Supporting Information

Novel Betulinic Acid-Nucleoside Hybrids with Potent Anti-HIV Activity

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Table of contents

1. Experimental Section

1.1 Biology

1.1.1 Multi-cycle viral replication in MT4 cell assay.

HIV-1 NL4-3 Nanoluc-sec at a dose of 50 TCID50/well was used to infect MT4 cells (1 × 105 cells/mL) in the presence of compounds at various concentrations in 96-well plates. The reporter virus, HIV-1 NL4-3 Nanoluc-sec, was created by inserting the secNluc sequence from pNL1.3[secNluc] (Promega Cat#: N1021) in place of the Nef sequence spanning nucleotide 8796-8892 of pNL4-3 plasmid (GenBank: AF324493.2) using Not I and Xho I restriction enzyme sites. Not I site was introduced into pNL4-3 by site directed mutagenesis and the Xho I site was a unique site in pNL4-3. On day 3 post-infection, supernatant samples were harvested and assayed for luciferase activity using the Promega Nano-Glo® luciferase assay system. The antiviral potency is defined as the drug concentration that reduces the luciferase activity by 50% (IC_{50}).

1.1.2 Cytotoxicity Assay.

A CellTiter-Glo® luminescent cytotoxicity assay (Promega) was used to determine the cytotoxicity of the synthesized compounds. MT4 cells were cultured in the presence of various concentrations of the compounds for 3 days. Cytotoxicity of the compounds was determined by following the protocol provided by the manufacturer. The 50% cytotoxic concentration (CC_{50}) was defined as the concentration that caused a 50% reduction of cell viability.

1.2 Chemistry

1.2.1 General Methods

The starting materials were purchased commercially and used directly. DMF and THF contained less than 50 ppm of water and were stored over 4Å molecular sieves. Progress of reactions was monitored using TLC visualized by UV lamp (254 nm) or $KMnO_4$ developer. Column chromatography was performed using 300 mesh silica gel (Yantai Xinnuo Co. Ltd.). Melting points (mp) were measured on a Shenguang WRR melting point apparatus (Shanghai Precision & Scientific Instrument Co. Ltd.). ^{1}H and ^{13}C NMR spectra were recorded using an Agilent 400 MR (400 MHz for ^{1}H; 100 MHz for ^{13}C) in deuterated solvents. Chemicals shifts are reported in parts per million (δ ppm) relative to TMS or the solvent peak. Coupling constants (*J*) are expressed in hertz (Hz). High-resolution mass spectrometry (HRMS) analysis was performed using an Agilent 1290-6540 Q-TOF mass spectrometer.

1.2.2 Synthetic procedures

Synthesis of betulonic acid (6).

To a solution of betulin (20.0g, 45.2 mmol) in acetone (400 mL) was added freshly prepared Jones' reagent (200 mL) dropwise over 30 min at 0 °C. The solution was stirred for 20 min at 0 °C, the ice bath was removed and stirring continued for 2 h (monitoring by TLC). The reaction was quenched with MeOH (300 mL) and water (300 mL). The solvent was removed under vacuum and the aqueous residue was extracted with EtOAc (3 × 200 mL).

The combined organic layer was dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by column chromatography on SiO_2 eluting with CH_2Cl_2/MeOH (10:1) to remove the impurities, then with petroleum ether/EtOAc (4:1) to afford betulonic acid as a white solid (12.2 g, 26.8 mmol, 59.3%), mp 191-193 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) *δ*: 12.10 (s, 1H), 4.69(s, 1H), 4.57 (s, 1H), 2.95 (td, J=11.1, 5.2 Hz, 1H), 2.48-2.30 (m, 2H), 2.26 (td, J=12.6, 3.2 Hz, 1H), 2.15-2.06 (m, 1H), 1.89-1.73 (m, 3H), 1.65 (s, 3H), 1.67-1.60 (m, 1H), 1.54 (t, J=11.3 Hz, 1H), 1.48-1.00 (m, 14H), 1.02-0.96 (m, 1H), 0.98(s, 3H), 0.95(s, 3H), 0.93(s, 3H), 0.90(s, 3H), 0.85(s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*：218.5, 177.2, 150.3, 109.7, 55.4, 53.8, 49.0, 48.4, 46.6, 46.5, 42.1, 40.1, 38.8, 37.7, 36.4, 36.3, 33.6, 33.1, 31.6, 30.1, 29.2, 26.4, 25.1, 21.0, 20.7, 19.2, 19.0, 15.7, 15.4, 14.3. HRMS (ESI) calcd for $C_{30}H_{46}O_3$ $[M+H]^+$ 455.3525, found 455.3519.

Synthesis of betulonic acid methyl ester (7).

To a solution of compound **6** (4.54 g, 10.0 mmol) in DMC (40 mL), DBU (6.0 mL, 40 mmol) was added and the mixture was stirred under reflux for 24 h (monitoring by TLC). The mixture was evaporated under vacuum and the residue was dissolved in EtOAc and washed twice with 10% HCl (aq) followed by saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed under vacuum. The residue was purified by column chromatography on SiO_2 eluting with petroleum ether/EtOAc (20:1) to afford compound **7** as a white solid (3.36 g, 7.2 mmol, 72.0%), mp167-169 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.74 (d, J=1.8 Hz, 1H), 4.60 (s, 1H), 3.67 (s, 3H), 3.00 (td, J=10.8, 4.3 Hz, 1H), 2.55-2.34 (m, 2H), 2.30-2.17 (m, 2H), 1.95-1.83 (m, 3H), 1.77-1.70 (m, 1H), 1.69 (s, 3H), 1.60 (t, J=11.5 Hz, 1H), 1.50-1.24 (m, 13H), 1.20-1.14 (m, 1H), 1.07 (s, 3H), 1.05-0.99 (m, 1H), 1.02 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ：218.2, 176.6, 150.5, 109.6, 56.5, 54.9, 51.3, 49.9, 49.3, 47.3, 46.9, 42.4, 40.6, 39.6, 38.3, 36.9, 36.9, 34.1, 33.6, 32.1, 30.5, 29.6, 26.6, 25.5, 21.4, 21.0, 19.6, 19.3, 15.9, 15.7, 14.6. HRMS (ESI) calcd for $C_{31}H_{48}O_3$ $[M+H]^+$ 469.3682, found 469.3675.

Synthesis of methyl-2α-propargyl-3-oxolup-20(29)-en-28-oate (8).

A 1M solution of $KN(SiMe_3)_2$ (32 mL, 32 mmol) in THF was added under nitrogen at room temperature to a stirred solution of compound **7** (2.54 g, 5.4 mmol) in DME (135 mL). After 30 min, 1M Et_3B (40 mL, 40 mmol) in DME was added and the mixture was stirred for 60 min. Then, a solution of propargyl bromide (4.0 mL, 48 mmol) was added. The reaction mixture was stirred for 6 h under nitrogen (monitoring by TLC), neutralized with 3 M HCl (aq), and diluted with water (300 mL). After extraction with EtOAc (3 × 150 mL), the organic layers were combined, washed with saturated $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography on SiO_2 eluting with petroleum ether/EtOAc (20:1). Compound **8** was obtained as a pale yellow powder (2.32 g, 4.58 mmol, 84.8%), mp 112-114 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) *δ*: 4.73-4.68 (m, 1H), 4.57 (s, 1H), 3.60 (s, 3H), 2.98-2.82 (m, 2H), 2.72 (t, J=2.5 Hz, 1H), 2.42 (ddd, *J* = 16.7, 4.3, 2.7 Hz, 1H), 2.25-2.07 (m, 4H), 1.85-1.73 (m, 2H), 1.71-1.62 (m, 1H), 1.65 (s, 3H), 1.56 (t, *J* = 11.4 Hz, 1H), 1.52-1.20 (m, 11H), 1.14-1.00 (m, 4H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 214.4, 175.6, 150.0, 109.8, 83.0, 72.0, 56.3, 55.8, 51.2, 49.2, 48.7, 47.5, 46.6, 45.4, 42.1, 40.4, 40.1, 37.6, 36.8, 36.1, 33.5, 31.4, 29.9, 29.1, 24.9, 24.8, 21.3,

20.7, 19.0, 18.8, 18.8, 15.7, 15.6, 14.3. HRMS (ESI) calcd for $C_{34}H_{50}O_3$ $[M+H]^+$ 507.3838, found 507.3831.

Synthesis of methyl-2α-propargyl-3β-hydroxylup-20(29)-en-28-oate (9).
Compound **8** (1.89 g, 3.7 mmol) was dissolved in isopropanol (120 mL), $NaBH_4$ (2.8 g, 7.4 mmol) was added, and the mixture was stirred at rt for 5h (monitoring by TLC). HCl (3 M, 60 mL) was added slowly. The solution was extracted with EtOAc (3 × 100 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on SiO_2 eluting with petroleum ether/EtOAc (20:1) to afford compound **9** as a white solid (0.98 g, 1.9 mmol, 51.4%), mp 134-136 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) *δ*: 4.70 (d, *J* = 2.1 Hz, 1H), 4.59-4.54 (m, 1H), 4.43 (d, *J* = 6.7 Hz, 1H), 3.60 (s, 3H), 2.92 (td, *J* = 10.7, 5.3 Hz, 1H), 2.73-2.65 (m, 2H), 2.43 (dt, *J* = 16.5, 3.0 Hz, 1H), 2.22 – 1.98 (m, 3H), 1.86-1.73 (m, 3H), 1.69-1.60 (m, 1H), 1.65 (s, 3H), 1.60-1.52 (m, 2H), 1.51-0.96 (m, 13H), 0.94 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H), 0.73-0.62 (m, 2H), 0.66 (s, 3H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 175.6, 150.0, 109.7, 83.5, 79.2, 72.0, 55.8, 55.0, 51.2, 49.9, 48.7, 46.6, 44.1, 42.0, 40.2, 38.8, 37.7, 36.7, 36.1, 34.4, 33.8, 31.4, 29.9, 29.1, 28.4, 24.9, 21.7, 20.5, 18.8, 18.1, 16.6, 16.5, 15.6, 14.4. HRMS (ESI) calcd for $C_{34}H_{52}O_3$ $[M+H]^+$ 509.3995, found 509.3988.

Synthesis of 2α-propargyl-3β-hydroxylup-20(29)-en-28-oic acid (10).
LiI (2.10g, 15 mmol) was added to a stirred solution of compound **9** (508 mg, 1 mmol) in DMF (15 mL). The reaction mixture was heated to reflux under nitrogen for 24 h (monitoring by TLC), diluted with water (10 mL), and neutralized with 10% HCl (aq). The product was extracted with EtOAc (3 × 30 mL), the extracts were combined and dried over Na_2SO_4, and the solvent was evaporated under vacuum. The residue was purified by column chromatography on SiO_2 eluting with petroleum ether/EtOAc (2:1) to give compound **10** as a white solid (386 mg, 0.78 mmol, 78.0%), mp 170-172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 4.77-4.71 (m 1H), 4.63-4.57 (m, 1H), 3.07-2.95 (m, 2H), 2.45-2.30 (m, 2H), 2.27 (dt, J=12.6, 2.9 Hz, 1H), 2.24-2.14 (m, 1H), 2.00-1.95 (m, 2H), 1.83 (dd, J=12.8, 3.6 Hz, 1H), 1.79-1.69 (m, 2H), 1.69 (s, 3H), 1.66-1.16 (m, 13H), 1.12-1.02 (m, 1H), 0.98 (s, 6H), 0.94 (s, 3H), 0.87 (s, 3H), 0.85-0.80 (m, 1H), 0.78(s, 3H), 0.76-0.70 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.2, 150.3, 109.8, 82.9, 81.5, 70.0, 56.2, 55.4, 50.4, 49.2, 46.9, 44.8, 42.5, 40.7, 39.1, 38.4, 37.3, 37.0, 34.8, 34.2, 32.1, 30.5, 29.6, 28.3, 25.5, 22.4, 20.9, 19.3, 18.5, 16.99, 16.2, 16.0, 14.7. HRMS (ESI) calcd for $C_{33}H_{50}O_3$ $[M+H]^+$ 495.3838, found 495.3835.

General Method for Click Reactions.
To a solution of the alkyne (0.24 mmol) in 2mL of t-BuOH/H_2O 1:1 (v:v) was added DIPEA (50 uL, 0.3 mmol) and azide (0.2 mmol). After the mixture was stirred for 15 min, a solution of CuI (4 mg, 0.02 mmol) in CH_3CN (1 mL) was added and the resulting mixture was stirred at rt until azide was gone (monitoring by TLC). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel (5-10% MeOH in DCM) to give compounds **8a-c**, **9a-c**, and **10a-c**.

Methyl 2α-{1N[1-(2-deoxy-2β-fluoro-*β-D*-arabinopentafuranosyl)cytosine-4-yl]-1H-1,2,3-triazole-4-yl}-3-oxolup-20(29)-en-28-oate (8a).
White solid, yield (62.2%), m.p.151-153 °C. ^{1}H NMR (MeOH-*d*$_4$, 400 MHz) ***δ***: 7.99 (d, *J* =

7.7 Hz, 1H), 7.87 (s, 1H), 6.80 (dd, *J* = 11.7, 4.9 Hz, 1H), 6.00 (d, *J*=7.2 Hz, 1H), 5.37 (dt, *J* = 53.9, 4.5 Hz, 1H), 4.79 (dd, *J* = 21.3, 4.2 Hz, 1H), 4.70 (d, *J*=2.0 Hz, 1H), 4.59 (s, 1H), 4.38~4.18 (m, 2H), 3.66 (s, 3H), 3.26~3.08 (m, 2H), 3.06~2.92 (m, 1H), 2.62 (dd, *J* = 14.4, 6.9 Hz, 1H), 2.30~2.16 (m, 2H), 2.04 (dd, *J* = 12.8, 4.9 Hz, 1H), 1.92~1.81 (m, 2H), 1.76~1.53 (m, 3H), 1.68 (s, 3H), 1.53-1.20 (m, 10H), 1.19-1.10 (m, 2H), 1.12 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.09-1.00 (m, 2H), 0.98 (s, 3H), 0.98(s, 3H). ^{13}C NMR (MeOH-d_4, 100 MHz) ***δ***: 218.6, 178.2, 167.0, 156.8, 151.8, 146.8, 143.8, 124.0, 110.4, 98.8 (d, J=7.3 Hz), 96.1(d, J=193.5 Hz), 96.1, 86.5 (d, J=15.6 Hz), 76.4 (d, J=25.4 Hz), 63.2, 58.9, 57.9, 51.9, 51.5, 50.7, 49.6, 48.6, 48.2, 43.7, 43.6, 42.1, 39.7, 38.7, 37.9, 35.4, 33.2, 31.7, 30.9, 27.0, 26.8, 25.7, 22.3, 22.1, 20.4, 19.6, 16.8, 16.6, 15.2. HRMS (ESI) calcd for $C_{43}H_{61}FN_6O_7$ $[M+H]^+$ 793.4664, found 793.4657.

Methyl 2α-{1N[1-(2-deoxy-2β-fluoro-*β*-*D*-arabinopentafuranosyl)uracil-4-yl]-1H-1,2,3-triazole-4-yl}-3-oxolup-20(29)-en-28-oate (8b).

White solid, yield (68.5%), m.p. 162-164 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) ***δ***: 11.56 (brs, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 6.70 (t, *J* = 6.9 Hz, 1H), 6.36 (d, *J* = 5.1 Hz, 1H), 5.99 (brs, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 5.40 (dt, *J* = 54.5, 5.7 Hz, 1H), 4.78 (dt, *J* = 25.9, 4.9 Hz, 1H), 4.69 (s, 1H), 4.56 (s, 1H), 4.28-4.02 (m, 2H), 3.60 (s, 3H), 3.21-3.00 (m, 2H), 2.98-2.83 (m, 1H), 2.43 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.22-2.05 (m, 2H), 2.04-1.92 (m, 1H), 1.86-1.70 (m, 2H), 1.64 (s, 3H), 1.61-1.16 (m, 14H), 1.15-1.06 (m, 2H), 1.04-0.93 (m, 1H), 1.03 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) ***δ***: 215.6, 175.6, 162.9, 150.2, 150.0, 144.5, 141.2, 122.2, 109.8, 101.8, 95.5 (d, J=11.0 Hz), 94.7 (d, J=192.5 Hz), 82.2, 74.0 (d, J=24.1 Hz), 60.6, 56.6, 55.8, 51.3, 49.2, 48.7, 47.7, 46.6, 46.2, 42.1, 41.1, 40.2, 37.6, 36.9, 36.1, 33.5, 31.4, 29.9, 29.1, 25.7, 25.1, 24.9, 21.2, 20.6, 18.9, 18.8, 15.7, 15.6, 14.3. HRMS (ESI) calcd for $C_{43}H_{60}FN_5O_8$ $[M+H]^+$ 794.4504, found 794.4500.

Methyl 2α-{1N[1-(2,3-dideoxy-*β*-*D*-ribopentafuranosyl)thymine-3-yl]-1H-1,2,3-triazole-4-yl}-3-oxolup-20(29)-en-28-oate (8c).

White solid, yield (74.8%), m.p.152-154 °C. ^{1}H NMR($CDCl_3$, 400 MHz) *δ*: 9.73 (s, 1H), 7.56 (s, 2H), 6.29 (t, *J* = 6.4 Hz, 1H), 5.47-5.34 (m, 1H), 4.72 (s, 1H), 4.58 (s, 1H), 4.45-4.34 (m, 1H), 4.11-3.94 (m, 2H), 3.88-3.74 (m, 1H), 3.67 (s, 3H), 3.24-3.12 (m, 1H), 3.09 (dd, *J* = 14.4, 6.9 Hz, 1H), 3.03-2.83 (m, 3H), 2.60 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.27-2.08 (m, 3H), 1.94-1.83 (m, 2H), 1.90 (s, 3H), 1.76-1.65 (m, 1H), 1.67 (s, 3H), 1.60-1.51 (m, 2H), 1.48-1.23 (m, 10H), 1.16-1.06 (m, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 217.4, 176.6, 164.1, 150.5, 150.3, 146.8, 137.7, 122.4, 111.0, 109.7, 87.9, 85.2, 61.3, 58.9, 57.5, 56.4, 51.2, 50.0, 49.3, 48.5, 47.9, 46.9, 42.4, 42.2, 40.7, 38.1, 37.6, 37.5, 36.9, 34.0, 32.1, 30.4, 29.5, 26.4, 25.3, 24.9, 21.4, 21.1, 19.2, 19.2, 16.1, 16.0, 14.6, 12.4. HRMS (ESI) calcd for $C_{44}H_{63}N_5O_7$ $[M+H]^+$ 774.4806, found 774.4802.

