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Novel *N*-Sulfonamide Platinum Complexes: Synthesis, Reactivity and Invitro Evaluation

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General Methods. NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, 75 and 64.51 MHz for ^{1}H, ^{13}C and ^{195}Pt respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR. Acetone-d_6, 2.05 ppm for ^{1}H NMR, acetone-d_6, 28.9, 205.2 ppm for ^{13}C NMR. DMSO-d_6, 2.50 ppm for ^{1}H NMR, DMSO-d_6, 39.5 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired on a broad band decoupled mode. ^{195}Pt NMR spectra were obtained with chemical shifts reported in ppm downfield relative to the external reference 1.0 M Na_2PtCl_6 in D_2O. Electronic absorption spectra were recorded on a Agilent 8452 diode array spectrophotometer over a 190-1100 nm range in 1 cm quartz cuvettes thermostatized by Unisoku cryostat over (-100)-100 °C range.

Materials. Commercially available starting materials and solvents were used without further purification.

Kinetic studies. 50 µl of a GMP solution (10^{-4} M) and 27 µl of a solution of **8d** compound (10^{-4} M) were diluted until 5ml with a mixture 1:1 MeOH:H_2O. UV-vis absorption was measured at 37°C every two hours during 24 hours.

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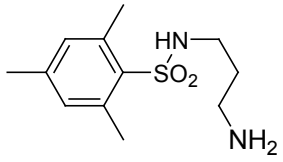
Experimental Procedures and Characterizations.

General Procedure of mono-*N*-sulfonamides

To a solution of the corresponding sulfonyl chloride (26 mmol) in 26 ml of dichloromethane at 0°C, was added rapidly propane-1,3-diamine or (*rac*)-cyclohexane-1,2-diamine (10 eq., 3M). The mixture was allowed to reach room temperature and was stirred during 10 hours. The crude mixture was filtered and the obtained oil was concentrated under reduced pressure. Then, 10 ml of water was added to the concentrated mixture and a white solid appeared. This white solid was filtrated and was washed with cool water and dried under vacuum for 12 hours.



6a

(3-Aminopropyl)-2,4,6-trimethylbenzene sulfonamide (6a). The product was directly obtained following the standard procedure as white solid (76% yield) without further purification. M.P. (°C): 123-124. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 2H) , 2.99 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 6.0 Hz, 2H), 2.64 (s, 3H), 2.62 (s, 3H), 2.30 (s, 3H), 1.67-1.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2 (C), 141.8 (C), 139.0 (C), 138.9 (C), 132.0 (CH), 131.8 (CH), 42.4 (CH_2), 41.0 (CH_2), 30.8 (CH_2), 22.9 (CH_3), 20.9 (CH_3). MS-FAB$^+$: $[M+H]^+$ calcd for $C_{12}H_{20}N_2O_2S$ 257.1318; found 257.1328.

(*rac*)-(2-Aminocyclohexyl)-2,4,6-trimethylbenzenesulfonamide (6b). The product was directly obtained following the standard procedure as white solid (66% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 2H), 2.66 (s, 6H), 2.65 (dt, *J* = 10.3, 4.0 Hz, 1H), 2.45 (dt, *J* = 10.3, 3.6 Hz, 1H), 2.30 (s, 3H), 1.97-1.85 (m, 2H), 1.65-1.59 (m, 2H), 1.28-1.04 (m, 4H).

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^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9 (C), 138.8 (C), 134.8 (C), 131.9 (CH), 60.2 (CH), 54.7 (CH), 35.7 (CH_2), 32.5 (CH_2), 25.0 (CH_2), 24.8 (CH_2), 23.1 (CH_3), 20.9 (CH_3). MS-FAB$^+$: $[M+H]^+$ calcd for $C_{15}H_{24}N_2O_2S$ 297.1637; found 297.1639.

(*rac*)-(2-Aminocyclohexyl)-4-methylbenzenesulfonamide (6c). The product was directly obtained following the standard procedure as white solid (82% yield) without further purification. M.P. (°C): 94.7-95.2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 3.72 (bs, 3H), 2.69 (dt, *J* = 10.1, 3.7 Hz, 1H), 2.48 (dt, *J* = 10.1, 3.9 Hz, 1H), 2.36 (s, 3H), 1.93-1.90 (m, 1H), 1.57-1.49 (m, 3H), 1.21-1.05 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (C), 138.3 (C), 129.6 (CH), 127.0 (CH), 60.0 (CH), 54.6 (CH), 34.7 (CH_2), 32.3 (CH_2), 25.0 (CH_2), 24.6 (CH_2), 21.5 (CH_3). MS-FAB$^+$: $[M+H]^+$ calcd for $C_{13}H_{20}N_2O_2S$ 269.1318; found 269.1326.

(*rac*)-(2-Aminocyclohexyl)-5-(dimethylamino)naphthalene-1-sulfonamide (6d). The product was directly obtained following the standard procedure as yellow solid (91% yield) without further purification. M.P. (°C): 161.8 (decomposed). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.29 (d, *J* = 7.1 Hz, 1H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 3.97 (bs, 3H), 2.79 (s, 6H), 2.77-2.69 (m, 1H), 2.57-2.49 (m, 1H), 1.91-1.86 (m, 1H), 1.46-1.43 (m, 1H), 1.40-1.33 (m, 2H), 1.05-0.89 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8 (C), 136.1 (C), 130.2 (CH), 129.7 (C), 129.6 (C), 129.4 (CH), 128.4 (CH), 123.2 (CH), 119.2 (CH), 115.2 (CH), 60.3 (CH), 54.4 (CH), 45.4 (CH_3), 34.5 (CH_2), 32.3 (CH_2), 25.0

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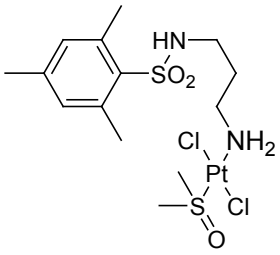
(CH_2), 24.5 (CH_2). MS-FAB$^+$: $[M+H]^+$ calcd for $C_{18}H_{25}N_3O_2S$ 348.1740; found 348.1741.

Procedure for the synthesis of mono-*N*-sulfonamides platinum complexes 8a and 8b

A solution of the corresponding sulfonamide **6a** or **6b** (0.2 mmol) in methanol (0.2 ml) was added $PtCl_2(DMSO)_2$ (0.22 mmol). The mixture was stirred at room temperature for 72 hours. Then, the reaction mixture was filtered and the solid was washed with cool methanol obtaining the pure platinum complexes, after vacuum line at 40°C for 12 hours.



8a

Platinum complex 8a. The product was directly obtained following the described above procedure as yellow solid (70% yield) without further purification. M.P. (°C): 172-175 °C ^{1}H NMR (300 MHz, acetone-d_6) δ 6.91 (s, 1H), 6.89 (S, 1H), 6.39 (t, *J* = 6.4 Hz, 1H), 6.22 (t, *J* = 6.4 Hz, 1H), 4.39 (bs, 1H), 3.18 (s, J^3_{Pt-CH} = 18.8 Hz, 6H), 2.92 (q, *J* = 6.6 Hz, 2H), 2.75 (q, *J* = 6.6 Hz, 2H), 2.51 (s, 3H), 2.45 (s, 3H), 2.16 (s, 3H), 1.85 (qt, *J* = 6.6 Hz, 1H), 1.51 (qt, *J* = 6.6 Hz, 1H). ^{13}C NMR (75 MHz, acetone-d_6) δ 141.7 (C), 138.8 (C), 134.8 (C), 131.8 (CH), 42.7 (CH_3), 39.7 (CH_2), 39.4 (CH_2), 30.3 (CH_2), 22.2 (CH_3), 22.1 (CH_3), 19.9 (CH_3). ^{195}Pt (64 MHz, acetone-d_6) δ -3115.5. MS-ESI$^+$: $[M+Na]^+$ calcd. for $C_{14}H_{26}Cl_2N_2O_3PtS_2$ 622.0302, found 622.0303. Anal. calcd. for $C_{14}H_{26}Cl_2N_2O_3PtS_2 \cdot C_3H_6O$: C, 31.00; H, 4.90; N, 4.25. Found: C, 31.39; H, 4.75; N, 4.24.

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Platinum complex 8b. The product was directly obtained following the described above procedure as pale yellow solid (79% yield) without further purification. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.75 (d, *J* = 9.3 Hz, 1H), 7.02 (s, 2H), 4.95 (t, *J* = 10.8 Hz, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 3.31 (s, 6H), 2.89-2.79 (m, 1H), 2.56 (s, 6H), 2.43-2.39 (m, 1H), 2.26 (s, 3H), 1.60-1.56 (m, 1H), 1.45-1.41 (m, 1H), 1.35-1.27 (m, 1H), 1.21-1.13 (m, 2H), 1.09-0.97 (m, 2H), 0.89-0.86 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.1 (C), 138.9 (C), 135.3 (C), 132.2 (C), 58.5 (CH), 56.2 (CH), 40.9 (CH_3), 31.0 (CH_2), 24.6 (CH_2), 24.2 (CH_2), 23.2 (CH_3), 20.9 (CH_3). ^{195}Pt (64 MHz, DMSO-d_6) δ -3120.1. MS-ESI$^+$: $[M+H]^+$ calcd for $C_{17}H_{30}Cl_2N_2O_3PtS_2Na$ 662.0615; found 662.0735. Anal. calcd. for $C_{17}H_{30}Cl_2N_2O_3PtS_2 \cdot 1/3H_2O \cdot 2/3KCl$: C, 29.33; H, 4.44; N, 4.02. Found: C, 29.12; H, 4.43; N, 4.16.

Procedure for the synthesis of mono-*N*-sulfonamides platinum complexes 8c and 8d

A solution of the corresponding sulphonamide **6c** or **6d** (0.2 mmol) in methanol (0.2 ml) was added $PtCl_2(DMSO)_2$ (0.22 mmol). The mixture was stirred at room temperature for 24-72 hours. Then the reaction mixture was filtered and the solid was washed with cold methanol. The filtrate was concentrated and washed with cold H_2O obtaining the pure platinum complex.

Platinum complex 8c. The product was directly obtained following the indicated above procedure as pale yellow solid (57% yield) without further purification. M.P. (°C): 195-196. ^{1}H NMR (300 MHz, $CDCl_3$) □δ

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7.81 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.23 (bs, 1H), 4.98 (d, *J* = 10.7 Hz, 1H), 3.45 (s, 6H), 2.95-8.79 (m, 3H), 2.38 (s, 3H), 1.79-1.66 (m, 1H), 1.53-1.49 (m, 1H), 1.33-1.26 (m, 1H), 1.24-1.15 (m, 2H), 1.14-0.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 137.5 (C), 130.1 (CH), 127.0 (CH), 58.9 (CH), 58.6 (CH), 44.2 (CH_3), 43.9 (CH_3), 32.6 (CH_2), 32.3 (CH_2), 24.9 (CH_2), 24.2 (CH_2), 21.6 (CH_3). ^{195}Pt (64 MHz, $CDCl_3$) δ -3112.7. MS-ESI$^+$: $[M+Na]^+$ calcd for $C_{15}H_{26}Cl_2N_2O_3PtS_2Na$ 634.0303; found 634.0283. Anal. calcd. for $C_{15}H_{26}Cl_2N_2O_3PtS_2 \cdot 1/2H_2O \cdot 1/2KCl$: C, 27.35; H, 4.13; N, 4.25. Found: C, 27.13; H, 4.13; N, 4.25.

