Electronic Supplementary Material

Not the usual suspect – an unexpected organometallic product during the synthesis of a cytotoxic platinum(II) complex

Thomas Maier,[a,b] Judith Wutschitz,[a] Natalie Gajic,[a] Michaela Hejl,[a] Klaudia Cseh,[a] Sebastian Mai,[c] Michael A. Jakupec,[a,d] Mathea S. Galanski,*[a] and Bernhard K. Keppler*[a,d]

[a] *University of Vienna, Faculty of Chemistry, Department of Inorganic Chemistry, Waehringer Strasse 42, 1090 Vienna, Austria.*

[b] *University of Vienna, Doctoral School in Chemistry (DoSChem), Waehringer Strasse 42, 1090 Vienna, Austria.*

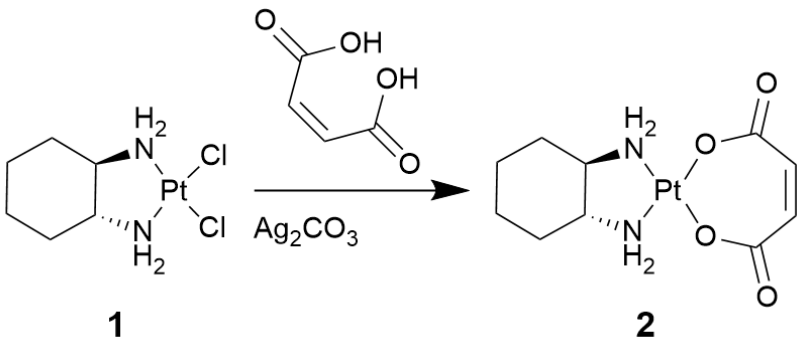
[c] *University of Vienna, Faculty of Chemistry, Department of Theoretical Chemistry, Waehringer Strasse 17, 1090 Vienna, Austria.*

[d] *Research Cluster "Translational Cancer Therapy Research", University of Vienna, Waehringer Strasse 42, 1090 Vienna, Austria.*

Email: mathea.galanski@univie.ac.at; bernhard.keppler@univie.ac.at

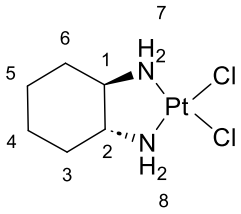
Contents

Planned reaction



Scheme S1 *Planned reaction to the target complex* ***2****, featuring a chelating maleato complex.*

NMR Numbering Scheme



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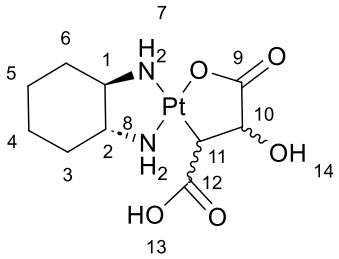

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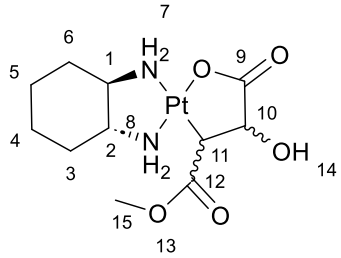

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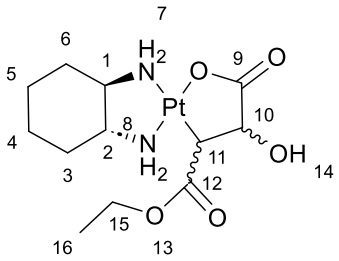

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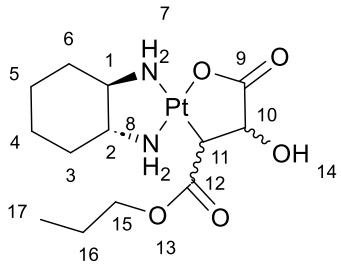

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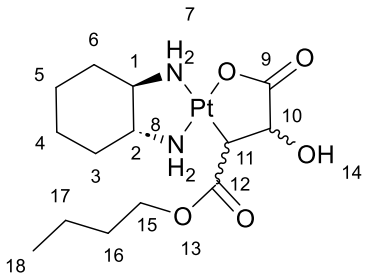

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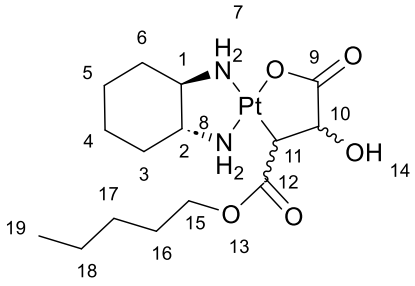

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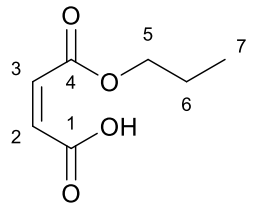
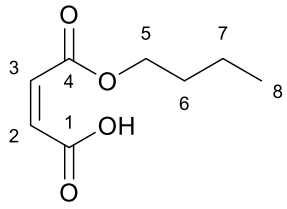
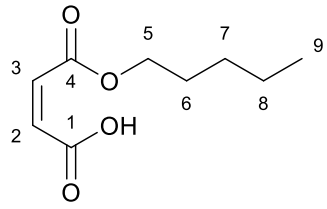


(Z)-4-oxo-4-propoxybut-2-enoic acid



(Z)-4-butoxy-4-oxobut-2-enoic acid



(Z)-4-oxo-4-(pentyloxy)but-2-enoic acid

Fig. S1 *Atom labeling as used for all descriptions. Both diastereomers are numbered in the same fashion.*

Cytotoxicity data

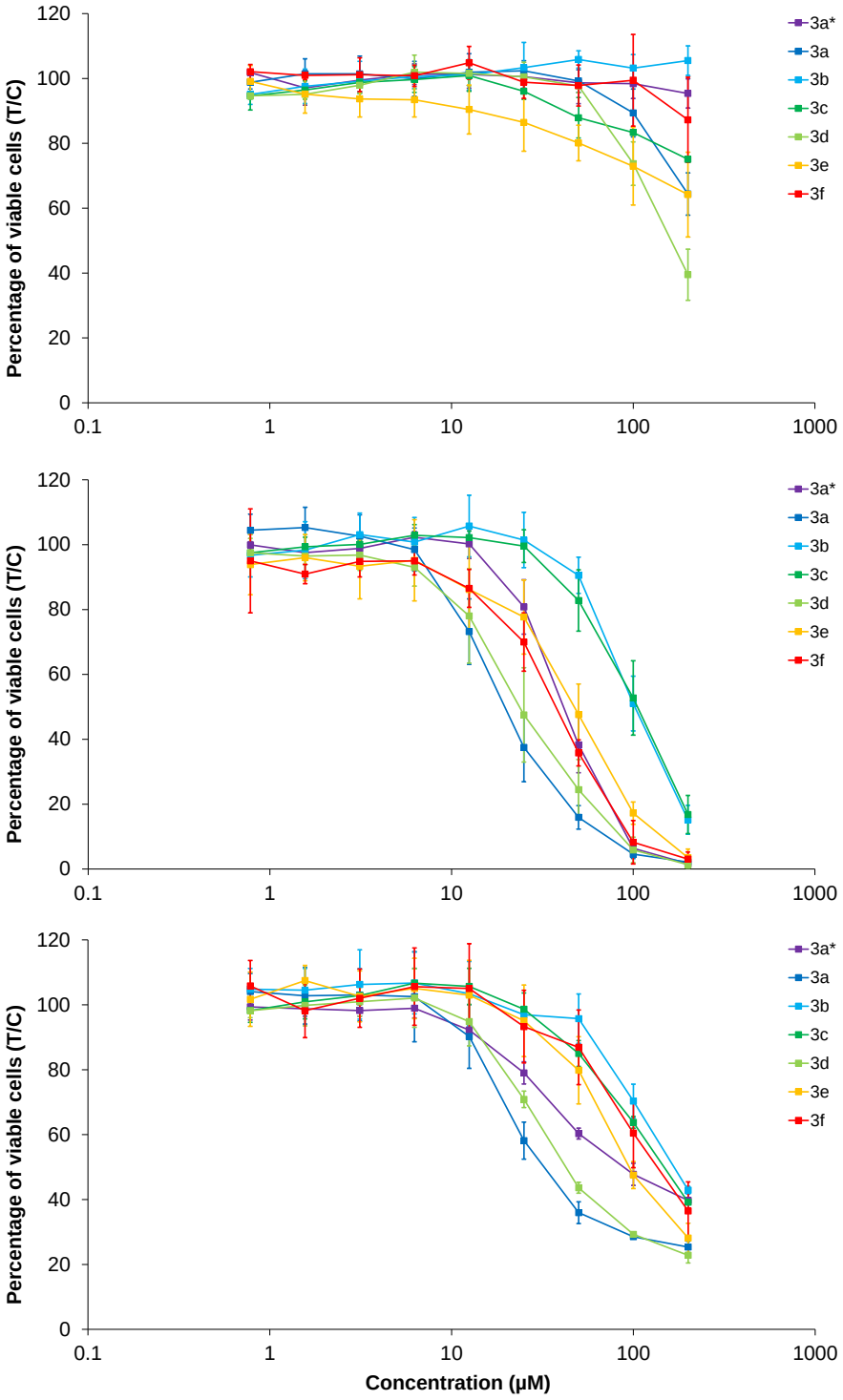


Fig. S2 *Concentration-effect curves of* ***3a*–3f*** *in A549 (top), CH1/PA-1 (middle) and SW480 (bottom) cells, obtained by MTT assays with 96 h exposure time. Values are means ± standard deviations from at least three independent experiments.*

DNA-interaction assay

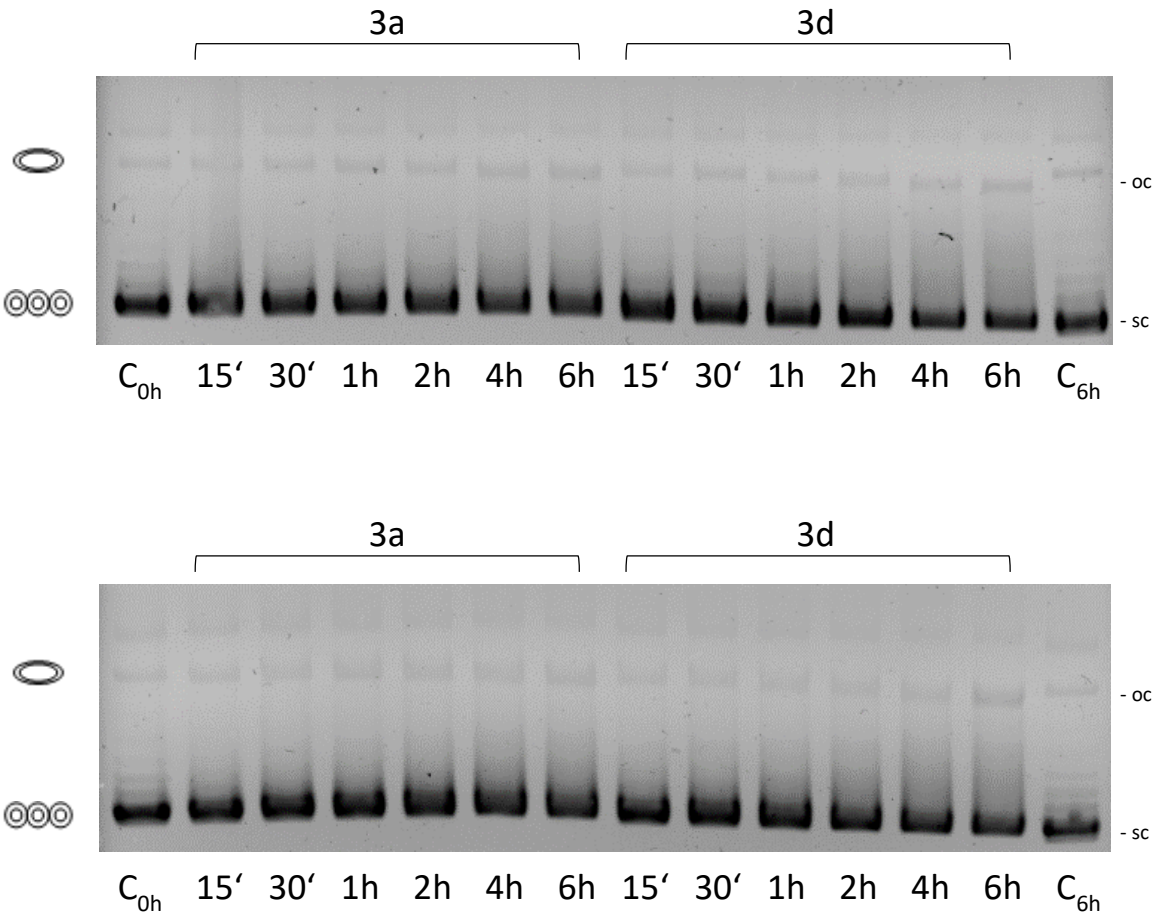


Fig. S3 *Electropherogram of plasmid dsDNA upon treatment with 50 µM of compounds **3a** and **3d**. The pUC19 plasmid was incubated with the complexes for 6 different time periods (from 15 min to 6 h) at 37 °C and then subjected to agarose gel electrophoresis. 'C_{0h}' corresponds to an untreated, non-preincubated control at the time point of gel loading, while 'C_{6h}' corresponds to an untreated, 6 h incubated control; oc, open circular; sc, supercoiled. (As a reference for analyzing the bands of the gel, Figure S80 from ref. doi:10.1021/acs.inorgchem.1c01083 was used.)*

Stability assessment via RP-HPLC

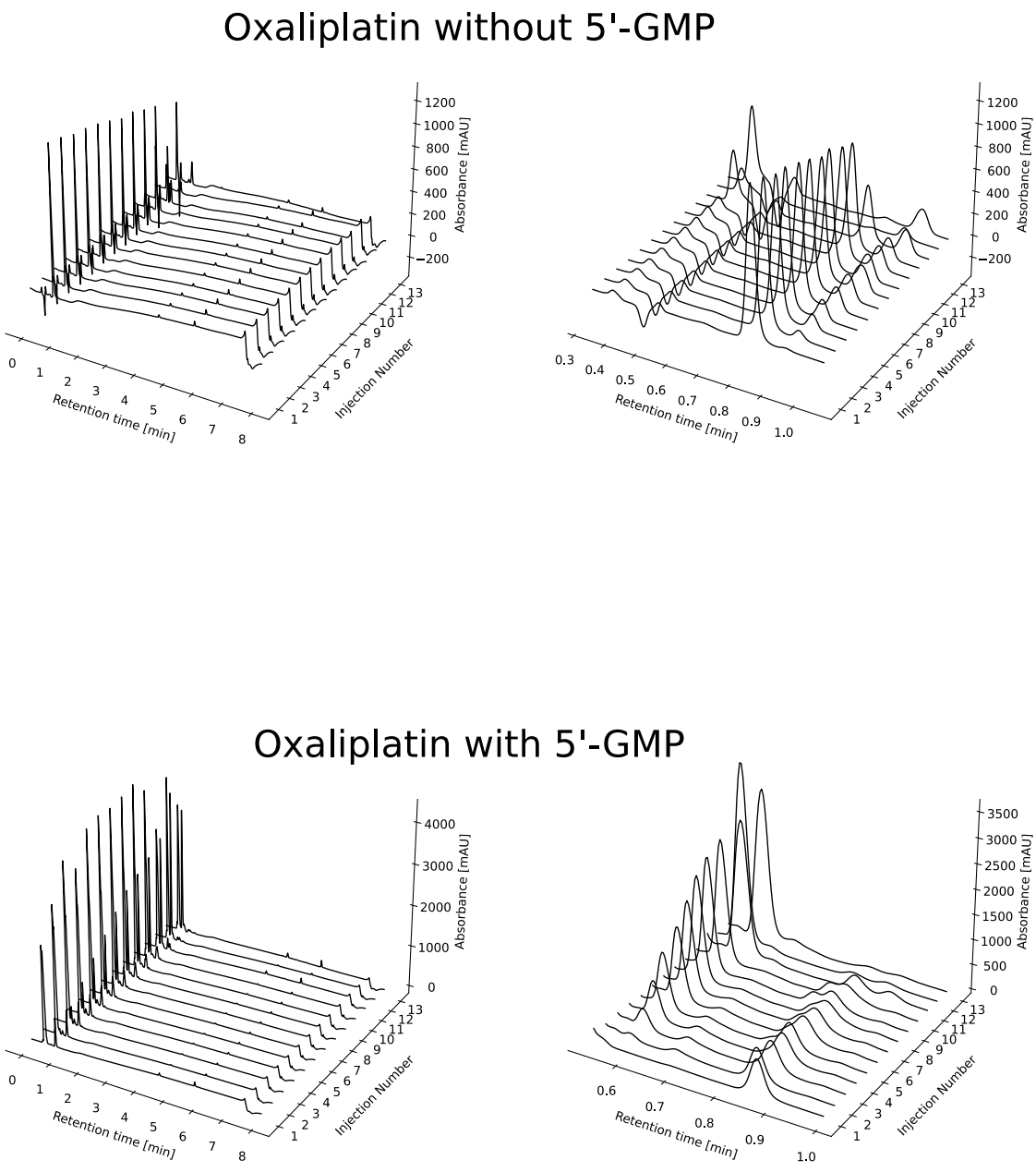


Fig. S4 *HPLC traces indicating the reactivity of oxaliplatin towards 5'-GMP under physiologically relevant conditions as described in the experimental section. The left image shows the complete HPLC run, whereas the right image is zoomed to the retention time window showing the relevant peaks. Retention time of oxaliplatin is 0.8 min and of GMP is 0.45 min respectively.*

