Electronic Supplementary Information for:

Linker design for the modular assembly of multifunctional and targeted platinum(II)-containing anticancer agents

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Content **Page**

S1. NMR SPECTROSCOPY

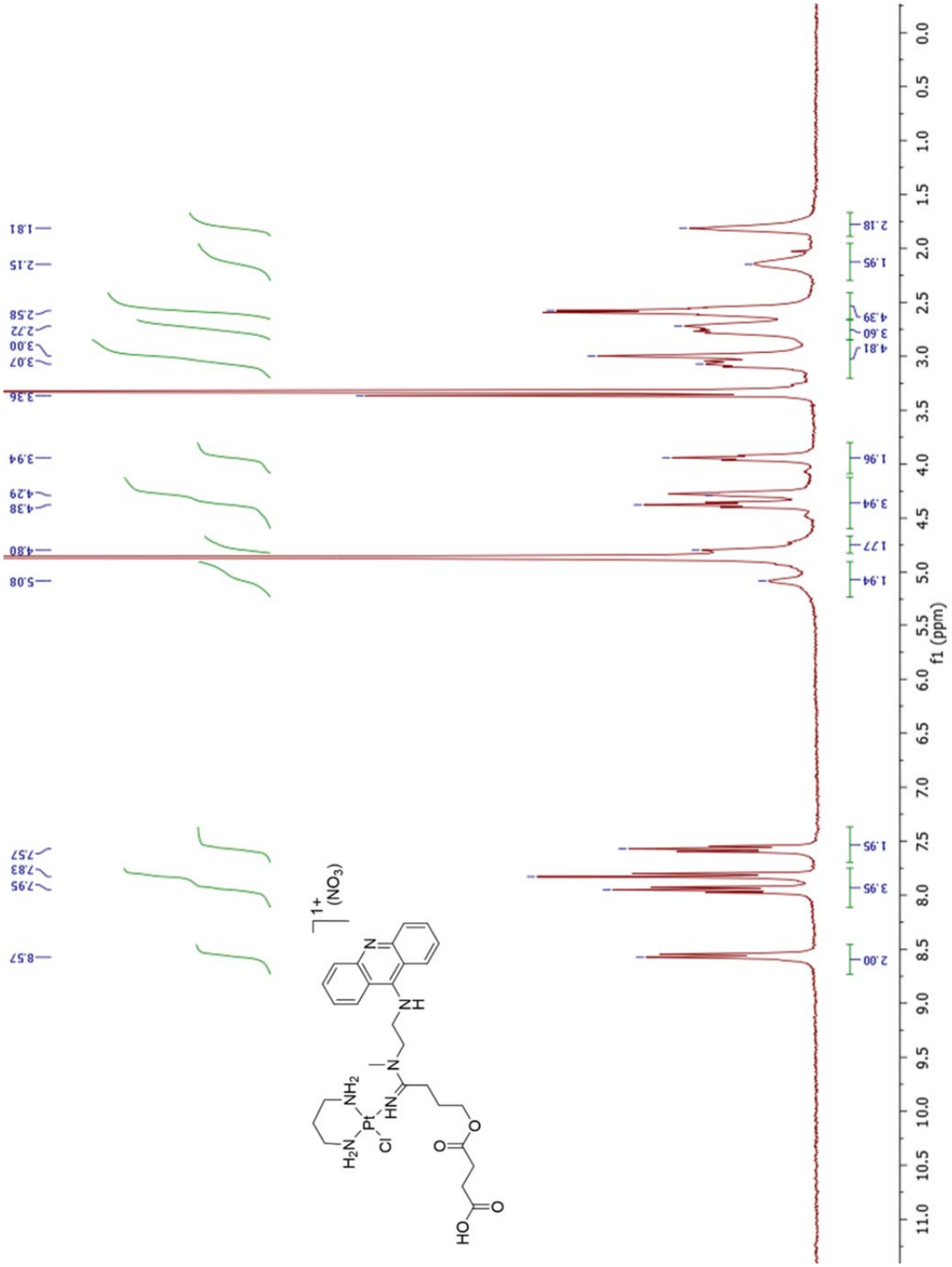


Figure S1. ^{1}H NMR spectrum of **P1** in MeOH-d_4.

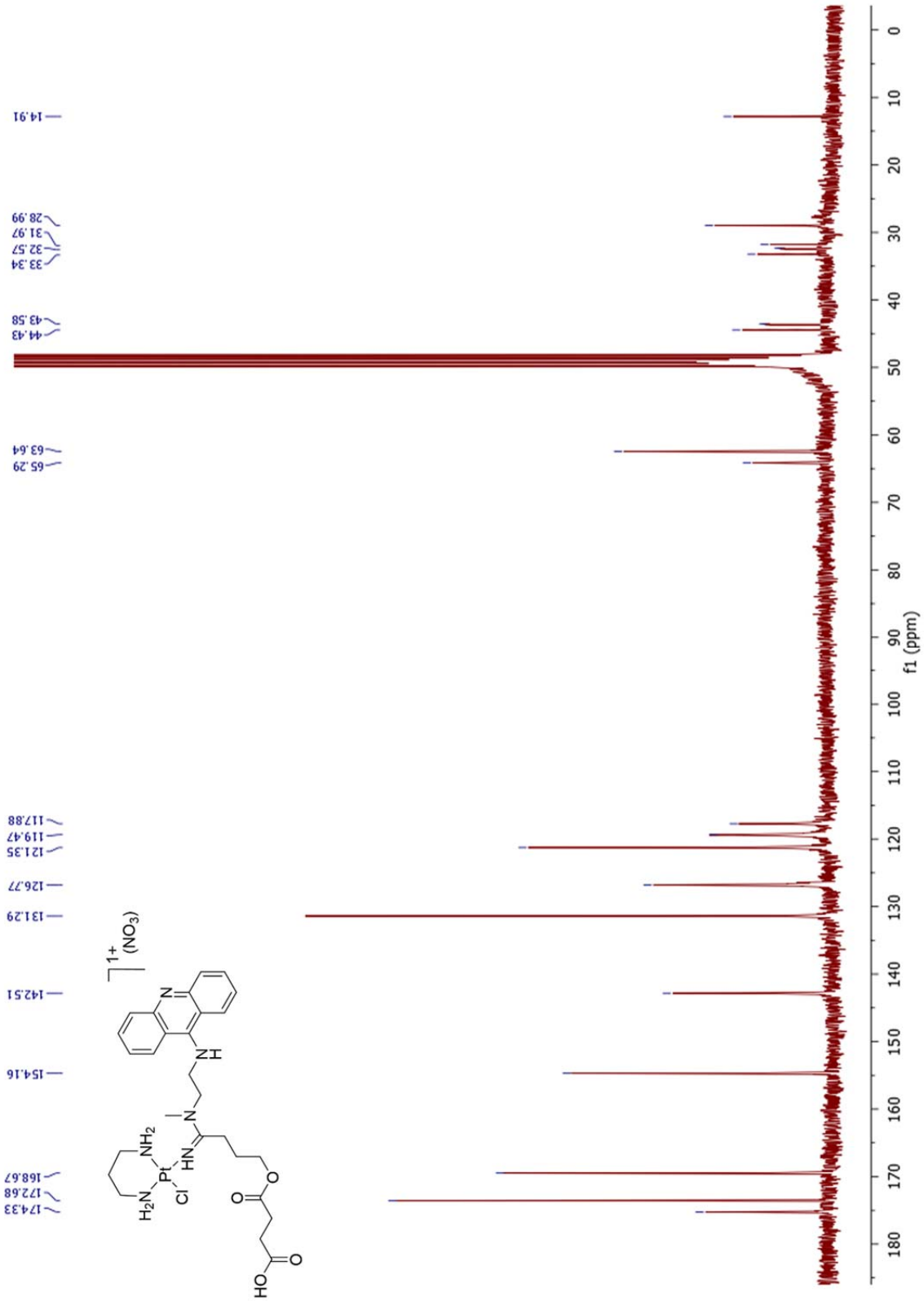


Figure S2. ^{13}C NMR spectrum of **P1** in MeOH-d_4.

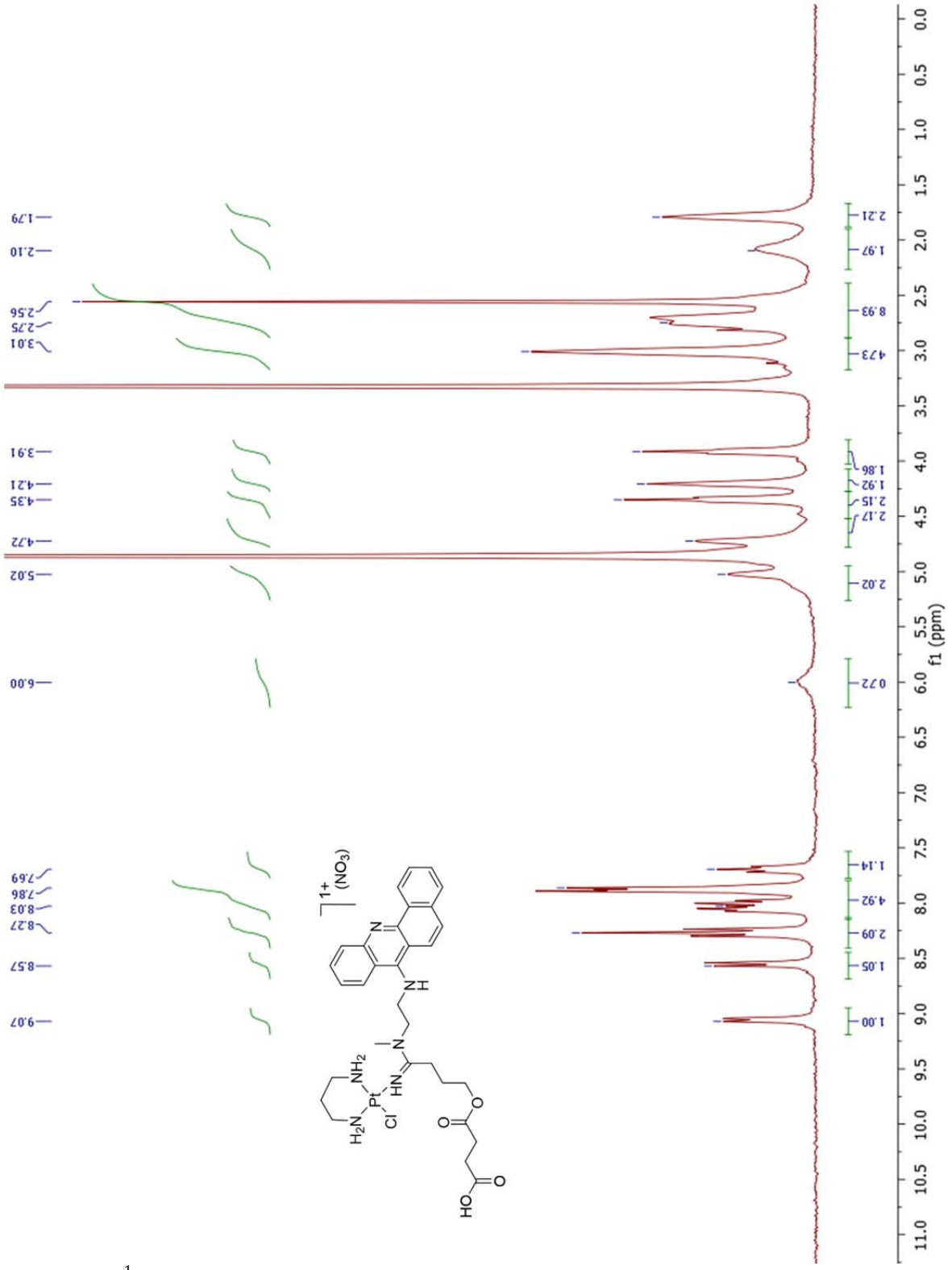


Figure S3. ^{1}H NMR spectrum of **P2** in MeOH-d_4.

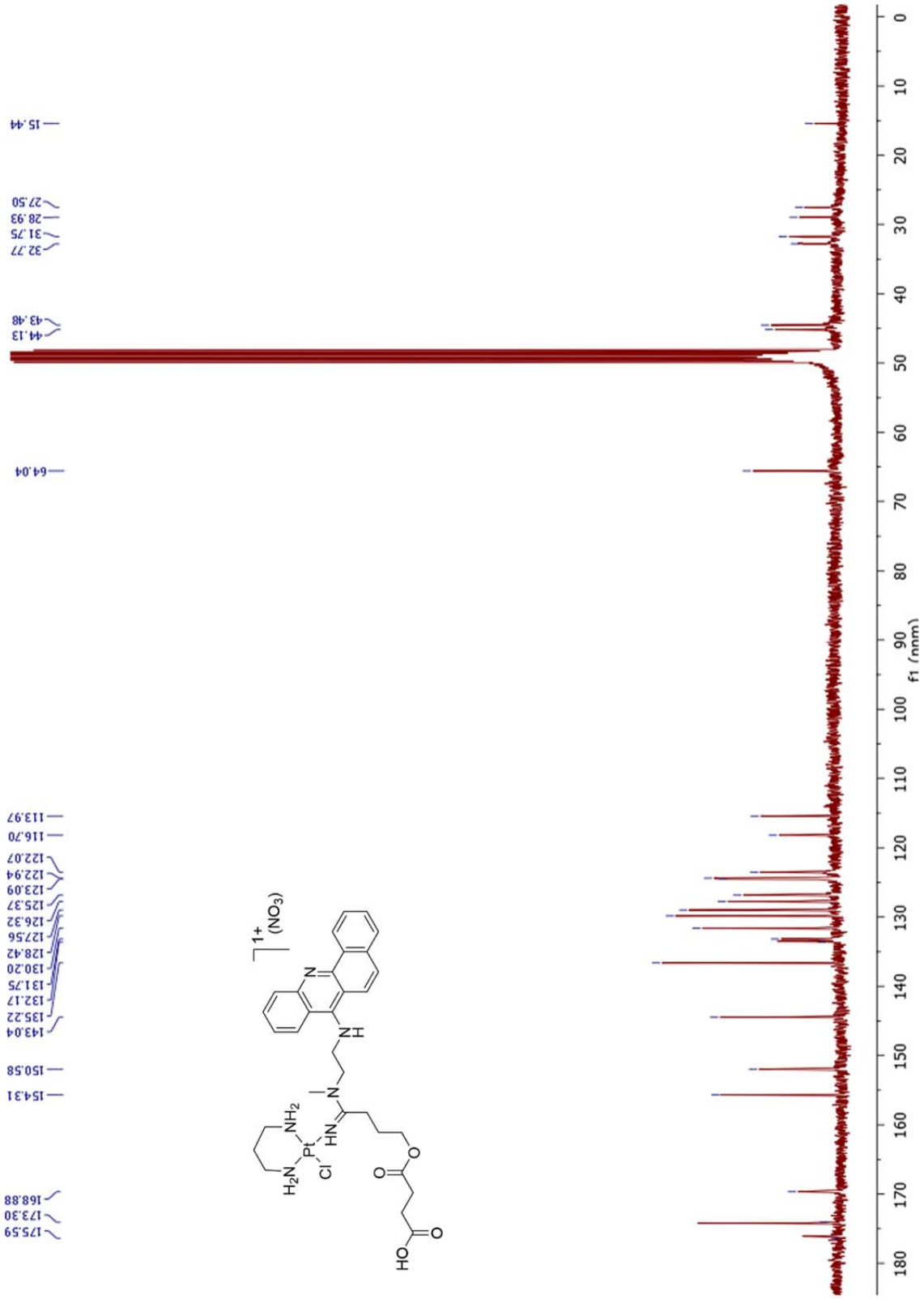


Figure S4. ^{13}C NMR spectrum of **P2** in MeOH-d_4.

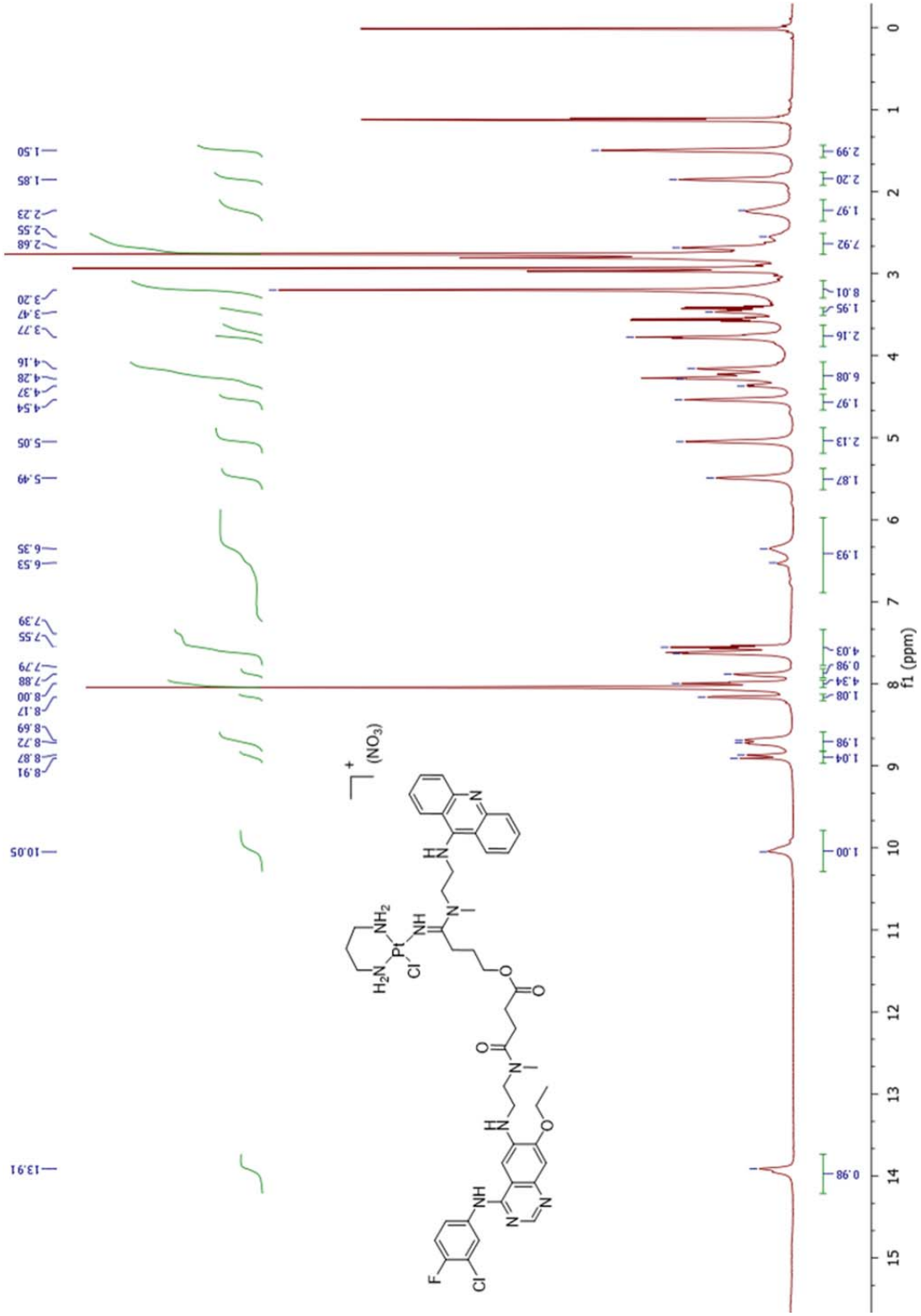


Figure S5. ^{1}H NMR spectrum of **P1-N7** in DMF-d_7.

