Simultaneously GSH-Depleted Bimetallic Cu(II) Complex for Enhanced Chemodynamic Cancer Therapy

Shuhua Cao[a], Xuezhao Li[b]*, Yong Gao[c], Fahui Li[d], Kaoxue Li[a], Xuanxuan Cao[a], Yiwen Dai[a], Lirong Mao[a], Shanshan Wang[a] and Xishi Tai[a]*

a. College of Chemistry, Chemical and Environmental Engineering, Weifang University, No. 5147 Dongfeng Street, Weifang, 261061, P. R. China. E-mail: taixs@wfu.edu.cn

b. State Key Laboratory of Fine Chemicals, Dalian University of Technology, No. 2 Linggong Road, Dalian 116024, P. R. China. E-mail: xuezhaoli@dlut.edu.cn

c. Dongying Shengli Hospital, No.107 Beier Road, Dongying, 257055, P. R. China

d. School of Pharmacy, Weifang Medical University, No. 7166 Baotong Street, Weifang, 261053, P. R. China

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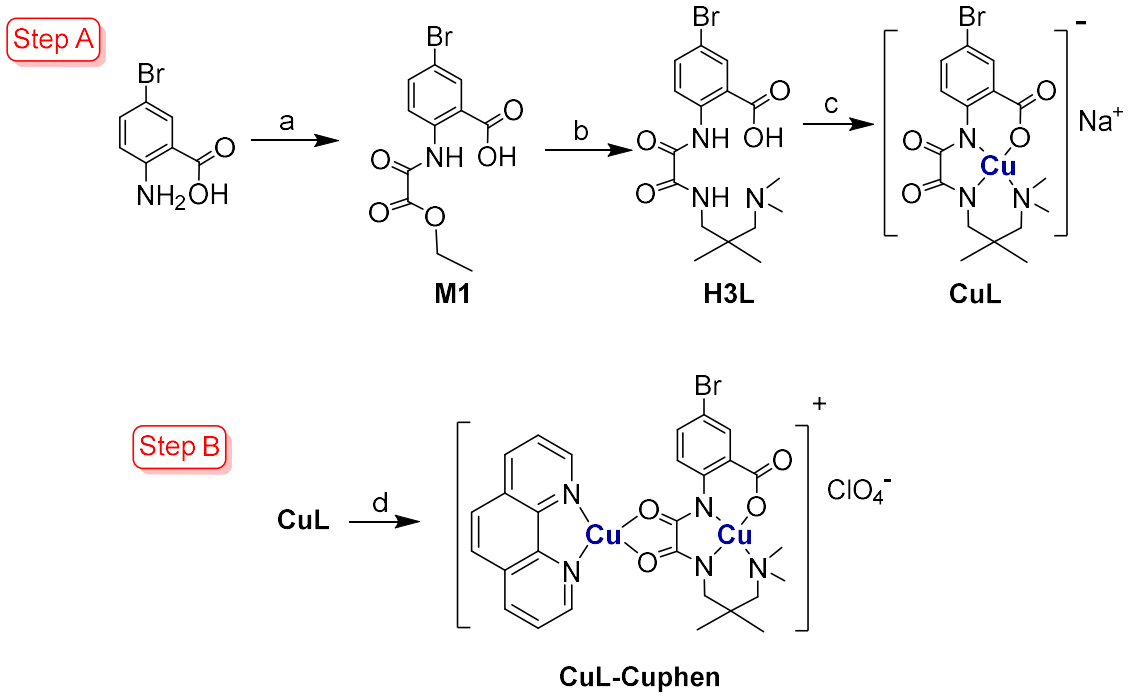
S1 Synthetic Procedures



Scheme 1. Schematic representation of the stepwise assembly route of bimetallic Cu(II) complex CuL-Cuphen.

