Electronic Supplementary information (ESI) for

From solid state to *in vitro* anticancer activity of copper(II) compounds with electronically-modulated NNO Schiff base ligands

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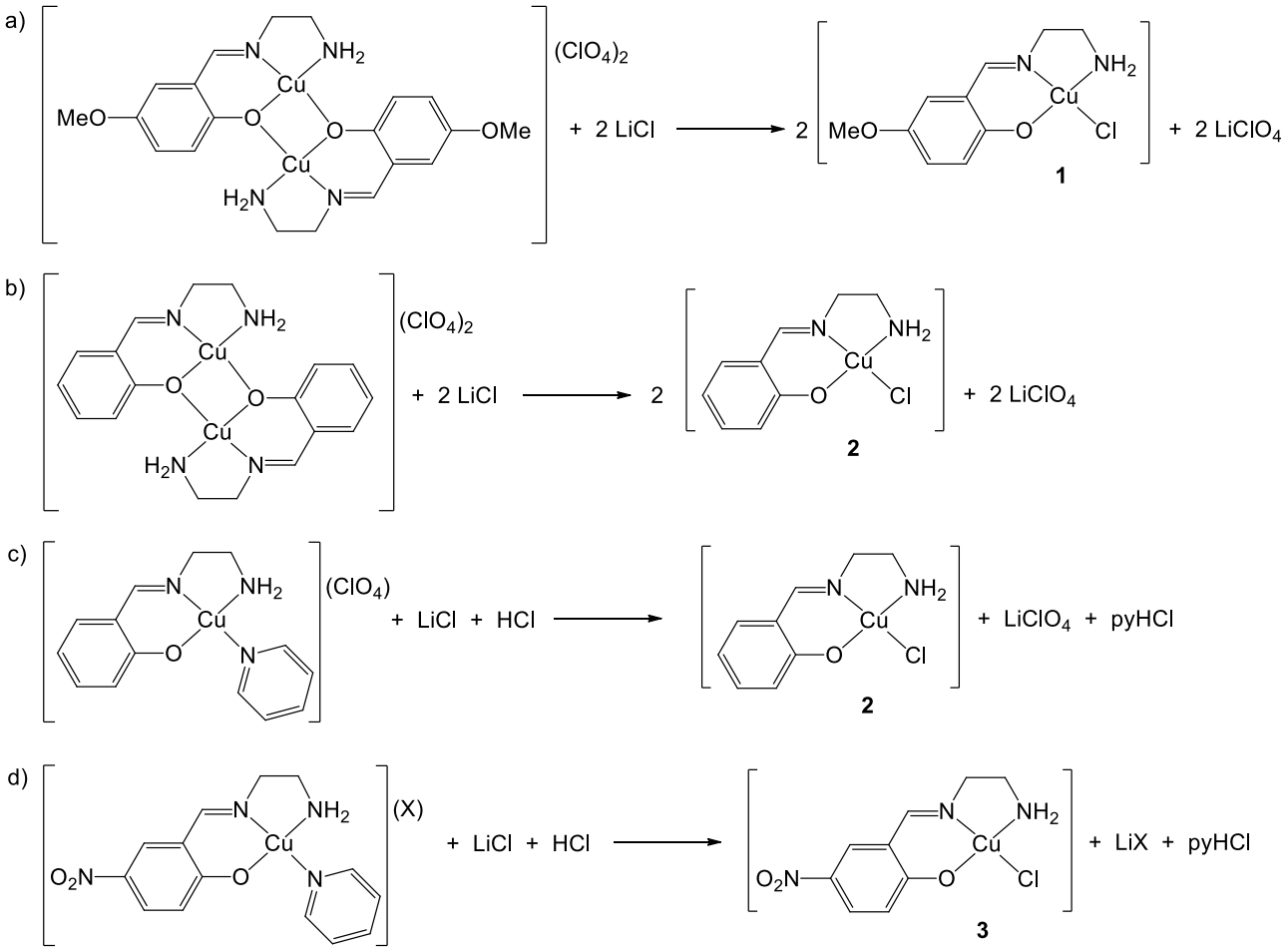
Table S1 Crystallographic data for **1**, **2**, **3** and **B1**·1.5H_2O.

