Electronic Supplementary Material (ESI) for Metallomics.

Supporting Information

Influence of reducing agents on the cytotoxic activity of platinum(IV) complexes: induction of G_2/M arrest, apoptosis and oxidative stress in A2780 and cisplatin resistant A2780cis cell lines

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1. Plasmid interaction studies

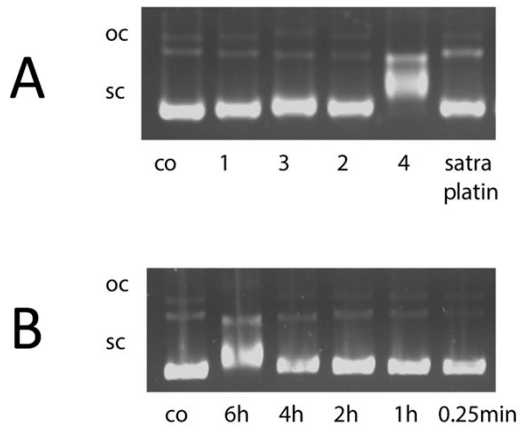

Figure S1: Plasmid interaction studies. pUC19 was incubated A) with Pt^{IV} compounds **1**-**4** and satraplatin (50 μM) for 6 h and B) with compound **4** for 15 min, 1 h, 2 h, 4 h and 6 h, each at 37 °C.

2. Cytotoxic activity

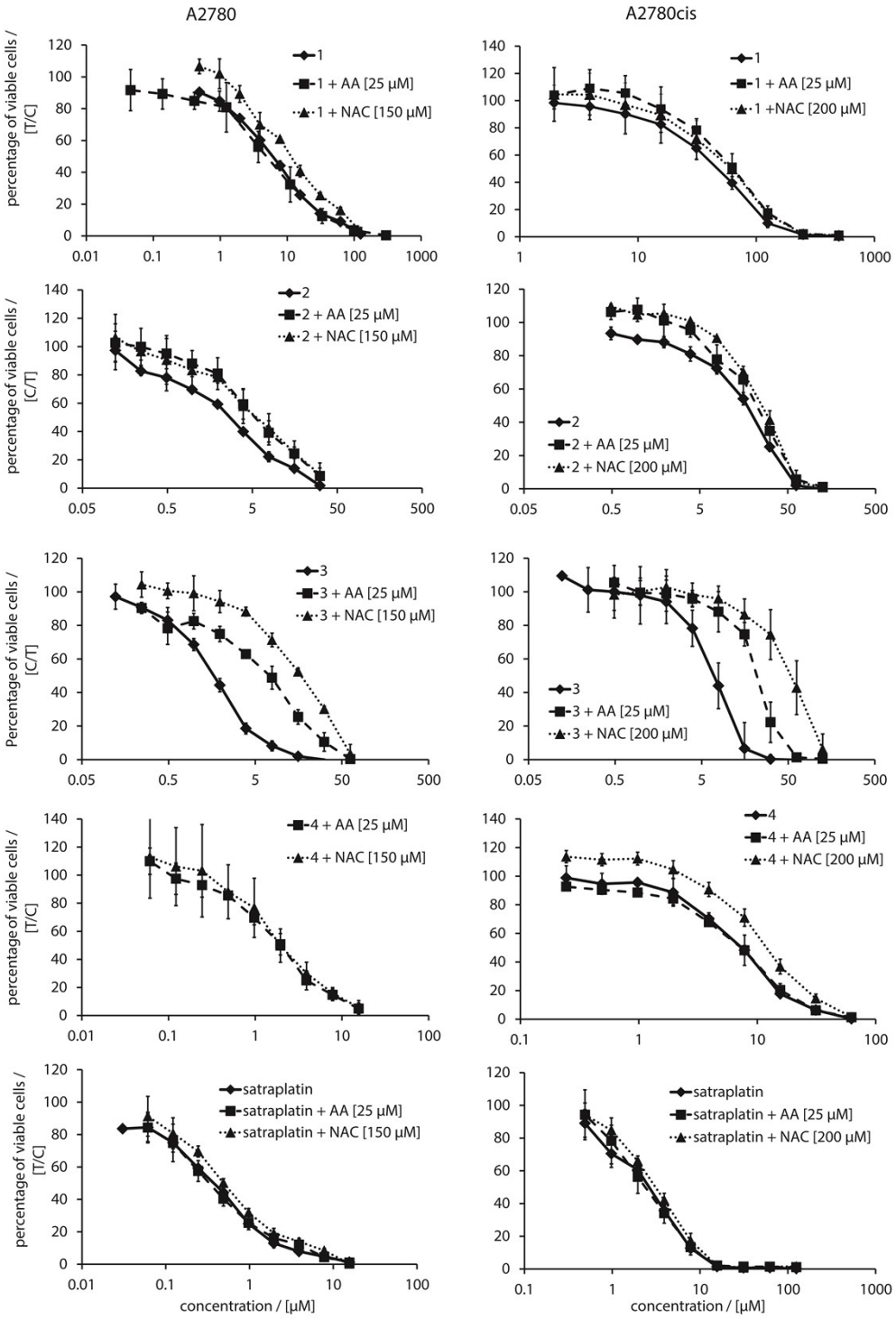

Figure S2: Impact of AA and NAC on the cytotoxicity of complexes **1**-**4**, and reference compound satraplatin after 96 h exposure in A2780 and cisplatin resistant A2780cis ovarian carcinoma cell lines.

