Electronic Supplementary Material (ESI) for Dalton Transactions.

Supporting Information

for

Copper(II)-thiosemicarbazone complexes induce marked ROS accumulation and promote nrf2-mediated antioxidant response in highly resistant breast cancer cells

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Keywords: Copper(II), 5-sulfonate salicylaldehyde thiosemicarbazones, pK_a value, solution stability, antiproliferative activity, ROS induction

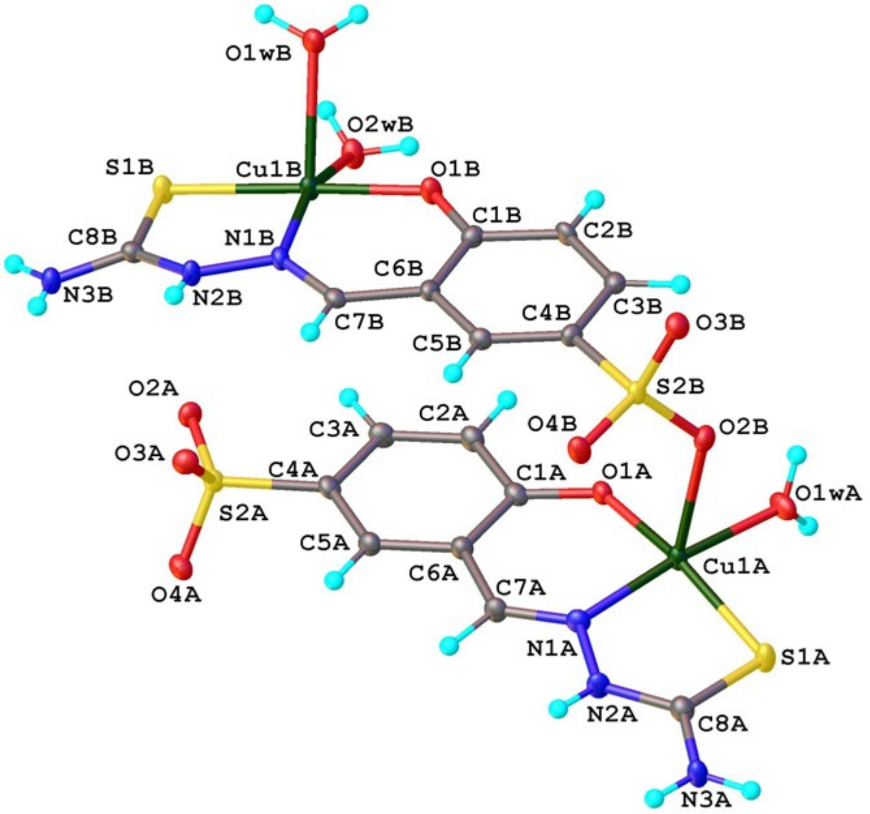

Figure S1. ORTEP view of crystal structures of **1′**with atom labeling schemes and thermal ellipsoids drawn at 50% probability level.

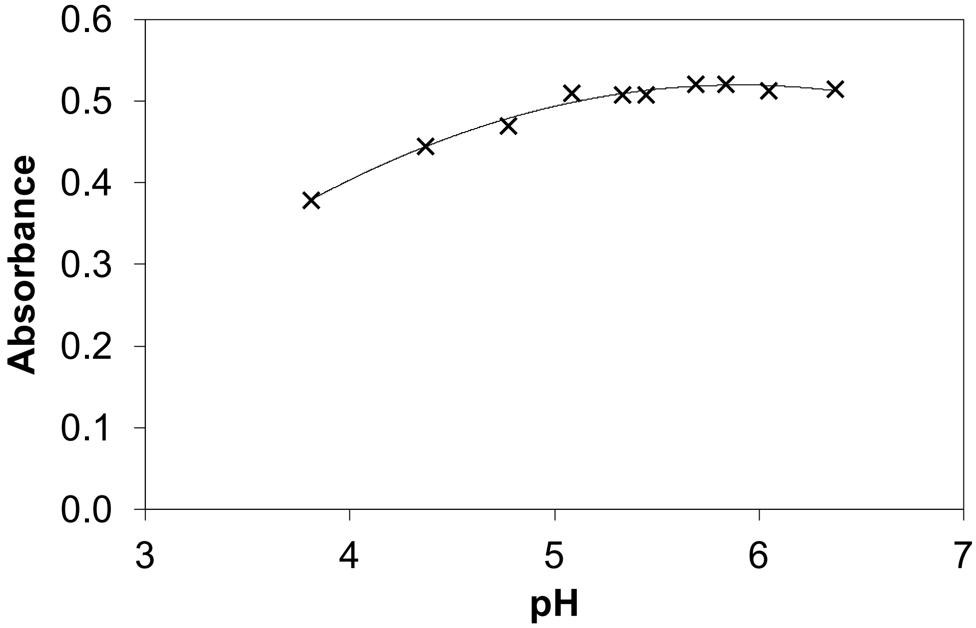

Figure S2. Dependence of absorbance recorded in the Cu(II) – NaH_2L^H system *vs* pH. (c_{ligand} = 64.8 μM, $c_{Cu(II)}$ = 48.0 μM, I = 0.10 M KCl, λ = 375 nm)

