Electronic Supporting Information Materials

Synthesis and biological evaluation of mixed-ligands cyclometalated iridium(III)-quinoline complexes

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Table S1. Crystal data and structure refinement details for **2c**.

Empirical formula	$C_{39}H_{24}ClIIrN_3O$
Formula weight	905.16
Temperature/K	293(2)
Crystal system	tetragonal
Space group	$I4_1/a$
a/Å	18.4197(4)
b/Å	18.4197(4)
c/Å	36.1009(13)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	12248.5(7)
Z	16
ρ_{calc}g/cm^3	1.963
μ/mm^{-1}	5.495
F(000)	6944.0
Crystal size/mm^3	0.36 × 0.25 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.652 to 58.07
Index ranges	$-22 \le h \le 25$, $-20 \le k \le 24$, $-46 \le l \le 49$
Reflections collected	45801
Independent reflections	7679 [R_{int} = 0.0650, R_{sigma} = 0.0478]
Data/restraints/parameters	7679/1434/403
Goodness-of-fit on F^2	1.029
Final R indexes [I>=2σ (I)]	R_1 = 0.0663, wR_2 = 0.1932
Final R indexes [all data]	R_1 = 0.1107, wR_2 = 0.2339
Largest diff. peak/hole / e Å^{-3}	2.86/-1.38

[a] $R_1 = \Sigma\ ||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$.

Table S2. Selected bond lengths (Å) for **2c**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Ir1	O1	2.152(8)	C7	C8	1.324(18)
Ir1	N1	2.103(10)	C8	C9	1.453(17)
Ir1	N2	2.103(10)	C9	C10	1.468(17)
Ir1	N3	2.208(6)	C10	C11	1.406(17)
Ir1	C15	1.997(12)	C10	C15	1.430(17)
Ir1	C16	1.990(12)	C11	C12	1.392(19)
I1	C32	2.090(13)	C12	C13	1.349(18)
Cl1	C34	1.725(14)	C13	C14	1.375(17)
O1	C31	1.357(15)	C14	C15	1.372(17)
N1	C22	1.350(16)	C16	C17	1.383(17)
N1	C30	1.411(16)	C16	C21	1.418(17)
N2	C1	1.396(16)	C17	C18	1.420(18)
N2	C9	1.308(15)	C18	C19	1.383(19)
C36	C35	1.3900	C19	C20	1.383(18)
C36	C39	1.3900	C20	C21	1.370(17)
C36	C34	1.436(15)	C21	C22	1.443(19)
C35	N3	1.3900	C22	C23	1.457(18)
C35	C31	1.425(15)	C23	C24	1.369(19)
N3	C37	1.3900	C24	C25	1.381(18)
C37	C38	1.3900	C25	C26	1.475(19)
C38	C39	1.3900	C25	C30	1.381(17)
C1	C2	1.443(18)	C26	C27	1.35(2)
C1	C6	1.407(17)	C27	C28	1.43(2)
C2	C3	1.372(18)	C28	C29	1.331(19)
C3	C4	1.393(19)	C29	C30	1.430(18)
C4	C5	1.32(2)	C31	C32	1.373(18)
C5	C6	1.469(19)	C32	C33	1.392(18)
C6	C7	1.344(18)	C33	C34	1.365(19)

Table S3. Selected bond angles (°) for **2c**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Ir1	N3	77.3(3)	N2	C9	C10	115.2(11)
N1	Ir1	O1	81.9(4)	C8	C9	C10	122.8(11)
N1	Ir1	N2	172.7(4)	C11	C10	C9	124.1(12)
N1	Ir1	N3	101.8(3)	C11	C10	C15	121.2(12)

N2	Ir1	O1	103.2(4)	C15	C10	C9	114.6(11)
N2	Ir1	N3	84.6(3)	C12	C11	C10	117.8(13)
C15	Ir1	O1	172.9(4)	C13	C12	C11	121.7(14)
C15	Ir1	N1	96.0(4)	C12	C13	C14	119.7(12)
C15	Ir1	N2	79.5(5)	C15	C14	C13	123.3(12)
C15	Ir1	N3	96.6(4)	C10	C15	Ir1	114.3(9)
C16	Ir1	O1	93.2(4)	C14	C15	Ir1	129.1(10)
C16	Ir1	N1	79.7(5)	C14	C15	C10	116.1(11)
C16	Ir1	N2	94.6(4)	C17	C16	Ir1	128.3(10)
C16	Ir1	N3	170.0(4)	C17	C16	C21	116.0(11)
C16	Ir1	C15	93.0(5)	C21	C16	Ir1	115.4(9)
C31	O1	Ir1	114.1(8)	C16	C17	C18	121.9(13)
C22	N1	Ir1	112.1(8)	C19	C18	C17	119.6(14)
C22	N1	C30	119.5(10)	C20	C19	C18	119.5(13)
C30	N1	Ir1	128.2(8)	C21	C20	C19	120.3(13)
C1	N2	Ir1	126.1(8)	C16	C21	C22	113.3(11)
C9	N2	Ir1	115.2(8)	C20	C21	C16	122.6(13)
C9	N2	C1	118.6(10)	C20	C21	C22	123.9(12)
C35	C36	C39	120.0	N1	C22	C21	117.2(11)
C35	C36	C34	116.7(8)	N1	C22	C23	118.4(12)
C39	C36	C34	123.2(8)	C21	C22	C23	124.4(12)
C36	C35	C31	122.6(7)	C24	C23	C22	122.4(13)
N3	C35	C36	120.0	C23	C24	C25	116.6(12)
N3	C35	C31	117.3(8)	C24	C25	C26	120.3(12)
C35	N3	Ir1	111.9(4)	C24	C25	C30	122.5(13)
C35	N3	C37	120.0	C30	C25	C26	117.2(12)
C37	N3	Ir1	128.1(4)	C27	C26	C25	121.6(13)
C38	C37	N3	120.0	C26	C27	C28	119.1(14)
C37	C38	C39	120.0	C29	C28	C27	120.2(14)
C38	C39	C36	120.0	C28	C29	C30	122.2(13)
N2	C1	C2	121.4(11)	N1	C30	C29	120.0(11)
N2	C1	C6	119.4(12)	C25	C30	N1	120.2(12)
C6	C1	C2	119.1(12)	C25	C30	C29	119.5(12)
C3	C2	C1	120.3(13)	O1	C31	C35	119.0(11)
C2	C3	C4	120.6(14)	O1	C31	C32	122.7(12)
C5	C4	C3	121.1(14)	C32	C31	C35	118.2(11)
C4	C5	C6	121.9(13)	C31	C32	I1	119.0(9)
C1	C6	C5	116.9(13)	C31	C32	C33	120.3(12)
C7	C6	C1	120.4(12)	C33	C32	I1	120.3(9)
C7	C6	C5	122.7(13)	C34	C33	C32	121.7(13)