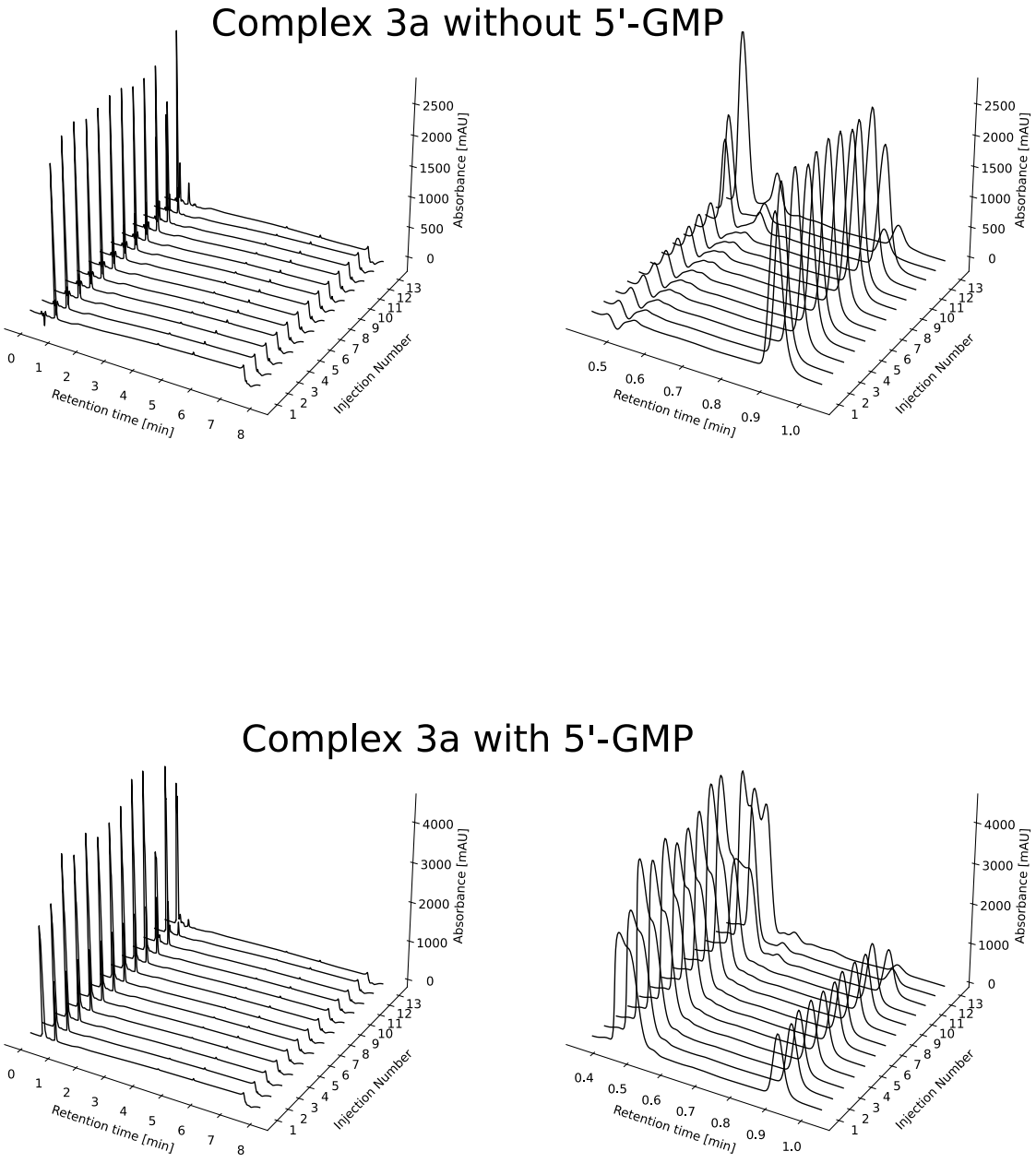


Fig. S5 *HPLC traces indicating the reactivity of complex* ***3a*** *towards 5'-GMP under physiologically relevant conditions as described in the experimental section. The left image shows the complete HPLC run, whereas the right image is zoomed to the retention time window showing the relevant peaks. Retention time of complex* ***3a*** *is 0.9 min and of GMP is 0.45 min, respectively.*

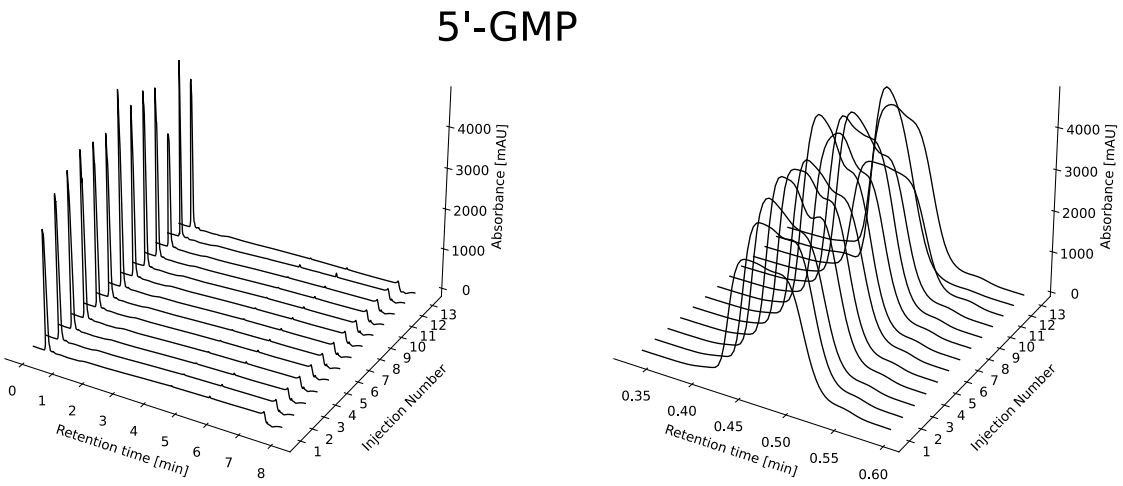


Fig. S6 *HPLC traces indicating the stability of 5'-GMP under physiologically relevant conditions as described in the experimental section. The left image shows the complete HPLC run, whereas the right image is zoomed to the retention time window showing the relevant peaks. Retention time of GMP is 0.45 min.*

^{1}H NMR spectrum of (Z)-4-oxo-4-propoxybut-2-enoic acid

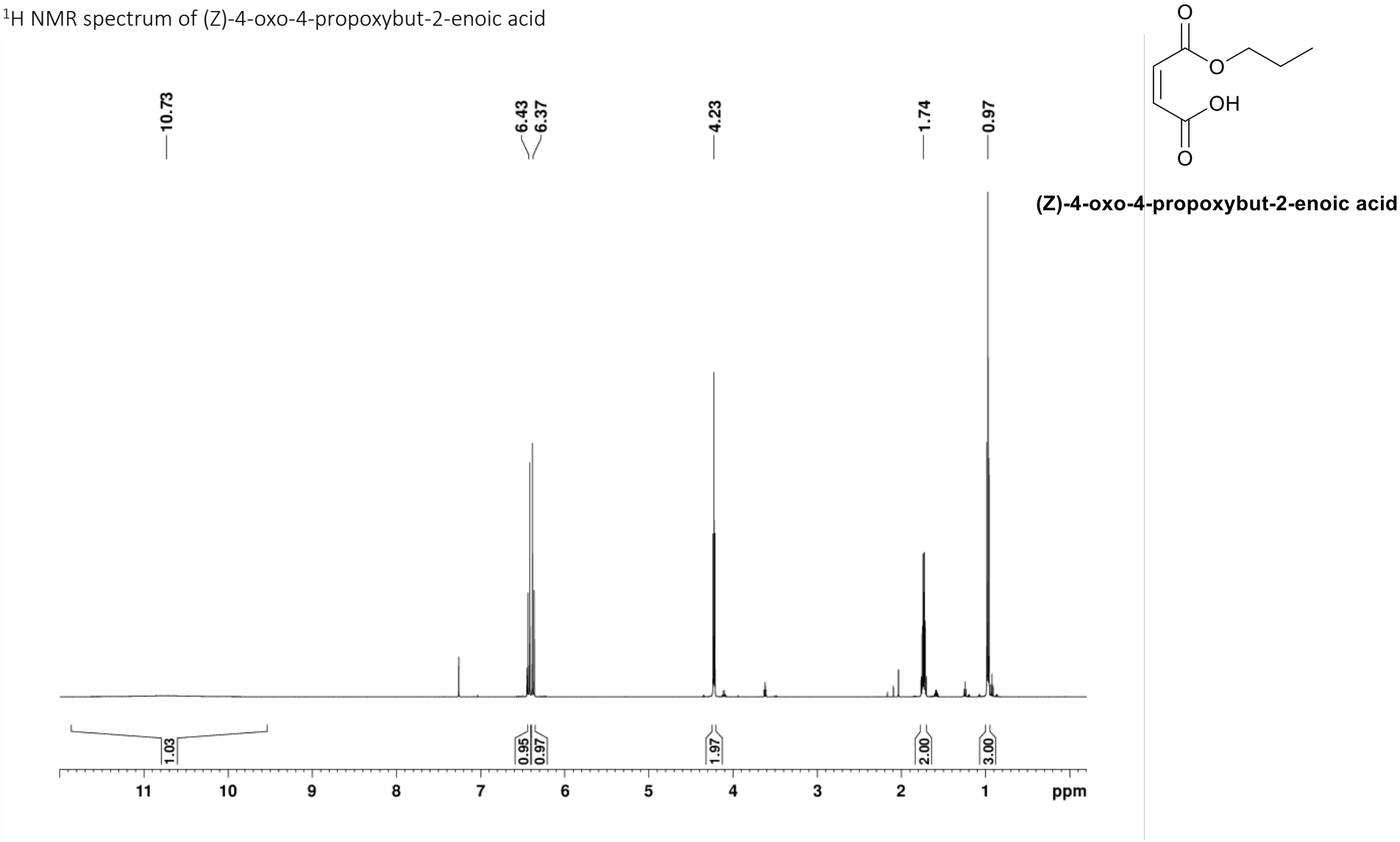
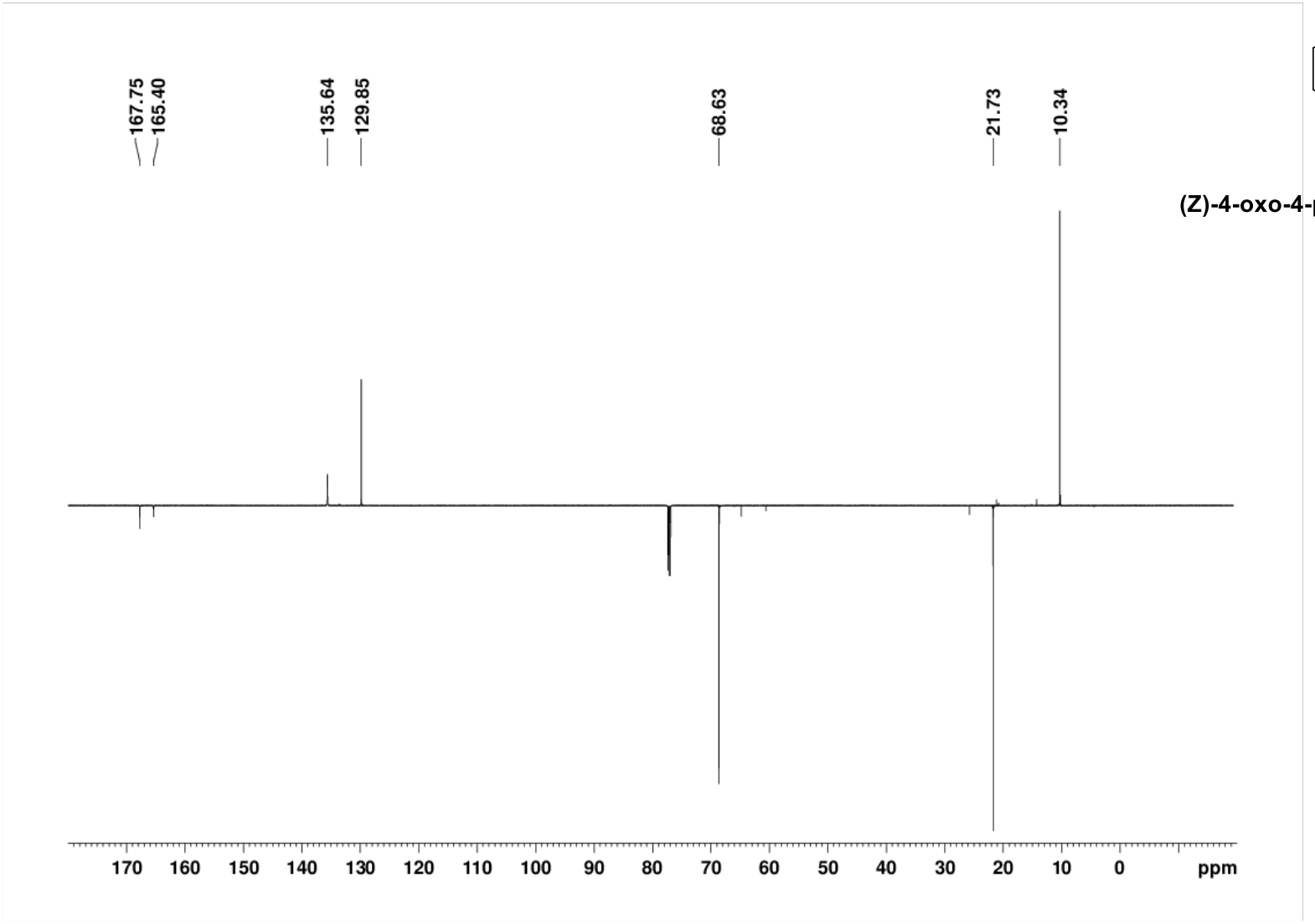
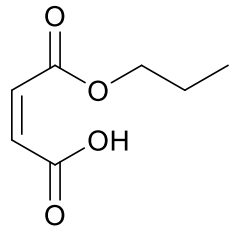


