# Supporting Information

## Design of a Novel Pt(II) Complex to Reverse Cisplatin-Induced Resistance in Lung Cancer via Multi-mechanism

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Tab. S1 Crystal data of the Pt(II) complexes

| Pt (II) complexes | **C1** | **C2** | **C3** | **C4** | **C5** | **C6** |
|---|---|---|---|---|---|---|
| Empirical formula | $C_{12}H_{18}N_8O_2PtS_4$ | $C_{12}H_{14}N_8PtS_4$ | $C_{22}H_{18}N_8PtS_4$ | $C_{24}H_{23}N_8PtS_4$ | $C_{18}H_{26}N_8PtS_4$ | $C_{14}H_{18}N_8PtS_4$ |
| Formula weight | 629.67 | 593.64 | 717.77 | 746.83 | 677.8 | 621.69 |
| Crystal system | orthorhombic | monoclinic | monoclinic | triclinic | monoclinic | monoclinic |
| Space group | Pbca | $P2_1/n$ | $P2_1/n$ | P-1 | $P2_1/n$ | $P2_1/c$ |
| a/Å | 12.0032(7) | 4.0079(3) | 8.35800(10) | 8.8378(6) | 9.62910(10) | 8.8524(2) |
| b/Å | 9.1694(4) | 17.0621(10) | 9.46980(10) | 11.4663(9) | 8.75510(10) | 4.00670(10) |
| c/Å | 19.1587(12) | 12.9516(6) | 16.0146(2) | 14.3741(12) | 14.4580(2) | 27.1392(6) |
| α/° | 90 | 90 | 90 | 68.768(8) | 90 | 90 |
| β/° | 90 | 95.180(5) | 99.0950(10) | 82.547(6) | 91.1320(10) | 90.532(2) |
| γ/° | 90 | 90 | 90 | 78.354(6) | 90 | 90 |
| Volume/Å$^3$ | 2108.65(19) | 882.06(9) | 1251.60(3) | 1327.25(19) | 1218.63(3) | 962.56(4) |
| Z | 4 | 2 | 2 | 2 | 2 | 2 |
| GOOF | 1.171 | 1.025 | 1.104 | 0.997 | 1.03 | 1.116 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0464, $wR_2$ = 0.0877 | $R_1$ = 0.0342, $wR_2$ = 0.0741 | $R_1$ = 0.0231, $wR_2$ = 0.0617 | $R_1$ = 0.0463, $wR_2$ = 0.0773 | $R_1$ = 0.0399, $wR_2$ = 0.0996 | $R_1$ = 0.0282, $wR_2$ = 0.0757 |
| Final R indexes [all data] | $R_1$ = 0.0799, $wR_2$ = 0.0965 | $R_1$ = 0.0524, $wR_2$ = 0.0847 | $R_1$ = 0.0251, $wR_2$ = 0.0631 | $R_1$ = 0.0861, $wR_2$ = 0.0957 | $R_1$ = 0.0412, $wR_2$ = 0.1015 | $R_1$ = 0.0306, $wR_2$ = 0.0778 |
| CCDC.No | 2015666 | 2015667 | 2015669 | 2015670 | 2015671 | 2015668 |

Tab. S2 Bond Angles /° for **C1-C6**.

| | **C1** | **C2** | **C3** | **C4** | **C5** | **C6** |
|---|---|---|---|---|---|---|
| $S1^1$-Pt1-S1 | 180.0 | 180.0 | 180.0 | 180.0 | 180.0 | 180.0 |
| $N2^1$-Pt1-S1 | 83.1(2) | 82.98(17) | 97.33(7) | 82.7(2) | 97.69(7) | 97.25(10) |
| N2-Pt1-S1 | 96.9(2) | 97.02(17) | 82.67(7) | 97.3(2) | 82.31(7) | 82.75(10) |
| N2-Pt1- $S1^1$ | 83.1(2) | 82.98(17) | 97.33(7) | 82.7(2) | 97.69(7) | 97.25(10) |
| $N2^1$-Pt1-$S1^1$ | 96.9(2) | 97.02(17) | 82.67(7) | 97.3(2) | 82.31(7) | 82.75(10) |
| $N2^1$-Pt1-N2 | 180.0 | 180.0 | 180.0 | 180.0 | 180.0 | 180.0 |

Tab. S3 Bond Lengths /Å for **C1-C6**

| | **C1** | **C2** | **C3** | **C4** | **C5** | **C6** |
|---|---|---|---|---|---|---|
| Pt1-S1 | 2.288(3) | 2.2968(19) | 2.2800(9) | 2.294(3) | 2.2800(8) | 2.2867(10) |
| Pt1-S1[1] | 2.288(3) | 2.2969(19) | 2.2800(9) | 2.294(3) | 2.2800(8) | 2.2867(10) |
| Pt1-N2 | 2.015(8) | 2.023(6) | 2.022(2) | 2.012(7) | 2.024(3) | 2.020(3) |
| Pt1-N2[1] | 2.015(8) | 2.023(6) | 2.022(2) | 2.012(7) | 2.024(3) | 2.020(3) |

Tab. S4 $IC_{50}$ values of the tested compounds against different cell lines for 72 h.

| Complexes | $IC_{50}$ (μM)[a] | | |
|---|---|---|---|
| | A549 | A549cisR | HL-7702 |
| $K_2PtCl_4$ | ＞40 | ＞40 | ＞40 |
| **L1** | ＞40 | ＞40 | ＞40 |
| **L2** | 38.63 ± 2.09 | ＞40 | ＞40 |
| **L3** | 31.74 ± 1.93 | ＞40 | ＞40 |
| **L4** | 27.98 ± 1.79 | ＞40 | ＞40 |
| **L5** | 25.68 ± 1.28 | 38.26 ± 1.87 | ＞40 |
| **L6** | 23.09 ± 1.02 | 33.55 ± 1.64 | 31.26 ± 1.17 |
| **C1** | 9.43 ± 0.44 | 13.35 ± 0.52 | 18.73 ± 0.83 |
| **C2** | 7.92 ± 0.31 | 11.50 ± 0.41 | 16.68 ± 0.67 |
| **C3** | 7.03 ± 0.28 | 8.11 ± 0.30 | 13.13 ± 0.45 |
| **C4** | 6.26 ± 0.21 | 7.36 ± 0.41 | 11.52 ± 0.54 |
| **C5** | 4.49 ± 0.18 | 6.65 ± 0.32 | 9.25 ± 0.43 |
| **C6** | 2.55 ± 0.12 | 3.18 ± 0.17 | 7.09 ± 0.31 |
| Cisplatin | 8.15 ± 0.39 | 25.97 ± 0.85 | 7.14 ± 0.22 |

Table S5 Acute toxicity of **C6** (alive/total)

| | 5 μmol/kg | 10 μmol/kg | 15 μmol/kg | 20 μmol/kg | 25 μmol/kg |
|---|---|---|---|---|---|
| **C6** | 10/10 | 3/10 | 5/10 | 6/10 | 9/10 |

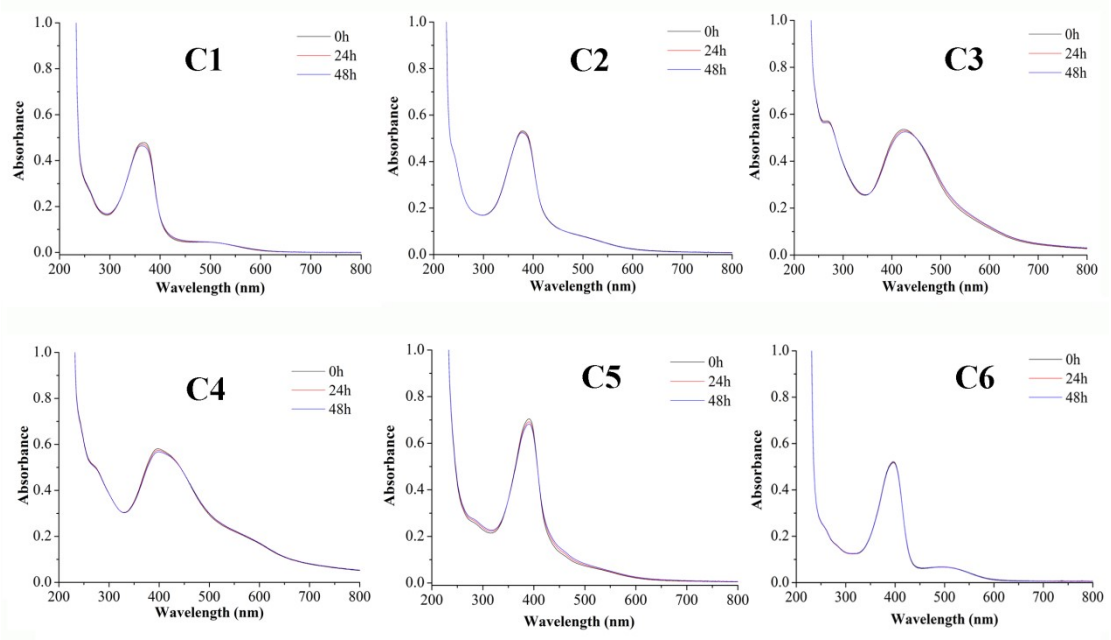


**Fig. S1** The stability of UV-Vis spectra of the complexes (**C1-C6**) in PBS at different times.

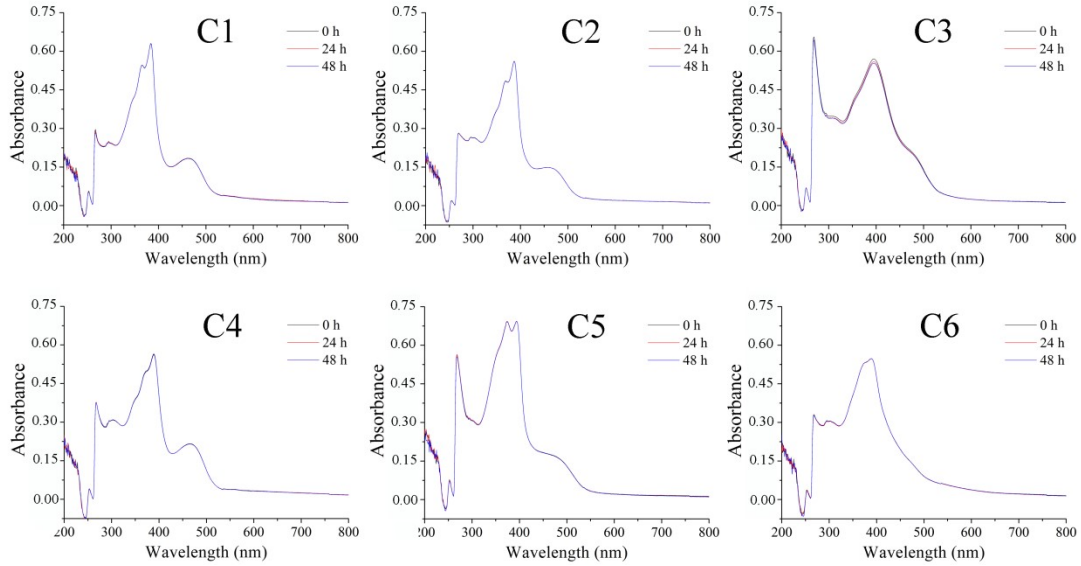


**Fig. S2** The stability of UV-Vis spectra of the complexes (**C1-C6**) in DMEM at different times.

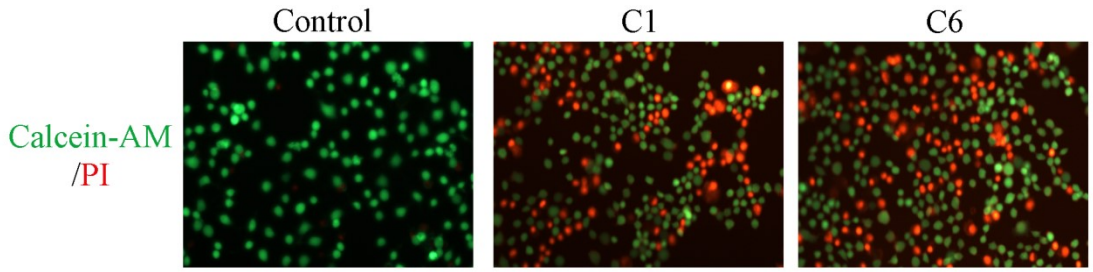


**Fig. S3** Detection of cytotoxicity after C1 and C6 (5 μM) treatment using fluorescent probes (double staining with calcein-AM/PI) for 24 h.

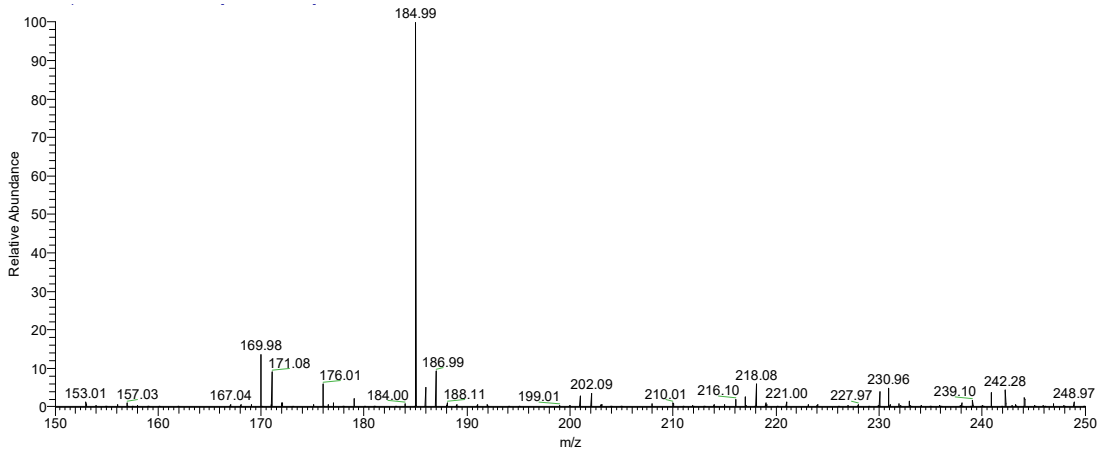


**Fig. S4** The ESI-MS of **L1**.

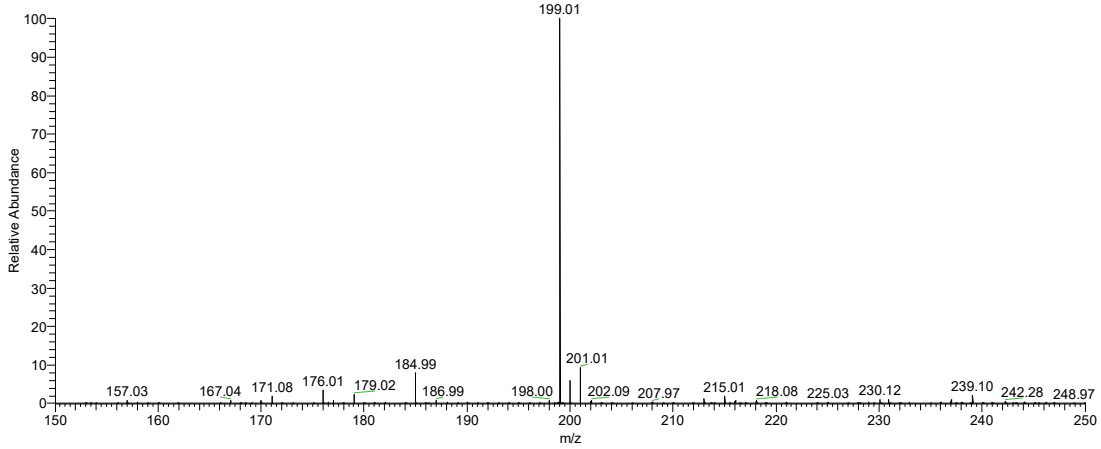


**Fig. S5** The ESI-MS of **L2**.

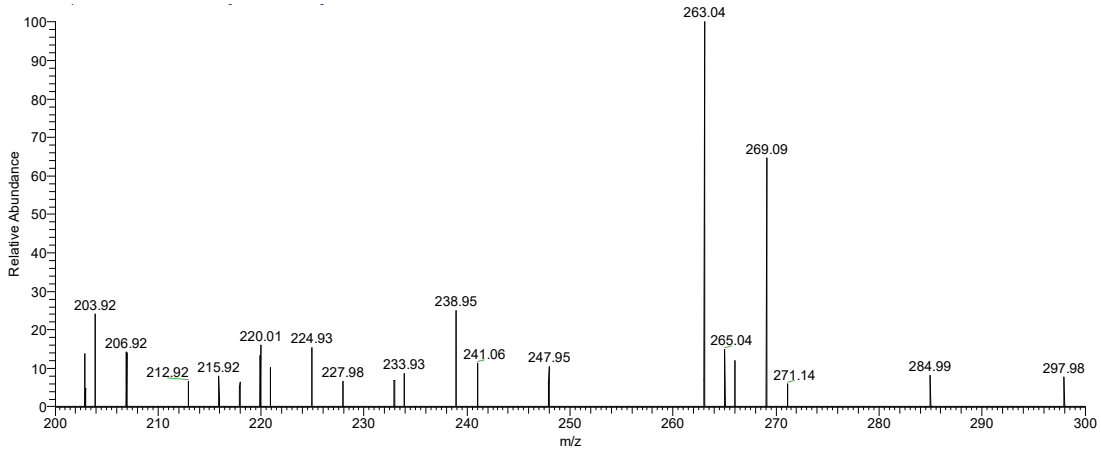


**Fig. S6** The ESI-MS of **L3**.

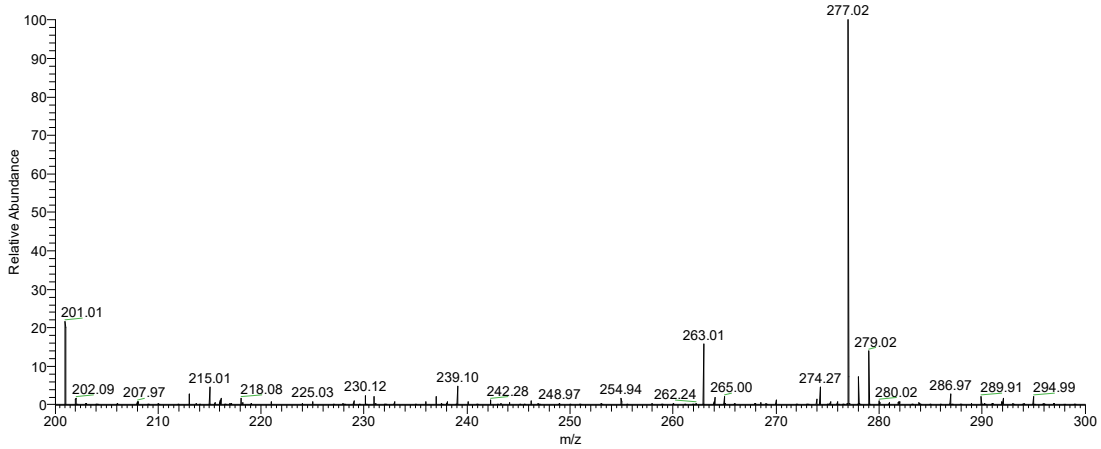


**Fig. S7** The ESI-MS of **L4**.

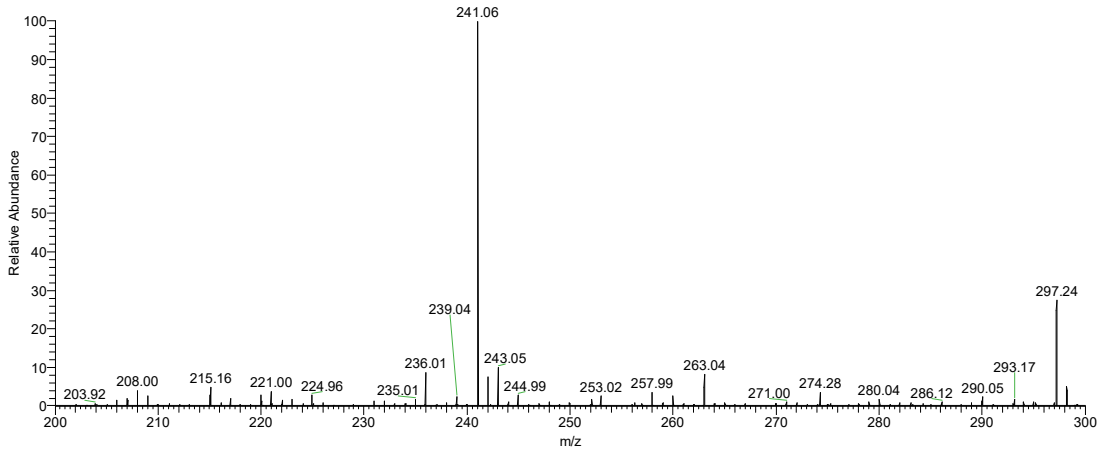


**Fig. S8** The ESI-MS of **L5**.

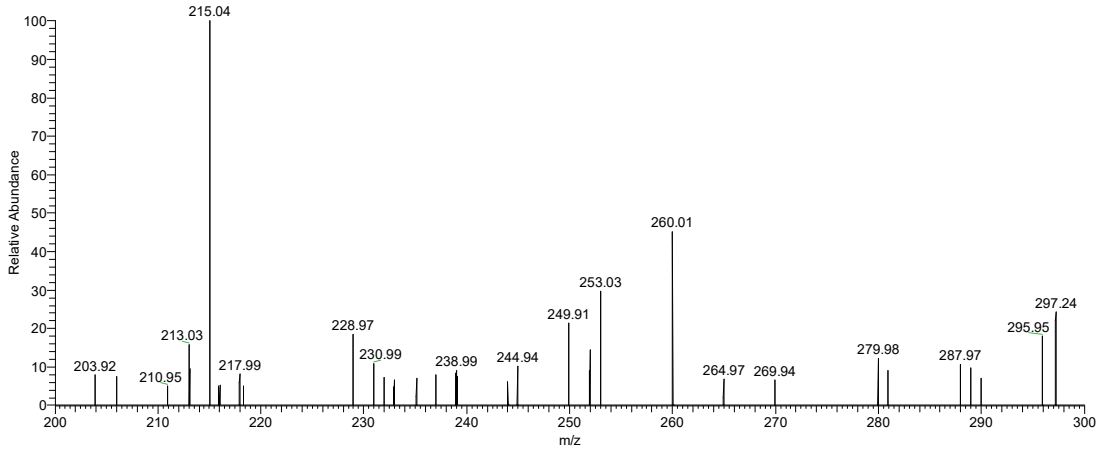


**Fig. S9** The ESI-MS of **L6**.

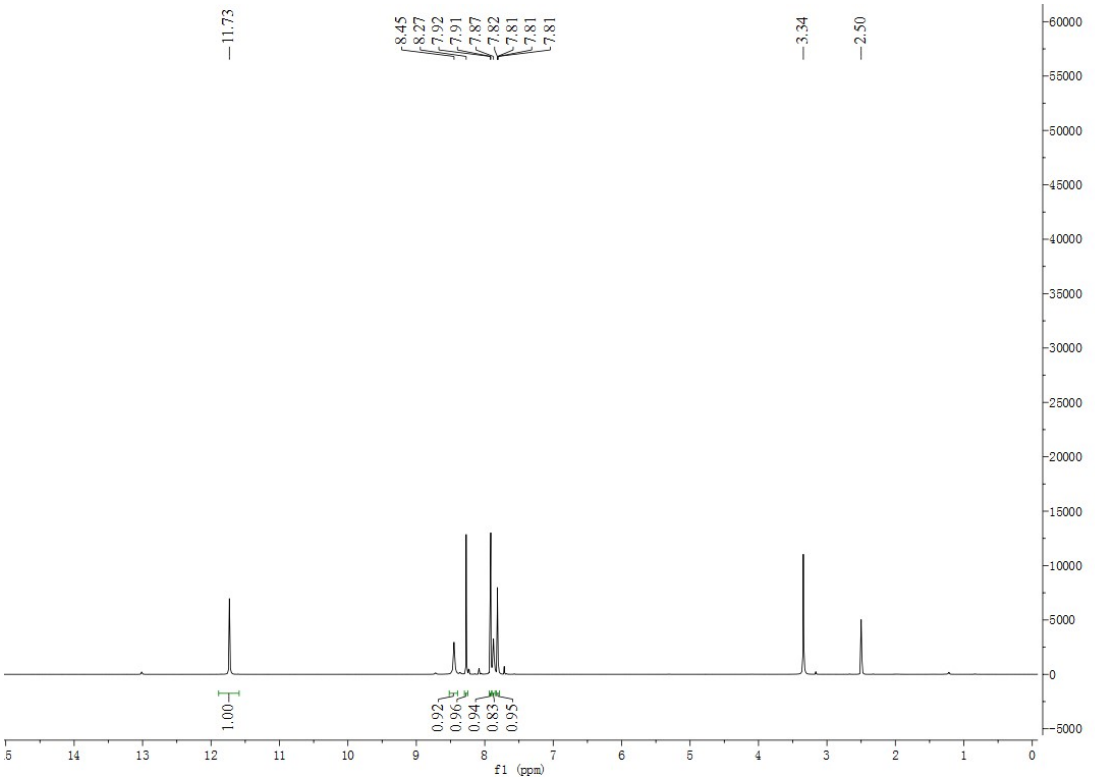


**Fig. S10** $^{1}$H NMR spectrum of **L1**.

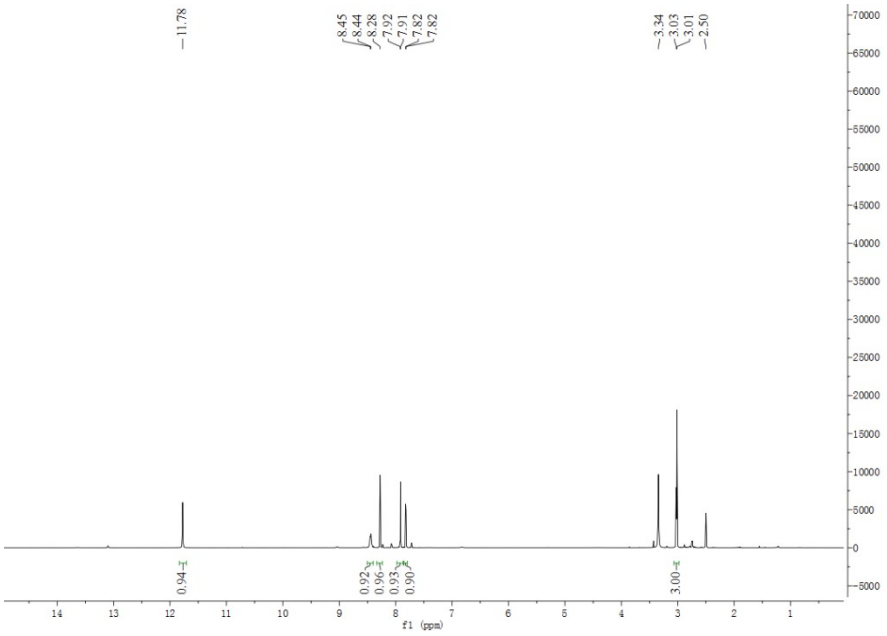


**Fig. S11** $^{1}$H NMR spectrum of **L2**.

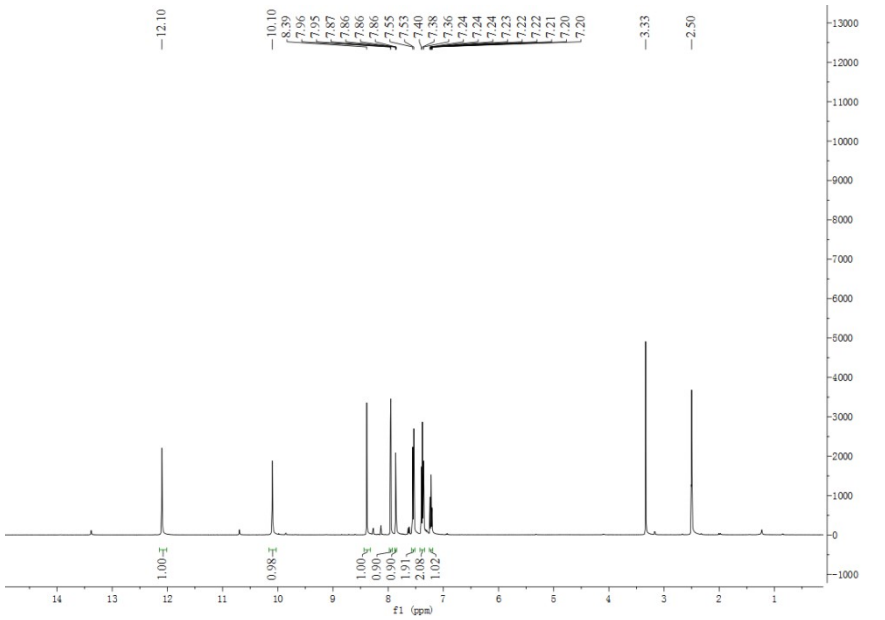


**Fig. S12** $^{1}$H NMR spectrum of **L3**.

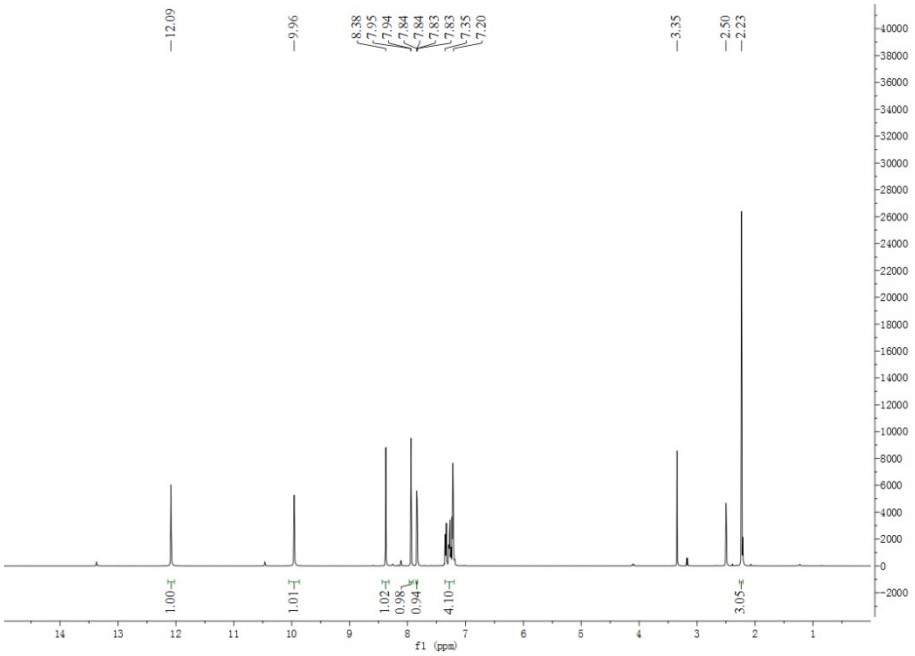


**Fig. S13** $^{1}$H NMR spectrum of **L4**.

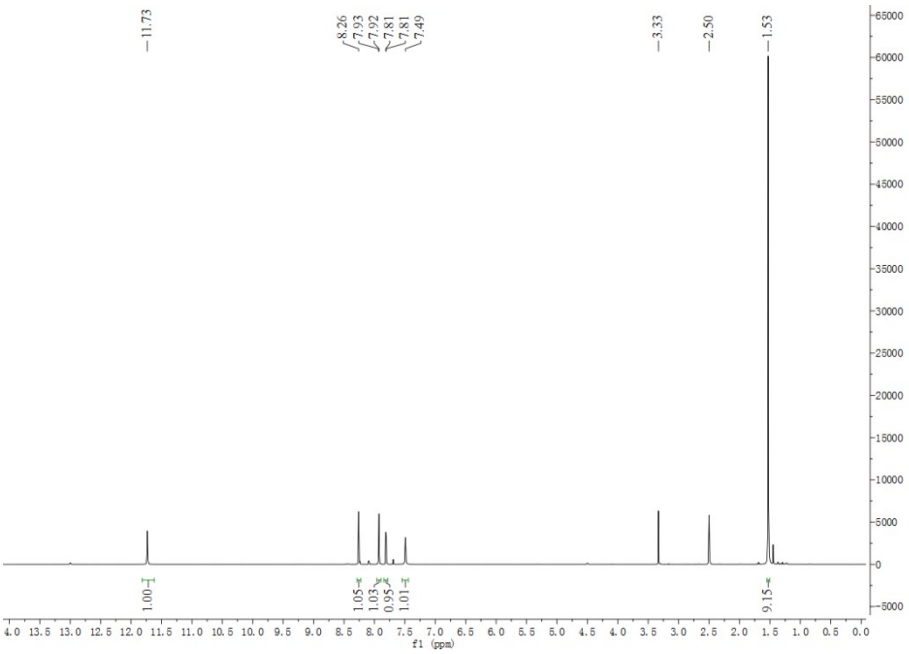


**Fig. S14** $^{1}$H NMR spectrum of **L5**.

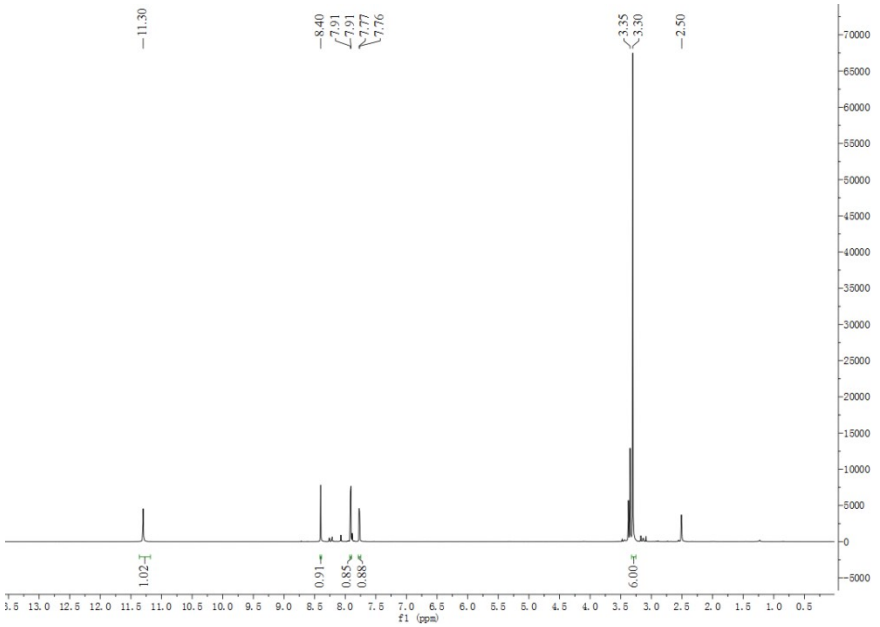


**Fig. S15** $^{1}$H NMR spectrum of **L6**.

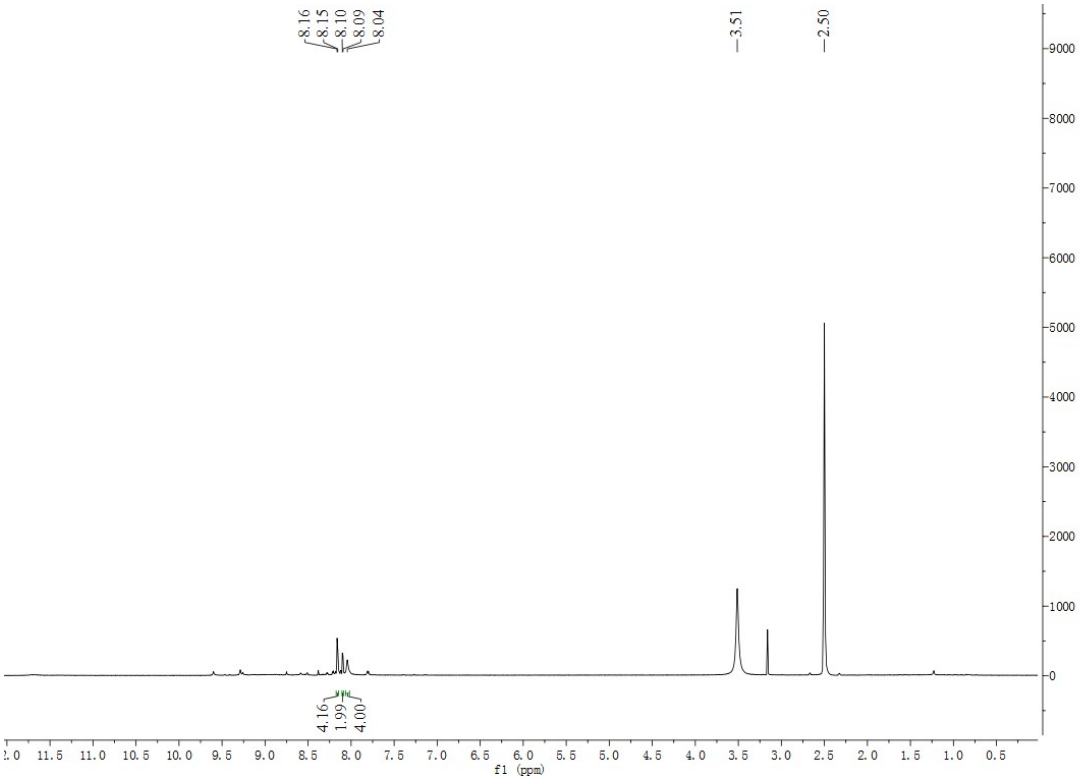


**Fig. S16** $^{1}$H NMR spectrum of **C1**.

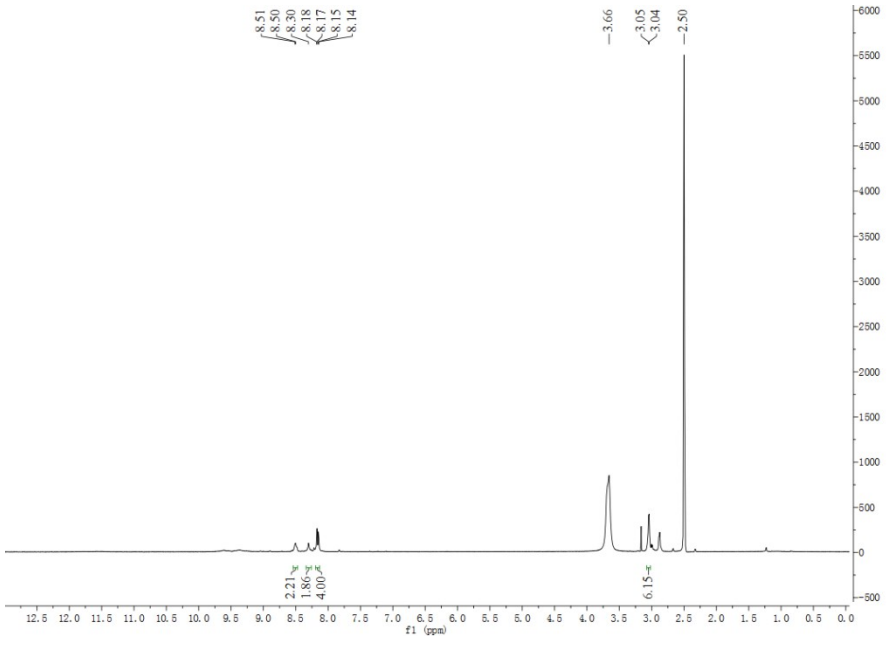


**Fig. S17** $^{1}$H NMR spectrum of **C2**.

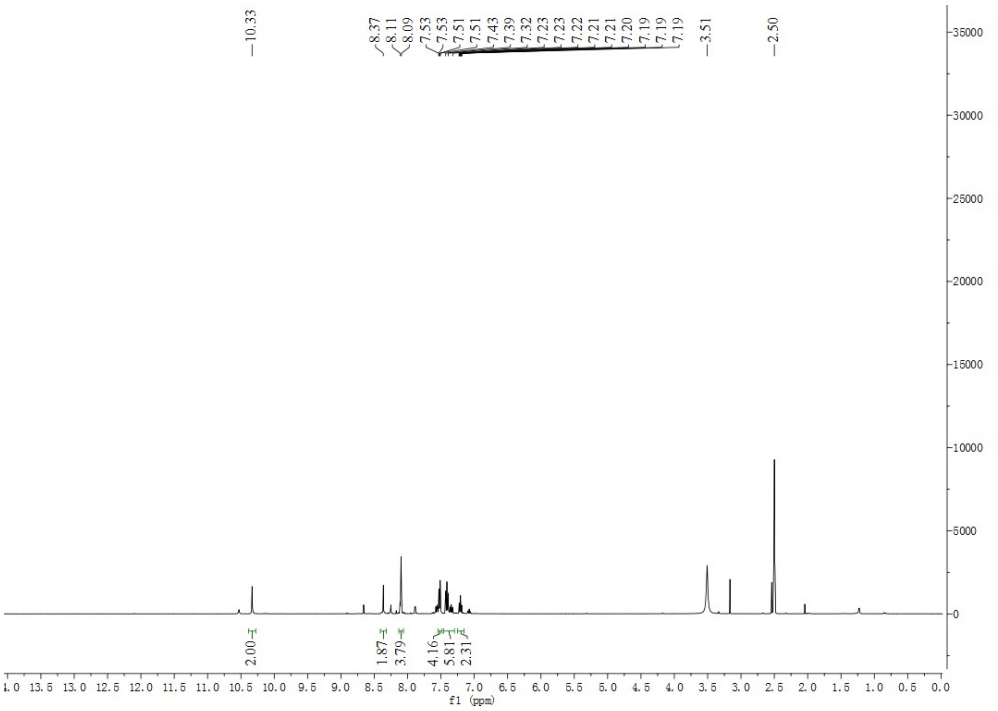


**Fig. S18** $^{1}$H NMR spectrum of **C3**.

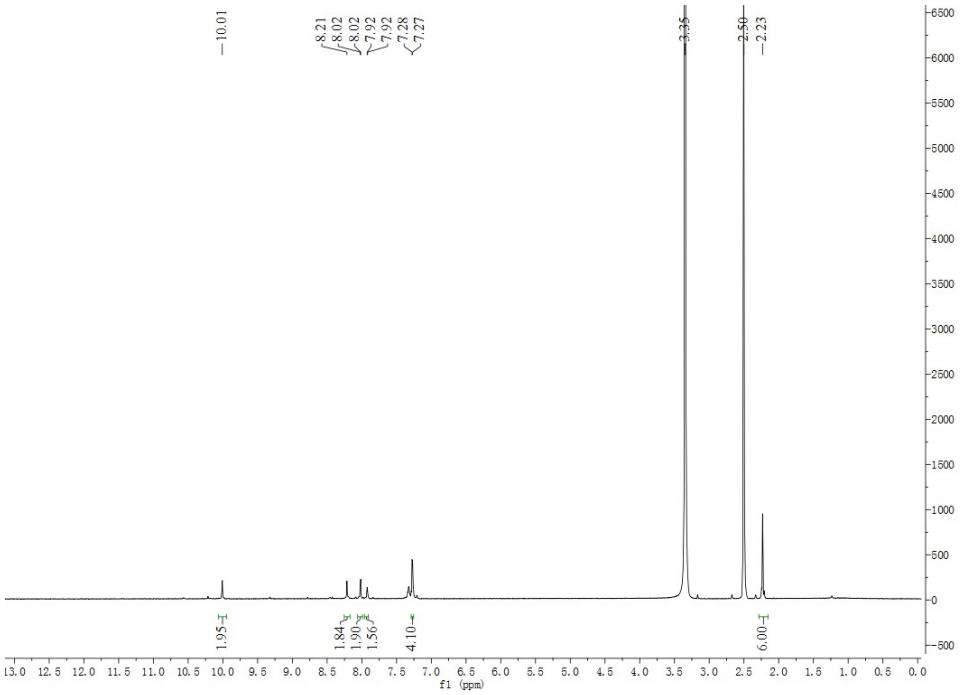


**Fig. S19** $^{1}$H NMR spectrum of **C4**.

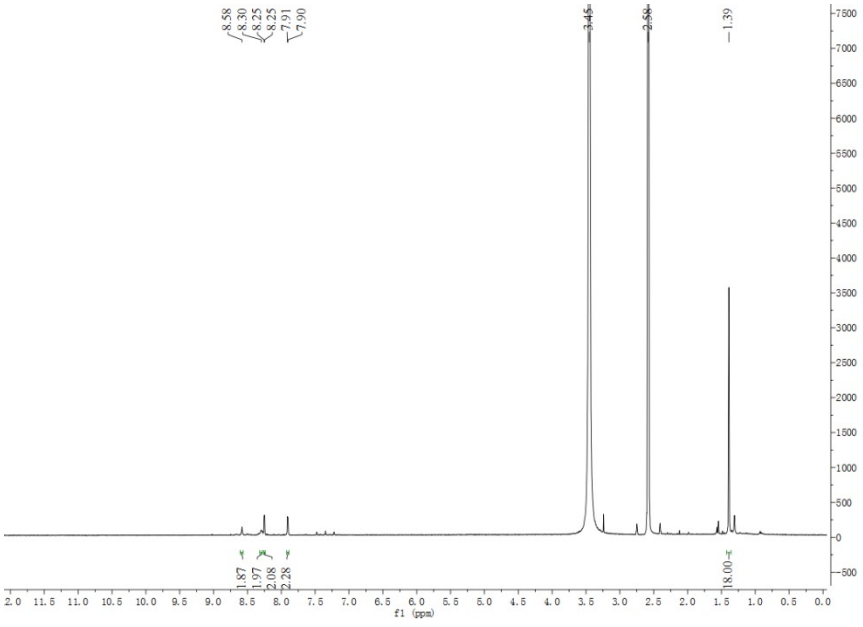


**Fig. S20** $^{1}$H NMR spectrum of **C5**.

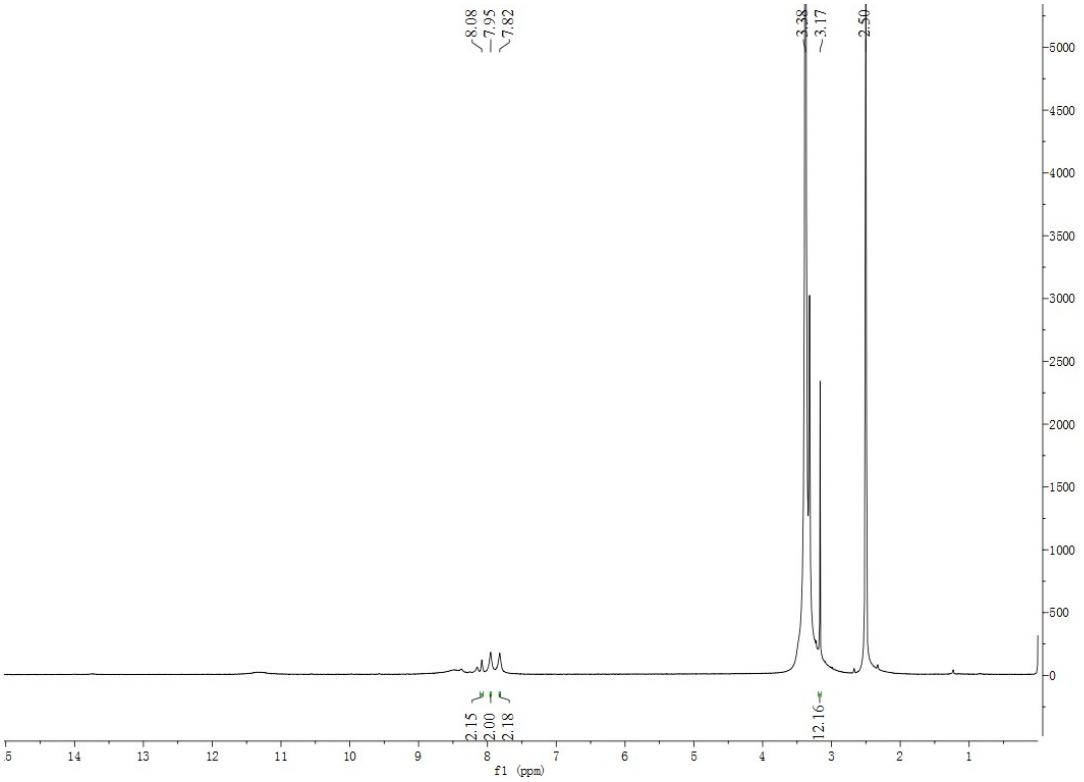


**Fig. S21** $^{1}$H NMR spectrum of **C6**.

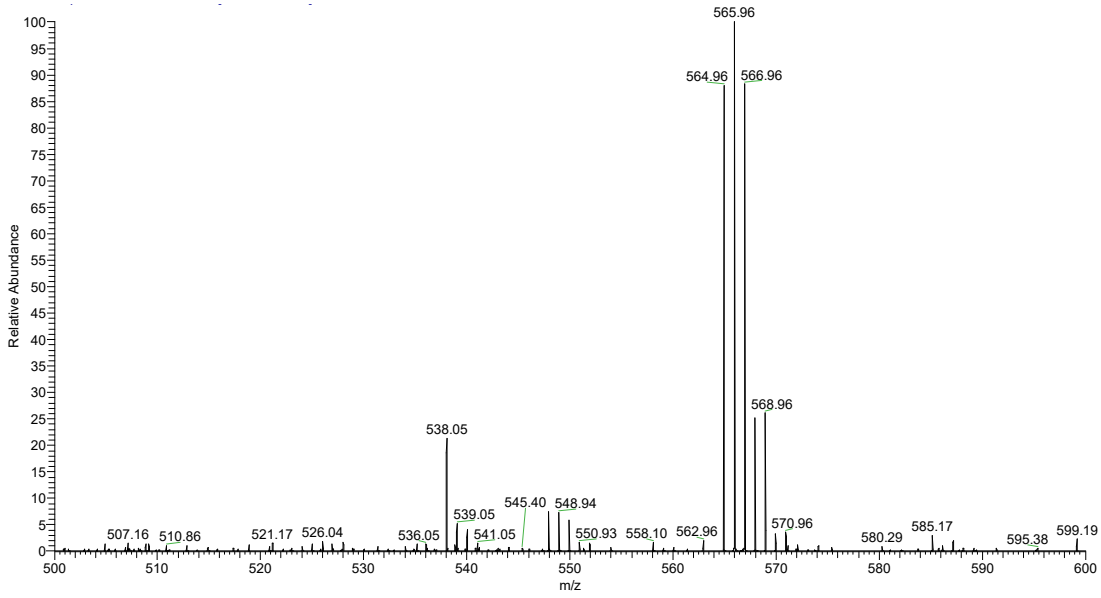


**Fig. S22** The ESI-MS of **C1**.

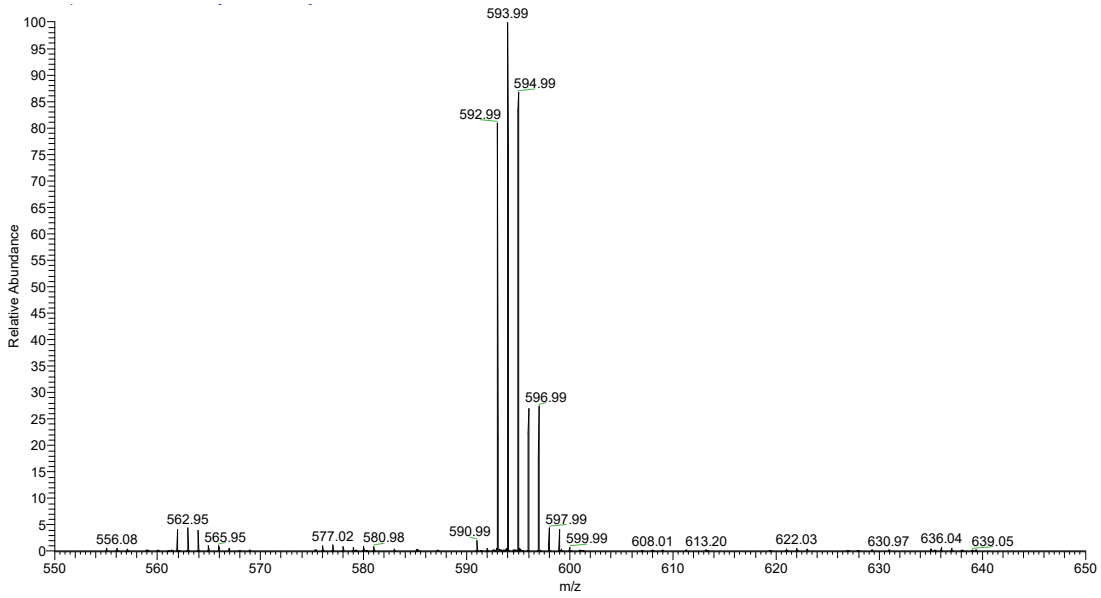


