Supplementary materials

Nucleolar Stress Induction by Oxaliplatin and Derivatives

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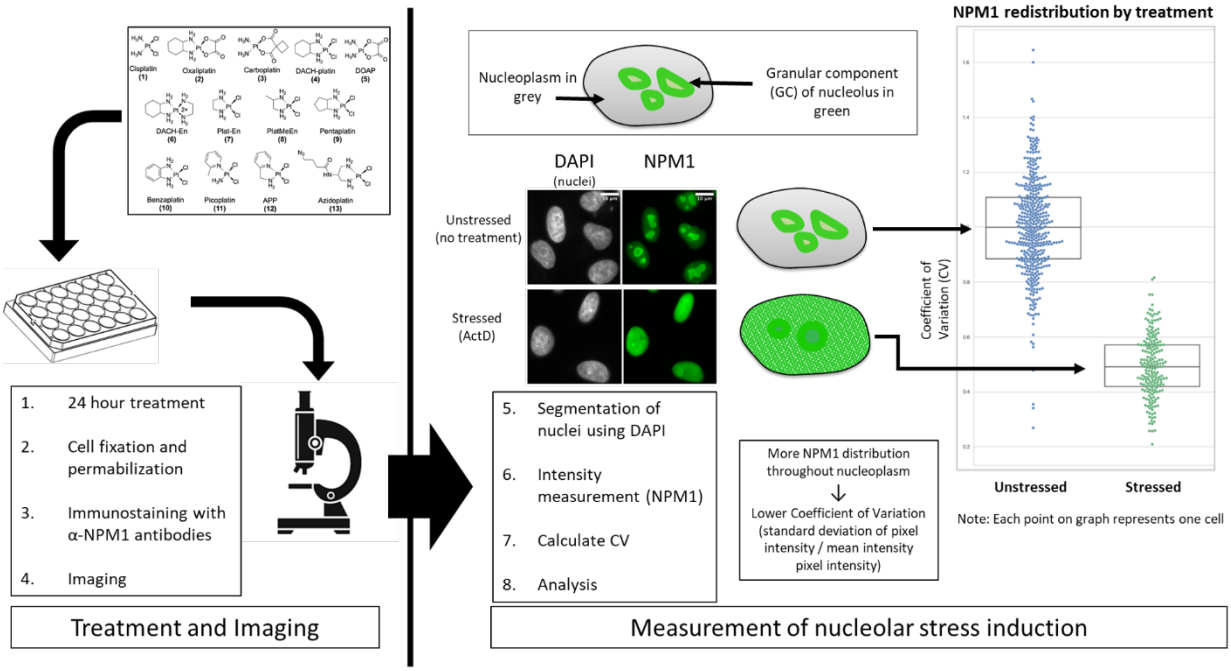
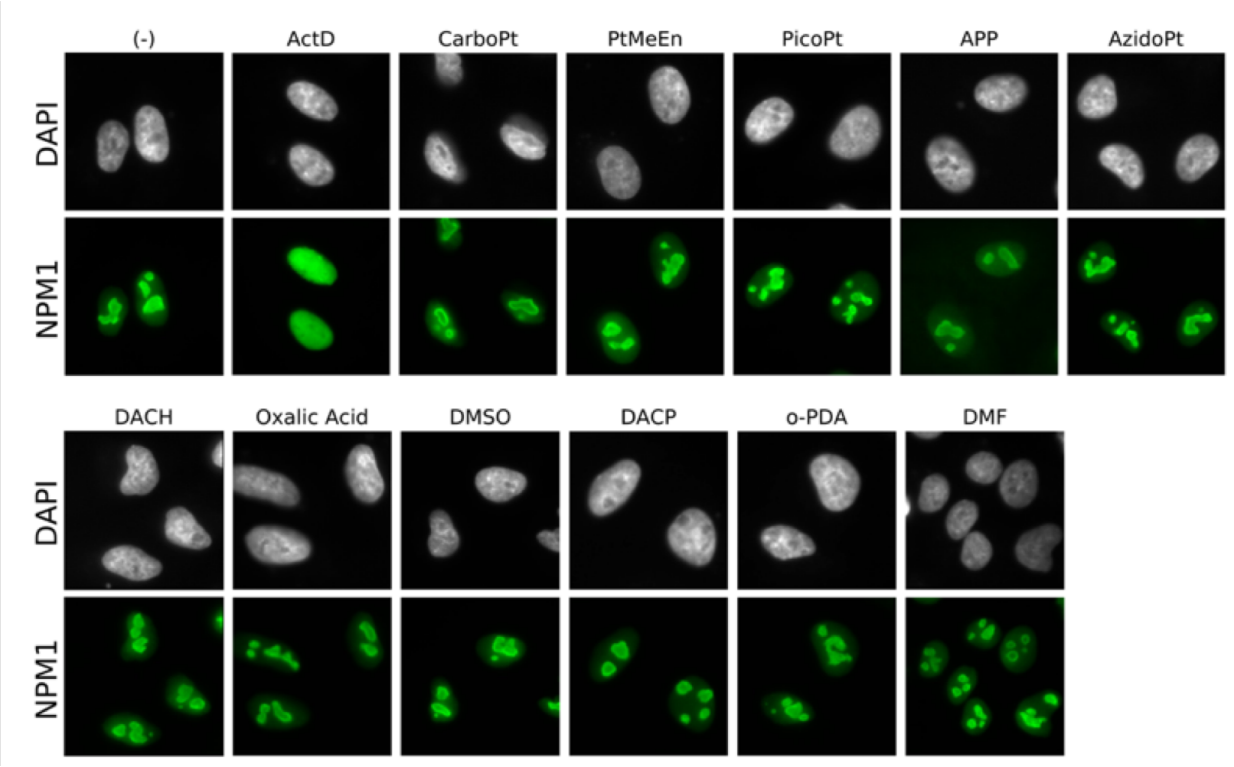
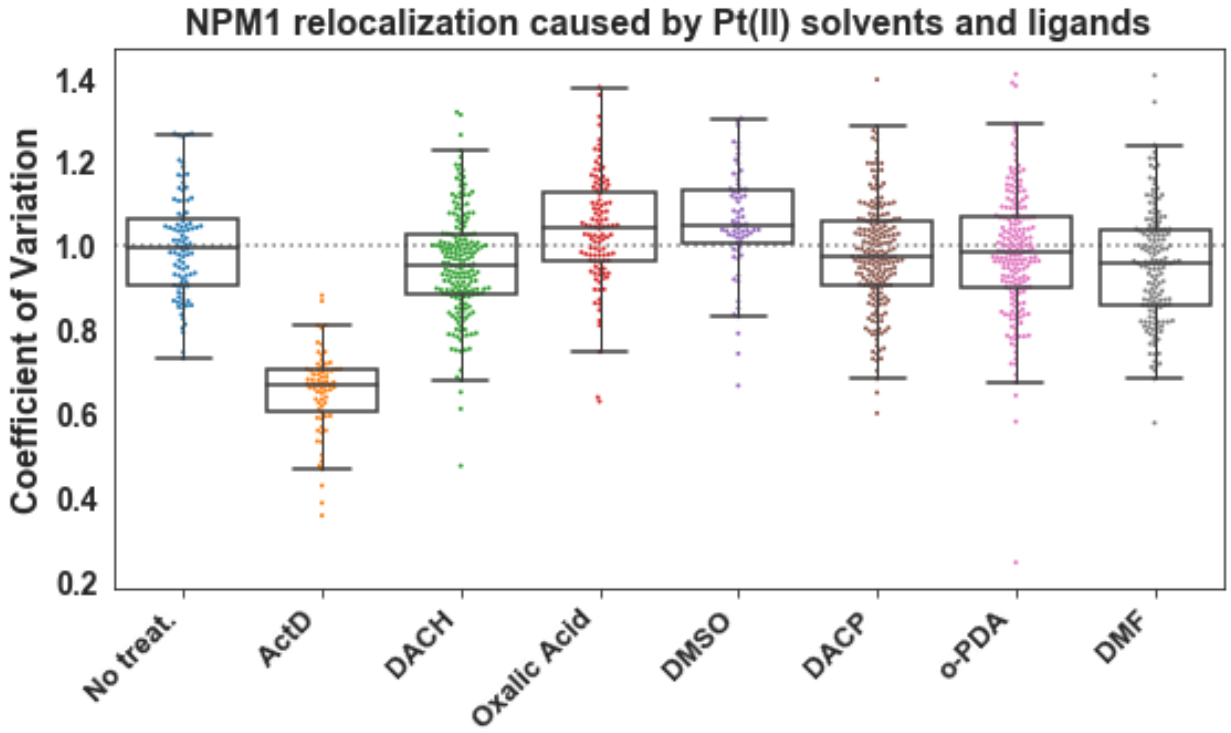
Supplementary Figures:



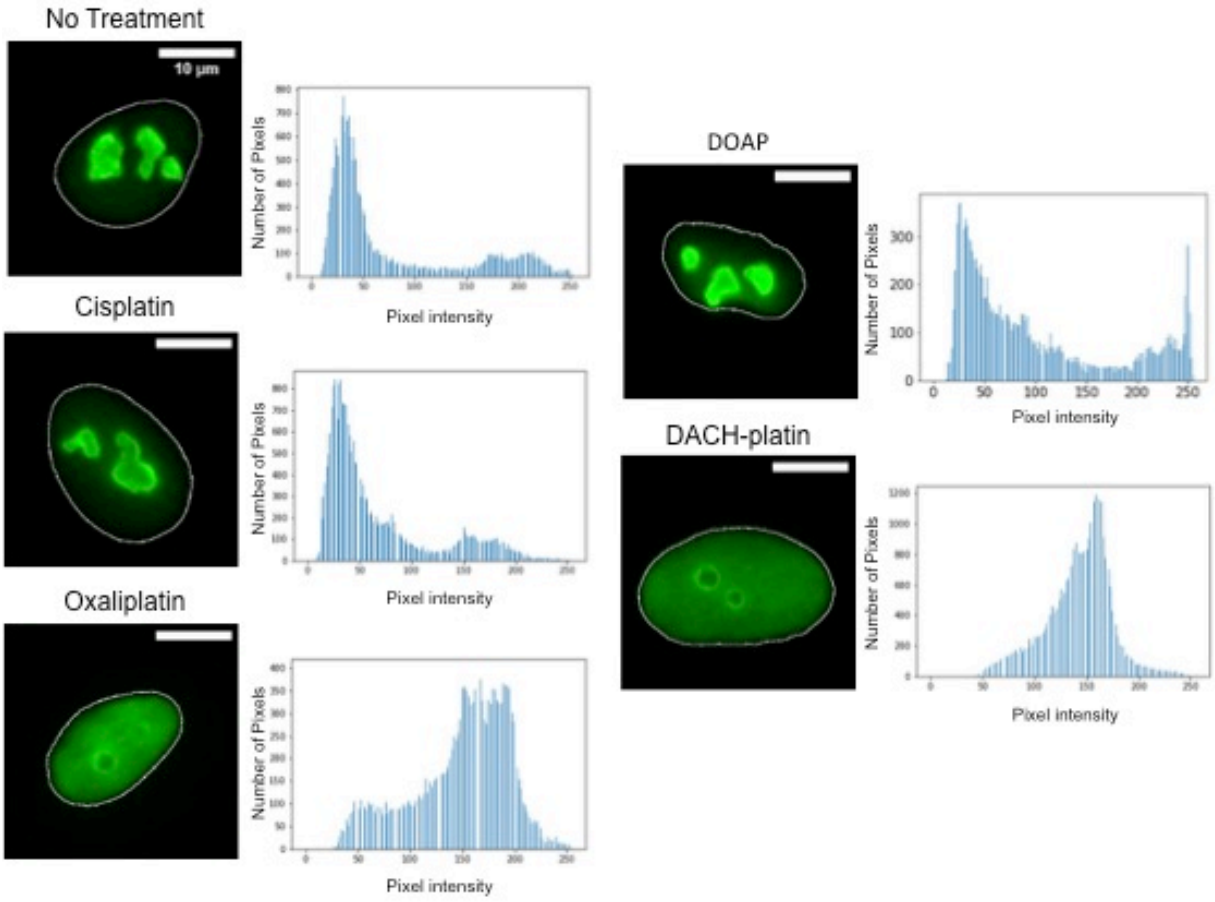
Supplementary Figure S1. NPM1 assay and quantification scheme. A549 cells were seeded on coverslips treated for 24 hours with the selected compound. Cells were fixed, permeabilized, and stained with an α-NPM1 antibody as described in Materials and Methods section. After imaging, nuclei were segmented using DAPI staining and pixel intensity from NPM1 imaging was measured. The Coefficient of Variation (CV, standard deviation over mean), was calculated for each nucleus, normalized to the mean CV for the no treatment control on that day, and plotted as above with each nucleus represented by one point on the plot. An average CV of 1.0 indicates no stress, whereas a lower CV (around 0.6) indicates diffusion of NPM1 throughout the nucleoplasm, a positive indicator of nucleolar stress. Treatment data sets are represented by box plots, where the center, top, and bottom lines of boxes represent the median, first and third quartile respectively.



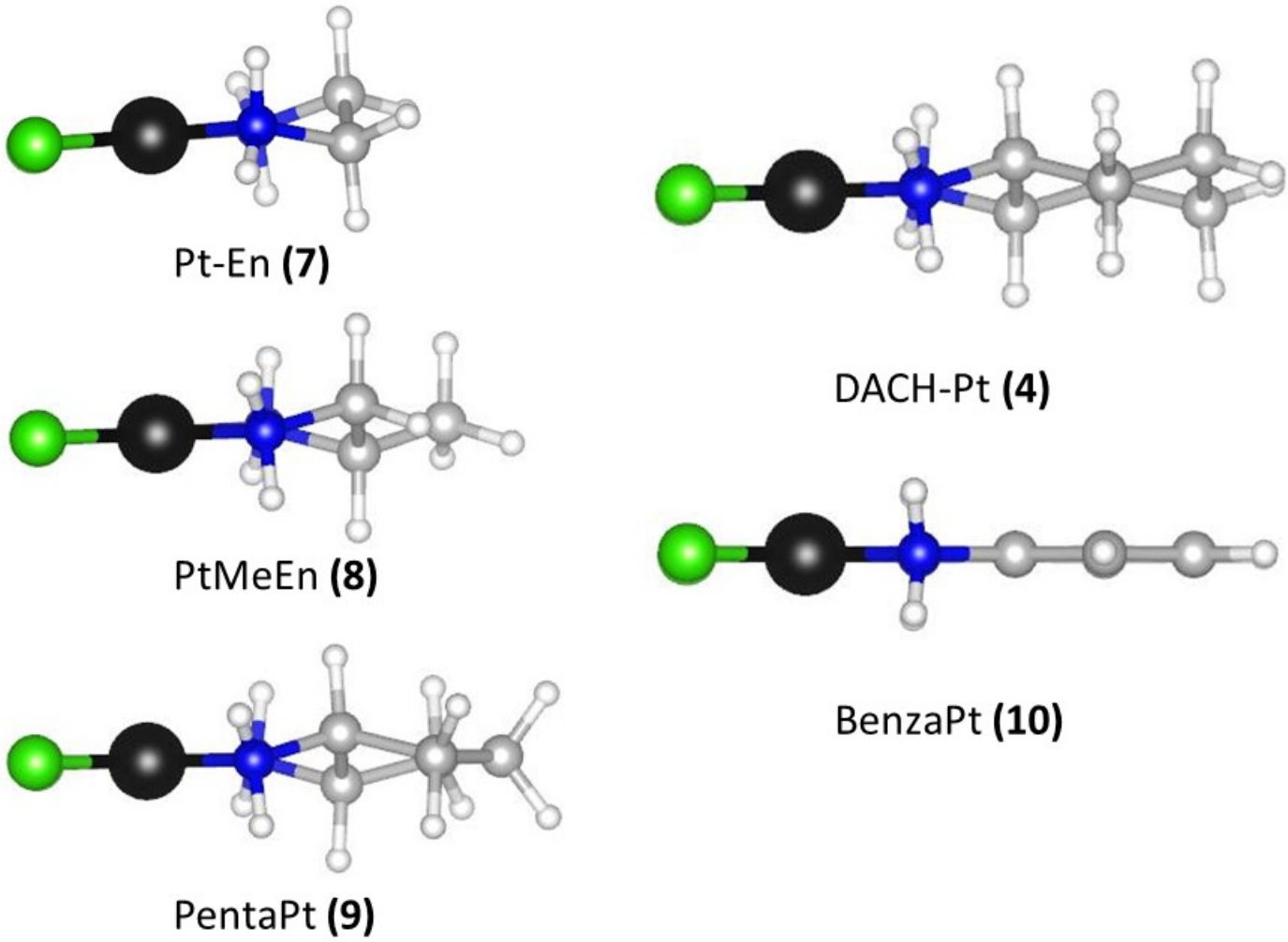
Supplementary Figure S2. Additional images for compounds tested. Top row shows negative and positive (Actinomycin D) controls, and Pt(II) compounds **3**, **8**, **11**, **12**, and **13**, — respectively CarboPt, PtMeEn, PicoPt, APP, and AzidoPt— none of which caused nucleolar stress. Bottom row shows Pt(II)-free ligands of stress-inducing Pt(II) compounds and solvents used (DMSO and DMF). Ligands alone do not induce nucleolar stress, and neither do solvents. All treatments were performed for 24 hours. Pt(II) compound and ligand treatments were conducted at 10 μM, with the exception of Actinomycin D, which was 5 nM, and **3** (CarboPt), which was 20 μM. DACP = 1*S*,2*S*-diaminocyclopentane, o-PDA = *o*-phenylenediamine.



Supplementary Figure S3. Quantification of nucleolar stress induction for Pt(II)-free ligands and solvents used. CV quantification confirms that ligands alone do not induce nucleolar stress, and neither do solvents. All treatments were performed for 24 hours. Treatments were conducted at 10 μM, with the exception of Actinomycin D, which was 5 nM. DACP = 1*S*,2*S*-diaminocyclopentane, o-PDA = *o*-phenylenediamine. Treatment data sets are represented by standard box plots, where the center, top, and bottom lines of boxes represent the median, first and third quartile respectively. The vertical lines represent the range of data within 1.5xIQR of the lower and upper quartiles, where IQR is the difference between first and third quartile; points outside this range are considered outliers.



Supplementary Figure S4. Histograms showing NPM1 intensity within a single nucleus in stressed and unstressed cells. X axis represents pixel intensity, and Y axis represents the number of pixels within a nucleus of the intensity on the X axis. Cells not undergoing nucleolar stress have a large number of low intensity pixels and a small number of high intensity pixels, indicating NPM1 is concentrated in the granular component of the nucleolus. Cells undergoing stress have a broader distribution of pixel intensities, with the histogram skewing towards high intensity, as NPM1 has redistributed throughout the entire nucleoplasm.



