Electronic Supplementary Information

Synthesis and characterization of thiocarbonato-linked platinum(IV) complexes

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Contents

Materials and Methods

EI mass spectra. Samples were measured on a MS system from Thermo (Bremen, Germany) consisting of an ITQ 900 ion trap mass spectrometer or an SSQ710 single quadrupole mass spectrometer using the direct insertion probe (DIP) technique. The sample was placed on the rhenium wire and evaporated using a current slope of 100 mA·sec^{-1} (from 0 to 800 mA); MS-parameters: scan range 50-900 *m/z* for ITQ and 20-500 *m/z* for SSQ710 respectively. Ion source was set to 200 °C.

ESI mass spectra. Automated samples were carried out by dissolving about 0.2 mg sample in 1 mL MeOH; 2 µL of the solvent were sampled by Agilent (Waldborn, Germany) 1100 G1313 A autosampler and delivered to mass spectrometer by binary pump module G1312A with isocratic elution (90 % MeOH, 10 % water with 0.1 % formic acid). Sample was eluted with 20 µL/min to Bruker (Bremen, Germany) MAXIS mass spectrometer. ESI_{pos}: 500 V end plate offset, 4500 V capillary voltage, 0.4 bar nebulizer pressure, 4 L/min dry gas flow, 180 °C dry temperature. Tune values for ion transfer were set to 200 Vpp Funnel 1 RF, 0.0 eV is CID Energy, 200 Vpp Multipole RF, eV Quadrupole Ion Energy with low mass setting of 100 *m/z*. Collision energy was set to 8 eV, 170 Vpp collision RF, 90 µs transfer time and 5 µs pre pule storage time. Mass window from 100 to 1500 *m/z* was monitored. Internal mass calibration was performed for each spectrum using sodium formate after sample elution with HPC-calibration algorithm using Bruker Compass Data Analysis 4.3 software.

LC-MS. Ultra-high performance liquid chromatography coupled with high resolution mass spectrometry was carried out using a THERMO (Bremen, Germany) UltiMate HPG-3400 RS binary pump, WPS-3000 auto sampler which was set to 10 °C and which was equipped with a 25 µL injection syringe and a 100 µL sample loop. The column was kept at 25 °C within the column compartment TCC-3200. Chromatography column was used THERMO Accucore® C-18 RP (100 × 2.1 mm; 2.6 µm) using the gradient in **Table S1** at a constant flow rate of 0.4 mL/min. Eluent A was water, with 2% acetonitrile and 0.1% formic acid. Eluent B was pure acetonitrile.

Mass spectra were recorded with THERMO QExactive plus orbitrap mass spectrometer coupled to a heated electrospray source (HESI). Column flow was switched at 0.5 min from waste to the MS and at 11.5 min again back to the waste, to prevent source contamination. For monitoring two full scan modes were selected with the following parameters. Polarity: positive; scan range: 100 to 1500 *m/z*; resolution: 70,000; AGC target: 3×10^6; maximum IT: 200 ms. General settings: sheath gas flow rate: 60; auxiliary gas flow rate 20; sweep gas flow rate: 5; spray voltage: 3.0 kV; capillary temperature: 360 °C; S-lens RF level: 50; auxiliary gas heater temperature: 400 °C; acquisition time frame: 0.5 - 11.5 min. For negative mode, all values were kept instead of the spray voltage which was set to 3.3 kV.

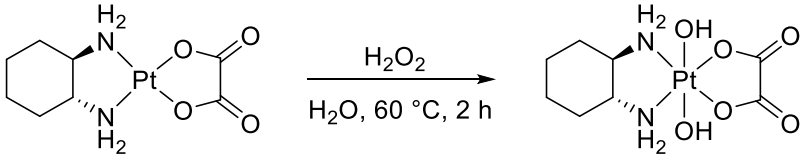
At the beginning and at the end a pooled (equal mixture (v/v) of all individual samples) sample was measured to guarantee system integrity. This pooled sample was additionally used to measure in data dependent mode MS^2 spectra with the following settings: scan range: auto, resolution: 17,500; AGC target: 3×10^6; maximum IT: 32 ms, loop count = 5, preferred charge state = 1, dynamic exclusion: 30 sec.

Table S1. Gradient for UHPLC / HRMS measurement.

Time / min	solvent B / %
0	0
0.2	0
8.0	100
11.0	100
11.1	0
12.0	0

Synthetic procedures

Preparation of compound oO[1]



Oxaliplatin (0.5 g, 1.25 mmol) was suspended in distilled water. After the addition of H_2O_2 (18 mL), the reaction mixture was stirred at 60 °C for 2 h. The solvent was evaporated to a volume of 2 mL and the product was precipitated by addition of EtOAc and washed with EtOH and ether (0.4 g, 74 %).

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra

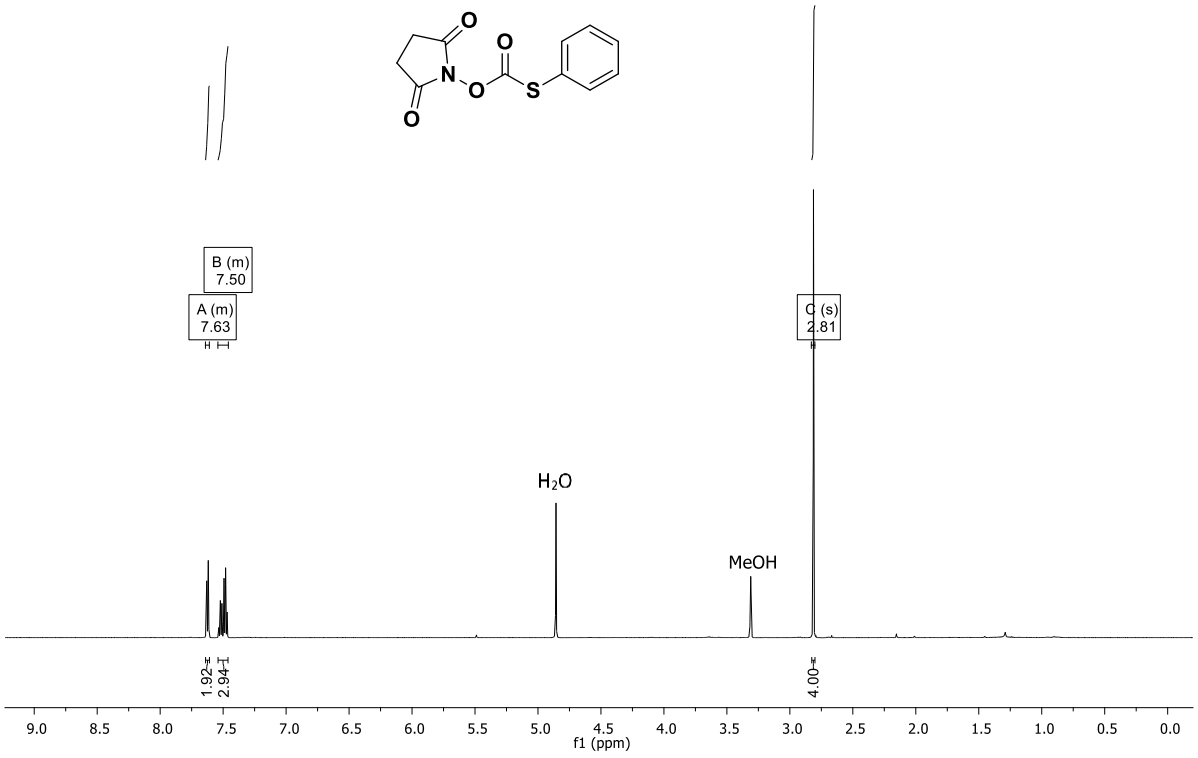


Fig. S1 ^{1}H NMR spectrum of **1** (MeOD, 600 MHz).

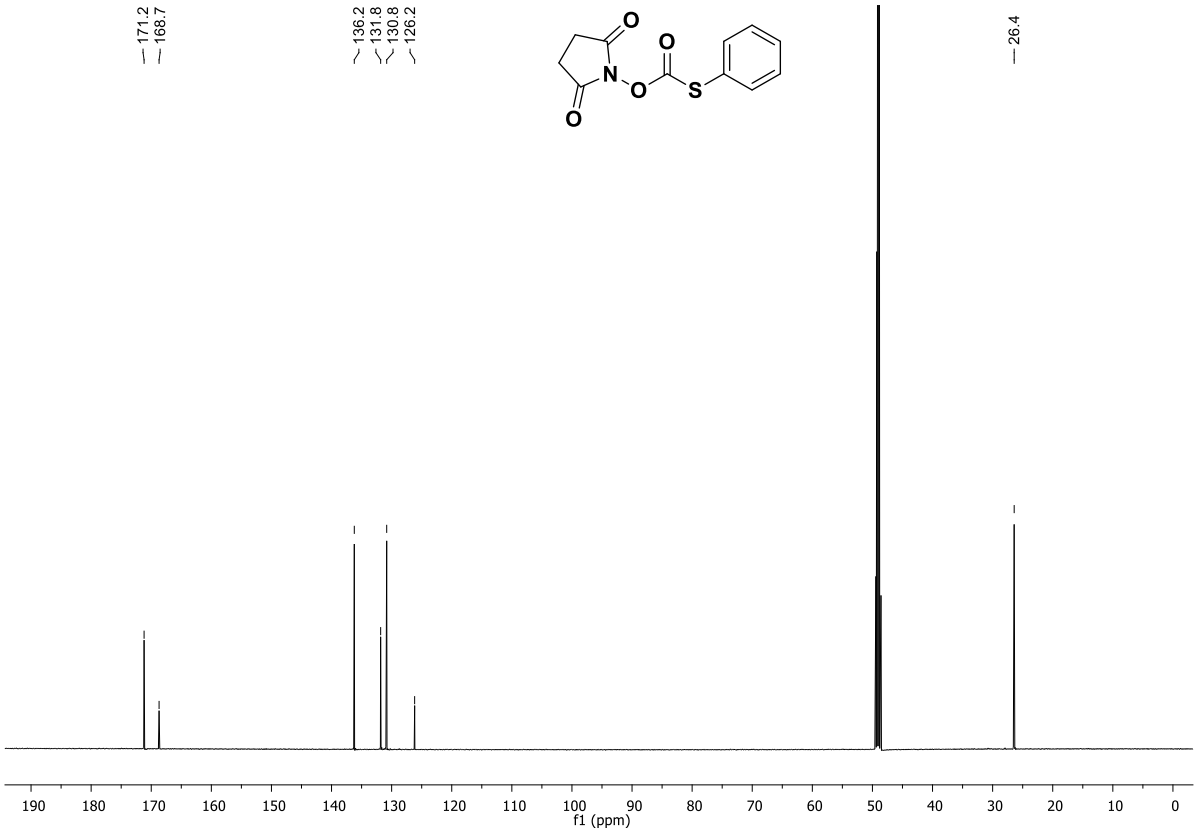


Fig. S2 $^{13}C\{^{1}H\}$ NMR spectrum of **1** (MeOD, 151 MHz).

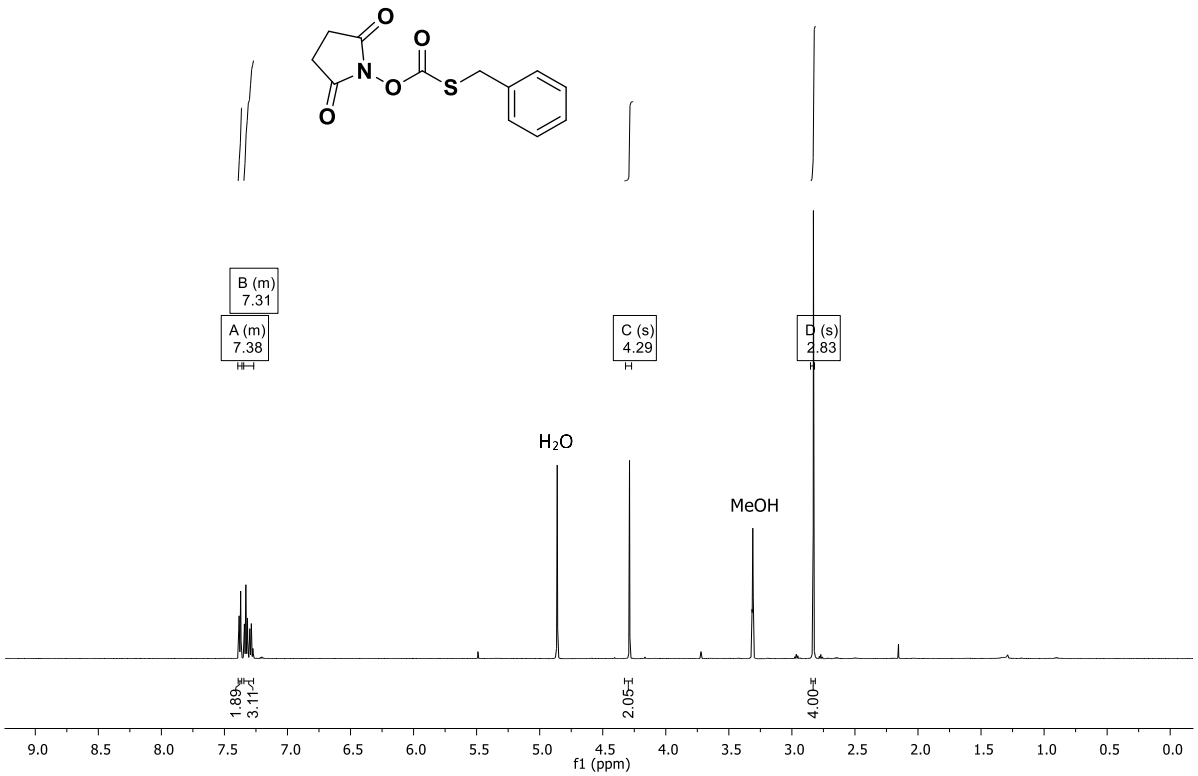


Fig. S3 ^{1}H NMR spectrum of **2** (MeOD, 600 MHz).

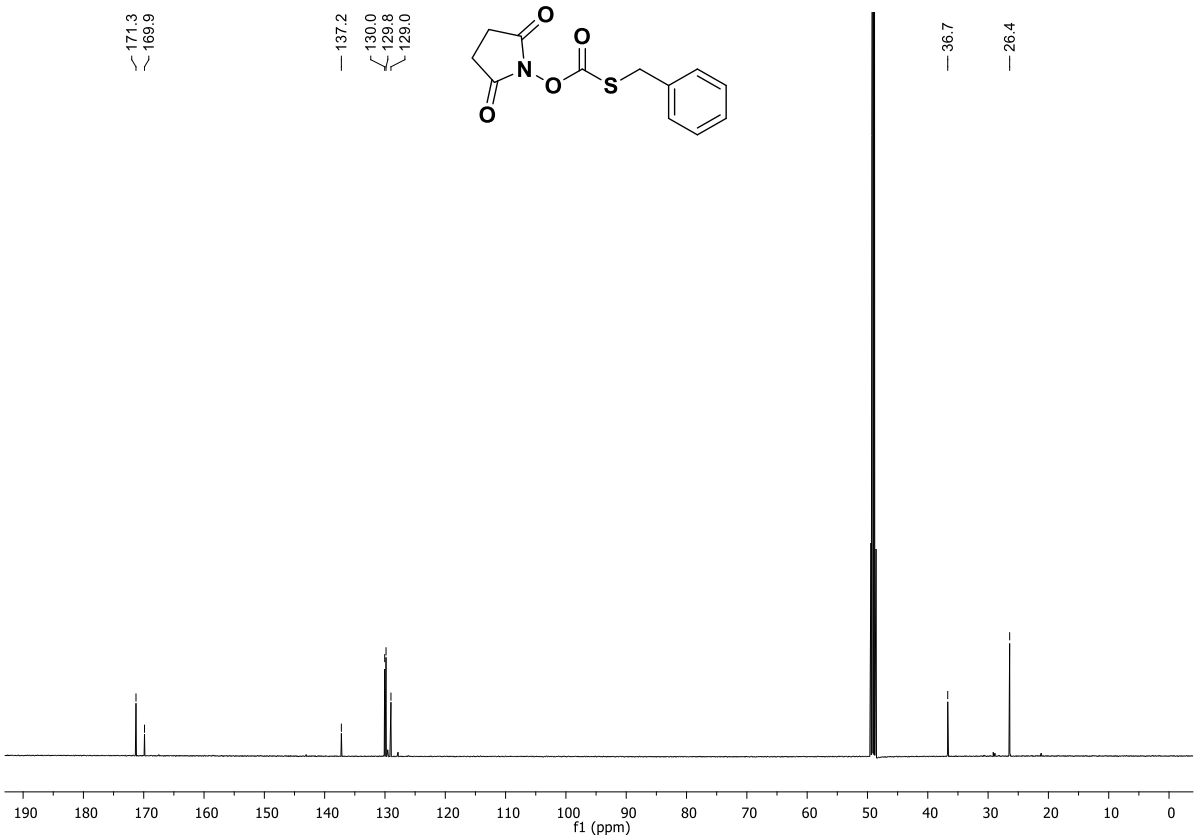


Fig. S4 $^{13}C\{^{1}H\}$ NMR spectrum of **2** (MeOD, 151 MHz).

