Electronic Supporting Information

For

The glycosylated platinum(IV) prodrugs demonstrated significant therapeutic efficacy in cancer cells and minimized side-effects

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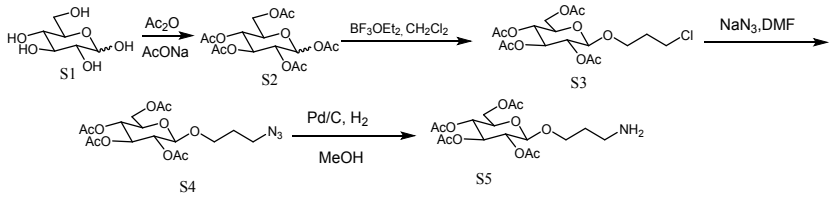
Synthetic procedures

Scheme for (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3-aminopropoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S5)



Preparation of (3R,4S,5R,6R)-6-(acetoxymethyl)tetrahydro-2H-pyran-2,3,4,5 -tetrayl tetraacetate (S2)

A mixture of *D*-glucose **S1** 25 g and sodium acetate 15 g in acetic anhydride 82 mL was stirred at 80 °C for 8 h. After that, the mixture was poured to ice-water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. The solid obtained was recrystallized with alcohol to afford pure compound **S2** as white solid (43.3 g, 80%).

Preparation for (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3-chloropropoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S3)

Boron trifluoride etherate (94.32 mmol) was added to a solution of **S2** (27.76 mmol) and 3-chloropropan-1-ol (27.65 mmol) in dry CH_2Cl_2. The reaction mixture was stirred in the dark under a nitrogen atmosphere. TLC analysis using ethyl acetate/hexane (1:1, v/v). CH_2Cl_2 (200mL) was added, the reaction mixture was neutralised by adding saturated sodium bicarbonate solution (200mL) and the resulting solution was washed with deionised water. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The resulting oil was then purified using column chromatography on silica gel. The relevant fractions were collected, combined and concentrated to dryness under reduced pressure to yield S3 (41%).

Preparation for (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3-azidopropoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S4)

A solution of **S3** (0.50 mmol) in anhydrous DMF was treated with sodium azide (3.05 mmol) and the reaction mixture stirred at 70 °C. TLC analysis, using ethyl acetate/hexane (2:1, v/v), sho wed that the reaction had gone to completion. The reaction mixture was concentrated to dryness under reduced pressure, dissolved in CH_2Cl_2 and then washed with deionised water. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The resulting oil was then purified using column chromatography on silica gel. The relevant fractions were collected, combined and concentrated to dryness under reduced pressure to yield **S4** (73%).

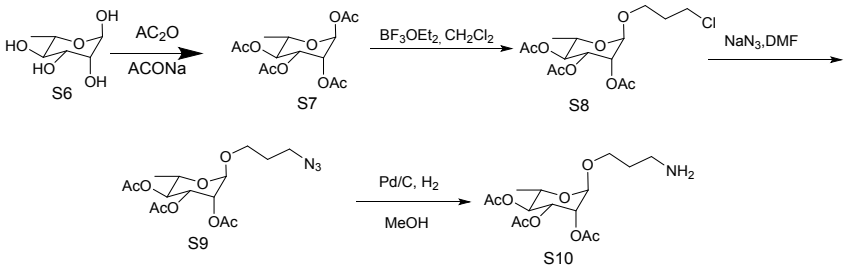
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 3.4 Hz, 1H), 5.44 (t, J = 9.9 Hz, 1H), 5.09 (qd, J = 10.6, 4.5 Hz, 3H), 4.29 – 4.20 (m, 1H), 4.07 (t, J = 9.7 Hz, 2H), 2.15 (m, 2H), 2.08 (m, 1H), 2.06 (m, 2H), 2.03 –

1.93 (m, 12H). ^{13}C NMR (100 MHz, CDCl3) δ 170.79, 170.38, 169.53, 169.44, 100.93, 77.16, 72.88, 71.94, 71.36, 68.48, 66.58, 62.01, 48.02, 29.06, 20.85, 20.77, 20.72.

Preparation for (2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(3-aminopropoxy)tetrah-ydr- o-2H-pyran-3,4,5-triyl triacetate (S5)

A solution of **S4** in dry methanol containing 10% palladium-oncharcoal was exposed to hydrogen at room temperature. TLC analysis of the reaction mixture was performed, using ethyl acetate/hexane (1:1, v/v) as the solvent system, and showed that the reaction had gone to completion. The catalyst was filtered off through Celitew and washed with methanol. The filtrate was concentrated in vacuo to yield **S5** as a yellow oil (85%) which was not purified further.

Scheme for (2R,3R,4R,5S,6S)-2-(3-aminopropoxy)-6-methyltetrahydro-2H-pyra-n-3,4,5-triyl triacetate (S10)

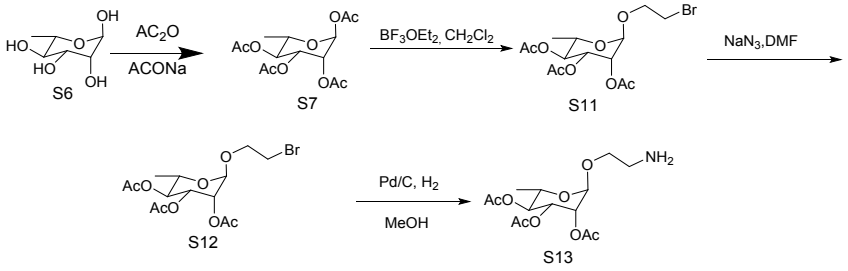


Preparation for (2R,3R,4R,5S,6S)-2-(3-azidopropoxy) -6-methyltetrahydro-2H-pyran-3,4,5-triyl triacetate (S9)

Compound **S9** was prepared according to the procedure described for compound **S4**, starting from *D*-rhamnose.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 – 5.14 (m, 2H), 5.02 (d, *J* = 9.8 Hz, 1H), 4.66 (d, *J* = 10.7 Hz, 1H), 3.91 – 3.61 (m, 2H), 3.53 – 3.26 (m, 3H), 2.17 – 1.90 (m, 9H), 1.82 (dt, *J* = 11.3, 5.7 Hz, 2H), 1.19 (t, *J* = 11.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.25, 170.22, 170.10, 97.59, 71.14, 69.92, 69.16, 66.57, 64.74, 48.30, 28.88, 21.01, 20.90, 20.83, 17.49.

Scheme for(2R,3R,4R,5S,6S)-2-(2-aminoethoxy) -6-methyltetrahydro -2H-pyran -3,4,5-triyl triacetate (S13)



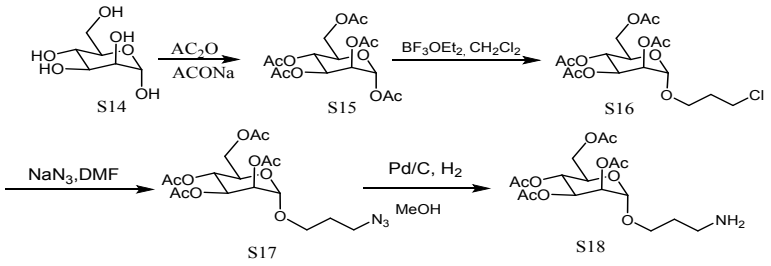
Preparation for (2R,3R,4R,5S,6S)-2-(2-bromoethoxy)-6-methyltetrahydro-2H-p-yran-3,4,5-triyl triacetate (S12)

Compound **S12** was prepared according to the procedure described for compound **S4**, starting from *D*-rhamnose.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 – 5.07 (m, 2H), 5.08 – 4.87 (m, 1H), 4.70 (d, *J* = 13.7 Hz, 1H), 4.05 – 3.69 (m, 2H), 3.67 – 3.44 (m, 1H), 3.36 (dd, *J* = 8.6, 3.8 Hz, 2H), 2.26 – 1.66 (m, 9H), 1.15 (dd,

J = 14.2, 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.98, 169.88, 169.73, 97.50, 70.76, 69.55, 68.83, 66.68, 66.60, 50.30, 20.72, 20.62, 20.56, 17.34.

