Supporting Information

A potent glucose-platinum conjugate exploits glucose transporters and preferentially accumulates in cancer cells

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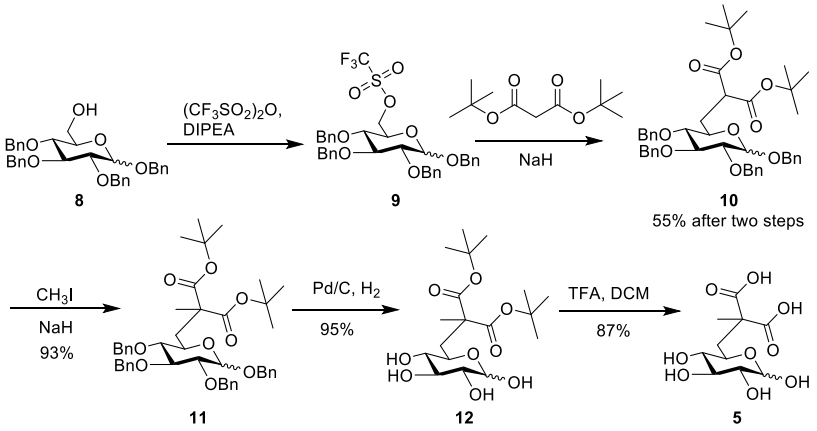
General information.

Materials. All chemicals were of reagent grade quality or better, obtained from commercial suppliers, and used without further purification. Solvents were used as received or dried over molecular sieves. All preparations were carried out using standard Schlenk techniques. Reactions involved in the preparation of platinum compounds were carried out in the dark. Dichloro(1*R*,2*R*)-cyclohexane-1,2-amine)platinum(II)[1] and benzyl 2,3,4-tri-*O*-benzyl-D-glucose (**8**) [2] were prepared following reported procedures.

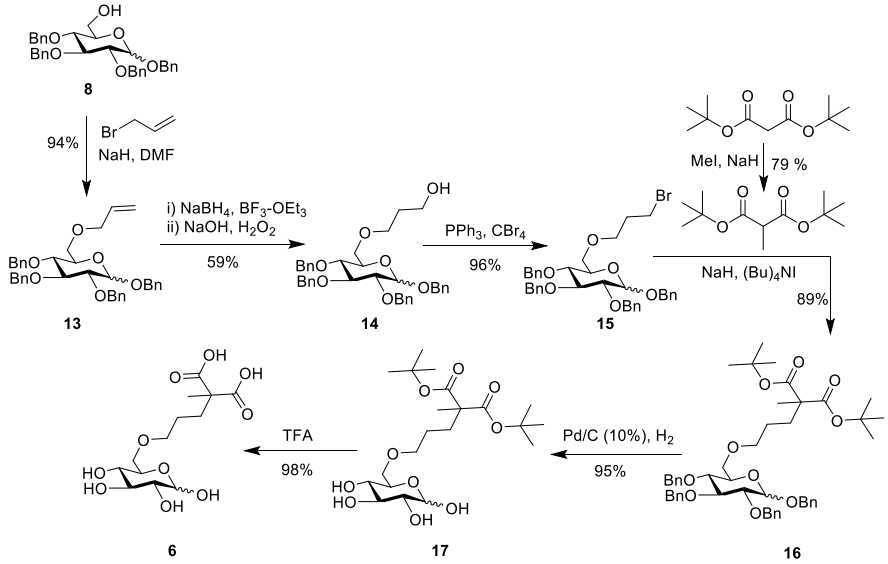
Instrumentation and methods. NMR spectra were recorded on Bruker DRX 400 spectrometers at 20 ^{0}C in the Department of Chemistry Instrumentation Facility (DCIF), MIT. All the measurements were carried out using deuterated solvents, chemical shifts δ are reported in ppm (parts per million), and coupling constants *J* are given as absolute values in Hz. The residual solvent peaks were used as an internal reference for ^{1}H and ^{13}C NMR spectra and chemical shifts are expressed relative to tetramethylsilane ($SiMe_4$, δ = 0 ppm). ^{195}Pt{^{1}H} NMR spectra were referenced externally to K_2PtCl_4 in D_2O as a standard (δ = −1628 ppm). Abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). ESI mass spectra were recorded on an Agilent

Technologies 1100 series LC-MSD trap. High-resolution mass spectrometry (HR-ESI-MS) was conducted by staff at the DCIF on a Bruker Daltonics APEXIV 4.7 T FT-ICR-MS instrument. Graphite furnace atomic absorption spectrometric measurements were carried out using a Perkin-Elmer AAnalyst600 GFAAS. Analytical HPLC was performed using an Agilent 1200 system fitted with a C18 reverse-phase column (Agilent Zorbax SB-C18, 4.6 mm × 250 mm, 5 μm). The flow rate was 1 mL min^{-1} and UV-absorption was measured at 220 nm. Semi-preparative HPLC was performed using an Agilent 1200 system fitted with a C18 reverse-phase column (Agilent Zorbax SB-C18, 21.2 mm × 250 mm, 7 μm). The flow rate was 4 mL min^{-1} and UV absorption was measured at 220 nm.

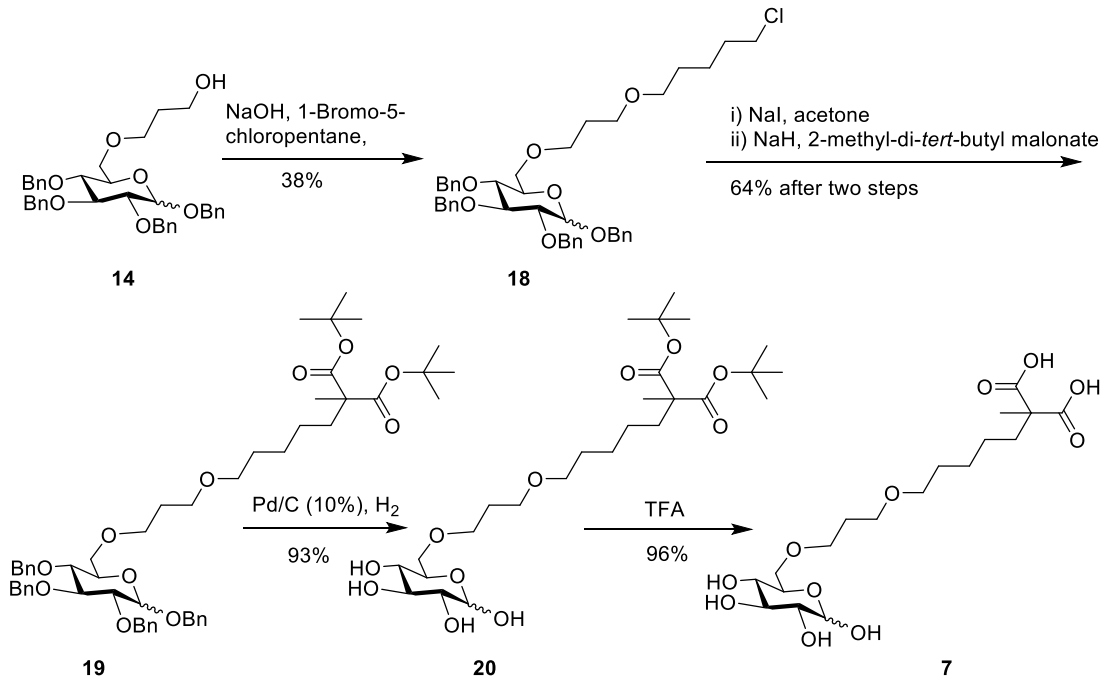
Scheme S1. Synthesis of ligand **5**.



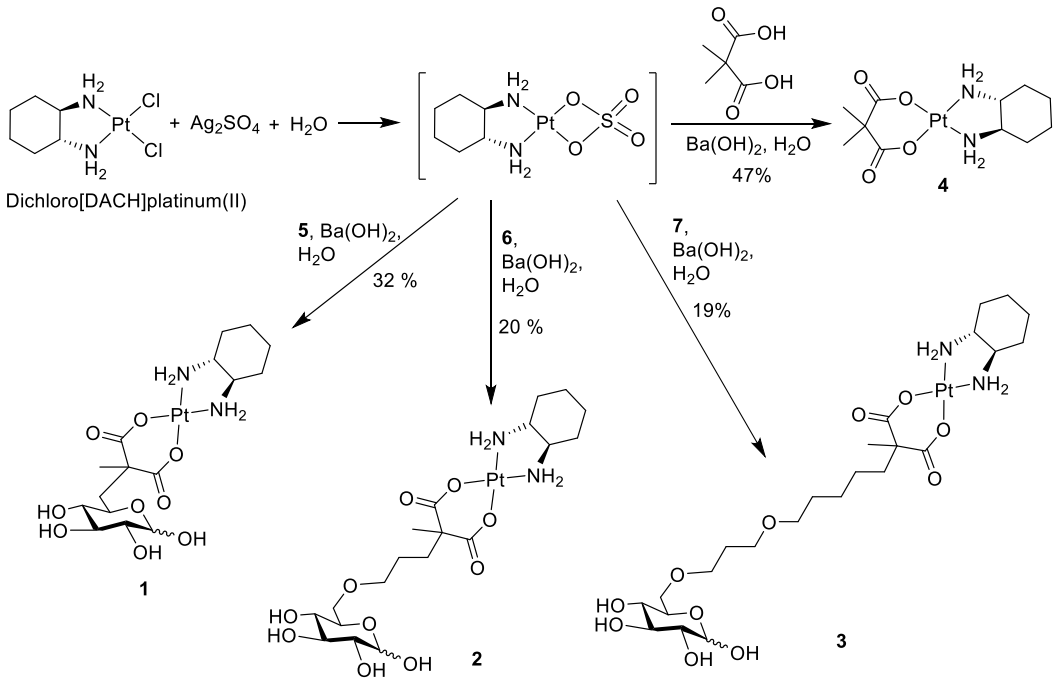
Scheme S2. Synthesis of ligand **6**.



Scheme S3. Synthesis of ligand **7**.

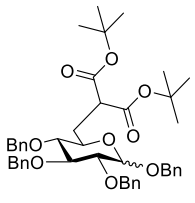


Scheme S4. Synthesis of Glc-Pts **1**–**3** and aglycone **4**.



Synthesis and characterization data of compounds.

Compound 10. A stirred solution of **8** (3.1 g, 5.7 mmol) and diisopropylethyl amine (2.5 mL, 14.4 mmol) in 30 mL dichloromethane under N_2 atmosphere was cooled to −40 ^{0}C. Trifluoromethanesulfonic anhydride (1.4 mL, 8.6 mmol) was added in a dropwise manner. The reaction mixture was then stirred for 3 h at the same temperature and afterwards allowed to warm to room temperature. Ethyl acetate (200 mL) was added and transferred to a separating funnel, washed with distilled water (200 mL), satd. $NaHCO_3$ solution (200 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and dried under vacuum to give intermediate **9** as dark-brown oil, which was used for the next step immediately.



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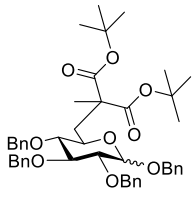
To a stirred DMF (12 mL) solution of di-*tert*-butyl malonate (3.1 g, 14.4 mmol), NaH (397 mg, 60 % in oil, 8.2 mmol) was added in portions under N_2 atmosphere. The mixture was stirred at room temperature for 1 h. A DMF (5 mL) solution of **9** was then added in a dropwise manner and the resulting mixture was heated at 70 ^{0}C for 15 h. The reaction was quenched using satd. NH_4Cl solution (200 mL) and extracted using Et_2O (300 mL). The organic layer was washed with distilled water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, hexane:EtOAc 7:1→6:1) to give **10** as light yellow oil (yield: 2.3 g, 55%, after two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.46 and 1.49 (s, 18H, C(CH_3)$_3$), 1.94-2.01 (m, 1H, CH_2), 2.48-2.58 (m, 1H, CH_2), 3.24-4.23 (m, 5H, 5×CH), 4.48-5.04 (m, 9H, 4×CH_2Ph, CH), 7.28-7.45 (m, 20H, 4×C$_6H_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 27.9, 28, 28.1, 28.2, 31.2, 31.3, 50.6, 51.2, 68.4, 68.7, 71.3, 72.4, 72.9, 74.9, 75.1, 75.2, 75.7, 75.8, 80.1, 81.41, 81.42, 81.43, 81.5, 81.8, 82.1, 82.3, 82.4, 84.7, 94.4, 102.6, 127.61, 127.62, 127.71, 127.72, 127.73, 127.8, 127.91, 127.92, 128, 128.1, 128.15, 128.4, 128.41, 128.42, 137.2, 137.4, 138.2, 138.3, 138.35, 138.4, 138.5, 138.8, 168.4, 168.5, 168.8, 168.9. ESI-MS (neg. detection mode): m/z (%): 737.6 (100) [M–H]$^-$, calculated m/z for [M–H]$^-$ 737.9.

Compound 11. To a stirred suspension of NaH (517 mg, 5 mmol, 60% in oil) in 7 mL DMF, **10** (2.5 g, 3.4 mmol) in 5 mL DMF was added in a dropwise manner under an N_2 atmosphere. After stirring for 30 min, iodomethane (1 g, 5 mmol) was added slowly and the resulting mixture was stirred 12 h at room temperature. The



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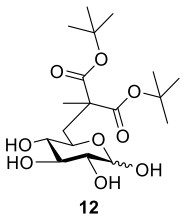
reaction was quenched by slow addition of satd. NH_4Cl solution (100 mL) and transferred to a separating funnel. The compound was extracted into EtOAc (2×100 mL). The combined organic layer was washed with distilled water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give the desired compound **11** as light yellow oil (yield: 2.4 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41-1.51 (m, 21H, C*H*$_3$ and C(C*H*$_3$)$_3$), 2.07-2.18 (m, 1H, C*H*$_2$), 2.47-2.63 (m, 1H, C*H*$_2$), 3.21-4.26 (m, 4H, 4×C*H*), 4.39-5.06 (m, 9H, 4×C*H*$_2$Ph, C*H*), 7.28-7.45 (m, 20H, 4×C$_6$*H*$_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 19.5, 19.6, 22.7, 25.4,27.8, 27.9, 28, 31.6, 34.5, 36.7, 37.3, 53.1, 53.3,67.5, 68.7, 71.2, 72.1, 72.8, 74.8, 75.4, 75.5, 75.6, 75.7, 80.2, 80.5, 80.8, 81.1, 81.2, 81.7, 82.4, 82.5, 82.8, 84.8, 94.2, 102.3, 127.5, 127.6, 127.65, 127.7, 127.75, 127.8, 127.9, 127.95, 128, 128.05, 128.1, 128.3, 128.35, 128.4, 137.5, 137.6, 138.2, 138.25, 138.3, 138.5, 138.6, 138.9, 171.4, 171.45, 171.5, 171.8. ESI-MS (pos. detection mode): m/z (%): 775.5 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 775.4.

Compound 12. To a stirred solution of **11** (1 g, 1.3 mmol) in 40 mL of methanol was added Pd/C (1 g, 0.93 mmol, 10% Pd) and the flask was evacuated carefully and flushed with H_2 gas using a balloon. The mixture was then stirred at room temperature for 72 h under a H_2 atmosphere. Then Pd/C was removed by filtration through a pad of Celite and the filtrate was concentrated to give white solid that was washed with pentane (30 mL) to give **12** as white power (yield: 515 mg, 95%. ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 1.36 and 1.38 (s, 3H, C*H*$_3$), 1.45, 1.36 and 1.48 (s, 18H, C(C*H*$_3$)$_3$), 1.91-2.02 (m, 1H, C*H*$_2$), 2.38-2.49 (m, 1H, C*H*$_2$), 3.01-3.36, 3.5-3.6 and 3.81-3.85 (m, 4H, 4×C*H*), 4.37 (d, 0.4H) and 5.11 (d, br, 0.7H) (C*Hanomeric*). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 18.2, 18.9, 26.7, 26.8, 26.9, 36.4, 36.5, 53.1, 53.4, 66.8, 72.3, 72.4, 73.4, 74, 74.8, 75, 76.6, 80.6, 81.0, 81.05, 81.1, 81.2, 90.9, 96.8, 171.7, 171.9, 172, 172.2. ESI-MS (pos. detection mode): m/z (%): 415.2 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 415.2.



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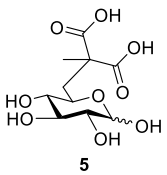
Ligand 5. To a stirred solution of **12** (480 mg, 1.2 mmol) in 12 mL of dichloromethane, TFA (2 mL) was added in a dropwise manner at 0 °C under a N_2 atmosphere and the resulting solution was stirred for additional 4 h at room temperature. The solvent was then removed using a rotary evaporator and the oily residue was dried using a high vacuum pump to give a white sticky solid. The solid was then washed with 15 mL (×3) of Et_2O:pentane (1:1) and finally with 15 mL of Et_2O and dried. The white powder was then dissolved in 5 mL of distilled water and filtered. The filtrate was



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lyophilized to give the desired compound **5** as white solid (yield: 300 mg, 87%). The compound was used for the next step without further purification. For ^{1}H and ^{13}C NMR spectroscopic measurements, *ca.* 40 mg of crude compound was purified by washing with CH_3CN (3×3 mL). ^{1}H NMR (400 MHz, D_2O, rotamers of α and β anomers): δ (ppm) 1.11, 1.45, 1.46 and 1.5 (s, 3H, C*H*$_3$), 2.19-2.41 (m, 1H, C*H*$_2$), 2.73-2.92 (m, 1H, C*H*$_2$), 3.26-3.37 (m, 1H, C*H*), 4.23-4.50 (m, 1.5H, C*H*), 4.82-5.39 (m, 1.5H, C*H*). ^{13}C {^{1}H} NMR (100 MHz, D_2O, rotamers of α and β anomers): δ (ppm) 19.6, 19.7, 19.8, 20.1, 20.2, 20.9, 21.1, 34.8, 35.1, 36.0, 48.8, 51.1, 51.2, 51.8, 55.5, 55.7, 74.5, 74.6, 74.7, 74.8, 75.7, 76.0, 76.1, 76.5, 76.9, 77.2, 77.3, 77.6, 77.7, 77.8, 77.85, 78, 79.6, 80.2, 80.25, 81.7, 81.8, 82.5, 82.6, 96.0, 96.1, 102, 102.2, 102, 3, 109.1, 109.3, 174.1, 174.4, 174.5, 178.6, 178.8, 178.9. ESI-MS (neg. detection mode): m/z (%): 522.9 (80) [2M–2H_2O–H]$^-$, 374.9 (100) [M+CF_3COOH–H_2O–H]$^-$, 278.9 (50) [M–H]$^-$, calculated m/z for [M–H]$^-$ 279.1.

2-Methyl-di-*tert*-butyl malonate. The compound was prepared by using a modified literature procedure.[3] To a stirred suspension of NaH (1.1 g, 26.8 mmol, 60% in oil) in 50 mL of THF, di-*tert*-butyl-malonate (6 g, 26.8 mmol) was added in a dropwise manner under a N_2 atmosphere and the mixture was stirred for 30 min at room temperature. Iodomethane (1.6 mL, 26.8 mmol) was then added to the mixture in a dropwise manner and stirred for an additional 20 h at room temperature. The reaction was then cooled to 0 ^{0}C using an ice bath and quenched by slow addition of a satd. NH_4Cl solution (100 mL). The compound was extracted with EtOAc (2×200 mL). The combined organic layers were washed with distilled water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, hexane:EtOAc 15:1→10:1) gave 2-methyl-di-*tert*-butyl malonate as colorless oil (yield: 5 g, 79%). Characterization data matched well with those reported earlier.[3]

Compound 13. An oven-dried two-necked flask fitted with a magnetic stirred was charged with NaH (1.2 g, 60 % in oil, 29.4 mmol) under a N_2 atmosphere. DMF (10 mL) was added and stirred for 10 min at room temperature. The suspension was then cooled on an ice bath and a DMF solution of **8** (8 g, 14.7 mmol, 15 mL DMF) was slowly added. After stirring at room temperature for 1 h, the reaction mixture was cooled again to 0^{0}C and allyl bromide (2.7 g, 22 mmol) was added and stirred at room temperature for an additional 10 h. The reaction was quenched using a satd. NH_4Cl

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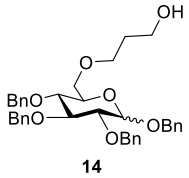
solution (200 mL) and extracted using EtOAc (300 mL). The organic layer was washed with distilled water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to give **13** as colorless oil that solidified upon standing at room temperature for several days (yield: 8 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.44-3.91 (m, 6H, 4×C*H*, CH_2), 4.01-4.20 (m, 2H, CH_2), 4.51-5.10 (m, 4×CH_2, C*H*), 5.21-5.41 (m, 2H, CHCH_2), 5.81-6.1 (m, 1H, C*H*CH$_2$), 7.31-7.51 (m, 20H, 4×C$_6H_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 68.5, 69.0, 69.1, 70.3, 71.2, 72.5, 72.6, 73.1, 74.9, 75.0, 75.1, 75.7, 77.7, 77.9, 79.9, 82.2, 82.4, 84.8, 95.8, 102.7, 117.1, 117.4, 127.6, 127.7, 127.8, 127.85, 127.9, 127.95, 128, 128.05, 128.1, 128.15, 128.2, 128.25, 128.3, 128.35, 128.5, 134.6, 134.8, 137.2, 137.5, 138.2, 138.3, 138.5, 138.7, 139. ESI-MS (pos. detection mode): m/z (%): 603.6 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 603.3.

Compound 14. To a stirred solution of **13** (9 g, 15.5 mmol) in 100 mL THF, $NaBH_4$ (1.1 g, 27.9 mmol) was added slowly under N_2 atmosphere. After stirring for 10 min, BF_3-OEt_2 (46.5 % BF_3 in Et_2O) solution (15.6 mL, 55.8 mmol) was added in a dropwise manner. The reaction mixture was stirred for 6 h. The cloudy mixture was then cooled to 0 ^{0}C using an ice bath and distilled water (*ca.* 10 mL) was added in a dropwise manner until hydrogen evolution ceased. Then 40 mL of a 4 M NaOH solution (pH >12) followed by 30 mL of H_2O_2 (30% in water) were added. After stirring at 0 ^{0}C for 30 min, the reaction mixture was stirred at room temperature for an additional 2 h. The reaction mixture was then transferred to a separating funnel containing 500 mL of EtOAc and shaken. The organic layer was collected and the aqueous layer was extracted again with 150 mL EtOAc. The combined organic phase was washed with distilled water (3×300 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, hexane:EtOAc 3:2→1:1) gave **14** as colorless oil that solidified slowly upon standing at room temperature for several day (yield: 5.5 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$, β anomer with trace of α anomer): δ (ppm) 1.81-1.90 (m, 2H, $CH_2CH_2CH_2$), 2.41 (s, br, 1H, OH), 3.41-3.91 (m, 10H, 4×C*H*, $CH_2CH_2CH_2$, CHCH_2O), 4.51-5.10 (m, 9H, 4×CH_2Ph, C*H*), 7.31-7.45 (m, 20H, 4×C$_6H_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 32.2, 62.0, 69.7, 70.6, 71.1, 74.6, 75.0, 75.1, 75.6, 77.9, 82.3, 84.6, 102.3, 127.5, 127.6, 127.8, 127.85, 127.9, 128.0, 128.1, 128.2, 128.4, 128.45, 128.5, 128.7, 137.5, 138.1, 138.2, 138.4, 138.6. ESI-MS (pos. detection mode): m/z (%): 621.6 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 621.3.



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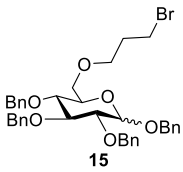
Benzyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside (**8**) was formed as a byproduct in this reaction (yield: 1.8 g).

Compound 15. To a stirred solution of **14** (3 g, 5 mmol) and CBr_4 (3.3 g, 10 mmol) in 60 mL of dry DCM, PPh_3 (2.6 g, 10 mmol) was added in portions at 0^0C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 20 h before the solvent was removed using a rotary evaporator. The residue obtained was purified by flash column chromatography (silica gel, hexane:EtOAc 5:1) to give **15** as colorless oil (yield: 3.2 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.21-2.03 (m, 2H, $CH_2CH_2CH_2$), 3.41-3.94 (m, 10H, 4×C*H*, $CH_2CH_2CH_2$, $CHCH_2O$), 4.51-5.09 (m, 9H, 4×CH_2Ph, C*H*), 7.28-7.44 (m, 20H, 4×C_6H_5). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 30.6, 30.8, 32.8, 32.9, 68.8, 68.9, 69.4, 69.5, 70.5, 71.2, 73.1, 74.8, 74.9, 75.1, 75.3, 75.8, 75.9, 77.7, 77.9, 80.0, 82.1, 82.4, 84.7, 96.7, 102.7, 127.7, 127.75, 127.8, 127.85, 127.9, 128, 128.1, 128.15, 128.2, 128.3, 128.4, 128.45, 128.5, 128.55, 137.2, 137.5, 138.2, 138.25, 138.4, 138.45, 138.6, 138.8. ESI-MS (pos. detection mode): m/z (%): 685.3 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 685.2.



