Supplemental Information

Novel Urea- and Piperazine-Functionalized Alepterolic Acid Derivatives: Synthesis, Anticancer Activity, and Mechanism of Action

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General Information for Chemical Synthesis

To a 500 mL round-bottom flask charged with alepterolic acid (4.99 mmol, 1.60 g, 1.00 eq) in CH_2Cl_2 (200 mL) were added *N*,*N*-diisopropylethylamine (DIPEA, 9.98 mmol, 1.74 mL, 2.00 eq) and HATU (7.49 mmol, 2.85 g, 1.50 eq). The mixture was stirred at room temperature with magnetic stirring for 1 h. The alepterolic acid was converted into the activated ester intermediate as confirmed by TLC (CH_2Cl_2: MeOH = 10:1). The resulting solution of activated ester intermediate was then added dropwise to a solution of piperazine (14.97 mmol, 1.29 g, 3.00 eq) in CH_2Cl_2 (200 mL). The resulted mixture was stirred at room temperature overnight. The reaction was quenched with water, extracted three times with CH_2Cl_2. The organic layer was washed once with saturated NaCl solution and then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (200- 300 mesh) to yield the intermediate **13** as white solid (yield: 95%).

For synthesis of the target compounds **14a~14g** and **15a~15t**, intermediate **13** (0.15 mmol, 58.29 mg, 1.50 eq) and DIPEA (0.30 mmol, 0.05 mL, 3.00 eq) was added to the solution of the isocyanate (0.30 mmol, 3.00 eq). The reaction was carried out at room temperature with stirring for 1 h. The reaction was confirmed to be complete by TLC (CH_2Cl_2: MeOH = 10:1). The solution was purified by silica gel column chromatography (200- 300 mesh) to obtain the target products. The isocyanates were commercially purchased, except from **14a**, **15s** and **15t**. These three isocyanates prepared from the reaction of corresponding amines (0.30 mmol, 3.00 eq), triphosgene (0.10 mmol, 1.00 eq) and DIPEA (0.60 mmol, 0.10 mL, 6.00 eq) in situ. The reaction was conducted in ice water for 1h to obtain as crude products, which used without further purification (yield: 70-96%).

For synthesis of the target compounds **15u~15x**, compound **13** (0.15 mmol, 58.29 mg, 1.50 eq) and DIPEA (0.30 mmol, 0.05 mL, 3.00 eq) was added to the solution of the isocyanate (0.08 mmol, 0.75 eq). The next operations were similar to the synthesis of **14a** (yield: 91-96%).

Detailed Information of Cell Lines Used in This Study

A549 human non-small cell lung cancer cells, MCF-7 human breast cancer cells, and LX-2 human normal hepatic cells were purchased from Shanghai Fuheng Biotechnology Co., Ltd (Shanghai, China). HepG2 cells were purchased from National Collection of Authenticated Cell Cultures, Chinese Academy of Sciences (Shanghai, China). H460 human large cell lung cancer cells and MDA-MB-231 human triple-negative breast cancer cells were purchased from Procell Life Science & Technology Co., Ltd. (Wuhan, China). 16HBE cells are a gift from Prof. Zi Liu, originally provided

by the Cell Resource Center of the Chinese Academy of Medical Sciences (Beijing, China)

Cell Viability Assay

Cells in exponential growth phase with good viability were selected and processed to generate a homogeneous single-cell suspension. Compounds were added, followed by continued incubation. After 72 h of treatment, 20 μL of MTT reagent was added to each well, and the incubation was prolonged for an additional 3 h. Subsequently, 100 μL solution (10% sodium dodecyl sulfate [SDS], 5% iso-butanol, 0.01 M hydrochloric acid [HCl]) was introduced into each well. Following a 12-h incubation period, the absorbance was measured at 570 nm using a microplate reader. Cell viability, inhibition rate, and half-maximal inhibitory concentration (IC_{50}) values for each compound were subsequently calculated using Microsoft Excel and GraphPad Prism software.

Cloning Assay

A549 cells in the logarithmic growth phase were selected and processed to generate a homogeneous single-cell suspension. Following 24 h of initial incubation, compounds were added (1, 2, 4 μM), and the incubation was continued for an additional 24 h. Subsequently, the culture medium was replaced with fresh medium, and the cells were further cultured. Fresh medium was renewed every 48 h until visible cell colonies emerged. After that, medium was discarded, and 1 mL of fixing agent (10% acetic acid, 10% methanol, 80% ultrapure water) was added to each well. After 15 min, the fixative was removed, and each well was rinsed with 1 mL PBS. Thereafter, 1 mL of crystal violet staining solution was added to each well. After 1 min, the crystal violet solution was recovered. The 6-well plate was gently rinsed for 30 s, then inverted on a clean bench and air-dried naturally. Images of the cell colonies were captured, and data analysis was performed using ImageJ and GraphPad Prism 8.0 software, followed by graph plotting.

Scratch Wound Healing Assay

A 6-well plate was prepared, and three parallel lines were marked at the bottom of each well. A549 cells in good growth status were selected, and the cells were plated at a density of 3.0×10^5 per well. A homogeneous single-cell suspension was prepared and seeded into the pre-marked 6-well plate. After 24 h, the scratch wound was made. Next, compounds were added to the corresponding wells, and images were captured at the pre-marked positions. The cells were continuously cultured for an additional 72 h, after which cell migration was observed and images were captured again at the same marked positions. Image analysis was performed using ImageJ software to measure scratch widths. Statistical analysis of the data was conducted using GraphPad Prism 8.0

software, and graphs were generated. The scratch healing rate was calculated using the following formula:

Scratch healing rate = (Scratch width at 0 h / Scratch width at 72 h) / Scratch width at 0 h × 100%

Cell Proliferation Assay

A549 cells in good growth status were selected and prepared to be a homogeneous single-cell suspension with a density of 1.0×10^5 cells/mL. The cell suspension was seeded at a volume of 2 mL per well. Experimental groups were set up with incubation time at 24 h, 48 h, and 72 h. After 24 h, compounds were added to the corresponding groups. At 24 h, 48 h, and 72 h, cell counts were determined using a cell counter. Finally, cell growth curves were plotted using GraphPad Prism software.

Cell Morphology Observation Assay

A549 cells in good growth status were selected and processed to a homogeneous single-cell suspension. The suspension was seeded into a 6-well plate at a density of 3.0×10^5 cells with a total volume of 2 mL per well. After 24 h of incubation, compounds at different concentrations were added to the respective wells. Following an additional 24 h of continuous incubation, the cells were observed under a phase-contrast microscope, and images were captured.

Nuclear Morphology Observation Assay

A549 cells in good growth status were selected and processed to a homogeneous single-cell suspension. The suspension was seeded into culture wells at a density of 2.0×10^5 cells with a total volume of 2 mL per well. After 24 h of incubation, compounds were added, and the incubation was continued for an additional 24 h. Subsequently, the supernatant was discarded, and 1 mL of cell staining buffer was added to each well, followed by the addition of 5 μL of Hoechst staining solution. The mixture was gently mixed and incubated on ice or at 4 °C for 20–30 min. After incubation, the cells were washed with PBS. One drop of fluorescence enhancer was added, and the cell-bearing coverslip was then inverted onto the slide. The samples were observed under a fluorescence microscope, and images were captured.

Cell Cycle Detection Assay

A549 cells in good growth status were selected and processed to a homogeneous single-cell suspension. The suspension was seeded into wells at a density of 3.0×10^5 cells with a total volume of 2 mL per well. After 24 h, compounds at different concentrations were added, and the incubation was continued for an additional 24 h. Subsequently, cell cycle detection was performed strictly following the manufacturer's

instructions provided by the cell cycle detection kit (Beyotime Biotechnology Co., Ltd.). Data analysis was performed using GraphPad Prism 8.0 software, and graphs were generated.

Apoptosis Detection Assay

A549 cells in good growth status were selected and processed to a homogeneous single-cell suspension. The suspension was seeded into wells at a density of 3.0×10^5 cells with a total volume of 2 mL per well. After 24 h of initial incubation, compounds were added, and the incubation was cultured for an additional 24 h. Subsequently, the staining solution was prepared in strict accordance with the instructions provided with the Beyotime Apoptosis Detection Kit, followed by the performance of relevant subsequent staining and detection procedures.

Mitochondrial Membrane Potential Detection Assay

A549 cells in good growth status were selected and processed to a homogeneous single-cell suspension. The suspension was seeded into wells at a density of 3.0×10^5 cells with a total volume of 2 mL per well, followed by initial incubation. After 24 h, test compounds were added, and incubation was continued for 24 h. Subsequently, carbonyl cyanide 3-chlorophenylhydrazone (CCCP), a positive control agent, was added to the positive control wells at a dilution ratio of 1:1000 for 20 min. Concurrently, relevant staining solutions were prepared and subsequent staining operations were performed in strict accordance with the instructions provided with the Beyotime Mitochondrial Membrane Potential Detection Kit.

Western blotting

Proteins were extracted using SDS lysis buffer and subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Subsequently, proteins separated on the gel were transferred onto a nitrocellulose membrane (NC membrane). The membrane was blocked with 5% non-fat milk in Tris-buffered saline containing Tween 20 (TBST). The aforementioned antibodies were used as primary antibodies for membrane probing, followed by incubation with a horseradish peroxidase (HRP)-conjugated secondary antibody. Target proteins on the membrane were visualized using an enhanced chemiluminescence (ECL) kit (Proteintech Group, Inc.). The density of the protein bands was quantitatively analyzed using ImageJ software.

ADMET Analysis

The physicochemical properties and pharmacokinetic profiles of the target compounds were evaluated using two online web databases: ADMET Lab 3.0 (https://admetlab3.scbdd.com/) and SwissADME (http://www.swissadme.ch/). These

properties primarily include five key aspects of drug disposition: absorption, distribution, metabolism, excretion, and toxicity (ADMET).

Protein Docking

The apoptotic protein structures were retrieved on online databases, including UniProt (https://www.uniprot.org/) and RCSB PDB (https://www.rcsb.org/). Compound structures were drawn using ChemDraw 20.0 software. AutoDock Tools software was employed to perform pre-docking optimization of both compound and apoptotic proteins, involving water molecule removal and hydrogenation; subsequently, the docking free energy was calculated. The binding modes of compound with apoptotic proteins were visualized using PyMOL software, and the resulting images were edited using PowerPoint software.

1□. Protein and PDB ID: Caspase-3（1GFW）、Bax（4BD6）、Bcl-2（1G5M）、Caspase-9 （2AR9）、PARP-1（4OPX）
2□. Software: AutoDockTools-1.5.7
3□. Scoring function: Vina default scoring
4□. Exhaustiveness: 8
5□. Flexible handling strategy: Rigid frame, flexible side chain
6□. Website for protein structures: https://www.uniprot.org/;https://www.rcsb.org/
7□. Treatment of small molecule ligands: Minimum binding free energy（ChemDraw 20.0; Chem3D 20.0 ）
8□. Grid spacing: 0.375 Å
9□. Clustering algorithms and clustering thresholds: No built-in clustering
10□. CPU model: Intel® Core (TM) i5-3210M CPU @ 2.50 GHZ 2.50GHZ
11□. OS version: Win_64 flagship version
12□. Connect pocket parameters (See Table 1 and Table 2)

Table 1. the connect pocket parameters of compound **15o**

Caspase-3	Bax	Bcl-2	Caspase-9	PARP-1
center x = 26.71	center x =-16.34	center x = 3.061	center x = 23.957	center x = 17.644
center y = 22.591	center y = -9.58	center y = -9.58	center y = 33.011	center y = 33.011
center z = 37.128	center z = 8.335	center z = 2.734	center z = 27.123	center z = 31.626
size x = 66.15	size x = 70.7	size x = 68.46	size x = 111.16	size x = 126.0
size y = 66.15	size y = 70.7	size y = 68.46	size y = 111.16	
size z = 66.15	size z = 70.7	size z = 68.46	size z = 111.16	

				size y = 126.0 size z = 126.0

Table 2. the connect pocket parameters of compound **15u**

Caspase-3	Bax	Bcl-2	Caspase-9	PARP-1
center x = 26.71 center y = 22.591 center z = 37.128 size x = 53.9 size y = 53.9 size z = 53.9	center x = -16.94 center y = -16.647 center z = -0.94 size x = 69.3 size y = 69.3 size z = 69.3	center x = 1.954 center y = -3.058 center z = 3.202 size x = 54.46 size y = 54.46 size z = 54.46	center x = 19.547 center y = 38.445 center z = 23.65 size x = 105.0 size y = 105.0 size z = 105.0	center x = 19.547 center y = 51.59 center z = 36.625 size x = 126.0 size y = 126.0 size z = 126.0

Data Processing and Statistical Analysis

All experiments were performed in triplicate at minimum. Image processing was conducted using Photoshop software, while cell count and quantitative analysis of band densities were performed using ImageJ software. Data collation and statistical analysis were carried out using GraphPad Prism 8.0 software, with statistical graphs generated simultaneously. Statistical comparisons were performed using the t-test. In the graphs, statistical significance was denoted as follows: *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Structural characterization of synthetic compounds

N-Butyl-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14a**)

Colorless oil, yield 70%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 4.86 (s, 1H), 4.51 (s, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 3.71 – 3.59 (m, 2H), 3.53 – 3.46 (m, 2H), 3.46 – 3.38 (m, 2H), 3.38 – 3.28 (m, 2H), 3.28 – 3.18 (m, 3H), 2.40 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.29 – 2.20 (m, 1H), 1.99 – 1.89 (m, 2H), 1.88 (s, 3H), 1.80 – 1.55 (m, 7H), 1.49 (t, *J* = 6.6 Hz, 3H), 1.40 – 1.30 (m, 3H), 1.15 (td, *J* = 13.1, 3.8 Hz, 1H), 1.06 (dd, *J* = 12.5, 2.8 Hz, 1H), 0.98 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.76 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.54, 157.60, 150.94, 147.75, 116.78, 106.80, 78.72, 55.92, 54.67, 45.94, 43.91, 43.60, 40.75, 40.65, 39.41, 39.13, 38.57, 38.17, 37.09, 32.30, 28.30, 27.87, 23.99, 21.57, 20.09, 18.72, 15.41, 14.52, 13.81. HRMS calc for $C_{29}H_{50}N_3O_3$ [M+H] $^+$: 488.3852, found 488.3854. HPLC purity: 97.86%, retention time: 12.640 min.

N-(tert-Butyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14b**)

Colorless oil, yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.84 (s, 1H), 4.49 (s, 1H), 4.33 (s, 1H), 3.67 – 3.58 (m, 2H), 3.50 – 3.42 (m, 2H), 3.38 – 3.31 (m, 2H), 3.30 – 3.23 (m, 2H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.38 (dt, *J* = 12.3, 3.2 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.97 – 1.89 (m, 2H), 1.86 (s, 3H), 1.77 – 1.51 (m, 7H), 1.39 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.32 (s, 9H), 1.12 (td, *J* = 13.1, 3.6 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.96 (s, 3H), 0.74 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.53, 156.74, 150.83, 147.75, 116.80, 106.79, 78.68, 55.90, 54.67, 50.98, 45.92, 44.07, 43.42, 40.74, 39.40, 39.13, 38.55, 38.16, 37.10, 29.40, 28.33, 27.86, 23.99, 21.56, 18.71, 15.43, 14.50. HRMS calc for $C_{29}H_{50}N_3O_3$ [M+H] $^+$: 488.3852, found 488.3856. HPLC purity: 98.66%, retention time: 12.953 min.

N-Cyclopentyl-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14c**)

Colorless oil, yield 91%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.83 (s, 1H), 4.53 (s, 1H), 4.48 (s, 1H), 4.07 – 4.01 (m, 1H), 3.69 – 3.57 (m, 2H), 3.51 – 3.43 (m, 2H), 3.42 – 3.36 (m, 2H), 3.33 – 3.24 (m, 2H), 3.21 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.37 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.26 – 2.18 (m, 1H), 1.99 – 1.86 (m, 4H), 1.84 (s, 3H), 1.77 – 1.49 (m, 11H), 1.39 – 1.27 (m, 3H), 1.12 (td, *J* = 13.2, 3.9 Hz, 1H), 1.03 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.95 (s, 3H), 0.73 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.60, 157.39, 150.91, 147.78, 116.79, 106.82, 78.67, 55.93, 54.70, 52.70, 45.98, 43.91, 43.60, 40.79, 39.43, 39.16, 38.57, 38.20, 37.14, 33.53, 28.36, 27.87, 24.03, 23.72, 21.59, 18.77, 15.49, 14.54. HRMS calc for $C_{30}H_{50}N_3O_3$ [M+H] $^+$: 500.3852, found 500.3855. HPLC purity: 98.66%, retention time: 12.953 min.

N-Cyclohexyl-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14d**)

Colorless oil, yield, 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.82 (s, 1H), 4.47 (s, 1H), 4.44 (s, 1H), 3.68 – 3.54 (m, 3H), 3.52 – 3.43 (m, 2H), 3.42 – 3.34 (m, 2H), 3.33 – 3.25 (m, 2H), 3.20 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.37 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.26 – 2.15 (m, 1H), 1.96 – 1.85 (m, 4H), 1.84 (s, 3H), 1.78 – 1.44 (m, 10H), 1.38 – 1.25 (m, 3H), 1.16 – 1.06 (m, 3H), 1.03 (dd, *J* = 12.5, 2.3 Hz, 2H), 0.95 (s, 3H), 0.73 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 156.92, 150.92, 147.77, 116.77, 106.82, 78.67, 55.91, 54.68, 49.66, 45.97, 43.88, 43.59, 40.78, 39.42, 39.16, 38.55, 38.19, 37.12, 33.92, 28.36, 27.84, 25.65, 25.11, 24.01, 21.57, 18.78, 15.50, 14.54. HRMS calc for $C_{31}H_{52}N_3O_3$ $[M+H]^+$: 514.4009, found 514.4008. HPLC purity: 100.00%, retention time: 13.993 min.

N-Dodecyl-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14e**)

Light yellow oil, yield 88%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.84 (s, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.50 (s, 1H), 3.67 – 3.58 (m, 2H), 3.51 – 3.44 (m, 2H), 3.44 – 3.37 (m, 2H), 3.35 – 3.27 (m, 2H), 3.26 – 3.16 (m, 3H), 2.39 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.95 – 1.89 (m, 2H), 1.86 (s, 3H), 1.78 – 1.47 (m, 9H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.29 – 1.21 (m, 18H), 1.13 (td, *J* = 13.1, 3.9 Hz, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.85 (t, *J* = 6.7 Hz, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.61, 157.68, 150.99, 147.83, 116.86, 106.87, 78.76, 56.00, 54.76, 46.02, 44.00, 43.68, 41.16, 40.83, 39.49, 39.22, 38.65, 38.25, 37.19, 31.99, 30.31, 29.69, 29.43, 28.41, 27.95, 27.06, 24.08, 22.76, 21.66, 18.80, 15.51, 14.58, 14.20. HRMS calc for $C_{37}H_{65}N_3O_3Na$ $[M+Na]^+$: 622.4924, found 622.4926. HPLC purity: 97.06%, retention time: 16.613 min.

N-(2-Chloroethyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**14f**)

Colorless oil, yield 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.83 (s, 1H), 4.48 (s, 1H), 4.01 (s, 1H), 3.77 – 3.59 (m, 4H), 3.61 – 3.32 (m, 8H), 3.21 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.38 (d, *J* = 13.9 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.96 – 1.87 (m, 2H), 1.85 (s, 3H), 1.77 – 1.45 (m, 7H), 1.36 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.13 (td, *J* = 13.1, 3.9 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.96 (s, 3H), 0.74 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.68, 157.26, 151.20, 147.78, 116.70, 106.86, 78.74, 55.93, 54.68, 45.91, 44.78, 43.85, 43.69, 42.73, 40.82, 39.44, 39.17, 38.59, 38.20, 37.13, 28.38, 27.86, 24.02, 21.60, 18.82, 15.52, 14.57. HRMS calc for $C_{27}H_{44}ClN_3O_3Na$ $[M+Na]^+$: 516.2969, found 516.2972. HPLC purity: 95.89%, retention time: 11.217 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(2,2,2-trifluoroethyl) piperazine-1-carboxamide (**14g**)

Colorless oil, yield 87%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 5.23 (t, *J* = 6.5 Hz, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.89 (qd, *J* = 9.1, 6.3 Hz, 2H), 3.71 – 3.60 (m, 2H), 3.55 – 3.34 (m, 6H), 3.22 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.40 (dd, *J* = 12.8, 2.4 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.99 – 1.90 (m, 2H), 1.87 (s, 3H), 1.78 – 1.52 (m, 7H), 1.38 (qd, *J* = 12.9, 4.0 Hz, 1H), 1.14 (td, *J* = 13.2, 3.9 Hz, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.98 (s, 3H), 0.76 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.67, 156.60, 151.49, 147.85, 124.56 (q, *J* = 278.4 Hz), 116.67, 106.90, 78.84, 56.05, 54.79, 45.87, 44.04, 43.93, 43.85, 42.09 (q, *J* = 34.3 Hz), 40.77, 39.52, 39.24, 38.72, 38.27, 37.21, 28.41, 27.97, 24.10, 21.71, 18.83, 15.51, 14.60. HRMS calc for $C_{27}H_{43}F_3N_3O_3$ $[M+H]^+$: 514.3257, found 514.3255. HPLC purity: 100.00%, retention time: 11.797 min. ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.99.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-phenylpiperazine-1-carboxamide (**15a**)

Colorless oil, yield 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.14 (m, 4H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.38 (s, 1H), 5.65 (s, 1H), 4.78 (s, 1H), 4.43 (s, 1H), 3.68 – 3.59 (m, 2H), 3.48 – 3.35 (m, 6H), 3.15 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.32 (ddd, *J* = 12.7, 4.2, 2.3 Hz, 1H), 2.20 – 2.14 (m, 1H), 1.89 – 1.83 (m, 2H), 1.81 (s, 3H), 1.72 – 1.50 (m, 7H), 1.30 (qd, *J* = 13.0, 4.2 Hz, 3H), 1.08 (td, *J* = 13.2, 3.7 Hz, 1H), 0.98 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.90 (s, 3H), 0.68 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.70, 155.12, 151.53, 147.92, 138.81, 129.13, 123.65, 120.31, 116.79, 106.98, 78.92, 56.10, 54.84, 46.04, 44.50, 43.98, 40.96, 39.59, 39.30, 38.80, 38.34, 37.27, 28.48, 28.05, 24.16, 21.77, 18.93, 15.57, 14.68. HRMS calc for $C_{31}H_{45}N_3O_3Na$ $[M+Na]^+$: 530.3359, found 530.3358. HPLC purity: 99.69%, retention time: 12.207 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(p-tolyl) piperazine-1-carboxamide (**15b**)

Colorless oil, yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 5.71 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.70 – 3.58 (m, 2H), 3.52 – 3.38 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.39 (d, *J* = 2.4 Hz, 1H), 2.27 (s, 3H), 2.25 – 2.19 (m, 1H), 1.97 – 1.88 (m, 2H), 1.86 (s, 3H), 1.80 – 1.45 (m, 7H),1.35 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.13 (td, *J* = 13.1, 3.9 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.96 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.67, 155.52, 151.16, 147.78, 136.28, 133.00, 129.40, 120.72, 116.72, 106.86, 78.71, 55.97, 54.71, 45.99, 44.32, 43.84, 40.94, 39.45, 39.17, 38.61, 38.22, 37.16, 28.38, 27.88, 24.04, 21.62, 20.84, 18.83, 15.52, 14.56. HRMS calc for $C_{32}H_{47}N_3O_3Na$ $[M + Na]^+$: 544.3515, found 544.3514. HPLC purity: 98.96%, retention time: 14.637 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(o-tolyl) piperazine-1-carboxamide (**15c**)

Colorless oil, yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H), 7.18 – 7.10 (m, 2H), 7.02 (td, *J* = 7.4, 1.3 Hz, 1H), 6.51 (s, 1H), 5.70 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.69 – 3.59 (m, 2H), 3.50 – 3.36 (m, 6H), 3.21 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.30 – 2.21 (m, 1H), 2.20 (s, 3H), 1.98 – 1.89 (m, 2H), 1.87 (s, 3H), 1.78 – 1.46 (m, 7H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.10 (td, *J* = 3.9 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.96 (s, 3H), 0.74 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.62, 155.75, 151.27, 147.76, 136.66, 130.51, 130.44, 126.63, 124.87, 123.93, 116.62, 106.80, 78.67, 55.91, 54.66, 45.87, 44.32, 43.93, 40.81, 39.41, 39.12, 38.59, 38.17, 37.11, 28.33, 27.80, 23.99, 21.58, 18.78, 17.89, 15.47, 14.53. HRMS calc for $C_{32}H_{48}N_3O_3$ [M+H] $^+$: 522.3696, found 522.3700. HPLC purity: 98.34%, retention time: 13.540 min.

N-Benzyl-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15d**)

Colorless oil, yield 91%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 5H), 5.69 (s, 1H), 4.87 (t, *J* = 5.1 Hz, 1H), 4.84 (s, 1H), 4.49 (s, 1H), 4.40 (d, *J* = 5.3 Hz, 2H), 3.67 – 3.57 (m, 2H), 3.51 – 3.37 (m, 4H), 3.37 – 3.25 (m, 2H), 3.21 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.38 (ddd, *J* = 12.8, 4.3, 2.4 Hz, 1H), 2.26 – 2.17 (m, 1H), 1.96 – 1.87 (m, 2H), 1.86 (s, 3H), 1.77 – 1.50 (m, 7H), 1.36 (qd, *J* = 13.0, 4.3 Hz, 1H), 1.12 (td, *J* = 13.0, 3.9 Hz, 1H), 1.03 (dd, *J* = 12.5, 2.6 Hz, 1H), 0.96 (s, 3H), 0.74 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 157.48, 151.15, 147.84, 139.20, 128.79, 127.91, 127.56, 116.82, 106.91, 78.82, 56.00, 54.75, 45.99, 45.17, 44.02, 43.78, 40.84, 39.51, 39.23, 38.67, 38.27, 28.43, 27.96, 24.09, 21.66, 18.84, 15.53, 14.61. HRMS calc for $C_{32}H_{48}N_3O_3$ [M+H] $^+$: 522.3696, found 522.3698. HPLC purity: 100.00%, retention time: 13.213 min.

N-(3,5-Dimethylphenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15e**)

White powder solid, melt point: 119 ℃, yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 6.75 (s, 1H), 6.67 (s, 1H), 5.72 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.69 – 3.59 (m, 2H), 3.53 – 3.39 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.39 (ddd, *J* = 12.6, 4.2, 2.4 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.24 (s, 6H), 1.97 – 1.89 (m, 2H), 1.87 (s, 3H), 1.78 – 1.47 (m, 7H), 1.37 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.13 (td, *J* = 13.1, 3.8 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.64, 155.33, 151.22, 147.79, 138.67, 138.54, 125.20, 118.15, 116.72, 106.87, 78.73, 55.97, 54.72, 46.00, 44.40, 43.87, 40.93, 39.46, 39.18, 38.64, 38.23, 37.16, 28.40, 27.91, 24.05, 21.63, 21.45, 18.83, 15.51, 14.56. HRMS calc for $C_{33}H_{50}N_3O_3$ [M+H] $^+$: 536.3852, found 536.3853. HPLC purity: 100.00%, retention time: 15.820 min.

N-(4-Ethylphenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-

methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15f**)

White solid, melt point: 184 ℃, yield 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.85 (s, 1H), 5.71 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.69 – 3.59 (m, 2H), 3.53 – 3.39 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.39 (dd, *J* = 12.7, 2.4 Hz, 1H), 2.28 – 2.20 (m, 1H), 1.97 – 1.89 (m, 2H), 1.87 (s, 3H), 1.78 – 1.46 (m, 7H), 1.37 (qd, *J* = 13.1, 4.3 Hz, 1H), 1.18 (t, *J* = 7.6 Hz, 3H), 1.12 (td, *J* = 13.1, 3.8 Hz, 1H), 1.04 (dd, *J* = 12.4, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.64, 155.48, 151.18, 147.80, 139.51, 136.44, 128.25, 120.74, 116.74, 106.87, 78.72, 55.98, 54.72, 46.00, 44.35, 43.86, 40.93, 39.46, 39.19, 38.63, 38.23, 37.16, 28.40, 28.38, 28.28, 27.90, 24.05, 21.63, 18.84, 15.80, 15.53, 14.59. HRMS calc for $C_{33}H_{49}N_3O_3Na$ [M+ Na] $^{+}$: 558.3672, found 558.3669. HPLC purity: 100.00%, retention time: 15.873 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-phenethylpiperazine-1-carboxamide (**15g**)

Colorless oil, yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 6.6 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.17 (d, *J* = 7.1 Hz, 2H), 5.70 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.68 – 3.54 (m, 2H), 3.52 – 3.42 (m, 4H), 3.41 – 3.32 (m, 2H), 3.30 – 3.18 (m, 3H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.39 (ddd, *J* = 12.7, 4.3, 2.4 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.99 – 1.88 (m, 2H), 1.87 (s, 3H), 1.78 – 1.45 (m, 7H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.14 (td, *J* = 13.1, 3.8 Hz, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 157.50, 151.12, 147.81, 139.26, 128.89, 128.70, 126.55, 116.77, 106.87, 78.75, 55.97, 54.72, 45.96, 43.86, 43.62, 42.16, 40.75, 39.47, 39.20, 38.64, 38.23, 37.16, 36.30, 28.40, 27.90, 24.06, 21.63, 18.81, 15.53, 14.59. HRMS calc for $C_{33}H_{50}N_3O_3$ [M+H] $^{+}$:536.3852, found 536.3854. HPLC purity: 100.00%, retention time: 13.837 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(2-isopropylphenyl) piperazine-1-carboxamide (**15h**)

Colorless oil, yield 87%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 1H), 7.27 – 7.24 (m, 1H), 7.17 – 7.11 (m, 2H), 6.38 (s, 1H), 5.72 (s, 1H), 4.86 (s, 1H), 4.51 (s, 1H), 3.71 – 3.61 (m, 2H), 3.54 – 3.40 (m, 6H), 3.22 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.02 (p, *J* = 6.9 Hz, 1H), 2.40 (ddd, *J* = 12.7, 4.2, 2.3 Hz, 1H), 2.29 – 2.20 (m, 1H), 1.97 – 1.90 (m, 2H), 1.89 (s, 3H), 1.79 – 1.53 (m, 7H), 1.38 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.15 (td, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.59, 156.14, 151.32, 147.86, 141.38, 135.24, 126.40, 125.73, 125.45, 116.75, 106.86, 78.74, 56.02, 54.76, 45.94, 44.41, 44.03, 40.87, 39.50, 39.21, 38.72, 38.26, 37.20, 28.40, 28.12, 27.94, 24.08, 23.15, 21.69, 18.82, 15.51, 14.61. HRMS calc for $C_{34}H_{51}N_3O_3Na$ [M +Na] $^{+}$: 572.3828, found 572.3825.

HPLC purity: 100.00%, retention time: 15.267 min.

N-(4-Chlorophenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carbothioamide (**15i**)

Colorless oil, yield 89%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.25 (d, *J* = 9.4 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 5.69 (s, 1H), 4.84 (s, 1H), 4.47 (s, 1H), 3.99 – 3.91 (m, 2H), 3.79 – 3.65 (m, 4H), 3.61 – 3.50 (m, 2H), 3.21 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.38 (d, *J* = 13.0 Hz, 1H), 2.22 (t, *J* = 9.1 Hz, 1H), 1.95 – 1.88 (m, 2H), 1.86 (s, 3H), 1.75 – 1.49 (m, 7H), 1.36 (qd, *J* = 12.7, 3.8 Hz, 1H), 1.12 (td, *J* = 13.5, 3.9 Hz, 1H), 1.03 (dd, *J* = 12.5, 1.8 Hz, 1H), 0.95 (s, 3H), 0.73 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.71, 152.34, 147.71, 138.47, 130.90, 129.01, 125.74, 116.21, 106.85, 78.73, 55.92, 54.63, 48.81, 48.18, 45.30, 40.38, 39.42, 39.15, 38.72, 38.17, 37.12, 28.36, 27.84, 23.99, 21.63, 18.87, 15.51, 14.56. HRMS calc for $C_{31}H_{44}ClN_3O_3K$ $[M+K]^+$: 580.2708, found 580.2705. HPLC purity: 100.00%, retention time: 17.027 min.

N-(2-Chlorophenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15j**)

Colorless oil, yield 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.00 (s, 1H), 6.96 (td, *J* = 7.7, 1.6 Hz, 1H), 5.74 (s, 1H), 4.86 (s, 1H), 4.51 (s, 1H), 3.81 – 3.67 (m, 2H), 3.63 – 3.48 (m, 6H), 3.22 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.40 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.30 – 2.19 (m, 1H), 1.98 – 1.90 (m, 2H), 1.90 (s, 3H), 1.81 – 1.45 (m, 7H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.14 (td, *J* = 13.1, 3.9 Hz, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.59, 154.13, 151.62, 147.82, 135.46, 128.90, 127.81, 123.62, 122.66, 121.23, 116.60, 106.87, 78.74, 55.97, 54.72, 45.81, 44.15, 43.87, 40.79, 39.48, 39.20, 38.71, 38.24, 37.16, 28.41, 27.92, 24.06, 21.65, 18.86, 15.51, 14.58. HRMS calc for $C_{31}H_{44}ClN_3O_3Na$ $[M + Na]^+$:564.2969, found 564.2968. HPLC purity: 96.77%, retention time: 14.910 min.

N-(3-Chlorophenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15k**)

Colorless oil, yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 1H), 7.33 – 7.26 (m, 1H), 7.26 – 7.22 (m, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.01 – 6.93 (m, 1H), 5.72 (s, 1H), 4.85 (s, 1H), 4.49 (s, 1H), 3.72 – 3.60 (m, 2H), 3.56 – 3.41 (m, 6H), 3.21 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.39 (ddd, *J* = 12.7, 4.2, 2.4 Hz, 1H), 2.30 – 2.18 (m, 1H), 1.96 – 1.89 (m, 2H), 1.86 (s, 3H), 1.77 – 1.45 (m, 7H), 1.37 (qd, *J* = 13.1, 4.3 Hz, 1H), 1.12 (td, *J* = 13.1, 3.9 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.77, 154.99, 151.44, 147.79, 140.43, 134.36, 129.87, 123.21, 120.28, 118.31, 116.64, 106.90, 78.77, 56.00, 54.74, 46.02,

44.41, 43.84, 40.99, 39.48, 39.20, 38.63, 38.24, 37.18, 28.42, 27.92, 24.05, 21.65, 18.90, 15.54, 14.59. HRMS calc for $C_{31}H_{44}ClN_3O_3Na$ [M +Na] $^+$: 564.2969, found 564.2966. HPLC purity: 98.76%, retention time: 16.310 min.

N-(2-Bromophenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15l**)

White solid, melt point:199 ℃, yield 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (td, *J* = 15.7, 1.3 Hz, 1H), 7.02 (s, 1H), 6.89 (td, *J* = 8.0, 1.5 Hz, 1H), 5.73 (s, 1H), 4.85 (s, 1H), 4.50 (s, 1H), 3.78 – 3.67 (m, 2H), 3.61 – 3.47 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.39 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.25 (td, *J* = 11.0, 6.2 Hz, 1H), 2.01 – 1.90 (m, 2H), 1.89 (s, 3H), 1.79 – 1.51 (m, 7H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.14 (td, *J* = 13.1, 3.9 Hz, 1H), 1.05 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.56, 154.12, 151.60, 147.79, 136.51, 132.08, 128.45, 124.15, 121.44, 116.58, 113.55, 106.86, 78.69, 55.93, 54.68, 45.79, 44.12, 43.83, 40.76, 39.45, 39.18, 38.68, 38.21, 37.13, 28.39, 27.90, 24.03, 21.61, 18.85, 15.51, 14.57. HRMS calc for $C_{31}H_{44}BrN_3O_3Na$ [M+Na] $^+$: 610.2443, found 610.2454. HPLC purity: 99.20%, retention time: 15.273 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(4-iodophenyl) piperazine-1-carboxamide (**15m**)

Colorless oil, yield 94%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.10 (s, 1H), 5.72 (s, 1H), 4.85 (s, 1H), 4.49 (s, 1H), 3.70 – 3.60 (m, 2H), 3.55 – 3.40 (m, 6H), 3.21 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.39 (ddd, *J* = 12.8, 4.2, 2.3 Hz, 1H), 2.30 – 2.18 (m, 1H), 1.98 – 1.87 (m, 3H), 1.87 (s, 3H), 1.79 – 1.47 (m, 7H), 1.37 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.13 (td, *J* = 13.1, 3.8 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.97 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.70, 154.75, 151.69, 147.87, 138.79, 137.90, 122.08, 116.65, 106.94, 86.39, 78.87, 56.07, 54.80, 45.99, 44.46, 43.84, 40.92, 39.55, 39.26, 38.77, 38.30, 37.24, 28.45, 28.01, 24.12, 21.73, 18.92, 15.54, 14.65. HRMS calc for $C_{31}H_{45}IN_3O_3$ [M+H] $^+$: 634.2506, found 634.2504. HPLC purity: 100.00%, retention time: 17.343 min.

N-(4-Cyanophenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15n**)

Colorless oil, yield 95%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.55 – 7.48 (m, 4H), 5.72 (s, 1H), 4.85 (s, 1H), 4.48 (s, 1H), 3.72 – 3.62 (m, 2H), 3.59 – 3.48 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.39 (dt, *J* = 12.4, 3.2 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.96 – 1.89 (m, 2H), 1.86 (s, 3H), 1.77 – 1.49 (m, 7H), 1.37 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.12 (td, *J* = 13.1, 3.8 Hz, 1H), 1.04 (dd, *J* = 12.4, 2.7 Hz, 1H), 0.96 (s, 3H), 0.75 (s,

3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.76, 154.38, 151.73, 147.78, 143.88, 133.09, 119.51, 119.34, 116.51, 106.86, 105.33, 78.75, 56.03, 54.75, 46.00, 44.51, 43.83, 40.98, 39.48, 39.20, 38.68, 38.22, 37.20, 28.41, 27.91, 24.05, 21.70, 18.88, 15.51, 14.58. HRMS calc for $C_{32}H_{45}N_4O_3$ [M+H] $^+$: 533.3492, found 533.3489. HPLC purity: 100.00%, retention time: 13.930 min.

4-((*E)*-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(2-nitrophenyl) piperazine-1-carboxamide (**15o**)

Yellow oil , yield 92%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.59 (dd, *J* = 8.7, 1.3 Hz, 1H), 8.18 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.07 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 5.74 (s, 1H), 4.86 (s, 1H), 4.51 (s, 1H), 3.79 – 3.67 (m, 2H), 3.65 – 3.55 (m, 6H), 3.23 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.40 (ddd, *J* = 12.7, 4.2, 2.3 Hz, 1H), 2.32 – 2.20 (m, 1H), 1.99 – 1.91 (m, 2H), 1.90 (s, 3H), 1.80 – 1.54 (m, 7H), 1.38 (qd, *J* = 13.0, 4.3 Hz, 1H), 1.15 (td, *J* = 13.2, 3.9 Hz, 1H), 1.06 (dd, *J* = 12.5, 2.8 Hz, 1H), 0.98 (s, 3H), 0.76 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.59, 153.62, 151.73, 147.82, 137.01, 136.20, 135.80, 125.89, 121.90, 121.54, 116.59, 106.91, 78.77, 56.01, 54.77, 45.76, 43.93, 41.82, 40.97, 39.51, 39.22, 38.73, 38.26, 37.20, 28.42, 27.95, 24.08, 21.67, 18.89, 15.51, 14.60. HRMS calc for $C_{31}H_{45}N_4O_5$ [M+H] $^+$: 553.3390, found 553.3392. HPLC purity: 100.00%, retention time: 15.457 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(3-methoxyphenyl) piperazine-1-carboxamide (**15p**)

Colorless oil, yield 90%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.1 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.84 (ddd, *J* = 8.1, 2.0, 0.9 Hz, 1H), 6.56 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 5.70 (s, 1H), 4.85 (s, 1H), 4.49 (s, 1H), 3.74 (s, 3H), 3.68 – 3.58 (m, 2H), 3.53 – 3.38 (m, 6H), 3.21 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.39 (ddd, *J* = 12.8, 4.2, 2.4 Hz, 1H), 2.24 (td, *J* = 10.7, 5.7 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.87 (s, 3H), 1.80 – 1.47 (m, 7H), 1.37 (qd, *J* = 12.9, 4.2 Hz, 1H), 1.12 (td, *J* = 13.1, 3.8 Hz, 1H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.96 (s, 3H), 0.74 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.71, 160.14, 155.26, 151.29, 147.78, 140.27, 129.54, 116.68, 112.48, 109.08, 106.86, 106.09, 78.73, 55.96, 55.30, 54.71, 45.99, 44.37, 43.86, 40.96, 39.45, 39.17, 38.61, 38.21, 37.15, 28.37, 27.87, 24.03, 21.62, 18.84, 15.52, 14.57. HRMS calc for $C_{32}H_{47}N_3O_4K$ [M+K] $^+$: 576.3204, found 576.3201. HPLC purity: 99.22%, retention time: 13.760 min

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(4-methoxybenzyl) piperazine-1-carboxamide (**15q**)

Colorless oil, yield 85%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.69 (s, 1H), 5.05 (t, *J* = 5.4 Hz, 1H), 4.84 (s, 1H), 4.49 (s, 1H),

4.31 (d, *J* = 5.2 Hz, 2H), 3.76 (s, 3H), 3.65 – 3.56 (m, 2H), 3.49 – 3.37 (m, 4H), 3.35 – 3.27 (m, 2H), 3.20 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.38 (ddd, *J* = 12.7, 4.3, 2.4 Hz, 1H), 2.22 (ddd, *J* = 13.7, 10.2, 3.6 Hz, 1H), 1.96 – 1.86 (m, 2H), 1.85 (s, 3H), 1.77 – 1.45 (m, 7H), 1.36 (qd, *J* = 13.0, 4.3 Hz, 1H), 1.12 (td, *J* = 13.0, 3.8 Hz, 1H), 1.03 (dd, *J* = 12.4, 2.7 Hz, 1H), 0.95 (s, 3H), 0.74 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.65, 158.94, 157.49, 151.06, 147.76, 131.24, 129.18, 116.71, 114.02, 106.84, 78.69, 55.90, 55.35, 54.66, 45.95, 44.52, 43.88, 43.66, 40.81, 39.42, 39.15, 38.56, 38.18, 37.11, 28.36, 27.82, 24.00, 21.57, 18.78, 15.49, 14.55. HRMS calc for $C_{33}H_{50}N_3O_4$ [M+H] $^+$: 552.3801, found 552.3802. HPLC purity: 98.39%, retention time: 12.950 min.

N-(4-Acetylphenyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide (**15r**)

White powder solid, melt point: 189 ℃, yield 86%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.77 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 5.71 (s, 1H), 4.83 (s, 1H), 4.47 (s, 1H), 3.70 – 3.60 (m, 2H), 3.57 – 3.48 (m, 6H), 3.20 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.52 (s, 3H), 2.37 (dt, *J* = 12.8, 2.6 Hz, 1H), 2.28 – 2.16 (m, 1H), 1.95 – 1.86 (m, 2H), 1.85 (s, 3H), 1.76 – 1.44 (m, 7H), 1.35 (qd, *J* = 13.0, 4.2 Hz, 1H), 1.11 (td, *J* = 13.0, 3.6 Hz, 1H), 1.02 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.95 (s, 3H), 0.73 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.50, 167.79, 154.72, 151.60, 147.73, 144.20, 131.54, 129.69, 118.83, 116.50, 106.85, 78.73, 55.93, 54.67, 46.01, 44.50, 43.88, 41.05, 39.42, 39.15, 38.59, 38.18, 37.13, 28.36, 27.81, 26.48, 24.00, 21.60, 18.87, 15.50, 14.55. HRMS calc for $C_{33}H_{47}N_3O_4Na$ [M +Na] $^+$: 572.3464, found 572.3463. HPLC purity: 99.40%, retention time: 12.800 min.

4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)-*N*-(3-(trifluoromethoxy) phenyl) piperazine-1-carboxamide (**15s**)

Colorless oil, yield 97%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.33 – 7.24 (m, 3H), 6.88 (d, *J* = 7.7 Hz, 1H), 5.74 (s, 1H), 4.88 (s, 1H), 4.52 (s, 1H), 3.73 – 3.63 (m, 2H), 3.59 – 3.46 (m, 6H), 3.24 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.42 (dt, *J* = 13.3, 3.1 Hz, 1H), 2.32 – 2.21 (m, 1H), 2.00 – 1.90 (m, 3H), 1.89 (s, 3H), 1.82 – 1.50 (m, 7H), 1.40 (qd, *J* = 13.1, 4.3 Hz, 1H), 1.16 (td, *J* = 13.1, 3.8 Hz, 1H), 1.07 (dd, *J* = 12.5, 2.7 Hz, 1H), 0.99 (s, 3H), 0.78 (s, 3H), 0.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.76, 154.85, 151.56, 149.61, 147.83, 140.70, 129.87, 120.54 (q, *J* = 257.2 Hz), 118.14, 116.61, 115.28, 112.77, 106.88, 78.81, 56.06, 54.78, 46.00, 44.44, 43.83, 40.98, 39.50, 39.22, 38.68, 38.26, 37.20, 28.40, 27.95, 24.08, 21.69, 18.84, 15.50, 14.58. HRMS calc for $C_{32}H_{44}F_3N_3O_4Na$ [M+Na] $^+$: 614.3182, found 614.3184. HPLC purity: 100.00%, retention time: 6.043 min. ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.72.

