Supporting Information for

The Effect of Ligand Lipophilicity on the Nanoparticle Encapsulation of Pt(IV) Prodrugs

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Contents

Characterization of 2 – 10

*Compound **2**. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOCCH_3)_2$]: Pale yellow solid, 222 mg (88%), mp. (dec) 245 – 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.89 (s, 6H), 6.52 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 22.94, 178.31; IR (KBr, cm^{-1}) 3270 (m), 3221 (m), 3080 (m), 1653 (s), 1429 (w), 1364 (s), 1300 (s), 1273 (s), 1023 (w), 943 (w), 702 (m); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 418.2 (calc. 418.0), $[M+TFA]^-$ 530.8 (calc. 531.0); Anal. Calc. for $C_4H_{12}Cl_2N_2O_4Pt$: C 11.49, H 2.89, N 6.70. Found: C 11.97, H 2.87, N 6.65.

*Compound **3**. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOCCH_2CH_3)_2$]: Pale yellow solid, 202 mg (76%), mp. (dec) 260 – 265 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.94 (t, 6H, 7.5 Hz), 2.24 (q, 4H, 7.5 Hz), 6.53 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 10.08, 28.73, 181.45; IR (KBr, cm^{-1}) 3230 (br m), 3101 (m), 2984 (w), 2945 (w), 1648 (s), 1575 (m), 1461 (w), 1416 (w), 1362 (m), 1241 (s), 1077 (w), 1014 (w), 810 (w), 671 (m); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 445.0 (calc. 445.0), $[M+TFA]^-$ 558.7 (calc. 559.0); Anal. Calc. for $C_6H_{16}Cl_2N_2O_4Pt$: C 16.15, H 3.61, N 6.28. Found: C 16.17, H 3.56, N 6.22.

*Compound **4**. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOC(CH_2)_2CH_3)_2$]: Off-white solid, 201 mg (71%), mp. (dec) 270 – 274 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.87 (t, 6H, 7.5 Hz), 1.47 (sext, 4H, 7.3 Hz), 2.19 (t, 4H, 7.25 Hz), 6.53 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.70, 18.86, 37.66, 180.77; IR (KBr, cm^{-1}) 3335 (m), 3193 (br s), 3092 (m), 2963 (m), 2933 (m), 2873 (m), 1662 (s), 1628 (s), 1567 (m), 1458 (w), 1412 (w), 1382 (m), 1293 (br s), 1216 (m), 1094 (w), 954 (w), 669 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 472.9 (calc. 473.0), $[M+TFA]^-$ 585.9 (calc. 586.0); Anal. Calc. for $C_8H_{20}Cl_2N_2O_4Pt$: C 20.26, H 4.25, N 5.91. Found: C 20.04, H 4.01, N 5.93.

*Compound **5**. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOC(CH_2)_3CH_3)_2$]: Off-white solid, 220 mg (73%), mp. (dec) 201 – 203 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.85 (t, 6H, 7.3 Hz), 1.28 (sext, 4H, 7.4 Hz), 1.43 (quin, 4H, 7.5 Hz), 2.21 (t, 4H, 7.5 Hz), 6.53 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.83, 21.75, 27.60, 35.42, 180.89; IR (KBr, cm^{-1}) 3261 (s), 3213 (s), 3110 (m), 2960 (s), 2934 (s), 2873 (m), 1659 (s), 1623 (s), 1584 (s), 1539 (m), 1464 (w), 1418 (w), 1372 (m), 1327 (s), 1289 (s), 1216 (s), 1103 (w), 946 (m), 890 (w), 798 (w), 762 (m), 715 (m), 443 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 501.7

(calc. 501.3), $[M+TFA]^-$ 614.7 (calc. 615.1); Anal. Calc. for $C_{10}H_{24}Cl_2N_2O_4Pt$: C 23.91, H 4.82, N 5.58. Found: C 23.48, H 4.65, N 5.43.

Compound ***6****. cis,cis,trans*-$[Pt(NH_3)_2Cl_2(OOC(CH_2)_4CH_3)_2]$: Off-white solid, 240 mg (75%), mp. (dec) 194 – 196 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.85 (t, 6H, 6.8 Hz), 1.25 (m, 8H), 1.45 (quin, 4H, 7.4 Hz), 2.20 (t, 4H, 7.5 Hz), 6.52 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.90, 21. 96, 25.12, 30.84, 35.65, 180.88; IR (KBr, cm^{-1}) 3257 (m), 3205 (m), 3118 (m), 2954 (m), 2931 (m), 2871 (w), 1658 (s), 1622 (m), 1584 (m), 1540 (w), 1466 (w), 1417 (w), 1373 (m), 1330 (m), 1287 (m), 1255 (m), 1215 (m), 1106 (w), 949 (w), 713 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 529.4 (calc. 529.1), $[M+TFA]^-$ 642.7 (calc. 643.1); Anal. Calc. for $C_{12}H_{28}Cl_2N_2O_4Pt$: C 27.18, H 5.32, N 5.28. Found: C 26.94, H 5.19, N 5.27.

Compound ***7****. cis,cis,trans*-$[Pt(NH_3)_2Cl_2(OOC(CH_2)_5CH_3)_2]$: Off-white solid, 197 mg (60%), mp. (dec) 185 – 191 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.86 (t, 6H, 6.8 Hz), 1.25 (m, 12H), 1.44 (quin, 4H, 7.3 Hz), 2.20 (t, 4H, 7.5 Hz), 6.52 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 15.13, 23.18, 26.57, 29.46, 32.31, 36.86, 182.03; IR (KBr, cm^{-1}) 3256 (s), 3201 (s), 2957 (s), 2929 (s), 2857 (m), 1658 (s), 1617 (s), 1582 (s), 1466 (m), 1415 (m), 1372 (s), 1333 (s), 1284 (s), 1242 (s), 1208 (s), 1107 (w), 951 (w), 888 (w), 725 (w), 676 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 557.1 (calc. 557.1), $[M+TFA]^-$ 670.9 (calc. 671.1); Anal. Calc. for $C_{14}H_{32}Cl_2N_2O_4Pt$: C 30.11, H 5.78, N 5.02. Found: C 30.60, H 5.76, N 5.19.

Compound ***8****. cis,cis,trans*-$[Pt(NH_3)_2Cl_2(OOC(CH_2)_6CH_3)_2]$: Off-white solid, 226 mg (64%), mp. (dec) 186 – 191 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.85 (t, 6H, 6.9 Hz), 1.24 (m, 16H), 1.44 (quin, 4H, 7.2 Hz), 2.20 (t, 4H, 7.5 Hz), 6.52 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.97, 22.09, 25.45, 28.58, 28.59, 31.21, 35.69, 180.87; IR (KBr, cm^{-1}) 3247 (m), 3205 (m), 3110 (m), 2955 (m), 2927 (s), 2855 (m), 1658 (s), 1618 (m), 1583 (m), 1537 (w), 1467 (w), 1414 (w), 1375 (m), 1331 (m), 1287 (m), 1234 (m), 1205 (m), 1109 (w), 724 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^-$ 585.4 (calc. 585.2), $[M+TFA]^-$ 698.9 (calc. 698.2); Anal. Calc. for $C_{16}H_{36}Cl_2N_2O_4Pt$: C 32.77, H 6.19, N 4.78. Found: C 32.79, H 6.16, N 4.69.

Compound ***9****. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOC(CH_2)_7CH_3)_2$]: White solid, 270 mg (73%), mp. (dec) 186 – 191 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.84 (t, 6H, 6.9 Hz), 1.24 (m, 20H), 1.44 (quin, 4H, 7.2 Hz), 2.19 (t, 4H, 7.5 Hz), 6.51 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.97, 22.12, 25.45, 28.645, 28.650, 28.89, 31.29, 35.69, 180.86; IR (KBr, cm^{-1}) 3246 (m), 3201 (m), 3114 (w), 2956 (m), 2925 (s), 2854 (m), 1664 (m), 1618 (m), 1577 (w), 1532 (w), 1467 (w), 1377 (m), 1315 (m), 1293 (m), 1227 (m), 1201 (m), 1111 (w), 949 (w), 723 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^–$ 613.5 (calc. 613.2), $[M+TFA]^–$ 726.9 (calc. 727.2); Anal. Calc. for $C_{18}H_{40}Cl_2N_2O_4Pt$: C 35.18, H 6.56, N 4.56. Found: C 35.25, H 6.21, N 4.60.

Compound ***10****. cis,cis,trans*-[$Pt(NH_3)_2Cl_2(OOC(CH_2)_8CH_3)_2$]: White solid, 264 mg (69%), mp. (dec) 185 – 190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 0.85 (t, 6H, 6.7 Hz), 1.24 (m, 24H), 1.44 (quin, 4H, 7.0 Hz), 2.19 (t, 4H, 7.5 Hz), 6.52 (s, 6H); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ = 13.97, 22.12, 25.46, 28.65, 28.72, 28.95, 28.96, 31.33, 35.70, 180.86; IR (KBr, cm^{-1}) 3244 (m), 3201 (m), 3110 (w), 2955 (m), 2922 (s), 2853 (m), 1661 (m), 1618 (m), 1580 (w), 1532 (w), 1468 (w), 1411 (w), 1376 (m), 1332 (m), 1292 (m), 1223 (m), 1198 (m), 1112 (w), 950 (w), 723 (w); ESI-MS (negative ion mode) *m*/*z* = $[M–H]^–$ 641.2 (calc. 641.2), $[M+TFA]^–$ 759.9 (calc. 755.2); Anal. Calc. for $C_{20}H_{44}Cl_2N_2O_4Pt$: C 37.38, H 6.90, N 4.36. Found: C 37.38, H 7.08, N 4.71.

X-ray Crystallography. Diffraction quality crystals of **2** were grown by room temperature vapor diffusion of diethyl ether into a DMSO solution of the compound. Crystals of **3** were grown by room temperature vapor diffusion of diethyl ether into a DMF solution of the compound. Suitable crystals were selected and mounted on a nylon cryoloop in Paratone oil and cooled to 100 K under a stream of nitrogen. A Bruker APEX CCD X-ray diffractometer controlled by the *APEX2* software[1] was used to collect data using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The data were integrated with *SAINT*[2] and absorption, Lorentz, and polarization corrections were calculated by *SADABS*.[3] The space group of the crystal of **2**·2DMSO was determined by analyzing the Laue symmetry and systematic absences of the diffraction pattern with *XPREP*.[4] Using the *SHELXTL-97* software package,[5,6] the structure was solved by the heavy atom method and refined against F^2 using standard procedures.[7] All non-hydrogen atoms were

located on difference Fourier maps and refined anisotropically. Hydrogen atoms were placed at calculated positions for coordinated NH_3 and terminal CH_3 groups and refined with their isotropic displacement parameters (U_{iso}) set equal to 1.5 times the U_{iso} of the atom to which they were attached. One of the DMSO molecules present in the asymmetric unit displays a pyramidal inversion disorder, equivalent to a 180° rotation about the long axis of the molecule, as commonly encountered.[8] The hydrogen atoms of this disordered solvent molecule were not included in the final model. Analysis of the Laue symmetry of the crystal of **3** revealed that it was twinned by merohedry. An initial solution was obtained with data preliminarily detwinned using *XPREP*. Subsequent refinement was performed as described above and the twin law (0 1 0) (1 0 0) (0 0 -1) was included in the final model. CIF data are provided in the Supporting Information along with tables of bond lengths and angles (Tables S1-S4). The structures, deposited in the Cambridge Structural Database, were checked for missed higher symmetry and twinning with *PLATON*[9] and were further validated using *CheckCIF*.