C8	C7	C6	121.2(13)	C36	C34	Cl1	120.5(10)
C7	C8	C9	118.4(13)	C33	C34	Cl1	119.2(11)
N2	C9	C8	121.9(11)	C33	C34	C36	120.3(12)

Table S4. Crystal data and structure refinement details for **2d**.

Empirical formula	$C_{39}H_{24}Br_2IrN_3O$
Formula weight	902.63
Temperature/K	293(2)
Crystal system	tetragonal
Space group	$I4_1/a$
a/Å	18.1807(5)
b/Å	18.1807(5)
c/Å	36.8214(13)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	12170.8(8)
Z	16
ρ_{calc}g/cm^3	1.970
μ/mm^{-1}	7.054
F(000)	6944.0
Crystal size/mm^3	0.36 × 0.29 × 0.18
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.714 to 58.368
Index ranges	-24 ≤ h ≤ 23, -24 ≤ k ≤ 24, -50 ≤ l ≤ 46
Reflections collected	46769
Independent reflections	7659 [R_{int} = 0.0502, R_{sigma} = 0.0345]
Data/restraints/parameters	7659/6/415
Goodness-of-fit on F^2	1.019
Final R indexes [I>=2σ (I)]	R_1 = 0.0515, wR_2 = 0.1434
Final R indexes [all data]	R_1 = 0.0846, wR_2 = 0.1676
Largest diff. peak/hole / e Å^{-3}	1.95/-0.91

[a] $R_1 = \Sigma ||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{½}$.

Table S5. Selected bond lengths (Å) for **2d**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Ir1	O1	2.166(6)	C12	C13	1.400(13)
Ir1	N1	2.125(7)	C13	C14	1.379(15)
Ir1	N2	2.093(7)	C14	C15	1.384(15)
Ir1	N3	2.107(7)	C16	C17	1.415(13)
Ir1	C11	2.003(8)	C16	C21	1.381(12)
Ir1	C16	1.998(9)	C17	C18	1.386(13)
Br1	C37	1.897(10)	C18	C19	1.369(14)
Br2	C35	1.878(9)	C19	C20	1.394(14)
O1	C38	1.305(10)	C20	C21	1.382(12)
N1	C31	1.299(12)	C21	C22	1.472(13)
N1	C39	1.389(12)	C22	C23	1.408(13)
N2	C1	1.408(11)	C23	C24	1.317(14)
N2	C9	1.323(11)	C24	C25	1.416(14)
N3	C22	1.359(11)	C25	C26	1.422(14)
N3	C30	1.369(11)	C25	C30	1.421(12)
C1	C2	1.387(12)	C26	C27	1.342(15)
C1	C6	1.405(12)	C27	C28	1.422(15)
C2	C3	1.372(14)	C28	C29	1.342(13)
C3	C4	1.432(16)	C29	C30	1.407(13)
C4	C5	1.347(16)	C31	C32	1.552(15)
C5	C6	1.430(14)	C32	C33	1.259(14)
C6	C7	1.395(13)	C33	C34	1.436(14)
C7	C8	1.341(13)	C34	C35	1.415(14)
C8	C9	1.412(12)	C34	C39	1.480(13)
C9	C10	1.467(12)	C35	C36	1.355(14)
C10	C11	1.400(12)	C36	C37	1.386(14)
C10	C15	1.402(13)	C37	C38	1.402(12)
C11	C12	1.386(12)	C38	C39	1.436(13)

Table S6. Selected bond angles (°) for **2d**.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
N1	Ir1	O1	77.5(3)	C14	C13	C12	120.7(10)
N2	Ir1	O1	103.3(3)	C13	C14	C15	119.0(9)

