Supplementary Data

Discovery of cyclosporine A and its analogs as broad-spectrum anti-influenza drugs with a high in vitro genetic barrier of drug resistance

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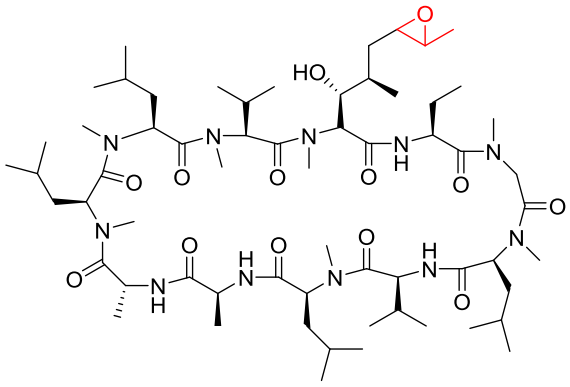
Chemistry

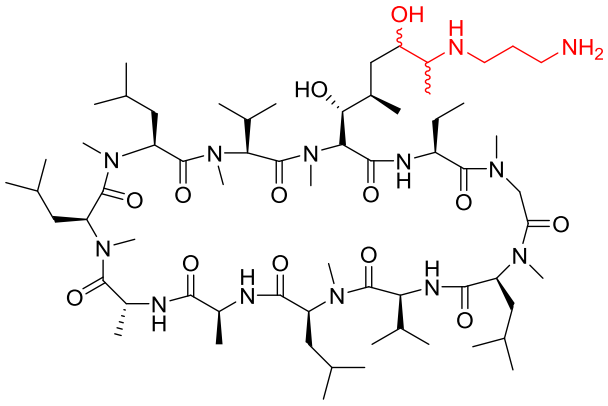
All chemicals were purchased from commercial vendors and used without further purification unless otherwise noted. All reactions were carried out under N_2 atmosphere, unless otherwise stated. HPLC grade solvents were used for all the reactions. All final compounds for antiviral testing were purified by preparative HPLC using a C18 column. The purity was assessed by using Shimadzu LC-MS with Waters XTerra MS C-18 column (part # 186000538), 50 X 2.1 mm, at a flow rate of 0.3 ml/min; $\lambda = 250$ and 220 nm; mobile phase A, 0.1% formic acid in H_2O, and mobile phase B', 0.1% formic in 60% isopropanol, 30% CH_3CN and 9.9% H_2O. The purified fractions were lyophilized. All compounds submitted for testing in plaque reduction assay were confirmed to be > 95.0% purity by LC-MS traces.



6

(3S,6S,9S,12R,15S,18S,21S,24S,30S,33R)-30-ethyl-33-((2R)-1-hydroxy-2-methyl-3-(3-methyloxiran-2-yl)propyl)-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone (**6**)

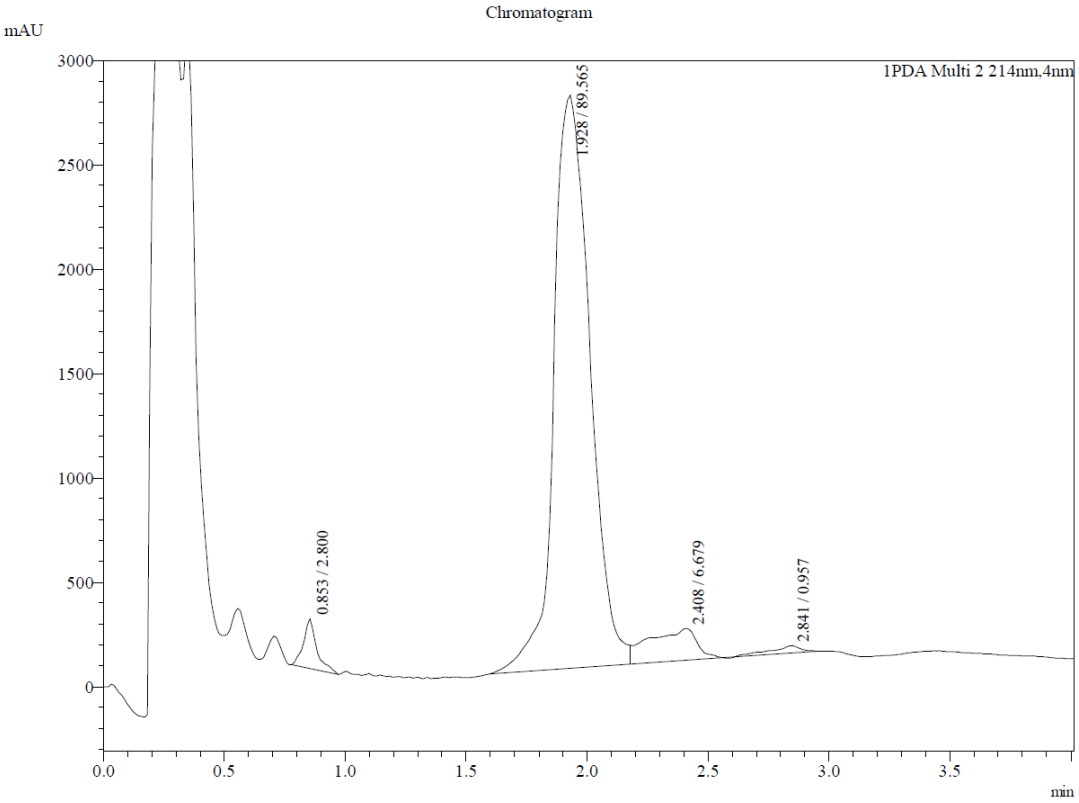
To a solution of cyclosporin A (100 mg, 0.083 mmol) in dichloromethane (10 mL) was added *m*-chloro-peroxybenzoic acid (16 mg, 0.093 mmol) and sodium carbonate (20 mg, 0.19 mmol). The mixture was stirred for 14 hrs at ambient temperature and then was washed by sodium thiosulfate solution (20%, 5 mL), sodium bicarbonate (20%, 5 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was collected, dried by anhydrous magnesium sulfate and concentrated to give **6** as a white solid which was used for the next step without purification.[1] The product was characterized by LC/MS. Calculated m/z 1218.8 $(M+H)^{1+}$, 609.9 $(M+2H)^{2+}$; found m/z 610 $(M+2H)^{2+}$.



7

(3S,6S,9S,12R,15S,18S,21S,24S,30S,33R)-33-((2R)-5-((3-aminopropyl)amino)-1,4-dihydroxy-2-methylhexyl)-30-ethyl-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone **(7)**

To a solution of **6** (86 mg, 0.058 mmol) in tetrahydrafuran (5 mL) was added 1, 3-diaminopropane (0.25 mL, 3 mmol) and the mixture was refluxed for 24 hours. After cooling down to room temperature, solvents were removed in vacuo and the mixture was purified by preparative HPLC to provide **7** as a white solid. The product was characterized by LC/MS. Calculated m/z 1292.9 $(M+H)^{1+}$, 646.9 $(M+2H)^{2+}$; found m/z 647 $(M+2H)^{2+}$.



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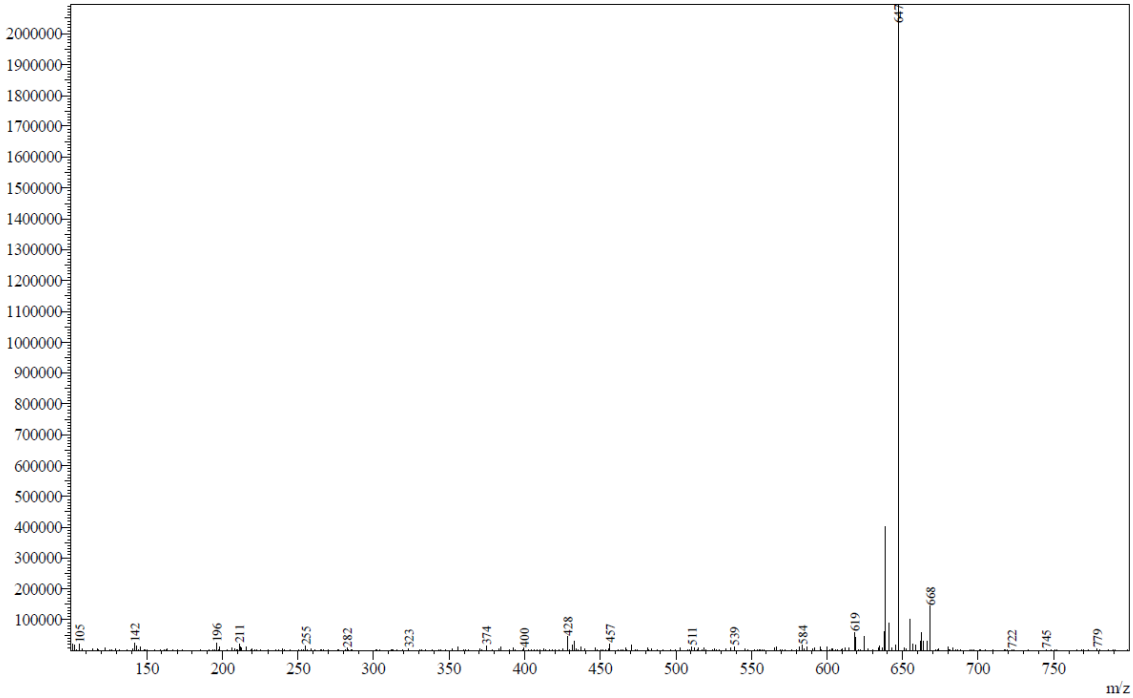
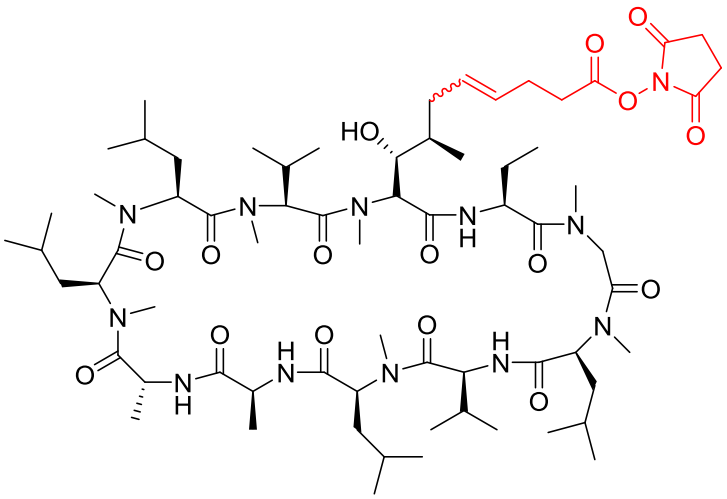


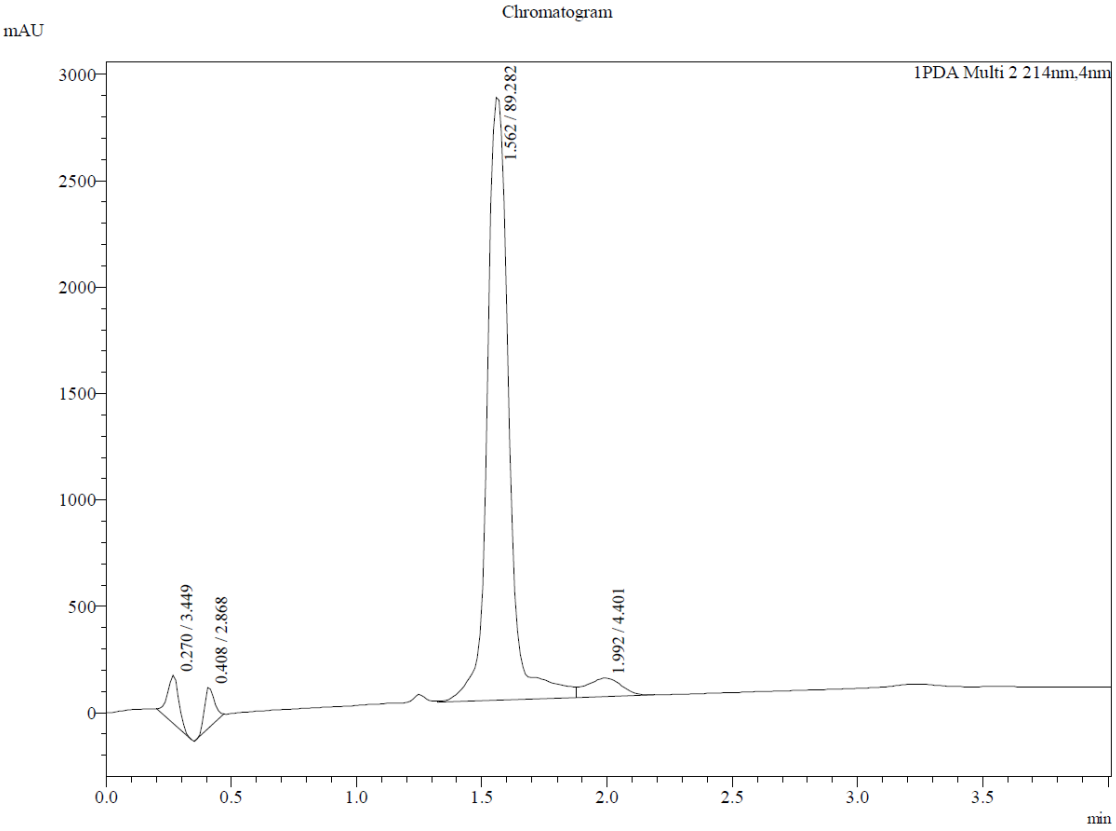


8

2,5-dioxopyrrolidin-1-yl (7R)-8-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-8-hydroxy-7-methyloct-4-enoate **(8)**

To a solution of cyclosporin A (100 mg, 0.083 mmol) and N-(Hydroxysuccinimidyl)4-pentenoate (147 mg, 0.75 mmol) in dry dichloromethane (5 mL)was added Grubbs 2nd generation catalyst (14 mg, 0.015 mmol). The mixture was refluxed for 22 hours, concentrated in vacuo and purified by preparative HPLC to give **8** as a white solid.[2] The product was characterized by LC/MS. Calculated m/z 1357.9 $(M+1H)^{1+}$, m/z 679.5 $(M+2H)^{2+}$; found 1358 $(M+1H)^{1+}$, m/z 680 $(M+2H)^{2+}$.