	1	**2**	**3**	**B1**·1.5H_2O
Crystal Data				
Moiety formula	$C_{10}H_{13}ClCuN_2O_2$	$C_9H_{11}ClCuN_2O$	$C_9H_{10}ClCuN_3O_3$	$C_{18}H_{21}CuN_2O_{5.5}$
M / Da	292.21	262.19	307.19	416.91
Crystal system	monoclinic	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/c$ (n. 14)	$P2_1/c$ (n. 14)	$Pna2_1$ (n. 33)	$C2/c$ (n. 15)
a / Å	14.252(3)	6.1590(12)	27.861(5)	21.258(4)
b / Å	7.9730(16)	11.379(2)	30.137(6)	8.1890(16)
c / Å	10.332(2)	14.193(3)	10.4650(10)	21.253(4)
α / °	90	90	90	90
β / °	107.38(3)	99.69(3)	90	111.37(3)
γ / °	90	90	90	90
V / Å^3, Z	1120.4(4), 4	980.5(3), 4	8787(3), 32	3445.4(14), 8
Temperature / K	100(2)	100(2)	100(2)	100(2)
Reflns for cell det	19573	9491	3560	19498
θ / ° for cell det	1.5-29.8	2.3-29.8	1.3-28.2	2.3-29.8
D_x / Mg m^{-3}	1.732	1.776	1.858	1.607
μ / mm^{-1}	2.009	2.283	2.059	1.196
Colour, habit	blue, thin plates	blue, thin plates	blue, needles	light blue, thin rods
Data Collection				
Temperature / K	100(2)	100(2)	100(2)	100(2)
radiation λ / Å	synchrotron, 0.700	synchrotron, 0.700	synchrotron, 0.700	synchrotron, 0.700
Scan type	φ	φ	φ	φ
$2\theta_{max}$ / °	59.6	59.5	60.0	59.7
h range	$-20 \rightarrow 20$	$-8 \rightarrow 8$	$-29 \rightarrow 39$	$-30 \rightarrow 30$
k range	$-10 \rightarrow 11$	$-16 \rightarrow 16$	$-43 \rightarrow 43$	$-11 \rightarrow 11$
l range	$-11 \rightarrow 14$	$-20 \rightarrow 20$	$-13 \rightarrow 13$	$-30 \rightarrow 30$
Measured reflns	19085	12049	66041	32313
Independent reflns	3242	2860	25579	5058
Reflns with $I>2\sigma(I)$	3080	2836	17321	4655
R_{int}	0.0405	0.0171	0.0707	0.0295
Refinement on F^2				
R_1, wR_2 [$F^2>2\sigma(F^2)$]	0.0389, 0.1135	0.0179,0.0500	0.0689, 0.1690	0.0270, 0.0761
R_1, wR_2 [all data]	0.0405, 0.1152	0.0180, 0.0501	0.1083, 0.1922	0.0296, 0.0779
S	1.053	1.097	1.006	1.048
Params, restraints	147, 0	128, 0	1209, 85	252, 6
$(\Delta/\sigma)_{max}$	0.001	0.005	0.007	0.003
$\Delta\rho_{max}$, $\Delta\rho_{min}$ / e Å^{-3}	1.154, –0.694	0.378, –0.454	1.539, –2.131	0.426, –0.560



Scheme S1 Reaction schemes for the synthesis of a) **1**, b) **2** *first method*, c) **2** *second method* and d) **3** (X^- = NO_3^- or ClO_4^-).

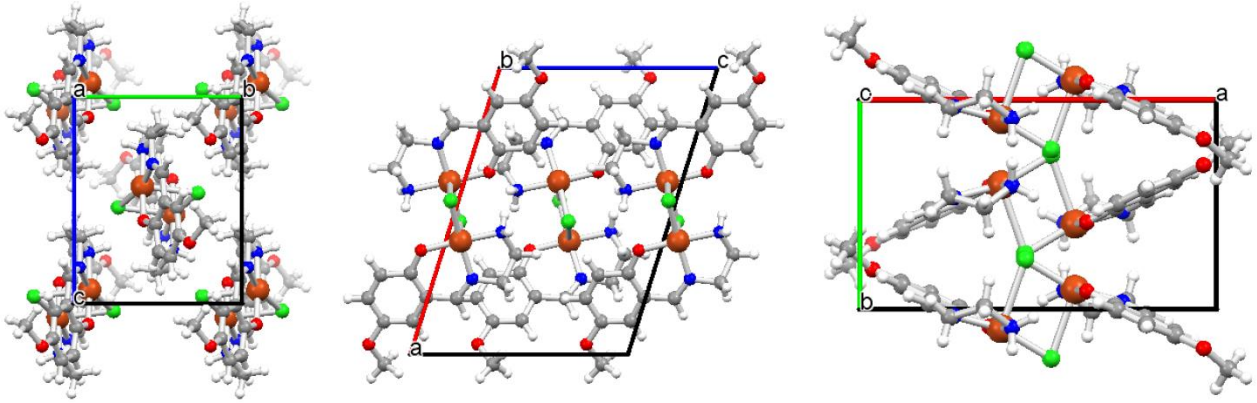


Fig. S1 Crystal packing of **1** along the three crystallographic axes; colour code: Cu = orange, Cl = green, O = red, N = blue, C = grey, H = white.