Supplemental Figure S5. DFT-optimized structures of compounds illustrating the relative size of compounds and planarity of BenzaPt **10** relative to DACH-Pt **4**

Supplementary Tables:

Table S1. IC_{50} values in A549 cells for selected compounds at 24 hours[a]

Compound	IC_{50} (μM)
Oxaliplatin, **2**	81.5±7
Cisplatin, **1**	12.8±2
DACHplatin, **4**	31.9±6
Pentaplatin, **9**	37.5±5
Benzaplatin, **10**	NR[b]
PlatEn, **7**	46.1±6
PlatMeEn, **8**	76.1±9
DOAP, **5**	36.6±5
APP, **12**	NR[b]

[a]IC_{50} values in A549 cells were determined after 24-hour treatment with indicated compound
[b]NR=IC_{50} value not reached, >500 μM

Table S2. IC_{50} values in A549 cells for selected compounds at 48 hours[a]

Compound	IC_{50} (μM)
Oxaliplatin, **2**	9.9±3.5
Cisplatin, **1**	4.6±0.7
Benzaplatin, **10**	6.9±0.7
APP, **12**	36.9±4.3

[a]IC_{50} values in A549 cells were determined after 48-hour treatment with indicated compound

Table S3. Volume and hydrophobicity data

Compound	Volume ($Å^3$)	Distance (Å)	logP
Cisplatin	19.46	3.40	-2.39±0.005
PlatMeEn	23.56	5.51	-1.68±0.014
PlatEn	21.47	4.41	-1.85±0.013
APP	27.66	6.21	-1.1±0.058
Picoplatin	27.69	6.21	-
Pentaplatin	27.85	6.21	-1.29±0.031
Benzaplatin	28.71	6.73	-0.92±0.038
DACH-platin	30.01	6.75	-0.89±0.011
Carboplatin	30.94	6.30	-
DACH-En	32.41	6.72	-
Azidoplatin	32.71	13.16	-1.2±0.059
Oxaliplatin	34.13	6.78	1.58±0.02

Materials and Methods:

1. Cell culture and treatment

A549 human lung carcinoma cells (#CCL-185, American Type Culture Collection) were cultured at 37°C, 5% CO_2 in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS) and 1% antibiotic-antimycotic. Treatments were conducted on cells that had been grown for 11-25 passages to 70% confluency. Except where noted otherwise, treatments were conducted for 24 hours at 10 μM. Compounds were made into 5mM stocks on the day of treatment in 0.9% NaCl (cisplatin), DMF (**4, 7, 8, 10, 11, 12, 13, 14**), DMSO (**5**), or water (**1, 2, 3, 6**). Stock solutions were diluted into media immediately prior to drug treatment.

2. Immunofluoresence

Cells to be imaged were grown on coverslips (Ted Pella product no 260368, Round glass coverslips, 10mm diam, 0.16-0.19mm thick) as described above. After treatment, cells were washed twice with phosphate buffered saline (PBS) and fixed for 20 minutes at room temperature in 4% paraformaldehyde in PBS. PFA was removed via aspiration and cells were then permeabilized with 0.5% Triton-X in PBS for 20 minutes at room temperature. Two ten-minute blocking steps were performed with 1% bovine serum albumin (BSA) in PBST (PBS with 0.1% Tween-20). Cells were incubated for one hour in primary antibody (NPM1 Monoclonal Antibody, FC-61991, from ThermoFisher, 1:200 dilution in PBST with 1% BSA) and 1 hour in secondary antibody (Goat Anti-Mouse IgG H&L Alexa Fluor® 488, ab150113, Abcam, 1:1000 dilution in PBST with 1% BSA), with 3 five minute wash steps using PBST between incubations, and were washed in the same manner again before mounting slides. Coverslips were mounted on slides with ProLong™ Diamond Antifade Mountant with DAPI (Thermo Fisher) according to manufacturer's instructions.

3. Cytotoxicity (MTT assay)

A549 cells were seeded in 24-well plates at a density of $5x10^4$ cells/mL. The following day cells were treated with 0-750 μM of compound in DMEM supplemented with 10% FBS and antibiotic-antimycotic. 24h after treatment, compound-containing media was removed and cells washed twice with PBS. MTT in DMEM supplemented with 10% FBS and antibiotic-antimycotic was then added to cells and incubated for 3h. DMSO was used to dissolve the formazan crystals and absorbance at 595 nm was then determined using a Tecan microplate reader. Percent viability was determined by comparing to vehicle-treated control for each compound and IC50 concentration calculated from triplicate measurements using the drc package in R.[1]

4. Image processing and quantification

Images were taken using a HC PL Fluotar 63x/1.3 oil objective mounted on a Leica DMi8 fluorescence microscope with Leica Application Suite X software. Quantification of NPM1 relocalization was performed in an automated fashion using a Python 3 script. Images were preprocessed in ImageJ[2,3] to convert the DAPI and NPM1 channels into separate 16-bit greyscale images. Between 70 and 225 cells were analyzed for each treatment group. Nuclei segmentation was determined with the DAPI images using Li thresholding functions in the Scikit- Image Python package.[4] The coefficient of variation (CV) for individual nuclei, defined as the standard deviation in pixel intensity divided by the mean pixel intensity, was calculated from

the NPM1 images using the SciPy Python package. All data were normalized to the no-treatment control in each experiment. NPM1 imaging results for each compound were observed on a minimum of two separate testing days. Data are represented as boxplots generated using Seaborn within Python.

5. Synthesis

Materials

Cisplatin used for cell treatments was purchased from Strem Chemicals. Cisplatin used as a synthetic precursor was synthesized as described below. Oxaliplatin and carboplatin were purchased from TCI. Unless otherwise noted, all other compounds were purchased from Sigma Aldrich or TCI. Picoplatin[5] and azidoplatin[6] were synthesized as previously reported.

Cisplatin **(1)**

Cisplatin was synthesized according to previously described methods by Dhara[7] and reviewed.[8] Briefly, potassium tetrachloroplatinate (62.7 mg, 0.151 mmol, 1 eq) was dissolved in 180 µL of water and stirred at 40°C. Potassium iodide (300 mg, 1.807 mmol, 12 eq) was dissolved separately in 500 µL of water and warmed to 40°C. 250 µL of the potassium iodide solution was added dropwise to the solution containing potassium tetrachloroplatinate. After addition of potassium iodide, the solution was warmed to 70°C. Once the solution reached 70°C it was removed from heat and cooled to room temperature. The solution was then filtered through celite. The filtrate was collected and used for the following reaction. A 2M solution of ammonium hydroxide in water (250 µL) was added dropwise. The solution was allowed to stand for 30 minutes, filtered, and washed with ethanol (x1) and ether (x2). The solid was collected to yield 56.2 mg *cis*-diamminediiodoplatinum(II). Silver sulfate (37 mg, 0.119 mmol, 1eq) was added to 5 mL of water. *Cis*-diamminediiodoplatinum(II) (56.2 mg, 0.116 mmol, 1eq) was added slowly. The solution was heated to 80°C. The solution was stirred overnight. The silver iodide was filtered using celite and the filtrate collected. This solution was concentrated to 1.5 mL. Potassium chloride (174.6 mg, 2.34 mmol, 20 eq) was added to the solution and then heated to 80°C. The solution was stirred at 80°C for another 20 minutes and cooled to room temperature. The solution was filtered and washed with ethanol (x1) and ether (x2) to yield 23.5 mg (52%) *cis*-diamminedichloroplatinum(II). ^{1}H NMR (500 MHz, DMF-d7) δ 3.99 (s, 6H).

Cis-(*trans*-1,2-diaminocyclohexane)dichloride Platinum(II) (DACH-Pt) **(4)**

Cis-(*trans(+/-)*-1,2-diaminocyclohexane)dichloride Platinum(II) was prepared using general methods previously described.[8] Potassium tetrachloroplatinate (100.3 mg, 0.242 mmol, 1 eq) was dissolved in 4 mL of water. *Trans*(+/-)-1,2-diaminocyclohexane (29.1 mg, 0.255 mmol, 1eq) was added dropwise to the dark red solution and stirred for 7.5 hours. A yellow precipitate formed. The solution was filtered and washed with ice-cold methanol (x1) and acetone (x1). The yellow solid was then collected to yield 70 mg (76 %). ^{1}H NMR (500 MHz, DMF-d7) δ 5.59 (d, J = 7.4 Hz, 2H), 5.02 (s, 2H), 2.50 (qq, J = 11.2, 5.6, 3.8 Hz, 2H), 2.15 – 2.04 (m, 2H), 1.56 (dd, J = 7.7, 3.3 Hz, 2H), 1.48 (tt, J = 11.9, 5.6 Hz, 2H), 1.15 (qd, J = 11.9, 2.9 Hz, 2H). ^{195}Pt NMR (107 MHz, DMF-d7) δ -2270.32.

Cis-(diammine)oxalic acid Platinum(II) (DOAP) **(5)**

Cis-(diammine)oxalic acid Platinum(II) was prepared using general methods previously described.[8] Sodium oxalate was prepared by introducing excess sodium hydroxide to oxalic acid and filtering the resulting solid. *Cis*-(diammine)diiodo platinum(II) (92.3 mg, 0.193 mmol, 1 eq) was dissolved in 5 mL water. Silver nitrate (82mg, 0.4823 mmol, 2.5eq) was added and the reaction stirred overnight protected from light. The reaction was then filtered through celite and the filtrate collected. Sodium oxalate (26 mg, 0.194 mmol, 1 eq) was added to the filtrate and

the reaction was stirred overnight and protected from light. The resulting light grey solid was filtered from the solution and washed with water (2x) and methanol (x2). Yield 33.3mg (54%). ^{1}H NMR (500 MHz, DMSO-d6) δ 4.27 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d6) δ 166.38. ^{195}Pt NMR (107 MHz, DMSO-d6) δ -1743.33.

