Supporting information

Macrocyclic peptides that selectively inhibit the *Mycobacterium tuberculosis* proteasome

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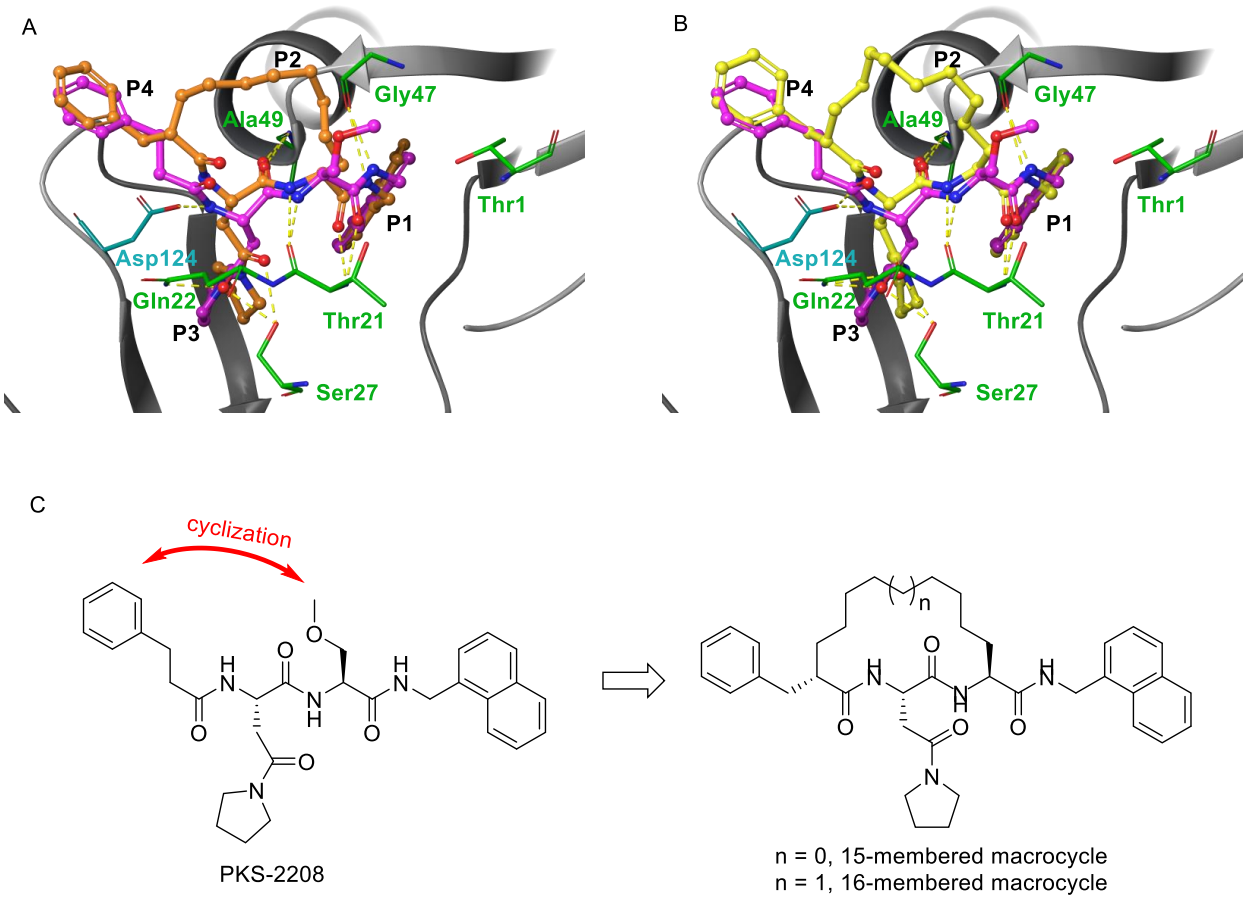

Figure S1. Molecular docking of 15- and 16-membered macrocycles to the cocrystal structure of Mtb20SOG (PDB: 5TS0) executed with Schrödinger's Glide. A) Overlay of 15-membered macrocycle (orange) and parent *N,C*-capped dipeptide PKS-2208 (magenta). Hydrogen bonds are indicated by dashed yellow lines. B) Overlay of 16-membered macrocycle (yellow) and parent *N,C*-capped dipeptide PKS-2208 (magenta). (C) The structure of parent *N,C*-capped dipeptide PKS-2208, 15- and 16 membered macrocycles.

Table S1. IC50s of the select compounds against β1c, β2c of the constitutive proteasome and β1i, β2i of the immunoproteasome

Macrocycle	IC50 (μM)			
	β1c - LLE	β2c - VLR	β1i -LLE	β2i - VLR
1	>100	>100	>100	>100
2	>100	>100	>100	>100
3	>100	>100	>100	>100
4	>100	>100	>100	>100
5	>100	>100	>100	>100
6	>100	>100	>100	>100
7	>100	>100	>100	>100
8	>100	>100	>100	>100
9	>100	>100	>100	>100
10	>100	>100	>100	>100
11	>100	>100	>100	44.5 ±1.2
12	>100	>100	>100	>100

LLE: Z-LLE-AMC; VLR: Z-VLR-AMC

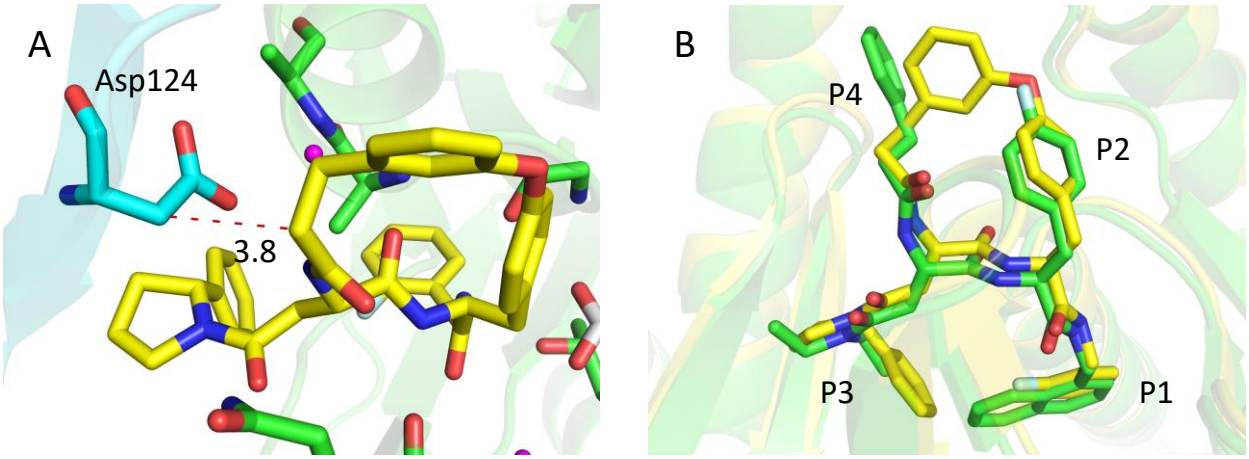

Figure S2. (**A**) The distance between macrocycle **6** and Asp-124 is 3.8 Å. This distance may be too short to accommodate an additional group (the proposed P5 groups). (**B**) Alignment of the β-subunits of the macrocycle **6**-bound Mtb20SOG and the DPLG2-bound Mtb20SOG core particles. Macrocycle **6** is in yellow and DPLG-2 in green.

Table S2 Data collection and refinement statistics

	Mtb20S- macrocycle **6**
Data collection	
Wavelength	1.07812
Space group	P 1 21 1
Cell dimensions	
a, *b*, *c* (Å)	155.63, 115.95, 208.11
α, β, γ (°)	90.00, 91.58, 90.00
Resolution (Å)	92.97 - 2.28 (2.40 - 2.28)*
Total reflections	2324702
Unique reflections	332027
Redundancy	7.0 (7.2)
Completeness (%)	98.2 (99.2)
Wilson B-factor	42.06
R_{merge}	0.11 (0.85)
Mean I / σI	10.7 (2.3)
CC1/2	0.997 (0.724)
Refinement	
Resolution (Å)	87.59 - 2.28
No. reflections	331867
R_{work} / R_{free}	0.1996/0.2381
No. of non-hydrogen atoms	48400
Macromolecule	46316
Ligand	908
Water	1176
B-factors	53.04
Macromolecule	53.51
Ligand	41.15
Water	43.71
R.m.s. deviations	
Bond lengths (Å)	0.003
Bond angles (°)	0.592
Ramachandran statistics (%)	
Favored	97.72
Allowed	2.21
Outliers	0.07

*Values in parentheses are for highest-resolution shell.
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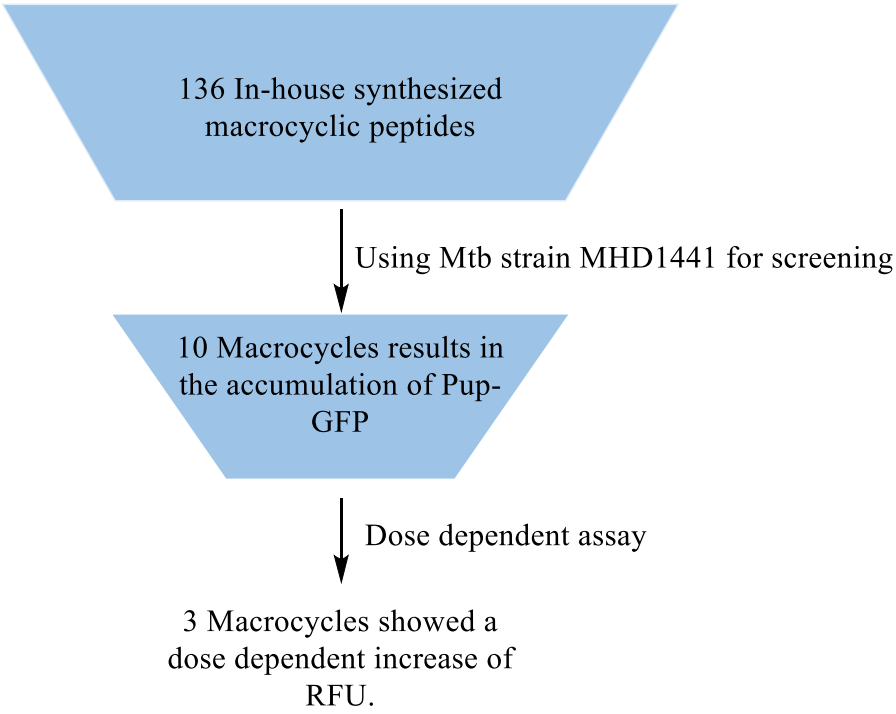


Figure S3. Funnel diagram depicting the workflow of screening Mtb proteasome inhibitors using Mtb strain MHD1441.

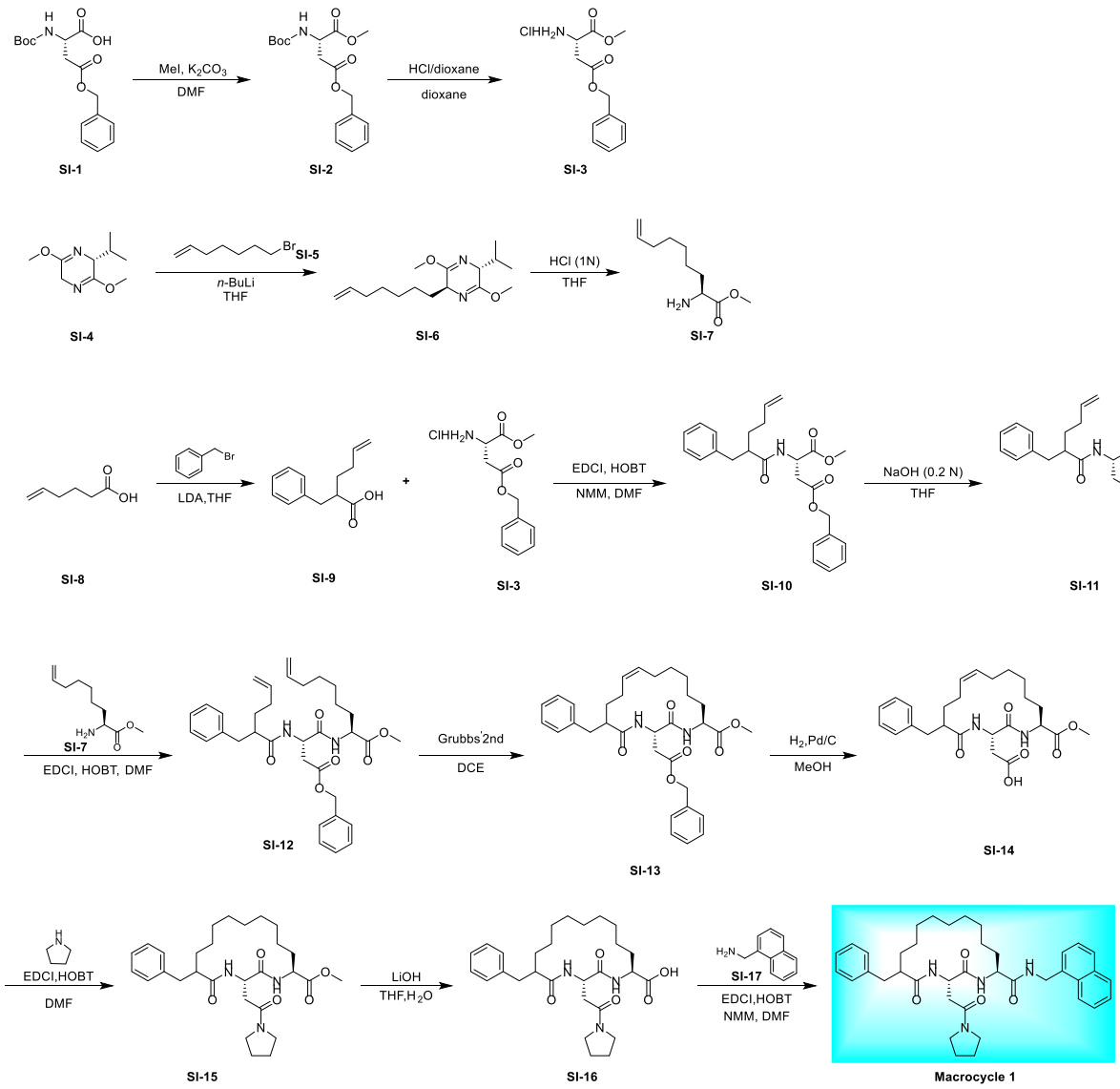
General synthetic methods

All commercially available reagents were used without further purification unless otherwise noted. All non-aqueous reactions were performed under argon in oven-dried glasswares. Routine monitoring of reactions were performed using Waters Acquity Ultra Performance Liquid Chromatography (UPLC/MS). Column chromatography was generally performed on silica gel (200-300 mesh). All HPLC purifications were done by Waters prep-HPLC (mass directed purification system) using Prep C18 column. The detailed information about C18 column, mobile phase, and methods are provided for individual compounds.

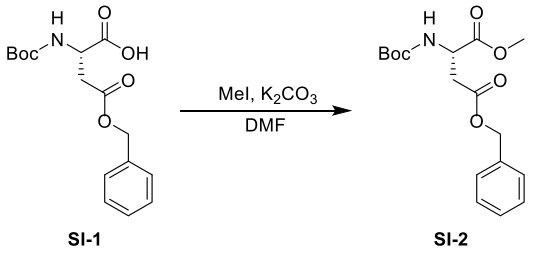
Analytical HPLC-MS was carried out using an Acquity™ Ultra Performance LC sysem, comprising a PDA detector, Binary Solvent Manager and SQ detector, tandem linked to a mass spectrometry system employing vendor software.Parallel evaporative light-scattering detection was incorporated into the system via a flow splitter. Column (C18 Column, 130Å, 1.7 µm, 2.1 mm X 100 mm) chromatography was carried out using a linear increasing gradient from 5-95% of solvent A (0.1% formic acid in water) to solvent B (0.1% formic acid in acetonitrile) at 0.5 ml/min over 4.0 min, or the same gradient applied over 8 min.

Chiral SFC was in general performed with Chiralcel Column (OD-3 50×4.6mm I.D., 3um) using a linear increasing gradient MeOH (0.05% DEA) in CO2 from 5% to 40% at 3mL/min, detection by UV absorbance.

^{1}H- and ^{13}C- NMR spectra were acquired on Bruker 400/500 MHz system. Chemical shifts δ are expressed in parts per million, with the solvent resonance as an internal standard (chloroform-*d*, ^{1}H: 7.26 ppm; Methanol-*d4*, ^{1}H: 3.31 ppm; DMSO-*d6*, ^{1}H: 2.50 ppm). NMR data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration.

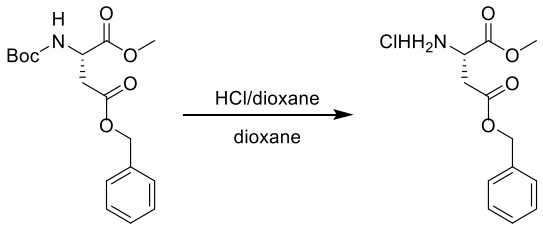


Scheme S1. Synthetic route of **Macrocycle 1**, **2**, and **3**.



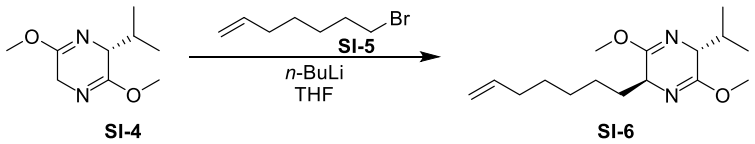
To a solution of compound **SI-1** (11.5 g, 35.6 mmol, 1.00 *eq,* 2 paralleled batches) and potassium carbonate (7.9 g, 56.9 mmol, 1.6 *eq*) in dimethyl formamide (100 mL) was added iodomethane (13.8 g, 96.9 mmol, 6.0 mL, 2.7 *eq*) drop wise. The mixture was

stirred at 20°C for 2 hours. TLC (petroleum ether: ethyl actate = 2:1) showed the starting materail was consumed. The reaction mixture was poured into water (200 mL), extracted with ethyl actate (300 mL*2). The combined organic phase was washed with brine (300mL*2), dired over anhydrous sodium sulfate and concentrated in reduced pressure to afford compound **SI-2** (23.5 g, 98% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37 - 7.32 (m, 5H), 5.49 (d, J = 4.0 Hz, 1H), 5.16 - 5.09 (m, 2H), 5.60 - 5.58 (m, 1H) , 3.70 (s, 3H) , 3.06 - 3.02 (m, 1H), 2.90 - 2.84 (m, 1H), 1.44 ppm (s, 9H).



SI-2 **SI-3**

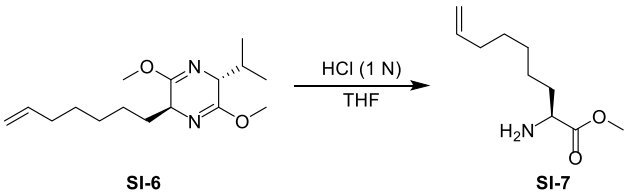
To a solution of compound **SI-2** (23.5 g, 69.7 mmol, 1.0 *eq*) in dioxane (100 mL) was added hydrochloric acid/dioxane (4 M, 100 mL). The mixture was stirred at 20°C for 1 hour. TLC (petroleum ether: ethyl actate = 1:1) showed the starting material was consumed. The reaction mixture was concentrated in reduced pressure to afford compound **SI-3** (20 g, crude, hydrochloride salt) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.88 (br. s, 3H) ,7.39 - 7.30 (m, 5H), 5.18 - 5.10 (m, 2H), 3.35 - 3.33 (m, 1H) , 3.66 (s, 3H) , 3.16 - 3.08 ppm (m, 2H).



SI-4 **SI-6**

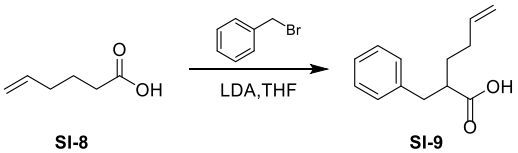
A solution of compound **SI-4** (8.9 g, 48.3 mmol, 8.64 mL, 1.07 *eq*) in tetrahydrofuran (100 mL) was cooled to -70°C and n-butyl lithium (2.5 M, 19.34 mL, 1.07 *eq*) was added under nitrogen while the temperature kept below -70°C, then a solution of compound **SI-5** (8 g, 45.18 mmol, 1.00 *eq*) in tetrahydrofuran (15 mL) was added at -70°C. The reaction mixture was stirred at -70°C for 2 hours, then slowly heated to 20°C and stirred for 1 hour. LCMS showed the starting material was consumed and desired product mass was observed. The reaction mixture was poured into saturated

ammonium chloride solution (50 mL), extracted with ethyl actate (200 mL *2). The combined organic phase was washed with brine (100 mL*2), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by column chromotography (petroleum ether to petroleum ether: ethyl actate = 50:1) to afford compound **SI-6** (7.0 g, 55% yield) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.86 - 5.76 (m, 1H), 5.03 - 4.92 (m, 2H), 4.05 - 4.01 (m, 1H), 3.94 (t, *J* = 3.2 Hz, 1H), 3.69 (d, *J* = 4.4 Hz, 6H), 2.30 - 2.26 (m, 1H), 2.06 - 2.01 (m, 2H), 1.88 - 1.71 (m, 2H), 1.44 - 1.37 (m, 3H), 1.33 - 1.24 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.69 ppm (d, *J* = 6.8 Hz, 3H).



SI-6 **SI-7**

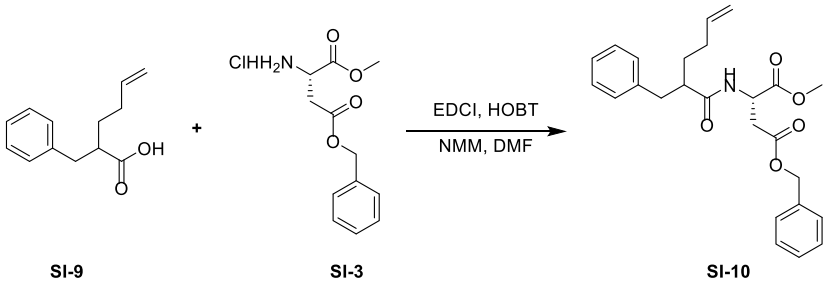
To a solution of compound **SI-6** (7 g, 24.96 mmol, 1.00 *eq*) in tetrahydrofuran (140 mL) was added hydrochloric acid (1 M, 140.28 mL, 5.62 *eq*) drop wise. The reaction mixture was stirred at 20°C for 6 hours. TLC (petroleum ether: ethyl actate = 1:1) showed the starting material was consumed. The reaction mixture was poured into saturated sodium bicarbonate (100 mL), extracted with ethyl actate (100 mL*3). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by column chromotography (petroleum ether: ethyl actate =10:1 ~ 1:2) to afford compound **SI-7** (3.6 g, 58% yield, 75% purity) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 5.82 - 5.76 (m, 1H), 5.01 - 4.92 (m, 2H), 3.61 (s, 3H), 3.28 - 3.25 (m, 1H), 2.03 - 1.98 (m, 2H), 1.58 - 1.49 (m, 1H), 1.42 - 1.35 (m, 1H), 1.35 - 1.18 ppm (m, 6H).



SI-8 **SI-9**

To a solution of diisopropylamine (15.5 g, 152.66 mmol, 21.46 mL, 2.05 *eq*) in tetrahydrofuran (100 mL) was added n-butyllithium (2.5 M, 63 mL, 2.10 *eq*) drop wise at

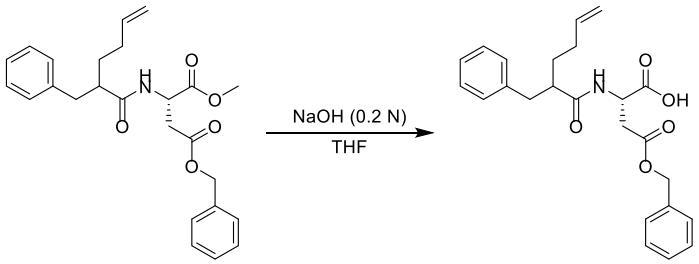
0°C and the mixture was stirred at 0°C for 15 min. Compound **SI-8** (8.5 g, 74.47 mmol, 8.85 mL, 1.00 *eq*) was added and the mixture was stirred for 15 min, then bromomethylbenzene (15.3 g, 89.36 mmol, 10.61 mL, 1.20 *eq*) was added. The mixture was stirred at 25°C for 10 hours. TLC (petroleum ether: ethyl actate = 5:1) showed all starting material was consumed and one new spot was detected. The reaction mixture was quenched with 5% hydrochloric acid (50 mL) and extracted with ethyl actate (25 mL*3). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by reversed flash column (trifluoroacetic acid/acetonitrile/water) to afford compound **SI-9** (11.8 g, 76% yield, 98% purity) as light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36 - 7.23 (m, 5H), 5.87 - 5.78 (m, 1H), 5.12 - 5.07 (m, 2H), 3.08 - 3.02 (m, 1H), 2.86 - 2.78 (m, 2H), 2.18 - 2.11 (m, 2H), 1.85 - 1.84 (m, 1H), 1.83 - 1.67 ppm (m, 1H).



SI-9 **SI-3** **SI-10**

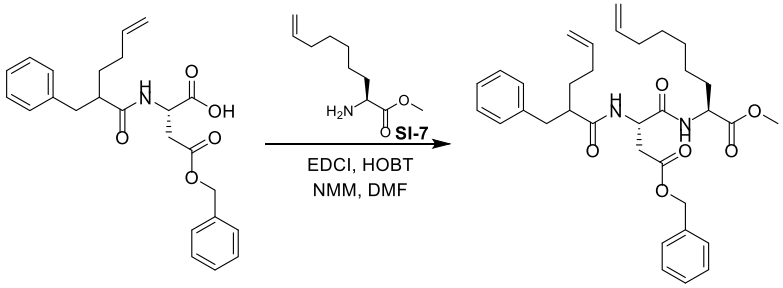
To a solution of compound **SI-9** (7.5 g, 36.72 mmol, 1.00 *eq*) and N-methylmorpholine (14.9 g, 146.88 mmol, 16.15 mL, 4.00 *eq*) in dimethyl formamide (130 mL) was added HOBt (2.5 g, 18.36 mmol, 0.50 *eq*) and EDCI (8.5 g, 44.06 mmol, 1.20 *eq*) portion wise at 0°C, then compound **SI-3** (10.1 g, 36.72 mmol, 1.00 *eq*, hydrochloride) was added portion wise at 0°C. The reaction mixture was slowly warmed to 20°C and stirred for 2 hours. LCMS showed the starrting mateiarl was consumed and desired product Mass was observed. The reaction mixture was poured into 1 N hydrochloric acid (50 mL) and water (100 mL), extracted with ethyl actate (200 mL*2). The combined organic phase was washed with brine (100 mL *3), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by column chromotography (petroleum ether: ethyl actate = 10:1 ~ 3:1) to afford compound **SI-10** (11 g, 71% yield) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.43 - 7.30 (m, 5H), 7.29 - 7.23 (m, 1H), 7.21 - 7.05 (m, 4H), 6.35 - 6.14 (m, 1H), 5.87 - 5.64 (m, 1H), 5.12 - 4.90 (m, 4H),

4.87 - 4.69 (m, 1H), 3.65 (d, *J* = 7.9 Hz, 3H), 3.07 - 2.66 (m, 3H), 2.46 - 2.30 (m, 1H), 2.24 - 2.05 (m, 1H), 2.00 - 1.47 ppm (m, 4H).



SI-10 **SI-11**

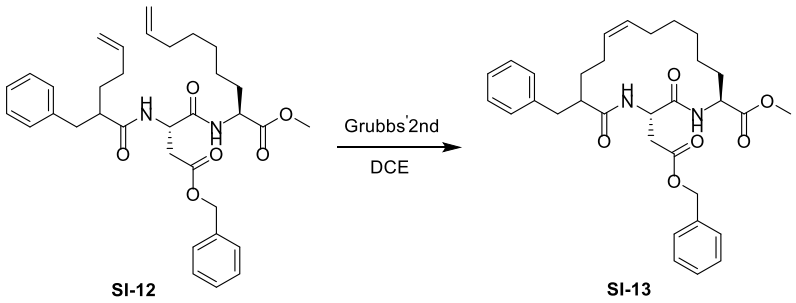
To a solution of compound **SI-10** (14 g, 33.06 mmol, 1.00 *eq*) in tetrahydrofuran (100 mL) was added sodium hydroxide (0.2 M, 200 mL, 1.21 *eq*) drop wise at 0°C. The mixture was stirred at 0°C for 2 hours. TLC (petroleum ether: ethyl actate = 3:1) showed most of the starting material was consumed. The reaction mixture was poured into 1 N hydrochloric acid (200 mL), extracted with ethyl actate (200 mL *3). The combined organic phase was washed with brine (100 mL *2), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by column chromotography (petroleum ether: ethyl actate = 10:1 ~ 1:1) to afford compound **SI-11** (9 g, 66% yield) as colorless gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40 - 7.30 (m, 4H), 7.24 - 7.06 (m, 6H), 6.98 (br. s, 1H), 6.44 - 6.34 (m, 1H), 5.78 - 5.66 (m, 1H), 5.13 - 4.93 (m, 4H), 4.86 - 4.77 (m, 1H), 3.05 - 2.73 (m, 4H), 2.42 - 2.33 (m, 1H), 2.22 - 2.05 (m, 1H), 1.97 - 1.77 (m, 2H), 1.61 - 1.53 ppm (m, 1H).



SI-11 **SI-12**

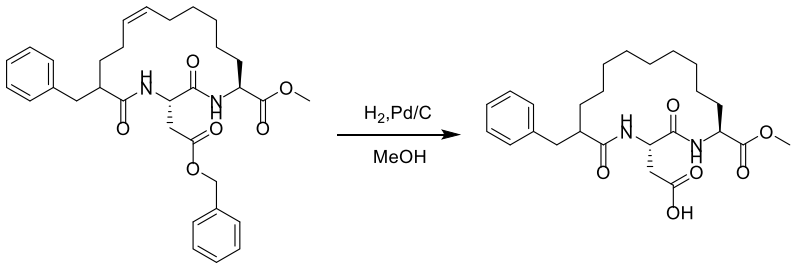
To a solution of compound **SI-11** (5.2 g, 12.70 mmol, 1.00 *eq*) and N-methylmorpholine (3.9 g, 38.10 mmol, 4.19 mL, 3.00 *eq*) in dimethyl formamide (50 mL) was added EDCI (3.7 g, 19.05 mmol, 1.50 *eq*) and HOBt (1 g, 7.62 mmol, 0.60 *eq*) at 0°C, then compound **SI-7** (2.4 g, 12.70 mmol, 1.00 *eq*, hydrochloride) was added. The mixture

was stirred at 20°C for 1 hour. TLC (petroleum ether: ethyl actate = 1:1) showed the starting mateiral was consumed. The reaction mixture was poured into 1 N hydrochloric acid (100 mL) and water (80 mL), extracted with ethyl actate (200 mL *2). The combined organic phase was washed with brine (100 mL*3), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by column chromotography (petroleum ether: ethyl actate = 30:1 ~ 3:1) to afford compound **SI-12** (5 g, 68% yield) as colorless gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41 - 7.35 (m, 5H), 7.26 - 7.11 (m, 5H), 6.96 - 6.89 (m, 0.5H), 6.69 - 6.57 (m, 1H), 6.45 (d, *J* = 8.4 Hz, 0.5H), 5.83 - 5.67 (m, 2H), 5.18 - 4.93 (m, 6H), 4.82 - 4.68 (m, 1H), 4.48 - 4.38 (m, 1H), 3.72 - 3.69 (m, 3H), 3.05 - 2.75 (m, 4H), 2.45 - 2.38 (m, 1H), 2.12 - 2.10 (m, 1H), 2.07 - 2.02 (m, 3H), 1.80 - 1.54 (m, 6H), 1.39 - 1.22 ppm (m, 4H).



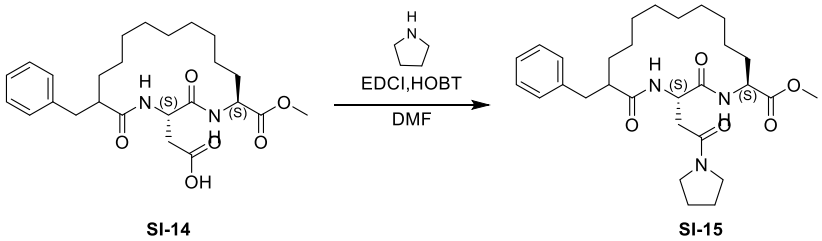
SI-12 **SI-13**

A solution of compound **SI-12** (2.5 g, 4.33 mmol, 1.00 *eq,* 2 paralleled batches) in dichloroethane (400 mL) was degassed and purged with nitrogen three times, then Grubbs'2nd catalyst (740 mg, 866.00 umol, 0.20 *eq*) was added in one portion. The mixture was stirred at 50°C for 24 hours under nitrogen atomosphere. TLC (petroleum ether: ethyl actate = 3:1) showed most of the starting material was consumed. The mixture was concentrated in reduced pressure. The residue was purified by column chromotography (Petroleum ether: ethyl actate = 10:1 ~ 3:1) to afford diastereoisomer compound **SI-13** (2.5 g, 4.56 mmol, 53% yield) as a gray solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41 - 7.33 (m, 5H), 7.23 - 7.19 (m, 2H), 7.15 - 7.11 (m, 3H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.02 (d, *J* = 8.4 Hz, 1H), 5.46 - 5.33 (m, 2H), 5.14 - 5.04 (m, 2H), 4.70 - 4.67 (m, 1H), 4.56 - 4.49 (m,1H), 3.71 (s, 3H), 2.80 - 2.78 (m, 2H), 2.56 (dd, *J* = 16.8, 4.0 Hz, 1H), 2.33 - 2.18 (m, 1H), 2.08 - 1.73 (m, 7H), 1.57 - 1.50 (m, 1H), 1.44 - 1.29 ppm (m, 7H).



SI-13 SI-14

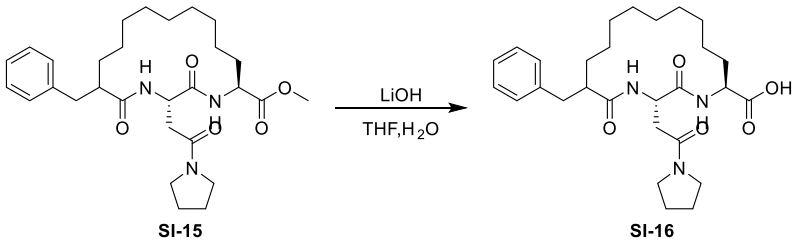
A solution of compound **SI-13** (3.2 g, 5.83 mmol, 1.00 *eq*) in methanol (30 mL) was degassed and purged with hydrogen three times，then Pd/C (400 mg, 5% purity) was added in one portion. The mixture was stirred at 20°C for 4 hours under hydrogen (15 psi). TLC (petroleum ether: ethyl actate = 3:1) showed the starting mateiral was consumed. The reaction mixture was filtered and concentrated in reduced pressure. The residue was purified by SFC (column: OD (250mm*30mm,10um); mobile phase: [0.1% ammonium hydroxide in methanol]; B%: 20%-20%, 3.55min; 500minmin), followed by prep-HPLC (Column: Daiso 150*25 5u; mobile phase: [water(0.1% trifluoroacetic acid)-acetonitrile]; B%: 45% - 70%, 27min; 65min) to afford **SI-14** (550.0 mg, 1.16 mmol, 60% yield, 97% purity) as a white solid. ^{1}H NMR (CD_3OD-d_4, 400 MHz) δ = 8.27 - 8.25 (m, 1H), 7.27 - 7.24 (m, 2H), 7.19 - 7.15 (m, 3H), 4.77 - 4.74 (m, 1H), 4.51 - 4.46 (m, 1H), 3.70 (s, 3H), 2.84 - 2.79 (m, 1H), 2.71 - 2.66 (m, 1H), 2.56 - 2.49 (m, 2H), 2.06 (dd, *J* = 15.6, 5.6 Hz, 1H), 1.82 - 1.78 (m, 1H), 1.72 - 1.61 (m, 2H), 1.41 - 1.15 ppm (m, 16H).



SI-14 SI-15

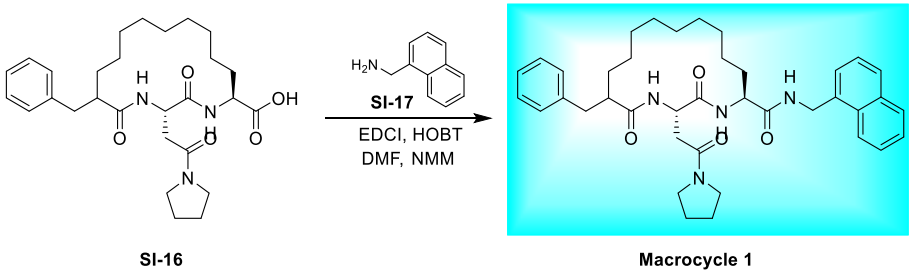
To a solution of compound **SI-14** (100 mg, 217 umol, 1.00 *eq*) and N-methylmorpholine (66 mg, 652 umol, 71.6 uL, 3.00 *eq*) in dimethyl formamide (2 mL) was added EDCI (63 mg, 326 umol, 1.50 *eq*) and HOBt (18 mg, 130 umol, 0.60 *eq*) at 0°C, then pyrrolidine (32 mg, 434 umol, 36.3 uL, 2.00 *eq*) was added. The mixture was stirred at 20°C for 2.5 hours. TLC (ethyl actate) showed the starting mateiral was consumed. The reaction

mixture was poured into water (20 mL), extracted with ethyl actate (30 mL *2). The combined organic phase was washed with 1 N hydrochloric acid (30 mL) and brine (20 mL *2), dried over anhydrous sodium sulfate and concentrated in reduced pressure to afford compound **SI-15** (130 mg, 76% yield, 65% purity) as a white solid.



SI-15 SI-16

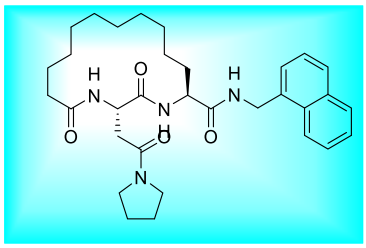
To a solution of compound **SI-15** (130 mg, 165 umol, 1.00 *eq*) in tetrahydrofuran (3 mL) was added a solution of lithium hydroxide hydrate (14 mg, 329 umol, 2.00 *eq*) in water (1 mL) drop wise at 0°C. The mixture was stirred at 20°C for 2 hours. LCMS showed the starting material was consuemd and desired product Mass was observed. The reaction mixtrue was concentratred, then water (10 mL) was added, adjusted to pH = 3 with 1N hydrochloric acid, a precipitate was formed. The mixture was filtrated and the solid was dried under *vacuo* to afford compound **SI-16** (100 mg, crude) as a white solid.



SI-16 Macrocycle 1

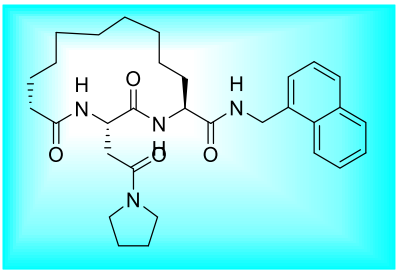
To a solution of compound **SI-16** (500 mg, 1.00 mmol, 1.00 *eq,* crude) and N-methylmorpholine (310 mg, 3.00 mmol, 330 uL, 3.00 *eq*) in dimethyl formamide (6 mL) was added a mixture of EDCI (290 mg, 1.50 mmol, 1.50 *eq*) and HOBt (70 mg, 500 umol, 0.50 *eq*) portion wise at 0°C, then compound **SI-17** (315 mg, 2.00 mmol, 294 uL, 2.00 *eq*) was added at 0°C. The mxiture was stirred at 20°C 1 hour. LCMS showed the starting mateiral was consumed. The reaction mixture was poured into water (20 mL), extracted with ethyl actate (20 mL*2). The combined organic phase was washed with

brine (20 mL*2), dried over anhydrous sodium sulfate and concentrated in reduced pressure. The residue was purified by prep-TLC (petroleum ether:ethyl actate = 2:1), followed by prep-HPLC (Column: Phenomenex Synergi C18 150*25*10 um; mobile phase: [water (0.1%trifluoroacetic acid)- acetonitrile]; B%: 55% - 85%, 13min) to afford **Macrocycle 1** (29.3 mg, 45.9 umol, 10% yield, 100% purity) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.02 (d, *J* = 7.6 Hz, 1H), 7.88 - 7.81 (m, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.70 (br. s, 1H), 7.54 - 7.45 (m, 2H), 7.41 - 7.37 (m, 2H), 7.27 - 7.20 (m, 2H), 7.18 - 7.09 (m, 3H), 6.78 (br. s, 1H), 6.21 (br. s, 1H), 4.87 (d, *J* = 3.6 Hz, 2H), 4.67 - 4.62 (m, 1H), 4.51 - 4.46 (m, 1H), 3.23 - 3.00 (m, 3H), 2.91 - 2.62 (m, 3H), 2.33 - 2.27 (m, 1H), 2.15 - 2.11 (m, 2H), 1.92 - 1.81 (m, 2H), 1.73 - 1.58 (m, 4H), 1.41 - 1.11 ppm (m, 16H). *m/z* 639.2 $[M+H]^+$.



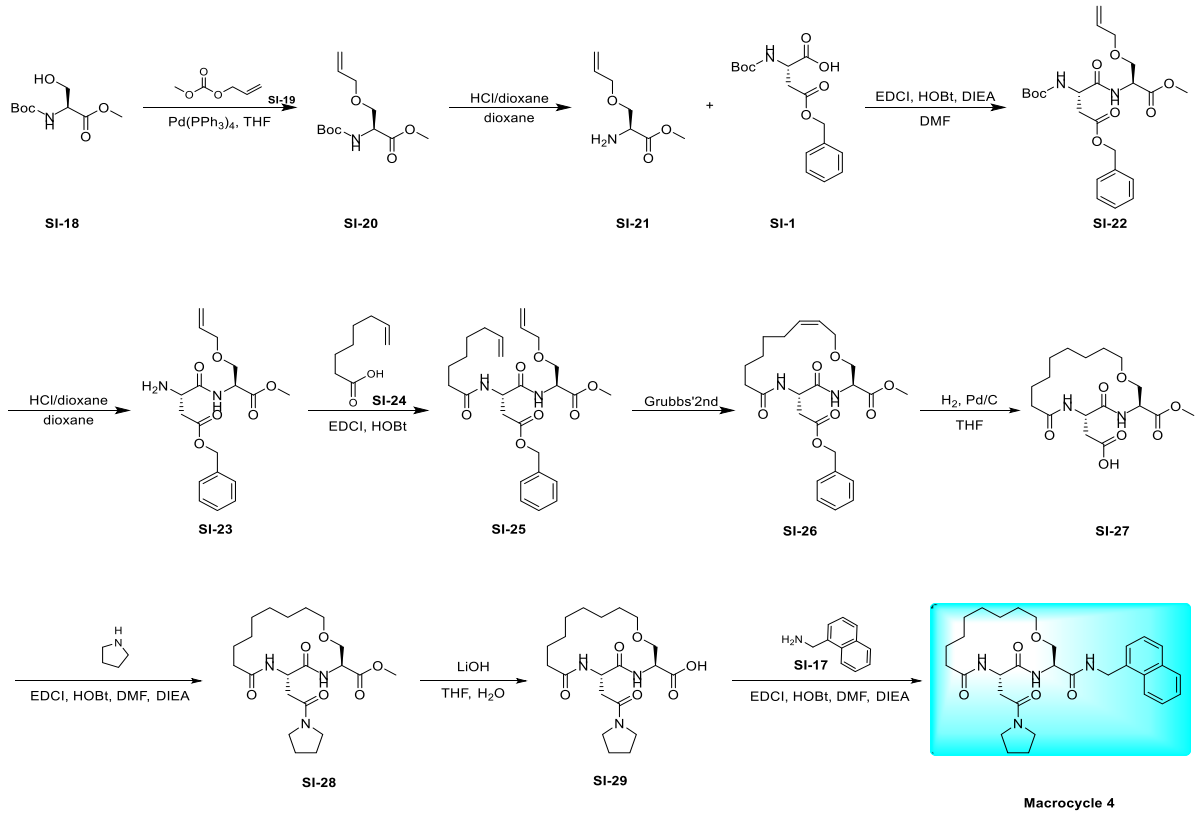
Macrocycle 2

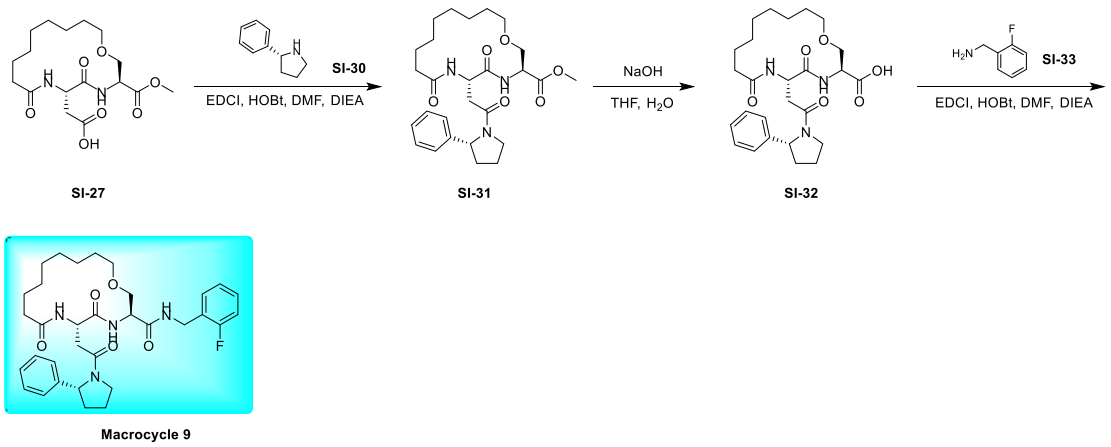
Macrocycle 2 was synthesized in a similar fashion to **Macrocycle 1**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.08 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* =7.8, 1.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 6.73 (dd, *J* = 8.6, 4.0 Hz, 2H), 4.96 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.85 (dd, *J* = 14.9, 5.5 Hz, 1H), 4,77 (td, *J* = 8.3, 4.5 Hz, 1H), 4,52 (ddd, *J* = 10.5, 8.8, 3.5 Hz, 1H), 3.33 – 3.18 (m, 2H), 3.13 (dt, *J* = 12.1, 7.0 Hz, 1H), 2.88 (dt, *J* = 12.1, 7.0 Hz, 1H), 2.82 – 2.51 (m, 2H), 2.32 (ddd, *J* = 14.2, 6.6, 4.1 Hz, 1H), 2.24 – 2.01 (m, 2H), 1.94 – 1.56 (m, 7H), 1.50 – 1.13 ppm (m, 14H). m/z 549.6 $[MS+H]^+$.