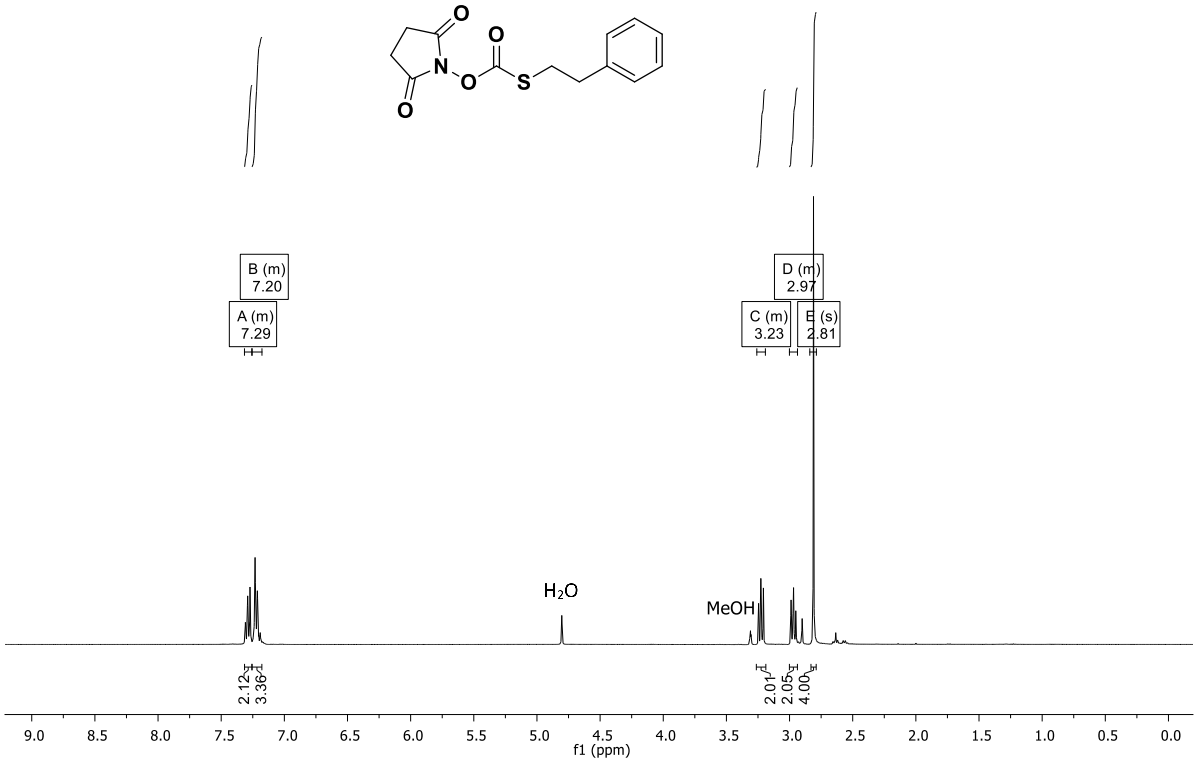


Fig. S5 ^{1}H NMR spectrum of **3** (MeOD, 600 MHz).

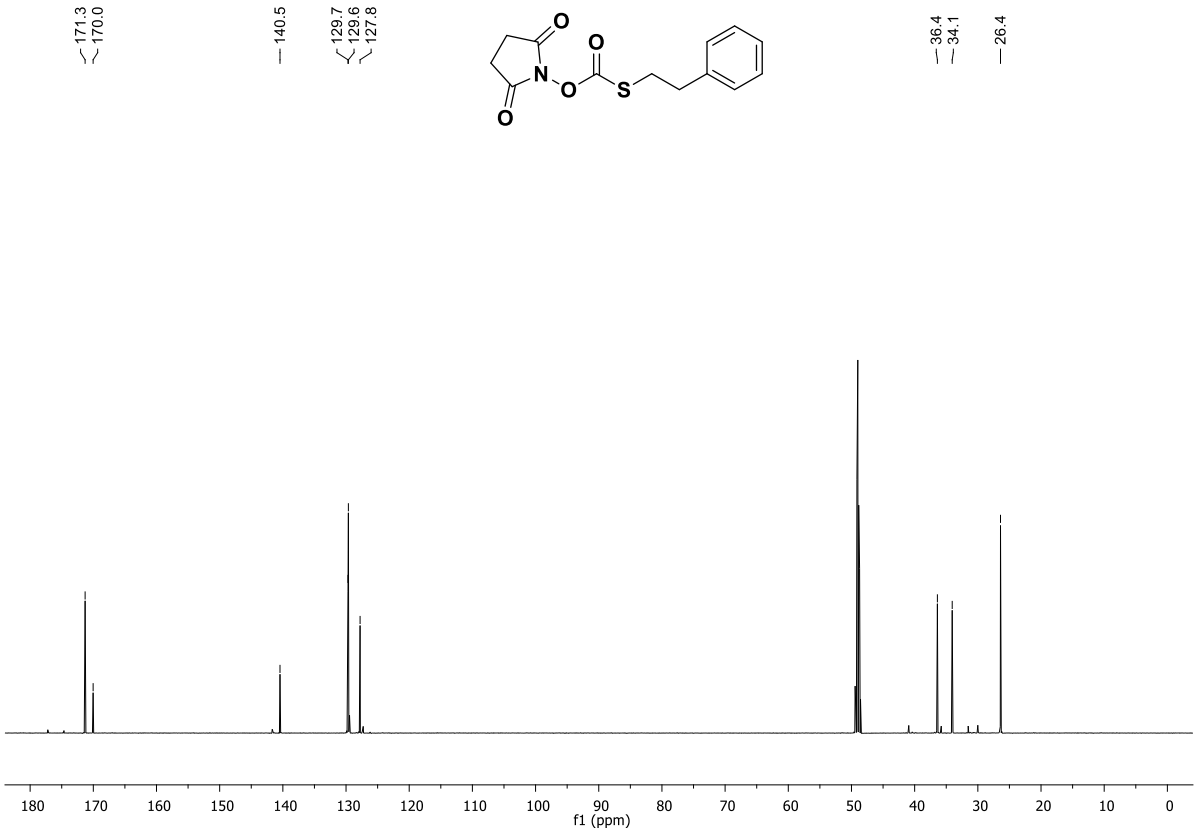


Fig. S6 $^{13}C\{^{1}H\}$ NMR spectrum of **3** (MeOD, 151 MHz).

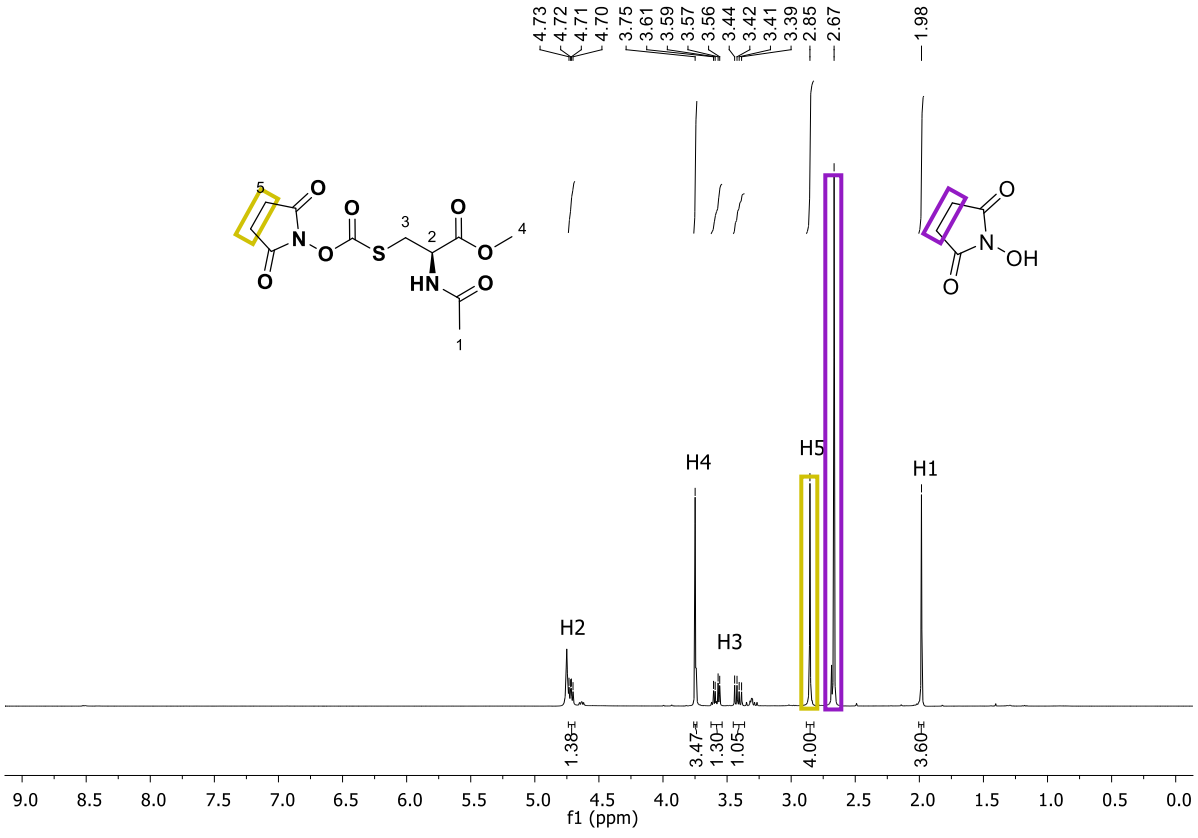


Fig. S7 ^{1}H NMR spectrum of **4** (MeOD, 400 MHz) and NHS formed during the synthesis of **4**.

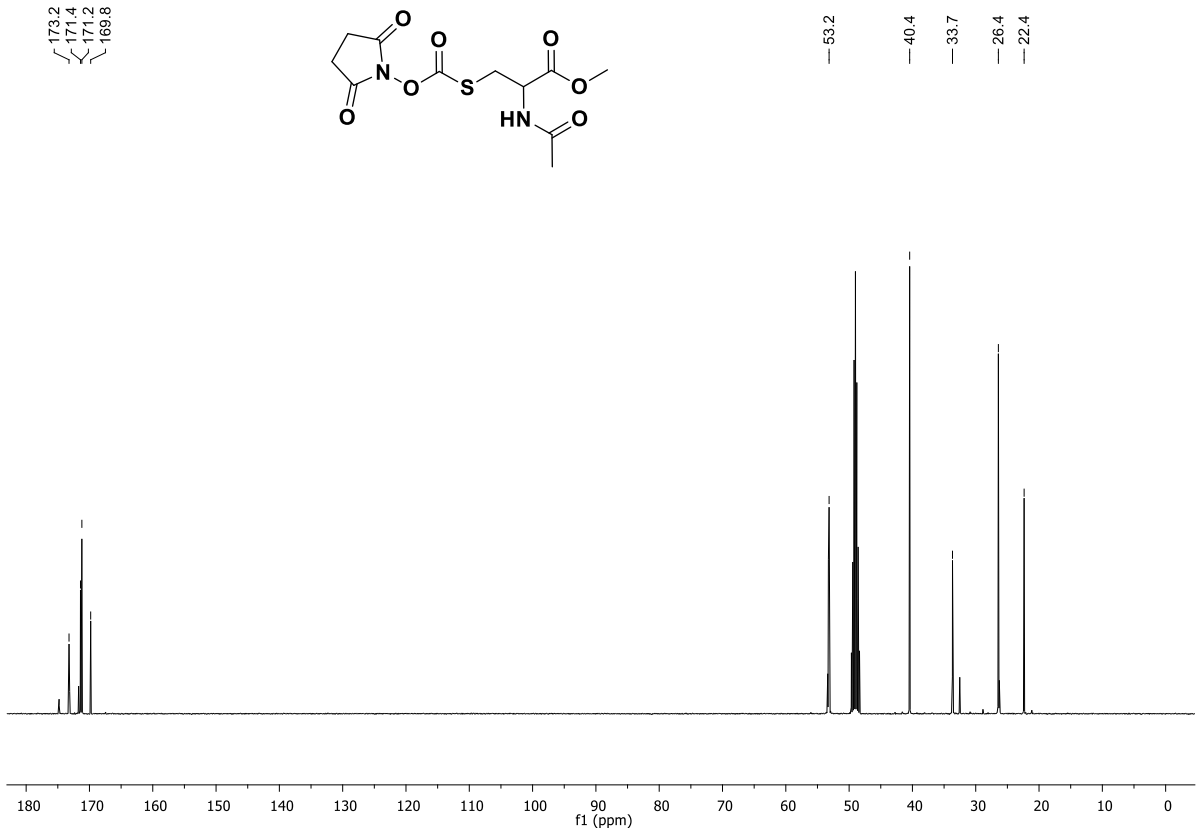


Fig. S8 $^{13}C\{^{1}H\}$ NMR spectrum of **4** (MeOD, 151 MHz).

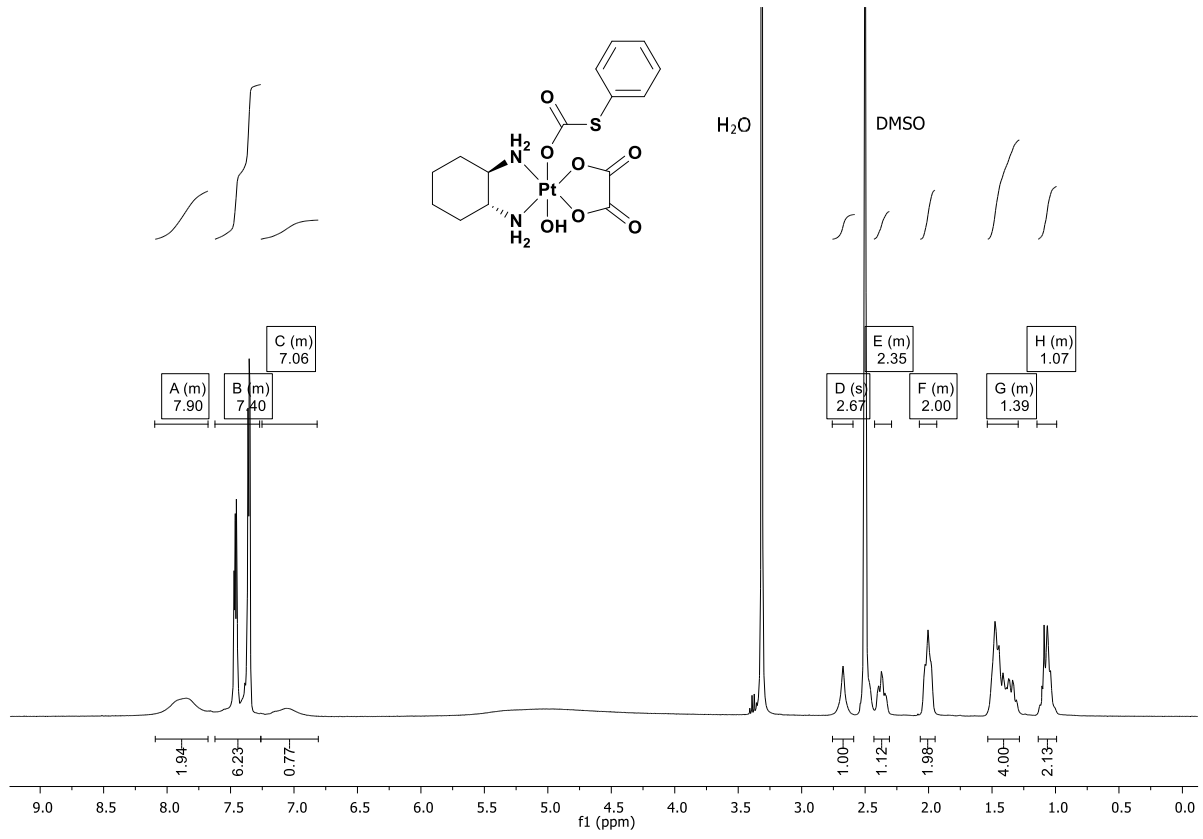


Fig. S9 ^{1}H NMR spectrum of **5** (DMSO-d_6, 400 MHz).

