Supplementary Information for

Trivalent PROTACs enhance protein degradation via combined avidity and cooperativity

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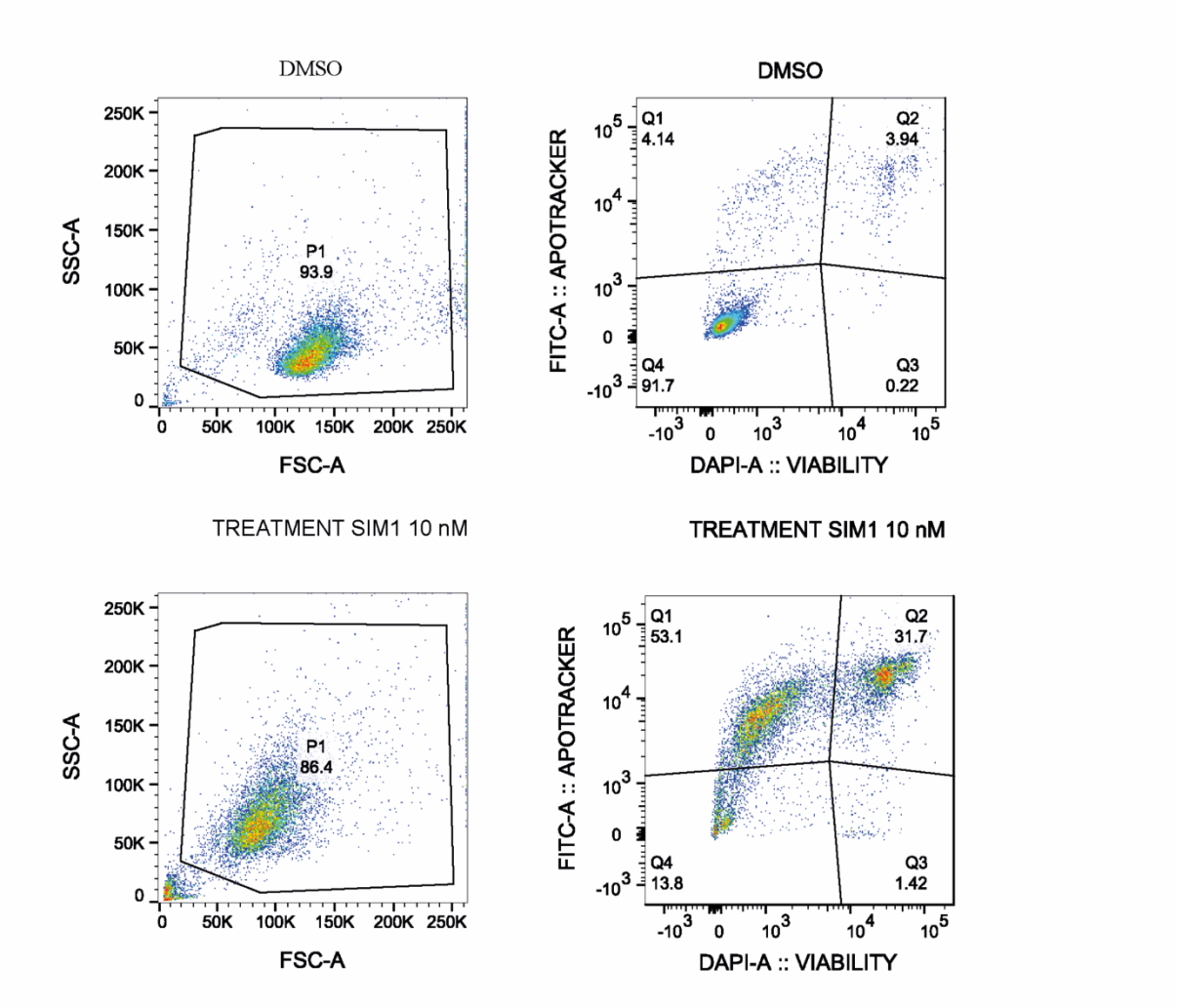
This PDF includes:

Supplementary Figures and Tables

Supplementary Note (Chemistry Methods)

NMR spectra



Supplementary Figure 1. Gating strategy used for apoptosis analysis by flow cytometry in Extended Data Fig. 5 (related to Fig. 3f).

Quadrant gates were set on population of 10,000 MV4;11 cells (P1) treated with DMSO and stained with DAPI and Apotracker Green-FITC (upper panel) and applied unchanged to all treated samples (lower panel). Early apoptotic and late apoptotic cells can be found in quadrants Q1 and Q2, respectively.

Supplementary Table 1. Fitted SPR data for SIM1 (binary) and SIM1:BET tandem complexes (ternary) binding to immobilized VHL.

	k_{on} (M^{-1} s^{-1}) × 10^5	k_{off} (s^{-1}) × 10^{-2}	$t_{1/2}$ (s)	K_d (nM)	α	% R_{max} (1:1 complex)
SIM1, MCK	1.12 ±0.32	6.87 ± 1.1	10 ± 1	624 ± 84	-	52 ± 3
SIM1 + BRD2(1,2), SCK	4.38 ± 0.07	1.96 ± 0.24	36 ± 4.5	45± 6	13.8	77 ± 9
SIM1 + BRD2(1,2), MCK	5.07 ± 0.40	2.22 ± 0.25	32 ± 4	44 ± 7	14.1	69 ± 7
SIM1 + BRD4(1,2), SCK	2.53 ± 0.34	2.46 ± 0.45	29 ± 5	98 ± 19	6.4	53 ± 5
SIM1 + BRD4(1,2), MCK	1.75 ± 0.31	2.51 ± 0.23	28 ± 2	146 ± 26	4.3	48 ± 6

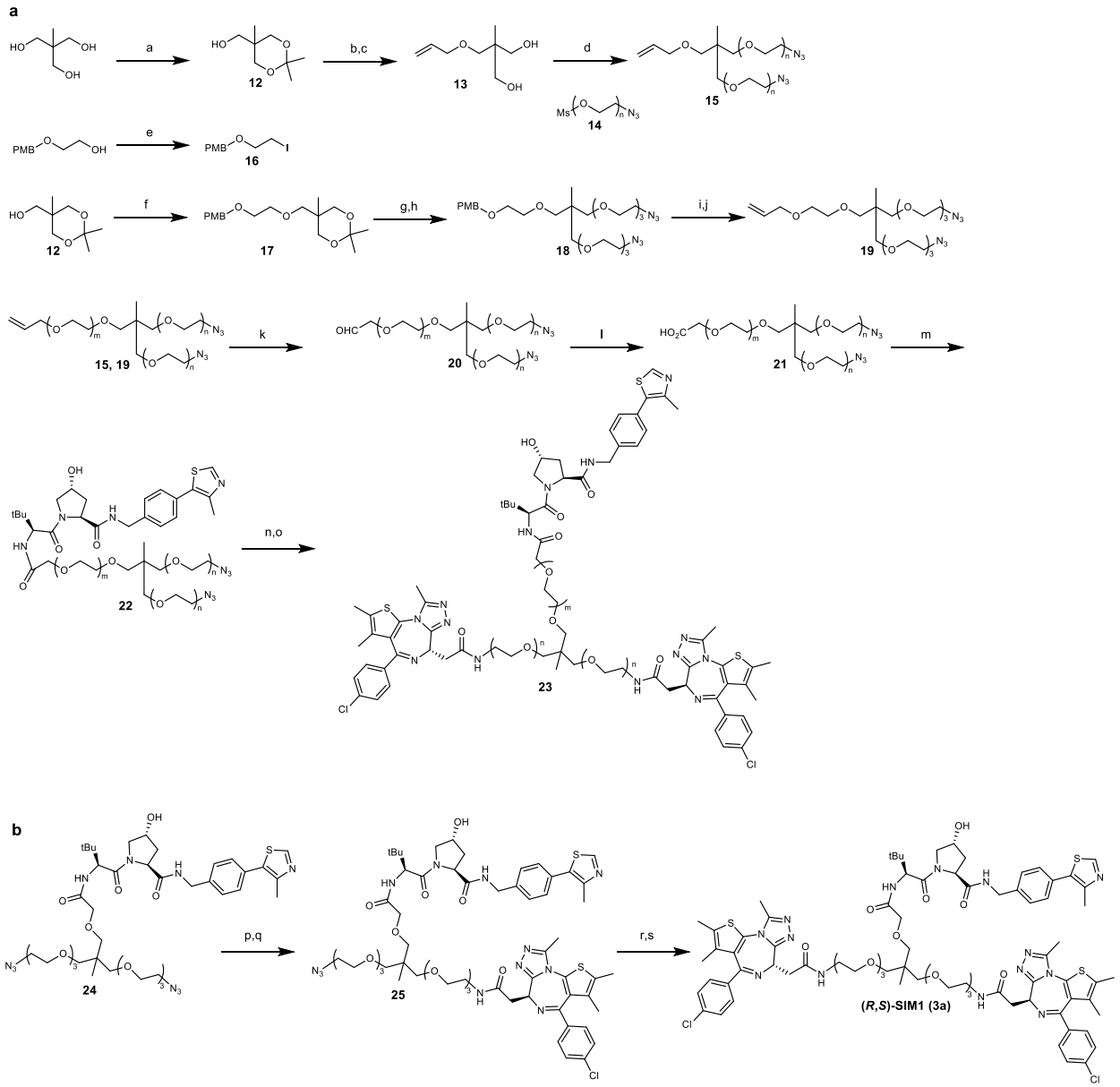
All binding experiments were performed at 295.15 K in multi-cycle kinetic (MCK) or single-cycle kinetic (SCK) format. Data were obtained from kinetic fitting using a 1:1 Langmuir model including a component for mass transfer effects. Values shown were calculated from fitted kinetic data as follows: dissociation constant ($K_d = k_{off}/k_{on}$), dissociative half-life ($t_{1/2} = \ln 2/k_{off}$), cooperativity ($\alpha = K_d^{binary}/K_d^{ternary}$). Values are mean ± SD (n≥2).

Supplementary Table 2. Calculated pharmacokinetic parameters for intravenous (i.v.) and subcutaneous (s.c.) administration of SIM1 (this work), alongside those of MZ1 (https://opnme.com/molecules/bet-mz-1) and JQ1 (Filippakopoulos et al. *Nature* **468,** 1067–1073 (2010)).

		SIM1	MZ1	JQ1
mouse *i.v.*	Dose [mg/kg]	5	5	5
	CL % Q_H | L/h/kg	3.35 | 0.181	20.7 | 1.18	43.5 | 2.35
	V_{ss} [l/kg]	0.35	0.38	2.02
	$AUC_{0\text{-}inf}$ [h· ng/mL]	27,550	4,520	2,130
	$t_{1/2,term}$ [h]	2.13	1.04	0.90
mouse *s.c.*	Dose [mg/kg]	5	5	
	$AUC_{0\text{-}inf}$ [h· ng/mL]	23,225	3,760	
	C_{max} [ng/mL]	3,827	2,070	
	T_{max} [h]	4.0	0.5	
	F [%]	88.4	83	

Supplementary Note

Synthetic Procedures



Synthetic route to (a) SIM1-SIM3 and (b) (*R*,*S*)-SIM1.

Reagents and conditions: (a) *p*-toluenesulfonic acid, acetone (96%). (b-c) allyl bromide, KOH, TBAB, Toluene, H_2O. TFA, methanol, H_2O (86% over two steps). (d) **14**, for n=3, NaH, DMF, 60 °C (60%); for n=4, KOH, TBAB, KI, 1,4-dioxane (9%). (e) PPh_3, I_2, imidazole, CH_2CH_2 (82%). (f) **16**, NaH, DMF (14%). (g) TFA, methanol, H_2O (89%). (h) **14** (n=3), KOH, TBAB, KI, 1,4-dioxane (55%). (i) DDQ, CH_2CH_2, H_2O (91%). (j) allyl bromide, KOH, 1,4-dioxane (72%). (k) OsO_4, $NaIO_4$, 2,6-luthidine, 1,4-dioxane, H_2O (m=0 n=3, 64%, m=1 n=3, 76%, m=0 n=4, 65%). (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-Butanol, H_2O. (m) VH032-amine

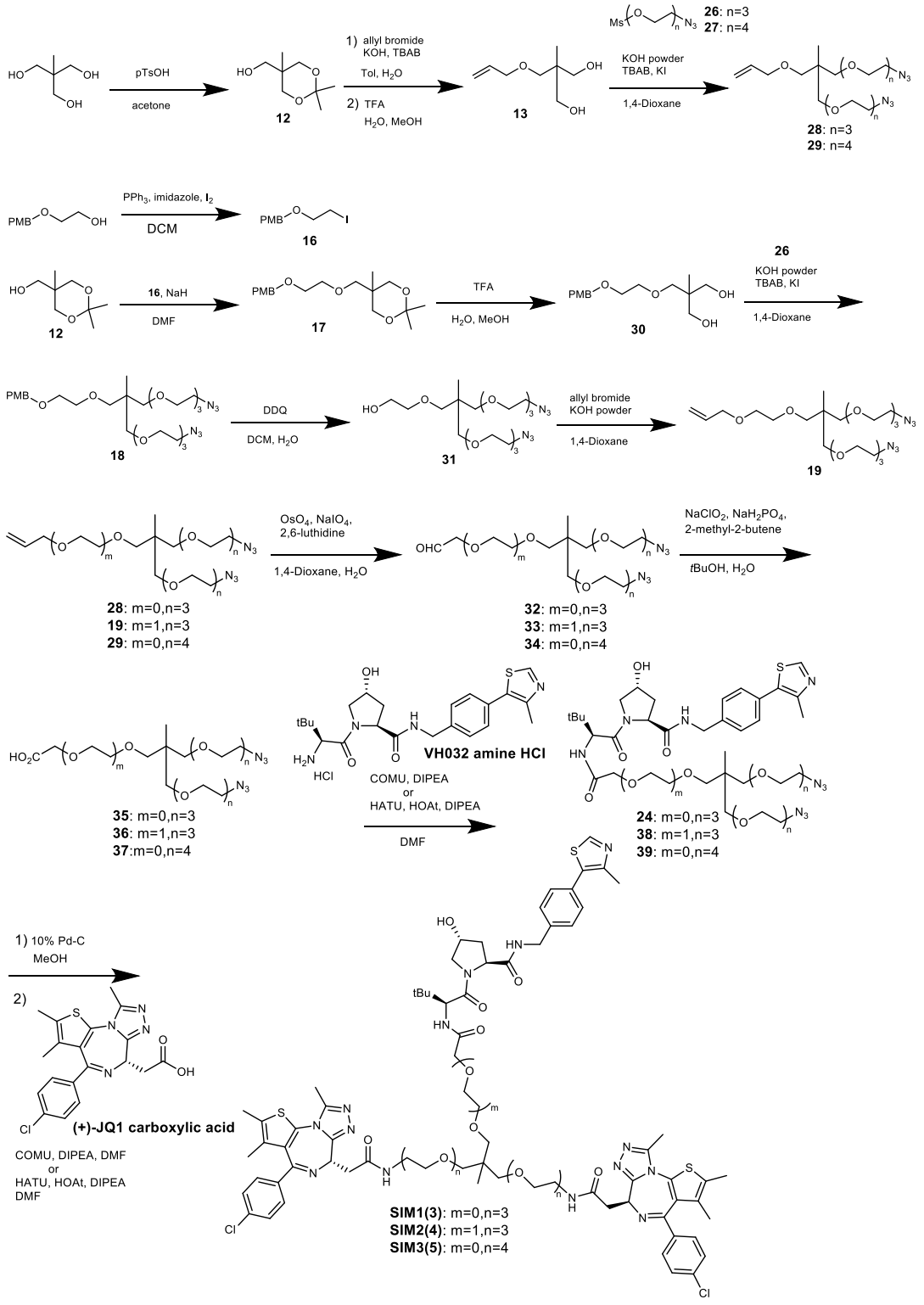
HCl, COMU, DIPEA, DMF (m=0 n=3, 52% over two steps). VH032-amine HCl, HATU, HOAt, DIPEA, DMF (m=1 n=3, 43% over two steps, m=0 n=4, 29% over two steps). (n) H_2, 10% Pd-C, methanol. (o) (+)-JQ1 carboxylic acid, COMU, DIPEA, DMF (m=0 n=3, 54% over two steps, m=1 n=3, 53% over two steps). (p) PPh_3, EtOAc/THF/1M HCl (24%). (q) (+)-JQ1 carboxylic acid, HATU, DIPEA, DMF (86%). (r) H_2, 10% Pd-C, methanol. (s) (-)-JQ1 carboxylic acid, HATU, DIPEA, DMF (31% over two steps). (*R,S*)-SIM1 was purified as a mixture of diasteroisomers. Abbreviations: (+)-JQ1 carboxylic acid, HATU, HOAt, DIPEA, DMF (m=0 n=4, 43% over two steps). PMB, *p*-methoxybenzyl; TBAB, tetrabutylammonium bromide; TFA, trifluoroacetic acid; DMF, *N*,*N*-dimethylformamide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; COMU, 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy) dimethylaminomorpholino)] uronium hexafluorophosphate; DIPEA, *N*,*N*-diisopropylethylamine; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole.

General information

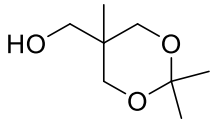
All chemicals unless otherwise stated, were commercially available, at least 90% pure and used without further purification. Commercially available dry solvents were used. Normal phase TLC was carried out on pre-coated silica plates (Kieselgel 60 F254, BDH) with visualization via UV light (UV 254 and/or 365 nm) and/or basic potassium permanganate solution. Flash column chromatography was performed using a Teledyne Isco Combiflash Rf with prepacked Redisep RF Normal phase disposable Columns. NMR Spectra were recorded on a Bruker Ascend 400 MHz or 500 MHz as specified. Chemical shifts are quoted in ppm and referenced to the residual solvent signals: ^{1}H NMR δ (ppm) = 7.26 ($CDCl_3$), ^{13}C NMR δ (ppm) = 77.16 ($CDCl_3$); ^{1}H NMR δ (ppm) = 5.32 (CD_2Cl_2), ^{13}C NMR δ (ppm) = 53.84 (CD_2Cl_2), ^{1}H NMR δ (ppm) = 2.50 (DMSO-d6); ^{1}H NMR δ (ppm) = 3.31 (CD_3OD), ^{13}C NMR δ (ppm) = 49.00 (CD_3OD). Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination thereof. Coupling constants (*J*) are measured in Hertz (Hz). High Resolution Mass Spectra (HRMS) were recorded on a Bruker microTOF. Other resolution MS and analytical HPLC traces were recorded on an Agilent Technologies 1200 series HPLC connected to an Agilent Technologies 6130 quadrupole LC/MS, connected to an Agilent diode array detector. The column used was a Waters XBridge column (50 mm × 2.1 mm, 3.5 µm particle size) and the compounds were eluted with a gradient 5−95% acetonitrile/water + 0.1 formic acid ("acidic method"). HPLC purification was performed on a Gilson Preparative HPLC System with a Waters XBridge C18 column (100 mm x 19 mm; 5 µm particle size) and a gradient of 5 % to 95 % acetonitrile in water over 10 min, flow 25 mL/min, with 0.1 % formic acid or ammonia in the aqueous phase.

Abbreviations used: DMSO for dimethylsulfoxide, PMB for *p*-methoxybenzyl, Ms for mesyl, tBu for *tert*-butyl, pTsOH for *p*-toluenesulfonic acid, TBAB for tetrabutylammonium bromide, TFA for trifluoroacetic acid, MeOH for methanol, DCM for dichloromethane, DDQ for 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, THF for tetrahydrofuran, HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, HOAt for 1-hydroxy-7-azabenzotriazole, DIPEA for *N*,*N*-diisopropylethylamine, DMF for *N*,*N*-dimethylformamide, MTBE for methyl *tert*-butyl ether, COMU for (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate.

