Electronic supplementary information (ESI)

Copper complexes as prospective anticancer agents: *In vitro* and *in vivo* evaluation, selective targeting of cancer cells by DNA damage and S phase arrest

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Table S1 Crystal data and structure refinement of the ligand L^4.

CCDC	1475312
Empirical formula	$C_9H_{11}N_3OS$
Formula weight	209.27
Temperature (K)	150(2)
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell (Å) dimensions (°)	a = 6.885(3)
	b = 7.108(3)
	c = 11.230(4)
	β = 76.662(4)
Volume (A^3)	500.9(3)
Z, Calculated density (Mg/m^3)	2, 1.387
Absorption coefficient (mm^{-1})	0.293
F(000)	220
Crystal size (mm^3)	0.25 × 0.19 × 0.04
Theta range for data collection (°)	1.910 to 27.519
Limiting indices	$-8 \le h \le 8$ $-9 \le k \le 9$ $-14 \le l \le 13$
Reflections collected/unique	4355/2227 [R(int) = 0.0249]
Completeness to theta (%)	99.30
Refinement method	Full-matrix least-squares on F^2
Data/restraints/ parameters	2227/0/129
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0382, wR2 = 0.0998
R indices (all data)	R1 = 0.0439, wR2 = 0.1042
Largest diff. Peak and hole (e A^{-3})	0.291 and –0.287

Table S2 Selected bond lengths (Å) and bond angles (°) of the ligand L^4.

Bond	Bond lengths (Å)	Bond	Bond angles (°)
S1–C9	1.7053(17)	C7–N1–N2	117.52(14)
N1–C7	1.3683(19)	C9–N2–N1	117.48(13)
N1–N2	1.286(2)	C9–N3–C10	122.62(14)
N2–C9	1.3897(19)	C2–C1–C6	117.54(15)
N3–C9	1.341(2)	C2–C1–C7	122.26(14)
N3–C10	1.320(2)	C6–C1–C7	120.20(14)
C1–C2	1.399(2)	C1–C2–C3	121.15(14)
C1–C6	1.400(2)	C4–C3–C2	120.14(15)
C1–C7	1.480(2)	C3–C4–C5	119.76(15)
C2–C3	1.383(2)	C4–C5–C6	119.63(14)
C3–C4	1.390(2)	C5–C6–C1	121.75(15)
C4–C5	1.390(2)	N1–C7–C1	115.28(14)
C5–C6	1.380(2)	N1–C7–C8	124.54(15)
C7–C8	1.496(2)	C1–C7–C8	120.18(14)
–	–	N3–C9–N2	117.30(14)
–	–	N3–C9–S1	122.56(12)
–	–	N2–C9–S1	120.14(12)

Table S3 Hydrogen bond geometry of the ligand L^4 [Å and °].

D–H···A	D–H	H···A	D···A	D–H···A
O(1)–H(1)…S(1) (i)	0.84	2.41	3.247(2)	177.3
N(2)–H(2)…S(1) (ii)	0.88	2.79	3.516(2)	140.6
N(3)–H(3A)…O(1) (iii)	0.88	2.20	2.953(2)	143.2
N(3)–H(3B)…S(1) (iv)	0.88	2.56	3.415(2)	165.3
C(8)–H(8A)…S1 (ii)	0.98	2.87	3.682(2)	140.0

Symmetry code: (i) x, y, z+1 (ii) -x+1, -y, -z (iii) -x+1, -y+1, -z+1 (iv) -x, -y+1, -z.

Table S4 B3LYP/LANL2DZ Bond lengths (Å) and bond angles (°) of complexes (**1–6**).

Bond lengths							
	1	2	3	4	5	6	Experimental [15, 16]
Cu1–S1	2.213	2.219	2.212	2.211	2.217	2.210	2.211 (11)
Cu1–S2	2.219	2.226	2.221	2.236	2.231	2.229	2.221 (12)
Cu1–Cl1	2.309	2.301	2.305	2.312	2.303	2.301	2.303 (12)
Bond angles							
S2–Cu1–S1	119.42	120.33	121.09	121.78	122.01	121.12	121.61
S2–Cu1–Cl1	116.47	117.28	116.76	118.03	117.95	118.69	118.33
S1–Cu1–Cl1	122.35	121.34	121.04	120.73	121.51	120.29	120.01

Table S5 Molecular docking parameters of the copper(I) complexes (**1–6**) with DNA.

Complexes	Final Intermolecular Energy (kcal/mol)			Final Total Internal Energy (2) (kcal/mol)	Torsional Free Energy (3) (kcal/mol)	Unbound System's Energy (4) (kcal/mol)	Estimated Free Energy of Binding [(1)+(2)+(3)–(4)] (kcal/mol)
	vdW + H bond + dissolving energy	Electrostatic Energy	Total (1)				
1	–5.84	–0.26	–6.10	–0.19	+1.09	–0.33	–4.87
2	–6.96	–0.97	–7.93	–0.32	+1.29	–0.44	–6.52
3	–6.82	–0.88	–7.70	–0.54	+1.62	–0.65	–5.97
4	–6.02	–0.74	–6.76	–0.28	+1.14	–0.36	–5.54
5	–4.67	–0.81	–5.48	–0.36	+1.28	–0.48	–4.08
6	–5.19	–0.27	–5.46	–0.49	+1.55	–0.47	–3.93

Table S6 Molecular docking parameters of the copper(I) complexes (**1**–**6**) with focal adhesion kinase (FAK) receptor.