Cis-(*trans*-1,2-diaminocyclohexane)1,2-ethylenediamine Platinum(II) (DACH-En) **(6)**

Cis-(*trans*(+/-)-1,2-diaminocyclohexane)dichloro platinum(II) (62 mg, 0.163 mmol, 1eq) was dissolved in 5 mL of water. 1,2-diaminoethane (32 mg, 0.533 mmol, 3.2eq) was added to the solution and refluxed for two days. The solution was then cooled room temperature over 24 hours. Solution was then evaporated to yield a yellow solid. ^{1}H NMR (500 MHz, Deuterium Oxide) δ 3.31 (t, *J* = 5.8 Hz, 1H), 3.05 (t, *J* = 5.8 Hz, 1H), 2.97 (s, 2H), 2.72 – 2.64 (m, 4H), 2.47 – 2.39 (m, 2H), 2.09 (dt, *J* = 12.8, 2.0 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.41 – 1.28 (m, 2H), 1.20 (td, *J* = 9.4, 8.9, 4.0 Hz, 2H). ^{13}C NMR (126 MHz, D_2O) δ 61.17, 46.83, 40.43, 32.14, 23.92. ^{195}Pt NMR (107 MHz, D2O) δ -3002.42. TOF MS ES+ for *m/z* $[(M)]^{2+}$ $C_8H_{21}Pt$ calculated: 368.1414 found: 368.1403 ($[(M]^{2+}$).

Cis-(1,2-diaminoethylene)dichloride Platinum(II) (Plat-En) **(7)**

Cis-(1,2-diaminoethylene)dichloride Platinum(II) was prepared using general methods previously described.[8] Potassium tetrachloroplatinate (66 mg, 0.159 mmol, 1eq) was dissolved in 500 µL of water. 1,2-diaminoethane (9.36 mg, 0.156 mmol, 1eq) was added to the dark red solution and allowed to stir at room temperature for 12 hours. A yellow precipitate formed. The solution was filtered and washed with ice-cold 0.1M HCl (x1), ethanol (x1), and ether (x1). The yellow solid was collected to yield 27.5 mg (53%). ^{1}H NMR (500 MHz, DMF-d7) δ 5.38 (s, 4H), 2.61 (s, 4H). ^{13}C NMR (126 MHz, DMF-d7) δ 50.52. ^{195}Pt NMR (107 MHz, DMF-d7) δ -2309.12.

Cis-(2,3-diaminopropane)dichloride Platinum(II) (Plat-MeEn) **(8)**

Cis-(2,3-diaminopropane)dichloride Platinum(II) was prepared according to previously reported methods and used as a mixture of isomers.[9] Potassium tetrachloroplatinate (34 mg, 0.082 mmol, 1eq) was dissolved in 1ml water and heated at 50 °C. Excess potassium iodide (40 mg, 0.24 mmol, 3eq) was dissolved in 0.5 mL water and added dropwise to the platinum. The solution was stirred for 10 minutes and became black. To the stirring solution, 1,2-diamino propane (7 µL, 0.08 mmol, 1 eq) was added and the solution was stirred for 40 minutes. Yellow precipitate formed immediately. The solution was cooled to room temperature and filtered. The solid was washed with ice-cold ethanol (1x) and ether (1x).

The solid was dissolved in 2ml water and silver nitrate (28 mg, 0.16 mmol, 2eq) was added. The reaction was stirred for 2 days protected from light. The solution was filtered through celite and concentrated to 1ml. Excess potassium chloride (120 mg, 1.61 mmol, 20 eq) was added rapidly to the concentrated solution and the mixture was stirred at 50 °C for 1 hour. The resulting yellow solid was filtered and washed with methanol (1x) and ether (1x). ^{1}H NMR (500 MHz, DMF-d_7) δ 5.74 (s, 1H), 5.55 (d, *J* = 40.1 Hz, 2H), 5.22 (s, 1H), 3.30 – 3.17 (m, 1H), 2.89 – 2.80 (m, 1H), 2.66 (td, *J* = 8.2, 6.1, 3.1 Hz, 1H), 1.53 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 56.00, 52.41, 16.38.

Cis-(*trans*-1,2-diaminocyclopentane)dichloride Platinum(II) (Penta-Pt) **(9)**

Cis-(*trans*-1*S*,2*S*-diaminocyclopentane)dichloride Platinum(II) was synthesized according to previously published methods.[10] Potassium tetrachloroplatinate (101 mg, 0.243 mmol, 1eq) was dissolved in 2 mL of water. (1*S*, 2*S*)-*trans*-diaminocyclopentane dihydrochloride (43.1 mg, 0.249 mmol, 1eq) was added and stirring continued. 73 mg of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.482 mmol, 2eq) was added to the solution. A yellow precipitate formed. The solution was filtered and washed with ethanol (x1) and ether (x2). The

yellow solid was collected to yield 50.5 mg (57%). ^{1}H NMR (500 MHz, DMF-d7) δ 5.18 (s, 2H), 5.00 (s, 2H), 3.41 – 3.31 (m, 2H), 2.16 (tdd, J = 9.6, 8.0, 5.3 Hz, 2H), 1.78 – 1.64 (m, 2H), 1.63 – 1.48 (m, 1H). ^{13}C NMR (126 MHz, DMF-d7) δ 70.21, 26.73, 23.93. ^{195}Pt NMR (107 MHz, DMF-d7) δ -1987.96.

Cis-(1,2-phenylenediamine)dichloride Platinum(II) (Benza-Pt) **(10)**

Cis-(1,2-phenylenediamine)dichloride Platinum(II) was prepared using general methods previously described.[8] Potassium tetrachloroplatinate (103 mg, 0.248 mmol, 1eq) was dissolved in 1 mL of water. A dark red solution formed. 1,2-phenylenediamine (26.8 mg, 0.248 mmol, 1eq) was added and stirring continued for 6 hours. The solution was filtered and washed with ice-cold ethanol (x1) and ether (x2). The dark yellow/brown solid was collected with a yield of 89.8 mg (96%). ^{1}H NMR (500 MHz, DMF-d_7) δ 7.72 (s, 2H), 7.46 (dd, *J* = 5.9, 3.5 Hz, 1H), 7.28 (dd, *J* = 6.0, 3.4 Hz, 1H). ^{13}C NMR (126 MHz, DMF-d7) δ 144.76, 128.85, 127.36. ^{195}Pt NMR (107 MHz, DMF-d7) δ -2199.18.

Cis-(2-aminomethylpyridine)dichloride Platinum(II) (APP) **(12)**

Cis-(2-aminomethylpyridine)dichloride Platinum(II) was synthesized according to previously described methods.[11] A solution of 2-picolylamine (120 µL, 0.075 mmol, 1 eq) was made in 1.2 mL water. Potassium tetrachloroplatinate (55mg, 0.133 mmol, 2eq) was dissolved in 1.2 mL water. The platinum solution was added to the 2-picolylamine and the pH was adjusted to pH 5 using concentrated HCl. The reaction was stirred for 4 hours. The pH of the solution was adjusted during the reaction to be around pH 5-6 using 1 M NaOH. The resulting yellow solid was filtered and washed with water (2x) to yield 38.7 mg (89%). ^{1}H NMR (500 MHz, DMF-d_7) δ 9.43 (d, *J* = 5.3 Hz, 1H), 8.37 (t, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 6.7 Hz, 1H), 6.42 (s, 2H), 4.55 (t, *J* = 5.9 Hz, 2H).

6. Measurement of partition coefficients

Water was mixed with octanol for 24 hours and left to stand for an additional 24 hours to obtain water-saturated octanol and octanol-saturated water that were used for determining partition coefficients. Measurements of the partition coefficients were performed using classical shake-flask method according to OECD guidelines.[12] Platinum complexes were dissolved in octanol-saturated water at concentrations between 0.5 mM and 5 mM. The octanol-saturated water mixtures were mixed with water-saturated octanol in a 1:1 ratio and vortexed for 30 minutes.[13] The mixtures were then centrifuged and 0.5 mL samples of both phases were collected and quantified using RP-HPLC as described by Klose et al.[10] An isocratic method was used for HPLC analysis with water and methanol. Methanol concentrations ranged from 10% to 30% with 30% being used for more hydrophobic compounds. The area of absorbance was used to calculate the ratio (P) of platinum in octanol and water as this area is proportional to the concentration according to the Lambert-Beer law. The column was washed with 95% methanol 5% water between each octanol sample and equilibrated before the next sample was introduced. The stock solution of each platinum compound was compared to the total from octanol and water samples as a check of this method. This procedure to calculate logP was performed in triplicate and standard deviations were determined.

7. Computations

Computations were performed as previously reported.[14] Briefly, compounds were optimized using density functional theory (DFT) in Gaussian09.[15] Optimizations to geometry were

performed using a RMS force convergence criterion of 10^{-5} hartree. The electronic wavefunction was minimized using GGA functional PBE,[16,17] with the DEF2TZP basis set. We did not explicitly include relativistic effects as these were not expected to impact the geometries of the compounds significantly.[18]

Two measures of size were used for the compounds: volume and longest vector between the platinum atom and the surface of the molecule. The vector represents the main steric component of the non-labile ligand of each compound to provide a direct comparison especially when comparing compounds that do not share the same aquation-labile ligand identity. In order to quantitatively assess the size of the molecules we used the presence of electric field, as derived from the electrostatic potential, to signify the location of the chemical system. DFT yields the electrostatic potential of the optimized, non-hydrolyzed compound structures and tools previously developed and reported were used to analyze the electrostatic potential of a chemical system.[19] We used the same file format to analyze the electrostatic potential and the result was the electrostatic potentials of the optimized structures were computed by minimizing the electronic wavefunction using 500 eV planewave cutoff, a gamma only k-grid, and a PBE functional utilizing a plane-augmented wave (PAW)[20,21] basis as implemented in the Vienna Ab Initio Software Package.[22–25]

All compounds were calculated in a sufficiently large computational box to minimize self-interaction. The electric field is the gradient of the electrostatic potential; therefore, the electric field includes the direction of the greatest increase in electrostatic potential. DFT calculations return electrostatic potential values on the order of 10^{-6} eV, therefore a change in less than 10^{-5} eV is considered negligible. This approach is based on previous atomic radii calculations which employ negligible change in electron density to assess the size of atoms. We used this measurement of the electric field and definition of the surface of the compound to find the total volume of the compounds as well as the longest vector from the platinum center to the farthest edge of the non-labile ligand.

