Electronic Supplementary Information (ESI)

Novel 5-fluorouracil complexes of Zn(II) with pyridine-based ligands as potential anticancer agents

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Table S1. Selected bond lengths (Å) and angles (°) for the Zn(II) complexes.

	1	**2**	**3**	**4**
Zn1−N1	2.070(5)	2.097(6)	2.146(3)	2.236(3)
Zn1−N2	1.978(5)	2.082(6)	2.141(3)	2.087(3)
Zn1−N3	-	1.973(5)	2.142(3)	2.188(3)
Zn1−N4	-	-	2.037(2)	2.032(3)
Zn1−N5	-	1.955(5)	-	-
Zn1−N6	-	-	2.068(2)	2.039(3)
N1−Zn1−N1^{i}	80.7(3)	-	-	-
N1−Zn1−N2	116.8(2)	79.9(2)	77.06(10)	74.15(11)
N2−Zn1−N1^{i}	113.7(2)	-	-	-
N2−Zn1−N2^{i}	112.0(3)	-	-	-
N1−Zn1−N3	-	109.9(2)	149.60(10)	149.18(11)
N1−Zn1−N4	-	-	104.29(10)	92.96(12)
N1−Zn1−N5	-	116.5(2)	-	-
N1−Zn1−N6	-	-	90.92(10)	99.68(11)
N2−Zn1−N3	-	111.4(2)	77.94(10)	75.86(11)
N2−Zn1−N4	-	-	110.09(12)	128.21(11)
N2−Zn1−N5	-	117.6(2)	-	-
N2−Zn1−N6	-	-	131.89(11)	112.39(11)
N3−Zn1−N5	-	116.2(2)	-	-
N3−Zn1−N4	-	-	100.33(9)	100.06(12)
N3−Zn1−N6	-	-	93.05(10)	98.08(11)
N4−Zn1−N6	-	-	118.02(10)	119.23(11)

Symmetry code (*i*): −*x*+1, *y*, −*z*+1/2.

Table S2. Crystallographic data and structure refinement for the Zn(II) complexes.

	1	**2**	**4**	**5**
empirical formula	$C_{18}H_{12}F_2N_6O_4Zn$	$C_{20}H_{12}F_2N_6O_4Zn$	$C_{20}H_{21}F_2N_7O_6Zn$	$C_{23}H_{17}F_2N_7O_5Zn$
formula weight	479.71	503.73	558.81	574.80
crystal system	monoclinic	triclinic	triclinic	triclinic
space group	C_2/c	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a, Å	16.103(3)	8.9142(19)	9.5983(4)	9.3416(12)
b, Å	8.1870(11)	8.956(2)	11.3429(6)	11.2656(15)
c, Å	15.934(3)	13.328(3)	12.5297(6)	12.8923(17)
α, deg	90	81.183(19)	105.715(4)	107.595(12)
β, deg	111.98(2)	73.210(19)	95.658(4)	107.564(12)
γ, deg	90	67.59(2)	110.128(4)	102.307(11)
V, Å^3	1948.1(7)	940.6(4)	1204.87(11)	1161.8(3)
T, K	150.01(10)	228(2)	293(2)	293(2)
Z	4	2	2	2
ρ_{calc} (g cm^{-3})	1.636	1.779	1.540	1.643
μ (mm^{-1})	1.319	1.371	1.085	1.125
F(000)	968	508	572	584
θ (°)	3.371-25.674	2.848-25.026	3.065-25.679	3.056-25.680
collected refls	3449	5757	7161	8765
R_{int}	0.1099	0.067	0.0212	0.0295
data/ parameters	1758 /141	3319/298	4536/335	4402/346
goodness-of-fit	1.010	1.009	1.031	1.065
R_1 [$I>2\sigma(I)$]	0.0639	0.0738	0.0430	0.047
R_1 (all data)	0.1458	0.0152	0.0613	0.678
wR_2 [$I>2\sigma(I)$]	0.1178	0.1082	0.0855	0.1054
wR_2 (all data)	0.1545	0.1357	0.0939	0.1173
CCDC number	2124448	2124449	2124451	2124450

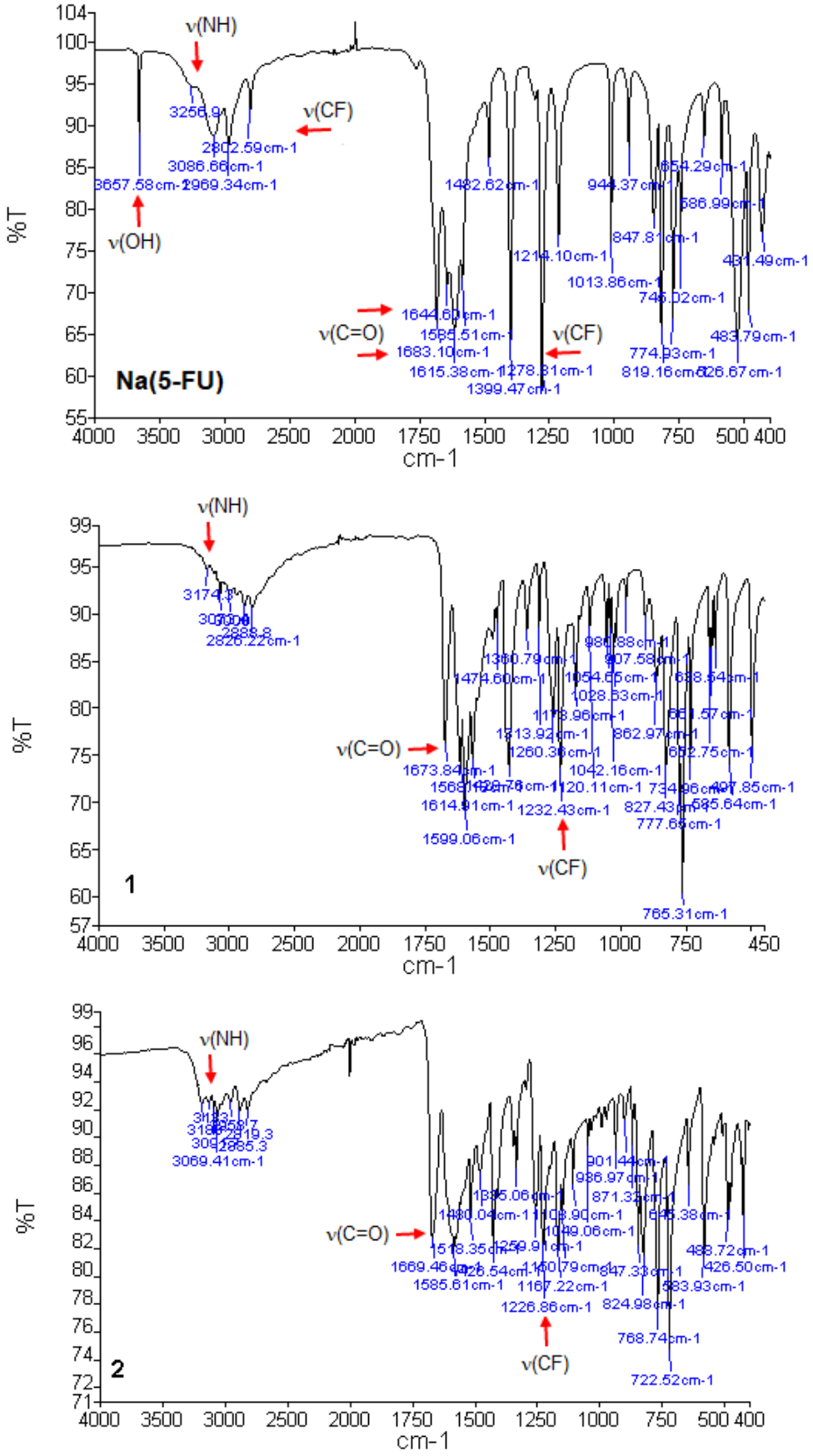

Fig. S1 (continued)