Methyl 2α-{1N[1-(2-deoxy-2β-fluoro-*β*-*D*-arabinopentafuranosyl)cytosine-4-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oate (9a).

White solid, yield (60.4%), m.p. 163-165 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.90 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.33 (br, 1H), 7.29 (br, 1H), 6.83-6.68 (m, 1H), 6.22 (d, *J* = 5.4 Hz, 1H), 5.85 (t, *J* = 4.8 Hz, 1H), 5.80 (d, *J* = 7.3 Hz, 1H), 5.32 (dt, *J* = 55.5, 5.6 Hz, 1H),

4.79-4.64 (m, 2H), 4.61-4.51 (m, 2H), 4.21-4.07 (m, 2H), 3.58 (s, 3H), 3.14 (d, *J* = 13.4 Hz, 1H), 2.89 (td, J=10.4, 5.0 Hz, 1H), 2.68 (dd, *J* = 10.3, 6.5 Hz, 1H), 2.26 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.18-2.04 (m, 2H), 1.86-1.72 (m, 3H), 1.64 (s, 3H), 1.62-1.53 (m, 3H), 1.47-1.03 (m, 13H), 0.91 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H), 0.71 (s, 3H), 0.70 (s, 3H), 0.73-0.63 (m, 1H), 0.49 (t, *J* = 12.7 Hz, 1H). ^{13}C NMR (DMSO-*d*$_6$, 400 MHz) δ：175.6, 165.6, 154.7, 150.0, 144.9, 141.8, 122.0, 109.8, 94.7 (d, J=191.6 Hz), 95.4 (d, J = 10.3 Hz), 94.1, 82.9, 80.3, 74.2 (d, J = 24.5 Hz), 60.8, 55.8, 55.0, 51.2, 49.8, 48.7, 46.6, 44.3, 41.9, 40.1, 38.9, 37.6, 36.7, 36.1, 35.5, 33.8, 31.4, 30.0, 29.1, 28.5, 28.5, 25.0, 20.3, 18.9, 18.2, 16.6, 16.6, 15.6, 14.4. HRMS (ESI) calcd for $C_{43}H_{63}FN_6O_7$ $[M+H]^+$ 795.4821, found 795.4816.

Methyl 2α-{1N[1-(2-deoxy-2β-fluoro-*β*-*D*-arabinopentafuranosyl)uracil-4-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oate (9b).

White solid, yield (68.8%), m.p.174-176 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 11.56 (s, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 6.72 (t, *J* = 7.1 Hz, 1H), 6.31 (d, *J* = 5.6 Hz, 1H), 5.96 (t, *J* = 5.6 Hz, 1H), 5.75 (d, *J* = 8.1 Hz, 1H), 5.41 (dt, *J* = 55.5, 6.0 Hz, 1H), 4.77 (dt, *J* = 25.8, 5.7 Hz, 1H), 4.68 (brs, 1H), 4.58 (d, *J* = 6.5 Hz, 1H), 4.56 (s, 1H), 4.15 (ddd, *J* = 32.8, 12.6, 5.5 Hz, 2H), 3.58 (s, 3H), 3.16-3.09 (m, 1H), 2.89 (td, *J* = 10.4, 5.1 Hz, 1H), 2.68 (dd, *J* = 10.4, 6.7 Hz, 1H), 2.25 (dd, *J* = 14.3, 9.5 Hz, 1H), 2.18-2.04 (m, 2H), 1.86-1.72 (m, 3H), 1.64 (s, 3H), 1.62-1.53 (m, 3H), 1.47-1.03 (m, 14H), 0.91 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H), 0.71 (s, 3H), 0.70 (s, 3H), 0.73-0.63 (m, 1H), 0.49 (t, *J* = 12.6 Hz, 1H). ^{13}C NMR (DMSO-*d*$_6$, 400 MHz) δ：175.6, 162.9, 150.2, 150.0, 145.0, 141.2, 122.1, 109.8, 101.8, 94.7 (d, J=192.1 Hz), 95.3 (d, J = 11.0 Hz), 82.2, 80.3, 74.0 (d, J = 25.2 Hz), 60.5, 55.8, 55.0, 51.2, 49.8, 48.7, 46.6, 44.3, 42.0, 40.2, 38.9, 37.6, 36.7, 36.1, 35.5, 33.8, 31.4, 30.0, 29.1, 28.5, 28.5, 25.0, 20.3, 18.9, 18.2, 16.6, 16.6, 15.6, 14.4. HRMS (ESI) calcd for $C_{43}H_{62}FN_5O_8$ $[M+H]^+$ 796.4661, found 796.4656.

Methyl 2α-{1N[1-(2,3-dideoxy-*β*-*D*-ribopentafuranosyl)thymine-3-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oate (9c).

White solid, yield (78.3%), m.p.164-166 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) *δ*: 11.4 (s, 1H), 8.00 (s, 1H), 7.82 (brs, 1H), 6.39 (t, *J* = 6.5 Hz, 1H), 5.35-5.28 (m, 1H), 5.27 (t, *J* = 5.3 Hz, 1H), 4.68 (s, 1H), 4.60-4.52 (m, 2H), 4.17 (dt, *J* = 5.8, 3.6 Hz, 1H), 3.74-3.54 (m, 2H), 3.58 (s, 3H), 3.15 (dd, *J* = 14.1, 2.3 Hz, 1H), 2.95-2.84 (m, 1H), 2.79-2.58 (m, 3H), 2.26 (dd, *J* = 14.5, 9.4 Hz, 1H), 2.16-2.04 (m, 2H), 1.81 (s, 3H), 1.80-1.68 (m, 3H), 1.64 (s, 3H), 1.62-1.50 (m, 3H), 1.50-1.16 (m, 10H), 1.12-0.93 (m, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H), 0.71 (s, 3H), 0.69 (s, 3H), 0.71-0.62 (m, 1H), 0.51 (t, *J* = 12.6 Hz, 1H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*：175.6, 163.7, 150.4, 150.0, 146.1, 136.2, 122.0, 109.8, 109.5, 84.5, 83.8, 80.3, 60.6, 58.7, 55.8, 55.0, 51.2, 49.9, 48.7, 46.6, 44.4, 42.0, 40.2, 38.9, 37.6, 37.0, 36.6, 36.1, 35.6, 33.8, 31.4, 29.9, 29.1, 28.7, 28.5, 25.0, 20.3, 18.9, 18.2, 16.6, 16.6, 15.6, 14.4, 12.3. HRMS (ESI) calcd for $C_{44}H_{65}N_5O_7$ $[M+H]^+$ 776.4962, found 776.4959.

2α-{1N[1-(2-Deoxy-2β-fluoro-*β*-*D*-arabinopentafuranosyl)cytosine-4-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oic acid (10a).

White solid, yield (42.6%), m.p. 189-191 °C. ^{1}H NMR (MeOH-*d*$_4$, 400 MHz) *δ*: 7.97 (d, J=7.0 Hz, 1H), 7.89 (s, 1H), 6.85 (dd, J=11.4, 3.6 Hz, 1H), 6.01 (brs, 1H), 5.38 (dt, J=54.1, 4.2 Hz, 1H), 4.80 (dd, J=21.4, 4.0 Hz, 1H), 4.69 (s, 1H), 4.58 (s, 1H), 4.39-4.20 (m, 2H), 3.15 (d, J=12.0 Hz, 1H), 3.06-2.93 (m, 1H), 2.81 (d, J=10.7 Hz, 1H), 2.55 (dd, J=14.1, 8.8 Hz, 1H),

2.36-2.16 (m, 2H), 2,01-1.93 (m, 3H), 1.71-1.57 (m, 3H), 1.68 (s, 3H), 1.46-1.24 (m, 10H), 1.19-1.00 (m, 3H), 0.98 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H), 0.72 (d, J=8.7 Hz, 1H), 0.60 (t, J=12.8 Hz, 1H). ^{13}C NMR (MeOH-*d*$_4$, 100 MHz) δ: 180.6, 167.7, 158.0, 152.1, 146.9, 143.4, 123.9, 110.2, 98.8 (d, J=6.0 Hz), 96.2 (d, J=193.2 Hz), 86.5 (d, J=13.9 Hz), 83.0, 76.4 (d, J=25.2 Hz), 63.2, 57.6, 57.1, 56.0, 52.0, 50.5, 48.6, 46.2, 43.7, 42.0, 40.5, 39.7, 38.5, 38.3, 37.3, 35.6, 33.5, 31.8, 30.9, 29.8, 29.1, 26.9, 22.1, 19.8, 19.7, 17.5, 17.1, 16.7, 15.2. HRMS (ESI) calcd for $C_{42}H_{61}FN_6O_7$ $[M+H]^+$ 781.4664, found 781.4657.

2α-{1N[1-(2-Deoxy-2β-fluoro-*β*-*D*-arabinopentafuranosyl)uracil-4-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oic acid (10b).

White solid, yield (48.8%), m.p. 195-197 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 12.03 (brs, 1H), 11.56 (s, 1H), 7.92 (s, 1H), 7.84 (d, J=8.3 Hz, 1H), 6.73 (t, J=7.0 Hz, 1H), 6.30 (d, J=5.6 Hz, 1H), 5.94 (t, J=5.5 Hz, 1H), 5.75 (dd, J=8.1, 1.5 Hz, 1H), 5.42 (dt, J=55.4, 6.0 Hz, 1H), 4.78 (dt, J=25.8, 5.7 Hz, 1H), 4.67 (s, 1H), 4.57 (d, J=6.2 Hz, 1H), 4.55 (s, 1H), 4.16 (ddd, J=31.0, 12.3, 5.8 Hz, 2H), 3.21-3.08 (m, 1H), 2.99-2.85 (m, 1H), 2.69 (dd, J=9.8, 6.3 Hz, 1H), 2.32-2.04 (m, 3H), 1.90-1.71 (m, 3H), 1.68-1.54 (m, 2H), 1.63 (s, 3H), 1.54-1.20 (m, 11H), 1.14-1.01 (m, 2H), 1.01-0.88 (m, 1H), 0.91 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H), 0.71 (s, 3H), 0.71 (s, 3H), 0.73-0.63 (m, 1H), 0.50 (t, J=12.4 Hz, 1H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ: 177.2, 162.8, 150.2, 145.1, 141.2, 122.2, 109.6, 101.8, 95.3 (d, J=10.9 Hz), 94.7 (d, J=192.3 Hz), 82.2 (d, J=16.0 Hz), 80.3, 74.0 (d, J=24.3 Hz), 60.6, 55.4, 55.0, 49.9, 48.5, 46.6, 44.3, 42.0, 40.2, 38.9, 37.5, 36.7, 36.3, 35.5, 33.8, 31.7, 30.0, 29.1, 28.5, 28.5, 25.0, 20.3, 18.9, 18.2, 16.7, 16.6, 16.6, 15.7, 14.3. HRMS (ESI) calcd for $C_{42}H_{60}FN_5O_8$ $[M+H]^+$ 782.4504, found 782.4498.

2α-{1N[1-(2,3-Dideoxy-*β*-*D*-ribopentafuranosyl)thymine-3-yl]-1H-1,2,3-triazole-4-yl}-3β-hydroxylup-20(29)-en-28-oic acid (10c).

White solid, yield (57.3%), m.p.190-192 °C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ: 12.06 (brs, 1H), 11.4 (s, 1H), 7.99 (s, 1H), 7.82 (d, *J* = 1.0 Hz, 1H), 6.39 (t, *J* = 6.6 Hz, 1H), 5.35-5.28 (m, 1H), 5.27 (t, *J* = 5.3 Hz, 1H), 4.67 (d, *J* = 1.8 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 1H), 4.55 (s, 1H), 4.17 (dt, *J* = 5.3, 3.3 Hz, 1H), 3.74-3.54 (m, 2H), 3.15 (dd, *J* = 14.3, 2.8 Hz, 1H), 2.93 (td, J=10.6, 5.1 Hz, 1H), 2.79-2.58 (m, 3H), 2.31-2.04 (m, 3H), 1.81 (s, 3H), 1.80-1.68 (m, 3H), 1.63 (s, 3H), 1.62-1.55 (m, 2H), 1.50 (t, J=11.5 Hz, 1H), 1.46-1.16 (m, 10H), 1.14-1.02 (m, 2H), 0.99-0.90 (m,1H), 0.92 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H), 0.71 (s, 3H), 0.69 (s, 3H), 0.71-0.62 (m, 1H), 0.51 (t, *J* = 13.1 Hz, 1H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ**:** 177.2, 163.7, 150.4, 150.3, 146.2, 136.2, 122.1, 109.7, 109.6, 84.5, 83.8, 80.3, 60.7, 58.8, 55.4, 55.0, 49.9, 48.5, 46.6, 44.5, 42.0, 40.3, 38.9, 37.5, 37.0, 36.7, 36.3, 35.6, 33.8, 31.7, 30.0, 29.1, 28.7, 28.5, 25.0, 20.4, 18.9, 18.2, 16.6, 16.6, 15.7, 14.4, 12.3. HRMS (ESI) calcd for $C_{43}H_{63}N_5O_7$ $[M+H]^+$ 762.4806, found 762.4802.

Methods for solubility determination of BA and compound 8B by quantitative ^{1}H NMR:

Preparation of internal standard solution

2,3,5-Triiodobenzoic acid (20.8 mg) was dissolved in methanol-d_4 (2.0 mL) to produce the internal standard solution with a concentration of 10.4 mg/mL. The standard solutions were prepared before use.

Preparation of samples for NMR spectroscopic analysis

Saturated solutions (300 μL) of BA and compound **8b** in methanol-d_4 were transferred into separate 5 mm NMR tubes. The same volume of internal standard (2,3,5-triiodobenzoic acid) was added into each tube before NMR analysis.

^{1}H NMR spectroscopy analysis and data processing

All ^{1}H NMR spectra were recorded on an Agilent 400 MR 400MHz spectrometer operating at a proton NMR frequency of 399.79 MHz. The spectra were measured without sample spinning at a temperature of 298K. Methanol-d_4 was used as the internal lock. The following parameters were used in all ^{1}H NMR experiments: 16 scans of 64K data points were acquired with a spectral width of 6410 Hz (16 ppm), an acquisition time of 2.56 s, a relaxation delay of 30 s to ensure relaxation for all signals; the exponential window function was selected and the line broadening (LB) was set to 0.3 Hz. Phase and baseline corrections were performed manually prior to signal integration by using MestReNova software (version 10.0.1, Mestrelabs Research SL, Santiago de Compostela, Spain).

Compound	MW	Weight (mg)	μmol	Volume (mL)	Area
BA	456.71 (M_X)	1.47	3.21	0.3	0.5250 (Ax)
8b	793.96 (M_X)	15.78	19.88	0.3	3.2499 (Ax)
2,3,5-triiodobenzoic acid	499.81 (M_{IS})	3.12 (W_{IS})	6.24	0.3	1 (A_{IS})

The quantification of BA and **8b** in this study can be performed by using the following equation:

$$Wx = \frac{Ax}{A_{IS}} \times \frac{N_{IS}}{Nx} \times \frac{Mx}{M_{IS}} \times W_{IS} \times P_{IS}$$

Wx is the mass of the analyte,

Ax and A_{IS} represent their integral areas of the analyte and internal standard (IS),

N_{IS} and Nx correspond to the numbers of spinning protons of internal standard and the analyte (in this experiment, both N_{IS} and Nx =1),

Mx and M_{IS} are the molecular masses of the analyte and IS,

W_{IS} is the weighed mass of IS,

P_{IS} is the purity of the internal standard. (98.0 %)

The equation can be simplified as follows:

$$Wx = Ax \times \frac{Mx}{M_{IS}} \times 3.0576$$

The calculated solubilities of BA and compound **8b** in methanol are 4.9 mg/mL and 52.6 mg/mL (10.7 mmol/L and 66.3 mmol/L), respectively.