Platinum complex 8d. The product was directly obtained following the indicated above procedure as yellow solid (71% yield) without further purification. M.P. (°C): 162-164. ^{1}H NMR (300 MHz, $CDCl_3$)δ 8.49 (d, *J* = 8.3 Hz, 1H), 8.22 (d, *J* = 7.4 Hz, 2H), 7.49 (q, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 7.3 Hz, 1H), 5.42 (d, *J* = 9.1 Hz, 1H), 4.74 (m, 1H), 3.56 (s, 6H), 2.83 (s, 6H), 2.83-2.74 (m, 2H), 1.81-1.75 (m, 1H), 1.63-1.57 (m, 1H), 1.36-1.28 (m, 1H), 1.20-1.07 (m, 2H), 0.96-0.81 (m, 3H). ^{13}C NMR (75Hz, $CDCl_3$) δ 152.3 (C), 134.2 (C), 131.1 (CH), 130.0 (CH), 129.8 (C), 129.3 (C), 129.2 (CH), 123.2 (CH), 118.0 (CH), 115.5 (CH), 58.9 (CH_3), 45.4 (CH_3), 44.1 (CH), 44.0 (CH), 32.6 (CH_2), 32.3 (CH_2), 24.8 (CH_2), 24.1 (CH_2). ^{195}Pt (64 MHz, $CDCl_3$) δ -3118.6. MS-FAB$^+$: $[M+H]^+$ calcd for $C_{20}H_{31}Cl_2N_3O_3PtS_2$ 691.0816; found 691.0819. Anal. calcd. for $C_{20}H_{31}Cl_2N_3O_3PtS_2 \cdot 1/2H_2O \cdot 1/2KCl$: C, 32.55; H, 4.37; N, 5.69. Found: C, 32.28; H, 4.32; N, 5.65.

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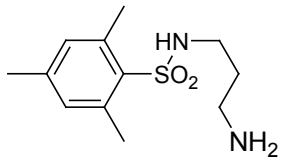
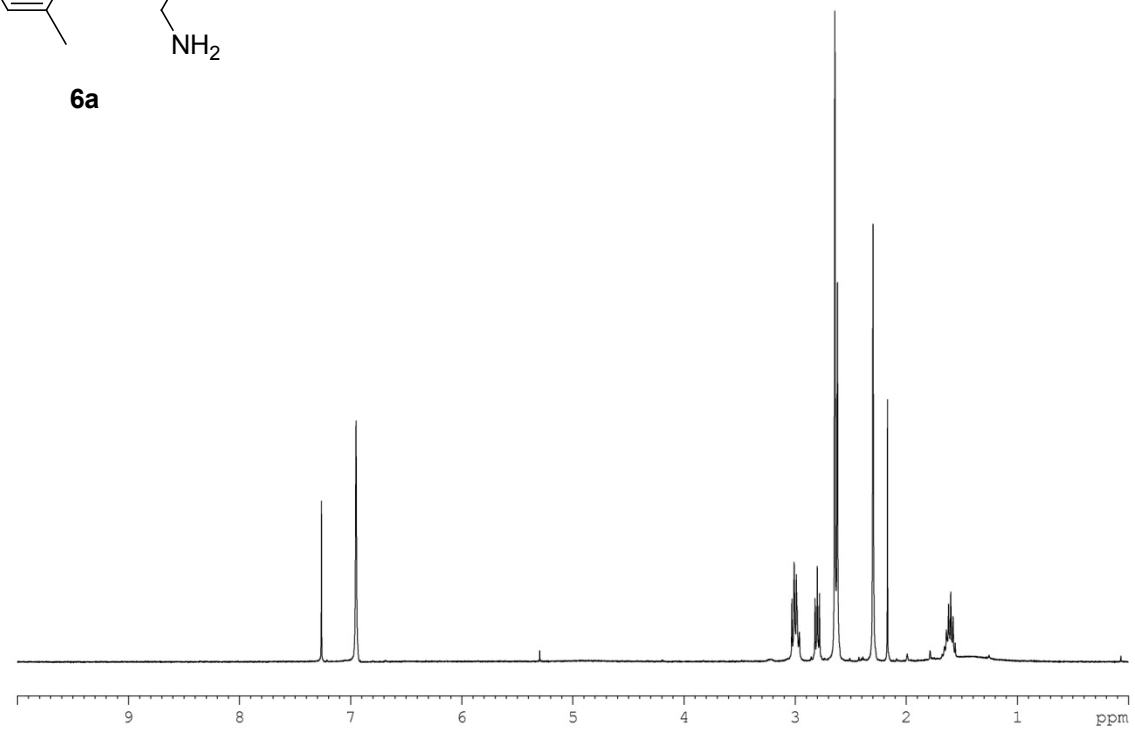
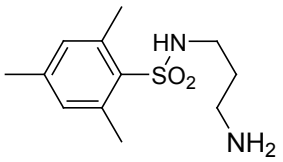


6a





6a

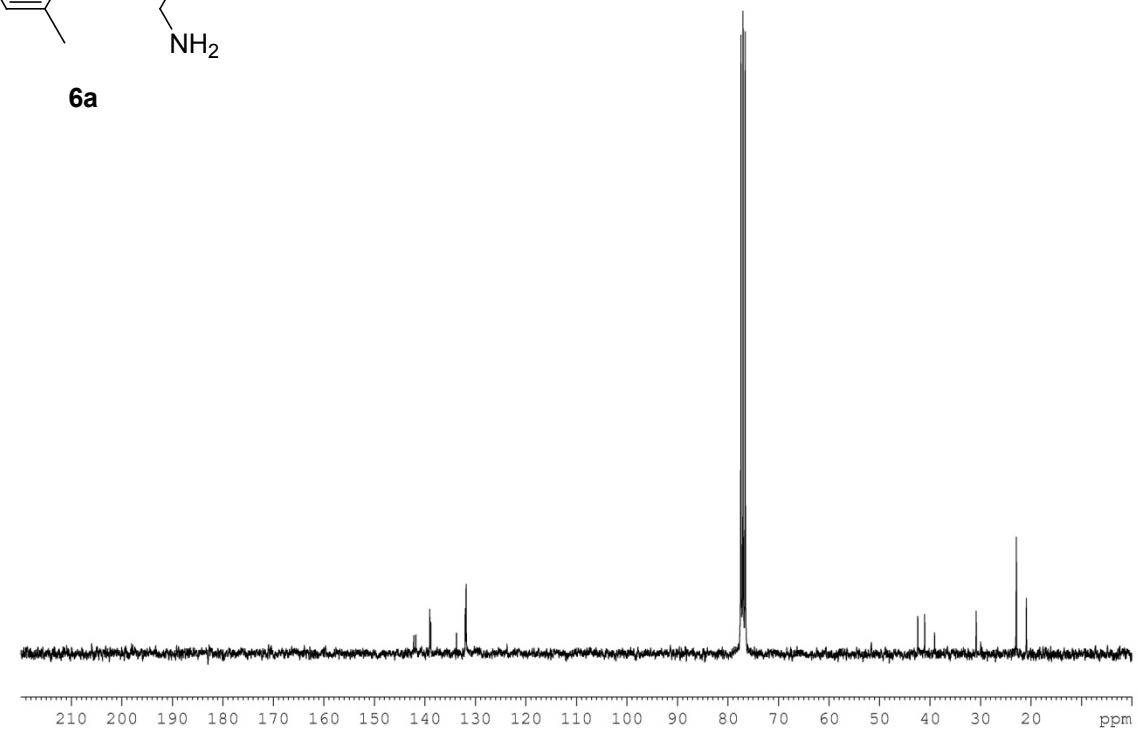


Figure S1. ^{1}H-NMR and ^{13}C-NMR of compound **6a**.

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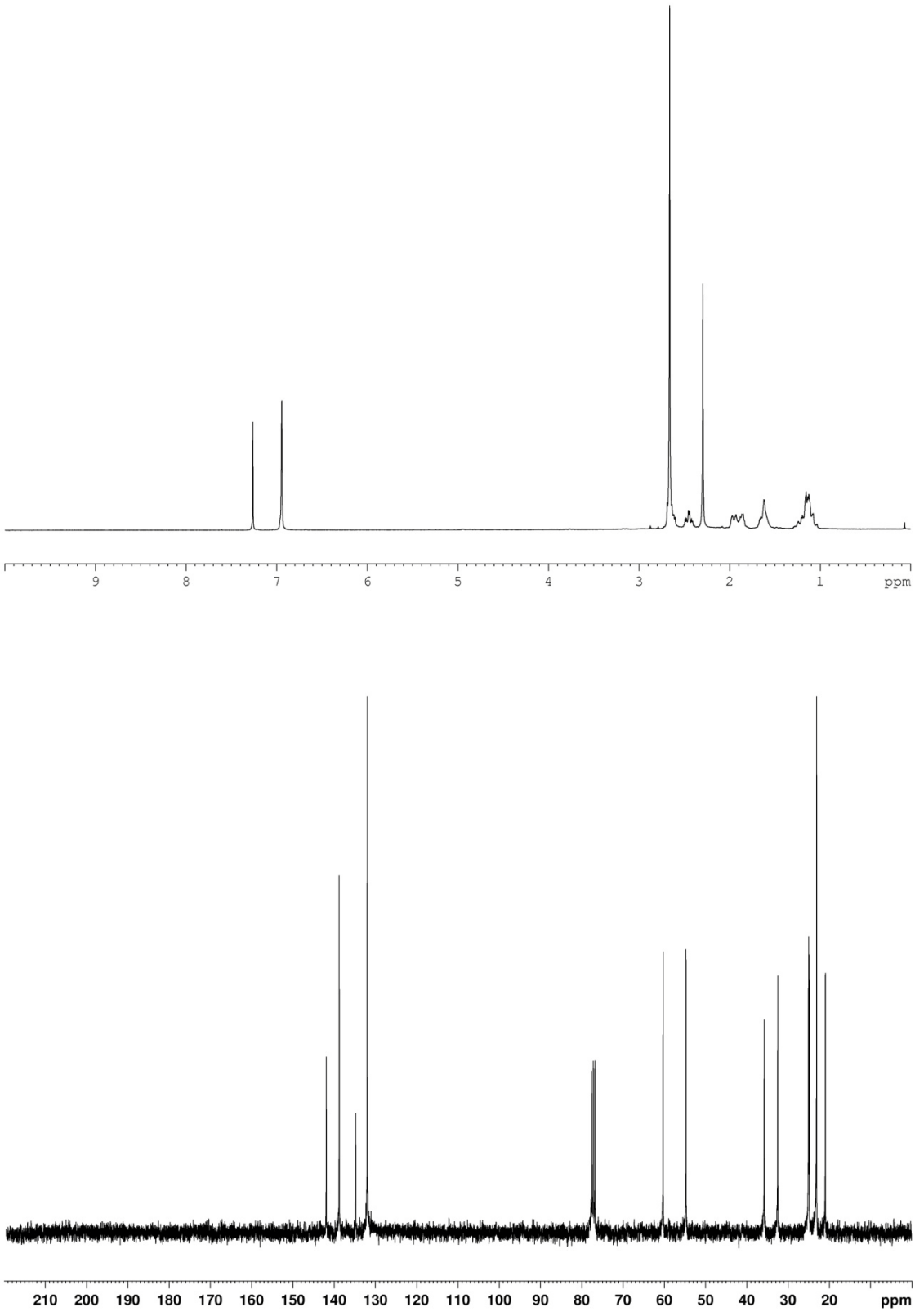

Figure S2. ^{1}H-NMR and ^{13}C-NMR of compound **6b**.