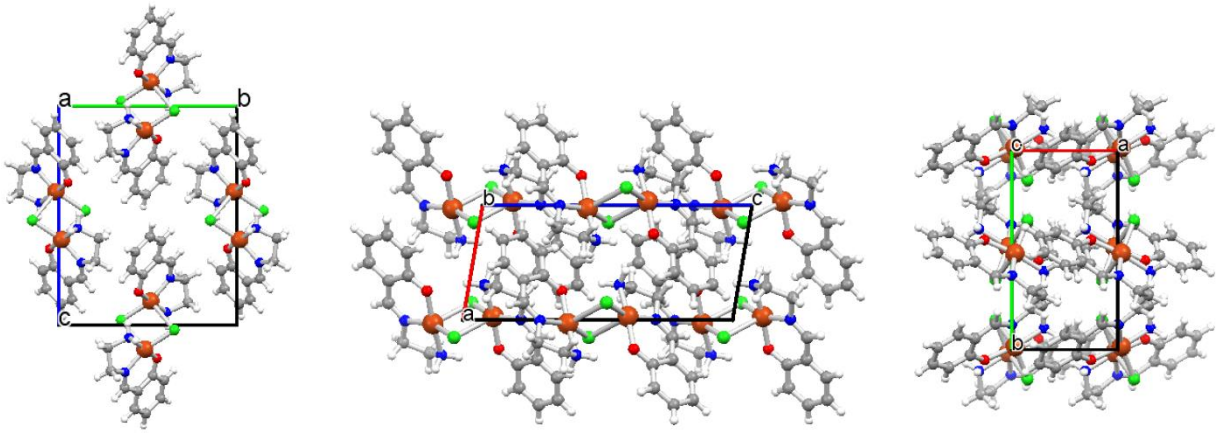


Fig. S2 Crystal packing of **2** along the three crystallographic axes; colour code: Cu = orange, Cl = green, O = red, N = blue, C = grey, H = white.