Scheme for (2R,3R,4S,5S,6S)-2-(acetoxymethyl) -6-(3-aminopropoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S18)

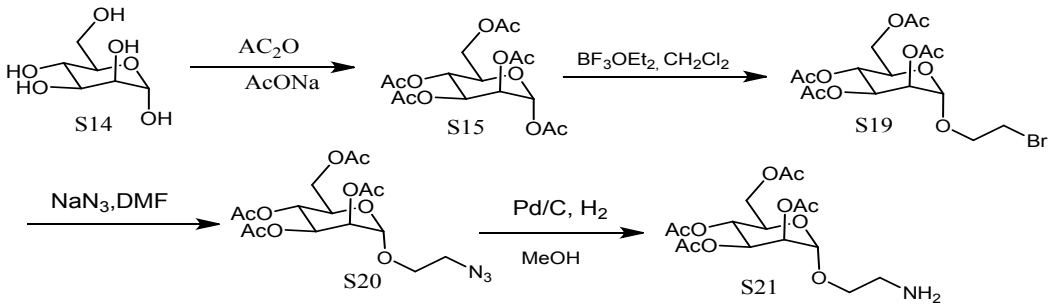


Preparation for (2R,3R,4S,5S,6S)-2-(acetoxymethyl) -6-(3-azidopropoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S17)

Compound **S17** was prepared according to the procedure described for compound **S4**, starting from *D*-mannose.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 – 4.98 (m, 2H), 4.71 (d, *J* = 2.4 Hz, 1H), 4.23 – 4.12 (m, 1H), 4.07 – 3.90 (m, 1H), 3.86 (d, *J* = 2.1 Hz, 1H), 3.77 – 3.64 (m, 1H), 3.46 – 3.39 (m, 1H), 3.34 (td, *J* = 10.3, 4.2 Hz, 1H), 2.81 (dd, *J* = 35.5, 4.1 Hz, 2H), 2.25 – 1.83 (m, 12H), 1.79 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.76, 170.19, 170.05, 169.86, 97.76, 69.61, 69.15, 68.77, 66.25, 64.97, 62.55, 48.31, 28.87, 21.01, 20.83.

Scheme for (2R,3R,4S,5S,6S)-2-(acetoxymethyl)-6-(2-aminoethoxy)tetrahydro-2-H-pyran-3,4,5-triyl triacetate (S21)

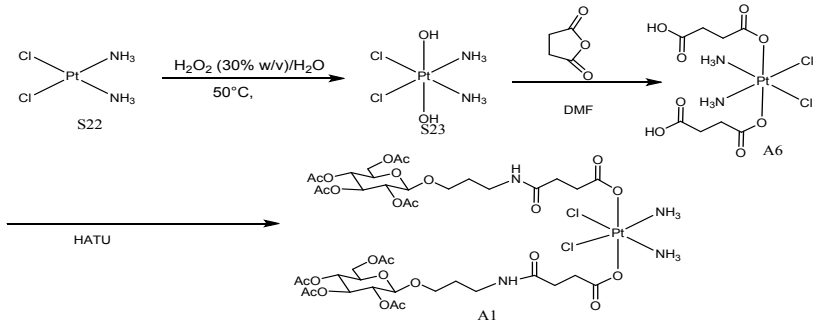


Preparation for (2R,3R,4S,5S,6S)-2-(acetoxymethyl)-6-(2-azidoethoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (S20)

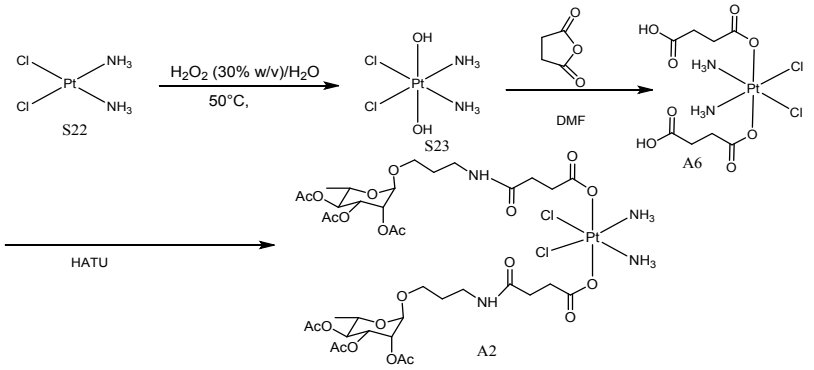
Compound **S20** was prepared according to the procedure described for compound **S4**, starting from *D*-mannose.

^{1}H NMR (400 MHz, $CDCl_3$) 5.18-5.24 (m, 2H), 4.78 (br, 1H), 4.18 (d, *J* = 2.0 Hz, 1H), 4.03 (m, 1H), 3.96 (m, 1H), 3.78 (m, 1H), 2.94-2.84 (m, 2H), 2.83-2.74 (m, 2H), 2.17 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.74, 170.14, 169.93, 169.88, 97.94, 69.50, 68.96, 67.17, 66.10, 62.57, 62.51, 50.47, 21.00, 20.86, 20.83, 20.78.

Scheme for A1

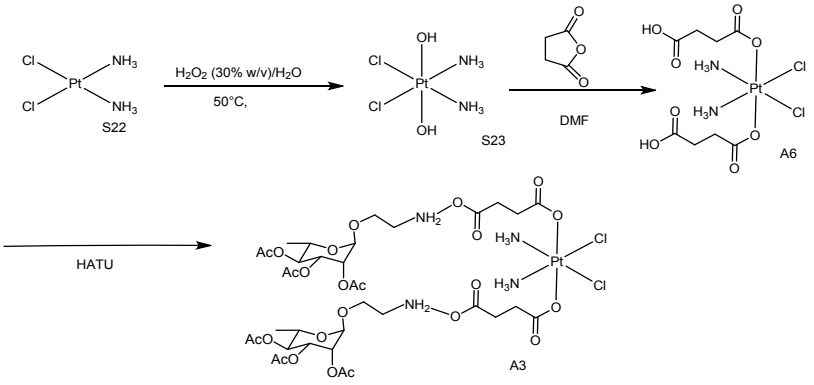


Scheme for A2



Compound **A2** was prepared according to the procedure described for compound **A1.** To a solution of **A6** (0.38 mmol) in DMF (10 mL) was added a DMF solution (0.5 mL) containing HATU (1.52 mmol). This mixture was stirred for 10 min at room temperature. To the resulting solution was added a DMF solution containing **S10** (3 mmol) and DIPEA (1.9 mmol). The mixture was stirred at room temperature for 24 h in the dark. The DMF was then removed under vacuum to afford a yellow oil. Compound **A2** was purified by silica gel column chromatography as yellow solid in yield of 25%.

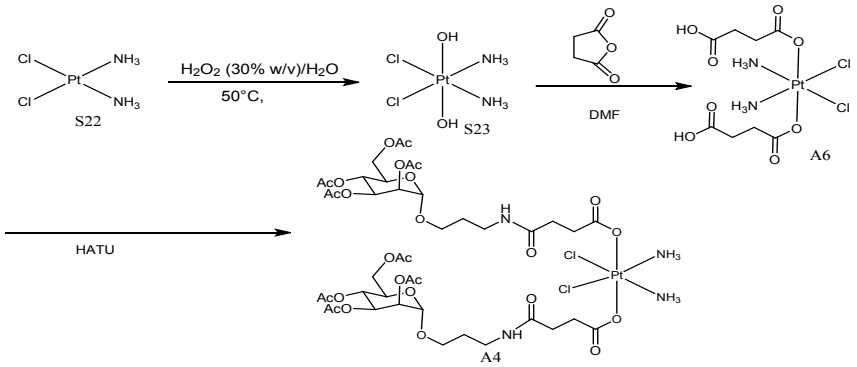
Scheme for A3



Compound **A3** was prepared according to the procedure described for compound **A1.** To a solution of **A6** (0.38 mmol) in DMF (10 mL) was added a DMF solution (0.5 mL) containing HATU (1.52 mmol). This mixture was stirred for 10 min at room temperature. To the resulting solution was added a DMF solution containing **S13** (3 mmol) and DIPEA (1.9 mmol). The mixture was stirred at room temperature for 24 h in the dark. The DMF was then removed under vacuum to afford a yellow oil.

