SUPPLEMENTARY INFORMATION

1. SUPPLEMENTARY FIGURES

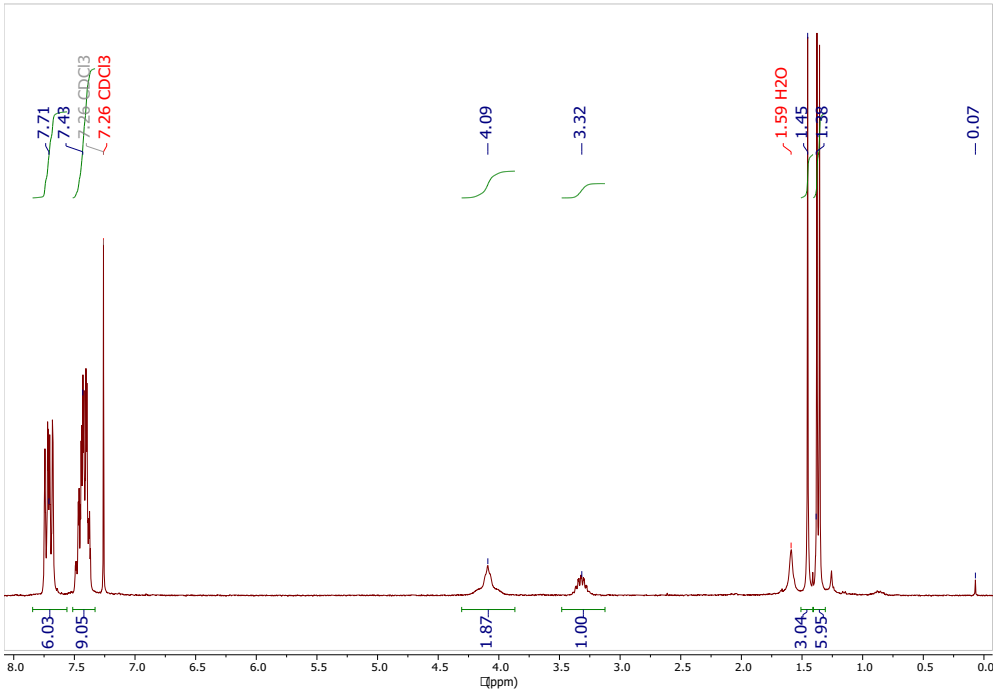

Figure S1. ^{1}H-NMR spectrum of DO1 in $CDCl_3$.

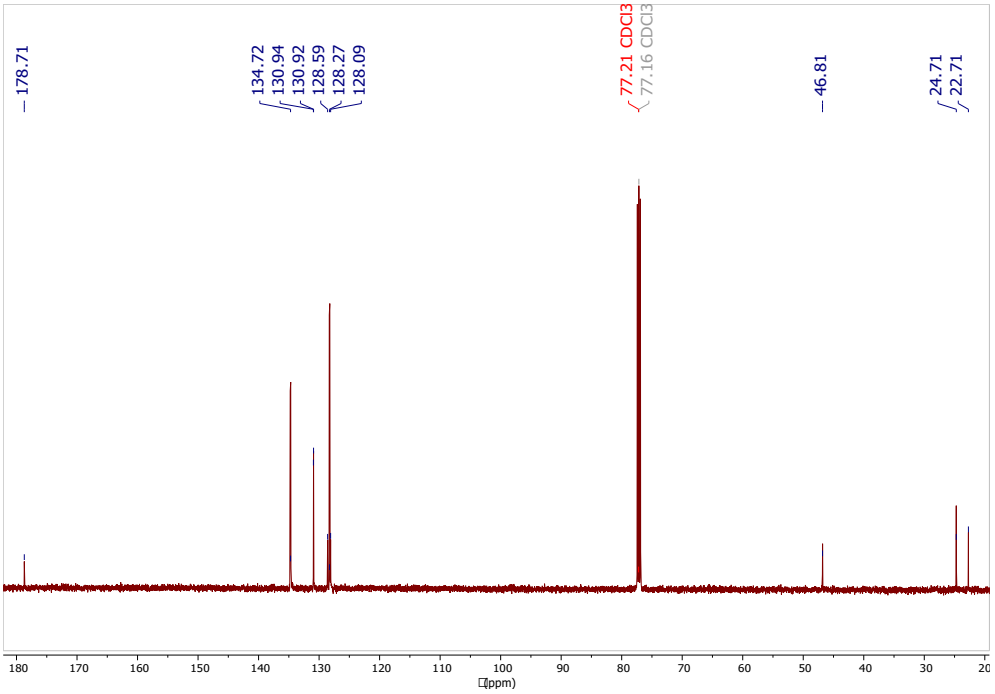

Figure S2. ^{13}C-NMR spectrum of DO1 in $CDCl_3$.

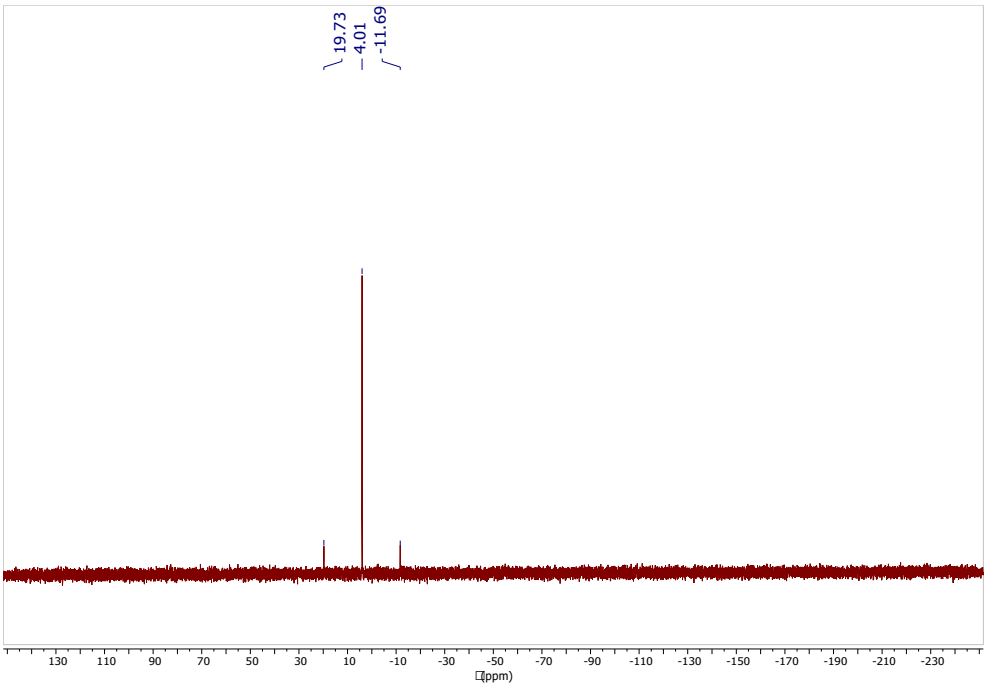

Figure S3. ^{31}P-NMR spectrum of DO1 in $CDCl_3$.

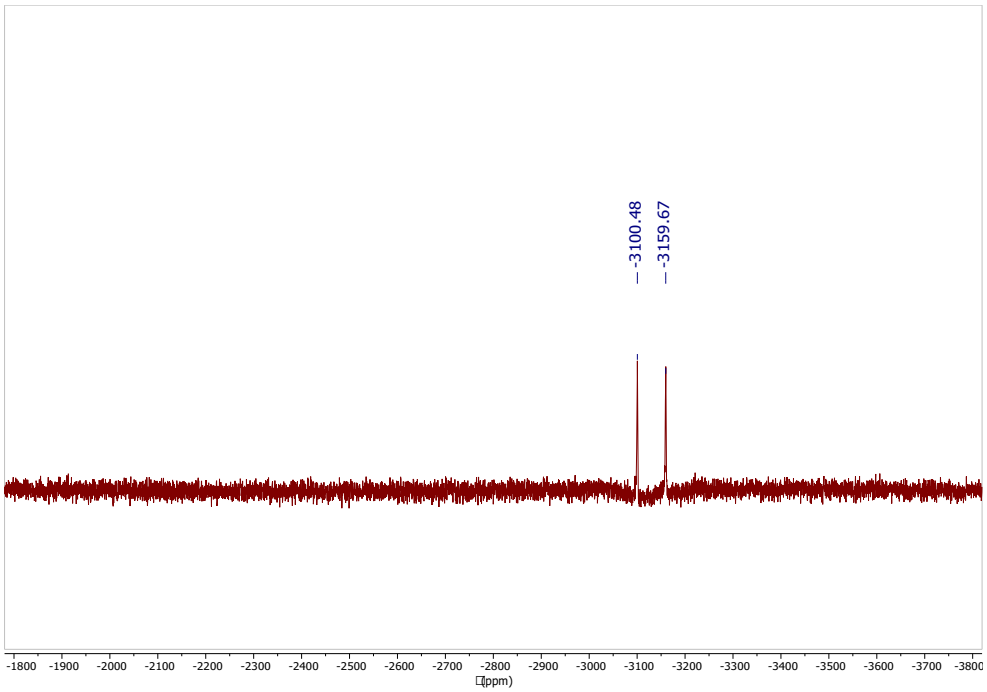

Figure S4. ^{195}Pt-NMR spectrum of DO1 in $CDCl_3$.