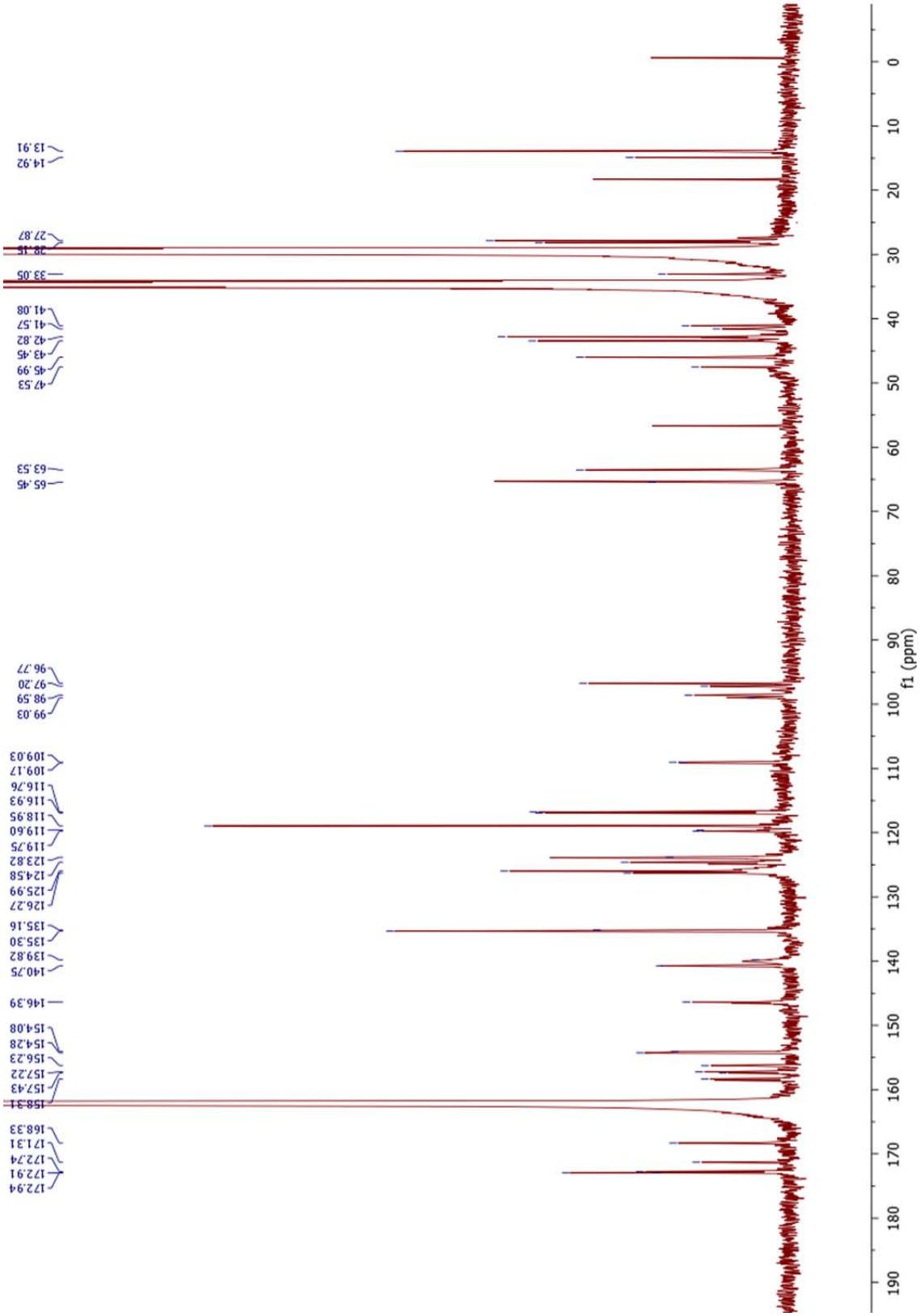


Figure S6. ^{13}C NMR spectrum of **P1-N7** in DMF-d_7.

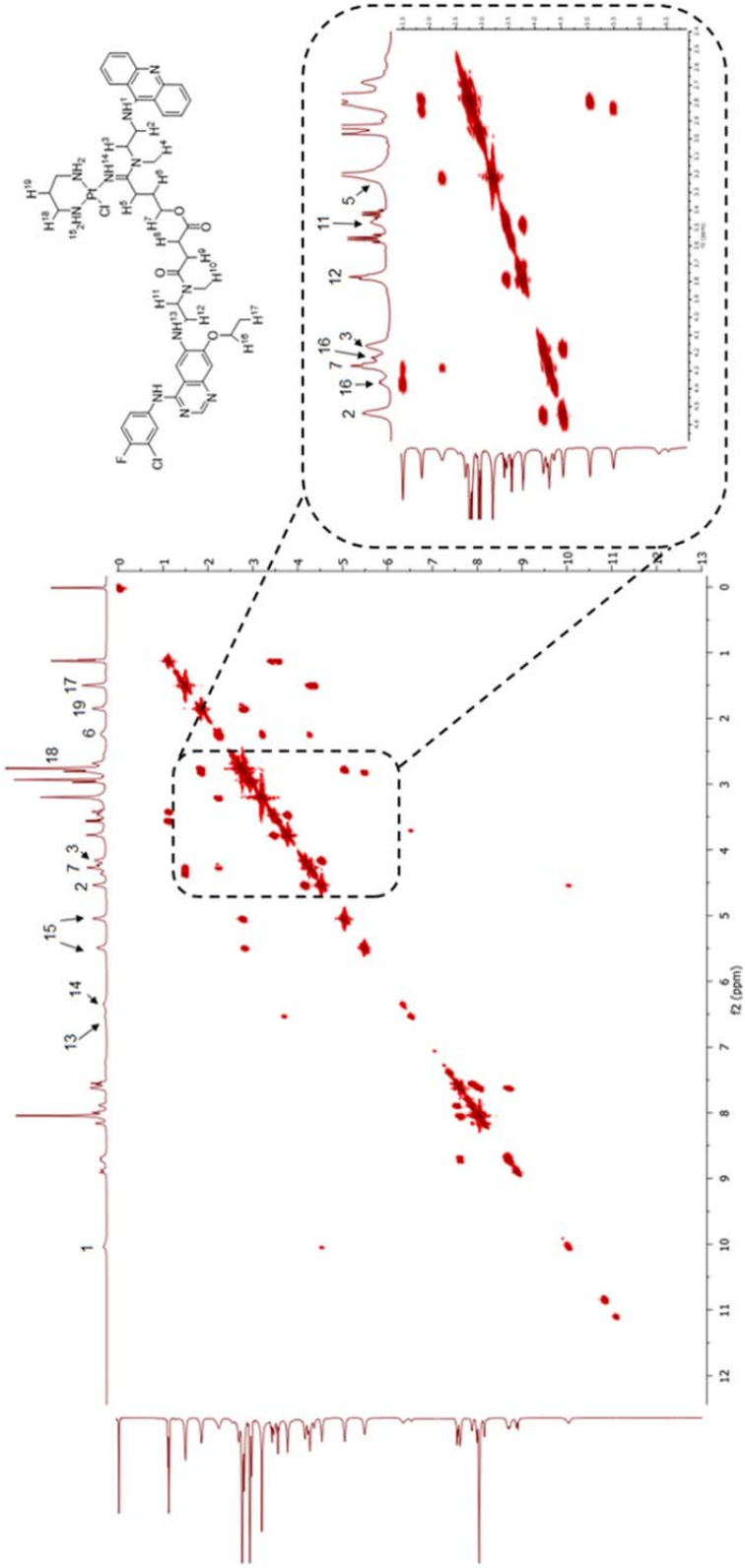


Figure S7. ^{1}H-^{1}H COSY spectrum of compound **P1-N7** in DMF-d_7**.**

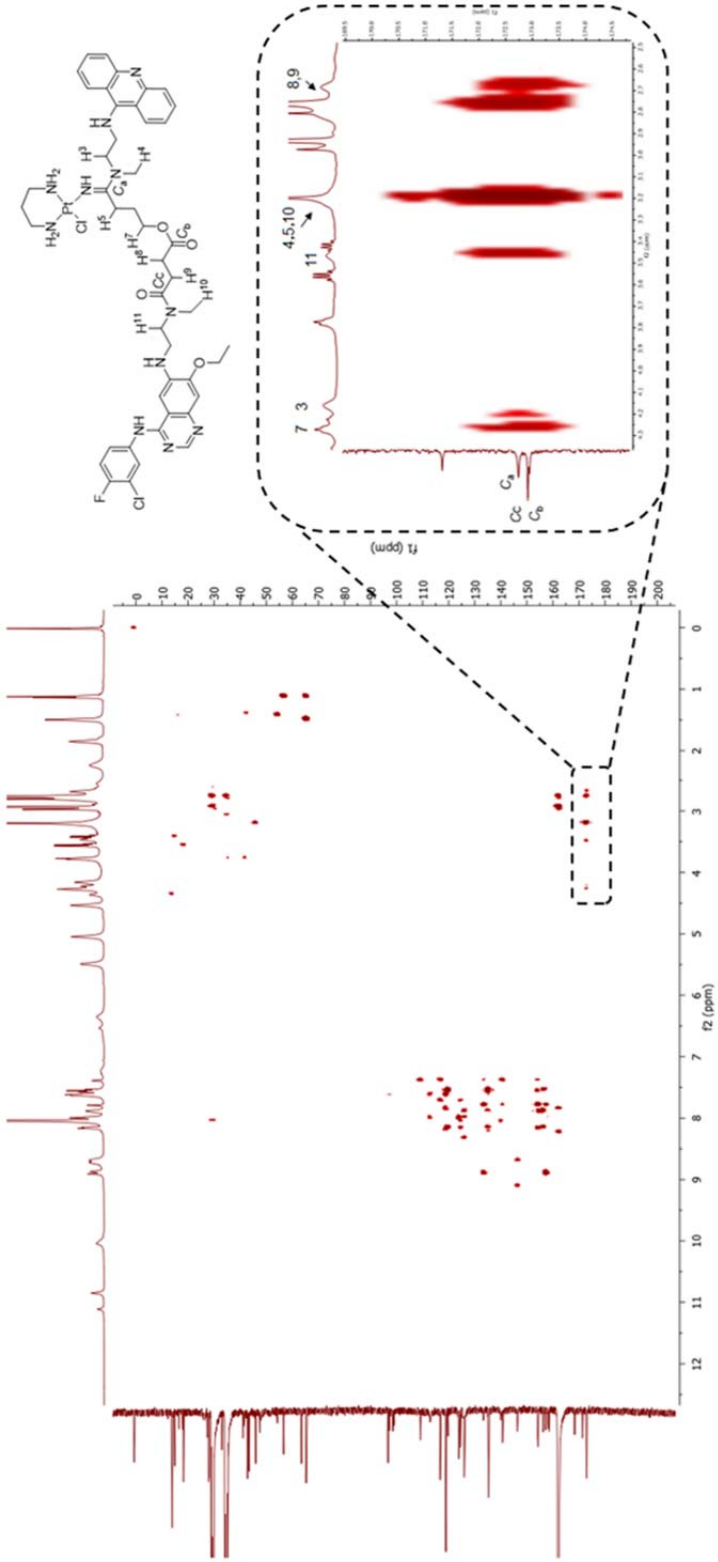


Figure S8. ^{1}H-^{13}C HMBC spectrum of compound **P1-N7** in DMF-d_7.