Complexes	Final Intermolecular Energy (kcal/mol)			Final Total Internal Energy (2) (kcal/mol)	Torsional Free Energy (3) (kcal/mol)	Unbound System's Energy (4) (kcal/mol)	Estimated Free Energy of Binding [(1)+(2)+(3)– (4)] (kcal/mol)
	vdW + H bond + dissolving energy	Electrostatic Energy	Total (1)				
1	–8.10	–0.16	–8.26	–1.26	–1.62	+3.29	–6.08
2	–11.35	–0.05	–11.40	–0.05	+3.84	+0.33	–7.94
3	–9.45	–0.36	–9.81	–0.36	+3.84	+0.15	–6.47
4	–8.35	–0.17	–8.52`	–1.54	+3.291	–0.47	–6.29
5	–8.15	+0.08	–8.06	–0.79	+3.29	+0.24	–5.06
6	–8.11	–0.16	–8.27	–0.34	+3.84	–0.46	–5.01

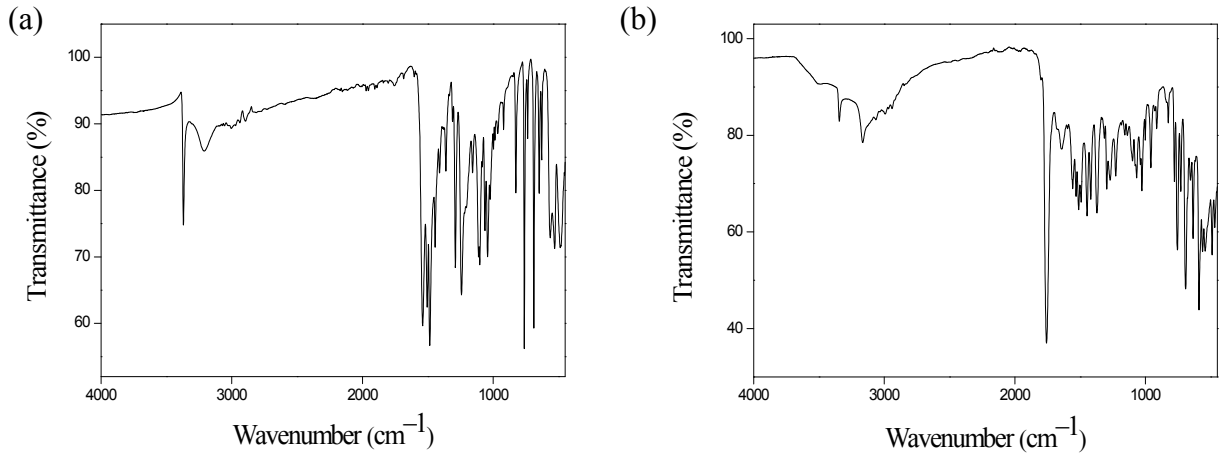


Fig. S1. FT IR spectra of ligand L^2 (a) and copper(I) complex **2** (b).

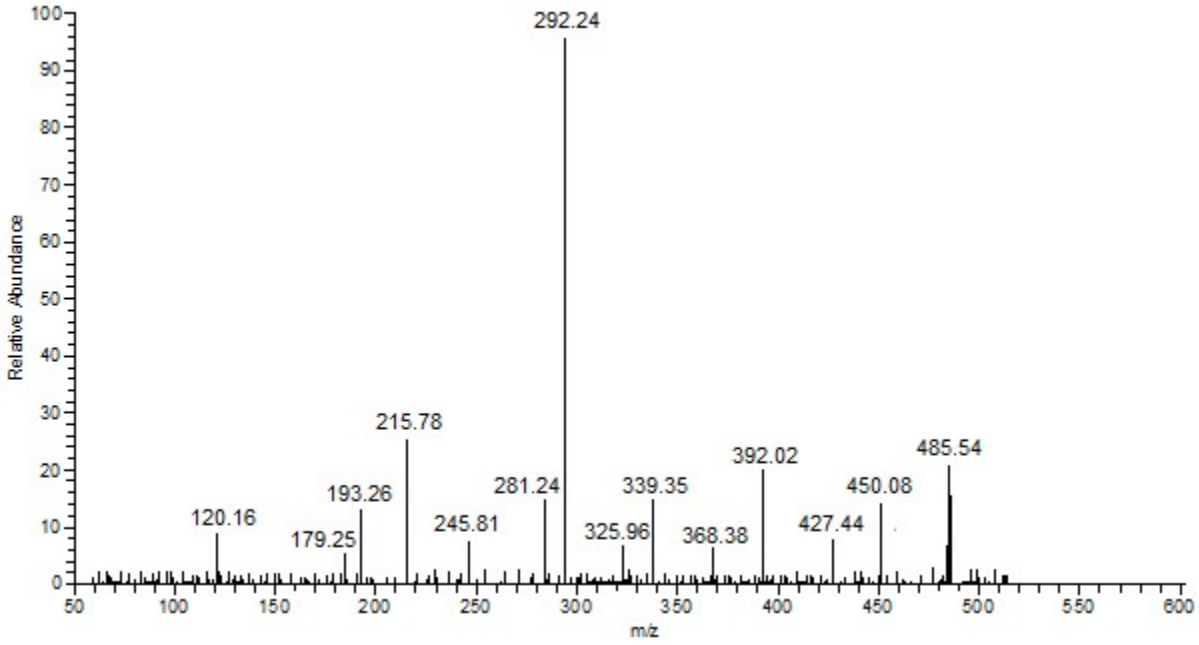


Fig. S2. ESI mass spectrum of complex **1**.