S2. NMR Spectra

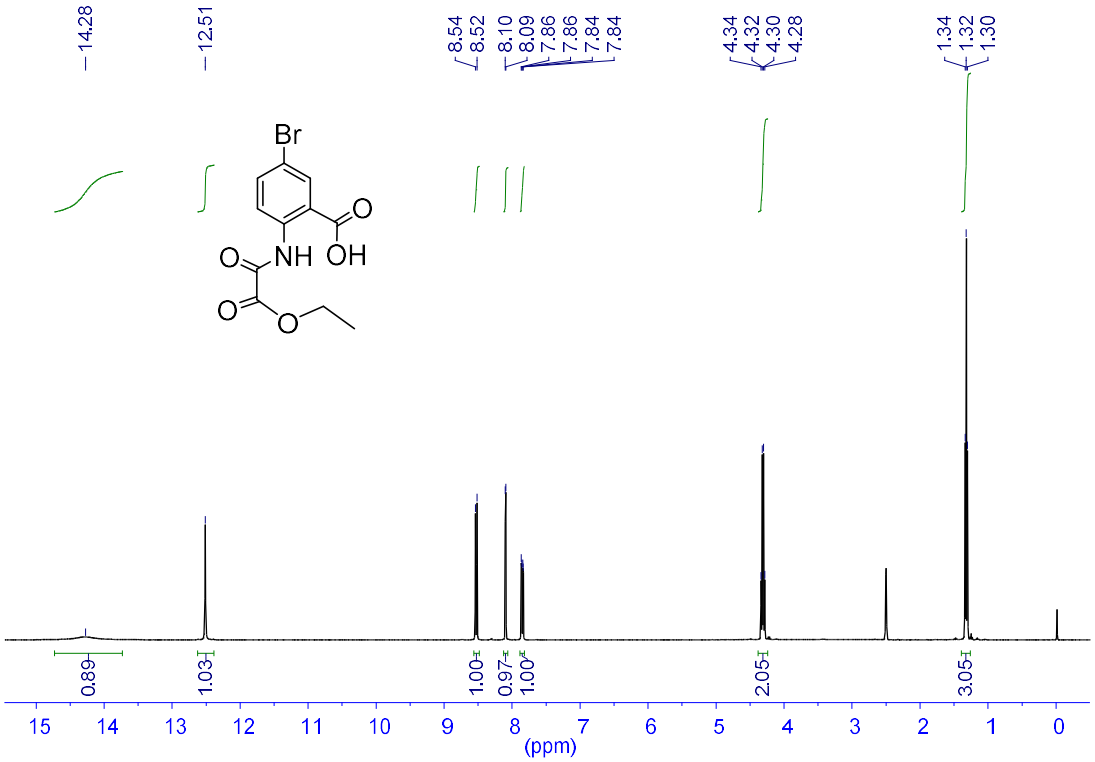


Figure S1. ^{1}H NMR spectrum (400 MHz, d^{6}-DMSO) of **M1**.

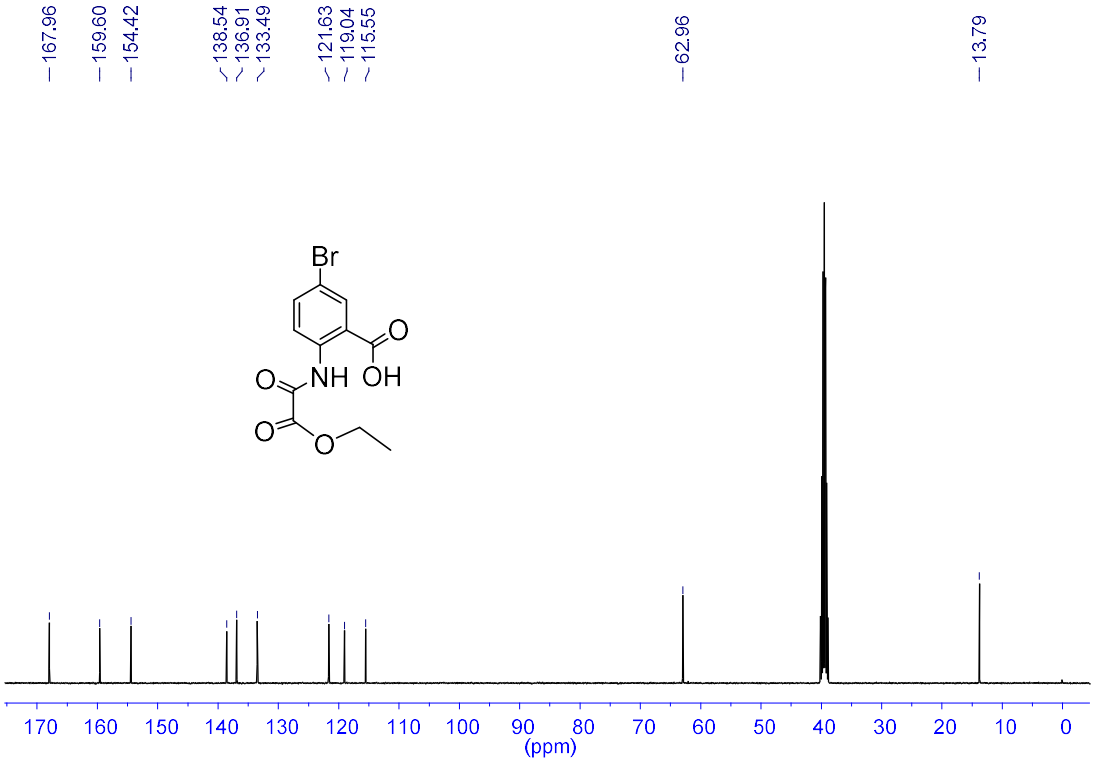


Figure S2. ^{13}C NMR spectrum (100 MHz, d^6-DMSO) of **M1**.