Fig. S4 *^{1}H NMR spectrum of (Z)-4-oxo-4-propoxybut-2-enoic acid.*

^{13}C NMR spectrum of (Z)-4-oxo-4-propoxybut-2-enoic acid

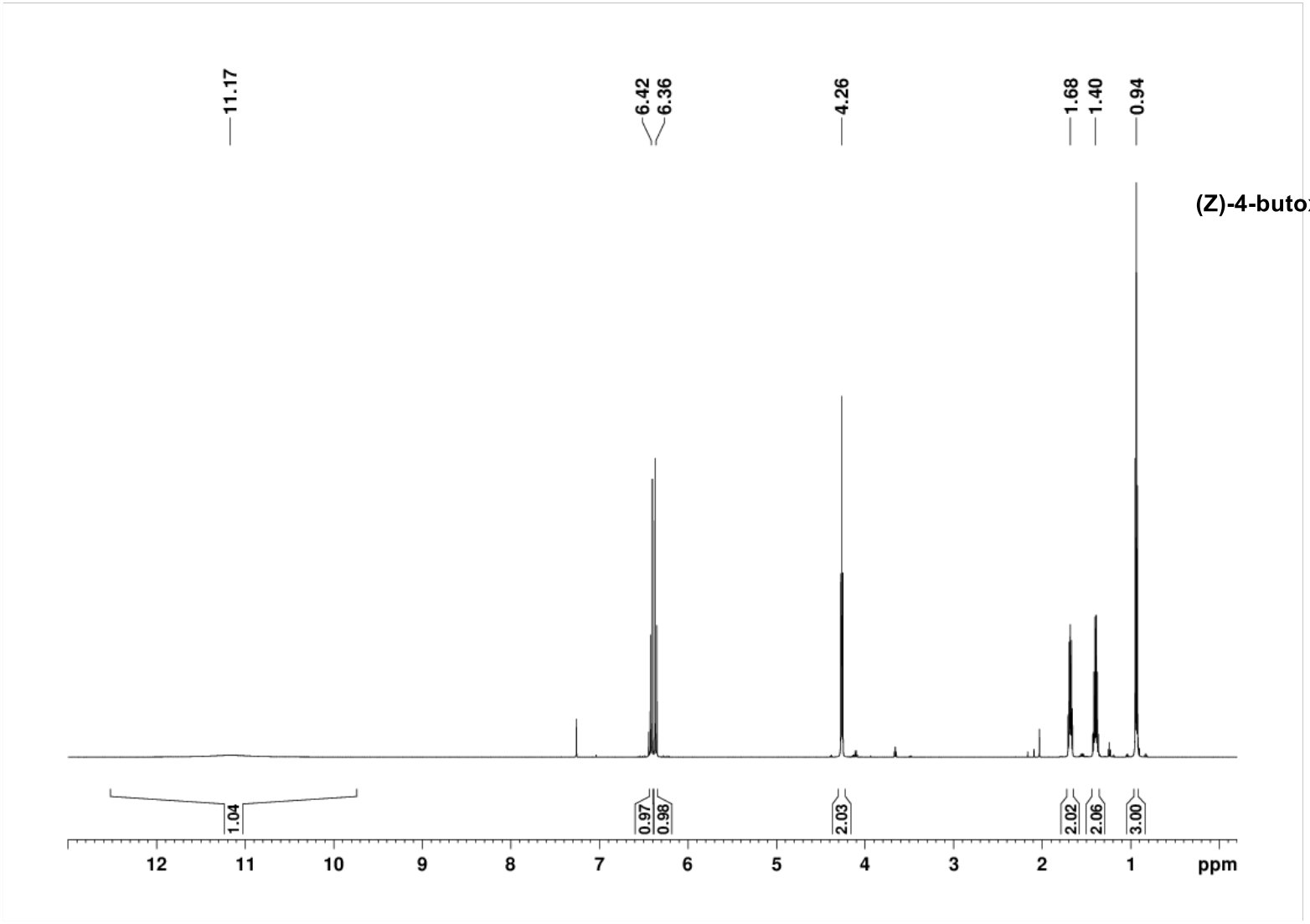


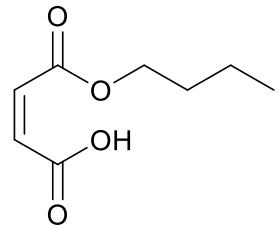


(Z)-4-oxo-4-propoxybut-2-enoic acid

Fig. S5 *^{13}C NMR spectrum of (Z)-4-oxo-4-propoxybut-2-enoic acid.*

^{1}H NMR spectrum of (Z)-4-butoxy-4-oxobut-2-enoic acid

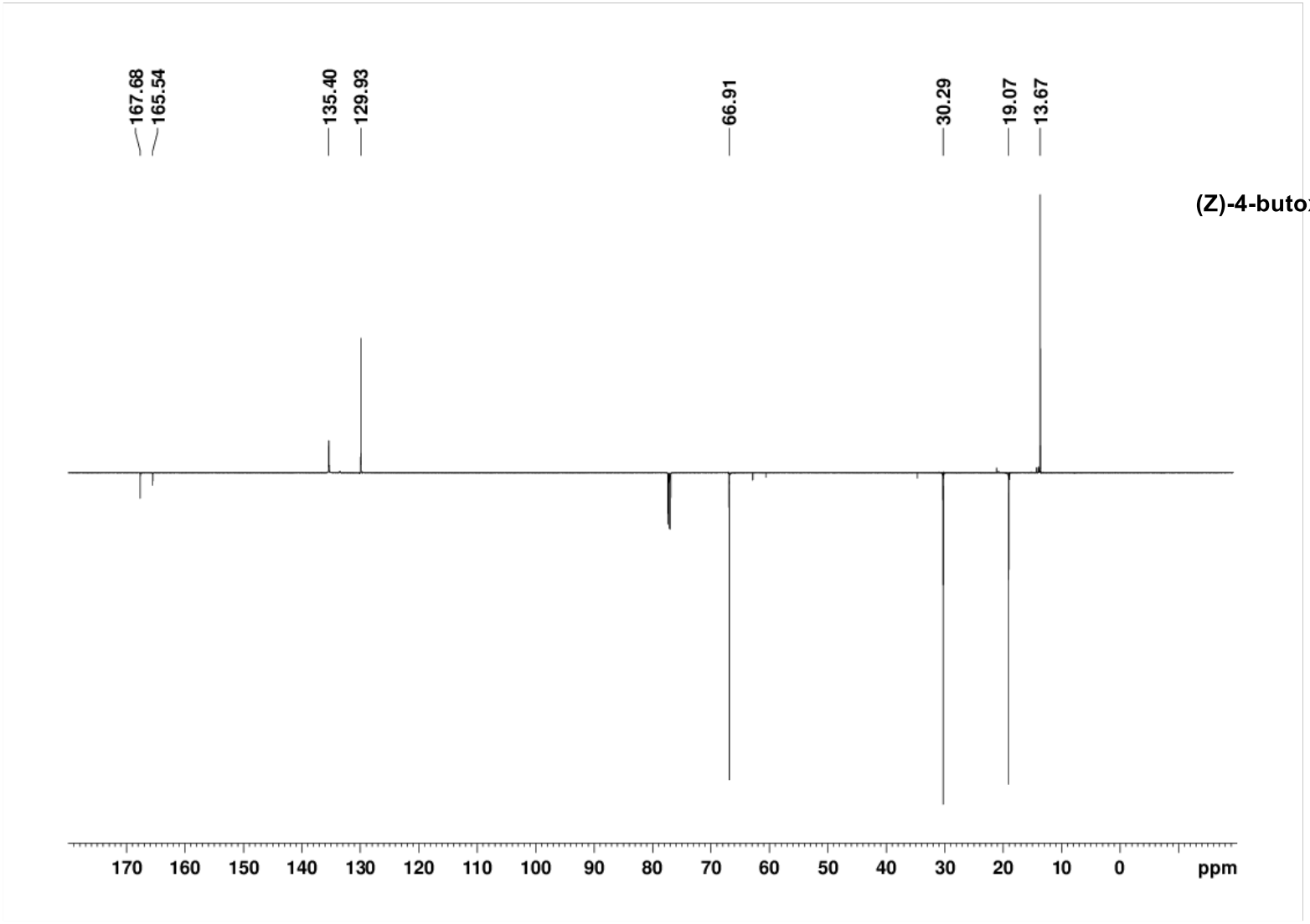


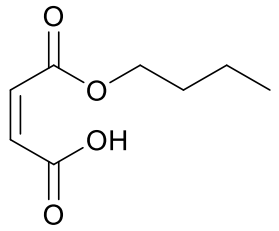


(Z)-4-butoxy-4-oxobut-2-enoic acid

Fig. S6 *^{1}H NMR spectrum of (Z)-4-butoxy-4-oxobut-2-enoic acid.*

^{13}C NMR spectrum of (Z)-4-butoxy-4-oxobut-2-enoic acid





(Z)-4-butoxy-4-oxobut-2-enoic acid

Fig. S7 *^{13}C NMR spectrum of (Z)-4-butoxy-4-oxobut-2-enoic acid*

^{1}H NMR spectrum of (Z)-4-oxo-4-(pentyloxy)but-2-enoic acid

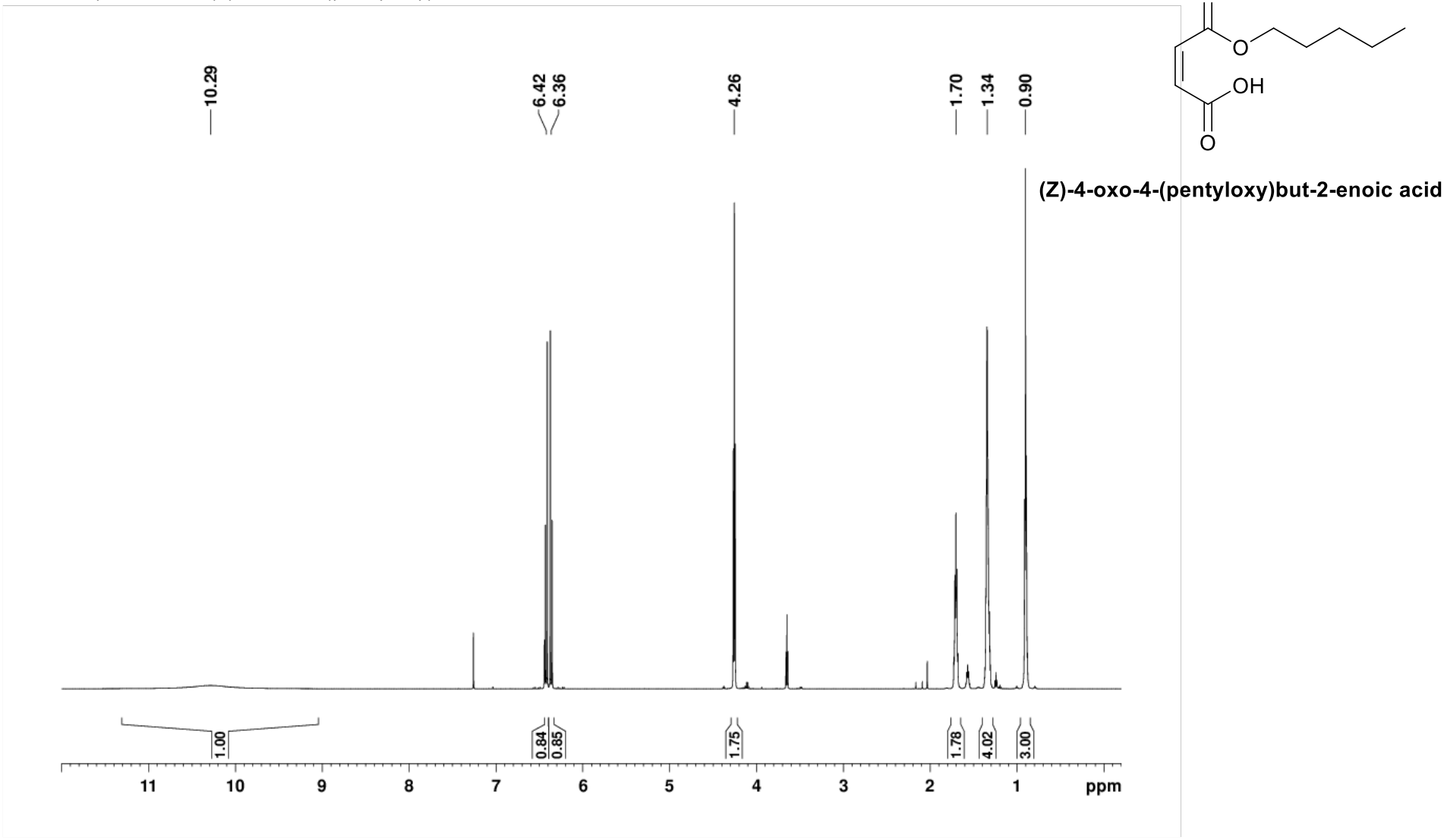
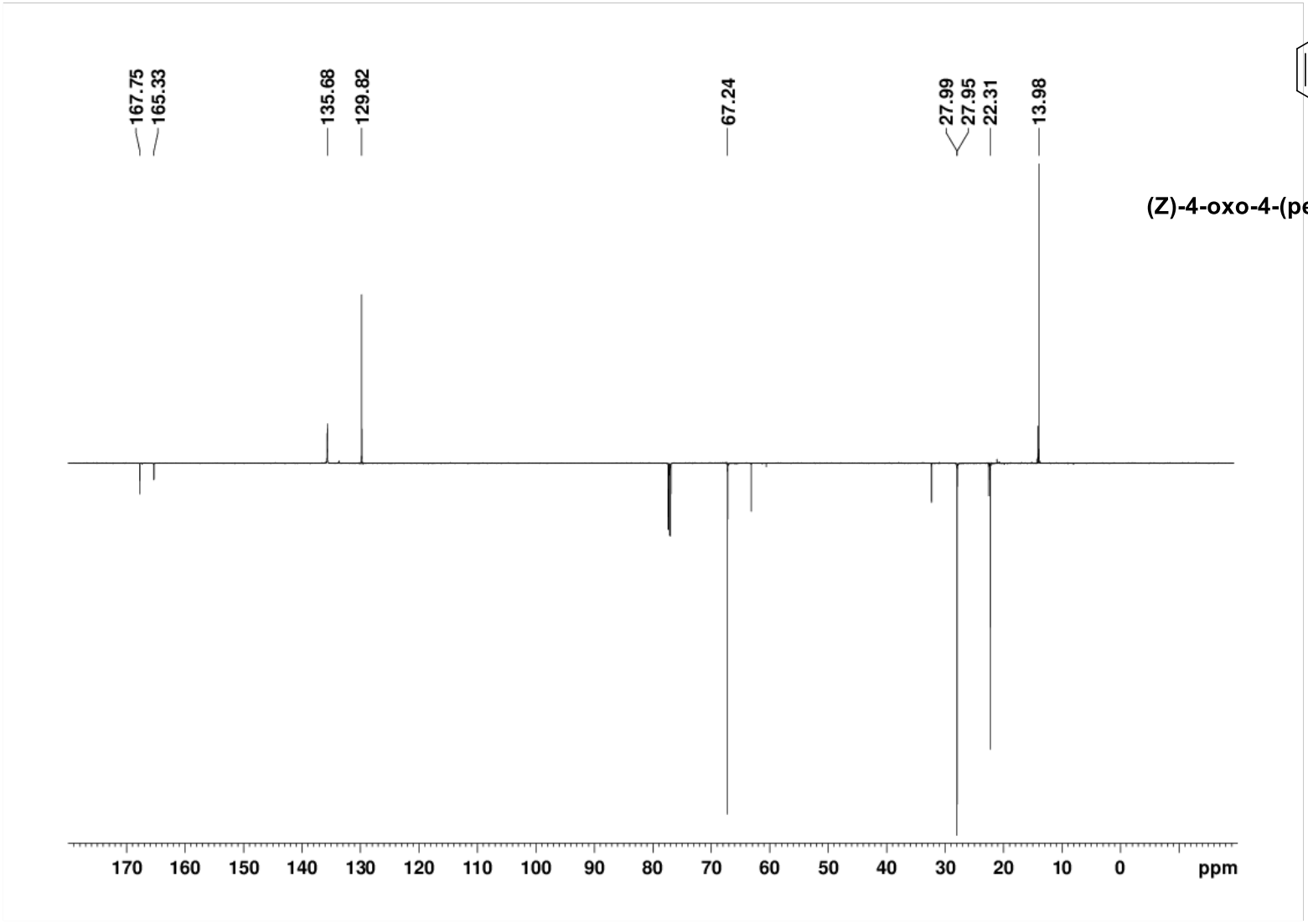
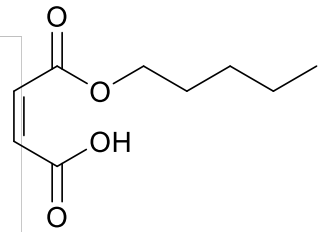