S2. LC-MS ANALYSIS OF PURIFIED COMPOUNDS

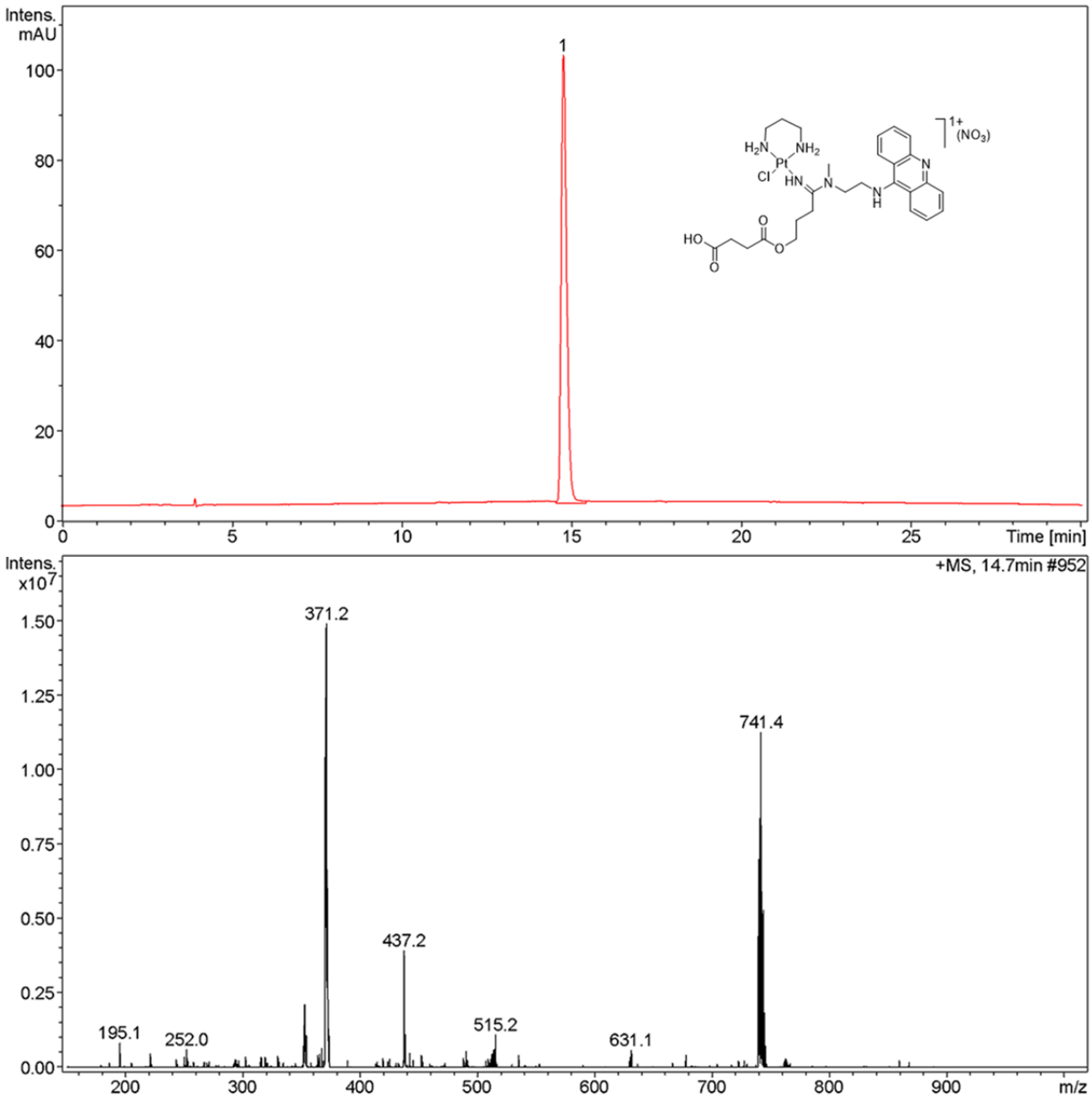


Figure S9. LC-MS analysis of purified **P1.**

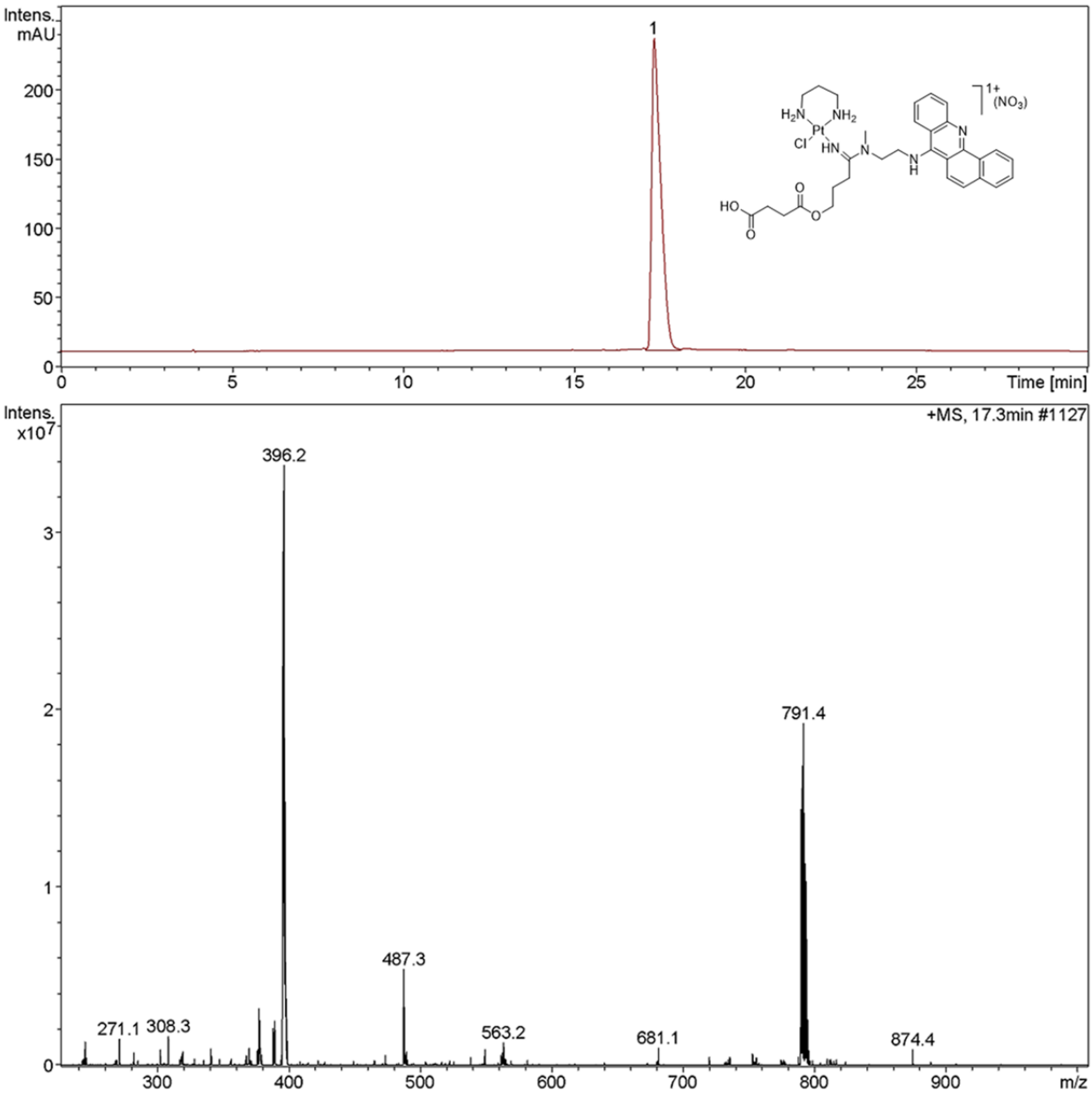


Figure S10. LC-MS analysis of purified **P2.**

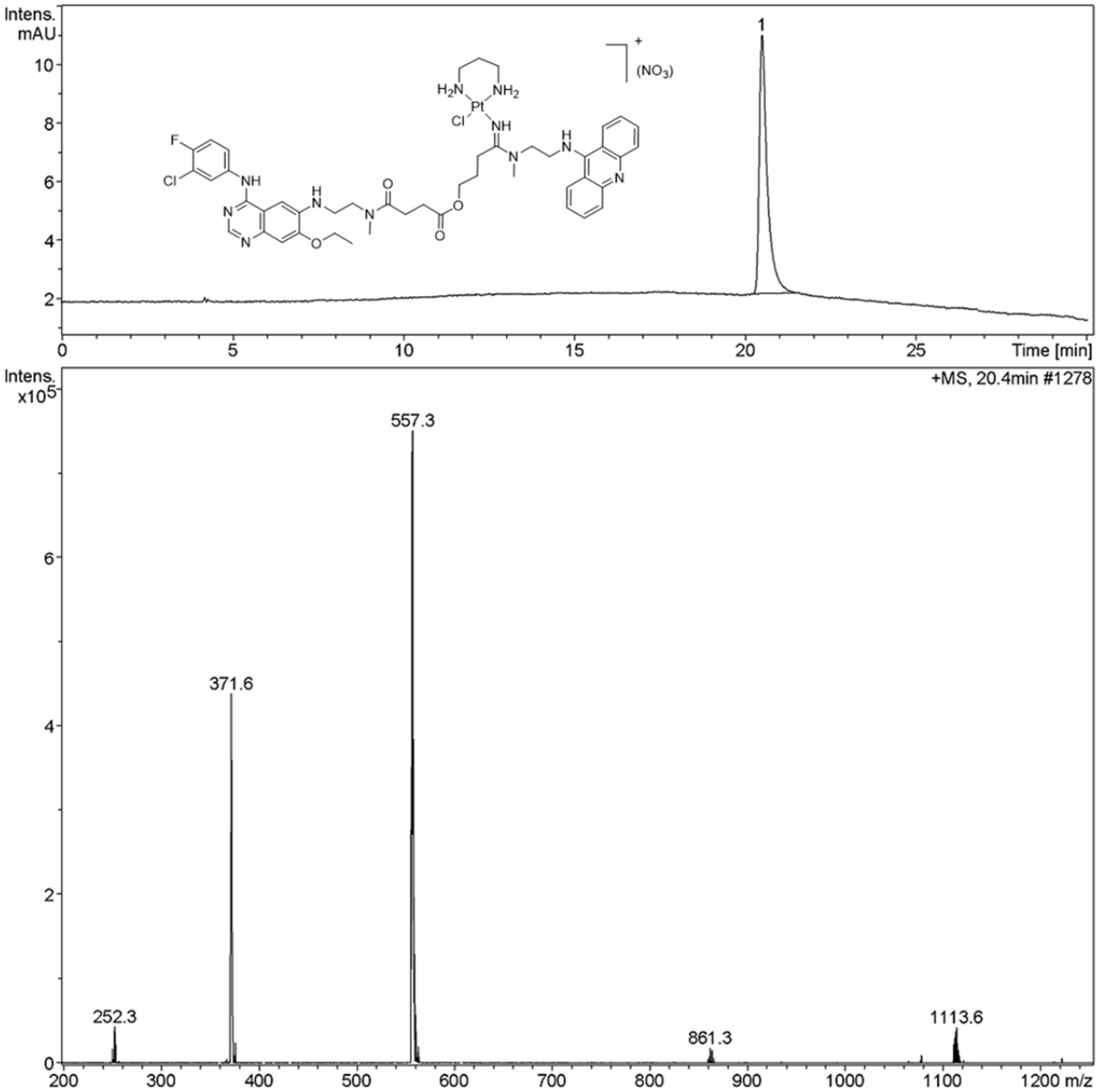


Figure S11. LC-MS analysis of purified **P1-N7.**

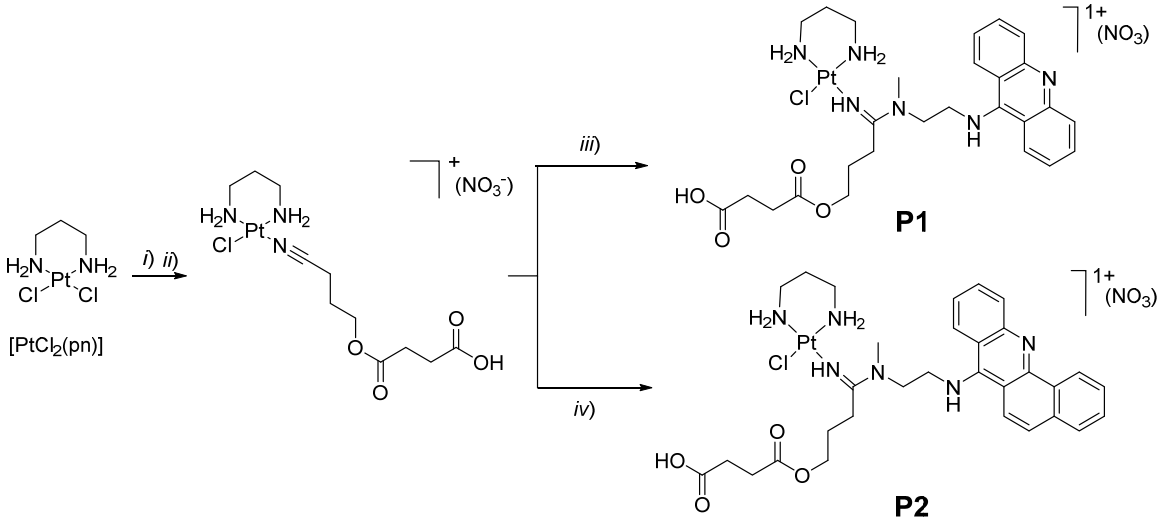


Figure S12. Synthesis of **P1** and **P2**. i) $AgNO_3$, DMF, rt, ii) $HOOC(CH_2)_2C(O)O(CH_2)_3CN$ (**3**), DMF, 60 °C, 4 h, iii) N^1-(acridin-9-yl)-N^2-methylethane-1,2-diamine (**A1**), DMF, 4 °C, iv) N^1-(benzo[*c*]acridin-7-yl)-N^2-methylethane-1,2-diamine (**B1**), DMF, 4 °C.

S3. LC-MS ANALYSIS OF COUPLING REACTIONS

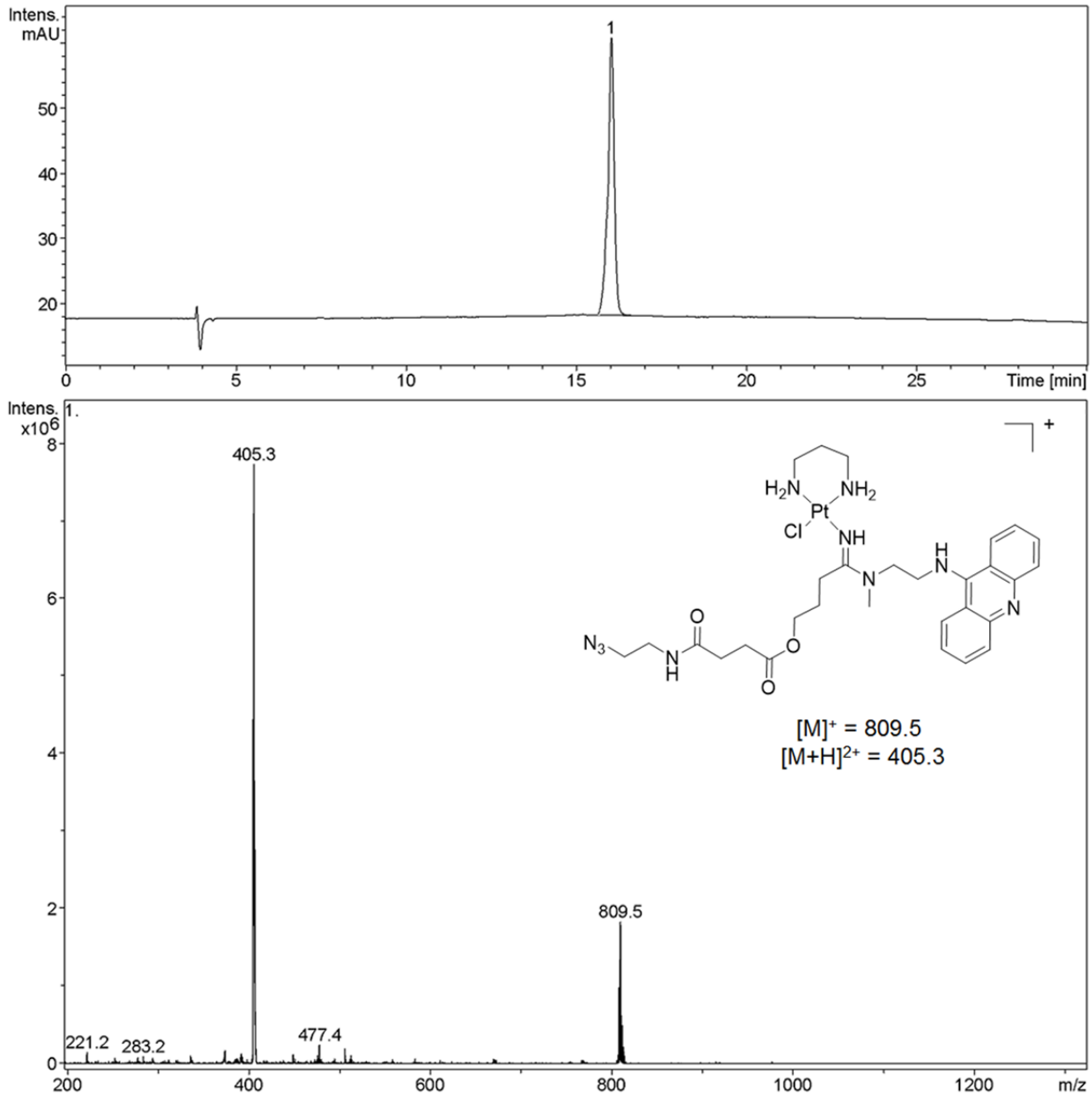


Figure S13. LC-MS analysis of the reaction mixture for the preparation of **P1-N1.**

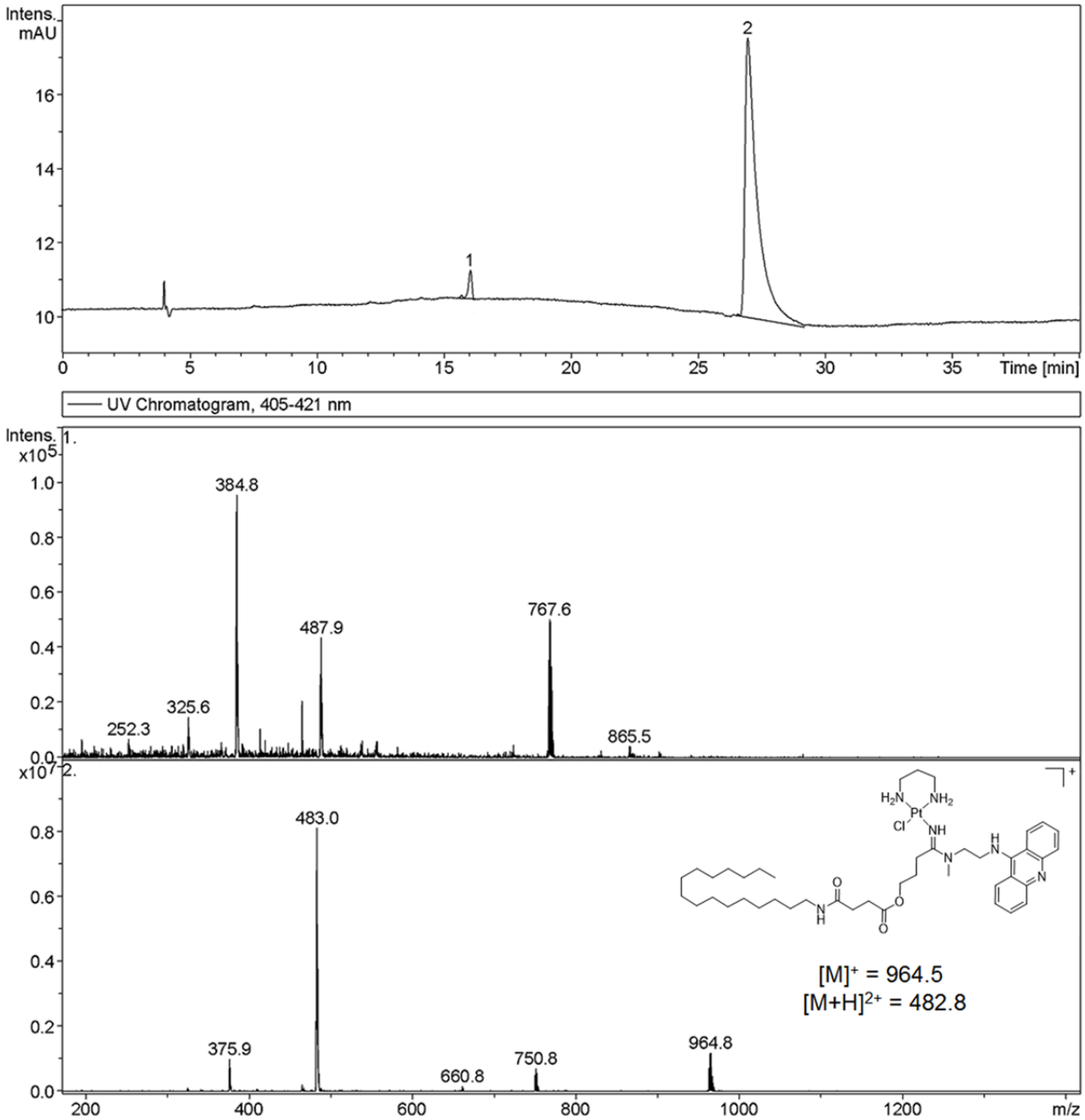


Figure S14. LC-MS analysis of the reaction mixture for the preparation of **P1-N2.**

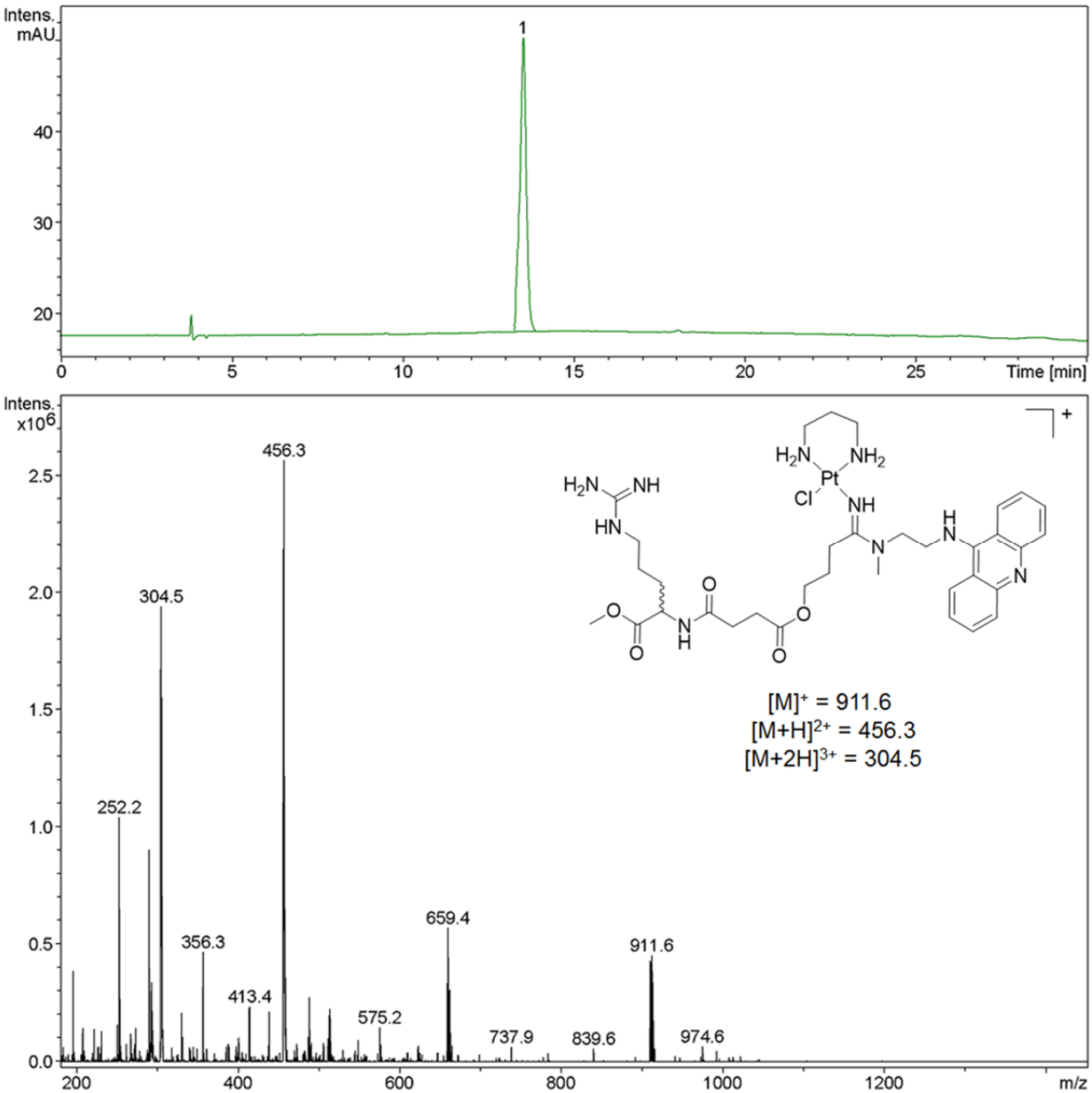


Figure S15. LC-MS analysis of the reaction mixture for the preparation of **P1-N4.**