(1) *APEX2*, 2008-4.0; Bruker AXS, Inc: Madison, WI, 2008.
(2) *SAINT: SAX Area-Detector Integration Program*, 2008/1; University of Göttingen: Göttingen, Germany, 2008.
(3) Sheldrick, G. M. *SADABS: Area-Detector Absorption Correction*, University of Gottingen: Gottingen, Germany, 2008.
(4) *XPREP*, 2008/2; Bruker AXS: Madison, WI, 2008.
(5) Sheldrick, G. M. *SHELXTL-97*, University of Göttingen: Göttingen, Germany, 2000.
(6) Sheldrick, G. M. *Acta Crystallogr. A* **2008**, *64*, 112-122.
(7) Müller, P. *Crystallogr. Rev.* **2009**, *15*, 57-83.
(8) Cruz-Cabeza, A. J.; Day, G. M.; Jones, W. *Phys. Chem. Chem. Phys.* **2011**, *13*, 12808-12816.
(9) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*, Utrecht University: Utrecht, The Netherlands, 2008.

Table S1. X-Ray Crystallographic Refinement Parameters of **2**·2DMSO.

Empirical formula	$C_8H_{18}Cl_2N_2O_6PtS_2$	
Formula weight	568.35	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 7.2454(7) Å	α = 72.516(2) °
	b = 10.2263(10) Å	β = 81.044(2) °
	c = 14.0657(14) Å	γ = 69.485(2) °
Volume	929.51(16) $Å^3$	
Z	2	
Density (calculated)	2.031 Mg/m^3	
Absorption coefficient	8.081 mm^{-1}	
F(000)	544	
Crystal size	0.11 x 0.04 x 0.04 mm^3	
Theta range for data collection	1.52 to 28.77°	
Index ranges	$-9\leq h\leq 9$, $-13\leq k\leq 13$, $-19\leq l\leq 18$	
Reflections collected	19028	
Independent reflections	4781 [R(int) = 0.0280]	
Completeness to theta = 28.77°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7381 and 0.4701	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4781 / 0 / 206	
Goodness-of-fit on F^2	1.308	
Final R indices [I>2sigma(I)]	$R_1 = 0.0342$, $wR_2 = 0.0879$	
R indices (all data)	$R_1 = 0.0365$, $wR_2 = 0.0912$	
Largest diff. peak and hole	3.121 and -2.772 e $Å^{-3}$	

Table S2. X-Ray Crystallographic Refinement Parameters of **3**.

Empirical formula	$C_6H_{16}Cl_2N_2O_4$
Pt	
Formula weight	446.20
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	$P4_3$
Unit cell dimensions	a = 9.2357(3) Å
	c = 13.9563(11) Å
Volume	1190.45(11) $Å^3$
Z	4
Density (calculated)	2.490 Mg/m^3
Absorption coefficient	12.232 mm^{-1}
F(000)	840
Crystal size	0.08 x 0.08 x 0.04 mm^3
Theta range for data collection	1.46 to 28.80°
Index ranges	$-12 \le h \le 12$, $-12 \le k \le 12$, $-18 \le l \le 18$
Reflections collected	24400
Independent reflections	3098 [R(int) = 0.0322]
Completeness to theta = 28.77°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6404 and 0.4411
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3098 / 1 / 141
Goodness-of-fit on F^2	1.065
Final R indices [I>2sigma(I)]	$R_1 = 0.0167$, $wR_2 = 0.0371$
R indices (all data)	$R_1 = 0.0168$, $wR_2 = 0.0371$
Largest diff. peak and hole	0.889 and -0.531 e $Å^{-3}$

Table S3. Selected Bond Lengths and Angles for **2**·2DMSO.

Pt(1)-O(21)	1.999(5)
Pt(1)-N(1)	2.034(5)
Pt(1)-N(2)	2.038(5)
Pt(1)-O(11)	2.050(4)
Pt(1)-Cl(2)	2.3211(17)
Pt(1)-Cl(1)	2.3286(16)
O(11)-C(11)	1.285(8)
O(12)-C(11)	1.233(9)
O(21)-C(21)	1.288(9)
O(22)-C(21)	1.229(10)
O(21)-Pt(1)-N(1)	94.8(2)
O(21)-Pt(1)-N(2)	90.9(2)
N(1)-Pt(1)-N(2)	93.5(2)
O(21)-Pt(1)-O(11)	175.5(2)
N(2)-Pt(1)-Cl(2)	87.30(17)
O(11)-Pt(1)-Cl(2)	93.64(14)
N(2)-Pt(1)-Cl(1)	178.17(17)
O(11)-Pt(1)-Cl(1)	87.89(13)
Cl(2)-Pt(1)-Cl(1)	91.48(7)
C(11)-O(11)-Pt(1)	125.7(4)
O(12)-C(11)-O(11)	126.6(7)
O(12)-C(11)-C(12)	120.8(6)

Table S4. Selected Bond Lengths and Angles for **3**.

Pt(1)-O(11)	2.013(4)
Pt(1)-O(21)	2.028(4)
Pt(1)-N(2)	2.039(6)
Pt(1)-N(1)	2.050(6)
Pt(1)-Cl(2)	2.2969(16)
Pt(1)-Cl(1)	2.3203(17)
O(11)-Pt(1)-O(21)	171.34(14)
O(11)-Pt(1)-N(2)	97.5(2)
O(21)-Pt(1)-N(2)	87.6(2)
O(11)-Pt(1)-N(1)	89.0(2)
O(21)-Pt(1)-N(1)	97.9(2)
C(21)-O(21)-Pt(1)	123.8(4)
C(11)-O(11)-Pt(1)	123.4(4)
O(22)-C(21)-O(21)	124.3(6)
O(22)-C(21)-C(22)	123.8(6)

Figure S1. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **2**.

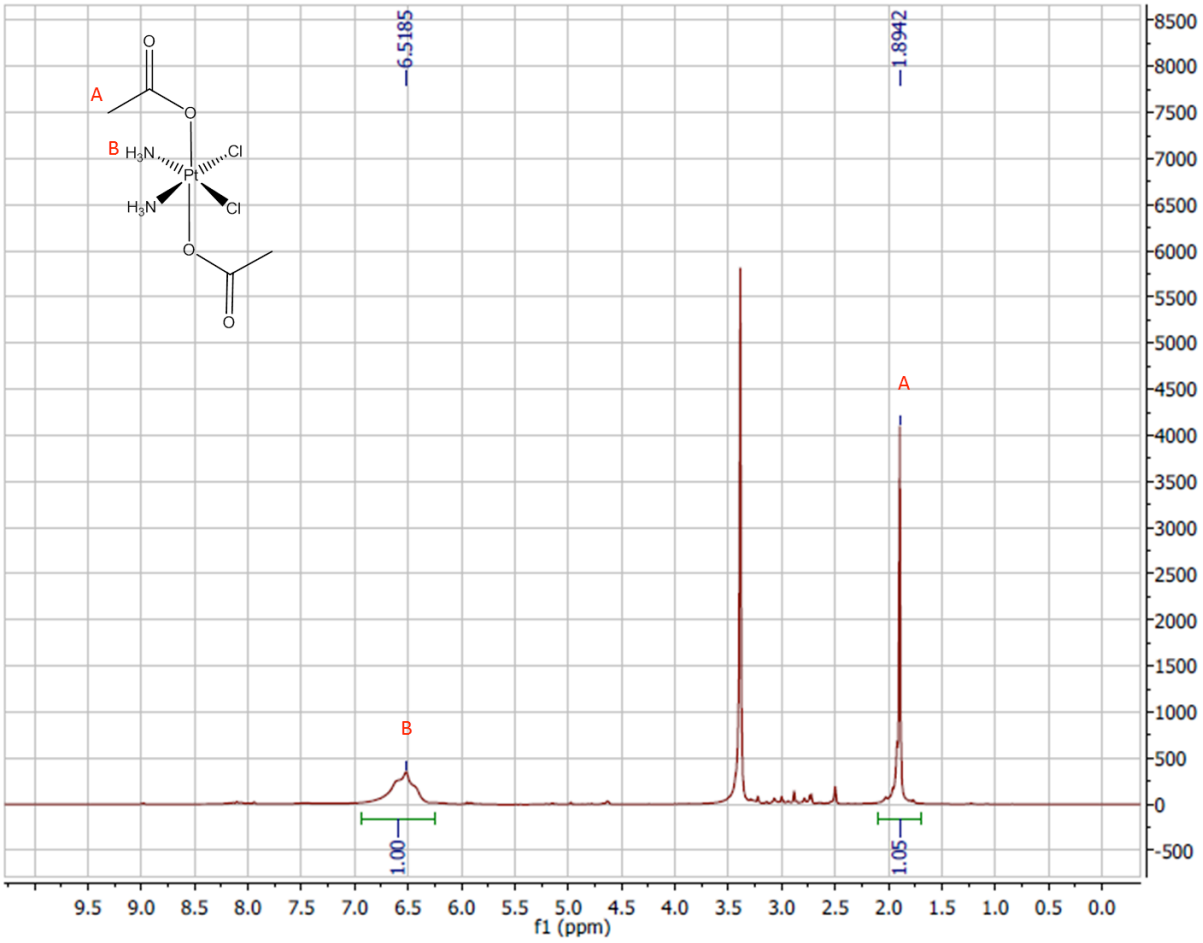


Figure S2. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **2**.