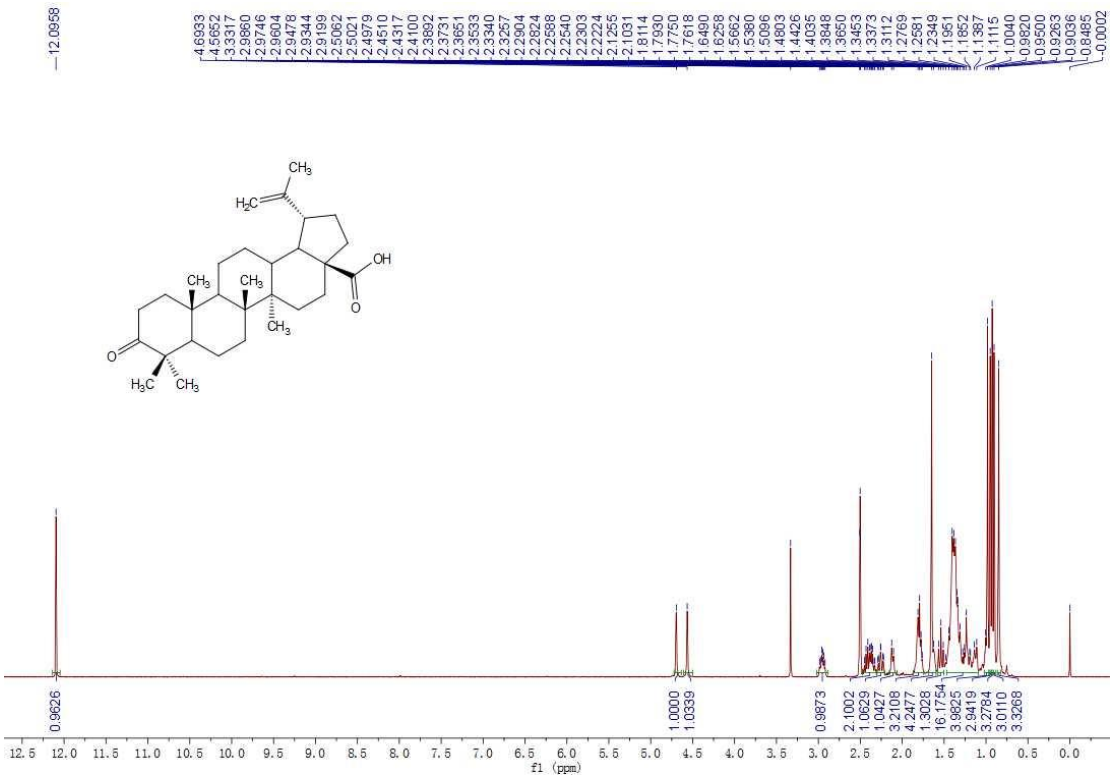


Fig. S1 ^{1}H NMR spectrum of compound **6** in DMSO-d_6

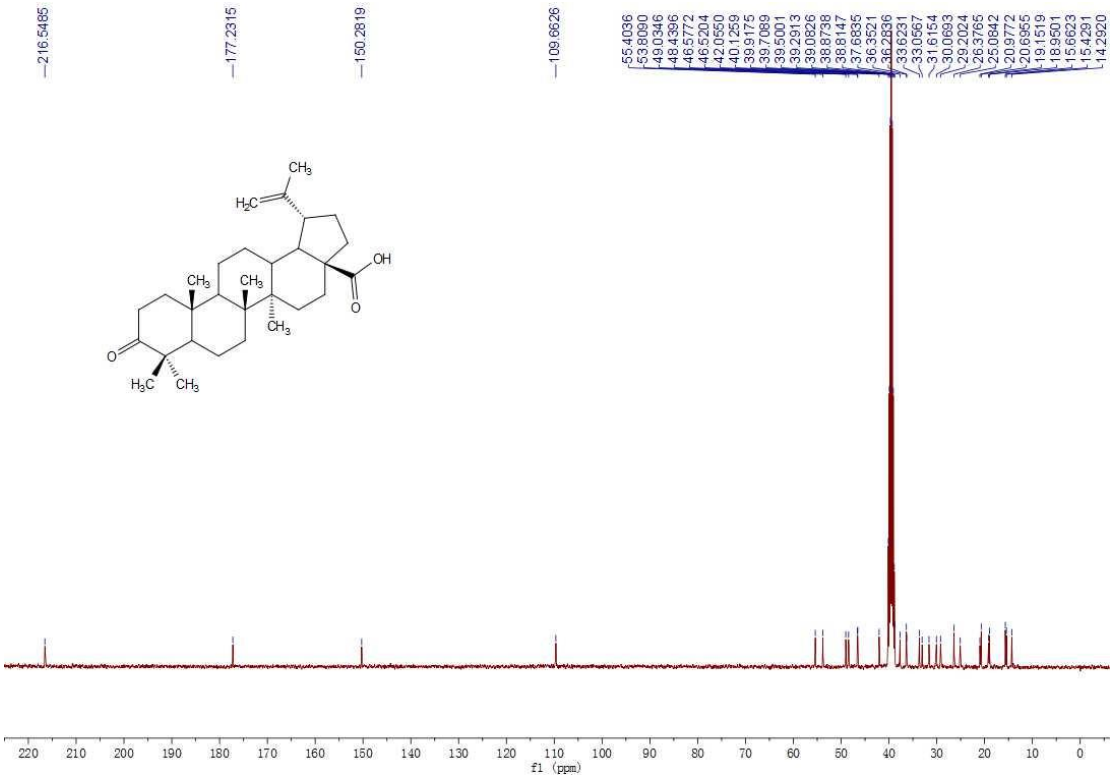


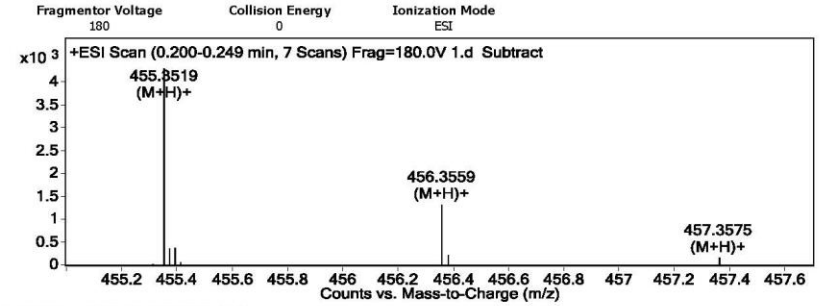
Fig. S2 ^{13}C NMR spectrum of compound **6** in DMSO-d_6

Qualitative Analysis Report

Data Filename	1.d	**Sample Name**	1
Sample Type	Sample	**Position**	P1-A1
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 2:53:41 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
S	0	5
Cl	0	3
N	0	10

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C30 H46 O3	TRUE	454.3446	454.3447	0.19	C30 H47 O3	98.49
C23 H46 N6 O S		454.3446	454.3454	1.66	C23 H47 N6 O S	87.92
C26 H42 N6 O		454.3446	454.342	-5.75	C26 H43 N6 O	85.3
C25 H46 N2 O5		454.3446	454.3407	-8.67	C25 H47 N2 O5	72.41
C19 H46 N6 O6		454.3446	454.3479	7.17	C19 H47 N6 O6	70.38

--- End Of Report ---

Fig. S3 HRMS spectrum of compound **6**

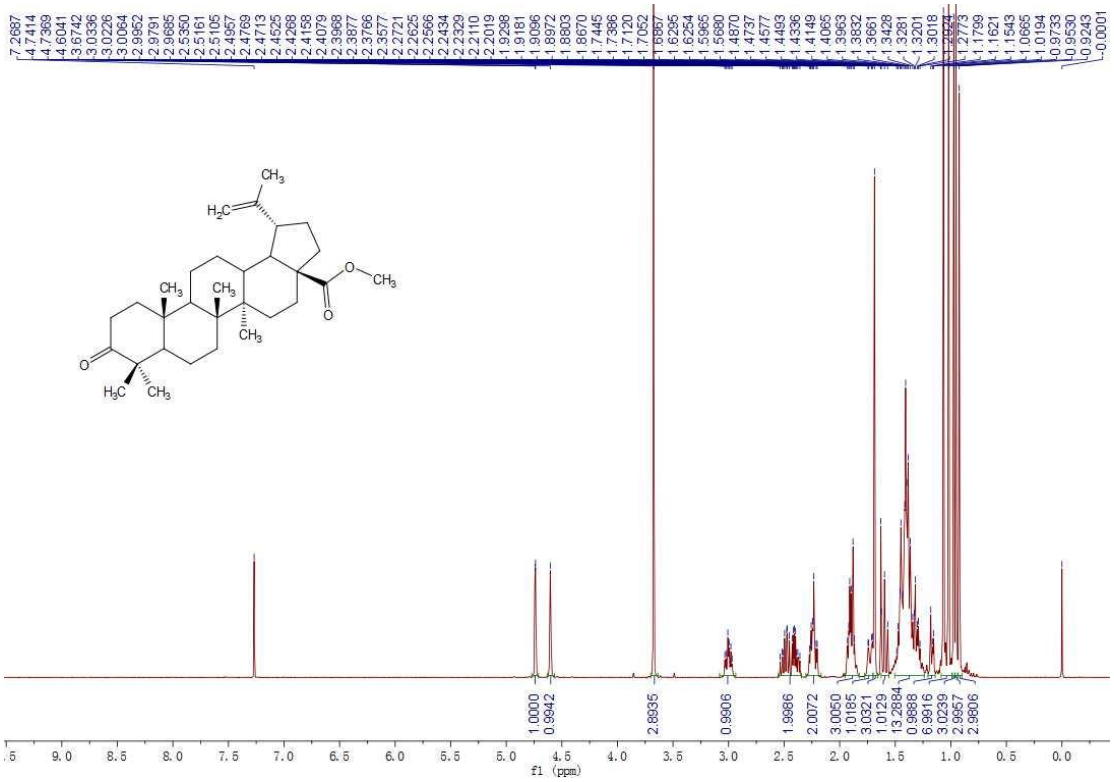


Fig. S4 ^{1}H NMR spectrum of compound **7** in $CDCl_3$

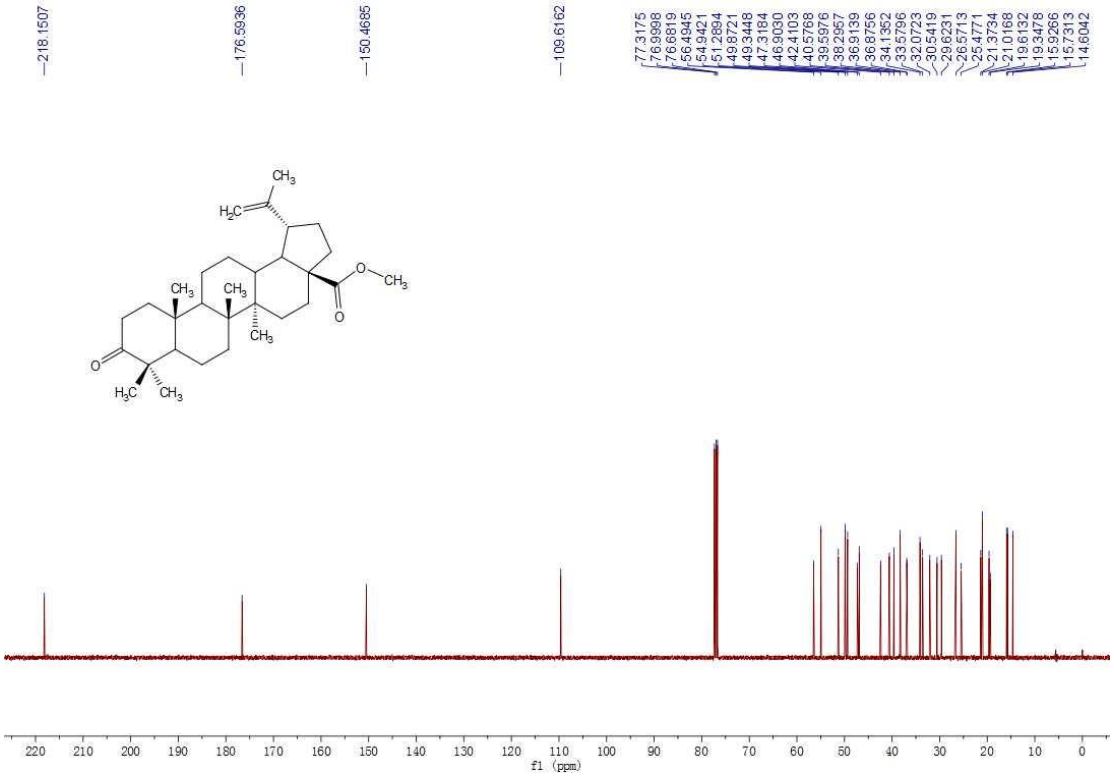


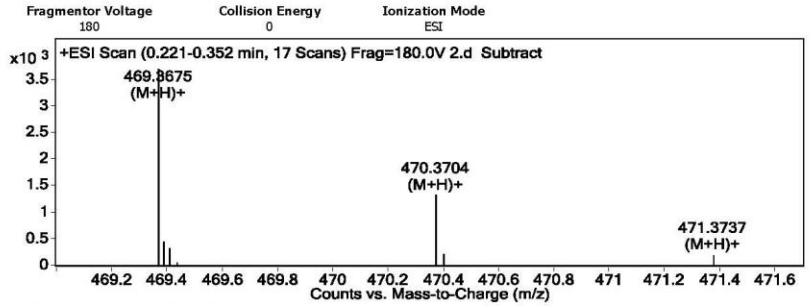
Fig. S5 ^{13}C NMR spectrum of compound **7** in $CDCl_3$

Qualitative Analysis Report

Data Filename	2.d	**Sample Name**	2
Sample Type	Sample	**Position**	P1-A2
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:00:34 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
S	0	5
Cl	0	3
N	0	10

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C31 H48 O3	TRUE	468.3602	468.3603	0.35	C31 H49 O3	98.74
C27 H44 N6 O		468.3602	468.3577	-5.43	C27 H45 N6 O	85.23
C24 H48 N6 O S		468.3602	468.361	1.76	C24 H49 N6 O S	84.87
C26 H48 N2 O5		468.3602	468.3563	-8.25	C26 H49 N2 O5	70.21

--- End Of Report ---

Fig. S6 HRMS spectrum of compound **7**

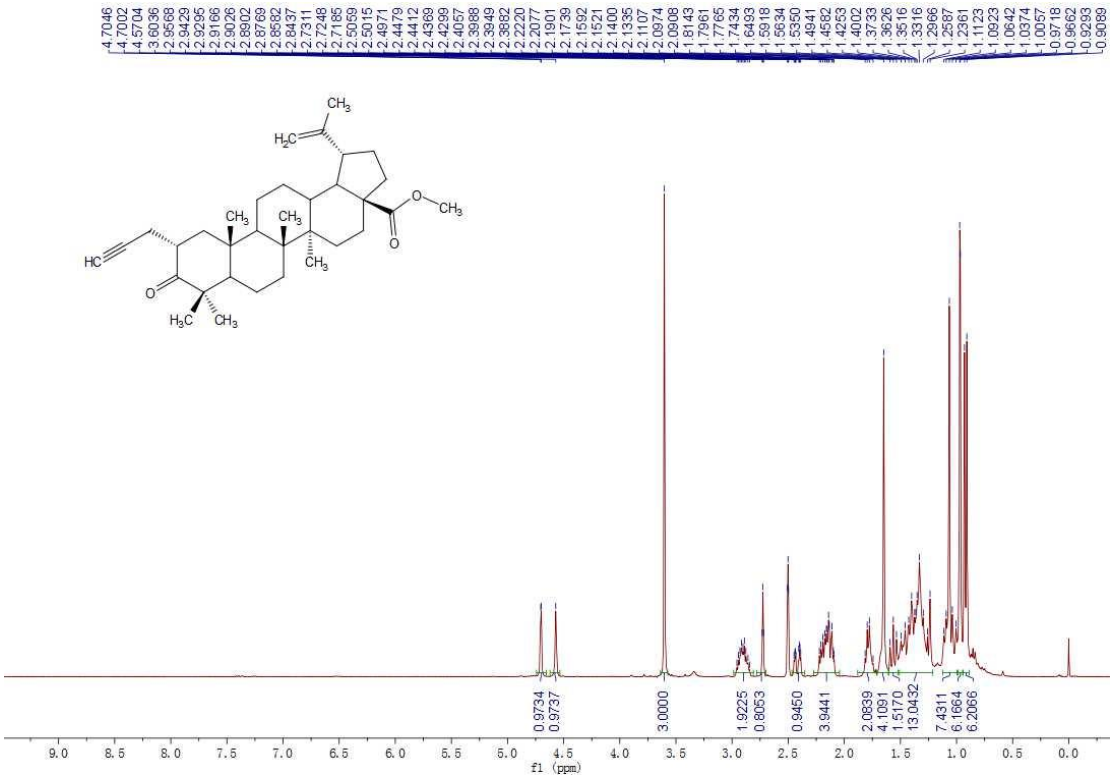


Fig. S7 ^{1}H NMR spectrum of compound **8** in DMSO-d_6

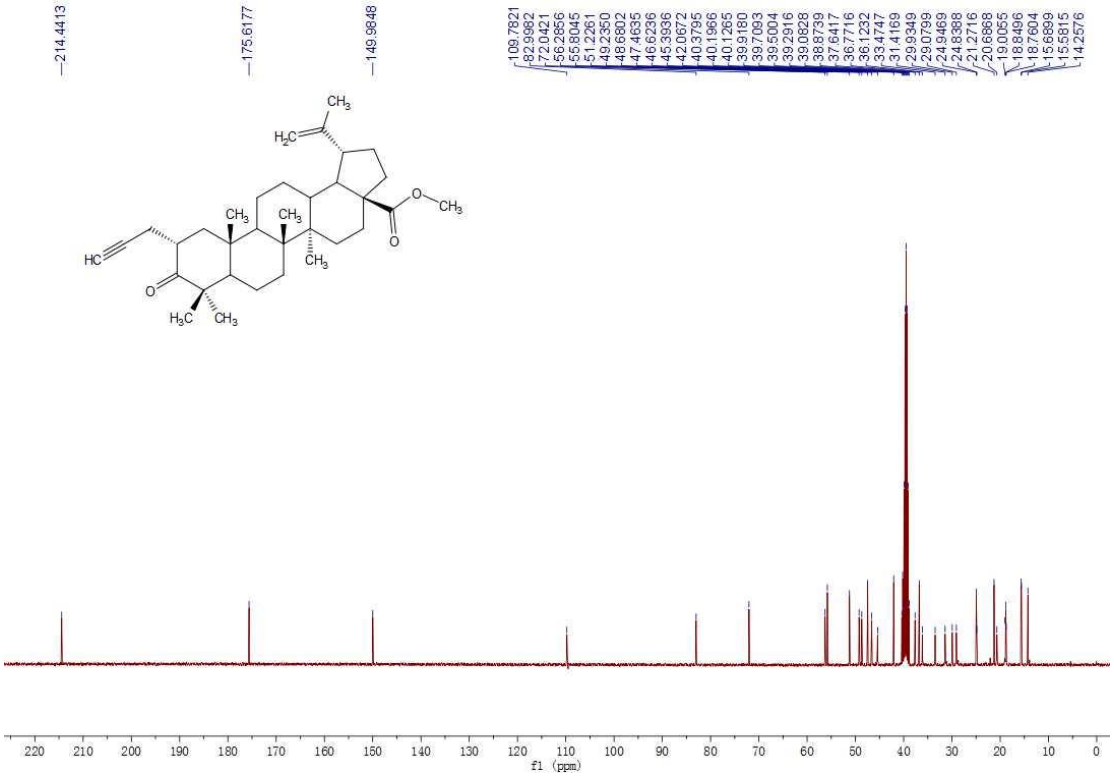


Fig. S8 ^{13}C NMR spectrum of compound **8** in DMSO-d_6

Qualitative Analysis Report

Data Filename	3.d	**Sample Name**	3
Sample Type	Sample	**Position**	P1-A3
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:02:16 PM
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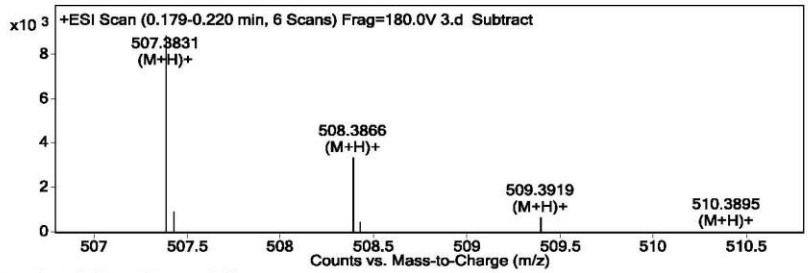
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
S	0	5
Cl	0	3
N	0	10

