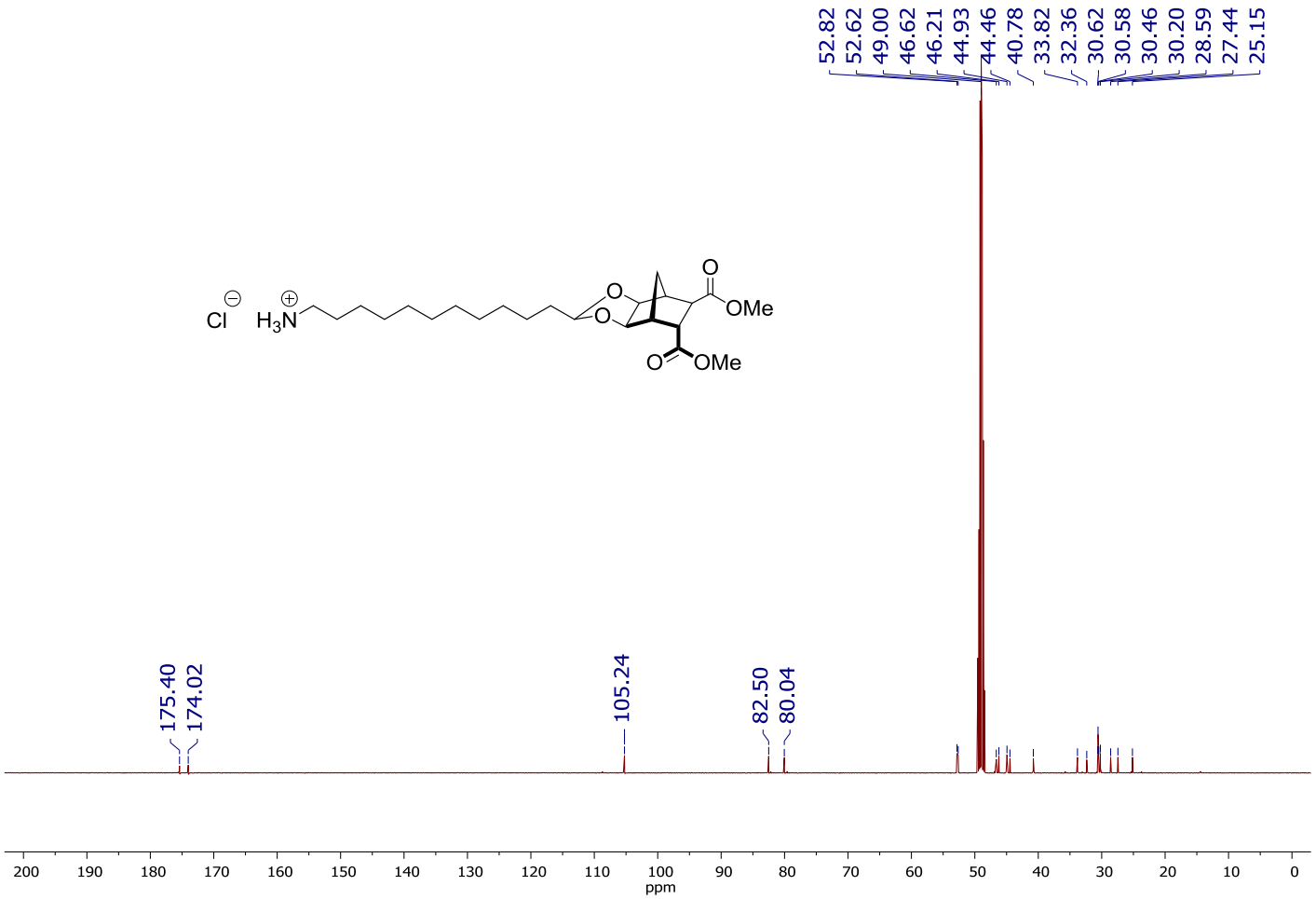


Figure S24: ^{13}C NMR spectrum of **23** in CD_3OD.

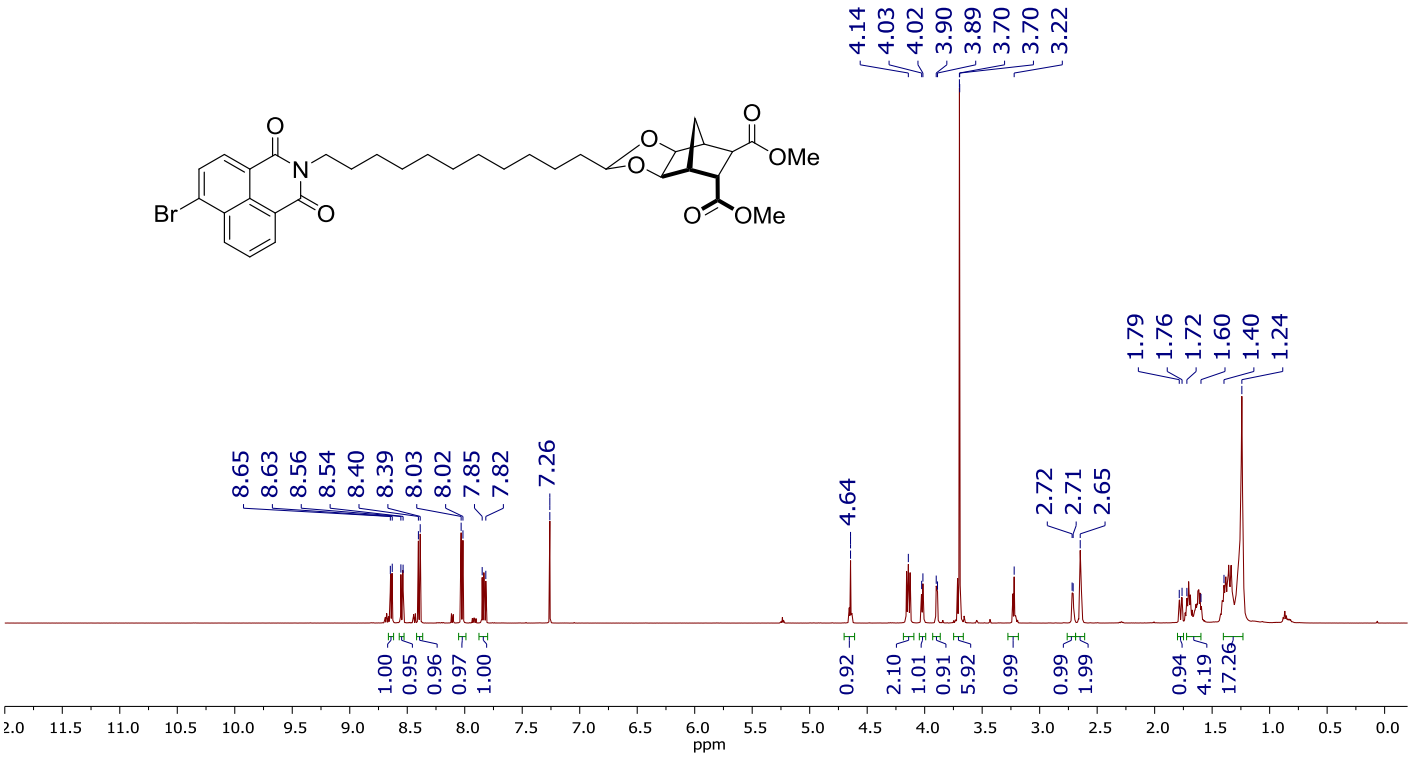


Figure S25: ^{1}H NMR spectrum of **25** in $CDCl_3$.

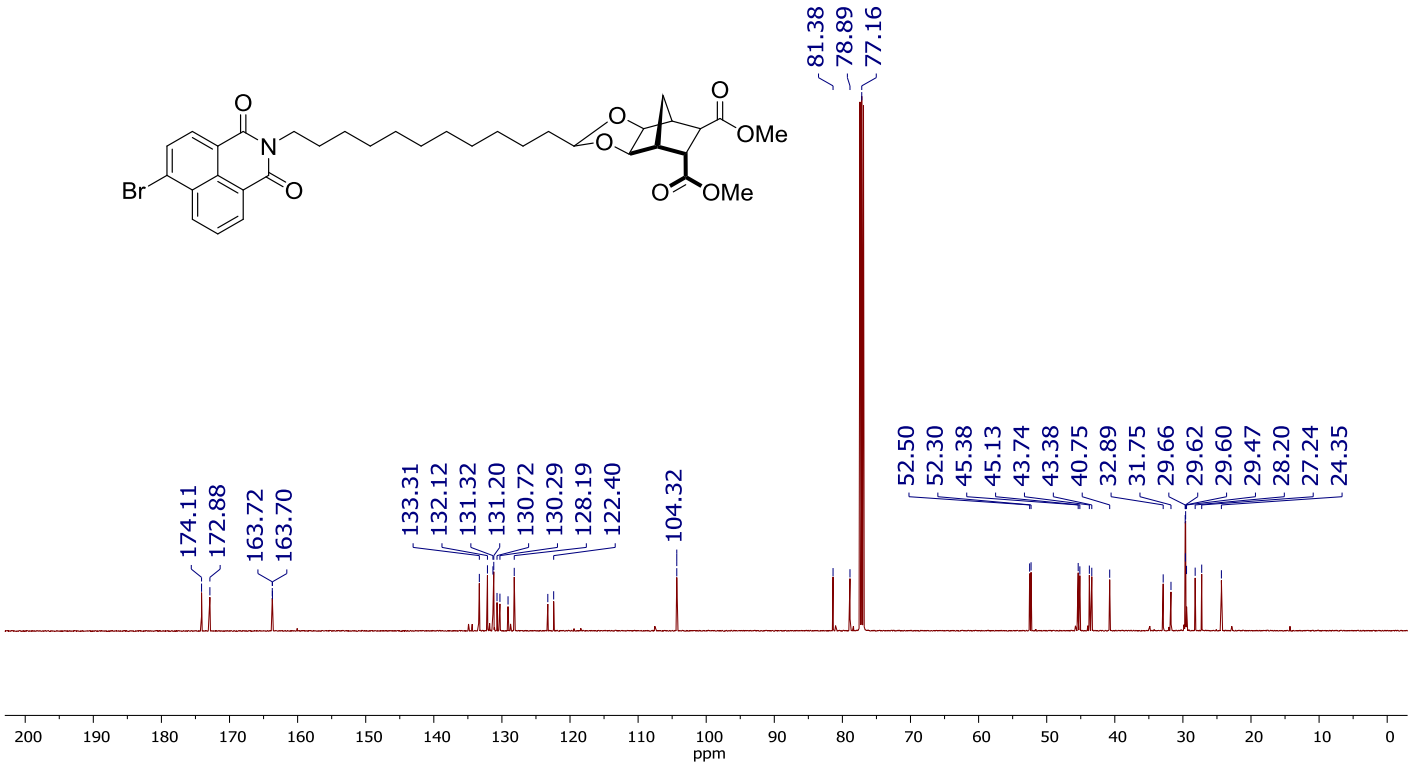


Figure S26: ^{13}C NMR spectrum of **25** in $CDCl_3$.