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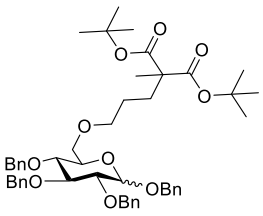
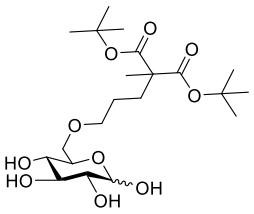
Compound 16. An oven-dried two-necked flask fitted with a magnetic stirrer was charged with NaH (326 g, 60 % in oil, 8.1 mmol) under a N_2 atmosphere. DMF (10 mL) was added and stirred for 10 min at room temperature. 2-Methyl-di-*tert*-butyl malonate (1.45 g, 6.3 mmol) in 5 mL DMF was then added in a dropwise manner to the suspension at room temperature and stirring was continued for 0.5 h until H_2 evolution ceased. **15** (3.2 g, 4.8 mmol) in 5 mL DMF followed by tetrabutyl ammonium iodide (15.3 mg, 0.48 mmol) was added and stirred at 90^0C for 24 h. The reaction mixture was then cooled to room temperature, 100 mL water and 100 mL brine were added, and the mixture was extracted with EtOAc (2×100 mL). The organic layer was washed with distilled water (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column chromatography (silica gel, hexane:EtOAc 5:1) gave **16** as light yellow oil (yield: 3.4 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41 and 1.43 (s, 3H, CH_3), 1.5 (s, 18H, $C(CH_3)_3$), 1.61-1.71 (m, 2H, CH_2), 1.81-2.10 (m, 2H, CH_2), 3.41-3.91 and 4.08-4.13 (m, 8H, 4×C*H*, $OCH_2CH_2CH_2$, $CHCH_2O$), 4.55-5.08 (m, 9H, 4×CH_2Ph, C*H*), 7.28-7.45 (m, 20H, 4×C_6H_5). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 19.7, 19.8, 24.7, 24.8, 27.9, 32.2, 34.4, 54.4, 69.1, 69.3, 69.8, 70.4, 71.1,



16

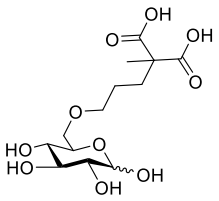
71.9, 72, 74.9, 75, 75.1, 75.2, 75.7, 77.8, 78, 80.1, 80.9, 82.2, 82.4, 84.8, 96.7, 102.6, 127.5, 127.6, 127.7, 127.8, 127.85, 127.9, 127.95, 128, 128.2, 128.4, 128.45, 128.5, 128.55, 137.3, 137.5, 138.2, 138.3, 138.5, 138.7, 139, 171.6, 171.7. ESI-MS (pos. detection mode): m/z (%): 833.8 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 833.4.

Compound 17. To a stirred solution of **16** (3.1 g, 3.8 mmol) in 60 mL methanol, Pd/C (2 g, 1.86 mmol, 10% Pd) was added and the flask was evacuated carefully and flushed with H_2 gas using a balloon. The mixture was then stirred at room temperature for 96 h under H_2 atmosphere. Then the Pd/C was filtered off using a pad of Celite and the filtrate was concentrated to give the desired compound **17** as hygroscopic white solid (yield: 1.7 g, 95%). The compound was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (s, 3H, C*H*$_3$), 1.43 (s, 18H, C(C*H*$_3$)$_3$), 1.52-1.61 (m, 2H, $OCH_2CH_2CH_2$), 1.72-1.81 (m, 2H, $OCH_2CH_2CH_2$), 3.41-5.61 (m, 13H, 5×C*H*, 4×OH, $OCH_2CH_2CH_2$, $CHCH_2O$). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl3): δ (ppm) 19.7, 24.2, 24.3, 24.4, 31.8, 31.9, 32, 54.4, 70.5, 70.8, 71.6, 71.7, 71.9, 73.4, 73.8, 74.5, 74.6, 81.2, 92.4, 96.5, 109.2, 171.8 . ESI-MS (pos. detection mode): m/z (%): 489.6 (100) $[M+K]^+$, calculated m/z for $[M+K]^+$ 489.6.



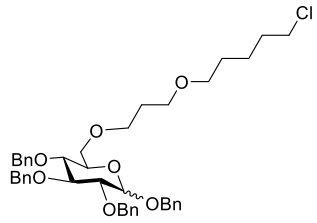
17

Ligand 6. To a stirred solution of **17** (1.5 g, 3.3 mmol) in 30 mL dichloromethane, TFA was added in a dropwise manner at 0°C under N_2 atmosphere and the resulting solution was stirred for an additional 5 h at room temperature. The solvent was then removed using a rotary evaporator and the oily residue was dried using high vacuum pump to give a white sticky solid. The solid was then washed with 30 mL (×3) of Et_2O:pentane (1:1) and finally with 30 mL of Et_2O (×2) and dried. The white powder was then dissolved in 8 mL of distilled water and filtered. The filtrate was lyophilized to give the desired compound **6** as white solid (yield: 1.1 g, 98%). The compound was used for the next step without further purification. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 1.32 (s, 3H, C*H*$_3$), 1.42-1.51 (m, 2H, $OCH_2CH_2CH_2$), 1.73-1.91 (m, 2H, $OCH_2CH_2CH_2$), 3.11-3.81 (m, 8H, 4×C*H*, $OCH_2CH_2CH_2$, $CHCH_2O$), 4.51 (d, 0.4H) and 5.11 (s, br, 0.5H) (C*Hanomeric*). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O): δ (ppm) 19.7, 23.7, 31.7, 53.2, 69.1, 69.2, 69.8, 69.9, 70.1, 71.1, 71.2, 71.4, 72.7, 74.1, 74.7, 75.6, 92.3, 95.7, 177.2. ESI-MS (neg. detection mode): m/z (%): 337.3 (100) $[M–H]^–$, calculated m/z for $[M–H]^–$ 337.3.



6

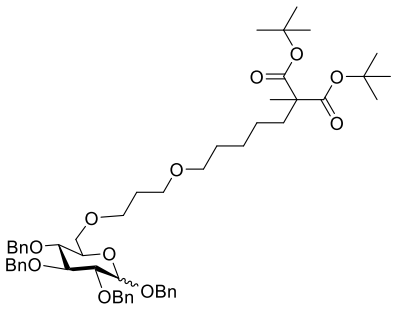
Compound 18. Aqueous NaOH (50%, 227 μL) was added slowly to a stirred solution of **14** (1 g, 1.7 mmol) in 2.8 mL DMSO and stirred for 10 min at room temperature. 1-Bromo-5-chloropentane (465 mg, 2.5 mmol) was then added and the mixture was stirred for 20 h. Then 1-bromo-5-chloropentane (465 mg, 2.5 mmol) was added again and the reaction mixture was stirred for an additional 24 h before being diluted with 150 mL Et_2O and washed with distilled water (200 mL×3) and brine.



18

The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, hexane:EtOAc 4:1→3:1), which gave **18** as a colorless oil (yield: 446 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.43-1.59 (m, 4H, 2×CH_2), 1.72-1.92 (m, 4H, 2×CH_2), 3.37-4.09 (m, 14H, 5×CH_2 and 4×C*H*), 4.52-5.01 (m, 9H, 4×PhCH_2 and CH_{anomeric}) 7.24-7.44 (m, 20H, 4×C$_6H_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 23.6, 29, 30.1, 30.15, 32.4, 45.0, 67.8, 68.6, 68.7, 69.1, 69.3, 69.7, 70.4, 70.7, 71.1, 73.0, 74.9, 75.0, 75.1, 75.5, 77.7, 77.8, 79.9, 82.1, 82.3, 84.7, 95.6, 102.6, 127.6, 127.65, 127.7, 127.8, 127.85, 127.9, 127.95, 128, 128.05, 128.2, 128.4, 128.45, 128.5, 137.2, 137.5, 138.2, 138.3, 138.4, 138.45, 138.7, 138.9. ESI-MS (pos. detection mode): m/z (%): 725.9 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 726.1.

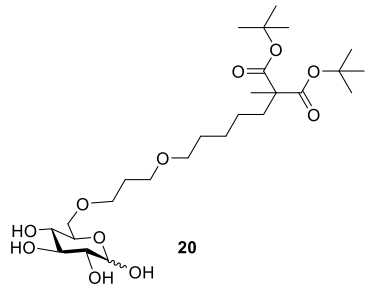
Compound 19. To a stirred acetone (30 mL) solution of **18** (1 g, 1.4 mmol), sodium iodide (840 mg, 5.6 mmol) was added and the mixture was refluxed for 30 h under N_2 atmosphere. The acetone was removed by using a rotary evaporator, 40 mL of Et_2O was added, and a white precipitate was filtered off. The filtrate was concentrated to give a light yellow oil. The oil was dissolved in 5 mL of anhydrous DMF and added in a dropwise manner to a mixture of NaH (83 mg, 60 % in oil, 2.1 mmol) and 2-methyl-di-*tert*-butyl malonate (483 mg, 2.1 mmol) in 5 mL of DMF, which had initially been stirred 30 min at room temperature under N_2 atmosphere. A catalytic amount of $(Bu_4N)I$ was then added and the mixture was heated at 70 ^{0}C for 24 h. The reaction was then cooled to room temperature, quenched by slow addition of a saturated aqueous NH_4Cl solution, and extracted by using EtOAc (2×100 mL). The organic layer was washed with distilled water (4×400 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash column



19

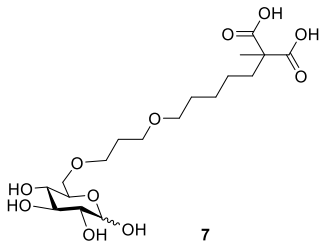
chromatography (silica gel, hexane:EtOAc 5:1→4:1) gave **19** as a colorless oil (yield: 800 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.15-1.38 (m, 7H, 2×CH_2 and CH_3), 1.46 (s, 18H, C(CH_3)$_3$), 1.56-1.59 (m, 2H, CH_2), 1.74-1.94 (m, 4H, 2×CH_2), 3.32-3.84 (m, 12H 4×CH_2 and 4×C*H*), 4.53-5.06 (m, 9H, 4×CH_2Ph, C*H*), 7.28-7.45 (m, 20H, 4×C$_6H_5$). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 19.7, 24.0, 26.6, 27.9, 29.6, 29.7, 30.1, 30.2, 35.3, 54.6, 67.8, 67.9, 68.7, 68.8, 69.1, 69.3, 69.8, 70.3, 70.9, 71.1, 73, 74.9, 75.1, 75.2, 75.25, 77.8, 77.9, 79.9, 80.8, 82.1, 82.2, 84.7, 95.6, 102.6, 127.6, 127.7, 127.8, 127.85, 127.9, 127.95, 128, 128.1, 128.2, 128.3, 128.4, 128.45, 128.48, 128.5, 137.2, 137.5, 138.2, 138.3, 138.4, 138.45, 138.6, 138.9, 171.8. ESI-MS (pos. detection mode): m/z (%): 919.5 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 919.5.

Compound 20. To a stirred solution of **19** (600 mg, 0.68 mmol) in 40 mL methanol, Pd/C (500 mg, 0.5 mmol, 10% Pd) was added and the flask was evacuated carefully and flushed with H_2 gas using a balloon. The mixture was then stirred at room temperature for 72 h under a H_2 atmosphere. Then the Pd/C was filtered off using a pad of Celite and the filtrate was concentrated to give the desired compound **20** as a colorless oil (yield: 340 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21-1.54 (m, 27H, 2×C(CH_3)$_3$, CH_3, 3×CH_2), 1.71-1.85 (m, 4H, 2×CH_2), 3.31-5.36 (m, 17H, 4×CH_2, 5×C*H*, 4×O*H*). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 19.6, 24.0, 26.5, 27.7, 29.5, 29.6, 29.8, 32.4, 35.3, 44.9, 54.5, 67.6, 67.7, 68.9, 69, 70.4, 70.5, 70.8, 71.8, 73.4, 74.6, 76.4, 80.8, 92.4, 96.4, 109.2, 171.8. ESI-MS (pos. detection mode): m/z (%): 559.4 (100) $[M+Na]^+$, calculated m/z for $[M+Na]^+$ 559.3.



20

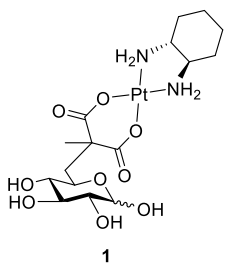
Ligand 7. To a stirred solution of **20** (340 mg, 0.6 mmol) in 10 mL dichloromethane, 2 mL TFA was added in a dropwise manner at 0 °C under N_2 atmosphere and the resulting solution was stirred for an additional 5 h at room temperature. The solvent was then removed by using a rotary evaporator and the oily residue was dried using high vacuum pump. The semi-solid residue was then washed with 10 mL Et_2O:pentane (1:1) and finally with 10 mL Et_2O and dried. The desired compound **7** was obtained as colorless sticky liquid (yield: 260 mg, 96%). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 1.15-1.29 (CH_3, 2×CH_2), 1.41-1.47 (m, 2H, CH_2), 1.71-1.74 (m, 4H, 2×CH_2), 3.13-3.91 (m, 12H, 4×CH_2, 4×C*H*), 4.47 (d,



7

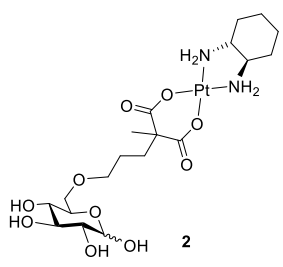
0.5H) and 5.07 (s, br, 0.4H) (C*Hanomeric*). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O): δ (ppm) 19.4, 23.4, 25.5, 28.2, 28.6, 30.2, 35.21, 53.8, 67.1, 68.1, 68.2, 68.3, 69.8, 69.85, 70.1, 70.4, 71.4, 72.2, 74.0, 74.6, 75.1, 75.7, 92.0, 95.9, 100.0, 176.7. ESI-MS (neg. detection mode): m/z (%): 423.2 (100) $[M-H]^-$, calculated m/z for $[M-H]^-$ 423.1.

Glc-Pt 1. A suspension of dichloro[(1*R*,2*R*)-cyclohexane-1,2-diamine]platinum(II)[1] (28.6 mg, 0.07 mmol) and Ag_2SO_4 (23 mg, 0.07 mmol) in 2 mL water was stirred overnight at room temperature in the dark. The precipitate was filtered off and the filtrate containing [(1*R*,2*R*)-cyclohexane-1,2-diamine]$PtSO_4$ was added in a dropwise manner to an aqueous solution of **5** (21 mg, 0.07 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (24 mg, 0.11 mmol) in 3 mL water, which had been initially stirred for 30 min at room temperature. The reaction mixture was then stirred for 24 h before being filtered to remove insoluble $BaSO_4$. The filtrate was lyophilized and the white solid obtained was purified using preparative HPLC. The runs were performed with linear gradients of millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-5 min, 0% B; t = 8 min, 5% B; t = 30 min, 20% B; t = 35 min, 95% B. The desired glucose-platinum conjugate **1** was obtained as a white powder (yield: 14 mg, 32%). t_R (RP-HPLC) = 6.1 min. ^1H NMR (400 MHz, D_2O): δ (ppm) 1.02-1.13 (m, 2H, C$H_{2\ DACH}$),1.17-1.29 (m, 5H, C$H_{2\ DACH}$ and CH_3), 1.46-1.53 (m, 2H, C$H_{2\ DACH}$), 1.91-2.01 (m, 2H, C$H_{2\ DACH}$), 2.27-2.35 (m, 2H, 2×C$H_{\ DACH}$), 2.91-3.88 (m, 6H, CH_2 and 4×C*H*), 4.49 (d, *J* = 7.9 Hz, 0.5H) and 5.04 (d, *J* = 3.8 Hz, 0.6H) (C*Hanomeric*). $^{13}C\{^1H\}$ NMR (100 MHz, D_2O): δ (ppm) 23.8, 23.9, 31.7, 31.8, 39.8, 39.9, 40.1, 55.3, 55.4, 62.2, 623, 62.5, 62.6, 67.7, 68.2, 71.5, 72.5, 72.9, 73.1, 73.6, 74.1, 75.8, 75.9, 91.8, 95.7, 181.4, 181.5, 181.7, 181.9. $^{195}Pt\{^1H\}$ NMR (86 MHz, D_2O): δ (ppm) −1911. ESI-MS (pos. detection mode): m/z (%): 610.2 (100) $[M+Na]^+$, 588.2 (60) $[M+H]^+$, 570.2 (40) $[M-H_2O+H]^+$, calculated m/z for $[M+Na]^+$ 610.1. HRMS (ESI). Calcd for $[M+Na]^+$: 610.1332, found 610.1322. Anal. Calcd for $C_{16}H_{28}N_2O_9Pt \cdot (H_2O)_{1.5} \cdot (CF_3COOH)_2$: C, 28.51; H, 3.95; N, 3.32. Found: C, 28.68; H, 4.39; N, 3.67.



1

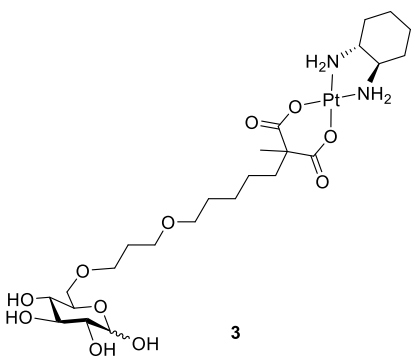
Glc-Pt 2. The compound was prepared and purified following a similar procedure as described for compound **1**. The preparative HPLC runs were performed with linear gradients of millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 0% B; t = 8 min, 10% B; t = 25 min, 25% B;



2

t = 30 min, 95% B. The glucose-platinum conjugate **2** was obtained as white powder (the reaction was done on a 0.3 mmol scale and yield: 39 mg, 20%). t_R (RP-HPLC) = 13.3 and 14.1 min. (α and β anomers). ^{1}H NMR (400 MHz, D_2O): δ (ppm) 1.02-1.12 (m, 2H, C$H_{2\ DACH}$),1.17-1.31 (m, 5H, C$H_{2\ DACH}$ and CH_3), 1.45-1.57 (m, 4H, OCH$_2$CH_2CH$_2$ and C$H_{2\ DACH}$), 1.90-2.01 (m, 2H, C$H_{2\ DACH}$), 2.27-2.36 (m, 2H, 2×C$H_{\ DACH}$), 2.65-2.93 (m, 2H, OCH$_2$CH$_2$CH_2) 3.11-3.91 (m, 8H, OCH_2CH$_2$CH$_2$, CHCH_2O and 4×CH), 4.53 (d, J = 7.9 Hz, 0.6H) and 5.12 (d, J = 3.9 Hz, 0.5H) (CHanomeric). ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ (ppm) 20.8, 20.85, 23.7, 23.9, 24.5, 31.7, 31.8, 35.9, 35.95, 56.9, 62.3, 62.5, 62.6, 64.2, 69.2, 69.3, 69.8, 69.9, 70.3, 71.2, 71.3, 71.5, 72.7, 74.1, 74.8, 75.7, 92, 96, 181.6, 181.8. ^{195}Pt{^{1}H} NMR (86 MHz, D_2O): δ (ppm) −1889. HRMS (ESI, pos. detection mode): m/z (%): 668.3 (100) $[M+Na]^+$, 646.9 (50) $[M+H]^+$; calculated m/z for $[M+Na]^+$ 668.2. HRMS (ESI). Calcd for $[M+Na]^+$: 668.1751, found 668.1744. Anal. Calcd for $C_{19}H_{34}N_2O_{10}Pt\cdot(H_2O)_2$: C, 33.48; H, 5.62; N, 4.11. Found: C, 33.47; H, 5.34; N, 3.84.

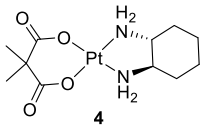
Glc-Pt 3. The compound was prepared and purified following a similar procedure as described for compound **1**. The preparative HPLC runs were performed with linear gradients of millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 20% B; t = 8 min, 40% B; t = 33 min, 85% B; t = 36 min, 95% B. The glucose-platinum conjugate **3** was obtained as white powder (the reaction was done on a 0.59 mmol scale and yield: 80 mg, 19%). t_R (RP-HPLC) = 13.6 and 14.2 min. (α and β anomers).



3

^{1}H NMR (400 MHz, D_2O): δ (ppm) 0.97-1.32 (m, 9H, CH_3, 3×C$H_{2\ DACH}$),1.35-1.49 (m, 4H, 2×C$H_{2\ DACH}$), 1.57-1.66 (m, 2H, CH_2), 1.76-1.82 (m, 2H, CH_2), 1.91-1.99 (m, 2H, CH_2), 2.27-2.37 (m, 2H, C$H_{2\ DACH}$) 2.68-3.87 (m, 12H, 4×CH_2 and 4×CH), 4.54 (d, J = 7.9 Hz, 0.6H) and 5.11 (d, J = 3.9 Hz, 0.4H) (CHanomeric). ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ (ppm) 20.8, 23.9, 24, 24.3, 25.5, 28.3, 28.6, 31.7, 32.1, 39.3, 57.4, 62.2, 62.3, 67.7, 68.2, 68.3, 69.4, 69.5, 69.8, 69.9, 70.2, 70.7, 71.4, 72.7, 74, 74.7, 75.7, 92, 95.9, 181.7, 181.8. ^{195}Pt{^{1}H} NMR (86 MHz, D_2O): δ (ppm) −1874. HRMS (ESI, pos. detection mode): m/z (%): 732.4 (100) $[M+H]^+$, 1463.6 (10) $[2M+H]^+$; calculated m/z for $[M+H]^+$ 732.3. HRMS (ESI). Calcd for $[M+H]^+$: 732.2664, found 732.2645. Anal. Calcd for $C_{24}H_{44}N_2O_{11}Pt\cdot H_2O$: C, 38.45; H, 6.18; N, 3.74. Found: C, 38.18; H, 5.92; N, 3.57.

Platinum complex 4. A suspension of dichloro[DACH]platinum(II)[1] (147 mg, 0.39 mmol) and



4

Ag_2SO_4 (119 mg, 0.39 mmol) in 6 mL water was stirred overnight at room temperature in the dark. The precipitate was filtered off and the filtrate containing [(1*R*,2*R*)-cyclohexane-1,2-diamine]$PtSO_4$ was added in a dropwise manner to an aqueous solution of 2,2-dimethylmalonic acid (51 mg, 0.39 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (122 mg, 0.39 mmol) in 20 mL water, which had been initially stirred for 30 min. at room temperature. The reaction mixture was then stirred for 24 h in dark before being filtered to remove insoluble $BaSO_4$. The filtrate was then lyophilized and the white solid obtained was purified using preparative HPLC. The runs were performed with linear gradients of millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 0% B; t = 7 min, 15% B; t = 40 min, 95% B. The desired platinum complex **4** was obtained as a white powder (yield: 80 mg 47%). t_R (RP-HPLC) = 12 min. ^{1}H NMR (400 MHz, D_2O): δ (ppm) 0.95-1.07 (m, 2H, C*H*$_2$), 1.09-1.23 (m, 2H, C*H*$_2$), 1.37-1.51 (m, 2H, C*H*$_2$), 1.67 (s, 6H, 2×C*H*$_3$), 1.84-1.96 (m, 2H, C*H*$_2$), 2.22-2.31 (m, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (100 MHz, D_2O): δ (ppm) 23.6, 25.1, 31.7, 52.4, 62.2, 182.8. ^{195}Pt{^{1}H} NMR (86 MHz, D_2O): δ (ppm) −1901. HRMS (ESI, pos. detection mode): m/z (%): 462.0 (100) $[M+Na]^+$; calculated m/z for $[M+Na]^+$ 462.1. Calcd for $[M+H]^+$: 440.1140, found 440.1134. Anal. Calcd for $C_{11}H_{20}N_2O_4Pt \cdot (H_2O)_2$: C, 27.79; H, 5.09; N, 5.89. Found: C, 27.93; H, 4.77; N, 5.71.

Analytical HPLC chromatograms and ESI mass spectra of platinum complexes 1–4.

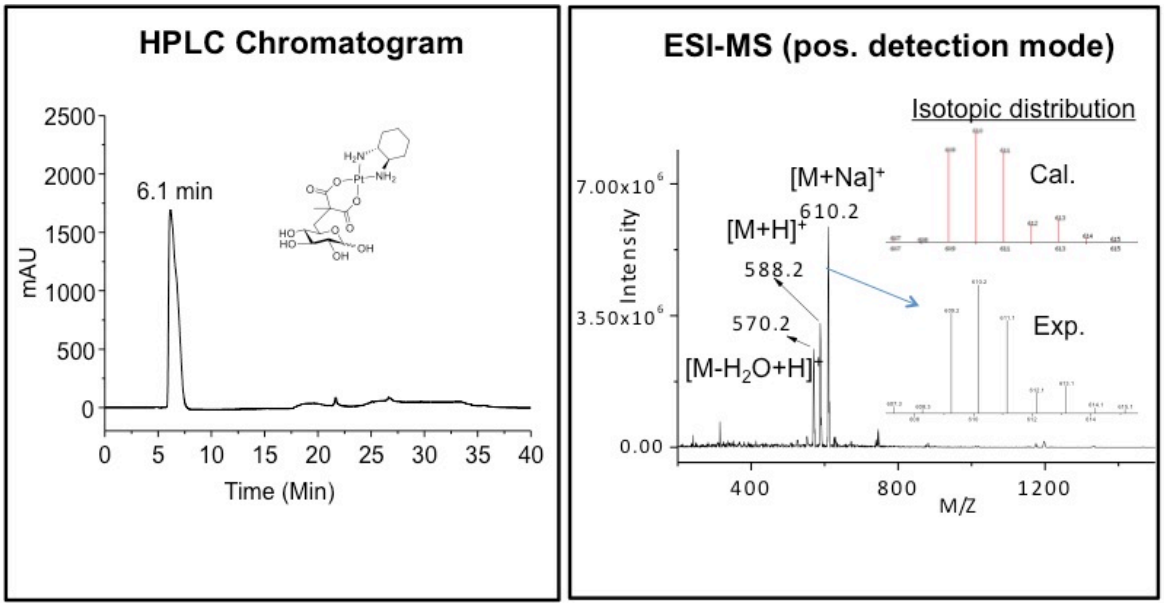


Figure S1. Analytical HPLC trace (220 nm) and ESI mass spectrum of **1.** HPLC condition**:** eluents, millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 0% B; t = 10 min, 2% B; t = 20 min, 50% B; t = 30 min, 95% B.