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C34 H50 O3	TRUE	506.3758	506.376	0.38	C34 H51 O3	98.75
C30 H46 N6 O		506.3758	506.3733	-4.96	C30 H47 N6 O	85.73
C27 H50 N6 O S		506.3758	506.3767	1.68	C27 H51 N6 O S	84.73
C26 H54 N2 O5 S		506.3758	506.3753	-0.93	C26 H55 N2 O5 S	82.2
C29 H50 N2 O5		506.3758	506.372	-7.57	C29 H51 N2 O5	73

--- End Of Report ---

Fig. S9 HRMS spectrum of compound **8**

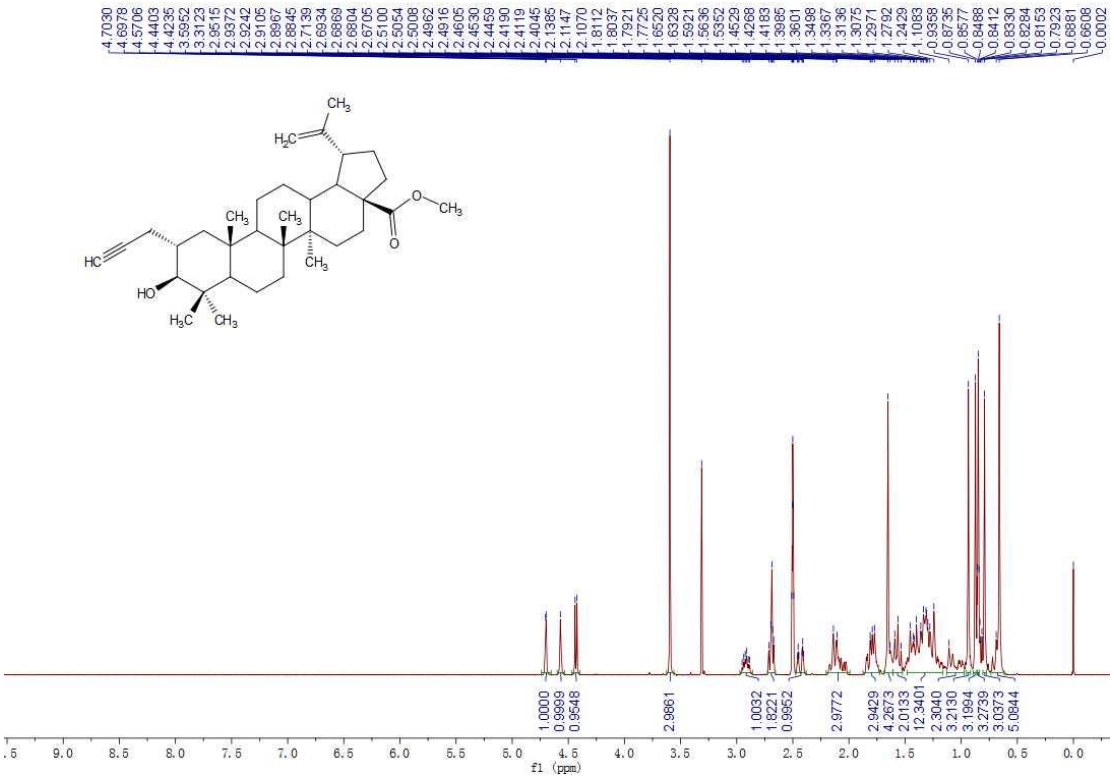


Fig. S10 ^{1}H NMR spectrum of compound **9** in DMSO-d_6

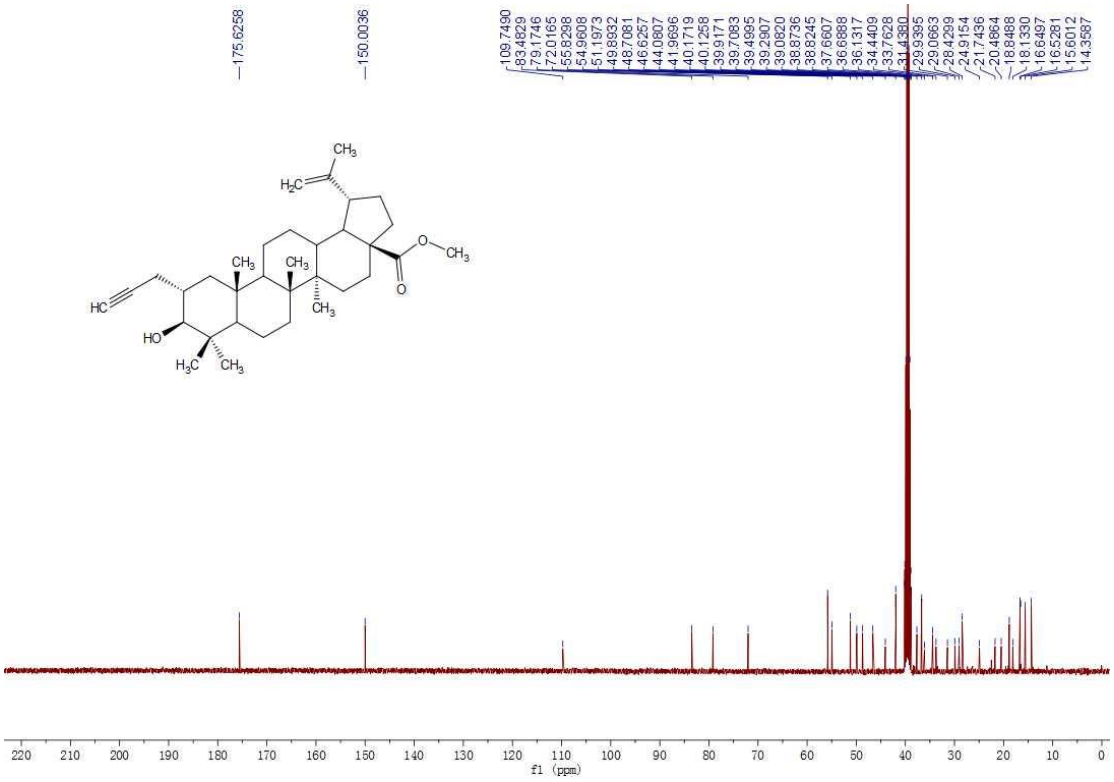


Fig. S11 ^{13}C NMR spectrum of compound **9** in DMSO-d_6

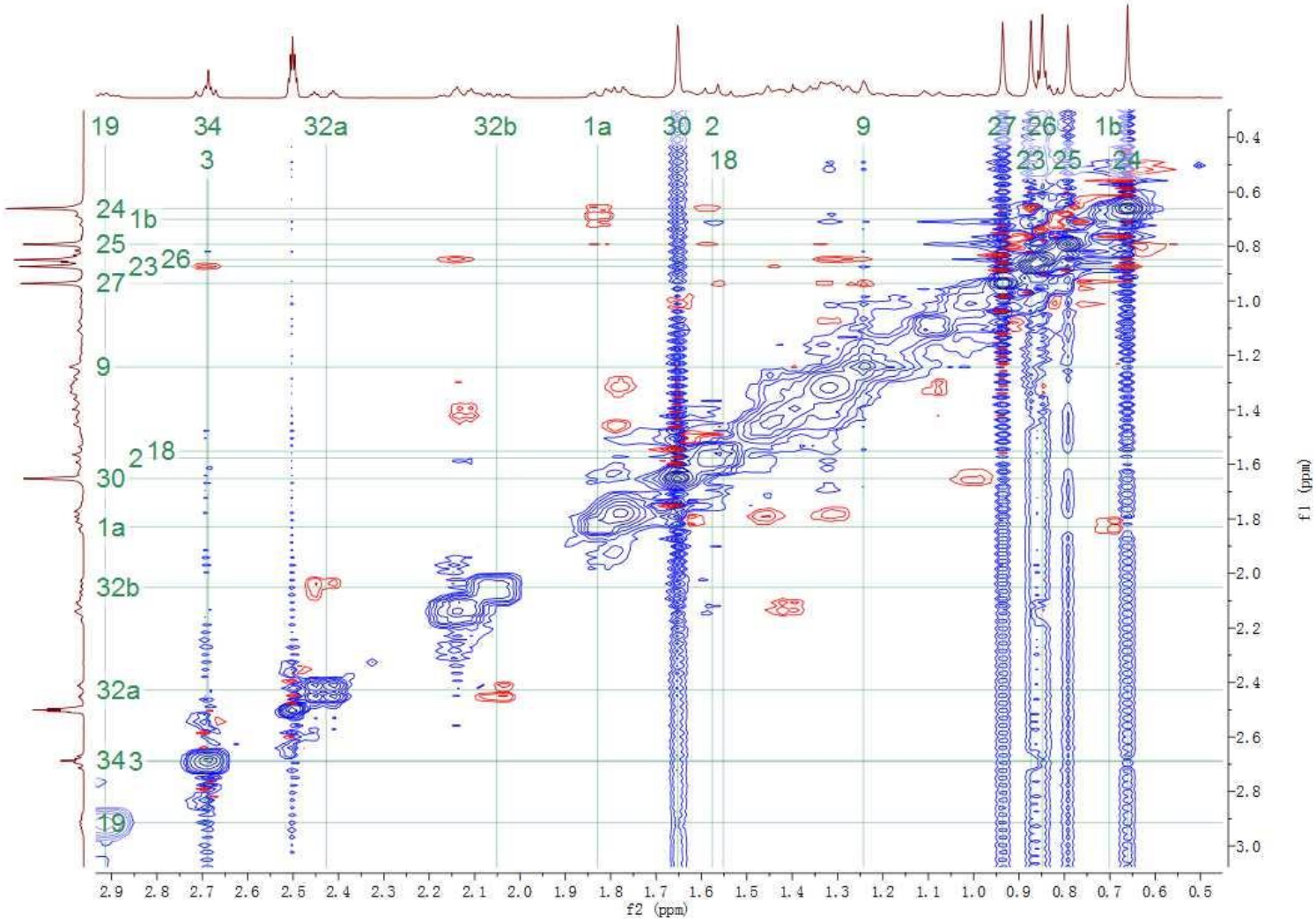


Fig. S12 NOESY spectrum of compound **9**

Qualitative Analysis Report

Data Filename	4b.d	**Sample Name**	4b
Sample Type	Sample	**Position**	P1-A5
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:15:54 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
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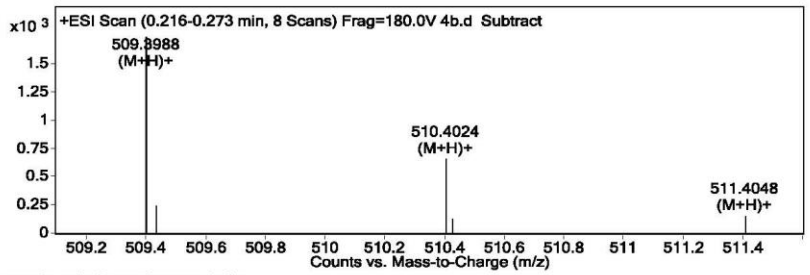


Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
S	0	5
Cl	0	3
N	0	10

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C34 H52 O3	TRUE	508.3915	508.3916	0.31	C34 H53 O3	98.84
C27 H52 N6 O S		508.3915	508.3923	1.6	C27 H53 N6 O S	87.47
C30 H48 N6 O		508.3915	508.389	-5.01	C30 H49 N6 O	85.74
C26 H56 N2 O5 S		508.3915	508.391	-1	C26 H57 N2 O5 S	84.97
C29 H52 N2 O5		508.3915	508.3876	-7.62	C29 H53 N2 O5	73.1
C31 H56 O3 S		508.3915	508.395	6.93	C31 H57 O3 S	72.41

--- End Of Report ---

Fig. S13 HRMS spectrum of compound **9**

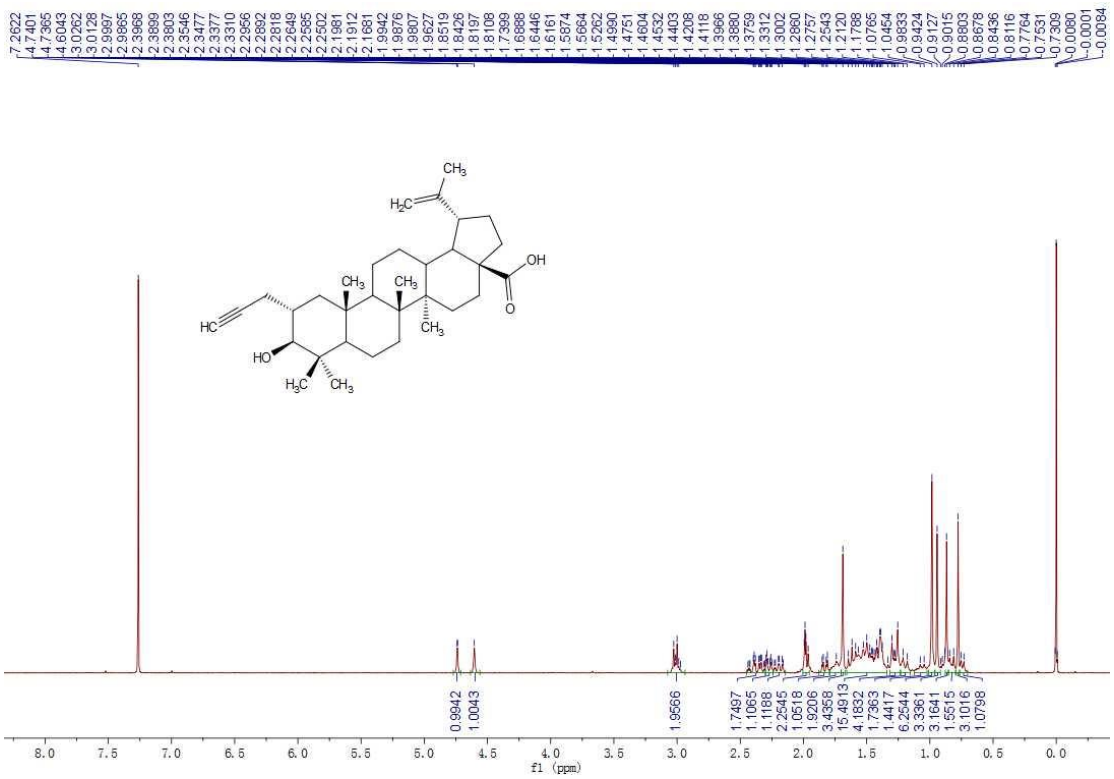


Fig. S14 ^{1}H NMR spectrum of compound **10** in $CDCl_3$

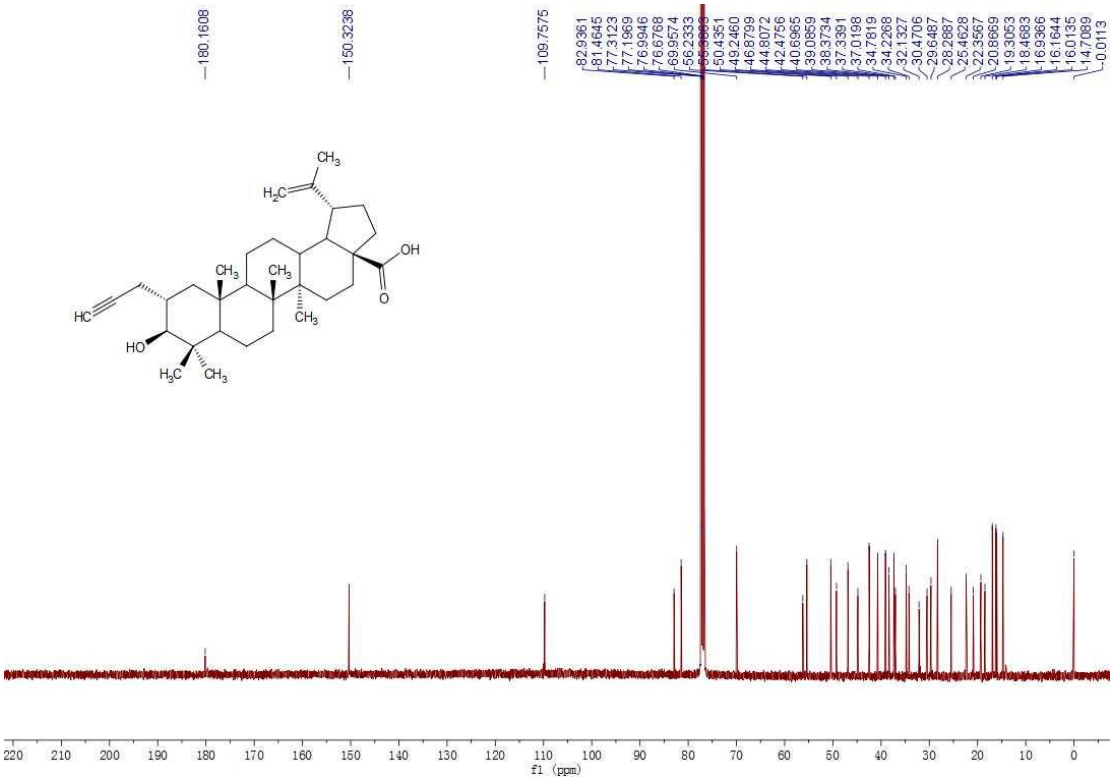


Fig. S15 ^{13}C NMR spectrum of compound **10** in $CDCl_3$

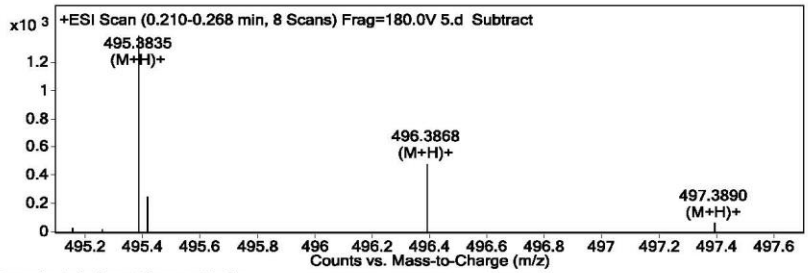
Qualitative Analysis Report

Data Filename	5.d	**Sample Name**	5
Sample Type	Sample	**Position**	P1-A6
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 5:59:33 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	10
S	0	5
Cl	0	3
N	0	10
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C33 H50 O3	TRUE	494.3762	494.376	-0.4	C33 H51 O3	98.76
C26 H50 N6 O S		494.3762	494.3767	0.94	C26 H51 N6 O S	89.01
C25 H54 N2 O5 S		494.3762	494.3753	-1.74	C25 H55 N2 O5 S	84.74
C29 H46 N6 O		494.3762	494.3733	-5.87	C29 H47 N6 O	84.53
C22 H50 N6 O6		494.3762	494.3792	6.01	C22 H51 N6 O6	74.79