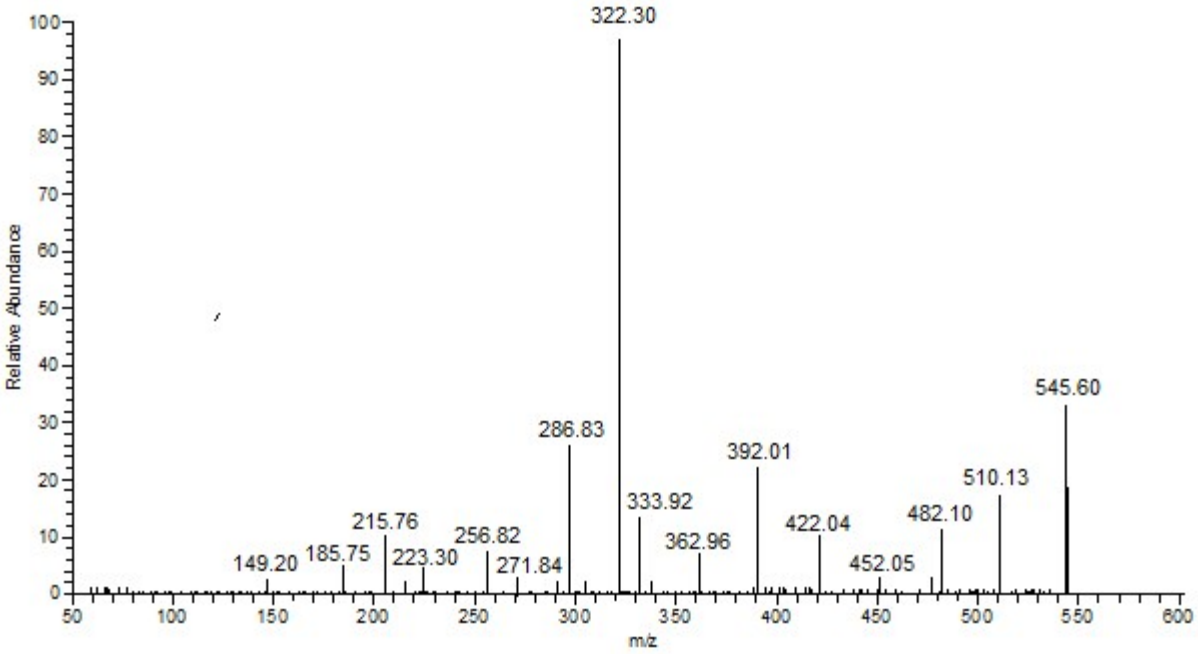


Fig. S3. ESI mass spectrum of complex **3**.

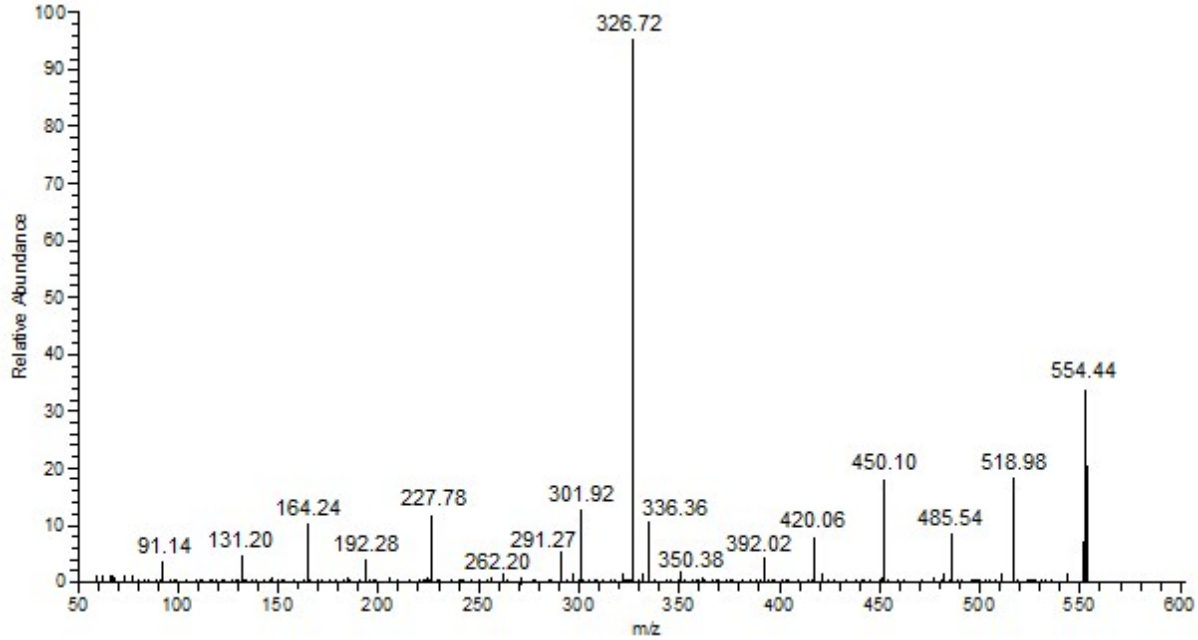


Fig. S4. ESI mass spectrum of complex **6**.

