

Supplementary Material for

Thiazole Functionalization of Thiosemicarbazone for Cu(II) Complexation: Moving toward Highly Efficient Anticancer Drugs with Promising Oral Bioavailability

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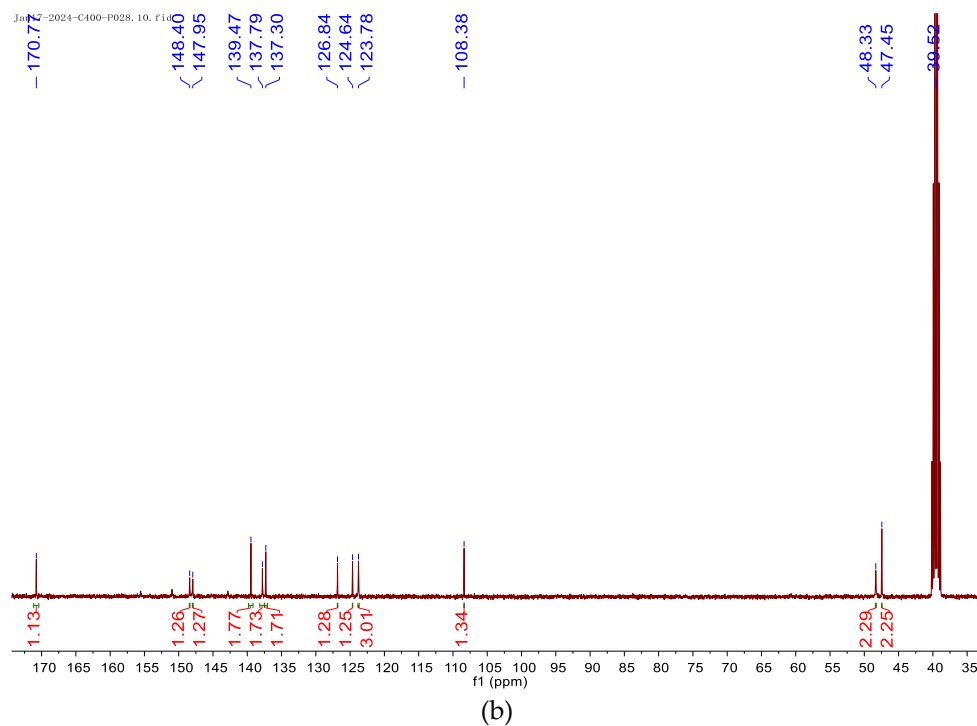
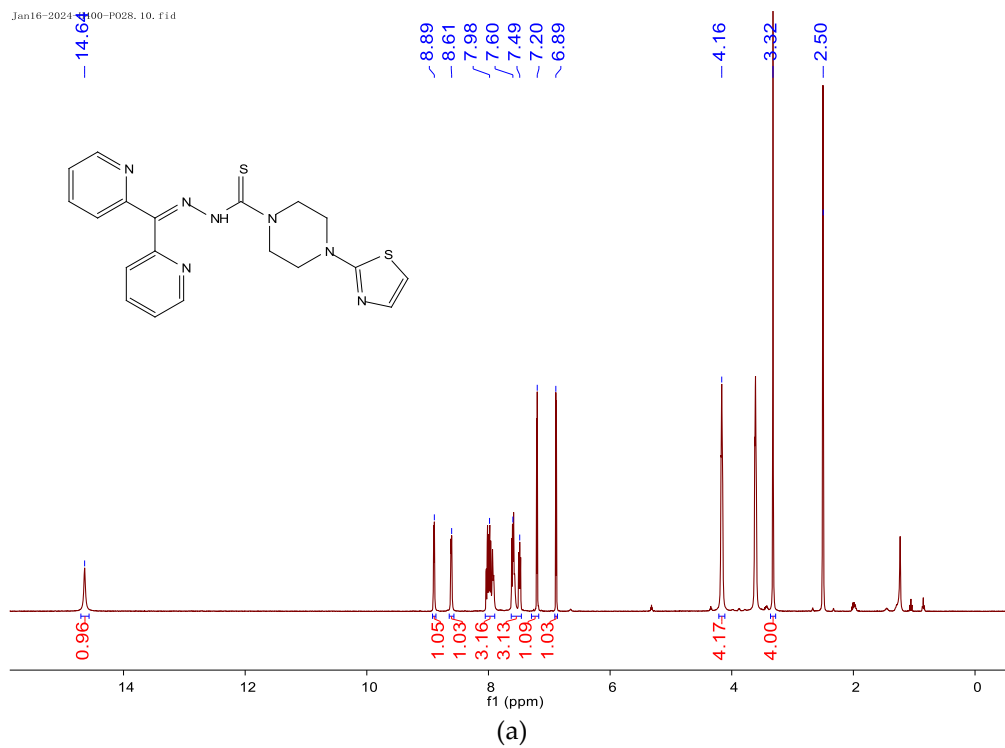
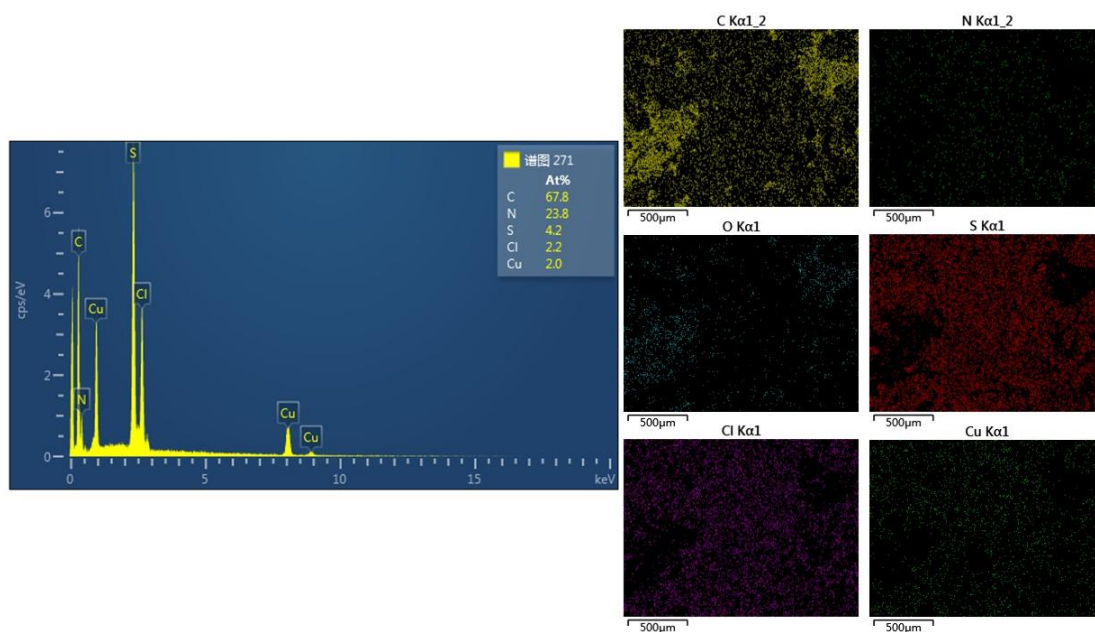
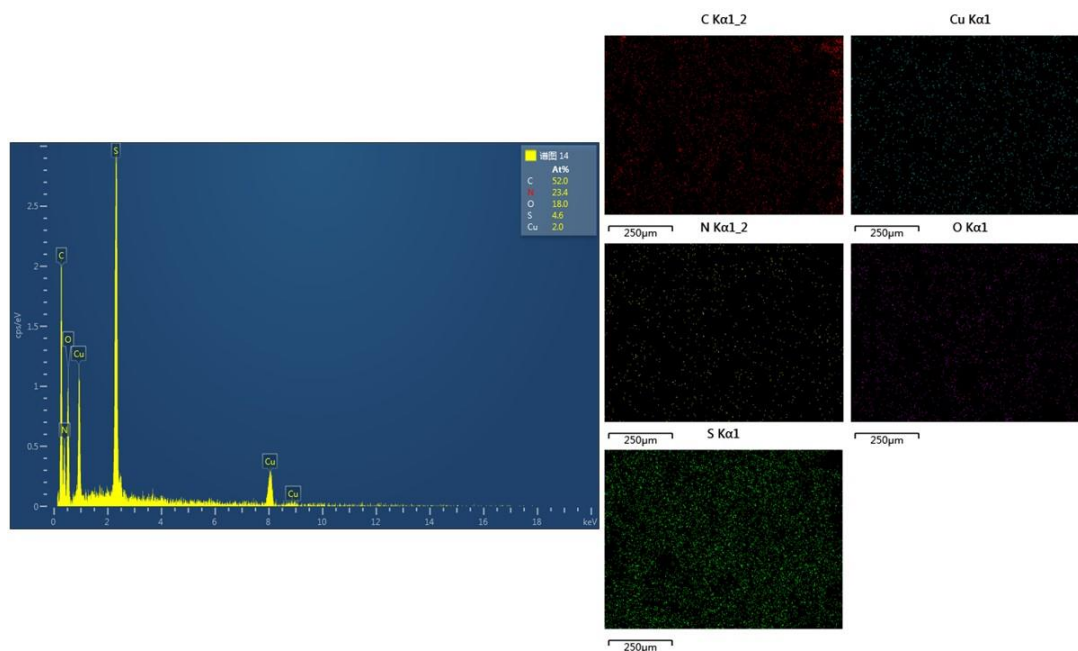