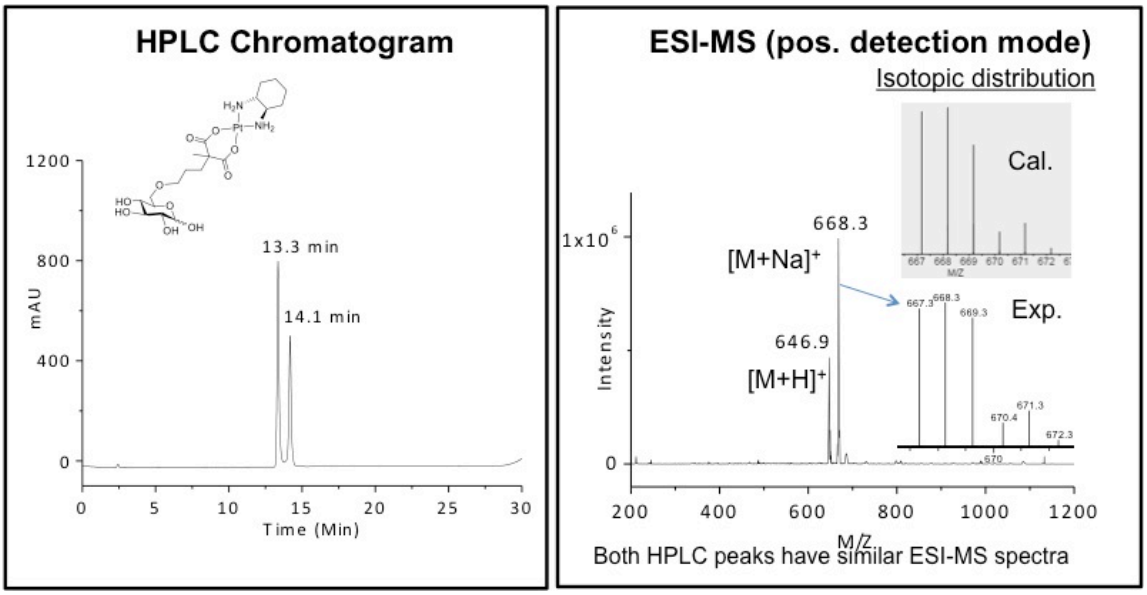


Figure S2. Analytical HPLC trace (220 nm) and ESI mass spectrum of **2.** HPLC condition**:** eluents, millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 0% B; t = 8 min, 10% B; t = 25 min, 20% B; t = 35 min, 95% B.

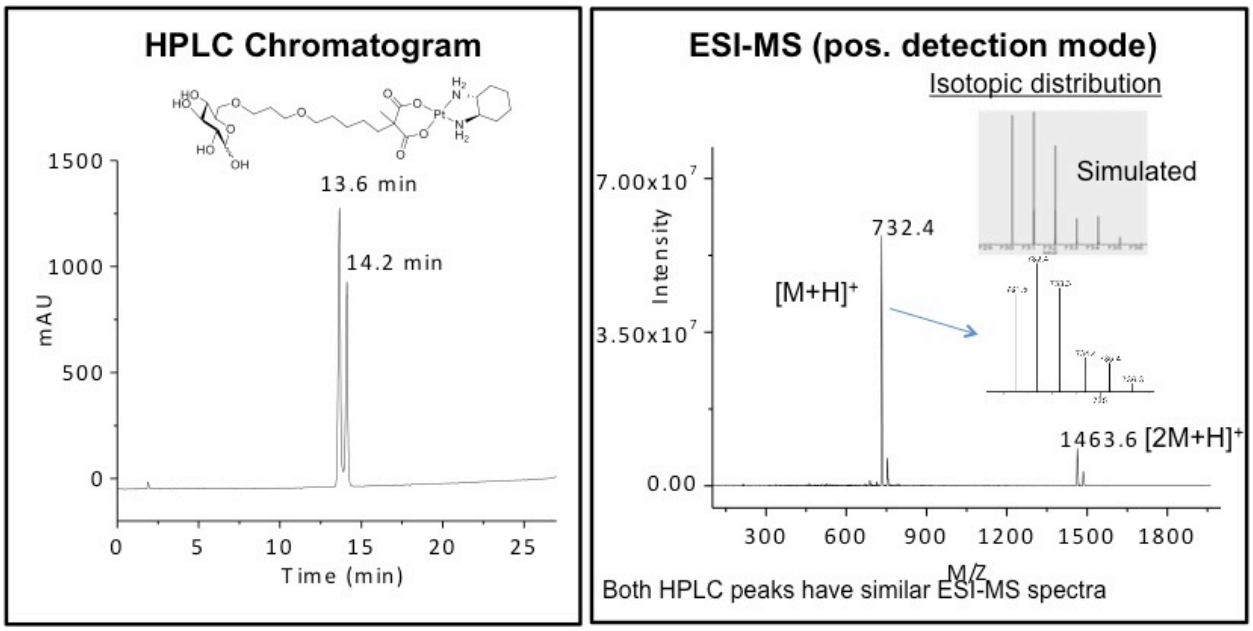


Figure S3. Analytical HPLC trace (220 nm) and ESI mass spectrum of **3.** HPLC condition**:** eluents, millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-5 min, 20% B; t = 30 min, 95% B; t = 35 min, 95% B.

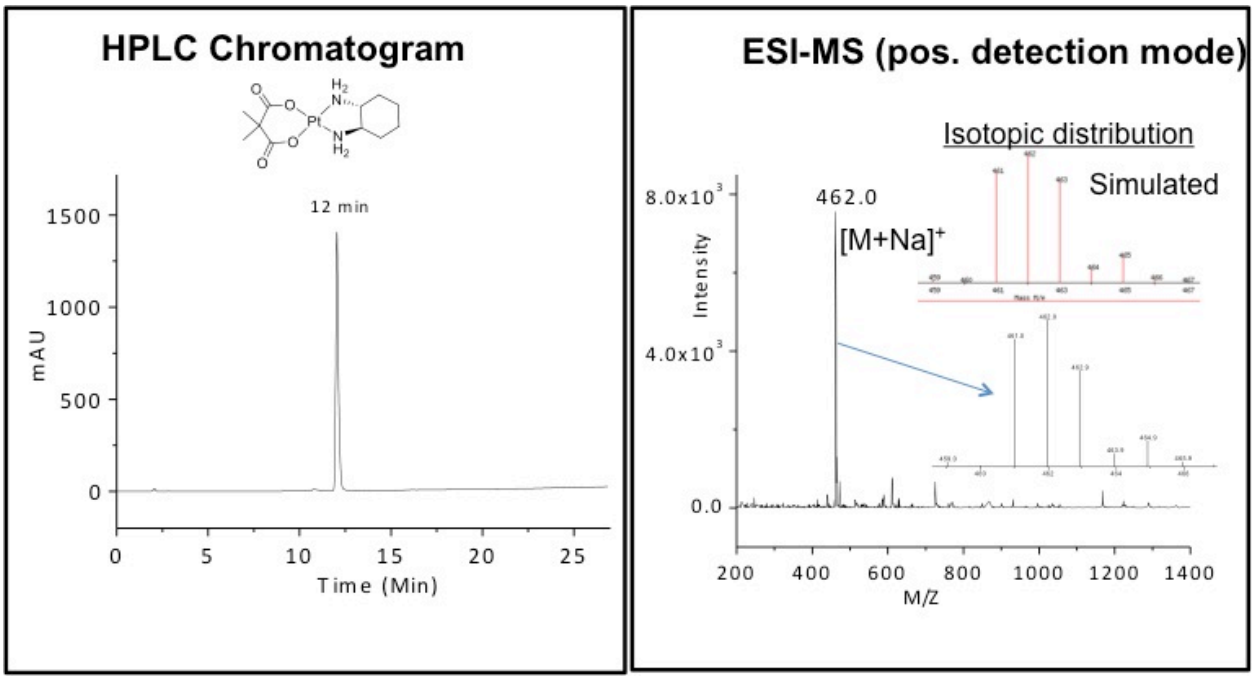


Figure S4. Analytical HPLC trace (220 nm) and ESI mass spectrum of **4.** HPLC condition**:** eluents, millipore water (A) and methanol (B; Sigma-Aldrich HPLC-grade): t = 0-4 min, 0% B; t = 8 min, 15% B; t = 40 min, 95% B.

Measurement of octanol-water partition coefficient (log *P*). The log *P* values for compounds **1–4** were determined by using the shake-flask method and GFAAS. Octanol used in this experiment was pre-saturated with PBS by overnight incubation with shaking of a biphasic mixture of the two at r.t. A portion of 0.3 mL PBS containing 50 μM of analyte was incubated with the pre-saturated octanol (0.3 mL) in a 1.5 mL tube. The tube was covered with aluminum foil and was shaken at 37 ^{0}C for 3 h using an automatic shaker. Two phases were then separated by centrifugation and the platinum content in each phase was determined by GFAAS. All the experiments were carried out in triplicate.

Cell lines and cell culture conditions. The A2780 (ovarian carcinoma), cisplatin-resistant A2780CP70 (ovarian carcinoma) and DU145 (prostate cancer) cells were grown in RPMI medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. A549 (lung adenocarcinoma), HeLa (cervical cancer), HT29 and HCT116 (colon carcinoma), MCF7 (breast cancer), A498 (kidney carcinoma), and Neuro-2A (mouse neuroblastoma) cell lines were maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. RWPE2 (normal prostate epithelial) cells were maintained in serum free keratinocyte media (KSFM) supplemented with 1% penicillin/streptomycin. F-12K media supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin was used to maintain CCD1105 KIDTr (normal kidney epithelial) cells. All cells were cultured at 37 ^{0}C in a humidified atmosphere containing 5% CO_2.

Cytotoxicity assays (MTT assays). The colorimetric MTT assay was used to determine the cytotoxicity of the compounds in vitro. Cells (2000/well in 100 μL medium) were seeded in a 96-well plate and incubated overnight. The following day, freshly prepared stock solutions (3-5 mM, concentration determined by GFAAS) of the platinum compounds in water were diluted using RPMI or DMEM and incubated for 72 h (total volume 200 μL/well). Subsequently, the medium was removed, 200 μL of a 0.4 mg/mL solution of MTT in DMEM or RPMI was added, and the plate was incubated for an additional 2-3 h. The DMEM/MTT or RPMI/MTT mixture was aspirated and 200 μL of DMSO was added to dissolve the resulting purple formazan crystals. The absorbance of the solution in each well was read at 570 nm using a BioTek Synergy HT multi-detection microplate plate reader. Absorbance values were normalized to control wells and plotted as concentration of test compound versus % cell viability. IC_{50} values were interpolated from the resulting dose-dependence curves. The reported IC_{50} values are the average

from at least three independent experiments, each of which consisted of either three or six replicates per concentration level.

For cytotoxicity assays using the GLUT1 inhibitor 4,6-*O*-ethylidene-α-D-glucose (EDG), a similar procedure as described above was followed except that A2780 cells (3500 cells in 100 uL media/well) were seeded on a 96 well plate in 100 μL RPMI, incubated for 24 h at 37 °C and EDG-containing RPMI medium (150 mM) was used to make the serial dilution of the concentrated solutions of the platinum compounds and 100 μL/well was added (resulting in a final inhibitor concentration of 75 mM). The cytotoxicity profiles of the compounds were evaluated by using the MTT assay.

Protein content determination using BCA assay. Petridishes (60 mm x 10 mm) containing cells were washed with PBS (3 x 3 mL). 0.5 mL RIPA lysis buffer (kept at 0 ^{0}C) added, incubated at room temperature for 5 min. A cell scraper was used to detach the cells from the surface and facilitate the lysis. The lysate was then collected in a 1.5 mL eppendorf tube and centrifuged at 13000 rpm for 20 min at 4 ^{0}C. The supernatant containing the soluble proteins was separated. 0.25 mL BPS was added to the eppendorf tube containing the pellet (insoluble membrane proteins) and sonicated to make the proteins soluble. The protein content in both fractions was then determined using standard BCA assay following the manufactures protocol (Thermo Scientific).

Whole cell uptake studies. Cells (1-1.5 million) were seeded on 60 mm x 10 mm petri dishes and incubated for 24 h at 37 ^{0}C. The medium was aspirated and 3.5 mL of fresh medium were added. Cells were then treated with the test compounds and subsequently incubated for a given period of time at 37 °C. The medium was then removed and cells were washed with ice cold PBS (3 x 3 mL). Cells were then digested using 70% HNO_3 (300 μL) for 1.5-2 h at room temperature and the platinum content was analyzed by GFAAS to obtain the whole cell uptake. For each condition one extra petri dish of cells was used to count the cells or to determine the protein content using BCA assay as described previously. For counting the cells, after aspirating the media, the petri dish was washed with 37 °C PBS (2 x 3 mL), cells were harvested by trypsinization (0.4 mL), petri dish washed with 0.8 mL ice cold PBS and collected in a 1.5 mL eppendorf tube. A 10 μL portion of the cell suspension was diluted five times using culture media and counted using a hemocytometer.

For the cellular uptake experiments using noncancerous cells RWPE2 and CCd1105 KIDTr, cells might take longer time (2-5 days) to reach 88-90% confluency. RWPE2 cells grow in serum free K-FSM media, and in order to have identical condition with its matched cancer cells DU145, the cellular uptake experiments was done using RPMI media supplemented with 10% FBS and 1% penicillin/streptomycin solution (8 h incubation) for both the cell lines. Once the RWPE2 cells reached the required confluency, the medium was replaced with RPMI and incubated for 12 h prior to the uptake experiment.

Intracellular distribution experiments. Five million A2780 cells were seeded on 100 mm x 20 mm petri dishes and incubated for 24 h at 37 ^{0}C. The medium was aspirated and 9 mL of fresh medium were added. These cells were then treated with compounds (20 μM) and subsequently incubated for required period at 37 °C. The medium was removed, cells were washed with PBS (3 x 8 mL), harvested by trypsinization (1 mL), and washed with 2 mL PBS. The cell suspension was centrifuged at 2000 rpm for 15 min at 4 °C. The cytoplasmic and nuclear fractions were then isolated using the Thermo Scientific NE-PER Nuclear and Cytoplasmic Extraction Kit. The platinum content in the cytoplasmic and nuclear fractions was analyzed by GFAAS. In addition, a whole cell uptake experiment was performed in parallel. All experiments were performed in triplicate.

Cellular uptake studies in A2780 in the presence of different additives. A2780 cells (1-1.5 million) were seeded on 60 mm x 10 mm petri dishes and incubated for 36-48 h at 37 ^{0}C (*ca.* 80-90 % confluent). The medium was aspirated, the cells were washed with 3 mL of PBS, 3.5 mL RPMI (FBS and antibiotic free) medium with or without specific inhibitor was added, and the cells were incubated for 30 min. Then an aliquot of a concentrated solution of the test compound was added to afford a final concentration of 10 μM, and the cells were incubated for a given period of time at 37 °C. The medium was then removed and cells were washed with ice cold PBS (3 x 3 mL). Cells were then digested using 70% HNO_3 (300 μL) for 1.5-2 h at room temperature and the platinum content was analyzed by GFAAS to obtain the whole cell uptake. For each condition one extra petri dish of cells was used to count the cells as described before.

For the D/L-glucose experiment, D-glucose or L-glucose (100 mM) was added to the medium and a similar procedure as discussed above was followed.

Note: prolonged incubation with the GLUT1 inhibitors may cause detachment of some cells from the surface of the petri dish due to glucose uptake inhibition.

Cellular uptake inhibition by cytochalasin B and cimetidine in DU145 cells. DU145 cells (*ca.* 1 million) were seeded on 60 mm x 10 mm petri dishes and incubated for 24-36 h at 37 ^{0}C (ca. 90 % confluent). The medium was aspirated, 3.5 mL RPMI (supplemented with 10% FBS and 1% penicillin/streptomycin) medium with or without cytochalasin B (100 μM final concentration) was added, and the cells were incubated for 2 h. Then a stock solution of Glc-Pt **1** was added to afford a final concentration of 50 μM and the cells were incubated for 2 h at 37 °C. The medium was then removed and cells were washed with ice cold PBS (3 x 3 mL), digested using 70% HNO_3 and the platinum content was analyzed by GFAAS to quantify the uptake. For each condition, one extra petri dish with same number of cells was used for quantifying the protein content using BCA assay as described above and uptake was normalized to per mg protein. Note: DU145 cells found to be somewhat unstable in FBS free media, therefore all the experiments carried out with DU145 cells are in RPMI media supplemented with 10% FBS and 1% penicillin/streptomycin solution.

A similar protocol was followed for the cellular uptake studies in absence and presence of OCT2 inhibitor cimetidine. In this experiment, cells were treated with cimetidine (2 mM final concentration) for 30 min prior to the addition of stock solution of **1** (final concentration 25 μM) and incubated for 5 h before the medium was aspirated.

DNA platination experiments. Five million A2780 cells were seeded on 100 mm × 20 mm petri dishes and incubated at 37 ^{0}C until cells are 80% confluent. These cells were then treated with the compounds (20 μM) in fresh medium (9 mL) and subsequently incubated for 24 h for glucose-platinum derivatives and 12 h for oxaliplatin (positive control) at 37 °C. The medium was replaced by fresh medium and cells were incubated for an additional 20 h for glucose-platinum derivatives and 12 h for oxaliplatin. The medium was then aspirated and the cells were washed with PBS (3 x 8 mL), harvested by trypsinization (1 mL), and washed with 2 mL PBS. The cell suspension was centrifuged at 2000 rpm for 15 min at 4 °C. The cell pellet was suspended in DNAzol (1 mL, genomic DNA isolation reagent, MRC). The DNA was precipitated with pure ethanol (0.5 mL), washed with 75% ethanol (0.75 mL × 3), and re-dissolved in 500 μL of 8 mM NaOH. The DNA concentration was determined by UV−Vis spectroscopy and the platinum content was quantified by GFAAS. All experiments were carried out in triplicate.

Immunoblotting analysis of DNA damage marker proteins, OCT2 and GLUT1 proteins. One and a half million A2780 cells were seeded on 60 mm x 10 mm petri dishes and incubated for 24 h at 37 ^{0}C. These cells were then treated with a given platinum complex and subsequently incubated at 37 °C for 72 h. Cells were then washed with PBS, scraped into SDS-PAGE loading buffer (64 mM Tris-HCl (pH 6.8)/9.6% glycerol/2% SDS/5% β-mercaptoethanol/0.01% bromophenol blue), and incubated at 90^{0}C for 10 min. Whole cell lysates were resolved by 4–20% sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE; 200 V for 25 min) followed by electro transfer to a polyvinylidene difluoride membrane, PVDF (350 mA for 1 h). Membranes were blocked using 5% (w/v) bovine serum albumin (BSA) in PBST (PBS/0.1% Tween 20) and incubated with specific primary antibodies (Cell Signaling Technology and Santa Cruz Biotechnology) overnight at 4 °C. On the following day, after washing with PBST (3×5 mL), the membrane was incubated with horseradish peroxidase-conjugated secondary antibodies (Cell Signaling Technology) in fresh BSA blocking solution. Immune complexes were detected with the ECL detection reagent (BioRad) and analyzed using an Alpha Innotech ChemiImagerTM 5500 fitted with a chemiluminescence filter.

A similar procedure was followed to analyze the GLUT1 and OCT2 expressions in different cell lines using GLUT1 and OCT2 specific primary antibodies (Santa Cruz Biotechnology), respectively.

Flow cytometric analysis. One million A2780 cells were seeded on 60 mm x 10 mm petri dishes and incubated for 24 h at 37 ^{0}C. These cells were then treated with compounds (4 μM final concentrations) and subsequently incubated at 37 °C for 24-72 h. A2780 cells were incubated with or without the test compounds for 24-72 h at 37 °C. Cells were harvested from adherent cultures by trypsinization. Following centrifugation at 2000 rpm for 15 min at 4 °C, cells were washed with PBS and then fixed with 70% ethanol in PBS. Fixed cells were collected by centrifugation at 2500 rpm for 3 min, washed with PBS, and centrifuged as before. Pellets were treated with 10 μL RNaseA solution (Qiagen) and resuspended in 300 μL propidium iodide (50 mg/mL in PBS, Sigma), for nucleic acids staining, and incubated for 20 min. DNA content was then measured on a FACSCalibur-HTS flow cytometer (BD Biosciences) using laser excitation at 488 nm and 20,000 events per sample were acquired. Cell cycle profiles were analyzed using the ModFit software. For the apoptosis experiments, the Annexin V-SYTOX apoptosis-dead cells assay detection kit was used. The manufacture's protocol was followed to

carry out this experiment. Briefly, untreated and treated cells (*ca.* 1×10^5) were suspended in 1× annexin binding buffer (96 μL) (10 mM HEPES, 140 mM NaCl, 2.5 mM CaCl2, pH 7.4), 5 μL APC-annexin V and 2 μL SYTOX green (10 μg/ mL) were added to each sample and incubated on ice for 15 min. After which more binding buffer (150 μL) was added while gently mixing. The samples were kept on ice prior to being read on the FACS Calibur-HTS flow cytometer (BD Biosciences) and 20,000 events per sample were acquired. Cell populations were analyzed using the FlowJo software (Tree Star).

DNA binding kinetics (precipitation method). Glc-Pt **1** could bind to DNA only after getting activated by dissociation of the malonate ligand from the platinum center. Therefore in order to investigate whether GLUT1 inhibitor EDG alters the ligand dissociation/DNA binding kinetics, we studied the DNA binding kinetics of Glc-Pt **1** in the absence and presence of 75 mM EDG. The amount of platinum not bound to ct-DNA was determined by modification of a previously reported protocol.[4] Briefly, a solution of ct-DNA (0.7 mM, base pair) was incubated with Glc-Pt **1** (20 μM) at a bp:metal complex ratio of 35:1 at 37 ºC in 1 mM sodium phosphate buffer containing 5 mM NaCl (pH 7.4) in the absence or presence of 75 mM 4,6-O-ethyledene-α-D-glucose (EDG). At certain time points, a 250 μL aliquot was removed and the DNA was precipitated by adding 20 μL of aqueous NaCl (2.5 M) and 1.0 mL of EtOH (stored at 4 °C). The solution was centrifuged to remove precipitated DNA, and the concentration of unbound platinum was determined by GF-AAS.

Cytotoxicity in cancer cells and matched normal cells. Cancer cells DU145 (prostate) and A498 (kidney), and matched normal cells RWPE2 (prostate epithelial) and CCD 1105 KIDTR (kidney epithelial) were used to evaluate the selectivity of Glc-Pt **1** towards cancer cells.

DU145 and A498 cells were seeded (2000 cells/well in 100 μL media supplemented with 10% FBS and 1% penicillin-streptomycin solution) in a 96-well plate and incubated overnight. The following day, the medium was aspirated and freshly prepared stock solutions (3-5 mM, concentration determined by GFAAS) of Glc-Pt **1** in water were diluted using culture media, added to the well (total volume 200 μL/well, final compound concentration 20 μM), and incubated for 8 h. The medium was then replaced with fresh medium (200 μL/well) and incubated for further 72 h before the cell viability was determined using MTT assay as described earlier.

Because of the slower proliferation rate of the normal cells, CCD1105 KIDTr cells were seeded at a density of 5000 cells/well in 100 µL media otherwise a similar procedure was followed as described for DU145 and A498 cells. RWPE2 cells grow under serum-free conditions (keratinocyte Serum Free Medium, K-SFM supplemented with 1% penicillin/streptomycin solution) and they do not attach strongly during the 24-36 h after subculture. Therefore the procedure was slightly modified. RWPE2 cells were seeded in at a density of 2000 cells/well in 200 µL K-SFM media supplemented with 1% penicillin/streptomycin solution in a 96-well plate and incubated for 48-72 h. Once the cell morphology looked normal under the microscope (*not round shape*), the medium was replaced with 100 µL RPMI supplemented with 10% FBS and 1% penicillin-streptomycin solution and incubated for 12 h. The following day, freshly prepared stock solutions (3-5 mM, concentration determined by GFAAS) of the platinum compounds in water were diluted using RPMI were added and incubated for 8 h (total volume 200 µL/well, final compound concentration 20 µM). The medium was then replaced with fresh K-FSM medium and incubated for further 72 h before the cell viability was determined using MTT assay as described earlier.