Fig. S8 *^{1}H NMR spectrum of (Z)-4-oxo-4-(pentyloxy)but-2-enoic acid.*

^{13}C NMR spectrum of (Z)-4-oxo-4-(pentyloxy)but-2-enoic acid

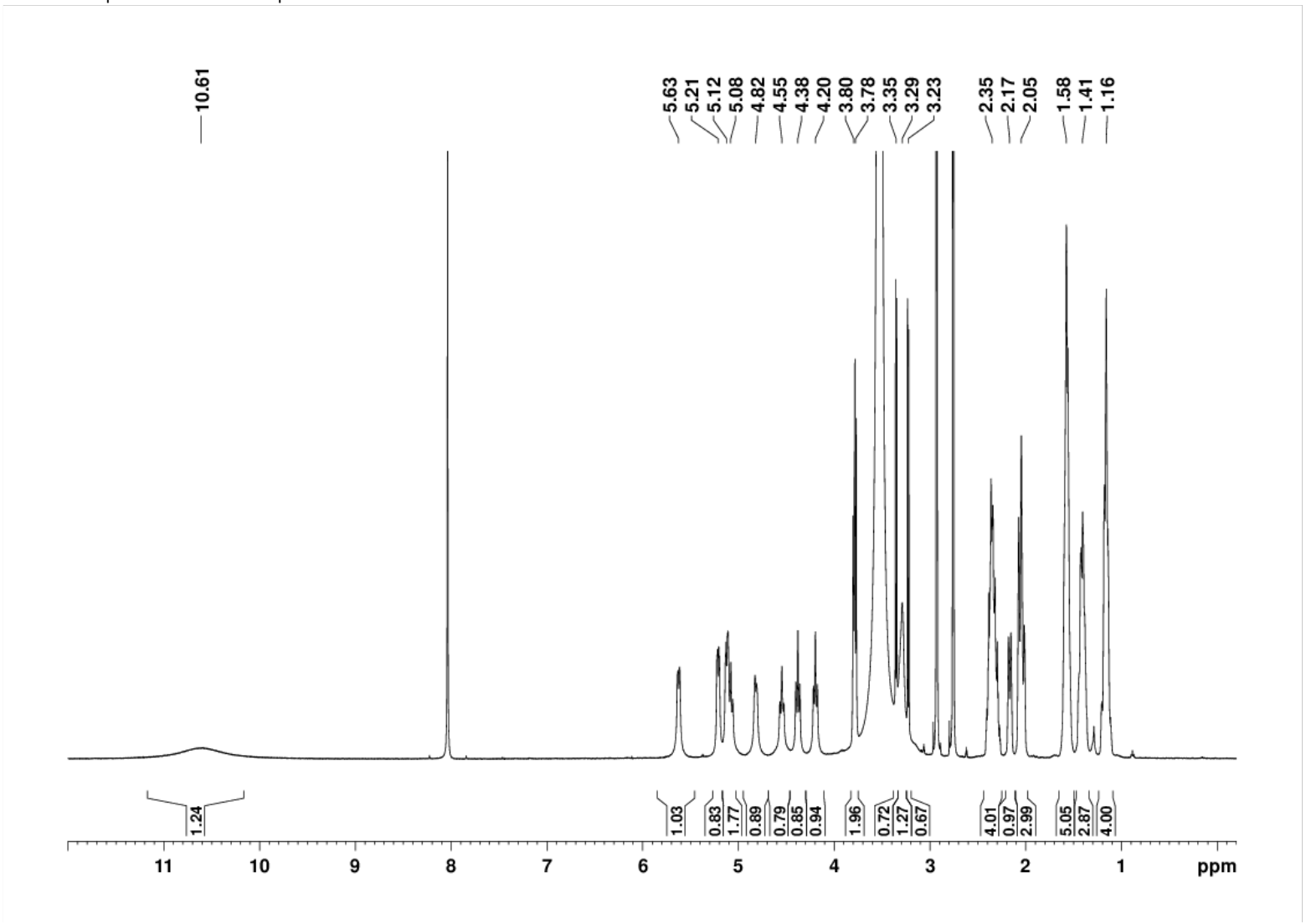


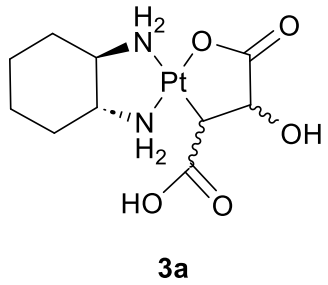


(Z)-4-oxo-4-(pentyloxy)but-2-enoic acid

Fig. S9 *^{13}C NMR spectrum of (Z)-4-oxo-4-(pentyloxy)but-2-enoic acid.*

^{1}H NMR spectrum of compound **3a**

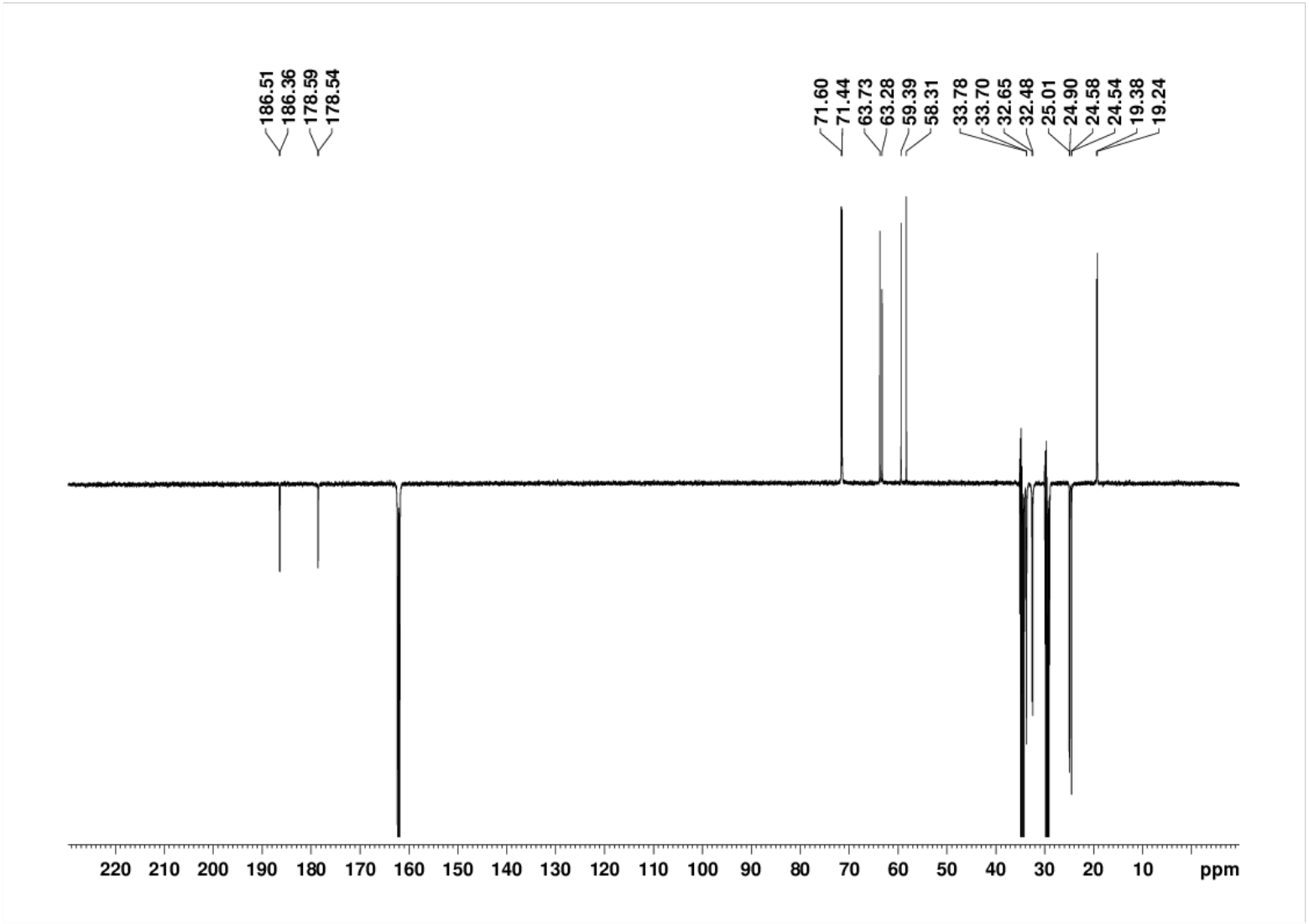


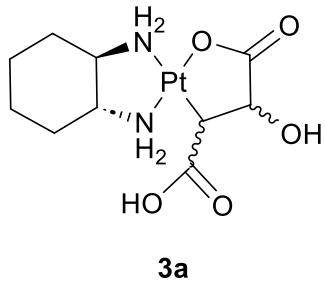


3a

Fig. S10 *^{1}H NMR spectrum of compound **3a**.*

^{13}C NMR spectrum of compound **3a**

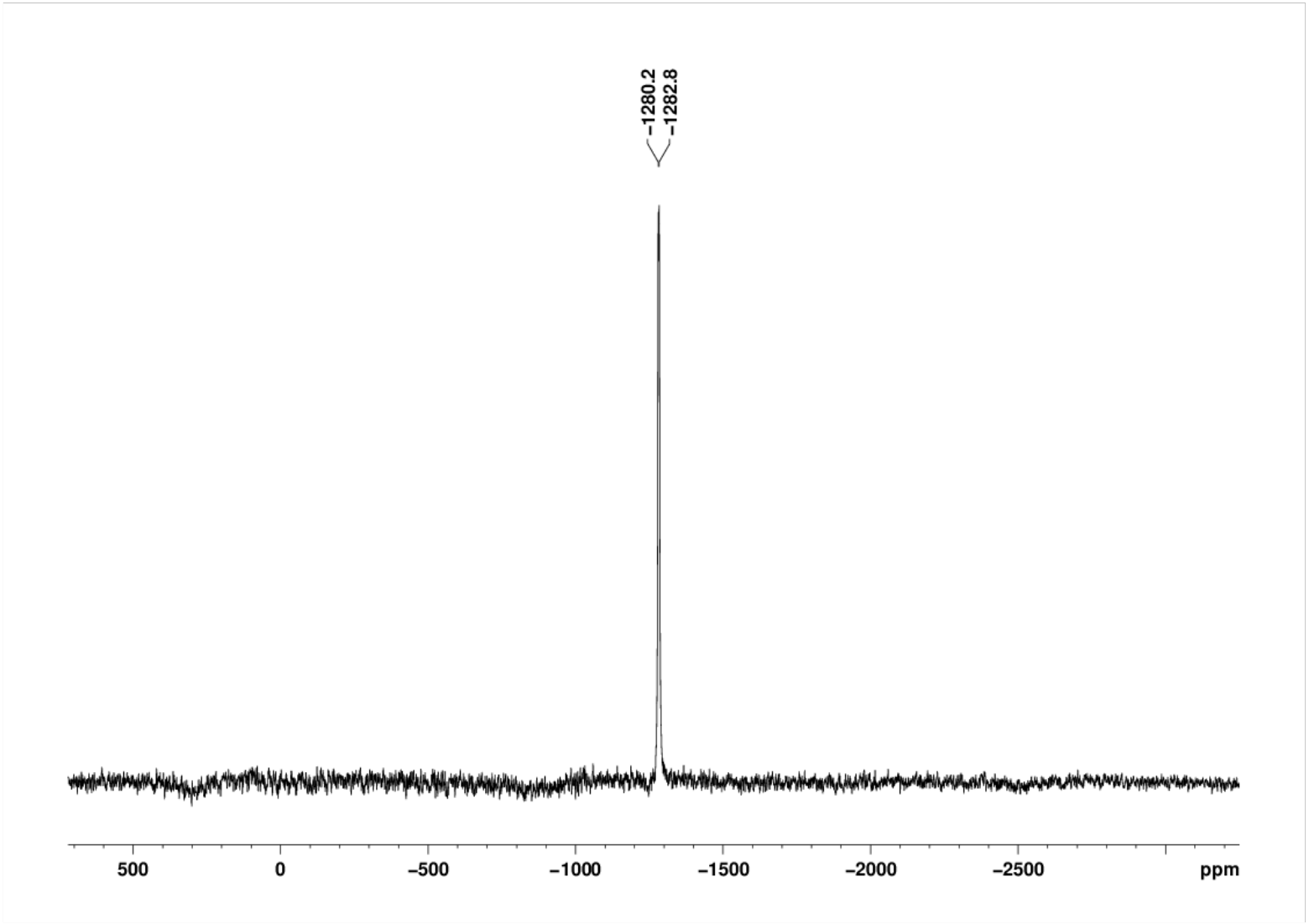


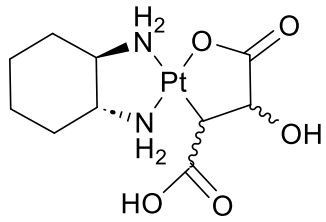


3a

Fig. S11 *^{13}C NMR spectrum of compound **3a**.*

^{195}Pt NMR spectrum of compound **3a**

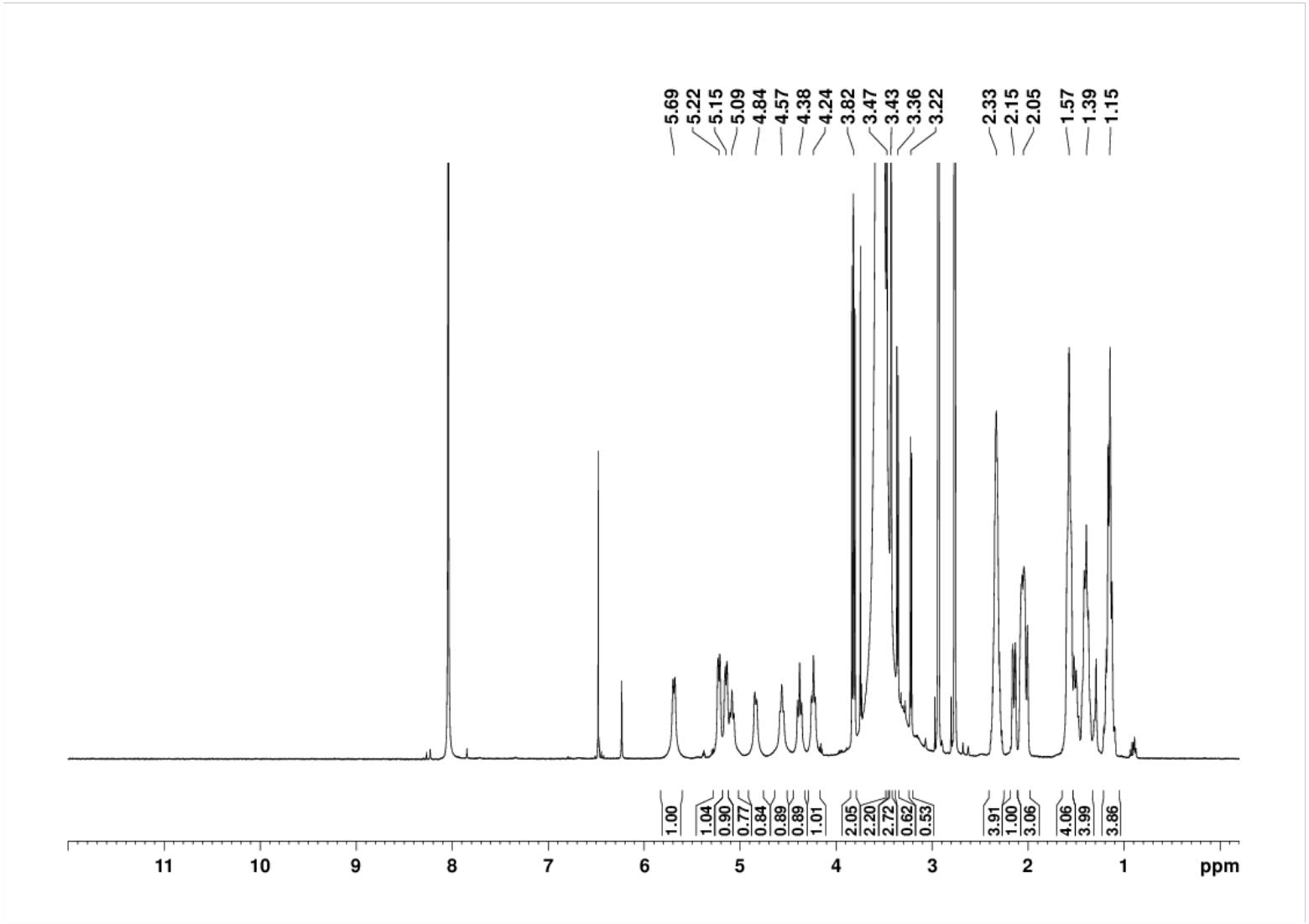


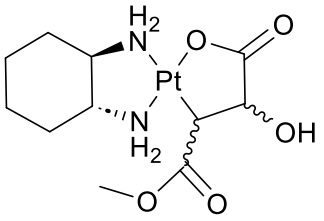


3a

Fig. S12 *^{195}Pt NMR spectrum of compound **3a**.*

^{1}H NMR spectrum of compound **3b**