Synthesis of SIM1, SIM2, SIM3

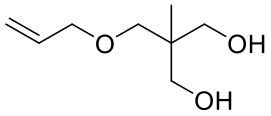


(2,2,5-trimethyl-1,3-dioxan-5-yl) methanol (12)



2-(Hydroxymethyl)-2-methylpropane-1,3-diol (50.0 g, 0.42 mol) and *p*-toluenesulfonic acid (50 mg) were dissolved in dry acetone (500 ml). The mixture was stirred for 2 days at room temperature. The solution was neutralized by adding solid potassium carbonate, filtrated, and evaporated under vacuum to give the desired product (64g, 96%, thick colourless oil) which was used without any further purification. Analytical data matched those reported in literature (Ouchi M. *et al. J. Org. Chem.* **1987**, 52, 2420).

2-((allyloxy)methyl)-2-methylpropane-1,3-diol (13)

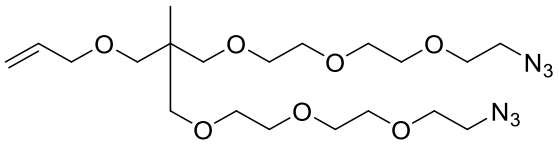


Potassium hydroxide (1.05 g, 16.75 mmol) in H_2O (1.05 ml), allyl bromide (1.54 ml, 18.75 mmol) and TBAB (202 mg, 0.625 mmol) were added to a solution of (2,2,5-trimethyl-1,3-dioxan-5-yl) methanol **12** (1.0g, 6.25 mmol) in toluene (6.25 ml). The resulting mixture was stirred at r.t. for 24 h. The reaction mixture was diluted with dichloromethane. The organic phase was separated and evaporated to dryness. The crude material was purified by column chromatography. The resulting allyl ether was dissolved in methanol (16 ml) and H_2O (3.2ml). After added trifluoroacetic acid (287 μL), the mixture was stirred at r.t. for 4 h. The reaction mixture was evaporated to dryness. The crude material was purified by column chromatography to afford title compound. Yield: 860 mg (86 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 5.98 - 5.83 (1H, m), 5.28 (1H, dd, *J* = 1.4, 17.3 Hz), 5.21 (1H, dd, *J* = 1.2, 10.5 Hz), 4.03 - 3.98 (2H, m), 3.73 (2H, dd, *J* = 4.8, 11.0 Hz), 3.62 (2H, dd, *J* = 5.5, 10.9 Hz), 3.47 (2H, d, *J* = 4.0 Hz), 2.70 (2H, s), 0.86 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 134.3, 117.2, 75.8, 72.5, 68.0, 40.8, 17.2.

11-((allyloxy)methyl)-1,21-diazido-11-methyl-3,6,9,13,16,19-hexaoxahenicosane (28)



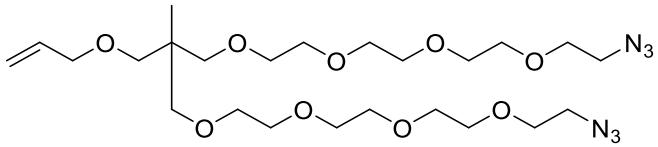
2-((allyloxy)methyl)-2-methylpropane-1,3-diol **13** (100 mg, 0.62 mmol) was dissolved in DMF (1 mL) and cooled to 0^{o}C. NaH (100 mg, 60% in oil, 2.47 mmol) was added and the reaction was stirred at 0 °C for 15 min. After that, 2-(2-(2-azidoethoxy)ethoxy)ethyl methanesulfonate **26** (750 mg, 1.85 mmol) was added and the reaction was stirred at 60 °C overnight. The mixture was then filtered on a celite pad and

concentrated. The crude material was purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 179 mg (61 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.96 - 5.84 (1H, m), 5.26 (1H, dd, *J* = 1.7, 17.2 Hz), 5.15 (1H, dd, *J* = 1.5, 10.4 Hz), 4.01 - 3.93 (2H, m), 3.76 - 3.61 (16H, m), 3.62 - 3.55 (4H, m), 3.44 - 3.37 (4H, m), 3.37 - 3.33 (4H, m), 3.33 - 3.29 (2H, m), 0.96 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 135.3, 116.0, 74.0, 73.0, 72.3, 71.1, 70.8, 70.7, 70.5, 70.0, 50.7, 41.0, 17.4.

14-((allyloxy)methyl)-1,27-diazido-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane (29)

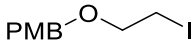


2-((allyloxy)methyl)-2-methylpropane-1,3-diol **13** (50 mg, 0.31 mmol), 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl methanesulfonate **27** (278 mg, 0.94 mmol) were dissolved in 1,4-dioxane (0.31 mL). TBAB (55 mg, 0.18 mmol), potassium iodide (2.6 mg, 0.016 mmol) and potassium hydroxide powder (52.5 mg, 0.94 mmol) were added and the reaction was stirred at 100 °C for 2 h. The reaction mixture was diluted with dichloromethane and filtrated. The organic phase was evaporated to dryness. The crude material was purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 15 mg (9 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.93 - 5.83 (1H, m), 5.25 (1H, dd, *J* = 1.3, 17.2 Hz), 5.16 - 5.11 (1H, m), 3.96 - 3.92 (2H, m), 3.71 - 3.54 (28H, m), 3.42 - 3.27 (10H, m), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 135.5, 116.2, 74.2, 73.2, 72.4, 71.2, 70.9, 70.8, 70.6, 70.2, 50.9, 41.2, 17.6.

1-((2-iodoethoxy)methyl)-4-methoxybenzene (16)

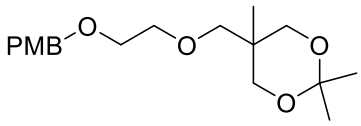


Iodine (180 mg, 0.71 mmol) was added at 0 °C to triphenylphosphine (187 mg, 0.71 mmol) and imidazole (48.6 mg, 0.71 mmol) solution in dichloromethane (3.8 mL). The resulting mixture was stirred at r.t. for 5 min. To the reaction mixture, 2-((4-methoxybenzy)oxy) ethan-1-ol (100 mg, 0.55 mmol) in dichloromethane (1.3 mL) was added at 0°C. The mixture was stirred at r.t. for 3 h. The reaction was quenched with Na_2SO_3 (aq) and $NaHCO_3$, then extracted with ethyl acetate. The organic phase were combined and evaporated to dryness. The crude material was purified by flush column chromatography to afford title compound. Yield: 131 mg (82 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.28 (2H, d, *J* = 8.8 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 4.51 (2H, s), 3.81 (3H, s), 3.71 (2H, t, *J* = 7.0 Hz), 3.26 (2H, t, *J* = 6.7 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 159.4, 129.9, 129.4, 113.9, 72.6, 70.5, 55.3, 3.0.

5-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-2,2,5-trimethyl-1,3-dioxane (17)

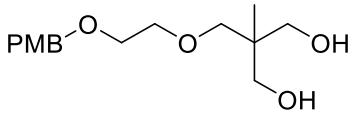


Sodium hydride 60 % dispersion in mineral oil (384 mg, 9.60 mmol) was added to a solution of (2,2,5-trimethyl-1,3-dioxan-5-yl) methanol **12** (1.54 g, 9.60 mmol) in DMF (3.0 mL) at 0 °C. The resulting mixture was stirred at r.t. for 30 min. To the mixture, 1-((2-iodoethoxy)methyl)-4-methoxybenzene **16** (700 mg, 2.40 mmol) in DMF (0.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 130 °C for 45 min. The mixture was quenched with H_2O and extracted with ethyl acetate. The organic phase was evaporated to dryness. The crude material was purified by flush column chromatography to afford title compound. Yield: 110 mg (14 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.29 (2H, d, *J* = 6.3 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 4.53 (2H, s), 3.83 (3H, s), 3.74 (2H, d, *J* = 11.9 Hz), 3.68 - 3.60 (4H, m), 3.56 (2H, d, *J* = 11.7 Hz), 3.49 (2H, s), 1.45 (3H, s), 1.42 (3H, s), 0.92 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 159.3, 130.7, 129.4, 113.9, 98.0, 74.3, 73.0, 71.3, 69.2, 66.7, 55.4, 34.6, 26.4, 21.5, 18.5.

2-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-2-methylpropane-1,3-diol (30)

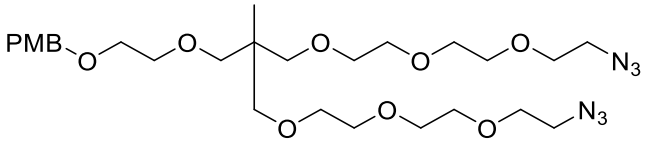


Trifluoroacetic acid (11 μL, 0.14 mmol) was added to 5-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-2,2,5-trimethyl-1,3-dioxane **17** (77 mg, 0.24 mmol) in methanol (0.6 mL) and H_2O (0.02 mL). The resulting mixture was stirred at r.t. for 16 h and then evaporated to dryness. The crude material was purified by flush column chromatography to afford title compound. Yield: 60 mg (89 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.26 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 4.49 (2H, s), 3.80 (3H, s), 3.51 (2H, s), 2.66 (2H, s), 0.80 (3H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 159.5, 130.1, 129.6, 114.0, 73.1, 70.9, 69.0, 68.3, 55.4, 41.0, 17.4.

1,21-diazido-11-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane (18)

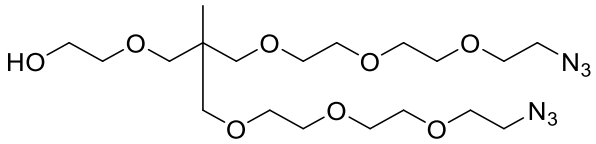


To a mixture of 2-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-2-methylpropane-1,3-diol **30** (73 mg, 0.26 mmol) and 2-(2-(2-azidoethoxy)ethoxy)ethyl methanesulfonate **26** (390 mg, 1.54 mmol) in 1,4-dioxane (0.51 mL), were added TBAB (25 mg, 0.077 mmol), potassium iodide (2.1 mg, 0.013 mmol) and potassium hydroxide powder (86 mg, 1.54 mmol). The resulting reaction mixture was stirred at 100 °C for 40 h. The reaction mixture was purified by flush column chromatography to afford title compound. Yield: 85 mg (55 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.26 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 4.49 (2H, s), 3.80 (3H, s), 3.70 - 3.53 (24H, m), 3.41 - 3.35 (4H, m), 3.35 - 3.30 (6H, m), 0.94 (3H, s)

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 159.3, 130.8, 129.3, 113.9, 74.1, 72.9, 71.2, 70.9, 70.8, 70.7, 70.2, 69.3, 55.4, 50.9, 41.2, 17.5.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-ol (31)

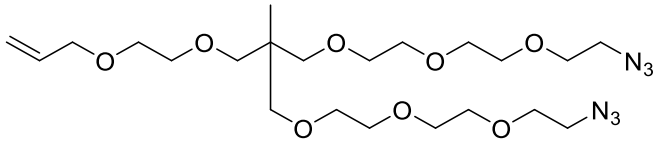


To a mixture of 1,21-diazido-11-((2-((4-methoxybenzyl)oxy)ethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane **18** (118 mg, 0.20 mmol) in H_2O (0.20 mL) and dichloromethane (2.0 mL), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (49.2 mg, 0.22 mmol) was added at 0 °C. The resulting reaction mixture was stirred at 4 °C for 16 h. The reaction mixture was quenched with $NaHCO_3$ (aq) and filtered to remove precipitate. The filtrate was evaporated and the remaining residue was purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 86 mg (91 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.71 - 3.61 (18H, m), 3.60 - 3.55 (4H, m), 3.55 - 3.51 (2H, m), 3.42 - 3.30 (10H, m), 2.48 (1H, t, J = 6.2 Hz), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 74.2, 73.5, 72.3, 71.2, 70.9, 70.8, 70.7, 70.2, 61.7, 50.9, 41.1, 17.7.

11-((2-(allyloxy)ethoxy)methyl)-1,21-diazido-11-methyl-3,6,9,13,16,19-hexaoxahenicosane (19)

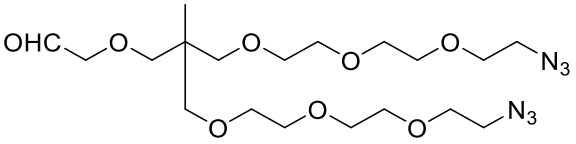


To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-ol **31** (50 mg, 0.10 mmol) in 1,4-dioxane (0.21 mL), were added allyl bromide (26 mg, 0.31 mmol), and potassium hydroxide powder (18 mg, 0.31 mmol). The resulting reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was diluted with dichloromethane and evaporated. The remaining residue was purified by flush column chromatography to afford title compound. Yield: 39 mg (72 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 5.95 - 5.85 (1H, m), 5.26 (1H, dd, *J* = 1.7, 17.2 Hz), 5.16 (1H, dd, *J* = 1.4, 10.5 Hz), 4.01 (2H, d, *J* = 6.0 Hz), 3.73 - 3.59 (16H, m), 3.58 - 3.52 (8H, m), 3.40 - 3.35 (4H, m), 3.35 - 3.28 (6H, m), 0.93 (3H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 135.1, 116.8, 74.1, 72.2, 71.2, 70.9, 70.8, 70.7, 70.2, 69.5, 50.8, 41.2, 17.5.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-al (32)

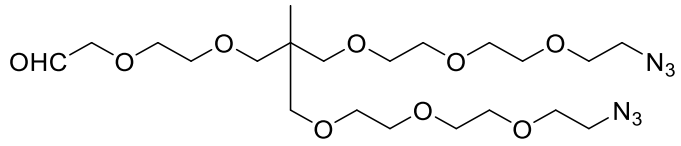


To a mixture of 11-((allyloxy)methyl)-1,21-diazido-11-methyl-3,6,9,13,16,19-hexaoxahenicosane **28** (25 mg, 0.053 mmol) in H_2O (0.3 mL) and 1,4-dioxane (1.0 mL), were added 2,6-luthidine (12.2 μL, 0.11 mmol), osmium tetroxide 4 % in H_2O (6.7 μL, 0.0011 mmol), sodium periodate (45 mg, 0.21 mmol). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with Na_2SO_3 (aq) and extracted with dichloromethane. The organic layer was concentrated and the remaining residue was purified by flush column chromatography to afford title compound. Yield: 16 mg (64 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.73 (1H, s), 4.02 (2H, s), 3.74 - 3.52 (20H, m), 3.46 - 3.26 (10H, m), 0.98 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 202.2, 77.0, 74.7, 73.9, 71.2, 70.9, 70.8, 70.7, 70.2, 50.9, 41.3, 17.5.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-al (33)



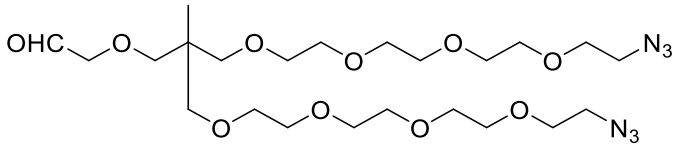
To a mixture of 11-((2-(allyloxy)ethoxy)methyl)-1,21-diazido-11-methyl-3,6,9,13,16,19-hexaoxahenicosane **19** (50 mg, 0.096 mmol) in H_2O (0.6 mL) and 1,4-dioxane (1.7 mL), were added 2,6-

luthidine (22.4 μL, 0.19 mmol), osmium tetroxide 4 % in H_2O (12.2 μL, 0.0019 mmol) and sodium periodate (82.5 mg, 0.39 mmol). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with Na_2SO_3 (aq) and extracted with dichloromethane. The organic layer was concentrated and the remaining residue was purified by flush column chromatography to afford title compound. Yield: 38 mg (76 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.71 (1H, s), 4.14 (2H, s), 3.71 - 3.50 (24H, m), 3.44 - 3.25 (10H, m), 0.92 (3H, s)

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 201.3, 77.0, 73.9, 73.4, 71.1, 70.8, 70.6, 70.1, 55.1, 50.8, 41.0, 17.5

1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-14-methyl-3,6,9,12,16-pentaoxaoctadecan-18-al (34)

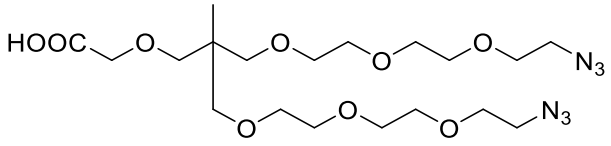


To a mixture of 14-((allyloxy)methyl)-1,27-diazido-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane **29** (35 mg, 0.062 mmol) in H_2O (0.4 mL) and 1,4-dioxane (1.7 mL) were added 2,6-luthidine (14.5 μL, 0.12 mmol), osmium tetroxide 4% in H_2O (12.2 μL, 0.0012 mmol), sodium periodate (53 mg, 0.25 mmol). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was quenched with Na_2SO_3 (aq) and extracted with dichloromethane. The organic layer was concentrated and the remaining residue was purified by flush column chromatography to afford title compound. Yield: 23 mg (65 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.75 (1H, s), 4.10 - 3.99 (2H, m), 3.77 - 3.29 (38H, m), 1.00 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 202.2, 74.7, 73.9, 71.2, 70.9, 70.8, 70.6, 70.2, 50.9, 41.3, 17.5.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-oic acid (35)

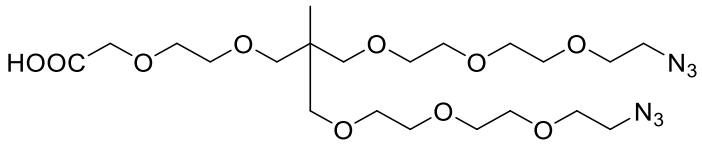


To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-al **32** (16 mg, 0.034 mmol) in *t*-BuOH (0.6 mL) were added 2M 2-methyl-2-butene in THF (84 μL, 0.168 mmol), NaH_2PO_4 (4.0 mg, 0.034 mmol), sodium chlorite (12.1 mg, 0.134 mmol) in H_2O (0.2 mL). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated and then diluted with NaOH (aq). The mixture was washed with MTBE and neutralized by 2M HCl. Extracted with dichloromethane, the organic layer was dried by Na_2SO_4 and concentrated. The remaining crude was used in next step without further purification. Yield: 16 mg (97 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.05 (2H, s), 3.70 - 3.58 (20H, m), 3.45 - 3.33 (10H, m), 0.95 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 172.1, 75.4, 74.7, 71.3, 70.9, 70.7, 70.4, 70.2, 68.8, 50.8, 40.8, 18.0.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-oic acid (36)

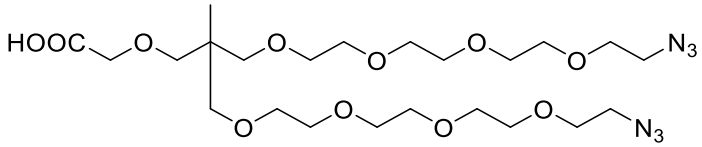


To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-al **33** (35 mg, 0.067 mmol) in *t*-butanol (1.2 mL), were added 2M 2-methyl-2-butene in THF (168 µL, 0.336 mmol), NaH_2PO_4 (8.1 mg, 0.067 mmol), sodium chlorite (24 mg, 0.265 mmol) in H_2O (0.4 mL). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated and then diluted with NaOH (aq). The mixture was washed with MTBE and neutralized with 2M HCl. Extracted with dichloromethane, the organic layer was dried by Na_2SO_4 and concentrated. The remaining crude was used in next step without further purification. Yield: 36 mg (quant.).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.09 (2H, s), 3.71 - 3.47 (24H, m), 3.37 - 3.21 (10H, m), 0.87 (3H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 172.2, 74.0, 73.9, 71.5, 71.1, 70.8, 70.7, 70.1, 68.9, 50.8, 41.0, 17.5.