N-(2-(1H-Indol-3-yl) ethyl)-4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-

carboxamide(**15t**)

Colorless oil, yield 84%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.15 – 7.06 (m, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.70 (s, 1H), 4.86 (s, 1H), 4.58 (t, *J* = 5.5 Hz, 1H), 4.51 (s, 1H), 3.63 – 3.52 (m, 4H), 3.50 – 3.40 (m, 2H), 3.39 – 3.30 (m, 2H), 3.27 – 3.16 (m, 3H), 2.99 (t, *J* = 6.5 Hz, 2H), 2.45 – 2.36 (m, 1H), 2.30 – 2.19 (m, 1H), 1.99 – 1.88 (m, 2H), 1.88 (s, 3H), 1.80 – 1.55 (m, 7H), 1.39 (qd, *J* = 13.0, 4.3 Hz, 1H), 1.13 (td, *J* = 13.2, 6.6 Hz, 1H), 1.05 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.99 (s, 3H), 0.77 (s, 3H), 0.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.65, 157.60, 151.01, 147.85, 136.58, 127.62, 122.34, 122.16, 119.55, 118.86, 116.95, 113.43, 111.47, 106.96, 78.89, 56.01, 54.82, 46.02, 43.85, 43.59, 41.59, 40.81, 39.53, 39.26, 38.65, 38.31, 37.24, 28.47, 28.01, 25.80, 24.12, 21.68, 18.86, 15.55, 14.64. HRMS calc for $C_{35}H_{51}N_4O_3$ [M+H] $^+$: 575.3961, found 575.3963. HPLC purity: 97.12%, retention time: 13.997 min.

N,*N*'-(1,4-Phenylene) bis(4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide) (**15u**)

White power solid, melt point: 190 ℃, yield 96%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 7.30 (s, 4H), 5.84 (s, 2H), 4.86 (s, 2H), 4.54 (s, 2H), 4.40 – 4.34 (m, 2H), 3.55 – 3.40 (m, 16H), 3.05 (d, *J* = 10.9 Hz, 2H), 2.42 – 2.34 (m, 2H), 2.22 – 2.11 (m, 2H), 1.98 – 1.86 (m, 4H), 1.82 (s, 6H), 1.77 – 1.45 (m, 14H), 1.32 (qd, *J* = 12.8, 4.0 Hz, 2H), 1.12 (td, *J* = 13.0, 4.2 Hz, 2H), 1.05 (dd, *J* = 12.7, 2.5 Hz, 2H), 0.91 (s, 6H), 0.67 (s, 6H), 0.64 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.64, 155.57, 149.50, 148.24, 135.22, 120.63, 118.05, 107.09, 77.17, 55.73, 54.58, 49.44, 45.93, 44.41, 40.40, 39.56, 39.24, 38.43, 38.17, 37.07, 28.86, 28.15, 24.14, 21.64, 18.71, 16.25, 14.80. HRMS calc for $C_{56}H_{85}N_6O_6$ [M+H] $^+$: 937.6531, found 937.6528. HPLC purity: 100.00%, retention time: 17.500 min.

N,*N*'-(1,3-Phenylene)bis(4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazine-1-carboxamide) (**15v**)

Light yellow oil, yield 91%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.28 (s, 2H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 5.71 (s, 2H), 4.86 (s, 2H), 4.51 (s, 2H), 3.63 – 3.53 (m, 4H), 3.52 – 3.31 (m, 12H), 3.21 (dd, *J* = 11.5, 4.4 Hz, 2H), 2.44 – 2.36 (m, 2H), 2.29 – 2.19 (m, 2H), 1.98 – 1.88 (m, 4H), 1.87 (s, 6H), 1.80 – 1.48 (m, 14H), 1.37 (qd, *J* = 12.9, 4.1 Hz, 2H), 1.12 (td, *J* = 13.4, 3.5 Hz, 2H), 1.04 (dd, *J* = 12.5, 2.7 Hz, 2H), 0.97 (s, 6H), 0.75 (s, 6H), 0.67 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.71, 155.53, 151.23, 147.79, 139.58, 129.01, 116.88, 116.01, 114.01, 106.96, 78.74, 55.93, 54.82, 46.04, 44.22, 43.86, 41.01, 39.49, 39.23, 38.59, 38.29, 37.25, 28.47, 27.94, 24.09, 21.62, 18.91, 15.58, 14.65. HRMS calc for $C_{56}H_{85}N_6O_6$ [M+H] $^+$: 937.6531, found 937.6530. HPLC purity: 99.45%, retention time: 4.390 min.

N, *N*'-(1,3-Phenylenebis(methylene)) bis(4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl) piperazine-1-carboxamide) (**15w**)

Colorless oil, yield 93%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 7.20 – 7.14 (m, 3H), 5.71 (s, 2H), 5.28 (d, *J* = 6.8 Hz, 2H), 4.86 (s, 2H), 4.51 (s, 2H), 4.36 (d, *J* = 5.7 Hz, 4H), 3.66 – 3.55 (m, 4H), 3.52 – 3.31 (m, 12H), 3.22 (dd, *J* = 11.7, 4.4 Hz, 2H), 2.44 – 2.35 (m, 2H), 2.29 – 2.19 (m, 2H), 1.98 – 1.88 (m, 4H), 1.87 (s, 6H), 1.78 – 1.53 (m, 14H), 1.38 (qd, *J* = 12.8, 4.0 Hz, 2H), 1.14 (td, *J* = 12.9, 2.8 Hz, 2H), 1.06 (dd, *J* = 11.6, 1.2 Hz, 2H), 0.98 (s, 6H), 0.76 (s, 6H), 0.68 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.64, 157.70, 151.22, 147.85, 139.87, 129.04, 127.00, 126.67, 116.86, 106.95, 78.82, 56.02, 54.83, 46.02, 44.93, 43.99, 43.87, 40.96, 39.53, 39.26, 38.69, 38.31, 37.25, 28.45, 27.99, 24.11, 21.69, 18.86, 15.55, 14.64. HRMS calc for $C_{58}H_{89}N_6O_6$ [M+H] $^{+}$: 965.6844, found 965.6841. HPLC purity: 98.75%, retention time: 17.390 min.

N,*N*'-(Naphthalene-1,5-diyl)bis(4-((*E*)-5-((1*R*,4a*S*,6*R*,8a*S*)-6-hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-3-methylpent-2-enoyl)piperazine-1-carboxamide) (**15x**)

Colorless oil, yield 96%, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.60 – 7.52 (m, 2H), 7.37 – 7.29 (m, 2H), 7.30 – 7.24 (m, 2H), 5.66 (s, 2H), 4.85 (s, 2H), 4.50 (s, 2H), 3.32 – 3.14 (m, 14H), 3.07 – 2.92 (m, 4H), 2.39 (d, *J* = 13.6 Hz, 2H), 2.26 – 2.18 (m, 2H), 1.97 – 1.86 (m, 4H), 1.85 (s, 6H), 1.78 – 1.50 (m, 14H), 1.37 (qd, *J* = 12.8, 3.9 Hz, 2H), 1.13 (td, *J* = 10.7, 6.9 Hz, 2H), 1.03 (dd, *J* = 12.3, 2.4 Hz, 3H), 0.95 (s, 6H), 0.74 (s, 6H), 0.67 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.48, 156.66, 150.63, 147.75, 134.82, 130.84, 125.37, 123.85, 121.05, 116.96, 106.81, 78.53, 55.95, 54.73, 45.89, 43.79, 43.60, 40.80, 39.41, 39.12, 38.53, 38.20, 37.18, 28.36, 27.85, 24.01, 21.63, 18.77, 15.49, 14.56. HRMS calc for $C_{60}H_{86}N_6O_6Na$ [M+Na] $^{+}$: 1009.6507, found 1009.6505. HPLC purity: 97.51%, retention time: 17.890 min.

^{1}H NMR, ^{13}C NMR, HRMS, ^{19}F NMR and HPLC spectra of synthetic compounds

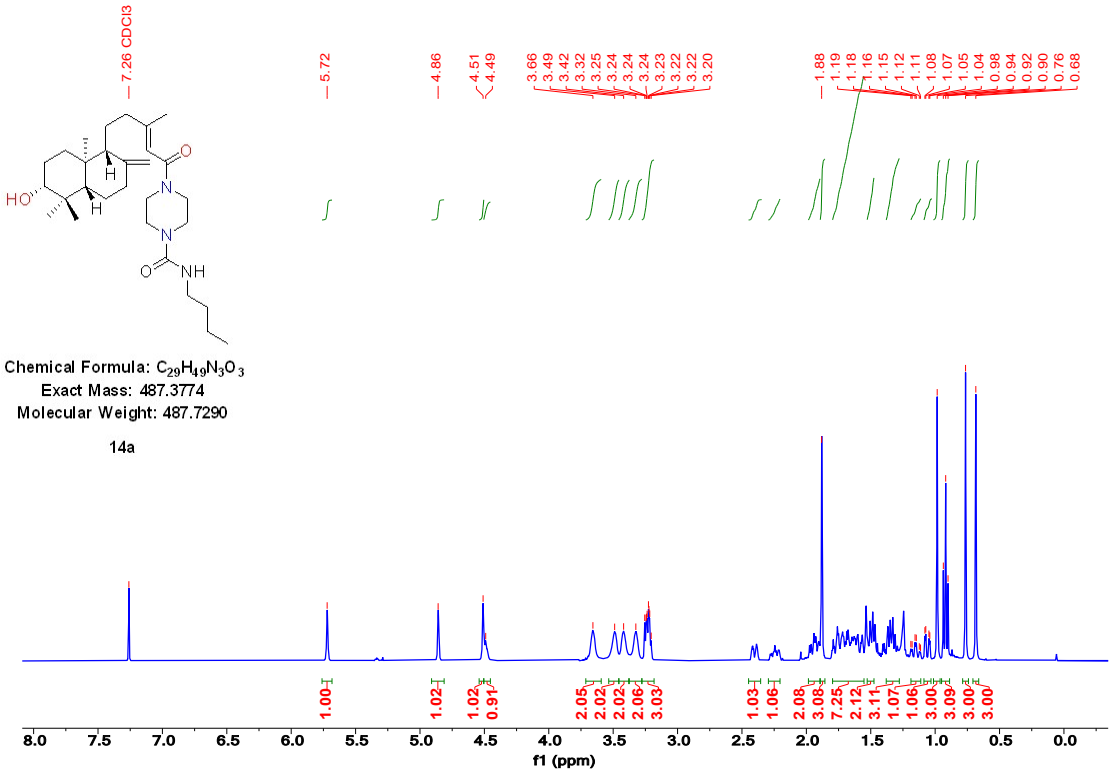


Figure S1. ^{1}H NMR spectrum of 14a

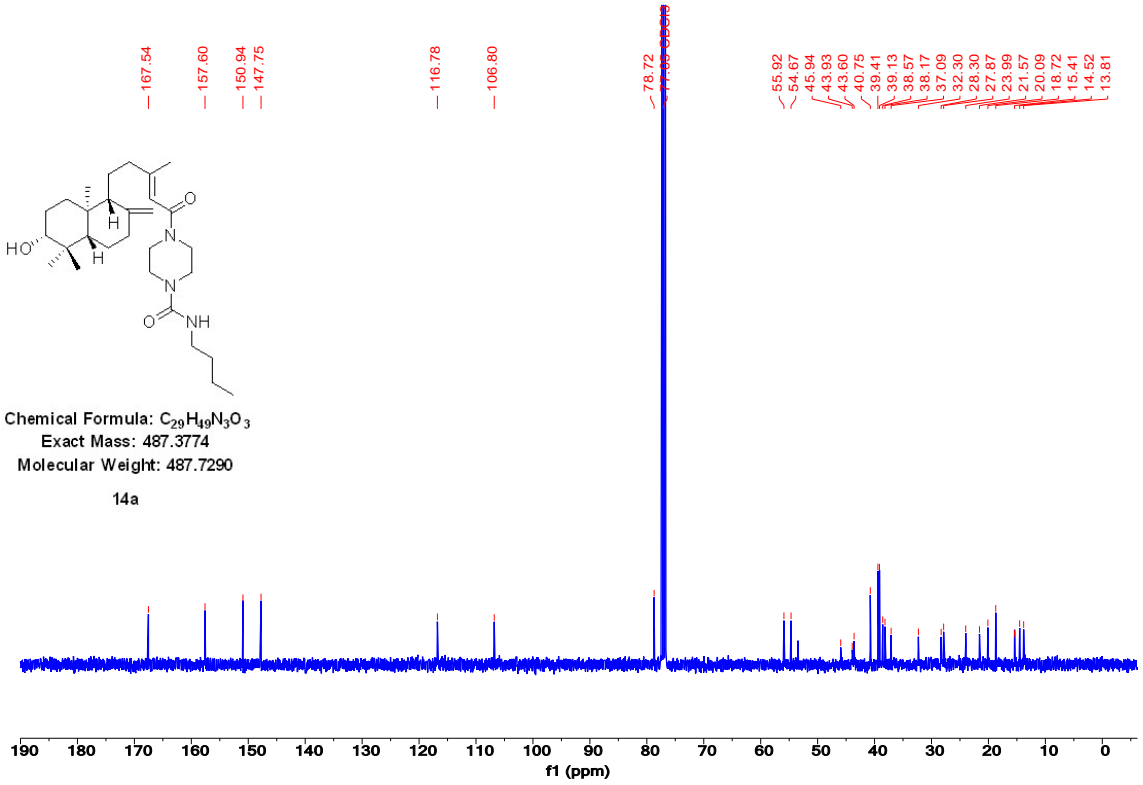


Figure S2. ^{13}C NMR spectrum of 14a

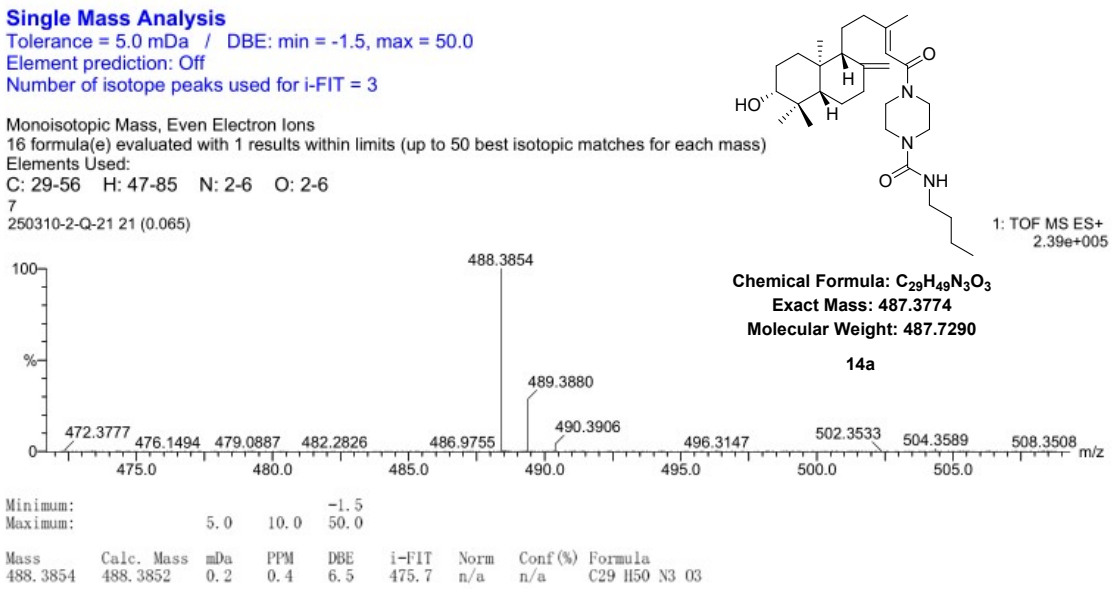
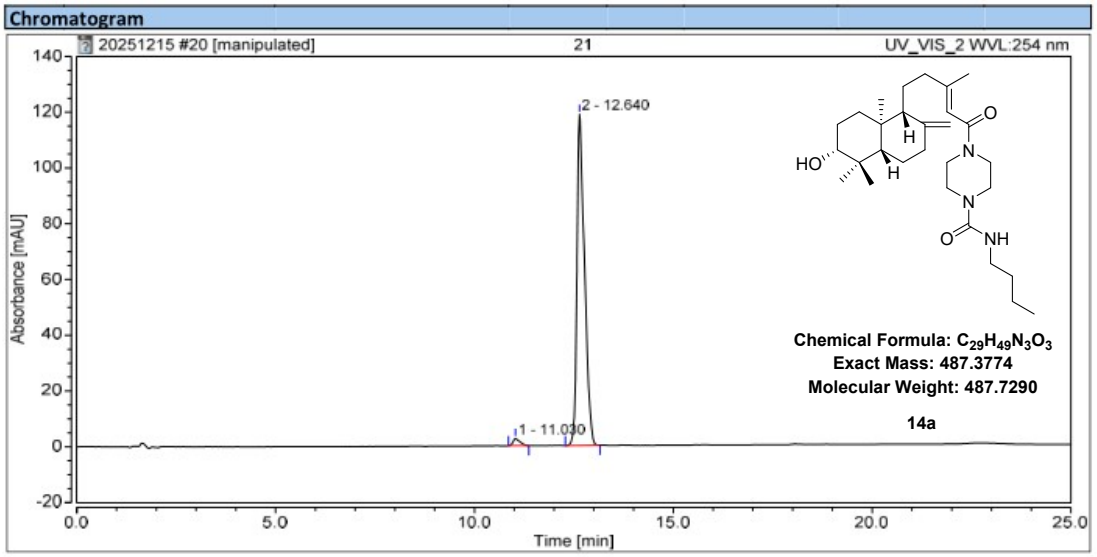


Figure S3. HRMS spectrum of 14a



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.030	0.525	2.598	1.97	2.14	n.a.
2		12.640	26.063	118.781	98.03	97.86	n.a.
Total:			**26.588**	**121.379**	**100.00**	**100.00**	

Figure S4. HPLC spectrum of 14a

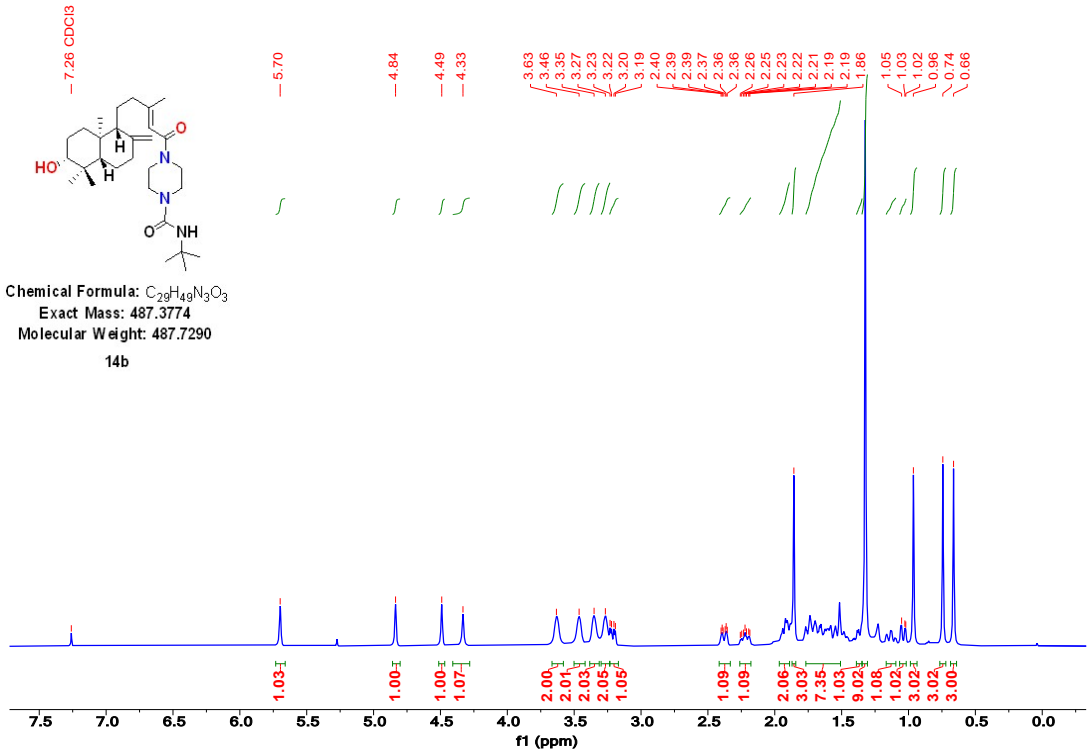


Figure S5. ^{1}H NMR spectrum of 14b

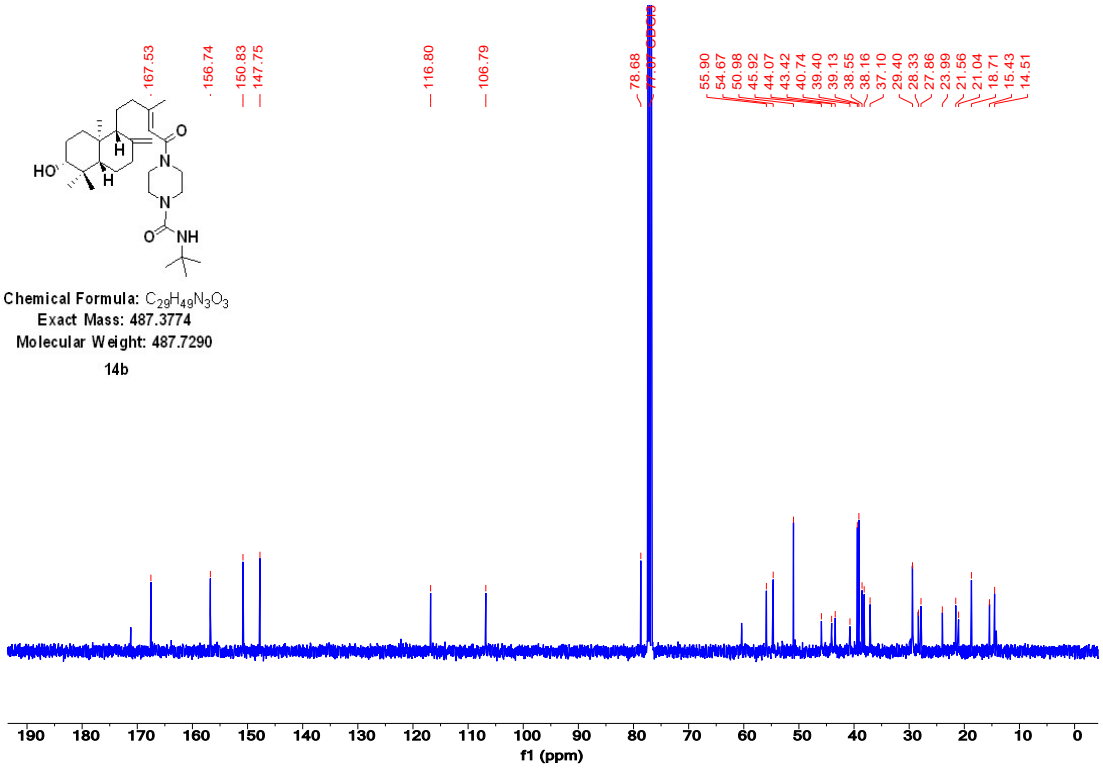


Figure S6. ^{13}C NMR spectrum of 14b

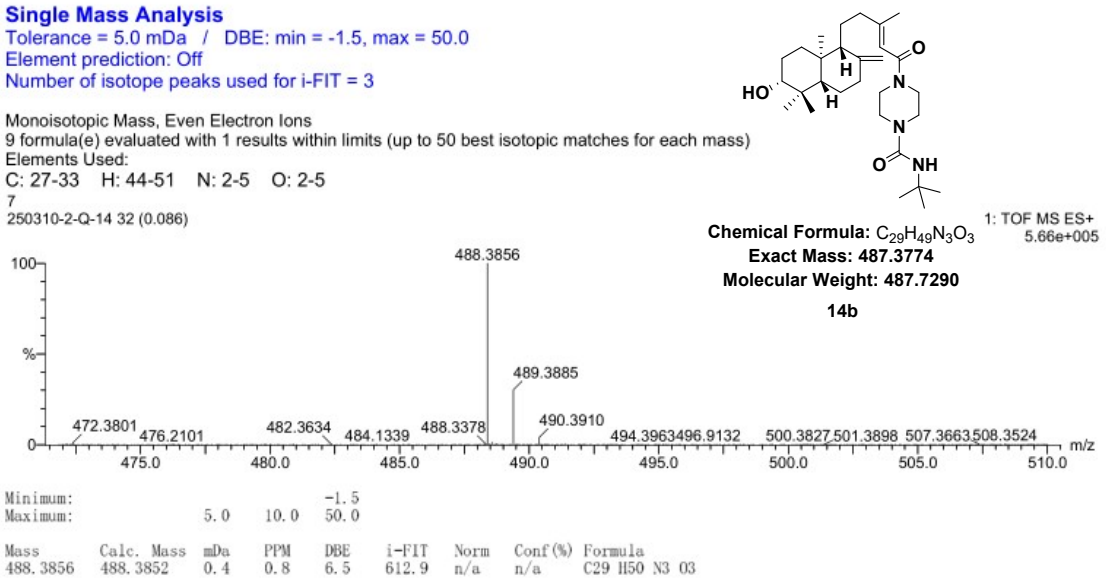
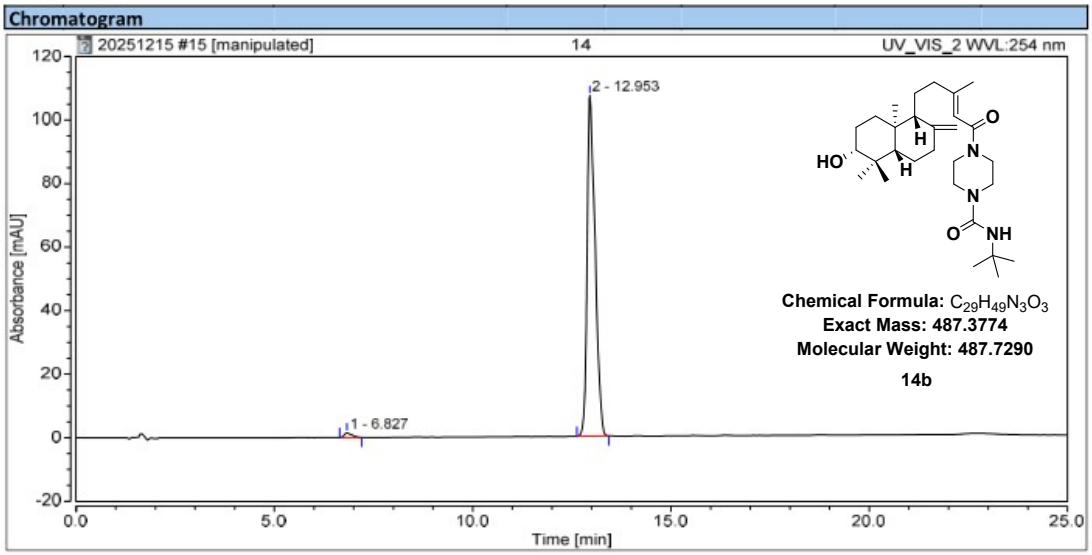


Figure S7. HRMS spectrum of 14b



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.827	0.322	1.453	1.29	1.34	n.a.
2		12.953	24.750	107.268	98.71	98.66	n.a.
Total:			**25.073**	**108.721**	**100.00**	**100.00**	

Figure S8. HPLC spectrum of 14b

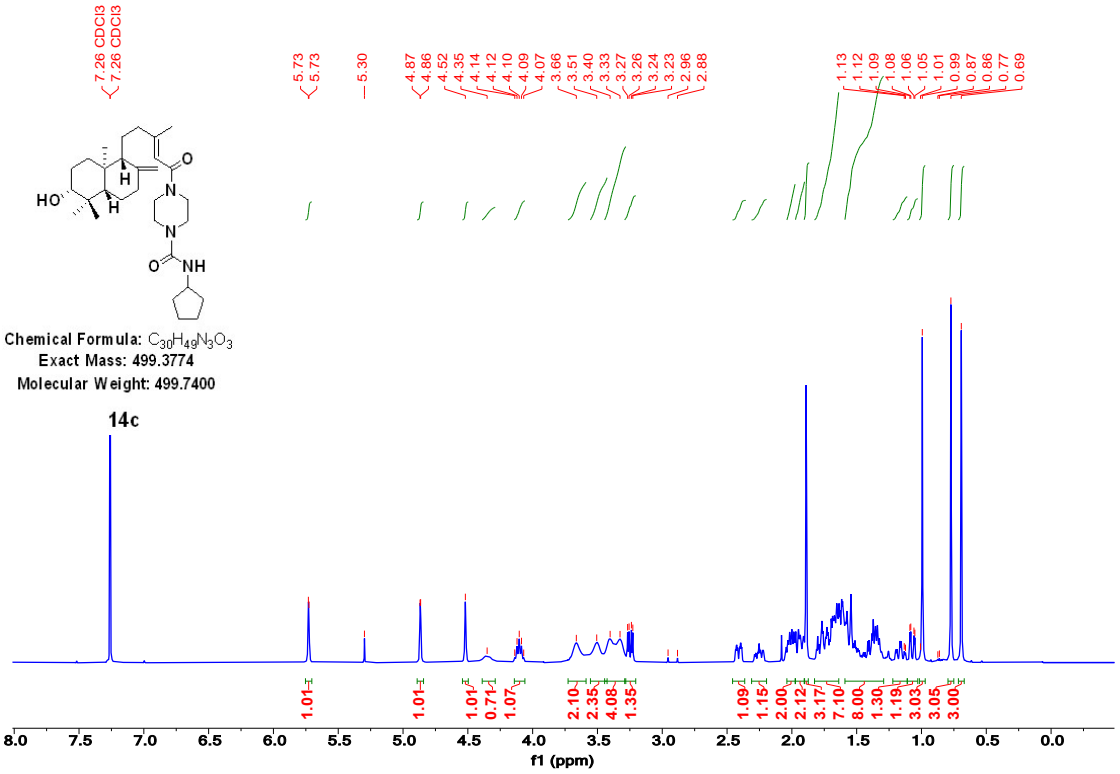


Figure S9. ^{1}H NMR spectrum of 14c

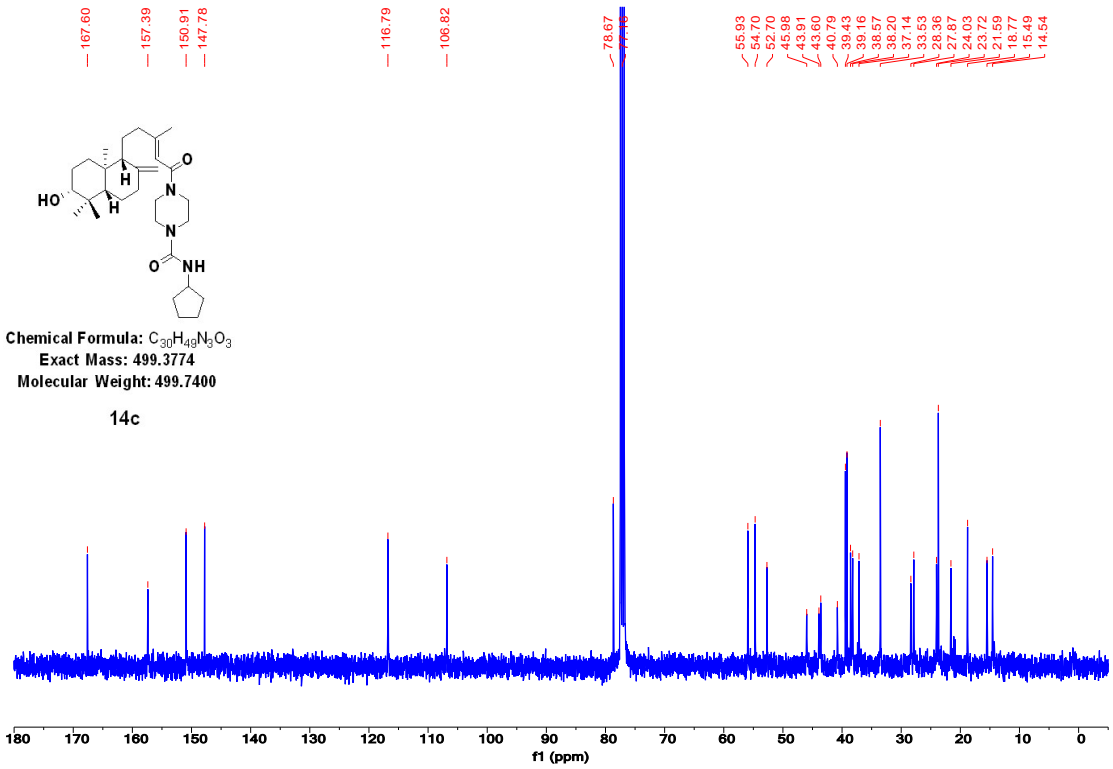


Figure S10. ^{13}C NMR spectrum of 14c

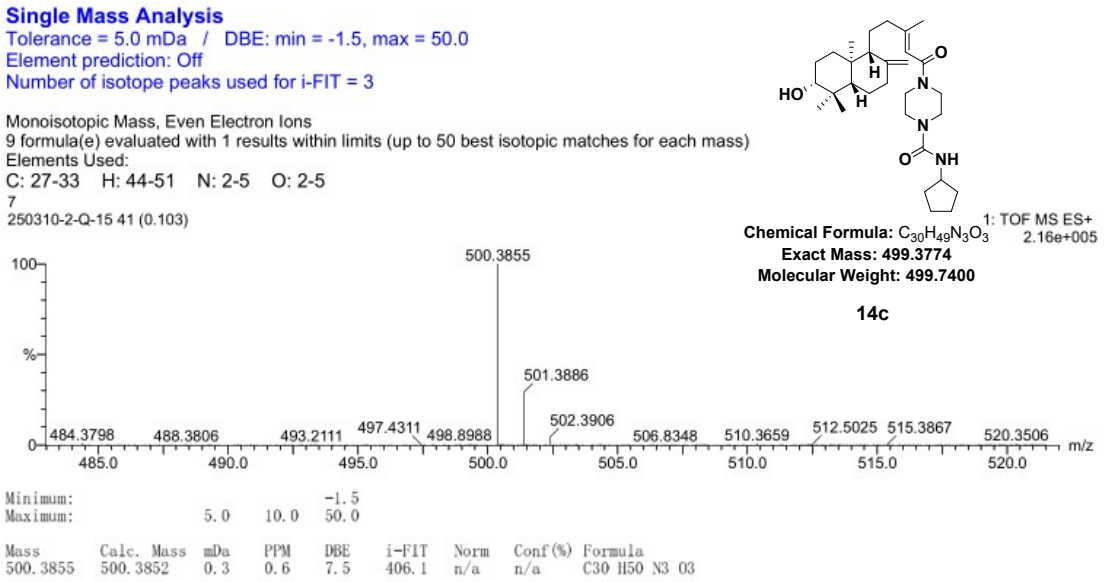
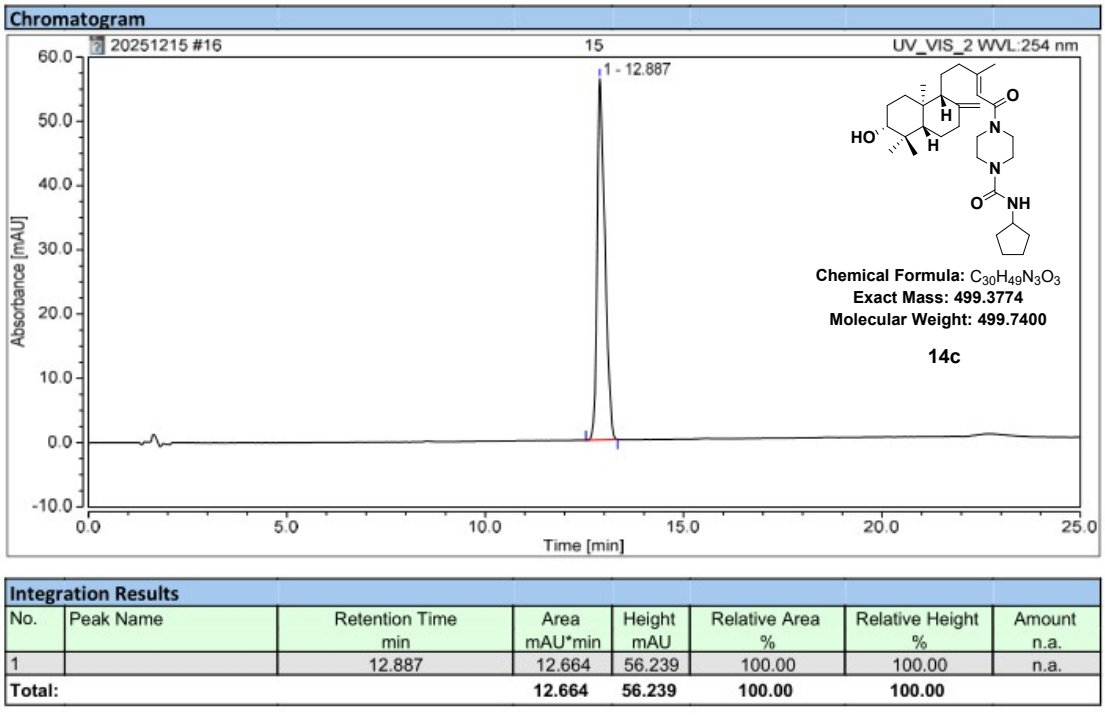


Figure S11. HRMS spectrum of 14c



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.887	12.664	56.239	100.00	100.00	n.a.
Total:			**12.664**	**56.239**	**100.00**	**100.00**	

Figure S12. HPLC spectrum of 14c

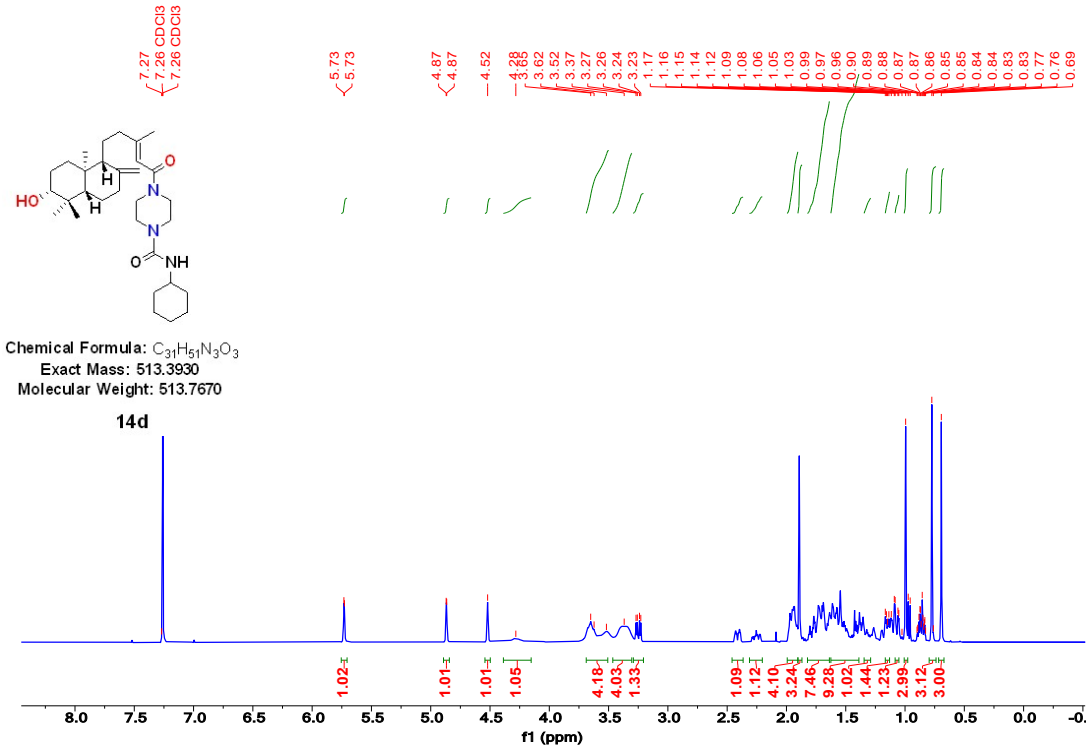


Figure S13. ^{1}H NMR spectrum of 14d

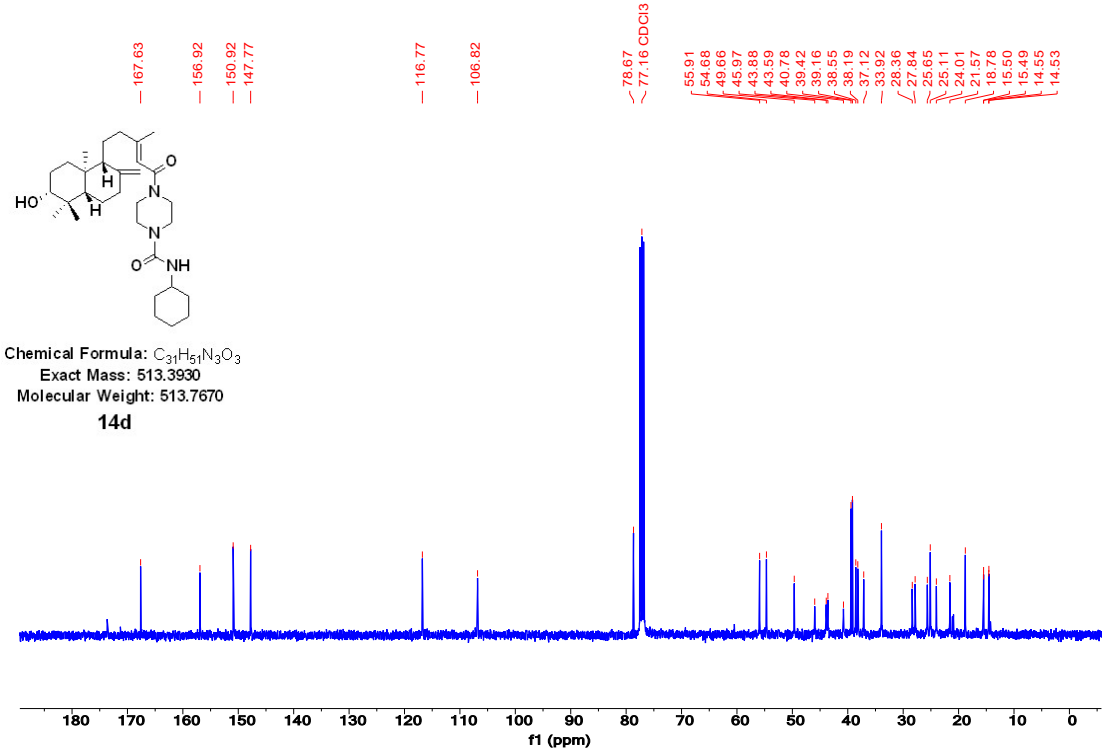


Figure S14. ^{13}C NMR spectrum of 14d

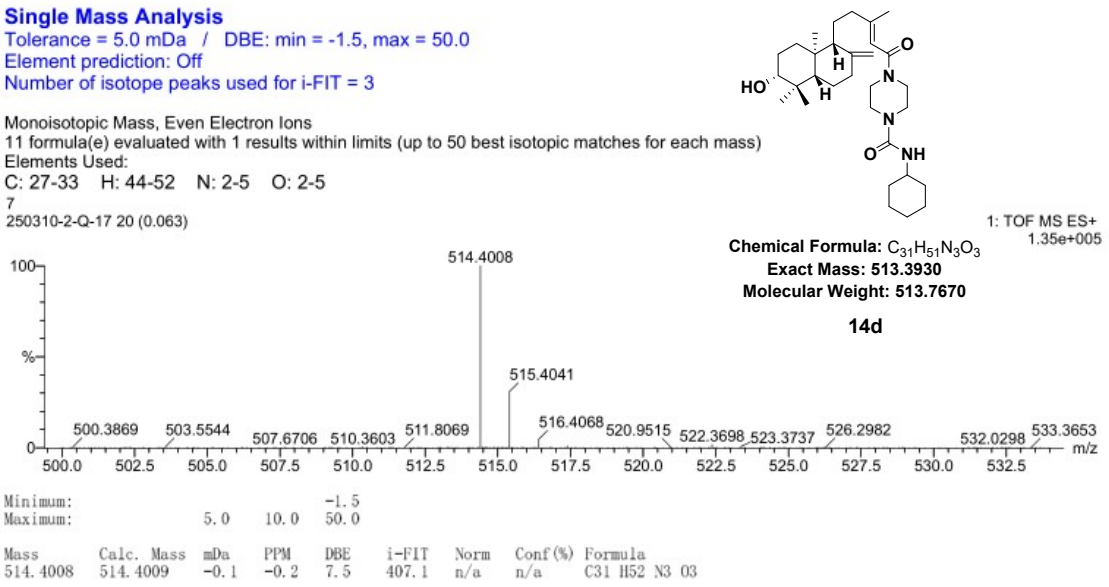
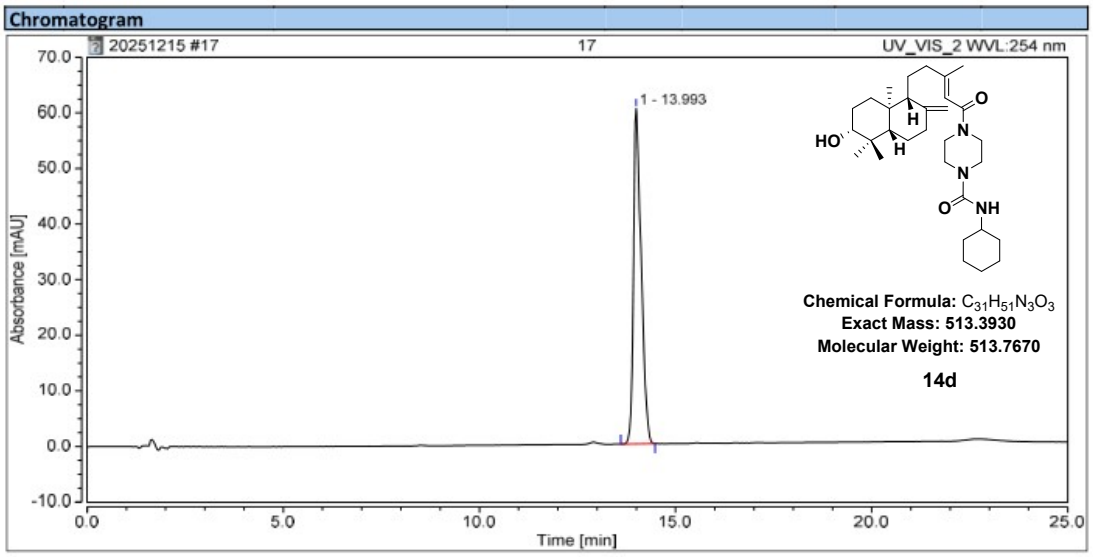


