Electronic Supplementary Material (ESI) for RSC Advances.
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Evaluation of Iridium(III)-based Metallodrugs with multi-target in antimicrobial resistance combat and infection therapy caused by *Staphylococcus aureus*

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Supplementary Materials

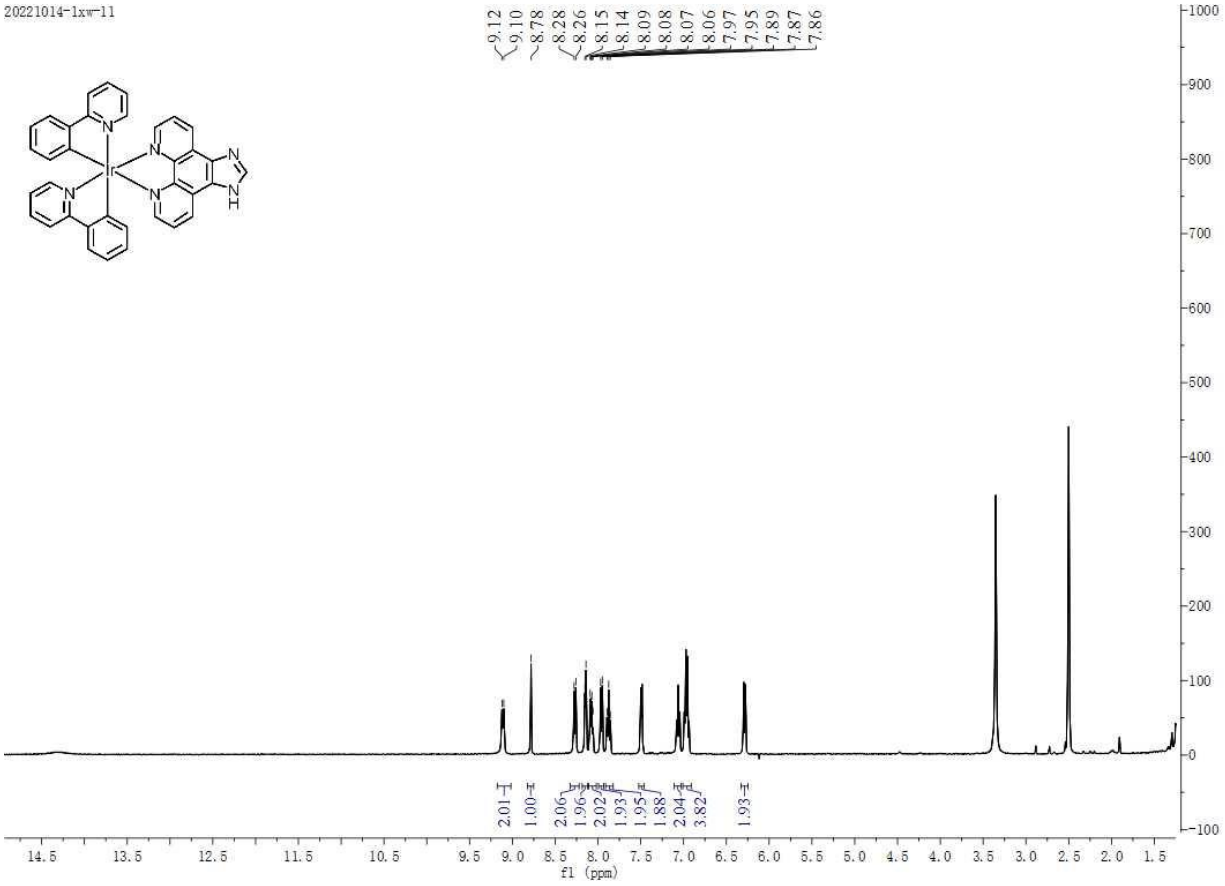
Ligands L1–L3: The synthesis of L1, L2, L3 were identical with the procedure as described previously[1-3].

Complex Ir1, Ir2 and Ir3: The synthesis of **Ir1, Ir2, Ir3** were identical with the procedure as described previously[4-6]. Briefly, **Ir1, Ir2, Ir3** (0.4 mmol, 2 equiv) and $[Ir(ppy)_2Cl]_2$ (0.2 mmol, 1 equiv) in CH_2Cl_2/CH_3OH (2:1, v/v) was heated to refluxed 65 ℃ for 8 h under N_2 atmosphere. After the resulting red solution cooled to room temperature, saturated KPF_6 aqueous solution (10 mL) were added to obtain a red precipitate. The mixture was filtered to remove insoluble salts, and then the filtrate was evaporated to dryness under reduced pressure to get the crude product. The crude product was then dissolved with a small amount of CH_2Cl_2 and purified by column chromatography with CH_2Cl_2/CH_3OH (10:1, v/v) as the eluent. It was obtained as a yellow powder. **Ir1**: yield: 73.0 %. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.11 (d, *J* = 8.0 Hz, 2H), 8.78 (s, 1H), 8.27 (d, *J* = 8.2 Hz, 2H), 8.15 (d, *J* = 5.0 Hz, 2H), 8.07 (dd, *J* = 8.2, 5.2 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.87 (t, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 5.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 2H), 6.96 (q, *J* = 7.2 Hz, 4H), 6.29 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 166.80 (s), 150.22 (s), 149.04 (s), 148.26 (s), 144.00 (d, J = 14.4 Hz), 142.99 (s), 138.55 (s), 132.03 (s), 131.14 (s), 130.14 (s), 127.01 (s), 124.95 (s), 123.70 (s), 122.25 (s), 119.84 (s). HRMS (ESI) m/z: calcd for C35H24N6Ir $[M-PF_6]^+$, 721.1693; found 721.1721. **Ir2**: yield: 75.0 %. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 14.36 (s, 1H), 9.20 (d, *J* = 8.2 Hz, 2H), 8.30 (dd, *J* = 15.4, 8.2 Hz, 4H), 8.17 (d, *J* = 4.7 Hz, 2H), 8.13 – 8.06 (m, 2H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.89 (t, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 5.6 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.98 (dt, *J* = 14.7, 7.3 Hz, 4H), 6.30 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 166.83 (s), 152.70 (s), 150.22 (s), 149.04 (s),