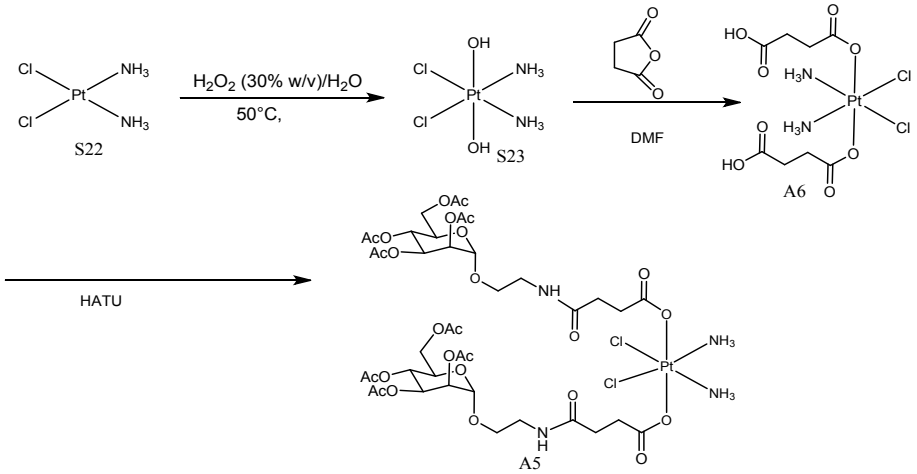
Compound **A3** was purified by silica gel column chromatography as yellow solid in yield of 22%.

Scheme for A4



Compound **A4** was prepared according to the procedure described for compound **A1.** To a solution of **A6** (0.38 mmol) in DMF (10 mL) was added a DMF solution (0.5 mL) containing HATU (1.52 mmol). This mixture was stirred for 10 min at room temperature. To the resulting solution was added a DMF solution containing **S18** (3 mmol) and DIPEA (1.9 mmol). The mixture was stirred at room temperature for 24 h in the dark. The DMF was then removed under vacuum to afford a yellow oil. Compound **A4** was purified by silica gel column chromatography as yellow solid in yield of 23%.

Scheme for A5

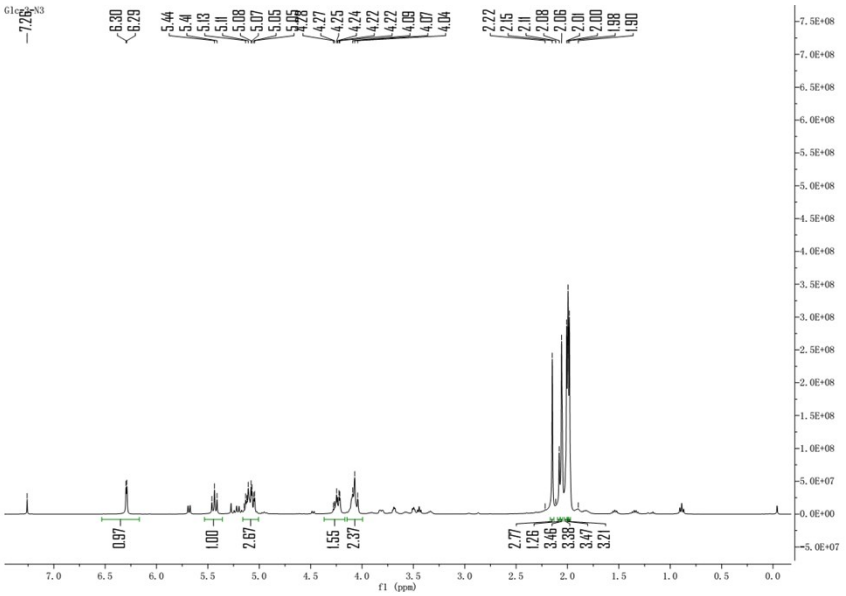


Compound **A5** was prepared according to the procedure described for compound **A1.** To a solution of **A6** (0.38 mmol) in DMF (10 mL) was added a DMF solution (0.5 mL) containing HATU (1.52 mmol). This mixture was stirred for 10 min at room temperature. To the resulting solution was added a DMF solution containing **S21** (3 mmol) and DIPEA (1.9 mmol). The mixture was stirred at room temperature for 24 h in the dark. The DMF was then removed under vacuum to afford a yellow oil. Compound **A5** was purified by silica gel column chromatography as yellow solid in yield of 28%.

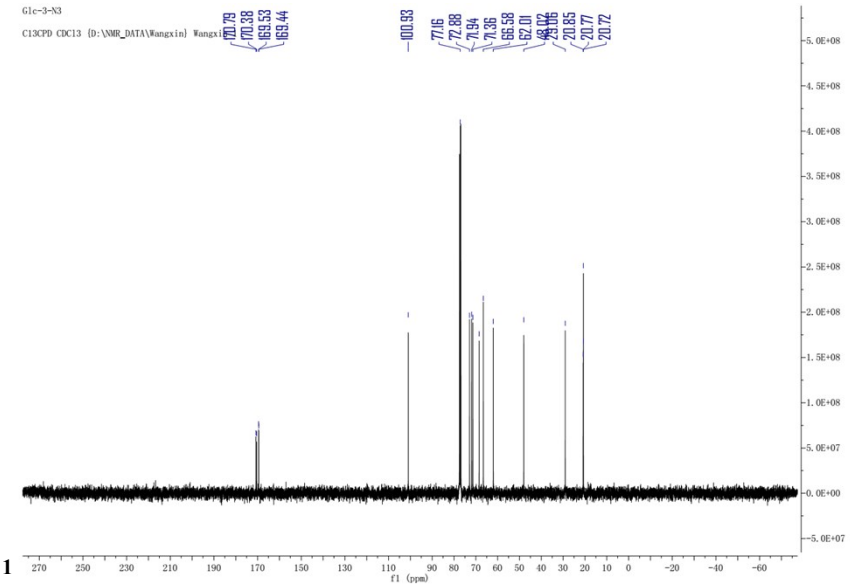
^{1}H NMR , ^{13}C NMR spectra and High resolution mass spectra

(HRMS)

