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A step-ladder manganese(III) metallacrown hosting mefenamic acid and a manganese(II)-mefanamato complex: synthesis, characterization and cytotoxic activity

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Supplementary Information

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Table S1. Selected bond angles (°) in complex **1**.

Bond angles	**(°)**	**Bond angles**	**(°)**
O10-Mn1-O1X	165.39 (19)	O2X-Mn4-O12	177.14 (17)
O10-Mn1-O5	85.37 (18)	O2X-Mn4-O13	89.59 (17)
O1X-Mn1-O5	91.62 (17)	O12-Mn4-O13	89.63 (18)
O10-Mn1-N5	90.4 (2)	O2X-Mn4-N6	89.4 (2)
O1X-Mn1-N5	88.84 (18)	O12-Mn4-N6	90.6 (2)
O5-Mn1-N5	164.9 (2)	O13-Mn4-N6	165.31 (17)
O10-Mn1-O1	98.64 (18)	O2X-Mn4-O3	91.49 (15)
O1X-Mn1-O1	95.96 (17)	O12-Mn4-O3	91.34 (16)
O5-Mn1-O1	99.66 (18)	O13-Mn4-O3	98.50 (16)
N5-Mn1-O1	95.32 (18)	N6-Mn4-O3	96.18 (18)
O6-Mn2-O1X	172.3 (2)	O2X-Mn4-O9	87.58 (14)
O6-Mn2-O7	90.74 (19)	O12-Mn4-O9	89.59 (15)
O1X-Mn2-O7	92.14 (17)	O13-Mn4-O9	81.14 (15)
O6-Mn2-N3	90.45 (19)	N6-Mn4-O9	84.17 (17)
O1X-Mn2-N3	87.25 (18)	O3-Mn4-O9	179.00 (14)
O7-Mn2-N3	175.24 (19)	O16-Mn5-O2X	174.1 (2)
O6-Mn2-O83	96.3 (2)	O16-Mn5-O11	90.36 (18)
O1X-Mn2-O83	90.98 (18)	O2X-Mn5-O11	92.12 (17)
O7-Mn2-O83	87.36 (18)	O16-Mn5-N8	90.15 (19)
N3-Mn2-O83	87.94 (19)	O2X-Mn5-N8	87.83 (18)
O6-Mn2-O84	89.0 (2)	O11-Mn5-N8	175.17 (19)
O1X-Mn2-O84	83.57 (19)	O16-Mn5-O82	93.8 (2)
O7-Mn2-O84	95.89 (19)	O2X-Mn5-O82	91.79 (18)
N3-Mn2-O84	88.7 (2)	O11-Mn5-O82	86.35 (19)
O83-Mn2-O84	173.7 (2)	N8-Mn5-O82	88.8 (2)

O1X-Mn3-O8	176.44 (17)	O16-Mn5-O81	92.7 (2)
O1X-Mn3-O9	89.65 (17)	O2X-Mn5-O81	81.57 (19)
O8-Mn3-O9	89.73 (18)	O11-Mn5-O81	97.72 (18)
O1X-Mn3-N4	89.2 (2)	N8-Mn5-O81	87.05 (19)
O8-Mn3-N4	90.5 (2)	O82-Mn5-O81	172.3 (2)
O9-Mn3-N4	166.11 (18)	O2X-Mn6-O14	167.32 (19)
O1X-Mn3-O2	91.31 (15)	O2X-Mn6-O15	91.21 (17)
O8-Mn3-O2	92.24 (16)	O14-Mn6-O15	85.47 (18)
O9-Mn3-O2	97.16 (18)	O2X-Mn6-N7	89.13 (18)
N4-Mn3-O2	96.71 (19)	O14-Mn6-N7	89.77 (19)
O1X-Mn3-O13	88.26 (14)	O15-Mn6-N7	159.6 (2)
O8-Mn3-O13	88.19 (15)	O2X-Mn6-O4	94.43 (18)
O9-Mn3-O13	80.62 (14)	O14-Mn6-O4	98.20 (18)
N4-Mn3-O13	85.51 (17)	O15-Mn6-O4	100.47 (18)
O2-Mn3-O13	177.74 (17)	N7-Mn6-O4	99.84 (18)
Mn1-O1X-Mn3	114.5 (2)	Mn6-O2X-Mn4	114.0 (2)
Mn1-O1X-Mn2	121.68 (19)	Mn6-O2X-Mn5	121.99 (19)
Mn3-O1X-Mn2	119.9 (2)	Mn4-O2X-Mn5	120.1 (2)
Mn3-O9-Mn4	99.67 (16)	Mn4-O13-Mn3	98.51 (16)

