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Supplementary Information for

Ligand substitution reactions afford oxaliplatin-based platinum(IV) complexes bearing axial alkoxido ligands

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Experimental procedures

Reagents and instruments

Unless stated otherwise, all chemicals were bought from commercial suppliers and used as received without further purification and dilution. All reactions were carried out under atmospheric pressure with protection from light by aluminum foil. ^{1}H, ^{13}C{^{1}H}, ^{19}F, and ^{195}Pt NMR spectra were recorded using a Bruker AVANCE III 300 MHz, a Bruker AVANCE NEO 400 MHz NMR spectrometer, a Bruker AVANCE III HD 500 MHz NMR spectrometer or a Bruker Ascend AVANCE III HD 600 MHz NMR spectrometer at room temperature. Chemical shifts (δ) were reported in parts per million (ppm) and referenced as described below. ^{1}H and ^{13}C{^{1}H} NMR spectra were referenced internally to residual solvent peaks, deuterated water (D_2O), deuterated methanol (CD_3OD), deuterated ethanol (CD_3CD_2OD) or deuterated dimethyl sulfoxide (DMSO-d_6) were used as solvents. ^{19}F NMR spectra were referenced externally using C_6F_6 (δ = -164.9 ppm vs. $CFCl_3$). ^{195}Pt NMR spectra were referenced externally using K_2PtCl_4 in D_2O (δ = -1628 ppm vs. Na_2PtCl_6). High-resolution mass spectrometry (HRMS) was carried out on a SCIEX X500R QTOF system. All the newly synthesized Pt(IV) complexes were purified by the Waters Alliance e2695 Seperations Module with a YMC-Pack Pro C18 RS column (5 µm, 80 Å, 250 x 10.0 mm, 3 mL/min flow). HPLC-MS was carried out to analyze the hydrolysis and reduction of Pt(IV) complexes, using an Agilent 1260-6125 + LC-MS System with a YMC J'sphere ODS-H80 column (4 µm, 80 Å, 100 x 2.0 mm, 0.3 mL/min flow) or a Phenomenex Kinetex C18 column (5 µm, 100 Å, 150 x 3.0 mm, 0.4 mL/min flow). The detectors were set at 254 nm and 365 nm.

Synthesis of platinum(IV) complexes

Synthesis of platinum(IV) complex 2. The platinum(IV) complex *t*-[Pt(DACH)(ox)(OAc)$_2$] **1** (100 mg, 0.19 mmol)[1] was suspended in 10 mL ethanol. Sodium ethoxide (NaOEt, 53 mg, 0.78 mmol) was then added to the mixture. The solution was stirred overnight at room temperature. After that, the white precipitate was collected by centrifugation and washed with 5 mL ethanol for twice. After drying in vacuum, the final product was obtained as a white solid.

***cis,trans* -[Pt(DACH)(OEt)$_2$(acetato)$_2$] (2).** Yield: 84%, 83 mg (0.16 mmol). ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.37 (q, *J* = 6.97 Hz, 4H), 2.58 (d, *J* = 9.11 Hz, 2H), 2.12 (d, *J* = 12.50 Hz, 2H), 2.03 (s, 6H), 1.55 (d, *J* = 9.03 Hz, 2H), 1.40 – 1.25 (m, 2H), 1.11 (t, *J* = 6.97 Hz, 8H). ^{13}C{^{1}H} NMR (75 MHz, Methanol-d_4) δ 182.1, 62.0, 61.1, 32.3, 24.0, 22.5, 16.5. ^{195}Pt NMR (129 MHz, Ethanol-d_6) δ 1825.8. ESI-MS: calcd for $C_{14}H_{29}N_2O_6Pt$ [M-H]$^-$: *m/z* 516.17; found: *m/z* 516.14.

Synthesis of platinum(IV) complexes 4a to 4e. The platinum(IV) complex *t*-[Pt(DACH)(ox)(TFA)$_2$] **3** (200 mg, 0.32 mmol)[2] was dissolved in 0.5 mL DMF. 1.5 mL alcohol [ethanol (**a**), isopropanol (**b**), 3-buten-1-ol (**c**), 3-butyn-1-ol (**d**), or benzyl alcohol (**e**)] was then added to the solution. After adding DIPEA (50 mg, 0.38 mmol), the solution was stirred overnight at room temperature. After purification by RP-HPLC and lyophilization, the final products were obtained as white solid.

***trans*-[Pt(DACH)(ox)(TFA)(OEt)] (4a).** Yield: 58%, 104 mg (0.19 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.79 (s, 1H), 7.48 (s, 1H), 7.21 (s, 1H), 3.31 – 3.15 (m, 2H), 2.44 (s, 2H), 2.04 (dd, *J* = 51.44, 12.53 Hz, 2H), 1.66 – 1.39 (m, 4H), 1.13 (t, *J* = 6.91 Hz, 3H), 1.05 (t, *J* = 10.46 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 164.6, 164.1, 161.2 (q, *J* = 36.86 Hz), 114.7 (q, *J* = 290.82 Hz), 65.0, 62.1, 61.1, 30.4, 29.7, 24.1, 24.0, 17.7. ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1361.1. ESI-HRMS: calcd for $C_{12}H_{20}F_3N_2O_7Pt$ [M+H]$^+$: *m/z* 556.0871; found: *m/z* 556.0838.

***trans*-[Pt(DACH)(ox)(TFA)(OiPr)] (4b).** Yield: 42%, 76 mg (0.13 mmol). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.78 (s, 1H), 7.36 (s, 1H), 6.89 (s, 1H), 3.33 – 3.23 (m, 1H), 2.46 (s, 5H), 2.06 (dd, *J* = 72.71, 13.05 Hz, 4H), 1.64 – 1.42 (m, 4H), 1.13 (d, *J* = 6.06 Hz, 3H), 1.07 (d, *J* = 6.00 Hz, 3H), 1.05 (t, *J* = 11.49 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 164.6, 164.3, 161.2 (q, *J* = 36.24 Hz), 114.6 (q, *J* = 291.43 Hz), 70.4, 62.2, 61.0, 30.5, 29.7, 25.7, 25.6, 24.1, 24.0. ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.8. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1384.1. ESI-HRMS: calcd for $C_{13}H_{22}F_3N_2O_7Pt$ [M+H]$^+$: *m/z* 570.1027; found: *m/z* 570.1056.

***trans*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$CH=CH$_2$)] (4c).** Yield: 50%, 93 mg (0.16 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.82 (s, 1H), 7.48 (s, 1H), 7.20 (s, 1H), 5.99 – 5.67 (m, 1H), 5.01 (d, *J* = 17.07 Hz, 1H), 4.94 (d, *J* = 10.36 Hz, 1H), 3.29 – 3.14 (m, 2H), 2.44 (s, 2H), 2.30 (q, *J* = 7.17 Hz, 2H), 2.05 (dd, *J* = 52.18, 12.54 Hz, 2H), 1.62 – 1.48 (m, 4H), 1.05 (t, *J* = 10.34 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 164.6, 164.1, 161.2 (q, *J* = 37.03 Hz), 136.9, 116.0, 114.6 (q, *J* = 290.60 Hz), 69.7, 62.1, 61.1, 36.6, 30.4, 29.7, 24.1, 24.0. ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1362.2. ESI-HRMS: calcd for $C_{14}H_{22}F_3N_2O_7Pt$ [M+H]$^+$: *m/z* 582.1027; found: *m/z* 582.1051.

***trans*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$C≡CH)] (4d).** Yield: 47%, 87 mg (0.15 mmol). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.85 (s, 1H), 7.56 (s, 1H), 7.26 (s, 1H), 3.19 (t, *J* = 7.79 Hz, 2H), 2.75 (t, *J* = 2.68 Hz, 1H), 2.44 (s, 2H), 2.41 – 2.37 (m,

2H), 2.12 – 1.95 (m, 2H), 1.67 – 1.40 (m, 4H), 1.08 – 1.03 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 164.5, 163.9, 161.2 (q, *J* = 36.76 Hz), 114.6 (q, *J* = 290.71 Hz), 82.7, 72.3, 68.8, 62.1, 61.1, 30.4, 29.7, 24.1, 24.0, 21.6. ^{19}F NMR (471 MHz, DMSO-d_6) δ -73.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1374.6. ESI-HRMS: calcd for $C_{14}H_{20}F_3N_2O_7Pt$ $[M+H]^+$: *m/z* 580.0871; found: *m/z* 580.0921.

***trans*-[Pt(DACH)(ox)(TFA)(OBn)] (4e).** Yield: 46%, 91 mg (0.15 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, *J* = 8.49 Hz, 1H), 7.90 (s, 1H), 7.60 (d, *J* = 8.45 Hz, 1H), 7.40 (d, *J* = 7.22 Hz, 2H), 7.36 (s, 1H), 7.28 (t, *J* = 7.34 Hz, 2H), 7.20 (t, *J* = 7.25 Hz, 1H), 4.47 (dd, *J* = 88.98, 11.52 Hz, 1H), 2.44 (s, 2H), 2.16 – 1.99 (m, 2H), 1.65 – 1.48 (m, 4H), 1.07 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 164.6, 164.0, 161.2 (q, *J* = 36.24 Hz), 141.3, 128.2, 128.0, 126.9, 114.6 (q, *J* = 290.55 Hz), 71.6, 62.1, 61.3, 30.5, 29.8, 24.1, 24.0. ^{19}F NMR (377 MHz, DMSO-d_6) δ -73.6. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1357.6. ESI-HRMS: calcd for $C_{17}H_{22}F_3N_2O_7Pt$ $[M+H]^+$: *m/z* 618.1027; found: *m/z* 618.1003.

Synthesis of platinum(IV) complexes 4a', 4c', and 4e'. The NHS ester of 4-pentenoic acid (100 mg, 0.51 mmol)[3] and *t*-[Pt(DACH)(ox)$(OH)_2$] (328 mg, 0.76 mmol) were dissolved in 4 mL DMSO. The mixture was stirred overnight at room temperature. After that, the unreacted platinum(IV) complex was removed by centrifuge. The supernatant was added to Et_2O (40 mL) to induce precipitate. The precipitate was collected and washed with E_2O (40 mL) for twice. After drying in vacuum, the *t*-[Pt(DACH)(ox)$(OOCCH_2CH{=}CH_2)(OH)$] (217 mg, 0.43 mmol) was obtained and directly used in the next step without any purification.

The platinum(IV) complexes (0.20 mmol), which is 105 mg *t*-[Pt(DACH)(ox)(OAc)(OH)],[4] 100 mg *t*-[Pt(DACH)(ox)$(OOCCH_2CH{=}CH_2)(OH)$] or 107 mg *t*-[Pt(DACH)(ox)(benzoato)(OH)],[4] were added to 4 mL mixture of trifluoroacetic anhydride and DCM (v/v, 1:1). The solution was stirred at room temperature for 30 min. After that, 40 mL Et_2O was added to the reaction. The precipitate was collected by centrifuge and washed with E_2O (40 mL) for twice. After purification by RP-HPLC and lyophilization, the desired products were obtained as white solid (Scheme S1).

***trans*-[Pt(DACH)(ox)(TFA)(OAc)] (4a').** Yield: 84%, 96 mg (0.17 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 2H), 8.16 (s, 1H), 7.81 (s, 1H), 2.61 (s, 2H), 2.11 (d, *J* = 11.49 Hz, 2H), 1.98 (s, 3H), 1.50 (s, 4H), 1.34 – 0.95 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 178.3, 164.0, 161.6 (q, *J* = 37.37 Hz), 113.3 (q, *J* = 290.88 Hz), 61.6, 61.1, 31.2, 31.1, 24.1, 24.0, 23.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.3. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1643.6. ESI-HRMS: calcd for $C_{12}H_{18}F_3N_2O_8Pt$ $[M+H]^+$: *m/z* 570.0663; found: *m/z* 570.0637.

***trans*-[Pt(DACH)(ox)(TFA)(OOCCH$_2$CH=CH$_2$)] (4c').** Yield: 65%, 77 mg (0.13 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 2H), 8.29 (s, 1H), 7.84 (s, 1H), 6.80 – 6.60 (m, 1H), 5.83 (dd, *J* = 15.42, 1.71 Hz, 1H), 5.18 – 4.95 (m, 1H), 2.60 (s, 2H), 2.10 (d, *J* = 11.62 Hz, 2H), 1.81 (dd, *J* = 6.87, 1.62 Hz, 2H), 1.50 (s, 4H), 1.14 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 173.5, 164.0, 163.9, 161.6 (q, *J* = 38.18 Hz), 143.2, 124.4, 113.3 (q, *J* = 290.37 Hz), 61.9, 61.1, 31.2, 31.1, 24.1, 24.0, 17.7. ^{19}F NMR (565 MHz, DMSO-d_6) δ -73.2. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1632.0. ESI-HRMS: calcd for $C_{14}H_{20}F_3N_2O_8Pt$ $[M+H]^+$: *m/z* 596.0820; found: *m/z* 596.0789.

***trans*-[Pt(DACH)(ox)(TFA)(benzoato)] (4e').** Yield: 89%, 113 mg (0.18 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 2H), 8.14 (s, 1H), 7.90 (s, 1H), 7.86 (d, *J* = 7.09 Hz, 2H), 7.57 (t, *J* = 7.37 Hz, 1H), 7.45 (t, *J* = 7.60 Hz, 2H), 2.67 (s, 2H), 2.14 (s, 2H), 1.73 – 1.41 (m, 4H), 1.17 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 172.7, 164.2, 161.6 (q, *J* = 38.01 Hz), 132.7, 132.4, 129.9, 128.7, 113.3 (q, *J* = 290.31 Hz), 61.7, 61.4, 31.2, 24.1. ^{19}F NMR (565 MHz, DMSO-d_6) δ -73.2. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1642.2. ESI-HRMS: calcd for $C_{17}H_{20}F_3N_2O_8Pt$ $[M+H]^+$: *m/z* 632.0820; found: *m/z* 632.0854.

Synthesis of platinum(IV) complexes 5a to 5e. The platinum(IV) complex *t*-[Pt(DACH)(ox)(TFA)(benzoato)] **4e'** (200 mg, 0.32 mmol) was dissolved in 0.5 mL DMF. 1.5 mL alcohol [ethanol (**a**), isopropanol (**b**), 3-buten-1-ol (**c**), 3-butyn-1-ol (**d**), or benzyl alcohol (**e**)] was then added to the solution. After adding DBU (58 mg, 0.38 mmol), the solution was stirred overnight at room temperature. After purification by RP-HPLC and lyophilization, the final products were obtained as a white solid.

***trans*-[Pt(DACH)(ox)(benzoato)(OEt)] (5a).** Yield: 53%, 94 mg (0.17 mmol). ^1H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.25 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 7.11 Hz, 2H), 7.52 (t, *J* = 7.36 Hz, 1H), 7.42 (t, *J* = 7.62 Hz, 2H), 7.01 (s, 1H), 3.16 – 3.02 (m, 2H), 2.62 (s, 2H), 2.10 (dd, *J* = 51.82, 12.09 Hz, 2H), 1.61 – 1.35 (m, 4H), 1.17 – 1.09 (m, 5H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.8, 164.2, 164.2, 134.7, 132.3, 129.7, 128.5, 64.6, 62.2, 60.2, 31.4, 31.0, 24.1, 16.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1384.6. ESI-HRMS: calcd for $C_{17}H_{25}N_2O_7Pt$ $[M+H]^+$: *m/z* 564.1310; found: *m/z* 564.1285.

***trans*-[Pt(DACH)(ox)(benzoato)(OiPr)] (5b).** Yield: 31%, 57 mg (0.10 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.29 (s, 1H), 7.81 (d, *J* = 7.18 Hz, 2H), 7.72 (s, 1H), 7.52 (t, *J* = 7.35 Hz, 1H), 7.42 (t, *J* = 7.56 Hz, 2H), 6.75 (s, 1H), 2.93 (td, *J* = 13.13, 12.53, 6.48 Hz, 1H), 2.64 (s, 2H), 2.23 – 2.00 (m, 2H), 1.60 – 1.37 (m, 4H), 1.22 – 1.10 (m, 2H), 1.08 (d, *J* = 6.04

Hz, 3H), 1.03 (d, *J* = 5.97 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 175.0, 164.4, 164.3, 134.7, 132.4, 129.7, 128.5, 69.9, 62.3, 60.3, 31.5, 31.0, 26.2, 25.9, 24.1. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1432.2. ESI-HRMS: calcd for $C_{18}H_{27}N_2O_7Pt$ $[M+H]^+$: *m/z* 578.1466; found: *m/z* 578.1493.

***trans*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2CH=CH_2$)] (5c).** Yield: 46%, 86 mg (0.14 mmol). ^1H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.27 (s, 1H), 7.87 (s, 1H), 7.83 (d, *J* = 7.01 Hz, 2H), 7.52 (t, *J* = 7.36 Hz, 1H), 7.42 (t, *J* = 7.51 Hz, 2H), 6.98 (s, 1H), 5.81 (ddt, *J* = 17.09, 10.20, 6.85 Hz, 1H), 5.05 – 4.90 (m, 2H), 3.09 (td, *J* = 7.17, 2.62 Hz, 2H), 2.64 (s, 2H), 2.29 (q, *J* = 6.97 Hz, 2H), 2.10 (dd, *J* = 33.88, 11.25 Hz, 2H), 1.51 (s, 4H), 1.14 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.7, 164.2, 164.1, 136.7, 134.6, 132.3, 129.7, 128.5, 116.4, 69.1, 62.1, 60.3, 35.5, 31.4, 31.0, 24.1. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1385.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1385.7. ESI-HRMS: calcd for $C_{19}H_{27}N_2O_7Pt$ $[M+H]^+$: *m/z* 590.1466; found: *m/z* 590.1435.

***trans*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2C\equiv CH$)] (5d).** Yield: 44%, 81 mg (0.14 mmol). ^1H NMR (600 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 7.83 (d, *J* = 6.99 Hz, 2H), 7.52 (t, *J* = 7.38 Hz, 1H), 7.42 (t, *J* = 7.69 Hz, 2H), 7.03 (s, 1H), 3.10 (t, *J* = 7.47 Hz, 2H), 2.80 (t, *J* = 2.64 Hz, 1H), 2.66 (s, 2H), 2.40 (td, *J* = 7.44, 2.62 Hz, 2H), 2.10 (dd, *J* = 43.12, 11.54 Hz, 2H), 1.58 – 1.39 (m, 4H), 1.20 – 1.06 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.6, 164.1, 164.0, 134.5, 132.3, 129.7, 128.5, 82.7, 72.4, 68.0, 62.1, 60.2, 31.4, 31.0, 24.1, 20.3. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1403.2. ESI-HRMS: calcd for $C_{19}H_{25}N_2O_7Pt$ $[M+H]^+$: *m/z* 588.1310; found: *m/z* 588.1329.

***trans*-[Pt(DACH)(ox)(benzoato)(OBn)] (5e).** Yield: 39%, 77 mg (0.12 mmol). ^1H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.35 (s, 1H), 8.04 (s, 1H), 7.86 (d, *J* = 7.02 Hz, 2H), 7.54 (t, *J* = 7.37 Hz, 1H), 7.44 (t, *J* = 7.68 Hz, 2H), 7.38 (d, *J* = 7.42 Hz, 2H), 7.29 (t, *J* = 7.49 Hz, 2H), 7.23 (t, *J* = 7.31 Hz, 1H), 7.15 (s, 1H), 4.36 – 4.07 (m, 2H), 2.69 (s, 2H), 2.23 – 2.07 (m, 2H), 1.61 – 1.42 (m, 4H), 1.22 – 1.08 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.7, 164.2, 164.1, 140.0, 134.6, 132.3, 129.8, 128.6, 128.4, 127.9, 127.1, 71.1, 62.2, 60.5, 31.5, 31.1, 24.1. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1391.2. ESI-HRMS: calcd for $C_{22}H_{27}N_2O_7Pt$ $[M+H]^+$: *m/z* 626.1466; found: *m/z* 626.1467.

Synthesis of platinum(IV) complexes 5a', 5c', and 5e'. The platinum(IV) complex **5a'** was synthesized by exactly following the reported method.[4]

The platinum(IV) complexes (0.20 mmol), which is 100 mg *t*-[Pt(DACH)(ox)($OOCCH_2CH=CH_2$)(OH)] or 107 mg *t*-[Pt(DACH)(ox)(benzoato)(OH)], were dissolved into 2 mL DMF. Benzoic anhydride (163 mg, 0.72 mmol) was added to the solution. The solution was stirred at 70 °C for 6 h. After cooling down, 40 mL Et_2O was added to the reaction. The precipitate was collected by centrifuge and washed with E_2O (40 mL) for twice. After purification by RP-HPLC and lyophilization, the desired products were obtained as white solid (Scheme S2).

***trans*-[Pt(DACH)(ox)(benzoato)(OAc)] (5a').[4]**

***trans*-[Pt(DACH)(ox)(benzoato)($OOCCH_2CH=CH_2$)] (5c').** Yield: 68%, 82 mg (0.14 mmol). ^1H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 3H), 8.22 (s, 1H), 7.87 (d, *J* = 7.06 Hz, 2H), 7.56 (t, *J* = 7.38 Hz, 1H), 7.45 (t, *J* = 7.61 Hz, 2H), 6.83 – 6.58 (m, 1H), 5.85 (dd, *J* = 15.39, 1.71 Hz, 1H), 5.19 – 4.97 (m, 1H), 2.72 – 2.63 (d, *J* = 34.27 Hz, 1H), 2.16 (d, *J* = 11.33 Hz, 2H), 1.82 (dd, *J* = 6.87, 1.56 Hz, 2H), 1.53 – 1.46 (m, 4H), 1.18 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.1, 173.2, 164.1, 142.8, 133.1, 132.5, 129.8, 128.6, 125.1, 61.9, 61.5, 31.4, 24.0, 17.7. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1602.0. ESI-HRMS: calcd for $C_{19}H_{25}N_2O_8Pt$ $[M+H]^+$: *m/z* 604.1259; found: *m/z* 604.1234.

***trans*-[Pt(DACH)(ox)(benzoato)$_2$] (5e').** Yield: 73%, 94 mg (0.15 mmol). ^1H NMR (600 MHz, DMSO-d_6) δ 8.57 (s, 2H), 8.32 (s, 2H), 7.89 (d, *J* = 7.69 Hz, 2H), 7.56 (t, *J* = 7.40 Hz, 1H), 7.46 (d, *J* = 7.58 Hz, 2H), 2.77 (s, 2H), 2.18 (d, *J* = 12.07 Hz, 2H), 1.58 – 1.53 (m, 4H), 1.20 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 173.3, 164.3, 133.1, 132.6, 129.9, 128.6, 61.8, 31.4, 24.1. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1606.6. ESI-HRMS: calcd for $C_{22}H_{25}N_2O_8Pt$ $[M+H]^+$: *m/z* 640.1259; found: *m/z* 640.1232.

Hydrolytic stability

The hydrolytic stability of Pt(IV) complexes **4a**, **4a'**, **4c**, **4c'**, **4e**, and **4e'** was tested by HPLC. Pt(IV) complexes (**4a**, **4a'**, **4c**, **4c'**, **4e**, and **4e'**) were separately dissolved in PBS (10 mM, pH 7.4) with a final concentration of 0.2 ± 0.1 mM. The resulting solutions were protected from light by aluminum foil and incubated at 37 °C on an orbital shaker (100 rpm). At each time point of 0, 2, 4, 6, 8, 12, and 24 h, the HPLC chromatograms of these Pt(IV) complexes were obtained. All the experiments were repeated three times and the amount of remaining Pt(IV) complex (%) was determined by the average change of peak area compared with the time 0 h (the representative results are shown in Figures S24-S29). Under pseudo first-order reaction conditions where there is excess amount of phosphate to maintain the pH value, the

half-lives ($t_{1/2}$) and rate constant (k) of these Pt(IV) complexes, which are independent of the concentration of Pt(IV) complexes, were calculated and showed in Figure 1.

The hydrolytic stability of Pt(IV) complexes **5a**, **5a'**, **5c**, **5c'**, **5e** and **5e'** was tested under same conditions. The representative results are shown in Figures 2A and S45-S50.

Reduction potential

Reduction potentials of Pt(IV) complexes **5a**, **5a'**, **5c**, **5c'**, **5e**, and **5e'** were measured in a three-electrode cell, including a 2.0 mm-diameter glassy carbon disk working electrode, a platinum auxiliary electrode, and a Ag/AgCl reference electrode in 3 M KCl. Samples were dissolved in a PBS (10 mM, pH 7.4) solution with potassium ferricyanide {$K_3[Fe(CN)_6]$} (2 mM) as a reference ($E_{1/2}$ = 0.361 V vs. NHE, 25 °C).[5] The cyclic voltammogram was recorded at room temperature, and the scan rate was set at 100 mV s^{-1} . The results are shown in Figures S51−S56. Then all the initial reduction potentials (vs Ag/AgCl) were recalculated vs NHE and listed in Table 2.

Reduction test

The reduction of Pt(IV) complexes **5a**, **5a'**, **5c**, **5c'**, **5e** and **5e'** by ascorbate was tested by HPLC. Pt(IV) complexes (**5a**, **5a'**, **5c**, **5c'**, **5e**, and **5e'**) were separately dissolved in PBS (10 mM, pH 7.4) with a final concentration of 0.2±0.1 mM. Then 1 mL PBS solution of platinum(IV) complexes was mixed with 1 mL PBS solution of ascorbate (6 mM, pH 7.4). The resulting solutions were protected from light by aluminum foil and incubated at 37 °C on an orbital shaker (100 rpm). At each time point of 0, 2, 4, 6, 8, 12, and 24 h, the HPLC chromatograms of these Pt(IV) complexes were obtained. All the experiments were repeated three times and the amount of remaining Pt(IV) complex (%) was determined by the average change of peak area compared with the time 0 h (the representative results are shown in Figures 2B and S57-S62).

Octanol/Water partition coefficient (Log $P_{o/w}$)

A shake-flask method was used to determine the log P values of the platinum(IV) complexes **5a**, **5a'**, **5c**, **5c'**, **5e**, and **5e'**. Five micromoles of platinum complexes were dissolved in 2 mL of PBS (10 mM, pH 7.4); a 0.5 mL solution of these platinum complexes was mixed with 0.5 mL of octanol that was presaturated with PBS (10 mM, pH 7.4). The two phases were stirred overnight at room temperature and then separated by centrifugation. The platinum content in the two phases was determined by HPLC. The log P values were calculated from an average of three independent measurements.

Cell culture

A2780 and A2780cisR cells were bought from Cobioer Biosciences (Nanjing, China) and maintained in Roswell Park Memory Institution (RPMI) 1640 medium supported with 10% FBS and 100 unit/mL penicillin/streptomycin. A549 and A549cisR cells were bought from Procells (Wuhan, China) and cultured in Dulbecco's modified Eagle's medium supported with 10% FBS and 100 unit/mL penicillin/streptomycin, 1 μM cisplatin was added to the culture medium of A549cisR cells every two passages to maintain the resistance. All the cells were incubated in a humidified incubator at 37 °C with 5% CO_2.