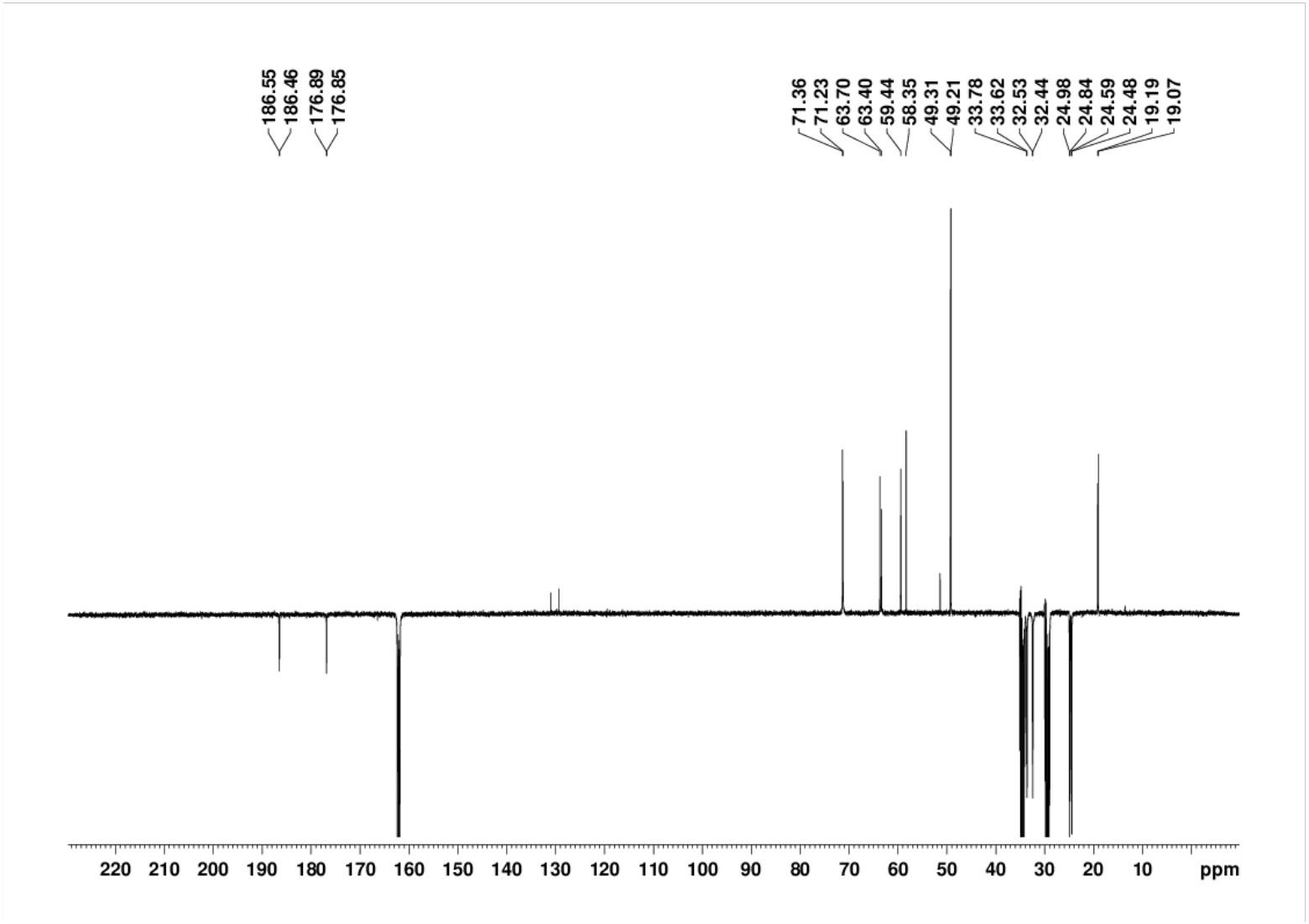


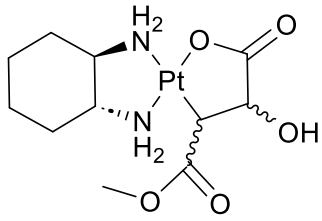


3b

Fig. S13 *^{1}H NMR spectrum of compound **3b**.*

^{13}C NMR spectrum of compound **3b**

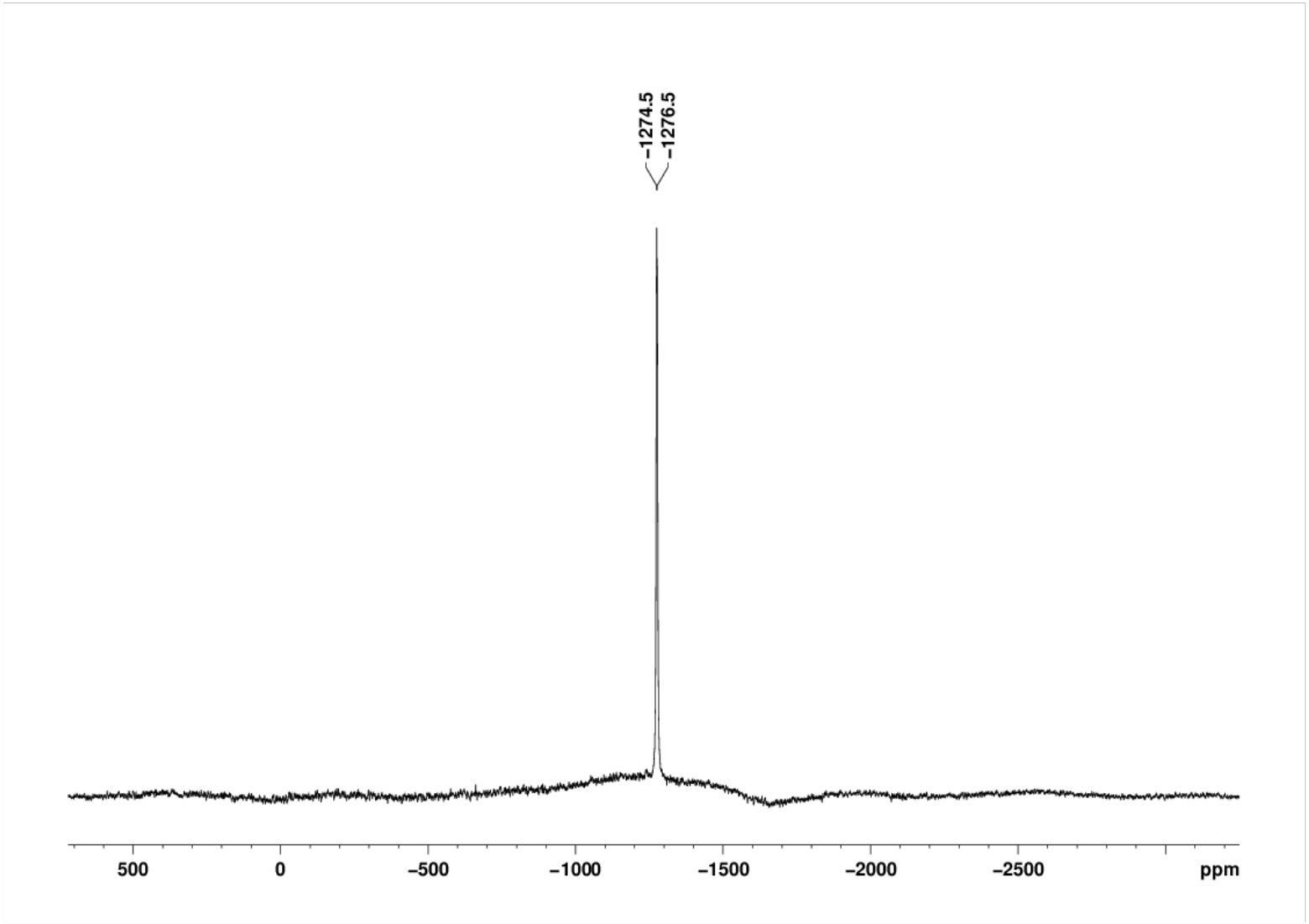


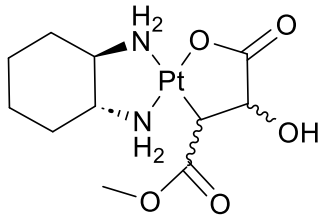


3b

Fig. S14 *^{13}C NMR spectrum of compound* ***3b.***

^{195}Pt NMR spectrum of compound **3b**

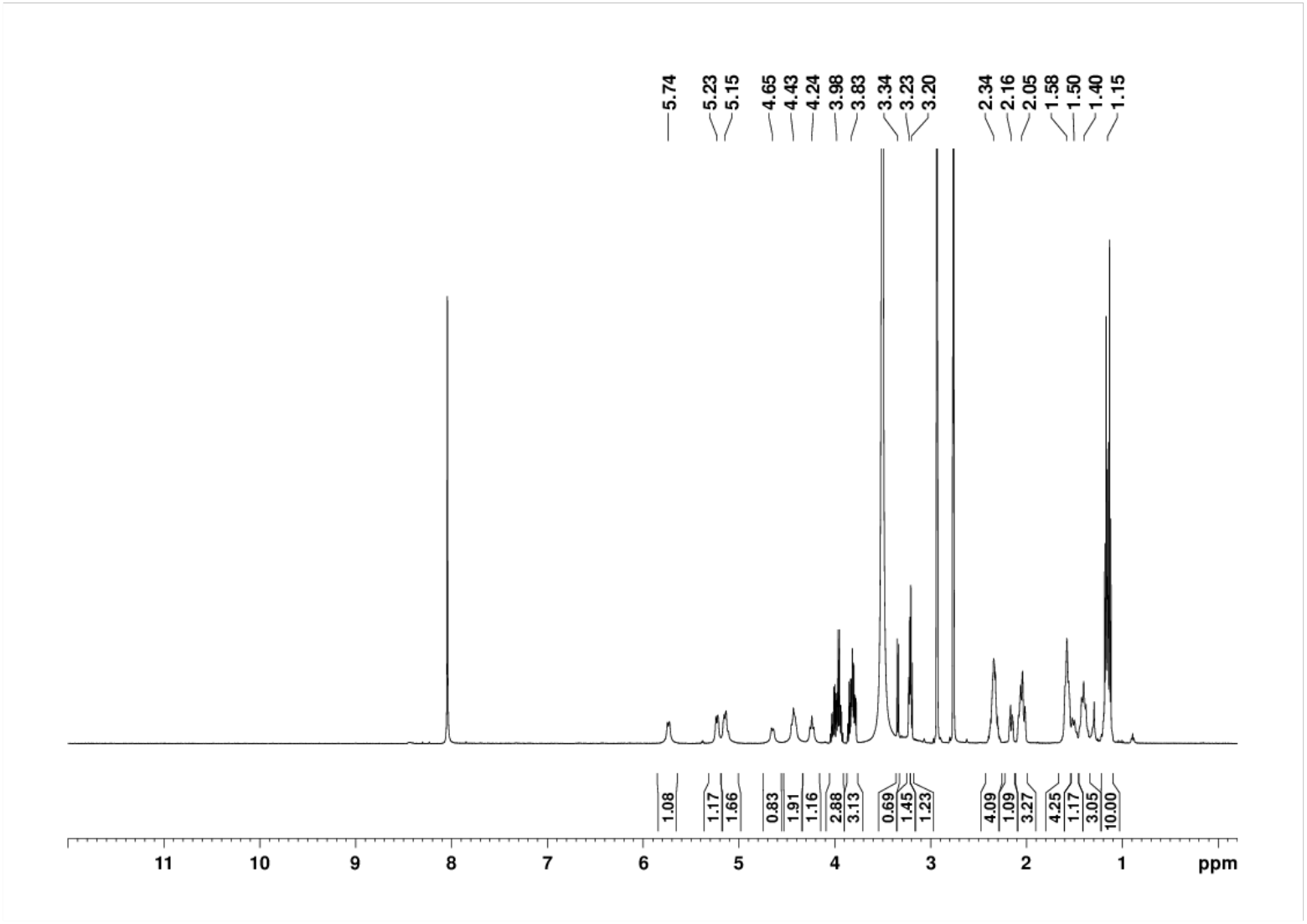


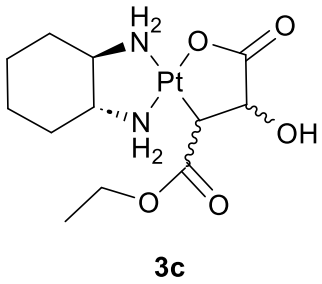


3b

Fig. S15 *^{195}Pt NMR spectrum of compound* ***3b.***

^{1}H NMR spectrum of compound **3c**

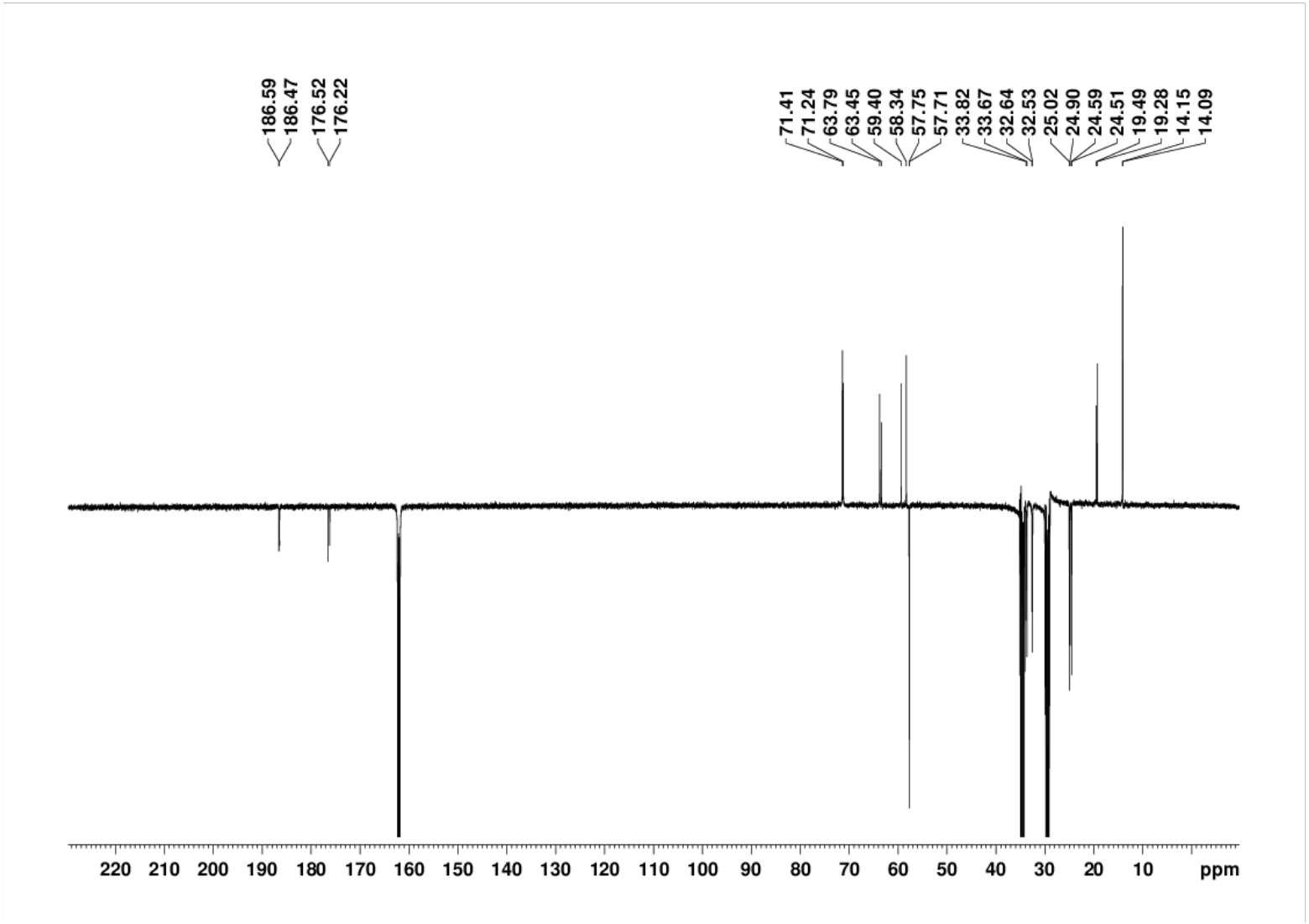


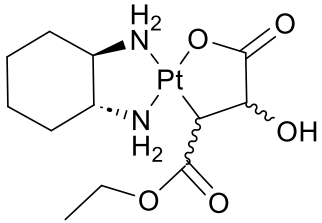


3c

Fig. S16 *1H NMR spectrum of compound* ***3c****.*

^{13}C NMR spectrum of compound **3c**

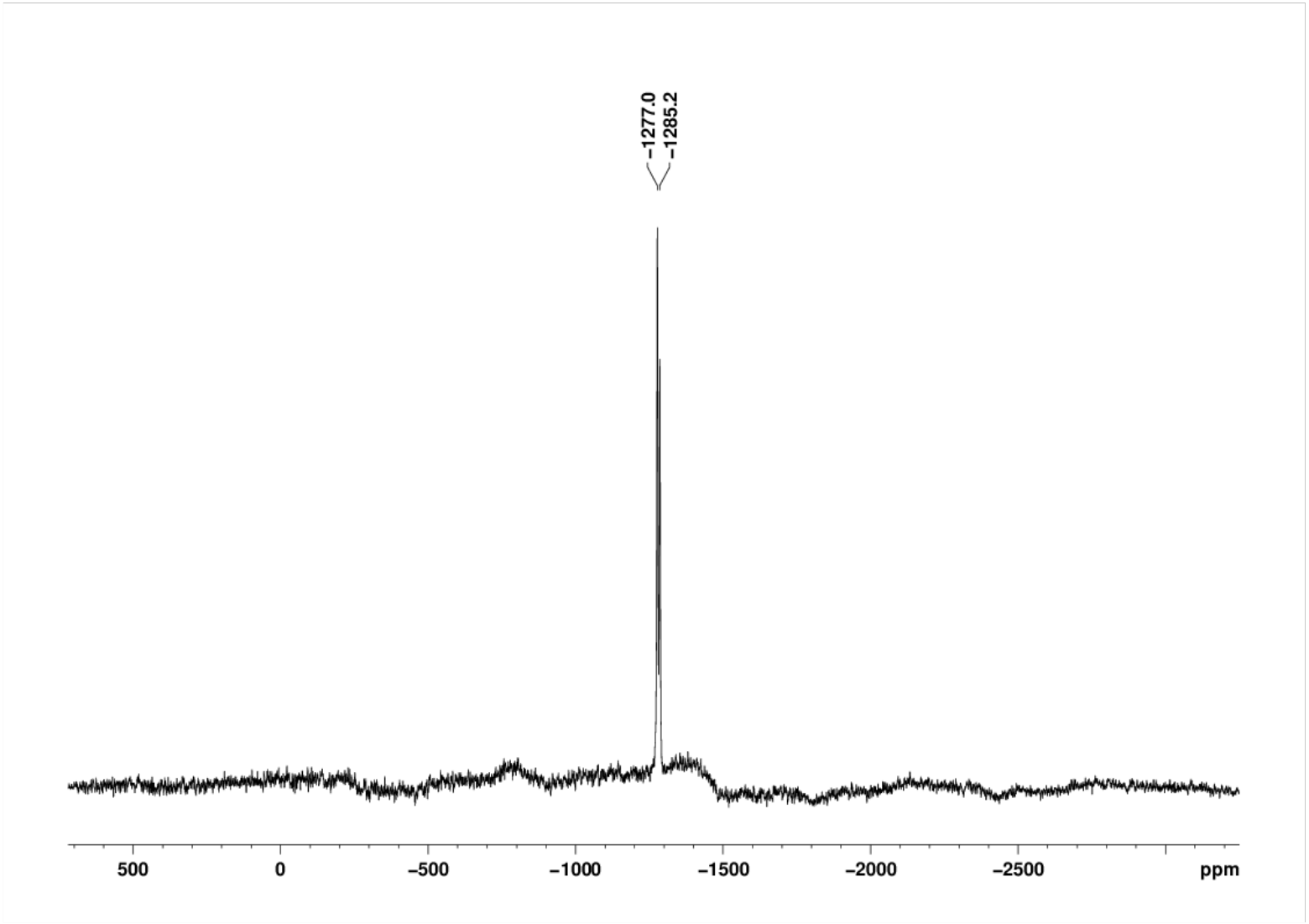


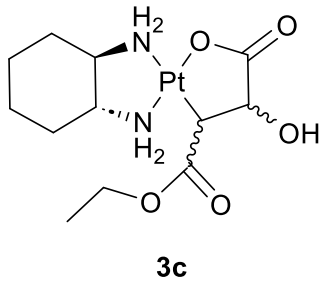


3c

Fig. S17 *^{13}C NMR spectrum of compound* ***3c.***

^{195}Pt NMR spectrum of compound **3c**

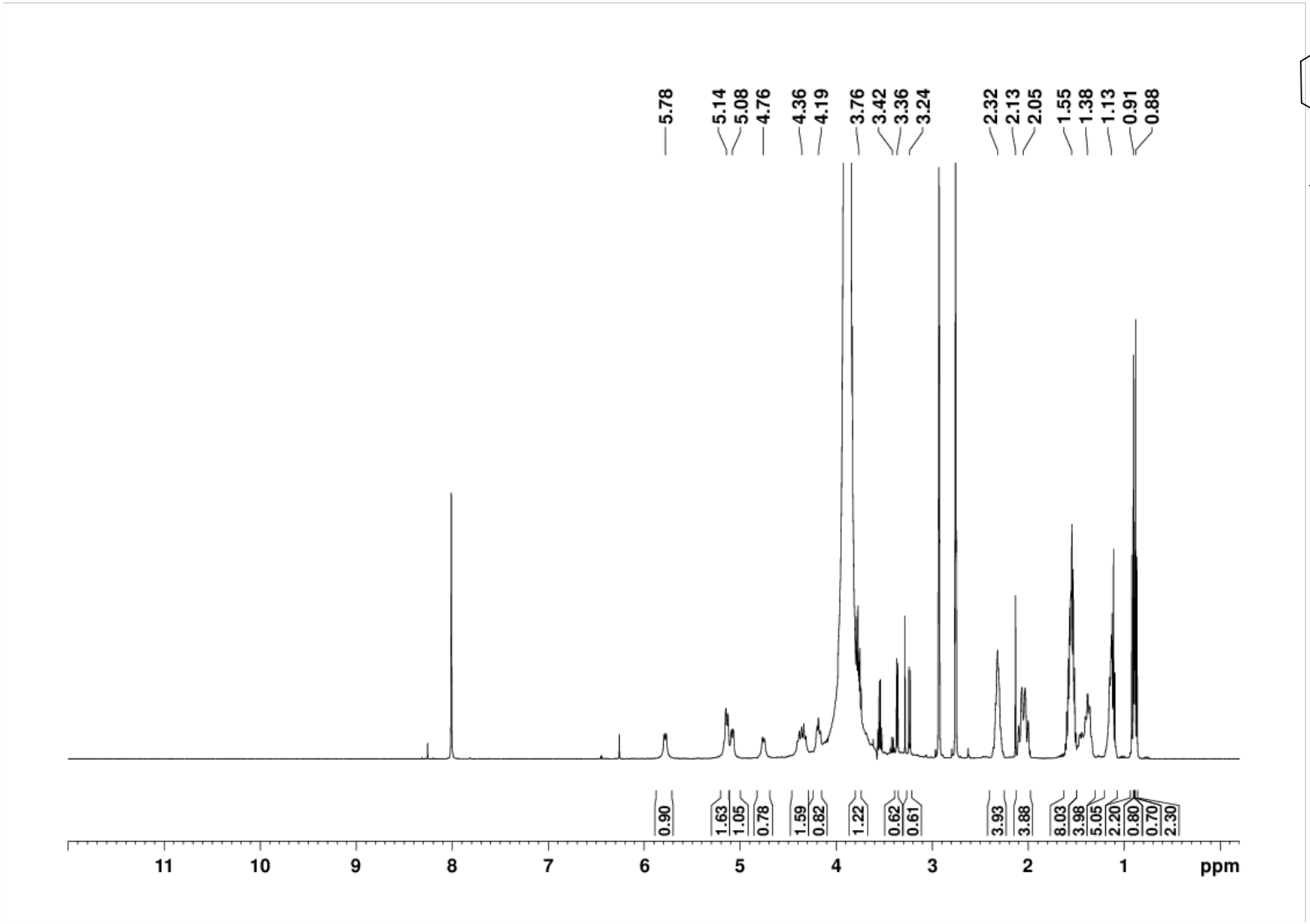