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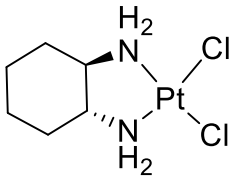
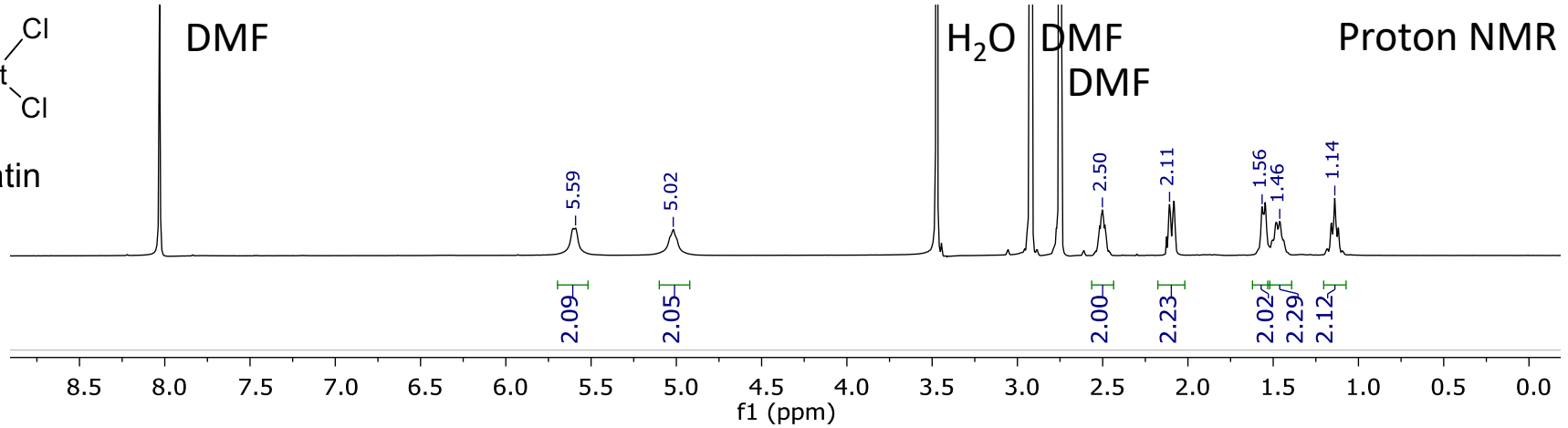
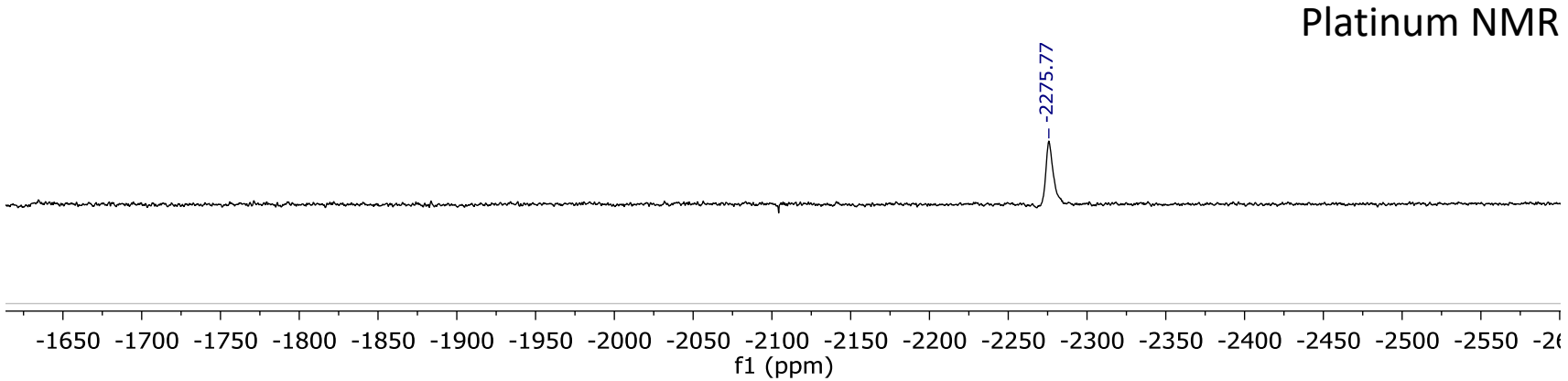
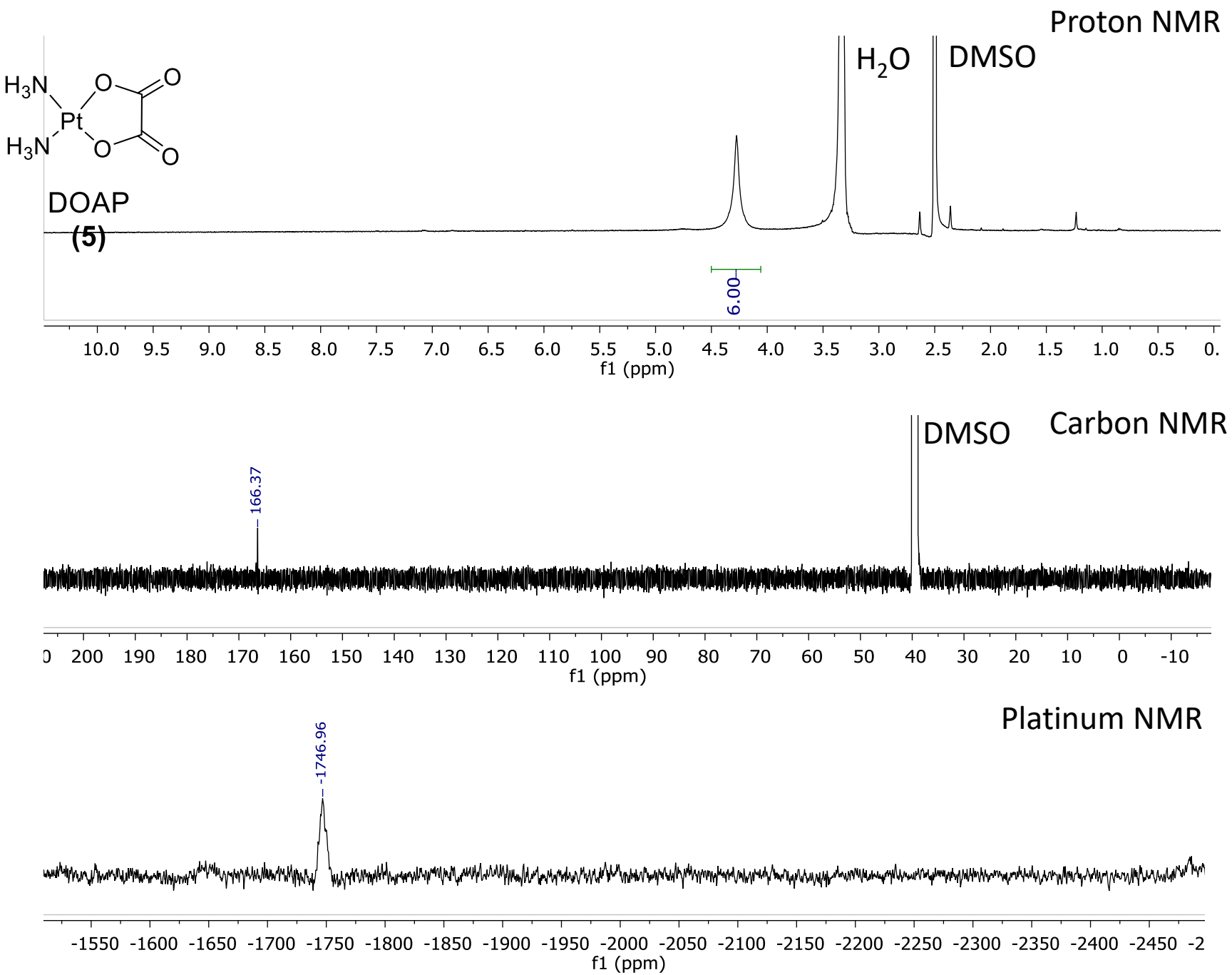
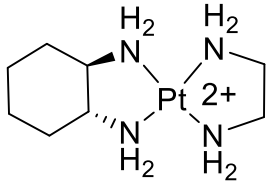


DACH-platin
(4)






Proton NMR
H2O
DMSO
DOAP
(5)
6.00
f1 (ppm)
Carbon NMR
DMSO
166.37
f1 (ppm)
Platinum NMR
-1746.96
f1 (ppm)