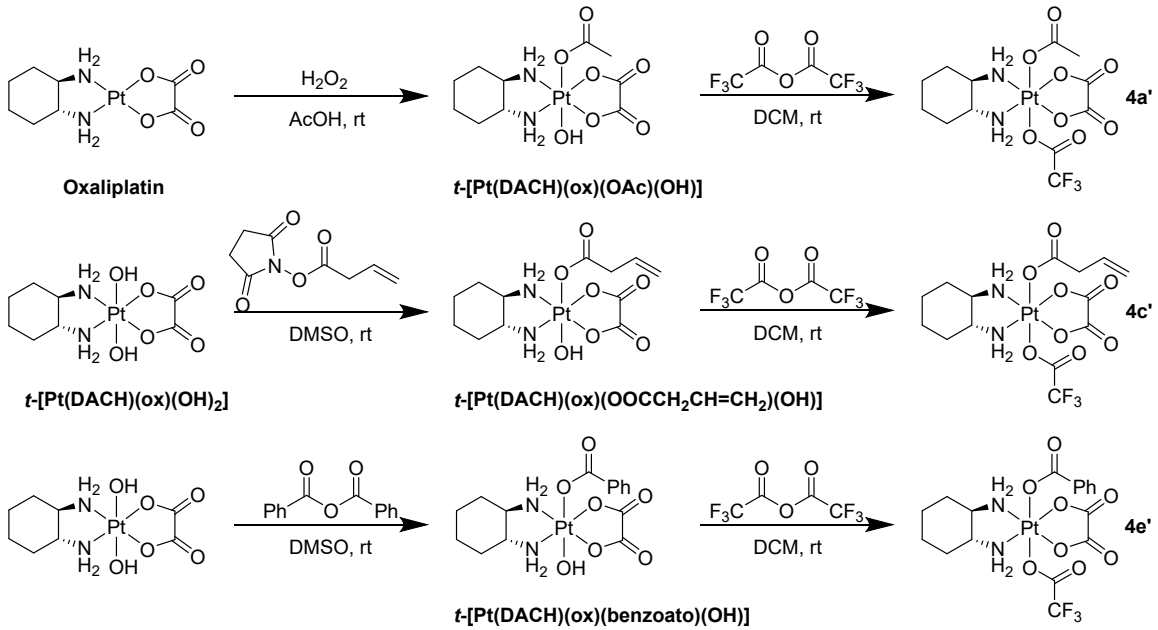
Cytotoxicity test

The cell cytotoxicity test of complexes was performed by CCK-8 assays. Cells were seeded in 96-well plates at a density of 3, 000 cells per well and incubated until the cell confluency reached to 30%. Subsequently, the medium was replaced with fresh medium containing various concentrations of complexes. 0.5% DMSO was added to increase the solubility of the complexes in culture medium. After 72h, the medium was removed and fresh medium containing CCK-8 was delivered to each well. After 30 mins to 1 h further incubation, the absorbance at 450 nm was measured on a microplate reader (Bio-Tek Synergy H1).

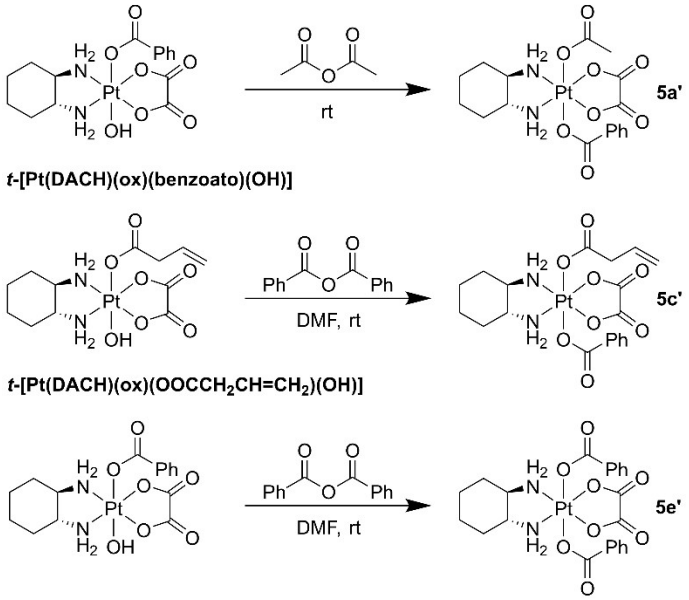
Cellular accumulation of platinum

A2780 cells were seeded in 60 mm dishes at a density of 500,000 cells per dish and incubated until the cell confluency reached 80%. Then, the medium was changed to fresh medium containing 10 μM complexes and incubated for 8 h. Subsequently, the cells were washed twice with PBS and collected by trypsinization. The cells were further washed twice with ice-cold PBS and resuspended in 5 mL PBS. The cell numbers were counted by Hemocytometer under a

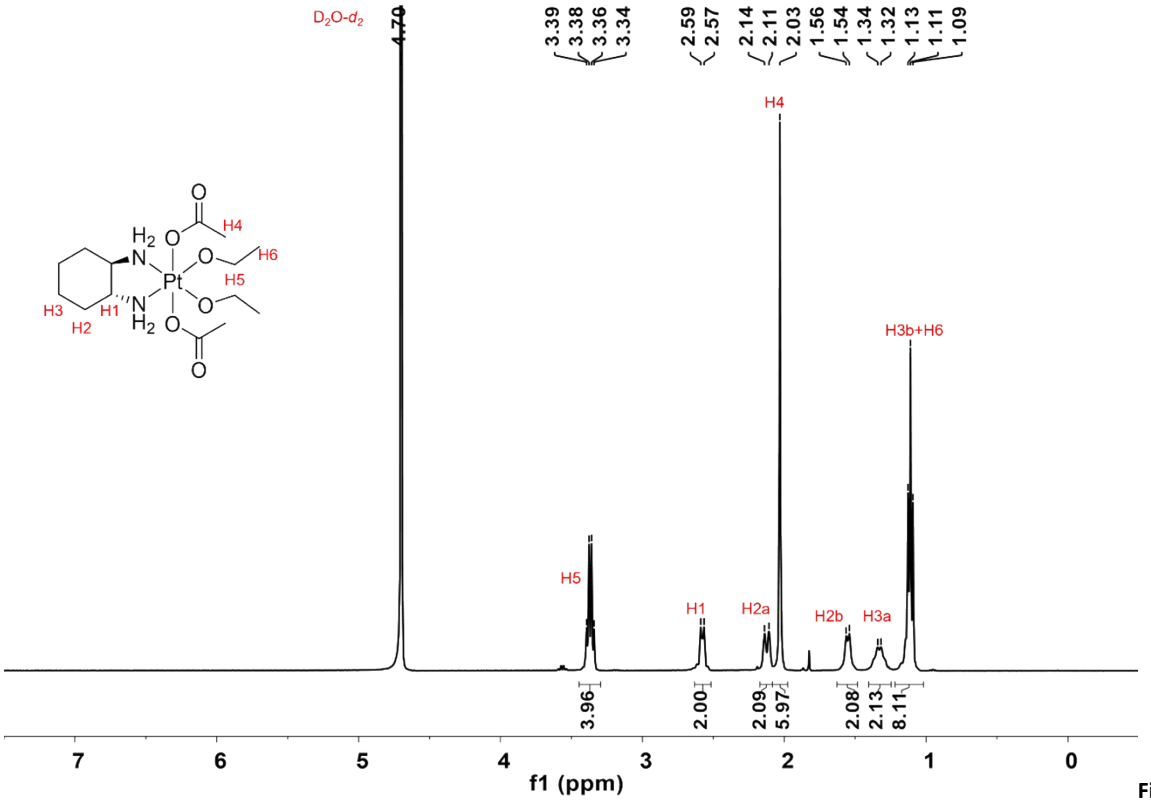
microscope. After that, the cells were pelleted by centrifugation and digested by 65% nitric acid for 3 days at 65 °C. The lysate was diluted with double-distilled H_2O to a final volume of 2 mL, and the Pt content was determined by inductively coupled plasma mass spectrometry (ICP-MS) (PE Nexion 2000).



Scheme S1. Synthesis of platinum(IV) complexes **4a'**, **4c'**, and **4e'**.

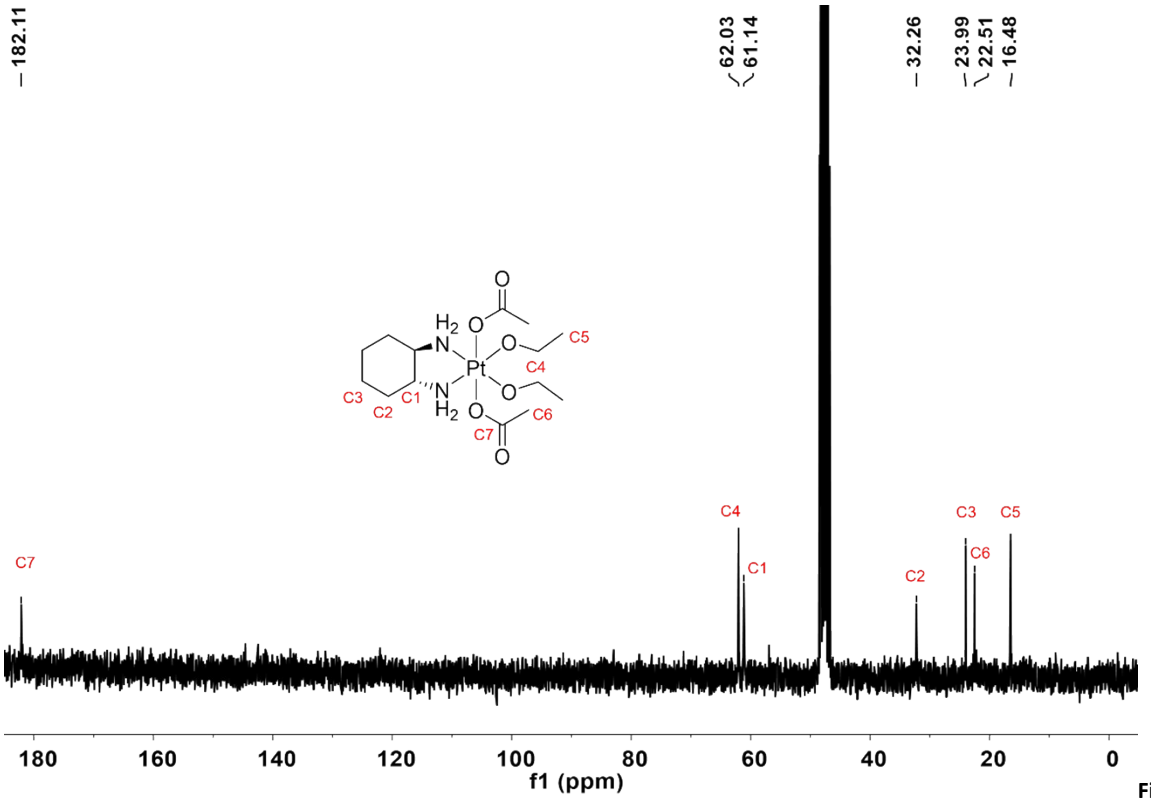


Scheme S2. Synthesis of platinum(IV) complexes **5a'**, **5c'**, and **5e'**.



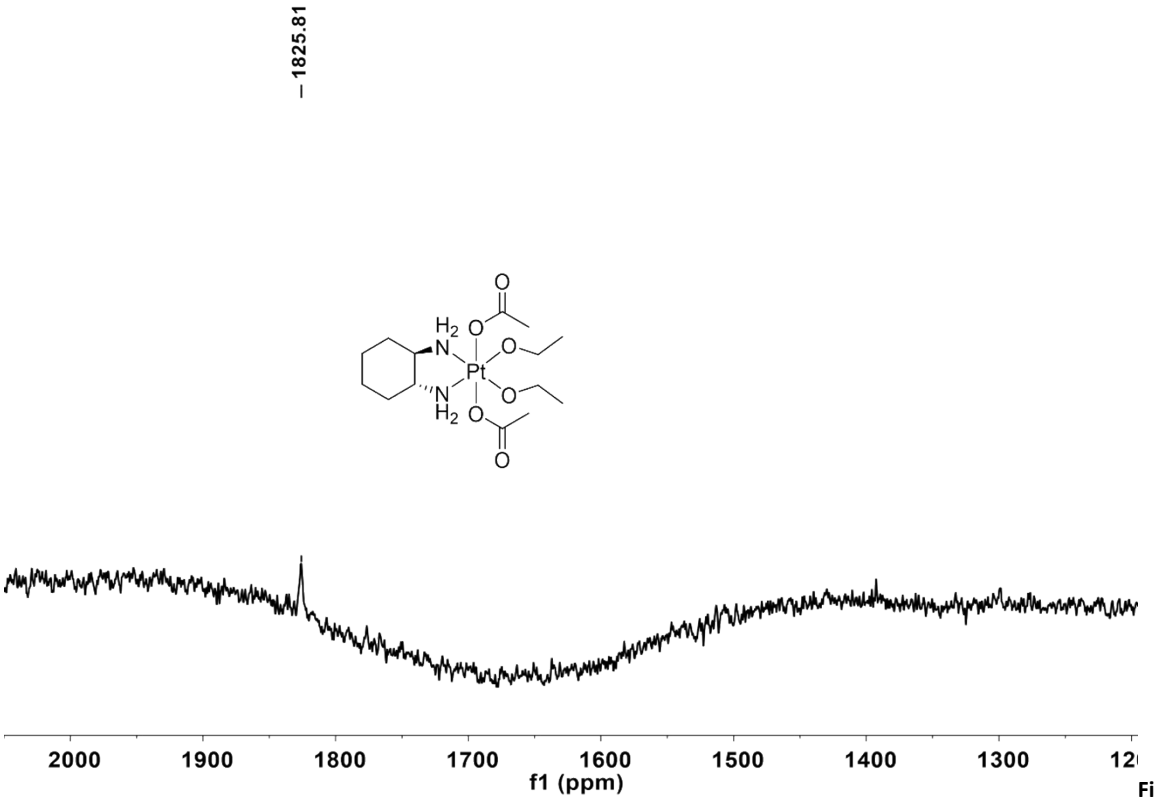
Fi

gure S1. ^{1}H NMR spectrum of platinum(IV) complex ***c,t*-[Pt(DACH)(OEt)$_2$(acetato)$_2$] 2** in D_2O.

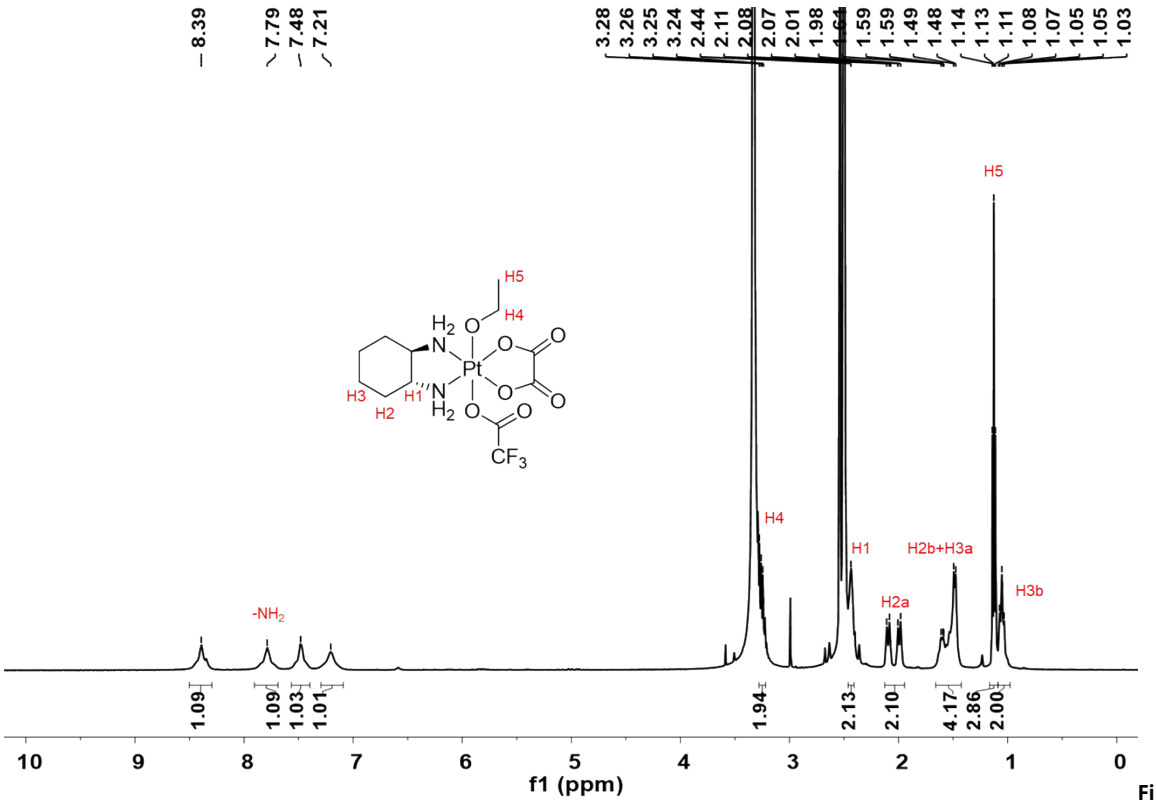


Fi

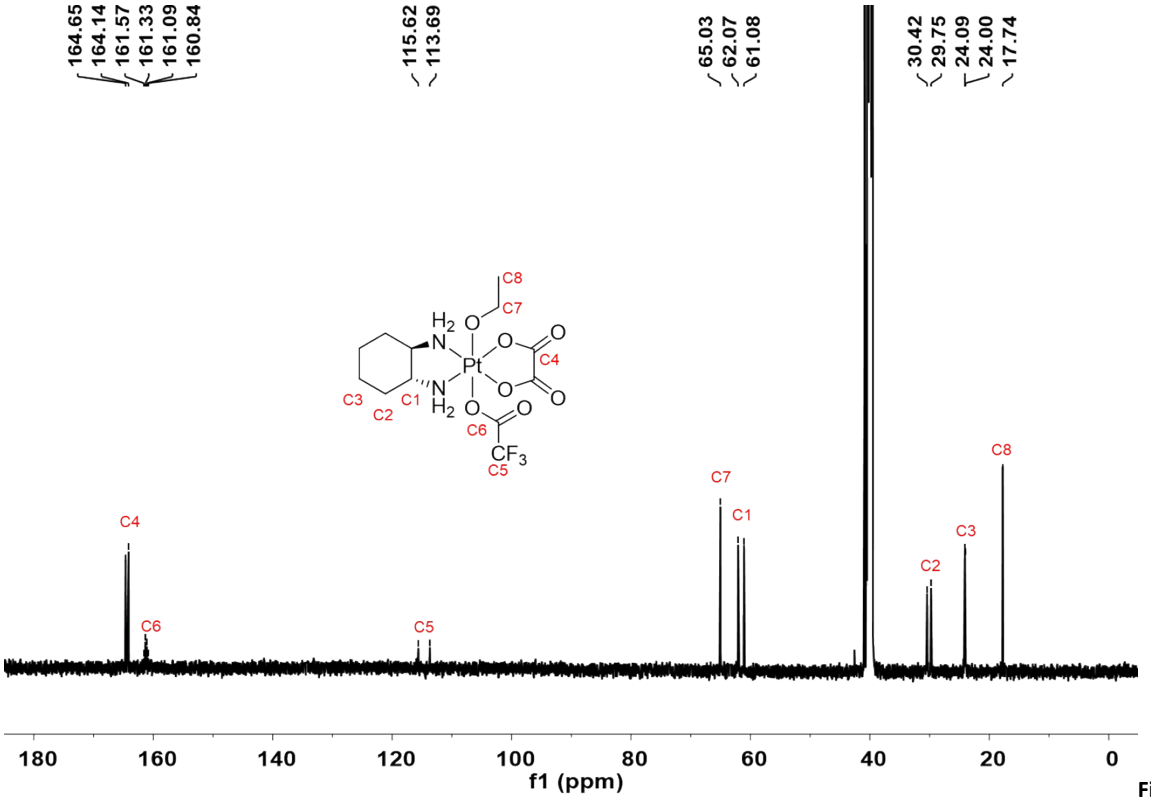
gure S2. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***c,t*-[Pt(DACH)(OEt)$_2$(acetato)$_2$] 2** in methanol-d_4.



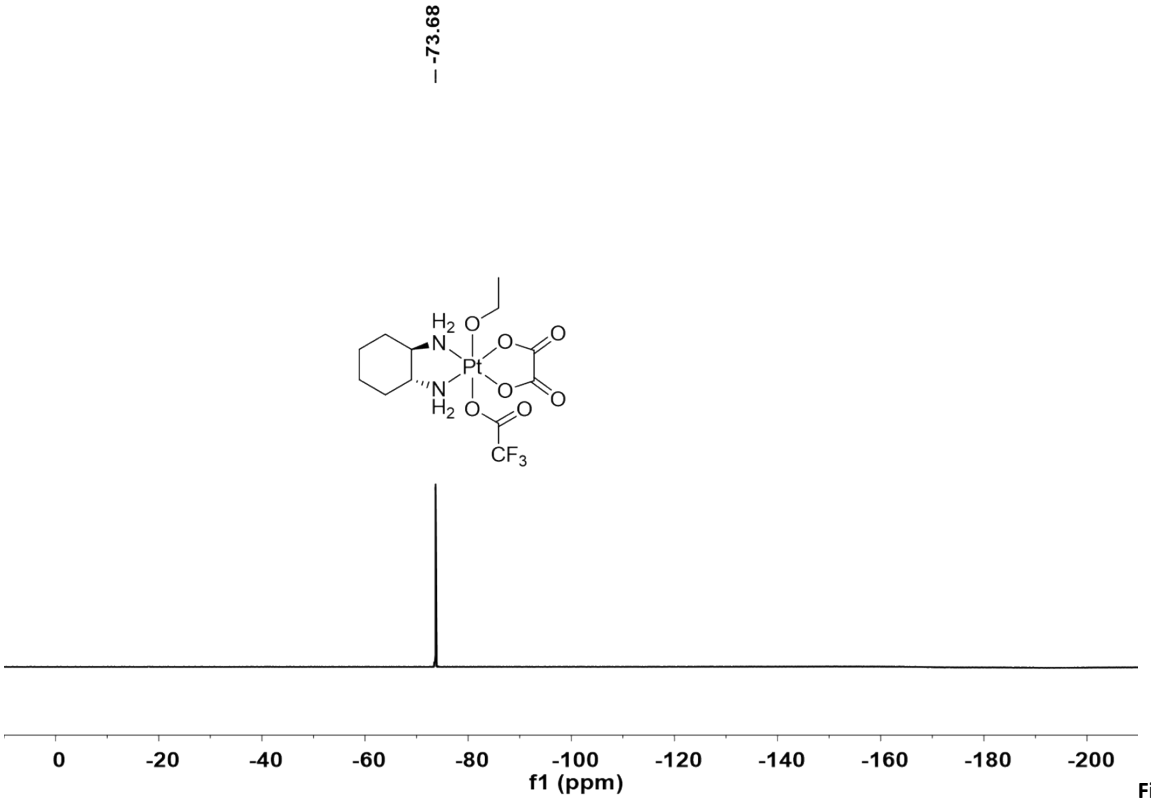
gure S3. ^{195}Pt NMR spectrum of platinum(IV) complex ***c,t*-[Pt(DACH)(OEt)$_2$(acetato)$_2$] 2** in ethanol-d_6.



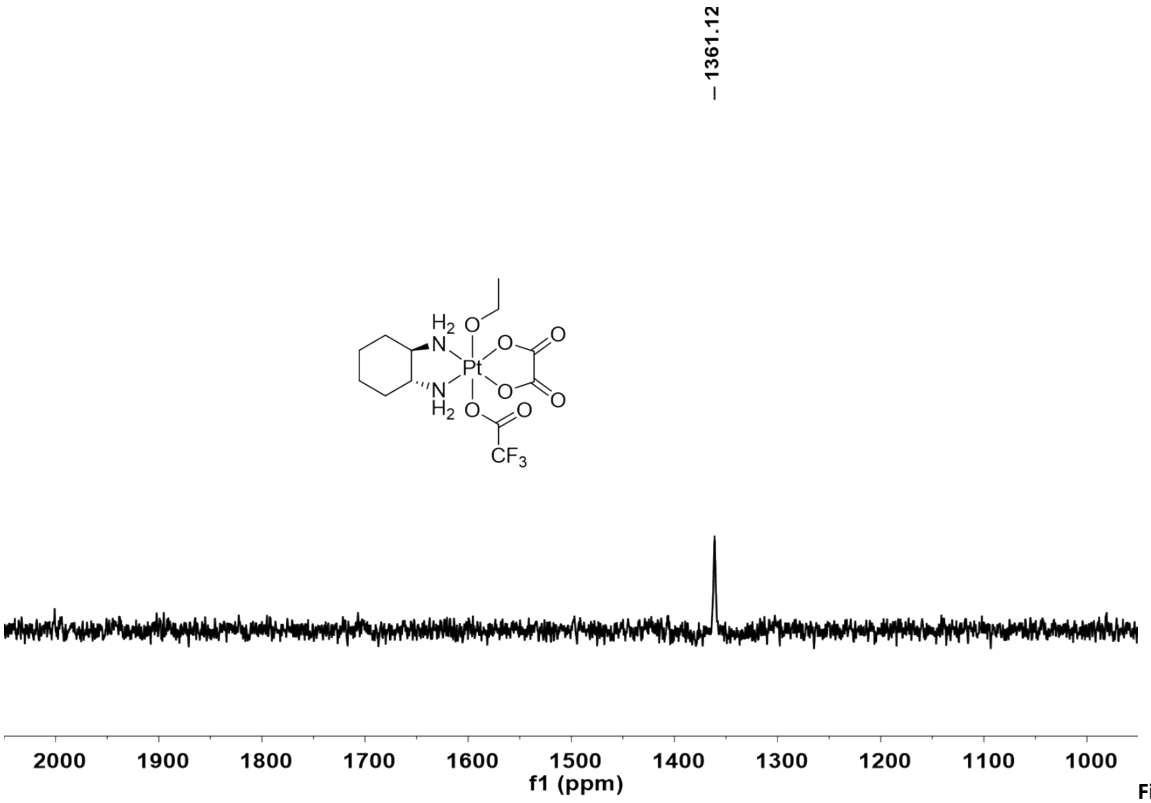
gure S4. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OEt)] 4a** in DMSO-d_6.