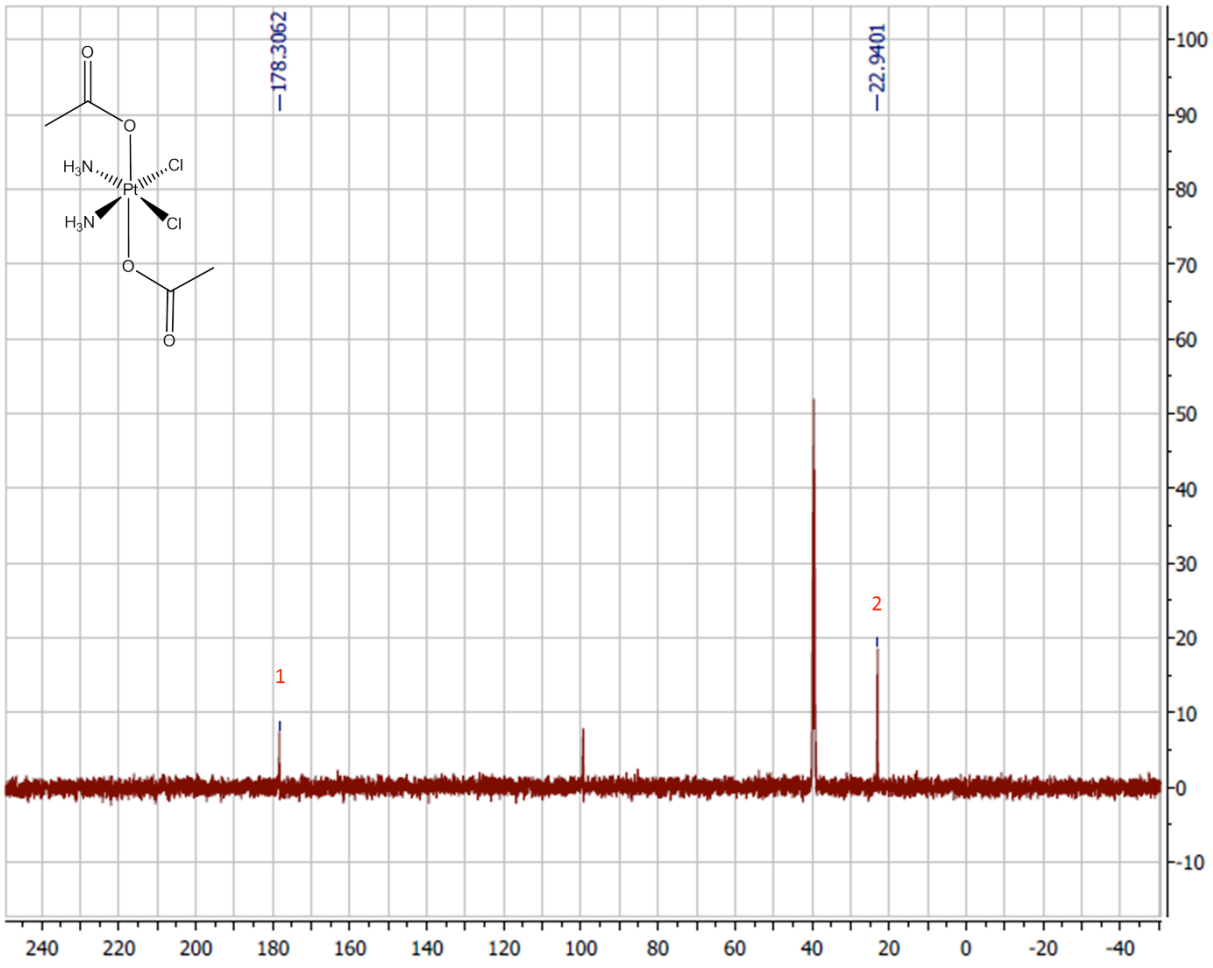


Figure S3. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **3**.

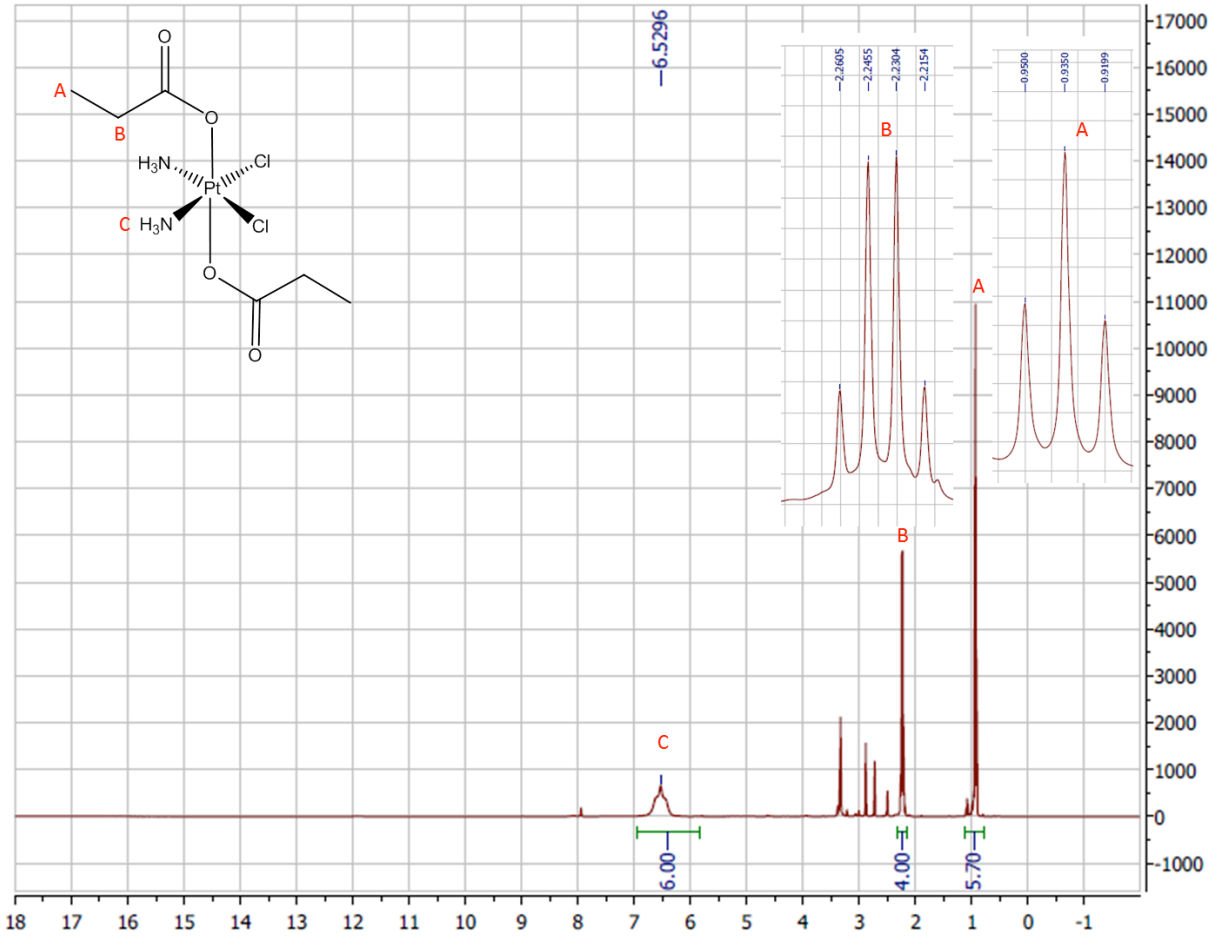


Figure S4. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **3**.

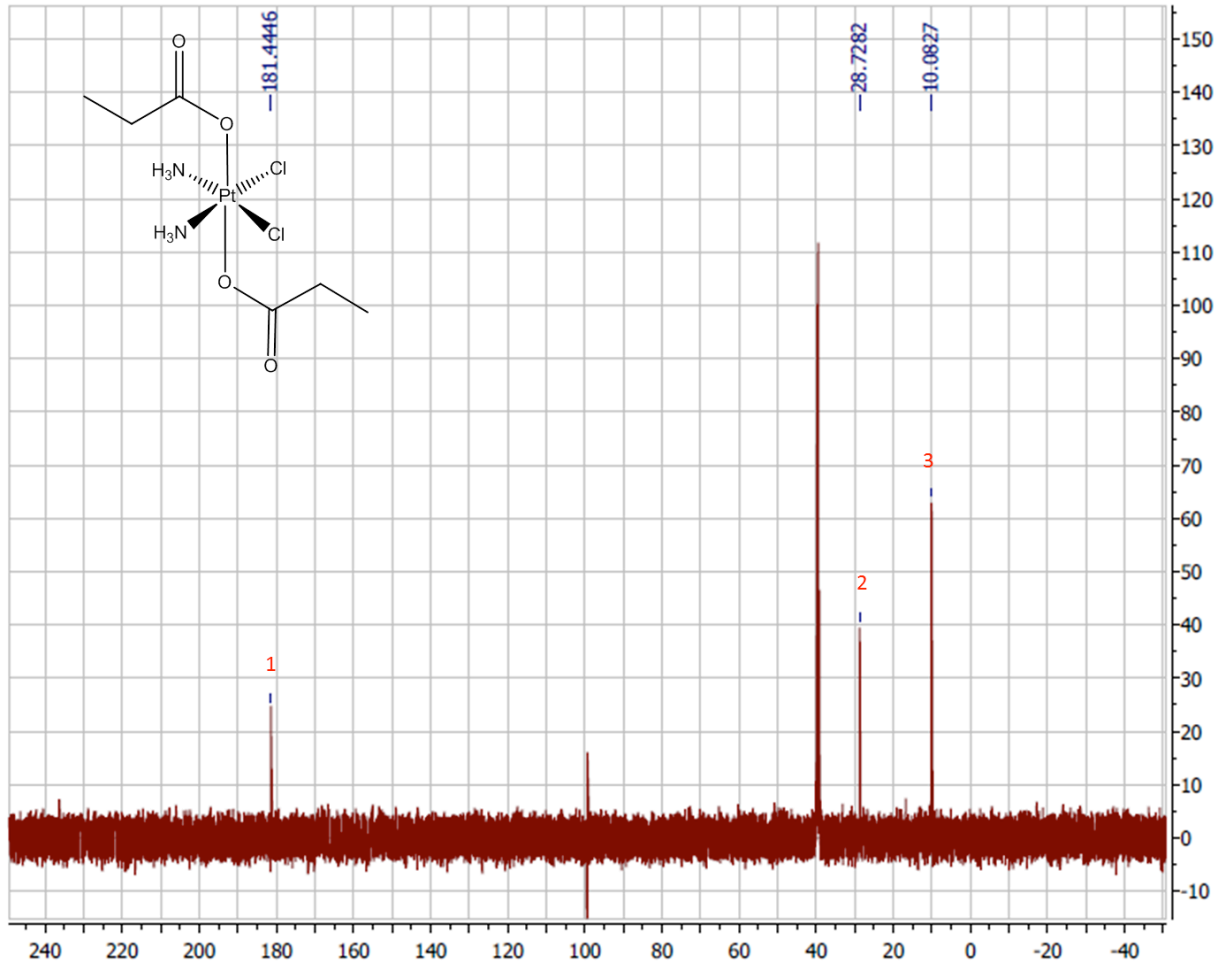


Figure S5. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **4**.

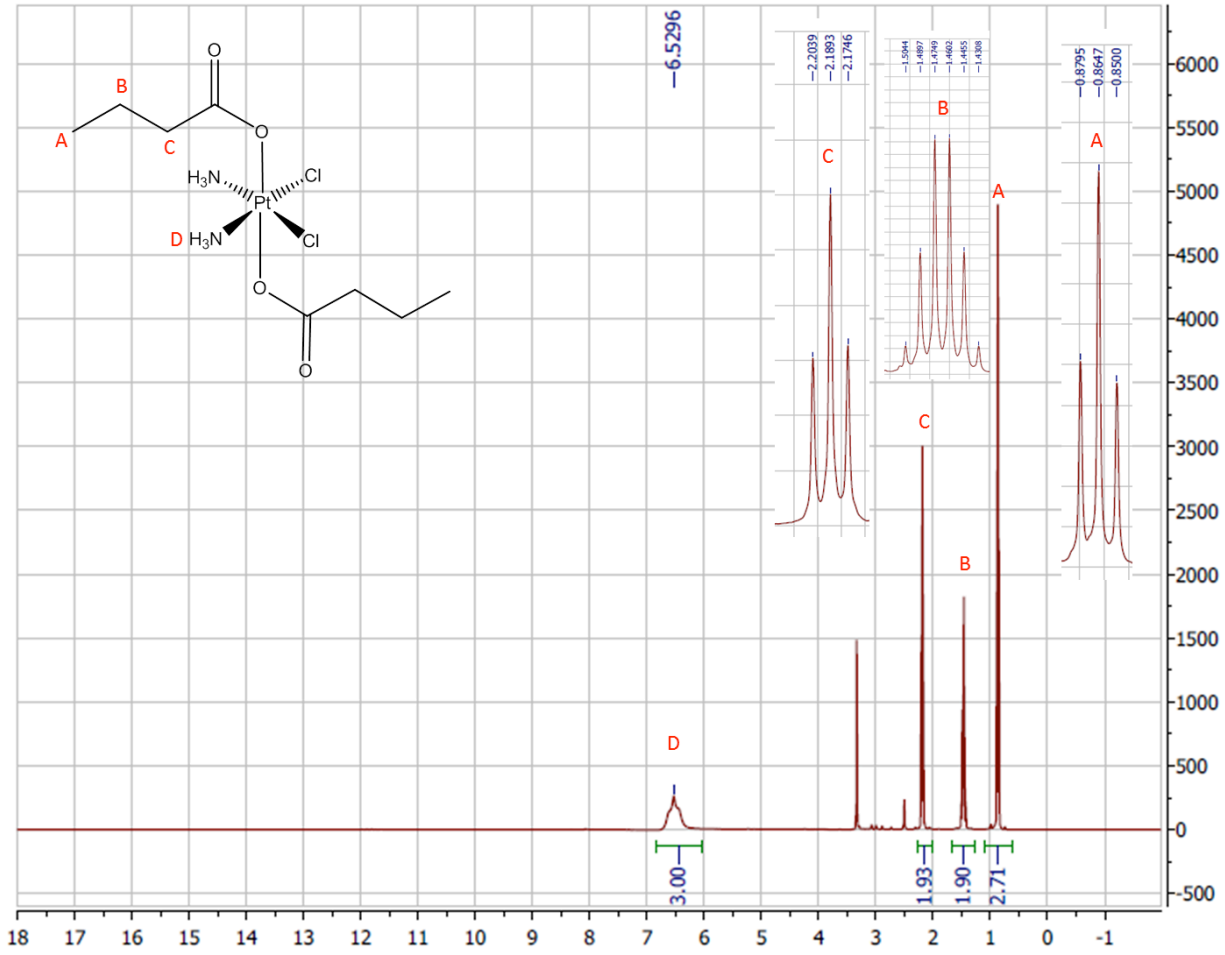


Figure S6. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **4**.