^{1}H-NMR spectrum for compound S4



^{13}C NMR spectra for compound S4



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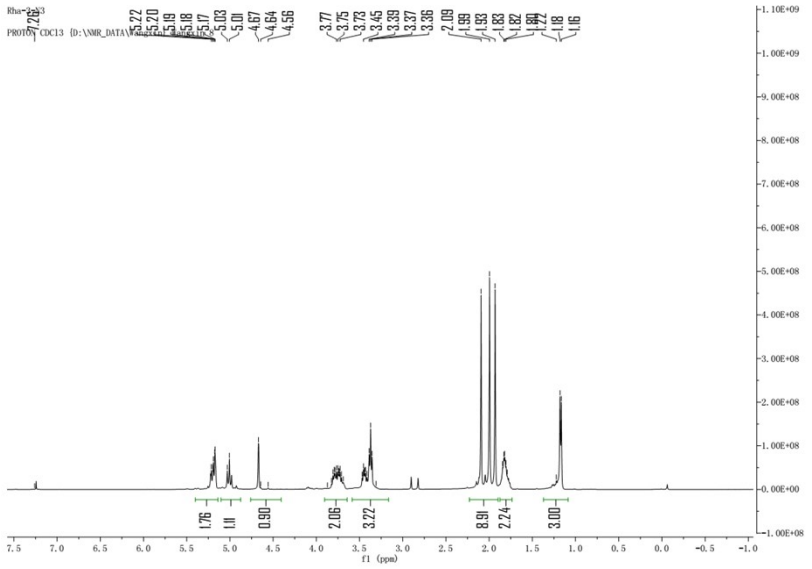
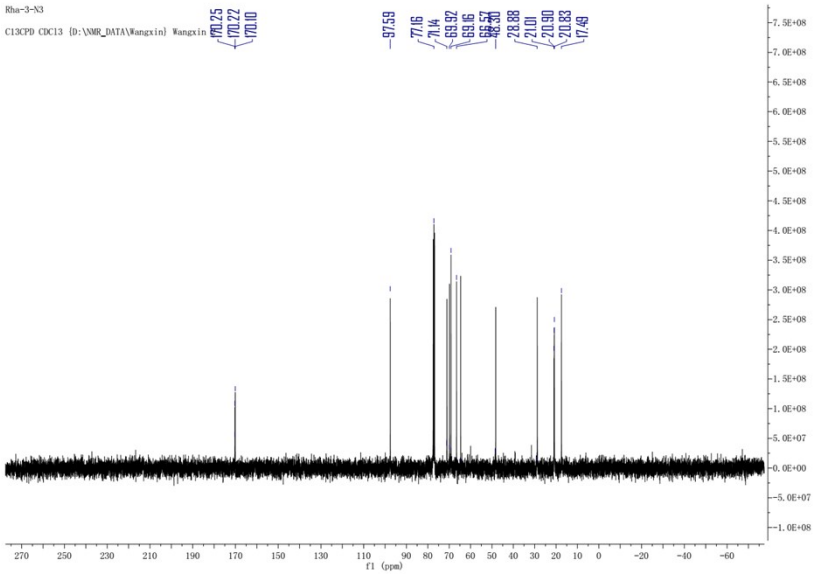
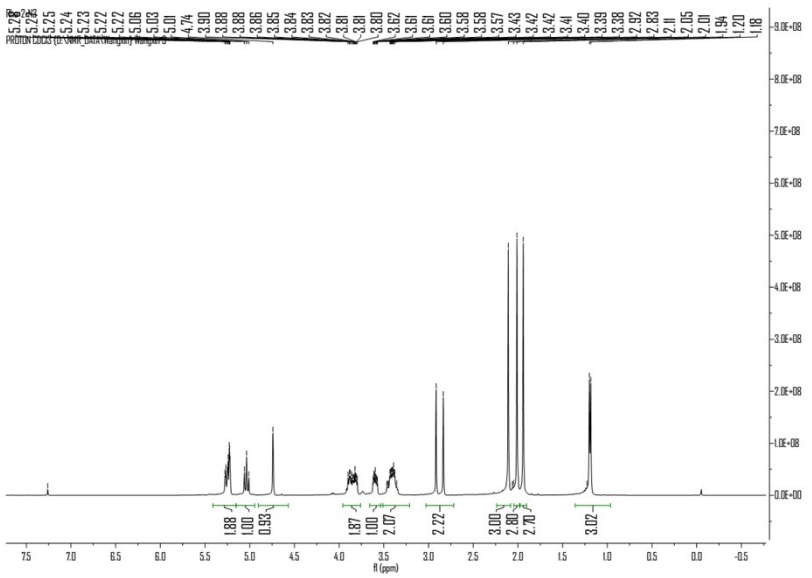
^{1}H-NMR spectrum for compound S9