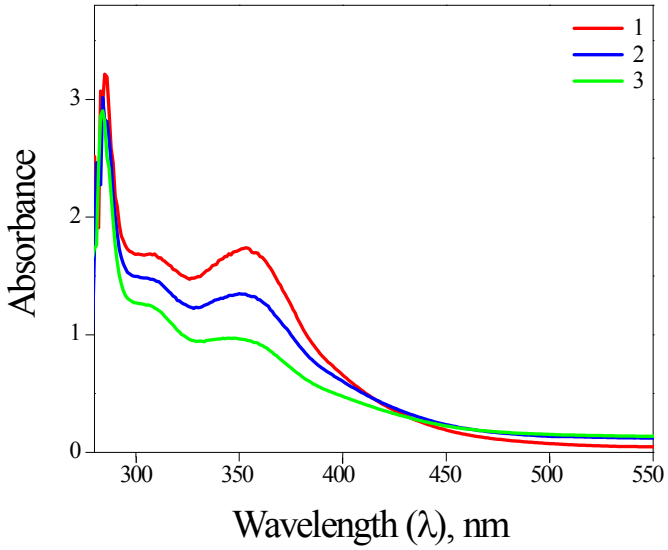
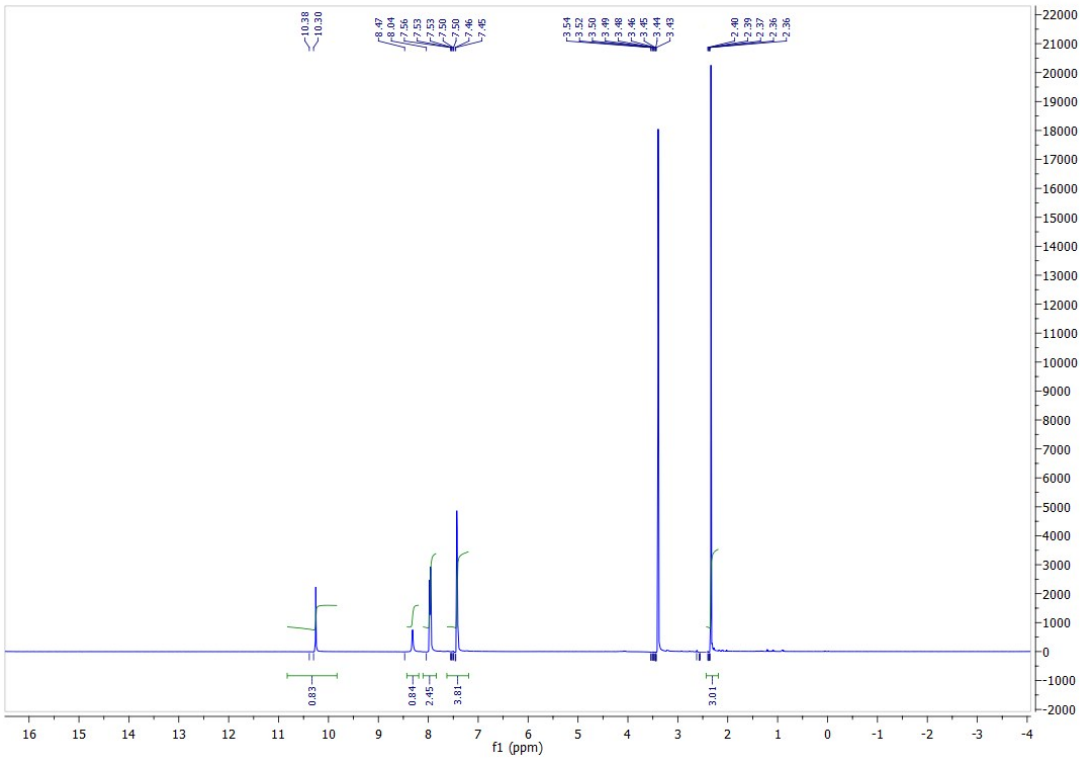


Fig. S5. UV-Vis absorption spectra of the copper(I) complexes **1**–**3**.

(a)



(b)