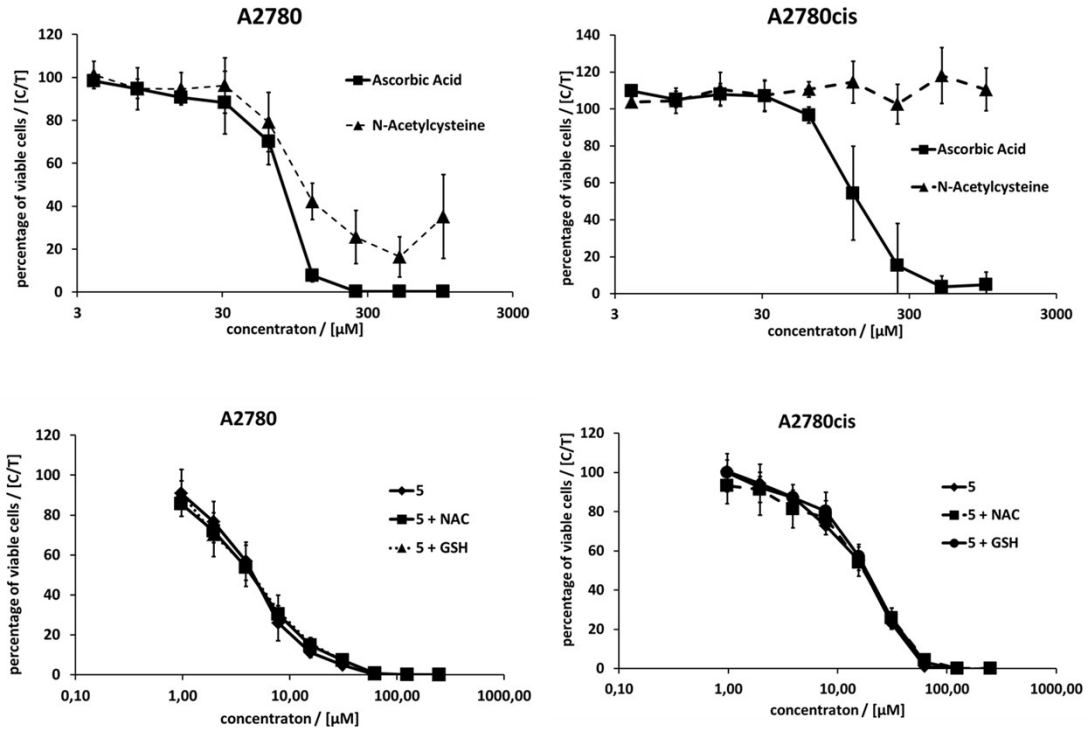

Figure S3: Cytotoxicity of AA and NAC, as well as Pt^{II} complex **5** without or in the presence of GSH or NAC (1:2 ratio complex : reductant) after 96 h in A2780 and cisplatin resistant A2780cis ovarian carcinoma cell lines.

3. Cell cycle

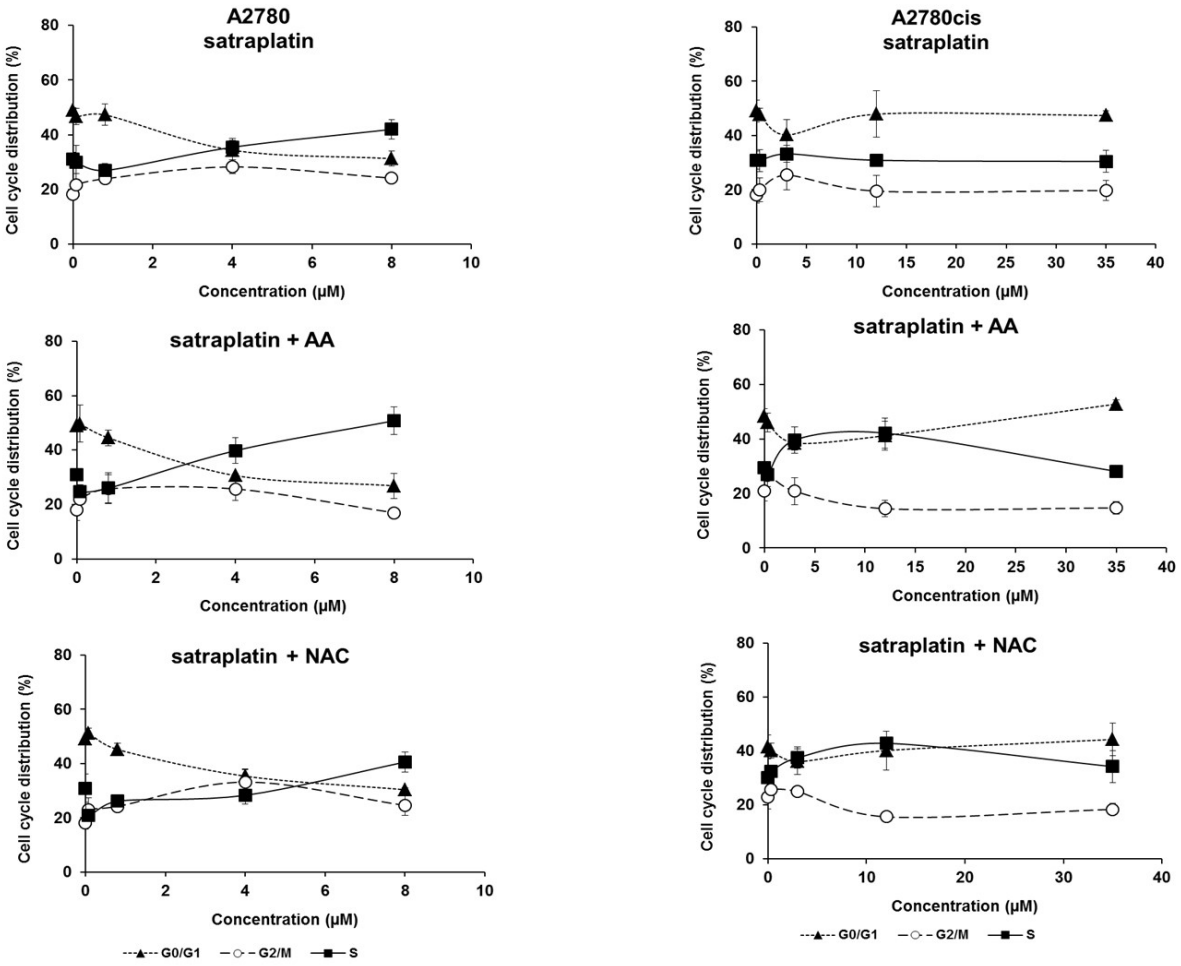

Figure S4: Impact of reference compound satraplatin on the cell cycle, alone or in presence of AA (25 µM) or NAC (150 µM in A2780 and 200 µM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 24 h of exposure to the complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