1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-14-methyl-3,6,9,12,16-pentaoxaoctadecan-18-oic acid (37)

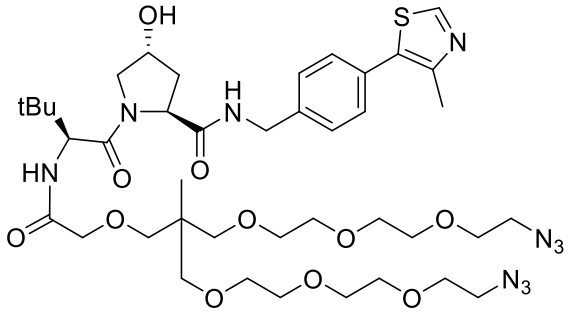


To a mixture of 1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-14-methyl-3,6,9,12,16-pentaoxaoctadecan-18-al **34** (14 mg, 0.025 mmol) in t-Butanol (0.45 mL), were added 2M 2-methyl-2-butene in THF (62 µL, 0.124 mmol), NaH_2PO_4 (3.0 mg, 0.025 mmol), sodium chlorite (8.9 mg, 0.099 mmol) in H_2O (0.15 mL). The resulting reaction mixture was stirred at r.t. for 16 h. The reaction mixture was concentrated and then diluted with NaOH (aq). The mixture was washed with MTBE and neutralized by 2M HCl. Extracted with dichloromethane, the organic layer was dried by Na_2SO_4 and concentrated. The remaining crude was used in next step without further purification. Yield: 8 mg (56 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 4.04 (2H, s), 3.71 - 3.55 (28H, m), 3.45 - 3.32 (10H, m), 0.95 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.9, 75.3, 74.7, 71.4, 70.9, 70.8, 70.7, 70.4, 70.2, 68.9, 50.9, 40.8, 18.0.

(2*S*,4*R*)-1-((*S*)-1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-17-(*tert*-butyl)-11-methyl-15-oxo-3,6,9,13-tetraoxa-16-azaoctadecan-18-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (24)



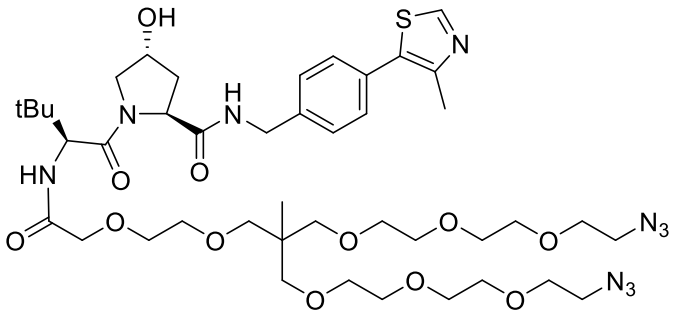
COMU (10.4 mg, 0.024 mmol), *N*,*N*-diisopropylethylamine (14.1 μL, 0.081 mmol) were added to a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-oic acid **35** (10 mg, 0.020 mmol) in DMF (0.20 mL). The resulting reaction mixture was stirred at r.t. for 2 min. VH032 amine hydrochloride [1] (14.2 mg, 0.031 mmol) was added to the mixture. Then, the mixture was stirred at r.t. for 16 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 10 mg (54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.68 (1H, s), 7.39 - 7.30 (5H, m), 7.10 (1H, d, *J* = 8.5 Hz), 4.73 (1H, t, *J* = 7.8 Hz), 4.59 - 4.51 (2H, m), 4.48 (1H, d, *J* = 8.7 Hz), 4.35 (1H, dd, *J* = 5.5, 15.0 Hz), 4.09 (1H, d, *J* = 12.0 Hz), 3.94 (2H, dd, *J* = 15.4, 17.7 Hz), 3.71 - 3.53 (21H, m), 3.46 - 3.30 (10H, m), 2.60 - 2.49 (1H, m), 2.51 (3H, s), 2.16 - 2.08 (1H, m), 0.96 (3H, s), 0.95 (9H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.5, 170.8, 170.7, 150.5, 148.6, 138.3, 131.8, 131.1, 129.7, 128.3, 74.8, 74.2, 74.1, 71.2, 70.9, 70.8, 70.7, 70.6, 70.3, 70.2, 58.5, 57.2, 56.7, 50.8, 43.4, 41.1, 35.9, 35.0, 26.5, 17.7, 16.2.

MS (ESI) for $C_{41}H_{65}N_{10}O_{11}S$ [M + H^+] calculated 905.5, obtained 905.3.

(2*S*,4*R*)-1-((*S*)-21-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-2-(*tert*-butyl)-11-methyl-4-oxo-6,9,13,16,19-pentaoxa-3-azahenicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (38)



To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-oic acid **36** (17 mg, 0.032 mmol) in DMF (0.32 mL), were added HATU (18 mg,

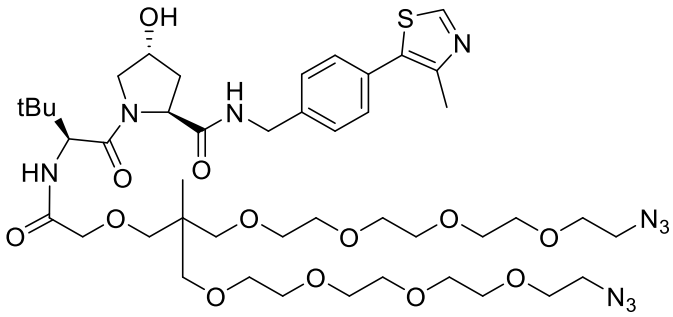
0.048 mmol), HOAt (6.5 mg, 0.048 mmol), *N*,*N*-diisopropylethylamine (22 μL, 0.127 mmol). The resulting reaction mixture was stirred at r.t. for 5 min. VH032 amine hydrochloride [1] (22.1 mg, 0.032 mmol) was added to the mixture. The mixture was then stirred at r.t. for 6 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 13 mg (43 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.75 (1H, s), 7.44 - 7.34 (5H, m), 7.21 (1H, d, *J* = 8.0 Hz), 4.76 (1H, t, *J* = 7.8 Hz), 4.61 - 4.50 (3H, m), 4.38 (1H, dd, *J* = 5.4, 14.8 Hz), 4.12 - 3.97 (3H, m), 3.74 - 3.55 (25H, m), 3.43 - 3.29 (10H, m), 2.61 - 2.51 (1H, m), 2.54 (3H, s), 2.17 - 2.10 (1H, m), 0.97 (9H, s), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.6, 170.8, 170.5, 150.6, 148.3, 138.4, 131.9, 130.9, 129.7, 128.3, 74.2, 74.1, 71.2, 71.1, 70.9, 70.8, 70.6, 70.3, 70.2, 58.6, 57.2, 56.8, 50.9, 43.4, 41.1, 36.0, 35.1, 26.6, 17.5, 16.0.

MS (ESI) for $C_{43}H_{69}N_{10}O_{12}S$ [M + H^+] calculated 949.5, obtained 949.4.

(2*S*,4*R*)-1-((*S*)-1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-20-(*tert*-butyl)-14-methyl-18-oxo-3,6,9,12,16-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (39)



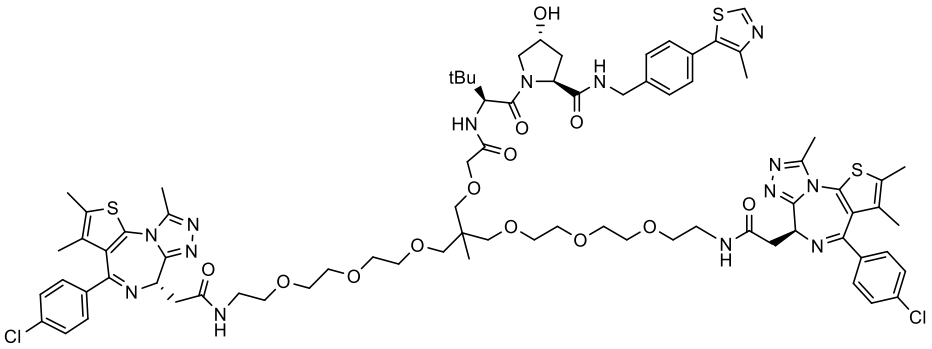
To a mixture of 1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-14-methyl-3,6,9,12,16-pentaoxaoctadecan-18-oic acid **37** (7.1 mg, 0.012 mmol) in DMF (0.20 mL), were added HATU (7.0 mg, 0.018 mmol), HOAt (2.5 mg, 0.018 mmol), *N*,*N*-diisopropylethylamine (8.5 μL, 0.127 mmol). The resulting reaction mixture was stirred at r.t. for 5 min. VH032 amine hydrochloride [1] (22.1 mg, 0.049 mmol) was added to the mixture. Then, the mixture was stirred at r.t. for 6 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 6.2 mg (51 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 8.90 (1H, s), 7.54 - 7.36 (5H, m), 4.69 (1H, d, *J* = 9.7 Hz), 4.61 - 4.48 (3H, m), 4.36 (1H, dd, *J* = 5.1, 15.6 Hz), 4.00 (1H, d, *J* = 14.8 Hz), 3.96 (1H, d, *J* = 15.4 Hz), 3.87 (1H, d, *J* = 11.5 Hz), 3.80 (1H, dd, *J* = 3.7, 10.8 Hz), 3.69 - 3.55 (28H, m), 3.48 (1H, d, *J* = 9.3 Hz), 3.44 (1H, d, *J* = 9.0 Hz), 3.41 - 3.34 (8H, m), 2.49 (3H, s), 2.27 - 2.19 (1H, m), 2.14 - 2.06 (1H, m), 1.05 (9H, s), 1.01 (3H, s)

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 174.4, 171.9, 171.6, 152.9, 149.0, 140.3, 133.5, 131.5, 130.4, 129.0, 75.5, 74.8, 74.8, 72.2, 71.7, 71.6, 71.5, 71.1, 60.8, 58.1, 51.8, 43.7, 42.1, 38.9, 37.3, 27.0, 18.0, 15.8.

MS (ESI) for $C_{45}H_{73}N_{10}O_{13}S$ [M + H^+] calculated 993.5, obtained 993.4.

***N*,*N*'-(11-((2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM1(3)**



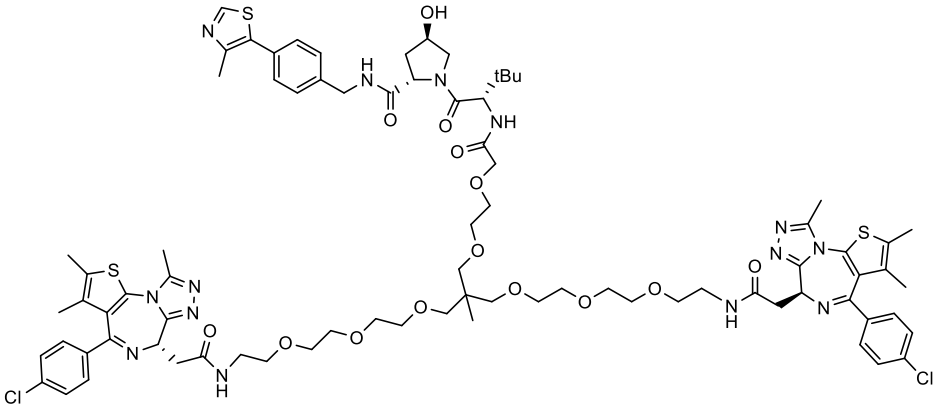
To a mixture of (2*S*,4*R*)-1-((*S*)-1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-17-(*tert*-butyl)-11-methyl-15-oxo-3,6,9,13-tetraoxa-16-azaoctadecan-18-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **24** (10 mg, 0.011 mmol) in MeOH (0.60 mL), were added 10%wt palladium on carbon (2.0 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. for 2 h. The mixture was then filtered on a celite pad and evaporated. A pre stirred mixture of (+)-JQ1 carboxylic acid (12.5 mg, 0.031 mmol), COMU (13.4 mg, 0.031 mmol), *N*,*N*-diisopropylethylamine (13.6 µL, 0.078 mmol) in DMF (0.20 mL) was added to the concentrated crude. Then, the mixture was stirred at r.t. for 3 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 10 mg (54 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.67 (1H, s), 7.47 - 7.28 (14H, m), 7.17 (1H, d, *J* = 9.7 Hz), 4.86 (1H, m), 4.83 (t, 1H, *J* = 7.9 Hz), 4.70 - 4.61 (3H, m), 4.53 (1H, dd, *J* = 5.7, 15.2 Hz), 4.48 - 4.42 (1H, m), 4.34 (1H, dd, *J* = 6.0, 14.9 Hz), 4.1 (1H, d, *J* = 11.1 Hz), 4.06 (1H, d, *J* = 15.3 Hz), 3.96 (1H, d, *J* = 15.3 Hz), 3.70 - 3.24 (31H, m), 3.21 (1H, d, *J* = 8.9 Hz), 2.63 (6H, s), 2.50 (3H, s), 2.44 (1H, m), 2.39 (6H, s), 2.15 (1H, m), 1.65 (6H, s), 0.97 (9H, s), 0.93 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.5, 171.2, 170.8, 170.7, 164.0, 155.9, 150.4, 149.9, 148.6, 138.5, 136.9, 132.3, 131.1, 130.9, 130.7, 130.1, 129.6, 128.8, 128.2, 73.7, 73.6, 73.5, 71.2, 70.8, 70.7, 70.6, 70.4, 70.3, 70.1, 59.0, 57.3, 56.7, 54.5, 43.3, 41.1, 39.6, 38.8, 36.5, 35.6, 26.6, 17.7, 16.2, 14.5.

HRMS (ESI) for $C_{79}H_{99}Cl_2N_{14}O_{13}S_3$ [M + H^+] calculated 1617.6050, obtained 1617.6390.

***N*,*N*'-(11-((2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM2(4)**



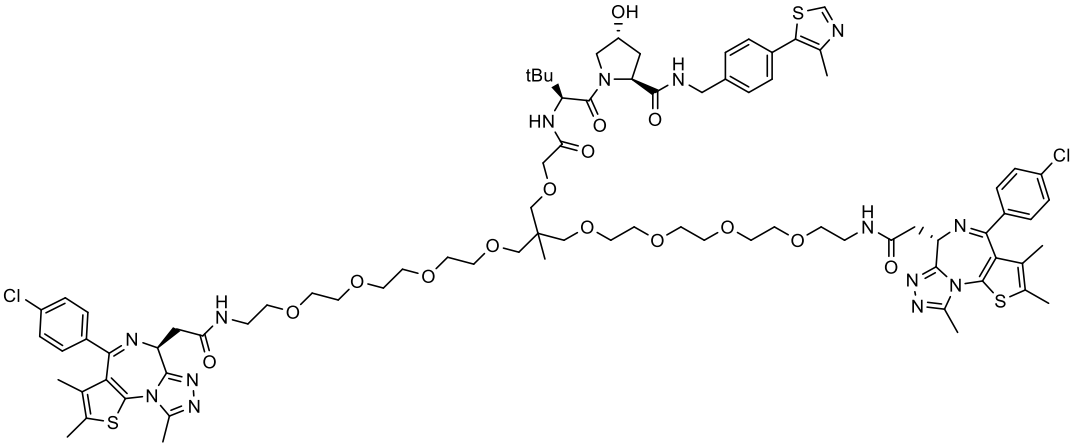
To a mixture of (2*S*,4*R*)-1-((*S*)-21-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-2-(*tert*-butyl)-11-methyl-4-oxo-6,9,13,16,19-pentaoxa-3-azahenicosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **38** (13 mg, 0.014 mmol) in MeOH (0.80 mL), were added 10%wt palladium on carbon (2.5 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. for 2 h. The mixture was then filtered on a celite pad and evaporated. A pre stirred mixture of (+)-JQ1 carboxylic acid (22.2 mg, 0.055 mmol), COMU (23.7 mg, 0.055 mmol), *N*,*N*-diisopropylethylamine (16 μL, 0.092 mmol) in DMF (0.20 mL) was added to the concentrated crude. Then, the mixture was stirred at r.t. for 16 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 12 mg (53 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.67 (1H, s), 7.57 (1H, t, *J* = 4.9 Hz), 7.42 - 7.28 (12H, m), 7.25 - 7.15 (2H, m), 4.81 (1H, t, *J* = 7.7 Hz), 4.69 - 4.60 (3H, m), 4.54 - 4.47 (2H, m), 4.46 - 4.42 (1H, m), 4.36 (1H, dd, *J* = 5.8, 15.3 Hz), 4.07 (1H, d, *J* = 15.4 Hz), 4.05 (1H, br d, *J* = 11.1 Hz), 3.98 (1H, d, *J* = 15.4 Hz), 3.73 - 3.23 (36H, m), 2.63 (3H, s), 2.62 (3H, s), 2.50 (3H, s), 2.47 - 2.40 (1H, m), 2.39 (6H, s), 2.23 - 2.16 (1H, m), 2.01 - 1.91 (4H, m), 1.66 (6H, s), 0.97 (9H, s), 0.92 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.4, 171.2, 170.7, 170.2, 163.9, 155.9, 150.3, 149.9, 148.6, 138.5, 136.9, 136.8, 132.3, 131.8, 131.1, 130.9, 130.7, 130.0, 129.6, 128.8, 128.2, 74.0, 73.8, 71.2, 71.1, 71.0, 70.7, 70.6, 70.1, 59.0, 57.2, 56.8, 54.5, 43.3, 41.2, 39.6, 39.0, 36.5, 35.8, 26.6, 17.6, 16.2, 14.5, 13.2, 11.9.

HRMS (ESI) for $C_{81}H_{103}Cl_2N_{14}O_{14}S_3$ [M + H^+] calculated 1661.6312, obtained 1661.8200.

***N*,*N*'-(14-((2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)methyl)-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM3(5)**



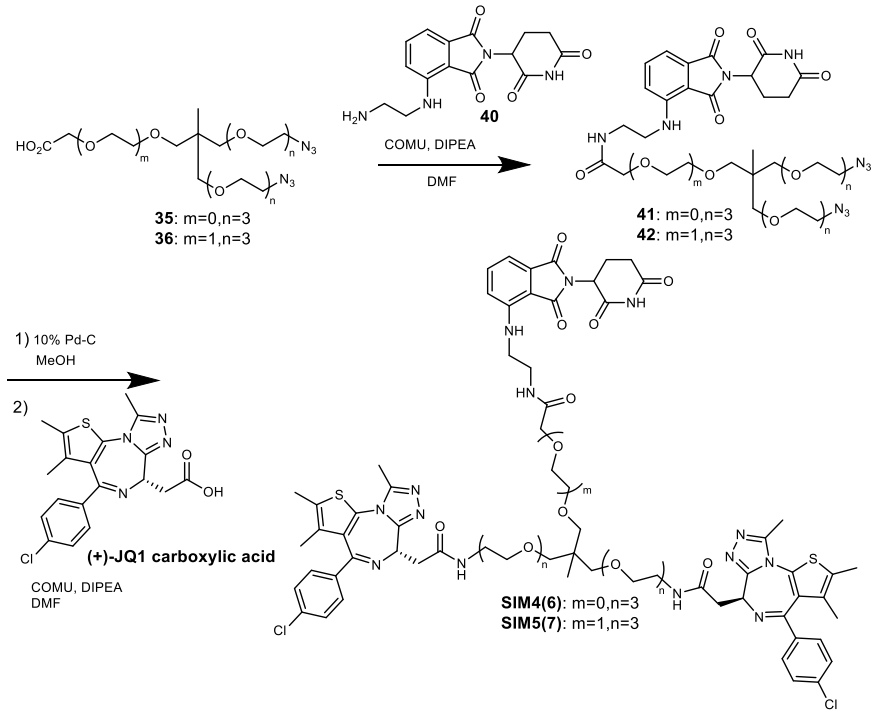
To a mixture of (2*S*,4*R*)-1-((*S*)-1-azido-14-(13-azido-2,5,8,11-tetraoxatridecyl)-20-(*tert*-butyl)-14-methyl-18-oxo-3,6,9,12,16-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **39** (10 mg, 0.020 mmol) in MeOH (0.20 mL), were added 10 % wt palladium on carbon (10.4 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. for 2 h. The mixture was then filtered on a celite pad and evaporated. A pre stirred mixture of (+)-JQ1 carboxylic acid (14.8 mg, 0.037 mmol), HATU (14 mg, 0.037 mmol), HOAt (5.0 mg, 0.037 mmol), *N*,*N*-diisopropylethylamine (12.8 μL, 0.074 mmol) in DMF (0.12 mL) was added to the concentrated crude. Then, the mixture was stirred at r.t. for 16 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 13 mg (43 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 8.86 (1H, s), 7.52 - 7.36 (12H, m), 4.71 - 4.40 (6H, m), 4.39 – 4.29 (1H, m), 3.97 (1H, d, *J* = 14.4 Hz), 3.93 (1H, d, *J* = 15.6 Hz), 3.85 (1H, d, *J* = 10.8 Hz), 3.79 (1H, dd, *J* = 3.9, 11.1 Hz), 3.68 - 3.33 (41H, m), 3.28 (1H, d, *J* = 5.1 Hz), 2.68 (6H, s), 2.46 (3H, s), 2.44 (6H, s), 2.26 - 2.18 (1H, m), 2.12 - 2.05 (1H, m), 1.69 (6H, s), 1.03 (9H, s), 0.97 (3H, s).