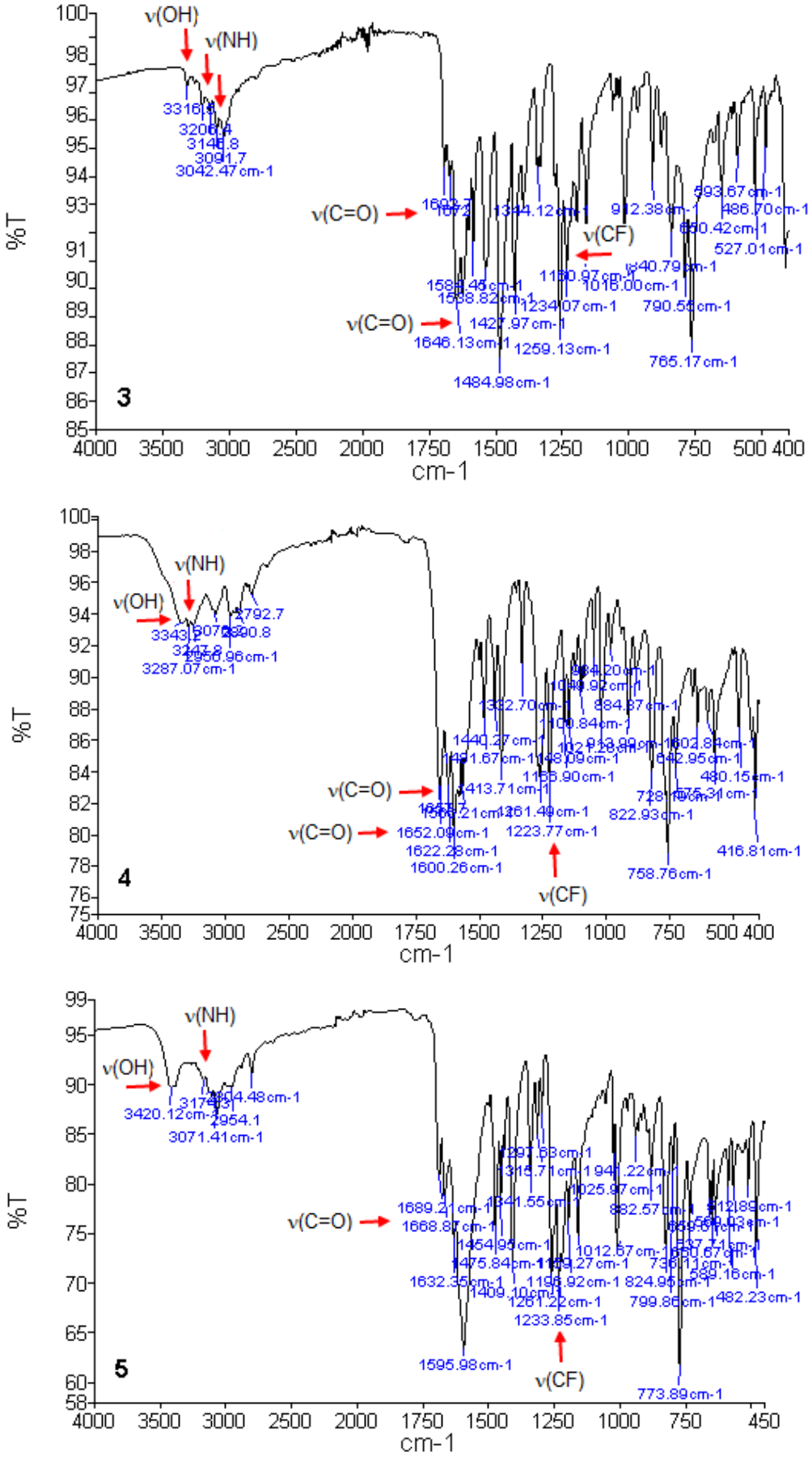

Fig. S1. IR spectra of Na(5-FU)·H_2O and **1**–**5** in the solid state.

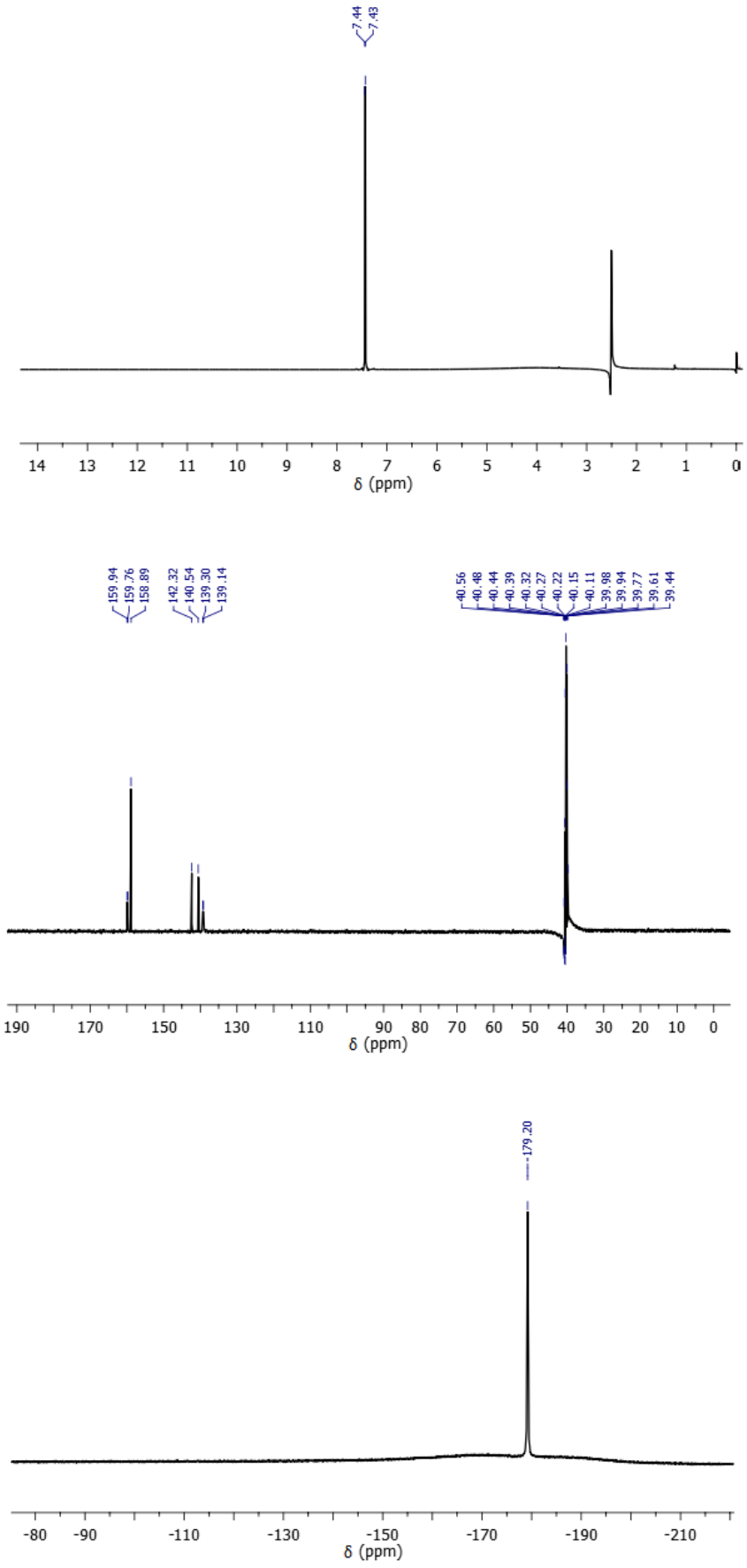

Fig. S2. ^{1}H, ^{13}C and ^{19}F spectra of Na(5-FU)·H_2O in DMSO-d_6.

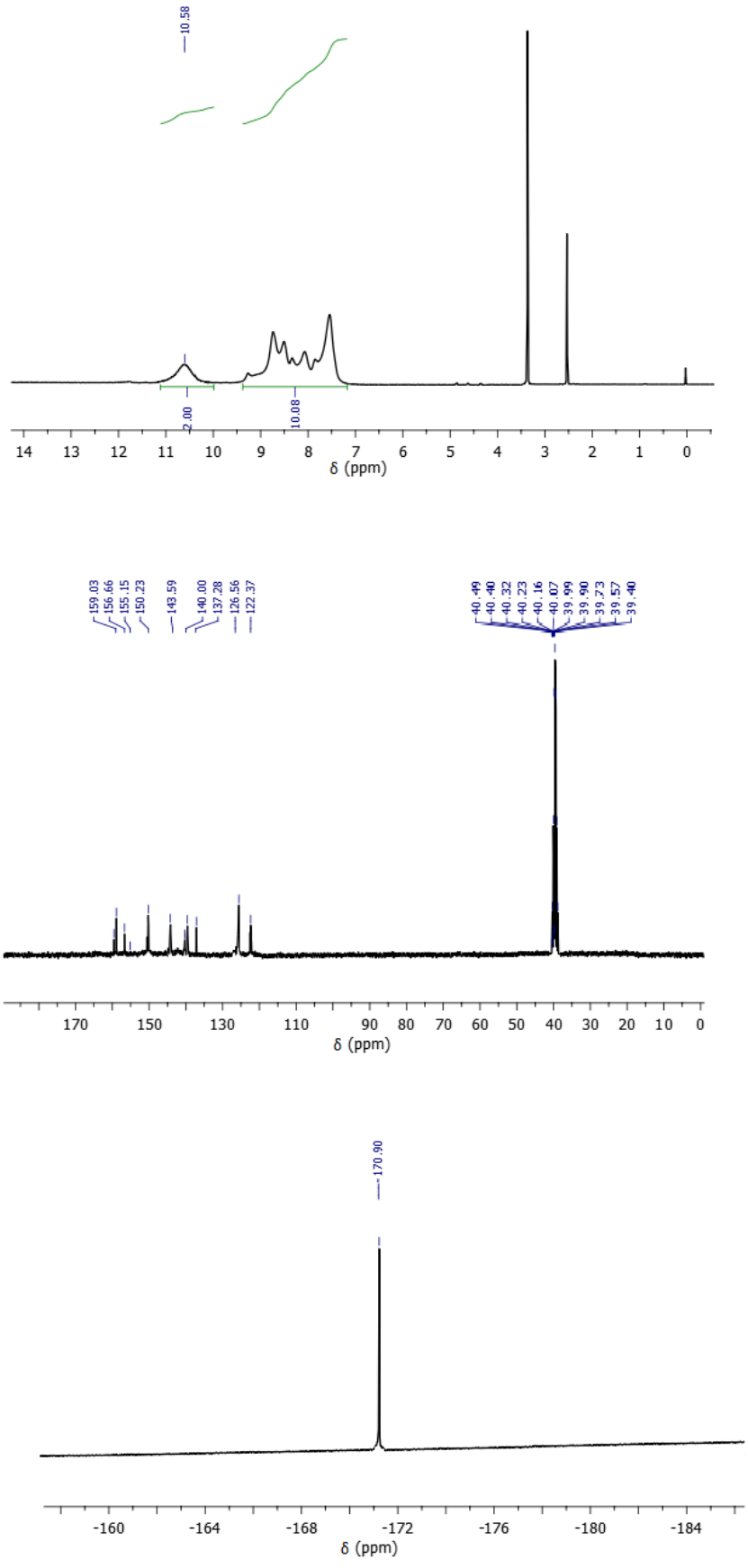

Fig. S3. ^{1}H, ^{13}C and ^{19}F spectra of **1** in DMSO-d_6.

