The 1,10-Phenanthroline Ligand Enhances the Antiproliferative Activity of DNA-Intercalating thiourea-Pd(II) and -Pt(II) Complexes Against Cisplatin-Sensitive and -Resistant Human Ovarian Cancer Cell Lines

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Supplementary Information

Table 1. IC_{50} values (μM ±SD) for the complexes against four human cancer cell lines.

2008 cells							
Pt(bipy)A $[Pt(bipy)tu_2]Cl_2$	240.6±32	**Pt(phen)1** $[Pt(phen)tu_2]Cl_2$	>100	**Pd(bipy)H** $[Pd(bipy)(tu)_2]Cl_2$	50±6	**Pd(phen)A** $[Pd(phen)tu_2]Cl_2$	4.5±0.5
Pt(bipy)B $[Pt(bipy)(Me\text{-}tu)_2]Cl_2$	145.4±18	**Pt(phen)6** $[Pt(phen)(Me\text{-}tu)_2]Cl_2$	59.4± 6	**Pd(bipy)I** $[Pd(bipy)(Me\text{-}tu)_2]Cl_2$	37.7±4	**Pd(phen)B** $[Pd(phen)(Me\text{-}tu)_2]Cl_2$	7.2±0.3
Pt(bipy)C $[Pt(bipy)(nBu\text{-}tu)_2]Cl_2$	137.3±16	**Pt(phen)7** $[Pt(phen)(nBu\text{-}tu)_2]Cl_2$	75.5± 6	**Pd(bipy)L** $[Pd(bipy)(nBu\text{-}tu)_2]Cl_2$	51.3±7	**Pd(phen)C** $[Pd(phen)(nBu\text{-}tu)_2]Cl_2$	3.9±0.2
Pt(bipy)D $[Pt(bipy)(Et_2\text{-}tu)_2]Cl_2$	142.4±15	**Pt(phen)2** $[Pt(phen)(Et_2\text{-}tu)_2]Cl_2$	41.5 ± 5	**Pd(bipy)-M** $[Pd(bipy)(Et_2\text{-}tu)_2]Cl_2$	55.3±4	**Pd(phen)-D** $[Pd(phen)(Et_2\text{-}tu)_2]Cl_2$	2±0.2
C13* cells							
Pt(bipy)A $[Pt(bipy)tu_2]Cl_2$	445.7±51	**Pt(phen)1** $[Pt(phen)tu_2]Cl_2$	>100	**Pd(bipy)H** $[Pd(bipy)(tu)_2]Cl_2$	55±7	**Pd(phen)A** $[Pd(phen)tu_2]Cl_2$	8.8±0.5
Pt(bipy)B $[Pt(bipy)(Me\text{-}tu)_2]Cl_2$	312.3±29	**Pt(phen)6** $[Pt(phen)(Me\text{-}tu)_2]Cl_2$	71.7±6	**Pd(bipy)I** $[Pd(bipy)(Me\text{-}tu)_2]Cl_2$	65.6±8	**Pd(phen)B** $[Pd(phen)(Me\text{-}tu)_2]Cl_2$	4.1±0.2
Pt(bipy)C $[Pt(bipy)(nBu\text{-}tu)_2]Cl_2$	155.5±12	**Pt(phen)7** $[Pt(phen)(nBu\text{-}tu)_2]Cl_2$	87.5±10	**Pd(bipy)L** $[Pd(bipy)(nBu\text{-}tu)_2]Cl_2$	45.6±5	**Pd(phen)C** $[Pd(phen)(nBu\text{-}tu)_2]Cl_2$	4.8±0.5
Pt(bipy)D $[Pt(bipy)(Et_2\text{-}tu)_2]Cl_2$	161.3±13	**Pt(phen)2** $[Pt(phen)(Et_2\text{-}tu)_2]Cl_2$	38.1±4	**Pd(bipy)-M** $[Pd(bipy)(Et_2\text{-}tu)_2]Cl_2$	50.3±6	**Pd(phen)-D** $[Pd(phen)(Et_2\text{-}tu)_2]Cl_2$	3.4±0.5
A2780 cells							
Pt(bipy)A $[Pt(bipy)tu_2]Cl_2$	224.8±23	**Pt(phen)1** $[Pt(phen)tu_2]Cl_2$	108.8± 13	**Pd(bipy)H** $[Pd(bipy)(tu)_2]Cl_2$	60±7	**Pd(phen)A** $[Pd(Fen)tu_2]Cl_2$	23±4
Pt(bipy)B	125.4±15	**Pt(phen)6**	51.4±4	**Pd(bipy)I**	52.3±6	**Pd(phen)B**	18.1±3