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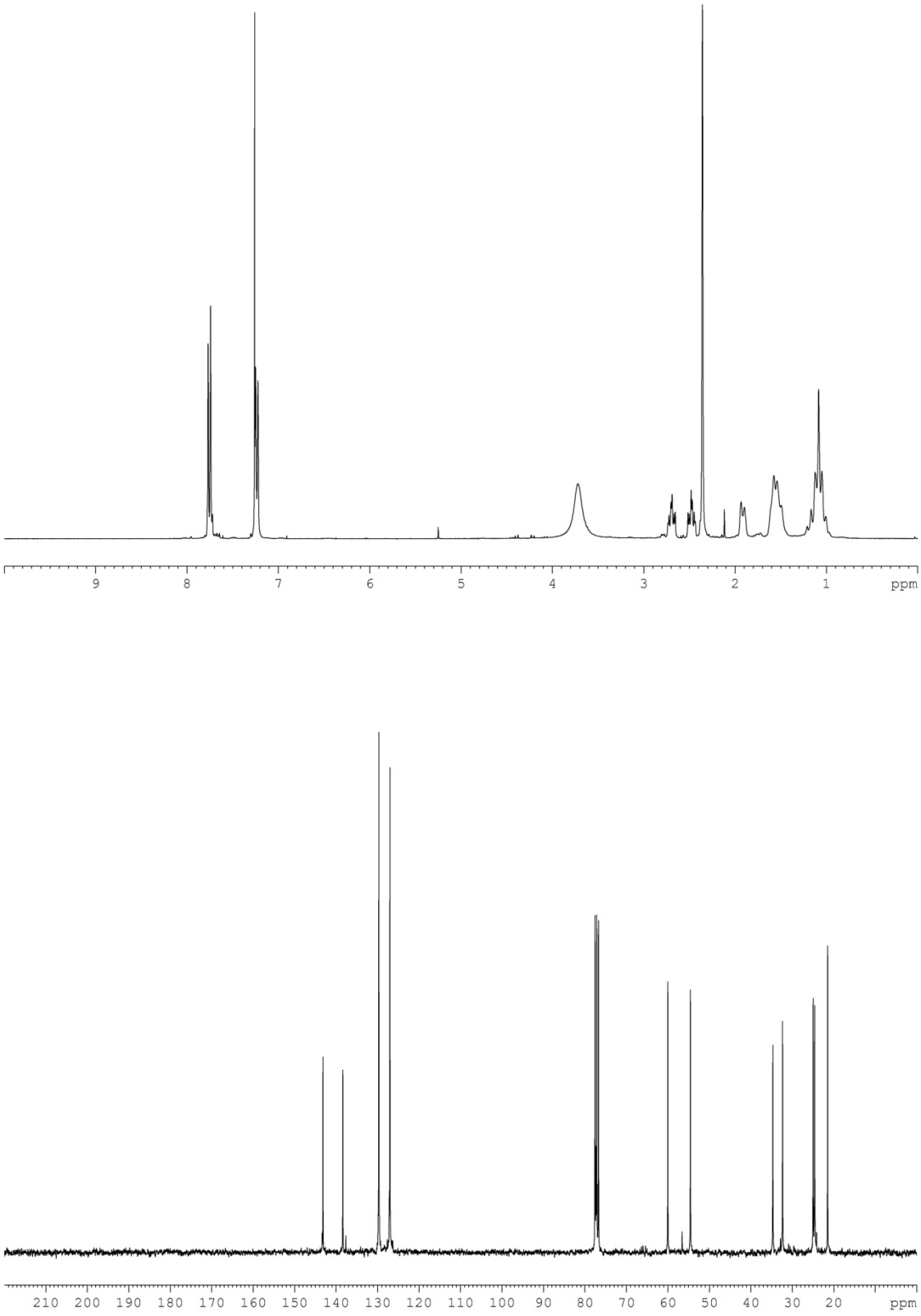

Figure S3. ^{1}H-NMR and ^{13}C-NMR of compound **6c**.

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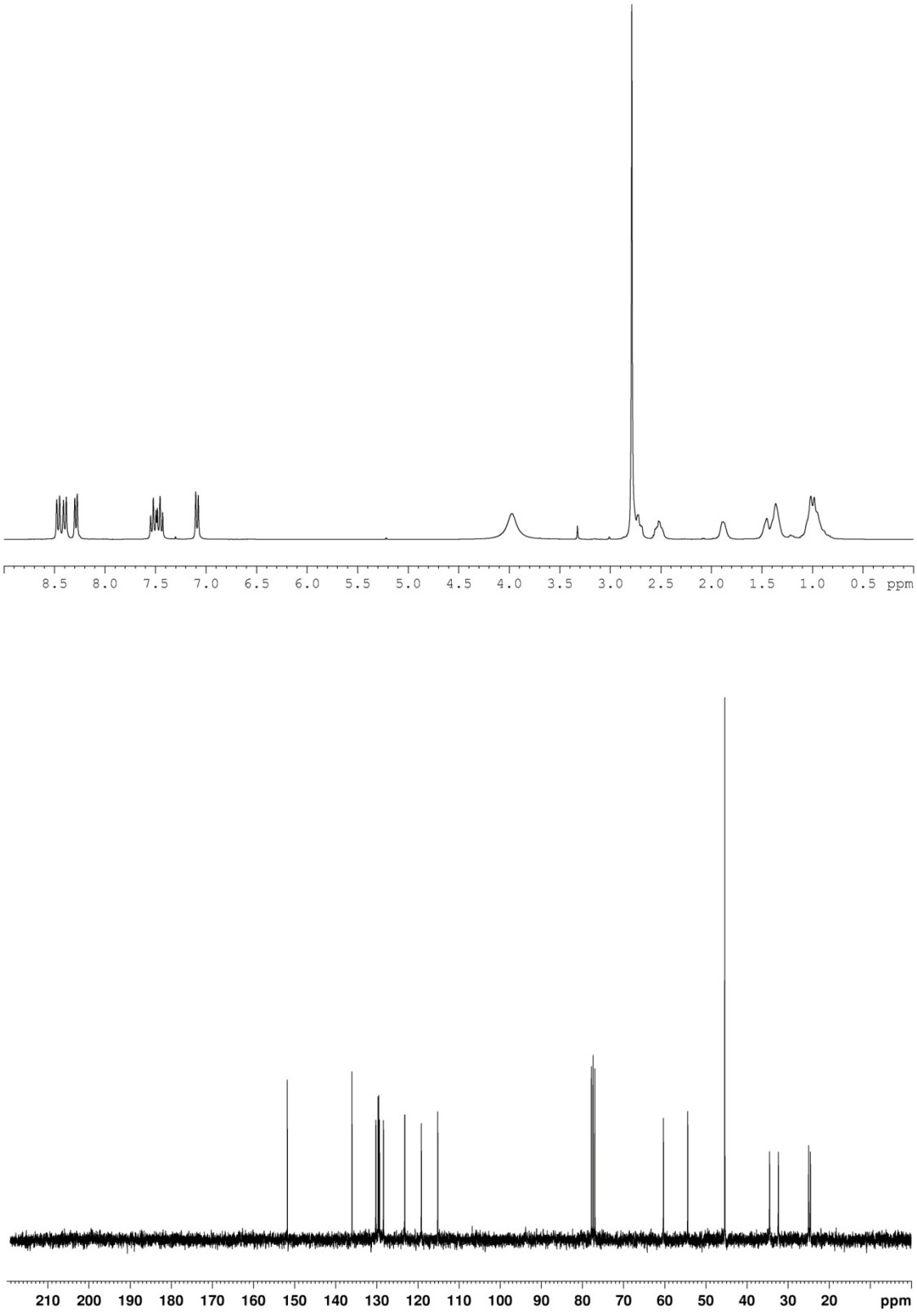

Figure S4. ^{1}H-NMR and ^{13}C-NMR of compound **6d**.

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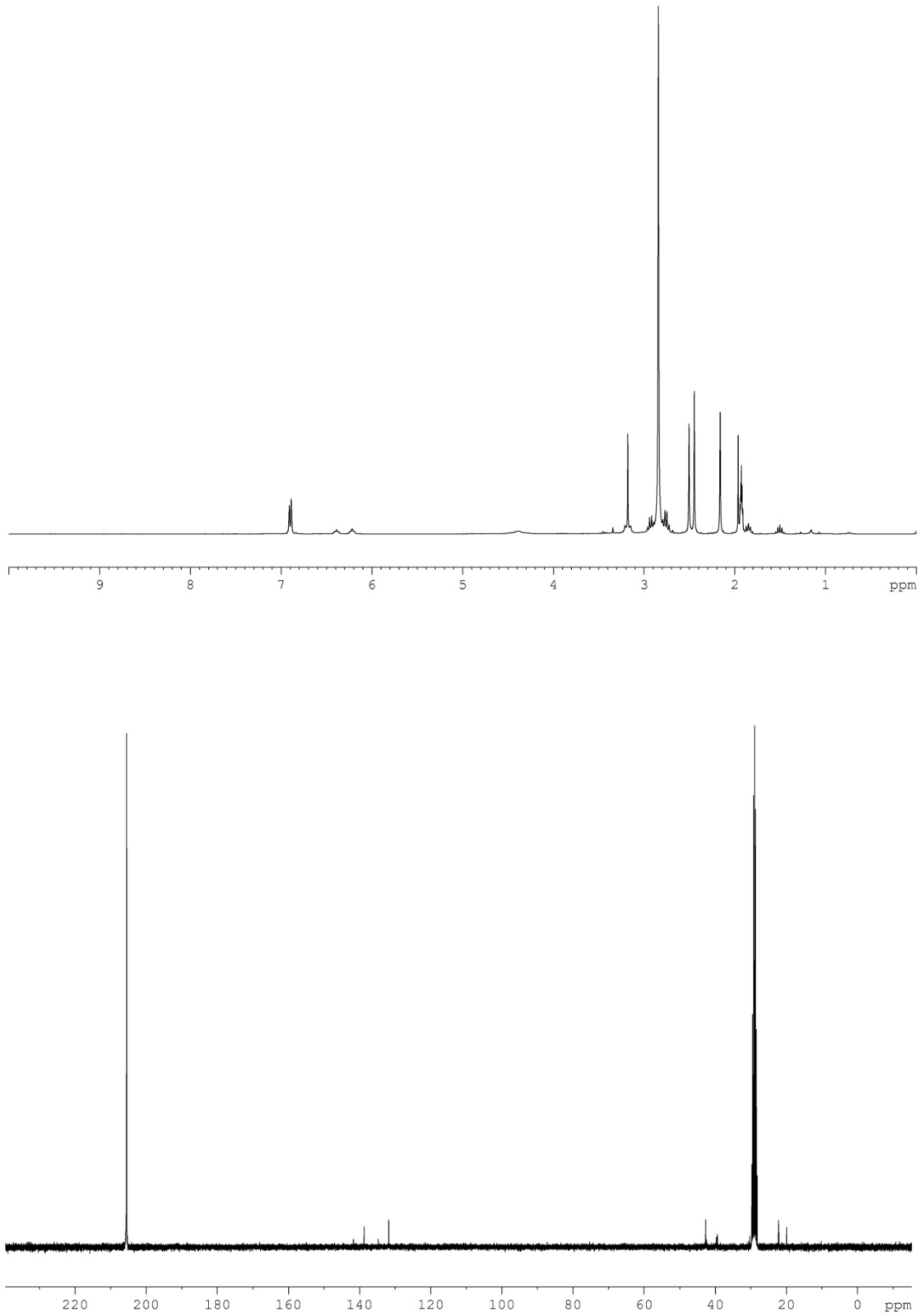