Figure S15. HRMS spectrum of 14d



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.993	13.678	60.346	100.00	100.00	n.a.
Total:			**13.678**	**60.346**	**100.00**	**100.00**	

Figure S16. HPLC spectrum of 14d

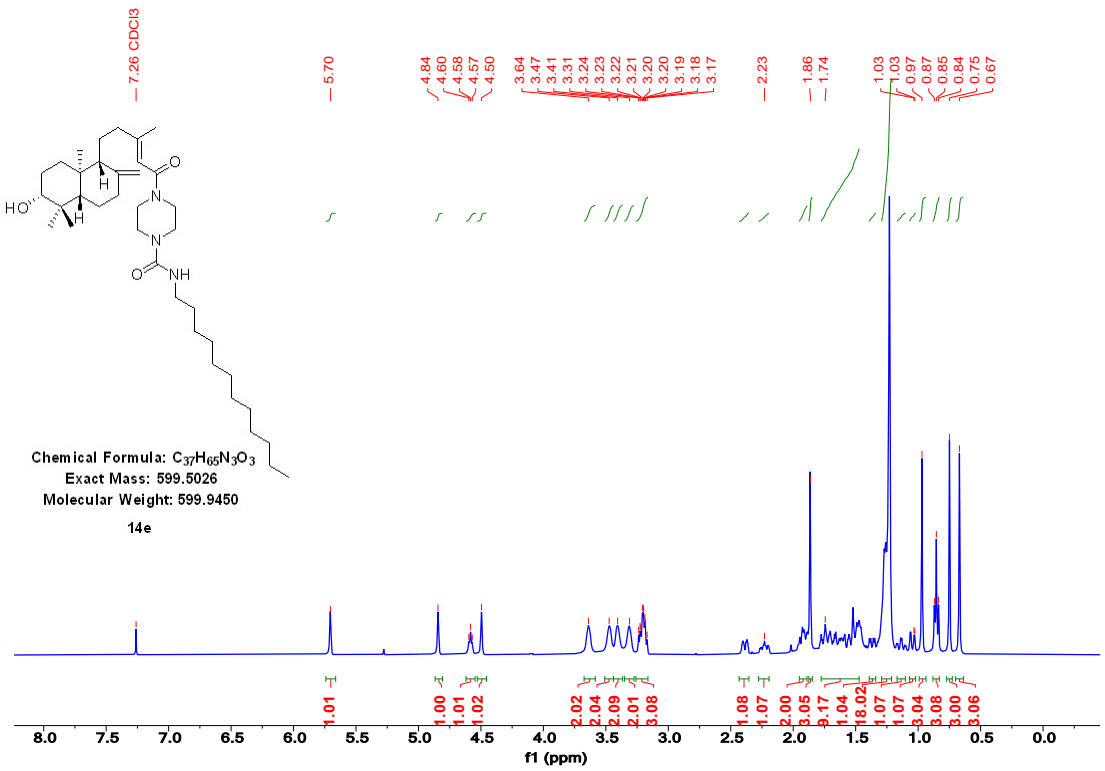


Figure S17. ^{1}H NMR spectrum of 14e

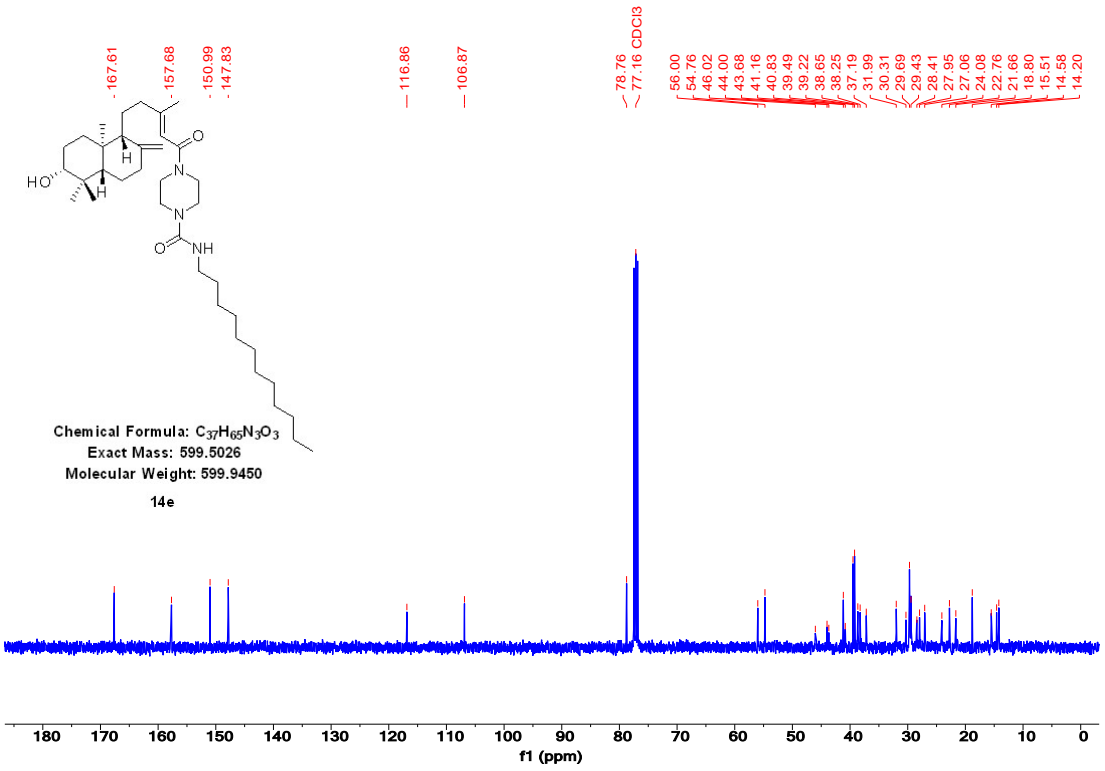


Figure S18. ^{13}C NMR spectrum of 14e

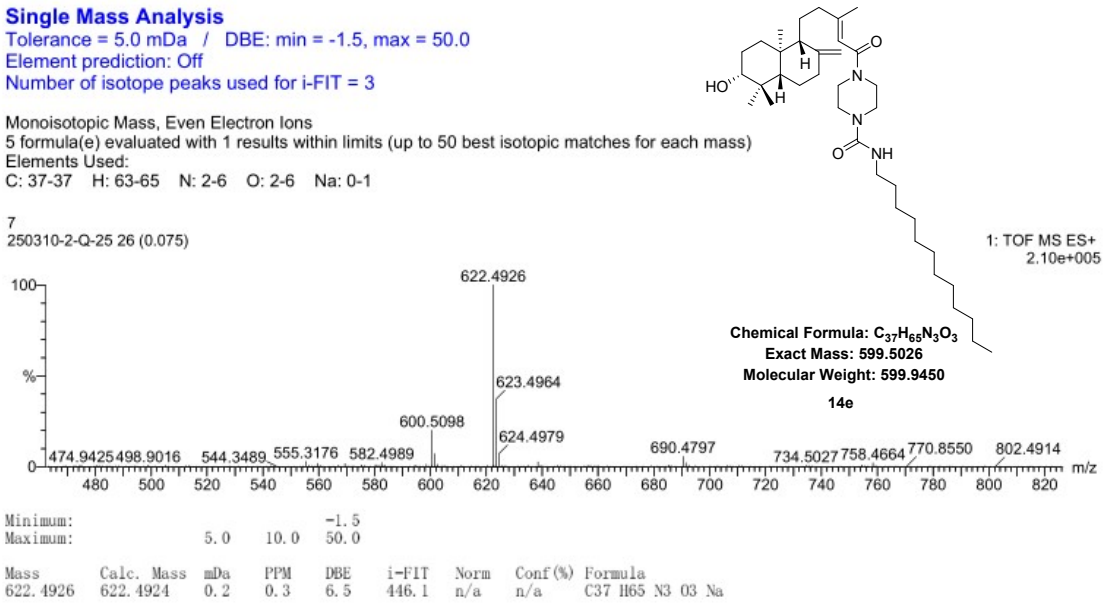
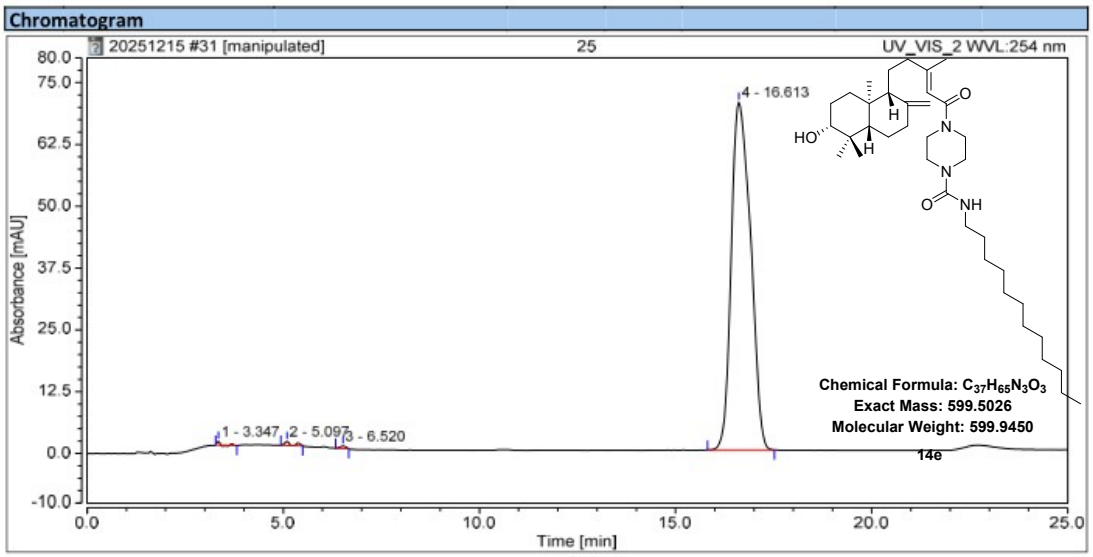


Figure S19. HRMS spectrum of 14e



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		3.347	0.056	0.817	0.14	1.13	n.a.
2		5.097	0.172	0.800	0.43	1.10	n.a.
3		6.520	0.087	0.516	0.22	0.71	n.a.
4		16.613	40.046	70.367	99.22	97.06	n.a.
Total:			**40.361**	**72.499**	**100.00**	**100.00**	

Figure S20. HPLC spectrum of 14e

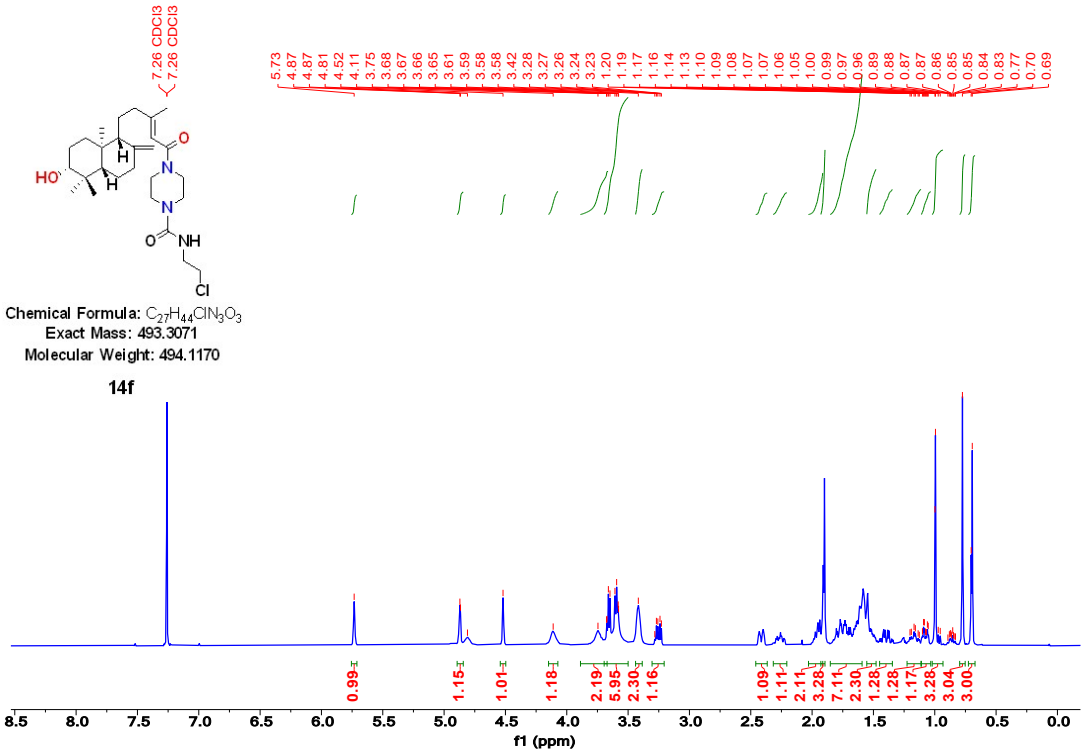


Figure S21. ^{1}H NMR spectrum of 14f

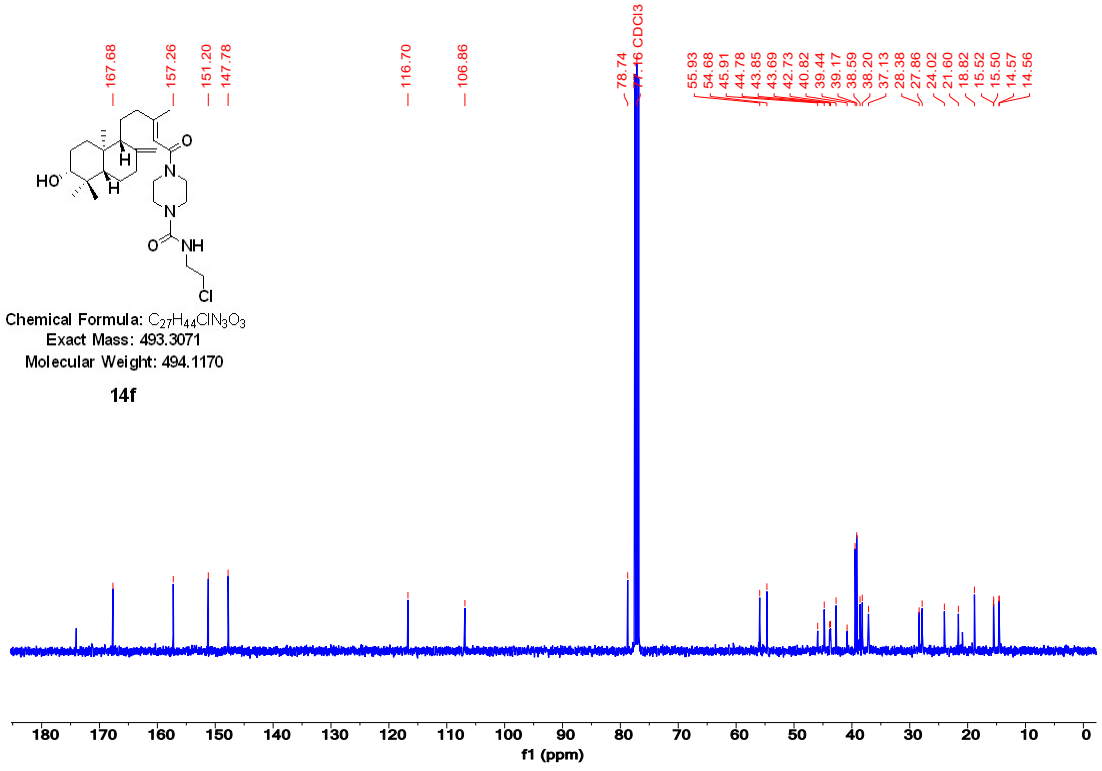


Figure S22. ^{13}C NMR spectrum of 14f

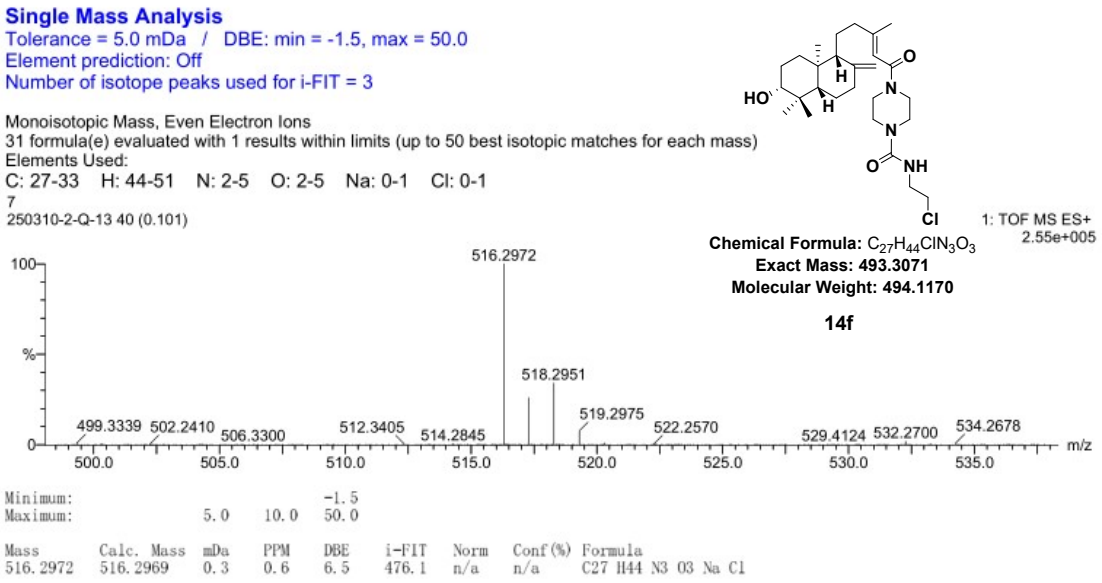
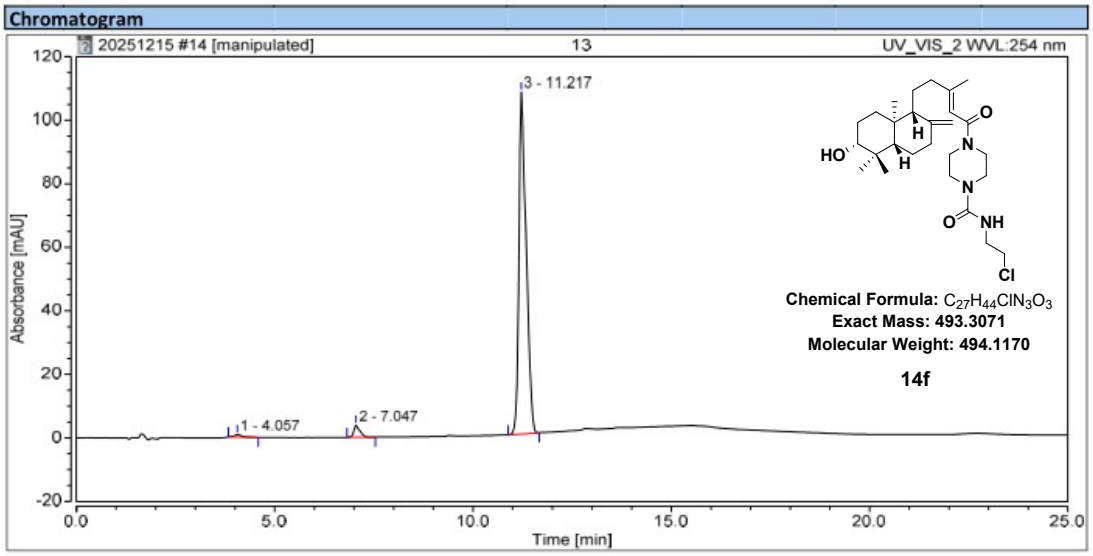


Figure S23. HRMS spectrum of 14f



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.057	0.156	0.743	0.66	0.66	n.a.
2		7.047	0.679	3.871	2.88	3.45	n.a.
3		11.217	22.693	107.674	96.45	95.89	n.a.
Total:			**23.527**	**112.288**	**100.00**	**100.00**	

Figure S24. HPLC spectrum of 14f

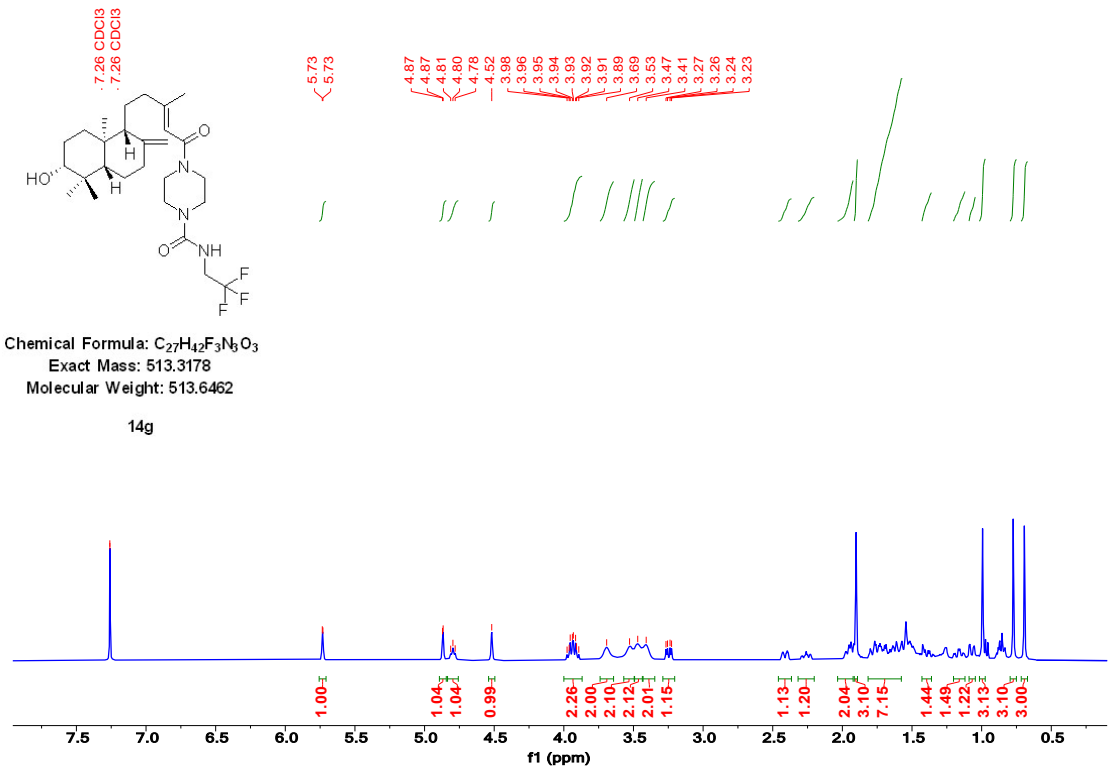


Figure S25. ^{1}H NMR spectrum of 14g

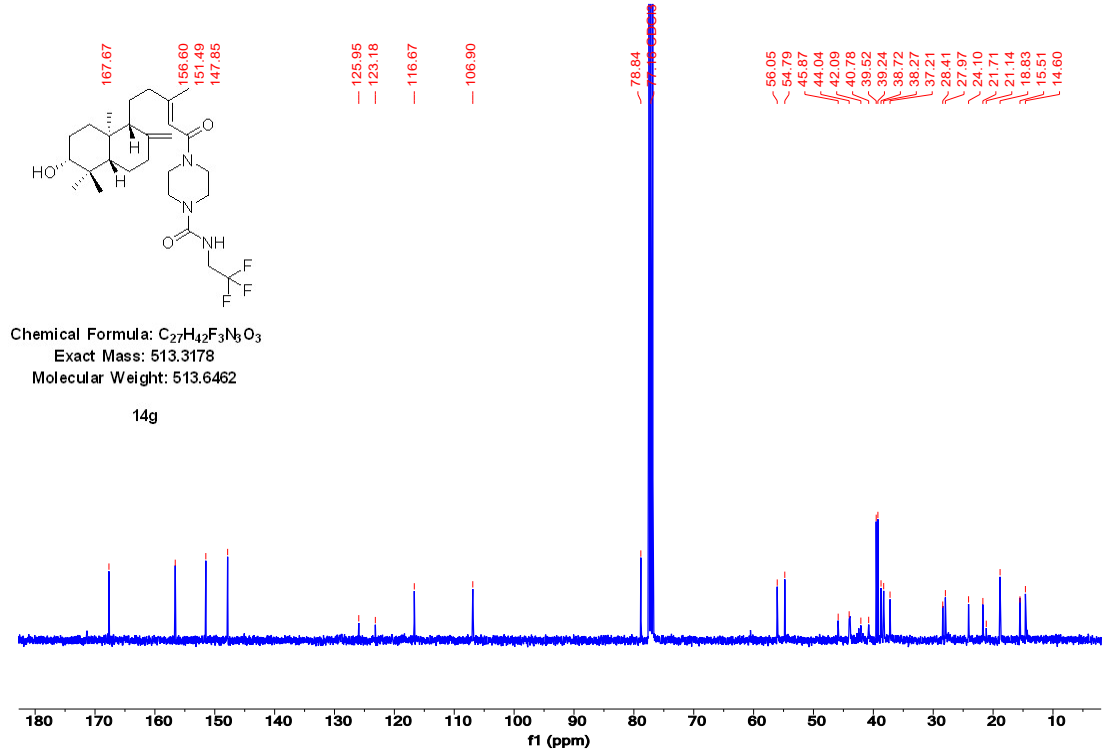


Figure S26. ^{13}C NMR spectrum of 14g

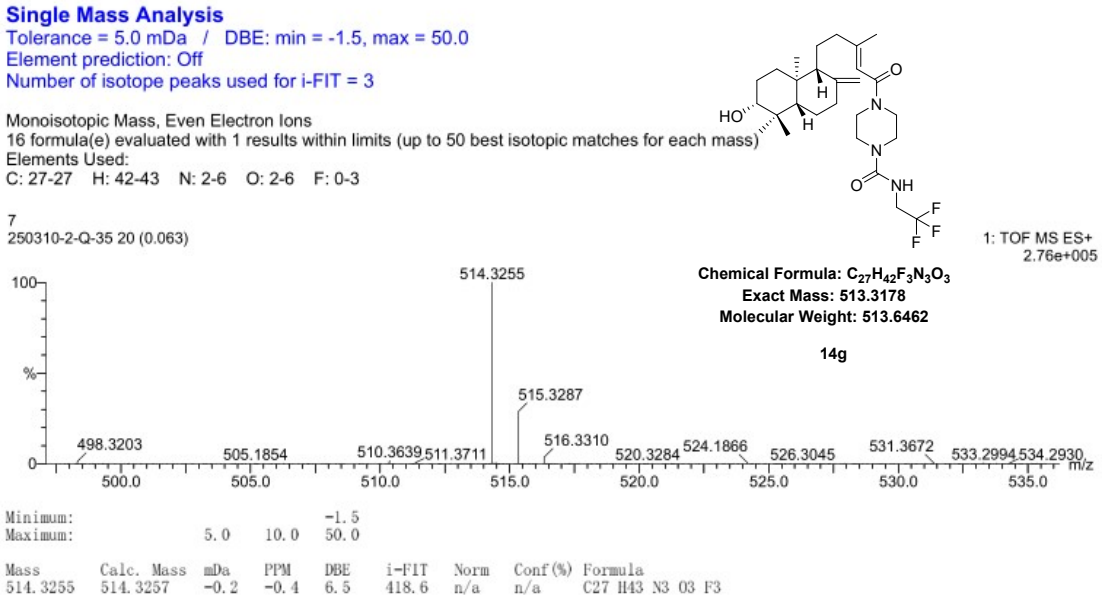
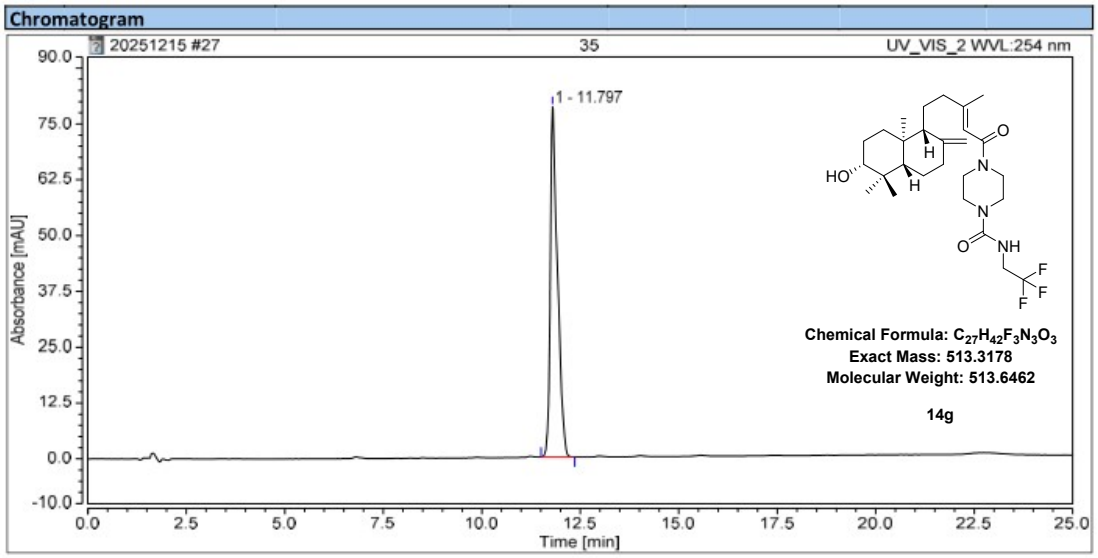


Figure S27. HRMS spectrum of 14g



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		11.797	16.615	78.538	100.00	100.00	n.a.
Total:			**16.615**	**78.538**	**100.00**	**100.00**	

Figure S28. HPLC spectrum of 14g

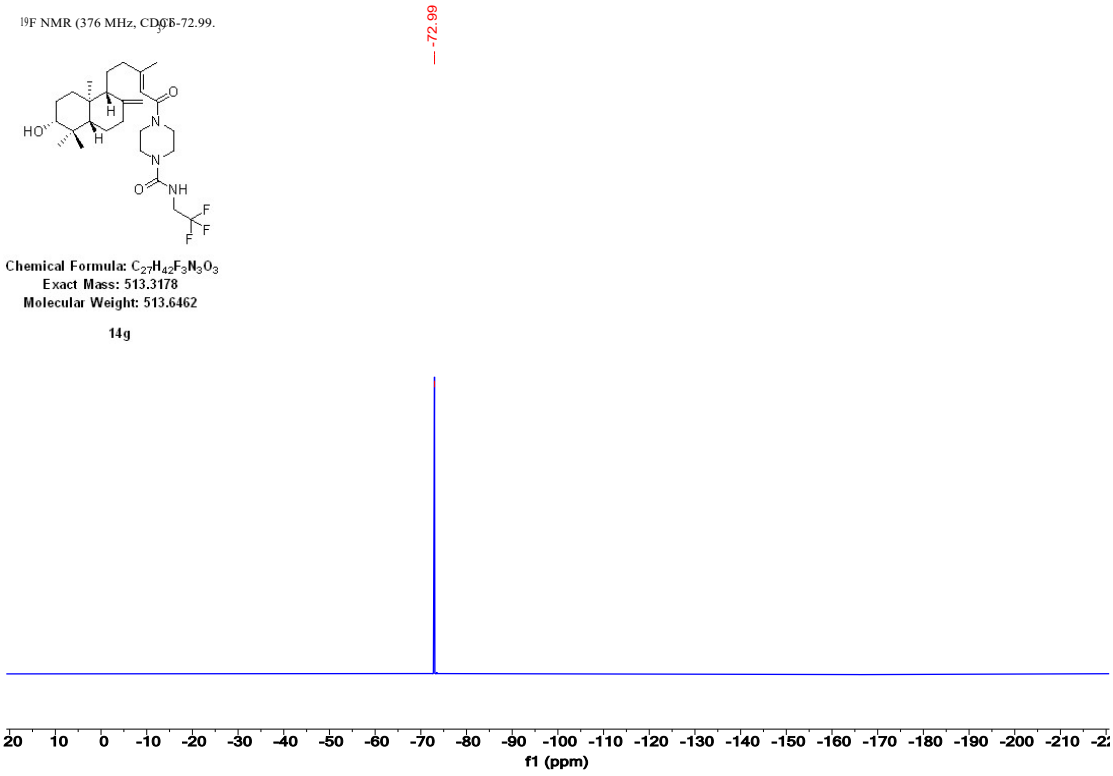


Figure S29. ^{19}F NMR spectrum of 14g

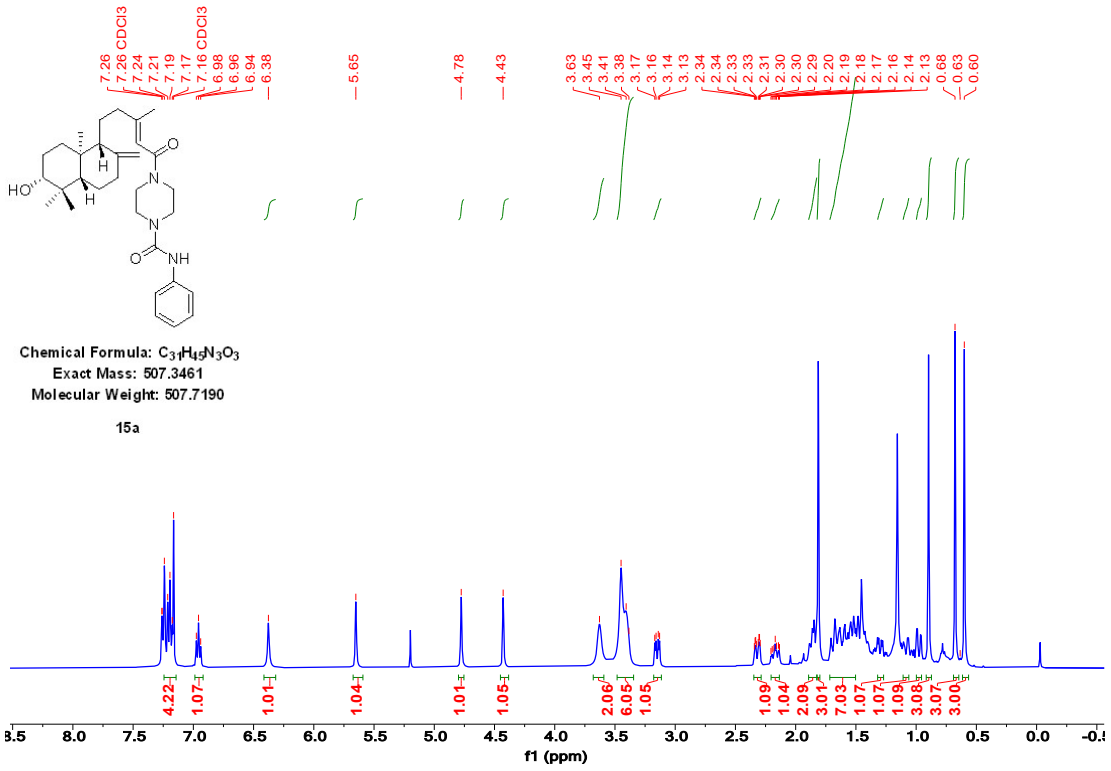


Figure S30. ^{1}H NMR spectrum of 15a

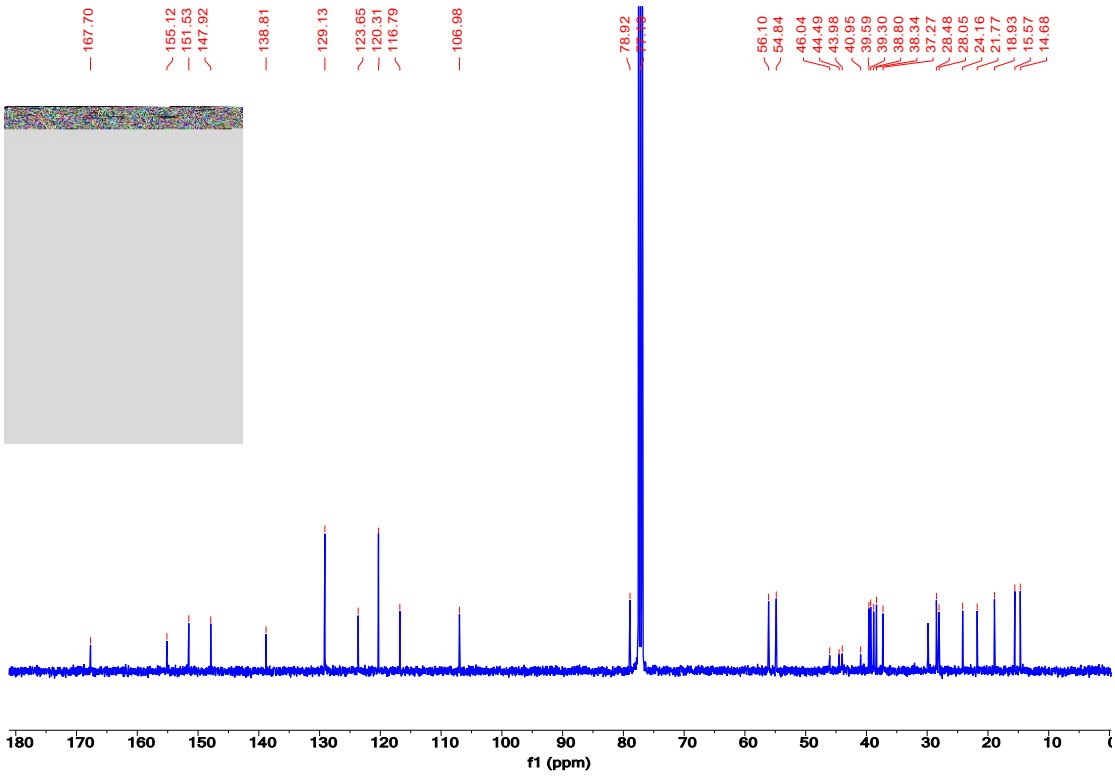


Figure S31. ^{13}C NMR spectrum of 15a

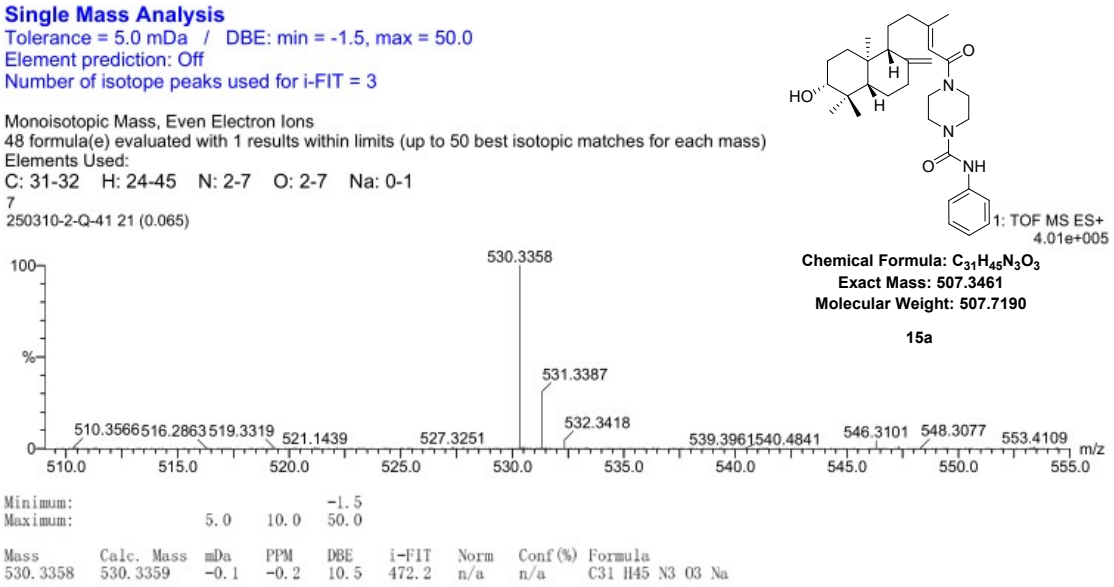
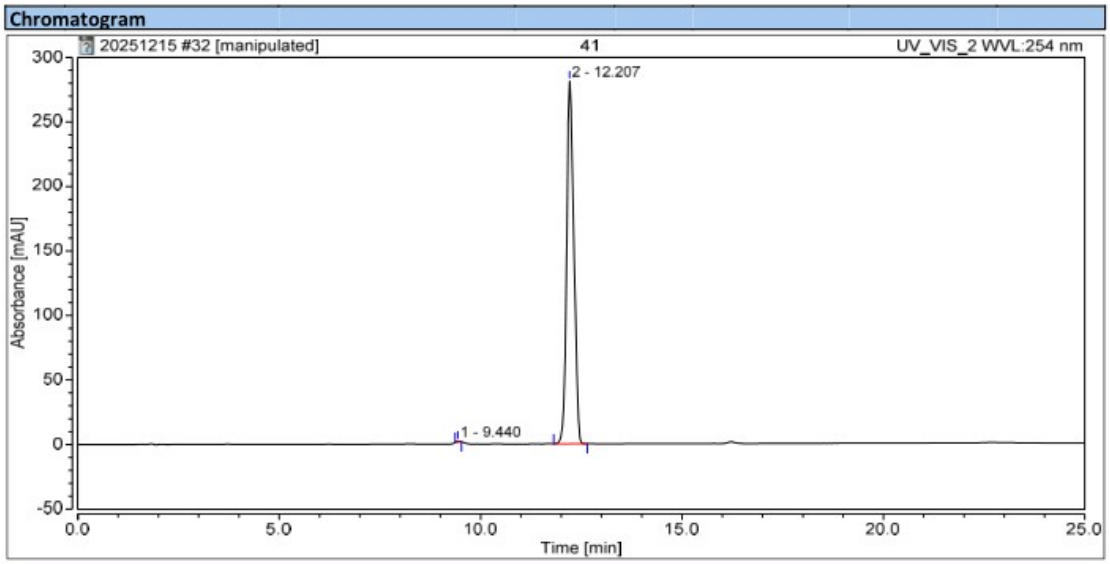


Figure S32. HRMS spectrum of 15a



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		9.440	0.090	0.887	0.16	0.31	n.a.
2		12.207	57.968	281.202	99.84	99.69	n.a.
Total:			**58.058**	**282.088**	**100.00**	**100.00**	