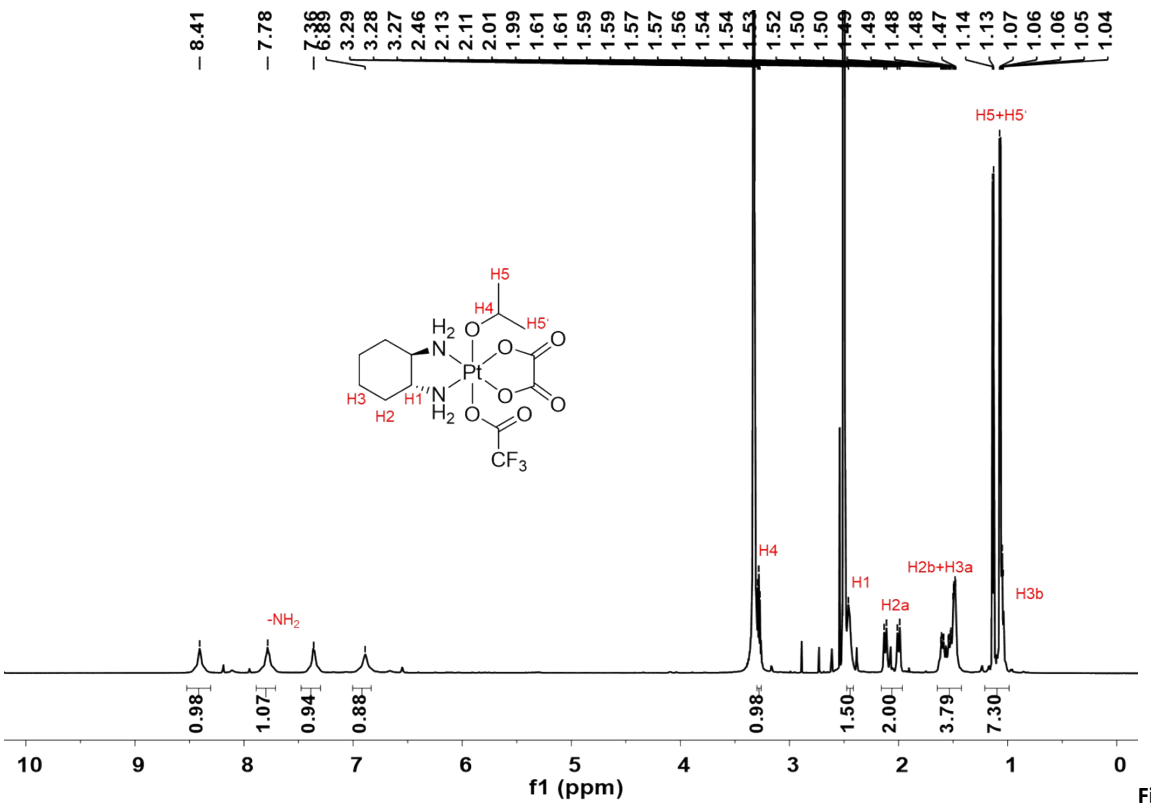
gure S5. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OEt)] 4a** in DMSO-d_6.



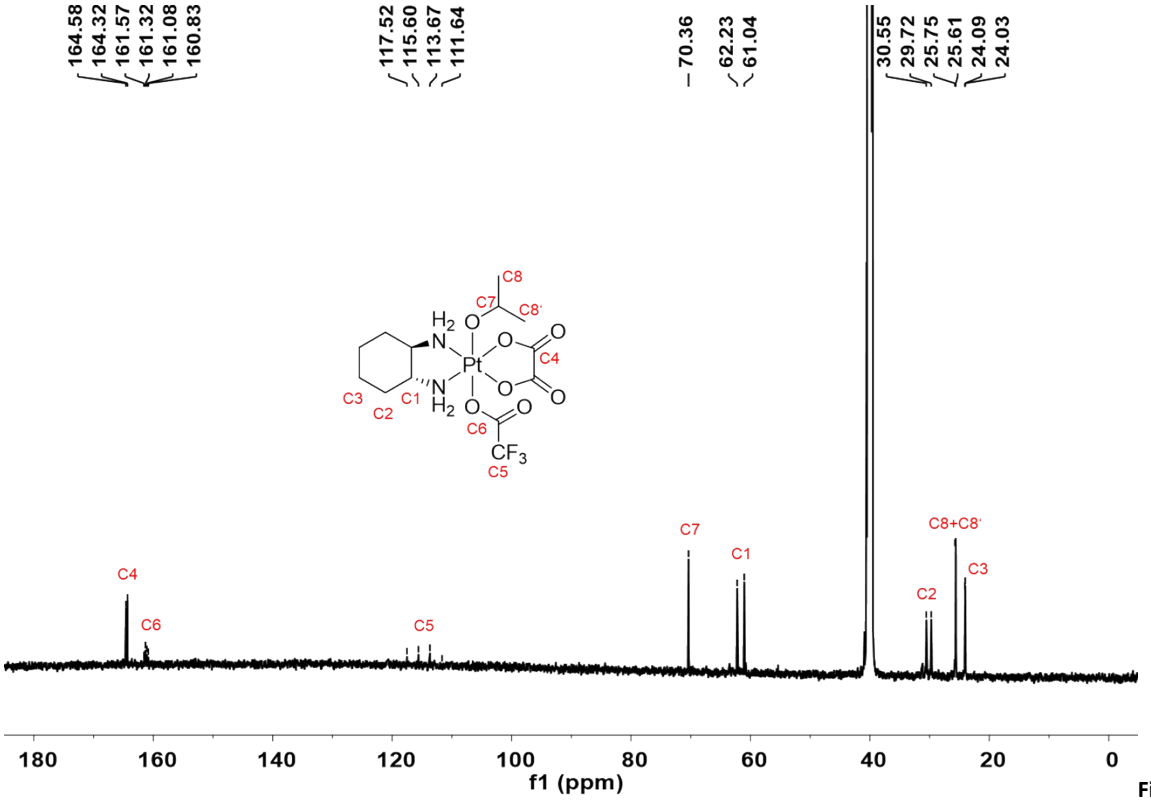
gure S6. ^{19}F NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OEt)] 4a** in DMSO-d_6.



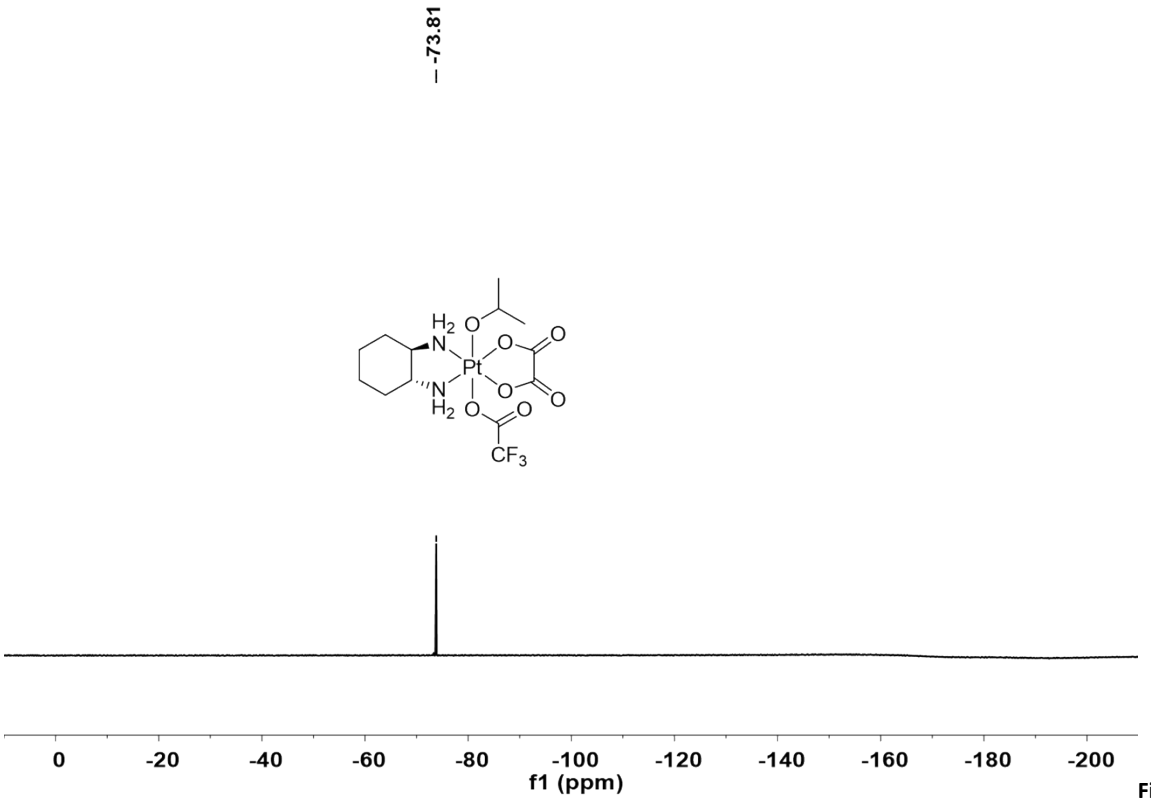
gure S7. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OEt)] 4a** in DMSO-d_6.



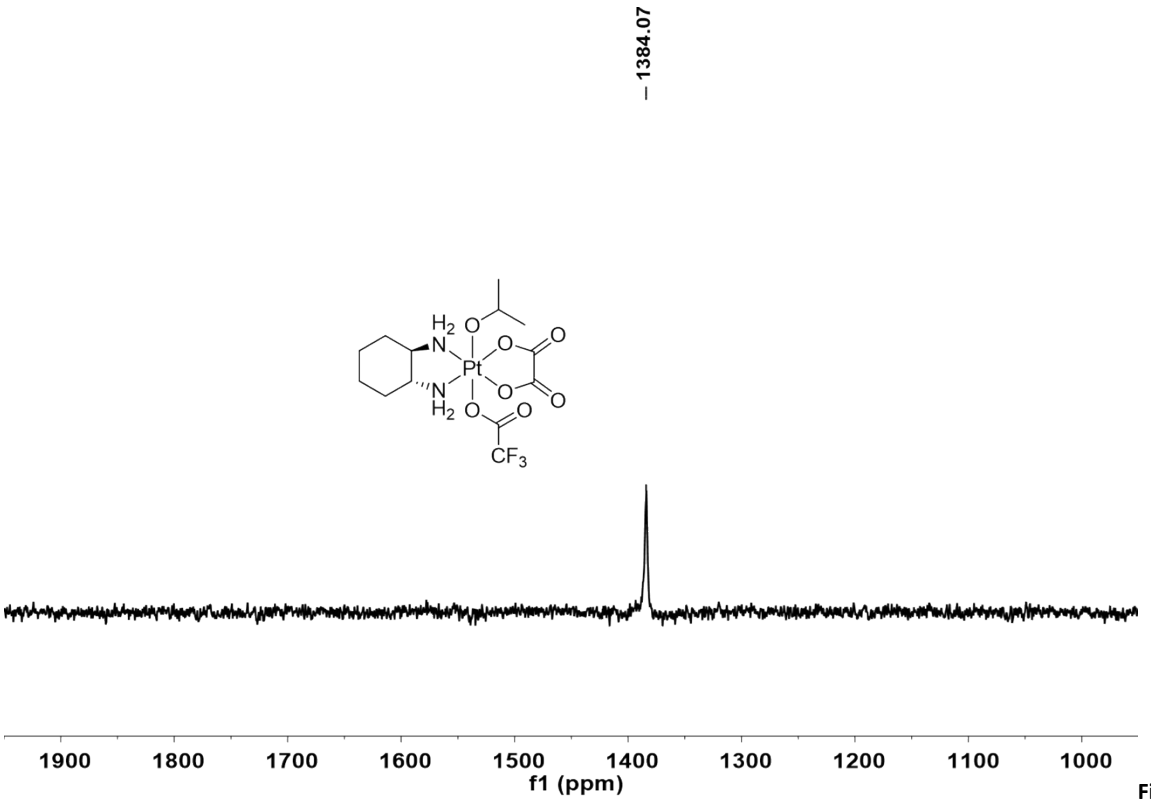
gure S8. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OiPr)] 4b** in DMSO-d_6.



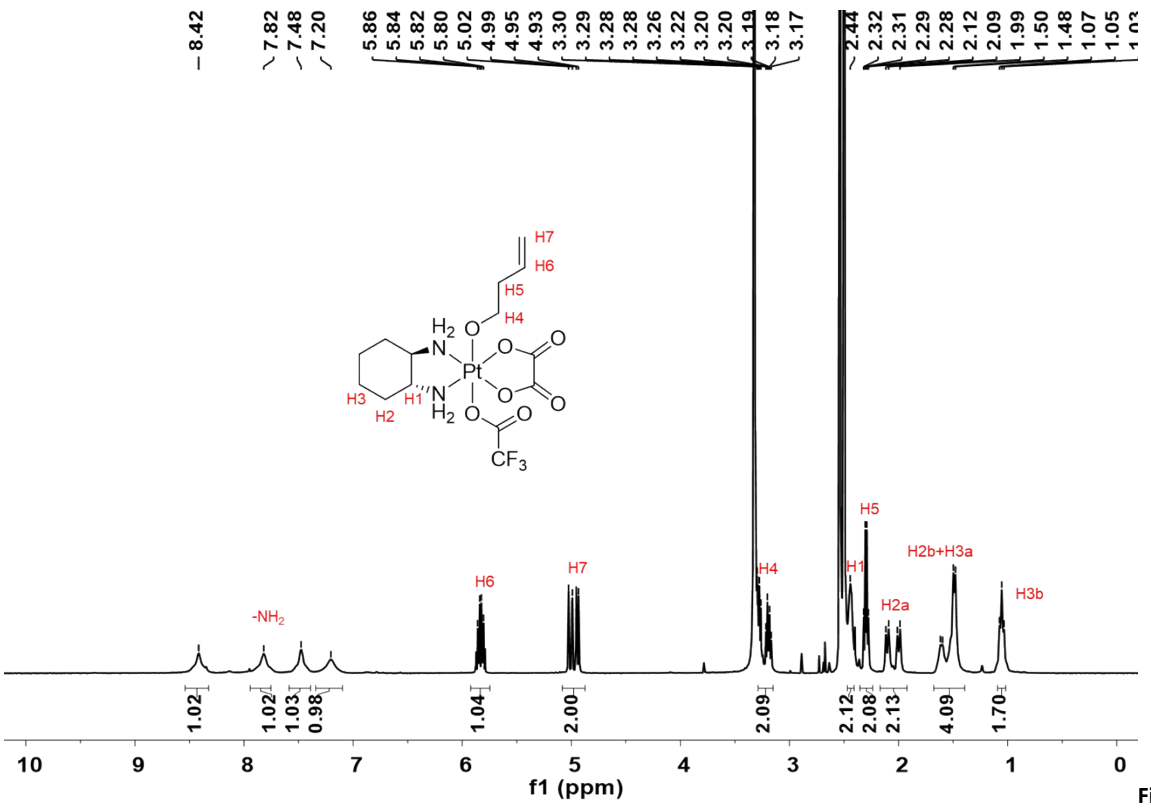
gure S9. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OiPr)] 4b** in DMSO-d_6.



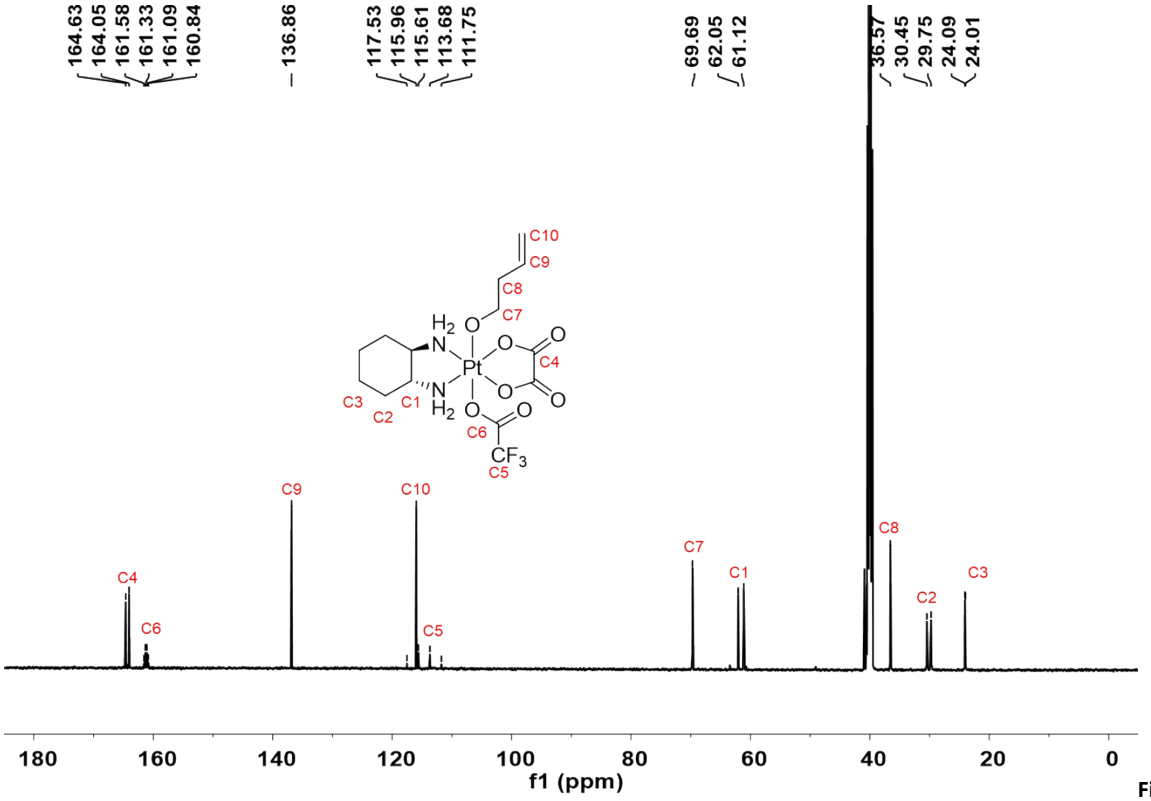
gure S10. ^{19}F NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OiPr)] 4b** in DMSO-d_6.



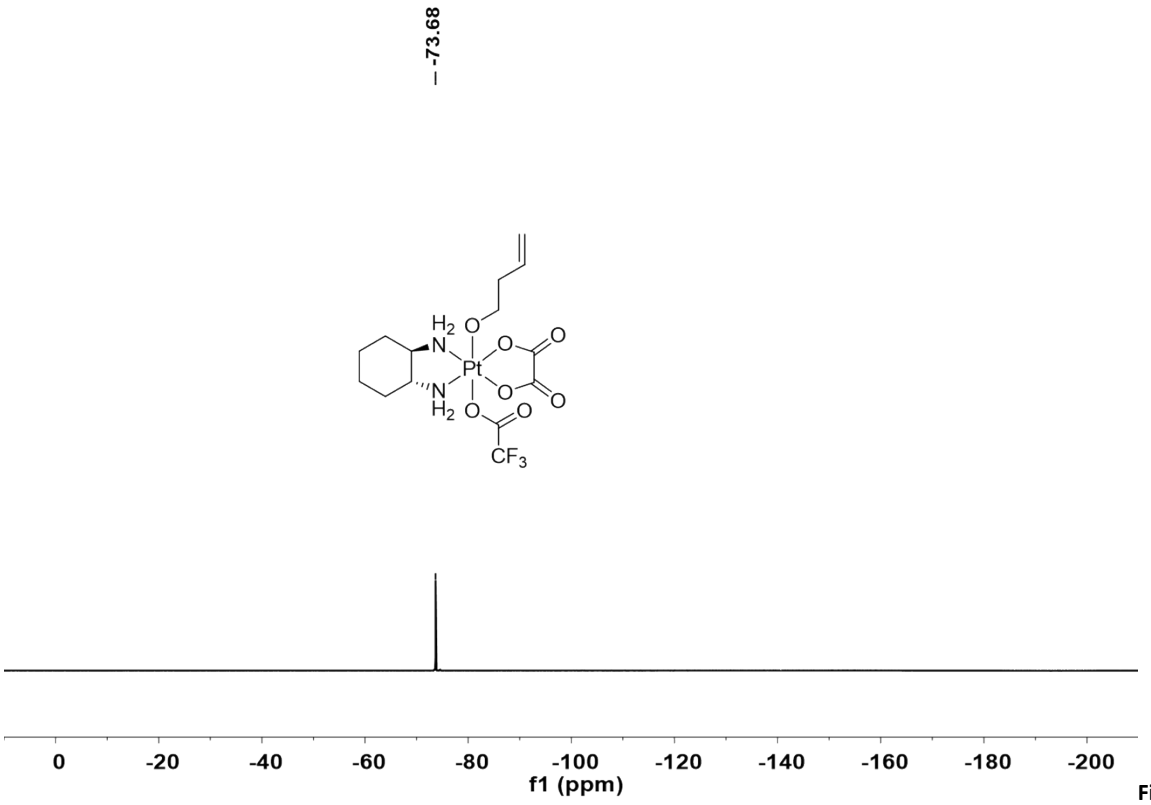
gure S11. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OiPr)] 4b** in DMSO-d_6.



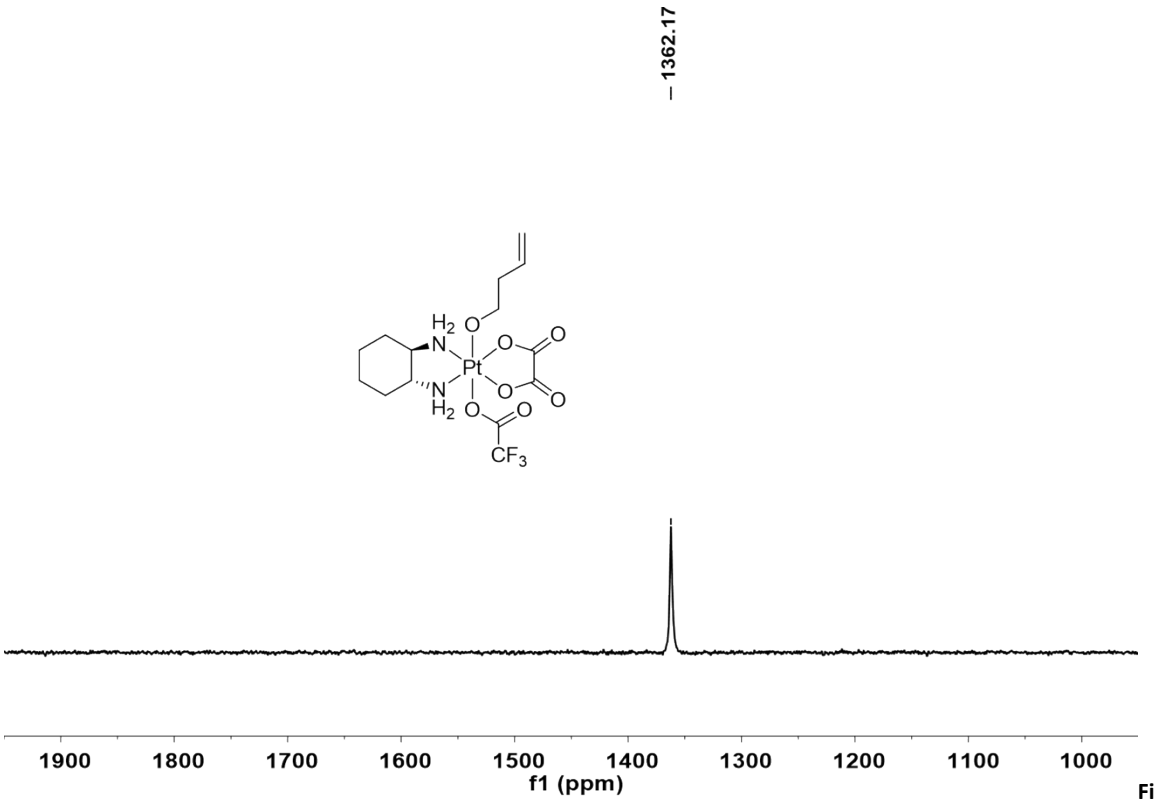
gure S12. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$CH=CH$_2$)] 4c** in DMSO-d_6.



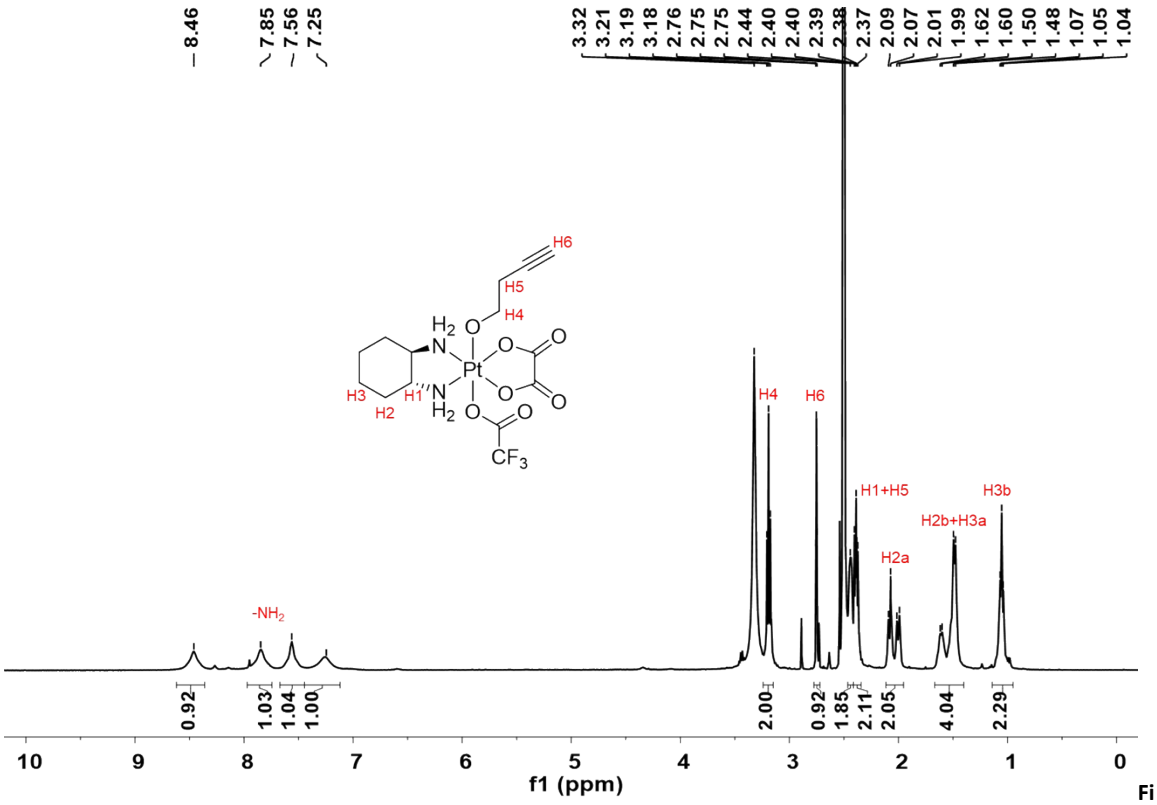
gure S13. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$CH=CH$_2$)] 4c** in DMSO-d_6.