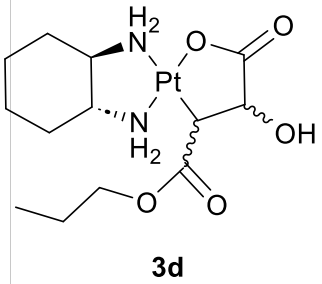


3c

Fig. S18 *^{195}Pt NMR spectrum of compound **3c**.*

^{1}H NMR spectrum of compound **3d**

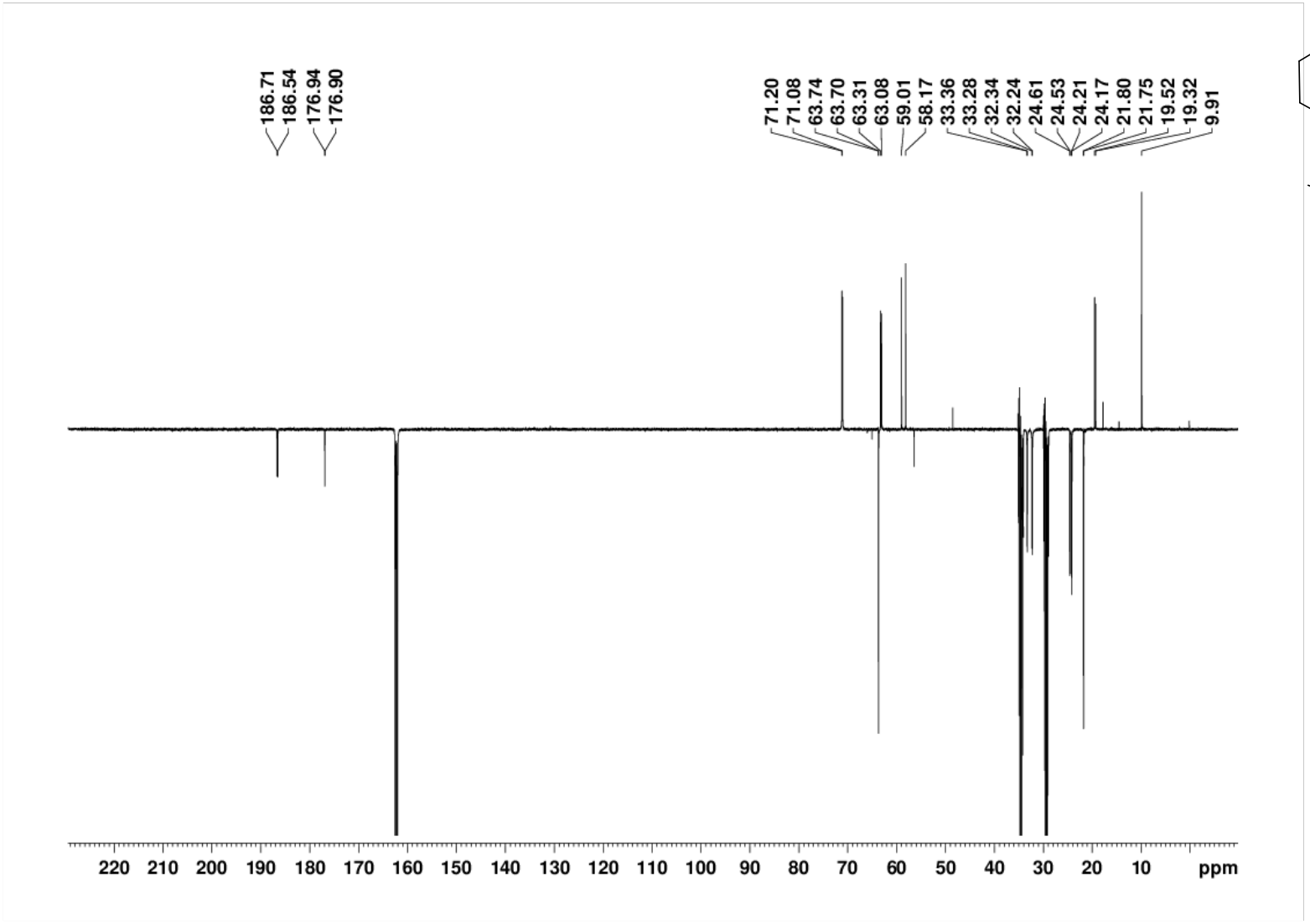


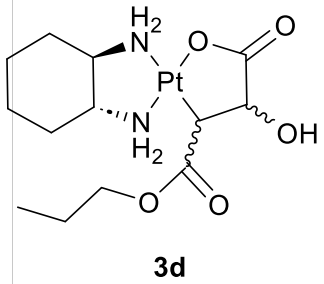


3d

Fig. S19 *^{1}H NMR spectrum of compound* ***3d.***

^{13}C NMR spectrum of compound **3d**

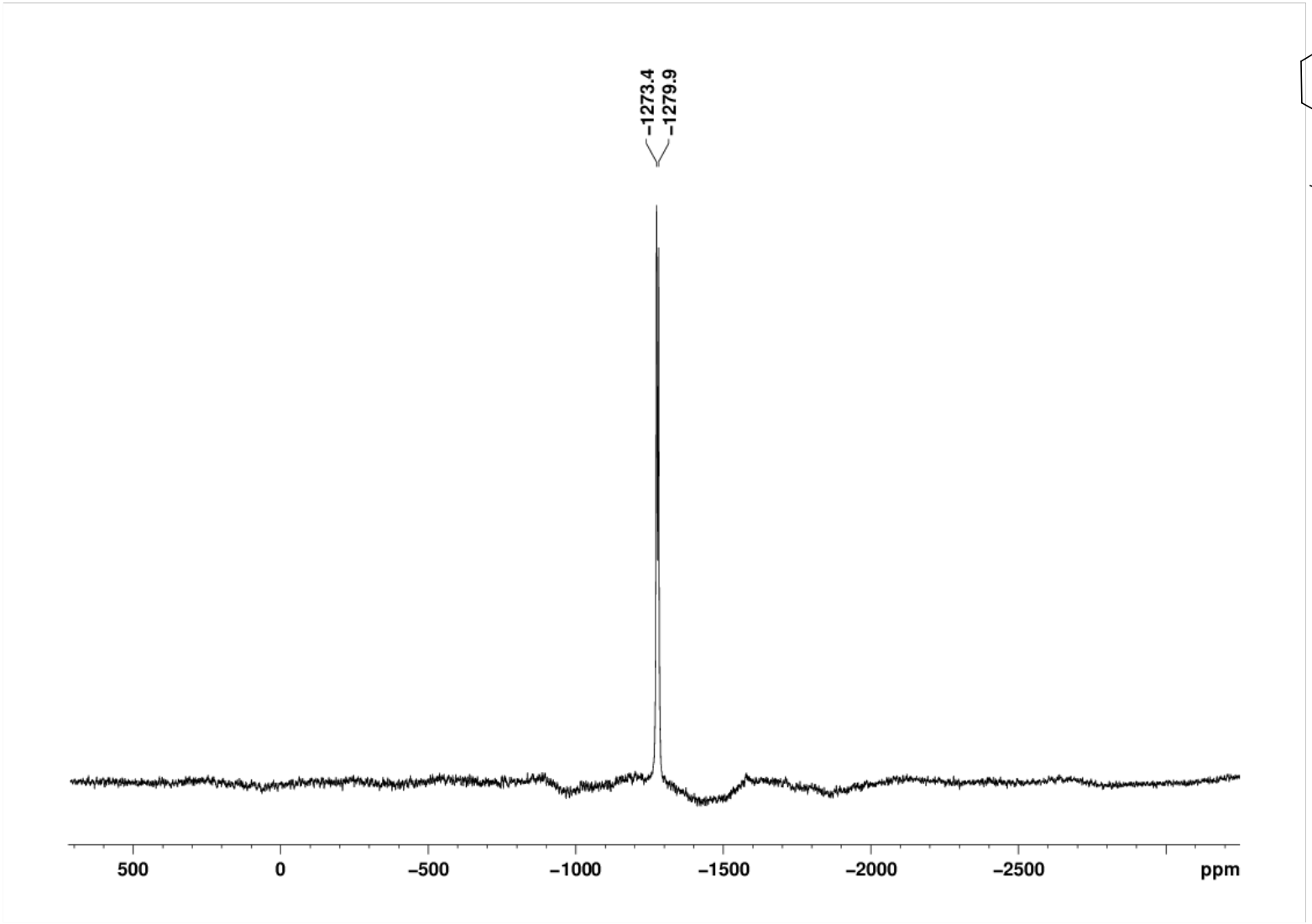


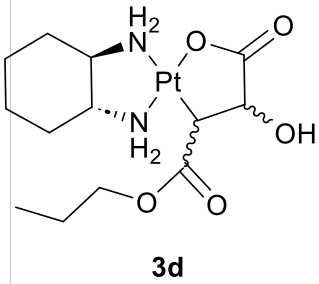


3d

Fig. S20 *^{13}C NMR spectrum of compound **3d**.*

^{195}Pt NMR spectrum of compound **3d**

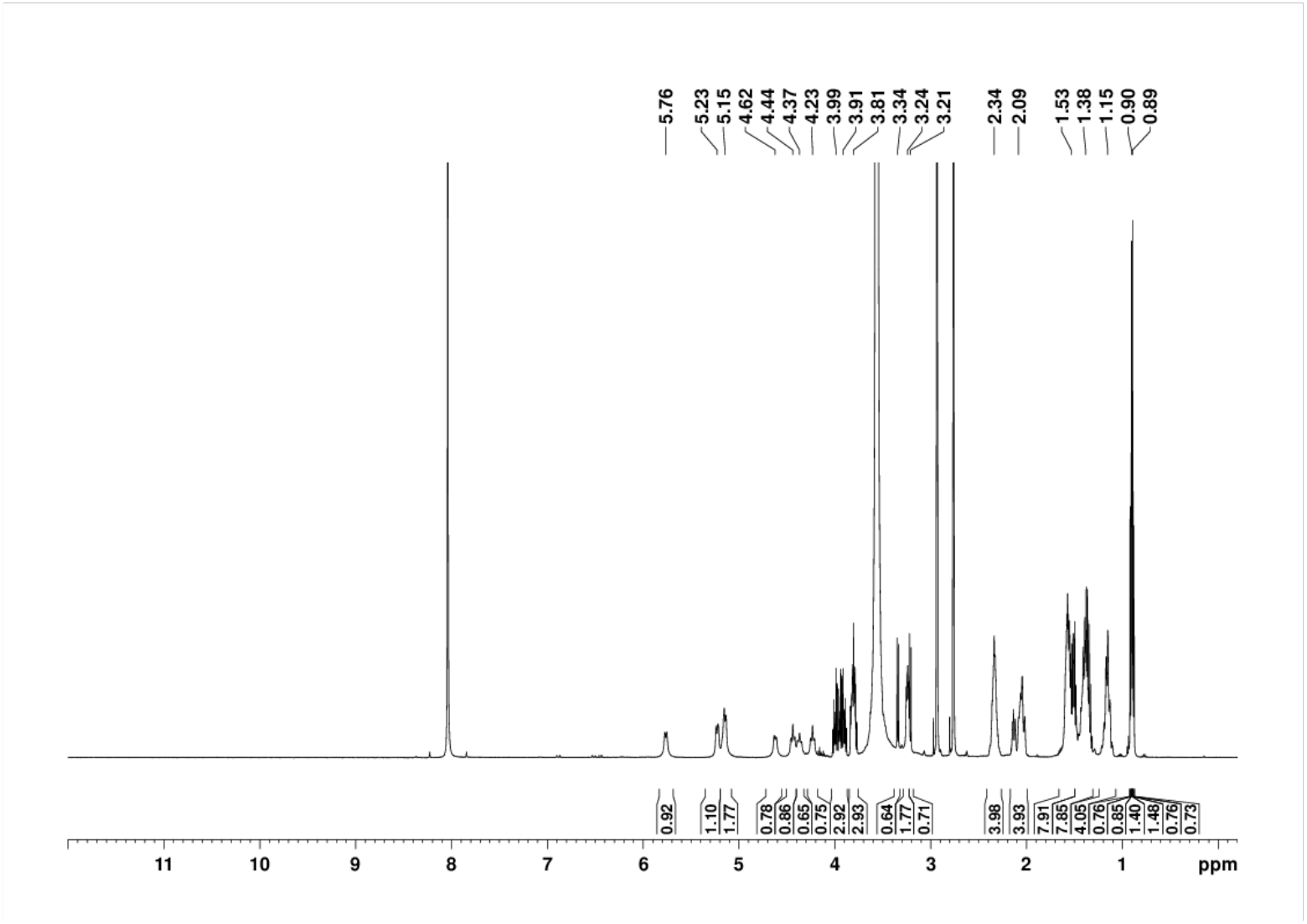


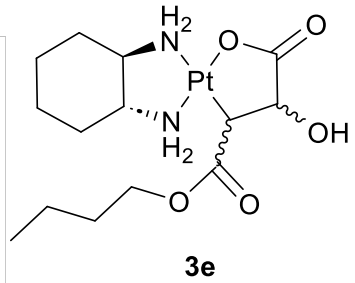


3d

Fig. S21 *^{195}Pt NMR spectrum of compound* ***3d.***

^{1}H NMR spectrum of compound **3e**

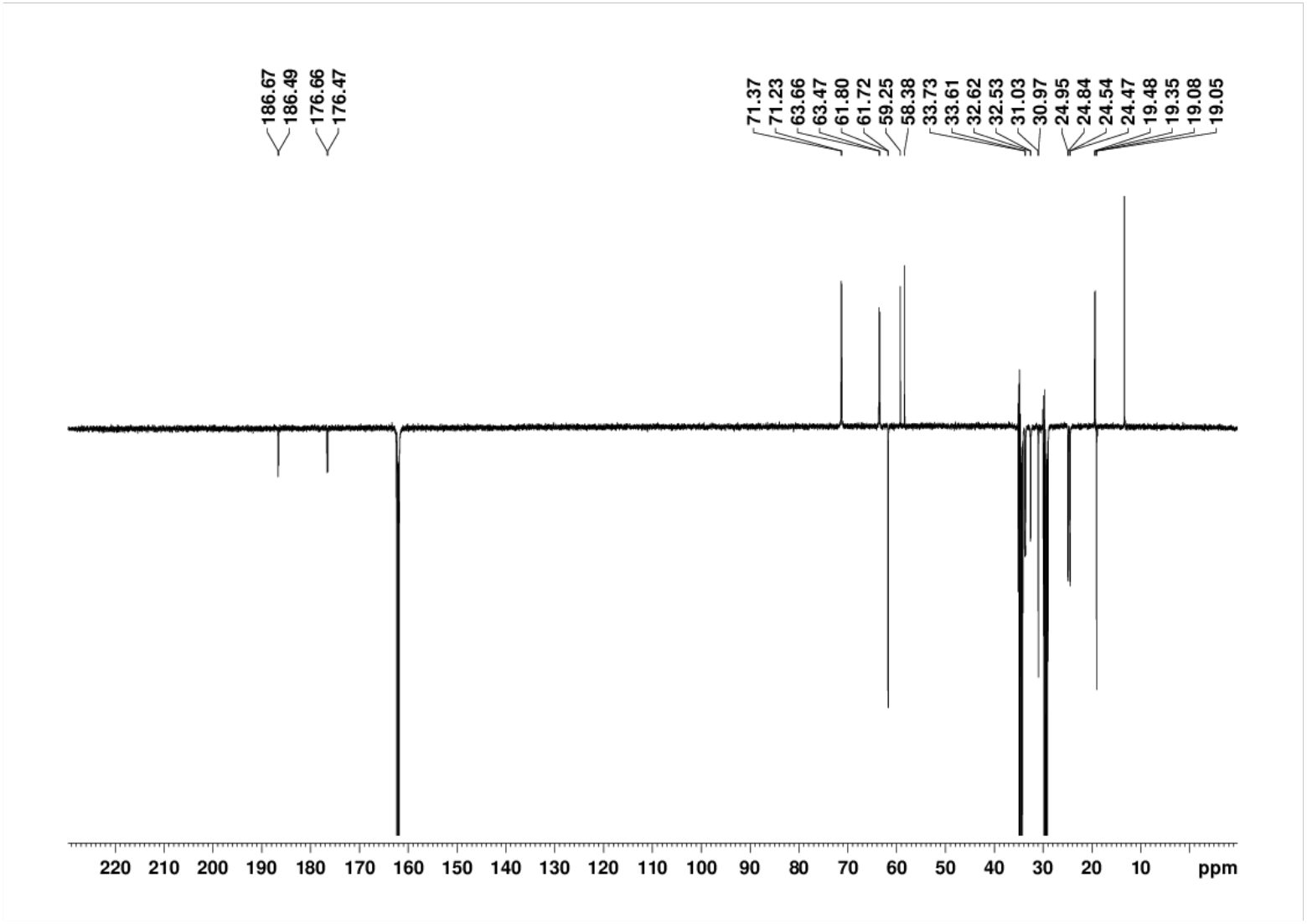


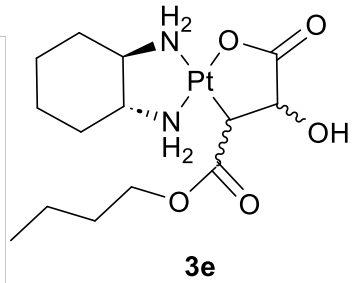


3e

Fig. S22 *^{1}H NMR spectrum of compound* ***3e.***

^{13}C NMR spectrum of compound **3e**

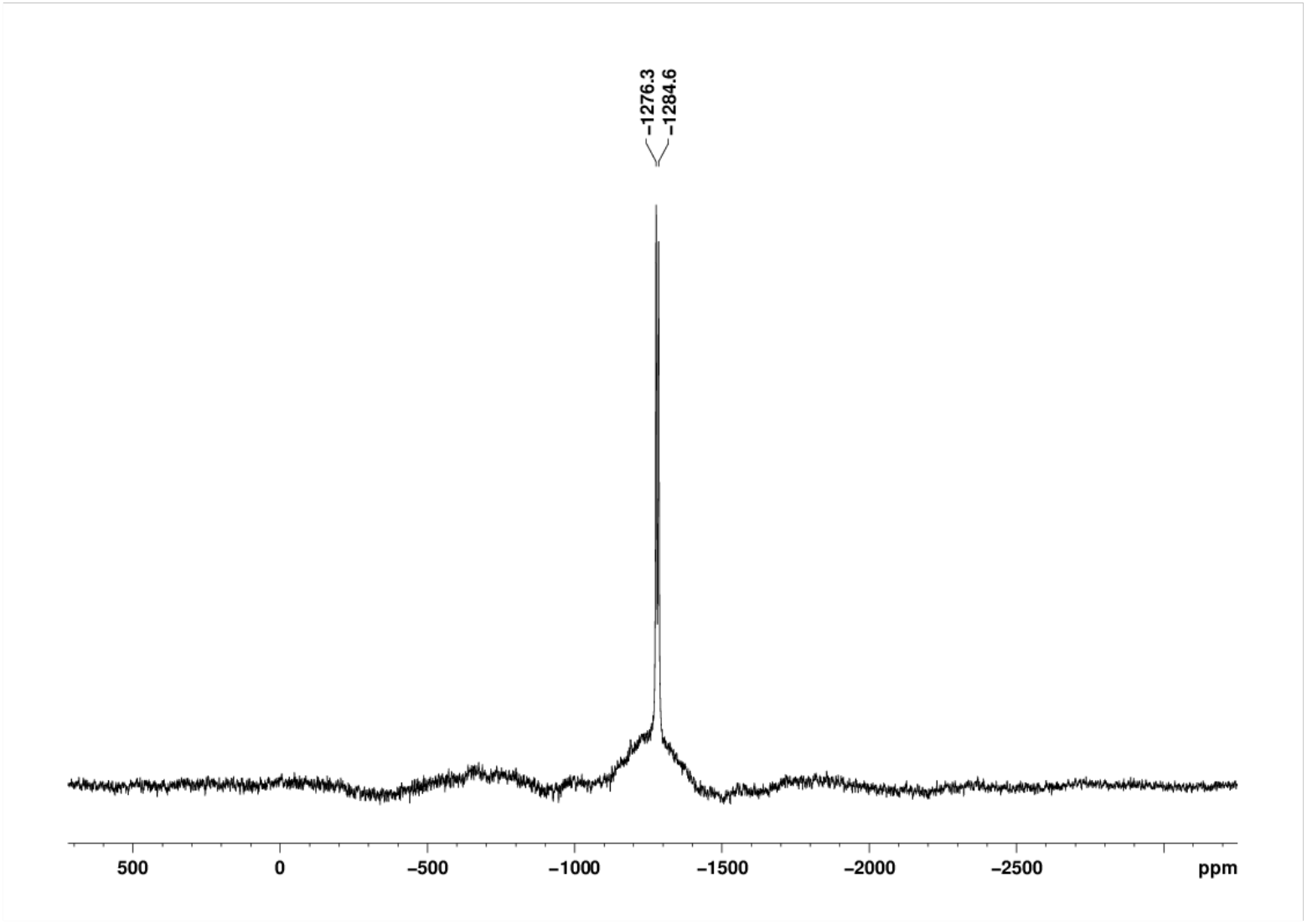