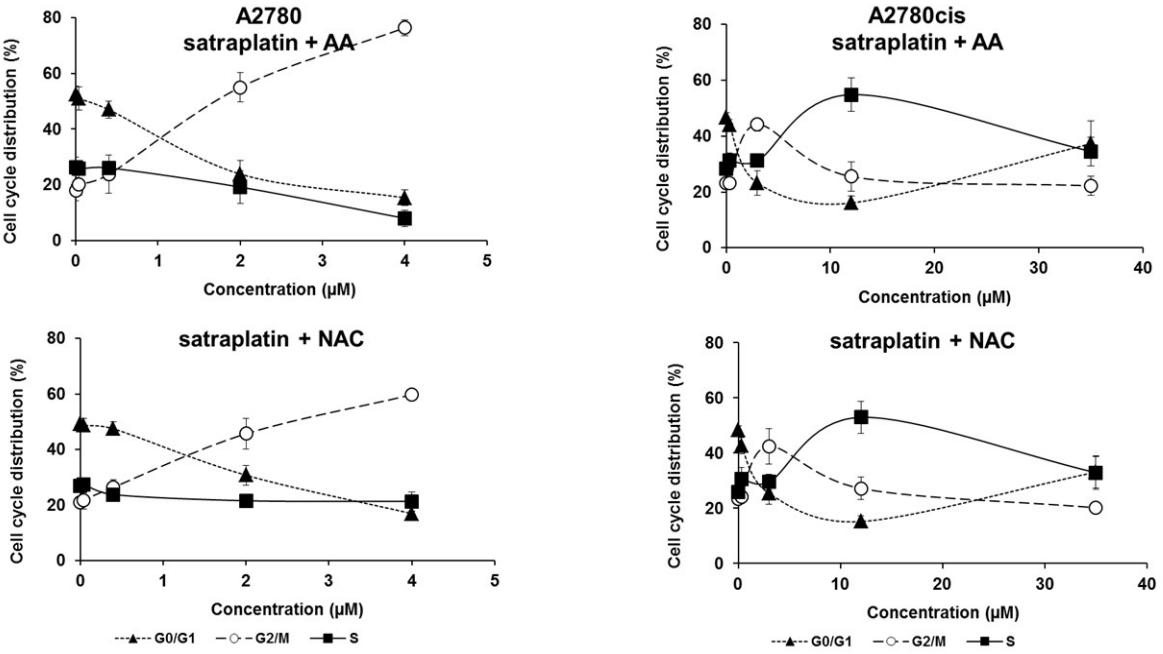

Figure S5: Impact of reference compound satraplatin on the cell cycle in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 48 h of exposure to the complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

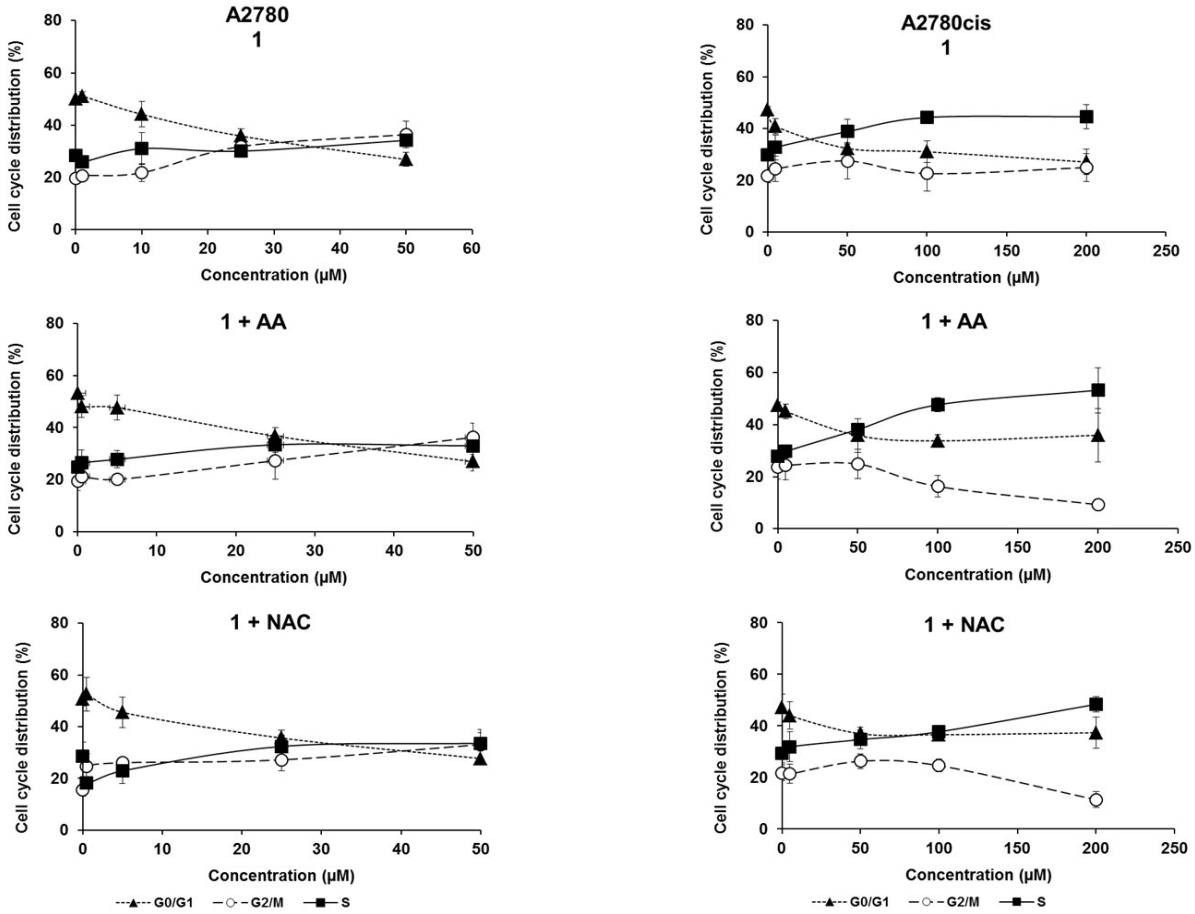

Figure S6: Impact of Pt^{IV} compound **1** on the cell cycle, alone or in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