[Pt(bipy)(Me-tu)$_2$]Cl$_2$		[Pt(phen)(Me-tu)$_2$]Cl$_2$		[Pd(bipy)(Me-tu)$_2$]Cl$_2$		[Pd(phen)(Me-tu)$_2$]Cl$_2$	
Pt(bipy)C [Pt(bipy)(nBu-tu)$_2$]Cl$_2$	123.7±13	**Pt(phen)7** [Pt(phen)(nBu-tu)$_2$]Cl$_2$	63.3±7	**Pd(bipy)L** [Pd(bipy)(nBu-tu)$_2$]Cl$_2$	30.5±7	**Pd(phen)C** [Pd(phen)(nBu-tu)$_2$]Cl$_2$	8.5±2
Pt(bipy)D [Pt(bipy)(Et$_2$-tu)$_2$]Cl$_2$	134.1± 21	**Pt(phen)2** [Pt(phen)(Et$_2$-tu)$_2$]Cl$_2$	41.5±5	**Pd(bipy)-M** [Pd(bipy)(Et$_2$-tu)$_2$]Cl$_2$	34.8±4	**Pd(phen)-D** [Pd(phen)(Et$_2$-tu)$_2$]Cl$_2$	10±2
A2780/CP cells							
Pt(bipy)A [Pt(bipy)tu$_2$]Cl$_2$	405.4±35	**Pt(phen)1** [Pt(phen)tu$_2$]Cl$_2$	>100	**Pd(bipy)H** [Pd(bipy)(tu)$_2$]Cl$_2$	53.3±6	**Pd(phen)A** [Pd(Fen)tu$_2$]Cl$_2$	19.5±3
Pt(bipy)B [Pt(bipy)(Me-tu)$_2$]Cl$_2$	342.6±32	**Pt(phen)6** [Pt(phen)(Me-tu)$_2$]Cl$_2$	66.3±5	**Pd(bipy)I** [Pd(bipy)(Me-tu)$_2$]Cl$_2$	45.9±6	**Pd(phen)B** [Pd(phen)(Me-tu)$_2$]Cl$_2$	15.3±3
Pt(bipy)C [Pt(bipy)(nBu-tu)$_2$]Cl$_2$	185.7±21	**Pt(phen)7** [Pt(phen)(nBu-tu)$_2$]Cl$_2$	67.2±4	**Pd(bipy)L** [Pd(bipy)(nBu-tu)$_2$]Cl$_2$	34.5±5	**Pd(phen)C** [Pd(phen)(nBu-tu)$_2$]Cl$_2$	13.7±2
Pt(bipy)D [Pt(bipy)(Et$_2$-tu)$_2$]Cl$_2$	151.2±23	**Pt(phen)2** [Pt(phen)(Et$_2$-tu)$_2$]Cl$_2$	43.1±6	**Pd(bipy)-M** [Pd(bipy)(Et$_2$-tu)$_2$]Cl$_2$	38±5	**Pd(phen)-D** [Pd(phen)(Et$_2$-tu)$_2$]Cl$_2$	9.1±3

The IC$_{50}$ is defined as the concentration causing 50% growth inhibition in treated cells when compared to control cells after 48 h drug exposure. Values are means ± SEM of three separate experiments performed in duplicate.

Table S2. IC$_{50}$ values and resistant factors (RF) for Pd(phen)-thioureas, cisplatin and doxorubicin against the 2008 and C13* cell lines. (IC$_{50}$ (μM) ± SD and resistant factor, RF=IC$_{50}$ resistant/IC$_{50}$ parent line).

Complexes	2008 cells	C13* cells	RF
[Pd(phen)tu$_2$]Cl$_2$	4.5±0.5	8.8±0.5	1.95
[Pd(phen)(Me-tu)$_2$]Cl$_2$	7.2±0.3	4.1±0.2	0.57
[Pd(phen)(nBu-tu)$_2$]Cl$_2$	3.9±0.2	4.8±0.5	1.23
[Pd(phen)(Et$_2$-tu)$_2$]Cl$_2$	2.0±0.2	3.4±0.5	1.70
Cisplatin	1.55 ± 0.13	11.3 ± 0.42	7.30
Doxorubicin	0.054 ± 0.007	0.157 ± 0.016	2.91