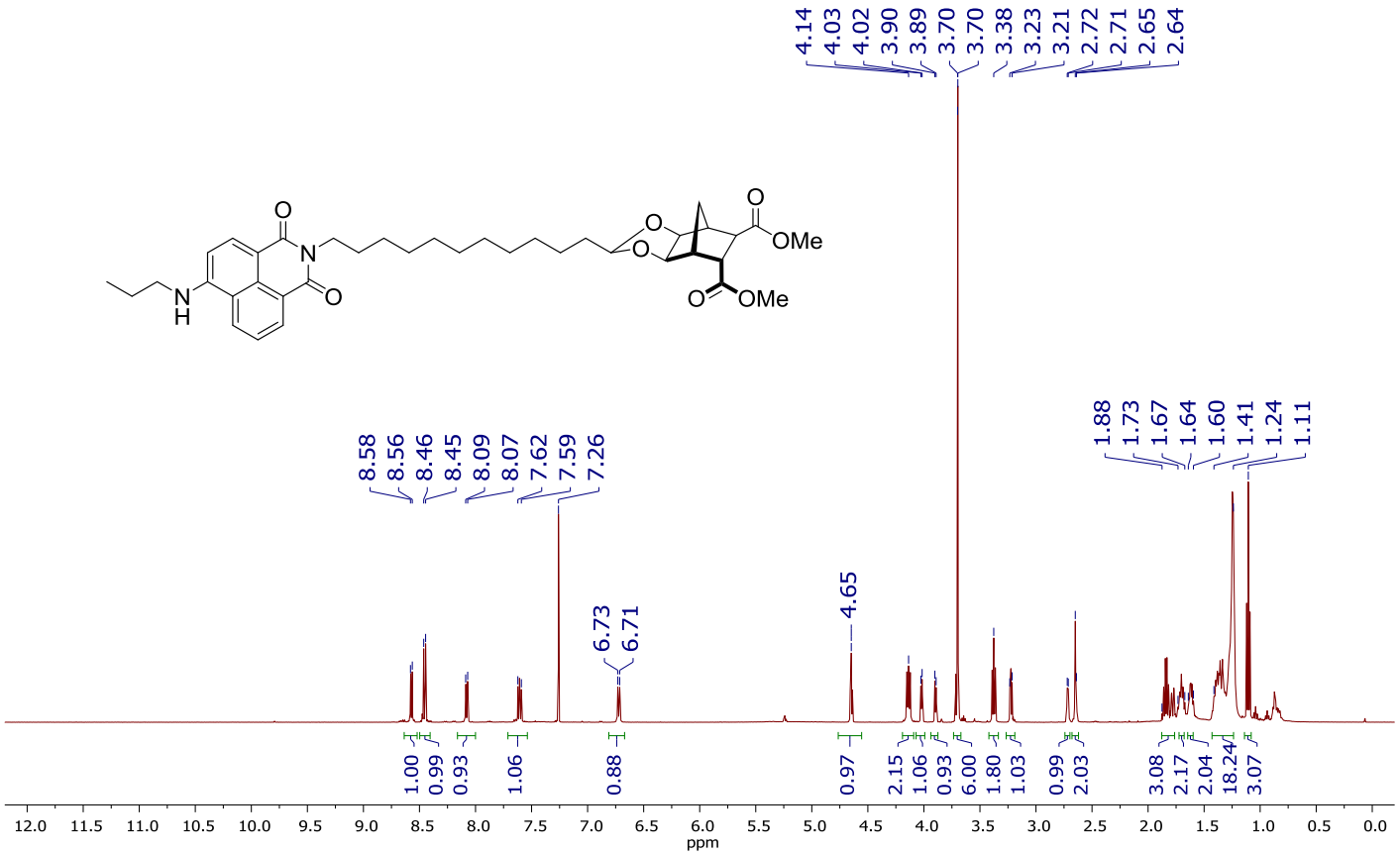


Figure S27: ^{1}H NMR spectrum of **26** in $CDCl_3$.

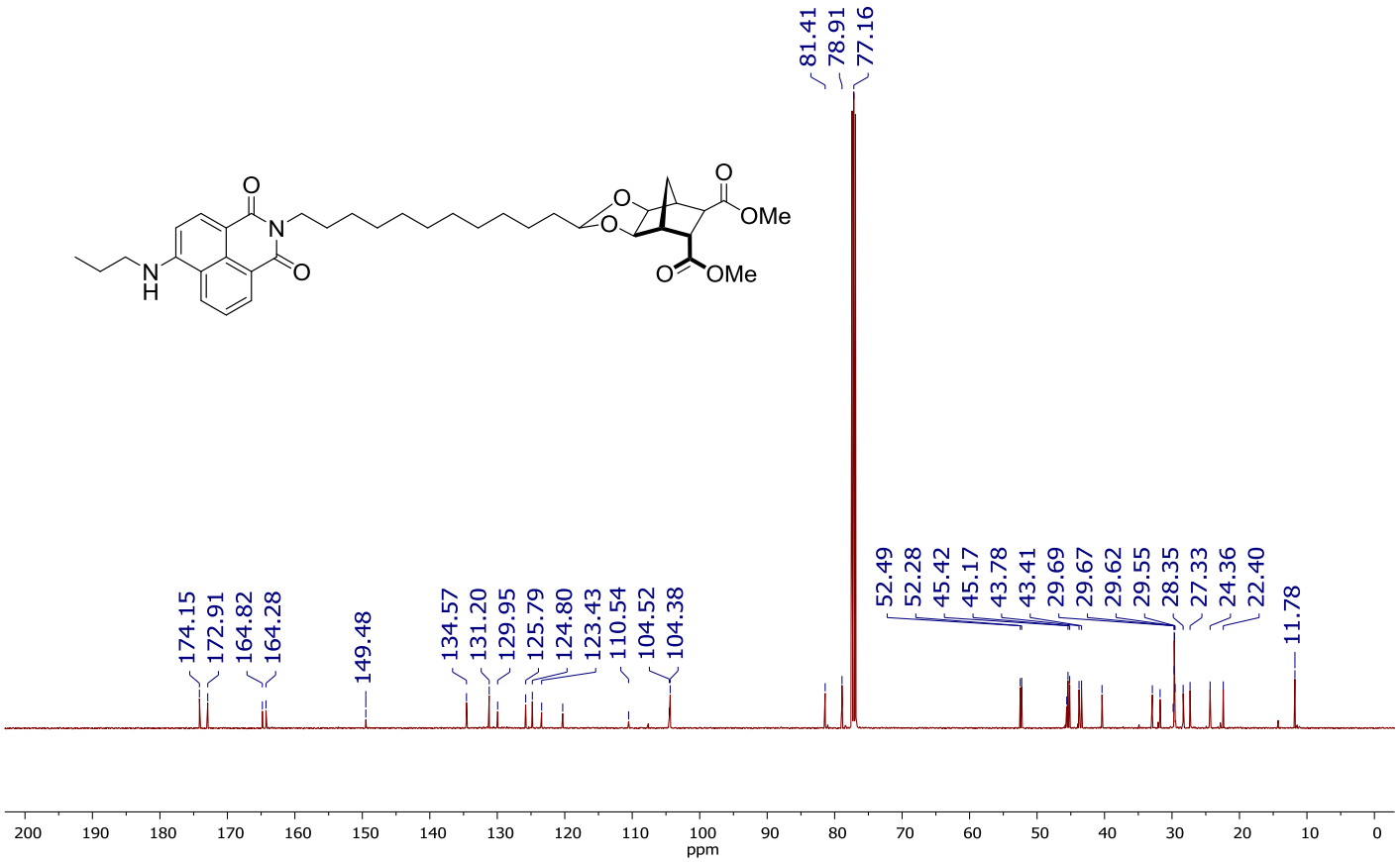


Figure S28: ^{13}C NMR spectrum of **26** in $CDCl_3$.

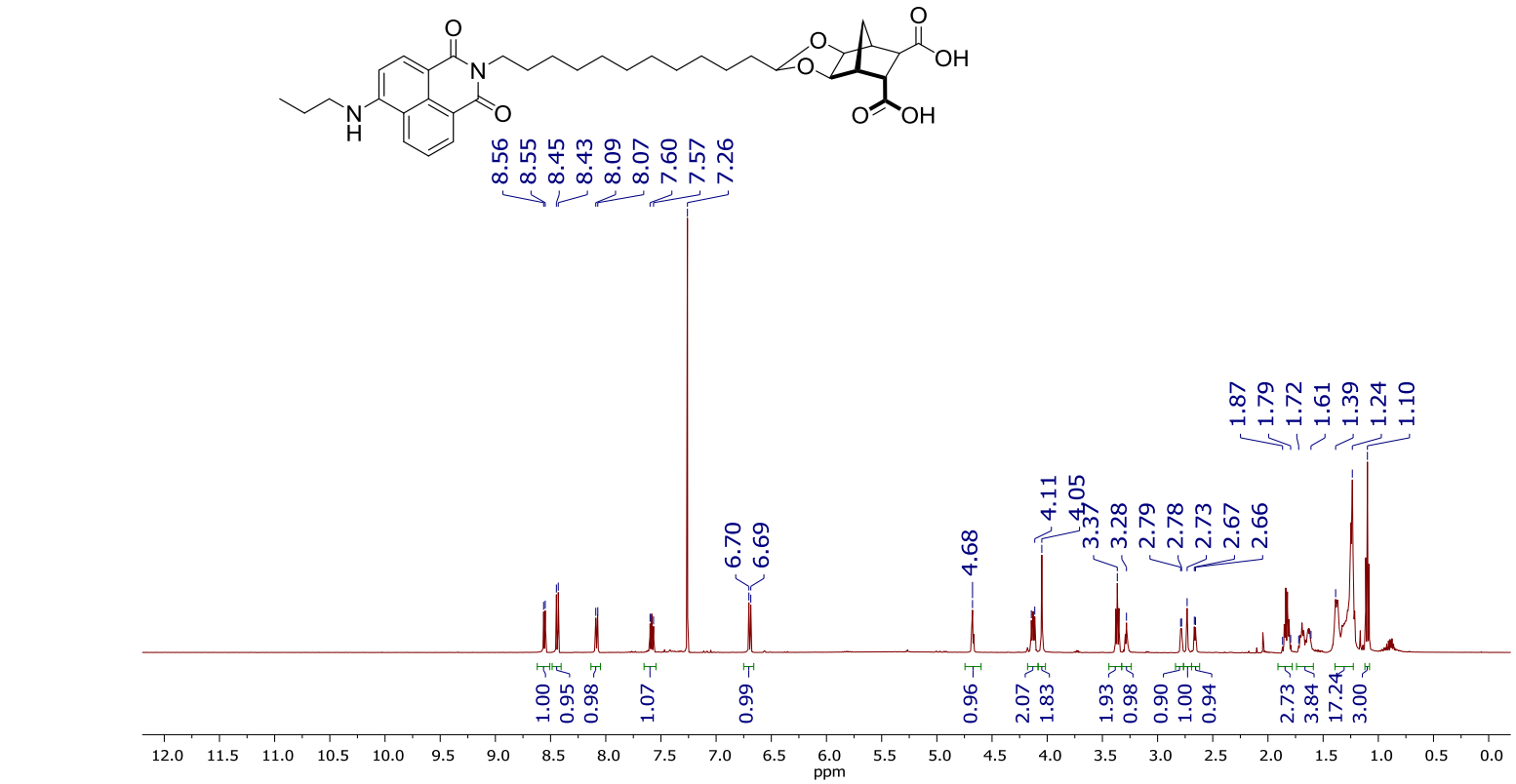


Figure S29: ^{1}H NMR spectrum of **27** in $CDCl_3$.