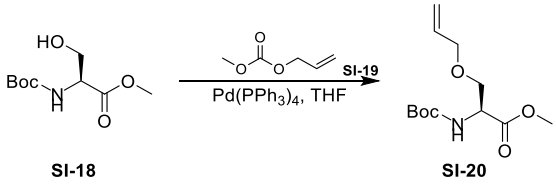
Macrocycle 3

Macrocycle 3 was synthesized in a similar fashion to **Macrocycle 1**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.08 (d, *J* = 8.3 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 5.7 Hz, 1H), 7.58 - 7.48 (m, 2H), 7.48 – 7.36 (m, 2H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 4.96 (dd, *J* = 14.9, 5.7 Hz, 1H), 4.85 (dd, *J* = 14.9, 5.6 Hz, 1H), 4.77 (td, *J* = 8.9, 3.8 Hz, 1H), 4.51 (ddd, *J* = 11.6, 8.5, 3.5 Hz, 1H), 3.34 – 3.21 (m, 2H), 3.16 (dt, *J* = 12.0, 6.9 Hz, 1H), 2.87 (dt, *J* = 12.1, 7.0 Hz, 1H), 2.74 – 2.50 (m, 2H), 2.33 (ddd, *J* = 14.7, 7.9, 3.5 Hz, 1H), 2.23 – 2.05 (m, 2H), 1.89 – 1.84 (m, 3H), 1.81 – 1.53 (m, 11H), 1.53 – 1.09 (m, 5H). m/z 535.5 $[MS+H]^+$.

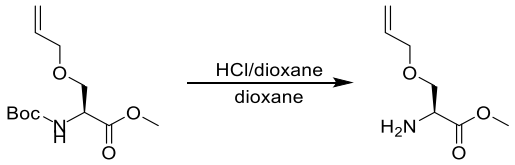




Scheme S2. Synthetic route of **Macrocycle 4** and **9.**

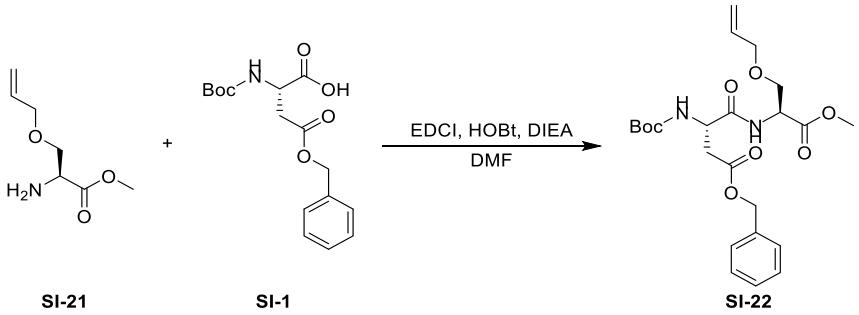


To a solution of compound **SI-18** (5 g, 22.81 mmol, 1.0 *eq*) in tetrahydrofuran (50 mL) was added compound **SI-19** (3.97 g, 34.22 mmol, 1.5 *eq*) at 26 °C, then Pd $(PPh_3)_4$ (527 mg, 456 umol, 0.02 *eq*) was added to the mixture. The reaction mixture was degassed in vacuum and purged with nitrogen for 3 times. The resulting mixture was stirred at 60°C for 4 hours. TLC (Petroleum ether: Ethyl acetate= 3:1) showed that the starting material was consumed completely and a new spot was formed. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL*3). The combined organic layer was dried over anhydrous sodium sulfate. After filtration and concentration in vacuum, the residue was purified by silica gel chromatography (petroleum ether: ethyl acetate= 20:1 to 10:1) to give compound **SI-20** (4 g, 58% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.86–5.78 (m, 1H), 5.41–5.35 (m, 1H), 5.22 (dd, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 5.18 (dd, J_1 = 1.2 Hz, J_2 = 10.4 Hz, 1H), 4.43-4.40 (m, 1H), 3.98–3.95 (m, 2H), 3.85 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.75 (s, 3H), 3.64 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H), 1.44 ppm (s, 9H).



SI-20 **SI-21**

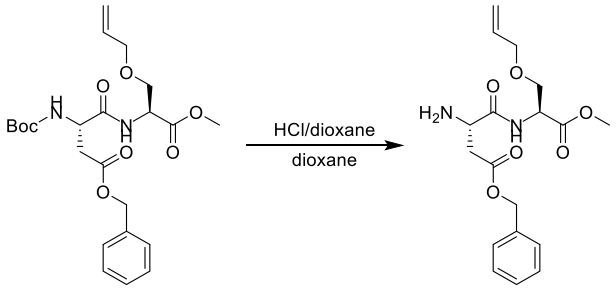
To a solution of compound **SI-20** (4 g, 15.43 mmol, 1.0 *eq*) in dioxane (20 mL) was added a solution of hydrogen chloride in dioxane (4M, 30.00 mL, 7.78 *eq*). The reaction mixture was stirred at 26°C for 2 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was concentrated in vacuum to provide compound **SI-21** (2.90 g, HCl salt) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.80 (br.s, 2H), 5.93–5.85 (m, 1H), 5.30 (dd, J_1 = 1.6 Hz, J_2 = 17.6 Hz, 1H), 5.20 (dd, J_1 = 1.2 Hz, J_2 = 10.4 Hz, 1H), 4.42-4.40 (m, 1H), 4.17–4.11 (m, 1H), 4.07–4.00 (m, 3H), 3.84 ppm (s, 3H).



SI-21 **SI-1** **SI-22**

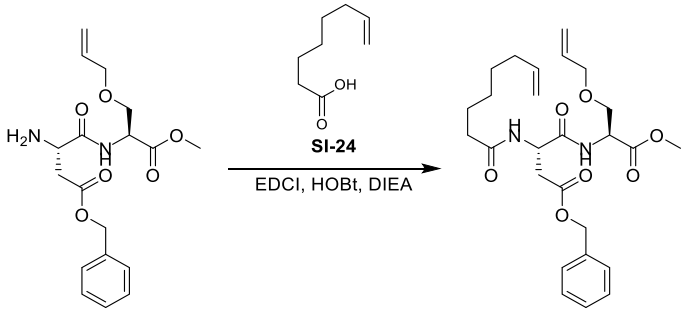
To a solution of compound **SI-1** (5.08 g, 15.7 mmol, 1.0 *eq*) in N,N-dimethylformamide (20 mL) was added diisopropylethylamine (6.09 g, 47.1 mmol, 8.23 mL, 3.0 *eq*), EDCI (4.52 g, 23.6 mmol, 1.5 *eq*), HOBt (3.18 g, 23.6 mmol, 1.5 *eq*) at 0°C. Then a solution of compound **SI-21** (2.5 g, 15.7 mmol, 1.0 *eq*) in DMF (10 mL) was added into the mixture and the resulting mixture was stirred at 26°C for 17 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The reaction mixture was diluted with water (20 mL), acidified by hydrochloric acid (1N) until pH = 4 and extracted with ethyl acetate (30 mL*3). The combined organic layer was washed with brine (30 mL*3) and dried over anhydrous sodium sulfate. After filtration and concentration in vacuum, the residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate= 15:1 to 6:1) to provide compound **SI-22** (5.3 g, 68% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.32 (m, 5H),

7.23 (br.s, 1H), 5.90–5.84 (m, 1H), 5.66 (br.s, 1H), 5.25 (dd, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 5.17 (dd, J_1 = 1.2 Hz, J_2 = 10.4 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 4.70–4.66 (m, 1H), 4.63-4.59 (m, 1H), 4.03–3.92 (m, 2H), 3.88 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.74 (s, 3H), 3.62 (dd, J_1 = 3.6 Hz, J_2 = 9.6 Hz, 1H), 3.06 (dd, J_1 = 4.4 Hz, J_2 = 17.2 Hz, 1H), 2.76 (dd, J_1 = 6.0 Hz, J_1 = 16.8 Hz, 1H), 1.46 ppm (s, 9H).



SI-22 **SI-23**

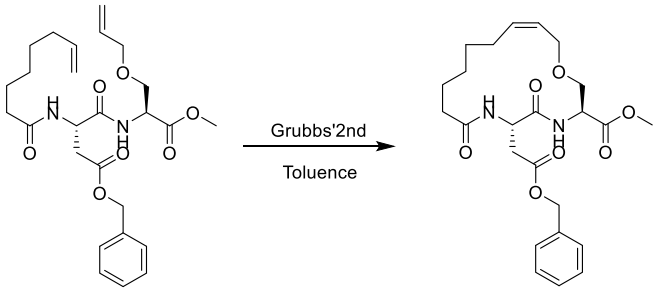
To a solution of compound **SI-22** (1.8 g, 3.88 mmol, 1.0 *eq*) in dioxane (10 mL) was added a solution of hydrogen chloride in dioxane (4M, 10 mL, 10.31 *eq*). The mixture was stirred at 25°C for 2 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was concentrated in vacuum to provide compound **SI-23** (2 g, crude, HCl salt) as colorless oil.



SI-23 **SI-25**

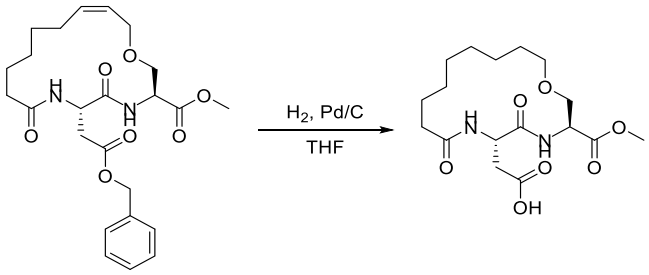
To a solution of compound **SI-24** (560 mg, 3.94 mmol, 1.0 *eq*) in N,N-dimethylformamide (10 mL) was added HOBt (692 mg, 5.12 mmol, 1.3 *eq*), EDCI (981 mg, 5.12 mmol, 1.3 *eq*) and N,N-diisopropylethylamine (2.55 g, 19.7 mmol, 3.44 mL, 5.0 *eq*) at 0°C under nitrogen. Then compound **SI-23** (2.01 g, 5.0 mmol, 1.27 *eq*, HCl salt) was added to above reaction mixture at 0°C under nitrogen. The resulting mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was diluted with water (40

mL) and extracted with ethyl acetate (20 mL*3). The combined organic phases were washed with saturated aqueous sodium carbonate solution (20 mL*3), brine (20 mL) and dried over sodium sulfate. After filtration and concentration in vacuum, the crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate= 15:1 to 2:1) to afford compound **SI-25** (1.48 g, 64% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.27–7.25 (m, 2H), 7.21–7.18 (m, 4H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.75–5.70 (m, 2H), 5.19–5.06 (m, 4H), 4.93–4.83 (m, 3H), 4.57 (d, *J* = 9.6 Hz, 1H), 3.90–3.87 (m, 2H), 3.78 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.64 (s, 3H), 3.55 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 2.93 (dd, J_1 = 4.4 Hz, J_2 = 16.8 Hz, 1H), 2.65 (dd, J_1 = 4.4 Hz, J_2 =16.8 Hz, 1H), 2.14 (t, *J* = 7.6 Hz, 2H), 1.98–1.93 (m, 2H), 1.56-1.52 (m, 2H), 1.33–1.24 ppm (m, 4H).



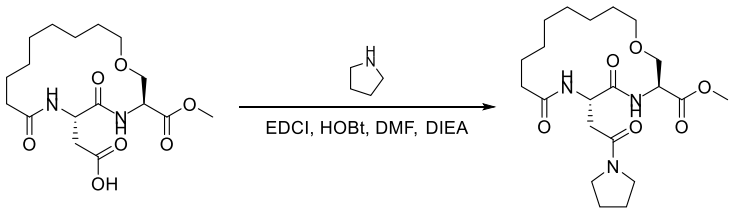
SI-25 **SI-26**

To a solution of compound **SI-25** (1.48 g, 3.03 mmol, 1.0 *eq*) in toluene (280 mL) was added Grubbs'2nd (2.57 g, 3.03 mmol, 1.0 *eq*) and then the mixture was degassed in vacuum and purged with nitrogen for 3 times. The mixture was stirred at 60°C for 16 hours under nitrogen. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate= 3:1 to 3:1) and recrystallized in methanol (20 mL) to afford **SI-26** (2.2 g, crude) as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.31 (m, 7H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.93 (d, *J* = 6.0 Hz, 1H), 5.20 (d, *J* = 12.0 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.02–4.96 (m, 1H), 4.74–4.71 (m, 1H), 4.31–4.26 (m, 1H), 4.15 (dd, J_1 = 3.2 Hz, J_2 = 9.6 Hz, 1H), 3.93 (dd, J_1 = 2.8 Hz, J_2 = 10.0 Hz, 1H), 3.77 (s, 3H), 3.13 (dd, J_1 = 4.8 Hz, J_2 = 17.2 Hz, 1H), 2.68 (dd, J_1 = 4.8 Hz, J_2 = 17.2 Hz, 1H), 2.42–2.35 (m, 1H), 2.32–2.29 (m, 1H), 2.16–2.09 (m, 1H), 1.96–1.85 (m, 2H), 1.48–1.32 ppm (m, 6H).



SI-26 **SI-27**

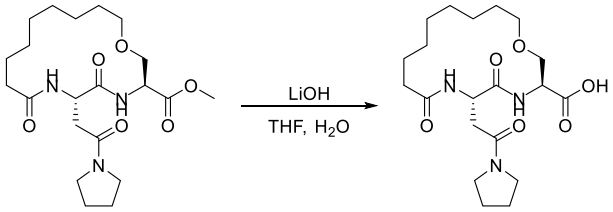
To a solution of **SI-26** (500 mg, 1.09 mmol, 1.0 *eq*) in tetrahydrofuran (4 mL) was added Pd/C (200 mg, 10% purity) and the mixture was degassed and purged with hydrogen for 3 times. The mixture was stirred at 25°C for 1 hour under hydrogen balloon. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was diluted with dichloromethane (10 mL) and methanol (2 mL) and then filtered. The filtrate was concentrated in vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex Synergi C18 150mm*25mm*10um; mobile phase: [water (0.1%TFA)-ACN]; B%: 18%-48%, 11min.) to afford **SI-27** (400 mg, 98% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 12.24 (br.s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 4.76-4.71 (m，1H), 4.55-4.53 (m, 1H), 3.66-3.64 (m, 1H), 3.63 (s, 3H), 3.59-3.58 (m, 1H), 3.37-3.34 (m, 2H), 2.66 (dd, J_1 = 6.4 Hz, J_2 = 16.4 Hz, 1H), 2.47 (dd, J_1 = 7.2 Hz, J_2 = 16.0 Hz, 1H), 2.28-2.15 (m, 1H), 2.10-2.04 (m, 1H), 1.67-1.65 (m, 1H), 1.41-1.36 (m, 1H), 1.25-1.22 ppm (m, 10H).



SI-27 **SI-28**

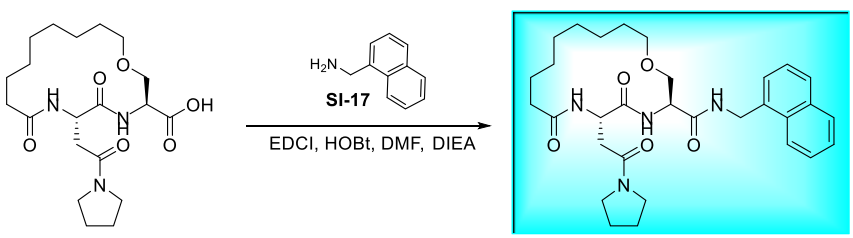
To a solution of **SI-27** (180 mg, 483 umol, 1.0 *eq*) in N,N-dimethylformamide (3 mL) was added HOBt (84 mg, 628 umol, 1.3 *eq*), EDCI (120 mg, 628 umol, 1.3 *eq*), N,N-diisopropylethylamine (124 mg, 966 umol, 168.8 uL, 2.00 *eq*) and amine (34 mg, 483 umol, 40.5 uL, 1.0 *eq*) at 0°C under nitrogen. The mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the

desired product MS was detected. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL*3). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reverse phase flash (TFA) to afford compound **SI-28** (70 mg, 165 umol, 34% yield, 100% purity) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.22 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 4.80-4.75 (m, 1H), 4.56–4.53 (m, 1H), 3.69-3.66 (m, 1H), 3.65 (s, 3H), 3.63-3.58 (m, 1H), 3.42–3.35 (m, 4H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.71–2.66 (m, 1H), 2.53–2.51 (m, 1H), 2.24–2.17 (m, 1H), 2.08–2.02 (m, 1H), 1.86 (t, *J* = 6.8 Hz, 2H), 1.75 (t, *J* = 6.8 Hz, 2H), 1.66-1.62 (m, 1H), 1.44-1.40 (m, 1H), 1.36–1.23 ppm (m, 10H).



SI-28 **SI-29**

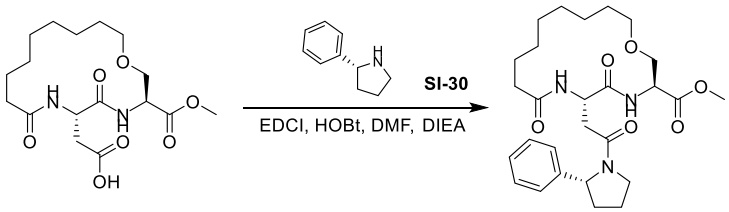
To a solution of compound **SI-28** (20 mg, 47 umol, 1 *eq*) in water (0.2 mL) and tetrahydrofuran (2 mL) was added sodium hydroxide (11 mg, 282 umol, 6 *eq*). The mixture was stirred at 0°C for 0.25 hour. TLC (petroleum ether: ethyl acetate= 0:1) indicated that the starting material was consumed completely and one new spot was formed. The mixture was acidified by 1N hydrochloric acid until pH= 3 and then adjusted to pH=8 with saturated aqueous sodium bicarbonate solution. The mixture was washed with ethyl acetate (10 mL*2). The aqueous layer was acidified by 1N hydrochloric acid to pH= 6 and then freeze-dried to afford compound **SI-29** (15 mg, 34.4 umol, 73% yield, 94% purity) as a white solid.



SI-29 **Macrocycle 4**

To a solution of compound **SI-29** (15 mg, 36 umol, 1 *eq*) in N,N-dimethylformamide (3 mL) was added N,N-diisopropylethylamine (12 mg, 91 umol, 15.9 uL, 2.5 *eq*), HOBt (6 mg, 47.39 umol, 1.3 *eq*) and EDCI (9 mg, 47 umol, 1.3 *eq*) at 0°C under nitrogen. Then compound **SI-17** (7 mg, 47 umol, 7.0 uL, 1.3 *eq*) was added to above mixture. The mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired product MS was detected. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL*3). The combined organic phases were washed with brine (20 mL*3), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was recrystallized by acetonitrile (3 mL, twice) to afford **Macrocycle 4** (18.2 mg, 90% yield) as a white solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.59 – 8.44 (m, 2H), 8.23 (d, *J* = 8.2 Hz, 1H), 8.15 – 8.08 (m, 1H), 7.97 – 7.91 (m, 1H), 7.85 – 7.77 (m, 1H), 7.57 – 7.49 (m, 2H), 7.45 – 7.36 (m, 2H), 4.85 – 4.72 (m, 2H), 4.66 (dd, *J* = 15.5, 5.7 Hz, 1H), 4.49 (t, *J* = 7.1 Hz, 1H), 3.76 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.59 (t, *J* = 9.6 Hz, 1H), 3.48 – 3.38 (m, 3H), 3.11 – 3.00 (m, 1H), 2.92 – 2.82 (m, 1H), 2.78 – 2.71 (m, 1H), 2.68 (d, *J* = 10.9 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.01 – 1.93 (m, 1H), 1.86 – 1.74 (m, 2H), 1.69 – 1.49 (m, 3H), 1.44 – 1.22 (m, 8H), 1.20 – 1.10 (m, 3H). m/z 551.5 $[MS+H]^{+}$.

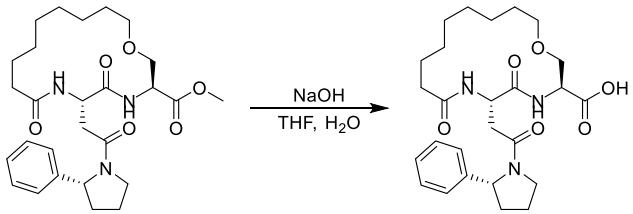
SFC of **Macrocycle 4**: RT= 1.397 min, de%=100%.



SI-27 **SI-31**

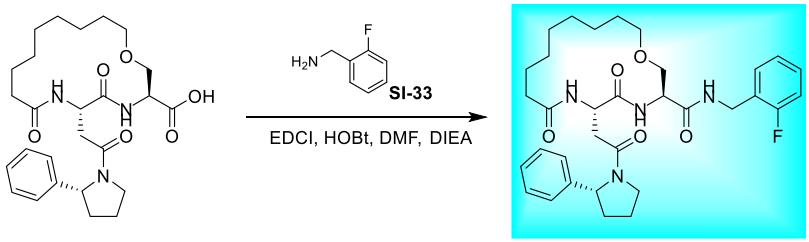
To a solution of **SI-27** (150 mg, 403 umol, 1.0 *eq*) in N,N-dimethylformamide (4 mL) was added N,N-diisopropylethylamine (104 mg, 806 umol, 140.7 uL, 2.0 *eq*), HOBt (70 mg, 523 umol, 1.3 *eq*), EDCI (100 mg, 523 umol, 1.3 *eq*) and compound **SI-30** (65 mg, 443 umol, 1.1 *eq*) at 0°C under nitrogen. The mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL*3). The combined organic phases were washed by brine (20 mL*3), dried over sodium sulfate. After filtration and concentration in vacuum, the crude

product was purified by prep-HPLC (column: Phenomenex Synergi C18 150mm*25mm*10um; mobile phase: [water (0.1%TFA)-ACN]; B%: 38%-68%, 2min) to afford compound **SI-31** (166 mg, 81% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.40–8.20 (m, 1H), 7.74–7.58 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.26–7.12 (m, 4H), 5.18–5.06 (m, 1H), 4.78–4.72 (m, 1H), 4.55–4.50 (m, 1H), 3.66–3.65 (m, 1H), 3.71–3.55 (m, 3H), 3.58–3.56 (m, 4H), 3.54–3.53 (m, 1H), 2.75 (t, *J* = 6.4 Hz, 1H), 2.22–2.14 (m, 2H), 2.00–1.93 (m, 1H), 1.91–1.63 (m, 4H), 1.34–1.15 ppm (m, 12H).



SI-31 **SI-32**

To a solution of compound **SI-31** (140 mg, 279 umol, 1.0 *eq*) in tetrahydrofuran (2 mL) and water (1 mL) was added sodium hydroxide (67 mg, 1.67 mmol, 6.0 eq). The mixture was stirred at 0°C for 0.5 hour. TLC (dichloromethane: methanol= 10:1) indicated that the starting material was consumed completely. The mixture was washed with ethyl acetate (10 mL*2). The aqueous layer acidified by 1N hydrochloric acid until pH= 6 and then freeze-dried to afford compound **SI-32** (140 mg, crude) as a white solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.38–8.18 (m, 1H), 7.56–7.40 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.26–7.12 (m, 4H), 5.13–5.01 (m, 1H), 4.79–4.71 (m, 1H), 4.46–4.42 (m, 1H), 3.67–3.50 (m, 4H), 2.81–2.73 (m, 1H), 2.53–2.52 (m, 2H), 2.27-2.16 (m, 2H), 2.06–1.96 (m, 1H), 1.88–1.56 (m, 4H), 1.36–1.15 ppm (m, 12H).

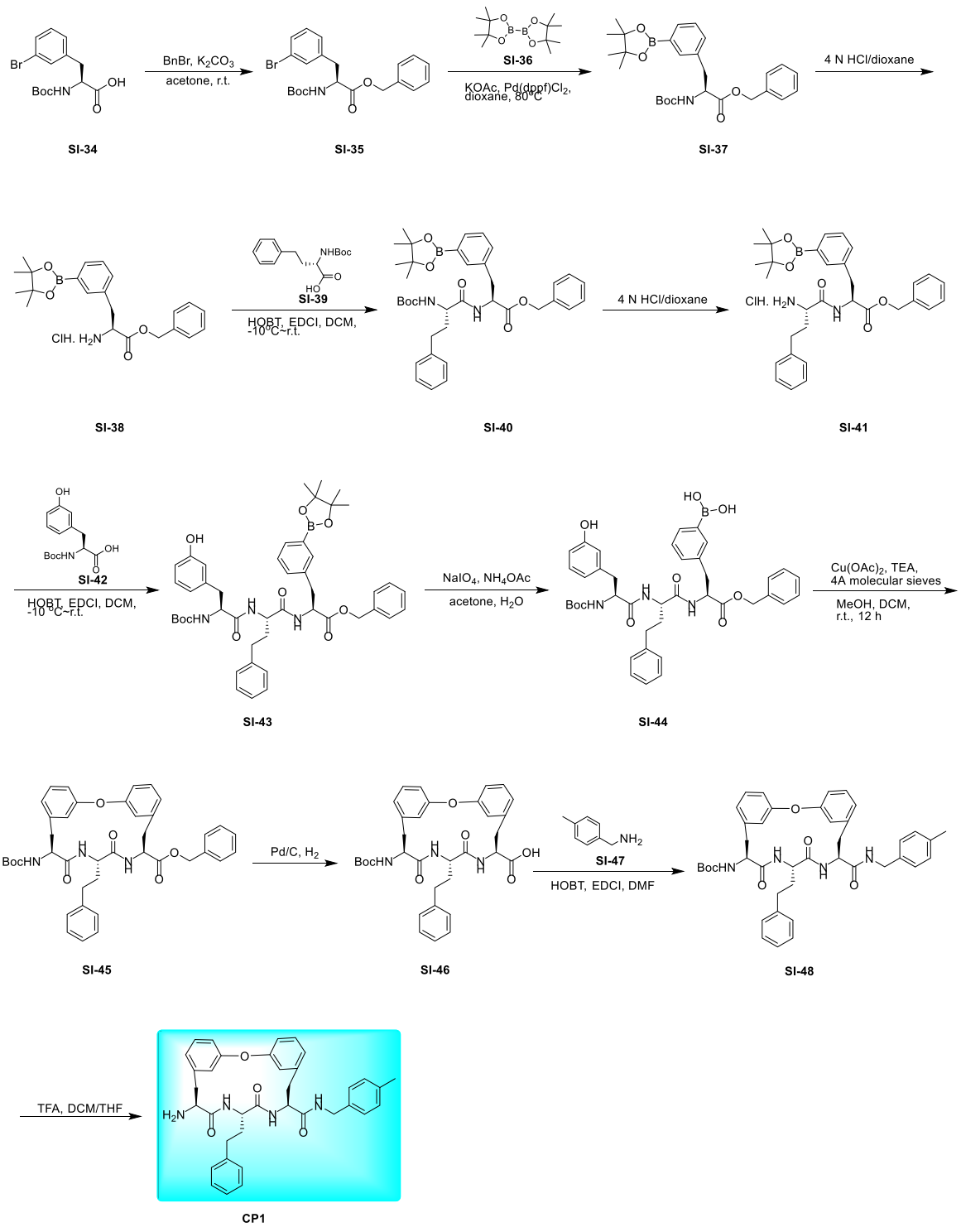


SI-32 **Macrocycle 9**

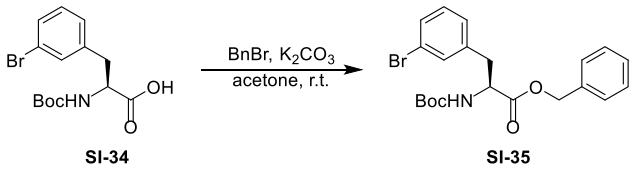
To a solution of compound **SI-32** (120 mg, 246 umol, 1 eq) in N,N-dimethylformamide (2 mL) was added N,N-diisopropylethylamine (79 mg, 615 umol, 2.5 *eq*), HOBt (43 mg, 320 umol, 1.3 *eq*) and EDCI (61 mg, 320 umol, 1.3 *eq*) at 0°C and then (2-

fluorophenyl)methanamine (46 mg, 369 umol, 42 uL, 1.5 *eq*) was added to the mixture. The resulting mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The mixture was poured into water (5 mL) and extracted with ethyl acetate (5 mL*3). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was recrystallized by methanol (3 mL, twice) to afford **Macrocycle 9** (51.8 mg, 35% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.62 – 8.29 (m, 2H), 8.29 – 8.09 (m, 1H), 7.46 – 6.84 (m, 9H), 5.15 – 5.06 (m, 0.48H), 4.81 – 4.67 (m, 1H), 4.54 – 4.37 (m, 2H), 4.37 – 4.26 (m, 1H), 4.24 – 4.15 (m, 0.55H), 3.81 – 3.40 (m, 4H), 3.20 – 2.62 (m, 3H), 2.35 – 2.13 (m, 2H), 2.02 – 1.92 (m, 1H), 1.86 – 1.75 (m, 1H), 1.75 – 1.65 (m, 1H), 1.64 – 1.45 (m, 2H), 1.44 – 1.03 ppm (m, 11H). m/z 595.5 $[MS+H]^+$.

SFC of **Macrocycle 9**: RT= 2.143 min, de %= 97%.

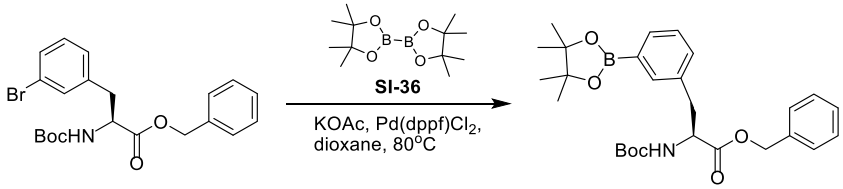


Scheme S3. Synthetic route of **CP1**.



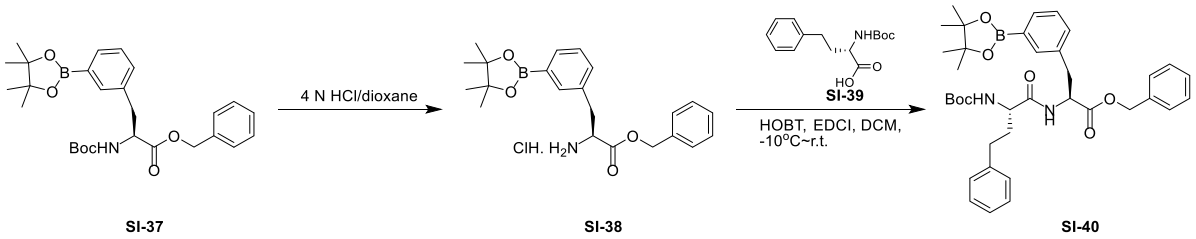
SI-34 **SI-35**

To a mixture of compound **SI-34** (8.0 g, 23.2 mmol, 1.0 eq) and potassium carbonate (3.37 g, 24.4 mmol, 1.05 eq) in acetone (800 mL) was added benzyl bromide (4.37 g, 25.6 mmol, 1.1 eq) at 25°C and then the reaction mixture was stirred for 12 hours at 25°C. LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (petroleum ether: ethyl acetate= 100:1 to 10:1) to give the desired product **SI-35** (10.0 g, 22.7 mmol, 97% yield, 98% purity) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39-7.36 (m, 4H), 7.33-7.30 (m, 2H), 7.26-7.25 (m, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 5.15 (q, J = 12.4 Hz, 2H), 5.05-5.02 (m, 1H), 4.64-4.59 (m, 1H), 3.14-2.99 (m, 2H), 1.44 ppm (s, 9H).



SI-35 **SI-37**

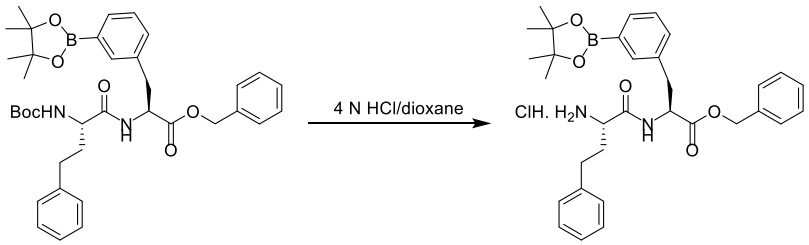
To a solution of compound **SI-35** (10.0 g, 23.0 mmol, 1.0 eq), compound **SI-36** (9.35 g, 36.8 mmol, 1.6 eq) and potassium acetate (6.78 g, 69.0 mmol, 3.0 eq) in dioxane (250 mL) was added Pd(dppf)Cl_2 (1.68 g, 2.3 mmol, 0.1 eq) at 25°C and then the reaction mixture was stirred at 80°C for 12 hours under nitrogen. LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate= 100:1 to 10:1) to give the product **SI-37** (10.0 g, 19.7 mmol, 85% yield, 95% purity) as yellow oil.



SI-37 SI-38 SI-40

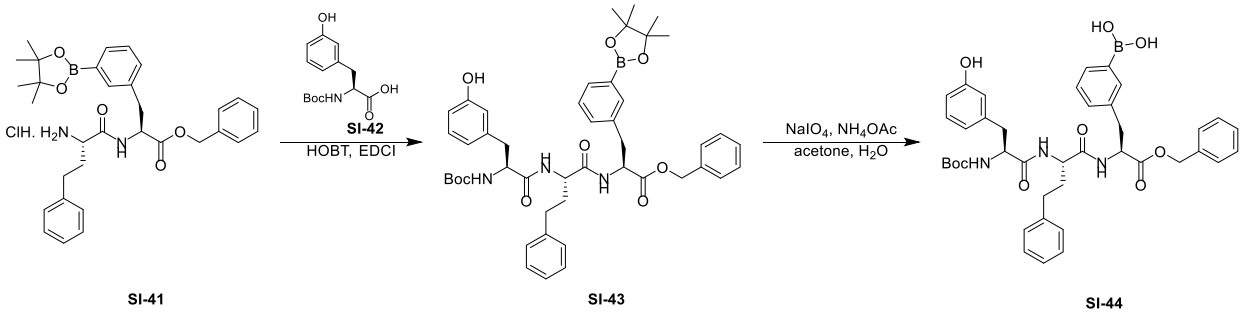
To a solution of compound **SI-37** (35.0 g, 72.7 mmol, 1.0 eq) in dioxane (50 mL) was added a solution of hydrogen chloride in dioxane (4 M, 300 mL) at 25°C and then the reaction mixture was stirred at 25°C for 0.5 hour. LCMS showed that the reaction was completed. Then the reaction mixture was concentrated in vacuum to give the product **SI-38** (30.0 g, crude, HCl salt) as yellow oil, which was used directly in the next step.

To a solution of compound **SI-39** (18.4 g, 65.8 mmol, 1.1 eq), 1-hydroxybenzotriazole (8.9 g, 65.8 mmol, 1.1 eq) in dichloromethane (250 mL) was added 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide hydrochloride (12.6 g, 65.8 mmol, 1.1 eq) at 0°C and then the reaction mixture was stirred for 30 mins. The compound **SI-38** (25 g, 59.8 mmol, 1.0 eq, HCl salt) and diisopropylethylamine (23.2 g, 179.5 mmol, 3.0 eq) in dichloromethane (120 mL) was added to above reaction mixture at 0°C and then the resulting mixture was stirred at 25°C for 11.5 hours. LCMS showed that the reaction was completed. The reaction mixture was quenched with hydrochloric acid solution (1 M, 400 mL) and extracted with dichloromethane (200 mL*2). The combined organic phases were washed with brine (400 mL*2), dried over sodium sulfate and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate= 50:1 to 2:1) to give the product **SI-40** (29.0 g, 38.5 mmol, 64% yield, 85% purity) as yellow oil. ^{1}H NMR δ = 7.67 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H), 7.40-7.29 (m, 6H), 7.28-7.20 (m, 6H), 7.17 (d, J = 7.2 Hz, 1H), 6.64 (br.s, 1H), 5.26-5.24 (s, 1H), 4.89-4.84 (m, 1H), 4.41-4.36 (m, 1H), 4.16-4.10 (m, 1H), 3.20-3.17 (m, 1H), 3.09-3.07 (m, 1H), 2.73-2.65 (m, 2H), 2.28-2.21 (m, 2H), 1.40 (s, 9H), 1.34 ppm (s, 12H).



SI-40 **SI-41**

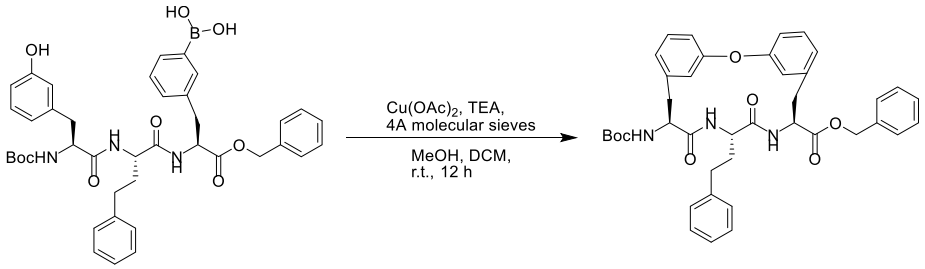
To a solution of compound **SI-40** (31.0 g, 48.2 mmol, 1.0 eq) in dioxane (50 mL) was added a solution of hydrogen chloride in dioxane (4 M, 250 mL, 20.7 eq) at 25°C and then the reaction mixture was stirred at 25°C for 30 min. LCMS showed that the reaction was completed. The reaction mixture was concentrated in vacuum to give the product **SI-41** (26.0 g, 38.0 mmol, 79% yield, 85% purity, HCl salt) as yellow oil. ^{1}H NMR (CD_3OD, 400 MHz) δ = 7.65-7.61 (m, 2H), 7.35-7.16 (m, 12H), 5.48 (s, 2H), 4.86-4.76 (m, 1H), 3.95-3.93 (m, 1H), 3.21-3.19 (m, 1H), 3.11-3.09 (m, 1H), 2.68-2.66 (m, 2H), 2.10-1.95 (m, 2H), 1.33 ppm (s, 12H).



SI-41 **SI-43** **SI-44**

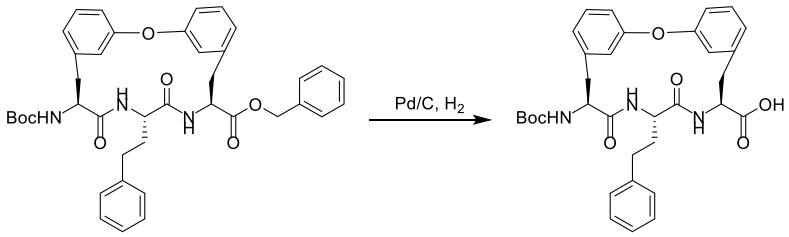
To a solution of compound **SI-41** (5.0 g, 9.2 mmol, 1.0 eq) and compound **SI-42** (2.6 g, 9.2 mmol, 1.0 eq) in N,N-dimethylformamide (150 mL) was added diisopropylethylamine (5.96 g, 46.1 mmol, 5.0 eq), 1-hydroxybenzotriazole (1.37 g, 10.1 mmol, 1.1 eq) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.94 g, 10.1 mmol, 1.1 eq) at 0°C and the reaction was stirred at 25°C for 12 hours. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH=4 with hydrochloric acid (0.5 M) and extracted with dichloromethane (150 mL*4). The orgainic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give the product **SI-43** (13.6 g, 4.35 mmol, 47% yield) as red oil, which was used directly in the next step.

To a solution of compound **SI-43** (30.0 g, 37.2 mmol, 1.0 eq) in acetone (300 mL) was added sodium periodate (23.89 g, 111.7 mmol, 3.0 eq) and ammonium acetate (8.61 g, 111.7 mmol, 3.0 eq) in water (240 mL) at 25°C and then the reaction mixture was stirred at 25°C for 12 hours. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH=4 with hydrochloric acid (0.5 M) and extracted with dichloromethane (300 mL*3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse phase flash (HCl condition) to give the product **SI-44** (9.30 g, 12.8 mmol, 25% yield, 100% purity) as a brown solid.



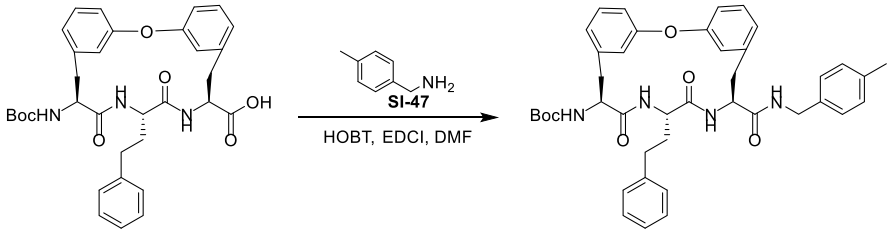
SI-44 **SI-45**

To a solution of compound **SI-44** (6.0 g, 8.29 mmol, 1.0 eq) in dichloromethane (600 mL) was added copper acetate (1.51 g, 8.29 mmol, 1.0 eq), triethylamine (8.39 g, 82.9 mmol, 10.0 eq), methanol (2.66 g, 82.9 mmol, 10.0 eq) and 4Å molecular sieves (6.0 g) at 25°C and then the reaction mixture was stirred at 25°C for 12 hours under oxygen. LCMS showed that the reaction was completed. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by re-crystallization from ethyl acetate (100 mL) and then re-crystallized from acetonitrile (100 mL) to give **SI-45** (2.60 g, 3.66 mmol, 44% yield, 95% purity) as a yellow solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.60 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.41-7.28 (m, 9H), 7.24-7.20 (m, 1H), 7.08-6.97 (m, 4H), 6.89-6.79 (m, 3H), 6.15-6.10 (m, 2H), 5.17 (s, 2H), 4.75-4.70 (m, 1H), 4.37-4.33 (m, 2H), 3.27-3.17 (m, 2H), 2.91-2.71 (m, 2H), 2.45-2.40 (m, 2H), 1.75-1.63 (m, 2H), 1.38 ppm (s, 9H).



SI-45 **SI-46**

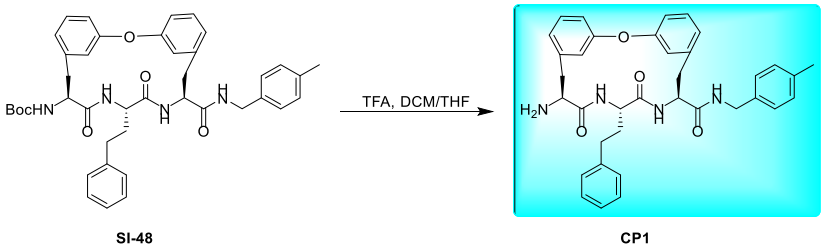
To a solution of **SI-45** (250 mg, 368 umol, 1.0 eq) in dichloromethane (10 mL) and isopropanol (20 mL) was added Pd/C (100 mg, 5% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen for several times. The mixture was stirred under hydrogen (15 psi) at 25°C for 4 hours. LCMS showed that the starting material was completed. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give compound **SI-46** (150 mg, 183 umol, 50% yield, 72% purity) as a brown solid.