--- End Of Report ---

Fig. S16 HRMS spectrum of compound **10**

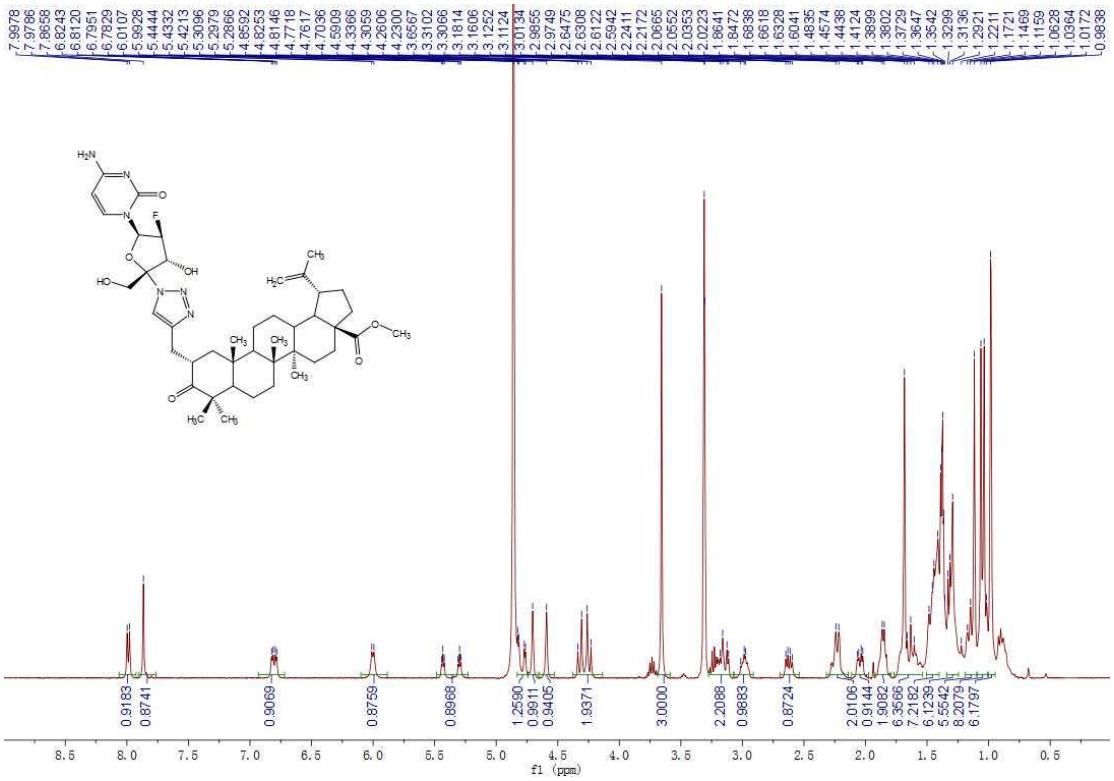


Fig. S17 ^{1}H NMR spectrum of compound **8a** in MeOH-d_4

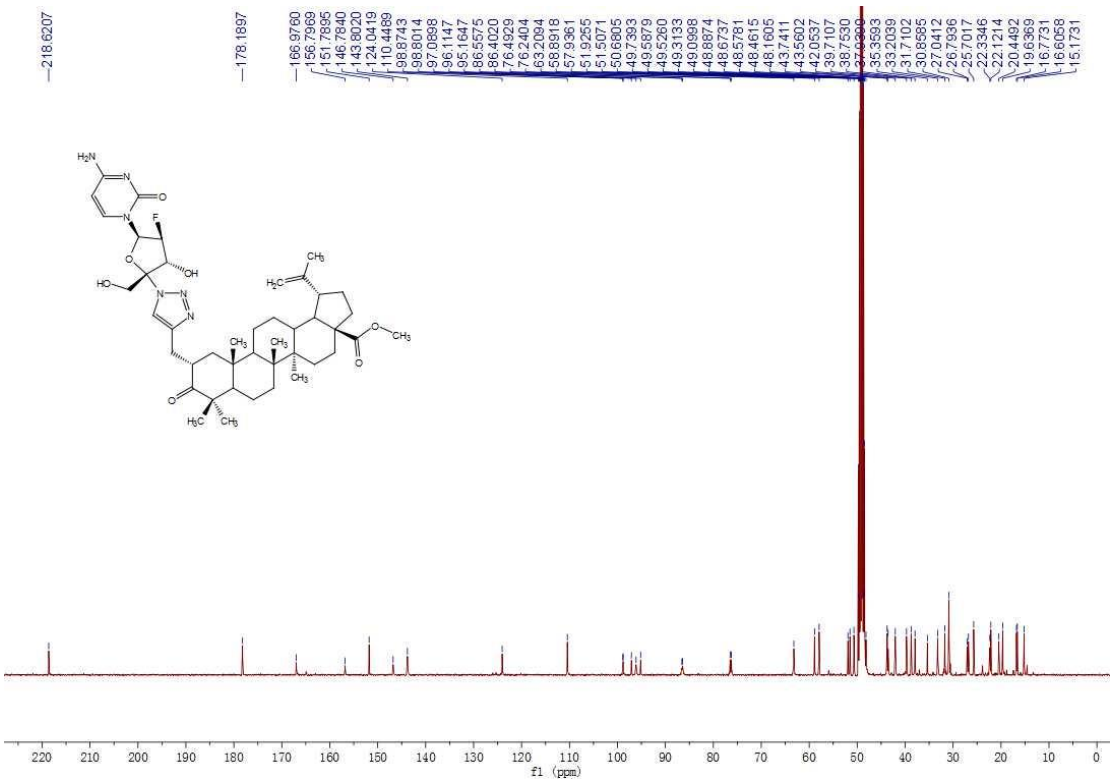


Fig. S18 ^{13}C NMR spectrum of compound **8a** in MeOH-d_4

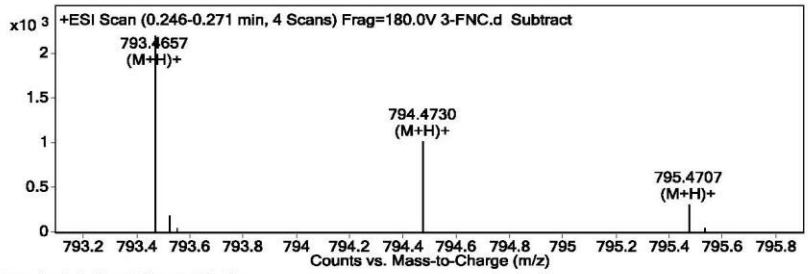
Qualitative Analysis Report

Data Filename	3-FNC.d	**Sample Name**	3-FNC
Sample Type	Sample	**Position**	P1-A7
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:29:39 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C43 H61 F N6 O7	TRUE	792.4588	792.4586	-0.29	C43 H62 F N6 O7	92.03
C40 H62 F2 N6 O8		792.4588	792.4597	1.15	C40 H63 F2 N6 O8	91.41
C41 H63 F3 N6 O4 S		792.4588	792.4584	-0.58	C41 H64 F3 N6 O4 S	89.99
C48 H63 F3 O6		792.4588	792.4577	-1.39	C48 H64 F3 O6	89.39
C44 H57 F N10 O3		792.4588	792.4599	1.38	C44 H58 F N10 O3	89.34

--- End Of Report ---

Fig. S19 HRMS spectrum of compound **8a**

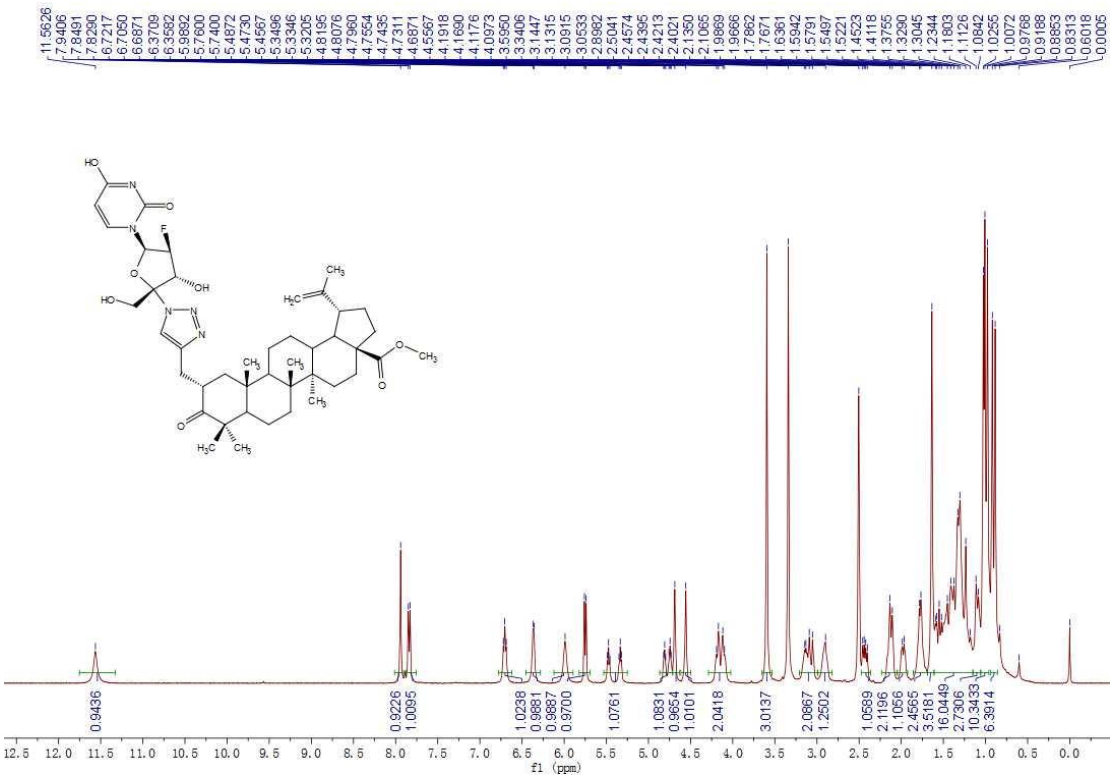


Fig. S20 ^{1}H NMR spectrum of compound **8b** in DMSO-d_6

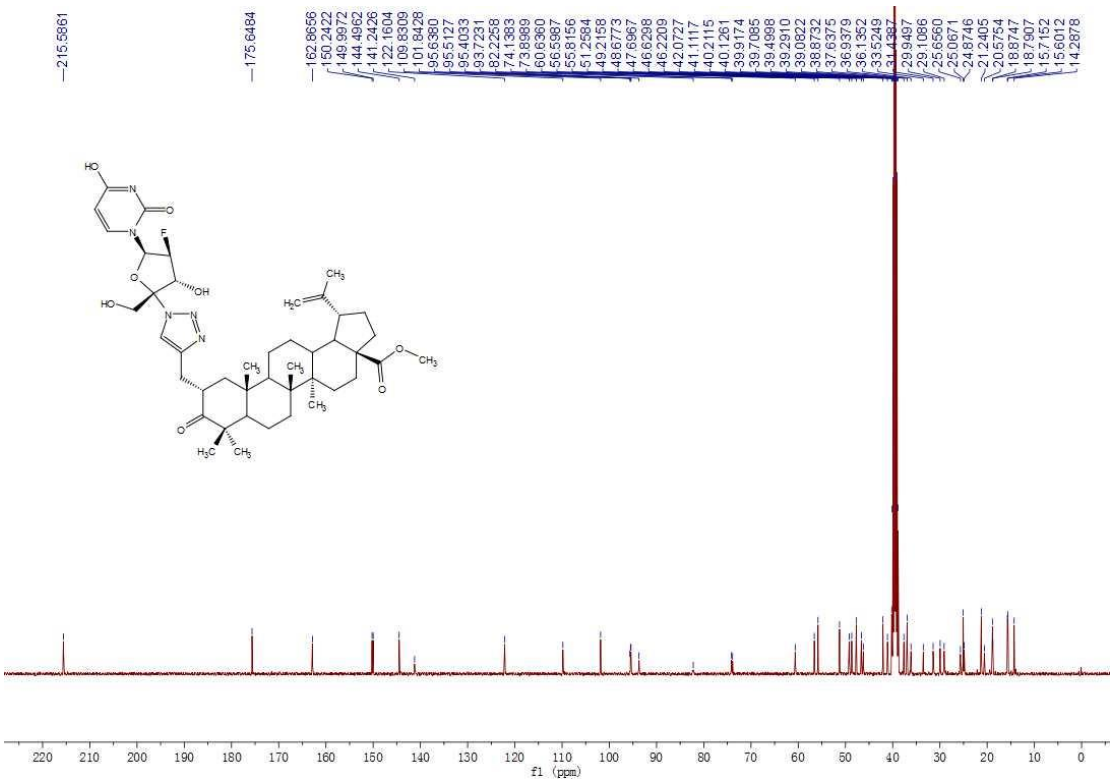


Fig. S21 ^{13}C NMR spectrum of compound **8b** in DMSO-d_6

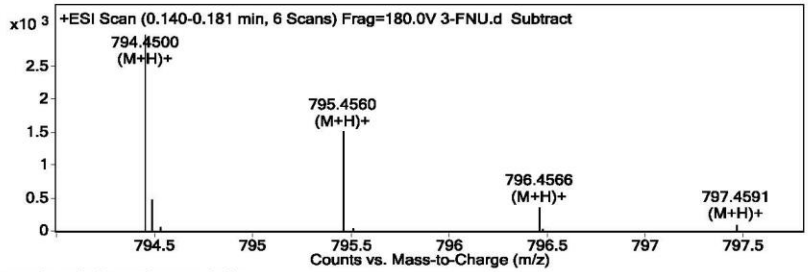
Qualitative Analysis Report

Data Filename	3-FNU.d	**Sample Name**	3-FNU
Sample Type	Sample	**Position**	P1-A8
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:19:49 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C43 H60 F N5 O8	TRUE	793.4431	793.4426	-0.61	C43 H61 F N5 O8	95.84
C49 H58 F3 N3 O3		793.4431	793.443	-0.05	C49 H59 F3 N3 O3	95.19
C44 H56 F N9 O4		793.4431	793.4439	1.05	C44 H57 F N9 O4	95.04
C47 H55 N9 O3		793.4431	793.4428	-0.39	C47 H56 N9 O3	94.55