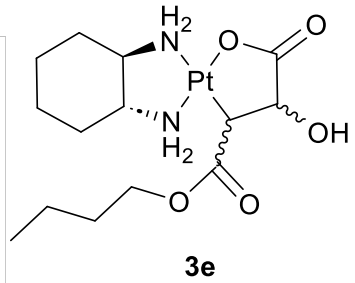


3e

Fig. S23 *^{13}C NMR spectrum of compound **3e**.*

^{195}Pt NMR spectrum of compound **3e**

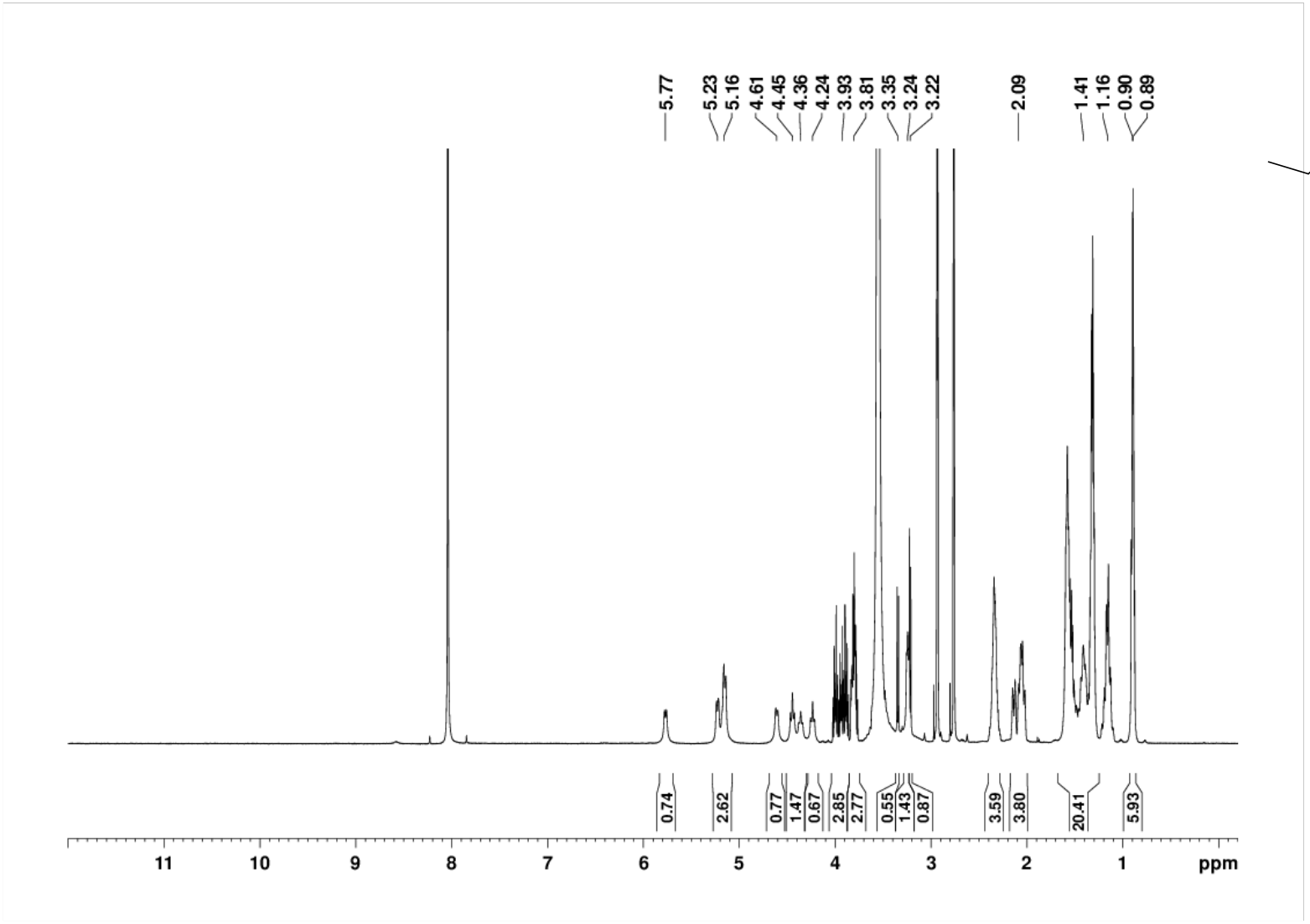


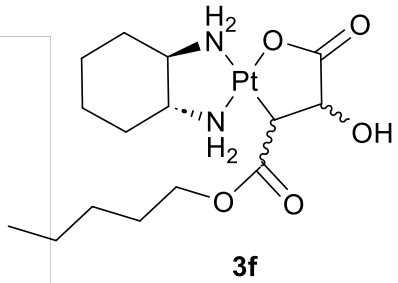


3e

Fig. S24 *^{195}Pt NMR spectrum of compound **3e**.*

^{1}H NMR spectrum of compound **3f**

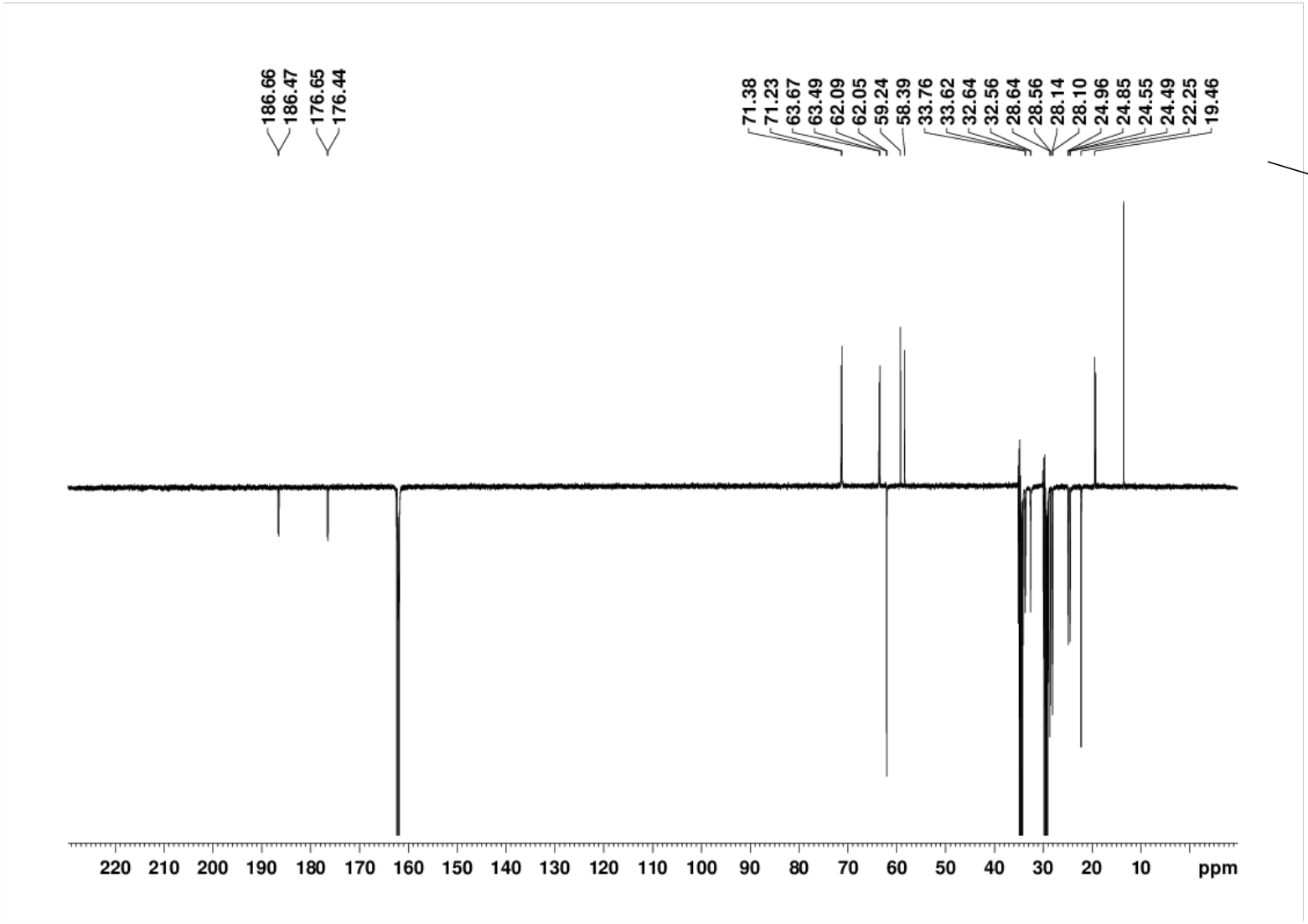


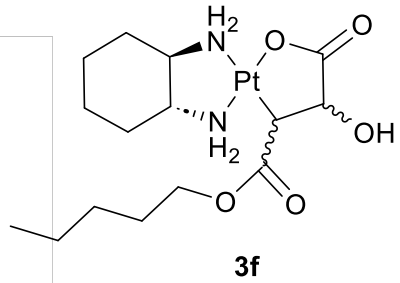


3f

Fig. S25 *^{1}H NMR spectrum of compound* ***3f.***

^{13}C NMR spectrum of compound **3f**

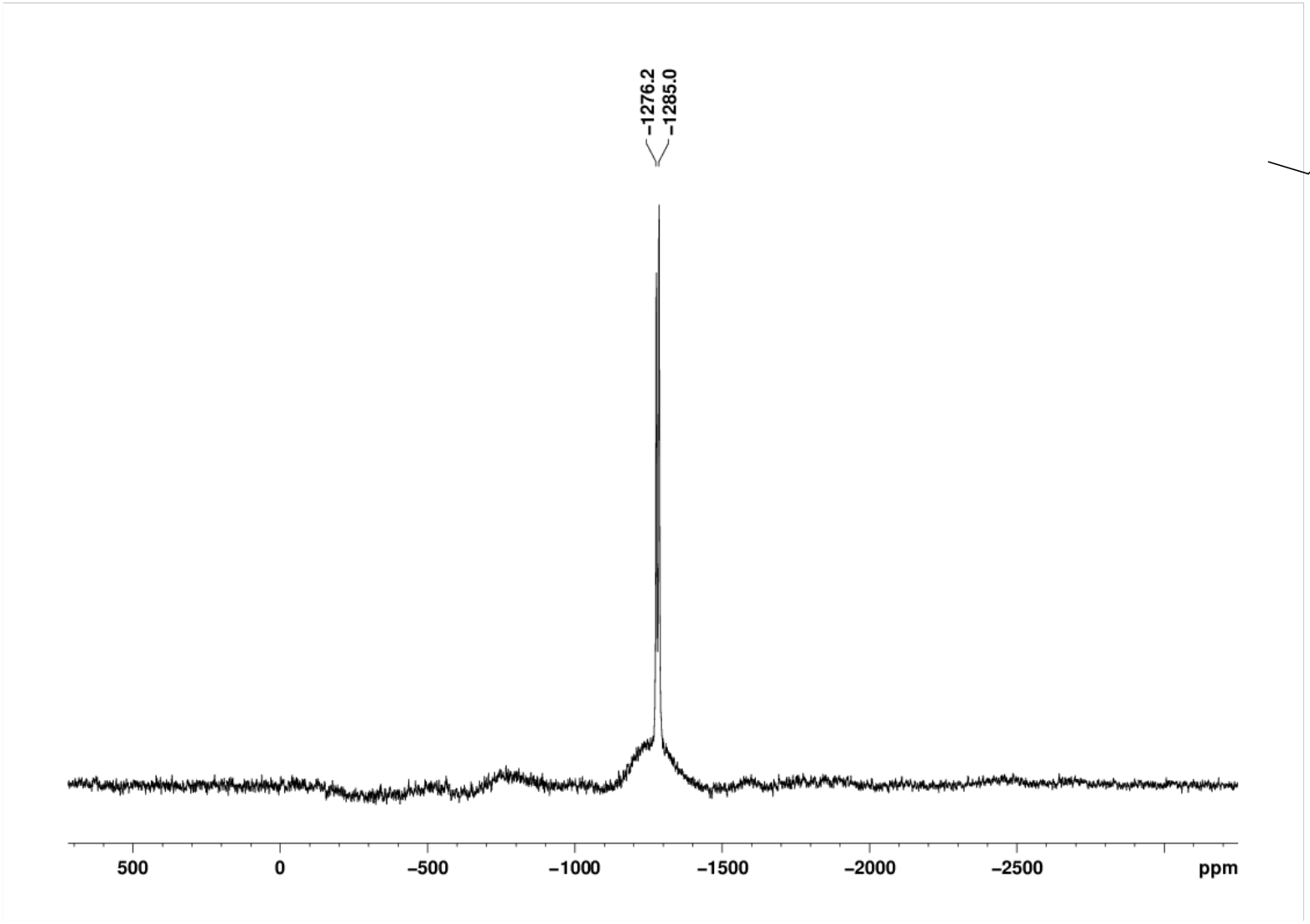


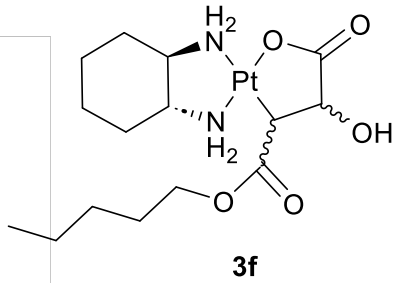


3f

Fig. S26 *^{13}C NMR spectrum of compound **3f**.*

^{195}Pt NMR spectrum of compound **3f**





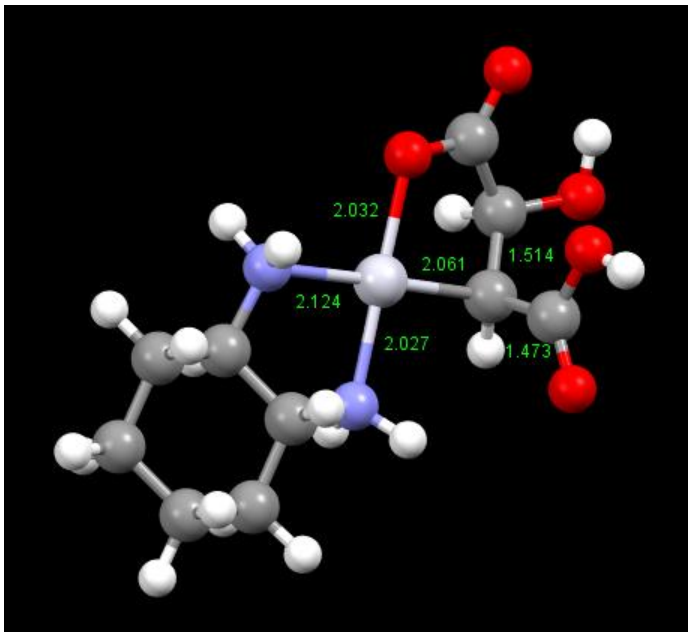
3f

Fig. S27 *^{195}Pt NMR spectrum of compound **3f**.*

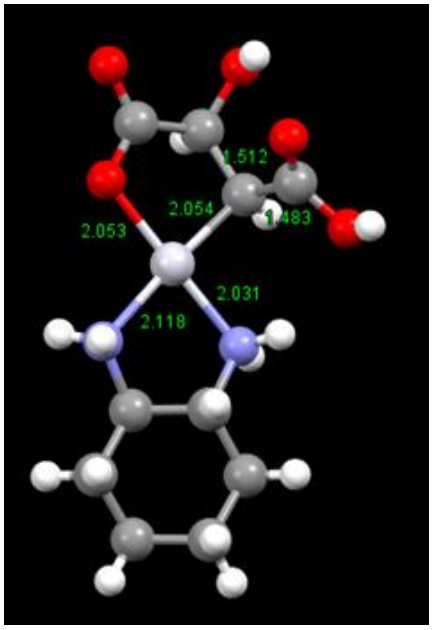
Comparison of calculated geometries of diastereoisomers A and B of complex **3a** with experimental geometries