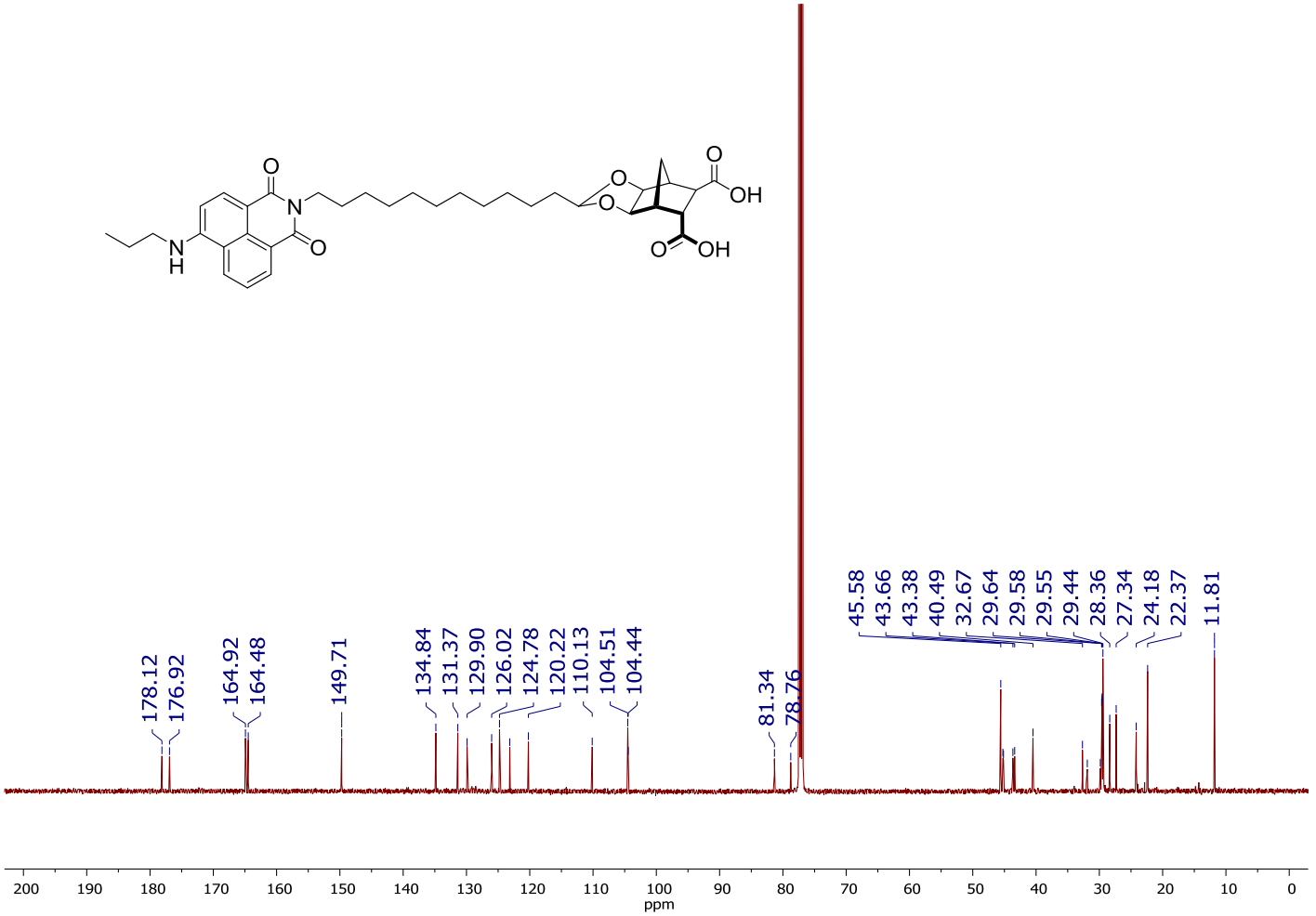


Figure S30: ^{13}C NMR spectrum of **27** in $CDCl_3$.

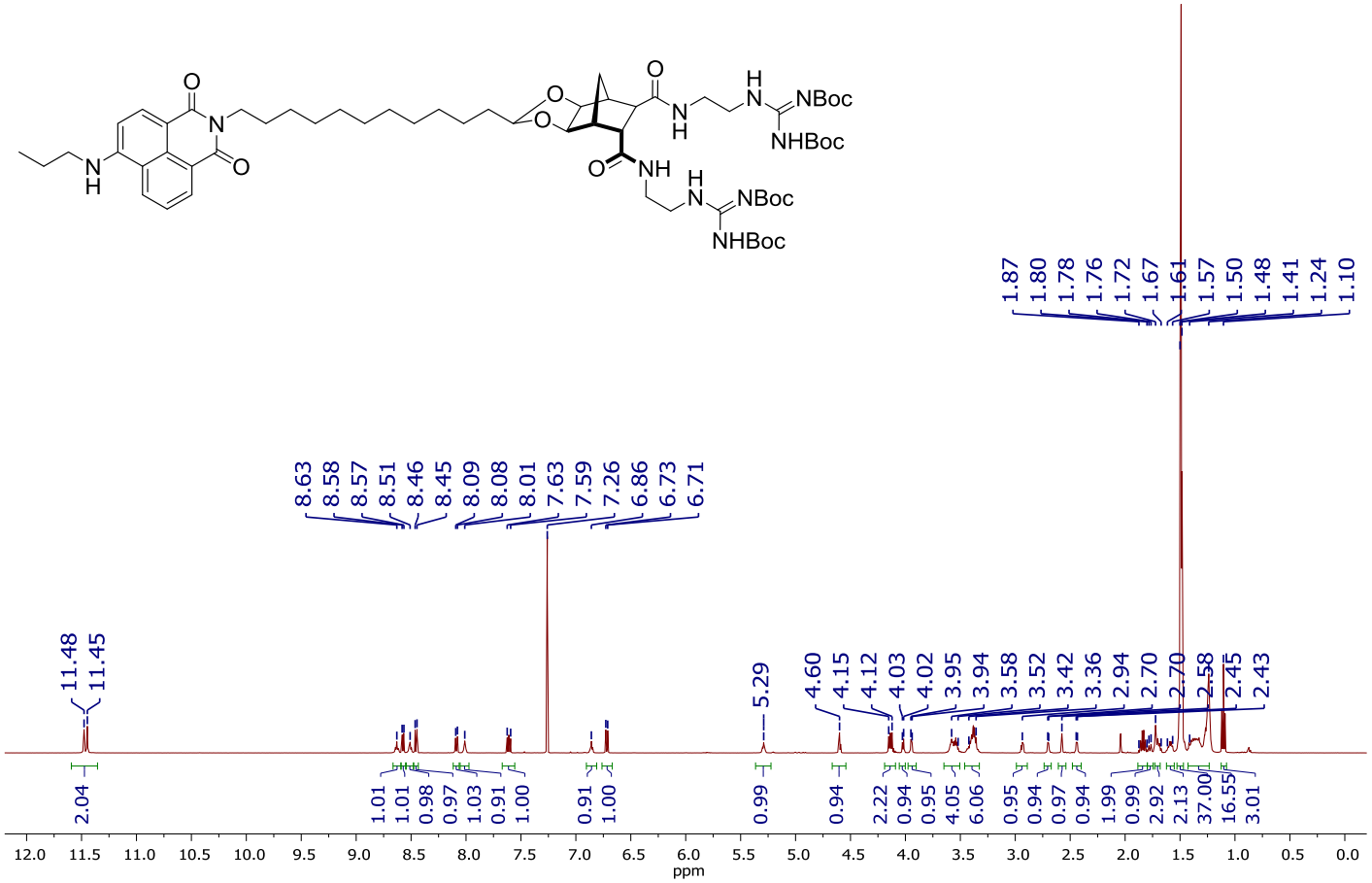


Figure S31: ^{1}H NMR spectrum of **28** in $CDCl_3$.

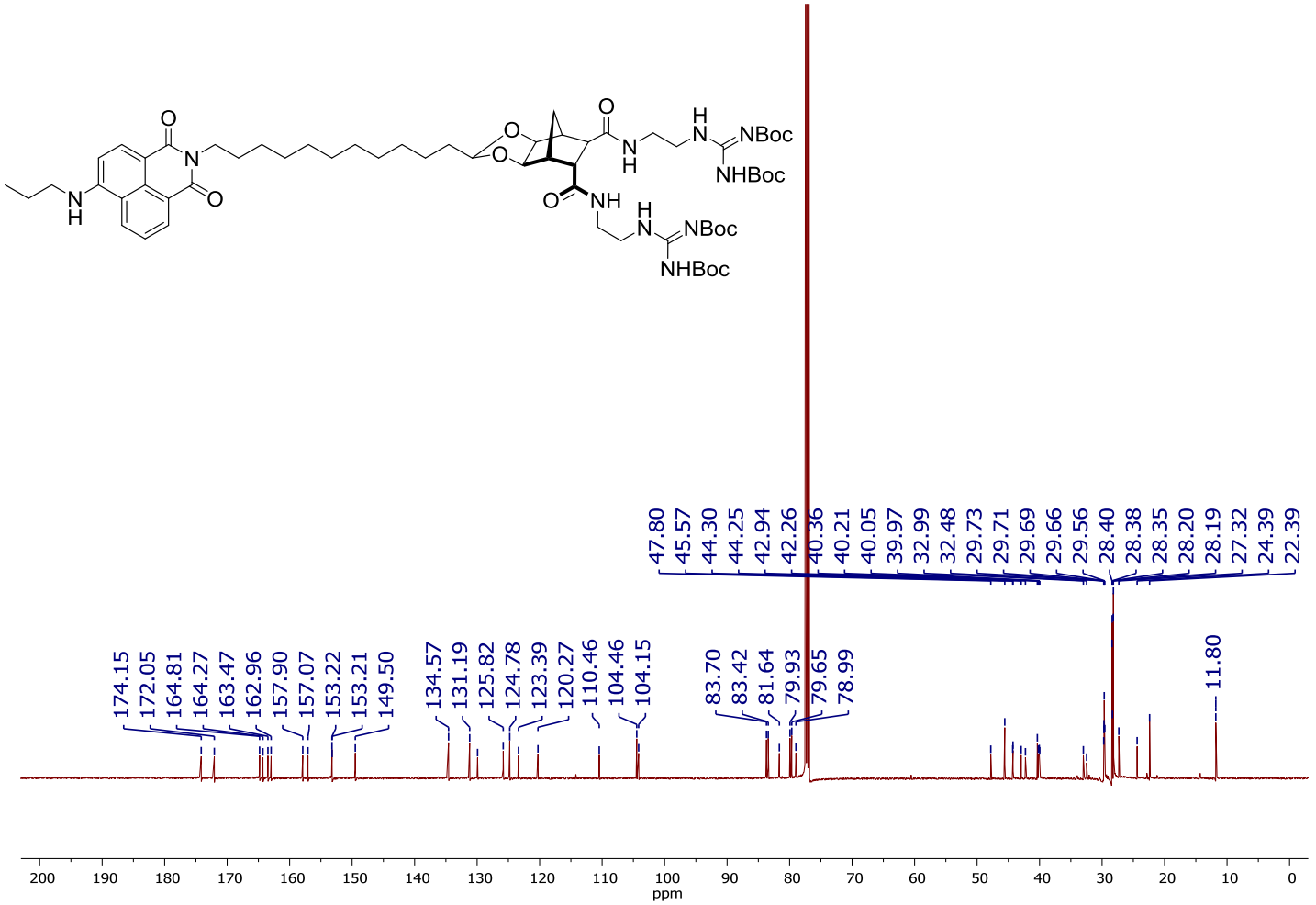


Figure S32: ^{13}C NMR spectrum of **28** in $CDCl_3$.

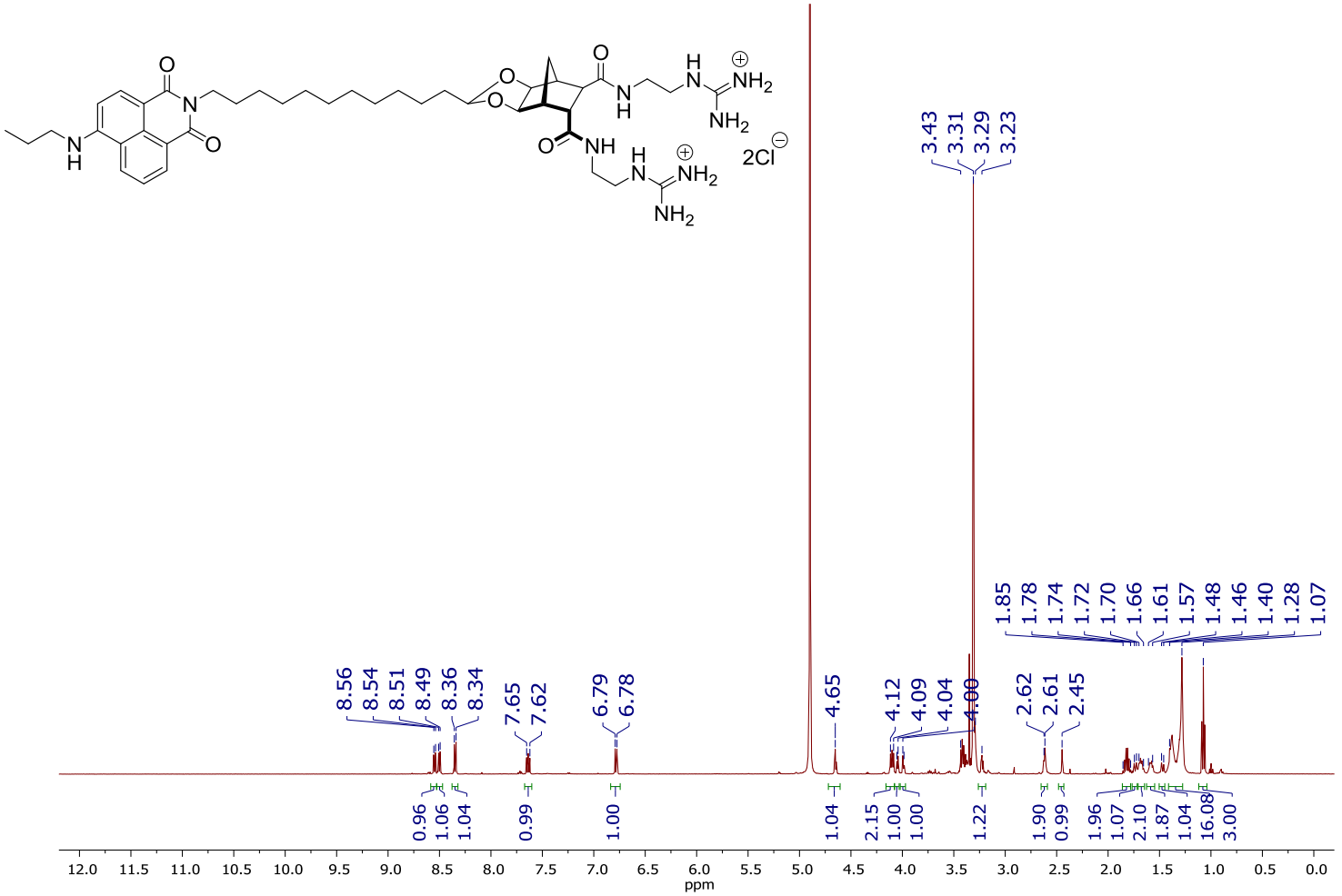


Figure S33: ^{1}H NMR spectrum of **29** in CD_3OD.