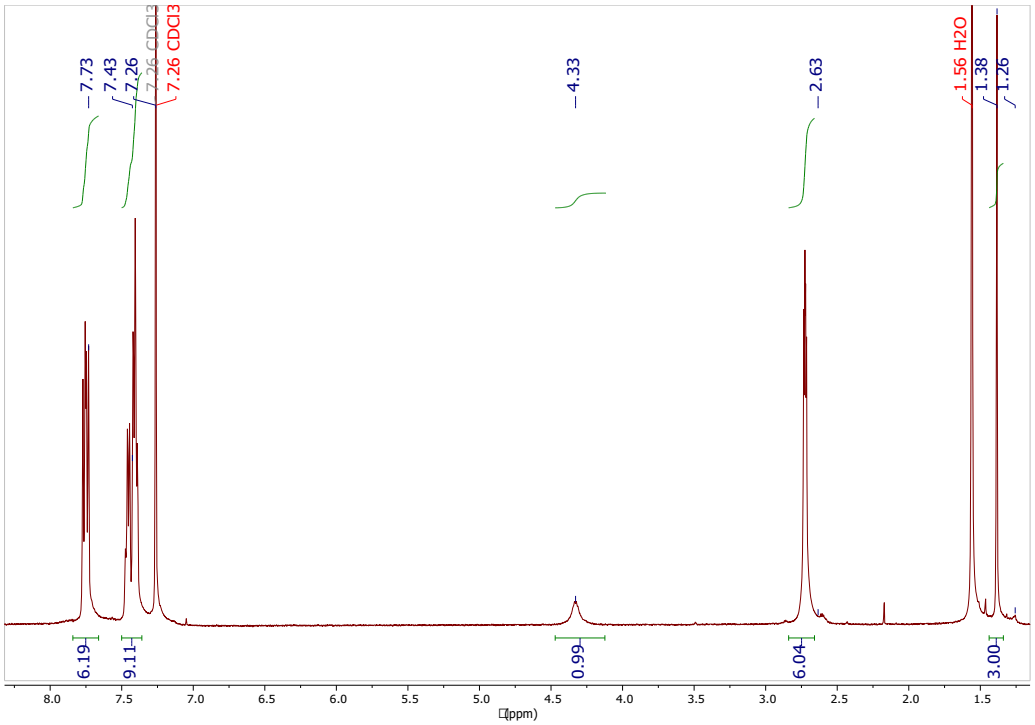

Figure S5. ^{1}H-NMR spectrum of DO2 in $CDCl_3$.

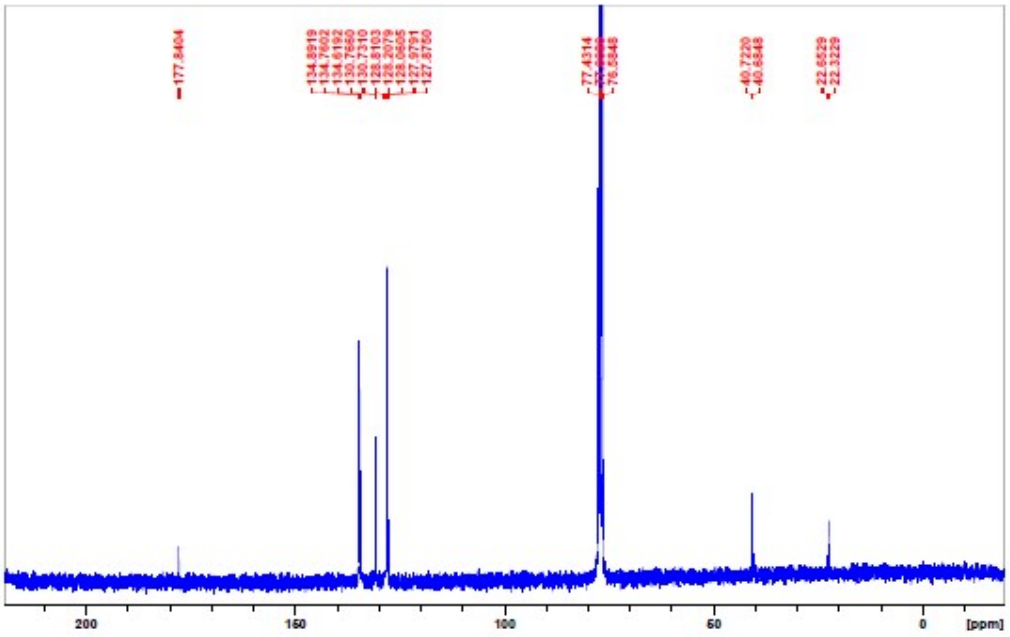

Figure S6. ^{13}**C-NMR spectrum of DO2 in** $CDCl_3$**.**

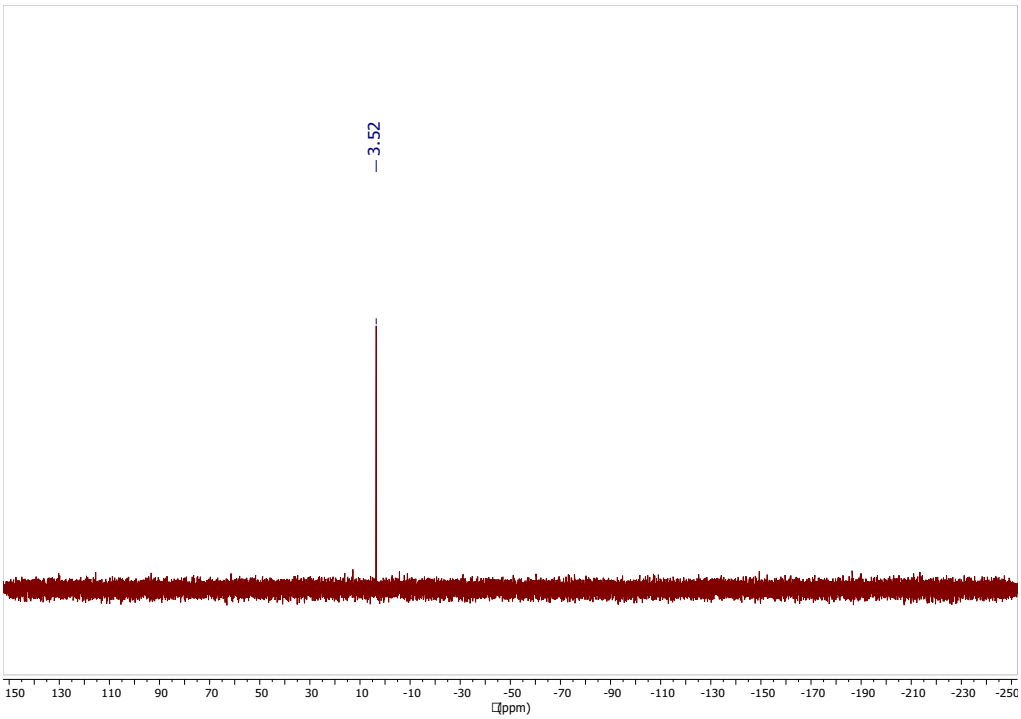

Figure S7. ^{31}P-NMR spectrum of DO2 in $CDCl_3$.

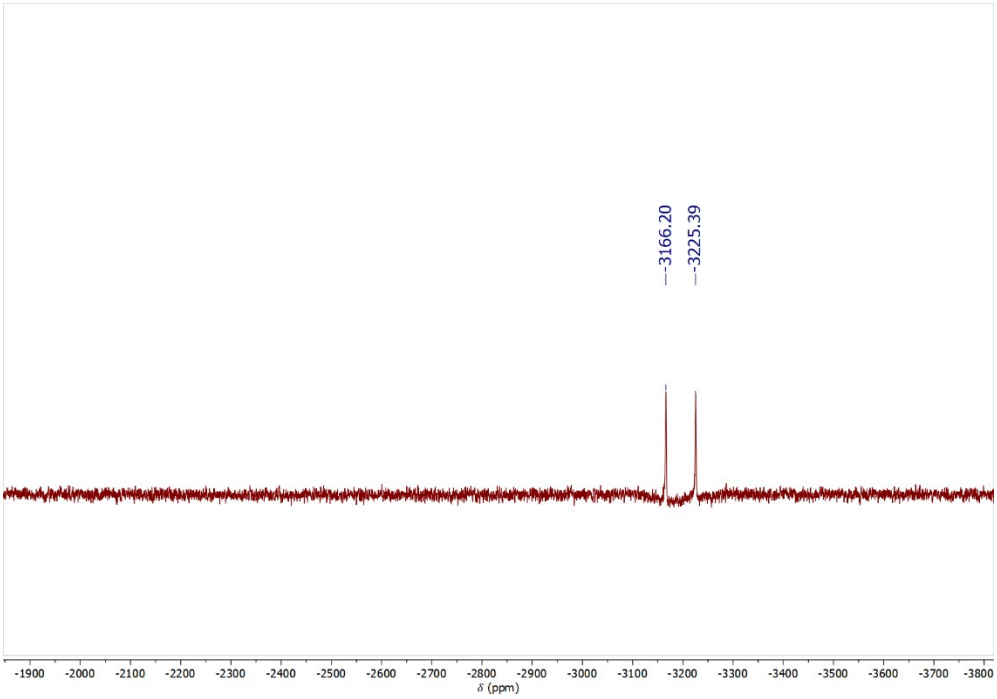

Figure S8. ^{195}Pt-NMR spectrum of DO2 in $CDCl_3$.