molecule A

calculated

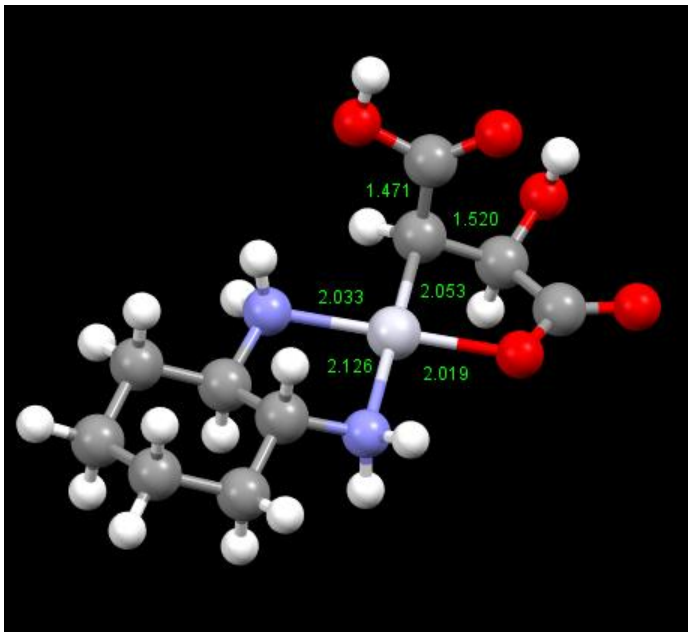


from cif



molecule B

calculated



from cif

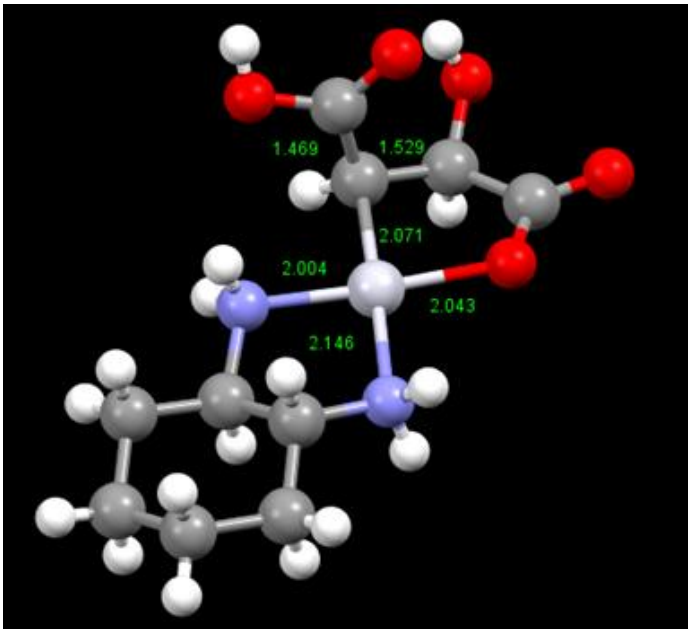
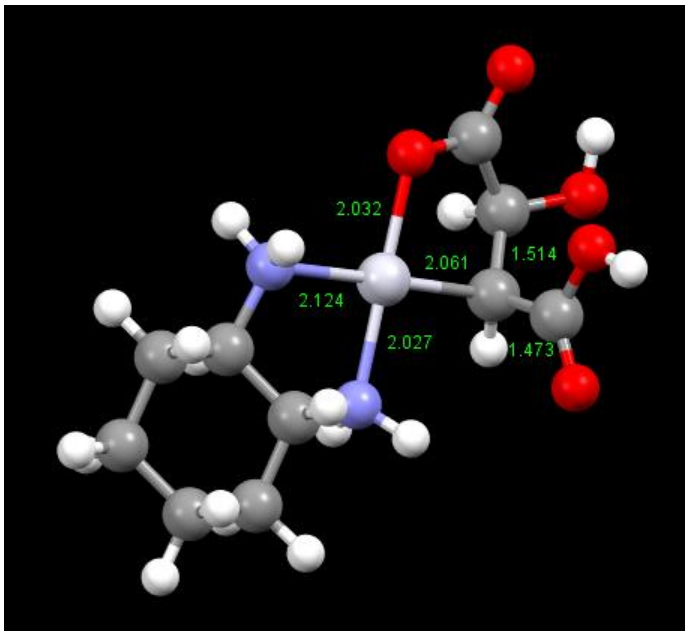


Fig. S28 *Comparison of calculated geometries of diastereoisomers A and B of complex* ***3a*** *with experimental geometries.*

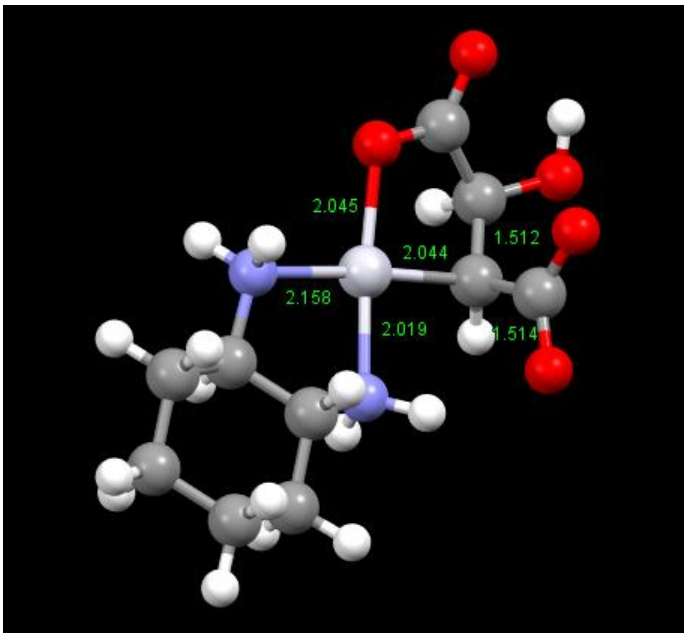
Comparison of calculated geometries of diastereoisomers A and B of complex **3a** with either carboxyl or carboxylate group

molecule A

with carboxyl group

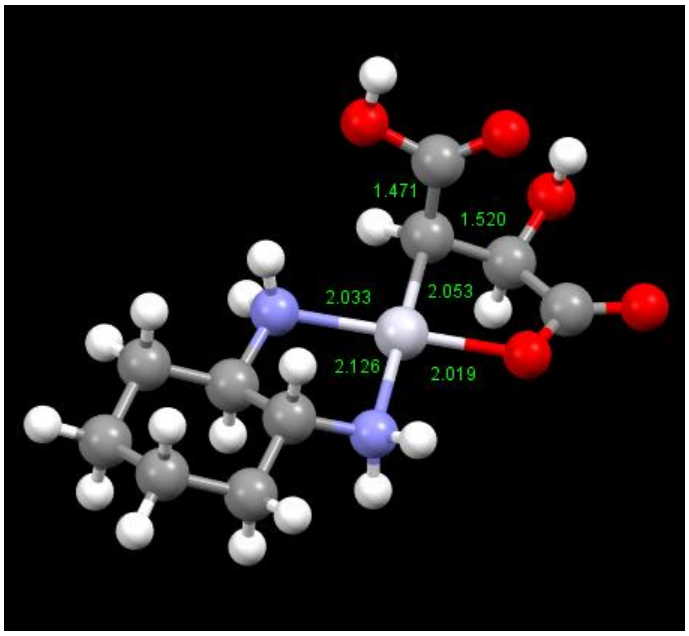


with carboxylate group



molecule B

with carboxyl group



with carboxylate group

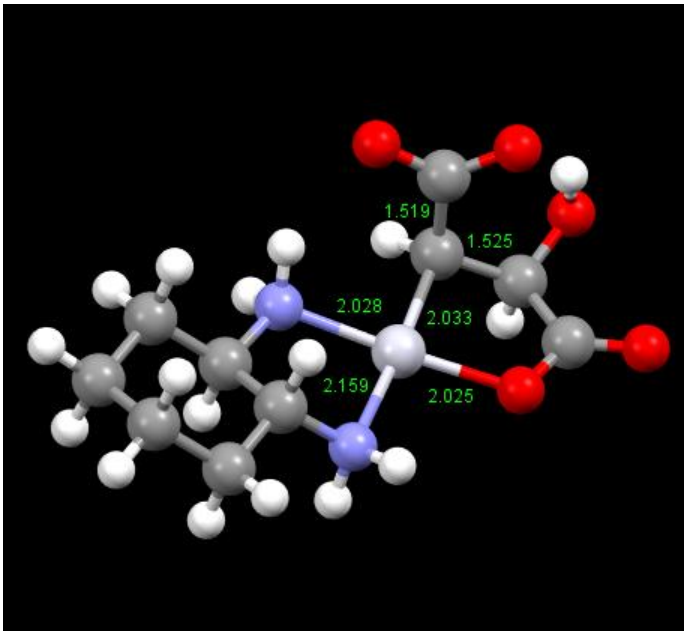


Fig. S29 *Comparison of calculated geometries of diasteroisomers A and B of complex **3a** with either carboxyl or carboxylate group.*

X-Ray Diffraction Analysis of complex **3a**

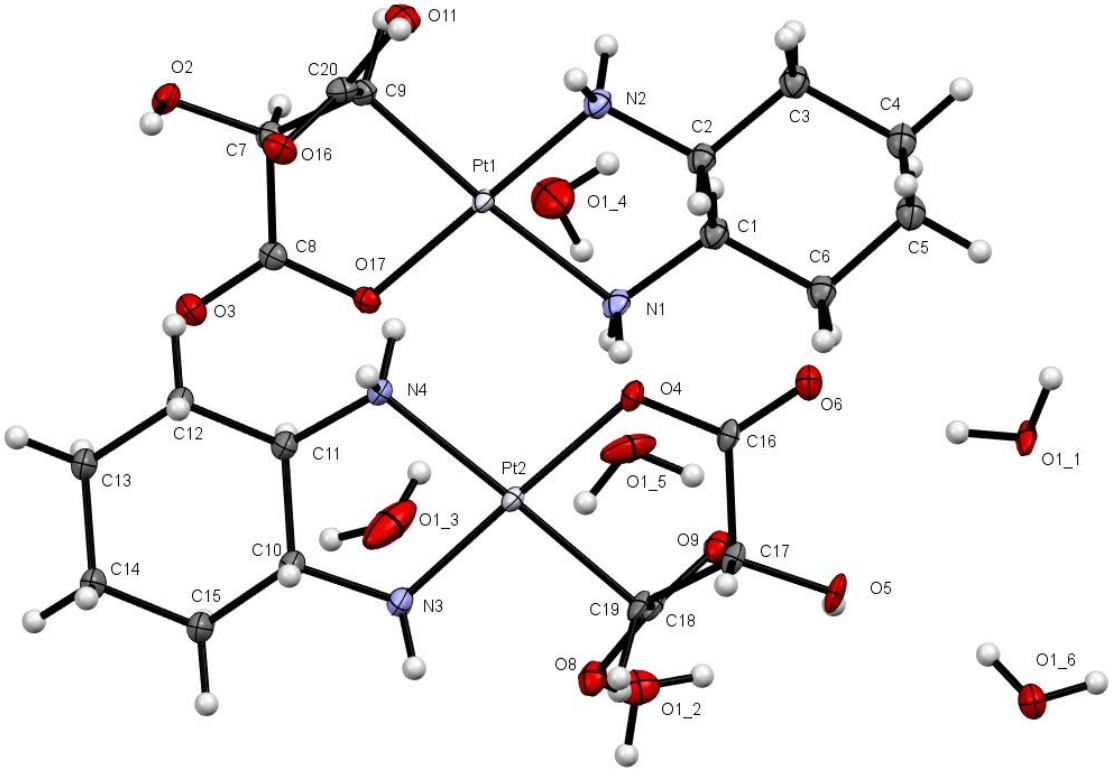


Fig. S30 ORTEP view of complex **3a** drawn with 50% displacement ellipsoids.

Table S1. Overview of the sample and crystal data, data collection and structure refinement for complex **3a**.

Identification code	mawa001_b	
Empirical formula	$C_{10}H_{24}N_2O_8Pt$	
Formula weight	495.40 g/mol	
Temperature	100 K	
Wavelength	1.54186 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.2831(17) Å	α= 73.15(3)°
	b = 9.6777(19) Å	β= 76.80(3)°
	c = 10.192(2) Å	γ = 80.70(3)°
Volume	757.23(4) $Å^3$	
Z	2	
Density (calculated)	2.173 g/cm^3	
Absorption coefficient	17.721 mm^{-1}	
F(000)	480	
Crystal size	0.130 x 0.070 x 0.050 mm^3	
Theta range for data collection	5.515° to 70.870°	
Index ranges	-6<=h<=10, -11<=k<=10, -10<=l<=12	
Reflections collected	15268	
Independent reflections	3380 [R(int) = 0.0164]	
Completeness to theta = 67.679°	94.9 %	
Absorption correction	Sphere	
Max. and min. transmission	0.4261 and 0.1088	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	3380 / 501 / 420	
Goodness-of-fit on F2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0178, wR2 = 0.0459	
R indices (all data)	R1 = 0.0185, wR2 = 0.0462	
Absolute structure parameter	0.087(15)	
Extinction coefficient	0.00154(9)	
Largest diff. peak and hole	0.960 and -1.462 e·$Å^3$	

Table S2. Overview of bond lengths [Å] for complex **3a**.

Pt(1)-N(2)	2.032(12)		N(3)-C(10)	1.506(13)
Pt(1)-O(17)	2.053(10)		N(4)-C(11)	1.492(14)
Pt(1)-C(9)	2.054(14)		C(1)-C(6)	1.527(14)
Pt(1)-N(1)	2.118(13)		C(1)-C(2)	1.535(10)
Pt(2)-N(3)	2.005(12)		C(2)-C(3)	1.517(13)
Pt(2)-O(4)	2.044(10)		C(3)-C(4)	1.534(13)
Pt(2)-C(19)	2.071(13)		C(4)-C(5)	1.518(10)
Pt(2)-N(4)	2.145(13)		C(5)-C(6)	1.500(15)
O(2)-C(7)	1.428(15)		C(7)-C(9)	1.512(14)
O(3)-C(8)	1.237(14)		C(7)-C(8)	1.518(13)
O(4)-C(16)	1.302(15)		C(9)-C(20)	1.483(19)
O(5)-C(17)	1.419(14)		C(10)-C(11)	1.525(10)
O(6)-C(16)	1.220(15)		C(10)-C(15)	1.529(13)
O(8)-C(18)	1.344(15)		C(11)-C(12)	1.505(14)
O(9)-C(18)	1.247(16)		C(12)-C(13)	1.560(15)
O(11)-C(20)	1.324(15)		C(13)-C(14)	1.523(10)
O(16)-C(20)	1.212(16)		C(14)-C(15)	1.529(14)
O(17)-C(8)	1.298(15)		C(16)-C(17)	1.547(14)
N(1)-C(1)	1.510(15)		C(17)-C(19)	1.529(14)
N(2)-C(2)	1.481(13)		C(18)-C(19)	1.469(19)

Table S3. Overview of angles [°] for complex **3a**.

N(2)-Pt(1)-O(17)	178.5(5)		O(3)-C(8)-O(17)	120.7(10)
N(2)-Pt(1)-C(9)	94.1(5)		O(3)-C(8)-C(7)	122.2(11)
O(17)-Pt(1)-C(9)	85.5(4)		O(17)-C(8)-C(7)	116.9(10)
N(2)-Pt(1)-N(1)	82.1(5)		C(20)-C(9)-C(7)	113.4(13)
O(17)-Pt(1)-N(1)	98.4(4)		C(20)-C(9)-Pt(1)	105.5(9)
C(9)-Pt(1)-N(1)	175.9(6)		C(7)-C(9)-Pt(1)	105.2(8)
N(3)-Pt(2)-O(4)	176.5(5)		N(3)-C(10)-C(11)	107.2(7)
N(3)-Pt(2)-C(19)	95.2(5)		N(3)-C(10)-C(15)	112.5(8)
O(4)-Pt(2)-C(19)	83.0(5)		C(11)-C(10)-C(15)	112.2(7)
N(3)-Pt(2)-N(4)	83.2(5)		N(4)-C(11)-C(12)	113.0(8)
O(4)-Pt(2)-N(4)	98.6(4)		N(4)-C(11)-C(10)	108.4(7)
C(19)-Pt(2)-N(4)	178.4(6)		C(12)-C(11)-C(10)	110.1(7)
C(16)-O(4)-Pt(2)	117.1(8)		C(11)-C(12)-C(13)	110.4(9)
C(8)-O(17)-Pt(1)	112.1(7)		C(14)-C(13)-C(12)	111.6(7)
C(1)-N(1)-Pt(1)	106.5(7)		C(13)-C(14)-C(15)	111.2(7)
C(2)-N(2)-Pt(1)	112.0(7)		C(10)-C(15)-C(14)	109.8(8)
C(10)-N(3)-Pt(2)	109.5(7)		O(6)-C(16)-O(4)	124.6(10)
C(11)-N(4)-Pt(2)	107.7(7)		O(6)-C(16)-C(17)	120.9(11)
N(1)-C(1)-C(6)	115.5(8)		O(4)-C(16)-C(17)	114.4(10)
N(1)-C(1)-C(2)	105.2(7)		O(5)-C(17)-C(19)	115.2(10)
C(6)-C(1)-C(2)	111.3(7)		O(5)-C(17)-C(16)	110.8(10)
N(2)-C(2)-C(3)	112.3(8)		C(19)-C(17)-C(16)	112.1(10)
N(2)-C(2)-C(1)	107.1(7)		O(9)-C(18)-O(8)	122.0(11)
C(3)-C(2)-C(1)	111.7(7)		O(9)-C(18)-C(19)	123.5(11)
C(2)-C(3)-C(4)	111.0(8)		O(8)-C(18)-C(19)	114.4(12)
C(5)-C(4)-C(3)	109.5(7)		C(18)-C(19)-C(17)	113.7(13)
C(6)-C(5)-C(4)	112.9(7)		C(18)-C(19)-Pt(2)	101.4(8)
C(5)-C(6)-C(1)	109.6(8)		C(17)-C(19)-Pt(2)	106.9(8)
O(2)-C(7)-C(9)	115.6(10)		O(16)-C(20)-O(11)	123.9(12)
O(2)-C(7)-C(8)	112.1(9)		O(16)-C(20)-C(9)	123.8(11)
C(9)-C(7)-C(8)	113.0(10)		O(11)-C(20)-C(9)	112.3(12)