N2	Ir1	N1	83.8(3)	C14	C15	C10	120.5(9)
N2	Ir1	N3	173.8(3)	C17	C16	Ir1	127.2(7)
N3	Ir1	O1	81.5(3)	C21	C16	Ir1	115.9(7)
N3	Ir1	N1	101.1(3)	C21	C16	C17	116.7(8)
C11	Ir1	O1	173.1(3)	C18	C17	C16	120.1(10)
C11	Ir1	N1	96.5(3)	C19	C18	C17	122.0(10)
C11	Ir1	N2	79.4(3)	C18	C19	C20	118.6(9)
C11	Ir1	N3	96.3(3)	C21	C20	C19	119.5(9)
C16	Ir1	O1	92.5(3)	C16	C21	C20	123.1(9)
C16	Ir1	N1	169.7(3)	C16	C21	C22	114.8(7)
C16	Ir1	N2	96.2(3)	C20	C21	C22	122.1(8)
C16	Ir1	N3	79.6(3)	N3	C22	C21	115.1(7)
C16	Ir1	C11	93.5(3)	N3	C22	C23	119.9(9)
C38	O1	Ir1	113.7(6)	C23	C22	C21	125.0(8)
C31	N1	Ir1	131.2(7)	C24	C23	C22	121.8(10)
C31	N1	C39	115.4(8)	C23	C24	C25	120.1(10)
C39	N1	Ir1	113.4(6)	C24	C25	C26	123.5(10)
C1	N2	Ir1	126.4(6)	C24	C25	C30	117.6(9)
C9	N2	Ir1	115.0(6)	C30	C25	C26	118.8(10)
C9	N2	C1	118.6(7)	C27	C26	C25	121.3(10)
C22	N3	Ir1	112.8(6)	C26	C27	C28	120.5(11)
C22	N3	C30	119.3(7)	C29	C28	C27	118.7(11)
C30	N3	Ir1	127.8(6)	C28	C29	C30	123.5(10)
C2	C1	N2	120.7(8)	N3	C30	C25	120.9(8)
C2	C1	C6	119.9(9)	N3	C30	C29	121.9(8)
C6	C1	N2	119.4(8)	C29	C30	C25	117.2(9)
C3	C2	C1	121.6(9)	N1	C31	C32	127.2(9)
C2	C3	C4	119.0(11)	C33	C32	C31	112.9(9)
C5	C4	C3	119.8(10)	C32	C33	C34	127.0(10)
C4	C5	C6	121.6(10)	C33	C34	C39	114.7(9)
C1	C6	C5	118.0(9)	C35	C34	C33	129.5(10)
C7	C6	C1	119.9(9)	C35	C34	C39	115.6(9)
C7	C6	C5	122.1(9)	C34	C35	Br2	117.8(8)
C8	C7	C6	119.7(9)	C36	C35	Br2	119.4(8)
C7	C8	C9	119.7(9)	C36	C35	C34	122.8(9)
N2	C9	C8	122.7(8)	C35	C36	C37	120.9(10)
N2	C9	C10	114.7(8)	C36	C37	Br1	119.7(7)
C8	C9	C10	122.6(8)	C36	C37	C38	122.6(9)
C11	C10	C9	115.2(8)	C38	C37	Br1	117.6(7)
C11	C10	C15	120.8(9)	O1	C38	C37	124.2(9)

C15	C10	C9	123.9(8)	O1	C38	C39	119.1(8)
C10	C11	Ir1	114.7(6)	C37	C38	C39	116.6(8)
C12	C11	Ir1	127.1(7)	N1	C39	C34	122.5(9)
C12	C11	C10	117.8(8)	N1	C39	C38	116.2(8)
C11	C12	C13	121.1(9)	C38	C39	C34	121.3(9)

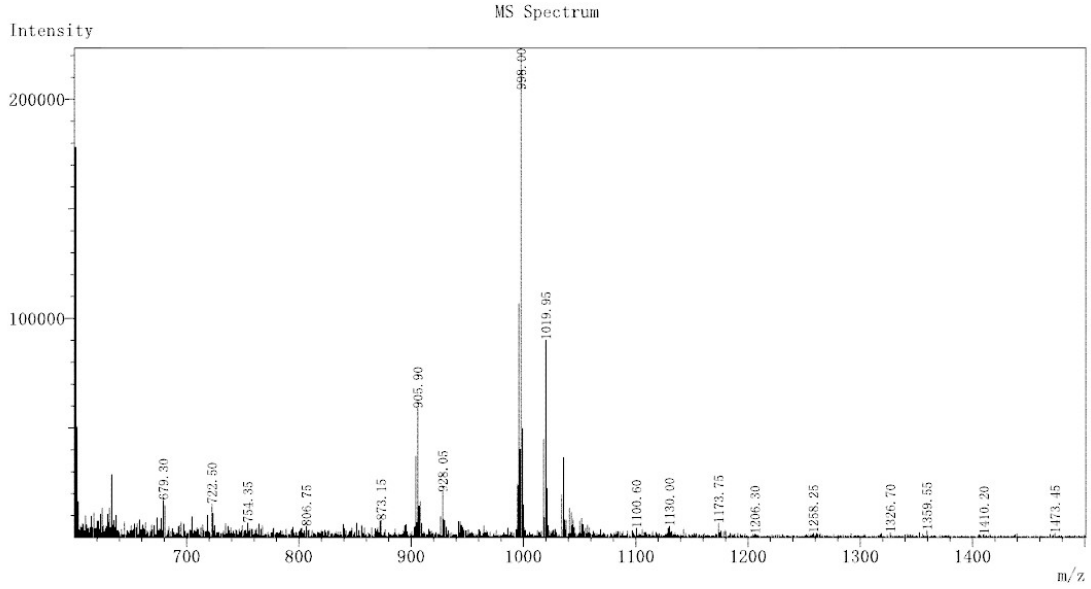

Figure S1. ESI-MS spectra of **2a** (2.0×10^{-5} M) in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

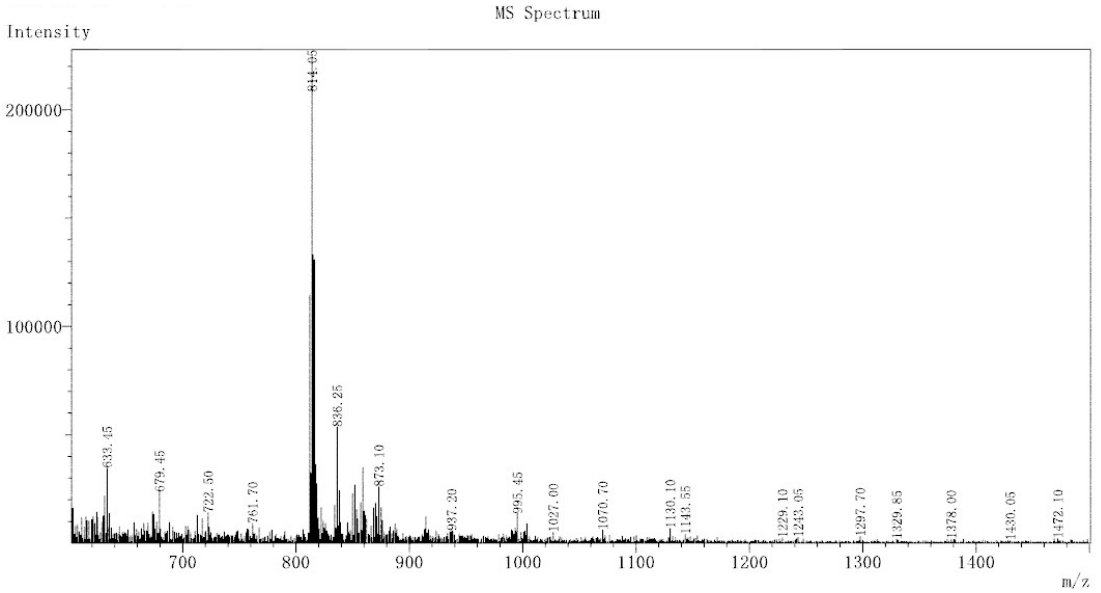

Figure S2. ESI-MS spectra of **2b** (2.0×10^{-5} M) in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