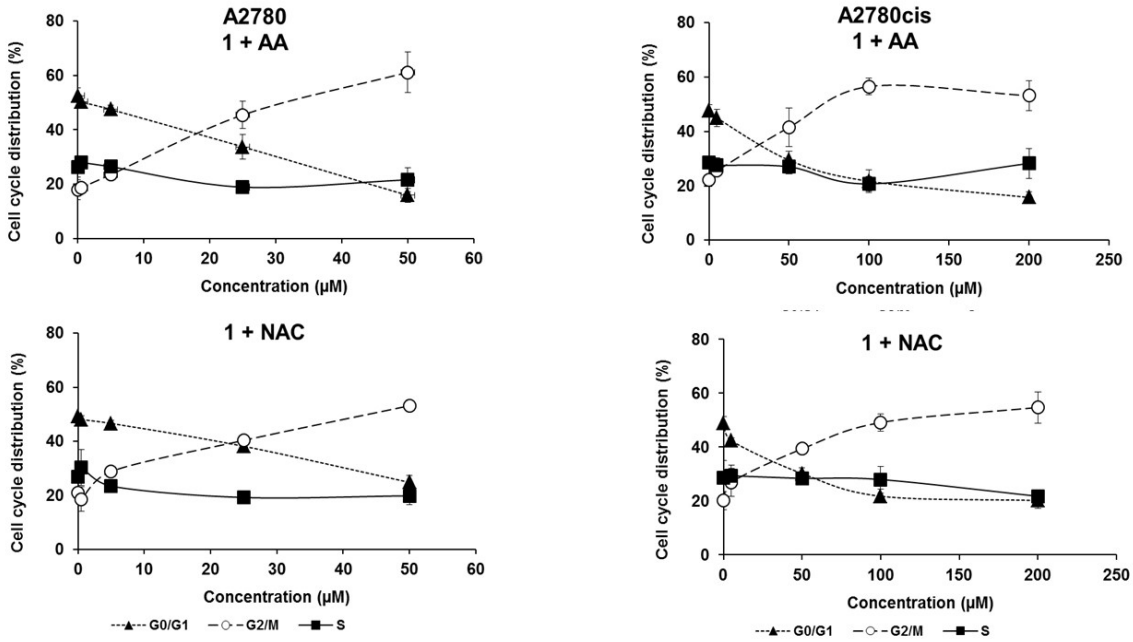

Figure S7: Impact of Pt^{IV} compound **1** on the cell cycle in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 48 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

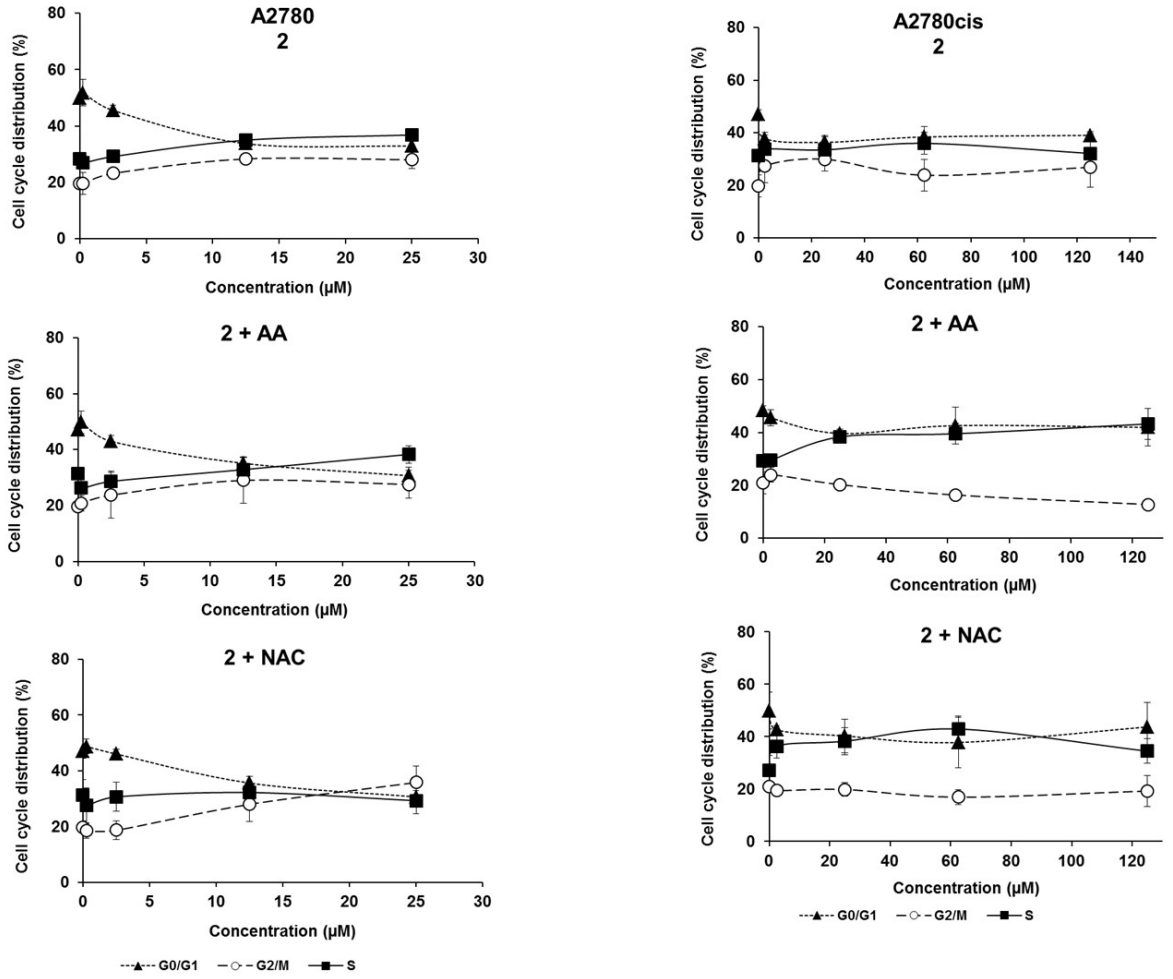

Figure S8: Impact of Pt^{IV} compound **2** on the cell cycle, alone or in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