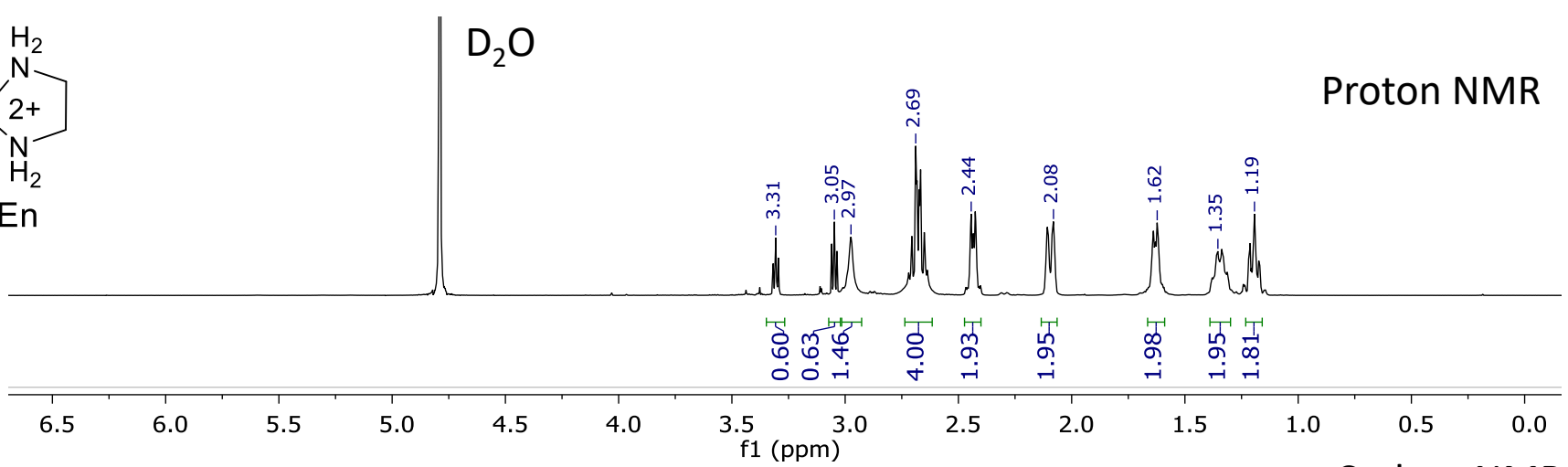


DACH-En

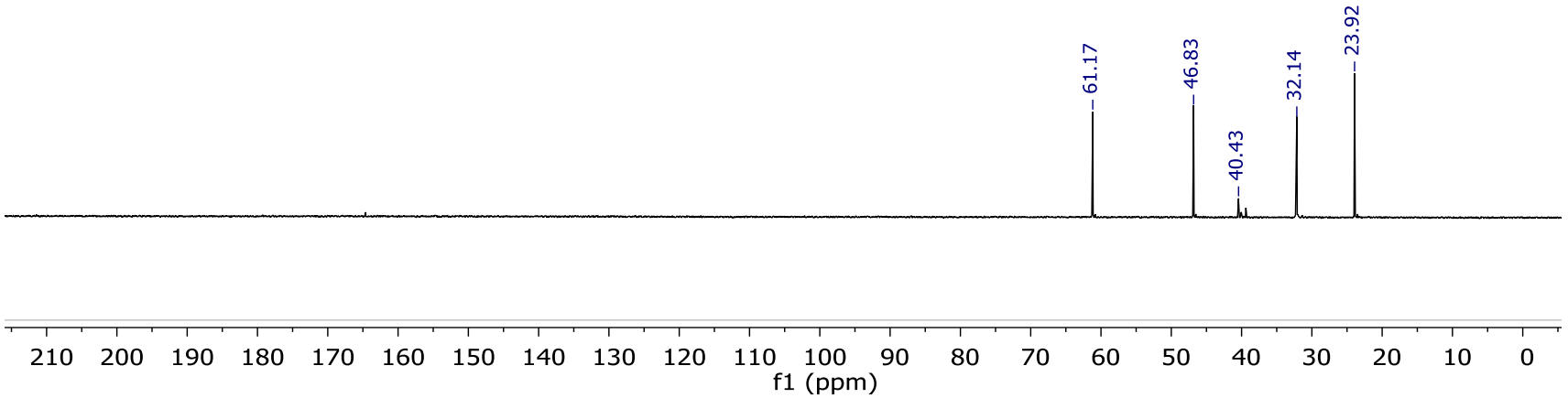
(6)