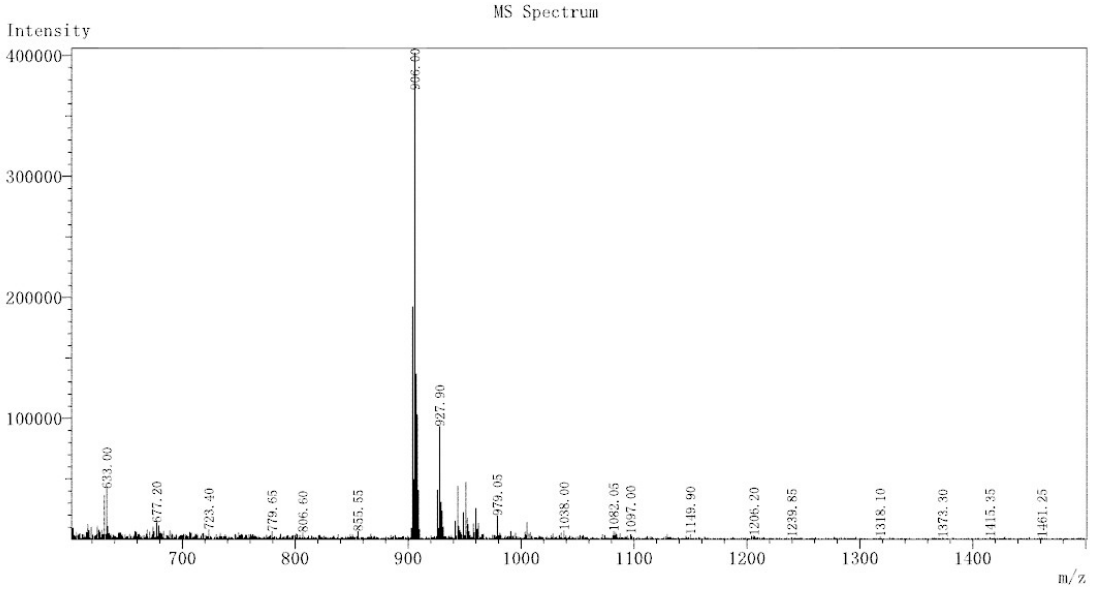

Figure S3. ESI-MS spectra of **2c** (2.0×10^{-5} M) in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

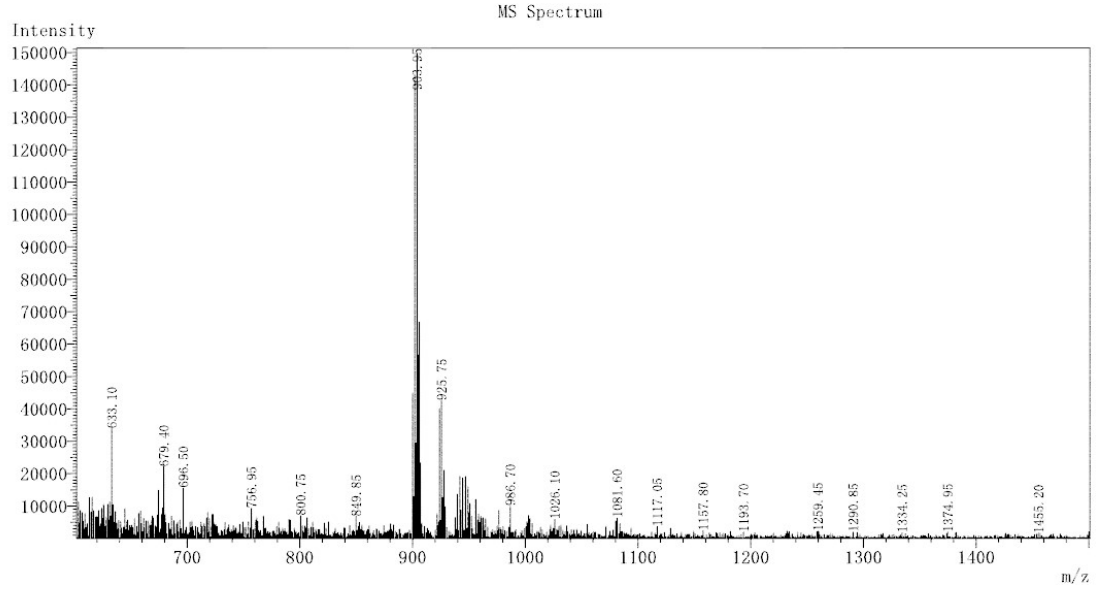

Figure S4. ESI-MS spectra of **2d** (2.0×10^{-5} M) in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