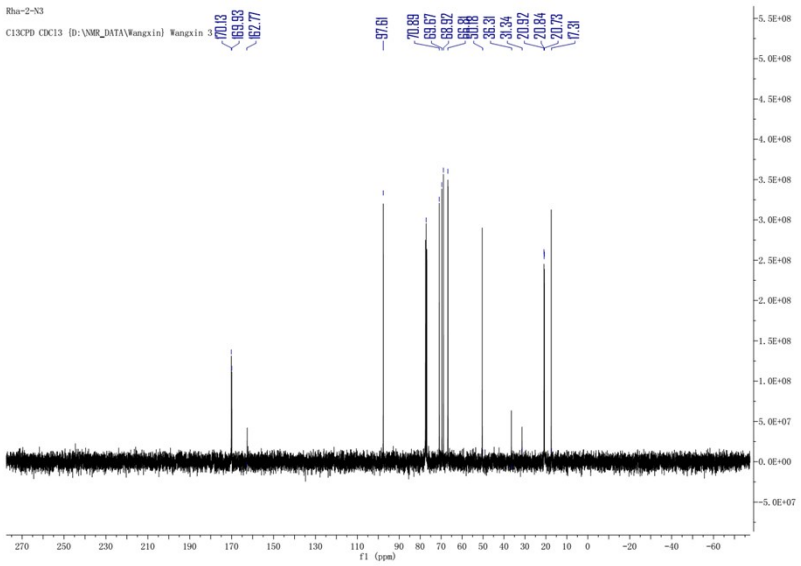
^{13}C-NMR spectrum for compound S9



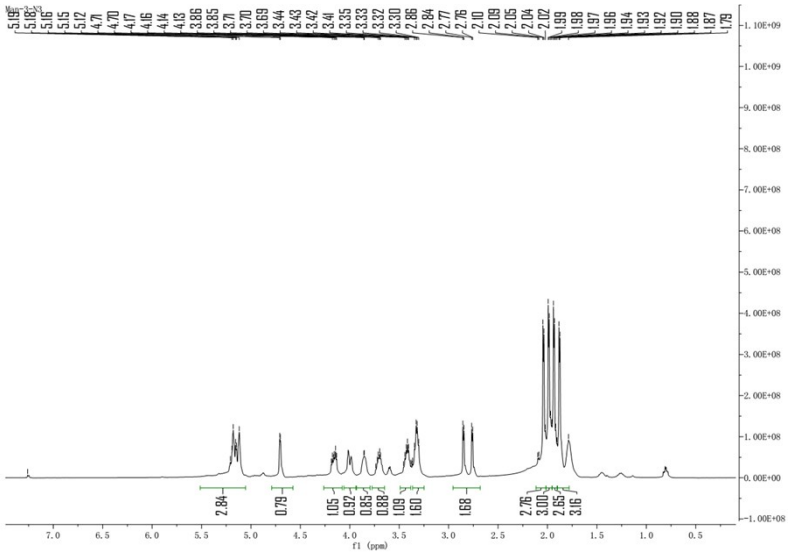
^{1}H-NMR spectrum for compound S12



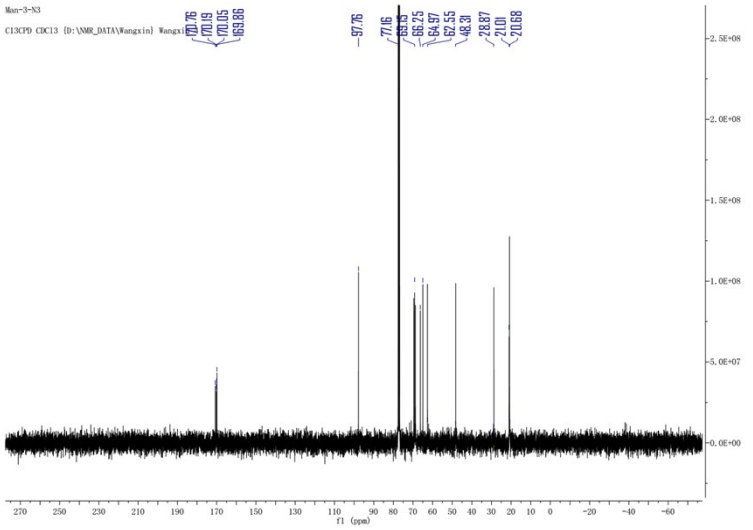
^{13}C-NMR spectrum for compound S12



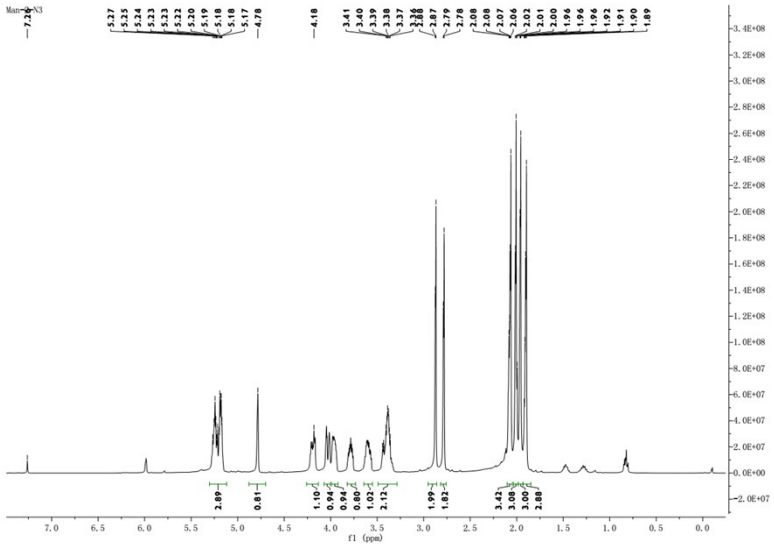
^{1}H-NMR spectrum for compound S17



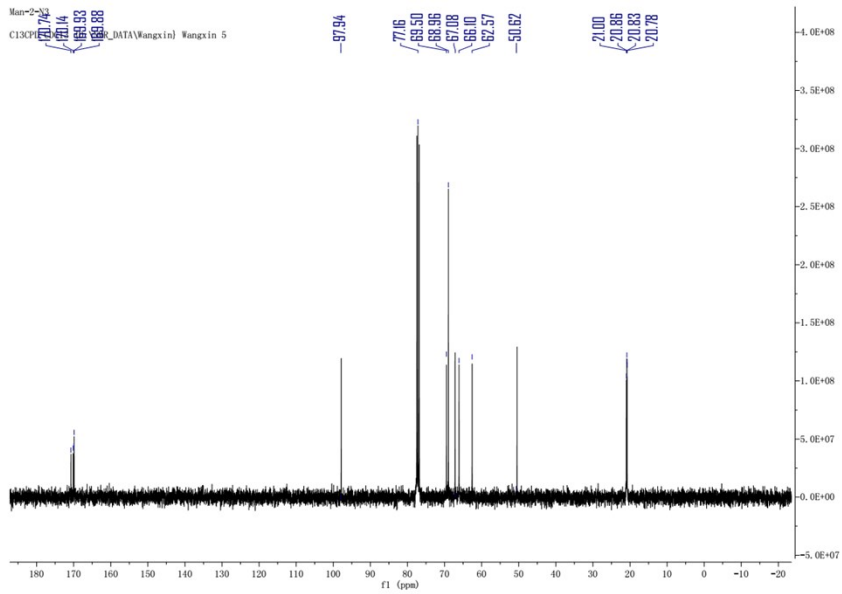
^{13}C-NMR spectrum for compound S17



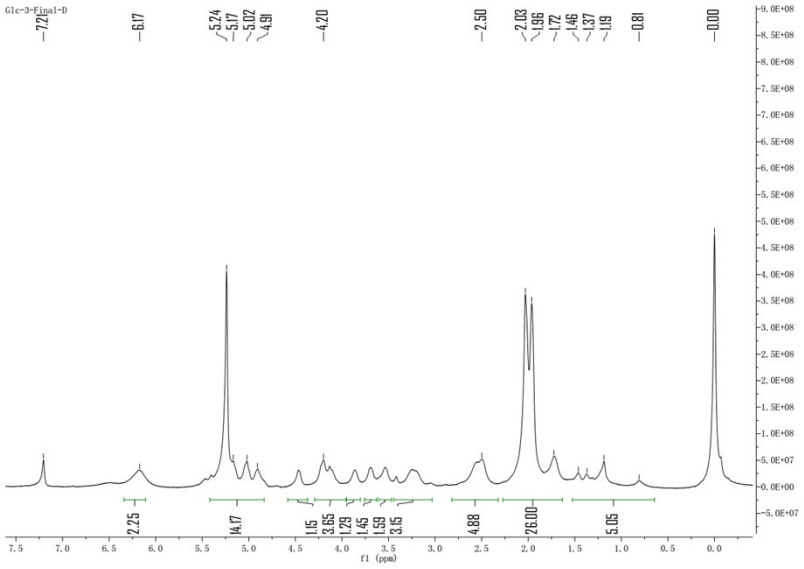
^{1}H-NMR spectrum for compound S20



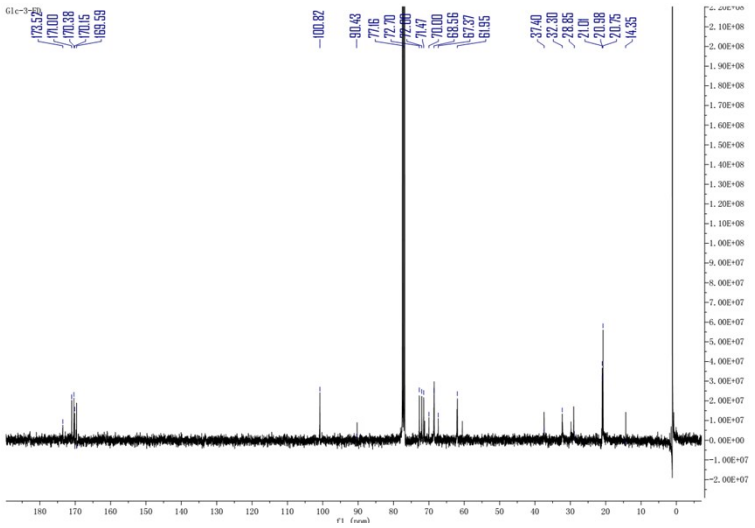
^{13}C-NMR spectrum for compound S20



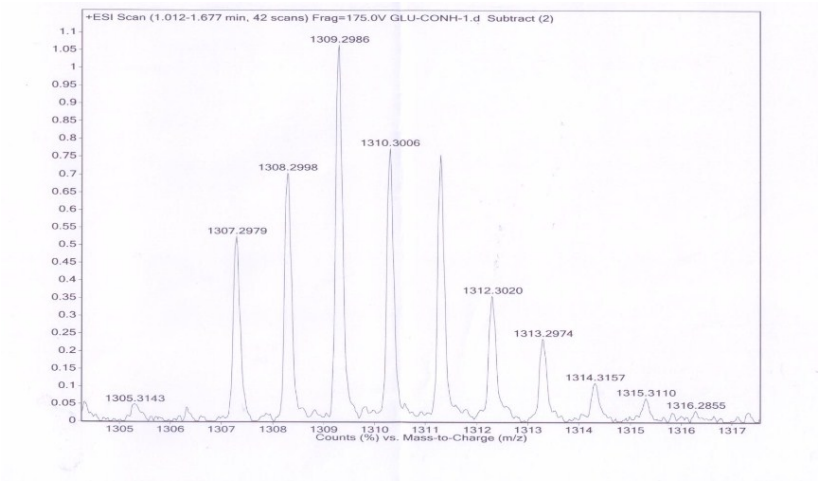