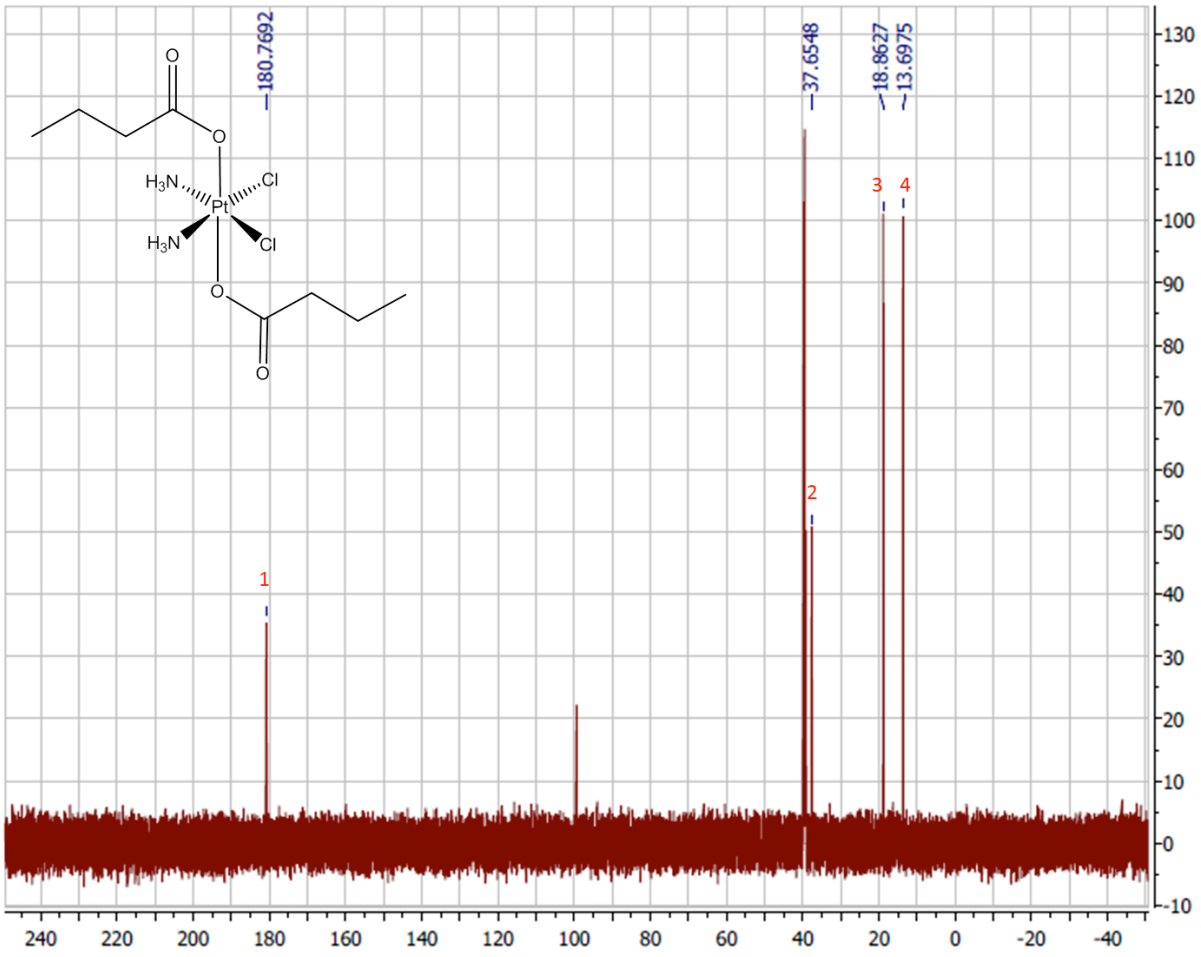


Figure S7. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **5**.

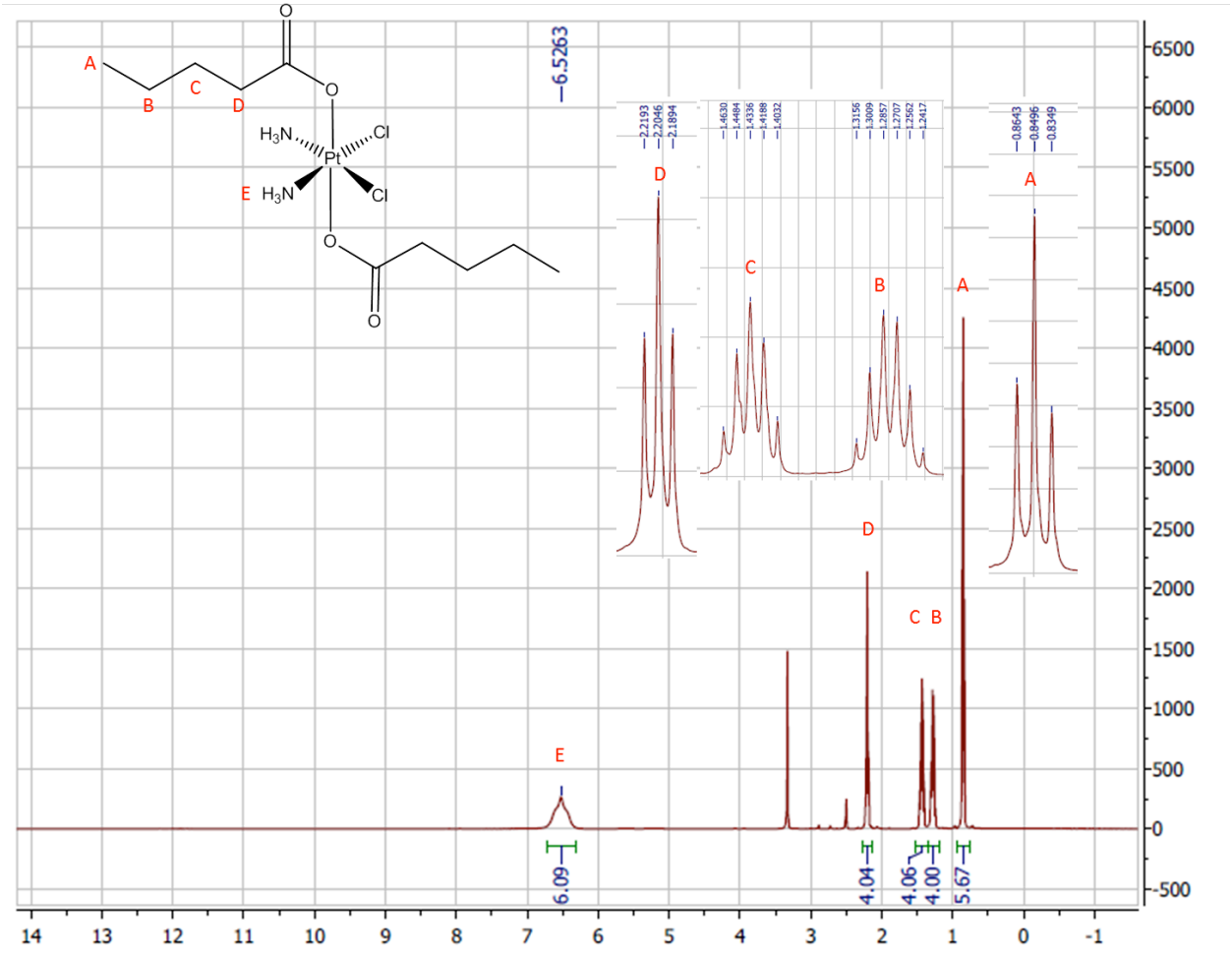


Figure S8. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **5**.

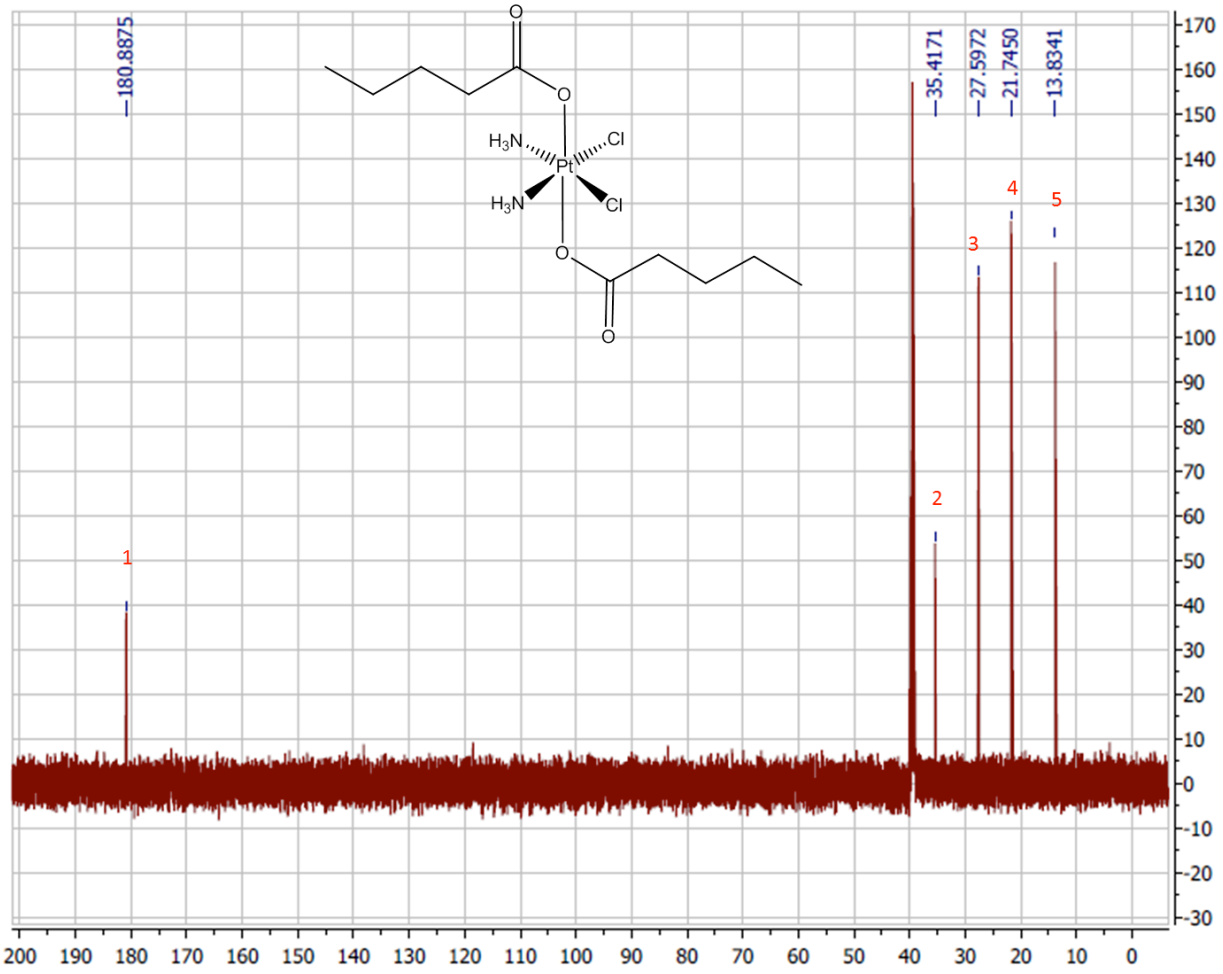


Figure S9. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **6**.