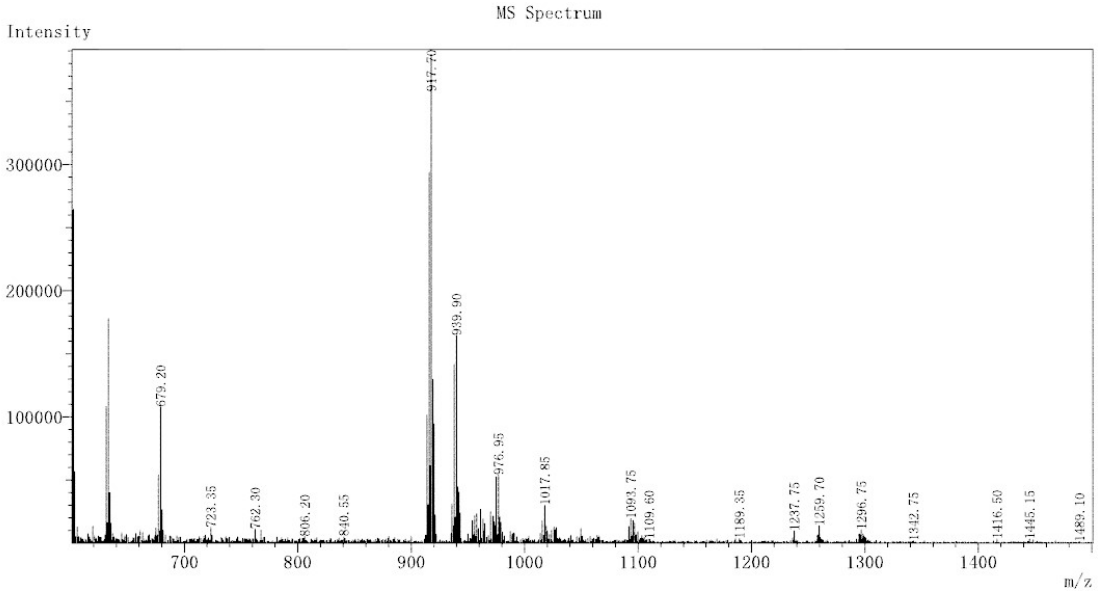

Figure S5. ESI-MS spectra of **2f** (2.0×10^{-5} M) in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

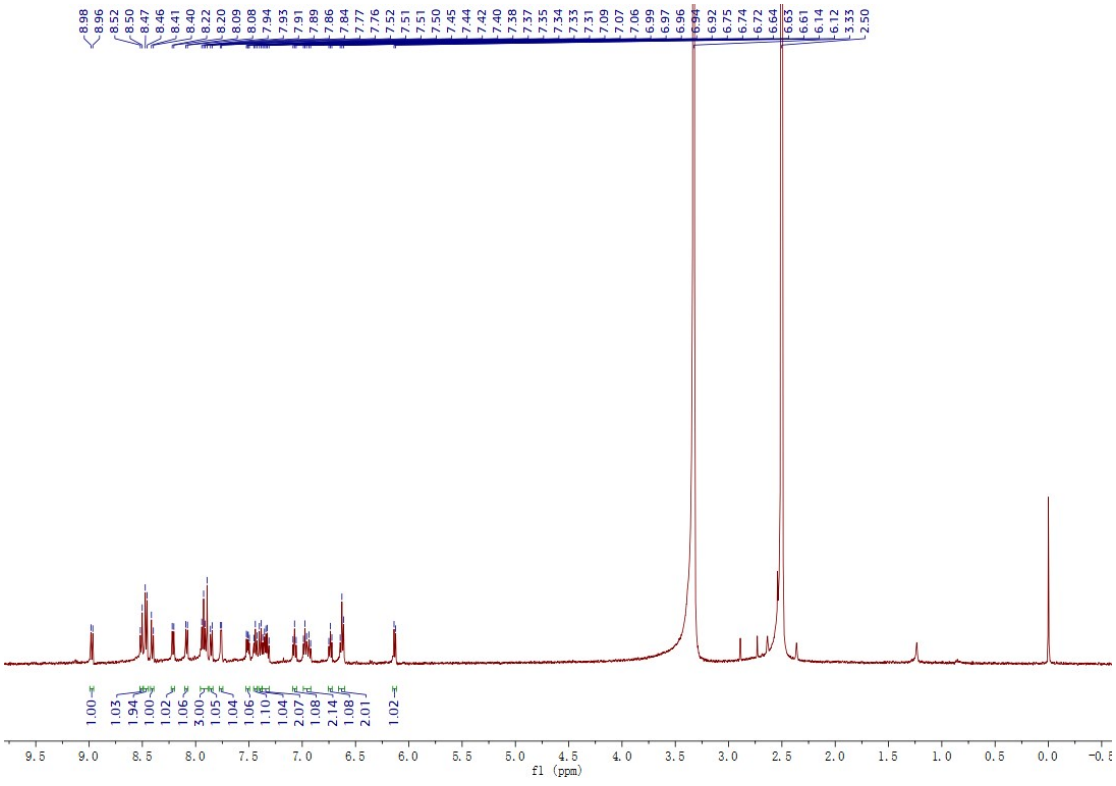

Figure S6. ^{1}H NMR (500MHz, DMSO-d_6) for **2a**.