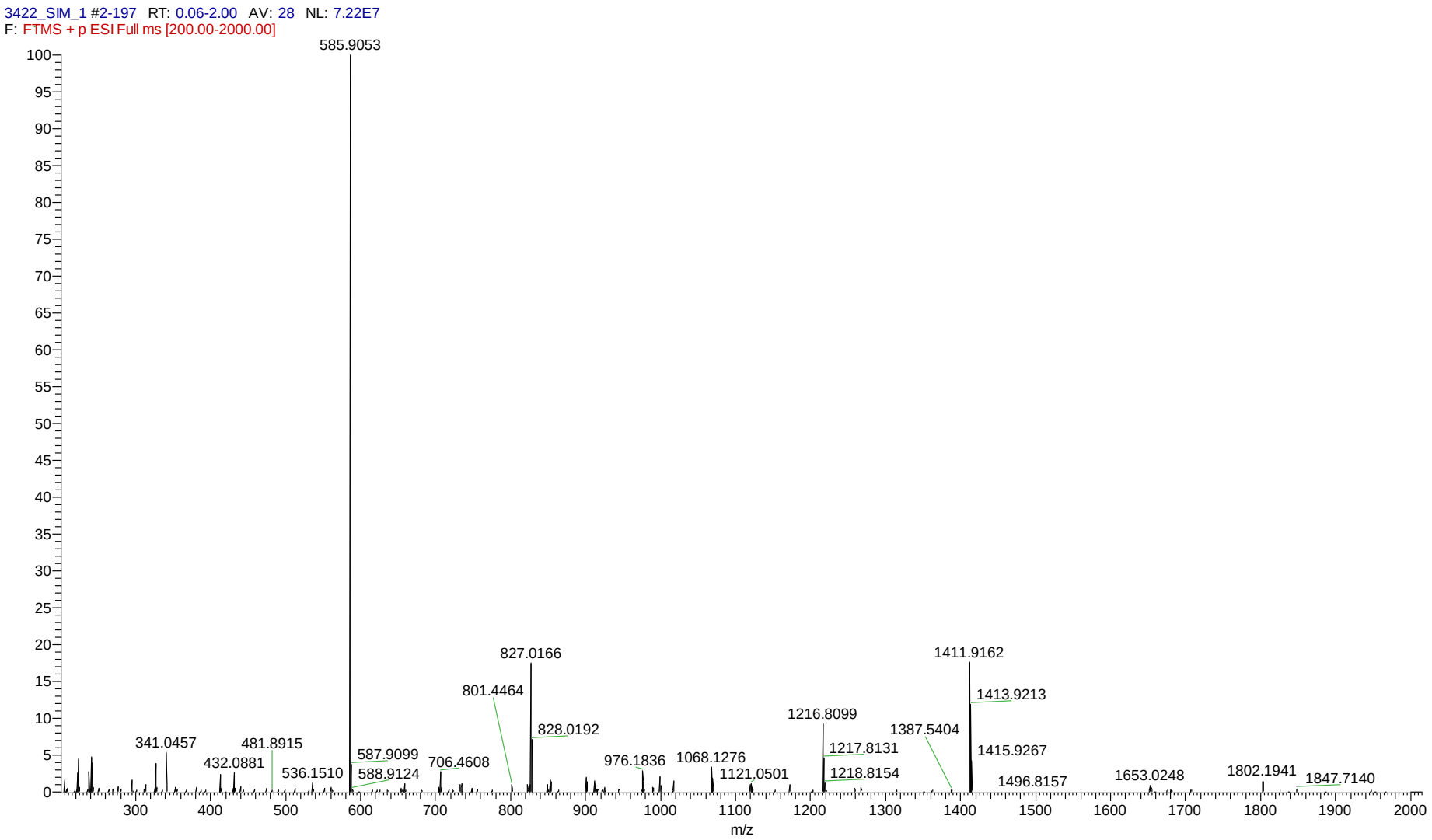
Table S2. Hydrogen bond interactions in the structure of complex **1**.

D*-H···*A	***D*-H (Å)**	**H···*A*(Å)**	***D*···*A* (Å)**	***D*-H···*A*(°)**
O81-H81*O*···O8	0.68 (5)	2.22 (6)	2.898 (7)	172 (7)
O84-H84*O*···O12	0.64 (5)	2.24 (5)	2.885 (7)	177 (7)
O82-H82*O*···O2*M*	0.67 (7)	1.98 (7)	2.644 (7)	171 (9)
O83-H83*O*···O1*M*	0.81 (6)	1.83 (6)	2.618 (6)	164 (6)
O1*M*-H1*OM*···O15^{i}	0.79 (8)	2.01 (8)	2.784 (7)	166 (8)
O2*M*-H2*OM*···O5^{ii}	0.78 (6)	2.19 (6)	2.890 (7)	150 (5)

Table S3. Dose reduction index (DRI) range values (for fraction affected (fa) values between 0.1-0.9) for compounds in drug combinations CDDP:**1** and 5FU:**1** against HeLa, MCF-7 and A549 human cancer cell lines 48 h after drug administration (data derived from Median Effect analysis).