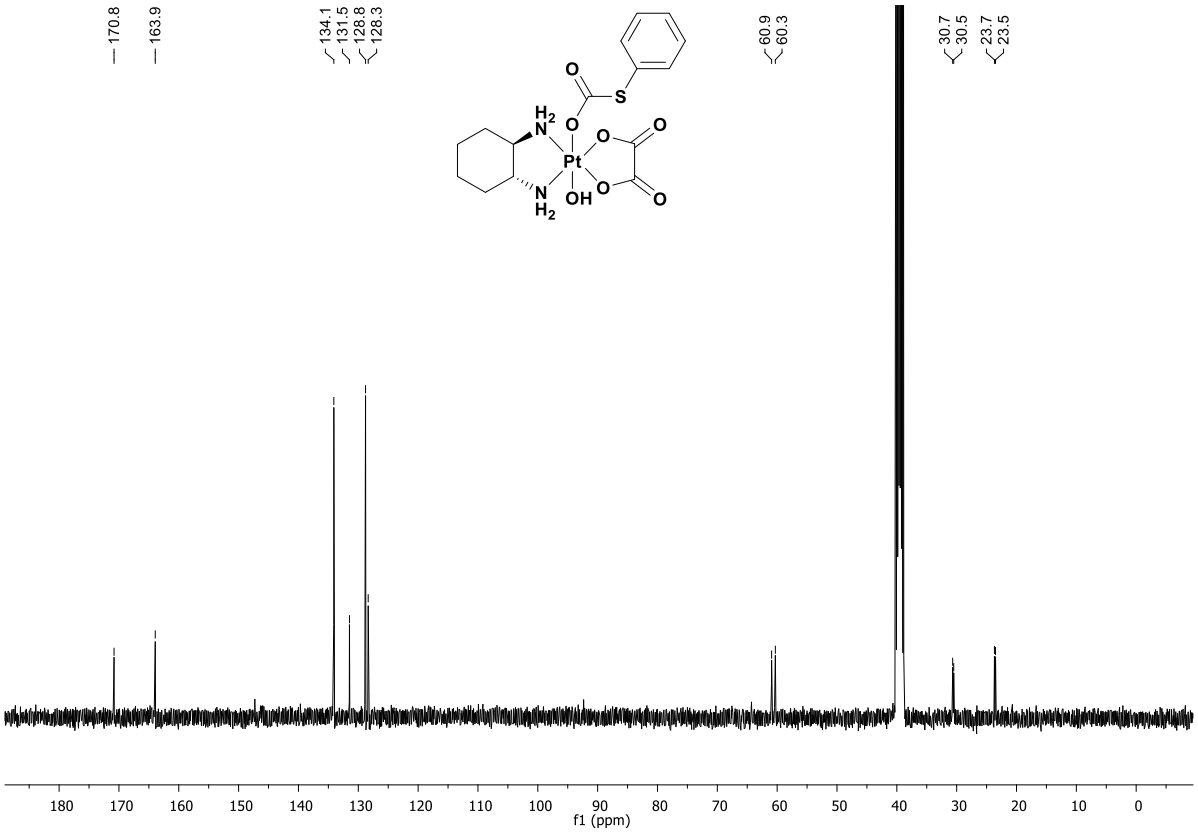


Fig. S10 $^{13}C\{^{1}H\}$ NMR spectrum of **5** (DMSO-d_6, 101 MHz).

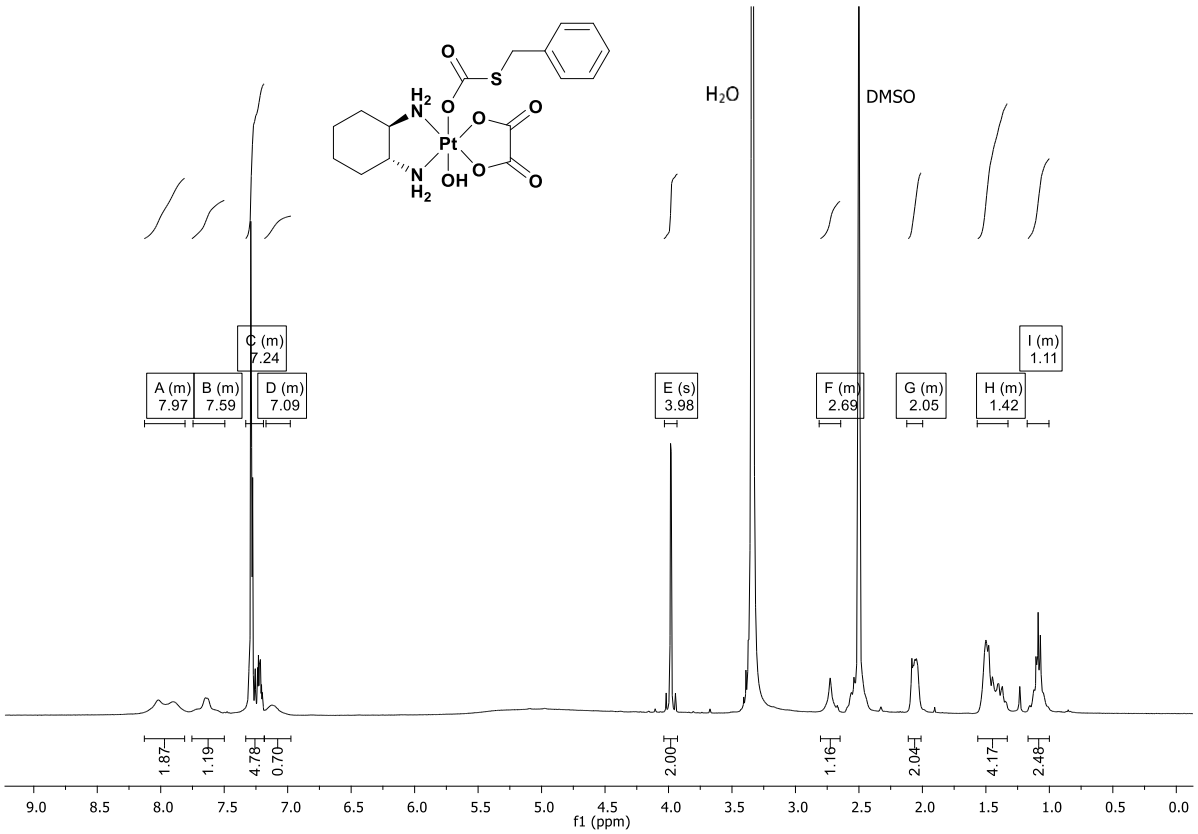


Fig. S11 ^{1}H NMR spectrum of **6** (DMSO-d_6, 400 MHz).

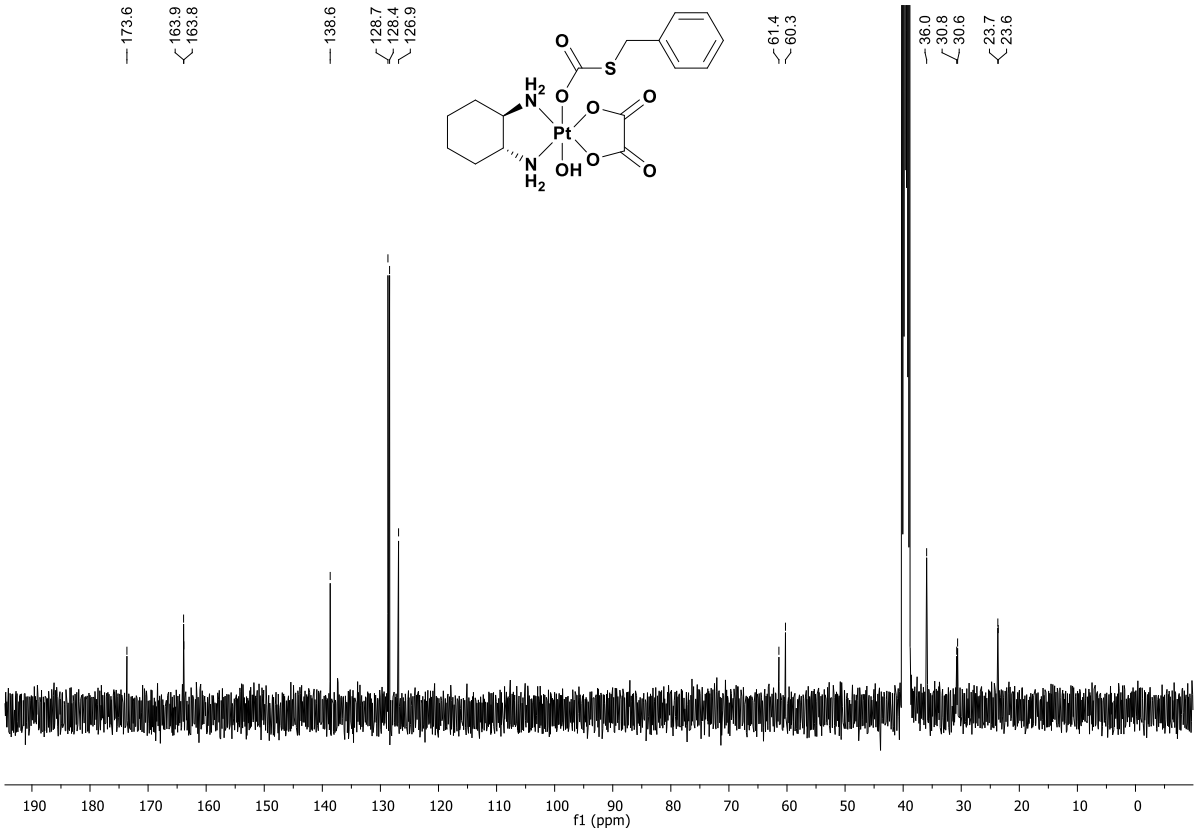


Fig. S12 $^{13}C\{^{1}H\}$ NMR spectrum of **6** (DMSO-d_6, 101 MHz).

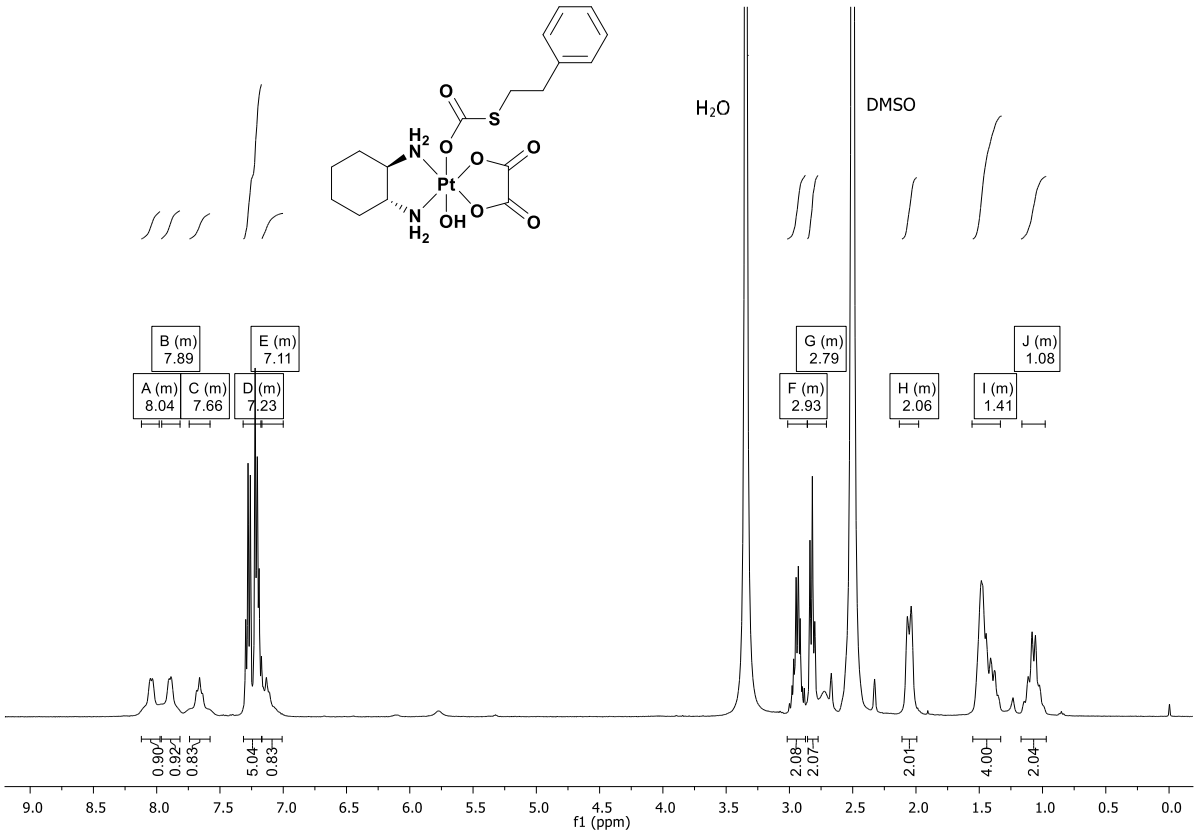


Fig. S13 ^{1}H NMR spectrum of **7** (DMSO-d_6, 400 MHz).

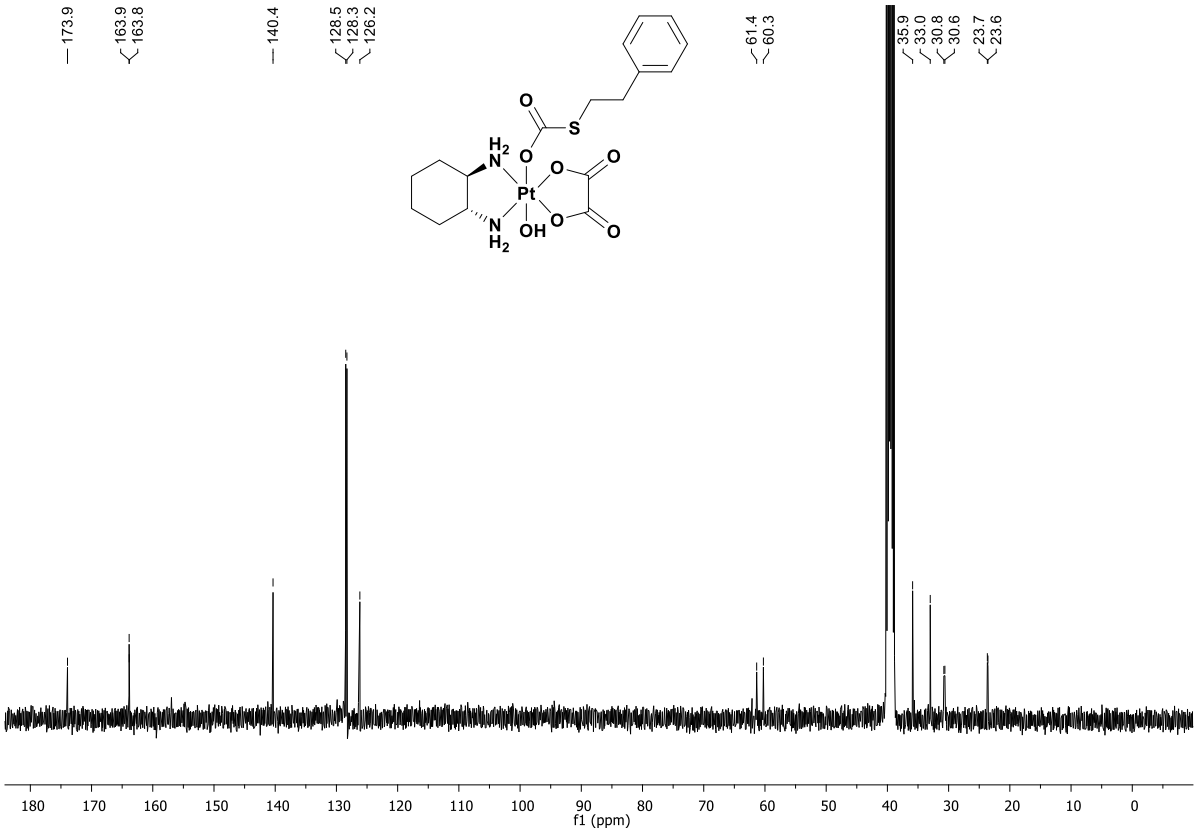


Fig. S14 $^{13}C\{^{1}H\}$ NMR spectrum of **7** (DMSO-d_6, 101 MHz).