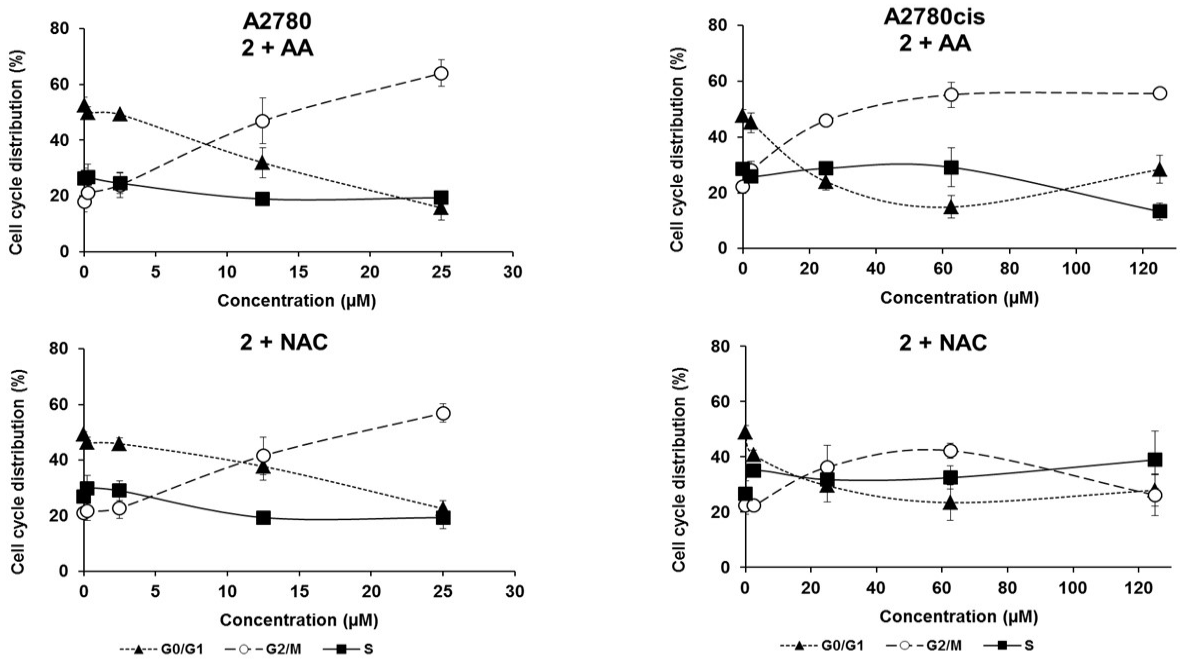

Figure S9: Impact of Pt^{IV} compound **2** on the cell cycle in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 48 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

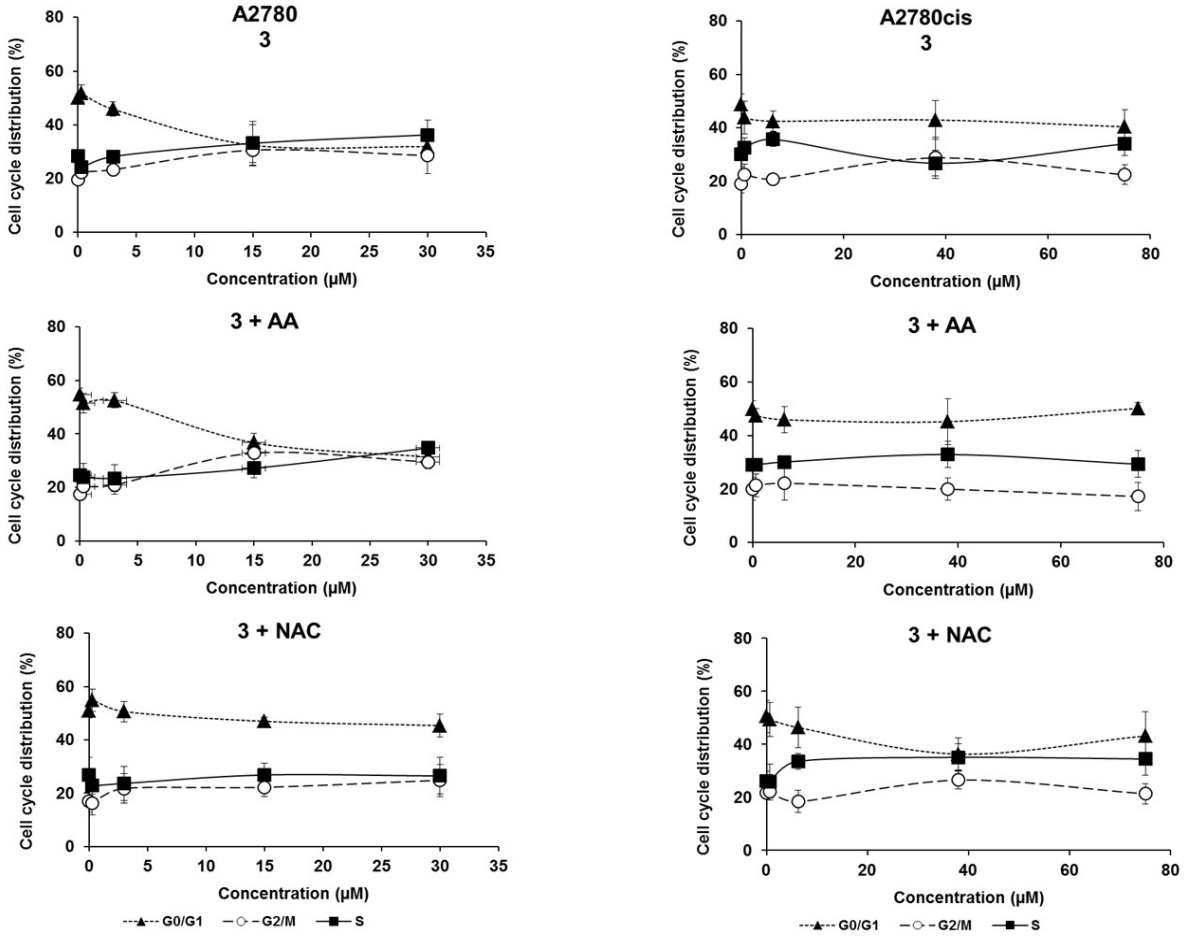

Figure S10: Impact of Pt^{IV} compound **3** on the cell cycle, alone or in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