Computational details. The geometries of compounds **1** and **3** were optimized using density functional theory methods with *ORCA 3.0*.[5] A generalized gradient approximation functional comprising Becke's exchange functional and Perdew's correlation functional was used (BP86).[6] The resolution of the identity (RI) approximation was applied in all calculations.[7] Relativistic effects were treated using the zero order regular approximation (ZORA). For all atoms, a variation on the balanced polarized split-valence Gaussian basis set developed by Ahlrichs (def2-SVP)[8] was used that was recontracted for use with ZORA (SV-ZORA).[9] The corresponding auxiliary basis set (def2-SVP/J) was chosen for use with the RI approximation.[10] The optimized structure was converted to the PDBQT file format using *AutoDock Tools* and non-cyclic, non-terminal bonds were designated as freely rotatable.[11] Non-polar hydrogen atoms were removed from the structure. The apo protein from the crystal structure of the *E. coli* xylose symporter XylE (PDB 4GBZ)[12] was also converted to the PDBQT format and polar hydrogen atoms were placed at calculated positions. *AutoDock Vina* was used to dock the platinum complex into the protein structure.[13] The surface of the protein cavity was generated using *Hollow*.[14] Results were visualized with *PyMol*.[15]

Table S1. Table of IC_{50} values (72 h incubation, MTT assay) of glucose-platinum derivatives **1**–**3**, aglycone **4**, and cisplatin in different human cancer cell lines.[a]

Compound	IC_{50} values (μM)							
	HT29 (Colon)	HCT116 (Colon)	MCF7 (Breast)	Hela (Cervical)	A2780 (Ovary)	A2780/CP70 (Ovary)	A549 (Lung)	DU145 (Prostate)
1	0.87±0.13	1.8± 0.42	1.5±0.3	0.56±0.14	0.15±0.06	0.33±0.03	4.0±0.7	1.7±0.21
2	1.2±0.5	3.3± 0.28	2.3±0.3	1.0±0.23	0.22±0.03	0.27±0.12	4.2±2.6	2.1±0.03
3	1.04±0.1	2.0±0.1	1.7±0.2	ND	0.20±0.01	ND	2.8±0.2	2.3±0.25
4	2.65±0.77	1.74±0.09	1.6±0.3	1.3±0.21	0.16±0.07	0.45±0.06	3.9±0.1	1.4±0.39
Cisplatin	21.5±2.1	5.3±0.14	9.6±0.2	ND	0.84±0.09	10.2±0.49	14.2±3	ND

ND = not determined. [a]Data reflect the mean±SD of results from three or more independent experiments, each performed in triplicate.

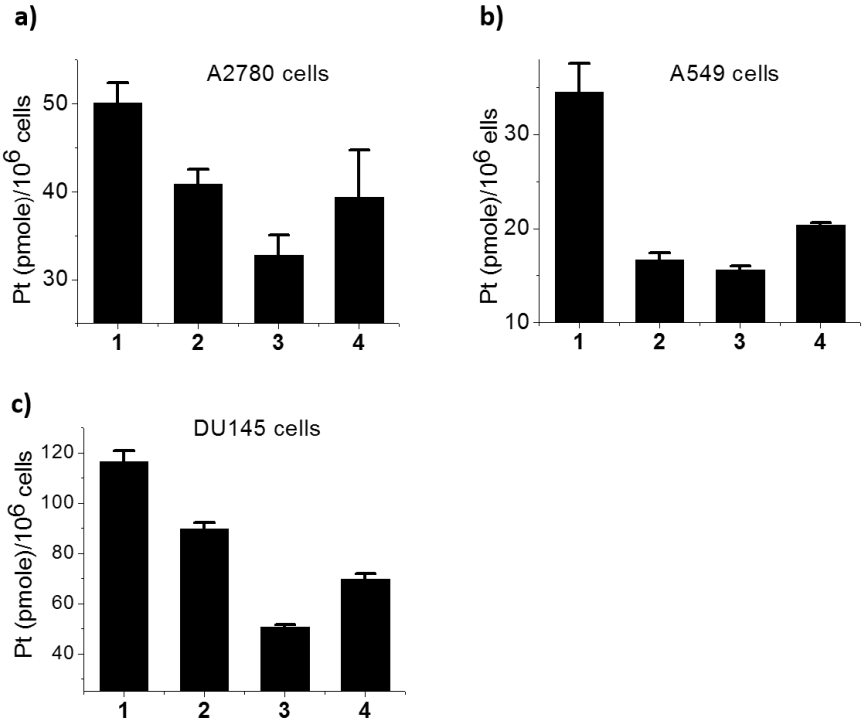


Figure S5. Whole cell uptake of compounds **1**–**4** in A2780 (a, 10 μM exposure for 17 h), A549 (b, 20 μM exposure for 8 h), and DU145 (c, 20 μM exposure for 8 h) cells.

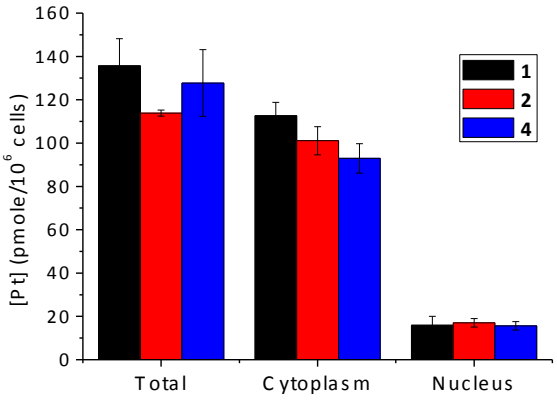


Figure S6. Intracellular distribution of compounds **1**, **2**, and **4** in A2780 cell (20 μM exposure concentrations for 20 h).

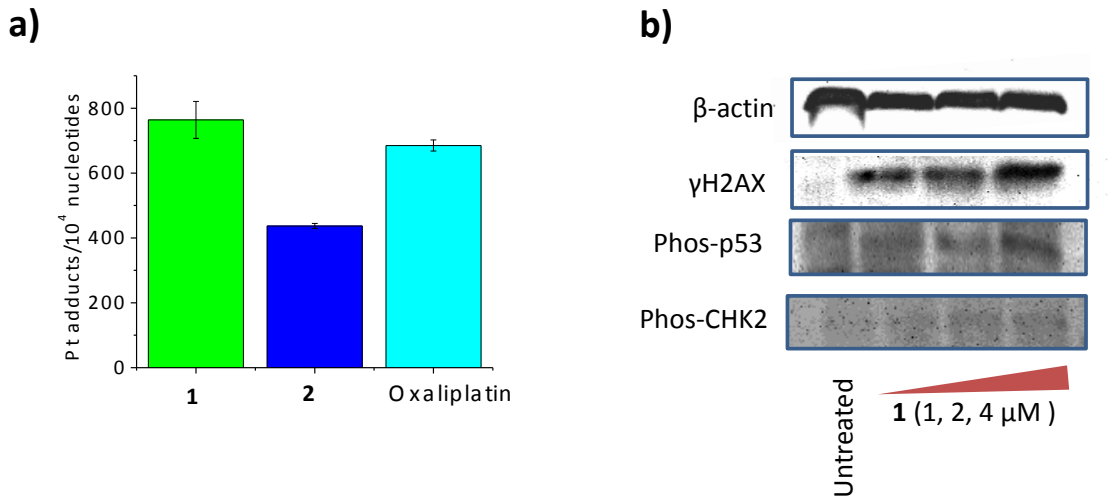


Figure S7. a) DNA platination study of **1**, **2** (20 μM for 24 h), and oxaliplatin (20 μM for 12 h, as positive control) in A2780 cells. b) Immunoblotting analysis of marker proteins indicative of DNA damage by compound **1**.[16] A2780 cells are treated with glucose-platinum derivative **1** (1–4 μM for 72 h). Whole cell lysates were resolved by SDS-PAGE and analyzed by immunoblotting against γH2AX, phos-p53, phos-CHK2, and β–actin (loading control).

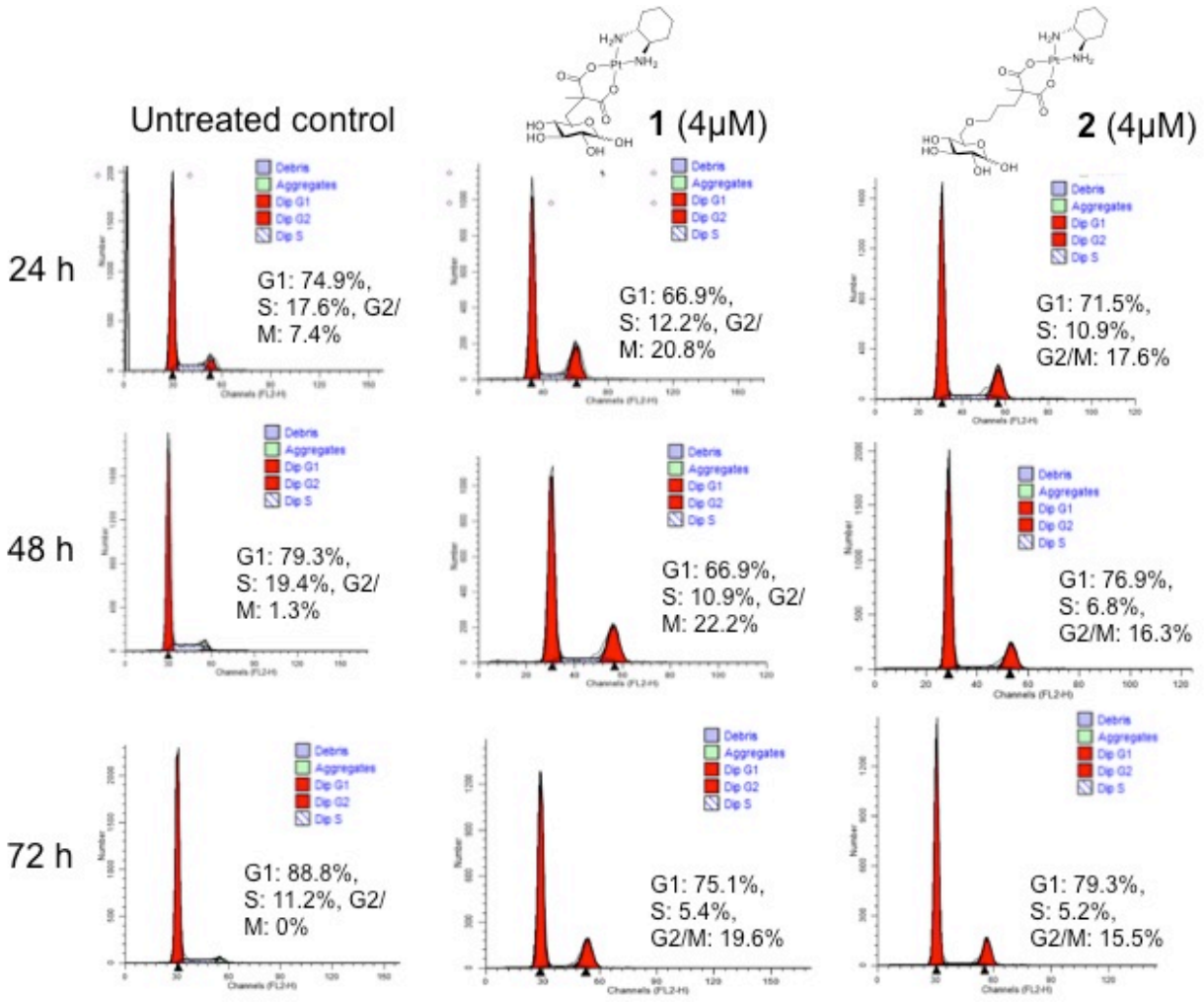
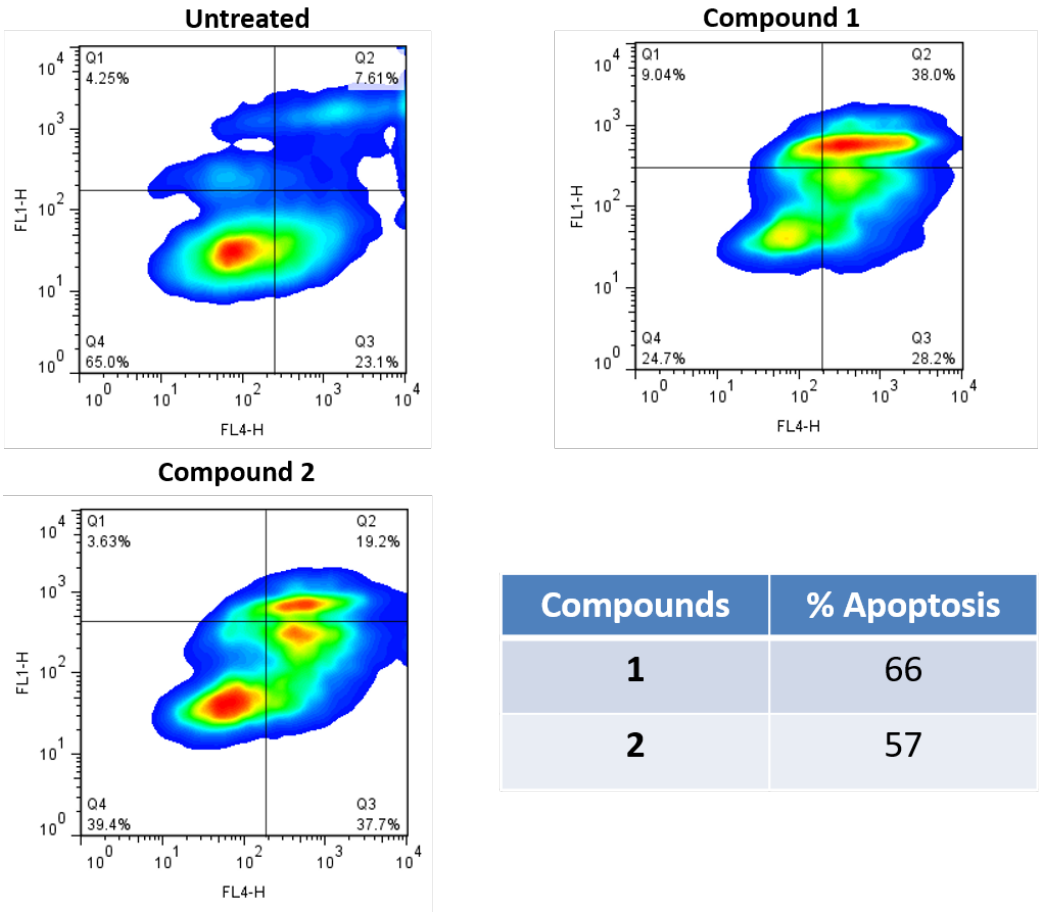


Figure S8. Histogram representing the different phases of the cell cycle for A2780 cells in the absence and presence of compounds **1** and **2** (4 μM) over the course of 24-72 h. Treatment of cells with **1** or **2** causes a significant increase in the G2/M phase compared to untreated control. Dead cells and cell debris were excluded from the cell cycle analysis.

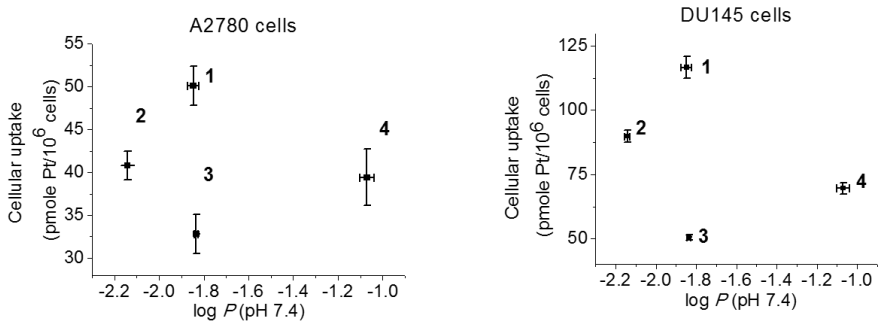


Compounds	% Apoptosis
1	66
2	57

Figure S9. APC Annexin V/Sytox flow cytometric analysis of A2780 cells untreated and treated with **1** and **2** (1 μM) for 72 h at 37 ^{0}C and 5% CO_2 atmosphere (FL1-H: Sytox; FL4-H: APC Annexin V). Apoptosis in the table refers to the sum of early and late stage apoptotic cells.

a)

Compounds	log*P* (pH 7.4)	A2780 (pmole Pt/10^6 cells)	DU145 (pmole Pt/10^6 cells)
1	−1.9±0.03	50.1±2.3	116.6±4.3
2	−2.1±0.01	40.8±1.7	89.8±2.3
3	−1.8±0.01	32.8±2.3	50.5±1.0
4	−1.0±0.03	39.4±3.4	69.6±2.2



b)

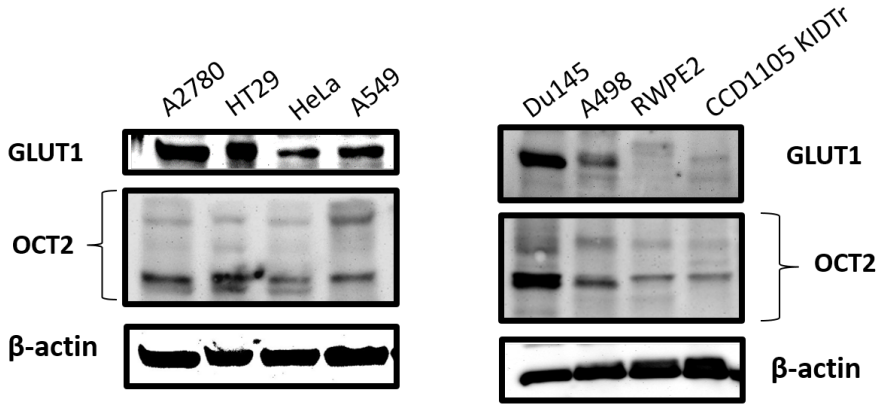


Figure S10. (a) Plot showing non-linear correlation between the log *P* values and cellular uptake of compounds **1**–**4** in A2780 (10 µM exposure concentration for 17 h) and DU145 (20 µM exposure concentration for 8 h). (b) Immunoblotting analysis of GLUT1 and OCT2 transporters expression level in A2780 (ovarian cancer), HT29 (colon cancer), HeLa (cervical cancer), A549 (lung cancer), DU145 (prostate cancer), A498 (kidney cancer), and RWPE2 (prostate epithelial), CCD1105 KIDTr (kidney epithelial) cells. Whole cell lysates were resolved by SDS-PAGE and analyzed by immunoblotting against either GLUT1 or OCT2 and β–actin (loading control).

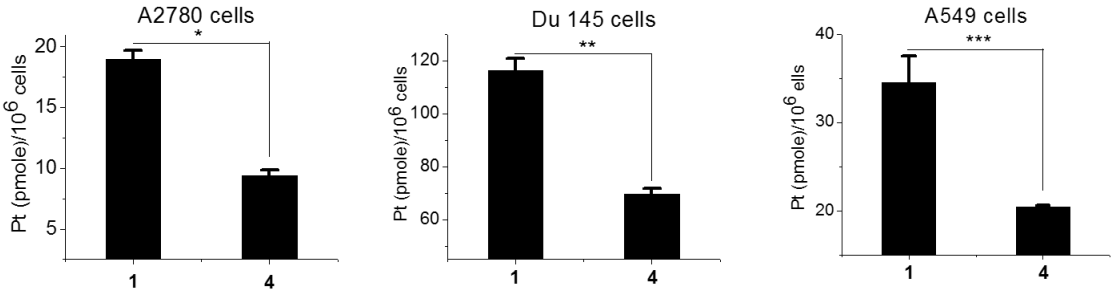


Figure S11. Differences in the cellular uptake of **1** and **4** in A2780 (10 μM exposure concentrations), A549 (20 μM exposure concentrations), and DU145 (20 μM exposure) cells in an 8 h incubation assay. Accumulation of **1** is significantly higher than **4** in all the three cell lines, despite **4** is more lipophilic compared to **1** by one log *P* unit. Data represent the mean ± SD of at least three or more replicates. The asterisks denote differences are statistically significant (**P* < 0.02, ***P*< 0.01, ****P* < 0.02).

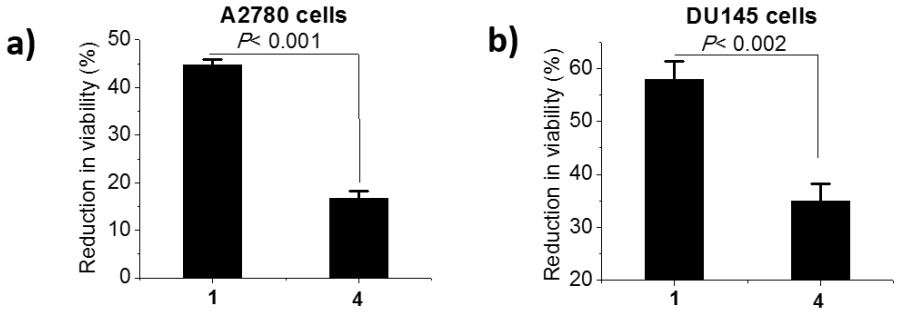
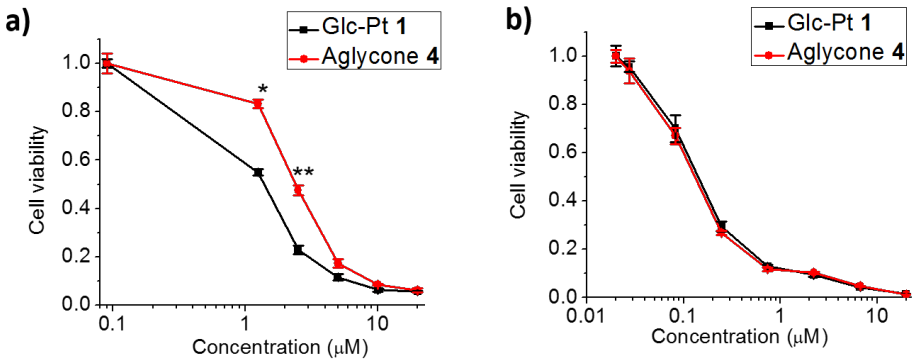


Figure S12. Differences in the potency of **1** and **4** in DU145 (20 μM exposure) and A2780 (1.25 μM exposure concentrations) cells. Cells were incubated with compounds for 8 h, followed by fresh media for 72 h. The viability was determined using MTT assay. Data represent the mean ± SD of six replicates.



c)

Incubation time	1 (pmole Pt/10^6 cells)	4 (pmole Pt/10^6 cells)	Differences in uptake relative to 1 (%)
8 h	19±0.7	9.4±0.5	50.5
17 h	50±2.3	39.4±5.3	21.2

Figure S13. (a and b) Dose response curves showing the effect of incubation time of **1** and **4** on the viability of A2780 cells. (c) Comparison of cellular uptake of **1** and **4** in an 8 h and a 17 h assays (A2780 cells, 10 μM exposure concentrations). In (a), cells were incubated with different concentrations of **1** and **4** for 8 h and then incubated in fresh media for 72 h. In (b), cells were incubated with different concentrations of **1** and **4** continuously for 72 h (conventional cytotoxicity assay). The viability was determined using MTT assay. Data represent the mean ± SD of six replicates. The asterisks denote differences are statistically significant (* & ** $P <$ 0.001). As shown in (a), there are no significant differences in the potencies of **1** and **4** when cells were incubated with compounds for 72 h. However, as shown in (b), when cells were incubated with compounds for 8 h and then with fresh media for 72 h, there are statistically significant differences in the potencies (differences are prominent at 1.25 and 2.5 μM compound concentrations) of **1** and **4**. Results suggest that the initial rate of accumulation of **1** in cells is faster than **4** and saturation was reached after certain time. Therefore it is reasonable to speculate that prolonged incubation (72) with **1** and **4** resulted in almost equal concentration of **1** and **4** in the cells and no differences in potencies observed. Indeed, as shown in (c), the differences between the uptake of **1** and **4** reduces with increasing incubation time.

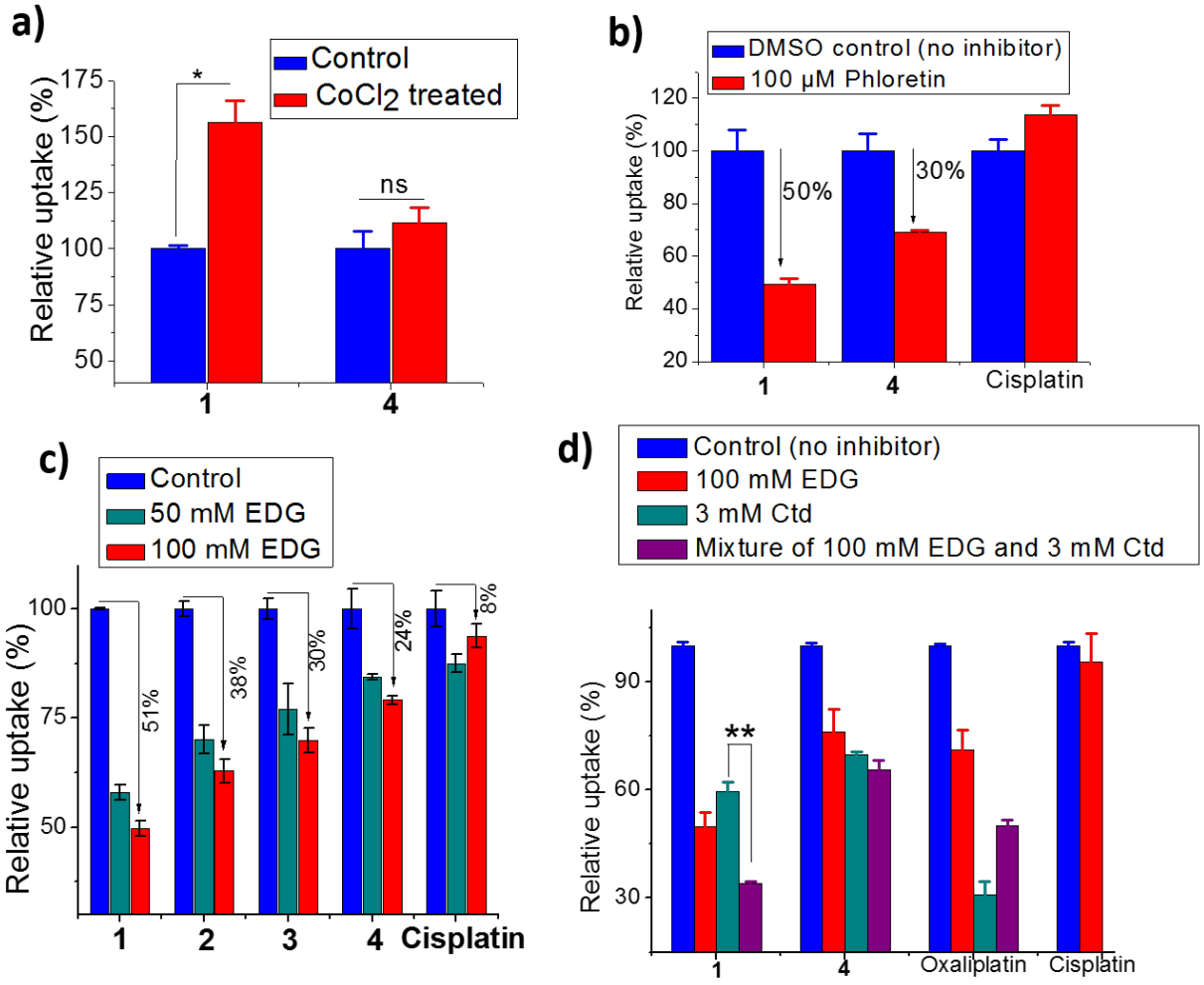


Figure S14. (a) Effect of chemical hypoxia inducing agent cobalt chloride on the cellular uptake of Glc-Pt **1** and aglycone **4** in A549 cells.[17] Cells were treated without or with 0.4 mM $CoCl_2$ for 24 h prior to the cellular uptake study (concentration of **1** and **4**, 20 μM, incubation 5 h). (b) Effect of GLUT1 inhibitor phloretin on the uptake of **1**, **4** and cisplatin (10 μM compounds, 17 h) in A2780 cells. (c) Effect of GLUT1 inhibitor 4,6-*O*-ethylidene-α-D-glucose (EDG) on the uptake of **1-4** and cisplatin in A2780 cells (10 μM compounds, 17 h incubation). (d) Effect of EDG, Cimetidine (Ctd), and their mixture on the cellular uptake of **1** **4**, and oxaliplatin (used as positive control for OCT2 transporter mediated uptake) in A2780 cells (10 μM compounds, 8 h incubation). Cellular uptake for the untreated controls were normalized to 100%. Data represent the mean ± SD of at least three or more replicates. The asterisks denote differences are statistically significant (*$p < 0.01$, **$p < 0.001$).

