Supplementary Material for

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

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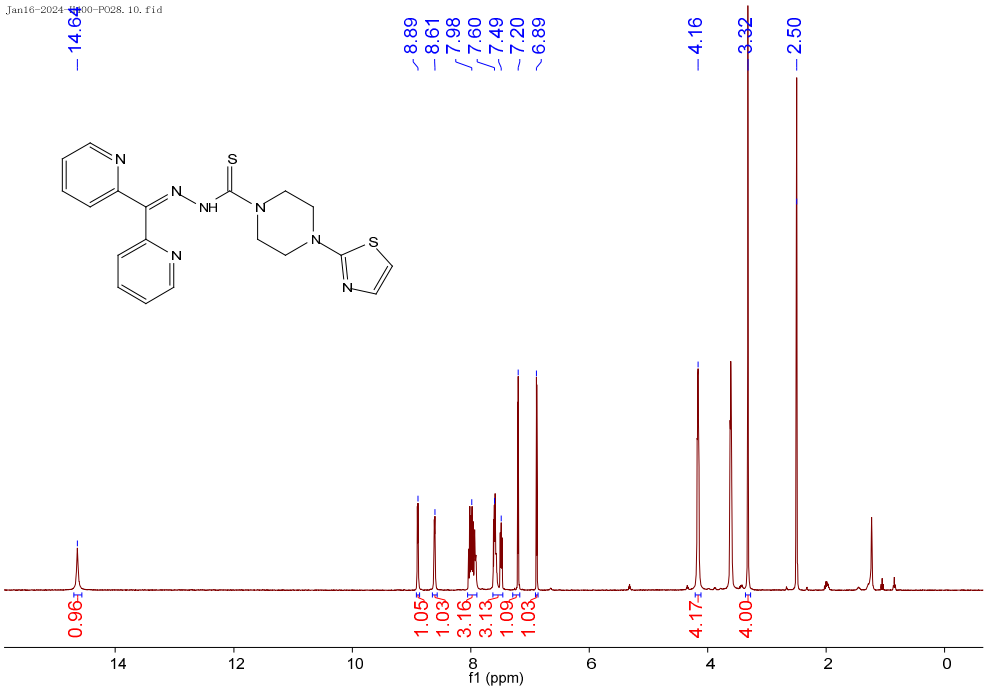
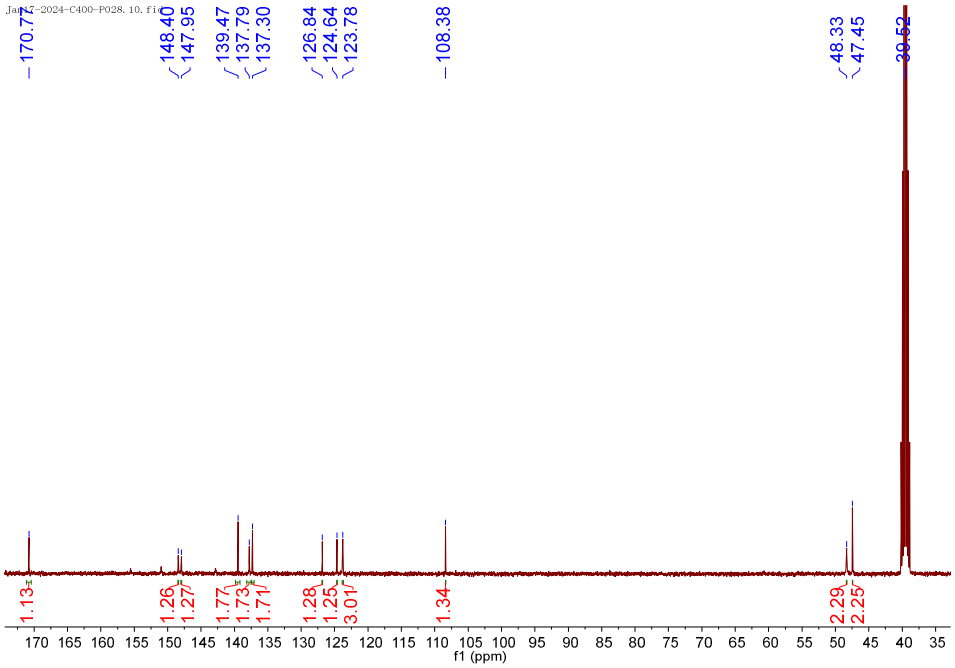
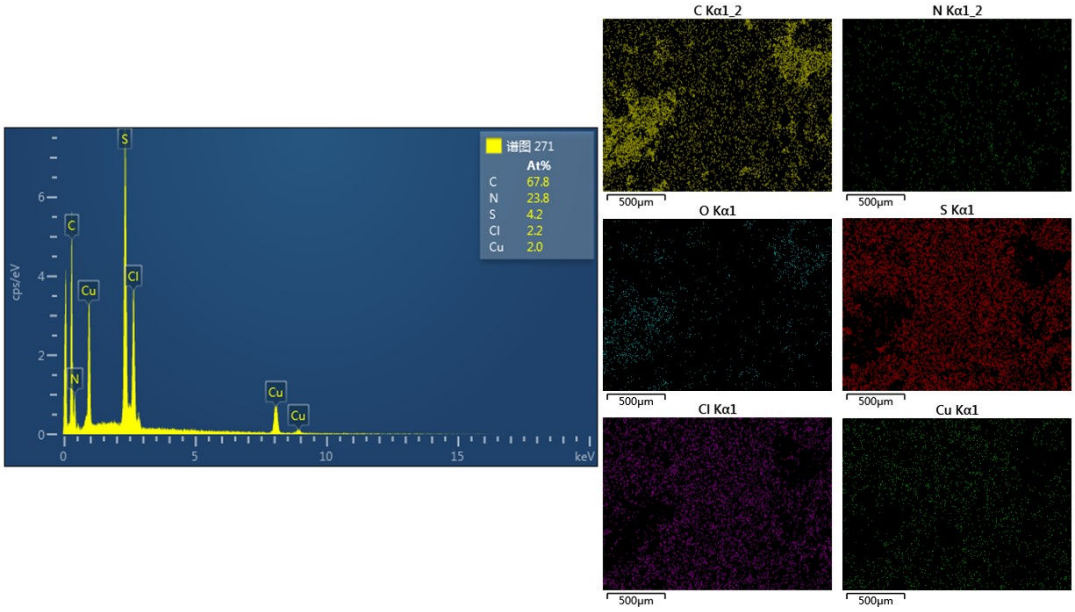