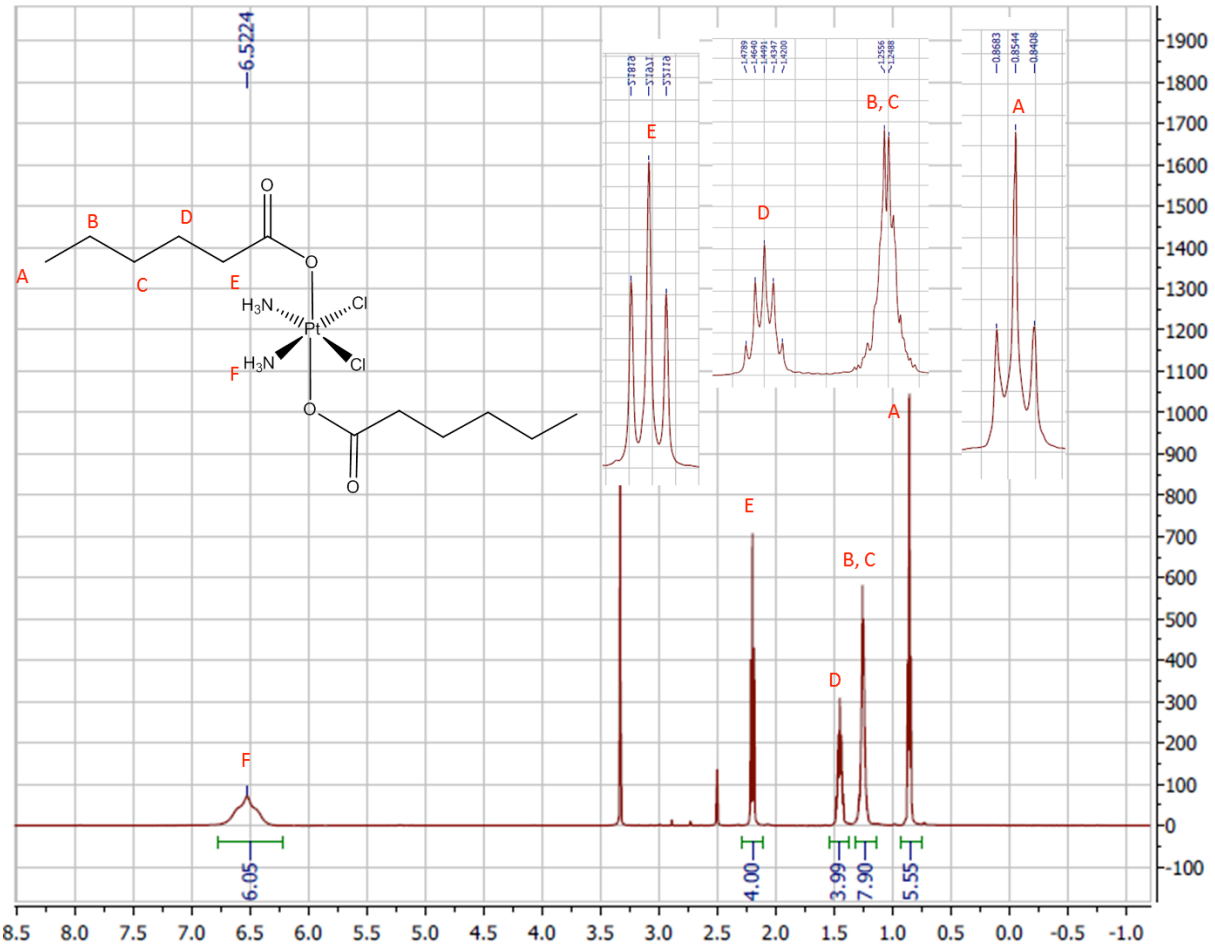


Figure S10. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **6**.

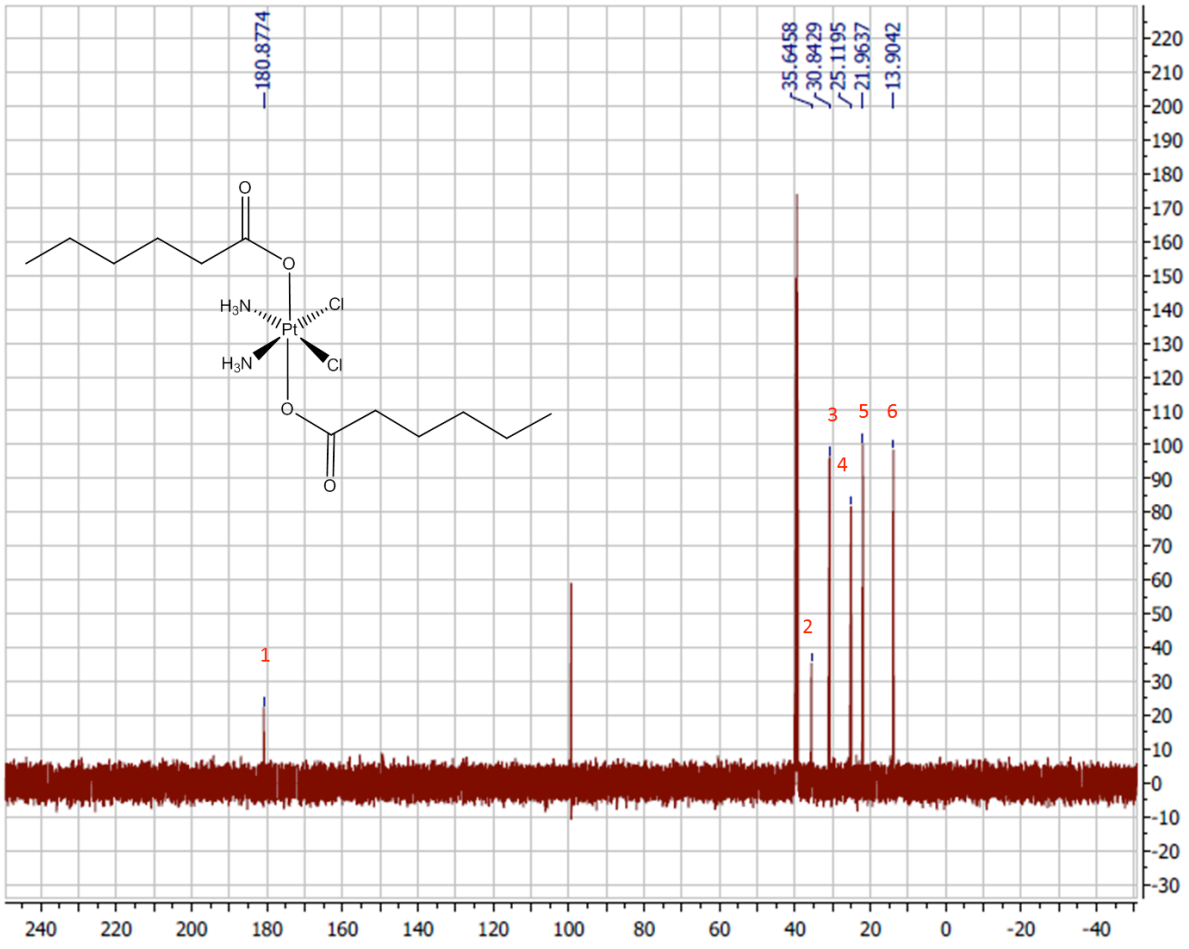


Figure S11. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **7**.

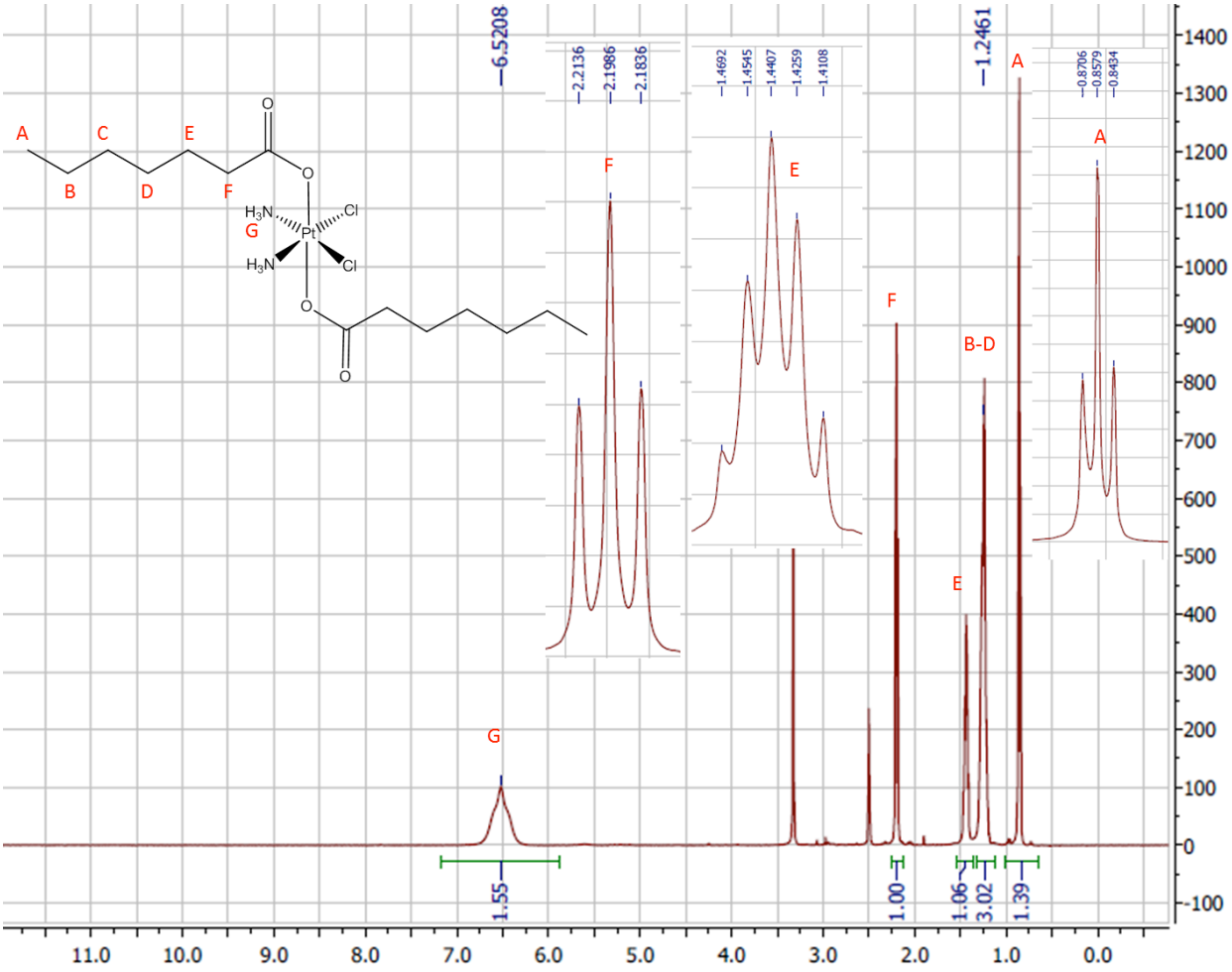


Figure S12. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **7**.