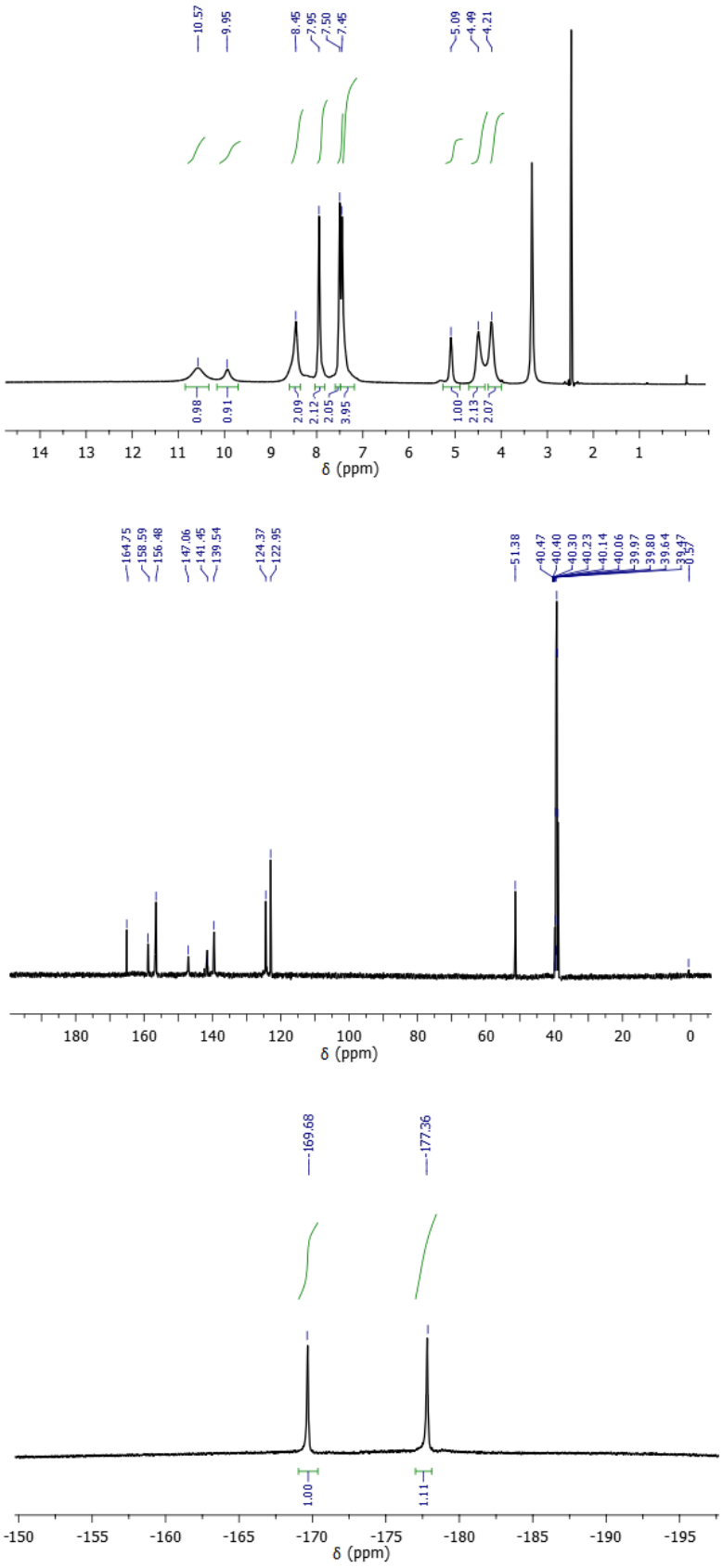

Fig. S4. ^{1}H, ^{13}C and ^{19}F spectra of **4** in DMSO-d_6.

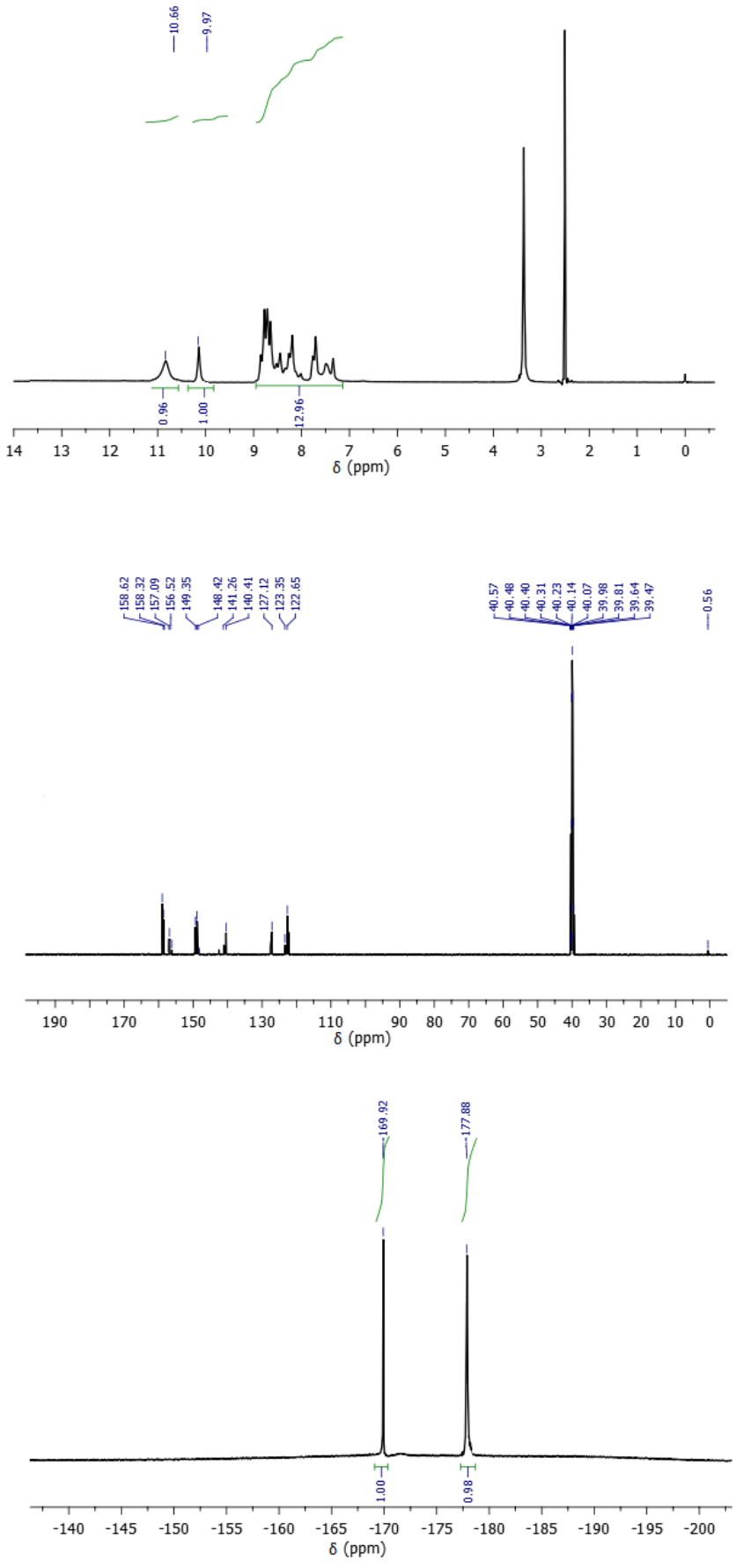

Fig. S5. ^{1}H, ^{13}C and ^{19}F spectra of **5** in DMSO-d_6.