Figure S1. ¹H (a) and ¹³C (b) NMR spectrum of HL in DMSO-*d*₆.



(a)



(b)

Figure S2. The EDS elemental ratios of **1** (a) and **2** (b) and their respective elemental mapping diagrams.

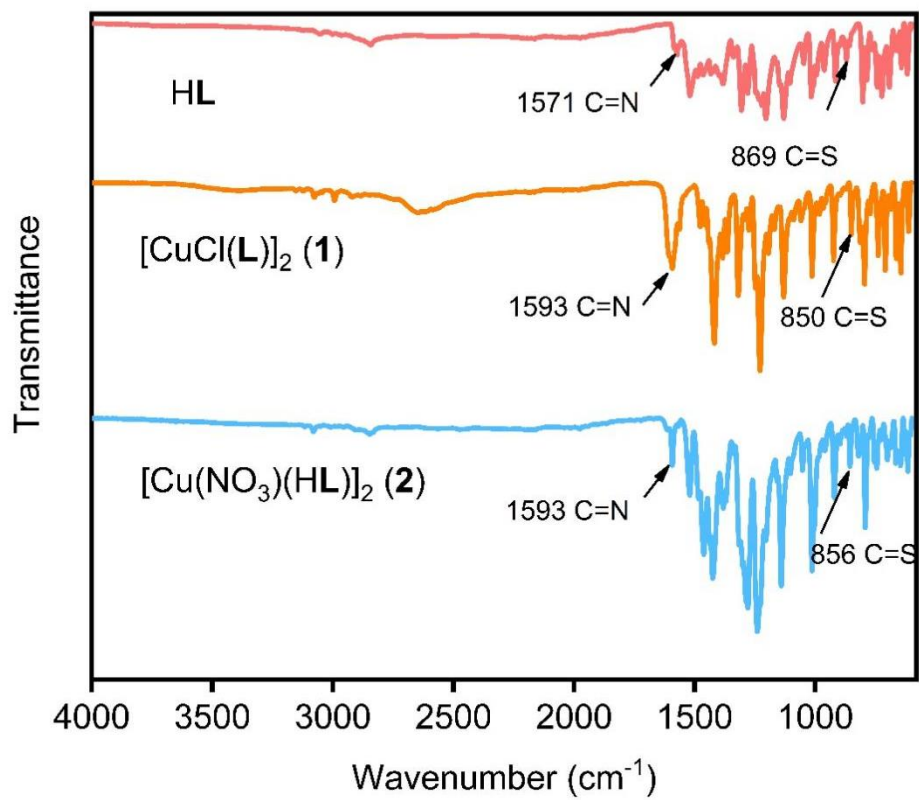


Figure S3. The FT-IR of HL (light red), 1 (light orange), and 2 (light blue).