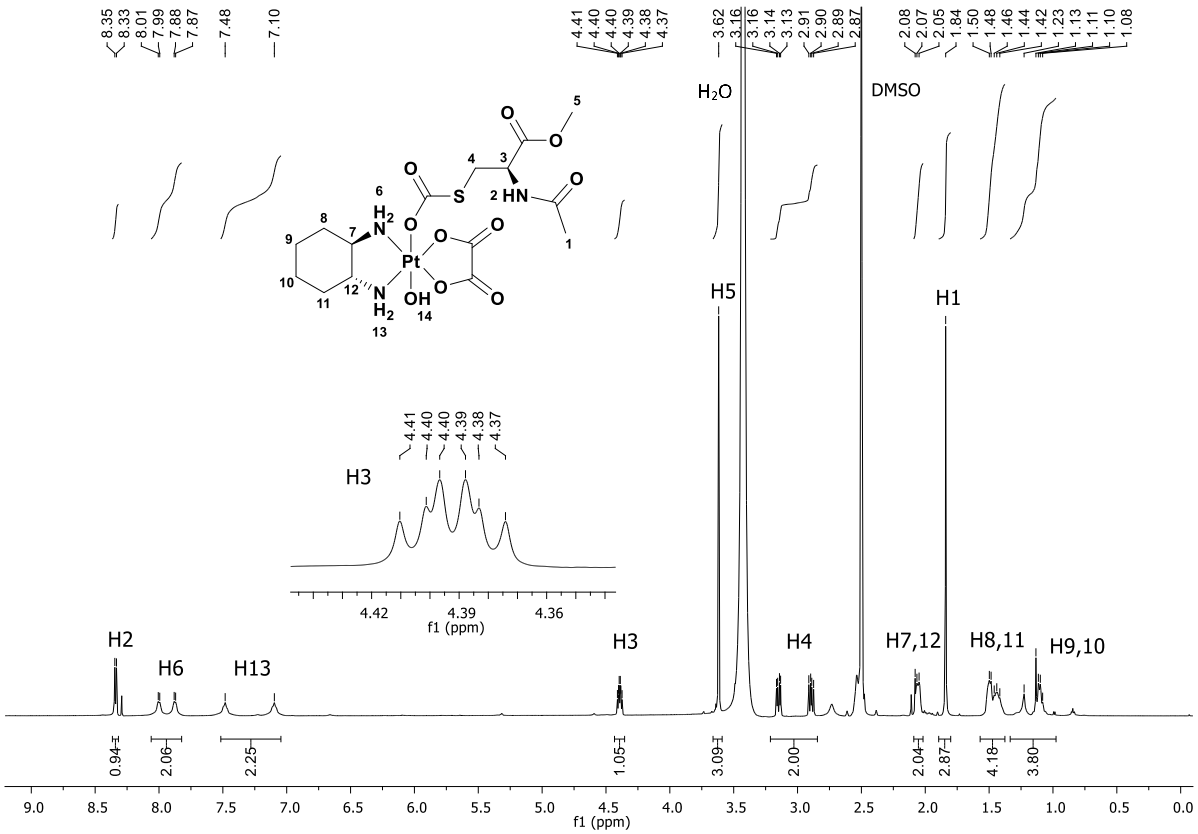


Fig. S15 ^{1}H NMR spectrum of **8** (DMSO-d_6, 600 MHz).

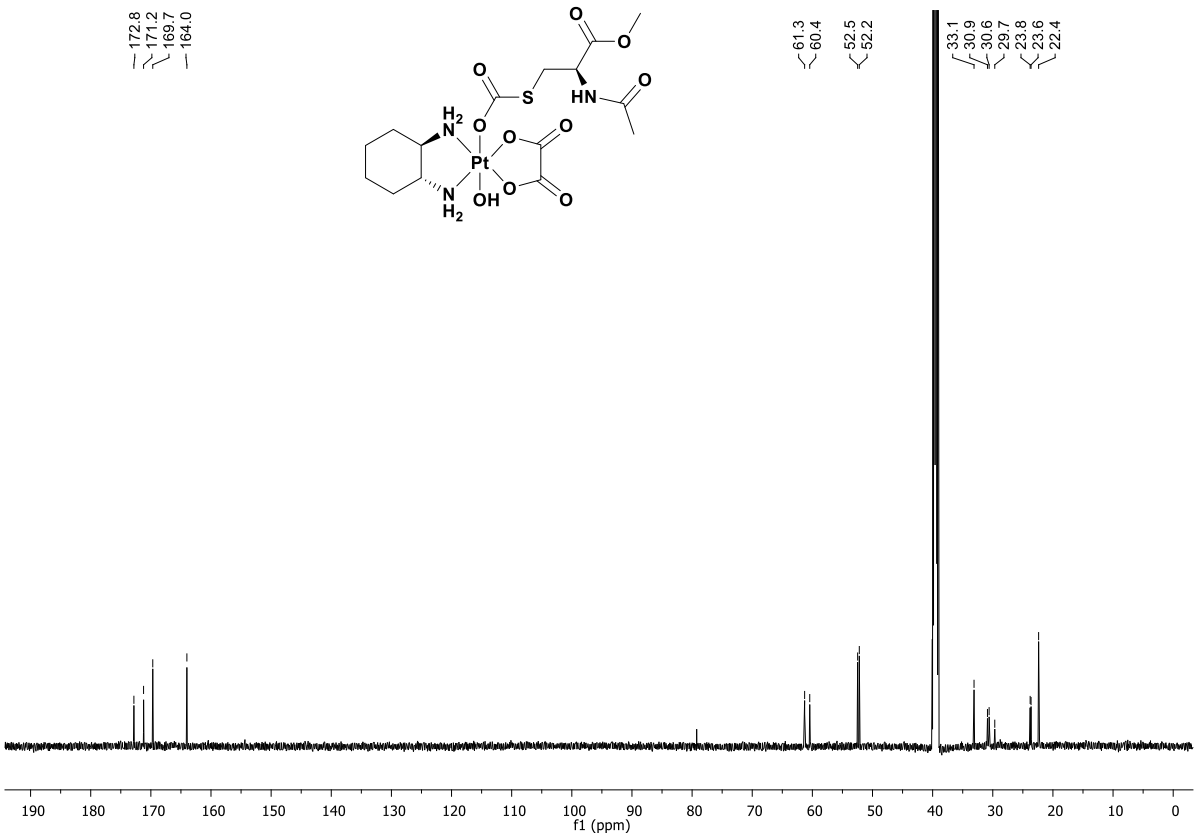


Fig. S16 $^{13}C\{^{1}H\}$ NMR spectrum of **8** (DMSO-d_6, 151 MHz).

Crystal structure data

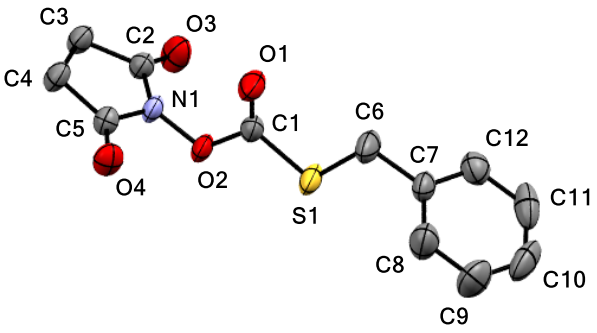


Table S2 Specific bond lengths [Å] and angles [°] for **2**.

Bond	[Å]
S1-C1	1.741(2)
S1-C6	1.824(2)
O2-C1	1.390(2)
O2-N1	1.3911(18)
Angle	**[°]**
C1-S1-C6	97.83(11)
C1-O2-N1	112.66(14)

Fig. S17 Molecular structure (50 % probability) of ligand **2**.
H atoms are omitted for clarity.

Crystal Data for **2**: $C_{12}H_{11}NO_4S$, Mr = 265.28 gmol^{-1}, colourless prism, size 0.112 x 0.102 x 0.088 mm^3, triclinic, space group P $\bar{1}$, a = 5.8270(2), b = 10.1224(3), c = 11.5866(3) Å, α = 109.654(1), β = 99.346(2), γ = 97.107(2)°, V = 623.25(3) Å^3 , T= -40 °C, Z = 2, $\rho_{calcd.}$ = 1.414 gcm^{-3}, μ (Mo-K$_\alpha$) = 2.65 cm^{-1}, multi-scan, transmin: 0.7027, transmax: 0.7456, F(000) = 276, 7554 reflections in h(-7/7), k(-13/10), l(-15/15), measured in the range 1.912° $\leq \Theta \leq$ 27.483°, completeness Θ_{max} = 99.5%, 2844 independent reflections, R_{int} = 0.0274, 2292 reflections with $F_o > 4\sigma(F_o)$, 207 parameters, 0 restraints, $R1_{obs}$ = 0.0486, wR^2_{obs} = 0.0903, $R1_{all}$ = 0.0635, wR^2_{all} = 0.0980, GOOF = 1.031, largest difference peak and hole: 0.221 / -0.252 e Å^{-3}.

Investigation on stability of complex 8 (analytical HPLC)

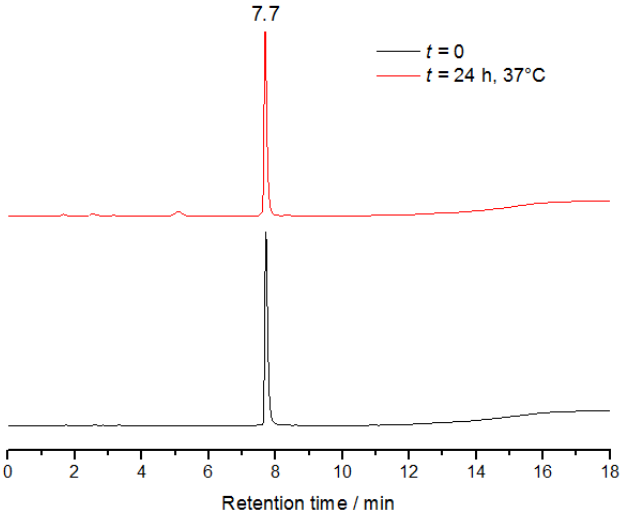


Fig. S18 HPLC chromatograms of complex **8** in aqueous phosphate buffer (pH 7.4) with t_R = 7.7 min (bottom: t = 0, top: after 24 h at 37 °C). Gradient: 5-95 % of acetonitrile in water (with 0.1 % formic acid); Chromatograms were recorded at 254 nm.

Reduction Experiment of complex 8 with ascorbic acid (analytical HPLC)

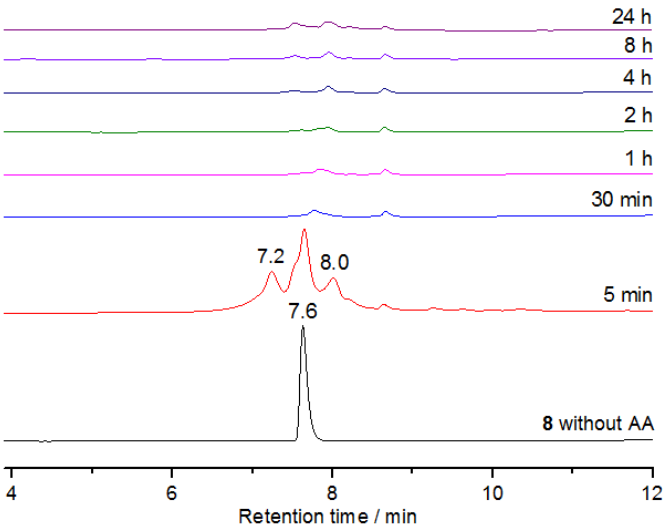


Fig. S19 HPLC chromatogram extracts of the reduction experiment of complex **8** with ascorbic acid (AA) in aqueous phosphate buffer (pH 7.4) at 37 °C. Chromatograms were recorded at 254 nm after the addition of ascorbic acid over time.

Reduction Experiment of complex 8 with ascorbic acid (UHPLC-HRMS)

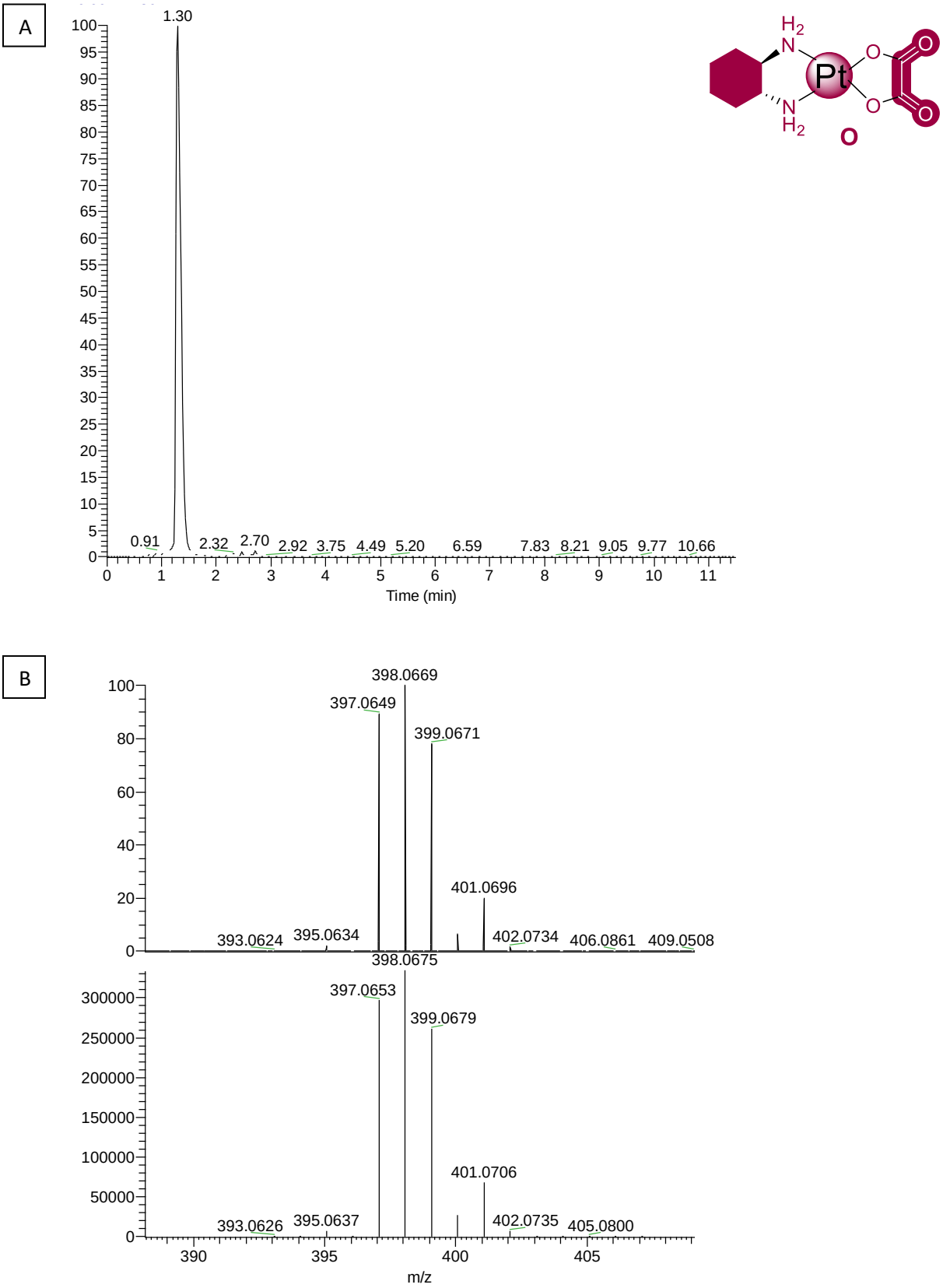


Fig. S20 LC-ESI-HRMS of **O**, calc. for $C_8H_{15}O_4N_2{}^{194}Pt$ $[M+H]^+$ = 397.0653, found 397.0649. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