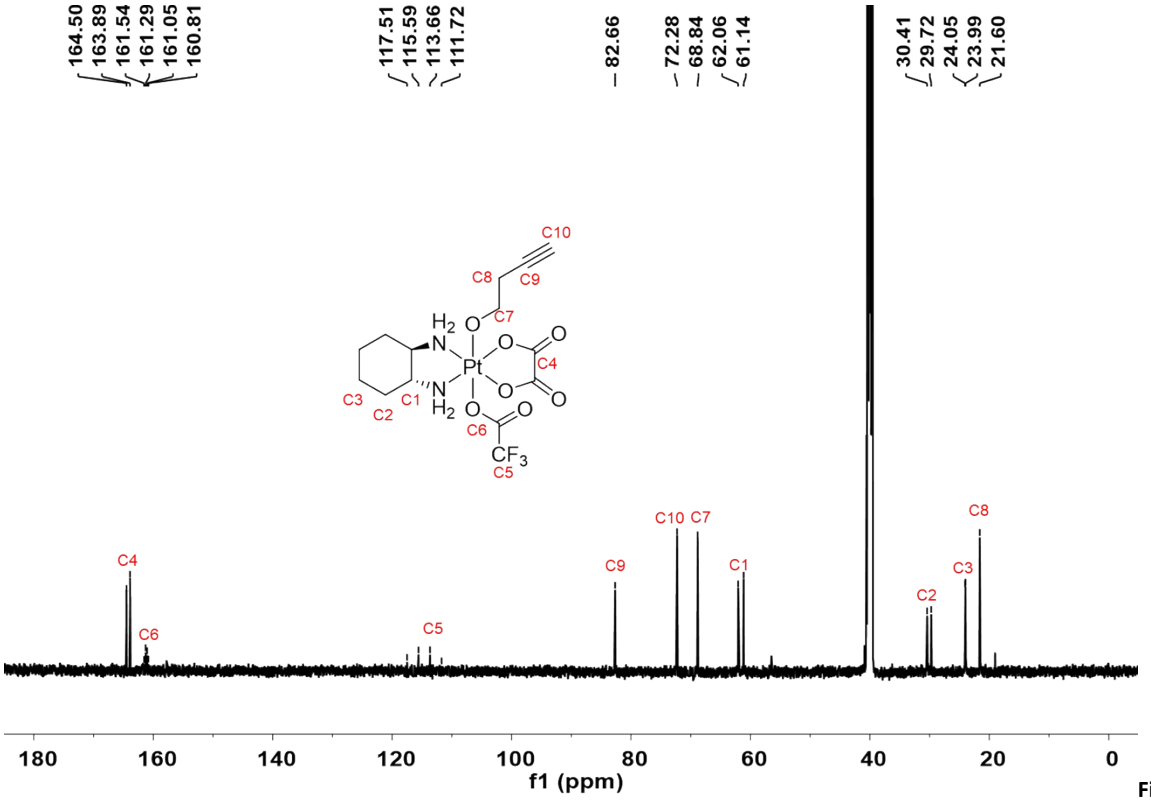
gure S14. ^{19}F NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$CH=CH$_2$)] 4c** in DMSO-d_6.



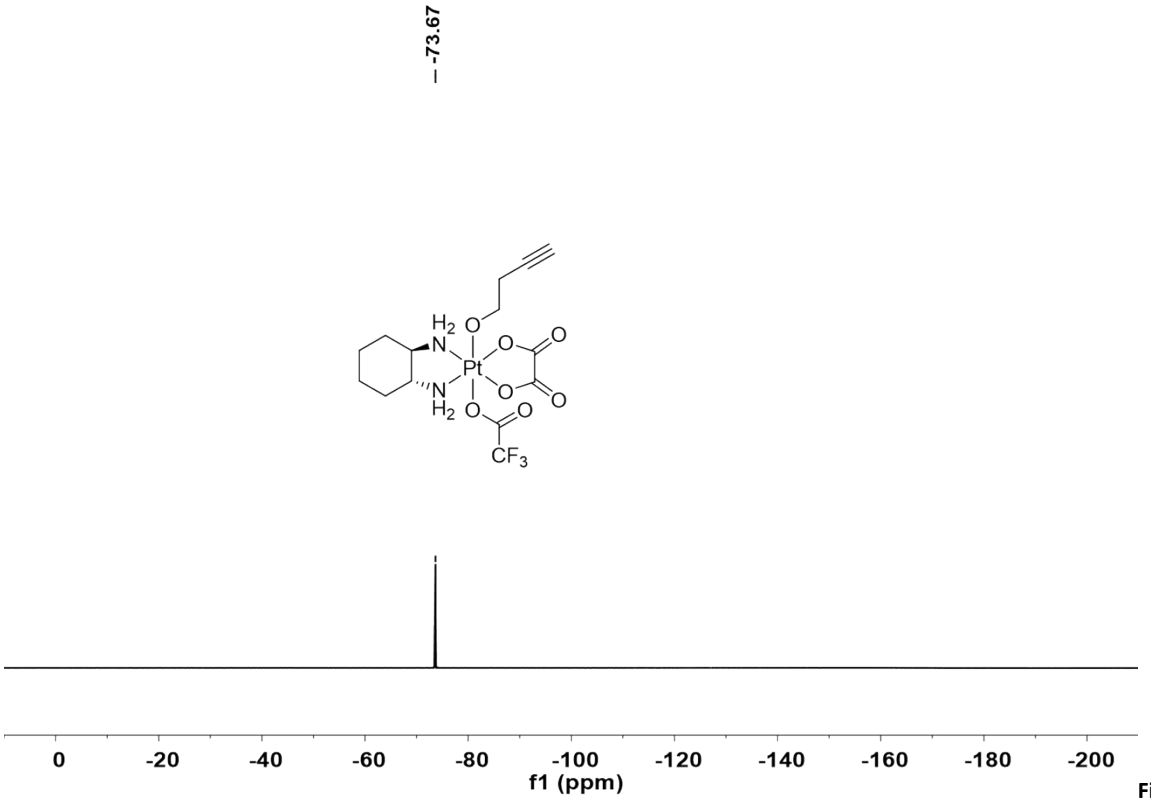
gure S15. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$CH=CH$_2$)] 4c** in DMSO-d_6.



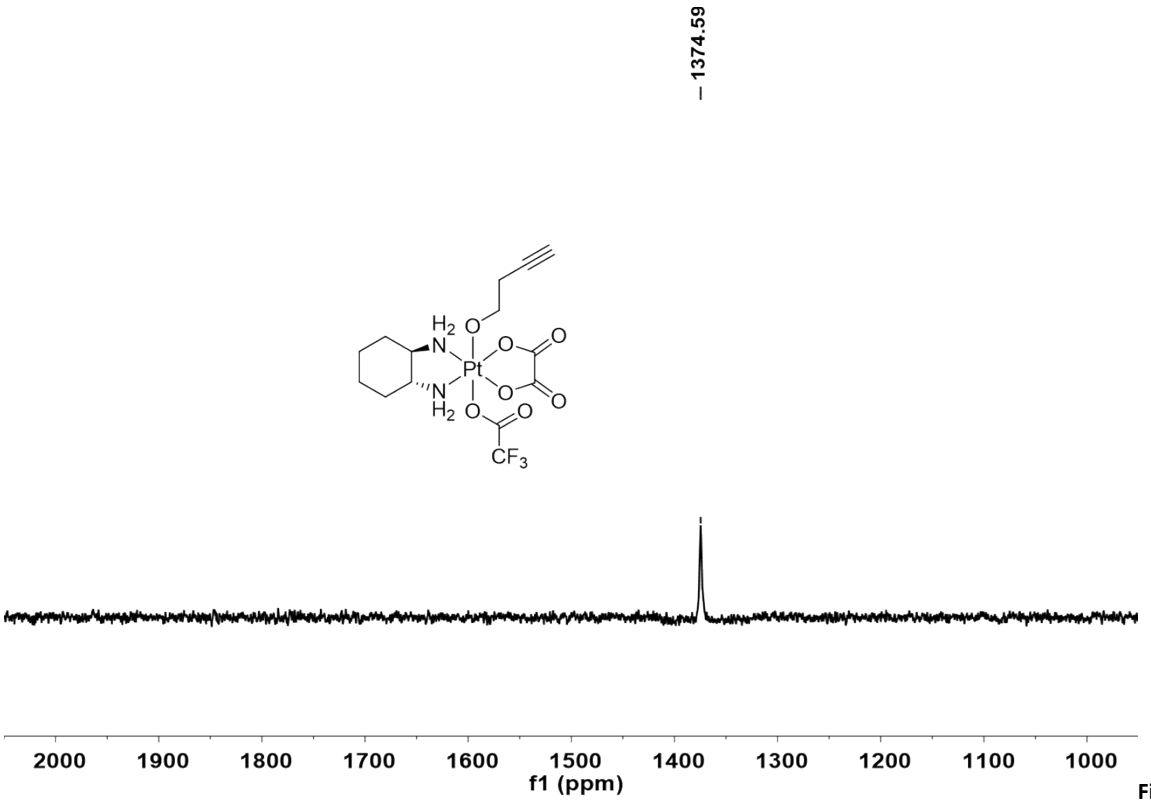
gure S16. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$C≡CH)] 4d** in DMSO-d_6.



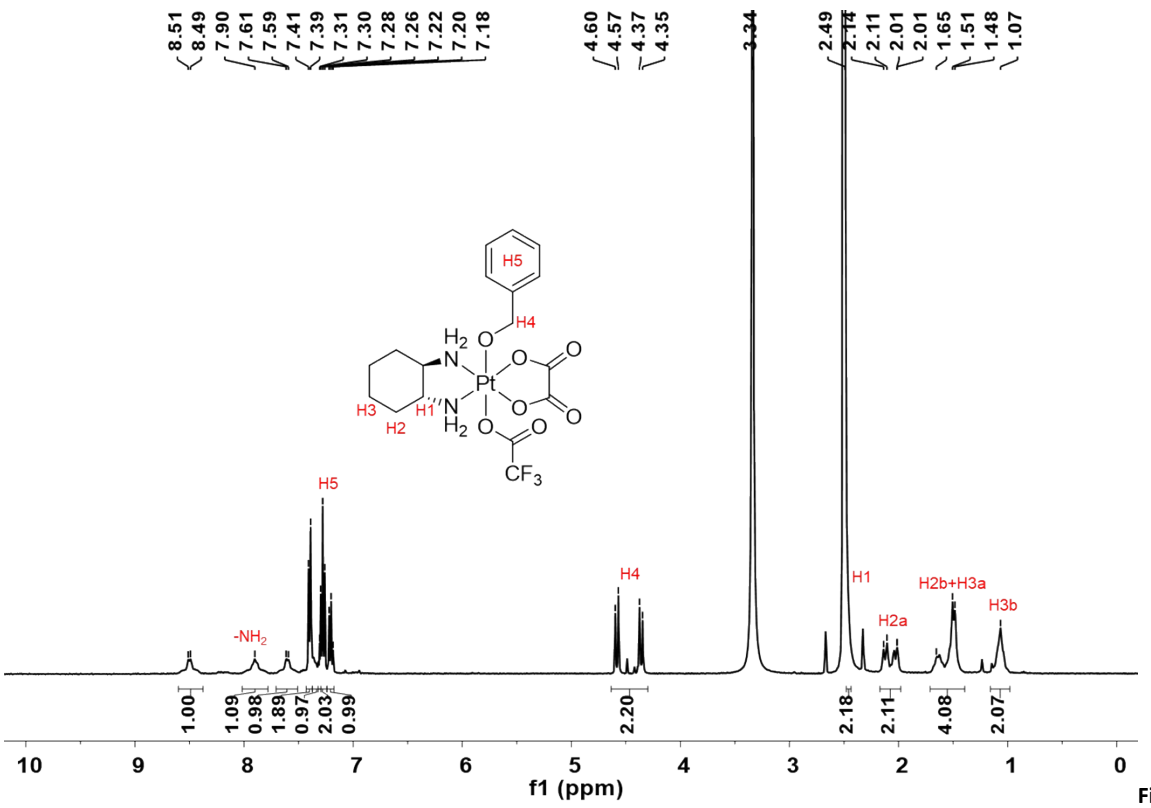
gure S17. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$C≡CH)] 4d** in DMSO-d_6.



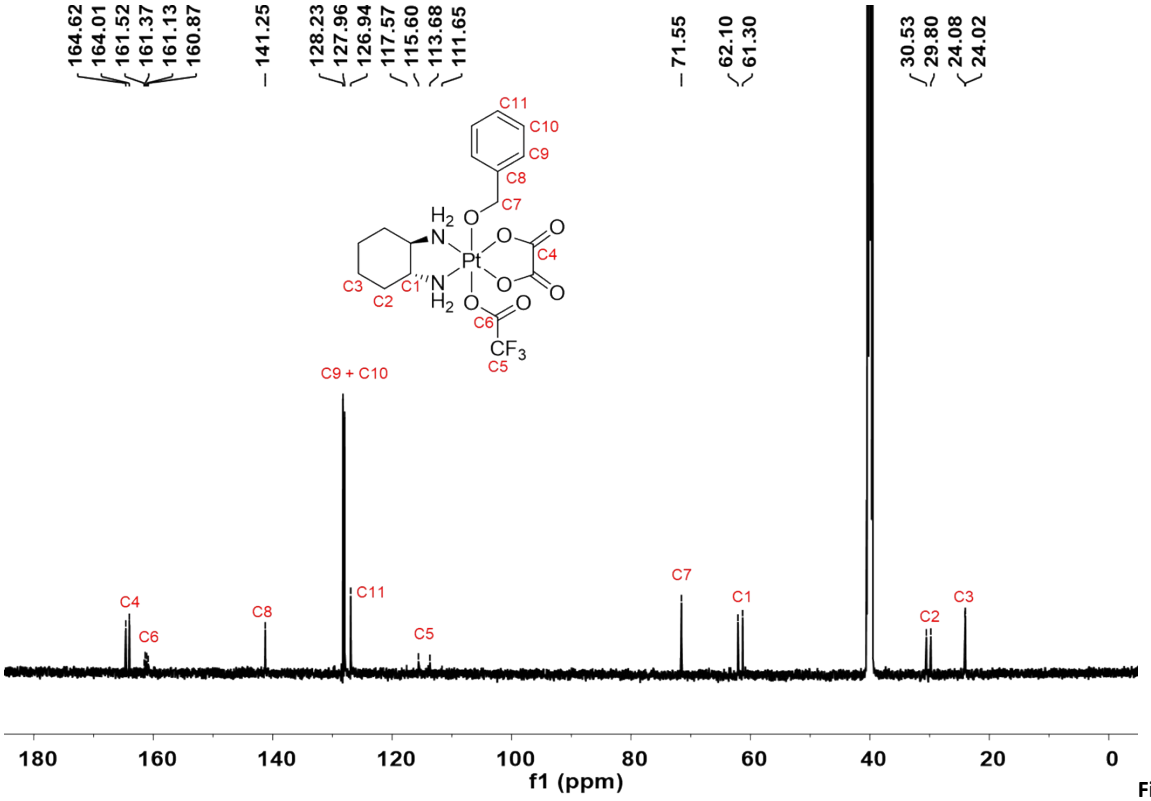
gure S18. ^{19}F NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$C≡CH)] 4d** in DMSO-d_6.



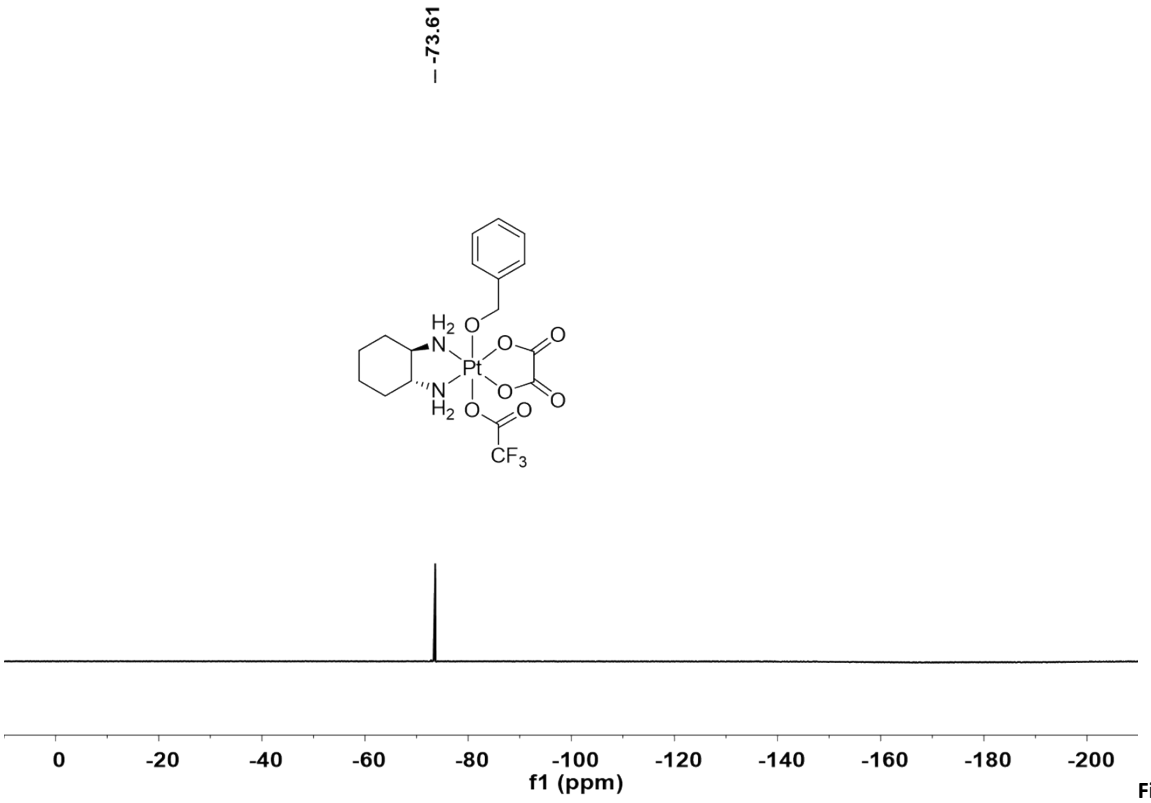
gure S19. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OCH$_2$CH$_2$C≡CH)] 4d** in DMSO-d_6.



gure S20. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OBn)] 4e** in DMSO-d_6.



gure S21. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OBn)] 4e** in DMSO-d_6.



gure S22. ^{19}F NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OBn)] 4e** in DMSO-d_6.

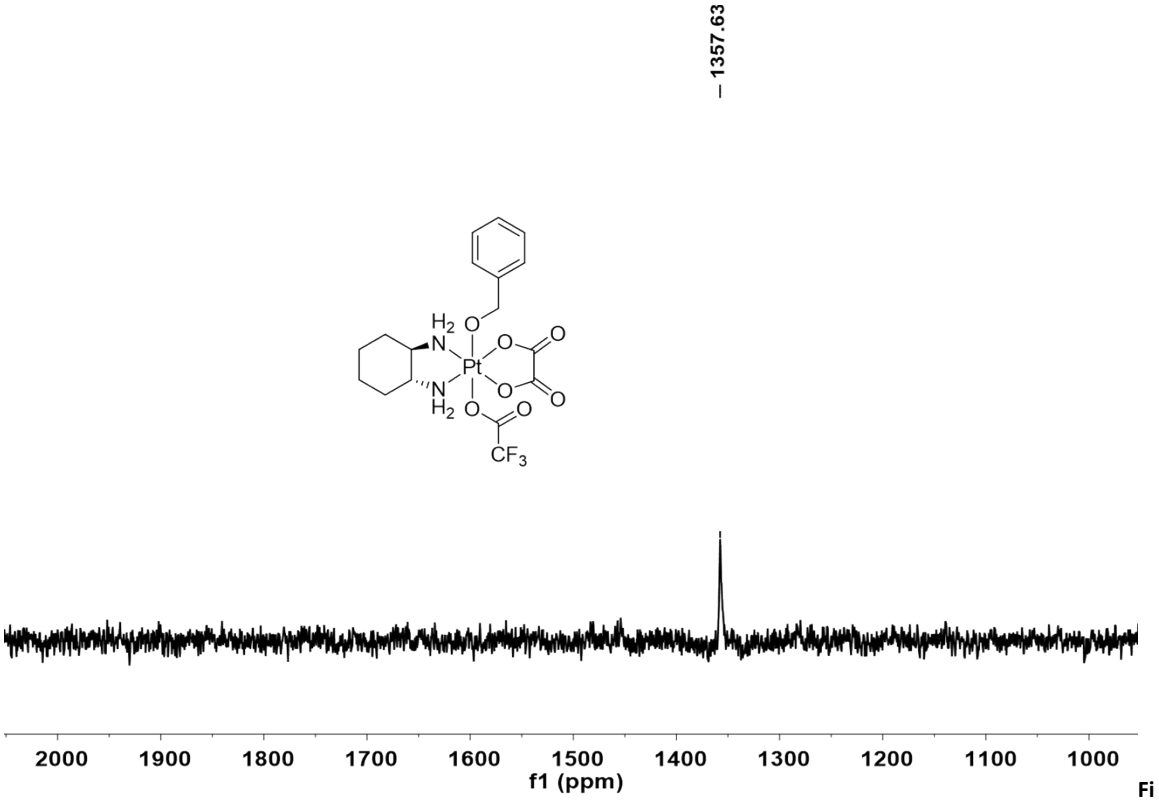


Figure S23. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OBn)] 4e** in DMSO-d_6.

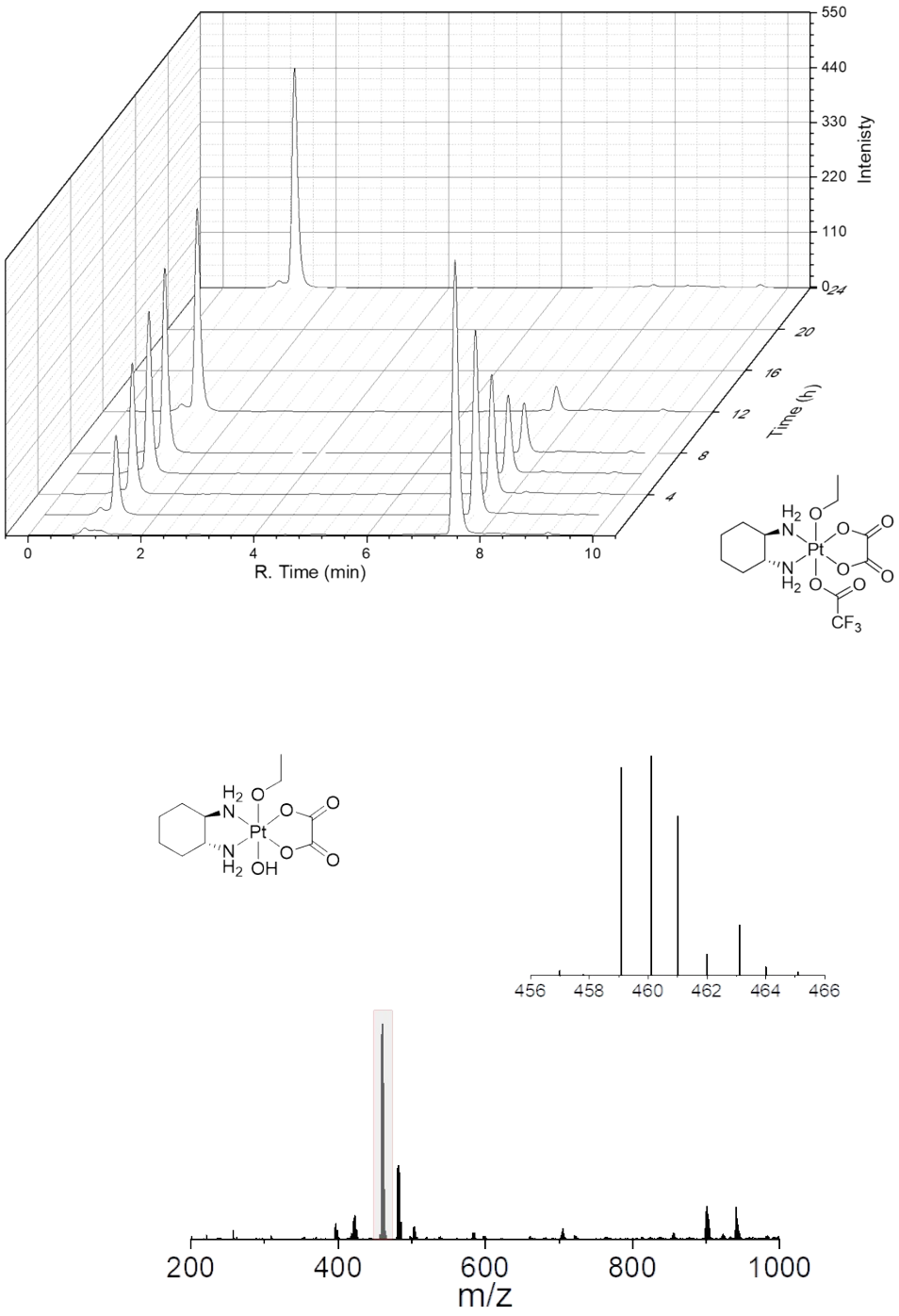


Figure S24. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OEt)] 4a** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.6 min belongs to complex **4a**. Chromatographic peak in 1.5 min contains the hydrolyzed product ***t*-[Pt(DACH)(ox)(OEt)(OH)]**. Under: Mass spectrum acquired on peak at 1.5 min in the 8 h chromatogram, ESI-MS: calcd for $C_{10}H_{21}N_2O_6Pt$ $[M+H]^+$: *m/z* 460.1; found: *m/z* 460.1

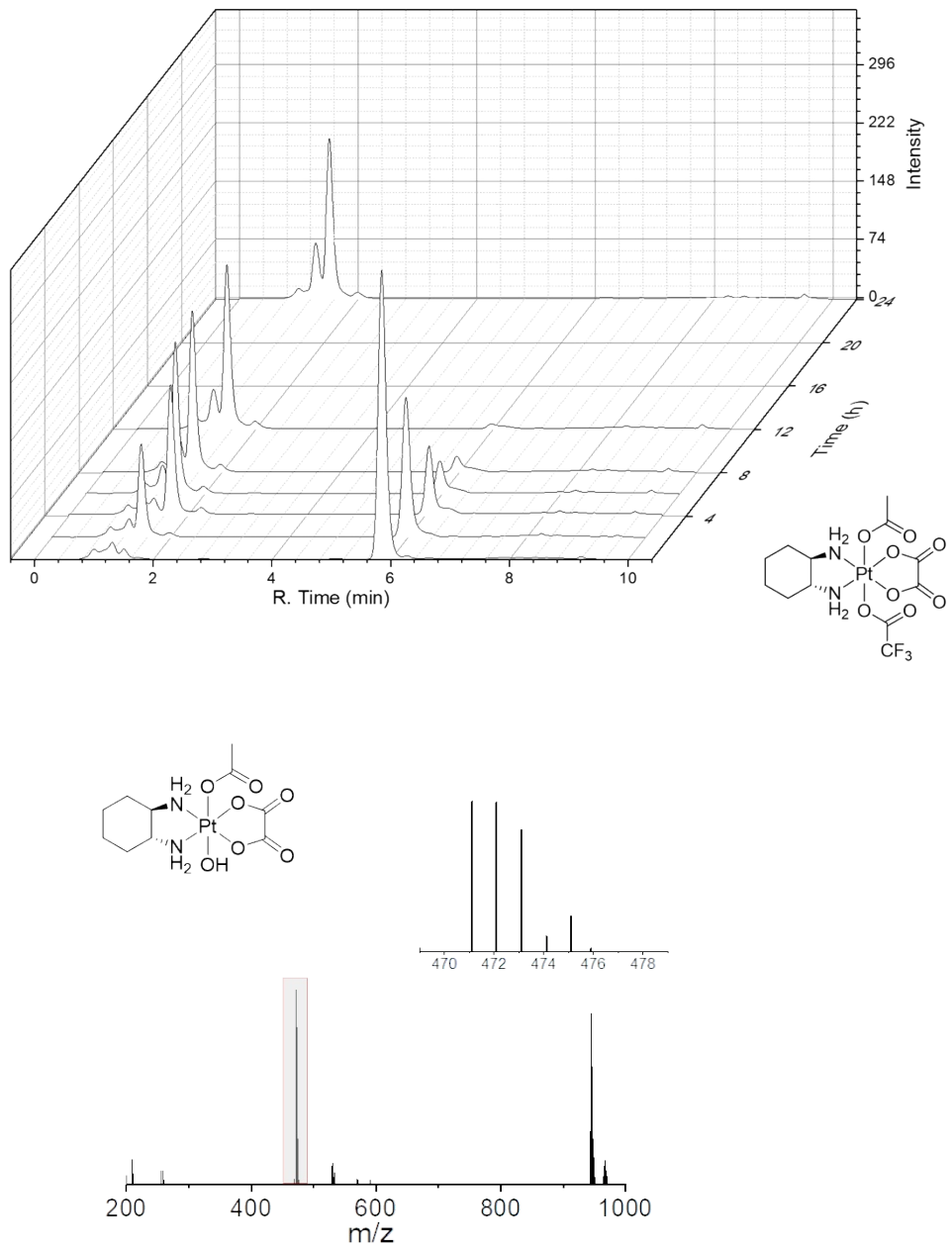


Figure S25. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OAc)] 4a'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 5.9 min belongs to complex **4a'**. Chromatographic peak in 1.4 min contains the hydrolyzed product ***t*-[Pt(DACH)(ox)(OAc)(OH)]**. Under: Mass spectrum acquired on peak at 1.4 min in the 8 h chromatogram, ESI-MS: calcd for $C_{10}H_{17}N_2O_7Pt$ $[M\text{-}H]^-$: *m/z* 472.1; found: *m/z* 472.1.