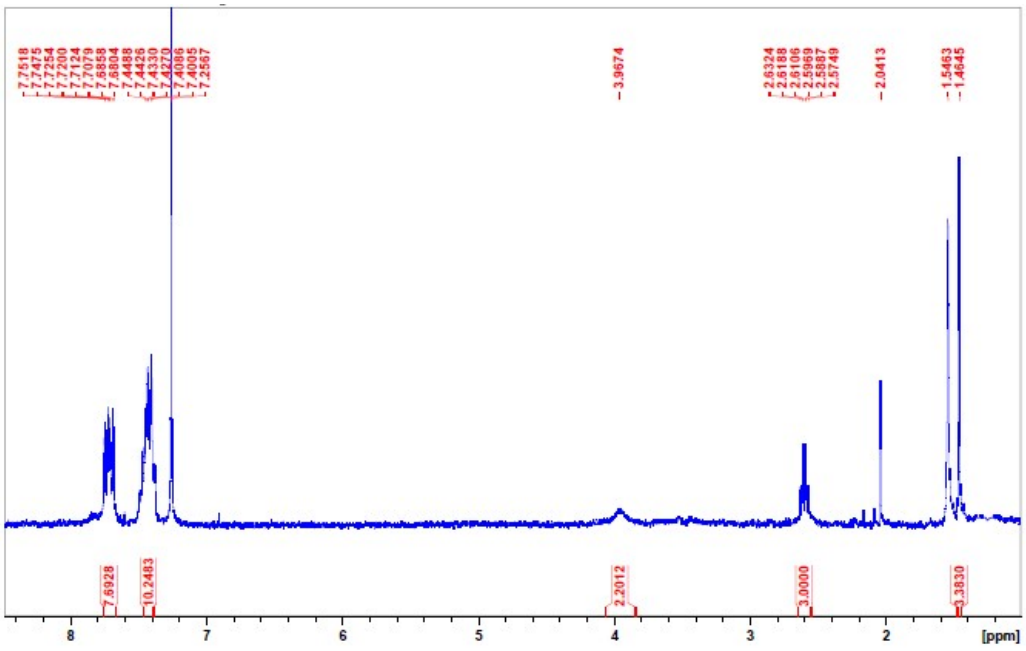

Figure S9. ^{1}H-NMR spectrum of DO3 in $CDCl_3$.

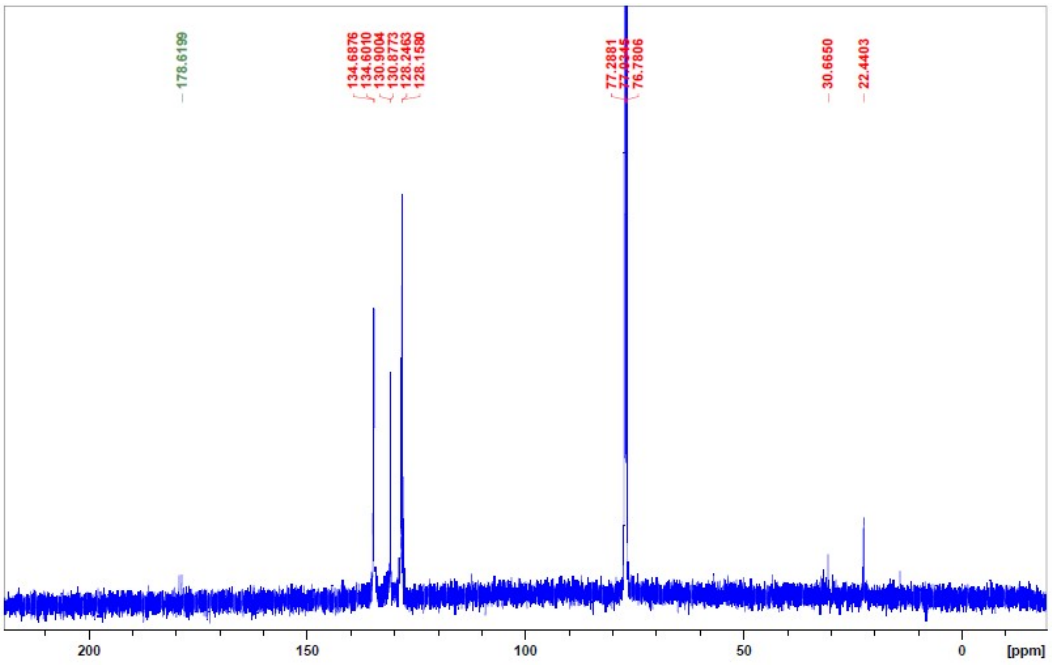

Figure S10. ^{13}C-NMR spectrum of DO3 in $CDCl_3$.

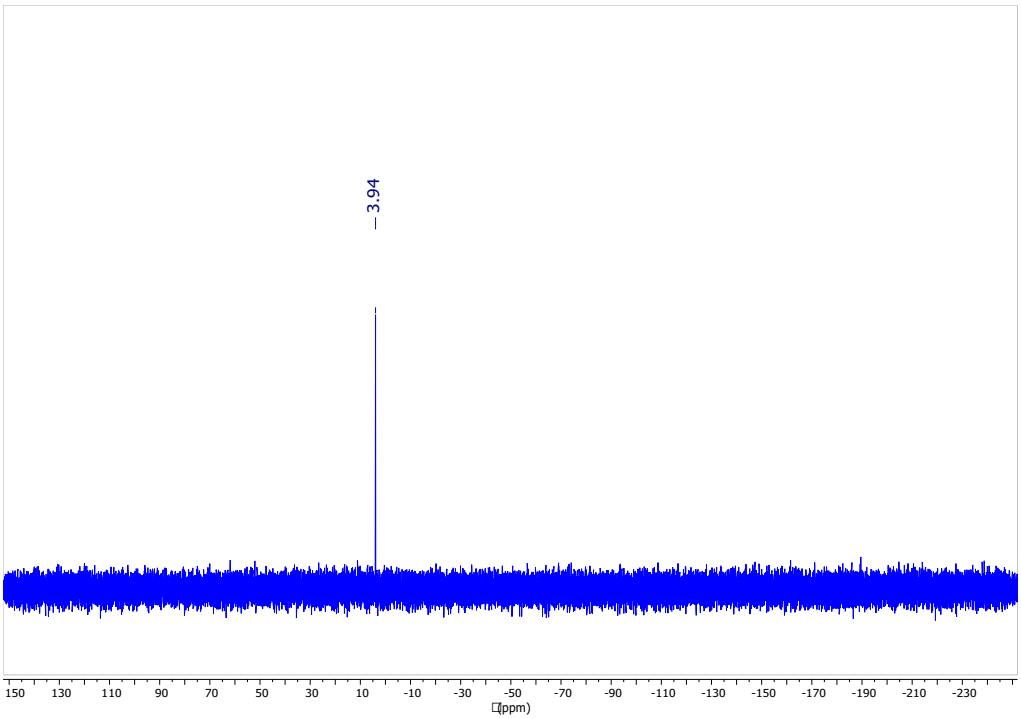

Figure S11. ^{31}P-NMR spectrum of DO3 in $CDCl_3$.

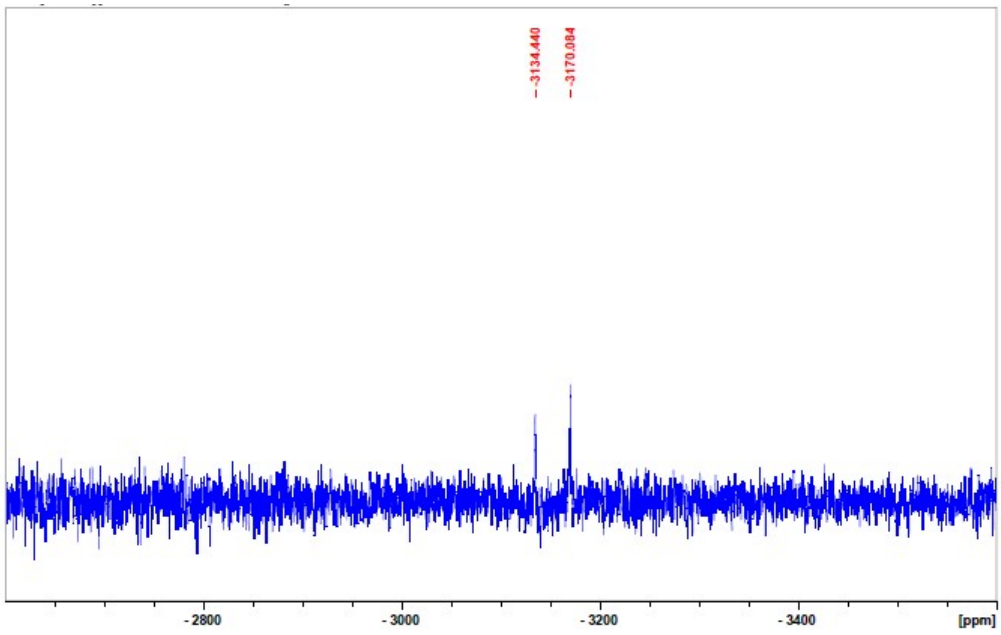

Figure S12. ^{195}Pt-NMR spectrum of DO3 in $CDCl_3$.