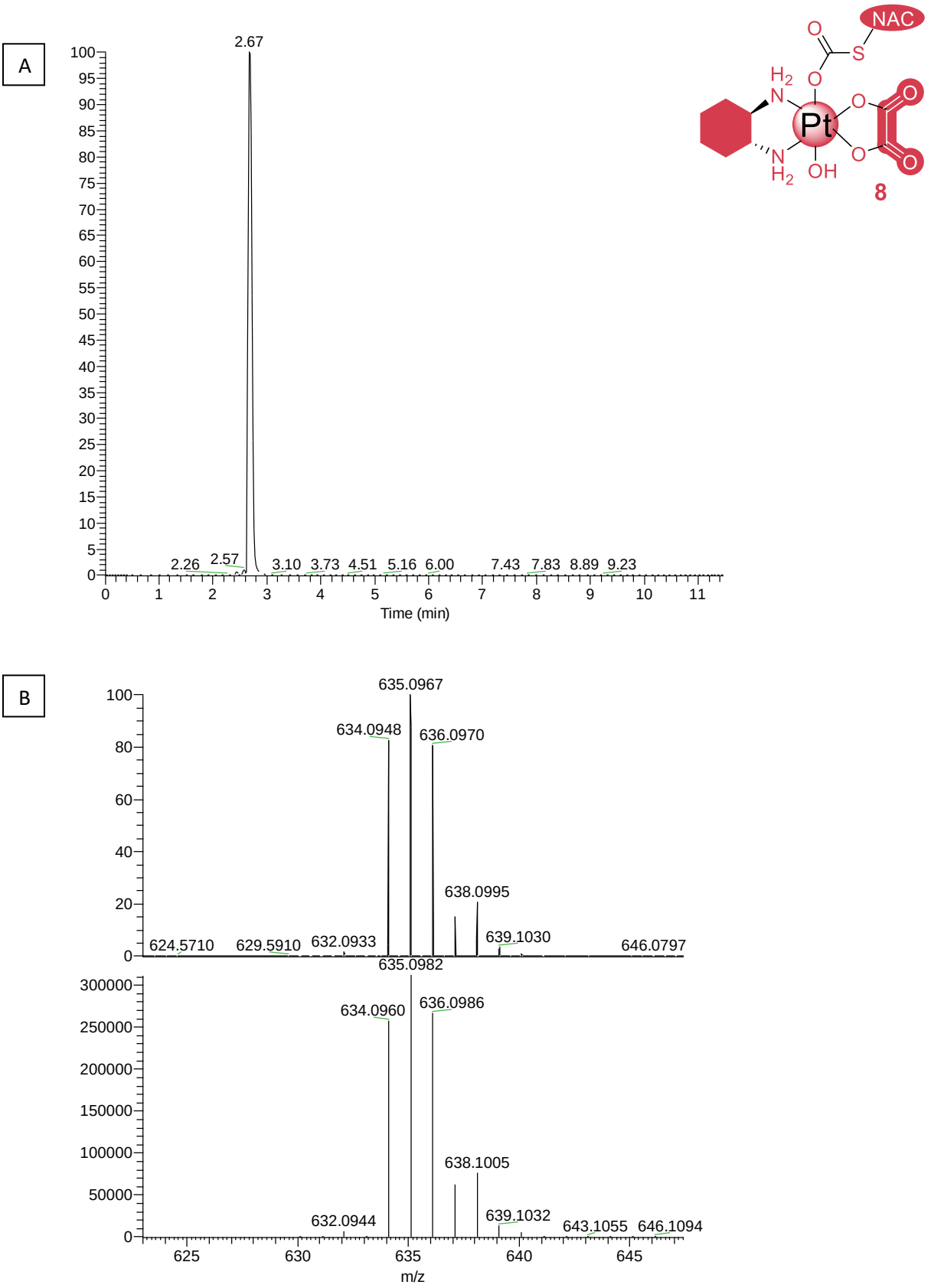


Fig. S21 LC-ESI-HRMS of **8**, calc. for $C_{15}H_{26}O_{10}N_3{}^{194}PtS$ $[M+H]^+$ = 634.0960, found 634.0948. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

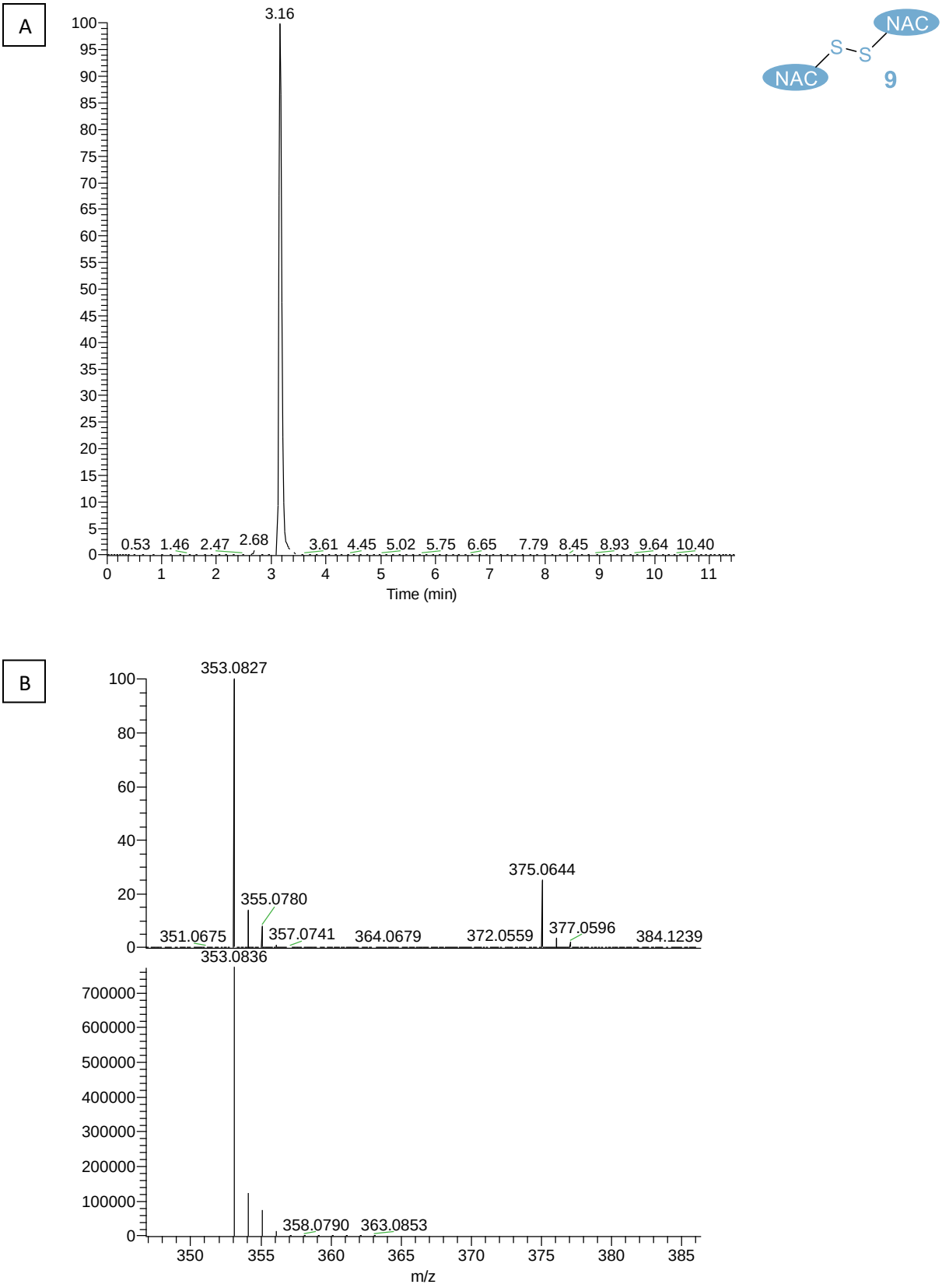


Fig. S22 LC-ESI-HRMS of **9**, calc. for $C_{12}H_{21}N_2O_6S_2$ $[M+H]^+$ = 353.0836, found 353.0827. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

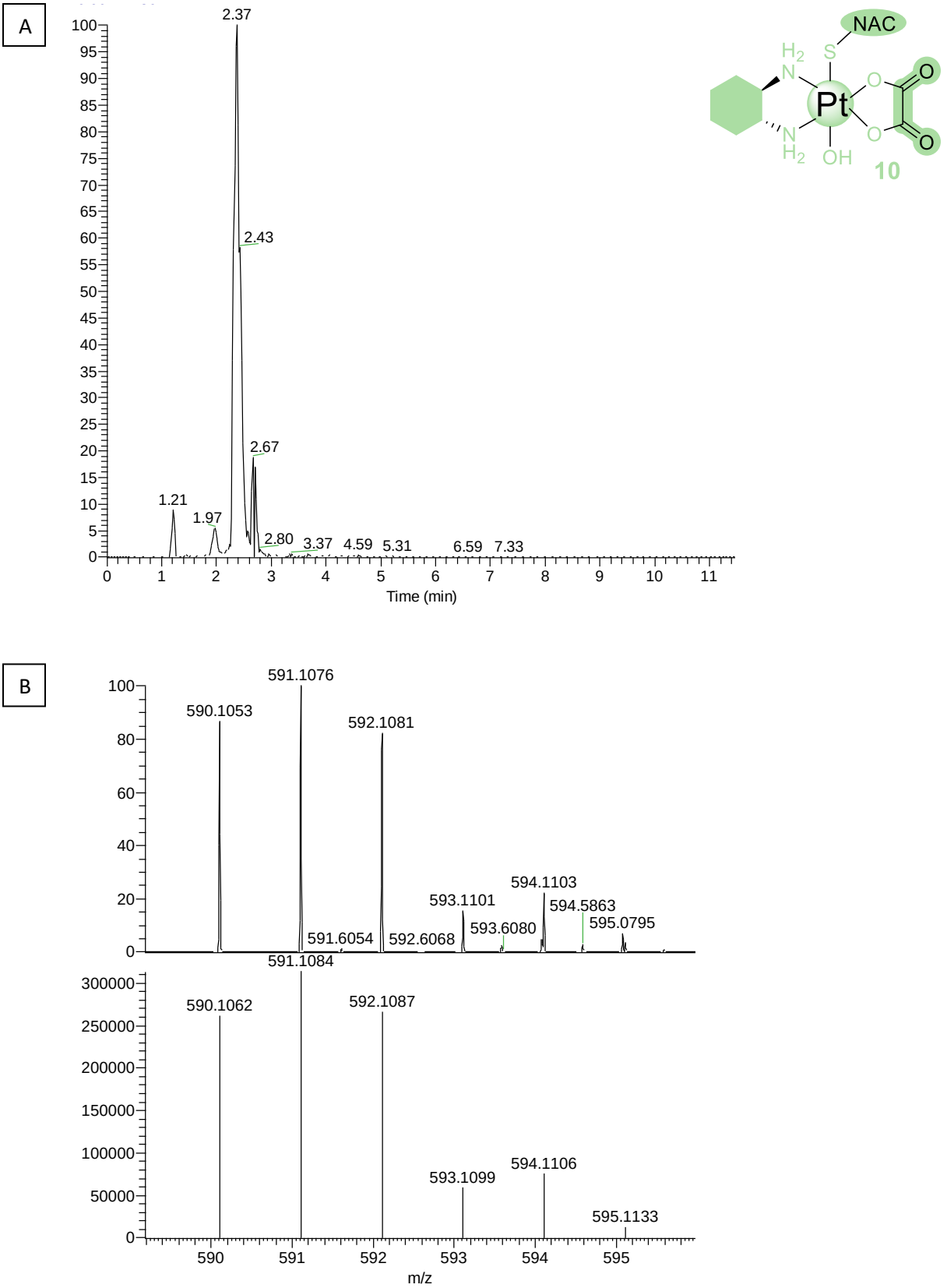


Fig. S23 LC-ESI-HRMS of **10**, calc. for $C_{14}H_{26}O_8N_3{}^{194}PtS$ $[M+H]^+$ = 590.1062, found 590.1053. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

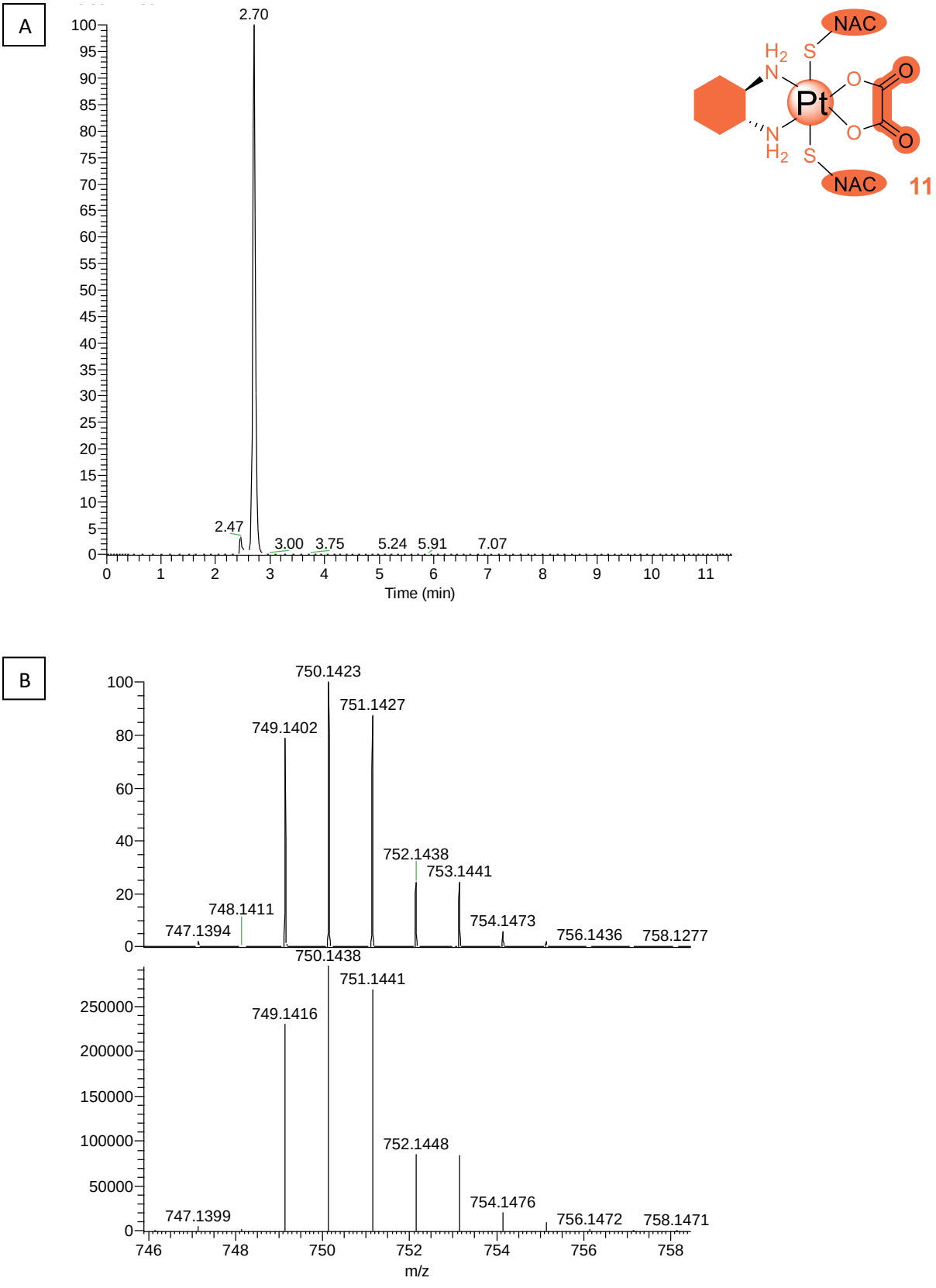


Fig. S24 LC-ESI-HRMS of **11**, calc. for $C_{20}H_{35}N_4O_{10}{}^{194}PtS_2$ $[M+H]^+$ = 749.1416, found 749.1402. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