Drug combination	**DRI values for cancer cell lines**		
	HeLa	**MCF-7**	**A549**
CDDP	0.148-0.571	63.879-18,200	4.336-6.884
Complex **1**	0.462-4.137	1.479-9.572	3.967-7.016
5-FU	4.449-2780.78	0.302-198.171	2.530-63.679
Complex **1**	1.510-15.627	0.877-1.705	1.831-11.503

(A)


3422_SIM_1 #2-197 RT: 0.06-2.00 AV: 28 NL: 7.22E7
F: FTMS + p ESI Full ms [200.00-2000.00]
585.9053
827.0166
1411.9162
801.4464
1413.9213
1216.8099
828.0192
1387.5404
341.0457
481.8915
1217.8131
1415.9267
587.9099
432.0881
706.4608
976.1836
1068.1276
1218.8154
536.1510
588.9124
1121.0501
1496.8157
1653.0248
1802.1941
1847.7140
m/z

(B)

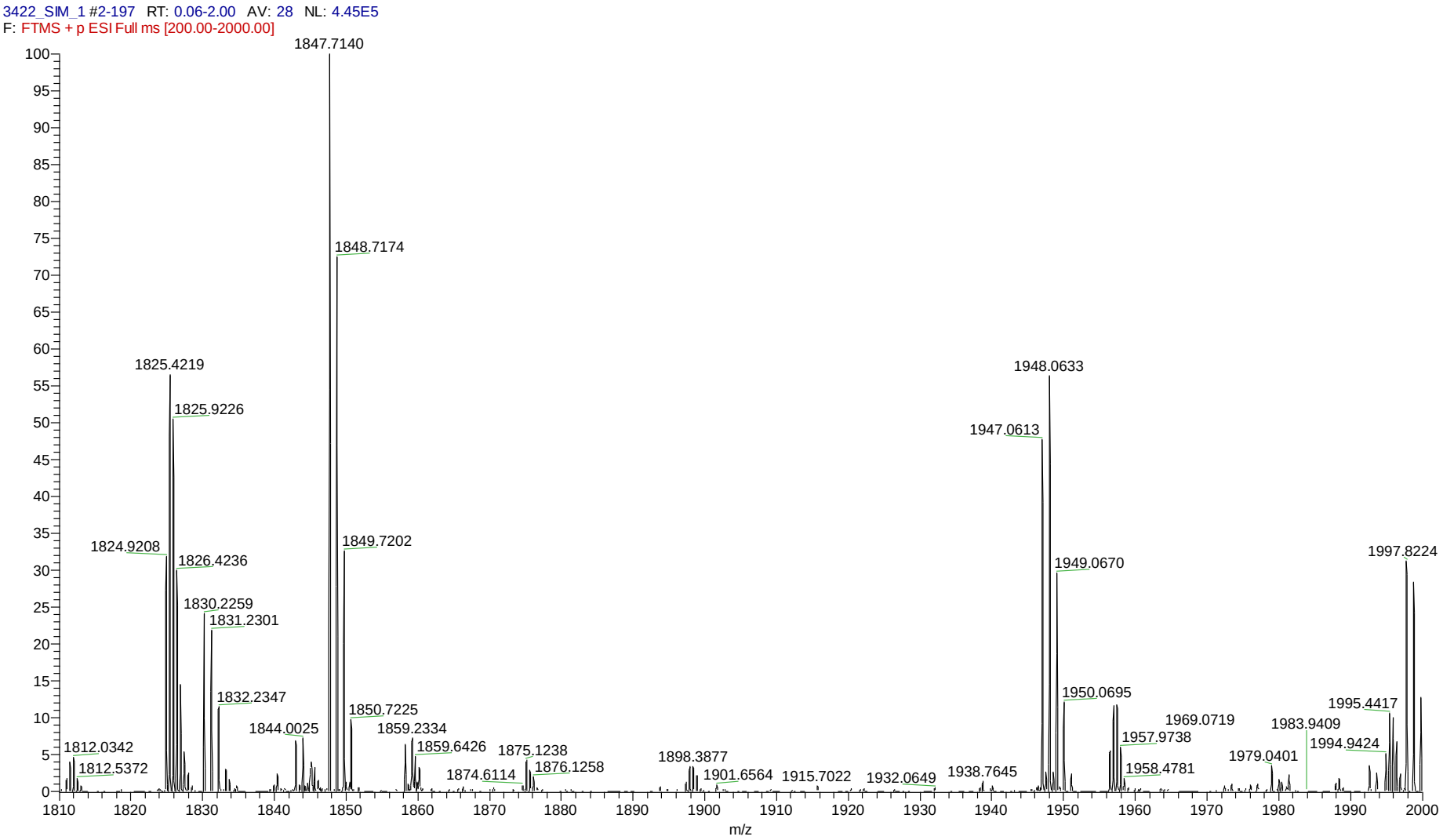
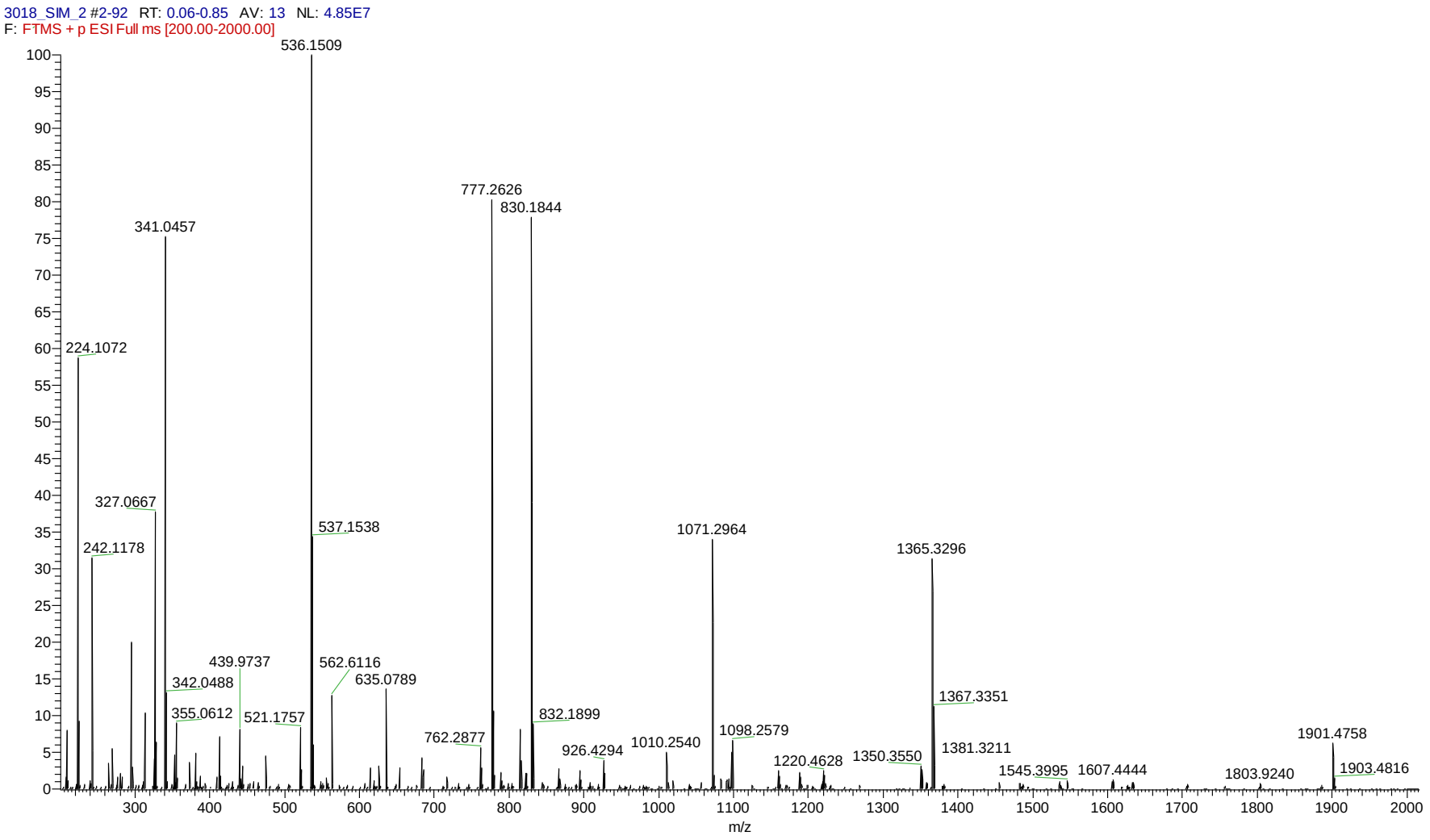