**Fig. S23** The ESI-MS of **C2**.

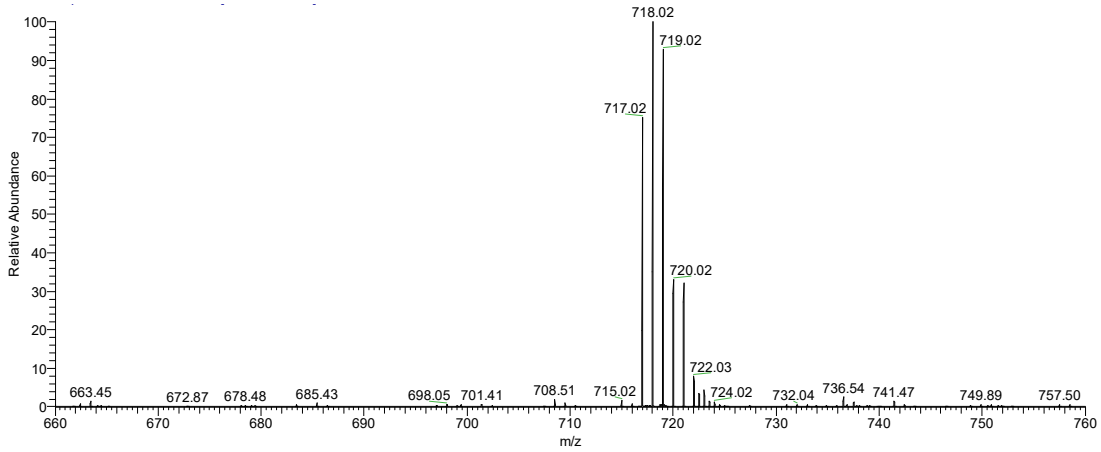


**Fig. S24** The ESI-MS of **C3**.

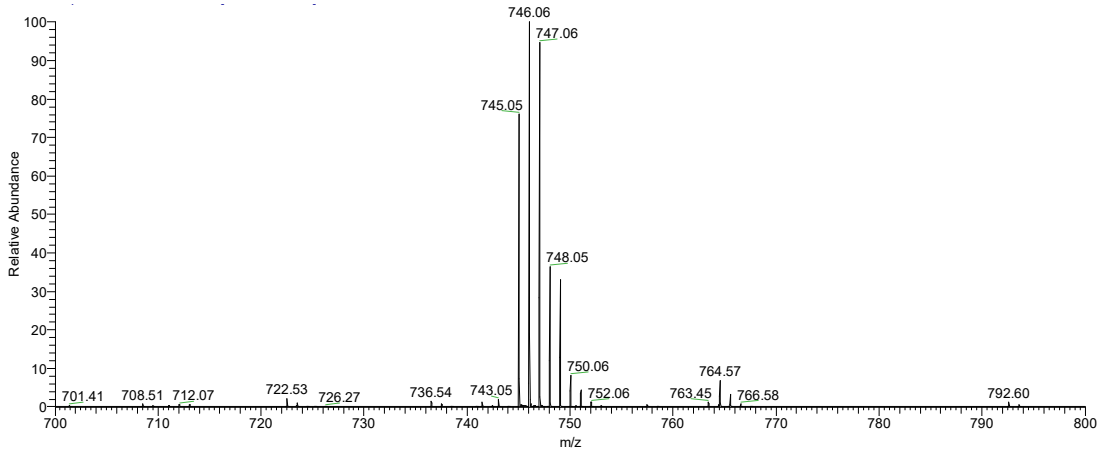


**Fig. S25** The ESI-MS of **C4**.

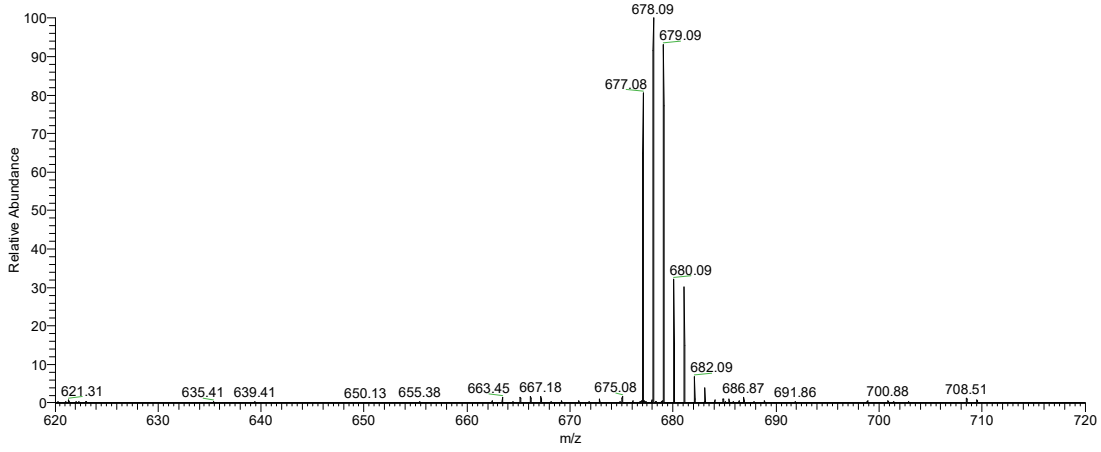


**Fig. S26** The ESI-MS of **C5**.

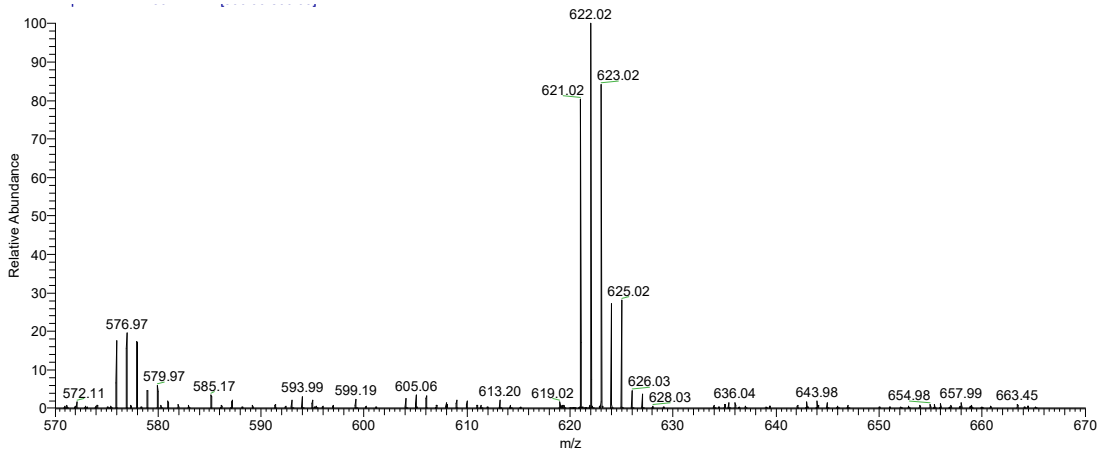


**Fig. S27** The ESI-MS of **C6**.