Chromatogram



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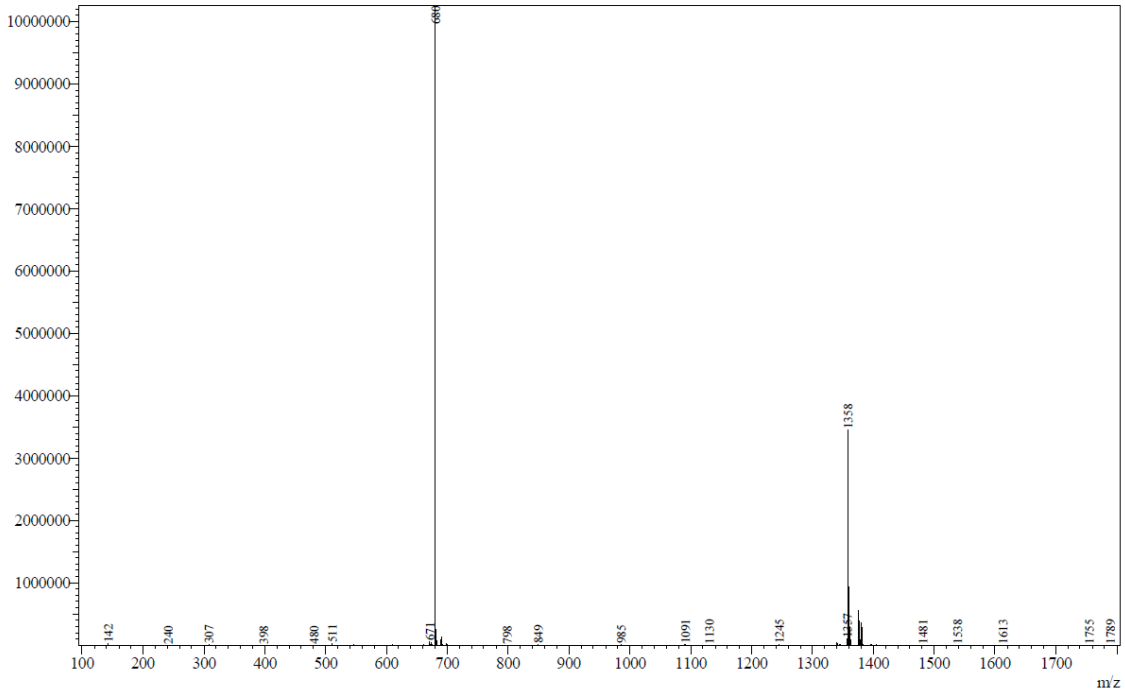
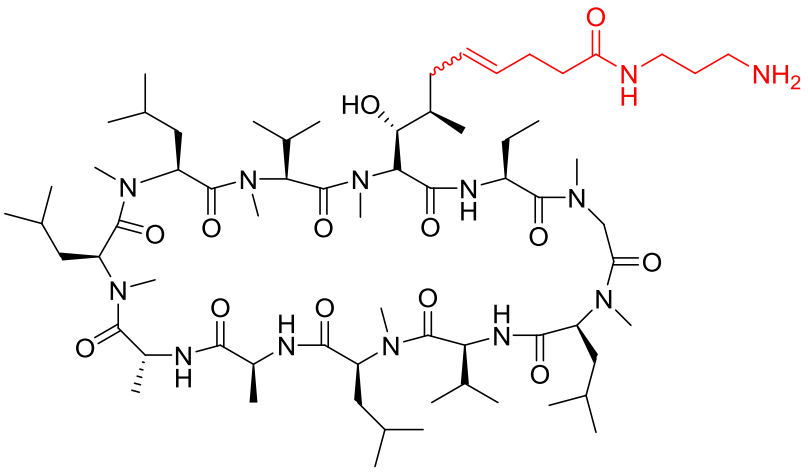
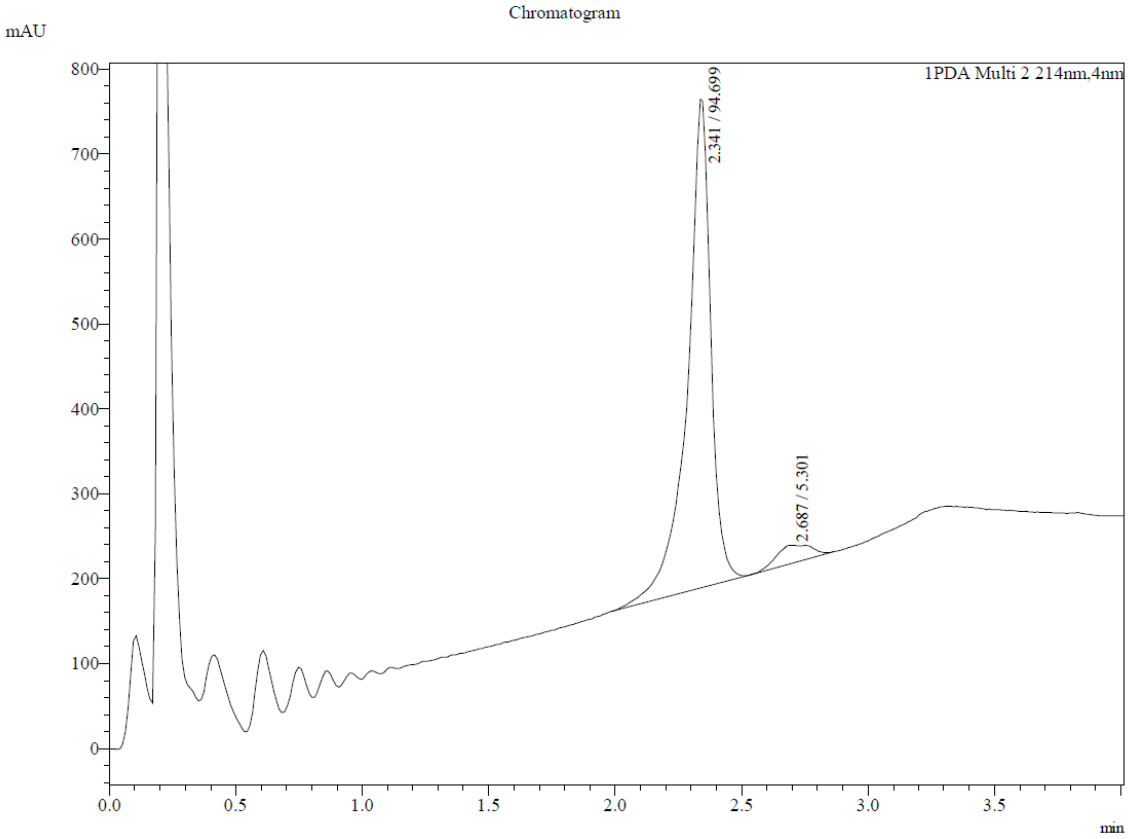




9

(7R)-N-(3-aminopropyl)-8-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-8-hydroxy-7-methyloct-4-enamide **(9)**

To a solution of **8** (72 mg, 0.053 mmol) in dichloromethane (2 mL) was added 1,3-diaminopropane (86 µL, 1 mmol) and stirred at ambient temperature for 14 hours. The reaction was concentrated in vacuo and purified by preparative HPLC to give **9** as a white solid.[2] The product was characterized by LC/MS. Calculated m/z 1316.9 $(M+1H)^{1+}$, m/z 658.8 $(M+2H)^{2+}$; found m/z 1317 $(M+1H)^{1+}$, m/z 659 $(M+2H)^{2+}$.



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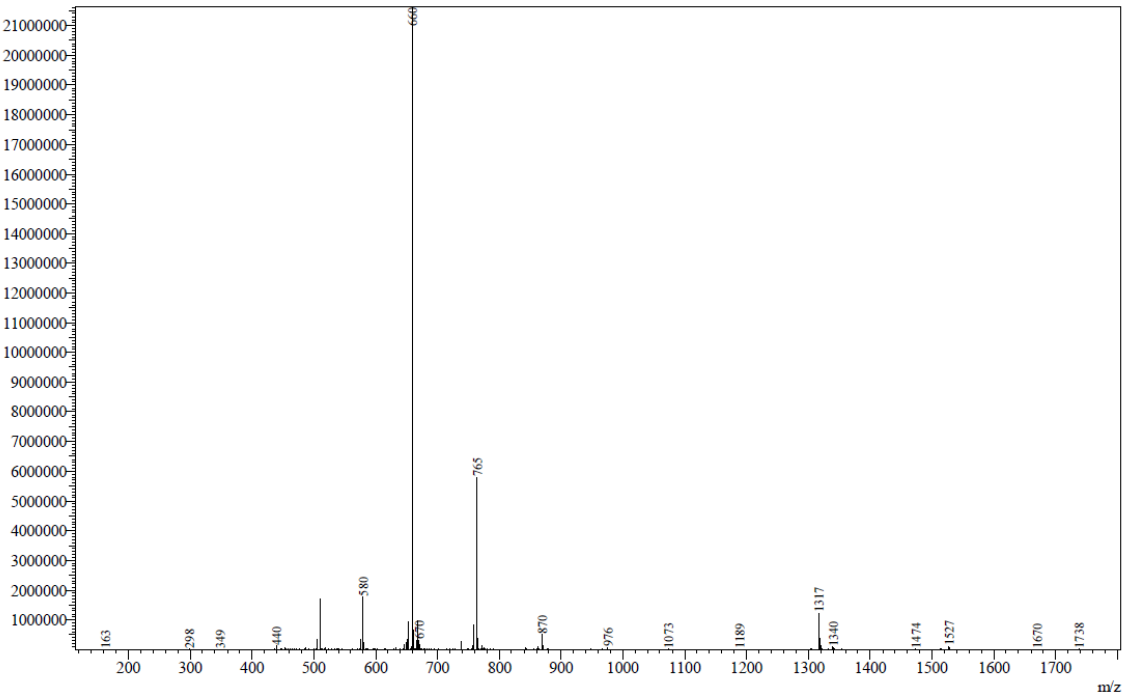
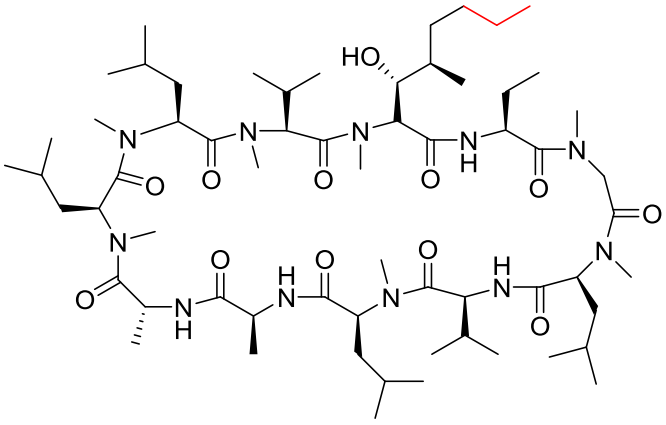
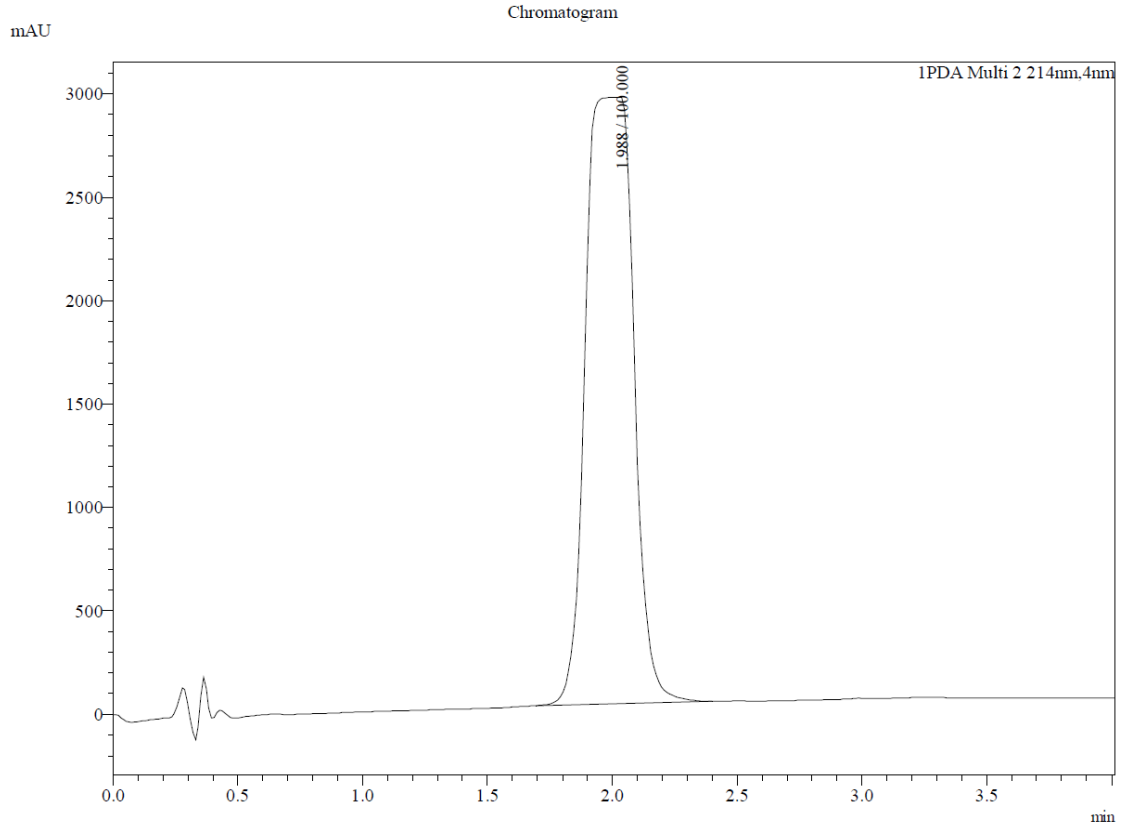




10

(3S,6S,9S,12R,15S,18S,21S,24S,30S,33R)-30-ethyl-33-((2R)-1-hydroxy-2-methylhexyl)-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,28-nonamethyl-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone **(10)**

To a solution of cyclosporin A (100 mg, 0.083 mmol) in THF was added palladium/carbon (27 mg, 10%) at room temperature. The mixture was exposed to a hydrogen balloon (1 atm) and stirred 10 hours at room temperature. Then the reaction was filed by celite and concentrated in vacuo and purified by preparative HPLC to give **10** as a white solid. The product was characterized by LC/MS. Calculated m/z 1204.9 $(M+1H)^{1+}$, m/z 602.9 $(M+2H)^{2+}$; found m/z 1205 $(M+1H)^{1+}$, m/z 604 $(M+2H)^{2+}$.