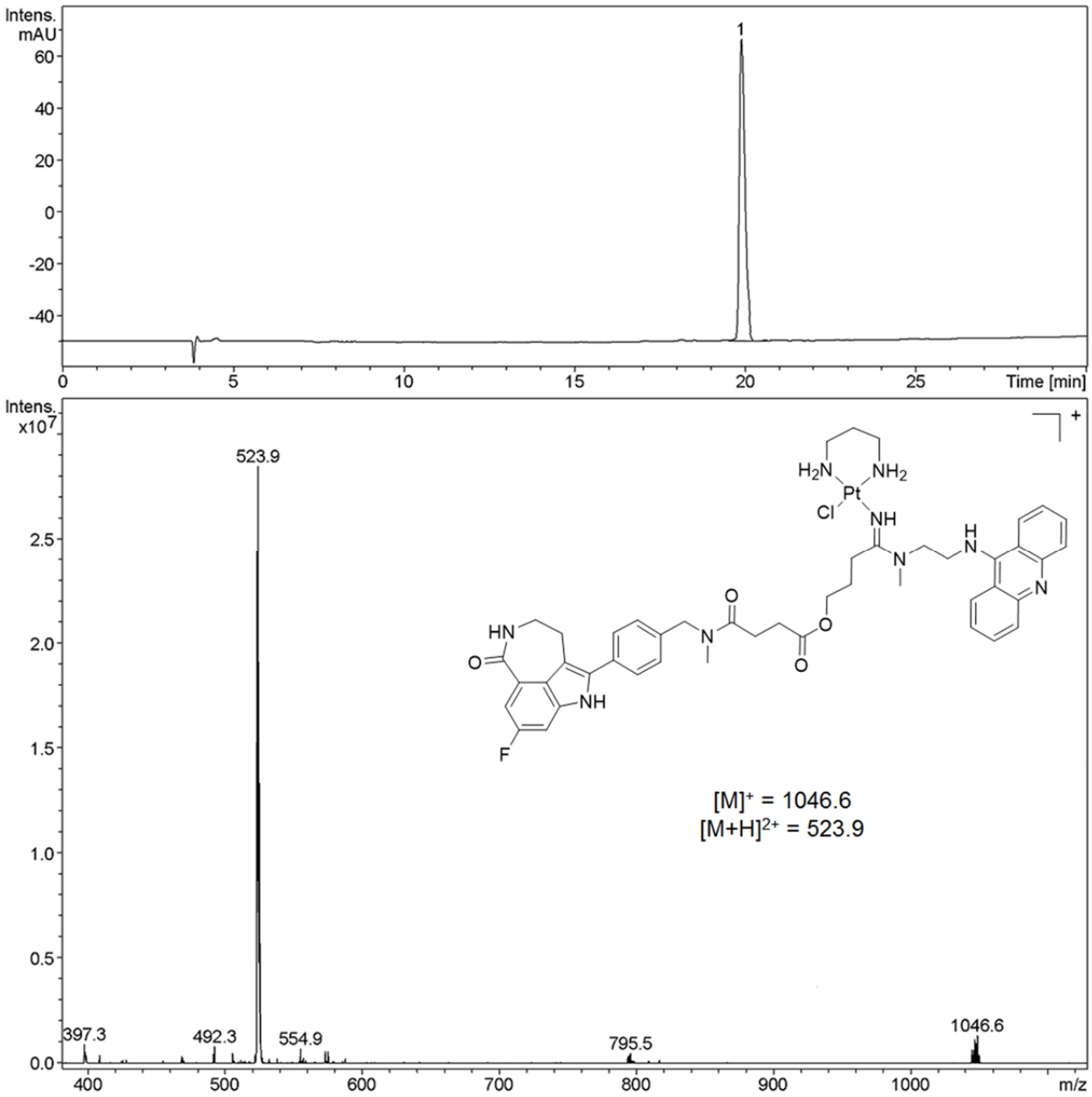


Figure S16. LC-MS analysis of the reaction mixture for the preparation of **P1-N5.**

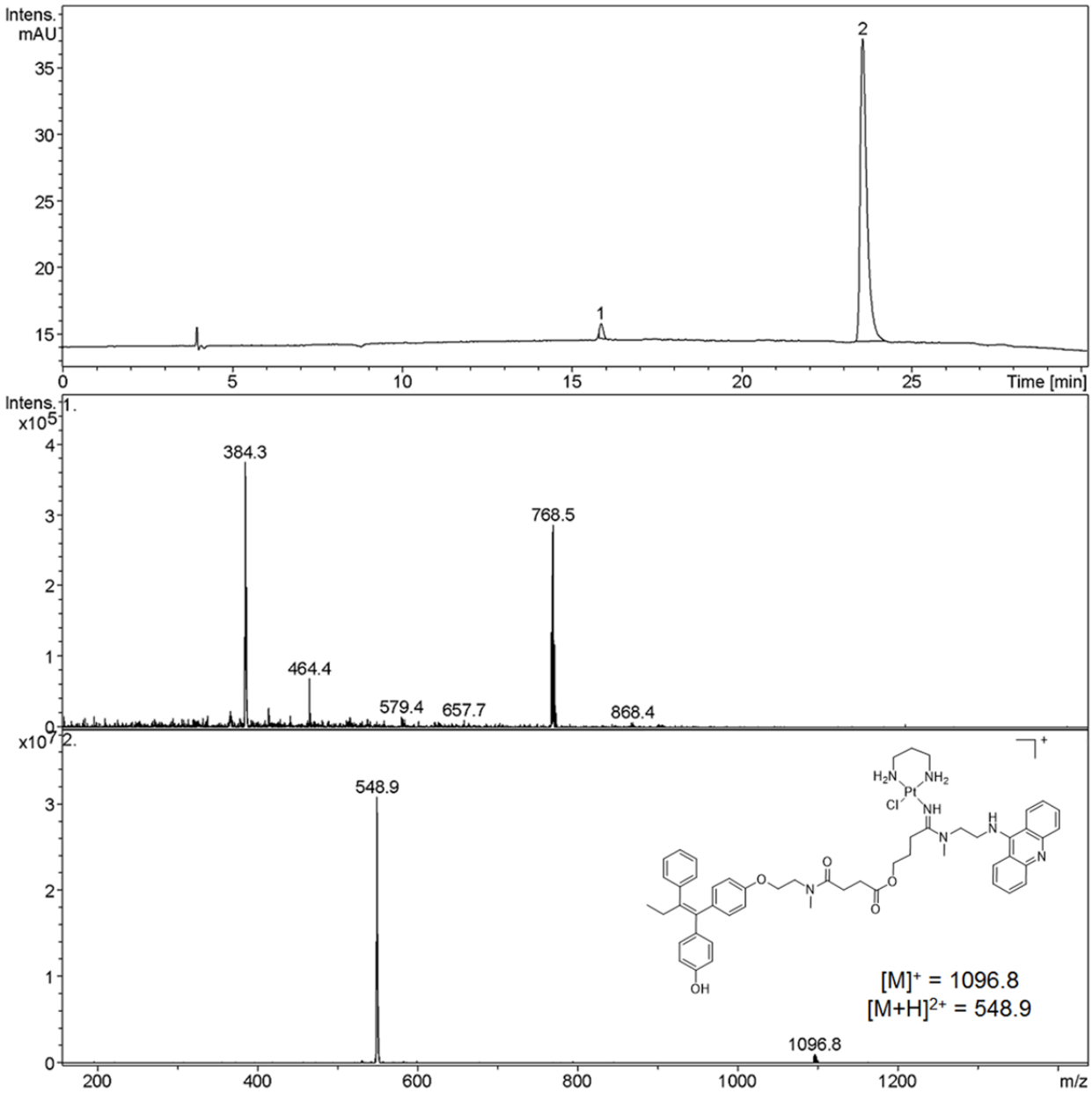


Figure S17. LC-MS analysis of the reaction mixture for the preparation of **P1-N6.**

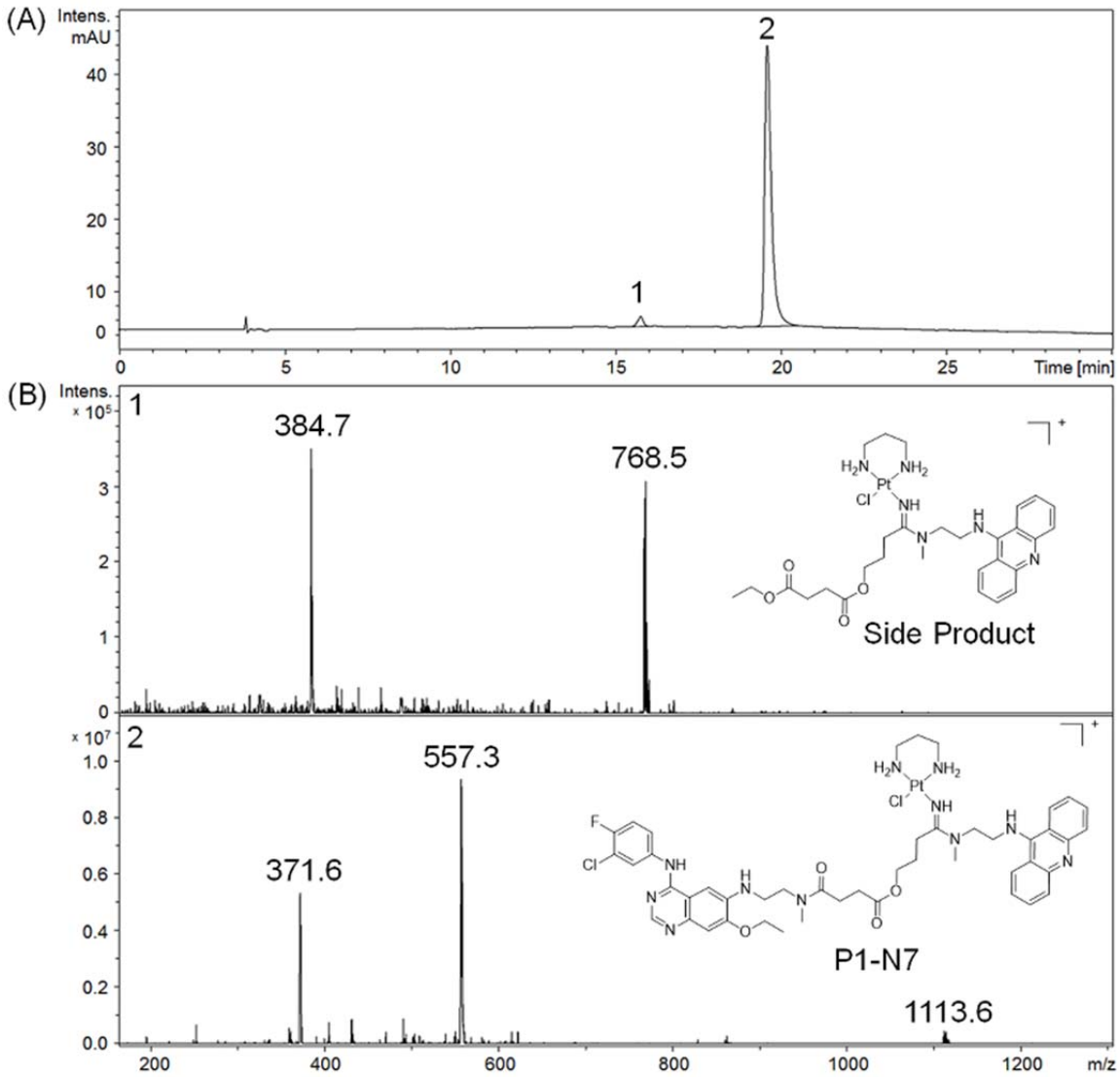


Figure S18. (A) Reverse-phase HPLC trace for the reaction of **P1** and **N7**. (B) ESMS spectrum recorded in positive-ion mode. Characteristic molecular and fragment ions for **P1-N7** are m/z $[M]^{+}$ 1113.6, $[M+H]^{2+}$ 557.3, $[M+2H]^{3+}$ 371.6.

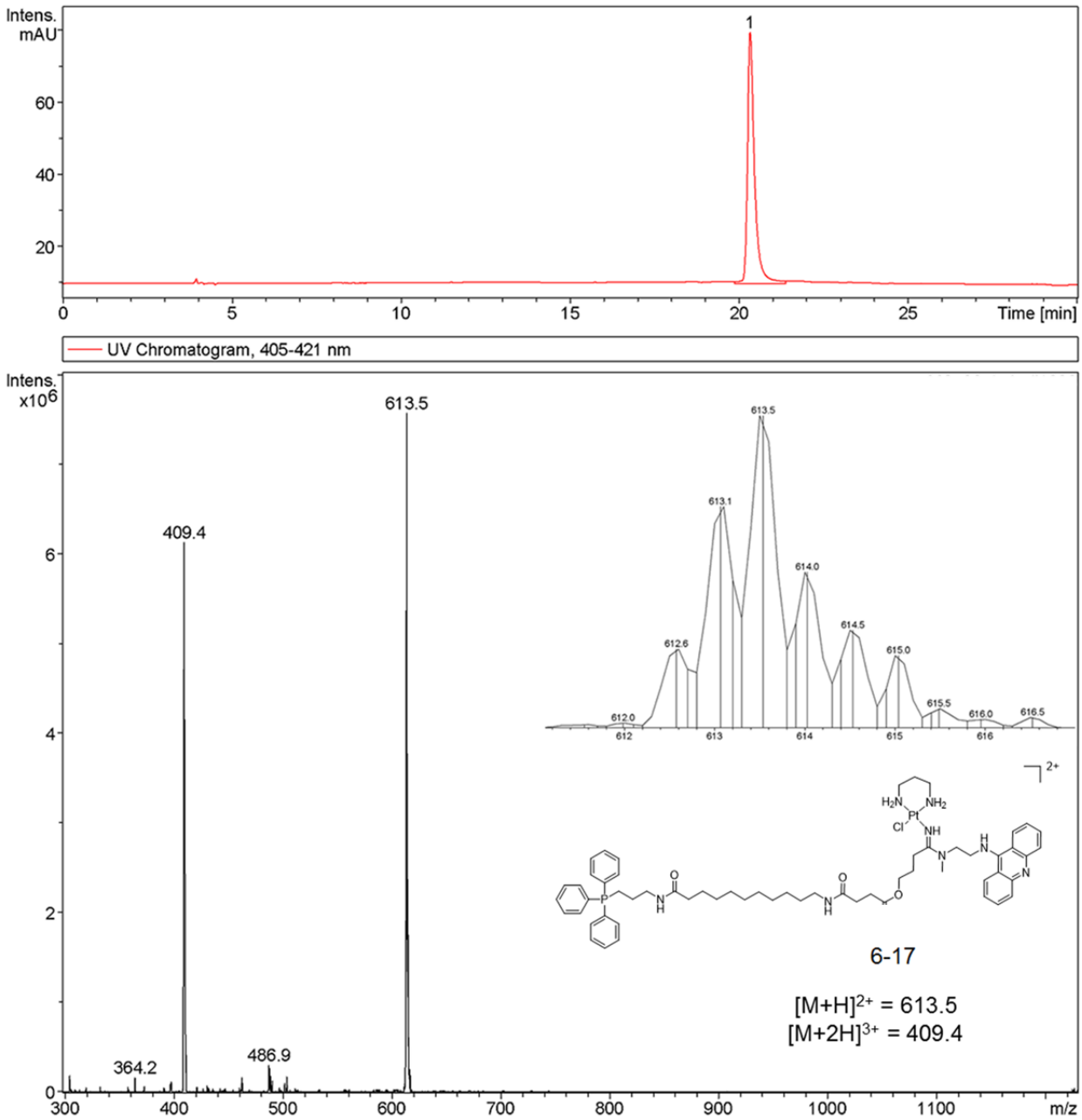


Figure S19. LC-MS analysis of the reaction mixture for the preparation of **P1-N9.**

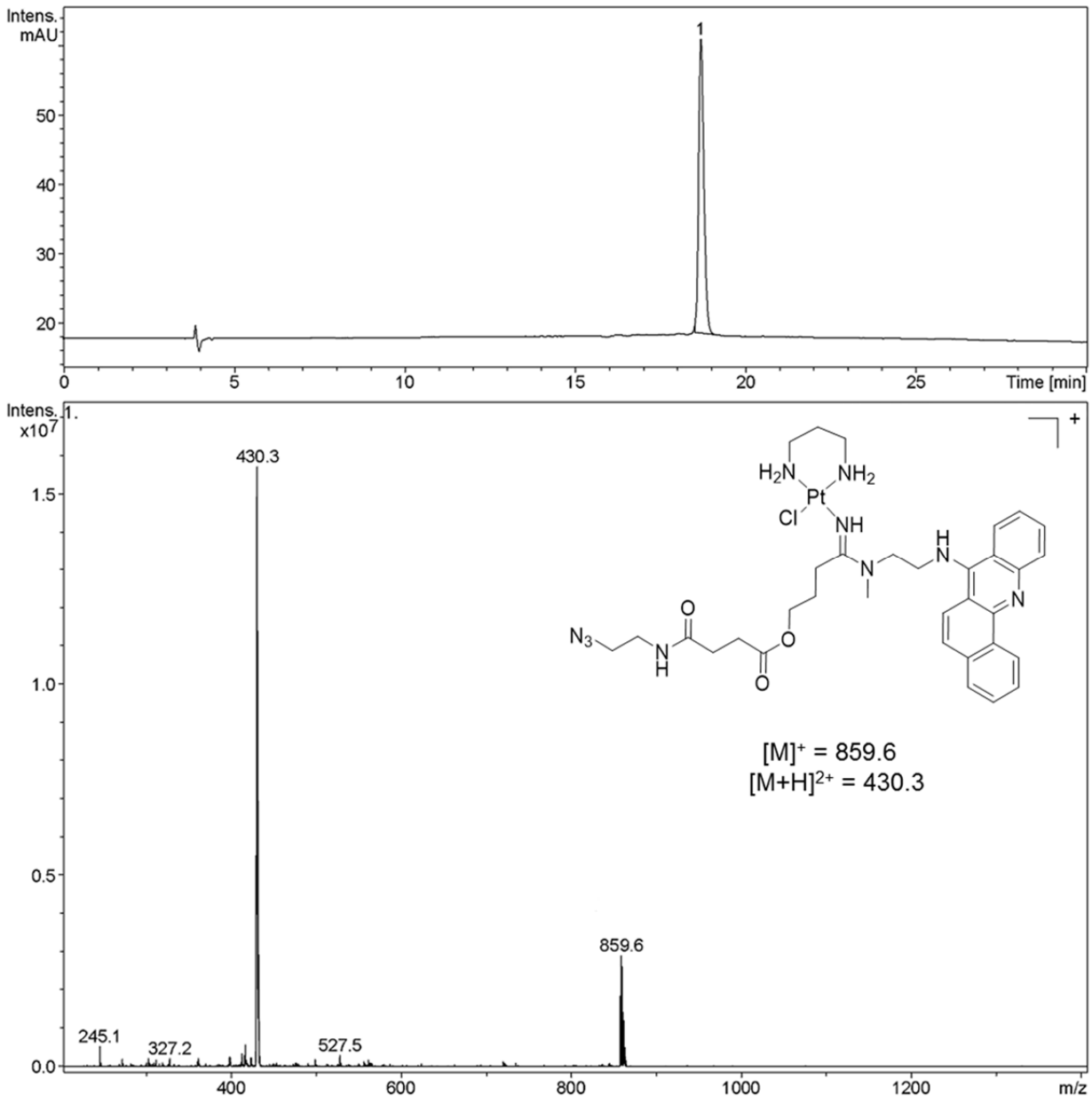


Figure S20. LC-MS analysis of the reaction mixture for the preparation of **P2-N1.**