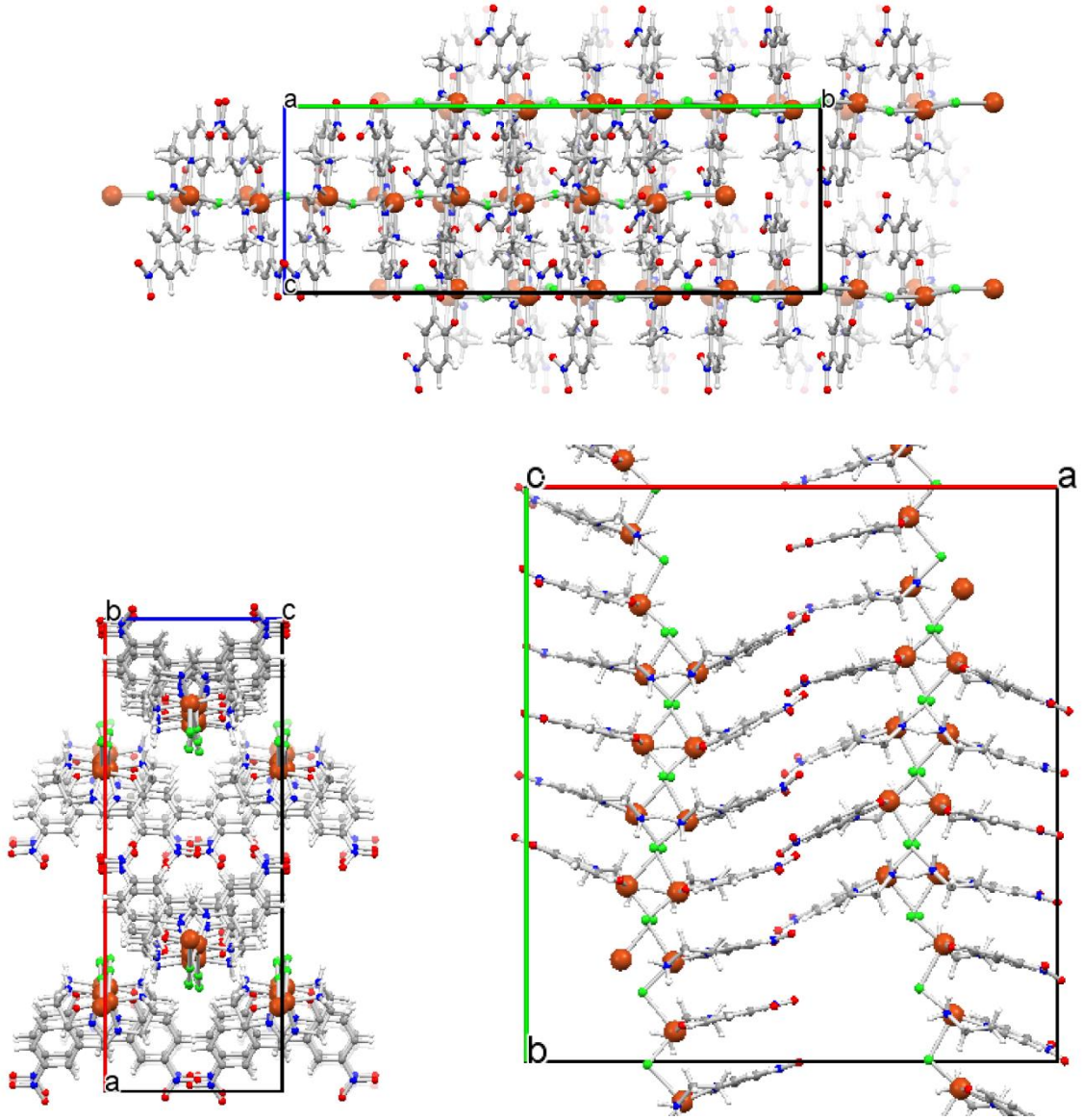


Fig. S3 Crystal packing of **3** along the three crystallographic axes; colour code: Cu = orange, Cl = green, O = red, N = blue, C = grey, H = white.

Table S2 H-bonds involving the primary amino groups in **3** (Å and °).

D–H···A [a,b]	***d*(H···A)**	***d*(D···A)**	**<(DHA)**
N1A–H1A1···O1H	2.55	3.344(14)	146.1
N1B–H1B2···O1D	3.09	3.864(14)	143.6
N1C–H1C2–O1A	2.46	3.249(13)	145.6
N1D–H1D1···O1G	2.97	3.740(14)	143.7
N1E–H1E1···O1B#1	2.92	3.701(14)	145.9
N1F–H1F1···O1C	2.56	3.352(14)	146.3
N1G–H1G2···O1F	2.76	3.546(14)	144.3
N1H–H1H2···O1E	2.69	3.480(14)	146.8
N1A–H1A2···O1D#4	2.31	3.177(13)	158.7
N1B–H1B1···O1C#4	2.30	3.173(12)	161.5
N1C–H1C1···O1B#4	2.32	3.196(13)	160.4
N1D–H1D2···O1A#4	2.30	3.165(13)	159.9
N1E–H1E2···O1F#4	2.28	3.149(14)	159.4
N1F–H1F2···O1E#4	2.32	3.184(14)	159.2
N1G–H1G1···O1H#4	2.29	3.154(16)	159.4
N1H–H1H1···O1G#4	2.28	3.150(15)	159.7
N1A–H1A1···Cl1D#4	2.85	3.314(11)	112,7
N1B–H1B2···Cl1C#4	2.76	3.270(11)	116.3
N1C–H1C2···Cl1B#4	2.89	3.330(11)	111.2
N1D–H1D1···Cl1A#4	2.78	3.282(12)	115.9
N1E–H1E1···Cl1F#4	2.78	3.286(12)	116.0
N1F–H1F1···Cl1E#4	2.85	3.318(12)	113.2
N1G–H1G2···Cl1H#4	2.78	3.275(12)	115.6
N1H–H1H2···Cl1G#4	2.83	3.297(13)	113.2

[a] *d*(N–H) are fixed to 0.91 Å; [b] symmetry transformations used to generate equivalent atoms: #1: *x*, *y*, *z*; #4: $-x + ½, y + ½, z + ½$.