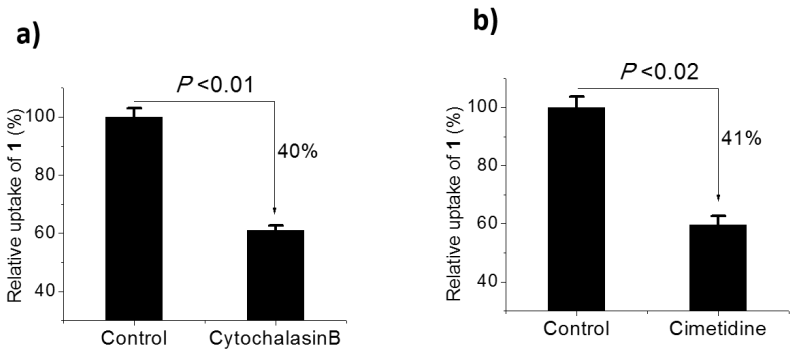


Figure S15. (a) Cellular uptake inhibition of **1** by GLUT1 inhibitor cytochalasin B (100 μM) in DU145 cells (50 μM **1**, 2 h incubation). (b) Cellular uptake inhibition of **1** by OCT2 inhibitor cimetidine (2 mM) in DU145 cells (25 μM **1**, 5 h incubation). The weak inhibition of cellular uptake by cytochalasin B is most likely due to the fact that we needed to use a relatively high concentration of compound **1** (50 μM**)** in order to have detectable amount of platinum inside the cells after two hours incubation.

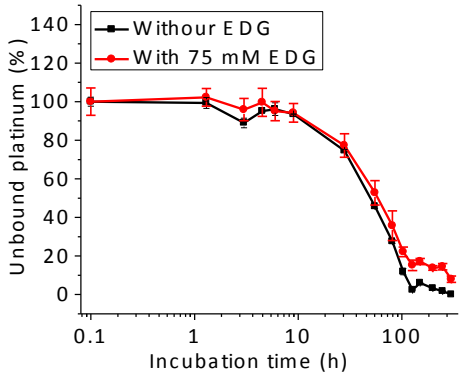


Figure S16. Percentage unbound platinum at various time points after exposure of ct-DNA (700 μM) to Glc-Pt **1** (20 μM). The ligand dissociation/DNA binding of 1 did not alter in the presence of 75 mM GLUT1 inhibitor 4,6-O-ethylidene-α-D-glucose (EDG).

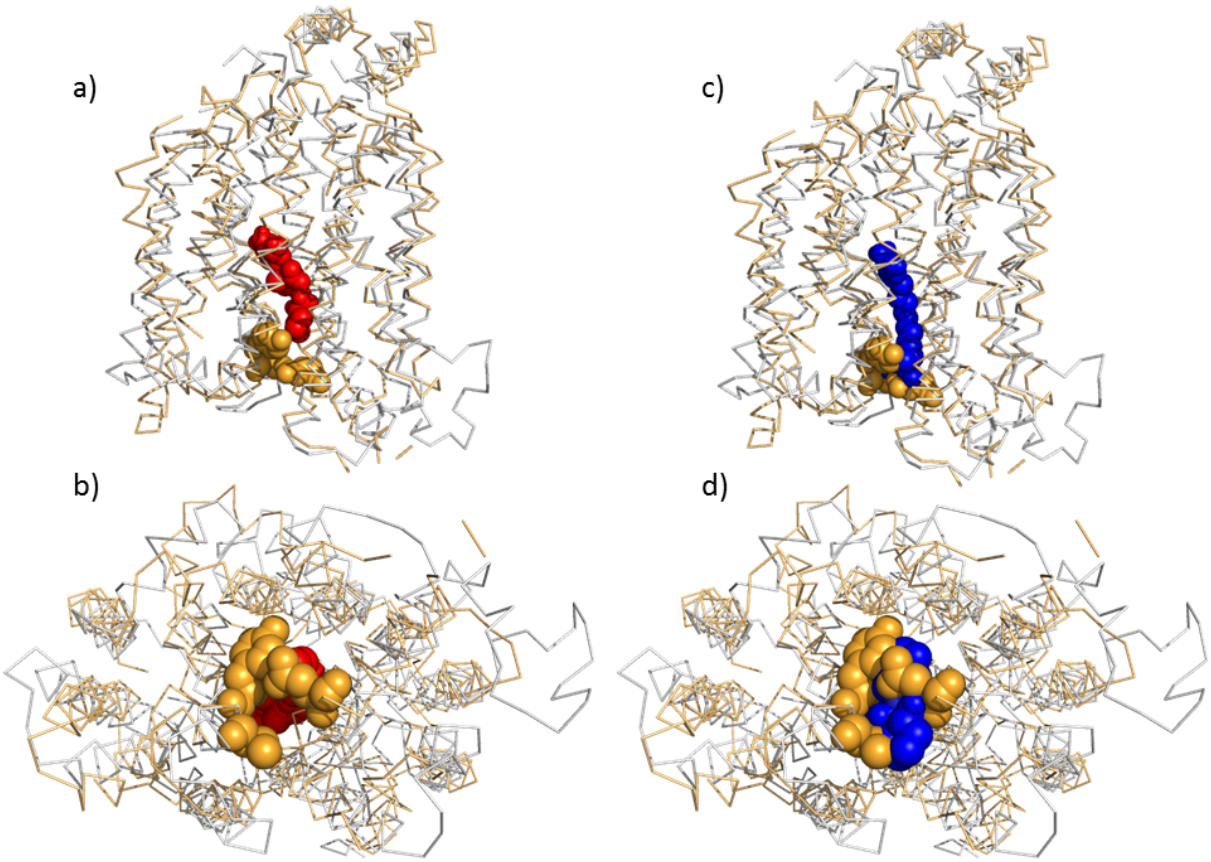


Figure S17. Side-on (a,c) and bottom (b,d) depictions of the steric interactions that inhibit translocation of the long-linker platinum conjugates. **1** (red spheres) and **3** (blue spheres) docked in the outward open XylE structure (PDB 4GBZ; grey ribbon).[Sun, 2012 #1164] Aligned with the XylE structure is the GLUT1 structure in the inward open conformation (PDB 4PYP; orange ribbon).[18] The side chains of the inward open GLUT1 residues that occlude the opening to the outside of the cell are shown as orange spheres. In c) and d) significant steric clashes are evident between residues and **3**. As shown in a) and b), such clashes do not occur with **1**.

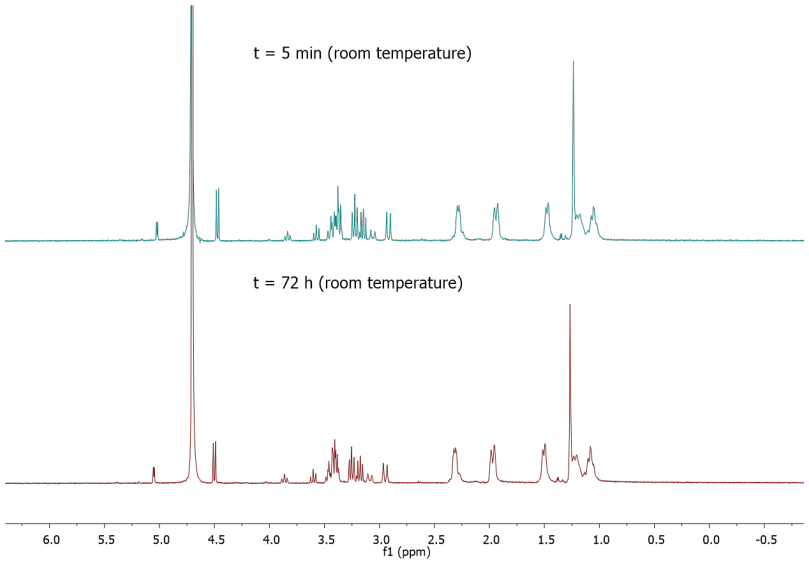


Figure S18. ^{1}H NMR spectra of **1** measured immediately after dissolving in D_2O (top) and after 72 h (bottom).

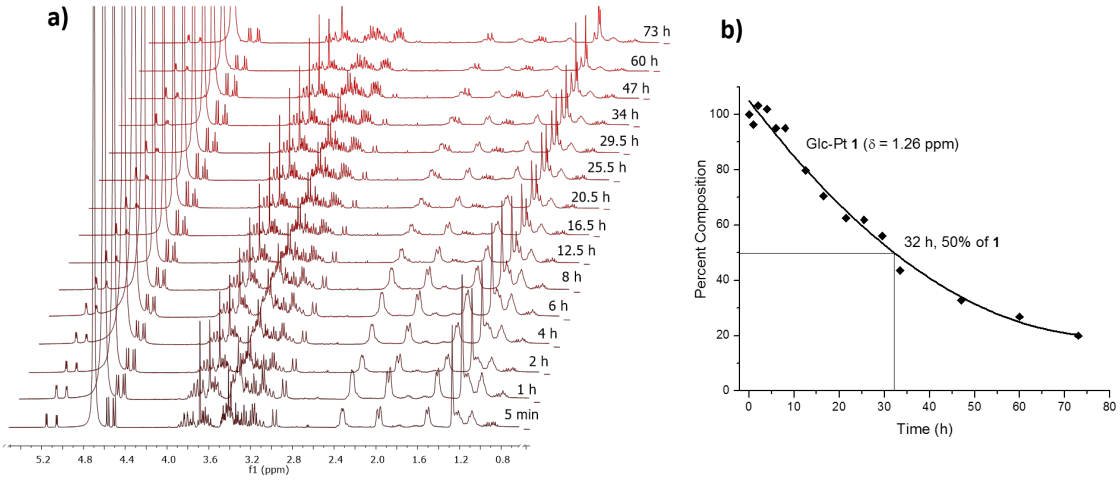


Figure S19. (a) ^{1}H NMR spectra of **1** incubated in RPMI-D_2O media (37 °C) at different time points. 1,4 Dioxane was introduced as internal standard. **(b)** Plot of integration of the peak at δ = 1.26 ppm (C*H*$_3$ of **1**) relative to the internal standard at different time points. RPMI-D_2O solvent for NMR study was prepared as follows. The RPMI 1640 cell culture medium (5 mL) (L-glutamine and phenol red free, from corning cellgro) was removed by lyophilization. The resulting white powder was dissolved in 5 mL D_2O to provide a RPMI-D_2O solution for NMR study of **1** in biologically relevant solution.

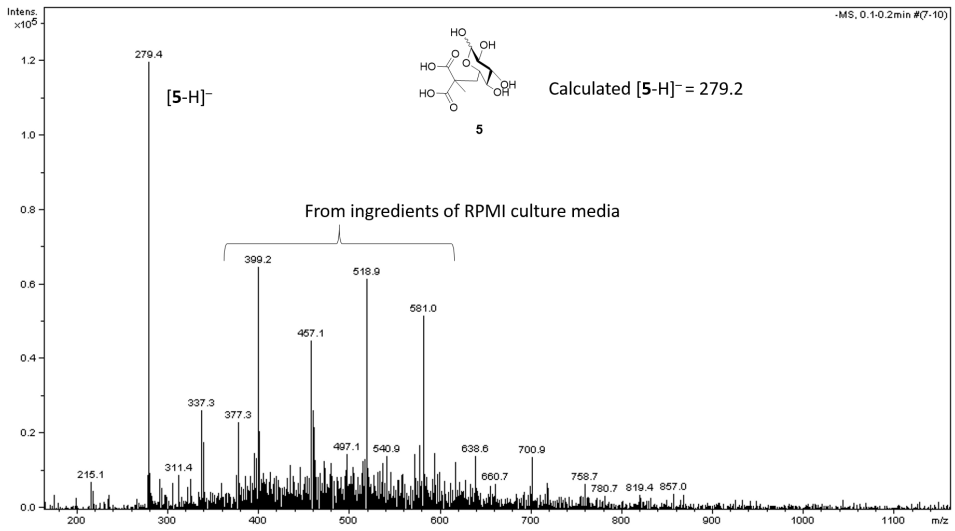


Figure S20. ESI-mass spectrum of **1** in RPMI-D_2O after incubating for 73 h at 37 ^{0}C, showing the release of leaving group **5** from the platinum center of **1**.

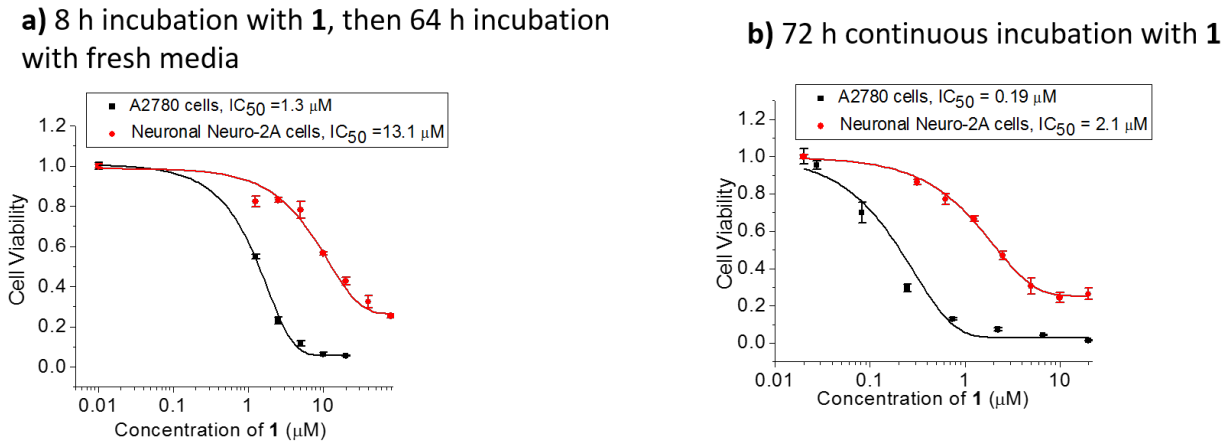


Figure S21. Representative examples of dose response curves showing the effect of **1** on the viability of ovarian cancer A2780 cells and mouse neuronal Neuro-2A cells in an 8 h (a) and 72 h (b) incubation assay.

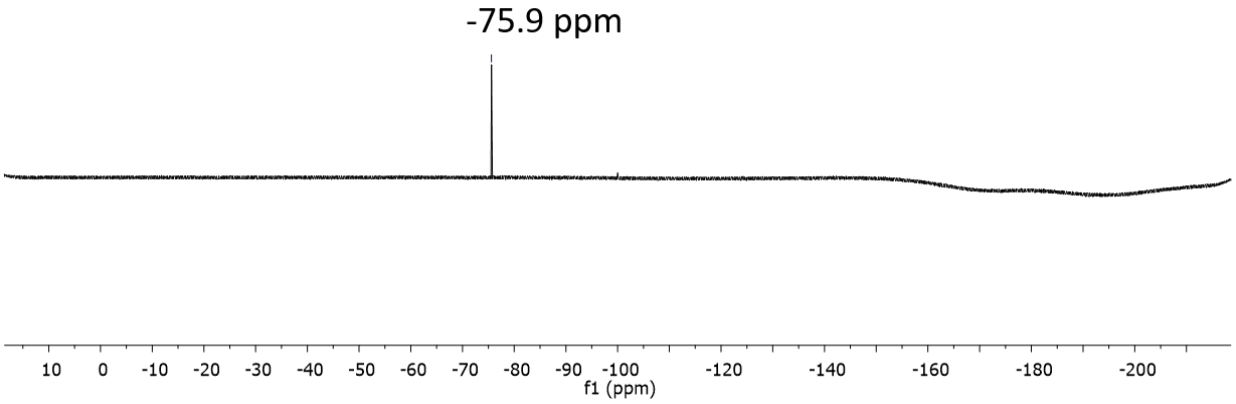
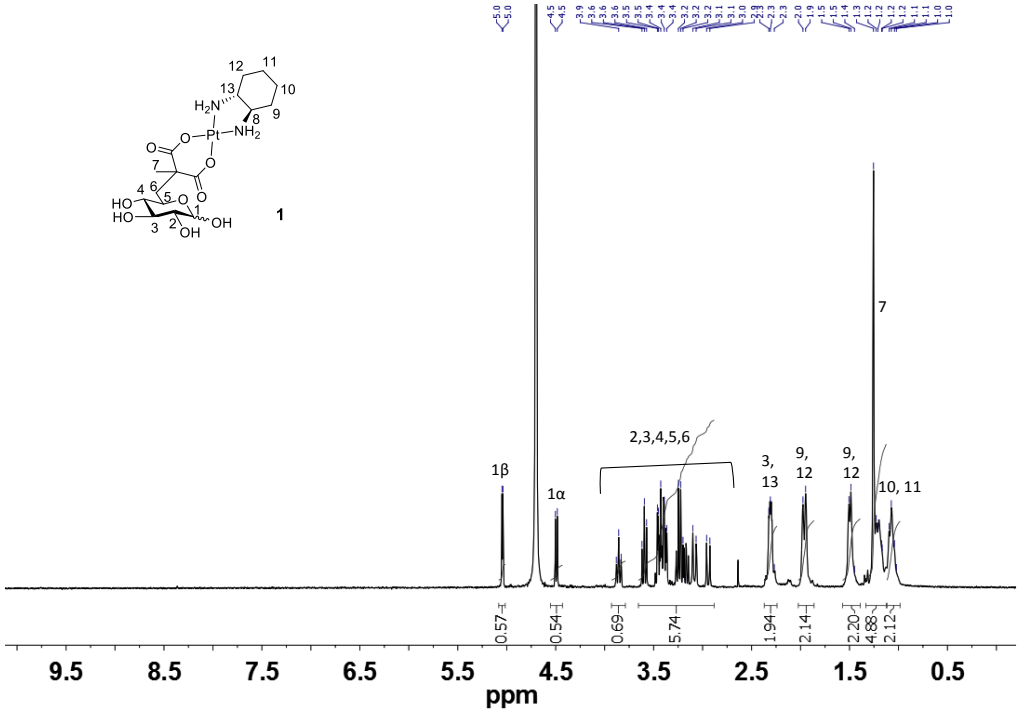


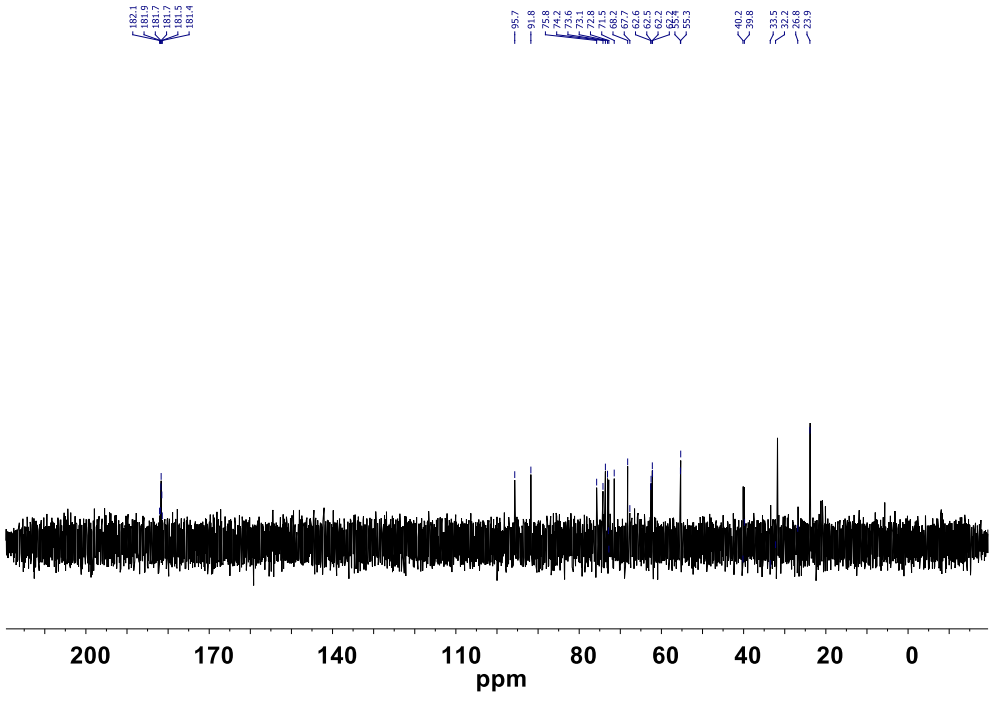
Figure S22. ^{19}F NMR spectrum of **1** in D_2O showing the presence of residual trifluoroacetic acid.

NMR spectra of compounds.