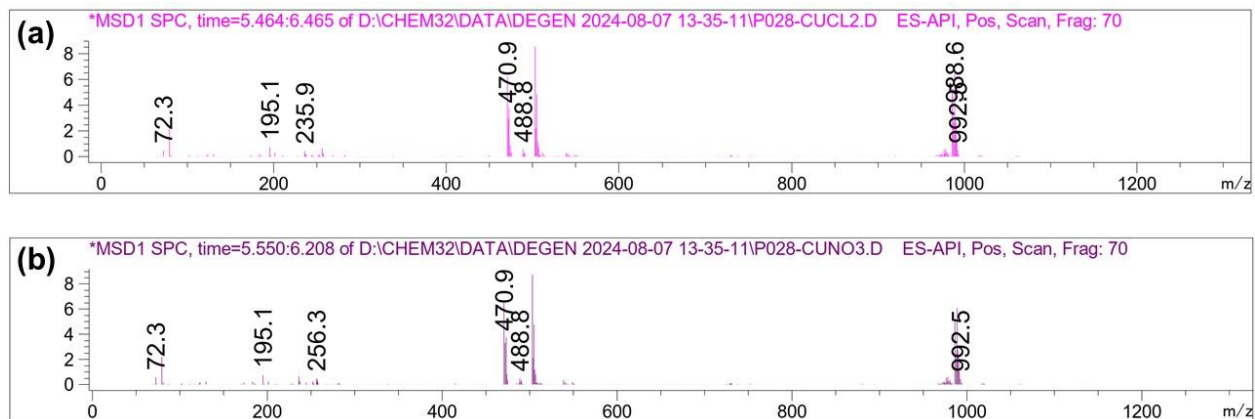


Figure S4. The liquid chromatography-mass spectrometry (LC-MS) for **1** (a) and **2** (b) using MeOH as the mobile phase.

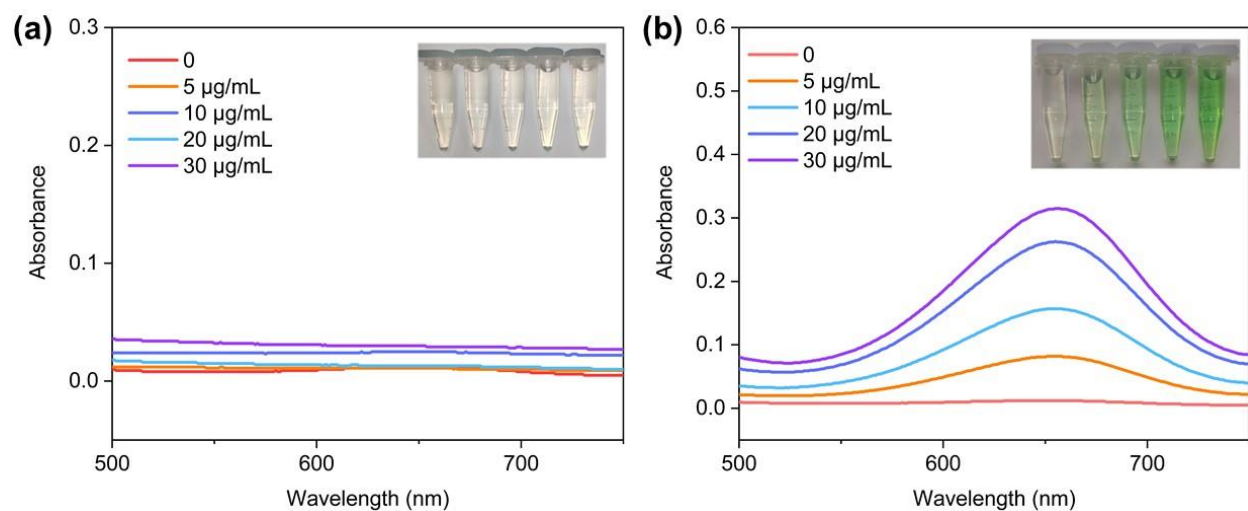


Figure S5. Change of UV-Vis absorption intensity in the range of 500–750 nm (peaked at 652 nm; oxTMB) upon treatment with different concentrations of HL (a) and **2** (b) in the presence of 100 μM H_2O_2 (insets: photographs showing color change upon introducing gradient concentrations of HL (a) and **2** (b)).