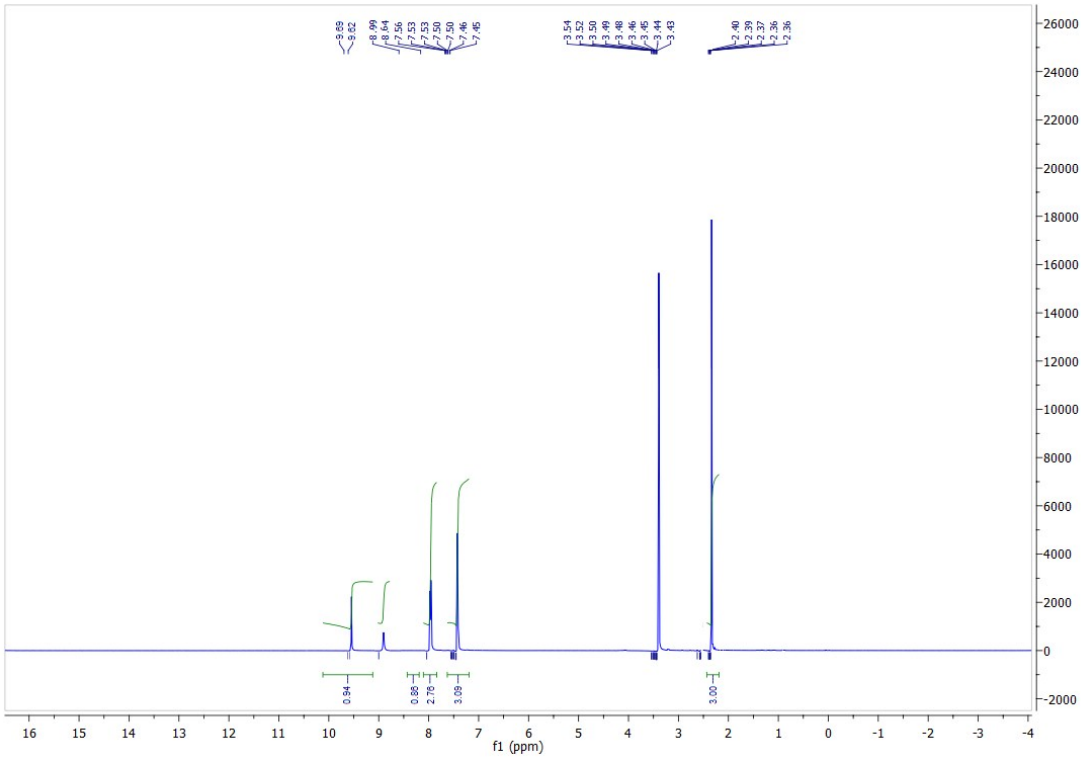
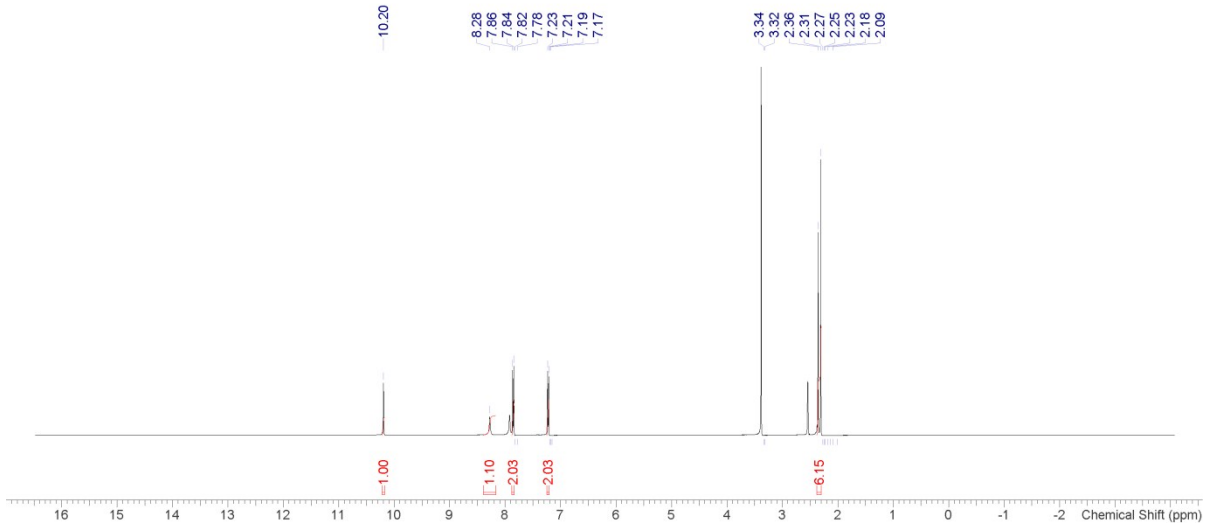


Fig. S6. ^{1}H NMR spectra of ligand L^{1} (a) and complex **1** (b).

(a)



(b)

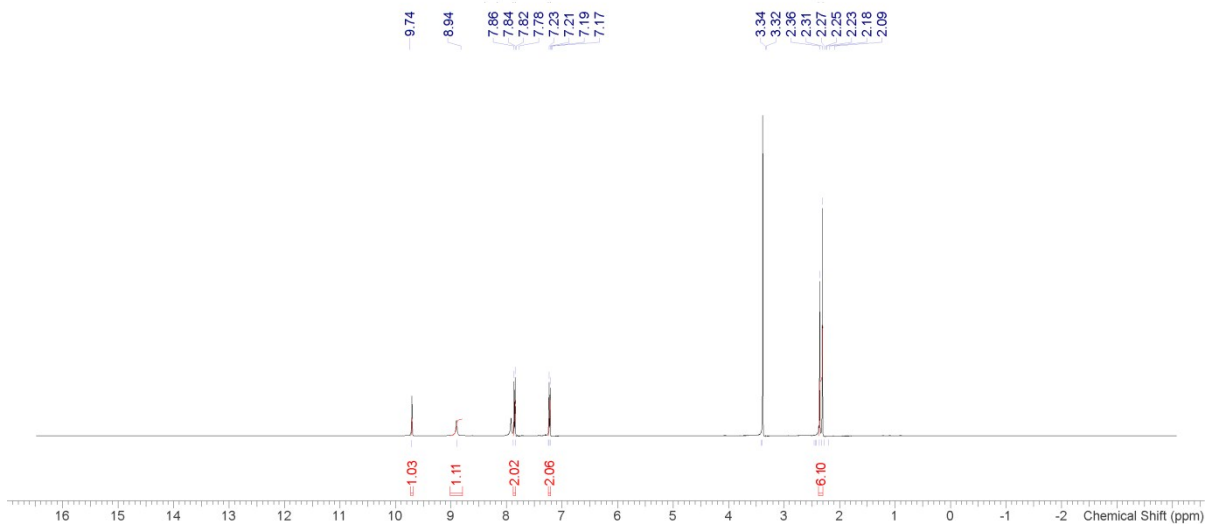


Fig. S7. ^{1}H NMR spectra of ligand L^{2} (a) and complex **2** (b).