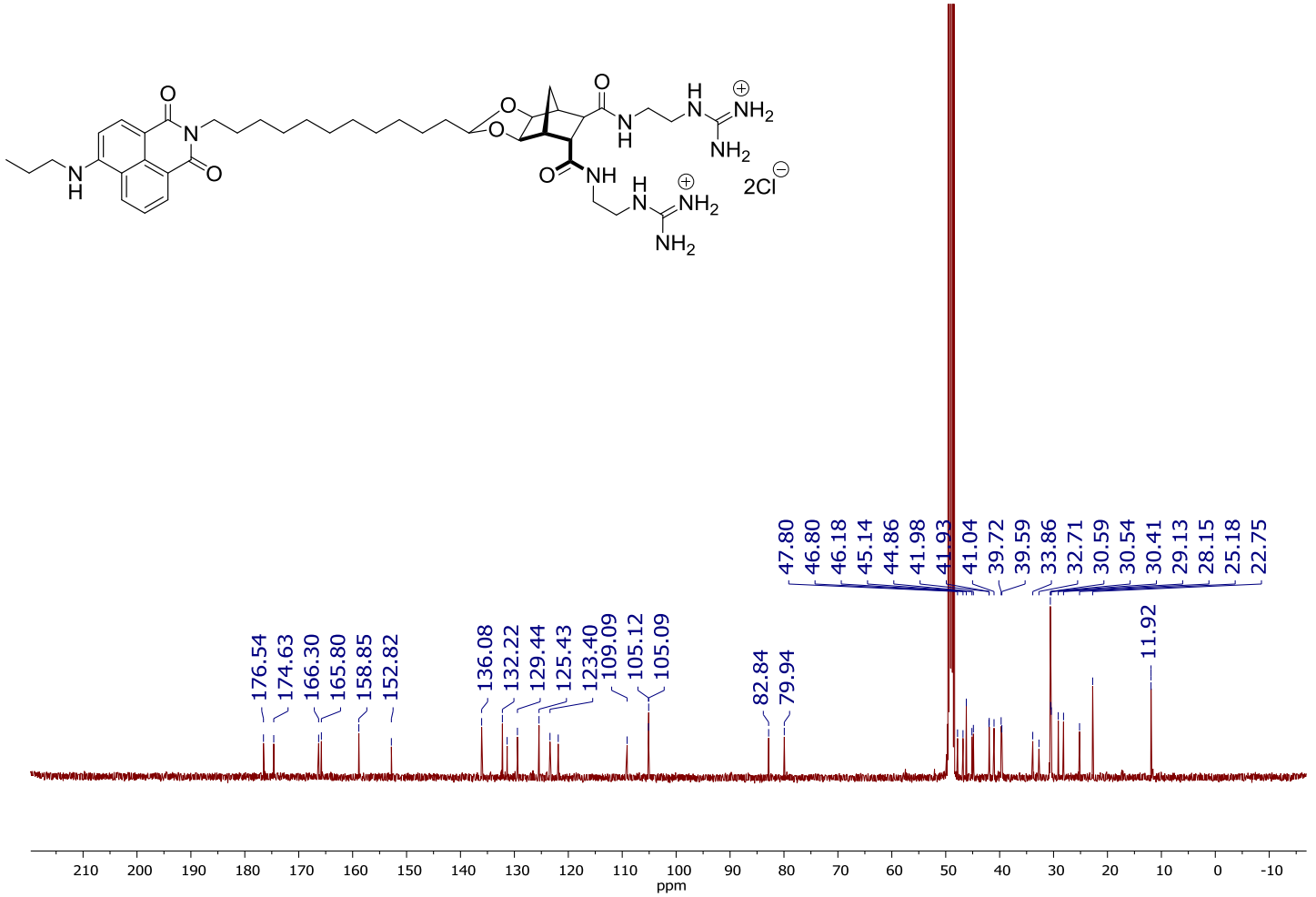


Figure S34: ^{13}C NMR spectrum of **29** in CD_3OD.

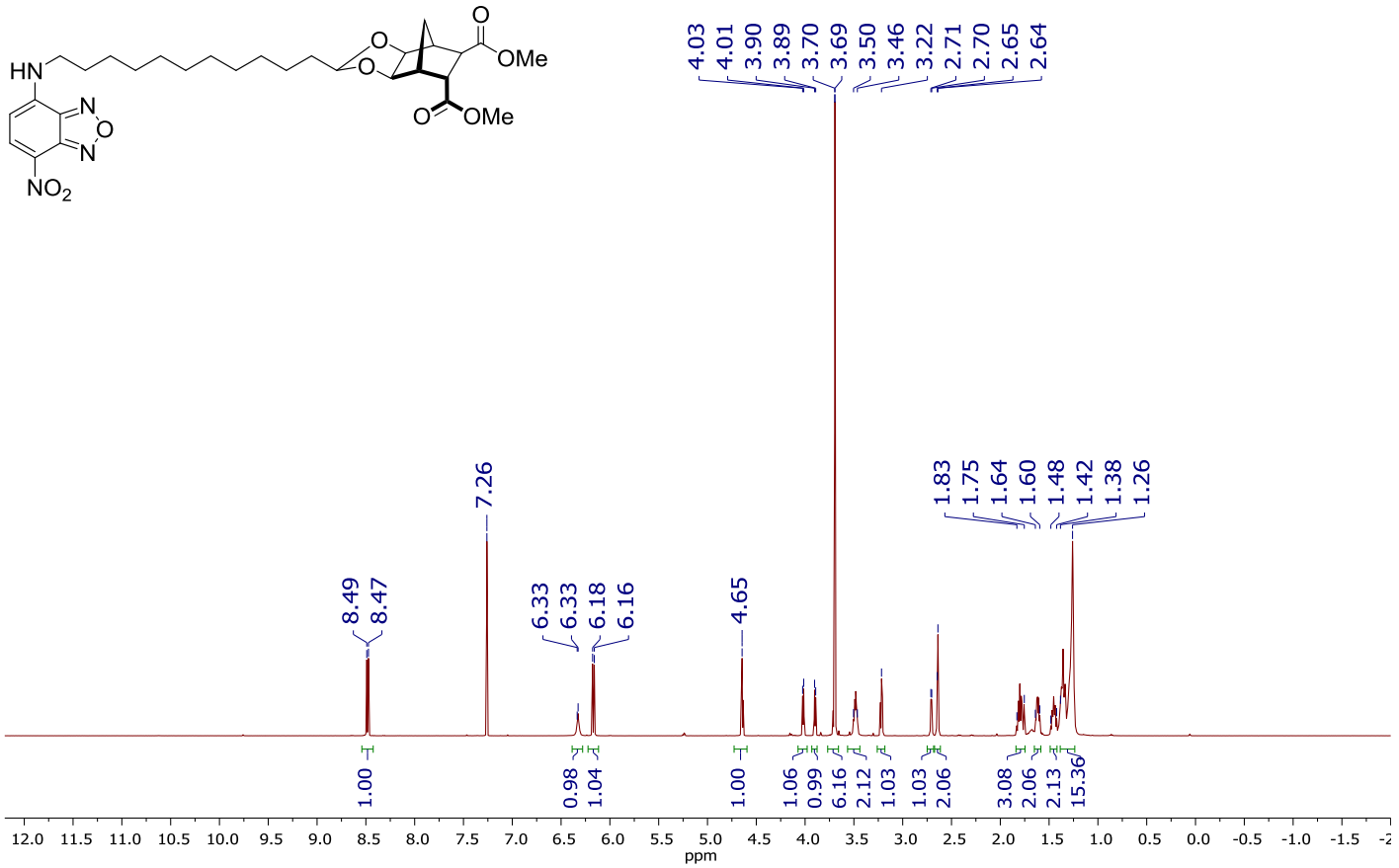


Figure S35: ^{1}H NMR spectrum of **31** in $CDCl_3$.

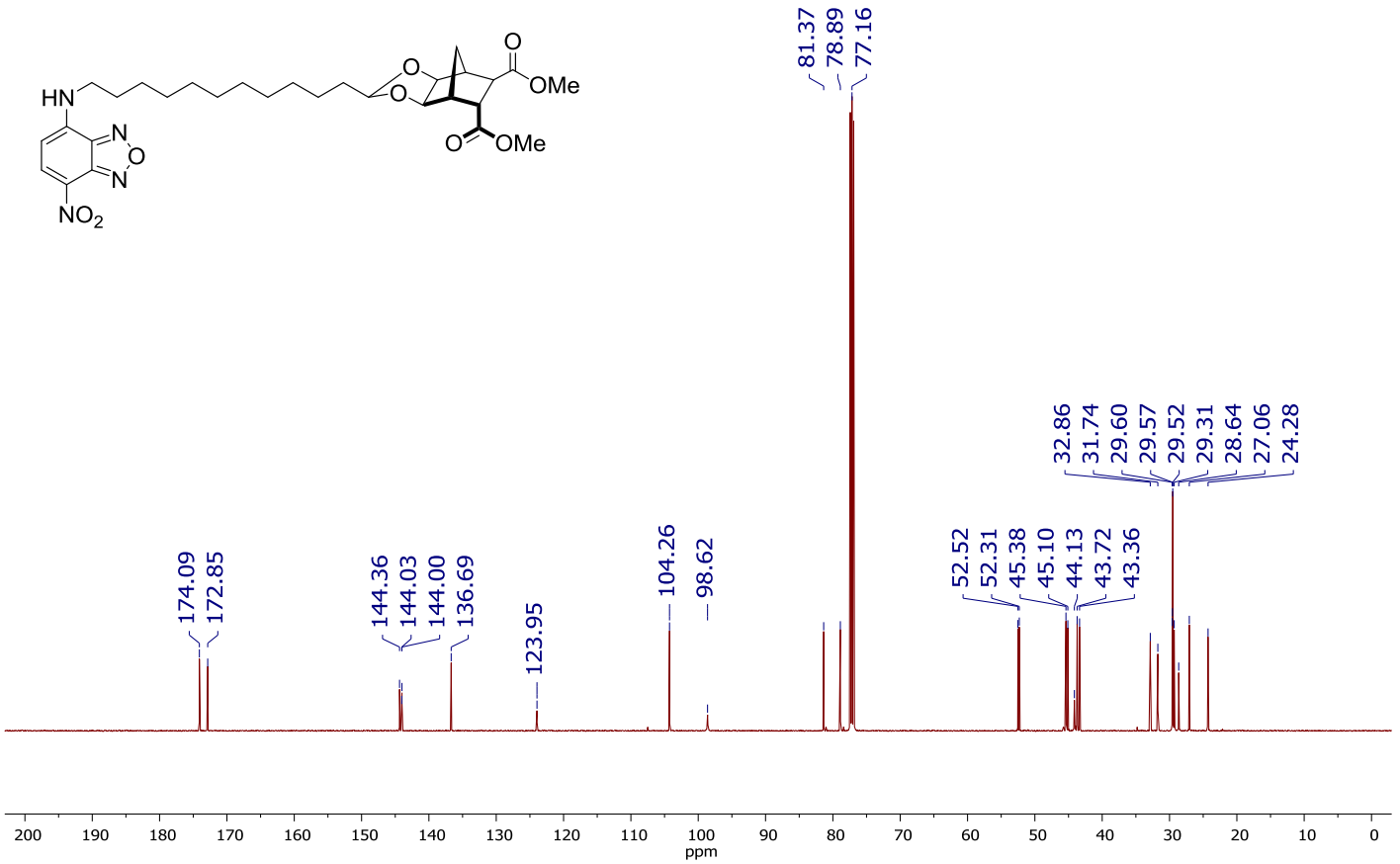


Figure S36: ^{13}C NMR spectrum of **31** in $CDCl_3$.

