Structure-activity relationship studies of antimalarial *Plasmodium* proteasome inhibitors – Part II

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Table of Contents

Table S1. In vivo pharmacokinetic profile of compound **9**

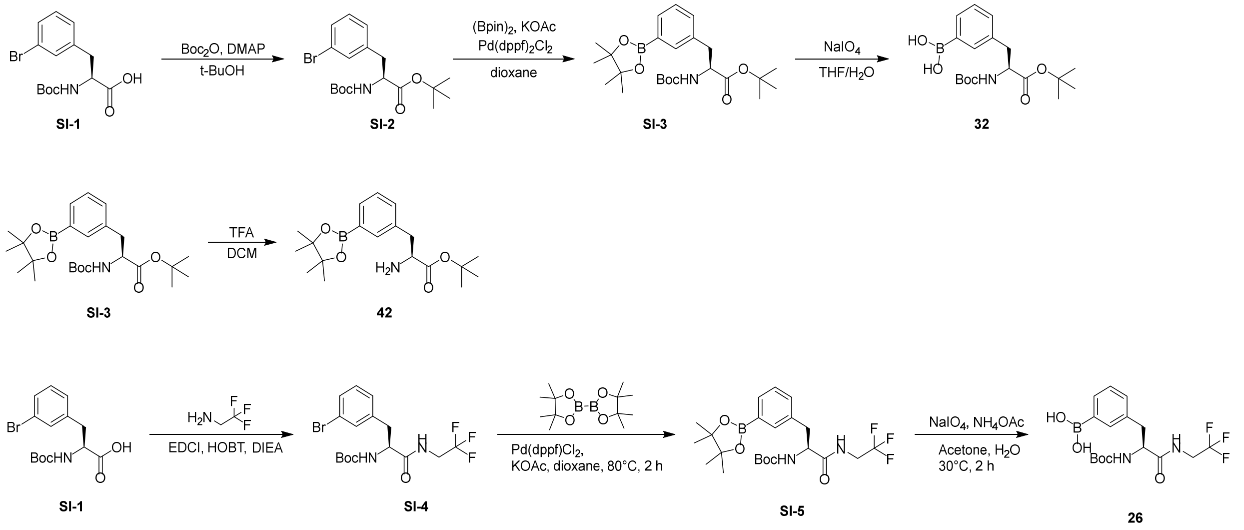
Mouse cassette PK, iv (0.3 mg/kg, mean, n=3)			
AUC_{iv}	MRT_{iv}	Vd(SS)	CL_{total}
(ng·h/mL)	(h)	(mL/kg)	(mL/h/kg)
1.5	0.3	19666	65640

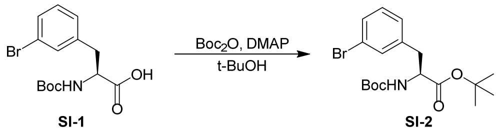
Table S2. IC_{50} of the select compounds against β1c, β2c, β1i, and β2i of the human constitutive proteasome and immunoproteasome.

Compound ID	IC_{50} (μM)			
	β1c - LLE	β2c - VLR	β1i - LLE	β2i - VLR
2	2.2	>100	1.5	>100
3	97	>100	>100	>100
4	>100	>100	>100	>100
5	>100	>100	>100	>100
6	>100	>100	>100	33
8	6.9	>100	12	>100
9	8.8	>100	11	>100
10	>100	>100	>100	>100
11	>100	>100	>100	>100
12	92	>100	80	>100
13	>100	>100	>100	>100
14	>100	>100	>100	>100
15	>100	>100	>100	>100
16	>100	>100	>100	>100
17	>100	>100	>100	>100
18	>100	>100	>100	>100
19	>100	>100	>100	>100
20	>100	>100	>100	>100
21	>100	>100	>100	>100
22	>100	>100	>100	>100
TDI8414	>100	>100	>100	>100
23	>100	>100	>100	>100
24	33	>100	34	>100
25	>100	>100	98	>100

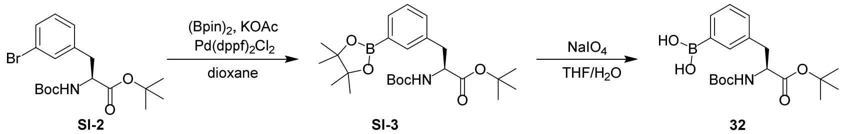
LLE: Z-LLE-AMC; VLR: Z-VLR-AMC

Scheme S1. Synthesis of fragments **26**, **32**, **42**

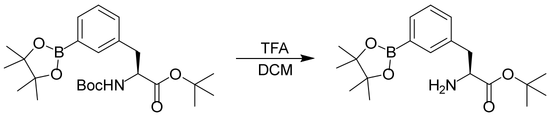




To a solution of compound **SI-1** (20.0 g, 58.1 mmol, 1.0 *eq*) in ter-butyl alcohol (108.5 g, 1.5 mol, 140.0 mL, 25.2 *eq*) was added dimethylaminopyridine (710.0 mg, 5.8 mmol, 0.1 *eq*) and di-tert-butyl dicarbonate (16.5 g, 75.5 mmol, 17.4 mL, 1.3 *eq*). The mixture was stirred at 20 °C for 18 hours under nitrogen atmosphere. TLC (petroleum ether：ethyl acetate = 0:1) showed the starting material was consumed. The mixture was dulited with ethyl acetate (500 mL) and then washed with brine (2 x 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 100/1 ~ 60/1) to give compound **SI-2** (14.9 g, 37.2 mmol, 64.1% yield, 100.0 % purity) as colorless gum. LCMS: RT = 0.92 min, m/z 422.1, 424.1 $[M+Na]^+$. ^1H NMR: ($CDCl_3$, 400 MHz) δ = 7.32 (d, J = 7.6 Hz, 1H), 7.33 (s, 1H), 7.18 - 7.16 (m, 2H), 5.04 (d, J = 7.6 Hz, 1H), 4.46 - 4.41 (m, 1H), 3.08 - 3.03 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H).



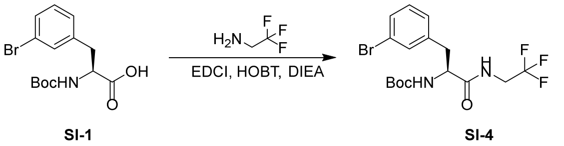
To a solution of compound **SI-2** (14.9 g, 37.2 mmol, 1.0 *eq*), 4, 4, 5, 5-tetramethyl-2- (4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (12.3 g, 48.4 mmol, 1.3 *eq*) and potassium acetate (9.1 g, 93.1 mmol, 2.5 *eq*) in dry dioxane (200 mL) was added Pd(dppf)Cl2 (1.1 g, 1.5 mmol, 0.04 *eq*) under nitrogen atmosphere. The mixture was degassed and then stirred at 80°C for 7 hours under nitrogen atmosphere. LCMS showed the starting material was consumed. The mixture was concentrated in vacuum. The residue was dulited with ethyl acetate (500 mL). The mixture was filtered and the solid was washed with ethyl acetate (3 x 30 mL). The combined organic layers were combined and concentrated in vacuum to give compound **SI-3** (26.6 g, crude) as black gum, which was used into the next step without further purification. To a solution of compound **SI-3** (26.6 g, 37.2 mmol, 1.0 *eq*) and ammonium acetate (14.4 g, 186.1 mmol, 5.0 *eq*) in acetone (300 mL) and water (150 mL) was added sodium periodate (31.8 g, 148.9 mmol, 8.3 mL, 4 *eq*) over a period of 1 hour. The mixture was stirred at 20°C for 18 hours. LCMS showed a part of starting material remained. Another batch of ammonium acetate (14.4 g, 186.1 mmol, 5.0 *eq*) and sodium periodate (31.8 g, 148.9 mmol, 8.3 mL, 4.0 *eq*) were added. The reaction mixture was stirred at 25°C for another 24 hours. TLC (petroleum ether：ethyl acetate = 10:1) showed most of the starting mateiral was consumed. The mixture was dulited with ethyl acetate (200 mL) and then filtered. The filtrate was extracted with ethyl acetate (4 x 200 mL). The combined organic layers were washed with saturated sodium sulfite solution (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient @ 80 mL/min) to give compound **32** (12.7 g, 34.7 mmol, 93.2% yield, 99.5% purity) as a red solid. LCMS: RT = 0.84 min, *m/z* 388.0 [M+Na]$^+$. ^{1}H NMR (Methanol-d4, 400 MHz) δ = 7.62 (s, 1H), 7.47 (s, 1H), 7.31 - 7.26 (m, 2H), 4.23 - 4.21 (m, 1H), 3.04 - 3.02 (m, 1H), 2.94 - 2.90 (m, 1H), 1.40 - 1.39 (m, 18H).



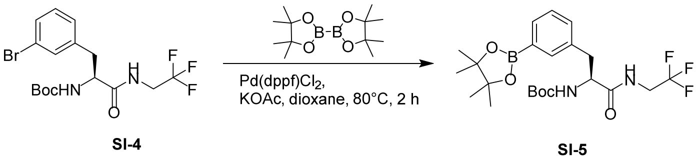
SI-3 **42**

To a solution of compound **SI-3** (5 g, 11.18 mmol, 1 *eq*) in dichloromethane (100 mL) was added trifluoroacetic acid (15.4 g, 135.06 mmol, 10 mL, 12.08 *eq*) at 0°C and the solution was stirred at 0°C for 4 hours. TLC (petroleum ether: ethyl acetate = 10:1) showed starting material was consumed completely and new spot was observed. The reaction was quenched with saturated sodium bicarbonate solution (50 mL) and the solution was extracted with dichloromethane (3 x 80 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography eluted with petroleum ether: ethyl acetate (5:1~ 1:4) to give compound **42** (2.1 g, 6.1 mmol, 54.1% yield) as light yellow oil. ^{1}H

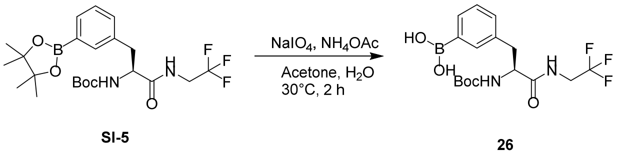
NMR ($CDCl_3$, 400 MHz): δ = 7.69 - 7.67 (m, 2H), 7.34 - 7.29 (m, 2H), 3.63 (dd, *J* = 8.0 Hz, 5.6 Hz, 1H), 3.06 (dd, *J* = 13.2 Hz, 5.2 Hz, 1H), 2.84 (dd, *J* = 13.6 Hz, 8.0 Hz, 1H), 1.44 (s, 9H), 1.35 (s, 12H).



To a solution of compound **SI-1** (2.0 g, 5.8 mmol, 1.0 *eq*) in dichloromethane (15mL) was added EDCI (1.5 g, 7.6 mmol, 1.3 *eq*), HOBT (1.0 g, 7.6 mmol, 1.3 *eq*) and diisopropylethylamine (2.3 g, 17.4 mmol, 3.0 mL, 3.0 *eq*) at 0°C under nitrogen and then compound **2** (944.8 mg, 6.9 mmol, 749.9 µL, 1.2 *eq*, hydrochloric acid) was added. The mixture was stirred at 25°C for 16 hours. LCMS showed starting material was consumed completely and desired mass was detected. The mixture was poured into water (40 mL) and 1 N hydrochloric acid (10 mL). The mixture was extracted by dichloromethane (3 x 40 mL). The combined organic phase was washed by saturated sodium carbonate (3 x 40 mL), brine (20 mL) and dried over sodium sulfate. After filtration and concentration, compound **SI-4** (2.0 g, 4.5 mmol, 77.1% yield, 94.7% purity) was obtained as a light yellow solid. LCMS: RT = 0.90 min, purity: 94.7%, *m*/*z* 326.9 $[M+H]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.40 – 7.36 (m, 2H), 7.20 – 7.12 (m, 2H), 6.61 (br.s, 1H), 5.00 (br.s, 1H), 4.38 – 4.35 (m, 1H), 3.89 – 3.85 (m, 2H), 3.19 – 2.98 (m, 2H), 1.42 (s, 9H).

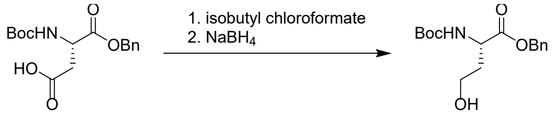


To a solution of compound **SI-4** (1.6 g, 3.6 mmol, 1.0 *eq*) in dioxane (15 mL) was added 4, 4, 5, 5-tetramethyl-2- (4, 4, 5, 5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.4 g, 5.5 mmol, 1.5 *eq*), Pd(dppf)Cl_2 (267.1 mg, 0.37 Mmol, 0.1 *eq*) and potassium acetate (1.1 g, 11.0 mmol, 3.0 *eq*). The mixture was degassed and purged with nitrogen for 3 times. The mixture was stirred at 80°C for 7 hours. LCMS showed most of starting material was consumed and desired Ms was detected. The mixture was filtered and then the filter liquor was concentrated to give compound **SI-5** (1.8 g, crude) as black oil. LCMS: RT = 0.91 min, purity: 50.5%, m/z 495.2 $[M+Na]^+$.



To a solution of compound **SI-5** (1.8 g, 3.8 mmol, 1.0 *eq*) in acetone (8 mL) and water (4 mL) was added ammonium acetate (881.3 mg, 11.4 mmol, 3.0 *eq*) and sodium periodate (2.5 g, 11.4 mmol, 633.6 µL, 3.0 *eq*). The mixture was stirred at 25°C for 40 hours. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was added ethyl acetate (10 mL) and then the mixture was filtered. The filter liquor was extracted by ethyl acetate (2 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by reverse flash (TFA) to afford compound **26** (900.0 mg, 2.3 mmol, 59.3% yield, 97.9% purity) as a yellow solid. LCMS: RT = 0.67 min, purity: 97.9%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.15 – 8.09 (m, 1H), 7.68 – 7.65 (m, 2H), 7.47 – 7.44 (m, 1H), 7.47 – 7.44 (m, 1H), 6.75 – 6.70 (m, 1H), 5.27 – 2.23 (m, 1H), 3.81 – 3.80 (m, 2H), 1.42 (s, 9H).

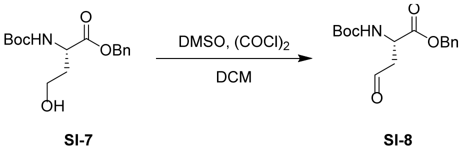
Scheme S2. Synthesis of fragments **29c**, **29g**, **29h**, **35a**, **35b**, **43**.



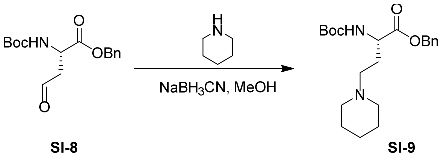
SI-6 **SI-7**

To a solution of compound **SI-6** (1.5 g, 4.6 mmol, 1.0 *eq*) in tetrahydrofuran (20 mL) was added N-methylmorpholine (469.2 mg, 4.6 mmol, 510.1 μL, 1.0 *eq*) and isobutyl chloroformate (633.6 mg, 4.6 mmol, 609.2 μL, 1.0 *eq*) at -20°C. The mixture was stirred for 20 minutes at -20°C. Then the mixture was filtrated and the filtrate was treated with a cold solution of sodium borohydride (263.2 mg, 6.9 mmol, 1.5 *eq*) in water (3 mL) at 0 - 10 °C and the mixture was stirred for 30 minutes at -20°C. TLC (petroleum ether: ethyl acetate =2:1) indicated starting material was consumed completely and one new spot formed. The mixture was poured into water (20 mL) and then extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtation and concentration, the residue was purified by column chromatography (petroleum ether: ethyl acetate =20:1 to 5:1) to compound **SI-7** (810.0 mg, 2.5 mmol, 53.5% yield, 94.8% purity) as a white solid. LCMS : RT = 0.77 min, purity: 94.8%, m/z 332.0 $[M+23]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 – 7.34 (m, 5H), 5.40 – 5.38 (m, 1H), 5.23 (dd, *J₁* = 12.0 Hz, *J₂* = 14.4Hz, 2H), 4.56 – 4.52 (m, 1H), 3.73 – 3.62 (m, 2H), 3.09 – 3.00 (m, 1H), 2.22 – 2.15 (m, 1H), 1.66 – 1.61 (m, 1H), 1.45 (s, 9H).

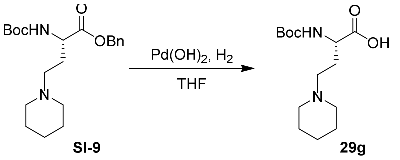
Ref. de la Torre-Martínez, R., Bonache, M.A., Llabrés-Campaner, P.J. et al. Synthesis, high-throughput screening and pharmacological characterization of β–lactam derivatives as TRPM8 antagonists. Sci Rep., 2017, 7, 10766.



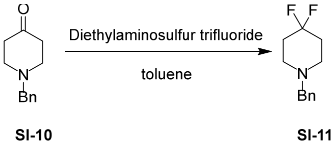
To a solution of oxalyl chloride (361.1 mg, 2.8 mmol, 249.0 µL, 1.1 *eq*) in dichloromethane (5 mL) was added with dimethylsulfoxide (404.1 mg, 5.2 mmol, 404.1 µL, 2.0 *eq*) in dichloromethane (5 mL) at -60°C and the mixture was stirred 10 minutes at -60°C. Compound **SI-7** (800.0 mg, 2.6 mmol, 1.0 *eq*) in dichloromethane (5 mL) was added into the mixture at -60°C and the mixture was stirred for 30 minutes. Triethylamine (1.1 g, 10.3 mmol, 1.4 mL, 4.0 *eq*) was added into the mixture and the resulting mixture was allowed to warmed to 20°C and stirred for 30 minutes LCMS showed starting material was consumed completely. The mixture was concentrated under vacuum and the crude product was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate=10:1 to 8:1) to afford compound **SI-8** (600.0 mg, 1.95 mmol, 75.5% yield) as colorless oil. ^{1}H NMR: ($CDCl_3$, 400 MHz): δ = 9.73 (s, 1H), 7.40 – 7.34 (m, 5H), 5.41 – 5.40 (m, 1H), 5.18 (s, 2H), 5.65 – 5.64 (m, 1H), 3.15 – 3.00 (m, 2H), 1.43 (s, 9H).



To a solution of compound **SI-8** (139.6 mg, 1.6 mmol, 161.9 µL, 1.2 *eq*) in dichloromethane (4 mL) was added piperidine (420.0 mg, 1.4 mmol, 1.0 *eq*) at 25°C and then stirred at 25°C for 30 minutes. Sodium cyanoborohydride (128.8 mg, 2.1 mmol, 1.5 *eq*) was added and the mixture was stirred at 25°C for 30 minuts. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (20 mL) and then extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by prep-HPLC (column: Gemini 5 μm C18 150 x 25 mm; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 57%-87%,12min) to afford compound **SI-9** (200.0 mg, 531.2 μmol, 38.8% yield) as colorless oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.37 – 7.30 (m, 5H), 6.73 (br.d, *J* = 6.4 Hz, 1H), 5.23 (dd, J_1 = 12.4 Hz, J_2 = 29.2 Hz, 2H), 4.39 – 4.36 (m, 1H), 2.35 – 2.28 (m, 6H), 2.01 – 2.00 (m, 1H), 1.86 – 1.85 (m, 1H), 1.56-1.55 (m, 4H), 1.45-1.44 (m, 11H).

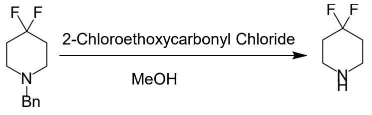


To a solution of compound **SI-9** (170.0 mg, 451.5 μmol, 1.0 *eq*) in tetrahydrofuran (4 mL) was added Palladium hydroxide (63.4 mg, 45.2 μmol, 10 % purity, 0.1 *eq*). The mixture was degassed and purged with hydrogen for 3 times. And the mixture was stirred at 20°C for 1 hour under hydrogen balloon. TLC (petroleum ether: ethyl acetate =1:1) indicated starting material was consumed completely. The mixture was filtered and then the filter was concentrated to afford compound **29g** (135.0 mg, crude) as a white solid. ^{1}H NMR: (CDCl$_3$, 400 MHz): δ = 3.92 – 3.88 (m, 1H), 3.44 – 3.27 (m, 2H), 3.09 – 3.02 (m, 1H), 2.92 – 2.87 (m, 1H), 2.65 (br.s, 1H), 2.38 – 2.32 (m, 1H), 2.22 (d, *J* = 14.4 Hz, 1H), 2.06 – 2.03 (m, 1H), 1.97 – 1.86 (m, 6H), 1.43 (s, 9H).



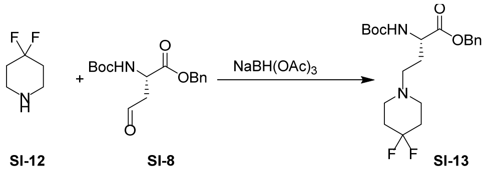
To a solution of Diethylaminosulfur trifluoride (1.1 g, 6.8 mmol, 900.0 μL, 2.6 *eq*) in toluene (20 mL) was added compound **SI-10** (500.0 mg, 2.6 mmol, 490.2 μL, 1.0 *eq*) dropwise at 0°C. The mixture was stirred for 30 minutes at 0°C, then heated to 80°C and stirred for 13.5 hours. TLC (petroleum ether: ethyl acetate =3:1) showed the starting material was consumed completely and a new spot was formed. The mixture was cooled to 0°C, and quenched by sodium bicarbonate (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried with anhydrous sodium sulfate. After filtration and concentration, the residue was purified by column chromatography SiO$_2$, Petroleum ether: ethyl acetate=20:1 to 5:1 to give compound **SI-11**

(400.0 mg, 65.0% yield) as yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 7.30 – 7.20 (m, 5H), 3.50 (s, 2H), 2.51 – 2.48 (m, 4H), 1.97 – 1.89 (m, 4H).



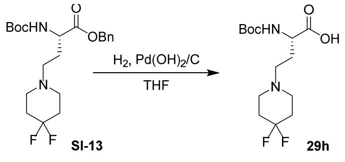
SI-11 **SI-12**

To a solution of compound **SI-11** (200.0 mg, 946.7 µmol, 1.0 *eq*) in dichloromethane (2 mL) was dropwise added 2-chloroethoxycarbonyl chloride (203.0 mg, 1.4 mmol, 146.1 µL, 1.5 *eq*) at 0°C. After addition, the reaction was stirred at 55°C for 2 hours. Then mixture was concentrated in vacuum. The residue was dissolved with methanol (4 mL), and refluxed at 60°C for 4 hours. TLC (petroleum ether: ethyl acetate = 5:1) showed the starting material was consumed completely and desired spot was formed. Then the mixture was concentrated in vacuum to give compound **SI-12** (110.0 mg, crude) as a yellow solid. ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 9.88 (br.s, 1H), 3.38 (m, 4H), 2.39 (m, 4H).



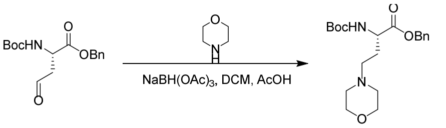
SI-12 **SI-8** **SI-13**

To a solution of compound **SI-8** (1.9 g, 6.2 mmol, 1.0 eq) in dichloromethane (15 mL) and methanol (15 mL) was added potassium acetate (1.5 g, 15.5 mmol, 2.5 eq) and compound **SI-12** (1.0 g, 6.5 mmol, 1.05 eq, HCl) at 25°C and the mixture was stirred at 25°C for 1 hour. Then NaBH(OAc)$_3$ (3.9 g, 18.6 mmol, 3.0 eq) was added the mixture and stirred at 25°C for 11 hours. LCMS showed the mixture was completed. The mixture was added aqueous sodium bicarbonate solution (50 mL), extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reverse flash (TFA condition, 0.1% of TFA in water-ACN) to give compound **SI-13** (1.2 g, 2.88 mmol, 46.55% yield, 98.911% purity) as colourless oil. LCMS: RT =0.66 min, purity: 98.9%, *m/z* 413.1 [M+H]$^+$. ^{1}H NMR: (CDCl$_3$, 400 MHz) δ = 7.37 - 7.34 (m, 5H), 5.25 - 5.13 (m, 2H), 4.36 - 4.23 (m, 1H), 3.36 - 2.96 (m, 6H), 2.45 - 2.21 (m, 6H), 1.42 (s, 9H).



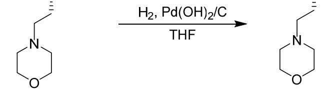
SI-13 **29h**

To a solution of compound **SI-13** (1.2 g, 2.9 mmol, 1.0 eq) in tetrahydrofuran (20 mL) was added $Pd(OH)_2$ (200.0 mg, 10% purity) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 25°C for 12 hours. TLC (Petroleum ether\Ethyl acetate = 1\1, Rf = 0.05) and LCMS showed the mixture was completed. The mixture was filtered and concentrated in vacuum to give compound **29h** (1.0 g, crude) as a white solid. LCMS: RT =0.79 min, purity: 77.3%, *m/z* 323.1 $[M+H]^+$. ^1H NMR: (CD_3OD, 400 MHz) δ = 4.25 - 4.10 (m, 1H), 3.55 - 3.36 (m, 4H), 3.30 - 3.17 (m, 2H), 2.39 - 2.22 (m, 5H), 2.14 - 2.06 (m, 1H), 1.45 (s, 9H).



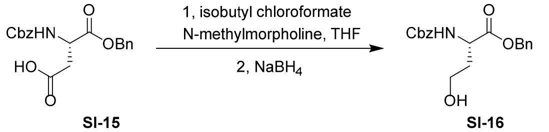
SI-8 SI-14

To a solution of compound **SI-8** (23.0 g, 74.8 mmol, 1.0 *eq*), acetic acid (4.5 g, 74.8 mmol, 4.3 mL, 1.0 *eq*) and 4A molecular sieve (23.0 g) in dichloromethane (230 mL) was added morpholine (13.0 g, 149.7 mmol, 13.2 mL, 2.0 *eq*) at 0°C. The mixture was stirred at 25°C for 15 minutes. Sodium triacetoxyborohydride (23.8 g, 112.3 mmol, 1.5 *eq*) was added at 0°C. The reaction mixture was stirred at 0°C for 15 minutes and then stirred at 20°C for another 14 hours. LCMS showed some of starting material remained. Another batch of sodium triacetoxyborohydride (3.2 g, 14.9 mmol, 0.2 *eq*) was added and the reaction mixture was stirred at 20°C for 14 hours. LCMS showed the starting material was consumed and desired product mass was detected. The mixture was quenched with saturated sodium bicarbonate solution (100 mL). The mixture was filtered through celit pad, the solid was washed with dichloromethane (3 x 100 mL). The organic layer was separated from the filtrate and then washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuum. The residue was purified by reverse flash column (basic condition) to give compound **SI-14** (14.3 g, 33.2 mmol, 44.3% yield, 87.8% purity) as light yellow gum. LCMS: RT = 0.68 min, *m/z* 379.2 $[M+H]^+$, purity: 87.8%. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.38 - 7.32 (m, 5H), 6.25 (d, J = 6.8 Hz, 1H), 5.23 - 5.14 (m, 2H), 4.45 - 4.42 (m, 1H), 3.68 - 3.67 (m, 4H), 2.41 - 2.33 (m, 6H), 2.05 - 2.00 (m, 1H), 1.89 - 1.84 (m, 1H), 1.45 (s, 9H).

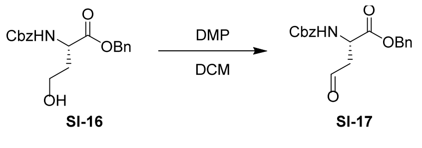


SI-14 43

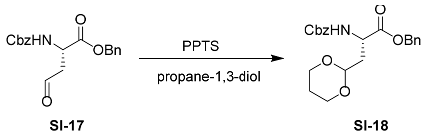
To a sloution of compound **SI-14** (14.3 g, 33.2 mmol, 1.0 *eq*) in tetrahydrofuran (150 mL) was added $Pd(OH)_2/C$ (0.5 g, 10% purity) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 20°C for 16 hours. TLC (petroleum ether: ethyl acetate = 1:1) showed the starting material remained. Pd(OH)$_2$/C (0.5 g, 10% purity) was added under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen several times. The mixture was stirred under hydrogen (15 psi) at 20°C for 6 hours. TLC (petroleum ether: ethyl acetate = 1:1) showed the starting material was consumed completely. The mixture was filtered throught the celite pad, the solid was washed with methanol (15 x 100 mL). The combined filtrate was concentrated in vacuum. The residue was triturated with ethyl acetate: methyl tert-butyl ether (30 mL/200 mL) to give compound **43** (9.4 g, 32.5 mmol, 97.8% yield) as a light yellow solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 7.01 (m, *J* = 7.6 Hz, 1H), 3.96 - 3.94 (m, 1H), 3.57 - 3.53 (m, 4H), 2.49 - 2.34 (m, 6H), 1.85 - 1.82 (m, 1H), 1.69 - 1.68 (m, 1H), 1.37 (s, 9H).



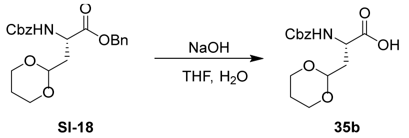
To a mixture of compound **SI-15** (58.0 g, 132.1 mmol, 1.0 *eq*) and N-methylmorpholine (13.4 g, 132.1 mmol, 14.5 mL, 1.0 *eq*) in tetrahydrofuran (500 mL) was added isobutyl carbonochloridate (18.0 g, 132.1 mmol, 17.4 mL, 1.0 *eq*) dropwise at -20°C under nitrogen atmosphere. The mixture was stirred at -20 °C for 2 hours. Then sodium borohydride (7.5 g, 198.2 mmol, 1.5 *eq*) in water (80 mL) was added drop wise. The mixture was stirred at -20 °C for 1 hour. The mixture was quenched with 1N hydrochloric acid (800 mL). The aqueous phase was extracted with ethyl acetate (3 x 500 mL). The combined organic phase was washed with brine (2 x 500 mL), dried with anhydrous anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate = 10/1 ~ 2/1) to afford the compound **SI-16** (46.5 g, 97.3 mmol, 73.6% yield, 71.8% purity) as a light-yellow oil. LCMS: RT = 0.65 min, *m*/*z* 366.1 [M+Na]$^+$, purity: 71.8%.



To a solution of compound **SI-16** (23.5 g, 49.3 mmol, 1.0 *eq*) in dichloromethane (500 mL) was added Dess-Martin (41.8 g, 98.5 mmol, 30.5 mL, 2.0 *eq*) at 0 °C under nitrogen atmosphere. The mixture was stirred at 20°C for 3 hours. TLC (petroleum ether： ethyl acetate = 2:1) indicated trace material remained and one new spot formed. The mixture was concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, Petroleum ether/Ethyl acetate = 10/1 ~ 3/1) to afford compound **SI-17** (11.0 g, 23.9 mmol, 48.5% yield, 74.2% purity) as a light-yellow oil. LCMS: RT = 0.66 min, *m/z* 342.1 [M+H]$^+$, purity: 58.2%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.63 (s, 1H), 7.29 - 7.25 (m, 10H), 5.72 - 5.60 (m, 1H), 5.11 - 4.96 (m, 4H), 4.63 - 4.61 (m, 1H), 3.07 - 2.82 (m, 2H).

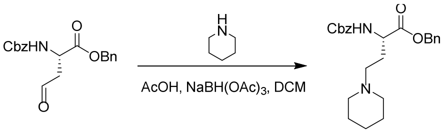


To a mixture of compound **SI-17** (2.2 g, 4.8 mmol, 1.0 *eq,* 5 batches) and propane-1, 3-diol (9.5 g, 124.2 mmol, 9.0 mL, 25.9 *eq*) was added PPTS (324.0 mg, 1.3 mmol, 0.3 *eq*) and 4A MS (4.4 g) in one portion at 20°C under nitrogen atmosphere. The mixture was stirred at 80°C for 12 hours. TLC (petroleum ether：ethyl acetate = 2:1) indicated the starting material was consumed completely and one new spot was formed. The mixture was cooled to 20°C and poured into water (100mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum to give compound **SI-18** (11.0 g, crude) as a light yellow oil, which was used for the next step directly without further purification. LCMS: RT = 1.00 min, *m/z* 400.1 [M+H]$^+$, purity: 31.9%.



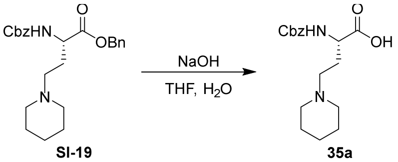
To a mixture of compound **SI-18** (5.5 g, 13.8 mmol, 1.0 *eq,* 2 batches) in tetrahydrofuran (50 mL) and water (50 mL) was added sodium hydroxide (3.8 g, 96.4 mmol, 7.0 *eq*) in one portion at 0°C under nitrogen atmosphere. The mixture was stirred at 0°C for 30 min. TLC (petroleum ether：ethyl acetate = 2:1) indicated the starting material was consumed completely and one new spot was formed. The mixture was poured into ice-water (50 mL) and the aqueous phase was extracted with ethyl acetate (2 x 200 mL). The combined organic phase was discarded, then the pH value of the aqueous phase was adjusted to 2 with 1 N hydrochloric acid aqueous (220 mL), extracted with ethyl acetate (3 x 200 mL). The combined organic phase was washed with brine (200 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum to give compound **35b** (4.6 g, 14.4 mmol, 52.4% yield, 97.0% purity) as a light-yellow oil. LCMS: RT = 0.75 min, *m/z* 310.1 [M+H]$^+$, purity: 97.4%. ^{1}H NMR (DMSO-d6, 400 MHz) δ = 7.58 (d, *J* = 8.0 Hz, 1H), 7.39 - 7.30 (m, 5H), 5.03 (s, 2H), 4.55 - 4.54 (m, 1H), 4.05 - 3.96 (m, 3H), 3.66 -

3.61 (m, 2H), 1.88 - 1.81 (m, 3H), 1.33 - 1.30 (m, 1H).



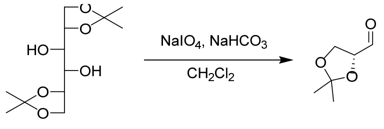
SI-17 **SI-19**

To a solution of compound **SI-17** (1.0 g, 2.9 mmol, 1.0 *eq*) in dichloromethane (10 mL) was added piperidine (748.0 mg, 8.8 mmol, 867.91 µL, 3.0 *eq*), acetic acid (176.0 mg, 2.9 mmol, 167.5 µL, 1.0 *eq*) and 4A molecular sieve (1.0 g, 1.2 mmol). The mixture was stirred at 25°C for 10 minutes and then sodium triacetoxyborohydride (931.0 mg, 4.4 mmol, 1.5 *eq*) was added. The reaction mixture was stirred at 25°C for 14 hours under nitrogen atmosphere. The mixture was filtered through the celite pad, the solid was washed with ethyl acetate (3 x 30 mL). The filtrate was washed with brine (2 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 3/1 ~ 1:1) to give compound **SI-19** (790.0 mg, 1.6 mmol, 54.5% yield, 82.9% purity) as yellow gum. LCMS: RT = 0.72 min, m/z 411.1 $[M+H]^+$.



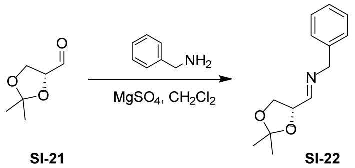
SI-19 **35a**

To a solution of compound **SI-19** (790.0 mg, 1.6 mmol, 1.0 *eq*) in tetrahydrofuran (8 mL) was added sodium hydroxide (447.0 mg, 11.2 mmol, 7.0 *eq*) in water (8 mL) dropwise at 0°C. The mixture was stirred at 0°C for 2 hours. TLC (petroleum ether: ethyl acetate = 0:1) showed a part of starting material remained. Sodium hydroxide (192.0 mg, 4.8 mmol, 3.0 *eq*) in water (1.5 mL) was added drop wise. The reaction mixture was stirred at 0°C for another 1 hours. TLC (petroleum ether: ethyl acetate = 0:1) showed the starting material was consumed. The mixture was adjusted to pH = 2 with 1N hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 20 mL). The aqueous layer was lyophilized. The residue was purified by reverse flash (trifluoroacetic acid condition) to give compound **35a** (750.0 mg, 1.6 mmol, 99.2% yield, 91.7% purity, trifluoroacetic acid salt) as light-yellow gum. LCMS: RT = 0.70 min, m/z 321.1 $[M+H]^+$, purity: 91.7%. ^{1}H NMR: (Methanol-d4, 400 MHz) δ = 7.42 - 7.32 (m, 5H), 5.11 (s, 2H), 4.30 - 4.27 (m, 1H), 3.49 (t, J = 14.0 Hz, 2H), 3.17 - 3.12 (m, 2H), 2.92 - 2.89 (m, 2H), 2.37 - 2.30 (m, 1H), 2.17 - 2.07 (m, 1H), 1.93 - 1.90 (m, 2H), 1.83 - 1.74 (m, 3H), 1.51 - 1.50 (m, 1H).



