Electronic Supplementary Material (ESI) for Dalton Transactions.
This journal is © The Royal Society of Chemistry 2021

Supporting Information for

Optimization of axial ligands to promote the photoactivation of BODIPY-conjugated platinum(IV) anticancer prodrugs

Houzong Yao,[ab] Yuliana F. Gunawan,[a] Gongyuan Liu,[ab] Man-Kit Tse,[a] and Guangyu Zhu[ab]*

[a] Department of Chemistry, City University of Hong Kong, 83 Tat Chee Avenue, Hong Kong SAR 999077, People's Republic of China

[b] City University of Hong Kong Shenzhen Research Institute, Shenzhen 518057, People's Republic of China

* Email: guangzhu@cityu.edu.hk

CONTENTS

Figure S11-S12. ^{1}H-NMR and ESI-MS spectra of compound **10**.

Figure S13-S14. ^{1}H-NMR and ESI-MS spectra of compound **11**.

Figure S15-S16. ^{1}H-NMR and ESI-MS spectra of compound **12**.

Figure S17-S18. ^{1}H-NMR and ESI-MS spectra of compound **13**.

Figure S19-S20. ^{1}H-NMR and ESI-MS spectra of compound **14**.

Figures S21-S25. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **OH3C**.

Figures S26-S30. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **OH4C**.

Figures S31-S35. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **OH6C**.

Figures S36-S40. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **OH8C**.

Figure S41-S42. ^{1}H-NMR and ESI-MS spectra of compound **15**.

Figure S43-S44. ^{1}H-NMR and ESI-MS spectra of compound **20**.

Figure S45-S46. ^{1}H-NMR and ESI-MS spectra of compound **21**.

Figure S47-S48. ^{1}H-NMR and ESI-MS spectra of compound **22**.

Figure S49-S50. ^{1}H-NMR and ESI-MS spectra of compound **23**.

Figure S51-S52. ^{1}H-NMR and ESI-MS spectra of compound **24**.

Figure S53-S54. ^{1}H-NMR and ESI-MS spectra of compound **25**.

Figure S55-S56. ^{1}H-NMR and ESI-MS spectra of compound **26**.

Figure S57-S58. ^{1}H-NMR and ESI-MS spectra of compound **27**.

Figures S59-S63. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **AC3C**.

Figures S64-S68. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **AC4C**.

Figures S69-S73. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **AC6C**.

Figures S74-S78. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, ^{195}Pt-NMR, and ESI-MS spectra of complex **AC8C**.

Figure S79. Purity of complexes **OH2C**-**OH8C** and **AC2C**-**AC8C**.

Figure S80. Absorbance and emission of BODIPY ligand.

Figure S81. Molar extinction coefficients of complexes **OH2C**-**OH8C**.

Figure S82. Molar extinction coefficients of complexes **AC2C**-**AC8C**.

Figure S83. Stability of complexes **OH2C**-**OH8C** in PBS by HPLC.

Figure S84. Stability of complexes **AC2C**-**AC8C** in PBS by HPLC.

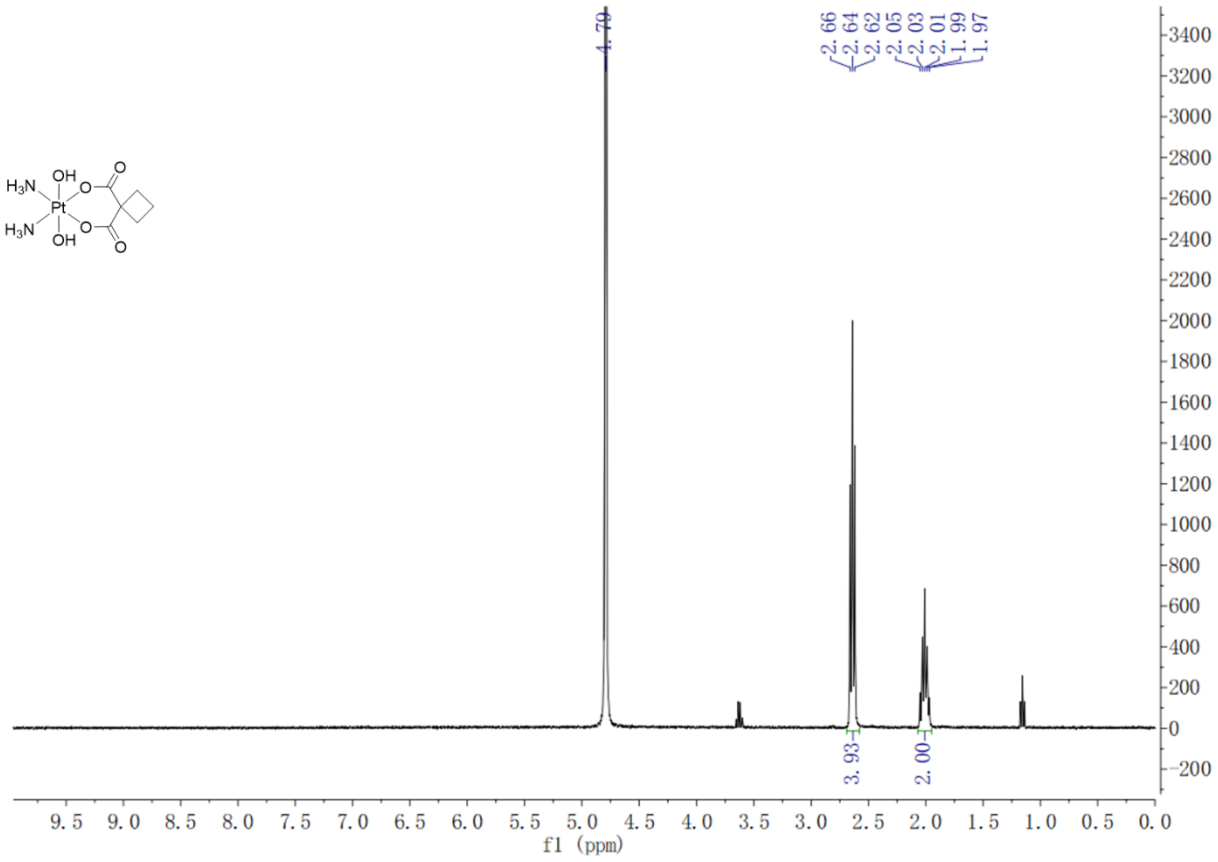

Figure S1. ^{1}H-NMR spectrum of compound **1** in D_2O.

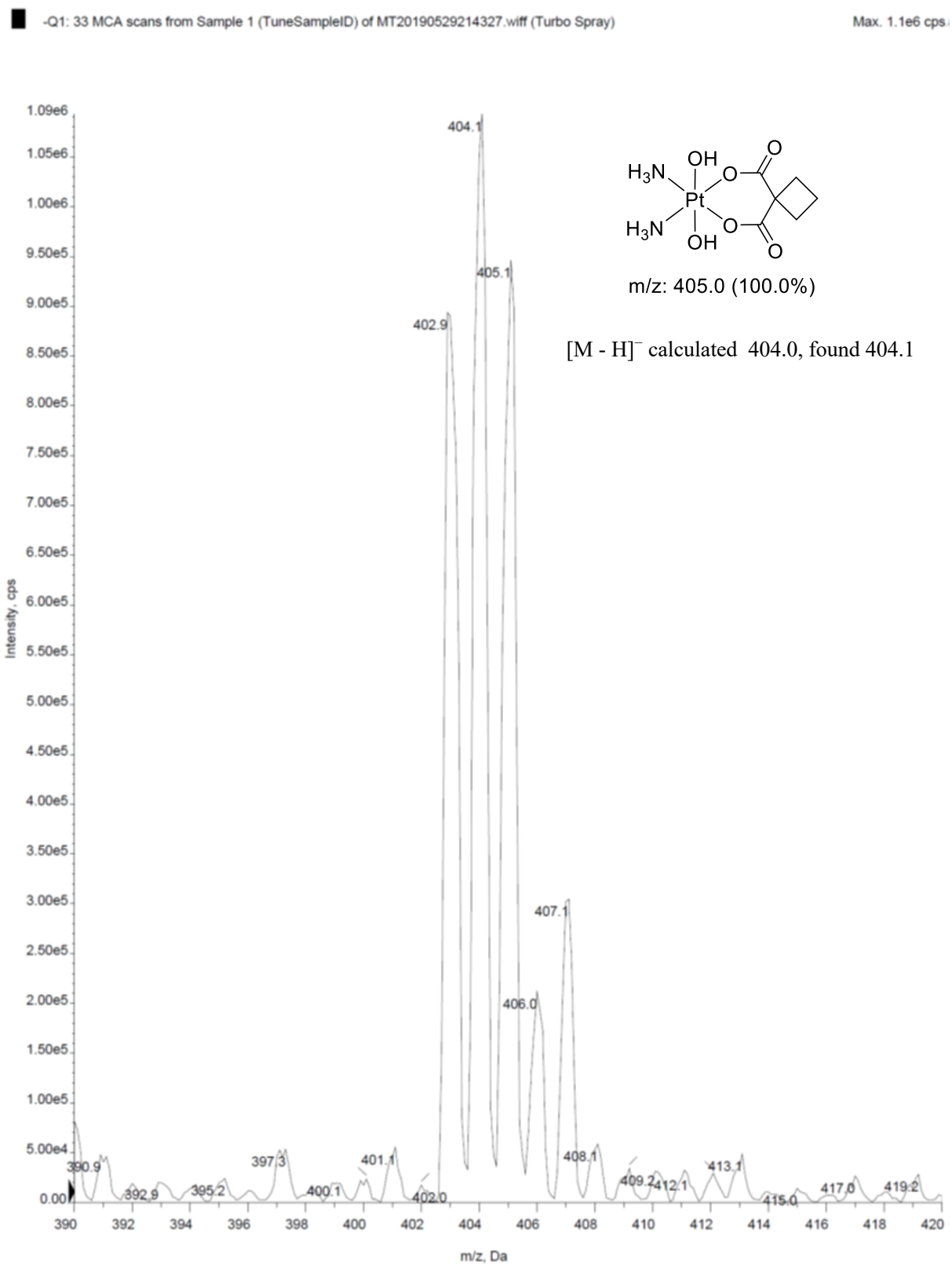

Figure S2. ESI-MS spectrum of compound **1**, negative mode in methanol.

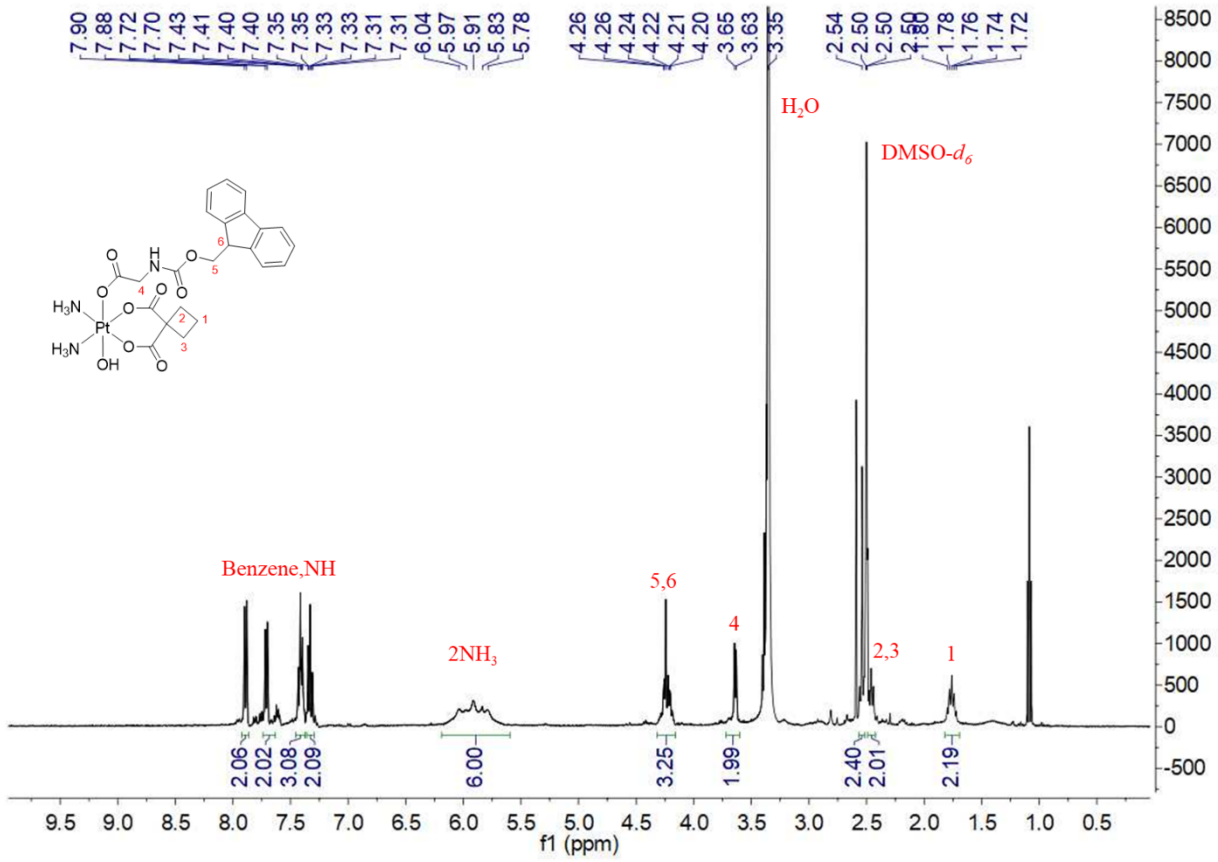

Figure S3. [1]H-NMR spectrum of compound **6** in DMSO-d_6.

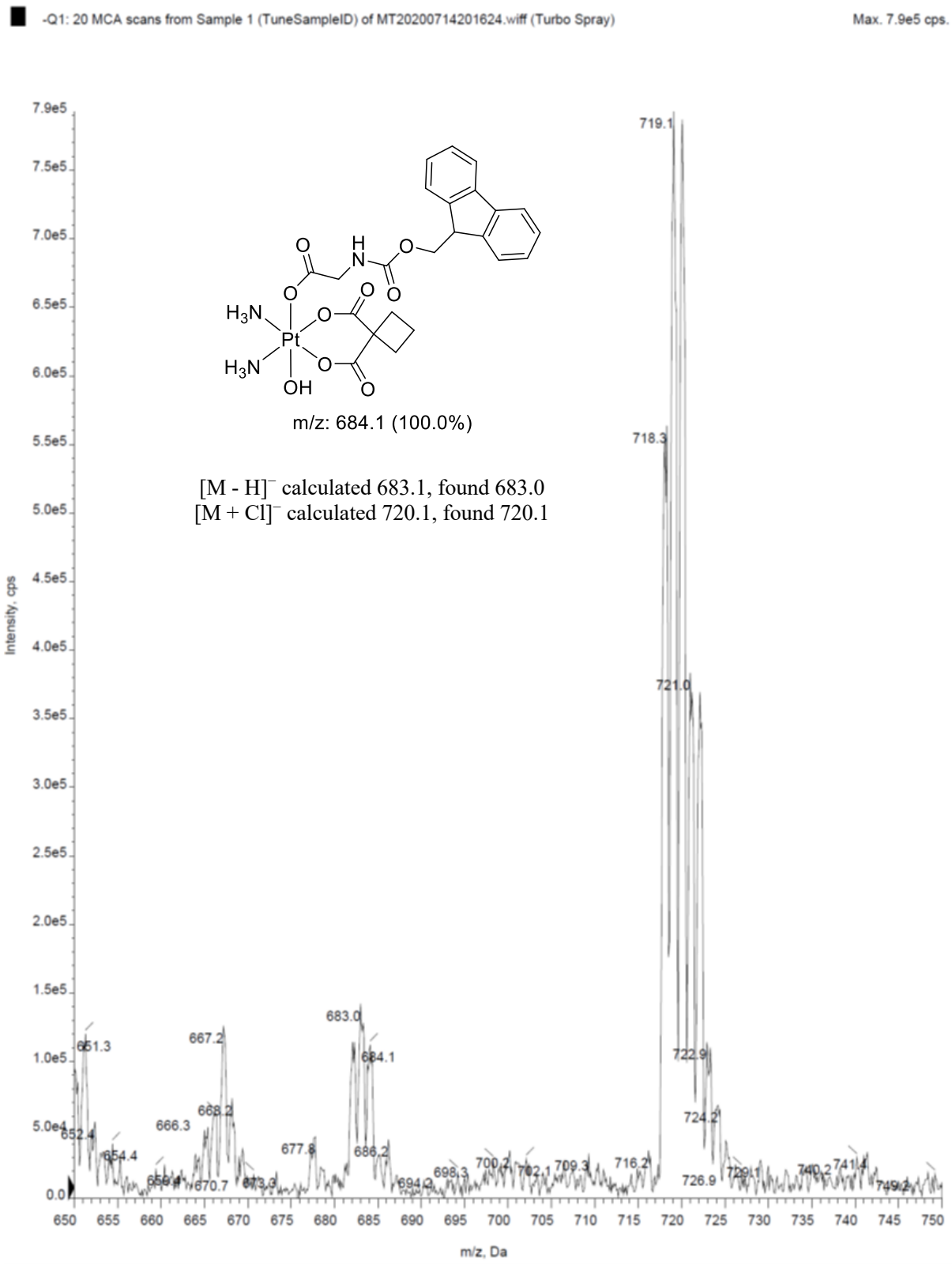

Figure S4. ESI-MS spectrum of compound **6**, negative mode in methanol.

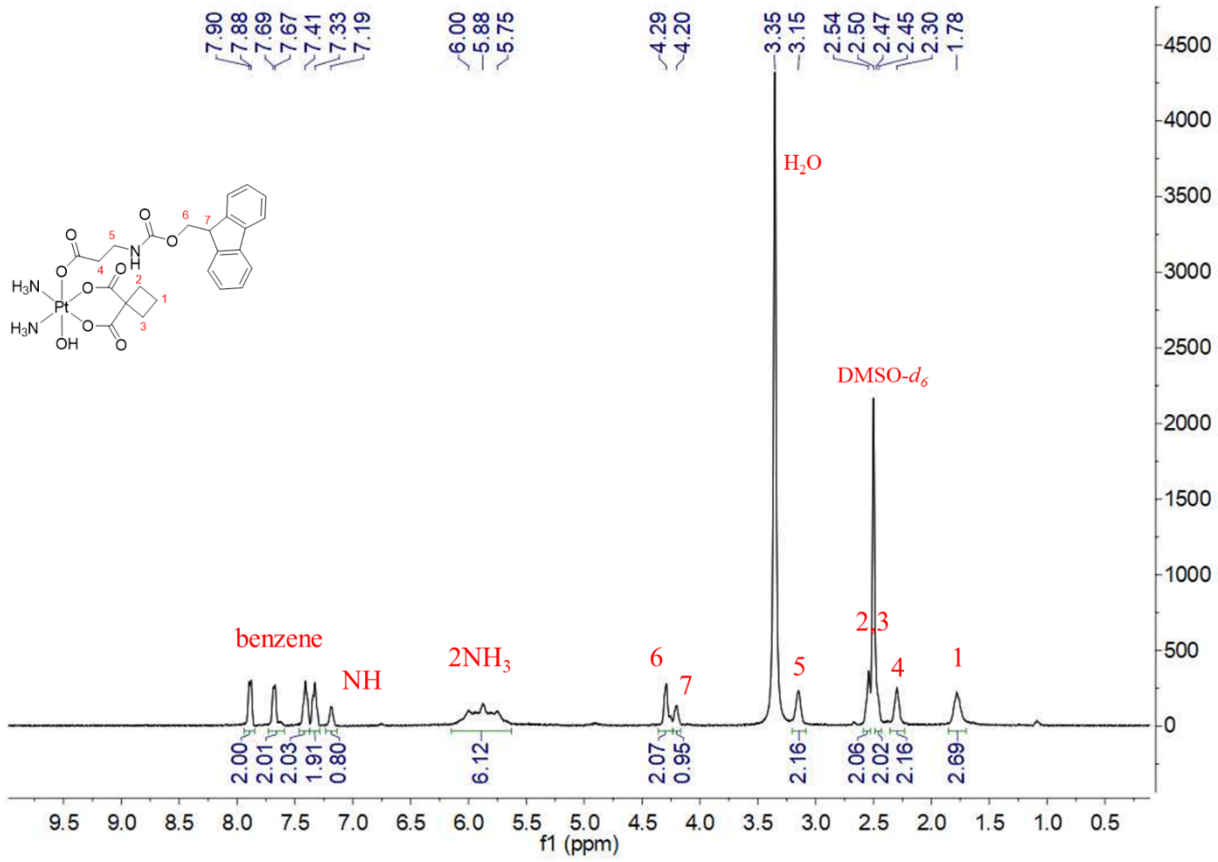

Figure S5. [1]H-NMR spectrum of compound **7** in DMSO-d_6.

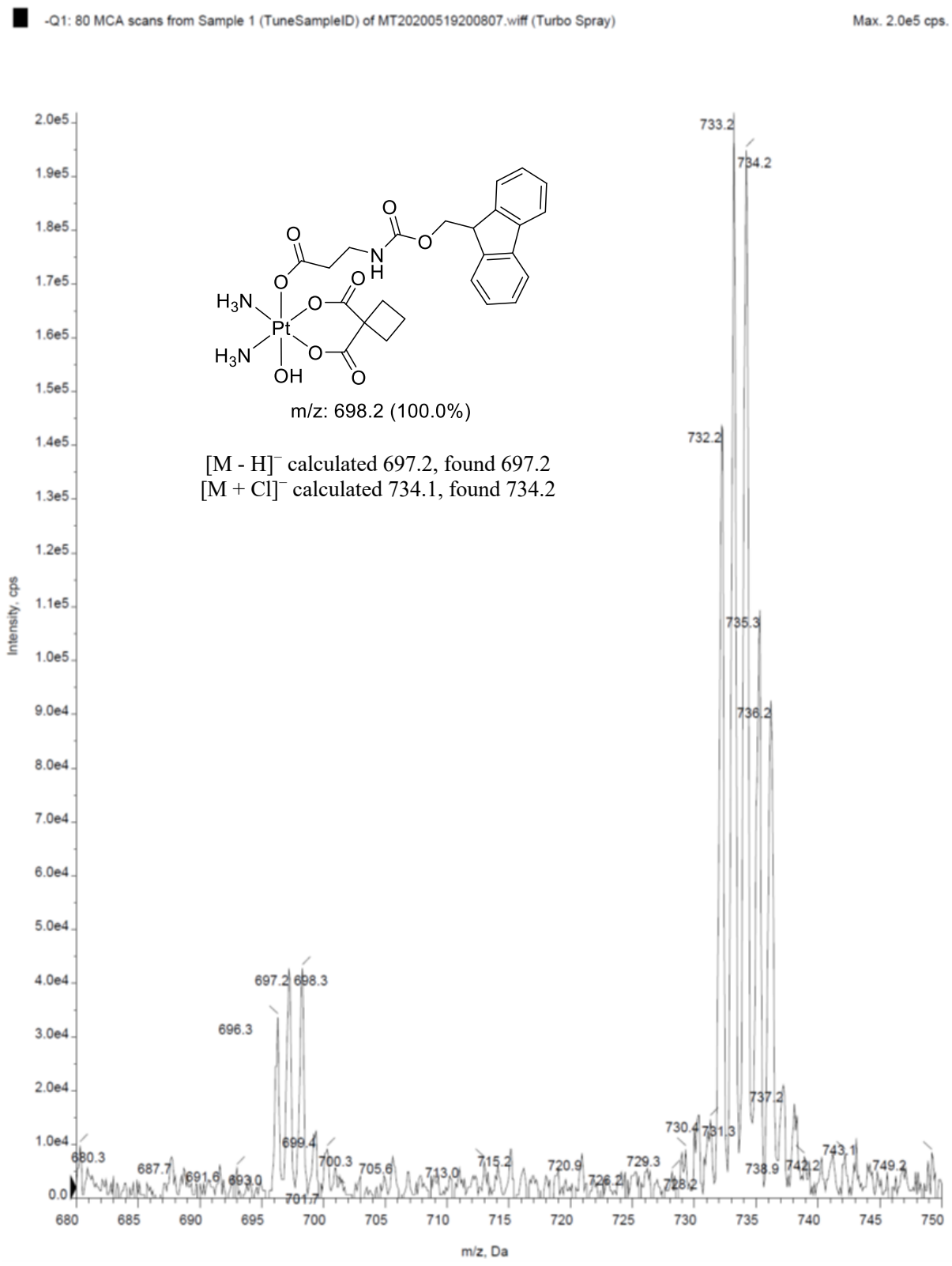

Figure S6. ESI-MS spectrum of compound **7**, negative mode in methanol.

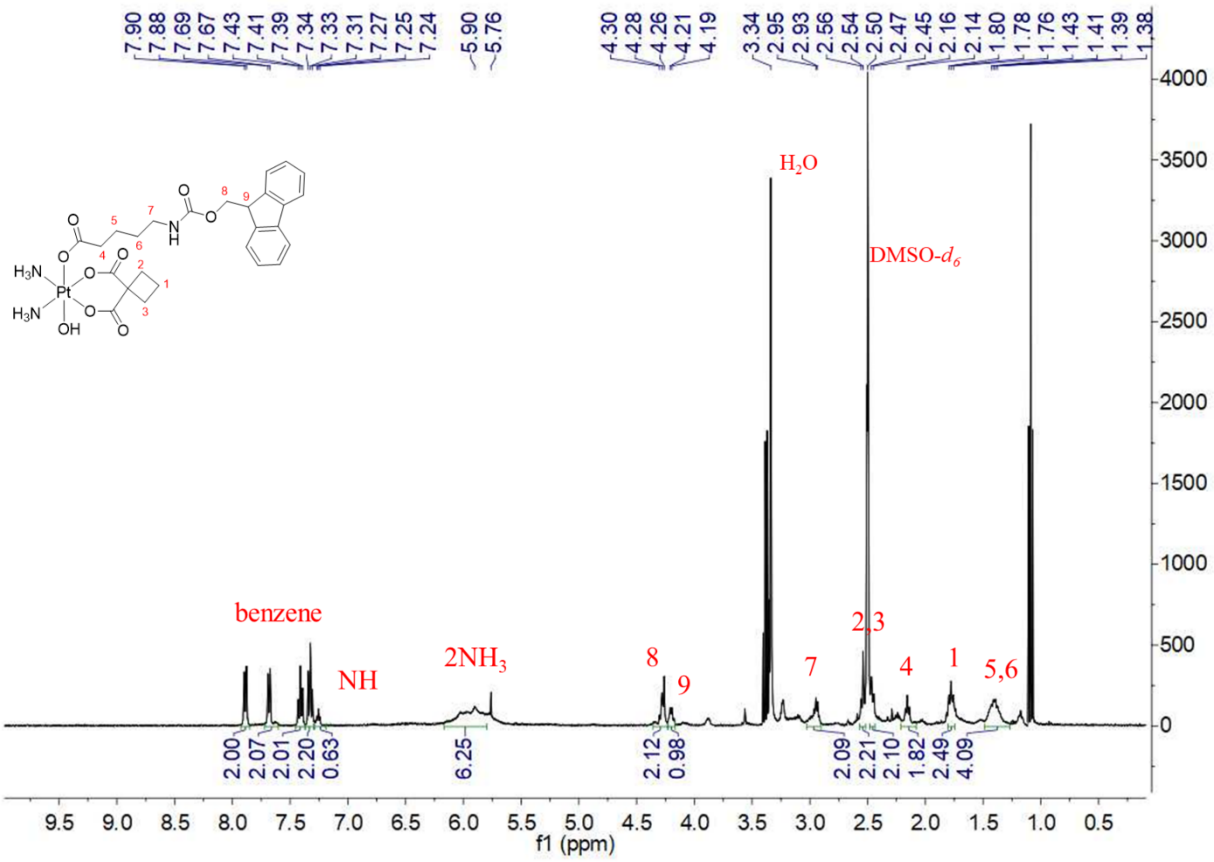

Figure S7. [1]H-NMR spectrum of compound **8** in DMSO-d_6.

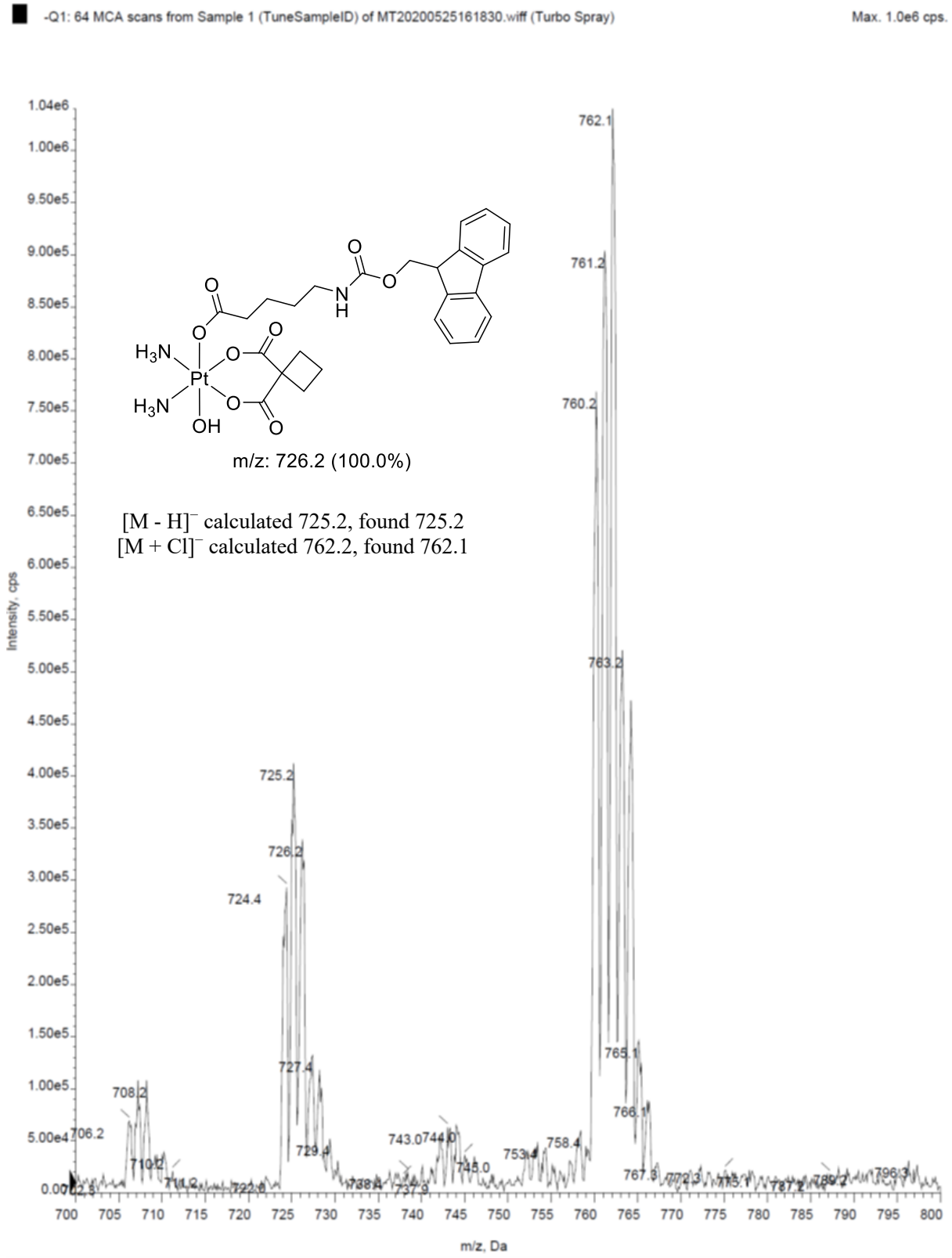

Figure S8. ESI-MS spectrum of compound **8**, negative mode in methanol.

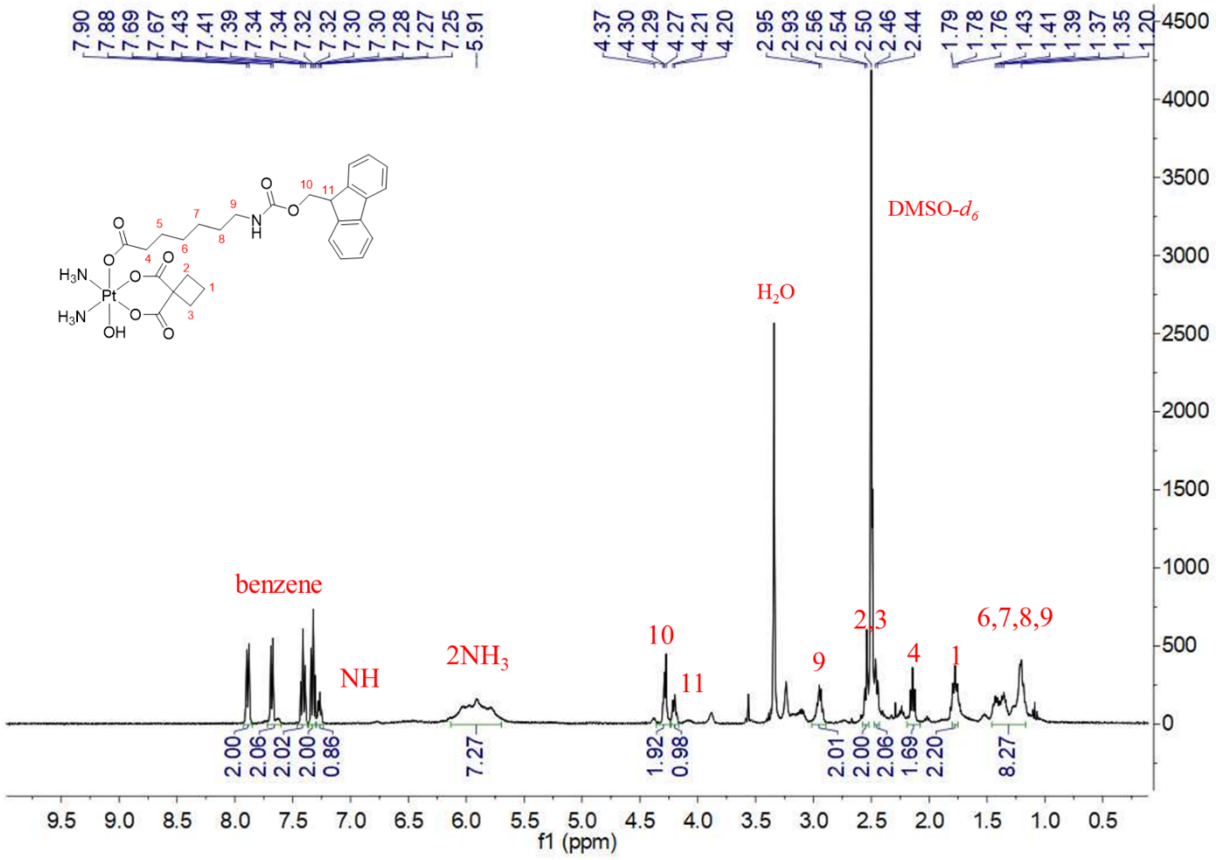

Figure S9. ^{1}H-NMR spectrum of compound **9** in DMSO-d_6.

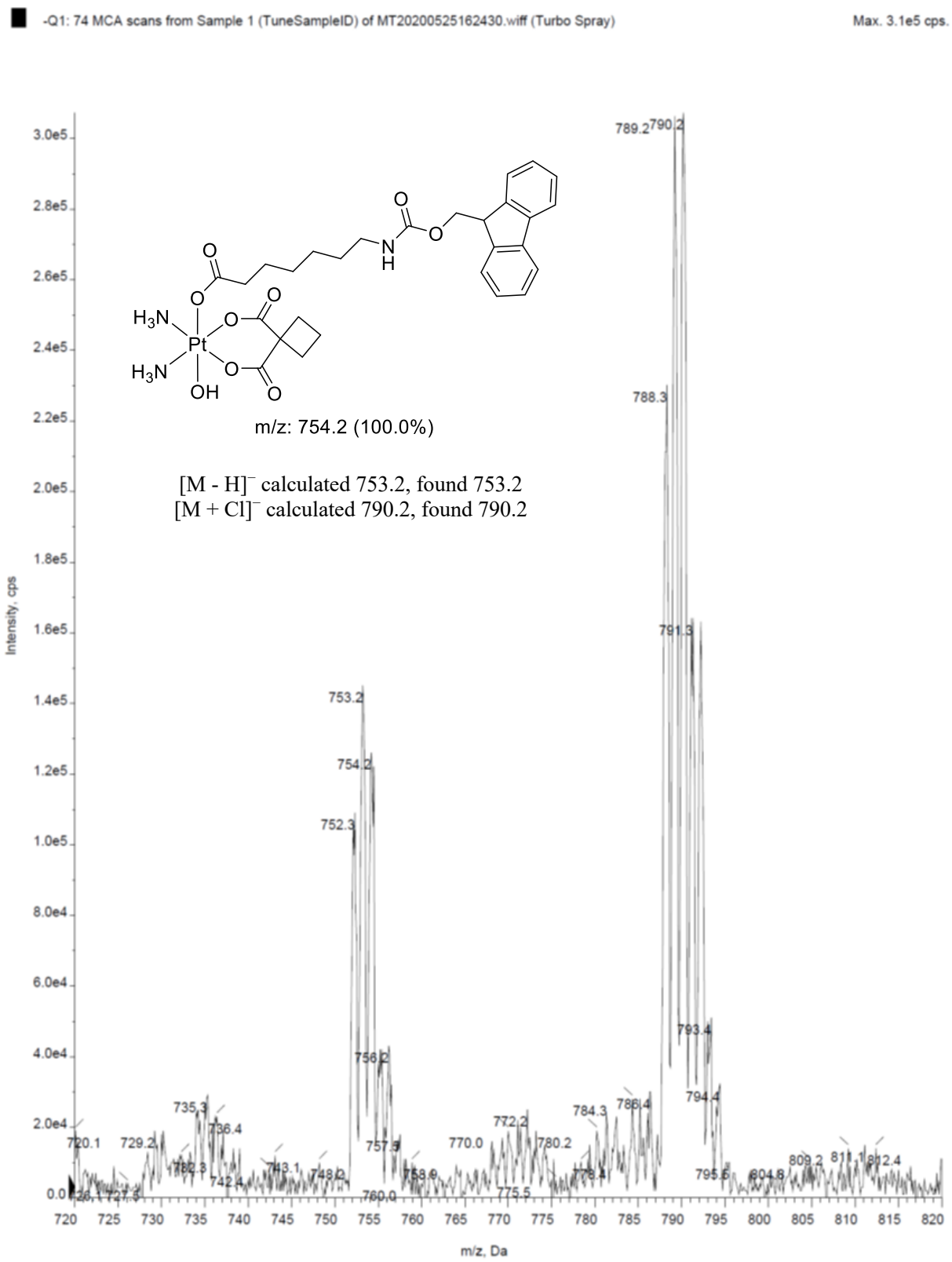

Figure S10. ESI-MS spectrum of compound **9**, negative mode in methanol.