Figure S33. HPLC spectrum of 15a

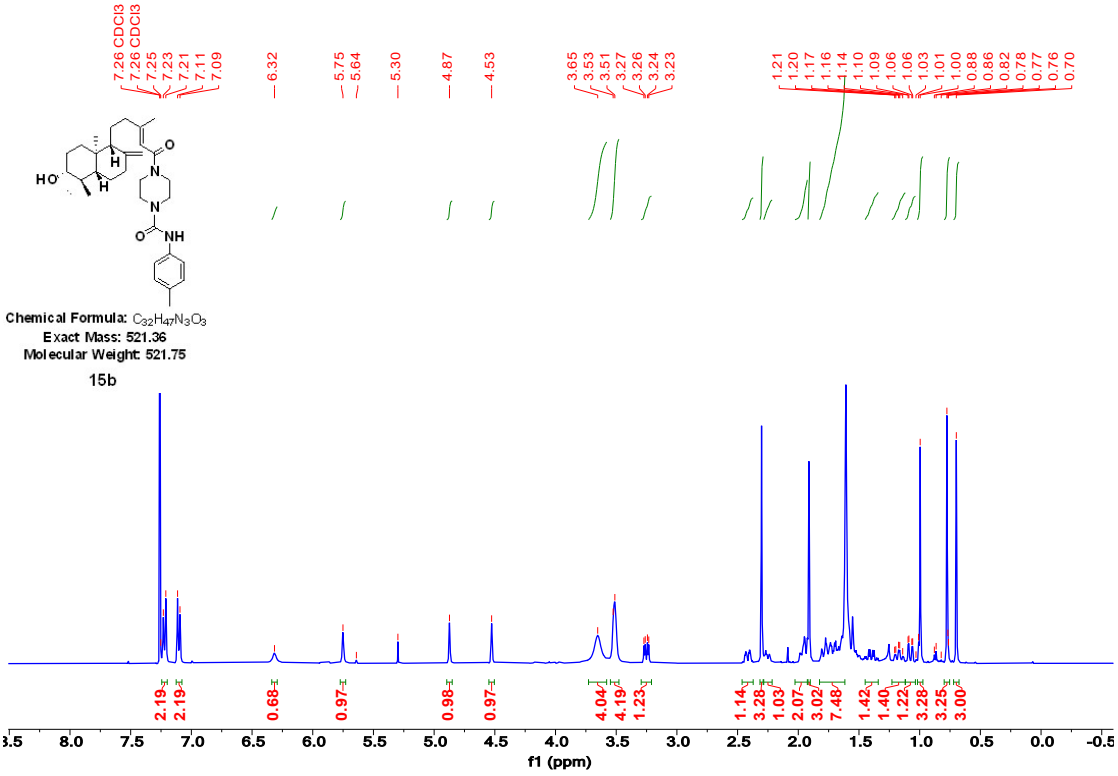


Figure S34. ^{1}H NMR spectrum of 15b

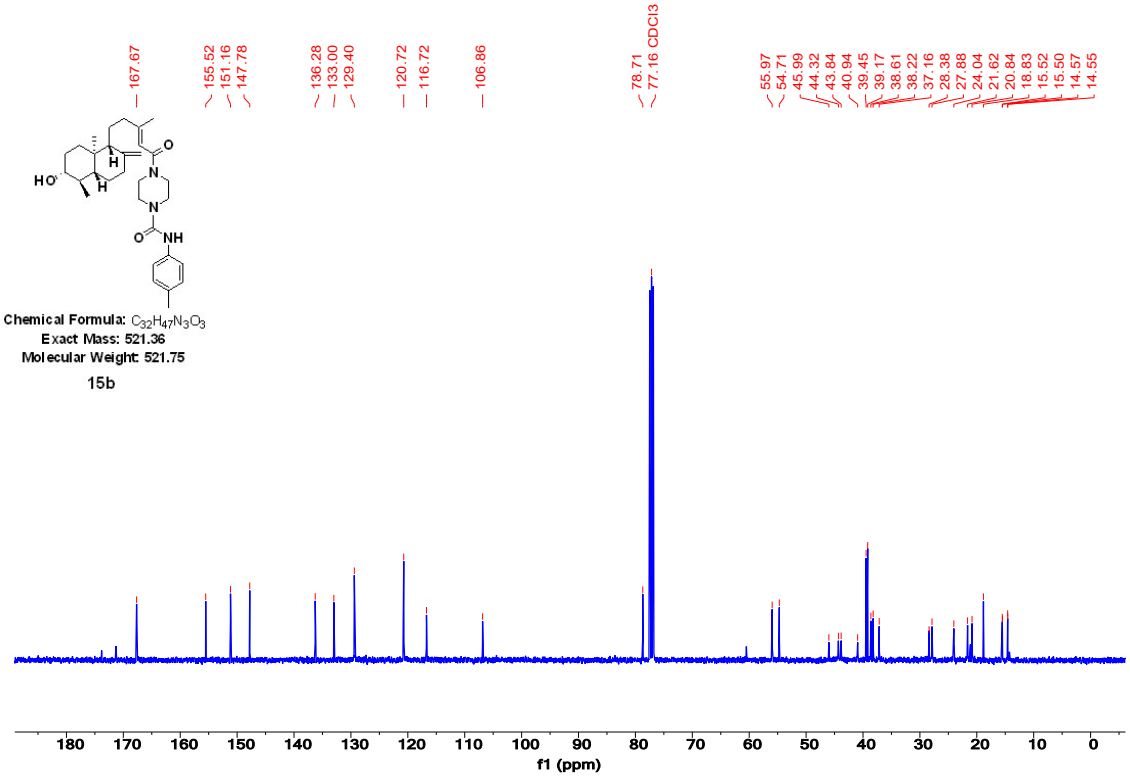


Figure S35. ^{13}C NMR spectrum of 15b

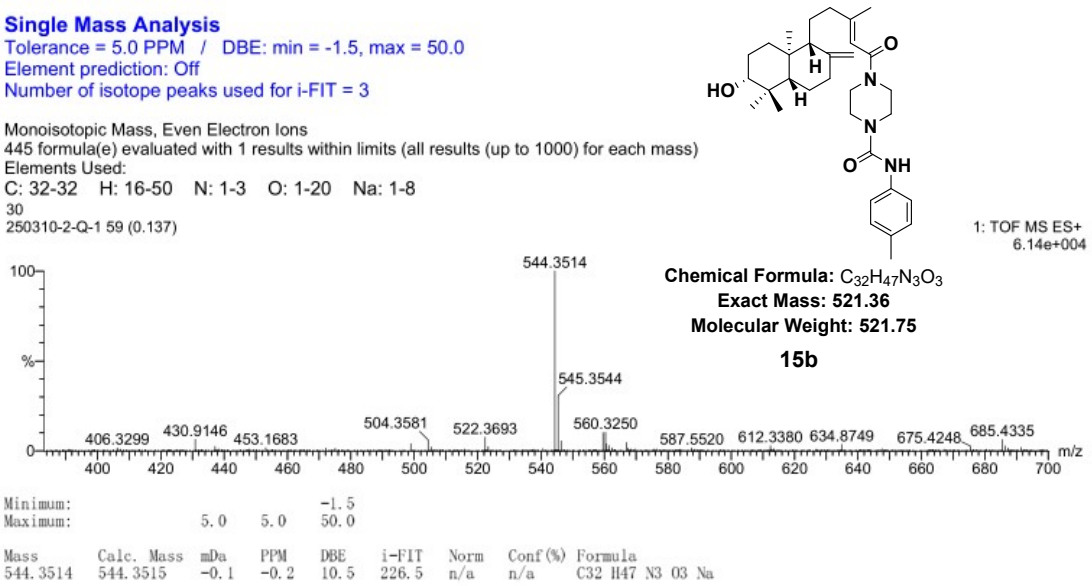
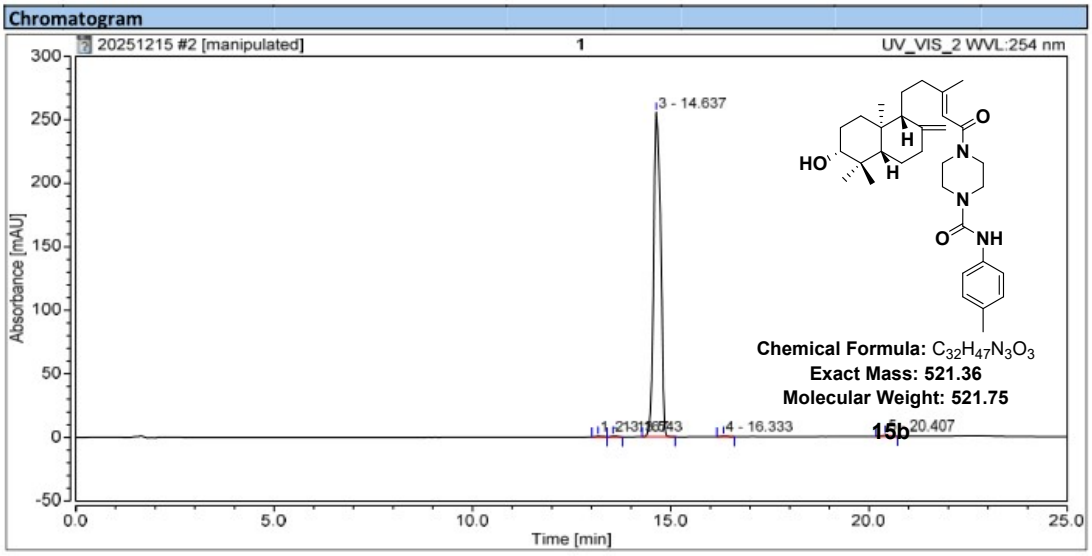


Figure S36. HRMS spectrum of 15b



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.167	0.111	0.557	0.21	0.22	n.a.
2		13.543	0.123	0.636	0.23	0.25	n.a.
3		14.637	52.236	255.633	99.02	98.96	n.a.
4		16.333	0.107	0.533	0.20	0.21	n.a.
5		20.407	0.177	0.964	0.34	0.37	n.a.
Total:			**52.754**	**258.322**	**100.00**	**100.00**	

Figure S37. HPLC spectrum of 15b

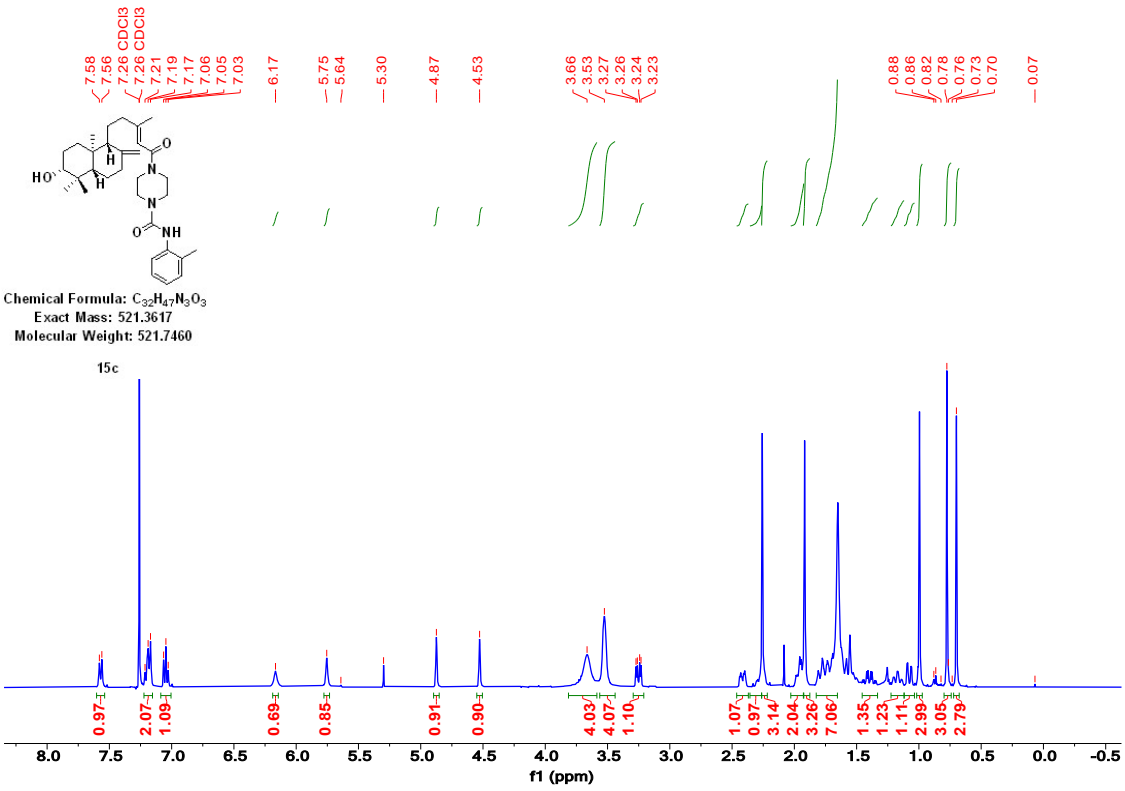


Figure S38. ^{1}H NMR spectrum of 15c

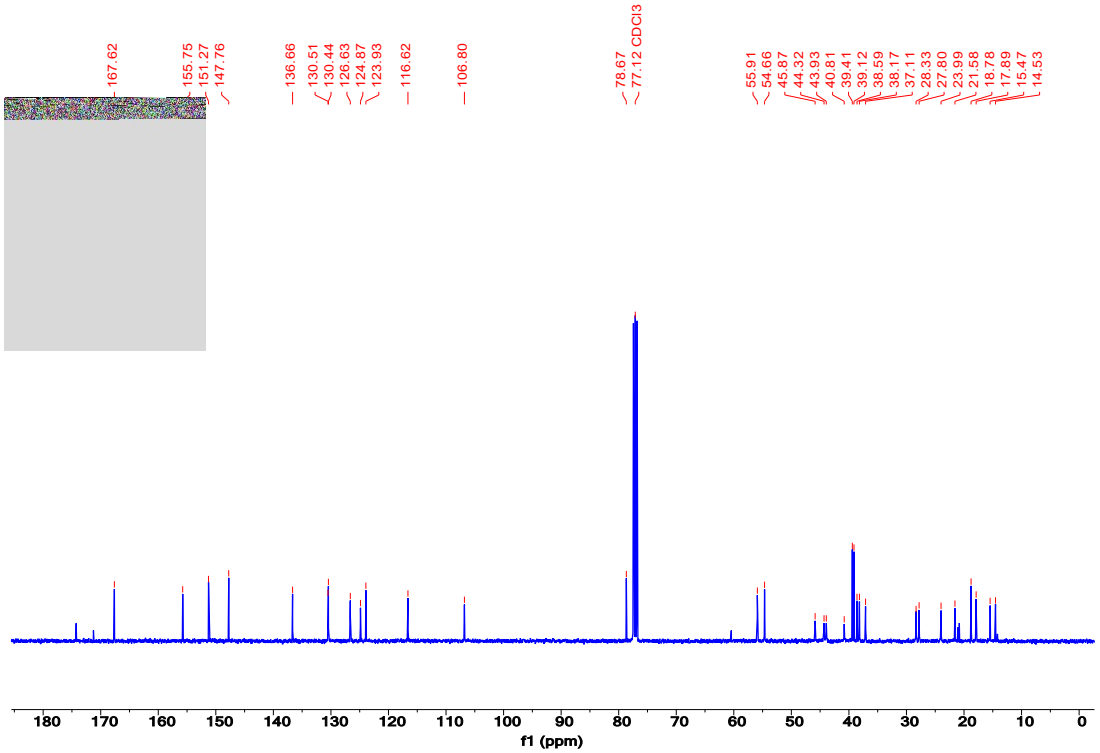


Figure S39. ^{13}C NMR spectrum of 15c

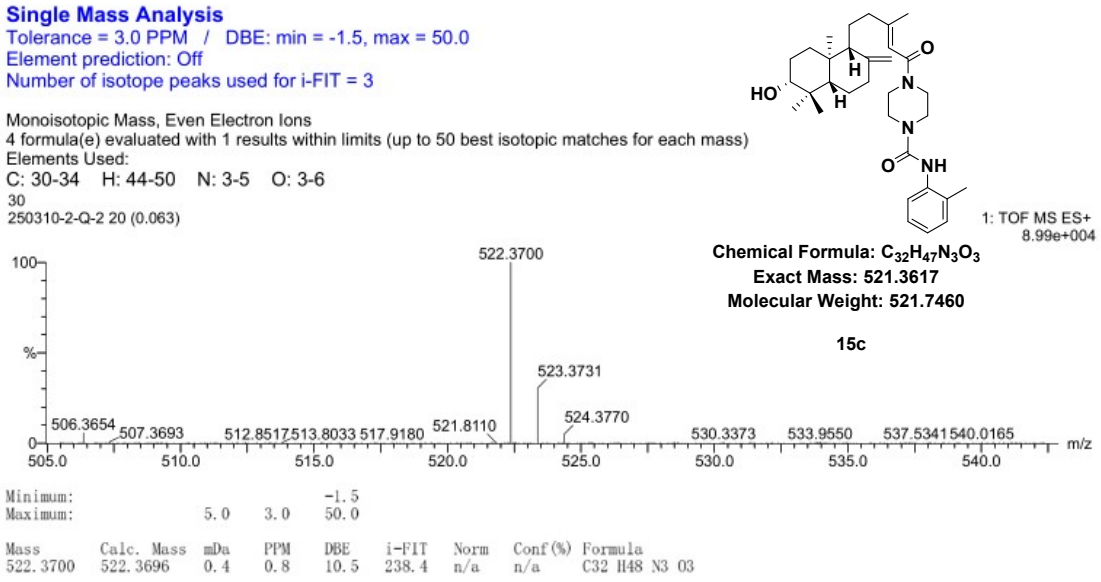
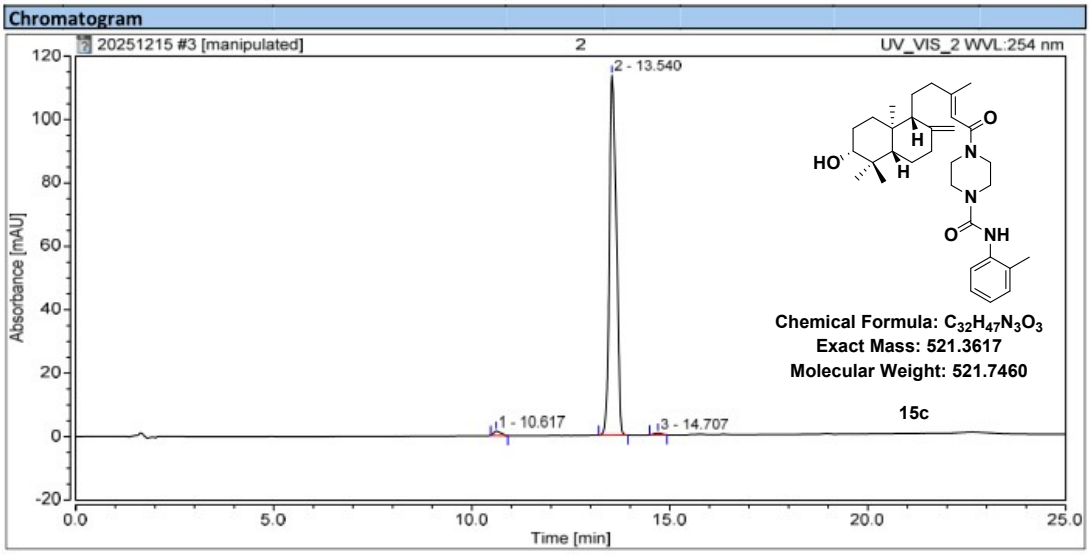


Figure S40. HRMS spectrum of 15c



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.617	0.288	1.384	1.23	1.20	n.a.
2		13.540	22.998	113.533	98.23	98.34	n.a.
3		14.707	0.127	0.538	0.54	0.47	n.a.
Total:			**23.412**	**115.455**	**100.00**	**100.00**	

Figure S41. HPLC spectrum of 15c

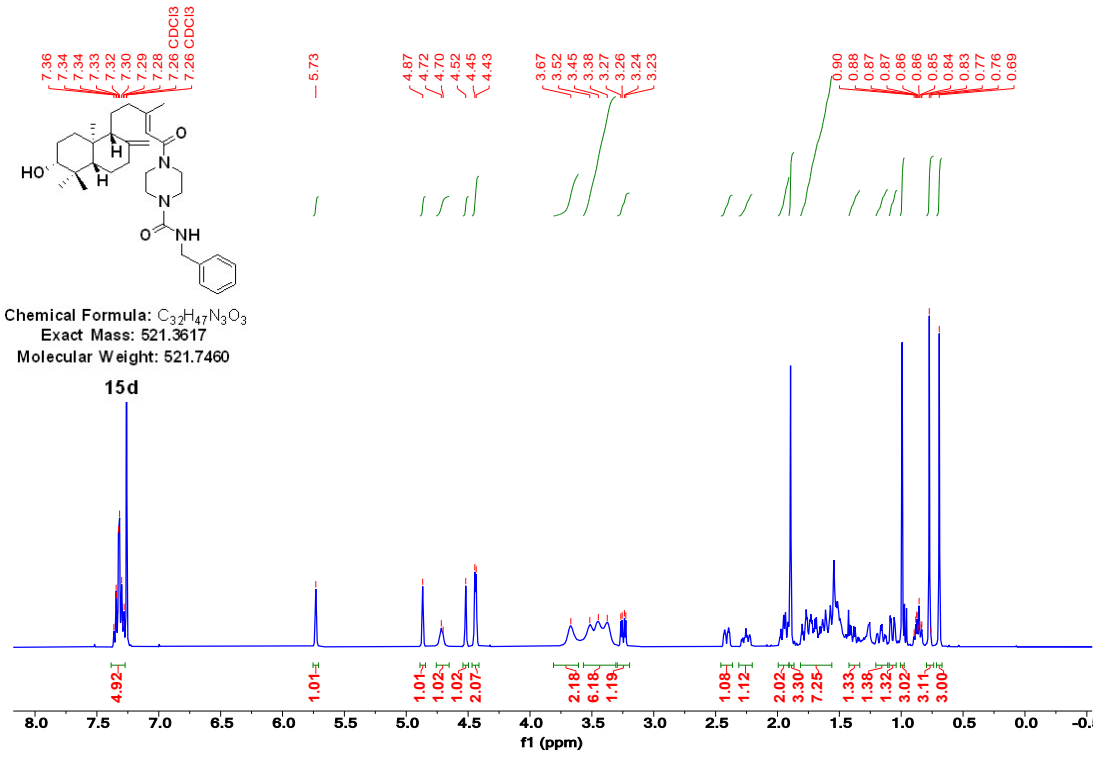


Figure S42. ^{1}H NMR spectrum of 15d

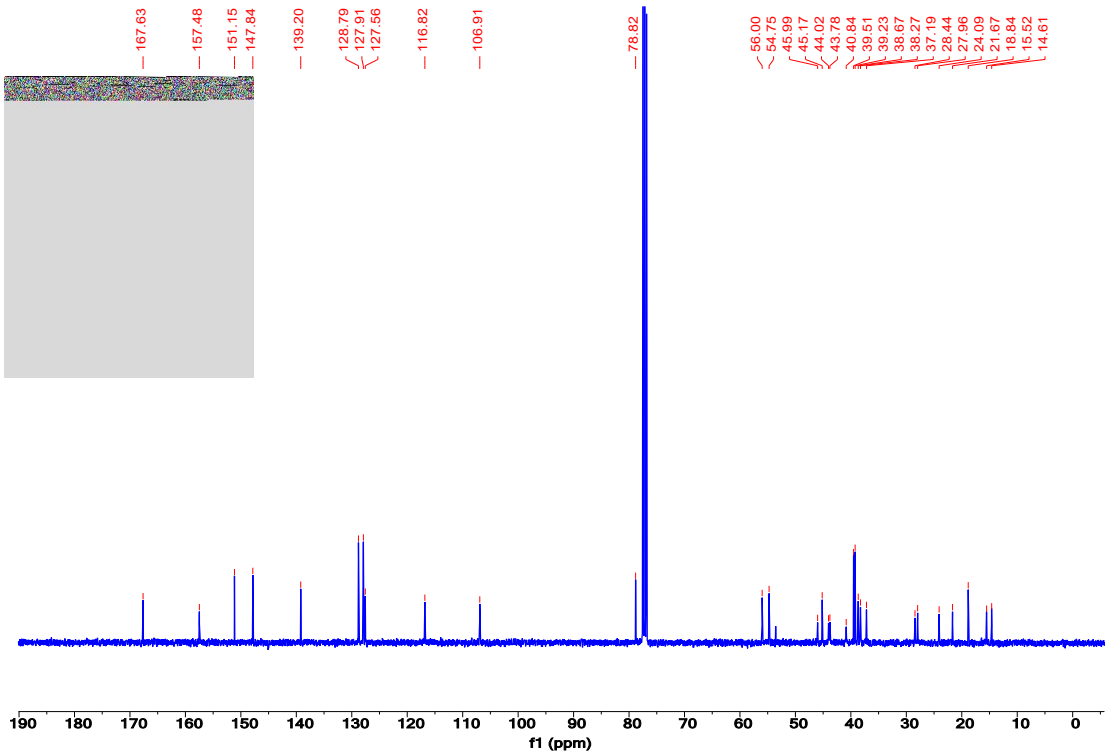


Figure S43. 13C NMR spectrum of 15d

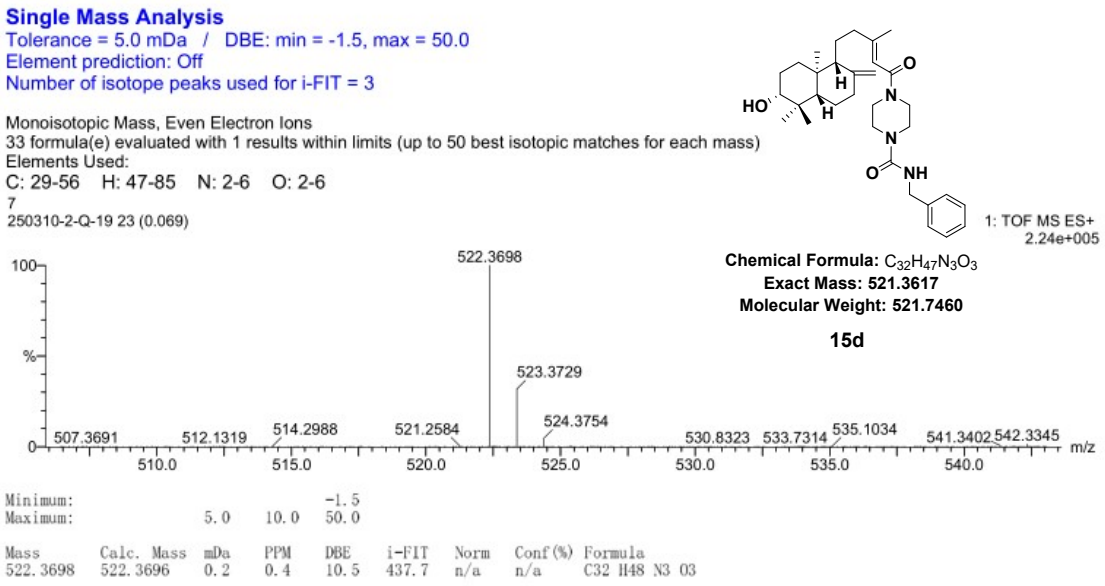
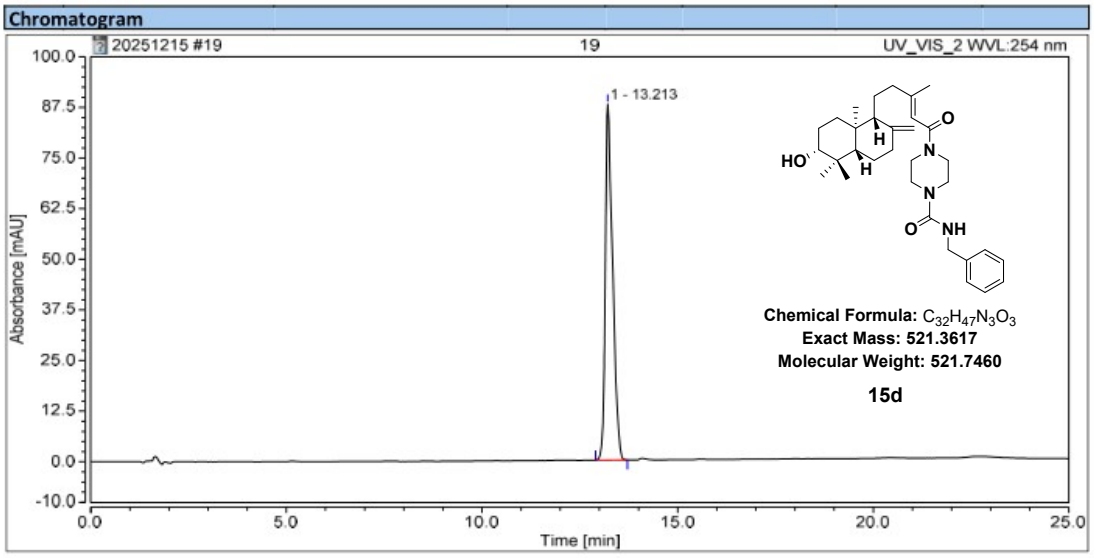


Figure S44. HRMS spectrum of 15d



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.213	19.026	87.926	100.00	100.00	n.a.
Total:			**19.026**	**87.926**	**100.00**	**100.00**	

Figure S45. HPLC spectrum of 15d

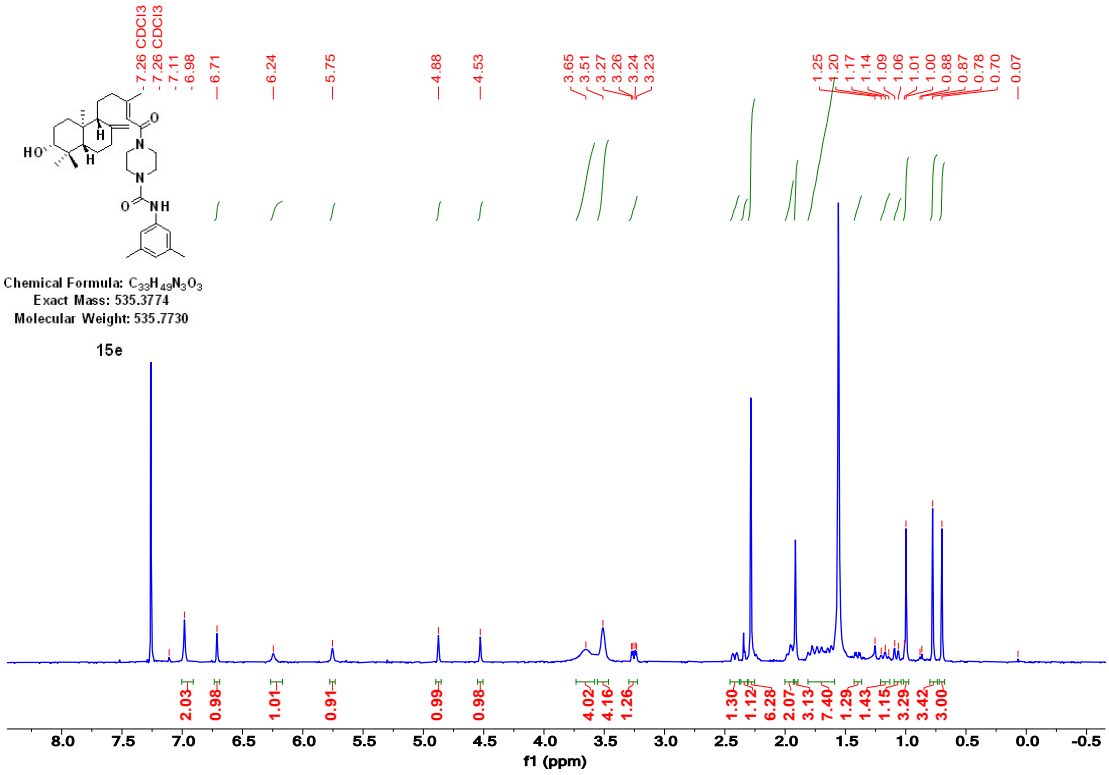


Figure S46. ^{1}H NMR spectrum of 15e

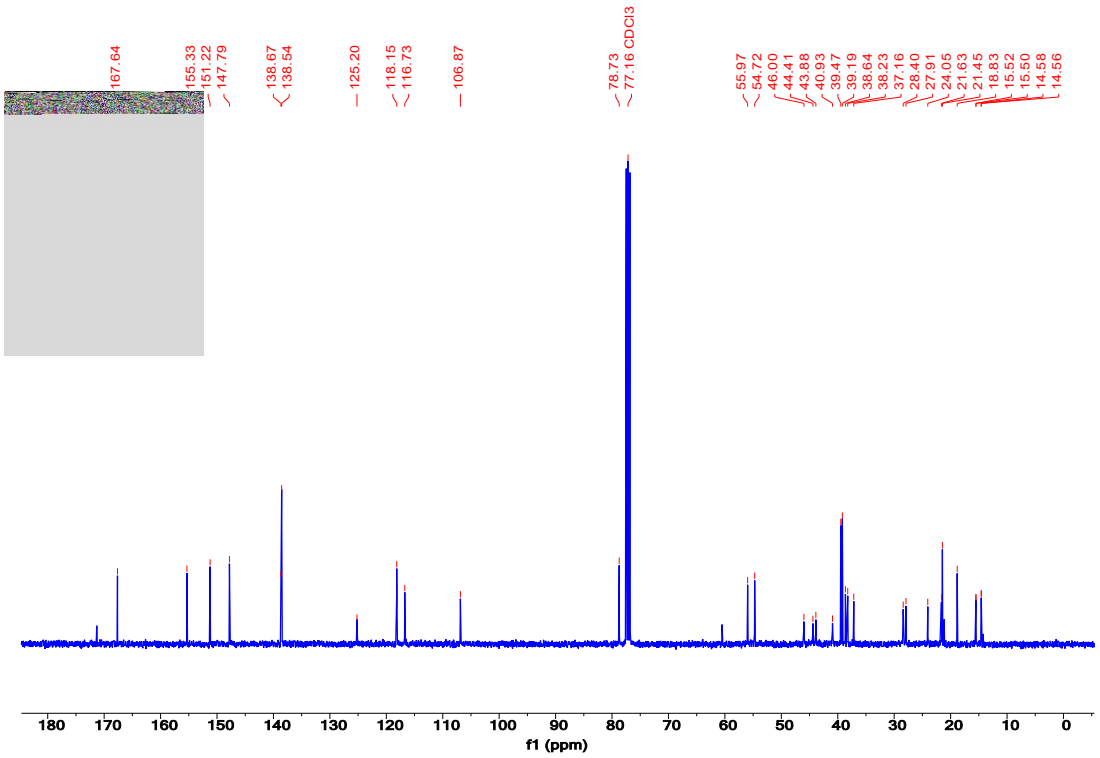


Figure S47. ^{13}C NMR spectrum of 15e

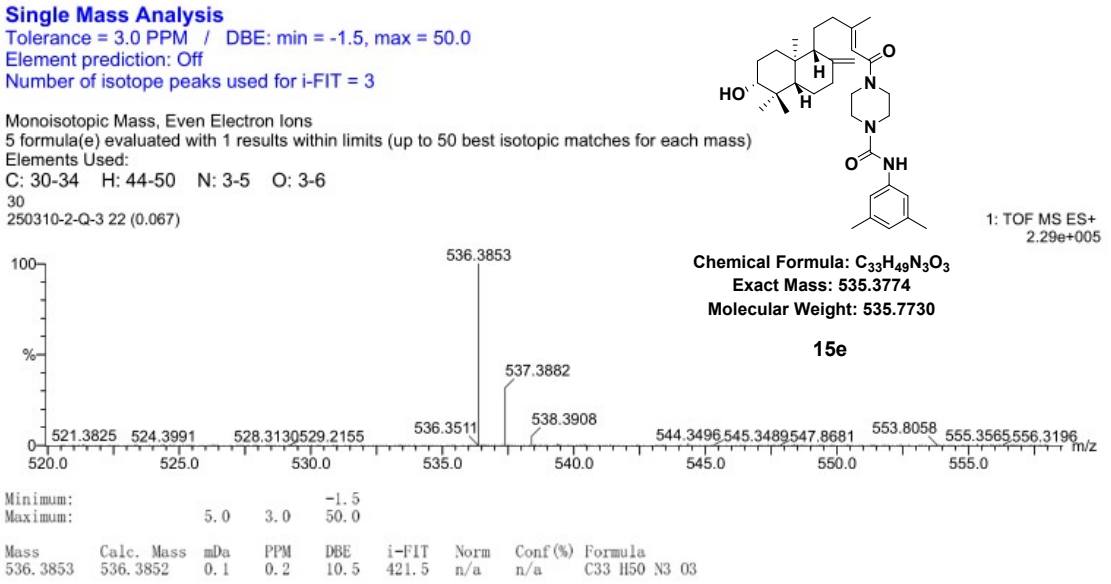
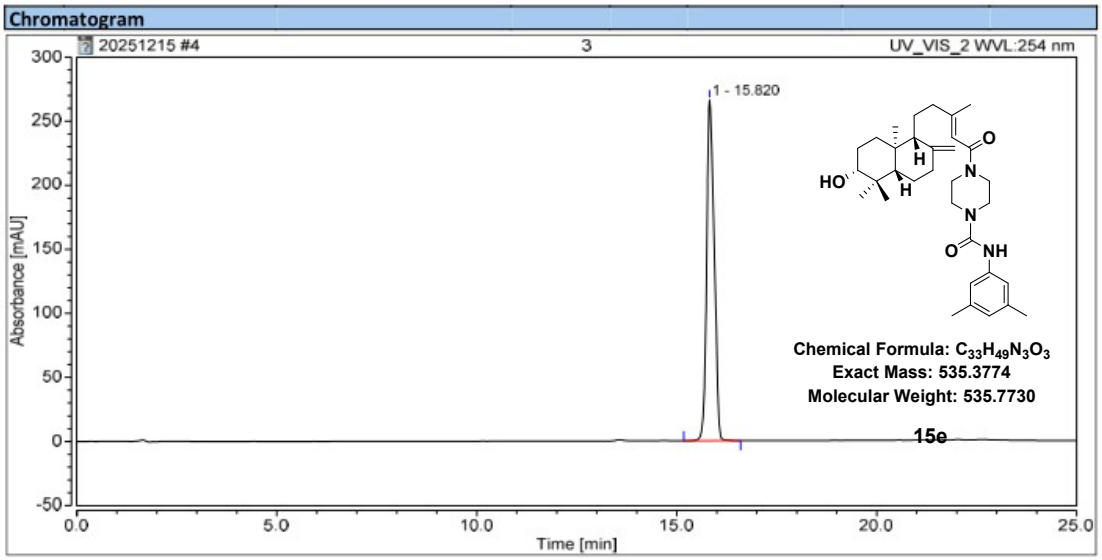


Figure S48. HRMS spectrum of 15e



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15.820	57.987	266.136	100.00	100.00	n.a.
Total:			**57.987**	**266.136**	**100.00**	**100.00**	

Figure S49. HPLC spectrum of 15e

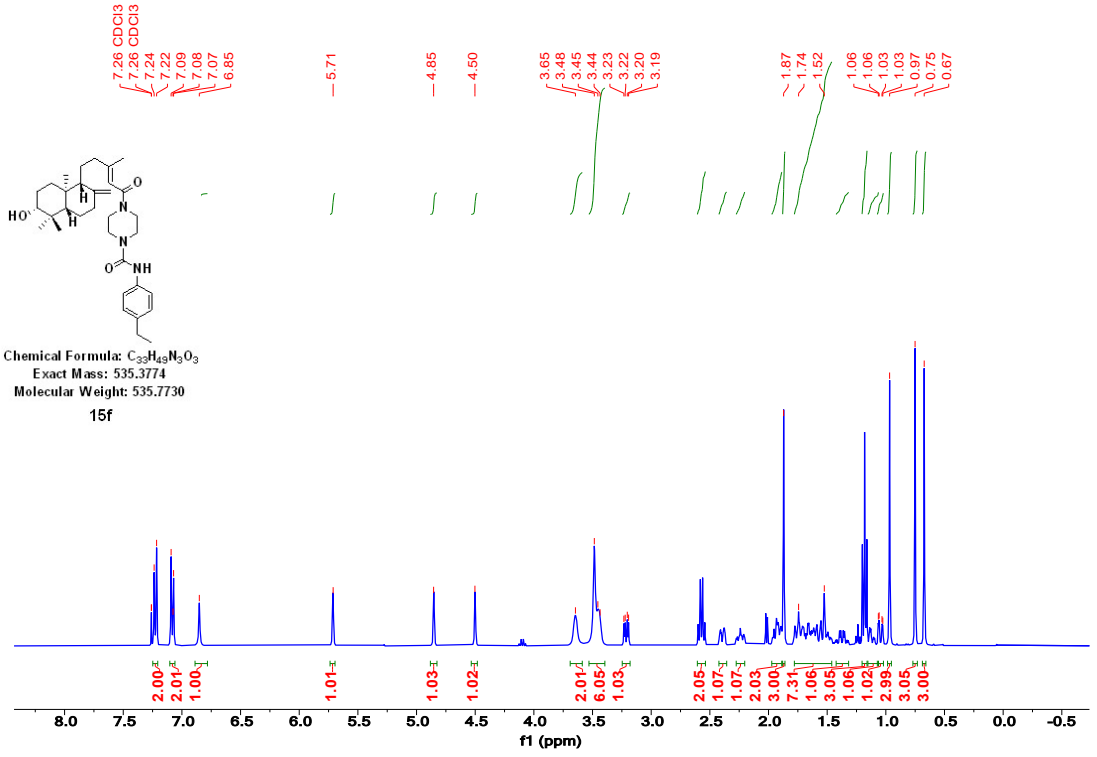


Figure S50. ^{1}H NMR spectrum of 15f

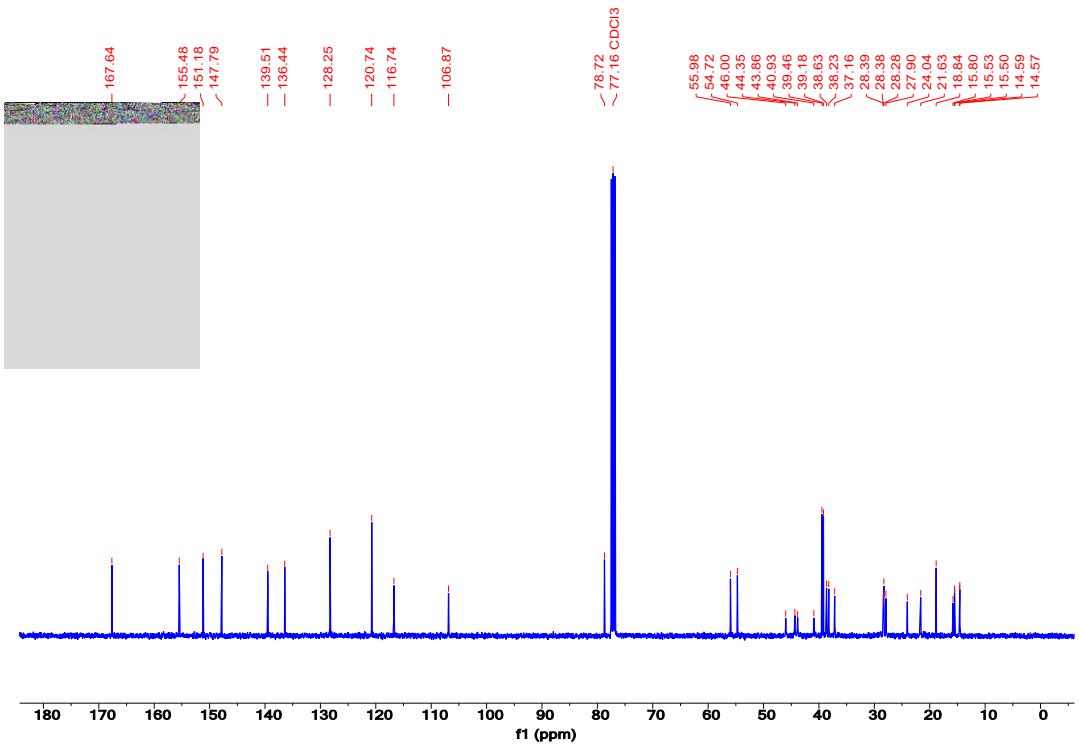


Figure S51. ^{13}C NMR spectrum of 15f

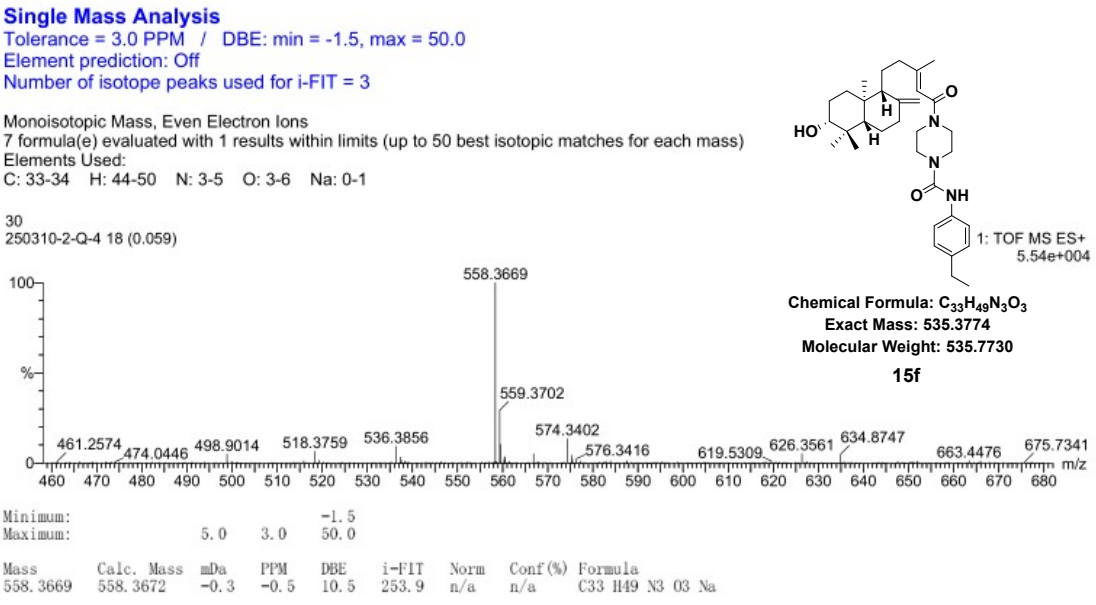
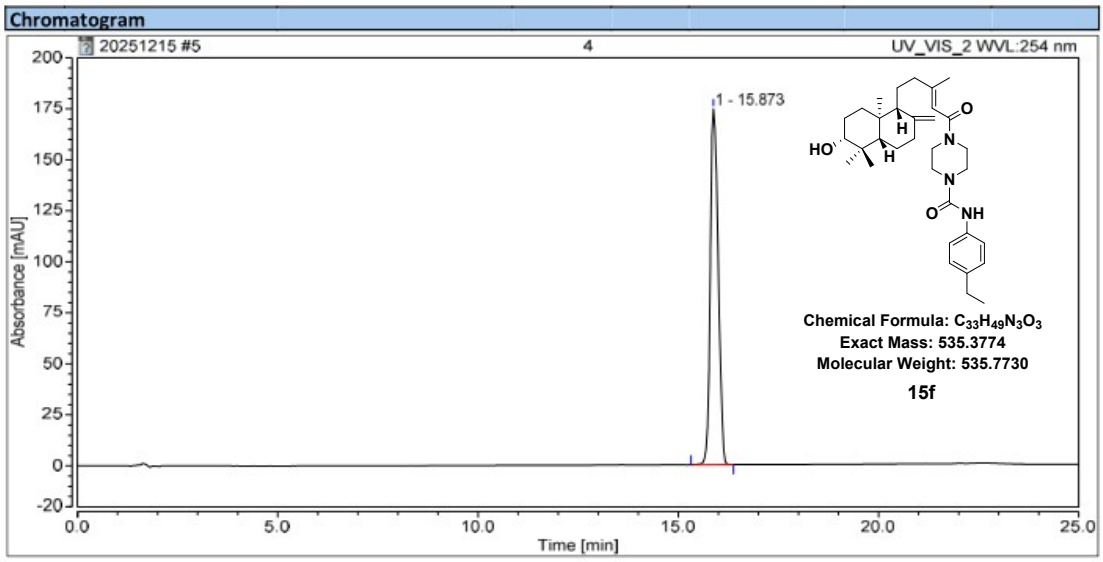