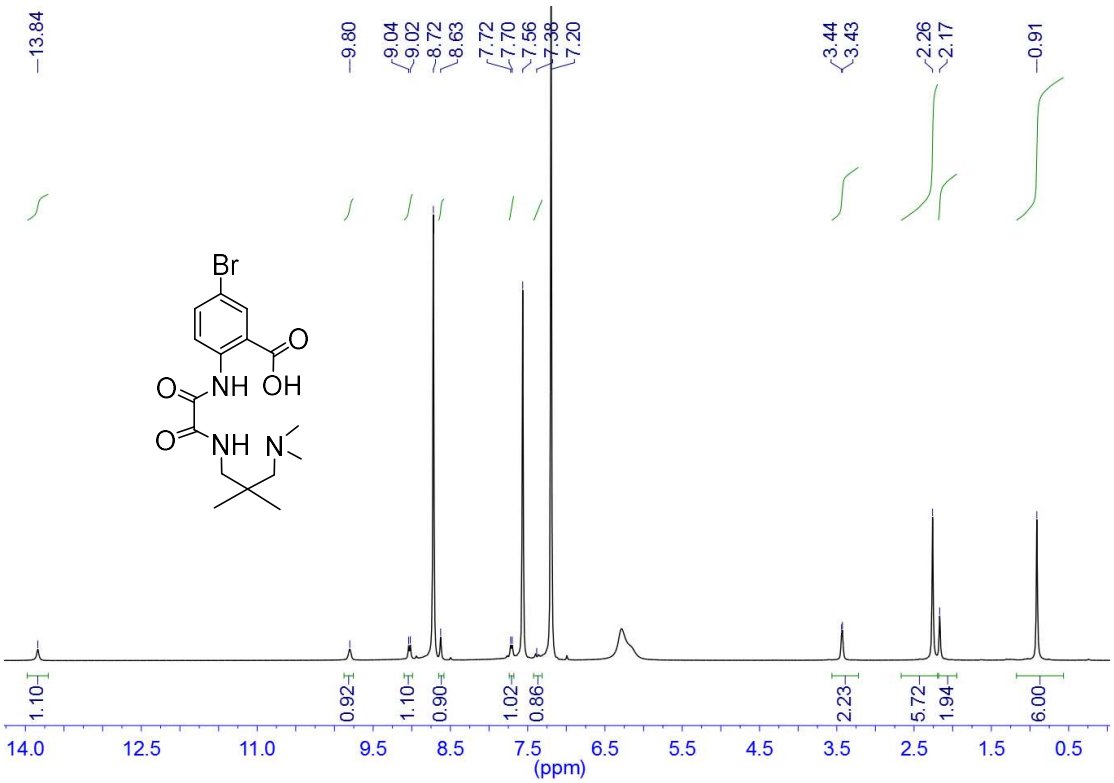


Figure S3. ^{1}H NMR spectrum (400 MHz, C_5D_5N) of **H_3L**

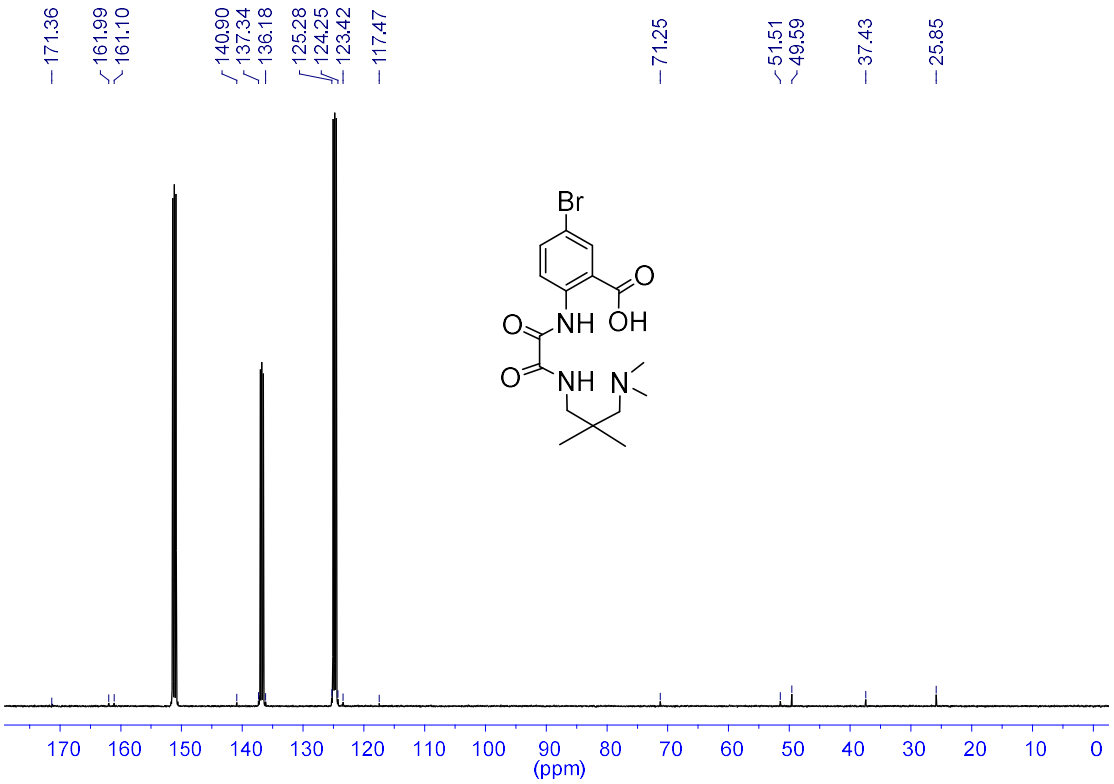


Figure S4. ^{13}C NMR spectrum (100 MHz, C_5D_5N) of **H_3L**

S3. HR-ESI mass spectra

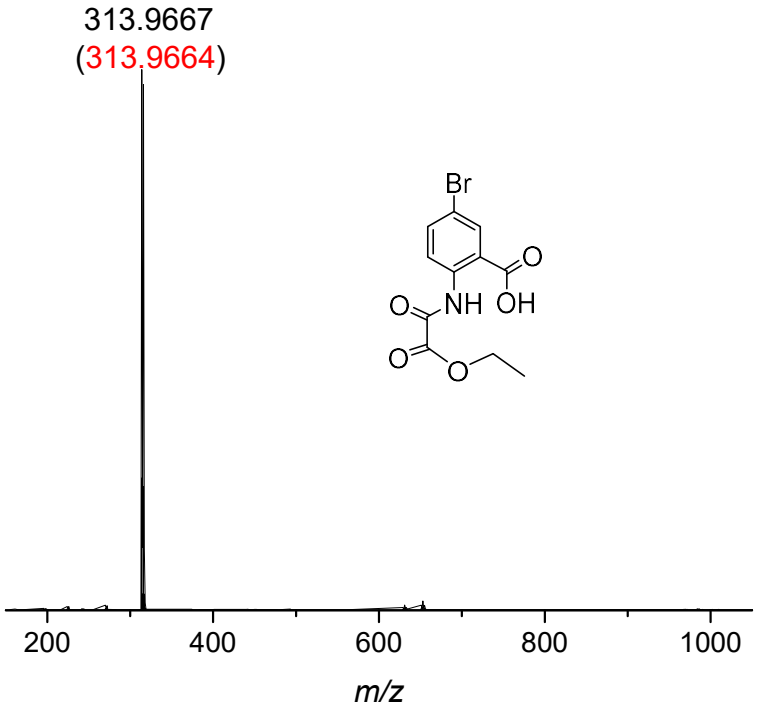