SI-46 **SI-48**

To a solution of compound **SI-46** (500 mg, 851 umol, 1.0 eq), diisopropylethylamine (121 mg, 935 umol, 1.1 eq) and 1-hydroxy benzotriazole (126 mg, 935 umol, 1.1 eq) in tetrahydrofuran (10 mL) and N,N-dimethylformamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (179 mg, 935 umol, 1.1 eq) at -10°C and then the reaction mixture was stirred for 0.5 hour at -10°C. Then *p*-tolylmethanamine (113 mg, 935 umol, 1.1 eq) was added to above reaction mixture and the reaction mixture was stirred for 11.5 hours at 25°C. LCMS showed that the reaction was completed. Water (20 mL) was added to the reaction mixture and the solid was precipitate out. Then the solid was collected and purified by prep-HPLC (TFA condition, column: Agela ASB 150mm*25mm*5um, mobile phase: [water (0.1%TFA)-ACN]; B%: 60%-85%, 11 min) to give **SI-48** (23.0 mg, 31 umol, 4% yield, 93% purity) as a white solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.57 (t, J = 5.6 Hz, 1H), 8.41 (d, J = 8.8 Hz,

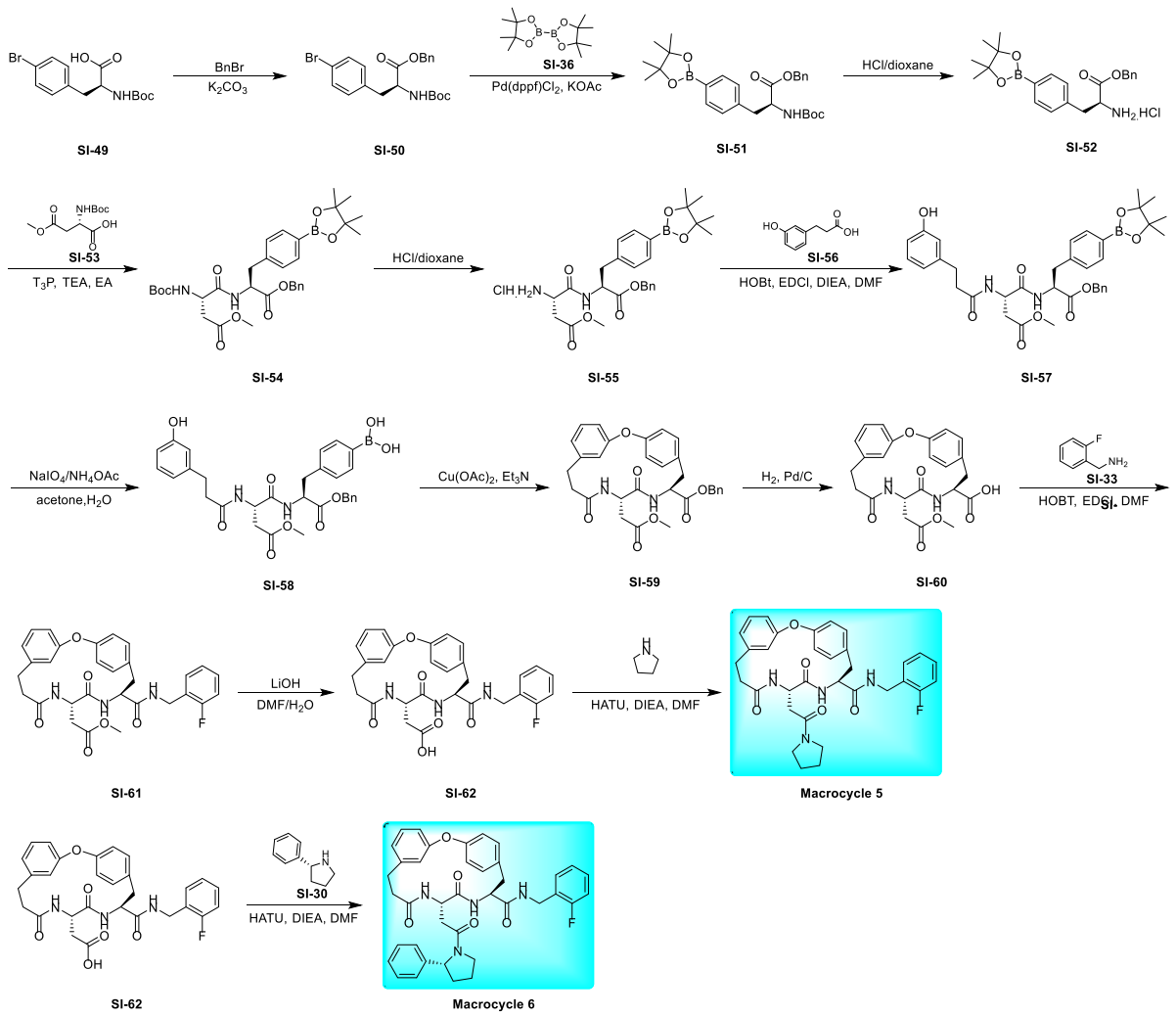
1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.32-6.95 (m, 13H), 6.86-6.80 (m, 3H), 6.13 (br.s, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 4.64-4.63 (m, 1H), 4.42-4.23 (m, 4H), 3.05-3.01 (m, 1H), 2.92-2.66 (m, 3H), 2.47-2.45 (m, 2H), 2.22 (s, 3H), 1.79-1.64 (m, 2H), 1.39 ppm (s, 9H).



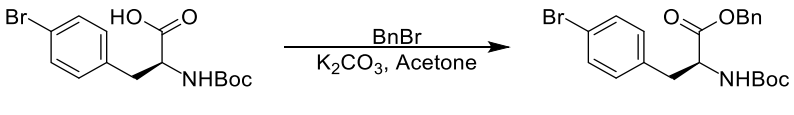
SI-48 **CP1**

To a solution of **SI-48** (150 mg, 217 umol, 1.0 eq) in dichloromethane (10 mL) and tetrahydrofuran (10 mL) was added trifluoroacetic acid (7.7 g, 67 mmol, 5 mL, 311.0 eq) at 25°C and then the reaction mixture was stirred for 12 hours at 25°C. LCMS showed that the reaction was completed. The reaction mixture was concentrated in vacuum. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Synergi C18 150mm*25mm*10um, mobile phase: [water (0.1%TFA)-ACN]; B%: 25%-55%, 12 min) to give the product with as TFA salt. The product was redissolved in water (5 mL) and the mixture was adjusted to pH=9 with aqueous sodium bicarbonate. The solid was precipitated out and collected to give **CP1** (32.0 mg, 54 umol, 25% yield, 100% purity) as a white solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 8.55 (t, *J* = 6.2 Hz, 1H), 8.42 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.35 – 7.19 (m, 4H), 7.18 – 6.99 (m, 8H), 6.99 – 6.89 (m, 2H), 6.89 – 6.84 (m, 1H), 6.75 (s, 1H), 6.19 (s, 1H), 4.62 (t, *J* = 10.7 Hz, 1H), 4.43 (dd, *J* = 15.0, 7.3 Hz, 1H), 4.29 (dd, *J* = 15.2, 6.2 Hz, 1H), 4.21 (dd, *J* = 15.1, 5.7 Hz, 1H), 3.57 (s, 1H), 3.00 (d, *J* = 12.9 Hz, 1H), 2.90 – 2.79 (m, 1H), 2.74 – 2.62 (m, 2H), 2.22 (s, 3H), 1.82 – 1.51 ppm (m, 4H). *m*/*z* = 591.5 $[MS+H]^+$

SFC of **CP1**: RT = 2.73 min; de% = 100%



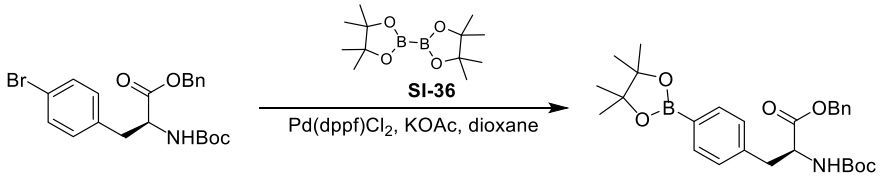
Scheme S4. Synthetic route of **Macrocycle 5** and **6**.



SI-49 **SI-50**

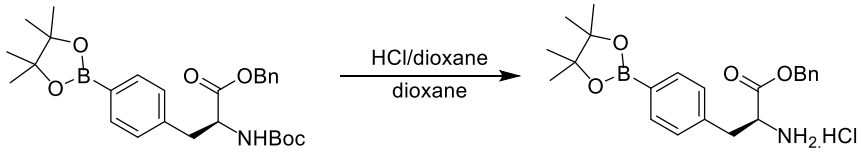
To a solution of compound **SI-49** (11 g, 31.9 mmol, 1.0 *eq*) in acetone (110 mL) was added potassium carbonate (4.86 g, 35.1 mmol, 1.1 *eq*) and benzyl bromide (6.01 g, 35.1 mmol, 1.1 *eq*). The reaction mixture was stirred at 26°C for 48 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The residue was filtered and the filtrate was concentrated in vacuum to give compound **SI-50** (14 g, 30.7 mmol, 96% yield, 95% purity) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28-7.16 (m, 7H), 6.79 (d, J = 8.4 Hz, 2H), 5.10 (d, J = 12.0 Hz,

1H), 5.00 (d, *J* = 12.4 Hz, 1H), 4.90 (d, *J* = 7.6 Hz, 1H), 4.53-4.48 (m, 1H), 2.96-2.91 (m, 2H), 1.32 ppm (s, 9H).



SI-50 **SI-51**

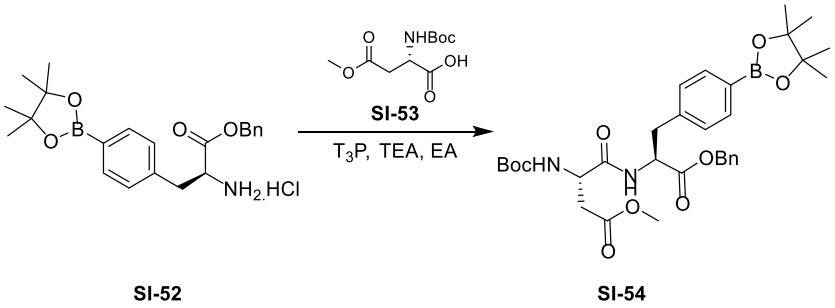
To a mixture of compound **SI-50** (21 g, 48.3 mmol, 1.0 eq), compound **SI-36** (12.28 g, 48.35 mmol, 1.0 eq), potassium acetate (14.24 g, 145.0 mmol, 3.0 eq) in dioxane (210 mL) was added $Pd(dppf)Cl_2$ (3.54 g, 4.84 mmol, 0.1 eq) under nitrogen. The reaction mixture was degassed in vacuum and purged with nitrogen for 3 times and stirred at 80°C for 12 hours under nitrogen. TLC (petroleum ether: ethyl acetate= 3:1) showed that the starting material was consumed completely and one main new spot was observed. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate= 10:1 to 3:1) to give compound **SI-51** (20 g, 39.9 mmol, 83% yield, 96% purity) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.70 (d, *J* = 7.6 Hz, 2H), 7.39-7.34 (m, 3H), 7.29-7.27 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 8.4 Hz, 1H), 4.66-4.60 (m, 1H), 3.16-3.06 (m, 2H), 1.42 (s, 9H), 1.34 ppm (s, 12H).



SI-51 **SI-52**

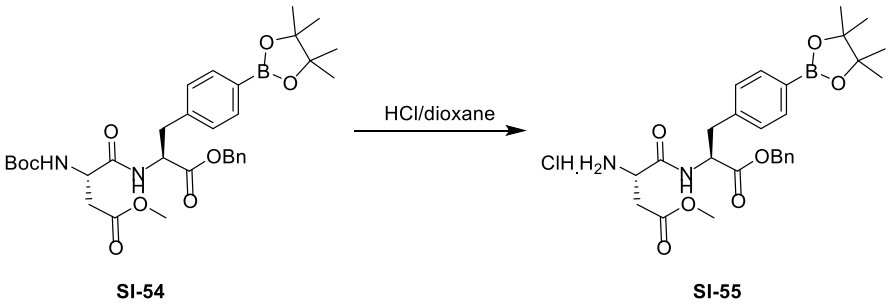
To a mixture of compound **SI-51** (5.3 g, 11.0 mmol, 1.0 eq) in dioxane (30 mL) was added a solution of hydrogen chloride in dioxane (4M, 50 mL, 18.17 eq). The mixture was stirred at 26°C for 4 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The reaction mixture was concentrated in vacuum to give compound **SI-52** (4.6 g, 9.4 mmol, 85% yield, 85% purity, HCl salt) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.87 (br.s, 2H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.27-7.25 (m, 3H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.13-7.11 (m, 2H), 5.09 (d, *J* = 12.0 Hz, 1H),

5.00 (d, *J* = 12.0 Hz, 1H),4.46-4.43 (m, 1H), 3.51-3.48 (m, 1H), 3.37-3.32 (m, 1H), 1.31 (s, 12H).



SI-52 **SI-54**

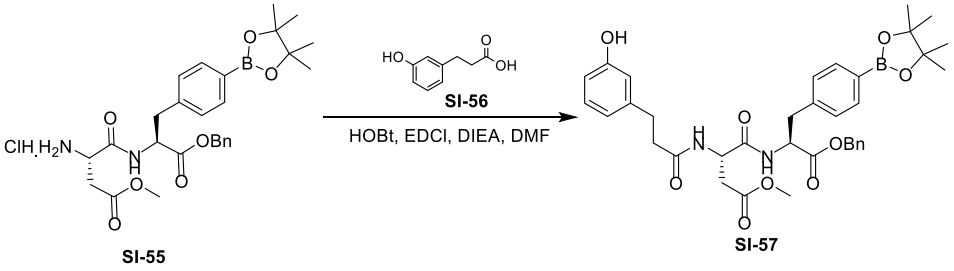
To a solution of compound **SI-53** (266 mg, 1.08 mmol, 1.5 *eq*) in ethyl acetate (5 mL) was added triethylamine (218 mg, 2.15 mmol, 3.0 *eq*) and propylphosphonic anhydride (914 mg, 1.44 mmol, 50% purity, 2.0 eq). Then compound **SI-52** (300 mg, 718 umol, 1.0 eq) was added into above reaction mixture and the resulting mixture was stirred at 26°C for 4 hours. LCMS showed that the starting material was consumed and the desired MS was detected. The reaction mixture was poured into water (15 mL) and extracted with ethyl acetate (30 mL*3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether: ethyl acetate= 10:1 to 3:1) to give compound **SI-54** (380 mg, 542 umol, 76% yield, 87% purity) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.71 (d, *J* = 7.6 Hz, 2H), 7.37-7.34 (m, 3H), 7.26-7.24 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 5.64 (d, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 4.88-4.83 (m, 1H), 4.52-4.49 (m, 1H), 3.68 (s, 3H), 3.13 (d, *J* = 6.0 Hz, 2H), 3.06-2.96 (m, 1H), 2.66 (dd, J_1 = 6.0 Hz, J_2 = 17.2 Hz, 1H), 1.42 (s, 9H), 1.35 (s, 12H).



SI-54 **SI-55**

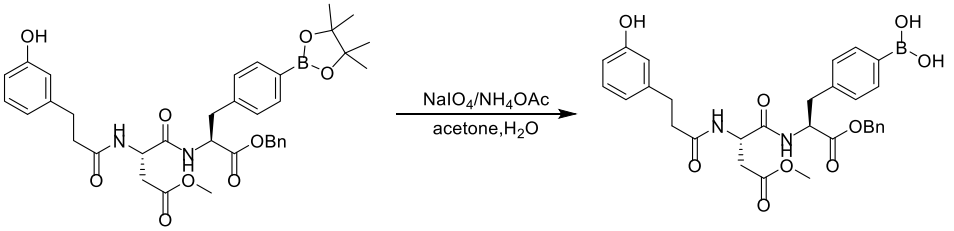
To a solution of compound **SI-54** (3.0 g, 4.9 mmol, 1.0 *eq*) in dioxane (10 mL) was added a solution of hydrogen chloride in dioxane (4M, 10 mL, 8.2 *eq*). The reaction mixture was stirred at 25°C for 2 hours. LCMS showed that the starting material was

consumed completely and the desired MS was detected. The reaction mixture was concentrated in vacuum to give compound **SI-55** (2.8 g, crude, HCl salt) as a white solid. ^{1}H NMR (CD_3OD, 400 MHz) δ = 7.66 (d, J = 8.0 Hz, 2H), 7.37-7.28 (m, 5H), 7.21 (d, J = 7.6 Hz, 2H), 5.16 (d, J = 12.0 Hz, 1H), 5.11 (d, J = 12.4 Hz, 1H), 4.80 (dd, J_1 = 5.6 Hz, J_2 = 8.8 Hz, 1H), 4.18 (dd, J_1 = 3.6 Hz, J_2 = 9.2 Hz, 1H), 3.73 (s, 3H), 3.25 (dd, J_1 = 5.6 Hz, J_2 = 14.0 Hz, 1H), 3.03 (dd, J_1 = 8.8 Hz, J_2 = 14.0 Hz, 1H), 2.93 (dd, J_1 = 9.2 Hz, J_2 = 14.0 Hz, 1H), 2.81-2.74 (m, 1H), 1.34 ppm (s, 12H).



SI-55 SI-57

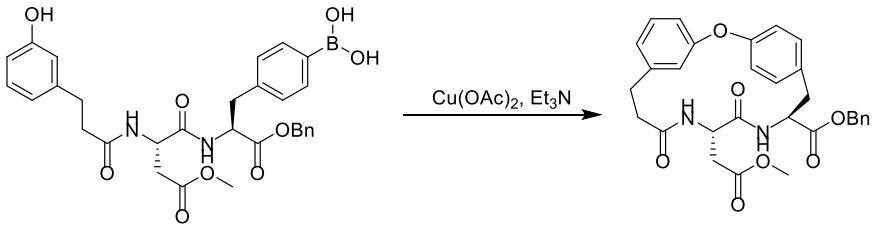
To a solution of compound **SI-55** (2.7 g, 4.9 mmol, 1.0 *eq*) in N,N-dimethylformamide (20 mL) was added 1-hydroxybenzotriazole (867 mg, 6.42 mmol, 1.3 *eq*), diisopropylethylamine (3.19 g, 24.7 mmol, 5.0 *eq*) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.23 g, 6.42 mmol, 1.3 *eq*). Then compound **SI-56** (820 mg, 4.94 mmol, 1.0 *eq*) was added into above mixture at 0°C. After addition, the reaction mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The reaction mixture was poured into hydrochloric acid (1M, 50 mL) at 0°C and extracted with EA (50 mL*3). The combined organic phases were washed with brine (50 mL*3), dried over sodium sulphate, filtered and concentrated in vacuum to give compound **SI-57** (3.2 g, crude) as yellow oil.



SI-57 SI-58

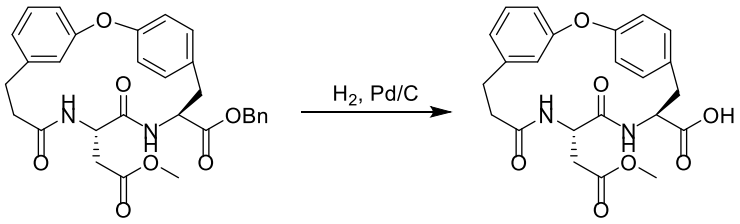
To a solution of compound **SI-57** (3.2 g, 4.8 mmol, 1.0 *eq*) in acetone (15 mL) and water (10 mL) was added sodium periodate (3.12 g, 14.6 mmol, 3.0 *eq*) and ammonium

acetate (1.12 g, 14.6 mmol, 3.0 *eq.*). The mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The reaction mixture was poured into water (40 mL) and then extracted by ethyl acetate (40 mL*3). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated in vacuum to give the crude product. The crude product was purified by reverse phase flash (formic acid) to give compound **SI-58** (920 mg, 1.56 mmol, 32% yield, 98% purity) as a yellow solid. ^{1}H NMR (CD_3OD, 400MHz) δ = 7.64 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.33-7.28 (m, 5H), 7.14-7.06 (m, 3H), 6.66-6.58 (m, 3H), 5.15-5.09 (m, 2H), 4.76-4.66 (m, 2H), 3.62 (s, 3H), 3.15-3.10 (m, 1H), 3.04-2.98 (m, 1H), 2.77 (t, J = 8.0 Hz, 2H), 2.68 (dd, J_1 = 6.4 Hz, J_2 = 8.4 Hz, 1H), 2.54 (dd, J_1 = 6.8 Hz, J_2 = 8.4 Hz, 1H), 2.42 ppm (t, J = 8.0 Hz, 2H).



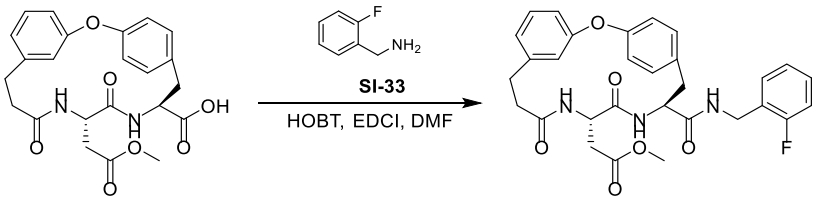
SI-58 **SI-59**

To a soluiton of compound **SI-58** (50 mg, 87 umol, 1.0 *eq*) in dichloromethane (2 mL) was added triethylamine (9 mg, 87 umol, 1.0 *eq*), copper acetate (16 mg, 87 umol, 1.0 *eq*) and 4Å molecular sieves (200 mg). The mixture was stirred at 20°C for 16 hours under oxygen. LCMS showed that the starting material was consumed completely and the desired product was detected. The mixture was filtered and the cake was washed with isopropanol (5 mL). The filtrate was concentrated in vacuum to give the crude product. The crude product was purified by silica gel chromatography column (petroleum ether: ethyl acetate= 5:1 to 2:1) to give compound **SI-59** (36 mg, 59 umol, 68% yield, 87% purity) as a yellow brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.41-7.38 (m, 5H), 7.31 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.09-7.04 (m, 2H), 7.00-6.96 (m, 2H), 6.87 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.48 (J = 6.8 Hz, 1H), 6.31 (br.s, 1H), 5.27 (d, J = 12.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.01-4.98 (m, 1H), 4.62-4.58 (m, 1H), 3.69 (s, 3H), 3.39 (dd, J_1 = 4.4 Hz, J_2 = 9.2 Hz, 1H), 3.30-3.24 (m, 1H), 2.82 (dd, J_1 = 3.2 Hz, J_2 = 17.2 Hz, 1H), 2.72-2.38 ppm (m, 5H).



SI-59 **SI-60**

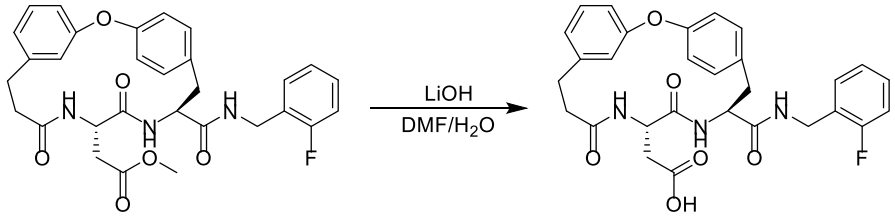
To a solution of compound **SI-59** (380 mg, 716 umol, 1.0 *eq*) in dichloromethane (7 mL) and isopropanol (15 mL) was added Pd/C (38 mg, 10% purity). The reaction mixture was degassed and purged with hydrogen for three times and then the mixture was stirred at 25°C for 2 hours under hydrogen balloon. LCMS showed that the starting material was consumed completely and the desired product was detected. The mixture was filtered and then the filtrate was concentrated in vacuum to give compound **SI-60** (330 mg, crude) as a white solid.



SI-60 **SI-61**

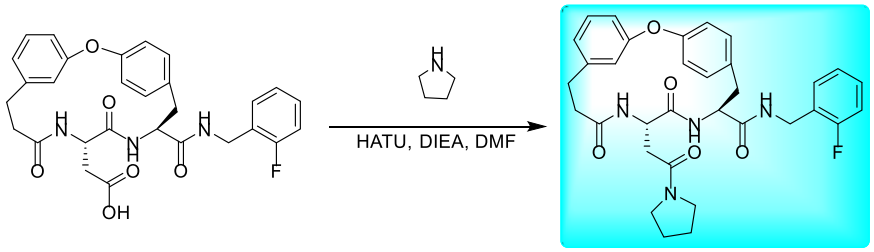
To a solution of compound **SI-60** (170 mg, 386 umol, 1.0 *eq*) in N,N-dimethyl formamide (5 mL) was added diisopropylethylamine (100 mg, 772 umol, 2.0 *eq*), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 502 umol, 1.3 *eq*) and 1-hydroxybenzotriazole (68 mg, 502 umol, 1.3 *eq.*) at 0°C under nitrogen. Then compound **SI-33** (58 mg, 463 umol, 1.2 *eq.*) was added to above mixture. The mixture was stirred at 25°C for 6 hours. LCMS showed that the desired MS was detected. The mixture was poured into water (20 mL) and extracted with ethyl acetate (20 mL*3). The combined organic phases were washed by brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give compound **SI-61** (190 mg, 337 umol, 87% yield, 97% purity) as a yellow solid. ^{1}H NMR (DMSO-*d6*, 400 MHz) δ = 8.42 (d, J = 9.6 Hz, 1H), 8.36 (t, J = 5.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.36-7.30 (m, 3H), 7.23-7.17 (m, 4H), 6.96 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.70 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 6.22 (br.s, 1H), 4.70-4.61 (m, 2H), 4.41-4.35 (m, 2H), 3.48 (s, 3H),

3.23 (dd, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 3.09 (dd, J_1 = 8.4 Hz, J_2 = 15.2 Hz, 1H), 2.64-2.55 (m, 3H), 2.44-2.39 (m ,2H), 2.18 ppm (dd, J_1 = 8.4 Hz, J_2 = 14.4 Hz, 1H).



SI-61 **SI-62**

To a solution of compound **SI-61** (180 mg, 328 umol, 1.0 eq) in N,N-dimethyl formamide (3 mL) was added a solution of lithium hydroxide monohydrate (41 mg, 986 umol, 3.0 eq) in water (3 mL) at 0°C. The reaction mixture was stirred at 26°C for 3 hours. LCMS showed that the starting material was consumed completely and the desired product was detected. The reaction mixture was diluted with water (5 mL), acidified by hydrochloric acid (1M, 5 mL) at 0°C and extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (20 mL*3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give compound **SI-62** (190 mg, 234 umol, 71% yield, 66% purity) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.36-8.28 (m, 1H), 8.06-7.92 (m, 2H), 7.72-7.69 (m, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.35-7.26 (m, 3H), 7.23-7.18 (m, 3H), 6.98-6.91 (m, 2H), 6.84 (t, J = 6.4 Hz, 1H), 6.74-6.71 (m, 1H), 6.21 (br.s, 1H), 4.70-4.60 (m, 2H), 4.40-4.33 (m, 2H), 3.25-2.99 (m, 1H), 2.67-2.65 (m, 2H), 2.61-2.55 (m, 2H), 2.34-2.32 (m, 2H), 2.23-2.13 ppm (m, 1H).

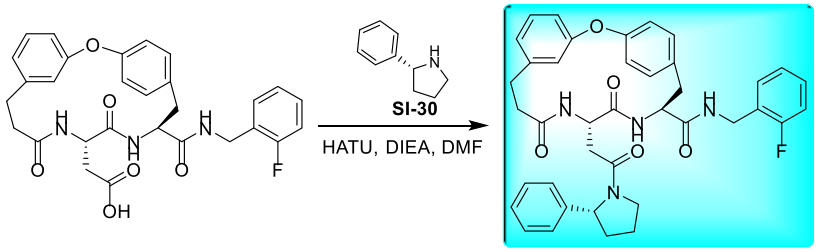


SI-62 **Macrocycle 5**

To a solution of compound **SI-62** (95 mg, 178 umol, 1.0 *eq*) in N,N-dimethyl formamide (3 mL) was added N, N-diisopropylethylamine (69 mg, 534 umol, 3.0 *eq*) and HATU (102 mg, 267 umol, 1.5 *eq*) at 0°C. Then amine (19 mg, 267 umol, 1.5 *eq*) was added

into above mixture and the reaction mixture was stirred at 26°C for 3 hours. LCMS showed that the starting material was consumed completely and the desired product was detected. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (20 mL*3). The combined organic layer was washed with brine (20 mL*3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by prep-HPLC (column: Phenomenex Synergi C18, 150 mm*25 mm*10 um; mobile phase: [water (0.1% TFA) –ACN]; B%: 32%-62%, 13min) to give the major product of **Macrocycle 5** (19.0 mg, 32 umol, 18% yield, 100% purity) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.50 (t, *J* = 6.0 Hz, 1H), 8.45 (d, *J* = 9.4 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.24 – 7.10 (m, 3H), 7.01 – 6.92 (m, 2H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.21 (s, 1H), 4.64 – 4.50 (m, 2H), 4.42 (dd, *J* = 15.5, 6.0 Hz, 1H), 4.32 (dd, *J* = 15.4, 5.6 Hz, 1H), 3.16 (d, *J* = 5.3 Hz, 1H), 3.14 – 3.03 (m, 3H), 3.02 – 2.92 (m, 1H), 2.73 – 2.64 (m, 3H), 2.38 – 2.30 (m, 3H), 2.24 (dd, *J* = 16.2, 7.7 Hz, 1H), 1.85 – 1.76 (m, 2H), 1.73 – 1.56 (m, 2H). *m*/*z*= 587.4 $[MS+H]^{+}$.

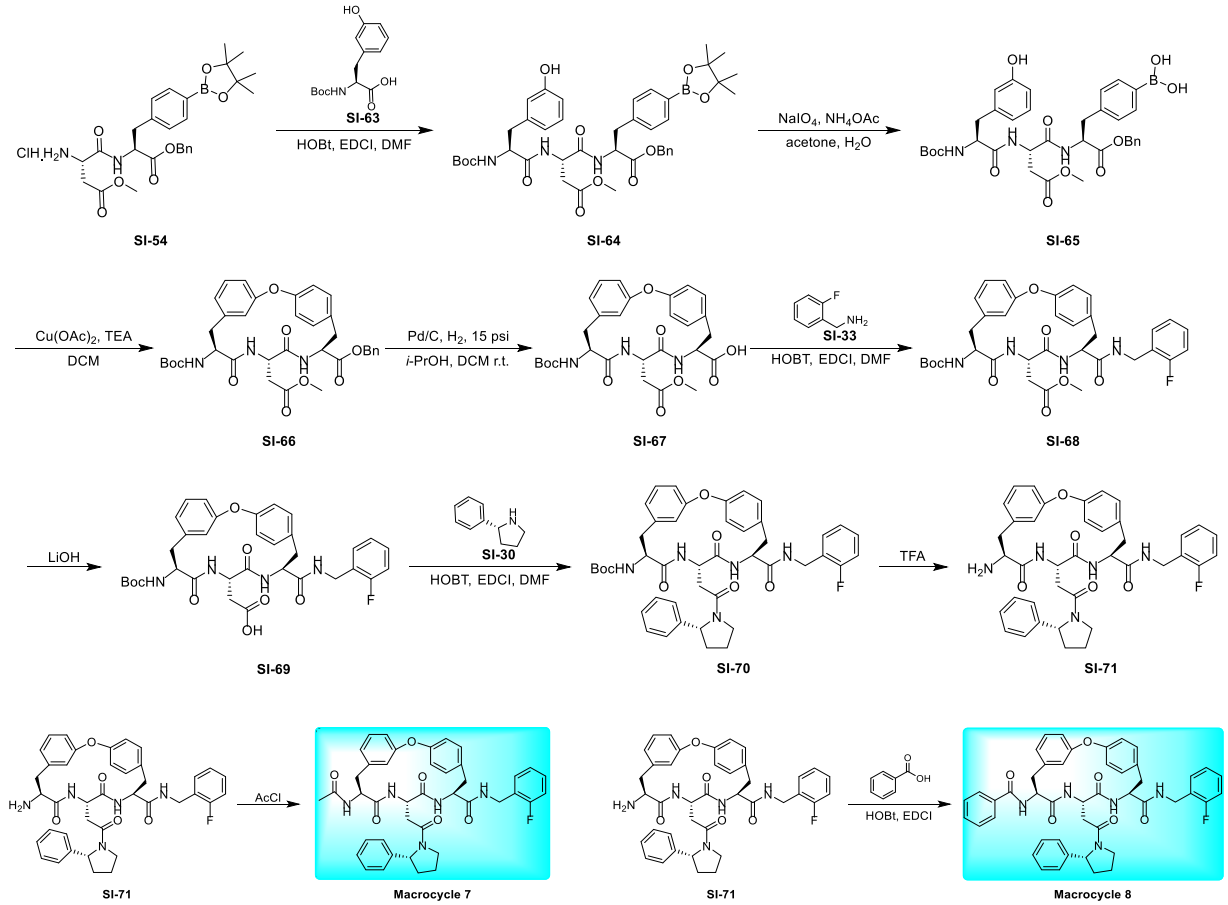
SFC of **Macrocycle 5**: RT_1 = 2.867 min; de% = 100%



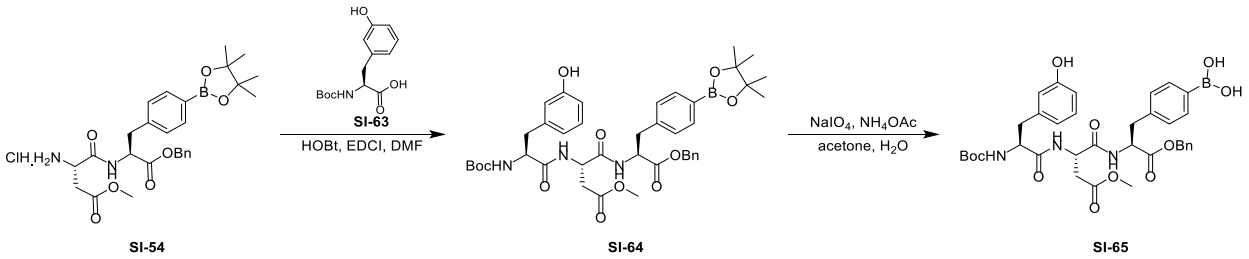
To a solution of compound **SI-62** (95 mg, 178 umol, 1.0 eq) in N,N-dimethyl formamide (3 mL) was added N,N-diisopropylethylamine (69 mg, 534 umol, 3.0 eq) and HATU (102 mg, 267 umol, 1.5 eq) at 0°C. Then compound **SI-30** (39 mg, 213 umol, 1.2 eq, HCl salt) was added into above mixture and the resulting mixture was stirred at 26°C for 3 hours. LCMS showed that the starting material was consumed completely and the desired MS was detected. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL*3). The combined organic layers were washed with brine (20 mL*3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18,

150mm*25mm*10um; mobile phase: [water (0.1%TFA)-ACN]; B%: 40%-70%, 13min) to give the major product **Macrocycle 6** (15.0 mg, 23 umol, 13% yield, 100% purity) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.58-7.56 (m, 0.4H), 7.51-7.46 (m, 0.7H), 7.36-7.28 (m, 5H), 7.25-7.14 (m, 3H), 7.10-6.94 (m, 7H), 6.87-6.83 (m, 2H), 6.62-6.49 (m, 0.4H), 6.22-6.14 (m, 2H), 4.89-4.72 (m, 2H), 4.59-4.41 (m, 3H), 3.73-3.47 (m, 3H), 3.33-3.20 (m, 1H), 2.81-2.78 (m, 0.4H), 2.71-2.60 (m, 2.6H), 2.55-2.25 (m, 3H), 2.12-1.76 ppm (m, 4H). *m/z*= 663.5 $[MS+H]^+$.

SFC of **Macrocycle 6**: RT_1 = 2.833 min; de% = 100%

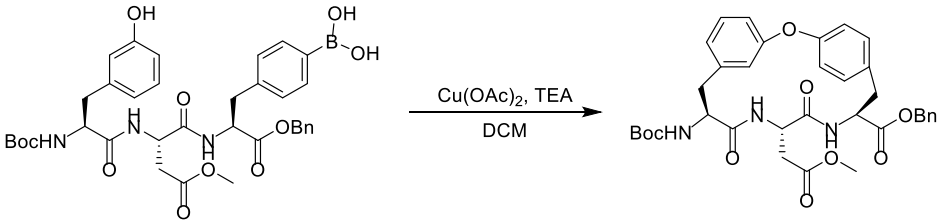


Scheme S5. Synthetic route of **Macrocycle 7** and **8**.



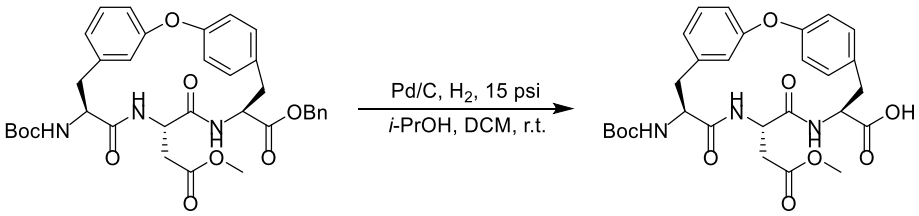
To a solution of compound **SI-54** (3.52 g, 6.44 mmol, 1.0 eq, HCl), 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride (1.72 g, 8.95 mmol, 1.4 eq), 1-hydroxy benzotriazole (1.21 g, 8.95 mmol, 1.4 eq) and diisopropylethylamine (4.46 g, 34.5 mmol, 5.4 eq) in N,N-dimethylformamide (30 mL) was added compound **SI-63** (2.14 g, 7.60 mmol, 1.2 eq) at 0°C under nitrogen. The mixture was stirred at 25°C for 16 hours. LCMS showed that the starting material was consumed completely. The mixture was diluted with water (50 mL) and extracted by ethyl acetate (100 mL*3). The combined organic phases were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated in vacuum to give compound **SI-64** (6 g, crude) as red oil, which was used directly in next step without purification.

To a solution of compound **SI-64** (5 g, 6.46 mmol, 1.0 eq) in acetone (50 mL) was added a solution of sodium periodate (4.15 g, 19.4 mmol, 3.0 eq) and ammonium acetate (1.49 g, 19.4 mmol, 3.0 eq) in water (40 mL) at 25°C and the reaction mixture was stirred for 12 hours at 25°C. LCMS showed that the starting material was consumed completely. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL*3). The combined organic phases were washed with brine (150 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse phase falsh (HCl condition) to give compound **SI-65** (1.4 g, 2.0 mmol, 31% yield, 99% purity) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.94 (d, *J* = 7.2 Hz, 0.7H), 7.63 (d, *J* = 7.2 Hz, 1.3H), 7.50-7.30 (m, 6H), 7.18-7.11 (m, 1.7H), 7.05-6.93 (m, 2.3H), 6.78-6.55 (m, 3H), 6.22 (br.s, 1H), 5.29-5.16 (m, 2H), 5.06-4.82 (m, 2H), 4.34-4.16 (m, 1H), 3.65 (s, 3H), 3.21-2.65 (m, 6H), 1.39 ppm (s, 9H).



SI-65 **SI-66**

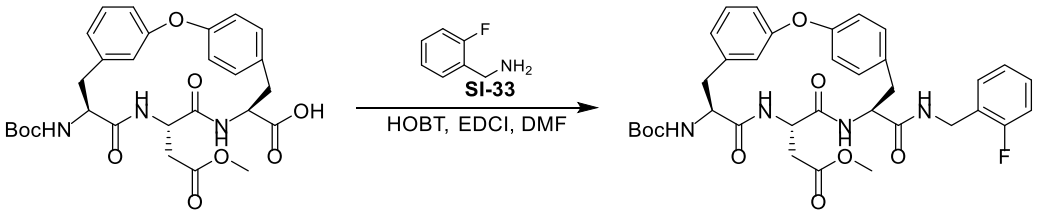
To a solution of compound **SI-65** (1.5 g, 2.17 mmol, 1.0 eq) in dichloromethane (150 mL) was added copper acetate (394 mg, 2.17 mmol, 1.0 eq), triethylamine (2.2 g, 21.7 mmol, 10.0 eq) and 4Å molecular sieves (2.0 g, 434 umol) at 25°C and the reaction mixture was stirred at 25°C for 12 hours under oxygen. LCMS showed that the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (SiO_2, petroleum ether: ethyl acetate= 10:1 to 1:1) to give compound **SI-66** (620 mg, 935 umol, 43% yield, 97% purity) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.43-7.29 (m, 8H), 7.22 (t, J = 8.0 Hz, 1H), 7.11 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.07-7.01 (m, 2H), 6.89 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 6.74-6.69 (m, 2H), 5.90 (br.s, 1H), 5.25-5.20 (m, 2H), 4.99-4.93 (m, 1H), 4.61-4.56 (m, 1H), 4.44-4.41 (m, 1H), 3.69 (s, 3H), 3.43 (dd, J_1 = 4.0 Hz, J_2 = 13.2 Hz, 1H), 3.21 (dd, J_1 = 5.6 Hz, J_2 = 14.0 Hz, 1H), 2.80-2.60 (m, 4H), 1.45 ppm (s, 9H).



SI-66 **SI-67**

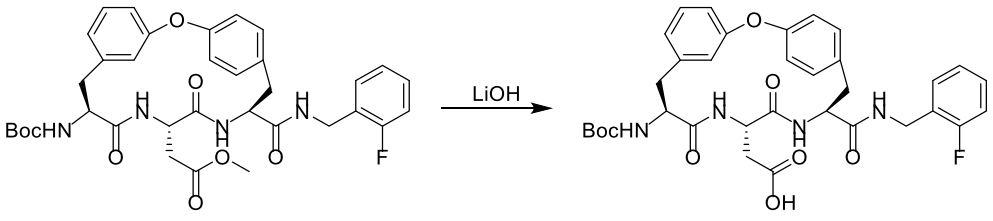
To a solution of compound **SI-66** (600 mg, 929 umol, 1.0 eq) in isopropanol (30 mL) and dichloromethane (5 mL) was added Pd/C (200 mg, 5% purity) under nitrogen. The suspension was degassed in vacuum and purged with hydrogen for several times. The mixture was stirred at 25°C for 12 hours under hydrogen (15 psi). LCMS showed that the starting material was consumed completely. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give compound **SI-67** (385 mg, 683 umol, 74% yield, 98% purity) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42 (d, J = 10.0 Hz,

1H), 7.36 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.28-7.22 (m, 3H), 7.13 (dd, J_1 = 1.2 Hz, J_2 =8.4 Hz, 1H), 7.05-7.02 (m, 2H), 6.89 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.88 (br.s, 1H), 5.32 (d, J = 8.0 Hz, 1H), 5.02-4.96 (m, 1H), 4.74-4.69 (m, 1H), 4.59-4.56 (m, 1H), 3.66 (s, 3H), 3.45 (dd, J_1 = 3.6 Hz, J_2 = 13.2 Hz, 1H), 3.11 (dd, J_1 = 5.6 Hz, J_2 = 14.4 Hz, 1H), 2.82-2.72 (m, 3H), 1.47 ppm (s, 9H).



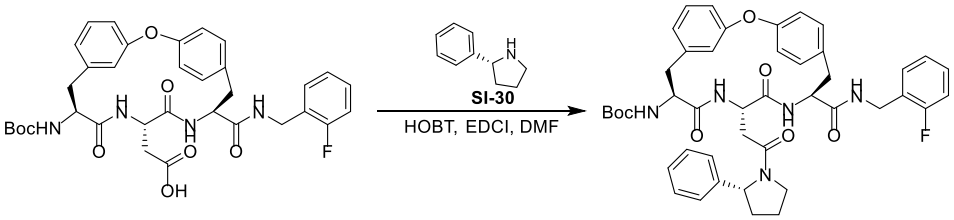
SI-67 **SI-68**

To a solution of compound **SI-67** (600 mg, 1.08 mmol, 1.0 eq) in N,N-dimethyl formamide (15 mL) was added 1-hydroxybenzotriazole (190 mg, 1.4 mmol, 1.3 eq), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (269 mg, 1.40 mmol, 1.3 eq) and diisopropylethylamine (279 mg, 2.16 mmol, 2.0 eq) at 0°C. Then compound **SI-33** (162 mg, 1.30 mmol, 1.2 eq) was added to above mixture. The reaction mixture was stirred at 25°C for 12 hours. LCMS showed that the starting material was consumed completely. The mixture was diluted with water (40 mL) and some solid was formed. The mixture was filtered to give compound **SI-68** (750 mg, 1.0 mmol, 92% yield, 88% purity) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.98-7.91 (m, 2H), 7.70 (d, J = 9.6 Hz, 1H), 7.30-7.14 (m, 6H), 7.08-6.98 (m, 3H), 6.89 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 7.2 Hz, 1H), 5.37 (d, J = 8.4 Hz, 1H), 5.04-4.99 (m, 1H), 4.90-4.80 (m, 1H), 4.75-4.70 (m, 1H), 4.63 (dd, J_1 = 6.4 Hz, J_2 = 15.2 Hz, 1H), 4.26 (dd, J_1 = 3.6 Hz, J_2 = 14.8 Hz, 1H), 3.51 (s, 3H), 3.25 (d, J = 10.4 Hz, 1H), 2.93-2.64 (m, 5H), 1.43 ppm (s, 9H).



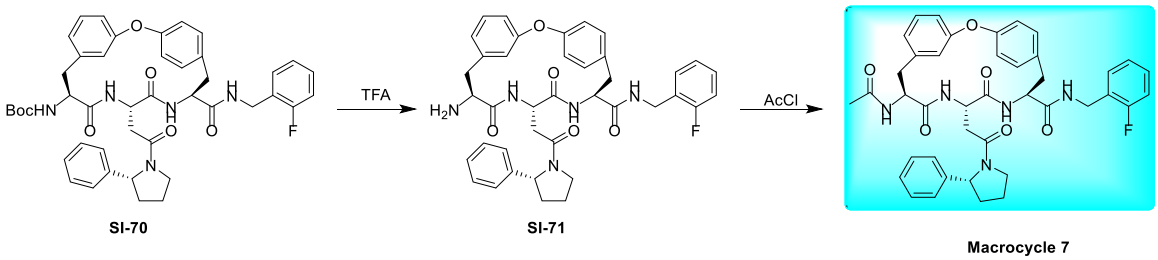
SI-68 **SI-69**

To a solution of compound **SI-68** (1.2 g, 1.8 mmol, 1.0 eq) in N,N-dimethyl formamide (15 mL) and water (10 mL) was added lithium hydroxide (228 mg, 5.43 mmol, 3.0 eq) at 0°C and the reaction mixture was stirred at 0°C for 30 min. LCMS showed that the starting material was consumed completely. The reaction mixture was acidified with hydrochloric acid (0.5M) to pH= 4~5. The reaction mixture was filtered and the cake was dried in vacuum to give compound **SI-69** (1.2 g, 1.77 mmol, 98% yield, 96% purity) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 12.50 (br.s, 1H), 8.63-8.60 (m, 1H), 8.00-7.95 (m, 2H), 7.39-7.14 (m, 8H), 7.01 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 6.36 (br.s, 1H), 6.27 (s, 1H), 4.68-4.62 (m, 1H), 4.38 (d, J = 5.6 Hz, 2H), 4.28-4.17 (m, 1H), 4.05-3.97 (m, 1H), 2.86-2.78 (m, 2H), 2.68-2.61 (m, 2H), 2.58-2.52 (m, 2H), 1.38 ppm (s, 9H).