^{1}H-NMR spectrum for compound A1



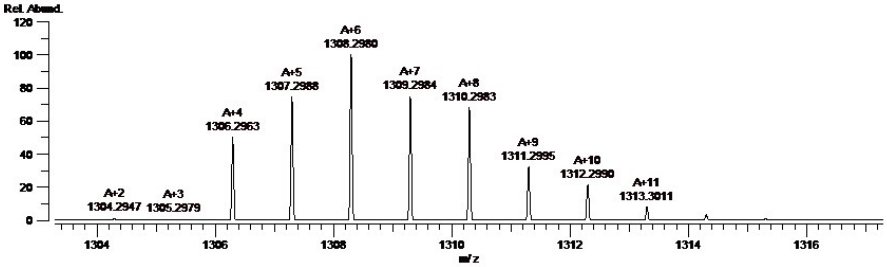
^{13}C-NMR spectrum for compound A1



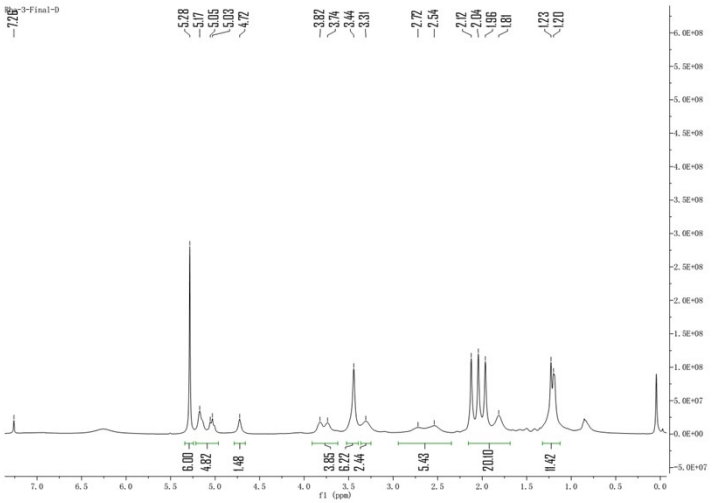
HRMS spectrum for compound A1



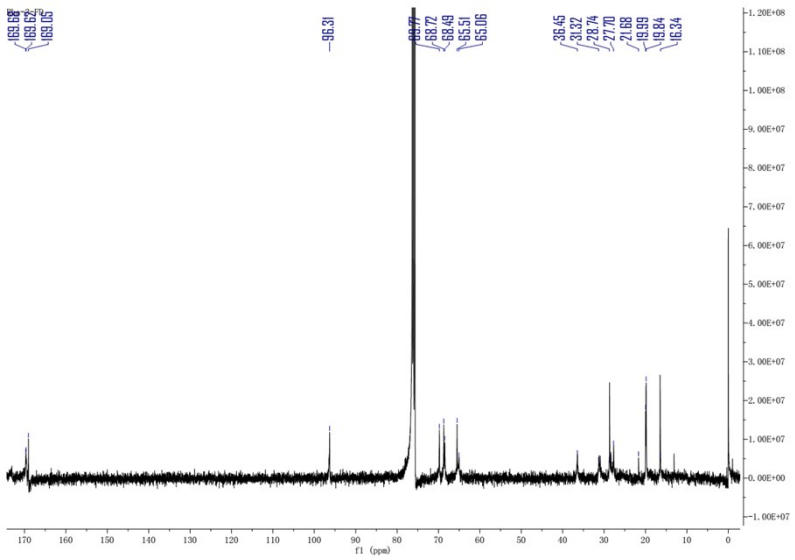
Calculated HRMS spectrum for compound A1



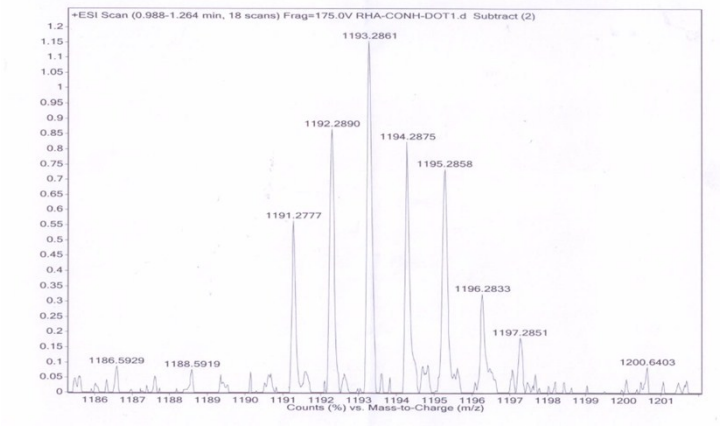
^{1}H-NMR spectrum for compound A2



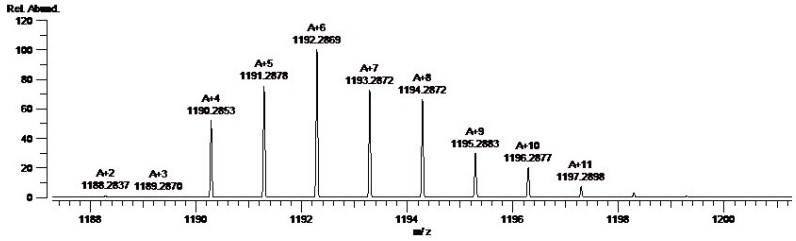
^{13}C-NMR spectrum for compound A2



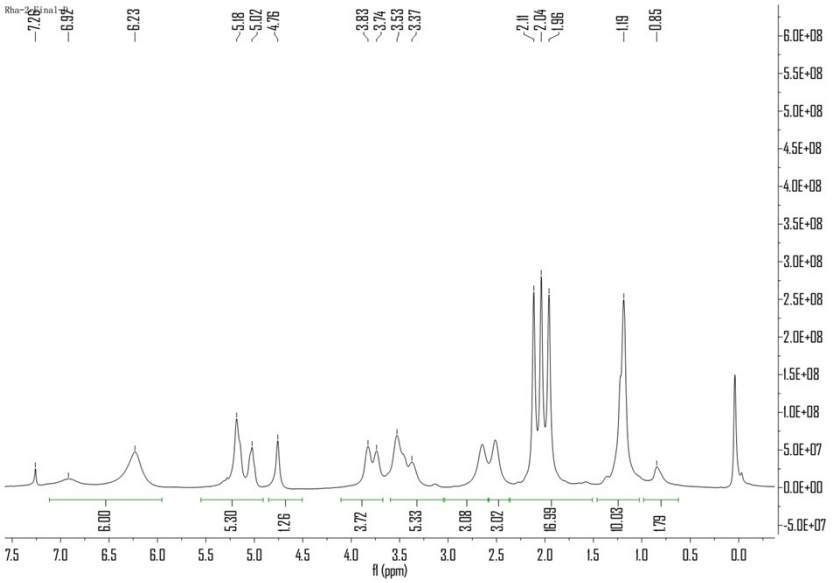
HRMS spectrum for compound A2



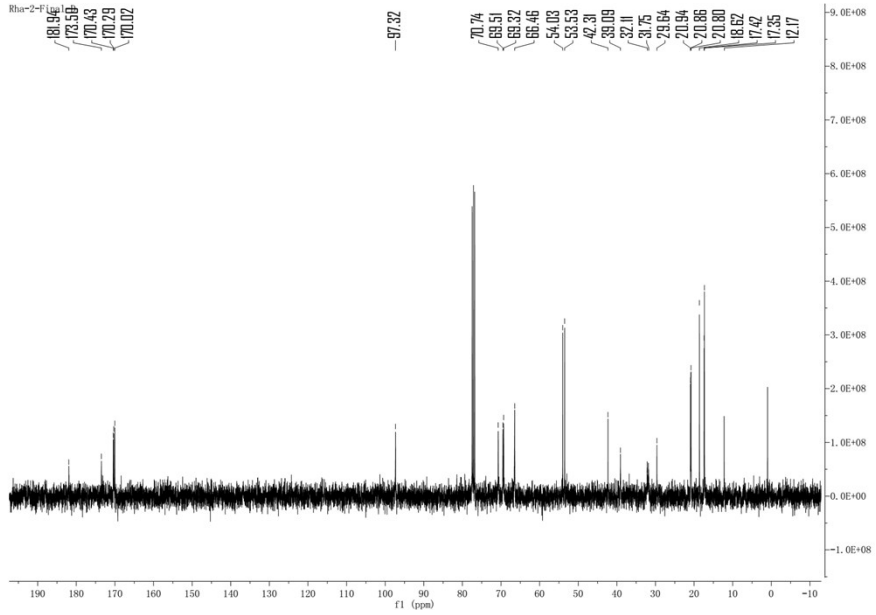
Calculated HRMS spectrum for compound A2