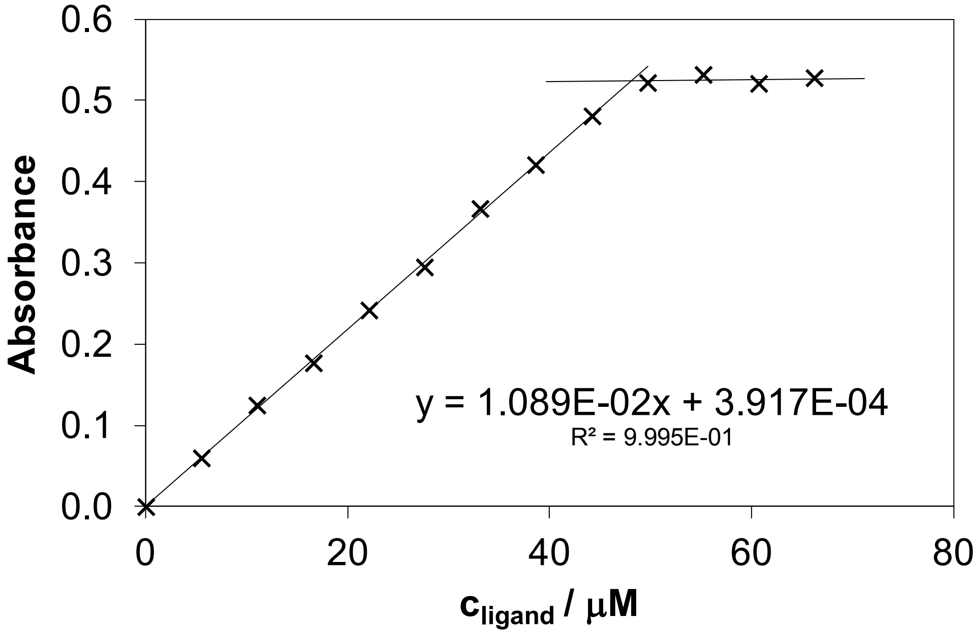

Figure S3. Dependence of absorbance at λ = 375 nm *vs* concentration of the proligand recorded for the Cu(II) – NaH_2L^H system at constant concnetration of Cu(II). (pH = 5.75, $c_{Cu(II)}$ = 48.0 μM, I = 0.10 M KCl)

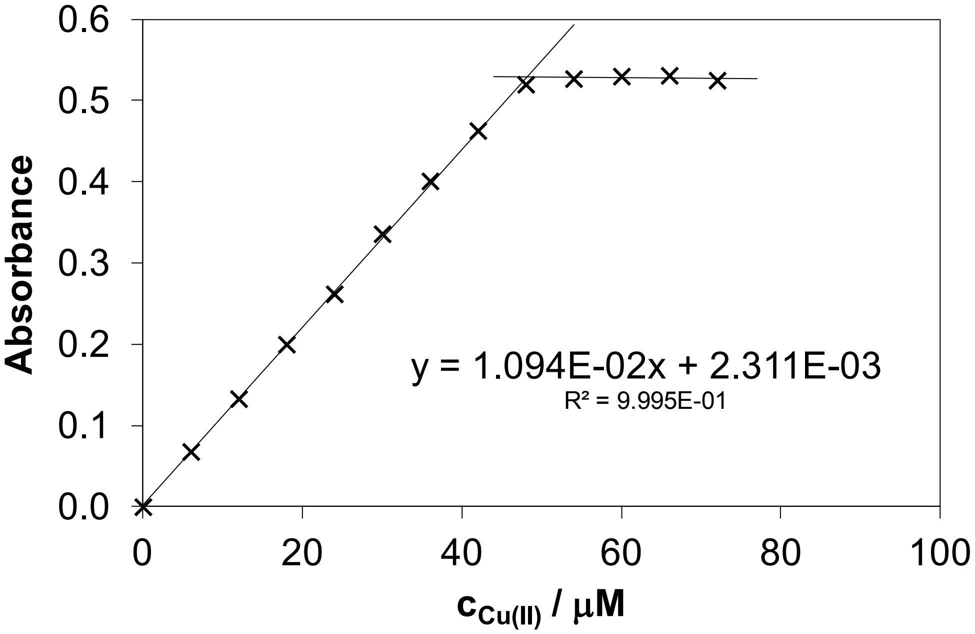

Figure S4. Dependence of absorbance at λ = 375 nm *vs* concentration of Cu(II) recorded for the Cu(II) – NaH_2L^H system at constant concnetration of the ligand. (pH = 5.75, c_{ligand} = 48.6 µM, I = 0.10 M KCl).