SI-69 **SI-70**

To a solution of compound **SI-69** (500 mg, 770 umol, 1.0 eq) in N,N-dimethyl formamide (10 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimidehy drochloride (222 mg, 1.16 mmol, 1.5 eq), 1-hydroxybenzotriazole (156 mg, 1.16 mmol, 1.5 eq) and diisopropylethylamine (398 mg, 3.08 mmol, 4.0 eq) at 0°C and then compound **SI-30** (156 mg, 847 umol, 1.1 eq, HCl salt) was added to above reaction mixture. The reaction mixture was stirred at 25°C for 12 hours. LCMS showed that the starting material was consumed completely. The reaction mixture was acidified with hydrochloric acid (0.5M) untill pH= 4~5. The reaction mixture was filtered and the cake was dried in vacuum. The residue was purified by prep-HPLC (HCl condition, column: PhenomenexSynergi C18, 150 mm*25mm*10um, mobile phase: [water (0.05%HCl)-ACN]; B%: 56%-76%, 7.8 min) to give the compound **SI-70** (260 mg, 334 umol, 43% yield, 100% purity) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.97 (m, 1H), 7.25-7.10 (m, 8H), 7.09-6.94 (m, 9H), 6.68-6.60 (m, 2H), 5.91 (br.s, 1H), 5.27-5.20 (m, 1H), 5.12-5.08 (m, 1H), 4.90-4.82 (m, 1H), 4.72-4.42 (m, 3H), 3.64-3.14 (m, 2H), 3.01-2.80 (m, 2H), 2.67-2.12 (m, 4H), 2.03-1.93 (m, 2H), 1.88-1.71 (m, 2H), 1.39 ppm (s, 9H).

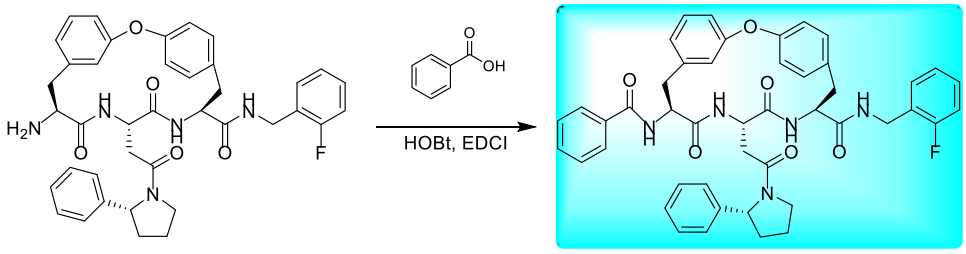


SI-70 SI-71 Macrocycle 7

To a solution of the major compound **SI-70** (270 mg, 347 umol, 1.0 eq) in dichloromethane (6 mL) was added trifluoroacetic acid (4.62 g, 40.5 mmol, 3 mL, 116.74 eq) at 25°C and the reaction mixture was stirred at 25°C for 1 hour. LCMS showed that the starting material was consumed completely. The reaction mixture was concentrated in vacuum to give the major compound **SI-71** (300 mg, crude, TFA salt) as yellow oil, which was used in next step directly.

To a solution of the major compound **SI-71** (120 mg, 152 umol, 1.0 eq, TFA salt) and triethylamine (46 mg, 455 umol, 3.0 eq) in dichloromethane (3 mL) was added acetyl chloride (15 mg, 303 umol, 2.0 eq) at 0°C and the reaction mixture was stirred at 25°C for 0.5 hour. LCMS showed that the starting material was consumed completely. The reaction mixture was concentrated in vacuum. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (20 mL*2). The combined organic phases were washed with brine (20 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (HCl condition, column: PhenomenexSynergi C18 150mm*25mm*10um, mobile phase: [water (0.05%HCl)- ACN]; B%: 45%-65%, 7.8 min) to give **Macrocycle 7** (60.0 mg, 83 umol, 55% yield, 100% purity) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.80 (t, *J* = 5.6 Hz, 1H), 8.56 (d, *J* = 9.7 Hz, 1H), 8.31 (d, *J* = 3.8 Hz, 1H), 7.46 – 7.28 (m, 6H), 7.25 – 7.16 (m, 6H), 7.10 (d, *J* = 7.3 Hz, 1H), 7.01 – 6.90 (m, 3H), 6.53 (d, *J* = 7.4 Hz, 1H), 5.84 (s, 1H), 5.00 (d, *J* = 6.2 Hz, 1H), 4.69 – 4.53 (m, 2H), 4.42 (d, *J* = 5.8 Hz, 2H), 4.23 – 4.12 (m, 1H), 4.07 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.84 (dd, *J* = 16.6, 8.6 Hz, 1H), 3.15 (d, *J* = 10.9 Hz, 1H), 2.97 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.77 – 2.57 (m, 3H), 2.11 (t, *J* = 12.5 Hz, 2H), 2.04 – 1.97 (m, 1H), 1.95 – 1.88 (m, 1H), 1.85 (s, 3H), 1.76 – 1.67 ppm (m, 1H). *m*/*z*= 720.6 $[MS+H]^+$.

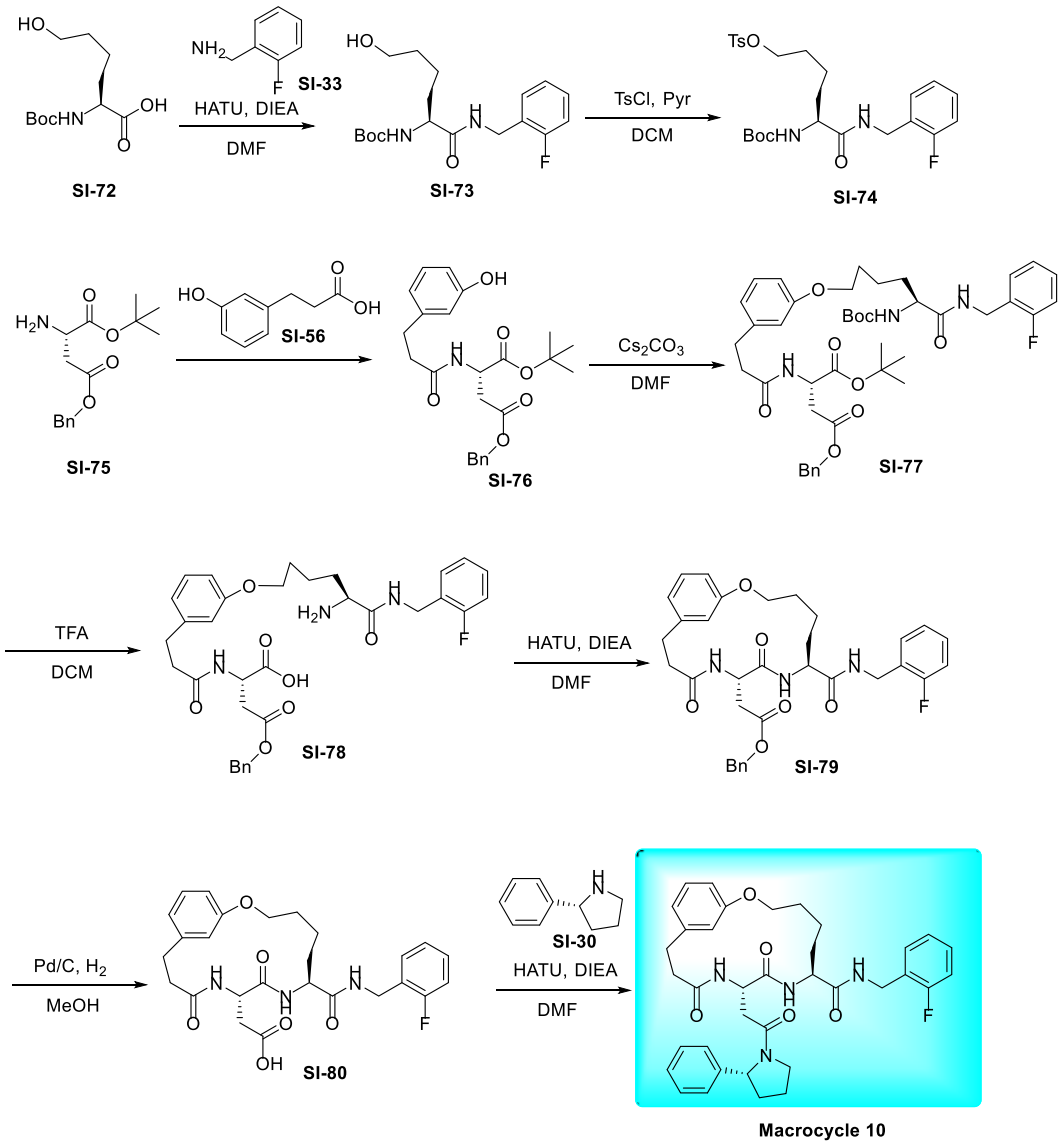
SFC of **Macrocycle 7**: RT = 1.52 min; de% = 100%



SI-71 **Macrocycle 8**

To a solution of benzoic acid (25 mg, 208 umol, 1.1 eq) and 1-hydroxybenzotriazole (38 mg, 284 umol, 1.5 eq), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (54 mg, 284 umol, 1.5 eq) and diisopropylethylamine (73 mg, 568 umol, 3.0 eq) in N,N-dimethylformamide (4 mL) was added the major compound **SI-71** (150 mg, 189.44 umol, 1.0eq, TFA) at 25°C and the reaction mixture was stirred at 25°C for 12 hours. LCMS showed that the starting material was consumed completely. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL*3). The combined organic phases were washed with brine (20 mL*3), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (HCl condition, column: PhenomenexSynergi C18, 150mm*25mm*10um, mobile phase: [water (0.05%HCl)-ACN]; B%: 52%-72%, 7.8 min) to give **Macrocycle 8** (69.2 mg, 88 umol, 47% yield, 99% purity) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.87 (t, J = 5.7 Hz, 1H), 8.66 (d, J = 9.8 Hz, 1H), 8.49 (d, J = 4.3 Hz, 1H), 7.68 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.50 – 7.41 (m, 4H), 7.39 – 7.28 (m, 4H), 7.24 – 7.17 (m, 6H), 7.07 (d, J = 7.2 Hz, 1H), 7.03 – 6.94 (m, 3H), 6.52 (d, J = 7.4 Hz, 1H), 5.92 (s, 1H), 4.98 (d, J = 7.9 Hz, 1H), 4.91 – 4.83 (m, 1H), 4.61 (t, J = 11.0 Hz, 1H), 4.42 (d, J = 5.7 Hz, 2H), 4.21 (t, J = 7.6 Hz, 1H), 4.10 (dd, J = 11.8, 3.6 Hz, 1H), 3.82 (dd, J = 16.3, 8.4 Hz, 1H), 3.23 – 3.10 (m, 2H), 2.76 – 2.61 (m, 3H), 2.19 – 2.06 (m, 2H), 2.06 – 1.99 (m, 1H), 1.98 – 1.85 (m, 1H), 1.74 – 1.65 ppm (m, 1H). m/z= 782.5 $[MS+H]^+$

SFC of **Macrocycle 8**: RT = 3.107 min; de% = 100%.



Scheme S6. Synthetic route of **Macrocycle 10**, **11**, and **12**.

To a solution of 0.500 g (2.02 mmol) of (S)-2-((tert-butoxycarbonyl)amino)-6-hydroxyhexanoic acid **SI-72** in DMF (20 mL) was added 0.28 mg (2.2mmol) of (2-fluorophenyl)methanamine **SI-33** followed by 1.0 mL of DIEA and 0.85 g (2.2 mmol) of HATU. The mixture was stirred at room temperature for 3 hours then diluted with water and extracted with EtOAc. The combined organic phase was washed with a 1N hydrochloric acid solution followed by saturated aqueous solution of sodium bicarbonate and brine. The organic phase was dried over anhydrous sodium sulfate then concentrated under reduced pressure. The residue was purified by flash silica gel

chromatography and the eluent was removed under reduced pressure to provide **SI-73** (0.533 g, 74% yield) as a clear oil.

To a solution of 0.266 g (0.75 mmol) of **SI-73** in DCM (4 mL) was added 0.17 g (0.89 mmol) of TsCl followed by 0.15 mL (1.9 mmol) of pyridine. The mixture was stirred overnight at room temperature then washed with a saturated aqueous solution of sodium bicarbonate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to provide **SI-74** (0.311 g, 81% yield) as a yellow oil. No further purification was performed.

To a solution of 0.250 g (1.50 mmol) of 3-(3-hydroxyphenyl)propanoic acid **SI-56** in DMF (7 mL) was added 0.500 g (1.58 mmol) of 4-benzyl 1-(tert-butyl) L-aspartate hydrochloride **SI-75** followed by 0.65 g (1.7 mmol) of HATU and 0.90 mL (5.2 mmol) of DIEA. The mixture was stirred at room temperatrue for 4 hours then diluted with water and extracted with EtOAc. The combined organic phase was washed with 1N HCl followed by saturated aqueous sodium bicarbonate and brine. The mixture was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography and the eluent was concentrated under reduced pressure to provide **SI-76** (0.587 g, 91%) as a clear oil

To a solution of 0.290 g (0.678 mmol) of **SI-76** in DMF (3 mL) was added 0.311 g (0.611 mmol) of **SI-74** was added as a solution in DMF (3 mL). To this was added 1.0 g (3.1 mmol) of cesium carbonate. The mixture was stirred at room temperature for 3 days then diluted with water and extracted with DCM. The combined organic phase was washed with water followed by brine then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography and the eluent was removed under reduced pressure to provide **SI-77** (0.227 g, 44% yield) as a light yellow oil.

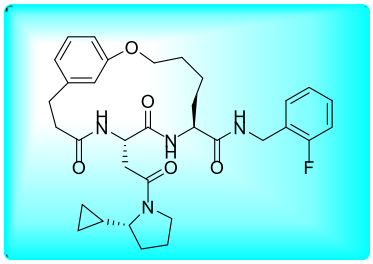
To a solution of 0.113 g (0.148 mmol) of **SI-77** in DCM (1 mL) was added 0.20 mL (2.6 mmol) of TFA. The mixture was stirred overnight at room temperature then concentrated under reduced pressure. The residue was purified by C18 flash reverse phase column chromatography using a gradient of acetonitrile in water w/ 0.1% formic

acid additive. The eluent was removed under reduced pressure to provide **SI-78** (0.090 g, 93% yield) as a clear film.

To a solution of 0.068 g (0.10 mmol) of **SI-78** in DMF (5 mL) was added 0.075 mL (0.43 mmol) of DIEA followed by 0.045 g (0.12 mmol) of HATU. The mixture was allowed to stir at room temperature for 4 days then purified by flash C18 reverse phase chromatography using a 5-95% gradient of acetonitrile in water w/ 0.1% formic acid additive. The eleunt was removed udner reduced pressure and the residue triturated with a 1:1 mixture of acetonitrile : water to provide **SI-79** (0.021 g, 34% yield) as a white powder.

To a flask containing 0.020 g (0.034 mmol) of **SI-79** was added 0.005 g (0.005 mmol) of 10% palladium on carbon. The flask was evacuated and refilled with nitogen three times. To this was added a 1:1 mixture of methanol : ethyl acetate (5 mL). The atmosphere was replaced with hydrogen and the mixture was stirred at room temperature for 1 hour. The mixutre was filtered through a syringe filter and concentrated under reduced pressure to provide **SI-80** (0.017 g, quant) as a white powder. No further purification was performed.

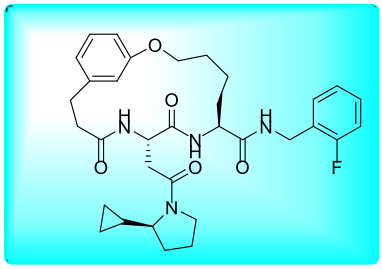
To a solution of 0.017 g (0.034 mmol) of **SI-80** in DMF (1 mL) was added 0.018 mL (0.10 mmol) of DIEA and 0.010 g (0.068 mmol) of (R)-2-phenylpyrrolidine. To the mixture was added 0.015 g (0.039 mmol) of HATU. The mixture was stirred overnight at room temperature then purified by preparative reverse phase chrmotography using a 5-95% gradient of acetonitrile in water w/ 0.1% formic acid additive. The eluent was removed under reduced pressure to provide **Macrocycle 10** (0.006 g, 28% yield) of as a white powder. ^{1}H NMR (500 MHz, CD3OD) δ = 7.40 – 7.17 (m, 4H), 7.17 – 6.97 (m, 5H), 6.97 – 6.92 (m, 1H), 6.76 – 6.65 (m, 3H), 5.04 (d, *J* = 7.4 Hz, 0.45H), 4.79 (td, *J* = 12.2, 3.8 Hz, 0.70H), 4.66 – 4.44 (m, 1H), 4.42 – 4.18 (m, 2H), 4.17 – 3.97 (m, 2H), 3.76 – 3.49 (m, 1H), 3.46 – 3.36 (m, 0.57H), 3.23 – 3.14 (m, 0.45H), 3.05 – 2.97 (m, 1H), 2.80 – 2.69 (m, 1H), 2.60 – 2.29 (m, 3H), 2.08 – 1.68 (m, 4H), 1.64 – 1.39 pppm (m, 4H). m/z 629.5 $[MS+H]^{+}$.



Macrocycle 11

Macrocycle 11 was synthesized in a similar fashion to **Macrocycle 10**. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.25 – 8.15 (m, 1H), 8.14 – 8.02 (m, 1H), 7.91 – 7.82 (m, 1H), 7.32 – 7.21 (m, 2H), 7.16 – 7.05 (m, 3H), 6.79 – 6.69 (m, 3H), 4.84 – 4.65 (m, 1H), 4.31 (d, *J* = 6.0 Hz, 2H), 4.21 – 4.12 (m, 1H), 4.10 – 3.99 (m, 2H), 3.60 – 3.42 (m, 1H), 3.32 – 3.28 (m, 1H), 3.03 – 2.94 (m, 2H), 2.89 – 2.79 (m, 1H), 2.76 – 2.63 (m, 2H), 2.43 – 2.32 (m, 2H), 1.97 – 1.71 (m, 4H), 1.64 – 1.51 (m, 4H), 1.45 – 1.34 (m, 2H), 0.89 – 0.77 (m, 1H), 0.40 – 0.18 (m, 3H), 0.11 – -0.06 ppm (m, 1H). m/z 593.5 $[MS+H]^+$.

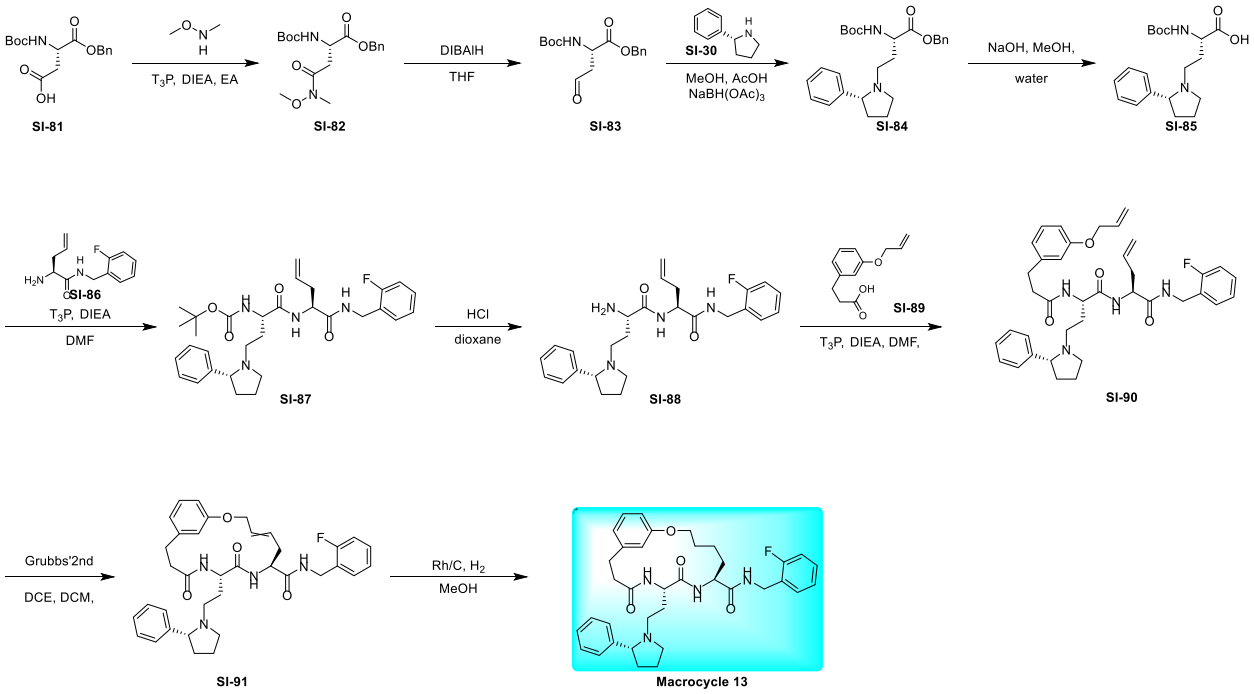
SFC of **Macrocycle 11**: RT= 2.342 min, de %= 100%.



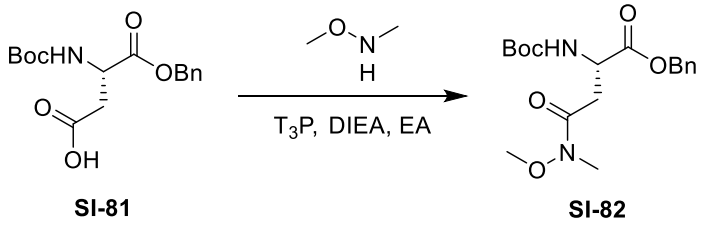
Macrocycle 12

Macrocycle 12 was synthesized in a similar fashion to **Macrocycle 10**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.84 – 7.51 (m, 1H), 7.30 – 7.23 (m, 1H), 7.23 – 7.12 (m, 2H), 7.09 – 7.01 (m, 1H), 7.01 – 6.93 (m, 1H), 6.81 – 6.67 (m, 3H), 6.65 – 6.12 (m, 2H), 4.93 – 4.73 (m, 1H), 4.56 – 4.33 (m, 2H), 4.33 – 4.22 (m, 1H), 4.19 – 4.05 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 0.60H), 3.44 – 3.35 (m, 1H), 3.32 – 3.27 (m, 0.40H), 3.25 – 2.99 (m, 2H), 2.99 – 2.56 (m, 4H), 2.41 – 2.25 (m, 1H), 2.17 – 1.71 (m, 7H), 1.61 – 1.34 (m, 3H), 0.91 – 0.72 (m, 1H), 0.69 – 0.45 (m, 1H), 0.42 – 0.21 (m, 2H), 0.20 – 0.02 ppm (m, 1H). m/z 593.5 $[MS+H]^+$.

SFC of **Macrocycle 12**: RT= 2.522 min, de %= 98%.

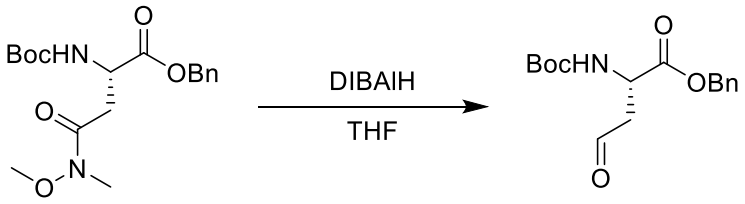


Scheme S7. Synthetic route of **Macrocycle 13**.



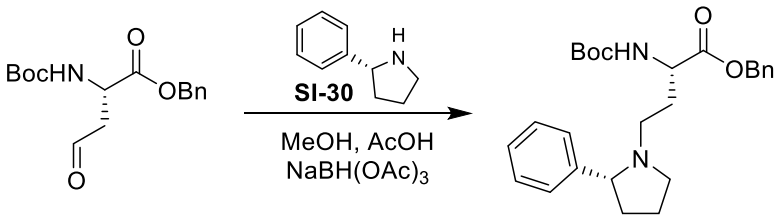
To a solution of (S)-4-(benzyloxy)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoic acid (**SI-81**) (2.00 g, 6.19 mmol), N-methoxymethanamine as the hydrochloric salt (0.756 g, 12.4 mmol) in dichloromethane (20 mL) was added diisopropylethylamine (4.00 g, 30.9 mmol) and T_3P (5.12 g, 8.05 mmol, 50% purity in ethyl acetate) at 0°C. The mixture was stirred for 1 hour at 0°C. The reaction mixture was diluted ethyl acetate (50 mL), washed with a saturated aqueous solution of sodium bicarbonate (50 mL), brine (50 mL), 1N hydrochloric acid (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to afford benzyl nitrogen-(tert-butoxycarbonyl)-N4-methoxy-N4-methyl -L-asparaginate (**SI-82**) (2.10 g, 5.73 mmol, 93%

yield) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 - 7.30 (m, 5H), 5.77 (d, J = 8.8 Hz, 1H), 5.32 - 5.08 (m, 2H), 4.71 - 4.55 (m, 1H), 3.64 (s, 3H), 3.29 - 3.10 (m, 4H), 3.02 - 2.82 (m, 1H), 1.43 ppm (s, 9H).



SI-82 **SI-83**

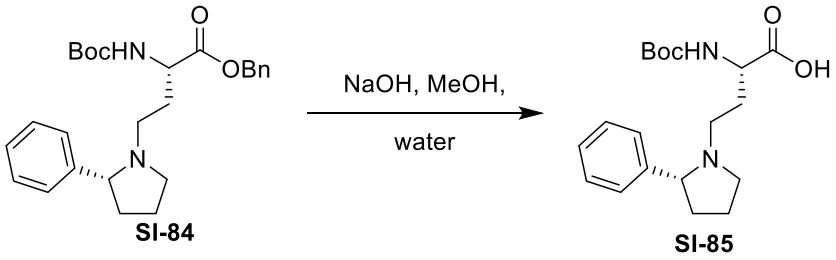
To a solution of benzyl benzyl nitrogen-(tert-butoxycarbonyl)-N4-methoxy-N4-methyl -L-asparaginate (**SI-82**) (1.00 g, 2.73 mmol) in tetrahydrofuran (10 mL) was cooled to -60°C and degassed with nitrogen three times, then DIBAL-H (1 M, 4.10 mL) was added drop-wise at -60°C under nitrogen atmosphere. The mixture was stirred for 30 min at -60°C. The reaction mixture was poured into 1N hydrochloric acid (50 mL), extracted with ethyl acetate (50 mL*2). The combined organic phase was washed with brine (50 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to afford benzyl (S)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate (**SI-83**) (0.800 g, 2.60 mmol, 95% yield) as colorless gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.60 (s, 1H), 7.54 - 7.46 (m, 3H), 7.38 - 7.29 (m, 5H), 5.12 (s, 2H), 4.56 - 4.52 (m, 1H), 2.85 - 2.75 (m, 2H), 1.36 ppm (s, 9H).



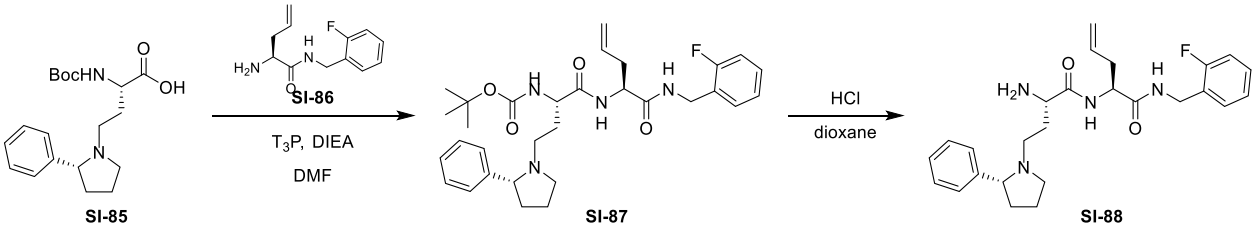
SI-83 **SI-84**

To a solution of benzyl (S)-2-((tert-butoxycarbonyl)amino)-4-oxobutanoate (**SI-83**) (0.700 g, 2.28 mmol), (R)-2-phenylpyrrolidine (**SI-30**) (0.335 g, 2.28 mmol) in methanol (8 mL) was stirred for 20 minutes at 25°C, then $NaBH(OAc)_3$ (0.966 g, 4.56 mmol) was added. The mixture was stirred for 2 hours at 25°C under nitrogen atmosphere. The reaction mixture was poured into water (10 mL), extracted with ethyl acetate (10 mL*2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

The residue was purified by column (SiO_2, petroleum ether: ethyl acetate = 20:1 ~ 10:1) to afford benzyl benzyl (S)-2-((tert-butoxycarbonyl)amino)-4-((R)-2-phenylpyrrolidin-1-yl) butanoate (**SI-84**) (0.700 g, 1.44 mmol, 55% yield) as colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 - 7.21 (m, 9H), 7.17 - 7.11 (m, 1H), 5.49 (d, *J* = 6.0 Hz, 1H), 5.05 (s, 2H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.26 (t, *J* = 7.2 Hz, 1H), 3.06 (t, *J* = 8.0 Hz, 1H), 2.56 - 2.39 (m, 1H), 2.12 - 2.00 (m, 3H), 1.88 - 1.58 (m, 5H), 1.33 ppm (s, 1H).

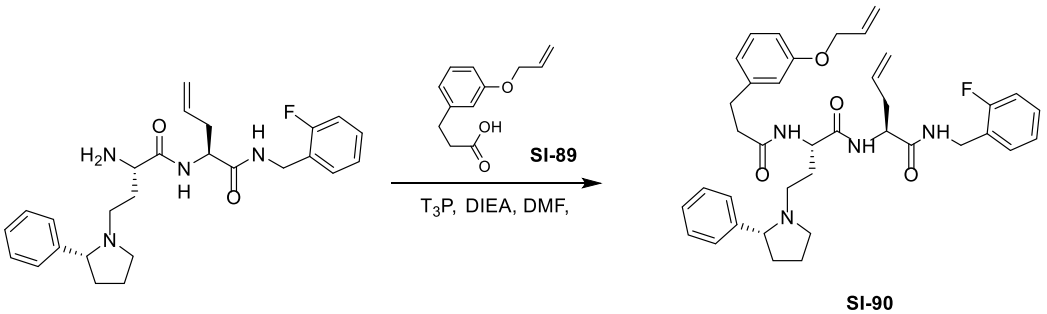


To a solution of benzyl benzyl (S)-2-((tert-butoxycarbonyl)amino)-4-((R)-2 -phenylpyrrolidin-1-yl)butanoate (**SI-84**) (0.600 g, 1.37 mmol) in methanol (0.5 mL) was added sodium hydroxide (0.219 g, 5.47 mmol) in water (0.2 mL) at 0°C. The mixture was stirred for 2 hours at 0°C. The reaction mixture was poured into water (20 mL), extracted with petroleum ether (20 mL*2). The aqueous phase was adjusted to pH = 6 with 1N hydrochloric acid, extracted with ethyl acetate (30 mL*2) and dichloromethane: methanol (v/v = 10:1, 40 mL*6). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to afford (S)-2-((tert-butoxy carbonyl)amino)-4-((R)-2-phenylpyrrolidin-1-yl)butanoic acid **(SI-85)** (0.300 g, 0.848 mmol, 62% yield) as colorless gum. ^{1}H NMR (400 MHz, Methanol-d_4) δ = 7.58 - 7.44 (m, 5H), 4.50 - 4.38 (m, 1H), 3.96 (t, J = 5.2 Hz, 1H), 3.89 - 3.76 (m, 1H), 3.41 - 3.34 (m, 1H), 3.14 (t, J = 8.0 Hz, 2H), 2.56 - 2.53 (m, 1H), 2.36 - 2.28 (m, 3H), 2.14 - 2.11 (m, 1H), 1.94 - 1.85 (m, 1H), 1.41 ppm (s, 9H).



To a solution of (S)-2-((tert-butoxycarbonyl)amino)-4-((R)-2-phenylpyrrolidin-1-yl) butanoic acid **(SI-85)** (0.300 g, 0.861 mmol), (S)-2-amino-N-(2-fluorobenzyl)pent-4-enamide as the hydrochloric salt **SI-86** (0.191 g, 0.861 mmol) in ethyl acetate (4 mL) was added diisopropylethylamine (0.334 g, 2.58 mmol) and T_3P (0.822 g, 1.29 mmol, 50% purity in ethyl acetate) at 0°C. The mixture was stirred for 1 hour at 0°C and 12 hours at 25°C. The reaction mixture was poured into water (30 mL), extracted with ethyl acetate (30 mL*3). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure. The residue was purified by prep-HPLC (column: Phenomenex Synergi C_{18} 150*25*10 um; mobile phase: [water (0.225% FA) - ACN]; B%: 27%-51%, 7 min) and lyophilized.

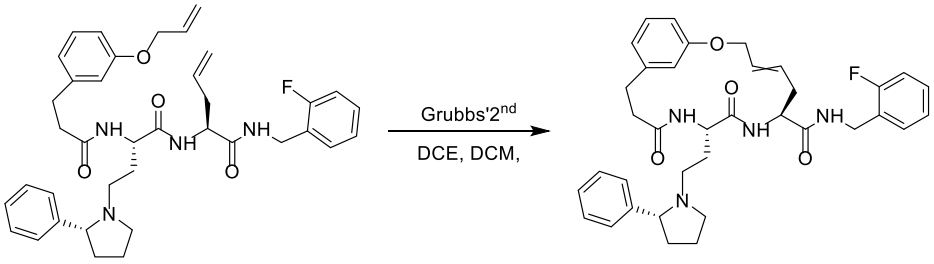
The residue was dissolved in dioxane (1 mL), then a solution of HCl in dioxane (4 M, 1 mL) was added at 0°C. The mixture was stirred for 2 hours at 20°C. The reaction mixture was concentrated under reduce pressure to afford (S)-2-((S)-2-amino-4-((R)-2-phenylpyrrolidin -1-yl)butanamido)-N-(2-fluorobenzyl)pent-4-enamide (**SI-88**) as hydrochloric salt (0.120 g, crude) as colorless gum. ^{1}H NMR (400 MHz, Methanol-d_4) δ = 7.69 - 7.57 (m, 2H), 7.54 - 7.46 (m, 3H), 7.45 - 7.37 (m, 1H), 7.36 - 7.26 (m, 1H), 7.19 - 7.04 (m, 2H), 5.93 - 5.75 (m, 1H), 5.25 - 5.07 (m, 2H), 4.51 - 4.45 (m, 2H), 4.40 - 4.34 (m, 1H), 3.97 - 3.90 (m, 1H), 3.88 - 3.79 (m, 1H), 3.46 - 3.36 (m, 1H), 3.32 - 3.25 (m, 1H), 3.24 - 3.11 (m, 1H), 2.60 - 2.44 (m, 3H), 2.38 - 2.27 (m, 3H), 2.26 - 2.16 ppm (m, 3H).



SI-88 SI-90

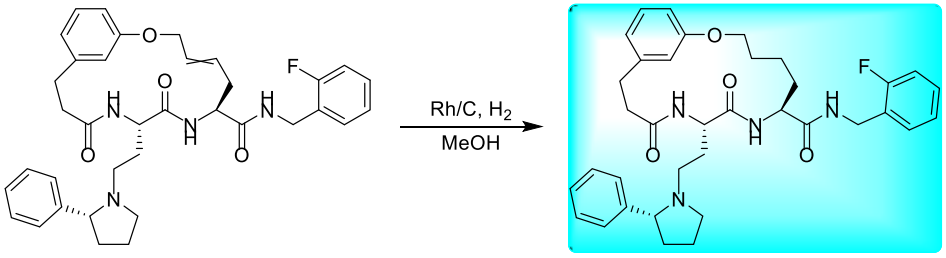
To a solution of (S)-2-((S)-2-amino-4-((R)-2-phenylpyrrolidin-1-yl)butanamido)-N-(2 -fluorobenzyl)pent-4-enamide (**SI-88**) as hydrochloric salt (0. 120 g, 0.245 mmol), 3-(3-(allyloxy)phenyl)propanoic acid (**SI-89**) (0.056 g, 0.270 mmol) in dimethylformamide (2 mL) was added diisopropylethylamine (0.159 g, 1.23 mmol) and T_3P (0.117 g, 0.368

mmol, 50% purity in ethyl acetate) at 0°C. The mixture was stirred for 1 hour at 0°C. The reaction mixture was poured into ice-water (20 mL). A large white precipitate was formed. The solid was collected by filtration and dried under *reduced pressure to a*fford (S)-2-((S)-2-(3-(3-(allyloxy)phenyl)propanamido)-4-((R)-2-phenylpyrrolidin-1-yl)butanamido)-N-(2-fluorobenzyl)pent-4-enamide (**SI-90**) (0.120 g, 0.182 mmol, 74% yield) as a white solid.



SI-90 **SI-91**

A solution of (S)-2-((S)-2-(3-(3-(allyloxy)phenyl)propanamido)-4-((R)-2-phenylpyrroli din-1-yl)butanamido)-N-(2-fluorobenzyl)pent-4-enamide (**SI-90**) (0.100 g, 0.156 mmol) in dichloromethane (20 mL) and dichloroethane (30 mL) was degassed and purged with nitrogen three times, then Grubbs catalyst 2nd generation (0.066 g, 0.078 mmol) was added. The mixture was stirred for 12 hours at 60°C under nitrogen atmosphere. The reaction mixture was concentrated under reduce pressure. The residue was purified by column(SiO_2, petroleum ether: ethyl acetate = 10:1 ~ ethyl acetate) to afford (7S,10S)-N-(2-fluorobenzyl) -9,12-dioxo-10-(2-((R)-2-phenylpyrrolidin-1-yl)ethyl)-2-oxa-8,11-diaza-1(1,3)-benzenacyclotetradecaphan-4-ene-7-carboxamide (**SI-91**) (0.080 g, 0.111 mmol, 59% yield) as yellow gum.

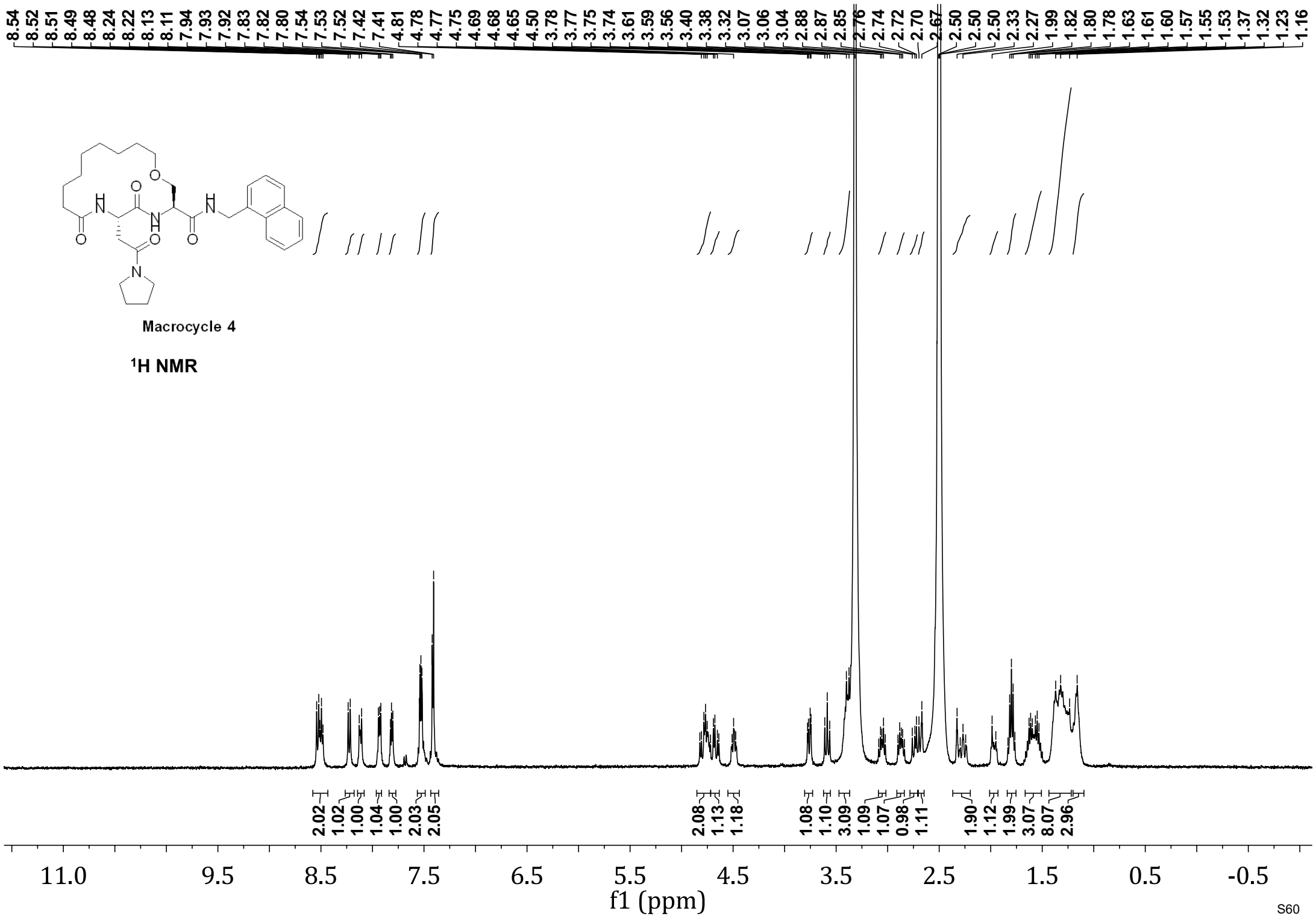


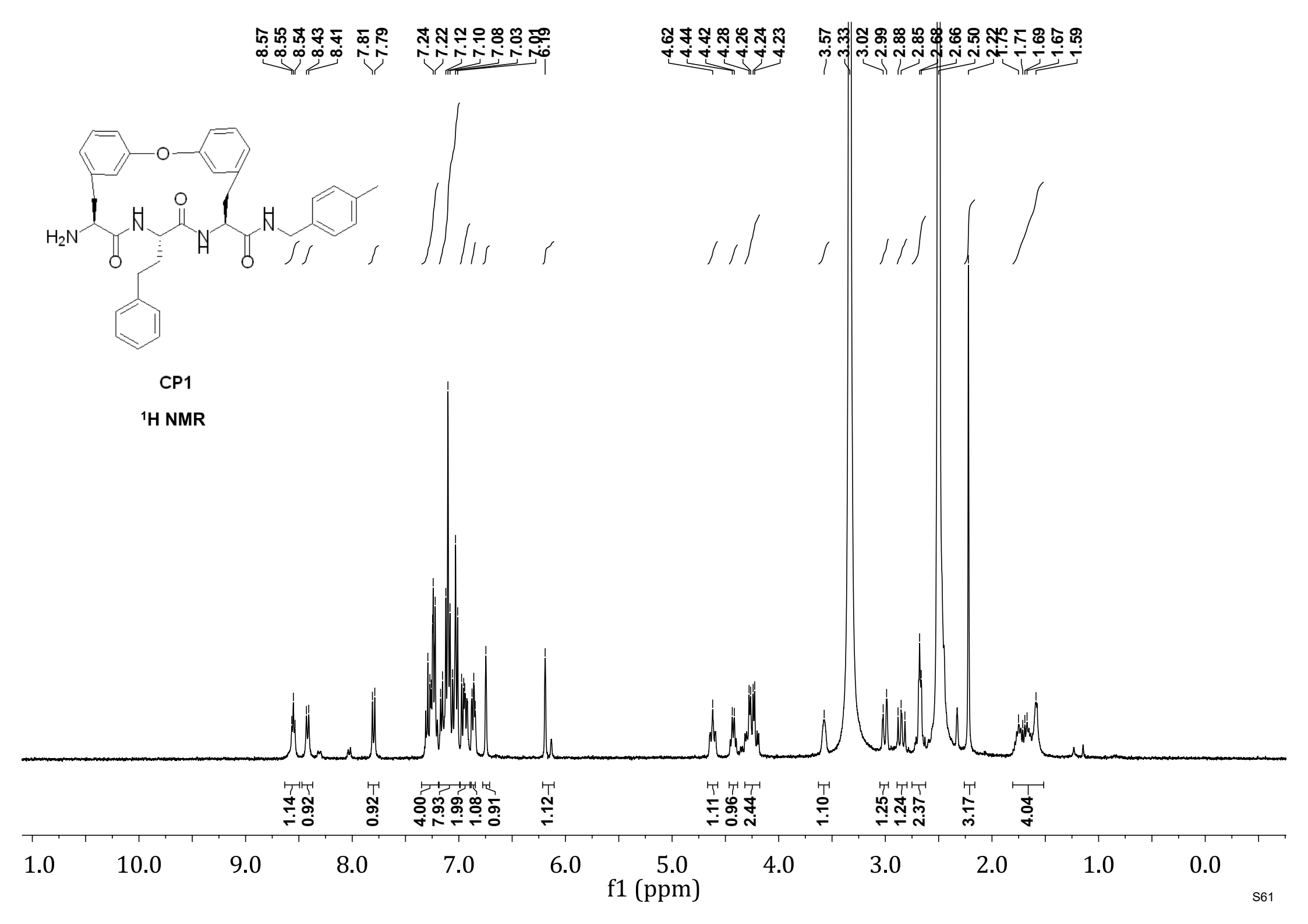
SI-91 **Macrocycle 13**

To a solution of (7S,10S)-N-(2-fluorobenzyl)-9,12-dioxo-10-(2-((R)-2-phenylpyrrolidin -1-yl)ethyl)-2-oxa-8,11-diaza-1(1,3)-benzenacyclotetradecaphan-4-ene-7-carboxamide (**SI-91**) (0.060 g, 0.083 mmol) in methanol (1 mL) was added Rhodium/C (0.020 g, 5%

purity on charcoal) under nitrogen. The mixture was degassed with hydrogen three times and stirred for 4 hours at 25°C under hydrogen atmosphere (15 psi). The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC(column: Waters Xbridge 150*25 5 u; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 38%-68%, 10 min) to afford (7S,10S)-N-(2-fluorobenzyl) -9,12-dioxo-10-(2-((R)-2-phenylpyrrolidin-1-yl)ethyl)-2-oxa-8,11-diaza-1(1,3)-benzenacyclotetradecaphane-7-carboxamide (**Macrocycle 13**) (3.6 mg, 5.4 umol, 7% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51 – 7.42 (m, 1H), 7.34 – 7.29 (m, 2H), 7.25 – 7.18 (m, 3H), 7.13 – 6.95 (m, 3H), 6.93 – 6.84 (m, 1H), 6.82 – 6.59 (m, 4H), 5.90 – 5.77 (m, 1H), 4.60 – 4.45 (m, 1H), 4.39 (d, *J* = 5.6 Hz, 2H), 4.27 – 4.20 (m, 1H), 4.18 – 4.02 (m, 3H), 3.39 – 3.28 (m, 1H), 3.25 – 3.17 (m, 1H), 3.06 – 2.96 (m, 1H), 2.86 – 2.77 (m, 1H), 2.63 – 2.51 (m, 2H), 2.46 – 2.32 (m, 2H), 2.32 – 2.12 (m, 4H), 2.00 – 1.94 (m, 1H), 1.93 – 1.74 (m, 5H), 1.46 – 1.37 ppm (m, 2H). m/z 615.5 $[MS+H]^+$.