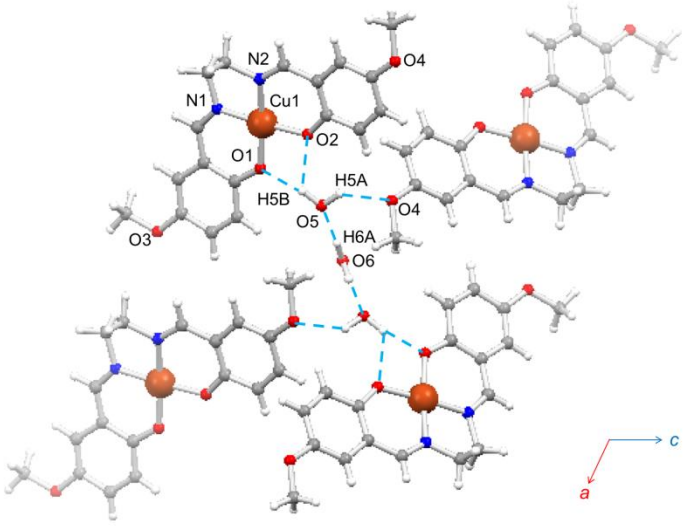


Fig. S4 Crystal structure of **B1**·1.5H_2O with main atom numbering, and crystal packing assembly of four molecules through the hydrogen-bonded water molecules (Table S3); colour code: Cu = orange, O = red, N = blue, C = grey, H = white, H-bonds = dashed azure lines. Main coordination distances (Å) and angles (°): Cu1–O1 = 1.909(1), Cu1–O2 = 1.910(1), Cu1–N2 = 1.940(1), Cu1–N1 = 1.944(1), O1–Cu1–O2 = 88.96(5), O1–Cu1–N2 = 172.74(4), O2–Cu1–N2 = 93.64(5), O1–Cu1–N1 = 93.28(5), O2–Cu1–N1 = 176.38(4), N2–Cu1–N1 = 84.47(5).

Table S3 H-bonds involving water molecules in **B1**·1.5H_2O (Å and °).

D–H···A [a,b]	***d*(H···A)**	***d*(D···A)**	**<(DHA)**
O5–H5B···O1#5	1.814(12)	2.7374(17)	168(3)
O5–H5B···O2#5	2.65(3)	3.2361(17)	121(2)
O5–H5A···O4#8	2.07(2)	2.8575(16)	140(3)
O6–H6A···O5#1	1.91(2)	2.849(16)	176(3)

[a] *d*(O–H) are 0.937(10) Å; [b] symmetry transformations used to generate equivalent atoms: #1: *x*, *y*, *z*; #5: '–*x*, –*y*, –*z*, #8: *x*+½, –*y*+½, *z*–½.