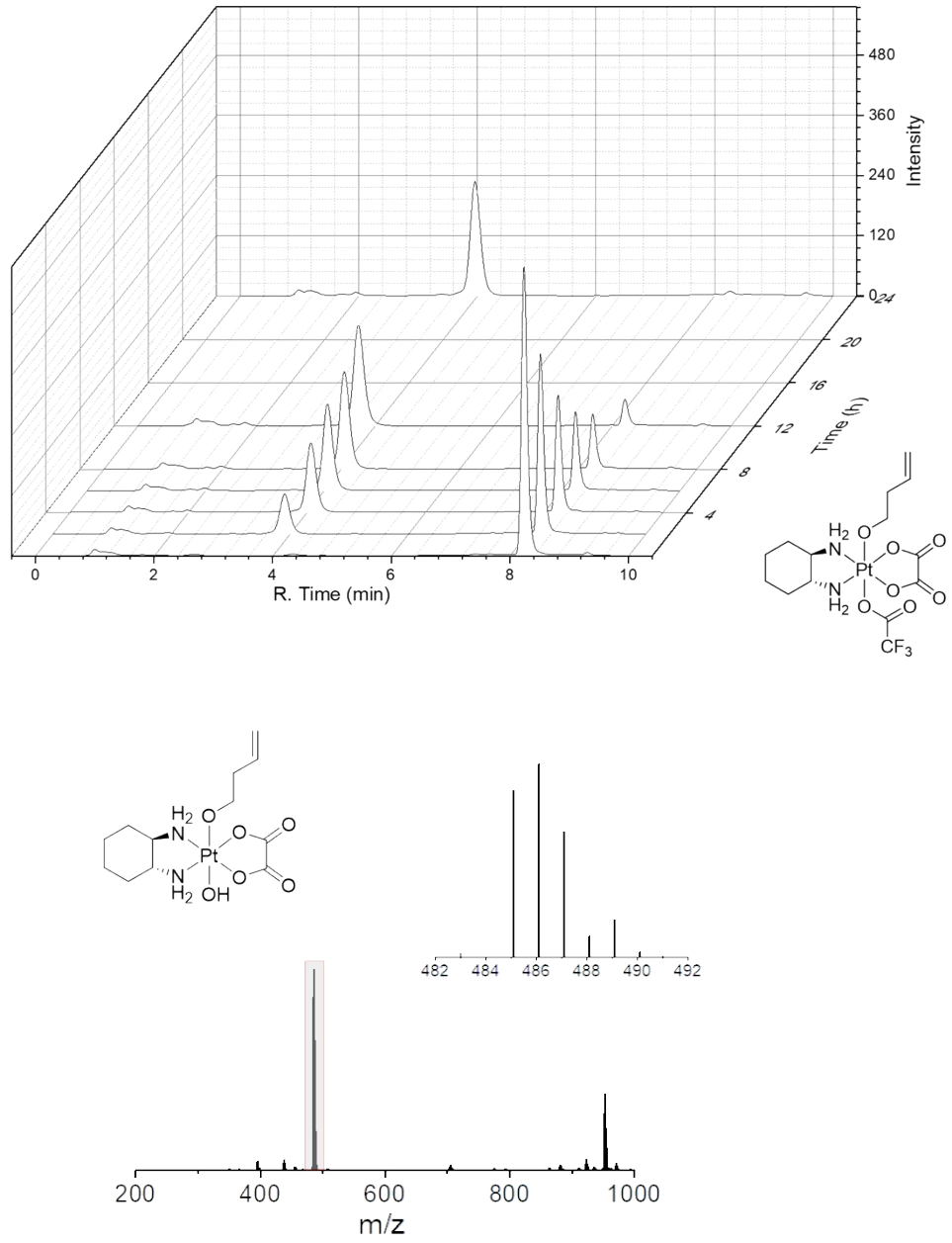


Figure S26. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)($OCH_2CH_2CH=CH_2$)] 4c** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.2 min belongs to complex **4c**. Chromatographic peak in 3.8 min belongs to the hydrolyzed product ***t*-[Pt(DACH)(ox)($OCH_2CH_2CH=CH_2$)(OH)]**. Under: Mass spectrum acquired on peak at 3.8 min in the 8 h chromatogram, ESI-MS: calcd for $C_{12}H_{23}N_2O_6Pt$ $[M+H]^+$: *m/z* 486.1; found: *m/z* 486.1

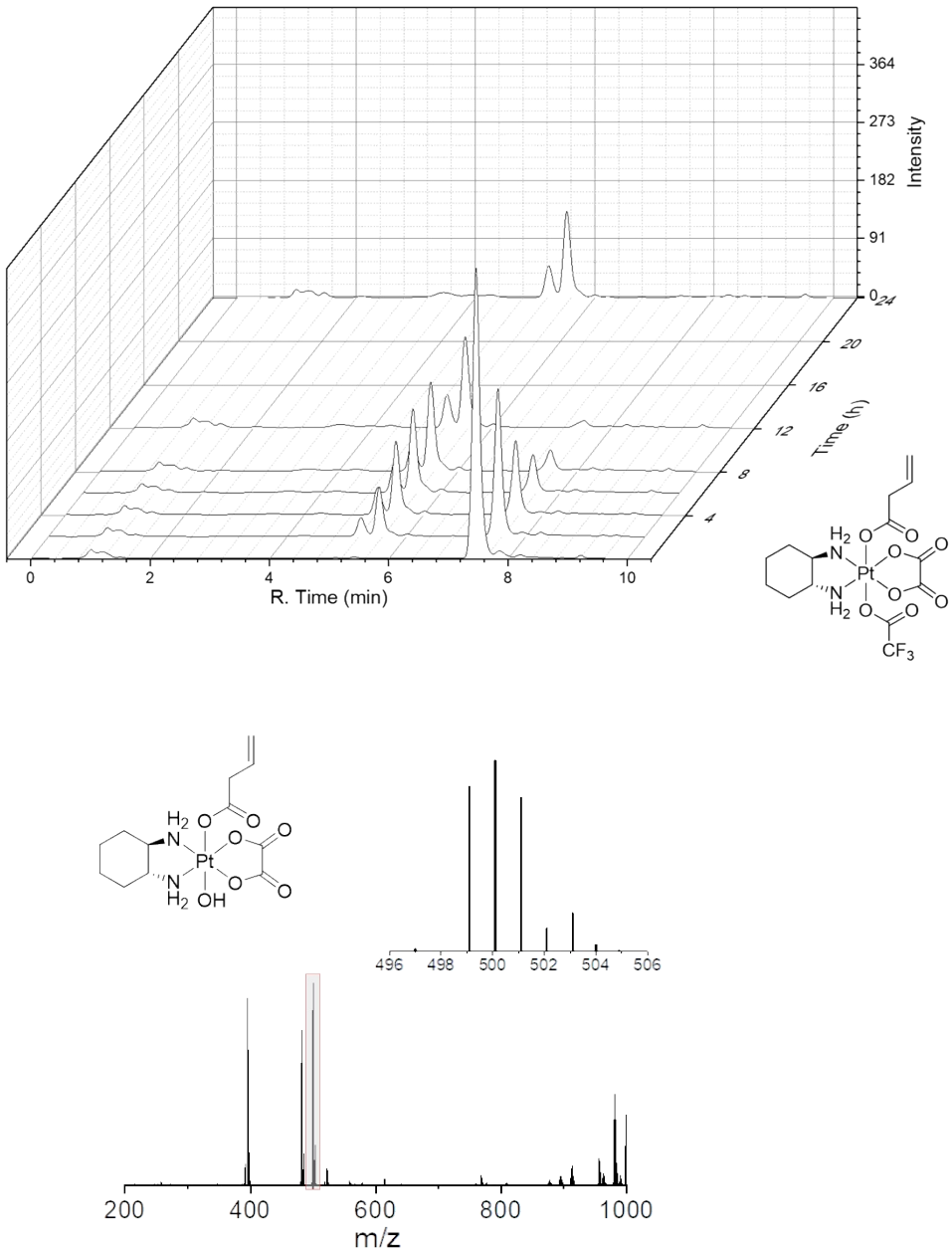


Figure S27. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OOCCH$_2$CH=CH$_2$)] 4c'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.5 min belongs to complex **4c'**, Chromatographic peak in 5.6 min belongs to the hydrolyzed product ***t*-[Pt(DACH)(ox)(OOCCH$_2$CH=CH$_2$)(OH)]**. Under: Mass spectrum acquired on peak at 5.6 min in the 8 h chromatogram, ESI-MS: calcd for $C_{12}H_{21}N_2O_7Pt$ $[M+H]^+$: *m/z* 500.1; found: *m/z* 500.1.

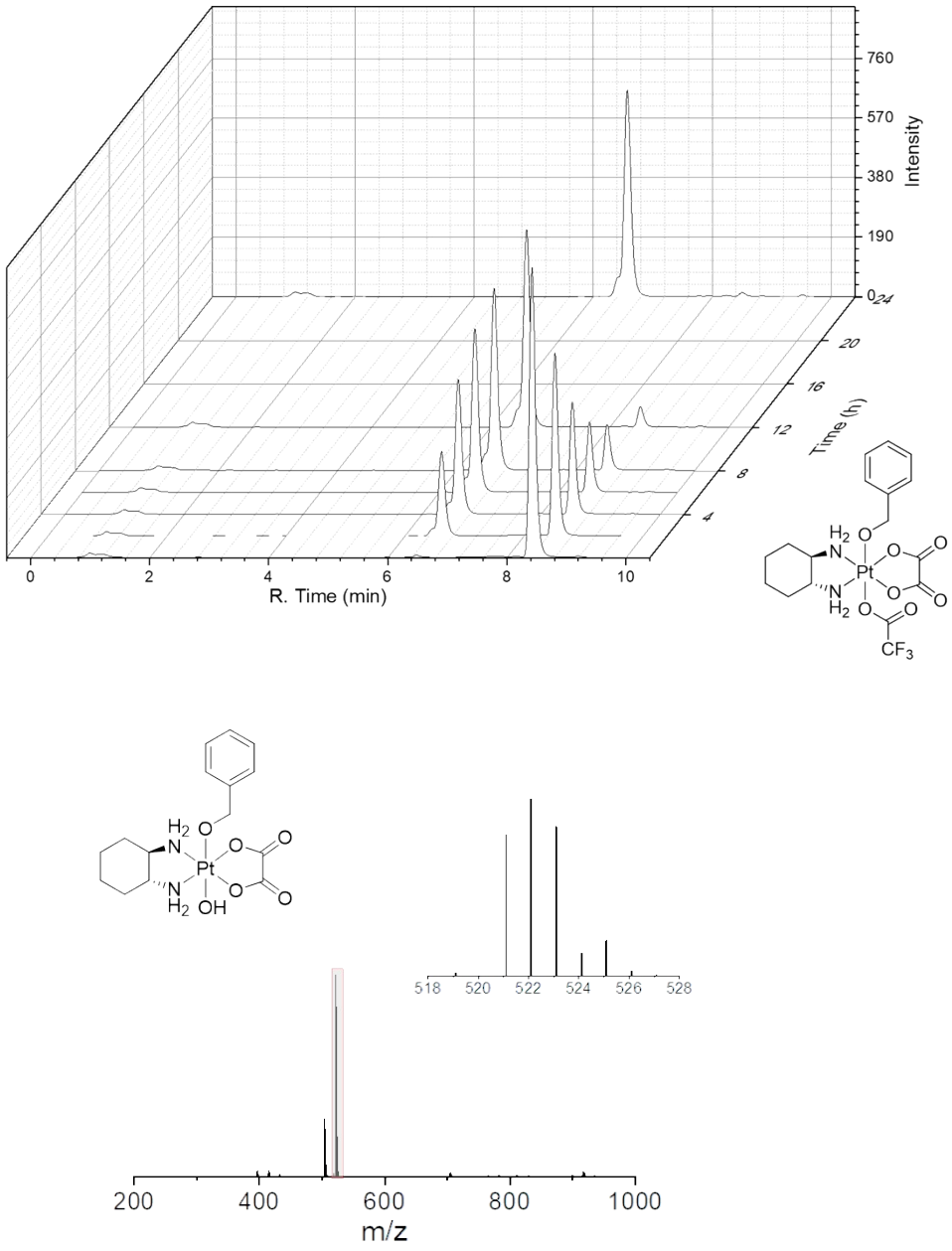


Figure S28. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(OBn)] 4e** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.5 min belongs to complex **4e**. Chromatographic peak in 6.6 min belongs to the hydrolyzed product ***t*-[Pt(DACH)(ox)(OBn)(OH)]**. Under: Mass spectrum acquired on peak at 6.6 min in the 8 h chromatogram, ESI-MS: calcd for $C_{15}H_{23}N_2O_6Pt$ $[M+H]^+$: *m/z* 522.1; found: *m/z* 522.1.

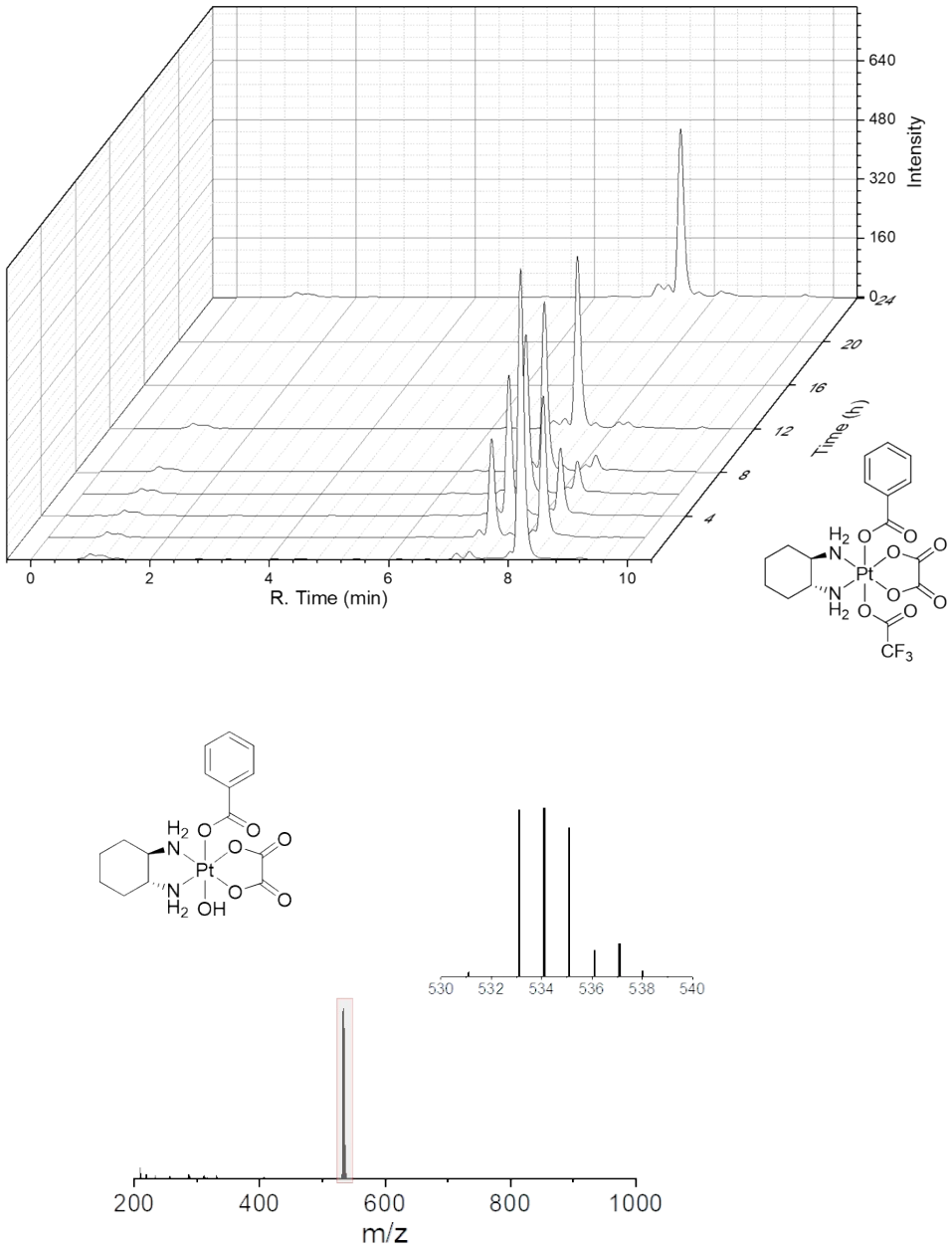
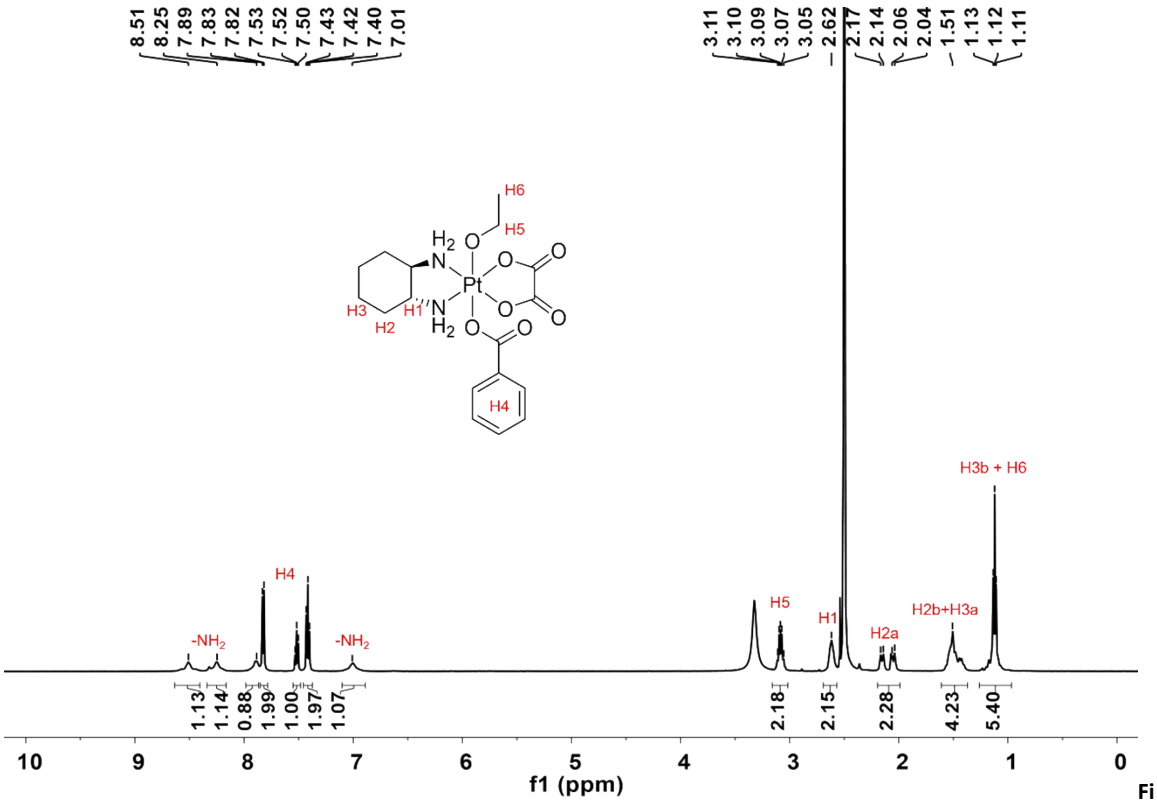
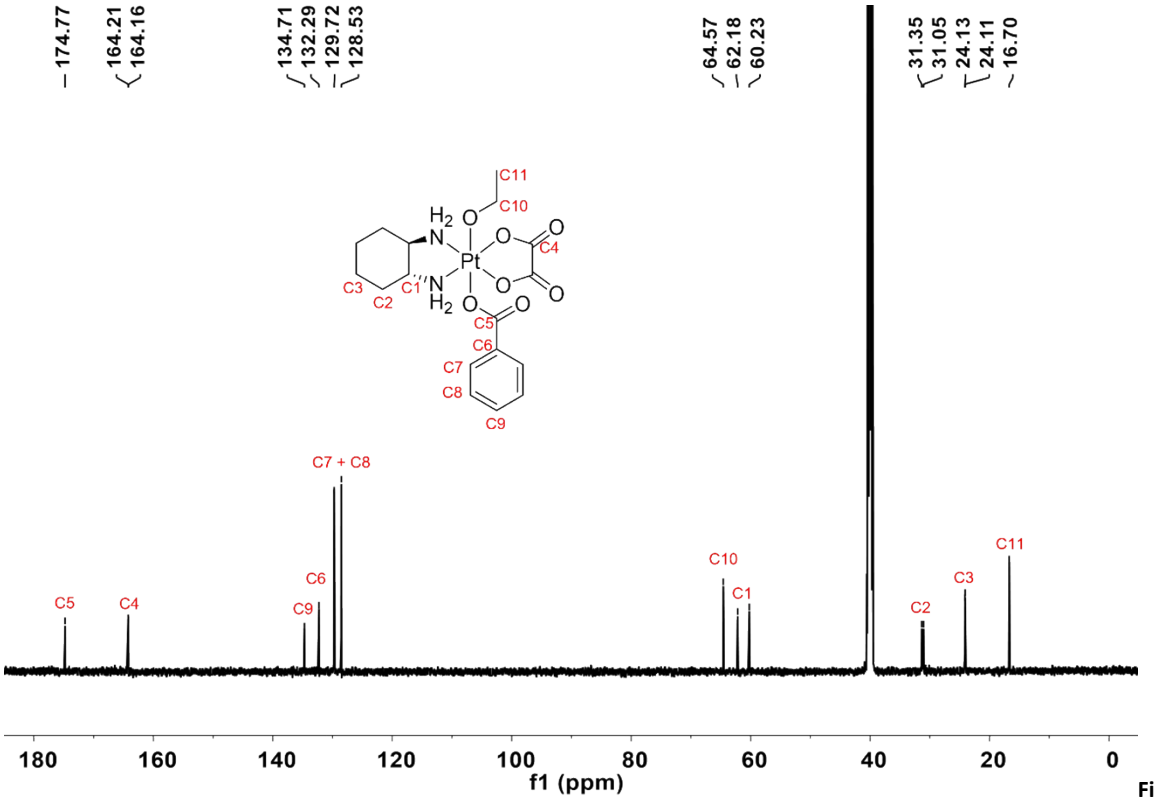


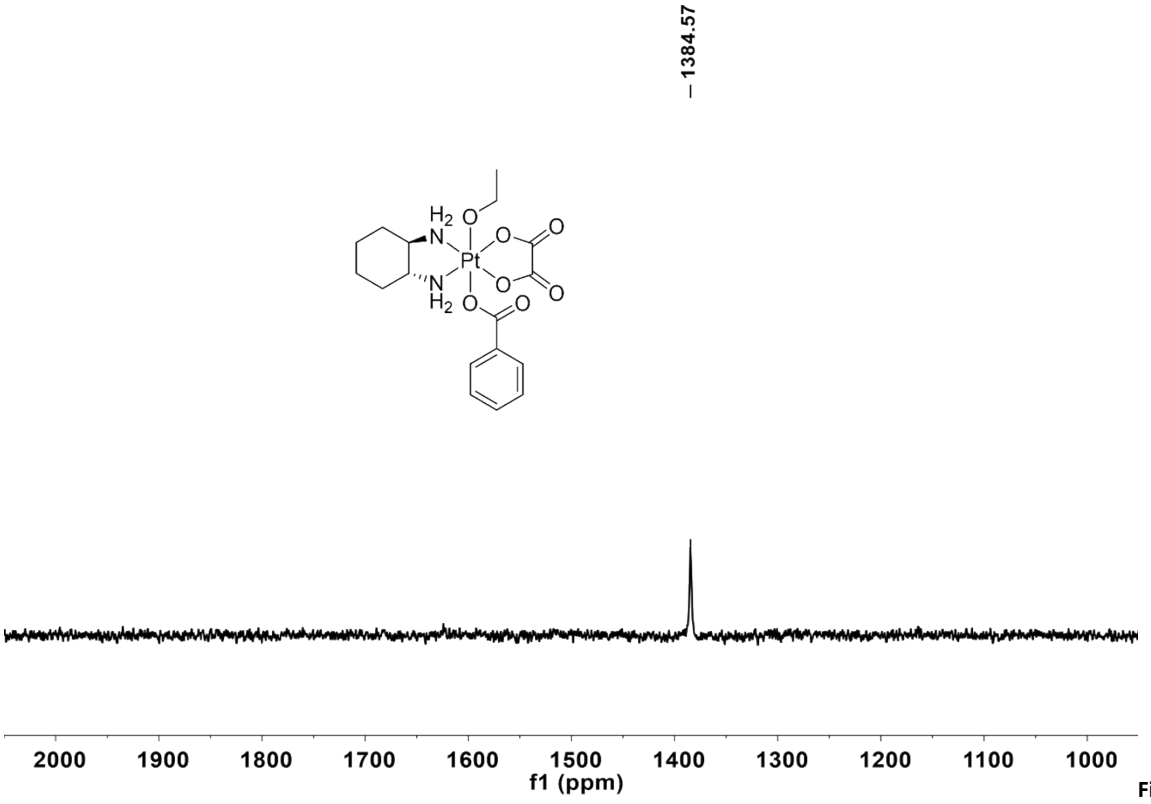
Figure S29. Upper: HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(TFA)(benzoato)] 4e'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.2 min belongs to complex **4e'**. Chromatographic peak in7.4 min belongs to the hydrolyzed product ***t*-[Pt(DACH)(ox)(benzoato)(OH)]**. Under: Mass spectrum acquired on peak at 7.4 min in the 8 h chromatogram, ESI-MS: calcd for $C_{15}H_{19}N_2O_7Pt$ $[M\text{-}H]^-$: *m/z* 534.1; found: *m/z* 534.1.