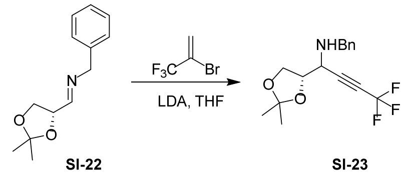
SI-20 **SI-21**

To a solution of compound **SI-20** (5.0 g, 19.1 mmol, 1.0 *eq*) in dichloromethane (30 mL) was added a solution of sat sodium bicarbonate (1.3 mL) and sodium periodate (8.2 g, 38.1 mmol, 2.1 mL, 2.0 *eq*). The resulting mixture was stirred at 20°C for 16 hours. TLC (Petroleum ether: Ethyl acetate= 2:1) showed the starting material was consumed completely. The mixture was filtrated out and the filter liquid was concentrated under vacuum. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate=10: 1~ Dichloromethane: Ethyl acetate=1: 1) to provide of compound **SI-21** (1.9 g, crude) as colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.76 (s, 1H), 4.41 – 4.39 (m, 1H), 4.17 – 4.12 (m, 2H), 1.51 (s, 3H), 1.44 (s, 3H).



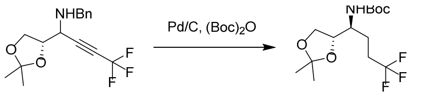
SI-21 **SI-22**

To a solution of compound **SI-21** (1.0 g, 7.7 mmol, 952.4 µL, 1.0 *eq*) in dichloromethane (10 mL) was added magnesium sulfate (9.2 g, 76.8 mmol, 10.0 *eq*) and phenylmethanamine (823.3 mg, 7.7 mmol, 840.1 µL, 1.0 *eq*). The mixture was stirred at 20°C for 48 hours. After filtration, The filtrate liquid was concentrated under vacuum to provide 1.9 g of crude compound **SI-22** as yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78 (d, J = 4.8 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.28 – 7.25 (m, 3H), 4.63 (s, 2H), 4.22 (dd, J_1 = 1.6 Hz, J_2 = 6.8 Hz, 1H), 3.98 (dd, J_1 = 2.4, J_2 = 6.0 Hz, 1H), 1.50 (s, 3H), 1.43 (s, 3H).



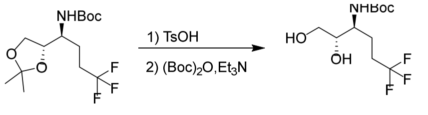
SI-22 **SI-23**

To a solution of diisopropylamine (4.2 g, 41.0 mmol, 5.7 mL, 3.0 *eq*) in tetrahydrofuran (20 mL) was added n-BuLi (2.5 M, 16.4 mL, 3.0 *eq*) at -78°C for 30 minutes. 2-Bromo-3,3,3-trifluoroprop-1-ene (4.8 g, 27.4 mmol, 2.0 *eq*) in tetrahydrofuran (10 mL) was added into the mixture at -78°C. After stirring for 30 minutes, compound **SI-22** (3.0 g, 13.7 mmol, 1.0 *eq*) was added into the mixture slowly. After addition, the resulting mixture was stirred for 2 hours at 0°C. TLC (Petroleum ether: Ethyl acetate=10: 1) showed the starting material was consumed completely. The mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with brine (30 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified with silica gel column (Petroleum ether: Ethyl acetate=10: 1) to provide compound **SI-23** (2.1 g, 6.7 mmol, 48.9% yield) as yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 – 7.28 (m, 5H), 4.26 – 4.23 (m, 1H), 4.11 – 4.04 (m, 2H), 3.97 – 3.89 (m, 1H), 3.84 – 3.80 (dd, J_1 = 6.4 Hz, J_2 = 13.2 Hz, 1H), 1.45 – 1.38 (d, J = 26.0 Hz, 3H), 1.36 (s, 3H).



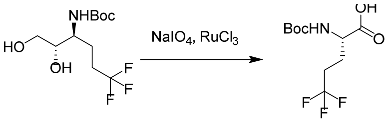
SI-23 **SI-24**

To a solution of compound **SI-23** (1.8 g, 5.7 mmol, 1.0 *eq*) in ethyl acetate (20 mL) was added $(Boc)_2O$ (2.5 g, 11.5 mmol, 2.6 mL, 2.0 *eq*) and Pd/C (300.0 mg, 10% purity). The mixture was degassed under vacuum and purged hydrogen for 3 times. The resulting mixture was stirred at 20°C for 16 hours under hydrogen balloon. TLC (Petroleum ether: Ethyl acetate=10: 1) showed the starting material was consumed completely. The mixture was filtrated out and the filter liquid was concentrated under vacuum. The residue was purified with column (Petroleum ether: Ethyl acetate=50: 1~30: 1) to provide impure product which was recrystallization with hexane (10 mL) to provide 660.0 mg of compound **SI-24** as a white solid. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 4.51 (d, J = 8.8 Hz, 1H), 4.08 – 4.04 (m, 2H), 3.82 – 3.79 (m, 1H), 3.65 (br.s, 1H), 2.27 – 2.17 (m, 2H), 1.98-1.96 (m, 1H), 1.57 – 1.53 (m, 1H), 1.45 (s, 12H), 1.34 (s, 3H).



SI-24 **SI-25**

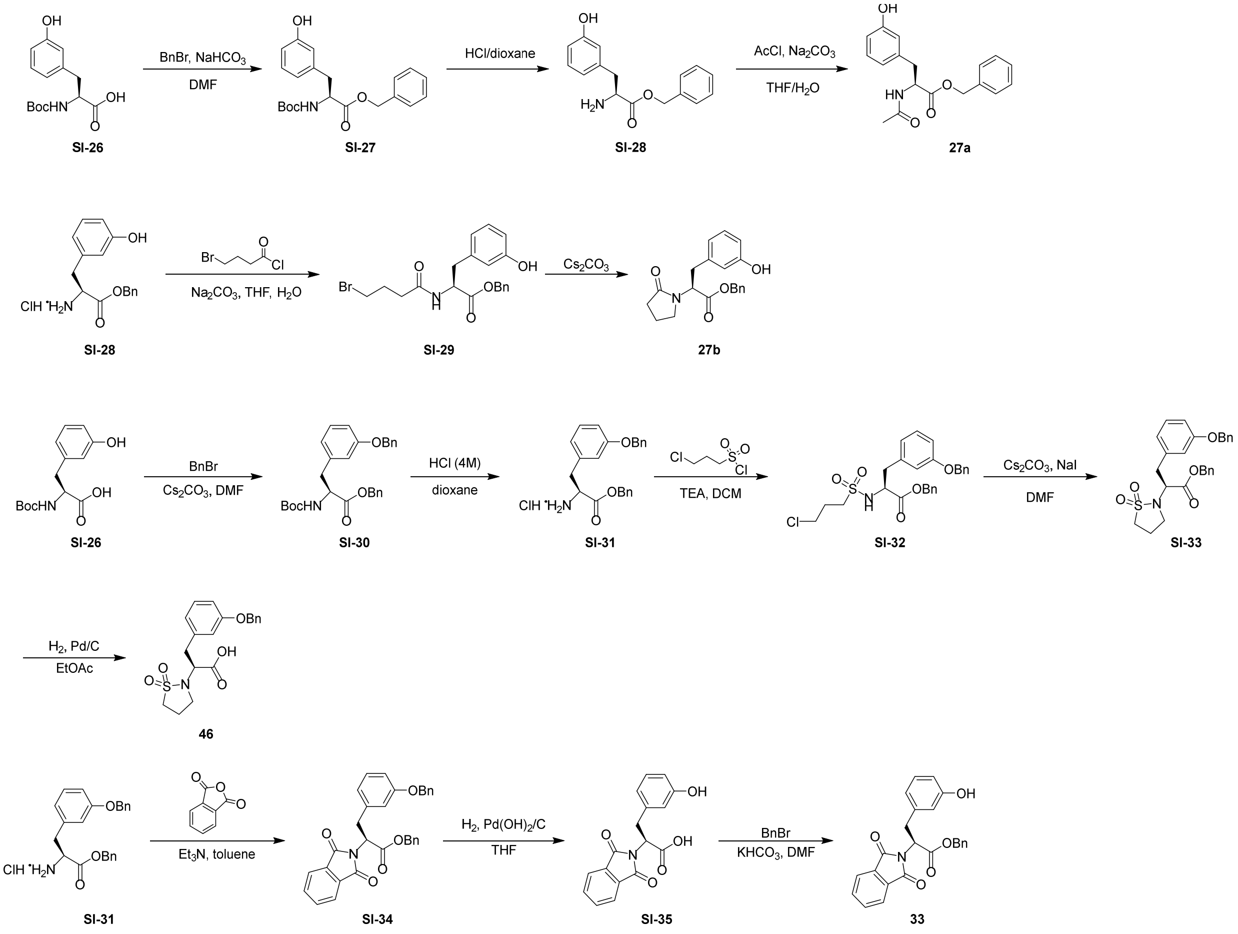
To a solution of compound **SI-24** (570.0 mg, 1.7 mmol, 1.0 *eq*) in methanol (10 mL) was added p-Methylbenzene sulfonic acid (330.9 mg, 1.7 mmol, 1.0 *eq*). The mixture was stirred for 16 hours at 20°C. TLC (Petroleum ether: Ethyl acetate=10: 1) showed the starting material was consumed completely. The mixture was concentrated under vacuum. The residue was triturated with ethyl acetate (10 mL) to provide compound **SI-24-amine** (650.0 mg, crude) as a white solid. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ = 3.73 – 3.70 (m, 1H), 3.51 – 3.46 (m, 1H), 3.41 – 3.38 (m, 1H), 3.27 (br.s, 1H), 2.44 – 2.37 (m, 2H), 1.84 – 1.74 (m, 2H). To a solution of compound **SI-24-amine** (660.0 mg, 3.5 mmol, 1.0 *eq*) in methanol (10 mL) was added triethylamine (1.1 g, 10.6 mmol, 1.5 mL, 3.0 *eq*) and $(Boc)_2O$ (2.3 g, 10.6 mmol, 2.4 mL, 3.0 *eq*). The mixture was stirred at 20°C for 1 hour. TLC (Petroleum ether: Ethyl acetate=1: 1) detected the desired product. The mixture was concentrated under vacuum to give a residue which was purified with silica gel column (Petroleum ether: Ethyl acetate=2: 1) to provide compound **SI-25** (500.0 mg, 1.7 mmol, 49.3% yield) as a white solid. ^{1}H NMR: (CDCl$_3$, 400 MHz) δ = 4.60 (d, J = 9.2 Hz, 1H), 3.71 – 3.65 (m, 2H), 3.56 – 3.54 (m, 1H), 3.34 – 3.32 (m, 1H), 2.28 – 2.14 (m, 3H), 1.56 – 1.53 (m, 1H), 1.53 (s, 9H).

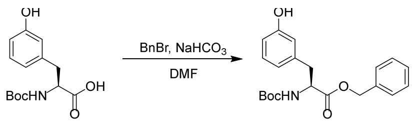


SI-25 **29c**

To a solution of compound **SI-25** (200.0 mg, 696.2 µmol, 1.0 *eq*) in tetrachloromethane (2 mL), acetonitrile (2 mL) and water (3 mL) was added Ruthenium(III) chloride (14.4 mg, 69.6 µmol, 4.6 µL, 0.1 *eq*) and sodium periodate (595.6 mg, 2.8 mmol, 154.3 µL, 4.0 *eq*). The mixture was stirred at 20°C for 2 hours. TLC (Petroleum ether: Ethyl acetate=1: 1) showed the starting material was consumed completely. The mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 30 mL). After filtration and concentration, compound **29c** (170.0 mg, 626.7 µmol, 90.0% yield) was obtained as a brown solid. ^{1}H NMR (CD$_3$COCD$_3$, 400 MHz): δ = 11.18 (br.s, 1H), 6.22 (d, J = 7.6 Hz, 1H), 4.16 – 4.11 (m, 1H), 2.27 – 2.23 (m, 2H), 2.00 (m, 1H), 1.88-1.82 (m, 1H), 1.28 (s, 9H).

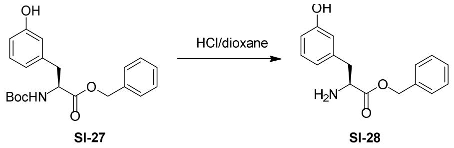
Scheme S3. Synthesis of fragments **27a**, **27b**, **33**, **46**.



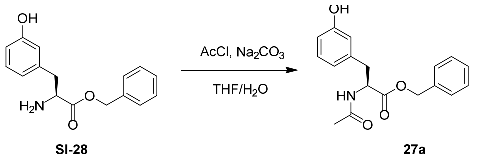


SI-26 **SI-27**

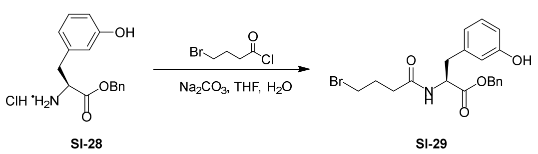
To a solution of compound **SI-26** (2.0 g, 7.1 mmol, 1.0 *eq*) in dimethylformamide (5 mL) was added sodium bicarbonate (895.9 mg, 10.7 mmol, 414.8 μL, 1.5 *eq*) and benzylbromide (1.3 g, 7.8 mmol, 928.9 μL, 1.1 *eq*). The mixture was stirred at 40°C for 16 hours. LCMS showed starting material was consumed completely and desired mass was detected. The mixture was cooled to 25°C and then poured into water (50 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic phase was washed with brine (50 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate=20:1 to 8:1) to give compound **SI-27** (1.2 g, 3.1 mmol, 44.0% yield, 98.6% purity) as yellow oil. LCMS: RT = 0.87 min, purity: 93.0%, *m*/*z* 394.0 $[M+23]^+$. ^{1}H NMR (MeOD, 400 MHz): δ = 7.37 – 7.29 (m, 5H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.67 – 6.65 (m, 3H), 5.13 (s, 2H), 4.40 (t, *J* = 8.0 Hz, 1H), 3.05 – 2.99 (m, 1H), 2.91 – 2.85 (m, 1H), 1.40 (s, 9H).



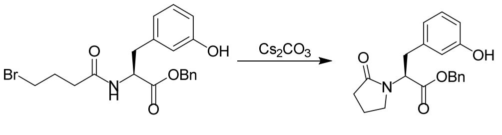
To a solution of compound **SI-27** (1.8 g, 4.8 mmol, 1.0 *eq*) in dioxane (10 mL) was added HCl/dioxane (80.0 mmol, 20.0 mL, 4.0 mol/L). The mixture was stirred at 25°C for 4 hours. TLC (petroleum ether: ethyl acetate=2:1) indicated starting material was consumed completely and one new spot formed. The mixture was concentrated under vacuum to afford compound **SI-28** (2.0 g, crude, HCl) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38 – 7.33 (m, 5H), 7.13 (t, J = 8.0 Hz, 1H), 6.75 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 6.69 – 6.64 (m, 2H), 5.28-5.26 (m, 2H), 4.31 (t, J = 6.8 Hz, 1H), 3.19 – 3.09 (m ,2H).



A solution of compound **SI-28** (2.0 g, 6.5 mmol, 1.0 *eq*, hydrochloric acid salt) and sodium carbonate (6.9 g, 65.0 mmol, 10.0 *eq*) in tetrahydrofuran (20 mL) and water (10 mL) was added dropwise a solution of acetyl chloride (2.6 g, 32.5 mmol, 2.3 mL, 5.0 *eq*) in tetrahydrofuran (5 mL) at 0°C. The mixture was stirred at 25°C for 3 hours. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (10 mL) and then added 1N hydrochloric acid (5 mL) until pH=6. The mixture was extracted by ethyl acetate (3 x 15 mL). The combined organic phase was washed by brine (20 mL), dried over sodium sulfate. After filtration and concentration, compound **27a** (840.0 mg, 2.6 mmol, 40.6% yield, 98.5% purity) was obtained as yellow oil. LCMS: RT = 0.75 min, purity: 98.5%, *m/z* 314.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 – 7.35 (m, 5H), 7.08 (t, J = 7.6 Hz, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 6.35 (s, 1H), 5.96-5.94 (m, 1H), 5.25 (d, J = 12.0 Hz, 1H), 5.13 (d, J = 12.0 Hz, 1H), 4.95 (dd, J_1 = 5.6, J_2 = 13.6 Hz, 1H), 3.11 – 3.02 (m, 2H), 1.99 (s, 3H).

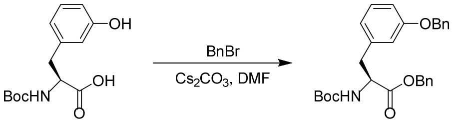


To a solution of compound **SI-28** (1.5 g, 4.8 mmol, 1.0 *eq*, hydrochloric acid salt) in tetrahydrofuran (20 mL) and water (10 mL) was added sodium carbonate (2.6 g, 24.4 mmol, 5.0 *eq*), then 4-bromobutanoyl chloride (1.4 g, 7.3 mmol, 846.7 μL, 1.5 *eq*) was added dropwise at 0°C. The mixture was stirred at 0°C for 1.5 hours. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (20 mL) and then extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by saturate sodium bicarbonate (3 x 20 mL), brine (20 mL), and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel column (petroleum ether: ethyl acetate=3:1 to 3:1) to afford compound **SI-29** (1.1 g, 2.5 mmol, 50.3% yield, 93.6% purity) as yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.29 (s, 1H), 8.41 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.62 – 6.60 (m, 3H), 5.11 (dd, J_1 = 12.8 Hz, J_2 =15.2 Hz, 2H), 4.50 – 4.45 (m, 1H), 3.54 (t, *J* = 6.8 Hz, 1H), 3.44 (t, *J* = 6.8 Hz, 1H), 2.98 – 2.79 (m, 2H), 2.28 – 2.16 (m, 2H), 1.96 – 1.83 (m, 2H).



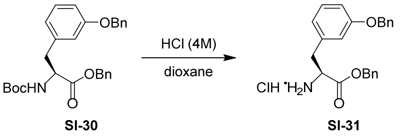
SI-29 **27b**

To a solution of compound **SI-29** (1.1 g, 2.5 mmol, 1.0 *eq*) in dimethyl formamide (10 mL) was added potassium carbonate (1.0 g, 7.5 mmol, 3.0 *eq*). The mixture was stirred at 25°C for 2 hours. TLC (petroleum ether: ethyl acetate =1:1) indicated a little of starting material was remained and one new spot was detected. The mixture was poured into water (10 mL) and then 1 N hydrogen chloride (5 mL) was added. The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed brine (20 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel column (petroleum ether: ethyl acetate =2:1 to 2:1) to afford compound **27b** (165.0 mg, 402.4 μmol, 16.1% yield, 82.7% purity) as light yellow oil. LCMS: RT = 0.76 min, purity:82.7%, m/z 340.1[M+H]$^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.29 (s, 1H), 7.38 – 7.29 (m, 5H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.63 – 6.58 (m, 3H), 5.17 (dd, J_1 = 12.8 Hz, J_2 = 15.2 Hz, 2H), 4.87 (dd, J_1 = 5.6 Hz, J_2 = 10.4 Hz, 1H), 3.39 – 3.35 (m, 1H), 3.23 – 3.10 (m, 2H), 2.96 (dd, J_1 = 10.4 Hz, J_2 = 15.0 Hz, 1H), 2.21 – 2.05 (m, 2H), 1.86 – 1.78 (m, 2H).

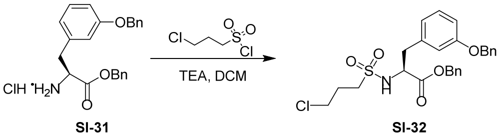


SI-26 **SI-30**

To a mixture of compound **SI-26** (4.0 g, 14.2 mmol) and cesium carbonate (9.0 g, 28.4 mmol) in dimethylformamide (40 mL) was added bromomethylbenzene (5.0 g, 31.3 mmol, 3.7 mL). The result mixture was stirred at 20°C for 2 hours. LCMS showed the starting material was consumed and desired product was detected. The reaction was quenched with water (250 mL) and extracted with ethyl acetate (3 x 100 mL), the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 50:1 - 10:1) to afford compound **SI-30** (6.4 g, 13.2 mmol, 92.6% yield, 95.0% purity) as a yellow solid. LCMS: RT = 1.01 min, *m/z* 362.1 [M-Boc+H]$^+$. Purity: 83.1%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 - 7.28 (m, 10H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.85 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 6.75 (br. s, 1H), 6.67 (d, *J* = 7.2 Hz, 1H), 5.17 - 5.09 (m, 2H), 5.02 (br. s, 1H), 4.99 (s, 2H), 4.65 - 4.63 (m, 1H), 3.12 - 3.03 (m, 2H), 1.43 (s, 9H).

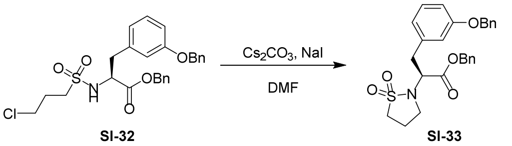


To a solution of compound **SI-30** (7.0 g, 15.2 mmol) in dioxane (70 mL) was added HCl/dioxane (4 M, 100 mL). The mixture was stirred at 20°C for 12 hours. The white solid was formed. LCMS showed desired mass was detected. The reaction mixture was concentrated in *vacuo* to afford compound **SI-31** (6.0 g, 15.1 mmol, 99.4% yield, 100.0% purity, HCl salt) as a white solid. LCMS: RT = 0.82 min, *m/z* 362.1 [M+H]$^+$. ^{1}H NMR (CD_3OD-d_4, 400 MHz): δ = 7.43 - 7.28 (m, 10H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.4Hz, 1H), 6.85 (t, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 2H), 5.04 (s, 2H), 4.35 (t, *J* = 6.8 Hz, 1H), 3.23 - 3.12 (m, 2H).

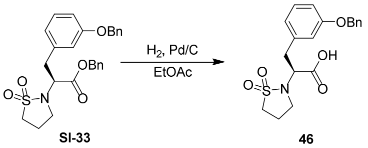


To a solution of compound **SI-31** (14.5 g, 36.4 mmol, 1.0 *eq*, HCl salt) and triethylamine (11.1 g, 109.3 mmol, 15.2 mL, 3.0 *eq*) in dichloromethane (150 mL) was added 3-chloropropane-1-sulfonyl chloride (7.7 g, 43.7 mmol, 5.3 mL, 1.2 *eq*) at 0°C. The mixture was stirred for 1 hour at 15°C. The solution turned to yellow and a lot of yellow precipitate was formed. TLC (petroleum ether: ethyl acetate = 1:1) showed the starting material was consumed. The reaction mixture was poured into water (200 mL), adjusted to pH = 4 with 1N hydrochloric acid aqueous, then extracted with ethyl acetate (3 x 200 mL). The combined organic phase was washed with brine (2 x 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo*. The residue was purified by column (SiO_2, petroleum ether: ethyl acetate = 10:1 ~ 1:1) to afford compound **SI-32** (15.0 g, 28.8 mmol, 79.1% yield, 96.5% purity) as yellow gum. LCMS:

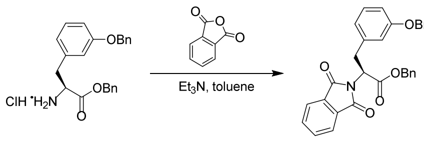
RT = 0.94 min, *m/z*: 502.1 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 - 7.32 (m, 10H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.79 (s, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 5.18 (s, 2H), 5.03 (s, 2H), 4.80 (d, *J* = 9.6 Hz, 1H), 4.44 - 4.40 (m, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.13 (dd, *J* = 5.2 Hz, 13.6 Hz, 1H), 2.99 (dd, *J* = 7.2 Hz, 13.6 Hz, 1H), 2.89 - 2.85 (m, 2H), 2.13 - 2.08 (m, 1H), 2.04 - 2.00 (m, 1H).



To a solution of compound **SI-32** (15.0 g, 29.9 mmol, 1.0 *eq*) and sodium iodide (896.0 mg, 5.9 mmol, 0.2 *eq*) in N, N-dimethyl formamide (150 mL) was added cesium carbonate (19.5 g, 59.7 mmol, 2.0 *eq*) at 0°C. The mixture was stirred at 0°C for 3 hours. TLC (petroleum ether: ethyl acetate = 2:1) showed the starting material was consumed and a more polar spot was observed. The reaction mixture was poured into water (300 mL), extracted with ethyl acetate (3 x 200 mL). The combined organic phase was washed with brine (3 x 300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo.* The residue was purified by column (SiO_2, petroleum ether: ethyl acetate = 10:1 ~ 2:1) to afford compound **SI-33** (12.5 g, 24.7 mmol, 82.8% yield, 92.2% purity) as a yellow solid. LCMS: RT = 1.00 min, *m/z*: 466.2 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 - 7.32 (m, 8H), 7.27 - 7.24 (m, 2H), 7.22 - 7.18 (m, 1H), 6.87 - 6.86 (m, 2H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.16 - 5.10 (m, 2H), 5.03 (s, 2H), 4.57 (dd, *J* = 7.2 Hz, 8.4 Hz, 1H), 3.60 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 3.40 - 3.33 (m, 1H), 3.26 (dd, *J* = 7.2 Hz, 14.0 Hz, 1H), 3.08 - 3.01 (m, 3H), 2.37 - 2.28 (m, 2H).

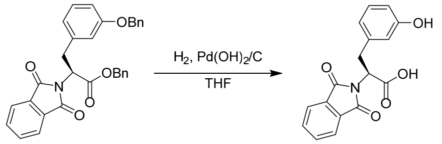


A solution of compound **SI-33** (5.5 g, 11.8 mmol, 1.0 *eq*) in ethyl acetate (50 mL) was purged with nitrogen 10 minutes, then Pd/C (0.5 g, 10% purity on carbon) was added in one portion. The mixture was degassed with hydrogen three times and stirred at 20°C for 1 hour under hydrogen atmosphere (15 psi). LCMS showed one main peak with desired mass was observed. The mixture was filtered, and the filtrate was concentrated in *vacuo* to afford compound **46** (8.0 g, 21.3 mmol, 90.2% yield) as a white solid. LCMS: RT = 0.78 min, purity: 85.7%, *m/z*: 376.1 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46 - 7.31 (m, 5H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.90 - 6.87 (m, 3H), 5.08 (s, 2H), 4.56 (dd, *J* = 6.0 Hz, 9.6 Hz, 1H), 3.54 (dd, *J* = 7.6 Hz, 16.0 Hz, 1H), 3.40 - 3.30 (m, 3H), 3.13 - 3.00 (m, 3H), 2.40 - 2.26 (m, 3H).



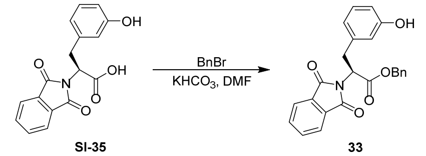
SI-31 SI-34

To a solution of compound **SI-31** (3.8 g, 9.5 mmol, 1.0 *eq*, HCl salt) and triethylamine (2.9 g, 28.6 mmol, 3.9 mL, 3.0 *eq*) in toluene (40 mL) was added isobenzofuran-1,3-dione (1.4 g, 9.6 mmol, 1.0 *eq*). The mixture was stirred at 20°C for 1 hour, then heated to 100°C and stirred for 12 hours. LCMS showed one main peak with desired mass was detected. The reaction mixture was poured into ethyl acetate (200 mL), washed with hydrochloric acid (1N, 100 mL) and brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo* to afford compound **SI-34** (5.9 g, crude) as yellow oil. LCMS: RT = 1.04 min, *m*/*z* 492.0 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81 - 7.78 (m, 2H), 7.72 - 7.69 (m, 2H), 7.39 - 7.29 (m, 10H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.79 - 6.74 (m, 3H), 6.28 - 5.21 (m, 3H), 4.90 (q, *J* = 11.6 Hz, 2H), 3.63 - 3.53 (m, 2H).



SI-34 SI-35

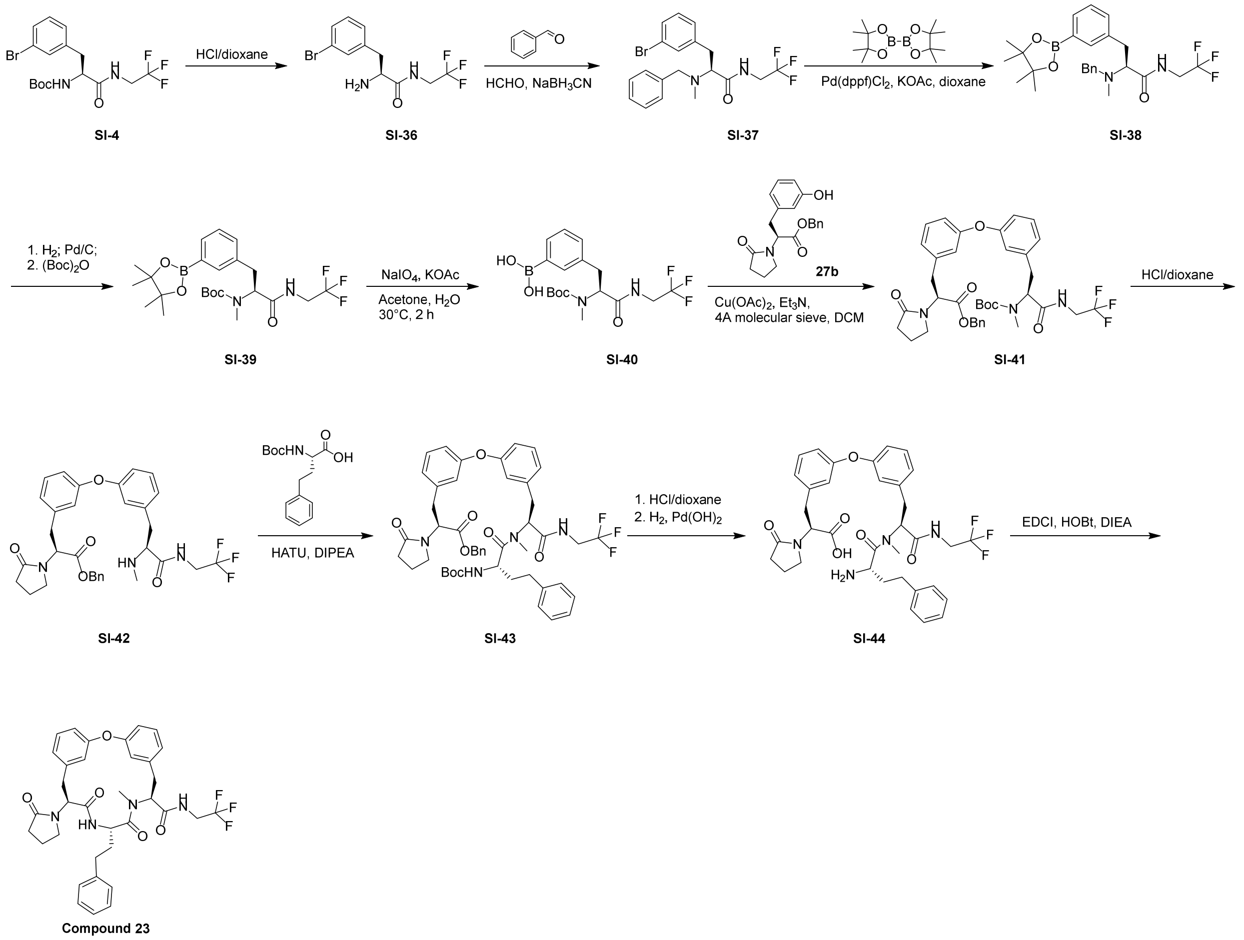
A solution of compound **SI-34** (5.9 g, 10.1 mmol, 1.0 *eq*) in tetrahydrofuran (50 mL) was purged with nitrogen 10 minutes, then $Pd(OH)_2$/C (300.0 mg, 10% purity on carbon) was added in one portion. The mixture was stirred for 24 hours at 20°C under hydrogen atmosphere (15 psi). LCMS showed about 35% of mono-benzyl intermediate mass was observed. The mixture was filtered and concentrated in *vacuo.* The residue was dissolved in methanol (20 mL) and tetrahydrofuran (20 mL) and purged with nitrogen 10 minutes, then $Pd(OH)_2$/C (300.0 mg, 10% purity on carbon) was added. The mixture was stirred for 12 hours at 20°C under hydrogen atmosphere (15 psi). LCMS showed one main peak with desired mass was detected. The reaction mixture was filtered, and the filtrate was concentrated in *vacuo* to afford compound **SI-35** (2.6 g, 8.4 mmol, 82.8% yield) as a white solid. LCMS: RT = 0.68 min, *m*/*z* 334.0 $[M+Na]^+$. ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.80 - 7.76 (m, 4H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.60 - 6.59 (m, 2H), 6.53 - 6.51 (m, 1H), 5.10 (dd, *J* = 5.2 Hz, 11.6 Hz, 1H), 3.49 - 3.39 (m, 2H).

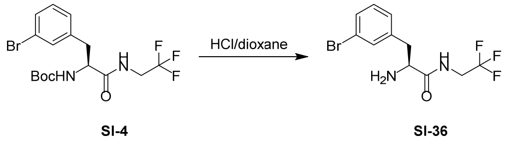


SI-35 33

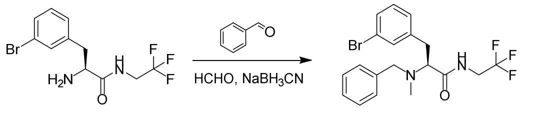
To a solution of compound **SI-35** (2.6 g, 8.4 mmol, 1.0 *eq*) in N, N-dimethyl formamide (30 mL) was added potassium bicarbonate (1.0 g, 10.0 mmol, 1.2 *eq*) portion wise at 0°C. The mixture was stirred at 0°C for 30 minutes. Benzyl bromide (1.6 g, 9.2 mmol, 1.1 mL, 1.1 *eq*) was added drop wise to the mixture at 0°C. The mixture was stirred for 2 hours at 20°C. TLC (petroleum ether: ethyl acetate = 3:1) showed the starting material was consumed. The reaction mixture was poured into water (50 mL), extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (3 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in *vacuo.* The residue was purified by column chromatography (petroleum ether: ethyl acetate = 10:1 ~ 2:1) to afford compound **33** (3.5 g, 7.6 mmol, 90.8% yield, 86.9% purity) as colorless gum. LCMS: RT = 0.91 min, *m*/*z* 424.1 $[M+Na]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81 - 7.79 (m, 2H), 7.71 - 7.69 (m, 2H), 7.38 - 7.29 (m, 5H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 7.2 Hz, 1H), 6.64 - 6.60 (m, 2H), 5.23 - 5.18 (m, 3H), 3.61 - 3.50 (m, 2H).

Scheme S4. Synthesis of compound **23**.



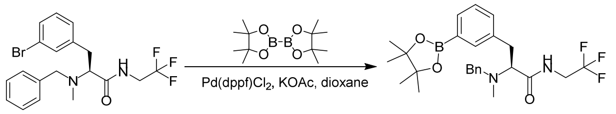


To a solution of compound **SI-4** (710.0 mg, 1.7 mmol, 1.0 *eq*) in dioxane (5 mL) was added hydrochloric acid/dioxane (4 M, 10 mL). The mixture was stirred at 25°C for 1.5 hours. TLC (petroleum ether: ethyl acetate=2:1) indicated starting material was consumed completely. The mixture was concentrated to afford compound **SI-36** (600.0 mg, 1.7 mmol, 99.4% yield, hydrochloric acid salt) as yellow oil. LCMS: RT = 0.62 min, *m*/*z* 326.9 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 9.32 (t, *J* = 6.0 Hz, 1H), 8.39 – 8.35 (m, 2H), 7.48 – 7.45 (m, 2H), 7.30 – 7.25 (m, 2H), 4.11 – 4.00 (m, 2H), 3.96 – 3.85 (m, 1H), 3.13 – 3.00 (m, 2H).



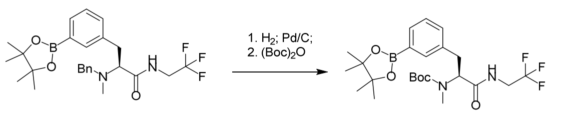
SI-36 SI-37

To a solution of compound **SI-36** (1.3 g, 4.1 mmol, 1.0 *eq*) in methanol (10 mL) was added benzaldehyde (520.8 mg, 4.9 mmol, 496.0 µL, 1.2 *eq*). The mixture was stirred at 25°C for 0.5 hour and then sodium cyanoborohydride (771.1 mg, 12.3 mmol, 3.0 *eq*) was added. The mixture was stirred at 25°C for 16 hours. The aqueous solution of formaldehyde (498.3 mg, 6.1 mmol, 457.2 µL, 37.0% purity, 1.5 *eq*) was added. The mixture was stirred at 25°C for 0.5 hour. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (20 mL) and then extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration, the residue was purified with silica gel coulmn (petroleum ether: ethyl acetate=5:1 to 4:1, TLC, petroleum ether: ethyl acetate=3:1) to afford compound **SI-37** (800.0 mg, 1.2 mmol, 28.2% yield, 61.8% purity) as light yellow oil. LCMS: RT = 0.75 min, purity: 61.8%, *m/z* 430.9 $[M+H]^+$.



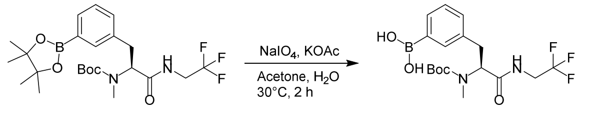
SI-37 SI-38

To a solution of compound **SI-37** (800.0 mg, 1.8 mmol, 1.0 *eq*) in dioxane (8 mL) was added compound **5** (946.5 mg, 3.7 mmol, 2.0 *eq*), potassium acetate (548.7 mg, 5.6 mmol, 3.0 *eq*) and Pd(dppf)Cl$_2$ (136.4 mg, 186.4 µmol, 0.1 *eq*). The mixture was degassed and purged with nitrogen for 3 times and then the mixture was stirred at 80°C for 3 hours under nitrogen atmosphere. LC-MS showed starting material was consumed completely and desired MS was detected. The mixture was concentrate to give crude product. The crude product was purified by silica gel column (petroleum ether: ethyl acetate=8:1 to 5:1, TLC, petroleum ether: ethyl acetate=3:1) to afford compound **SI-38** (1.1 g, crude) as light yellow oil. LCMS: RT = 0.81 min, *m/z* 477.1 $[M+H]^+$. ^{1}H NMR (MeOD, 400 MHz): δ = 7.71 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 6.4 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.33 – 7.20 (m, 3H), 7.17 (d, *J* = 6.8 Hz, 2H), 4.01 – 3.95 (m, 1H), 3.84 – 3.80 (m, 1H), 3.61 – 3.47 (m, 3H), 3.36 (dd, J_1 = 6.4 Hz, J_2 = 14.0 Hz, 1H), 3.00 (dd, J_1 = 7.2 Hz, J_2 = 14.0 Hz, 1H), 2.35 (s, 3H), 1.36 (s, 12H).



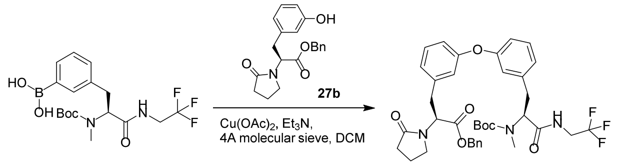
SI-38 SI-39

To a solution of compound **SI-38** (1.0 g, 2.1 mmol, 1.0 *eq*) was added Palladium hydroxide (200.0 mg, 10% purity). The mixture was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 25°C for 6 hours under hydrogen atmosphere. TLC (petroleum ether: ethyl acetate =3:1) indicated a little of starting material was remained. The mixture was concentrated to afford compound **SI-38-amine** (800.0 mg, 1.7 mmol, 82.4% yield) as black oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (d, *J* = 6.4Hz, 1H), 7.66 – 7.64 (m, 2H), 7.38 – 7.31 (m, 3H), 3.98 – 3.88 (m, 2H), 3.32 (dd, J_1 = 4.0 Hz, J_2 = 9.6 Hz, 1H), 3.23 (dd, J_1 = 4.4 Hz, J_2 = 14.0 Hz, 1H), 2.70 (dd, J_1 = 9.6 Hz, J_2 = 13.6 Hz, 1H), 2.26 (s, 3H), 1.35 (s, 12H). To a solution of compound **SI-38-amine** (800.0 mg, 2.1 mmol, 1.0 *eq*) in methanol (10 mL) was added triethylamine (628.8 mg, 6.2 mmol, 861.4 μL, 3.0 *eq*) and $(Boc)_2O$ (1.4 g, 6.2 mmol, 1.4 mL, 3.0 *eq*). The mixture was stirred at 25°C for 2 hours. LC-MS showed starting material was consumed completely and desired MS was detected. The mixture was concentrated to give crude product. The crude product was purified by silica gel column chromatography (Petroleum ether: Ethyl acetate=15:1 to 15:1) to afford compoud **SI-39** (670.0 mg, 1.1 mmol, 53.7% yield, 80.6% purity) as colorless oil. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.661 (s, 0.5H), 7.54 – 7.59 (m, 1.5H), 7.35 – 7.27 (m, 3H), 4.88 – 4.83 (m, 1H), 3.93 – 3.83 (m, 2H), 3.17 – 3.14 (m, 1H), 2.93 – 2.86 (m, 1H), 2.68 (s, 3H), 1.28 (s, 12H), 1.08 (s, 9H).



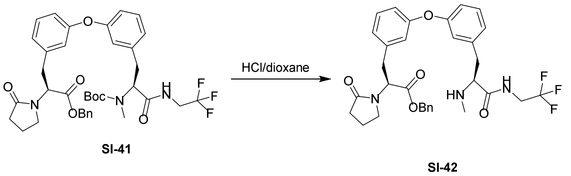
SI-39 **SI-40**

To a solution of compound **SI-39** (650.0 mg, 1.3 mmol, 1.0 *eq*) in acetone (5 mL) and water (5 mL) was added ammonium acetate (309.1 mg, 4.0 mmol, 3.0 *eq*) and sodium periodate (857.6 mg, 4.0 mmol, 222.2 μL, 3.0 *eq*). The mixture was stirred at 25°C for 16 hours. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (40 mL) and then hydrochloric acid (1M) was added until pH=8. The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL), dried over sodium sulfate. After filtration and concentration, compound **SI-40** (400.0 mg, 892.8 μmol, 66.8% yield, 90.2% purity) was obtained as yellow oil. LCMS: RT = 0.78 min.

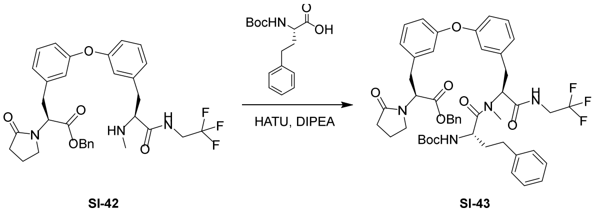


SI-40 **SI-41**

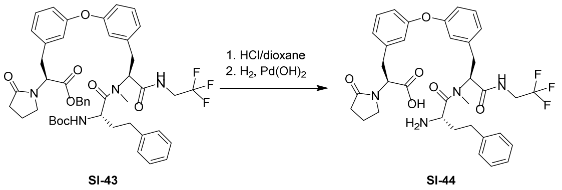
To a solution of compound **SI-40** (400.0 mg, 989.6 μmol, 1.3 *eq*) and compound **27b** (250.0 mg, 736.6 μmol, 1.0 *eq*) in dichloromethane (5mL) was added 4A MS (600.0 mg), triethylamine (745.4 mg, 7.4 mmol, 1.0 mL, 10.0 *eq*) and copper acetate (200.7 mg, 1.1 mmol, 1.5 *eq*). The mixture was stirred at 25°C for 2 hour. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was filtered and then the filter liquor was concentrated to give crude product. The crude product was purified by silica gel column (petroleum ether: ethyl acetate=10:1 to 3:1) to afford compound **SI-41** (330.0 mg, 412.2 μmol, 55.9% yield, 87.1% purity) as yellow oil. LCMS: RT = 1.08 min, *m*/*z* 698.3 $[M+H]^+$. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ = 8.59 – 8.57 (m, 1H), 7.37 – 7.27 (m, 8H), 7.01 – 6.96 (m, 1H), 6.91 – 6.78 (m, 4H), 5.17 – 5.10 (m, 2H), 4.95 – 4.90 (m, 1H), 4.68 – 4.66 (m, 1H), 4.04 – 3.08 (m, 4H), 3.21 – 3.12 (m, 5H), 2.67 – 2.62 (m, 4H), 1.82 – 1.74 (m, 2H), 1.28 – 1.26 (m, 9H).



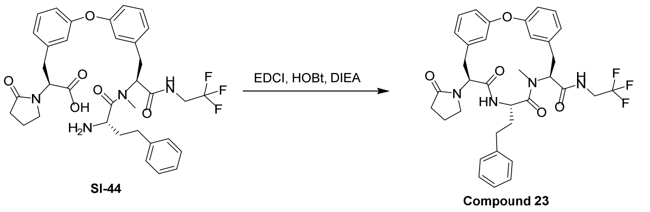
To a solution of compound **SI-41** (300.0 mg, 429.9 μmol, 1.0 *eq*) in dioxane (4 mL) was added hydrochloric acid/dioxane (4 M, 10 mL). The mixture was stirred at 25°C for 0.5 hour. TLC (petroleum ether: ethyl acetate=1:1) indicated starting material was consumed completely and one new spot formed. The mixture was concentrated to afford compound **SI-42** (300.0 mg, 367.2 μmol, 85.4% yield, 77.6% purity, hydrochloric acid salt) was obtained as yellow solid. LCMS: RT = 0.78 min. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ = 9.42 – 9.29 (m, 1H), 7.37 – 7.29 (m, 8H), 7.03 – 6.97 (m, 2H), 6.91 (s, 1H), 6.87 – 6.84 (m, 2H), 5.19 (dd, J_1 = 12.8 Hz, J_2 = 16.0 Hz, 2H), 4.96 (dd, J_1 = 5.2 Hz, J_2 = 10.8 Hz, 1H), 4.11 (m, 2H), 4.00 - 3.92 (m, 4H), 3.21 – 3.18 (m, 2H), 3.10 – 3.04 (m, 2H), 2.50 (s, 3H), 2.20 – 2.08 (m, 2H), 1.91 – 1.74 (m, 2H).



To a solution of (S)-2-((tert-butoxycarbonyl)amino)-4-phenylbutanoic acid (145.4 mg, 520.4 μmol, 1.1 *eq*) in dimethyl formamide (5 mL) was added HOBt (83.1 mg, 615.1 μmol, 1.3 *eq*), EDCI (117.9 mg, 615.1 μmol, 1.3 *eq*) and diisopropylethylamine (183.4 mg, 1.4 mmol, 247.2 μL, 3.0 *eq*) at 0°C under nitrogen and then compound **SI-42** (300.0 mg, 473.1 μmol, 1.0 *eq*, hydrochloric acid salt) was added. The mixture was stirred at 25°C for 16 hours. LCMS showed the desired MS was detected. The mixture was poured into water (40 mL) and then added 1 N hydrochloric acid (10 mL). The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by prep-HPLC (column: Phenomenex Synergi 10 µm C18 150 x 25 mm; mobile phase: [water(0.1%TFA)-ACN]; B%: 62%-92%,2min) to afford compound **SI-43** (120.0 mg, 126.7 µmol, 26.8% yield, 90.6% purity) as a white solid. LCMS: RT = 1.14 min, *m*/*z* 859.6 [M+H]$^+$.



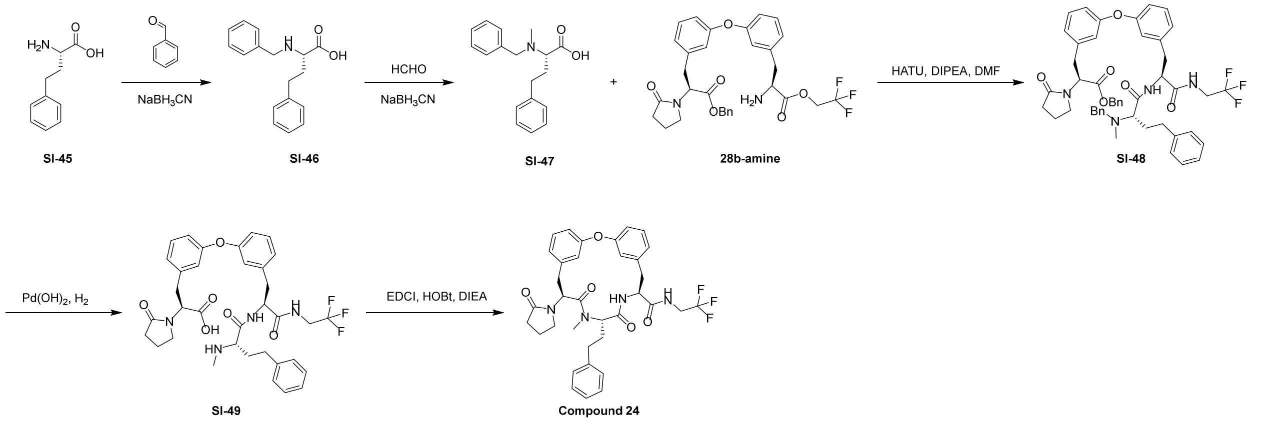
To a solution of compound **SI-43** (115.0 mg, 133.9 µmol, 1.0 *eq*) in dioxane (2 mL) was added hydrochloric acid/dioxane (4 M, 5 mL). The mixture was stirred at 25°C for 1.5 hours. LCMS most starting material was consumed and desired Ms was detected. The mixture was concentrated to afford compound **SI-43-amine** (100.0 mg, 115.3 µmol, 86.1% yield, 91.7% purity, hydrochloric acid salt) as a black brown solid. LCMS: RT = 0.85 min, *m*/*z* 759.4 [M+H]$^+$. To a solution of compound **SI-43-amine** (100.0 mg, 125.7 µmol, 1.0 *eq*, hydrochloric acid salt) in tetrahydrofuran (5 mL) was added Palladium hydroxide (30.0 mg, 21.4 µmol, 10% purity, 0.17 *eq*). The mixture was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 25°C for 8 hours under hydrogen balloon. The LCMS showed starting material was consumed completely and desired MS was detected. The mixture was filtered and then the filter was concentrated to afford compound **SI-44** (100.0 mg, 124.7 µmol, 99.2% yield, 87.9% purity, hydrochloric acidsalt) as an off-white solid. LCMS: RT = 0.75 min, *m*/*z* 669.4 [M+H]$^+$. ^{1}H NMR: (DMSO-d6, 400 MHz) δ = 8.77 (t, *J* = 6.0 Hz, 1H), 7.32 – 7.26 (m, 4H), 7.22 – 7.17 (m, 4H), 7.06 – 6.96 (m, 3H), 6.86 – 6.75 (m, 3H), 5.16 (dd, J_1 = 6.0 Hz, J_2 = 9.6 Hz, 1H), 4.78 (dd, J_1 = 4.4 Hz, J_2 = 10.8 Hz, 1H), 3.89 – 3.86 (m, 2H), 3.46 – 3.45 (m, 2H), 3.21 – 3.17 (m, 2H), 3.05 – 2.95 (m, 2H), 2.91 – 2.88 (m, 3H), 2.64 – 2.62 (m, 1H), 2.44 (t, *J* = 8.0 Hz, 3H), 2.18 – 1.99 (m, 3H), 1.87 – 1.86 (m, 3H).

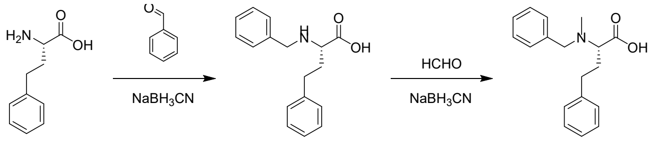


To a solution of compound **SI-44** (80.0 mg, 113.5 µmol, 1.0 *eq*, hydrochloric acid salt) in dimethyl formamide (6 mL) was added diisopropylethylamine (43.9 mg, 340.4 µmol, 59.3 µL, 3.0 *eq*), EDCI (32.6

mg, 170.2 μmol, 1.5 *eq*) and HOBT (22.9 mg, 170.2 μmol, 1.5 *eq*) at 0°C under nitrogen. The mixture was stirred at 25°C for 16 hours. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was poured into water (20 mL) and then added 1 N hydrochloric acid (5 mL). The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (column: Phenomenex Synergi 10 μm C18 150 x 25 mm; mobile phase: [water(0.1%TFA)-ACN];B%: 46%-76%,13min) to afford **compound 23** (19.8 mg, 29.8 μmol, 26.3% yield, 97.7% purity) as a white solid. LCMS: RT = 3.21 min, m/z 651.3 $[M+H]^+$. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.32 – 7.28 (m, 2H), 7.26 – 7.22 (m, 2H), 7.17 – 7.14 (m, 1H), 7.11 – 6.93 (m, 6H), 6.79 (t, *J* = 1.6 Hz, 1H), 6.39 (t, *J* = 1.6 Hz, 1H), 5.66 (t, *J* = 8.8 Hz, 1H), 4.73 (dd, J_1 = 2.8 Hz, J_2 = 12.0 Hz, 1H), 4.59 – 4.54 (m, 1H), 3.98 – 3.81 (m, 2H), 3.62 – 3.50 (m, 2H), 3.29 (t, *J* = 12.8 Hz, 1H), 3.19 (d, *J* = 8.4 Hz, 2H), 2.71 (s, 3H), 2.70 (dd, J_1 = 3.2 Hz, J_2 = 13.2 Hz, 1H), 2.65 (q, *J* = 6.8 Hz, 1H), 2.50 – 2.34 (m, 3H), 2.12 (m, 2H), 1.84 (m, 2H).

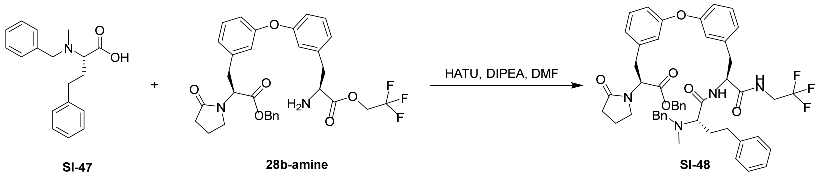
Scheme S5. Synthesis of compound **24**.





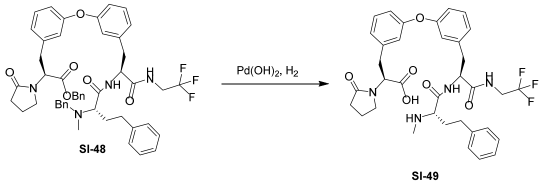
SI-45 **SI-46** **SI-47**

To a solution of compound **SI-45** (770.0 mg, 3.6 mmol, 1.0 *eq*, hydrochloric acid salt) in methanol (15 mL) was added benzaldehyde (378.8 mg, 3.6 mmol, 360.8 µL, 1.0 *eq*), sodium bicarbonate (1.5 g, 17.8 mmol, 694.4 µL, 5.0 *eq*) and calcium chloride (998.5 mg, 9.0 mmol, 2.5 *eq*). The mixture was stirred at 25°C for 16 hours and then sodium cyanoborohydride (1.1 g, 17.8 mmol, 5.0 *eq*) was added. The mixture was stirred at 25°C for 2 hours and aqueous solution of formaldehyde (579.5 mg, 7.1 mmol, 531.6 µL, 37% purity, 2.0 *eq*) was added. The mixture was stirred at 25°C another 1 hour. LCMS showed compound **SI-46** was consumed completely and desired MS was detected. The mixture was filtered and then the filter was concentrated to give crude product. The crude product was purified by reverse phase flash (TFA) to afford compound **SI-47** (500.0 mg, 1.7 mmol, 49.3% yield, 100.0% purity) as a white solid. LCMS: RT = 0.69 min, m/z 284.1 $[M+H]^+$. ^{1}H NMR (MeOD, 400 MHz): δ = 7.53 – 7.45 (m, 5H), 7.33 – 7.20 (m, 5H), 4.46 (dd, J_1 = 12.8 Hz, J_2 = 48.0 Hz, 2H), 3.97 (t, J = 6.0 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.83 (s, 3H), 2.81 – 2.75 (m, 1H), 2.41 – 2.75 (m, 2 H).

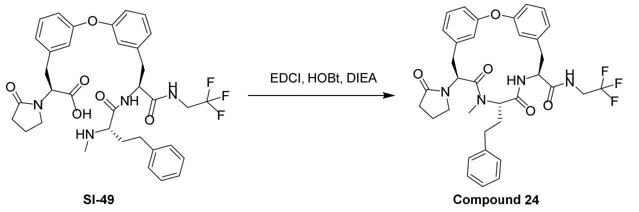


SI-47 **28b-amine** **SI-48**

To a solution of **SI-47** (115.0 mg, 405.8 µmol, 1.0 *eq*) in dimethyl formamide (4 mL) was added diisopropylethylamine (209.8 mg, 1.6 mmol, 282.7 µL, 4.0 eq), DIEA (71.3 mg, 527.6 µmol, 1.3 eq) and EDCI (101.1 mg, 527.6 µmol, 1.3 eq) at 0°C under nitrogen and then compound **28b-amine** (302.5 mg, 487.0 μmol, 1.2 eq, hydrochloric acid salt) was added to the mixture. The mixture was stirred at 25°C for 16 hours. The mixture was poured into water (10 mL) and then added 1 N hydrochloric acid (2 mL). The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude product was purified by column (petroleum ether: ethyl acetate=5:1 to dichloromethane: methanol =2:1) and prep-HPLC (column: Phenomenex Synergi 10 μm C18 150 x 25 mm; mobile phase: [water (0.1%TFA)-ACN]; B%: 38%-68%, 2min) to afford compound **SI-48** (130.0 mg, 153.1 μmol, 37.7% yield, 100.0% purity) as a white solid. LCMS: RT = 0.88 min, m/z 849.4 $[M+H]^+$.

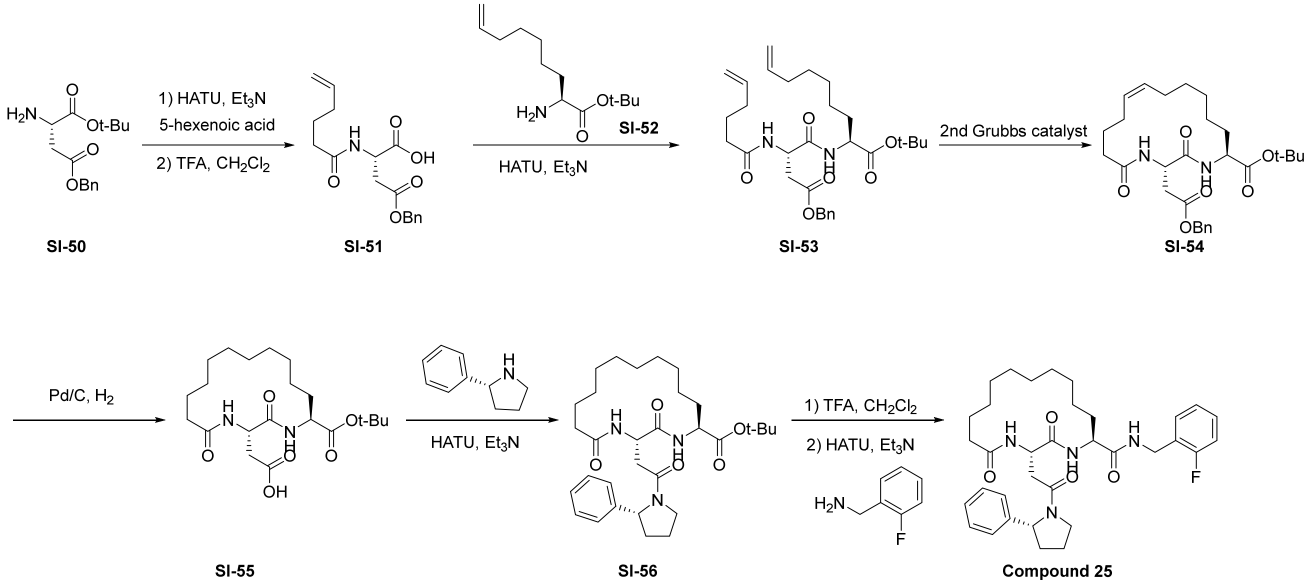


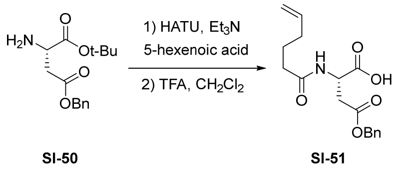
To a solution of compound **SI-48** (127.0 mg, 149.6 μmol, 1.0 *eq*) in tetrahydrofuran (4 mL) was added Palladium hydroxide (21.0 mg, 14.9 μmol, 10% purity, 0.1 *eq*). The mixture was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 25°C for 2 hours under hydrogen atmosphere. LCMS showed starting material was consumed completely and desired MS was detected. The mixture was filtered and then the filter was concentrated to afford compound **SI-49** (100.0 mg, 128.5 μmol, 85.9% yield, 85.9% purity) as a white solid. LCMS: RT = 0.74 min, m/z 669.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ = 12.96 (br.s, 1H), 9.05 (d, J = 8.4 Hz, 1H), 8.96 (t, J = 6.4 Hz, 1H), 8.83 (s, 1H), 7.32 – 7.26 (m, 4H), 7.23 – 7.19 (m, 1H), 7.16 (d, J = 6.8 Hz, 2H), 7.07 – 7.01 (m, 3H), 6.87 (s, 1H), 6.83 – 6.77 (m, 2H), 4.85 – 4.76 (m, 2H), 4.06 – 3.97 (m, 2H), 3.95 – 3.89 (m, 1H), 3.37 – 3.33 (m, 2H), 3.30 – 3.24 (m, 1H), 3.22 (dd, J_1 = 4.8 Hz, J_2 = 14.4 Hz, 1H), 3.08 – 2.97 (m, 2H), 2.84 (dd, J_1 = 10.8 Hz, J_2 = 14.0 Hz, 1H), 2.21 (s, 3H), 2.18 – 2.12 (m, 1H), 2.08 - 2.05 (m, 1H), 1.95 – 1.83 (m, 2H), 1.78 – 1.67 (m, 2H).



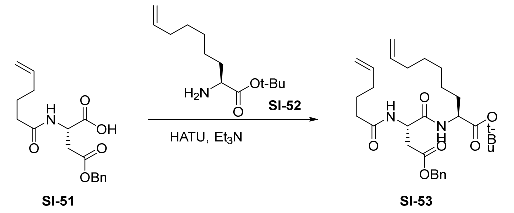
To a solution of compound **SI-49** (100.0 mg, 149.5 μmol, 1.0 *eq*) in dimethyl formamide (4 mL) was added diisopropylethylamine (48.3 mg, 373.8 μmol, 65.1 μL, 2.5 *eq*), HOBT (26.3 mg, 194.4 μmol, 1.3 *eq*) and EDCI (37.3 mg, 194.4 μmol, 1.3 *eq*) at 0°C under nitrogen and then the mixture was stirred at 25°C for 16 hours. LCMS showed starting material was consumed completely with desired MS was detected. The mixture was poured into water (20 mL) and then added 1 N hydrochloric acid (5 mL). The mixture was extracted by ethyl acetate (3 x 20 mL). The combined organic phase was washed by brine (20 mL) and dried over sodium sulfate. After filtration and concentration under reduced pressure, the crude product was purified by prep-HPLC (column: Phenomenex Synergi 10 μm C18 150 x 25 mm; μmobile phase: [water (0.1%TFA)-ACN]; B%: 42%-72%,2min) to afford **compound 24** (25.3 mg, 37.5 μmol, 25.1% yield, 96.6% purity) as a white solid. LCMS: RT = 3.21 min, m/z 651.3 $[M+H]^+$. ^{1}H NMR (MeOD, 400 MHz): δ = 8.73 (t, *J* = 6.4 Hz, 1H), 8.11 (d, *J* = 4.0 Hz, 1H), 7.36 (q, *J* = 8.0 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.16 – 7.07 (m, 4H), 7.01 – 6.97 (m, 3H), 6.58 (d, *J* = 2.0 Hz, 2H), 5.31 (dd, J_1 = 2.8 Hz, J_2 = 12.0 Hz, 1H), 5.00 (dd, J_1 = 6.8 Hz, J_2 = 8.4 Hz, 1H), 4.80 – 4.75 (m, 1H), 4.06 – 3.79 (m, 2H), 3.56 – 3.52 (m, 1H), 3.43 – 3.36 (m, 2H), 3.08 – 2.93 (m, 2H), 2.85 (s, 3H), 2.71 (dd, J_1 = 2.4 Hz, J_2 = 12.8 Hz, 1H), 2.49 – 2.34 (m, 4H), 2.11 – 1.78 (m, 4H).

Scheme S6. Synthesis of compound **25**.

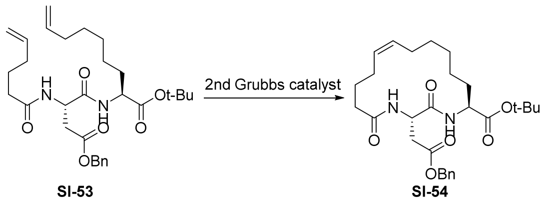




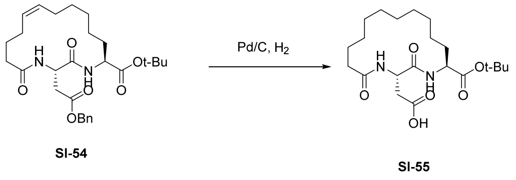
To a solution of O4-benzyl O1-tert-butyl (2S)-2-aminobutanedioate **SI-50** (25.0 g, 79.0 mmol, CL) and 5-hexenoic acid (10.0 g, 91.0 mmol) in DMF (500.0 mL) was added HATU (37.0 g, 99.0 mmol) at room temperature. After being stirred for 5 min, TEA (43.9 mL, 320.0 mmol) was added at room temperature and the mixture was stirred at room temperature for 16h. Water was added and the mixture was extracted with EtOAc. The extract was washed with brine and water then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (ISCO, 330 g, 20-40% EtOAc in hexane) to afford a residue (26.7 g, 89.8% yield) as a pale brown oil which was used as is. To the solution of residue in CH_2Cl_2 was added 2,2,2-trifluoroacetic acid (121.6 g, 1.1 mol) in an ice-bath, and the mixture was stirred at room temperature for 16h. Then the reaction mixture was concentrated under reduced pressure and azeotroped with toluene 3 times to afford, **SI-51** (23.0 g, 100.0% yield) as a pale brown oil which was used for next step without further purification.



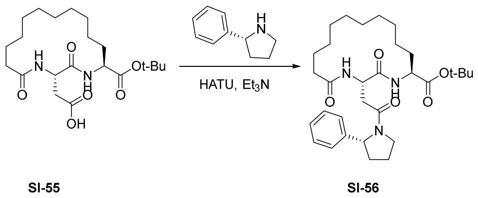
To a solution of **SI-51** (7.8 g, 24.7 mmol) and tert-butyl (2S)-2-aminonon-8-enoate **SI-52** (6.2 g, 23.5 mmol) in DMF (350 mL) was added HATU (10.6 g, 28.2 mmol) at room temperature. After being stirred for 5 min, TEA (7.1 g, 70.5 mmol) was added, and the mixture was stirred at room temperature for 1h. Water was added and the mixture was extracted with EtOAc. The extract was washed with brine and water, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ISCO, 330 g, 40-60% EtOAc in hexane) to afford **SI-53** (8.6 g, 69.5% yield) as a pale brown oil, which was used in the next step without further purification.



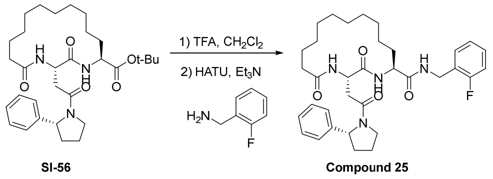
A solution of tert-butyl **SI-53** (2.0 g, 3.8 mmol) in toluene (3.0 L) was degassed by bubbling nitrogen through for 15 min then Grubbs 2nd Generation catalyst (0.80 g, 0.94 mmol) was added at room temperature. After being stirred for 16h at 40°C under N_2 the mixture was concentrated under reduced pressure. The residue was triturated with ether (200 mL) and filtrated. The filtrated was concentrated under reduced pressure and the residue was purified by column chromatography (220 g, ISCO, 40-50% EtOAc in hexane) to afford **SI-54** (610.0 mg, 92.6% yield).



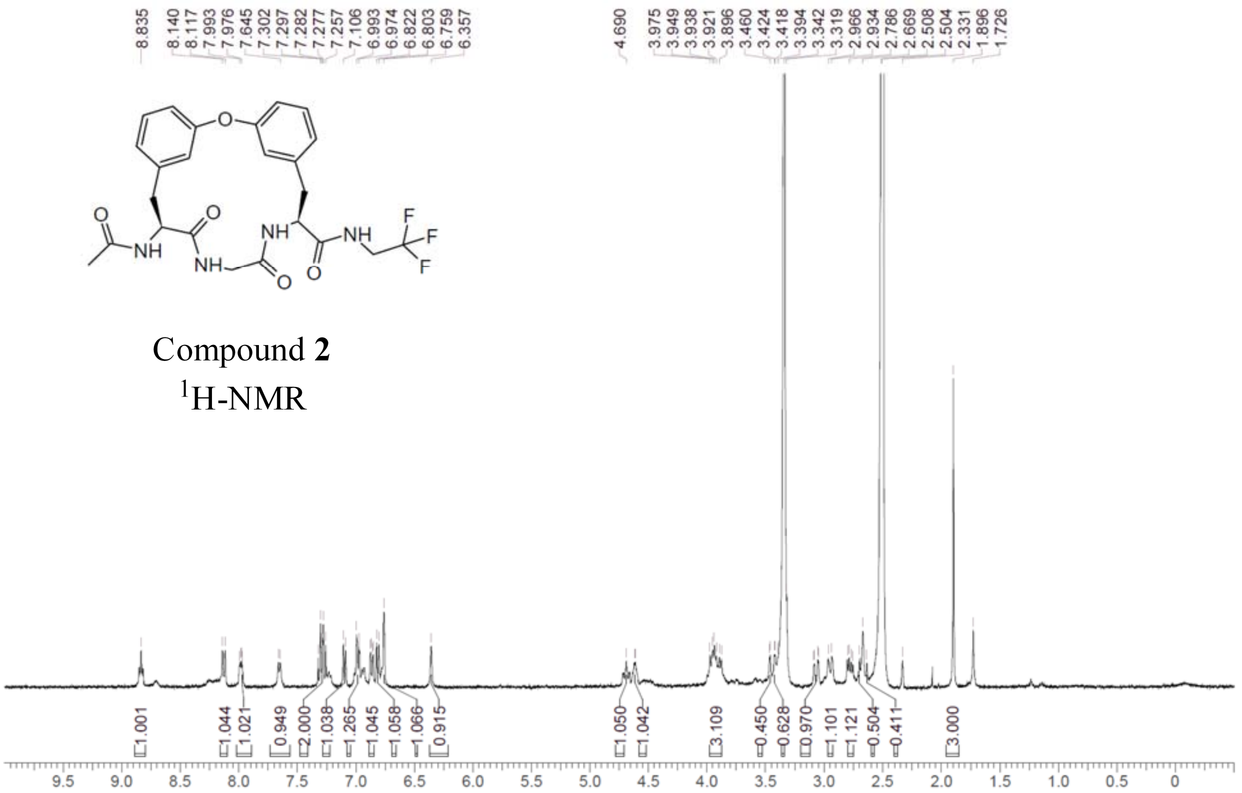
A mixture of **SI-54** (640.0 mg, 1.3 mmol), and 10% palladium on carbon (360.0 mg, 1.3 mmol), in MeOH (200 mL) was hydrogenated under a balloon pressure of H_2. After being stirred for 2 h, insoluble materials were removed by filtration through celite, and the filter pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford **SI-55** (540.0 mg, 100.0% yield, crude) as a pale brown amorphous solid which was used in the next step without further purification.



To a solution of **SI-55** (450.0 mg, 1.1 mmol) and (R)-2-phenylpyrrolidine (177.0 mg, 1.2 mmol) in DMF (5.0 mL) was added HATU (535.0 mg, 1.4 mmol) at room temperature. After being stirred for 5 min, triethylamine (552 mg, 5.45 mmol) was added, and the mixture was stirred at room temperature for 24h. Water was added and the mixture was extracted with EtOAc. The extract was washed with brine and water, then dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (40 g, ISCO, 0-5% MeOH in EtOAc) to afford **SI-56** (280.0 mg, 47.0% yield) as a white solid.

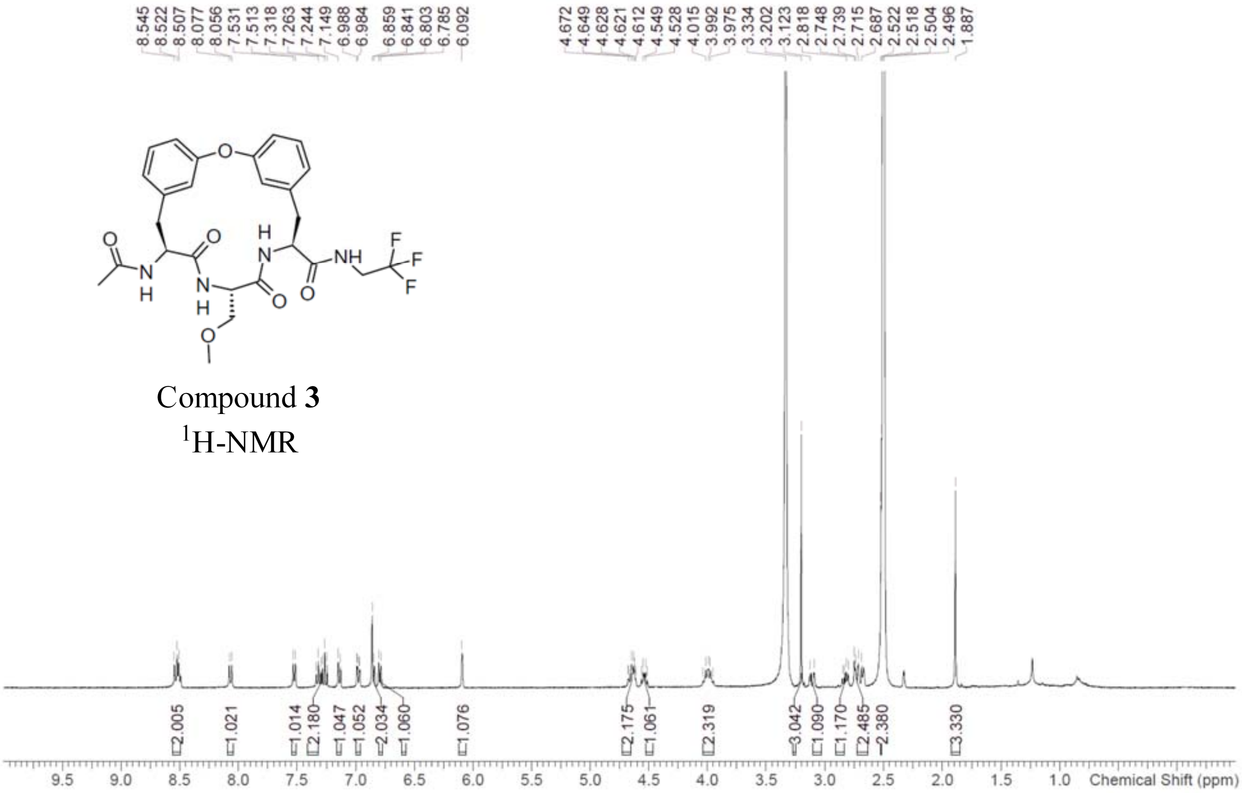


To **SI-56** (250.0 mg, 461.0 μmol) in CH_2Cl_2 chilled over ice-bath was added trifluoroacetic acid (1.1 g, 9.2 mmol). The mixture was stirred at room temperature for 3h then concentrated under reduced pressure. The residue was crystallized with ether to afford the **SI-56-acid** (180.0 mg) as a pale brown solid which was used without further purification. A mixture of the **SI-56-acid** (240.0 mg, 494.0 μmol), 2-fluorobenzylamine (74.2 mg, 593.1 μmol), HATU (279.7 mg, 741.3 μmol) and TEA (342.0 μL, 2.5 mmol) in DMF (4.00 mL) was stirred at room temperature for 16 h. The reaction was diluted with water and EtOAc. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give a black oil. The residue was purified by column chromatography (40 g, ISCO, 90-100% EtOAc in hexana) to afford **compound 25** (16 mg, 5.6% yield) as a pale brown solid. LCMS: RT: 2.40, m/z: 593.46$[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6) δ = 8.60 – 8.03 (m, 3H), 7.42 – 7.24 (m, 3H), 7.23 – 7.11 (m, 4H), 7.12 – 6.97 (m, 2H), 5.10 - 4.50 (m, 2H), 4.45 – 3.99 (m, 3H), 3.82 – 3.40 (m, 1H), 3.21 – 2.19 (m, 3H), 2.19 – 1.89 (m, 2H), 1.88 – 1.78 (m, 2H), 1.76 – 1.67 (m, 1H), 1.64 – 1.43 (m, 3H), 1.37 – 1.06 (m, 16H).



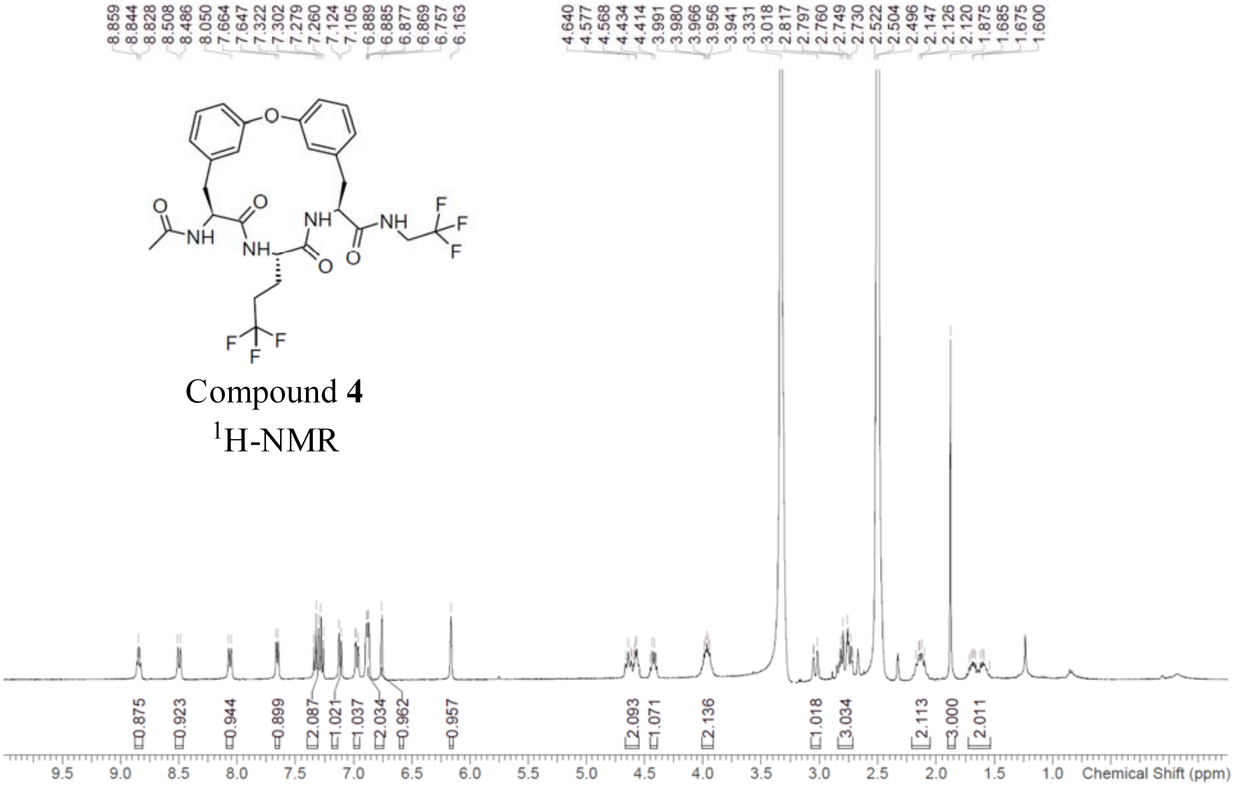
Compound **2**

^{1}H-NMR



Compound **3**

^{1}H-NMR



Compound **4**
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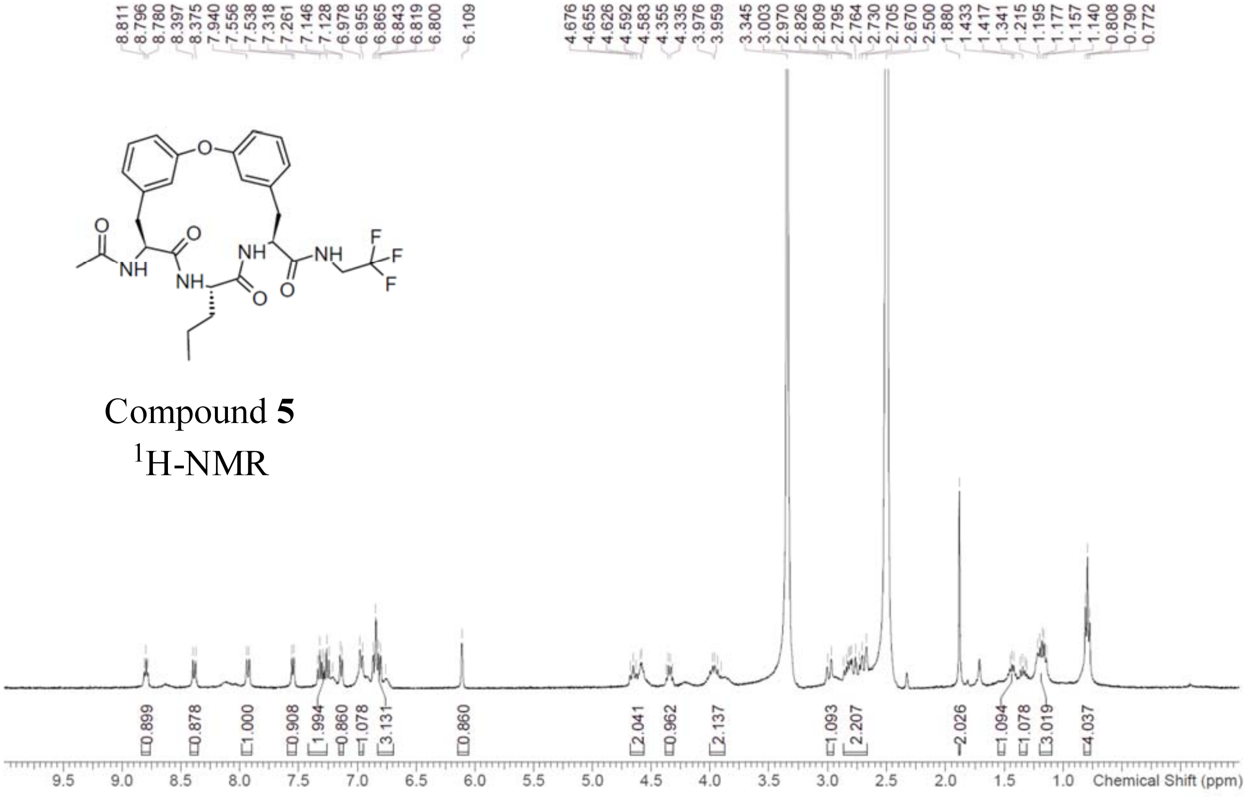

Compound **5**
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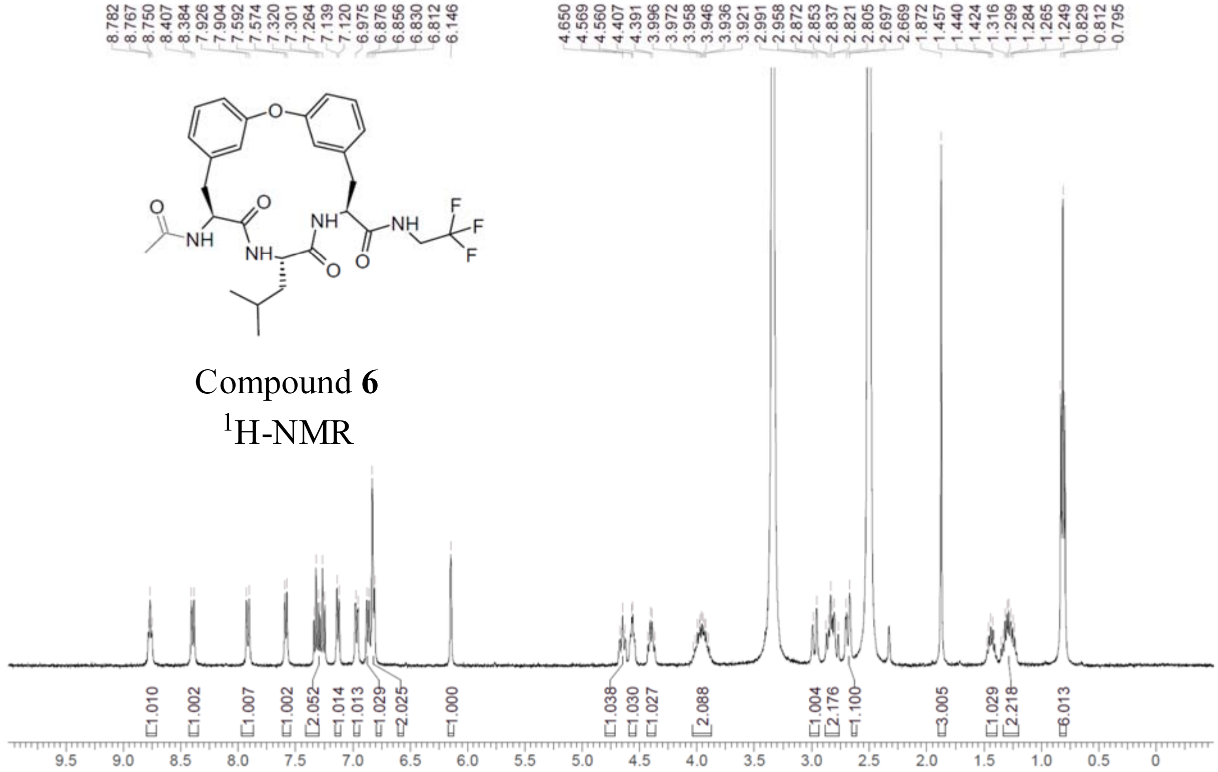
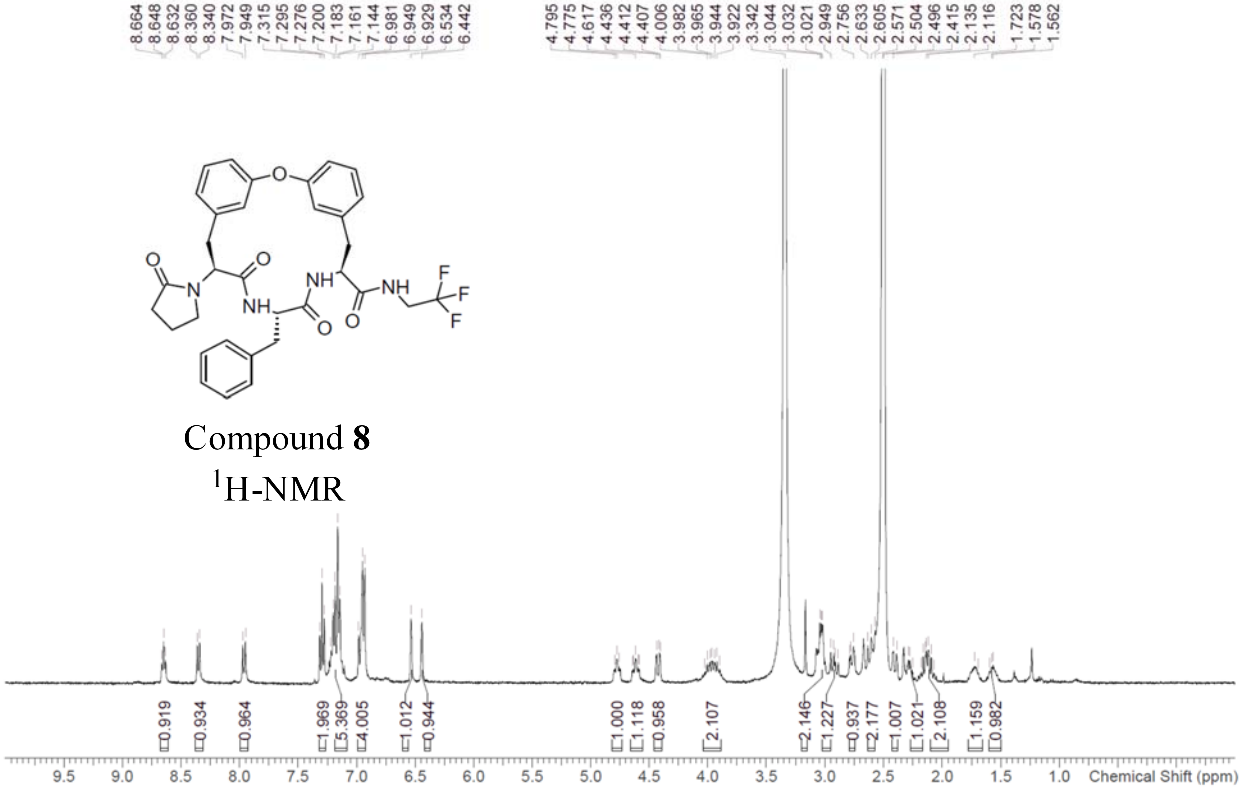
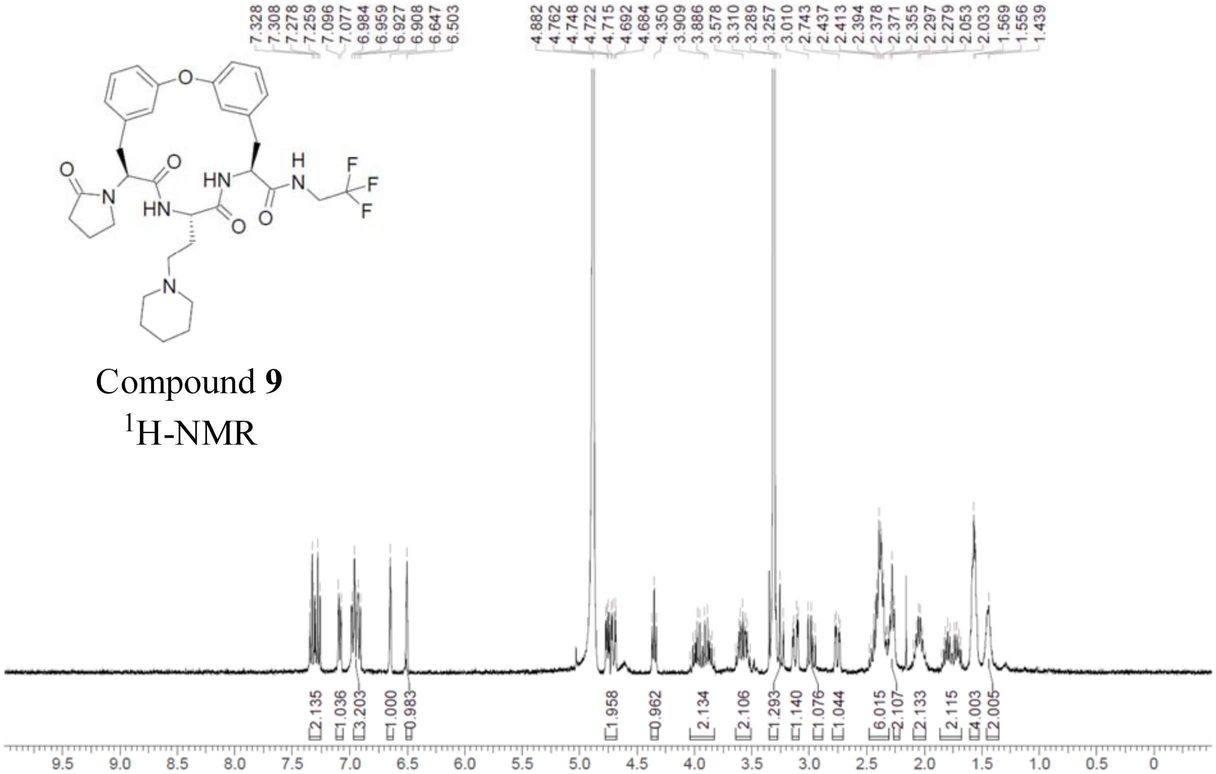

Compound **6**

^{1}H-NMR


Compound **8**

^{1}H-NMR



Compound **9**
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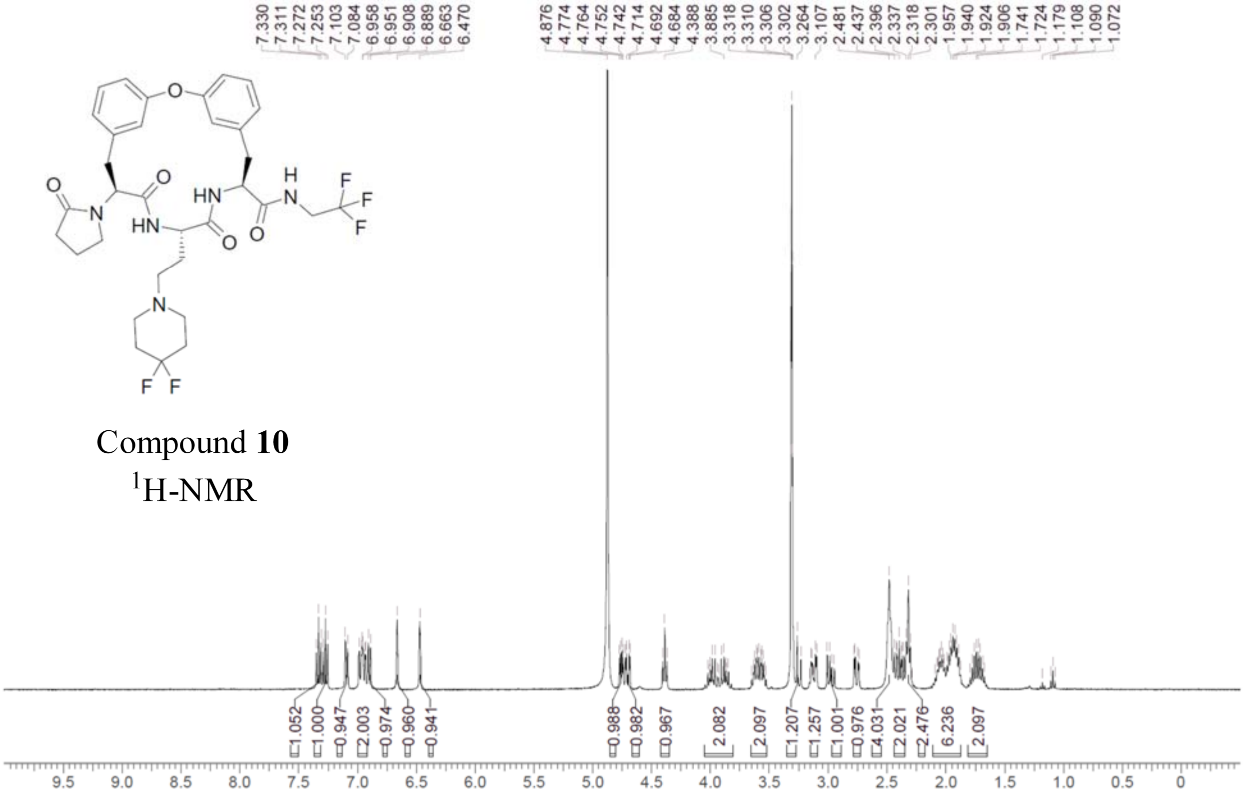

Compound **10**
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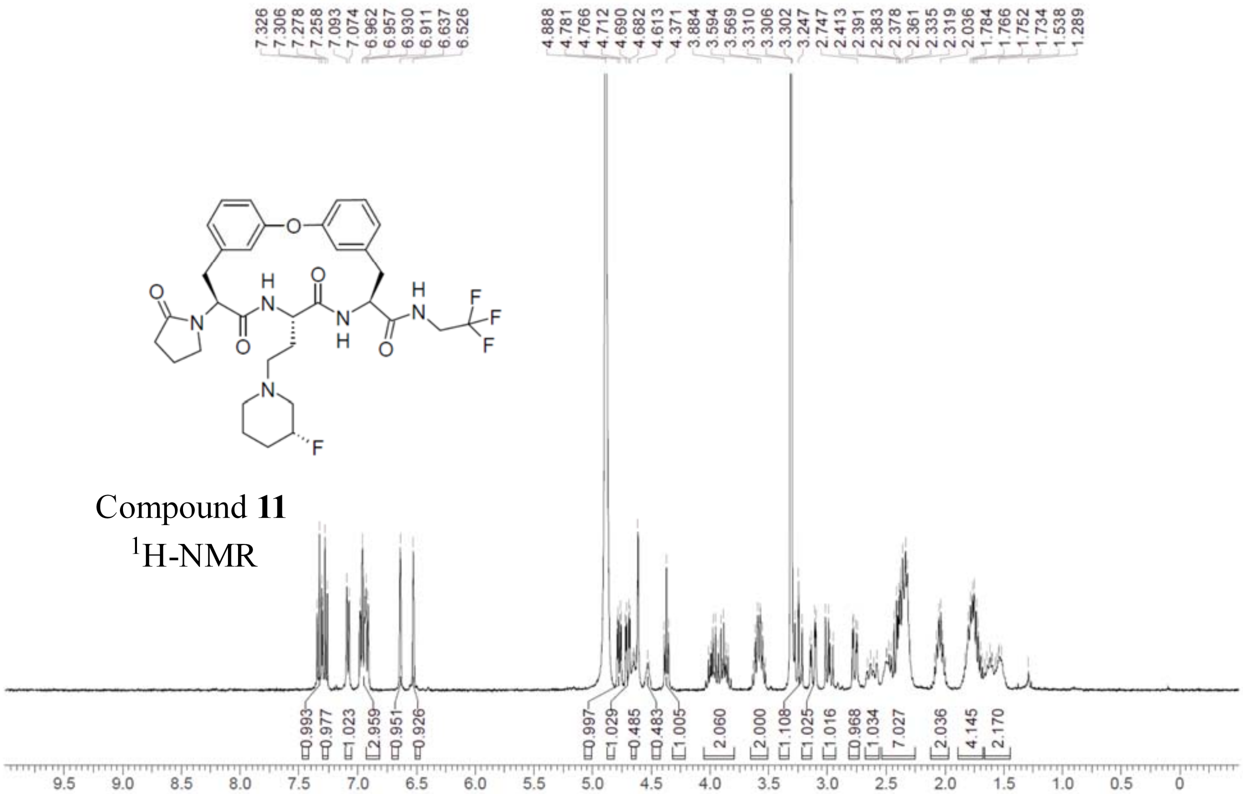

Compound **11**
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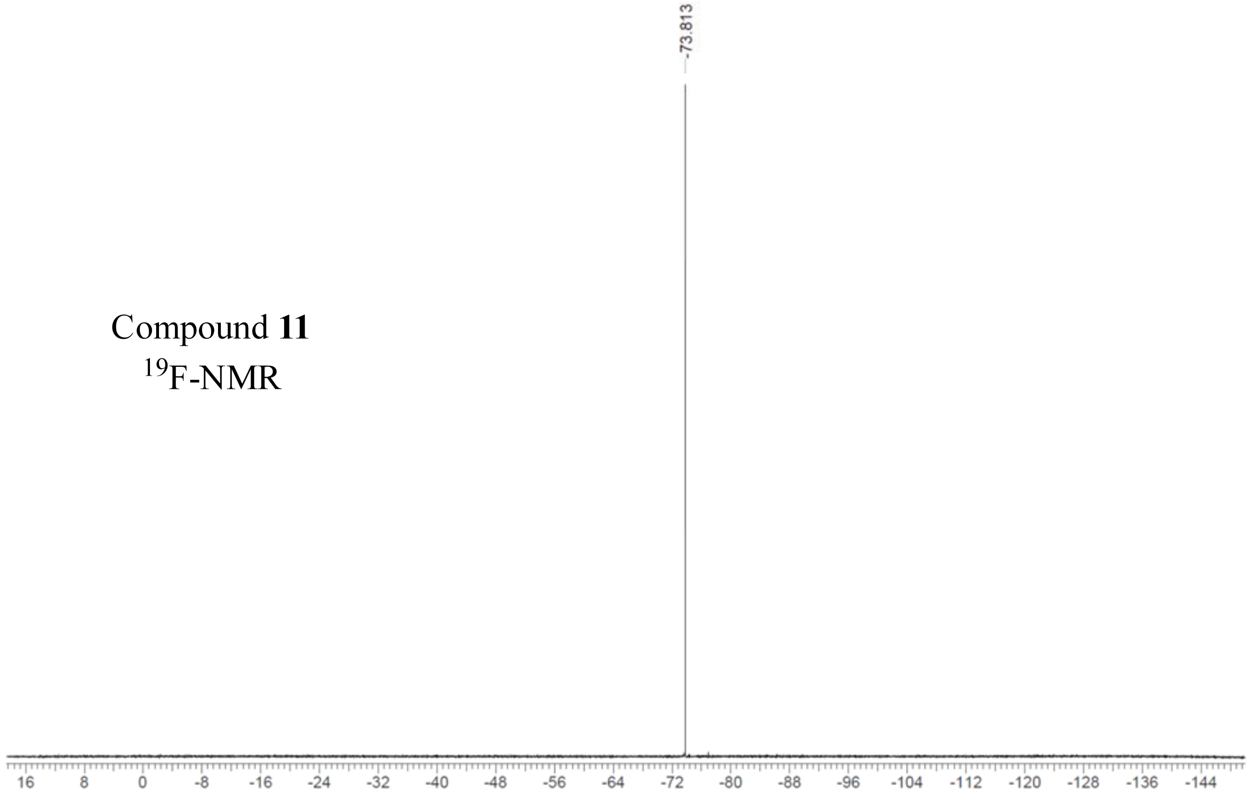

Compound **11**
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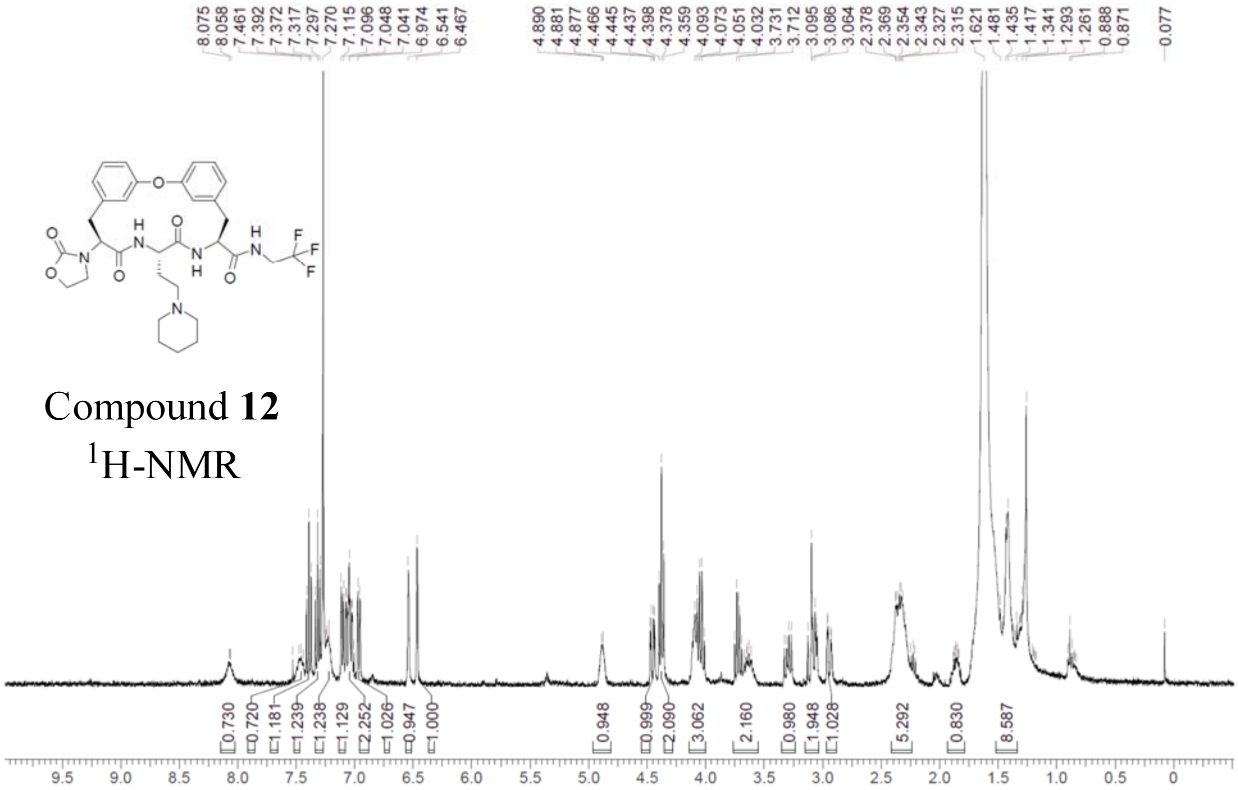
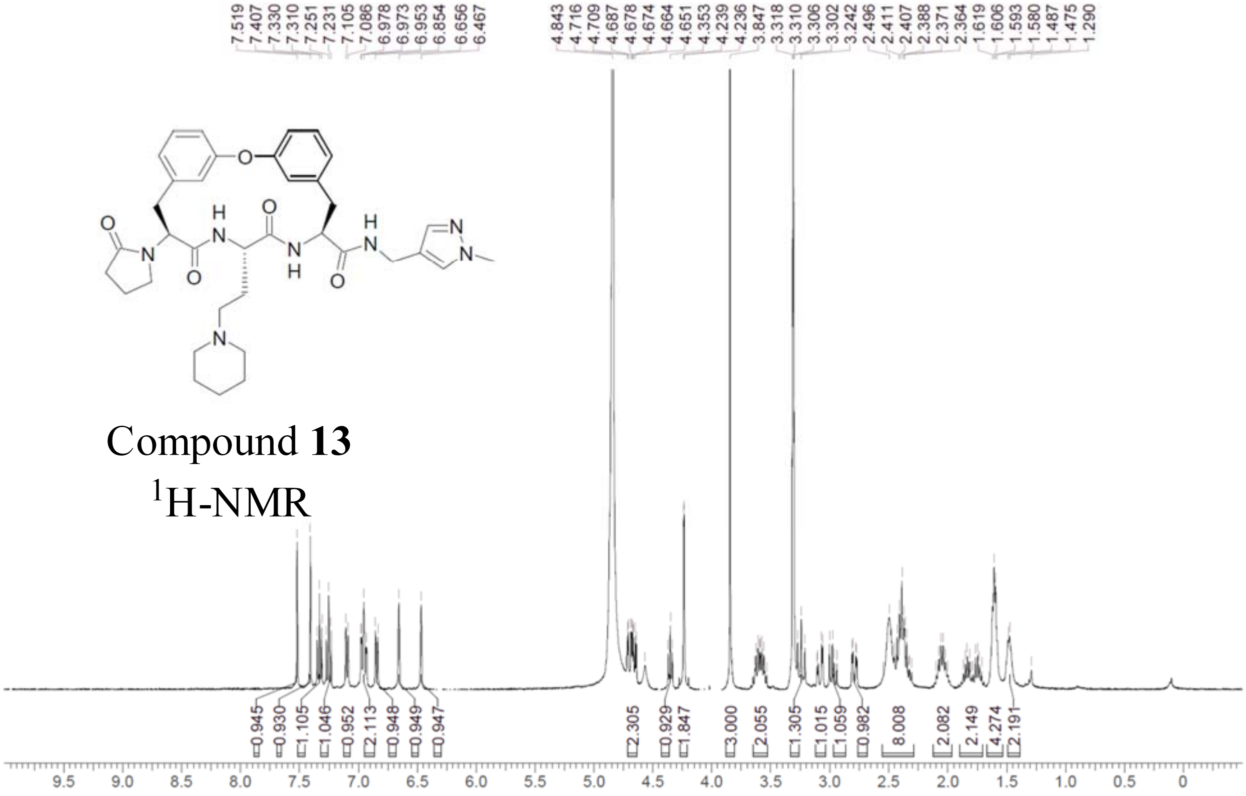