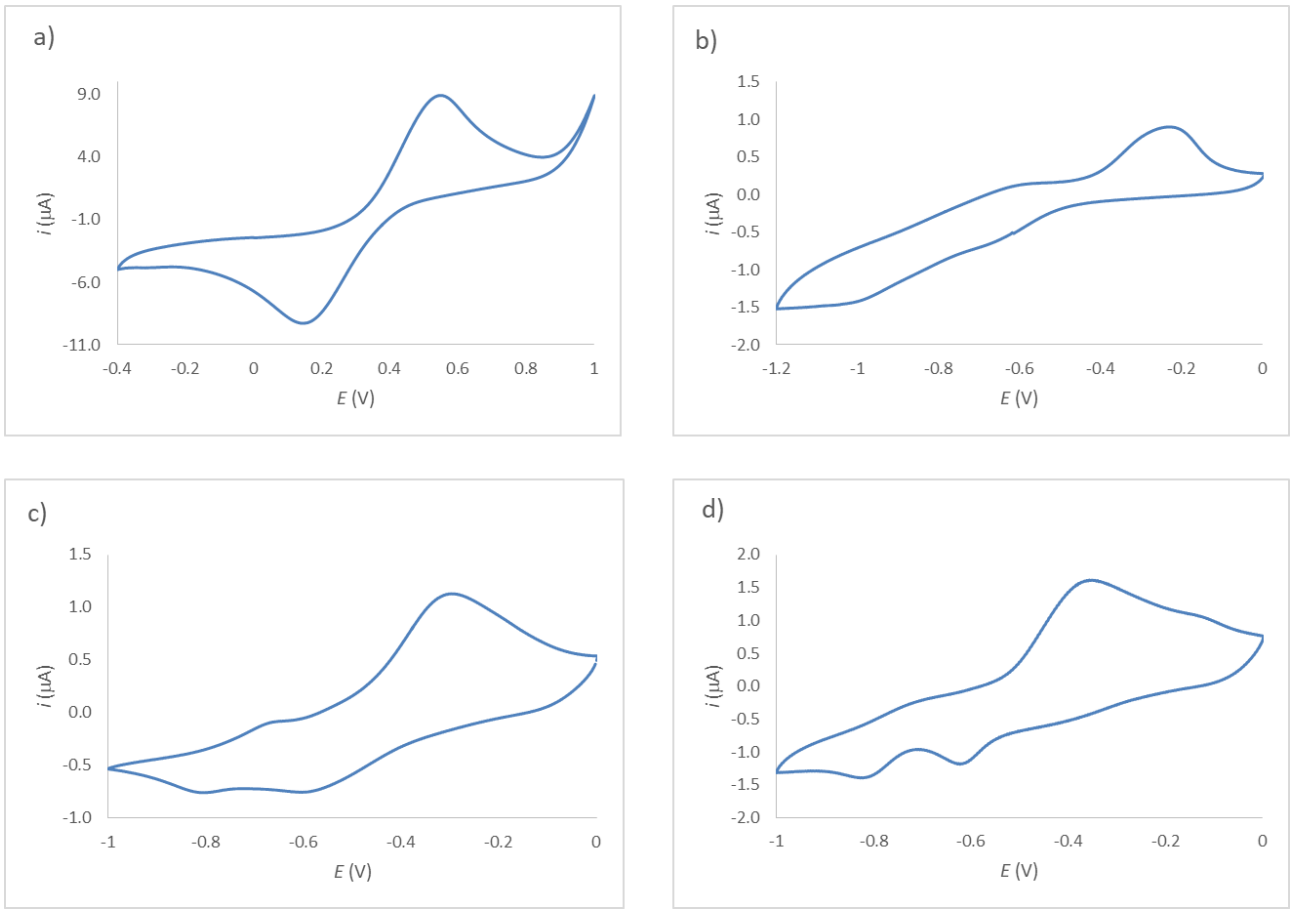


Fig. S5 CV scans of a) $CuCl_2$, b) **1**, c) **2** and d) **3** recorded in DMSO, 0.1 M $TBAPF_6$ at 50 mV/s scan rate; potentials measured *vs* Ag/AgCl, 3 M KCl reference electrode.

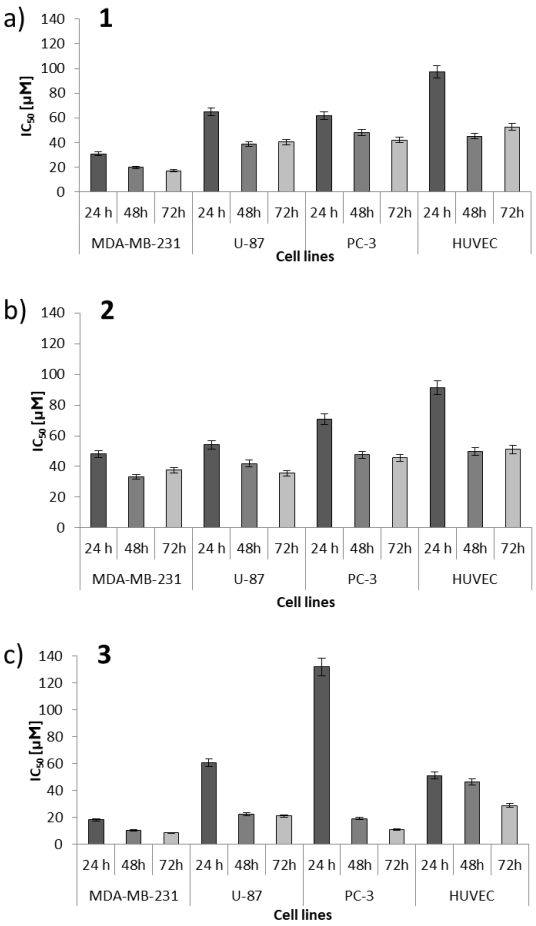


Fig. S6 Time-dependent cytotoxicity of **1**–**3** against malignant MDA-MB-231, U-87 and PC-3 human cell lines, together with healthy HUVEC cell line.