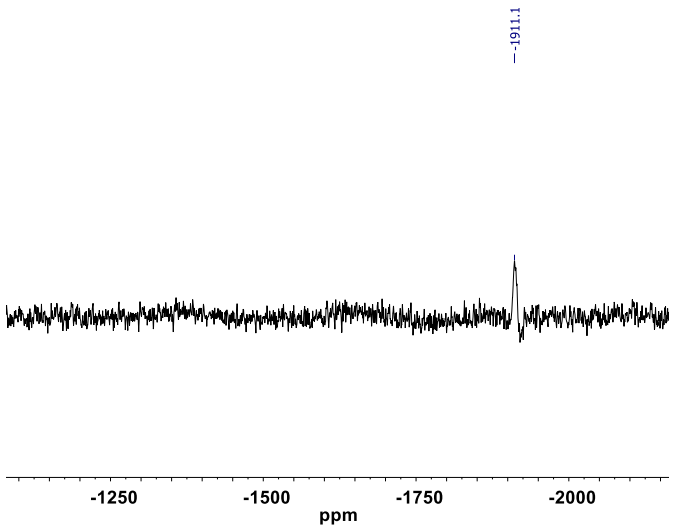
^{1}H, D_2O, 400 MHz



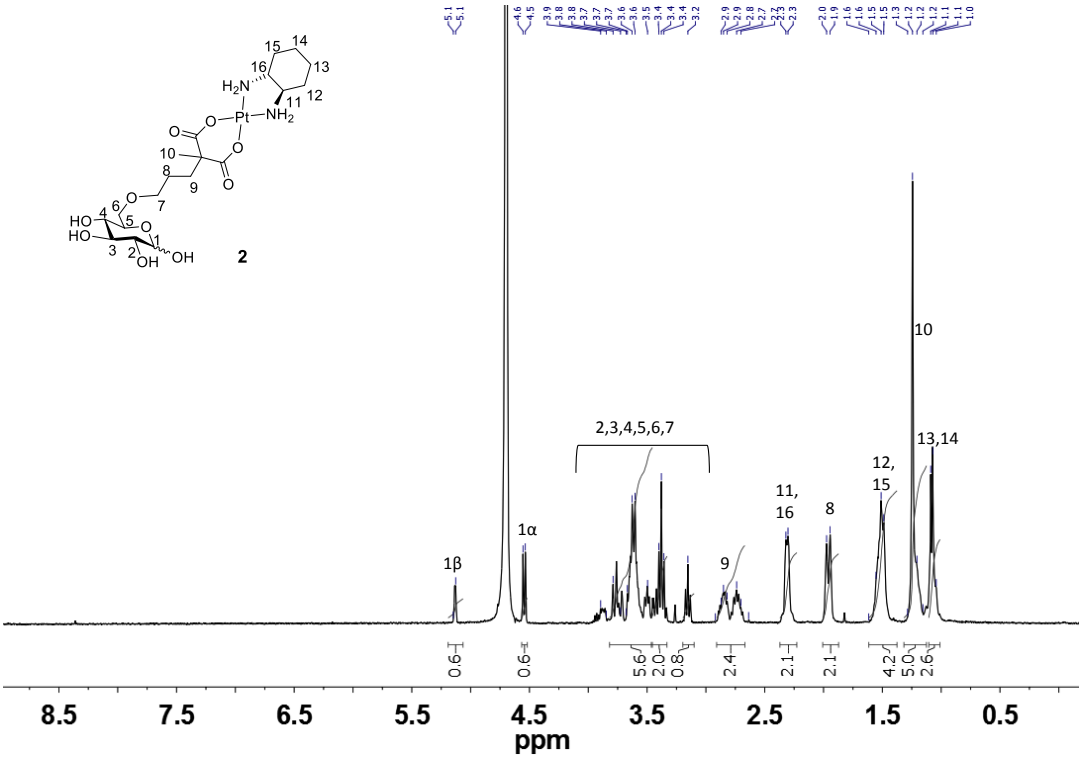
^{13}C{^{1}H}, D_2O, 100 MHz



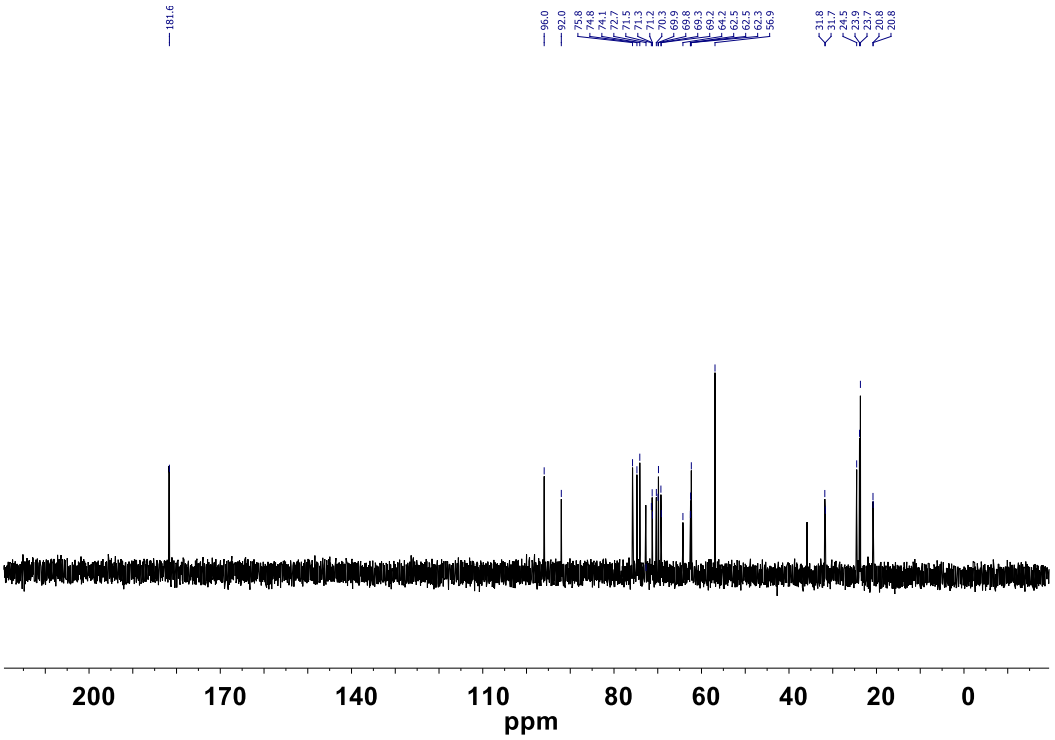
$^{195}Pt\{^{1}H\}$, D_2O, 86 MHz



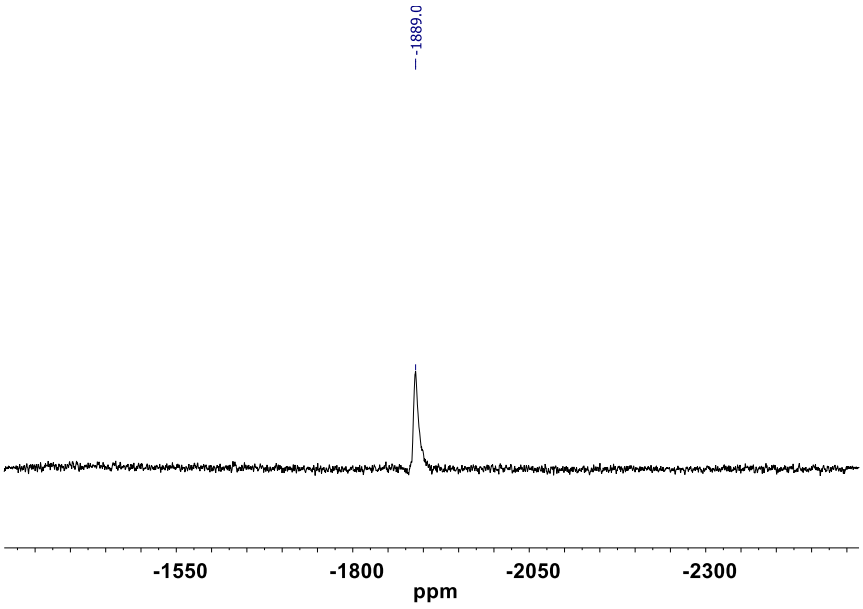
^{1}H, D_2O, 400 MHz



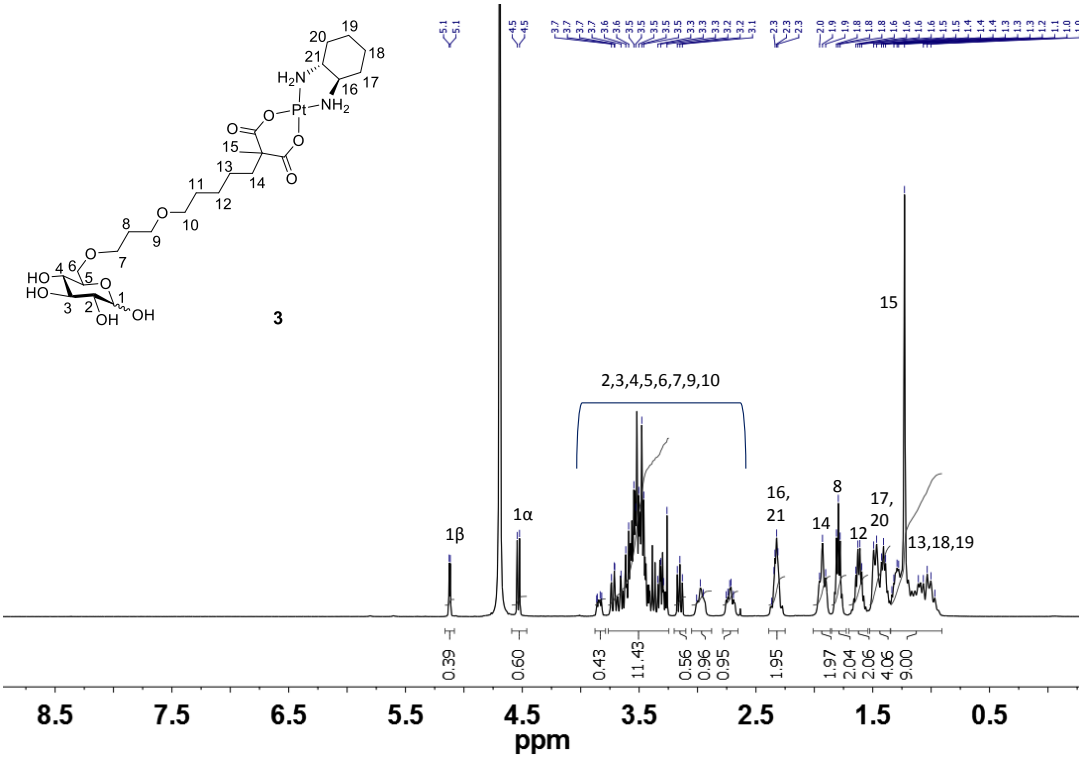
$^{13}C\{^{1}H\}$, D_2O, 100 MHz



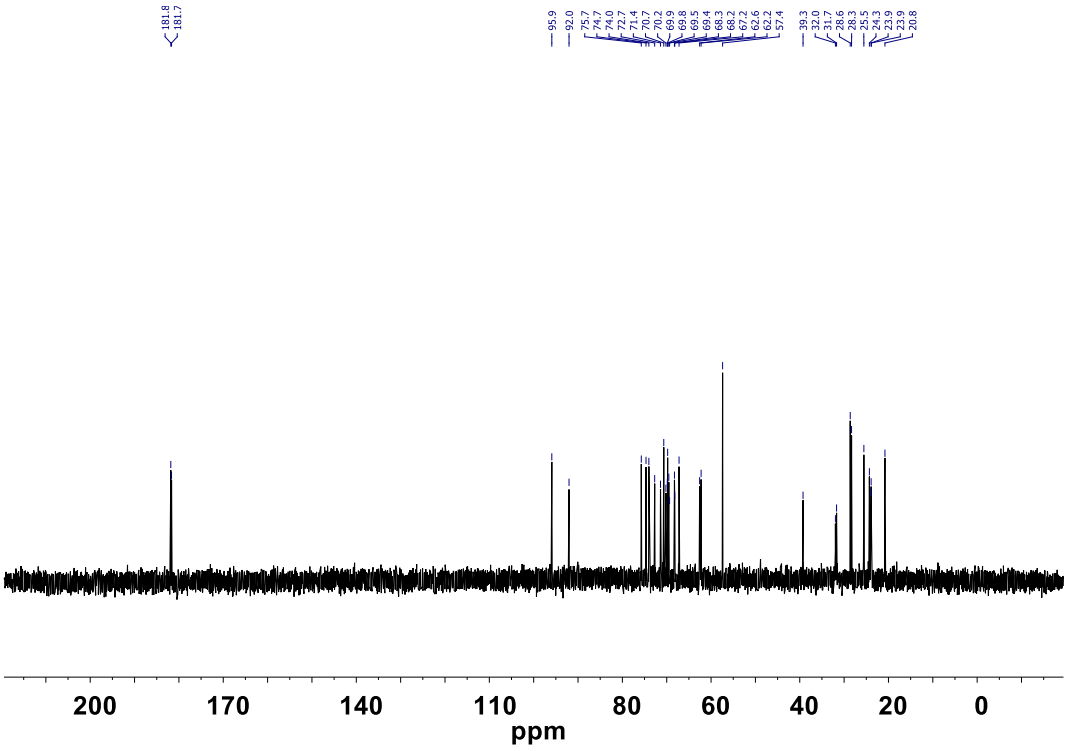
$^{195}Pt\{^{1}H\}$, D_2O, 86 MHz



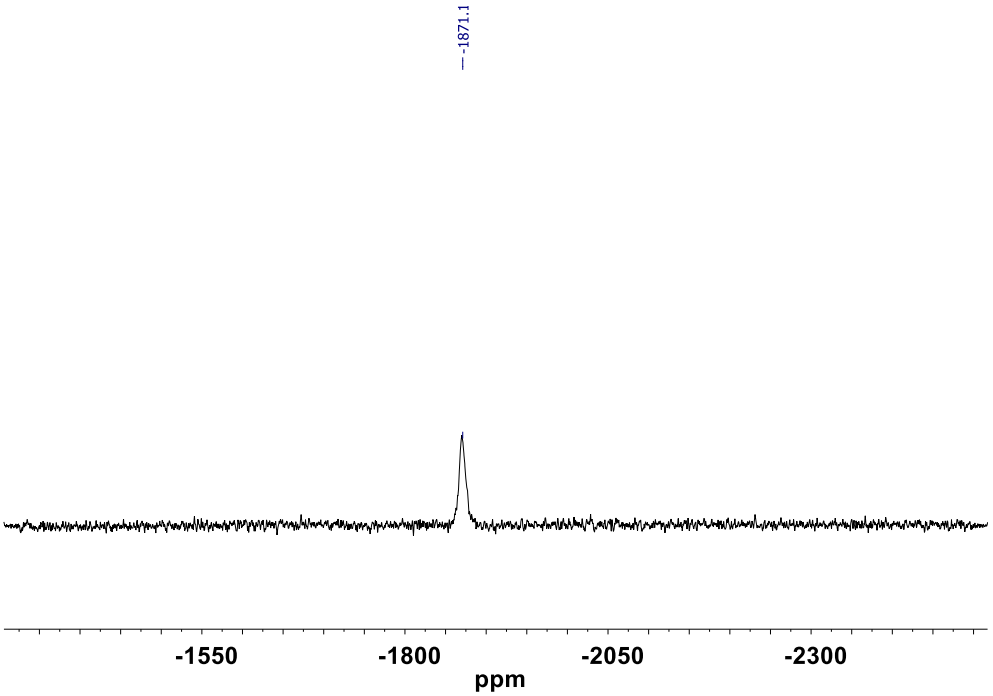
^{1}H, D_2O, 400 MHz



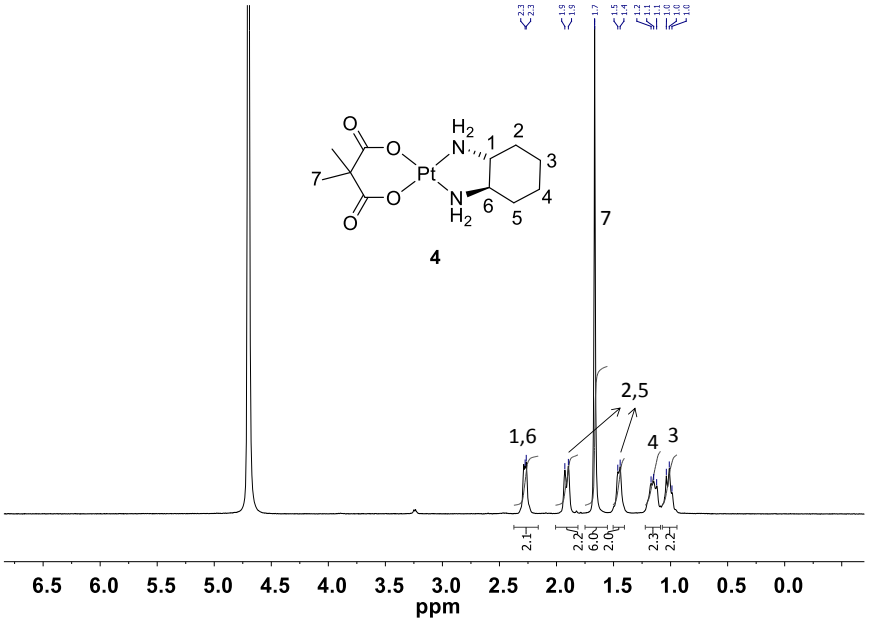
^{13}C{^{1}H}, D_2O, 100 MHz



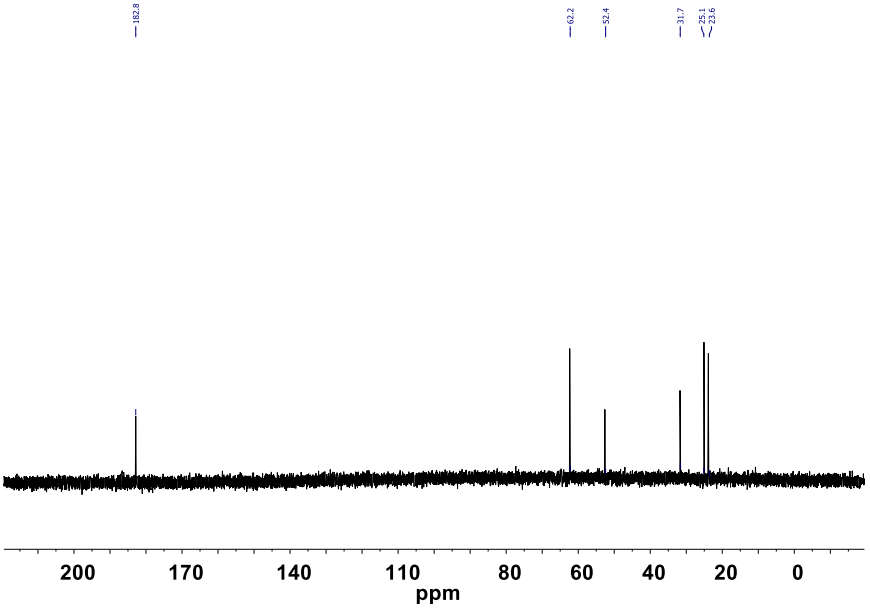
$^{195}Pt\{^{1}H\}$, D_2O, 86 MHz



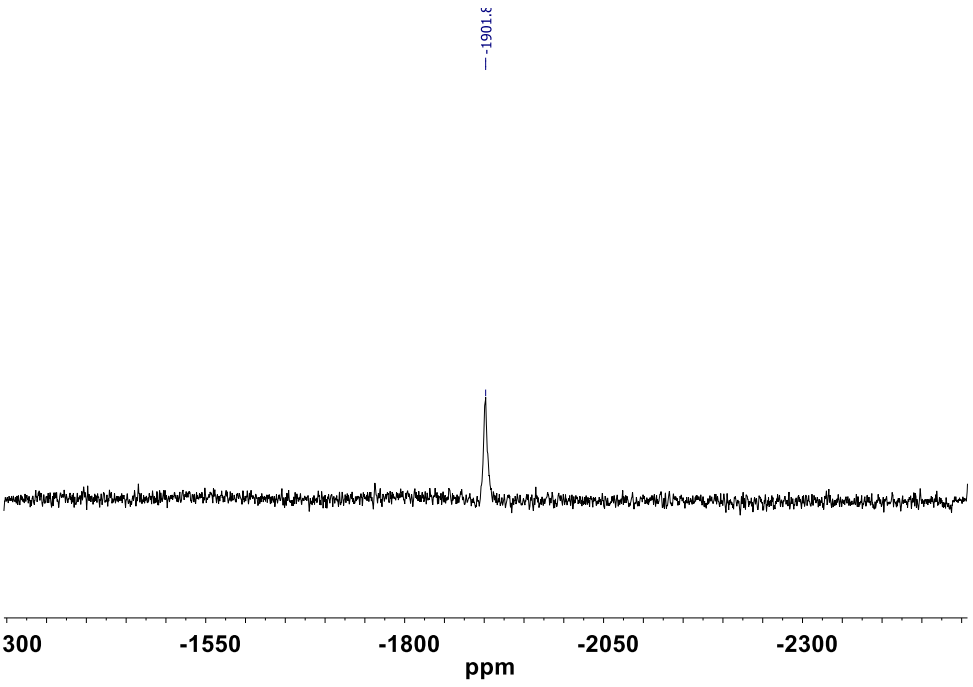
^{1}H, D_2O, 400 MHz

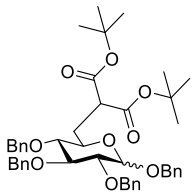


$^{13}C\{^{1}H\}$, D_2O, 100 MHz



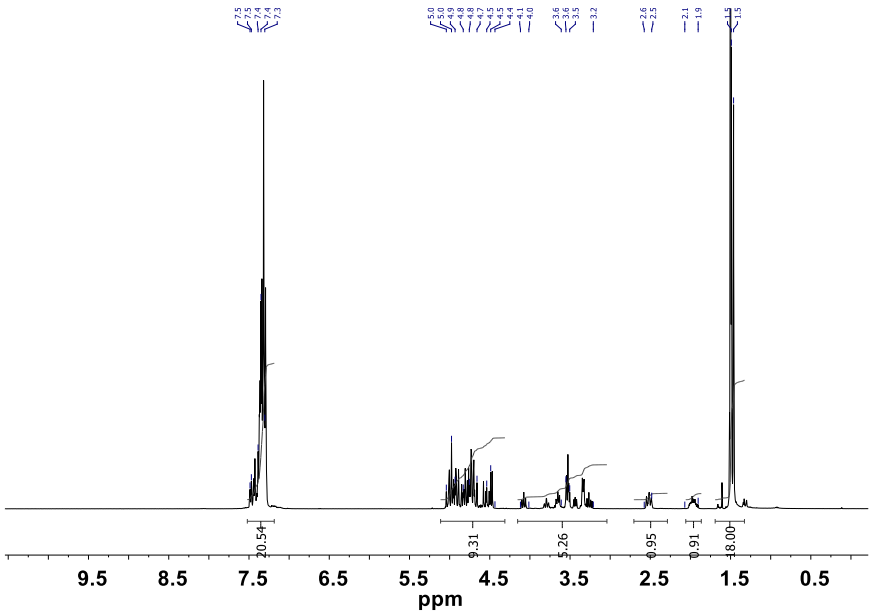
$^{195}Pt\{^{1}H\}$, D_2O, 86 MHz



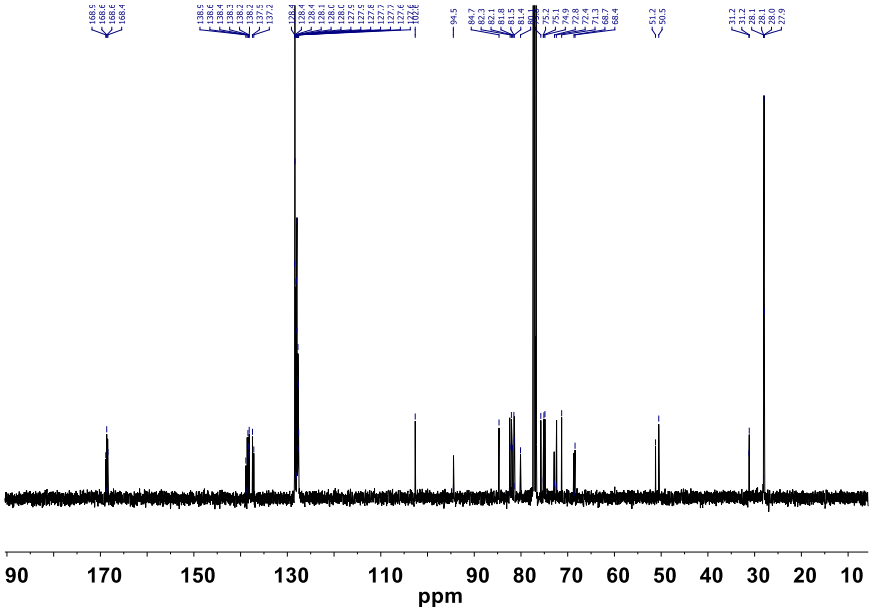


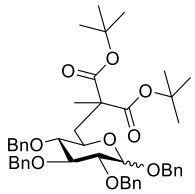
10

^{1}H, $CDCl_3$, 400 MHz



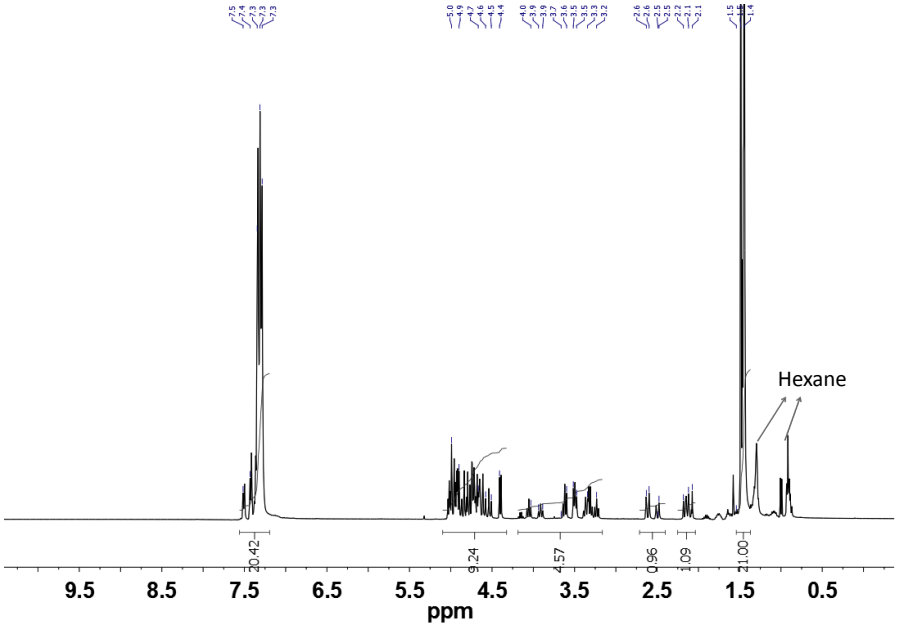
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