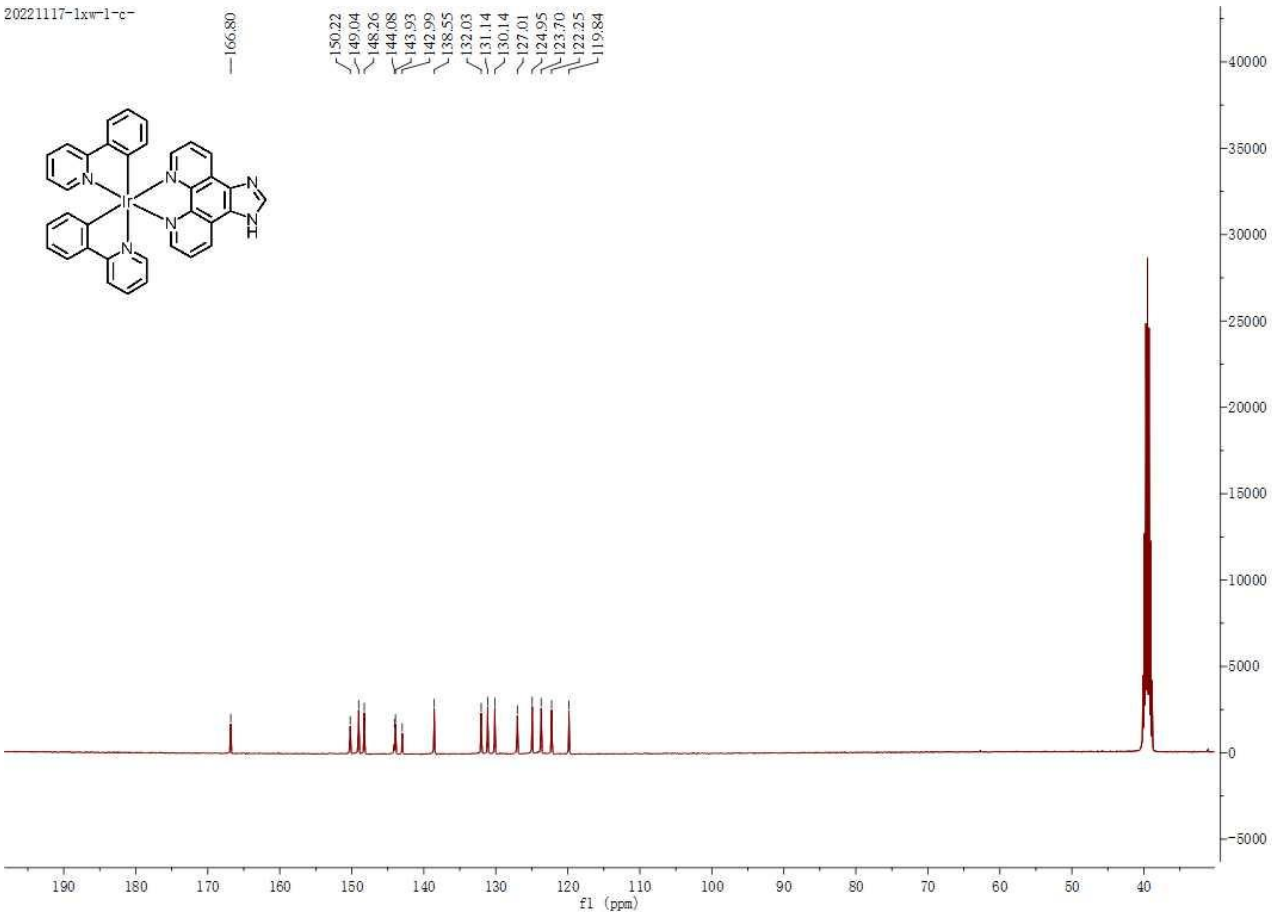
148.31 (s), 144.01 (d, J = 14.6 Hz), 138.57 (s), 132.11 (s), 131.13 (s), 130.23 (d, J = 15.3 Hz), 129.45 (d, J = 11.7 Hz), 129.26 (d, J = 25.7 Hz), 126.95 (s), 126.51 (s), 124.95 (s), 123.71 (s), 122.26 (s), 119.85 (s). HRMS (ESI) *m/z*: calcd for $C_{41}H_{28}N_6Ir$ $[M\text{-}PF_6]^+$, 797.2007; found 797.2009. **Ir3**: yield: 76.0 %.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.18 (d, *J* = 8.3 Hz, 2H), 8.27 (d, *J* = 8.2 Hz, 2H), 8.15 (dd, *J* = 9.3, 7.0 Hz, 4H), 8.07 (dd, *J* = 8.1, 5.3 Hz, 2H), 7.96 (d, *J* = 7.9 Hz, 2H), 7.88 (t, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 5.7 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 2H), 6.98 (dt, *J* = 14.6, 7.6 Hz, 6H), 6.29 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.85 (s), 159.55 (s), 153.44 (s), 150.35 (s), 149.04 (s), 148.03 (s), 143.86 (d, J = 20.0 Hz), 143.60 – 142.14 (m), 138.58 (s), 132.08 (s), 131.16 (s), 130.17 (s), 128.36 (s), 126.78 (s), 124.97 (s), 123.74 (s), 122.26 (s), 120.44 (s), 119.87 (s), 115.87 (s). HRMS (ESI) *m/z*: calcd for $C_{41}H_{28}N_6IrO$ $[M\text{-}PF_6]^+$, 813.1956; found 813.1974.

Spectra of Ligands and Complexes

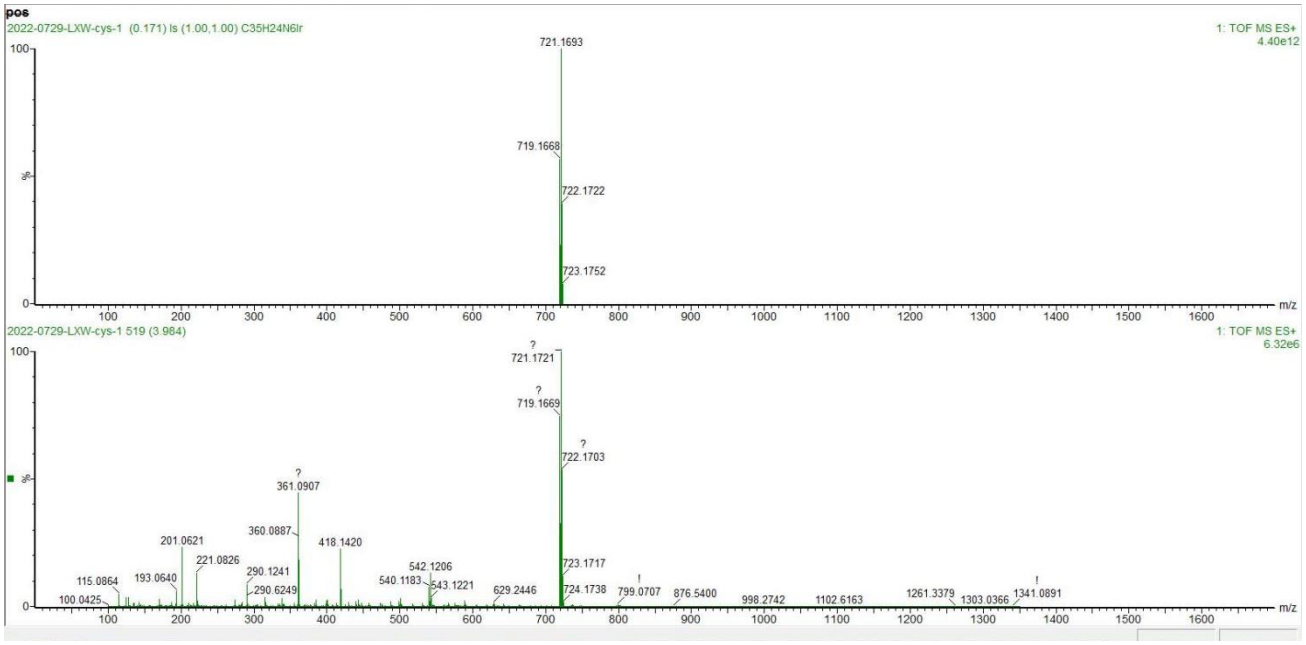
^{1}H NMR of Ir1



^{1}C NMR of Ir1



HRMS of Ir1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719.1668
722.1722
723.1752
m/z
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1: TOF MS ES+
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721.1721
719.1669
722.1703
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360.0887
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201.0621
221.0826
290.1241
193.0640
115.0864
100.0425
290.6249
542.1206
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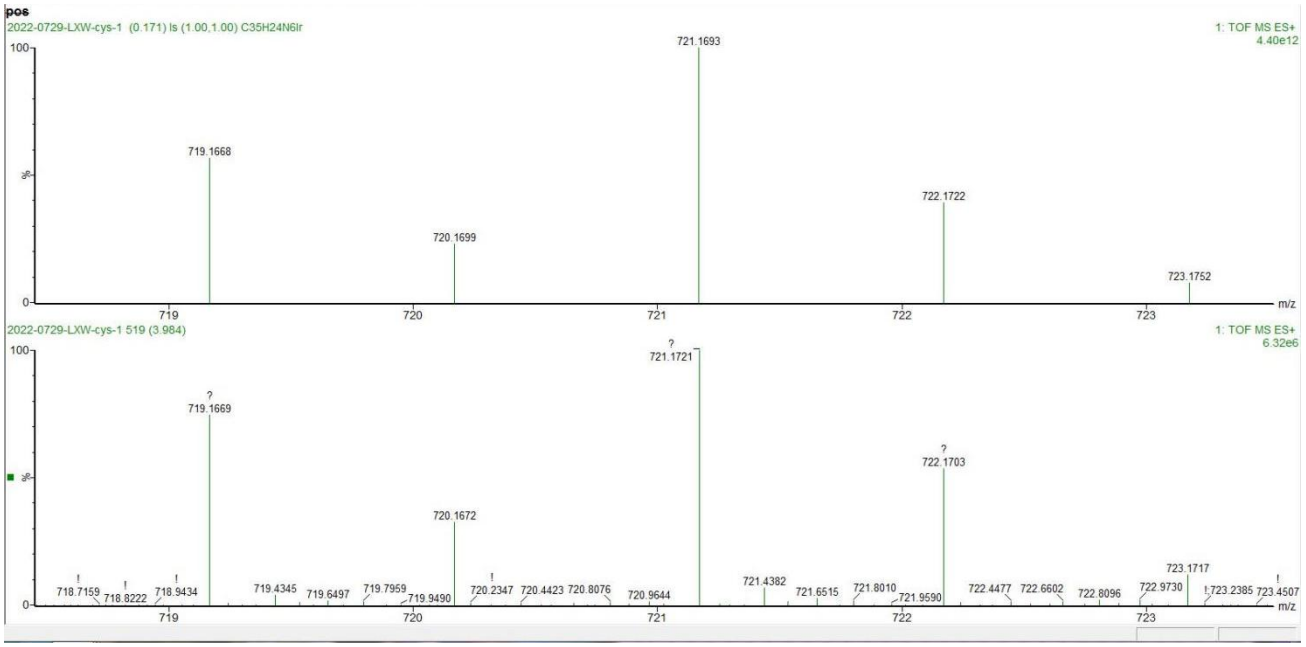
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722.1722
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723.1752
m/z
2022-0729-LXW-cys-1 519 (3.984)
1: TOF MS ES+
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719.1669
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721.6515
721.8010
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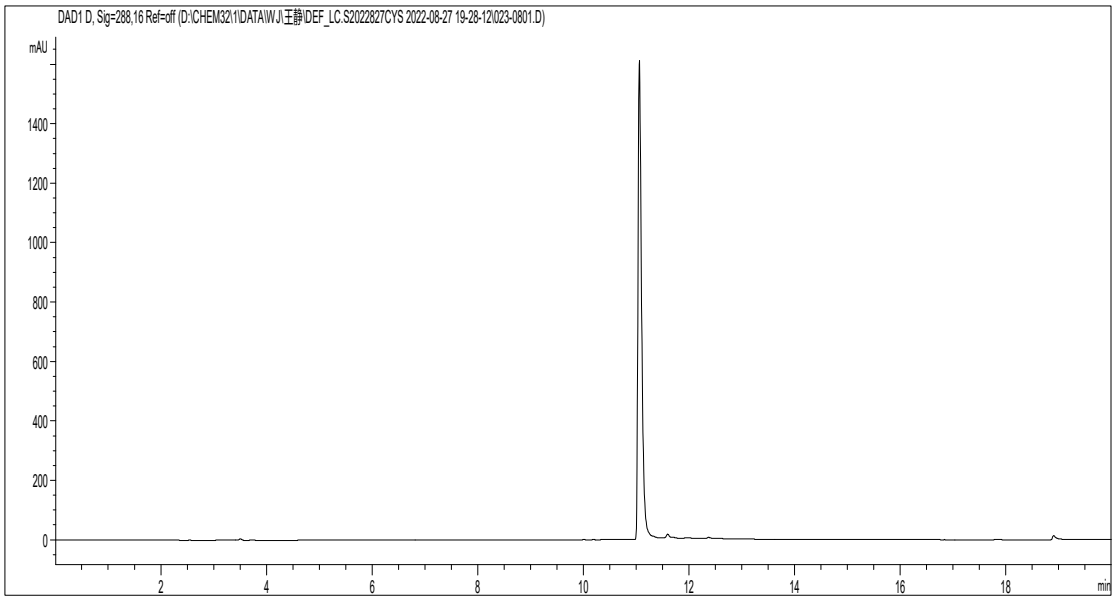
m/z

HPLC of Ir1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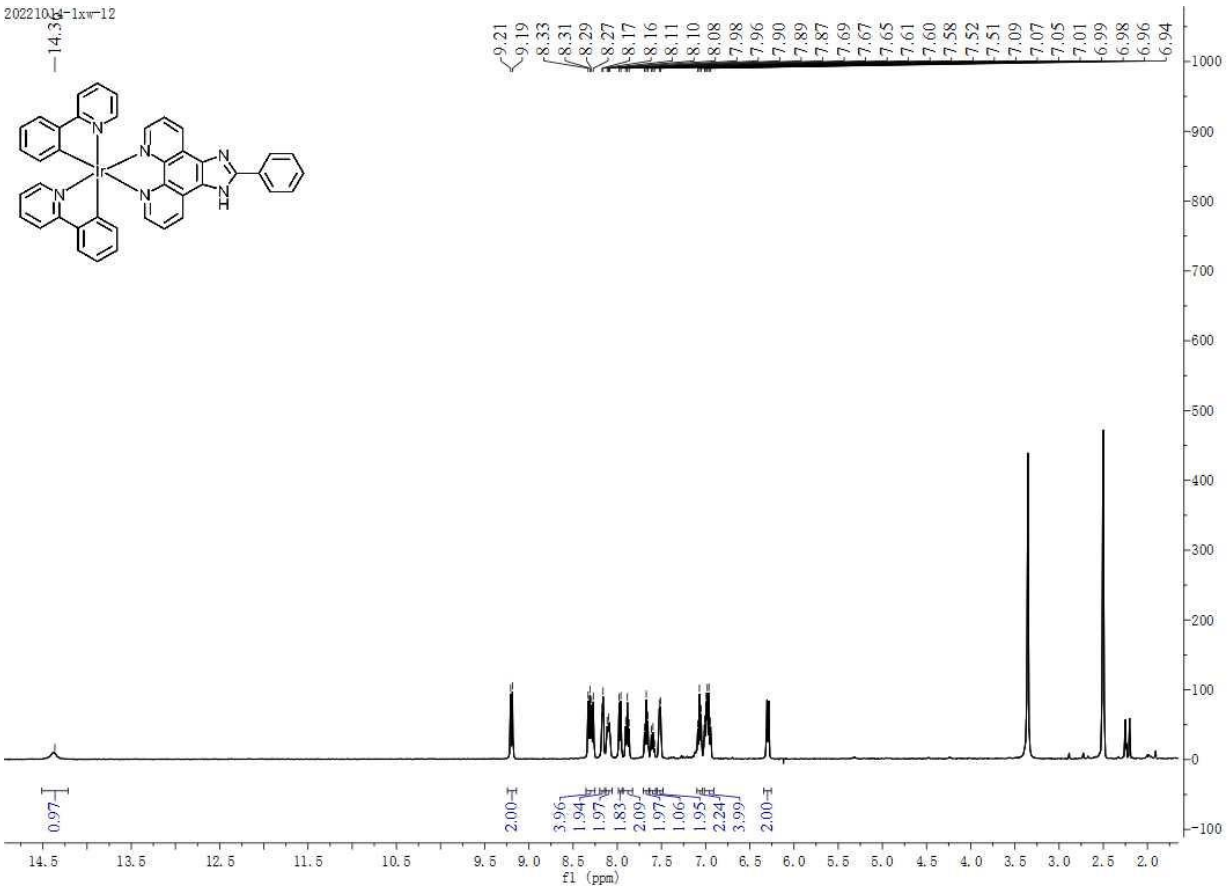
600
400
200
0
2
4
6
8
10
12
14
16
18
min

[1]H NMR of Ir2



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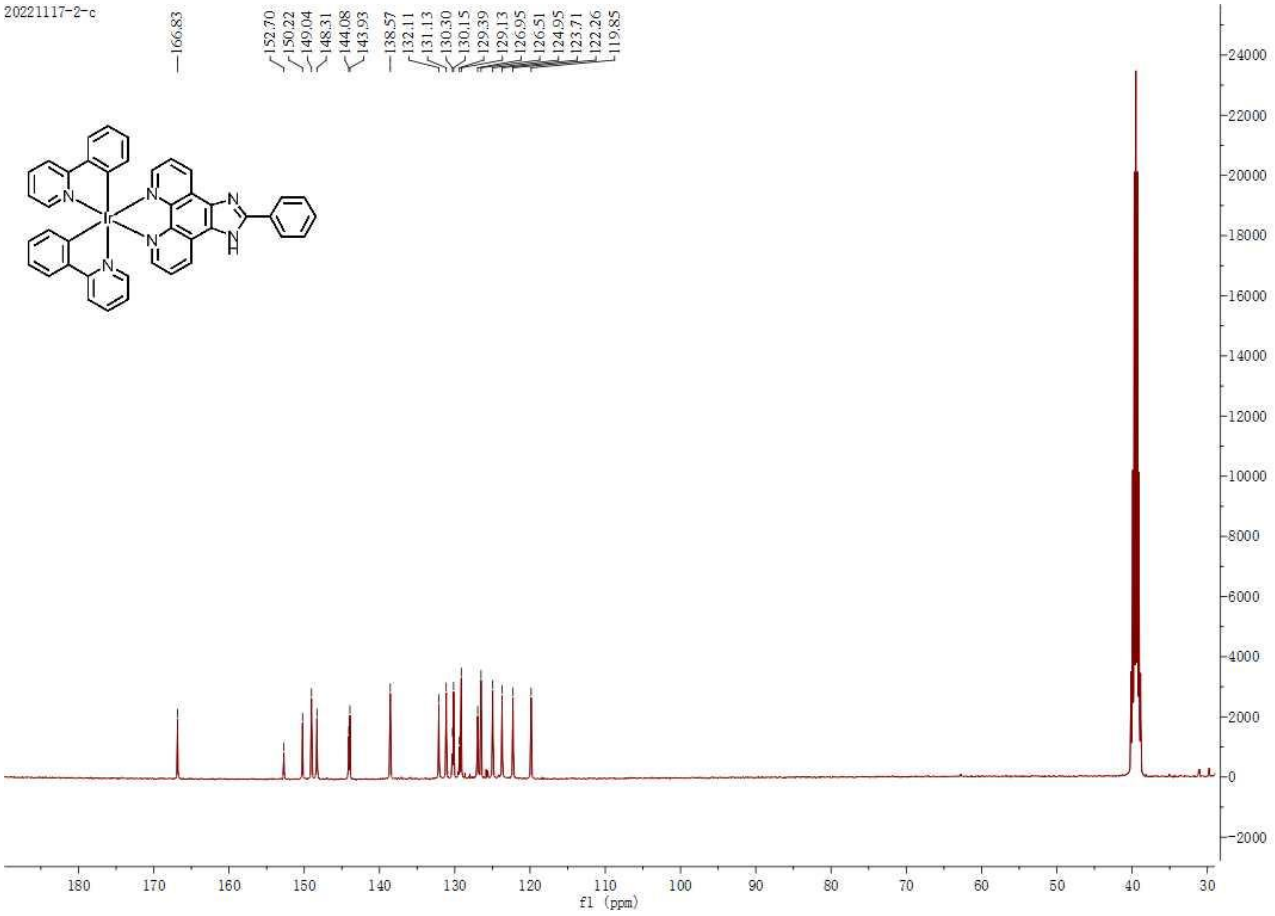

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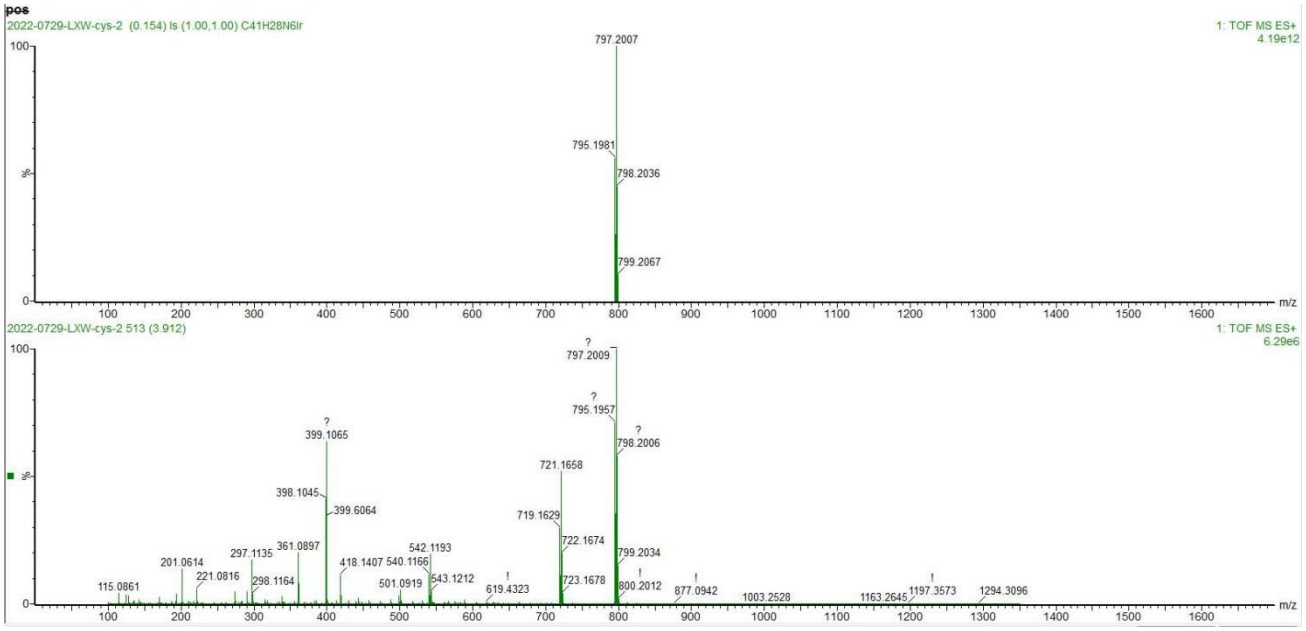
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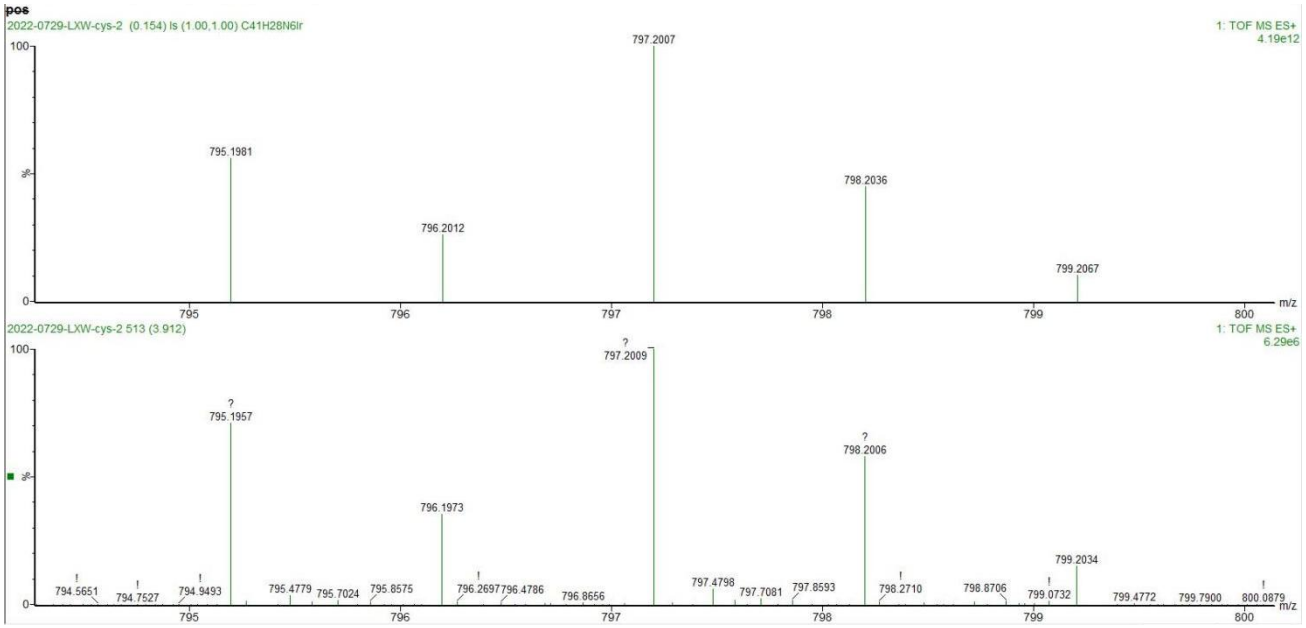
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797.2007
795.1981
798.2036
796.2012
799.2067
m/z
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797.4798
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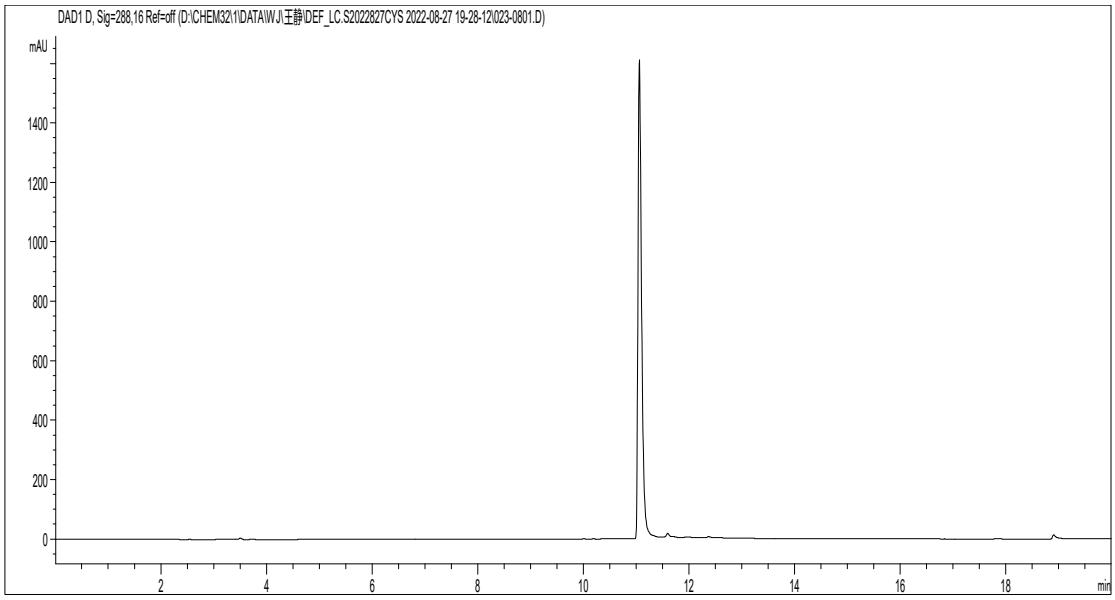
m/z

HPLC of Ir2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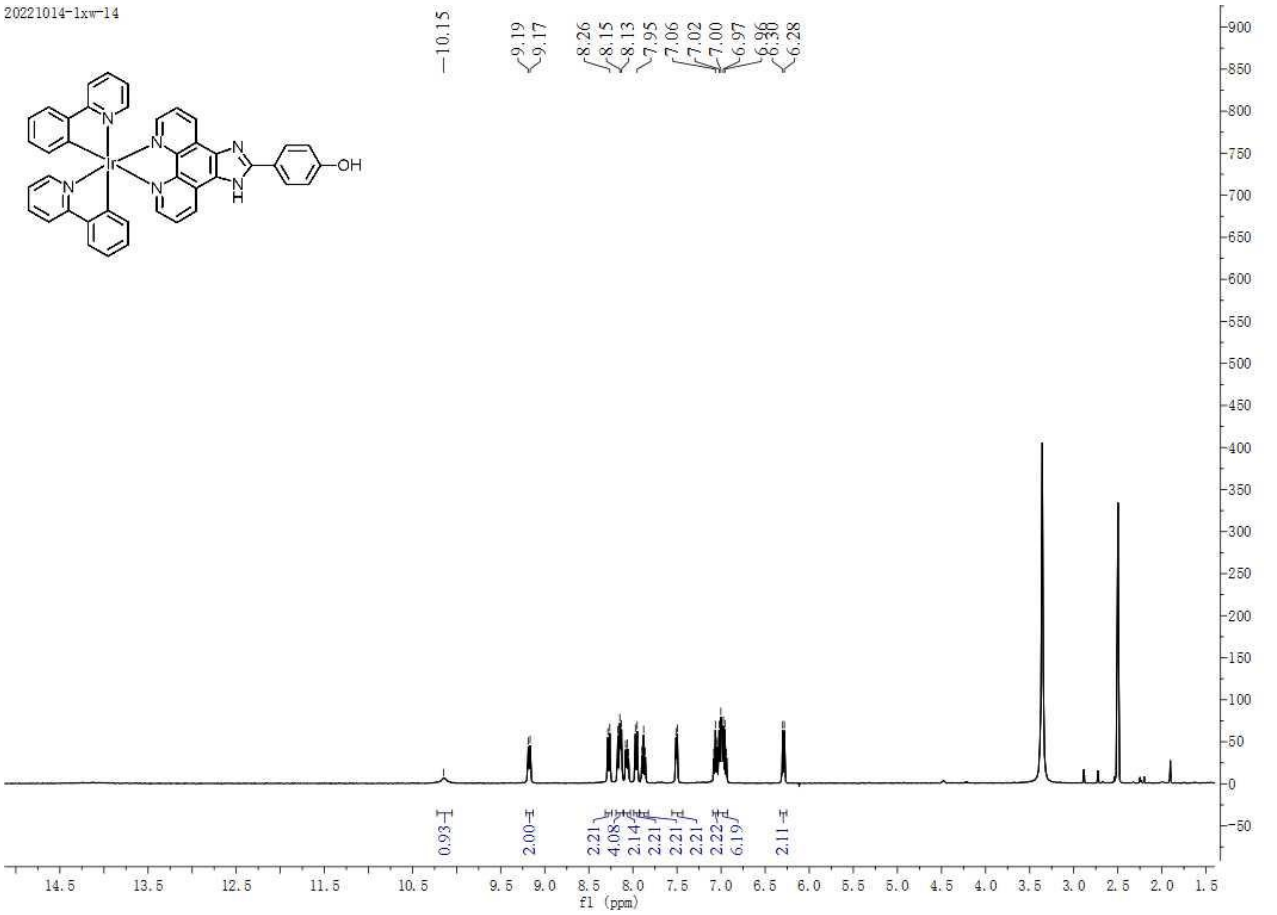
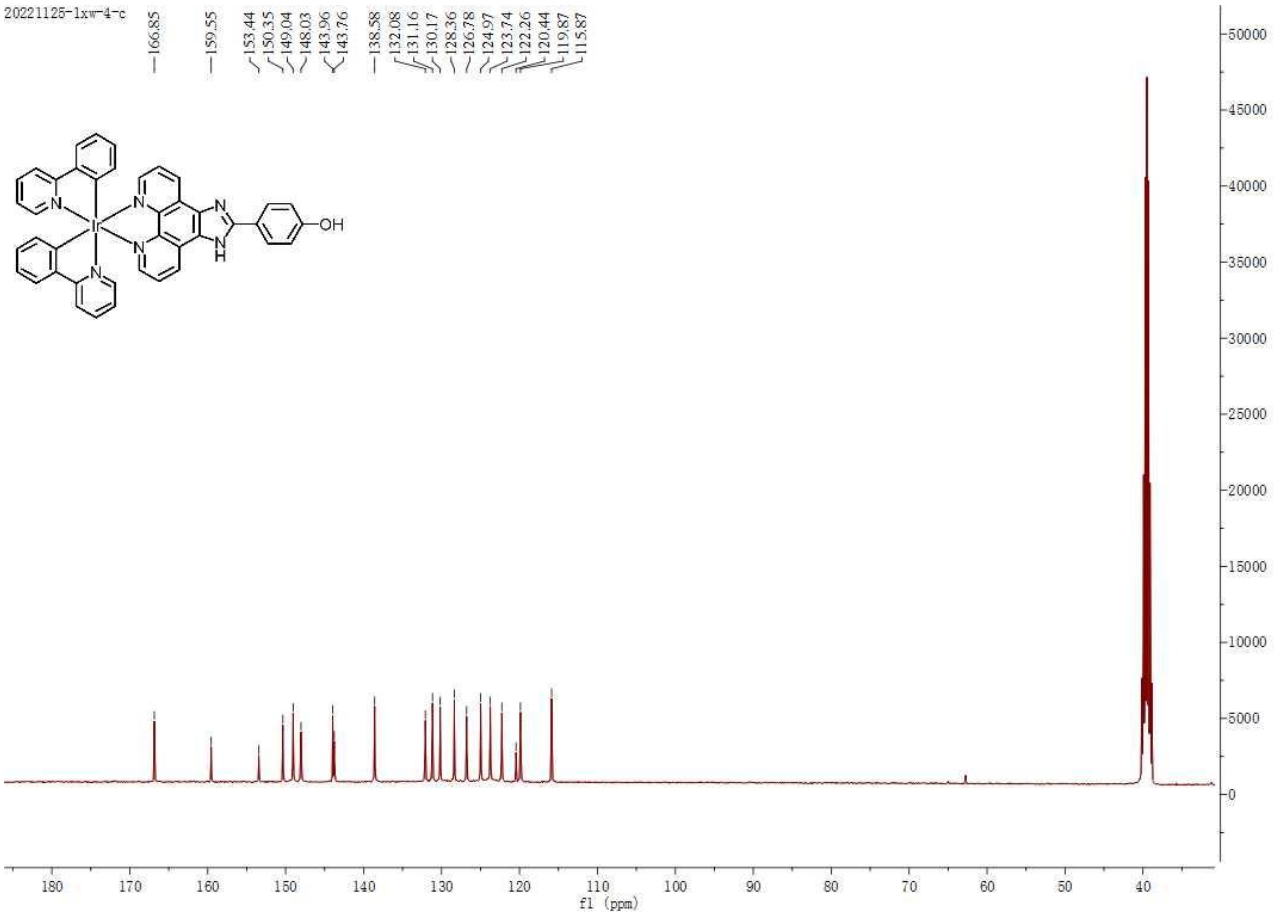
400
200
0
2
4
6
8
10
12
14
16
18
min