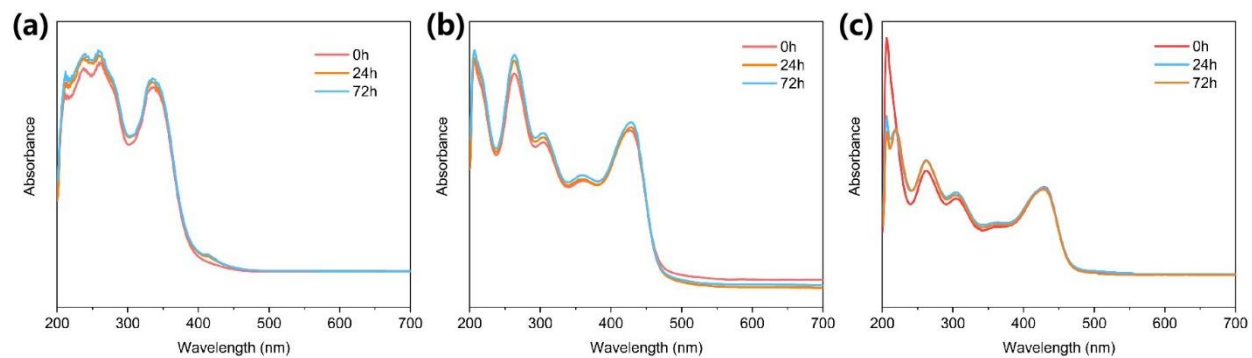


Figure S6. The UV-Vis spectrum of HL (a), **1** (b), and **2** (c) in MeOH solutions upon keeping for 24 and 72 h, demonstrating the stability of these species in solutions.

	Group	Ear Tag	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	
Sterilizing Solution	1	1														
		2														
		3														
	AV															
	SD															
HL 5 mg/kg (12.2 µmol/kg)	2	1														
		2														
		3														
	AV															
	SD															
HL 5 mg/kg (12.2 µmol/kg)	3	4														
		5														
		6														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	4	4														
		5														
		6														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	5	7														
		8														
		9														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	6	7														
		8														
		9														
	AV															
	SD															
	Group	Ear Tag	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27
Sterilizing Solution	1	1														
		2														
		3														
	AV															
	SD															
HL 5 mg/kg (12.2 µmol/kg)	2	1														
		2														
		3														
	AV															
	SD															
HL 5 mg/kg (12.2 µmol/kg)	3	4														
		5														
		6														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	4	4														
		5														
		6														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	5	7														
		8														
		9														
	AV															
	SD															
HL 10 mg/kg (24.4 µmol/kg)	6	7														
		8														
		9														
	AV															
	SD															

Figure S7. The record of CD®(SD) IGS Rats as ministered orally with sterilizing solution (groups 1, 2), 5 mg kg⁻¹ (groups 3, 4), and 10 mg kg⁻¹ (groups 5, 6) of HL. Color codes: green: normal; light blue: died; pink: euthanized; cyan: drug suspended.

Table S1. Selected bond lengths (Å) and bond angles (°) for HL, **1** and **2**.

Compound HL			
S(1)-C(1)	1.706(6)	S(1)-C(3)	1.731(5)
S(2)-C(8)	1.681(5)	N(1)-C(3)	1.314(6)
N(1)-C(2)	1.385(7)	N(2)-C(3)	1.363(6)
N(2)-C(7)	1.401(7)	N(2)-C(4)	1.430(6)
N(3)-C(8)	1.356(6)	N(3)-C(6)	1.453(6)
N(3)-C(5)	1.467(6)	N(4)-N(5)	1.354(5)
N(4)-C(8)	1.363(6)	C(4)-C(5)	1.462(7)
N(5)-C(9)	1.308(6)	N(6)-C(10)	1.325(6)
N(6)-C(14)	1.352(7)	N(7)-C(19)	1.334(6)
N(7)-C(15)	1.350(6)	C(1)-C(2)	1.317(8)
C(9)-C(15)	1.473(6)	C(6)-C(7)	1.414(8)
C(10)-C(11)	1.364(7)	C(11)-C(12)	1.372(7)
C(9)-C(10)	1.501(6)	C(12)-C(13)	1.348(8)
C(17)-C(18)	1.383(8)	C(13)-C(14)	1.352(8)
C(15)-C(16)	1.386(7)	C(16)-C(17)	1.390(7)
C(18)-C(19)	1.371(7)		
C(1)-S(1)-C(3)	89.2(3)	C(3)-N(1)-C(2)	108.6(5)
C(3)-N(2)-C(7)	121.7(4)	C(3)-N(2)-C(4)	119.3(4)
C(7)-N(2)-C(4)	113.2(4)	C(8)-N(3)-C(6)	123.7(4)
C(8)-N(3)-C(5)	119.5(4)	C(6)-N(3)-C(5)	114.7(4)
N(5)-N(4)-C(8)	120.5(4)	C(9)-N(5)-N(4)	118.4(4)
C(10)-N(6)-C(14)	115.9(5)	C(19)-N(7)-C(15)	118.8(4)
C(2)-C(1)-S(1)	110.2(4)	C(1)-C(2)-N(1)	117.5(5)
N(1)-C(3)-N(2)	124.1(5)	N(1)-C(3)-S(1)	114.5(4)
N(2)-C(3)-S(1)	121.4(4)	N(2)-C(4)-C(5)	112.8(5)
C(4)-C(5)-N(3)	113.7(5)	C(7)-C(6)-N(3)	115.6(5)
N(3)-C(8)-N(4)	113.7(4)	N(2)-C(7)-C(6)	119.4(6)
N(3)-C(8)-S(2)	124.0(4)	N(4)-C(8)-S(2)	122.3(4)
N(5)-C(9)-C(15)	128.5(4)	N(5)-C(9)-C(10)	110.6(4)
C(15)-C(9)-C(10)	121.0(4)	N(6)-C(10)-C(11)	122.0(5)
N(6)-C(10)-C(9)	116.4(4)	C(11)-C(10)-C(9)	121.5(5)