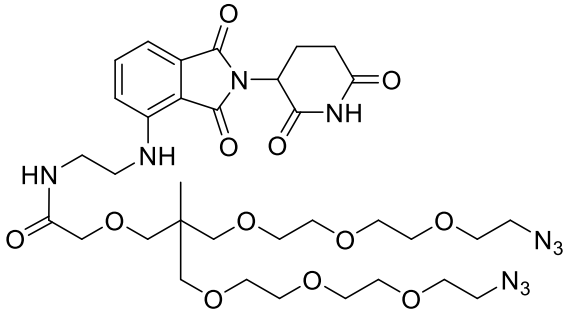
^{13}C NMR (126 MHz, CD_3OD) δ (ppm) = 174.4, 172.9, 171.8, 171.6, 166.1, 157.1, 152.8, 149.1, 140.3, 138.2, 137.9, 133.5, 133.2, 132.0, 131.5, 131.4, 130.5, 130.4, 129.8, 129.0, 75.5, 74.8, 72.2, 71.7, 71.6, 71.5, 71.4, 71.1, 70.7, 60.9, 58.1, 58.0, 55.2, 43.7, 42.1, 40.6, 38.9, 38.8, 37.3, 27.0, 18.0, 15.9, 14.4, 12.9, 11.6.

HRMS (ESI) for $C_{83}H_{107}Cl_2N_{14}O_{15}S_3$ [M + H^+] calculated 1705.6574, obtained 1705.6430.

Synthesis of SIM4, SIM5



1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-amide (41)



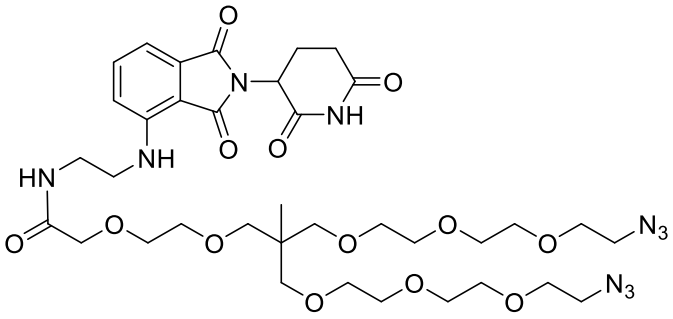
To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-oic acid **35** (14 mg, 0.0284 mmol) in DMF (0.2 mL), were added COMU (13.4 mg, 0.031 mmol), *N*,*N*-diisopropylethylamine (14.8 μL, 0.085 mmol). The resulting reaction mixture was stirred at r.t. for 2 min. 4-[(2-aminoethyl)amino]-2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2*H*)-dione **40** [2] (10.8 mg, 0.034 mmol) was added to the mixture. Then, the mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 12.5 mg (56 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.27 (1H, s), 7.54 (1H, t, *J* = 7.8 Hz), 7.14 (1H, d, *J* = 7.1 Hz), 7.07 (1H, d, *J* = 8.6 Hz), 6.50 (1H, t, *J* = 5.7 Hz), 4.94 (1H, dd, *J* = 5.3, 12.3 Hz), 4.00 - 3.95 (2H, m), 3.73 - 3.49 (24H, m), 3.45 - 3.32 (10H, m), 2.94 - 2.70 (3H, m), 2.21 - 2.11 (1H, m), 0.92 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.4, 171.1, 169.5, 168.4, 167.7, 147.0, 136.4, 132.7, 117.0, 112.0, 110.5, 75.0, 74.4, 71.2, 70.8, 70.7, 70.5, 70.1, 50.9, 49.1, 42.3, 40.9, 38.7, 31.6, 22.9.

MS (ESI) for $C_{34}H_{51}N_{10}O_{12}$ [M + H^+] calculated 791.4, obtained 791.3.

1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-amide (42)



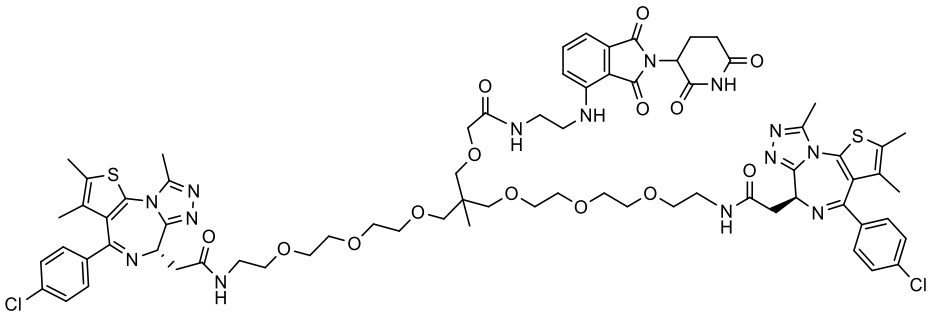
To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-oic acid **36** (14 mg, 0.026 mmol) in DMF (0.42 mL), were added COMU (12 mg, 0.029 mmol), *N*,*N*-diisopropylethylamine (14 μL, 0.078 mmol). The resulting reaction mixture was stirred at r.t. for 2 min. 4-[(2-aminoethyl)amino]-2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2*H*)-dione **40**[2] (22.1 mg, 0.032 mmol) was added to the mixture. Then, the mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 12 mg (55 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.36 (1H, s), 7.53 (1H, t, *J* = 7.8 Hz), 7.22 (1H, t, *J* = 5.6 Hz), 7.14 (1H, d, *J* = 6.8 Hz), 7.05 (1H, d, *J* = 8.7 Hz), 6.49 (1H, t, *J* = 5.7 Hz), 4.94 (1H, dd, *J* = 5.2, 12.2 Hz), 4.07 - 4.01 (2H, m), 3.72 - 3.47 (28H, m), 3.44 - 3.29 (10H, m), 2.95 - 2.69 (3H, m), 2.18 - 2.10 (1H, m), 0.95 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.2, 169.4, 168.4, 167.7, 146.9, 136.4, 132.7, 116.9, 112.1, 110.6, 74.2, 74.1, 71.2, 71.1, 70.9, 70.8, 70.7, 70.6, 70.1, 50.9, 49.1, 42.3, 41.2, 38.6, 31.6, 22.9, 17.6.

MS (ESI) for $C_{36}H_{55}N_{10}O_{13}$ [M + H^+] calculated 835.4, obtained 835.3.

***N*,*N*'-(11-((2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-2-oxoethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM4(6)**



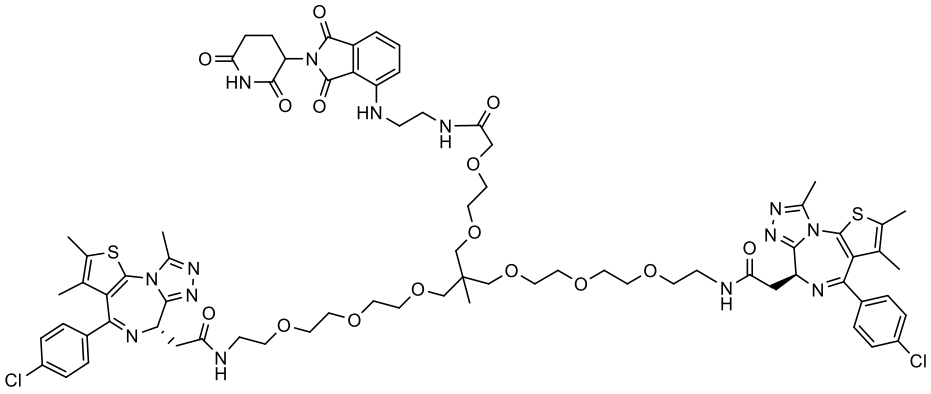
To the 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-11-methyl-3,6,9,13-tetraoxapentadecan-15-amide **41** (12.5 mg, 0.0158 mmol) in MeOH (0.8 mL), were added 10%wt palladium on carbon (2.5 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. for 2 h. The mixture was then filtered on a celite pad and solvent evaporated. A pre stirred mixture of (+)-JQ1 carboxylic acid (12.5 mg, 0.031 mmol), COMU (13.4 mg, 0.031 mmol), *N*,*N*-diisopropylethylamine (13.6 μL, 0.078 mmol) in DMF (0.20 mL) was added to the concentrated crude. Then, the mixture was stirred at r.t. for 4 h and purified by HPLC under acidic condition (5-95 % CH3CN in 0.1 % aq. HCO2H) to afford title compound. Yield: 1.3 mg (5 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 8.53 (1H, s), 7.51 (1H, dd, *J* = 7.3, 8.5 Hz), 7.44 (4H, d, *J* = 8.4 Hz), 7.39 (4H, dd, *J* = 2.2, 8.8 Hz), 7.08 (1H, d, *J* = 8.6 Hz), 7.02 (1H, d, *J* = 7.2 Hz), 4.99 (1H, ddd, *J* = 2.0, 5.5, 12.6 Hz), 4.65 - 4.59 (2H, m), 3.92 - 3.86 (2H, m), 3.69 - 3.38 (32H, m), 3.31 - 3.25 (6H, m), 2.89 - 2.78 (1H, m), 2.75 - 2.62 (8H, m), 2.43 (6H, s), 2.12 - 2.03 (1H, m), 1.68 (6H, s), 0.87 (3H, s).

^{13}C NMR (126 MHz, CD_3OD) δ (ppm) = 174.7, 173.5, 172.9, 171.4, 170.3, 169.2, 166.1, 157.0, 152.2, 148.1, 138.1, 137.9, 137.3, 133.5, 133.2, 132.0, 131.4, 130.4, 129.8, 129.5, 118.0, 112.1, 111.3, 75.4, 74.7, 72.1, 71.6, 71.4, 70.7, 55.2, 42.6, 41.8, 40.6, 39.6, 38.7, 32.2, 30.8, 23.8, 18.0, 14.5.

HRMS (ESI) for $C_{72}H_{85}Cl_2N_{14}O_{14}S_2$ [M + $2H^+$]/2 calculated 752.2633, obtained 752.2732

***N*,*N*'-(11-((2-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-2-oxoethoxy)ethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM5(7)**



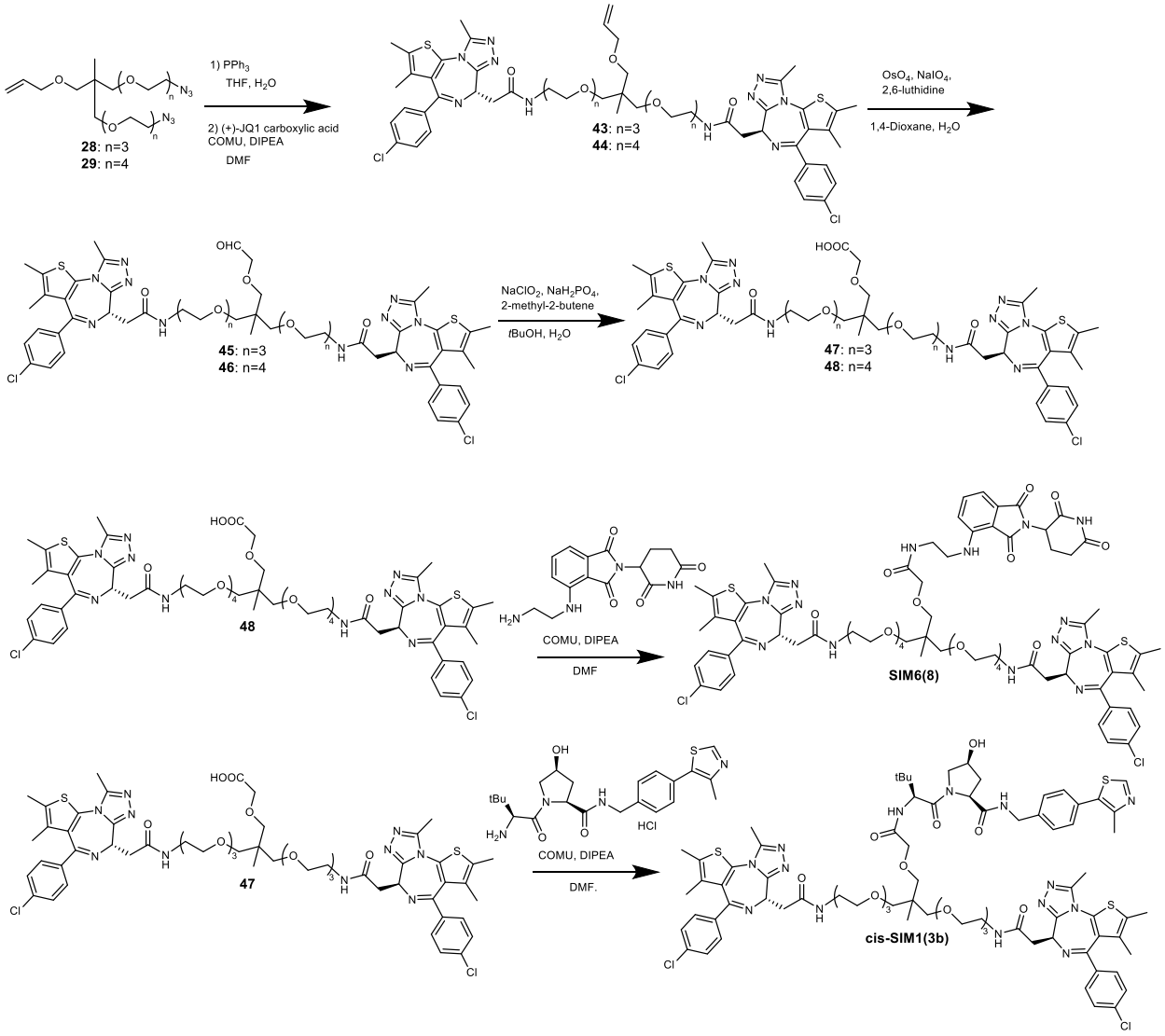
To a mixture of 1-azido-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-*N*-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-11-methyl-3,6,9,13,16-pentaoxaoctadecan-18-amide **42** (12 mg, 0.0144 mmol) in MeOH (0.80 mL), were added 10 % wt palladium on carbon (2.5 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. for 2 h. The mixture was then filtered on a celite pad and solvent evaporated. A pre stirred mixture of (+)-JQ1 carboxylic acid (13.8 mg, 0.035 mmol), COMU (14.8 mg, 0.035 mmol), *N*,*N*-diisopropylethylamine (15 μL, 0.086 mmol) in DMF (0.20 mL) was added to the concentrated crude. Then, the mixture was stirred at r.t. for 16 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 1.8 mg (8 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 7.52 (1H, dd, *J* = 7.4, 8.2 Hz), 7.44 (4H, d, *J* = 8.4 Hz), 7.39 (4H, dd, *J* = 1.4, 8.7 Hz), 7.10 (1H, d, *J* = 8.6 Hz), 7.02 (1H, d, *J* = 7.1 Hz), 5.00 (1H, dd, *J* = 5.3, 13.0 Hz), 4.62 (2H, dd, *J* = 5.2, 8.9 Hz), 3.99 - 3.94 (2H, m), 3.67 - 3.38 (36H, m), 3.36 - 3.23 (7H, m), 2.88 - 2.78 (1H, m), 2.76 - 2.61 (2H, m), 2.68 (6H, s), 2.43 (6H, s), 2.12 - 2.04 (1H, m), 1.69 (6H, s), 0.88 (3H, s).

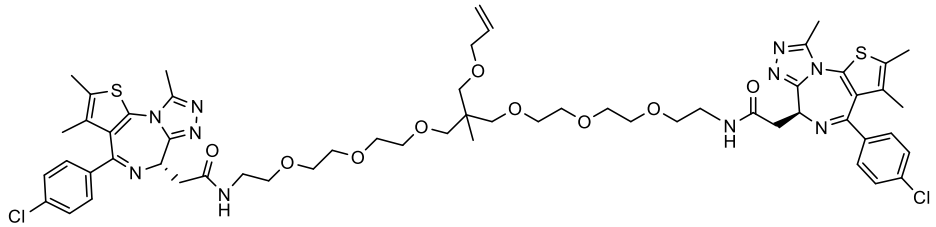
^{13}C NMR (126 MHz, CD_3OD) δ (ppm) = 174.6, 173.5, 172.9, 171.4, 170.5, 169.2, 166.1, 157.0, 152.2, 148.0, 138.1, 137.9, 137.3, 133.5, 133.2, 132.0, 131.4, 129.8, 118.1, 112.1, 111.4, 74.8, 72.1, 71.9, 71.7, 71.6, 71.4, 71.3, 70.7, 55.2, 42.6, 42.0, 40.6, 39.4, 38.7, 32.2, 30.8, 23.7, 18.0, 14.5, 12.9, 11.6.

HRMS (ESI) for $C_{74}H_{89}Cl_2N_{14}O_{15}S_2$ [M + H^+] calculated 1547.5445, obtained 1547.5989

Synthesis of SIM6, *cis*-SIM1



***N*,*N*'-(11-((allyloxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) (43)**



To a mixture of 11-((allyloxy)methyl)-1,21-diazido-11-methyl-3,6,9,13,16,19-hexaoxahenicosane **28** (25 mg, 0.053 mmol) in THF (0.53 mL), was added PPh_3 (41.7 mg, 0.16 mmol). The resulting mixture was stirred at 50 °C for 1 h. H_2O (0.05 mL) was added to the reaction mixture. Then, the mixture was stirred at 50 °C for 1 h and concentrated. A pre stirred mixture of (+)-JQ1 carboxylic acid (64 mg, 0.16 mmol), COMU (20.5

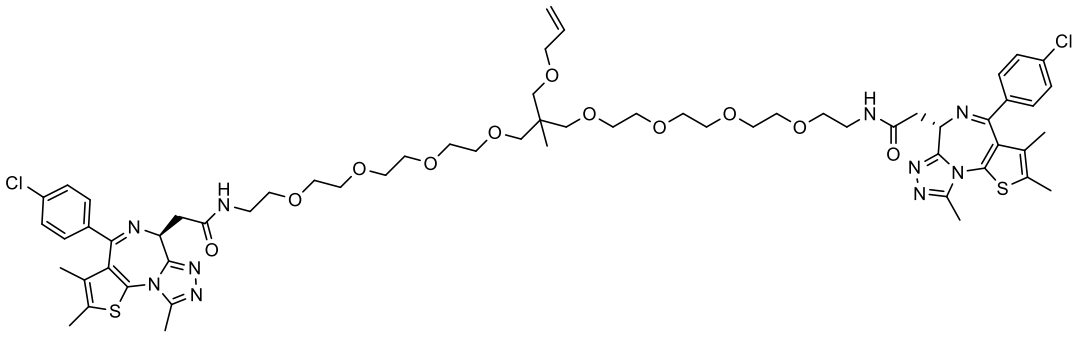
mg, 0.16 mmol), *N*,*N*-diisopropylethylamine (55.4 μL, 0.32 mmol) in DMF (0.42 mL) was added to the concentrated crude. Then, the resulting mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 17 mg (27 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.40 (4H, d, *J* = 8.1 Hz), 7.31 (4H, d, *J* = 7.9 Hz), 6.98 - 6.89 (2H, m), 5.93 - 5.80 (1H, m), 5.23 (1H, d, *J* = 17.2 Hz), 5.12 (1H, d, *J* = 11.0 Hz), 4.65 (2H, t, *J* = 6.8 Hz), 3.93 (2H, d, *J* = 5.2 Hz), 3.72 - 3.24 (32H, m), 2.66 (6H, s), 2.39 (6H, s), 1.66 (6H, s), 0.94 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 170.7, 164.0, 155.8, 150.0, 136.9, 136.8, 135.4, 132.3, 131.0, 130.9, 130.6, 130.0, 116.3, 74.1, 73.1, 72.4, 71.2, 70.7, 70.6, 70.5, 70.0, 54.5, 41.1, 39.6, 39.2, 17.6, 14.5, 13.2, 11.9.