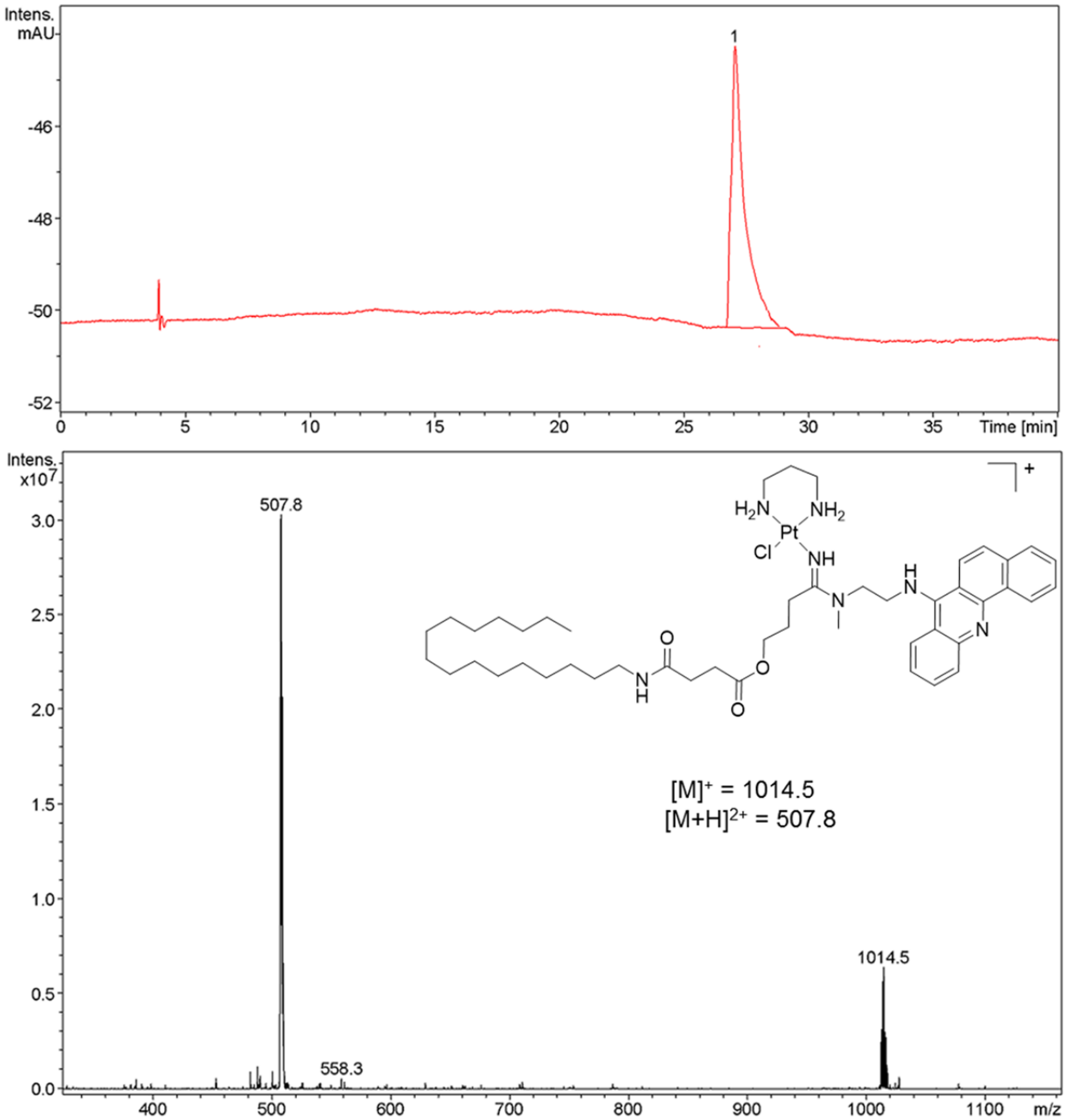


Figure S21. LC-MS analysis of the reaction mixture for the preparation of **P2-N2.**

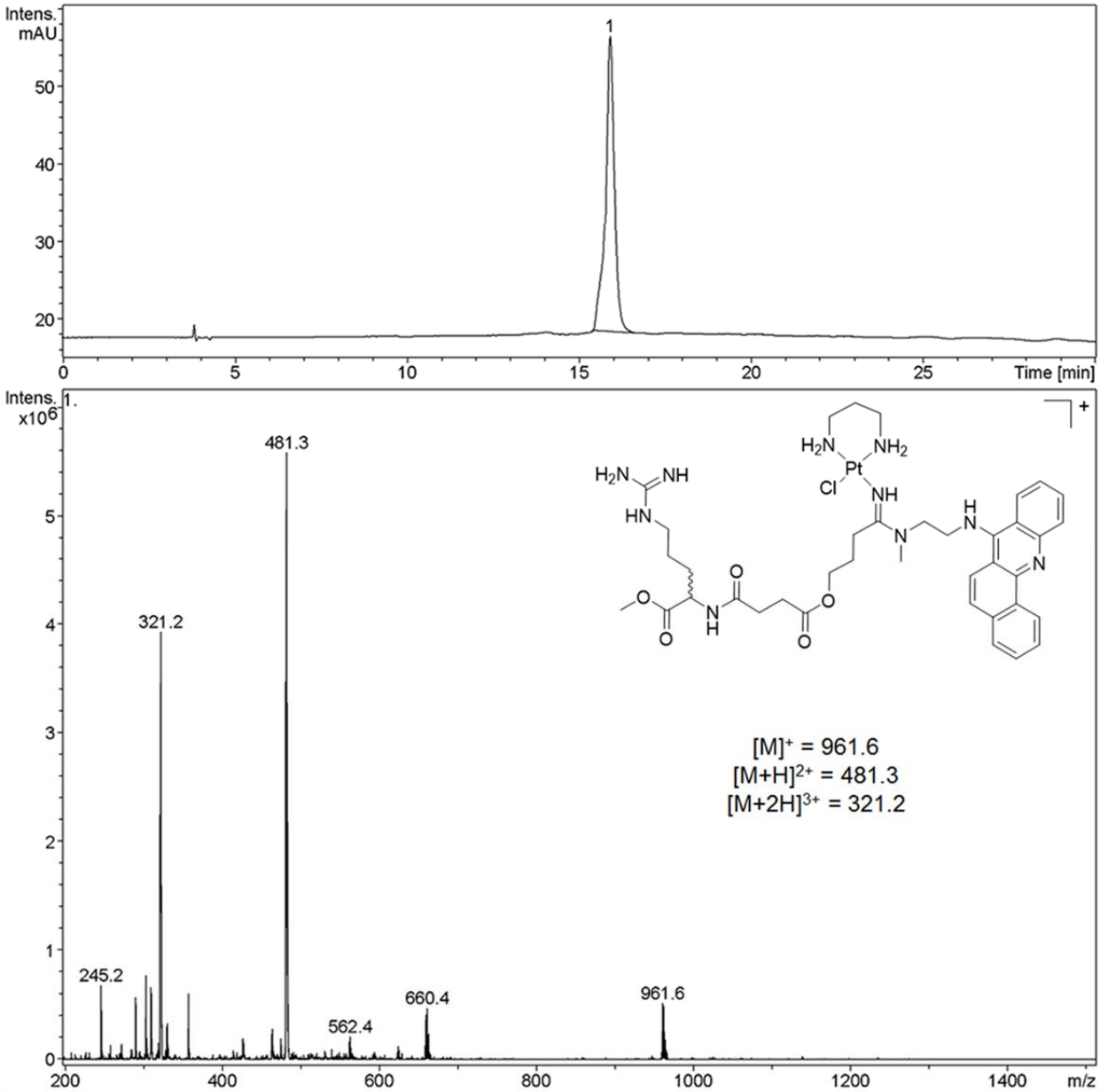


Figure S22. LC-MS analysis of the reaction mixture for the preparation of **P2-N4.**

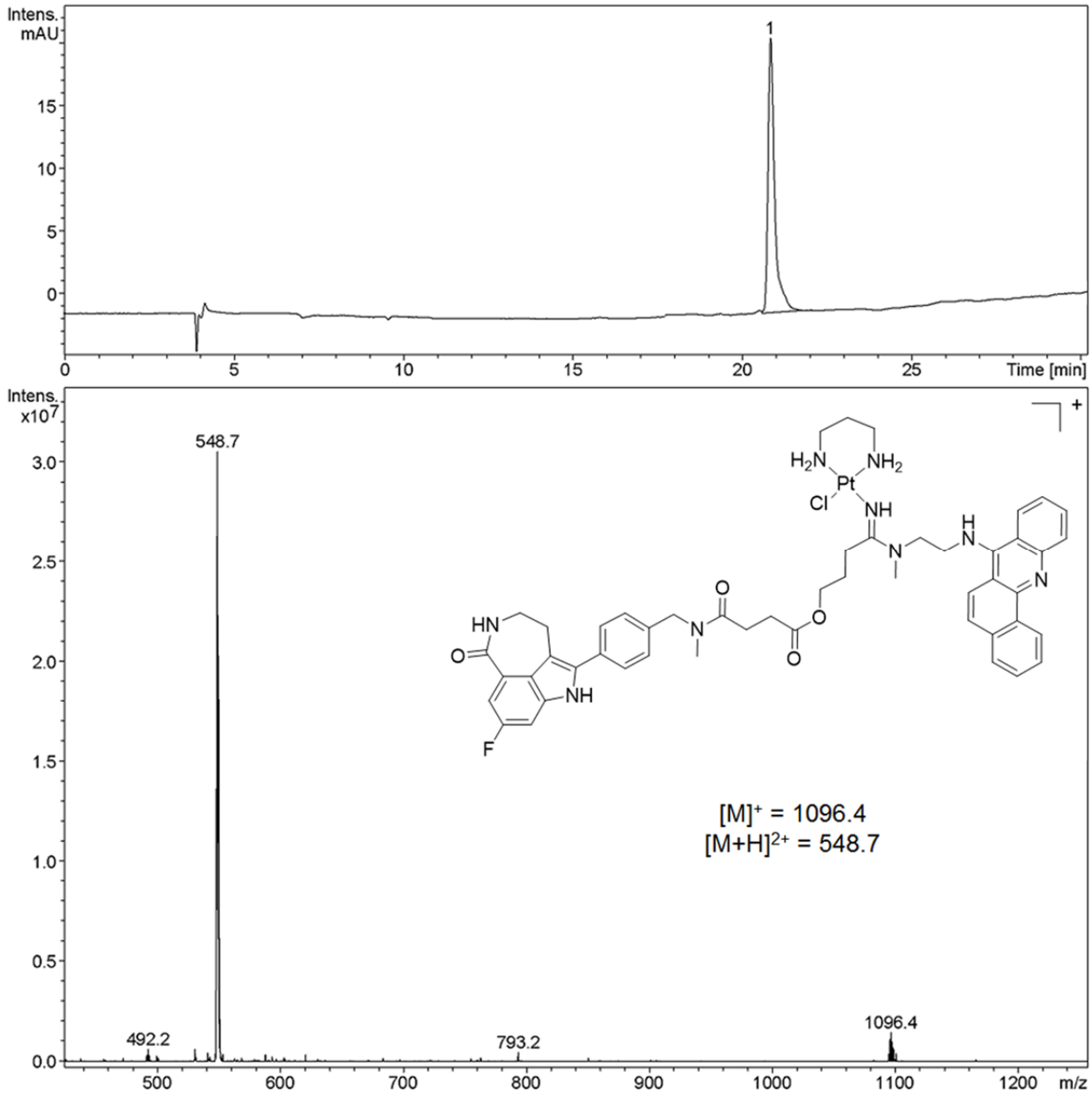


Figure S23. LC-MS analysis of the reaction mixture for the preparation of **P2-N5.**

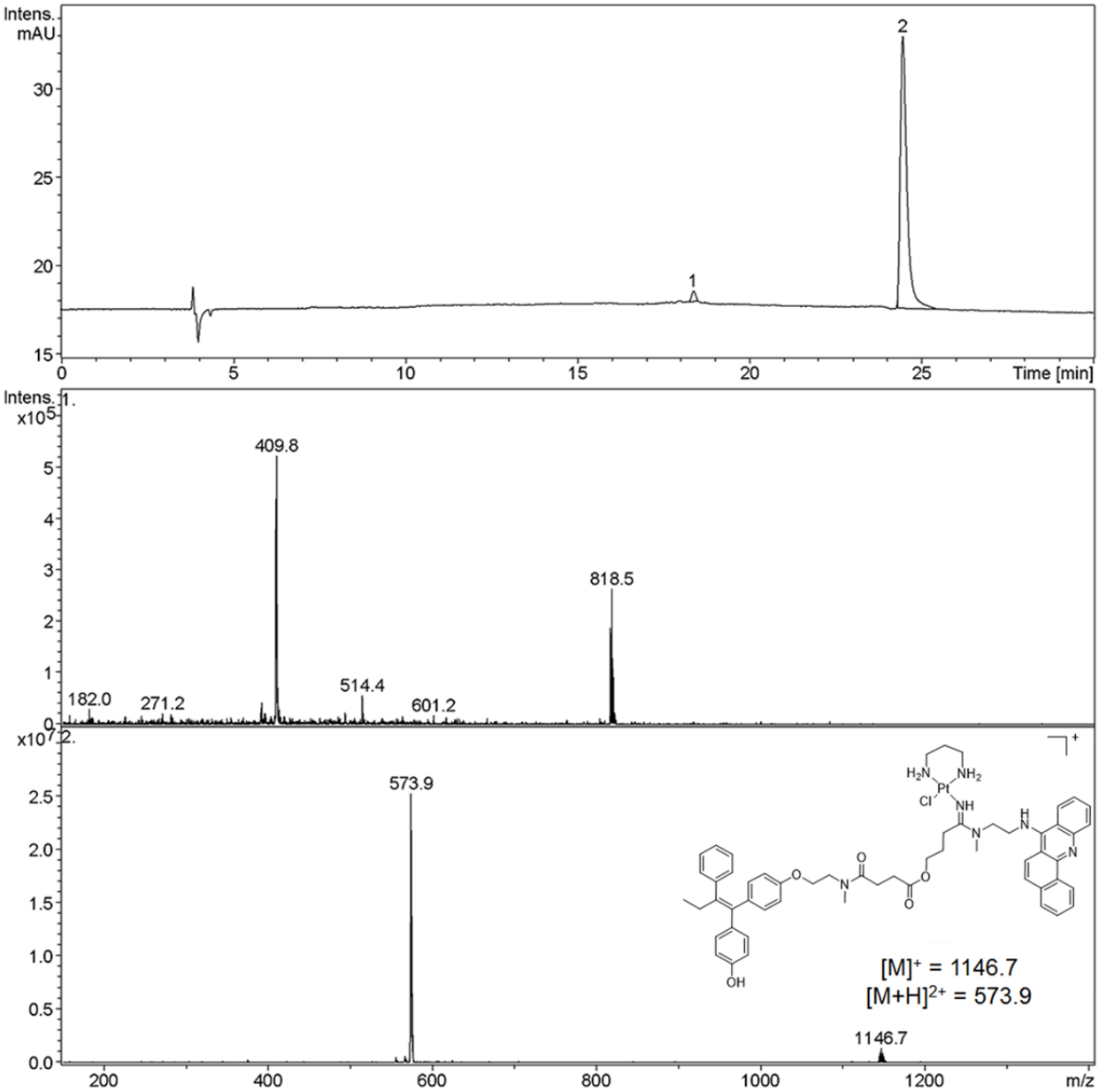


Figure S24. LC-MS analysis of the reaction mixture for the preparation of **P2-N6.**

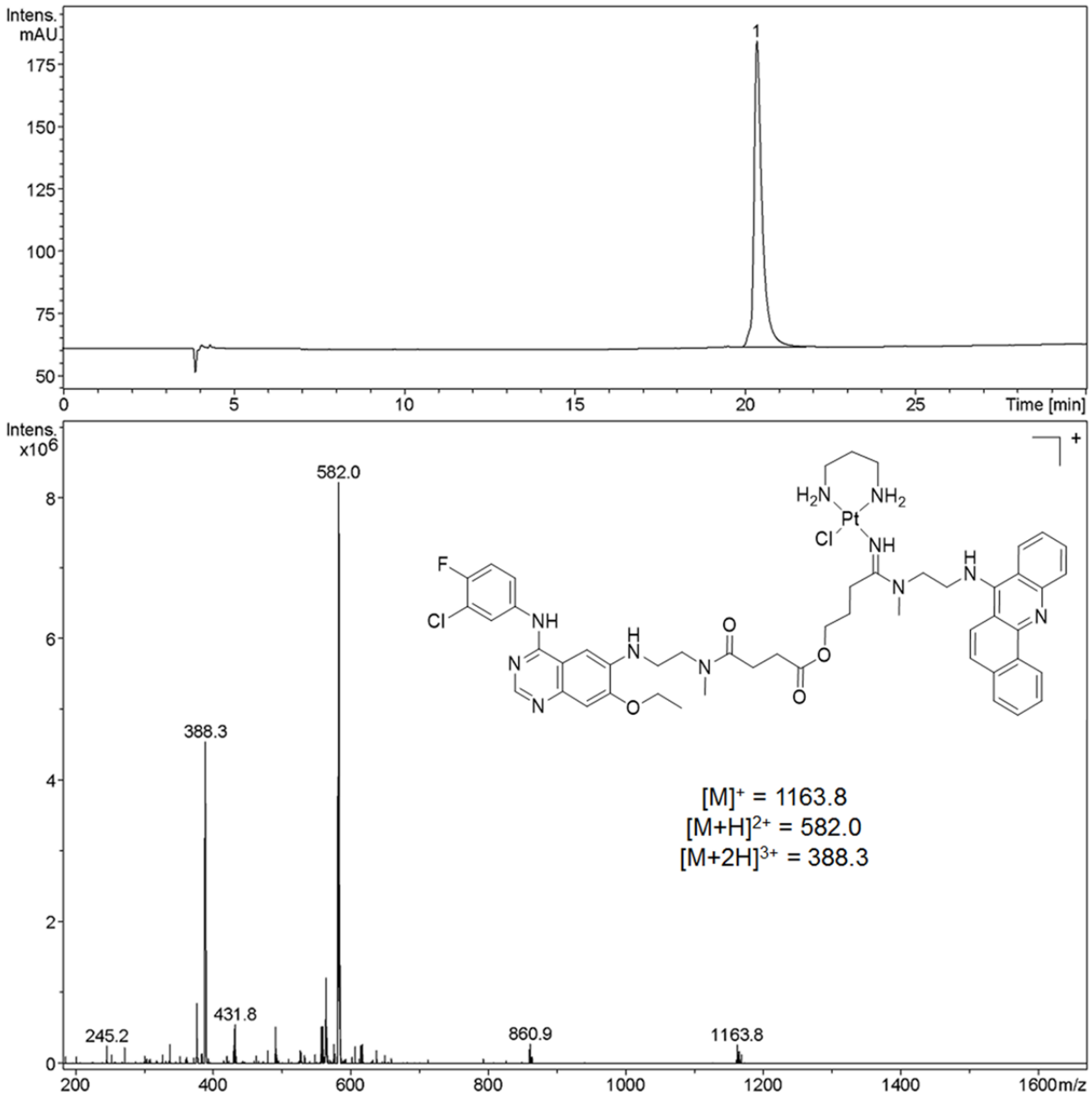


Figure S25. LC-MS analysis of the reaction mixture for the preparation of **P2-N7.**