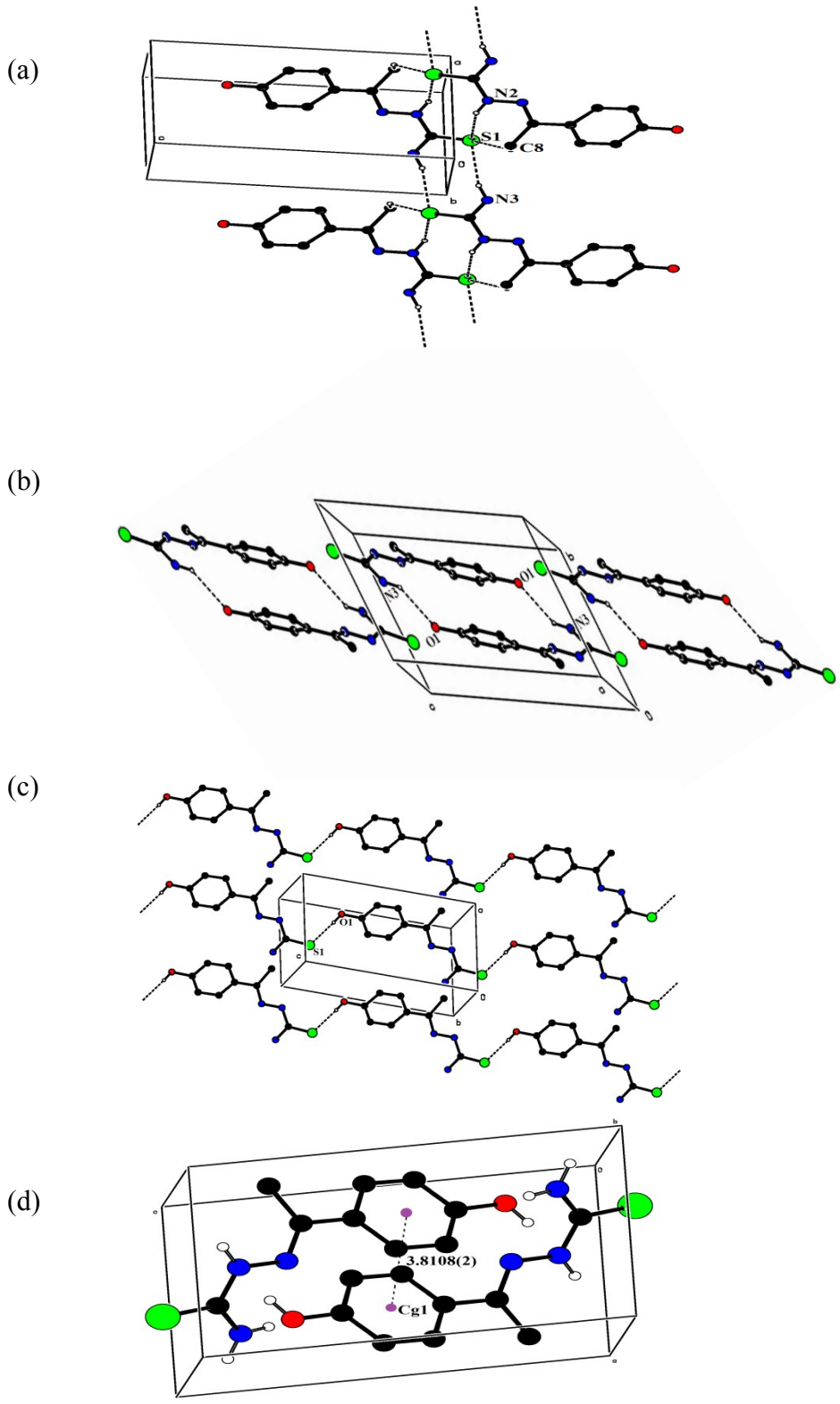


Fig. S8. N2–H2···S1, N3–H3B···S1 and C8–H8A···S1 intermolecular interaction generating $R_2^2(8)$ ring motif (a), N3–H3A···O1 intermolecular interaction generating $R_2^2(22)$ ring motif viewed down '*a*′ axis (b), the intermolecular O1–H1···S1 hydrogen bonds forming a C(11) chain running along '*c*′ axis (c) and π–π stacking interactions (d) for the ligand L^4.