MS (ESI) for $C_{58}H_{73}Cl_2N_{10}O_9S_2$ [M + H^+] calculated 1187.4, obtained 1187.4.

_N_,_N_'-(14-((allyloxy)methyl)-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((_S_)-4-(4-chlorophenyl)-2,3,9-trimethyl-6_H_-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) (44)



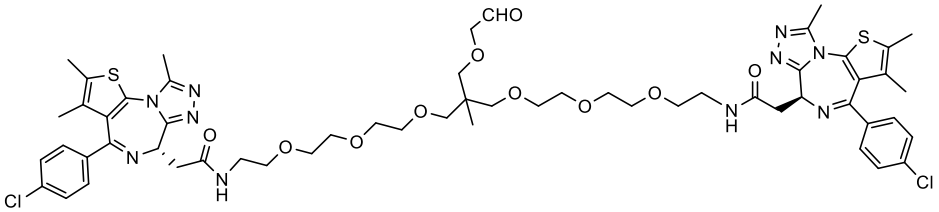
To a mixture of 14-((allyloxy)methyl)-1,27-diazido-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane **29** (67 mg, 0.119 mmol) in THF (1.2 mL), was added PPh_3 (93.5 mg, 0.36 mmol). The resulting mixture was stirred at 50 °C for 1 h. H_2O (0.12 mL) was added to the reaction mixture. Then, the mixture was stirred at 50 °C for 1 h and concentrated. A pre stirred mixture of (+)-JQ1 carboxylic acid (143 mg, 0.36 mmol), COMU (153 mg, 0.36 mmol), *N*,*N*-diisopropylethylamine (124 μL, 0.72 mmol) in DMF (0.95 mL) was added to the concentrated crude. Then, the resulting mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 87 mg (57 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.38 (4H, d, *J* = 8.2 Hz), 7.28 (4H, d, *J* = 8.0 Hz), 7.09 - 6.93 (2H, m), 5.89 - 5.76 (1H, m), 5.20 (1H, d, *J* = 18.0 Hz), 5.08 (1H, d, *J* = 10.2 Hz), 4.62 (2H, t, *J* = 6.0 Hz), 3.89 (2H, d, *J* = 4.8 Hz), 3.82 - 3.18 (40H, m), 2.62 (6H, s), 2.36 (6H, s), 1.64 (6H, s), 0.90 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 170.5, 163.7, 155.6, 149.7, 136.6, 135.2, 132.0, 130.8, 130.4, 129.8, 128.6, 116.0, 73.9, 72.9, 72.1, 71.0, 70.6, 70.5, 70.3, 69.7, 54.3, 40.9, 39.4, 38.9, 17.4, 14.3, 13.0, 11.7.

MS (ESI) for $C_{62}H_{81}Cl_2N_{10}O_{11}S_2$ [M + H^+] calculated 1275.5, obtained 1275.5.

***N*,*N*'-(11-methyl-11-((2-oxoethoxy)methyl)-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) (45)**



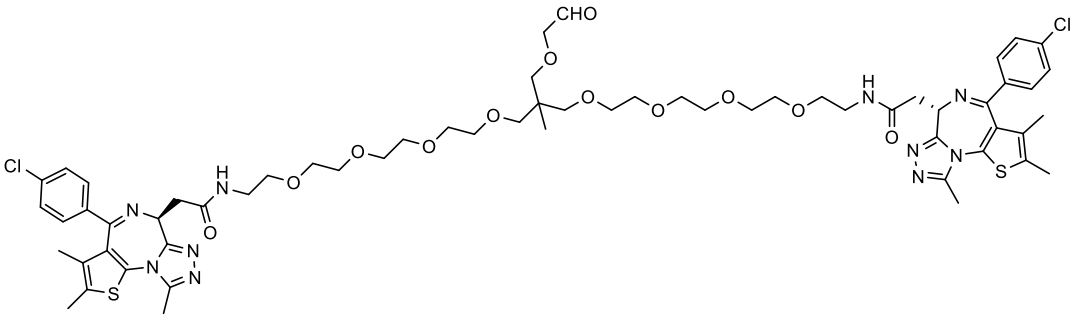
To a mixture of *N*,*N*'-(11-((allyloxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) **43** (17 mg, 0.014 mmol) in H_2O (0.09 mL) and 1,4-dioxane (0.26 mL), were added 2,6-luthidine (3.3 μL, 0.029 mmol), osmium tetroxide 4% in H_2O (1.8 μL, 0.0003 mmol), sodium periodate (12.2 mg, 0.058 mmol). The resulting reaction mixture was stirred at r.t. for 8 h. The reaction mixture was quenched with Na_2SO_3 (aq) and extracted with dichloromethane. The organic layer was concentrated and the remaining residue was purified by flush column chromatography to afford title compound. Yield: 14 mg (82 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.69 (1H, s), 7.40 (4H, d, *J* = 7.9 Hz), 7.31 (4H, d, *J* = 8.0 Hz), 7.00 - 6.90 (2H, m), 4.66 (2H, t, *J* = 6.7 Hz), 4.04 - 3.98 (2H, m), 3.74 - 3.27 (32H, m), 2.65 (6H, s), 2.39 (6H, s), 1.66 (6H, s), 0.97 (3H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) = 202.4, 170.7, 163.9, 155.8, 150.0, 136.8, 132.3, 131.0, 130.8, 130.6, 130.0, 128.8, 74.7, 73.9, 71.2, 70.7, 70.6, 70.0, 54.5, 41.2, 39.5, 39.2, 29.8, 17.5, 14.5, 13.2, 12.0.

MS (ESI) for $C_{57}H_{71}Cl_2N_{10}O_{10}S_2$ [M + H^+] calculated 1189.4, obtained 1189.4.

***N*,*N*'-(14-methyl-14-((2-oxoethoxy)methyl)-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) (46)**



To a mixture of *N*,*N*'-(14-((allyloxy)methyl)-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) **44** (87 mg, 0.068 mmol) in H_2O (0.41 mL) and 1,4-dioxane (1.2 mL), were added 2,6-luthidine (15.9 μL, 0.136 mmol), osmium tetroxide 4% in H_2O (1.8 μL, 0.0014 mmol), sodium periodate (58 mg, 0.27 mmol). The resulting reaction mixture was stirred at r.t. for 8 h. The reaction mixture was quenched with

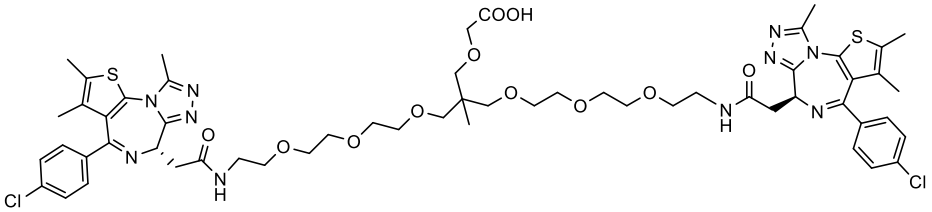
Na_2SO_3 (aq) and extracted with dichloromethane. The organic layer was concentrated and the remaining residue was purified by flush column chromatography to afford title compound. Yield: 74 mg (85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 9.70 (1H, s), 7.41 (4H, d, J = 8.3 Hz), 7.32 (4H, d, J = 8.6 Hz), 6.93 - 6.85 (2H, m), 4.65 (2H, t, J = 6.9 Hz), 4.07 - 4.01 (2H, m), 3.73 - 3.45 (36H, m), 3.44 - 3.29 (6H, m), 2.66 (6H, s), 2.39 (6H, s), 1.67 (6H, s), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 202.0, 170.6, 163.7, 155.7, 149.8, 136.7, 136.7, 132.2, 130.9, 130.7, 130.4, 129.9, 128.6, 76.9, 74.6, 73.8, 71.0, 70.6, 70.5, 70.4, 70.3, 69.8, 54.4, 41.0, 39.4, 39.0, 17.4, 14.3, 13.0, 11.8.

MS (ESI) for $C_{61}H_{79}Cl_2N_{10}O_{12S2}$ [M + H^+] calculated 1277.5, obtained 1277.5.

1-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-14-(13-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-12-oxo-2,5,8-trioxa-11-azatridecyl)-14-methyl-2-oxo-6,9,12,16-tetraoxa-3-azaoctadecan-18-oic acid (47)



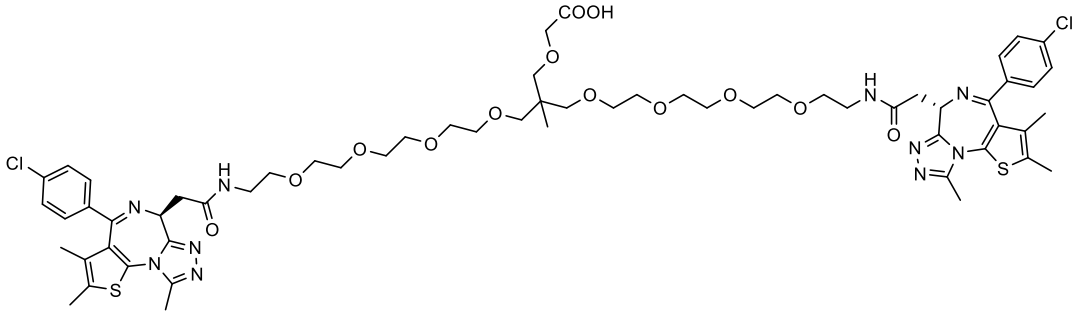
To a mixture of *N*,*N*'-(11-methyl-11-((2-oxoethoxy)methyl)-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) **45** (14 mg, 0.012 mmol) in t-BuOH (0.21 mL), were added 2M 2-methyl-2-butene in THF (59 µL, 0.12 mmol), NaH_2PO_4 (1.4 mg, 0.012 mmol), sodium chlorite (4.6 mg, 0.047 mmol) in H_2O (0.07 mL). The resulting reaction mixture was stirred at r.t. for 4 h. The reaction mixture was evaporated and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 6.2 mg (44 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.41 (4H, d, J = 8.7 Hz), 7.32 (4H, d, J = 8.7 Hz), 4.68 (2H, t, J = 7.1 Hz), 4.11 - 4.05 (2H, m), 3.72 - 3.31 (34H, m), 2.66 (6H, s), 2.40 (6H, s), 1.68 (6H, s), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 170.7, 164.0, 155.8, 150.0, 137.0, 136.7, 132.1, 131.1, 130.9, 130.0, 128.9, 74.4, 71.4, 70.8, 70.6, 70.1, 54.6, 41.0, 39.6, 39.1, 17.8, 14.5, 13.2, 11.9.

MS (ESI) for $C_{57}H_{71}Cl_2N_{10}O_{11}S_2$ [M + H^+] calculated 1205.4, found 1205.4.

1-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-17-(16-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-15-oxo-2,5,8,11-tetraoxa-14-azahexadecyl)-17-methyl-2-oxo-6,9,12,15,19-pentaoxa-3-azahenicosan-21-oic acid (48)



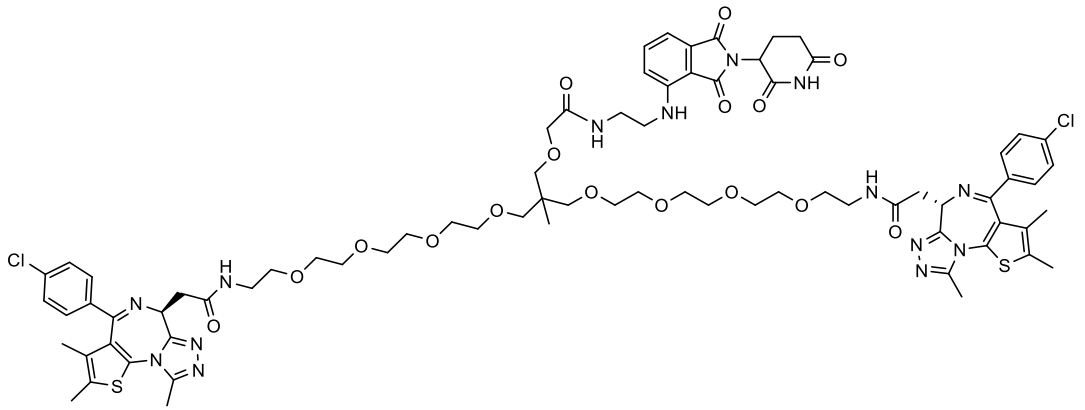
To a mixture of *N*,*N*'-(14-methyl-14-((2-oxoethoxy)methyl)-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) **46** (74 mg, 0.058 mmol) in *t*-butanol (1.0 mL), were added 2M 2-methyl-2-butene in THF (290 μL, 0.58 mmol), NaH_2PO_4 (7.0 mg, 0.058 mmol), sodium chlorite (22.4 mg, 0.23 mmol) in H_2O (0.35 mL). The resulting reaction mixture was stirred at r.t. for 4 h. The reaction mixture was evaporated and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO2H) to afford title compound. Yield: 63 mg (84 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.41 (4H, d, *J* = 8.8 Hz), 7.33 (4H, d, *J* = 8.6 Hz), 7.04 - 6.94 (2H, m), 4.66 (2H, t, *J* = 7.1 Hz), 4.09 - 4.05 (2H, m), 3.74 - 3.43 (36H, m), 3.41 - 3.30 (6H, m), 2.67 (6H, s), 2.40 (6H, s), 1.68 (7H, s), 0.94 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 172.7, 170.6, 163.9, 155.6, 149.9, 136.8, 136.6, 132.0, 131.0, 130.7, 129.9, 128.7, 74.7, 74.2, 71.1, 70.7, 70.5, 70.3, 69.7, 69.1, 54.4, 40.9, 39.5, 38.9, 17.5, 14.4, 13.1, 11.7.

MS (ESI) for $C_{61}H_{79}Cl_2N_{10}O_{12S2}$ [M + H^+] calculated 1293.5, obtained 1293.4.

***N*,*N*'-(14-((2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-2-oxoethoxy)methyl)-14-methyl-3,6,9,12,16,19,22,25-octaoxaheptacosane-1,27-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) SIM6(8)**



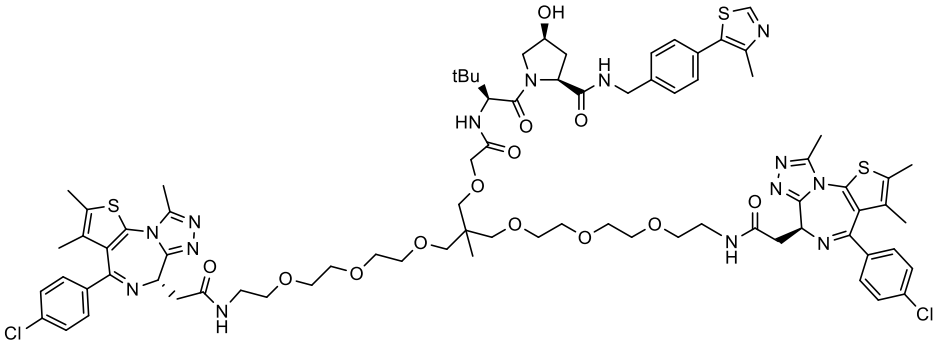
To a mixture of 1-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-17-(16-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-15-oxo-2,5,8,11-tetraoxa-14-azahexadecyl)-17-methyl-2-oxo-6,9,12,15,19-pentaoxa-3-azahenicosan-21-oic acid **48** (10 mg, 0.0078 mmol) in DMF (0.12 mL), were added COMU (3.7 mg, 0.0086 mmol), *N*,*N*-diisopropylethylamine (4.1 μL, 0.023 mmol). The resulting reaction mixture was stirred at r.t. for 5 min. The mixture was added to 4-[(2-aminoethyl)amino]-2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2*H*)-dione **40** [2] (3.7 mg, 0.012 mmol). Then, the mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 5.0 mg (41 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 7.51 (1H, dd, *J* = 7.3, 8.5 Hz), 7.44 (4H, d, *J* = 8.6 Hz), 7.39 (4H, dd, *J* = 1.3, 8.5 Hz), 7.09 (1H, d, *J* = 8.6 Hz), 7.01 (1H, d, *J* = 6.9 Hz), 5.00 (1H, ddd, *J* = 2.3, 5.3, 12.8 Hz), 4.65 - 4.59 (2H, m), 3.91 - 3.86 (2H, m), 3.66 - 3.38 (40H, m), 3.30 - 3.23 (6H, m), 2.89 - 2.78 (1H, m), 2.76 - 2.61 (2H, m), 2.69 (6H, s), 2.43 (6H, s), 2.11 - 2.04 (1H, m), 1.69 (6H, s), 0.85 (3H, s).

^{13}C NMR (126 MHz, CD_3OD) δ (ppm) = 174.6, 173.5, 172.9, 171.3, 170.6, 169.2, 166.1, 157.1, 152.1, 148.2, 138.2, 137.9, 137.3, 133.9, 133.5, 133.2, 132.0, 131.4, 129.8, 118.1, 112.2, 111.4, 75.6, 74.8, 72.1, 71.7, 71.6, 71.4, 70.7, 55.2, 50.2, 42.6, 41.9, 40.6, 39.6, 38.8, 32.2, 23.8, 18.0, 14.4, 12.9, 11.6.

HRMS (ESI) for $C_{76}H_{93}Cl_2N_{14}O_{16}S_2$ [M + H^+] calculated 1591.5707, obtained 1591.5343

***N*,*N*'-(11-((2-(((*S*)-1-((2*S*,4S)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)methyl)-11-methyl-3,6,9,13,16,19-hexaoxahenicosane-1,21-diyl)bis(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide) *cis*-SIM1(3b)**



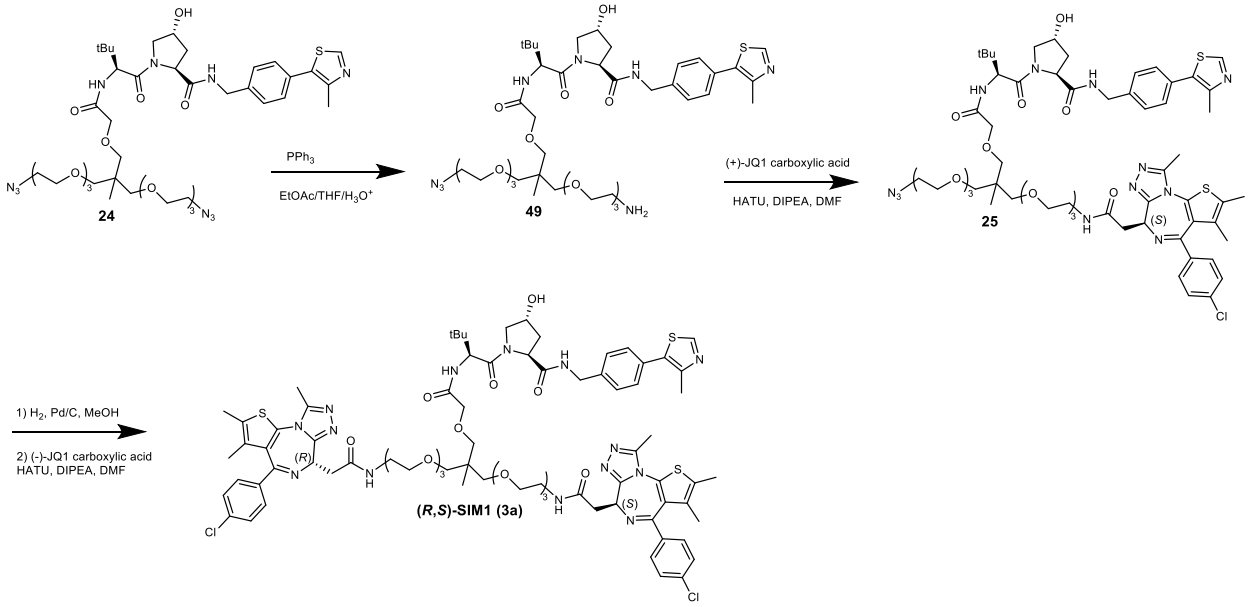
To a mixture of 1-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-14-(13-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-12-oxo-2,5,8-trioxa-11-azatridecyl)-14-methyl-2-oxo-6,9,12,16-tetraoxa-3-azaoctadecan-18-oic acid **47** (5.2 mg, 0.0043 mmol) in DMF (0.07 mL), were added COMU (2.0 mg, 0.0047 mmol), *N*,*N*-diisopropylethylamine (2.3 μL, 0.013 mmol). The resulting reaction mixture was stirred at r.t. for 5 min. The mixture was added to *cis*-VH032 amine hydrochloride [3] (3.0 mg, 0.0065 mmol). Then, the mixture was stirred at r.t. for 1 h and purified by HPLC under acidic condition (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford title compound. Yield: 4.4 mg (63 %).