Figure S5. ^{1}H-NMR and ^{13}C-NMR of compound **8a**.

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Figure S6. ^{195}Pt-NMR of compound **8a**[1].

[1] Because of the next experiments we have done, we could say that the minor signal [^{195}Pt (64 MHz, acetone-d_6) δ -2965.7) is an isomer of the **8a** compound [^{195}Pt (64 MHz, acetone-d_6) δ -3115.5].

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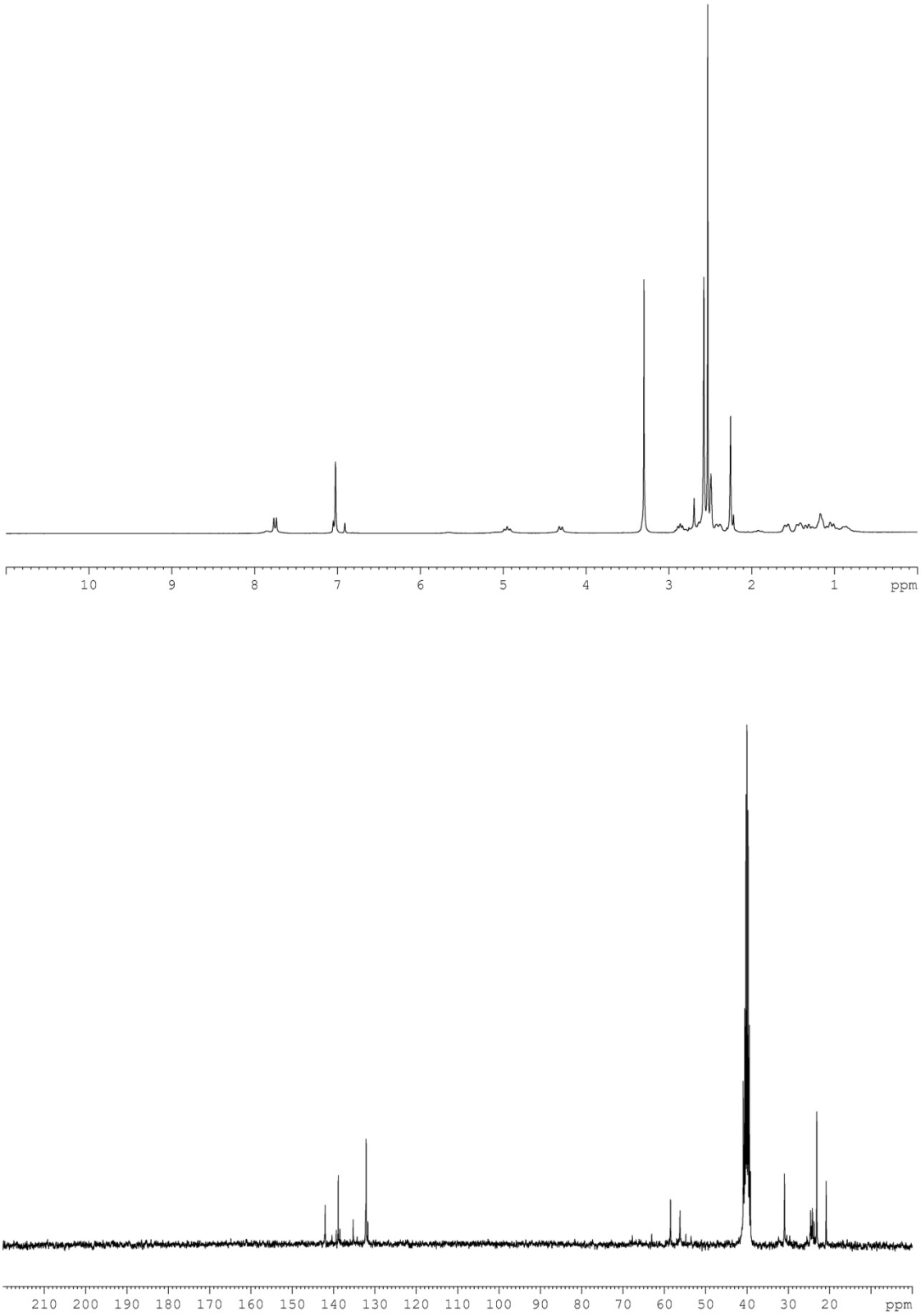

Figure S7. ^{1}H-NMR and ^{13}C-NMR of compound **8b**.

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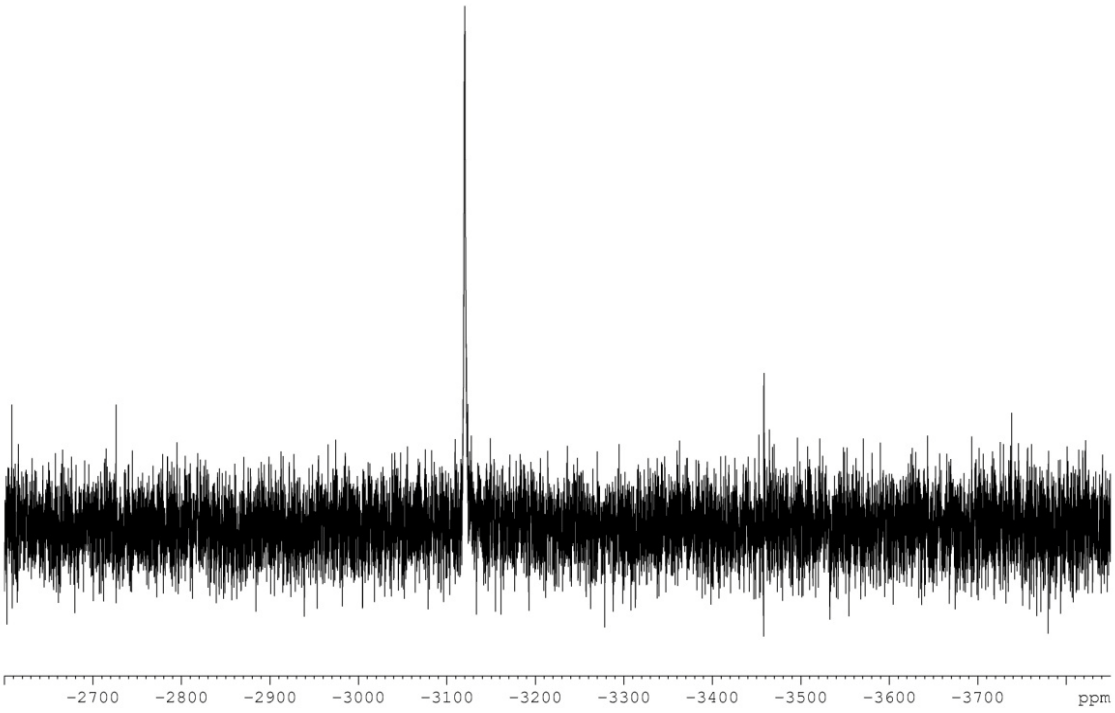

Figure S8. ^{195}Pt-NMR of compound **8b**.

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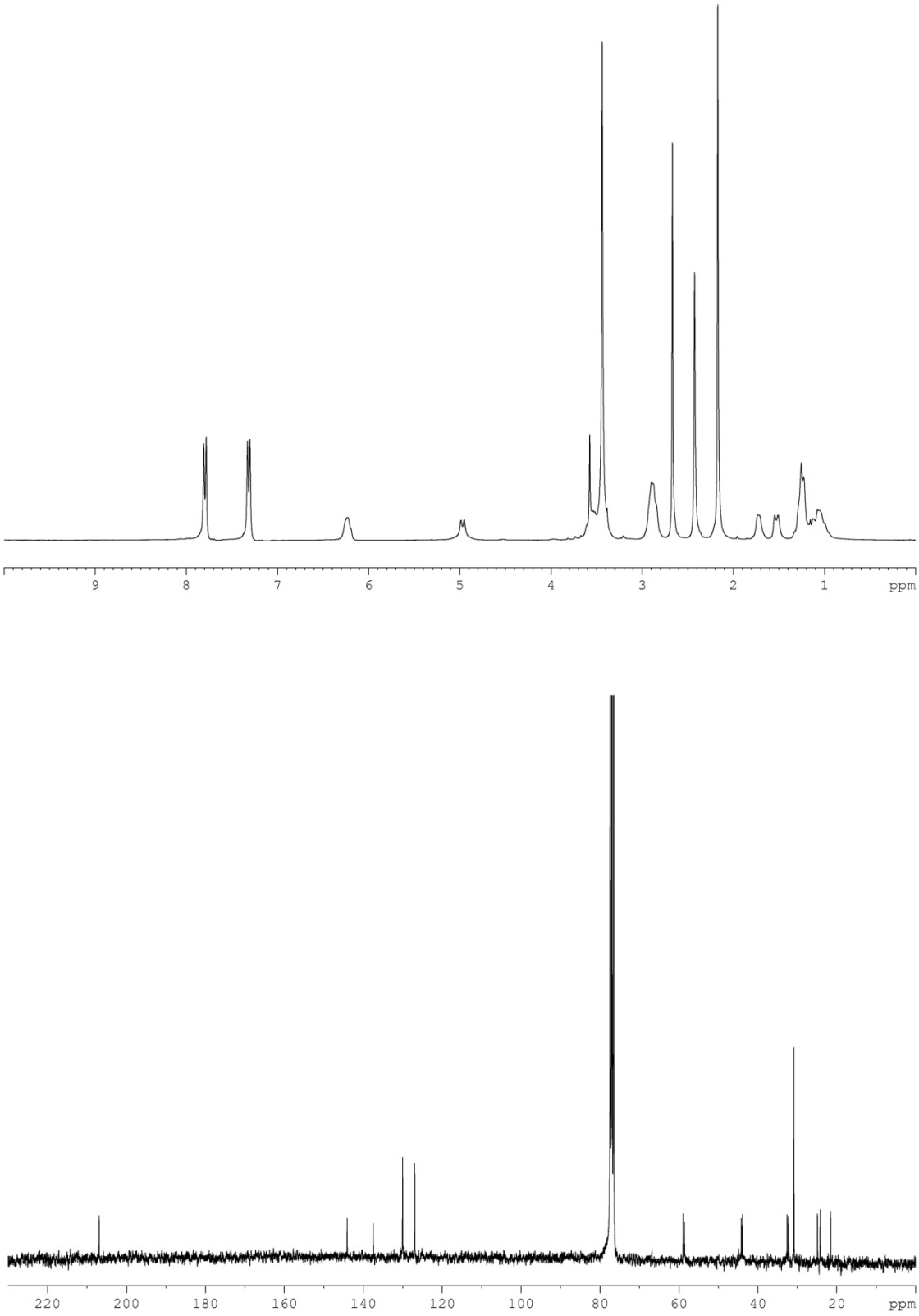