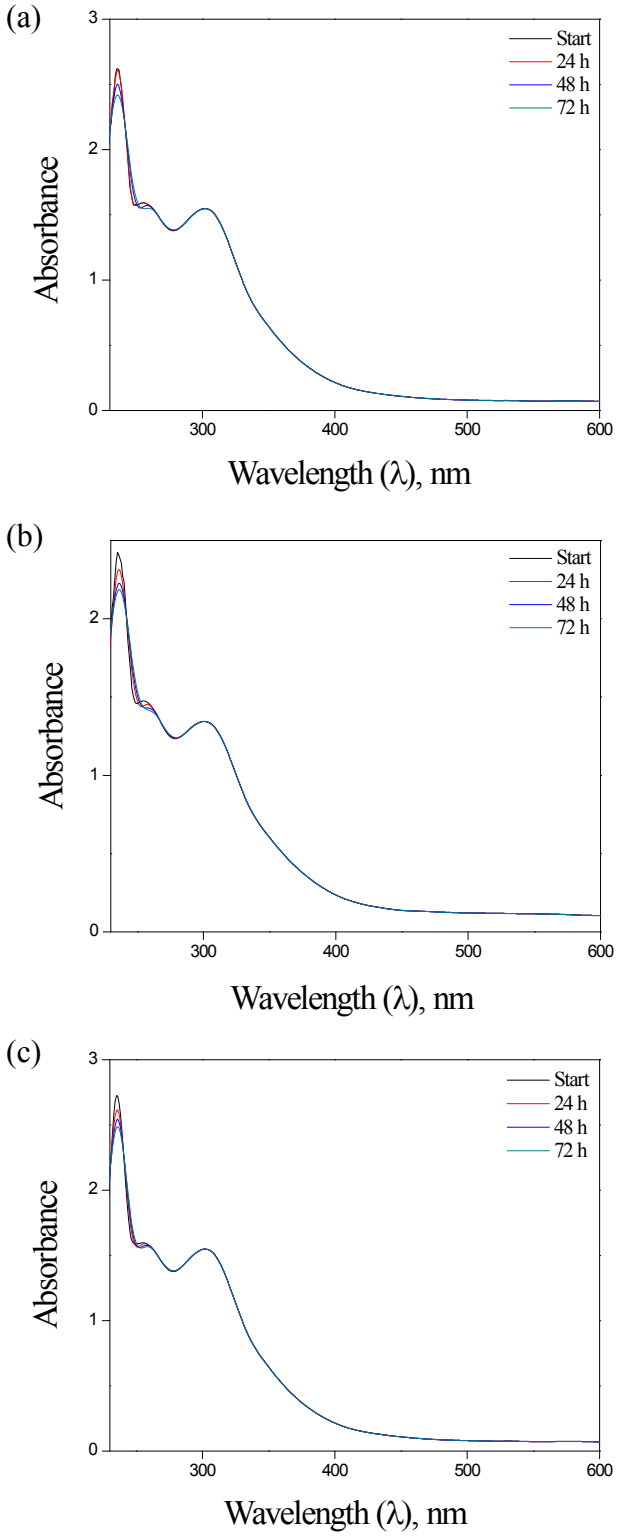


Fig. S9. Stability of copper(I) complexes **1** (a), **2** (b) and **3** (c) measured by UV-Vis spectroscopy.

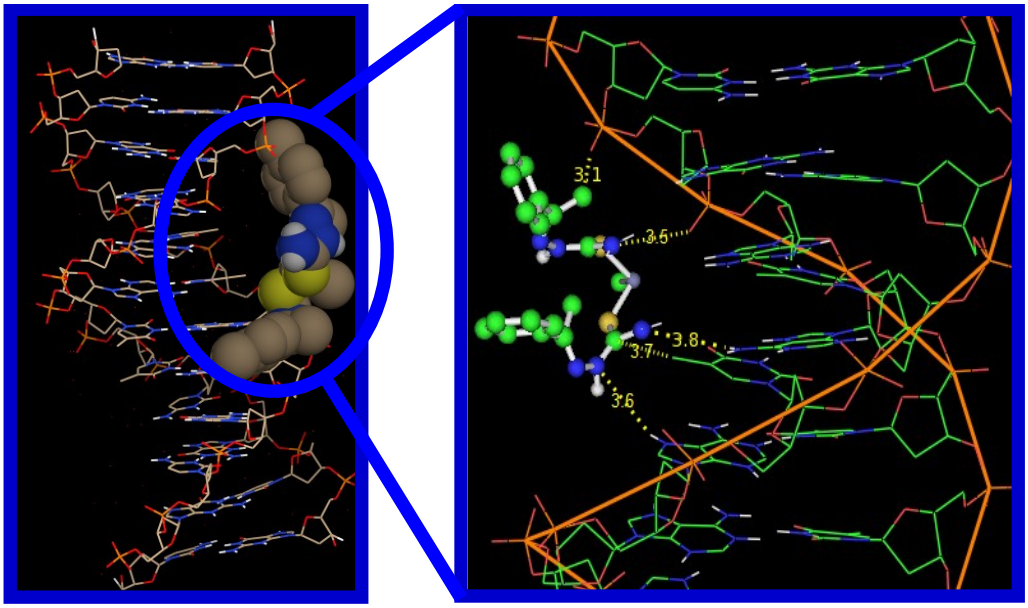


Fig. S10. Molecular docking view of complex **1** with DNA (PDB ID: 1BNA) dodecamer duplex of sequence d(CGCGAATTCGCG)$_2$.

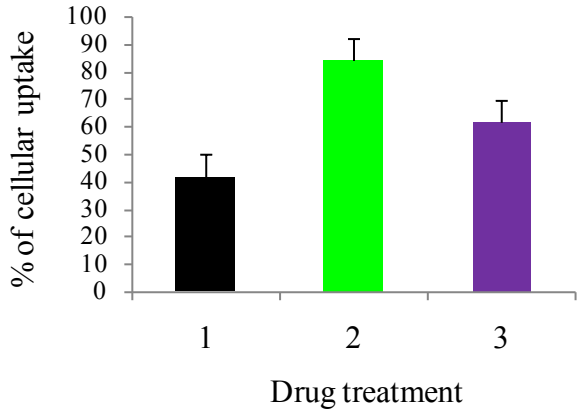


Fig. S11. Scar bar diagram of complexes (**1**–**3**) for 24 h.