Figure S5. HR-ESI mass spectrum of **M1** in CH_3OH. The simulated spectra for [**M1**-H]$^-$, calcd for $C_{11}H_9BrNO_5^-$: 313.9664; found: 313.9667.

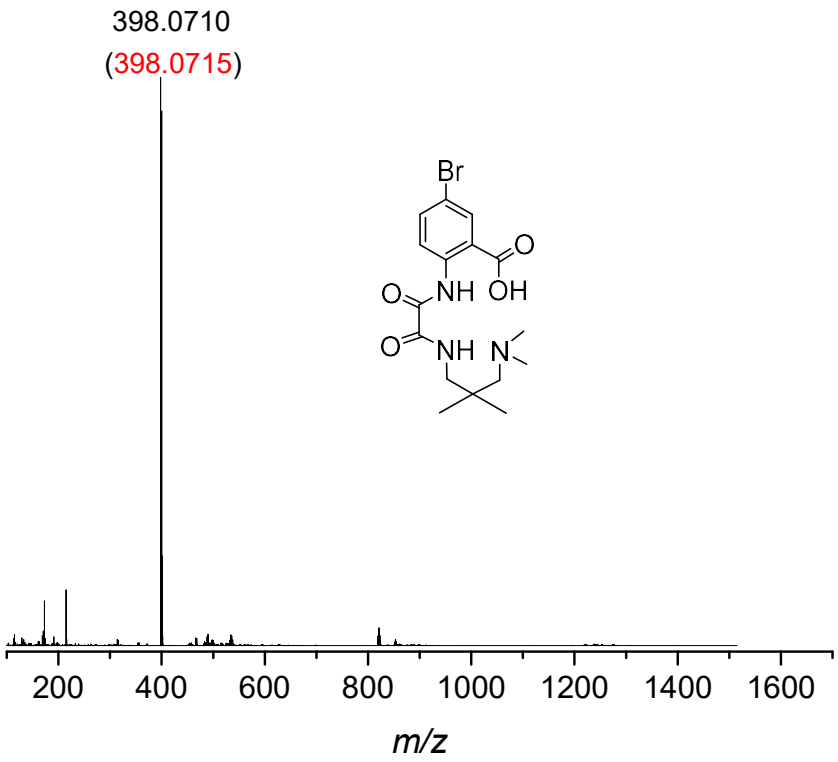


Figure S6. HR-ESI mass spectrum of **H3L** in CH_3OH. The simulated spectra for [**H3L**-H]$^-$, calcd. for $C_{16}H_{21}BrN3O_4^-$: 398.0715; found: 398.0710.