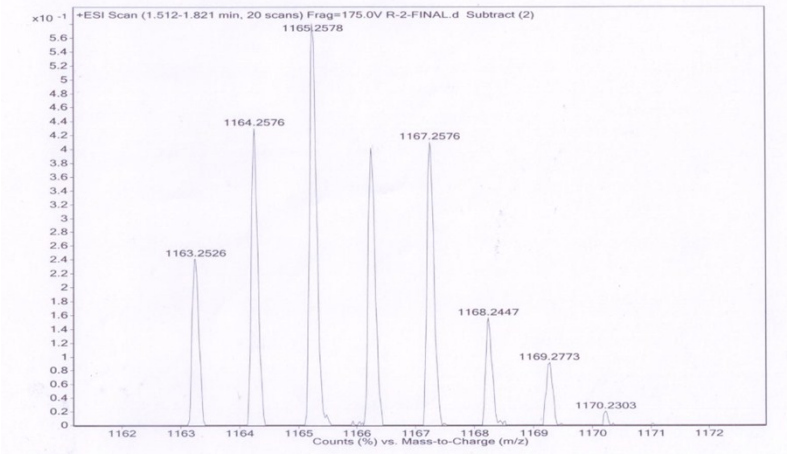
HRMS spectrum for compound A3



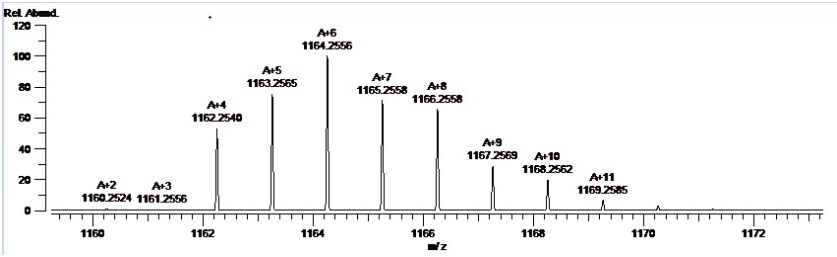
^{13}C-NMR spectrum for compound A3



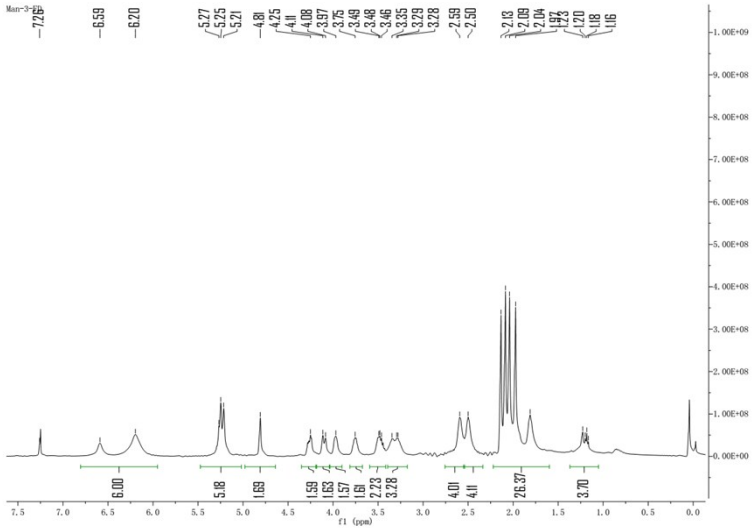
HRMS spectrum for compound A3



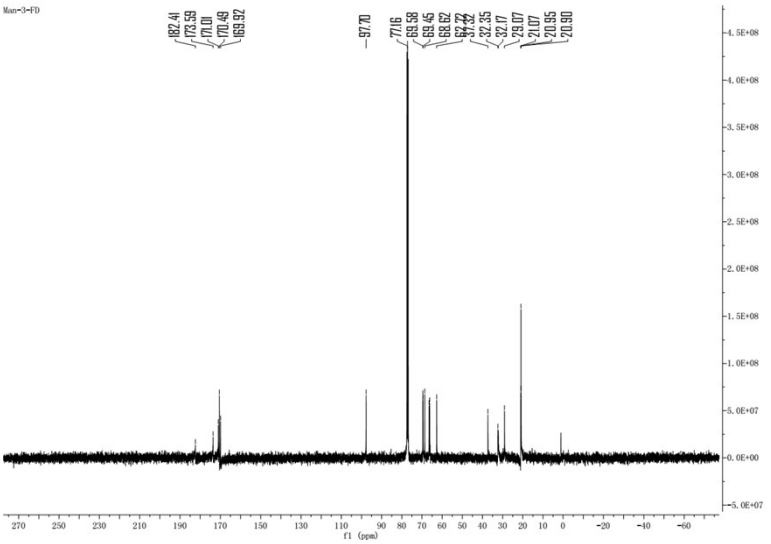
Calculated HRMS spectrum for compound A3



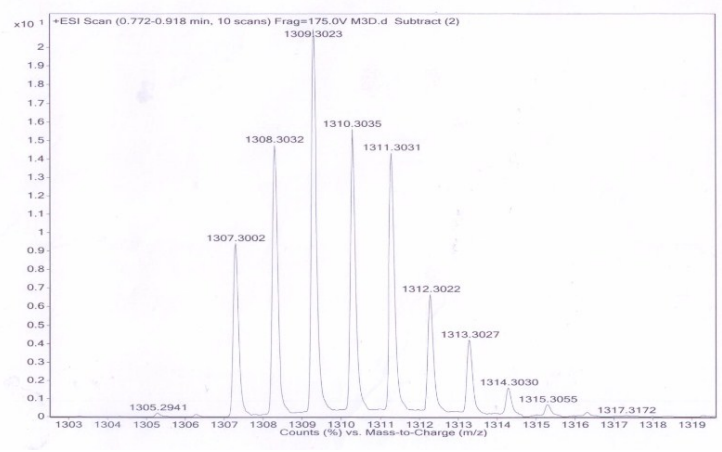
HRMS spectrum for compound A4



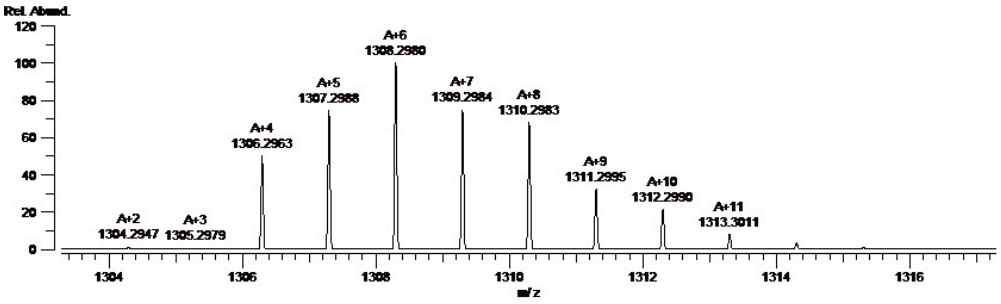
^{13}C-NMR spectrum for compound A4



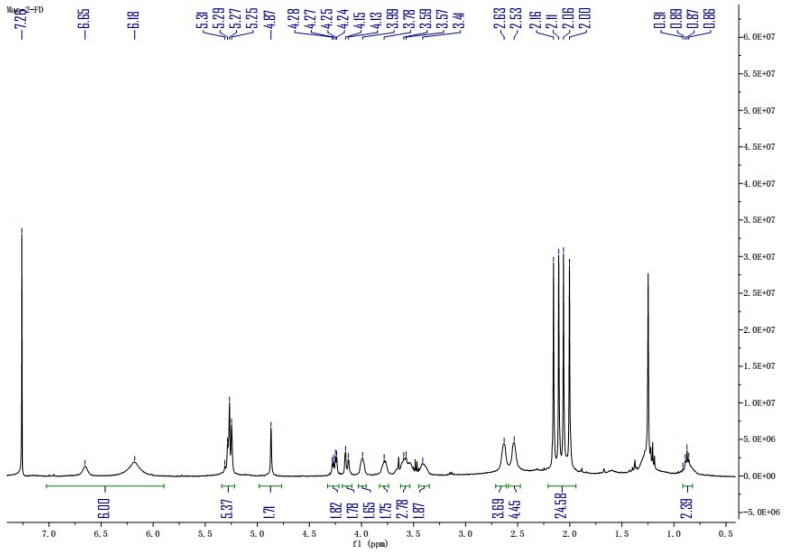
HRMS spectrum for compound A4



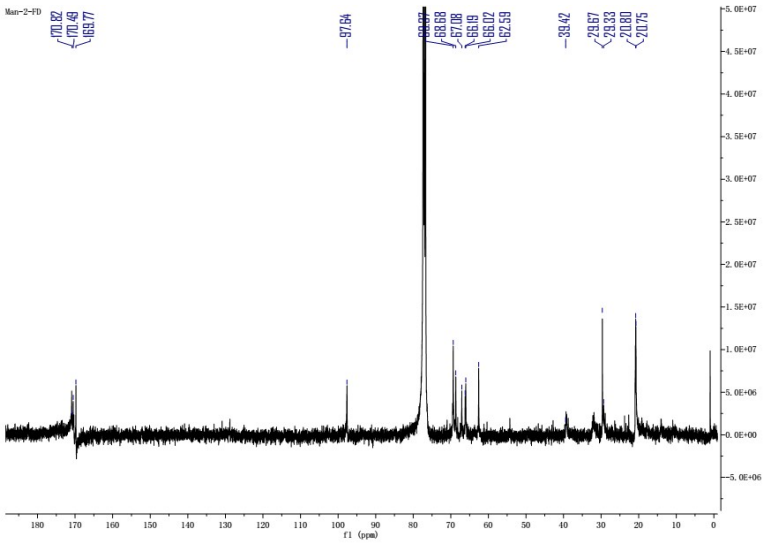
Calculated HRMS spectrum for compound A4