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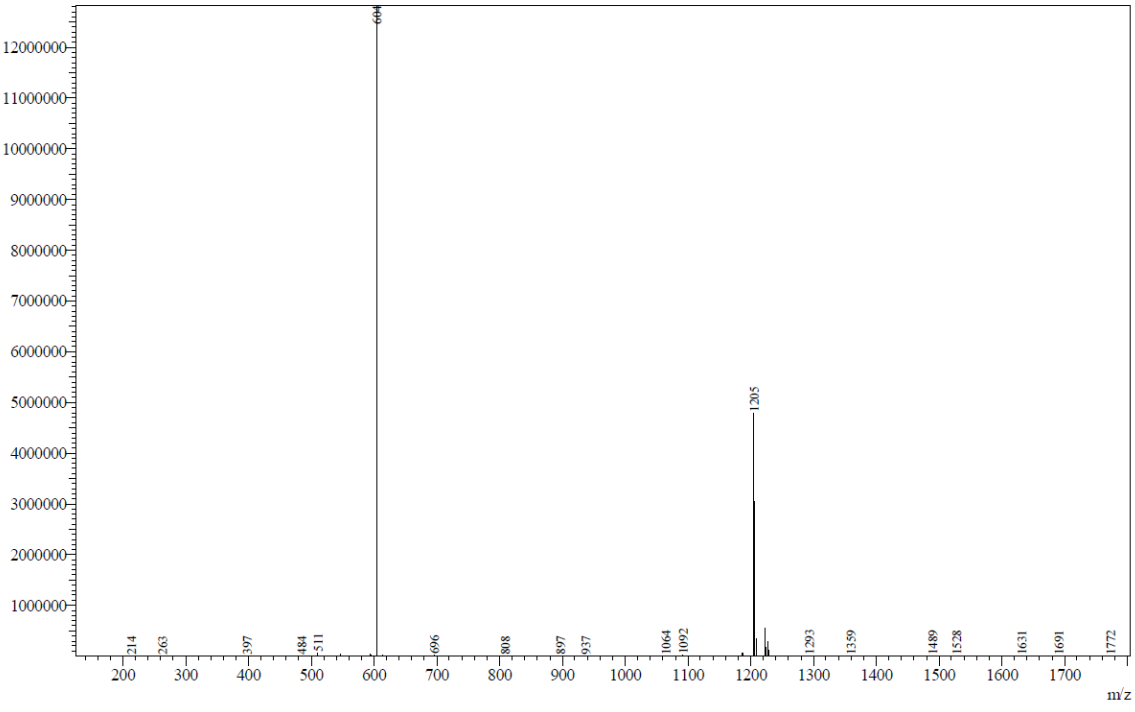
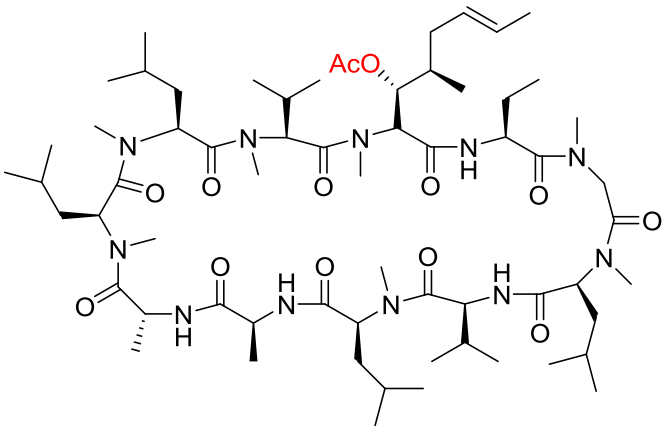
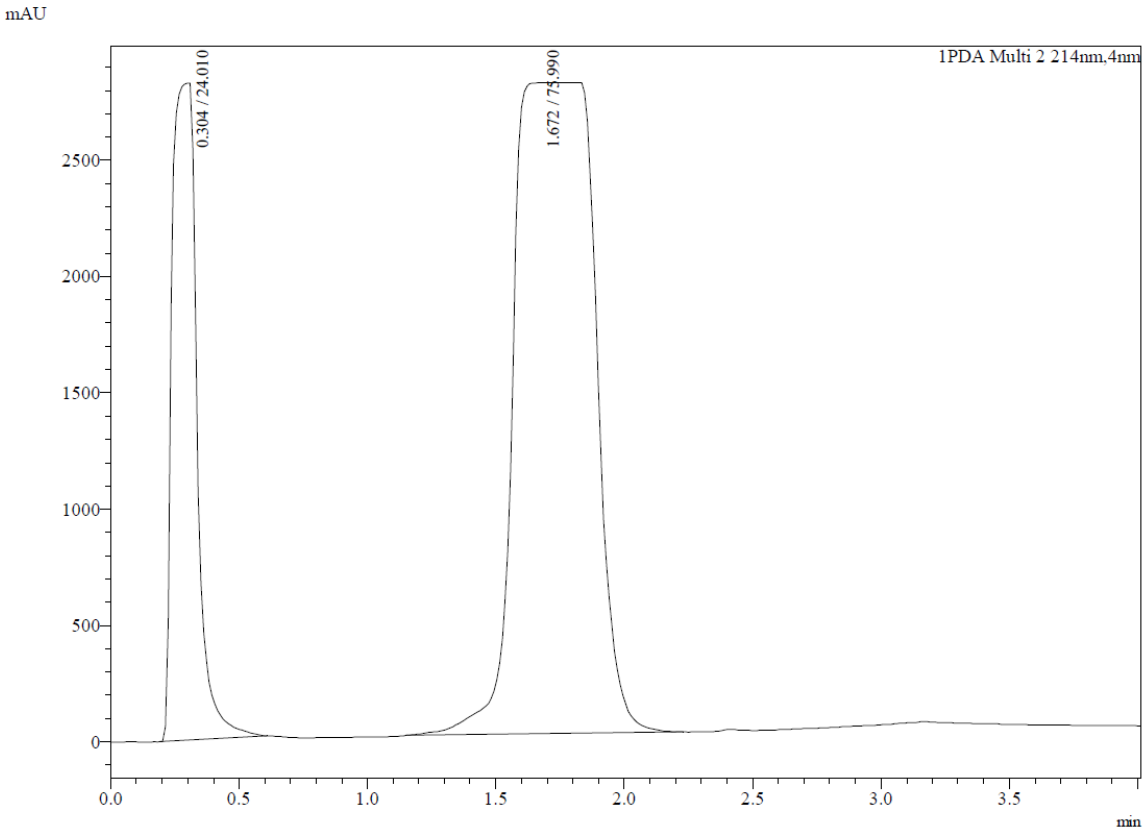




11

(2R,E)-1-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-2-methylhex-4-en-1-yl acetate **(11)**

To a solution of cyclosporin A (100 mg, 0.083 mmol) in dichloromethane (3 mL) was added acetic anhydride (0.078 mL, 0.83 mmol), pyridine (0.1 mL, 1.24 mmol), and 4-Dimethylaminopyridine (1.5 mg, 0.012 mmol) and stirred at ambient temperature for 48 hours. The mixture was then poured into ice-cooled saturated sodium bicarbonate solution. After stirring for 20 min, the reaction was extracted with dichloromethane (3 × 5 mL). The organic layer was collected, dried by anhydrous magnesium sulfate, concentrated, and purified by flash column chromatography using methanol/dichloromethane (0-5%) and provided **11** as a white solid (92 mg, 0.007 mmol, yield 89%)[3]. The product was characterized by LC/MS. Calculated m/z 1244.9 $(M+1H)^{1+}$, m/z 622.9 $(M+2H)^{2+}$; found m/z 1246 $(M+1H)^{1+}$, m/z 623 $(M+2H)^{2+}$.



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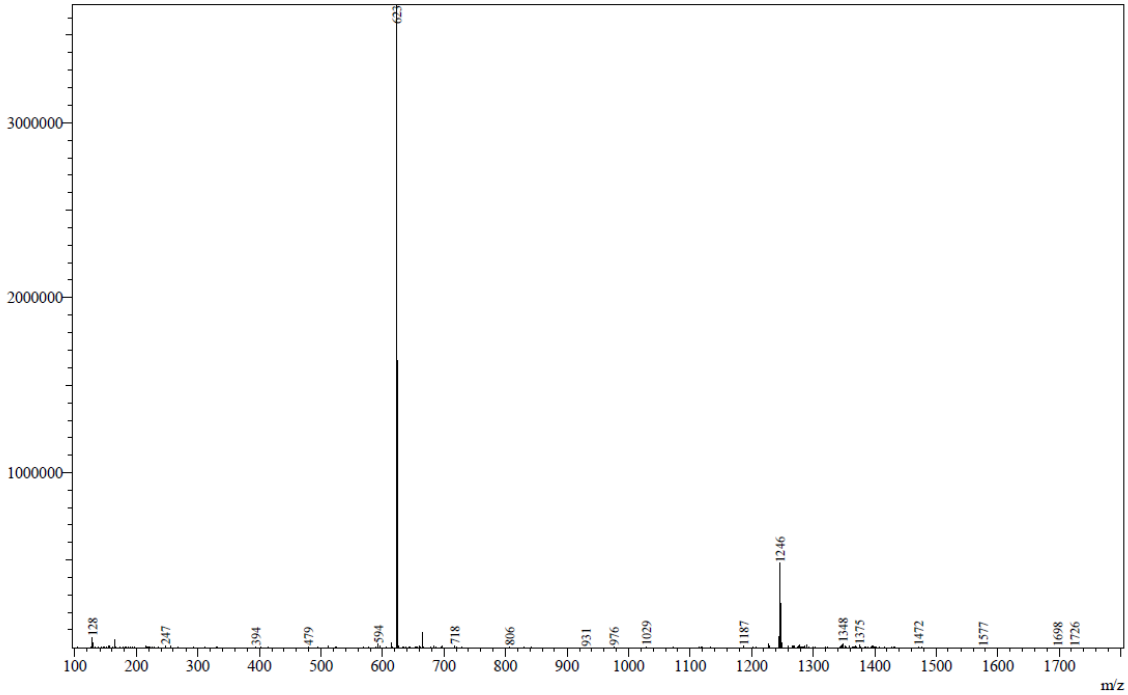
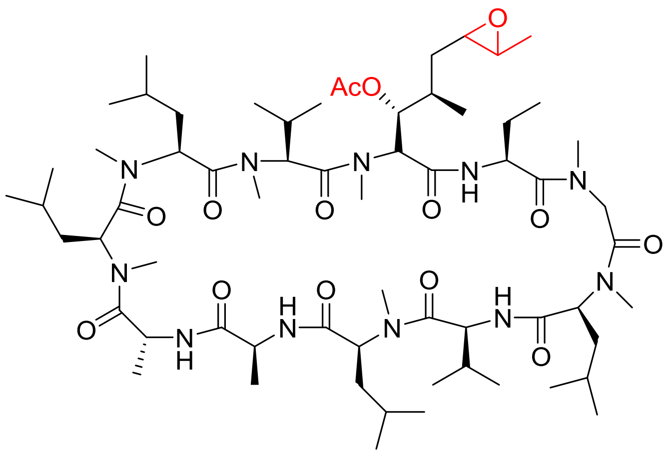
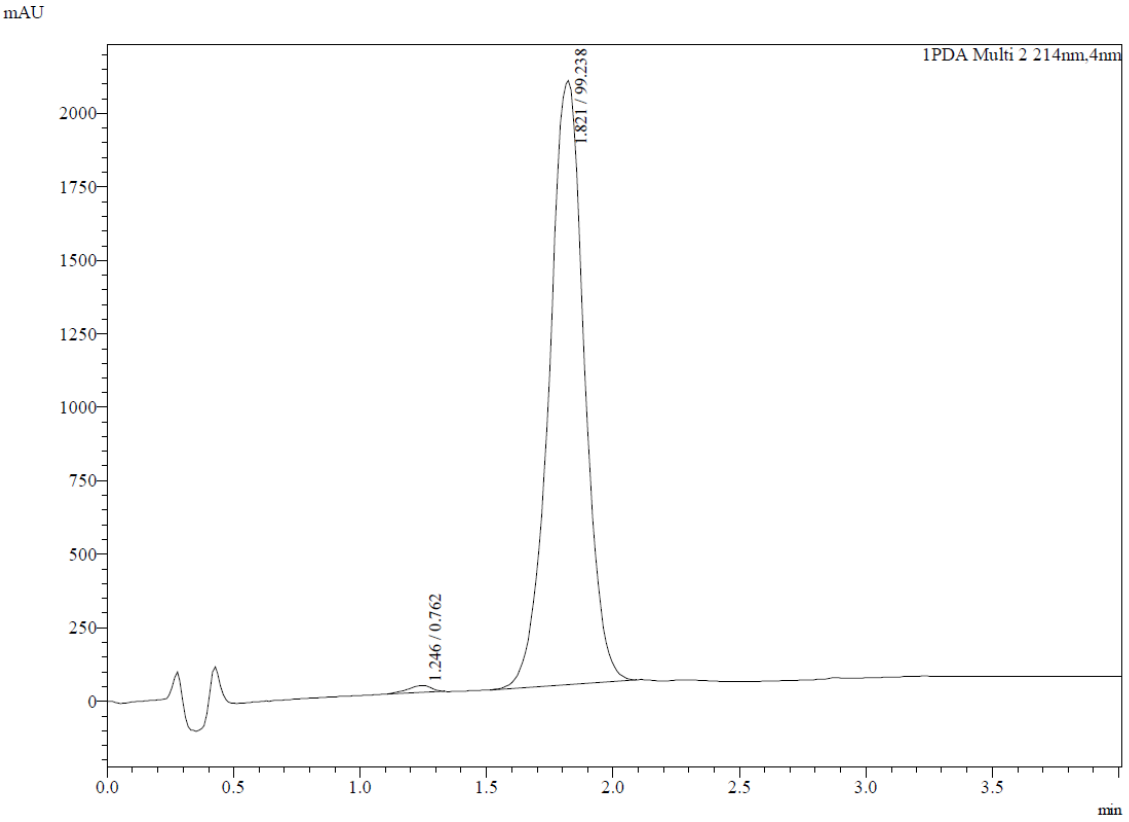