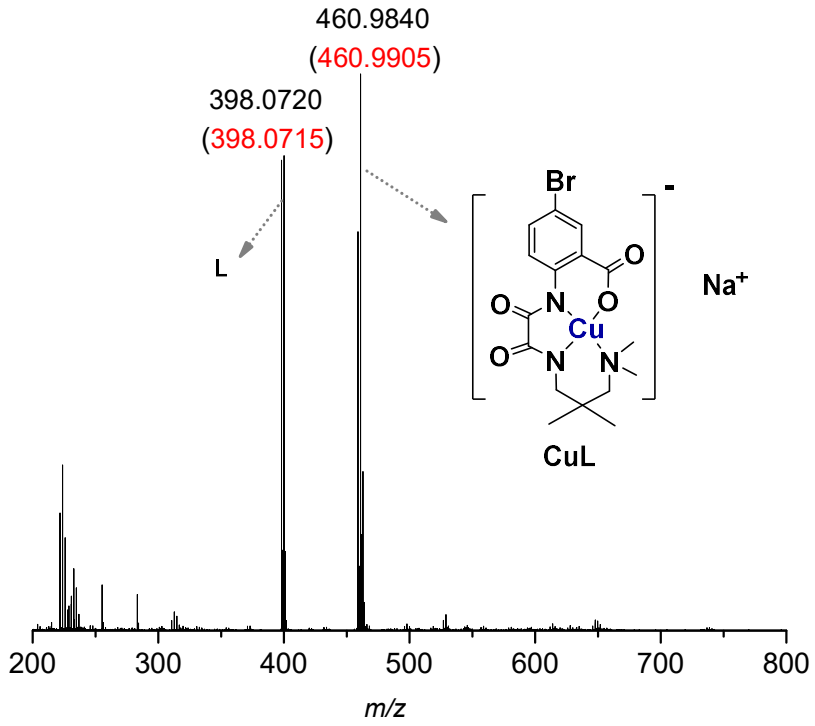


Figure S7. HR-ESI mass spectrum of **CuL** in CH_3OH. The simulated spectra for [**CuL**]$^-$, calcd. for $CuC_{16}H_{19}BrN_3O_4^-$: 460.9905; found: 460.9840.

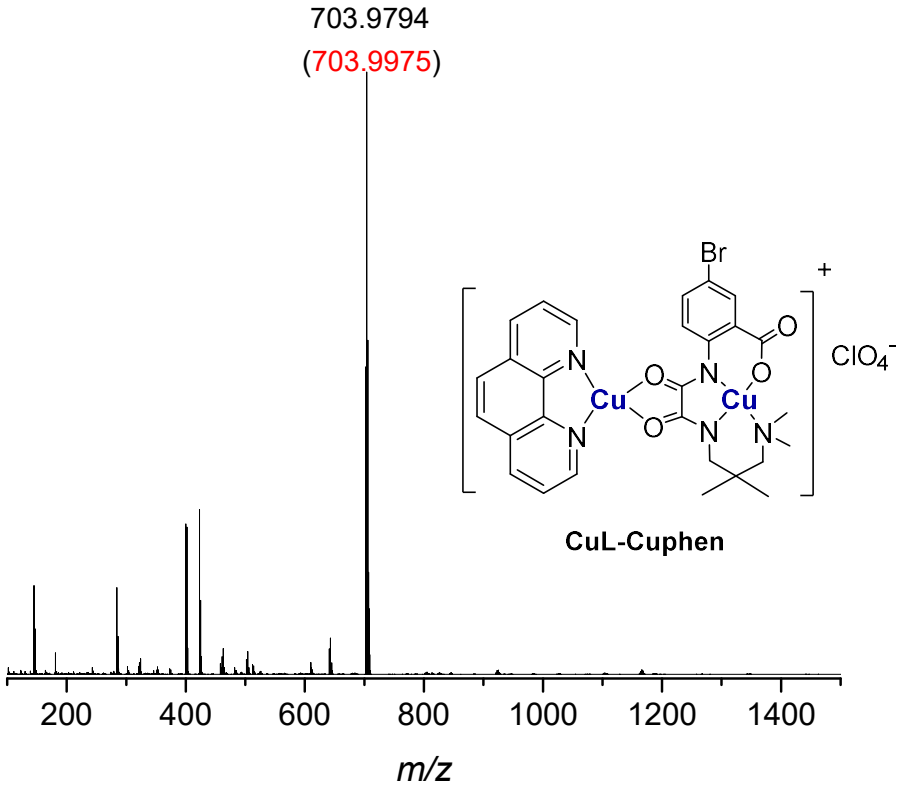


Figure S8. HR-ESI mass spectrum of **CuL-Cuphen** in CH_3OH. The simulated spectra for [**CuL-Cuphen**]$^+$, calcd. for $Cu_2C_{28}H_{27}BrN_5O_4^+$: 703.9975; found: 703.9794.