--- End Of Report ---

Fig. S22 HRMS spectrum of compound **8b**

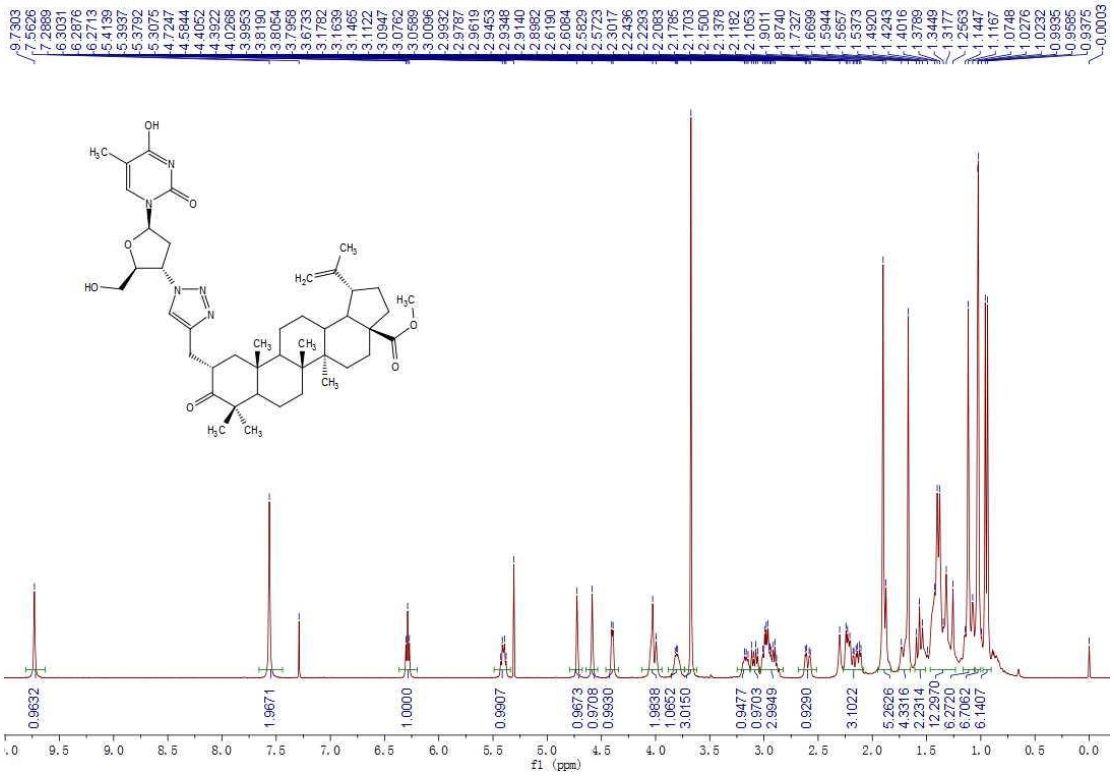


Fig. S23 ^{1}H NMR spectrum of compound **8c** in $CDCl_3$

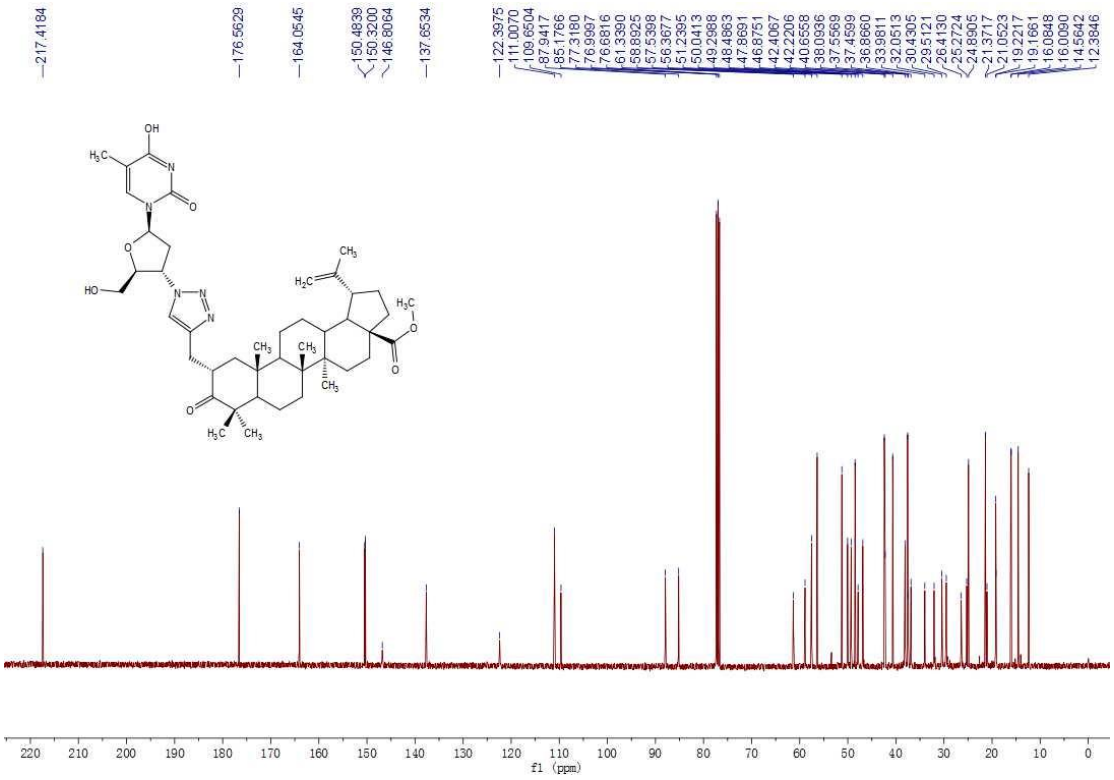


Fig. S24 ^{13}C NMR spectrum of compound **8c** in $CDCl_3$

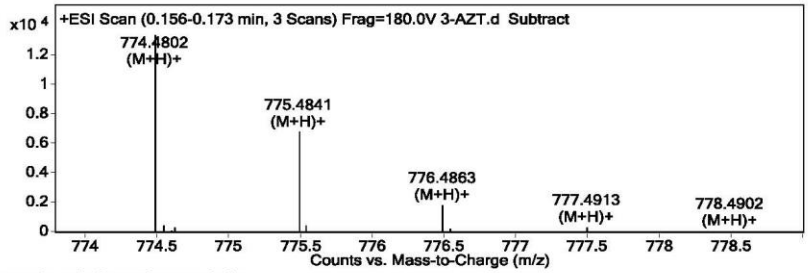
Qualitative Analysis Report

Data Filename	3-AZT.d	**Sample Name**	3-AZT
Sample Type	Sample	**Position**	P1-A9
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:33:28 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C44 H63 N5 O7	TRUE	773.473	773.4727	-0.36	C44 H64 N5 O7	99.62
C45 H59 N9 O3		773.4731	773.4741	1.34	C45 H60 N9 O3	98.07
C50 H61 F2 N3 O2		773.473	773.4732	0.21	C50 H62 F2 N3 O2	98.06
C41 H64 F N5 O8		773.473	773.4739	1.11	C41 H65 F N5 O8	97.97
C47 H62 F3 N3 O3		773.473	773.4743	1.69	C47 H63 F3 N3 O3	97.5

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Fig. S25 HRMS spectrum of compound **8c**

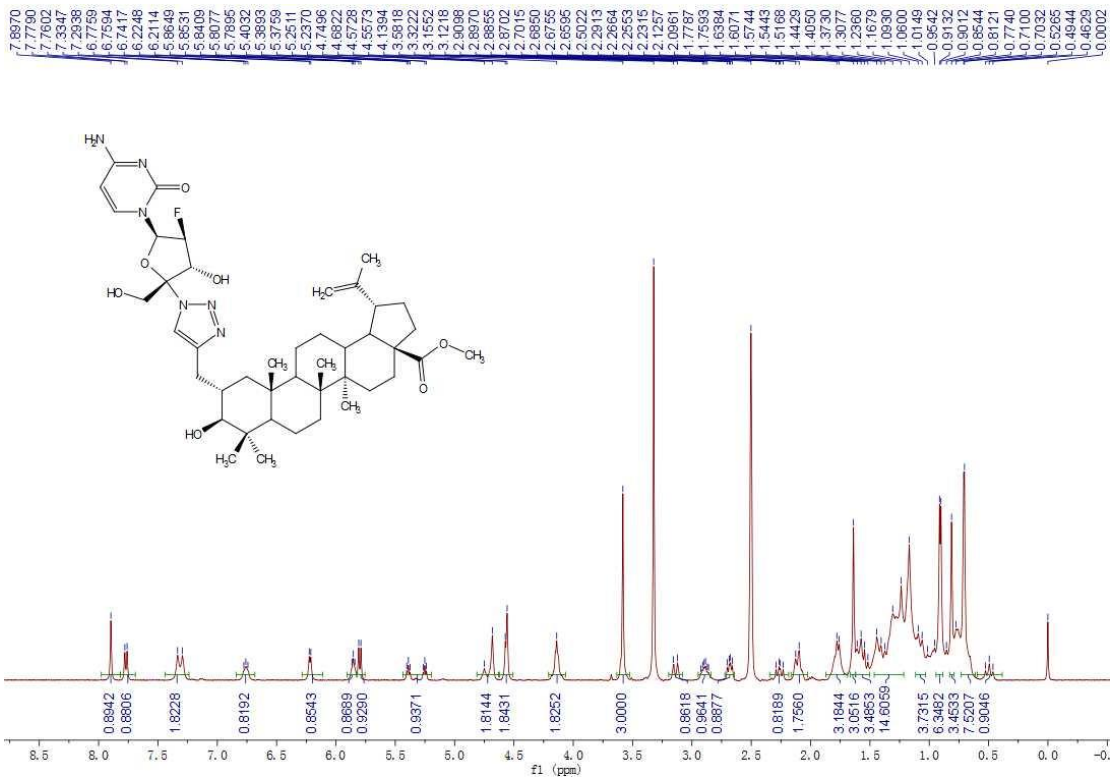


Fig. S26 ^{1}H NMR spectrum of compound **9a** in DMSO-d_6

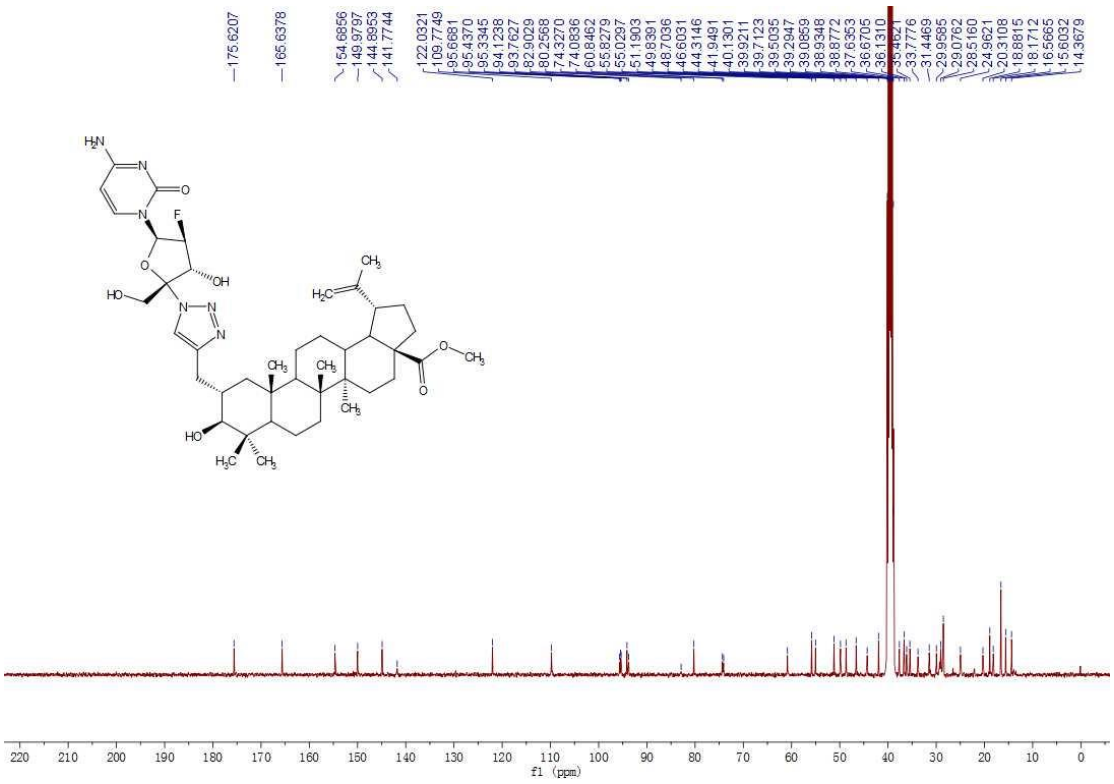


Fig. S27 ^{13}C NMR spectrum of compound **9a** in DMSO-d_6

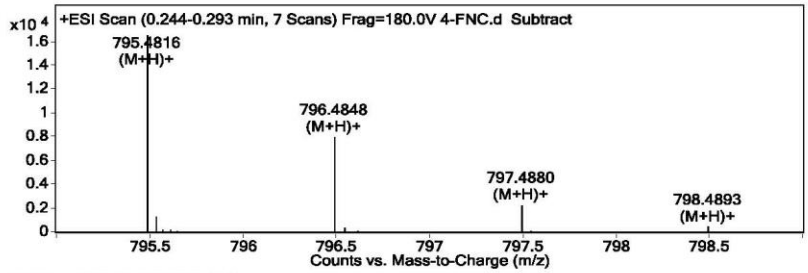
Qualitative Analysis Report

Data Filename	4-FNC.d	**Sample Name**	4-FNC
Sample Type	Sample	**Position**	P1-B1
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:36:06 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C43 H63 F N6 O7	TRUE	794.4744	794.4742	-0.19	C43 H64 F N6 O7	99.69
C40 H64 F2 N6 O8		794.4744	794.4754	1.24	C40 H65 F2 N6 O8	98.27
C48 H65 F3 O6		794.4744	794.4733	-1.29	C48 H66 F3 O6	97.47
C44 H59 F N10 O3		794.4744	794.4756	1.47	C44 H60 F N10 O3	97.17

--- End Of Report ---

Fig. S28 HRMS spectrum of compound **9a**

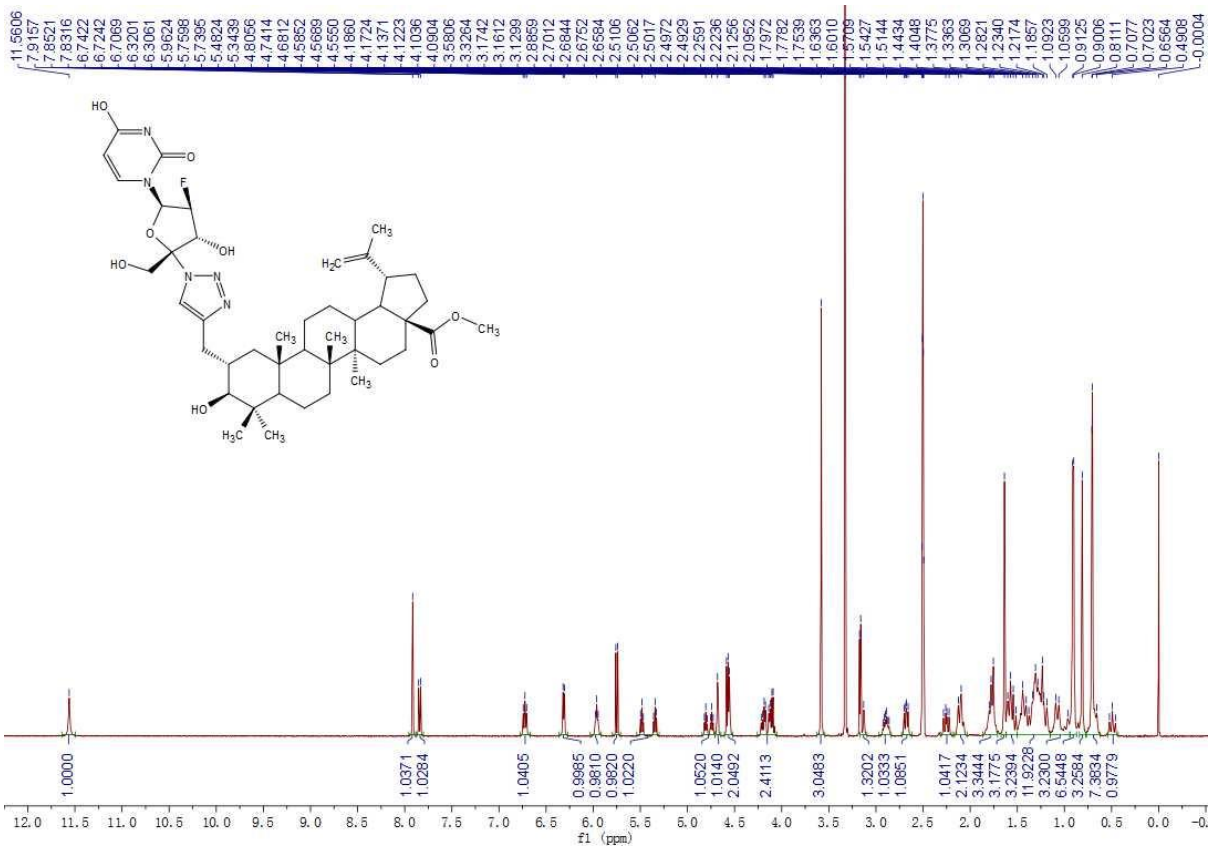


Fig. S29 ^{1}H NMR spectrum of compound **9b** in DMSO-d_6

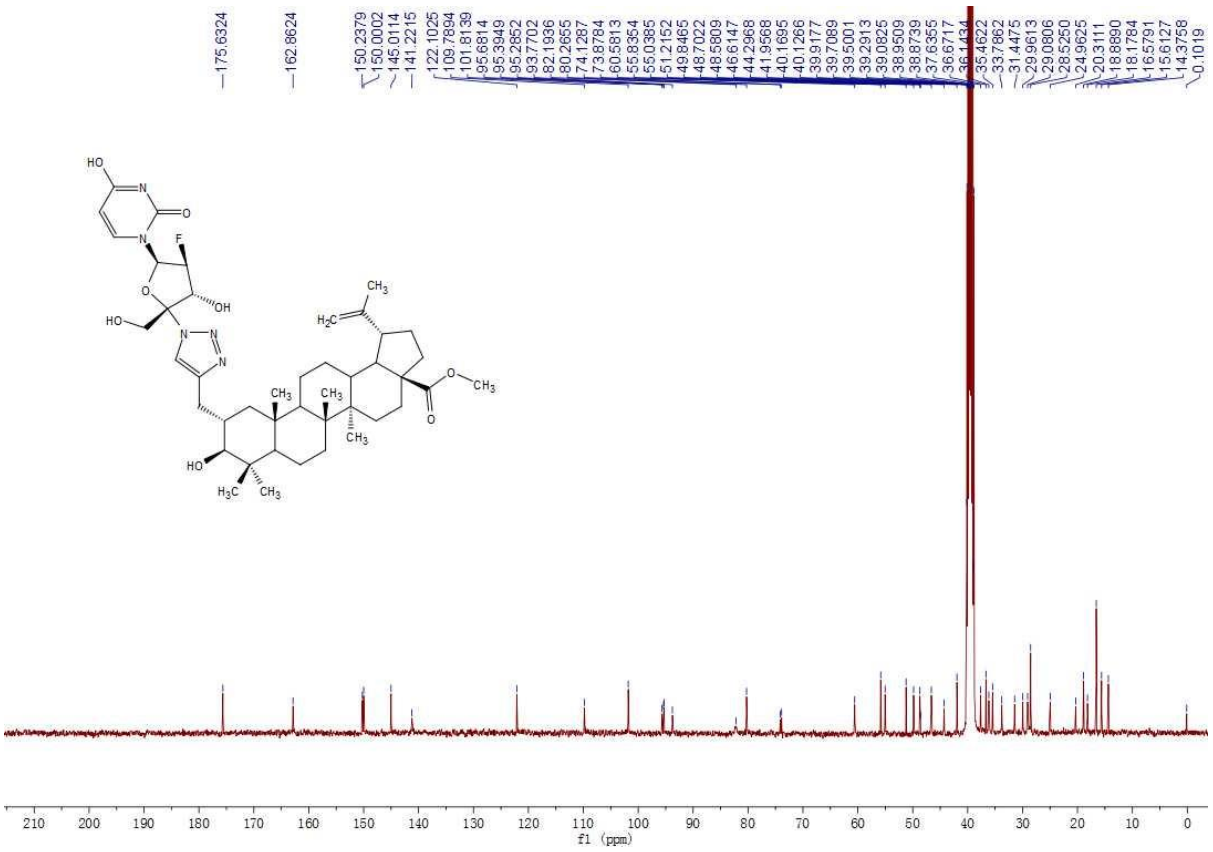


Fig. S30 ^{13}C NMR spectrum of compound **9b** in DMSO-d_6

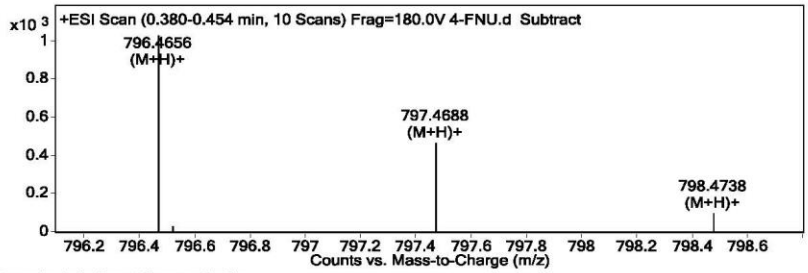
Qualitative Analysis Report

Data Filename	4-FNU.d	**Sample Name**	4-FNU
Sample Type	Sample	**Position**	P1-B2
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:41:50 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C43 H62 F N5 O8	TRUE	795.4583	795.4582	-0.09	C43 H63 F N5 O8	95.96
C44 H58 F N9 O4		795.4583	795.4596	1.57	C44 H59 F N9 O4	93.24
C49 H60 F3 N3 O3		795.4583	795.4587	0.46	C49 H61 F3 N3 O3	92.41
C47 H57 N9 O3		795.4583	795.4584	0.13	C47 H58 N9 O3	92.18
C46 H61 N5 O7		795.4583	795.4571	-1.53	C46 H62 N5 O7	92.16