12

(2R)-1-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-2-methyl-3-(3-methyloxiran-2-yl)propyl acetate **(12)**

To a solution of **11** (100 mg, 0.08 mmol) in dichloromethane (10 mL) was added *m*-chloro-peroxybenzoic acid (17 mg, 0.099 mmol) and sodium carbonate(20 mg, 0.19 mmol). The mixture was stirred for 14 hours at ambient temperature and then was washed by sodium thiosulfate solution (20%, 5 mL), sodium bicarbonate (20%, 5 mL) and extracted with dichloromethane (3 × 10 mL). The organic layer was collected, dried by anhydrous magnesium sulfate and concentrated. The mixture was purified by preparative HPLC and provided **12** as a white solid.[1] The product was characterized by LC/MS. Calculated m/z 1260.8 $(M+1H)^{1+}$, m/z 630.9 $(M+2H)^{2+}$; found m/z 1261 $(M+1H)^{1+}$, m/z 631 $(M+2H)^{2+}$.



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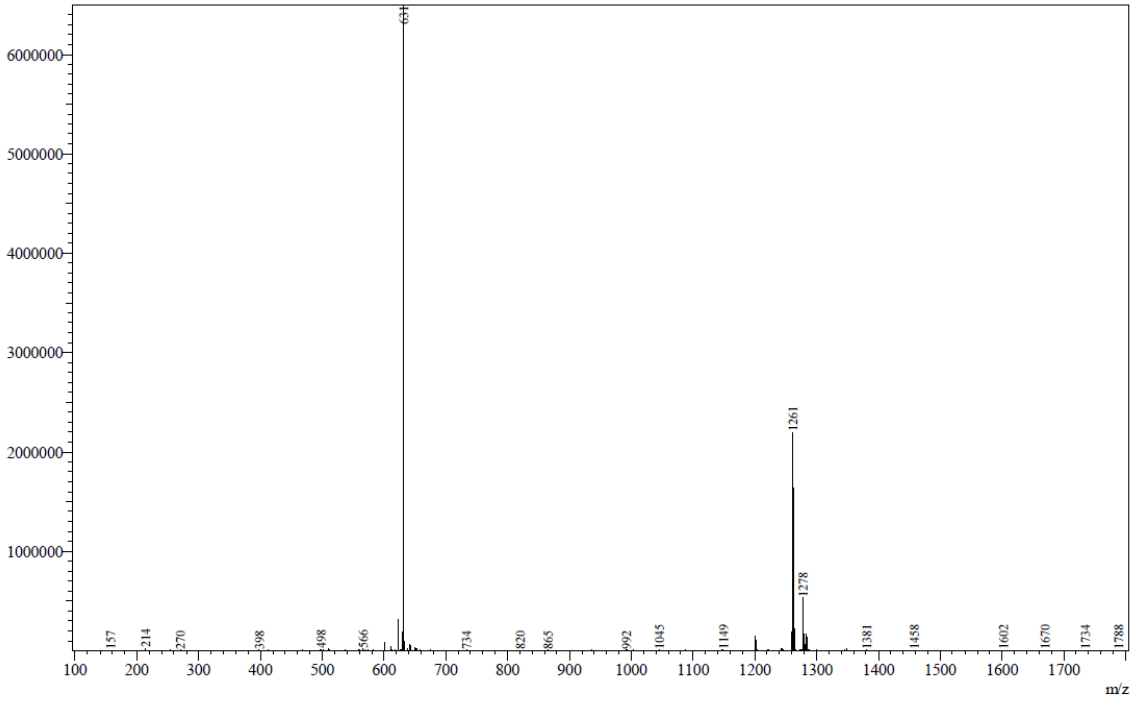
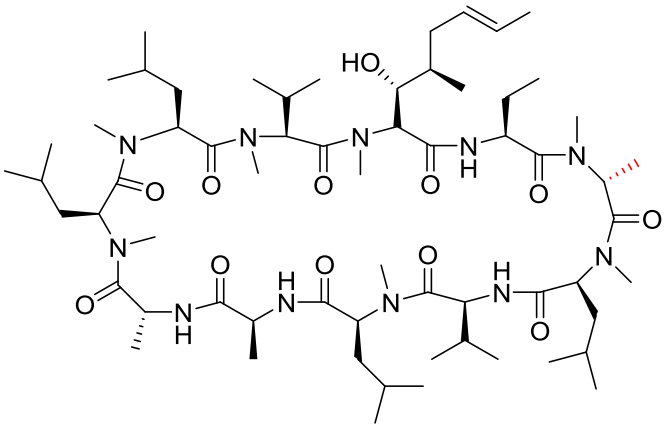
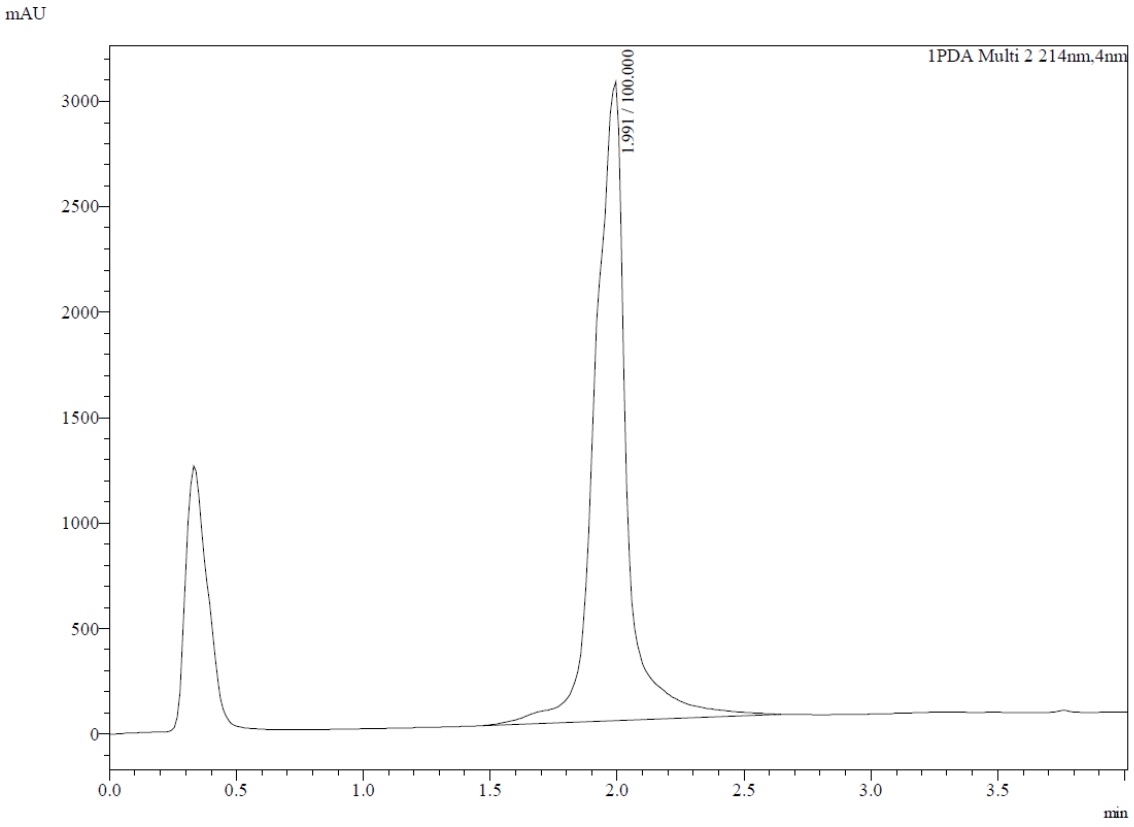




13

(3S,6S,9S,12R,15S,18S,21S,24S,27R,30S,33R)-30-ethyl-33-((2R,E)-1-hydroxy-2-methylhex-4-en-1-yl)-6,9,18,24-tetraisobutyl-3,21-diisopropyl-1,4,7,10,12,15,19,25,27,28-decamethyl-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2,5,8,11,14,17,20,23,26,29,32-undecaone **(13)**

To a solution of cyclosporin A (50 mg, 0.041 mmol) in tetrahydrofuran (5 mL) at -78 °C was added Lithium bis(trimethylsilyl)amide (410 µL, 1 M, 0.041 mmol). Methyl iodide was added at -78° C after 10 min. The mixture was stirred for 2 hours at -78 °C then was allowed to warm up to room temperature and stirred for 12 h. The reaction was then quenched by water (5 mL) at 0 °C and diluted dichloromethane (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude was purified by preparative HPLC and provided **13** as a white solid.[4] The product was characterized by LC/MS. Calculated m/z 1216.9 $(M+1H)^{1+}$, m/z 608.9 $(M+2H)^{2+}$; found m/z 609 $(M+2H)^{2+}$.



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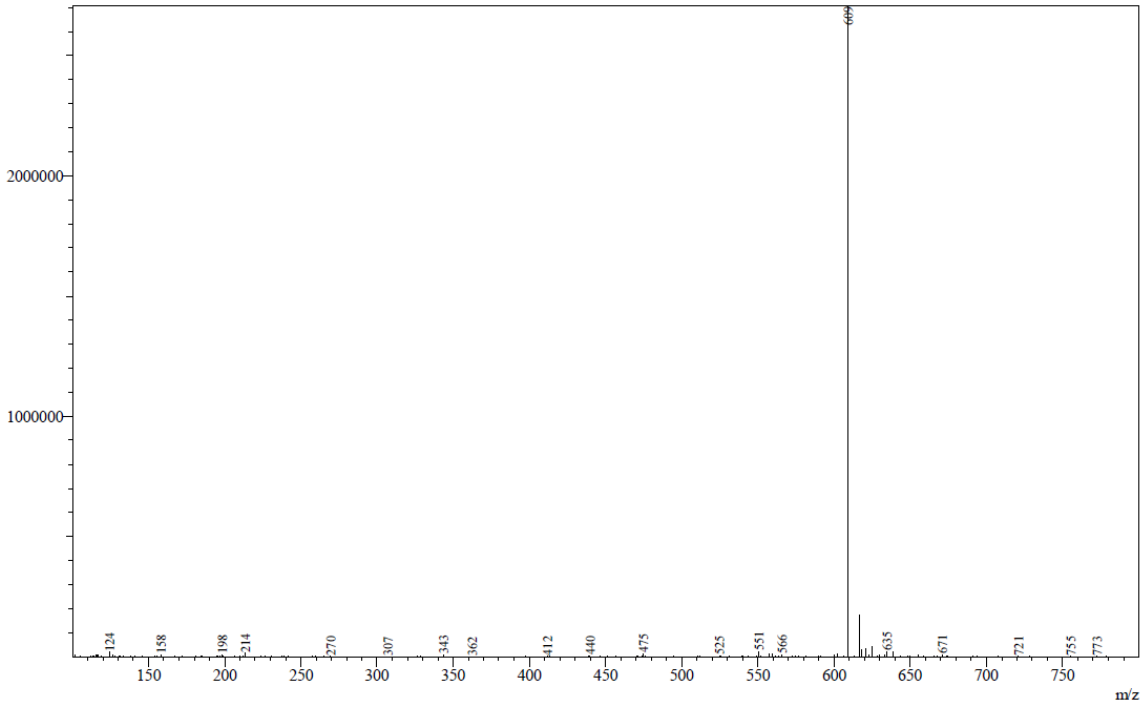
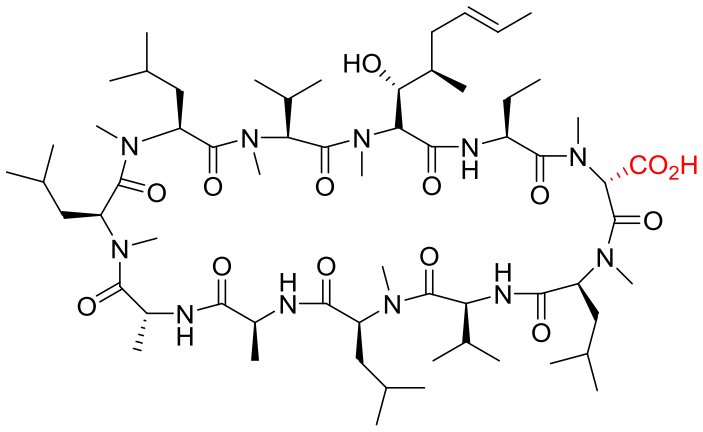