D_2O

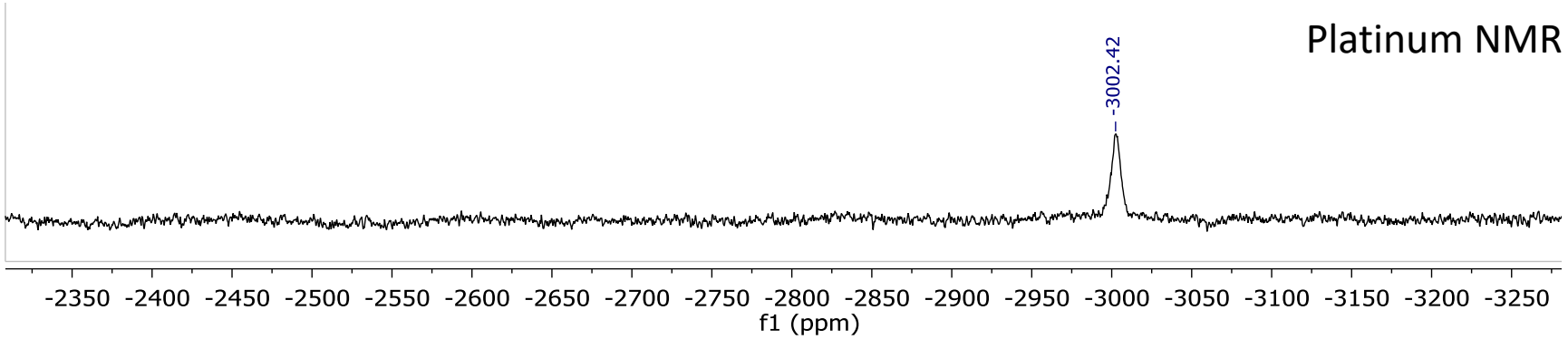
Proton NMR

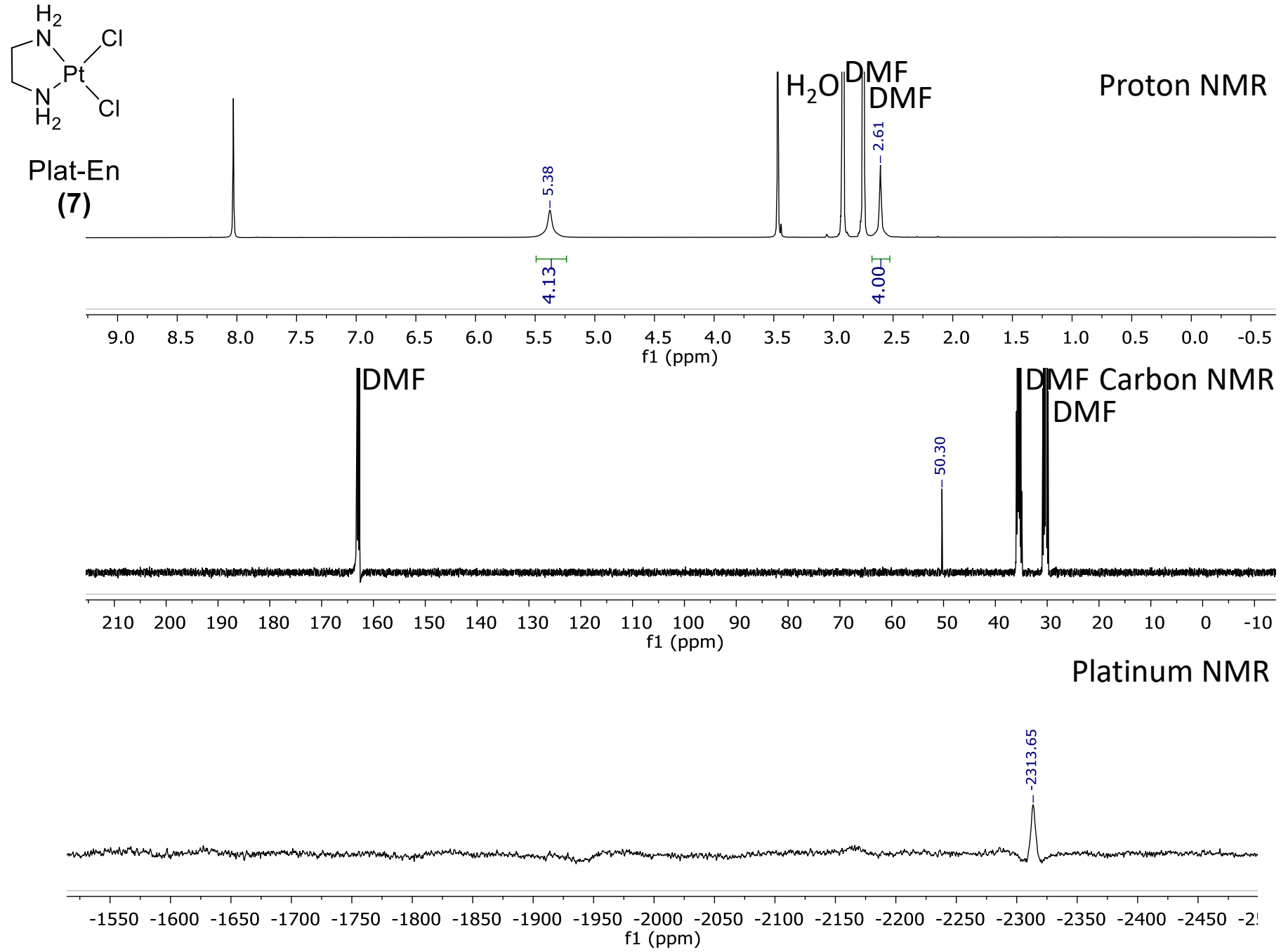


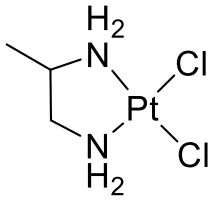
Carbon NMR



Platinum NMR



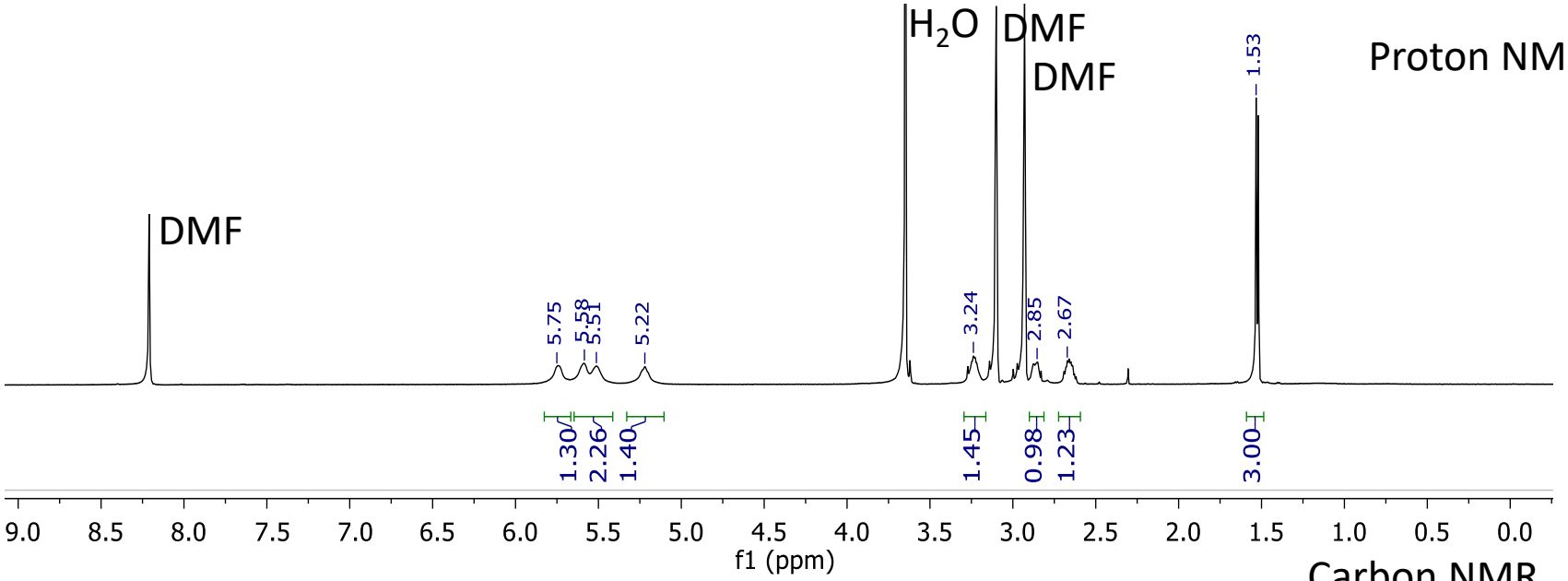

Plat-En
(7)
Proton NMR
H2O
DMF
DMF
5.38
2.61
4.13
4.00
f1 (ppm)
DMF
DMF Carbon NMR
DMF
50.30
f1 (ppm)
Platinum NMR
-2313.65
f1 (ppm)



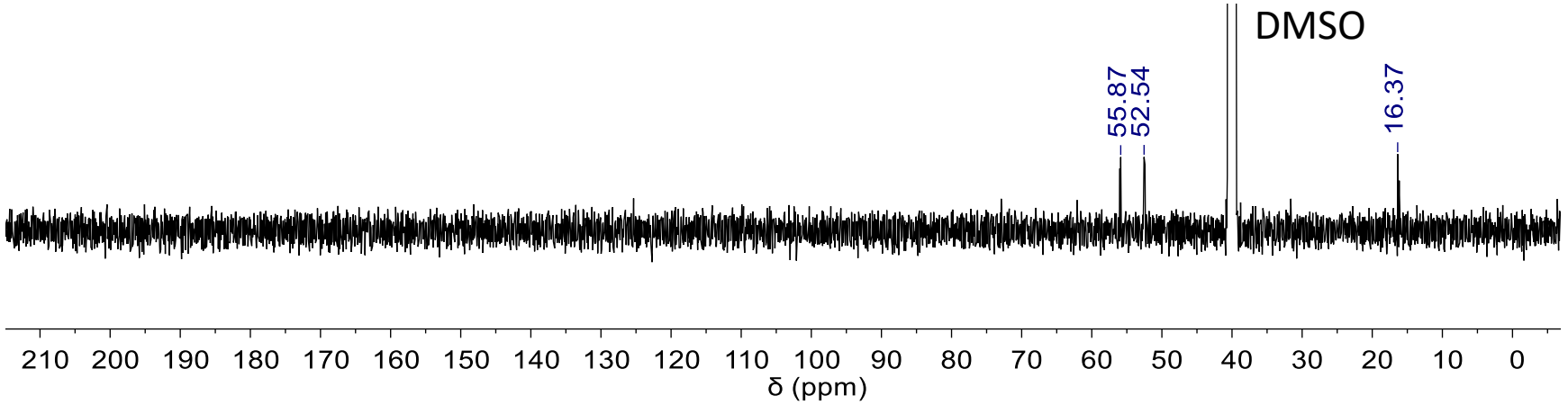
PlatMeEn

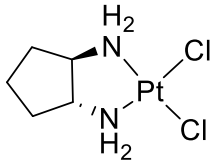
(8)