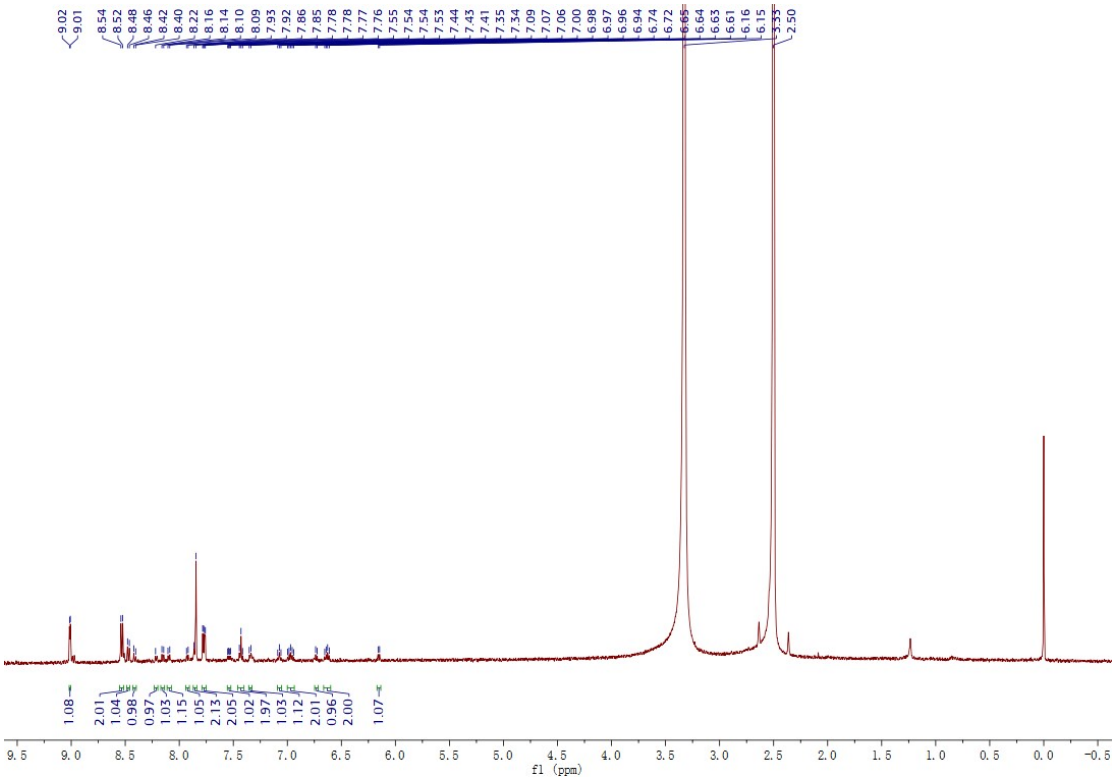

Figure S7. ^{1}H NMR (500MHz, DMSO-d_6) for **2b**.

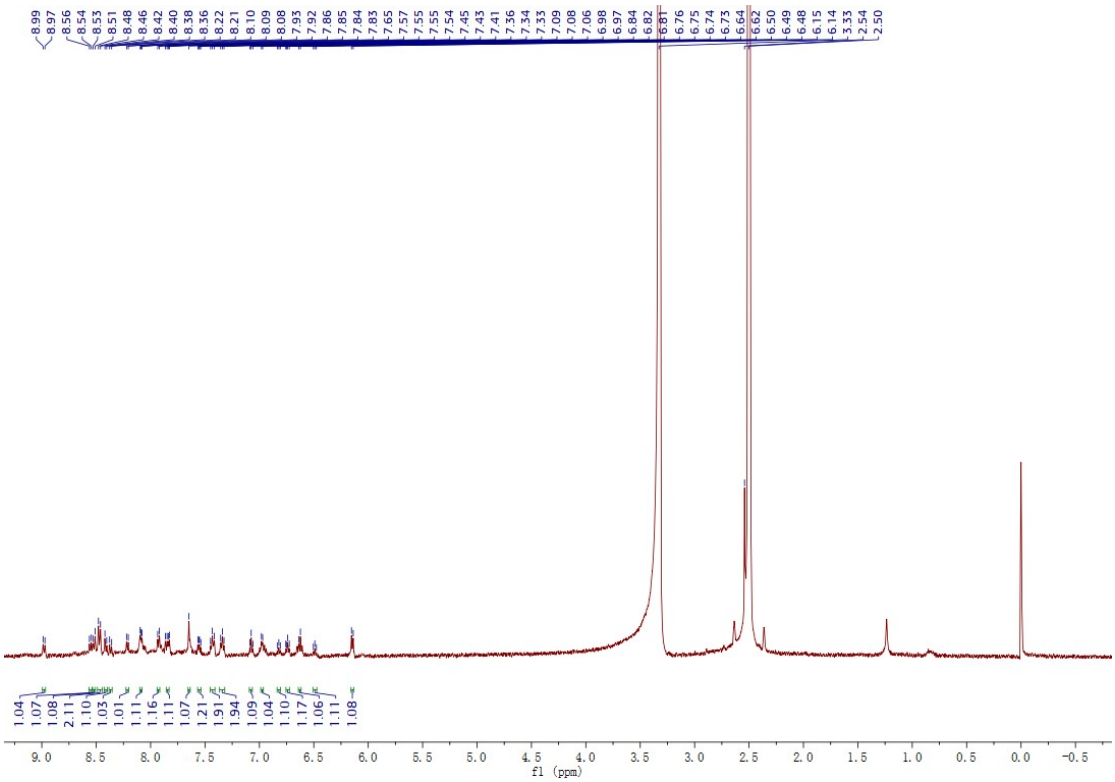

Figure S8. ^{1}H NMR (500MHz, DMSO-d_6) for **2d**.