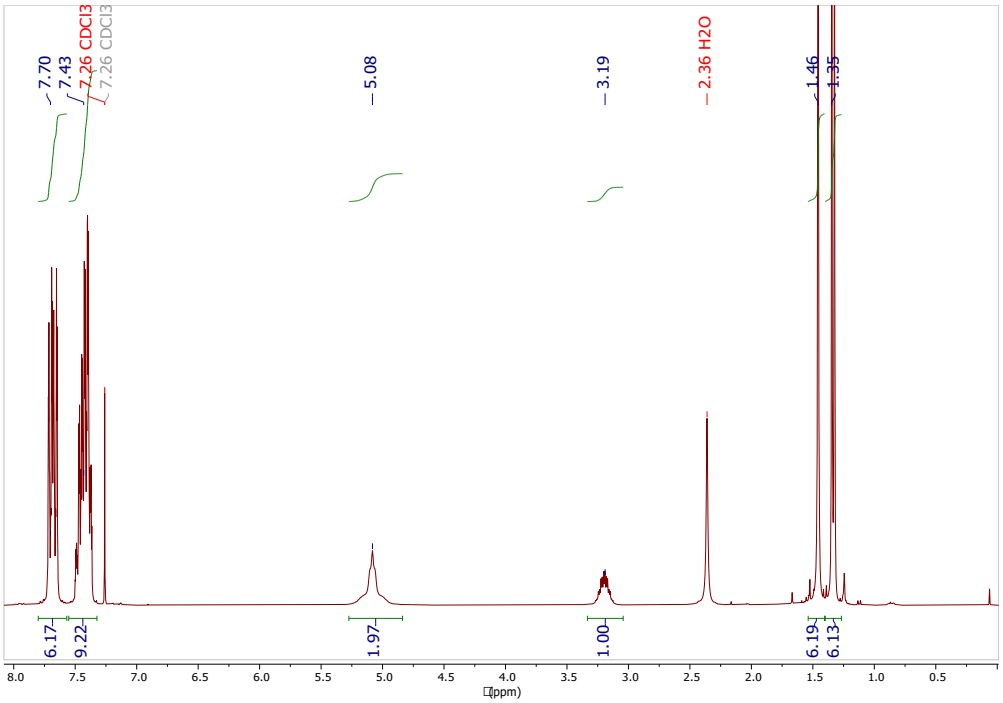

Figure S13. ^{1}H-NMR spectrum of DO4 in $CDCl_3$.

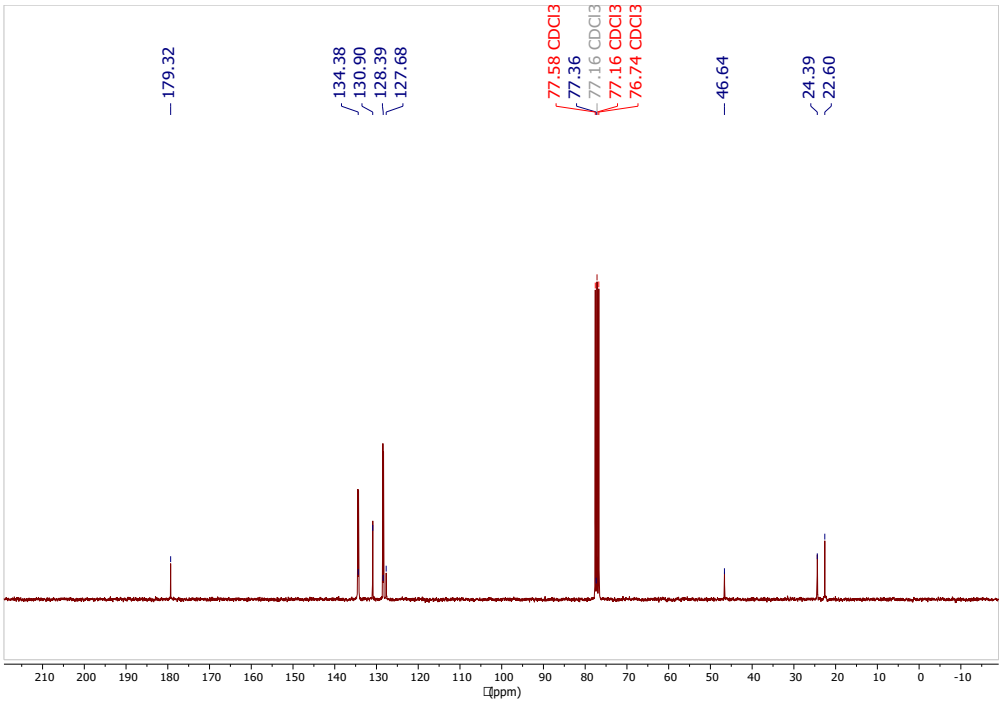

Figure S14. ^{13}C-NMR spectrum of DO4 in $CDCl_3$.

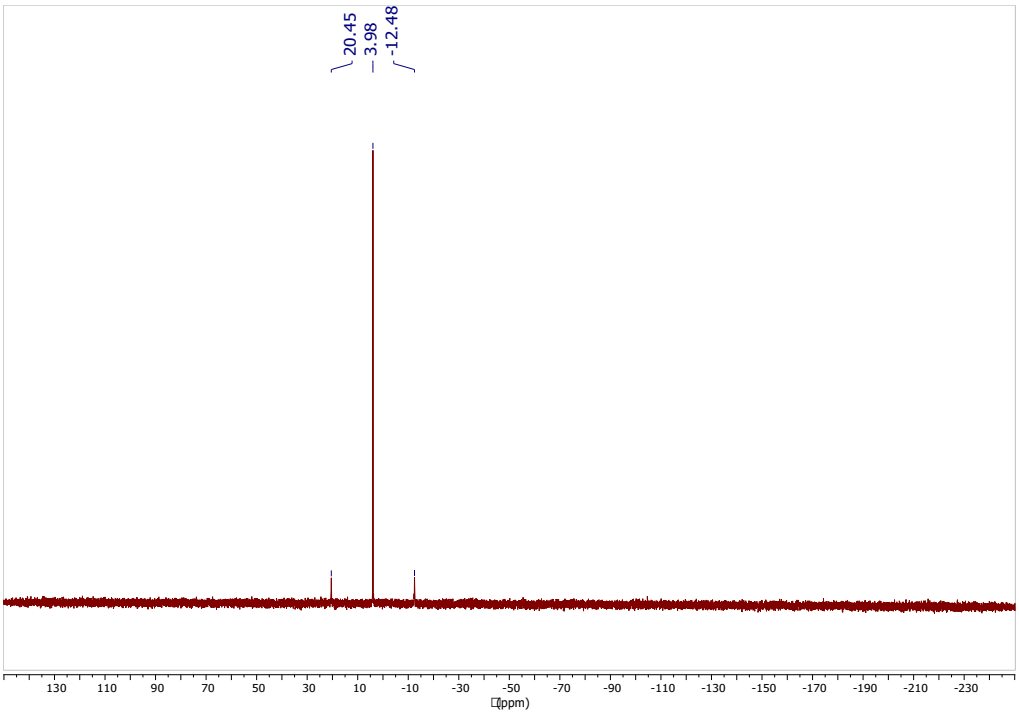

Figure S15. ^{31}P-NMR spectrum of DO4 in $CDCl_3$.

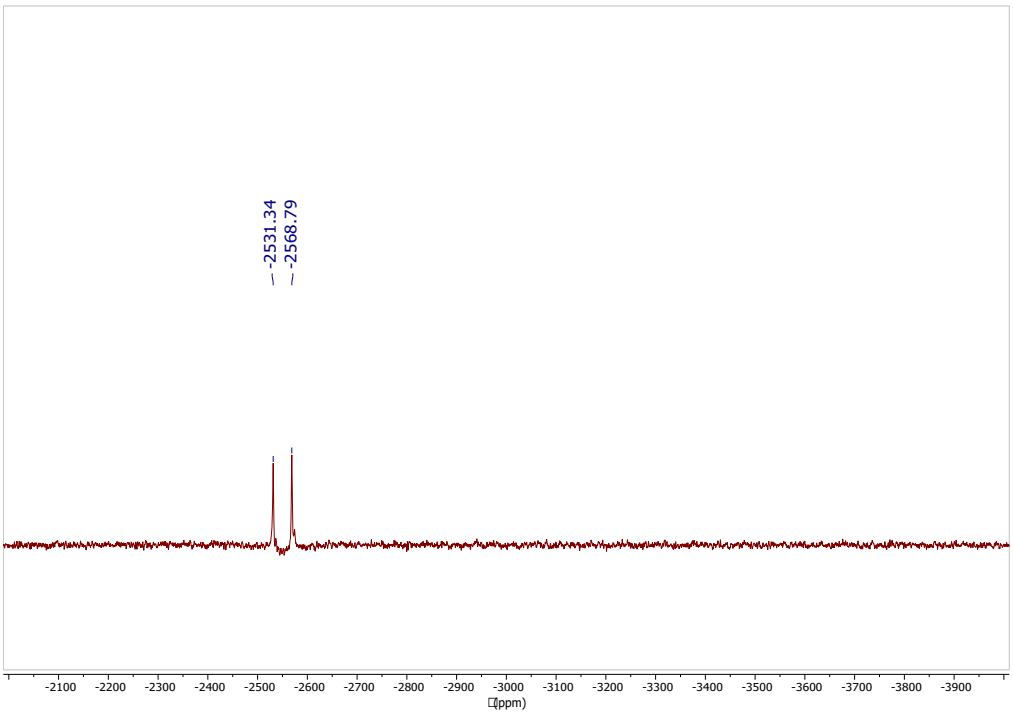

Figure S16. ^{195}Pt-NMR spectrum of DO4 in $CDCl_3$.