Figure S1. ESI(+)-MS for a methanolic solution a complex **1** (A) in the range 200-2000 (m/z) and (B) enlargement of the region 1800-2000 (m/z). Fragments found: 1847.71, 1948.06; MW = 1845.14 calcd. for $[Mn_6(O)_2(mef)_2(sao)_6(MeOH)_4]$, **1**.

(A)


3018_SIM_2 #2-92 RT: 0.06-0.85 AV: 13 NL: 4.85E7
F: FTMS + p ESI Full ms [200.00-2000.00]
536.1509
777.2626
830.1844
341.0457
224.1072
327.0667
537.1538
1071.2964
1365.3296
242.1178
439.9737
562.6116
635.0789
342.0488
355.0612
521.1757
832.1899
762.2877
926.4294
1010.2540
1098.2579
1220.4628
1350.3550
1367.3351
1381.3211
1901.4758
1545.3995
1607.4444
1803.9240
1903.4816
m/z

(B)

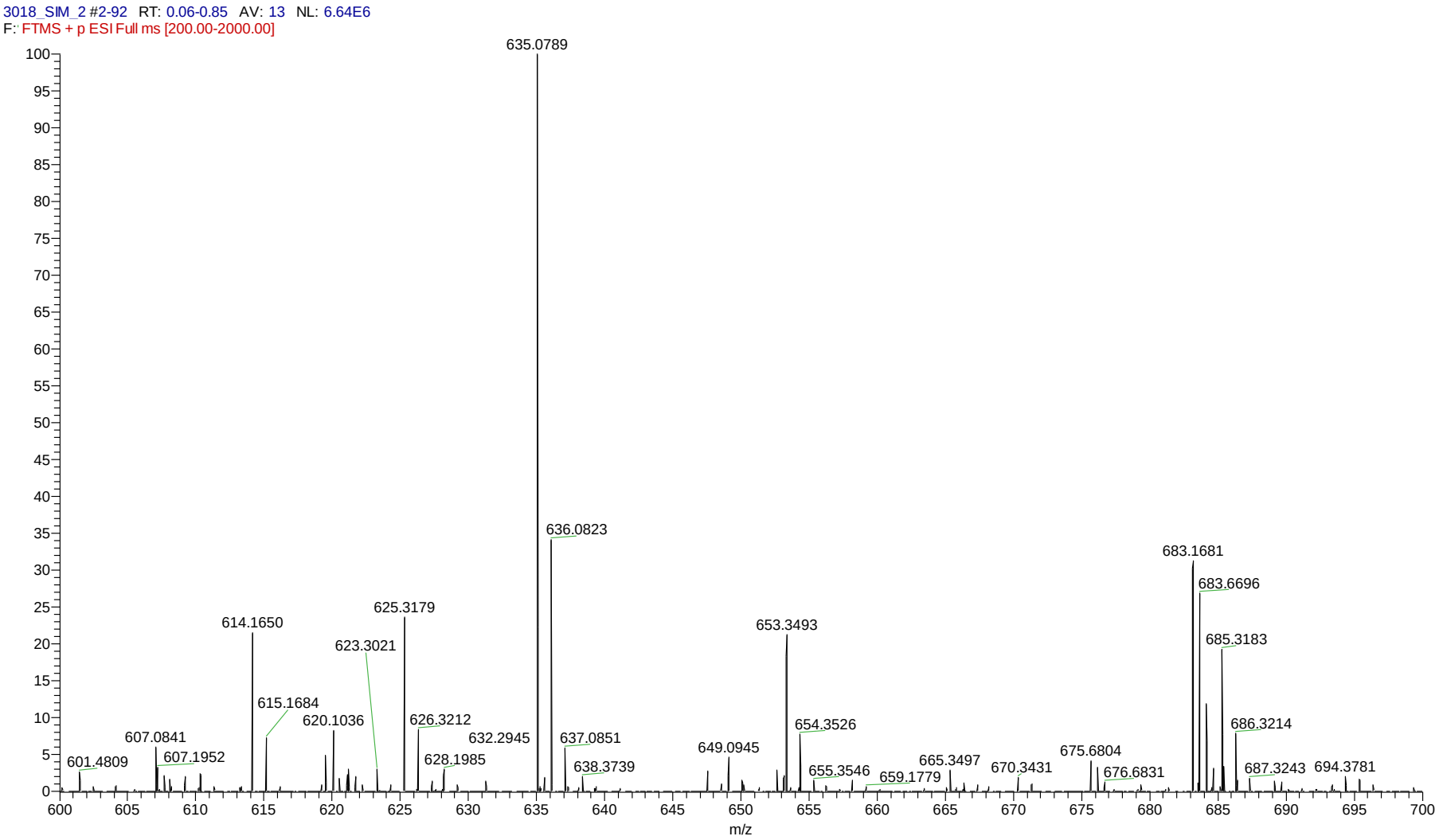


Figure S2. ESI(+)-MS for a methanolic solution a complex **2** (A) in the range 200-2000 (m/z) and (B) enlargement of the region 600-700 (m/z). Fragments found: 635.08, 665.35, 683.17; MW = 663.67 calcd. for $[Mn(mef)_2(MeOH)_4]$, **2**.