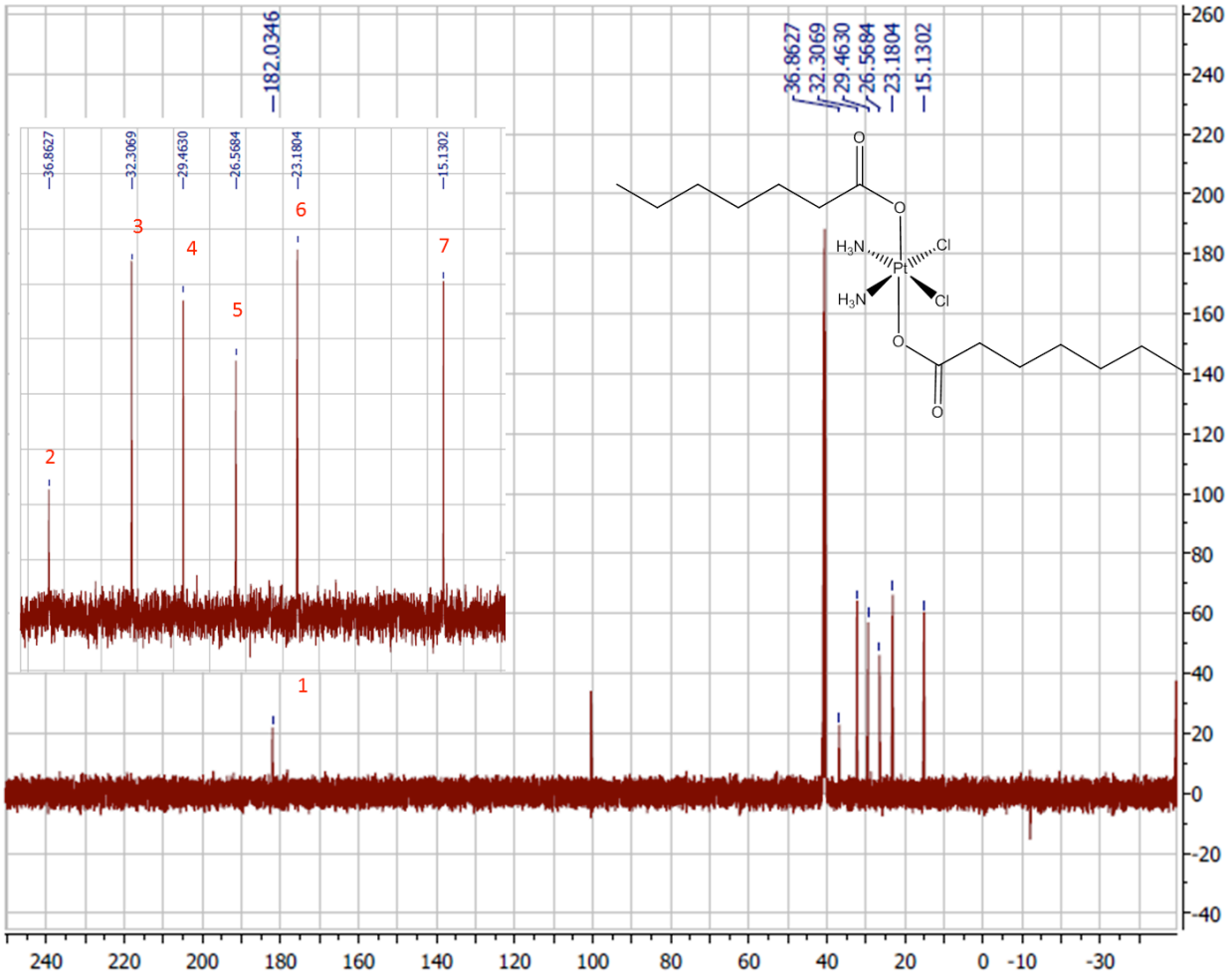


Figure S13. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **8**.

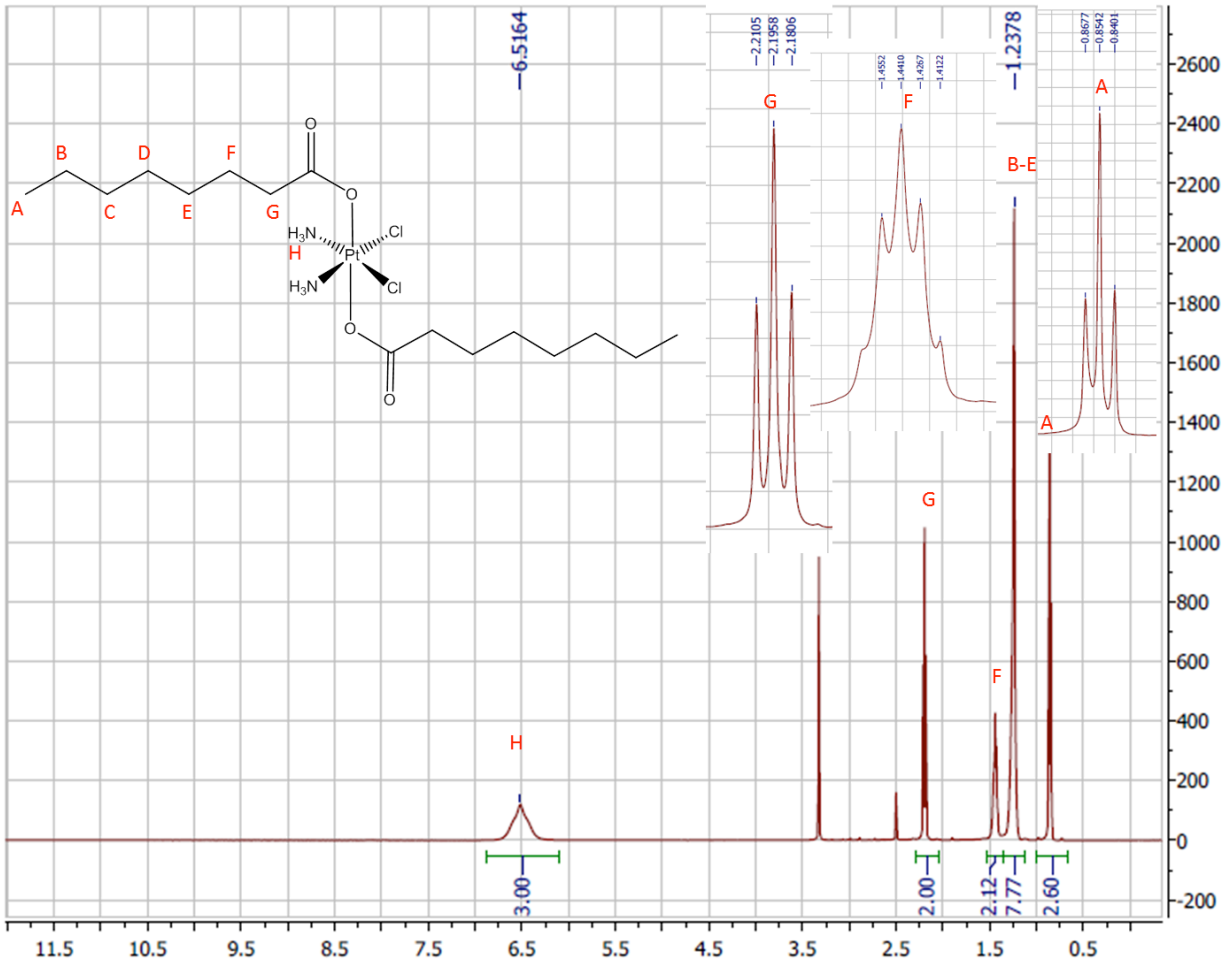


Figure S14. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **8**.

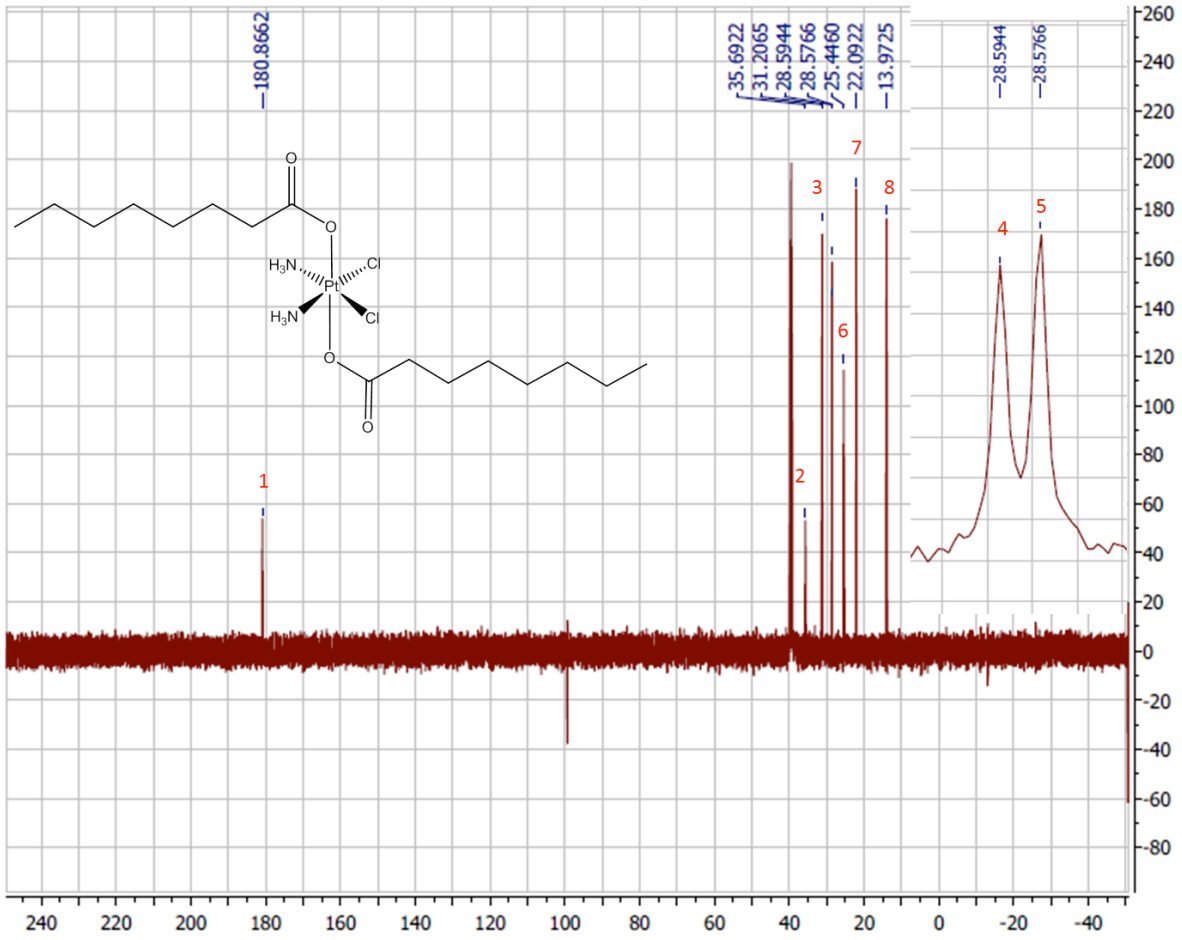


Figure S15. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **9**.