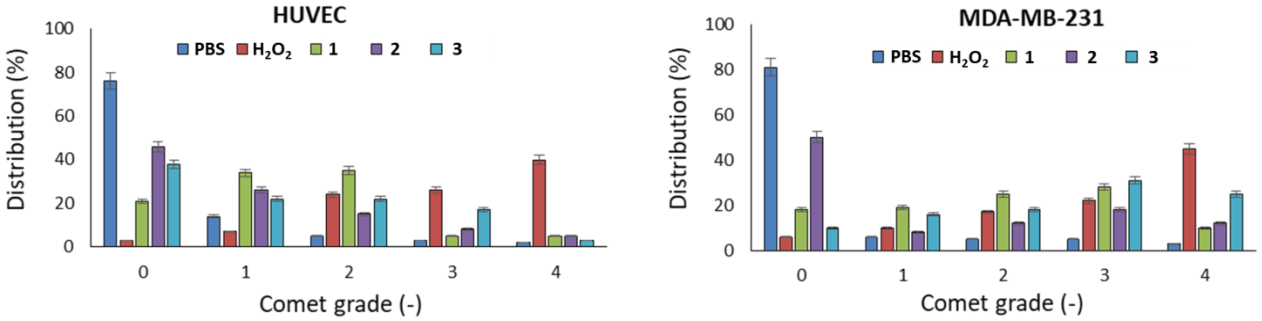


Fig. S7 Quantitation of distribution of comet grades from SCGE micrographs in MDA-MB-231 and HUVEC cells treated with **1**–**3** (24hIC_{50} values) for 24 h; PBS and H_2O_2 were employed as negative and positive controls, respectively; grade goes from 0 (no visible tail) to 4 (DNA in tail).

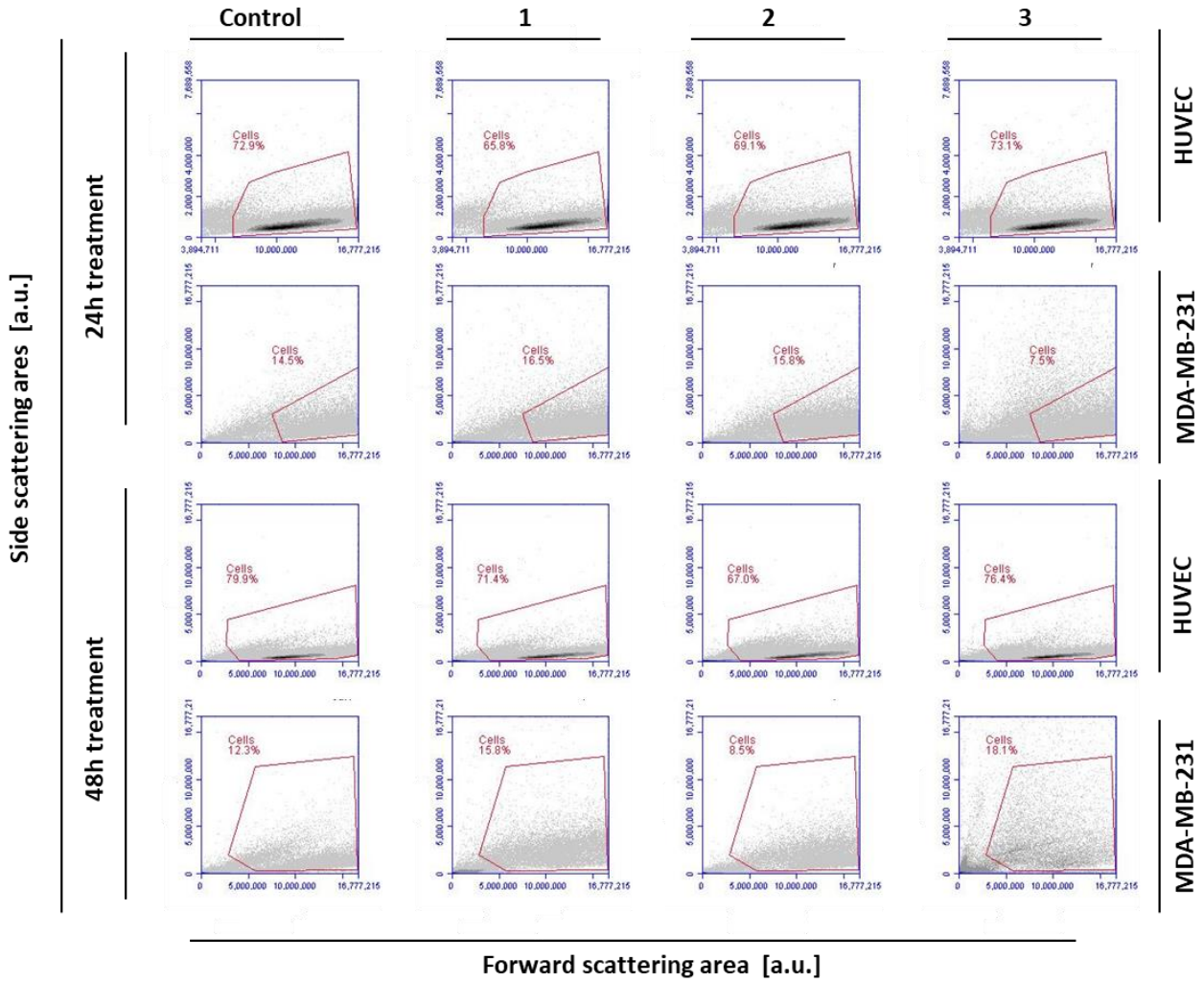


Fig. S8 Forward *vs.* side scattering areas for analyses of apoptosis induction of **1**–**3** in MDA-MB-231 and HUVEC cell lines at 24 and 48 h after administration of 24hIC_{50} doses of each complex in fresh medium.