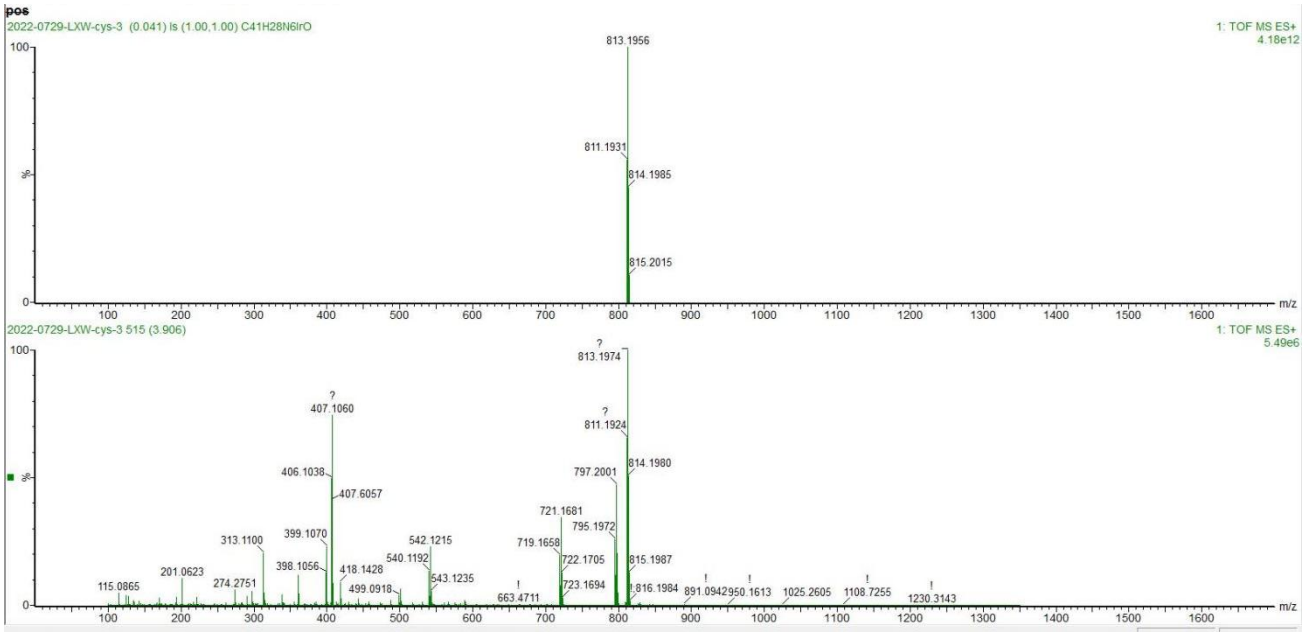
^{1}H NMR of Ir3



^{1}H NMR of Ir3



HRMS of Ir3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811.1931
814.1985
815.2015
m/z
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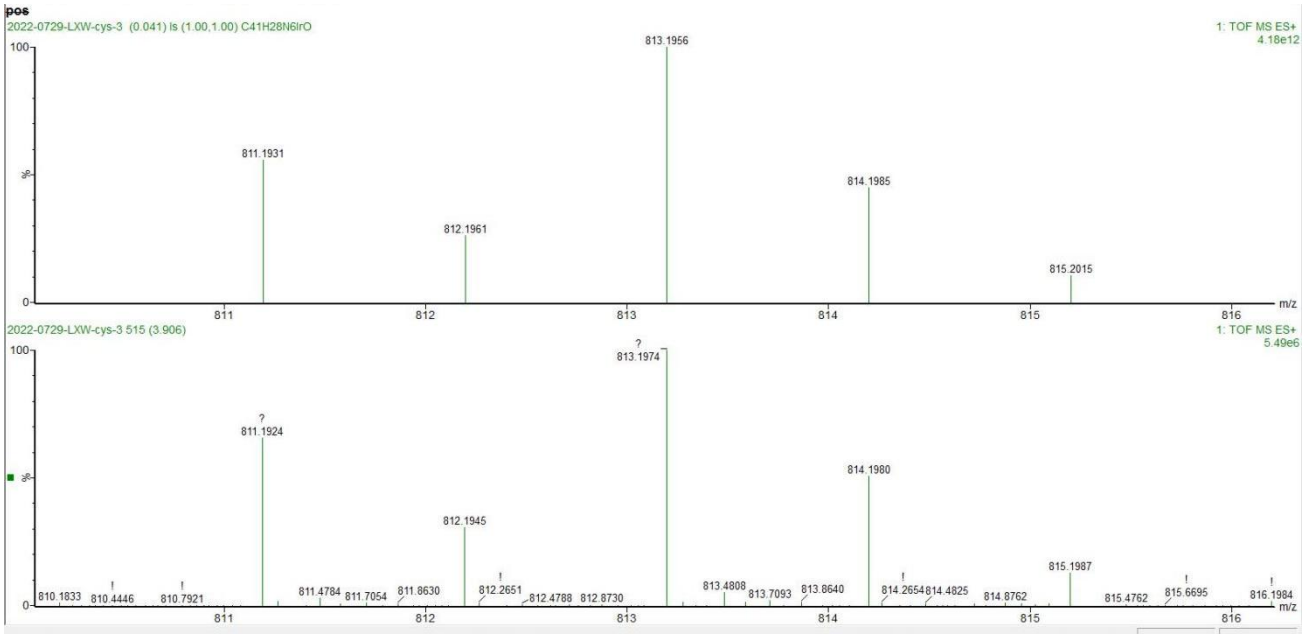
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m/z
2022-0729-LXW-cys-3 515 (3.906)
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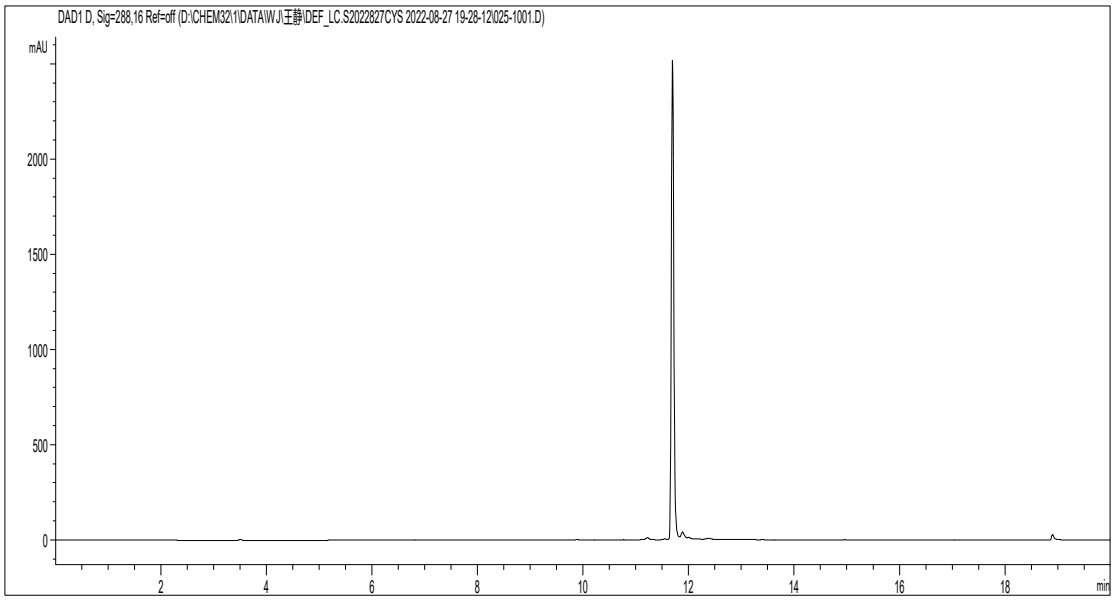
816.1984

HPLC of Ir3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1500
1000
500
0
2
4
6
8
10
12
14
16
18
min

Table S1. Minimum inhibitory concentration (MIC) values of **Ir3** against drug-resistant *S. aureus* (MRSA) isolated from the clinic.

Compound	MIC μg/mL
Ir3	3.9
Oxacillin	Resistance
Benzylpenicillin	Resistance

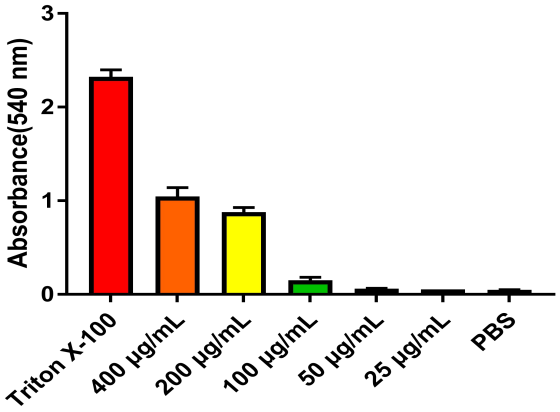

Figure S1. The hemolytic activities of Ir3 towards rabbit erythrocytes; the results are shown as mean ± sd.

[1] A. Pinto, M. Echeverri, B. Gomez-Lor, L. Rodriguez, Highly emissive supramolecular gold(I)-BTD materials, Dalton Trans, 51 (2022) 8340-8349.