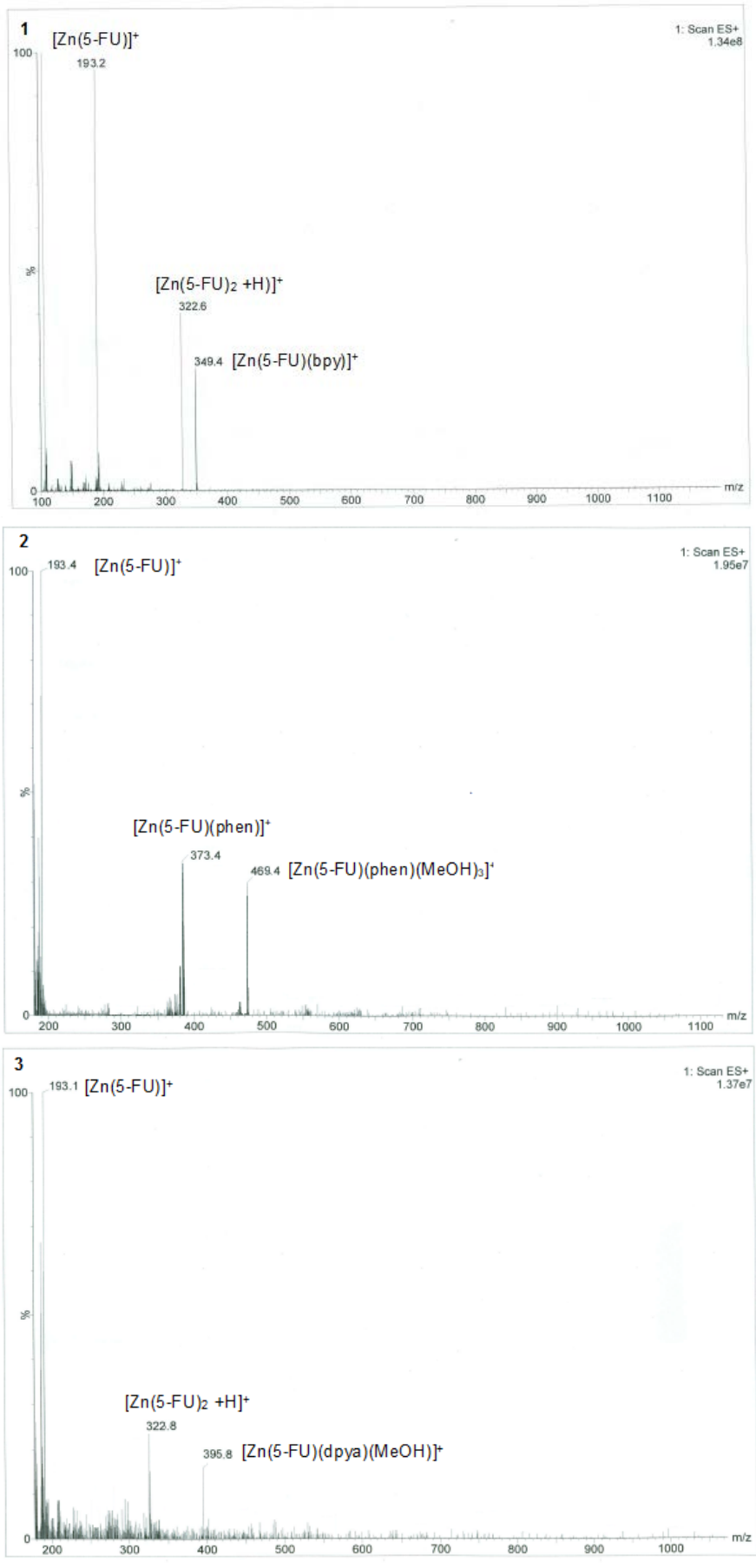

Fig. S6 (Continued)

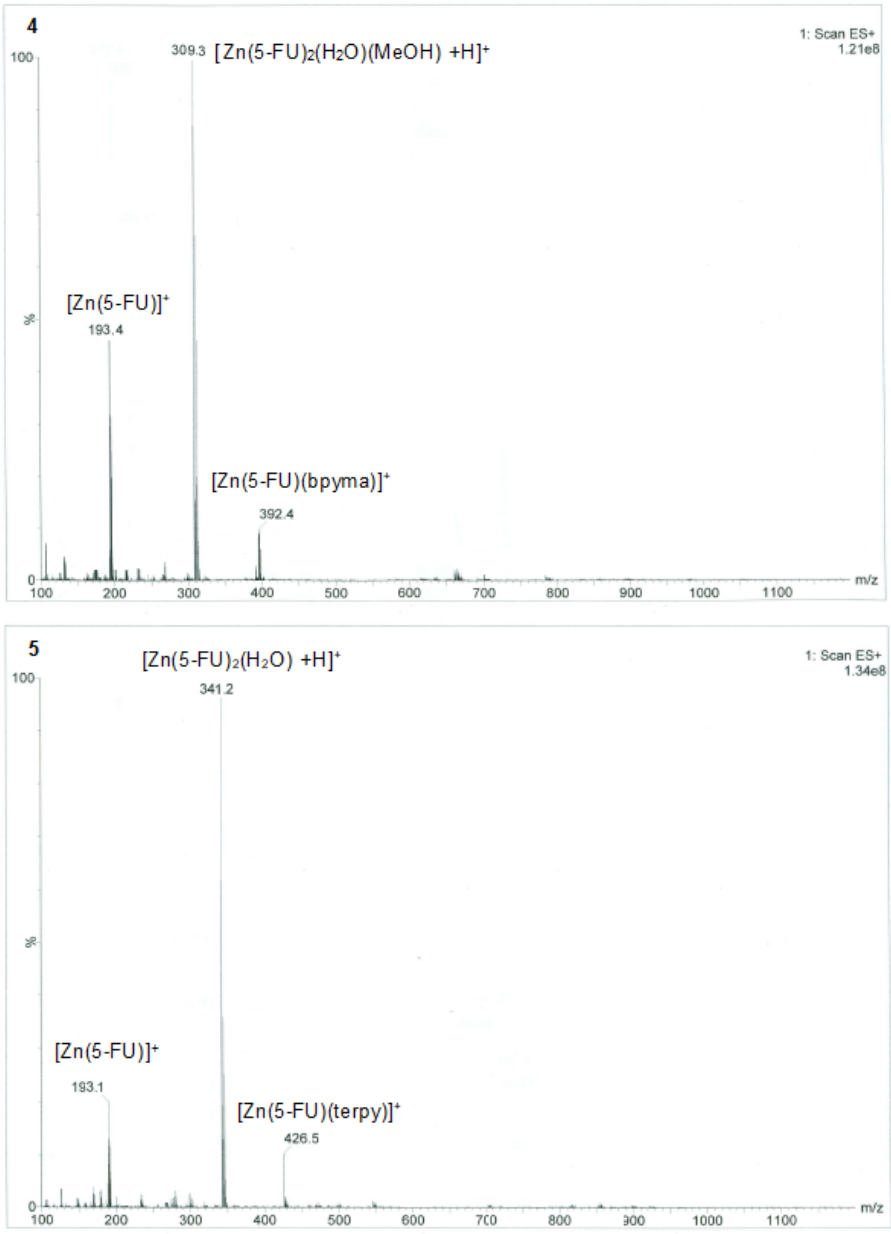

Fig. S6. ESI-MS spectra of **1**–**5**.