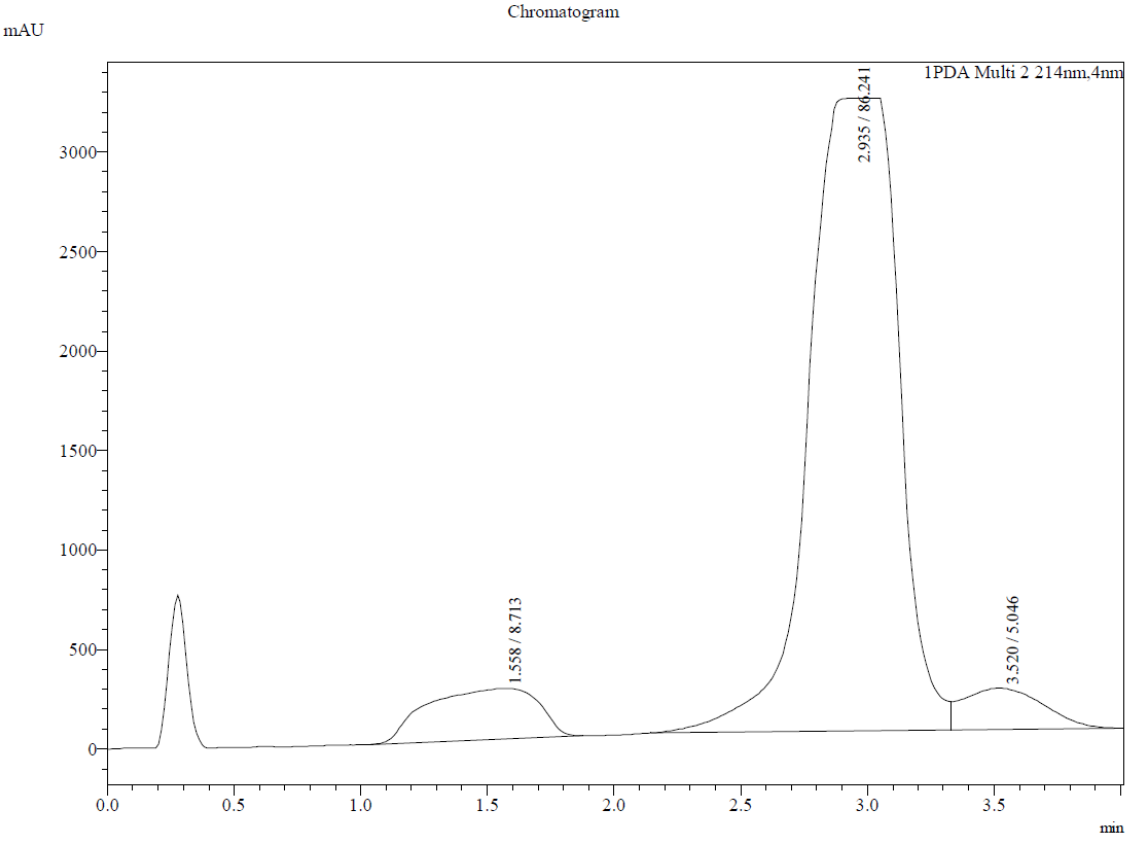


14

(2S,5S,8S,11S,14S,17R,20S,23S,26S,29R,32S)-32-ethyl-29-((2R,E)-1-hydroxy-2-methylhex-4-en-1-yl)-5,11,20,23-tetraisobutyl-8,26-diisopropyl-1,4,10,14,17,19,22,25,28-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontane-2-carboxylic acid **(14)**

To a solution of cyclosporin A (1 g, 0.83 mmol) in tetrahydrofuran (50 mL) at -78 °C was added Lithium diisopropylamide (5.3 mL, 1 M, 5.3 mmol). The reaction was stirred for 30 min at -78 °C. Then carbon dioxide was bubbled into the mixture and kept stirring at -78 °C for 60 min. The resulting mixture was then allowed to warm back to 0 °C. Citric acid (10 mL, 1M) was added to quench the reaction. The mixture was separated and the organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude was purified by preparative HPLC and provided **14** as white solid.[5] The product was characterized by LC/MS. Calculated m/z 1246.8 $(M+1H)^{1+}$, m/z 623.9 $(M+2H)^{2+}$; found m/z 1247 $(M+1H)^{1+}$, m/z 624 $(M+2H)^{2+}$.

Chromatogram



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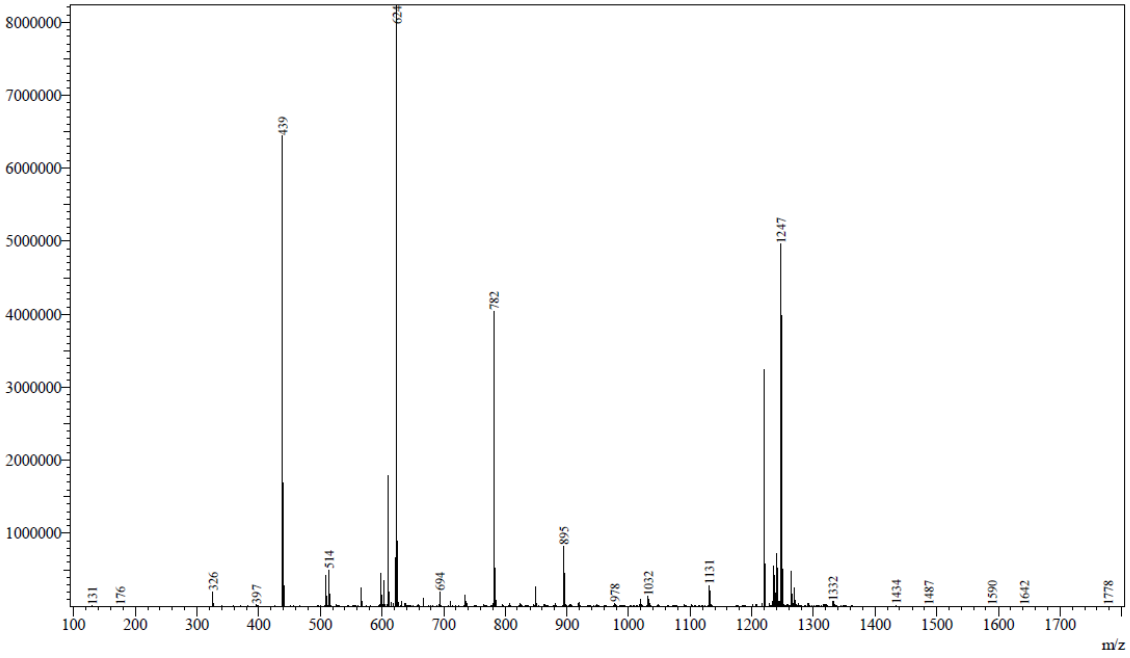
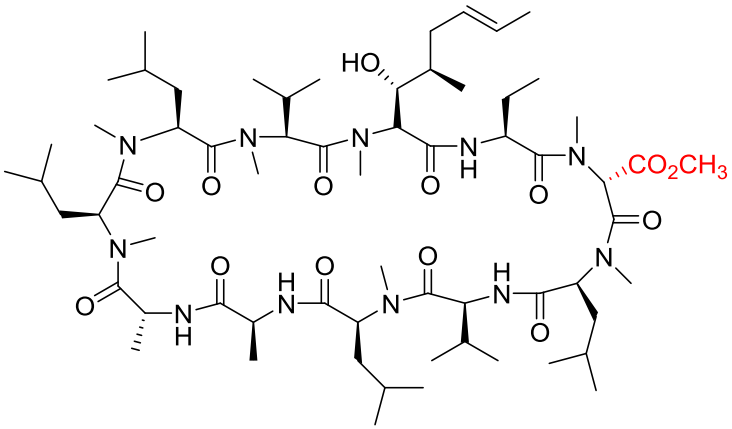
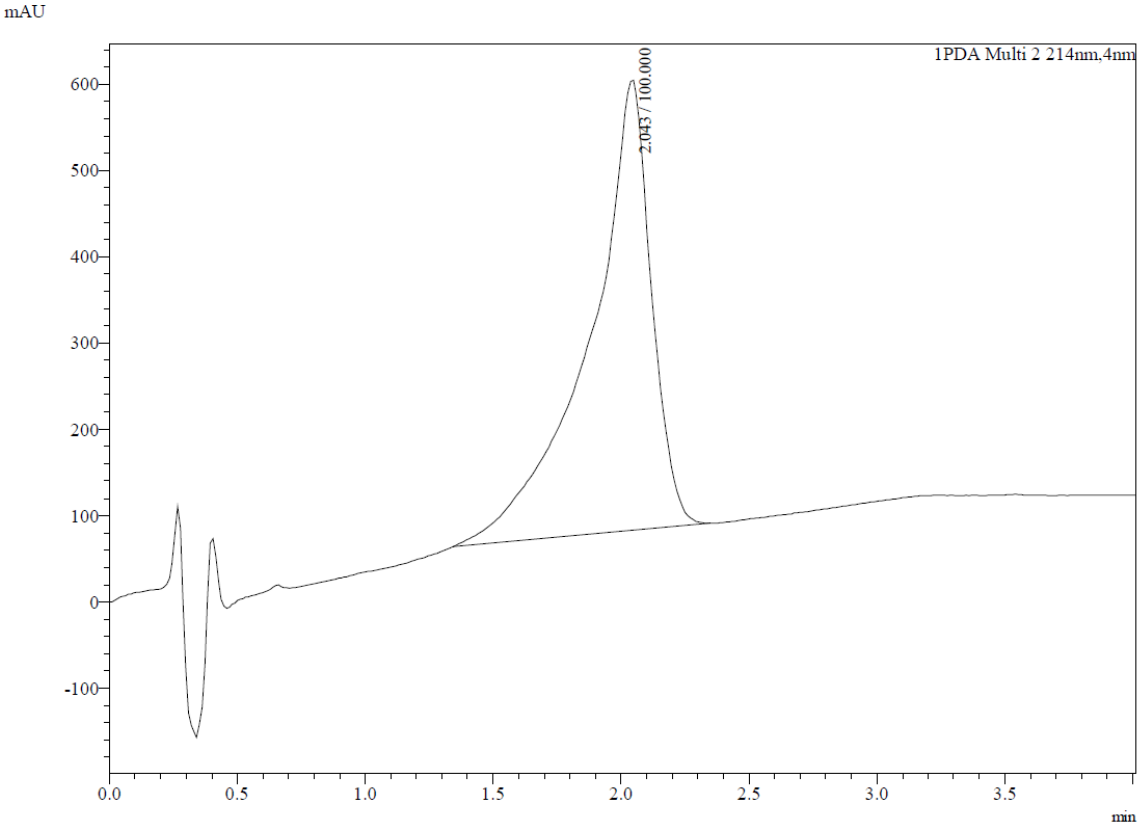




15

methyl (2S,5S,8S,11S,14S,17R,20S,23S,26S,29R,32S)-32-ethyl-29-((2R,E)-1-hydroxy-2-methylhex-4-en-1-yl)-5,11,20,23-tetraisobutyl-8,26-diisopropyl-1,4,10,14,17,19,22,25,28-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontane-2-carboxylate **(15)**

To a solution of **14** (0.096 g. 0.077 mmoL) in dimethylformamide (10 mL) was added potassium carbonate (39 mg, 0.285 mmol) and methyl iodide (24 μL, 0.385 mmol). The resulting mixture was stirred at ambient temperature for 14 hours. Then dichloromethane (3 mL) and water (3 mL) were added. The mixture was separated and the organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude was purified by preparative HPLC and provided **15** as a white solid.[5] The product was characterized by LC/MS. Calculated m/z 1260.8 $(M+1H)^{1+}$, m/z 630.9 $(M+2H)^{2+}$; found m/z 1262 $(M+1H)^{1+}$, m/z 631 $(M+2H)^{2+}$.