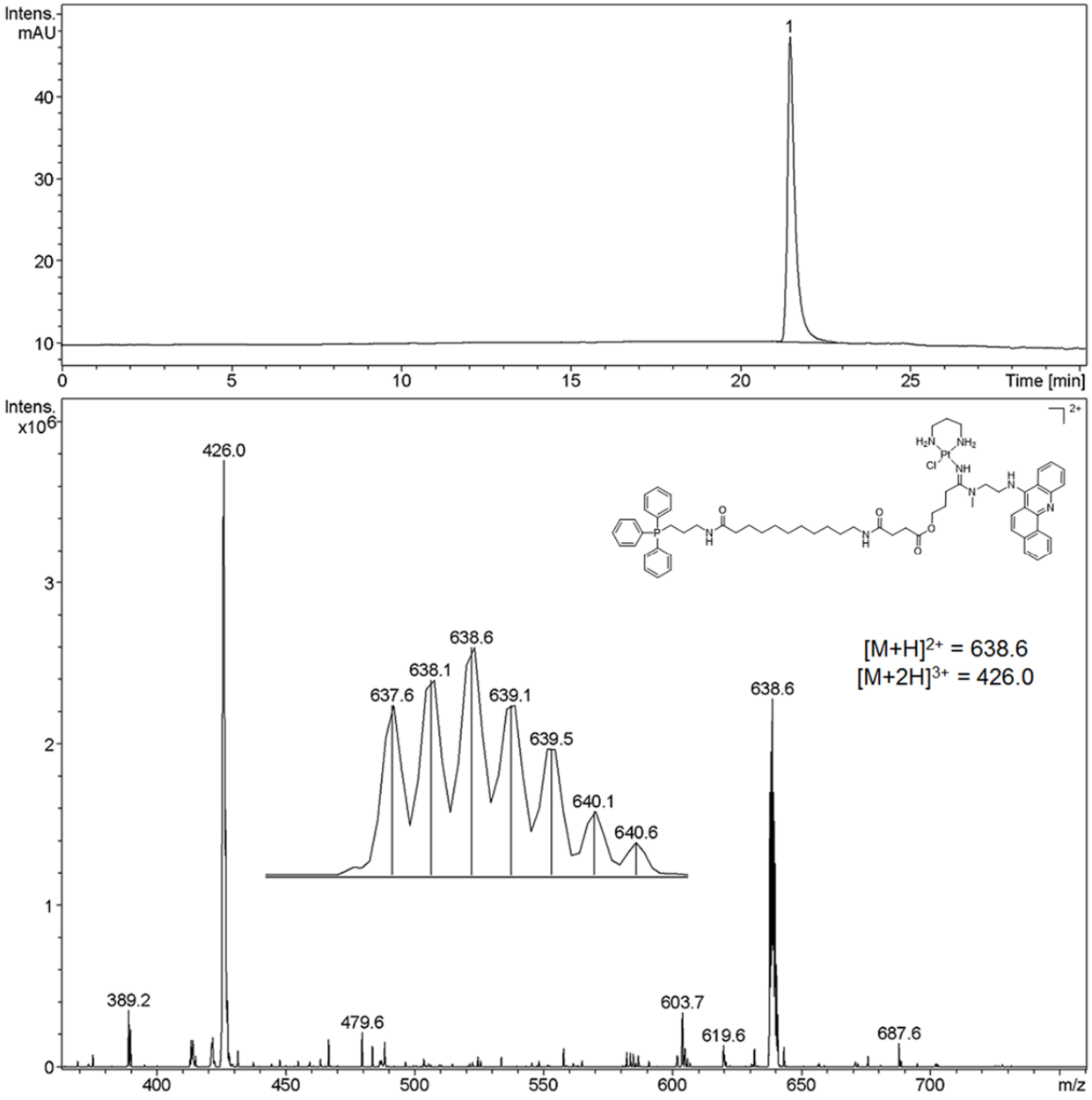


Figure S26. LC-MS analysis of the reaction mixture for the preparation of **P2-N9.**

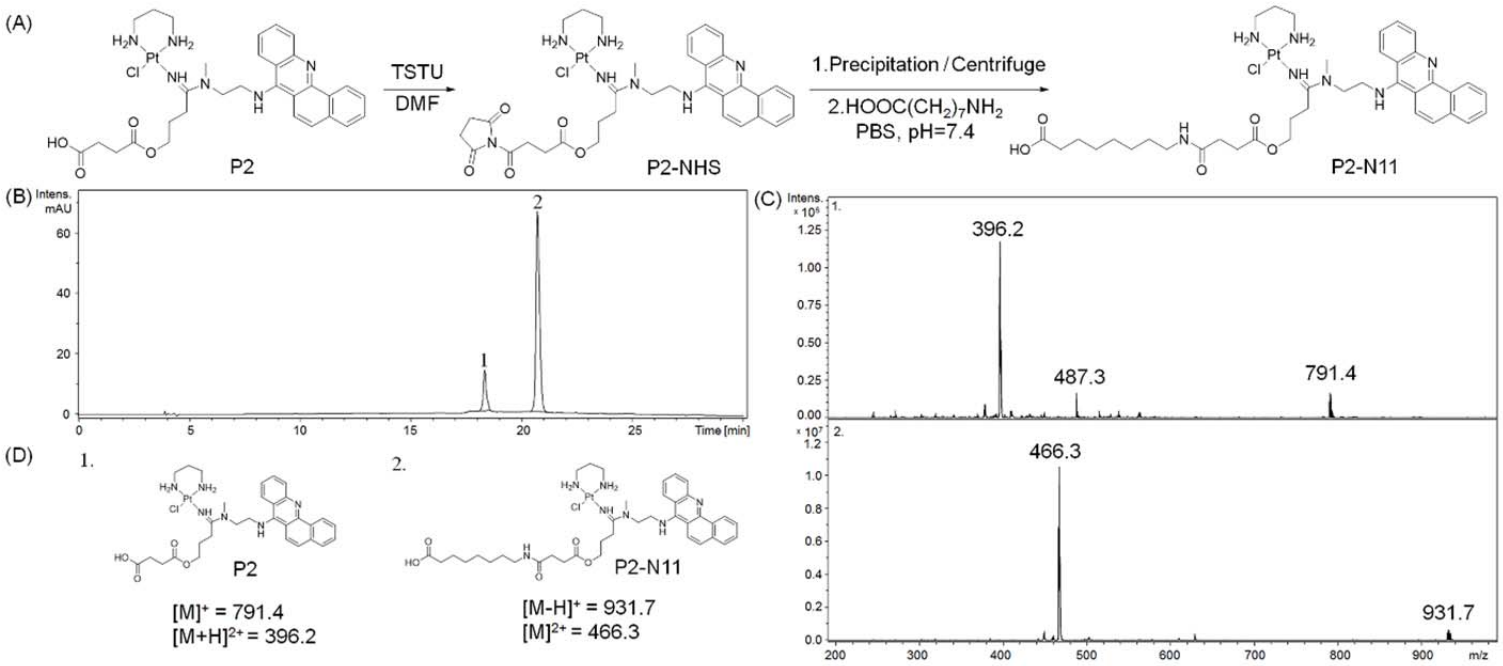


Figure S27. (A) "Two-step" synthesis of platinum-acridine conjugates under aqueous conditions. (B) Reverse-phase HPLC trace of the reaction mixture for the preparation of **P2-N11**. (C) ESMS spectrum of **P2** and target conjugate **P2-N11** recorded in positive-ion mode. (D) Structures and characteristic molecular ions and fragment ions (m/z) for **P2** and **P2-N11**.

S.4. LC-MS ANALYSIS OF ESTER REACTIVITY

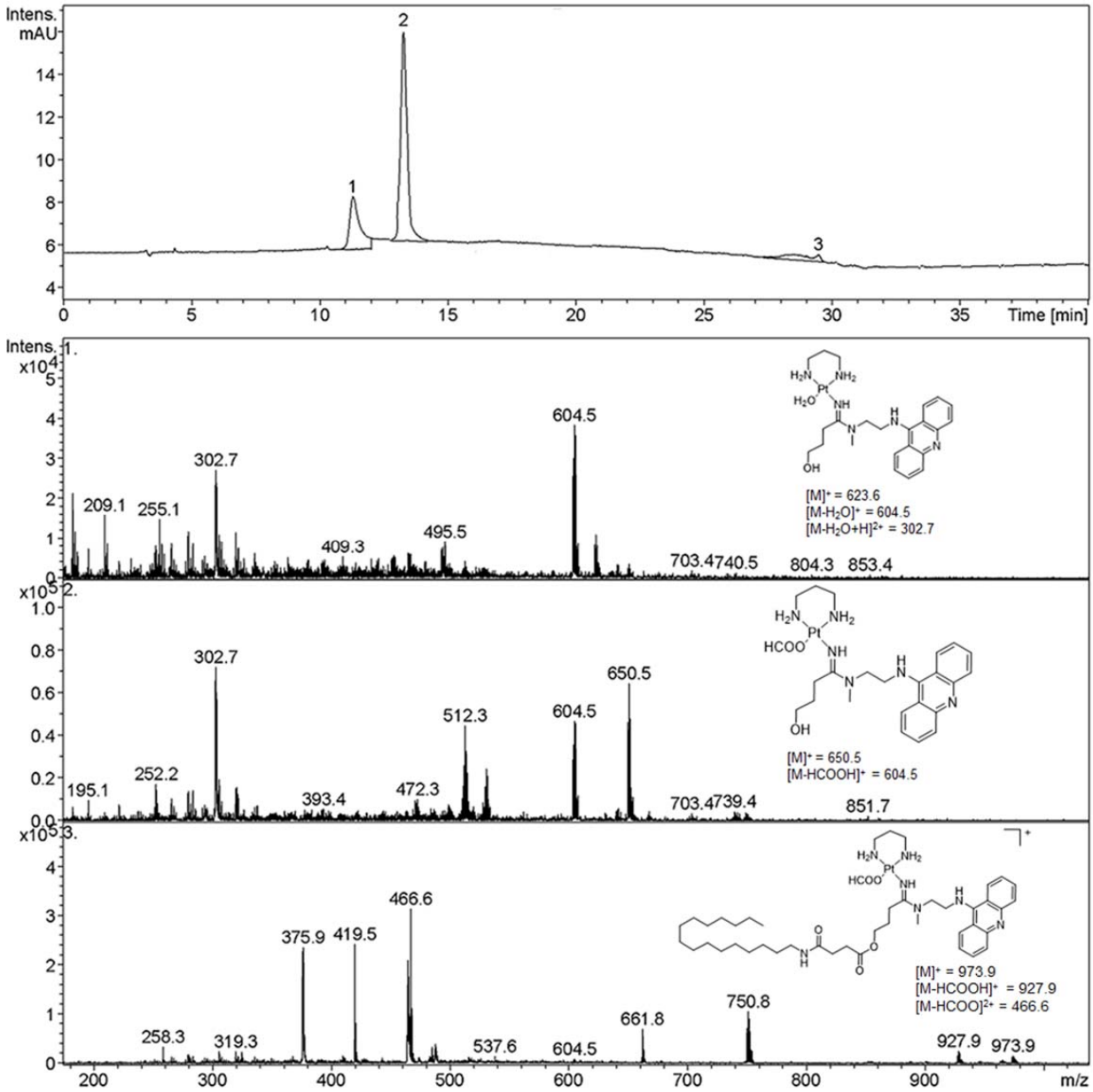


Figure S28. LC-ESMS analysis of the mixture of compound **P1-N2** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

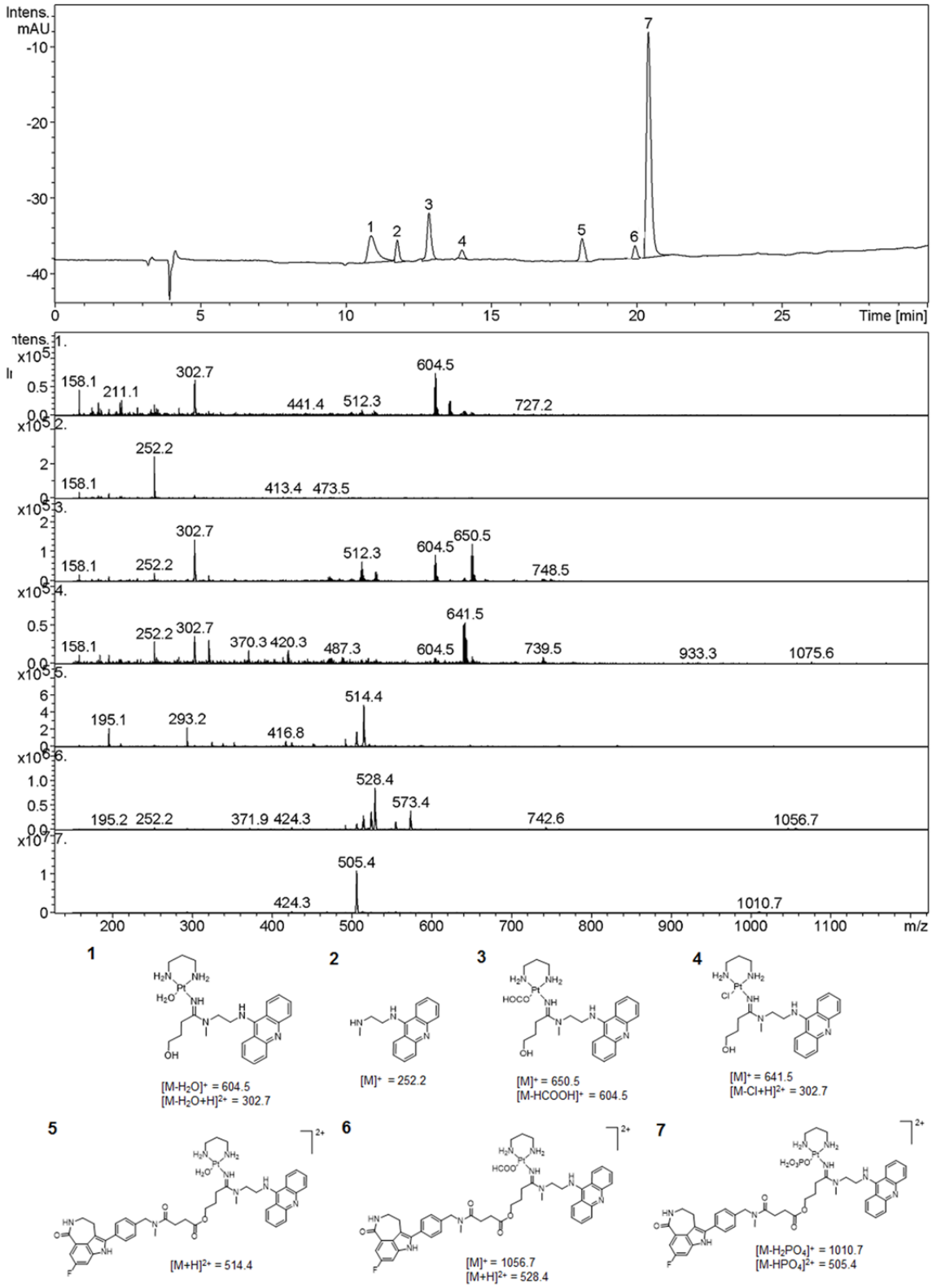


Figure S29. LC-ESMS analysis of the mixture of compound **P1-N5** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

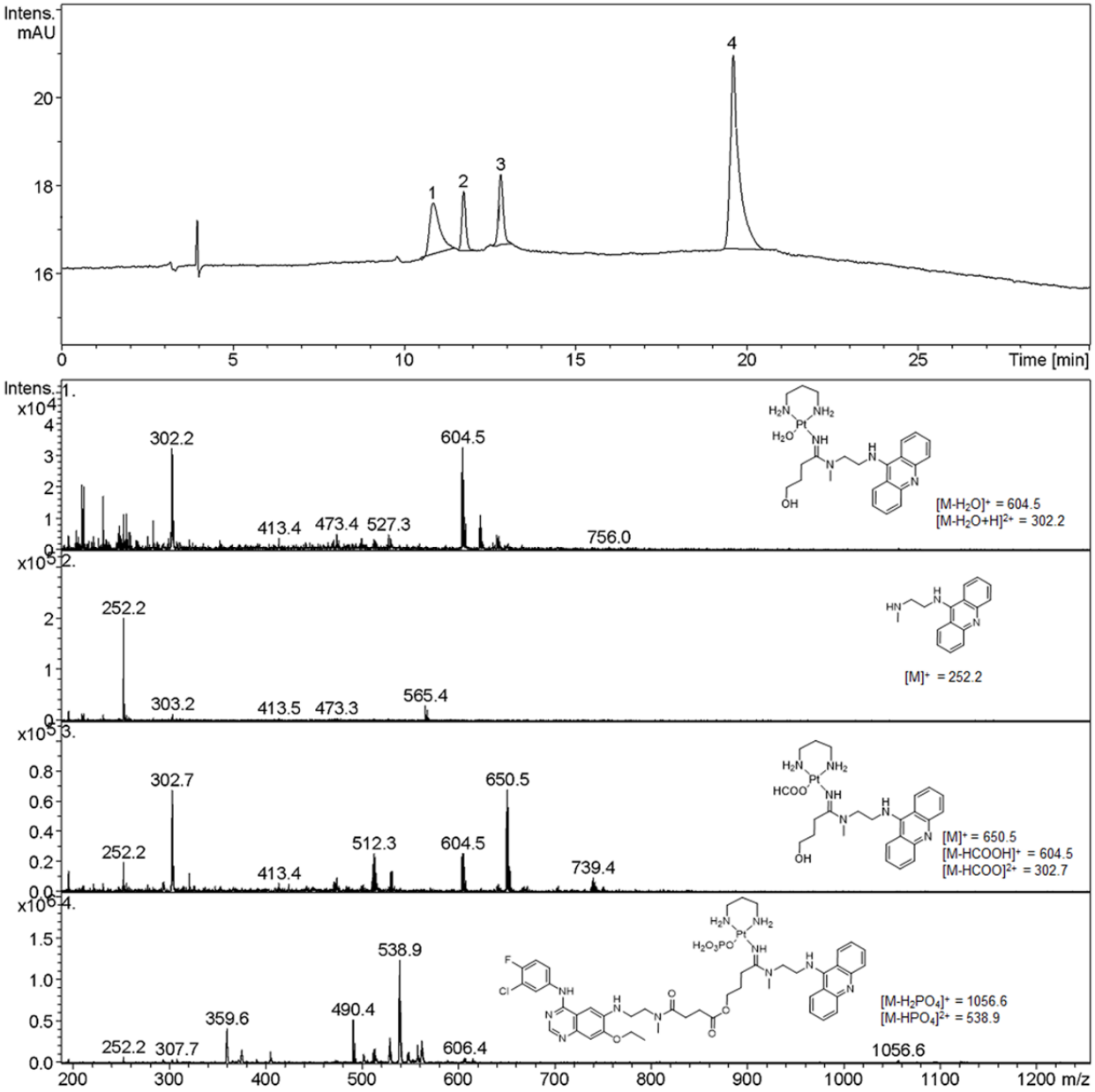


Figure S30. LC-ESMS analysis of the mixture of compound **P1-N7** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