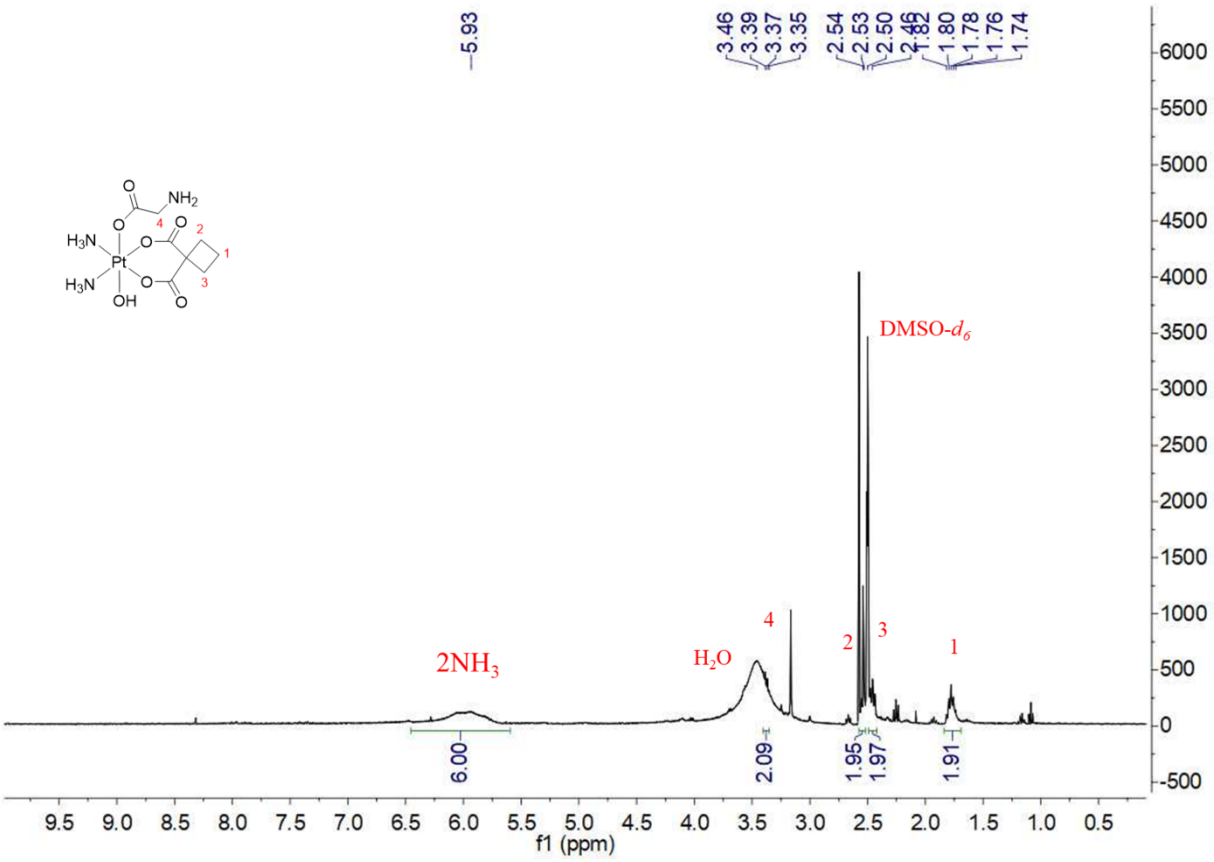

Figure S11. ^{1}H-NMR spectrum of compound **10** in DMSO-d_6.

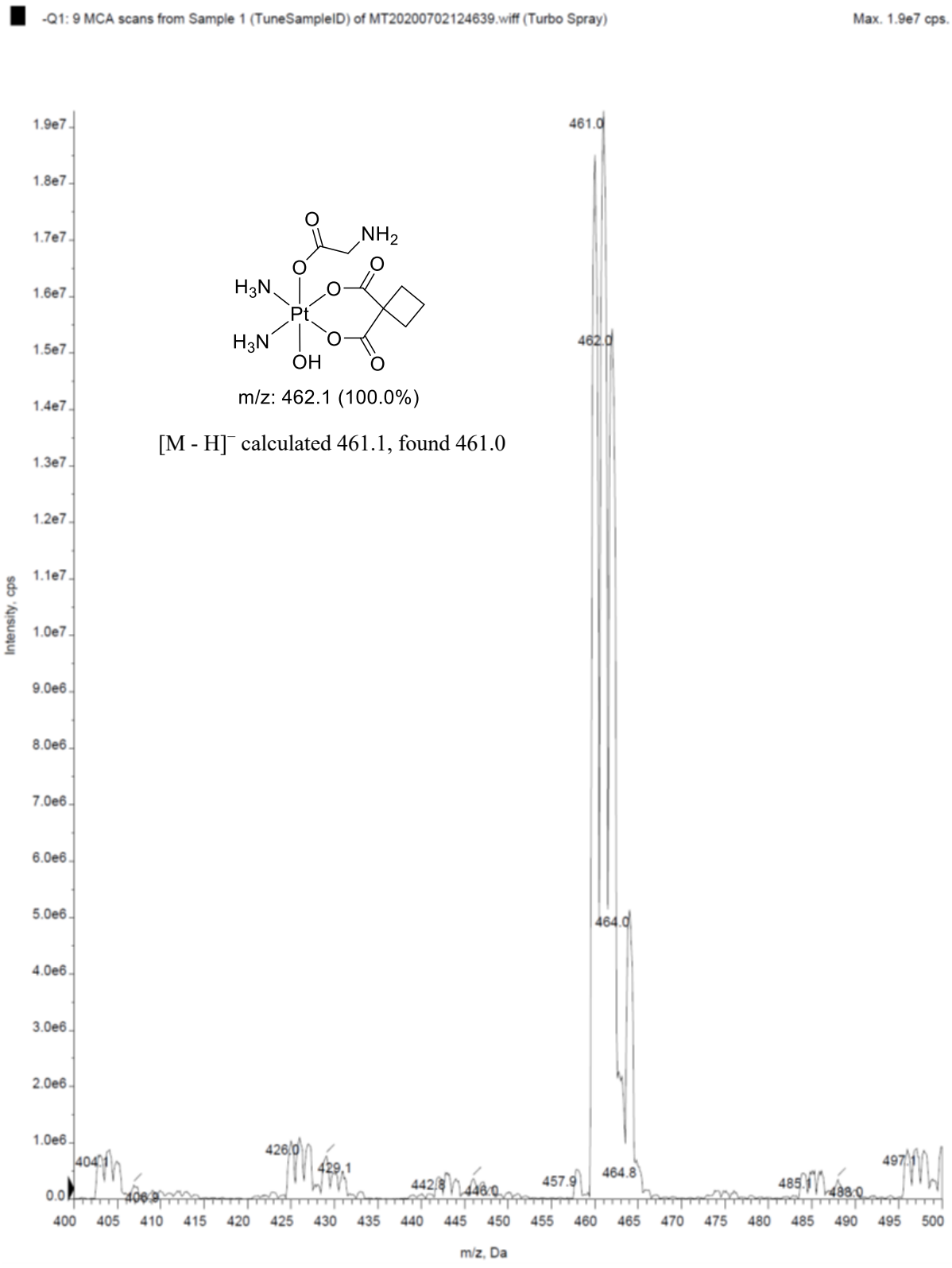

Figure S12. ESI-MS spectrum of compound **10**, negative mode in methanol.

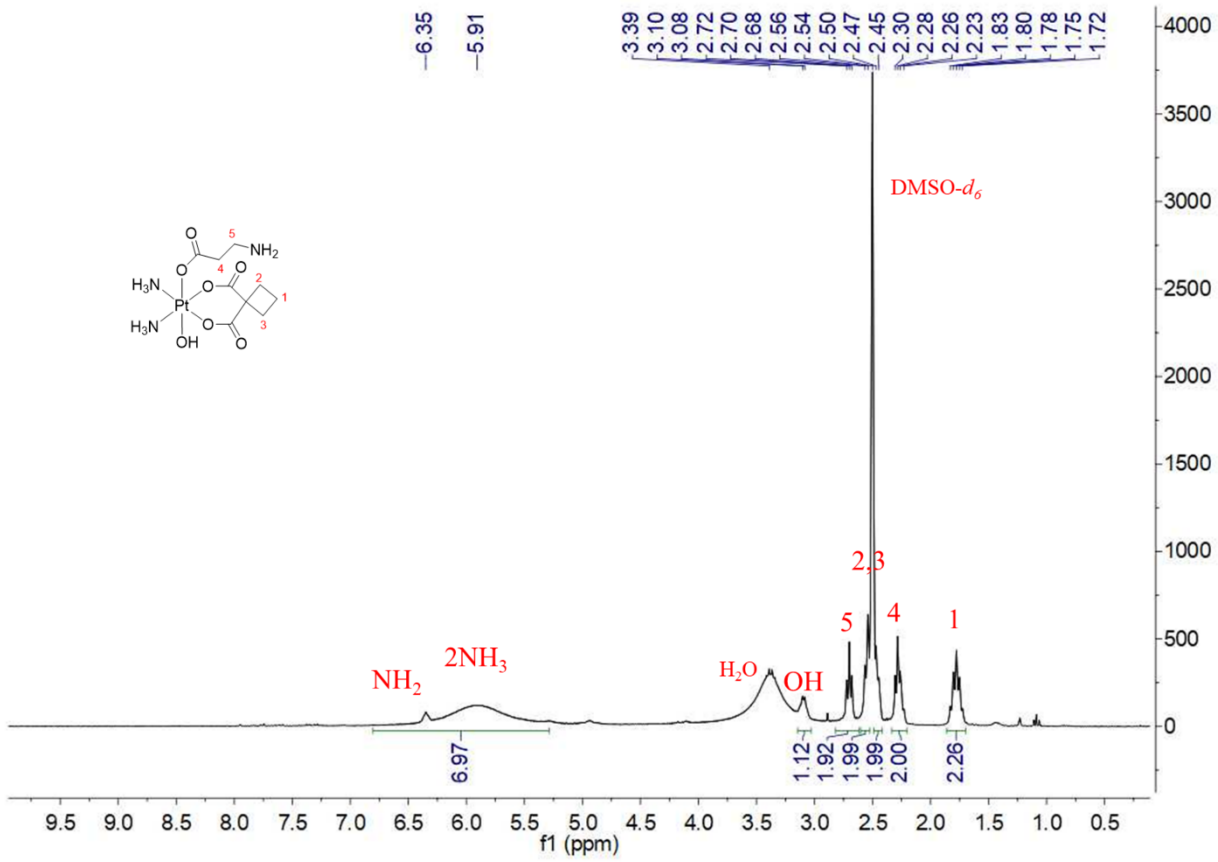

Figure S13. ^{1}H-NMR spectrum of compound **11** in DMSO-d_6.

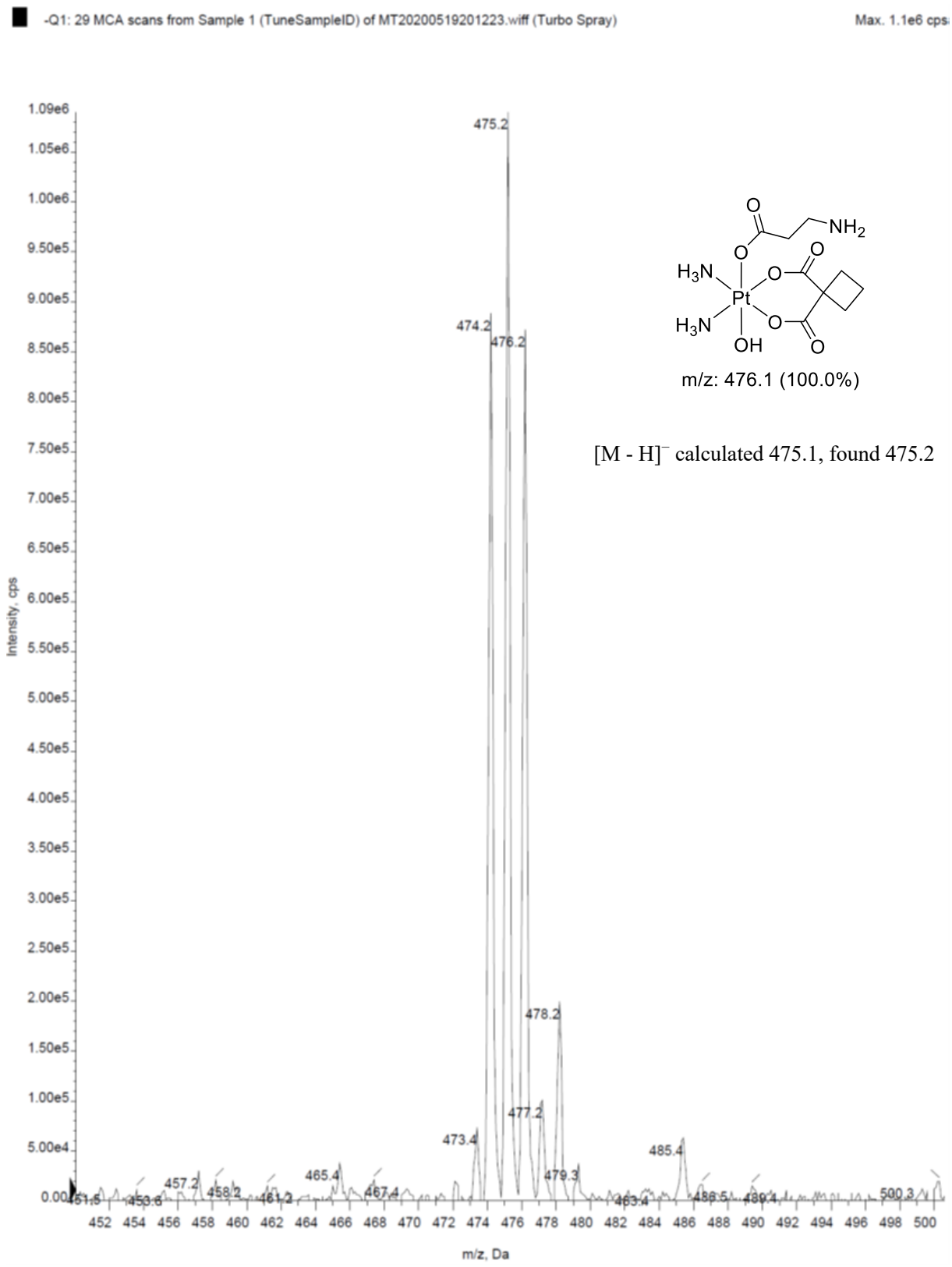

Figure S14. ESI-MS spectrum of compound **11**, negative mode in methanol.

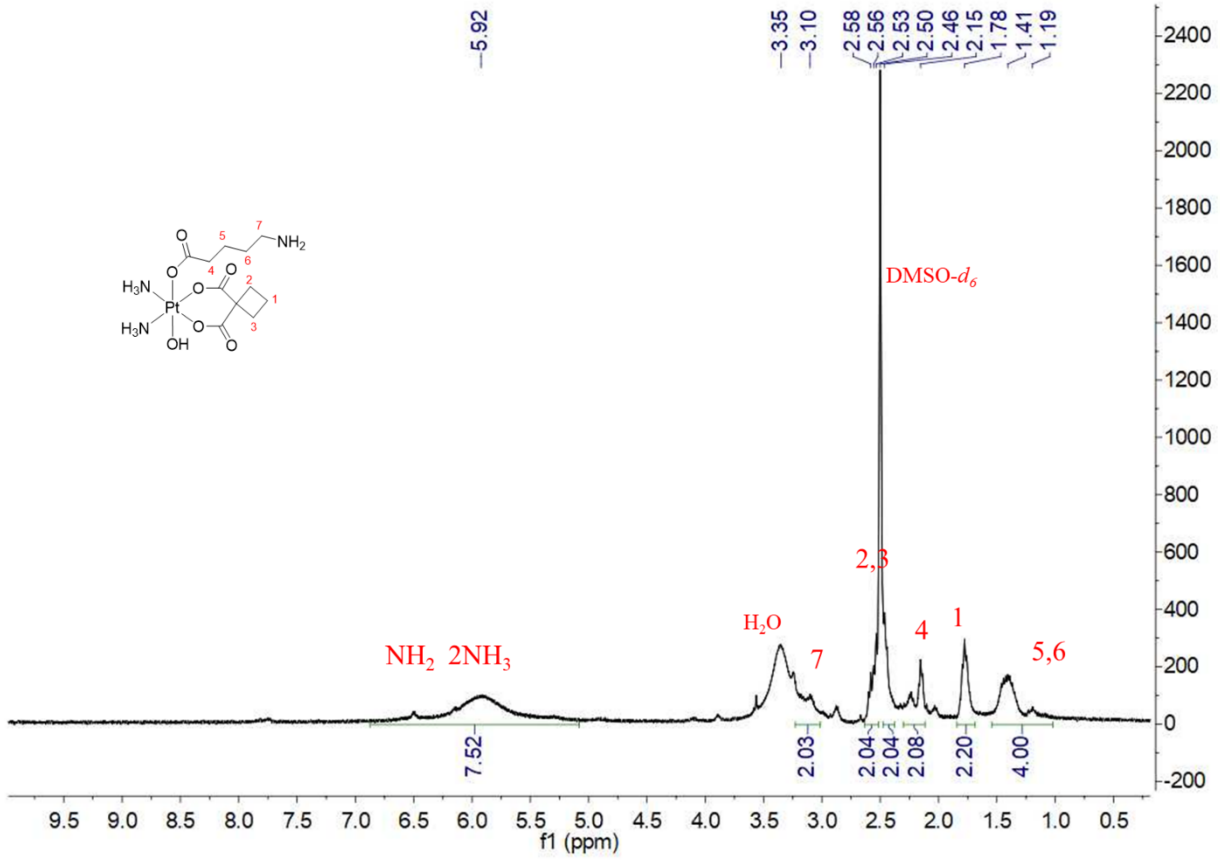

Figure S15. ^{1}H-NMR spectrum of compound **12** in DMSO-d_6.

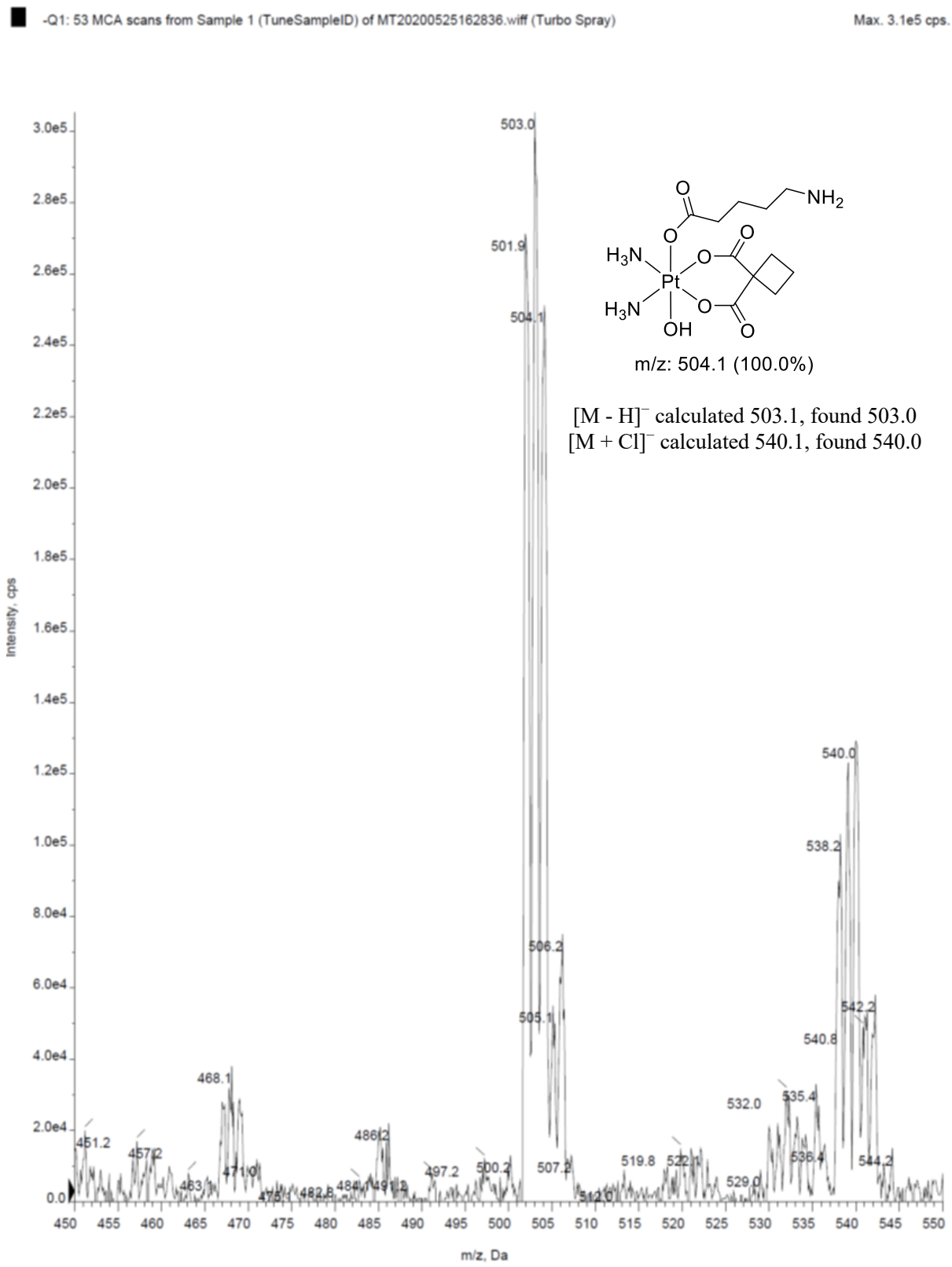

Figure S16. ESI-MS spectrum of compound **12**, negative mode in methanol.

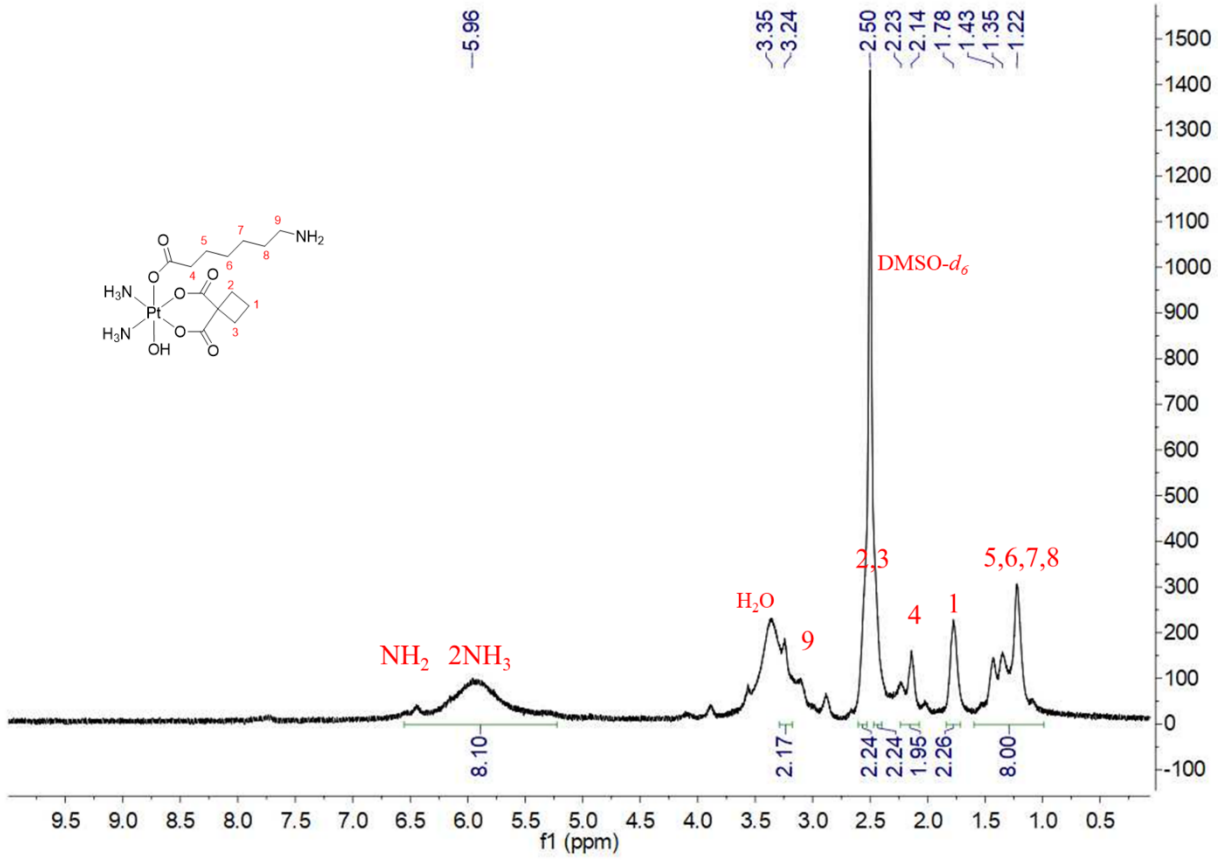

Figure S17. ^{1}H-NMR spectrum of compound **13** in DMSO-d_6.

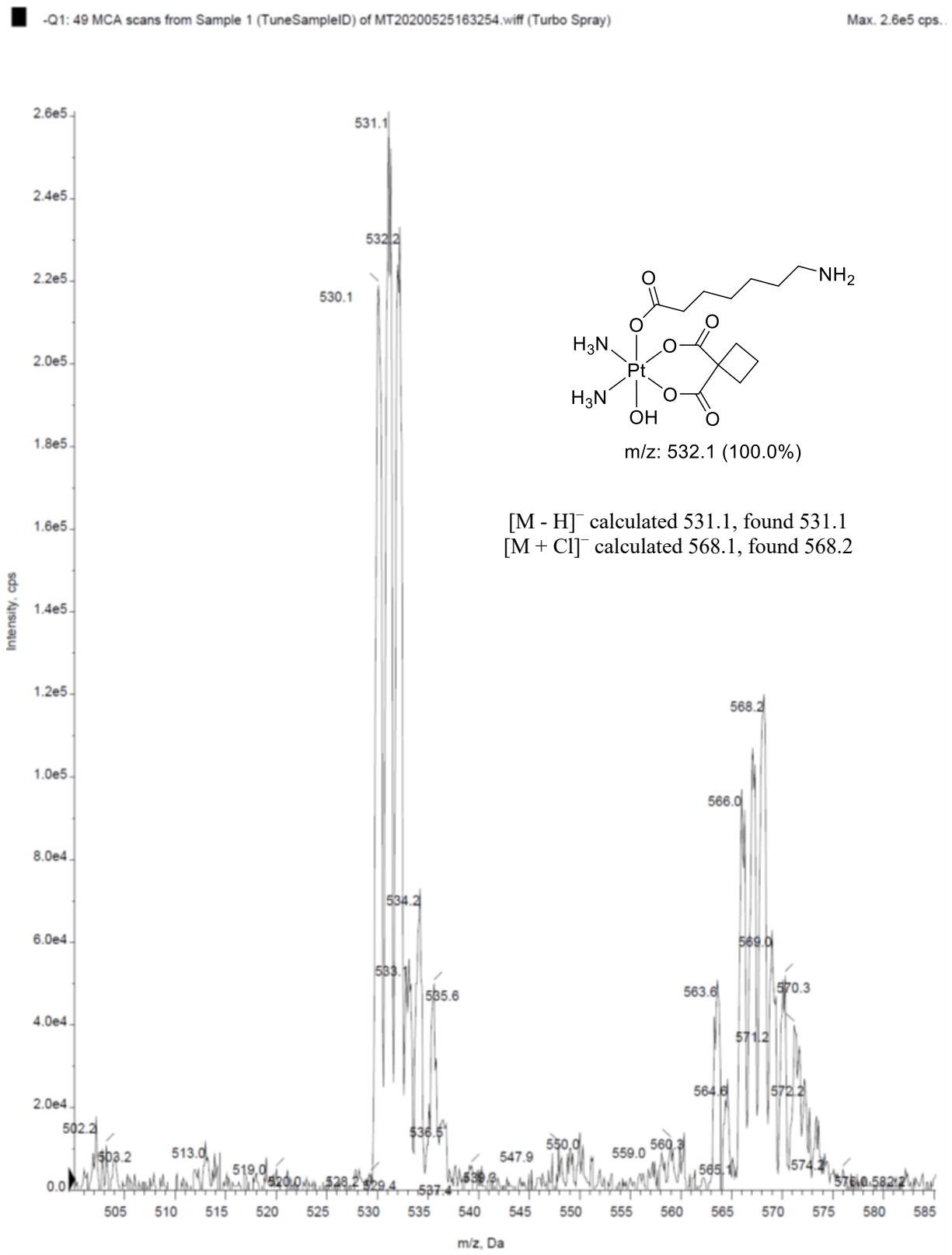

Figure S18. ESI-MS spectrum of compound **13**, negative mode in methanol.

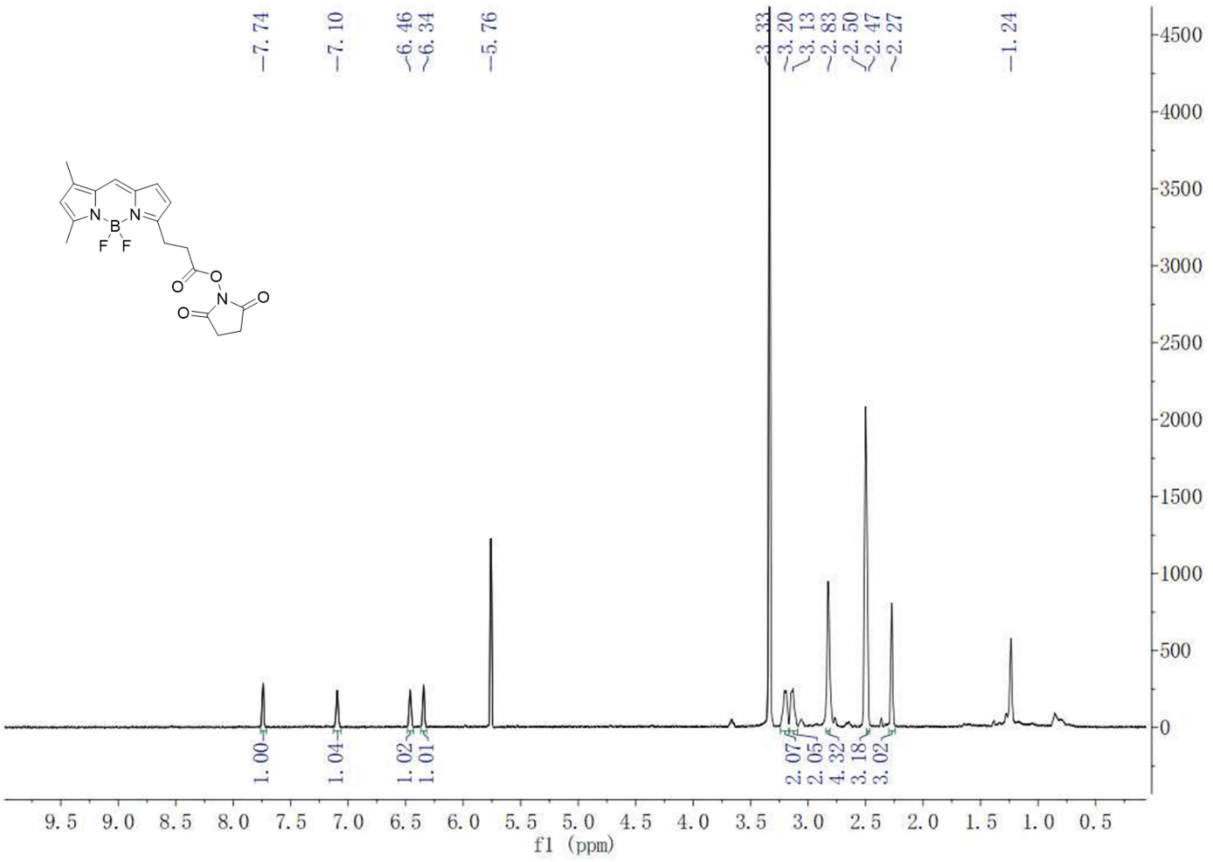

Figure S19. [1]H-NMR spectrum of compound **14** in DMSO-d_6.

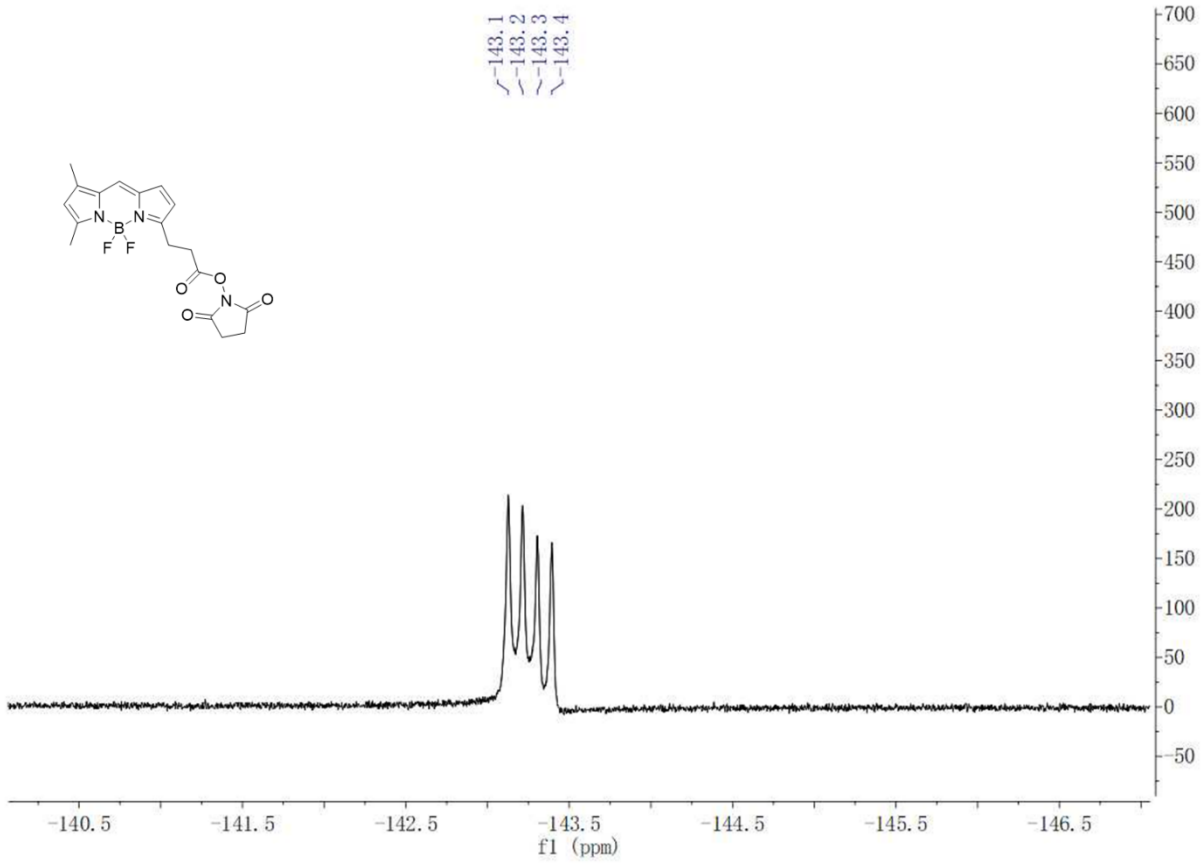

Figure S20. ^{19}F-NMR spectrum of compound **14** in DMSO-d_6.

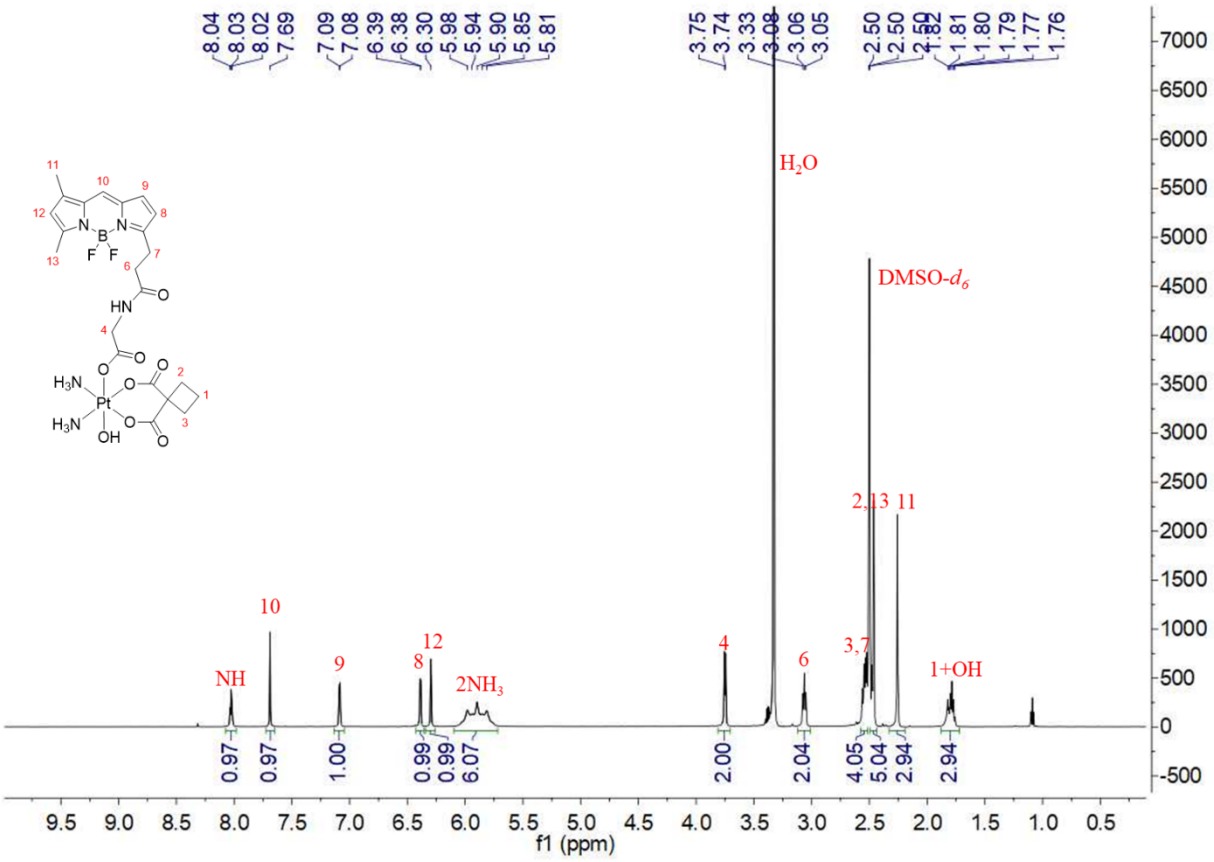

Figure S21. [1]H-NMR spectrum of complex **OH3C** in DMSO-d_6.