[2] S. De, R. Selva Kumar, A. Gauthaman, S.K. Ashok Kumar, P. Paira, A. Moorthy, S. Banerjee, Luminescent ruthenium(II)-para-cymene complexes of aryl substituted imidazo-1,10-phenanthroline as anticancer agents and the effect of remote substituents on cytotoxic activities, Inorganica Chimica Acta, 515 (2021).
[3] F.L. Xie, Z.T. Huang, L. Bai, J.W. Zhu, H.H. Xu, Q.Q. Long, Q.F. Guo, Y. Wu, S.H. Liu, Antitumor activity studies of iridium (III) polypyridine complexes-loaded liposomes against gastric tumor cell in vitro, J Inorg Biochem, 225 (2021) 111603.
[4] W.Y. Zhang, F. Du, M. He, L. Bai, Y.Y. Gu, L.L. Yang, Y.J. Liu, Studies of anticancer activity in vitro and in vivo of iridium(III) polypyridyl complexes-loaded liposomes as drug delivery system, Eur J Med Chem, 178 (2019) 390-400.
[5] J. Q. Wang, X. J. Hou, H. B. Bo, Q. Z. Chen, A cyclometalated iridium(III) complex that induces apoptosis in cisplatin-resistant cancer cells, Inorganic Chemistry Communications, 61 (2015) 31-34.
[6] L. He, M.F. Zhang, Z.Y. Pan, K.N. Wang, Z.J. Zhao, Y. Li, Z.W. Mao, A mitochondria-targeted iridium(iii)-based photoacid generator induces dual-mode photodynamic damage within cancer cells, Chem Commun, 55 (2019) 10472-10475.