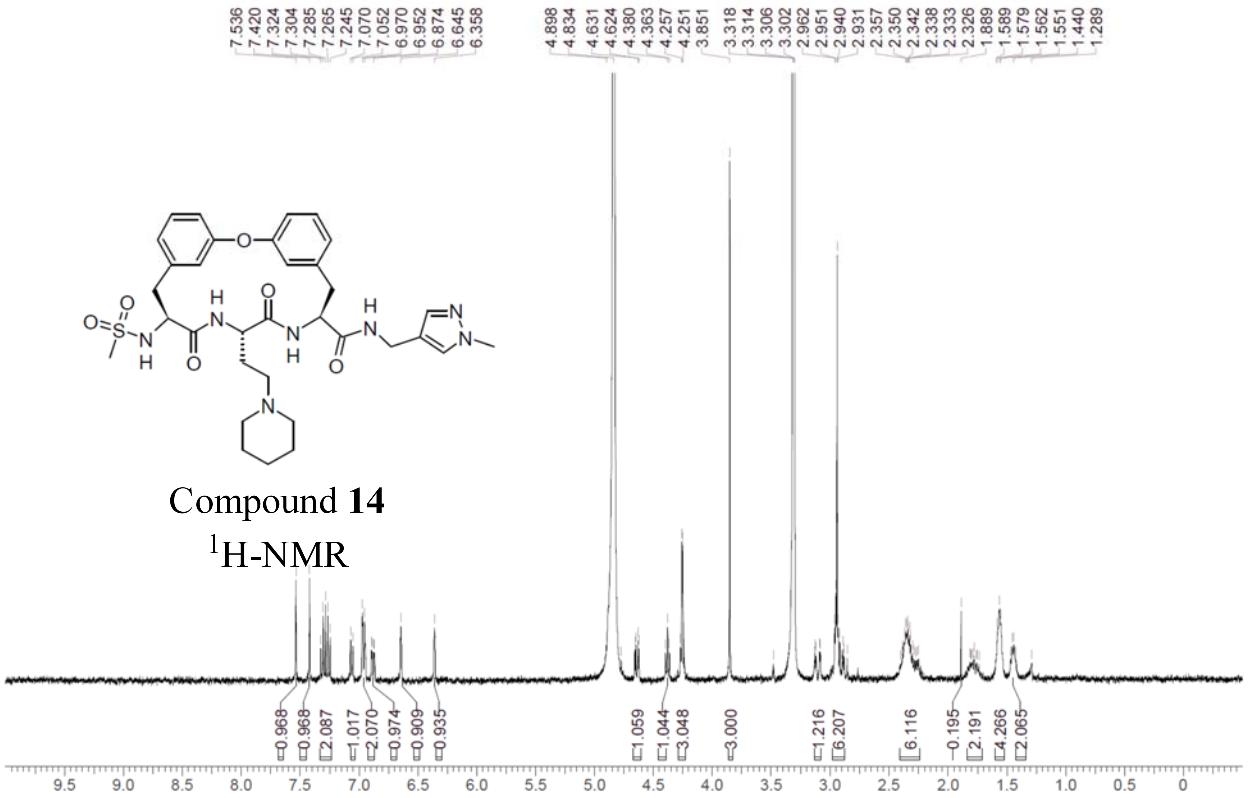
Compound **12**

^{1}H-NMR



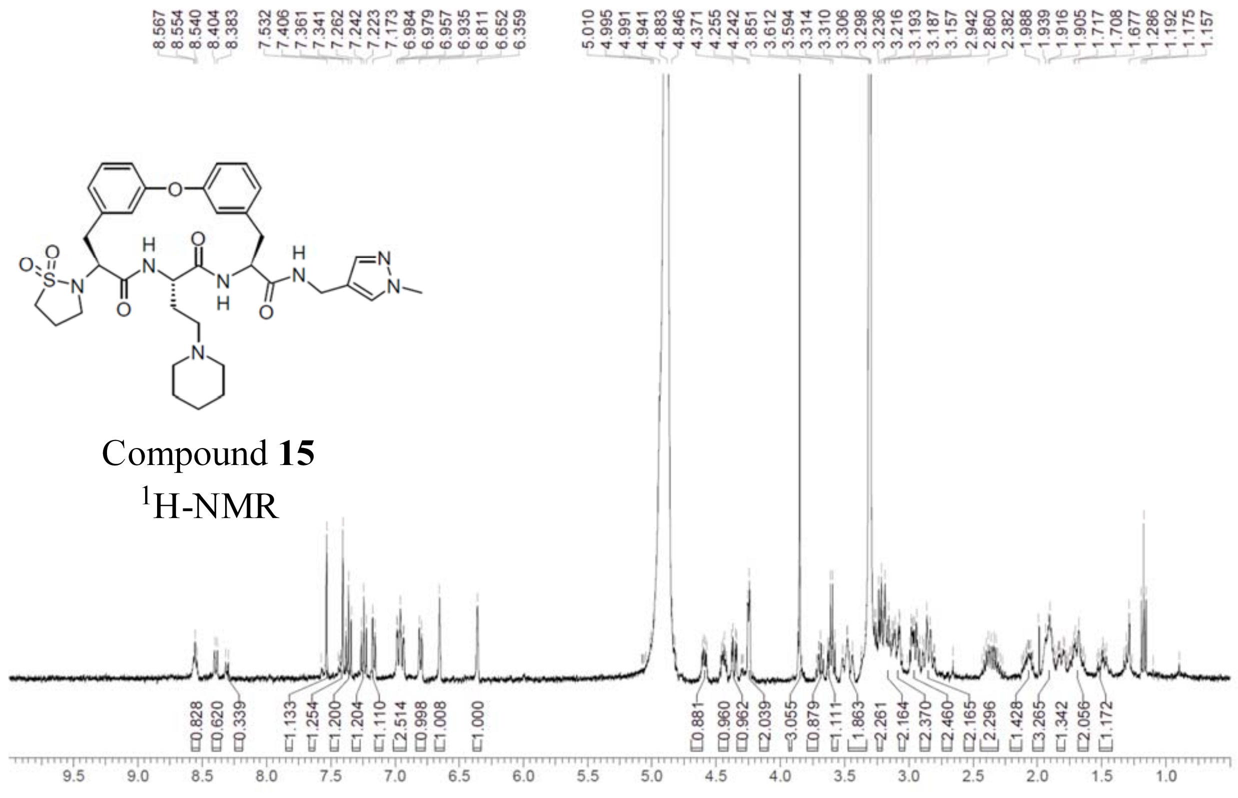
Compound **13**

^{1}H-NMR



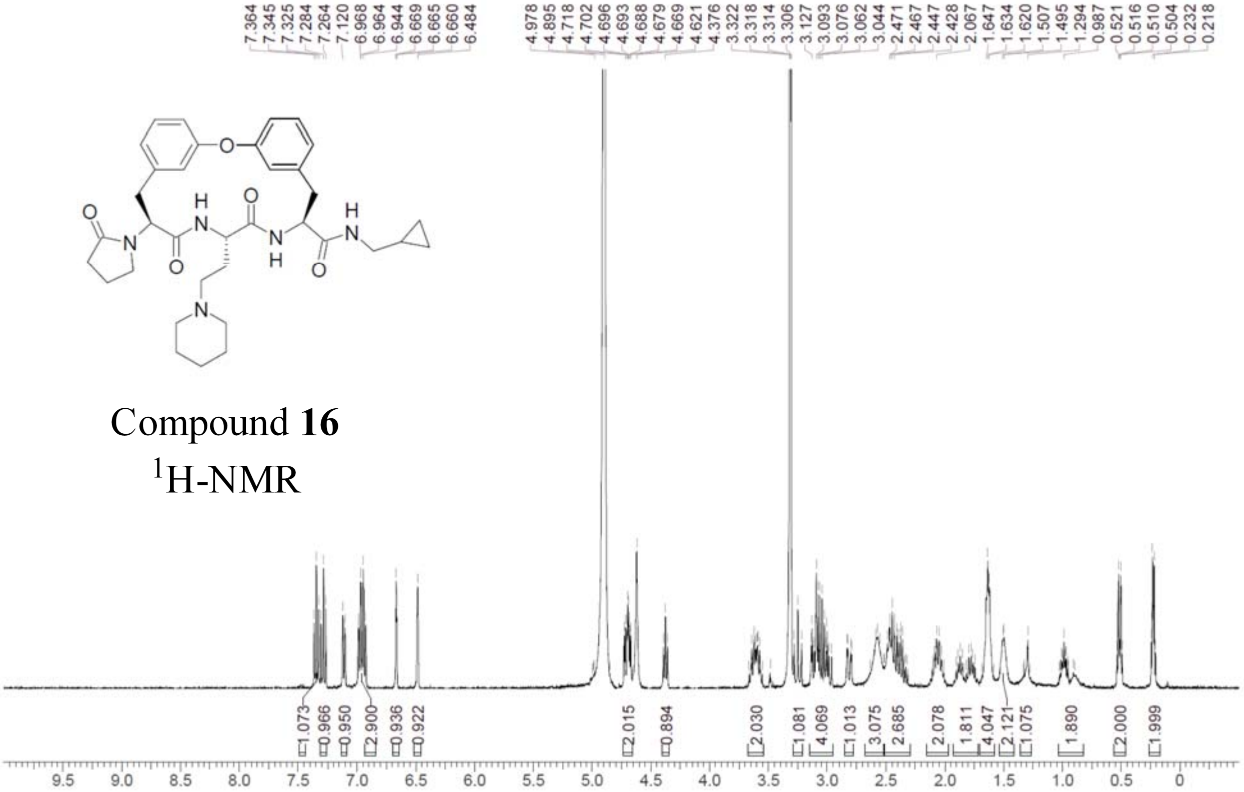
Compound **14**

^{1}H-NMR



Compound **15**

^{1}H-NMR



Compound **16**
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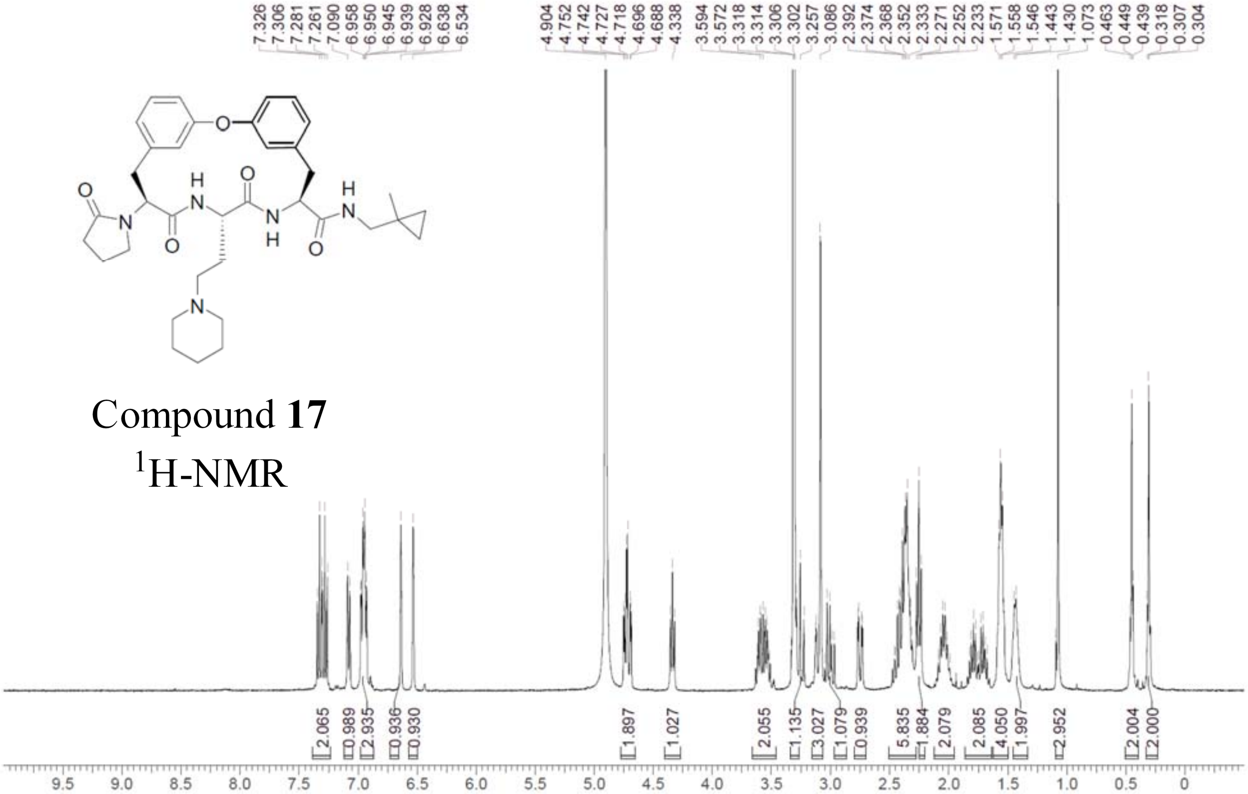

Compound **17**
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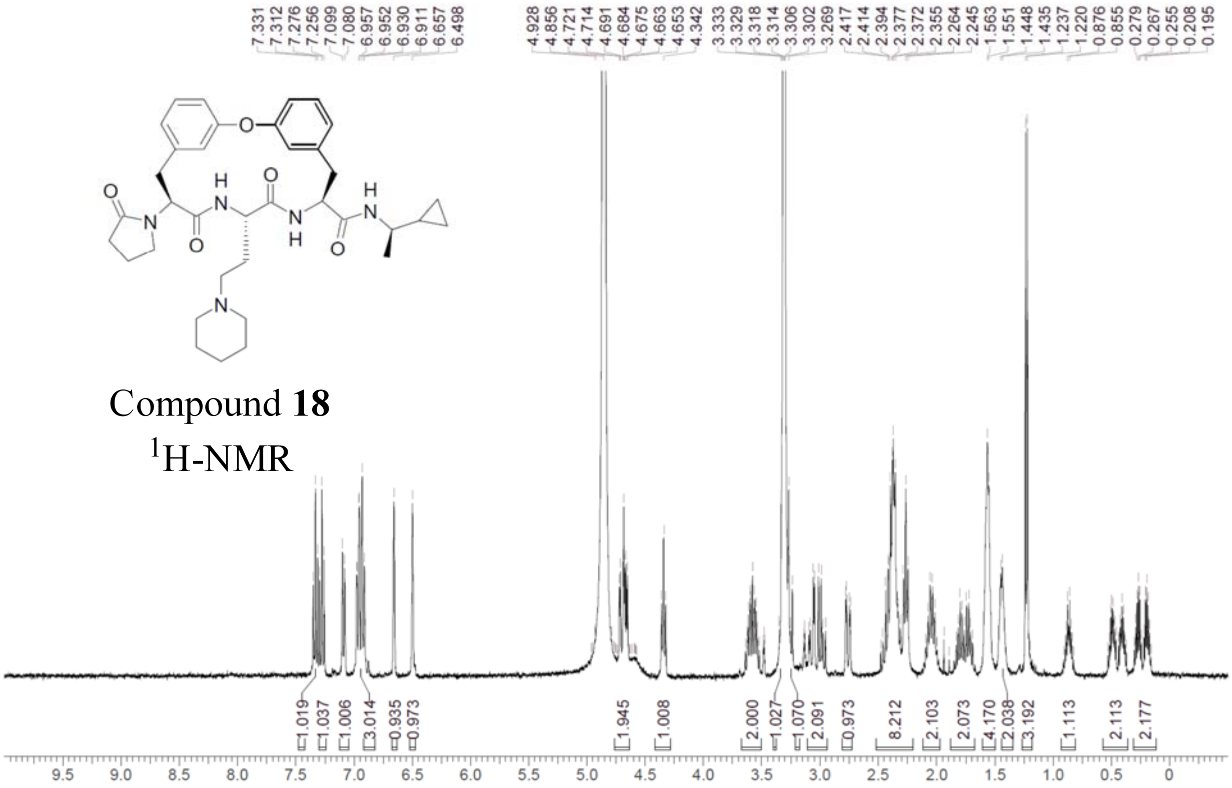

Compound **18**

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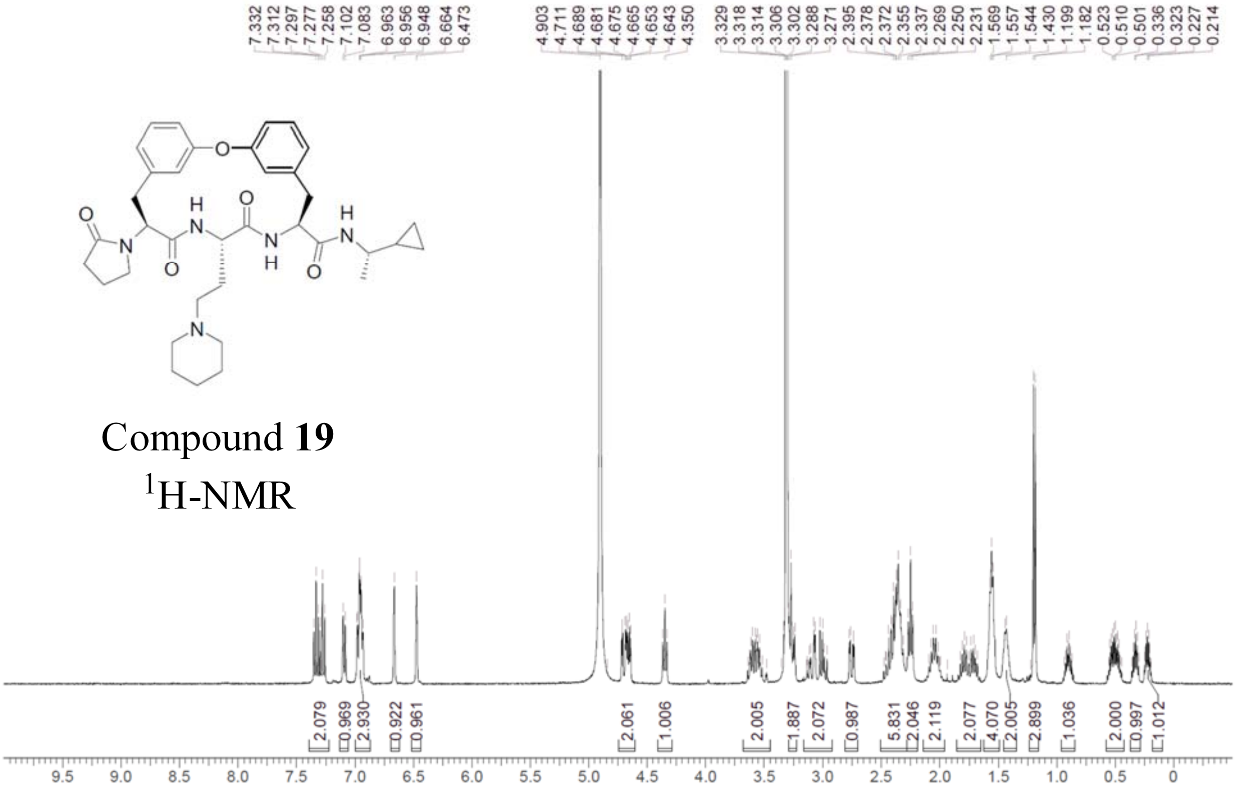
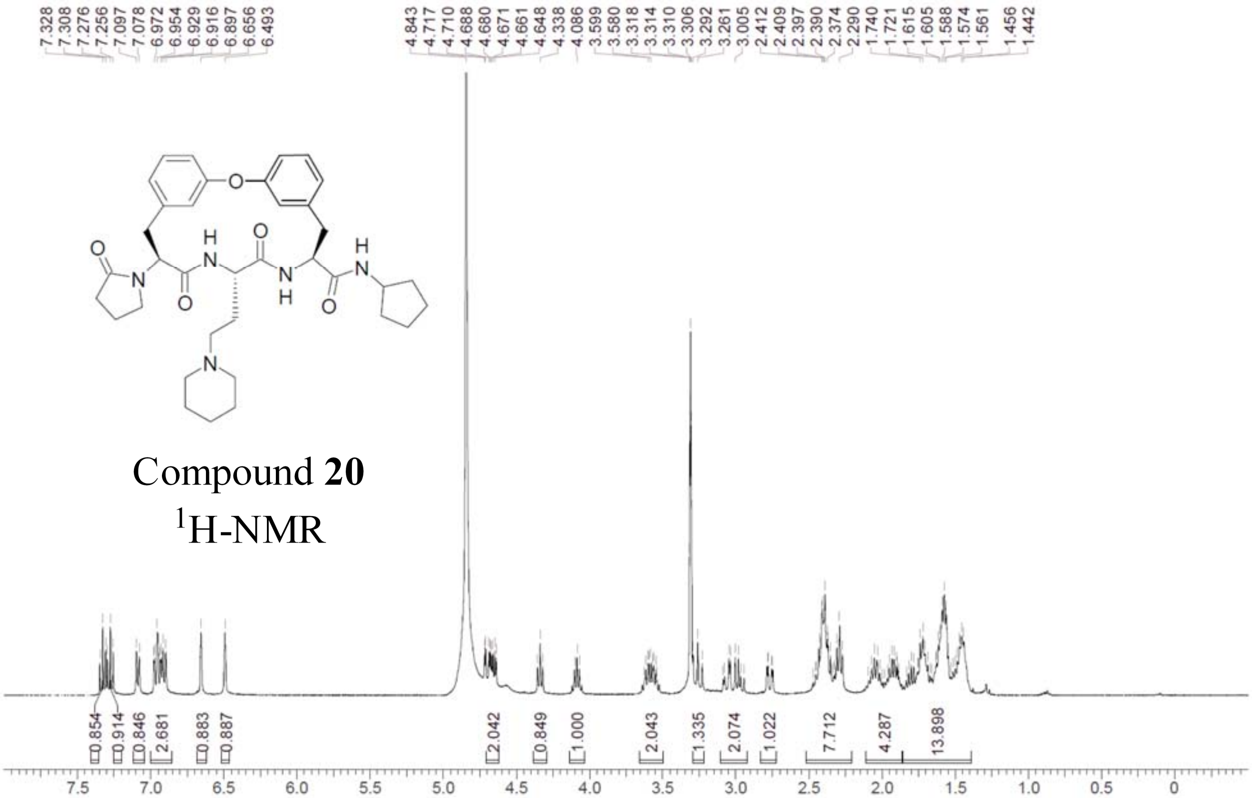


Compound **19**

^{1}H-NMR



Compound **20**
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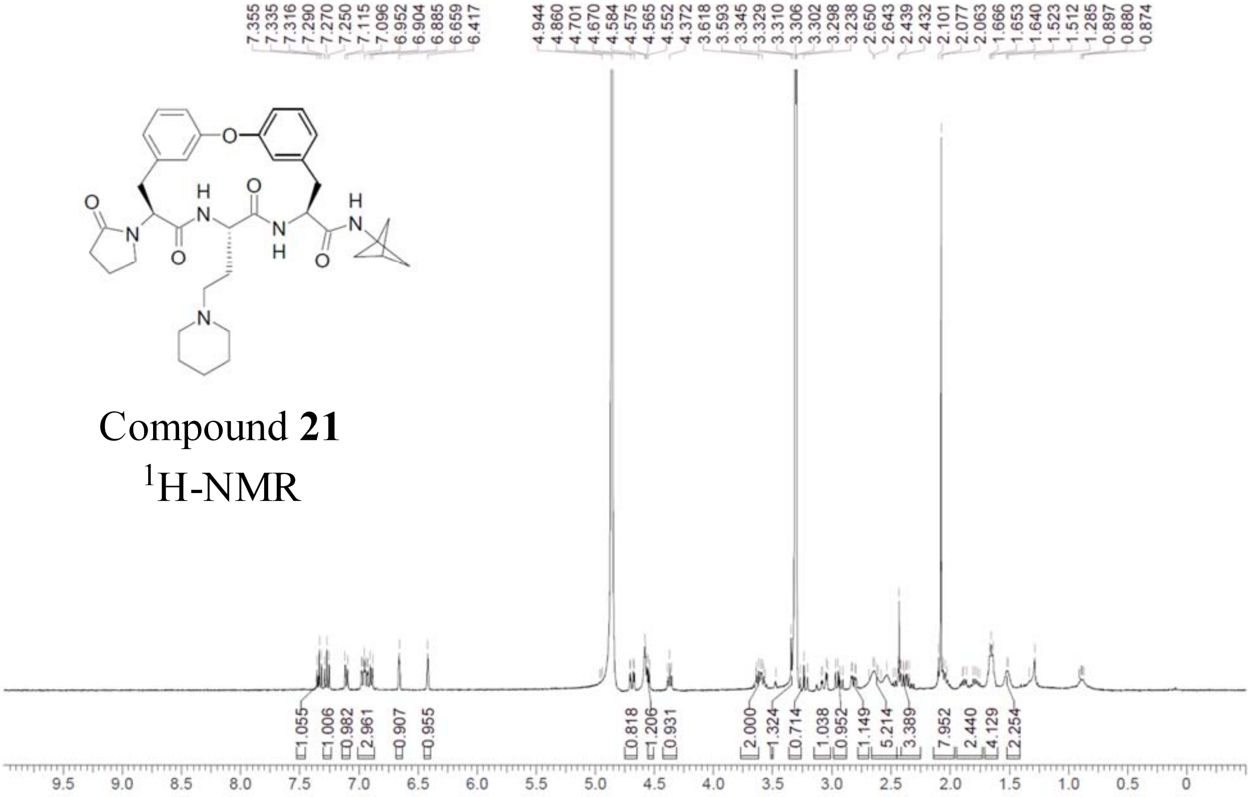

Compound **21**
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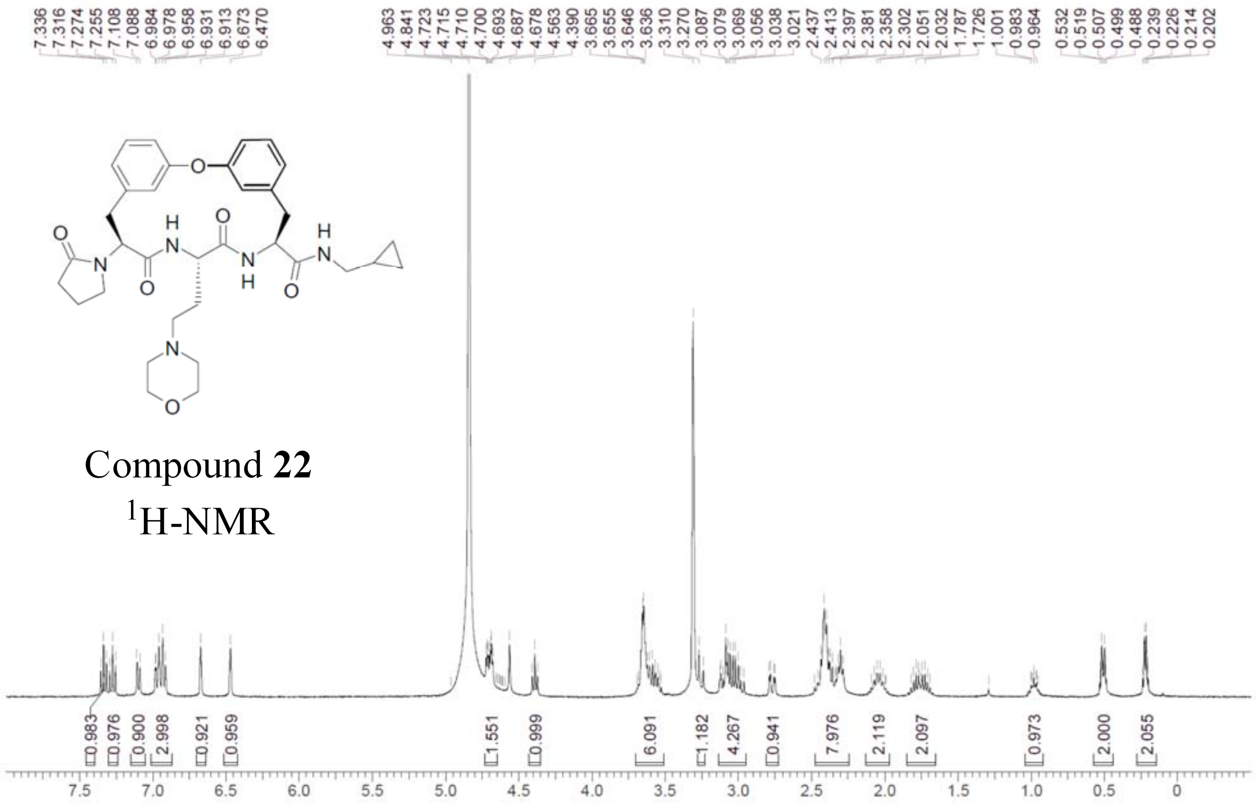
Compound **22**
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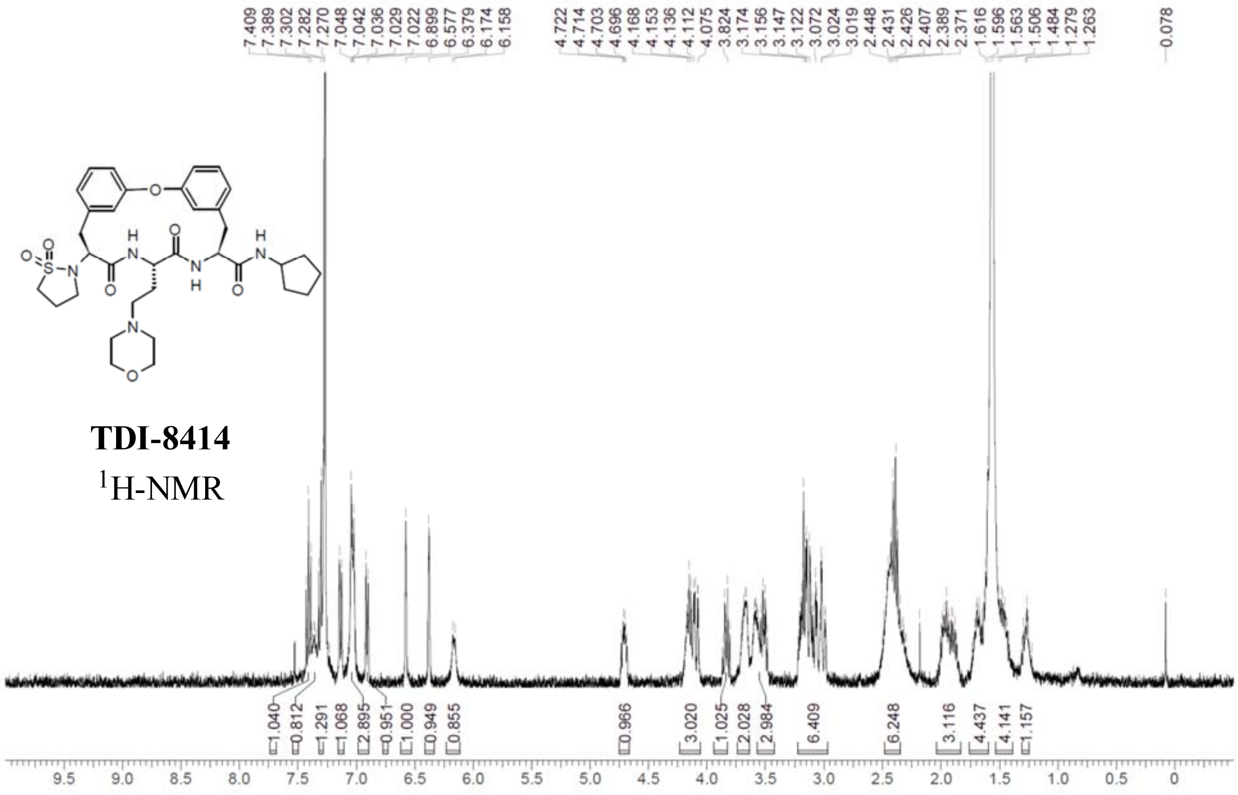
TDI-8414
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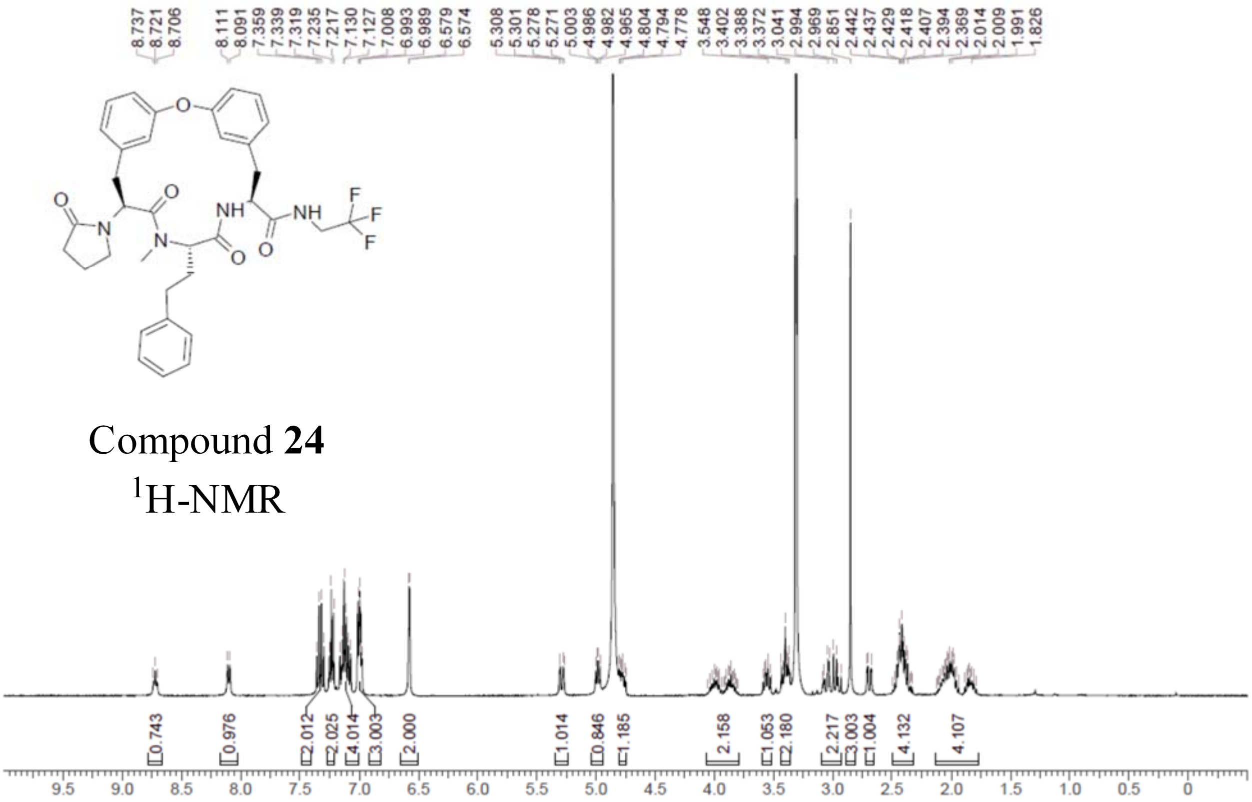

Compound **24**
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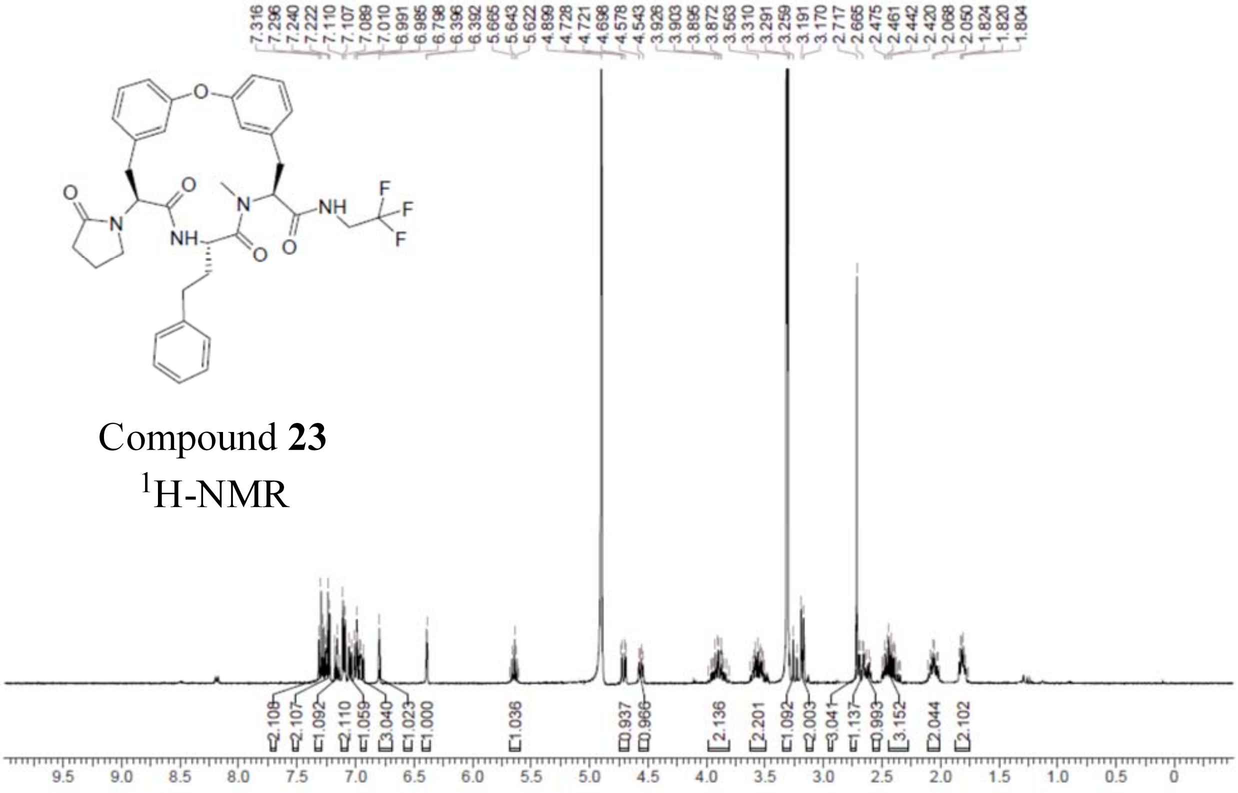