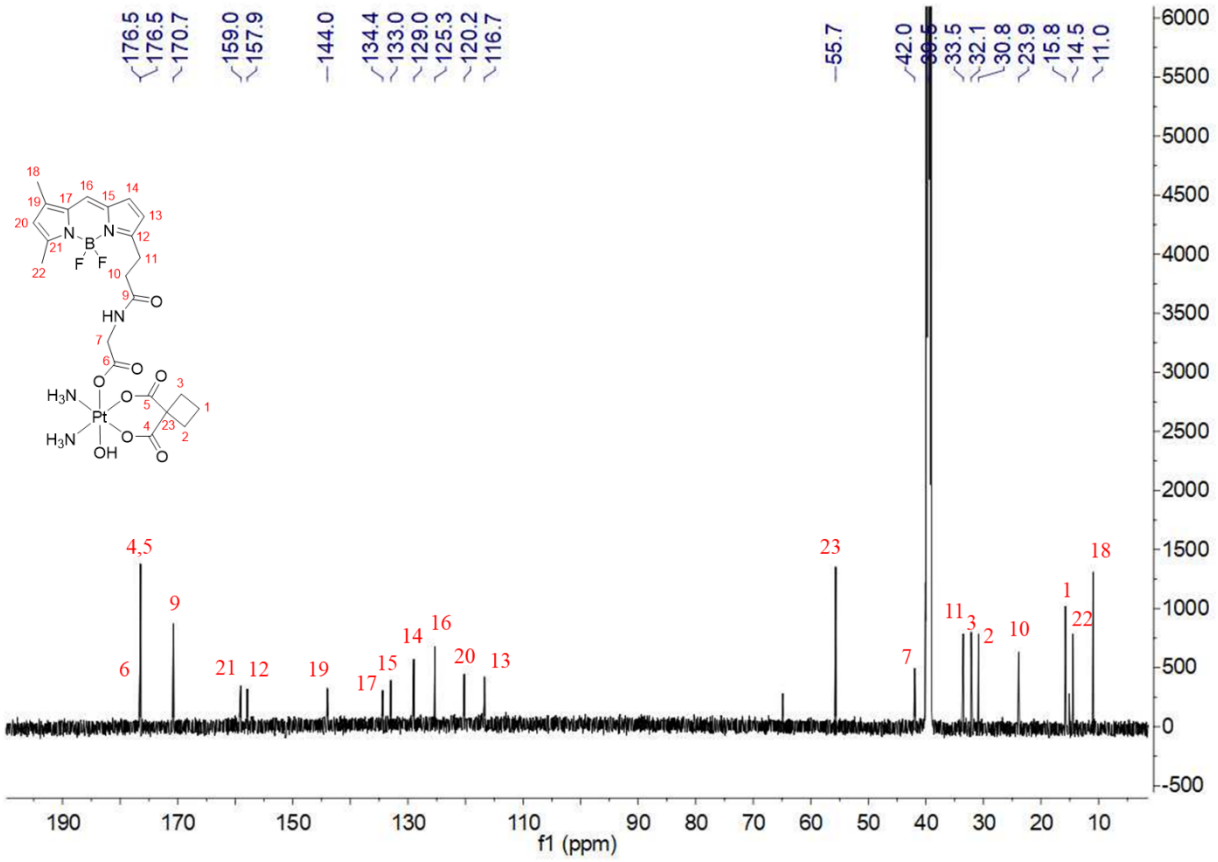

Figure S22. ^{13}C-NMR spectrum of complex **OH3C** in DMSO-d_6.

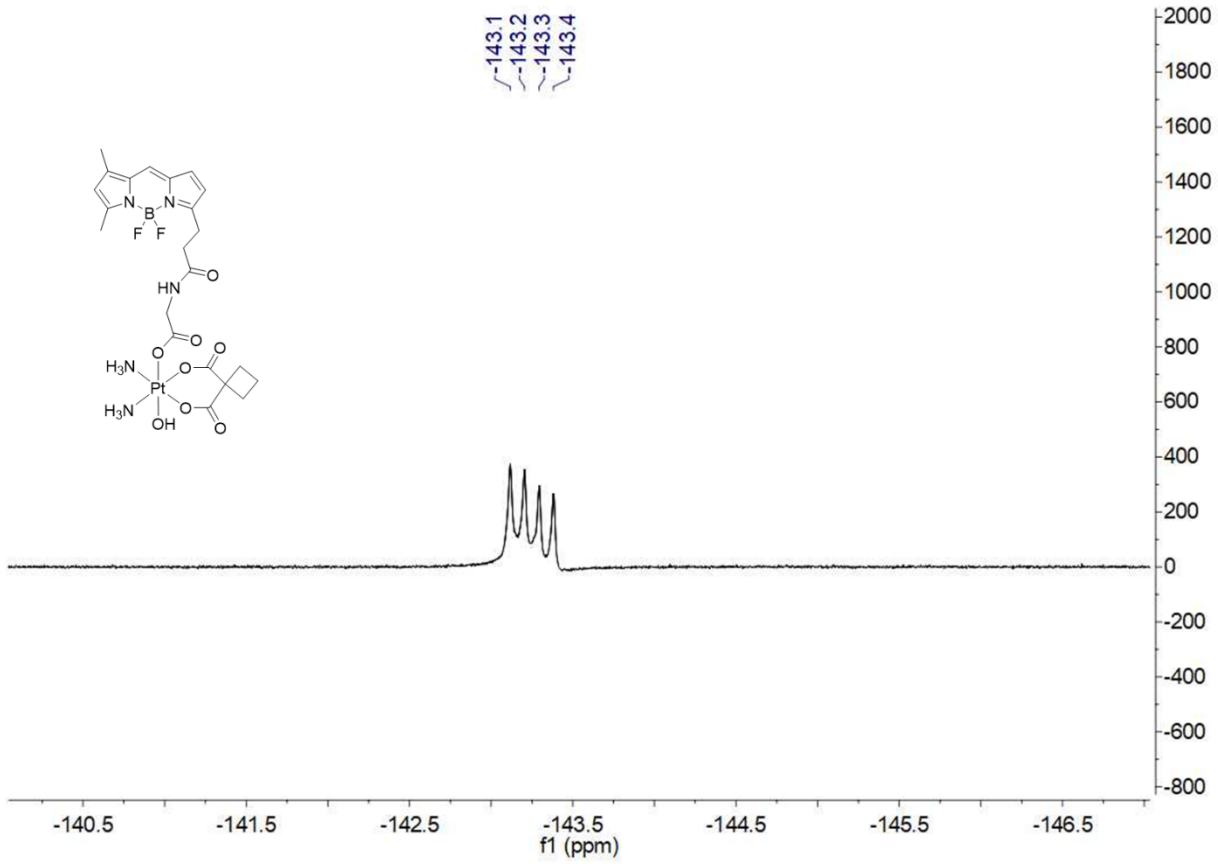

Figure S23. ^{19}F-NMR spectrum of complex **OH3C** in DMSO-d_6.

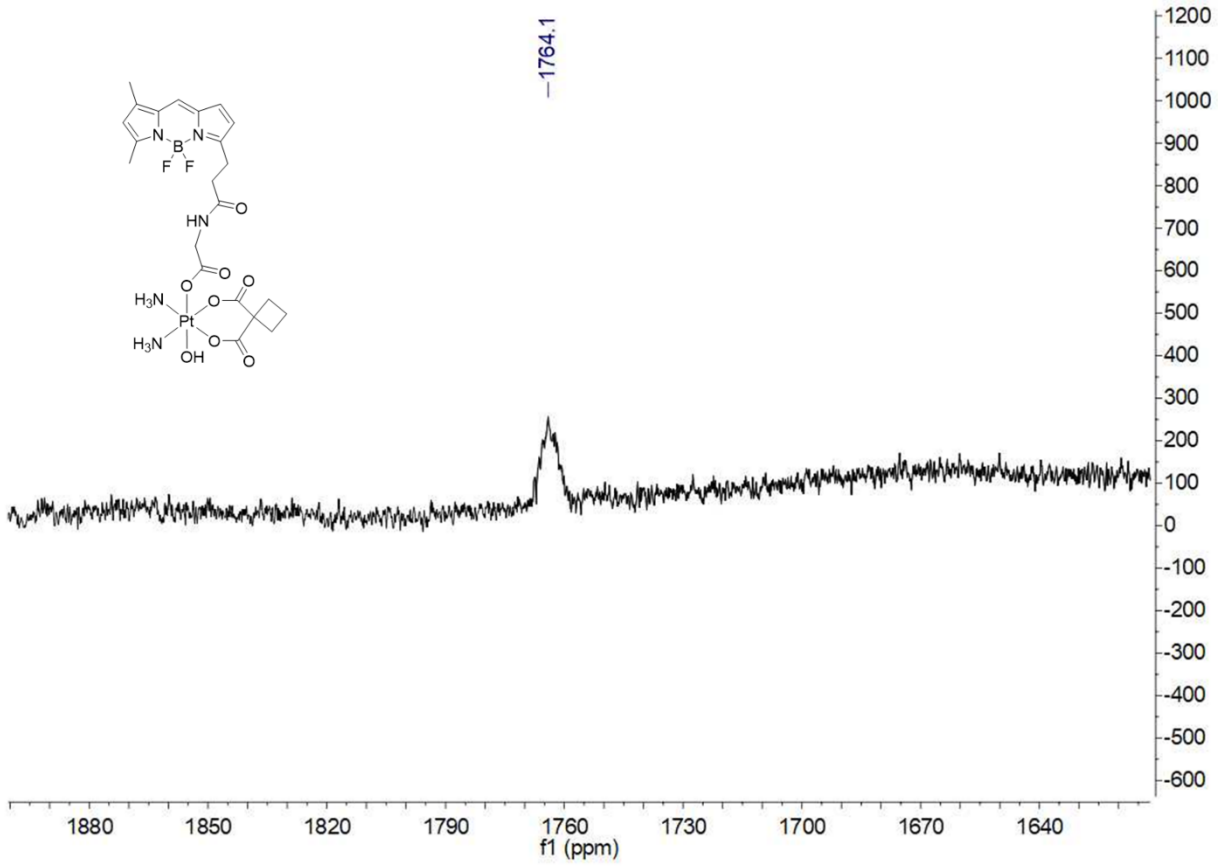

Figure S24. ^{195}Pt-NMR spectrum of complex **OH3C** in DMSO-d_6.

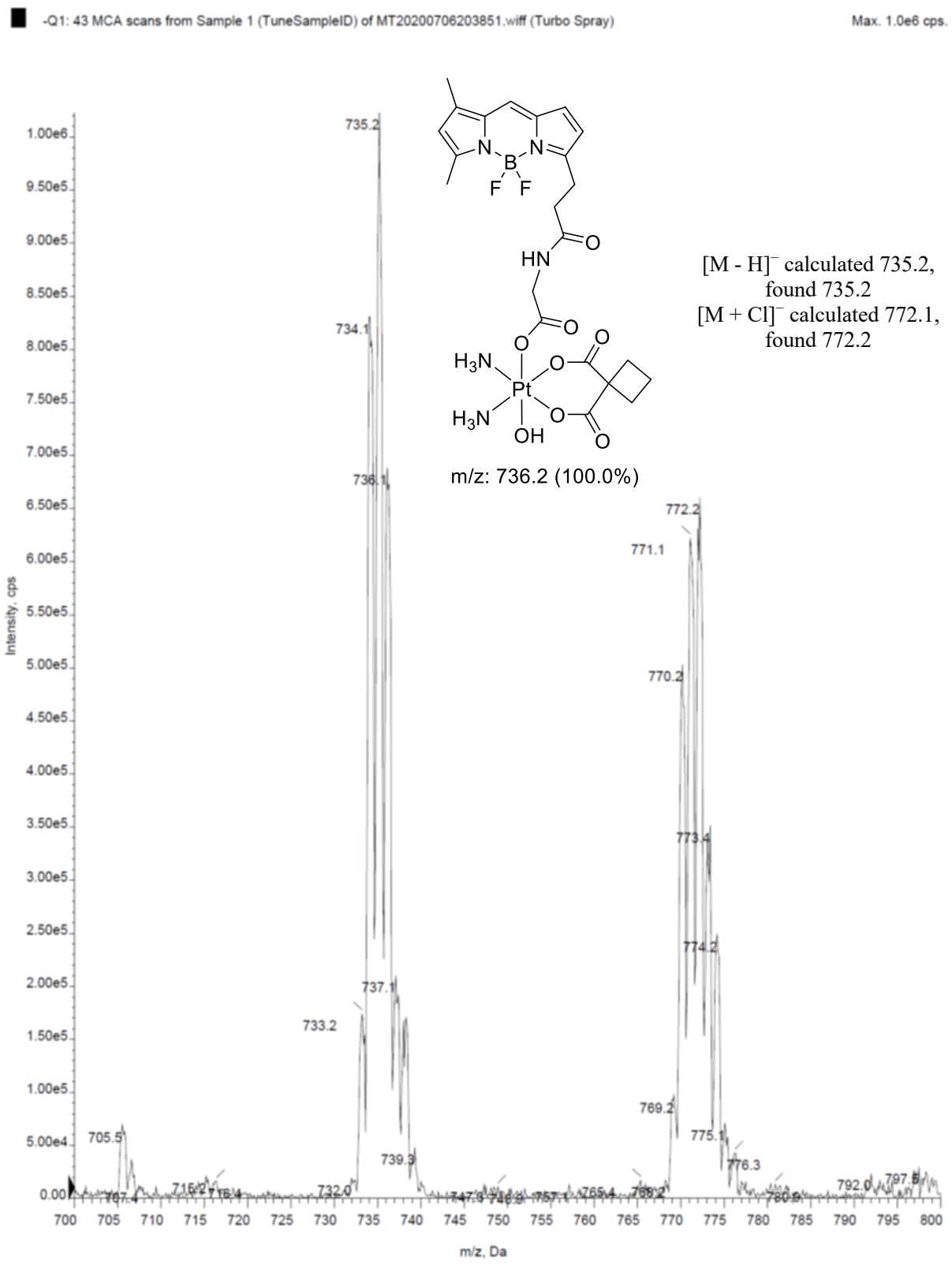

Figure S25. ESI-MS spectrum of complex **OH3C**, negative mode in methanol.

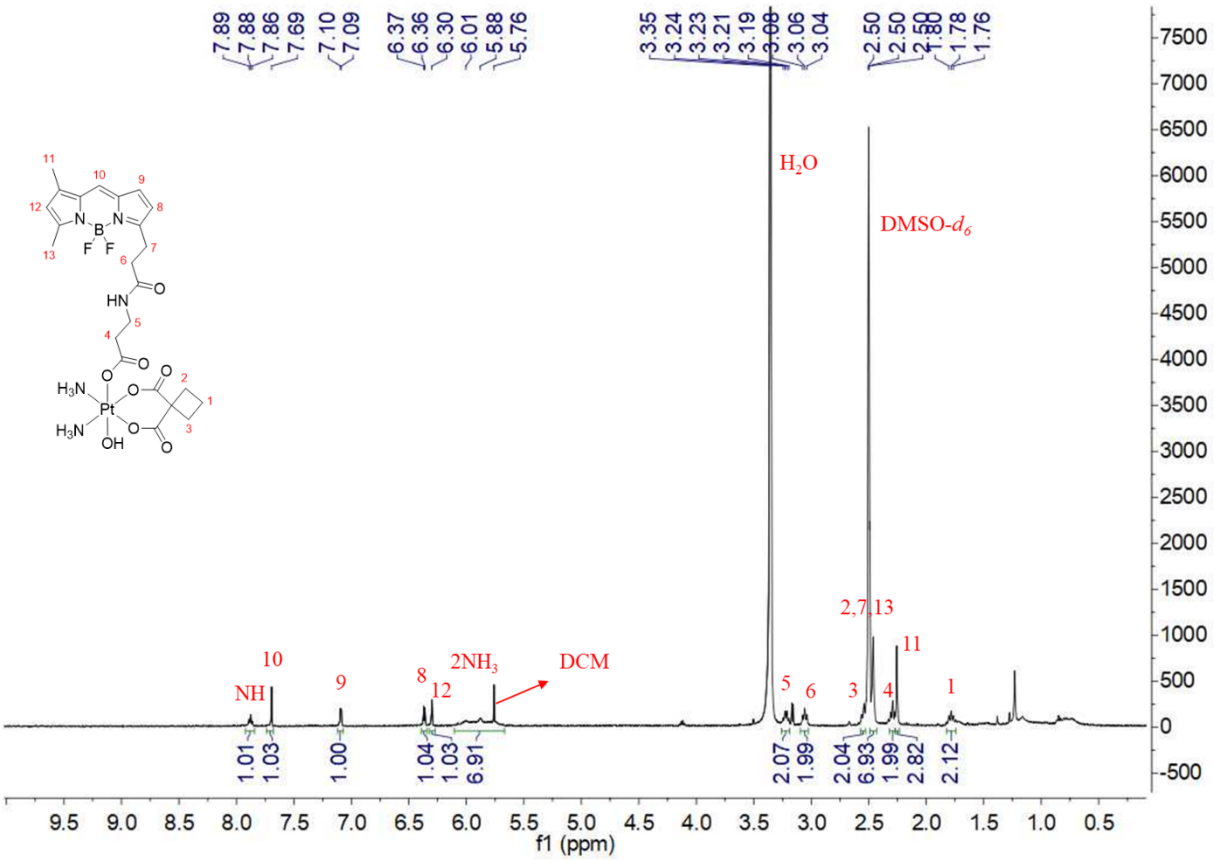

Figure S26. [1]H-NMR spectrum of complex **OH4C** in DMSO-d_6.

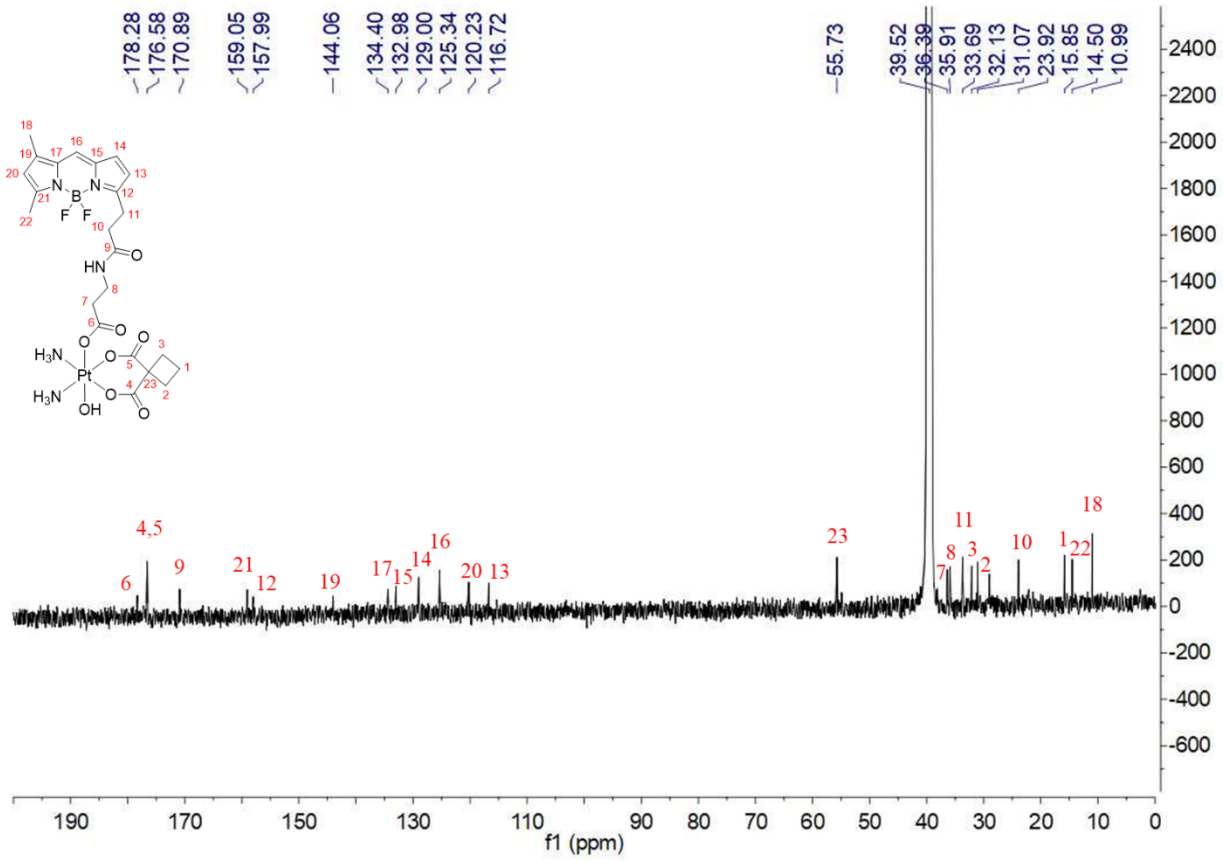

Figure S27. ^{13}C-NMR spectrum of complex **OH4C** in DMSO-d_6.

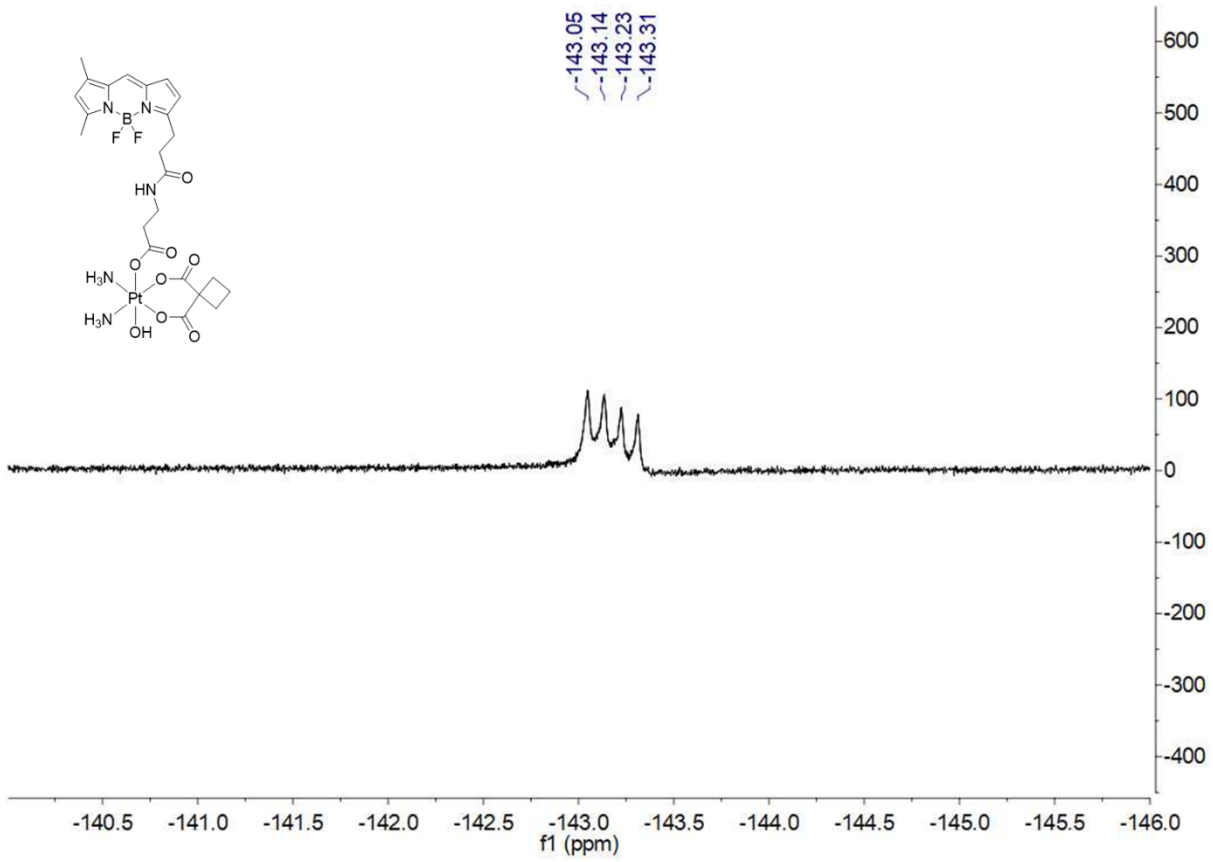

Figure S28. ^{19}F-NMR spectrum of complex **OH4C** in DMSO-d_6.

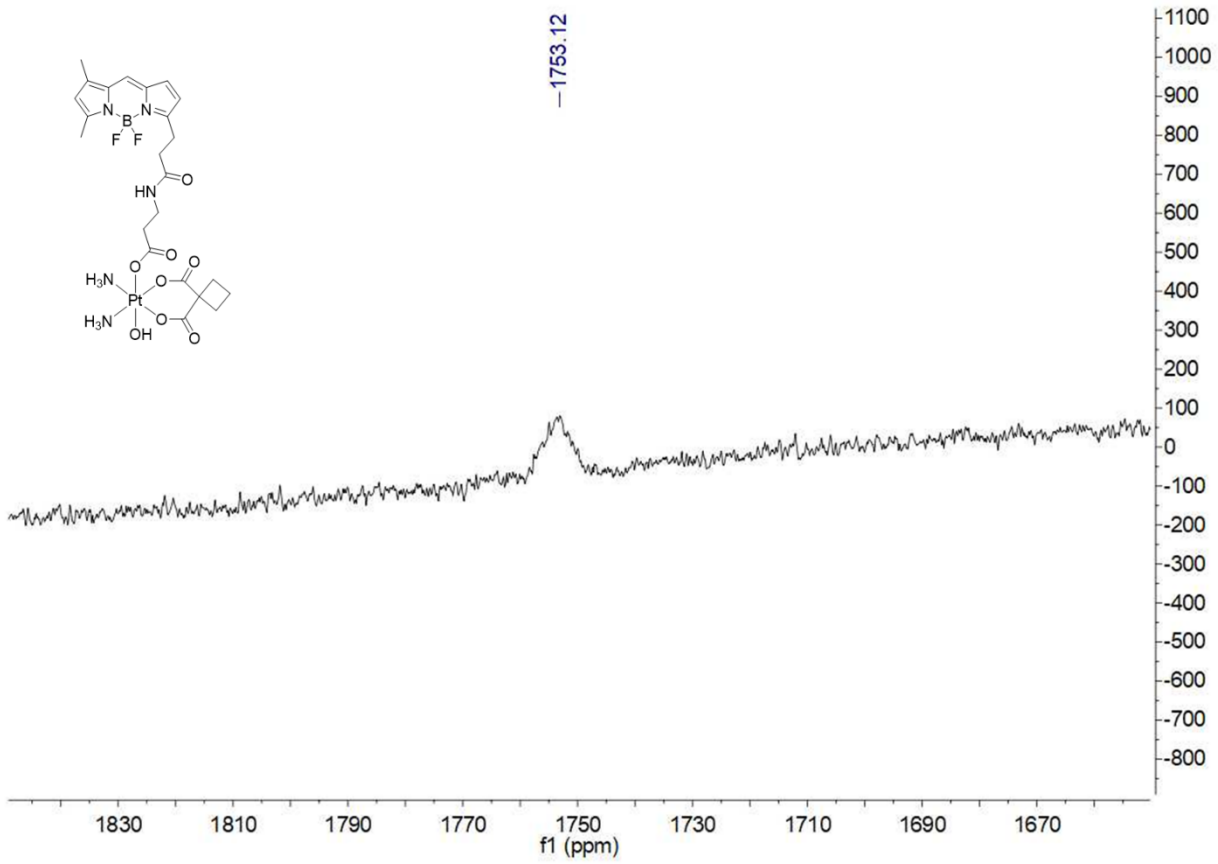

Figure S29. ^{195}Pt-NMR spectrum of complex **OH4C** in DMSO-d_6.

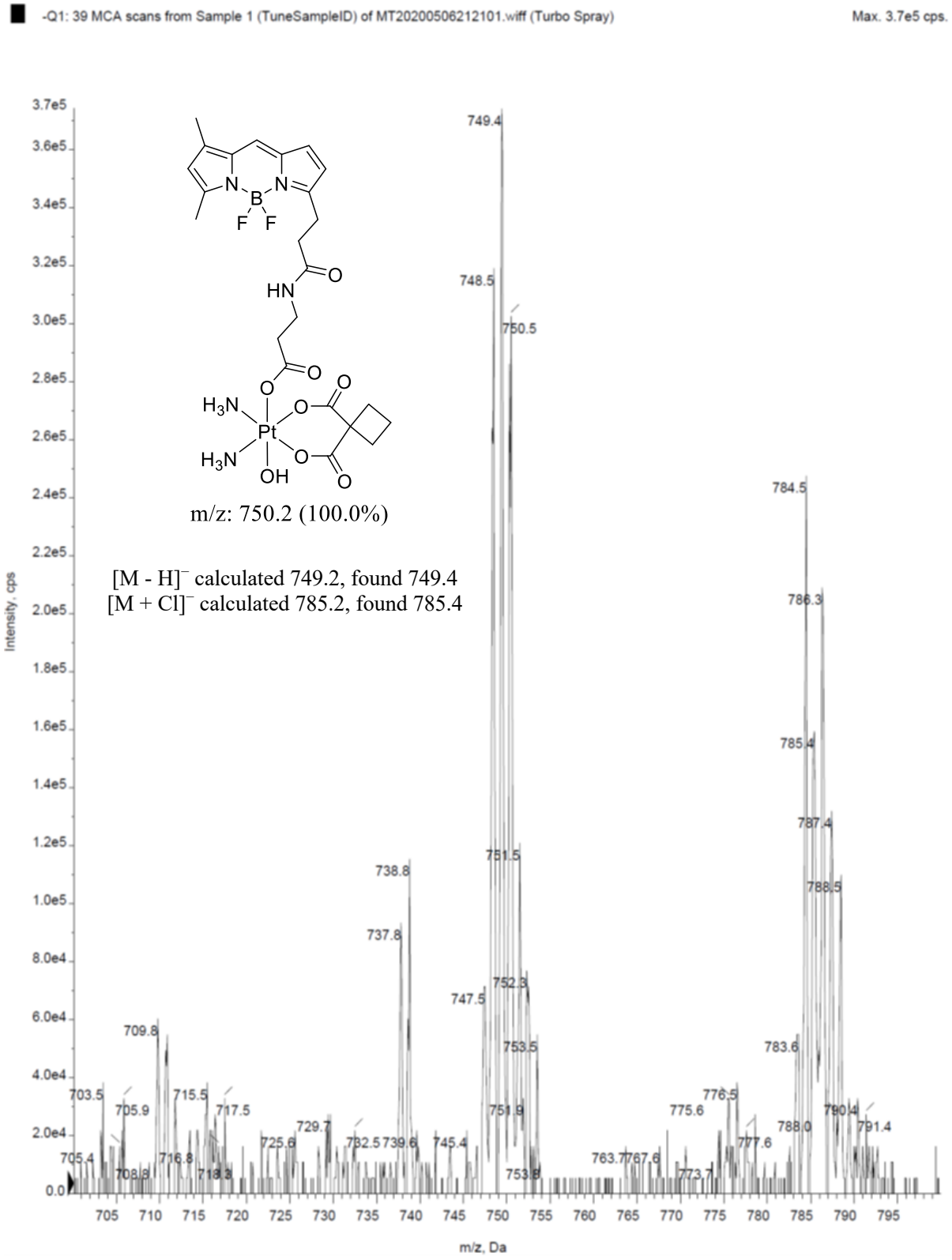

Figure S30. ESI-MS spectrum of complex **OH4C**, negative mode in methanol.

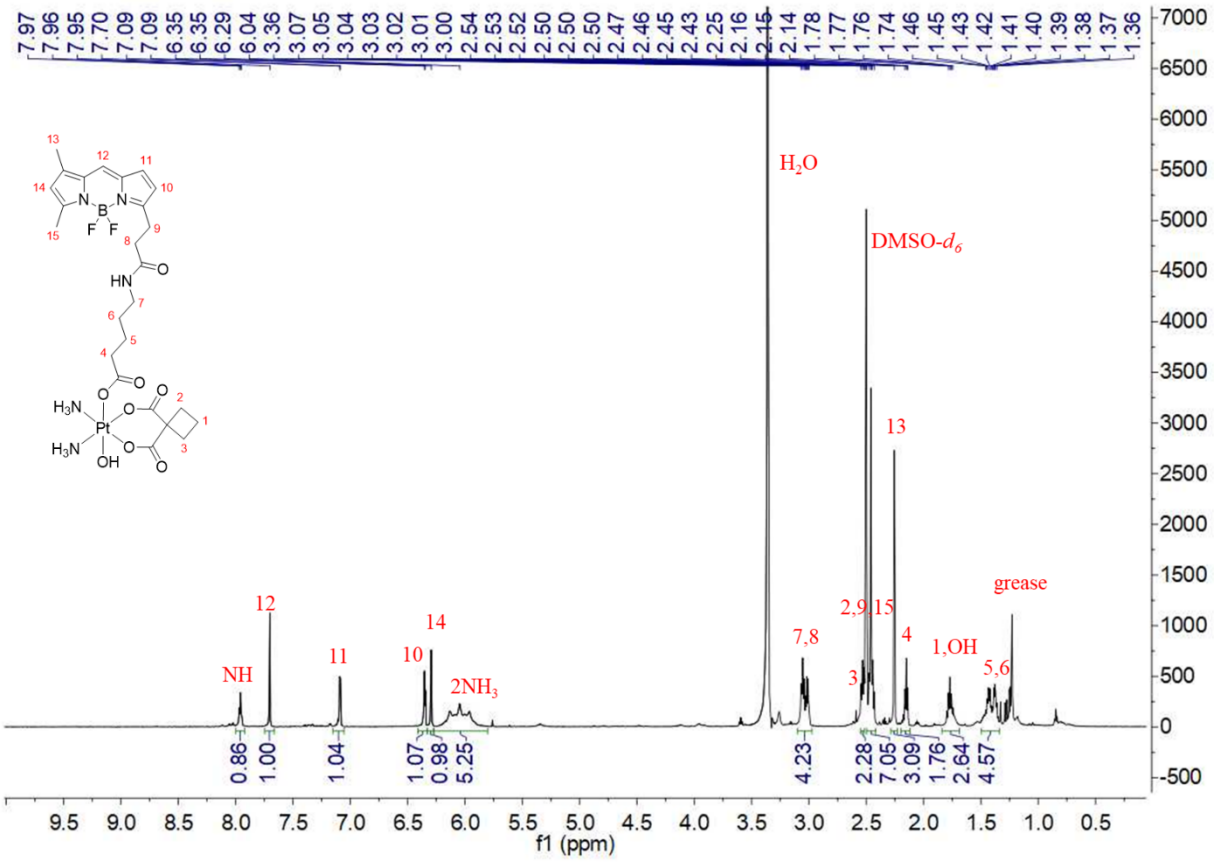

Figure S31. [1]H-NMR spectrum of complex **OH6C** in DMSO-d_6.

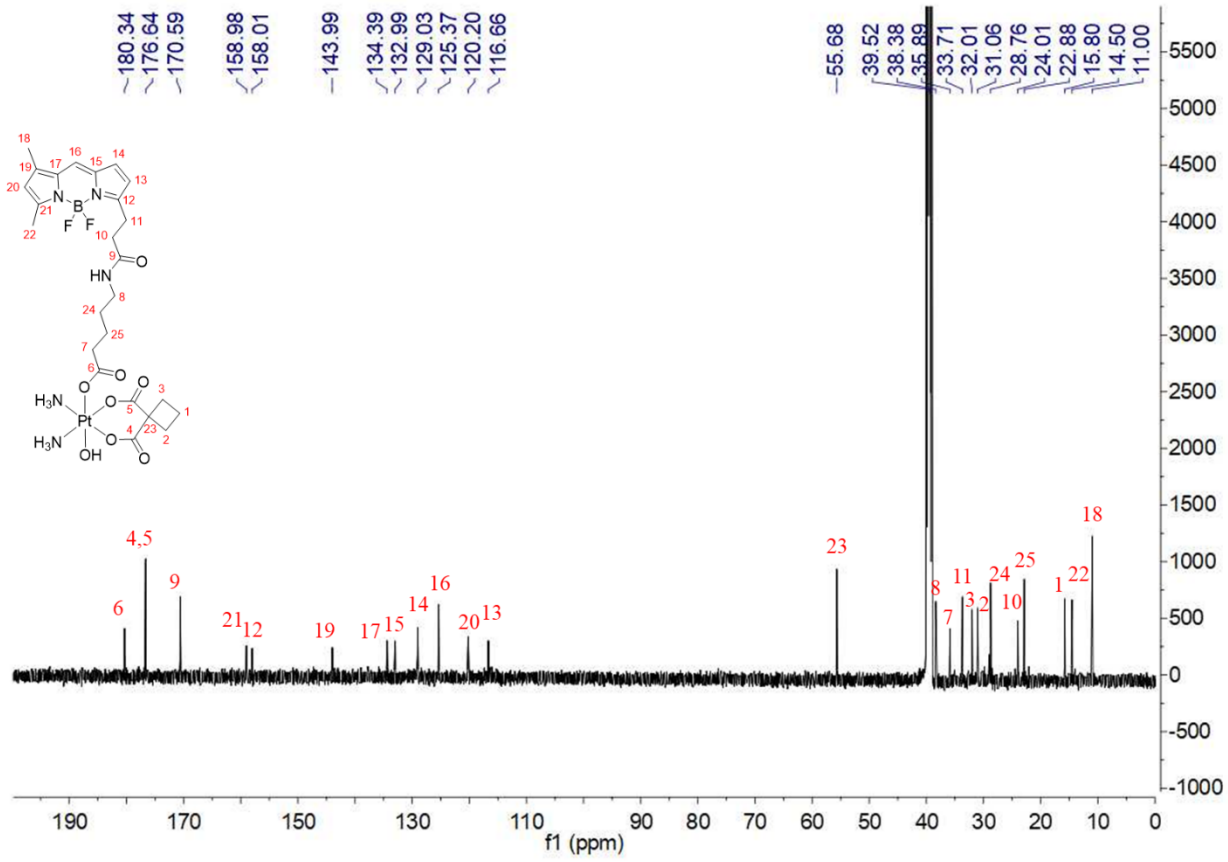

Figure S32. ^{13}C-NMR spectrum of complex **OH6C** in DMSO-d_6.

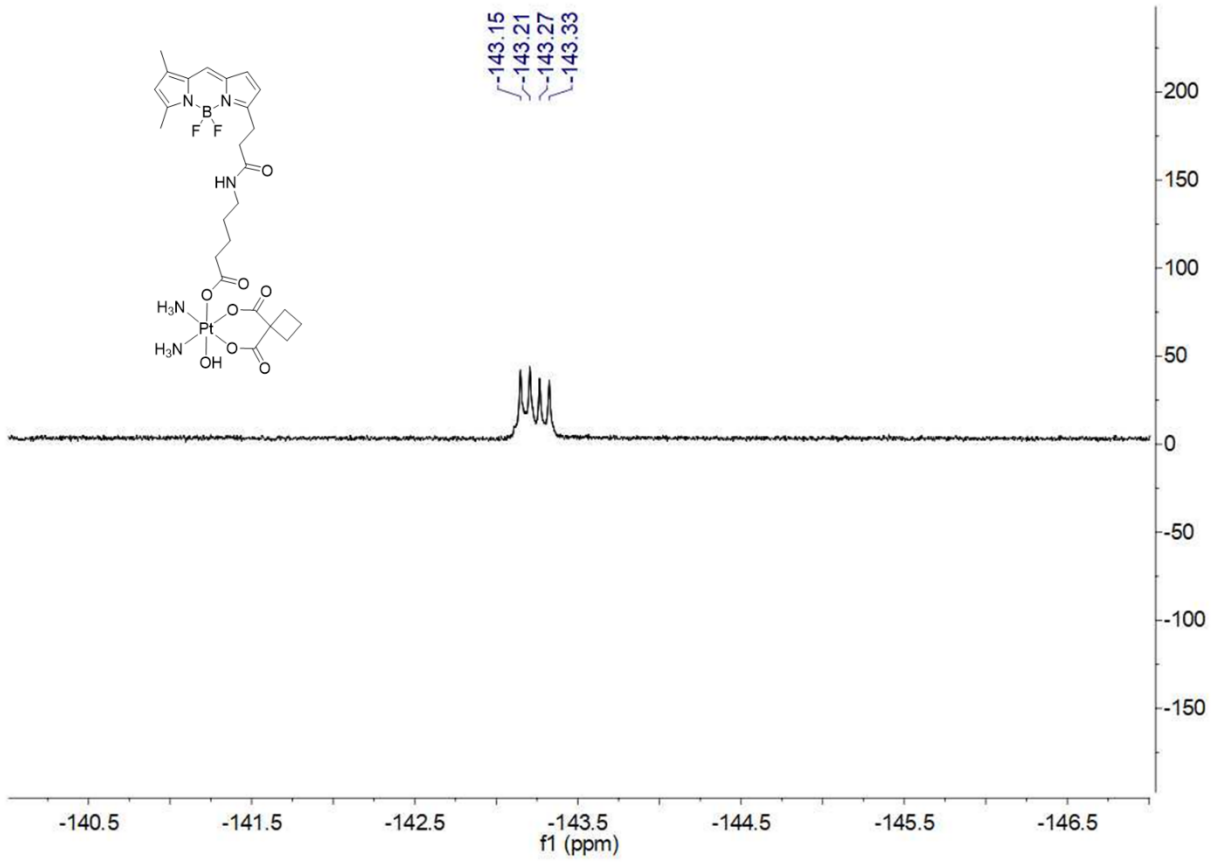

Figure S33. ^{19}F-NMR spectrum of complex **OH6C** in DMSO-d_6.