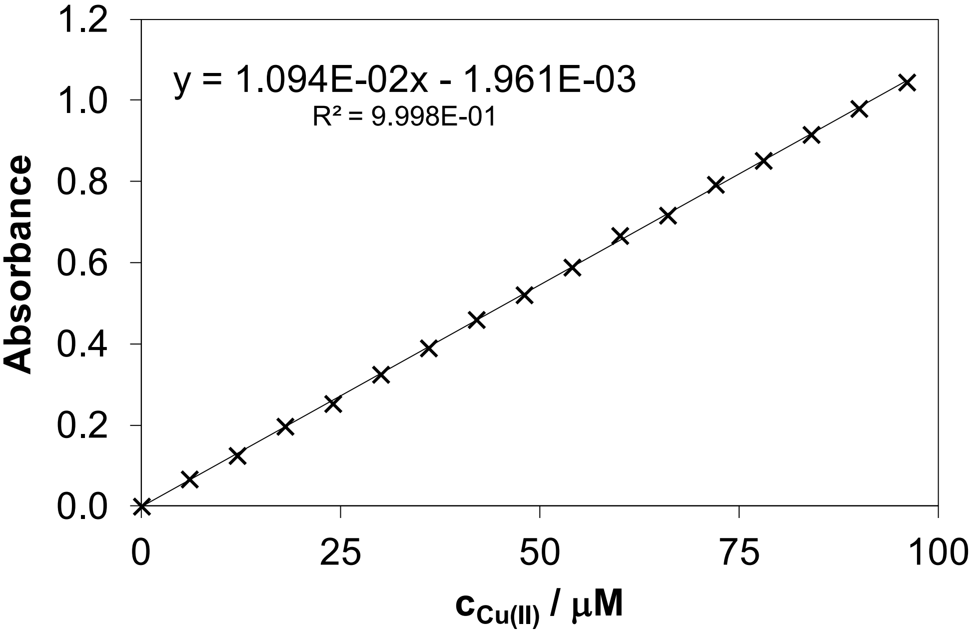

Figure S5. Calibration curve for the Cu(II) – NaH_2L^H system at λ = 375 nm. ($c_{(proligand}$ = 120 µM, I = 0.10 M KCl, pH = 5.75).

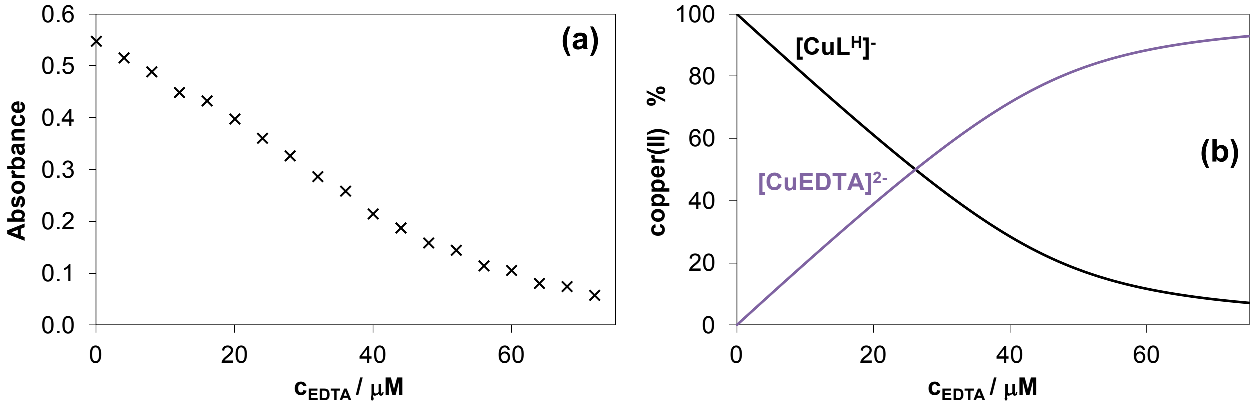

Figure S6. (a) Dependence of absorbance at λ = 375 nm *vs* concentration of EDTA recorded for the Cu(II) – NaH_2L^H – EDTA ternary system (pH = 5.75, c_{ligand} = 50.0 μM, $c_{Cu(II)}$ = 50.0 μM, c_{EDTA} = 72.0 μM, I = 0.10 M KCl); (b) Concentration distribution curves calculated for the Cu(II) – NaH_2L^H – EDTA ternary system under the same condition.