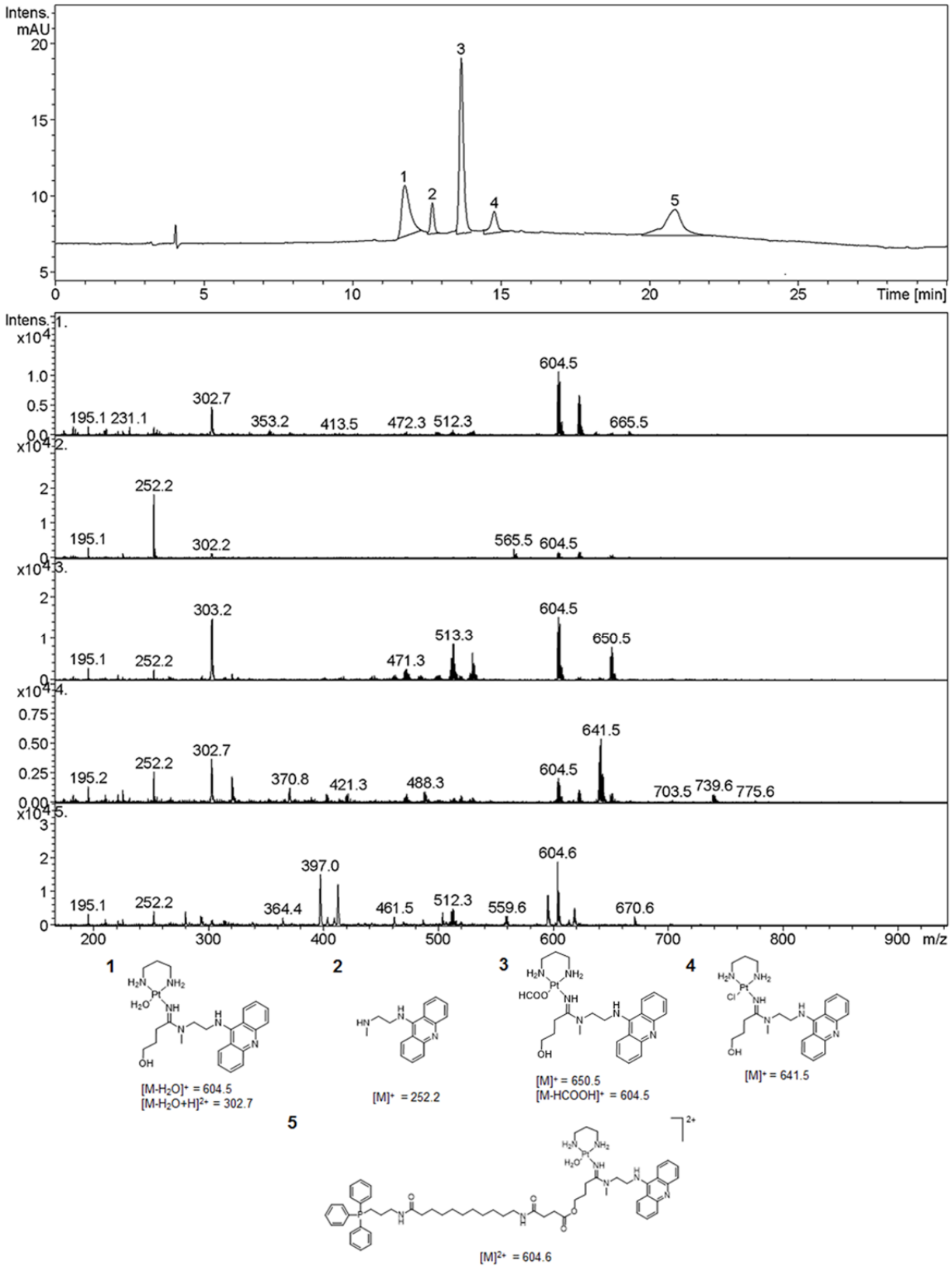


Figure S31. LC-ESMS analysis of the mixture of compound **P1-N9** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

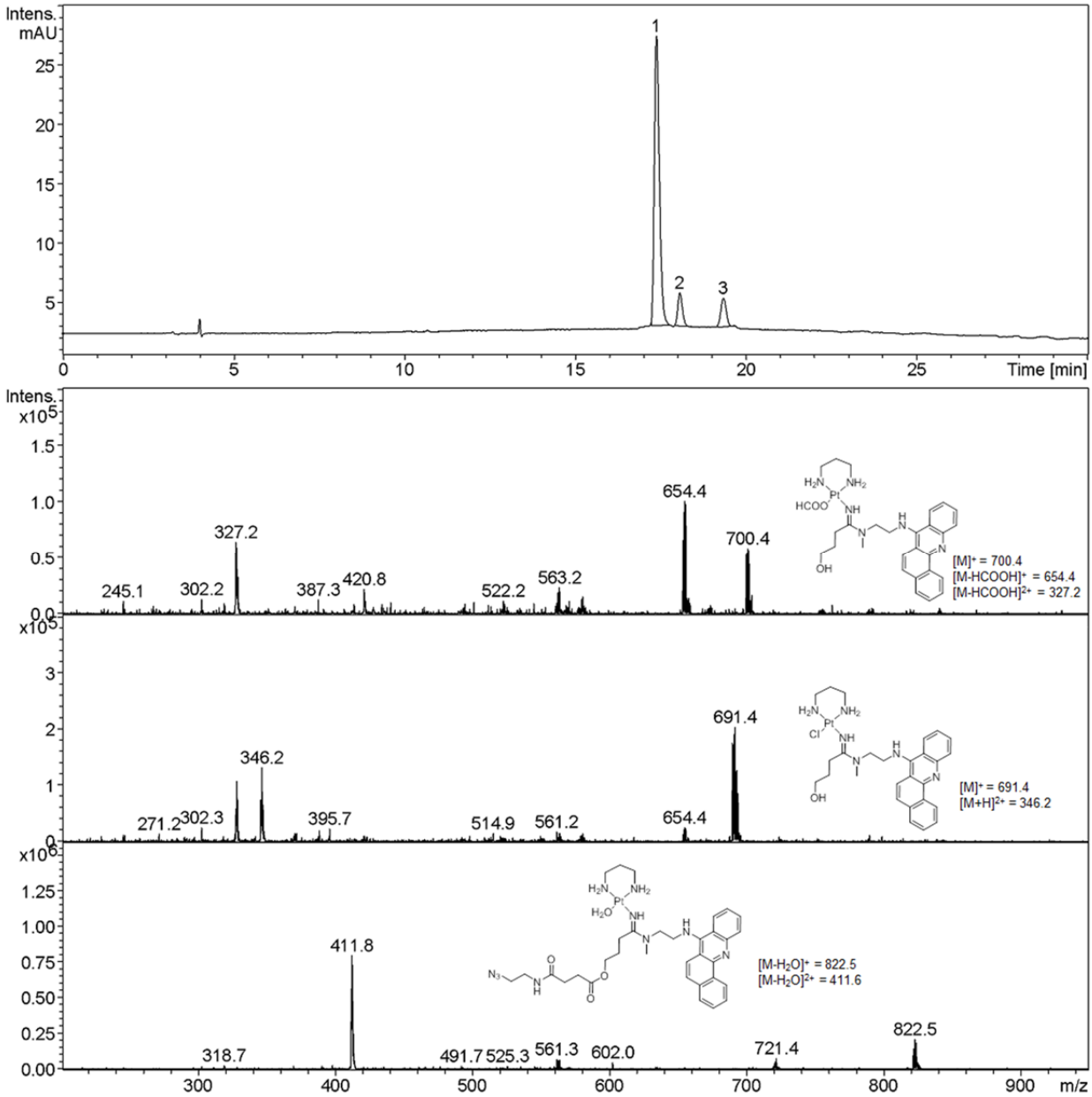


Figure S32. LC-ESMS analysis of the mixture of compound **P2-N1** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

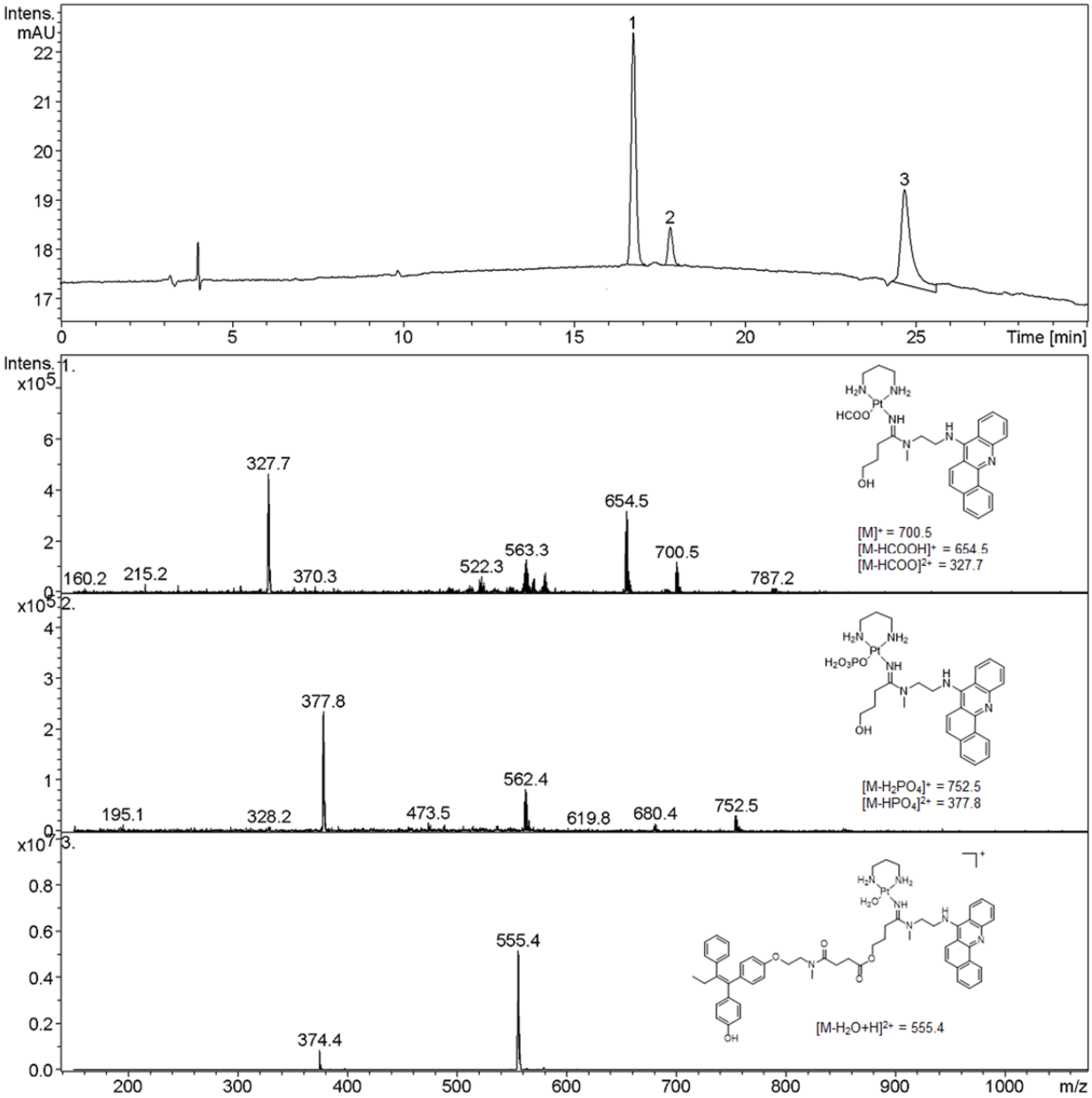


Figure S33. LC-ESMS analysis of the mixture of compound **P2-N6** in phosphate buffer (PB, pH 7.4) incubated at 37 °C.

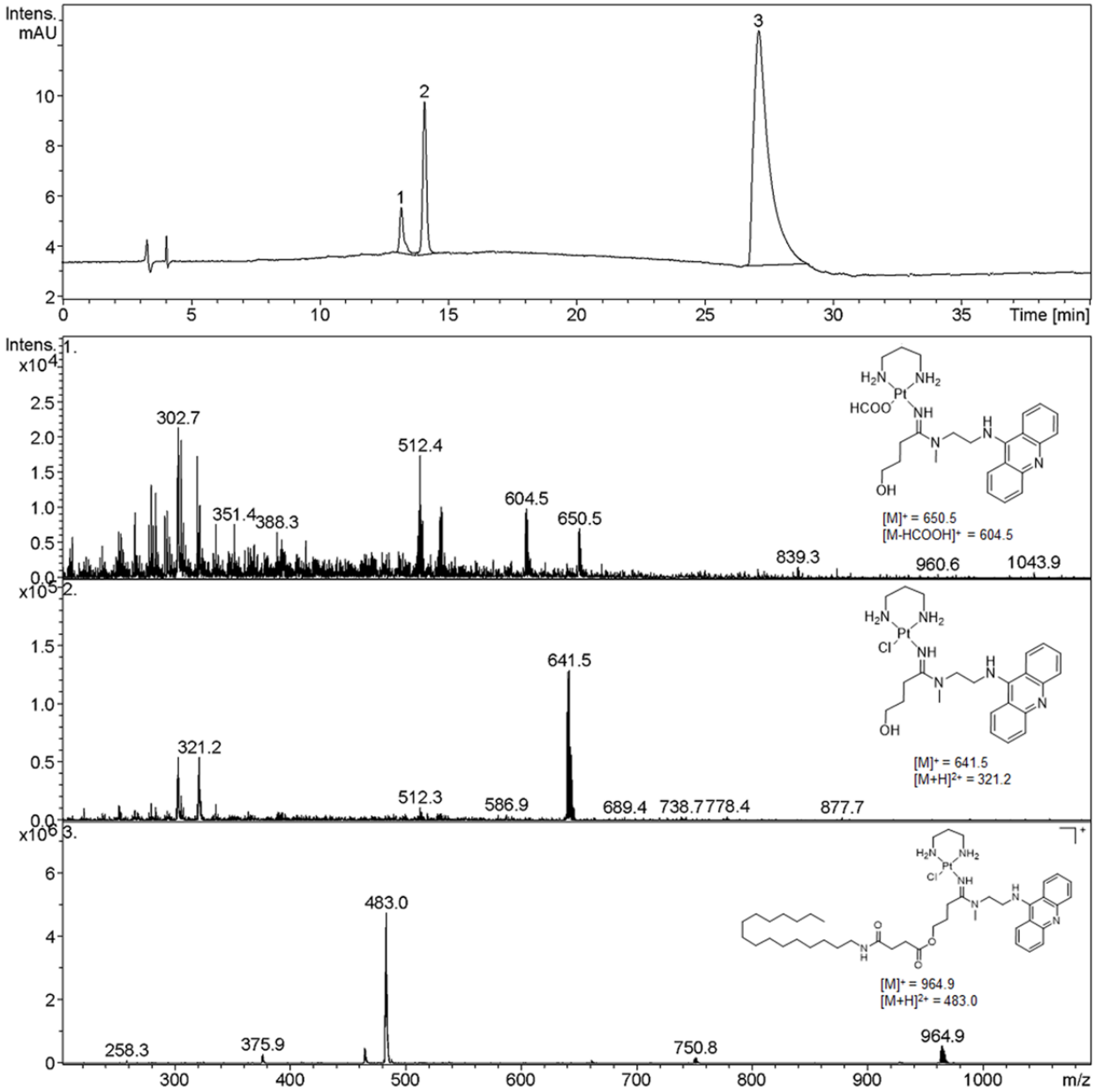


Figure S34. LC-ESMS analysis of the mixture of compound **P1-N2** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

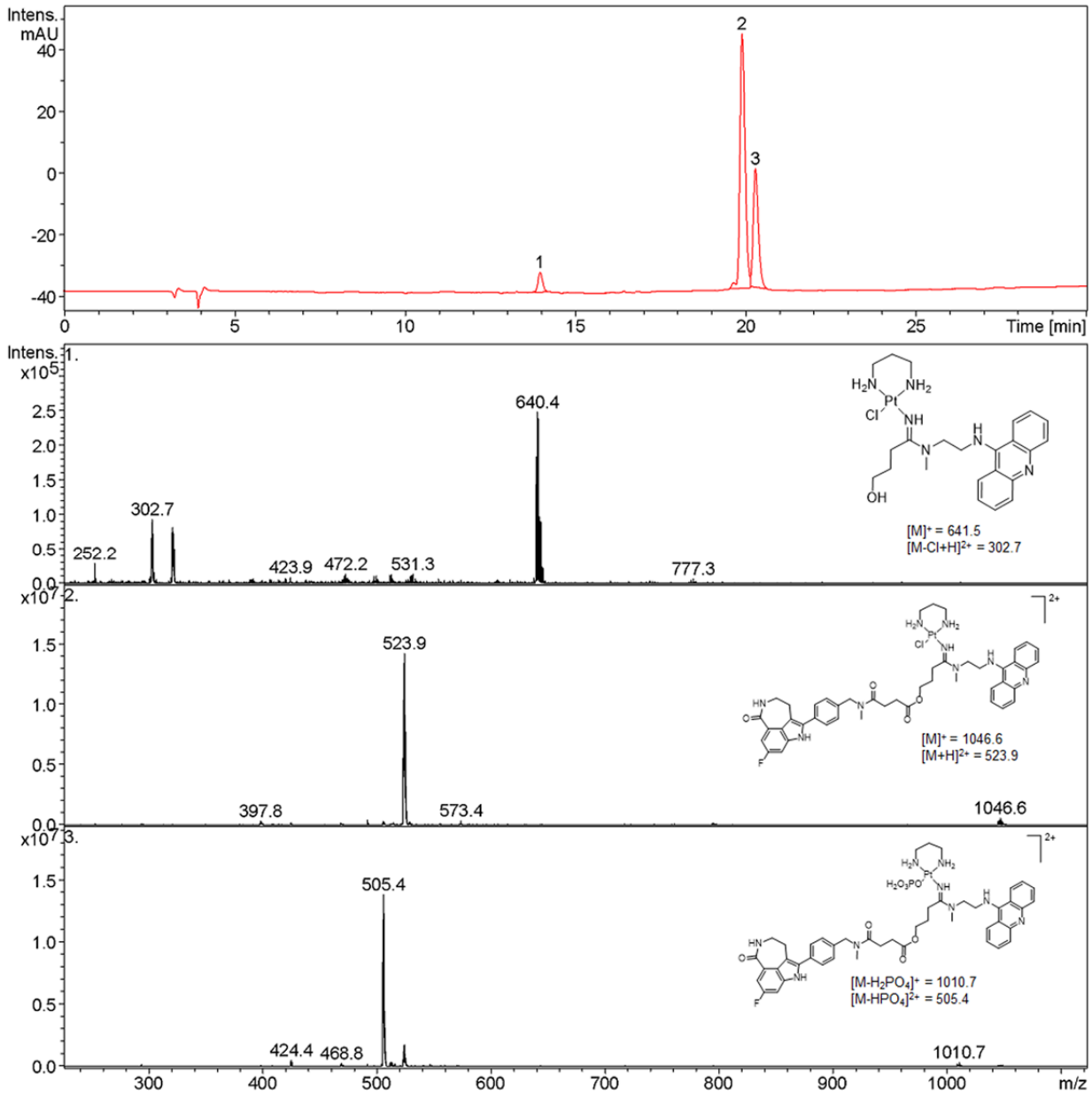


Figure S35. LC-ESMS analysis of the mixture of compound **P1-N5** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