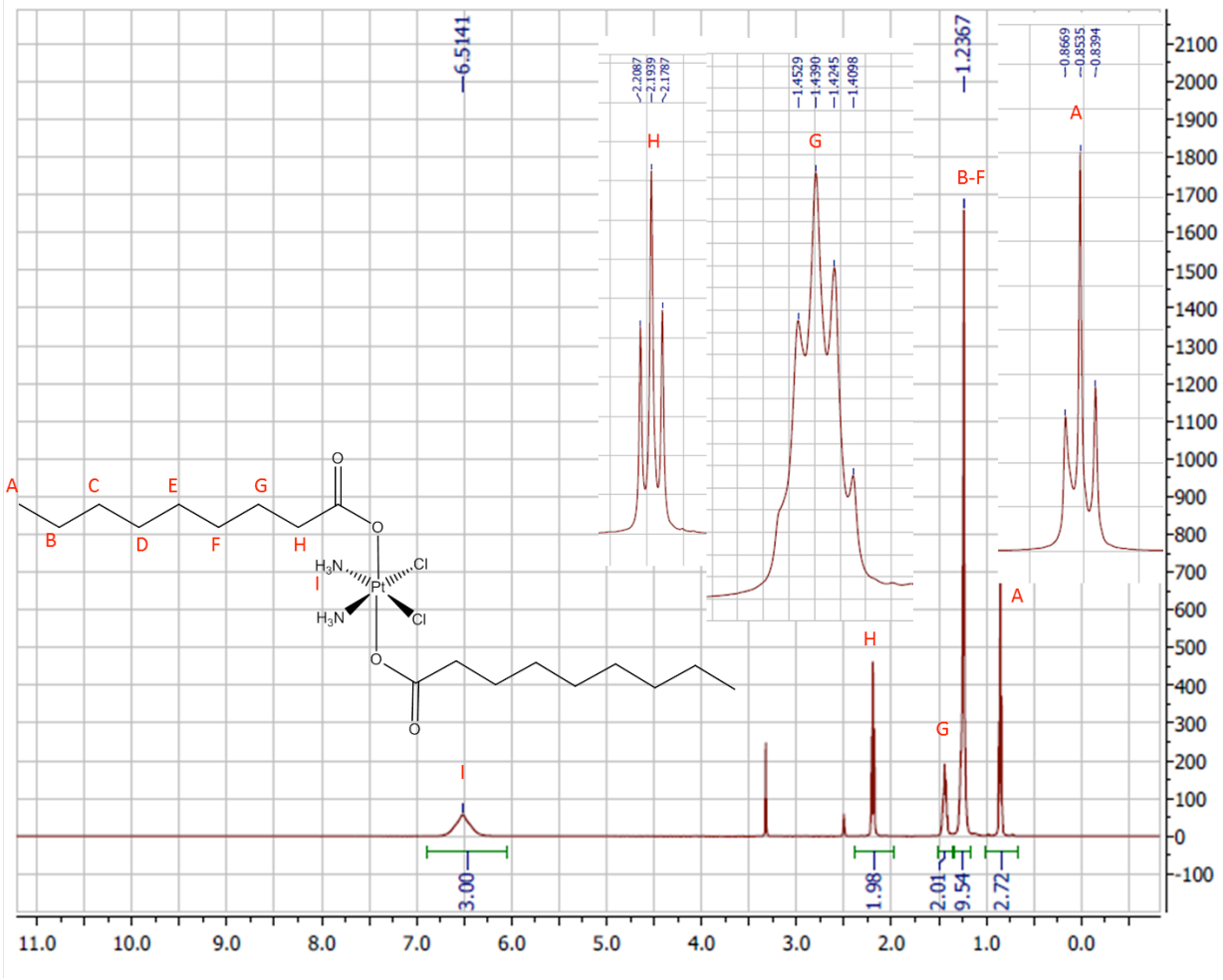


Figure S16. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **9**.

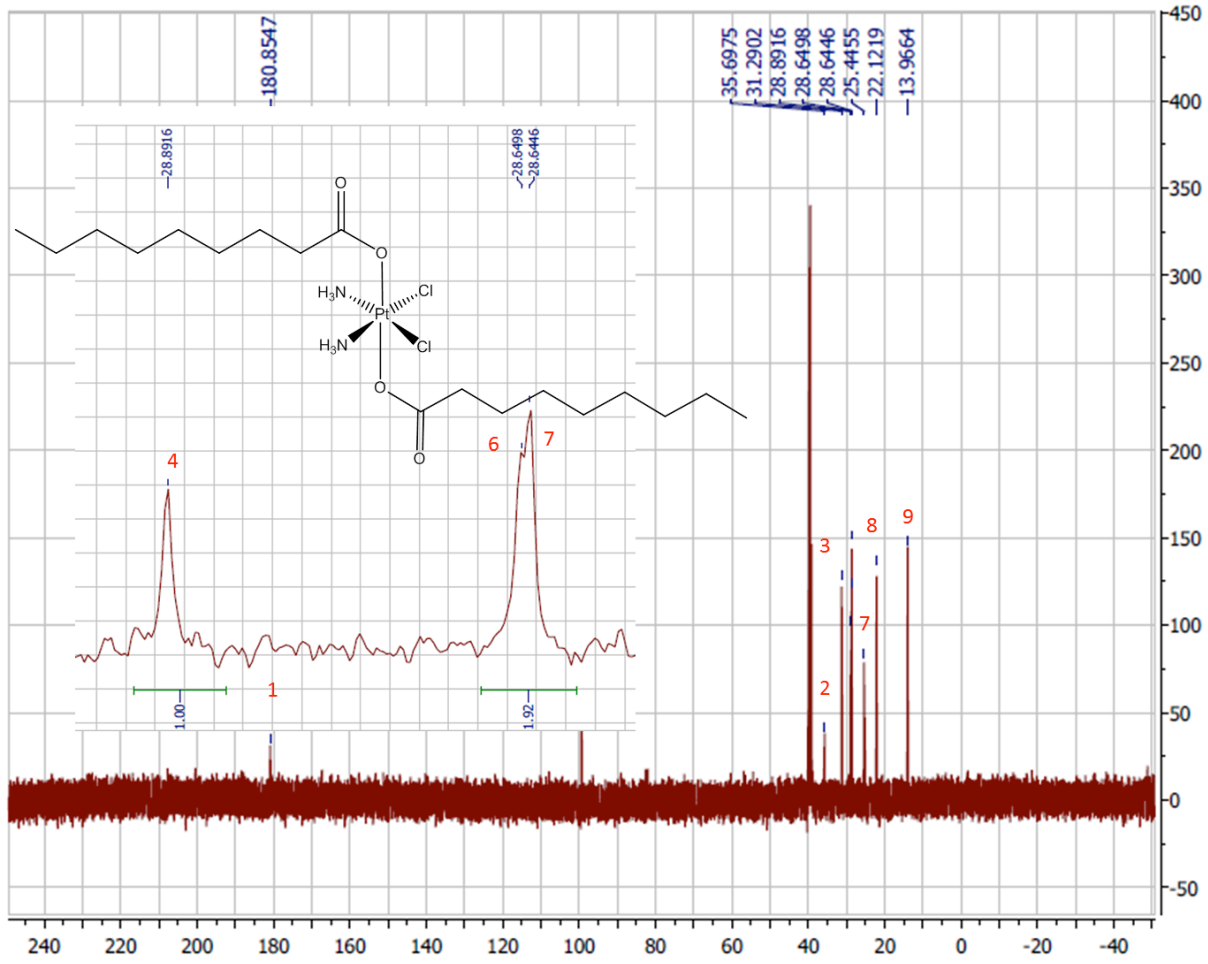


Figure S17. ^{1}H NMR Spectrum (500 MHz, DMSO-d_6) of **10**.

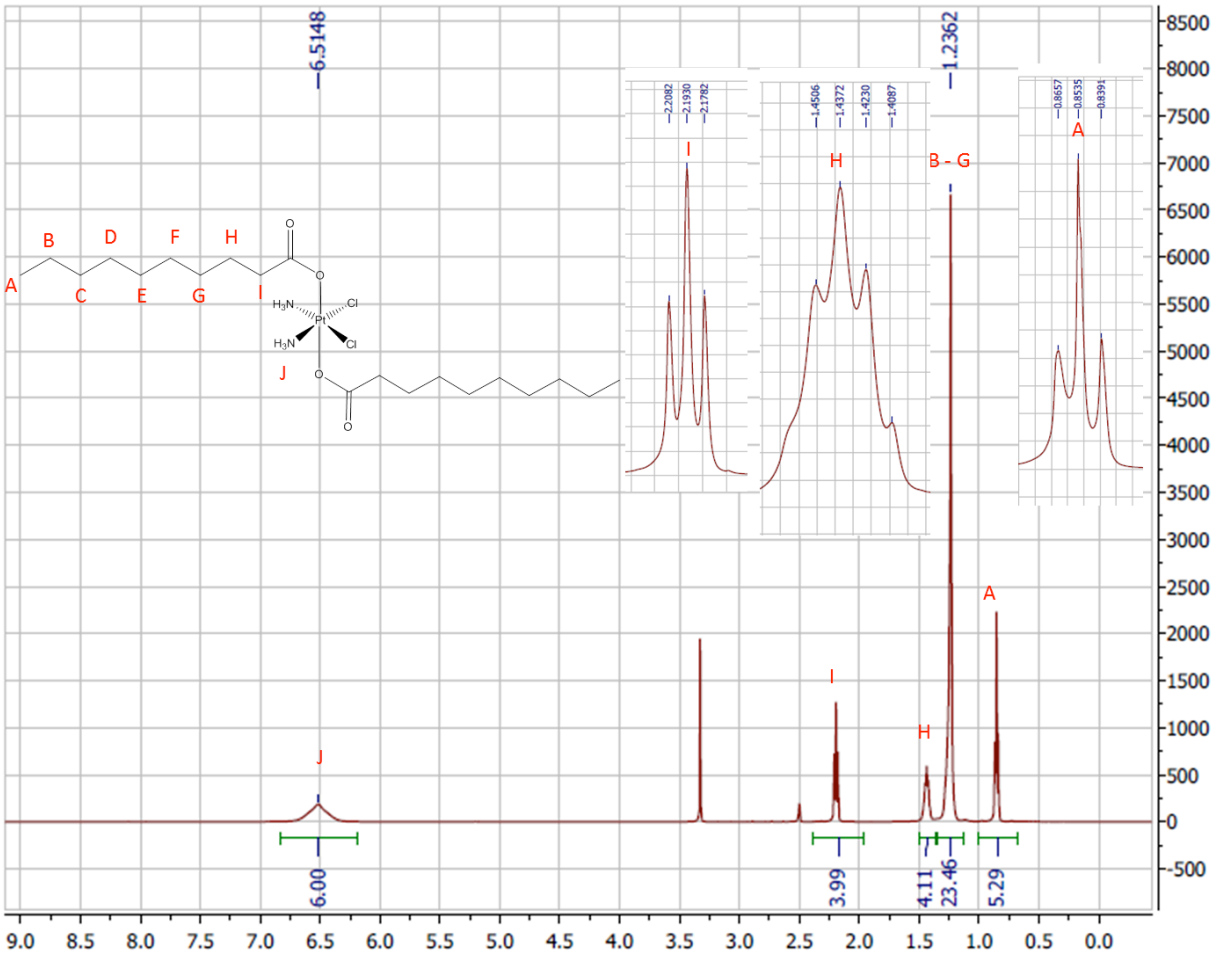


Figure S18. ^{13}C NMR Spectrum (125 MHz, DMSO-d_6) of **10**.