Compound **23**
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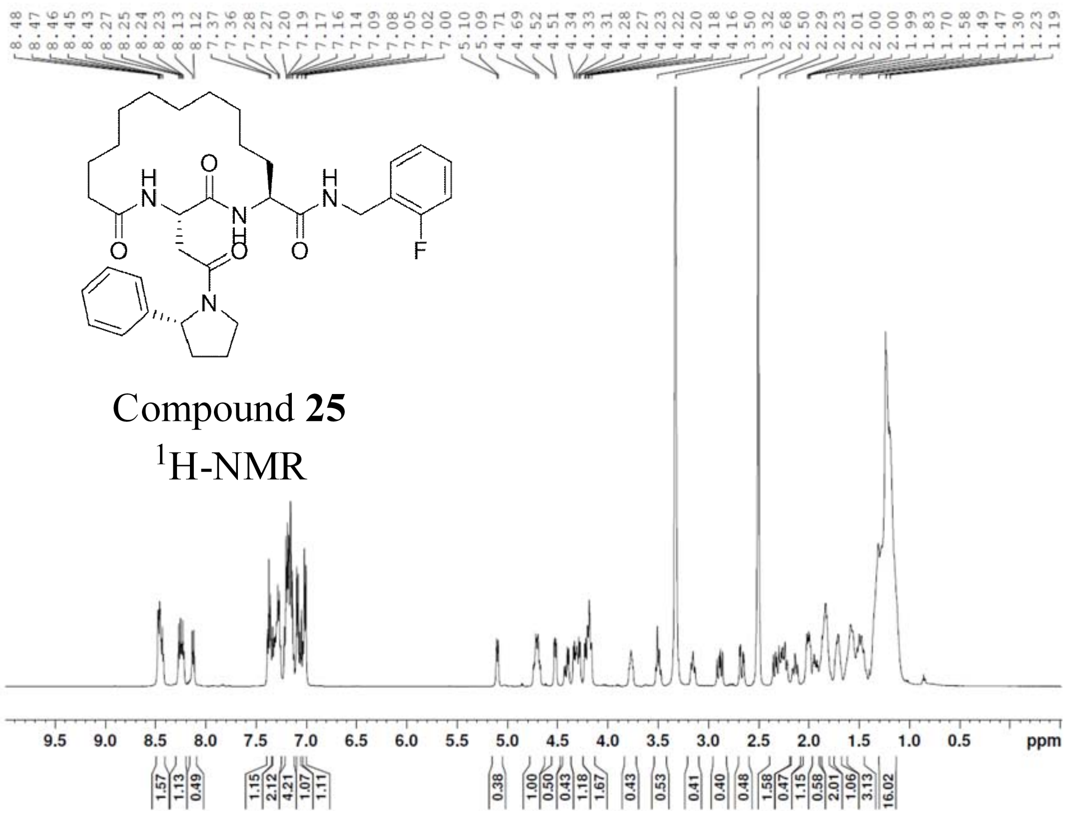
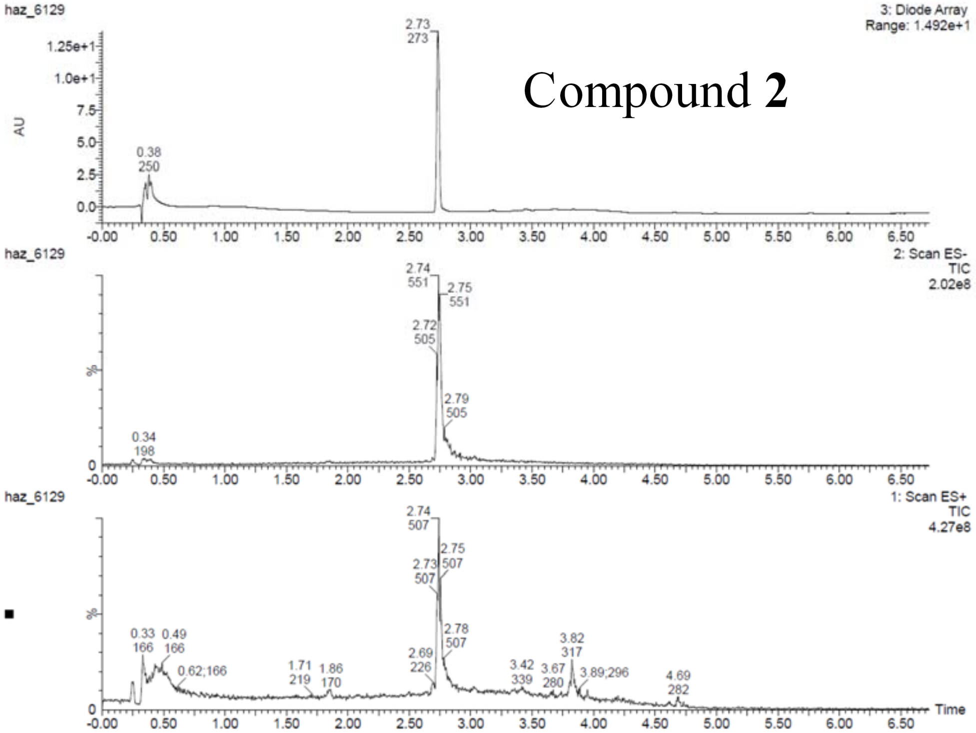


Compound **25**

^{1}H-NMR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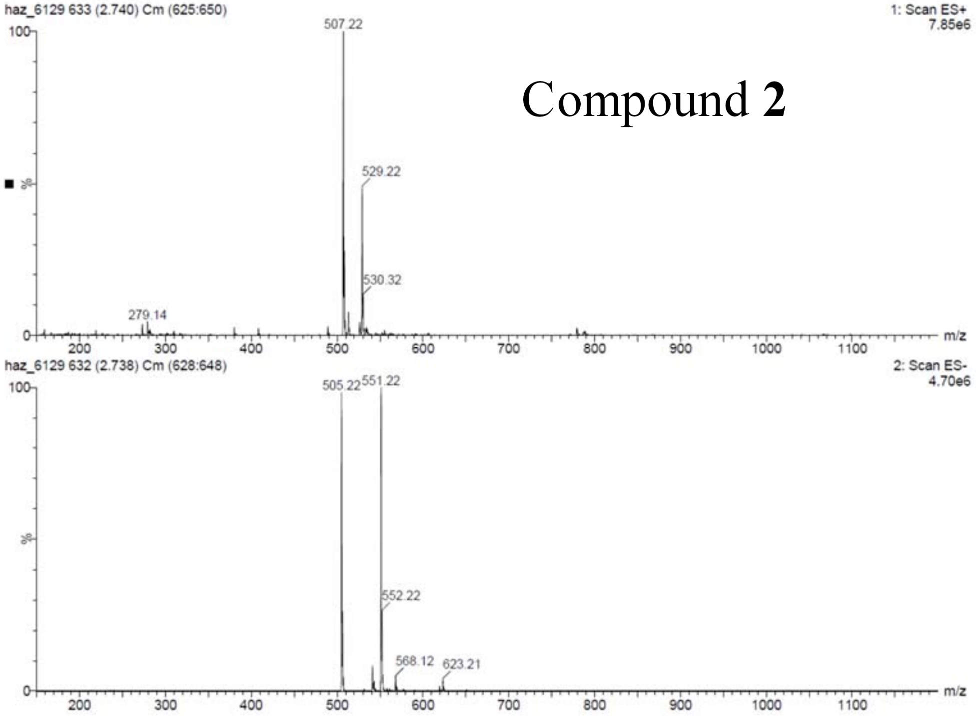
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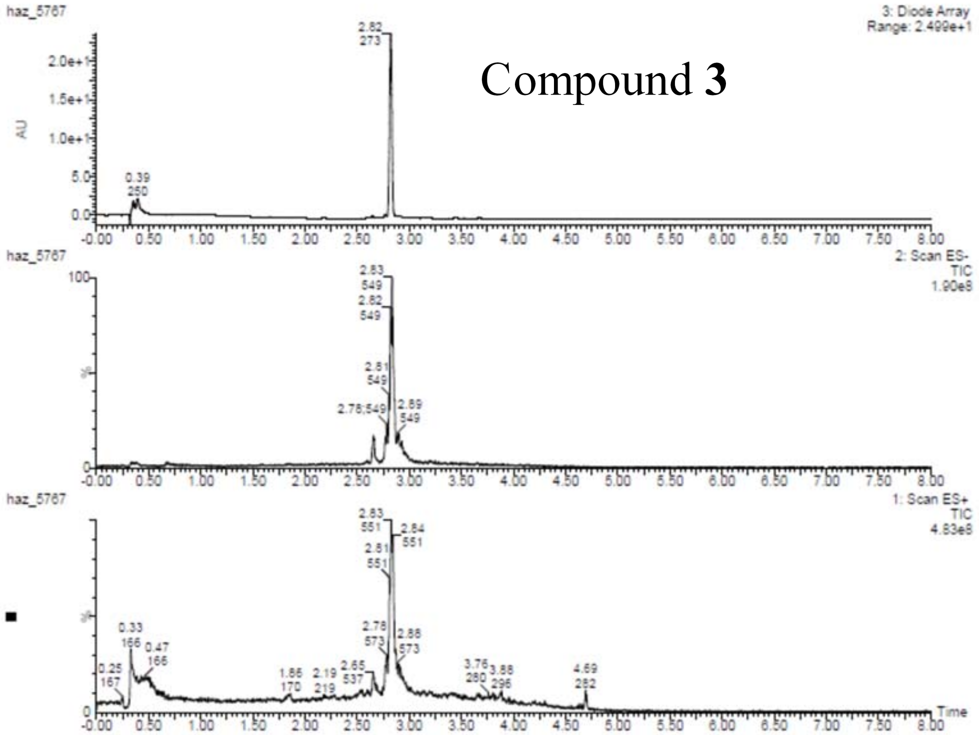

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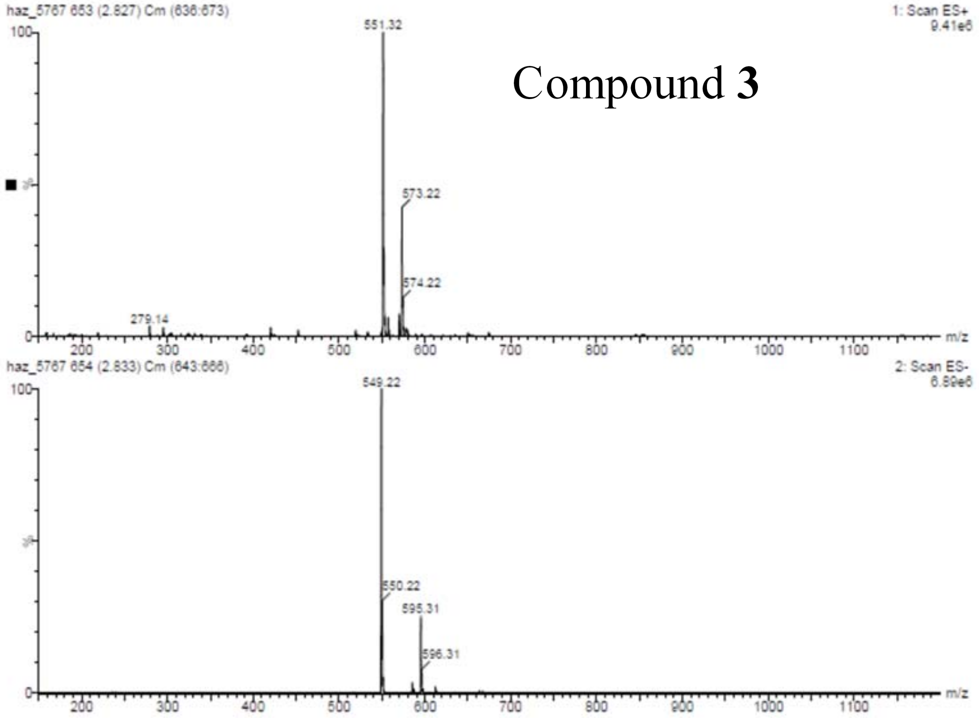
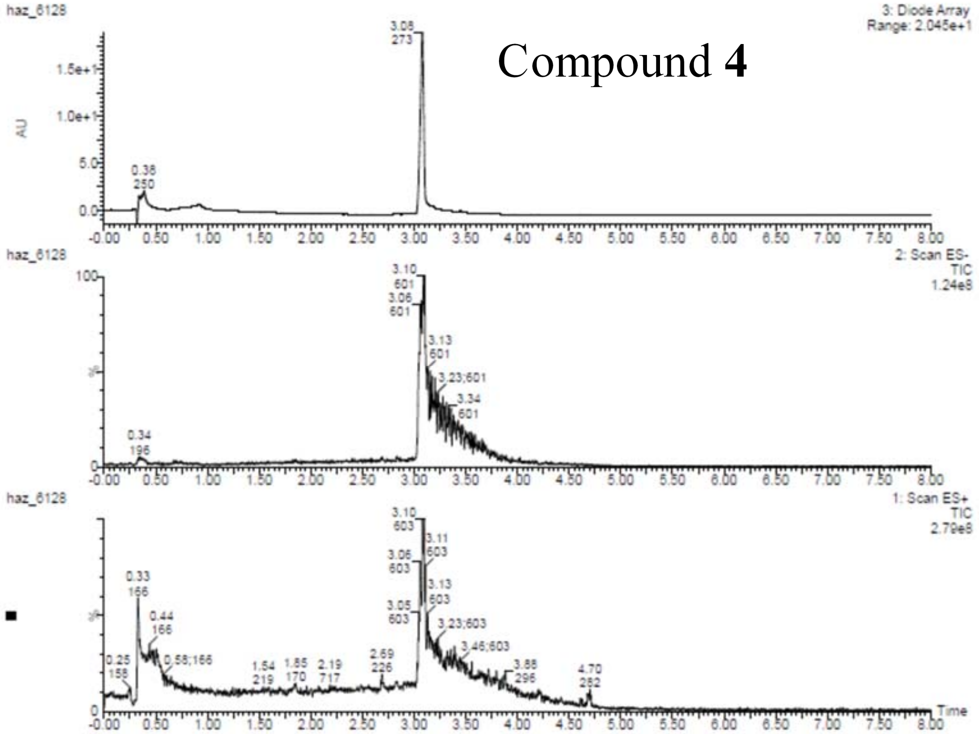


Compound **3**

Compound **4**



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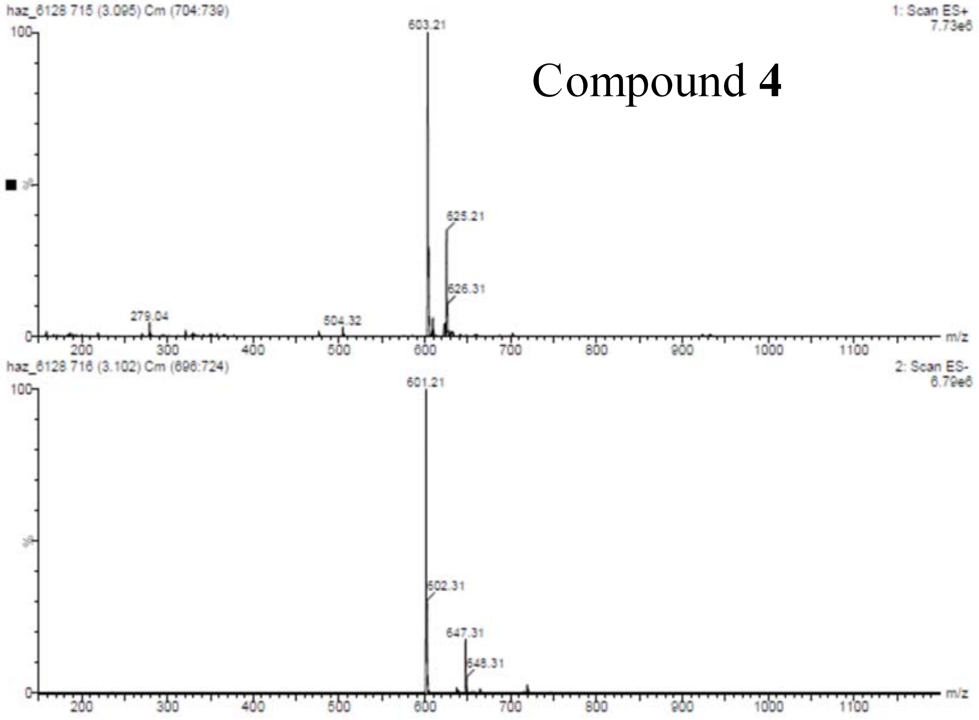

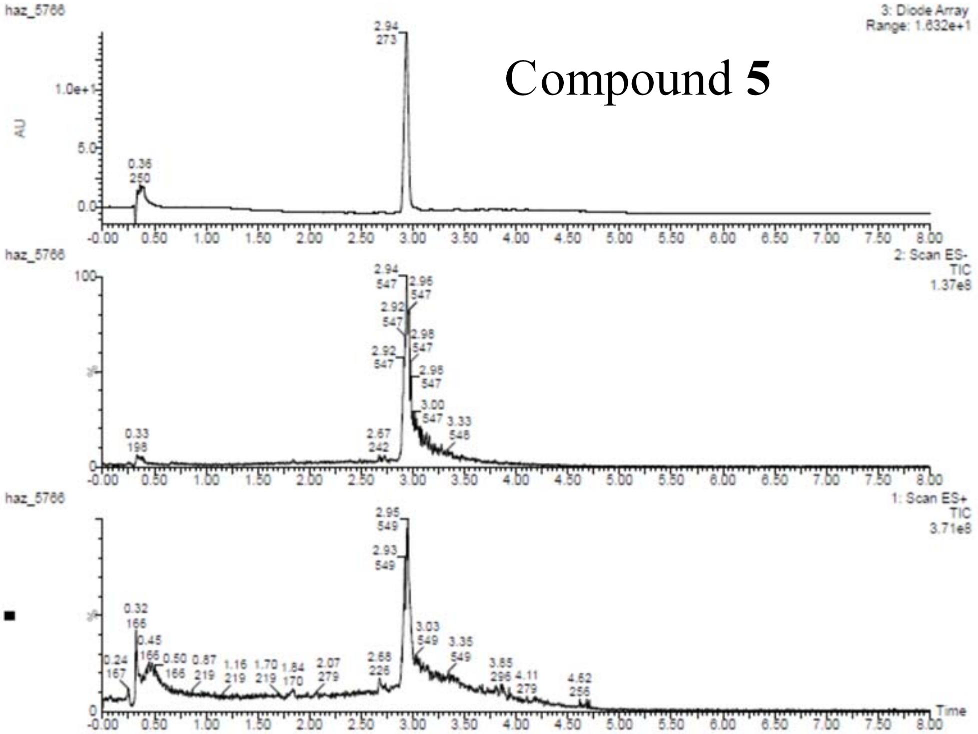
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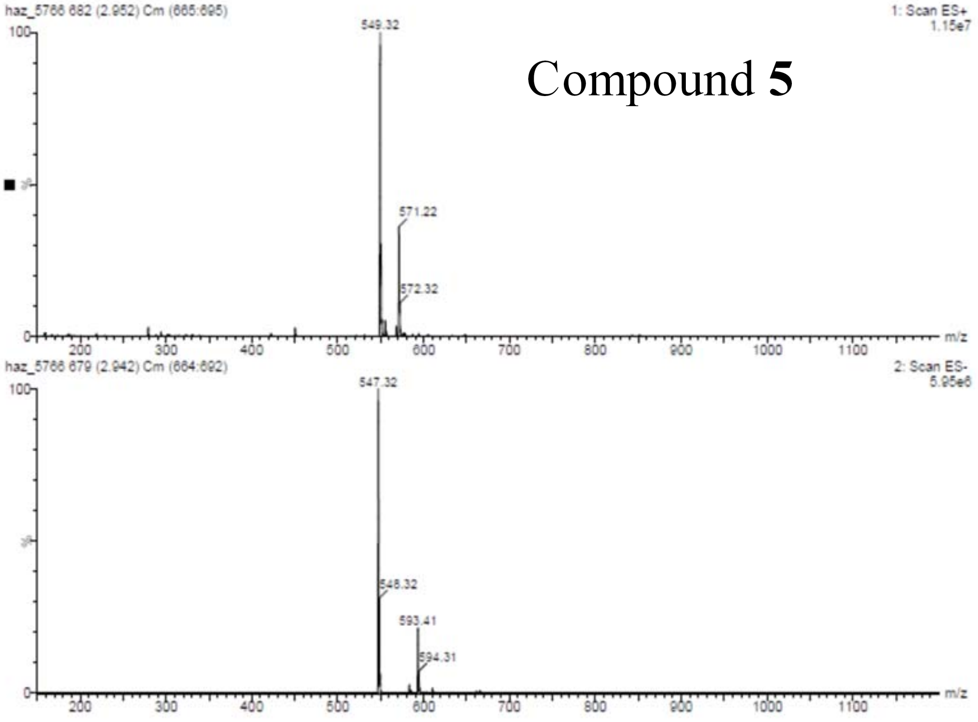
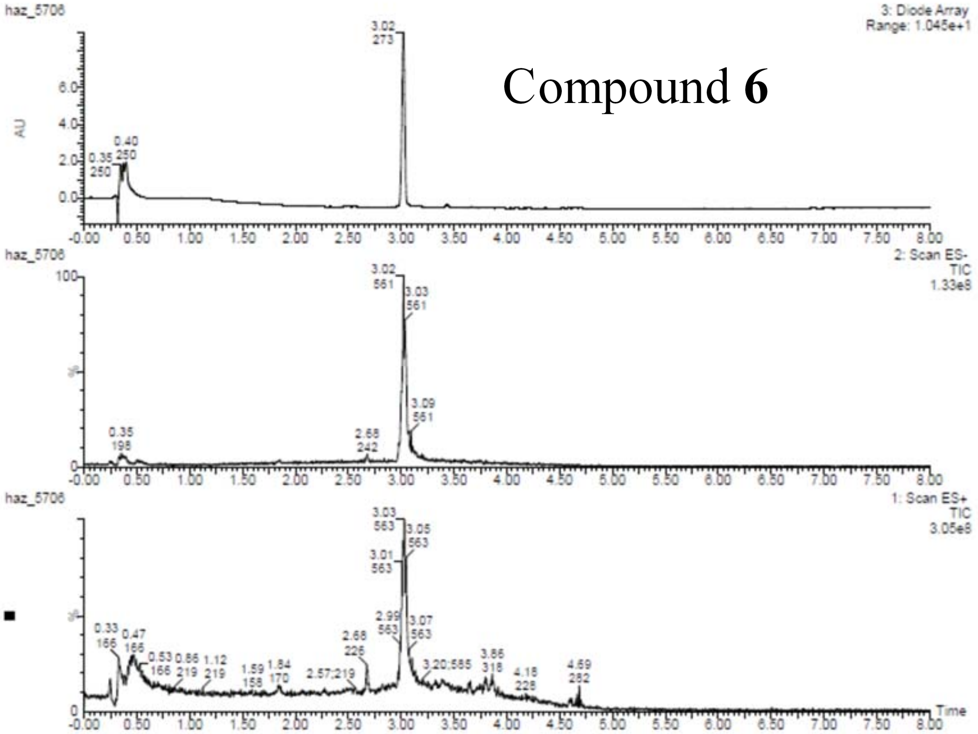

Compound **5**

Compound **6**



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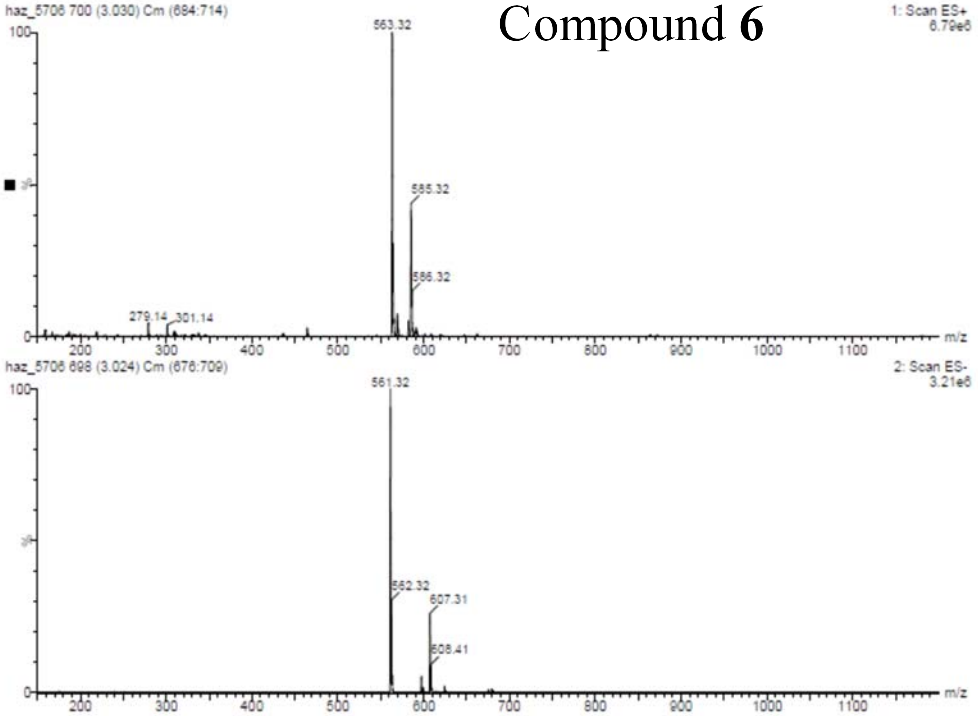

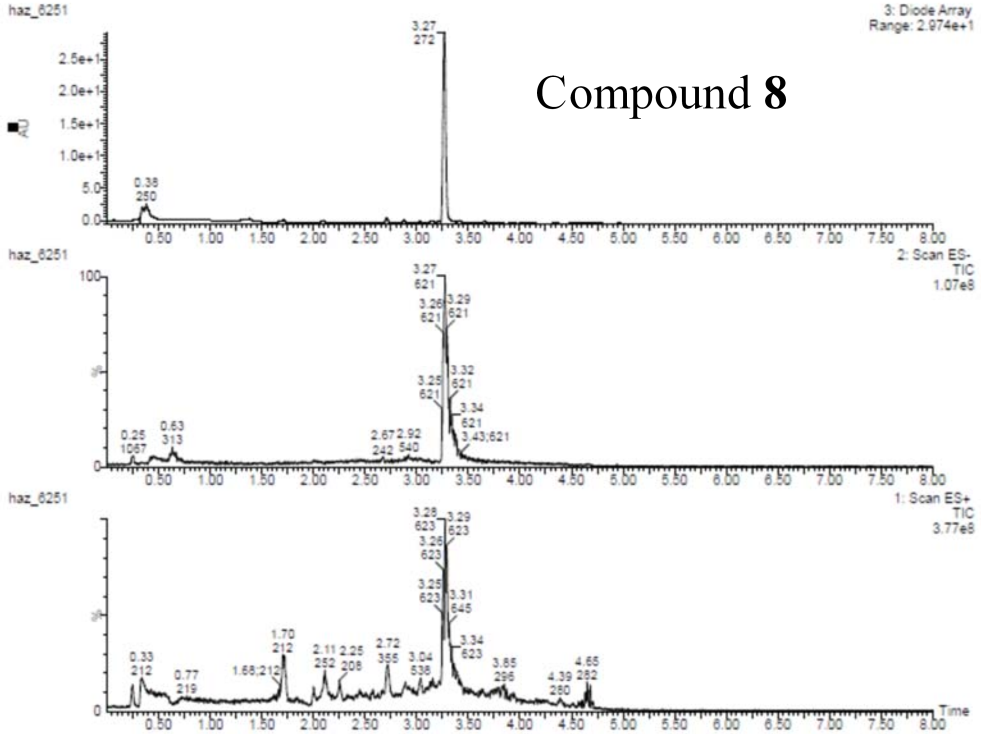

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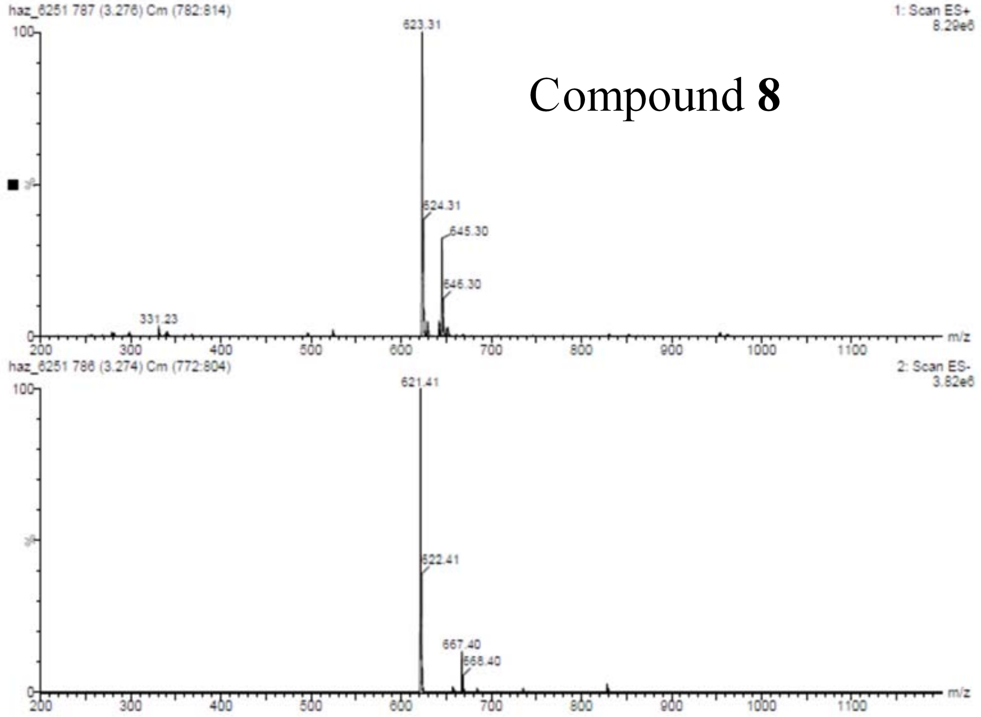

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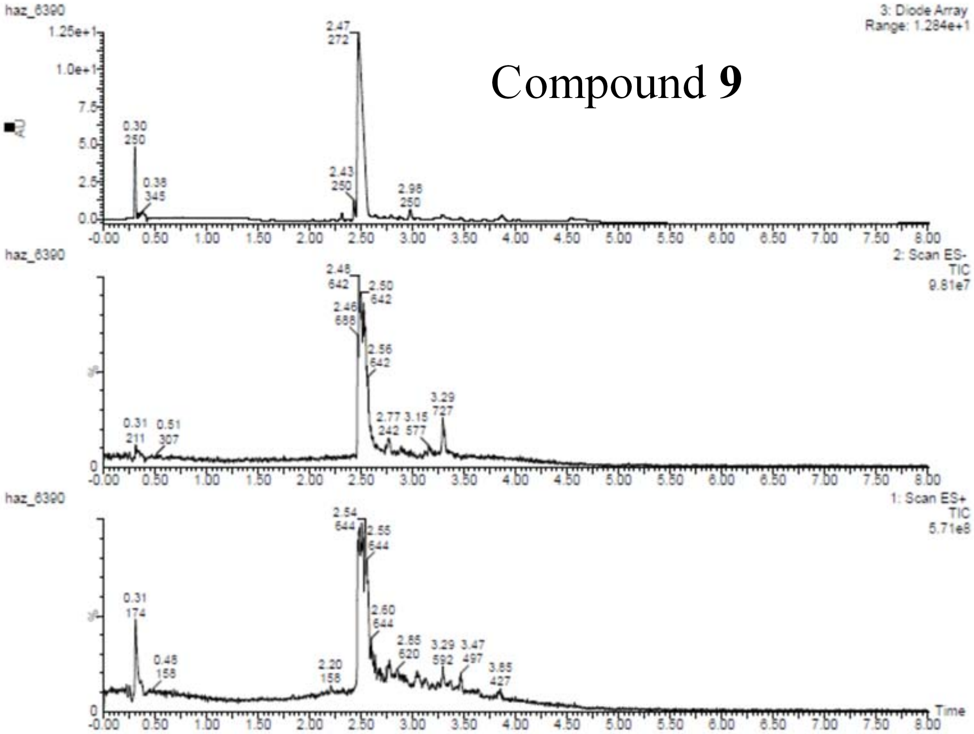

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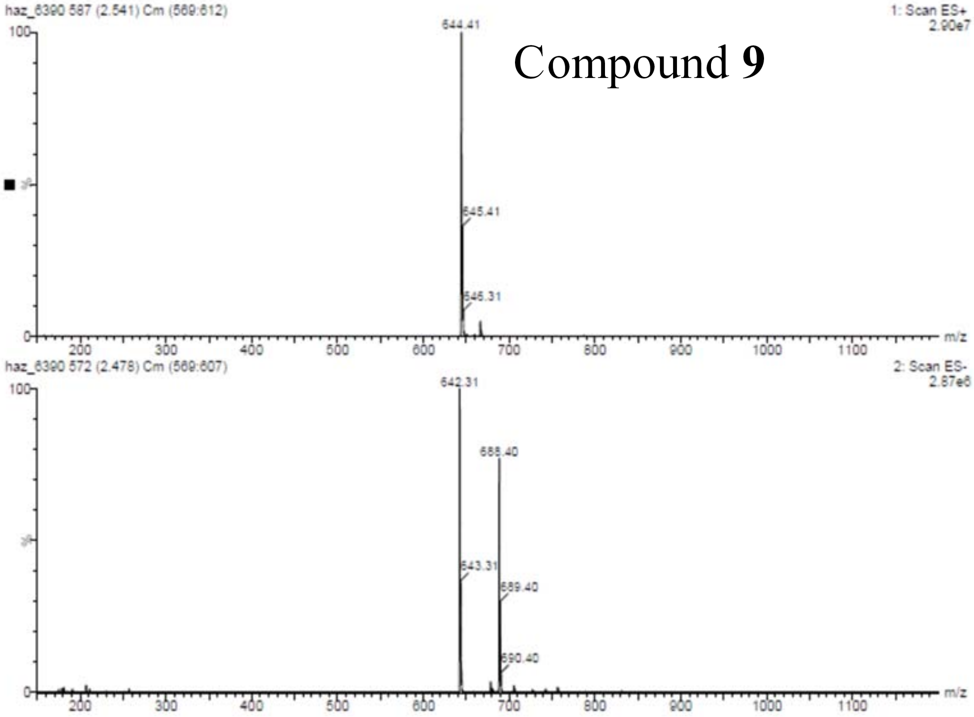