Crystal Structures. Two Cu(HL^H) moieties (denoted as **A** and **B**) are linked through Cu1A–O2B bond of 2.432(2) Å. The copper atoms are coordinated by a tridentate ONS Schiff base ligand and their coordination polyhedra are completed by one (for Cu1A) and two (for Cu1B) water molecules as monodentate ligands. The crystal structures of **1** and **2** are stabilized by a system of N–H···O hydrogen bonds to form a 3D supramolecular network (Figures S6 and S7). A fragment of the crystal structure of **1′** is shown in Figure S8. Two of the asymmetric entities in **3** are linked through the centre of symmetry to form a tetranuclear complex (Figure S9), which is additionally sustained *via* hydrogen bonding involving coordinated water molecules and stacking interaction at centroid-to-centroid distance of 3.682 Å and shift distance of 0.640 Å. As could be seen the role of four sulfonate groups is essentially different. Two of them do not coordinate to copper atoms, while the other two act as syn-syn bidentate-bridging ligands with Cu1A···Cu1B′ separation at 4.795(3) Å. As in **1**, **1′** and **2** the value of τ parameter of 0.127 for Cu1A and 0.077 for Cu1B in **3** indicate square-pyramidal coordination geometry for the central atoms. As expected due to the presence of non-covalent intermolecular interactions, the main crystal structural motif for **3** can be described as a 3D supramolecular network based on O–H···O and O–H···N hydrogen bonding (Figure S10).

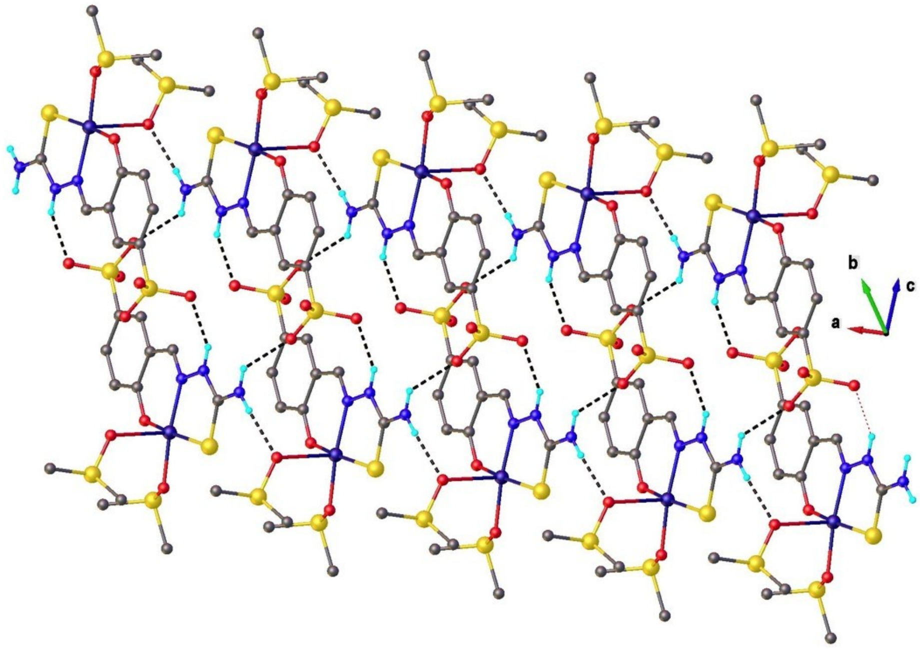

Figure S7. 1D supramolecular architecture in the crystal structure **1**.

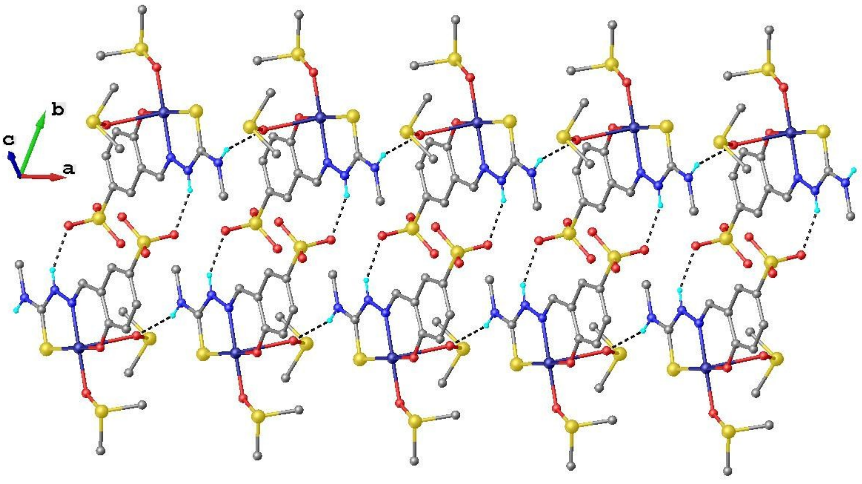

Figure S8. 1D supramolecular architecture in the crystal structure **2**.