S4 IR spectra

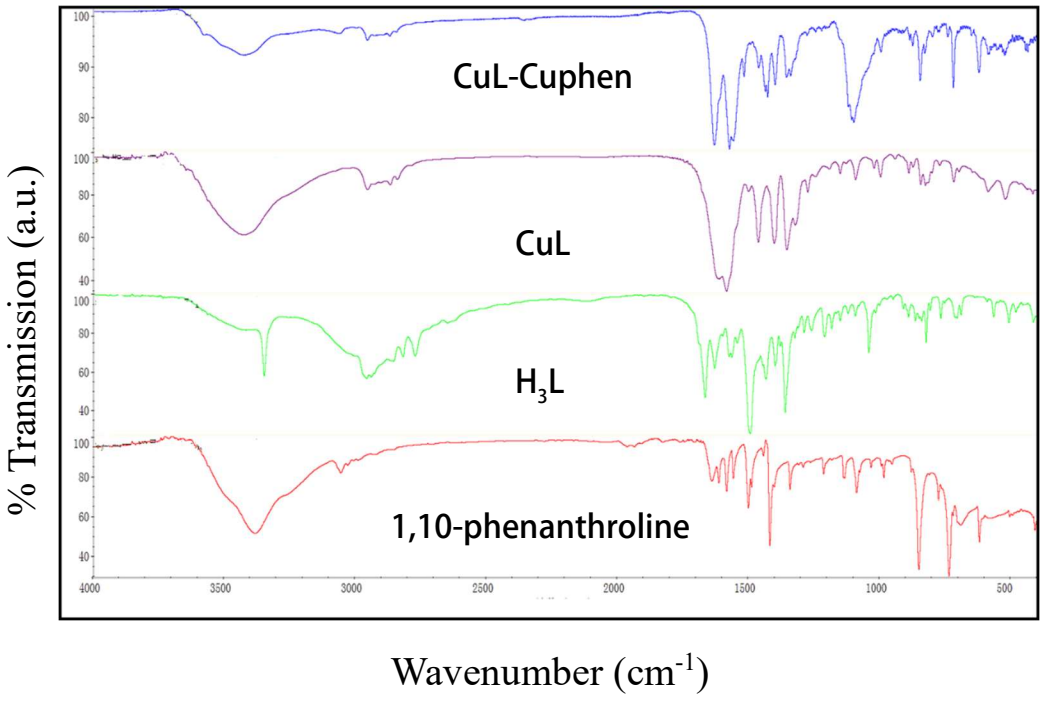


Figure S9. IR spectrum of 1,10-phenanthrolin, **H_3L**, **CuL**, and **CuL-Cuphen**.

S5 Single crystal X-ray crystallography.

Table S1 Bond Lengths for **CuL-Cuphen**.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cu1	O1	1.917(12)	O1	C1	1.274(19)
Cu1	N2	1.961(14)	O2	C1	1.285(19)
Cu1	N1	2.051(13)	O2	Cu2[1]	2.290(12)
Cu1	N3	2.065(13)	O3	C8	1.224(18)
Cu2	O4	1.946(10)	O4	C9	1.295(18)
Cu2	O3	1.964(11)	C1	C2	1.53(2)
Cu2	N5	2.021(13)	C2	C7	1.35(2)
Cu2	N4	2.059(14)	C2	C3	1.43(2)
Cu2	O2[1]	2.290(12)	C3	C4	1.40(2)
Br1	C6	1.940(15)	C4	C5	1.32(2)
Cl1	O6	1.40(7)	C5	C6	1.42(2)
Cl1	O5	1.40(9)	C6	C7	1.41(2)
Cl1	O6'	1.40(7)	C8	C9	1.56(2)
Cl1	O7'	1.40(8)	C10	C11	1.57(2)
Cl1	O8'	1.41(10)	C11	C14	1.50(3)
Cl1	O7	1.41(7)	C11	C13	1.52(2)
Cl1	O5'	1.41(4)	C11	C12	1.55(2)
Cl1	O8	1.42(11)	C17	C18	1.45(2)
N1	C8	1.38(2)	C18	C19	1.35(2)
N1	C3	1.39(2)	C19	C20	1.46(2)
N2	C9	1.294(19)	C20	C21	1.35(2)
N2	C10	1.537(19)	C20	C27	1.51(2)
N3	C12	1.53(2)	C21	C22	1.44(2)
N3	C16	1.54(3)	C22	C23	1.45(2)
N3	C15	1.56(2)	C23	C28	1.42(2)
N4	C17	1.253(19)	C23	C24	1.46(2)
N4	C21	1.41(2)	C24	C25	1.39(2)
N5	C26	1.351(19)	C25	C26	1.43(2)
N5	C22	1.37(2)	C27	C28	1.28(2)

Table S2 Bond Angles for **CuL-Cuphen**.