Figure S9. ^{1}H-NMR and ^{13}C-NMR of compound **8c**.

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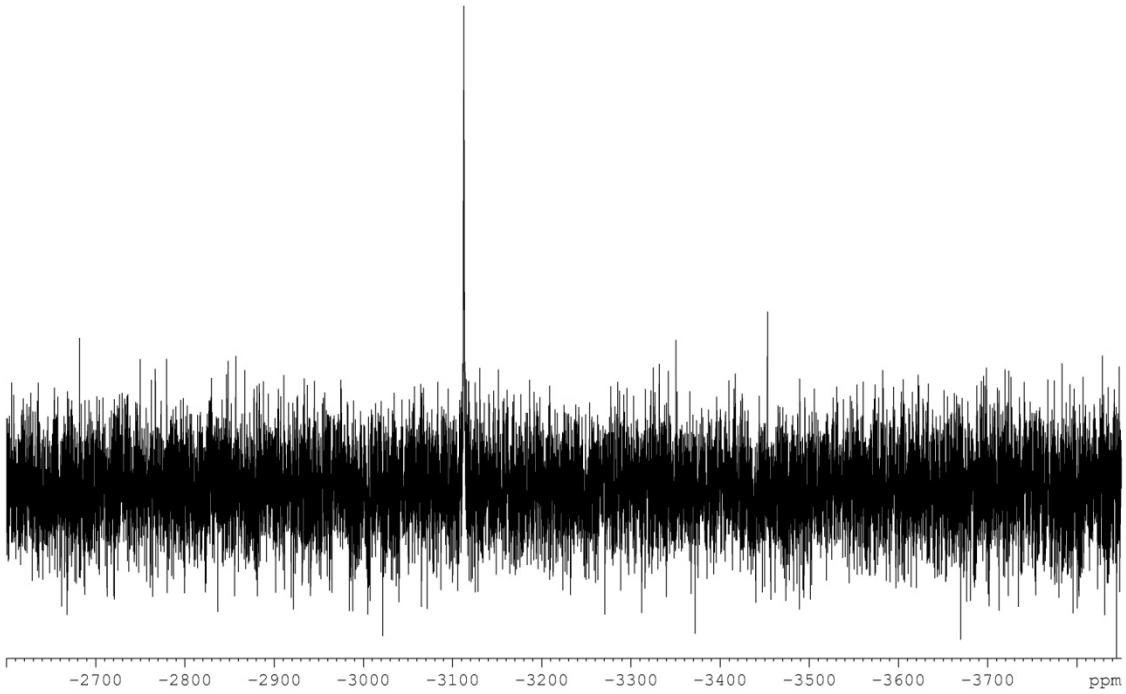

Figure S10. ^{195}Pt-NMR of compound **8c**.

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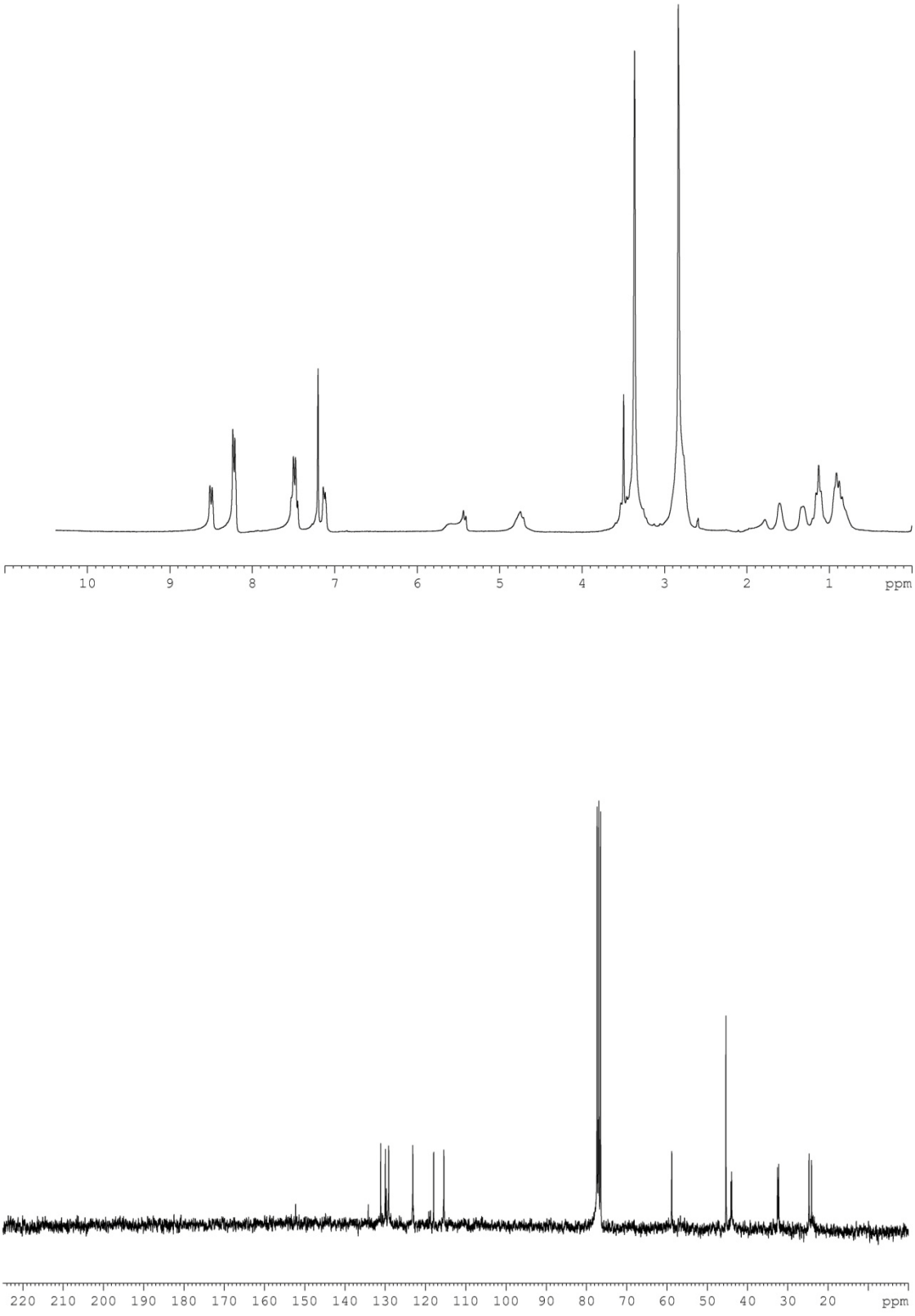

Figure S11. ^{1}H-NMR and ^{13}C-NMR of compound **8d**.