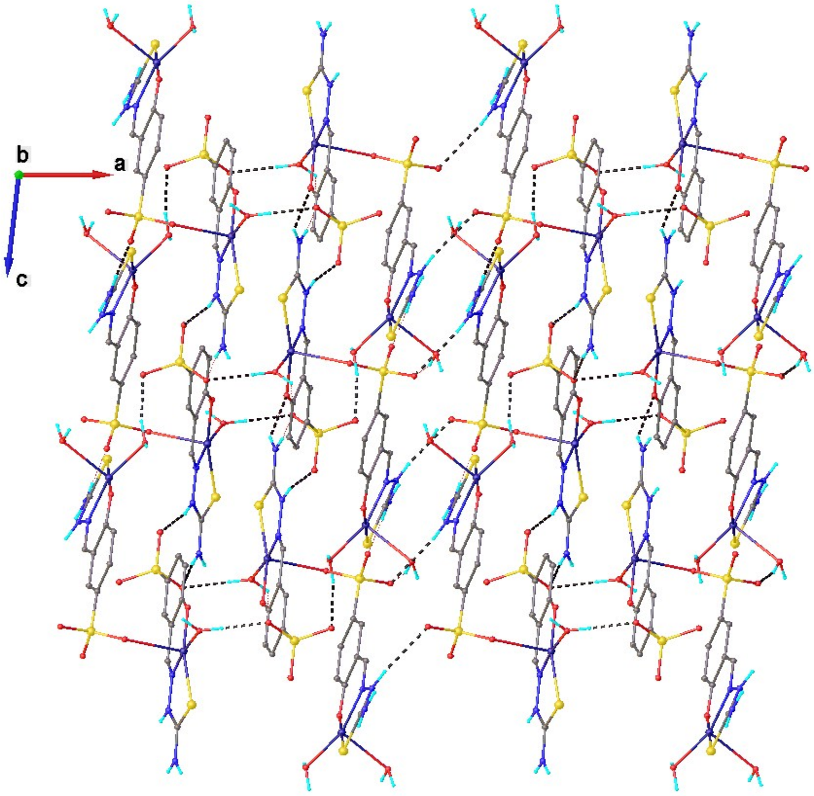

Figure S9. View of 3D supramolecular network in **1′**along ***b***-axis.

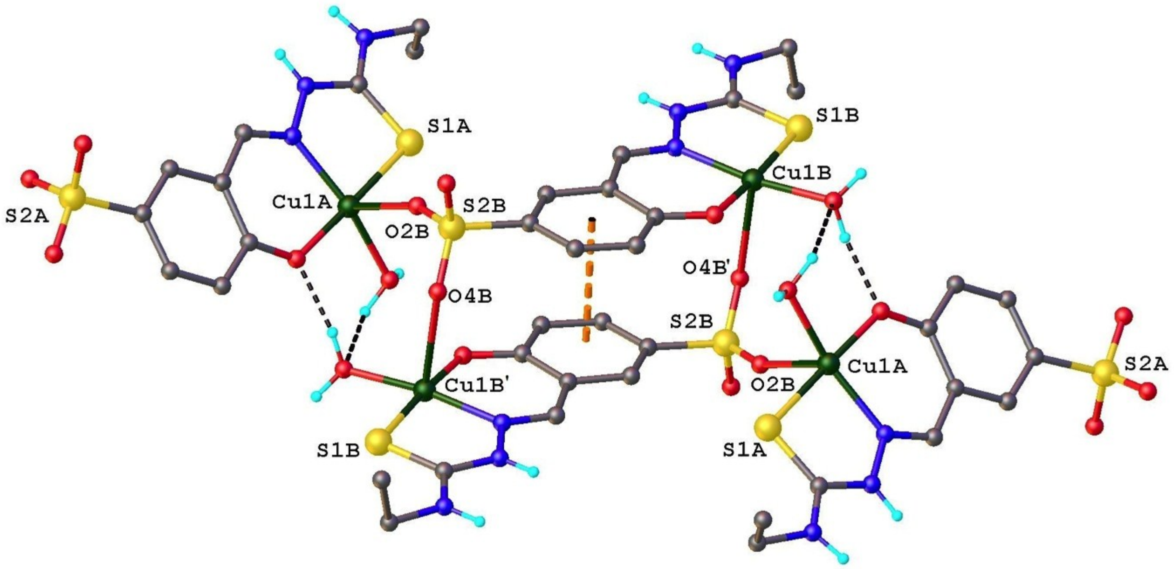

Figure S10. The structure of tetranuclear complex molecule in **3** with selected atom labeling scheme. Centroid-to-centroid contact is shown by a dashed orange line.