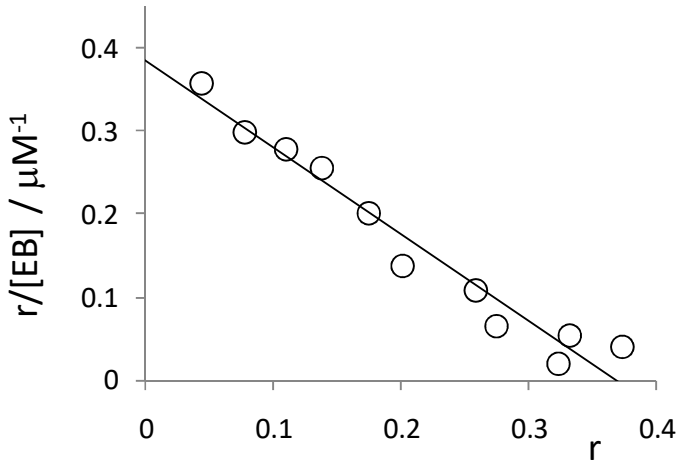

Figure S1. Scatchard plot for the ethydium bromide (EB)/calf thymus DNA binding equilibrium. r = fraction of occupied EB-binding sites in the DNA; [EB] = molar concentration of free EB. T = 22 ± 2 °C.

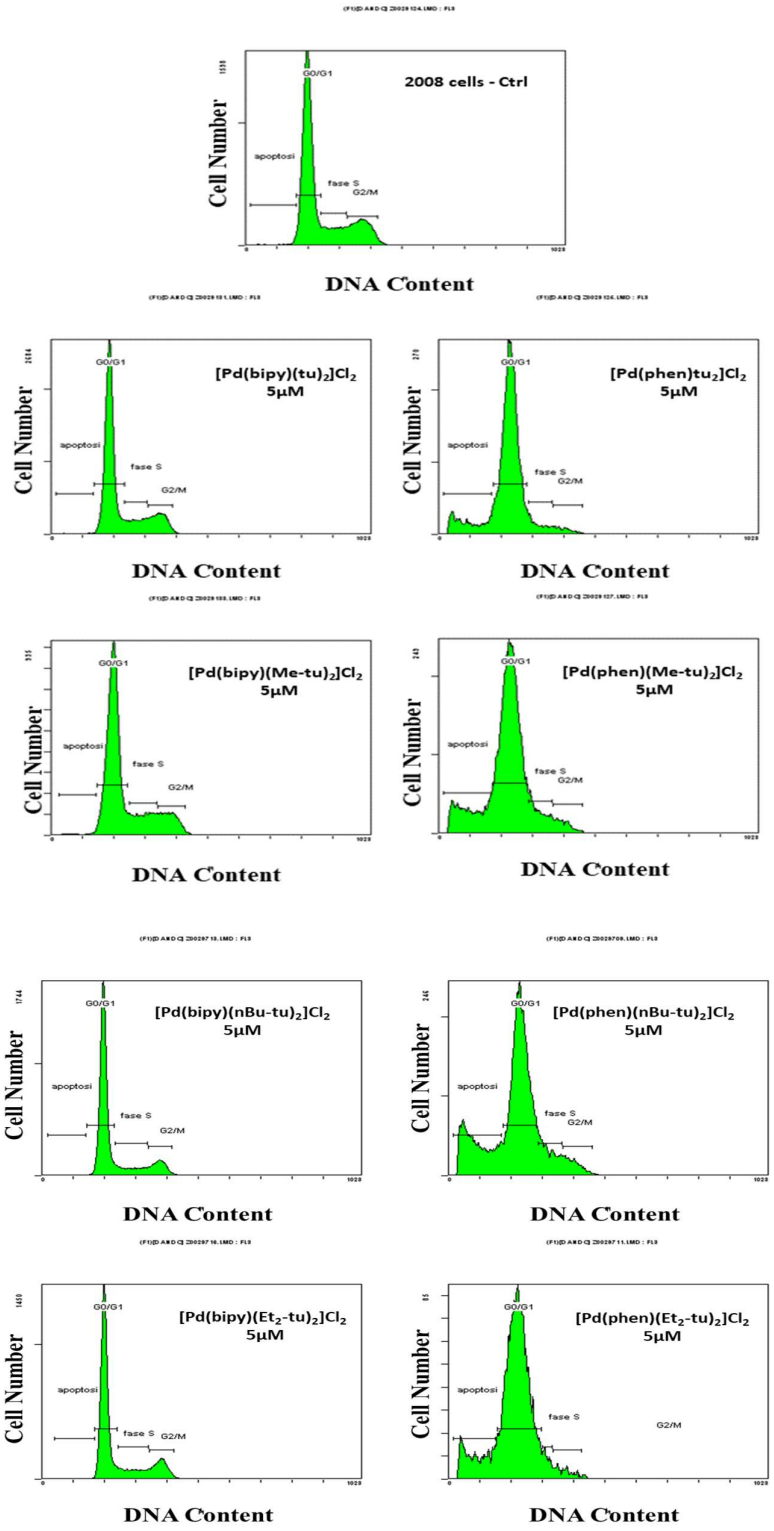

Figure S2. Cell cycle-related analysis of the cDDP-sensitive human cancer 2008 cells after treatment with the Pd(bipy)-thiourea and Pd(phen)-thiourea complexes. Cells were seeded in 6-well plates for 24 h, and then treated with the indicated drug concentration. After 48 hr, cells were harvested and subjected to cell cycle analyses as described in Methods. All results shown are representative of two/three independent assays.