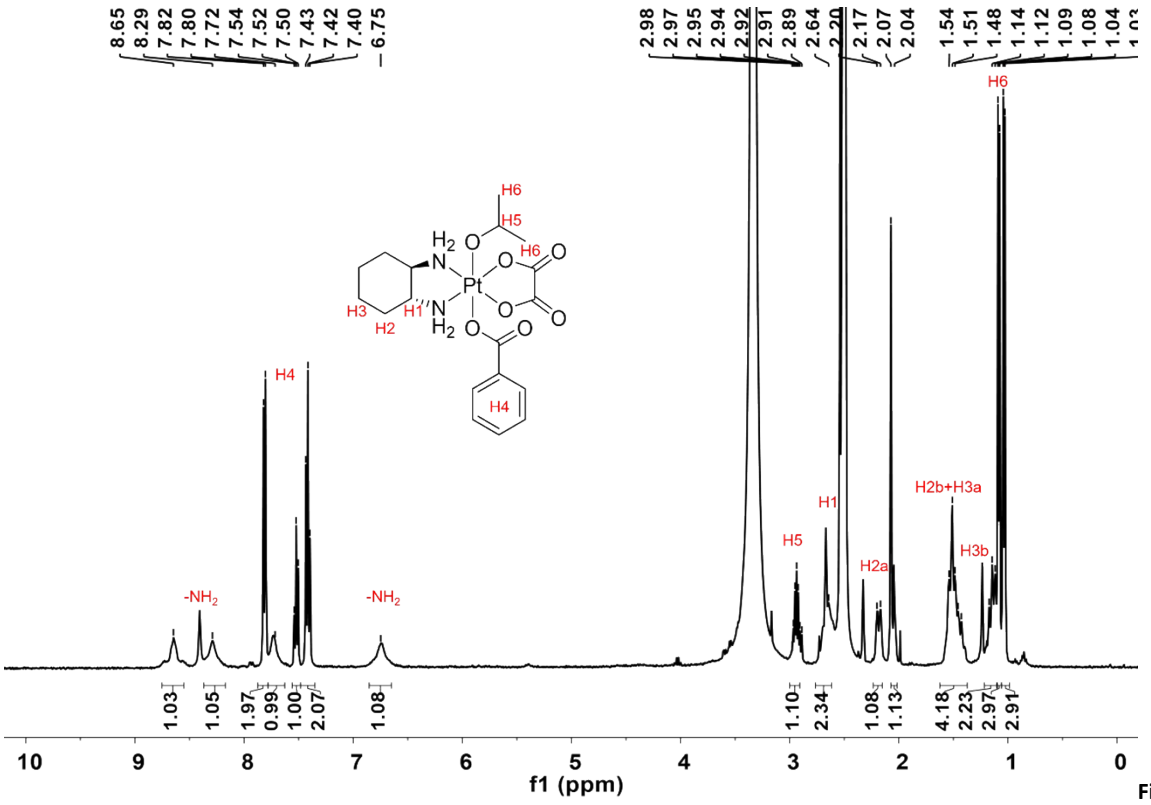
gure S30. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** in DMSO-d_6.



gure S31. ^{13}C{^{1}H} NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** in DMSO-d_6.



gure S32. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** in DMSO-d_6.



gure S33. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OiPr)] 5b** in DMSO-d_6.

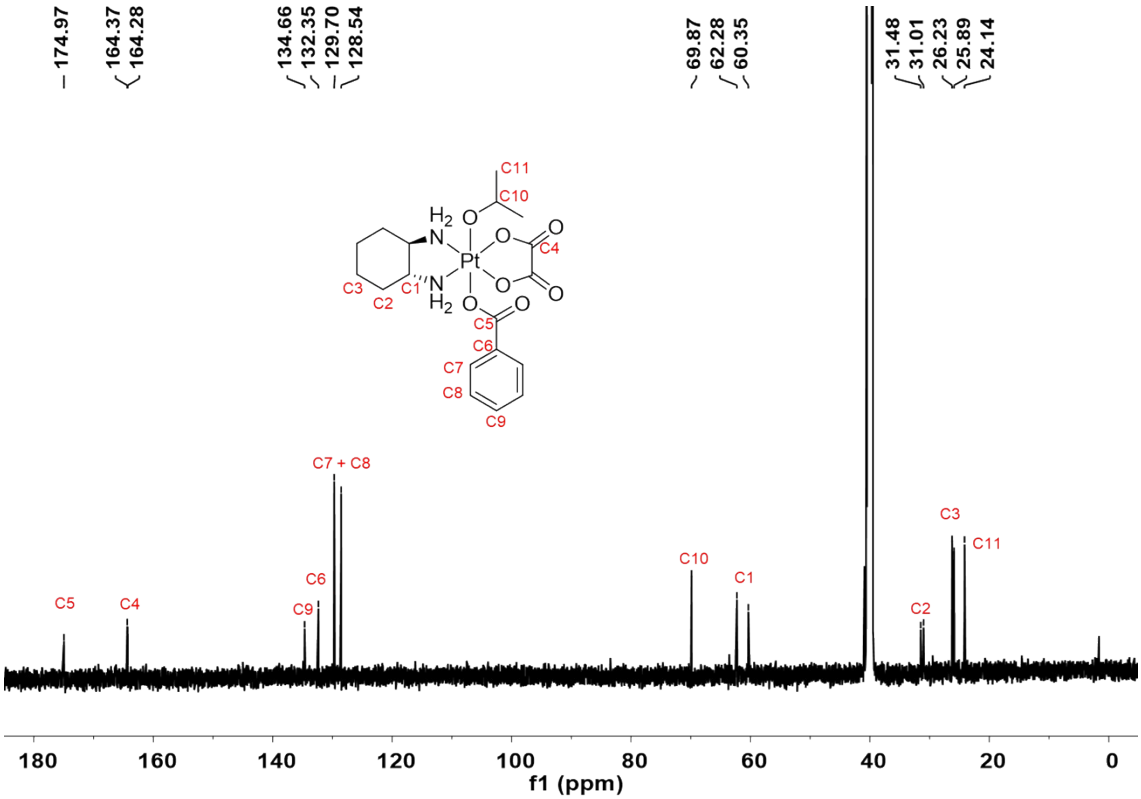


Figure S34. $^{13}C\{^{1}H\}$ NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OiPr)] 5b** in DMSO-d_6.

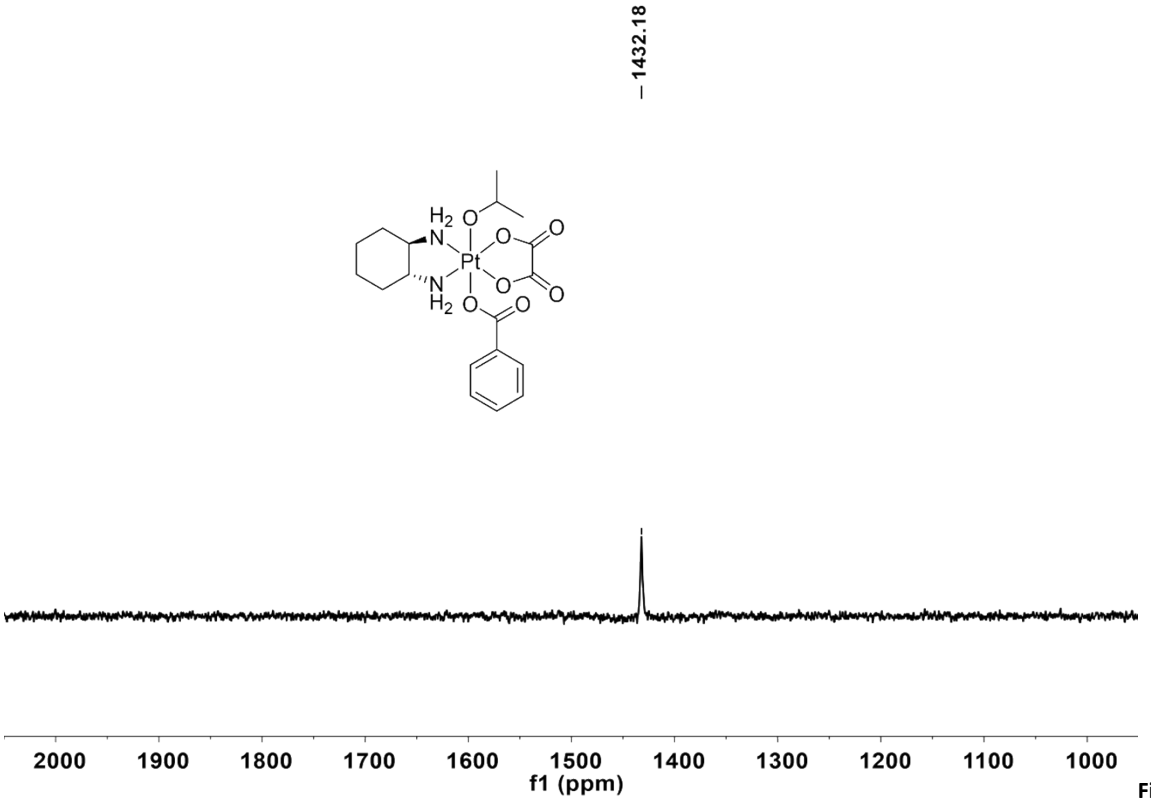
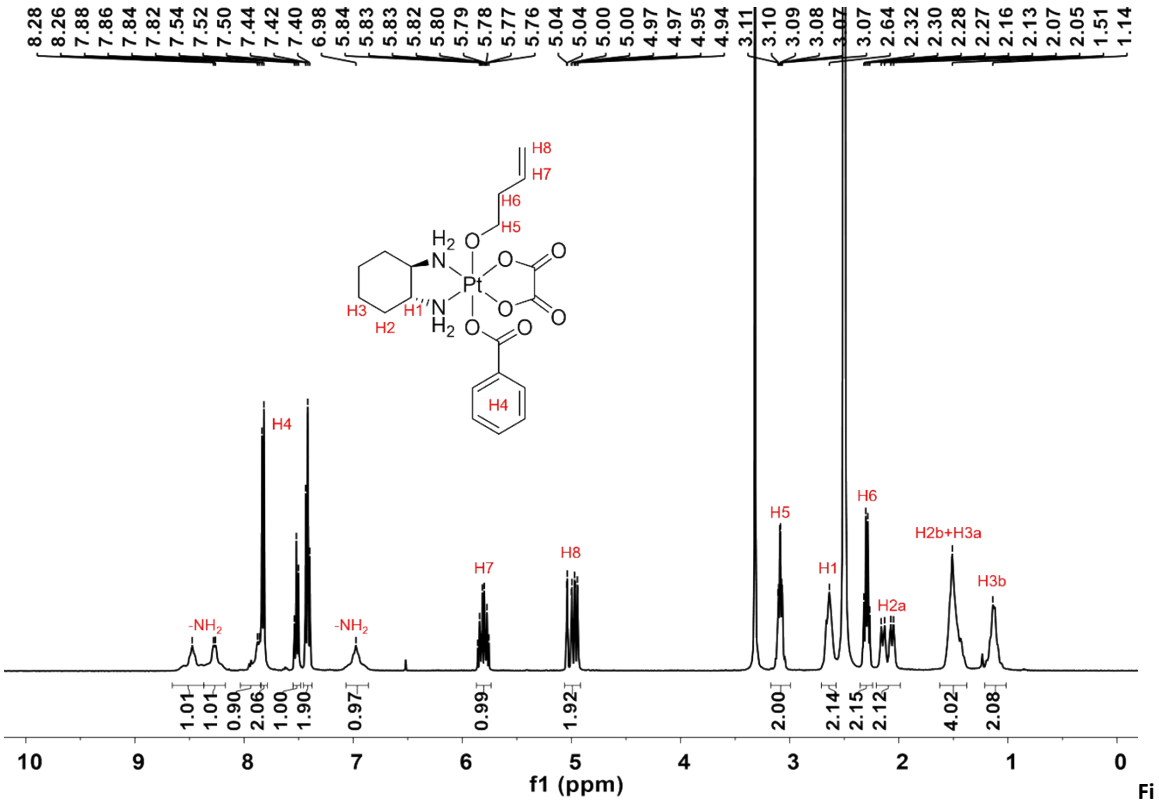
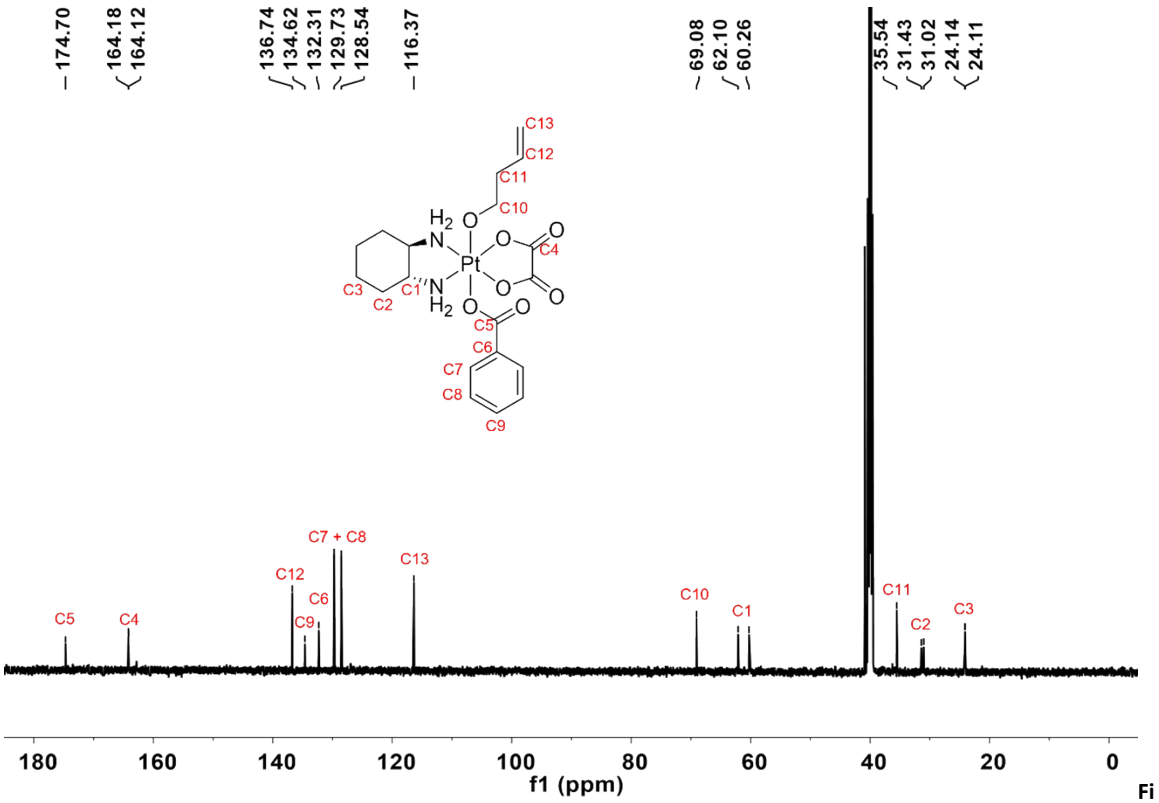


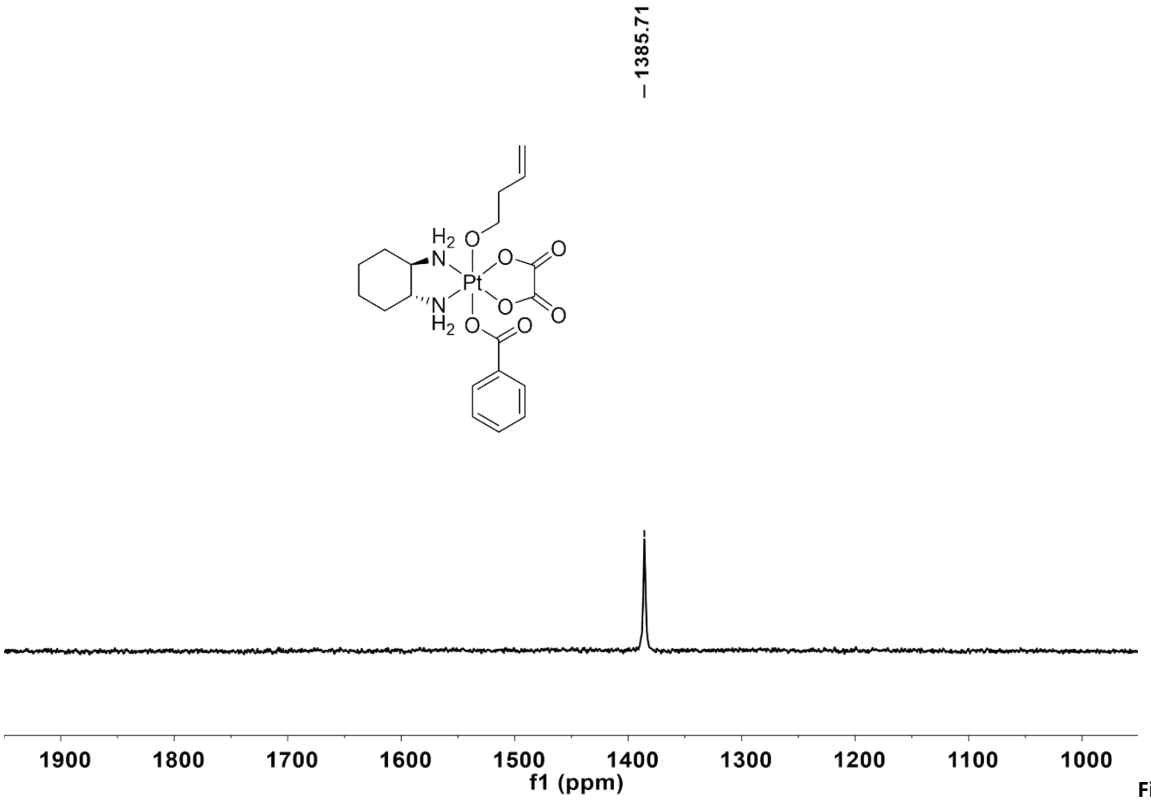
Figure S35. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OiPr)] 5b** in DMSO-d_6.



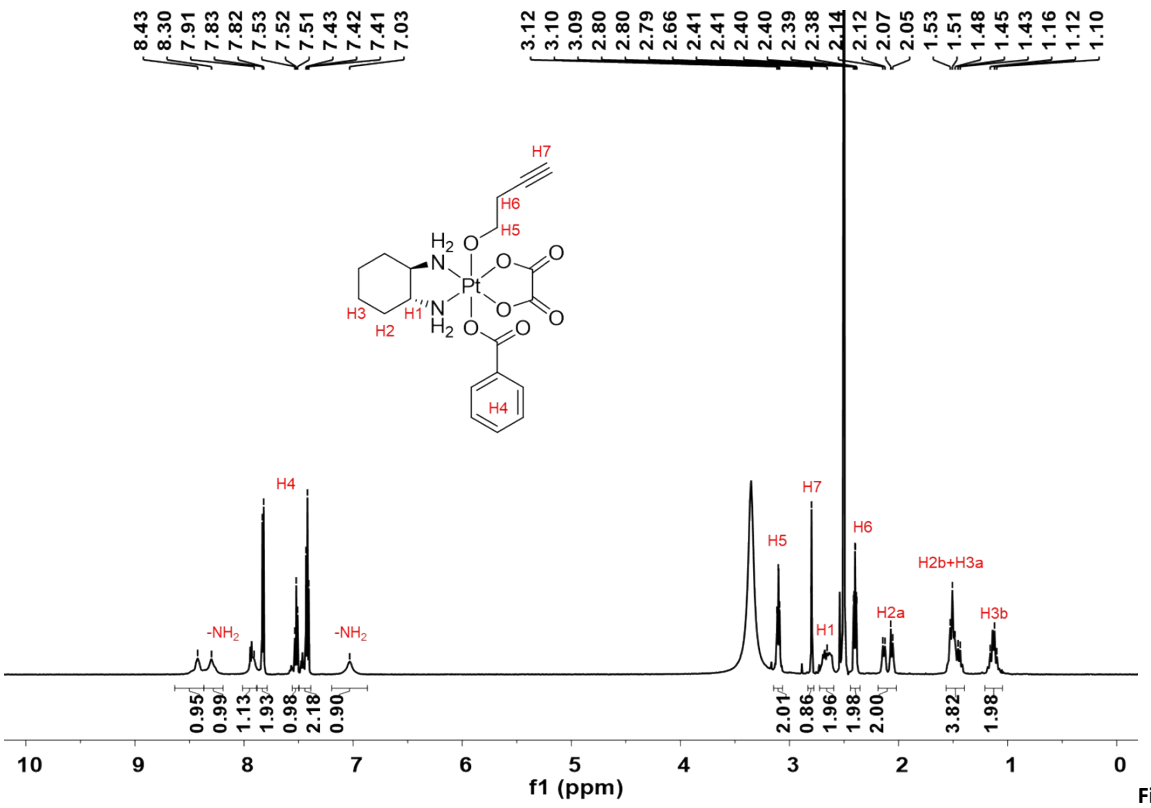
gure S36. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OCH$_2$CH$_2$CH=CH$_2$)] 5c** in DMSO-d_6.



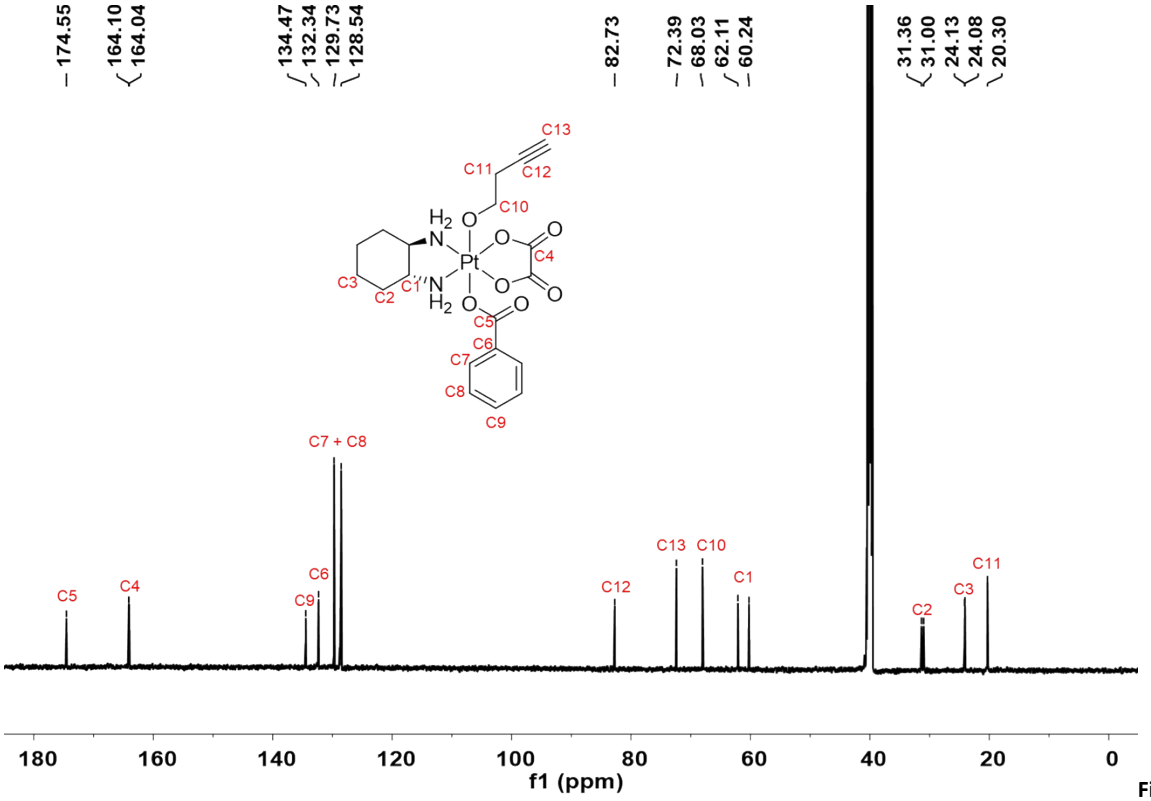
gure S37. ^{13}C{^{1}H} NMR spectrum of Pt(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OCH$_2$CH$_2$CH=CH$_2$)] 5c** in DMSO-d_6.