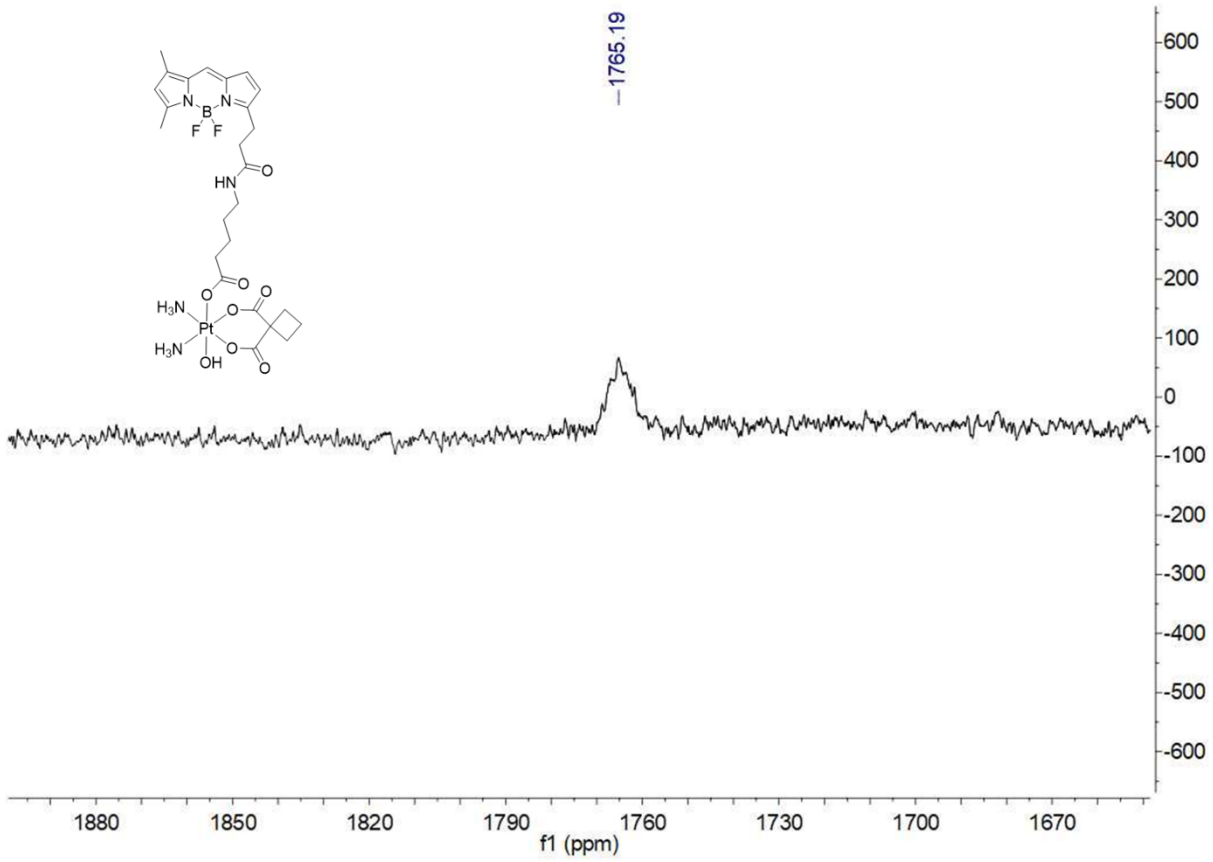

Figure S34. ^{195}Pt-NMR spectrum of complex **OH6C** in DMSO-d_6.

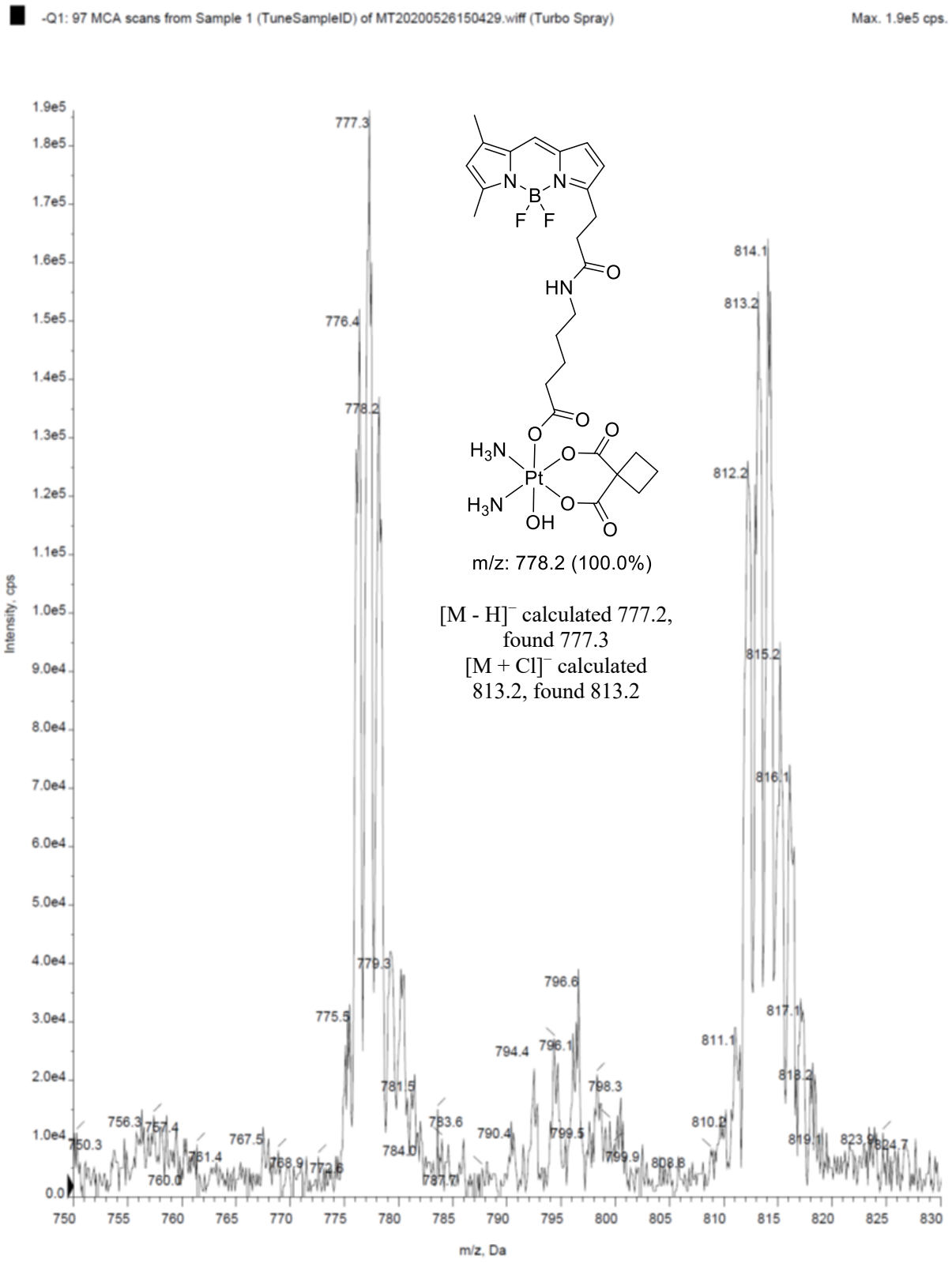

Figure S35. ESI-MS spectrum of complex **OH6C**, negative mode in methanol.

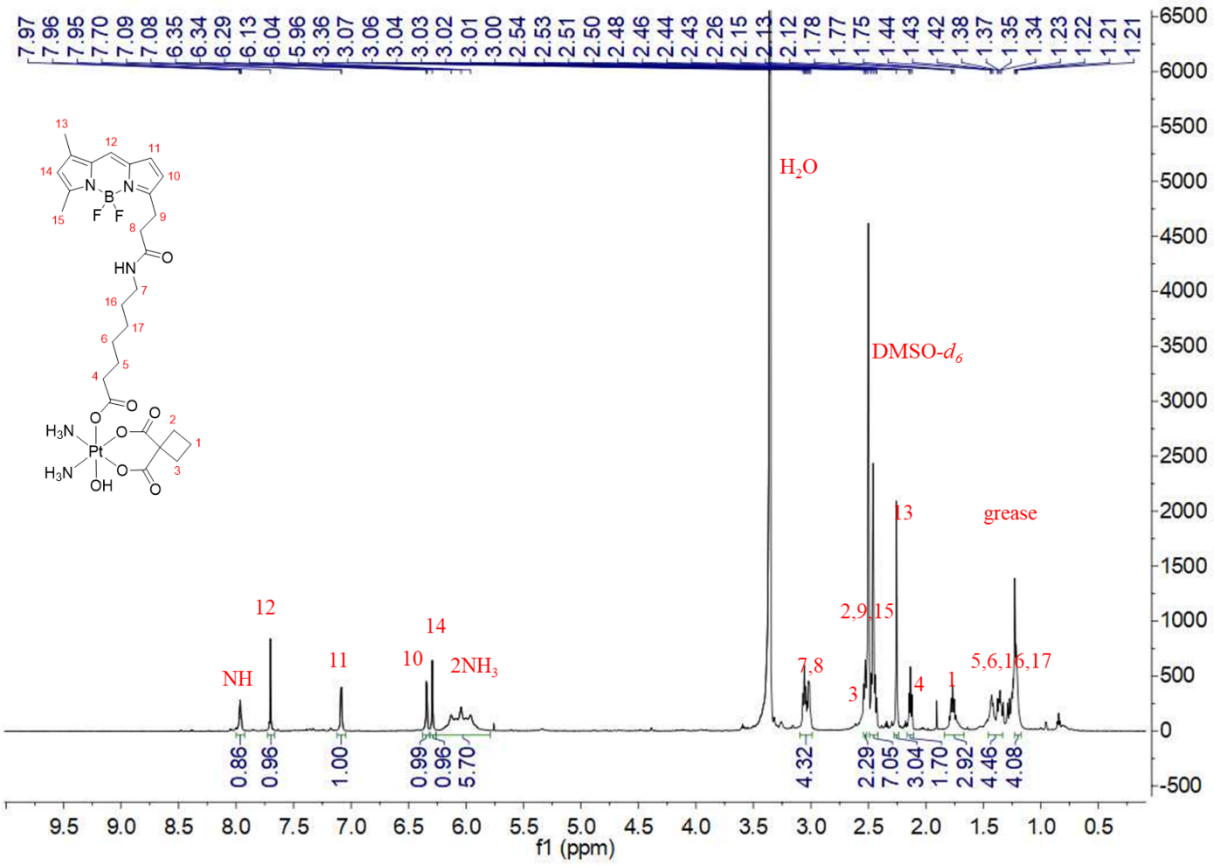

Figure S36. [1]H-NMR spectrum of complex **OH8C** in DMSO-d_6.

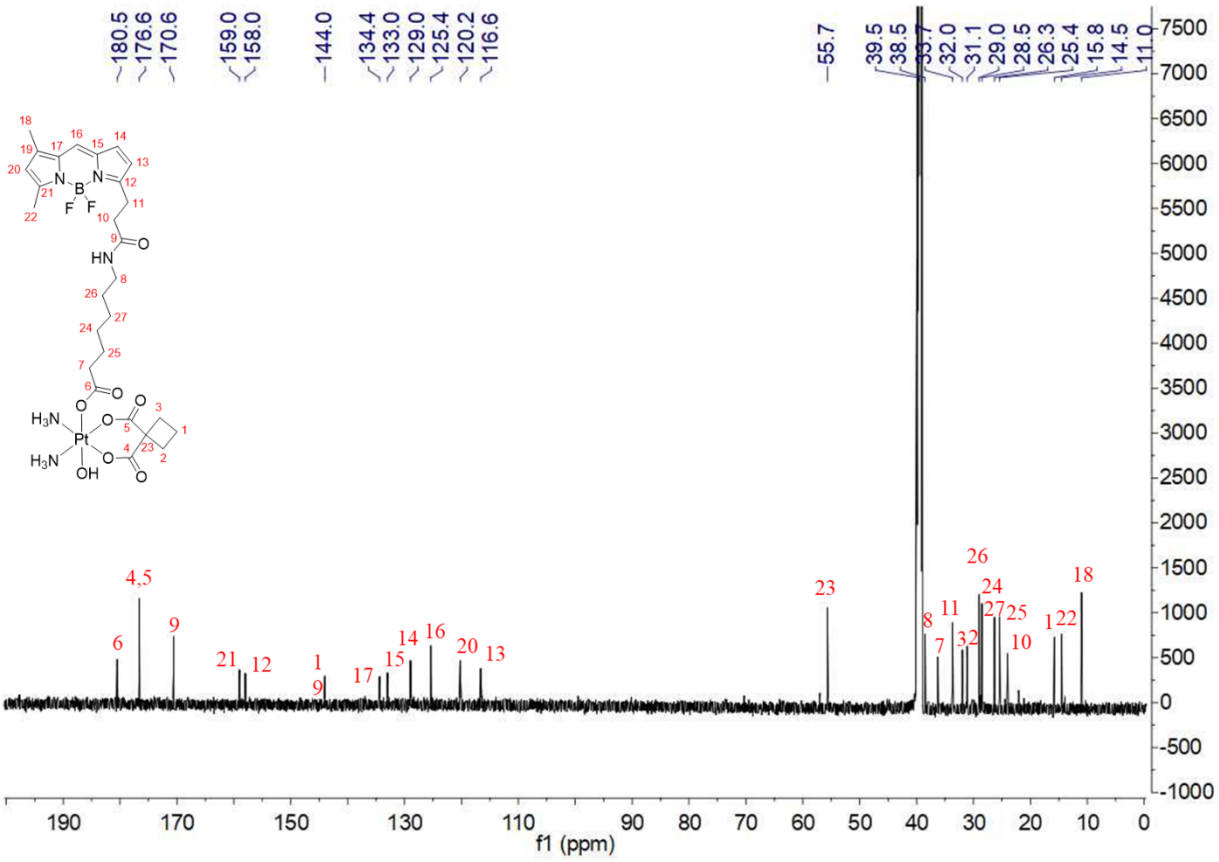

Figure S37. ^{13}C-NMR spectrum of complex **OH8C** in DMSO-d_6.

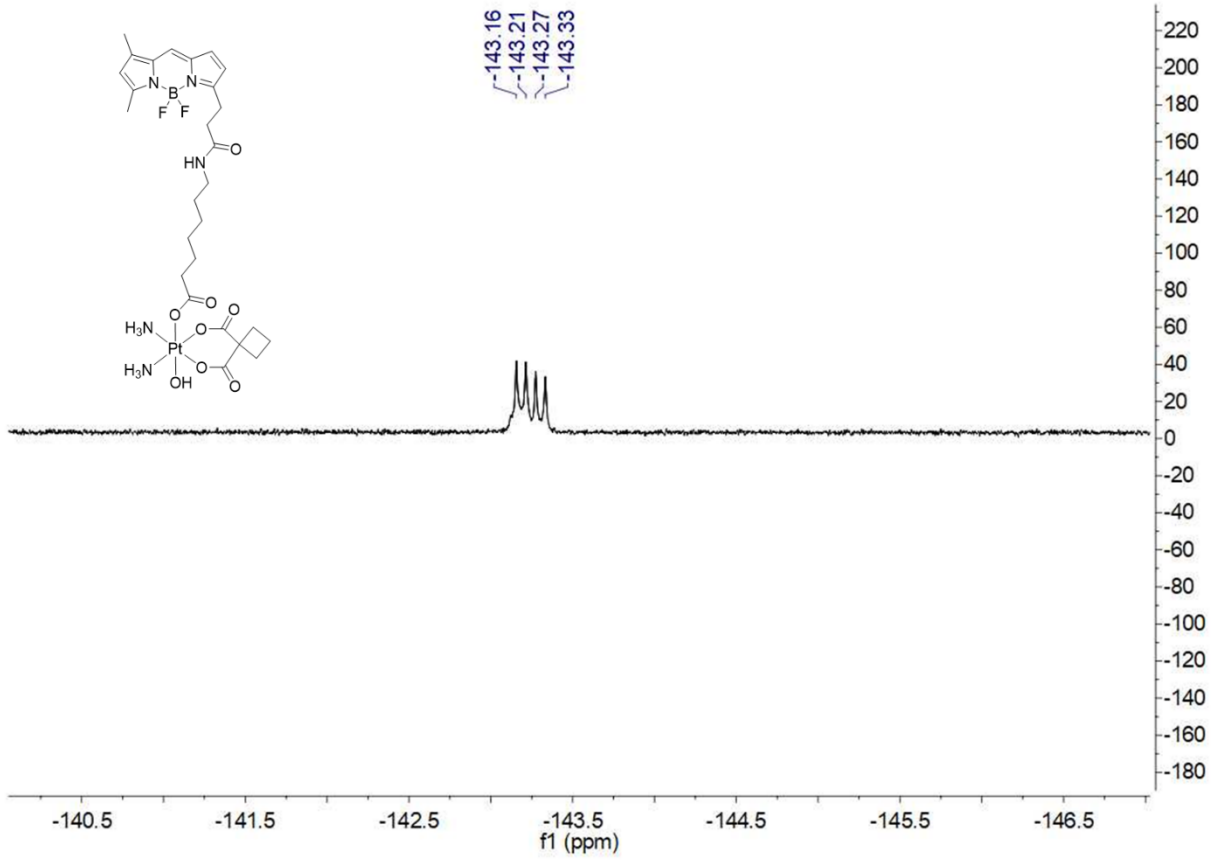

Figure S38. ^{19}F-NMR spectrum of complex **OH8C** in DMSO-d_6.

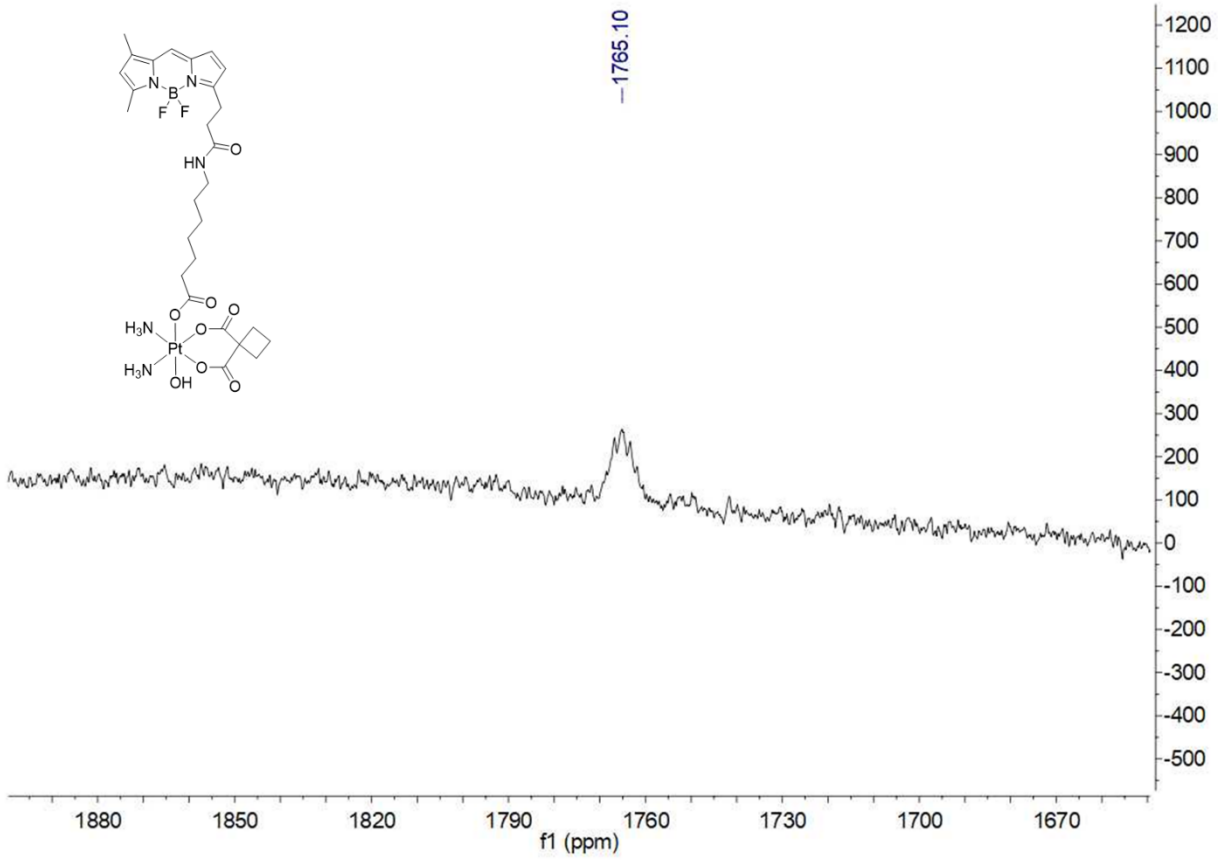

Figure S39. ^{195}Pt-NMR spectrum of complex **OH8C** in DMSO-d_6.

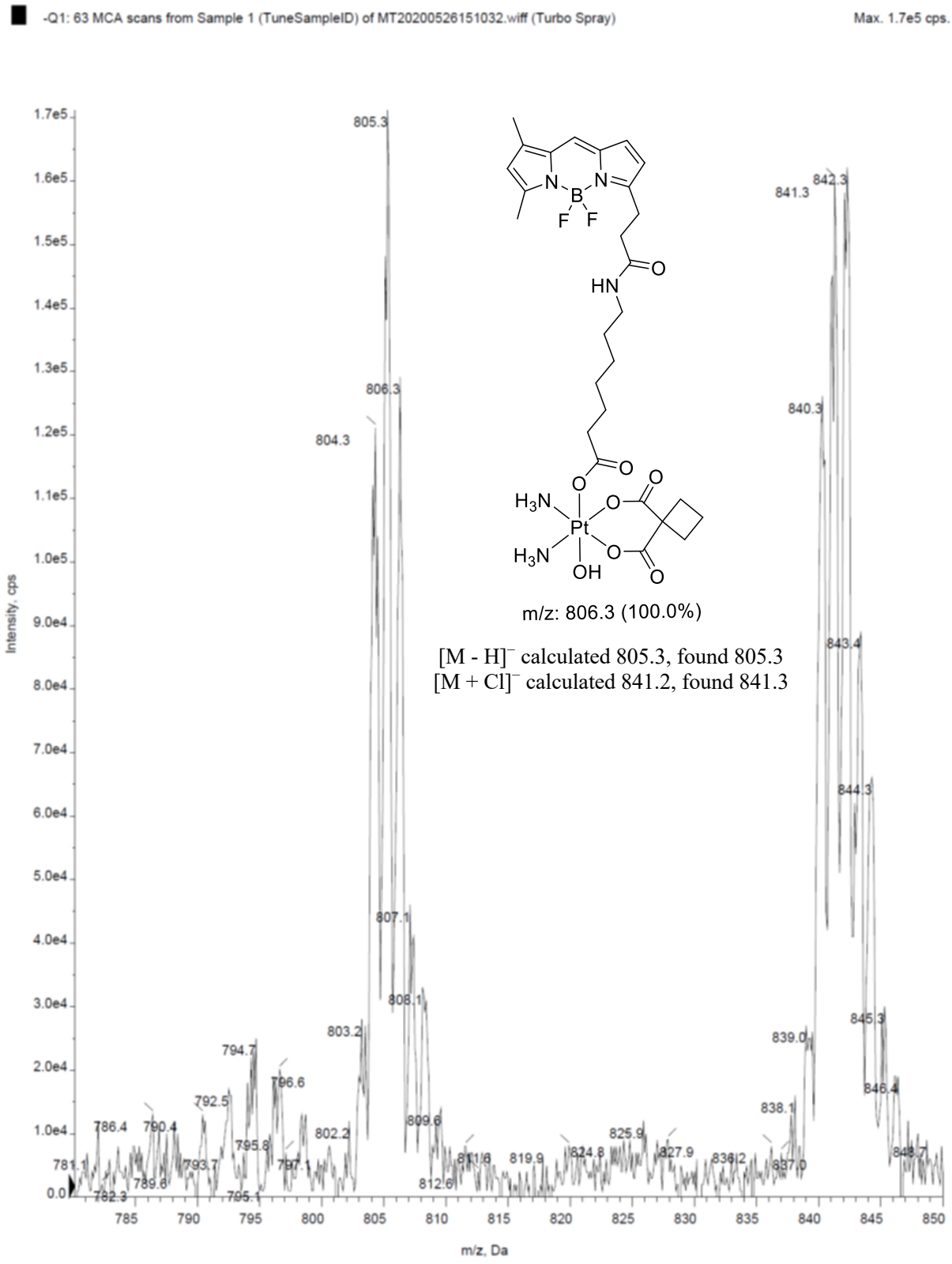

Figure S40. ESI-MS spectrum of complex **OH8C**, negative mode in methanol.

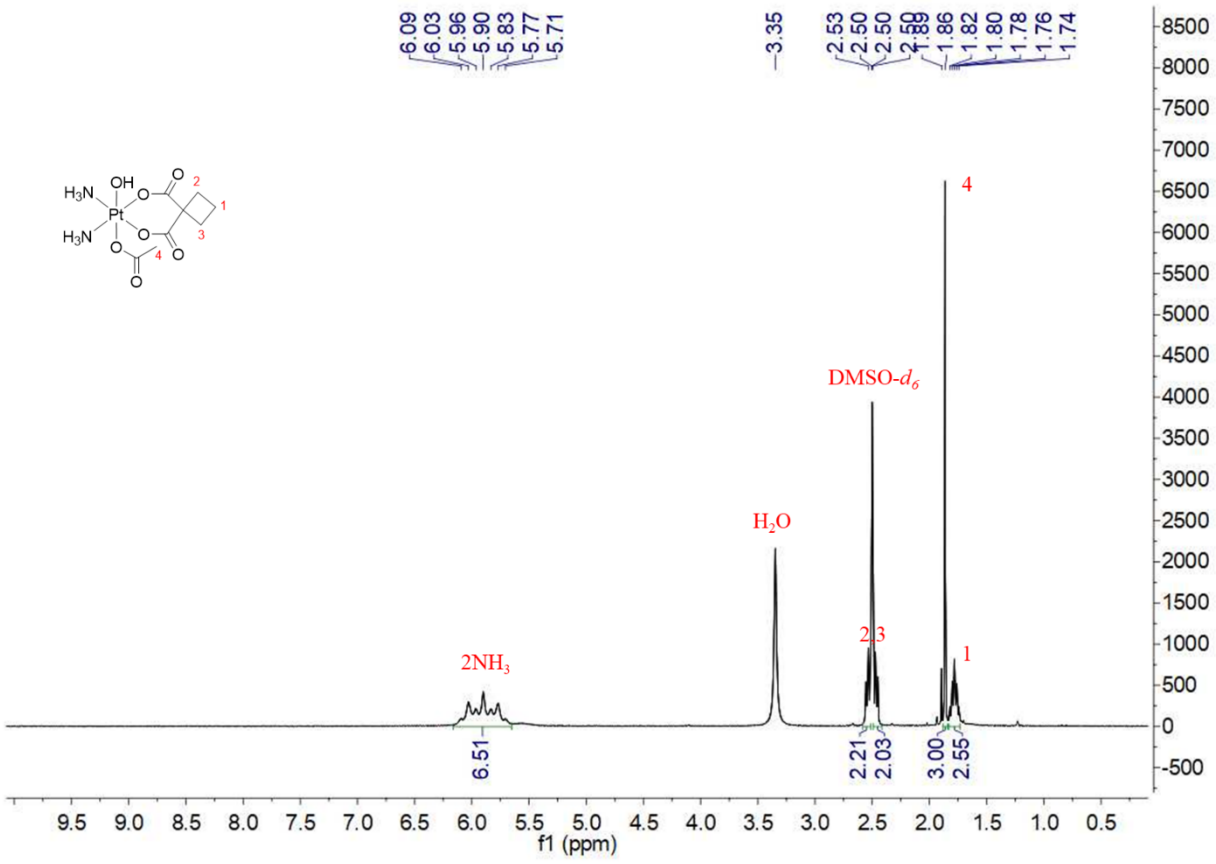

Figure S41. [1]H-NMR spectrum of compound **15** in DMSO-d_6.

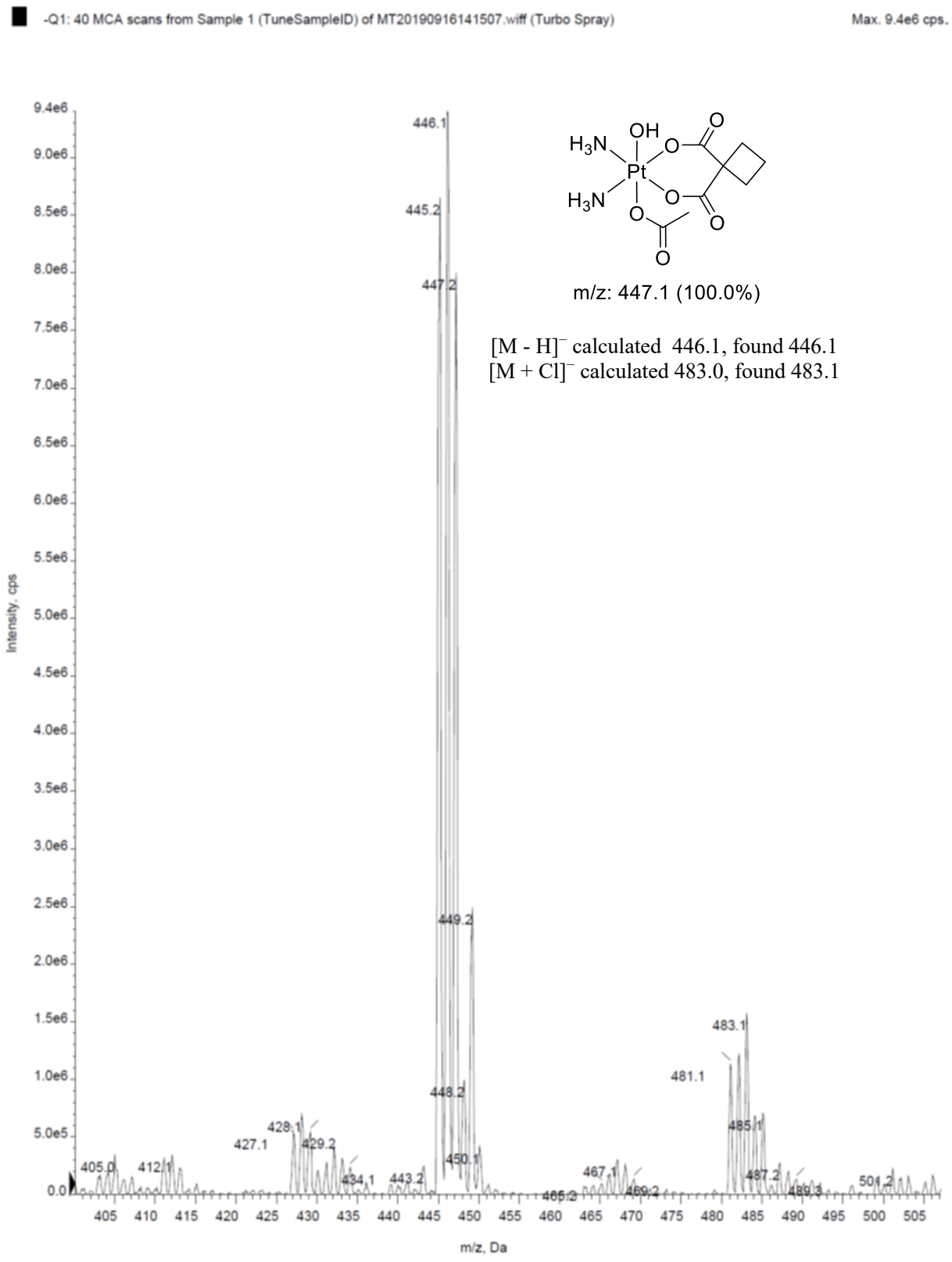

Figure S42. ESI-MS spectrum of compound **15**, negative mode in methanol.

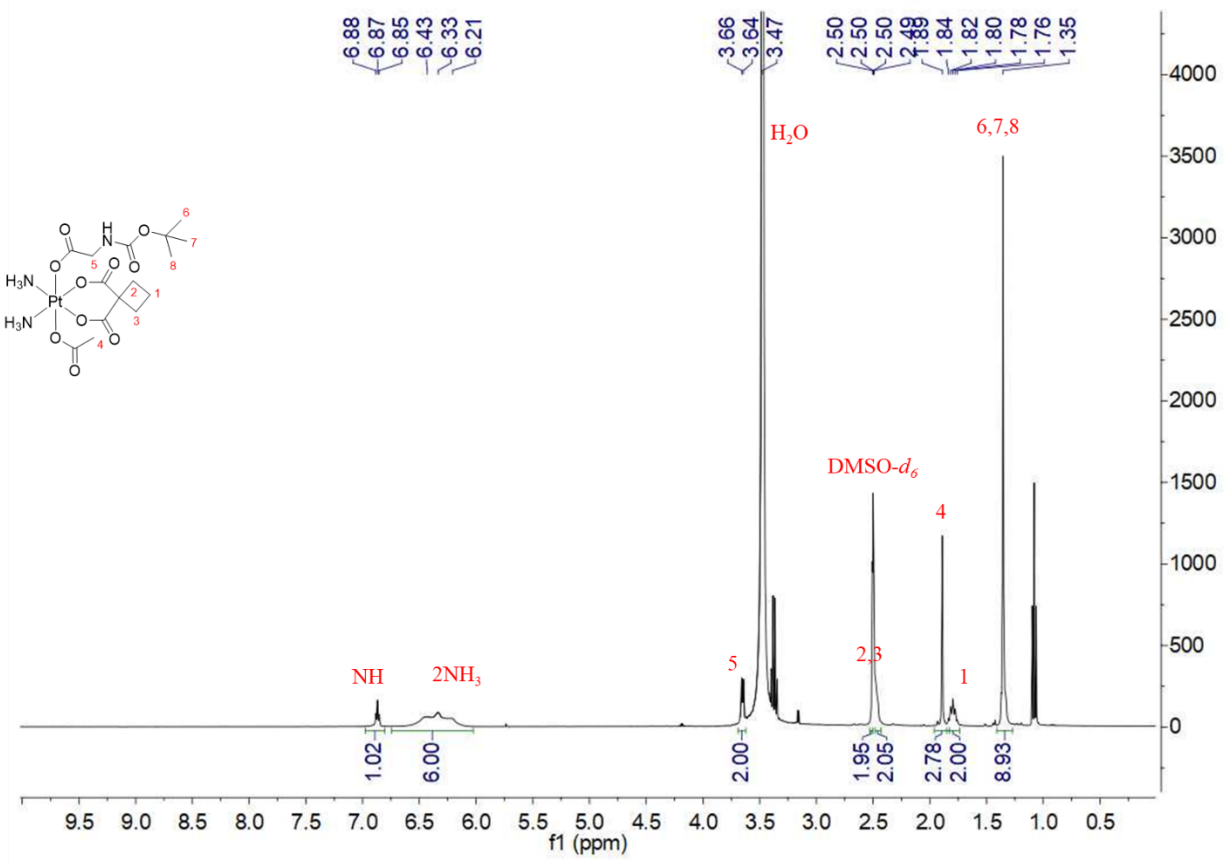

Figure S43. ^{1}H-NMR spectrum of compound **20** in DMSO-d_6.

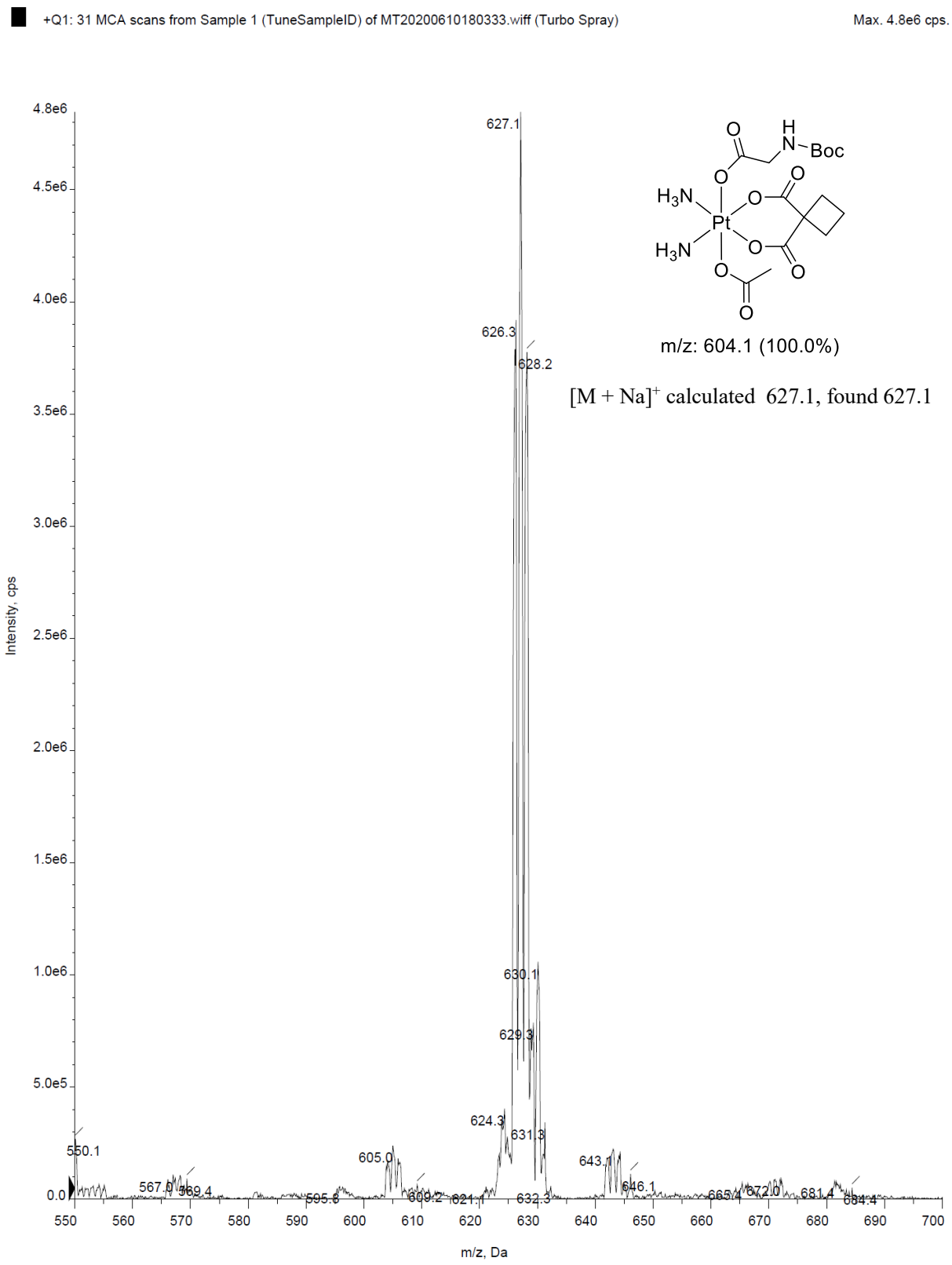

Figure S44. ESI-MS spectrum of compound **20**, positive mode in methanol.