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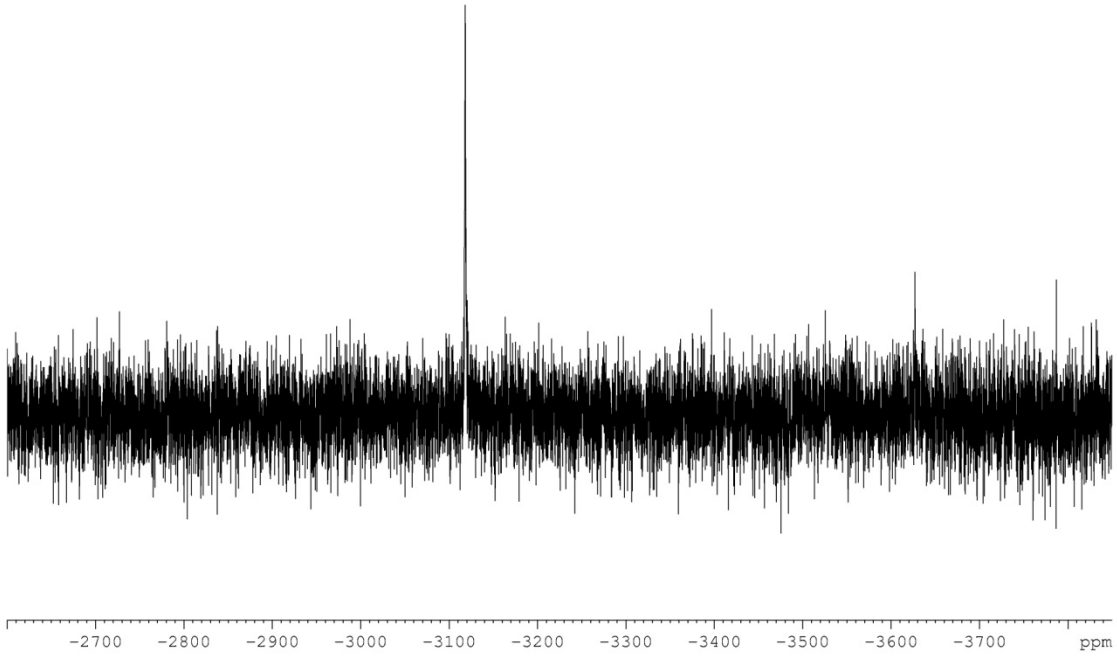
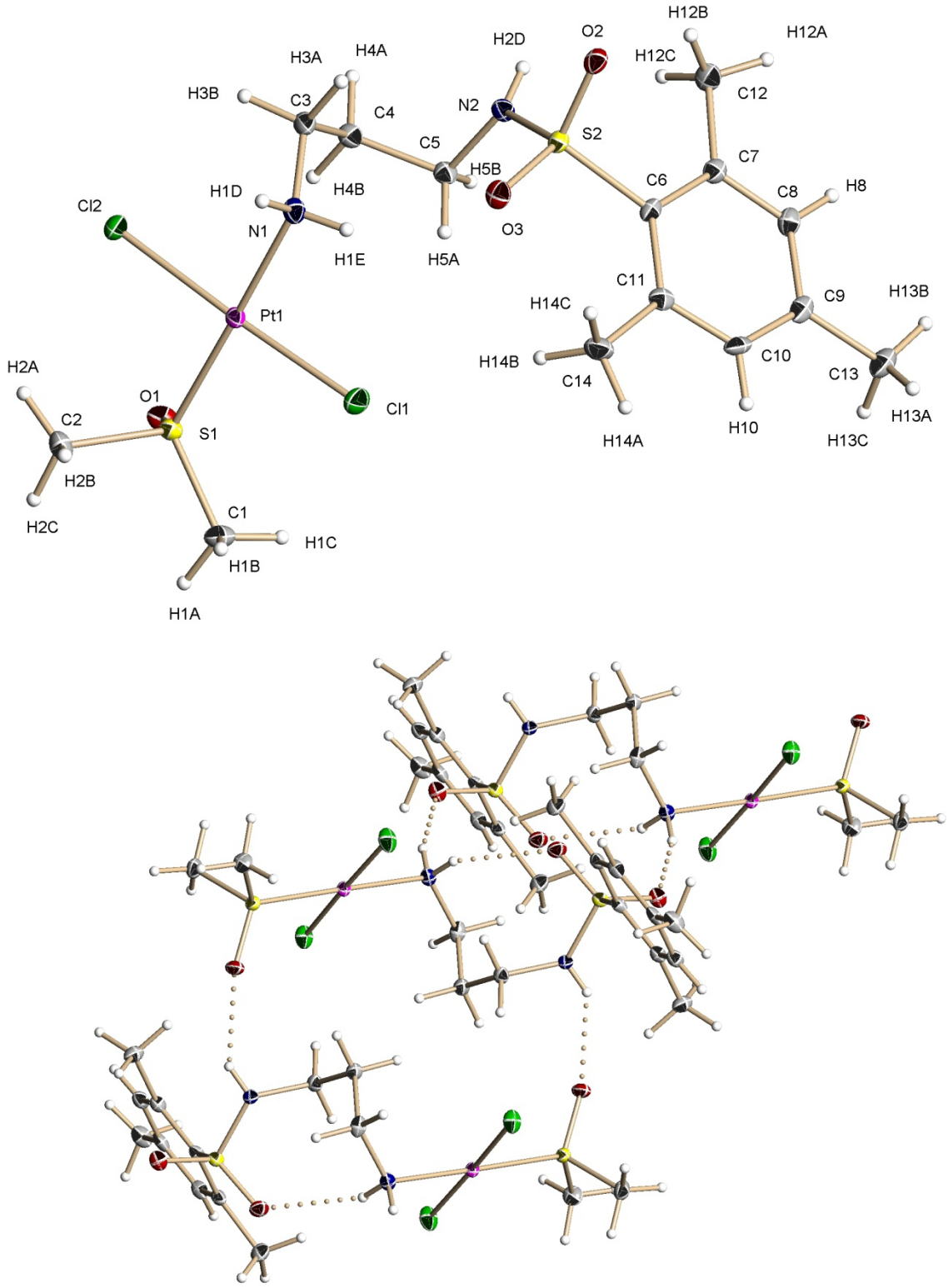


Figure S12. ^{195}Pt-NMR of compound **8d**.

DIFFERENT VIEWS OF THE ORTEP OF COMPOUNDS **8A**



Different inter and intramolecular hydrogen bonds observed in crystals of compound **8a**.

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Table 1. Crystal data and structure refinement for 8a

Identification code	datos_0m	
Empirical formula	C14 H26 Cl2 N2 O3 Pt S2	
Formula weight	600.48	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9973(4) Å	α= 95.196(3)°.
	b = 10.8873(6) Å	β= 98.091(3)°.
	c = 11.5879(6) Å	γ = 90.511(3)°.
Volume	994.56(9) $Å^3$	
Z	2	
Density (calculated)	2.005 Mg/m^3	
Absorption coefficient	7.548 mm^{-1}	
F(000)	584	
Crystal size	0.20 x 0.10 x 0.05 mm^3	
Theta range for data collection	2.47 to 26.37°.	
Index ranges	-9<=h<=9, -13<=k<=13, -14<=l<=14	
Reflections collected	40543	
Independent reflections	4005 [R(int) = 0.0378]	
Completeness to theta = 26.37°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7040 and 0.3136	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4005 / 0 / 242	
Goodness-of-fit on F^2	1.092	
Final R indices [I>2sigma(I)]	R1 = 0.0126, wR2 = 0.0307	
R indices (all data)	R1 = 0.0138, wR2 = 0.0311	
Largest diff. peak and hole	0.919 and -0.481 $e.Å^{-3}$	

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Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 8a U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pt(1)	2884(1)	3652(1)	11876(1)	10(1)
S(1)	1622(1)	5281(1)	12617(1)	12(1)
S(2)	3910(1)	852(1)	7791(1)	11(1)
C(1)	-586(3)	5312(2)	12168(2)	19(1)
C(2)	1701(3)	5199(2)	14142(2)	19(1)
C(3)	5807(3)	2356(2)	10836(2)	15(1)
C(4)	5788(3)	3376(2)	10031(2)	14(1)
C(5)	4612(3)	3115(2)	8883(2)	13(1)
C(6)	2400(3)	1246(2)	6603(2)	12(1)
C(7)	3022(3)	1584(2)	5594(2)	14(1)
C(8)	1874(3)	1854(2)	4642(2)	15(1)
C(9)	146(3)	1809(2)	4657(2)	15(1)
C(10)	-426(3)	1480(2)	5659(2)	15(1)
C(11)	645(3)	1188(2)	6650(2)	13(1)
C(12)	4871(3)	1696(2)	5474(2)	17(1)
C(13)	-1076(3)	2104(2)	3609(2)	19(1)
C(14)	-189(3)	831(2)	7667(2)	18(1)
Cl(1)	579(1)	2998(1)	10557(1)	21(1)
Cl(2)	5276(1)	4227(1)	13179(1)	18(1)
N(1)	4111(3)	2147(2)	11196(2)	14(1)
N(2)	5158(2)	2011(2)	8222(2)	13(1)
O(1)	2311(2)	6491(1)	12438(1)	17(1)
O(2)	4928(2)	-109(1)	7337(1)	15(1)
O(3)	3050(2)	621(1)	8755(1)	16(1)

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Table 3. Bond lengths [Å] and angles [°] for 8a

Pt(1)-N(1)	2.0692(19)
Pt(1)-S(1)	2.2138(5)
Pt(1)-Cl(1)	2.2867(6)
Pt(1)-Cl(2)	2.3072(6)
S(1)-O(1)	1.4663(16)
S(1)-C(2)	1.769(2)
S(1)-C(1)	1.771(2)
S(2)-O(3)	1.4315(16)
S(2)-O(2)	1.4383(16)
S(2)-N(2)	1.6006(19)
S(2)-C(6)	1.785(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-H(2A)	0.9800
C(2)-H(2B)	0.9800
C(2)-H(2C)	0.9800
C(3)-N(1)	1.496(3)
C(3)-C(4)	1.512(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.520(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-N(2)	1.469(3)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.410(3)
C(6)-C(11)	1.413(3)
C(7)-C(8)	1.388(3)
C(7)-C(12)	1.510(3)
C(8)-C(9)	1.385(3)
C(8)-H(8)	0.91(3)
C(9)-C(10)	1.380(3)
C(9)-C(13)	1.508(3)
C(10)-C(11)	1.395(3)

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C(10)-H(10)	0.90(3)
C(11)-C(14)	1.513(3)
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
N(1)-H(1D)	0.86(3)
N(1)-H(1E)	0.87(3)
N(2)-H(2D)	0.81(3)

N(1)-Pt(1)-S(1)	178.82(6)
N(1)-Pt(1)-Cl(1)	86.73(6)
S(1)-Pt(1)-Cl(1)	94.37(2)
N(1)-Pt(1)-Cl(2)	90.51(6)
S(1)-Pt(1)-Cl(2)	88.39(2)
Cl(1)-Pt(1)-Cl(2)	177.22(2)
O(1)-S(1)-C(2)	107.91(11)
O(1)-S(1)-C(1)	106.72(10)
C(2)-S(1)-C(1)	101.06(12)
O(1)-S(1)-Pt(1)	116.31(7)
C(2)-S(1)-Pt(1)	108.78(8)
C(1)-S(1)-Pt(1)	114.80(8)
O(3)-S(2)-O(2)	118.26(9)
O(3)-S(2)-N(2)	106.77(10)
O(2)-S(2)-N(2)	106.29(10)
O(3)-S(2)-C(6)	109.04(10)
O(2)-S(2)-C(6)	107.30(10)
N(2)-S(2)-C(6)	108.89(10)
S(1)-C(1)-H(1A)	109.5
S(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
S(1)-C(1)-H(1C)	109.5

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H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
S(1)-C(2)-H(2A)	109.5
S(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
S(1)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
N(1)-C(3)-C(4)	111.97(18)
N(1)-C(3)-H(3A)	109.2
C(4)-C(3)-H(3A)	109.2
N(1)-C(3)-H(3B)	109.2
C(4)-C(3)-H(3B)	109.2
H(3A)-C(3)-H(3B)	107.9
C(3)-C(4)-C(5)	113.93(19)
C(3)-C(4)-H(4A)	108.8
C(5)-C(4)-H(4A)	108.8
C(3)-C(4)-H(4B)	108.8
C(5)-C(4)-H(4B)	108.8
H(4A)-C(4)-H(4B)	107.7
N(2)-C(5)-C(4)	109.83(17)
N(2)-C(5)-H(5A)	109.7
C(4)-C(5)-H(5A)	109.7
N(2)-C(5)-H(5B)	109.7
C(4)-C(5)-H(5B)	109.7
H(5A)-C(5)-H(5B)	108.2
C(7)-C(6)-C(11)	120.9(2)
C(7)-C(6)-S(2)	117.38(16)
C(11)-C(6)-S(2)	121.70(16)
C(8)-C(7)-C(6)	118.6(2)
C(8)-C(7)-C(12)	116.8(2)
C(6)-C(7)-C(12)	124.6(2)
C(9)-C(8)-C(7)	122.1(2)
C(9)-C(8)-H(8)	119.4(17)
C(7)-C(8)-H(8)	118.5(17)
C(10)-C(9)-C(8)	118.0(2)
C(10)-C(9)-C(13)	121.0(2)
C(8)-C(9)-C(13)	121.0(2)