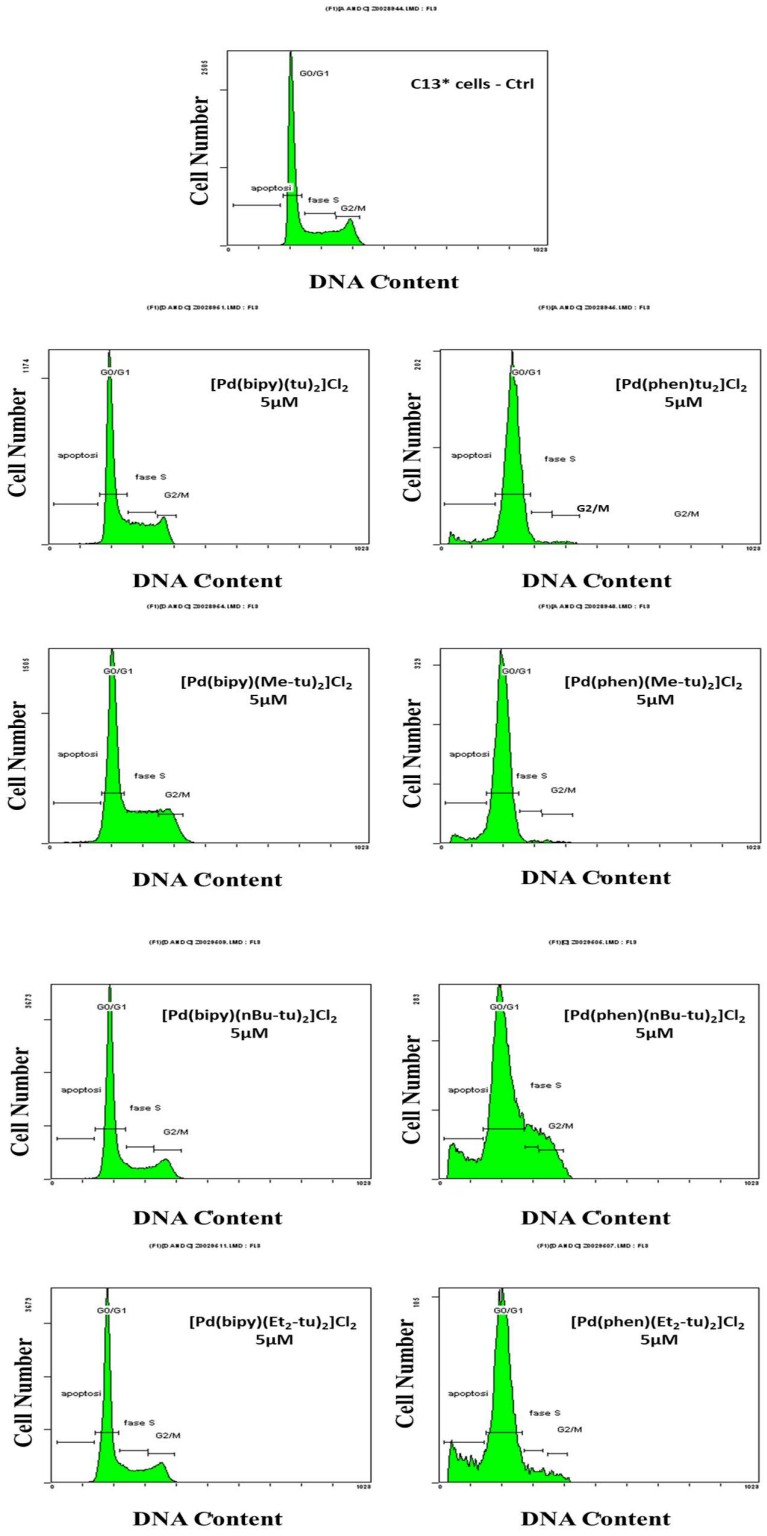

Figure S3. Cell cycle-related analysis of the cDDP-resistant human cancer C13* cells after treatment with the Pd(bipy)-thiourea and Pd(phen)-thiourea complexes. Cells were seeded in 6-well plates for 24 h, and then treated with the indicated drug concentration. After 48 hr, cells were harvested and subjected to cell cycle analyses as described in Methods. All results shown are representative of two/three independent assays.