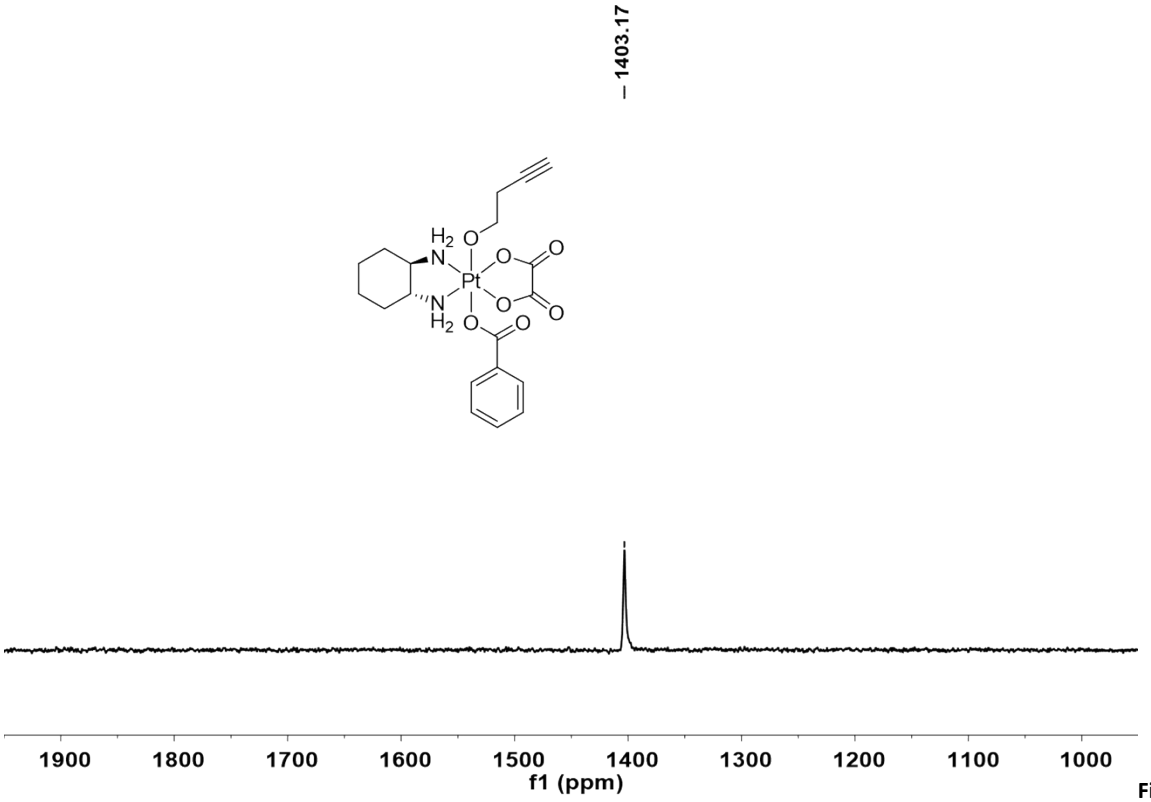
gure S38. ^{195}Pt NMR spectrum of Pt(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OCH$_2$CH$_2$CH=CH$_2$)] 5c** in DMSO-d_6.



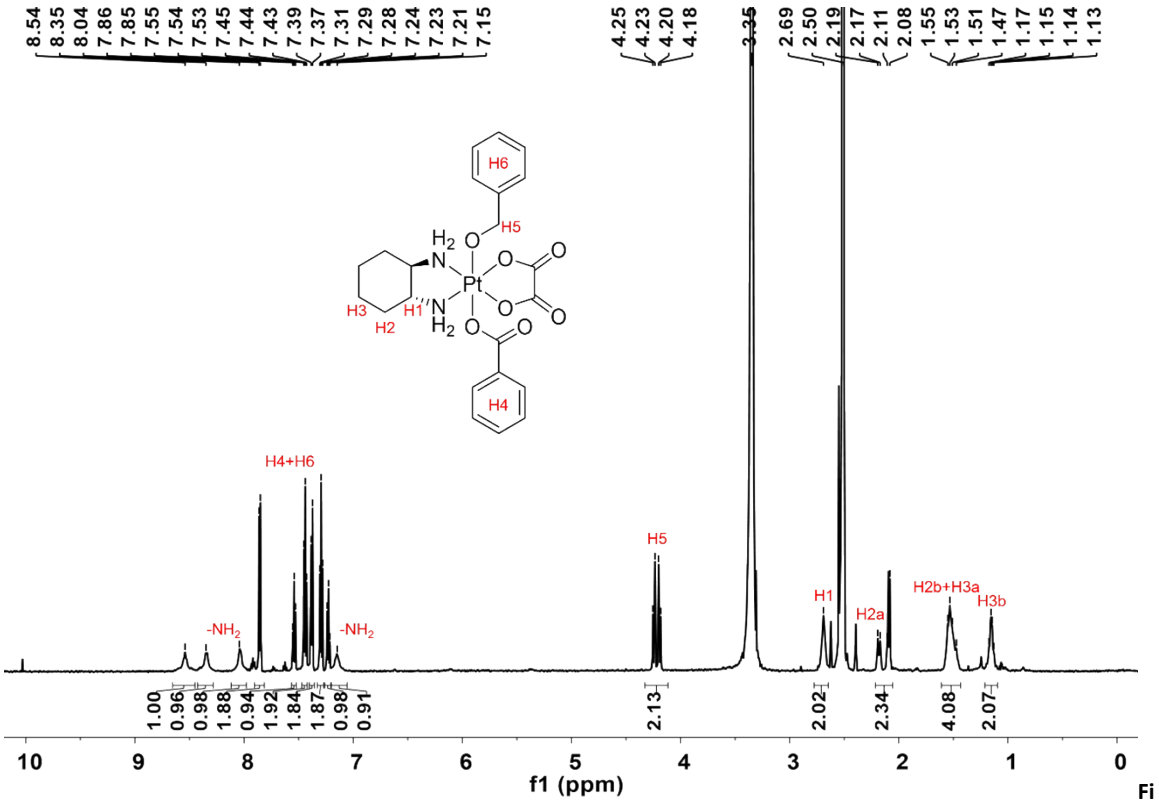
gure S39. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OCH$_2$CH$_2$C≡CH)] 5d** in DMSO-d_6.



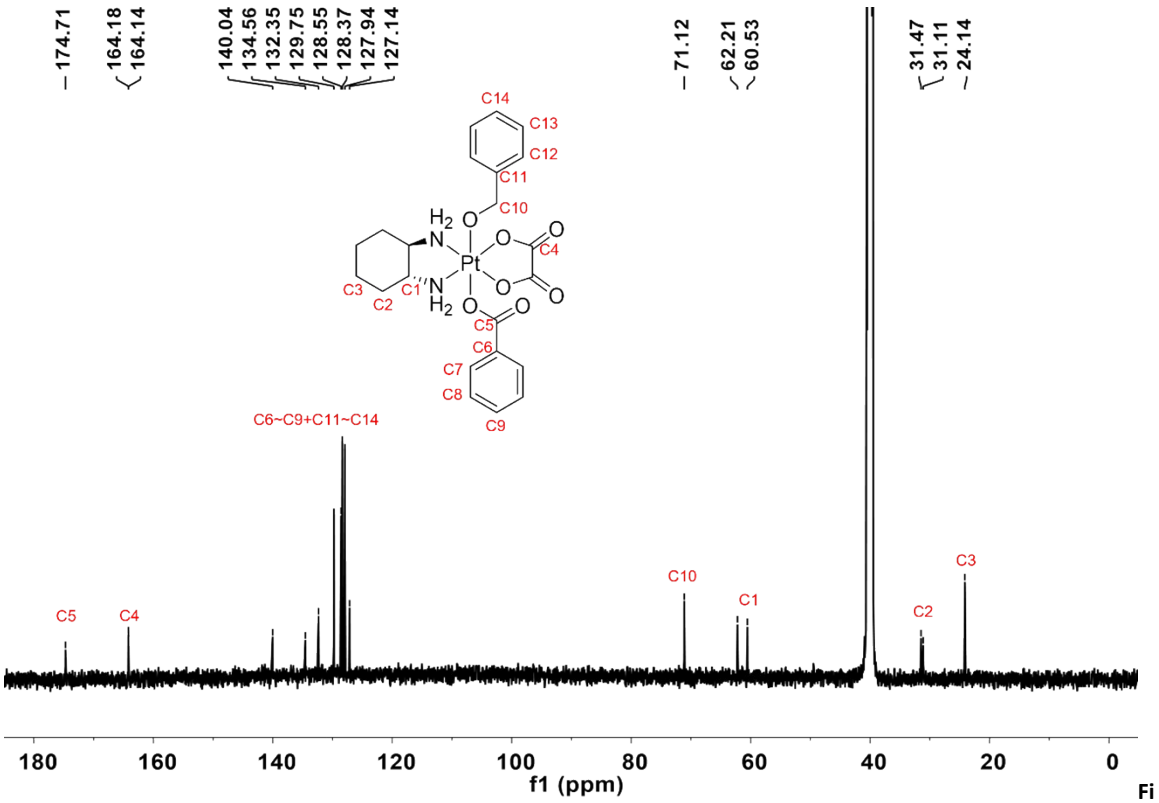
gure S40. $^{13}C\{^{1}H\}$ NMR spectrum of Pt(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2C{\equiv}CH$)] 5d** in DMSO-d_6.



gure S41. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2C{\equiv}CH$)] 5d** in DMSO-d_6.



gure S42. ^{1}H NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** in DMSO-d_6.



gure S43. ^{13}C{^{1}H} NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** in DMSO-d_6.

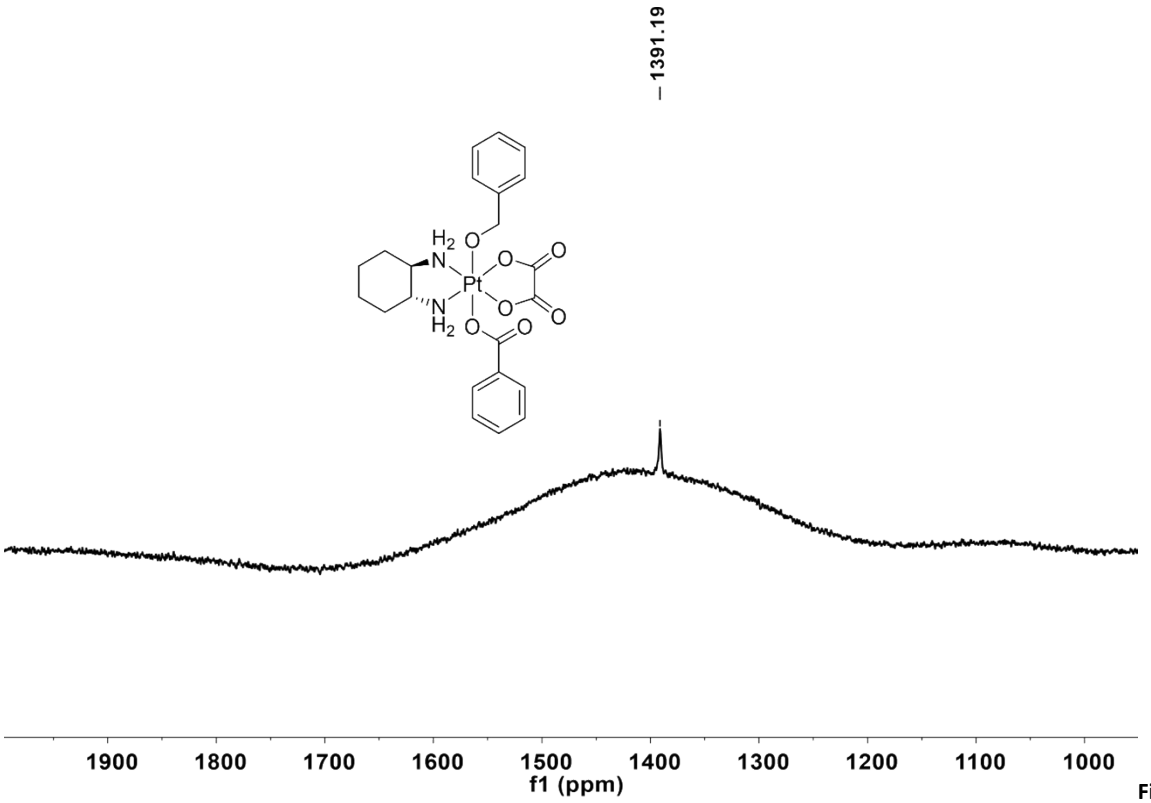


Figure S44. ^{195}Pt NMR spectrum of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** in DMSO-d_6.

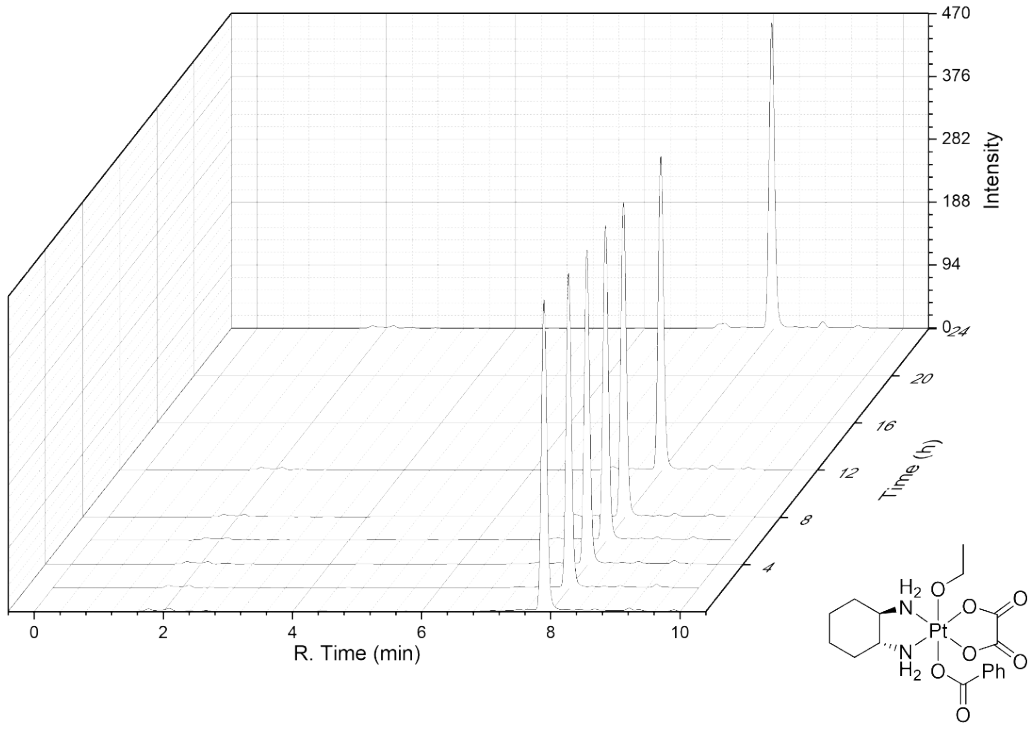


Figure S45. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.9 min belongs to complex **5a**.

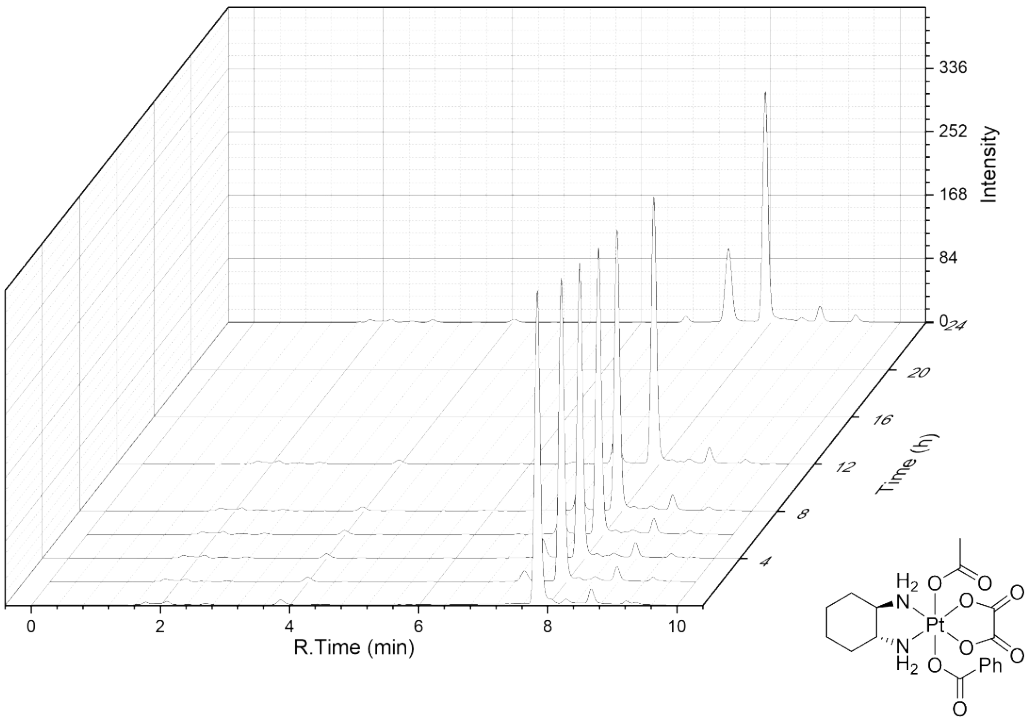


Figure S46. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OAc)] 5a'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.8 min belongs to complex **5a'**.

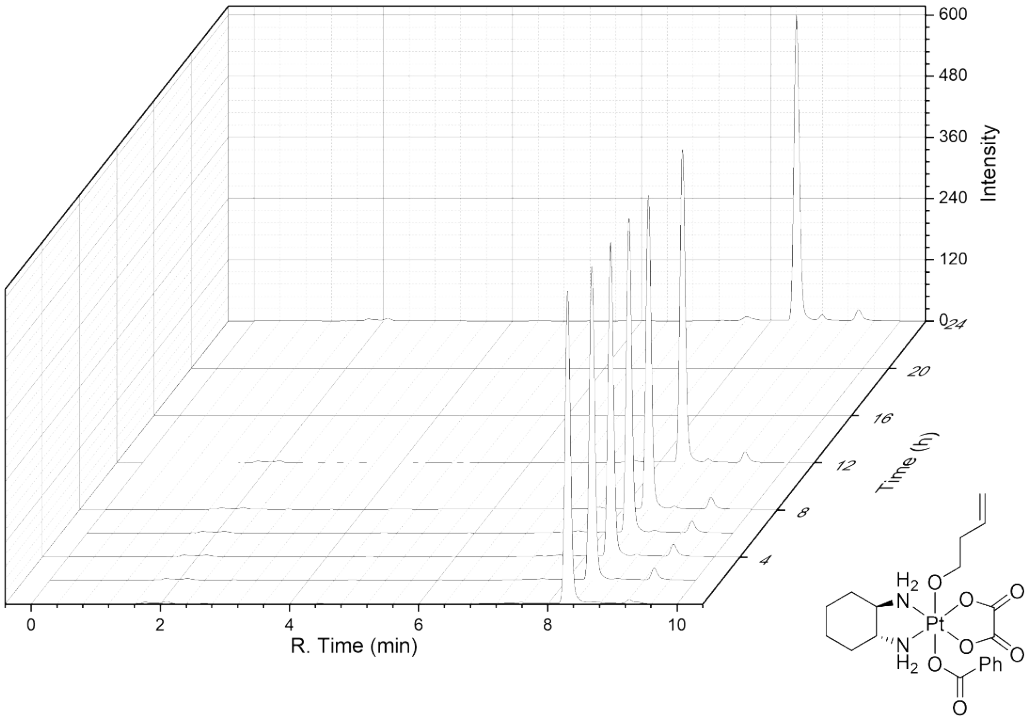


Figure S47. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2CH{=}CH_2$)] 5c** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.3 min belongs to complex **5c**.

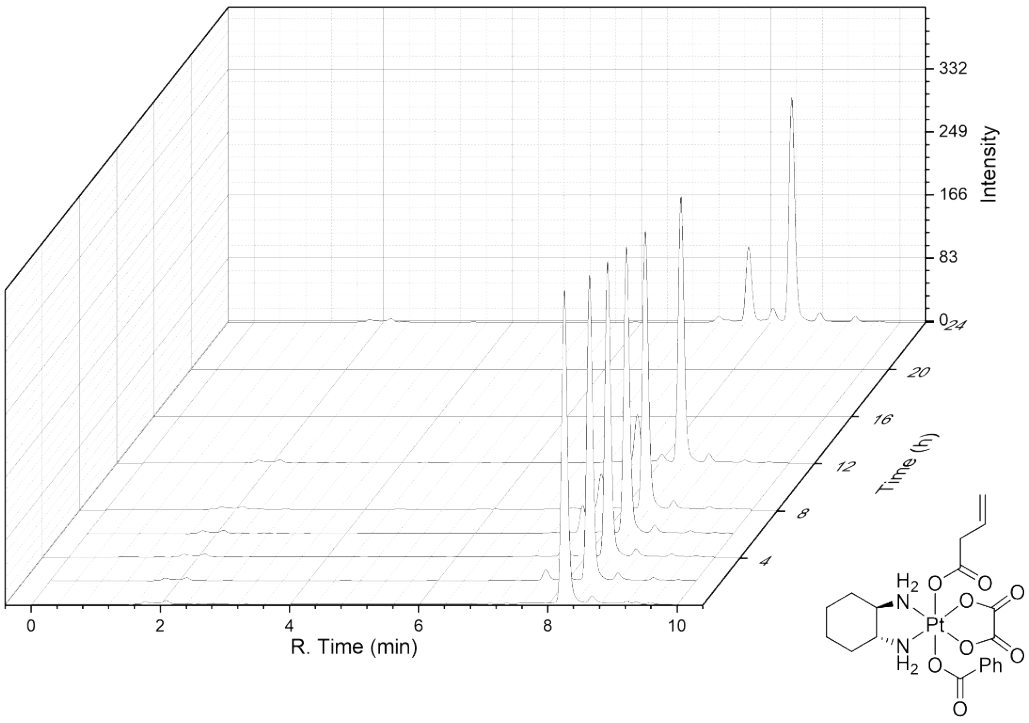


Figure S48. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OOCCH_2CH=CH_2$)] 5c'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.3 min belongs to complex **5c'**.

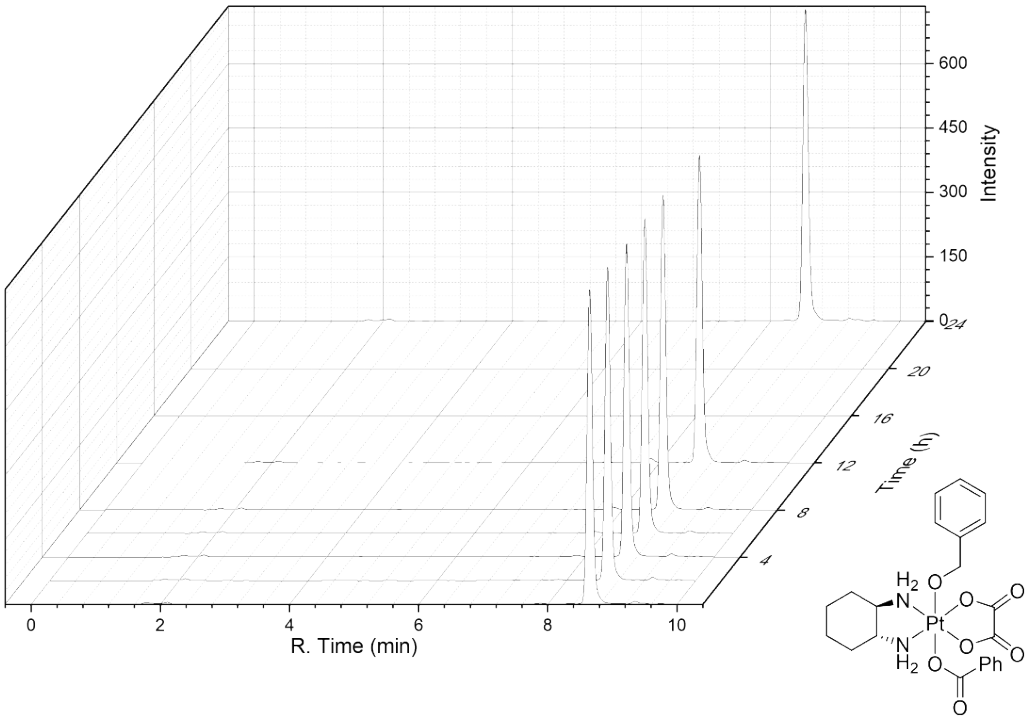


Figure S49. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.6 min belongs to complex **5e**.

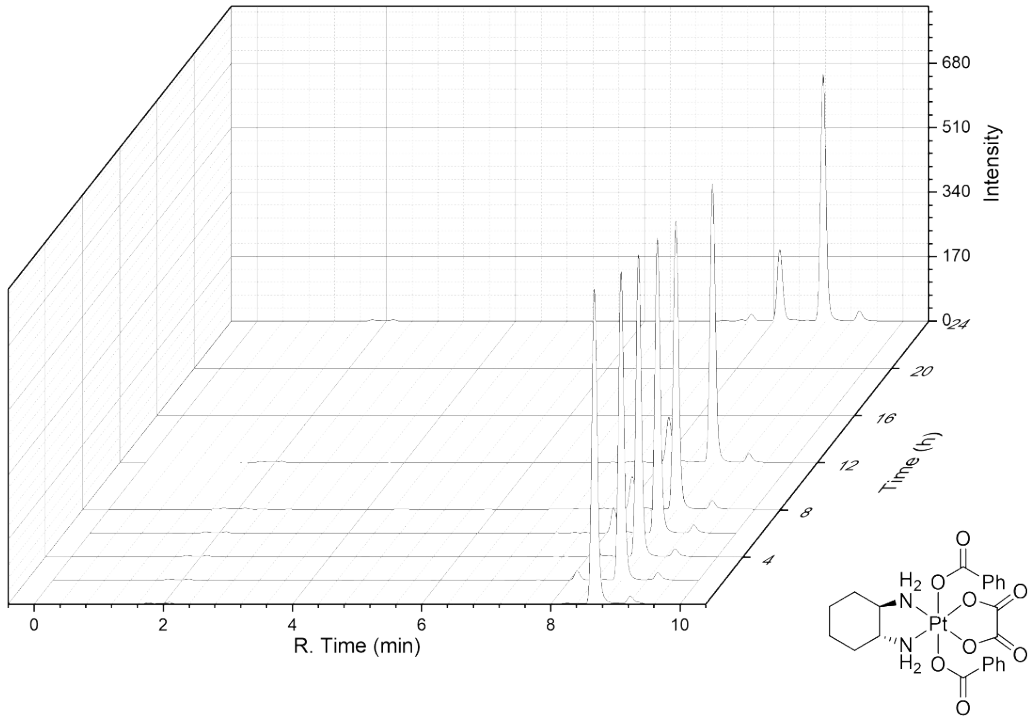


Figure S50. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)$_2$] 5e'** in PBS (10 mM, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.7 min belongs to complex **5e'**.