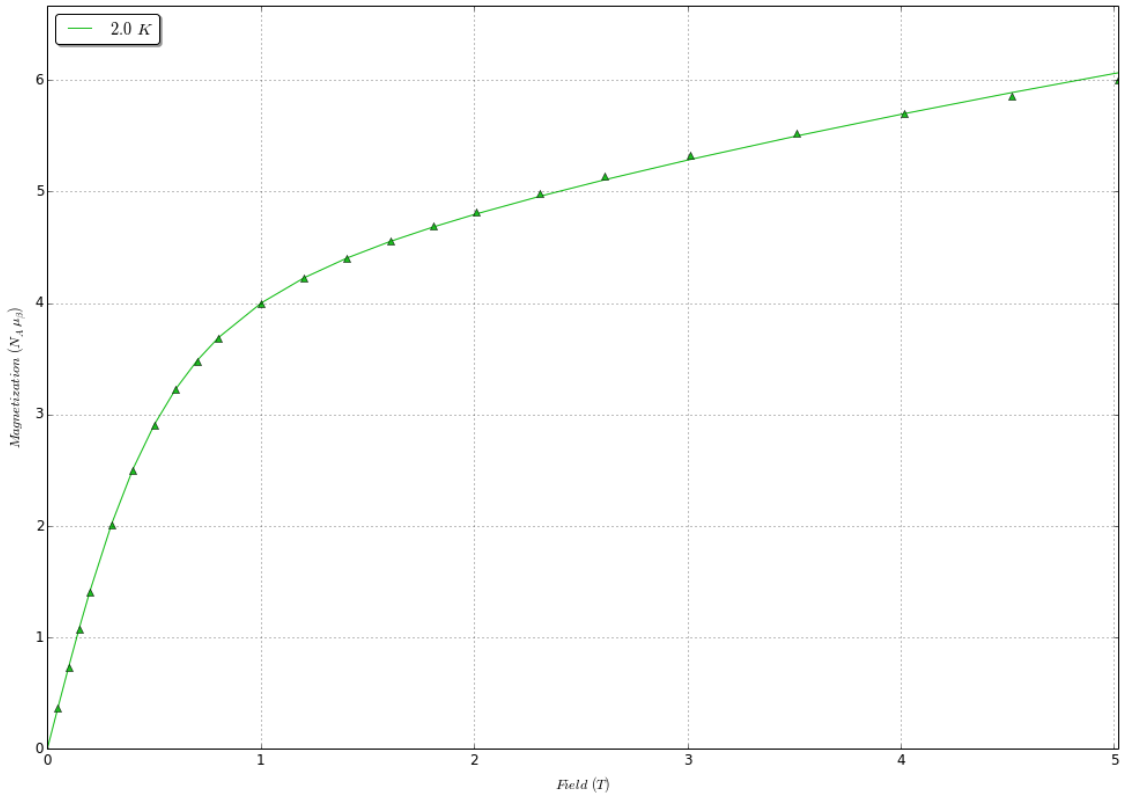


Figure S3. Magnetization curve of compound **1** at 2 K. The solid line is the fitting results using the giant model for a S=4.