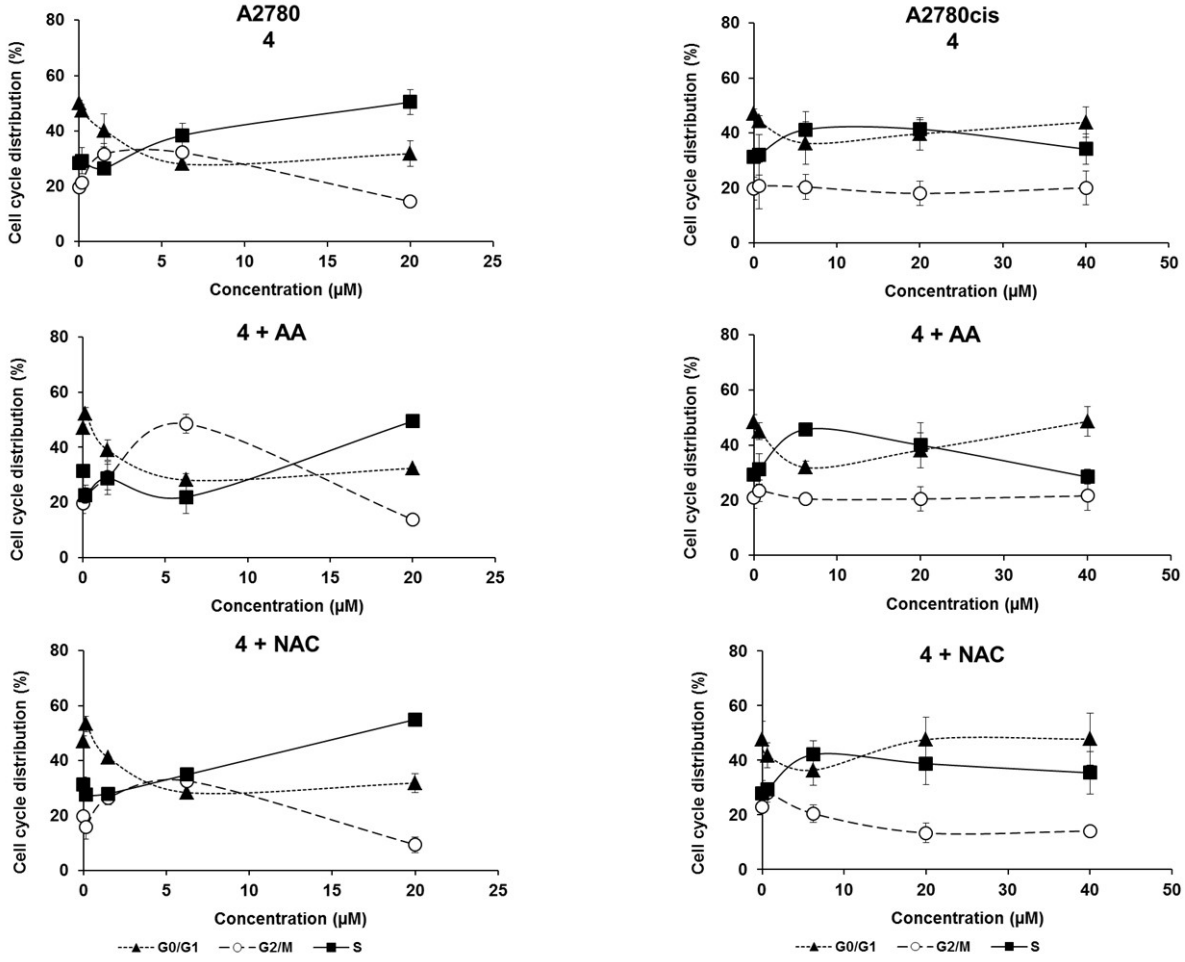

Figure S11: Impact of Pt^{IV} compound **2** on the cell cycle, alone or in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

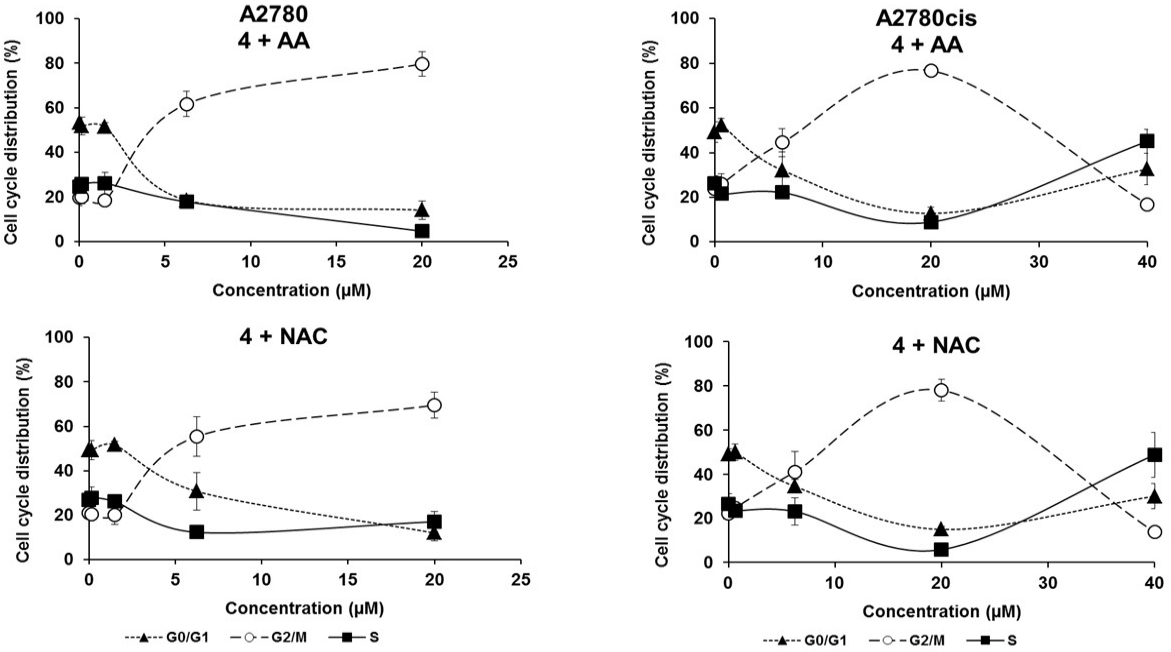

Figure S12: Impact of Pt^{IV} compound **4** on the cell cycle in presence of AA (25 μM) or NAC (150 μM in A2780 and 200 μM in A2780cis cells). PI staining and FACS analyses were performed in A2780 and A2780cis cells after 48 h of exposure to the respective complex at the indicated drug concentrations. Percentage of cells in G_0/G_1, S, and G_2/M phase of the cell cycle are shown.