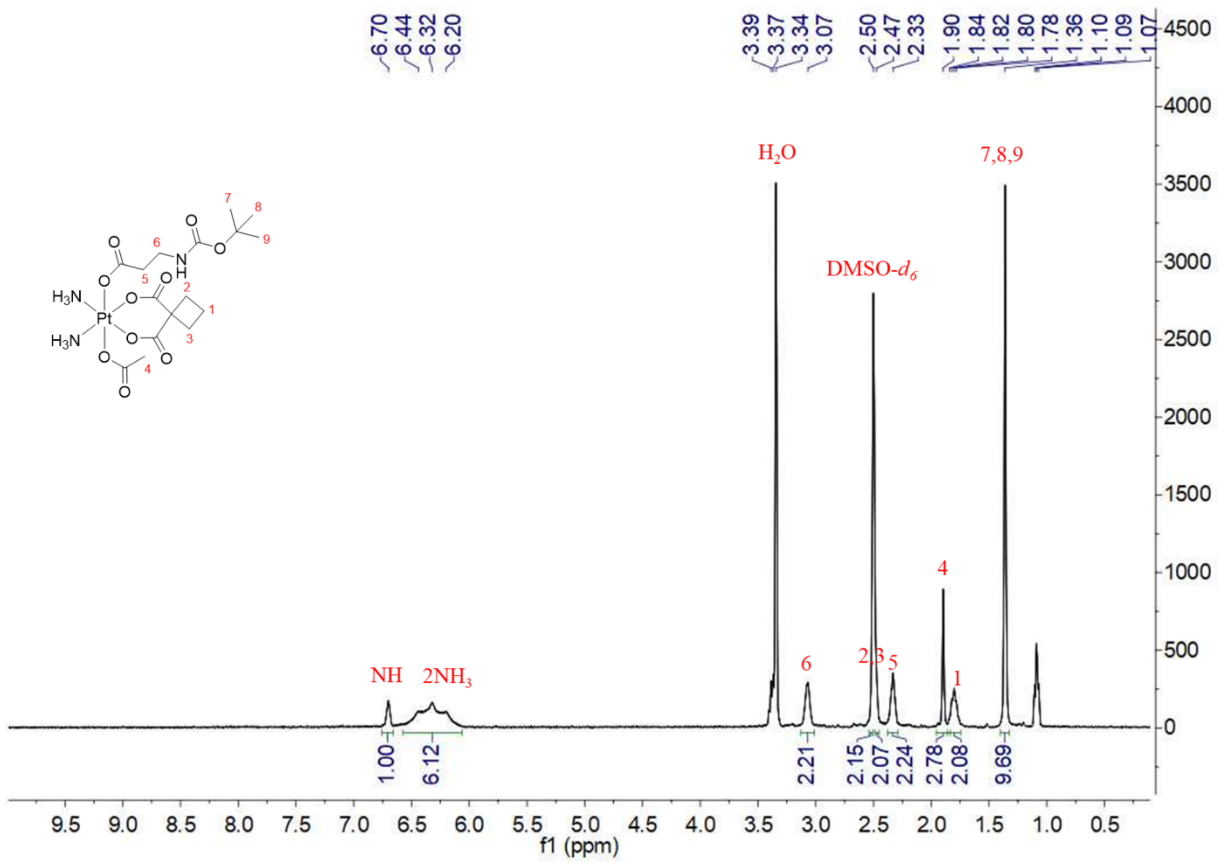

Figure S45. [1]H-NMR spectrum of compound **21** in DMSO-d_6.

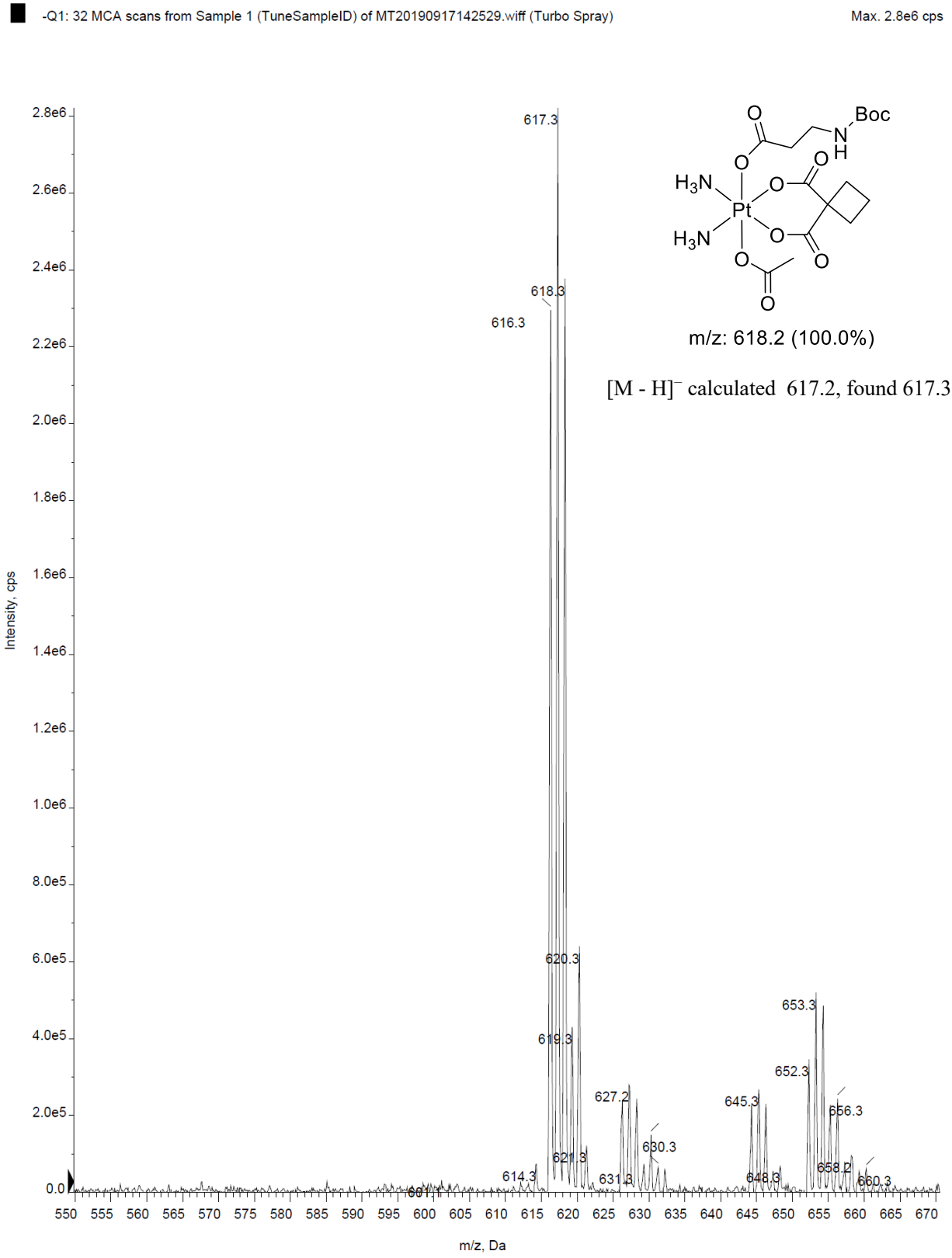

Figure S46. ESI-MS spectrum of compound **21**, negative mode in methanol.

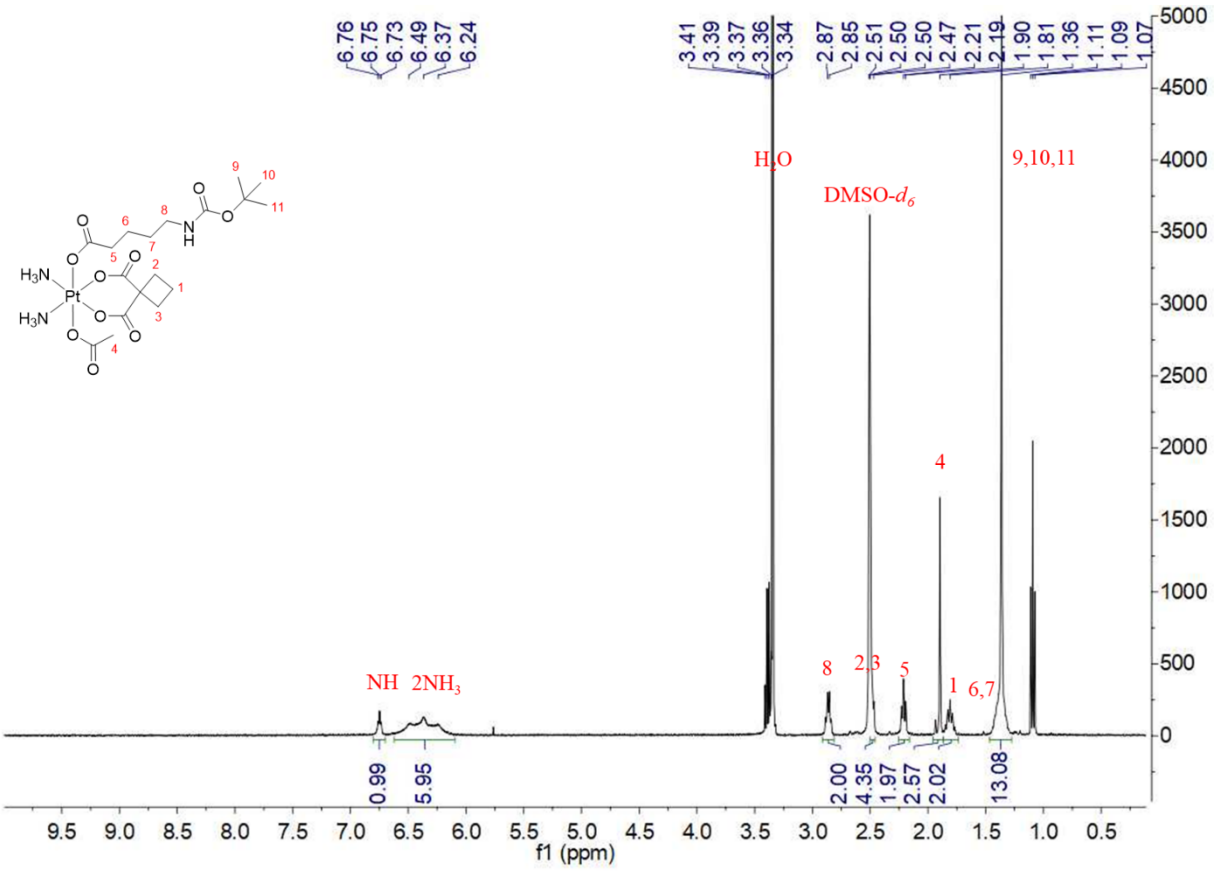

Figure S47. ^{1}H-NMR spectrum of compound **22** in DMSO-d_6.

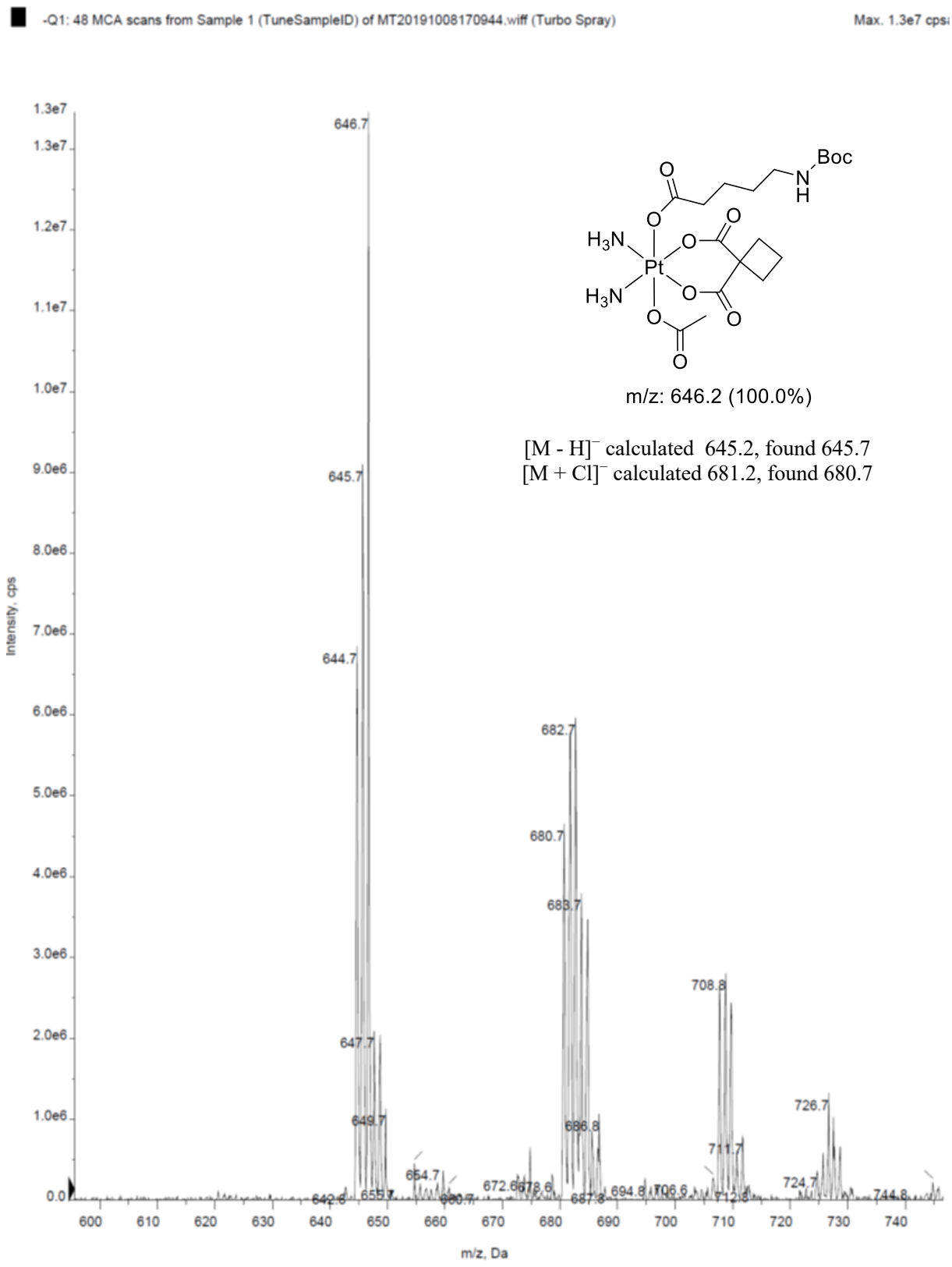

Figure S48. ESI-MS spectrum of compound **22**, negative mode in methanol.

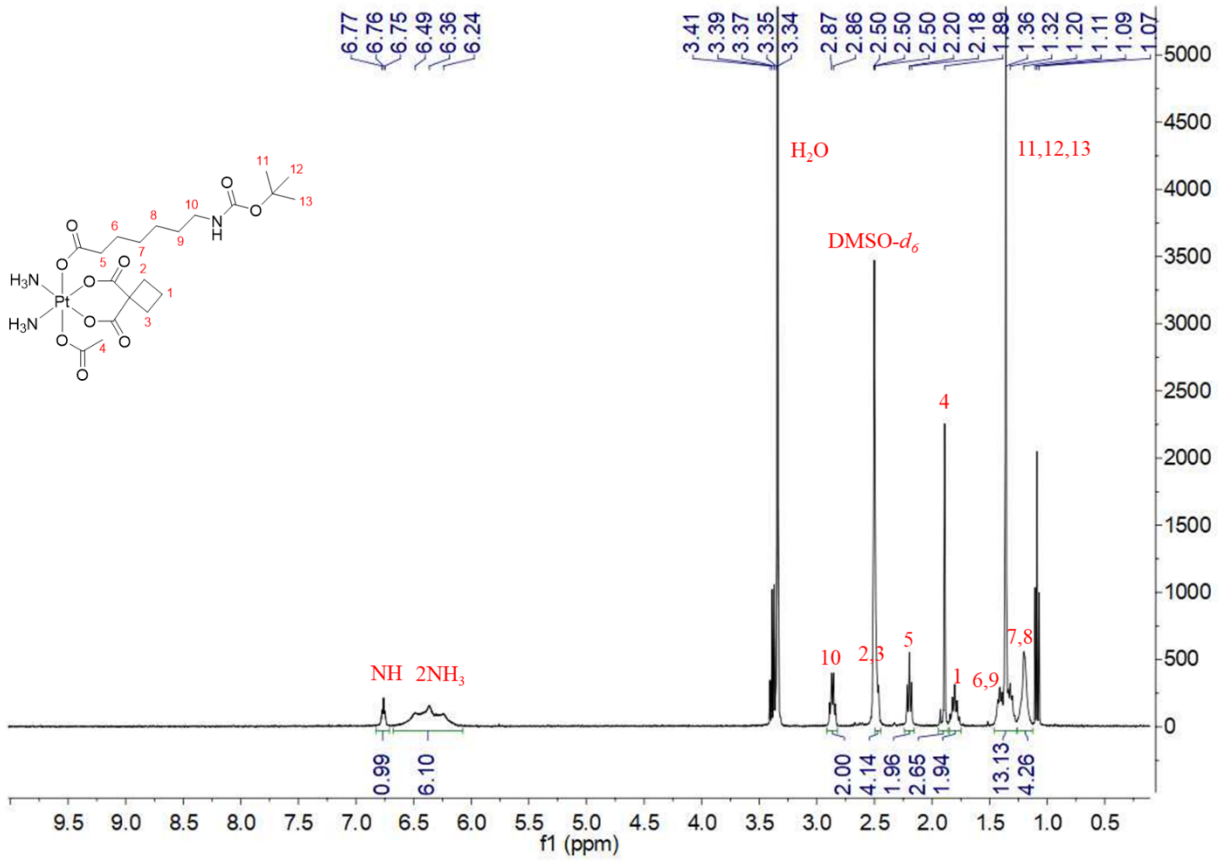

Figure S49. ^{1}H-NMR spectrum of compound **23** in DMSO-d_6.

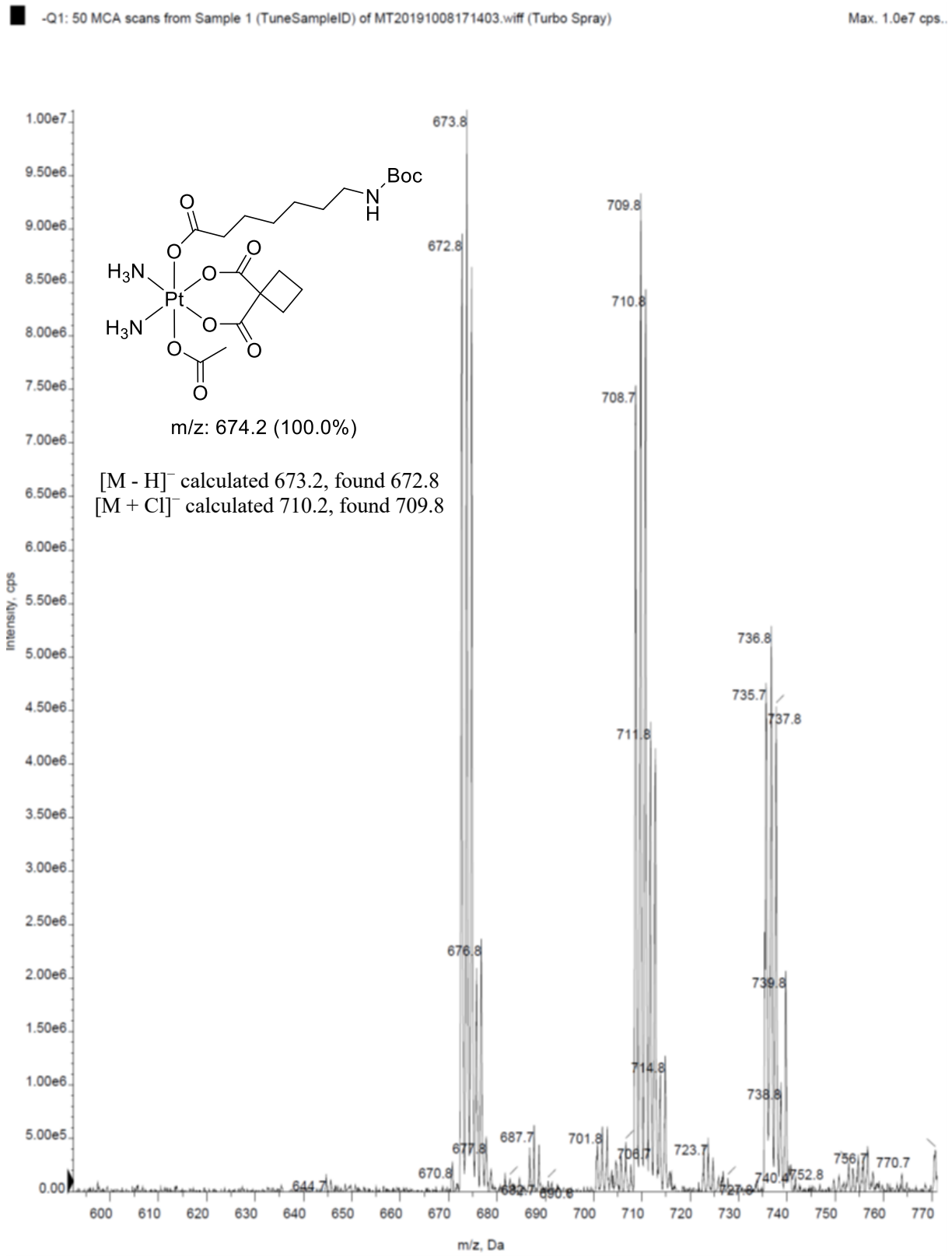

Figure S50. ESI-MS spectrum of compound **23**, negative mode in methanol.

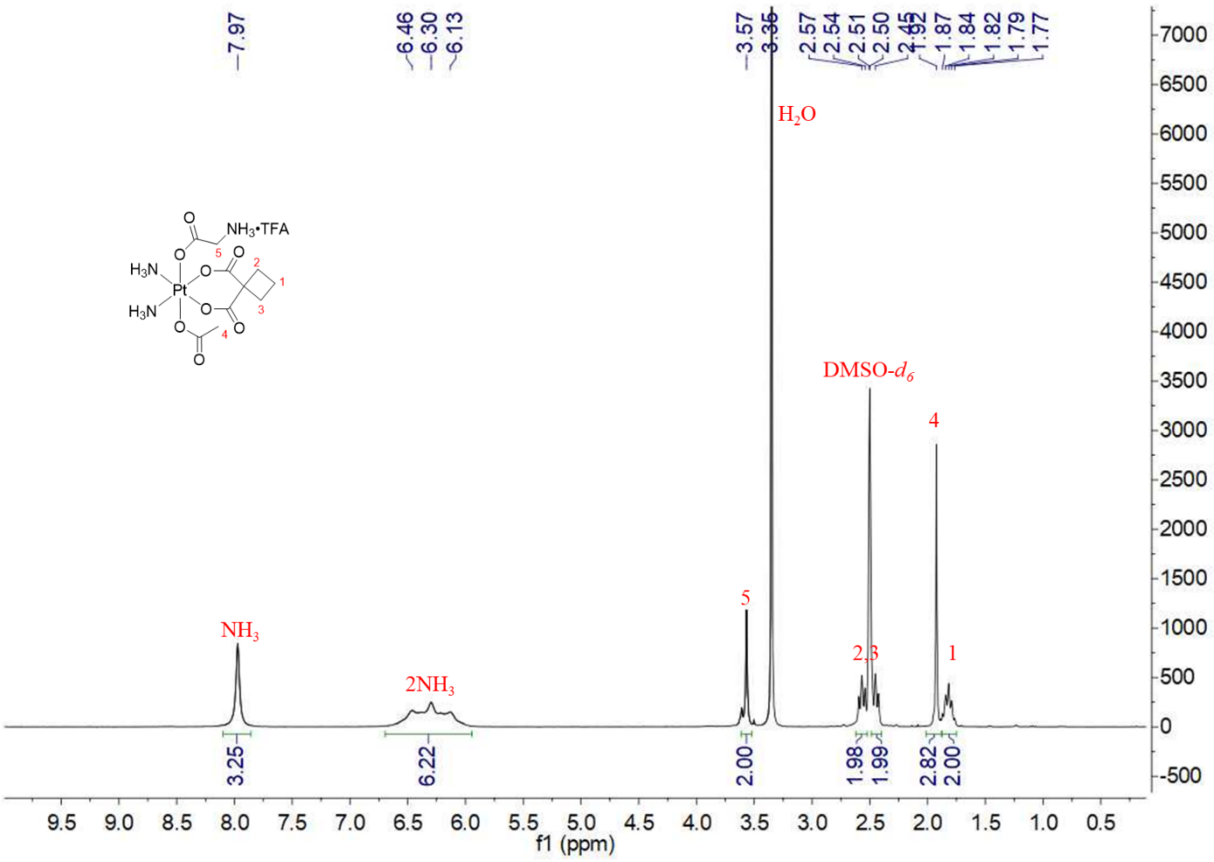

Figure S51. [1]H-NMR spectrum of compound **24** in DMSO-d_6.

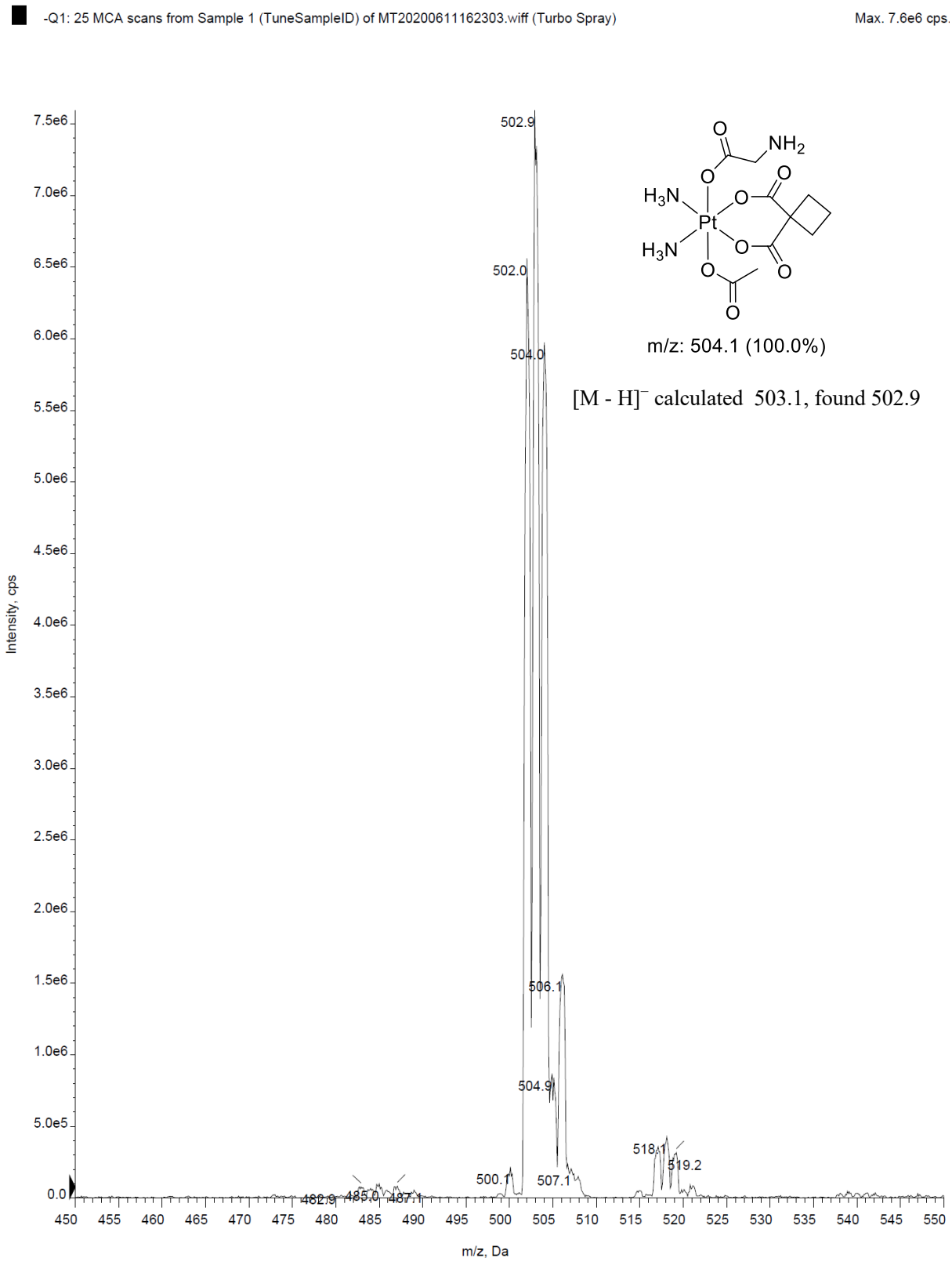

Figure S52. ESI-MS spectrum of compound **24**, negative mode in methanol.

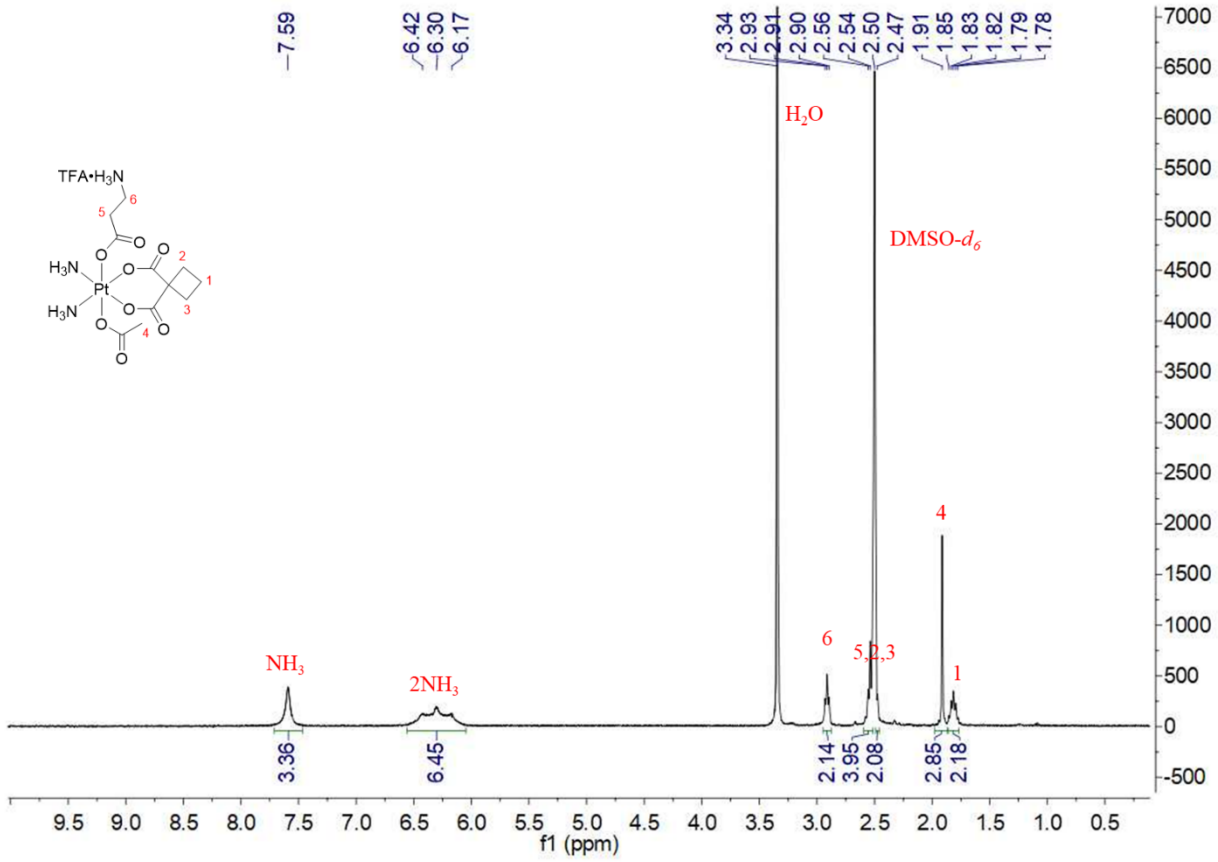

Figure S53. [1]H-NMR spectrum of compound **25** in DMSO-d_6.

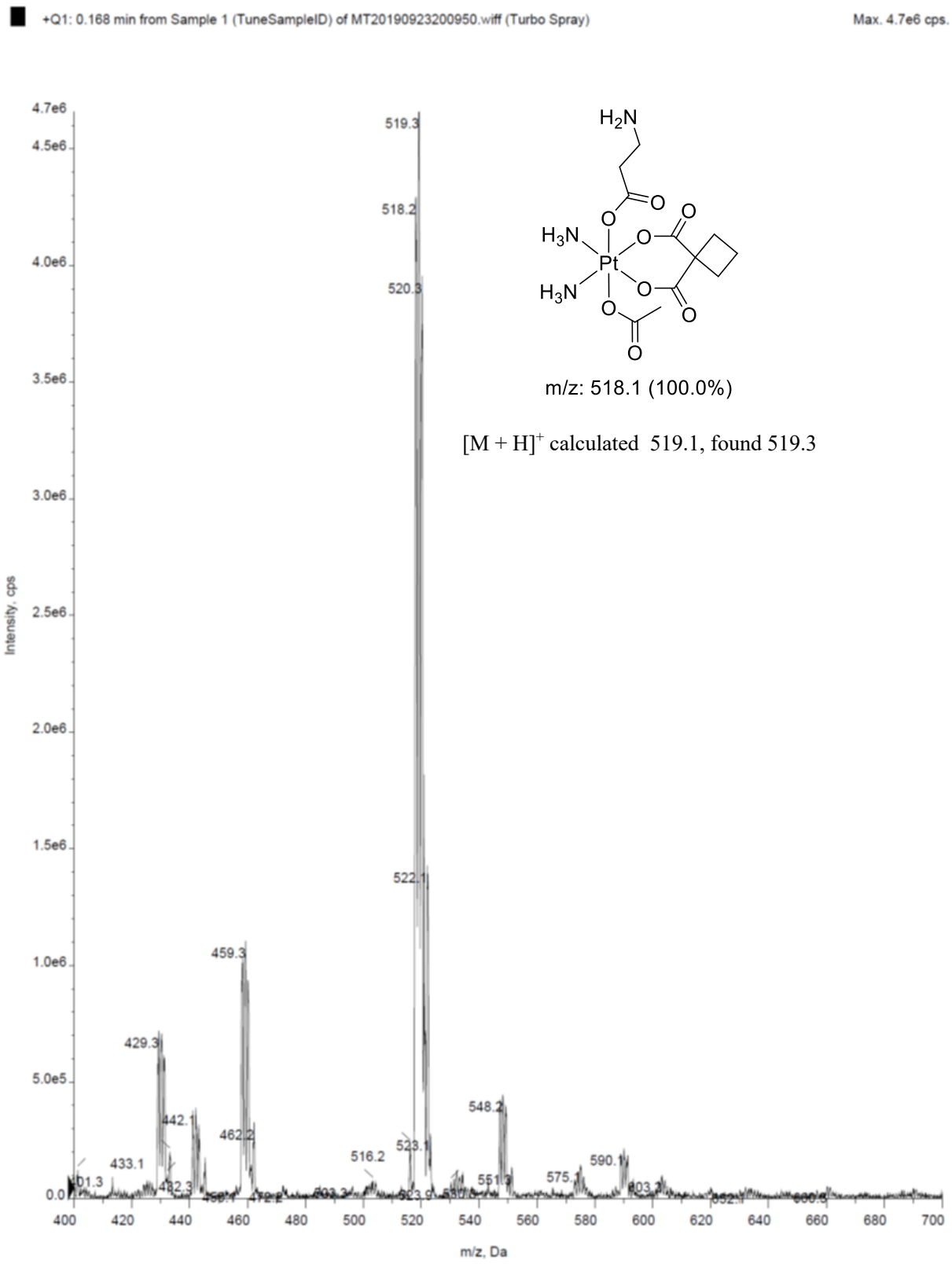

Figure S54. ESI-MS spectrum of compound **25**, positive mode in methanol.

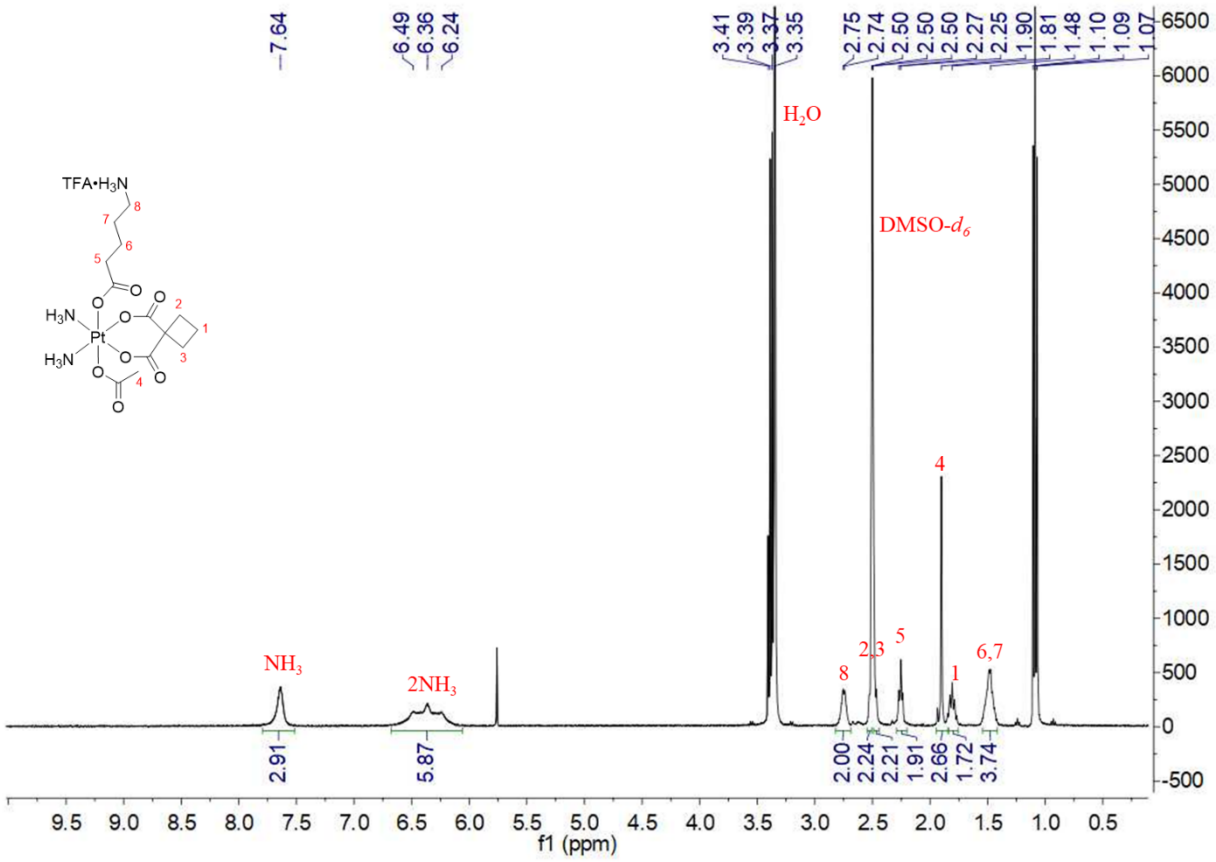

Figure S55. [1]H-NMR spectrum of compound **26** in DMSO-d_6.