Table S1 Continued

C(10)-C(11)-C(12)	120.4(5)	C(13)-C(12)-C(11)	118.6(6)
C(12)-C(13)-C(14)	118.0(5)	C(13)-C(14)-N(6)	125.0(6)
N(7)-C(15)-C(16)	120.7(4)	N(7)-C(15)-C(9)	117.0(4)
C(16)-C(15)-C(9)	122.2(4)	C(15)-C(16)-C(17)	119.7(5)
C(18)-C(17)-C(16)	119.0(5)	C(19)-C(18)-C(17)	118.1(5)
N(7)-C(19)-C(18)	123.7(5)		

Compound 1

Cu(1)-N(3)	1.989(3)	Cu(1)-N(2)	2.016(3)
Cu(1)-Cl	2.2435(10)	Cu(1)-S(2)	2.2518(10)
N(1)-C(1)	1.344(5)	N(1)-C(5)	1.353(4)
N(2)-C(11)	1.336(4)	N(2)-C(7)	1.350(4)
N(3)-C(6)	1.306(4)	N(3)-N(4)	1.354(4)
N(4)-C(12)	1.343(4)	N(5)-C(12)	1.352(5)
N(5)-C(15)	1.472(4)	N(5)-C(13)	1.474(4)
N(6)-C(17)	1.378(5)	N(6)-C(14)	1.444(5)
N(6)-C(16)	1.476(4)	N(7)-C(18)	1.361(5)
N(7)-C(17)	1.373(5)	C(1)-C(2)	1.387(5)
C(6)-C(7)	1.477(5)	C(2)-C(3)	1.393(5)
C(8)-C(9)	1.390(5)	C(3)-C(4)	1.377(5)
C(9)-C(10)	1.376(5)	C(4)-C(5)	1.396(5)
C(10)-C(11)	1.388(5)	C(5)-C(6)	1.482(5)
C(12)-S(2)	1.739(4)	C(7)-C(8)	1.395(5)
C(13)-C(14)	1.536(5)	C(15)-C(16)	1.529(5)
C(17)-S(1)	1.730(4)	C(18)-C(19)	1.336(6)
C(19)-S(1)	1.713(4)		

N(3)-Cu(1)-N(2)	80.60(12)	N(6)-C(14)-C(13)	111.4(3)
N(3)-Cu(1)-Cl	165.09(9)	N(2)-Cu(1)-Cl	97.99(9)
N(3)-Cu(1)-S(2)	83.91(9)	N(2)-Cu(1)-S(2)	163.71(9)
Cl-Cu(1)-S(2)	95.66(4)	C(1)-N(1)-C(5)	116.7(3)
C(11)-N(2)-C(7)	119.5(3)	C(11)-N(2)-Cu(1)	126.7(2)
C(7)-N(2)-Cu(1)	113.5(2)	C(6)-N(3)-N(4)	120.4(3)
C(6)-N(3)-Cu(1)	116.1(2)	N(4)-N(3)-Cu(1)	123.4(2)
C(12)-N(4)-N(3)	111.9(3)	C(12)-N(5)-C(15)	120.6(3)

Table S1 Continued

C(12)-N(5)-C(13)	122.1(3)	C(15)-N(5)-C(13)	111.3(3)
C(17)-N(6)-C(14)	116.9(3)	C(17)-N(6)-C(16)	119.9(3)
C(14)-N(6)-C(16)	112.0(3)	C(18)-N(7)-C(17)	108.0(3)
N(1)-C(1)-C(2)	124.3(3)	C(3)-C(4)-C(5)	119.3(3)
C(4)-C(3)-C(2)	119.0(3)	C(1)-C(2)-C(3)	117.9(3)
N(1)-C(5)-C(4)	122.6(3)	N(1)-C(5)-C(6)	116.4(3)
C(4)-C(5)-C(6)	121.0(3)	N(3)-C(6)-C(7)	114.8(3)
N(3)-C(6)-C(5)	123.9(3)	C(7)-C(6)-C(5)	121.1(3)
N(2)-C(7)-C(8)	121.0(3)	N(2)-C(7)-C(6)	114.7(3)
C(8)-C(7)-C(6)	124.3(3)	C(9)-C(8)-C(7)	118.7(3)
C(10)-C(9)-C(8)	120.1(3)	C(9)-C(10)-C(11)	118.0(3)
N(2)-C(11)-C(10)	122.6(3)	N(4)-C(12)-N(5)	116.7(3)
N(4)-C(12)-S(2)	124.6(3)	N(5)-C(12)-S(2)	118.7(3)
N(5)-C(13)-C(14)	107.9(3)	N(5)-C(15)-C(16)	109.1(3)
N(6)-C(16)-C(15)	111.1(3)	C(18)-C(19)-S(1)	110.2(3)
N(7)-C(17)-N(6)	124.8(3)	N(7)-C(17)-S(1)	113.9(3)
N(6)-C(17)-S(1)	121.1(3)	C(19)-C(18)-N(7)	118.4(4)
C(12)-S(2)-Cu(1)	95.73(12)	C(19)-S(1)-C(17)	89.5(2)

Compound 2

Cu(1)-N(5)	1.961(4)	Cu(1)-N(6)	2.017(4)
Cu(1)-O(1)	2.024(4)	Cu(1)-S(2)	2.2733(16)
Cu(1)-N(7)#1	2.357(5)	S(1)-C(1)	1.724(7)
S(1)-C(3)	1.748(6)	S(2)-C(8)	1.744(6)
O(1)-N(8)	1.281(6)	O(2)-N(8)	1.226(6)
O(3)-N(8)	1.235(7)	N(1)-C(3)	1.300(8)
N(1)-C(2)	1.379(8)	N(2)-C(3)	1.368(7)
N(2)-C(7)	1.428(8)	N(2)-C(4)	1.444(8)
N(3)-C(8)	1.353(7)	N(3)-C(6)	1.451(8)
N(3)-C(5)	1.469(8)	N(4)-C(8)	1.323(7)
N(4)-N(5)	1.351(6)	N(5)-C(9)	1.301(7)
N(6)-C(14)	1.333(7)	N(6)-C(10)	1.347(7)
N(7)-C(15)	1.335(7)	N(7)-C(19)	1.341(7)
C(1)-C(2)	1.332(10)	C(4)-C(5)	1.402(10)
C(6)-C(7)	1.393(11)	C(9)-C(10)	1.468(7)