SFC of **Macrocycle 13**: RT= 1.705 min, de %= 100%.


8.54 8.52 8.51 8.49 8.48 8.24 8.22 8.13 8.11 7.94 7.93 7.92 7.83 7.82 7.80 7.54 7.53 7.52 7.42 7.41 4.81 4.78 4.77 4.75 4.69 4.68 4.65 4.50 3.78 3.77 3.75 3.74 3.61 3.59 3.56 3.40 3.38 3.32 3.07 3.06 3.04 2.88 2.87 2.85 2.76 2.74 2.72 2.70 2.67 2.50 2.50 2.50 2.33 2.27 1.99 1.82 1.80 1.78 1.63 1.61 1.60 1.57 1.55 1.53 1.37 1.32 1.23 1.16
Macrocycle 4
1H NMR
2.02 1.02 1.00 1.04 1.00 2.03 2.05
2.08 1.13 1.18
1.08 1.10 3.09 1.09 1.07 0.98 1.11
1.90 1.12 1.99 3.07 8.07 2.96
11.0 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5
f1 (ppm)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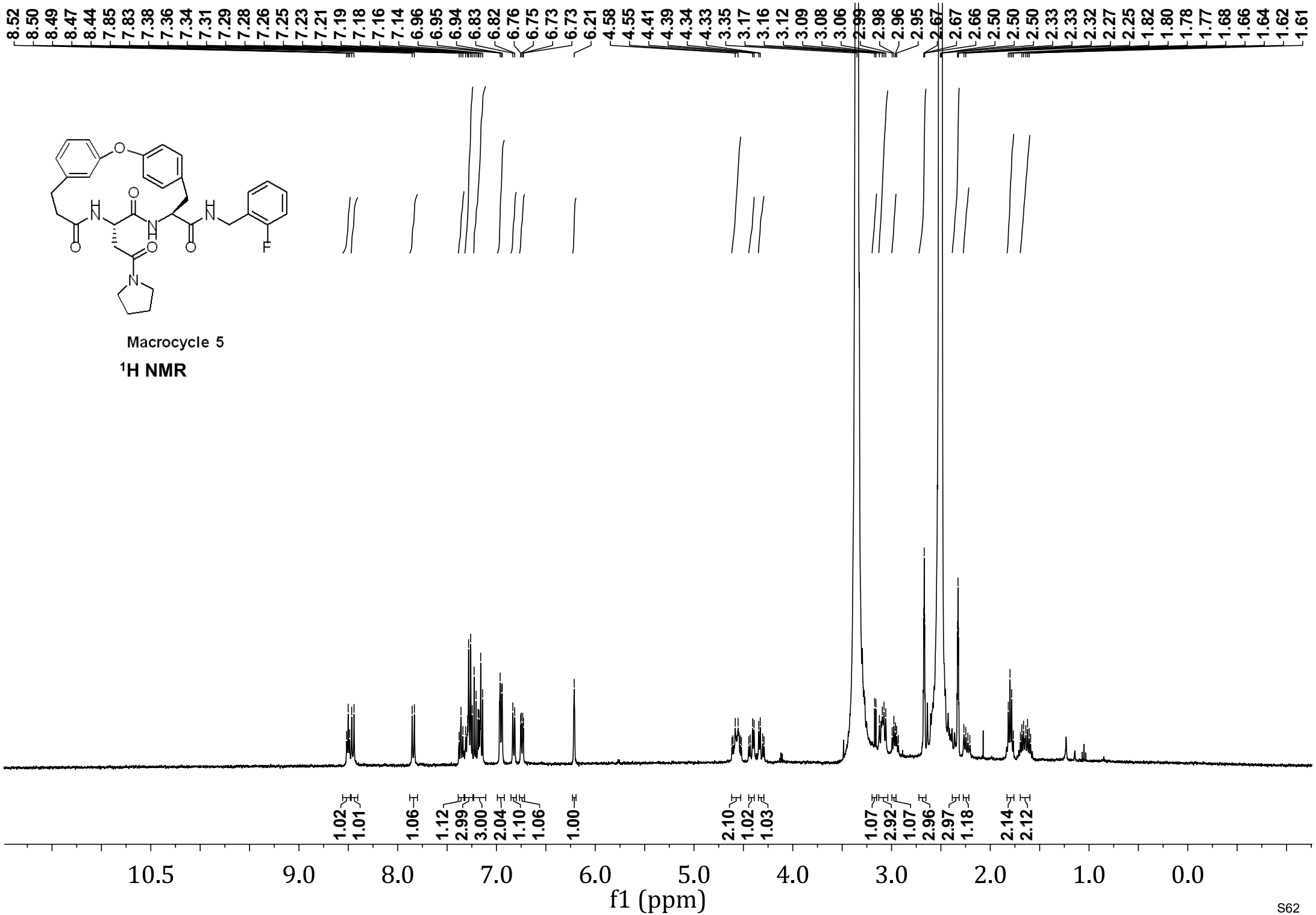
7.81
7.79
7.24
7.22
7.12
7.10
7.08
7.03
7.01
6.19
4.62
4.44
4.42
4.28
4.26
4.24
4.23
3.57
3.33
3.02
2.99
2.88
2.85
2.68
2.66
2.50
2.22
1.75
1.71
1.69
1.67
1.59
H2N
O
N
H
O
N
H
O
O
CP1
1H NMR
1.14
0.92
0.92
4.00
7.93
1.99
1.08
0.91
1.12
1.11
0.96
2.44
1.10
1.25
1.24
2.37
3.17
4.04
1.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)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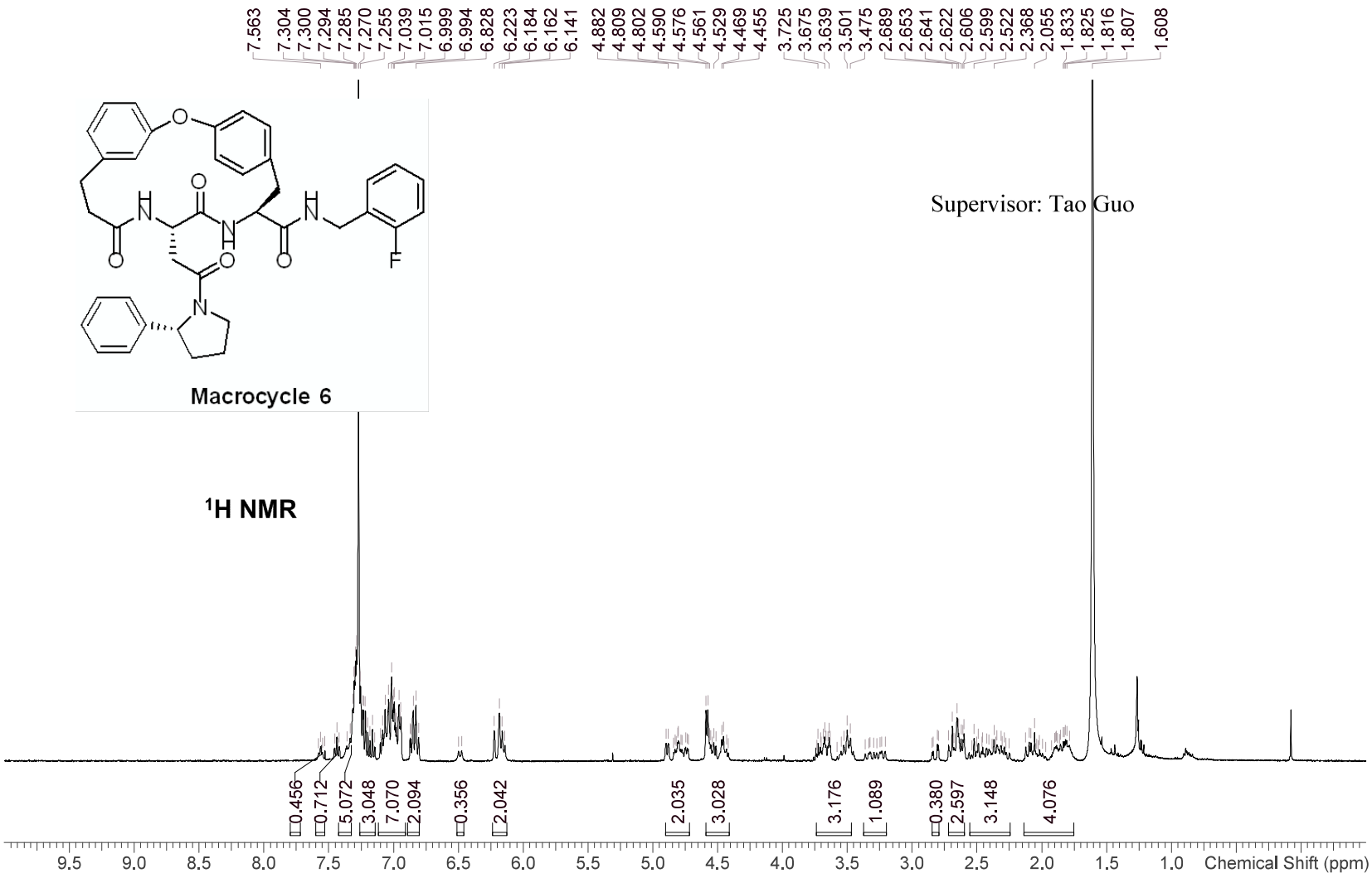
Macrocycle 5
1H NMR
1.02 1.01 1.06 1.12 2.99 3.00 2.04 1.10 1.06 1.00 2.10 1.02 1.03 1.07 2.92 1.07 2.96 2.97 1.18 2.14 2.12
10.5 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)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7.015
6.999
6.994
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6.184
6.162
6.141
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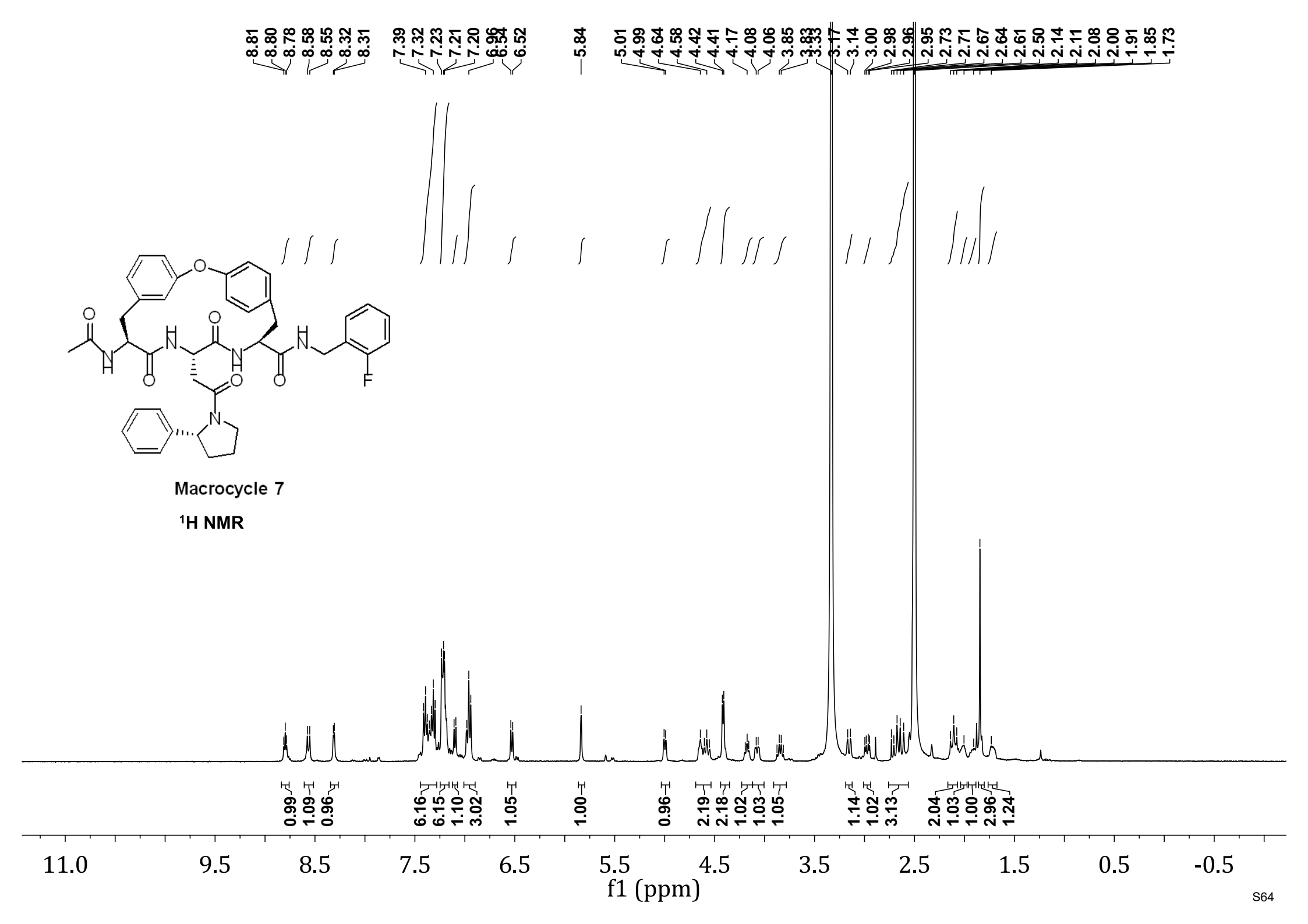
4.809
4.802
4.590
4.576
4.561
4.529
4.469
4.455
3.725
3.675
3.639
3.501
3.475
2.689
2.653
2.641
2.622
2.606
2.599
2.522
2.368
2.055
1.833
1.825
1.816
1.807
1.608
Supervisor: Tao Guo
Macrocycle 6
1H NMR
0.456
0.712
5.072
3.048
7.070
2.094
0.356
2.042
2.035
3.028
3.176
1.089
0.380
2.597
3.148
4.076
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


8.81
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8.55
8.32
8.31
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7.32
7.23
7.21
7.20
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6.54
6.52
5.84
5.01
4.99
4.64
4.58
4.42
4.41
4.17
4.08
4.06
3.85
3.83
3.33
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3.00
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2.61
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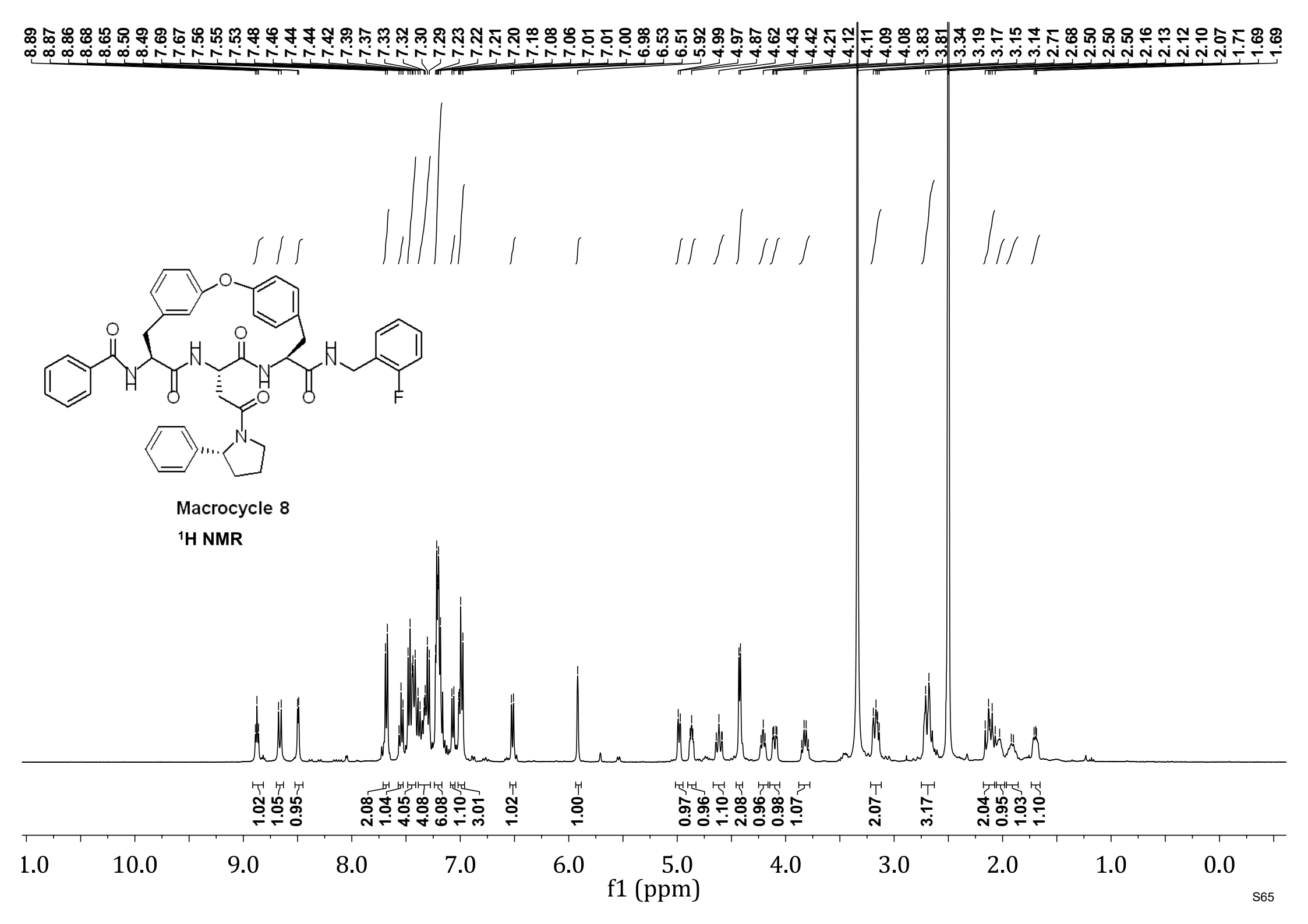
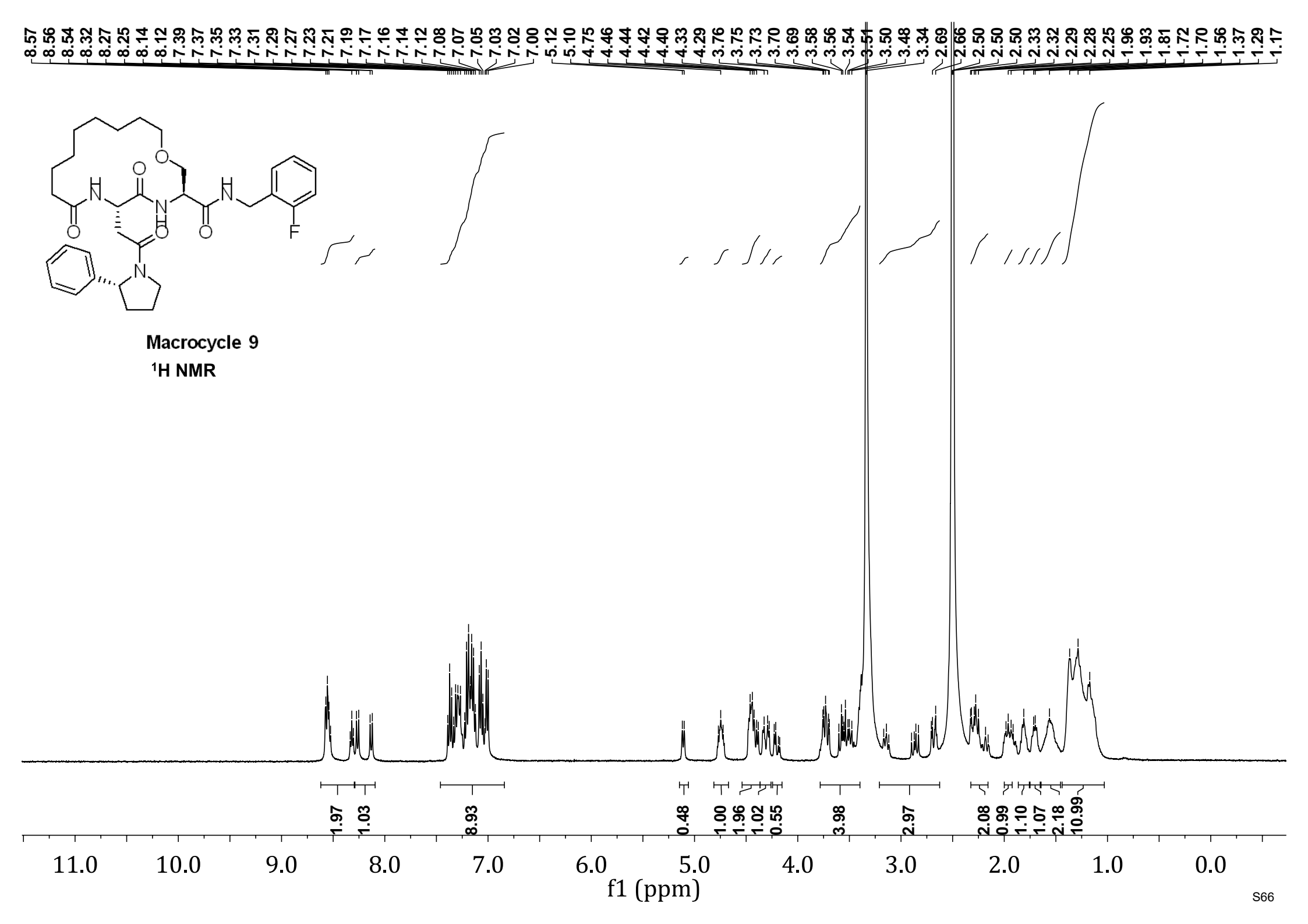
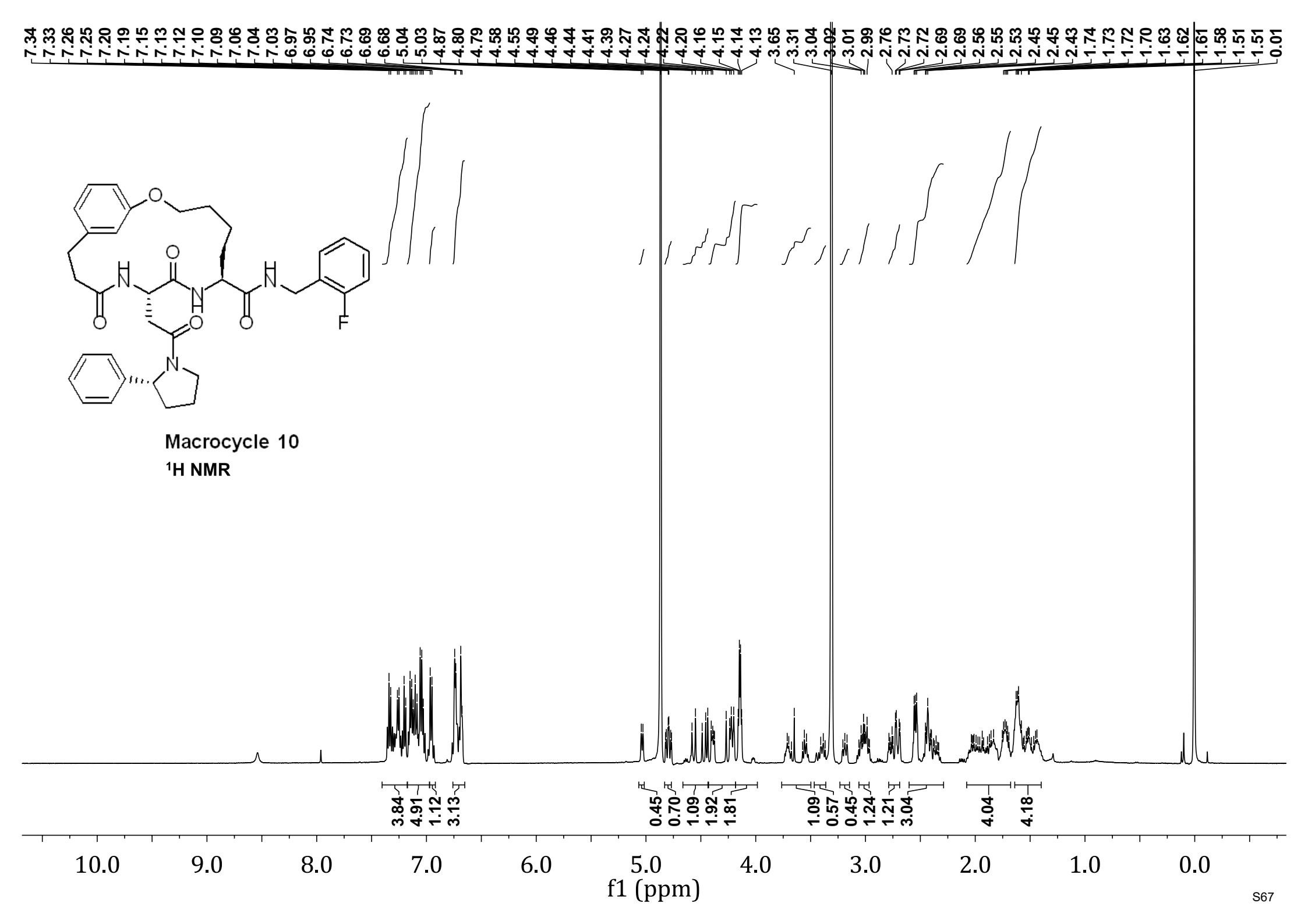
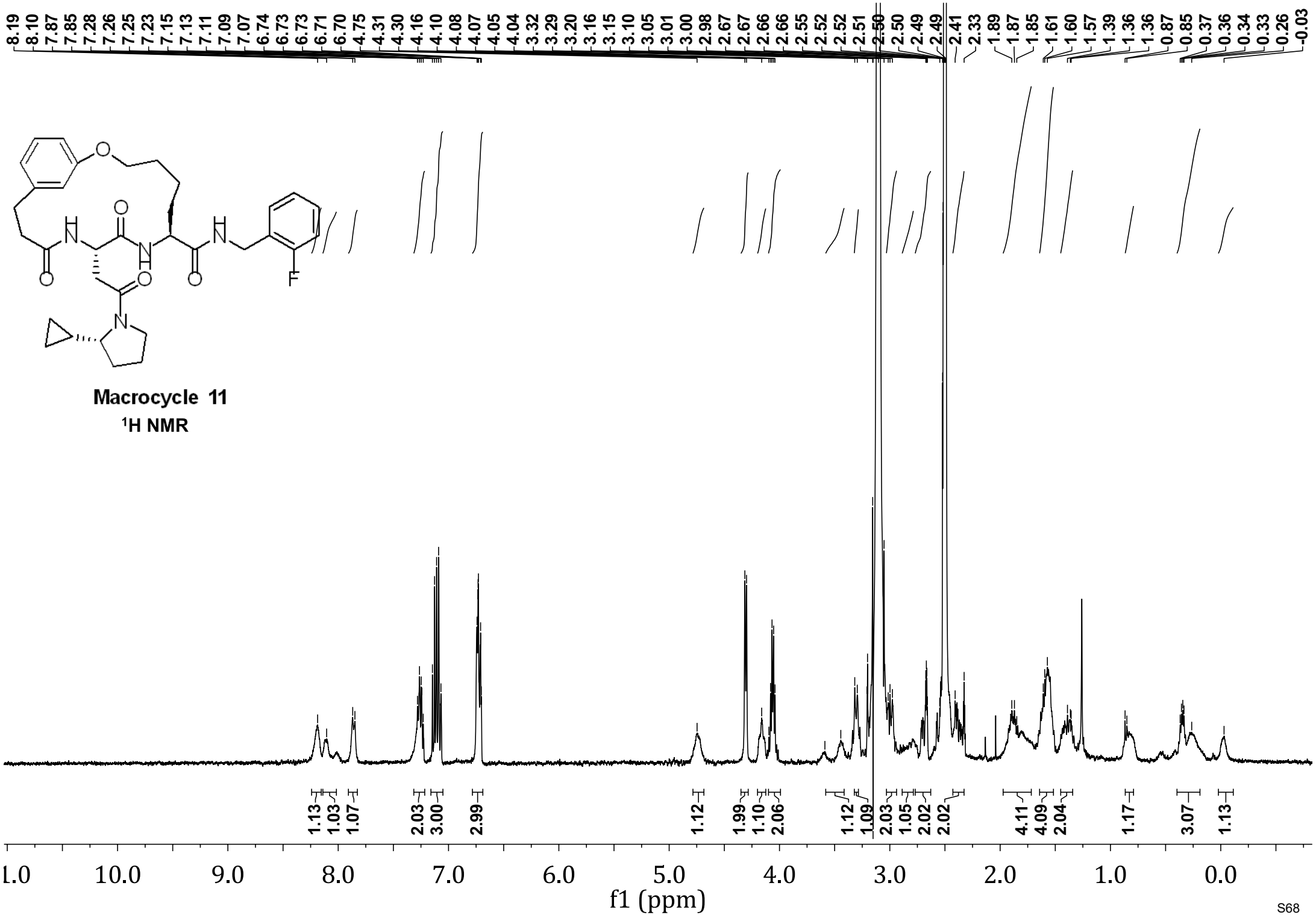
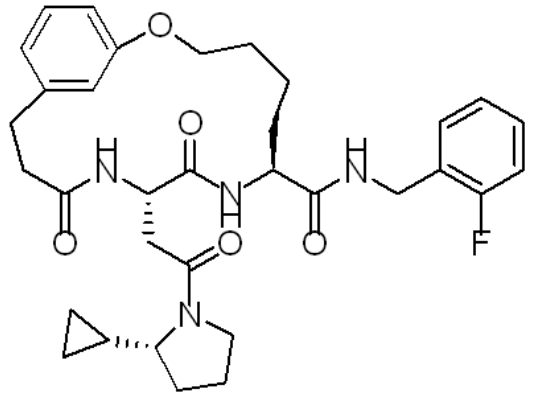
2.14
2.11
2.08
2.00
1.91
1.85
1.73
O
O
H
N
O
H
N
O
O
O
H
N
F
N
Macrocycle 7
1H NMR
0.99
1.09
0.96
6.16
6.15
1.10
3.02
1.05
1.00
0.96
2.19
2.18
1.02
1.03
1.05
1.14
1.02
3.13
2.04
1.03
1.00
2.96
1.24
11.0
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


8.89 8.87 8.86 8.68 8.65 8.50 8.49 7.69 7.67 7.56 7.55 7.53 7.48 7.46 7.44 7.44 7.42 7.39 7.37 7.33 7.32 7.30 7.29 7.23 7.22 7.21 7.20 7.18 7.08 7.06 7.01 7.01 7.00 6.98 6.53 6.51 5.92 4.99 4.97 4.87 4.62 4.43 4.42 4.21 4.12 4.11 4.09 4.08 3.83 3.81 3.34 3.19 3.17 3.15 3.14 2.71 2.68 2.50 2.50 2.50 2.16 2.13 2.12 2.10 2.07 1.71 1.69 1.69
Macrocycle 8
1H NMR
1.02 1.05 0.95 2.08 1.04 4.05 4.08 6.08 1.10 3.01 1.02 1.00 0.97 0.96 1.10 2.08 0.96 0.98 1.07 2.07 3.17 2.04 0.95 1.03 1.10
1.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


8.57 8.56 8.54 8.32 8.27 8.25 8.14 8.12 7.39 7.37 7.35 7.33 7.31 7.29 7.27 7.23 7.21 7.19 7.17 7.16 7.14 7.12 7.08 7.07 7.05 7.03 7.02 7.00
5.12 5.10 4.75 4.46 4.44 4.42 4.40 4.33 4.29 3.76 3.75 3.73 3.70 3.69 3.58 3.56 3.54 3.51 3.50 3.48 3.34 2.69 2.66 2.50 2.50 2.50 2.33 2.32 2.29 2.28 2.25 1.96 1.93 1.81 1.72 1.70 1.56 1.37 1.29 1.17
Macrocycle 9
1H NMR
1.97 1.03 8.93 0.48 1.00 1.96 1.02 0.55 3.98 2.97 2.08 0.99 1.10 1.07 2.18 10.99
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

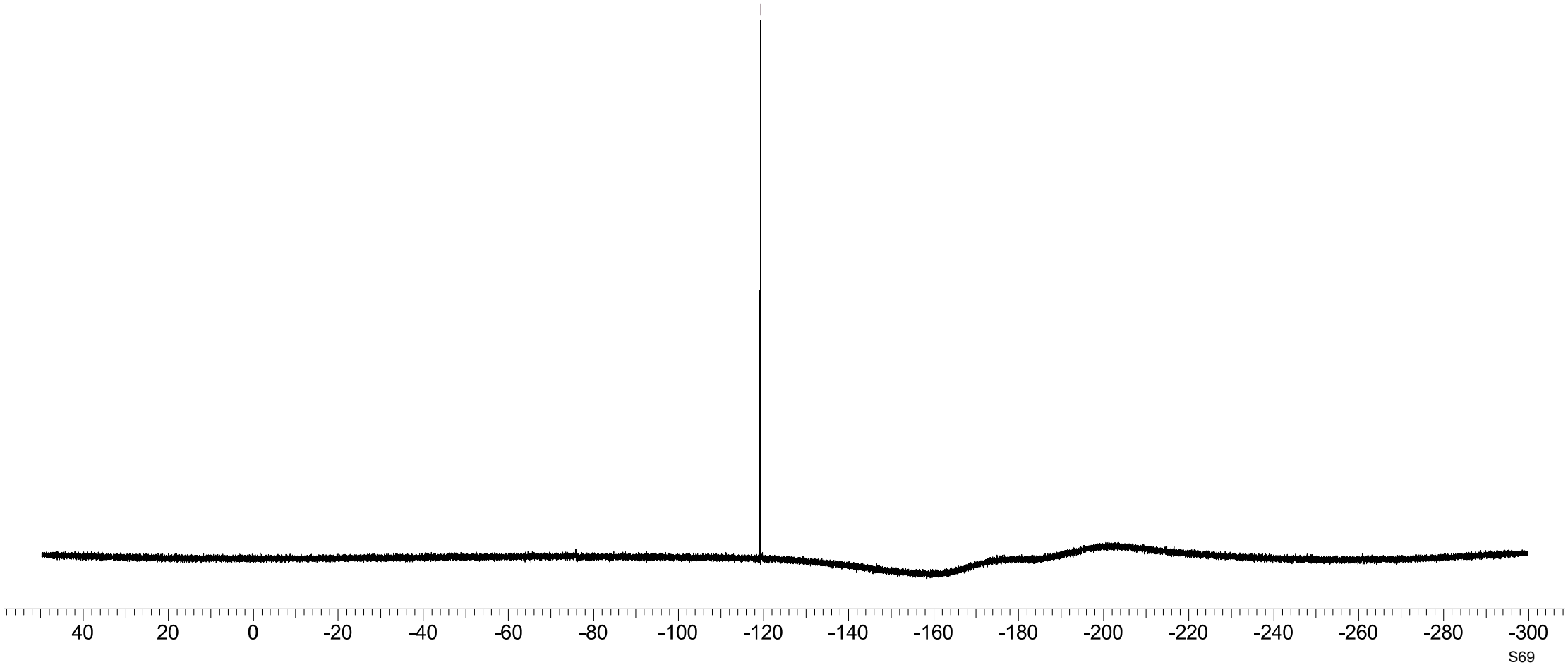

7.34 7.33 7.26 7.25 7.20 7.19 7.15 7.13 7.12 7.10 7.09 7.06 7.04 7.03 6.97 6.95 6.74 6.73 6.69 6.68 5.04 5.03 4.87 4.80 4.79 4.58 4.55 4.49 4.46 4.44 4.41 4.39 4.27 4.24 4.22 4.20 4.16 4.15 4.14 4.13 3.65 3.31 3.04 3.02 3.01 2.99 2.76 2.73 2.72 2.69 2.69 2.56 2.55 2.53 2.45 2.45 2.43 1.74 1.73 1.72 1.70 1.63 1.62 1.61 1.58 1.51 1.51 0.01
Macrocycle 10
1H NMR
3.84 4.91 1.12 3.13 0.45 0.70 1.09 1.92 1.81 1.09 0.57 0.45 1.24 1.21 3.04 4.04 4.18
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

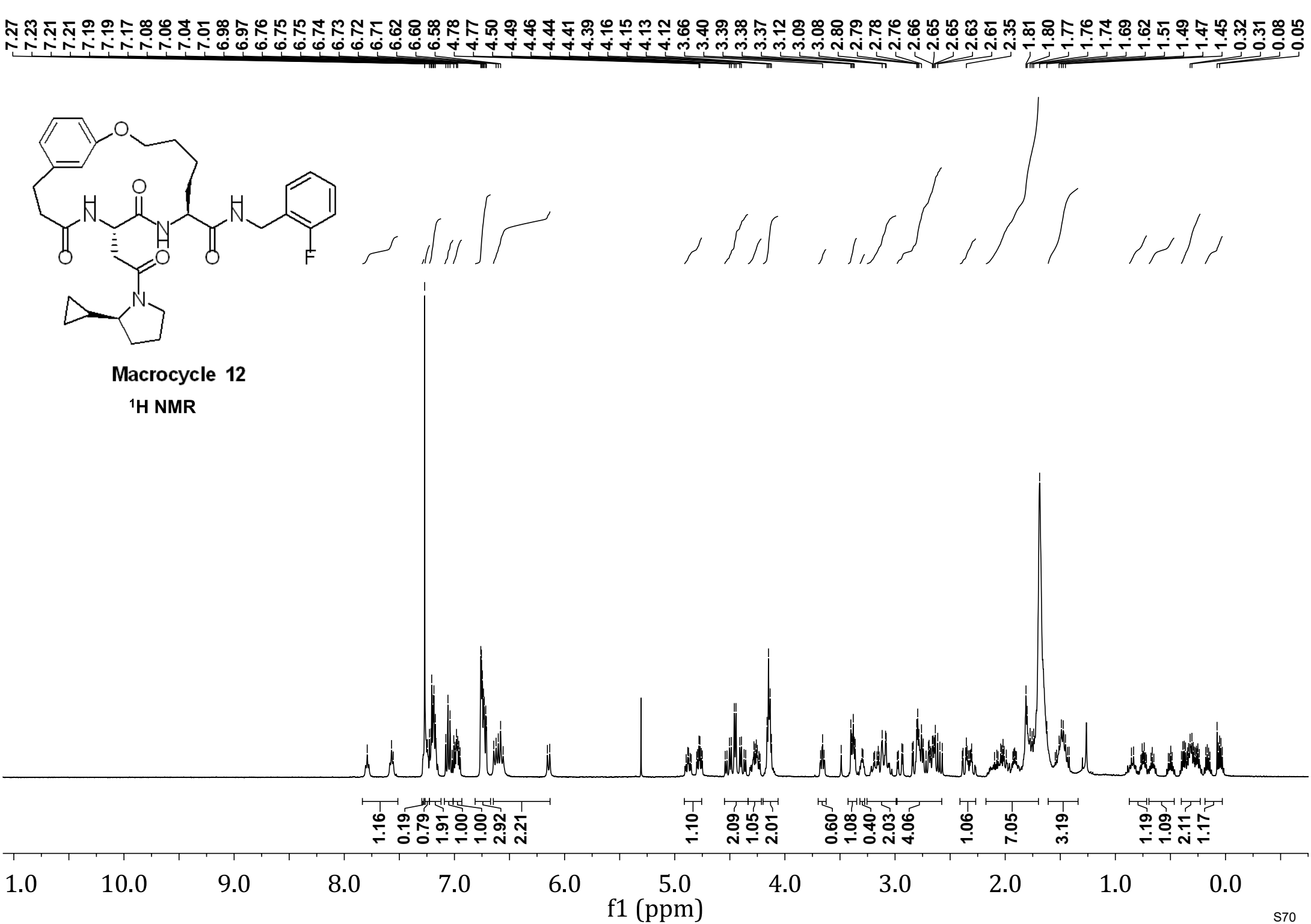

8.19 8.10 7.87 7.85 7.28 7.26 7.25 7.23 7.15 7.13 7.11 7.09 7.07 6.74 6.73 6.73 6.71 6.70 4.75 4.31 4.30 4.16 4.10 4.08 4.07 4.05 4.04 3.32 3.29 3.20 3.16 3.15 3.10 3.05 3.01 3.00 2.98 2.67 2.67 2.66 2.66 2.55 2.52 2.52 2.51 2.50 2.50 2.49 2.49 2.41 2.33 1.89 1.87 1.85 1.61 1.60 1.57 1.39 1.36 1.36 0.87 0.85 0.37 0.36 0.34 0.33 0.26 -0.03
Macrocycle 11
1H NMR
1.13 1.03 1.07 2.03 3.00 2.99 1.12 1.99 1.10 2.06 1.12 1.09 2.03 1.05 2.02 2.02 4.11 4.09 2.04 1.17 3.07 1.13
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

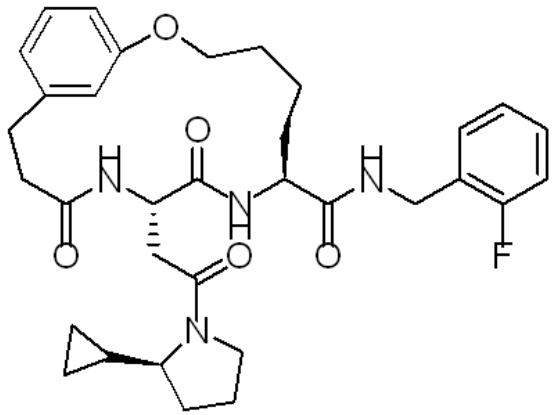


Macrocycle 11

^{19}F NMR

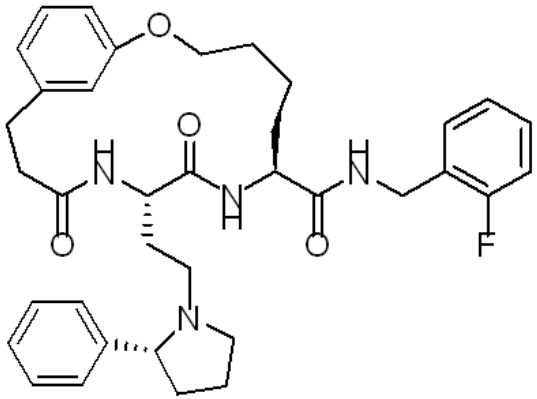



7.27 7.23 7.21 7.21 7.19 7.19 7.17 7.08 7.06 7.04 7.01 6.98 6.97 6.76 6.75 6.75 6.74 6.73 6.72 6.71 6.62 6.60 6.58 4.78 4.77 4.50 4.49 4.46 4.44 4.41 4.39 4.16 4.15 4.13 4.12 3.66 3.40 3.39 3.38 3.37 3.12 3.09 3.08 2.80 2.79 2.78 2.76 2.66 2.65 2.65 2.63 2.61 2.35 1.81 1.80 1.77 1.76 1.74 1.69 1.62 1.51 1.49 1.47 1.45 0.32 0.31 0.08 0.05
Macrocycle 12
1H NMR
1.16 0.19 0.79 1.91 1.00 1.00 2.92 2.21 1.10 2.09 1.05 2.01 0.60 1.08 0.40 2.03 4.06 1.06 7.05 3.19 1.19 1.09 2.11 1.17
1.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)