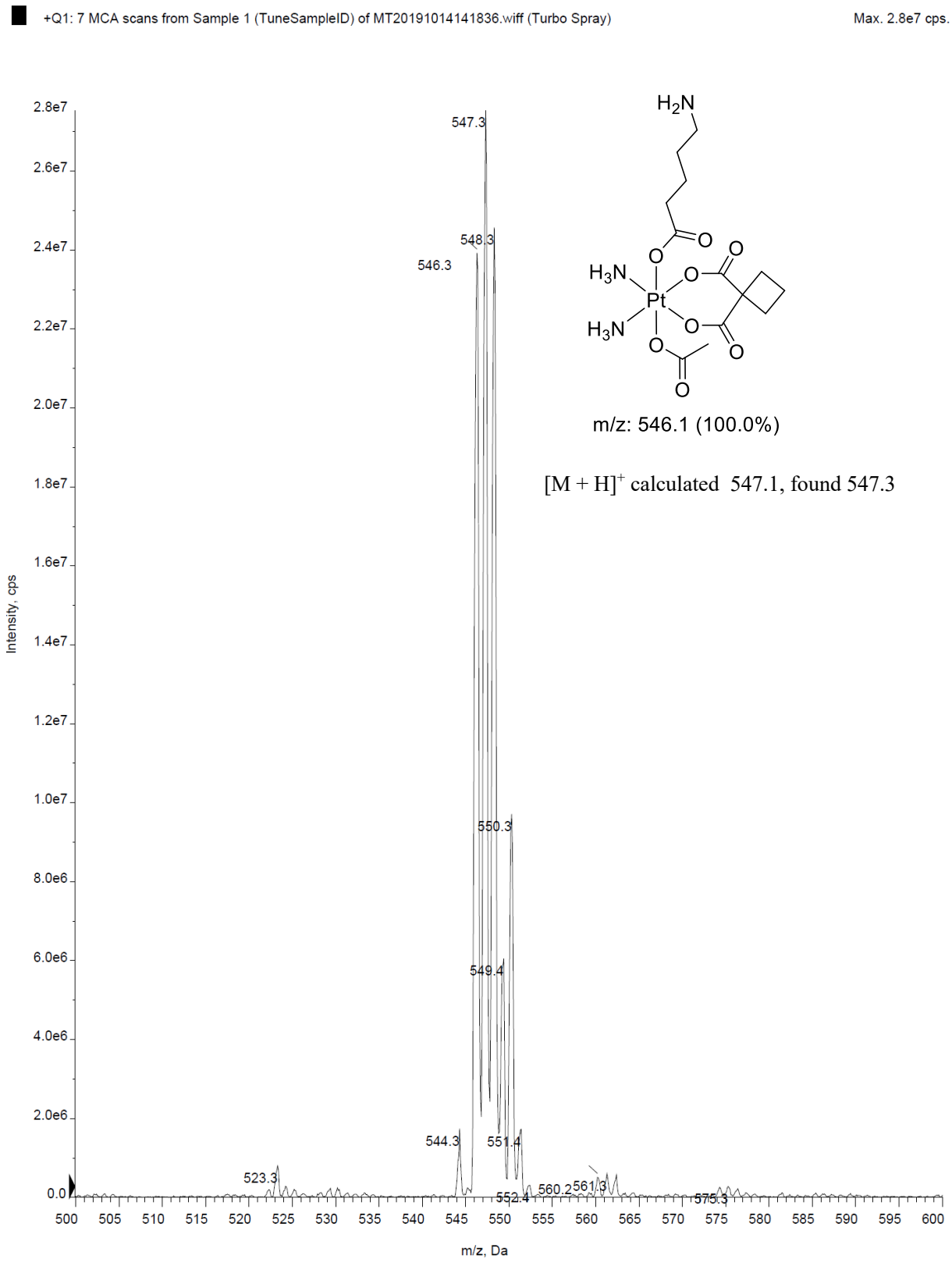

Figure S56. ESI-MS spectrum of compound **26**, positive mode in methanol.

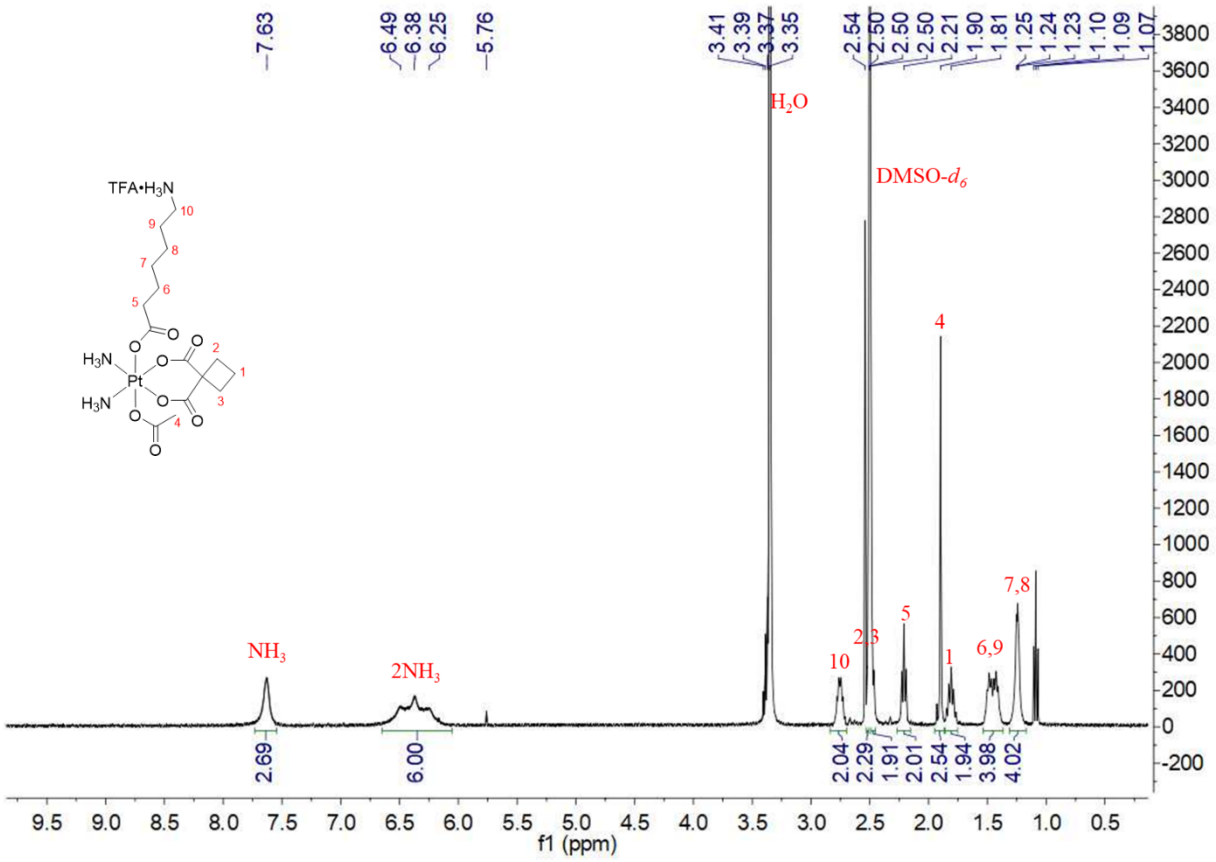

Figure S57. [1]H-NMR spectrum of compound **27** in DMSO-d_6.

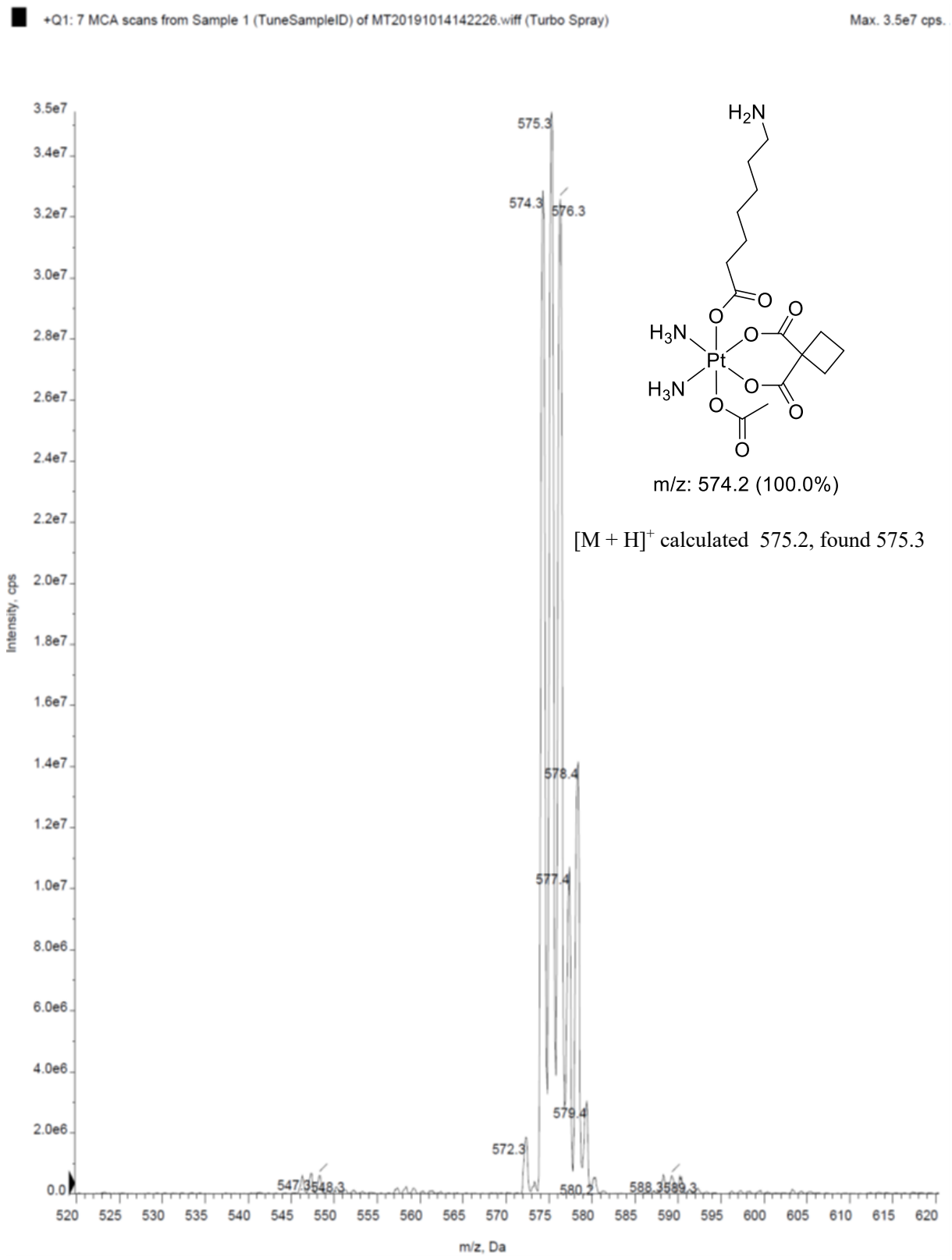

Figure S58. ESI-MS spectrum of compound **27**, positive mode in methanol.

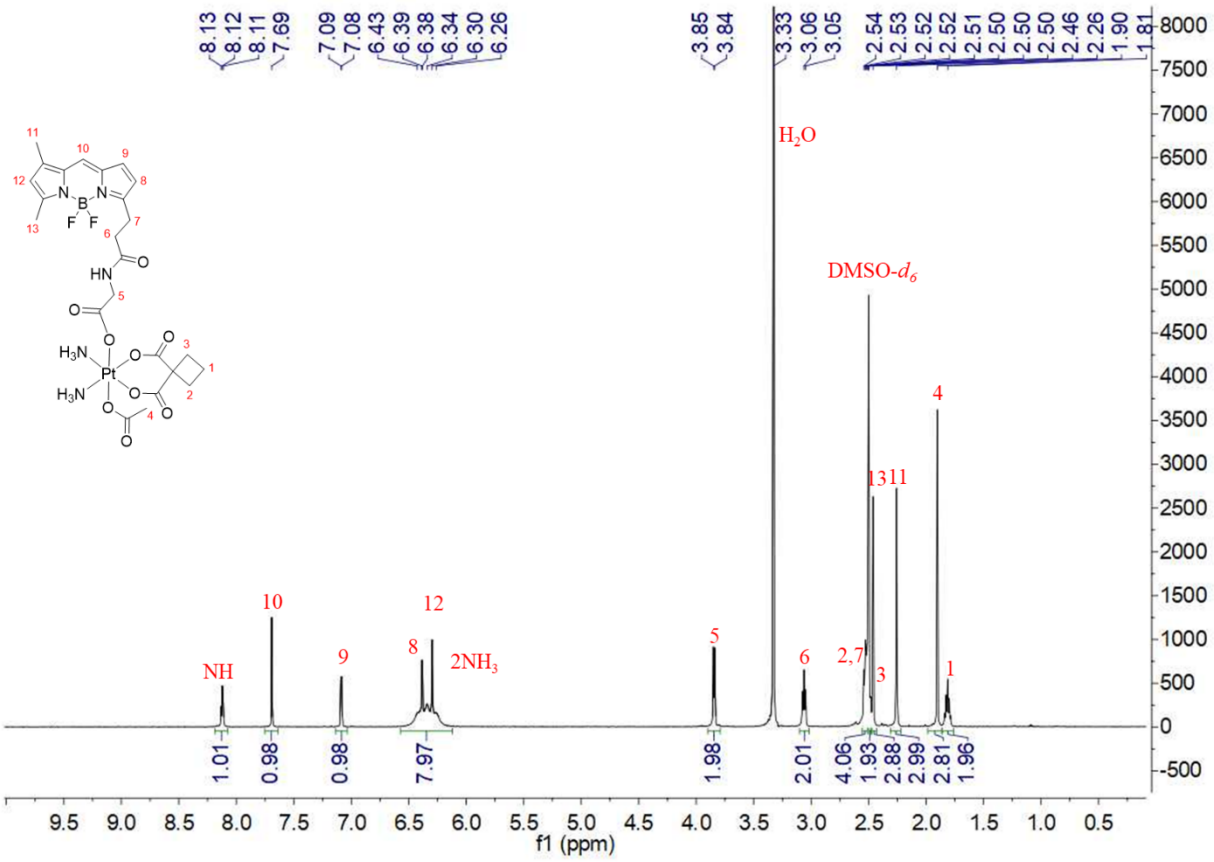

Figure S59. [1]H-NMR spectrum of complex **AC3C** in DMSO-d_6.

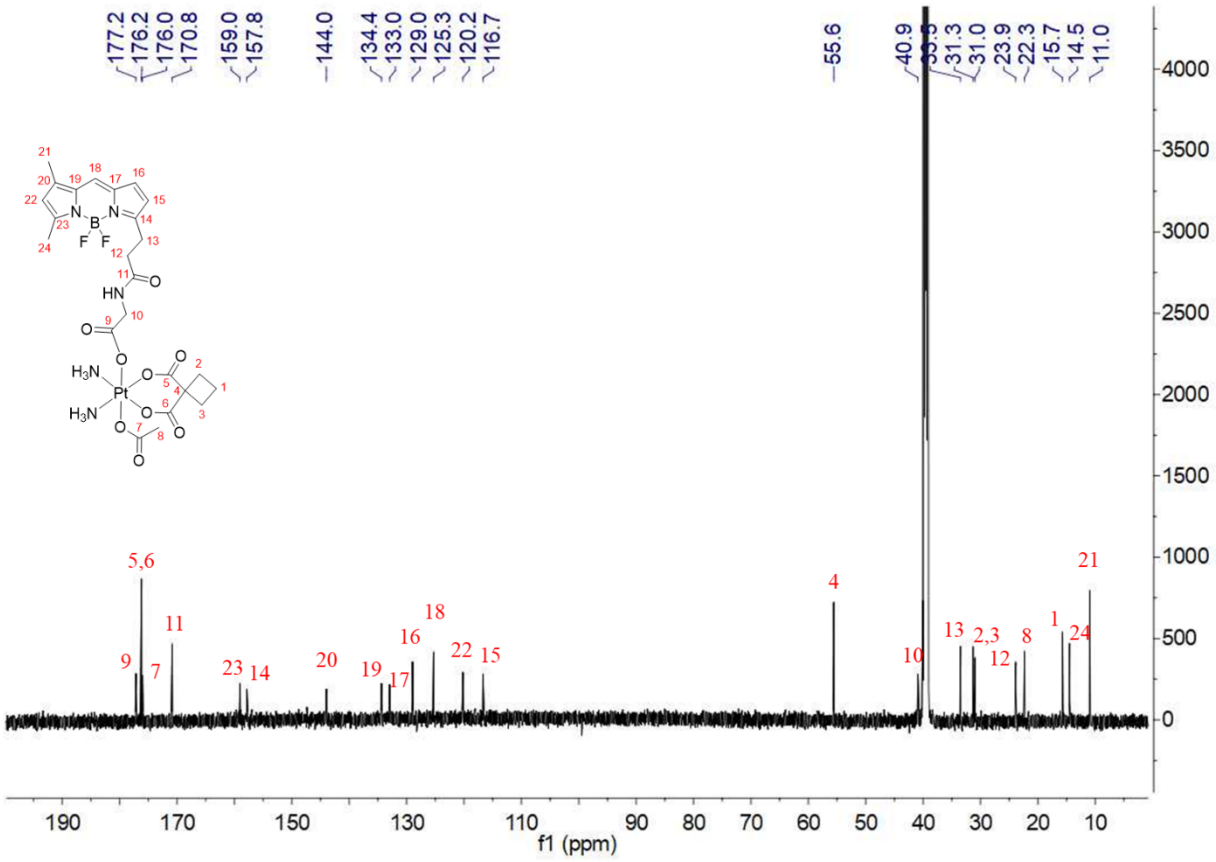

Figure S60. ^{13}C-NMR spectrum of complex **AC3C** in DMSO-d_6.

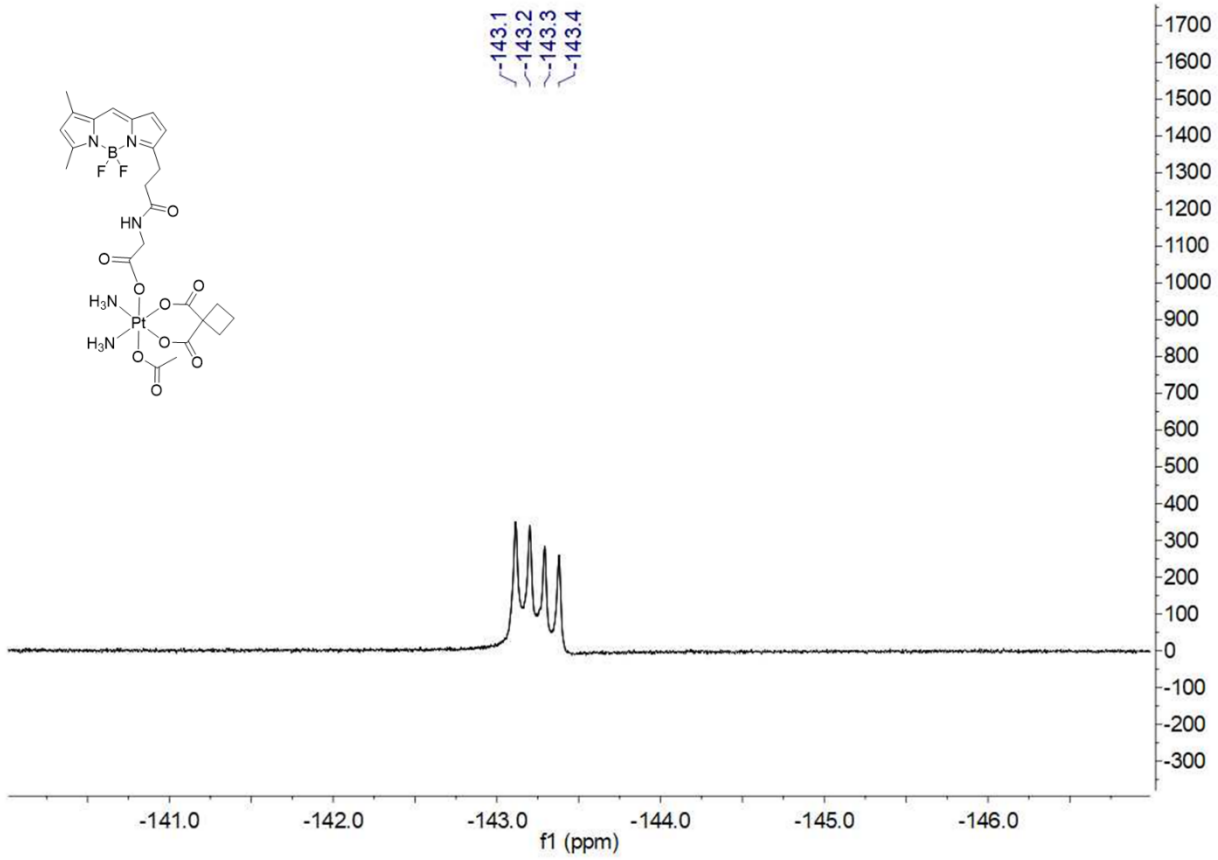

Figure S61. ^{19}F-NMR spectrum of complex **AC3C** in DMSO-d_6.

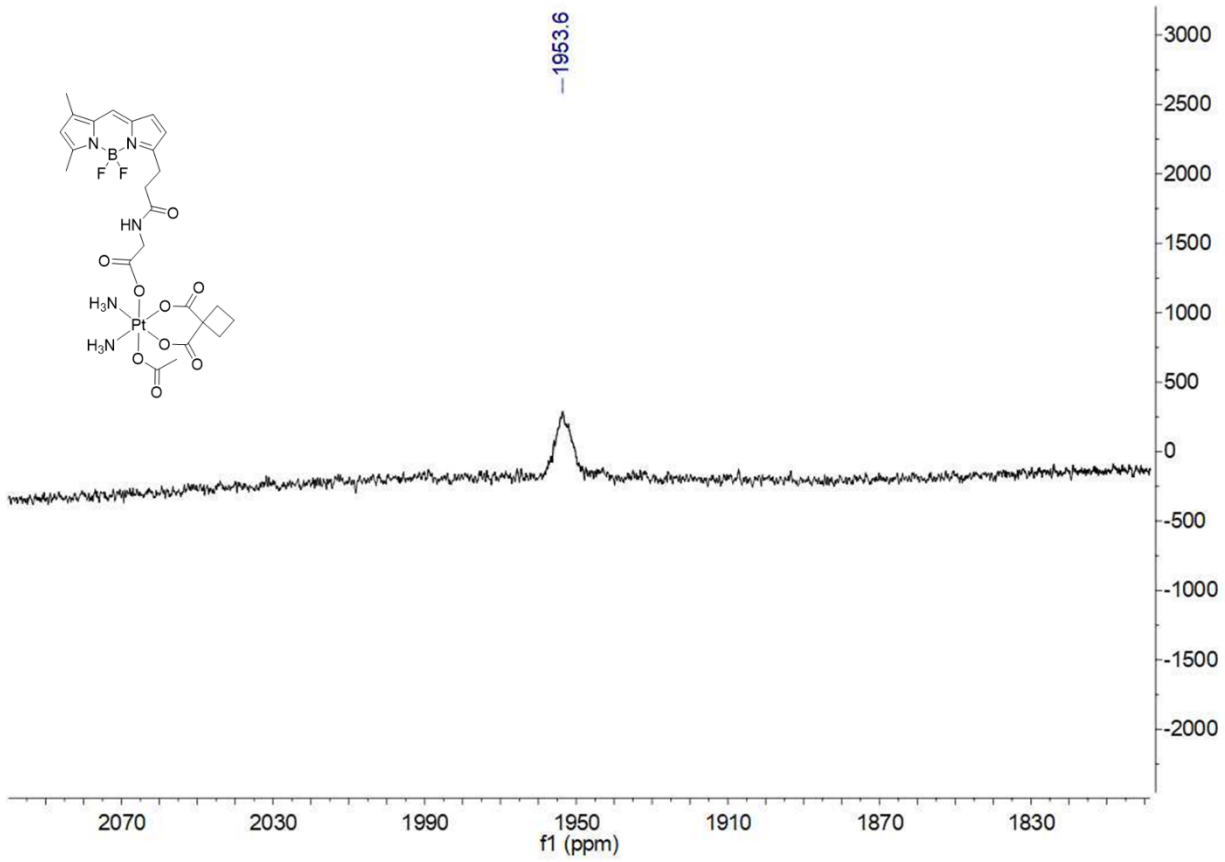

Figure S62. ^{195}Pt-NMR spectrum of complex **AC3C** in DMSO-d_6.

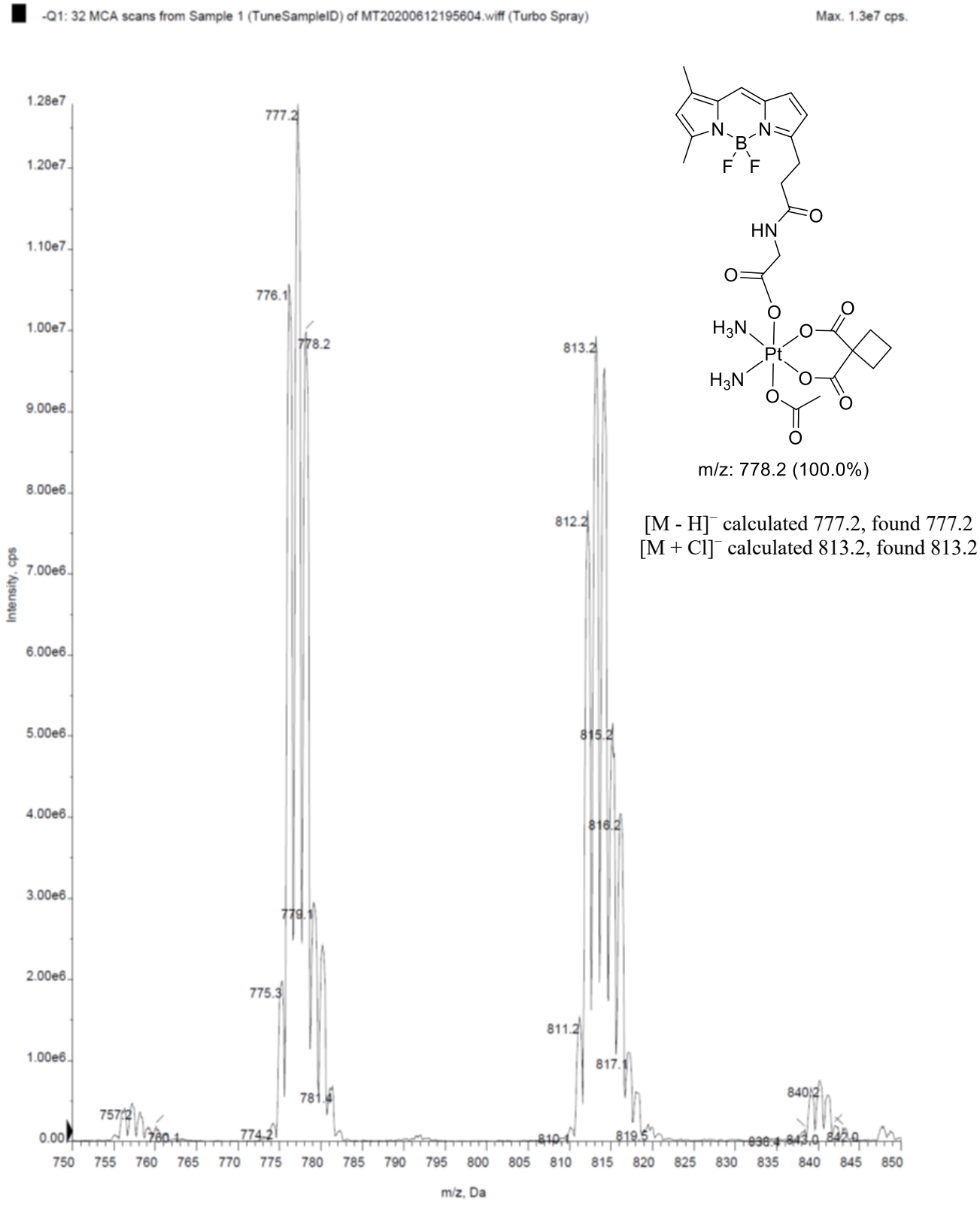

Figure S63. ESI-MS spectrum of complex **AC3C**, negative mode in methanol.

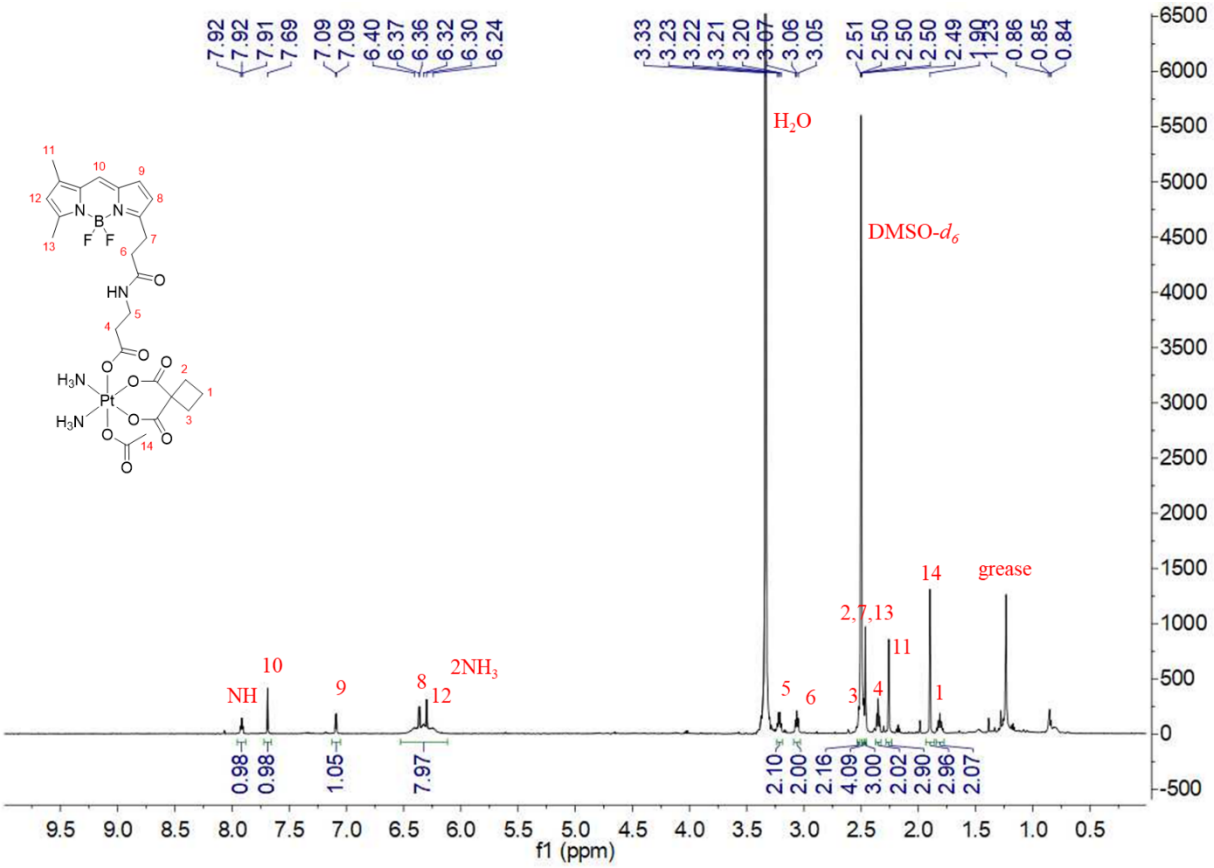

Figure S64. [1]H-NMR spectrum of complex **AC4C** in DMSO-d_6.

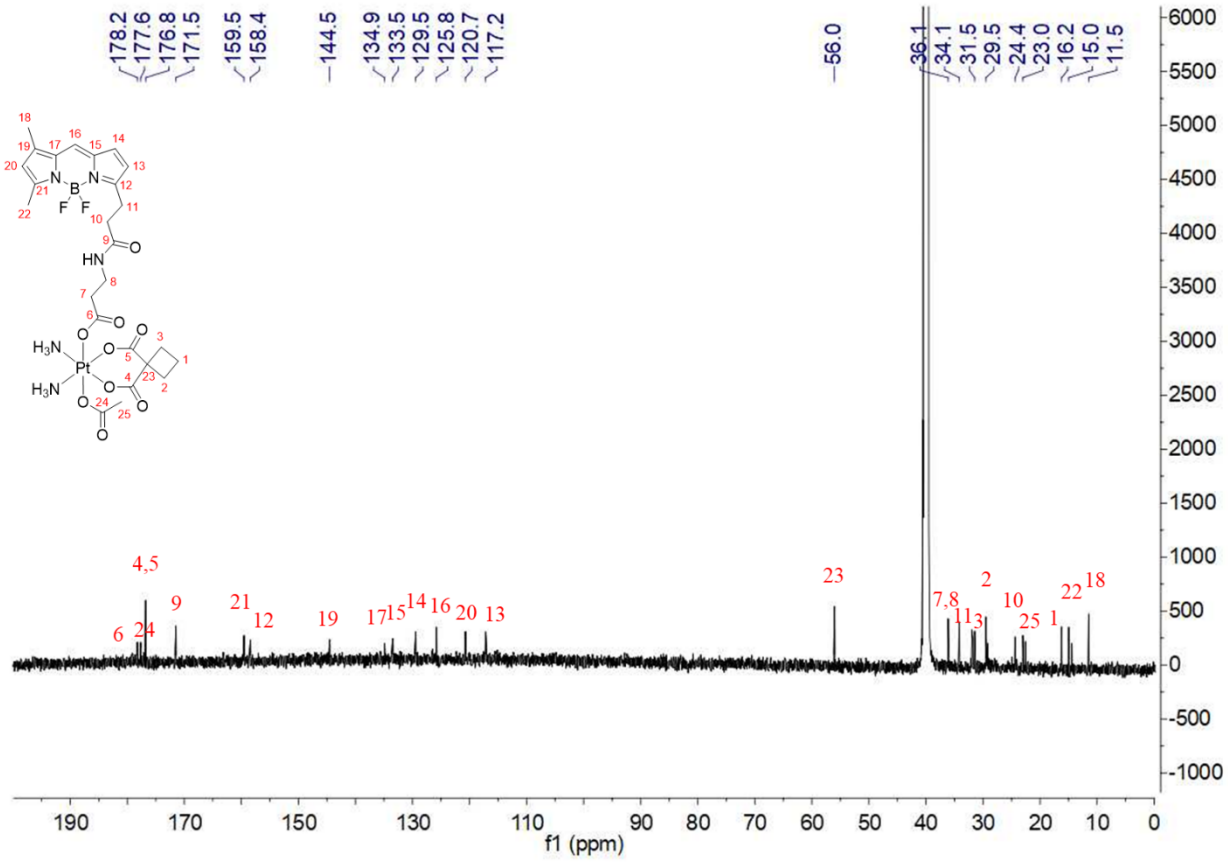

Figure S65. ^{13}C-NMR spectrum of complex **AC4C** in DMSO-d_6.

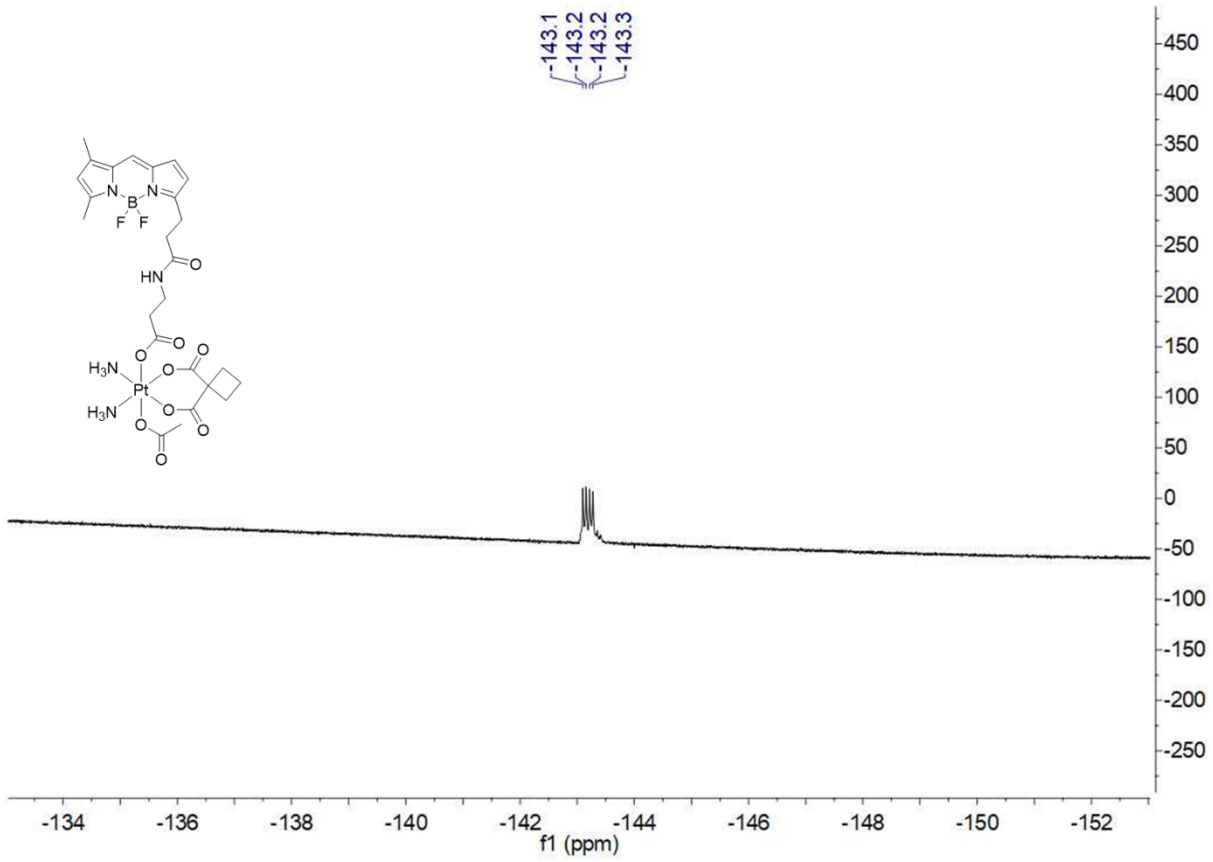

Figure S66. ^{19}F-NMR spectrum of complex **AC4C** in DMSO-d_6.