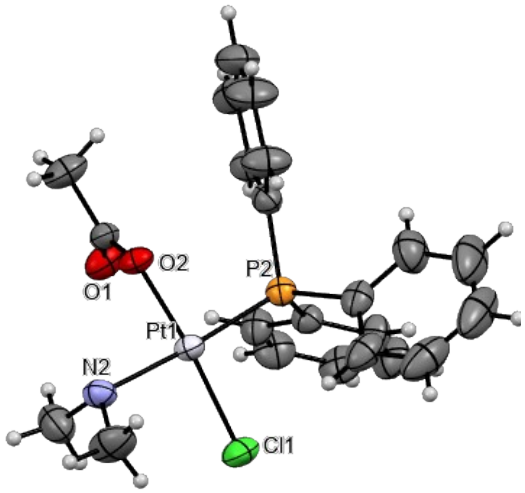

Figure S17. SC-XRD structure of complex DO2.

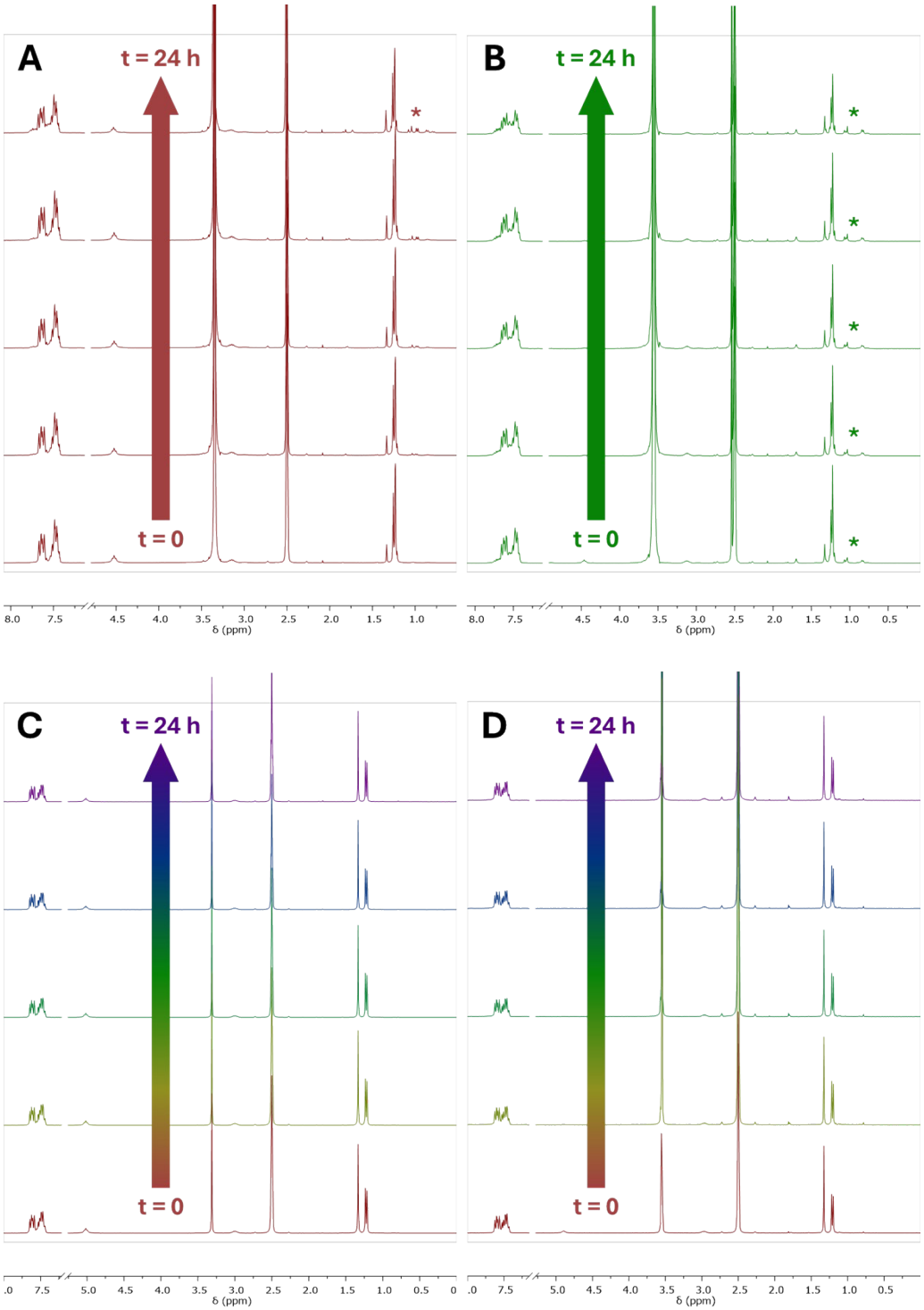

Figure S18. ^{1}H-NMR spectra monitoring from fresh to 24 h of A) DO1 in 100% DMSO-d_6, B) DO1 in DMSO-d_6:D_2O, C) DO4 in 100% DMSO-d_6, and D) DO4 in DMSO-d_6:D_2O.

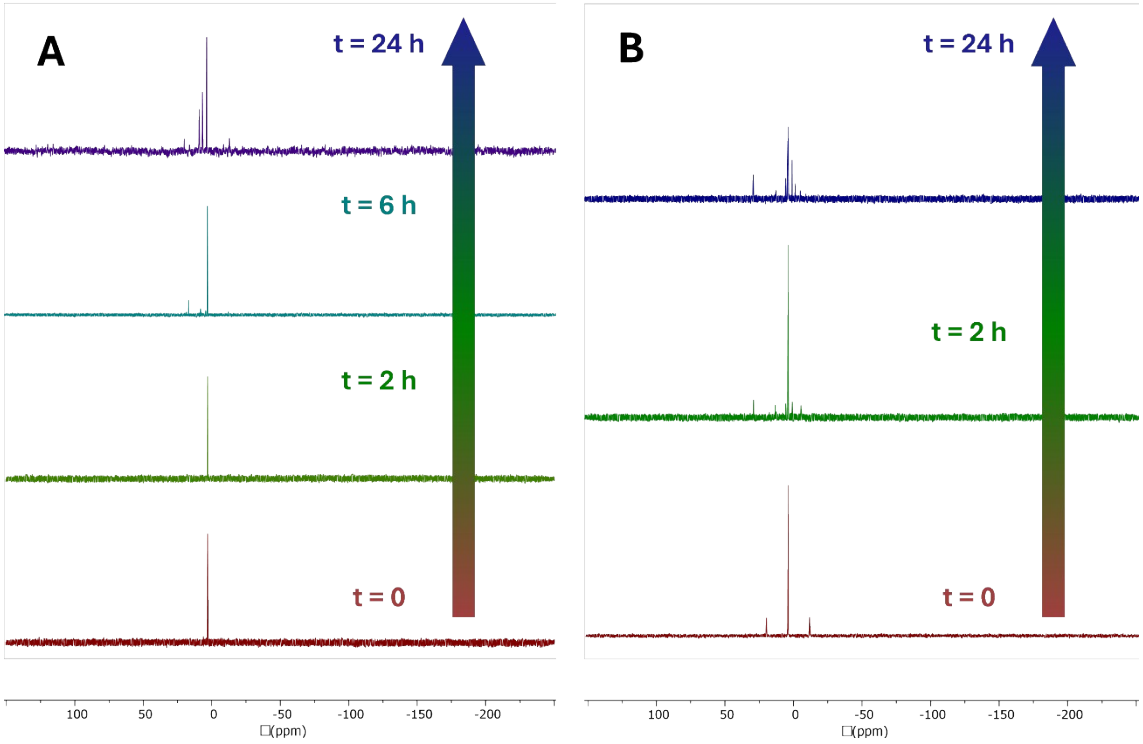

Figure S19. ^{31}P-NMR spectra monitoring from fresh to 24 h of A) DO2 and B) DO3 in DMSO-d_6/D_2O mixtures.

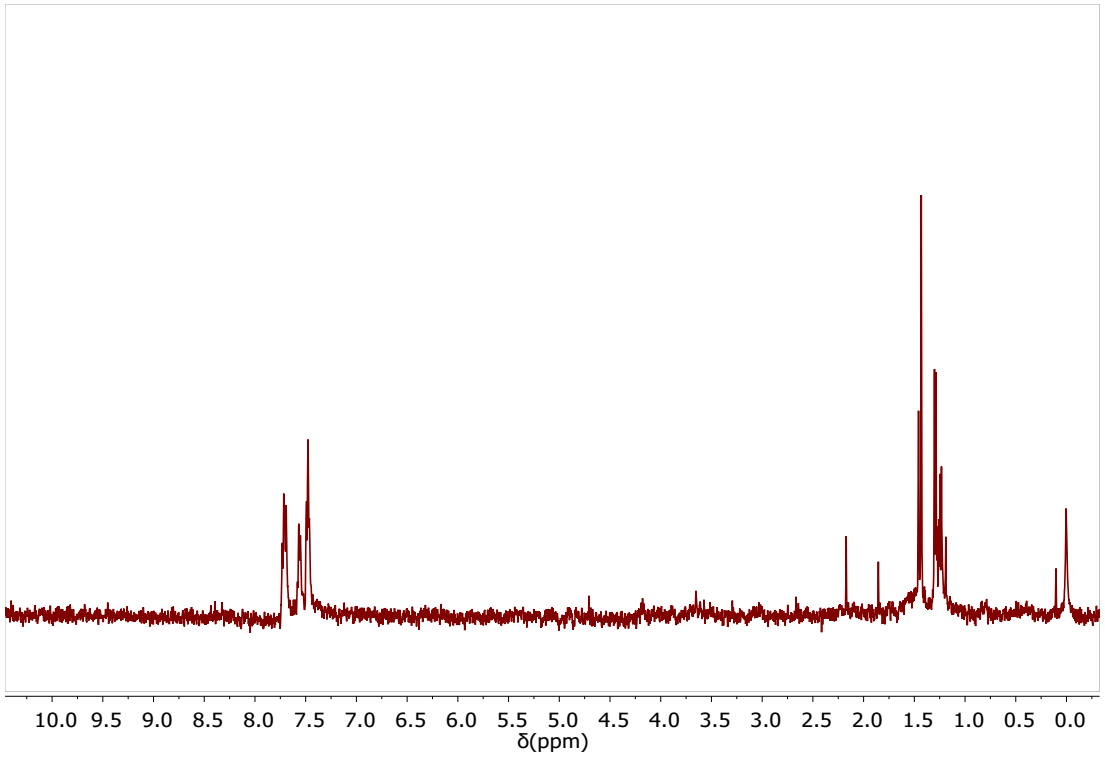

Figure S20.^{1}H-NMR spectrum of complex DO1 in D_2O (with water suppression)**.**