(a)

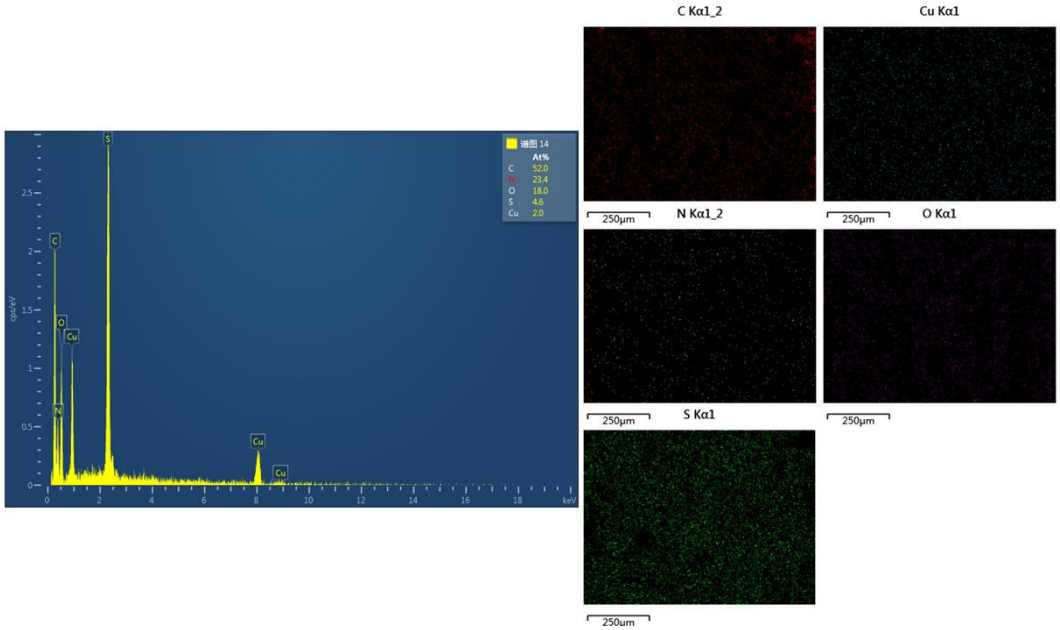


(b)

Figure S1. ^{1}H (a) and ^{13}C (b) NMR spectrum of H**L** in DMSO-d_6.



(a)



(b)

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

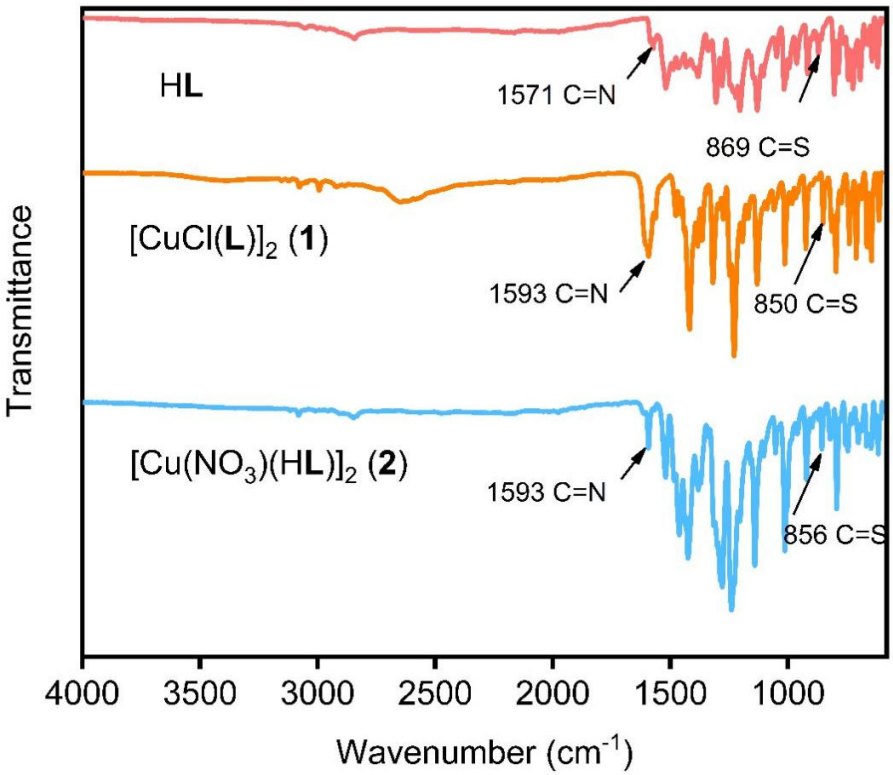


Figure S3. The FT-IR of H**L** (light red), **1** (light orange), and **2** (light blue).