4. Annexin V/PI staining

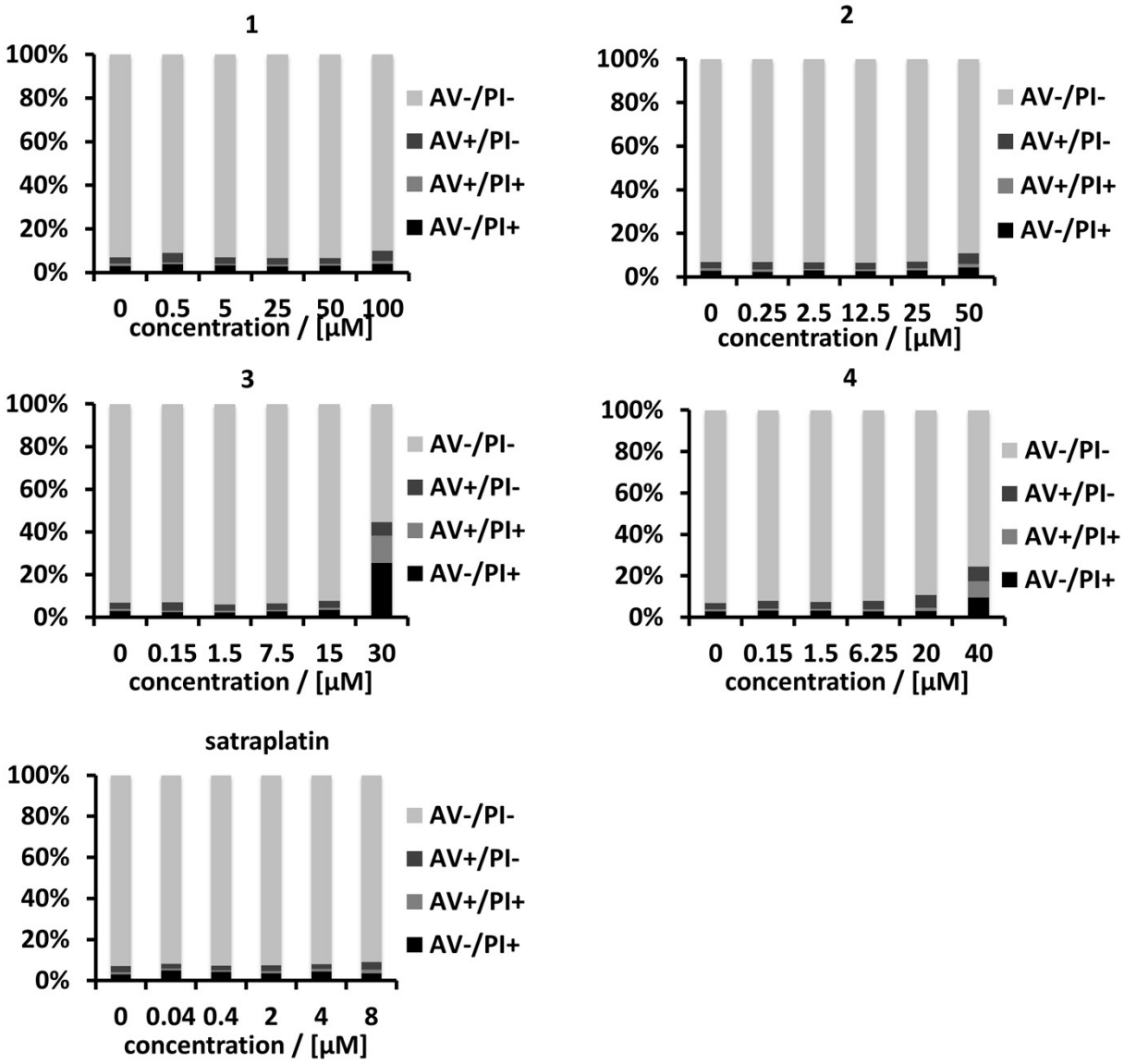

Figure S13: Induction of apoptosis of platinum complexes **1**–**4** and reference compound satraplatin. Annexin V/PI staining and FACS analyses were performed in A2780 cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of viable (AV-/PI-), early apoptotic (AV+/PI-), apoptotic (AV+/PI+), and necrotic (AV-/PI+) cells are drawn.