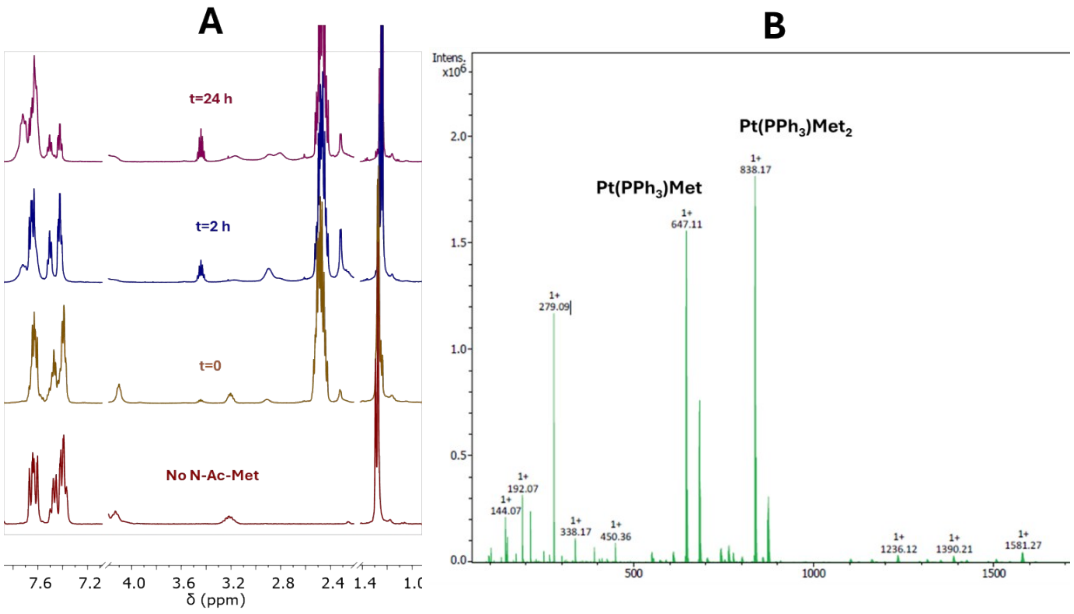

Figure S21. A) Monitoring by ^{1}H-NMR of the reaction between DO1 and N-Acetyl-Met at different times. B) ESI^{+}-MS spectra of the sample after 24 h incubation (with NH_4OAc).

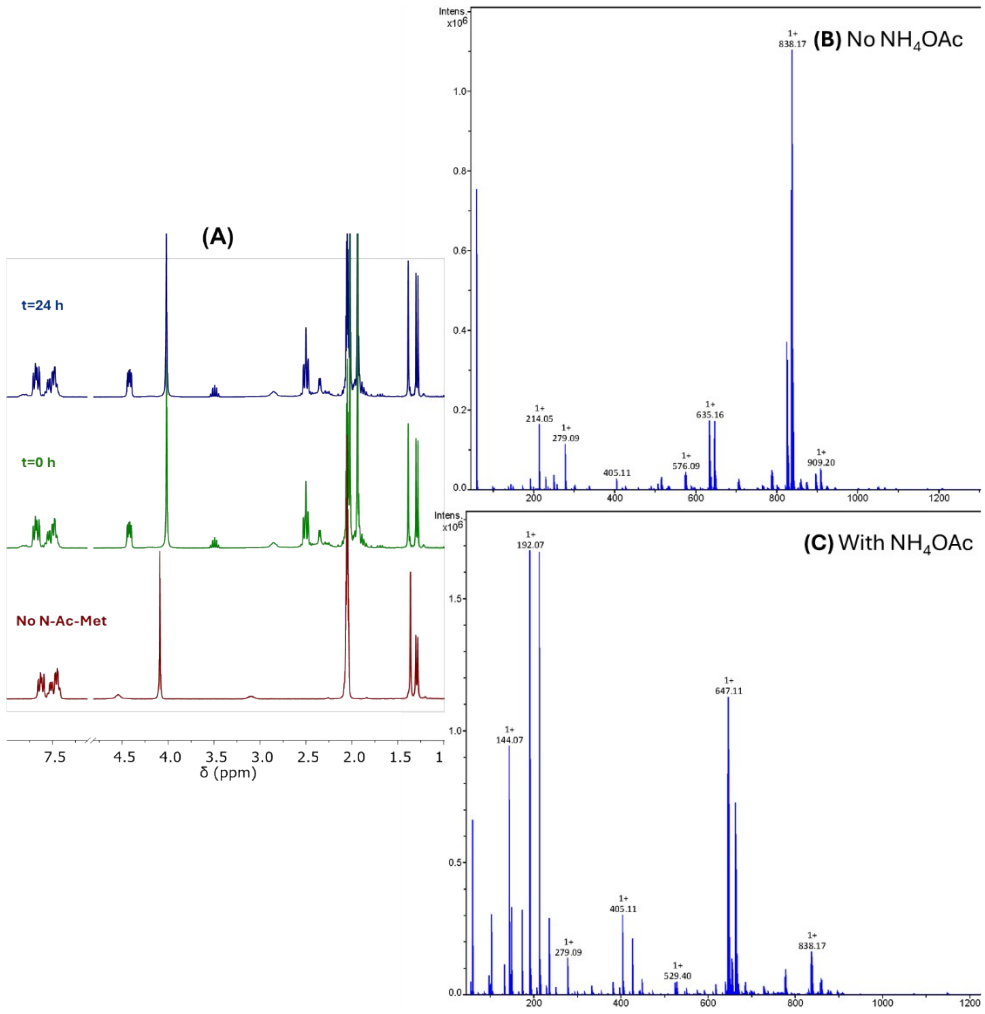

Figure S22. A) Monitoring by 1H-NMR of the reaction between DO1 and N-Acetyl-Met at different times, B) ESI+-MS spectra of the interaction between DO4 and N-Acetyl-Met after 24 h reaction with buffer (NH_4OAc) and C) without buffer.

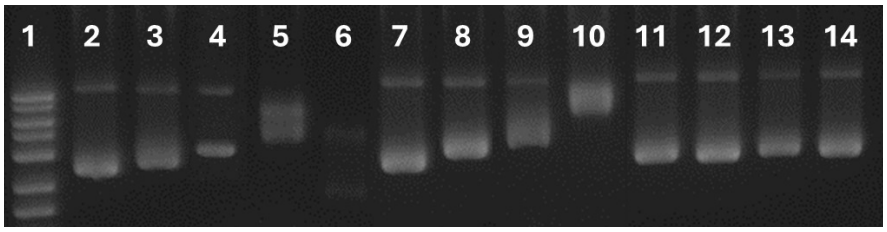

Figure S23. Gel electrophoresis with SC and OC forms. Lane 1 and 18: 1 kb DNA ladder; lane 2: pBR322 control; lanes 3–6: cisplatin at r_i: 0.01 to 0.20; lanes 7-10: DO1 at r_i: 0.01 to 0.20; lanes 11–14: DO4 at r_i: 0.01 to 0.20. C_{DNA} = 0.0625 µg µL^{-1}. r_i = complex:DNA (base pair) ratio.

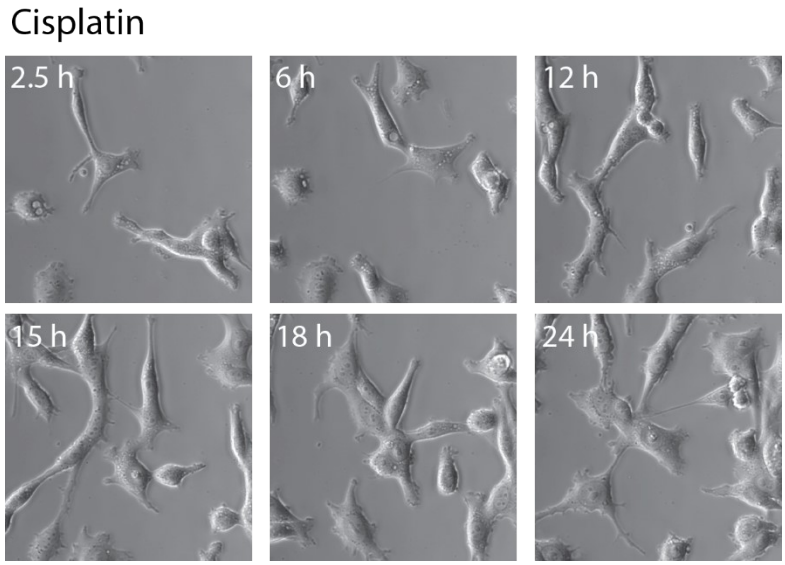

Figure S24. Live-cell microscopy of cisplatin-treated CT26 cells (5 µM) after various time points (20x and additional 1.5x magnification).