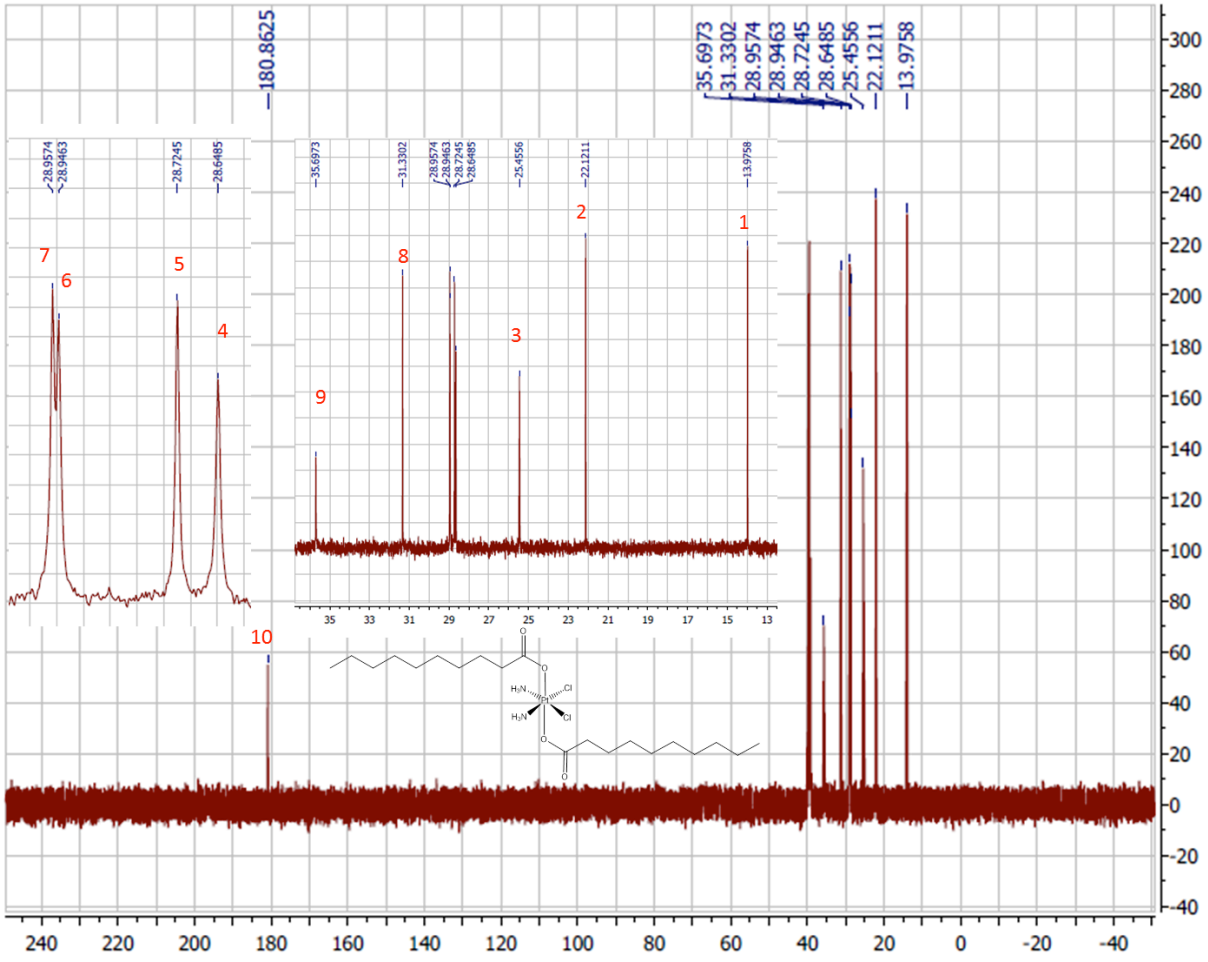
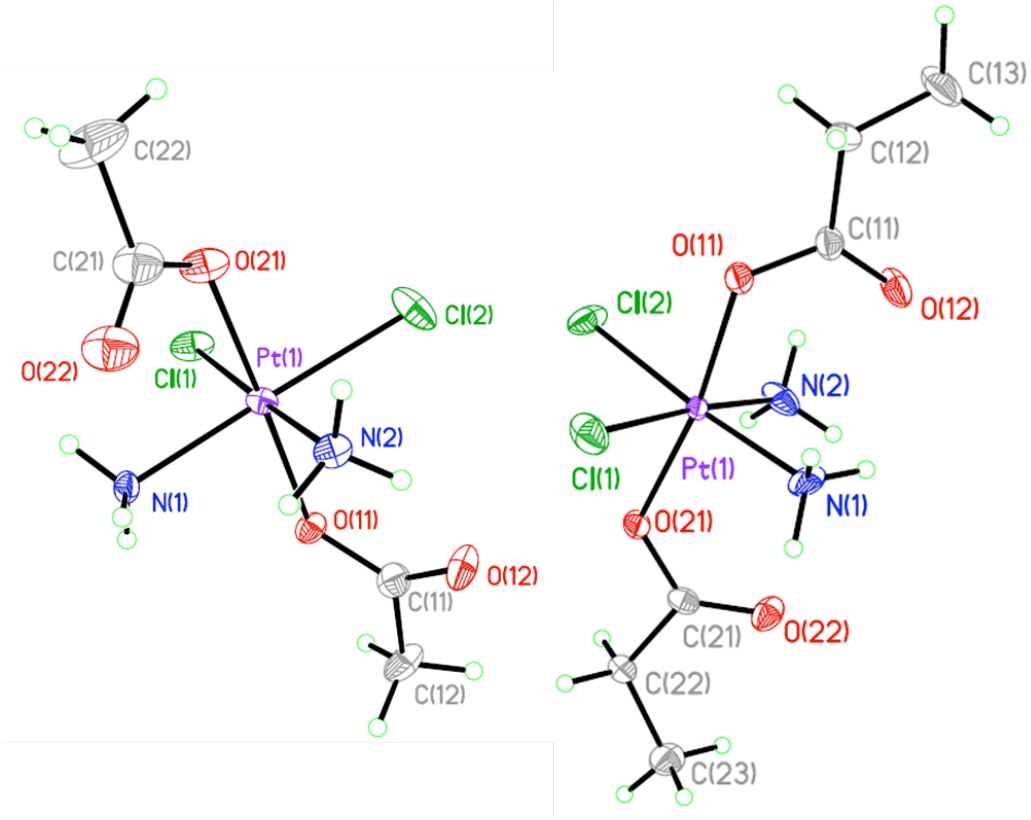


Figure S19. Molecular Structures of **2** (left) and **3** (right). Ellipsoids are drawn at the 50% probability level.



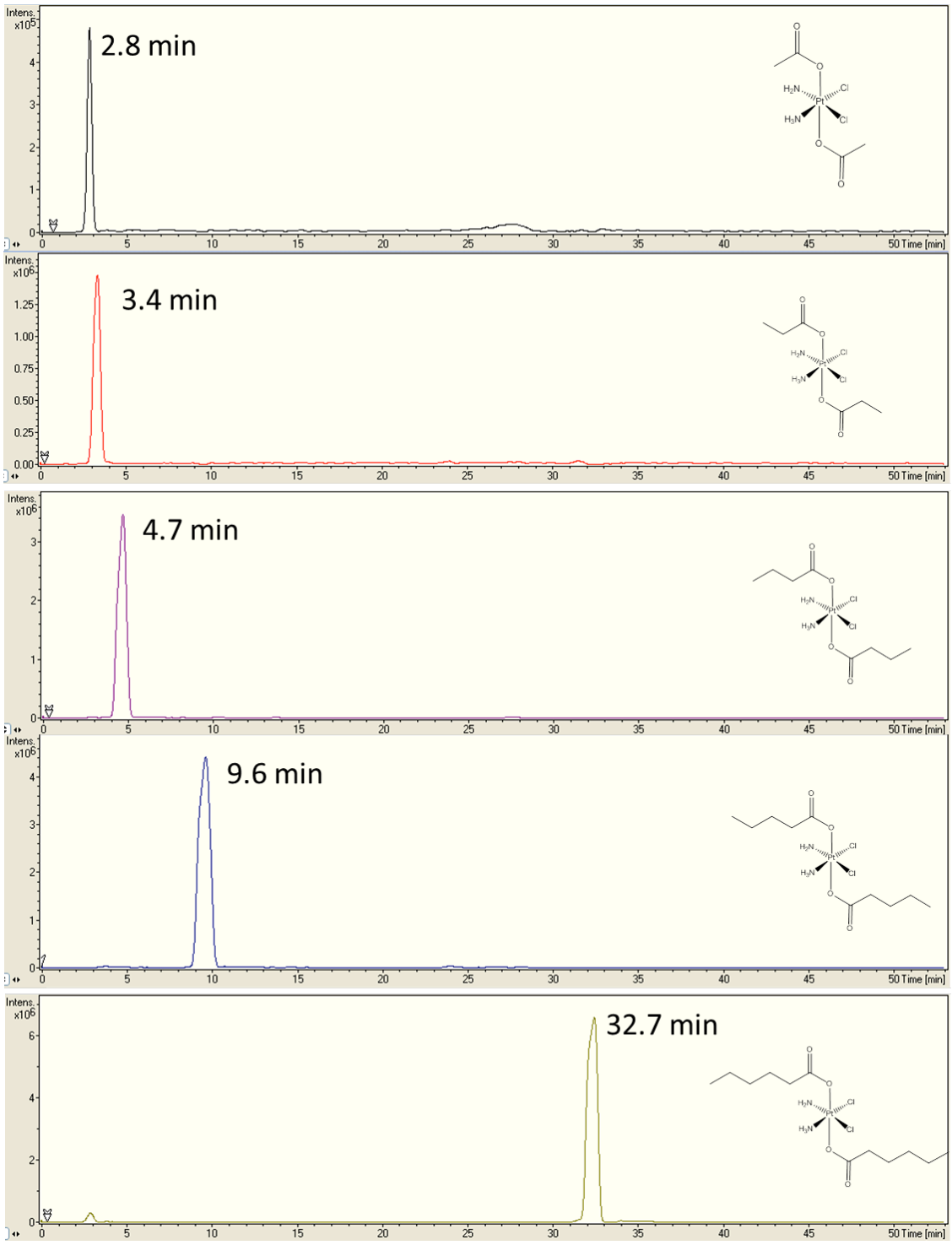


Figure S20. LC-MS Chromatograms for **2** - **6** (conditions are described in the main text).