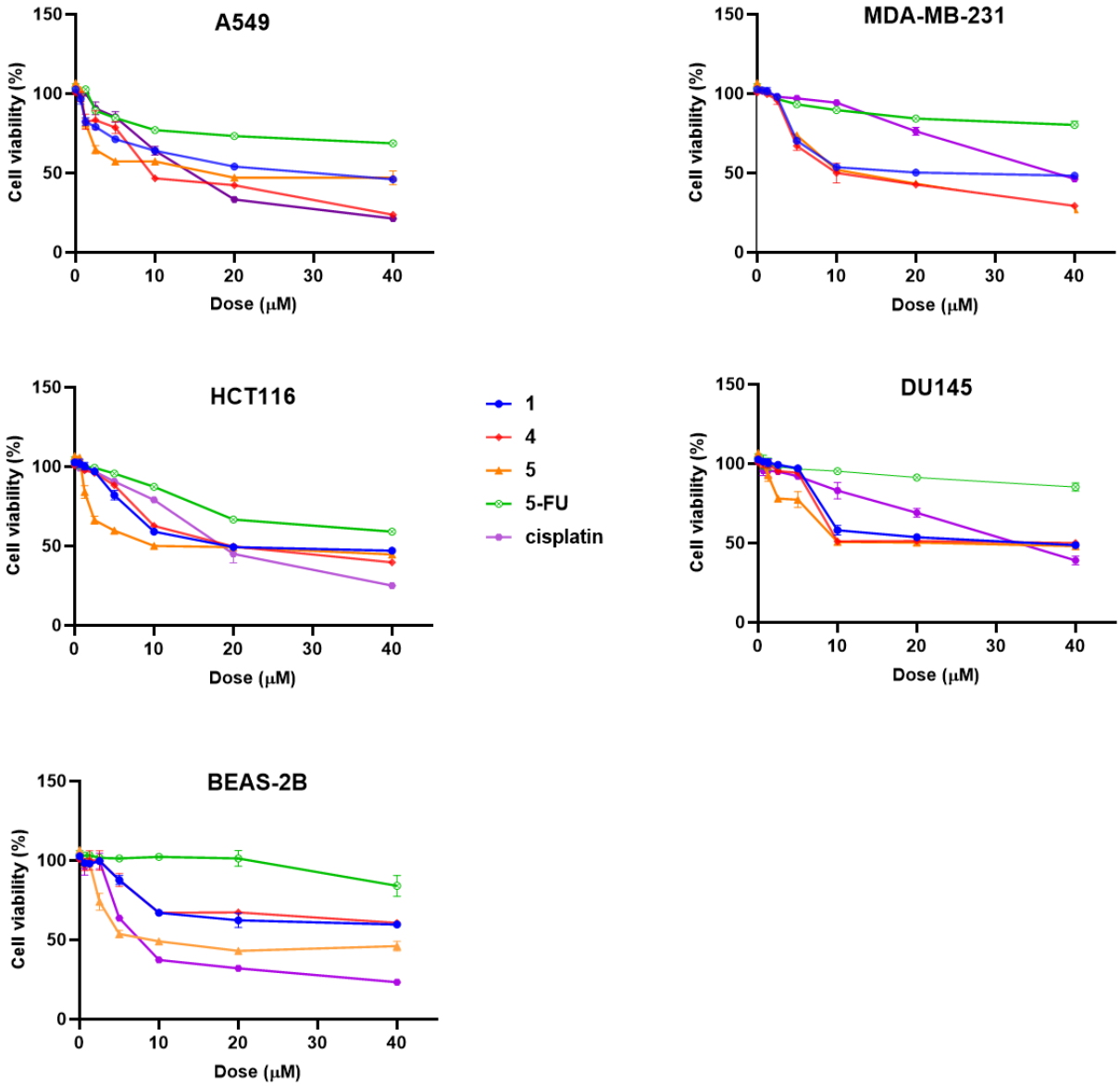

Fig. S7a. The dose-response graphics for **1**, **4**, **5**, 5-FU and cisplatin obtained from SRB assay, showing the effect of the complexes on the growth of the cell lines after 48 h of treatment. Results are represented as mean ± standard deviation (*n* = 3).

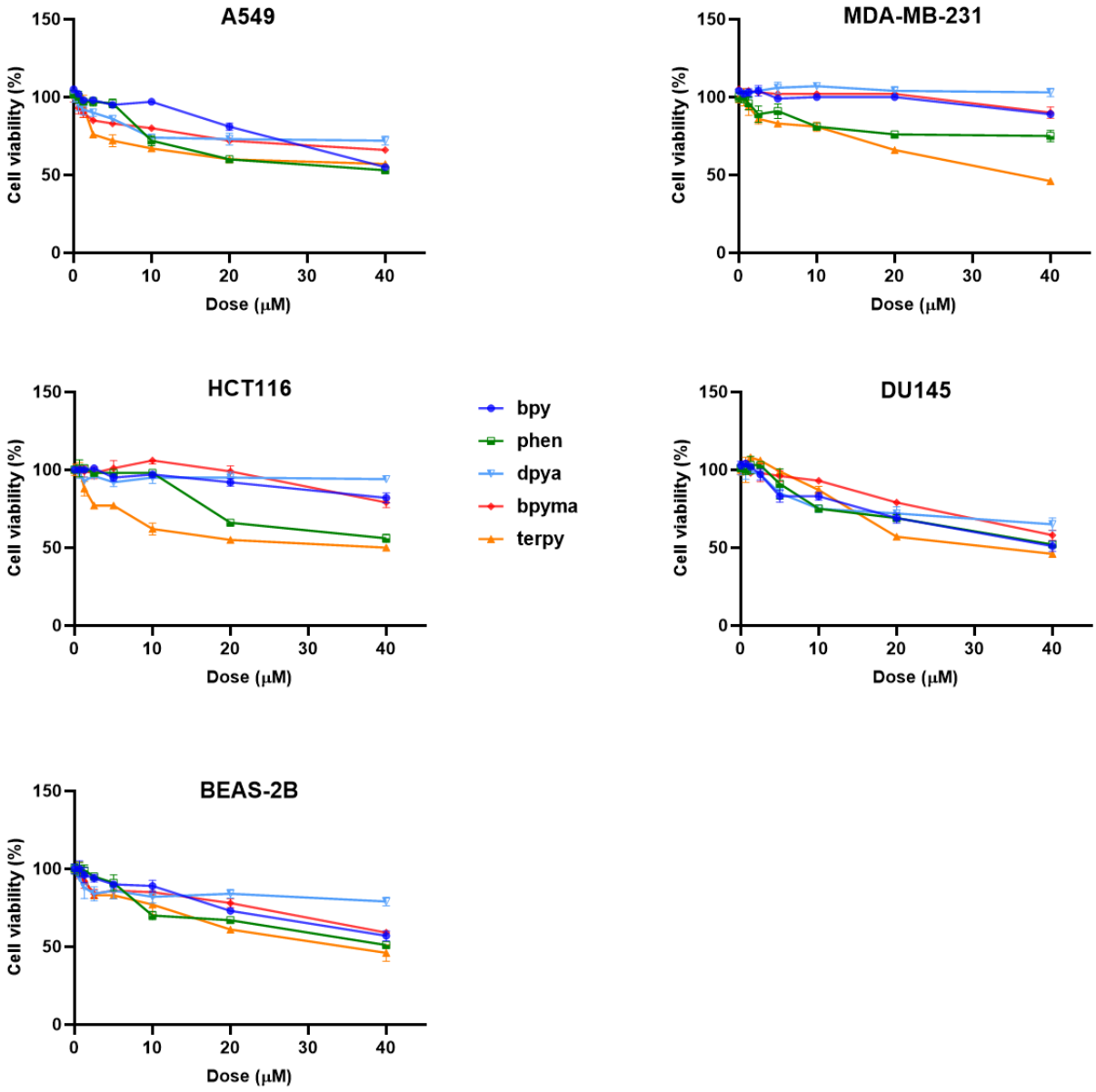

Fig. S7b. The dose-response graphics for bpy, phen, dpya, bpyma and terpy obtained from SRB assay, showing the effect of the complexes on the growth of the cell lines after 48 h of treatment. Results are represented as mean ± standard deviation (*n* = 3).

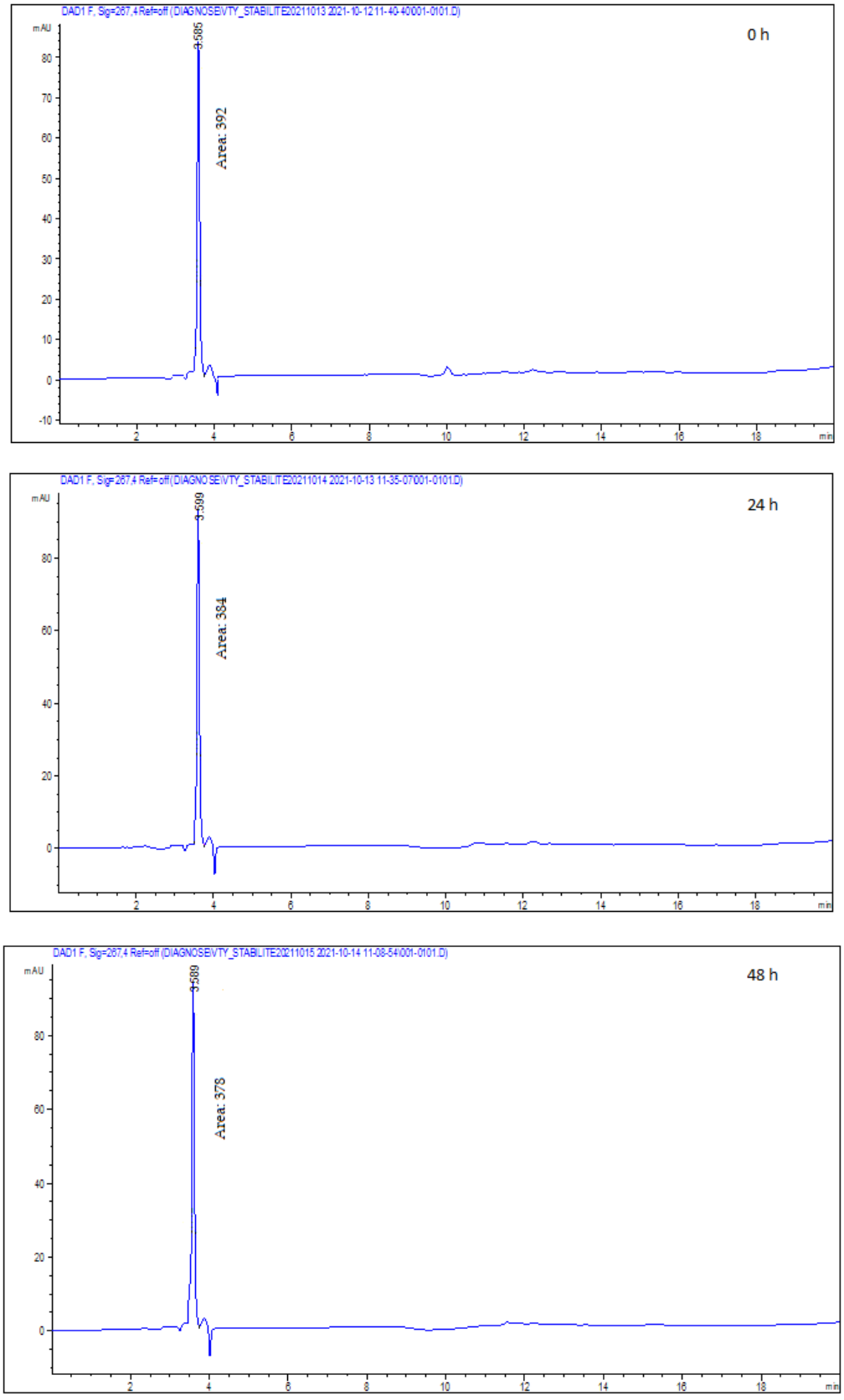

Fig. S8. Time-dependent stability of **4** (20 µM) in saline measured by the reverse phase HPLC at 267 nm.