Table S1 Continued

C(9)-C(15)	1.491(7)	C(10)-C(11)	1.396(8)
C(11)-C(12)	1.389(8)	C(12)-C(13)	1.368(9)
C(13)-C(14)	1.382(9)	C(15)-C(16)	1.380(8)
C(16)-C(17)	1.376(8)	C(17)-C(18)	1.377(9)
C(18)-C(19)	1.373(9)		
N(5)-Cu(1)-N(6)	80.90(18)	N(7)-C(19)-C(18)	123.5(6)
N(5)-Cu(1)-O(1)	156.10(17)	N(6)-Cu(1)-O(1)	93.88(17)
N(5)-Cu(1)-S(2)	84.14(13)	N(6)-Cu(1)-S(2)	164.95(14)
O(1)-Cu(1)-S(2)	99.18(12)	N(5)-Cu(1)-N(7)#1	116.76(17)
N(6)-Cu(1)-N(7)#1	89.60(18)	O(1)-Cu(1)-N(7)#1	86.32(16)
S(2)-Cu(1)-N(7)#1	98.63(12)	C(1)-S(1)-C(3)	88.2(3)
C(8)-S(2)-Cu(1)	94.53(19)	N(8)-O(1)-Cu(1)	109.3(3)
C(3)-N(1)-C(2)	109.1(5)	C(3)-N(2)-C(7)	121.5(5)
C(3)-N(2)-C(4)	118.7(5)	C(7)-N(2)-C(4)	115.6(5)
C(8)-N(3)-C(6)	123.4(5)	C(8)-N(3)-C(5)	121.2(5)
C(6)-N(3)-C(5)	114.4(5)	C(8)-N(4)-N(5)	112.4(4)
C(9)-N(5)-N(4)	119.6(4)	C(9)-N(5)-Cu(1)	116.6(4)
N(4)-N(5)-Cu(1)	123.7(3)	C(14)-N(6)-C(10)	119.6(5)
C(14)-N(6)-Cu(1)	127.5(4)	C(10)-N(6)-Cu(1)	112.8(4)
C(15)-N(7)-C(19)	117.3(5)	C(15)-N(7)-Cu(1)#1	123.3(4)
C(19)-N(7)-Cu(1)#1	114.7(4)	O(2)-N(8)-O(3)	122.5(5)
O(2)-N(8)-O(1)	118.9(5)	O(3)-N(8)-O(1)	118.6(5)
C(2)-C(1)-S(1)	110.1(5)	C(1)-C(2)-N(1)	117.3(6)
N(1)-C(3)-N(2)	124.7(5)	N(1)-C(3)-S(1)	115.3(4)
N(2)-C(3)-S(1)	120.0(4)	C(5)-C(4)-N(2)	115.6(6)
C(4)-C(5)-N(3)	114.7(6)	C(7)-C(6)-N(3)	115.1(7)
C(6)-C(7)-N(2)	117.2(7)	N(4)-C(8)-N(3)	115.7(5)
N(4)-C(8)-S(2)	125.2(4)	N(3)-C(8)-S(2)	119.2(4)
N(5)-C(9)-C(10)	114.7(5)	N(5)-C(9)-C(15)	123.1(5)
C(10)-C(9)-C(15)	122.2(5)	N(6)-C(10)-C(11)	121.1(5)
N(6)-C(10)-C(9)	114.9(5)	C(11)-C(10)-C(9)	124.0(5)
C(12)-C(11)-C(10)	118.5(6)	C(13)-C(12)-C(11)	119.6(6)
C(12)-C(13)-C(14)	119.1(6)	N(6)-C(14)-C(13)	122.0(6)
N(7)-C(15)-C(16)	122.9(5)	N(7)-C(15)-C(9)	116.3(5)

Table S1 Continued

C(16)-C(15)-C(9)	120.9(5)	C(17)-C(16)-C(15)	118.7(6)
C(16)-C(17)-C(18)	119.3(6)	C(19)-C(18)-C(17)	118.2(6)

Symmetry transformations used to generate equivalent atoms: #1 $-x - 2, -y + 2, -z + 1$

Table S2. The half-maximal inhibitory concentrations (IC₅₀) of HL, **1**, and **2** against different cell lines.

	IC ₅₀ (nmol/mL)		
	HL	1	2
Hep-G2	78.83	38.11	16.86
PLC/PRF/5	3.26	2.18	2.54×10 ⁻⁵
HuH-7	192.20	176.60	87.53

Table S3. The pharmacokinetic data for HL via i.v. administration with dosages of 0.5 mg kg⁻¹ in ICR mice (n = 3).