Figure S52. HRMS spectrum of 15f



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15.873	40.006	174.420	100.00	100.00	n.a.
Total:			**40.006**	**174.420**	**100.00**	**100.00**	

Figure S53. HPLC spectrum of 15f

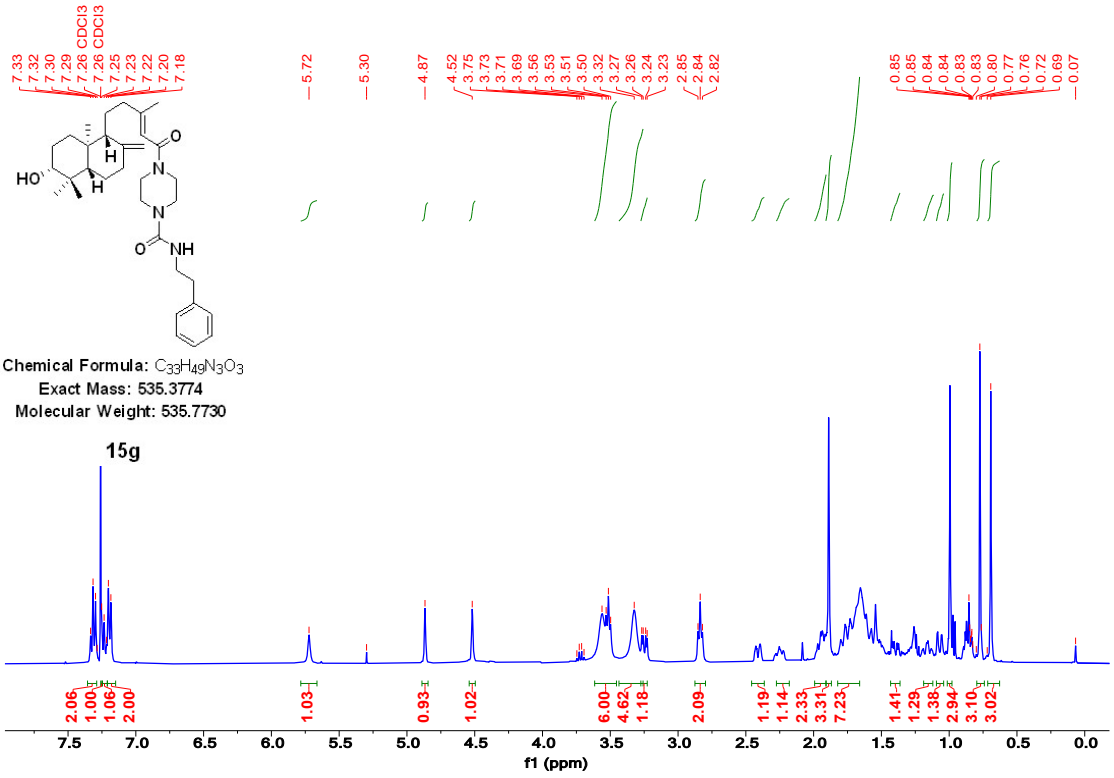


Figure S54. ^{1}H NMR spectrum of 15g

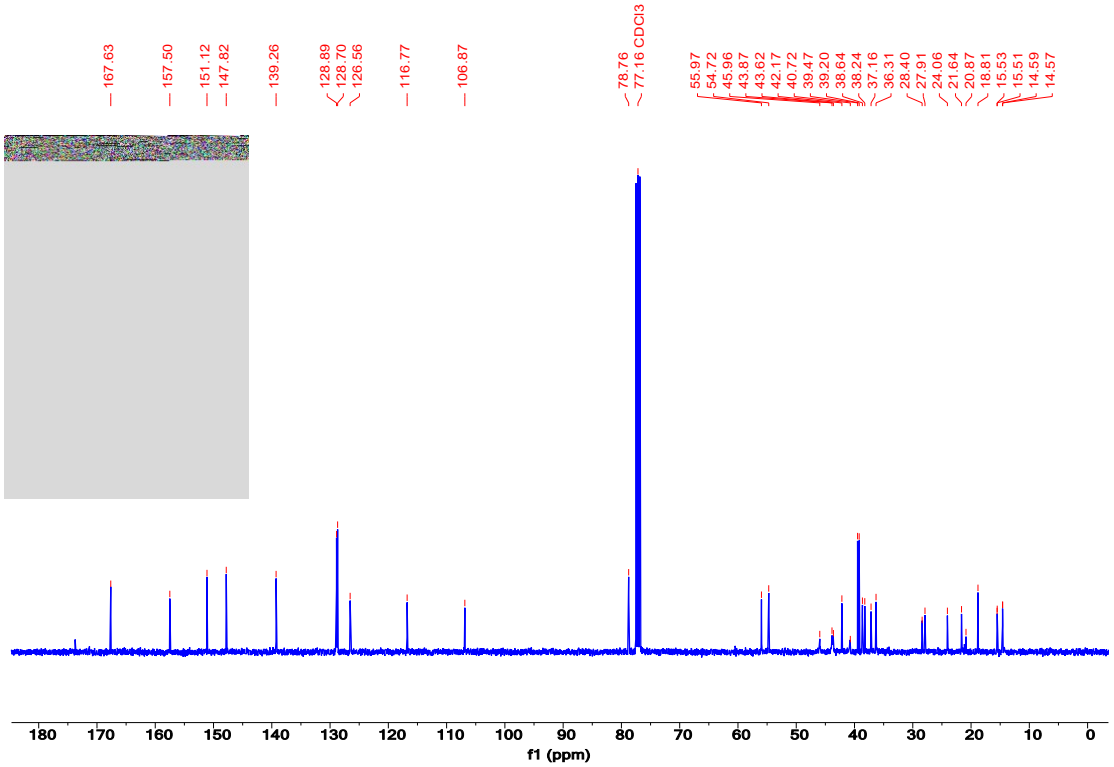


Figure S55. ^{13}C NMR spectrum of 15g

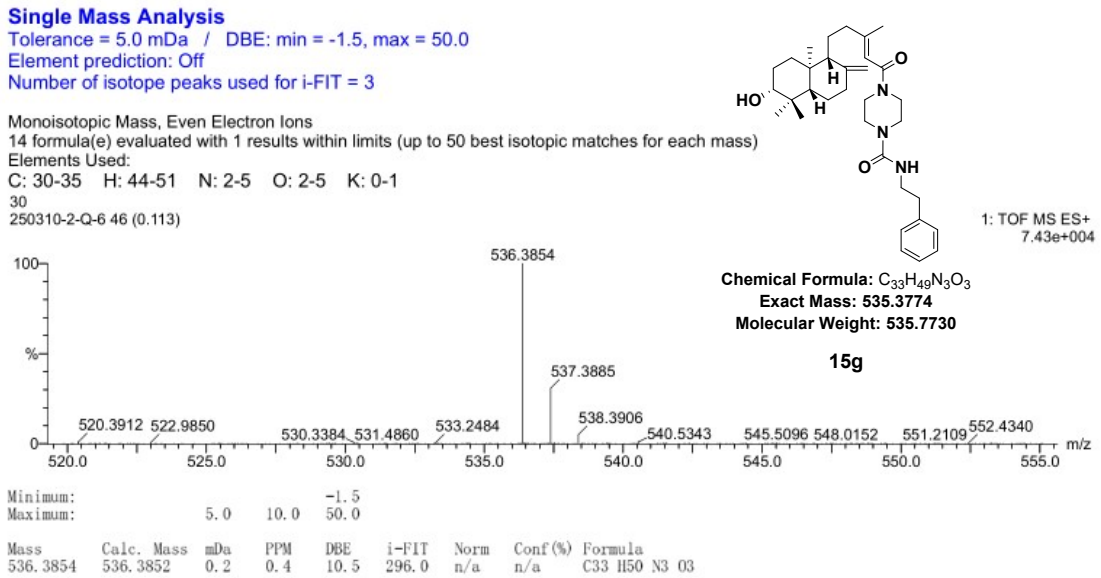
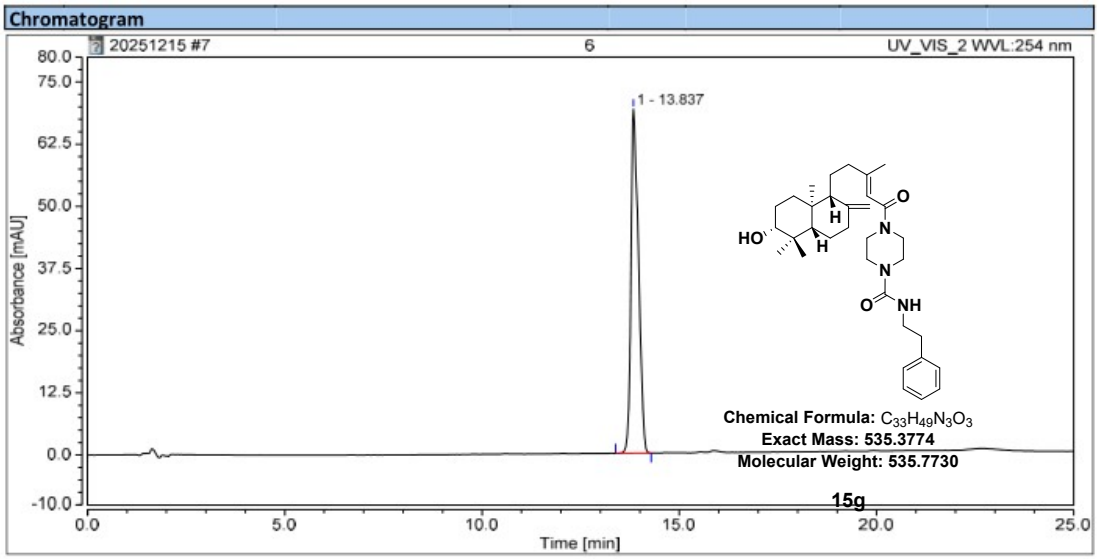


Figure S56. HRMS spectrum of 15g



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.837	15.263	69.196	100.00	100.00	n.a.
Total:			**15.263**	**69.196**	**100.00**	**100.00**	

Figure S57. HPLC spectrum of 15g

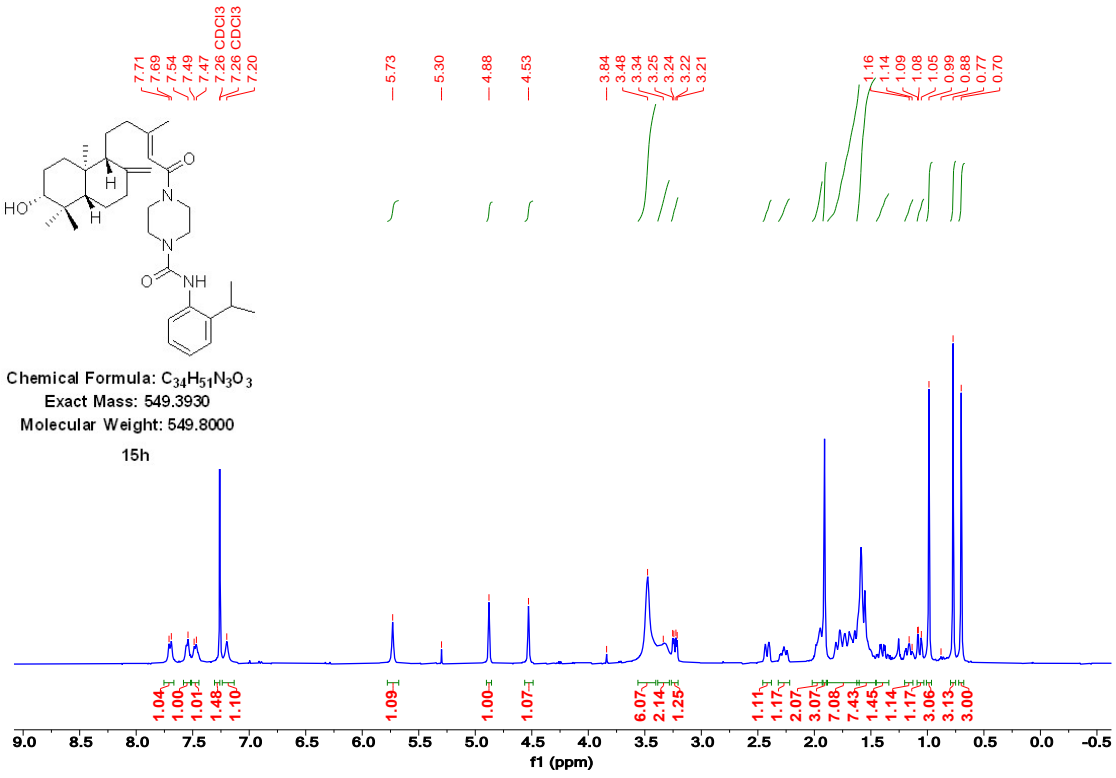


Figure S58. ^{1}H NMR spectrum of 15h

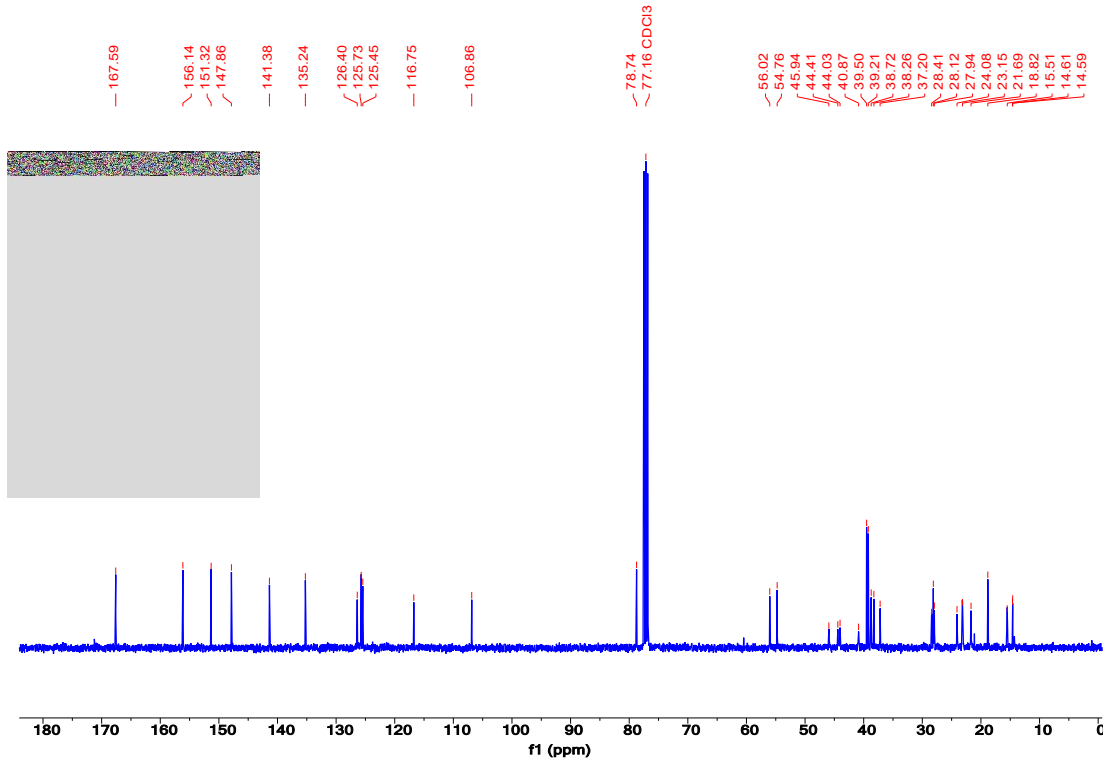


Figure S59. ^{13}C NMR spectrum of 15h

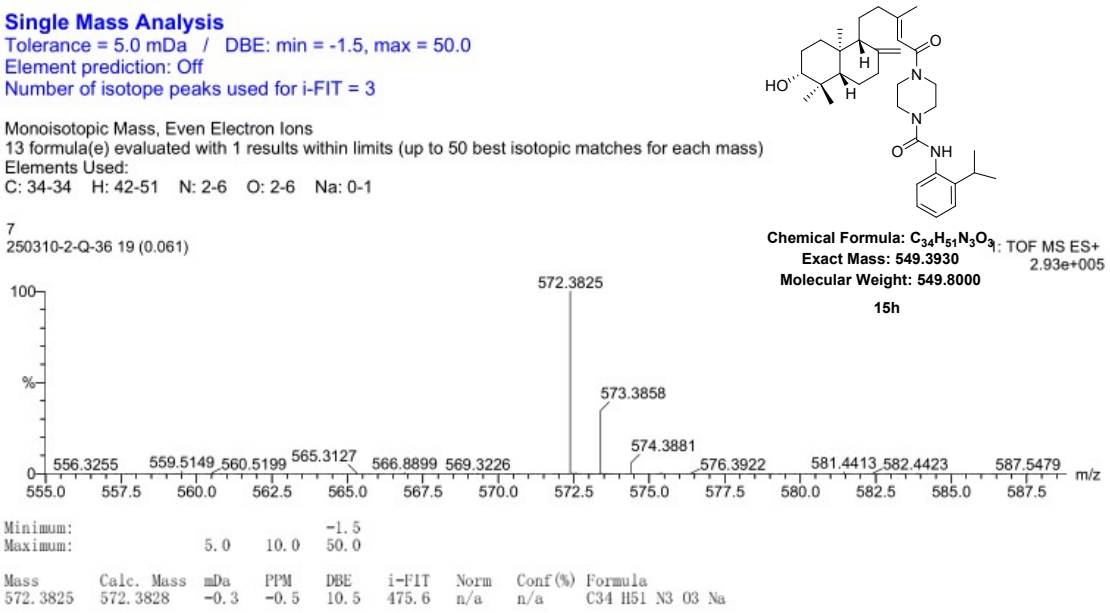
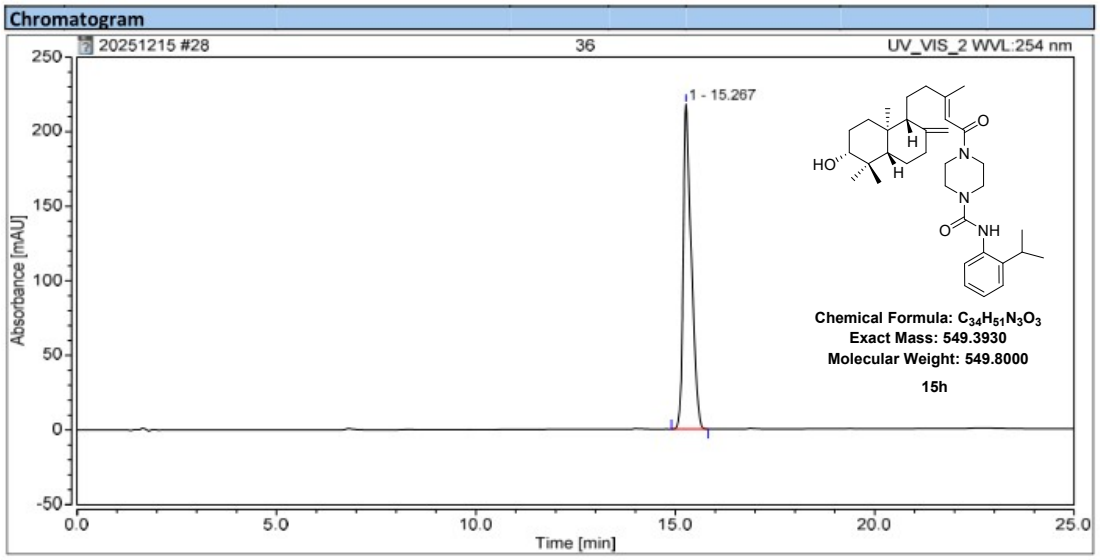


Figure S60. HRMS spectrum of 15h



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15.267	51.010	217.797	100.00	100.00	n.a.
Total:			**51.010**	**217.797**	**100.00**	**100.00**	

Figure S61. HPLC spectrum of 15h

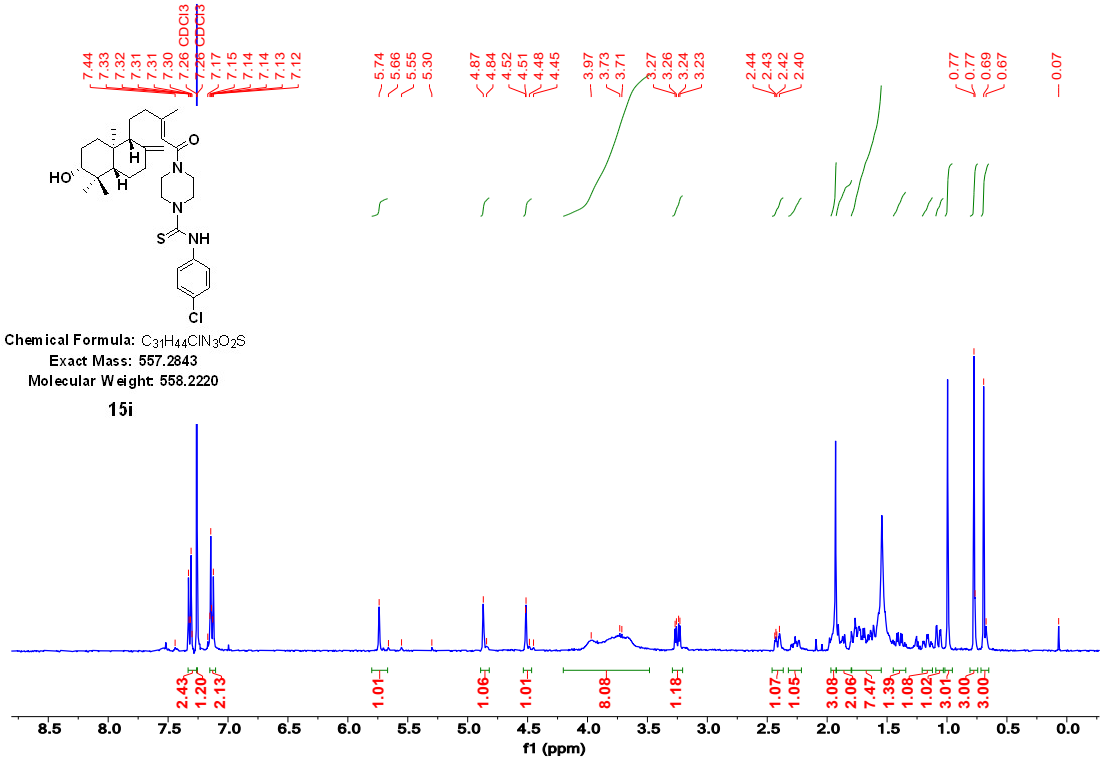


Figure S62. ^{1}H NMR spectrum of 15i

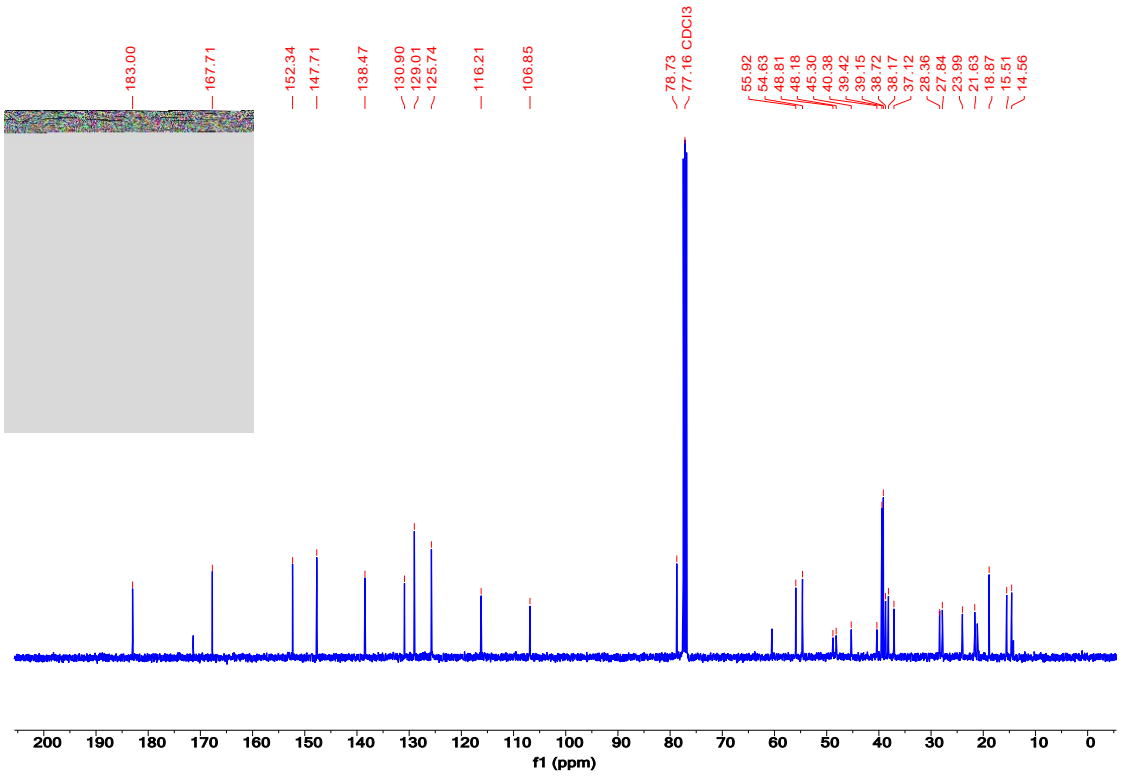


Figure S63. ^{13}C NMR spectrum of 15i

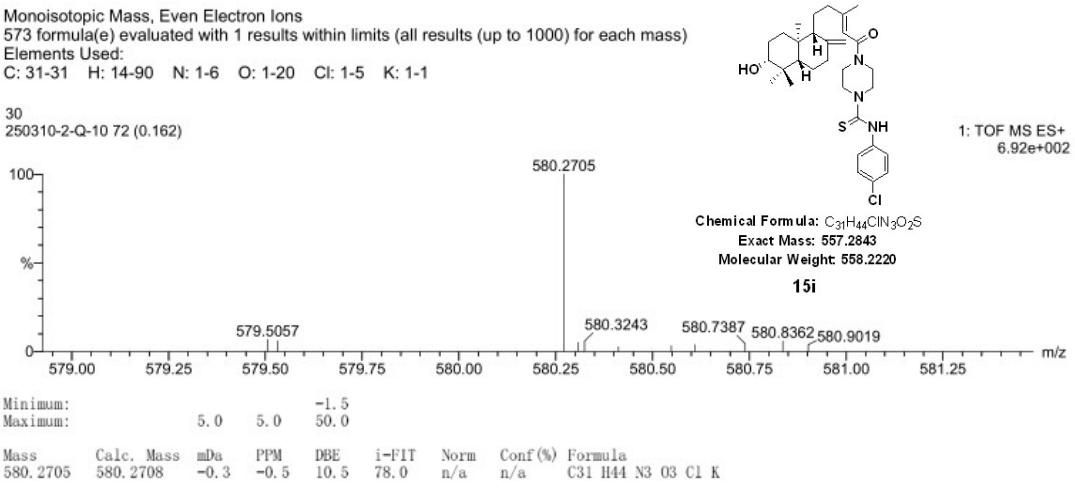
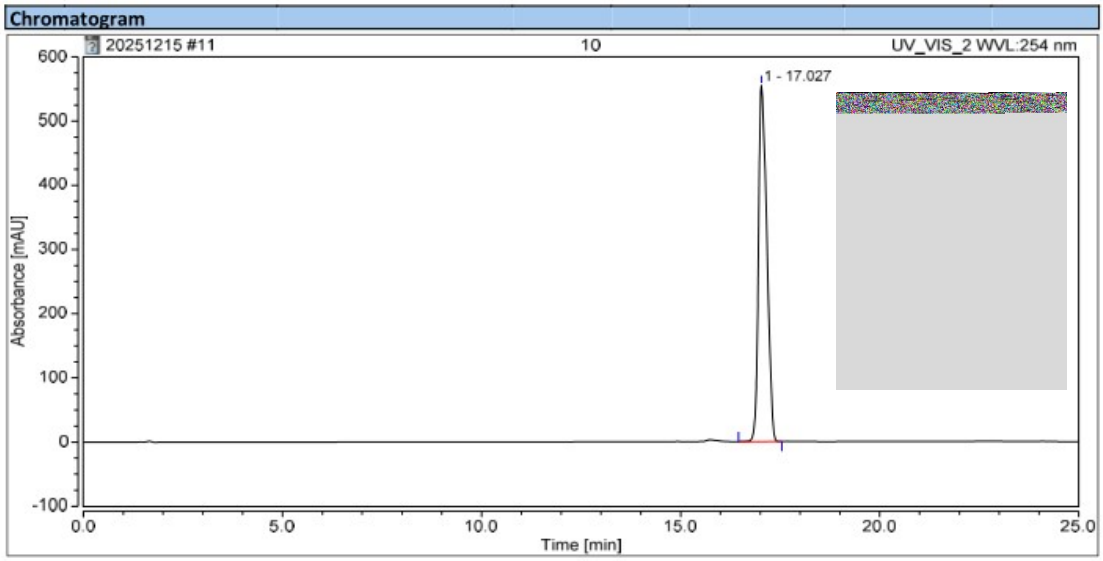


Figure S64. HRMS spectrum of 15i



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.027	134.931	554.635	100.00	100.00	n.a.
Total:			**134.931**	**554.635**	**100.00**	**100.00**	

Figure S65. HPLC spectrum of 15i

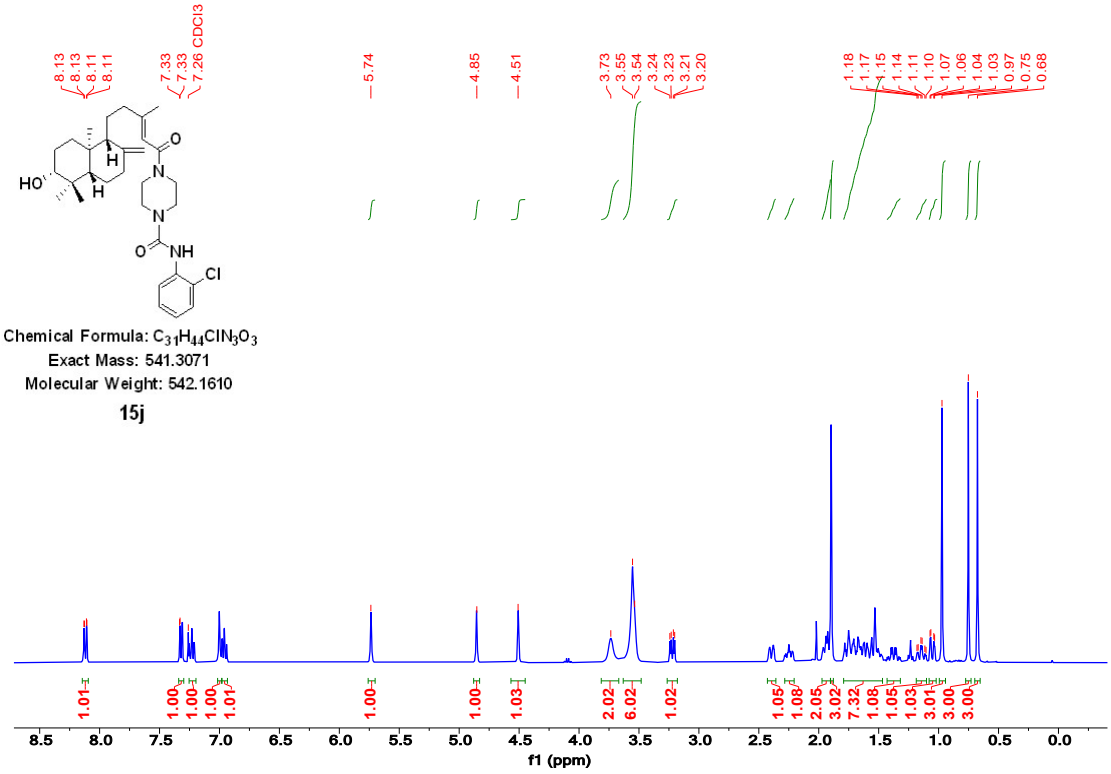


Figure S66. ^{1}H NMR spectrum of 15j

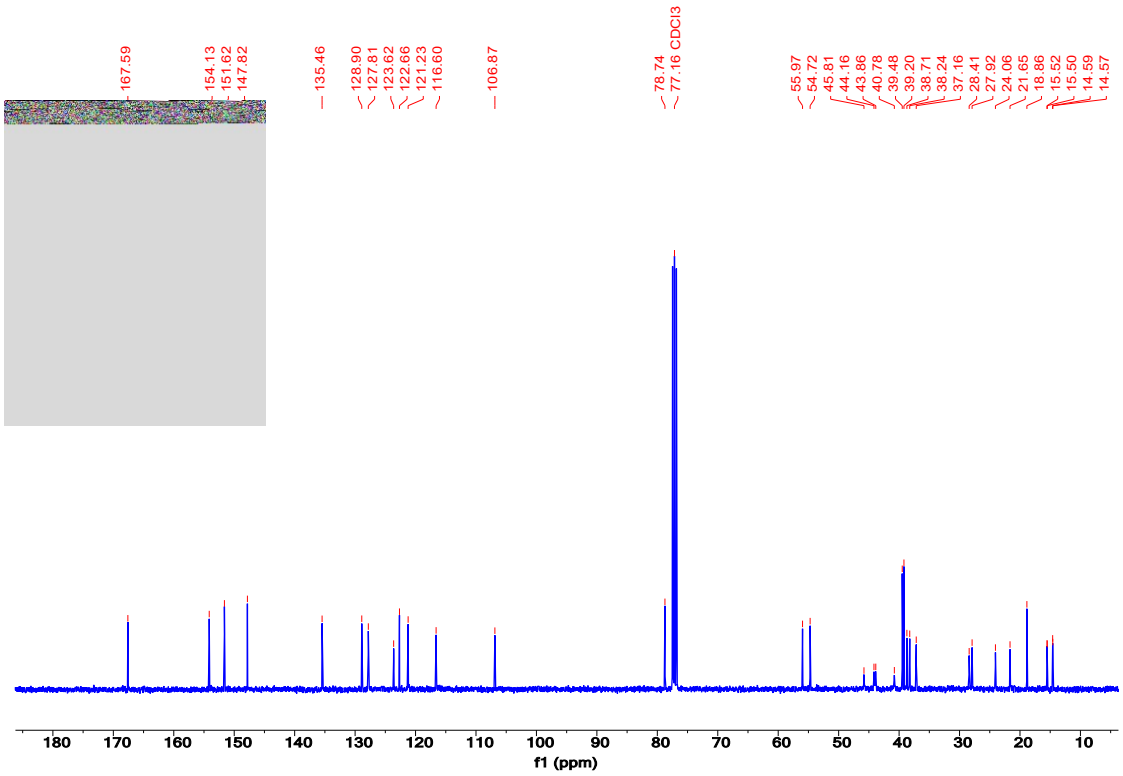


Figure S67. ^{13}C NMR spectrum of 15j

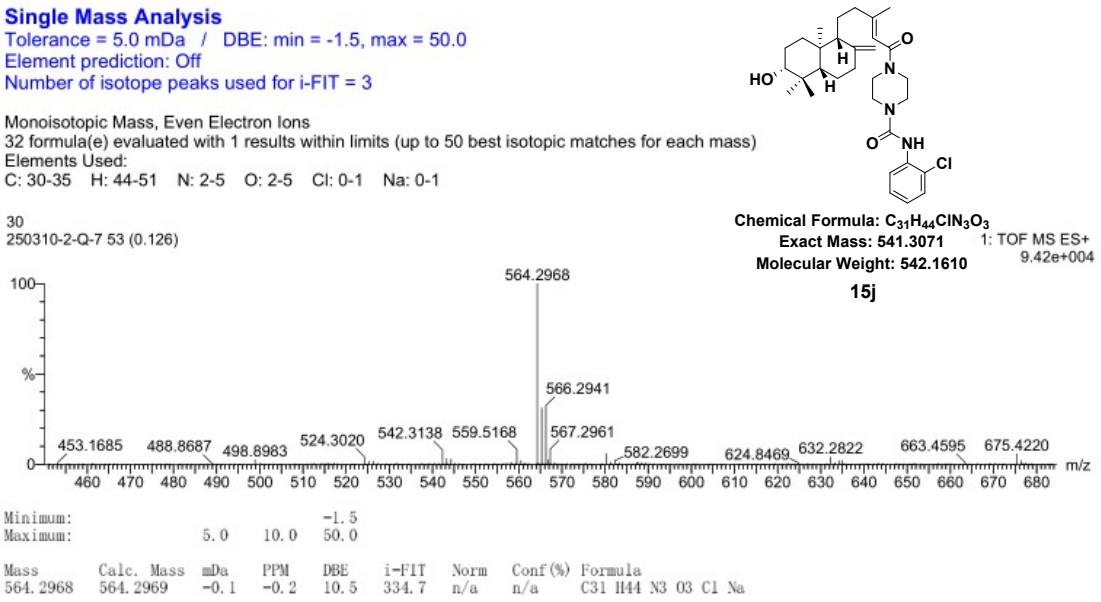
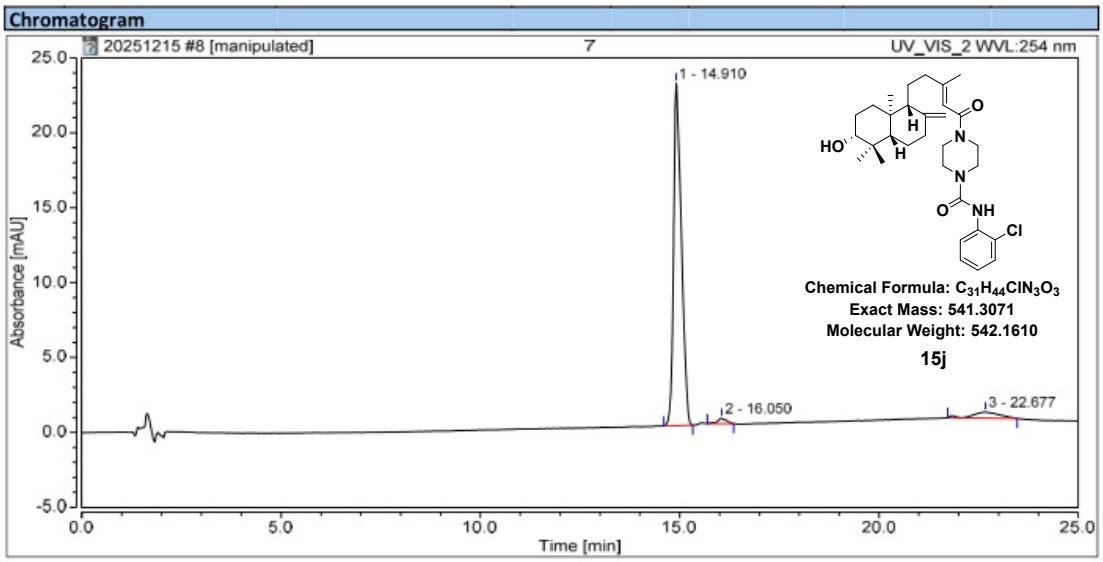


Figure S68. HRMS spectrum of 15j



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		14.910	5.160	22.871	92.85	96.77	n.a.
2		16.050	0.096	0.360	1.73	1.52	n.a.
3		22.677	0.301	0.403	5.42	1.70	n.a.
Total:			**5.557**	**23.634**	**100.00**	**100.00**	

Figure S69. HPLC spectrum of 15j

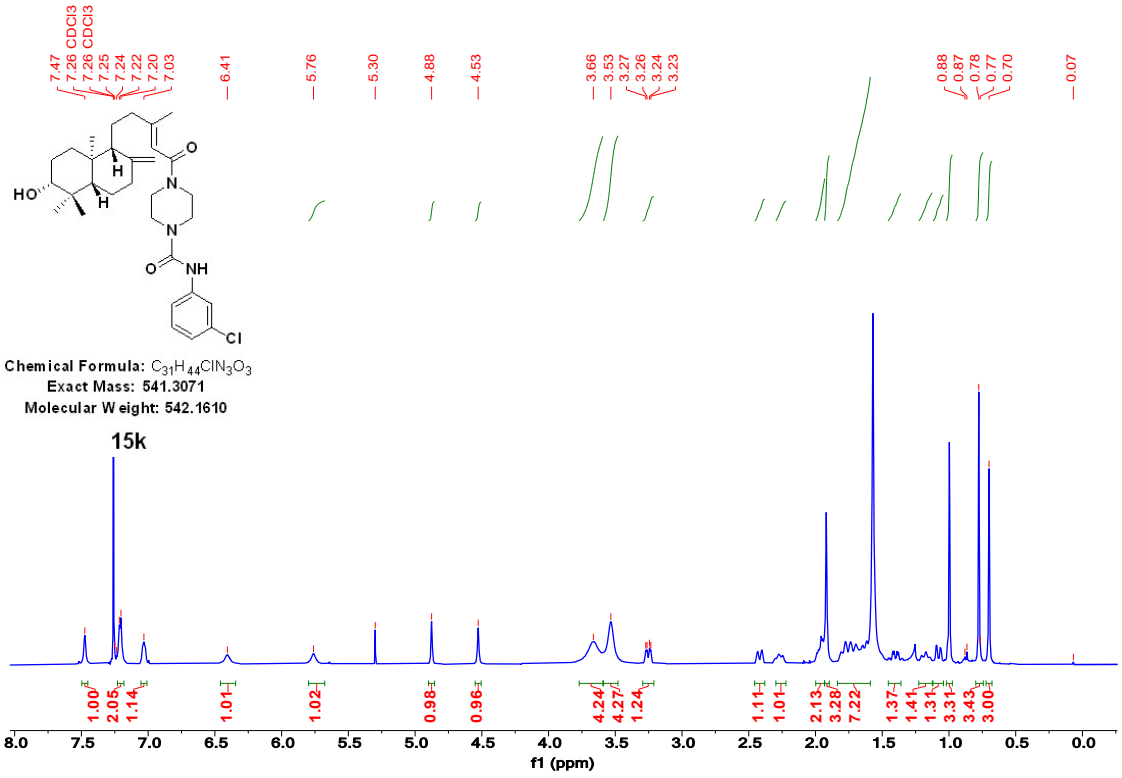


Figure S70. ^{1}H NMR spectrum of 15k

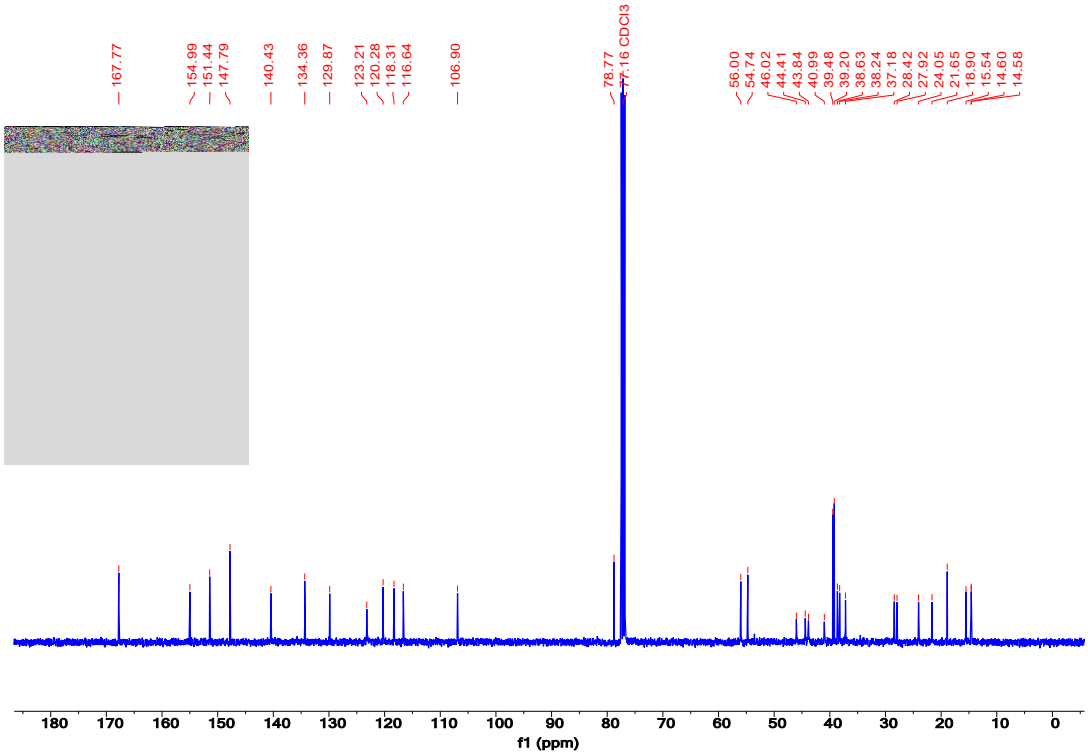


Figure S71. ^{13}C NMR spectrum of 15k

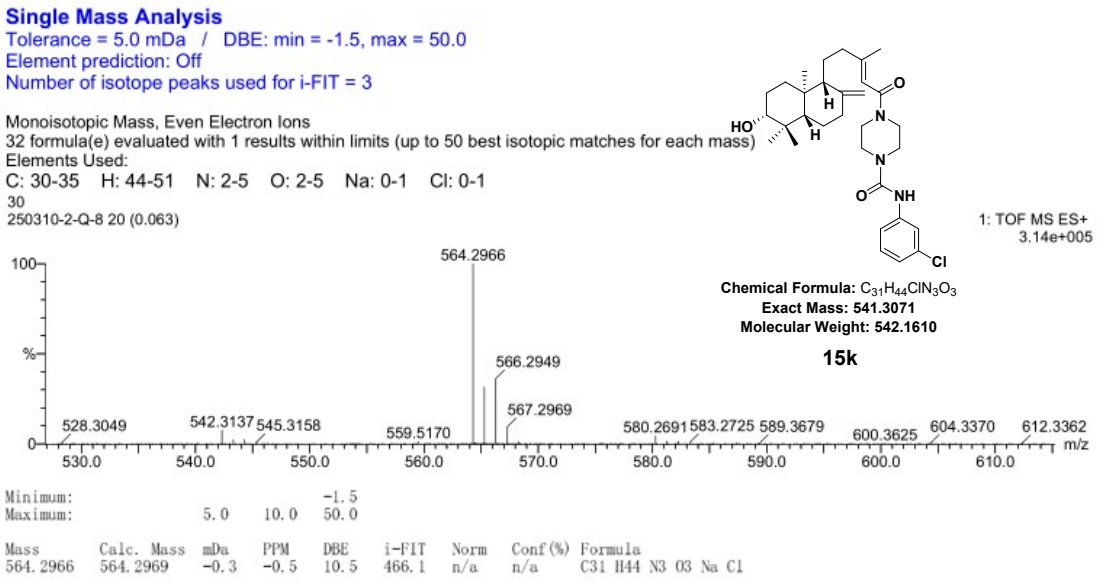
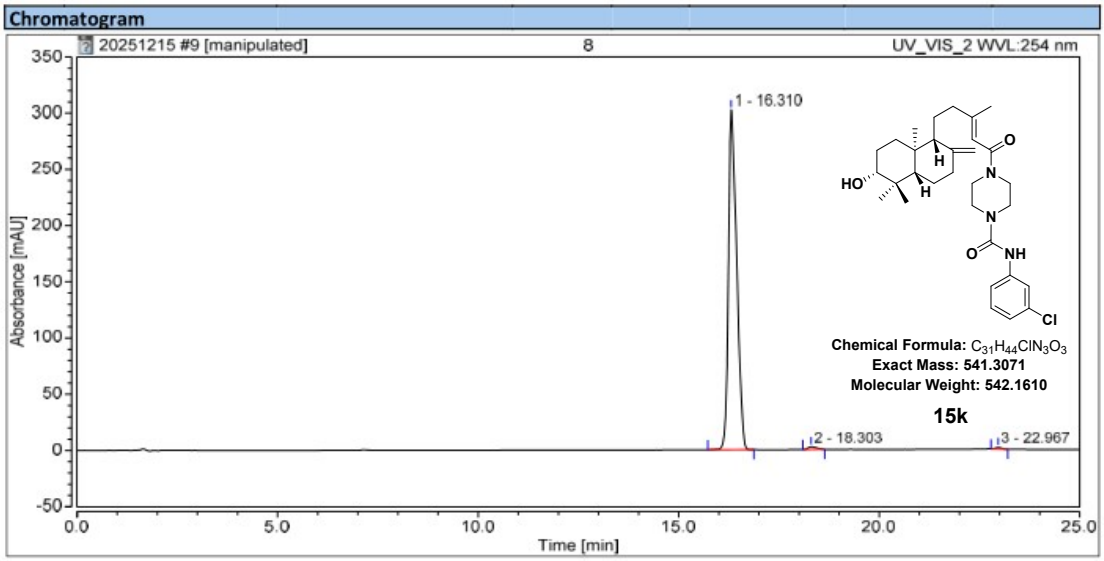