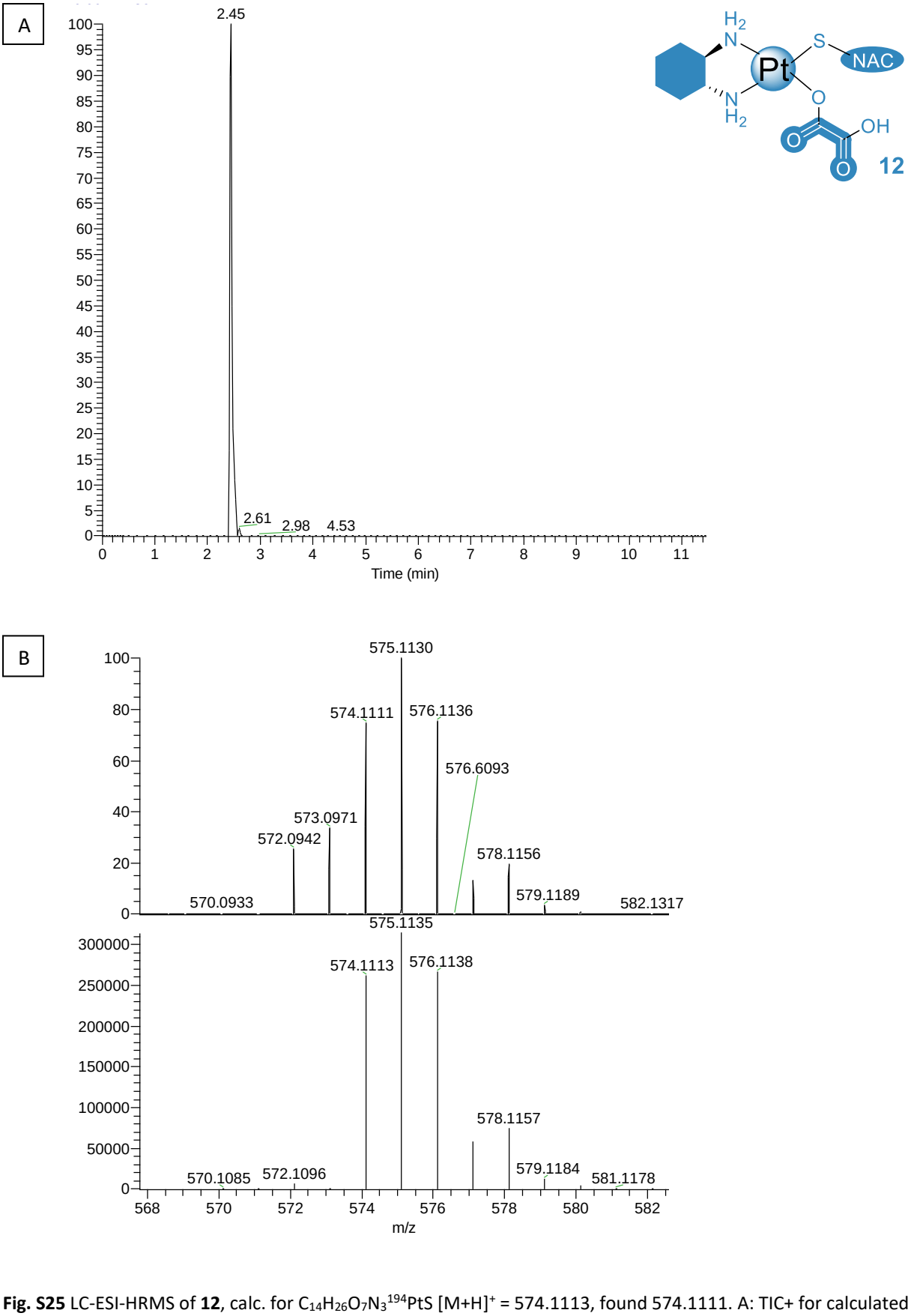
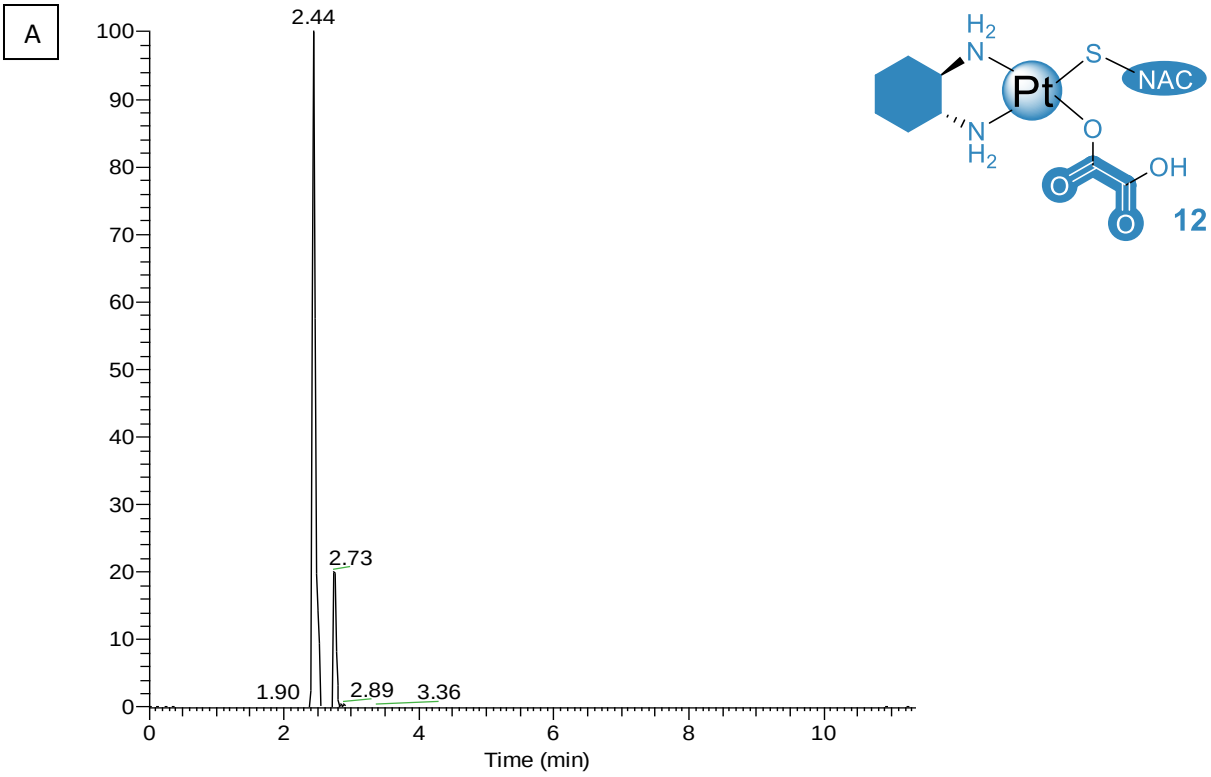


Fig. S25 LC-ESI-HRMS of **12**, calc. for $C_{14}H_{26}O_7N_3{}^{194}PtS$ $[M+H]^+$ = 574.1113, found 574.1111. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top) with partial overlap from **17**, calculated isotope pattern (bottom).



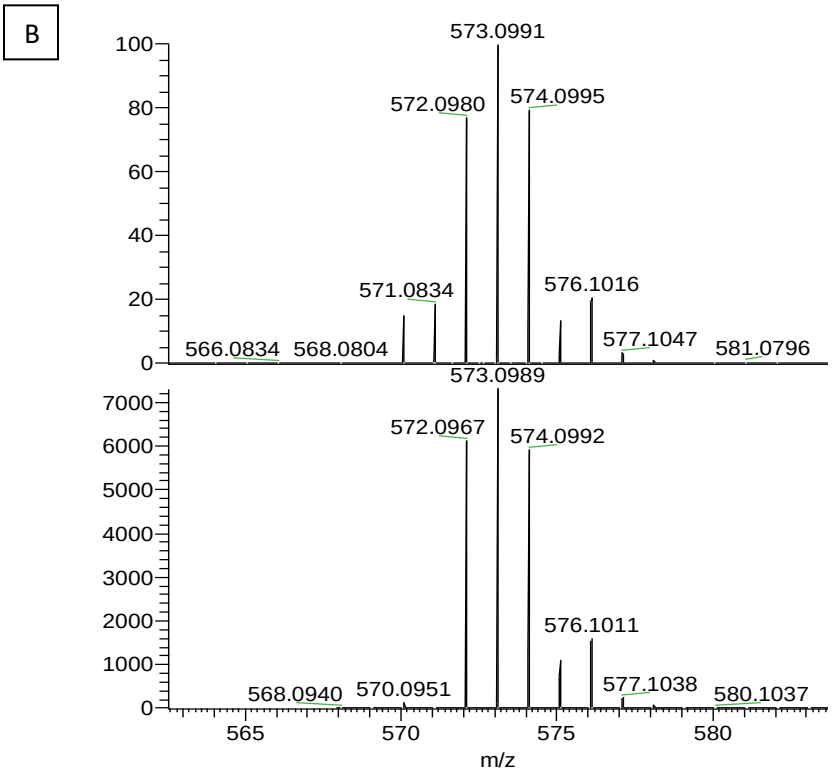
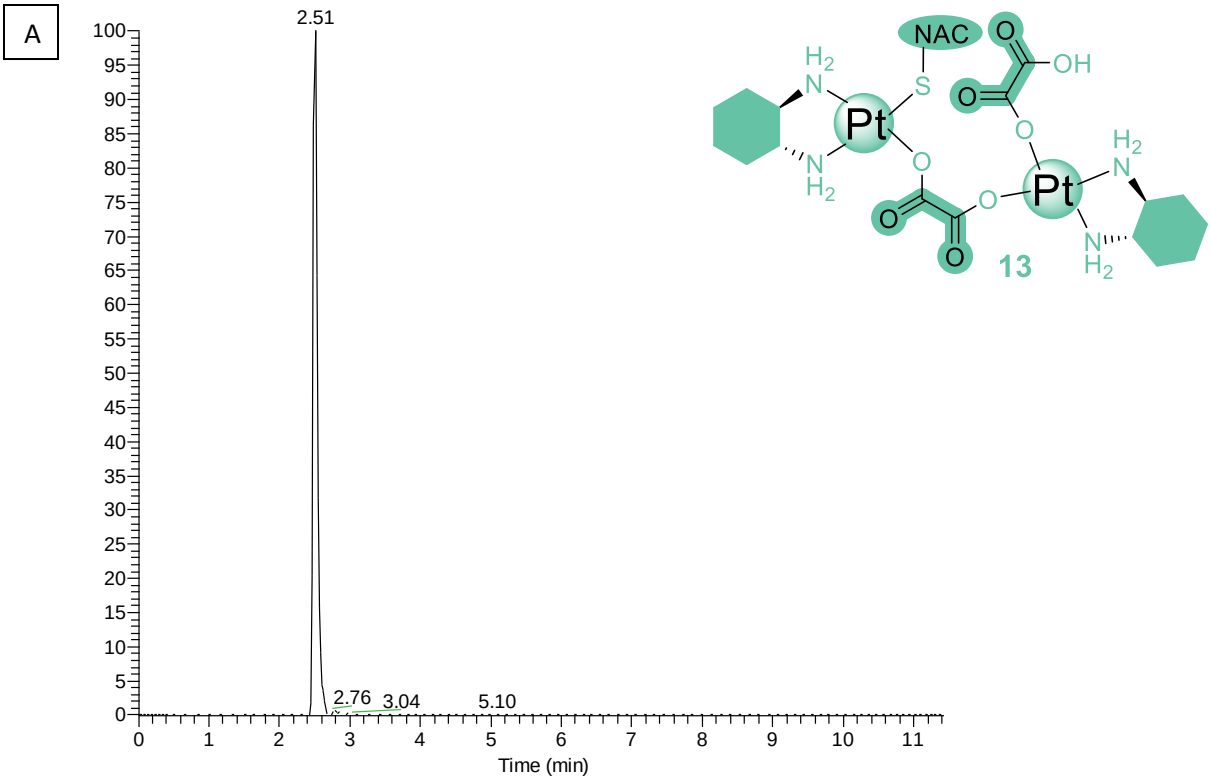


Fig. S26 LC-ESI-HRMS of **12**, calc. for $C_{14}H_{24}O_7N_3{}^{194}Pt_2S$ $[M–H]^-$ = 572.0967, found 572.0980. A: TIC– for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).



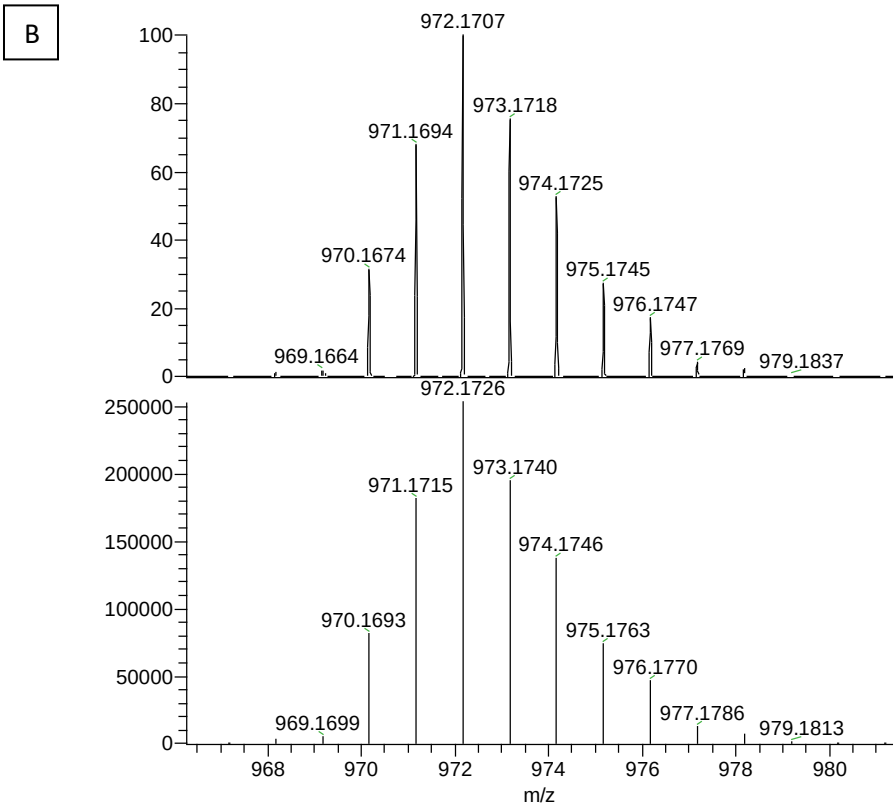
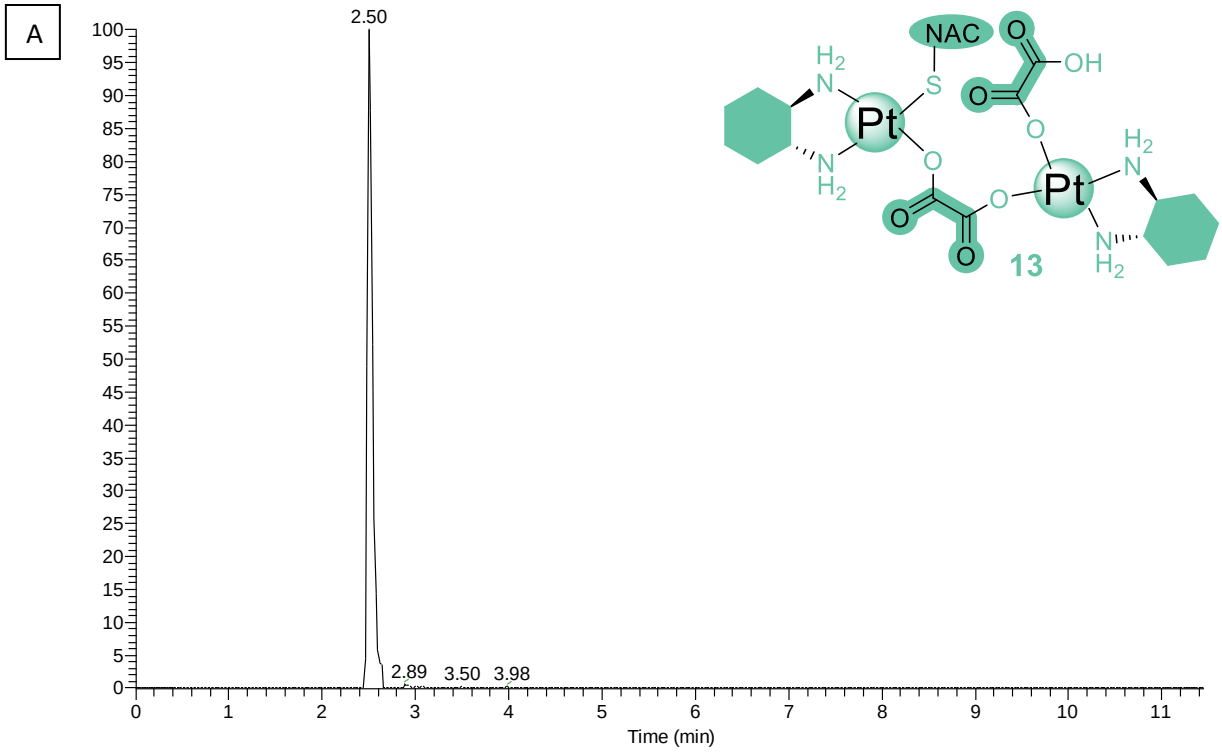


Fig. S27 LC-ESI-HRMS of **13**, calc. for $C_{22}H_{40}O_{11}N_5{}^{194}Pt_2S$ $[M+H]^+$ = 970.1693, found 970.1674. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).



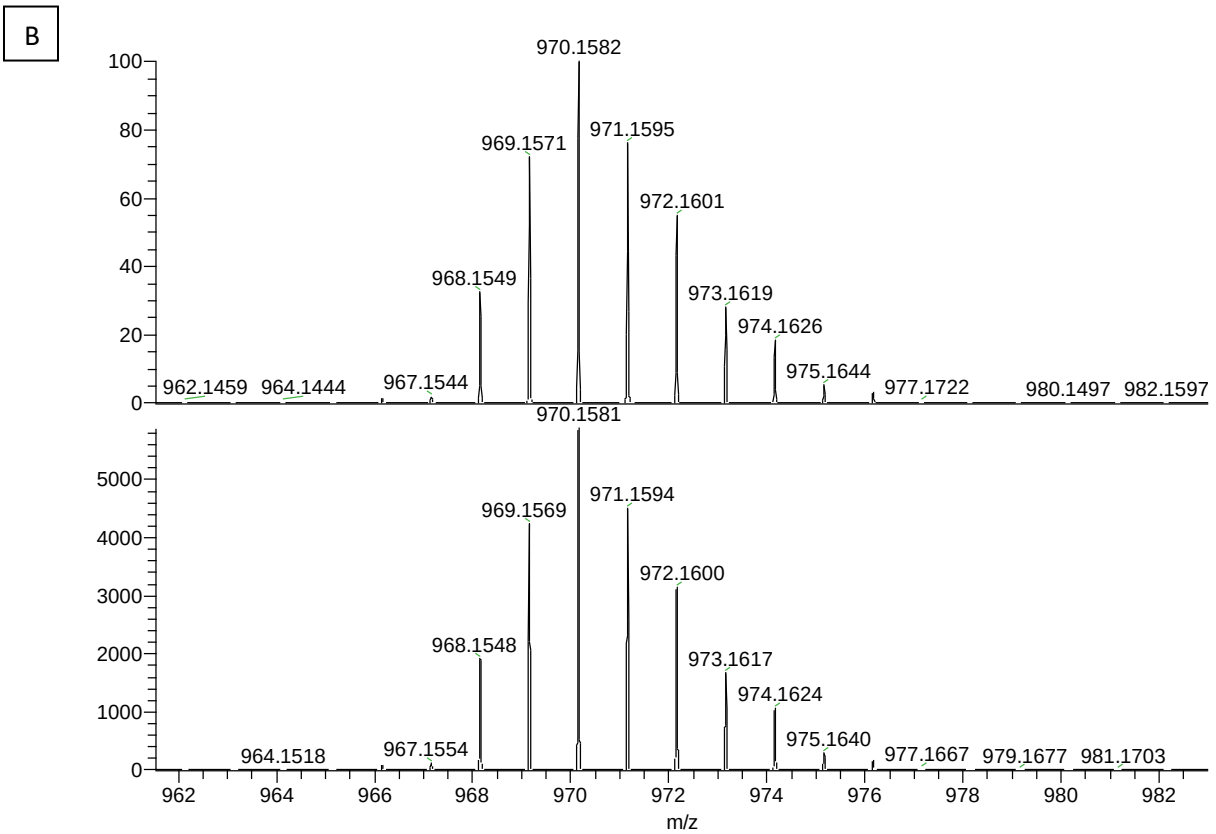


Fig. S28 LC-ESI-HRMS of **13**, calc. for $C_{22}H_{38}O_{11}N_5{}^{194}Pt_2S$ $[M–H]^-$ = 970.1548, found 970.1549. A: TIC– for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

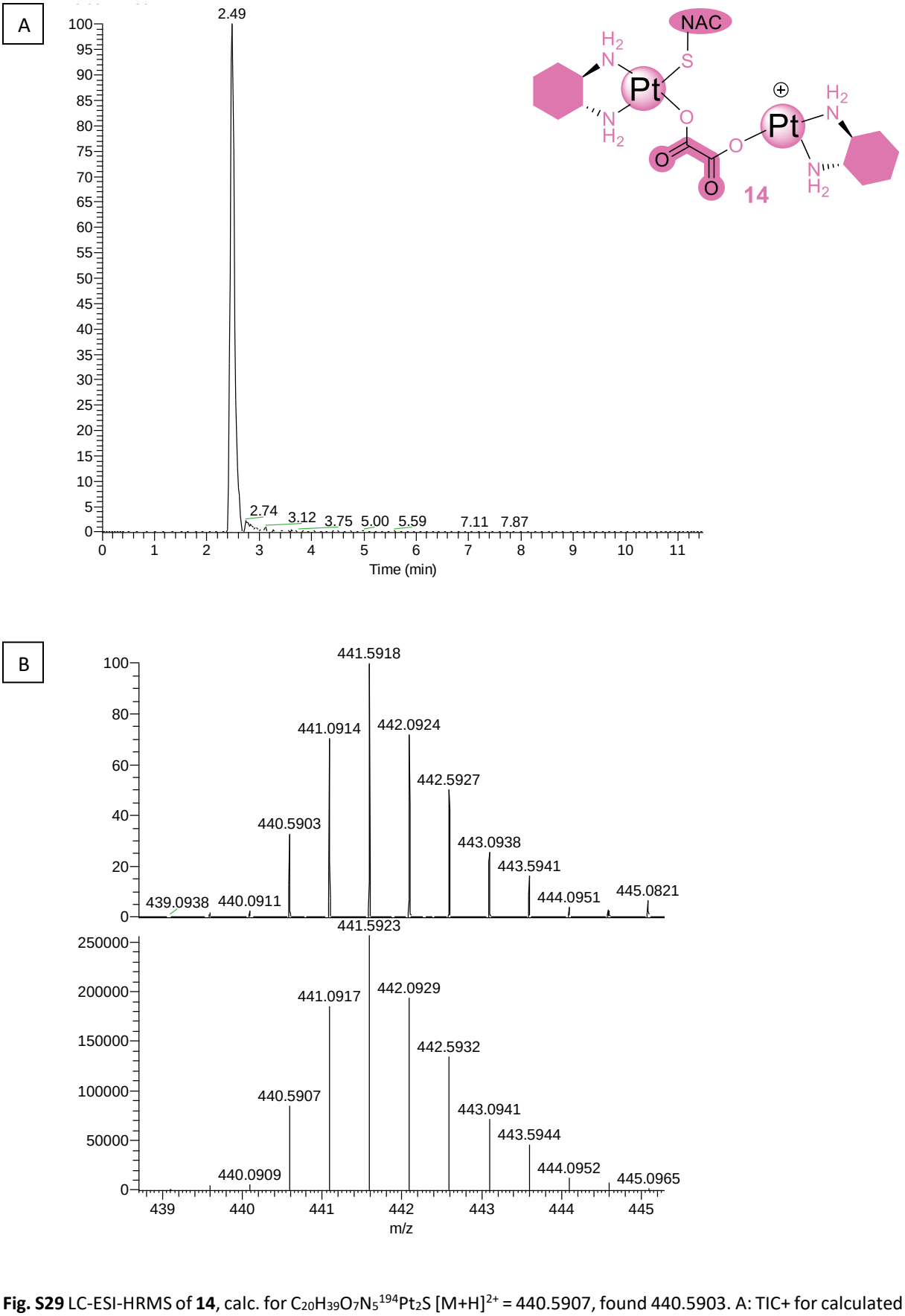
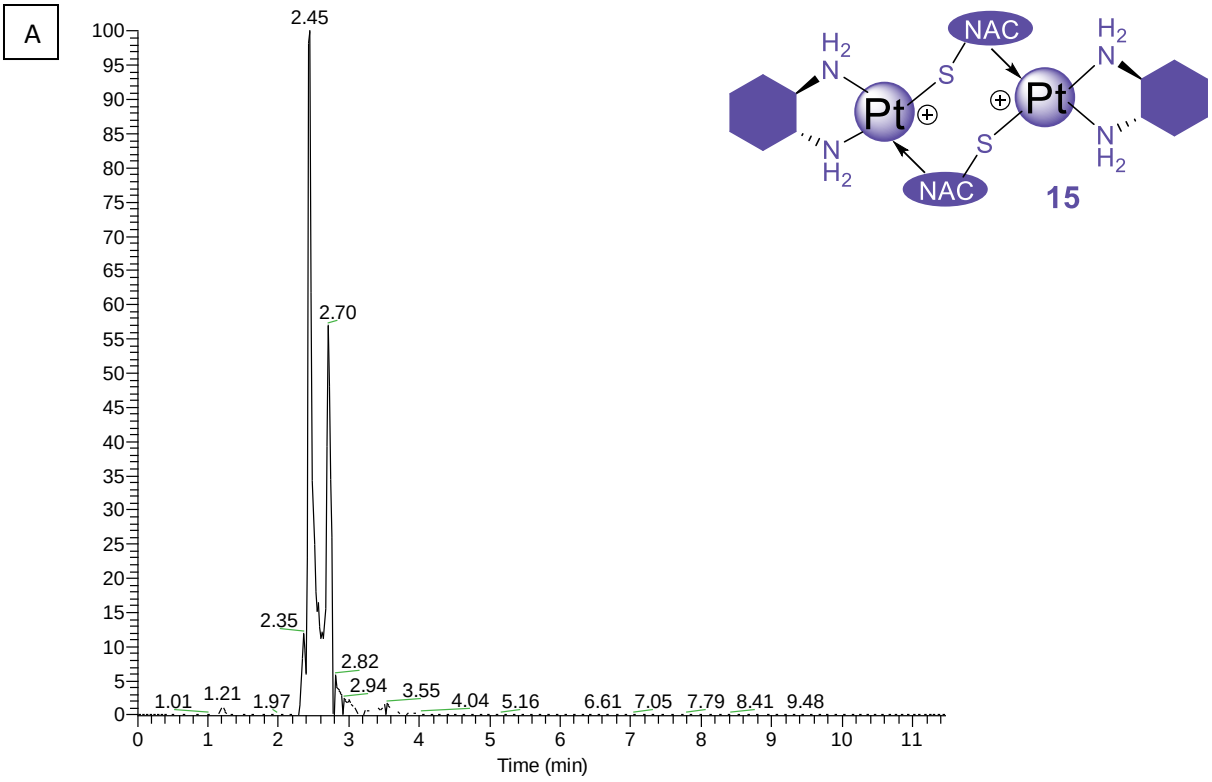


Fig. S29 LC-ESI-HRMS of **14**, calc. for $C_{20}H_{39}O_7N_5{}^{194}Pt_2S$ $[M+H]^{2+}$ = 440.5907, found 440.5903. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).



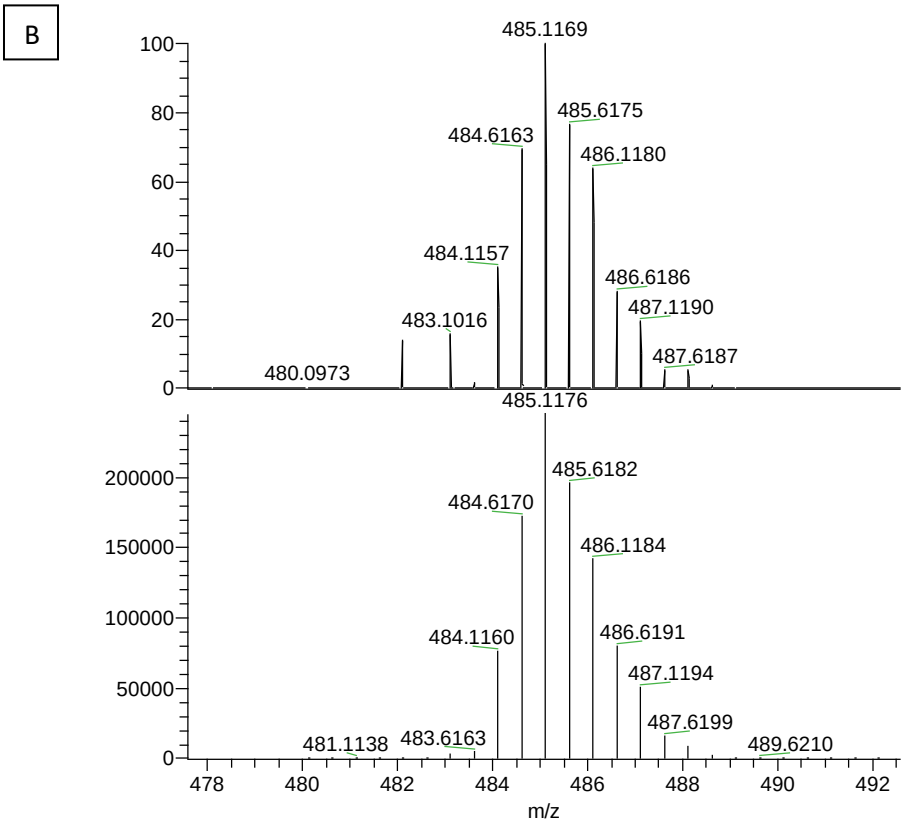


Fig. S30 LC-ESI-HRMS of **15**, calc. for $C_{24}H_{48}O_6N_6{}^{194}Pt_2S_2$ $[M]^{2+}$ = 484.1160, found 484.1157. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

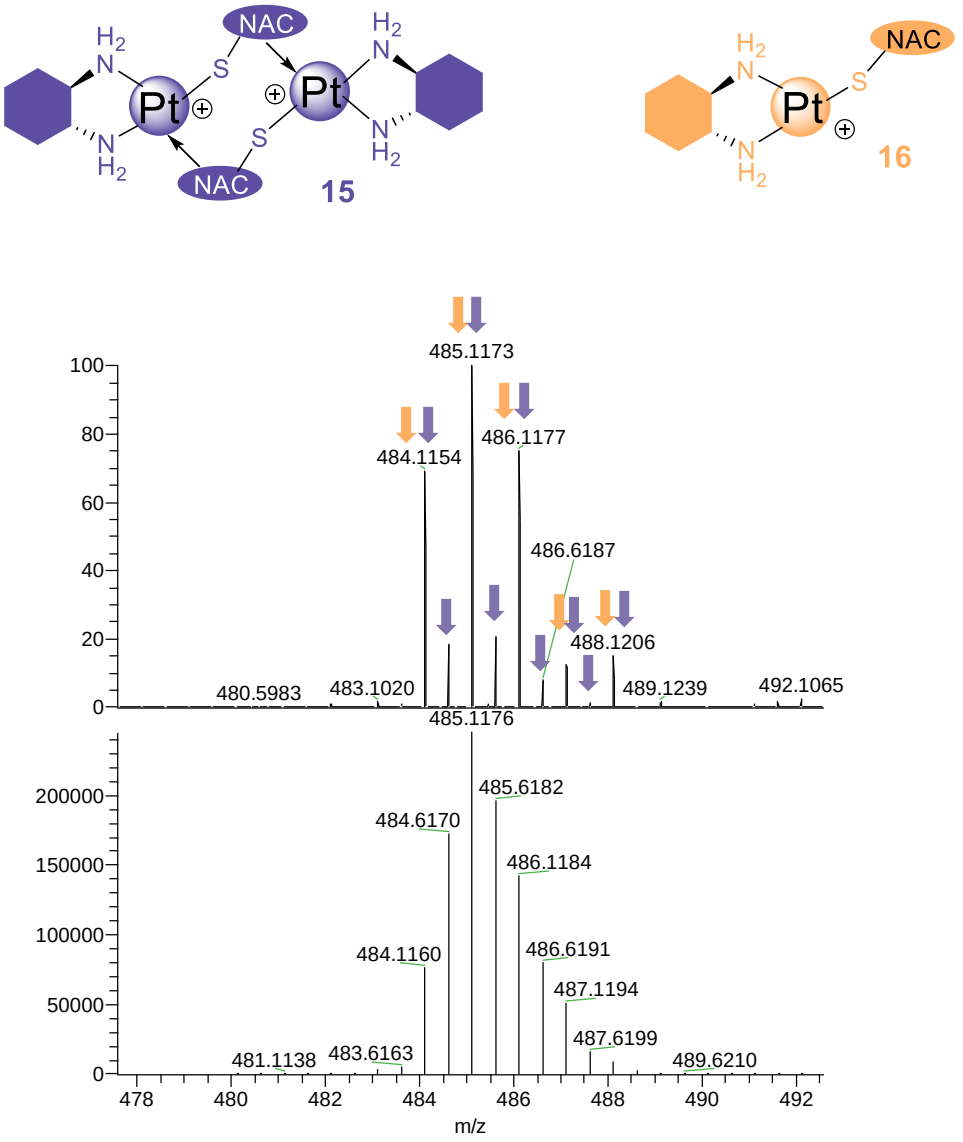


Fig. S31 Mass spectrum of **15** (t_R = 2.45 min). Top: found isotope pattern, bottom: calculated isotope pattern. The mass spectrum shows the overlap of species **15** and **16**.

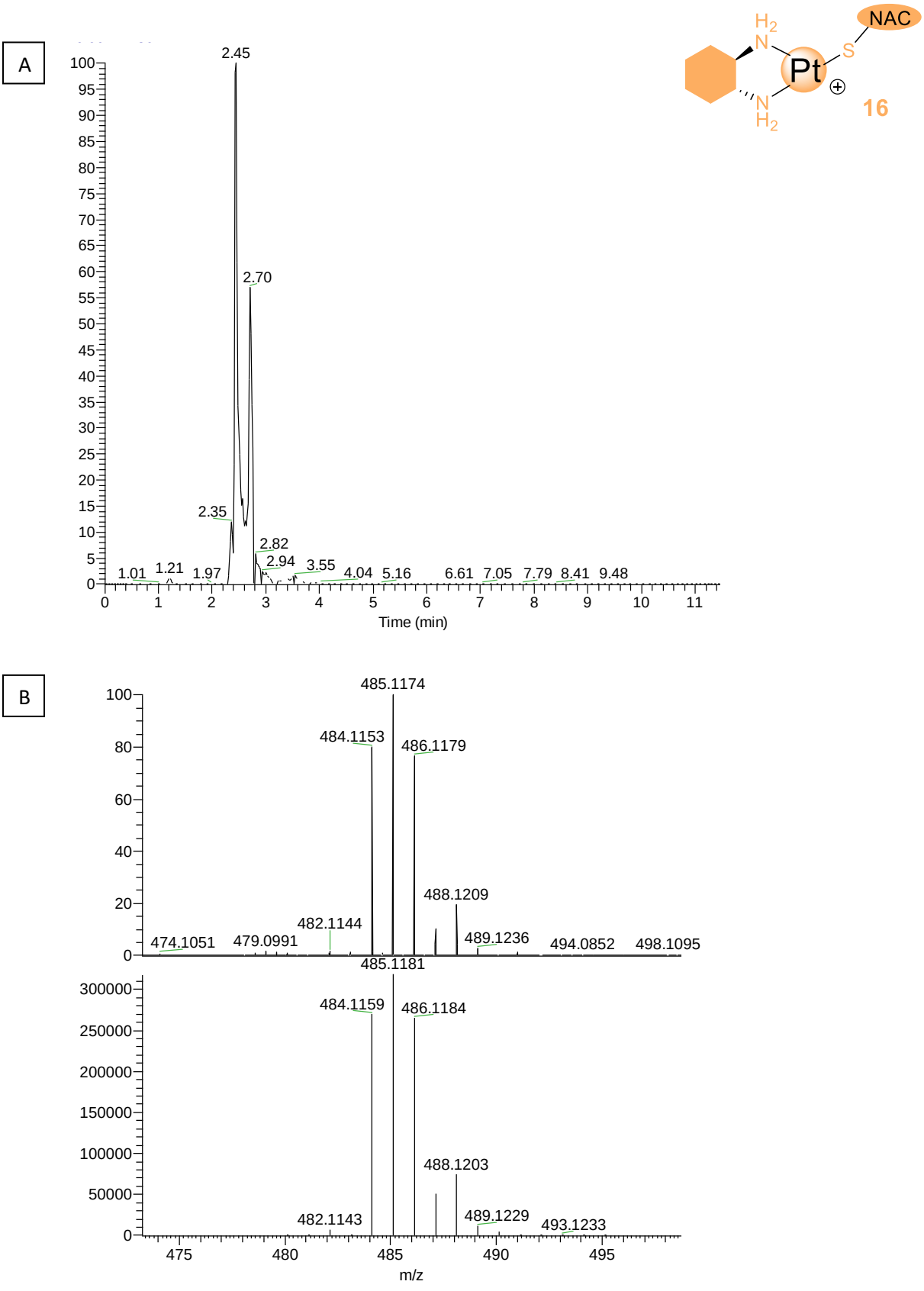
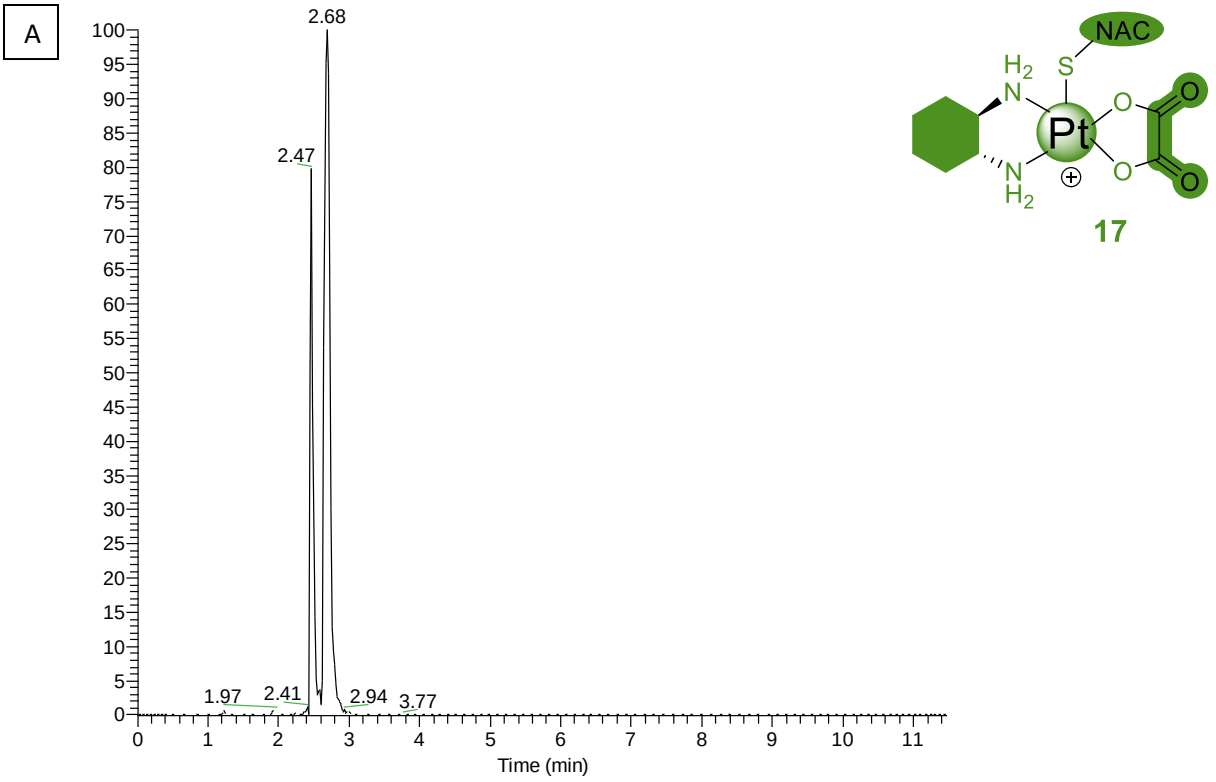


Fig. S32 LC-ESI-HRMS of **16**, calc. for $C_{12}H_{24}O_3N_3{}^{194}PtS$ $[M+H]^+$ = 484.1159, found 484.1153. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).



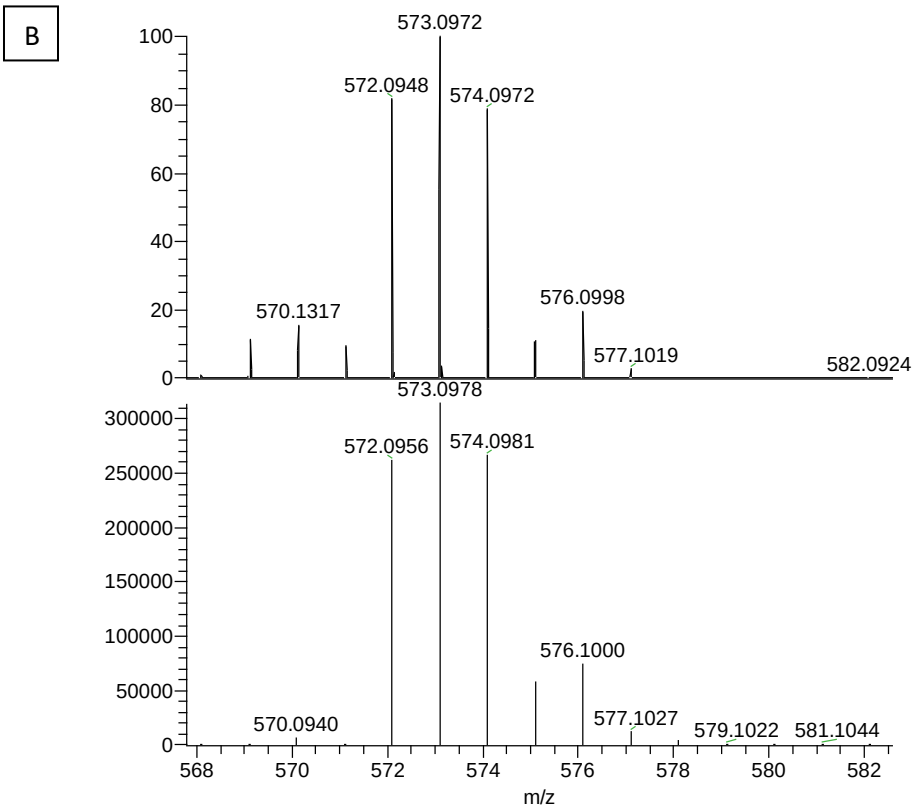


Fig. S33 LC-ESI-HRMS of **17**, calc. for $C_{14}H_{24}O_7N_3{}^{194}PtS$ $[M+H]^+$ = 572.0956, found 572.0948. A: TIC+ for calculated mass ± 5 ppm; B: found isotope pattern (top), calculated isotope pattern (bottom).

Reduction Experiment of complex 8 with ascorbic acid (UHPLC-HRMS; 1:10 dilution)

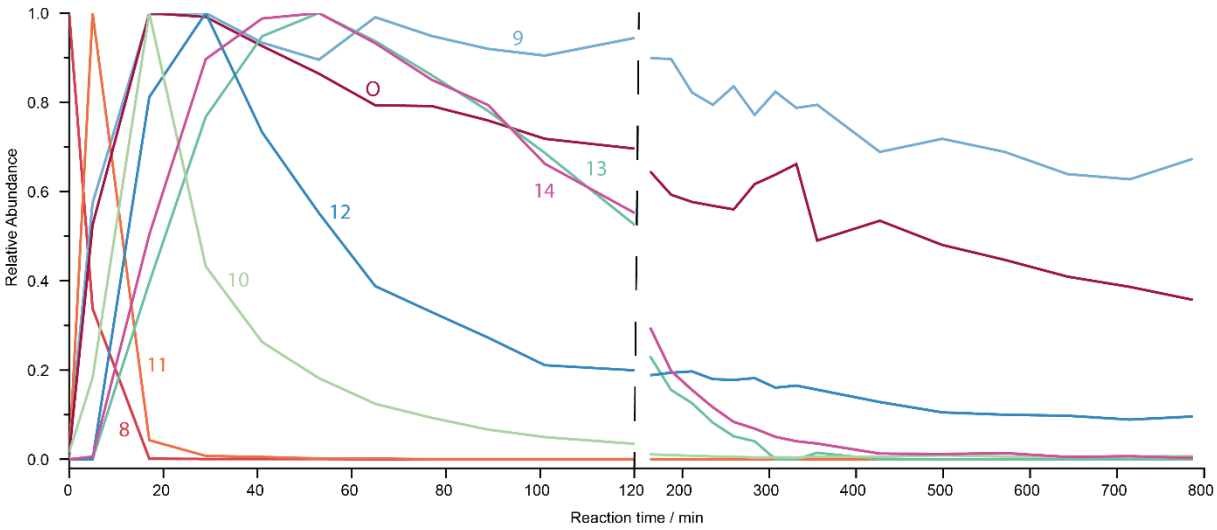


Fig. S34 Reduction experiment of **8** (0.3 mM) with 10-fold excess ascorbic acid (3 mM) in phosphate buffer (pH 7.4) at 37 °C in 1:10 dilution. Kinetic illustration of the relative abundance of the compounds mentioned in Fig. 3A. The dashed line marks different time intervals after 120 min.

References

1. D. A. Tolan, Y. K. Abdel-Monem and M. A. El-Nagar, *Appl. Organomet. Chem.*, 2019, **33**, e4763.