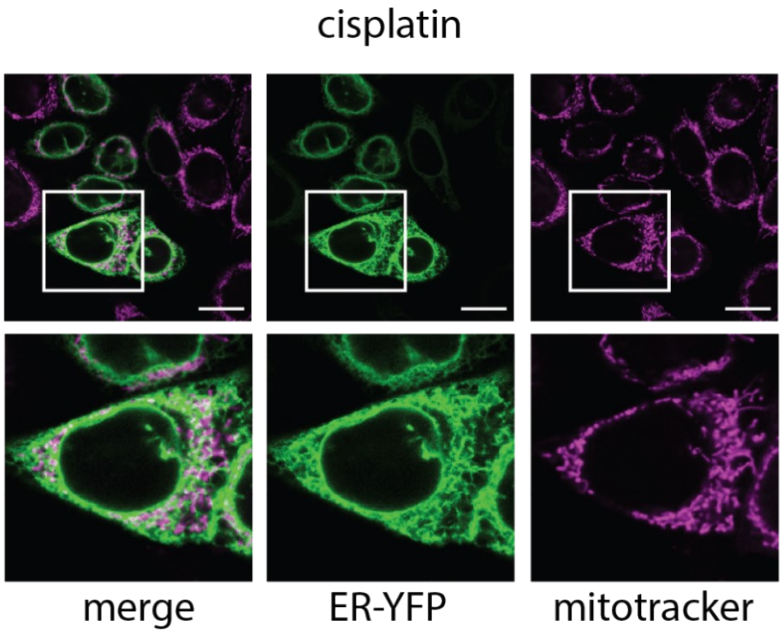

Figure S25. Representative confocal microscopy images of SW480-ER/YFP cells. Cells were treated with 5 µM cisplatin and imaged after 3 h (63x magnification). ER-YFP is indicated in green, mitochondria (pink) were co-stained with 1 µM of MitoTracker™ Red CMXRos.

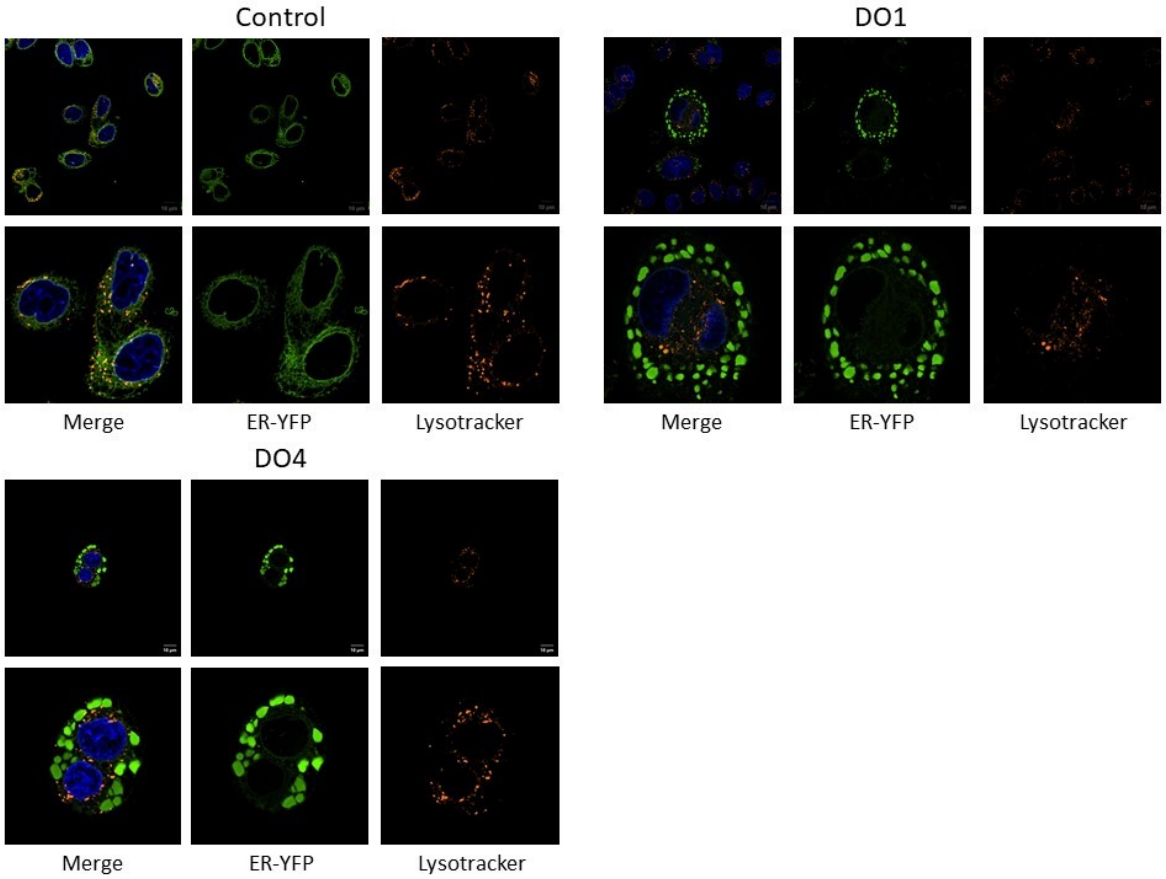

Figure S26. Representative confocal microscopy images of SW480-ER/YFP cells. Cell were treated with 30µM of DO1 or DO4 and taken after 3 and 6 hours respectively. **ER-**

YFP is indicated in green, lysosomes (orange/red) were co-stained with 0,1 µM of LysoTracker™ Red DND-99 and nuclei with 1µM of Hoechst 33342

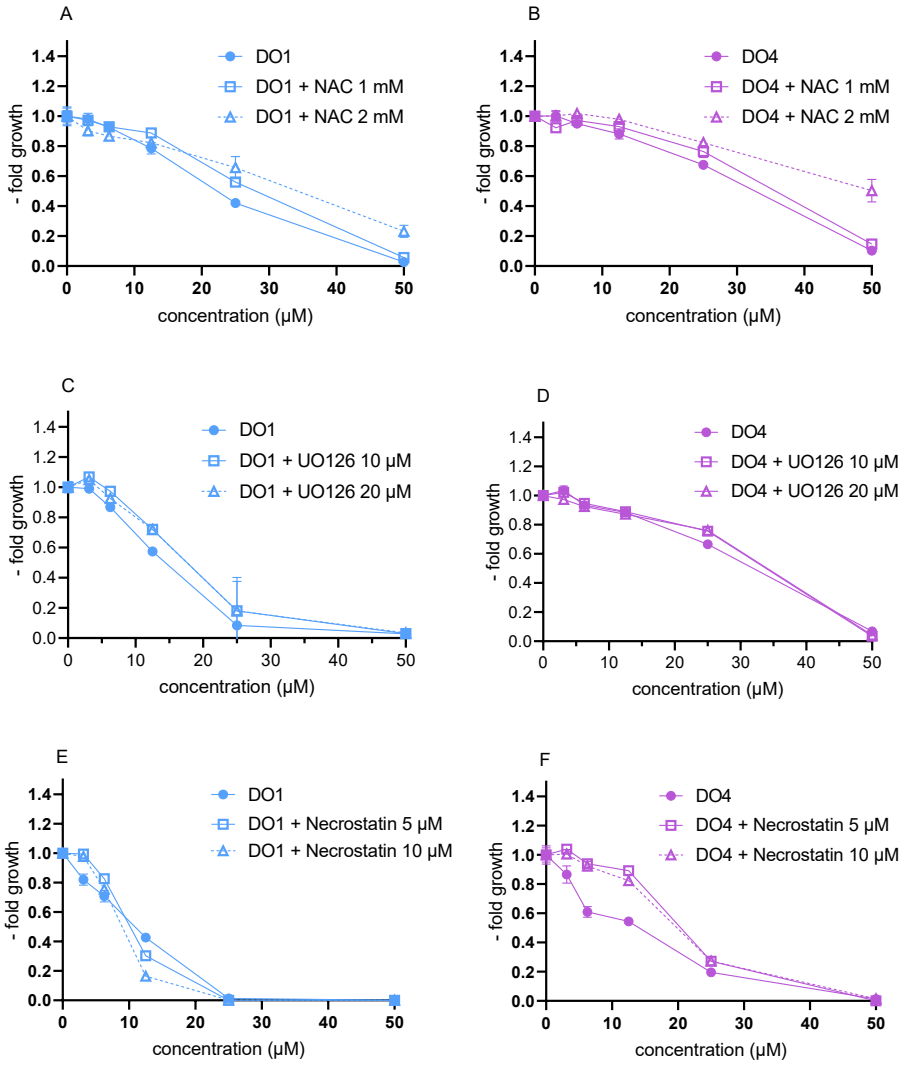

Figure S27. Impact of NAC (antioxidant and ROS scavenger), UO126 (MEK1/2 inhibitor) and necrostatin (necroptosis inhibitor) on the anticancer activity of A), C) & E) DO1 and B), D) & F) DO4. Cell viability was tested by MTT assay after 24h incubation.