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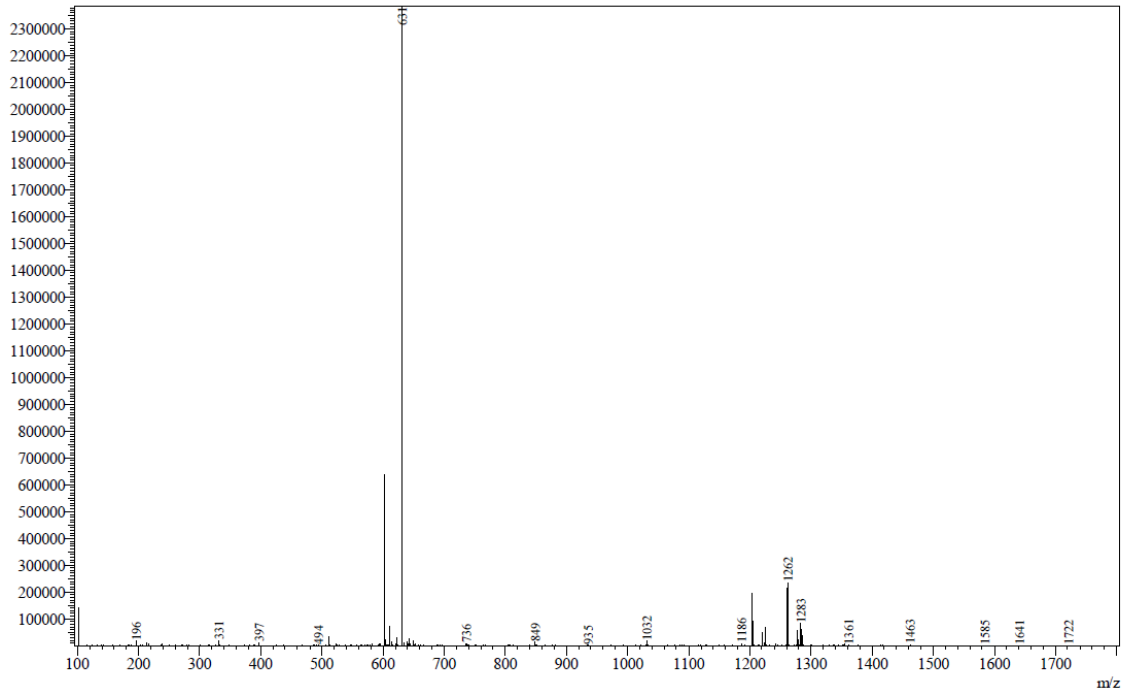
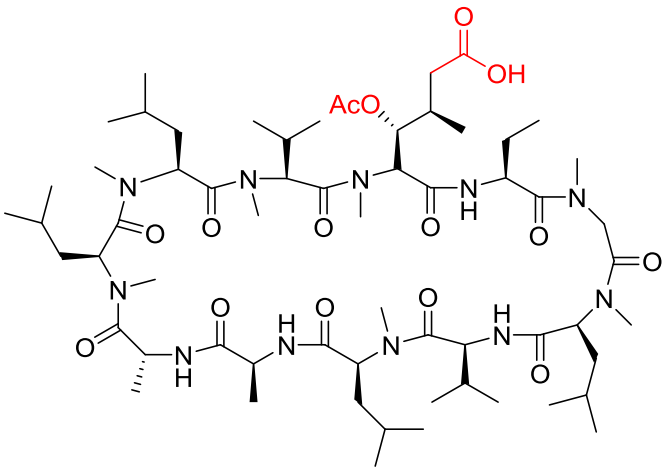
BG Mode:Calc Segment 1 - Event 1

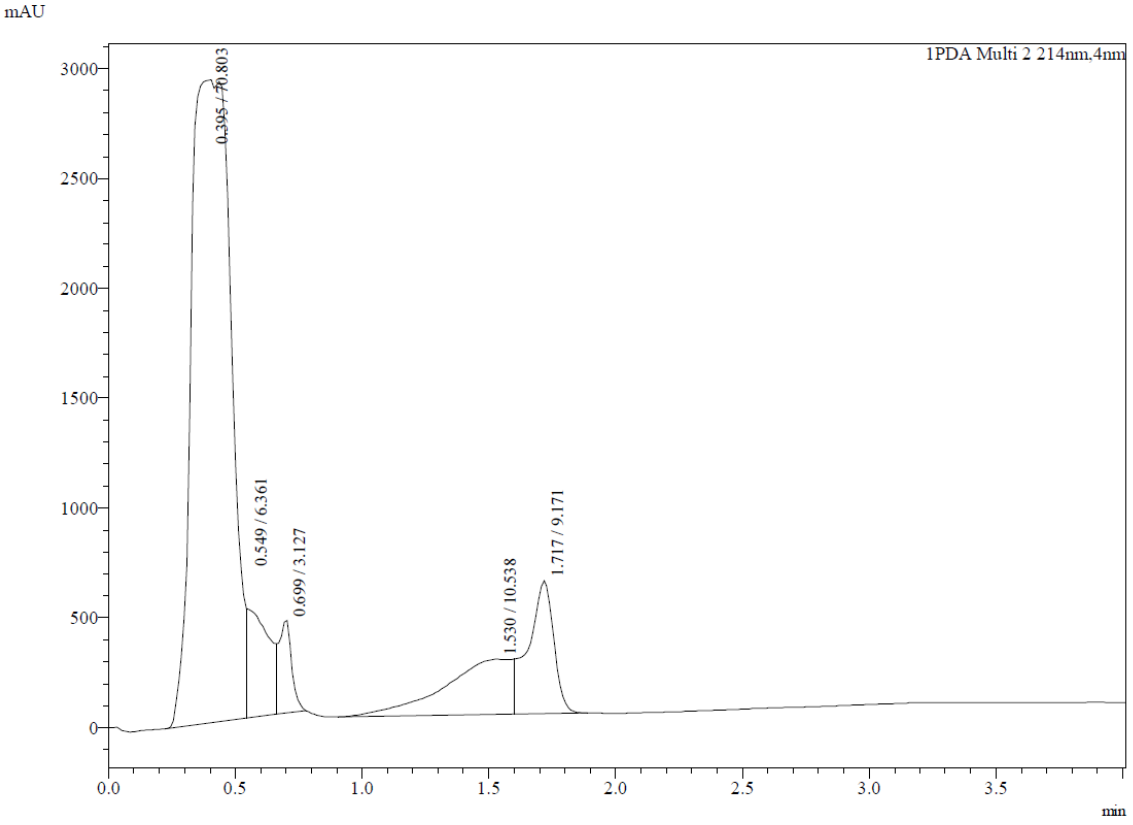




16

(3R)-4-acetoxy-4-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-3-methylbutanoic acid **(16)**

To a solution of **11** (1.03 g, 0.83 mmol) in *tert*-butanol (120 mL) were added potassium carbonate solution (33 mL, 0.15 M) and sodium periodate (33 mL, 0.2 M). Distilled water was added into the mixture until all sodium periodate had dissolved. Then potassium permanganate (6.6 mL, 0.025 M) was added and the resulting mixture was stirred for 14 hours under nitrogen. Then an additional 6.6mL of 0.025M potassium permanganate was added to the reaction mixture. Stirring at room temperature under nitrogen was continued for an additional 6 hours before quenching by sodium thiosulfate solution (20 mL, 40%). The reaction was extracted with dichloromethane (3 × 10 mL). The organic layer was collected, dried by anhydrous magnesium sulfate, concentrated, and purified by flash column chromatography using methanol/dichloromethane (0-5%)and provided **16** as a white solid (0.85 g, 0.07 mmol, yield 82%)[6]. The product was characterized by LC/MS. Calculated m/z 1248.8 $(M+1H)^{1+}$, m/z 624.9 $(M+2H)^{2+}$; found m/z 1249 $(M+1H)^{1+}$, m/z 626 $(M+2H)^{2+}$.



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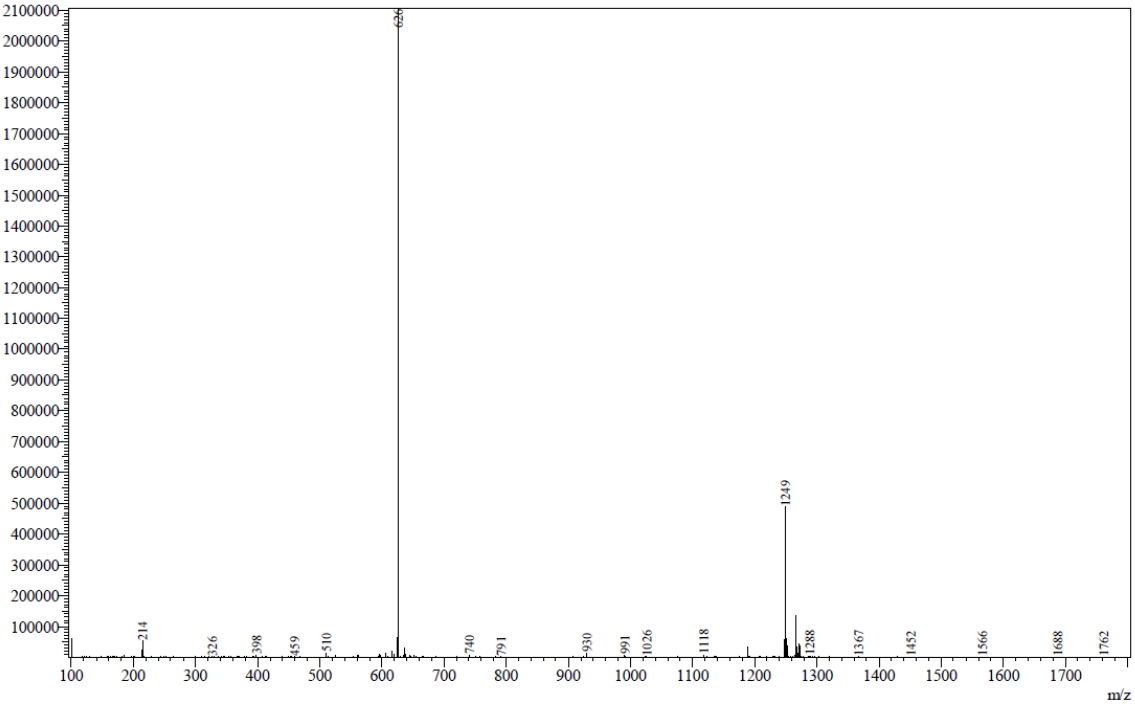
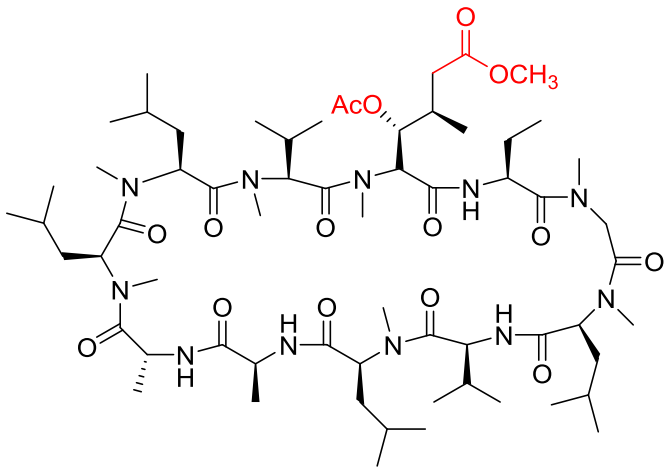
MassPeaks:777
Spectrum Mode:Averaged 1.741-1.748(494-496)
BG Mode:Calc Segment 1 - Event 1