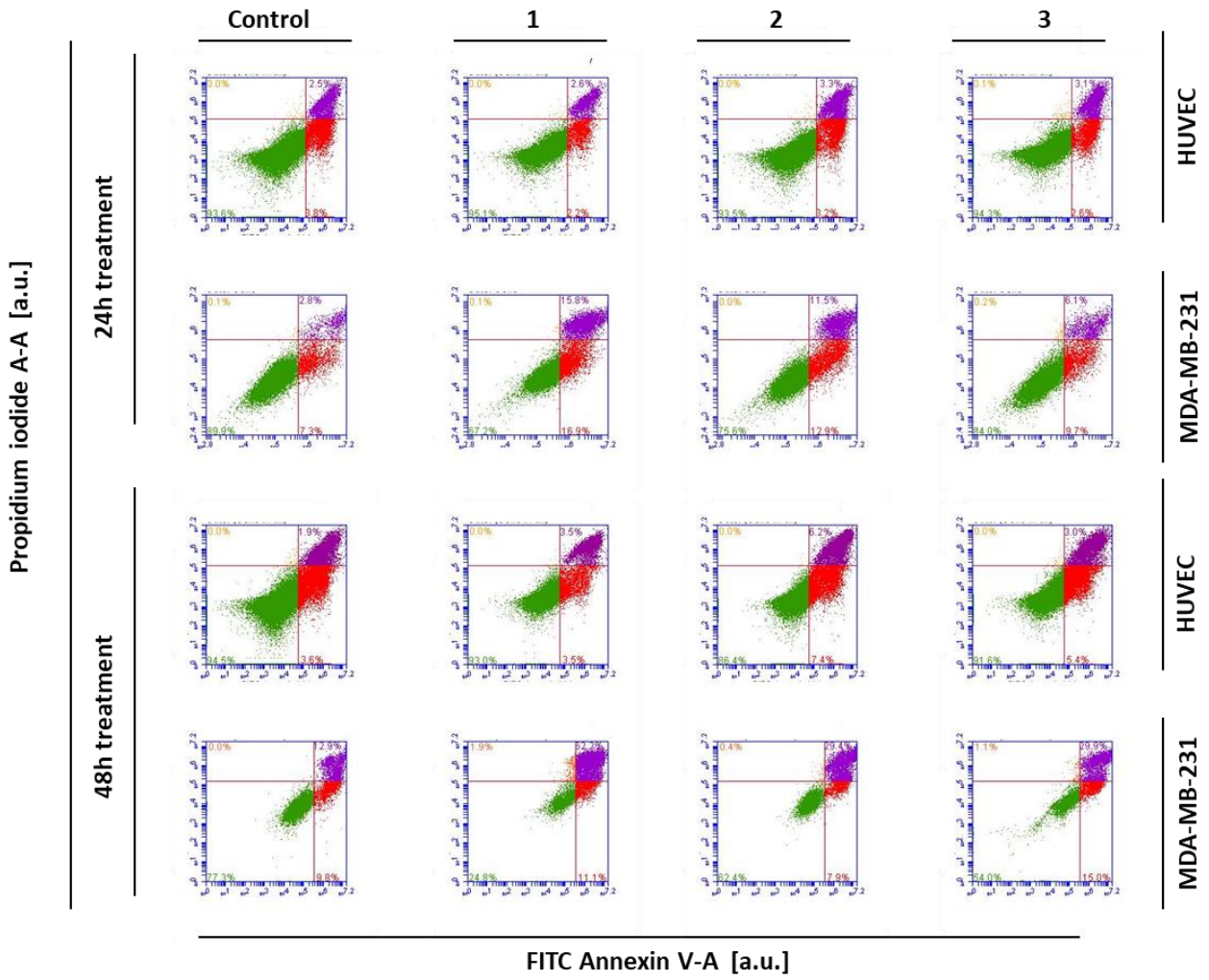


Fig. S9 Necrosis induction of **1**–**3** in MDA-MB-231 and HUVEC cell lines at 24 and 48 h after administration of 24hIC_{50} doses of each complex in fresh medium.