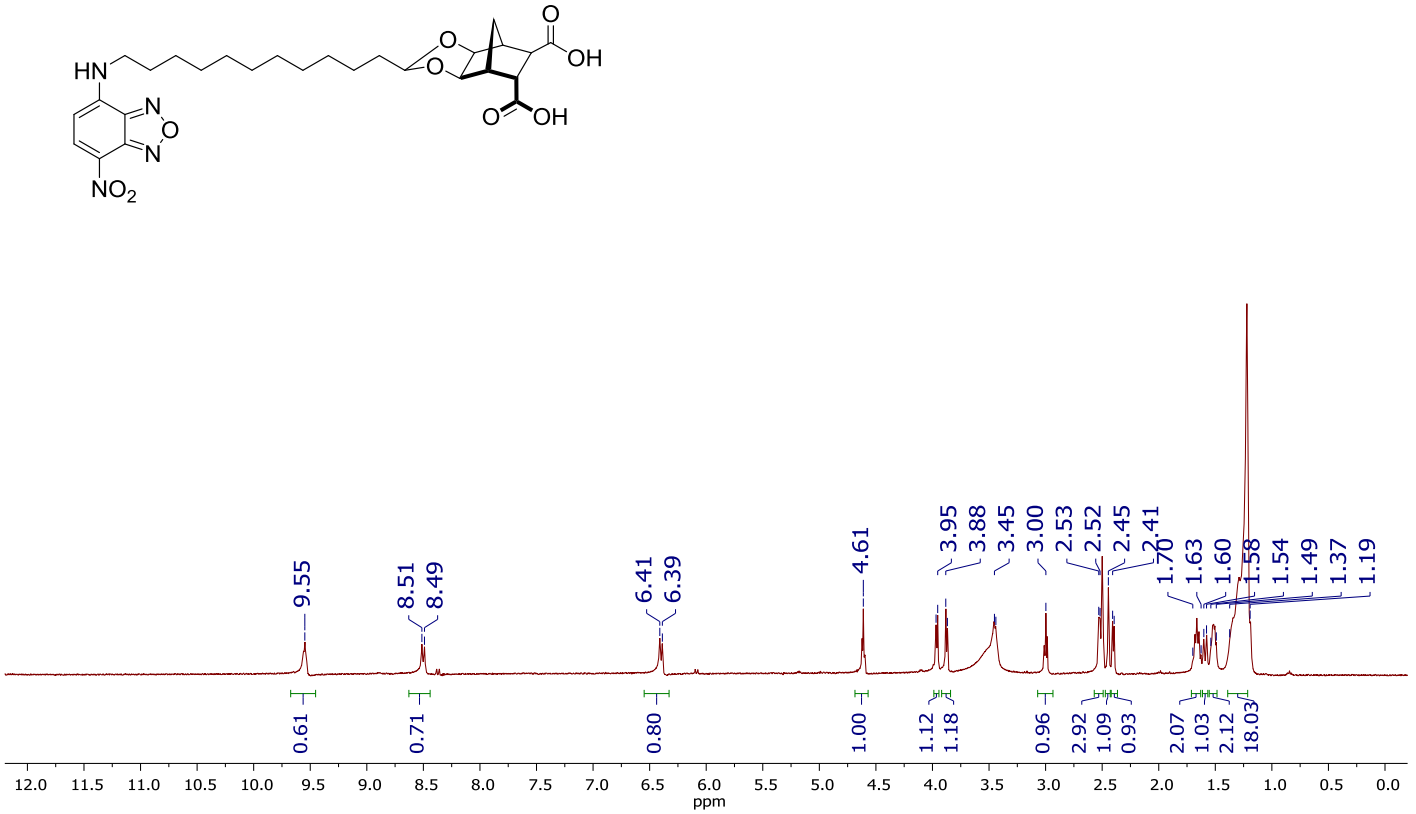


Figure S37: ^{1}H NMR spectrum of **32** in DMSO-*d*$_6$.

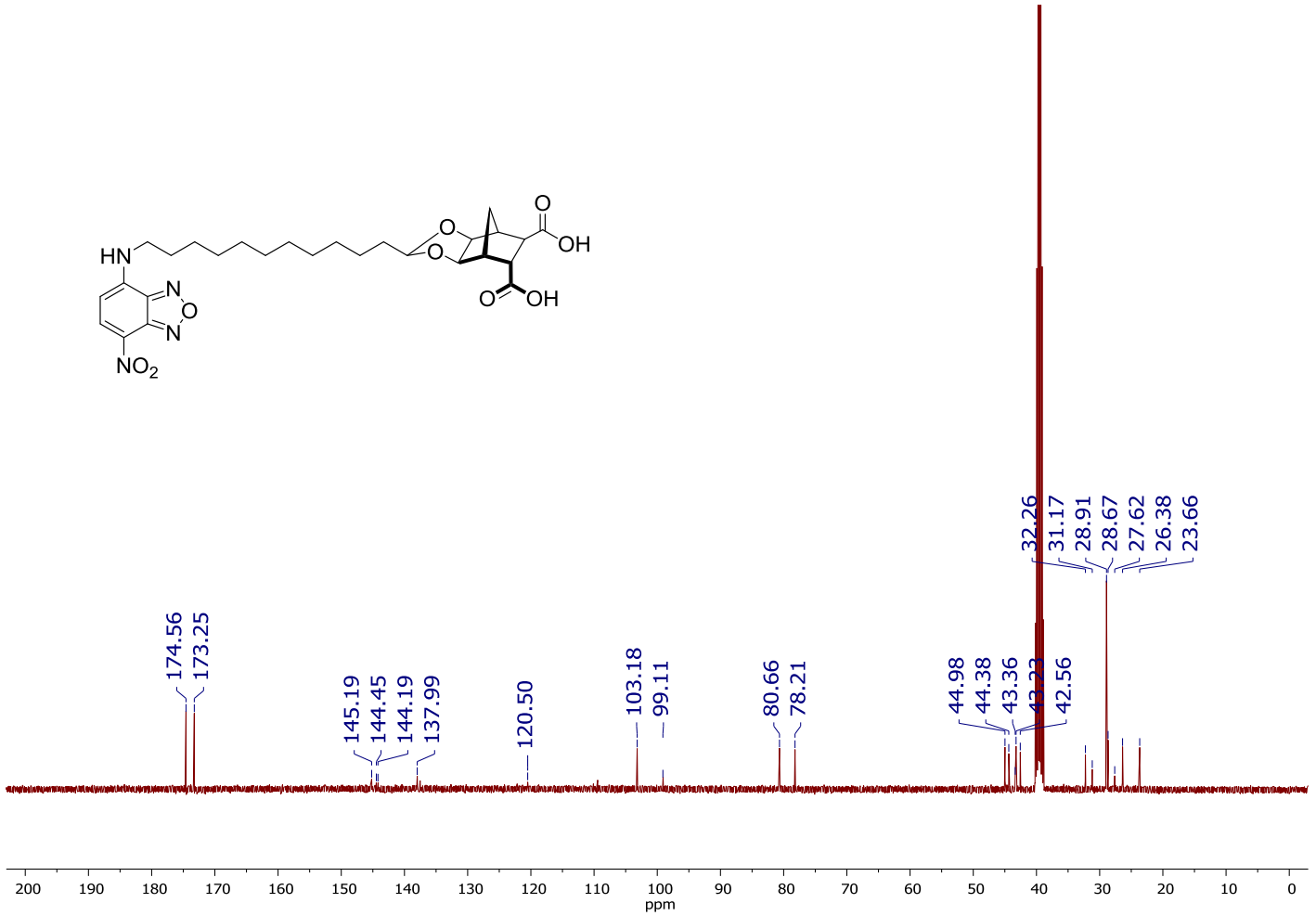


Figure S38: ^{13}C NMR spectrum of **32** in DMSO-d_6.

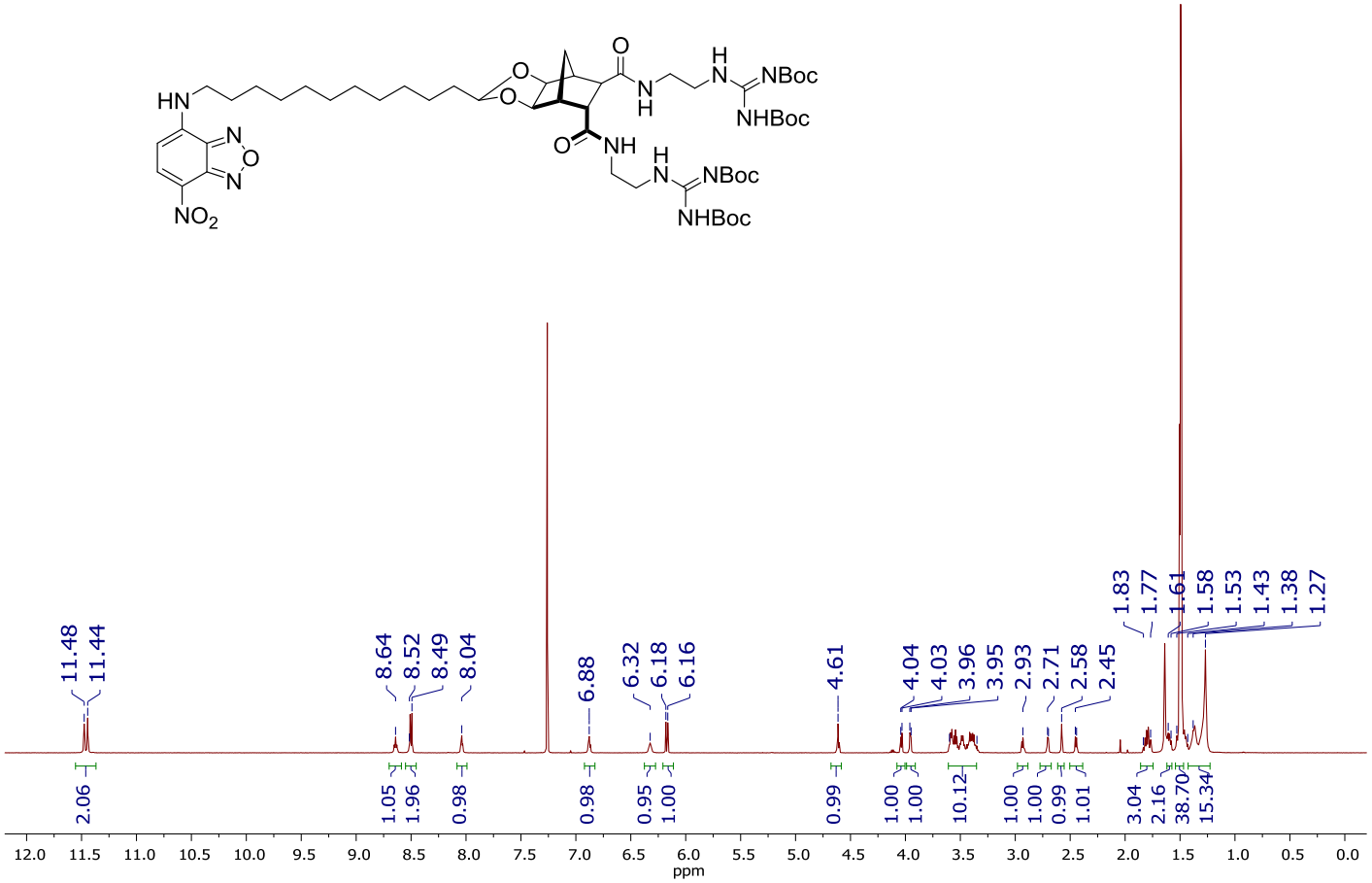


Figure S39: ^{1}H NMR spectrum of **33** in $CDCl_3$.