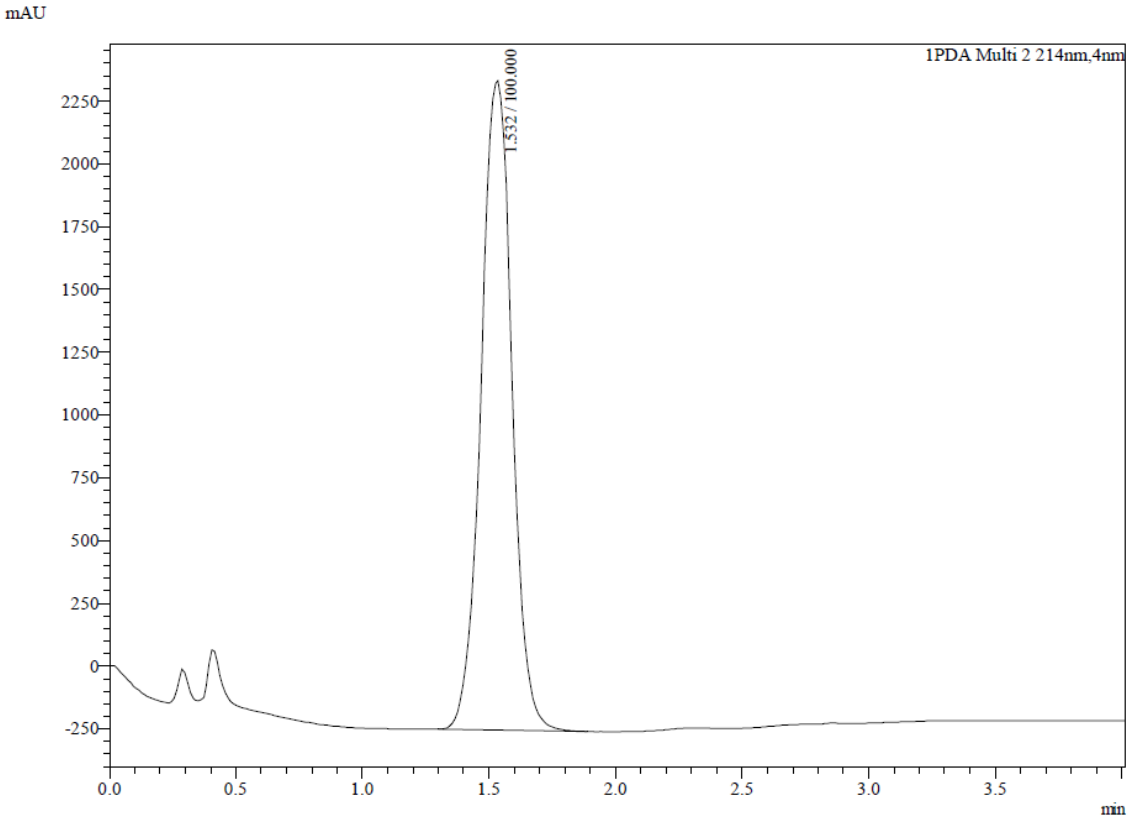




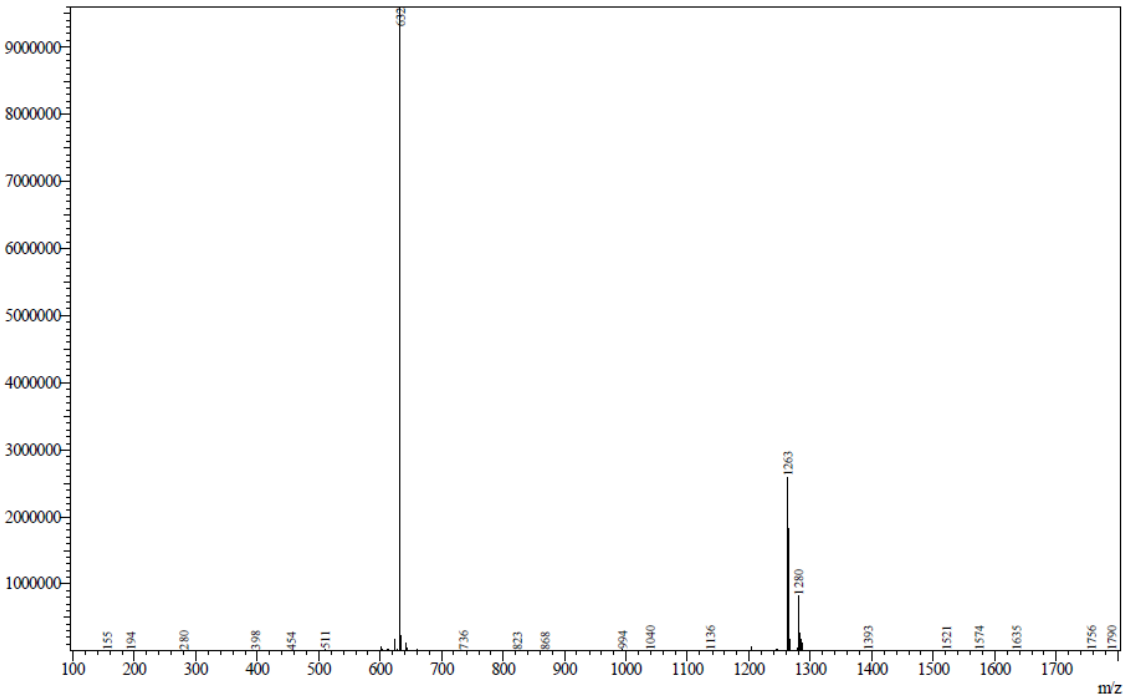
17

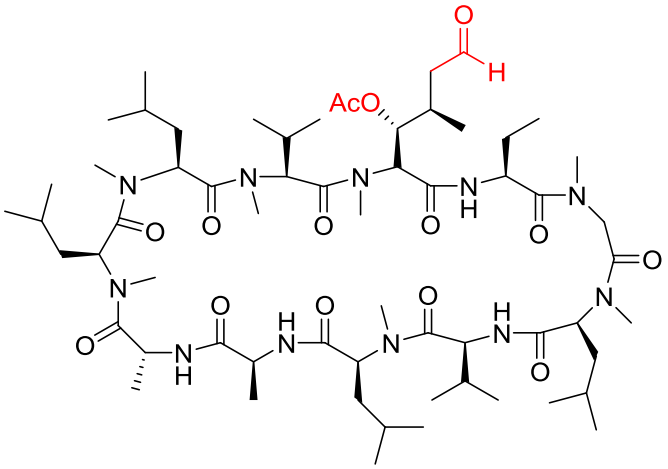
methyl (3R)-4-acetoxy-4-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-3-methylbutanoate **(17)**

To a solution of **16** (122 mg. 0.098 mmoL) in dimethylformamide (2 mL) was added potassium carbonate (50 mg, 0.36 mmol) and methyl iodide (31 µL, 0.49 mmol). The resulting mixture was stirred at ambient temperature for 14 hours. Then dichloromethane (5 mL) and water (5 mL) were added. The mixture was separated and the organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude was purified by preparative HPLC and provided **17** as a white solid. The product was characterized by LC/MS. Calculated m/z 1262.8 $(M+1H)^{1+}$, m/z 631.9 $(M+2H)^{2+}$; found m/z 1263 $(M+1H)^{1+}$, m/z 632 $(M+2H)^{2+}$.



Peak#:2 R.Time:1.550(Scan#:442)
MassPeaks:637
SpectrumMode:Averaged 1.547-1.554(441-443)
BGMode:Calc Segment 1 - Event 1

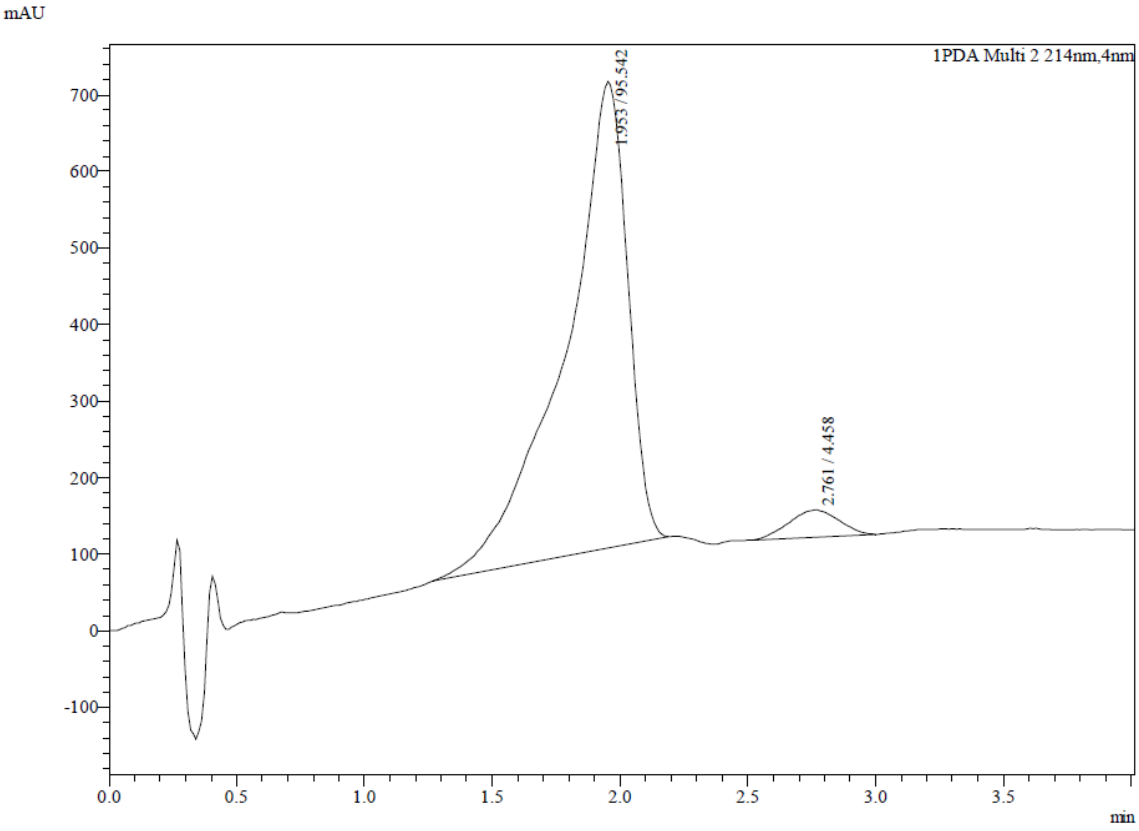




18

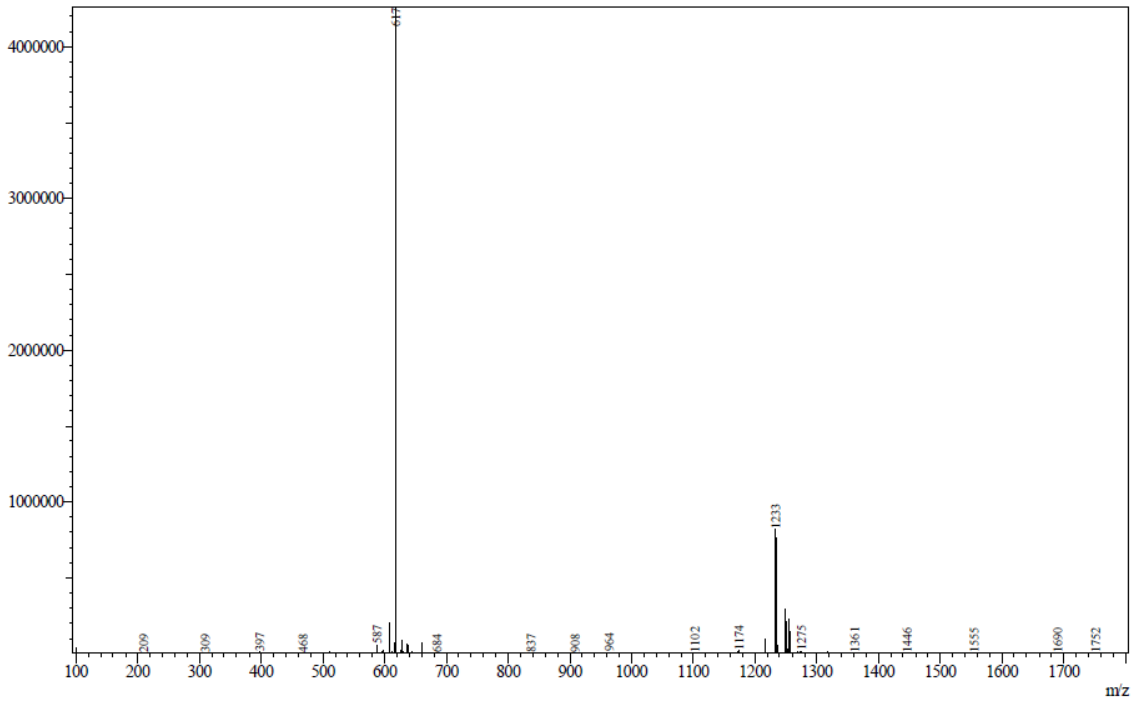
(2R)-1-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-2-methyl-4-oxobutyl acetate **(18)**

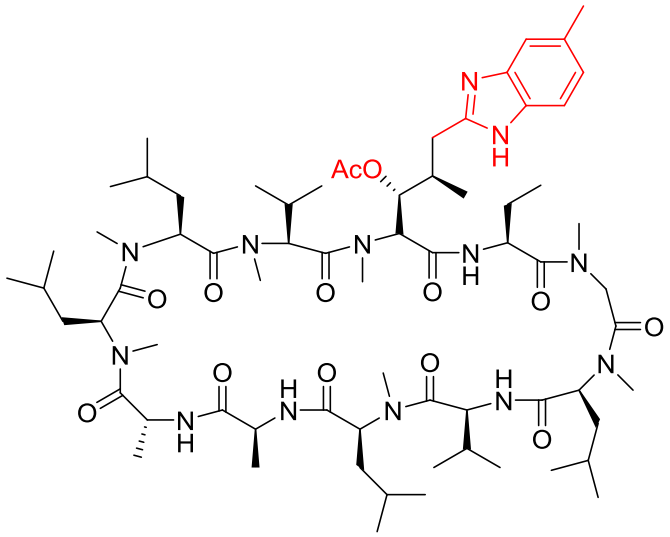
To a solution of **11** (0.83 mmol) and ruthenium(III) Chloride hydrate (9 mg, 0.041 mmol) in acetonitrile (10 mL) and water (1.3 mL) was added dropwise a solution of sodium periodate (355 mg; 1.66 mmol) in water (2.3 mL). The mixture was stirred overnight at room temperature. Ethyl acetate (60 mL) was added, and the solution was washed with brine (3 × 30 mL). The organic layer was dried over magnesium sulfate and concentrated. The crude was purified by preparative HPLC and provided **18** as a white solid.[7] The product was characterized by LC/MS. Calculated m/z 1232.8 $(M+1H)^{1+}$, m/z 616.9 $(M+2H)^{2+}$; found m/z 1233 $(M+1H)^{1+}$, m/z 617 $(M+2H)^{2+}$.