--- End Of Report ---

Fig. S31 HRMS spectrum of compound **9b**

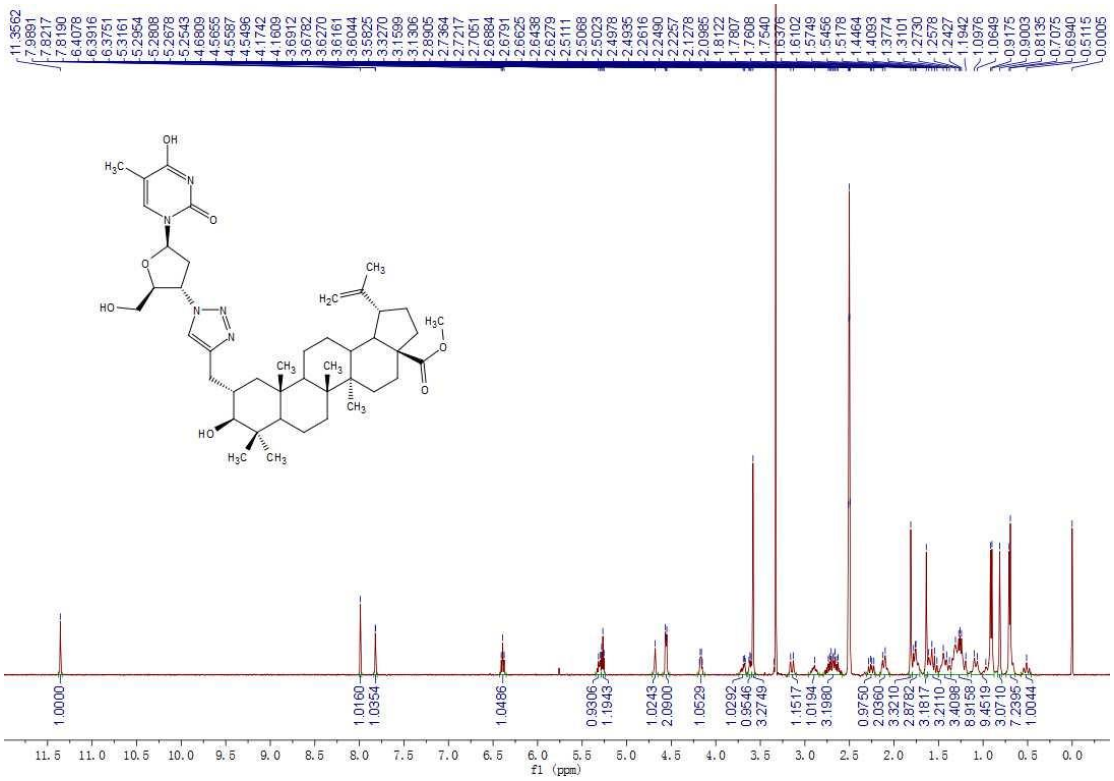


Fig. S32 ^{1}H NMR spectrum of compound **9c** in DMSO-d_6

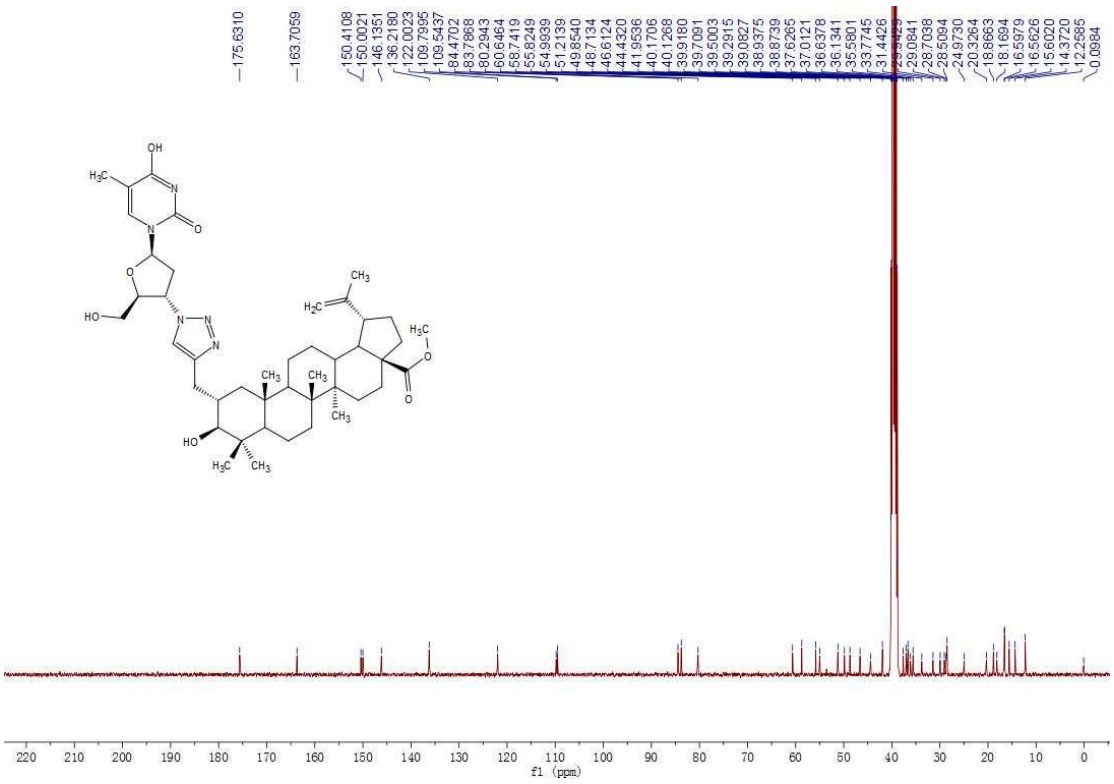


Fig. S33 ^{13}C NMR spectrum of compound **9c** in DMSO-d_6

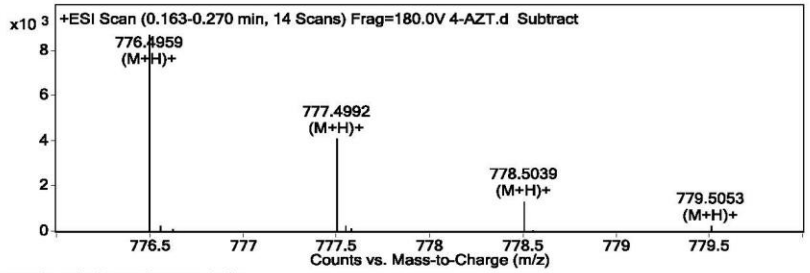
Qualitative Analysis Report

Data Filename	4-AZT.d	**Sample Name**	4-AZT
Sample Type	Sample	**Position**	P1-B3
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 3:43:07 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	8
S	0	5
Cl	0	3
N	0	10
F	0	3
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C44 H65 N5 O7	TRUE	775.4887	775.4884	-0.33	C44 H66 N5 O7	97.26
C41 H66 F N5 O8		775.4887	775.4895	1.14	C41 H67 F N5 O8	96.64
C42 H67 F2 N5 O4 S		775.4887	775.4882	-0.63	C42 H68 F2 N5 O4 S	95.54
C39 H68 F3 N5 O5 S		775.4887	775.4893	0.84	C39 H69 F3 N5 O5 S	94.77

--- End Of Report ---

Fig. S34 HRMS spectrum of compound **9c**

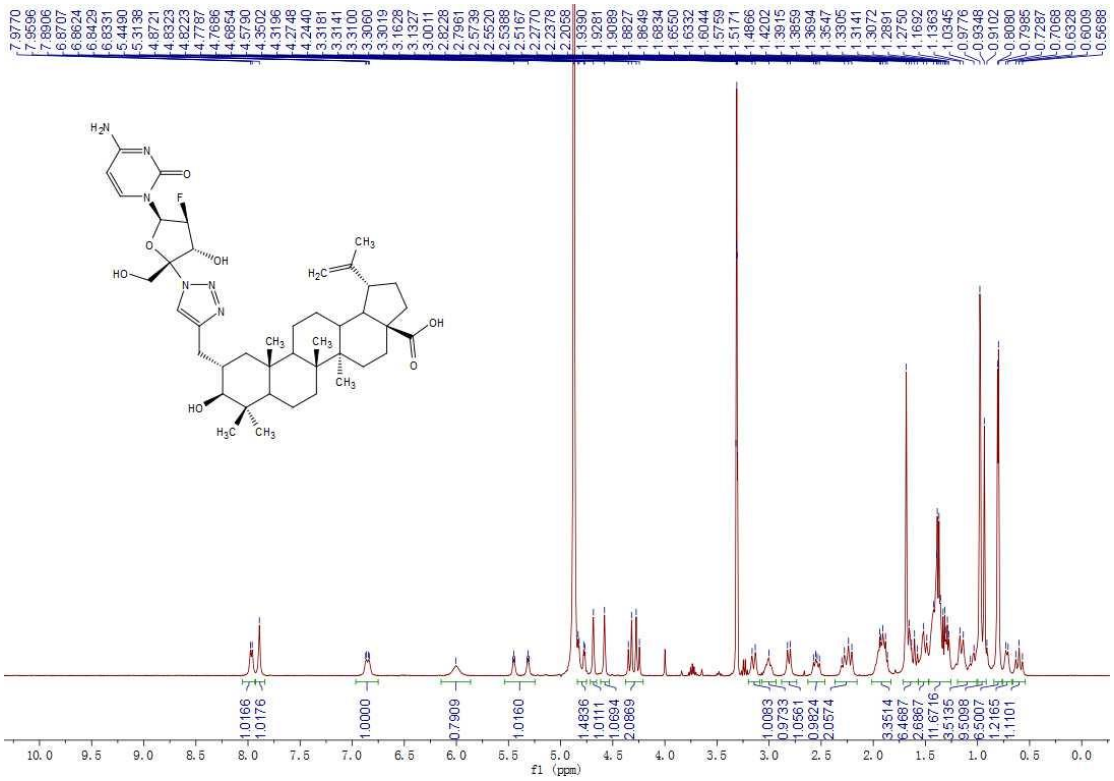


Fig. S35 ^{1}H NMR spectrum of compound **10a** in MeOH-d_4

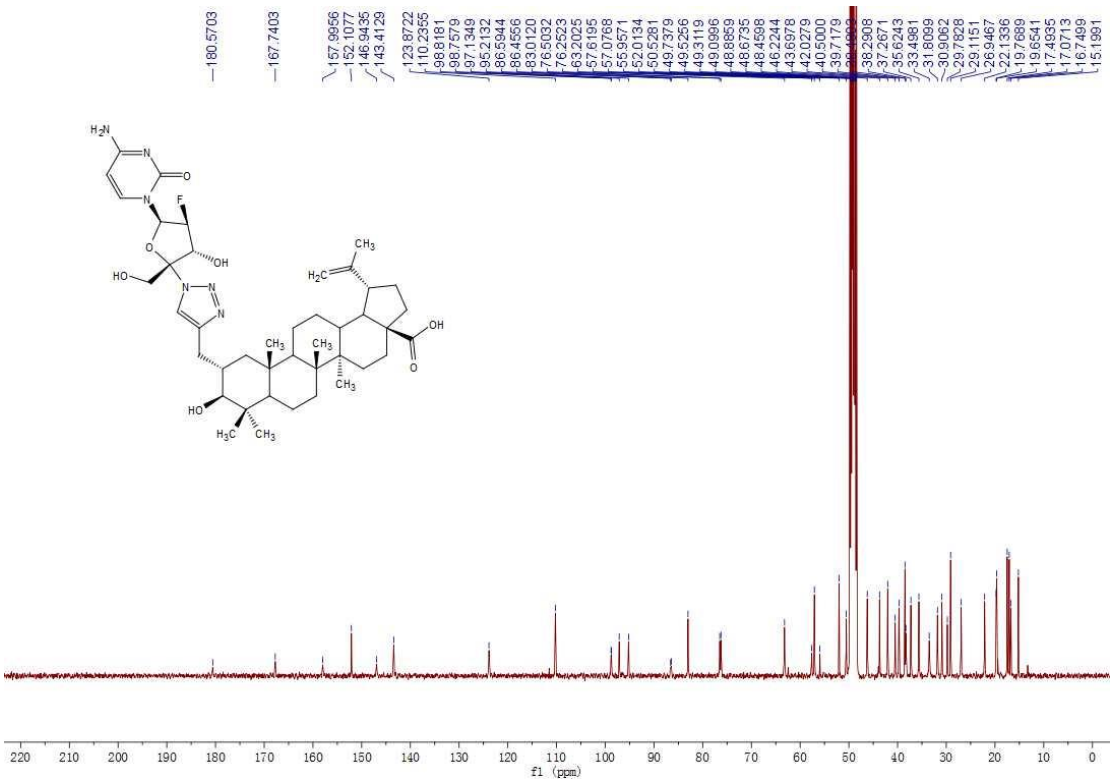


Fig. S36 ^{13}C NMR spectrum of compound **10a** in MeOH-d_4

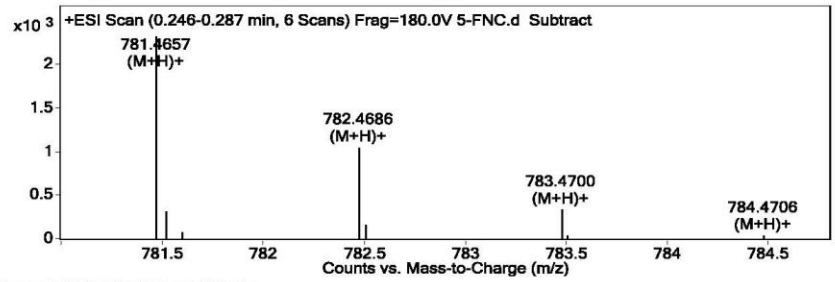
Qualitative Analysis Report

Data Filename	5-FNC.d	**Sample Name**	5-FNC
Sample Type	Sample	**Position**	P1-C6
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	7/3/2019 11:47:29 AM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
Cl	0	3
Br	0	3
N	0	20
F	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C42 H61 F N6 O7	TRUE	780.4584	780.4586	0.21	C42 H62 F N6 O7	97.42
C38 H66 F2 N2 O12		780.4584	780.4584	-0.02	C38 H67 F2 N2 O12	97.33
C36 H54 F2 N16 O2		780.4585	780.4584	-0.11	C36 H55 F2 N16 O2	96.6
C41 H65 F N2 O11		780.4584	780.4572	-1.48	C41 H66 F N2 O11	96.57
C39 H62 F2 N6 O8		780.4584	780.4597	1.67	C39 H63 F2 N6 O8	95.77