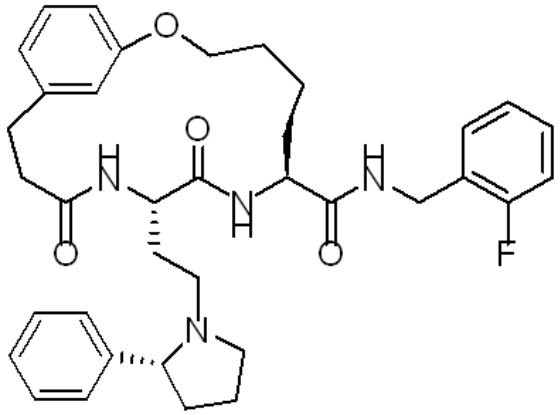
Macrocycle 12

^{19}F NMR



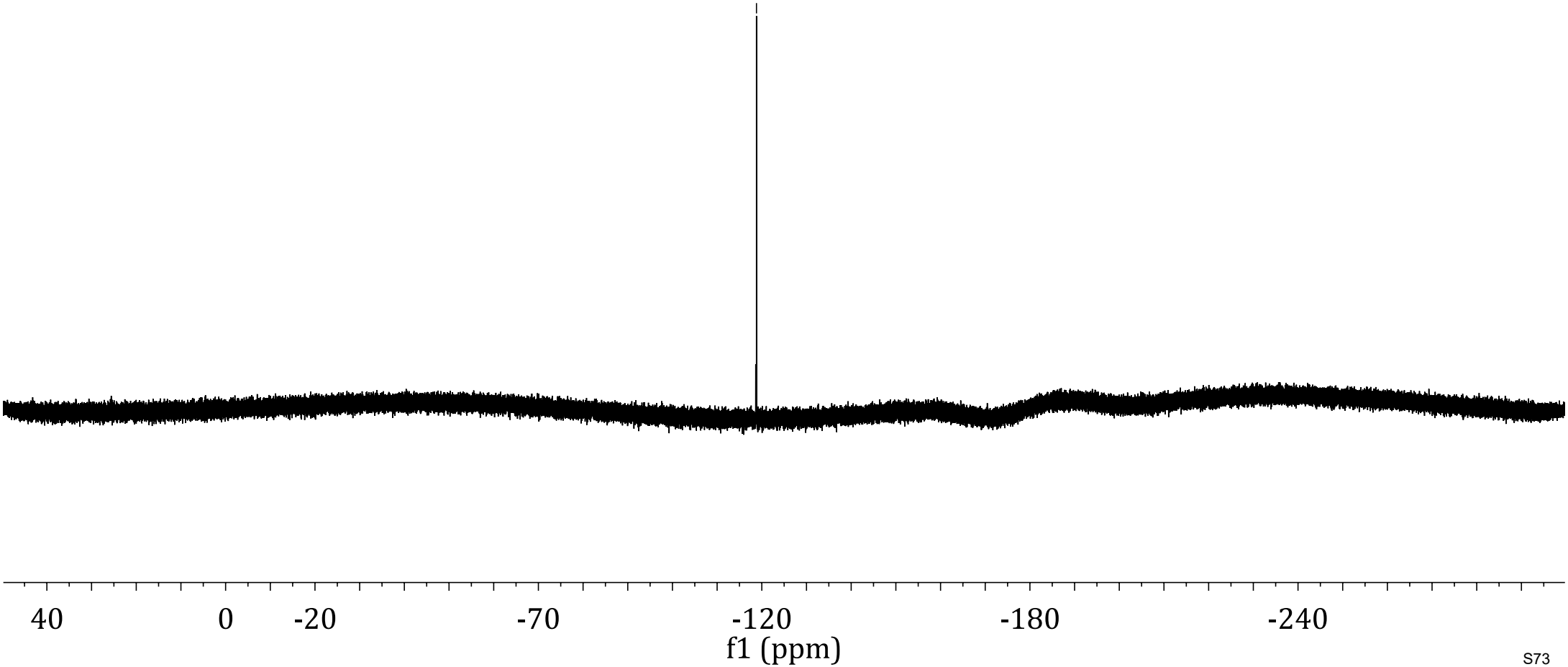
Macrocycle 13

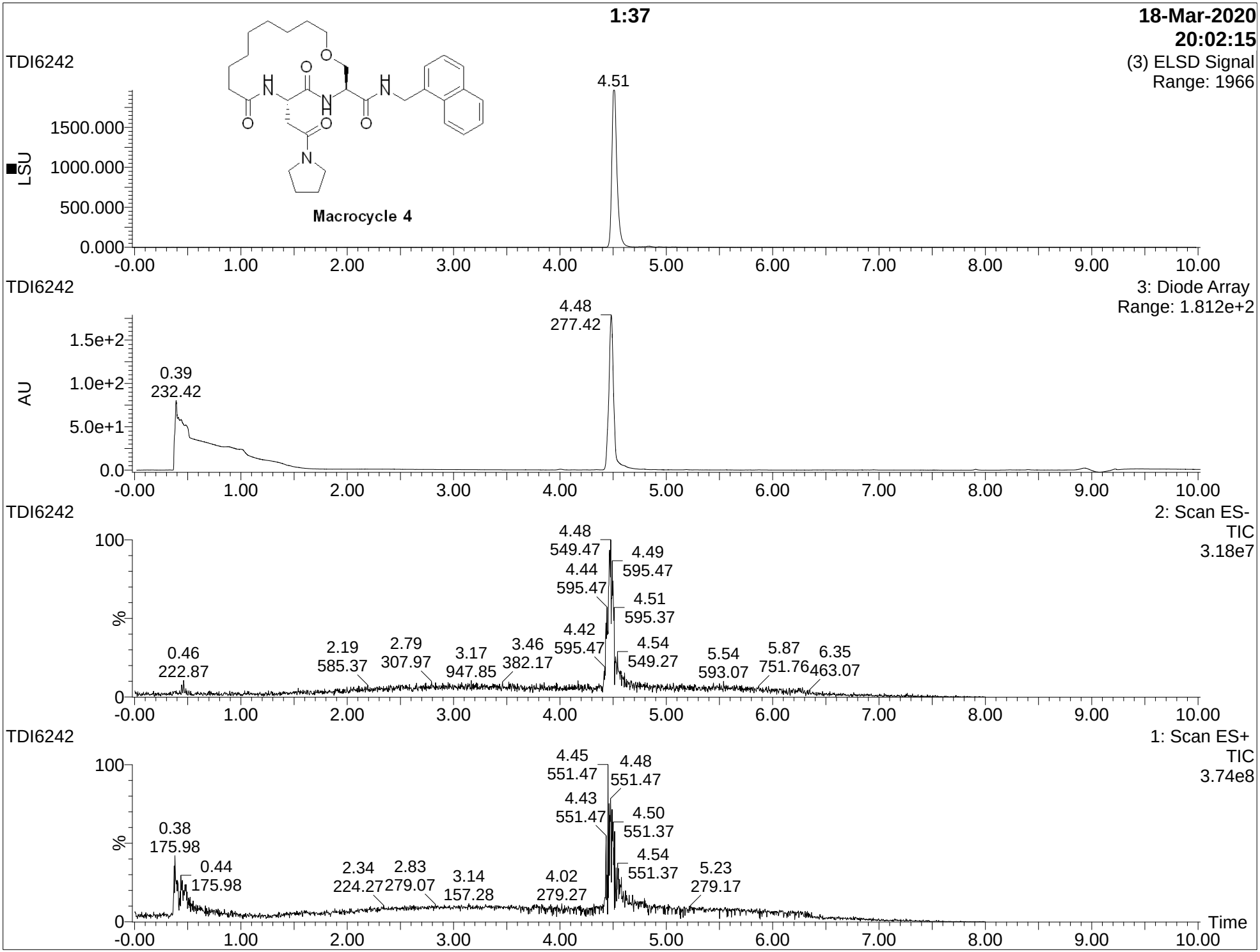
^{1}H NMR

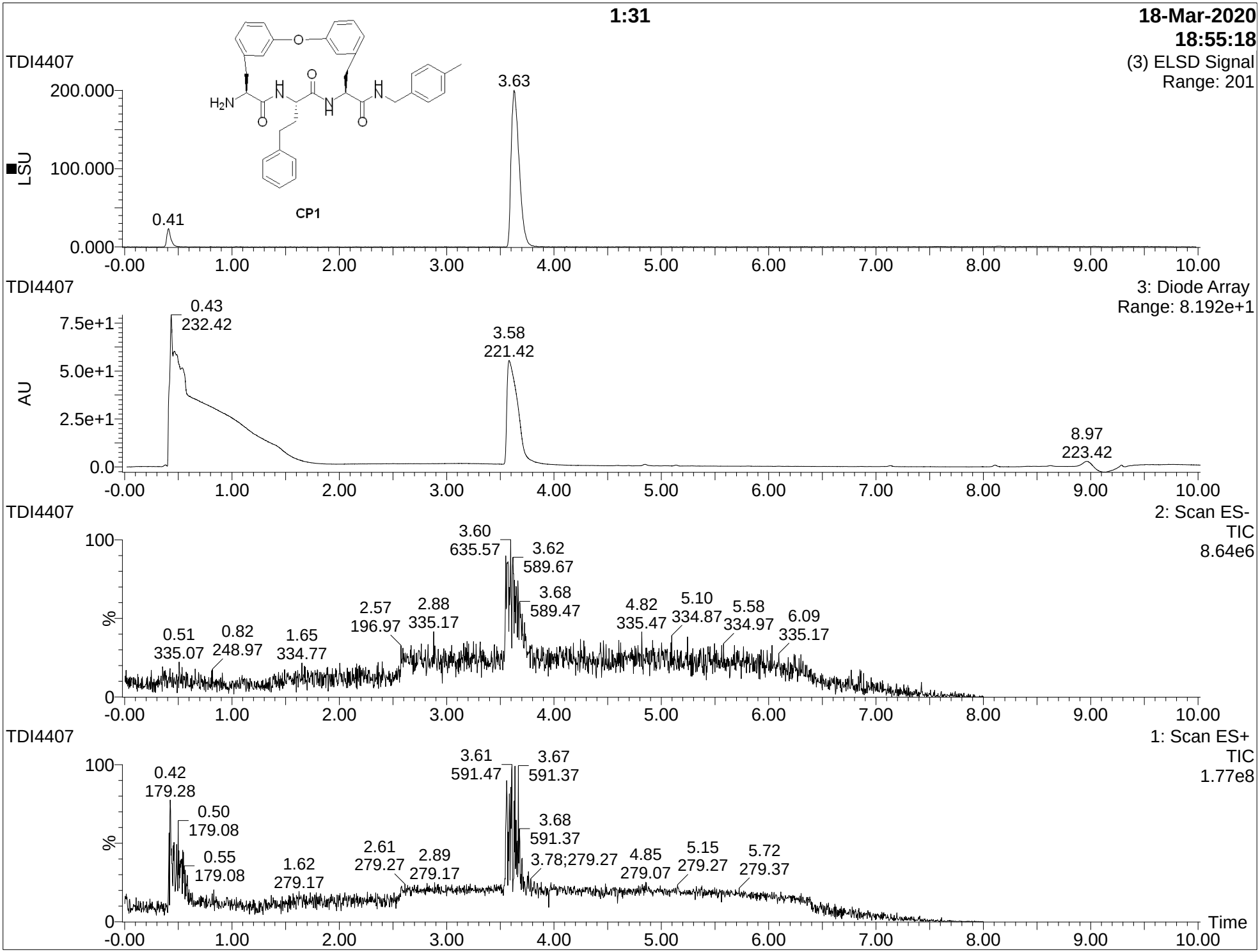


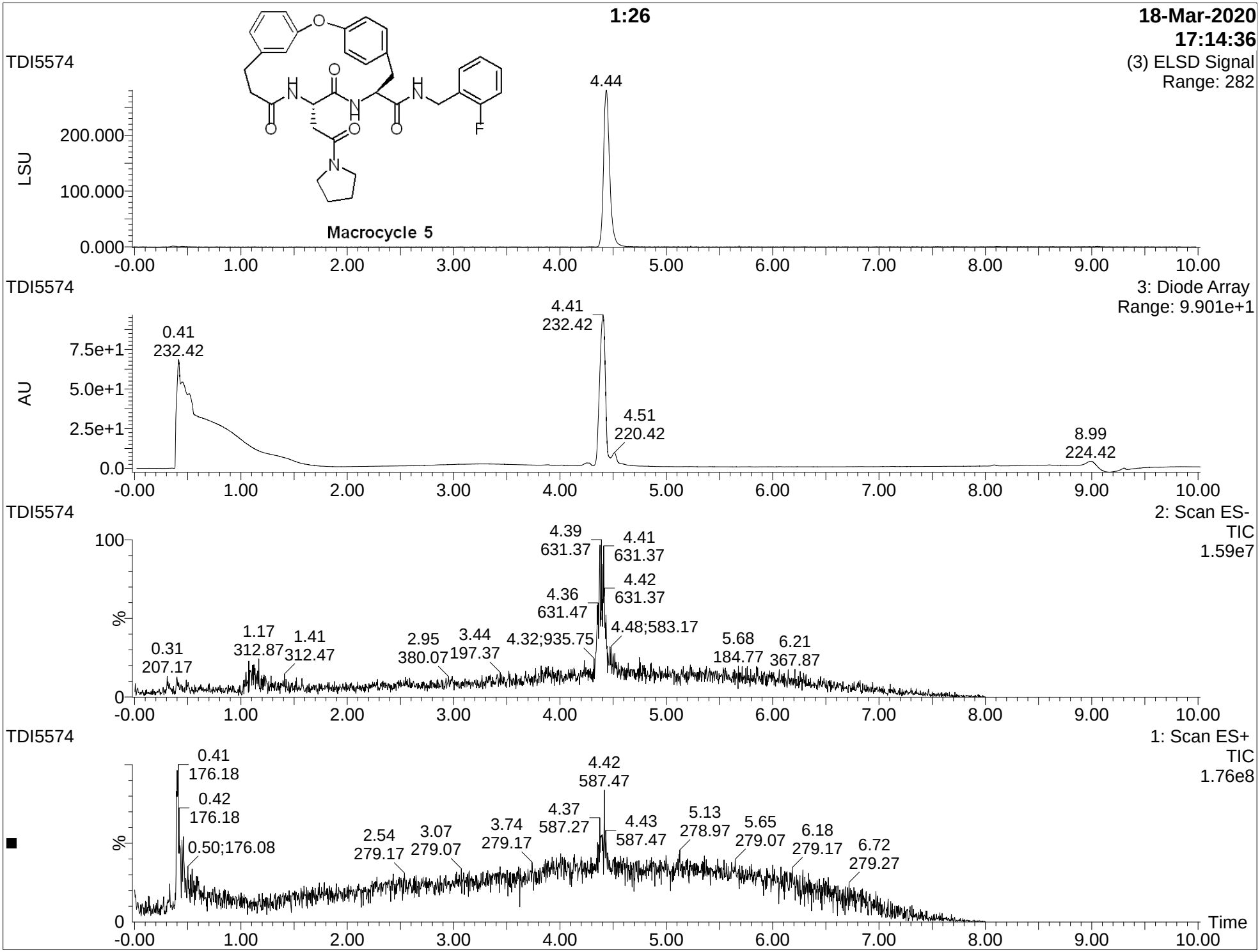
Macrocycle 13

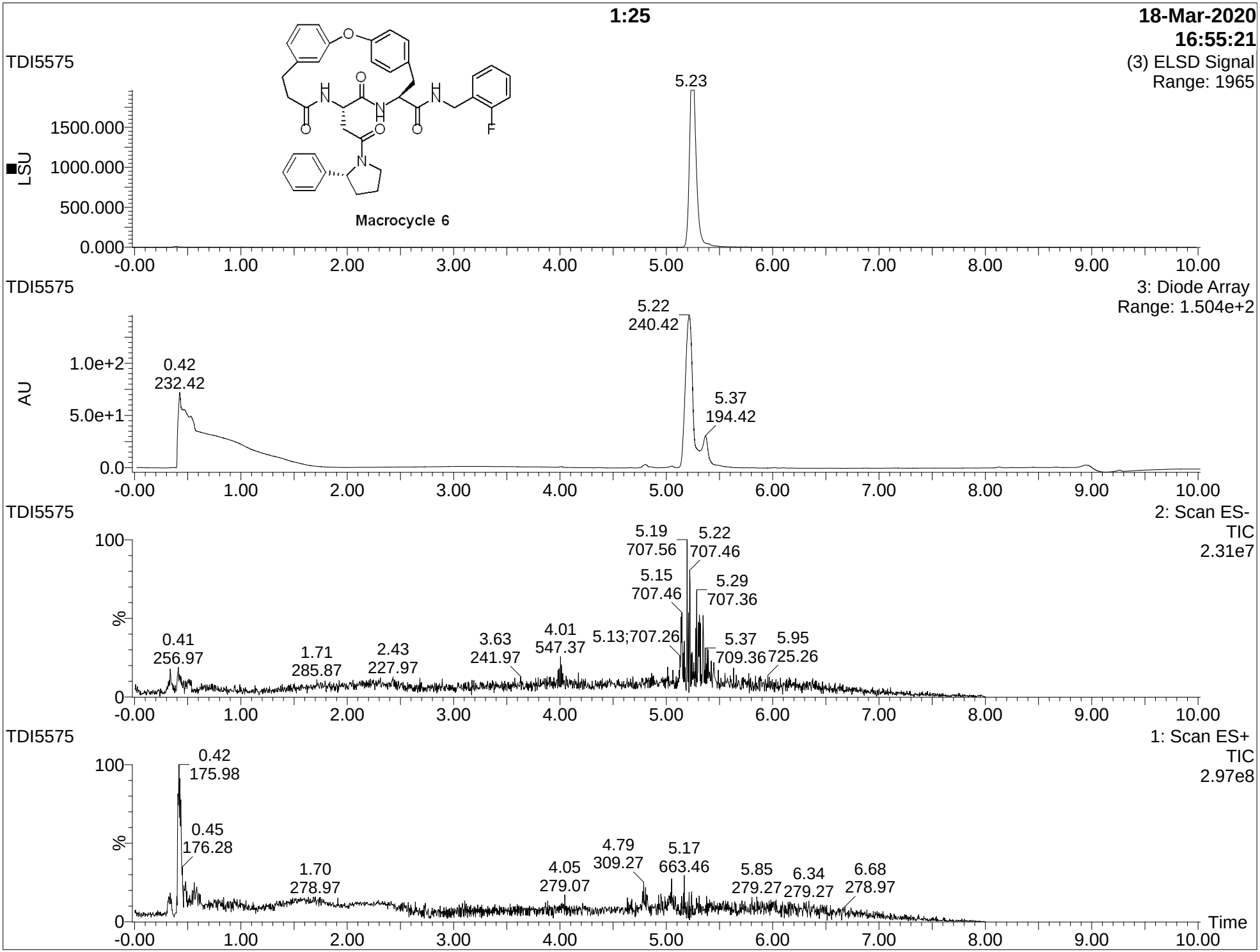
^{19}F NMR

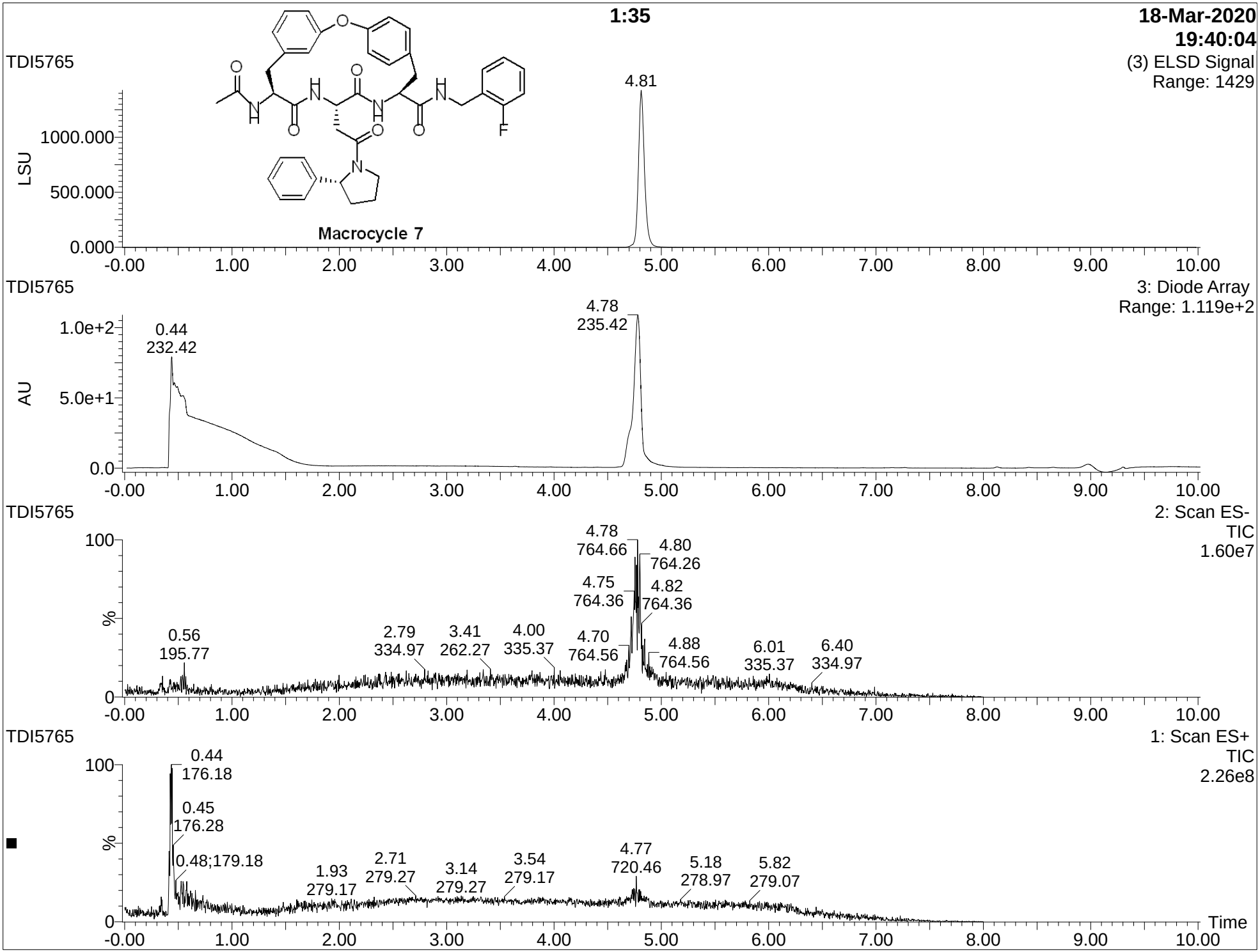


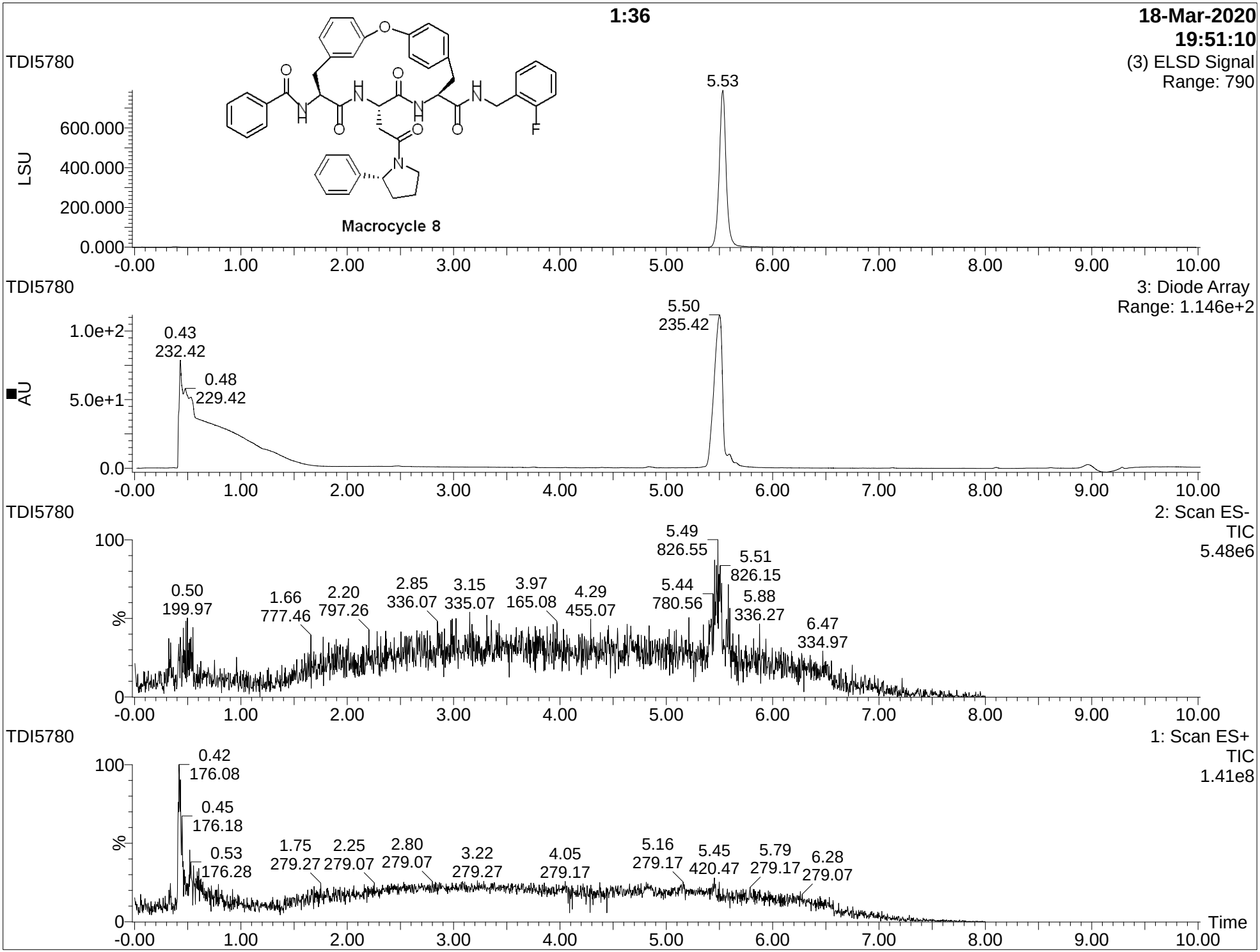

1:37
18-Mar-2020
20:02:15
TDI6242
(3) ELSD Signal
Range: 1966
4.51
LSU
1500.000
1000.000
500.000
0.000
Macrocycle 4
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI6242
3: Diode Array
Range: 1.812e+2
4.48
277.42
0.39
232.42
AU
1.5e+2
1.0e+2
5.0e+1
0.0
TDI6242
2: Scan ES-
TIC
3.18e7
4.48
549.47
4.49
595.47
4.44
595.47
4.51
595.37
4.42
595.47
4.54
549.27
0.46
222.87
2.19
585.37
2.79
307.97
3.17
947.85
3.46
382.17
5.54
593.07
5.87
751.76
6.35
463.07
100
%
0
TDI6242
1: Scan ES+
TIC
3.74e8
4.45
551.47
4.48
551.47
4.43
551.47
4.50
551.37
4.54
551.37
0.38
175.98
0.44
175.98
2.34
224.27
2.83
279.07
3.14
157.28
4.02
279.27
5.23
279.17
Time

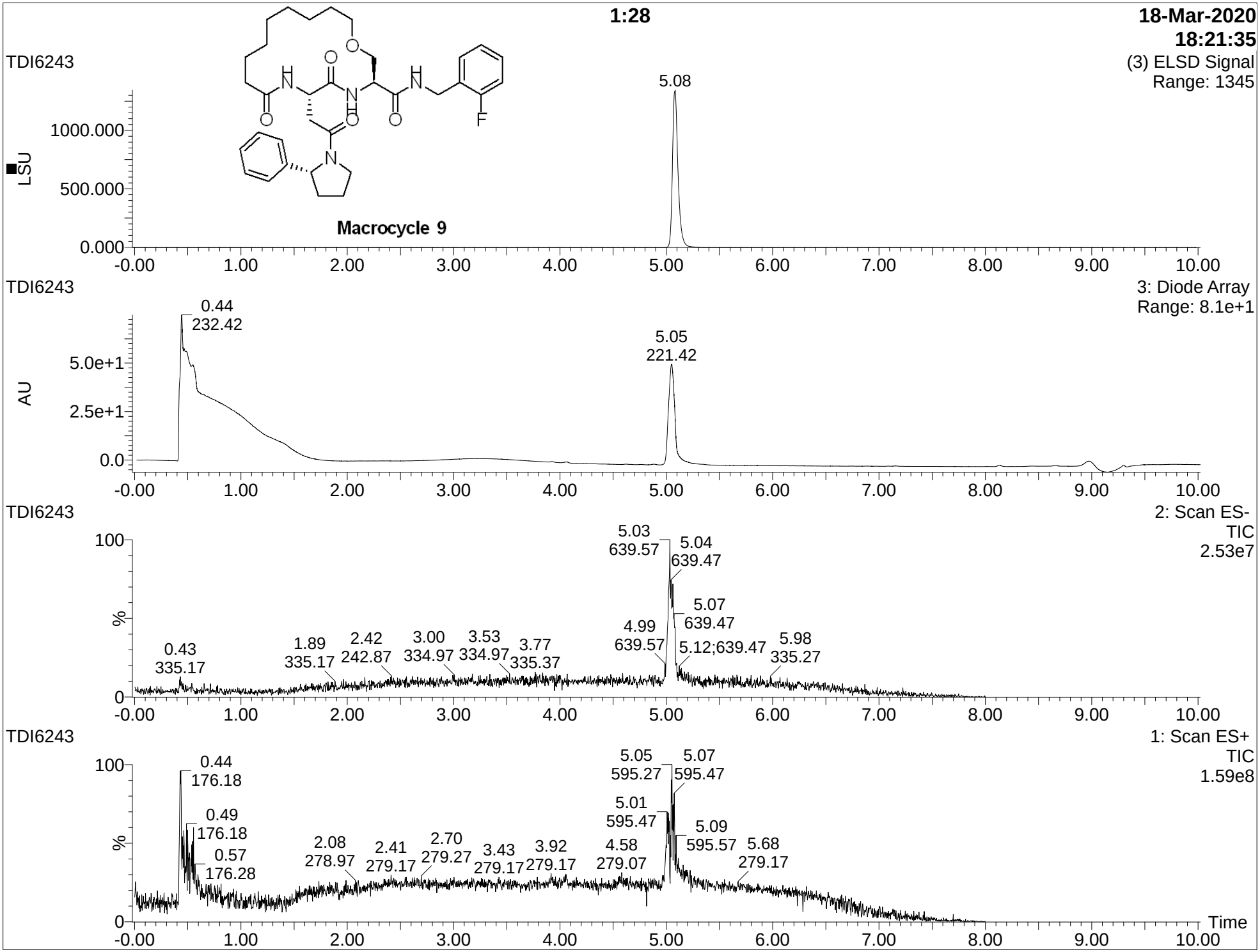

1:31
18-Mar-2020
18:55:18
TDI4407
(3) ELSD Signal
Range: 201
LSU
200.000
100.000
0.000
0.41
3.63
CP1
-0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
10.00
TDI4407
3: Diode Array
Range: 8.192e+1
AU
7.5e+1
5.0e+1
2.5e+1
0.0
0.43
232.42
3.58
221.42
8.97
223.42
TDI4407
2: Scan ES-
TIC
8.64e6
%
100
0
3.60
635.57
3.62
589.67
3.68
589.47
0.51
335.07
0.82
248.97
1.65
334.77
2.57
196.97
2.88
335.17
4.82
335.47
5.10
334.87
5.58
334.97
6.09
335.17
TDI4407
1: Scan ES+
TIC
1.77e8
%
100
0
0.42
179.28
0.50
179.08
0.55
179.08
1.62
279.17
2.61
279.27
2.89
279.17
3.61
591.47
3.67
591.37
3.68
591.37
3.78;279.27
4.85
279.07
5.15
279.27
5.72
279.37
Time

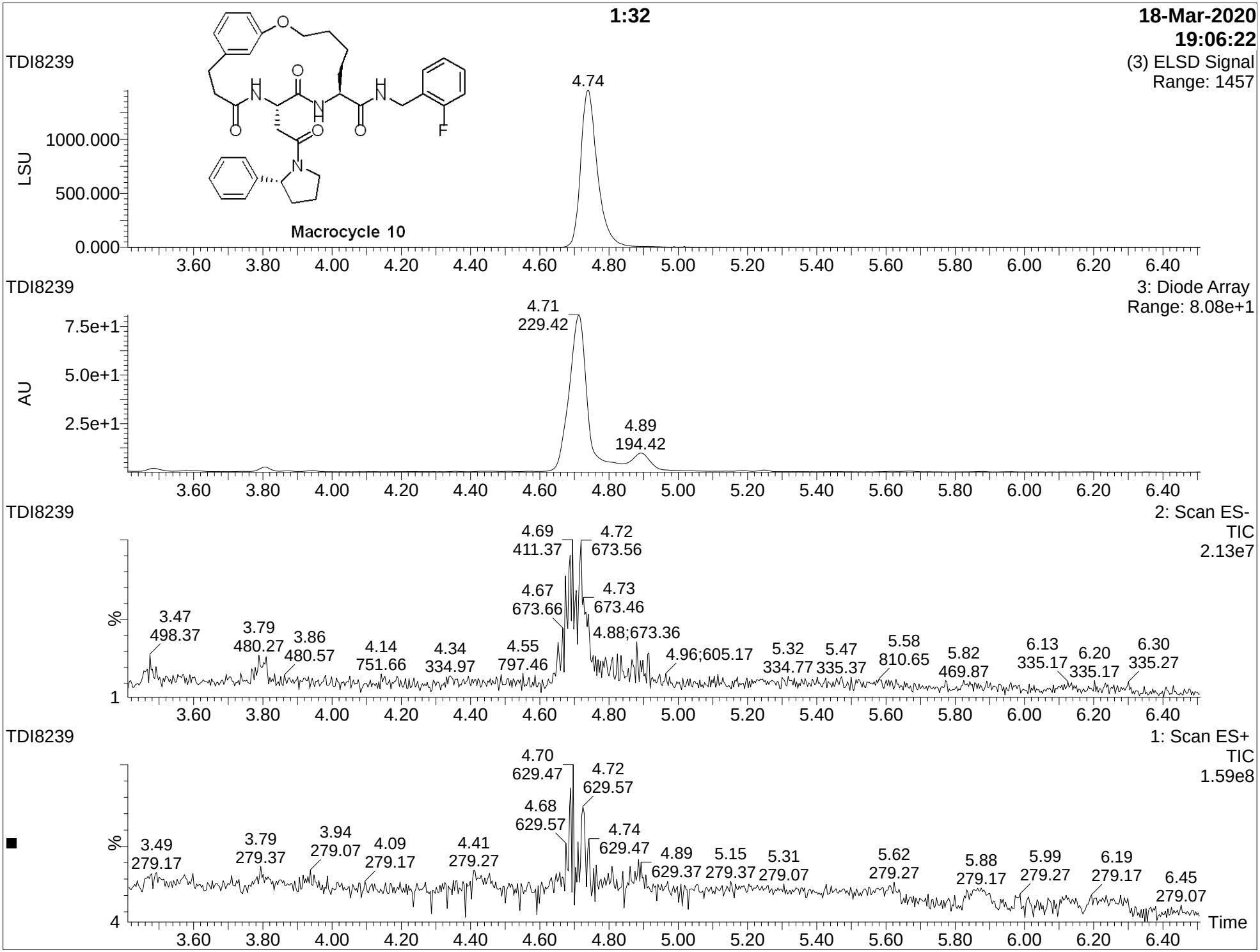

1:26
18-Mar-2020
17:14:36
TDI5574
(3) ELSD Signal
Range: 282
4.44
LSU
200.000
100.000
0.000
Macrocycle 5
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI5574
3: Diode Array
Range: 9.901e+1
4.41
232.42
0.41
232.42
AU
7.5e+1
5.0e+1
2.5e+1
0.0
4.51
220.42
8.99
224.42
TDI5574
2: Scan ES-
TIC
1.59e7
4.39
631.37
4.41
631.37
4.42
631.37
4.36
631.47
4.48;583.17
100
%
0.31
207.17
1.17
312.87
1.41
312.47
2.95
380.07
3.44
197.37
4.32;935.75
5.68
184.77
6.21
367.87
0
TDI5574
1: Scan ES+
TIC
1.76e8
4.42
587.47
0.41
176.18
0.42
176.18
4.37
587.27
5.13
278.97
4.43
587.47
5.65
279.07
6.18
279.17
3.74
279.17
3.07
279.07
2.54
279.17
6.72
279.27
0.50;176.08
%
0
Time

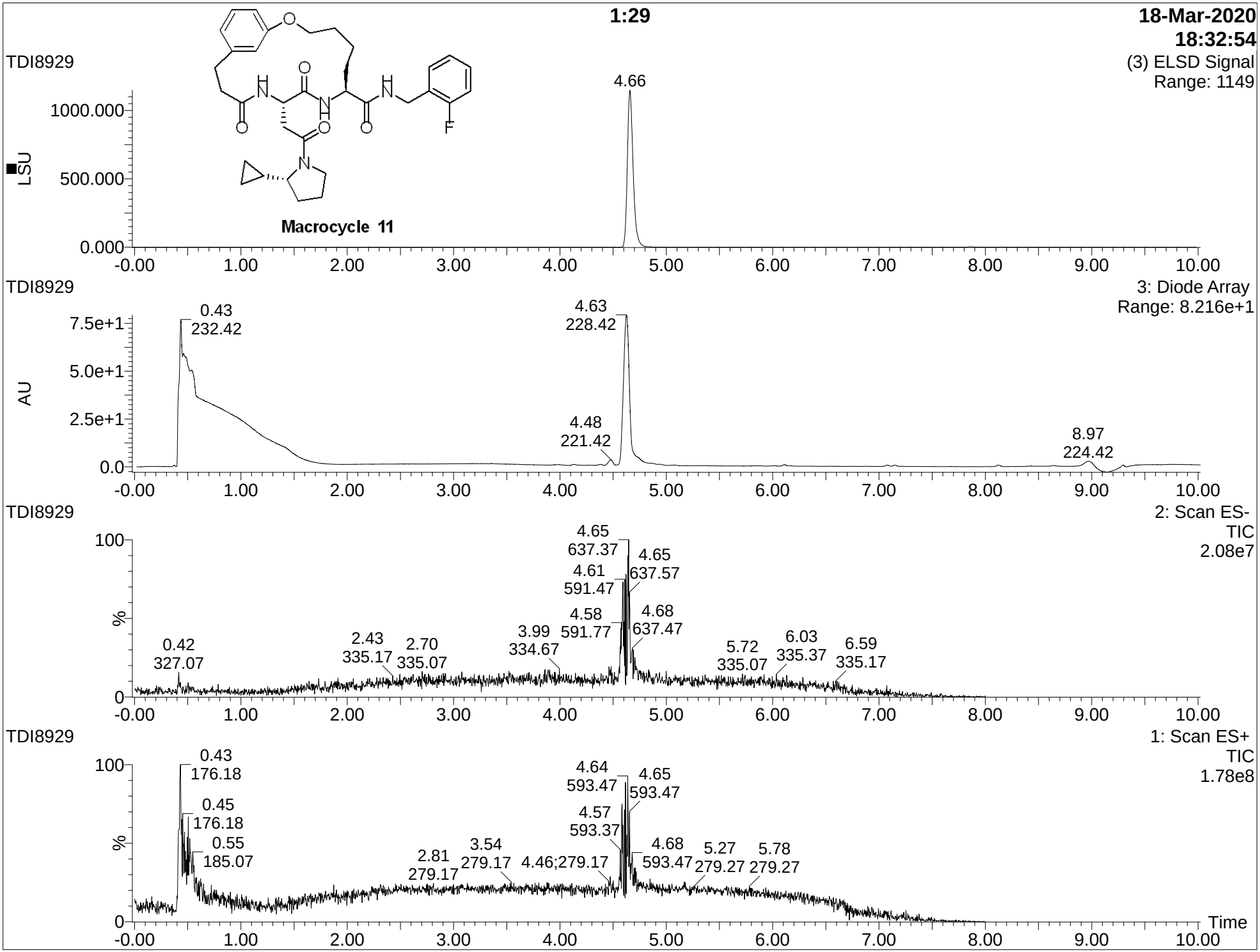

1:25
18-Mar-2020
16:55:21
TDI5575
(3) ELSD Signal
Range: 1965
5.23
LSU
1500.000
1000.000
500.000
0.000
Macrocycle 6
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI5575
3: Diode Array
Range: 1.504e+2
5.22
240.42
0.42
232.42
5.37
194.42
AU
1.0e+2
5.0e+1
0.0
TDI5575
2: Scan ES-
TIC
2.31e7
5.19
707.56
5.22
707.46
5.15
707.46
5.29
707.36
0.41
256.97
1.71
285.87
2.43
227.97
3.63
241.97
4.01
547.37
5.13;707.26
5.37
709.36
5.95
725.26
%
100
0
TDI5575
1: Scan ES+
TIC
2.97e8
0.42
175.98
0.45
176.28
1.70
278.97
4.05
279.07
4.79
309.27
5.17
663.46
5.85
279.27
6.34
279.27
6.68
278.97
Time

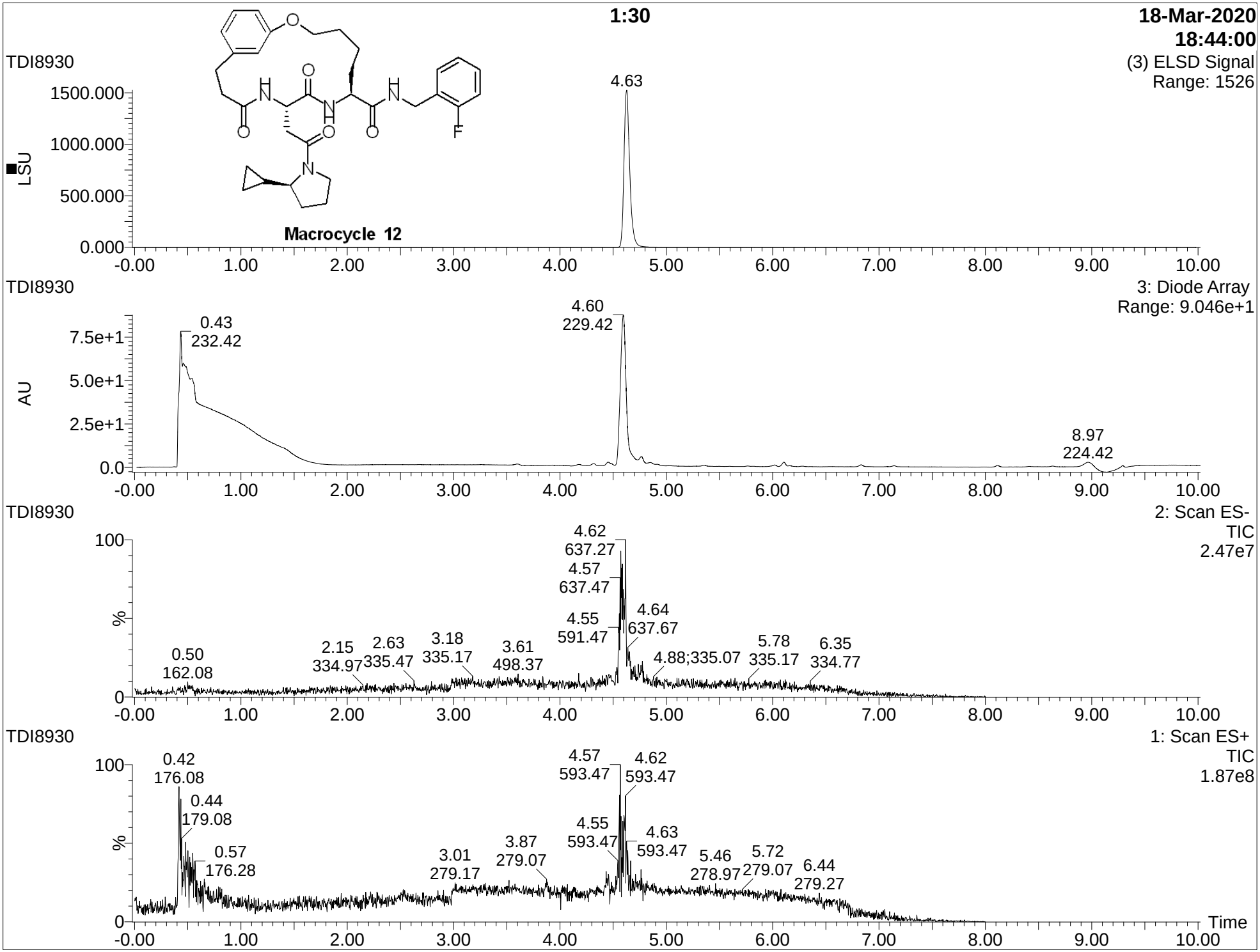

1:35
18-Mar-2020
19:40:04
TDI5765
(3) ELSD Signal
Range: 1429
4.81
LSU
1000.000
500.000
0.000
Macrocycle 7
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI5765
3: Diode Array
Range: 1.119e+2
4.78
235.42
0.44
232.42
AU
1.0e+2
5.0e+1
0.0
TDI5765
2: Scan ES-
TIC
1.60e7
4.78
764.66
4.80
764.26
4.75
764.36
4.82
764.36
0.56
195.77
2.79
334.97
3.41
262.27
4.00
335.37
4.70
764.56
4.88
764.56
6.01
335.37
6.40
334.97
%
100
0
TDI5765
1: Scan ES+
TIC
2.26e8
0.44
176.18
0.45
176.28
0.48;179.18
1.93
279.17
2.71
279.27
3.14
279.27
3.54
279.17
4.77
720.46
5.18
278.97
5.82
279.07
Time