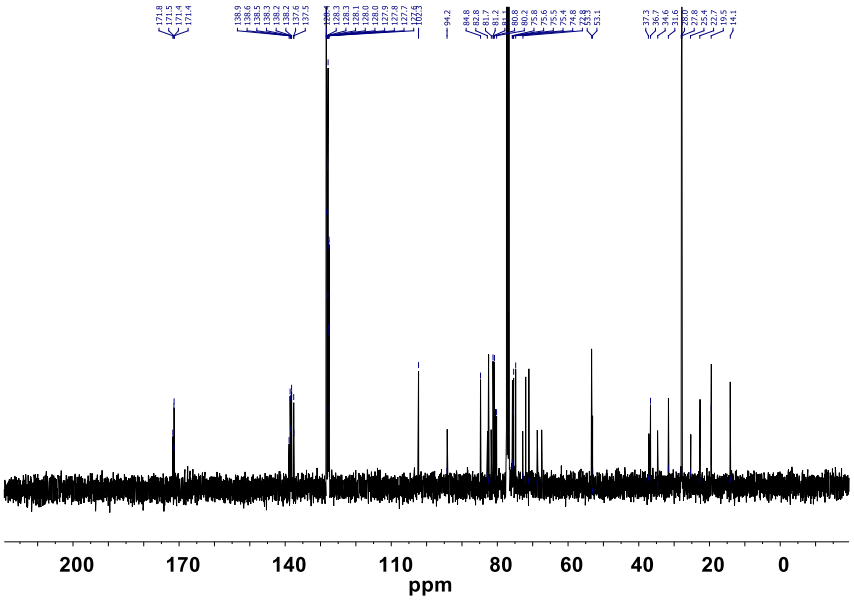


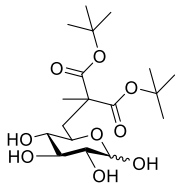
11

^{1}H, $CDCl_3$, 400 MHz



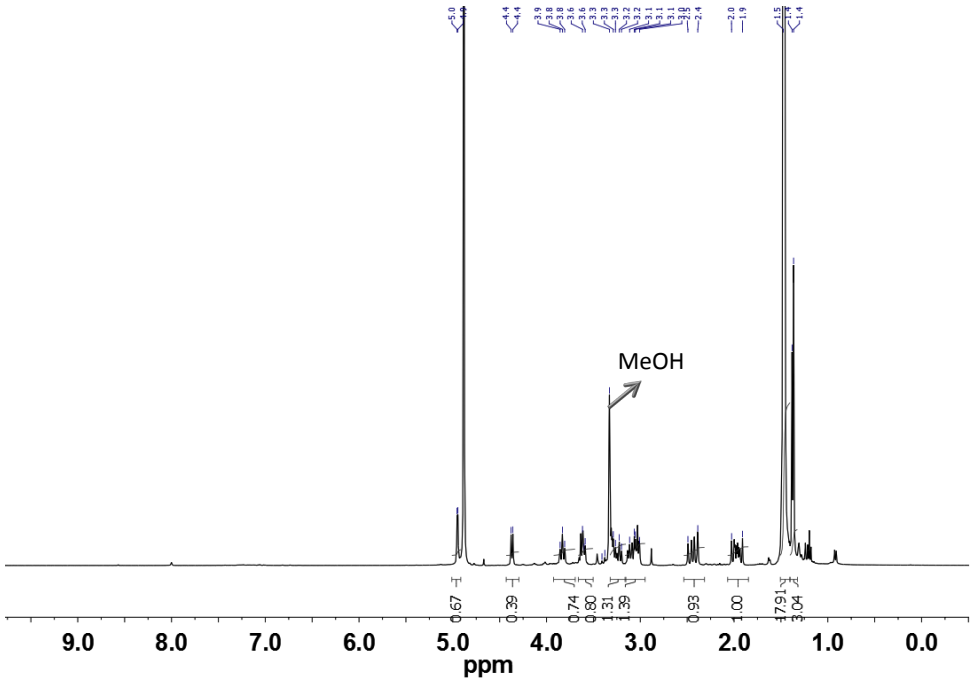
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



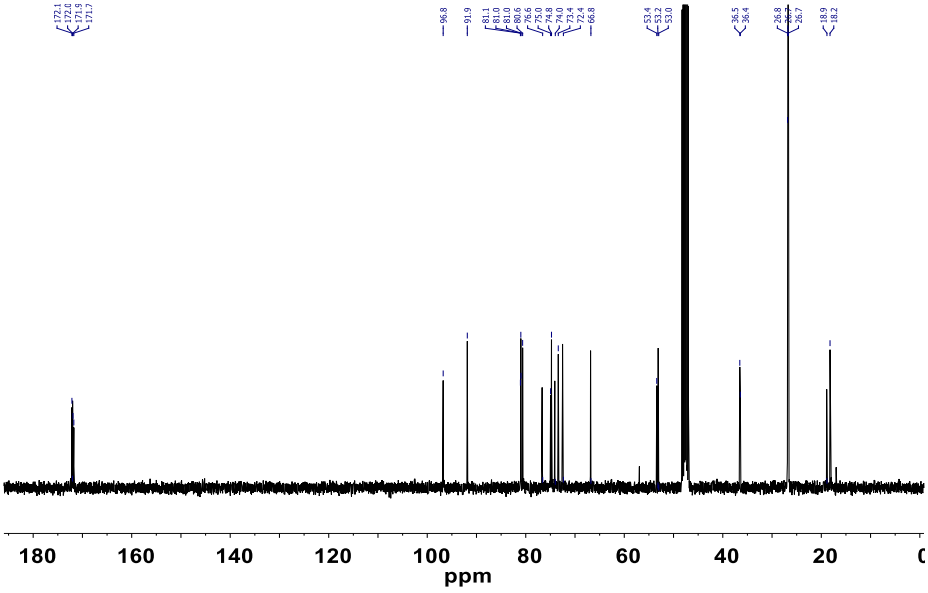


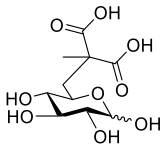
12

^{1}H, CD_3OD, 400 MHz



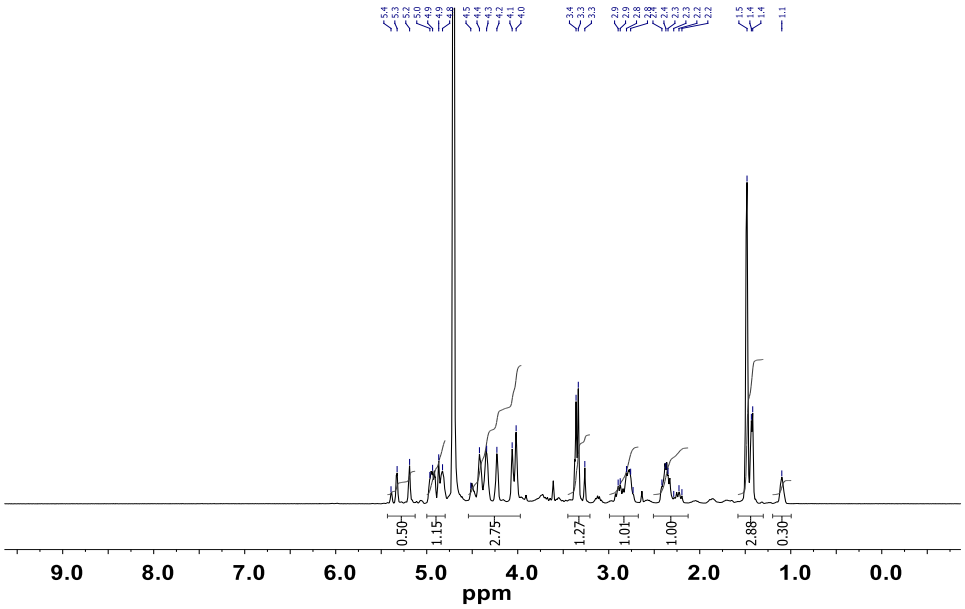
^{13}C{^{1}H}, CD_3OD, 100 MHz



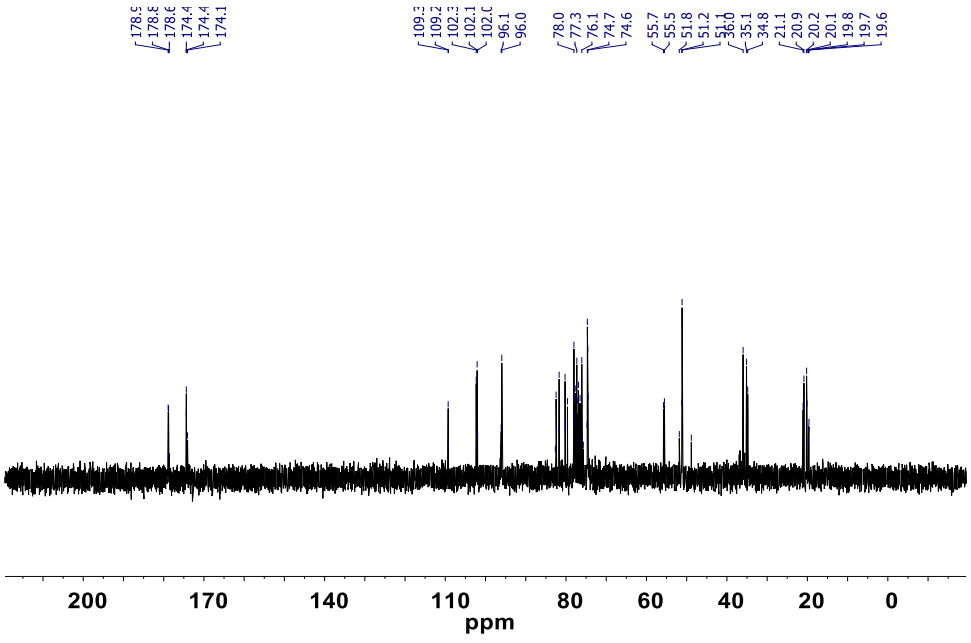


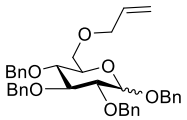
5

^{1}H, D_2O, 400 MHz



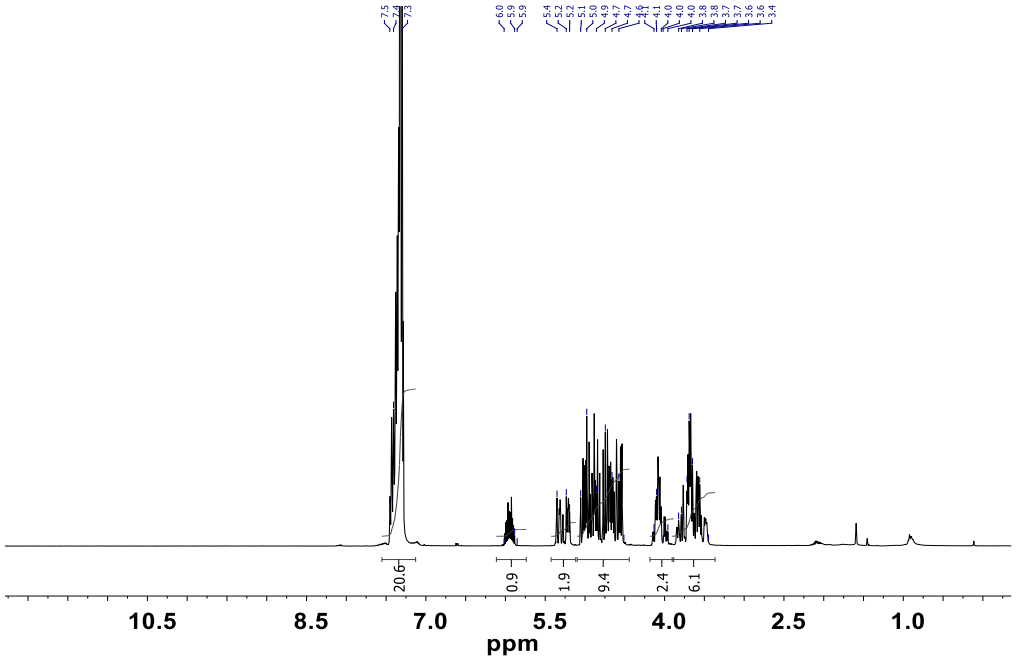
^{13}C{^{1}H}, D_2O, 100 MHz



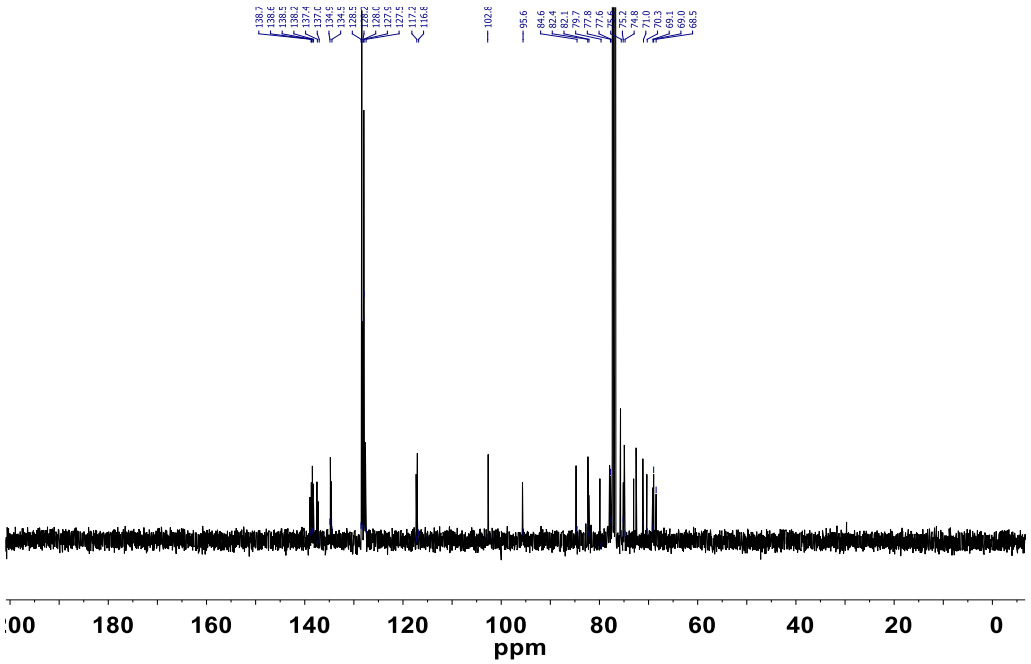


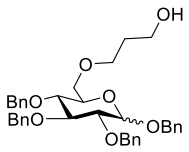
13

^{1}H, $CDCl_3$, 400 MHz



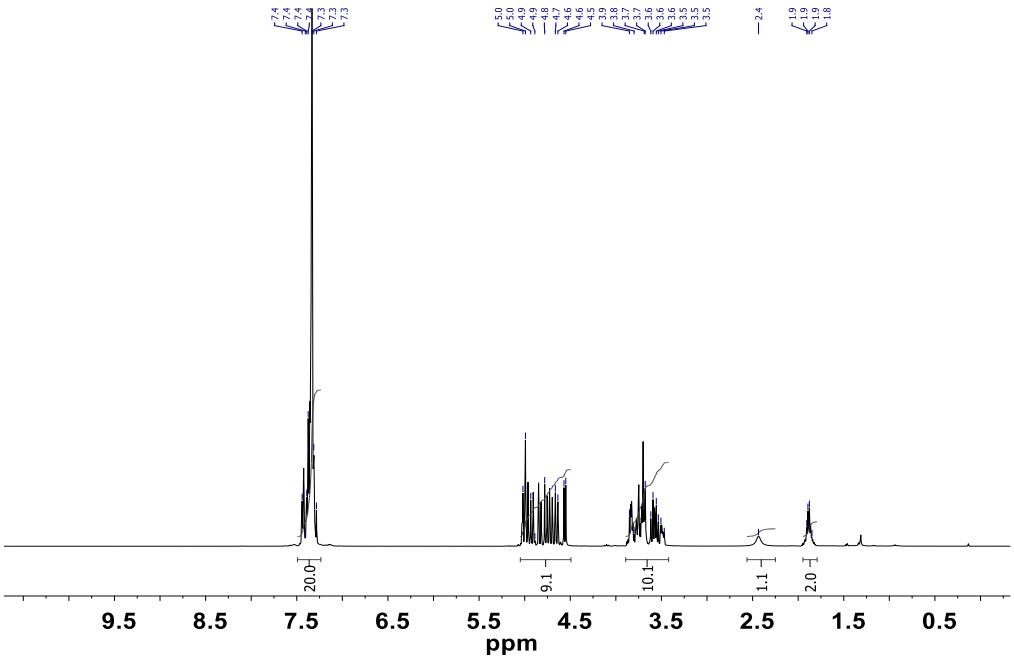
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



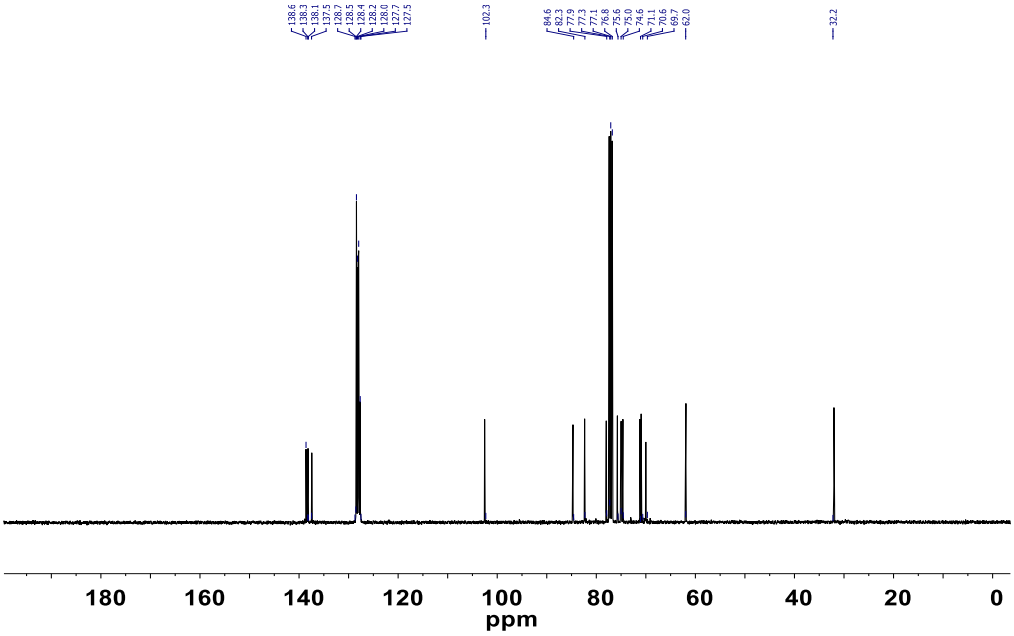


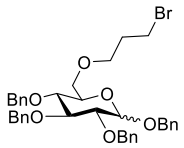
14

^{1}H, $CDCl_3$, 400 MHz



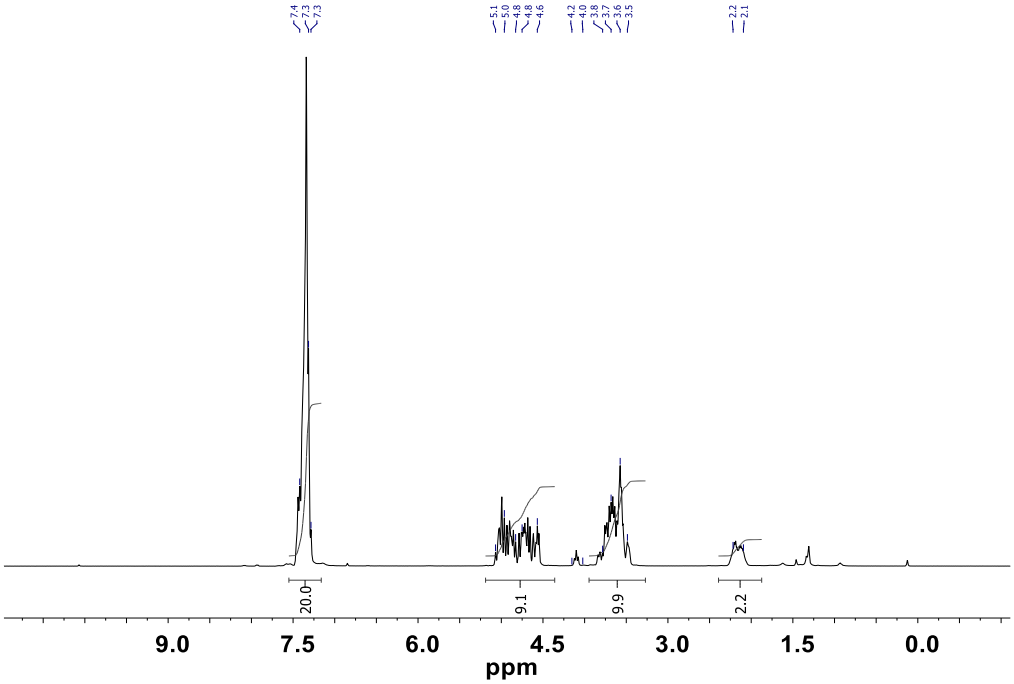
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



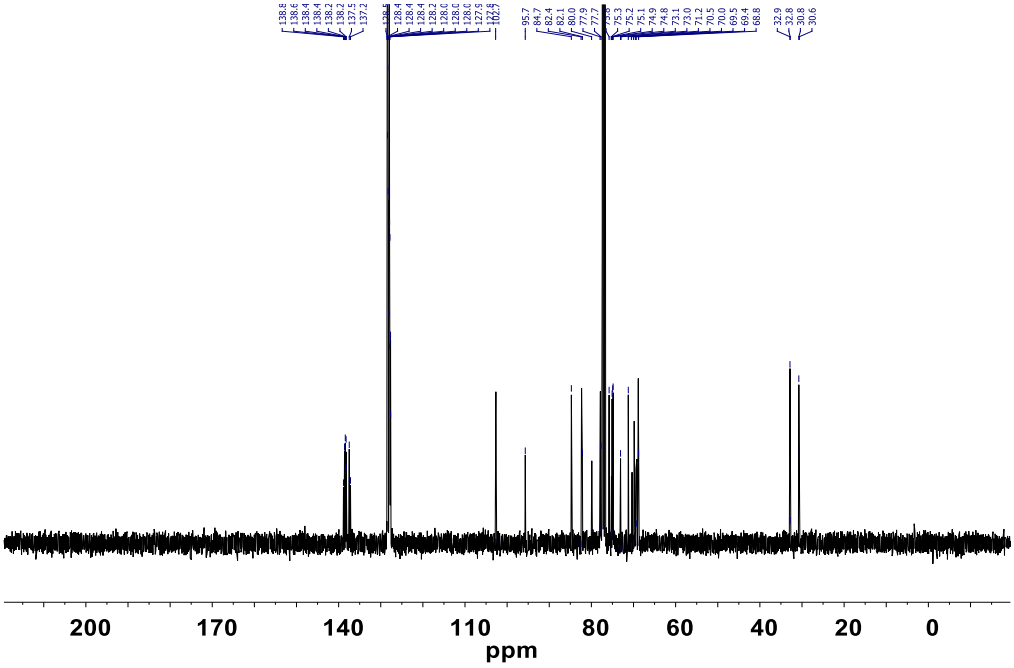


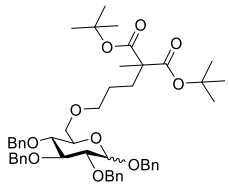
15

^{1}H, $CDCl_3$, 400 MHz



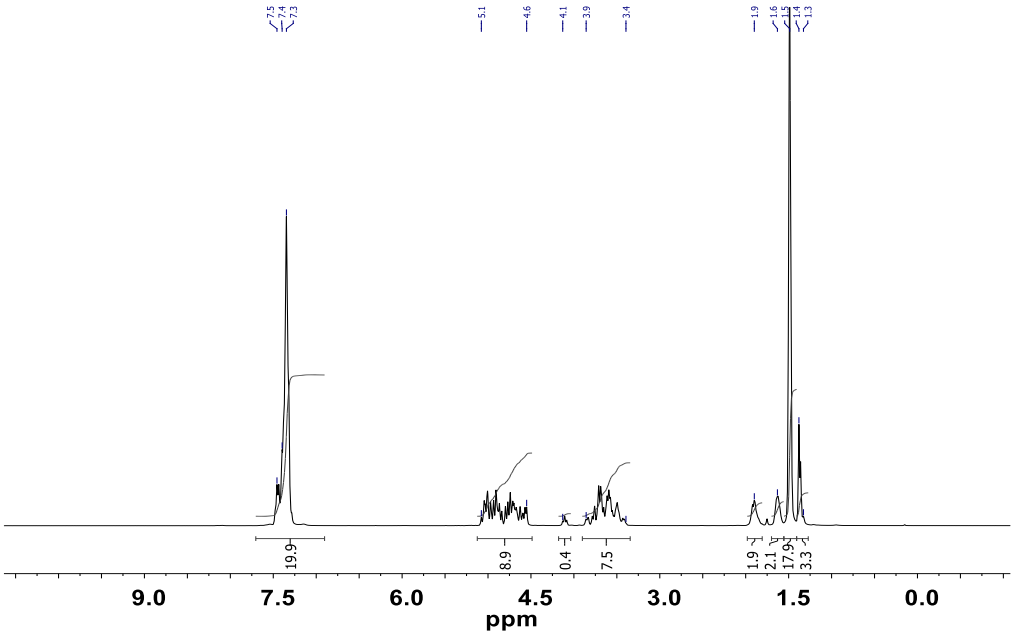
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