--- End Of Report ---

Fig. S37 HRMS spectrum of compound **10a**

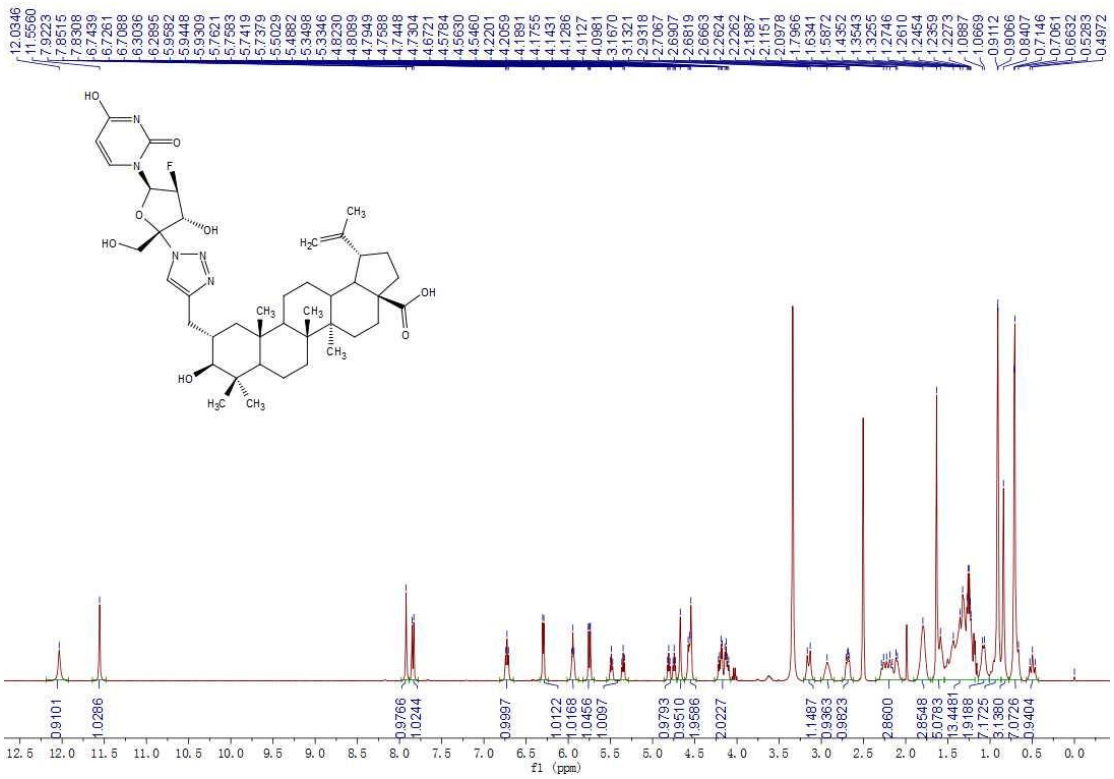


Fig. S38 ^{1}H NMR spectrum of compound **10b** in DMSO-d_6

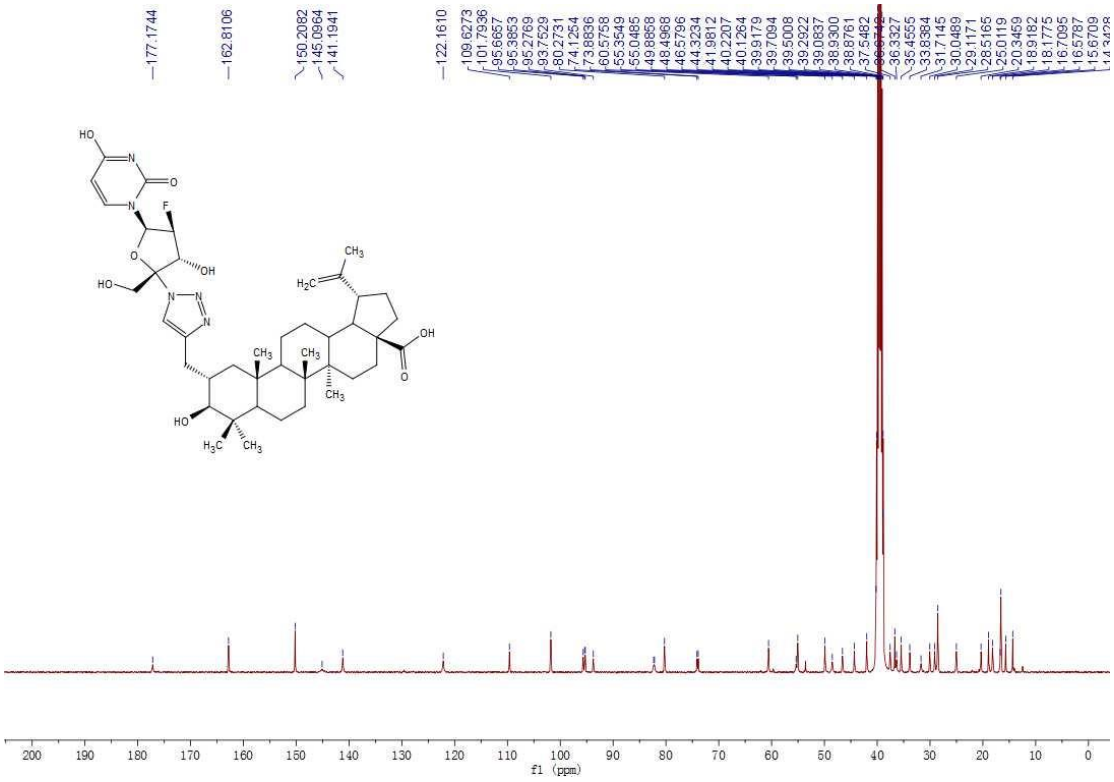


Fig. S39 ^{13}C NMR spectrum of compound **10b** in DMSO-d_6

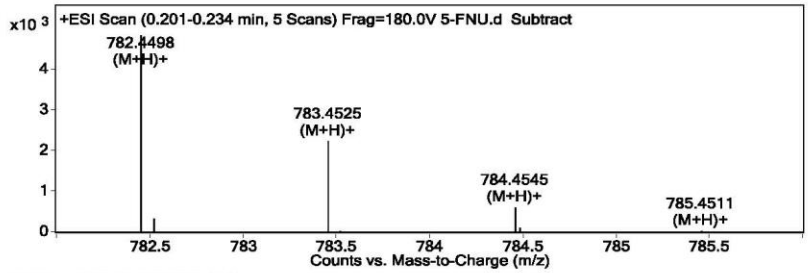
Qualitative Analysis Report

Data Filename	5-FNU.d	**Sample Name**	5-FNU
Sample Type	Sample	**Position**	P1-A2
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	6/19/2019 3:52:14 PM
IRM Calibration Status	Some Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
N	0	30
S	0	5
Cl	0	3
F	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C42 H60 F N5 O8	TRUE	781.4425	781.4426	0.11	C42 H61 F N5 O8	98.86
C36 H53 F2 N15 O3		781.4426	781.4424	-0.22	C36 H54 F2 N15 O3	98.77
C39 H52 F N15 O2		781.4426	781.4412	-1.68	C39 H53 F N15 O2	97.14
C38 H65 F2 N O13		781.4425	781.4424	-0.12	C38 H66 F2 N O13	96.99
C39 H61 F2 N5 O9		781.4425	781.4437	1.57	C39 H62 F2 N5 O9	96.89
C41 H64 F N O12		781.4425	781.4413	-1.58	C41 H65 F N O12	96.66

--- End Of Report ---

Fig. S40 HRMS spectrum of compound **10b**

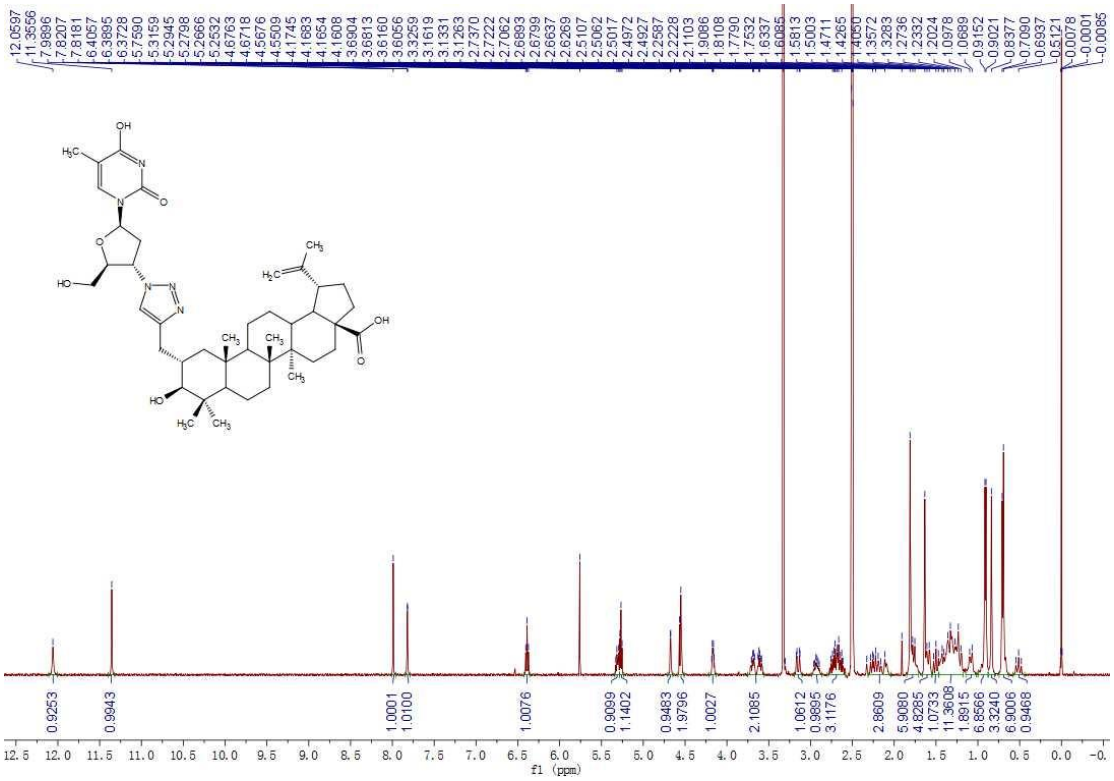


Fig. S41 ^{1}H NMR spectrum of compound **10c** in DMSO-d_6

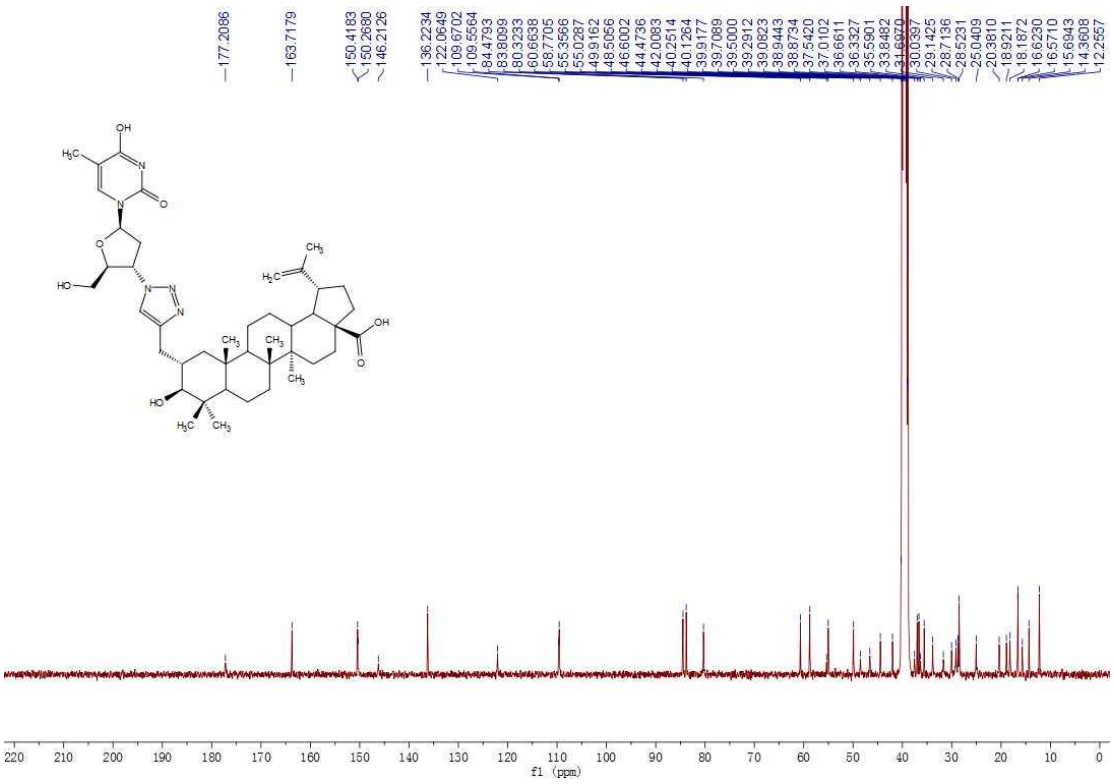


Fig. S42 ^{13}C NMR spectrum of compound **10c** in DMSO-d_6

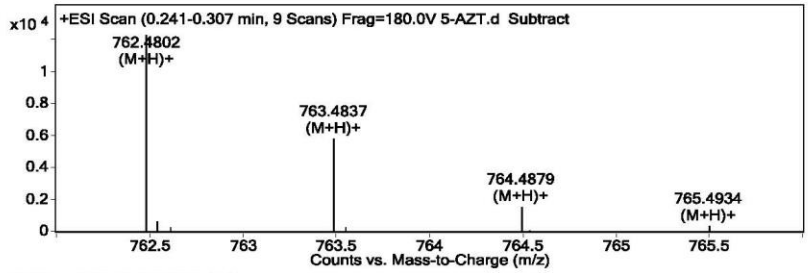
Qualitative Analysis Report

Data Filename	5-AZT.d	**Sample Name**	5-AZT
Sample Type	Sample	**Position**	P1-B4
Instrument Name	Instrument 1	**User Name**	
Acq Method	test.m	**Acquired Time**	5/28/2019 5:52:21 PM
IRM Calibration Status	All Ions Missed	**DA Method**	Default.m
Comment			

Sample Group **Info.**

User Spectra

Fragmentor Voltage	Collision Energy	Ionization Mode
180	0	ESI



Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	10
S	0	5
Cl	0	3
N	0	10
Br	0	3

Formula Calculator Results

Formula	Best	Mass	Tgt Mass	Diff (ppm)	Ion Species	Score
C43 H63 N5 O7	TRUE	761.473	761.4727	-0.29	C43 H64 N5 O7	98.96
C44 H59 N9 O3		761.473	761.4741	1.45	C44 H60 N9 O3	96.18
C35 H67 N7 O9 S		761.473	761.4721	-1.18	C35 H68 N7 O9 S	89.79
C52 H63 N3 S		761.473	761.4743	1.71	C52 H64 N3 S	87.08
C55 H59 N3		761.473	761.4709	-2.7	C55 H60 N3	85.27

--- End Of Report ---

Fig. S43 HRMS spectrum of compound **10c**

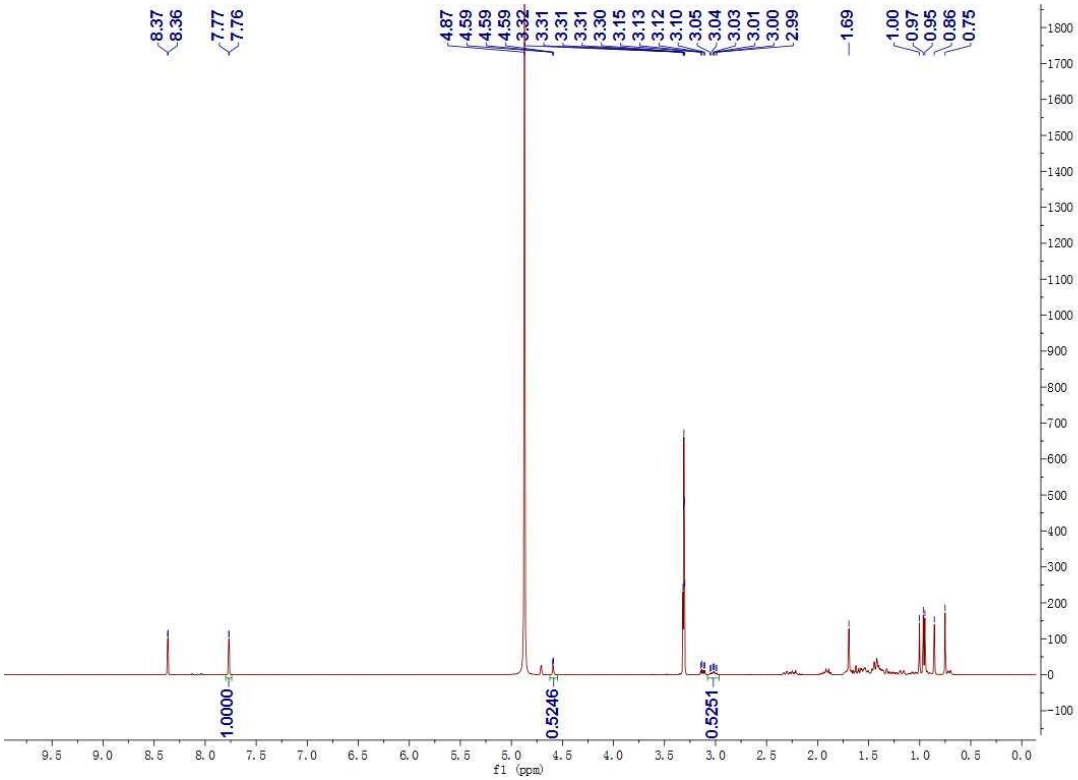


Fig. S44. Quantitative ^{1}H NMR spectrum of betulinic acid with internal standard

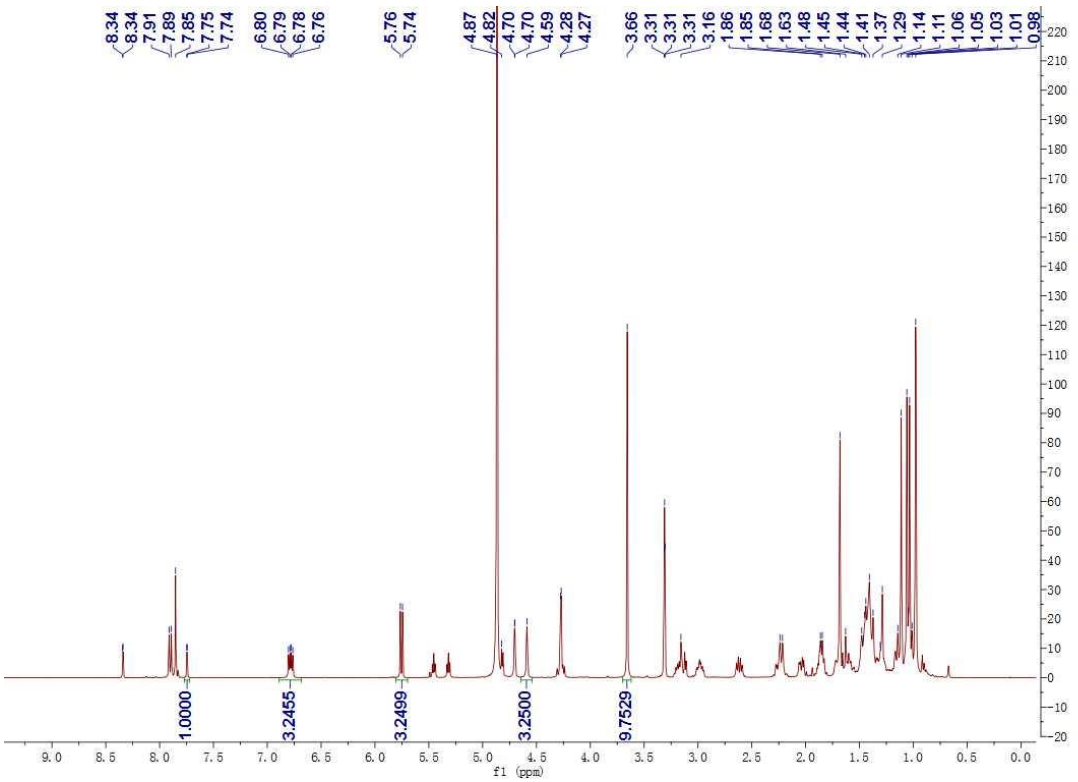


Fig. S45. Quantitative ^{1}H NMR spectrum of compound **8b** with internal standard