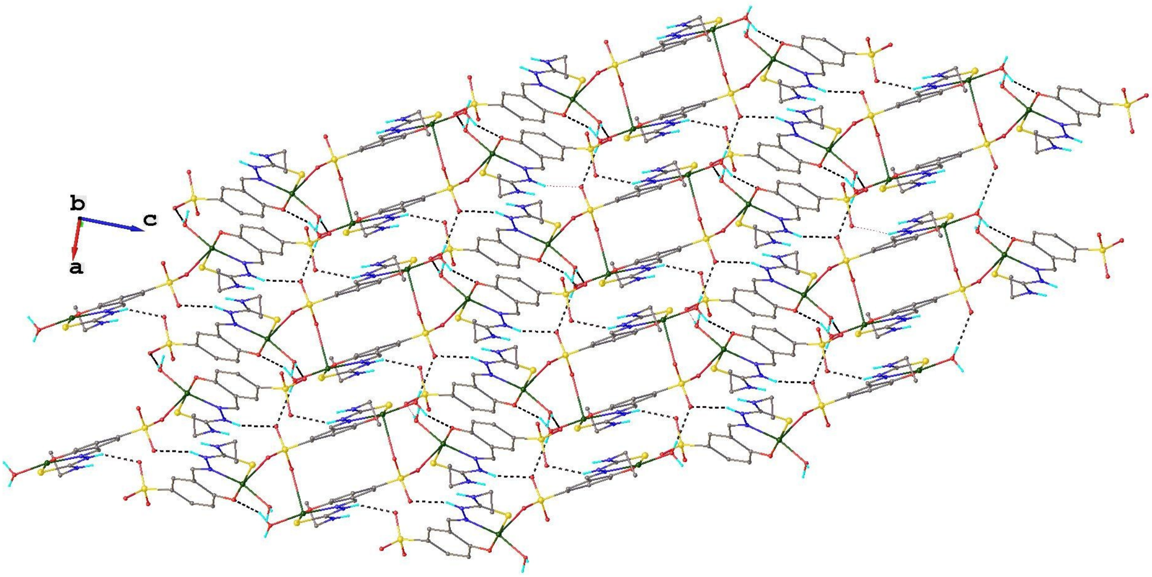

Figure S11. View of the crystal structure **3** along ***b***-axis.