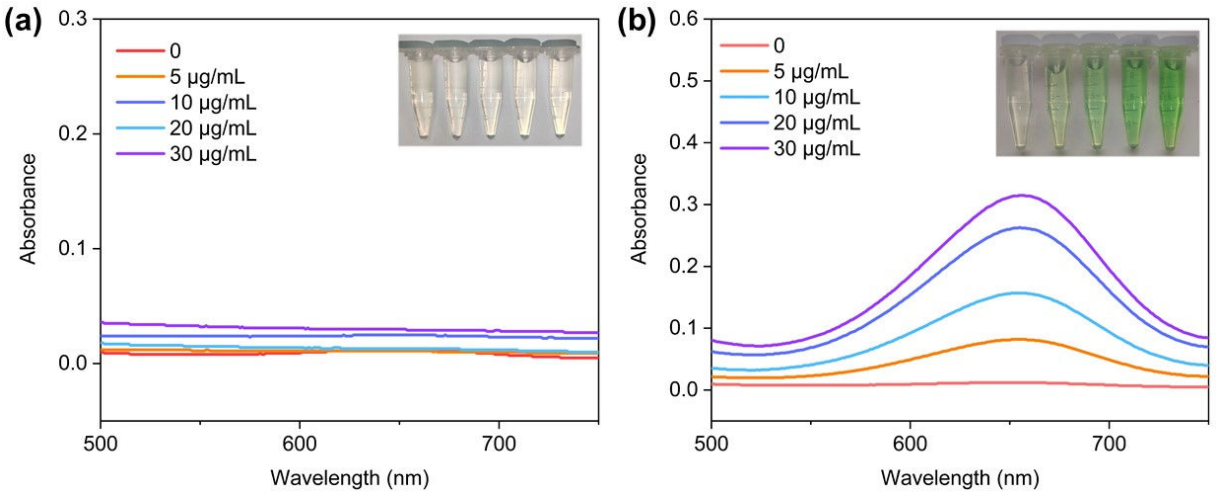


Figure S4. Change of UV-Vis absorption intensity in the range of 500–750 nm (peaked at 652 nm; oxTMB) upon treatment with different concentrations of H**L** (a) and **2** (b) in the presence of 100 μM H_2O_2 (insets: photographs showing color change upon introducing gradient concentrations of H**L** (a) and **2** (b)).

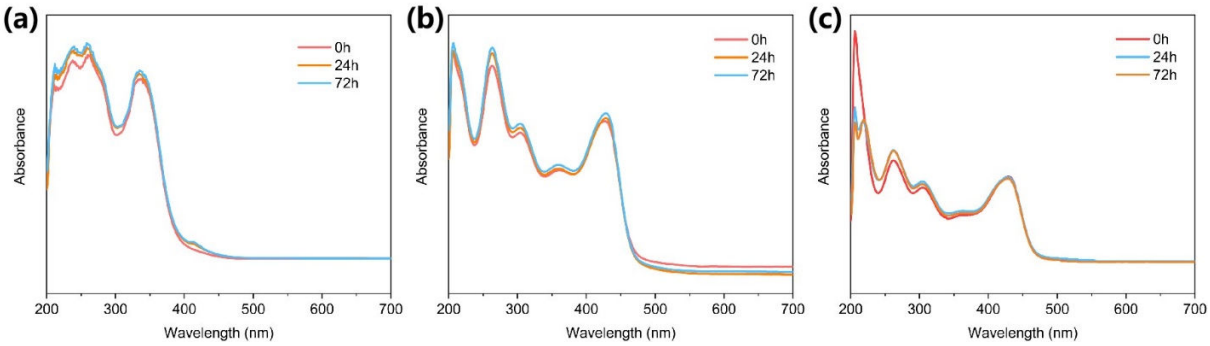


Figure S5. The UV-Vis spectrum of H**L** (a), **1** (b), and **2** (c) in MeOH solutions upon keeping for 24 and 72 h, demonstrating the stability of these species in solutions.

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

Compound H**L**			
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 (IC_{50}) of H**L**, **1**, and **2** against different cell lines.

	IC_{50} (nmol/mL)		
	H**L**	**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 H**L** 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 ($mg \cdot kg^{-1}$)	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
$AUC_{0\text{-}inf}$		h*ng/mL	7738.05	6656.93	2709.11	5701.36	2647.1	46.43
Vz_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
Vss_obs		mL/kg	1170.20	1177.58	2918.63	1755.47	1007.3	57.38

Table S4. The pharmacokinetic data for H**L** via PO administration with dosages of 30 mg kg^{-1} in ICR mice (n = 3).

Individual and mean plasma concentration-time data								
Dose ($mg \cdot kg^{-1}$)	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
$AUC_{0\text{-}inf}$		h*ng/mL	16512.12	7901.48	6813.43	10409.01	5313.4	51.0
Vz_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