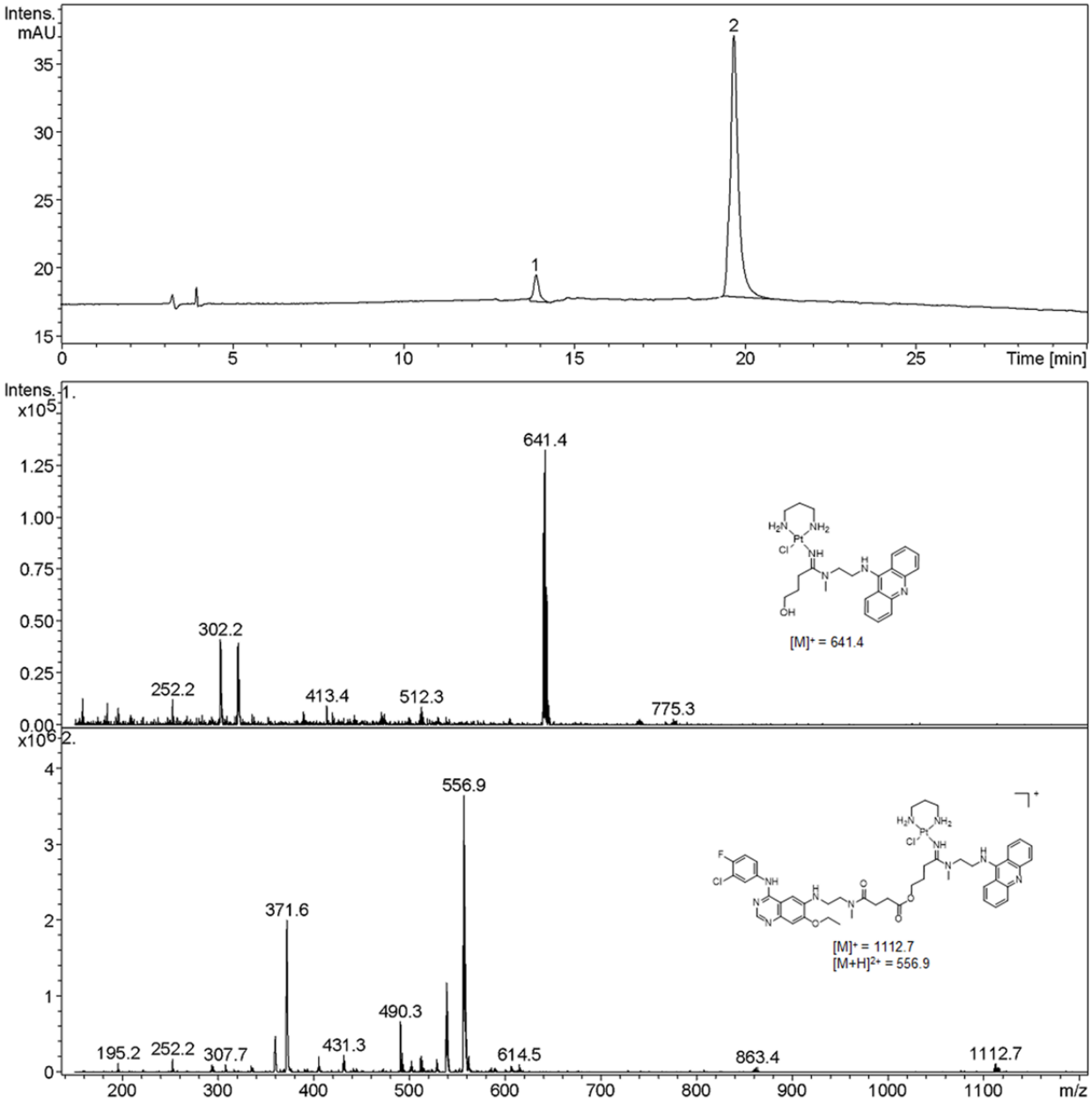


Figure S36. LC-ESMS analysis of the mixture of compound **P1-N7** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

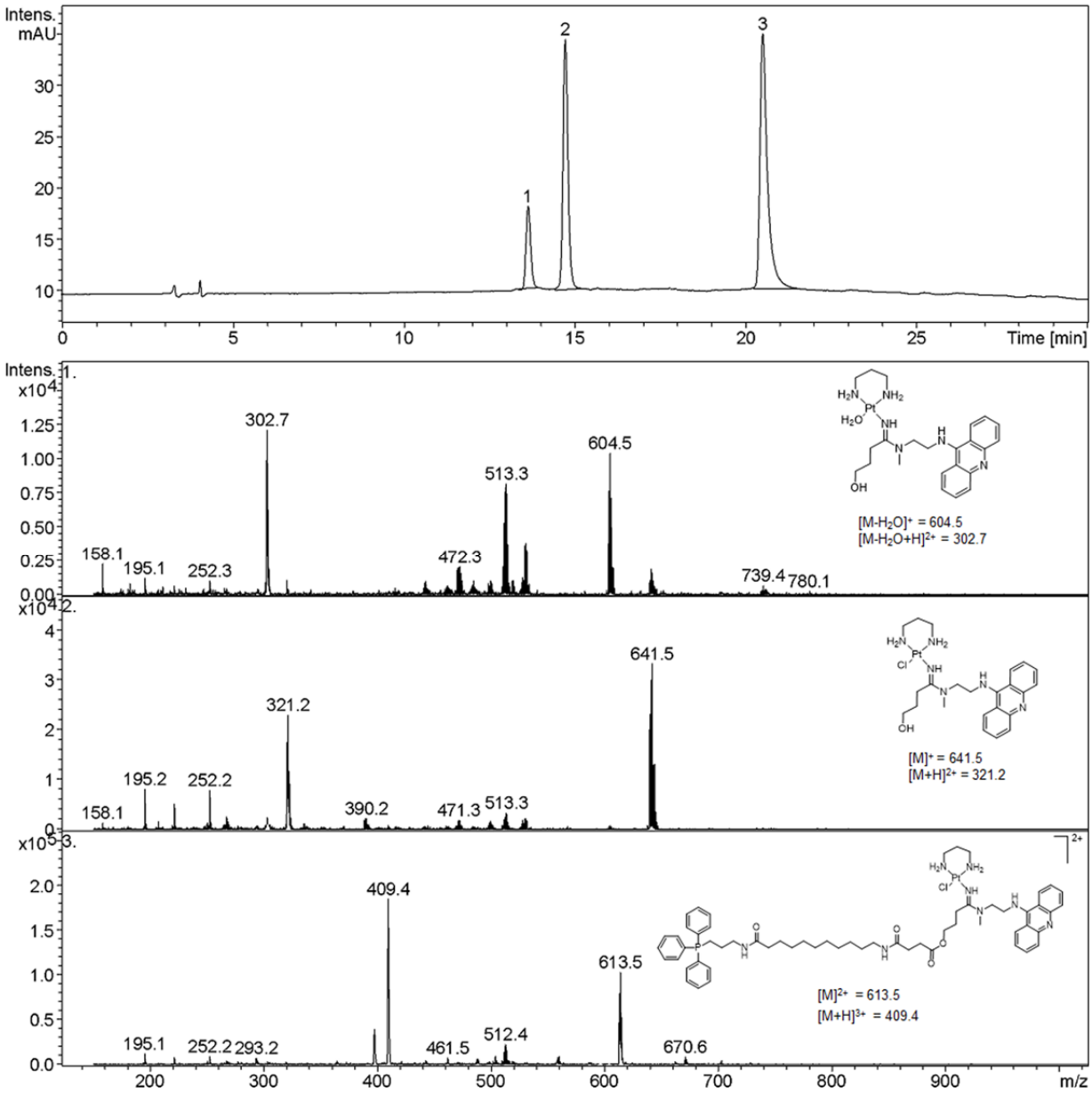


Figure S37. LC-ESMS analysis of the mixture of compound **P1-N9** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

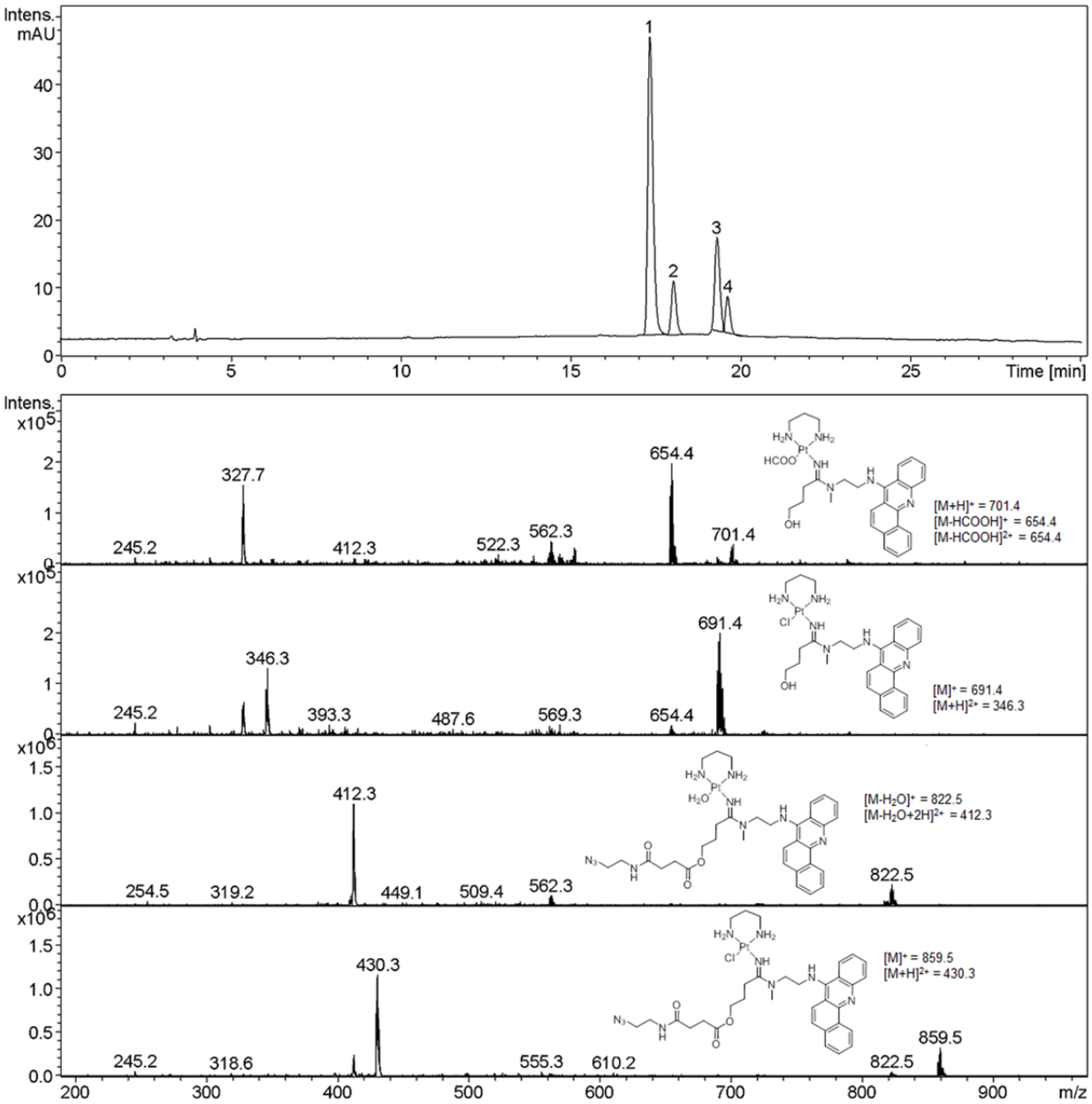


Figure S38. LC-ESMS analysis of the mixture of compound **P2-N1** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

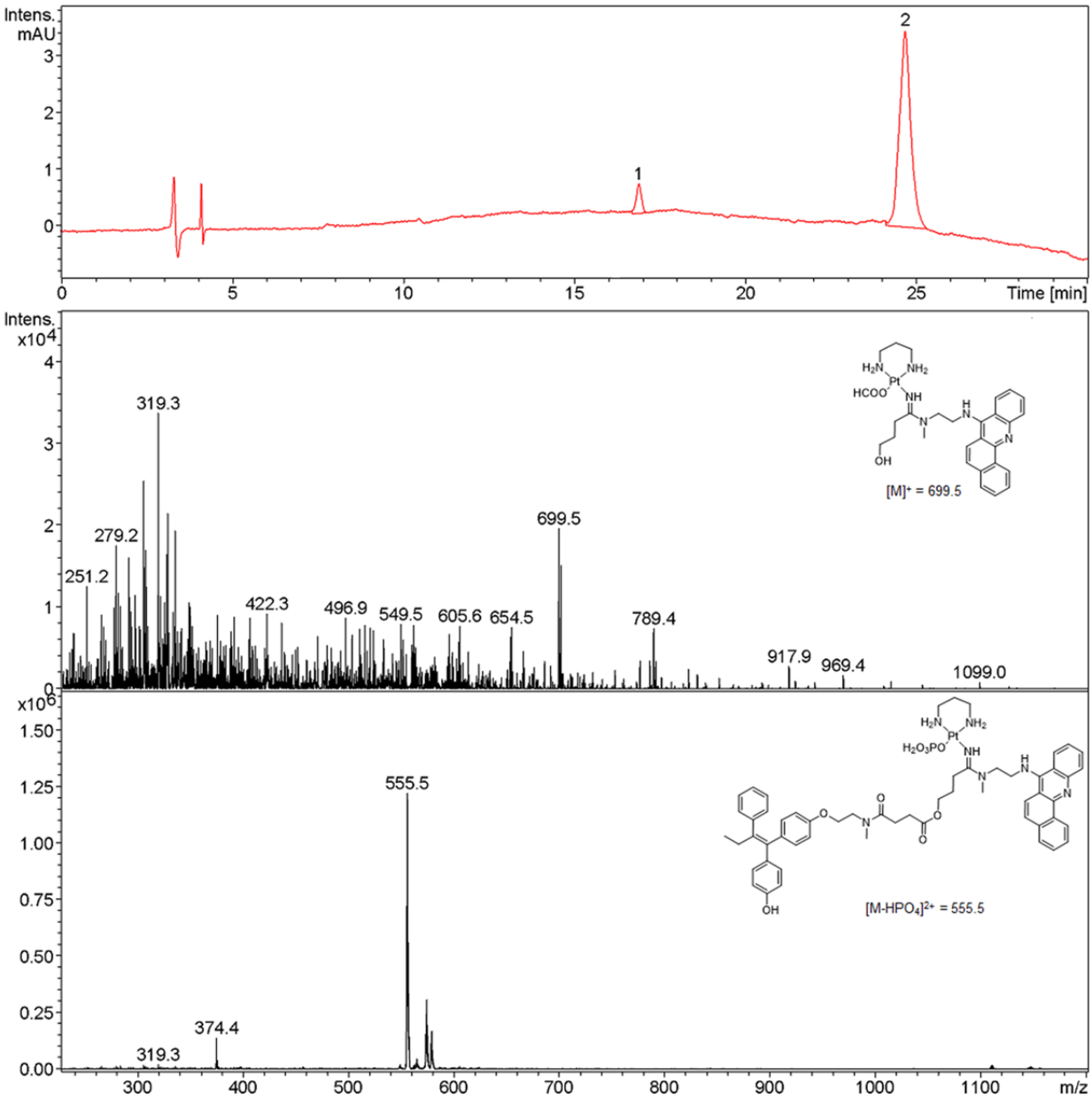
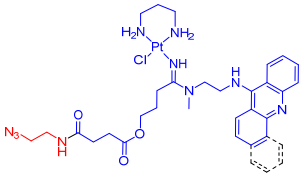
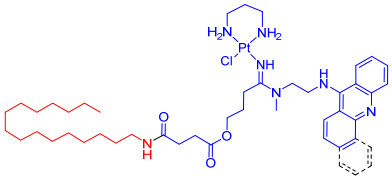
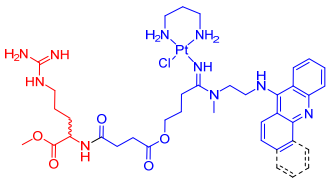
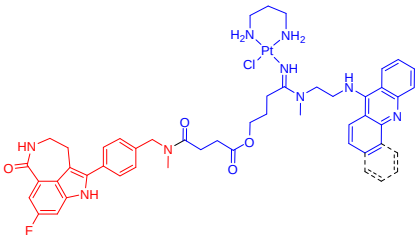
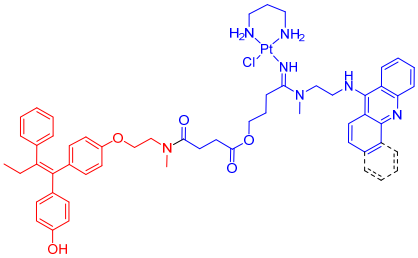
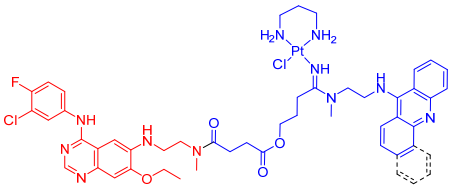
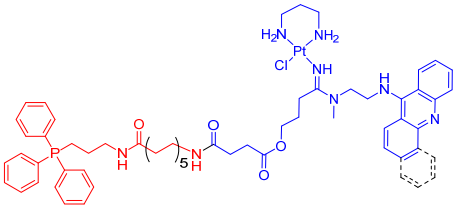


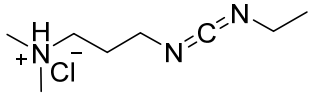
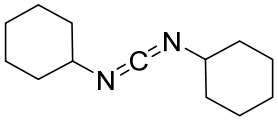
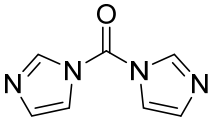
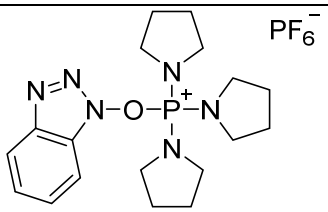
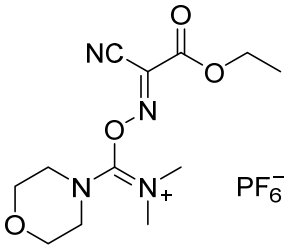
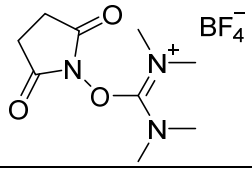
Figure S39. LC-ESMS analysis of the mixture of compound **P2-N6** in phosphate buffered saline (PBS, pH 7.4) incubated at 37 °C.

Table S1. Conversion Yields and HR-ESMS Results for Conjugates

Compd	Conjugate structures	Conv. (%) ± S.D.[a]	Calculated $[M]^+$	Observed $[M]^+$
P1-N1		98.9 ± 1.4	808.2778	808.2786
P2-N1		98.1 ± 1.7	858.2934	858.2940
P1-N2		96.6 ± 1.2	963.4955	963.4954
P2-N2		96.9 ± 2.3	1013.5111	1013.5125
P1-N4		99.5 ± 1.9	910.3458	910.3466
P2-N4		99.4 ± 1.1	960.3615	960.3610
P1-N5		96.4 ± 2.5	1045.3619	1045.3645
P2-N5		98.9 ± 1.4	1095.3776	1095.3784
P1-N6		97.1 ± 2.3	1095.4227	1095.4242
P2-N6		96.7 ± 0.9	1145.4383	1145.4391
P1-N7		97.8 ± 1.5	1111.3604	1111.3615
P2-N7		96.4 ± 2.5	1162.3760	1162.3744
P1-N9		99.8 ± 0.2	612.7688	612.7696
P2-N9		99.7 ± 0.5	637.7766 (2+)[b]	637.7769 (2+)[b]

[a] Each reaction was performed in triplicate. The conversion yields were determined from HPLC traces recorded at an acridine-specific wavelength. Reactions with conversion yields lower than 90% are not reported. [b] Singly charged $[M]^+$ not observed in positive-ion mode. The additional fused ring in the benz[c]acridine derivatives (**P2**) is shown as dashed bonds.

Table S2. Summary of Coupling Reagents Used

Acronym, Common Name	System. Nomenclature	Structure
EDC	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride	
DCC	*N,N'*-Dicyclohexylcarbodiimide	
CDI	1,1'-Carbonyldiimidazole	
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate	
COMU	1-[(1-(Cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate	
TSTU	O-(*N*-Succimidinyl)- *N,N,N',N'*-tetramethyluronium tetrafluoroborate	
HBTU	*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate