Unprecedented one-pot synthesis of an unsymmetrical cisplatin-based Pt(IV)-acetamidato complex.

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ELECTRONIC SUPPLEMENTARY INFORMATION

Content:

EXPERIMENTAL SECTION

General procedures. All chemicals (Johnson Matthey and Co. and Aldrich) were used without further purification. *Cis*-diamminedichloridoplatinum(II) (cisplatin) was synthesized according to the Dhara's method.[1] Elemental analyses were carried out with a EA3000 CHN Elemental Analyzer (EuroVector, Milano, Italy). Purity of compounds was assessed by analytical HPLC-MS and NMR. NMR spectra were measured on a Bruker Advance III NMR spectrometer operating at 500 MHz (^{1}H), 125.7 MHz (^{13}C) and 107.2 MHz (^{195}Pt), respectively. ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million (ppm) referenced to solvent resonances. ^{195}Pt NMR spectra were recorded using a solution of $K_2[PtCl_4]$ in saturated aqueous KCl as the external reference. The shift for $K_2[PtCl_4]$ was adjusted to -1628 ppm from $Na_2[PtCl_6]$ ($\delta = 0$ ppm). RP-HPLC and mass analysis were performed using a Waters HPLC-MS instrument equipped with Alliance 2695 separations module, 2487 dual lambda absorbance detector, and 3100 mass detector. Stationary phase: 5 μm Phenomenex Phenosphere Next C18 column, 250×46 mm ID. Mobile phase: flow rate = 0.5 mL min^{-1}, isocratic elution, eluent 15 mM HCOOH / CH_3OH 90/10. UV-visible detector set at 210 nm. Electrospray ionization mass spectra (ESI-MS) were obtained setting the source and desolvation temperatures to 150 °C and 250 °C, respectively, with nitrogen used both as a drying and a nebulizing gas. The cone and the capillary voltages were usually +30 V and 2.70 kV, respectively. Ion peaks were assigned on the basis of the *m/z* values and of the simulated isotope distribution patterns. IR spectra (KBr plates, 2 cm^{-1} resolution) were recorded on a Bruker FTIR Equinox 55 spectrometer in the range 4000–400 cm^{-1}.
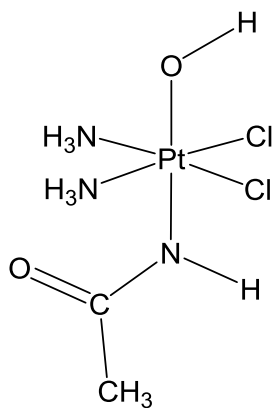
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Synthesis of cis,cis,trans [PtCl₂(NH₃)₂(OH)(CH₃CONH)], 1. A mixture of acetonitrile (10 mL) and of 50% H_2O_2 (1 mL) was stirred for 30 min at 25 °C. Cisplatin (0.33 mmol, 100 mg) was added to this mixture and the resulting suspension was stirred for 5 min. Methanol (5 mL) was then added and the reaction mixture was stirred at room temperature for 24 h. The resulting pale yellow precipitate was separated by centrifugation and was washed with diethyl ether. Yield: 76% (124 mg). ¹H NMR (d⁶-DMSO, 500 MHz): δ 1.90 (s, 3H, CH_3), 5.97 (m, 6H, NH_3) ppm. ¹³C NMR (d⁶-DMSO, 125.7 MHz): δ 25.9 (CH₃), 176.5 (CO) ppm. ¹⁹⁵Pt NMR (d⁶-DMSO, 107.2 MHz): δ 422 ppm. ESI-MS (positive ion mode): 376 *m/z* [M+H]⁺ calcd for $C_2H_{12}Cl_2N_3O_2Pt^+$ 376 *m/z*; 358 *m/z* [M-OH]⁺; 358 *m/z* calcd for $C_2H_{10}Cl_2N_3OPt^+$ [M-OH]⁺. Anal. Calcd for ($C_2H_{11}Cl_2N_3O_2Pt$): C 6.40, H 2.96, N 11.20; found: C 6.20, H 2.71, N 10.98.
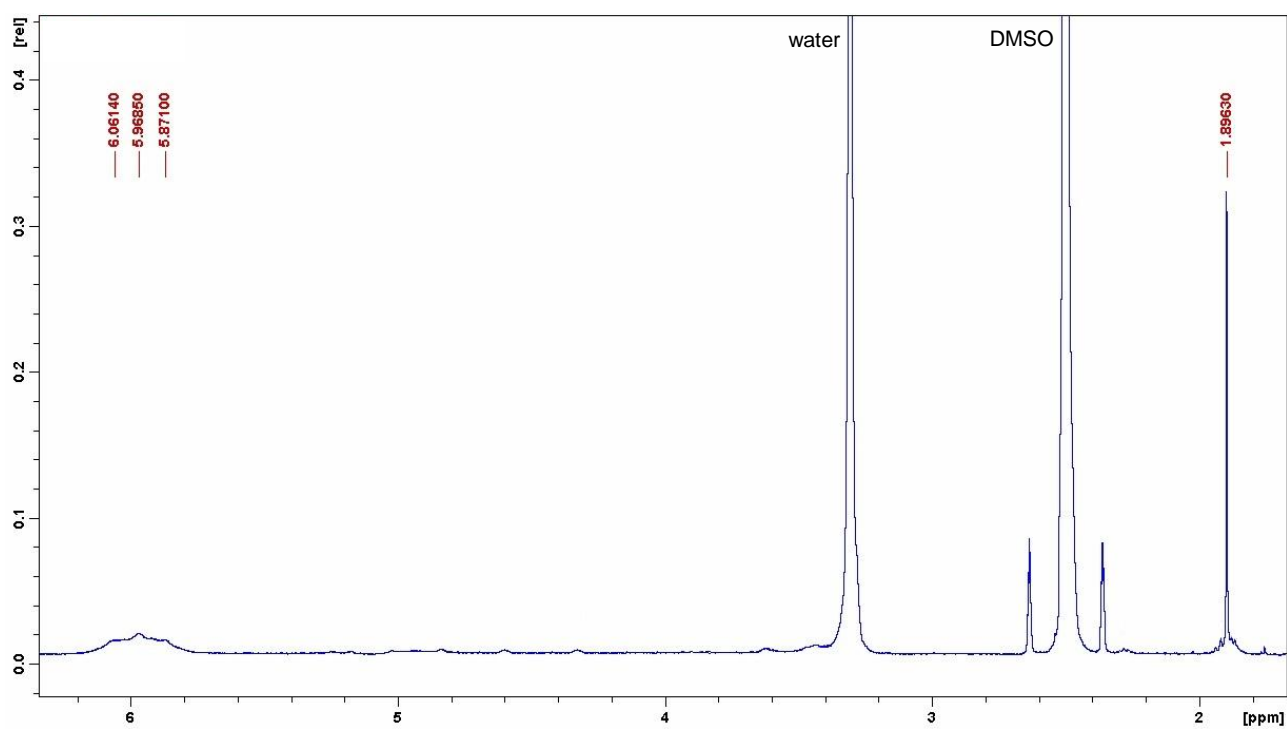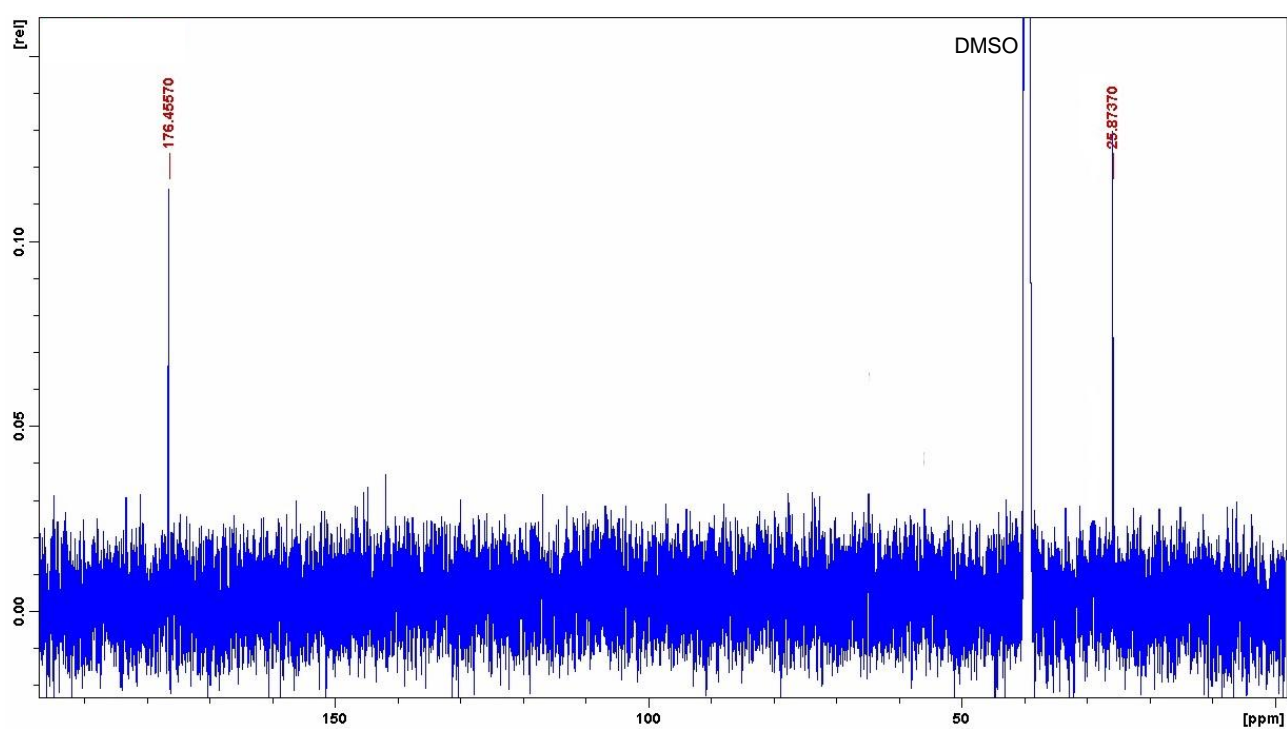
Figure S1. ^{1}H NMR spectrum of **1** in d[6]-DMSO.
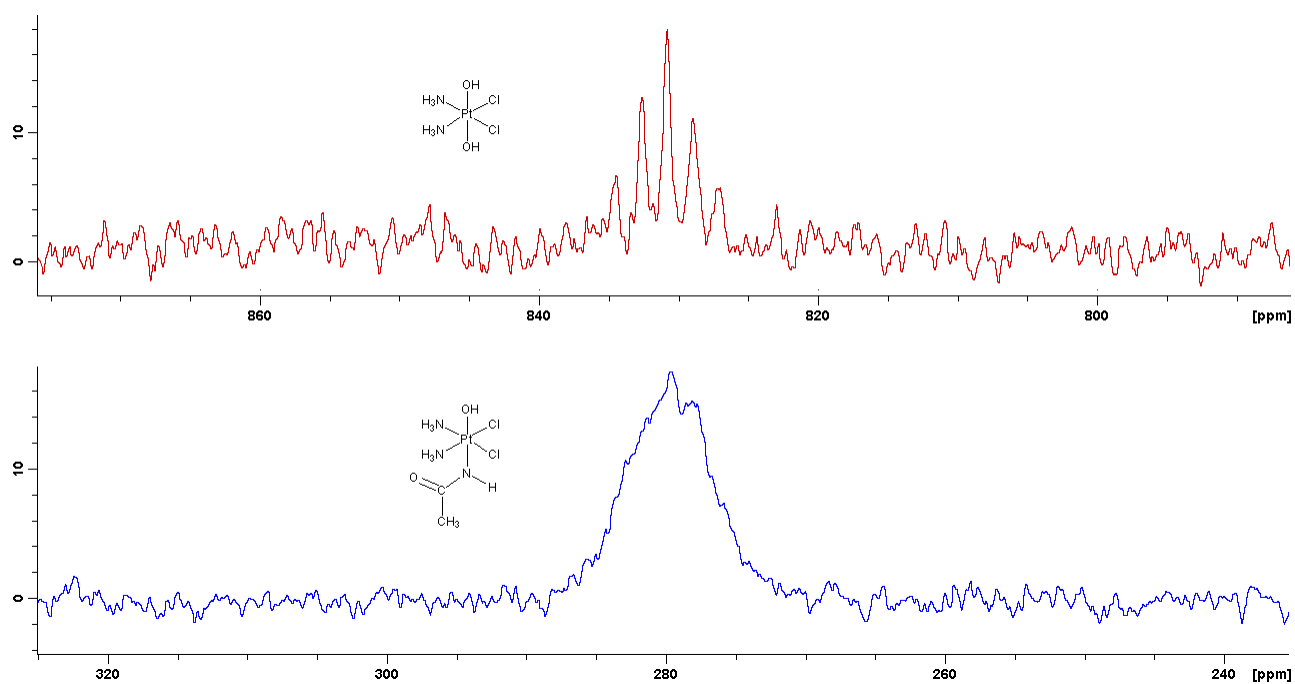

Figure S2. ^{13}C NMR spectrum of **1** in d[6]-DMSO.

Figure S3. $^{195}Pt\{^{1}H\}$ NMR spectrum of **1** (bottom) in d^{6}-DMSO. The spectrum of *cis,cis,trans-*[PtCl$_2$(NH$_3$)$_2$(OH)$_2$] in the same solvent (top) is added for comparison purposes.
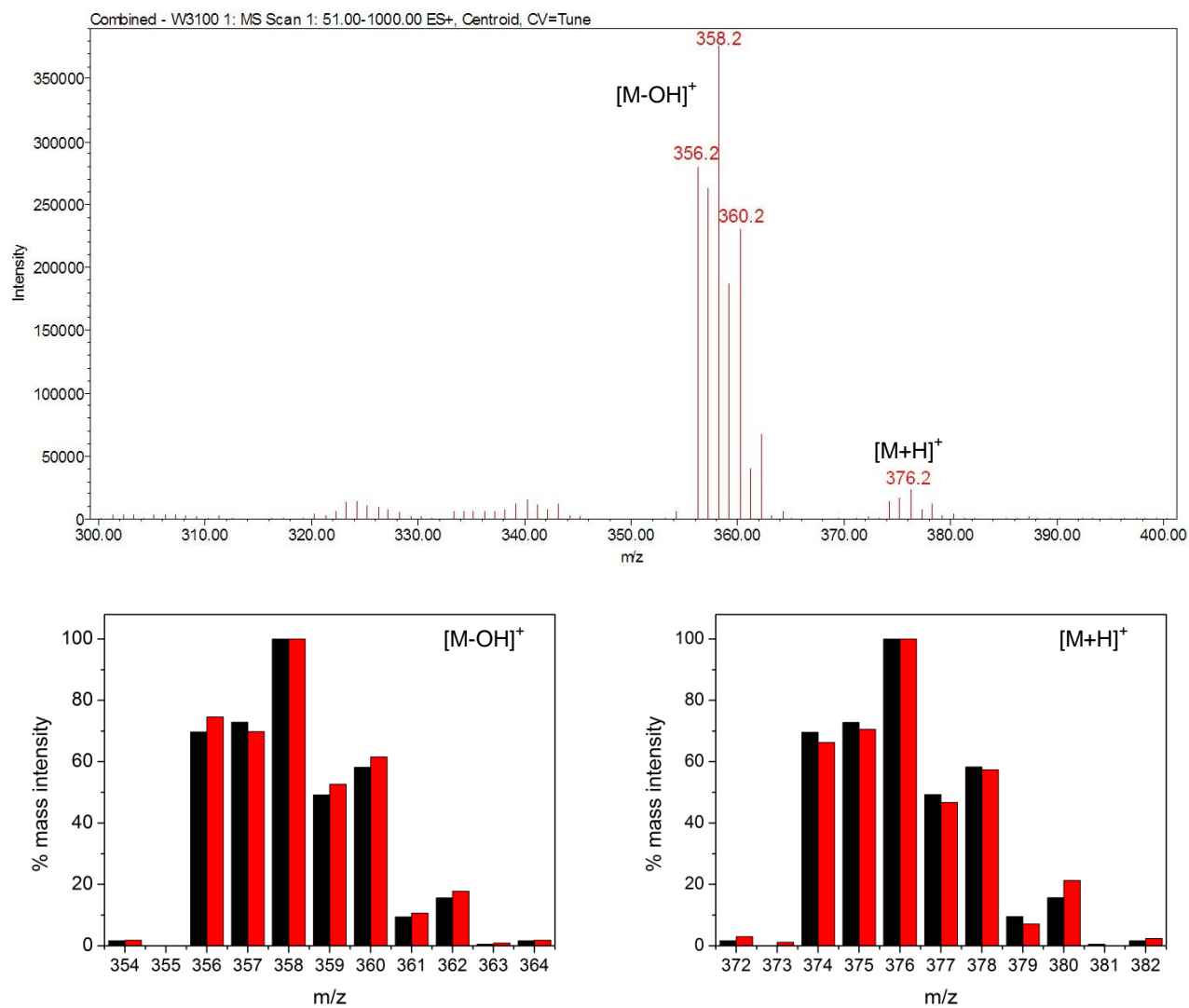
Figure S4. ESI-MS spectrum of **1** (top) and isotope pattern simulation of the two relevant peaks [M-OH]$^+$ (bottom left) and [M+H]$^+$ (bottom right). The black and the red columns represent the simulated and the experimental patterns, respectively.

X-ray structure. Suitable crystals were grown by slow evaporation of a water solution of complex **1**. A single crystal, of size 0.4×0.4×0.3 mm, was mounted on top of a glass fiber and used for X-ray diffraction data collection on a SMART APEX2 diffractometer [λ(Mo-Ka) = 0.71073 Å]. The crystal is triclinic, space group $P\bar{1}$, cell parameters of a = 7.103(1), b = 9.028(1), c = 13.105(2) Å, a = 90.17(2)°, β = 94.67(2)°, γ = 90.44(2)°, V = 837.5(2) Å^3. The asymmetric unit is formed by two independent molecules of formula $C_2H_{11}Cl_2N_3O_2Pt$, M = 375.12 Da, Z = 4, D_c = 2.98 g cm^{-3}, μ = 17.34 mm^{-1}, F(000) =688. A semi-empirical absorption correction, based on multiple scanned equivalent reflections, has been carried out and gave 0.2205 < T < 0.7460). A total of 13393 reflections were collected up to a θ range of 25.24° (±10 h, ±12 k, ±18 l), 4956 unique reflections (R_{int} = 0.085). The SAINT software was used for integration of reflection intensity and scaling, SADABS for absorption correction.[2] Structures were solved by direct methods using SIR97[3] and refined by full-matrix least-squares on all F^2 using SHELXL97[4] implemented in the WinGX package.[5] All the non-hydrogen atoms in the molecules were refined anisotropically. The hydrogen atoms were partly found and partly placed in the ideal positions using riding models. CCDC 1049243 contains the supplementary crystallographic data (see also the attached CIF file). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. A summary of the crystal data, structure solution and refinement parameters are given in Table S1.

Table S1. Crystal data and structure refinement for complex **1**.

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Chemical formula	$C_2H_{11}Cl_2N_3O_2Pt_1$
Formula Mass	375.12
Crystal system	Triclinic
a/Å	7.103(1)
b/Å	9.028(1)
c/Å	13.105(2)
α/°	90.17(2)
β/°	94.67(2)
γ/°	90.44(2)
Unit cell volume/Å^3	837.5(2)
Temperature/K	293(2)
Space group	$P\bar{1}$
No. of formula units per unit cell, Z	4
Radiation type	MoKα
Absorption coefficient, μ/mm^{-1}	17.341
No. of reflections measured	13393
No. of independent reflections	4956
R_{int}	0.085
Final R_1 values ($I > 2\sigma(I)$)	0.0483
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1149
Final R_1 values (all data)	0.0664
Final $wR(F^2)$ values (all data)	0.1252
Goodness of fit on F^2	1.040
CCDC number	CCDC 1049243
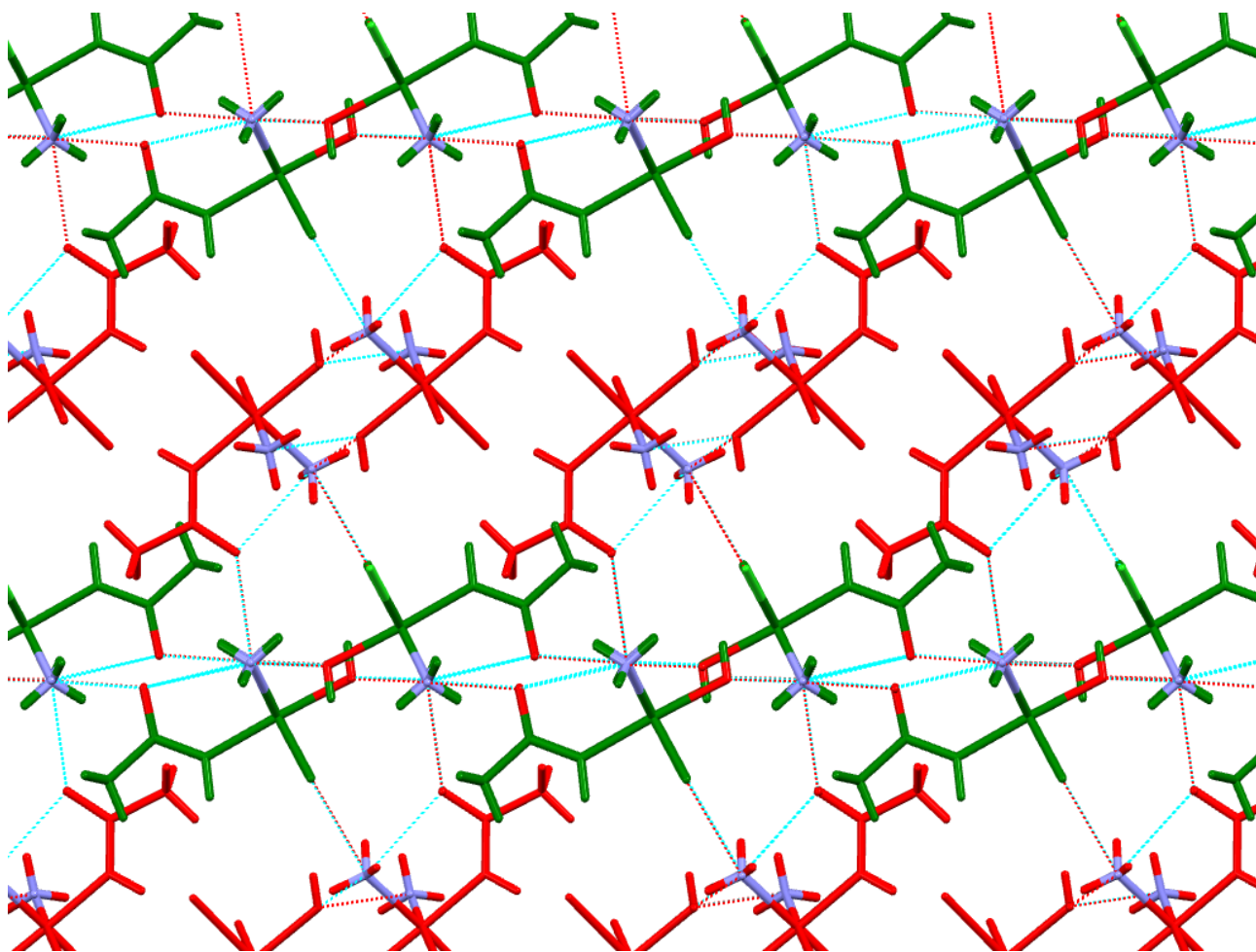
Figure S5. Crystal packing of **1** showing the two independent molecules (differently colored) constituting the asymmetric unit.
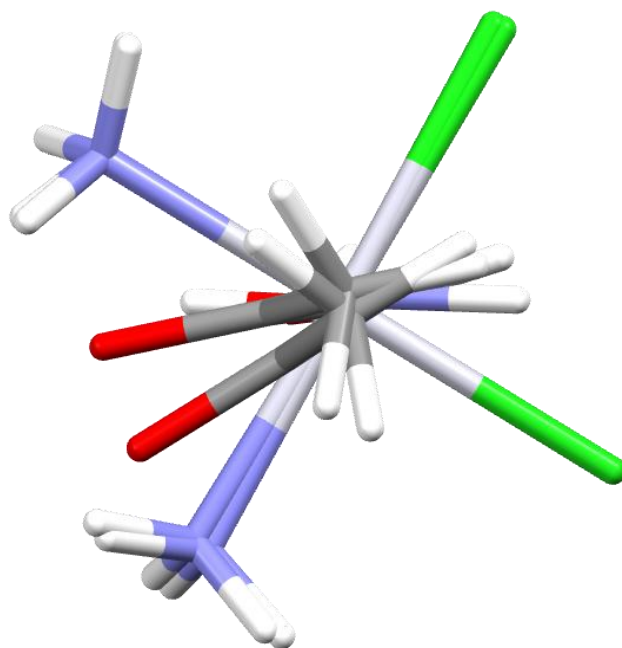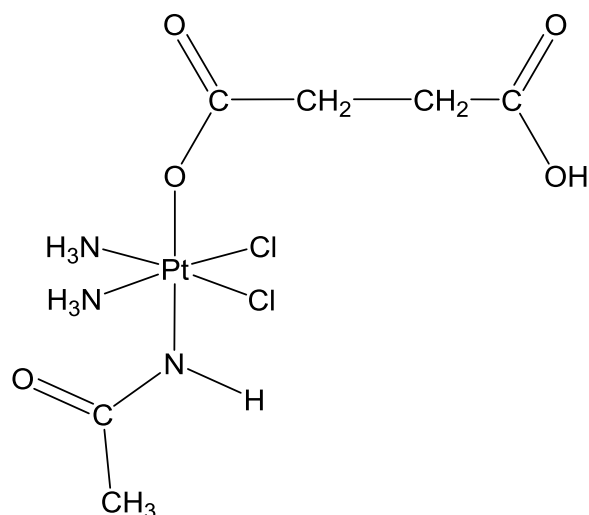
Figure S6. Overlap of the two independent molecules highlighting the different orientation of the

acetamidato ligand.

2

Synthesis of cis,cis,trans [PtCl₂(NH₃)₂(HOOC(CH₂)₂COO)(CH₃CONH)], **2**. Complex **1** (0.266 mmol, 100 mg) was suspended in DMF (10 mL) at 50 °C. After 5 min succinic anhydride (2.66 mmol, 266 mg) was added. The reaction mixture was stirred at 50 °C until complete dissolution of the suspended solid (about 3 h). The solution was then filtered, the solvent removed under reduced pressure and the residue triturated with diethyl ether. Yield: 91 mg (72%). ^{1}H NMR (d^6-DMSO, 500 MHz): δ 1.93 (s, 3H, Pt-NH=CO-C*H*₃), 2.38 (m, 2H, Pt-O-CO-CH₂-C*H*₂-COOH), 2.42 (m, 2H, Pt-O-CO-C*H*₂-CH₂-COOH), 5.16 (s, 1H, Pt-N*H*=CO-CH₃), 6.46 (m, 6H, N*H*₃) ppm. ^{13}C NMR (d^6-DMSO, 125.7 MHz): δ 25.1 (Pt-NH=CO-*C*H₃), 30.1 (Pt-O-CO-CH₂-*C*H₂-COOH), 31.4 (Pt-O-CO-*C*H₂-CH₂-COOH), 174.0 (Pt-O-CO-CH₂-CH₂-*C*OOH), 175.5 (Pt-NH=*C*O-CH₃), 179.6 (Pt-O-*C*O-CH₂-CH₂-COOH) ppm. ^{195}Pt NMR (d^6-DMSO, 107.2 MHz): δ 494 ppm. ESI-MS (positive ion mode): 476.3 *m/z* [M+H]$^+$; calcd for C₆H₁₆Cl₂N₃O₅Pt 475.20 *m/z* [M+H]$^+$.
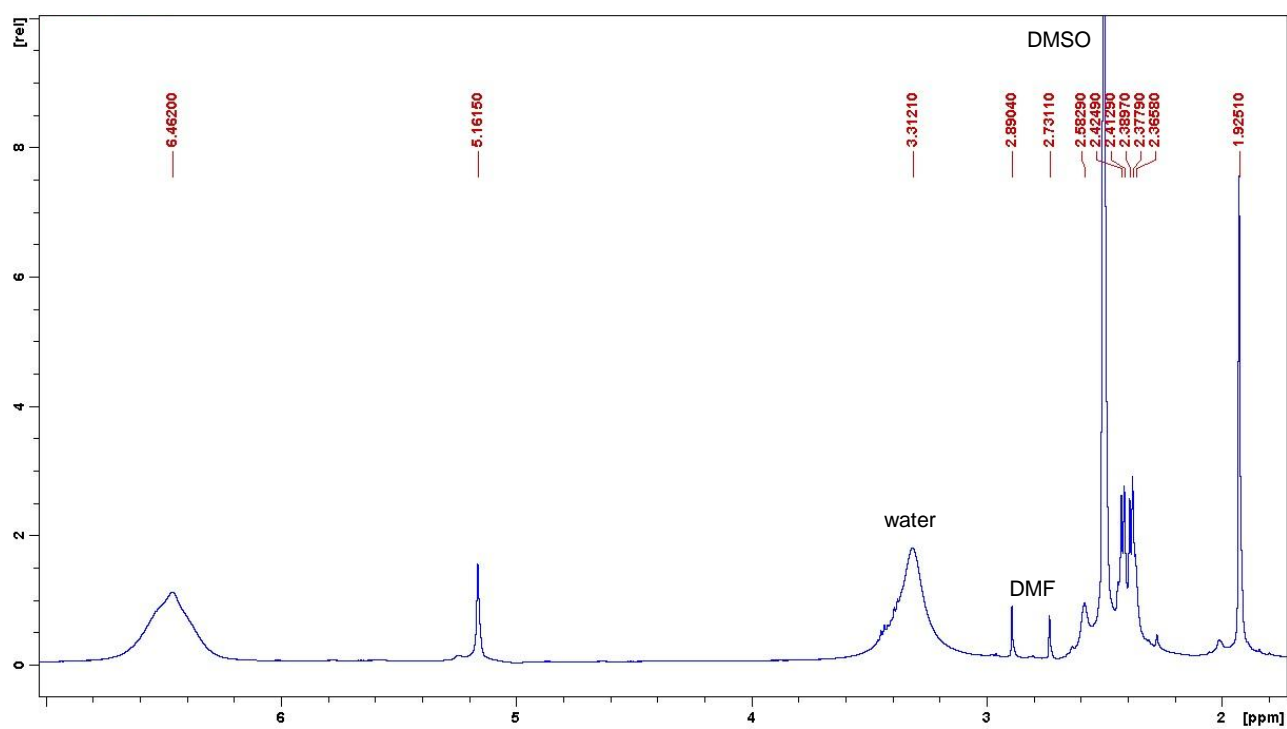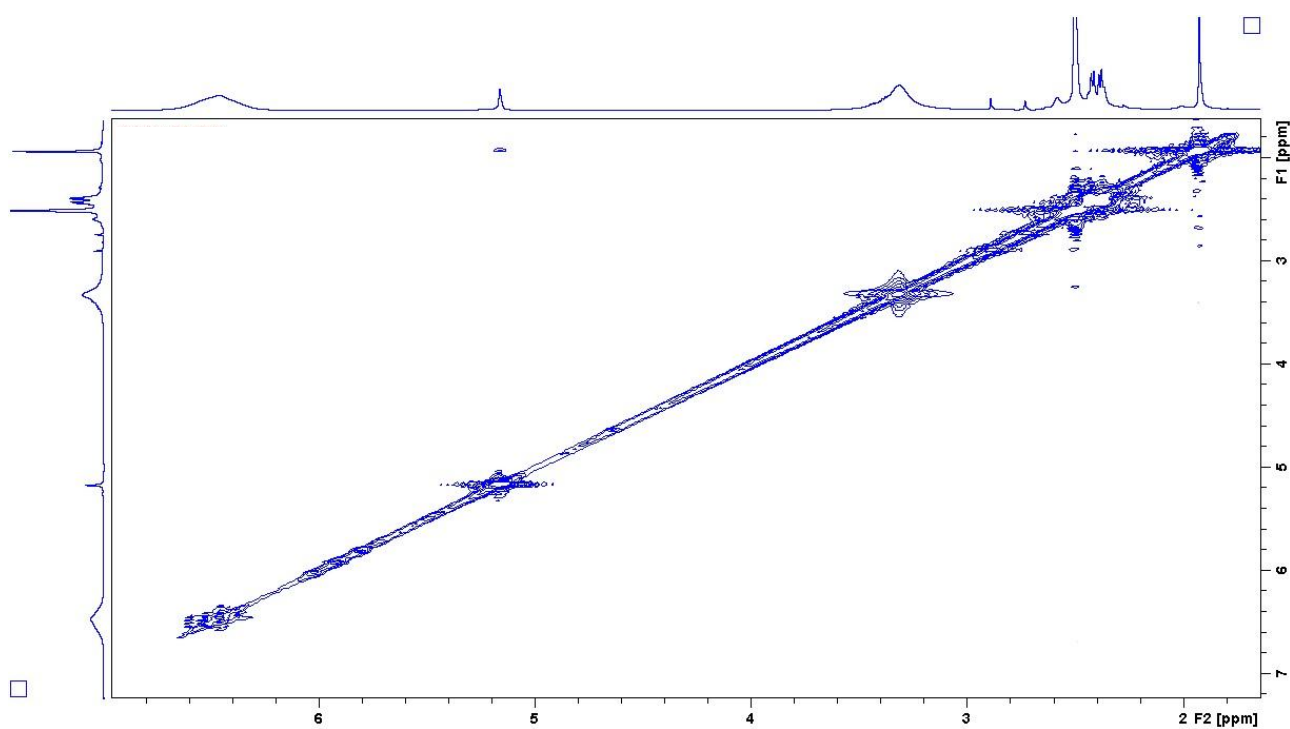
Figure S7. ^{1}H NMR spectrum of **2** in d^6-DMSO.
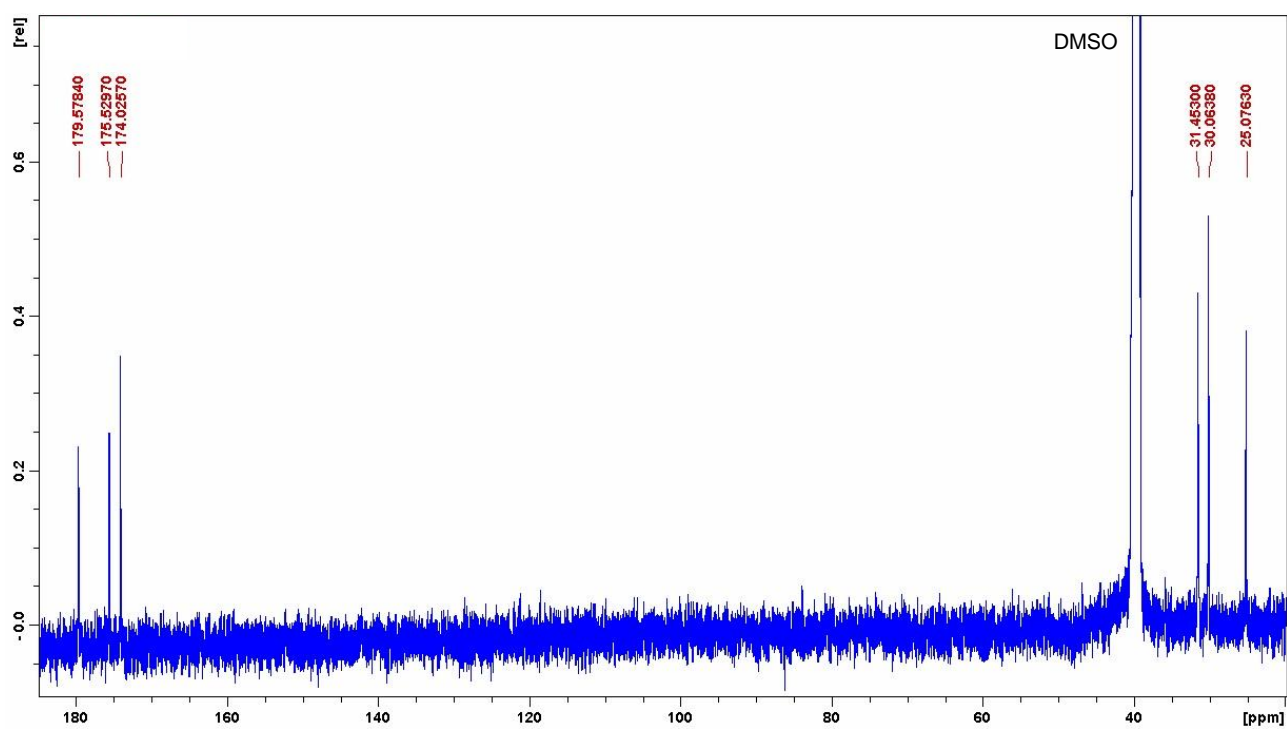

Figure S8. COSY NMR spectrum of **2** in d^6-DMSO.

Figure S9. ^{13}C NMR spectrum of **2** in d^6-DMSO.
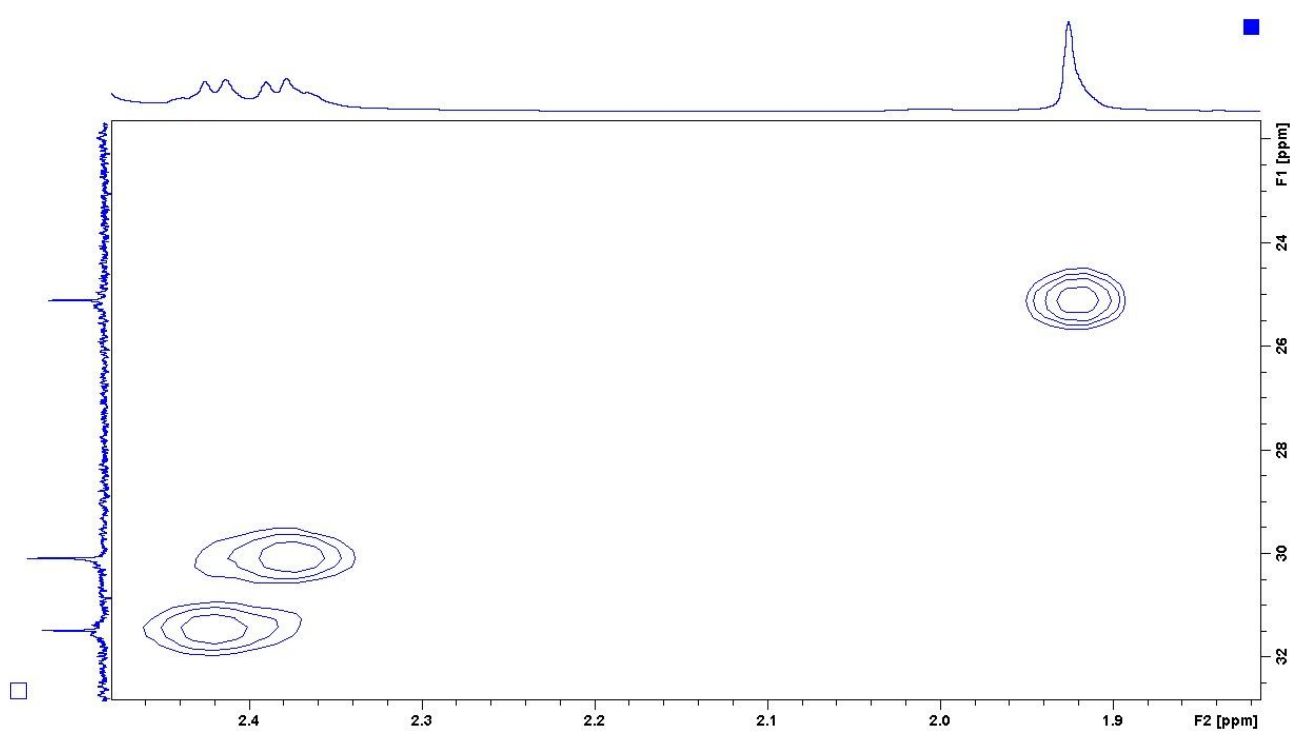
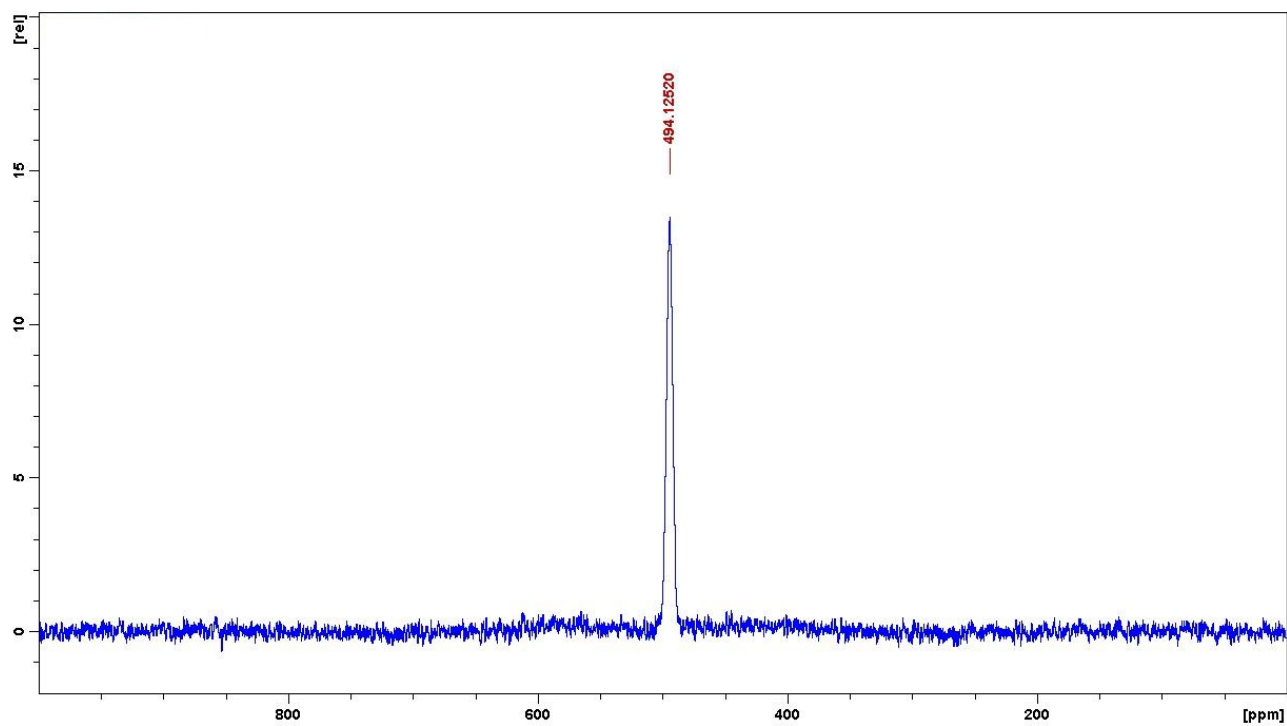**Figure S10.** ^{1}H-^{13}C HSQC NMR spectrum of **2** in d^6-DMSO.

Figure S11. ^{195}Pt$\{^1$H$\}$ NMR spectrum of **2** in d^6-DMSO.
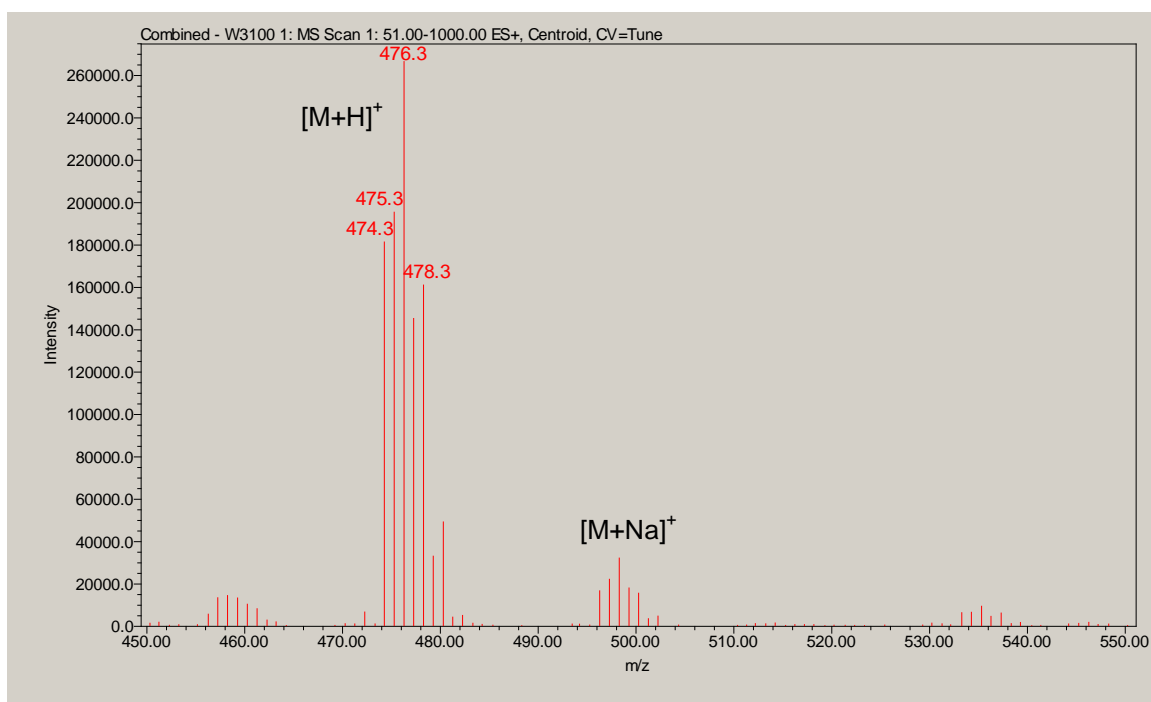

Figure S12. ESI-MS spectrum of **2**.

REFERENCES

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2   (*a*) SAINT: SAX, Area Detector Integration, Siemens Analytical Instruments Inc., Madison, Wisconsin, USA; (*b*) G. Sheldrick, SADABS: Siemens Area Detector Absorption Correction Software, University of Goettingen, Germany, 1996.

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