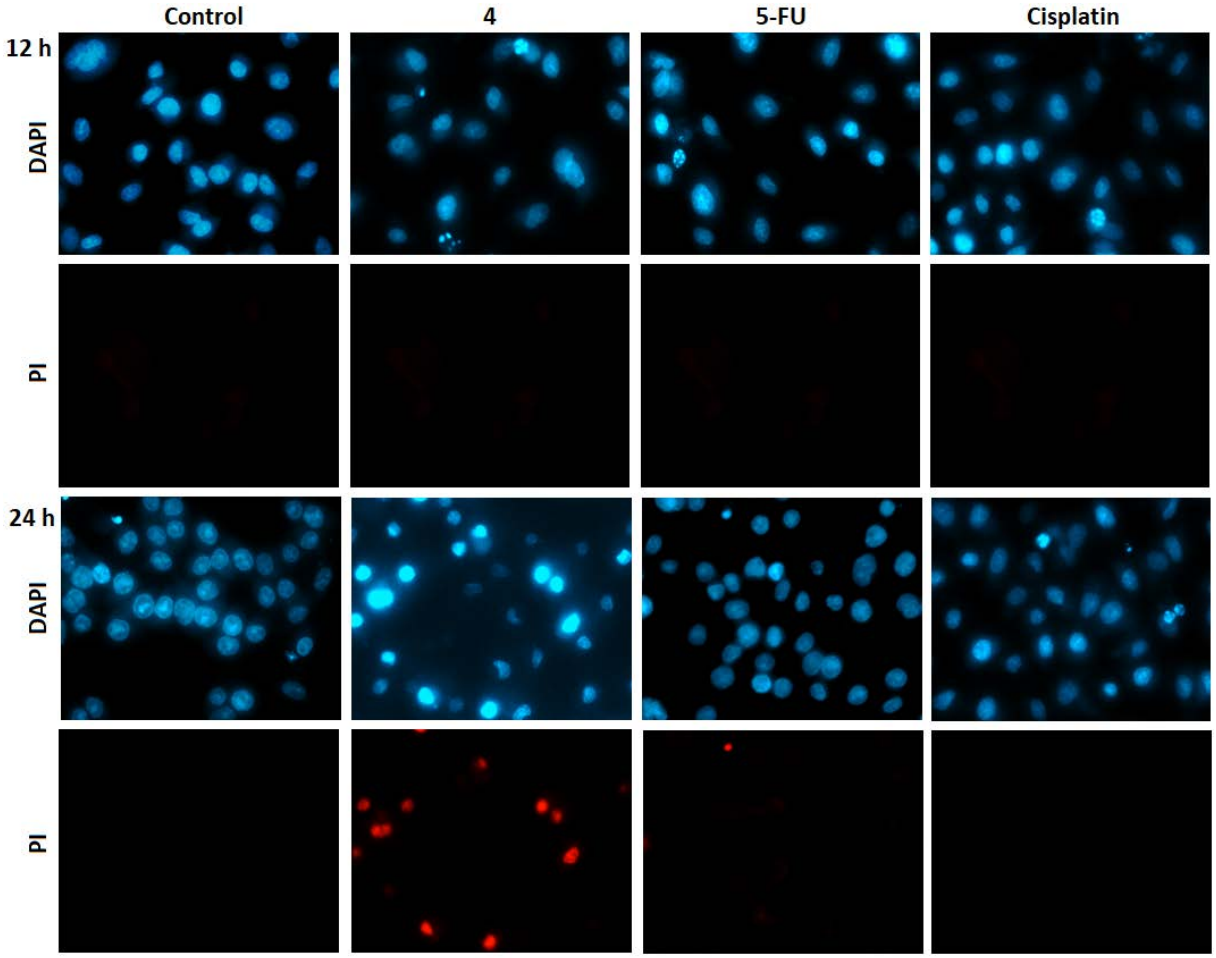

Fig. S9. Morphological changes in A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 12 and 24 h. Cells were stained with DAPI/PI followed by detection using a fluorescence microscope. DAPI stained the live cells with intact plasma membrane (blue fluorescence), while PI stained dead and apoptotic ones (red fluorescence) with disrupted plasma membrane. Magnification: 40×.

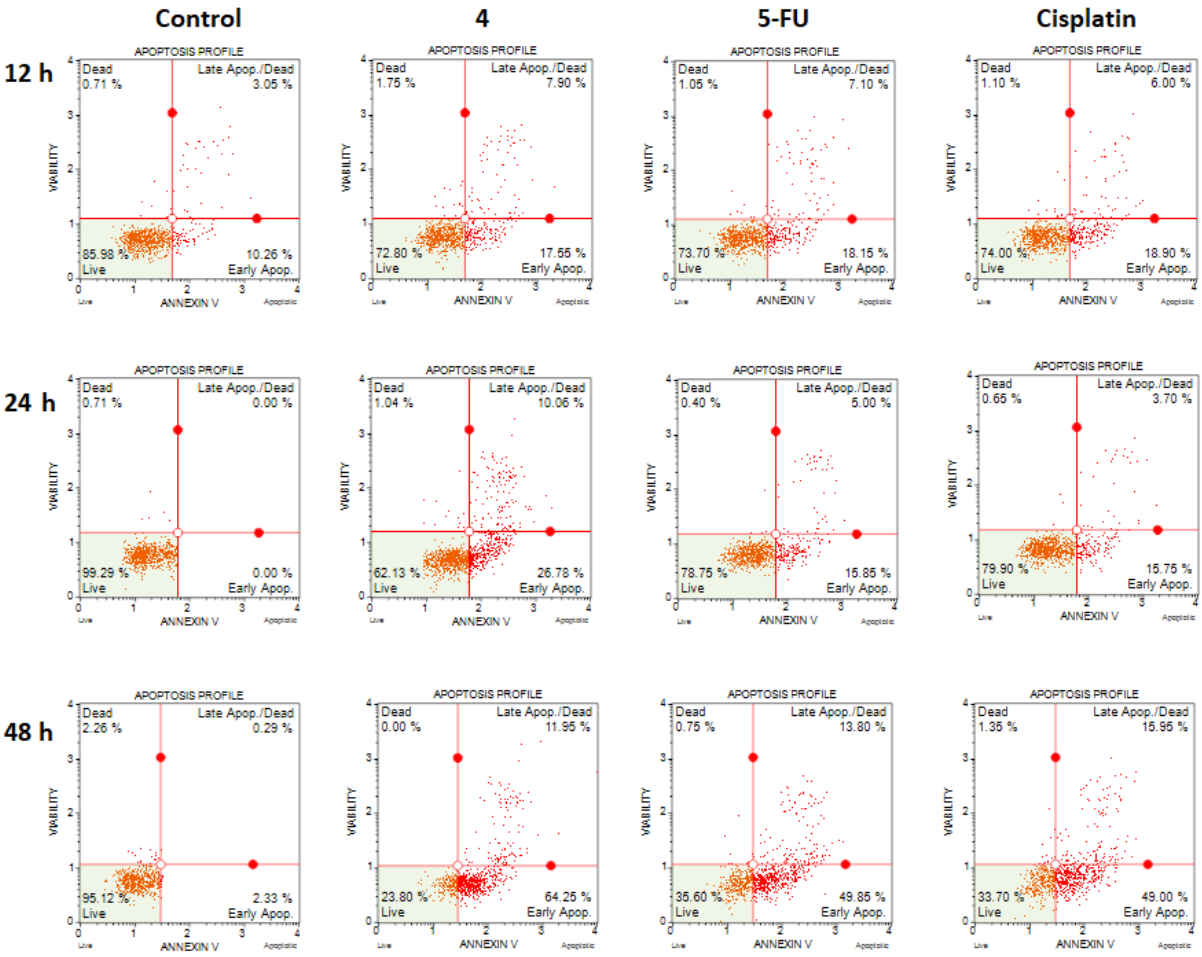

Fig. S10. Annexin-V/7-AAD staining assay. A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls. The quadrants show populations for A549 cells in four stages treated by the compounds.