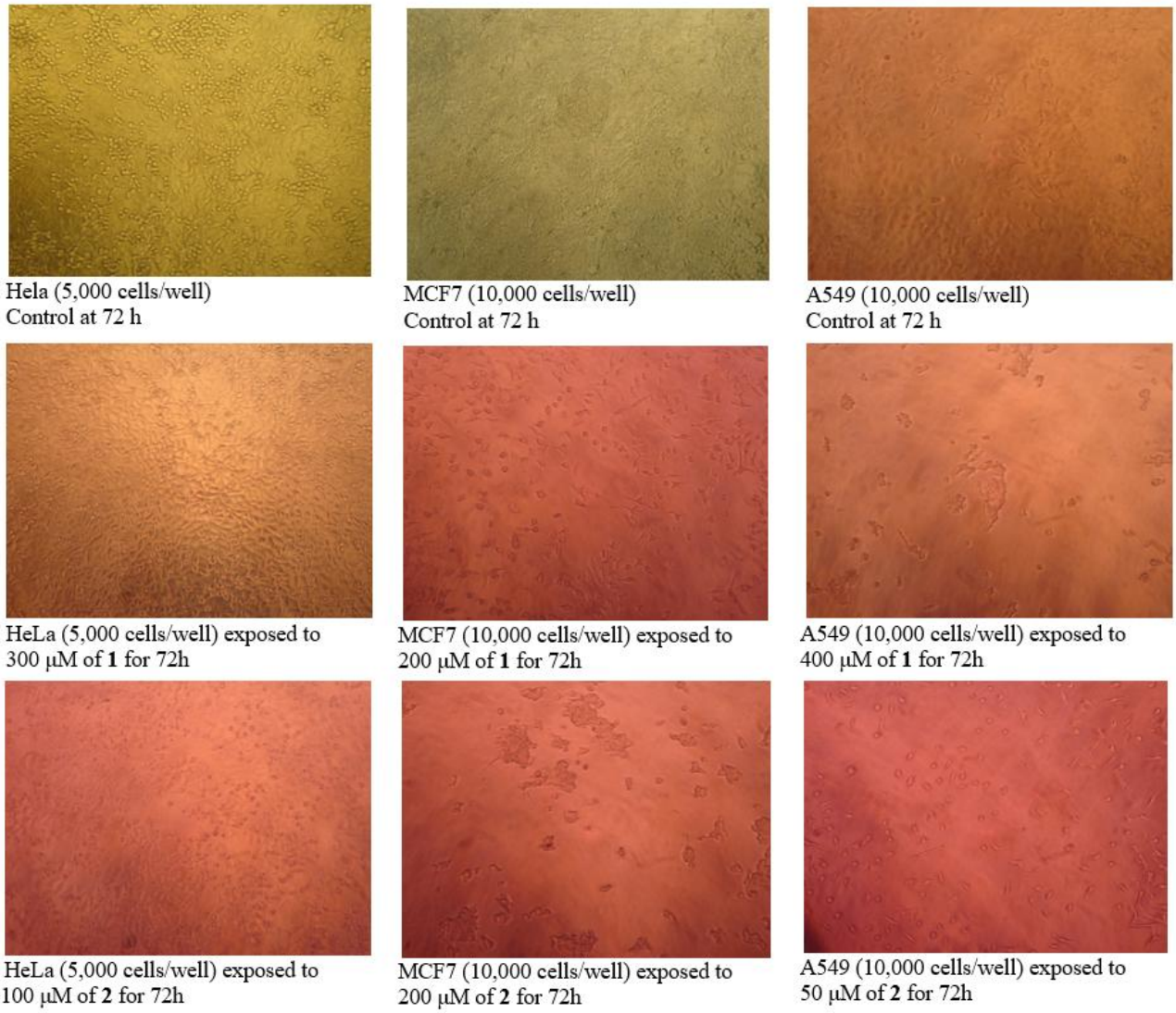
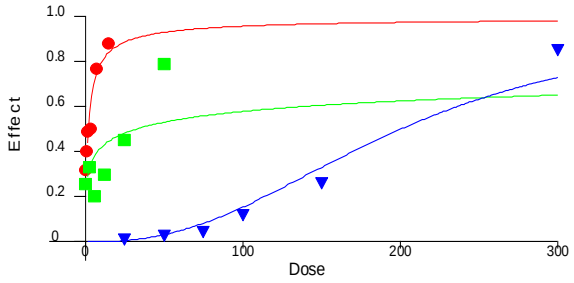
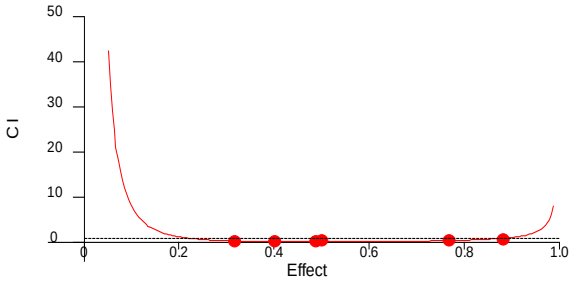
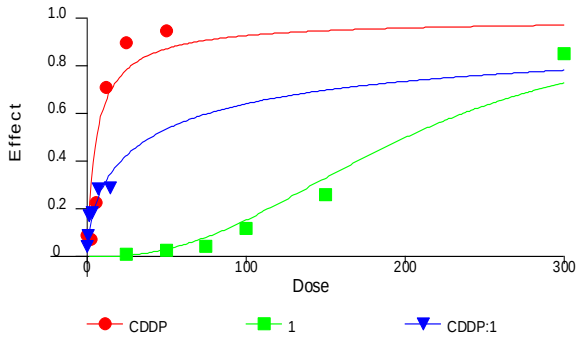