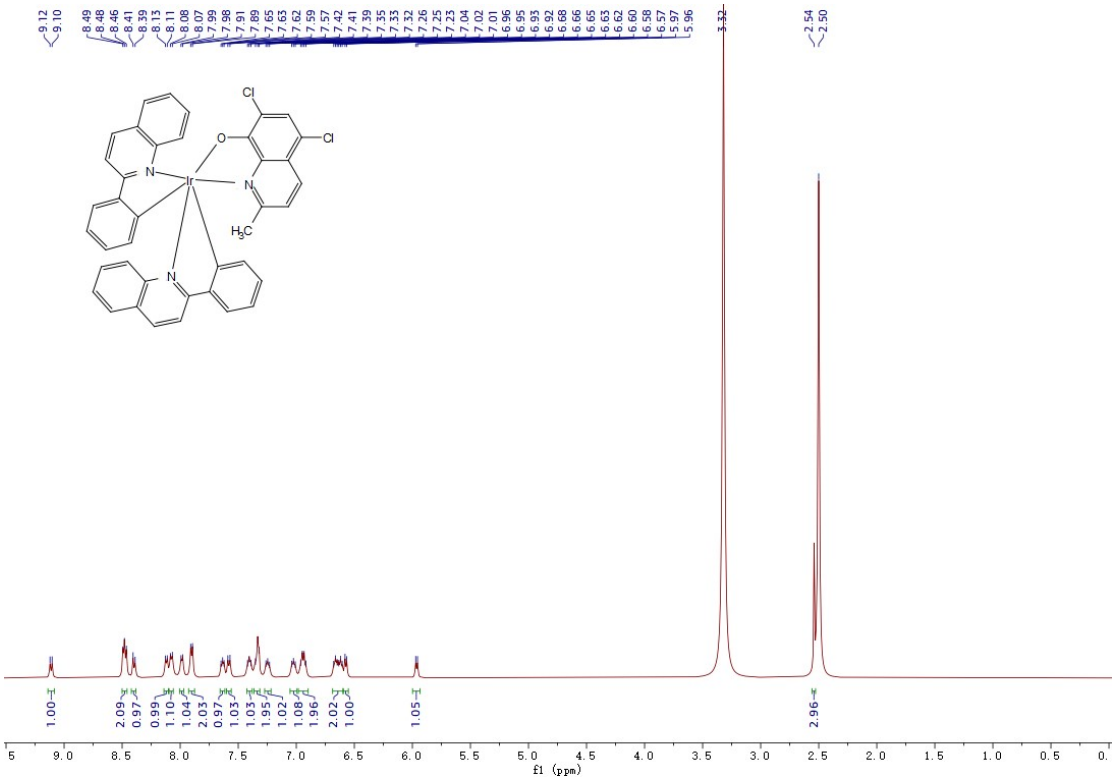

Figure S9. ^{1}H NMR (500MHz, DMSO-d_6) for **2e**.

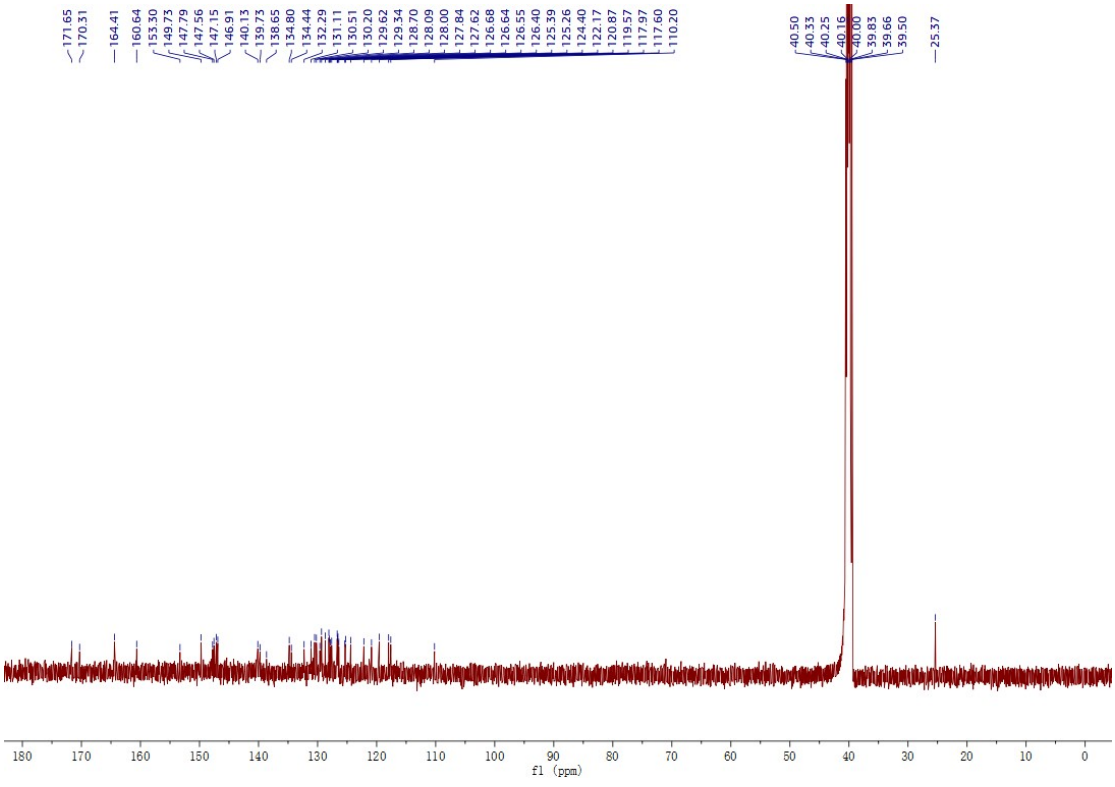

Figure S10. ^{13}C NMR (126MHz, DMSO-d_6) for **2e**.