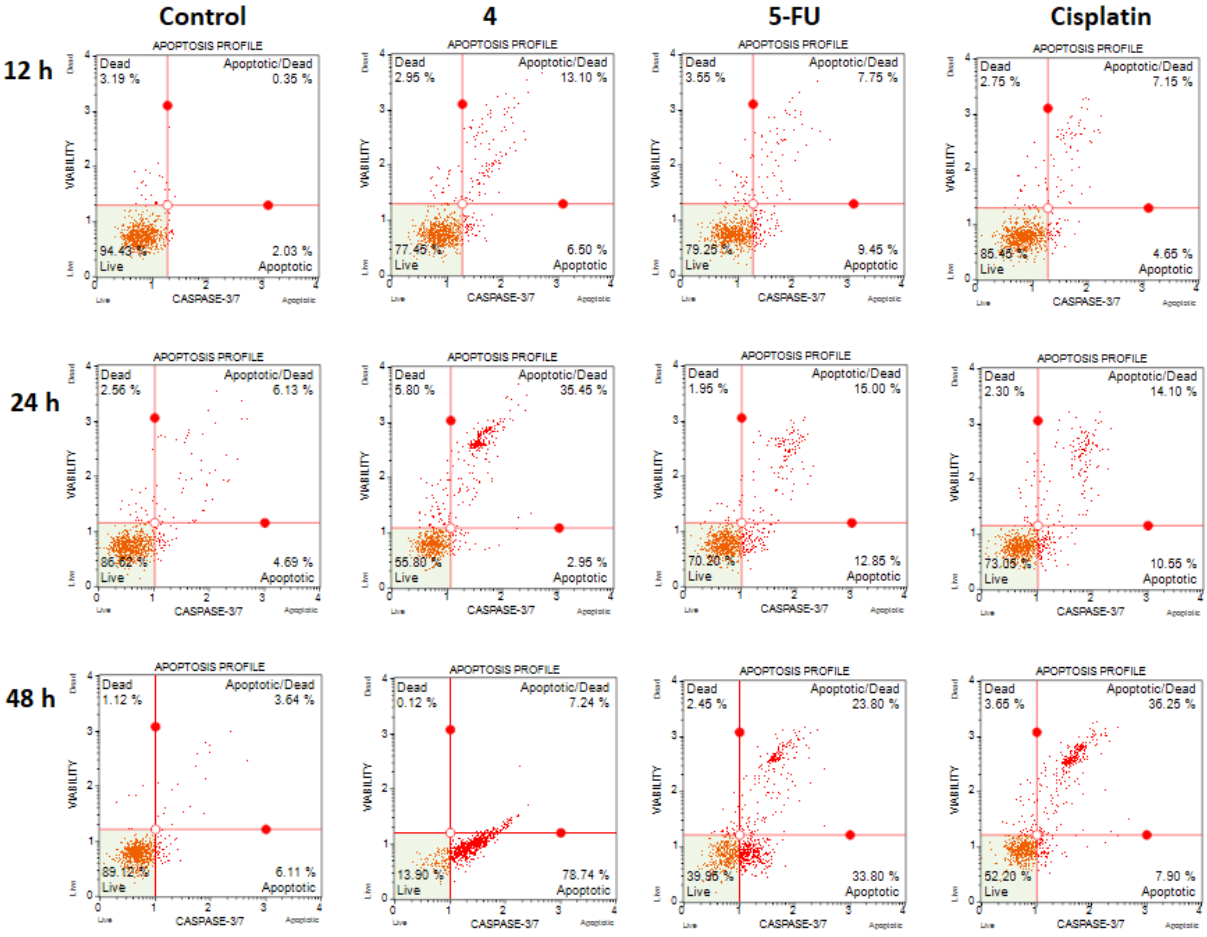

Fig. S11. Caspase 3/7 activity in A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls. The quadrants show populations for A549 cells in four stages treated by the compounds.

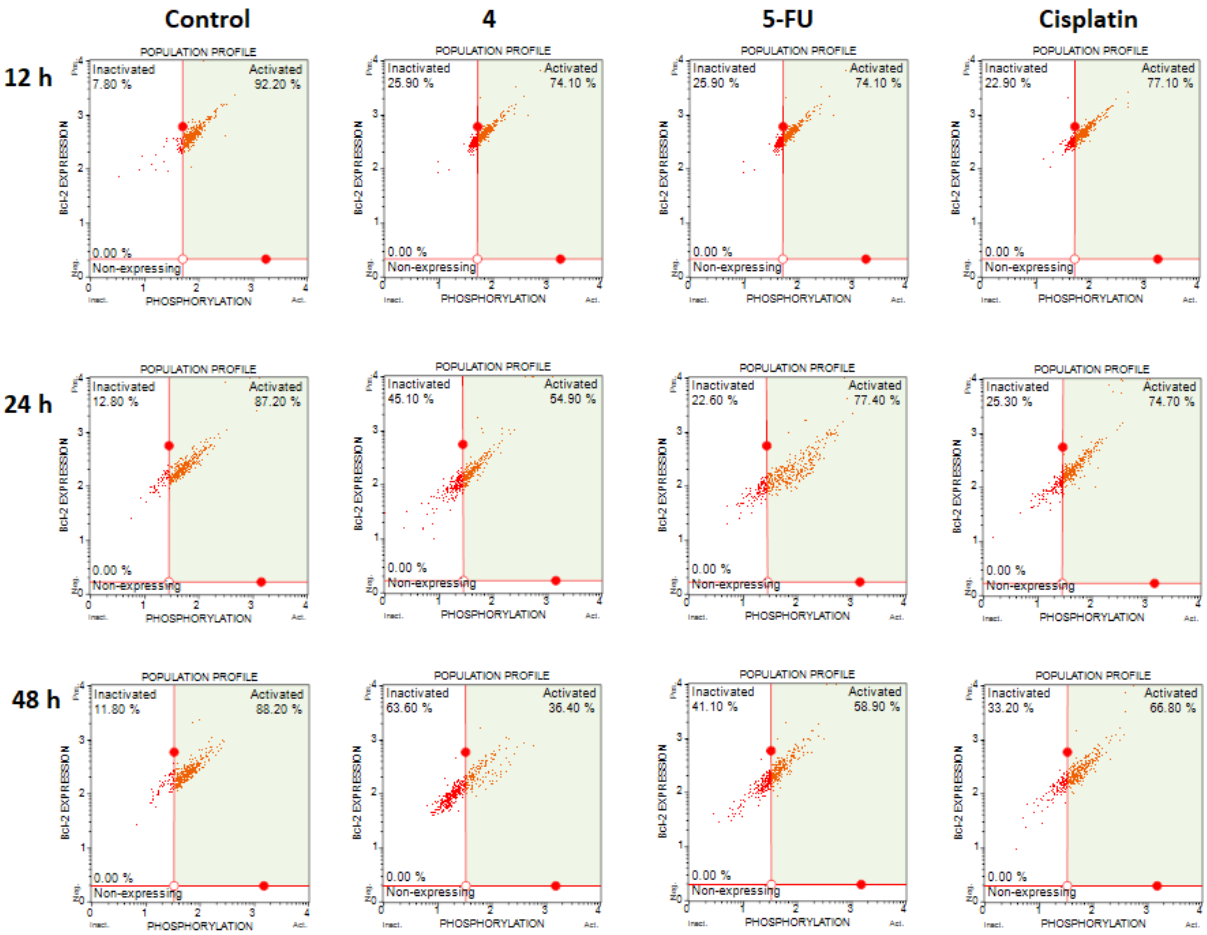

Fig. S12. Bcl2 expression in A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls.

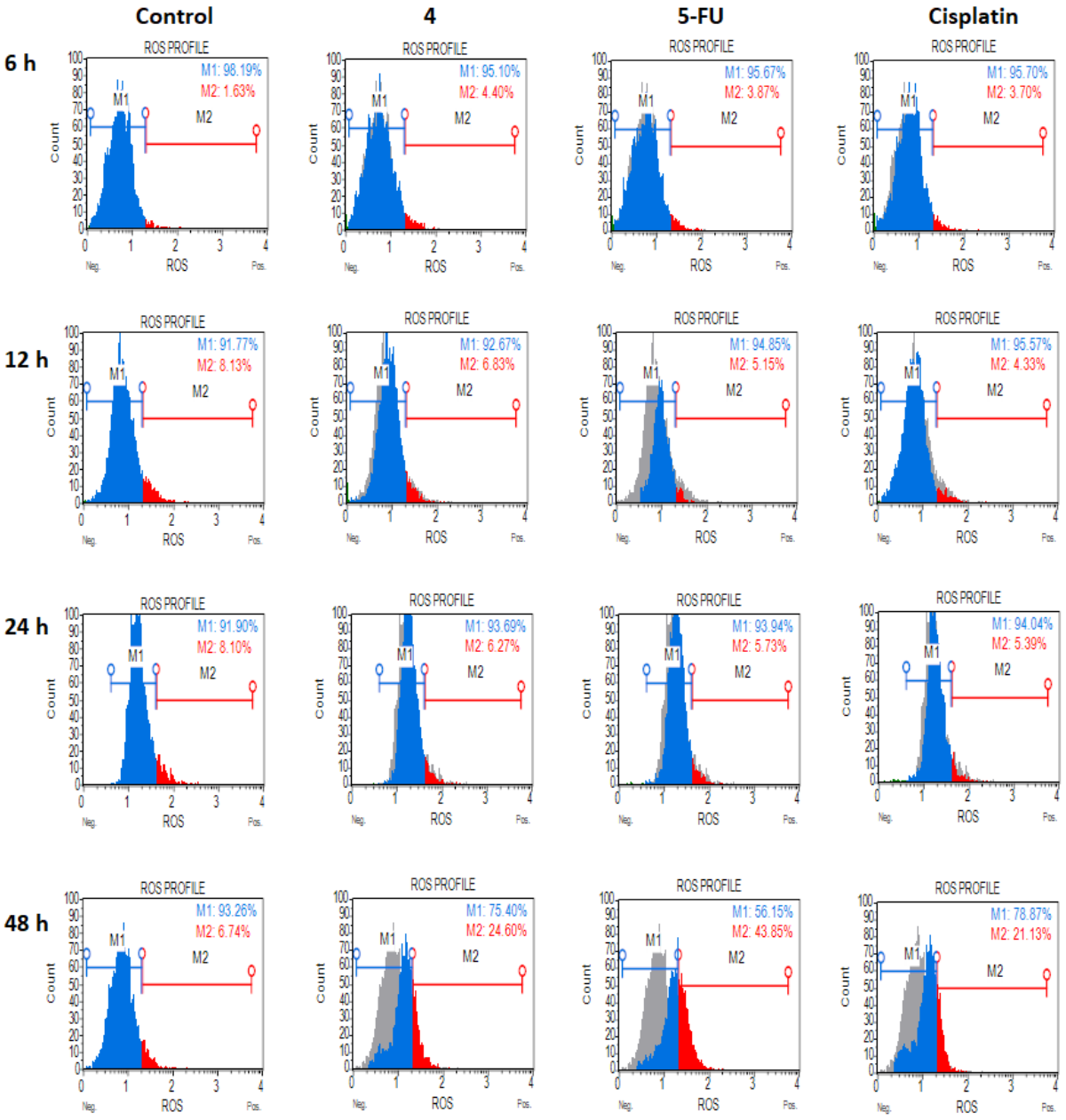

Fig. S13. ROS generation in A549 cells treated with **4** (40 μM), 5-FU (172 μM) and cisplatin (33.9 μM), respectively, for 6, 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls.