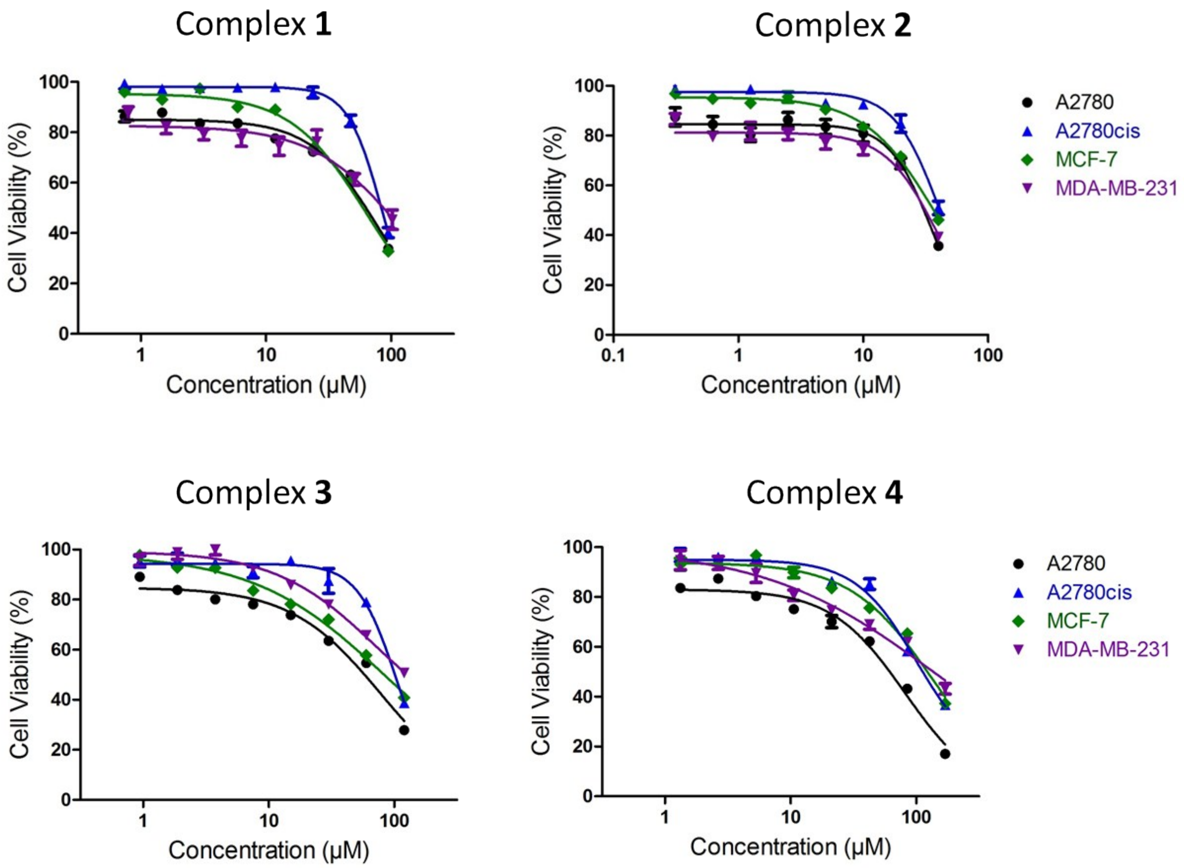

Figure S12. Concentration–effect curves of complexes **1-4** in the human cancer cell lines A2780 (•), A2780cis (□）， MCF-7 (◆) and MDA-MB-231 (∇）. Values were obtained by the MTT assay and are means ± standard deviations from at least three independent experiments using exposure times of 72 h.

Table S1. Crystal data and details of data collection for **1**, **2**, **1´** and **3**.

Compound	**1**	**2**	**1´**	**3**
empirical formula	$C_{12}H_{19}CuN_3O_6S_4$	$C_{13}H_{21.3}CuN_3O_{6.15}S_4$	$C_{16}H_{20}Cu_2N_6O_{11}S_4$	$C_{40}H_{60}Cu_4N_{12}O_{24}S_8$
Fw	493.08	509.81	727.70	1603.64
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a [Å]	6.3750(3)	7.6632(4)	13.5205(8)	8.0020(4)
b [Å]	12.3166(9)	11.5805(6)	11.0919(6)	13.1053(6)
c [Å]	13.7976(12)	12.2566(8)	16.2446(9)	14.1945(7)
α [°]	75.444(7)	86.844(5)	90	88.965(3)
β [°]	77.550(6)	72.387(6)	96.219(5)	88.544(3)
γ [°]	76.945(5)	79.287(5)	90	80.556(3)
V [Å^3]	1006.90(12)	1018.63(10)	2421.8(2)	1467.76(12)
Z	2	2	4	1
λ [Å]	0.71073	0.71073	1.54184	1.54184
ρ_{calcd} [g cm^{-3}]	1.626	1.662	1.996	1.814
Crystal size [mm]	0.45 × 0.20 × 0.15	0.45 × 0.20 × 0.15	0.29 × 0.05 × 0.03	0.03 × 0.03 × 0.09
T [K]	293	200	100	130
μ [mm^{-1}]	1.532	1.518	6.054	5.086
2Θ range	3.1 to 50.06	3.58 to 50.06	9.674 to 133.184	6.23 to 100.866
Reflections collected	6669	7072	9210	30234
Independent reflections	3554 [R_{int}= 0.0233]	3601[R_{int}= 0.0253]	4226 [R_{int}= 0.0370]	3010 [R_{int}= 0.2465]
Data/restraints/parameters	3554/22/237	3601/8/261	4226/0/387	3010/12/403
R_1[a]	0.0601	0.0382	0.0334	0.0721
wR_2[b]	0.1376	0.0839	0.0894	0.1748
GOF[c]	1.051	1.058	1.040	1.100

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] GOF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

Table S2. Bond Lengths (Å) and angles (º) for **1** and **2**.

	1	**2**
Cu1-S1	2.26232)	2.254(1)
Cu1-O1	1.898(4)	1.881(3)
Cu1-O5	1.970(4)	1.972(3)
Cu1-O6	2.560(4)	2.659(7)
Cu1-O1W	-	-
Cu1A-O2	-	-
Cu1-N1	1.946(4)	1.953(4)
S1-C8	1.694(5)	1.717(5)
S2-O2	1.461(4)	1.449(4)
S2-O3	1.447(4)	1.431(4)
S2-O4	1.445(4)	1.448(4)
S2-C4	1.769(5)	1.772(5)
S3-O5	1.591(5)	1.537(3)
S3-C10	1.75(1)	1.770(5)
S3-C11	1.7311)	1.780(5)
S4-O6	1.509(4)	1.524(7)
S4-C12	1.774(7)	1.850(8)
S4-C13	1.770(6)	1.83(1)
O1-C1	1.300(6)	1.302(6)
N1-N2	1.391(6)	1.387(5)
N1-C7	1.285(6)	1.285(6)
N2-C8	1.352(6)	1.342(6)
N3-C8	1.319(6)	1.315(6)
N3-C9	-	1.453(6)
C1-C2	1.403(7)	1.412(7)
C1-C6	1.432(7)	1.422(6)
C2-C3	1.377(7)	1.373(7)
C3-C4	1.408(7)	1.392(7)
C4-C5	1.364(7)	1.375(7)
C5-C6	1.405(7)	1.410(7)
C6-C7	1.434(7)	1.435(6)