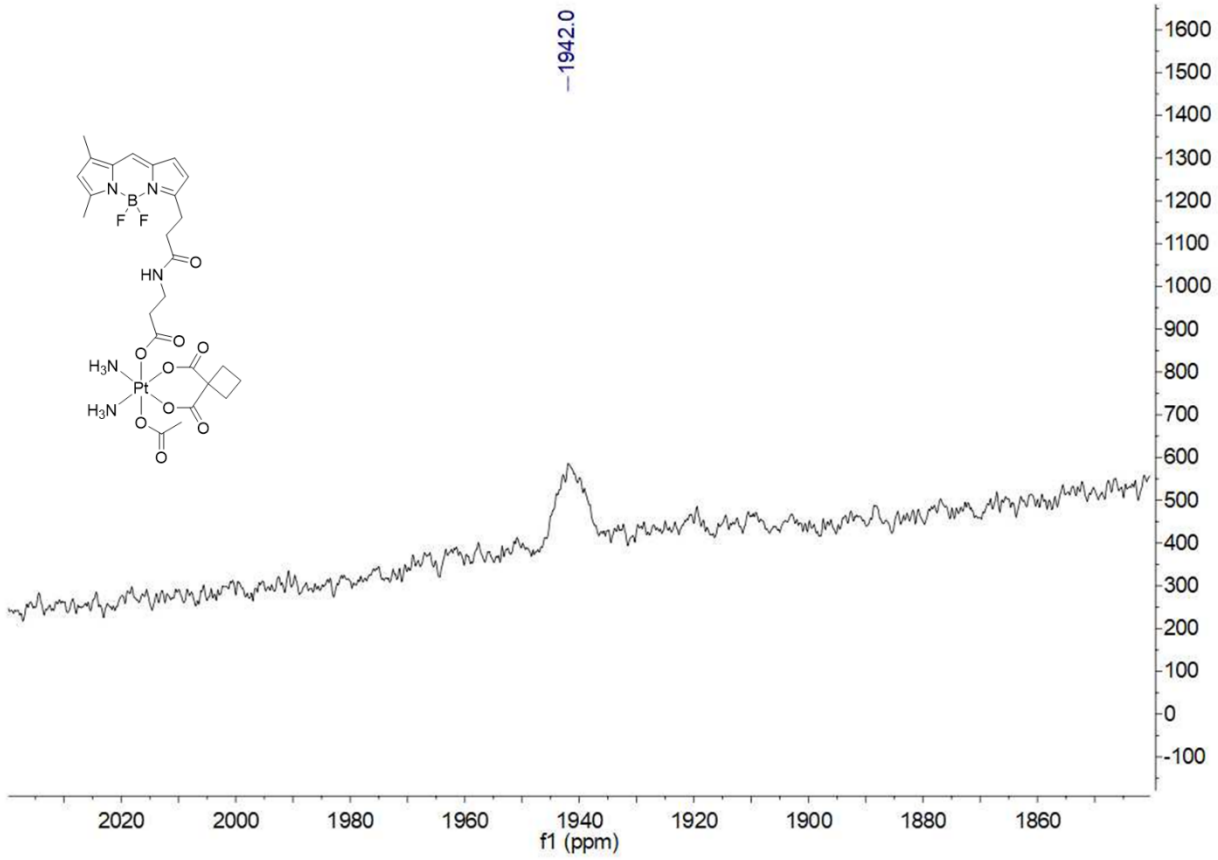

Figure S67. ^{195}Pt-NMR spectrum of complex **AC4C** in DMSO-d_6.

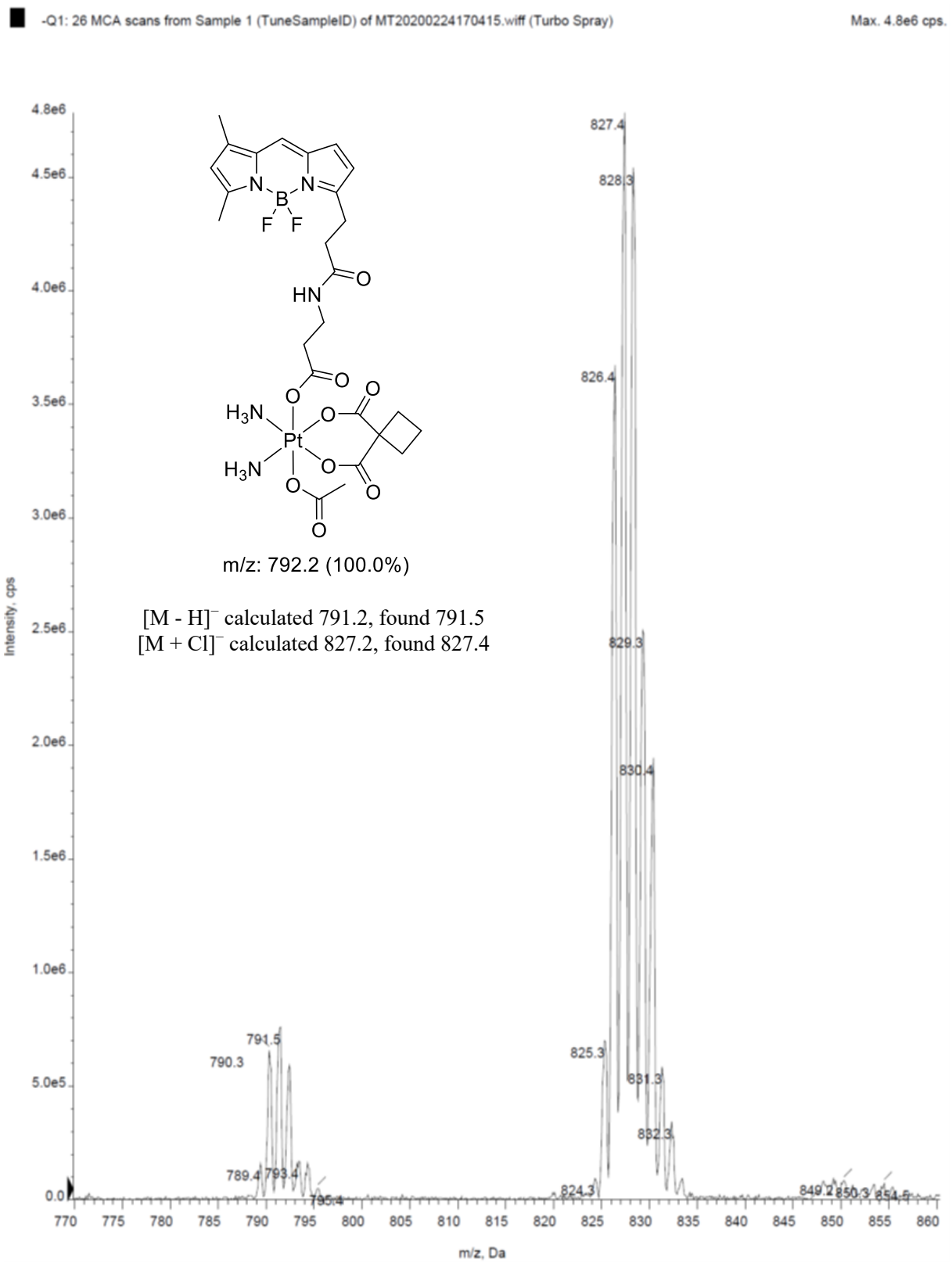

Figure S68. ESI-MS spectrum of complex **AC4C**, negative mode in methanol.

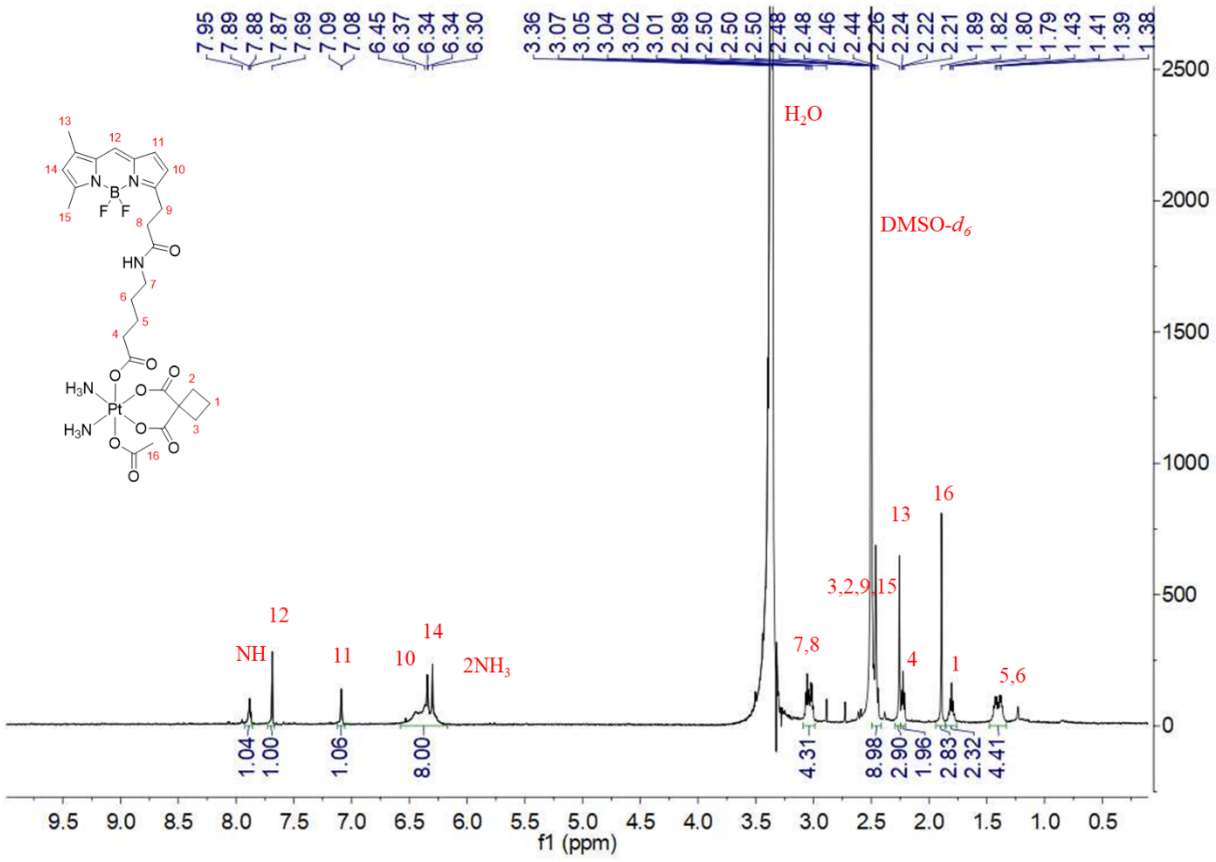

Figure S69. ^{1}H-NMR spectrum of complex **AC6C** in DMSO-d_6.

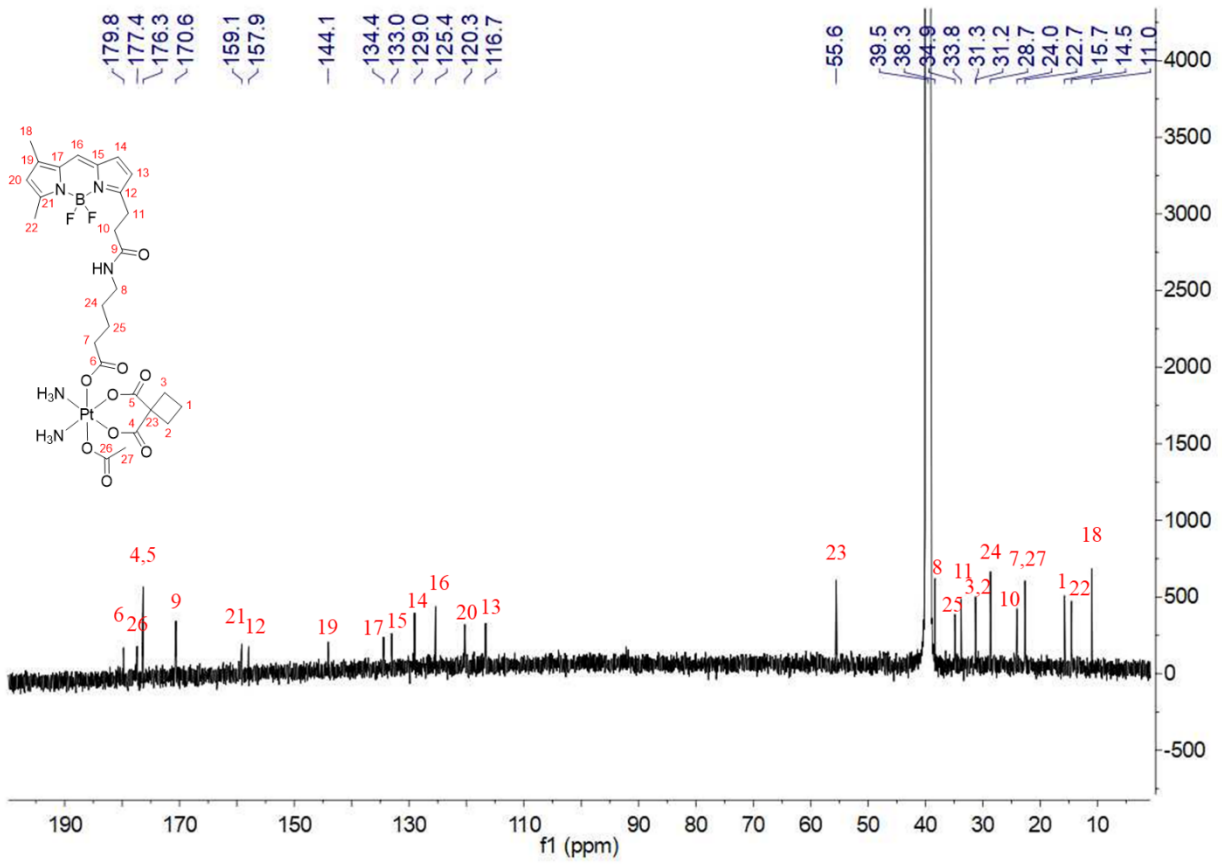

Figure S70. ^{13}C-NMR spectrum of complex **AC6C** in DMSO-d_6.

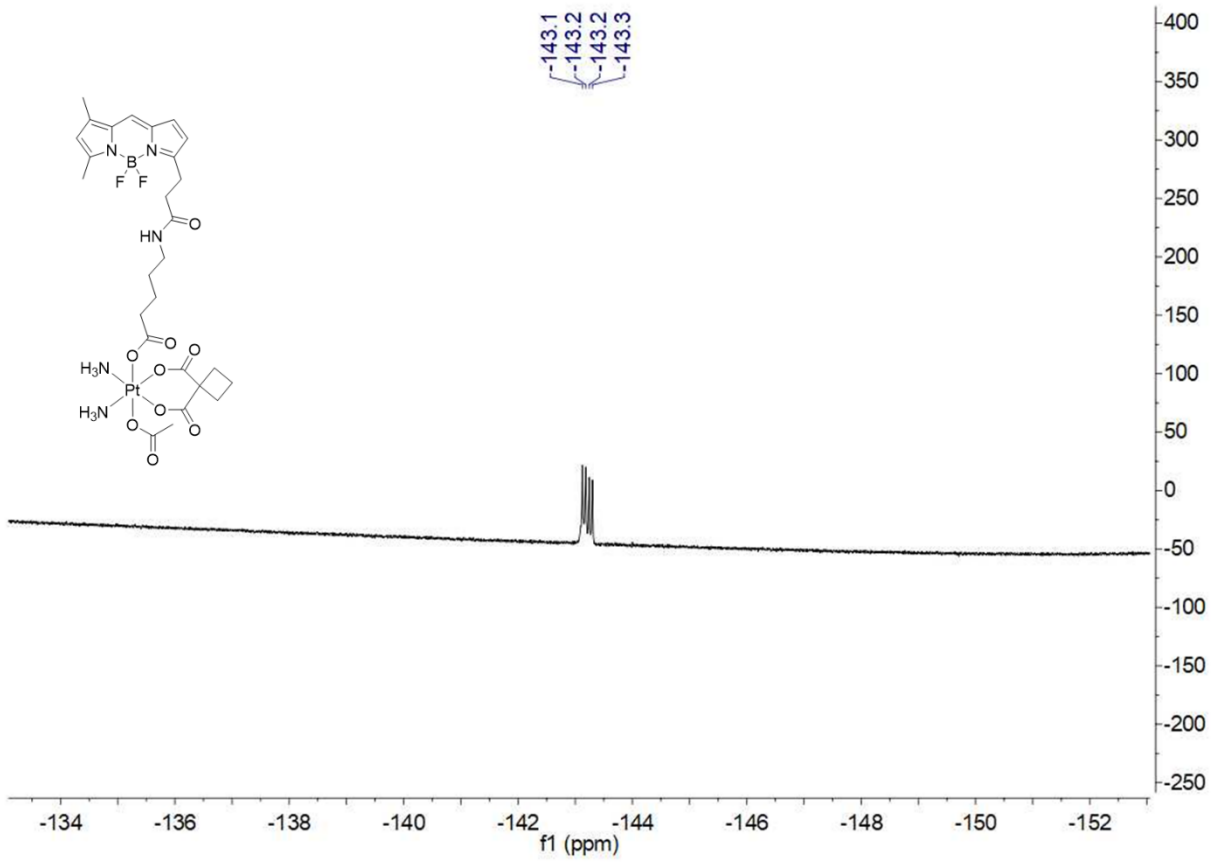

Figure S71. ^{19}F-NMR spectrum of complex **AC6C** in DMSO-d_6.

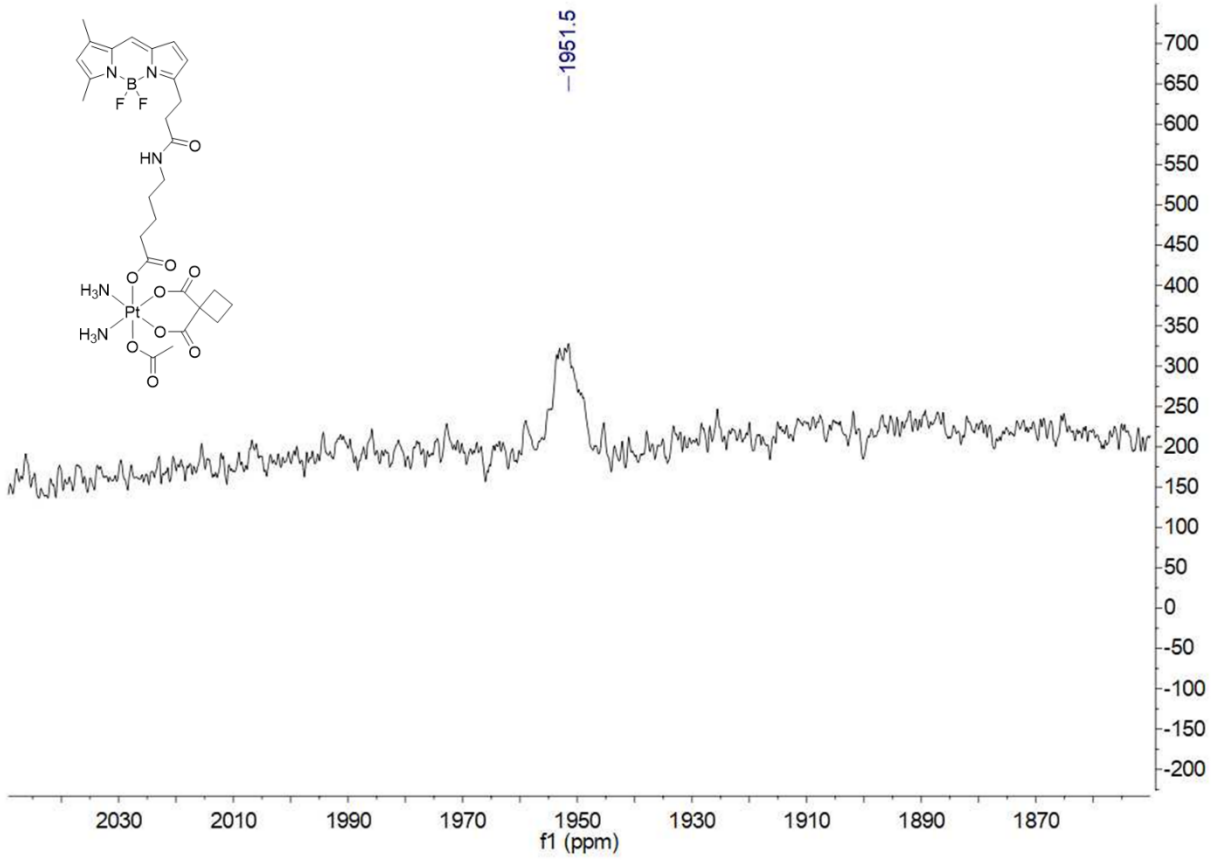

Figure S72. ^{195}Pt-NMR spectrum of complex **AC6C** in DMSO-d_6.

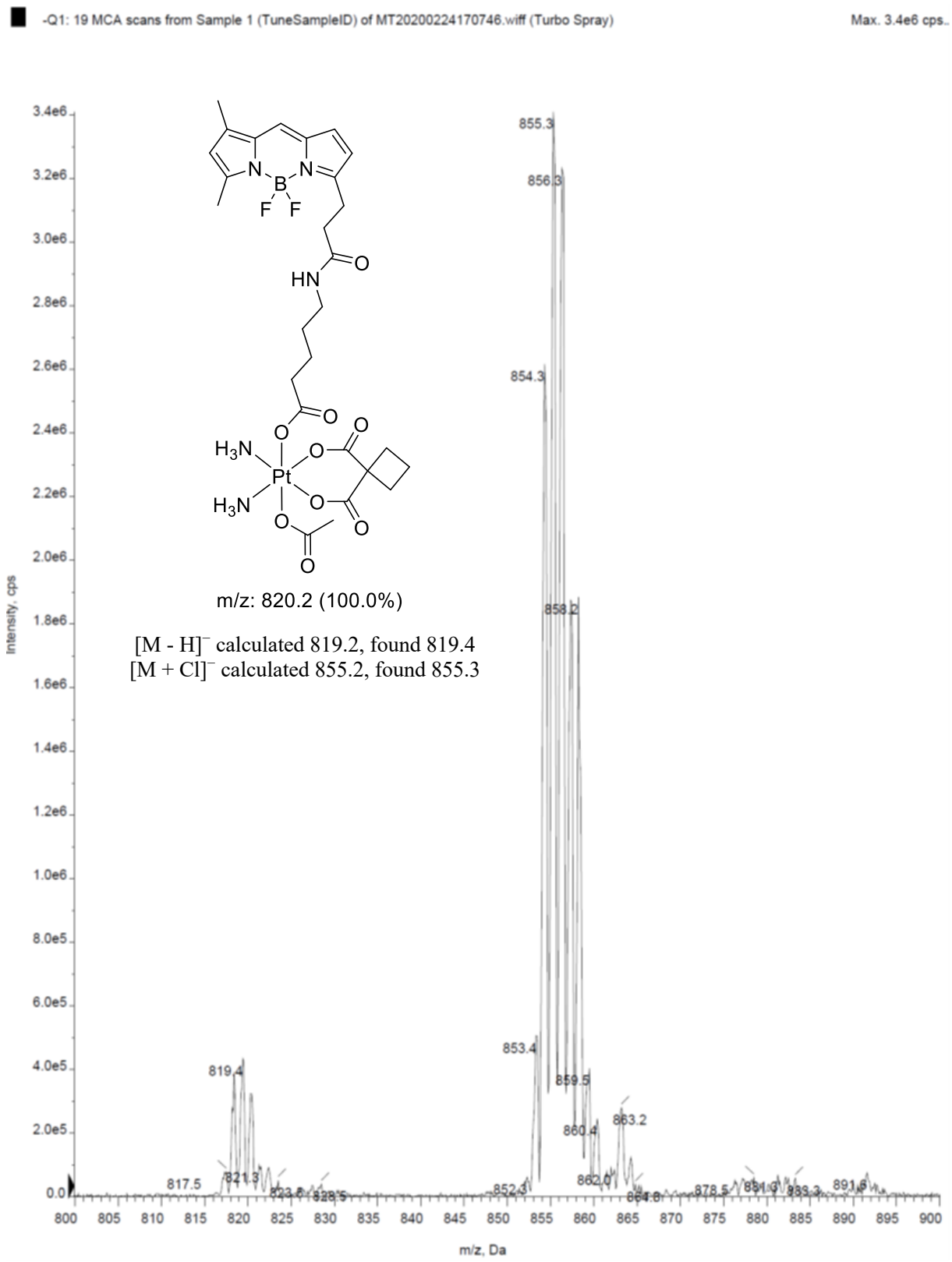

Figure S73. ESI-MS spectrum of complex **AC6C**, negative mode in methanol.

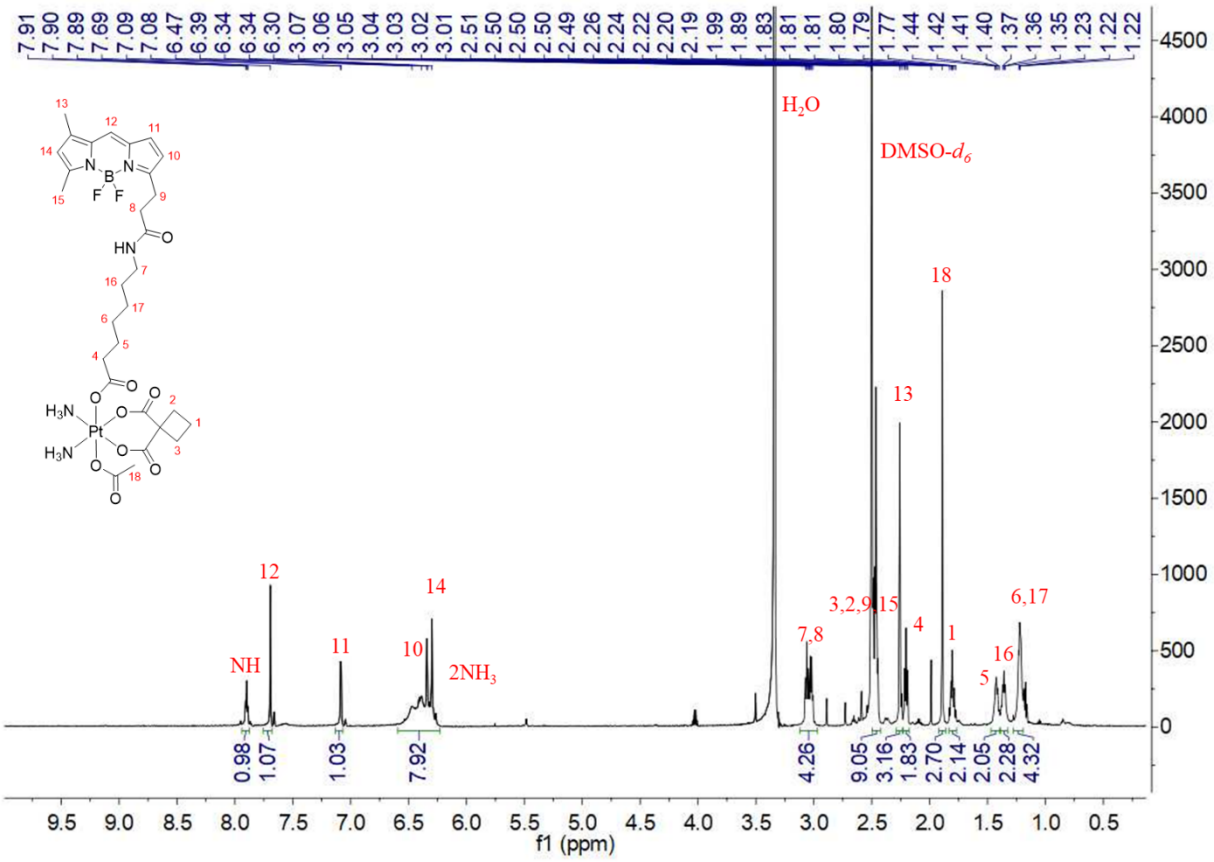

Figure S74. [1]H-NMR spectrum of complex **AC8C** in DMSO-d_6.

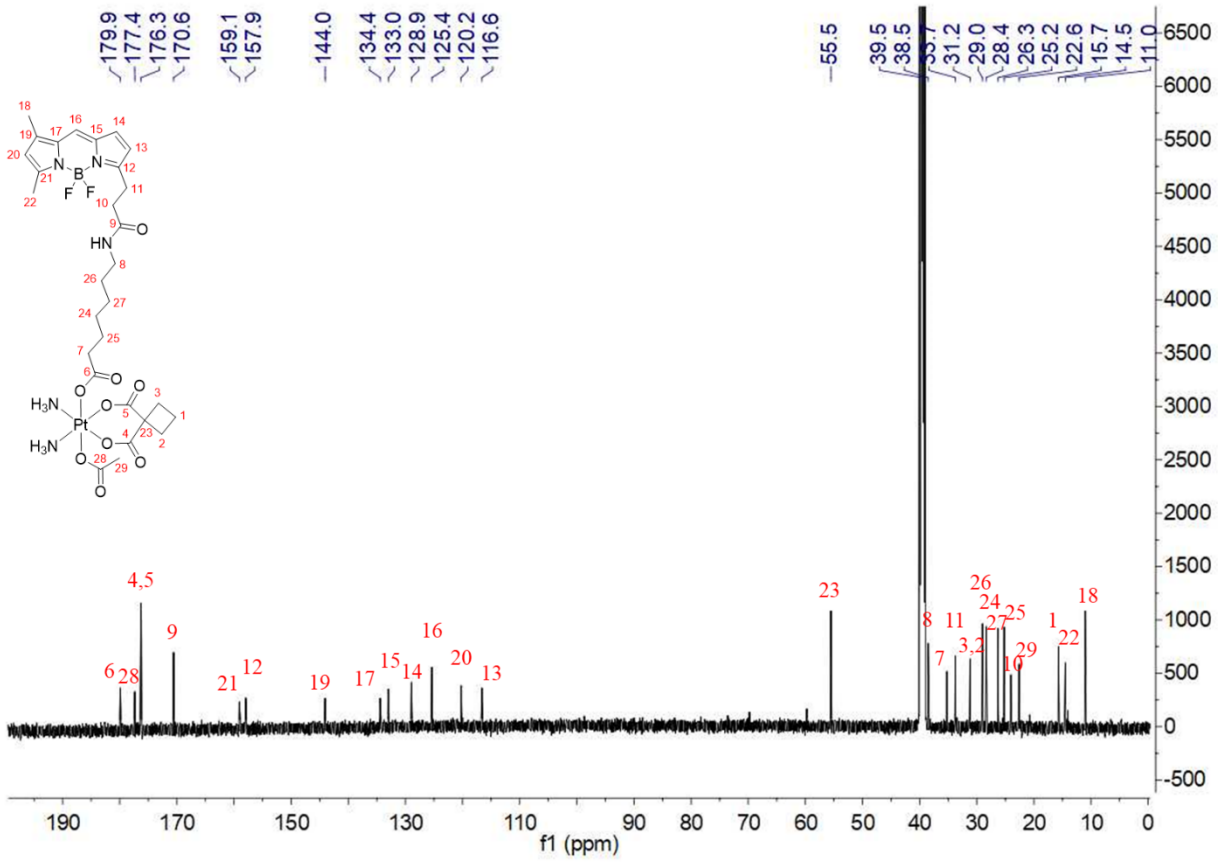

Figure S75. ^{13}C-NMR spectrum of complex **AC8C** in DMSO-d_6.

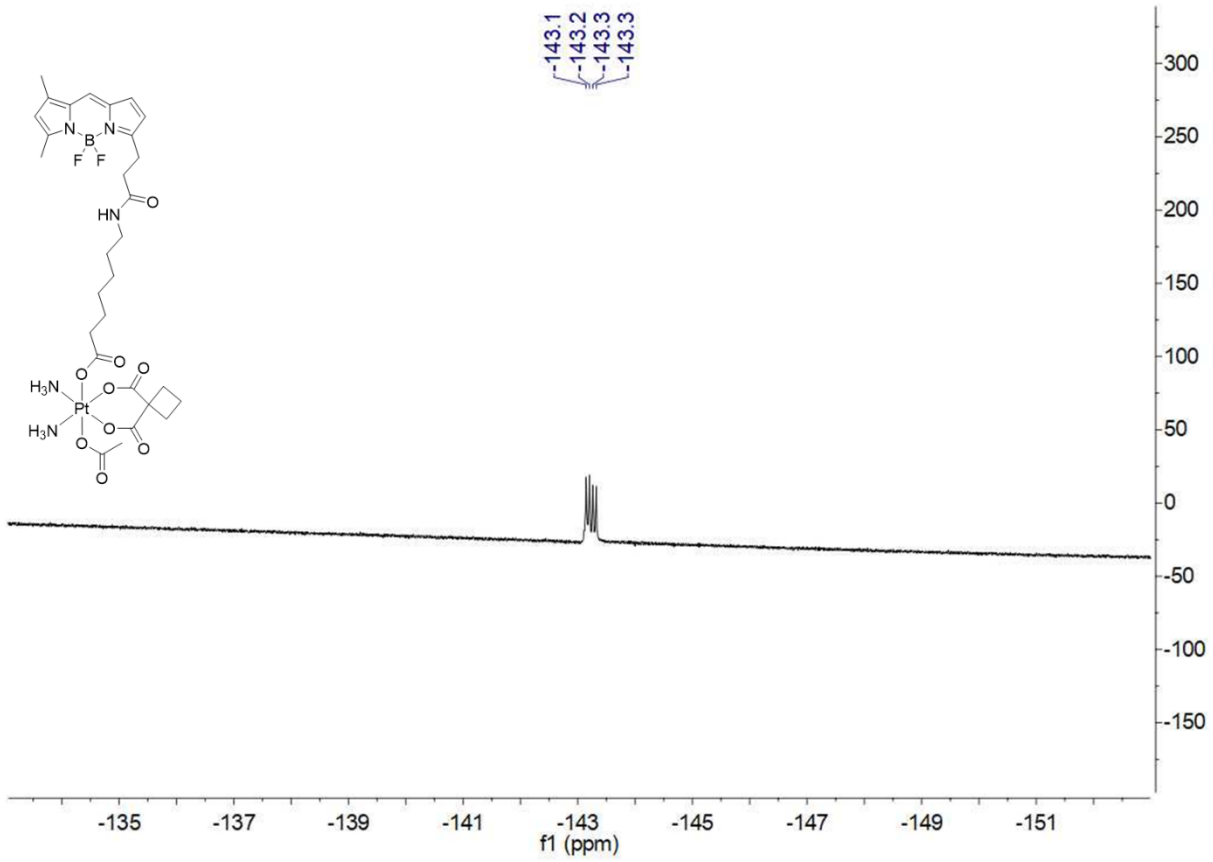

Figure S76. ^{19}F-NMR spectrum of complex **AC8C** in DMSO-d_6.

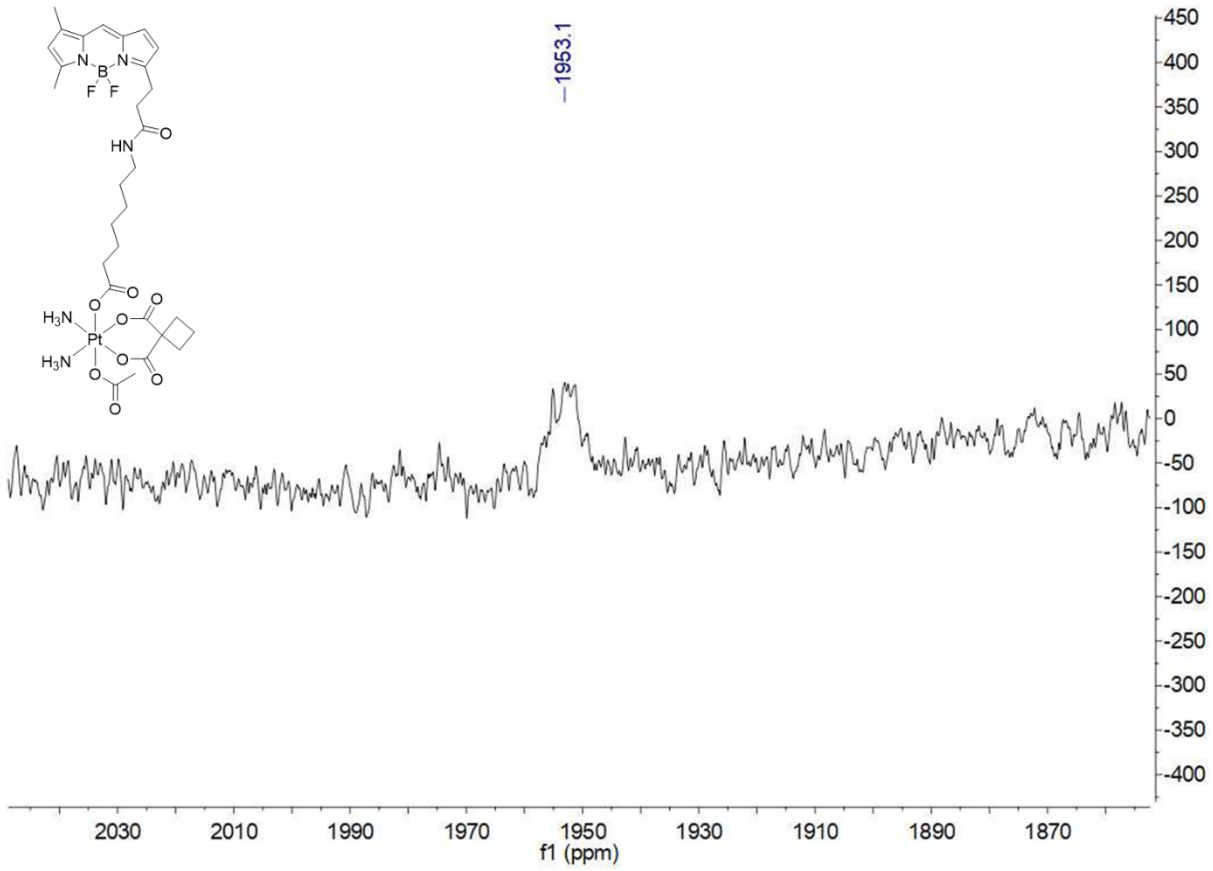

Figure S77. ^{195}Pt-NMR spectrum of complex **AC8C** in DMSO-d_6.

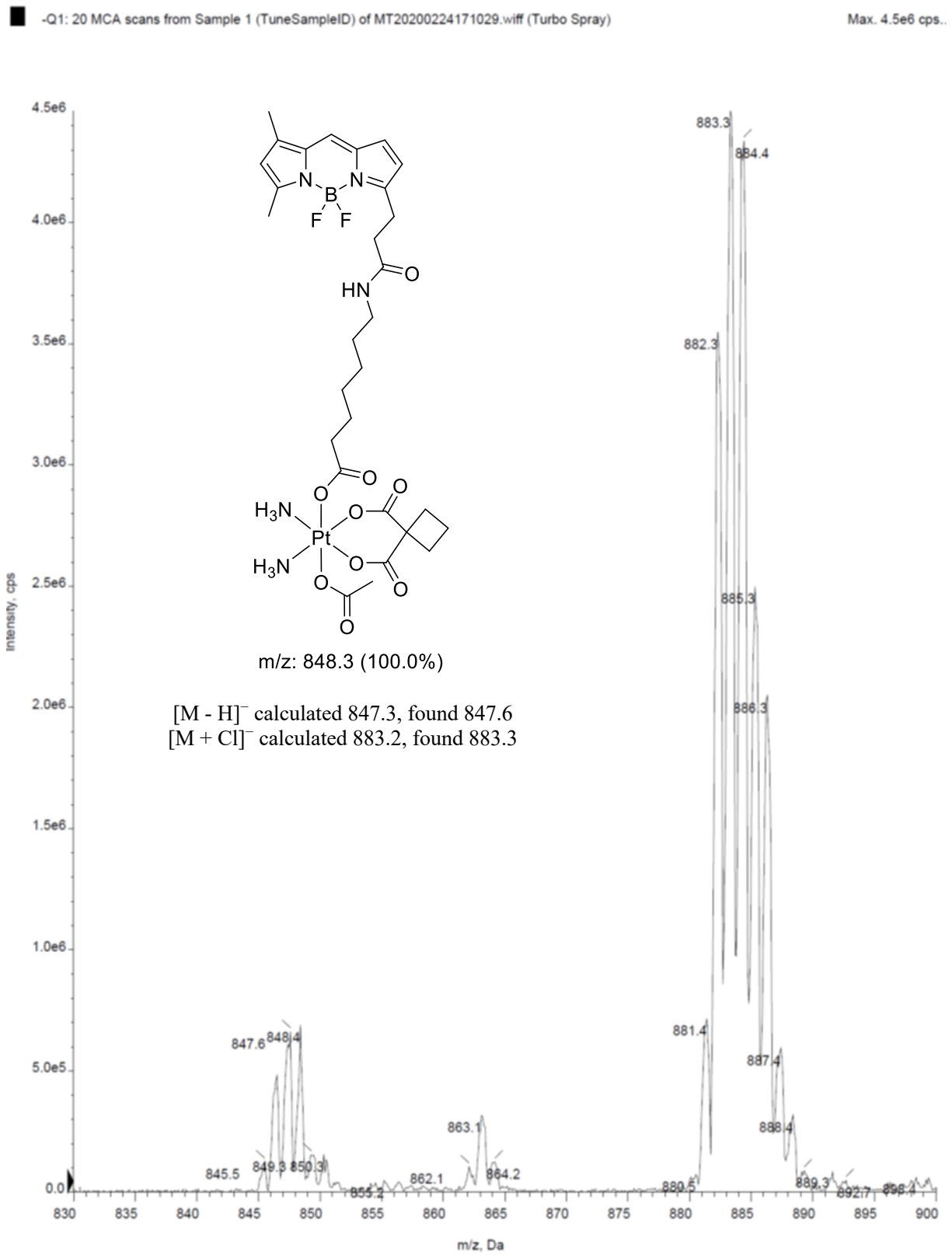

Figure S78. ESI-MS spectrum of complex **AC8C**, negative mode in methanol.