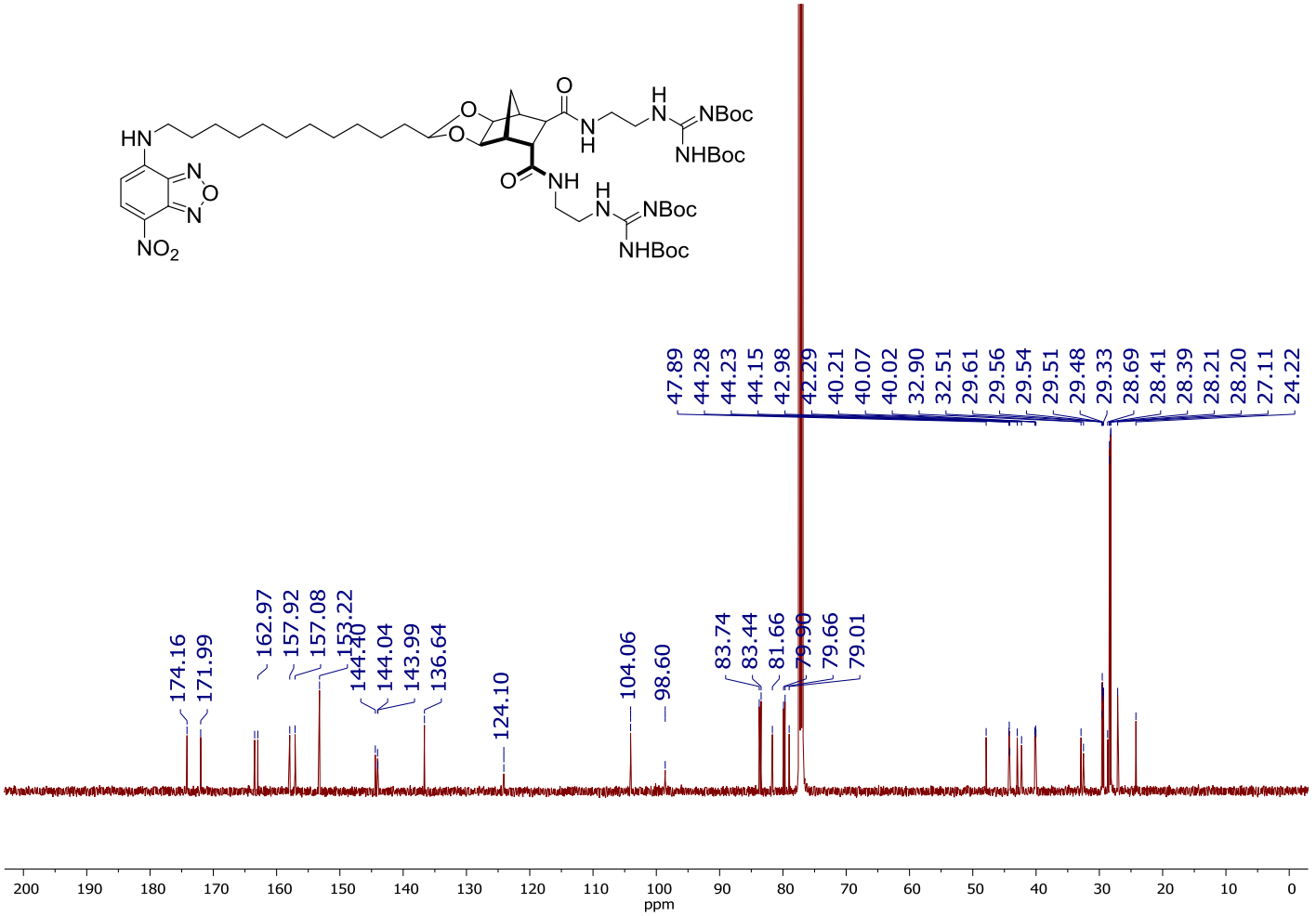


Figure S40: ^{13}C NMR spectrum of **33** in $CDCl_3$.

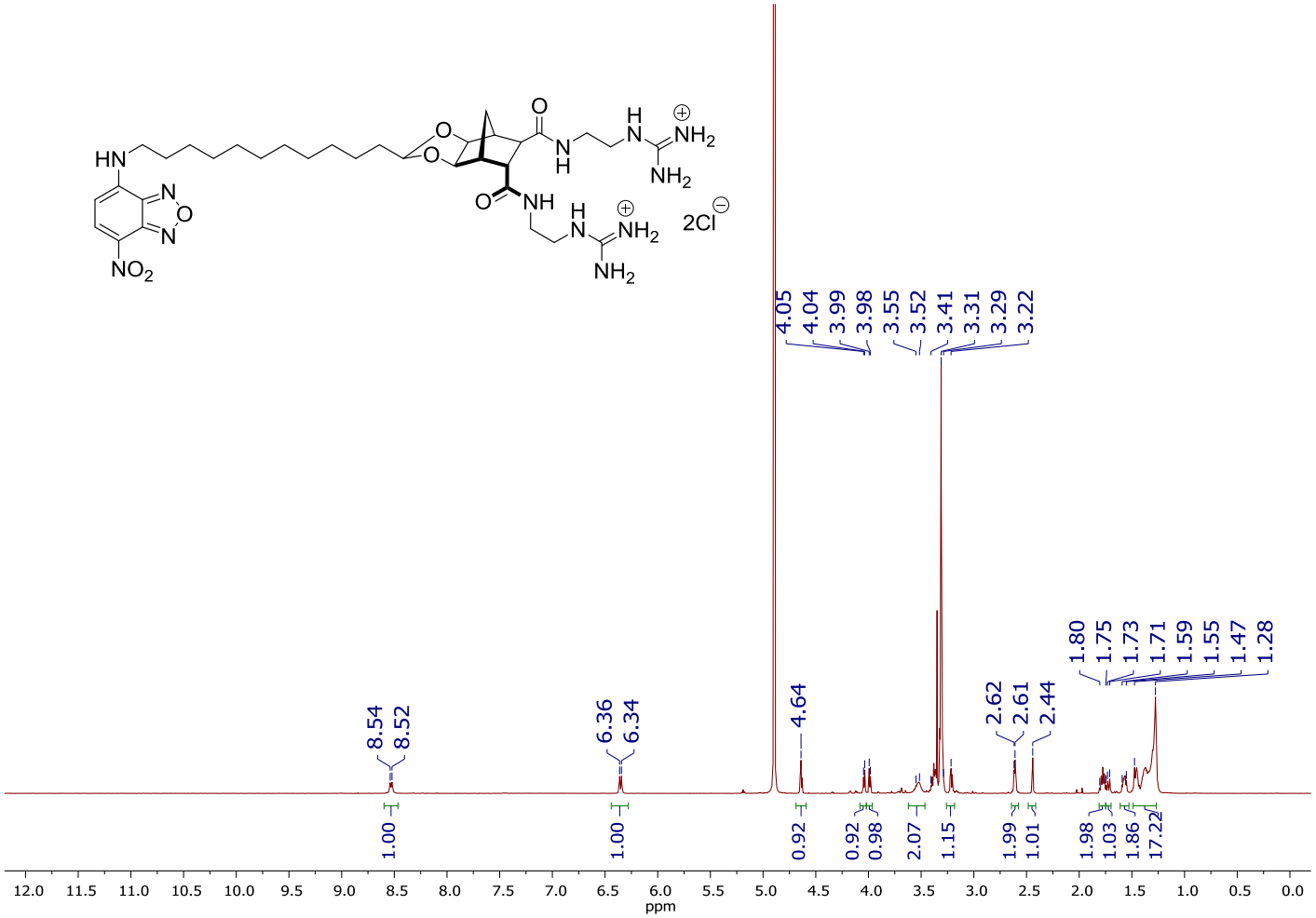


Figure S41: ^{1}H NMR spectrum of **34** in CD_3OD.

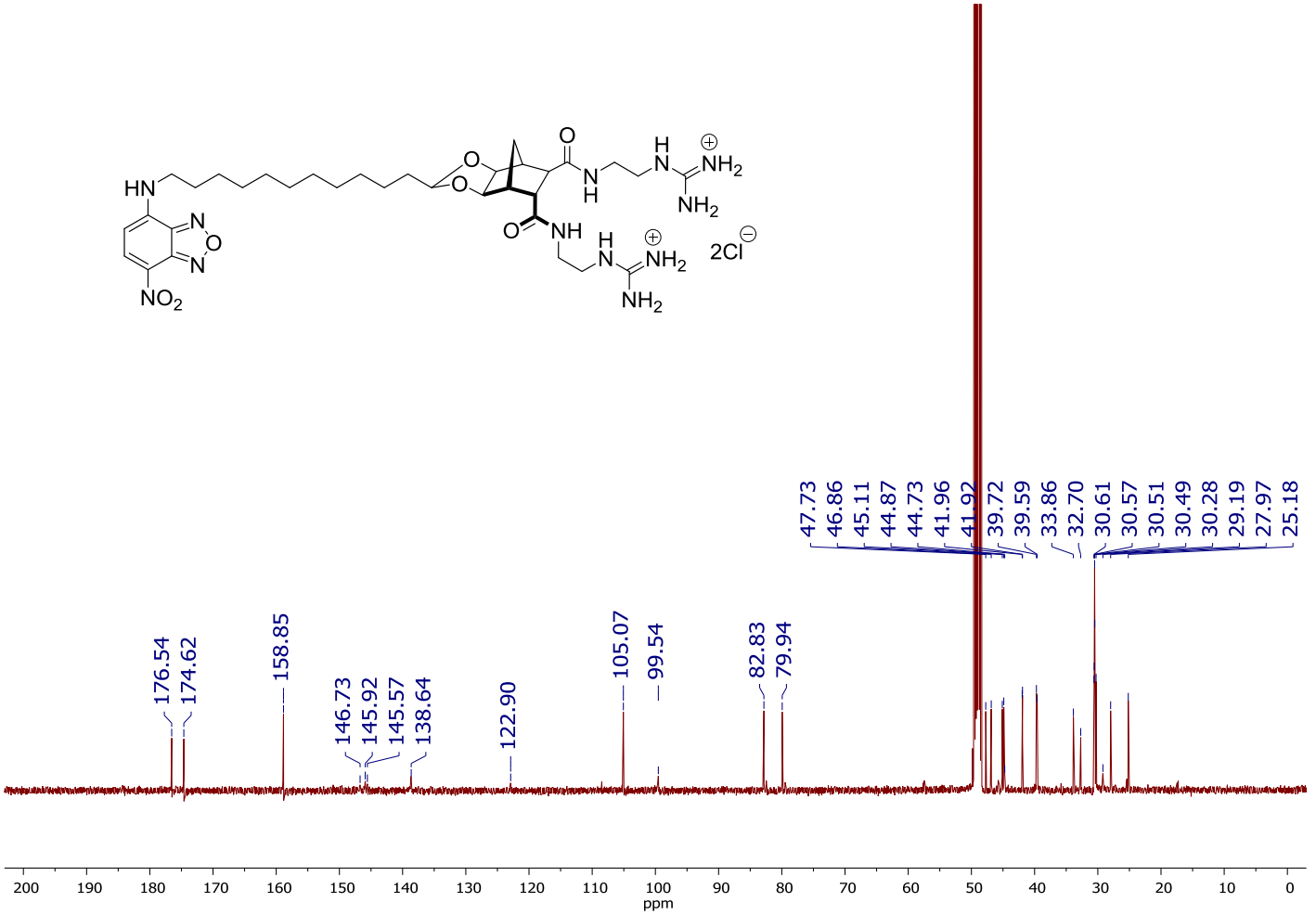


Figure S42: ^{13}C NMR spectrum of **34** in CD_3OD.