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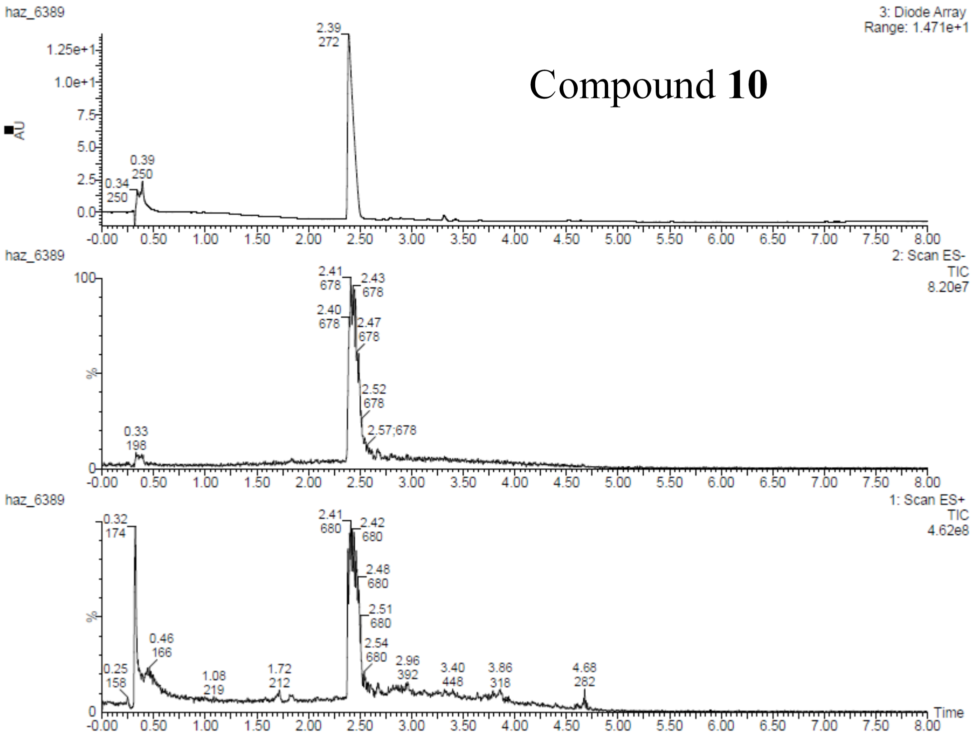
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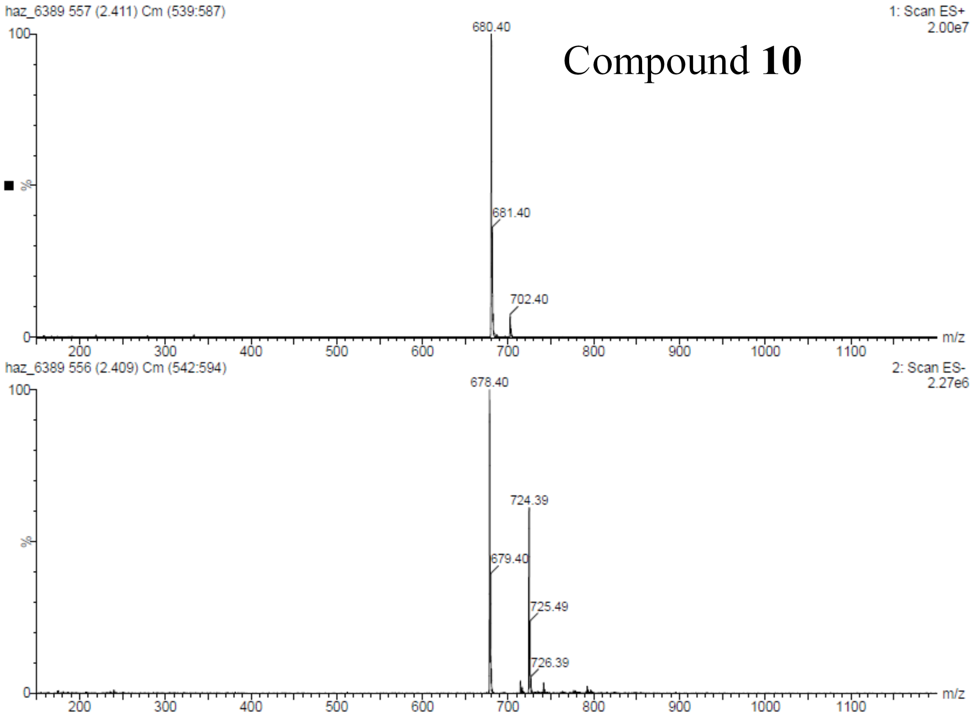
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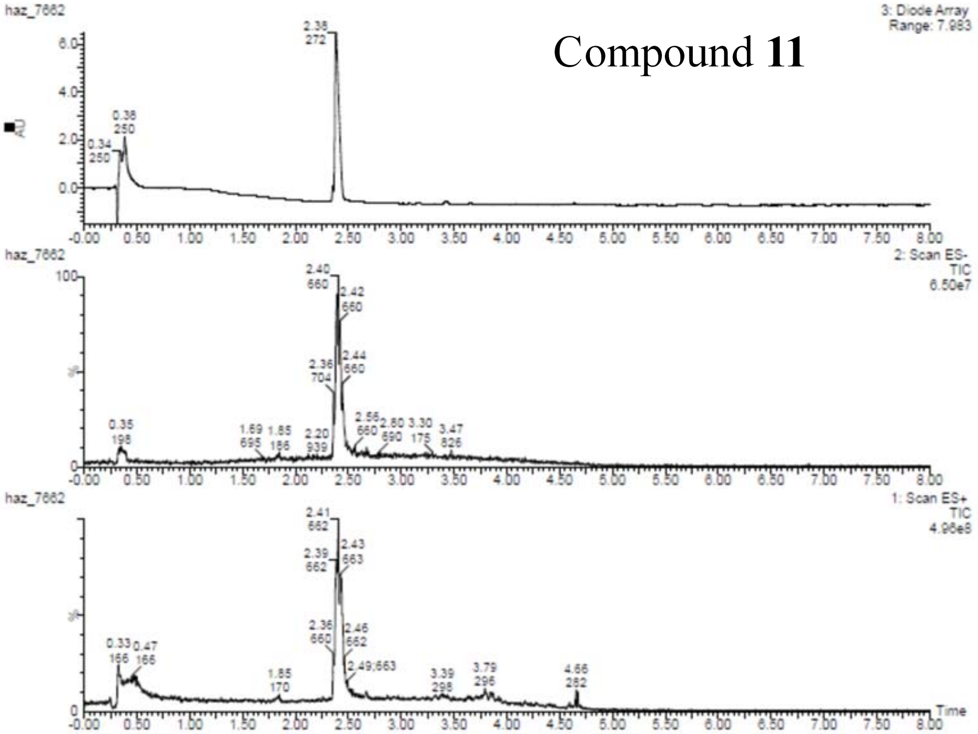

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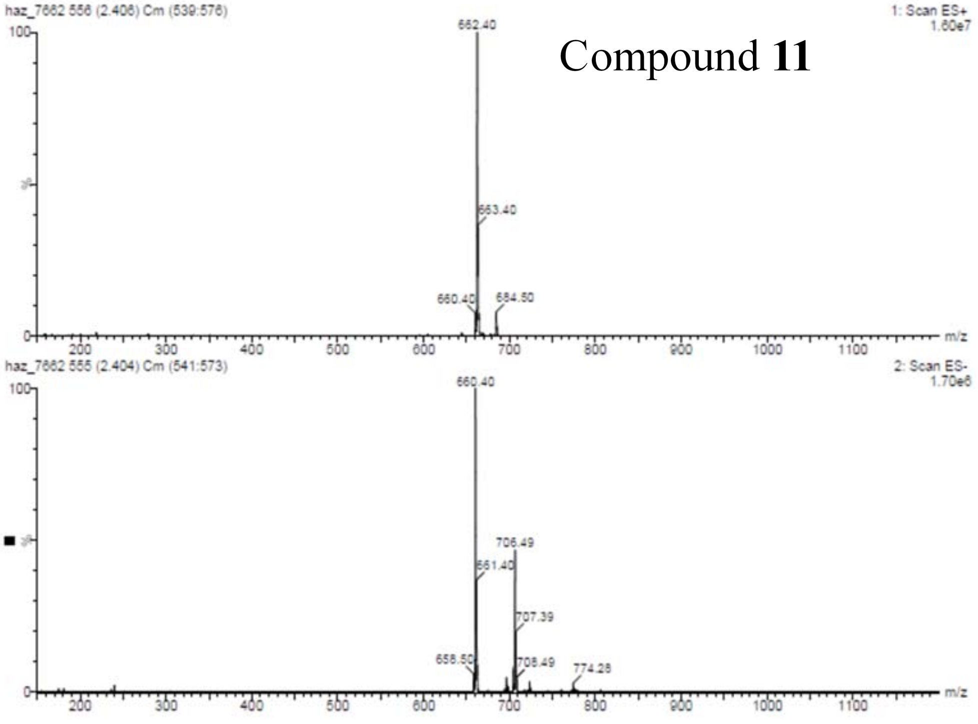

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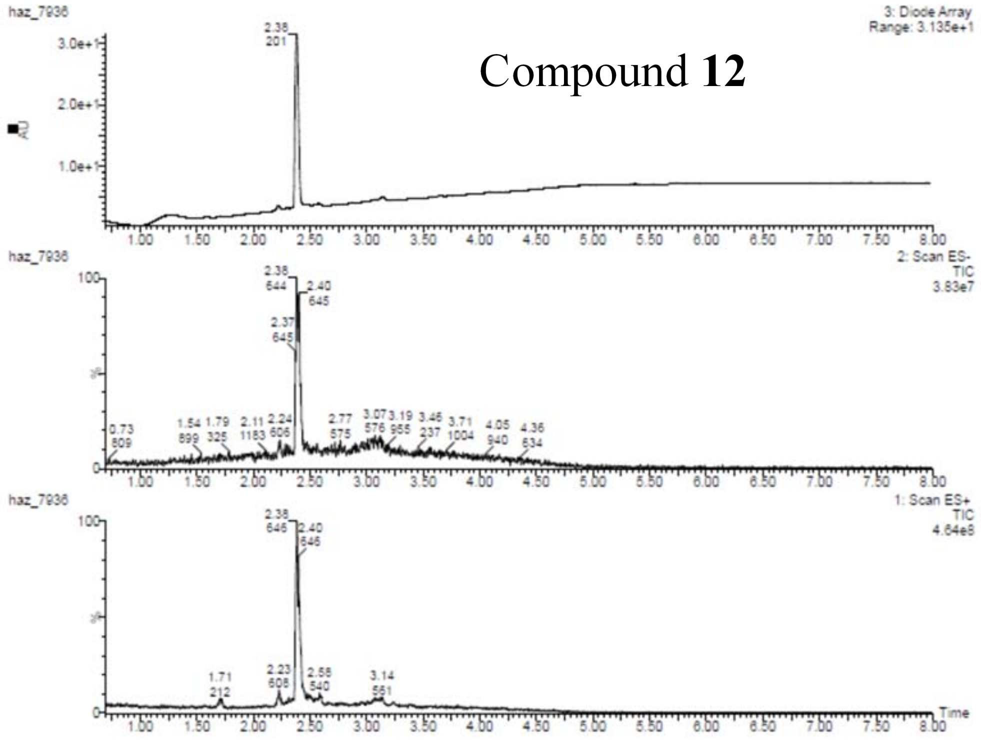
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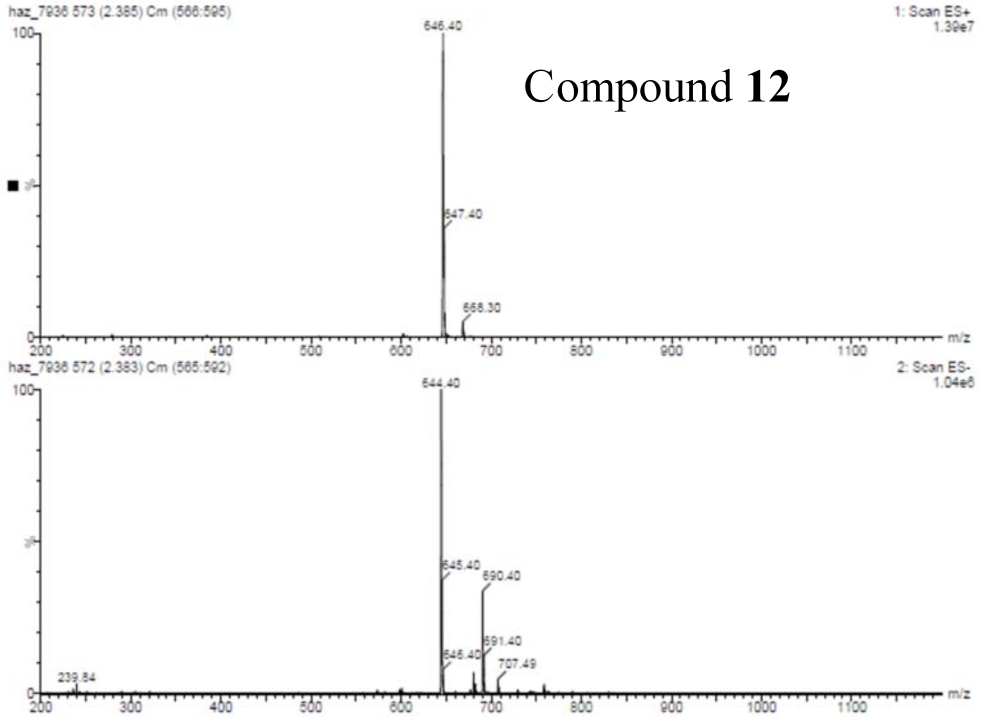
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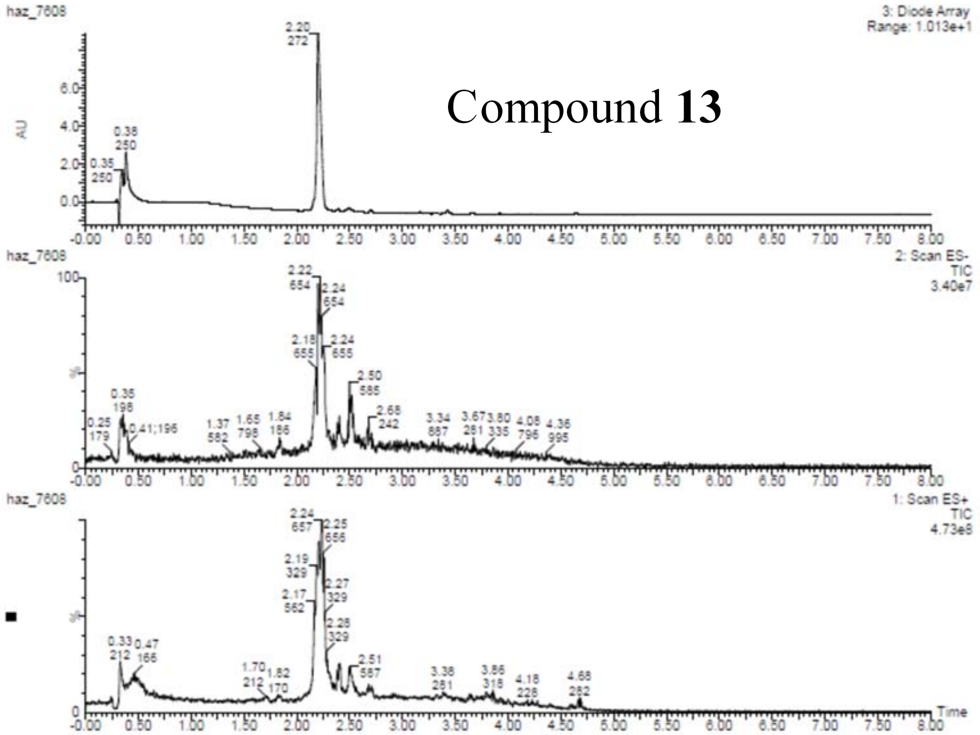
Compound **13**



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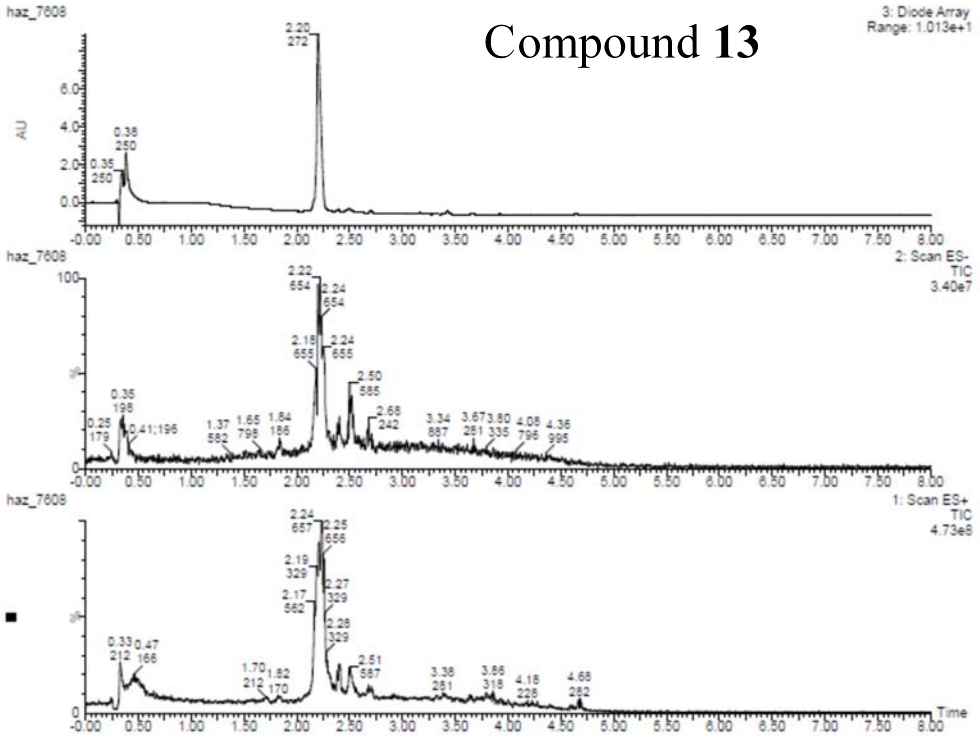

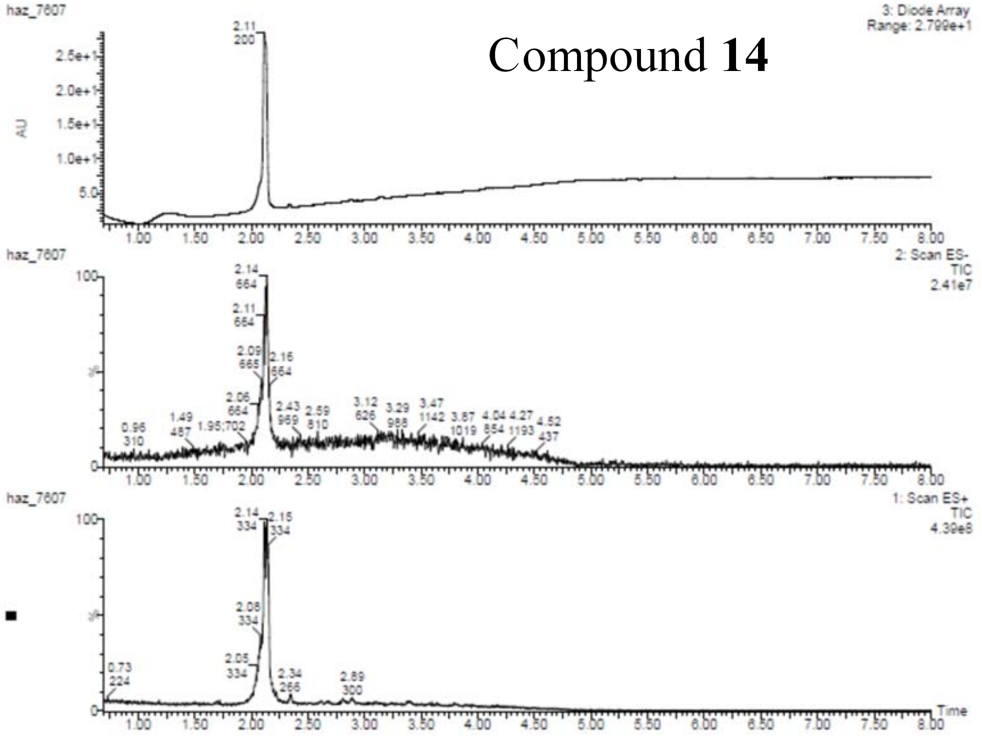

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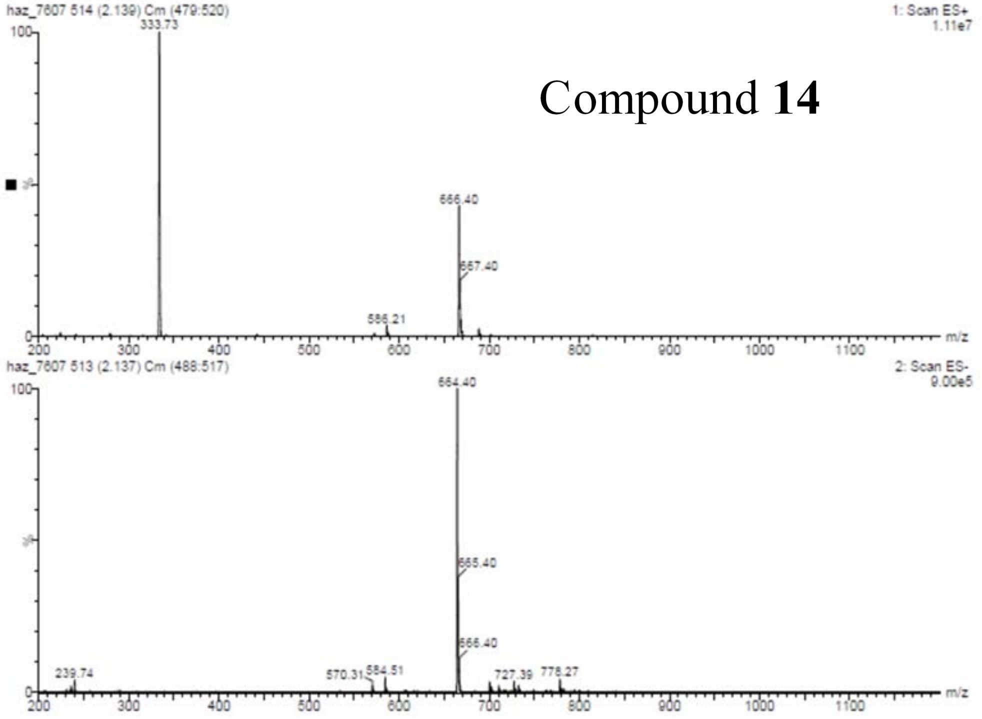

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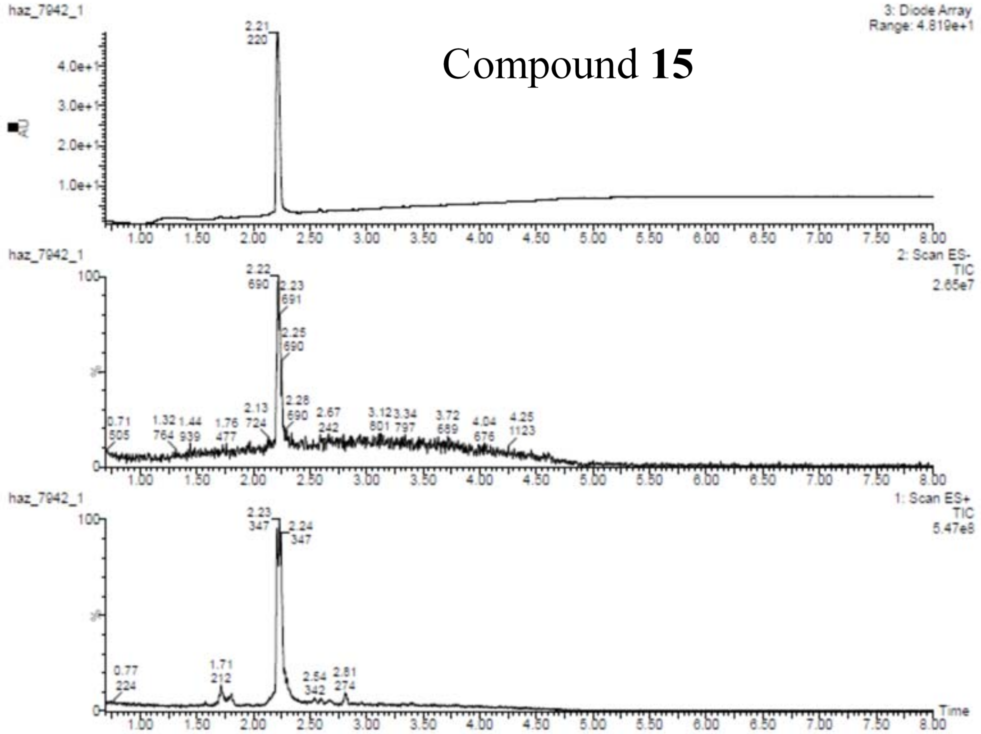
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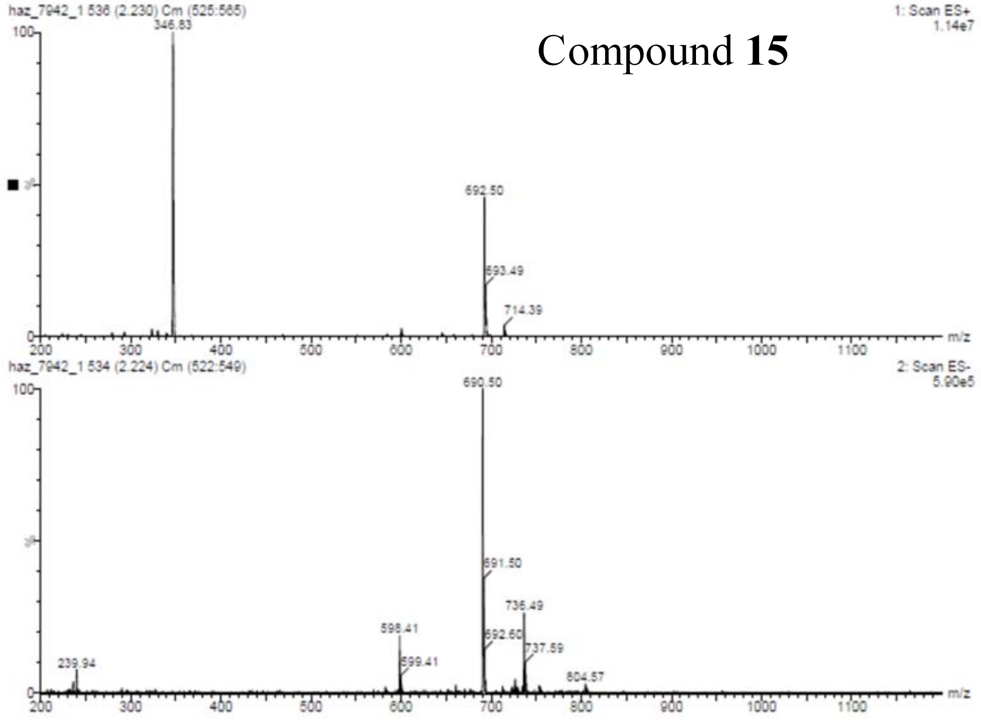
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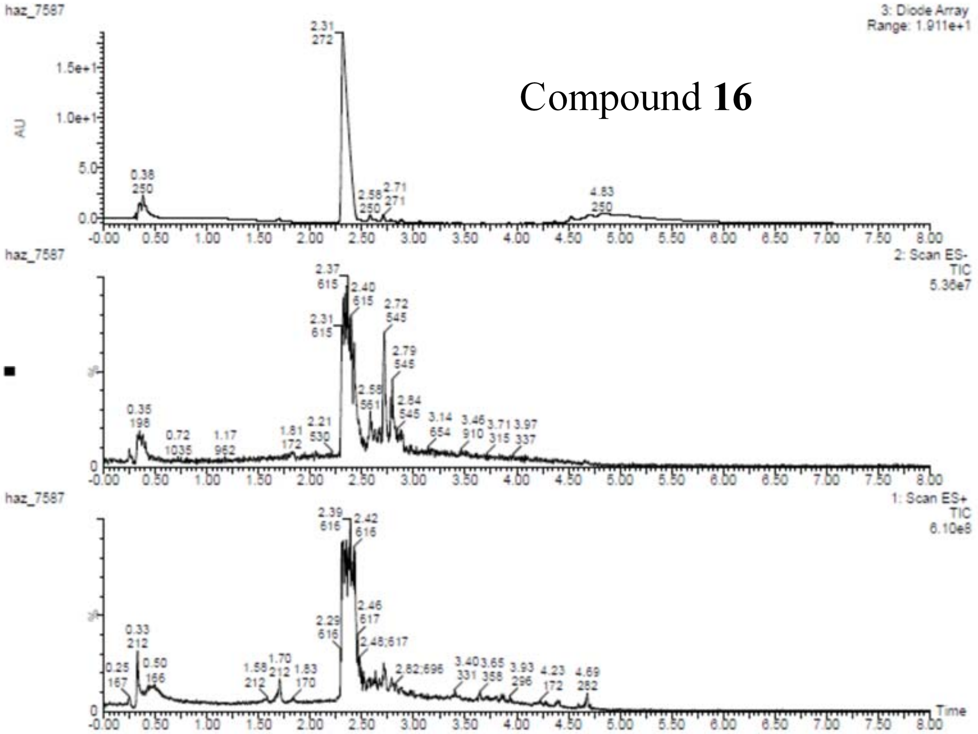
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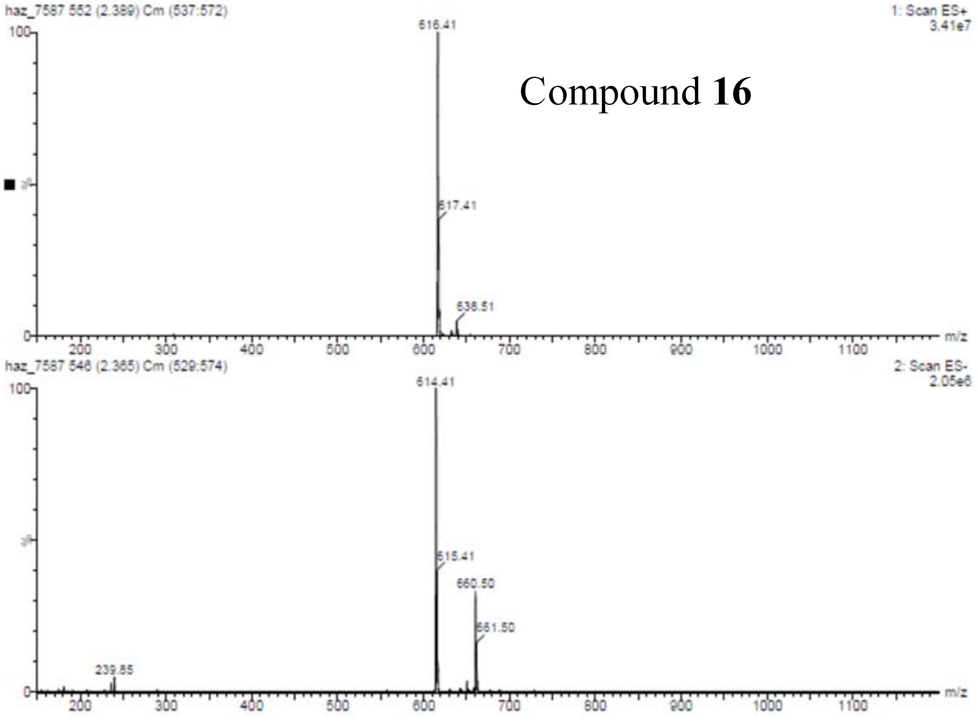
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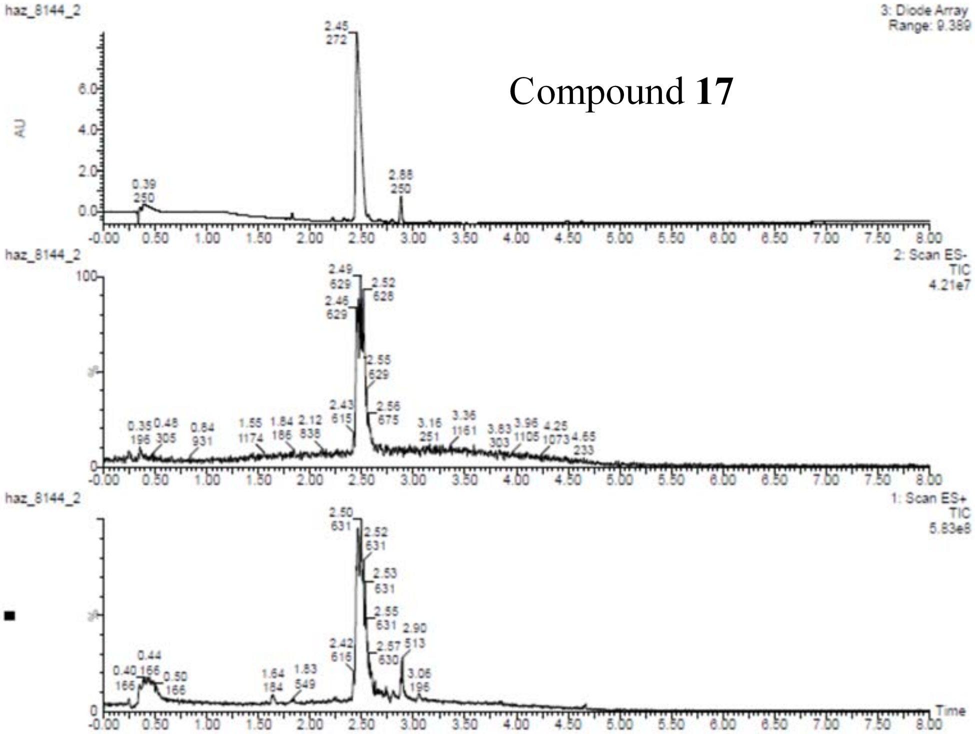

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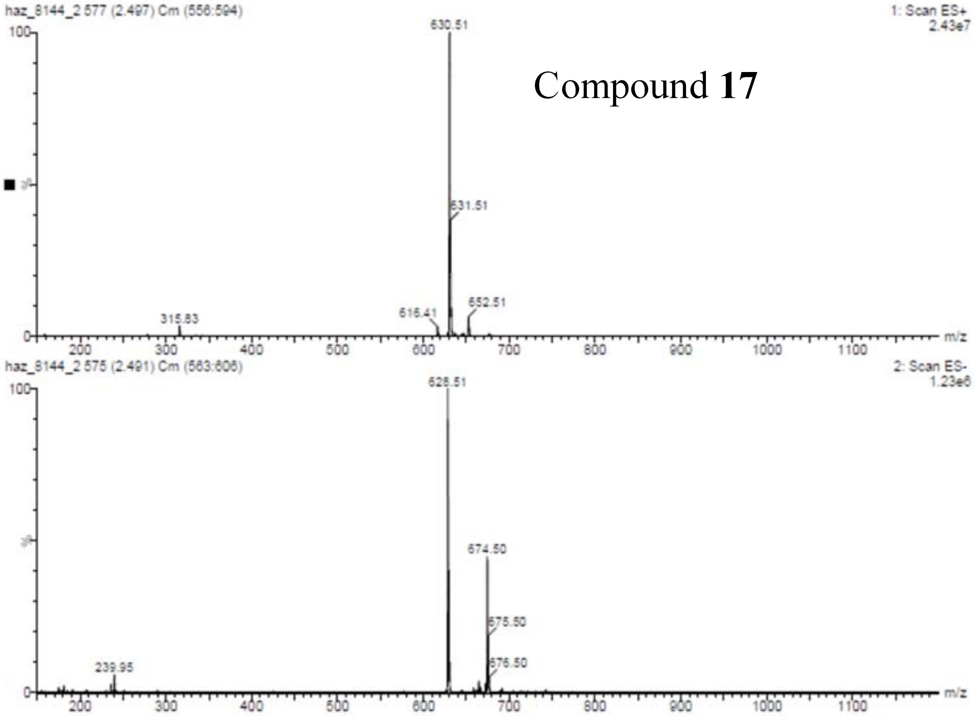

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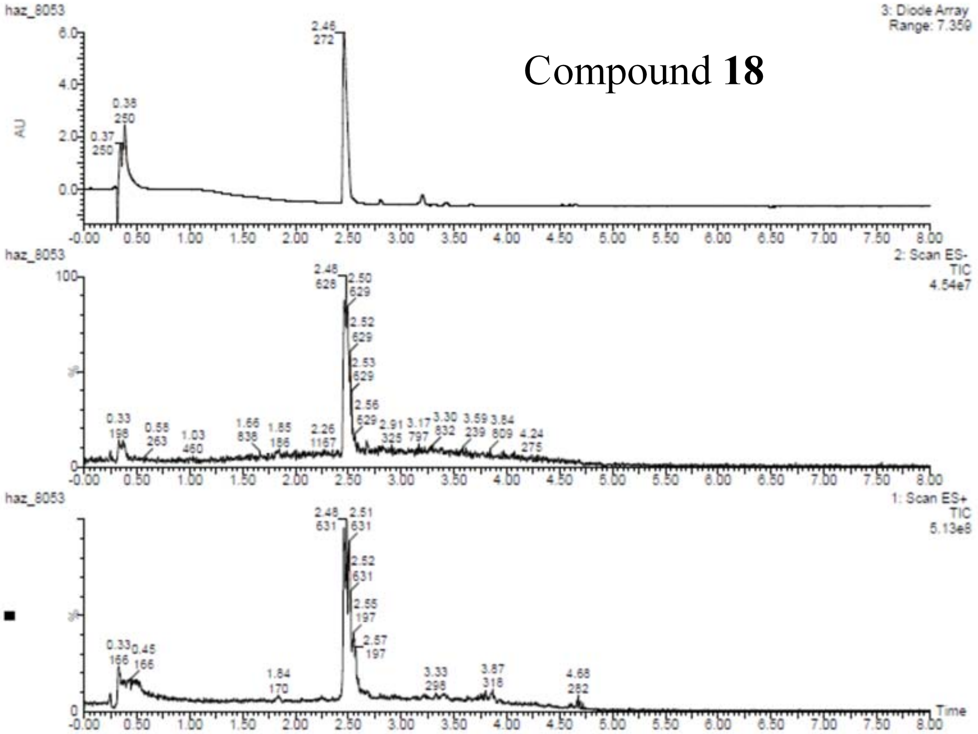

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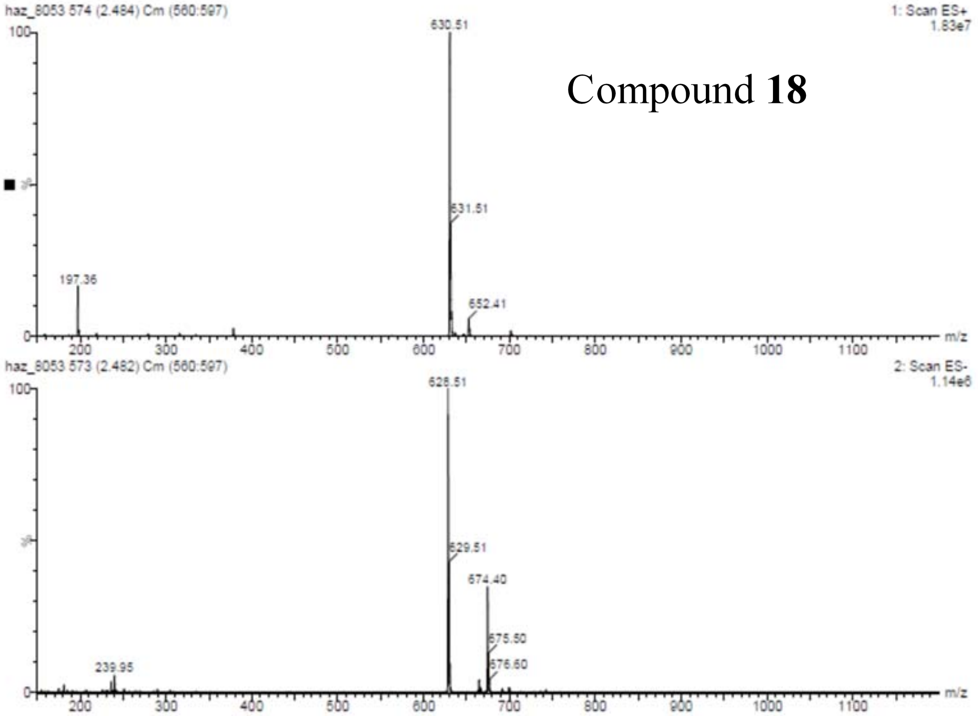