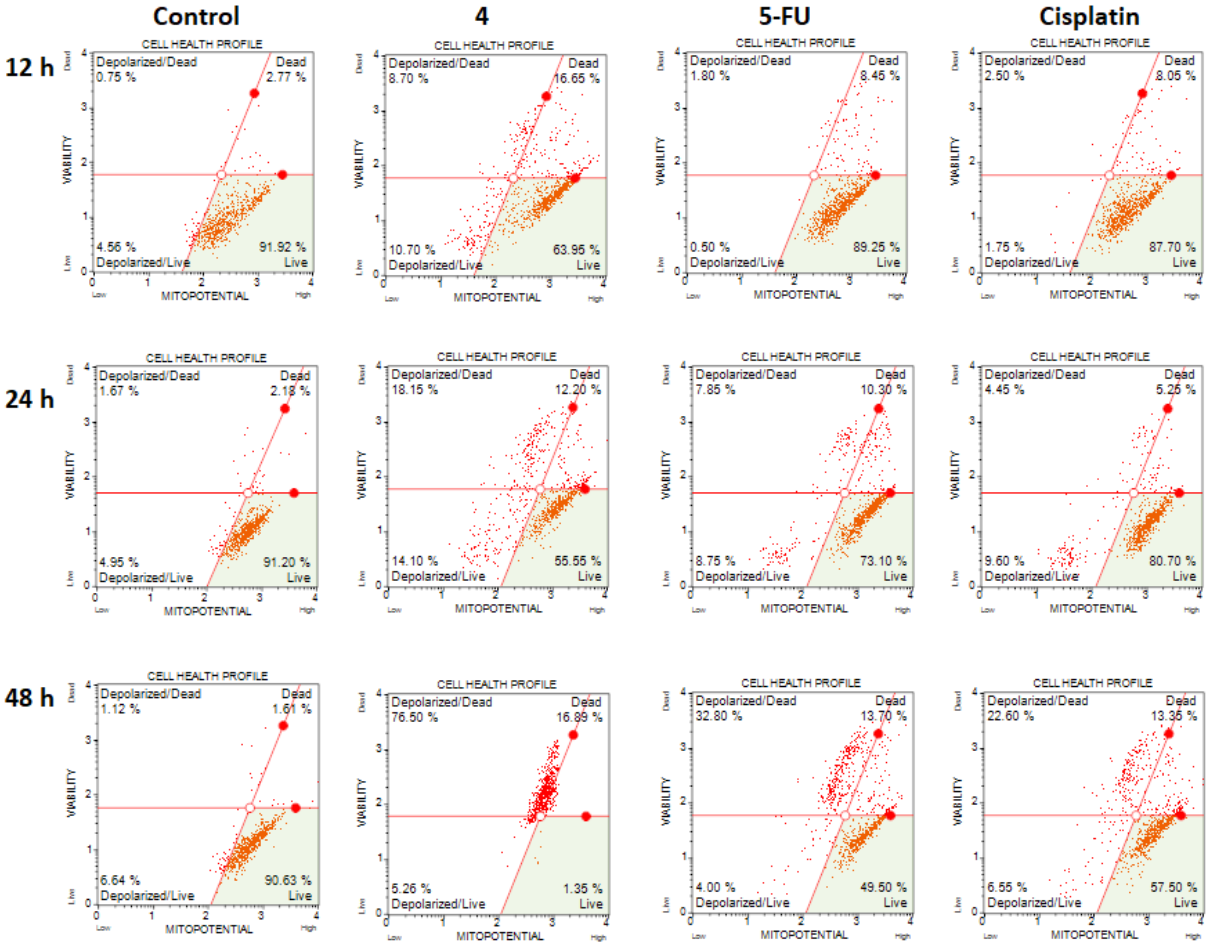

Fig. S14. Mitochondrial membrane depolarization in A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls.

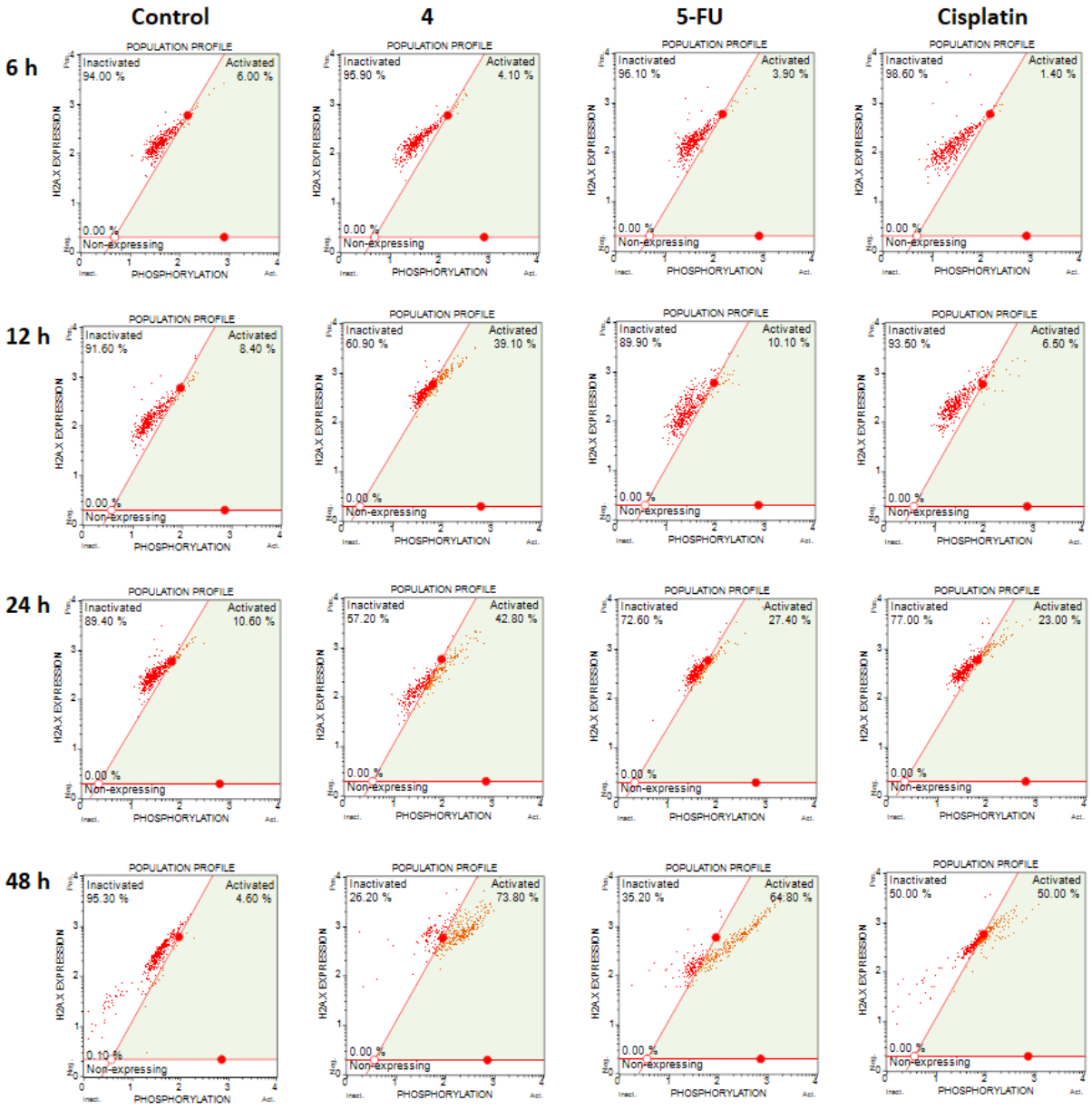

Fig. S15. Formation of DNA double-strand breaks in A549 cells treated with **4** (40 µM), 5-FU (172 µM) and cisplatin (33.9 µM), respectively, for 6, 12, 24 and 48 h. 5-FU and cisplatin were used as positive controls.