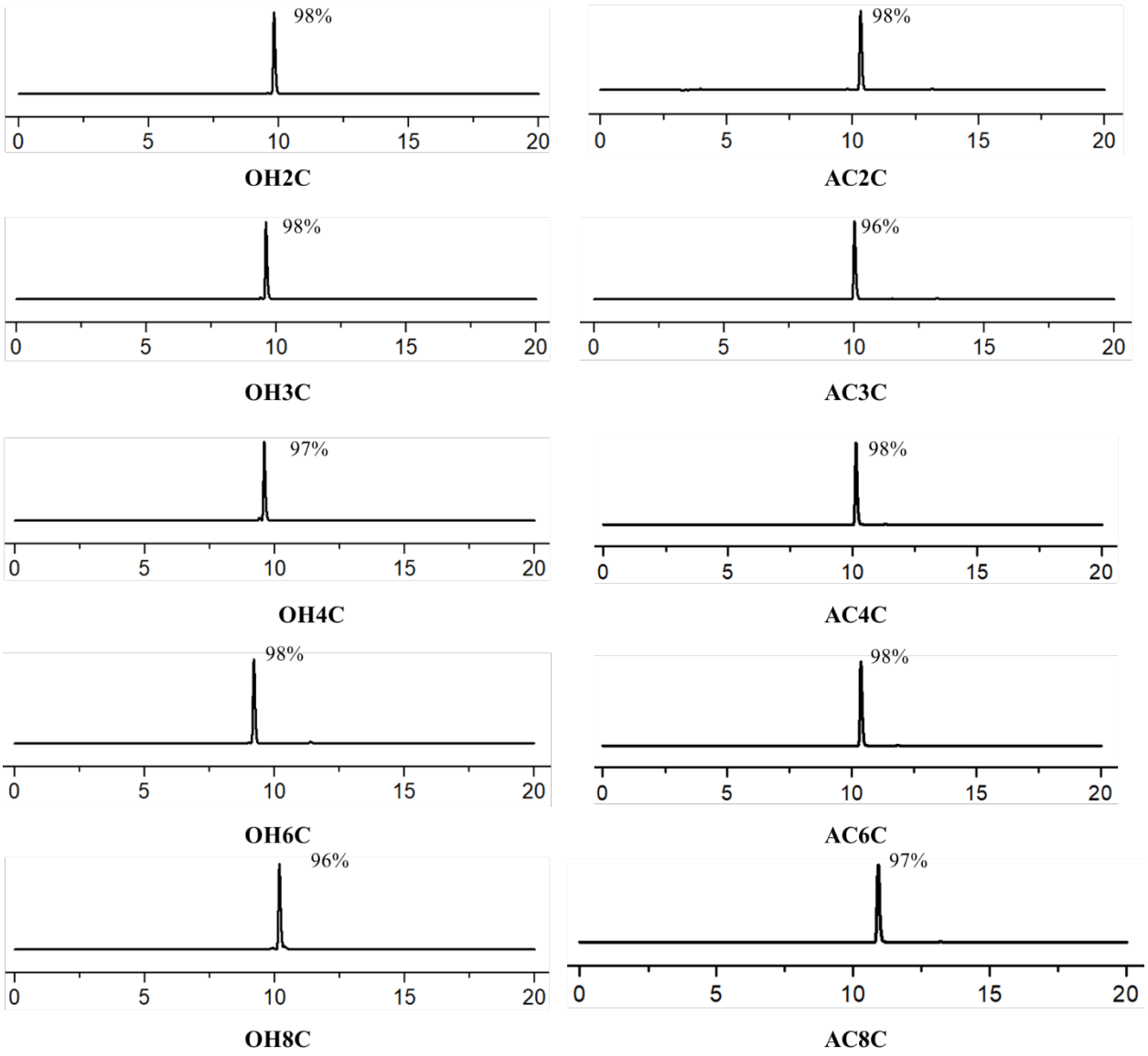

Figure S79. Purity of complexes **OH2C**-**OH8C** and **AC2C**-**AC8C**, determined by HPLC. HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. Flow rate: 1 mL/min. wavelength: 504 nm.

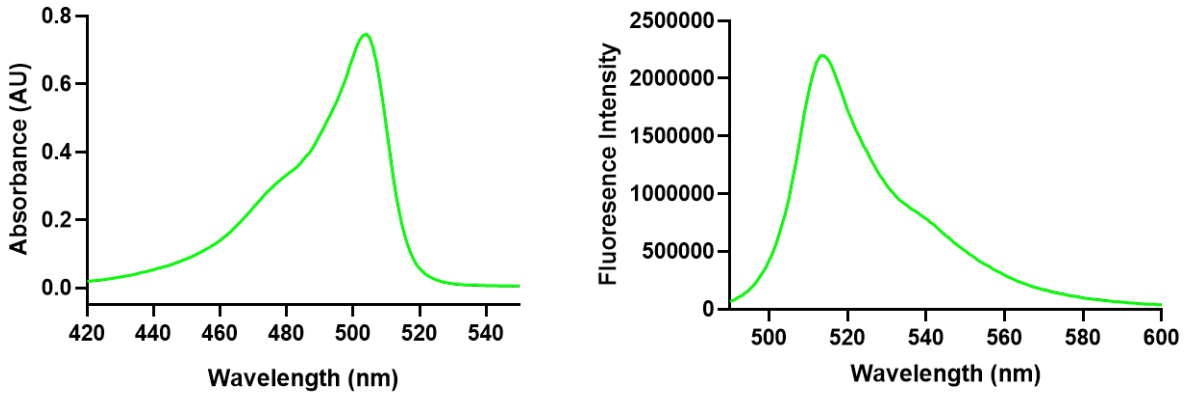

Figure S80. Absorbance and emission of the BODIPY ligand. 10 μM compound was dissolved in PBS buffer (pH 7.4) with 1% DMF. Ex = 470 nm.

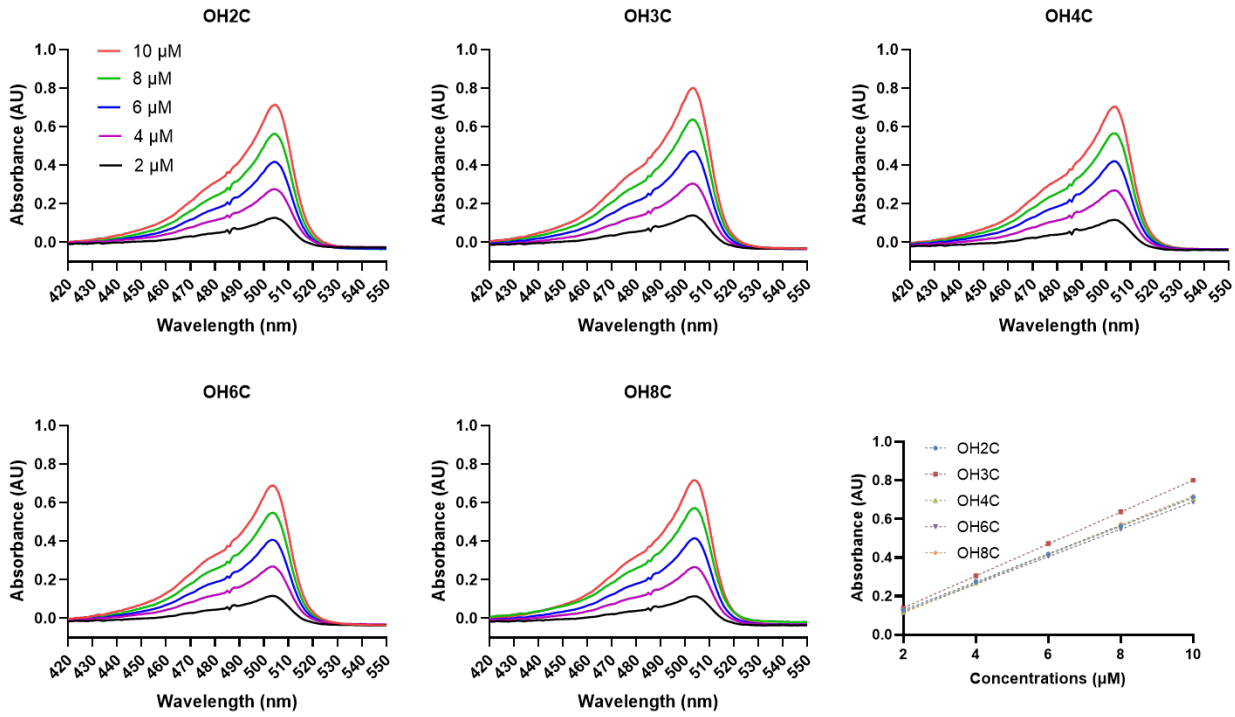

Figure S81. Molar extinction coefficients of complexes **OH2C**-**OH8C**. 10, 8, 6, 4, and 2 μM of compounds were dissolved in PBS buffer (pH 7.4) with 1% DMF. The absorbances were recorded by a UV-Vis spectrophotometer. The maximum absorbances at each concentration were plotted with the concentrations of complexes.

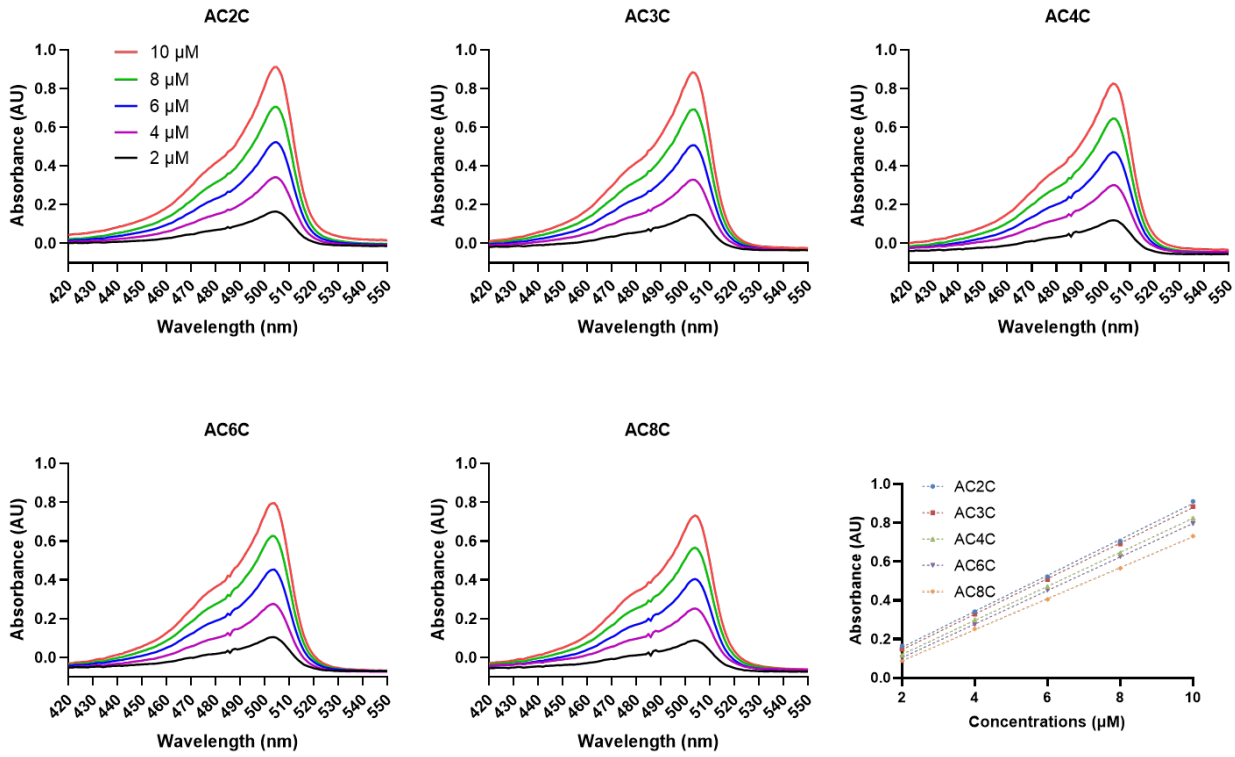

Figure S82. Molar extinction coefficients of complexes **AC2C**-**AC8C**. 10, 8, 6, 4, and 2 μM of compounds were dissolved in PBS buffer (pH 7.4) with 1% DMF. The absorbances were recorded by a UV-Vis spectrophotometer. The maximum absorbances at each concentration were plotted with the concentrations of complexes.

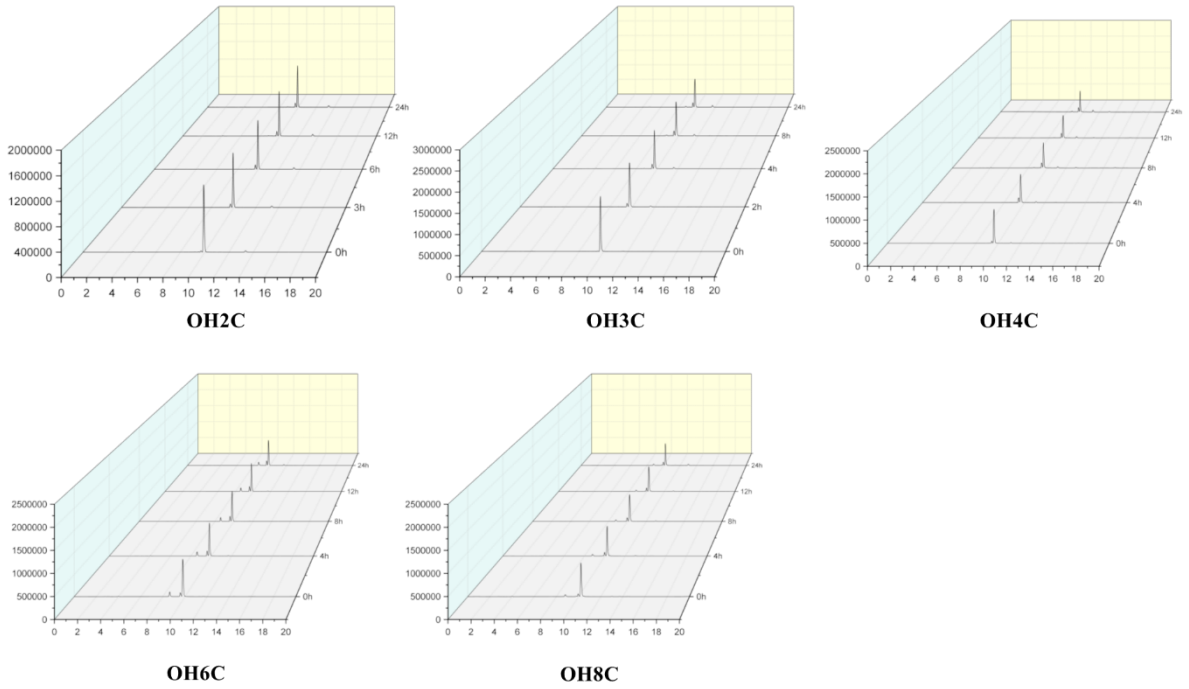

Figure S83. Stability of complexes **OH2C-OH8C** in PBS buffer (pH 7.4) at 37 °C in the dark. HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

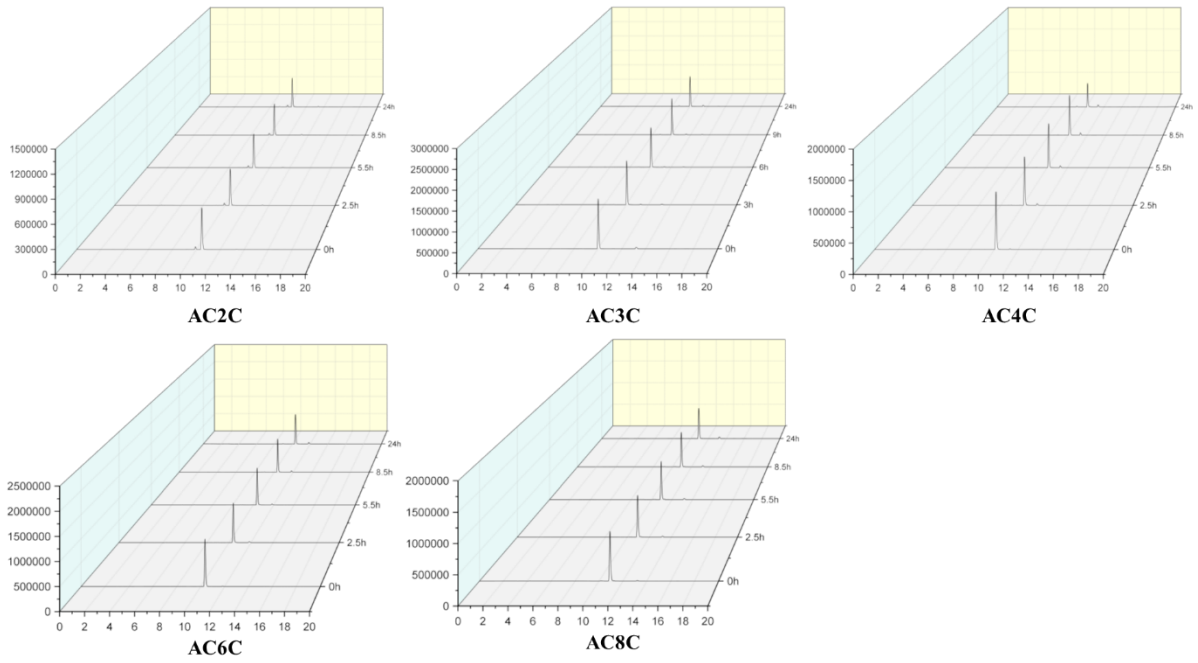

Figure S84. Stability of complexes **AC2C-AC8C** in PBS buffer (pH 7.4) at 37 °C in the dark. HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

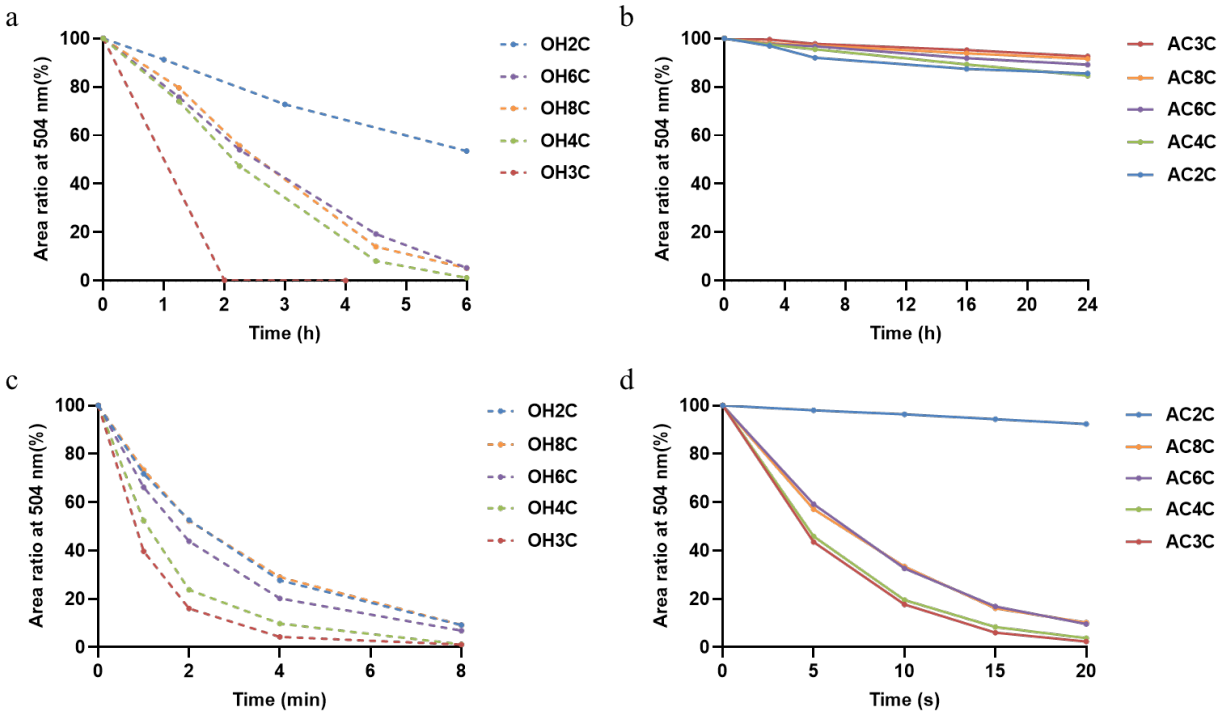

Figure S85. a. HPLC results of 10 μM complexes **OH2C**-**OH8C** in PBS buffer (pH = 7.4) with 1 mM sodium ascorbate in the dark at 37 ℃. b. HPLC results of 10 μM complexes **AC2C**-**AC8C** in PBS buffer (pH = 7.4) with 1 mM sodium ascorbate in the dark at 37 ℃. c. HPLC results of 10 μM complexes **OH2C**-**OH8C** under white light (2 mW/cm^2) in PBS buffer (pH = 7.4) with 1 mM sodium ascorbate. d. HPLC results of 10 μM complexes **AC2C**-**AC8C** under white light (2 mW/cm^2) in PBS buffer (pH = 7.4) with 1 mM sodium ascorbate.

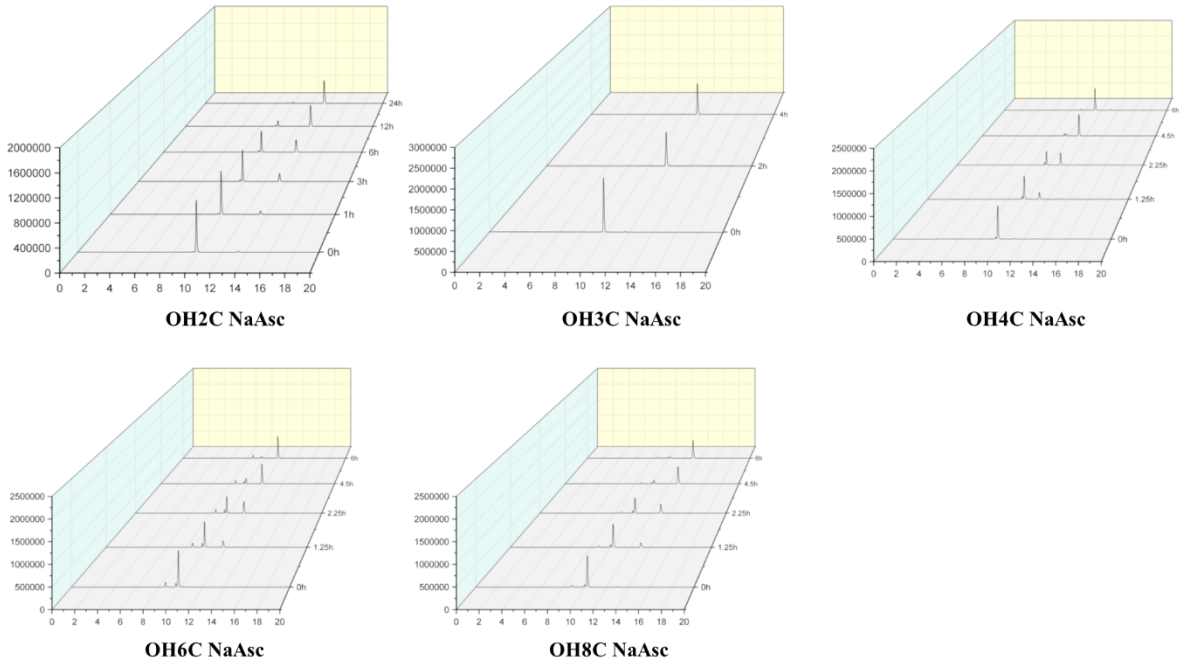

Figure S86. Reduction of complexes **OH2C**-**OH8C** in PBS buffer (pH 7.4) with 1 mM sodium ascorbate (NaAsc) at 37 °C in the dark. HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

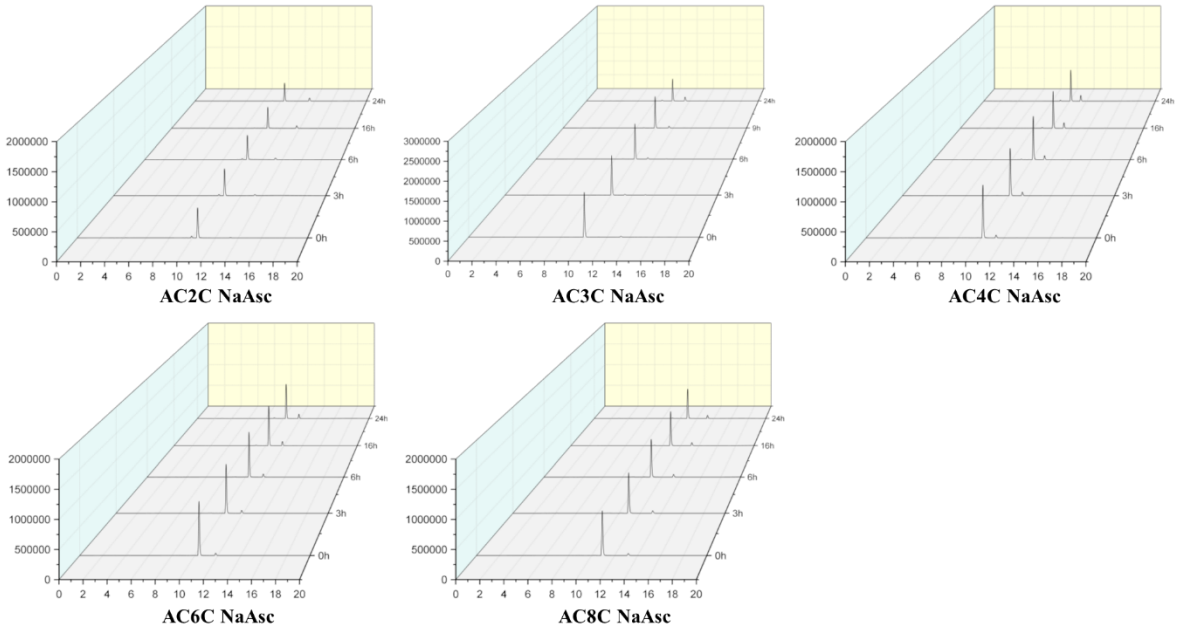

Figure S87. Reduction of complexes **AC2C-AC8C** in PBS buffer (pH 7.4) with 1 mM sodium ascorbate (NaAsc) at 37 °C in the dark. HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

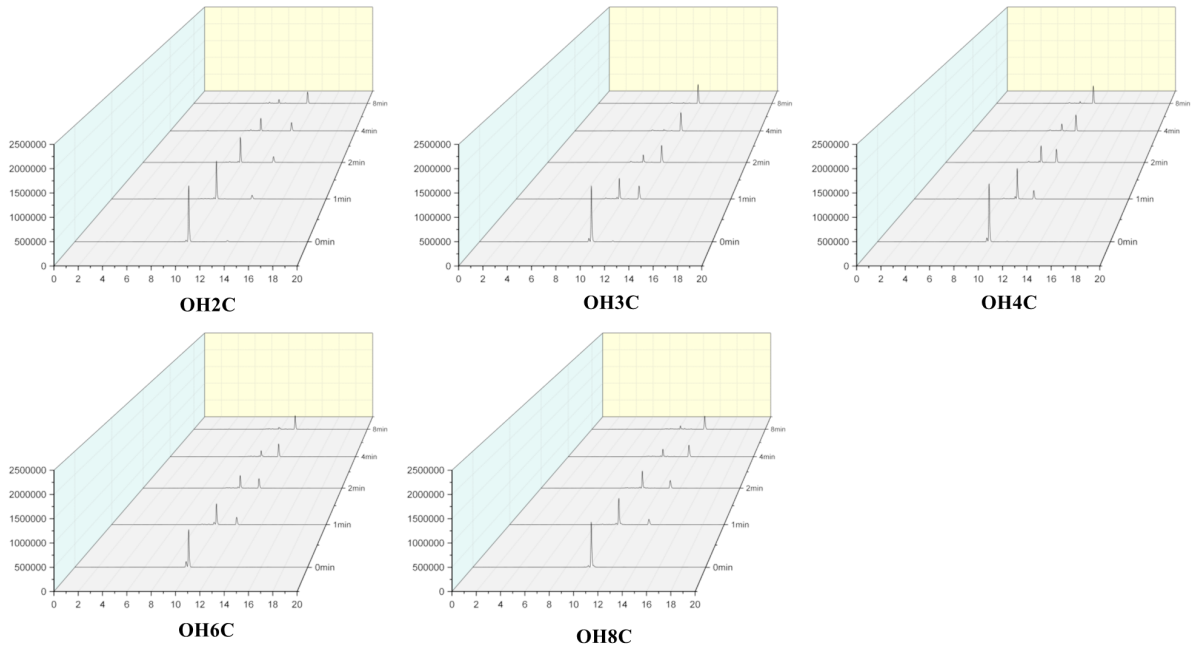

Figure S88. Photoactivation of complexes **OH2C**-**OH8C** under white light (2 mW/cm^2) in PBS buffer (pH 7.4). HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

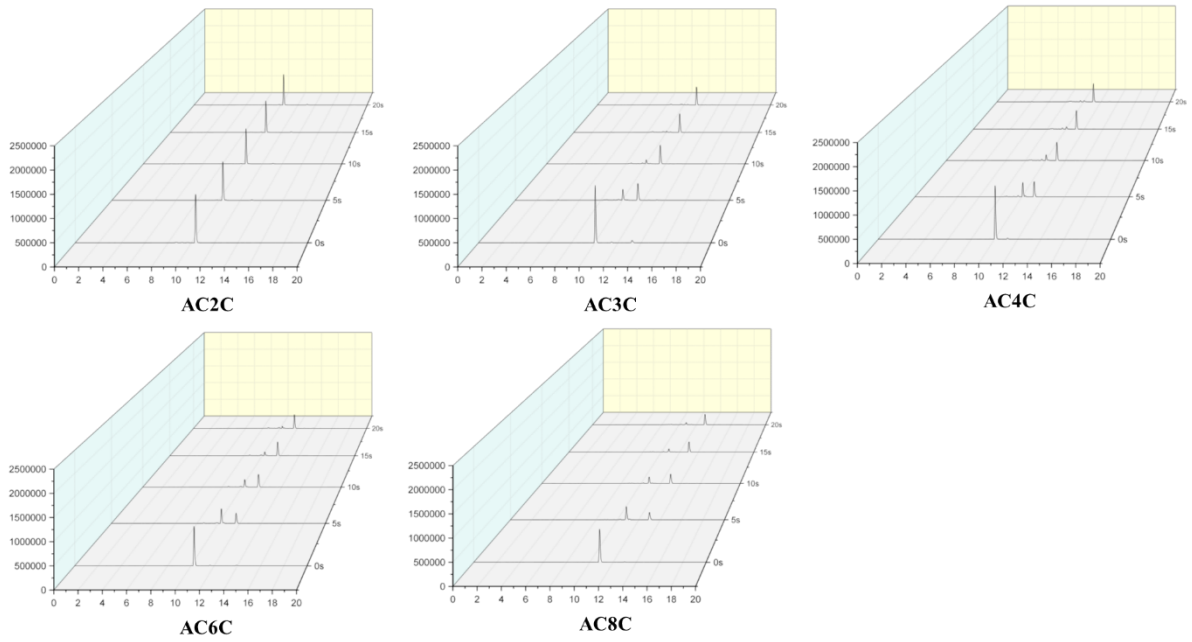

Figure S89. Photoactivation of complexes **AC2C**-**AC8C** under white light (2 mW/cm^2) in PBS buffer (pH 7.4). HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

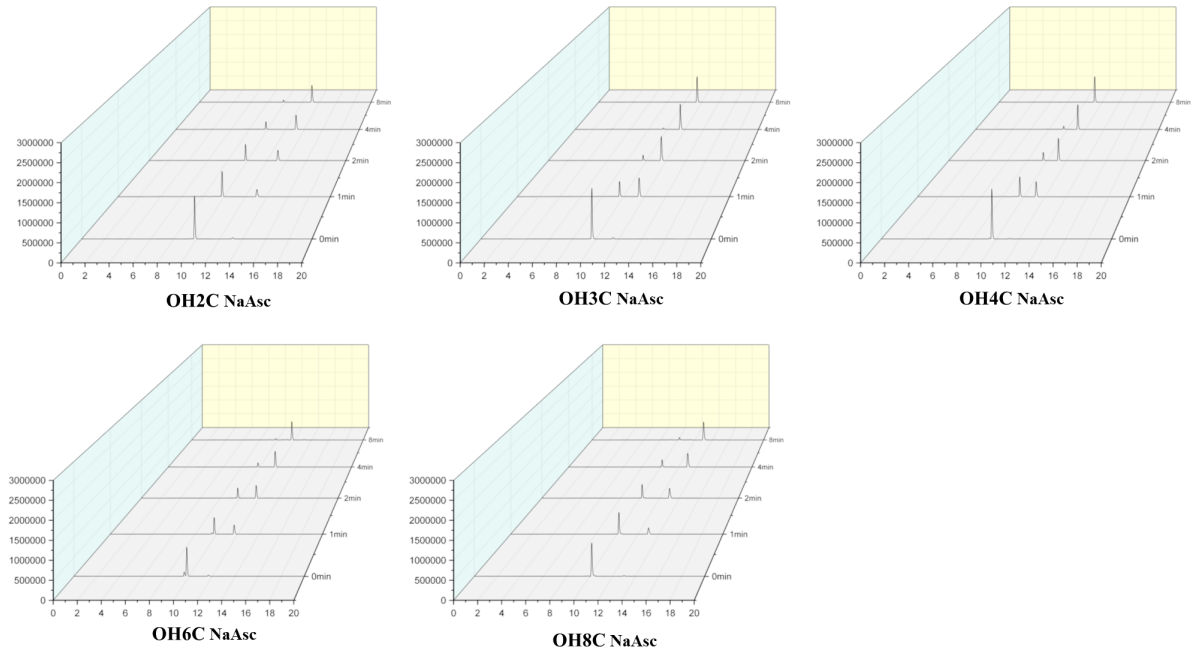

Figure S90. Photoactivation of complexes **OH2C**-**OH8C** under white light (2 mW/cm^2) in PBS buffer (pH 7.4) with 1 mM sodium ascorbate (NaAsc). HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

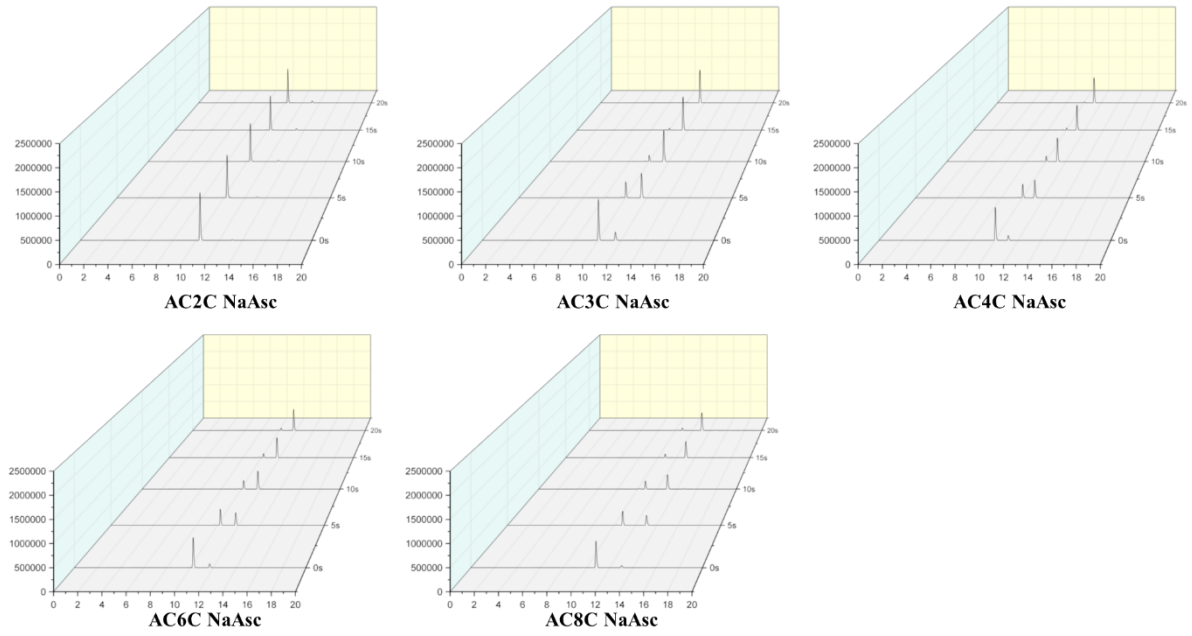

Figure S91. Photoactivation of complexes **AC2C-AC8C** under white light (2 mW/cm^2) in PBS buffer (pH 7.4) with 1 mM sodium ascorbate (NaAsc). HPLC condition: 0 - 3 - 16 - 17 - 20 min, 10 - 50 - 63 - 10 - 10% acetonitrile with 0.1% HCOOH. 1 mL/min. wavelength: 504 nm.

Table S1. Cellular accumulation of 10 μM complexes carboplatin, **OH2C**-**OH8C**, and **AC2C**-**AC8C** in A2780 cells.

Compounds	Pt concentration (ng Pt/ 10^6 cells)
OH2C	26.5 ± 2.5
OH3C	66.0 ± 6.0
OH4C	44.1 ± 3.9
OH6C	52.6 ± 1.9
OH8C	57.3 ± 2.8
AC2C	23.8 ± 3.7
AC3C	48.1 ± 4.0
AC4C	34.0 ± 4.7
AC6C	33.3 ± 3.4
AC8C	31.1 ± 2.6
Carboplatin	13.3 ± 1.0

Table S2. IC_{50} (μM) of complexes carboplatin, **OH2C**-**OH8C**, and **AC2C**-**AC8C** in A2780 cells.

Compounds	Light (+)	Light (-)
OH2C	> 100	> 100
OH3C	43.9 ± 5.2	69.8 ± 4.9
OH4C	48.3 ± 2.0	74.8 ± 8.2
OH6C	76.8 ± 9.9	> 100
OH8C	> 100	> 100
AC2C	66.6 ± 7.0	> 100
AC3C	43.8 ± 3.9	> 100
AC4C	88.6 ± 15.7	> 100
AC6C	> 100	> 100
AC8C	> 100	> 100
Carboplatin	104 ± 11.1	106.6 ± 8.4

Cells were treated with complexes carboplatin, **OH2C**-**OH8C**, and **AC2C**-**AC8C** at different concentrations for 12 h before irradiation under white light (2 mW/cm^2) (+) or keep in the dark (-) for 30 min and then incubation in fresh media for another 72 h.