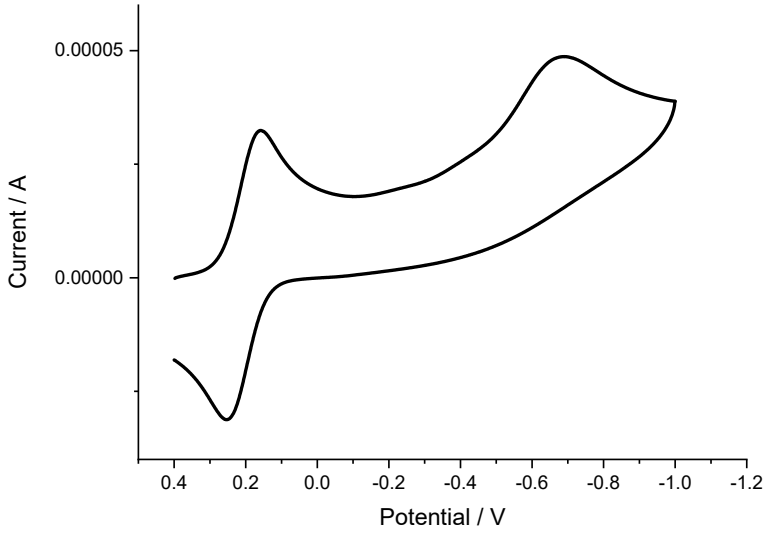


Figure S51. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** with $K_3[Fe(CN)_6]$ as an internal reference.

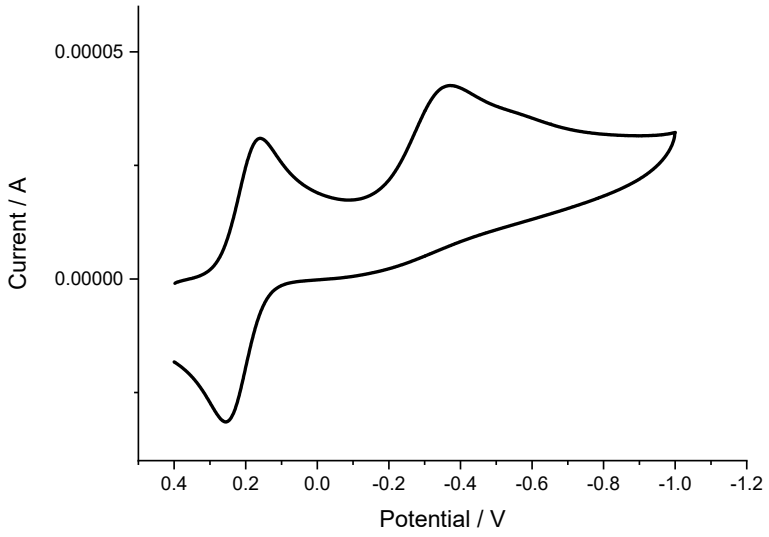


Figure S52. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OAc)] 5a'** with $K_3[Fe(CN)_6]$ as an internal reference.

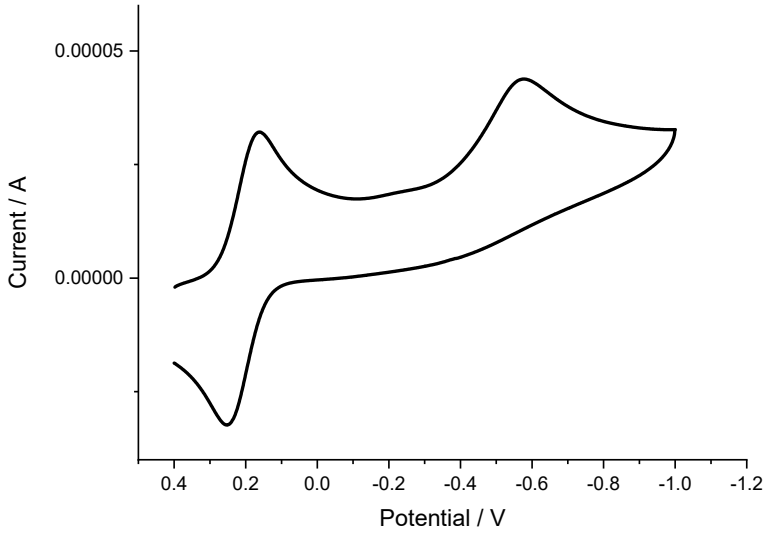


Figure S53. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2CH=CH_2$)] 5c** with $K_3[Fe(CN)_6]$ as an internal reference.

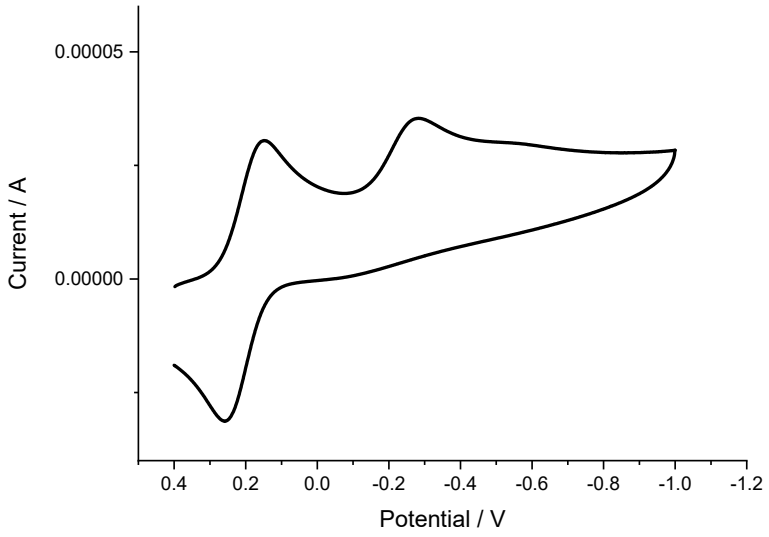


Figure S54. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OOCCH$_2$CH=CH$_2$)] 5c'** with $K_3[Fe(CN)_6]$ as an internal reference.

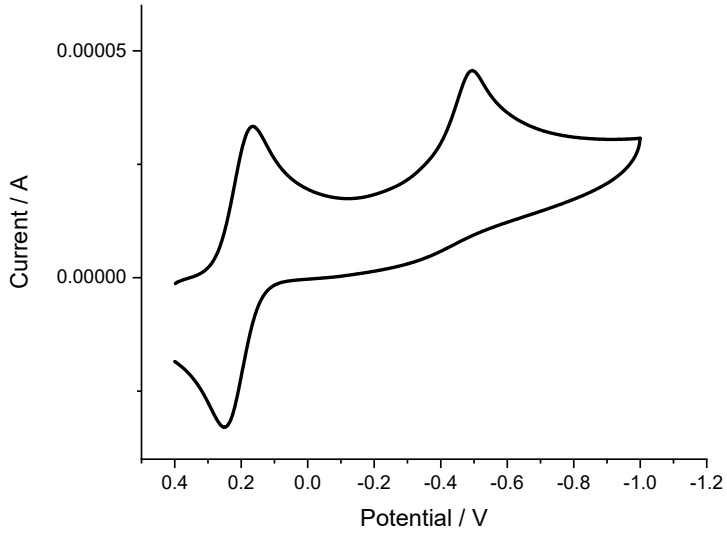


Figure S55. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** with $K_3[Fe(CN)_6]$ as an internal reference.

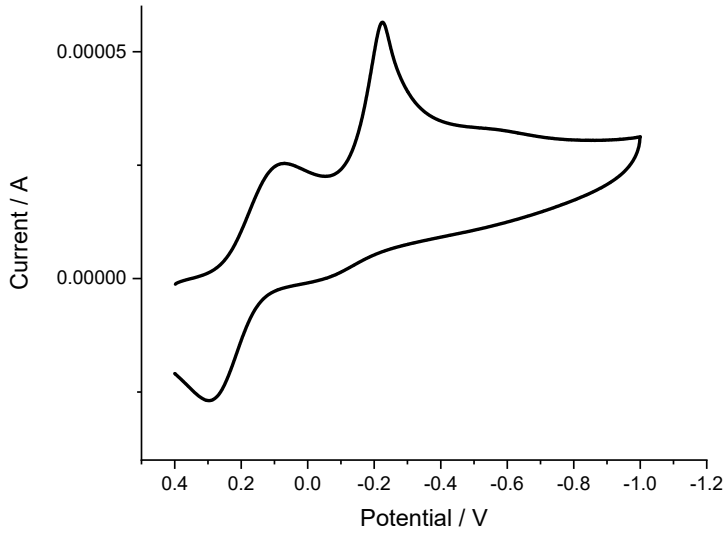


Figure S56. Cyclic voltammetry of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)$_2$] 5e'** with $K_3[Fe(CN)_6]$ as an internal reference.

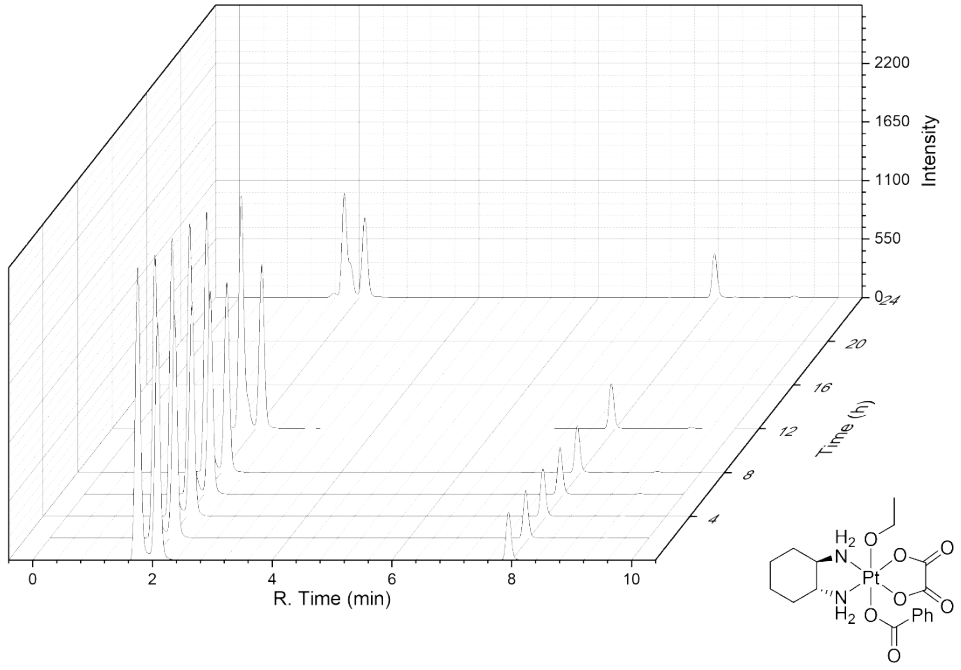


Figure S57. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OEt)] 5a** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.9 min belongs to complex **5a**.

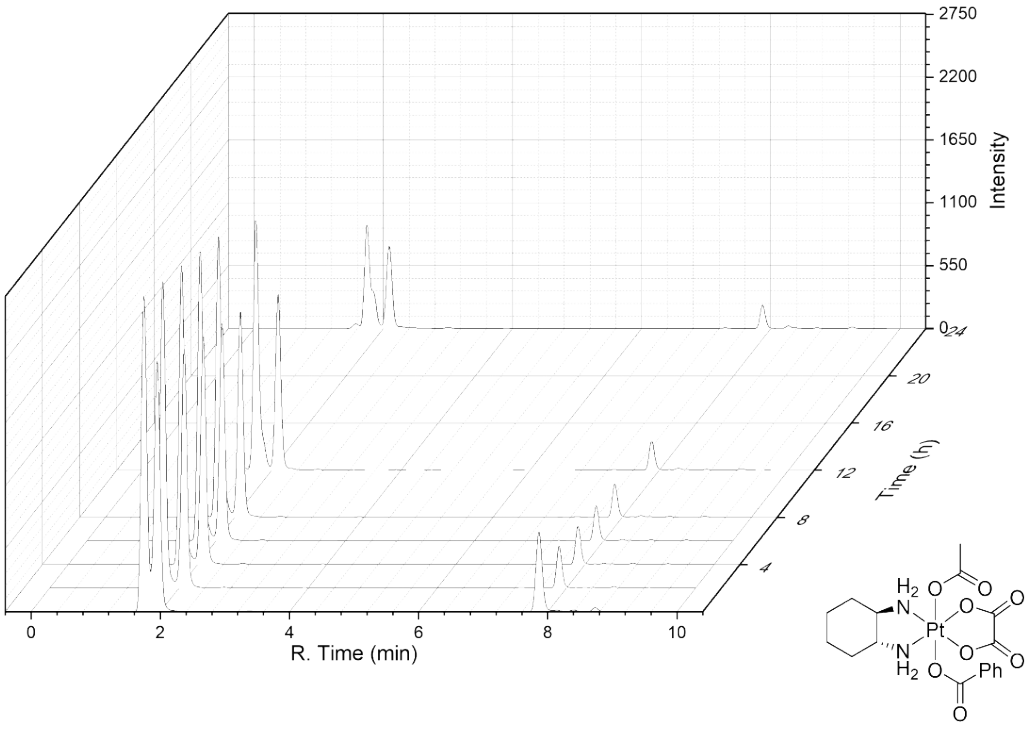


Figure S58. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OAc)] 5a'** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 7.8 min belongs to complex **5a'**.

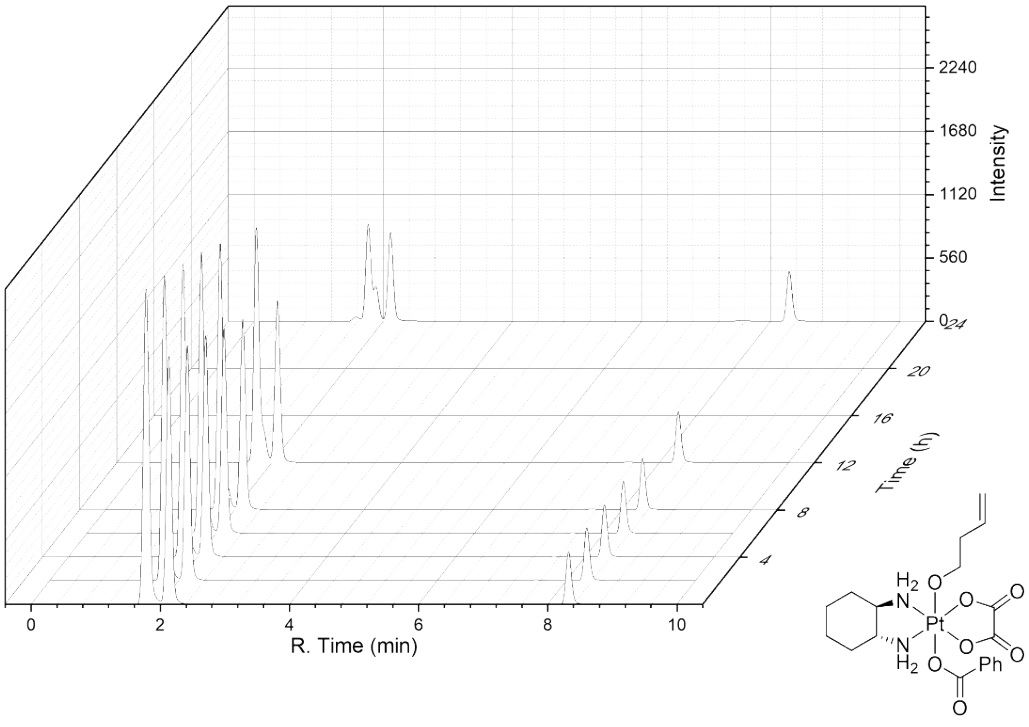


Figure S59. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)($OCH_2CH_2CH{=}CH_2$)] 5c** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.3 min belongs to complex **5c**.

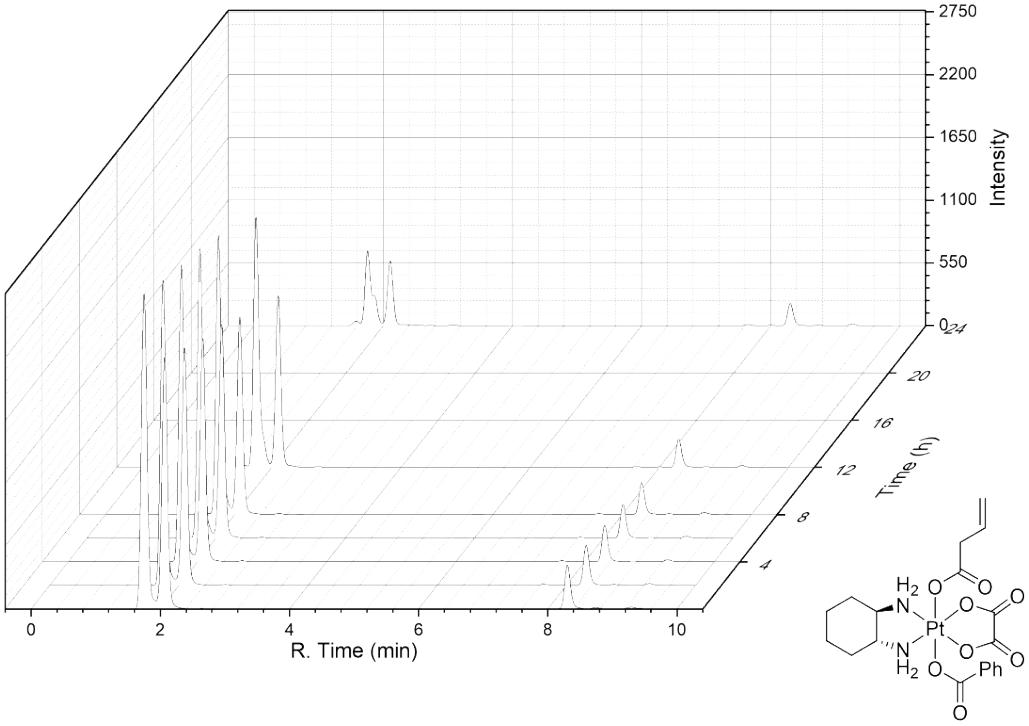


Figure S60. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OOCCH$_2$CH=CH$_2$)] 5c'** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.3 min belongs to complex **5c'**.

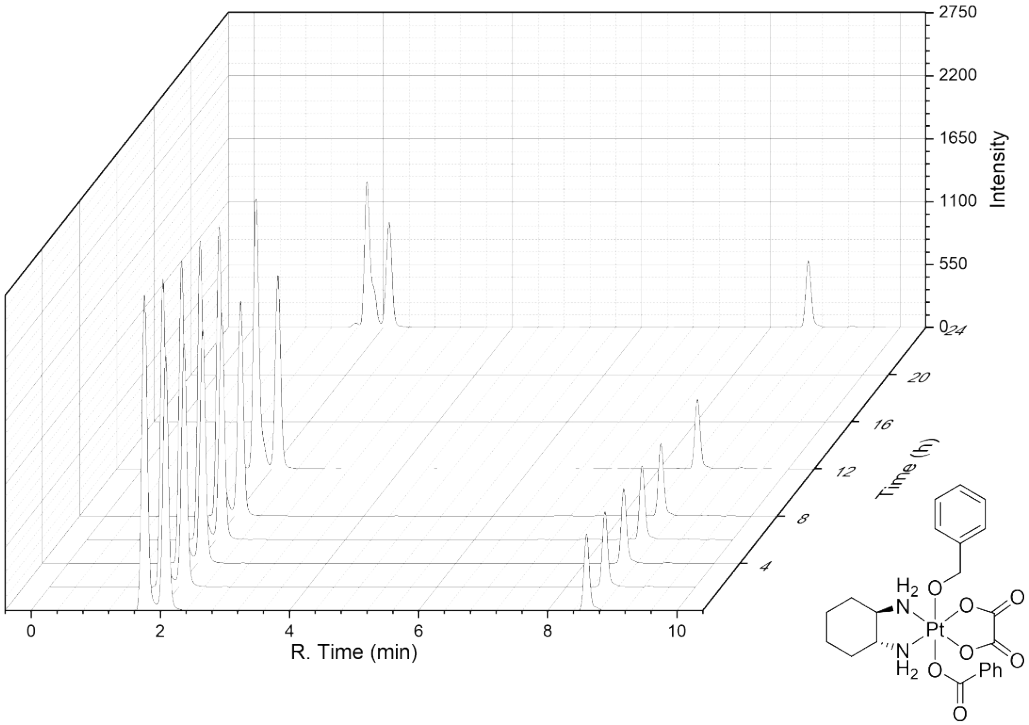


Figure S61. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)(OBn)] 5e** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.6 min belongs to complex **5e**.

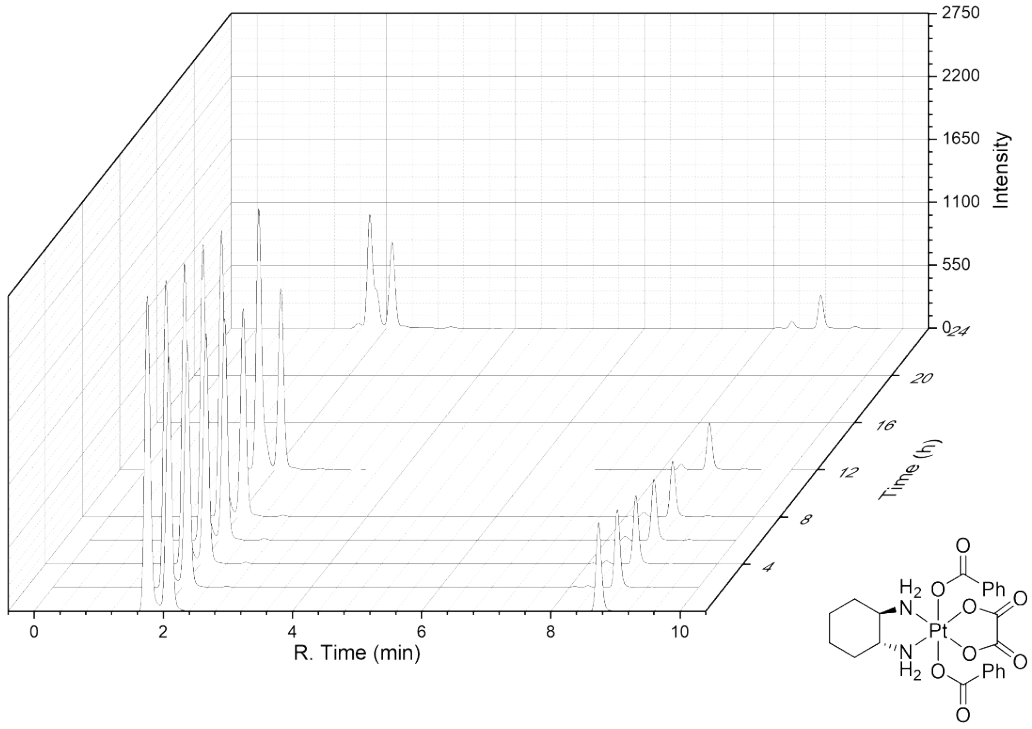
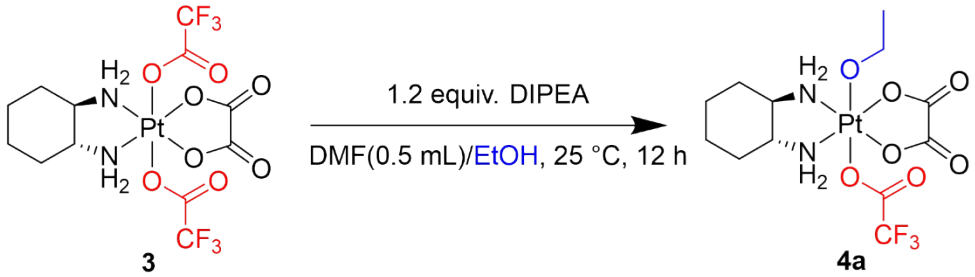


Figure S62. HPLC chromatograms of platinum(IV) complex ***t*-[Pt(DACH)(ox)(benzoato)$_2$] 5e'** in PBS (10 mM, 3 mM ascorbate, pH 7.4) at 37 °C from 0 to 24 h. Chromatographic peak in 8.7 min belongs to complex **5e'**.

Table S1. Optimization of reaction conditions for platinum(IV) complex **4a**.

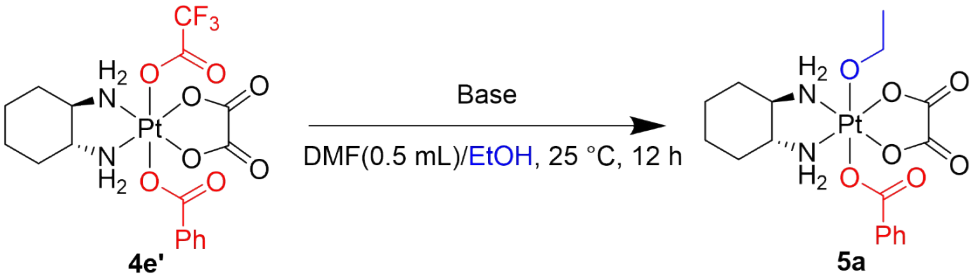


3
50 mg

4a

Entry	Solvent	Volume	Equiv.	Yield (%)
1	EtOH	1.5 mL	320	64
2	EtOH	500 µL	107	50
3	EtOH	250 µL	54	45
4	EtOH	125 µL	27	36
5	EtOH	50 µL	10	20
6	EtOH	25 µL	5	16
7	EtOH	10 µL	2	8

Table S2. Optimization of reaction conditions for platinum(IV) complex **5a**.



4e'
50 mg

5a

Entry	Base	Equiv.	EtOH	Yield (%)
1	KOAc	1.2	1.5 mL (324 equiv.)	10
2	$NaHCO_3$	1.2	1.5 mL	29
3	Et_3N	1.2	1.5 mL	30
4	DIPEA	1.2	1.5 mL	38
5	DBU	1.2	1.5 mL	53
6	KO*t*Bu	1.2	1.5 mL	49
7	DBU	1.2	500 µL (108 equiv.)	50
8	DBU	1.2	250 µL (54 equiv.)	39
9	DBU	1.2	125 µL (27 equiv.)	26
10	DBU	1.2	50 µL (10 equiv.)	19
11	DBU	1.2	25 µL (5 equiv.)	12
12	DBU	1.2	10 µL (2 equiv.)	8

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