Photophysical Properties

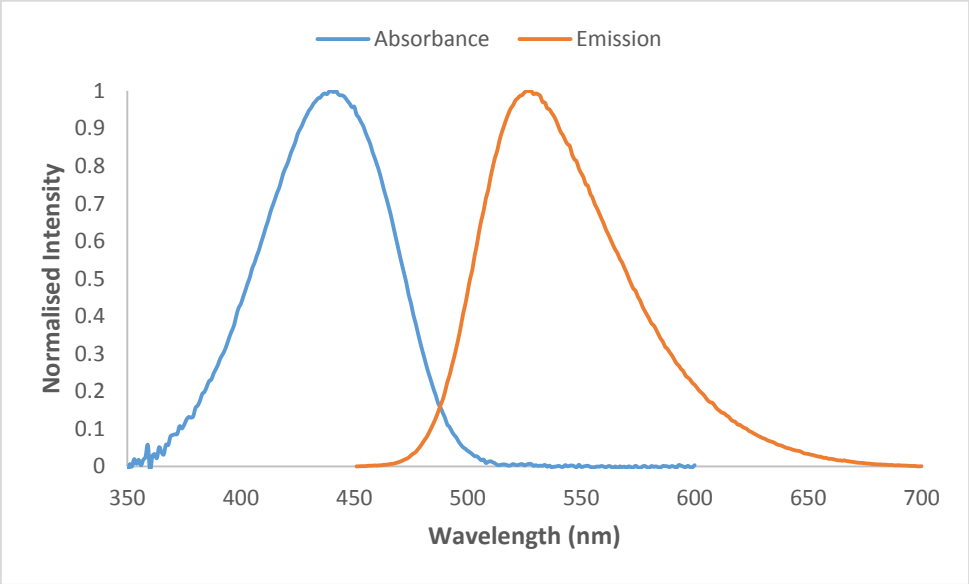


Figure S43: Normalised absorption and emission spectra of naphthalimide **28** in DMSO; λ_{ex} = 442 nm, λ_{em} = 526 nm and ϕ_f = 0.89.

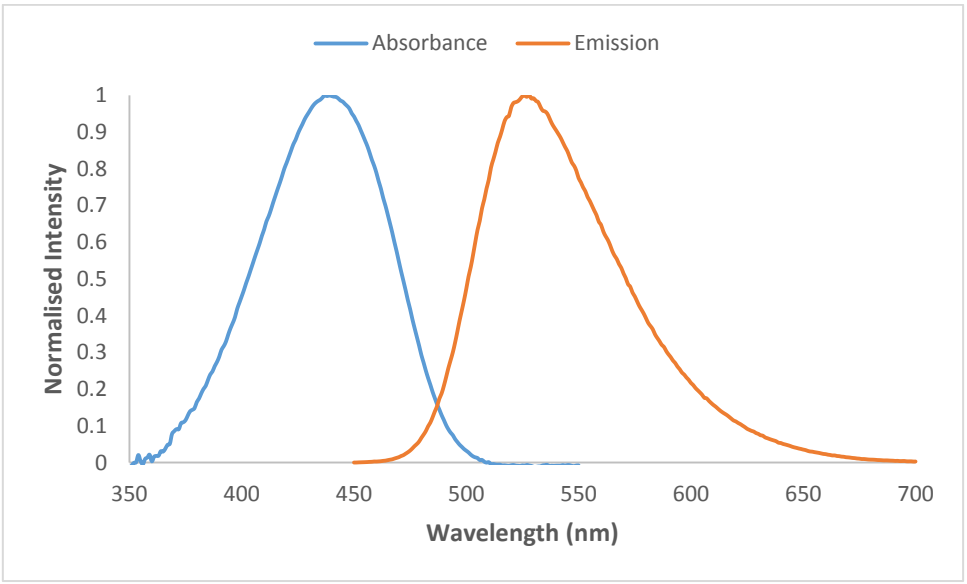


Figure S44: Normalised absorption and emission spectra of naphthalimide **29** in DMSO; λ_{ex} = 437 nm, λ_{em} = 528 nm and ϕ_f = 0.88.

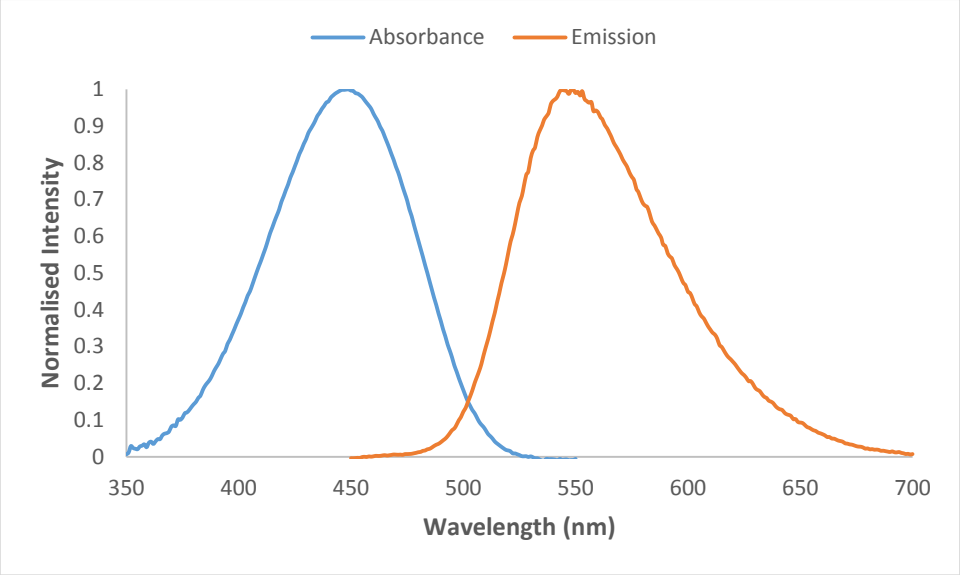


Figure S45: Normalised absorption and emission spectra of naphthalimide **29** in H_2O; λ_{ex} = 449 nm, λ_{em} = 549 nm and ϕ_f = 0.16.

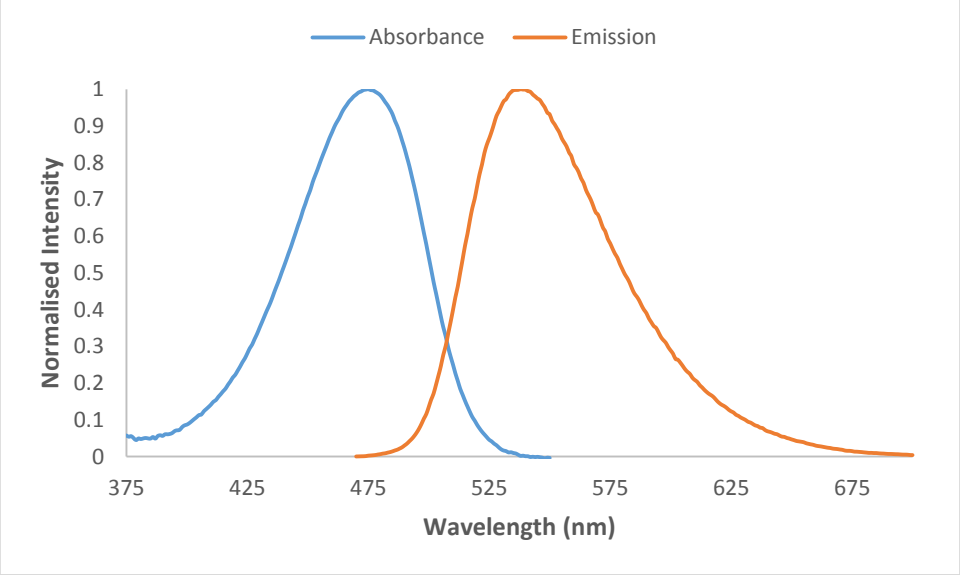


Figure S46: Normalised absorption and emission spectra of NBD **33** in DMSO; λ_{ex} = 475 nm, λ_{em} = 538 nm and ϕ_f = 0.55.

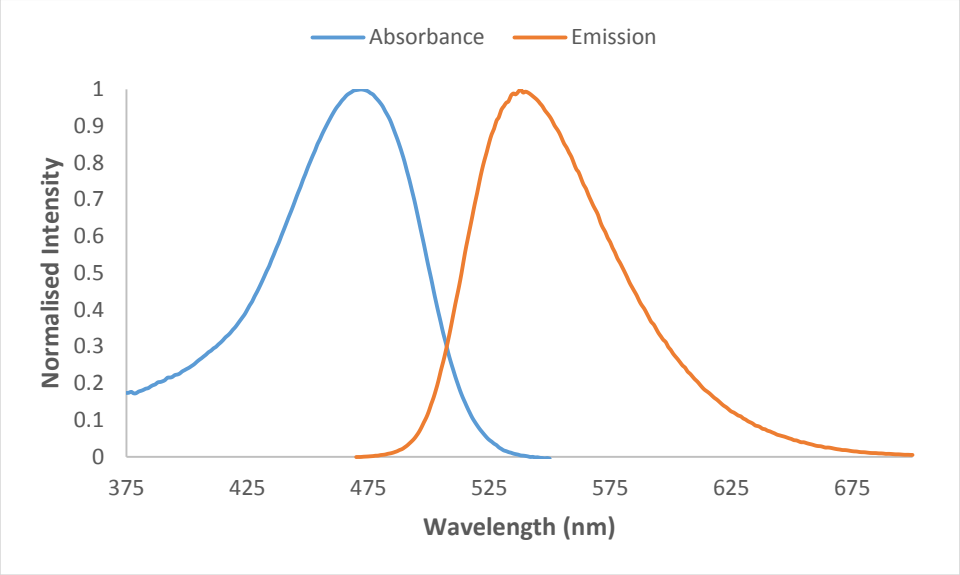


Figure S47: Normalised absorption and emission spectra of NBD **34** in DMSO; λ_{ex} = 472 nm, λ_{em} = 538 nm and ϕ_f = 0.55.

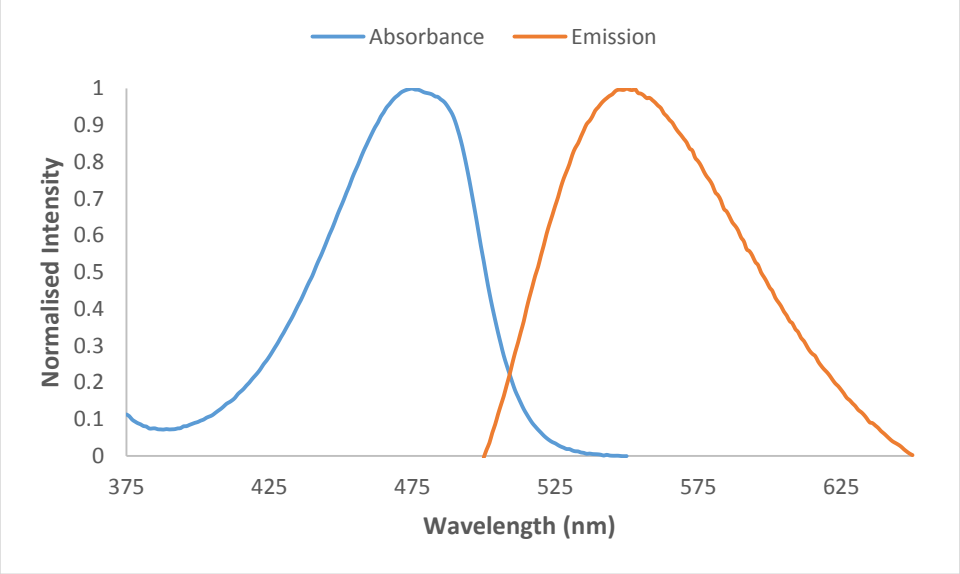


Figure S48: Normalised absorption and emission spectra of NBD **34** in H_2O; λ_{ex} = 475 nm, λ_{em} = 550 nm and ϕ_f = 0.02.