S1-Cu1-O6	90.38(10)	109.06(15)
O1-Cu1-S1	169.24(15)	170.84(13)
O1-Cu1-O5	90.40(16)	90.57(14)
O1-Cu1-O6	100.38(16)	80.05(19)
O1-Cu1-N1	92.45(16)	93.15(15)
O5-Cu1-S1	89.62(13)	90.26(10)
O5-Cu1-O6	89.52(17)	91.16(19)
N1-Cu1-S1	86.52(12)	86.47(12)
N1-Cu1-O5	173.64(18)	175.53(16)
N1-Cu1-O6	95.55(15)	87.0(2)
C8-S1-Cu1	96.47(18)	96.49(17)
O2-S2-C4	106.5(2)	105.4(2)

O3-S2-O2	111.6(3)	113.0(3)
O3-S2-C4	106.6(3)	106.8(2)
O4-S2-O2	111.7(2)	111.3(3)
O4-S2-O3	113.7(3)	113.5(3)
O4-S2-C4	106.1(2)	106.2(2)
O5-S3-C10	102.4(7)	105.0(2)
O5-S3-C11	104.2(7)	103.5(2)
C11-S3-C10	101.0(7)	97.8(3)
O6-S4-C12	105.1(3)	99.4(7)
O6-S4-C13	106.6(3)	101.9(9)
C13-S4-C12	98.5(3	91.8(11)
C1-O1-Cu1	128.9(3)	128.4(3)
S3-O5-Cu1	117.5(3)	120.0(2)
S4-O6-Cu1	114.5(2)	128.4(4)
N2-N1-Cu1	117.2(3)	117.5(3)
C7-N1-Cu1	126.8(3)	126.3(3)
C7-N1-N2	116.0(4)	116.2(4)
C8-N2-N1	118.4(4)	118.4(4)
C8-N3-C9	-	124.3(4)
O1-C1-C2	119.6(5)	118.7(4)
O1-C1-C6	123.6(5)	123.8(4)
C2-C1-C6	116.9(5)	117.5(4)
C3-C2-C1	122.3(5)	121.7(4)
C2-C3-C4	120.3(5)	120.6(5)
C3-C4-S2	120.4(4)	120.8(4)
C5-C4-S2	120.6(4)	119.8(4)
C5-C4-C3	118.9(5)	119.3(4)
C4-C5-C6	122.0(5)	121.4(4)
C1-C6-C7	122.8(4)	123.6(4)
C5-C6-C1	119.7(4)	119.3(4)
C5-C6-C7	117.6(4)	117.0(4)
N1-C7-C6	125.1(5)	124.4(4)
N2-C8-S1	120.9(4)	120.7(4)
N3-C8-S1	121.4(4)	120.2(4)
N3-C8-N2	117.7(5)	119.2(4)

Table S3. Bond Lengths (Å) for **1′** and **3.**

	1′		**3**	
	A	**B**	**A**	**B**
Cu1-S1	2.2814(8)	2.2692(8)	2.274(4)	2.262(4)
Cu1-O1	1.930(2)	1.890(2)	1.932(8)	1.912(8)
Cu1-O1*w*	1.977(2)	2.344(2)	1.946(8)	1.964(8)
Cu1A-O2B	2.432(2)	2.016(2)	-	2.396(9)
Cu1-N1	1.950(2)	1.956(2)	1.954(10)	1.936(10)
Cu1B-O4B[1]	-	-	-	2.512(9)
S1-C8	1.713(3)	1.712(3)	1.688(12)	1.717(13)
S2-O2	1.457(2)	1.470(2)	1.468(8)	1.445(9)
S2-O3	1.460(2)	1.472(2)	1.464(8)	1.496(8)
S2-O4	1.482(2)	1.447(2)	1.498(8)	1.483(8)
S2-C4	1.755(3)	1.759(3)	1.763(12)	1.751(12)
O1-C1	1.301(4)	1.292(3)	1.322(13)	1.325(13)
N1-N2	1.389(3)	1.380(3)	1.384(13)	1.393(13)
N1-C7	1.283(4)	1.301(4)	1.295(14)	1.290(14)
N2-C8	1.334(4)	1.349(4)	1.347(15)	1.379(15)
N3-C8	1.324(4)	1.316(4)	1.320(15)	1.301(15)
N3-C9	-	-	1.470(15)	1.459(14)
C1-C2	1.423(4)	1.420(4)	1.414(17)	1.398(16)
C1-C6	1.426(4)	1.431(4)	1.425(17)	1.421(16)
C2-C3	1.370(4)	1.377(4)	1.358(16)	1.382(16)
C3-C4	1.407(4)	1.405(4)	1.378(17)	1.404(17)
C4-C5	1.382(4)	1.378(4)	1.395(17)	1.364(17)
C5-C6	1.403(4)	1.407(4)	1.381(16)	1.424(16)
C6-C7	1.444(4)	1.438(4)	1.461(17)	1.420(17)
C9-C10		--	1.501(18)	1.501(17)

Symmetry code 1) 1 - *x*, 1 - *y* , -*z*.