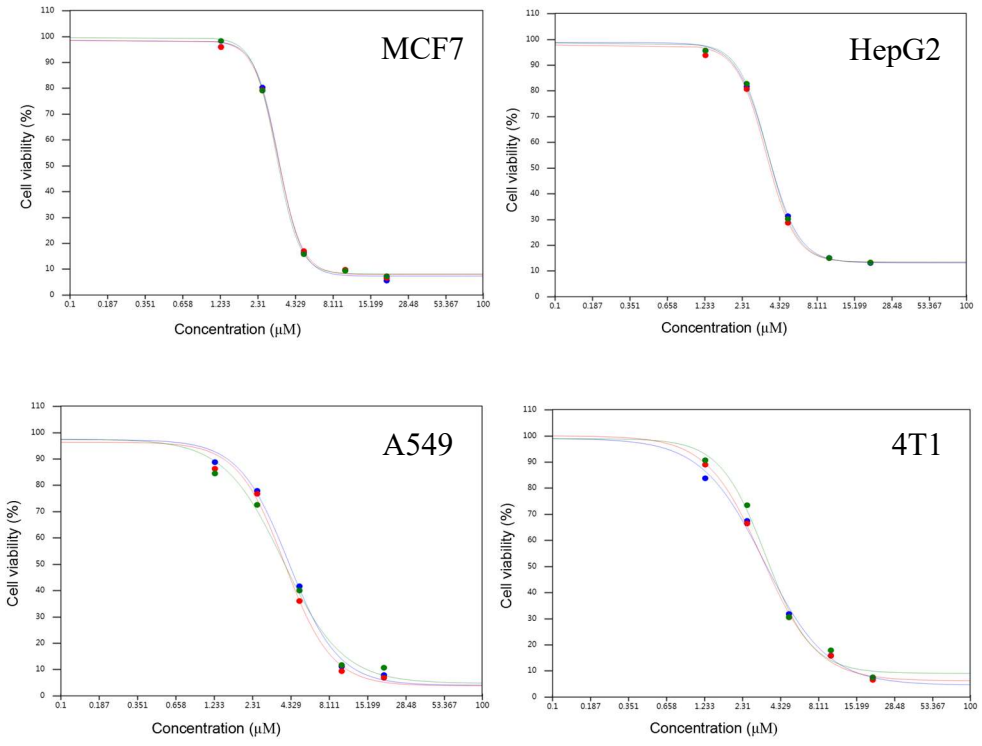
Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O1	Cu1	N2	174.4(5)	C21	N4	Cu2	110.2(10)
O1	Cu1	N1	90.3(5)	C26	N5	C22	119.4(14)
N2	Cu1	N1	84.8(5)	C26	N5	Cu2	130.1(11)

O1	Cu1	N3	88.6(5)	C22	N5	Cu2	110.5(10)
N2	Cu1	N3	95.9(5)	C1	O1	Cu1	127.8(11)
N1	Cu1	N3	172.3(6)	C1	O2	Cu2[1]	120.5(11)
O4	Cu2	O3	84.7(4)	C8	O3	Cu2	113.3(10)
O4	Cu2	N5	165.4(5)	C9	O4	Cu2	111.3(9)
O3	Cu2	N5	99.3(5)	O1	C1	O2	120.7(15)
O4	Cu2	N4	90.0(5)	O1	C1	C2	120.5(14)
O3	Cu2	N4	170.1(5)	O2	C1	C2	117.9(14)
N5	Cu2	N4	83.9(5)	C7	C2	C3	123.4(14)
O4	Cu2	O2[1]	100.2(4)	C7	C2	C1	113.9(14)
O3	Cu2	O2[1]	90.6(4)	C3	C2	C1	122.6(14)
N5	Cu2	O2[1]	93.8(4)	N1	C3	C4	125.5(15)
N4	Cu2	O2[1]	98.6(5)	N1	C3	C2	120.5(14)
O6	Cl1	O5	110(3)	C4	C3	C2	113.9(14)
O6	Cl1	O6'	37(3)	C5	C4	C3	125.4(16)
O5	Cl1	O6'	138(4)	C4	C5	C6	119.3(15)
O6	Cl1	O7'	85(3)	C7	C6	C5	118.9(14)
O5	Cl1	O7'	29(2)	C7	C6	Br1	119.1(12)
O6'	Cl1	O7'	109(3)	C5	C6	Br1	122.0(11)
O6	Cl1	O8'	93(4)	C2	C7	C6	119.1(15)
O5	Cl1	O8'	95(5)	O3	C8	N1	131.5(15)
O6'	Cl1	O8'	109(5)	O3	C8	C9	115.6(14)
O7'	Cl1	O8'	111(5)	N1	C8	C9	112.5(13)
O6	Cl1	O7	113(3)	N2	C9	O4	126.7(14)
O5	Cl1	O7	109(5)	N2	C9	C8	118.1(14)
O6'	Cl1	O7	79(3)	O4	C9	C8	115.1(13)
O7'	Cl1	O7	109(4)	N2	C10	C11	110.5(13)
O8'	Cl1	O7	133(4)	C14	C11	C13	106.0(15)
O6	Cl1	O5'	147(3)	C14	C11	C12	117.4(16)
O5	Cl1	O5'	93(4)	C13	C11	C12	106.4(14)
O6'	Cl1	O5'	111(4)	C14	C11	C10	110.2(14)
O7'	Cl1	O5'	109(4)	C13	C11	C10	105.7(15)
O8'	Cl1	O5'	108(3)	C12	C11	C10	110.3(14)
O7	Cl1	O5'	35(3)	N3	C12	C11	120.7(13)
O6	Cl1	O8	110(5)	N4	C17	C18	125.3(16)
O5	Cl1	O8	109(6)	C19	C18	C17	115.5(15)
O6'	Cl1	O8	109(5)	C18	C19	C20	120.3(15)
O7'	Cl1	O8	133(5)	C21	C20	C19	118.6(15)
O8'	Cl1	O8	28(4)	C21	C20	C27	116.7(15)
O7	Cl1	O8	105(4)	C19	C20	C27	124.6(14)

O5'	Cl1	O8	82(4)	C20	C21	N4	120.1(15)
C8	N1	C3	122.9(13)	C20	C21	C22	124.2(15)
C8	N1	Cu1	110.6(10)	N4	C21	C22	115.4(14)
C3	N1	Cu1	126.2(11)	N5	C22	C21	119.7(14)
C9	N2	C10	114.8(14)	N5	C22	C23	126.2(15)
C9	N2	Cu1	113.1(10)	C21	C22	C23	114.0(15)
C10	N2	Cu1	131.2(10)	C28	C23	C22	122.6(15)
C12	N3	C16	108.6(13)	C28	C23	C24	126.6(15)
C12	N3	C15	105.6(13)	C22	C23	C24	110.6(14)
C16	N3	C15	113.2(15)	C25	C24	C23	124.6(16)
C12	N3	Cu1	116.2(11)	C24	C25	C26	117.7(15)
C16	N3	Cu1	106.5(10)	N5	C26	C25	121.3(15)
C15	N3	Cu1	107.0(10)	C28	C27	C20	122.3(16)
C17	N4	C21	119.6(14)	C27	C28	C23	119.8(16)
C17	N4	Cu2	129.9(12)				

S6 IC_{50} values determination.

All the IC_{50} values were determined as duplicates of triplicates in three independent sets of experiments. The raw data were fitted as a sigmoidal dose response using the IC_{50} Calculator. The standard deviations were calculated for the three independent experiments using the STDEV function in Excel software.[1]



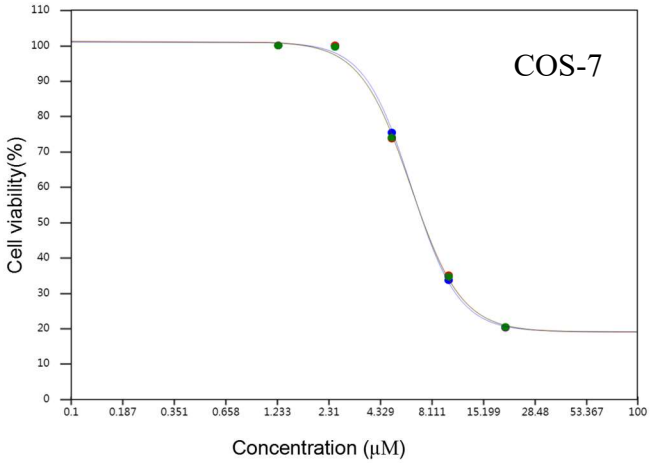


Table S3. The IC_{50} (μM) values toward different cells.

Cells	MCF7	HepG2	A549	4T1	COS7
CuL-Cuphen	3.227±0.052	3.532±0.055	3.984±0.185	3.311±0.100	6.319±0.022
CuL	>40	>40	>40	>40	>40

S7 Reference

1. AAT Bioquest, Inc. (2020, June 16). Quest Graph™ *IC_{50} Calculator (v.1)*. Retrieved from https://www.aatbio.com/tools/ic50-calculator-v1.