Figure S72. HRMS spectrum of 15k



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		16.310	71.536	302.474	98.80	98.76	n.a.
2		18.303	0.626	2.465	0.86	0.80	n.a.
3		22.967	0.245	1.347	0.34	0.44	n.a.
Total:			**72.408**	**306.286**	**100.00**	**100.00**	

Figure S73. HPLC spectrum of 15k

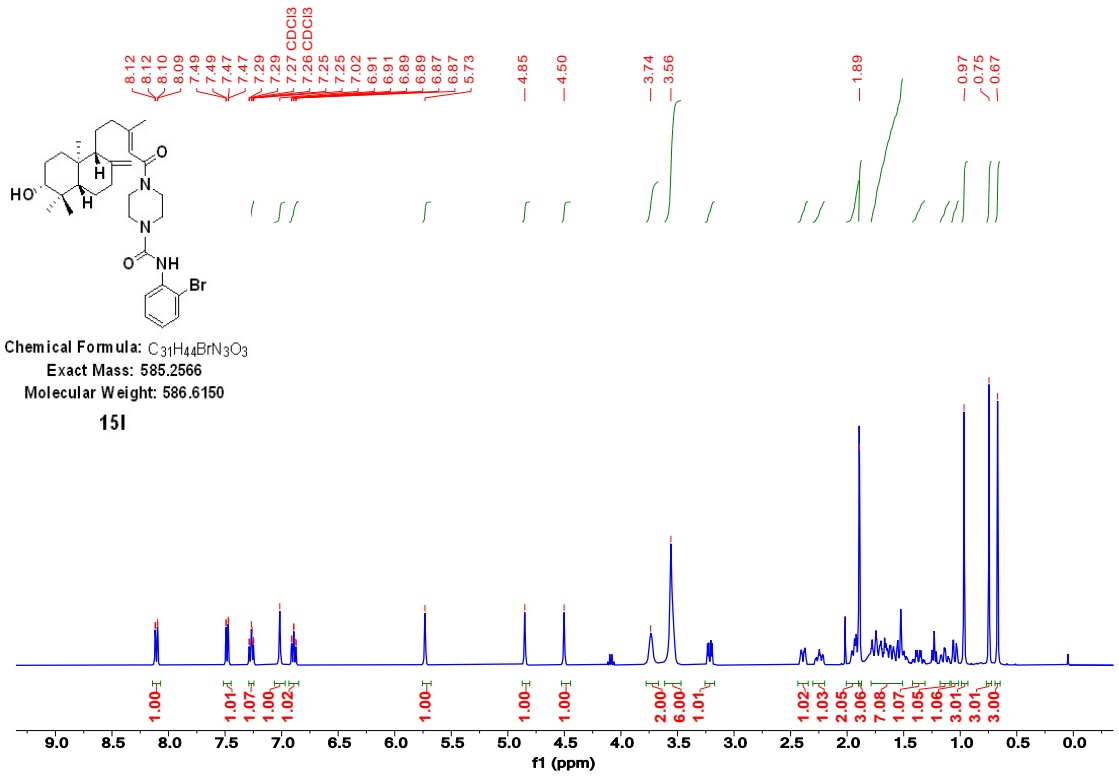


Figure S74. ^{1}H NMR spectrum of 15l

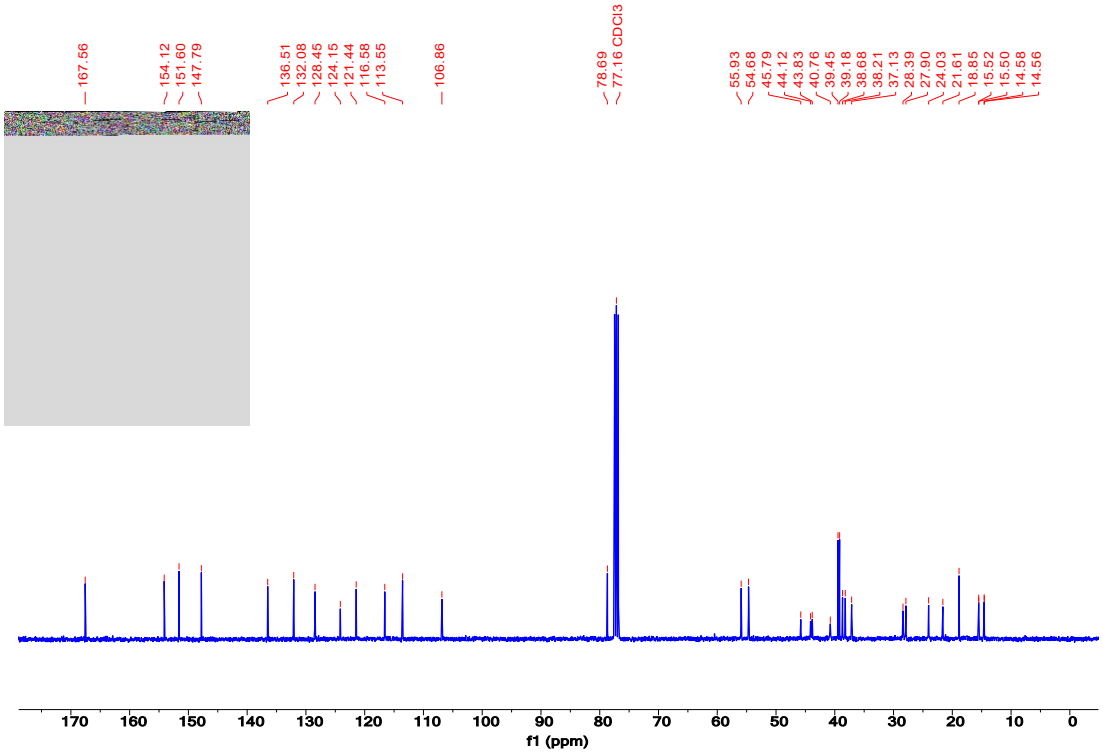


Figure S75. ^{13}C NMR spectrum of 15l

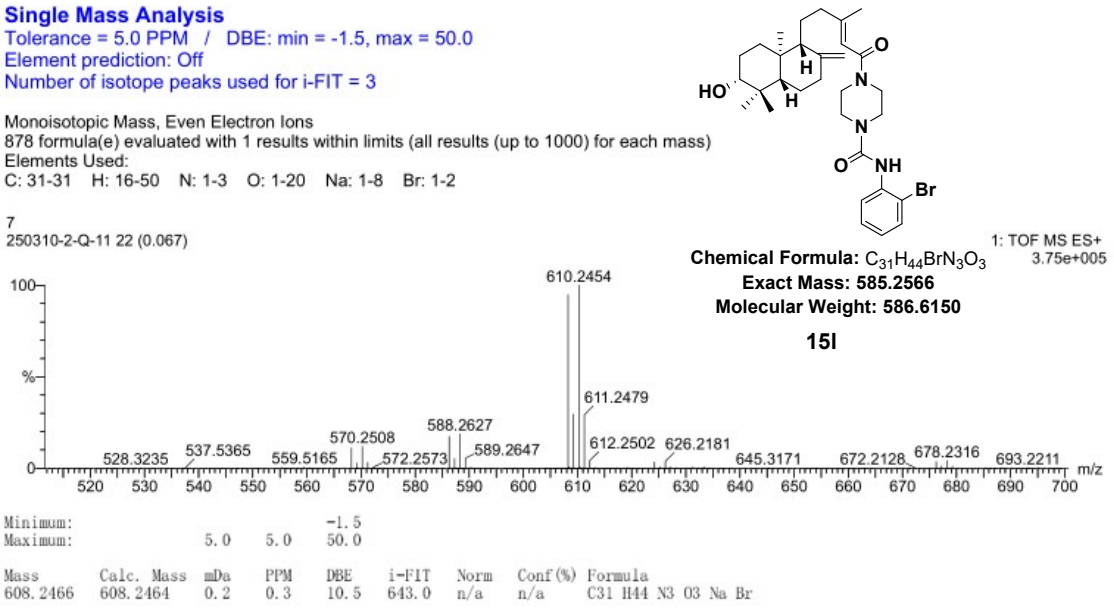
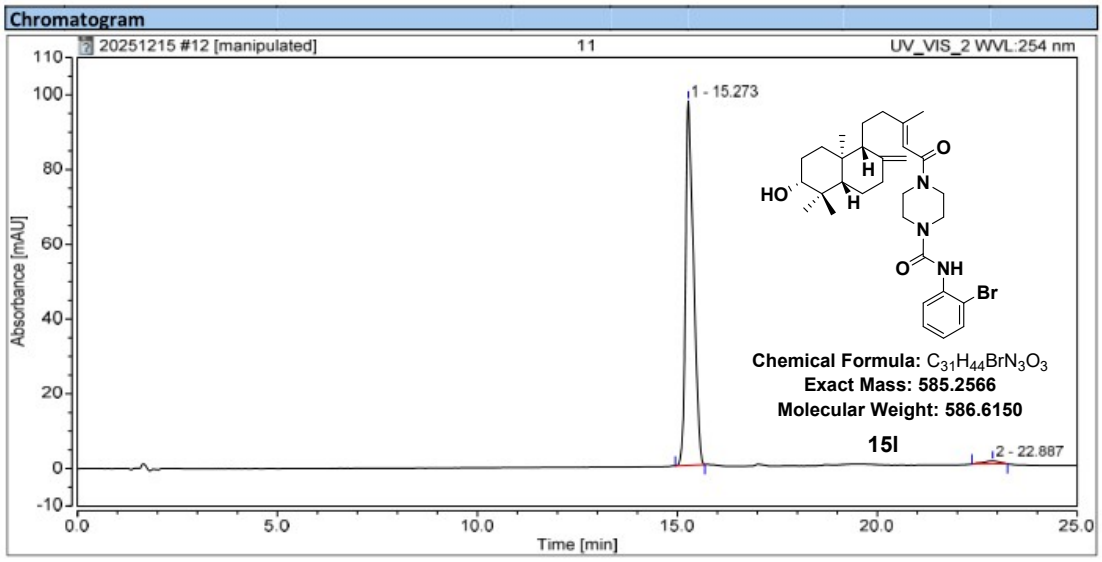


Figure S76. HRMS spectrum of 15l



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15.273	22.319	97.528	98.32	99.20	n.a.
2		22.887	0.381	0.786	1.68	0.80	n.a.
Total:			**22.700**	**98.315**	**100.00**	**100.00**	

Figure S77. HPLC spectrum of 15l

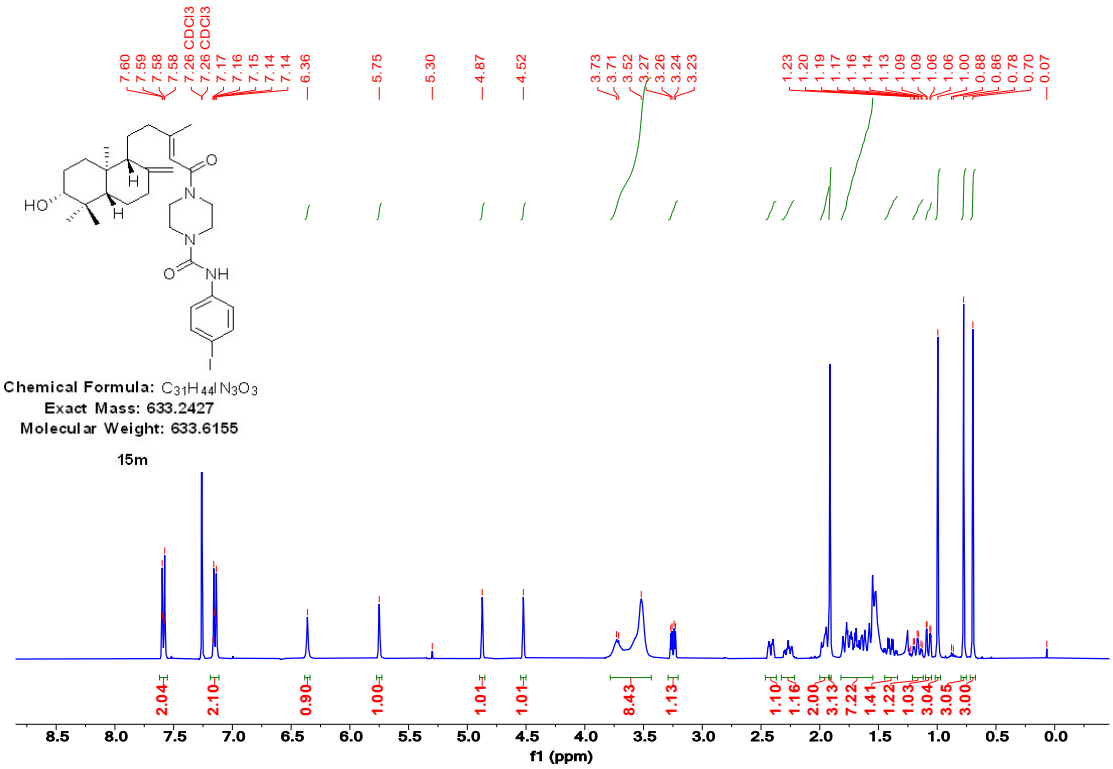


Figure S78. ^{1}H NMR spectrum of 15m

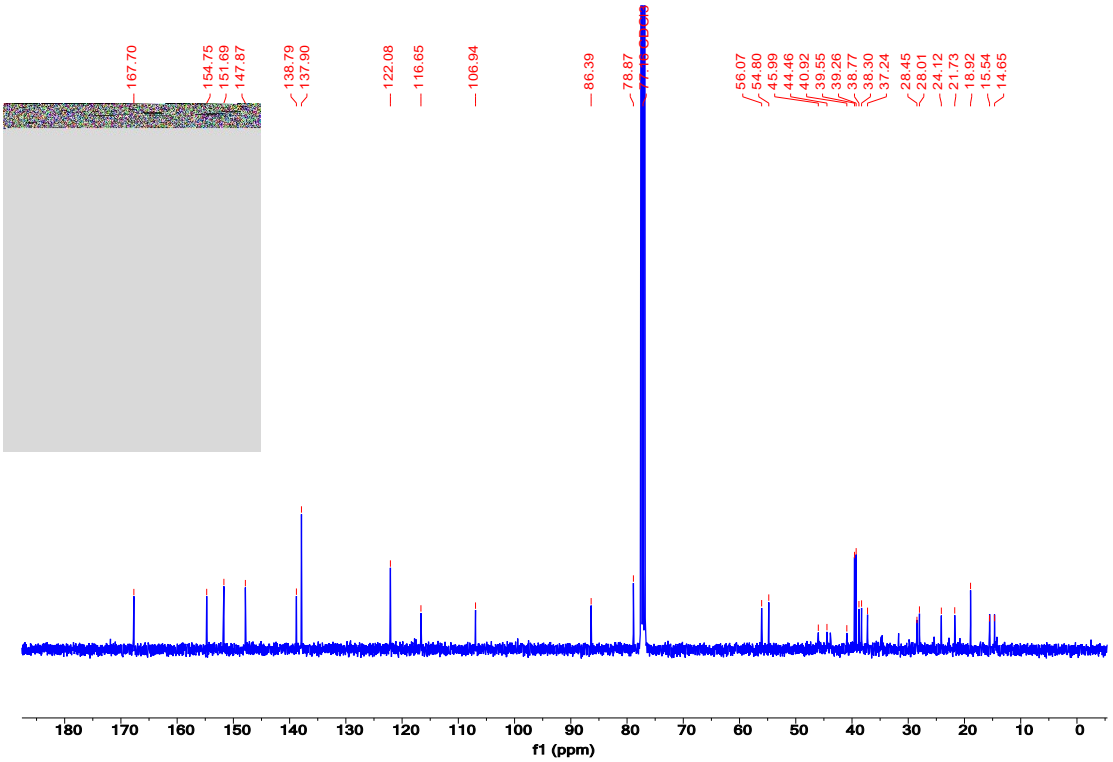


Figure S79. ^{13}C NMR spectrum of 15m

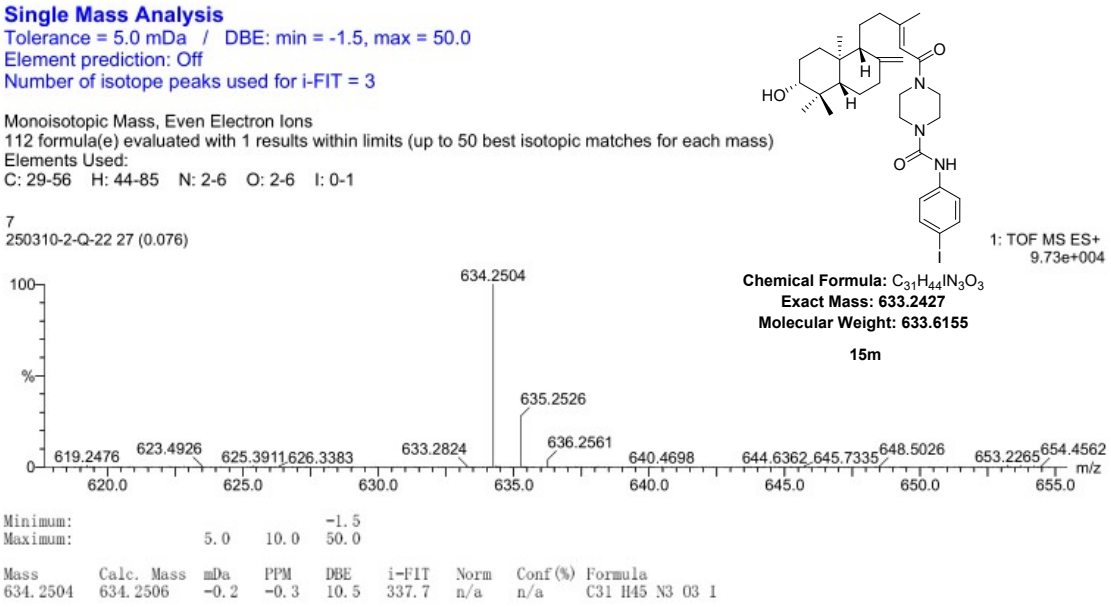
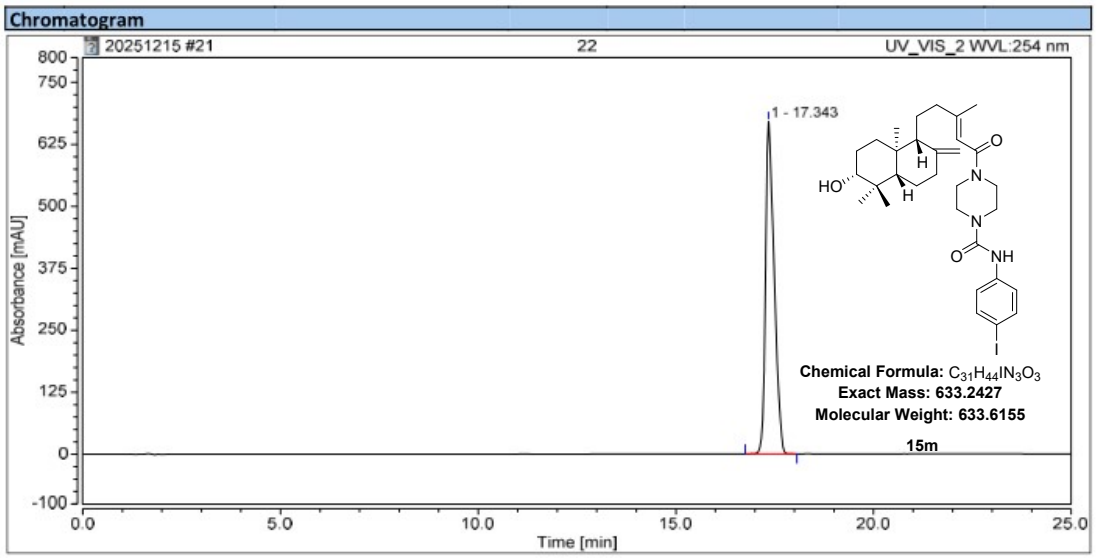


Figure S80. HRMS spectrum of 15m



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.343	169.222	670.465	100.00	100.00	n.a.
Total:			**169.222**	**670.465**	**100.00**	**100.00**	

Figure S81. HPLC spectrum of 15m

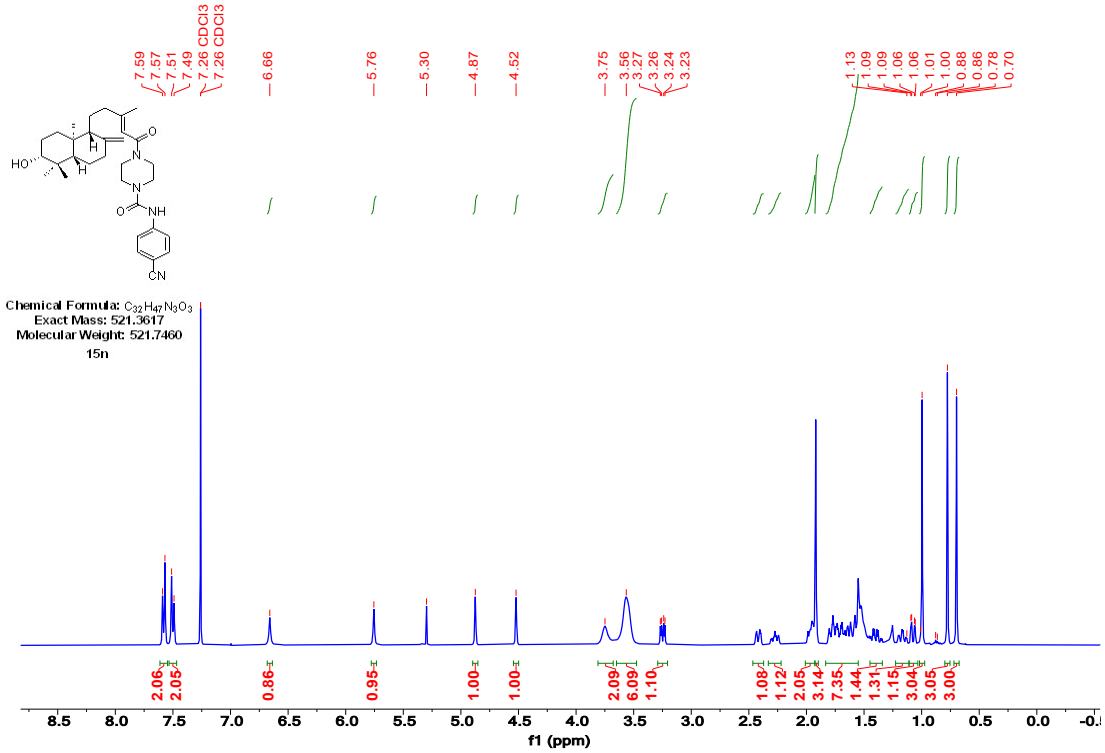


Figure S82. ^{1}H NMR spectrum of 15n

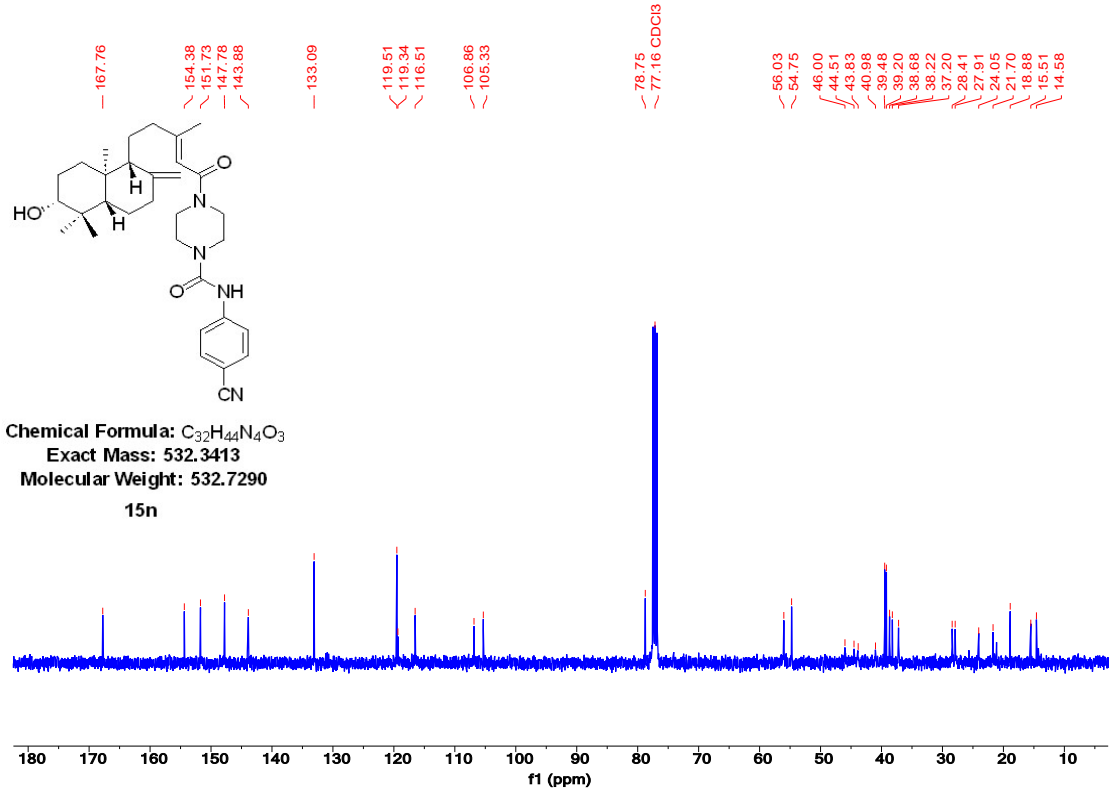


Figure S83. ^{13}C NMR spectrum of 15n

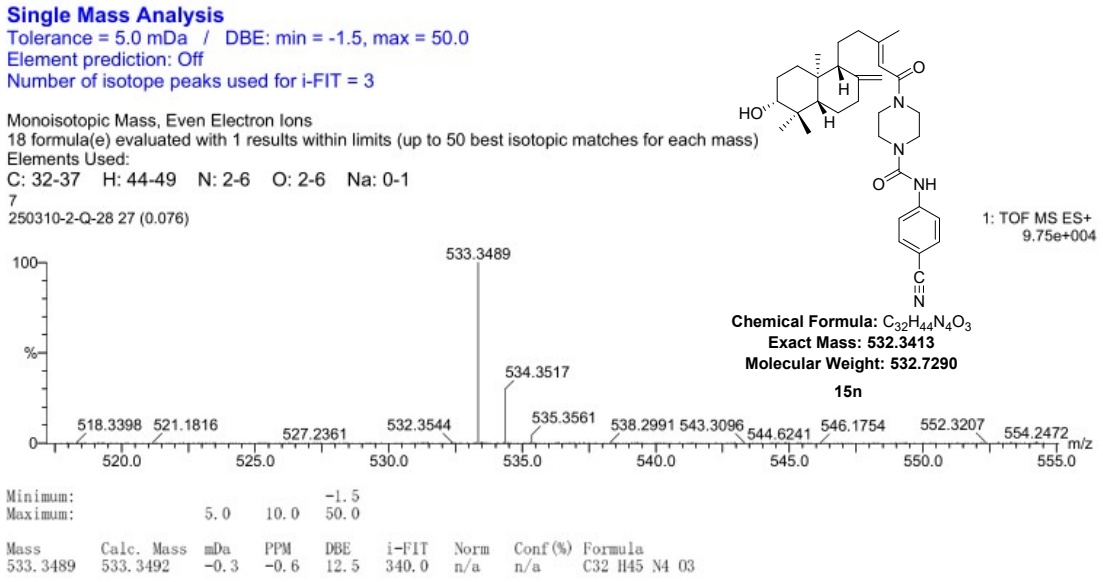
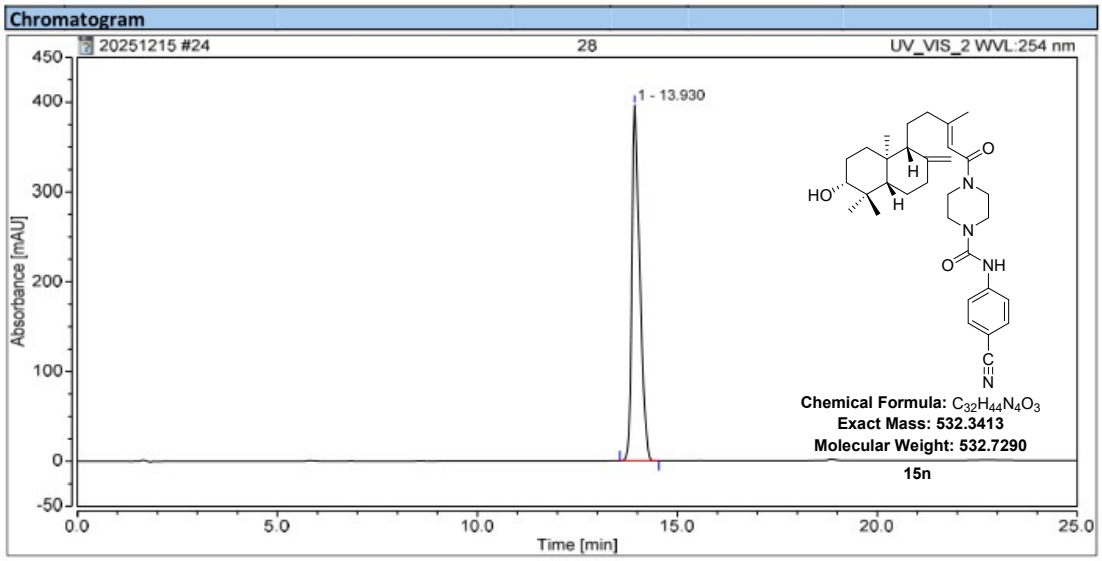


Figure S84. HRMS spectrum of 15n



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		13.930	90.274	396.385	100.00	100.00	n.a.
Total:			**90.274**	**396.385**	**100.00**	**100.00**	

Figure S85. HPLC spectrum of 15n

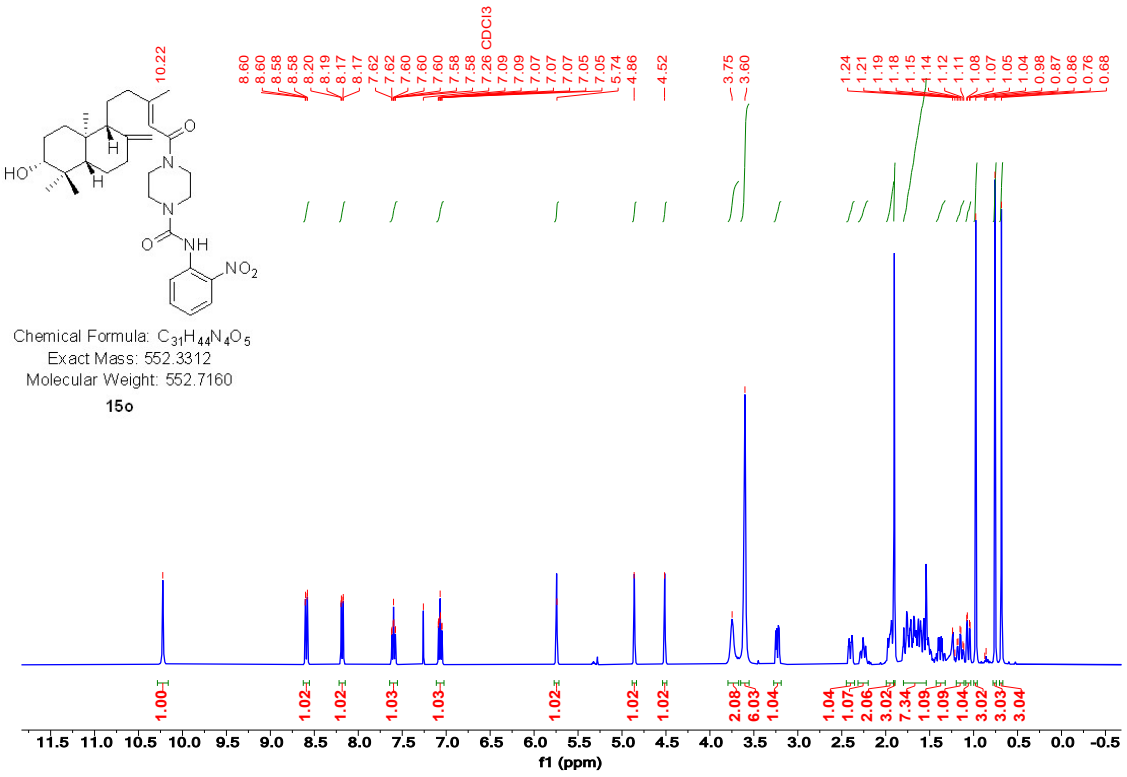


Figure S86. ^{1}H NMR spectrum of 15o

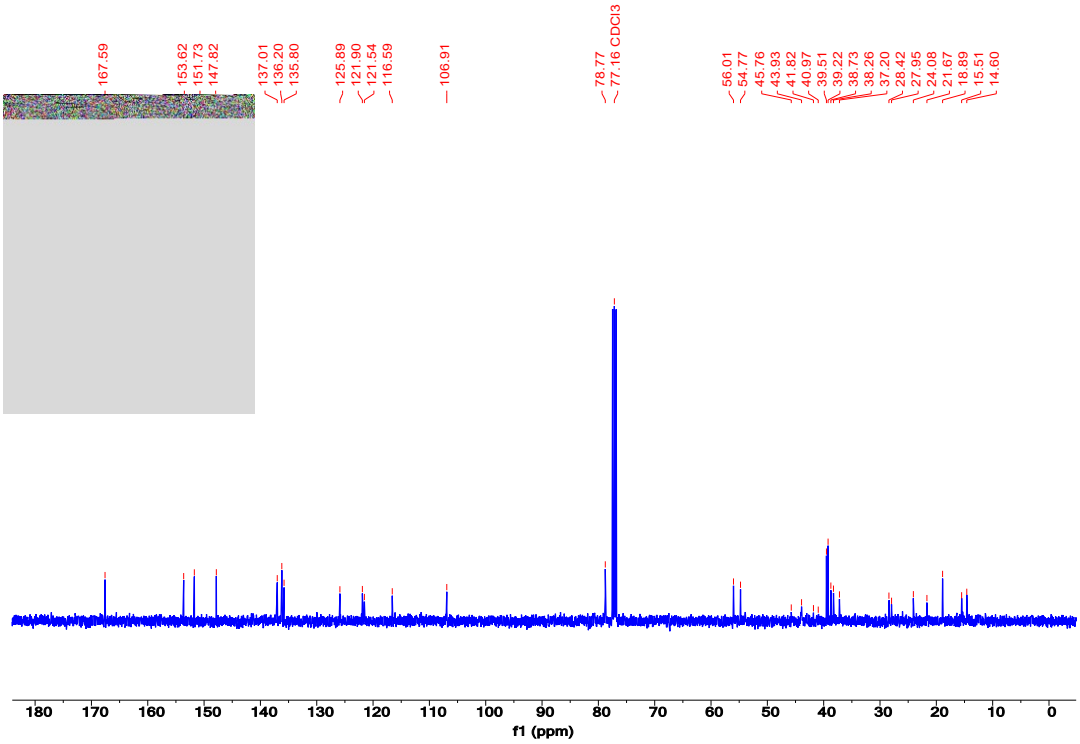


Figure S87. ^{13}C NMR spectrum of 15o

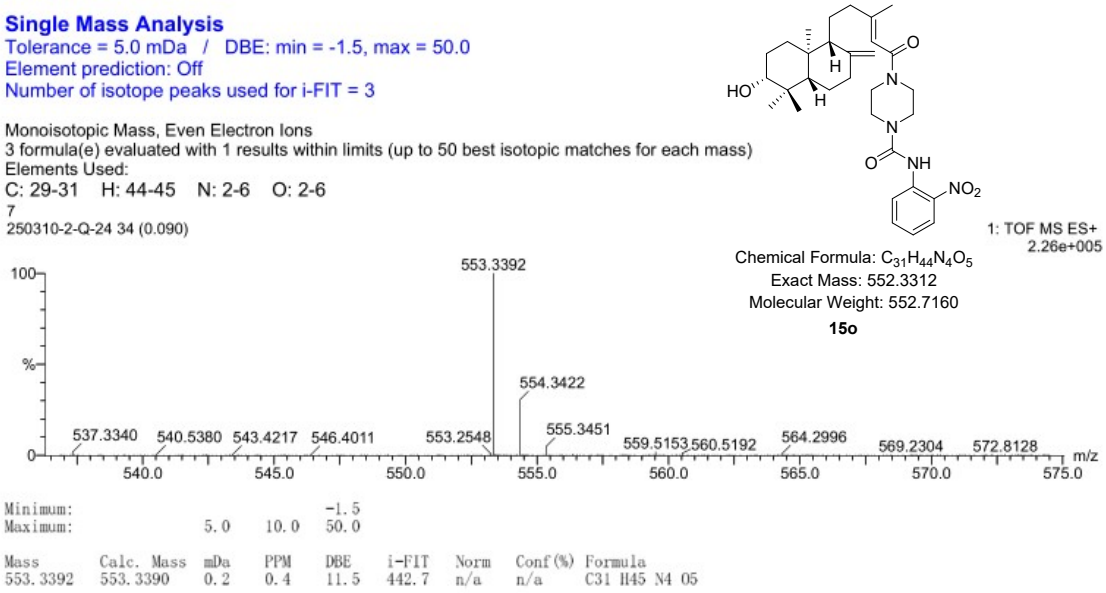
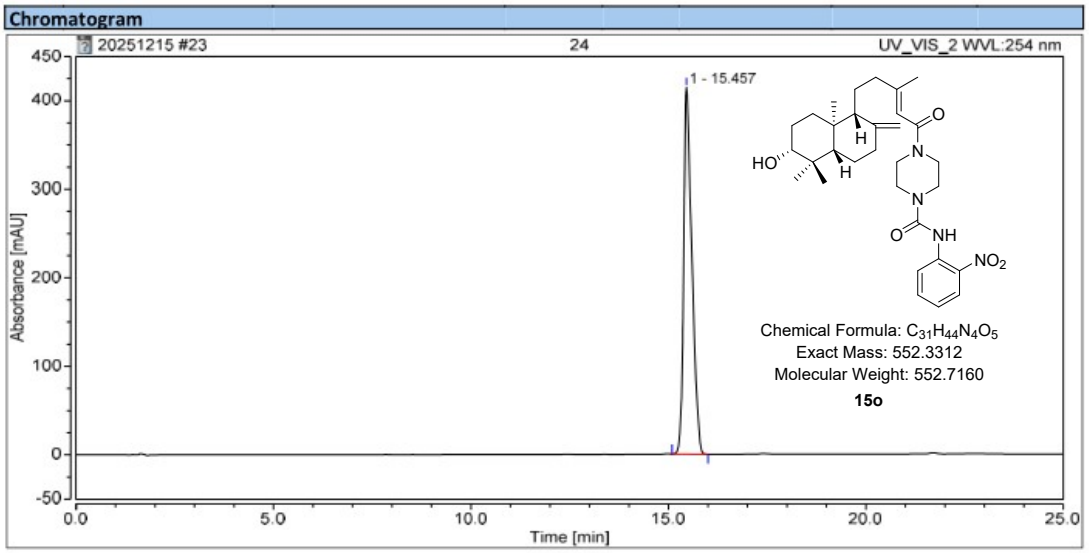


Figure S88. HRMS spectrum of 15o



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		15.457	99.792	414.383	100.00	100.00	n.a.
Total:			**99.792**	**414.383**	**100.00**	**100.00**	