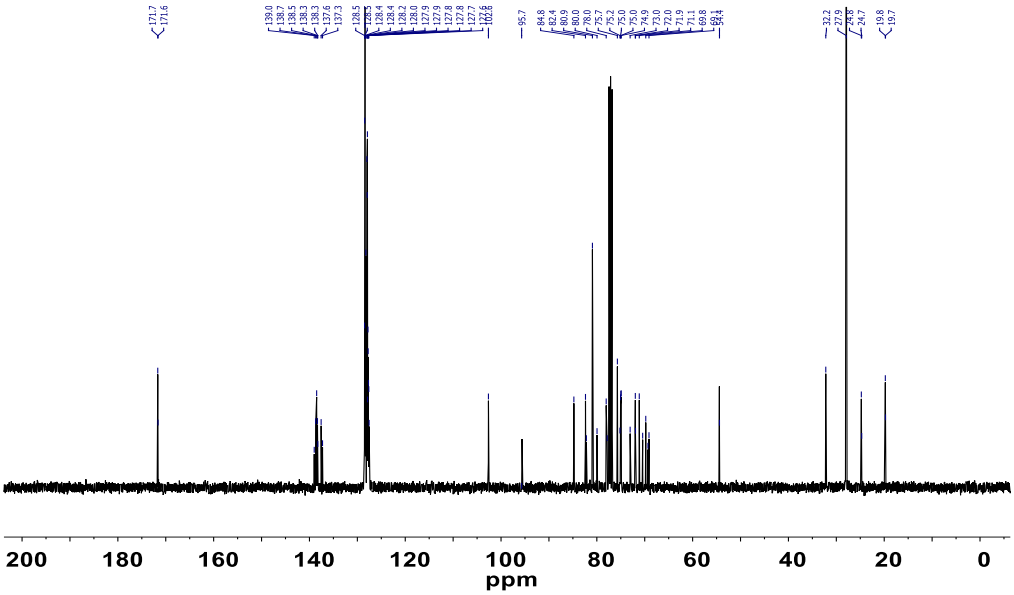


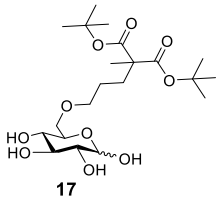
16

^{1}H, $CDCl_3$, 400 MHz

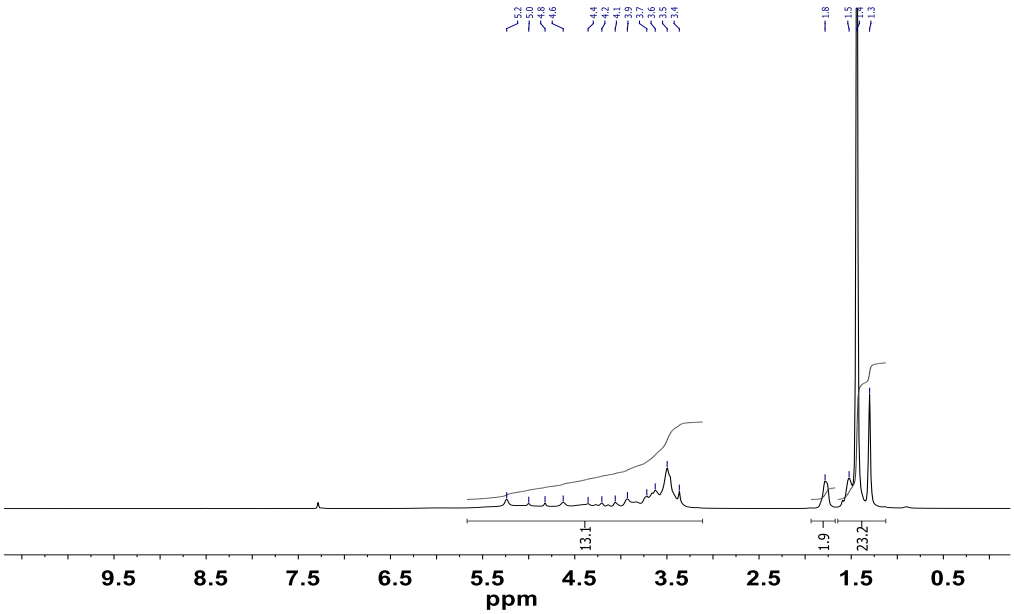


^{13}C{^{1}H}, $CDCl_3$, 100 MHz

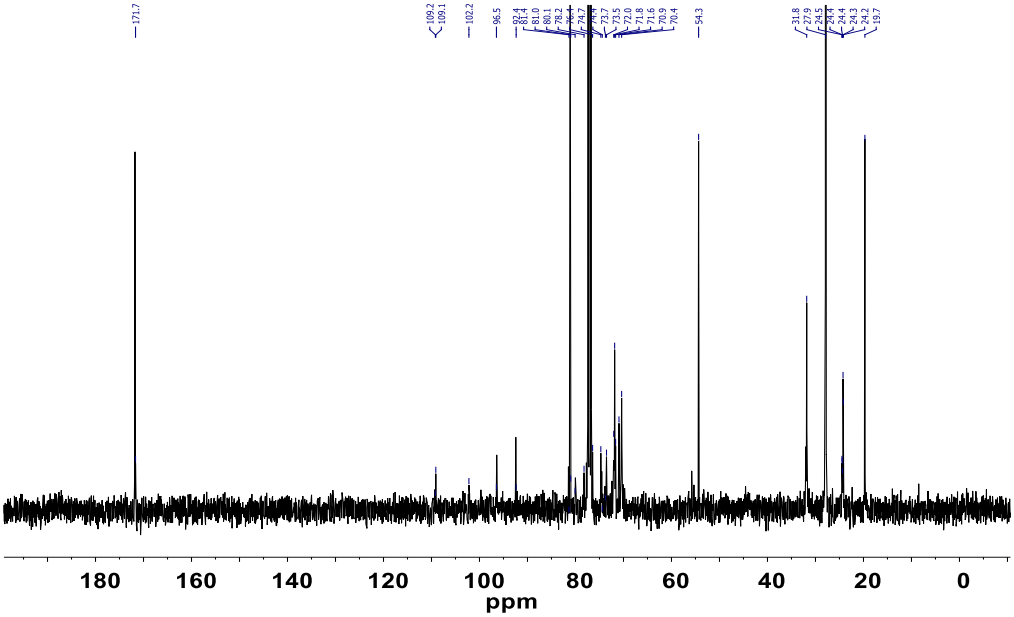


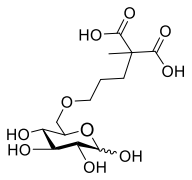


^{1}H, $CDCl_3$, 400 MHz



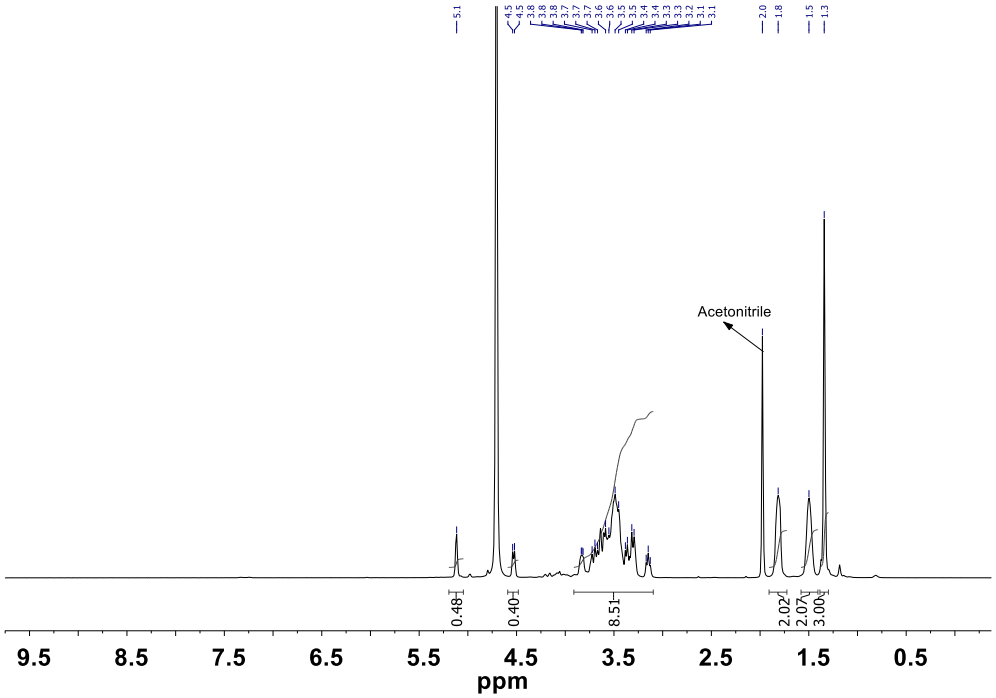
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



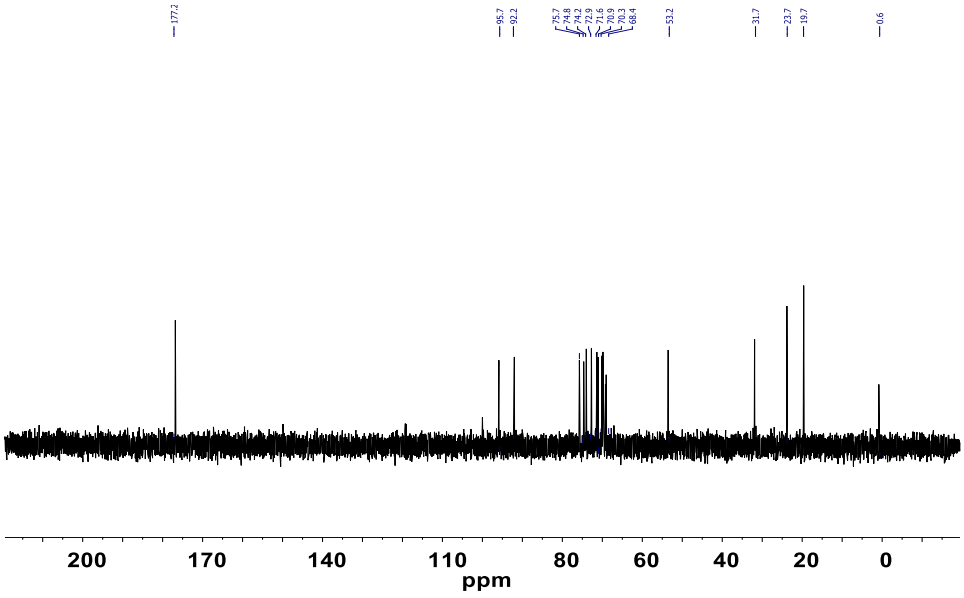


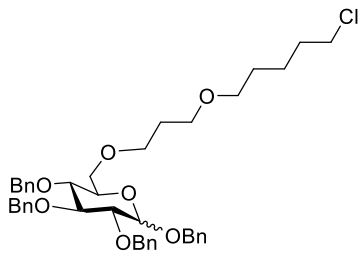
6

^{1}H, D_2O, 400 MHz



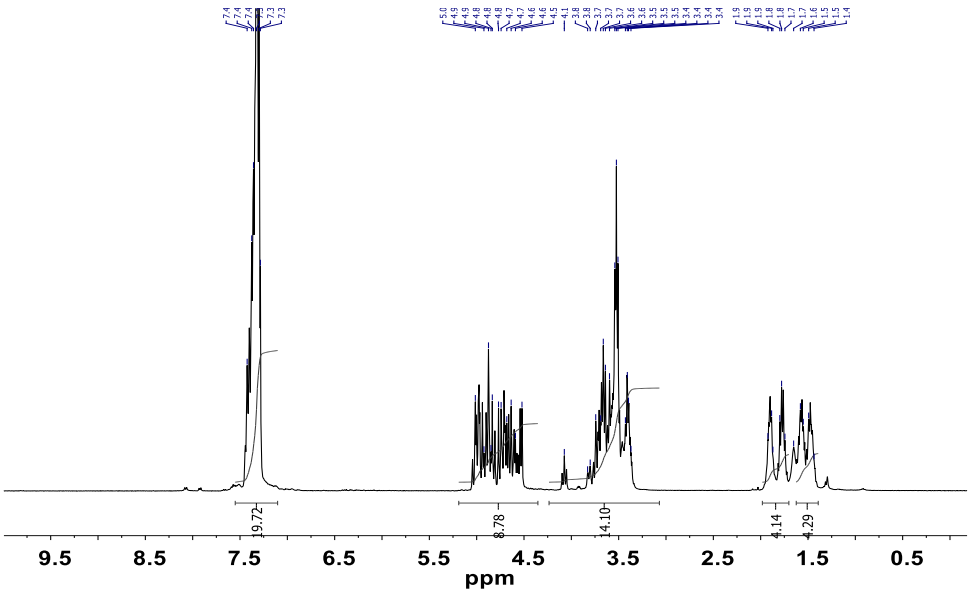
^{13}C{^{1}H}, D_2O, 100 MHz



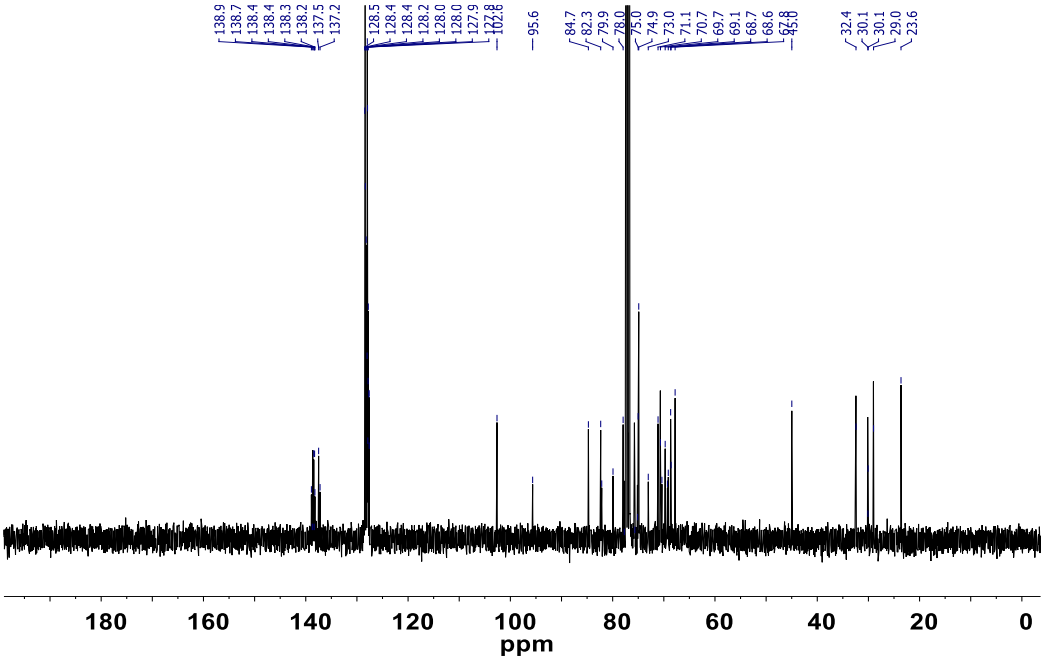


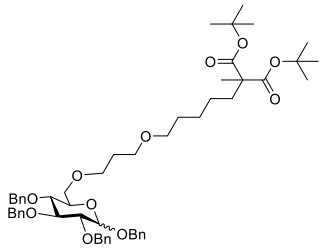
18

^{1}H, $CDCl_3$, 400 MHz



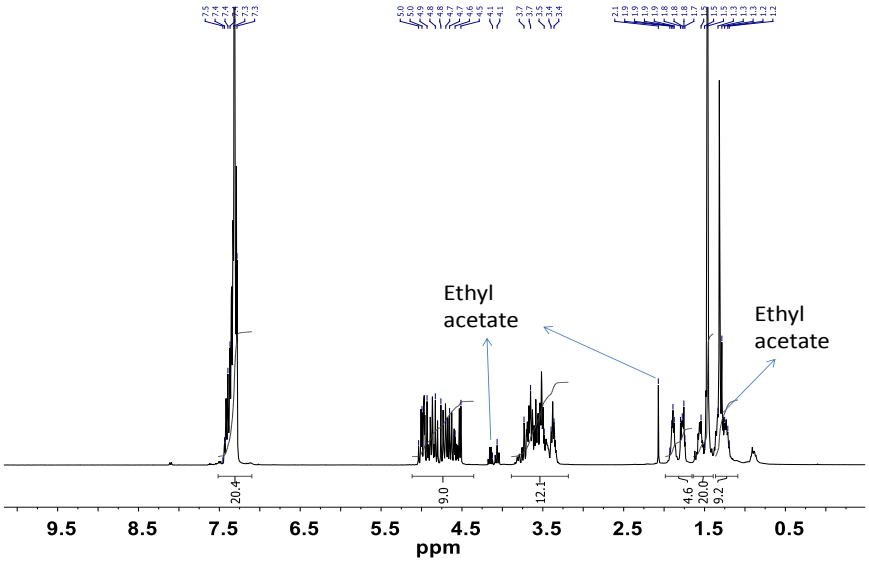
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



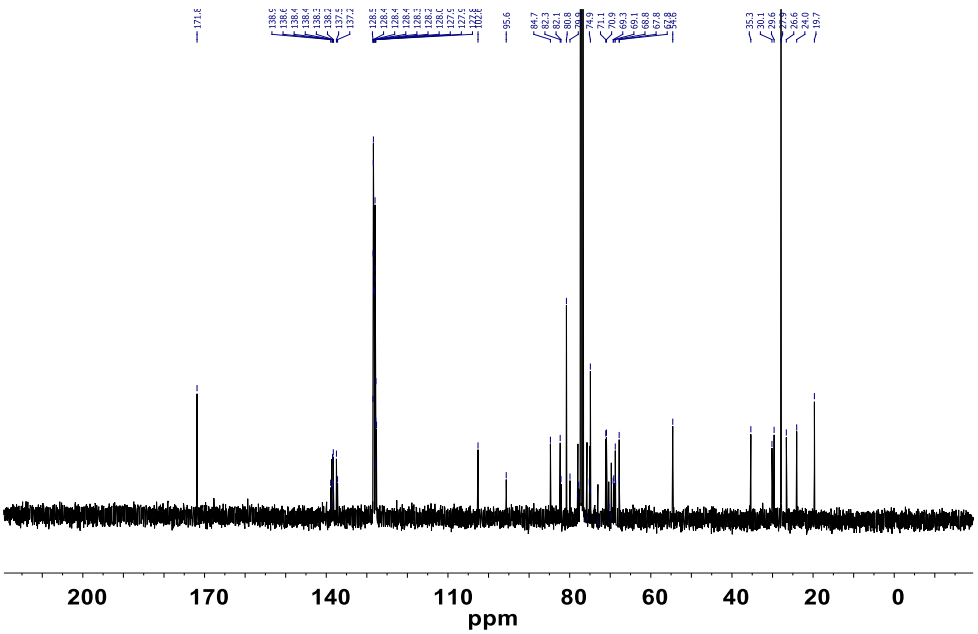


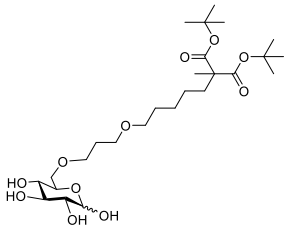
19

^{1}H, $CDCl_3$, 400 MHz



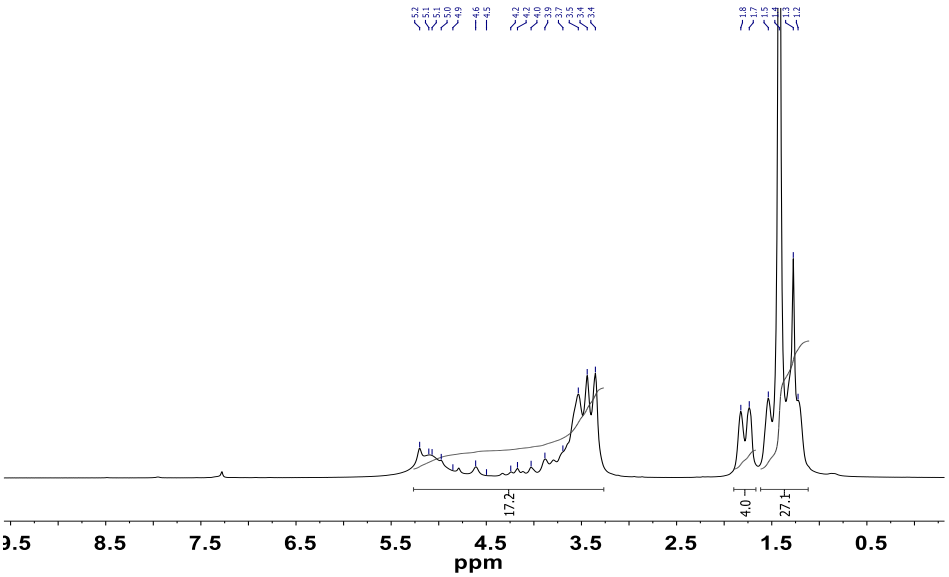
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



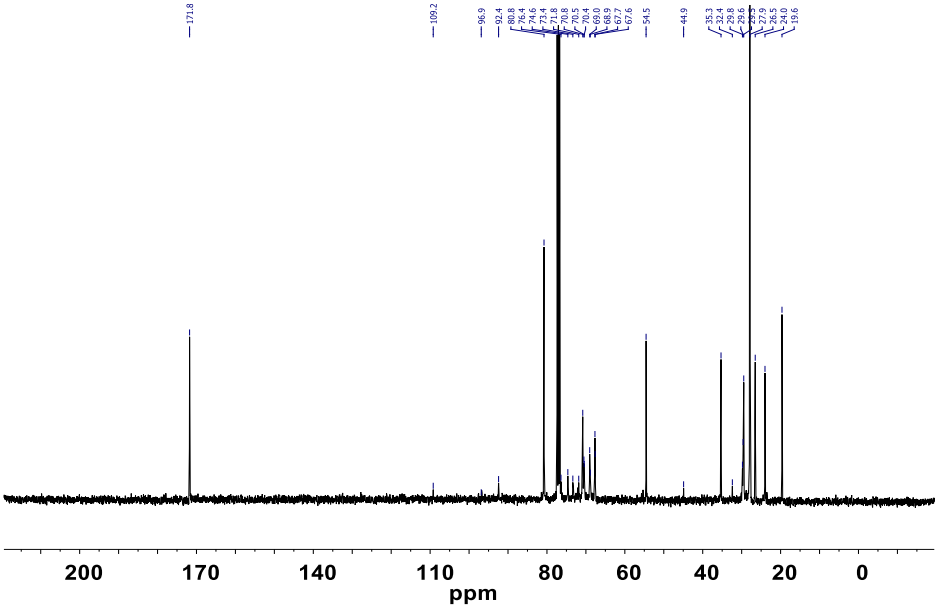


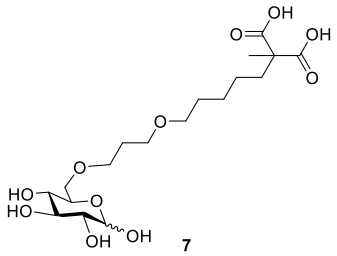
20

^{1}H, $CDCl_3$, 400 MHz



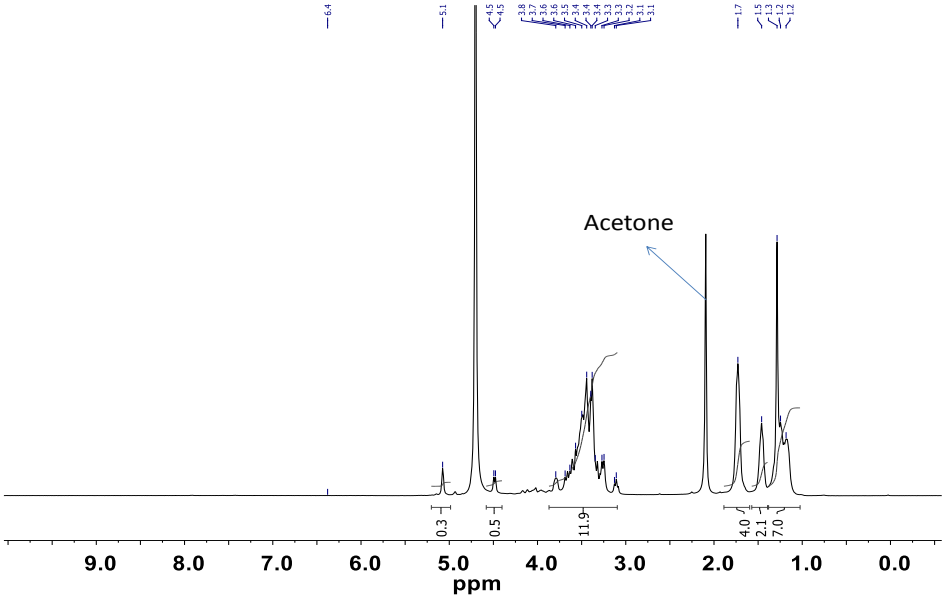
^{13}C{^{1}H}, $CDCl_3$, 100 MHz



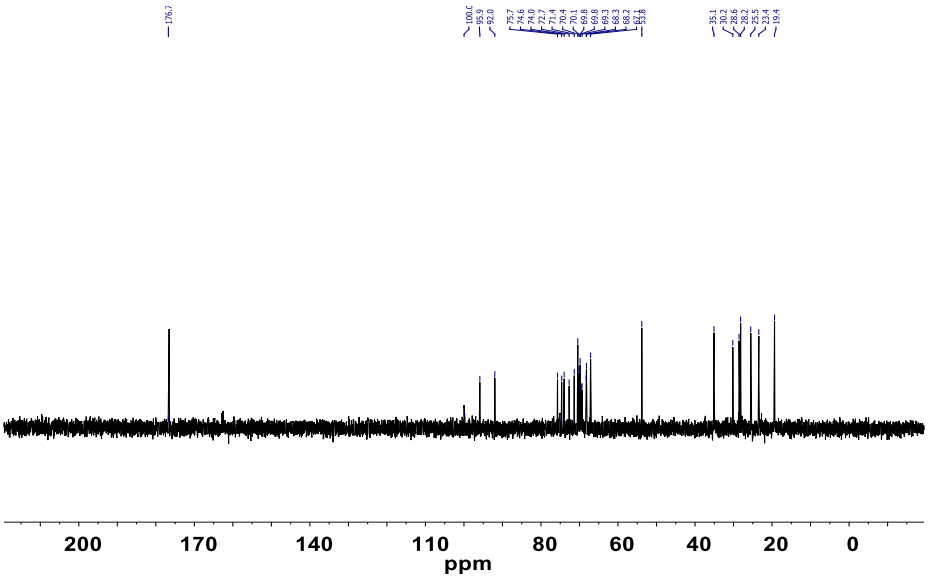


7

^{1}H, D_2O, 400 MHz



^{13}C{^{1}H}, D_2O, 100 MHz



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