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C(9)-C(10)-C(11)	123.4(2)
C(9)-C(10)-H(10)	116.4(16)
C(11)-C(10)-H(10)	120.2(17)
C(10)-C(11)-C(6)	117.0(2)
C(10)-C(11)-C(14)	116.7(2)
C(6)-C(11)-C(14)	126.3(2)
C(7)-C(12)-H(12A)	109.5
C(7)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(7)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(9)-C(13)-H(13A)	109.5
C(9)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(9)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(11)-C(14)-H(14A)	109.5
C(11)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(11)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(3)-N(1)-Pt(1)	118.31(14)
C(3)-N(1)-H(1D)	108.1(18)
Pt(1)-N(1)-H(1D)	106.8(18)
C(3)-N(1)-H(1E)	110.0(16)
Pt(1)-N(1)-H(1E)	106.5(16)
H(1D)-N(1)-H(1E)	107(2)
C(5)-N(2)-S(2)	121.78(16)
C(5)-N(2)-H(2D)	115.5(19)
S(2)-N(2)-H(2D)	117.6(19)

Symmetry transformations used to generate equivalent atoms:

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Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 8a The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pt(1)	11(1)	11(1)	9(1)	1(1)	1(1)	1(1)
S(1)	12(1)	12(1)	13(1)	1(1)	3(1)	0(1)
S(2)	12(1)	11(1)	11(1)	2(1)	0(1)	0(1)
C(1)	13(1)	19(1)	24(1)	1(1)	3(1)	3(1)
C(2)	25(1)	20(1)	12(1)	0(1)	5(1)	1(1)
C(3)	16(1)	18(1)	11(1)	2(1)	1(1)	7(1)
C(4)	15(1)	14(1)	14(1)	1(1)	3(1)	1(1)
C(5)	15(1)	11(1)	14(1)	2(1)	3(1)	3(1)
C(6)	12(1)	9(1)	13(1)	1(1)	-2(1)	0(1)
C(7)	14(1)	11(1)	14(1)	0(1)	1(1)	-1(1)
C(8)	18(1)	13(1)	13(1)	1(1)	-1(1)	-1(1)
C(9)	18(1)	8(1)	17(1)	-2(1)	-4(1)	1(1)
C(10)	9(1)	13(1)	21(1)	-3(1)	0(1)	2(1)
C(11)	14(1)	9(1)	16(1)	0(1)	3(1)	2(1)
C(12)	16(1)	22(1)	15(1)	4(1)	3(1)	-3(1)
C(13)	20(1)	17(1)	20(1)	1(1)	-5(1)	2(1)
C(14)	14(1)	21(1)	21(1)	1(1)	6(1)	1(1)
Cl(1)	16(1)	25(1)	20(1)	-7(1)	-3(1)	1(1)
Cl(2)	15(1)	23(1)	15(1)	-2(1)	-3(1)	4(1)
N(1)	18(1)	13(1)	12(1)	2(1)	1(1)	2(1)
N(2)	12(1)	13(1)	13(1)	0(1)	3(1)	-2(1)
O(1)	18(1)	11(1)	24(1)	3(1)	8(1)	-2(1)
O(2)	17(1)	14(1)	14(1)	2(1)	-2(1)	4(1)
O(3)	18(1)	17(1)	14(1)	5(1)	2(1)	-2(1)

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 8a

	x	y	z	U(eq)
H(1A)	-1057	6020	12587	28
H(1B)	-1115	4549	12345	28
H(1C)	-809	5385	11324	28
H(2A)	2878	5270	14519	28
H(2B)	1212	4408	14284	28
H(2C)	1056	5875	14467	28
H(3A)	6166	1583	10432	18
H(3B)	6642	2572	11543	18
H(4A)	6949	3511	9857	17
H(4B)	5442	4147	10444	17
H(5A)	3443	2983	9043	16
H(5B)	4624	3831	8415	16
H(12A)	4993	1723	4647	26
H(12B)	5467	983	5775	26
H(12C)	5355	2454	5921	26
H(13A)	-1929	1439	3407	29
H(13B)	-461	2183	2944	29
H(13C)	-1631	2881	3795	29
H(14A)	-1418	789	7441	28
H(14B)	99	1449	8337	28
H(14C)	210	24	7884	28
H(1D)	4220(30)	1630(30)	11720(30)	21(7)
H(1E)	3420(30)	1800(20)	10610(20)	11(6)
H(2D)	5930(40)	2120(20)	7850(20)	17(7)
H(8)	2270(30)	2040(20)	3980(20)	20(7)
H(10)	-1560(40)	1490(20)	5660(20)	17(7)

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Table 6. Torsion angles [°] for 8a

N(1)-Pt(1)-S(1)-O(1)	44(3)
Cl(1)-Pt(1)-S(1)-O(1)	-114.93(8)
Cl(2)-Pt(1)-S(1)-O(1)	65.32(8)
N(1)-Pt(1)-S(1)-C(2)	-78(3)
Cl(1)-Pt(1)-S(1)-C(2)	123.03(9)
Cl(2)-Pt(1)-S(1)-C(2)	-56.73(9)
N(1)-Pt(1)-S(1)-C(1)	170(3)
Cl(1)-Pt(1)-S(1)-C(1)	10.68(9)
Cl(2)-Pt(1)-S(1)-C(1)	-169.08(9)
N(1)-C(3)-C(4)-C(5)	-61.9(2)
C(3)-C(4)-C(5)-N(2)	-61.7(2)
O(3)-S(2)-C(6)-C(7)	176.04(16)
O(2)-S(2)-C(6)-C(7)	-54.76(19)
N(2)-S(2)-C(6)-C(7)	59.90(19)
O(3)-S(2)-C(6)-C(11)	-5.8(2)
O(2)-S(2)-C(6)-C(11)	123.37(18)
N(2)-S(2)-C(6)-C(11)	-121.98(18)
C(11)-C(6)-C(7)-C(8)	-0.3(3)
S(2)-C(6)-C(7)-C(8)	177.85(16)
C(11)-C(6)-C(7)-C(12)	178.7(2)
S(2)-C(6)-C(7)-C(12)	-3.2(3)
C(6)-C(7)-C(8)-C(9)	0.4(3)
C(12)-C(7)-C(8)-C(9)	-178.6(2)
C(7)-C(8)-C(9)-C(10)	-0.2(3)
C(7)-C(8)-C(9)-C(13)	-179.8(2)
C(8)-C(9)-C(10)-C(11)	-0.2(3)
C(13)-C(9)-C(10)-C(11)	179.4(2)
C(9)-C(10)-C(11)-C(6)	0.3(3)
C(9)-C(10)-C(11)-C(14)	-179.3(2)
C(7)-C(6)-C(11)-C(10)	-0.1(3)
S(2)-C(6)-C(11)-C(10)	-178.12(16)
C(7)-C(6)-C(11)-C(14)	179.5(2)
S(2)-C(6)-C(11)-C(14)	1.4(3)
C(4)-C(3)-N(1)-Pt(1)	-51.3(2)
S(1)-Pt(1)-N(1)-C(3)	-29(3)
Cl(1)-Pt(1)-N(1)-C(3)	129.60(16)

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Cl(2)-Pt(1)-N(1)-C(3)	-50.66(16)
C(4)-C(5)-N(2)-S(2)	124.29(18)
O(3)-S(2)-N(2)-C(5)	-44.54(19)
O(2)-S(2)-N(2)-C(5)	-171.64(16)
C(6)-S(2)-N(2)-C(5)	73.05(19)

Symmetry transformations used to generate equivalent atoms:

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Table 7. Hydrogen bonds for datos_0m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2D)...O(1)#1	0.81(3)	2.14(3)	2.819(2)	141(2)
N(1)-H(1E)...O(3)	0.87(3)	2.38(3)	3.151(3)	148(2)
N(1)-H(1D)...O(2)#2	0.86(3)	2.13(3)	2.958(2)	161(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+2 #2 -x+1,-y,-z+2