Figure S89. HPLC spectrum of 15o

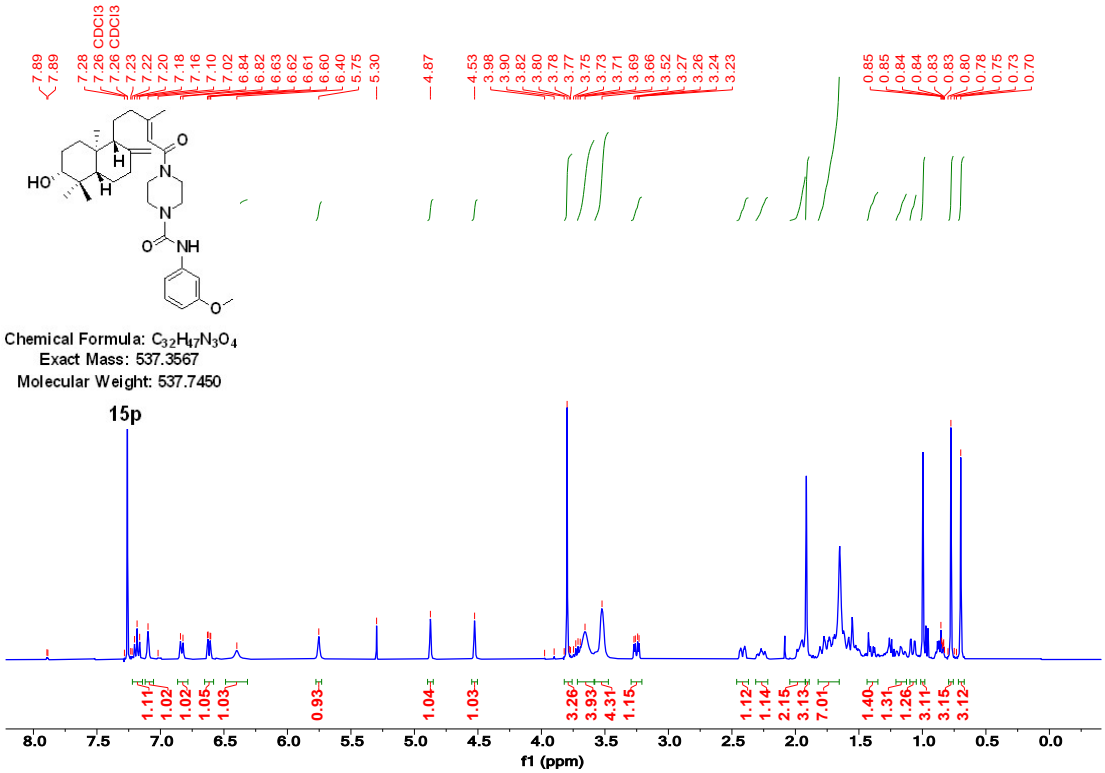


Figure S90. ^{1}H NMR spectrum of 15p

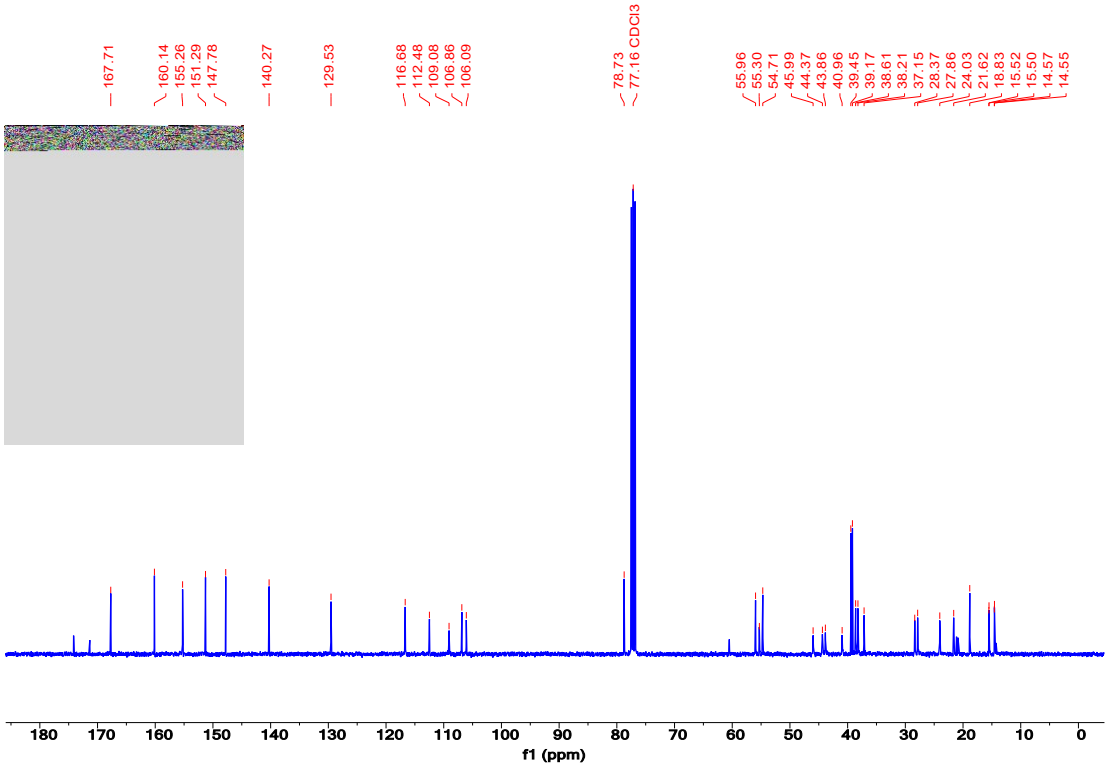


Figure S91. ^{13}C NMR spectrum of 15p

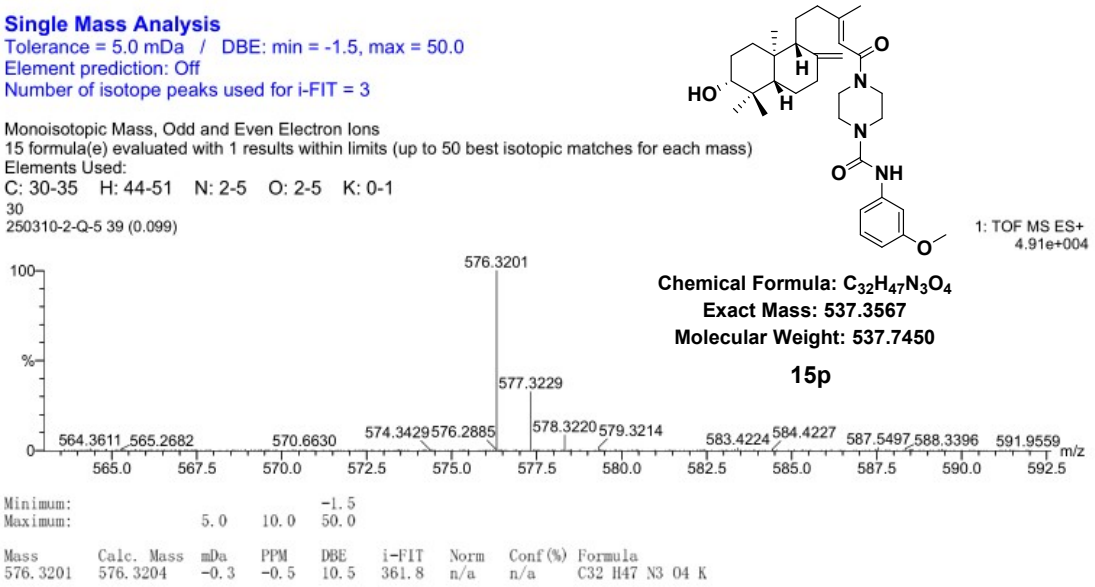
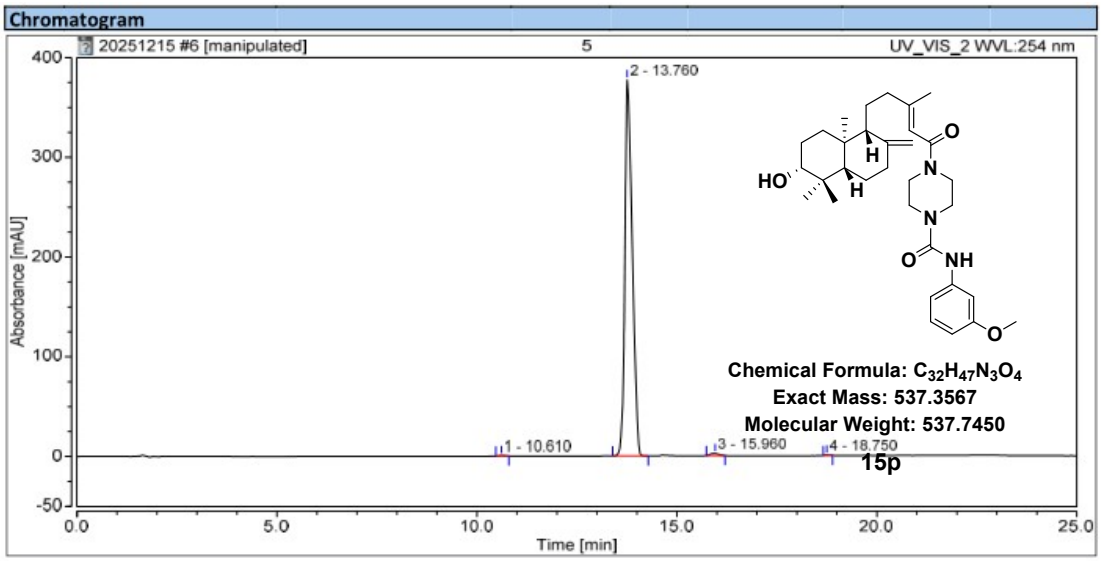


Figure S92. HRMS spectrum of 15p



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		10.610	0.097	0.576	0.12	0.15	n.a.
2		13.760	80.976	377.287	99.17	99.22	n.a.
3		15.960	0.518	1.954	0.63	0.51	n.a.
4		18.750	0.061	0.437	0.07	0.11	n.a.
Total:			**81.651**	**380.254**	**100.00**	**100.00**	

Figure S93. HPLC spectrum of 15p

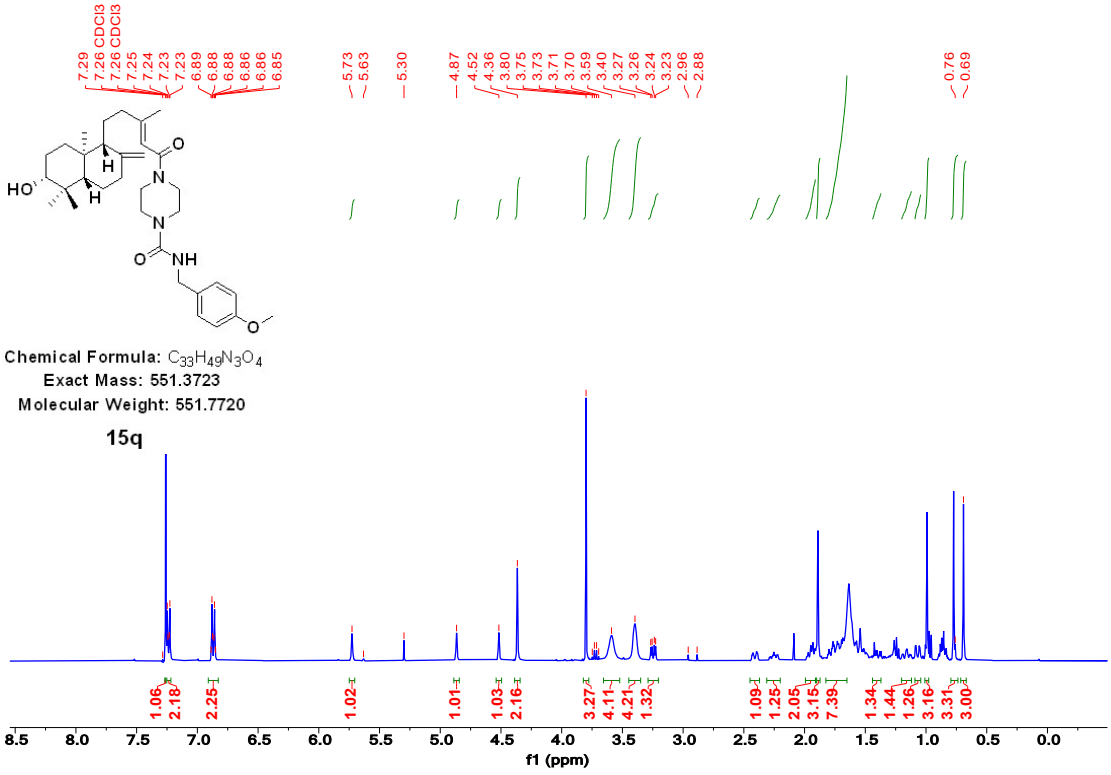


Figure S94. ^{1}H NMR spectrum of 15q

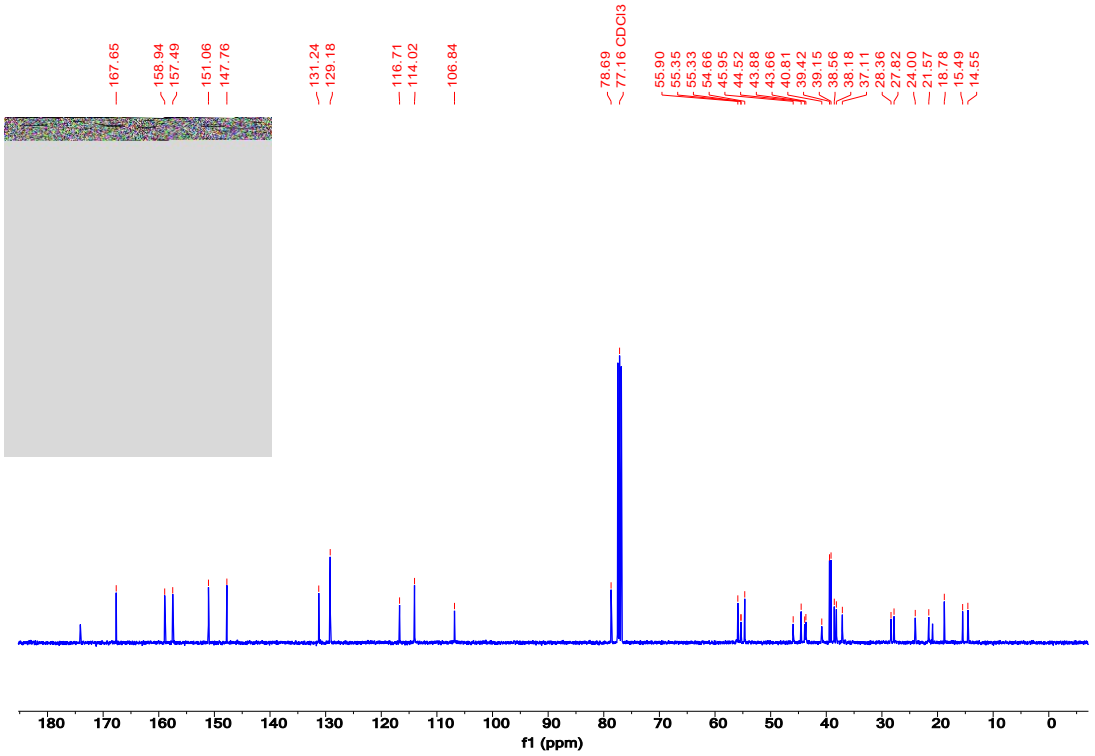


Figure S95. ^{13}C NMR spectrum of 15q

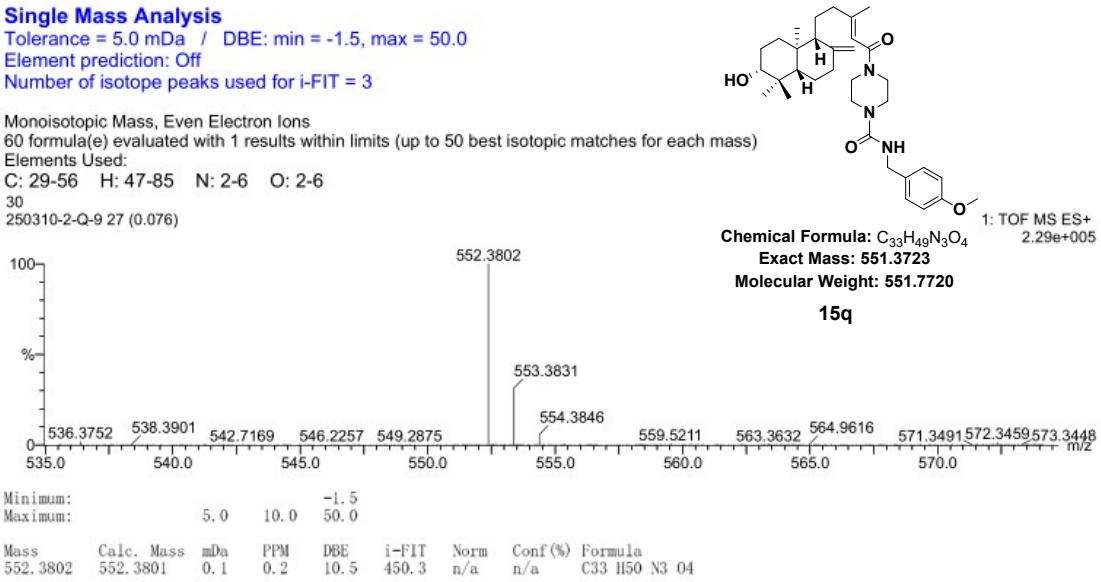
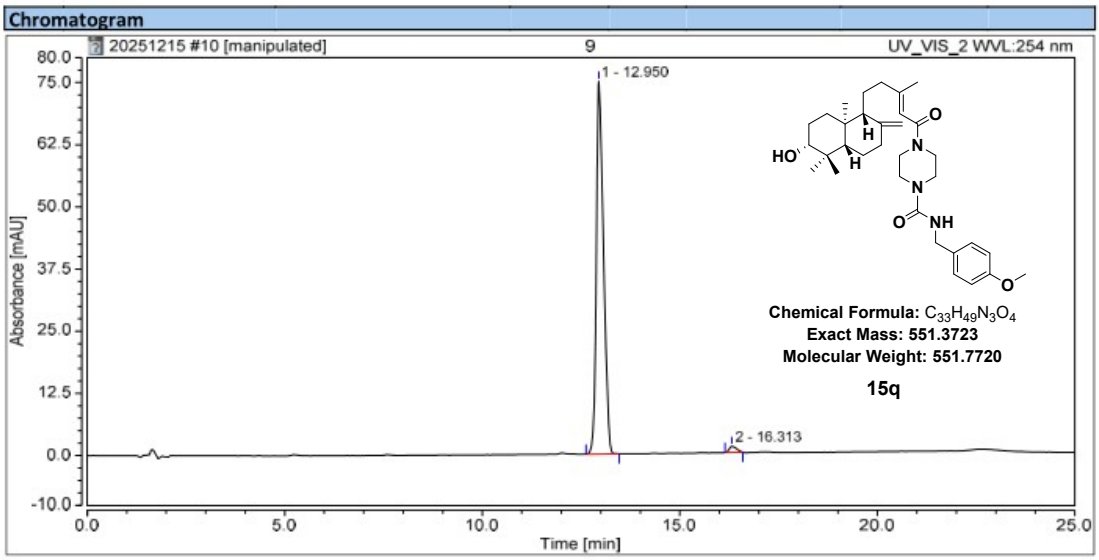


Figure S96. HRMS spectrum of 15q



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.950	15.670	74.964	98.33	98.39	n.a.
2		16.313	0.266	1.230	1.67	1.61	n.a.
Total:			**15.936**	**76.193**	**100.00**	**100.00**	

Figure S97. HPLC spectrum of 15q

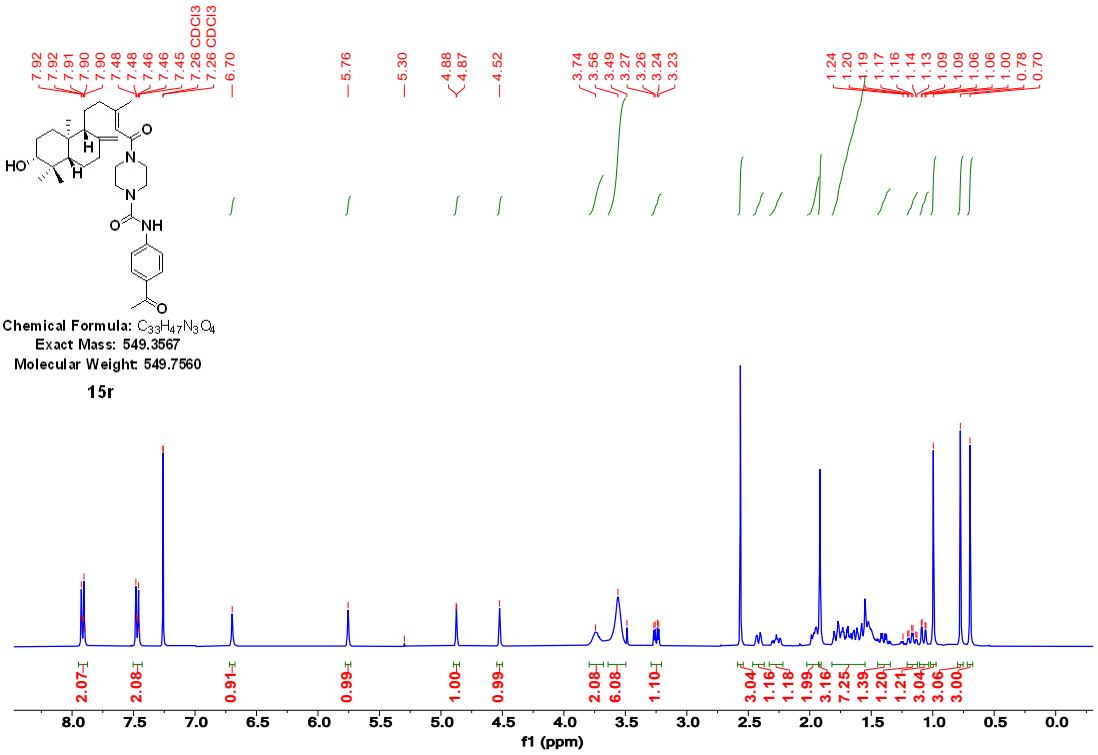


Figure S98. ^{1}H NMR spectrum of 15r

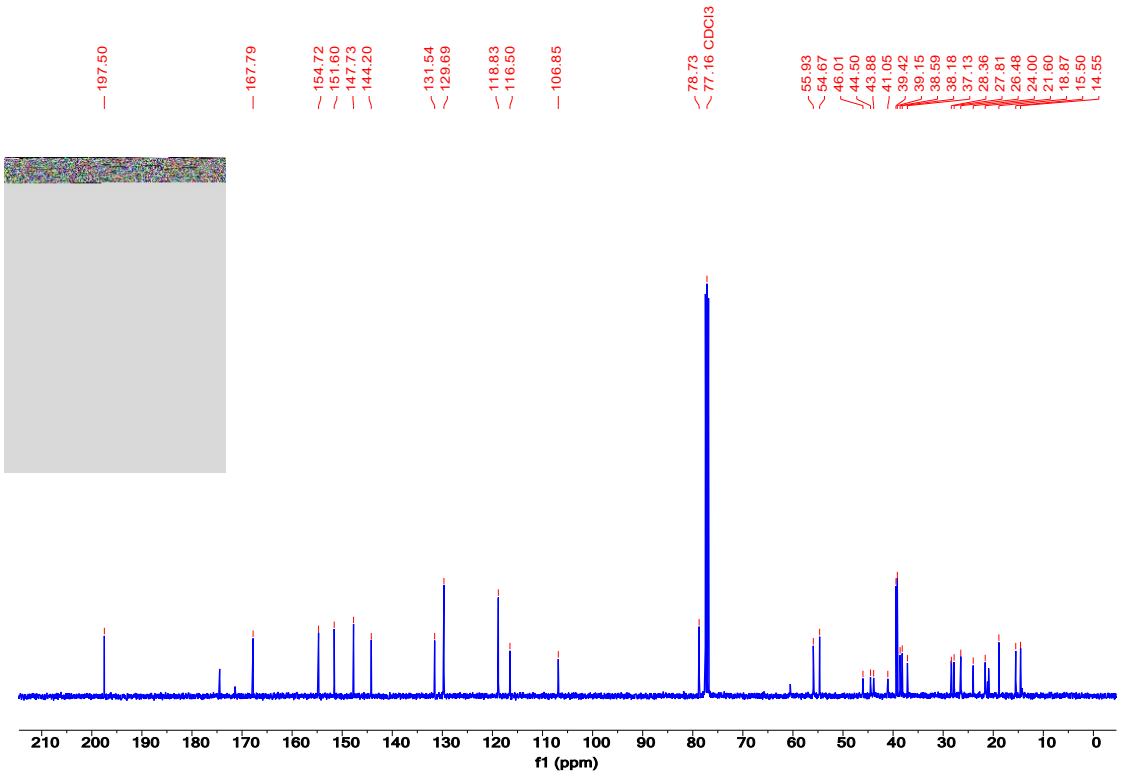


Figure S99. ^{13}C NMR spectrum of 15r

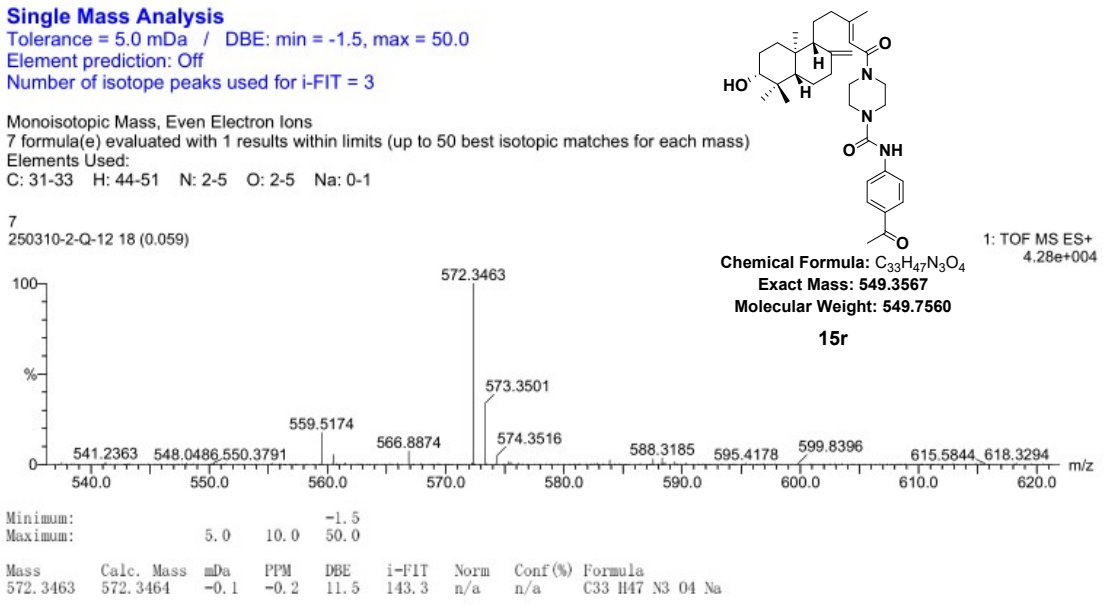
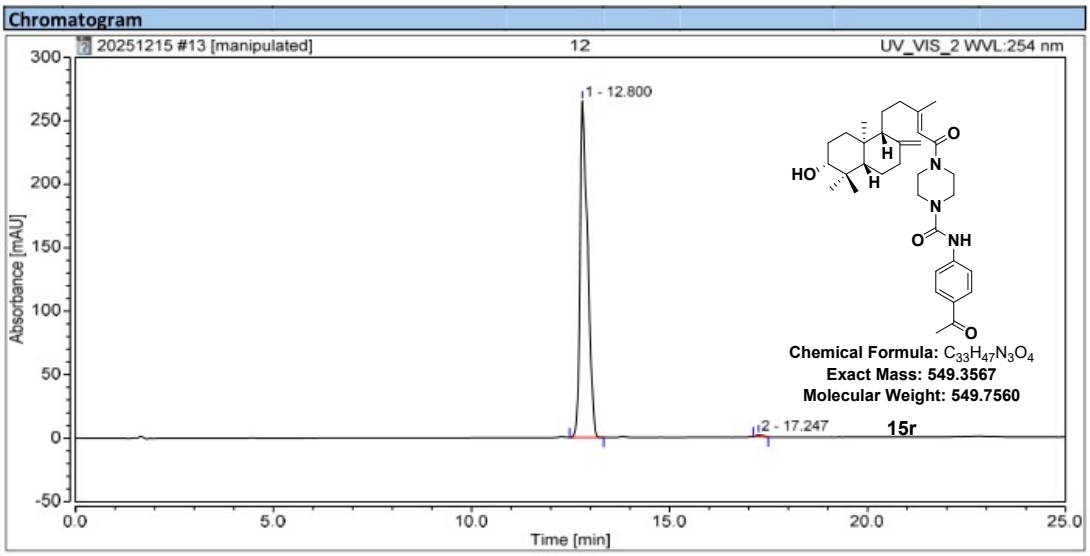


Figure S100. HRMS spectrum of 15r



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		12.800	58.775	265.279	99.46	99.40	n.a.
2		17.247	0.320	1.588	0.54	0.60	n.a.
Total:			**59.095**	**266.867**	**100.00**	**100.00**	

Figure S101. HPLC spectrum of 15r

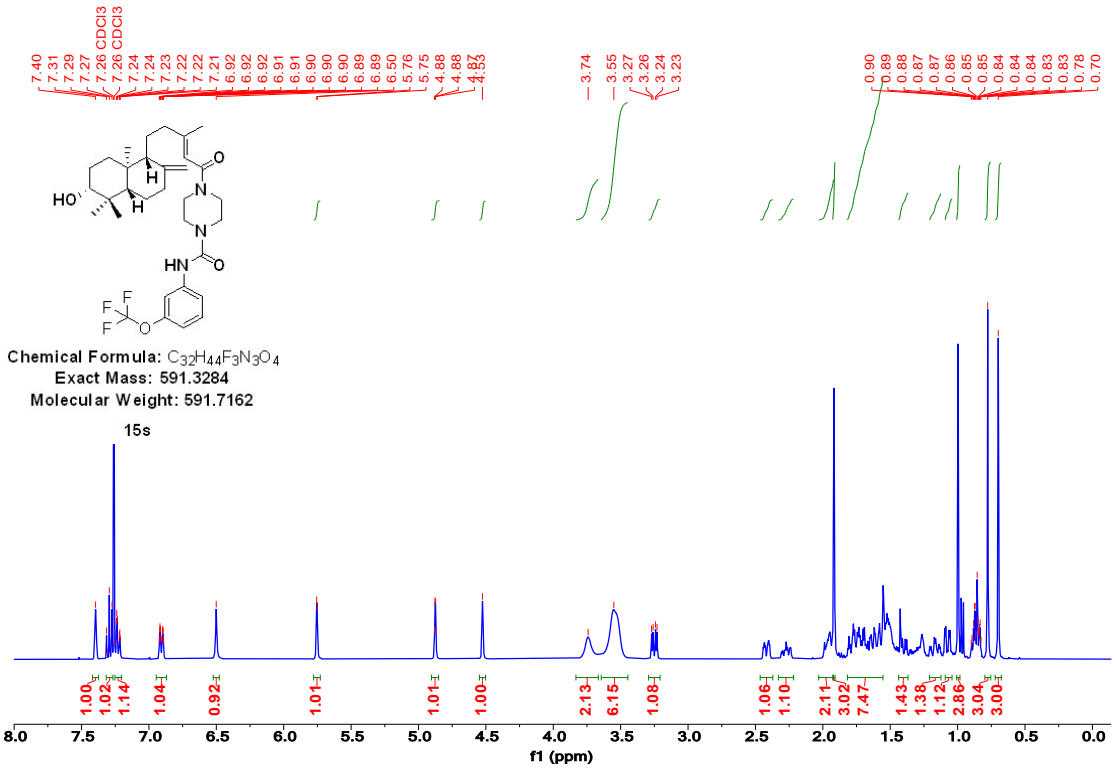


Figure S102. ^{1}H NMR spectrum of 15s

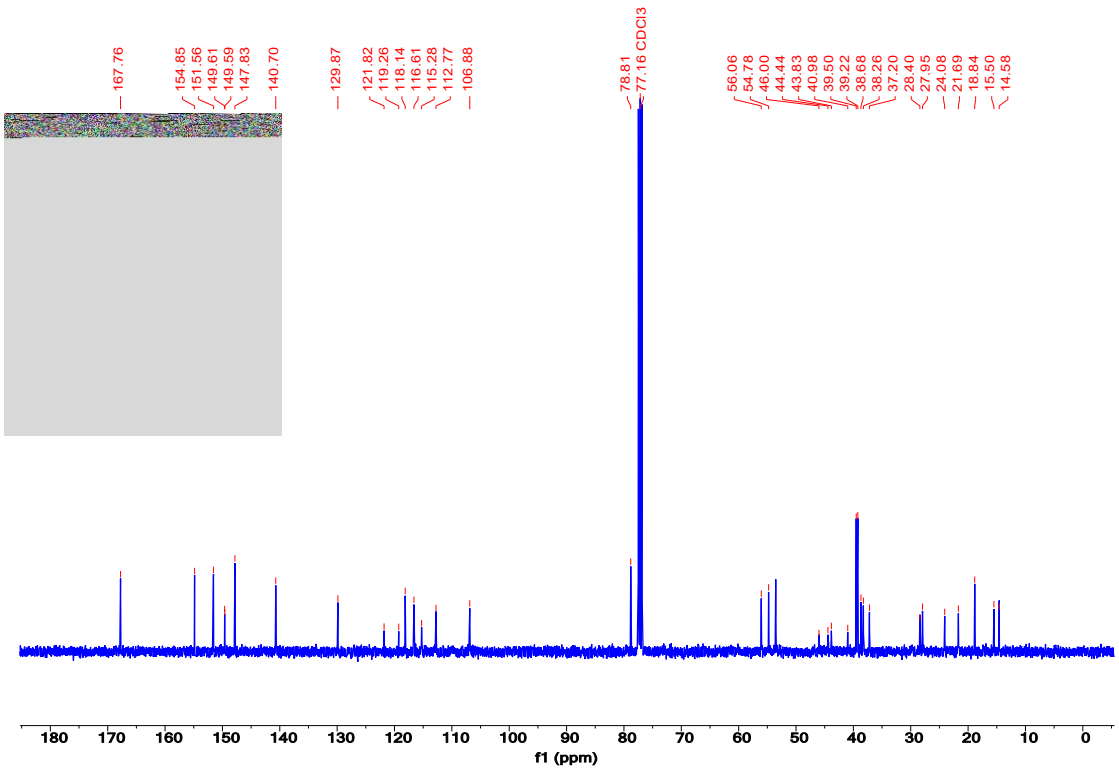


Figure S103. ^{13}C NMR spectrum of 15s

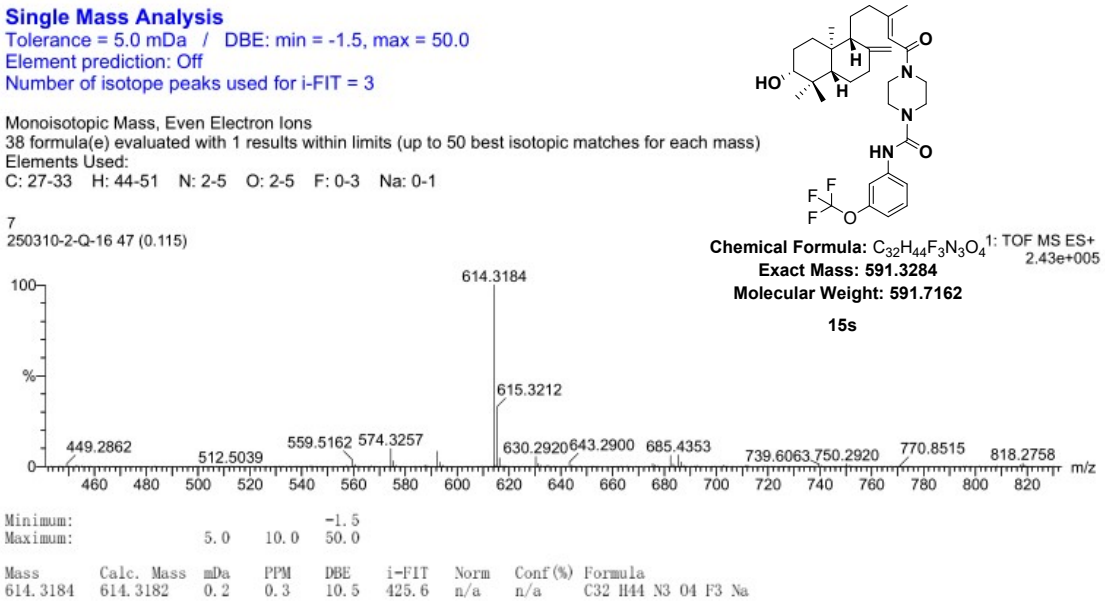
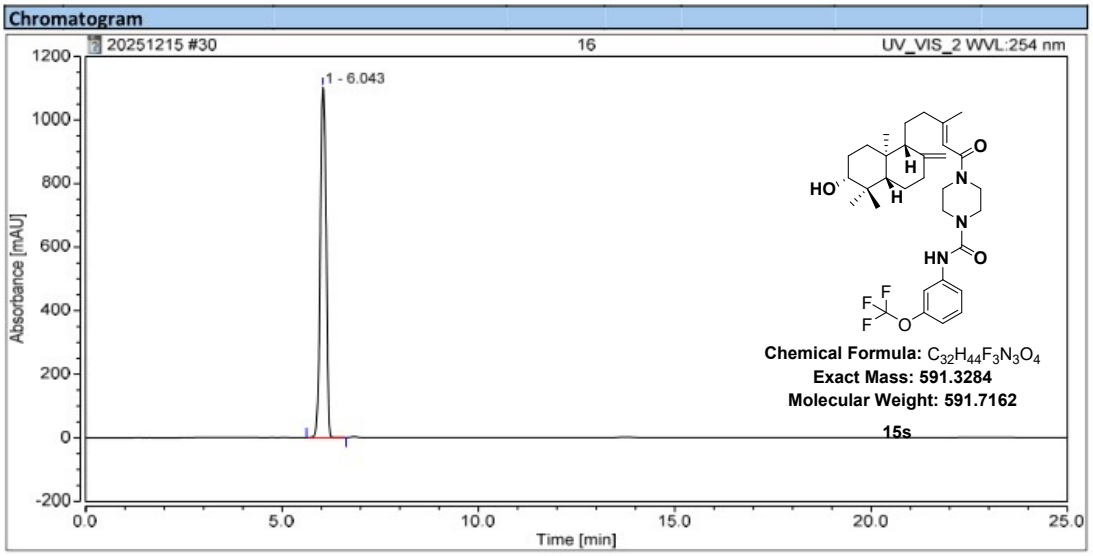


Figure S104. HRMS spectrum of 15s



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.043	189.064	1102.248	100.00	100.00	n.a.
Total:			**189.064**	**#######**	**100.00**	**100.00**	

Figure S105. HPLC spectrum of 15s

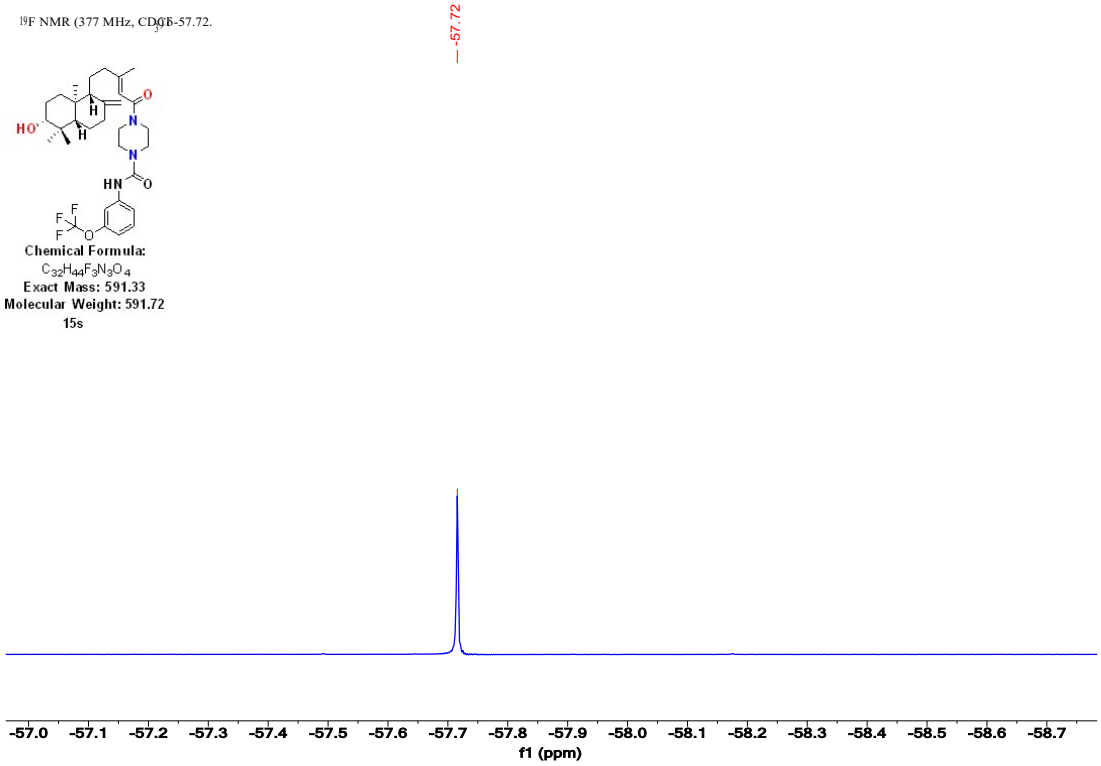


Figure S106. ^{19}F NMR spectrum of 15s

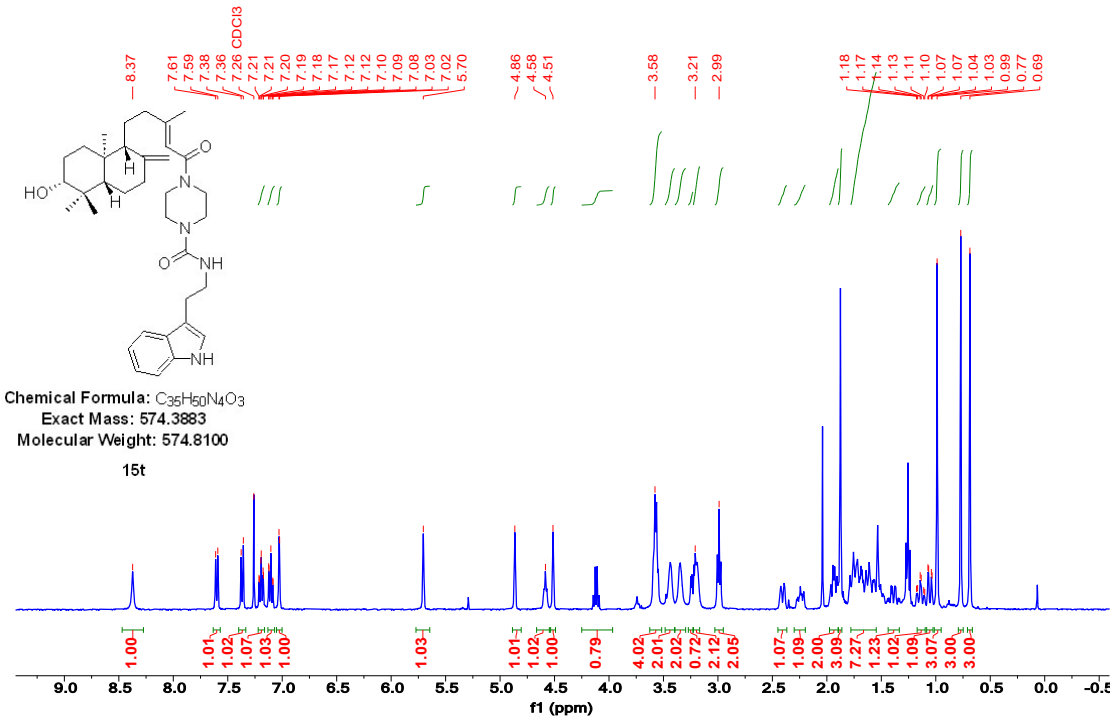


Figure S107. ^{1}H NMR spectrum of 15t

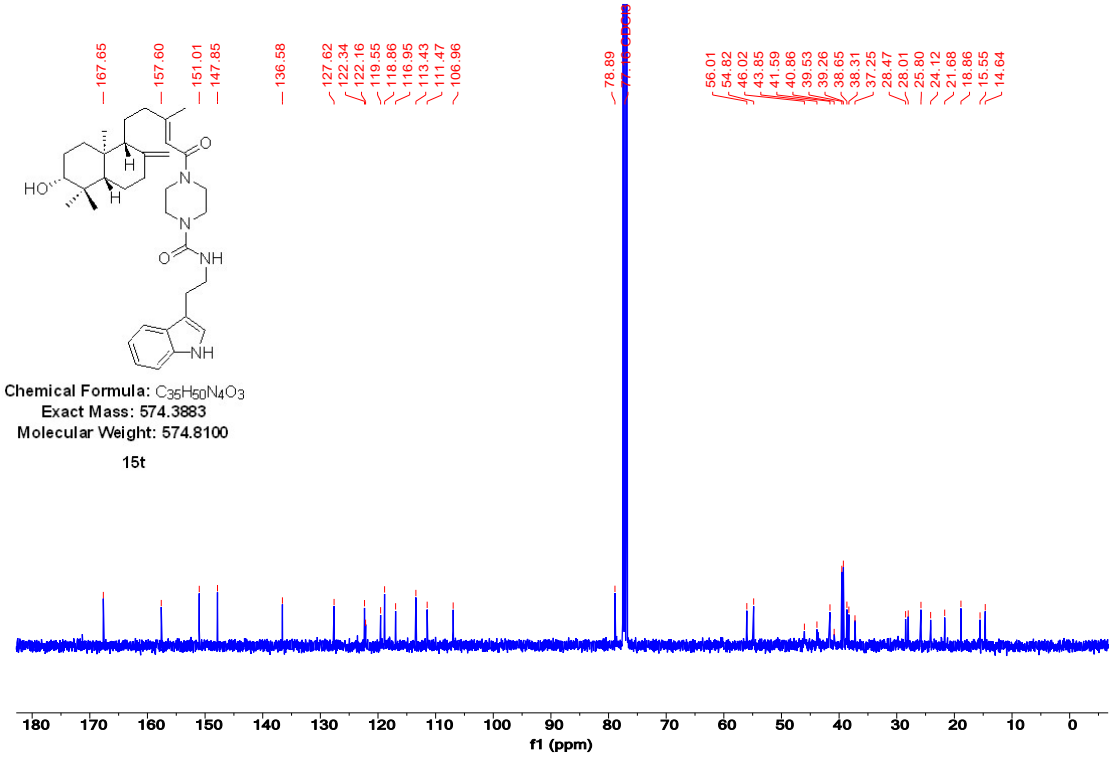


Figure S108. ^{13}C NMR spectrum of 15t

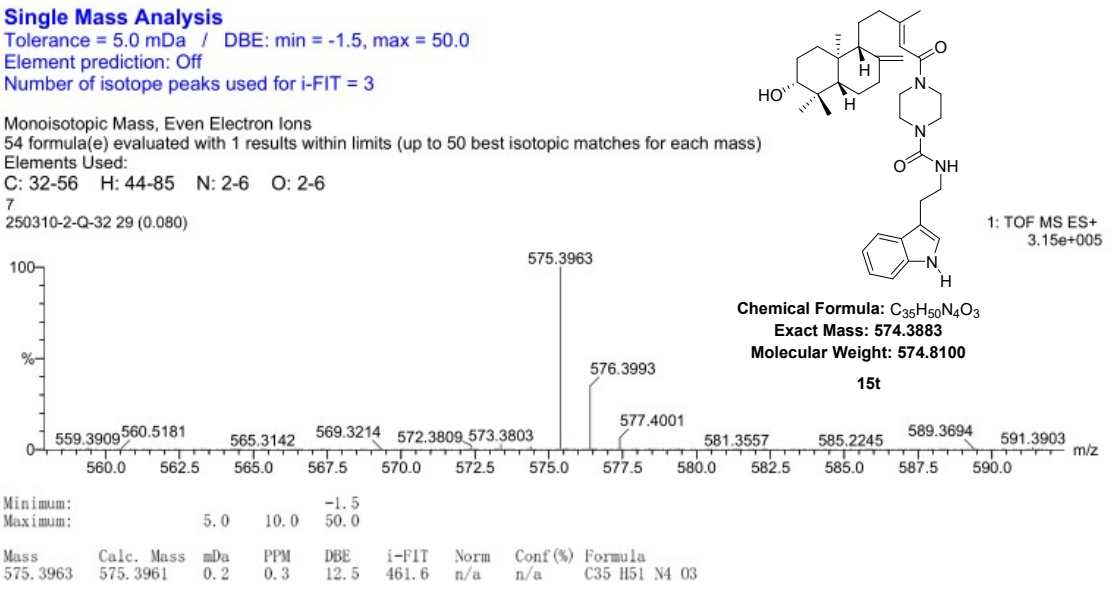
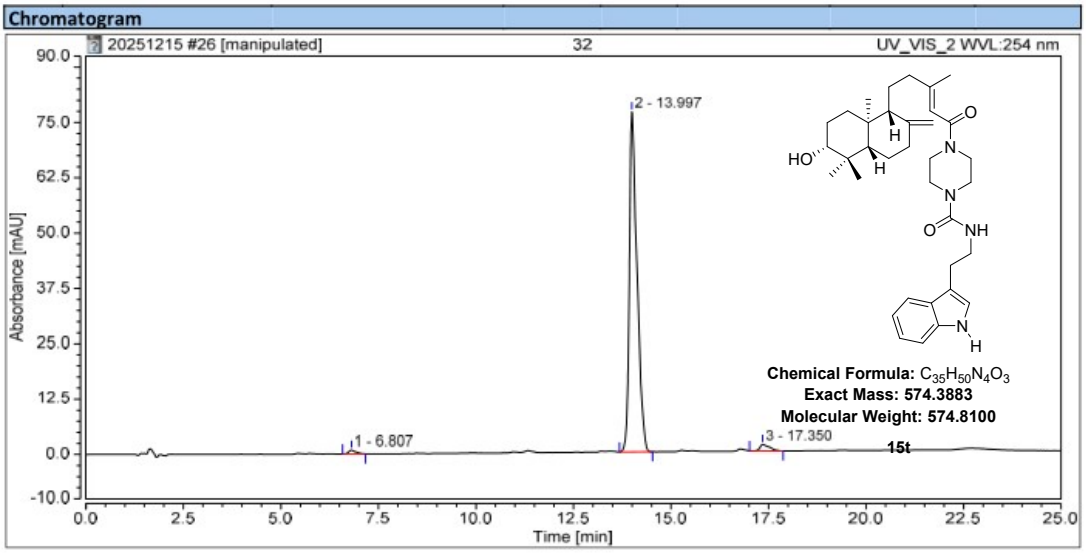