^{1}H NMR (500 MHz, CD_3OD) δ (ppm) = 8.85 (1H, s), 7.48 - 7.36 (12H, m), 4.65 - 4.59 (3H, m), 4.58 - 4.50 (2H, m), 4.40 - 4.32 (2H, m), 4.01 - 3.89 (3H, m), 3.73 - 3.34 (35H, m), 3.27 (1H, d, *J* = 5.1 Hz), 2.68 (6H, s), 2.46 (3H, s), 2.44 - 2.36 (1H, m), 2.43 (6H, s), 1.96 (1H, dt, *J* = 4.4, 13.3 Hz), 1.69 (6H, s), 1.02 (9H, s), 0.97 (3H, s).

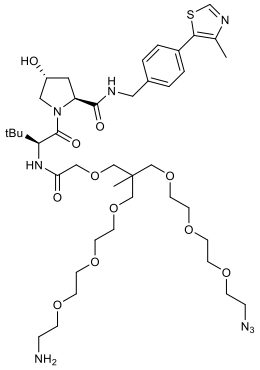
^{13}C NMR (126 MHz, CD_3OD) δ (ppm) = 174.8, 172.9, 172.0, 171.8, 166.1, 157.1, 152.8, 152.1, 149.1, 140.0, 138.2, 137.9, 133.5, 133.2, 132.0, 131.4, 130.4, 129.8, 129.1, 75.4, 74.8, 74.7, 72.2, 71.7, 71.5, 71.4, 70.7, 61.0, 57.9, 57.6, 55.2, 43.9, 42.1, 40.6, 38.8, 37.8, 36.8, 27.0, 18.0, 15.9.

MS (ESI) for $C_{79}H_{99}Cl_2N_{14}O_{13}S_3$ [M + H^+] calculated 1617.6050, obtained 1617.5716

Synthesis of *(R,S)*-SIM1



(2*S*,4*R*)-1-((17*S*)-1-amino-11-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-17-(tert-butyl)-11-methyl-15-oxo-3,6,9,13-tetraoxa-16-azaoctadecan-18-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (49)



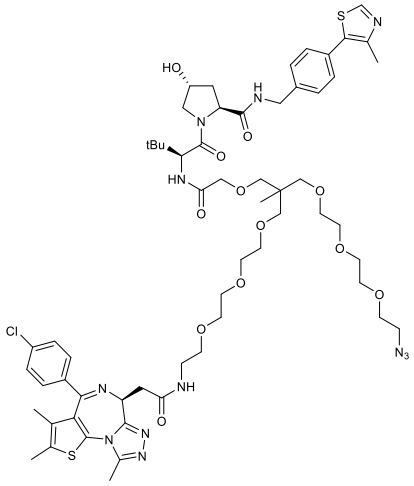
Triphenyl phosphine (15 mg, 0.057 mmol) in ethyl acetate (1.5 mL) was added dropwise over a 3 h period to compound **24** (53 mg, 0.058 mmol) in EtOAc/THF/HCl 1M (4 mL, 4:1:5) at r.t. The reaction mixture was vigorously stirred overnight before 4M HCl (2mL) was added and the ethyl acetate layer was removed. The aqueous layer was washed with EtOAc and concentrated. The crude was purified by HPLC (5-95 % CH_3CN in water with 0.1% ammonia) to give 11 mg of the starting material **24** and 10 mg (24%, based on the recovered starting material) of a desired monoamine **52**.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.67 (1H, s), 8.52 (1H, br), 7.38-7.33 (4H, m), 7.17 (1H, m), 4.67 (1H, m), 4.55-4.47 (3H, m), 4.38 (1H, m), 4.07-3.94 (4H, m), 3.70-3.21 (31H, m), 2.98 (2H, m), 2.51 (3H, s), 2.31 (1H, s), 2.23 (1H, s), 1.02-0.93 (12H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.4, 171.03, 170.98, 170.72, 170.65, 169.4, 150.2, 148.4, 138.51, 138.47, 131.6, 130.67, 130.66, 129.36, 129.35, 127.97, 74.2, 74.1, 74.0, 73.9, 73.1, 71.1, 70.87, 70.84, 70.80, 71.72, 70.70, 70.62, 70.45, 70.42, 70.38, 70.34, 70.3, 70.2, 70.2, 70.0, 69.9, 68.6, 68.5, 59.0, 57.3, 57.0, 50.6, 43.0, 42.99, 41.03, 41.01, 39.8, 37.07, 36.98, 35.17, 35.10, 26.4, 17.5, 16.0

MS (ESI) for $C_{41}H_{67}N_8O_{11}S_1$ $[M + H^+]^+$ calculated 879.5, obtained 879.5.

(2*S*,4*R*)-1-((20*S*)-14-((2-(2-(2-azidoethoxy)ethoxy)ethoxy)methyl)-20-(tert-butyl)-1-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-14-methyl-2,18-dioxo-6,9,12,16-tetraoxa-3,19-diazahenicosan-21-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (25)



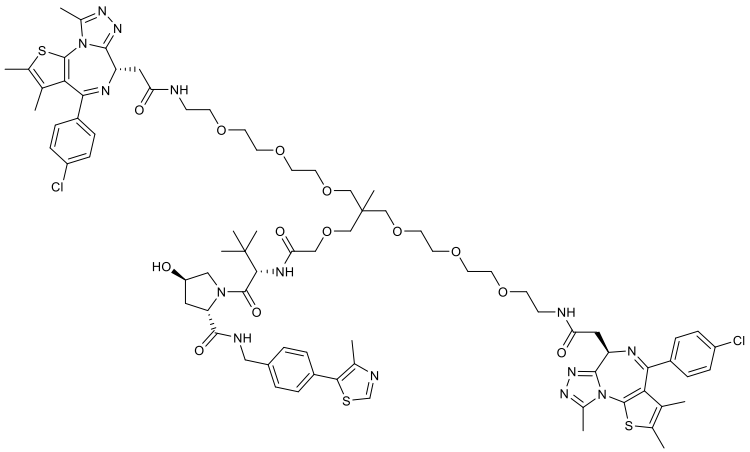
A pre stirred mixture of (+)-JQ1 carboxylic acid (4.5 mg, 0.011 mmol), HATU (4.2 mg, 0.011 mmol), *N*,*N*-diisopropylethylamine (5 µL, 0.03 mmol) in DMF (0.2 mL) was added to compound **49** (10 mg, 0.011 mmol). The resulting mixture was stirred at r.t. for 1 h and purified by HPLC (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford the title compound **25**. Yield: 12 mg (86 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) = 8.67 (1H, s), 7.69 (1H, m), 7.43 - 7.28 (10H, m), 7.15 (1H, d, *J* = 9.0 Hz), 4.82 (1H, m), 4.64 (2H, m), 4.54 (1H, m), 4.47 (1H, m), 4.35 (1H, dd, *J* = 5.4, 16.0 Hz), 4.10 (1H, m), 4.04 (1H, m), 3.95 (1H, m), 3.70 - 3.18 (38H, m), 2.62 (3H, s), 2.51 (3H, s), 2.48 (1H, m), 2.39 (3H, s), 2.14 (1H, m), 1.65 (3H, s), 0.97 (9H, s), 0.95 (1.5H, s), 0.93 (1.5H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm) = 171.2, 171.1, 170.8, 170.55, 170.52, 163.9, 162.3, 155.8, 150.2, 149.8, 148.4, 138.3, 136.7, 132.0, 131.7, 131.0, 130.8, 130.7, 129.9, 129.5, 128.7, 128.1, 74.5, 73.9, 73.8, 73.5, 73.0, 72.7, 71.1, 70.95, 70.92, 70.8, 70.7, 70.51, 70.47, 70.3, 70.24, 70.21, 70.0, 58.7, 57.0, 56.6, 54.3, 50.7, 43.2, 40.9, 39.5, 38.4, 38.3, 36.2, 35.3, 35.2, 26.4, 17.54, 17.48, 16.0, 14.4, 13.1, 11.8.

MS (ESI) for $C_{60}H_{83}ClN_{12}O_{12}S_2$ $[M + 2H^+]^{2+}$ calculated 631.3, obtained 631.8.

(2*S*,4*R*)-1-((20*S*)-20-(tert-butyl)-1-((*R*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-14-(13-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-12-oxo-2,5,8-trioxa-11-azatridecyl)-14-methyl-2,18-dioxo-6,9,12,16-tetraoxa-3,19-diazahenicosan-21-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (*R,S*)-SIM1(3a)



To a mixture of compound **25** (12 mg, 0.01 mmol) in MeOH (1 mL), were added 10%wt palladium on carbon (0.5 mg). The resulting reaction mixture was stirred under hydrogen atmosphere at r.t. overnight. The mixture was then filtered on a celite pad and evaporated. A pre stirred mixture of (-)-JQ1 carboxylic acid (4 mg, 0.01 mmol), HATU (4 mg, 0.01 mmol), *N*,*N*-diisopropylethylamine (5 µL, 0.03 mmol) in DMF (0.20 mL) was added to the concentrated crude. The mixture was stirred at r.t. for 1 h and purified by HPLC (5-95 % CH_3CN in 0.1 % aq. HCO_2H) to afford the title compound. Yield: 4.7 mg (31 %).

^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ (ppm) = 8.70 (1H, s), 7.57 - 7.28 (14H, m), 7.20 (1H, m), 4.76 (1H, m), 4.72-4.60 (3H, m), 4.58-4.44 (2H, m), 4.43-4.33 (1H, m), 4.14-3.95 (3H, 3H), 3.69-3.25 (38H, m), 2.68-2.60 (6H, m), 2.50 (3H, s), 2.39 (6H, s), 2.36-2.29 (1H, m), 2.22-2.12 (1H, m), 1.68-1.61 (6H, m), 1.00-0.95 (9H, m), 0.92 (3H, s).

^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereomers) δ (ppm) = 171.46, 171.41, 170.89, 170.86, 170.7 (br), 170.6, 164.4 (br), 155.5, 150.4, 150.0, 148.1, 138.59, 138.55, 137.0 (br), 136.2 (br), 132.1 (br), 131.9, 131.2 (br), 131.11, 131.09, 130.47, 130.42, 130.1 (br), 129.33, 129.30, 128.7, 128.0, 73.8 (br), 70.92, 70.86, 70.61, 70.58, 70.4, 70.2 (br), 70.1, 69.9, 59.2, 59.1, 57.3, 56.8 (br), 53.9, 43.0, 41.0, 40.8, 39.3 (br), 38.0 (br), 36.7 (br), 35.59, 35.55, 29.7, 26.4, 17.75, 17.71, 15.95, 14.42, 14.39, 14.37, 13.1, 11.7

HRMS (ESI) for $C_{79}H_{99}Cl_2N_{14}O_{13}S_3$ [M + H+] calculated 1617.6050, obtained 1617.6025.

References

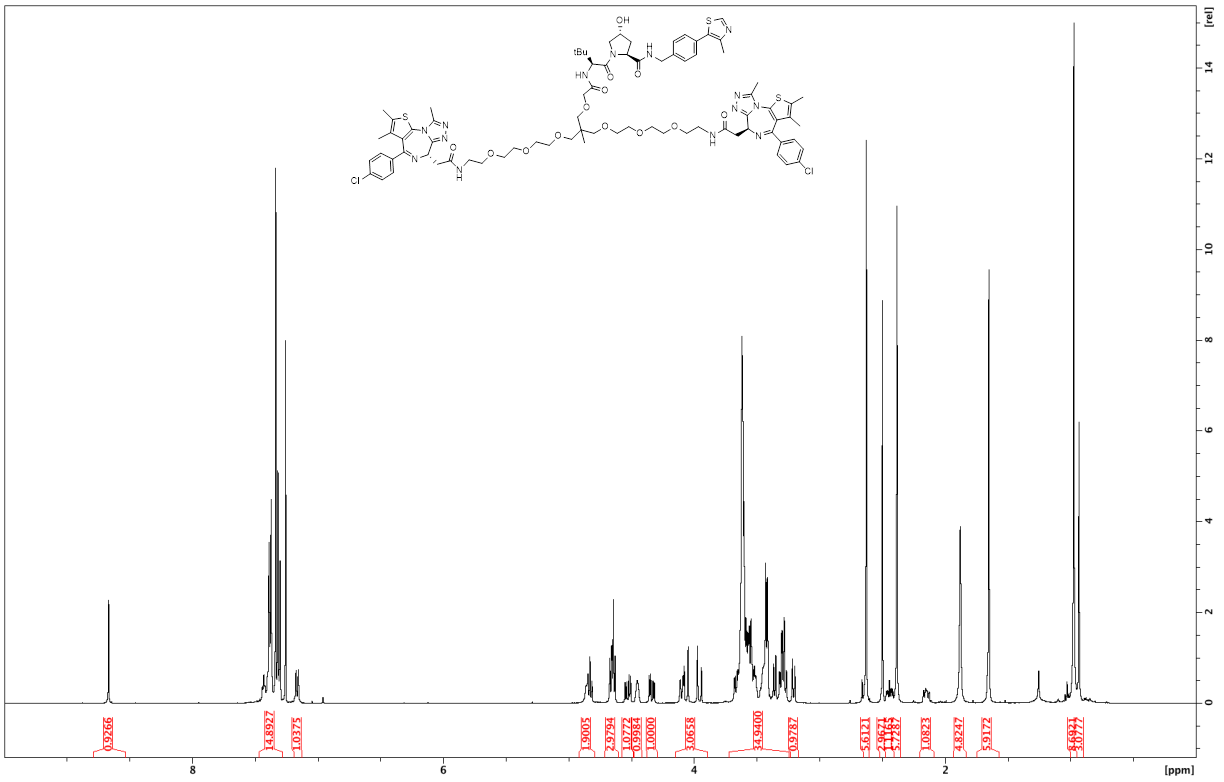
1. Galdeano, C. *et al. J. Med. Chem.* **2014**, 57, 20, 8657. VH032 amine was synthesized according to the procedure reported in this publication.

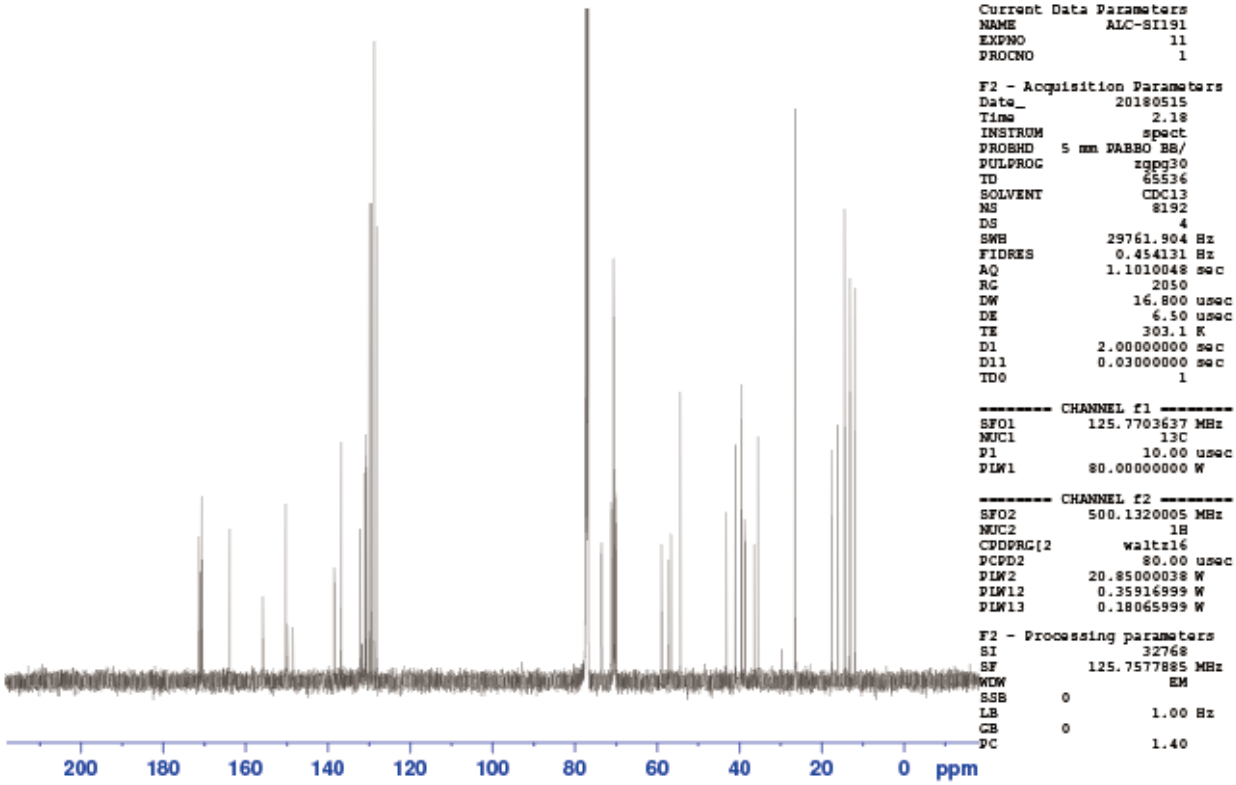
2. Girardini, M. *et al*. *Bioorg. Med. Chem*. **2019**, 27, 2466. Pomalidomide analogue was synthesized according to the procedure reported in this publication.

3. Zengerle, M. *et al*. *ACS Chem. Biol*. **2015**, 10, 1770. *cis*-VH032 was synthesized according to the procedure reported in this publication.