Individual and mean plasma concentration-time data								
Dose (mg·kg ⁻¹)	Dose route	Sampling time (h)	Concentration (ng/mL)			Mean (ng/mL)	SD	CV (%)
			4	5	6			
0.50	IV	0.03	853.50	805.60	760.20	806.43	46.66	5.79
		0.50	407.40	426.80	213.60	349.27	117.89	33.75
		1.00	419.70	361.50	242.30	341.17	90.43	26.51
		2.00	447.60	405.10	263.20	371.97	96.56	25.96
		4.00	346.80	274.20	98.40	239.80	127.72	53.26
		8.00	218.90	227.60	41.40	162.63	105.08	64.61
		24.00	113.30	88.60	49.40	83.77	32.22	38.47
PK Parameters		Unit	4	5	6	Mean	SD	/
R ²		NA	0.89	1.00	0.44	0.78	0.30	38.00
T _{1/2}		h	13.40	12.12	10.12	11.88	1.66	13.93
T _{max}		h	0.03	0.03	0.03	0.03	0.00	0.00
C ₀		ng/mL	899.29	842.59	831.55	857.81	36.35	4.24
AUC _{last}		h*ng/mL	5547.17	5107.84	1987.97	4214.32	1940.5	46.05
AUC _{0-inf}		h*ng/mL	7738.05	6656.93	2709.11	5701.36	2647.1	46.43
V _{z_obs}		mL/kg	1249.48	1313.23	2694.23	1752.31	816.35	46.59
Cl _{obs}		mL/h/kg	64.62	75.11	184.56	108.10	66.43	61.45
MRT _{last}		h	8.15	7.85	7.55	7.85	0.30	3.81
V _{ss_obs}		mL/kg	1170.20	1177.58	2918.63	1755.47	1007.3	57.38

Table S4. The pharmacokinetic data for HL via PO administration with dosages of 30 mg kg⁻¹ in ICR mice (n = 3).

Individual and mean plasma concentration-time data								
Dose (mg·kg ⁻¹)	Dose route	Sampling time (h)	Concentration (ng/mL)			Mean (ng/mL) /	SD	CV (%)
			1	2	3			
30	PO	0.50	280.8	350.5	95.9	242.40	131.6	54.3
		1.00	400.3	264.1	613.4	425.93	176.1	41.3
		2.00	452.9	314.0	462.6	409.83	83.1	20.3
		4.00	408.7	221.3	317.2	315.73	93.7	29.7
		8.00	253.0	163.0	236.7	217.57	48.0	22.0
		24.00	226.5	114.6	93.3	144.80	71.6	49.4
PK Parameters		Unit	1	2	3	Mean	SD	/
R ²		NA	0.21	0.83	1.00	0.68	0.4	61.1
T _{1/2}		h	30.06	23.26	11.49	21.61	9.4	43.5
T _{max}		h	2.00	0.50	1.00	1.17	0.8	65.5
C _{max}		ng/mL	452.90	350.50	613.40	472.27	132.5	28.1
AUC _{last}		h*ng/mL	6688.08	4055.03	5266.90	5336.67	1317.9	24.7
AUC _{0-inf}		h*ng/mL	16512.12	7901.48	6813.43	10409.01	5313.4	51.0
V _{z_F_obs}		mL/kg	78802.61	127435.04	72984.82	93074.16	29899.	32.1
Cl _{F_obs}		mL/h/kg	1816.85	3796.76	4403.07	3338.89	1352.5	40.5
MRT _{last}		h	10.52	9.60	8.07	9.40	1.2	13.1

Table S5. The weight record of CD®(SD) IGS Rats as ministered orally with sterilizing solution (groups 1, 2), 5 mg kg⁻¹ (groups 3, 4), and 10 mg kg⁻¹ (groups 5, 6) of HL.