Proton NMR

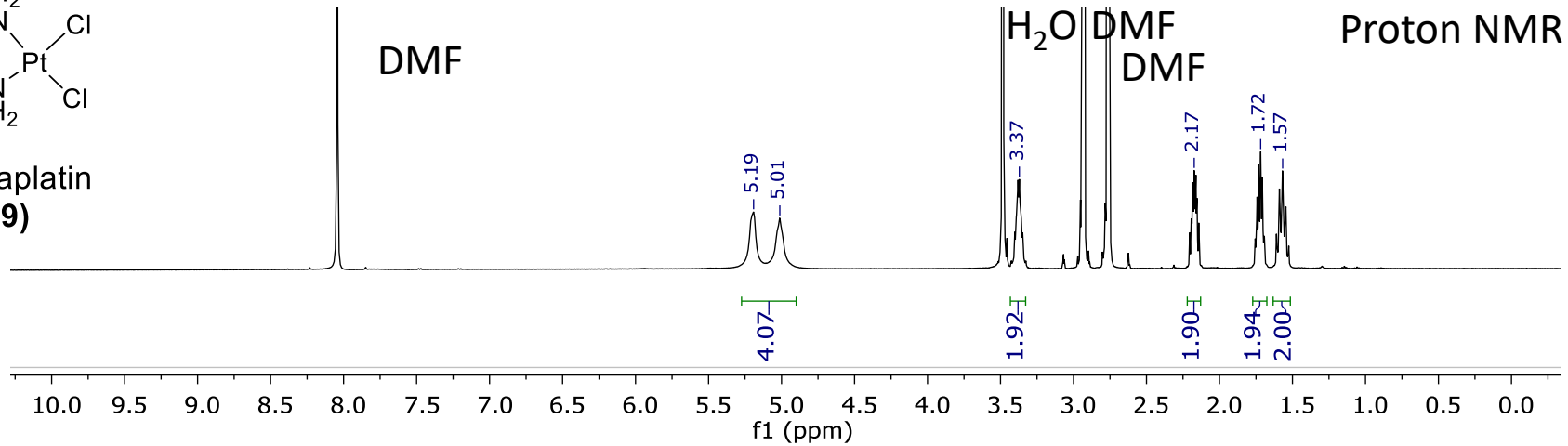


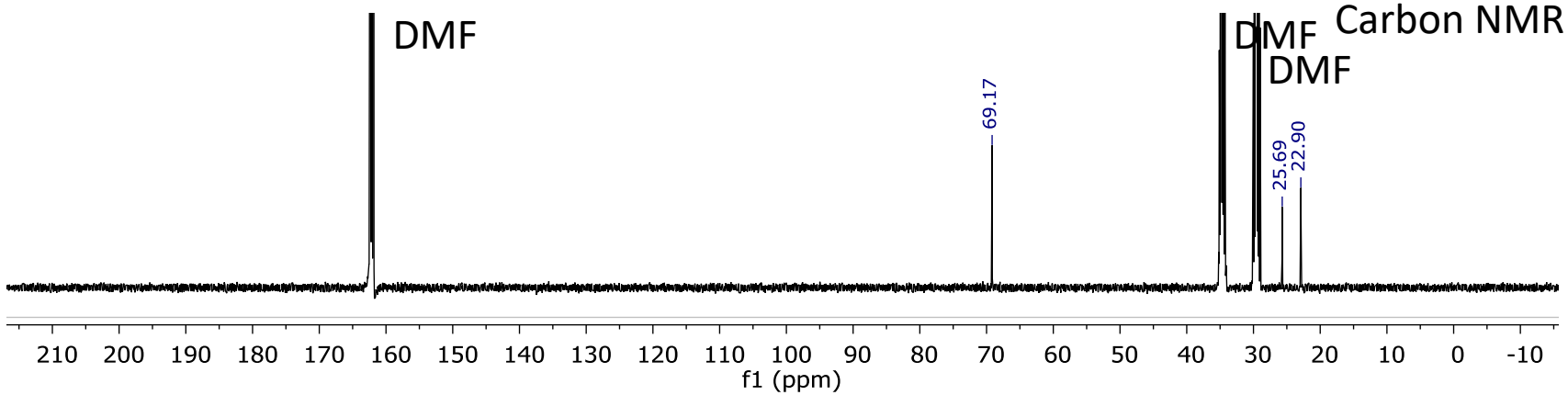
Carbon NMR

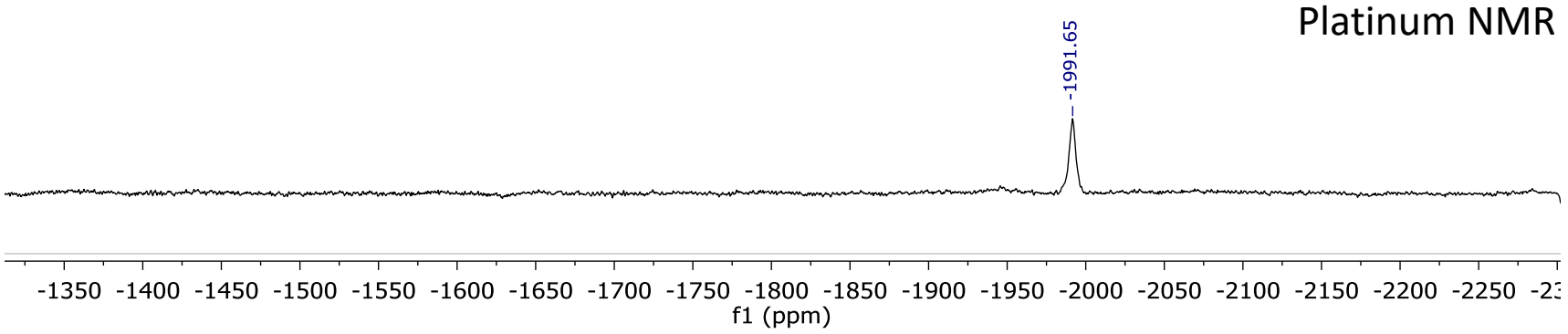


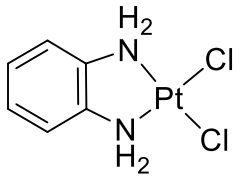


Pentaplatin
(9)



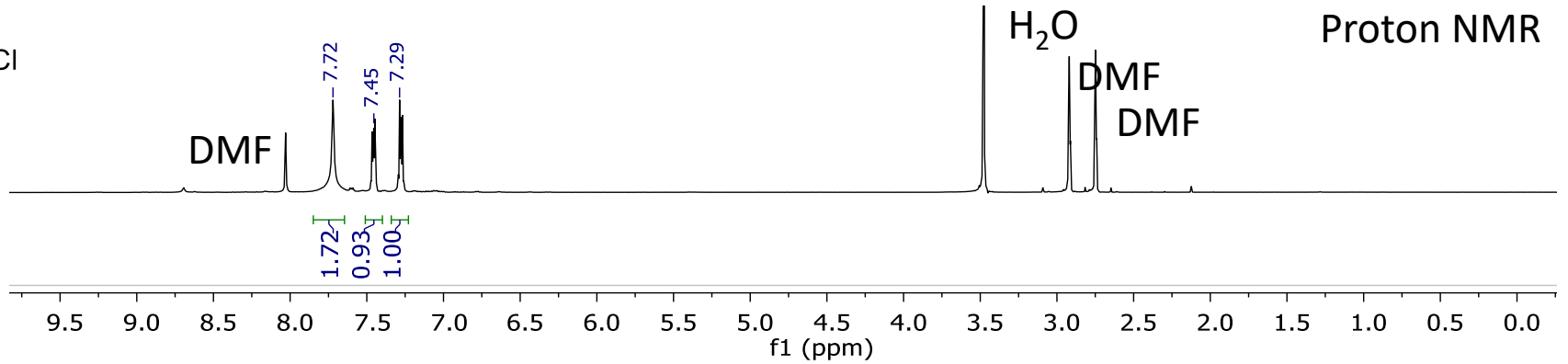




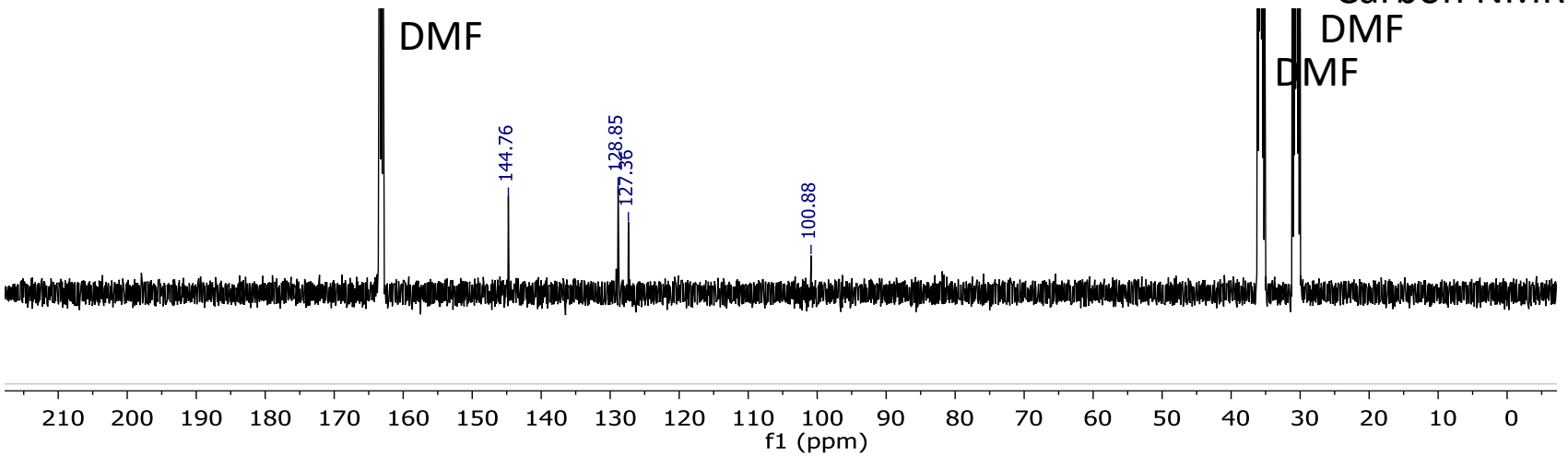


Benzaplatin
(10)

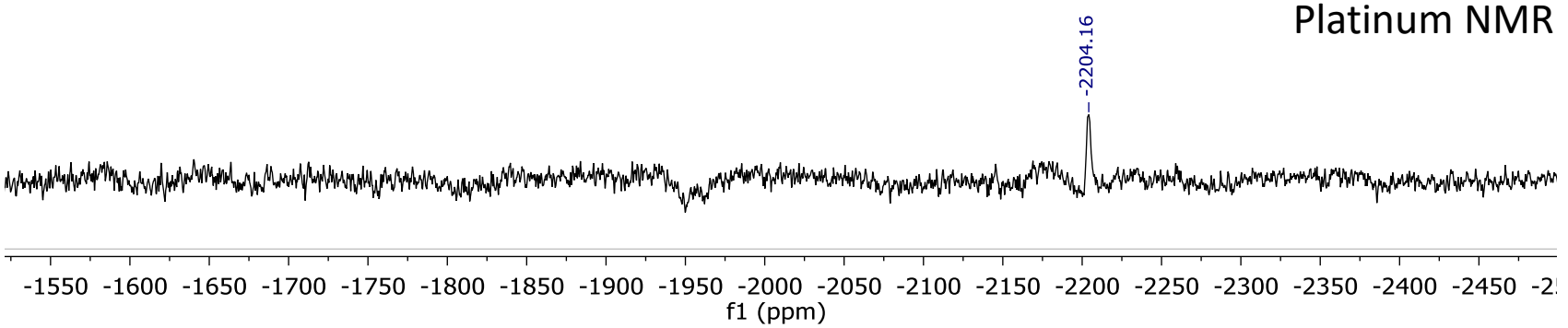
Proton NMR

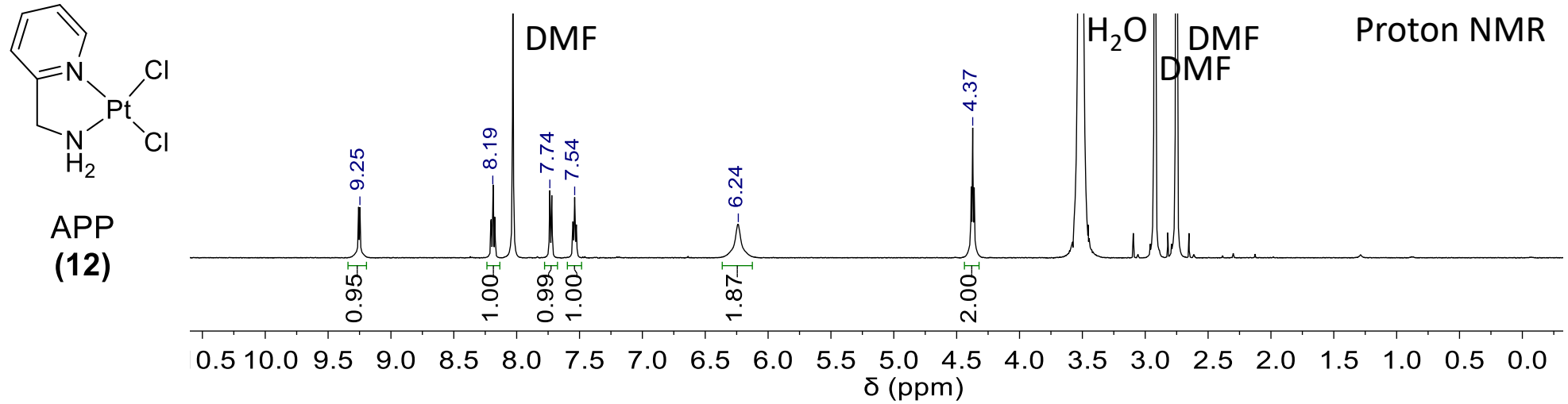


Carbon NMR



Platinum NMR




N
Cl
Pt
N
Cl
H2
APP
(12)
DMF
H2O
DMF
DMF
Proton NMR
9.25
8.19
7.74
7.54
6.24
4.37
0.95
1.00
0.99
1.00
1.87
2.00
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)