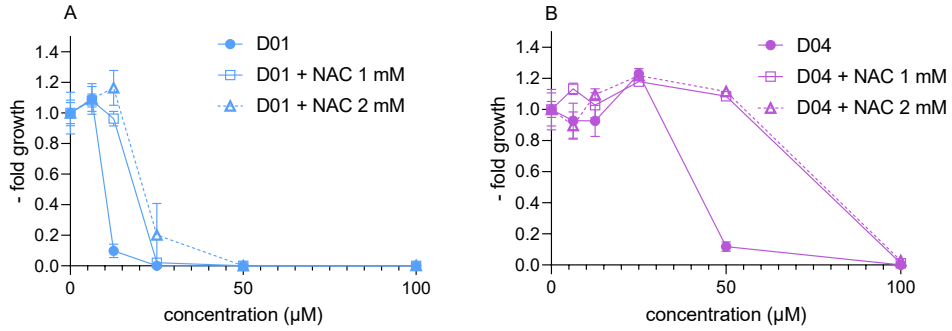

Figure S28. Impact of NAC (antioxidant and ROS scavenger) on the anticancer activity of A) DO1 and B) DO4. Cell viability was tested by MTT assay after 72h incubation.

2. SUPPLEMENTARY TABLES

Table S1. Crystal data and structure refinement for DO1, DO2, DO4 and *cis*-$[Pt_2Cl_2(PPh_3)_2(\mu\text{-}S\text{-}CH_3)_2]$

	DO1	**DO2**	**DO4**	***cis*-$[Pt_2Cl_2(PPh_3)_2(\mu\text{-}S\text{-}CH_3)_2]$**
Chemical formula	$C_{23}H_{27}ClNO_2PPt$	$C_{22}H_{24}ClNO_2PPt$	$C_{25}H_{30}NO_4PPt$	$C_{39.5}H_{36}Cl_2D_3O_{0.5}P_2Pt_2S_2$
Formula weight	610.96	595.93	634.56	1111.86
Temperature	296(2) K	296(2) K	200(2) K	250(10) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	1.54184
Crystal size (mm^3)	0.04 x 0.04 x 0.06	0.08 x 0.10 x 0.12	0.03 x 0.09 x 0.28	0.17 x 0.09 x 0.01
Crystal habit	Prismatic pale yellow	Light yellow prismatic	Clear colorless prismatic	Clear colorless ribbon
Crystal system	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	P 1 21/n 1	P 1 21/c 1	P -1	P -1
a (Å) b (Å) c (Å)	9.9846(5) 17.4069(8) 14.0618(7)	13.9336(4) 8.8725(2) 18.2392(4)	9.6908(10) 11.1810(10) 12.9271(12)	11.51520(10) 13.61580(10) 14.18740(10)
α (º) β (º) γ (º)	90 98.257(2) 90	90 96.3720(10) 90	96.506(5) 110.784(4) 96.938(5)	97.9880(10) 112.9470(10) 93.2230(10)
Volume ($Å^3$)	2418.6(2)	2240.91(10)	1281.4(2)	2013.60(3)
Z	4	4	2	2
Density (calculated)	1.678 g/cm^3	1.766 g/cm^3	1.655 g/cm^3	1.834 g/cm^3
Absorption coefficient	5.996 mm^{-1}	6.469 mm^{-1}	5.568 mm^{-1}	15.962 mm^{-1}
Θ range for data collection	2.35 to 25.35º	1.47 to 26.43°	1.71 to 25.35°	3.30 to 68.32º
Reflections collected	44392	73522	22161	54595
Independent reflections	4413 [R(int) = 0.0495]	4607 [R(int) = 0.0503]	4692 [R(int) = 0.0769]	7351 [R(int) = 0.0337]
Coverage of independent reflections	99.9%	99.8%	99.7%	99.8%
Data/restraints/ parameters	4413 / 0 / 265	4607 / 0 / 256	4692 / 257 / 323	7351 / 0 / 455
Goodness of Fit	1.017	1.204	1.066	1.063
Final R indices [*I* > 20(I)]/all data	R1 = 0.0245/0.0437 wR2 = 0.0454/0.0504	R1 = 0.0196/0.0272 wR2 = 0.0504/0.0640	R1 = 0.0418/0.0579 wR2 = 0.0997/0.1217	R1 = 0.0219/0.0234 wR2 = 0.0638/0.0647
Largest diff. peak and holes	0.765 and -0.531 $eÅ^{-3}$	0.452 and -0.789 $eÅ^{-3}$	2.582 and -1.359 $eÅ^{-3}$	1.042 and -0.471 $eÅ^{-3}$

Table S2. Selected bond lengths (Å) and angles (°) for DO1.

Selected Bond distances (Å)			
Pt1-O1	2.016(4)	Pt1-Cl1	2.2935(16)
Pt1-N1	2.101(5)	Pt1-P1	2.2273(15)
Selected angles (°)			
O1-Pt1-Cl2	173.12(13)	O1-Pt1-N1	86.82(18)
N1-Pt1-P1	175.79(14)	O1-Pt1-P1	96.12(13)

The supramolecular structure of complex DO1 is stabilized by intermolecular hydrogen bonds (Table S3).

Table S3. Hydrogen bond information for DO1.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
N1	H1B	O2[1]	0.89	1.98	2.821(5)	156.3

[1] -x, -y, 2-z

Table S4. Selected bond lengths (Å) and angles (°) for DO2.

Selected Bond distances (Å)			
Pt1-O2	2.015(2)	Pt1-Cl1	2.2952(10)
Pt1-N2	2.122(3)	Pt1-P2	2.2254(10)
Selected angles (°)			
O2-Pt1-Cl2	174.56(8)	O1-Pt1-N2	83.05(10)
N2-Pt1-P2	175.34(8)	O2-Pt1-P2	92.72(7)

Table S5. Selected bond lengths (Å) and angles (°) for DO4.

Selected Bond distances (Å)			
Pt1-O1	2.024(6)	Pt1-O3	2.014(5)
Pt1-N1	2.111(6)	Pt1-P1	2.234(2)
Selected angles (°)			
O1-Pt1-O3	173.9(2)	O1-Pt1-N1	89.7(3)
N1-Pt1-P1	176.78(17)	O1-Pt1-P1	91.45(18)

The supramolecular structure of complex DO4 is stabilized by intermolecular hydrogen bonds (Table S6).

Table S6. Hydrogen bond information for DO4.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
N1	H1NA	O2	0.91	2.59	3.205(9)	125.1

Table S7. Selected bond lengths (Å) and angles (°) for *cis*-[$Pt_2Cl_2(PPh_3)_2(\mu\text{-}SCH_3)_2$].

Selected Bond distances (Å)			
Pt1-Cl1	2.3285(9)	Pt2-Cl2	2.3398(10)
Pt1-S1	2.2852(8)	Pt2-S2	2.3692(9)
Pt1-P1	2.2587(9)	Pt2-P2	2.2661(9)
Pt1-S2	2.3594(9)	Pt2-S1	2.2755(9)
Selected angles (°)			
Cl1-Pt1-S2	173.9(2)	O1-Pt1-N1	89.7(3)
S1-Pt1-Cl1	176.78(17)	O1-Pt1-P1	91.45(18)

Table S8. Cell lines used in this manuscript.

Cell line	Species	Origin	Source	Medium
HCT116	h	colon carcinoma	Horizon Discovery Ltd., Cambridge, UK	McCoy's 5A
HCT116oxR	h	colon carcinoma	CCR [1]	McCoy's 5A, 10 µM oxaliplatin
CT26	m	colon carcinoma	ATCC	DMEM/F12 (1:1)
Capan-1	h	pancreatic carcinoma	ATCC	RPMI-1640
B16	m	melanoma	ATCC	RPMI-1640
p31	h	mesothelioma	K. Grankvist (Umeå University, Sweden) [2]	MEM
p31/cis	h	mesothelioma	K. Grankvist (Umeå University, Sweden) [2]	MEM, 4 µM cisplatin
MCF7	h	mammacarcinoma	ATCC	RPMI-1640
HaCaT	h	keratinocyte	ATCC	DMEM
HUVEC	h	endothelial cells	ATCC	Endothelial cell growth medium
BEC	h	endothelial cells	ATCC	Endothelial cell growth medium
MCF-10A	h	epithelial cells	ATCC	DMEM/F12 (1:1)

Abbreviations: American Type Culture Collection (ATCC), Center for Cancer Research (CCR), minimum essential medium (MEM), Dulbecco's modified Eagle's medium (DMEM), DMEM with Ham's F-12 basal media (DMEM/F12), non-essential amino acid (NEAA), Roswell Park Memorial Institute (RPMI)

3. REFERENCES

1 U. Jungwirth, D. N. Xanthos, J. Gojo, A. K. Bytzek, W. Körner, P. Heffeter, S. A. Abramkin, M. A. Jakupec, C. G. Hartinger, U. Windberger, M. Galanski, B. K. Keppler and W. Berger, Anticancer Activity of Methyl-Substituted Oxaliplatin Analogs, *Mol. Pharmacol.*, 2012, **81**, 719–728.

2 V. Janson, A. Johansson and K. Grankvist, Resistance to caspase-8 and -9 fragments in a malignant pleural mesothelioma cell line with acquired cisplatin-resistance, *Cell Death Dis.*, 2010, **1**, e78–e78.