Figure S109. HRMS spectrum of 15t



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.807	0.183	0.846	1.02	1.07	n.a.
2		13.997	17.451	76.864	96.75	97.12	n.a.
3		17.350	0.403	1.430	2.24	1.81	n.a.
Total:			**18.038**	**79.140**	**100.00**	**100.00**	

Figure S110. HPLC spectrum of 15t

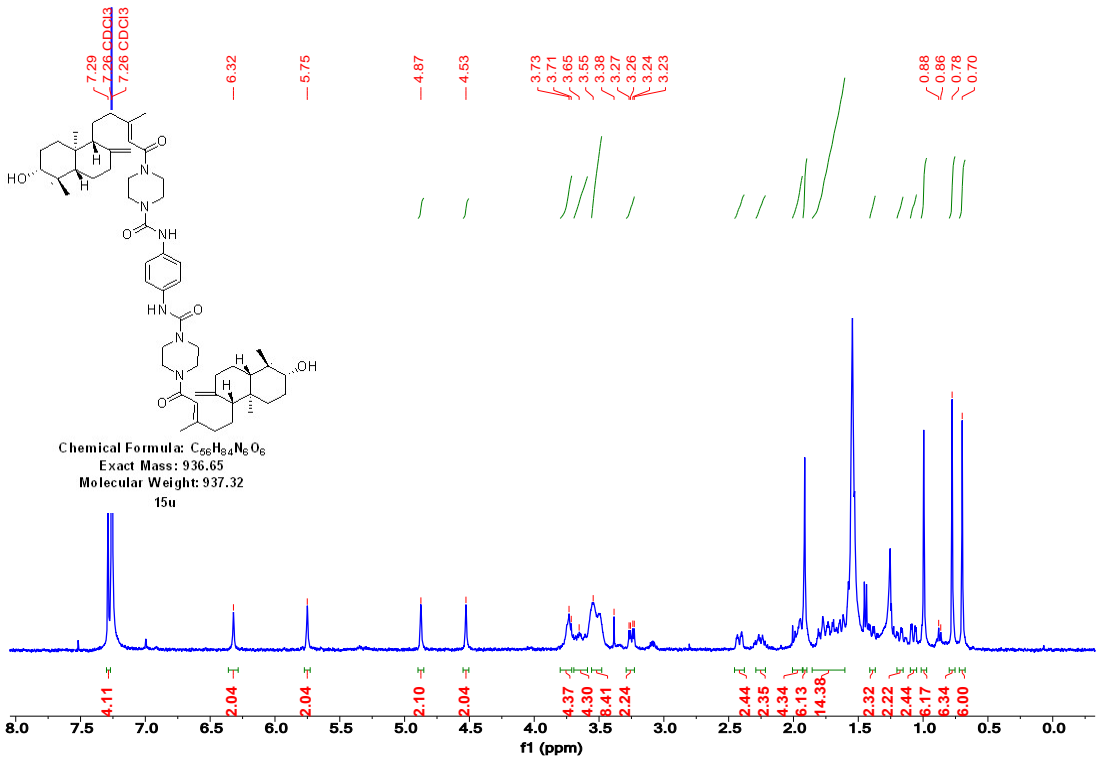


Figure S111. ^{1}H NMR spectrum of 15u

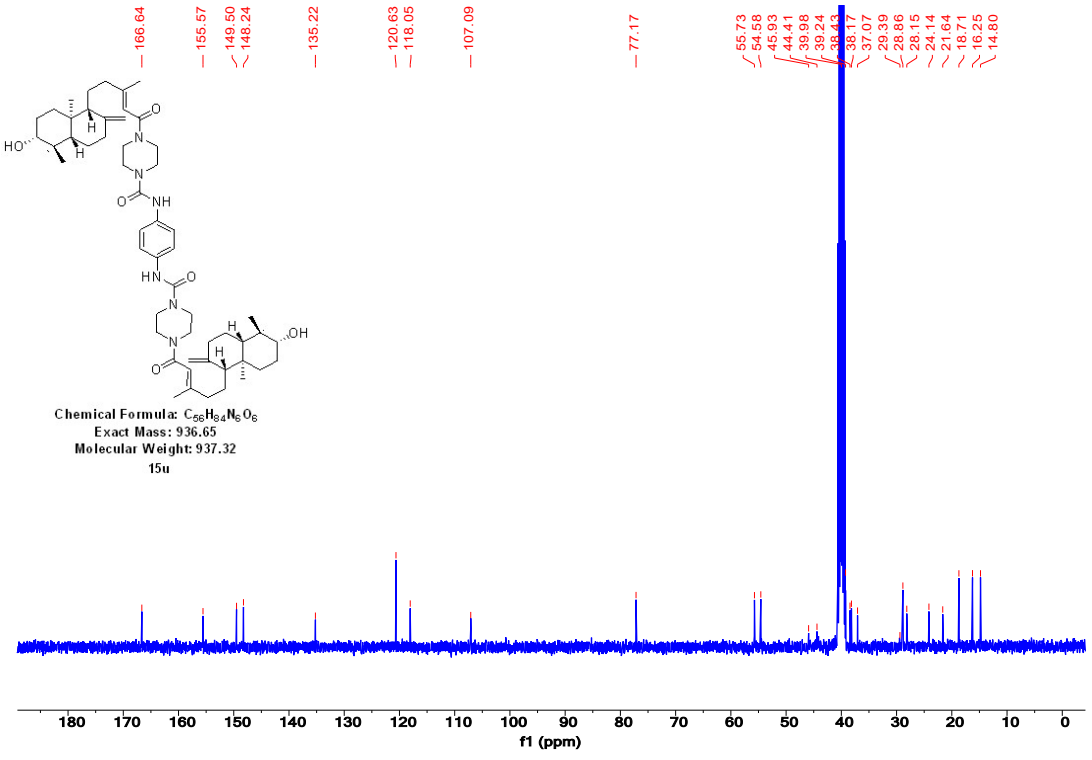


Figure S112. ^{13}C NMR spectrum of 15u

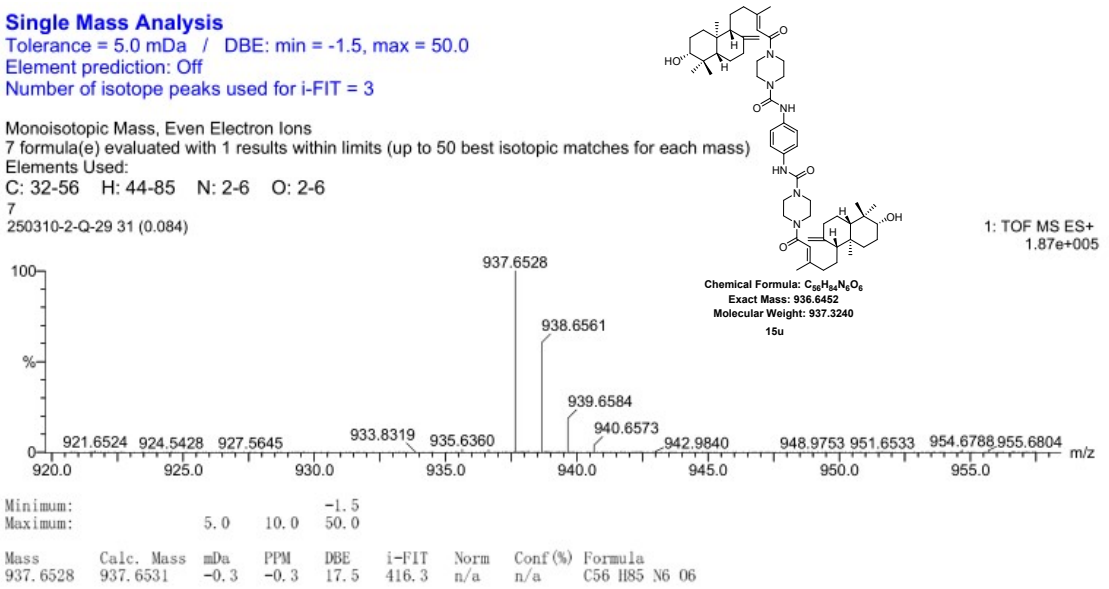
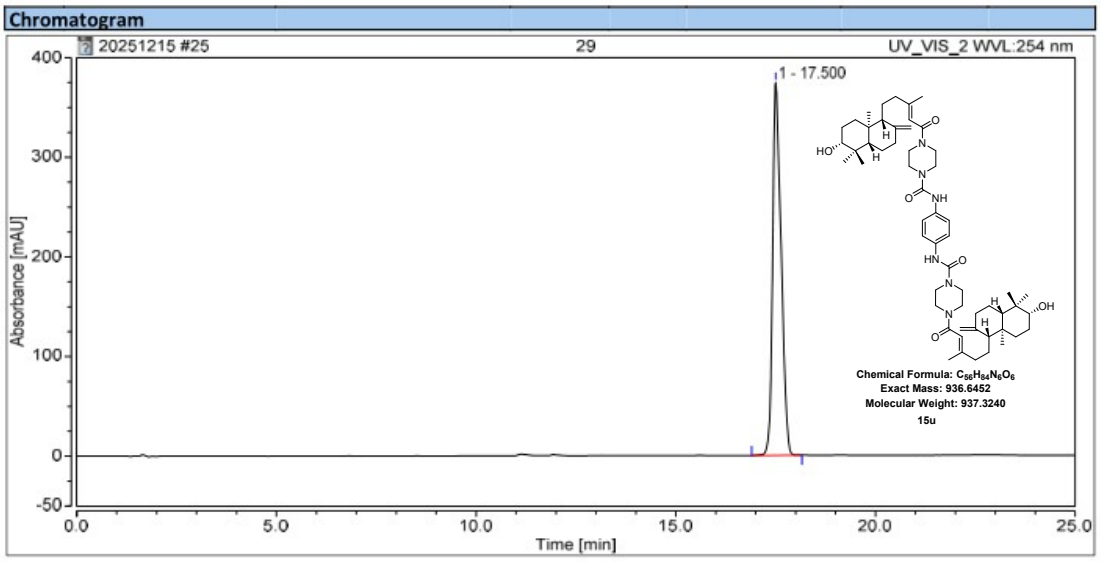


Figure S113. HRMS spectrum of 15u



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		17.500	91.730	374.563	100.00	100.00	n.a.
Total:			**91.730**	**374.563**	**100.00**	**100.00**	

Figure S114. HPLC spectrum of 15u

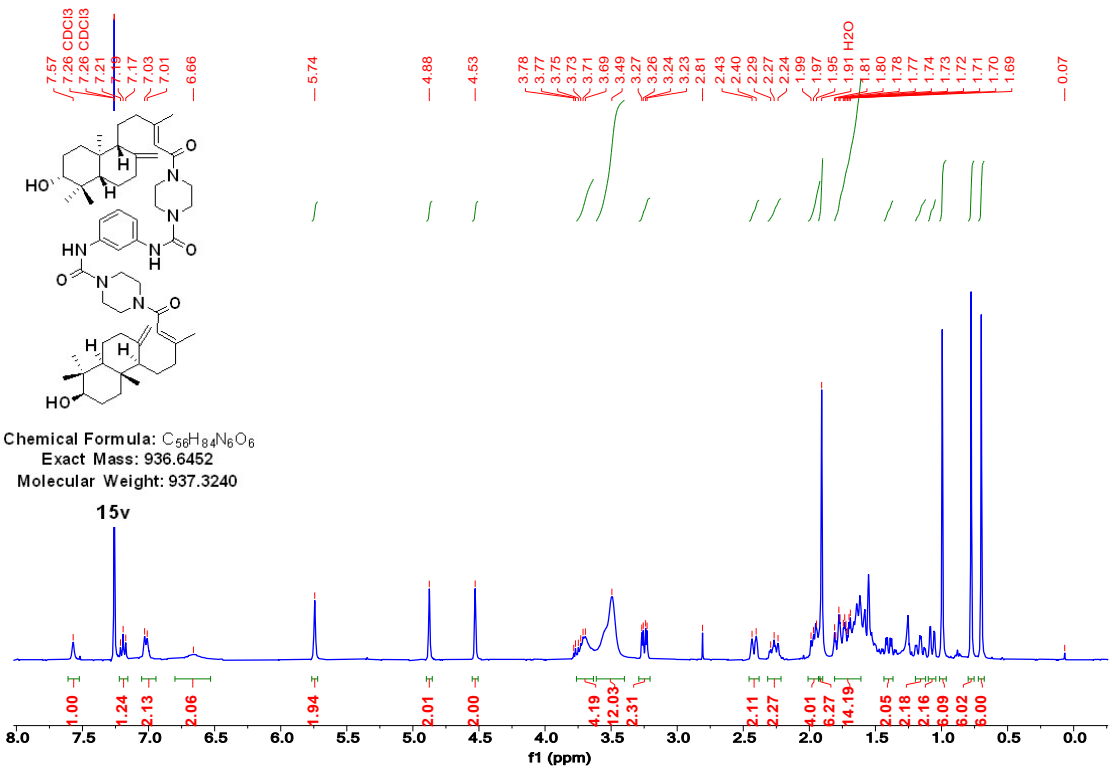


Figure S115. ^{1}H NMR spectrum of 15v

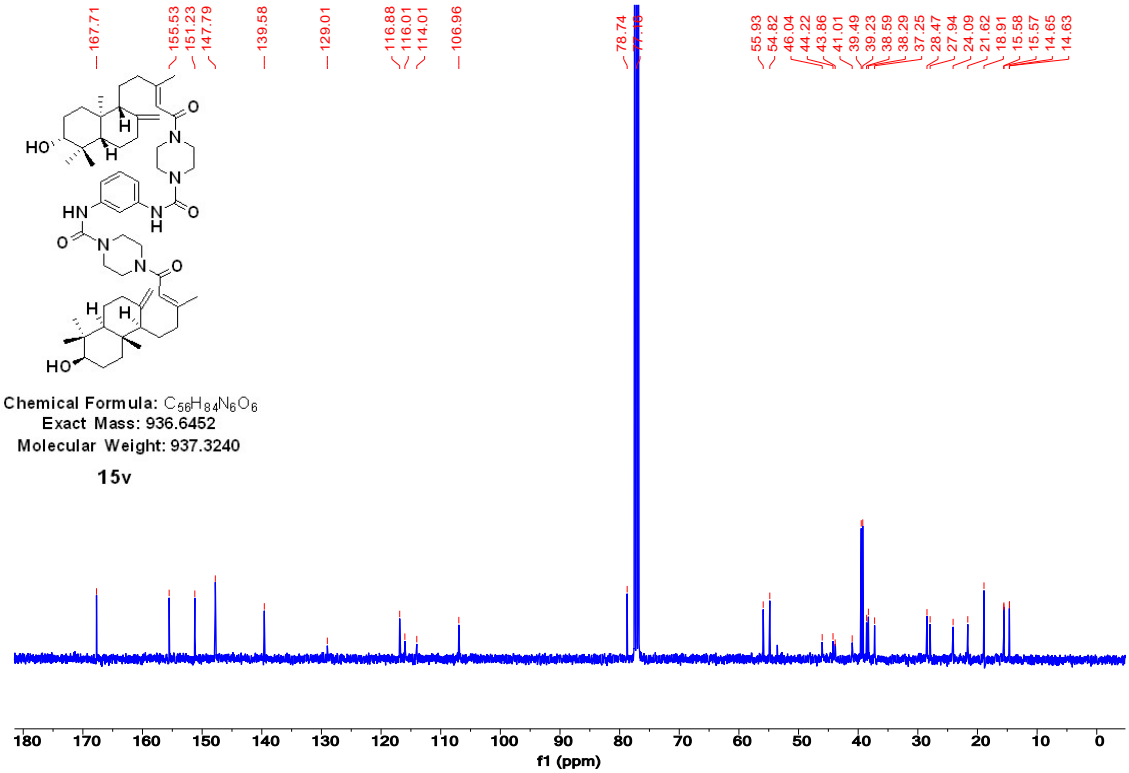


Figure S116. ^{13}C NMR spectrum of 15v

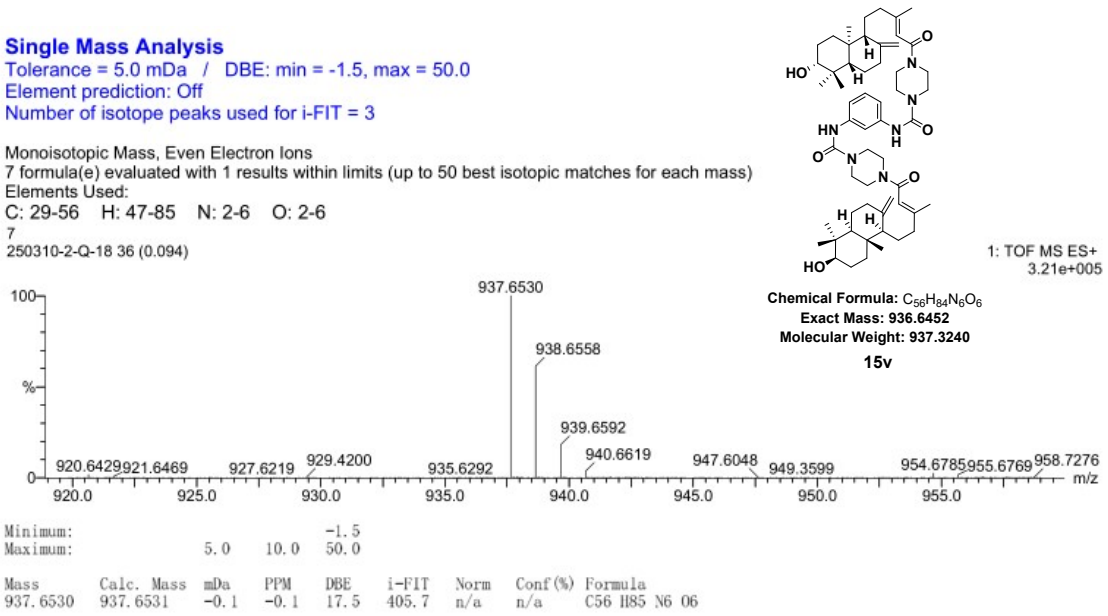
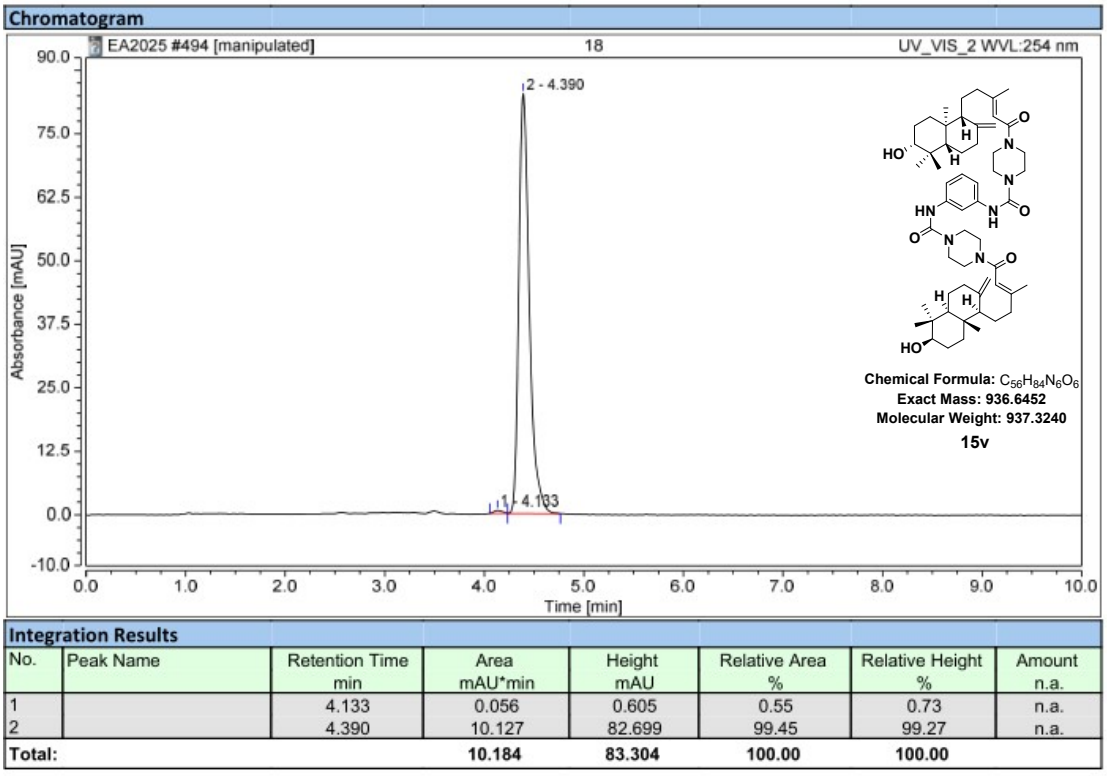


Figure S117. HRMS spectrum of 15v



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		4.133	0.056	0.605	0.55	0.73	n.a.
2		4.390	10.127	82.699	99.45	99.27	n.a.
Total:			**10.184**	**83.304**	**100.00**	**100.00**	

Figure S118. HPLC spectrum of 15v

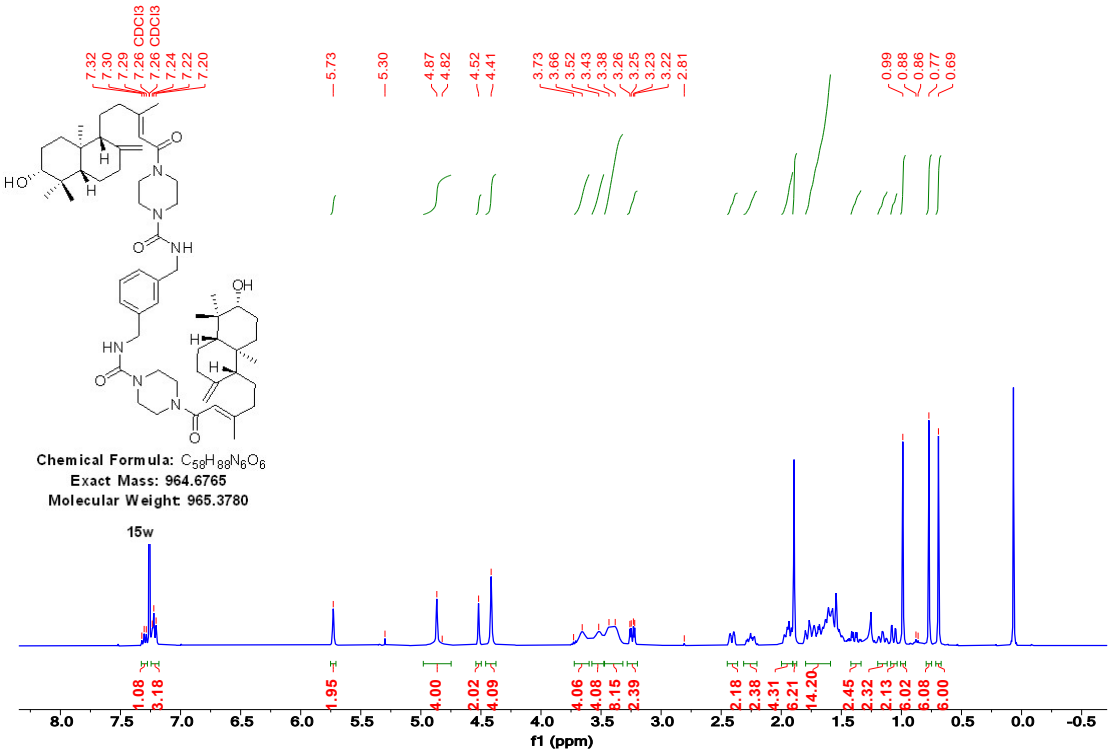


Figure S119. ^{1}H NMR spectrum of 15w

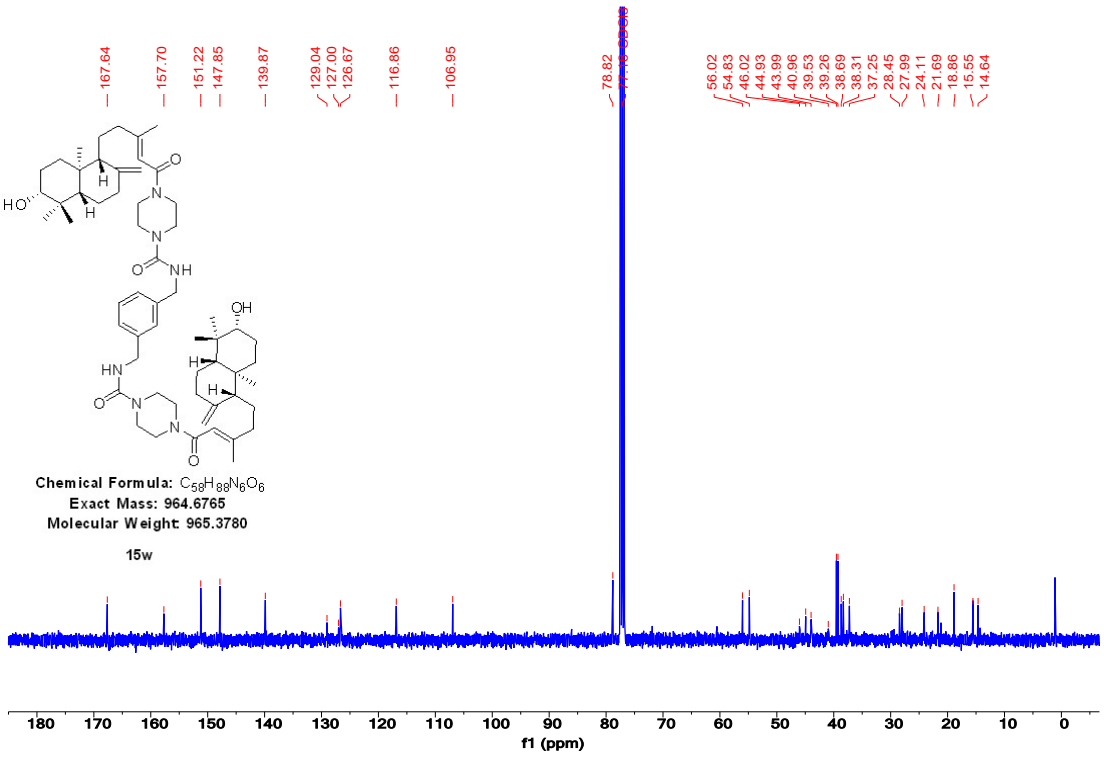


Figure S120. 13C NMR spectrum of 15w

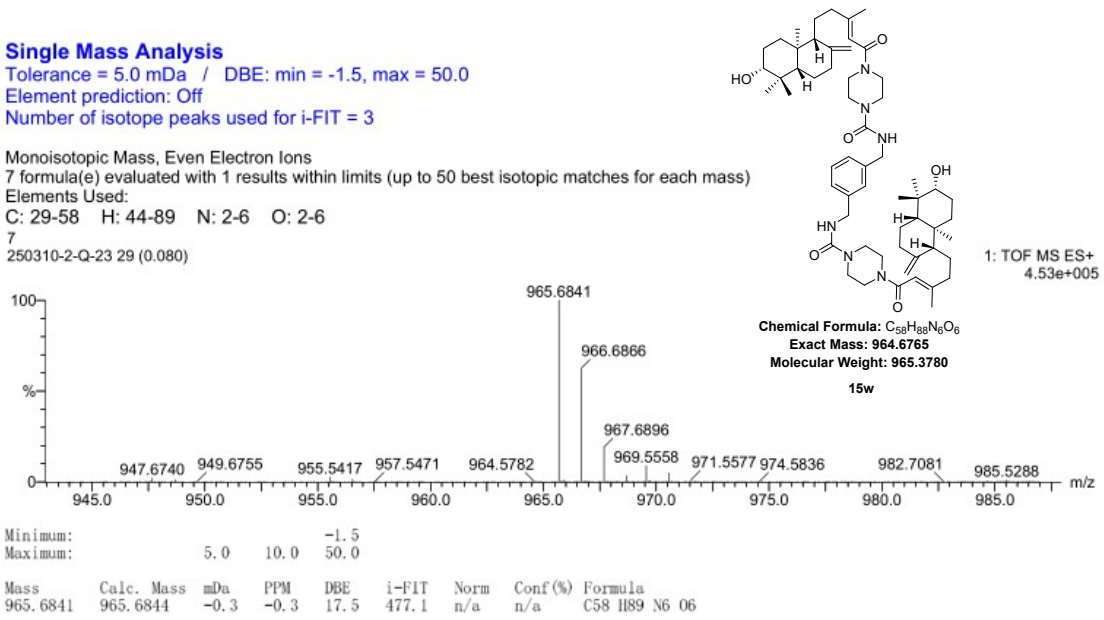
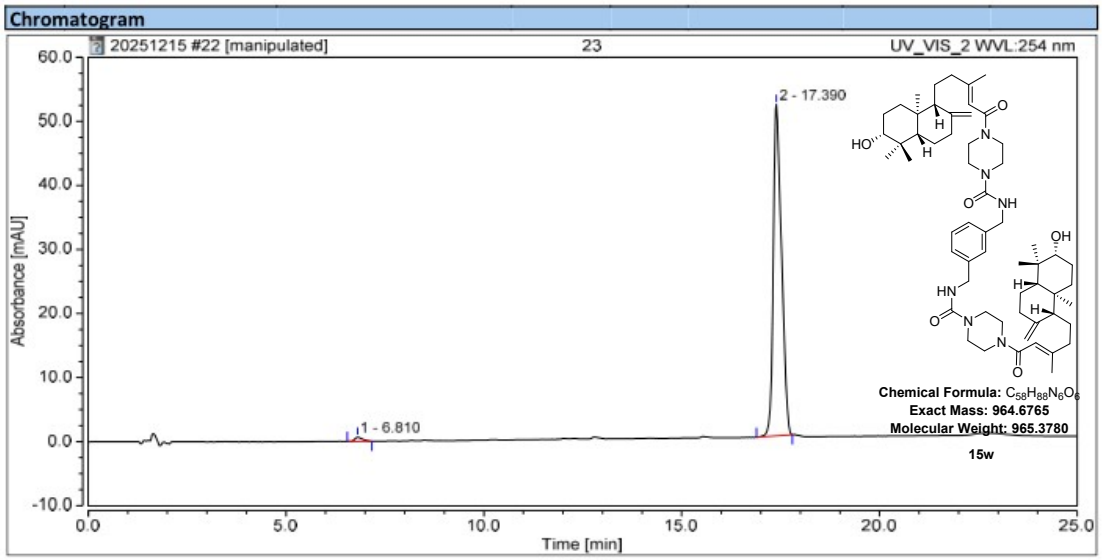


Figure S121. HRMS spectrum of 15w



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.810	0.144	0.658	1.15	1.25	n.a.
2		17.390	12.384	51.772	98.85	98.75	n.a.
Total:			**12.528**	**52.429**	**100.00**	**100.00**	

Figure S122. HPLC spectrum of 15w

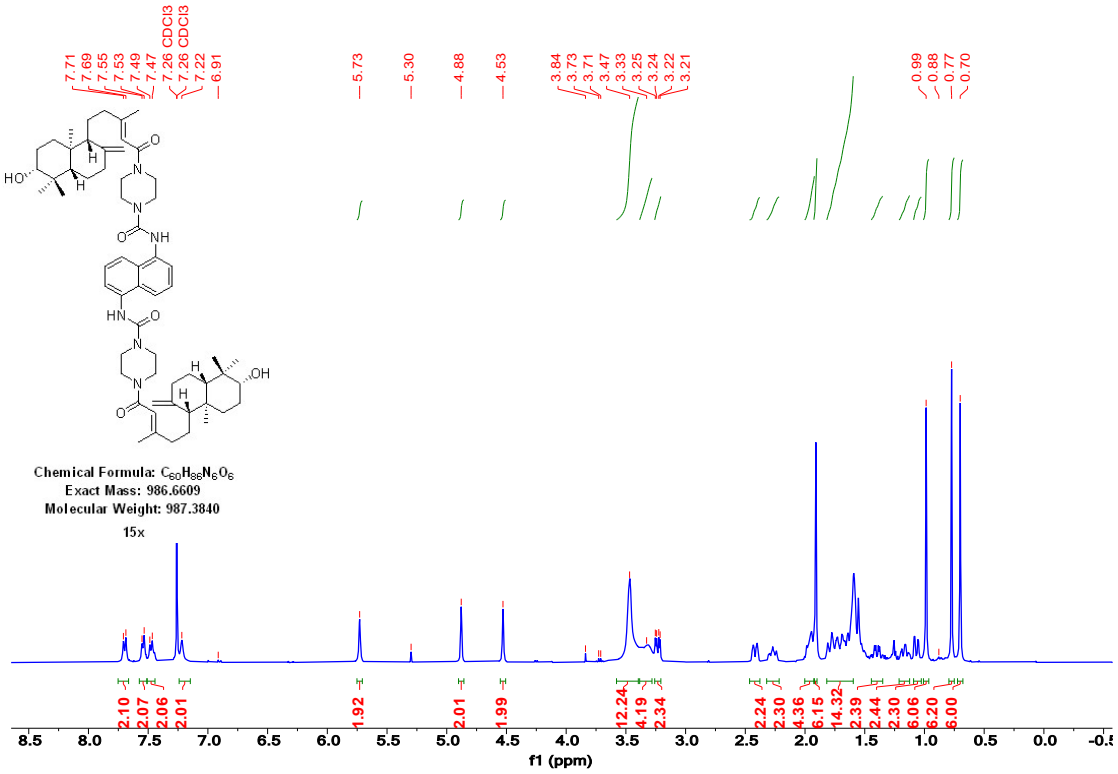


Figure S123. ^{1}H NMR spectrum of 15x

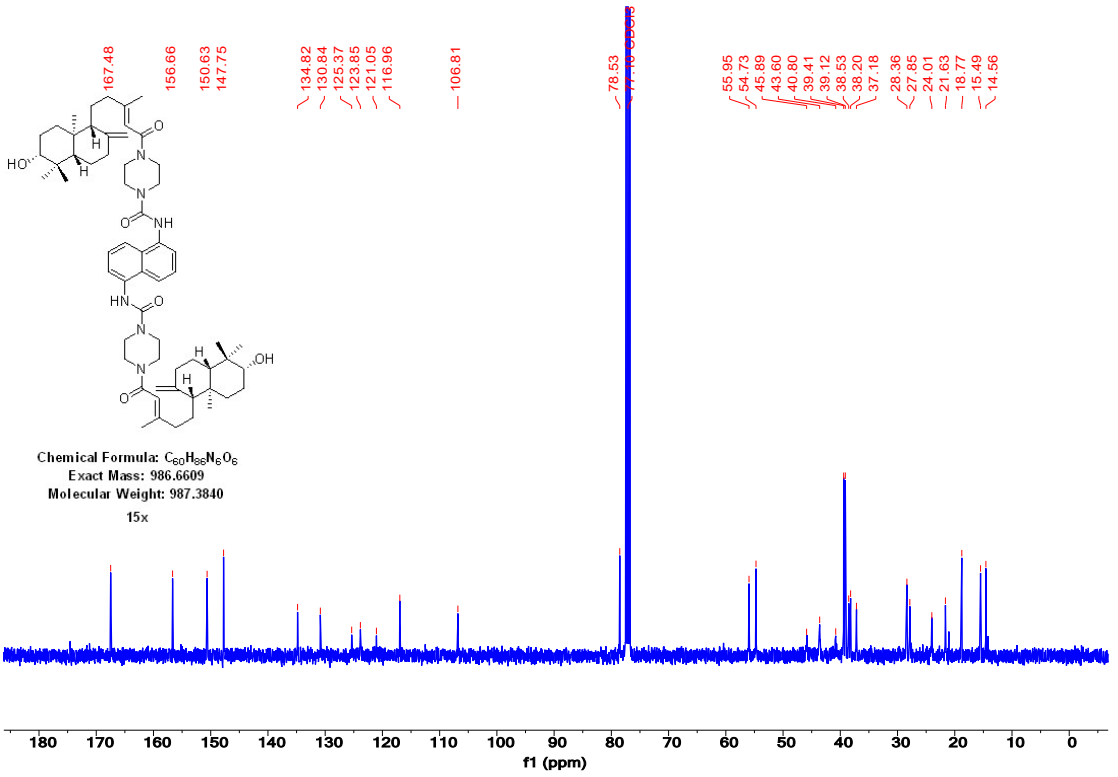


Figure S124. 13C NMR spectrum of 15x

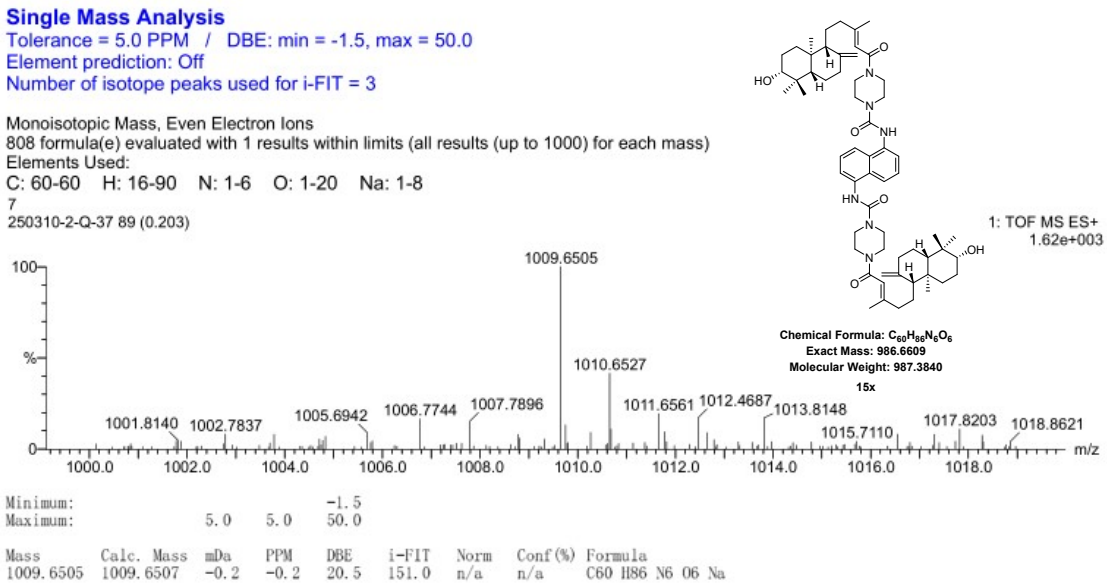
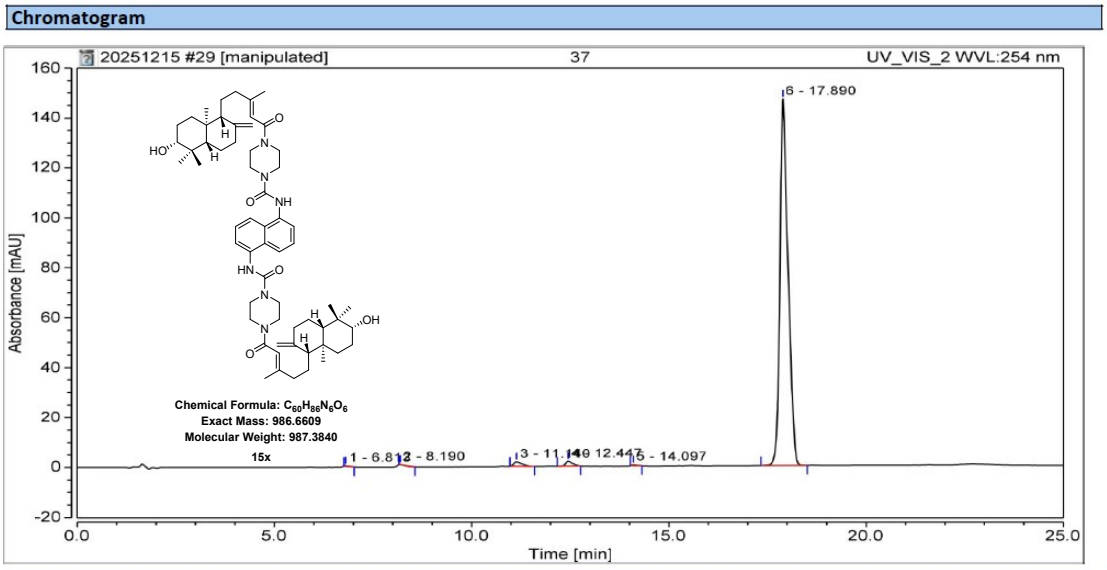


Figure S125. HRMS spectrum of 15x



Integration Results

No.	Peak Name	Retention Time min	Area mAU*min	Height mAU	Relative Area %	Relative Height %	Amount n.a.
1		6.813	0.020	0.166	0.05	0.11	n.a.
2		8.190	0.017	0.146	0.05	0.10	n.a.
3		11.140	0.429	1.797	1.18	1.19	n.a.
4		12.447	0.394	1.956	1.09	1.29	n.a.
5		14.097	0.054	0.347	0.15	0.23	n.a.
6		17.890	35.374	146.782	97.48	97.08	n.a.
Total:			**36.288**	**151.194**	**100.00**	**100.00**	

Figure S126. HPLC spectrum of 15x