	Group	Ear Tag	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	
Sterilizing Solution	1	1	182.5	178.9	189.5	195.1	196.4	190.2	194.3	208.9	209.5	216.2	218.8	230.1	234.1	
		2	193.2	191.2	196.9	191.0	200.9	205.7	207.6	211.4	210.7	216.5	222.8	224.0	225.8	
		3	189.4	193.3	204.1	208.3	215.2	218.6	225.1	232.6	235.2	242.3	244.7	250.3	260.9	
	AV		188.4	187.8	196.8	198.1	204.2	204.8	209.0	217.6	218.5	225.0	228.8	234.8	240.3	
		SD	5.4	7.8	7.3	9.0	9.8	14.2	15.4	13.0	14.5	15.0	13.9	13.8	18.3	
	2	1	179.6	192.7	202.6	213.5	223.4	234.8	248.2	257.7	263.6	273.9	286.5	290.4	309.3	
		2	204.9	209.9	221.3	228.6	234.8	246.6	254.4	264.1	266.8	273.6	285.3	292.9	305.7	
		3	197.3	209.9	219.2	225.7	228.9	243.2	253.1	262.4	264.8	274.6	288.3	290.1	302.2	
	AV		193.9	204.2	214.4	222.6	229.0	241.5	251.9	261.4	265.1	274.0	286.7	291.1	305.7	
		SD	13.0	9.9	10.2	8.0	5.7	6.1	3.3	3.3	1.6	0.5	1.5	1.5	3.6	
HL 5 mg/kg (12.2 µmol/kg)	3	4	189.1	186.5	198.3	199.2	204.6	204.5	211.1	209.3	199.7	183.6	178.8	179.1	181.3	
		5	191.2	193.0	193.1	203.8	205.1	215.4	214.8	210.2	216.9	227.8	229.7	226.4	227.2	
		6	187.7	185.7	193.9	197.8	196.9	194.1	204.6	207.8	211.0	203.5	212.3	216.5	219.3	
	AV		189.3	188.4	195.1	200.3	202.2	204.7	210.2	209.1	209.2	205.0	206.9	207.3	209.3	
		SD	1.8	4.0	2.8	3.1	4.6	10.7	5.2	1.2	8.7	22.1	25.9	24.9	24.5	
	4	4	191.4	198.6	209.6	220.3	225.1	232.6	245.6	253.8	263.8	275.4	284.0	292.5	299.6	
		5	192.0	203.2	213.9	224.9	230.1	241.3	249.9	265.7	264.6	280.0	289.3	293.9	302.9	
		6	194.1	204.2	211.8	223.9	231.6	243.1	256.0	266.3	272.9	284.1	293.6	301.3	311.5	
	AV		192.5	202.0	211.8	223.0	228.9	239.0	250.5	261.9	267.1	279.8	289.0	295.9	304.7	
		SD	1.4	3.0	2.2	2.4	3.4	5.6	5.2	7.1	5.0	4.4	4.8	4.7	6.1	
HL 10 mg/kg (24.4 µmol/kg)	5	7	191.0	185.1	198.5	202.4	204.7	206.9	200.8	194.1	197.2	190.1	193.6	191.3	197.5	
		8	190.4	187.1	202.5	207.8	199.9	189.7	186.4	168.8	157.8	140.2	-	-	-	
		9	180.9	177.2	190.5	190.4	186.3	187.8	172.1	156.4	145.9	134.5	-	-	-	
	AV		187.4	183.1	197.2	200.2	197.0	194.8	186.4	173.1	167.0	154.9	193.6	191.3	197.5	
		SD	5.7	5.2	6.1	8.9	9.5	10.5	14.4	19.2	26.9	30.6	111.8	110.4	114.0	
	6	7	197.7	202.9	215.0	219.4	228.9	241.5	250.7	266.0	272.8	269.1	291.9	298.9	308.1	
		8	195.7	208.1	218.2	227.8	235.2	244.8	251.5	257.6	264.3	259.9	274.7	274.9	275.3	
		9	189.5	200.0	210.5	219.1	220.7	233.3	243.0	252.9	260.0	259.3	277.1	282.3	291.8	
	AV		194.3	203.7	214.6	222.1	228.3	239.9	248.4	258.8	265.7	262.8	281.2	285.4	291.7	
		SD	4.3	4.1	3.9	4.9	7.3	5.9	4.7	6.6	6.5	5.5	9.3	12.3	16.4	
	Group	Ear Tag	D14	D15	D16	D17	D18	D19	D20	D21	D22	D23	D24	D25	D26	D27
Sterilizing Solution	1	1	234.4	240.4	243.6	241.5	235.9	235.1	231.5	225.6	230.6	231.2	236.6	234.6	235.1	239.3
		2	230.7	232.3	235.7	236.7	240.3	242.0	246.8	244.2	241.2	242.9	247.5	254.7	251.6	247.3
		3	261.5	263.6	265.6	269.8	270.5	265.1	274.6	279.1	284.0	279.2	288.6	293.5	299.9	303.9
	AV		242.2	245.4	248.3	249.3	248.9	247.4	251.0	249.6	251.9	251.1	257.6	260.9	262.2	263.5
		SD	16.8	16.2	15.5	17.9	18.8	15.7	21.9	27.2	28.3	25.0	27.4	29.9	33.7	35.2
	2	1	318.8	320.5	326.0	340.7	347.7	349.1	353.9	364.4	366.5	373.4	383.1	393.8	401.0	402.3
		2	314.7	314.1	328.9	334.2	343.3	350.2	358.1	366.5	379.2	375.9	386.5	395.6	401.2	407.3
		3	306.9	316.5	324.9	330.7	335.8	341.7	352.2	357.3	367.0	373.5	389.5	392.3	402.6	397.7
	AV		313.5	317.0	326.6	335.2	342.3	347.0	354.7	362.7	370.9	374.3	386.4	393.9	401.6	402.4
		SD	6.0	3.2	2.1	5.1	6.0	4.6	3.0	4.8	7.2	1.4	3.2	1.7	0.9	4.8
HL 5 mg/kg (12.2 µmol/kg)	3	4	177.3	177.0	-	-	-	-	-	-	-	-	-	-	-	-
		5	233.1	233.7	241.9	238.4	226.5	220.9	213.6	204.5	205.8	192.8	197.6	198.3	198.6	207.3
		6	213.4	222.1	224.9	227.6	221.6	232.9	234.1	235.0	234.1	230.1	242.3	238.0	243.8	237.3
	AV		207.9	210.9	233.4	233.0	224.1	226.9	223.9	219.8	220.0	211.5	220.0	218.2	221.2	222.3
		SD	28.3	30.0	135.0	134.6	129.4	131.1	129.6	127.8	127.8	123.5	128.9	127.5	129.7	129.2
	4	4	305.1	316.9	321.7	333.5	339.6	347.6	352.0	361.5	365.9	372.6	386.3	386.8	399.0	404.0
		5	309.8	320.1	-	-	-	-	-	-	-	-	-	-	-	-
		6	320.6	329.6	335.4	348.8	356.8	367.9	373.5	382.0	387.8	393.6	400.9	406.9	409.9	412.1
	AV		311.8	322.2	328.6	341.2	348.2	357.8	362.8	371.8	376.9	383.1	393.6	396.9	404.5	408.1
		SD	7.9	6.6	189.8	197.1	201.2	206.8	209.7	214.9	217.8	221.4	227.4	229.3	233.6	235.6
HL 10 mg/kg (24.4 µmol/kg)	5	7	202.5	203.5	-	-	-	-	-	-	-	-	-	-	-	-
		8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		9	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	AV		202.5	203.5	-	-	-	-	-	-	-	-	-	-	-	-
		SD	116.9	117.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	6	7	314.9	324.3	330.3	345.5	351.4	358.9	364.2	374.1	372.9	377.8	378.5	387.9	368.4	364.5
		8	254.4	231.4	199.4	-	-	-	-	-	-	-	-	-	-	-
		9	299.6	305.6	315.2	325.1	330.1	334.3	339.4	343.4	349.1	346.3	345.1	344.0	350.4	358.9
	AV		289.6	287.1	281.6	335.3	340.8	346.6	351.8	358.8	361.0	362.1	361.8	366.0	359.4	361.7
		SD	31.5	49.1	71.6	193.9	197.0	200.5	203.5	207.7	208.8	209.6	209.6	212.4	207.7	208.8