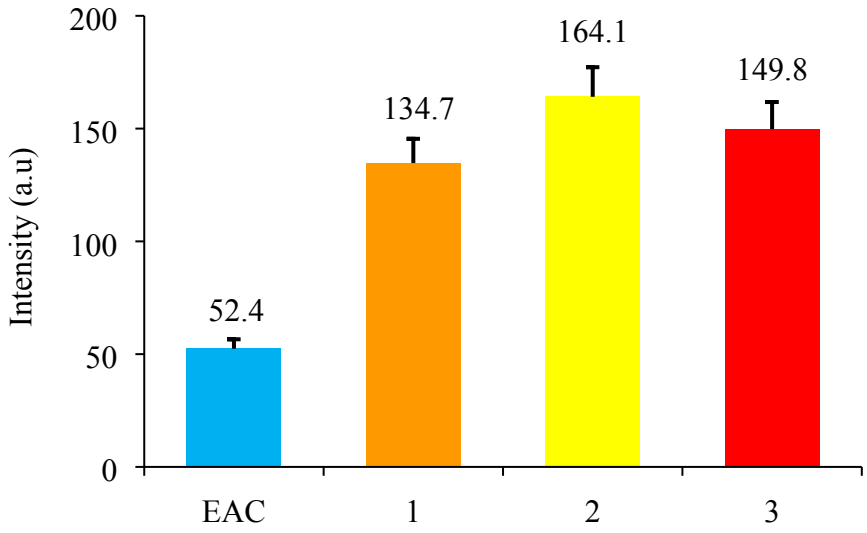


Fig. S12. ROS generation in EAC cells exposed to copper(I) complexes **1**–**3** for 24 h.

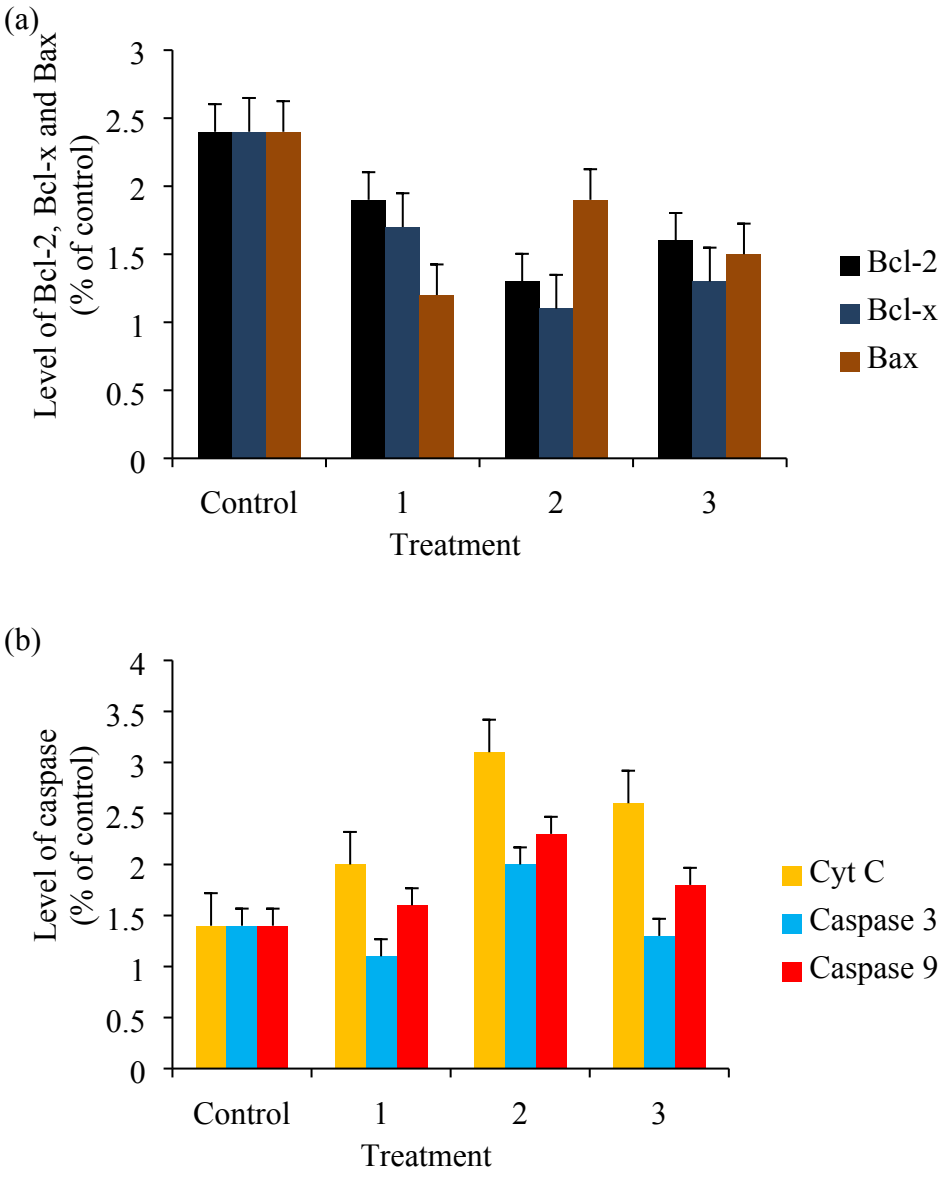


Fig. S13. Percentage expression levels of Bcl-2, Bcl-x and Bax (a). Percentage expression levels of caspase 3/9 and cytochrome c (b); The percentage values are those relative to the control.