Mass Spectrum

Peak#:1 R.Time:1.954(Scan#:552)
MassPeaks:692
Spectrum Mode:Averaged 1.950-1.957(551-553)
BG Mode:Calc Segment 1 - Event 1

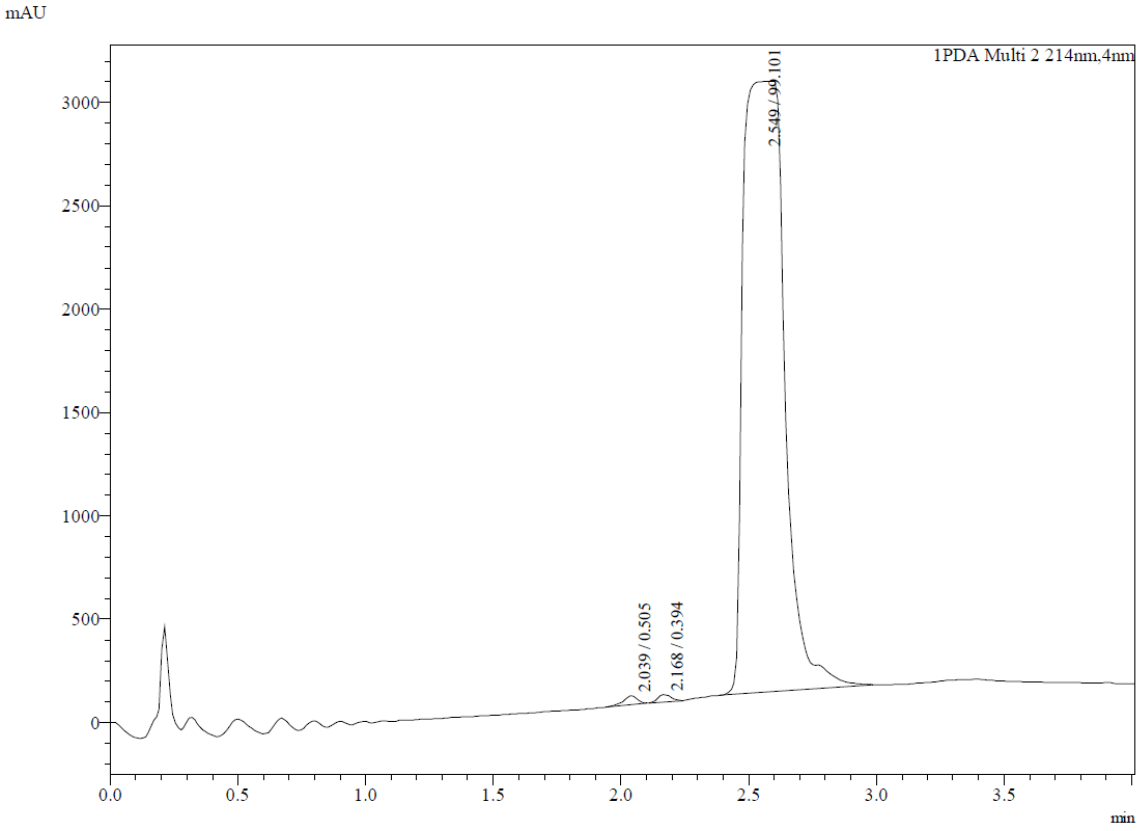




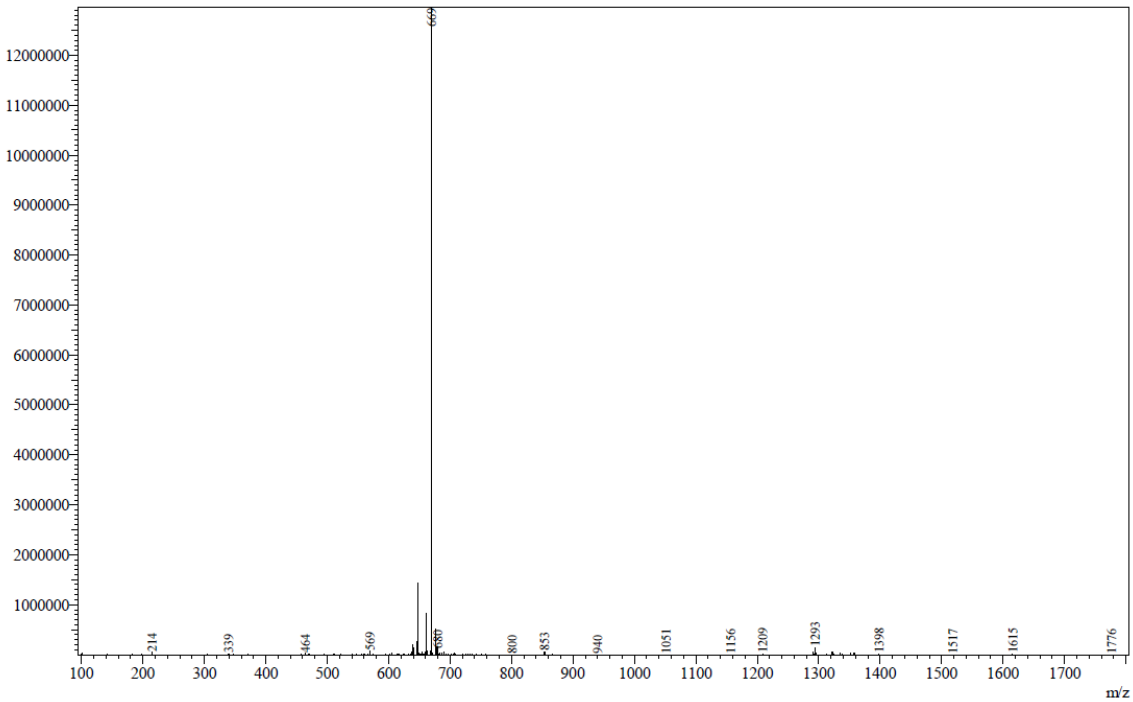
19

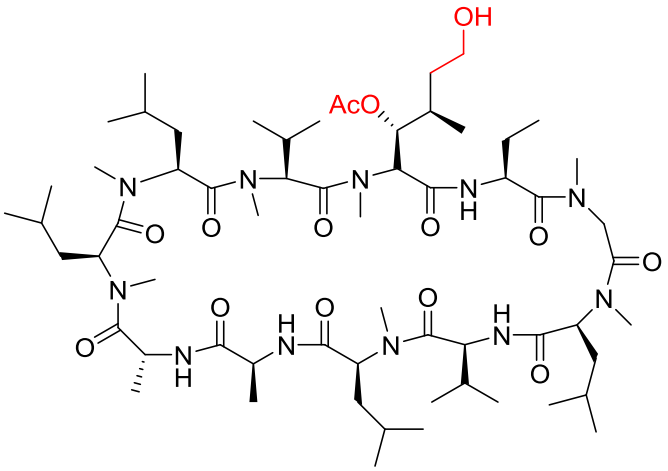
(2R)-1-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-2-methyl-3-(5-methyl-1H-benzo[d]imidazol-2-yl)propyl acetate **(19)**

To a solution of **18** in dimethylformamide was added 3,4-diaminotoluene. The solution was stirred in an open flask at room temperature for 14 hours. Solvents were evaporated and the acetyl group was hydrolyzed with a solution of 0.1 M sodium hydroxide in 50% methanol at 5 °C. The solution was acidified with diluted HCl (1 M), purified by preparative HPLC to provide **19** as a white solid.[7] The product was characterized by LC/MS. Calculated m/z 1334.9 $(M+1H)^{1+}$, m/z 667.9 $(M+2H)^{2+}$; found m/z 669 $(M+2H)^{2+}$.



Peak#:4 R.Time:2.522(Scan#:707)
MassPeaks:981
Spectrum Mode:Averaged 2.518-2.526(706-708)
BG Mode:Calc Segment 1 - Event 1

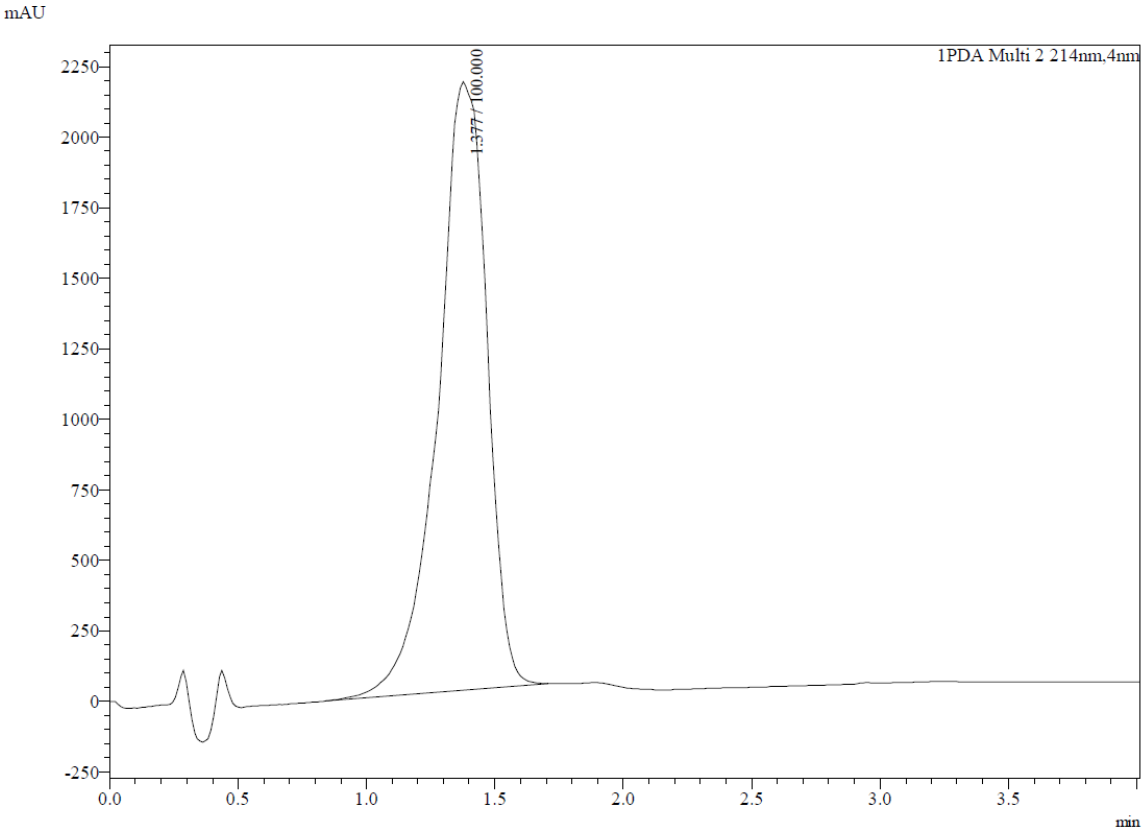




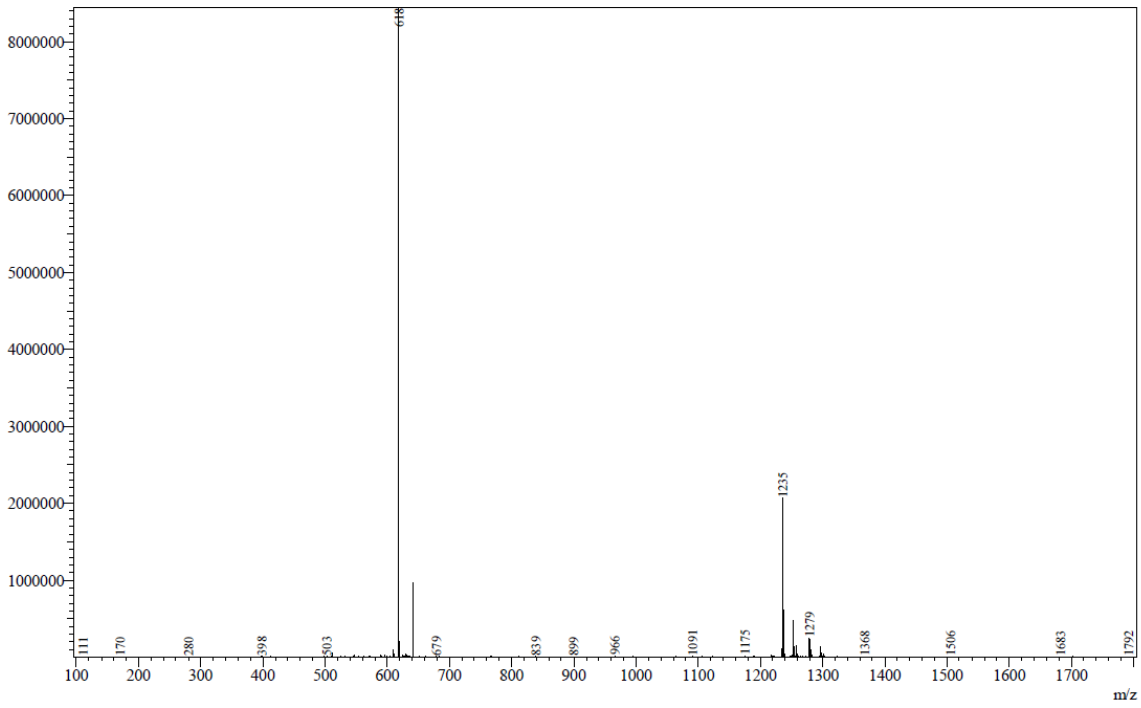
20

(2R)-1-((2R,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undecaoxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-4-hydroxy-2-methylbutyl acetate **(20)**

To a solution of **18** (91 mg, 0.073 mmol) in methanol (1.5 mL) at 0 °C was added sodium borohydride (14 mg) and stirred for 1 hour at 0 °C. The reaction was allowed to warm up to room temperature and stirred 2 hours before quenching with saturated ammonium chloride solution. The mixture was extracted by dichloromethane (3 × 5 mL) and the organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude was purified by preparative HPLC and provided **20** as a white solid. The product was characterized by LC/MS. Calculated m/z 1234.8 $(M+1H)^{1+}$, m/z 617.9 $(M+2H)^{2+}$; found m/z 1235 $(M+1H)^{1+}$, m/z 618 $(M+2H)^{2+}$.



Peak#:2 R.Time:1.421(Scan#:407)
MassPeaks:828
Spectrum Mode:Averaged 1.418-1.426(406-408)
BG Mode:Calc Segment 1 - Event 1



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