Table S1: Microbial strains used for Minimum Inhibitory Concentration (MIC) and disk diffusion (DD) assay

Organism	Strain	Strain description	Assay
Escherichia coli	ATCC 25922	FDA control strain Seattle 1946	MIC
Klebsiella pneumoniae	ATCC 13883	Control strain	DD
Klebsiella pneumoniae	ATCC 700603	Multi-drug resistant	MIC
Acinetobacter baumannii	ATCC 19606	Type strain	MIC/DD
Pseudomonas aeruginosa	ATCC 27853	Type strain	MIC/DD
Staphylococcus aureus	ATCC 43300	MRSA (methicillin resistant *S. aureus*)	MIC/DD
Enterococcus faecium	ATCC 700221	VRE (vancomycin resistant Enterococcus)	DD
Streptococcus pneumoniae	ATCC 700677	Multi-drug resistant	MIC
Staphylococcus aureus	NRS 17	GISA (glycopeptide-intermediate *S. aureus*)	MIC
Staphylococcus aureus	NRS 1	GISA, MRSA	MIC
Staphylococcus aureus	VRS 10	Vancomycin Resistant *S. aureus*	MIC
Candida albicans	ATCC 90028	CLSI reference	MIC
Cryptococci neoformans H99	ATCC 208821	Type strain	MIC

Disk Diffusion Results

Table S2: ZOI as measured (in mm) using disk diffusion assay[a]

Compound	*A. baumannii* **ATCC 19606**	*P. aeruginosa* **ATCC 27853**	*K. pneumoniae* **ATCC 13883**	*S. aureus* **MRSA ATCC 43300**	*E. faecium* **VRE ATCC 700221**
7	10	13	15	17	18
21	12	12	14.5	14	-
29	-	-	-	-	-
34	-	9	8.5	9	-
COL[b]	*20*	*19*	*20*	-	-

[a] Measured after incubation of disk (6 mm diameter, 50 μg/disk) at 37 °C for 20 h.

[b] Tested at 10 μg/disk.

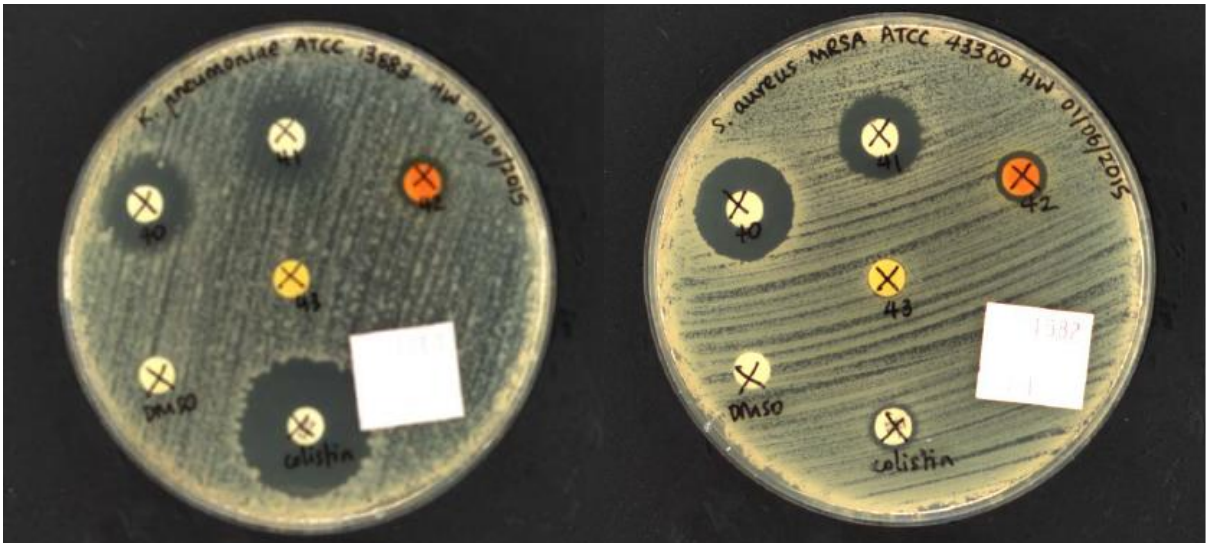


Figure S49: Antibacterial activity against *K. pneumoniae* (LHS) and MRSA (RHS) at 50 μg/disk. Compounds are numbered as such; **29** (43), **34** (42), **7** (40) and **21** (41). Colistin and DMSO were used as controls and are labelled accordingly.

Molecular Dynamics Simulation Images

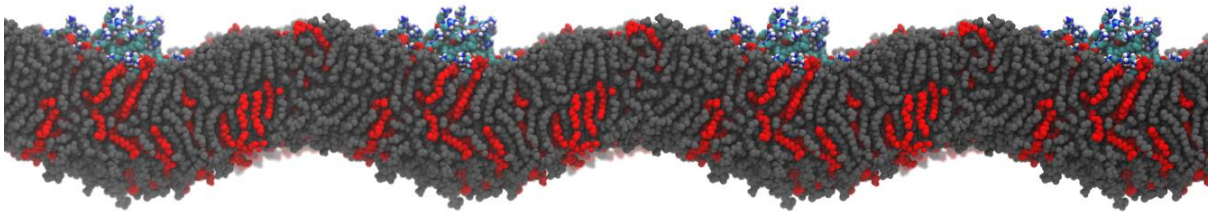


Figure S50: A snapshot of the curvature in the 2nd replicate of the simulation of compound **2** interacting with the membrane. Colours as per Figure 3 in the main text. Periodic images of the simulation system have been included to emphasise the curvature of the membrane.

A video depicting compound $\mathbf{2}_{28}$ interacting with the model Gram-negative membrane can be made available upon request.

Fluorescence Microscopy

A video depicting a 3D-representation of naphthalimide **29** in *E. coli* cells can be made available upon request.

Anti-fungal Activity

Table S3: **MIC values (μg/mL)**

Fungal strain	**7**	**29**	**34**	*FLU*[a]
C. albicans ATCC 90028	128	128	**16**	1
C. neoformans ATCC 20881	**2**	**0.25**	**4**	8

[a] FLU = Fluconazole

The antifungal properties were evaluated for compounds **7**, **29** and **34** and excellent activity was observed against *Cryptococcus neoformans* for all compounds (MIC = 2, 0.25 and 4 μg/mL respectively); a result comparable to the activity range displayed by commercially available Fluconazole.

References

[1] H.E. Gottlieb, V. Kotlyar, A. Nudelman, NMR chemical shifts of common laboratory solvents as trace impurities, J. Org. Chem., 62 (1997) 7512-7515.
[2] G. Moss, Extension and revision of the von Baeyer system for naming polycyclic compounds (including bicyclic compounds), Pure Appl. Chem., 71 (1999) 513-529.
[3] G. Radau, S. Schermuly, A. Fritsche, New cyanopeptide-derived low molecular weight inhibitors of trypsin-like serine proteases, Arch. Pharm., 336 (2003) 300-309.
[4] A. Kraus, P. Ghorai, T. Birnkammer, D. Schnell, S. Elz, R. Seifert, S. Dove, G. Bernhardt, A. Buschauer, NG-Acylated aminothiazolylpropylguanidines as potent and selective histamine H2 receptor agonists, ChemMedChem, 4 (2009) 232-240.
[5] C. Liu, W. Guo, X. Shi, M.A. Kaium, X. Gu, Y.Z. Zhu, Leonurine-cysteine analog conjugates as a new class of multifunctional anti-myocardial ischemia agent, Euro. J. Med. Chem., 46 (2011) 3996-4009.
[6] S.M. Hickey, T.D. Ashton, S.K. Khosa, F.M. Pfeffer, An optimised synthesis of 2-[2, 3-Bis (tert-butoxycarbonyl) guanidino] ethylamine, Synlett, 23 (2012) 1779-1782.
[7] L.D. Van Vliet, T. Ellis, P.J. Foley, L. Liu, F.M. Pfeffer, R.A. Russell, R.N. Warrener, F. Hollfelder, M.J. Waring, Molecular recognition of DNA by rigid [*n*]-polynorbornane-derived bifunctional intercalators: synthesis and evaluation of their binding properties, J. Med. Chem., 50 (2007) 2326-2340.
[8] L. He, H.-S. Byun, R. Bittman, A stereocontrolled, efficient synthetic route to bioactive sphingolipids: Synthesis of phytosphingosine and phytoceramides from unsaturated ester precursors *via* cyclic sulfate intermediates, J. Org. Chem., 65 (2000) 7618-7626.
[9] C.-X. Miao, L.-N. He, J.-L. Wang, F. Wu, Self-neutralizing *in situ* acidic CO_2/H_2O system for aerobic oxidation of alcohols catalyzed by TEMPO functionalized imidazolium salt/$NaNO_2$, J. Org. Chem., 75 (2009) 257-260.
[10] C.C. Forbes, K.M. DiVittorio, B.D. Smith, Bolaamphiphiles promote phospholipid translocation across vesicle membranes, J. Am. Chem. Soc., 128 (2006) 9211-9218.
[11] C.M. Jakobsen, S.R. Denmeade, J.T. Isaacs, A. Gady, C.E. Olsen, S.B. Christensen, Design, synthesis, and pharmacological evaluation of thapsigargin analogues for targeting apoptosis to prostatic cancer cells, J. Med. Chem., 44 (2001) 4696-4703.
[12] M.M. Flook, J. Börner, S.M. Kilyanek, L.C.H. Gerber, R.R. Schrock, Five-coordinate rearrangements of metallacyclobutane intermediates during ring-opening metathesis polymerization of 2,3-dicarboalkoxynorbornenes by molybdenum and tungsten monoalkoxide pyrrolide initiators, Organometallics, 31 (2012) 6231-6243.
[13] M. Dejmek, H. Hrebabecky, M. Sala, M. Dracinsky, R. Nencka, Microwave-assisted solvent-free Diels-Alder reaction-a fast and simple route to various 5, 6-substituted norbornenes and polychlorinated norbornenes, Synthesis, (2011) 4077-4083.
[14] S.M. Hickey, S.K. Tripcony, R. Li, R.J. Williams, F.M. Pfeffer, Organogelators based on the norbornane scaffold, Supramol. Chem., 27 (2015) 425-435.
[15] L.C. Henderson, J. Li, R.L. Nation, T. Velkov, F.M. Pfeffer, Developing an anion host for lipid A binding and antibacterial activity, Chem. Commun., 46 (2010) 3197-3199.
[16] T.J. Donohoe, A. Jahanshahi, M.J. Tucker, F.L. Bhatti, I.A. Roslan, M. Kabeshov, G. Wrigley, Exerting control over the acyloin reaction, Chem. Commun., 47 (2011) 5849-5851.
[17] S.M. Hickey, T.D. Ashton, S.K. Khosa, R.N. Robson, J.M. White, J. Li, R.L. Nation, H.Y. Yu, A.G. Elliott, M.S. Butler, J.X. Huang, M.A. Cooper, F.M. Pfeffer, Synthesis and evaluation of cationic norbornanes as peptidomimetic antibacterial agents, Org. Biomol. Chem., 13 (2015) 6225-6241.
[18] W. Xuan, R. Pan, Y. Cao, K. Liu, W. Wang, A fluorescent probe capable of detecting H2S at submicromolar concentrations in cells, Chem. Commun., 48 (2012) 10669-10671.
[19] K.N. Hearn, T.D. Nalder, R.P. Cox, H.D. Maynard, T.D.M. Bell, F.M. Pfeffer, T.D. Ashton, Modular synthesis of 4-aminocarbonyl substituted 1,8-naphthalimides and application in single molecule fluorescence detection, Chem. Commun., 53 (2017) 12298-12301.
[20] M.K. Buchanan, C.N. Needham, N.E. Neill, M.C. White, C.B. Kelly, K. Mastro-Kishton, L.M. Chauvigne-Hines, T.J. Goodwin, A.L. McIver, L.J. Bartolotti, A.R. Frampton, A.J. Bourdelais, S. Varadarajan, Glycoconjugated site-selective DNA-methylating agent targeting glucose transporters on glioma cells, Biochemistry, 56 (2017) 421-440.