NMR SPECTRA OF SIM1 – SIM6, *cis*-SIM1, (*R,S*)-SIM1

SIM1



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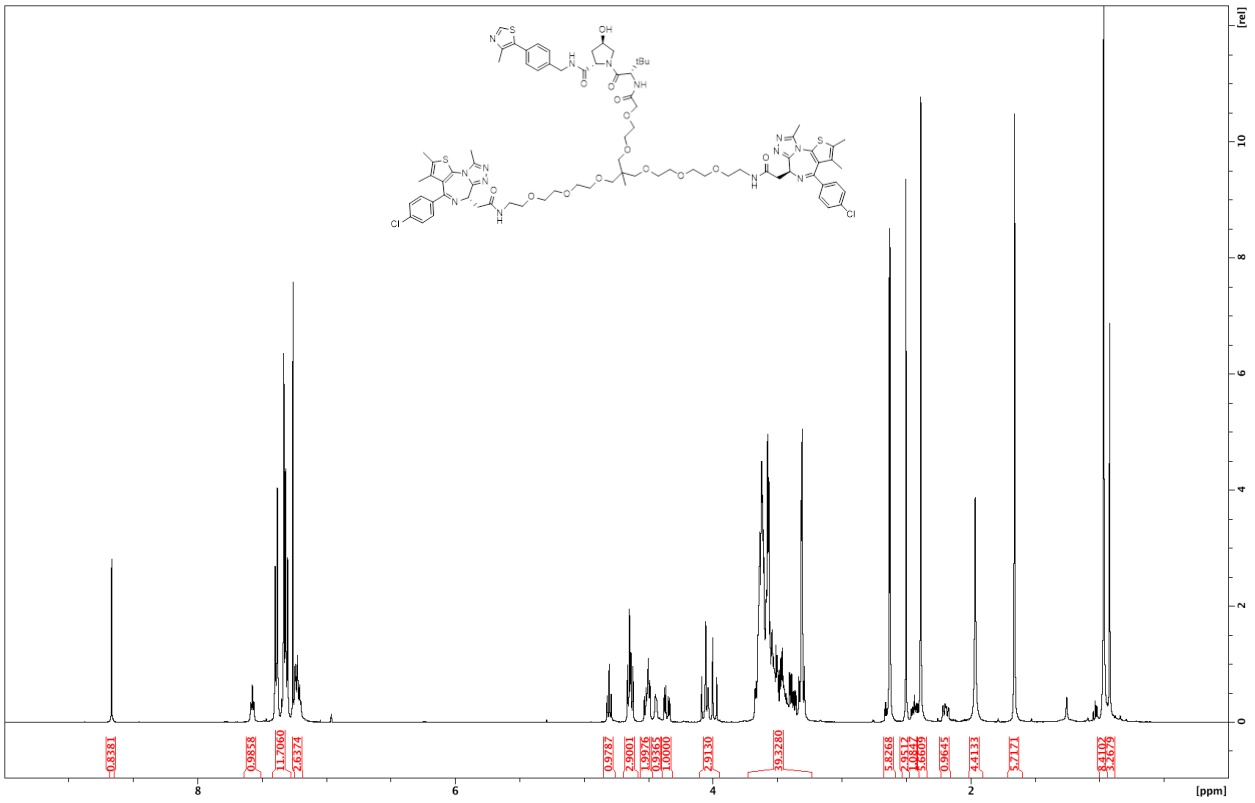
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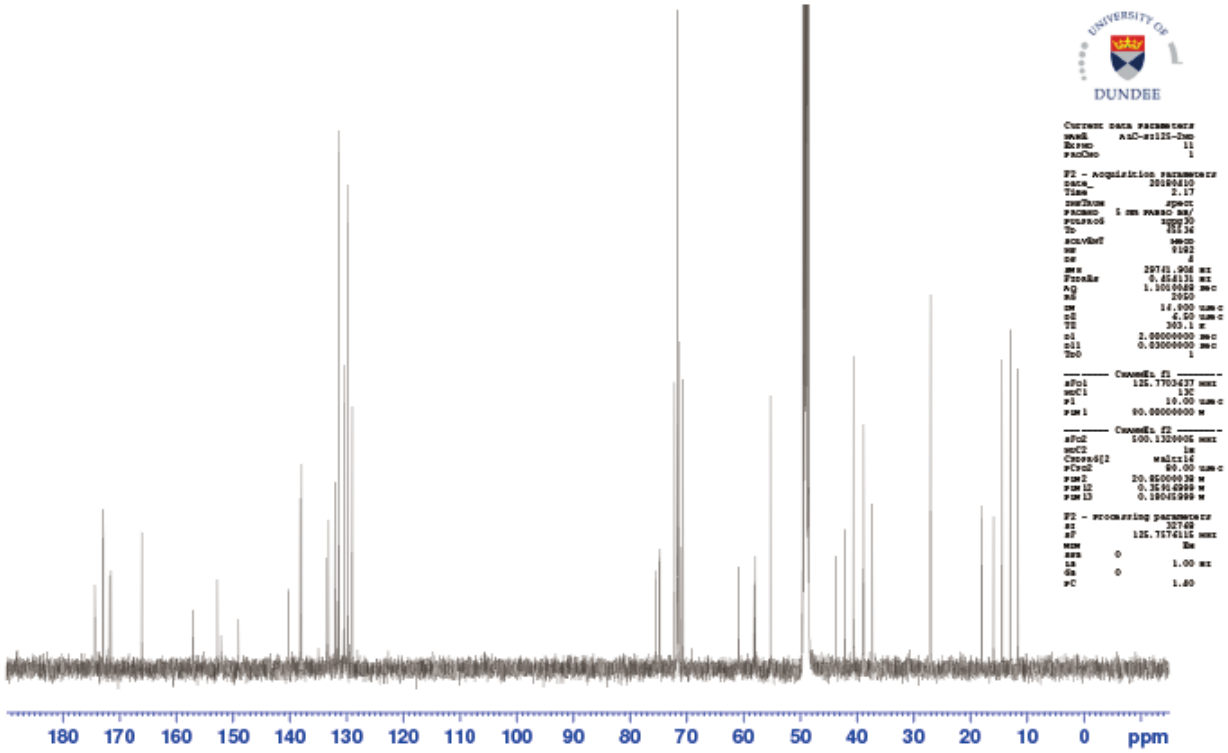
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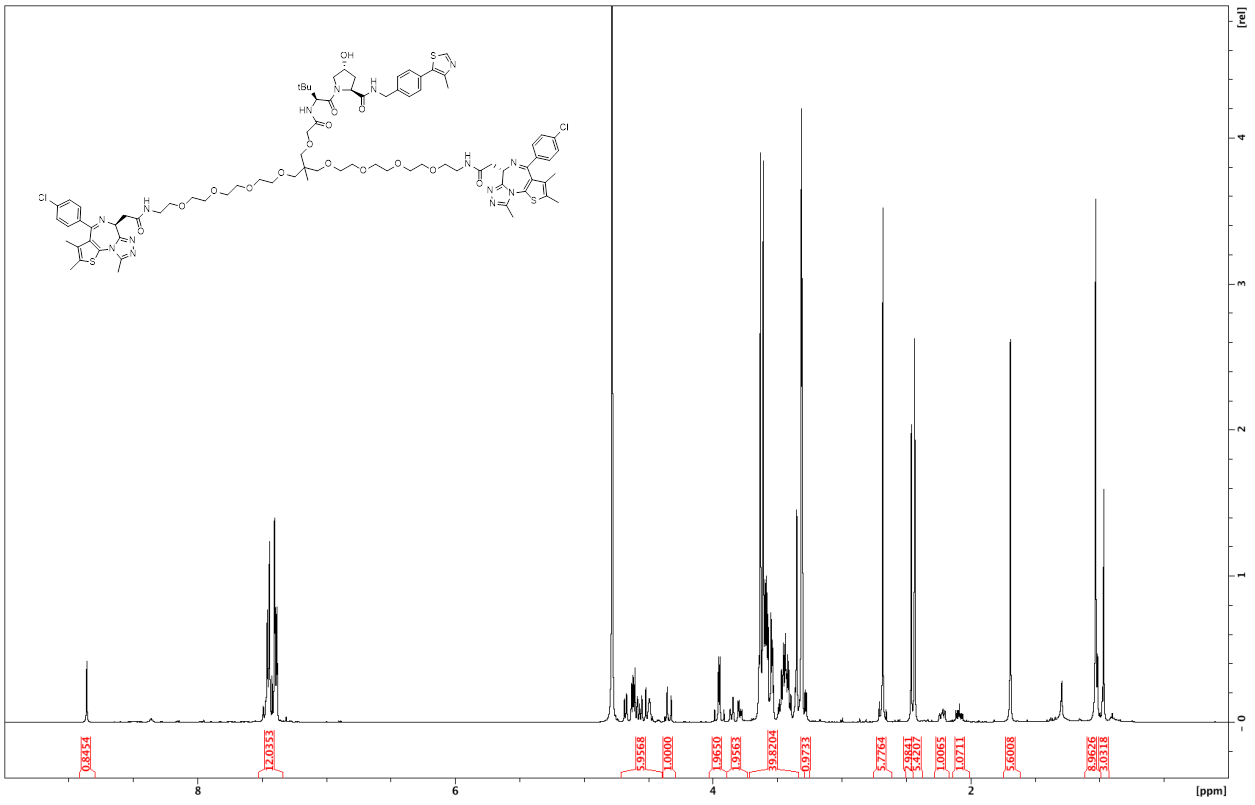
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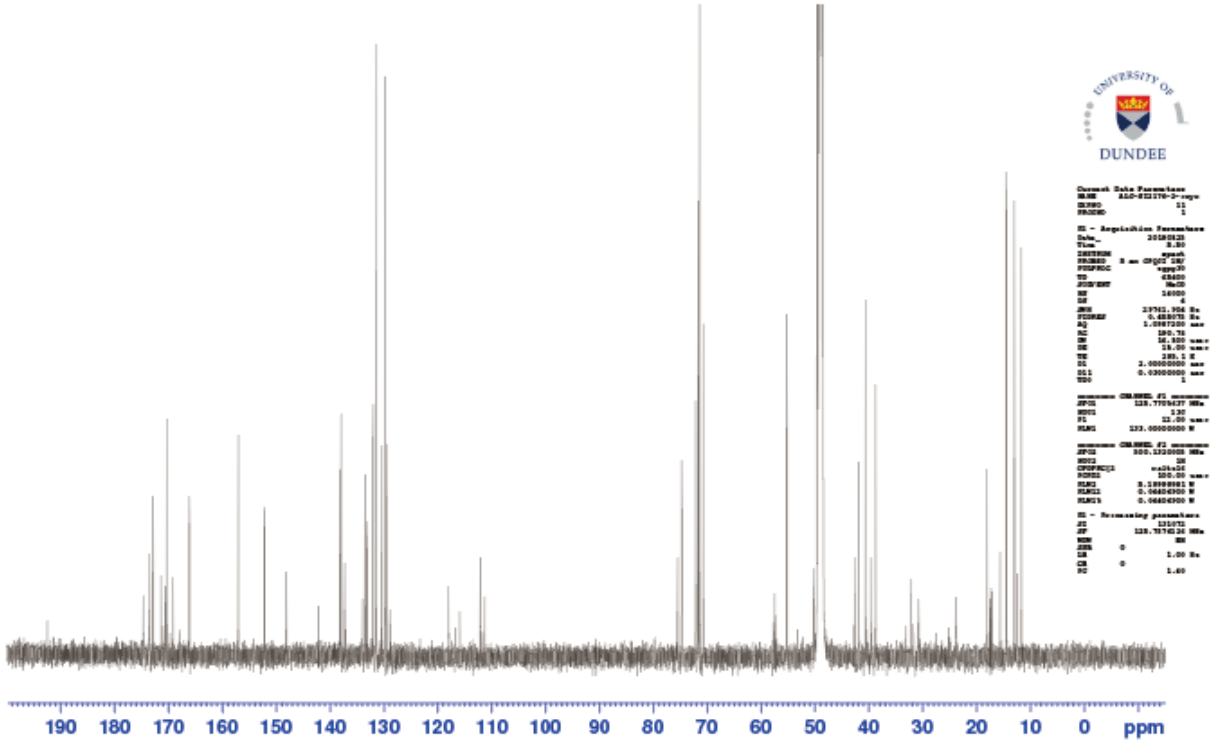
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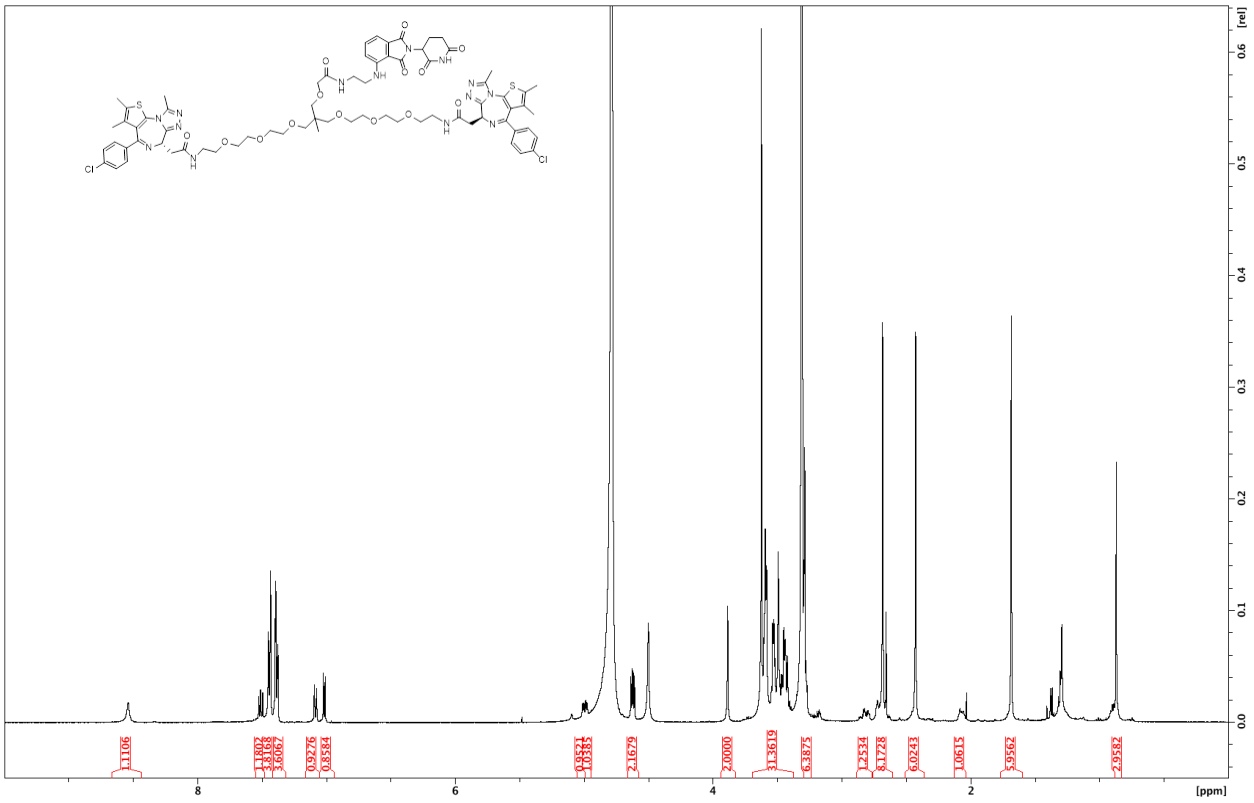
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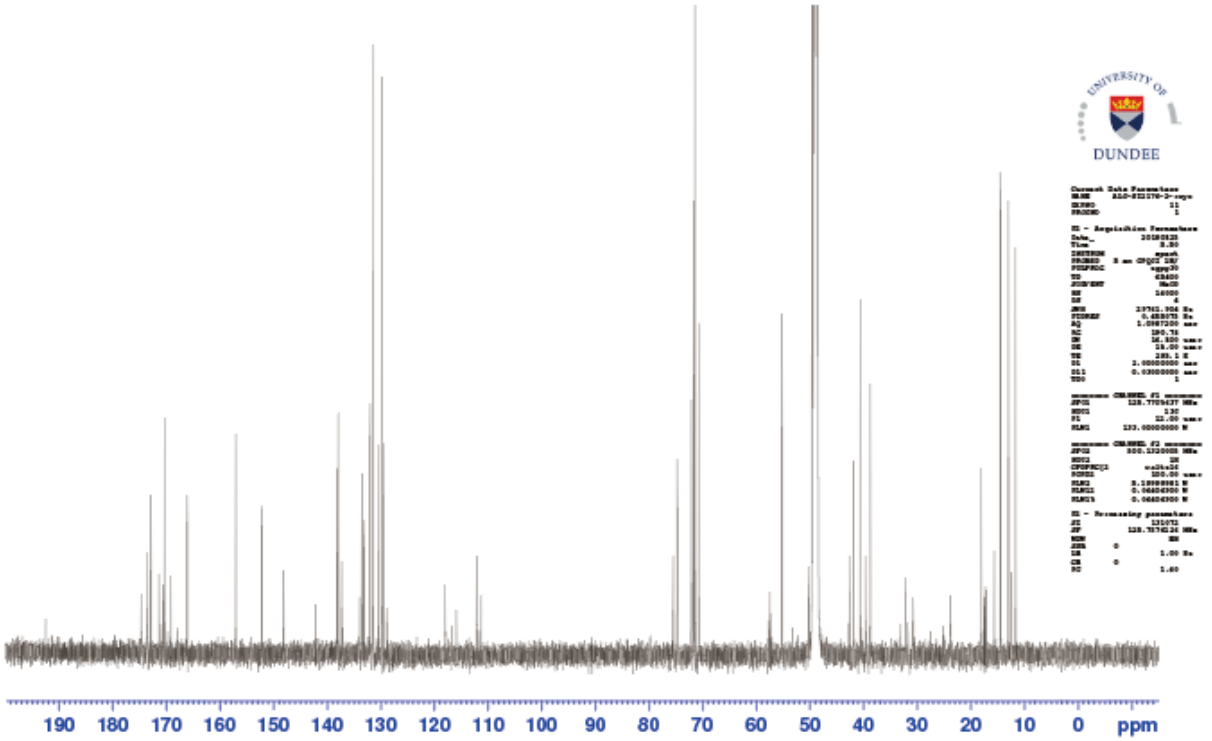
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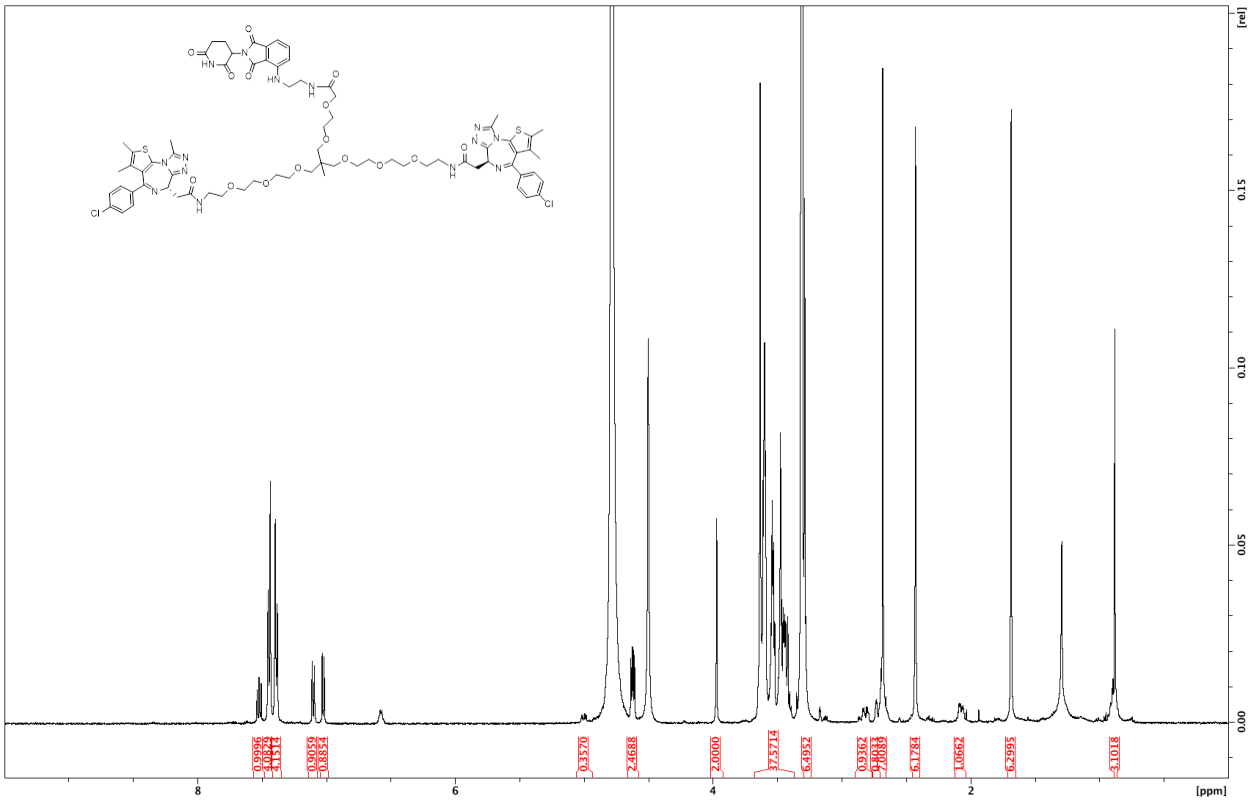