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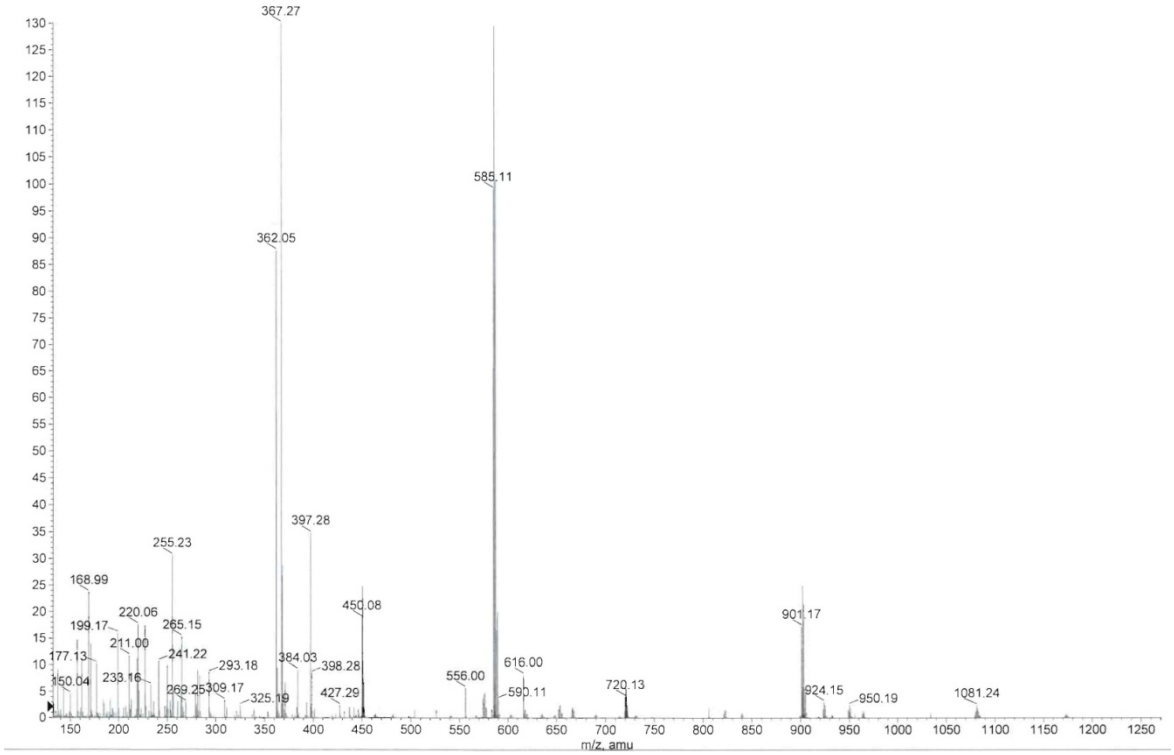
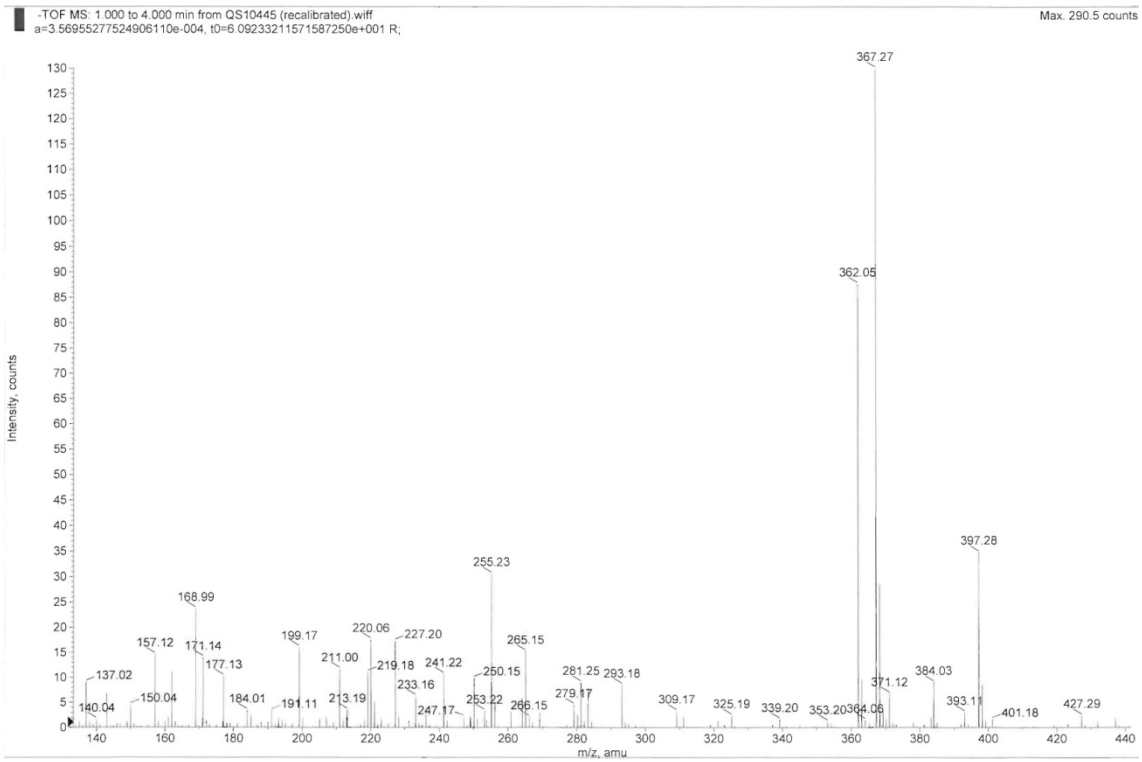
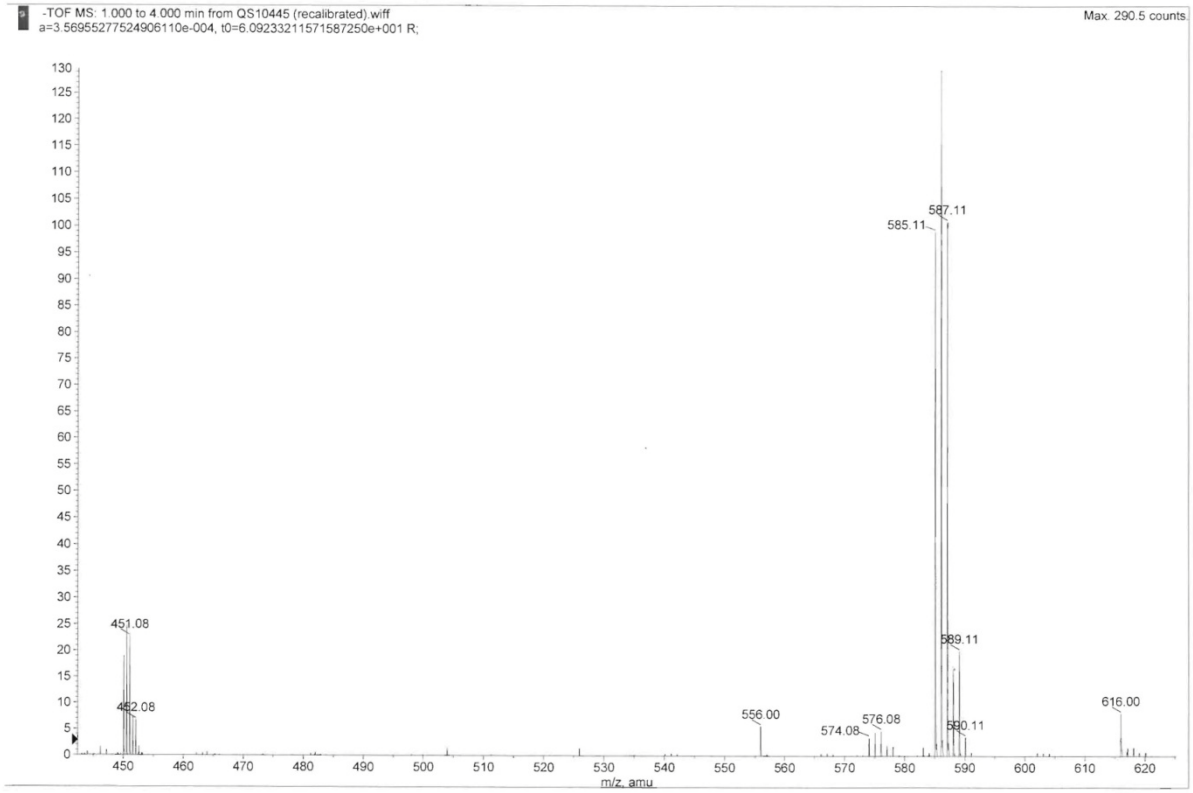
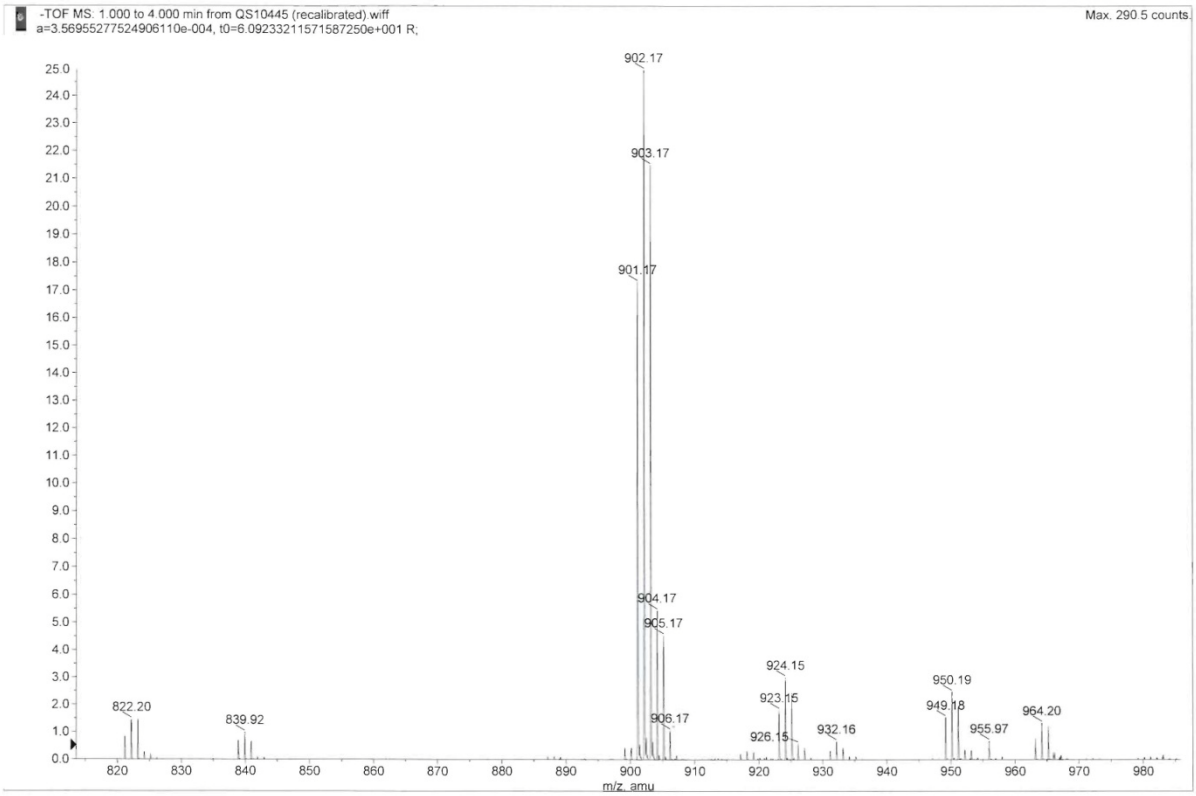
Mass-Spectra experiments in the interaction of compound 8d with GMP



Enlargement of the main signals:




-TOF MS: 1.000 to 4.000 min from QS10445 (recalibrated).wiff
a=3.5695527752490611 0e-004, t0=6.0923321157158725 0e+001 R;
Max. 290.5 counts.
587.11
585.11
451.08
589.11
452.08
556.00
576.08
574.08
590.11
616.00
m/z, amu


-TOF MS: 1.000 to 4.000 min from QS10445 (recalibrated).wiff
a=3.5695527752490611 0e-004, t0=6.0923321157158725 0e+001 R;
Max. 290.5 counts.
902.17
903.17
901.17
904.17
905.17
924.15
950.19
923.15
949.18
964.20
822.20
839.92
906.17
932.16
926.15
955.97
m/z, amu

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Biological section

All starting materials were commercially available research-grade chemicals and used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal calf serum (FCS) was from Gibco (Grand Island, NY), trichloroacetic acid (TCA) and glutamine were from Merck (Darmstadt, Germany), and penicillin G, streptomycin, DMSO and sulforhodamine B (SRB) were from Sigma (St Louis, MO).

Cells, culture and plating

The human solid tumor cell lines HBL-100, HeLa, Ishikawa, SW1573, and WiDr were used in this study. These cell lines were a kind gift from Prof. G. J. Peters (VU Medical Center, Amsterdam, The Netherlands). Cells were maintained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat inactivated fetal calf serum and 2 mM L-glutamine in a 37°C, 5% CO_2, 95% humidified air incubator. Exponentially growing cells were trypsinized and re-suspended in antibiotic containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single cell suspensions displaying >97% viability by trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 mL per well at densities 10 000 (SW1573 and HBL-100) of 15 000 (HeLa, and Ishikawa), and 20 000 (WiDr) cells per well, based on their doubling times.

Chemosensitivity testing

Compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (0.25% v/v, negative control). Each agent was tested in triplicate at different dilutions in the range of 1–100 µM. The drug treatment was started on day 1 after plating. Drug incubation times were 48 h, after which time cells were

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precipitated with 25 µL ice-cold TCA (50% w/v) and fixed for 60 min at 4°C. Then the SRB assay was performed. The optical density (OD) of each well was measured at 492 nm, using BioTek's PowerWave XS Absorbance Microplate Reader. Values were corrected for background OD from wells only containing medium.