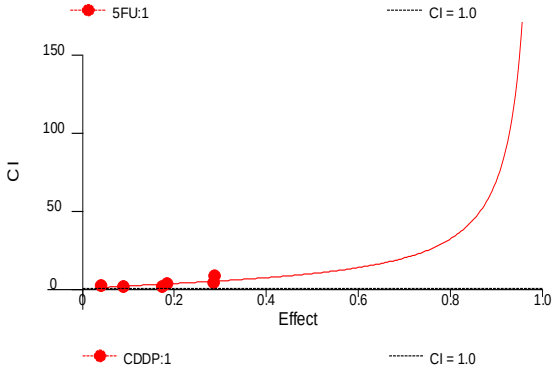
Figure S4. Photographs from inverted microscope at phase contrast setting with 100X magnification of HeLa, MCF7 and A549 cells (untreated and exposed to 50, 100, 200, 300 and 400 μM of complexes **1** and **2**, after 72 h).

HeLa

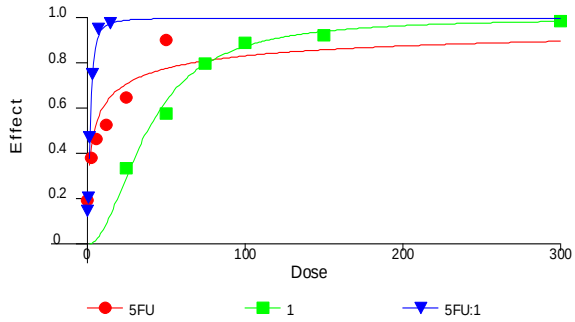

Effect
Dose
5FU:1
5FU
1

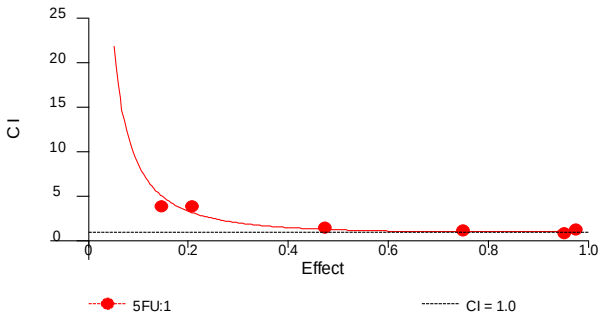

CI
Effect
5FU:1
CI = 1.0

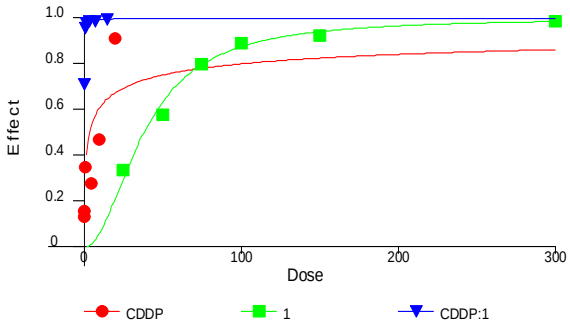

Effect
Dose
CDDP
1
CDDP:1

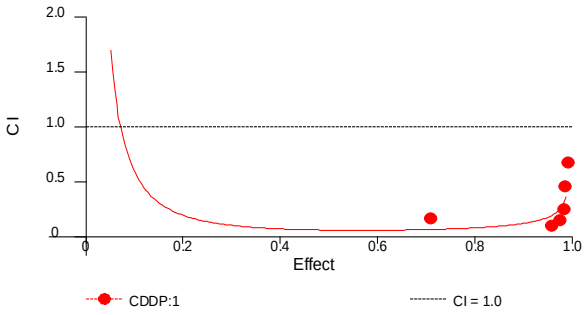

CI
Effect
CDDP:1
CI = 1.0

MCF-7


Effect
Dose
5FU
1
5FU:1


CI
Effect
5FU:1
CI = 1.0


Effect
Dose
CDDP
1
CDDP:1


CI
Effect
CDDP:1
CI = 1.0

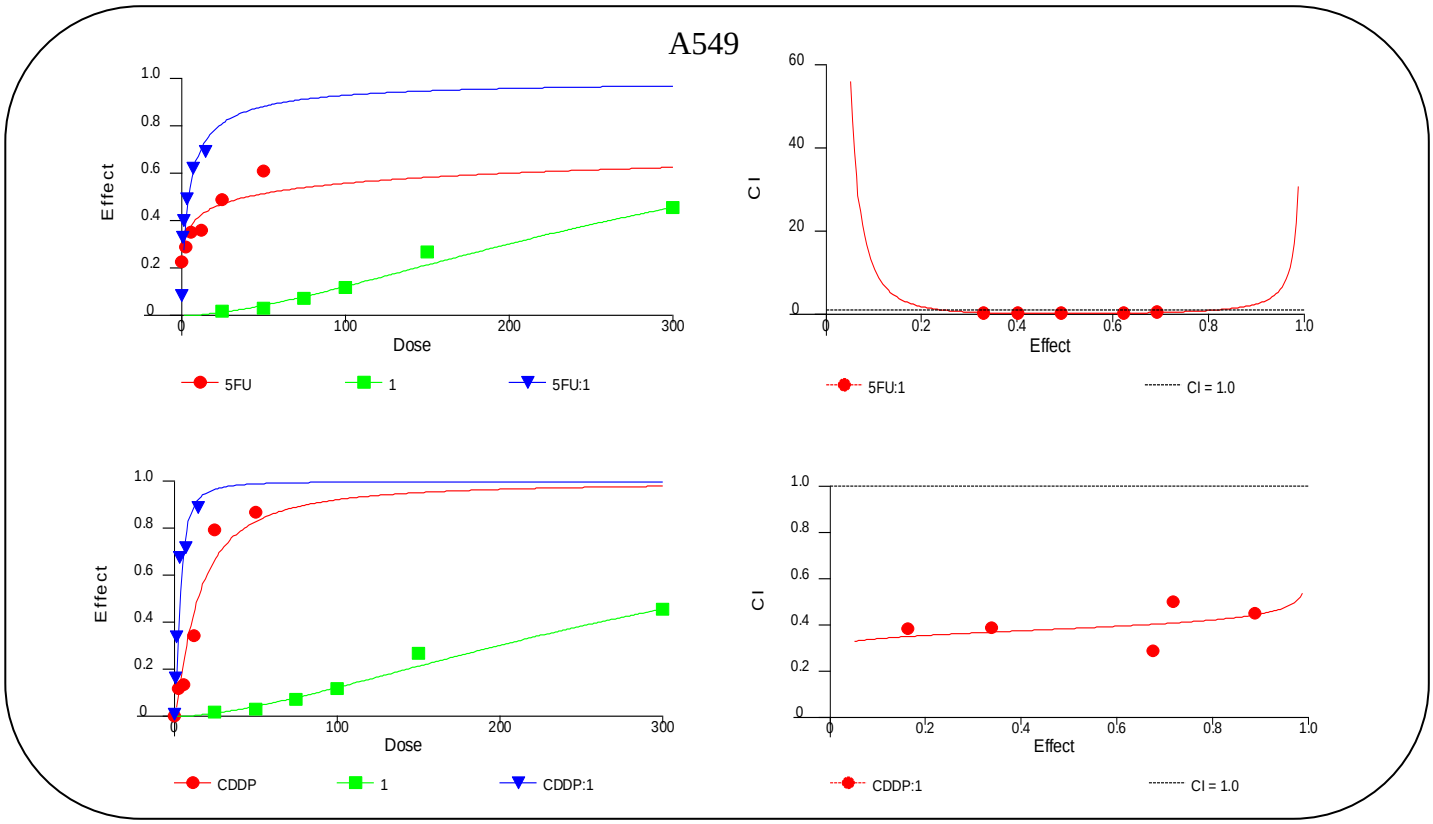


Figure S5. (left) Dose-effect plots for combinations between complex **1** with 5-FU and CDDP against HeLa, MCF-7 and A549 human cancer cell lines. (right) Combination Index (CI)-effect plots for the simultaneous exposure of HeLa, MCF-7 and A549 cells to 5-FU and CDDP with the addition of complex **1** for 48 h (absolute concentration ratios, 1:20 for 5-FU:**1** and CDDP:**1** drug combinations). Cytotoxicity was evaluated 48 h after treatment by means of SRB assay and drug interaction was estimated with Median effect analysis integrated in CalcuSyn software (each point represents mean of six replicate wells). CI values < 1, = 1 or > 1 indicate synergistic, additive or antagonistic interactions, respectively.