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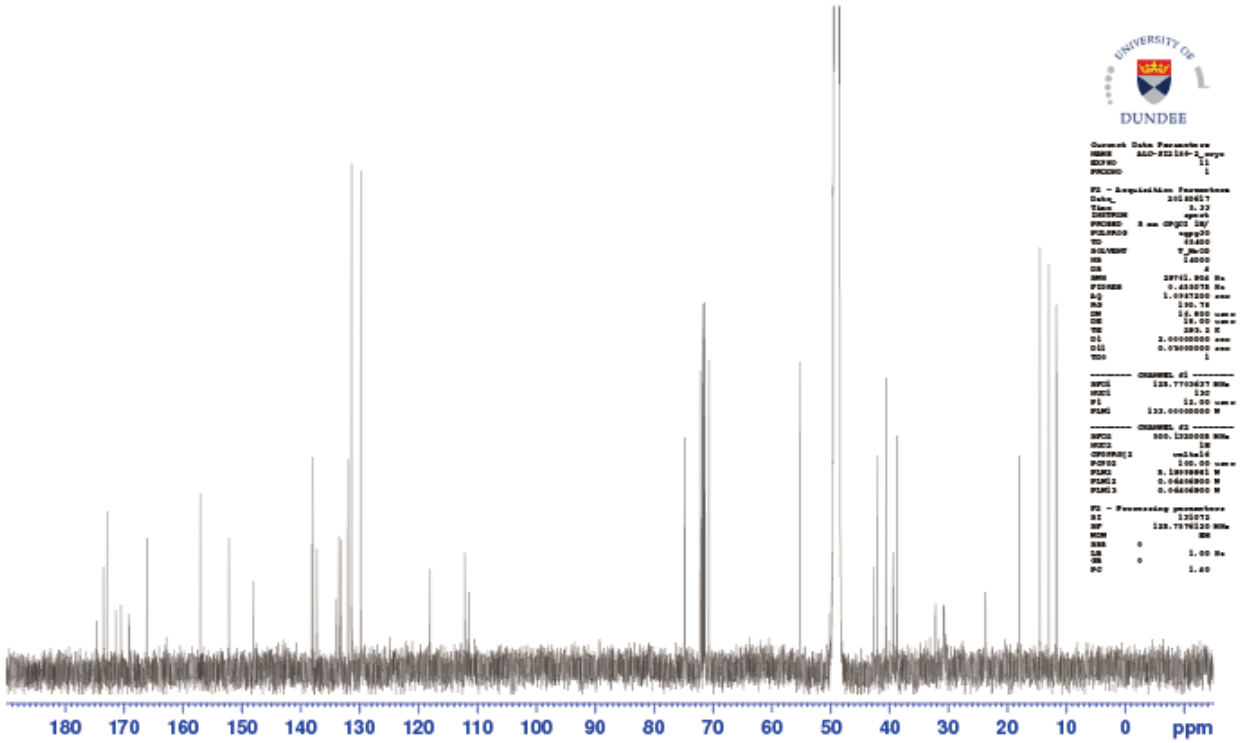
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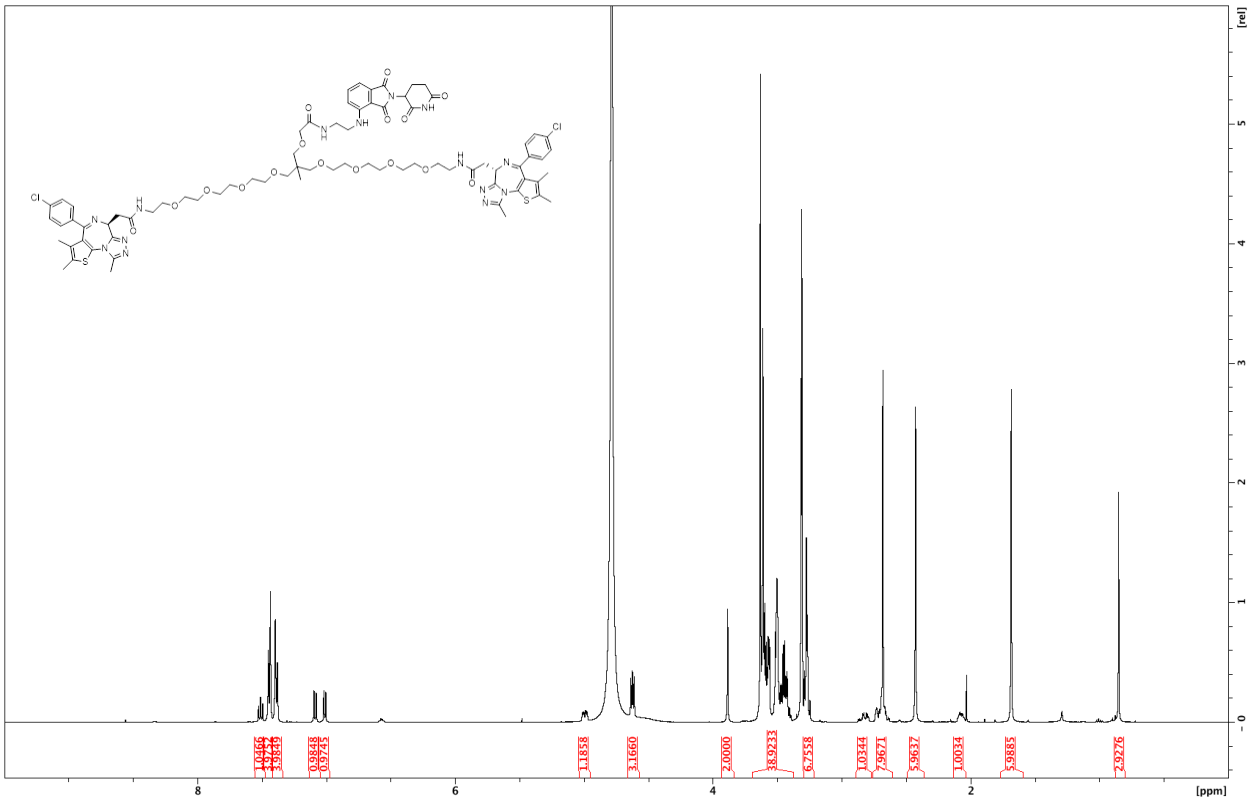
SIM6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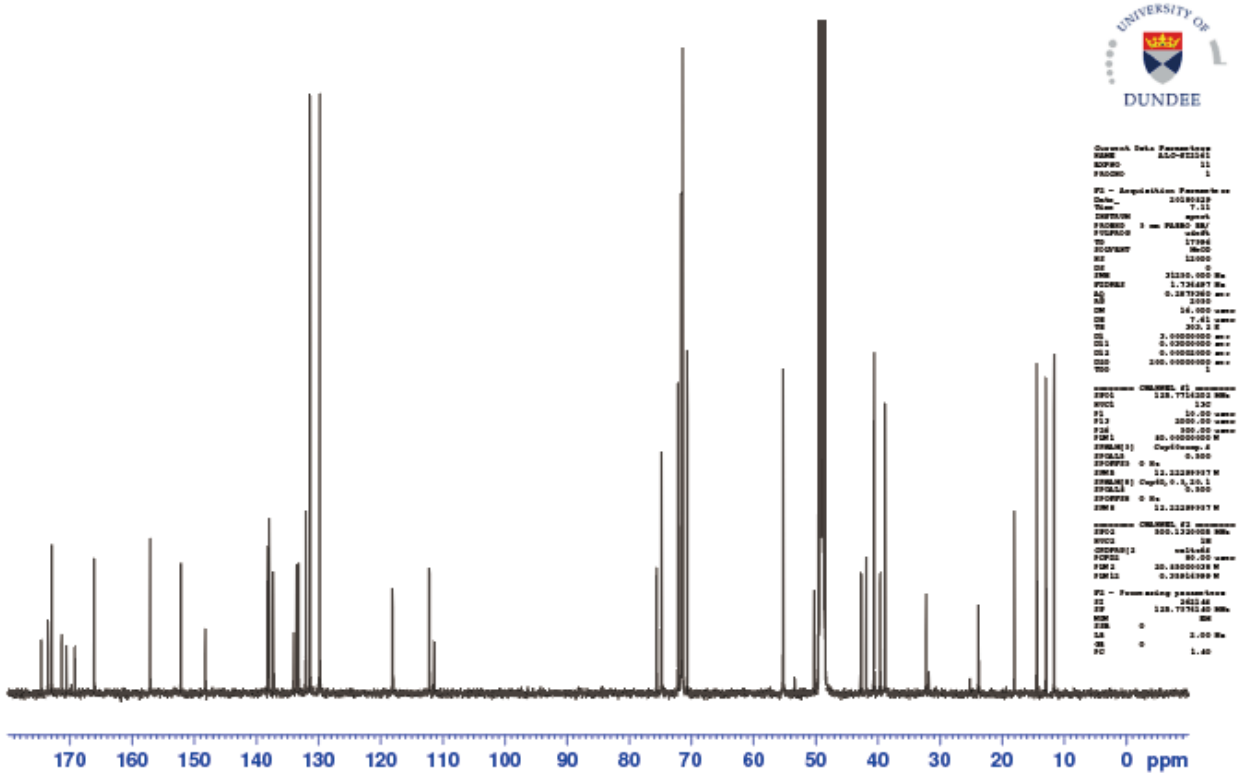
UNIVERSITY OF
DUNDEE
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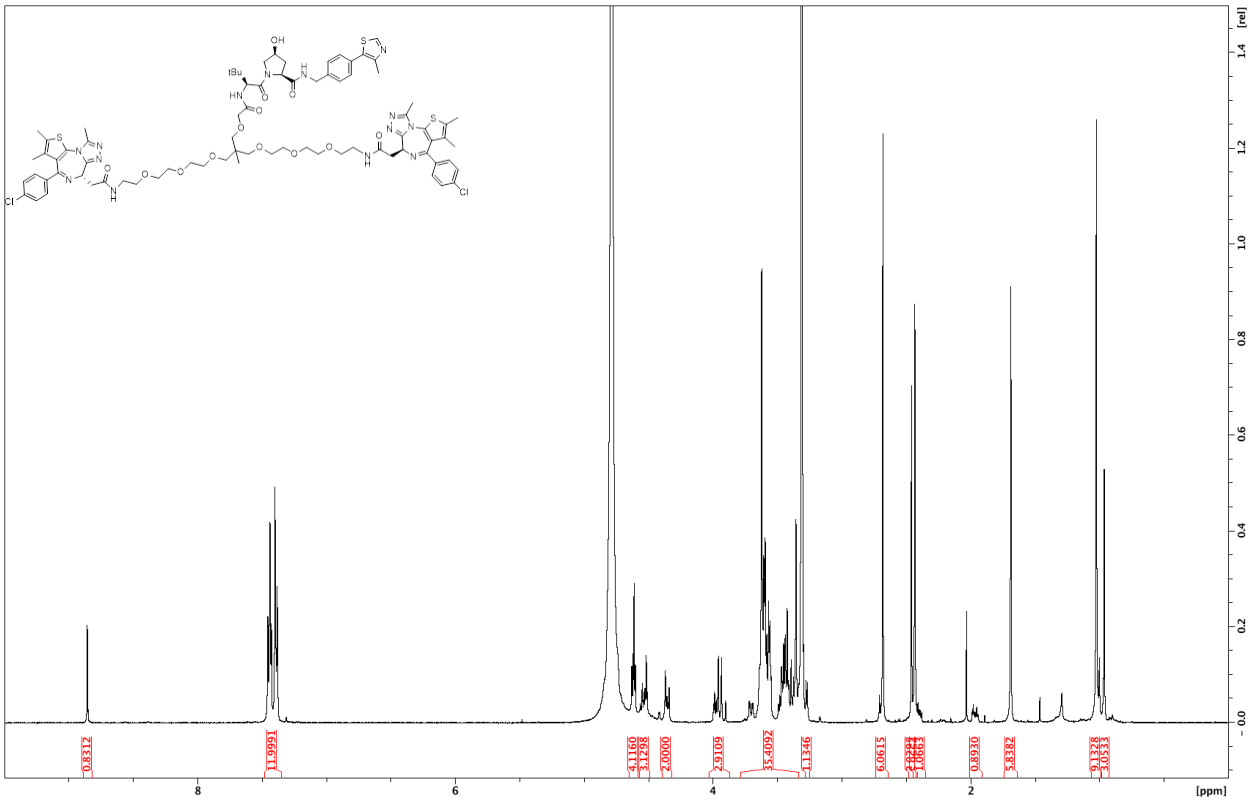
***cis*-SIM1**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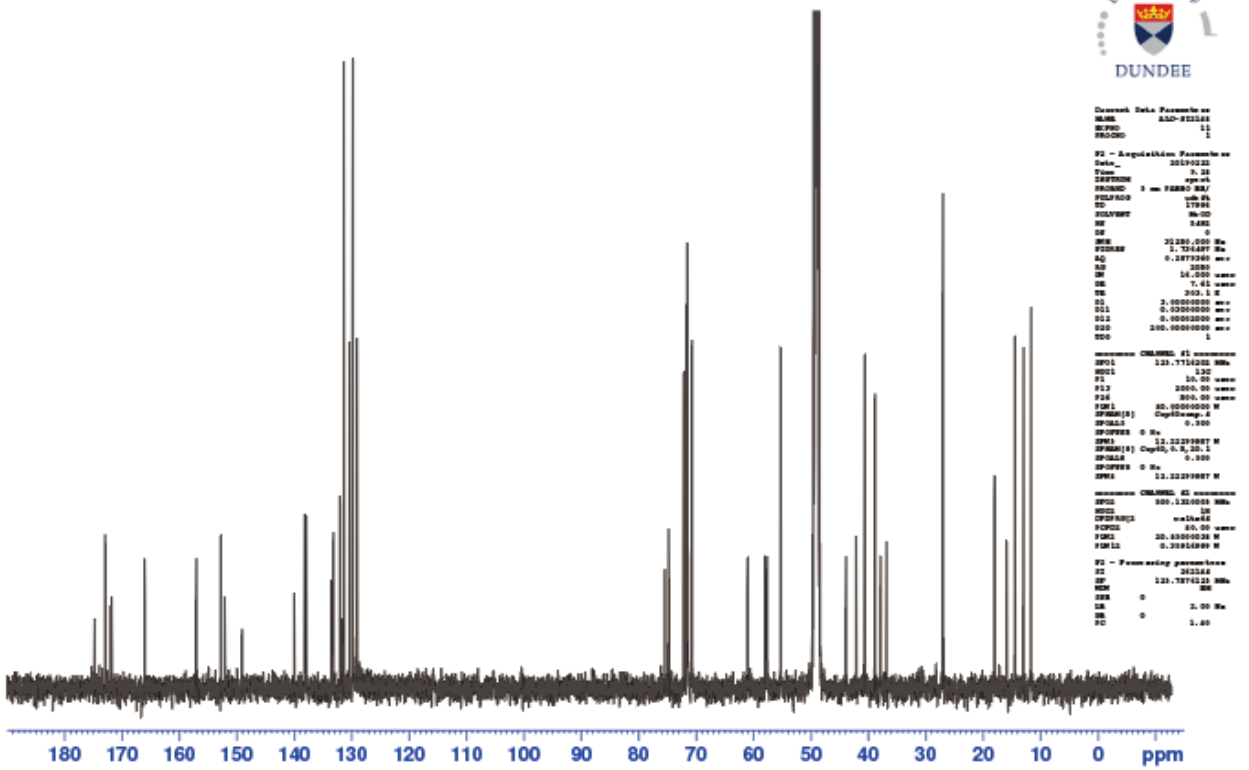
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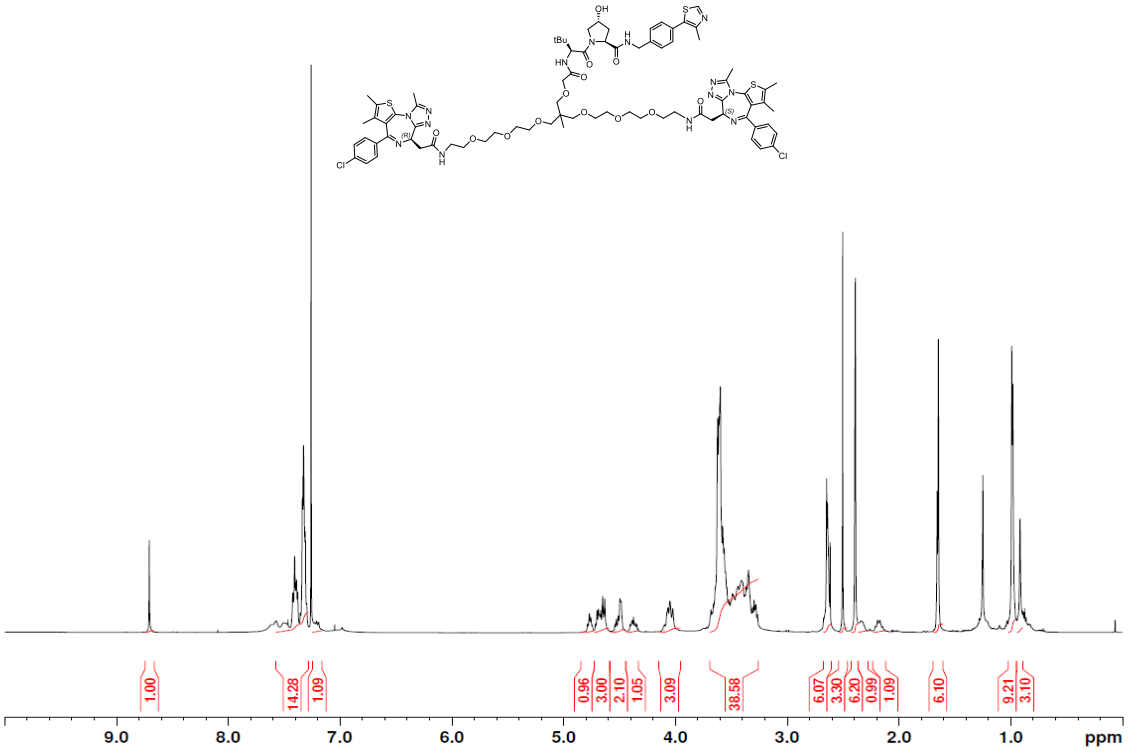
(*R,S*)-SIM1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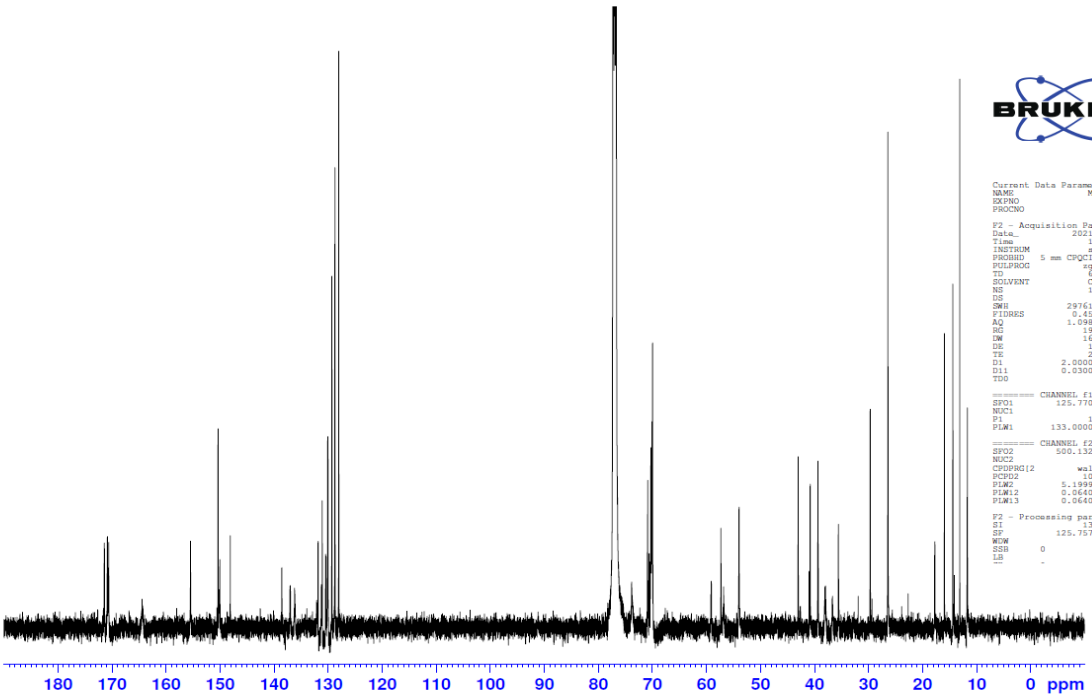
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