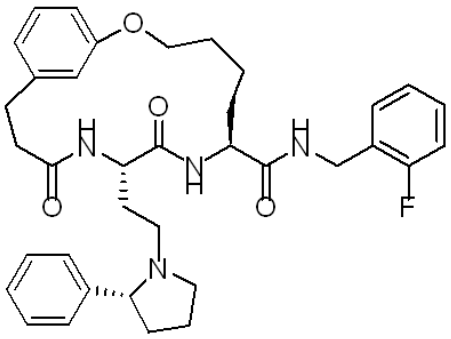

1:36
18-Mar-2020
19:51:10
TDI5780
(3) ELSD Signal
Range: 790
5.53
LSU
600.000
400.000
200.000
0.000
Macrocycle 8
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI5780
3: Diode Array
Range: 1.146e+2
5.50
235.42
0.43
232.42
0.48
229.42
AU
1.0e+2
5.0e+1
0.0
TDI5780
2: Scan ES-
TIC
5.48e6
5.49
826.55
5.51
826.15
0.50
199.97
1.66
777.46
2.20
797.26
2.85
336.07
3.15
335.07
3.97
165.08
4.29
455.07
5.44
780.56
5.88
336.27
6.47
334.97
%
100
0
TDI5780
1: Scan ES+
TIC
1.41e8
0.42
176.08
0.45
176.18
0.53
176.28
1.75
279.27
2.25
279.07
2.80
279.07
3.22
279.27
4.05
279.17
5.16
279.17
5.45
420.47
5.79
279.17
6.28
279.07
Time


1:28
18-Mar-2020
18:21:35
TDI6243
(3) ELSD Signal
Range: 1345
5.08
LSU
1000.000
500.000
0.000
Macrocycle 9
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI6243
3: Diode Array
Range: 8.1e+1
0.44
232.42
5.05
221.42
AU
5.0e+1
2.5e+1
0.0
TDI6243
2: Scan ES-
TIC
2.53e7
5.03
639.57
5.04
639.47
5.07
639.47
4.99
639.57
5.12;639.47
5.98
335.27
0.43
335.17
1.89
335.17
2.42
242.87
3.00
334.97
3.53
334.97
3.77
335.37
%
100
0
TDI6243
1: Scan ES+
TIC
1.59e8
5.05
595.27
5.07
595.47
0.44
176.18
5.01
595.47
0.49
176.18
0.57
176.28
2.08
278.97
2.41
279.17
2.70
279.27
3.43
279.17
3.92
279.17
4.58
279.07
5.09
595.57
5.68
279.17
Time


1:32
18-Mar-2020
19:06:22
TDI8239
(3) ELSD Signal
Range: 1457
LSU
1000.000
500.000
0.000
4.74
Macrocycle 10
3.60 3.80 4.00 4.20 4.40 4.60 4.80 5.00 5.20 5.40 5.60 5.80 6.00 6.20 6.40
TDI8239
3: Diode Array
Range: 8.08e+1
AU
7.5e+1
5.0e+1
2.5e+1
4.71
229.42
4.89
194.42
TDI8239
2: Scan ES-
TIC
2.13e7
%
1
4.69
411.37
4.72
673.56
4.67
673.66
4.73
673.46
4.88;673.36
3.47
498.37
3.79
480.27
3.86
480.57
4.14
751.66
4.34
334.97
4.55
797.46
4.96;605.17
5.32
334.77
5.47
335.37
5.58
810.65
5.82
469.87
6.13
335.17
6.20
335.17
6.30
335.27
TDI8239
1: Scan ES+
TIC
1.59e8
%
4
4.70
629.47
4.72
629.57
4.68
629.57
4.74
629.47
3.49
279.17
3.79
279.37
3.94
279.07
4.09
279.17
4.41
279.27
4.89
629.37
5.15
279.37
5.31
279.07
5.62
279.27
5.88
279.17
5.99
279.27
6.19
279.17
6.45
279.07
Time

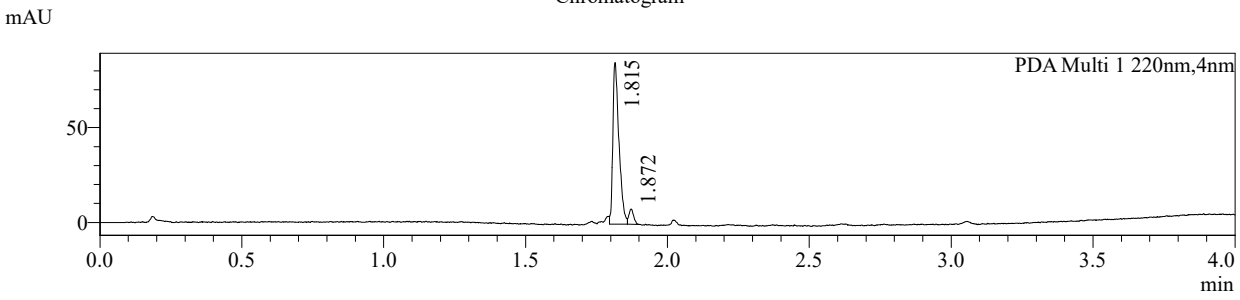

1:29
18-Mar-2020
18:32:54
TDI8929
(3) ELSD Signal
Range: 1149
4.66
LSU
1000.000
500.000
0.000
Macrocycle 11
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI8929
3: Diode Array
Range: 8.216e+1
0.43
232.42
4.63
228.42
4.48
221.42
8.97
224.42
AU
7.5e+1
5.0e+1
2.5e+1
0.0
TDI8929
2: Scan ES-
TIC
2.08e7
4.65
637.37
4.65
637.57
4.61
591.47
4.58
591.77
4.68
637.47
3.99
334.67
0.42
327.07
2.43
335.17
2.70
335.07
5.72
335.07
6.03
335.37
6.59
335.17
%
100
0
TDI8929
1: Scan ES+
TIC
1.78e8
0.43
176.18
0.45
176.18
0.55
185.07
4.64
593.47
4.65
593.47
4.57
593.37
4.68
593.47
2.81
279.17
3.54
279.17
4.46;279.17
5.27
279.27
5.78
279.27
Time

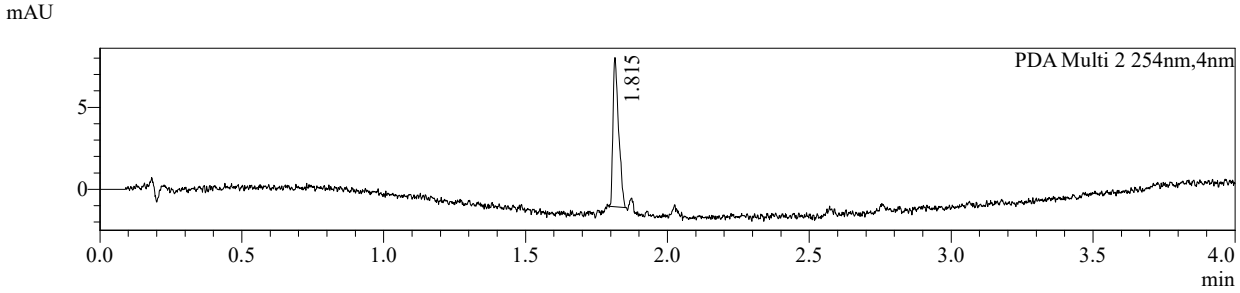

1:30
18-Mar-2020
18:44:00
TDI8930
(3) ELSD Signal
Range: 1526
4.63
LSU
1500.000
1000.000
500.000
0.000
Macrocycle 12
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00 8.00 9.00 10.00
TDI8930
3: Diode Array
Range: 9.046e+1
4.60
229.42
0.43
232.42
8.97
224.42
AU
7.5e+1
5.0e+1
2.5e+1
0.0
TDI8930
2: Scan ES-
TIC
2.47e7
4.62
637.27
4.57
637.47
4.55
591.47
4.64
637.67
0.50
162.08
2.15
334.97
2.63
335.47
3.18
335.17
3.61
498.37
4.88;335.07
5.78
335.17
6.35
334.77
%
100
0
TDI8930
1: Scan ES+
TIC
1.87e8
0.42
176.08
0.44
179.08
0.57
176.28
3.01
279.17
3.87
279.07
4.57
593.47
4.62
593.47
4.55
593.47
4.63
593.47
5.46
278.97
5.72
279.07
6.44
279.27
Time



Macrocycle 13

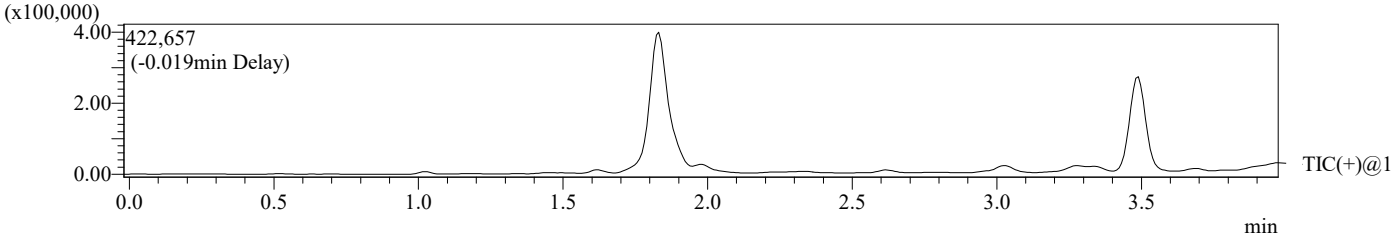
Chromatogram





1 PDA Multi 1 / 220nm,4nm
2 PDA Multi 2 / 254nm,4nm

MS Chromatogram



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Integration Result

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Peak Table

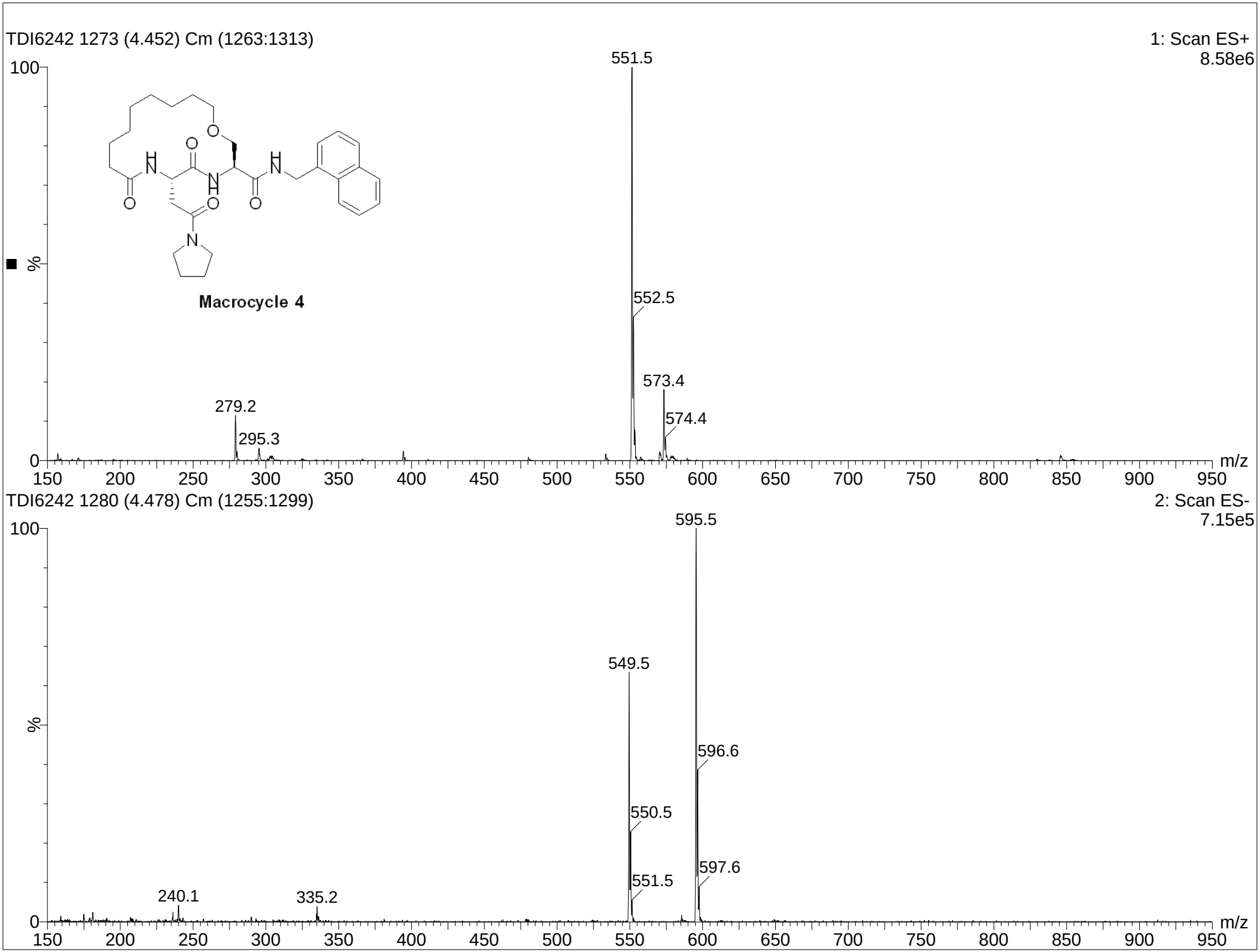
PDA Ch1 220nm

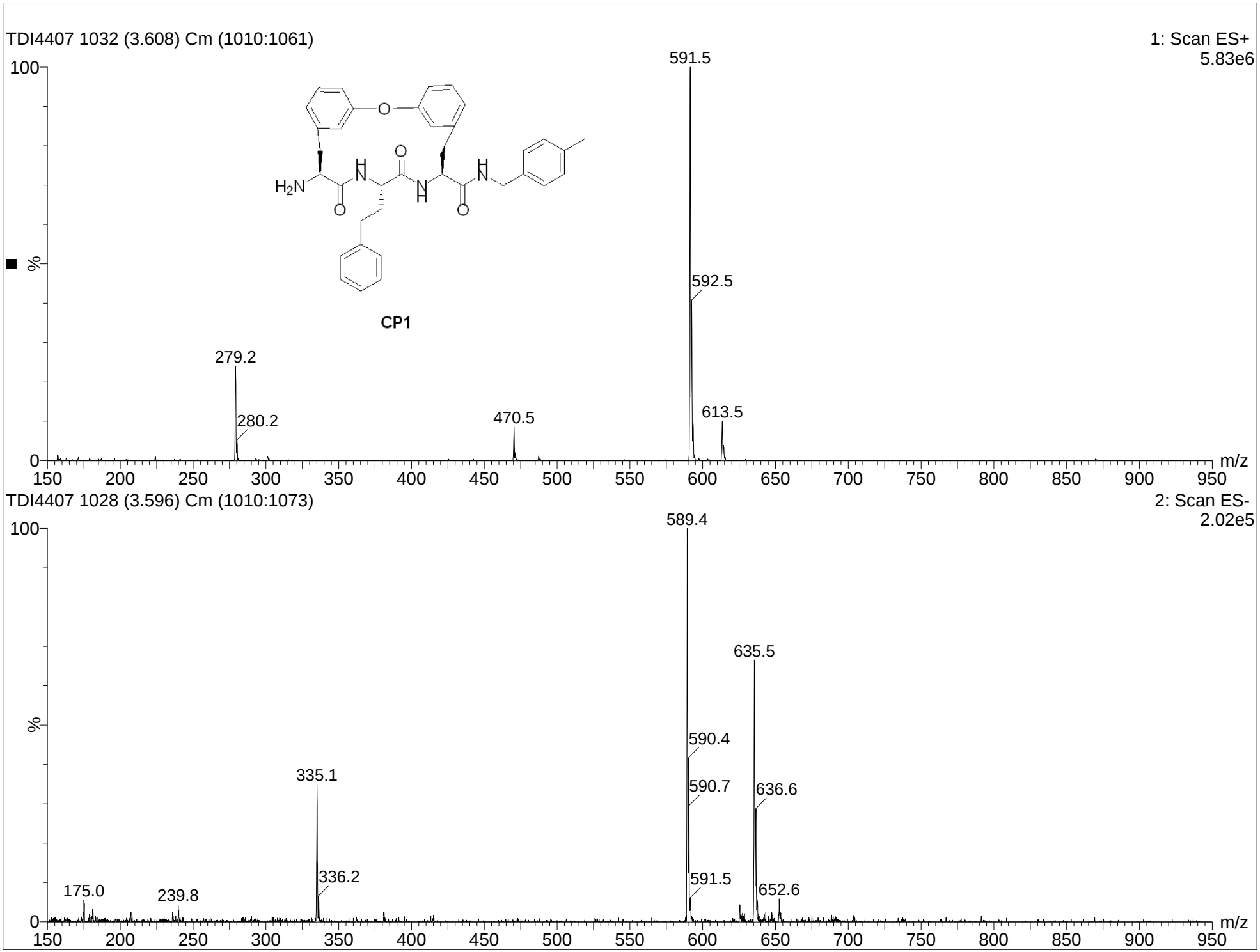
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	1.815	85256	91.377	0.040	128035	93.142
2	1.872	8046	8.623	0.035	9427	6.858

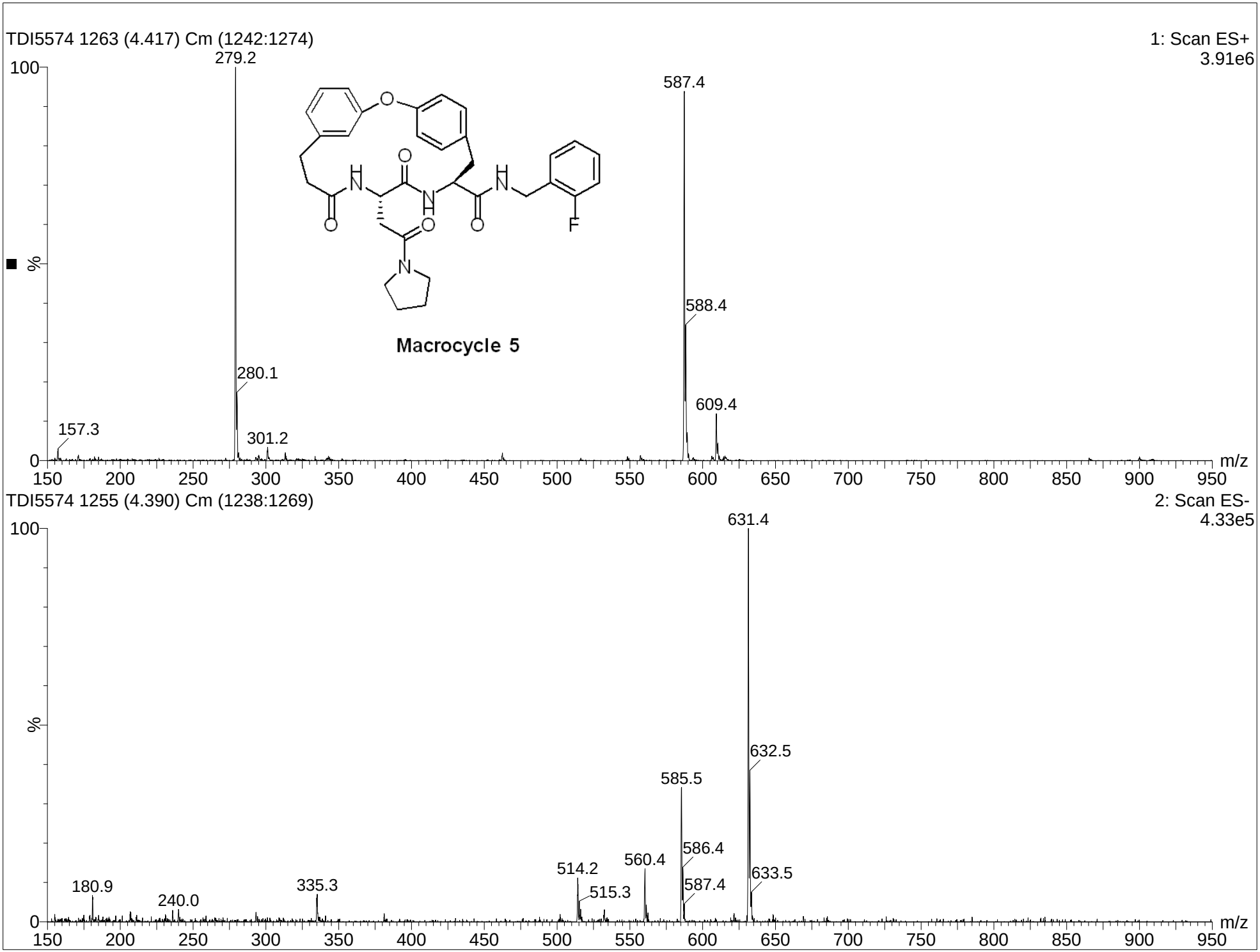
Peak Table

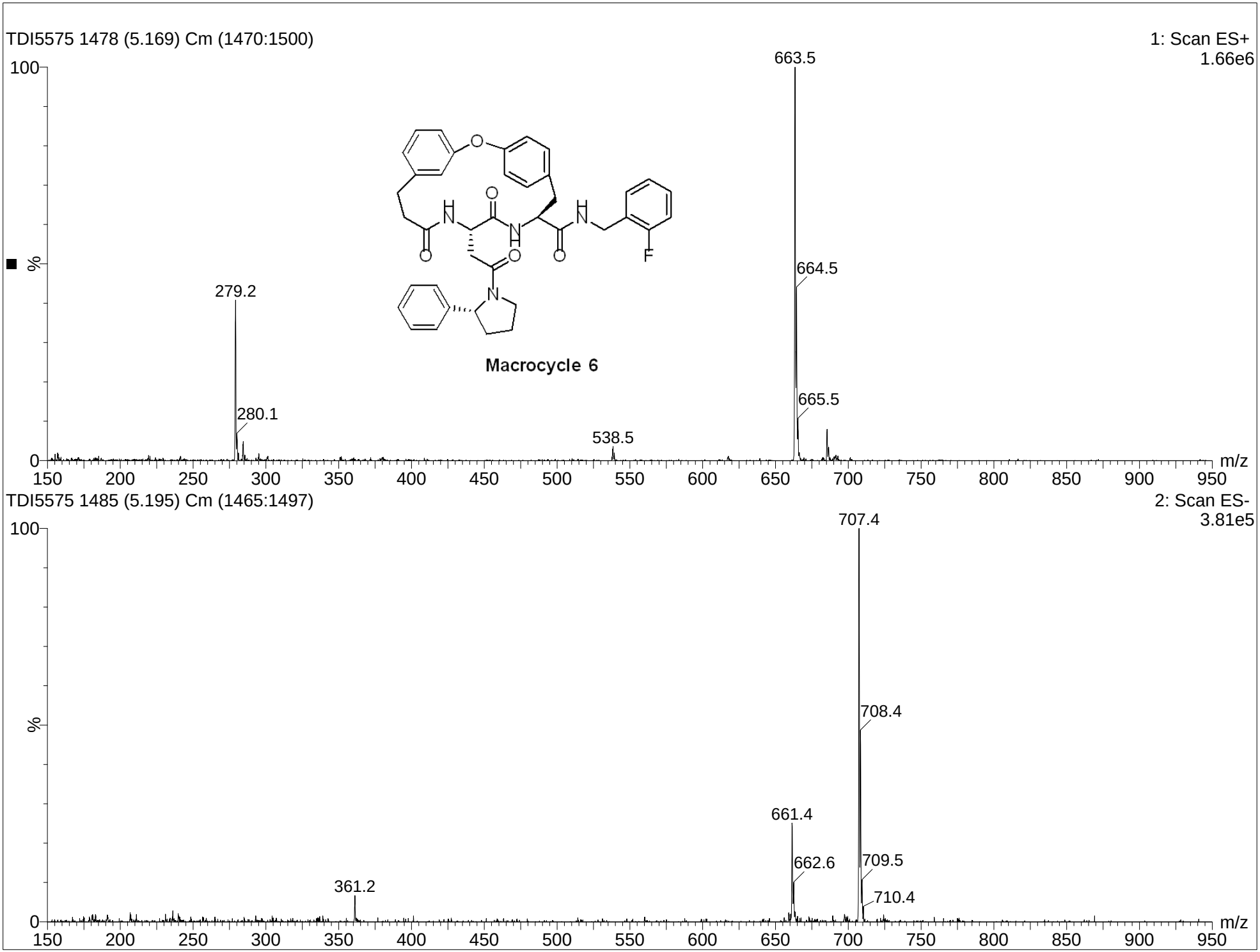
PDA Ch2 254nm

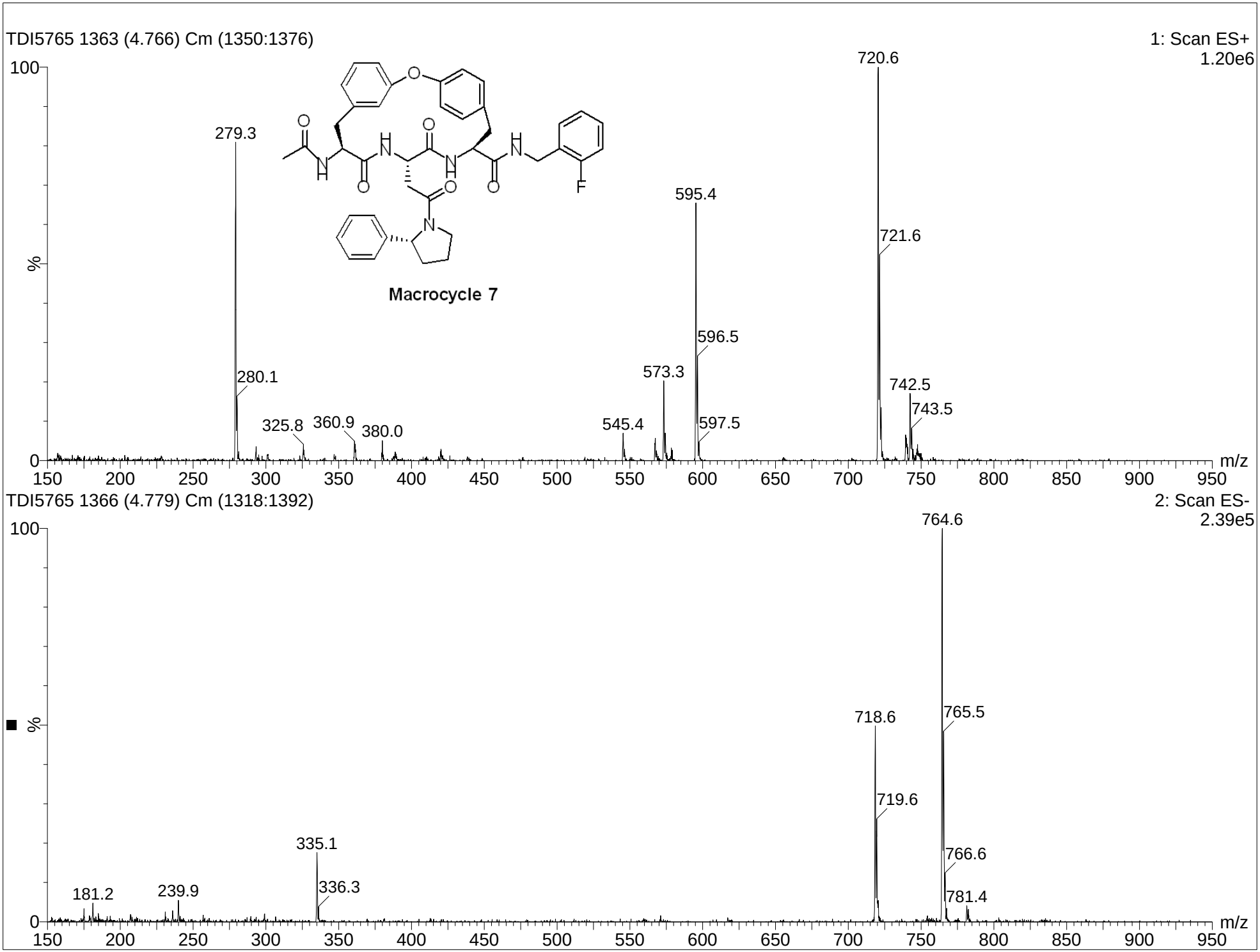
Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	1.815	9100	100.000	0.039	12595	100.000

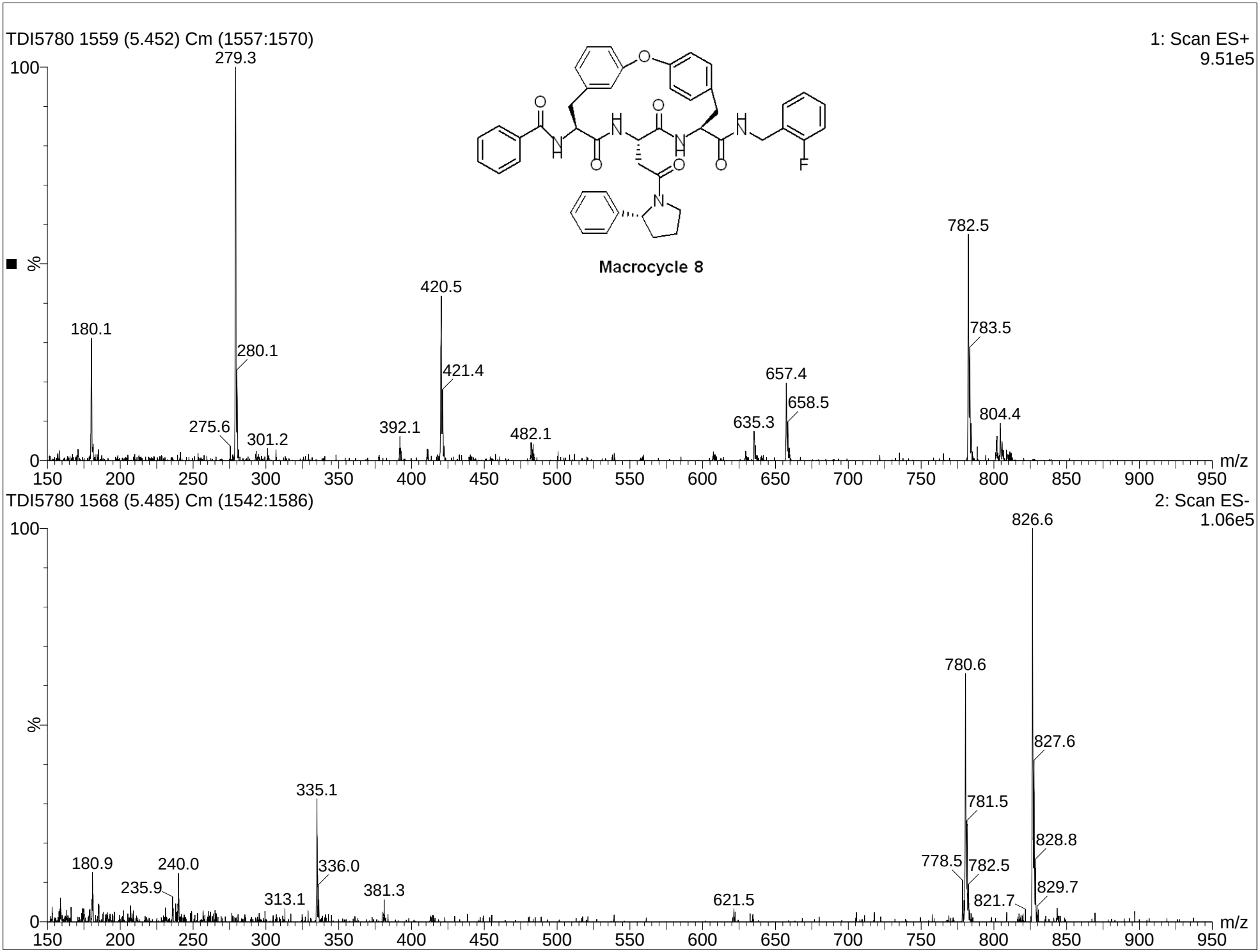

TDI6242 1273 (4.452) Cm (1263:1313)
1: Scan ES+
8.58e6
100
%
0
551.5
552.5
573.4
574.4
279.2
295.3
Macrocycle 4
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z
TDI6242 1280 (4.478) Cm (1255:1299)
2: Scan ES-
7.15e5
100
%
0
595.5
549.5
596.6
550.5
597.6
551.5
240.1
335.2
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z

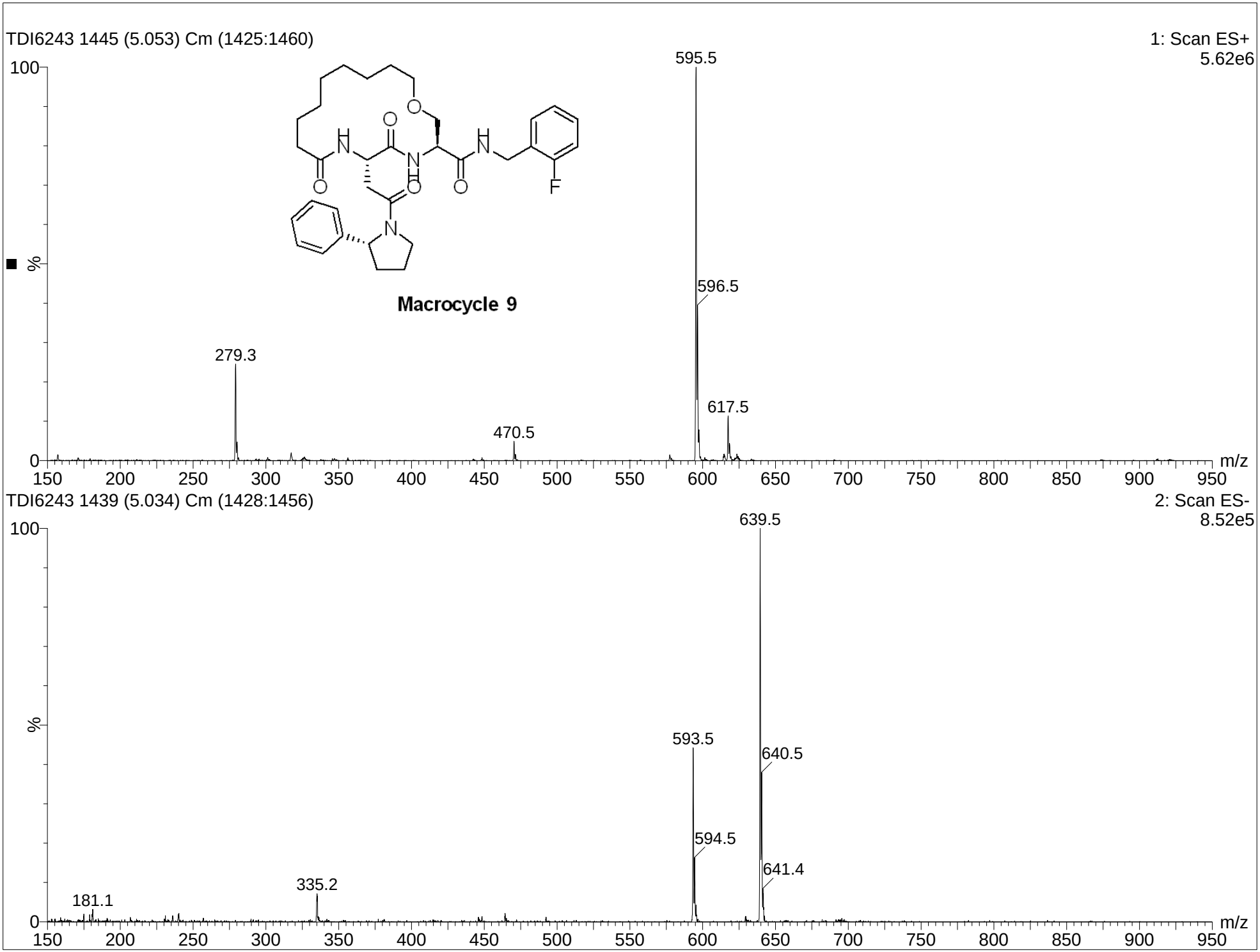

TDI4407 1032 (3.608) Cm (1010:1061)
1: Scan ES+
5.83e6
100
%
0
591.5
592.5
279.2
280.2
470.5
613.5
CP1
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z
TDI4407 1028 (3.596) Cm (1010:1073)
2: Scan ES-
2.02e5
100
%
0
589.4
635.5
590.4
590.7
636.6
335.1
336.2
591.5
652.6
175.0
239.8
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z

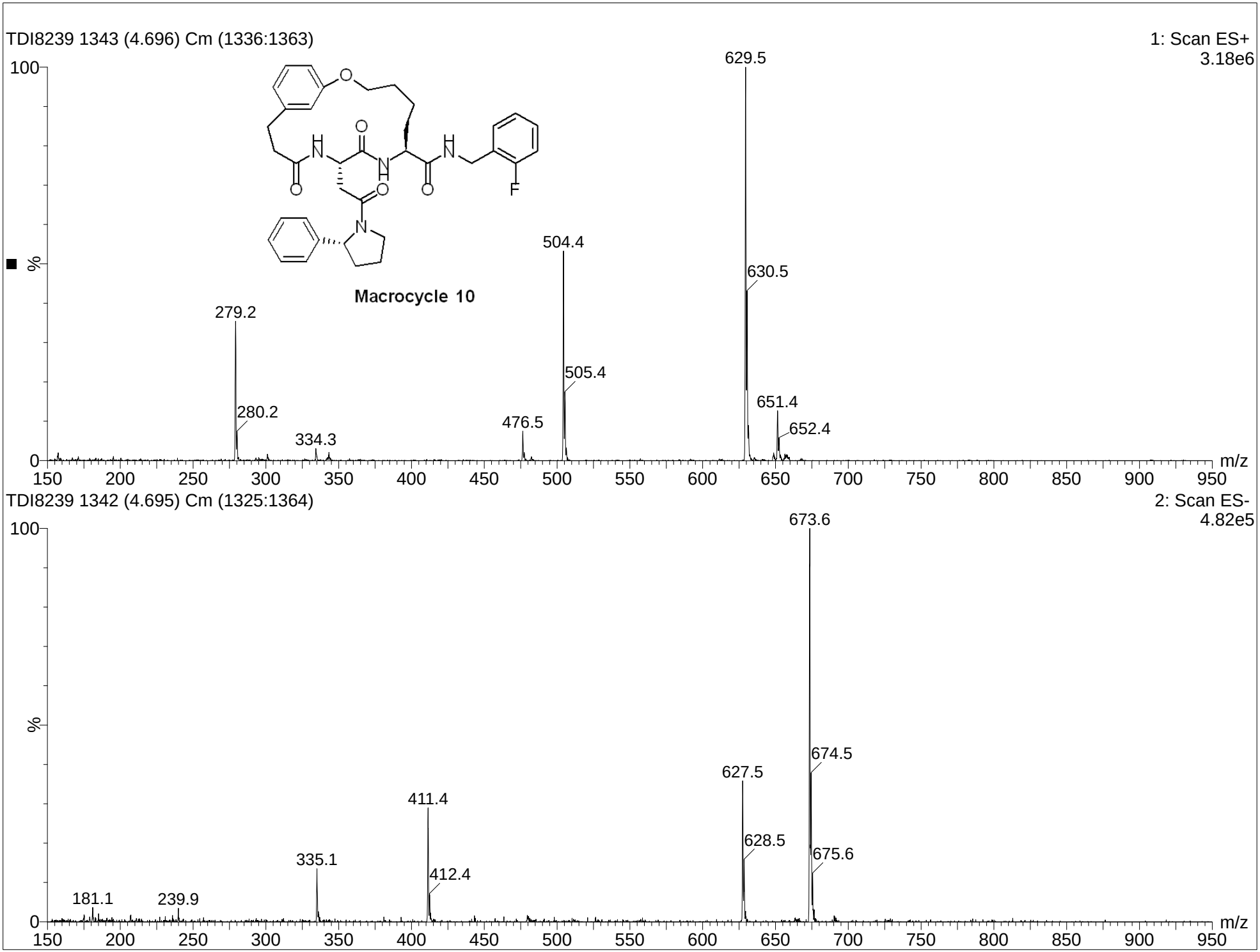

TDI5574 1263 (4.417) Cm (1242:1274)
1: Scan ES+
3.91e6
100
%
0
279.2
587.4
588.4
280.1
609.4
157.3
301.2
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z
Macrocycle 5
TDI5574 1255 (4.390) Cm (1238:1269)
2: Scan ES-
4.33e5
100
%
0
631.4
632.5
585.5
586.4
560.4
514.2
633.5
587.4
515.3
180.9
240.0
335.3
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
m/z

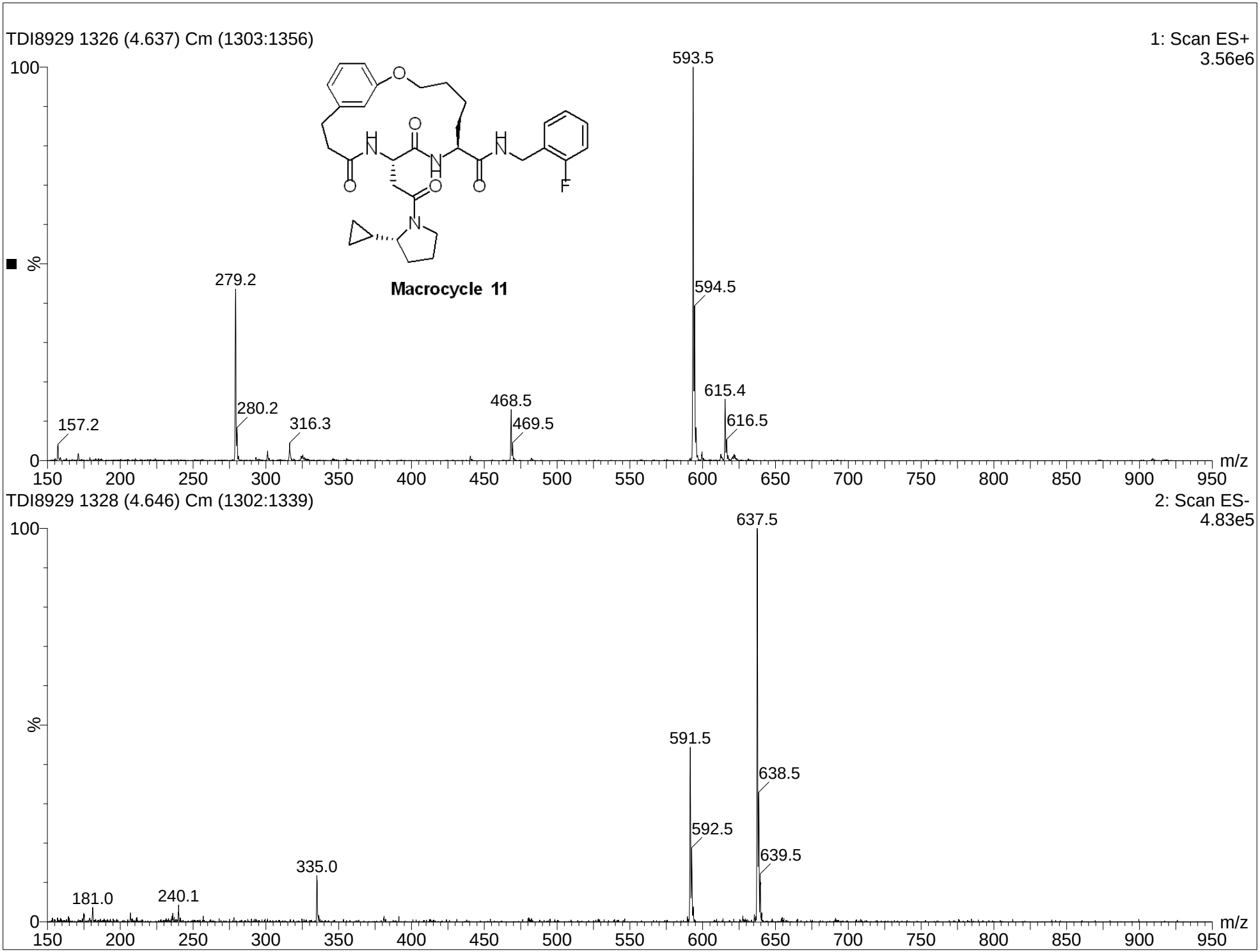

TDI5575 1478 (5.169) Cm (1470:1500)
1: Scan ES+
1.66e6
100
%
0
663.5
664.5
665.5
279.2
280.1
538.5
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
Macrocycle 6
TDI5575 1485 (5.195) Cm (1465:1497)
2: Scan ES-
3.81e5
100
%
0
707.4
708.4
709.5
710.4
661.4
662.6
361.2
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950