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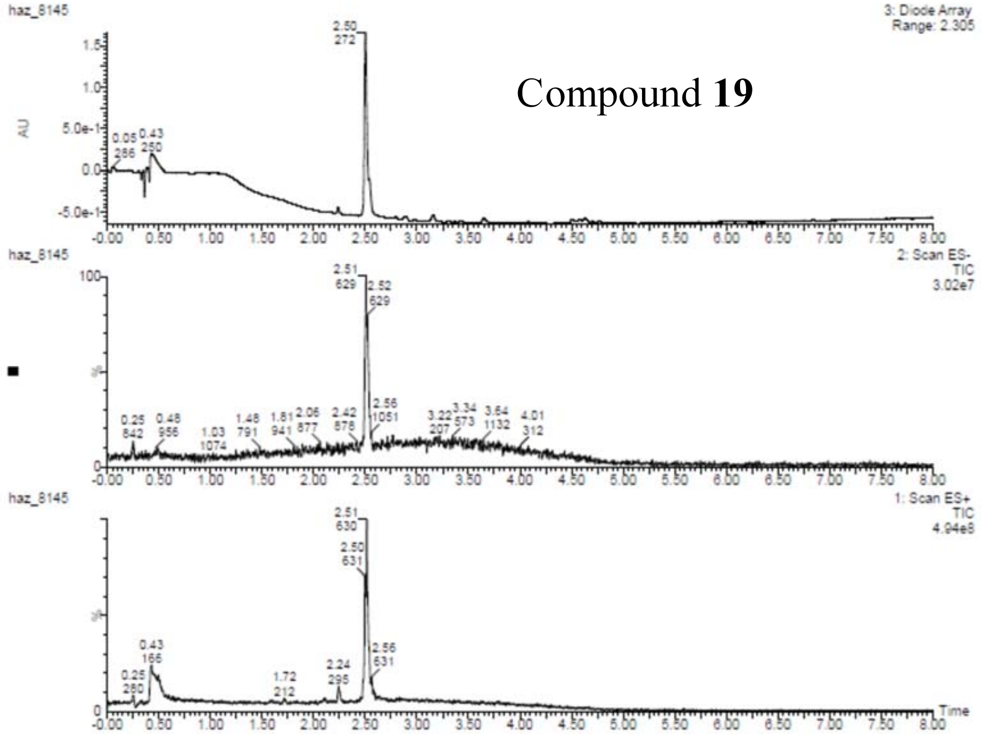

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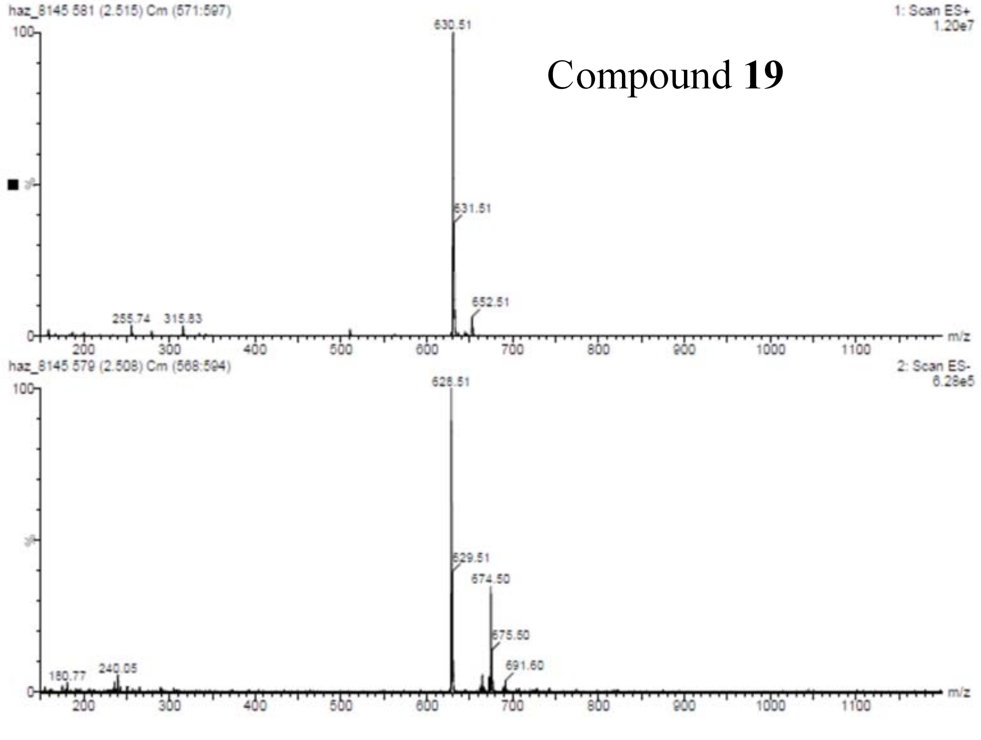

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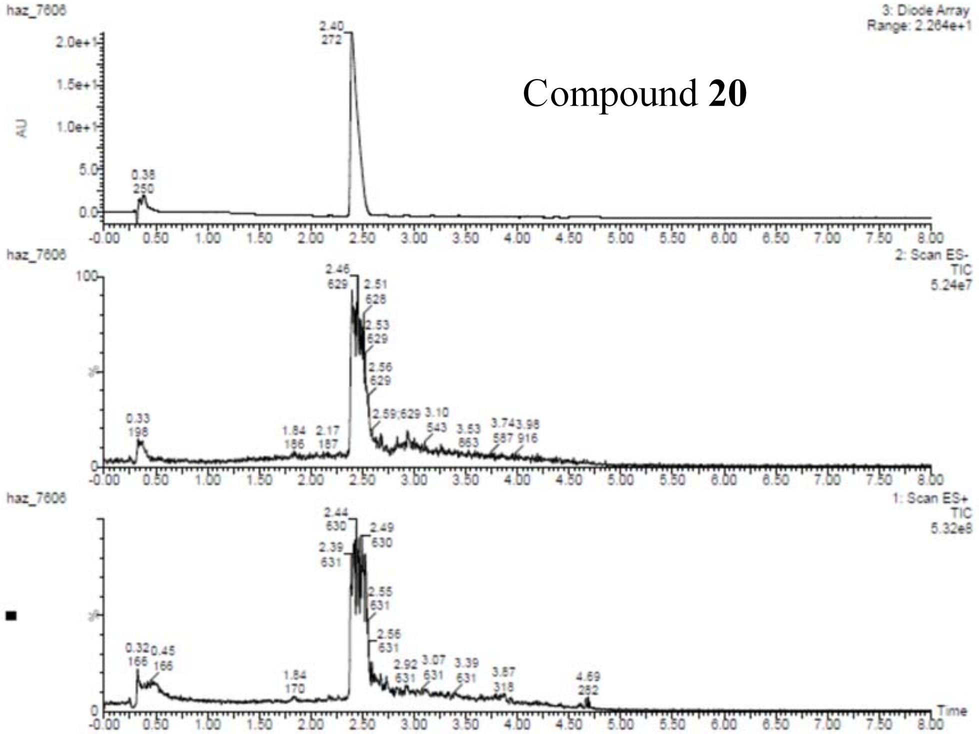
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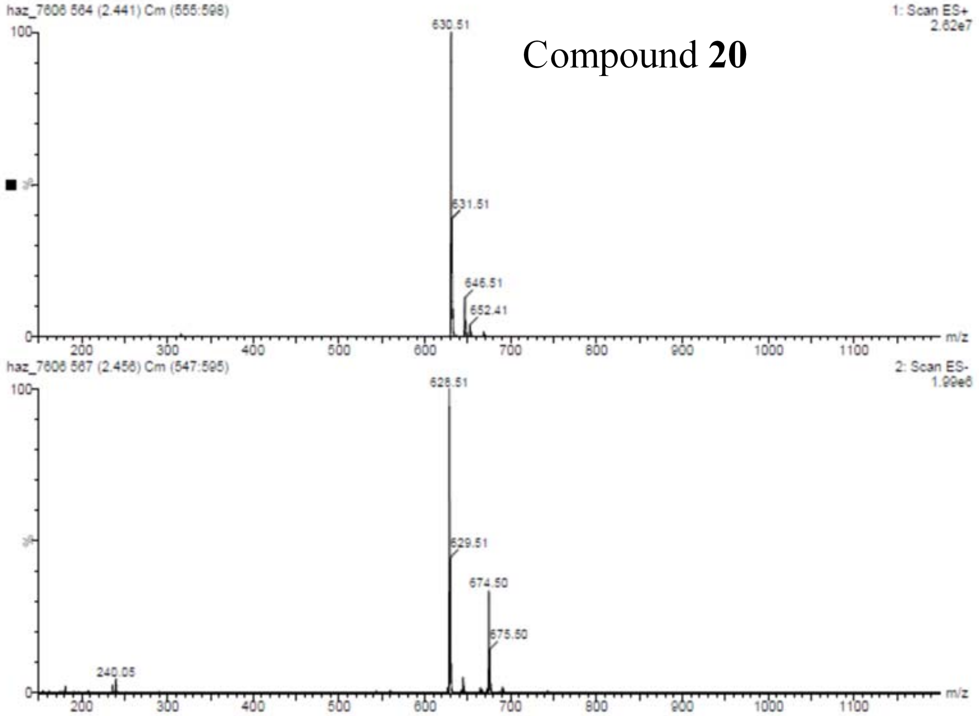
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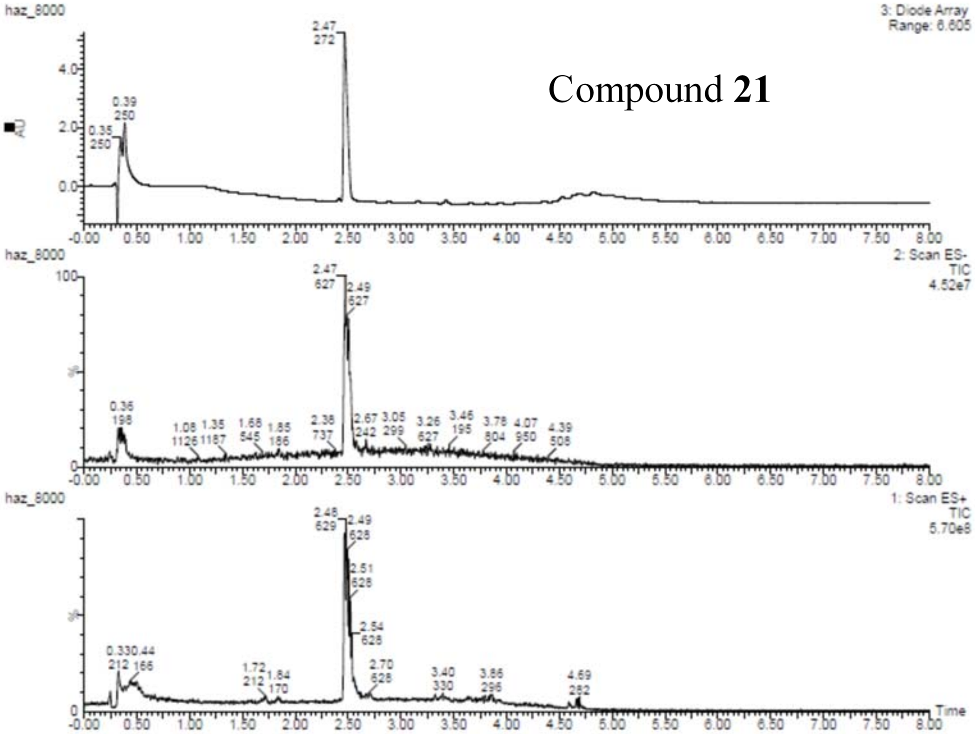

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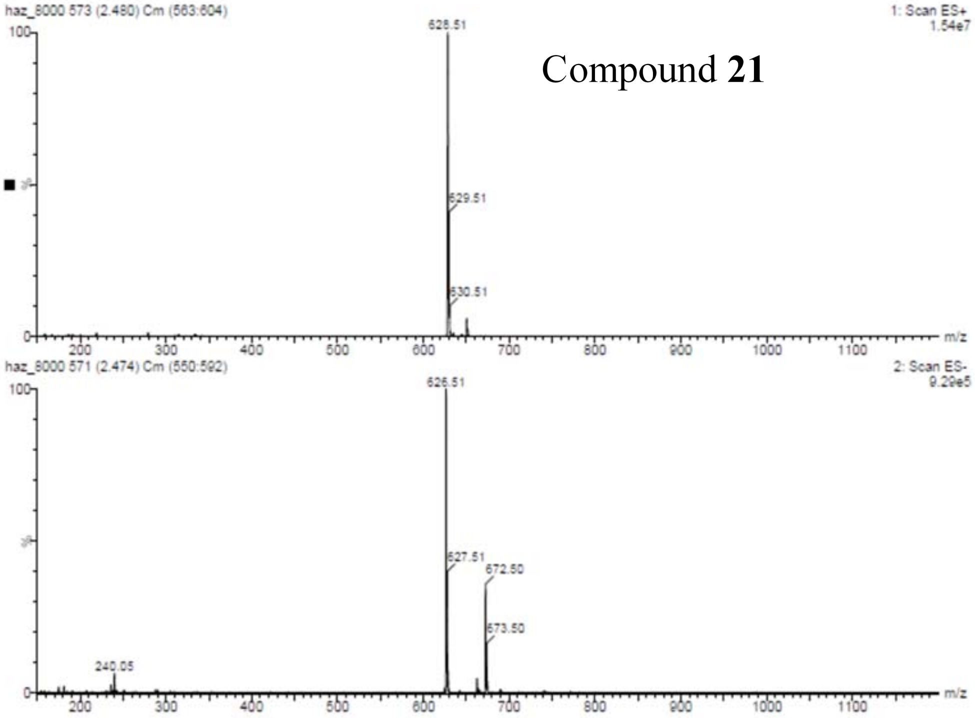

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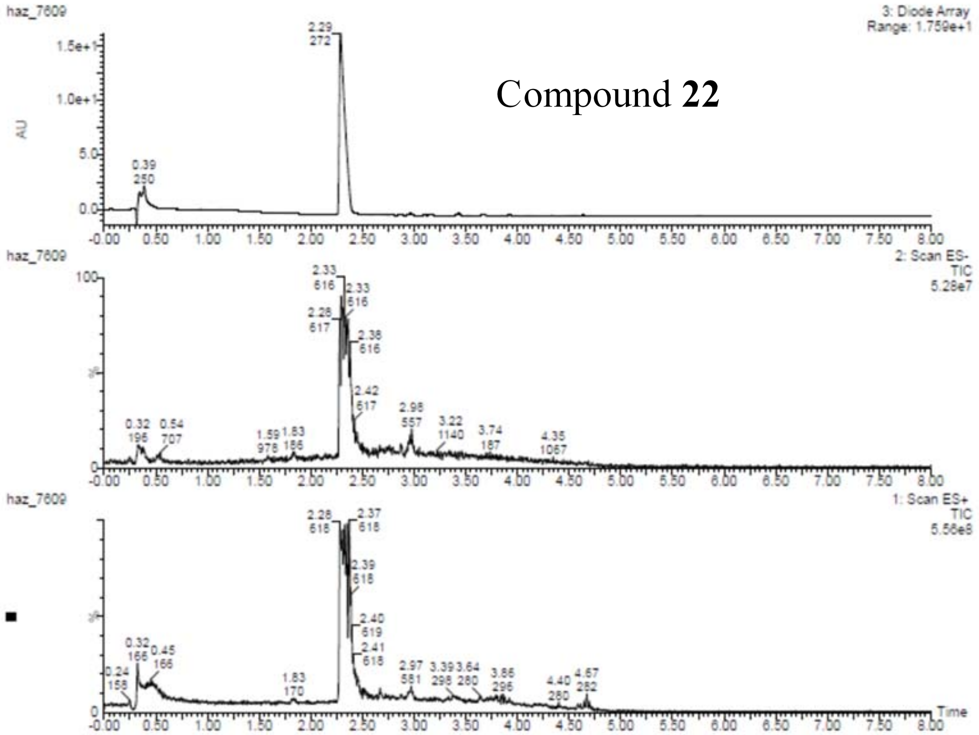

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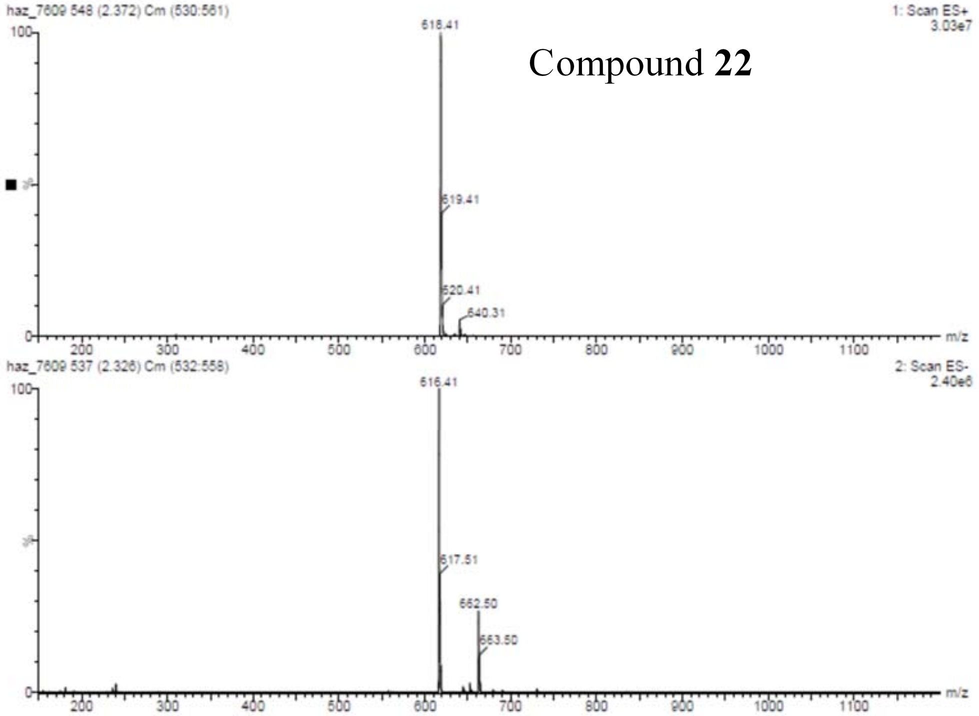
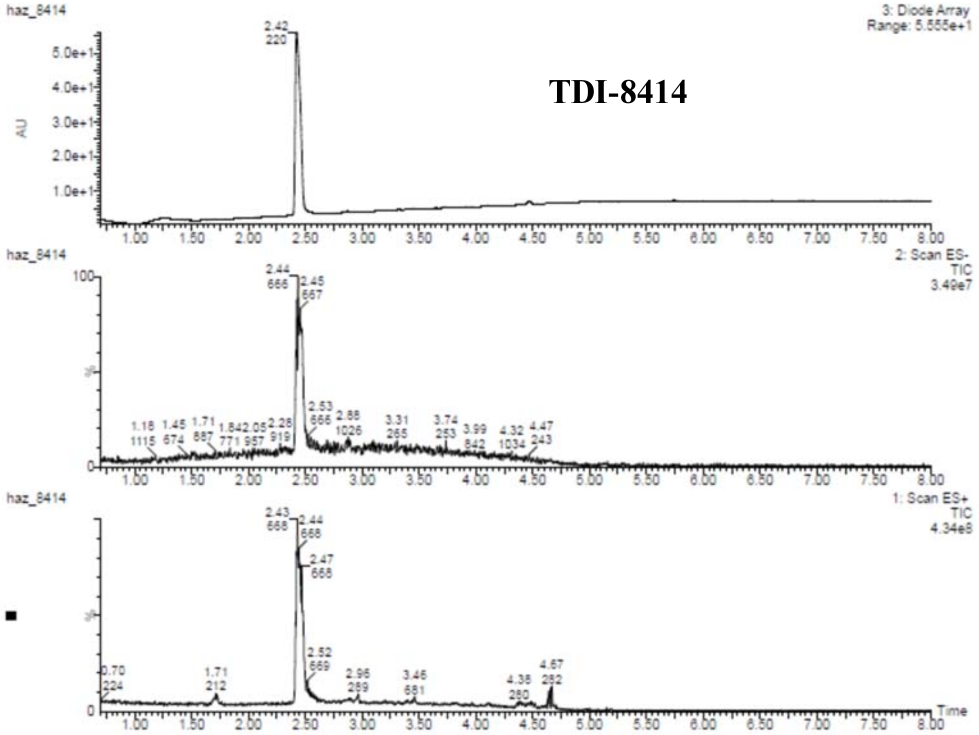


Compound **22**

TDI-8414



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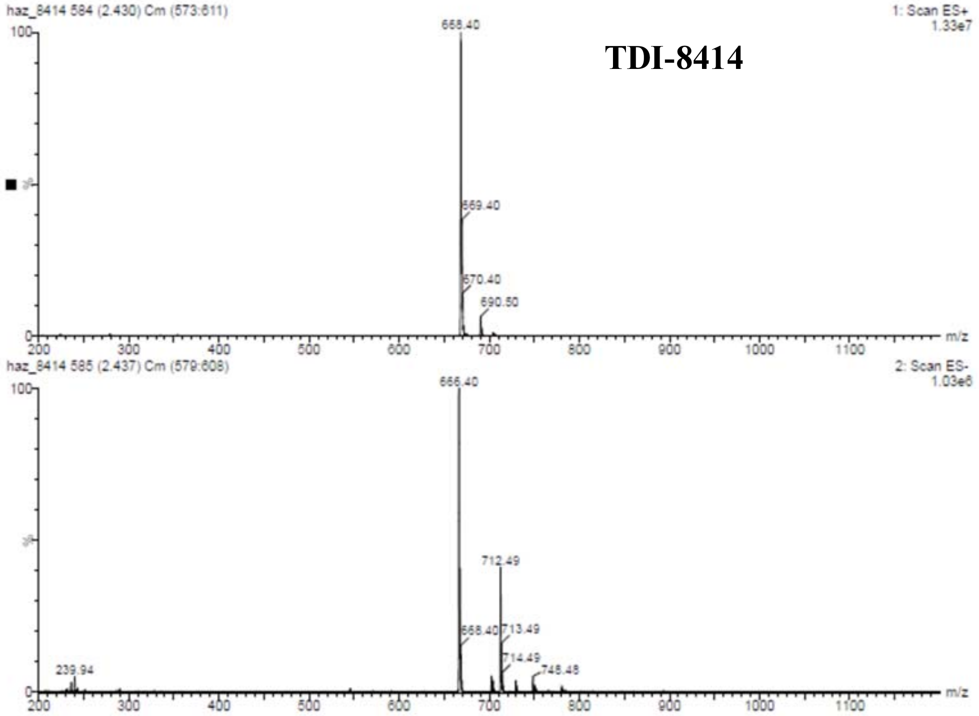

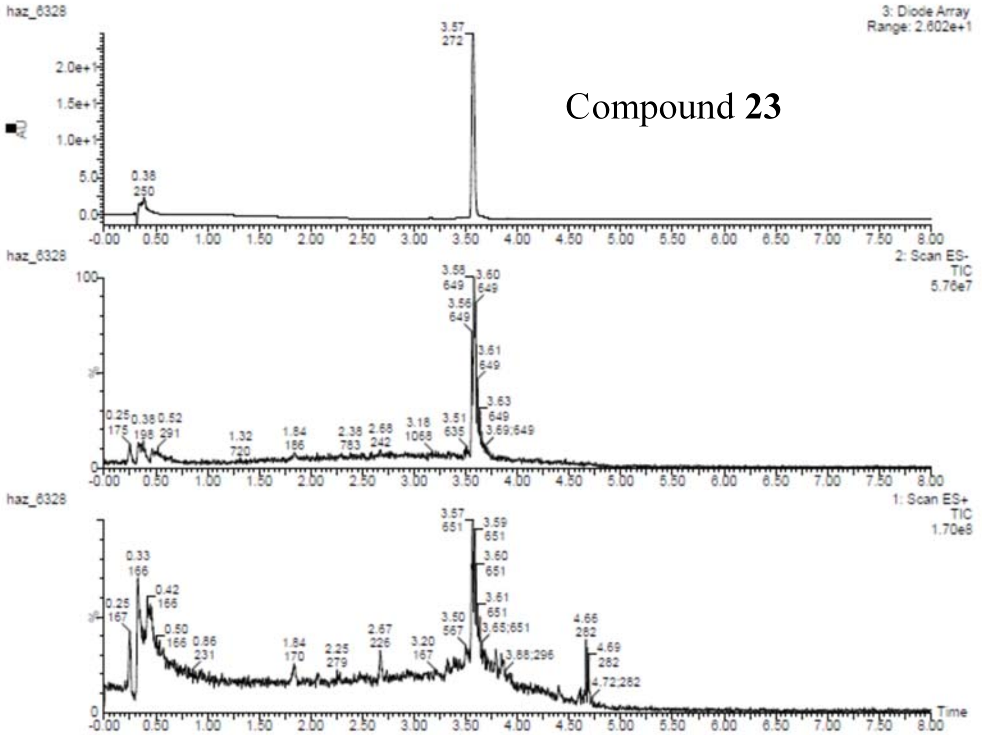
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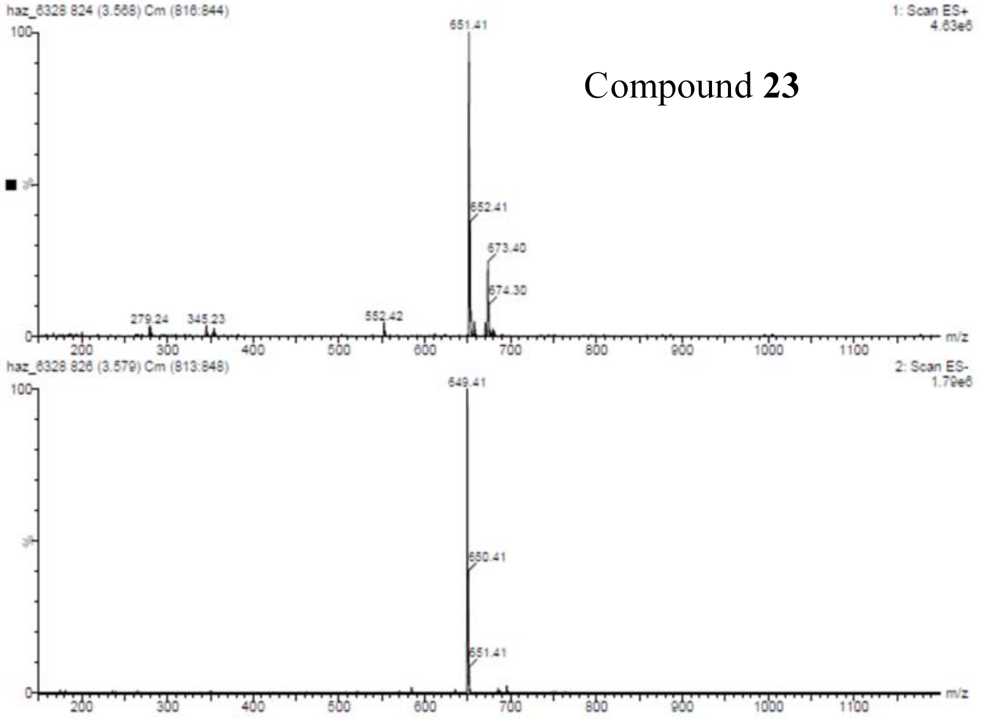
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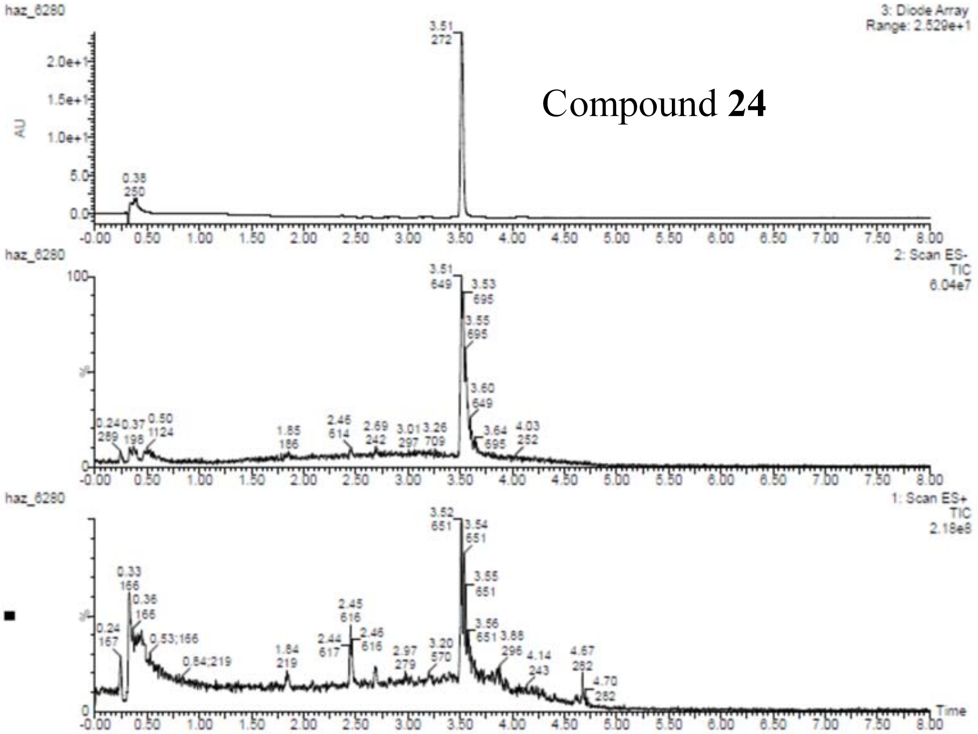

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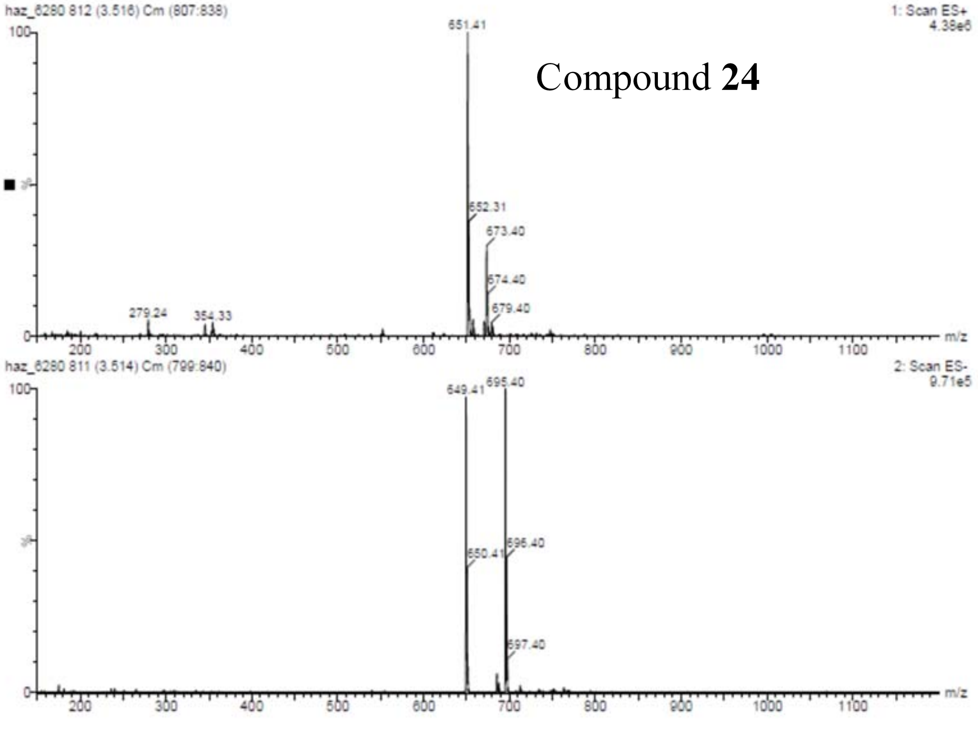

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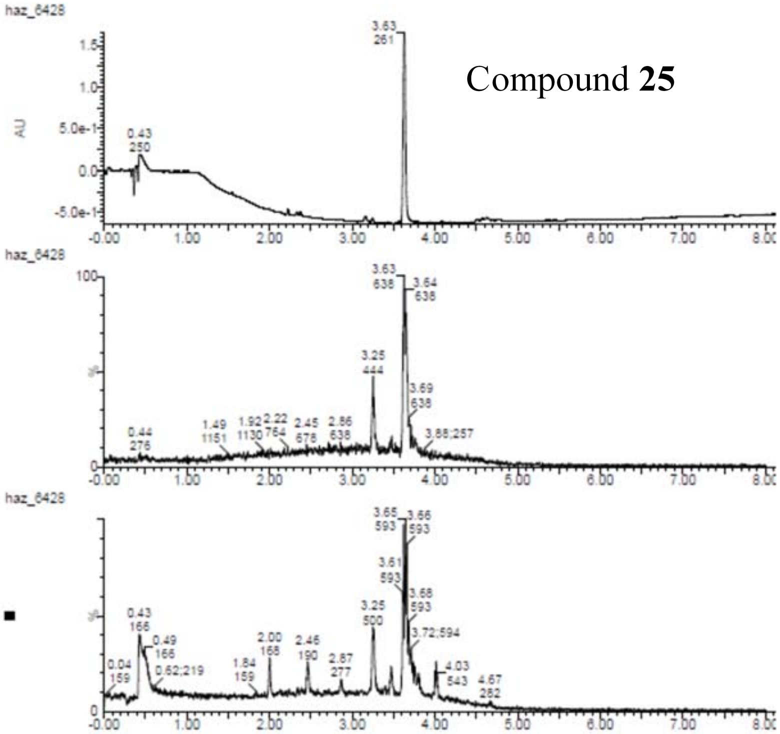

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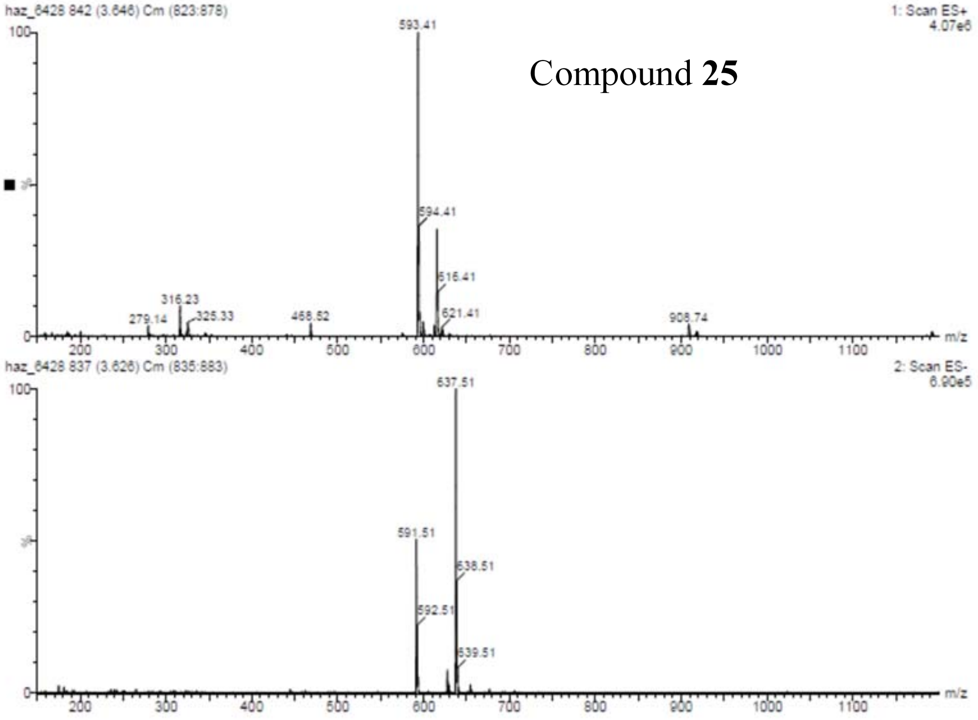

Compound **25**