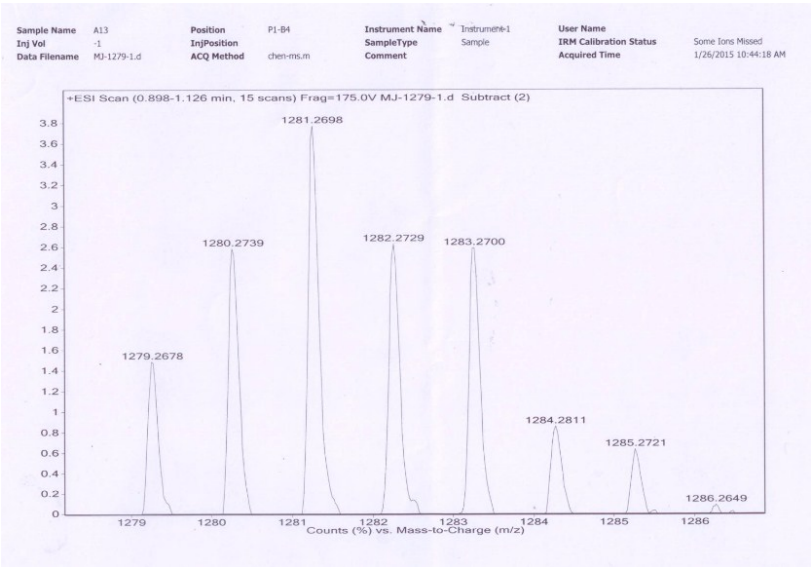
HRMS spectrum for compound A5



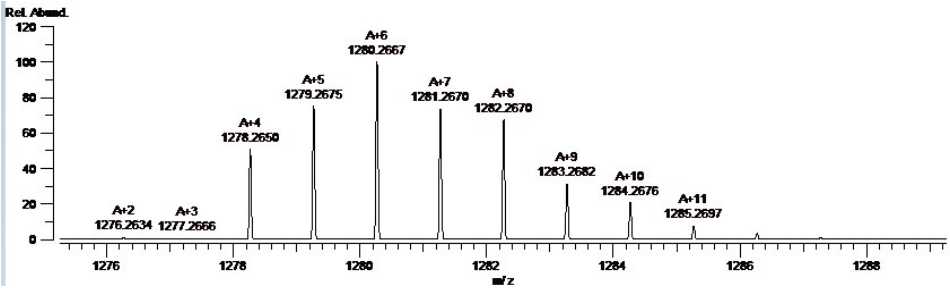
^{13}C-NMR spectrum for compound A5



HRMS spectrum for compound A5

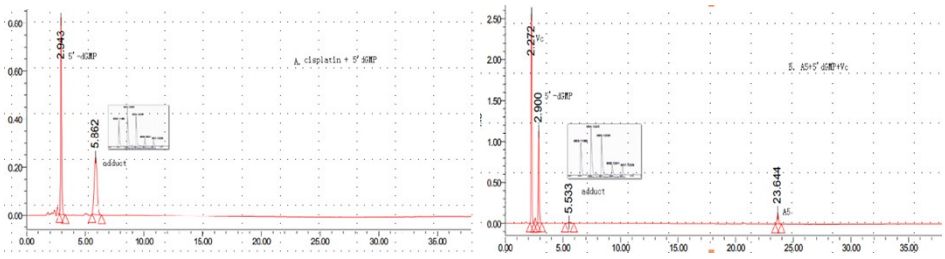


Calculated HRMS spectrum for compound A5

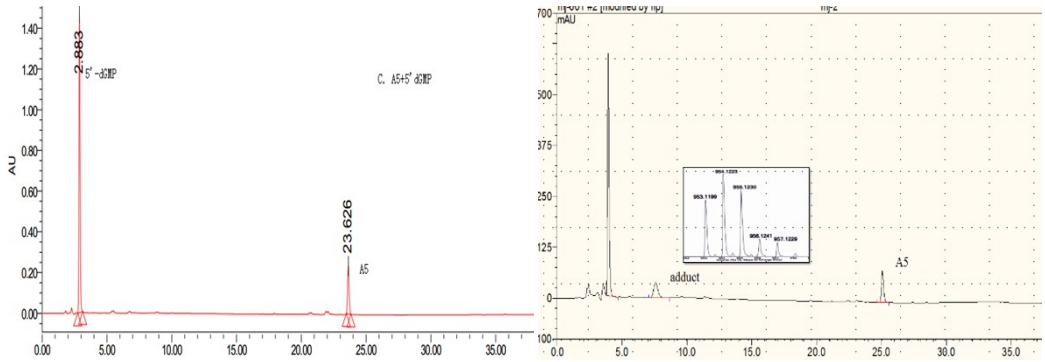


Analytical HPLC trace

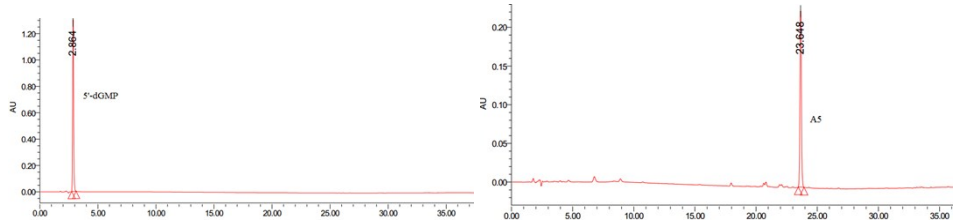
A. B.



C. D.



E. F.



G.

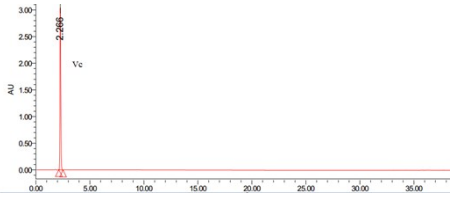
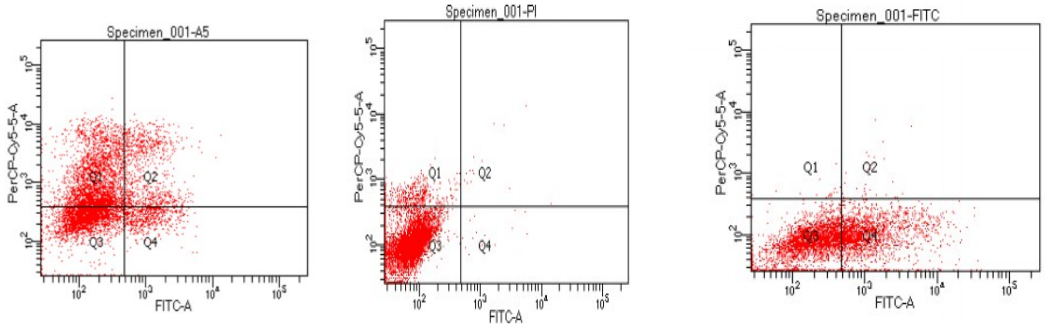


Fig.S1. HPLC chromatograms showing the reduction of A5. A. reaction of cisplatin with 5′-dGMP, B. reaction of A5 with 5′-dGMP in the presence of ascorbic acid incubated at 37 °C after 24h, C. reaction of A5 with 5′-dGMP without ascorbic acid. D. reaction of A5 with 5′-dGMP in the presence of ascorbic acid incubated at 37 °C after 72 h. E. 5'-dGMP, F. A5, G. Vc.

HPLC condition: eluents, millipore water (a) and methanol (b)(Sigma-Aldrich HPLC-grade): t = 0-5 min, 10 % b; t = 5-30 min, 85 % b; t = 30-40 min, 100 % b.



A4 (30 h) Untreated (30 h) Cisplatin (30 h)

Fig.S2. Annexin Ⅴ/PI coupled flow cytometric analysis in a large population of cells at 10 μM(30 h, Hela).