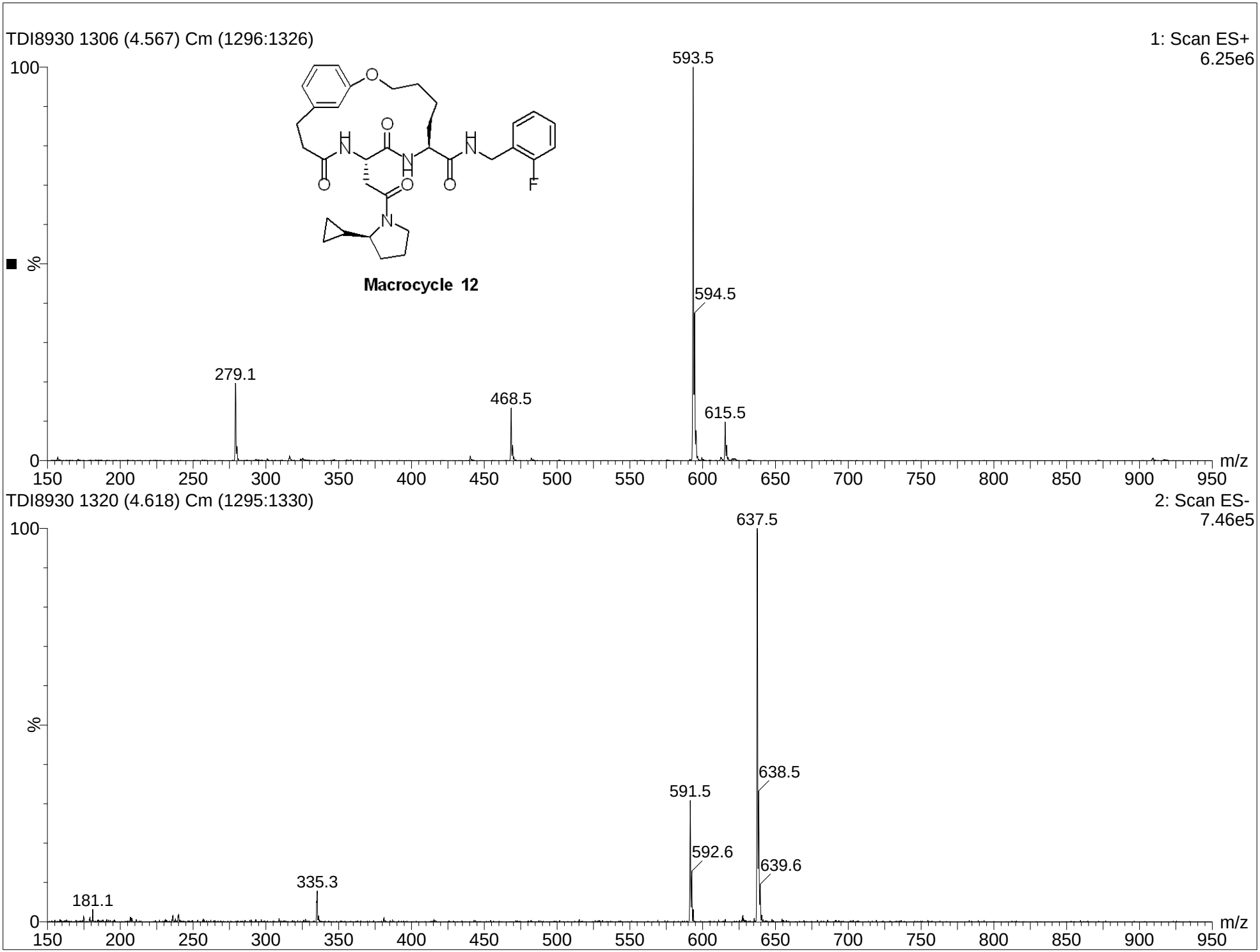

TDI5765 1363 (4.766) Cm (1350:1376)
1: Scan ES+
1.20e6
100
%
0
279.3
280.1
325.8
360.9
380.0
545.4
573.3
595.4
596.5
597.5
720.6
721.6
742.5
743.5
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
Macrocycle 7
TDI5765 1366 (4.779) Cm (1318:1392)
2: Scan ES-
2.39e5
100
%
0
181.2
239.9
335.1
336.3
718.6
719.6
764.6
765.5
766.6
781.4
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950

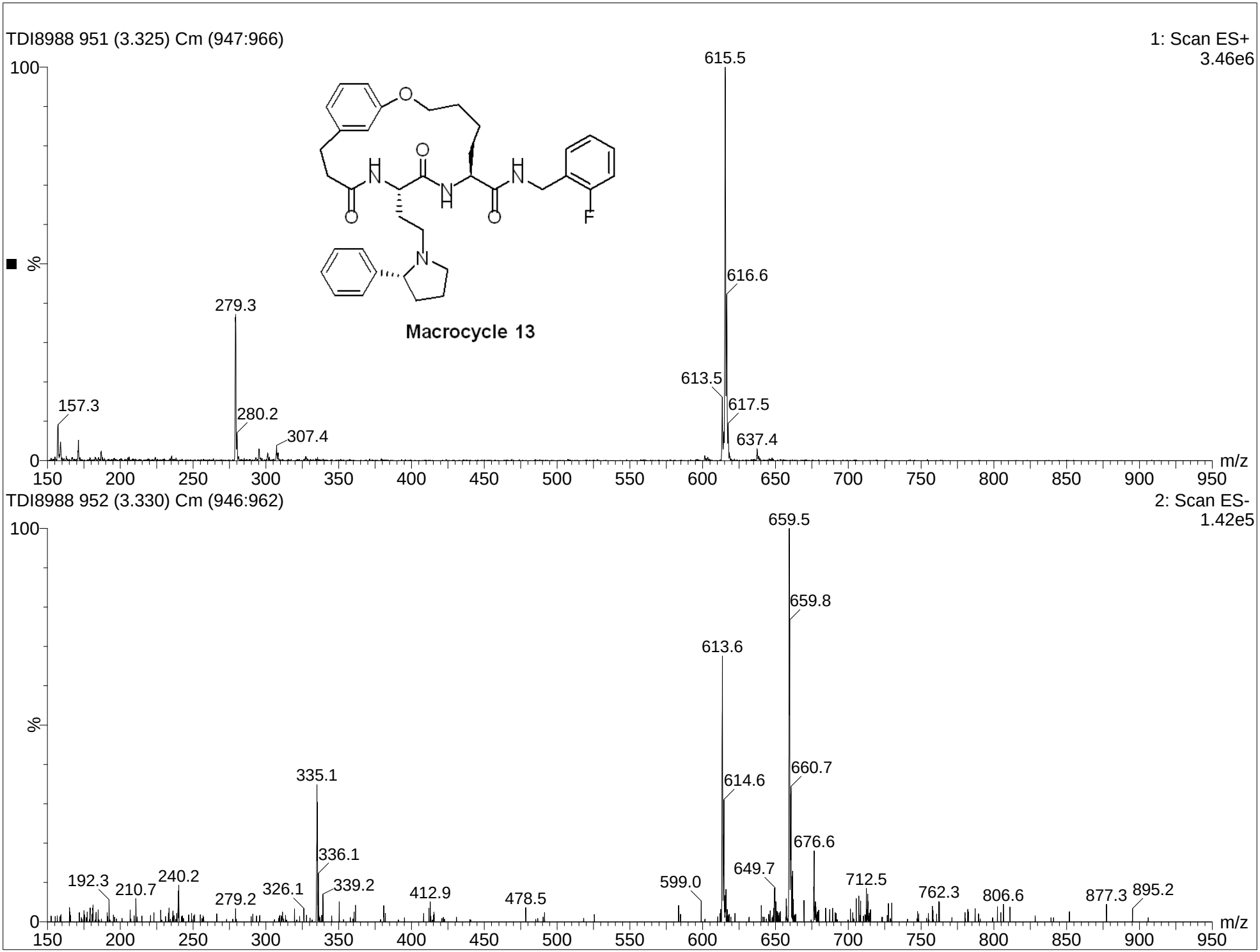

TDI5780 1559 (5.452) Cm (1557:1570)
1: Scan ES+
9.51e5
100
%
0
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
279.3
180.1
280.1
275.6
301.2
392.1
420.5
421.4
482.1
635.3
657.4
658.5
782.5
783.5
804.4
Macrocycle 8
TDI5780 1568 (5.485) Cm (1542:1586)
2: Scan ES-
1.06e5
100
%
0
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
180.9
235.9
240.0
313.1
335.1
336.0
381.3
621.5
778.5
780.6
781.5
782.5
821.7
826.6
827.6
828.8
829.7

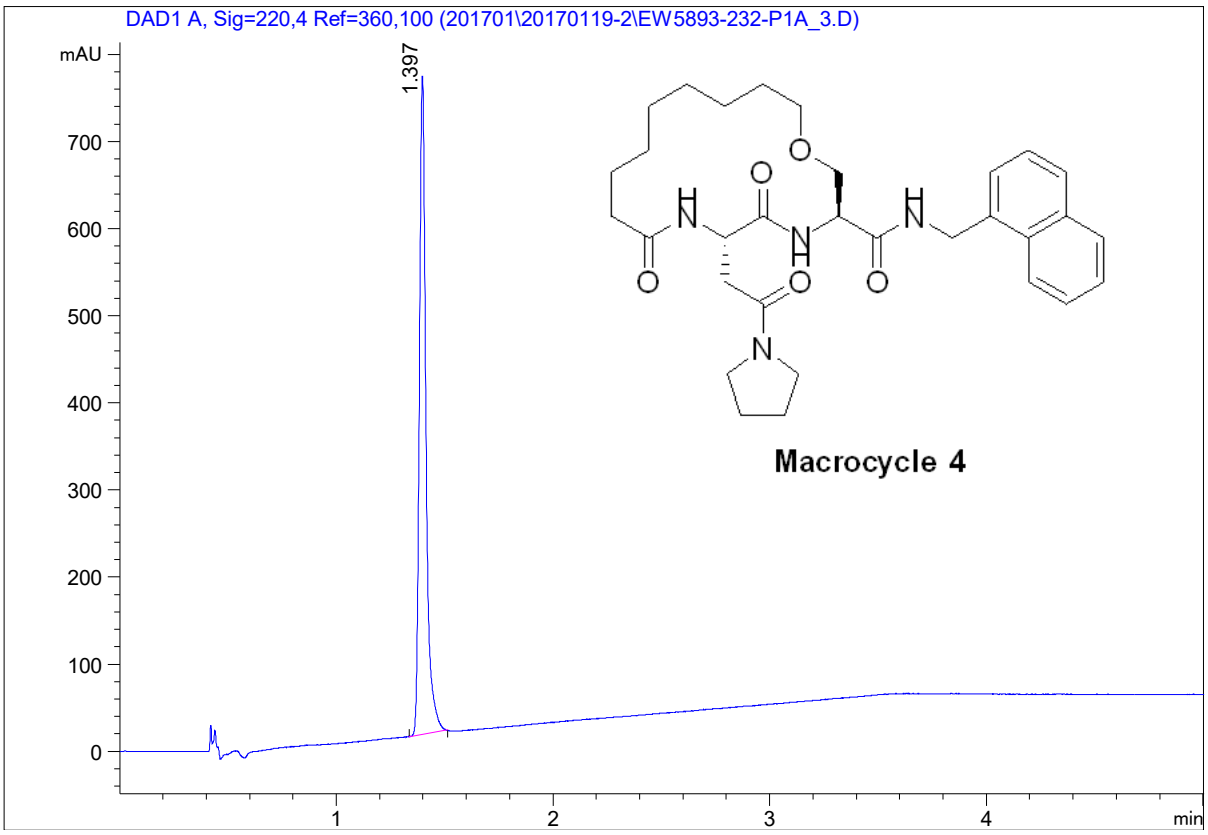

TDI6243 1445 (5.053) Cm (1425:1460)
1: Scan ES+
5.62e6
595.5
596.5
279.3
617.5
470.5
Macrocycle 9
TDI6243 1439 (5.034) Cm (1428:1456)
2: Scan ES-
8.52e5
639.5
593.5
640.5
594.5
641.4
335.2
181.1
%
m/z
100
0
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
900
950


TDI8239 1343 (4.696) Cm (1336:1363)
1: Scan ES+
3.18e6
100
%
0
629.5
504.4
630.5
279.2
505.4
651.4
280.2
476.5
652.4
334.3
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
Macrocycle 10
TDI8239 1342 (4.695) Cm (1325:1364)
2: Scan ES-
4.82e5
100
%
0
673.6
674.5
627.5
411.4
628.5
335.1
675.6
412.4
181.1
239.9
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950


TDI8929 1326 (4.637) Cm (1303:1356)
1: Scan ES+
3.56e6
100
%
0
593.5
594.5
279.2
280.2
316.3
157.2
468.5
469.5
615.4
616.5
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
Macrocycle 11
TDI8929 1328 (4.646) Cm (1302:1339)
2: Scan ES-
4.83e5
100
%
0
637.5
591.5
638.5
592.5
639.5
335.0
181.0
240.1
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950

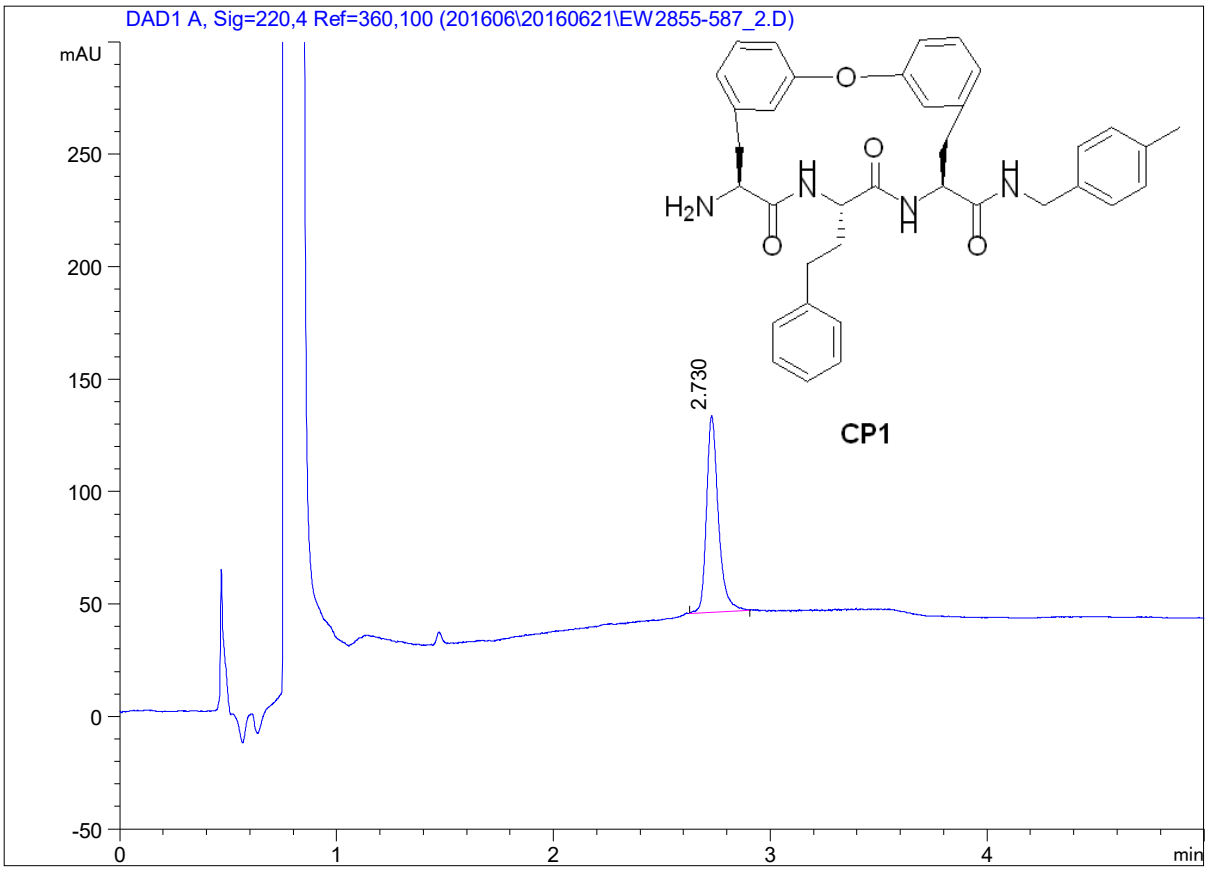

TDI8930 1306 (4.567) Cm (1296:1326)
1: Scan ES+
6.25e6
593.5
594.5
279.1
468.5
615.5
Macrocycle 12
%
m/z
TDI8930 1320 (4.618) Cm (1295:1330)
2: Scan ES-
7.46e5
637.5
638.5
591.5
592.6
639.6
335.3
181.1


TDI8988 951 (3.325) Cm (947:966)
1: Scan ES+
3.46e6
100
%
0
615.5
616.6
279.3
613.5
617.5
157.3
280.2
307.4
637.4
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950
Macrocycle 13
TDI8988 952 (3.330) Cm (946:962)
2: Scan ES-
1.42e5
100
%
0
659.5
659.8
613.6
660.7
614.6
335.1
676.6
336.1
649.7
192.3
240.2
210.7
339.2
279.2
326.1
412.9
478.5
599.0
712.5
762.3
806.6
877.3
895.2
m/z
150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950



DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	1.397	763.937	0.035	0.683	1606.708	100.000



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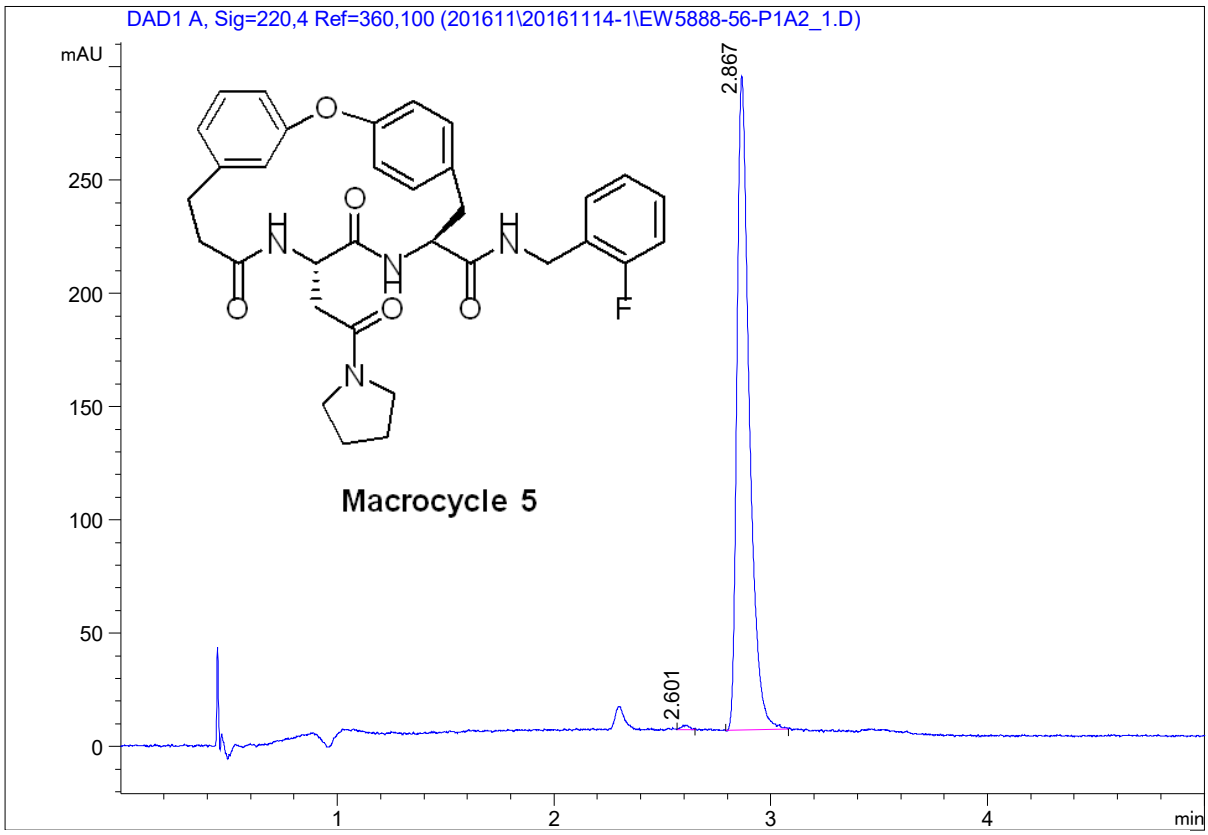
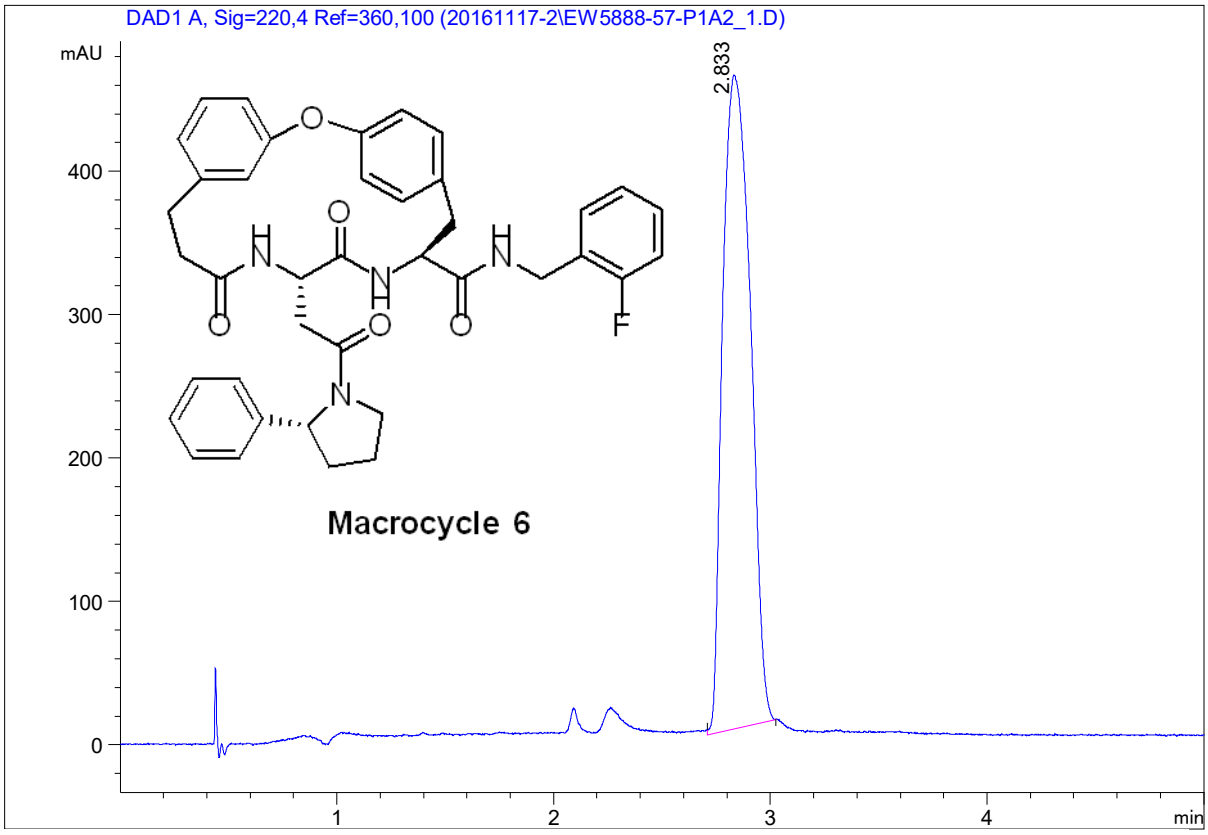
DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	2.730	87.688	0.063	0.706	331.189	100.000



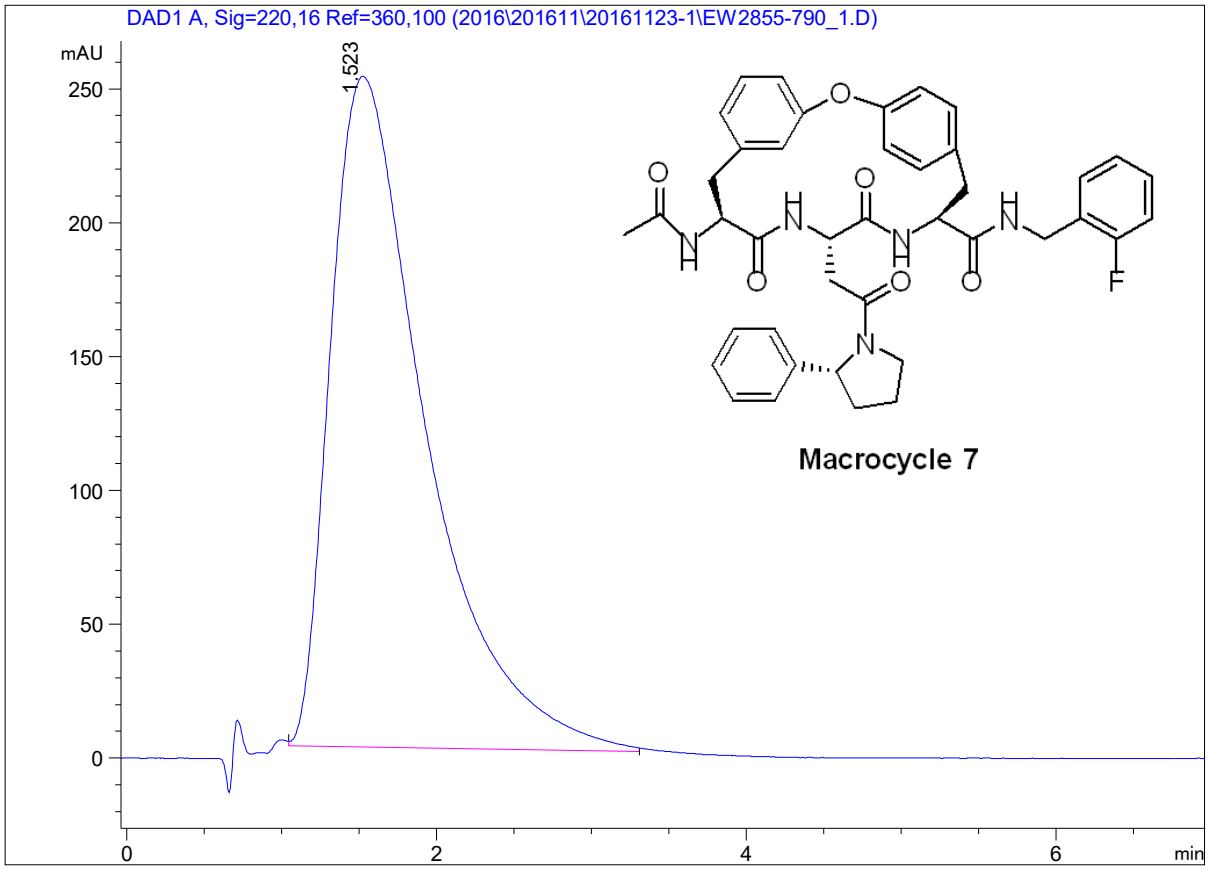
DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	2.601	1.925	0.042	0.676	4.799	0.418
2	2.867	289.557	0.066	0.620	1142.939	99.582



DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	2.833	456.259	0.148	0.738	4055.742	100.000



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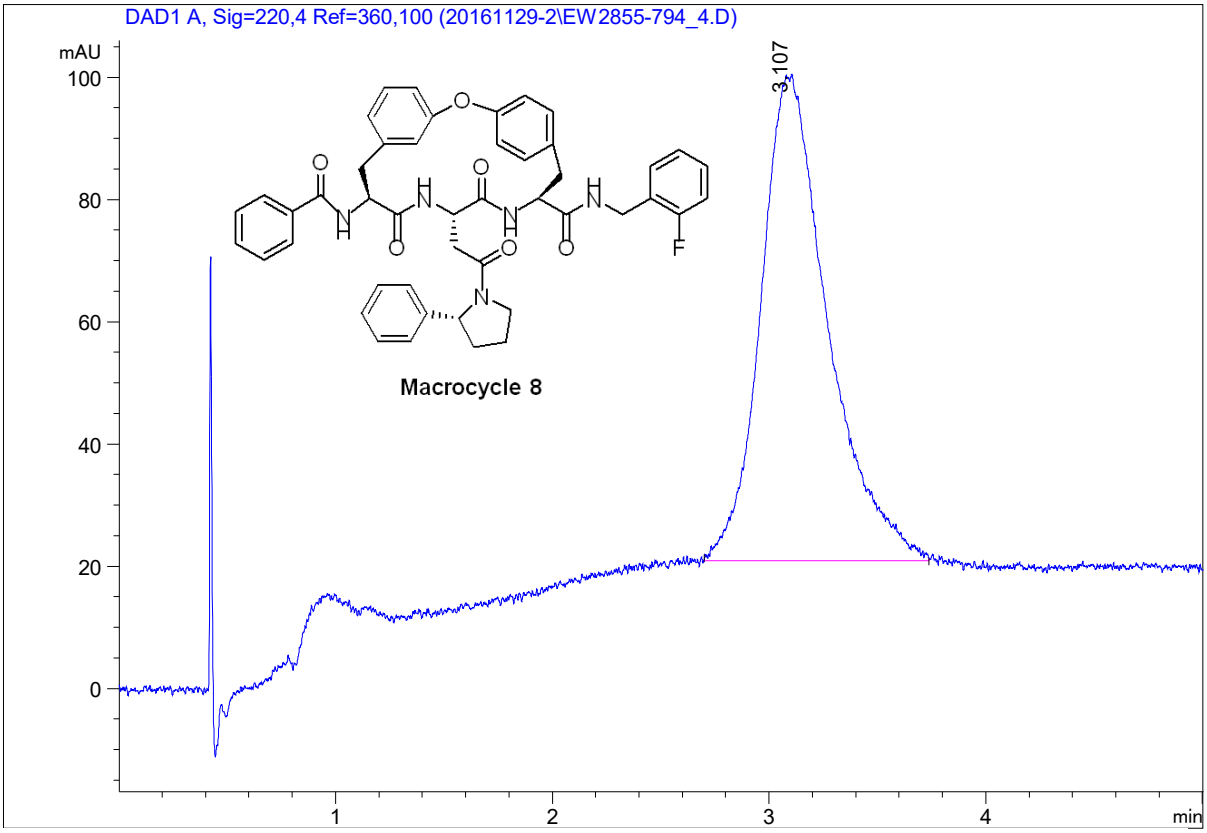
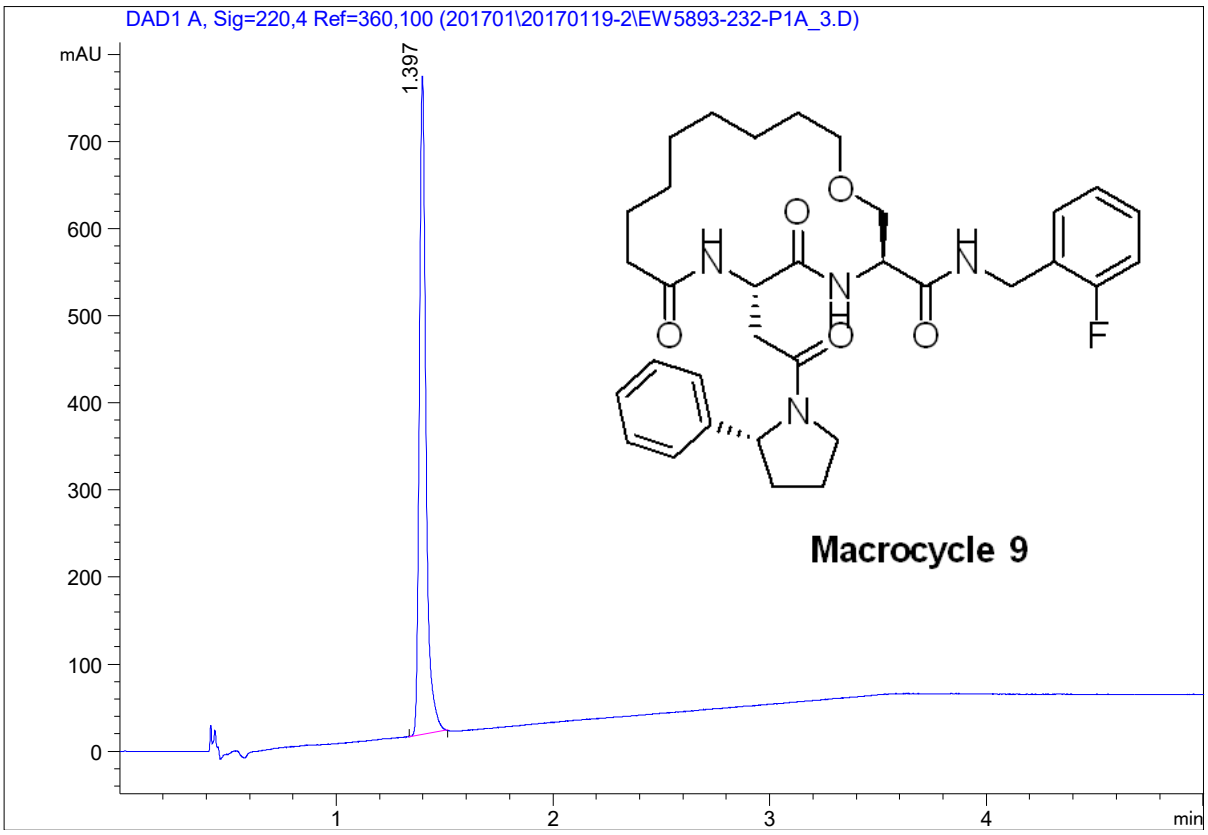
DAD1 A, Sig=220,16 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	1.523	250.441	0.715	0.494	10739.552	100.000



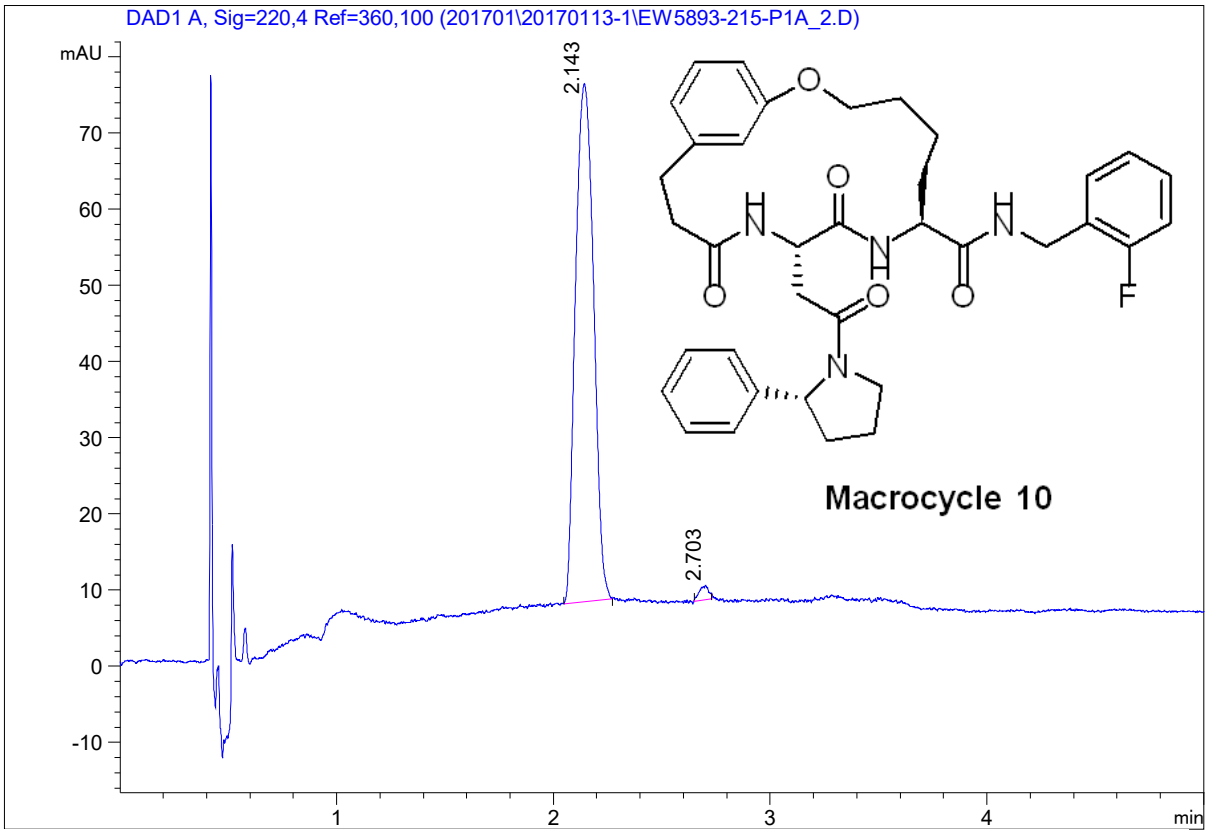
DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	3.107	79.509	0.358	0.619	1709.520	100.000



DAD1 A, Sig=220,4 Ref=360,100

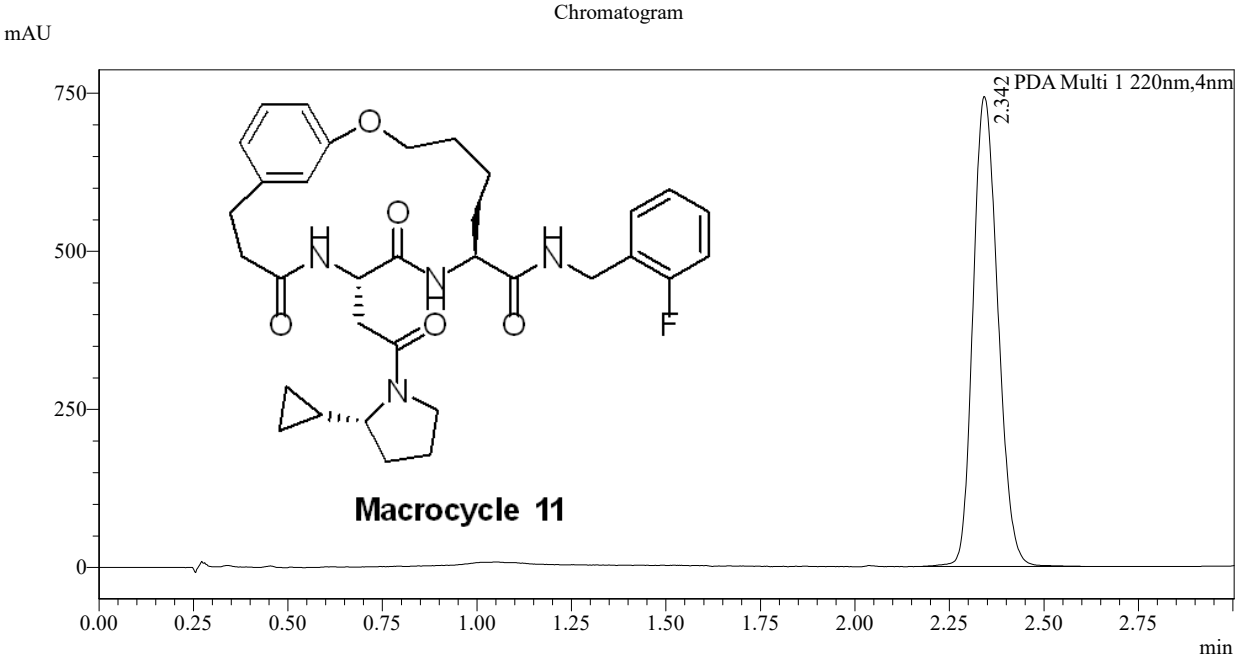
#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	1.397	763.937	0.035	0.683	1606.708	100.000



DAD1 A, Sig=220,4 Ref=360,100

#	Meas. Ret. Time	Height	Width	Symmetry	Area	Area %
1	2.143	68.151	0.096	0.890	394.294	98.598
2	2.703	1.893	0.049	2.044	5.605	1.402

Chromatogram



1 PDA Multi 1 / 220nm,4nm

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Integration Result

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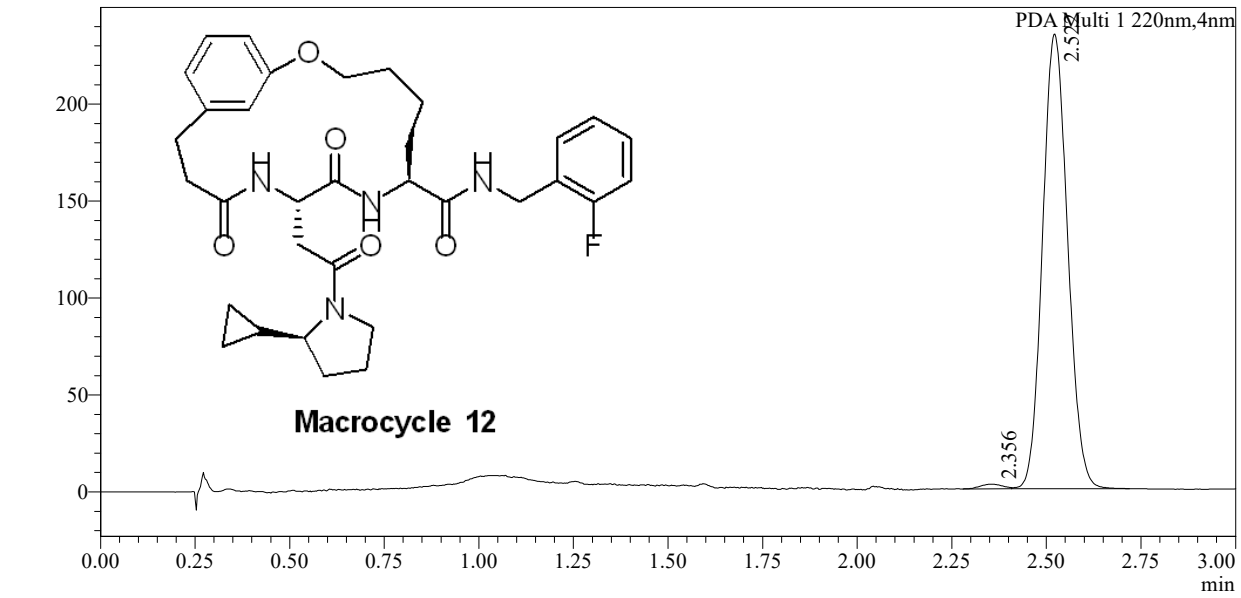
Peak Table

PDA Ch1 220nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	2.342	741389	100.000	0.122	3398304	100.000

Chromatogram



1 PDA Multi 1 / 220nm,4nm

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Integration Result

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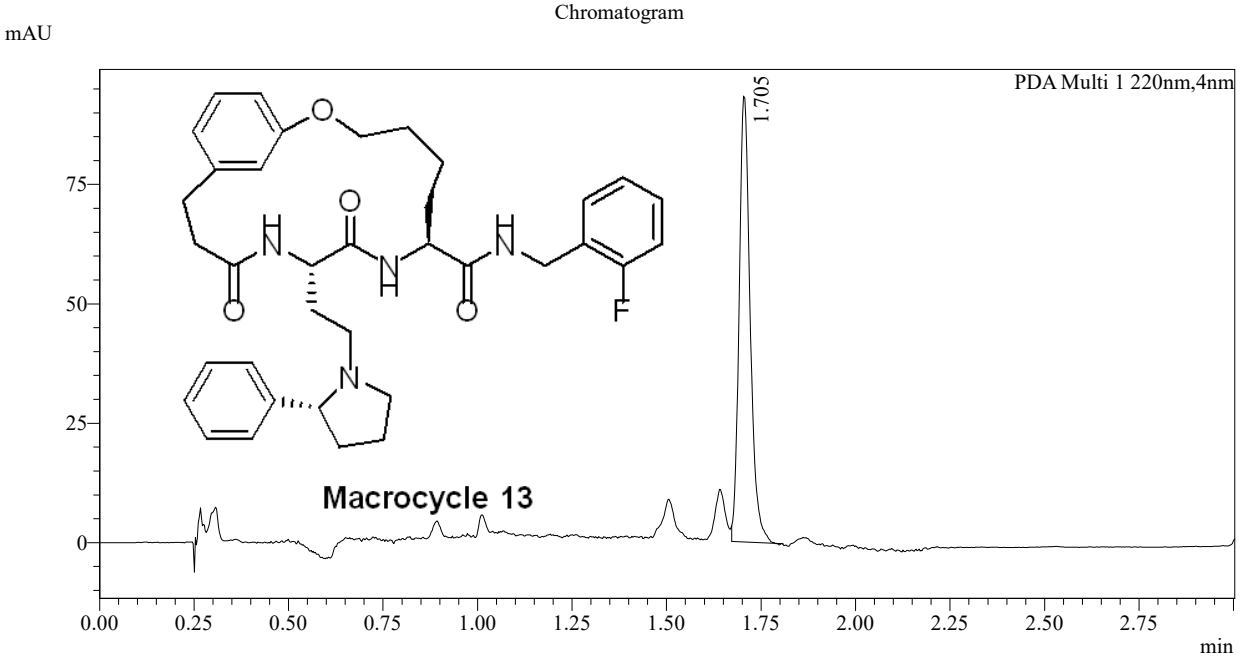
Peak Table

PDA Ch1 220nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	2.356	2433	1.038	0.119	10076	0.921
2	2.522	231981	98.962	0.124	1083543	99.079

Chromatogram



1 PDA Multi 1 / 220nm,4nm

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Integration Result

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Peak Table

PDA Ch1 220nm

Peak#	Ret. Time	Height	Height%	USP Width	Area	Area%
1	1.705	87957	100.000	0.056	190029	100.000