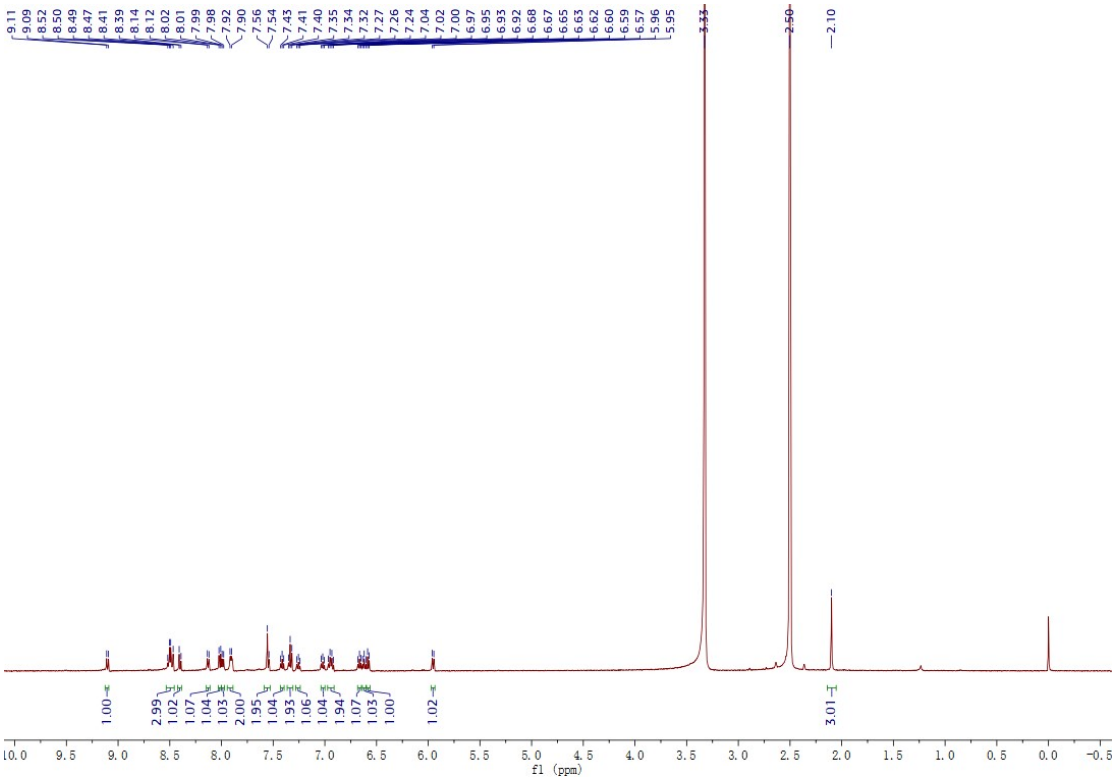

Figure S11. ^{1}H NMR (500MHz, DMSO-d_6) for **2f**.

Table S7. Comet assays of A549/DDP cells after treated with **2b** (0.42μM) and **2e** (0.11μM) for 6.0 h.

Name	Head Area	Tail Area	Head DNA	Tail DNA	Head DNA%	Tail DNA%	Head Radius	Tail Length	Comet Length	Head MeanX	Tail MeanX	Tail Moment	Olive Tail Moment
control	2178	301	356.86	8.74246	97.6088	**2.39**	26	10	63	57.0665	85.7666	0.239125	0.686291
2e	2674	3737	699.989	303.75	69.7382	**30.26**	29	122	181	75.3637	142.441	36.9194	20.2987
2b	2063	1388	415.532	70.5308	85.4894	**14.51**	26	62	115	62.1208	108.182	8.99659	6.6837

	mg/kg	1day	3d			5d			7d		
		Tumor Volume (mm^3)	Tumor Volume (mm^3)	RTV	T/C%	Tumor Volume (mm^3)	RTV	T/C%	Tumor Volume (mm^3)	RTV	T/C %
Control	_	93.2±10.0	128.4±7.2	1.386±0.119	100.0	164.1±19.8	1.760±0.086	100.0	255.3±27.3	2.755±0.342	100.0
2e	2.0	98.0±5.8	127.2±5.4	1.301±0.086	99.5	161.4±20.9	1.656±0.275	95.0	220.1±31.2	2.254±0.364	88.3
2e	10.0	93.5±10.9	121.6±1.0	1.309±0.119	94.7	152.9±15.5	1.645±0.164	93.2	188.6±16.3*	2.034±0.242**	73.9

Table S8. The tumor volume in treated and non-treated mice from the date of surgery to the study end point in the A549/DDP xenograft model.

	mg/kg	9d			11d			13d		
		Tumor Volume (mm^3)	RTV	T/C %	Tumor Volume (mm^3)	RTV	T/C%	Tumor Volume (mm^3)	RTV	T/C%
Control	_	402.3±55.4	4.369±0.861	100.0	619.7±104.2	6.767±1.623	100.0	810.1±113.9	8.812±1.818	100.0
2e	2.0	341.7±22.4	3.501±0.362	84.9	505.0±71.7	5.193±0.989	81.5	652.3±119.5	6.714±1.536	80.5
2e	10.0	246.3±16.3**	2.653±0.217**	61.2	300.9±17.6**	3.240±0.248**	48.5	338.2±28.0**	3.645±0.389**	41.7

	mg/kg	15d		
		Tumor Volume (mm^3)	RTV	T/C%
Control	_	1038.9±106.5	11.303±2.048	100.0
2e	2.0	766.5±110.7*	7.867±1.414**	73.8
2e	10.0	365.9±32.6**	3.944±0.434**	35.2

* p <0.05, ** p <0.01, p *vs* vehicle control (5.0% v/v DMSO/ saline vehicle).

Table S9. Average body weight in treated and non-treated mice from the date of surgery to the study end point in the A549/DDP xenogfart model.

	mg/kg	1 d	3 d	5 d	7 d	9 d	11 d	13 d	15 d
Control	_	19.7±0.5	19.9±0.5	20.1±0.5	20.3±0.5	20.4±0.6	20.6±0. 6	20.8±0.6	21.0±0.6
2e	2.0	19.8±0.2	20.0±0.2	20.1±0.2	20.3±0.2	20.5±0.3	20.7±0.3	20.9±0.3	21.1±0.3
2e	10.0	19.7±0.5	19.8±0.4	19.9±0.4	20.0±0.4	20.1±0.4	20.3±0.4	20.4±0.4	20.5±0.4

* p <0.05, ** p <0.01, p *vs* vehicle control (5.0% v/v DMSO/ saline vehicle).

Table S10. In Vivo Anticancer Activity of **2e** toward A549/DDP Tumor Xenograft.

	mg/kg	average tumor weight (mean ± SD, g)	inhibition of tumor growth (%)
Control	-	1.415±0.015	—

2e	2.0	1.049±0.058**	25.8
2e	10.0	0.508±0.013**	64.1

* p <0.05, ** p <0.01, p *vs* vehicle control (5.0% v/v DMSO/ saline vehicle).

Methods

The experimental steps for antitumor activities of **2a**-**2f** were similar to those illustrated in Qin, Liu and Chao *et al*[1-3]. The stock solutions of the compounds were made in DMSO, and further dilutions to working concentrations were made with the PBS and Tris-HCl buffer solution. Moreover, the A549/DDP xenograft mouse models were purchased from Changzhou Cavens Experimental Animal Co., Ltd (Jiangsu, China, Approval No. SCXK 2016-0010). The animal procedures were approved by Changzhou Cavens Experimental Animal Co., Ltd (Jiangsu, China, Approval No. 2017-0040). Further, all the experimental procedures were conducted in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals. Animal experiments were approved by Changzhou Cavens Experimental Animal Co., Ltd ((Jiangsu, China).

Notes and references

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