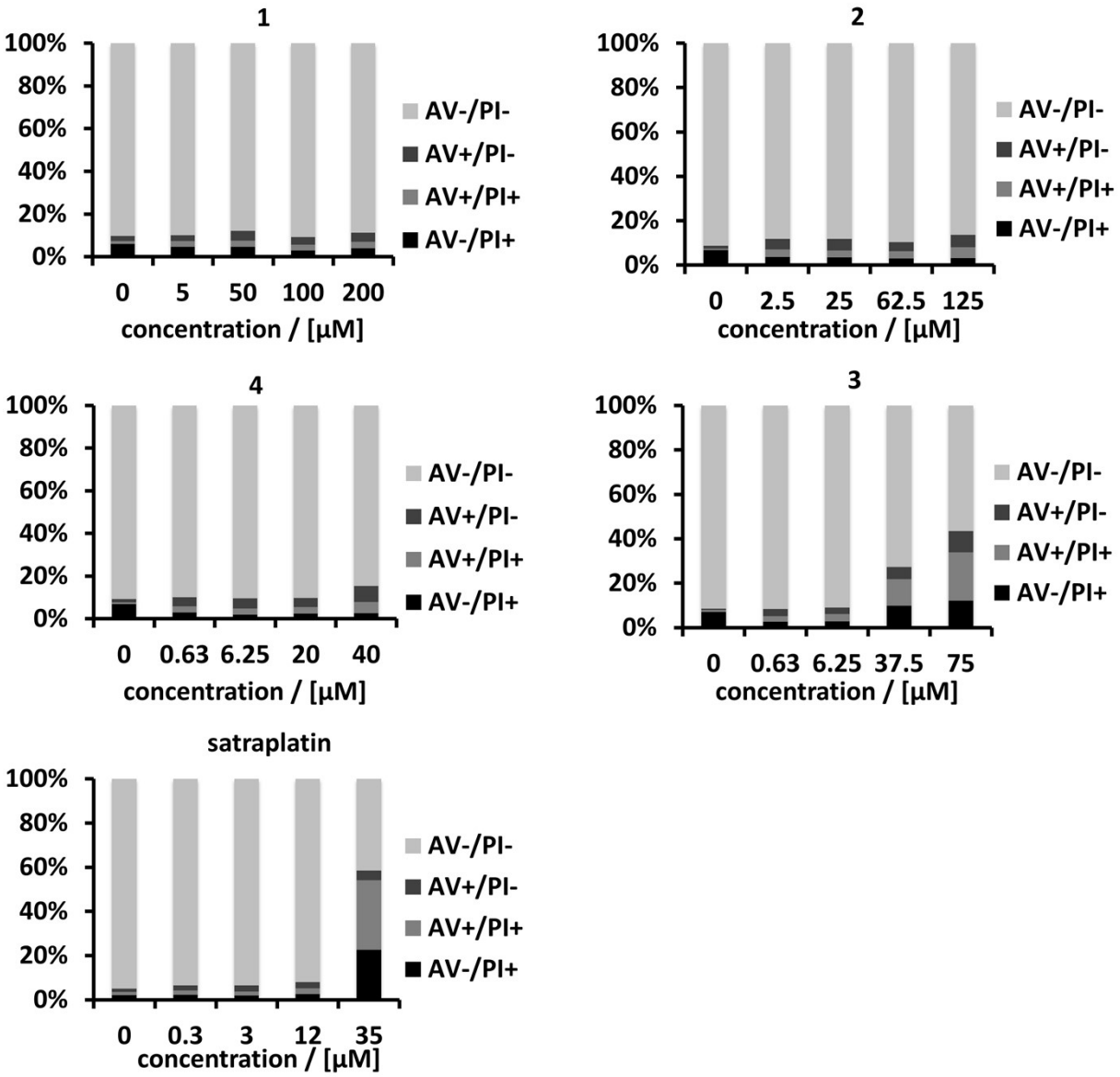

Figure S14: Induction of apoptosis of platinum complexes **1**–**4** and reference compound satraplatin. Annexin V/PI staining and FACS analyses were performed in A2780cis cells after 24 h of exposure to the respective complex at the indicated drug concentrations. Percentage of viable (AV-/PI-), early apoptotic (AV+/PI-), apoptotic (AV+/PI+), and necrotic (AV-/PI+) cells are drawn.

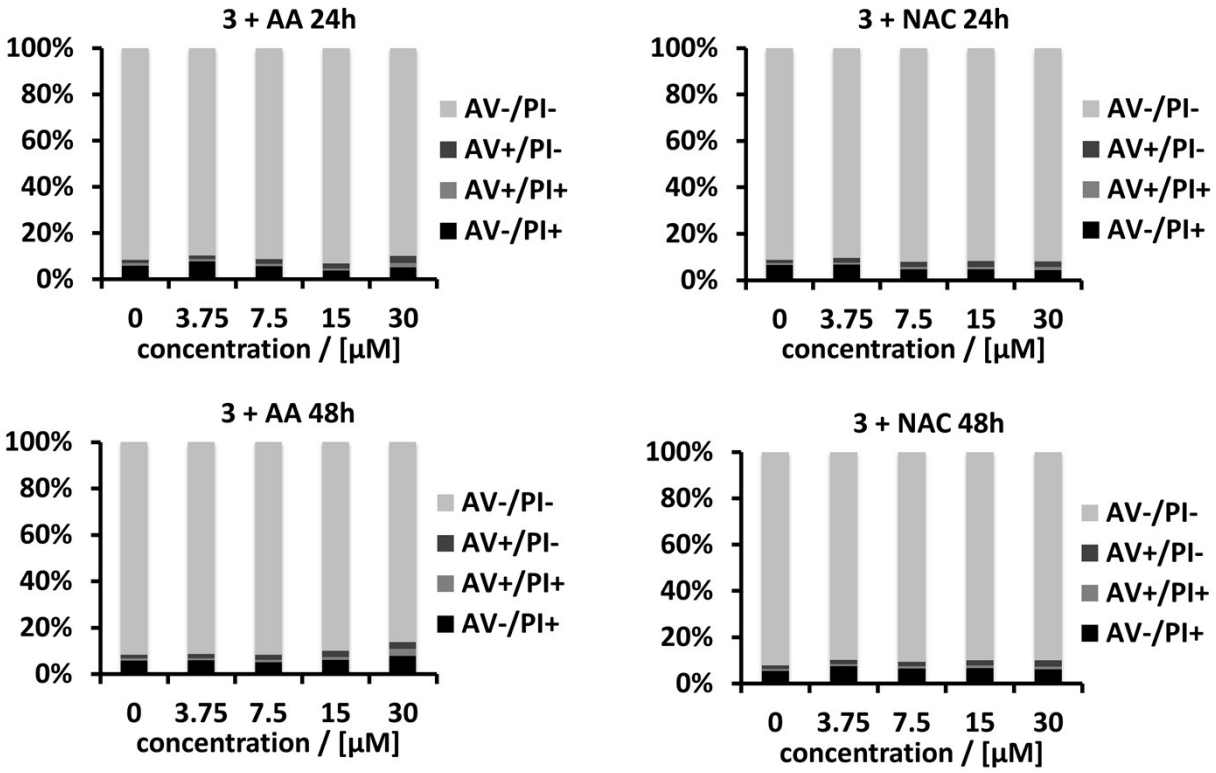

Figure S15: Induction of apoptosis of Pt^{IV} complex **3** in the presence of AA (25 µM) or NAC (150 µM). Annexin V/PI staining and FACS analyses were performed in A2780 cells after 24 h or 48 h of exposure to the respective complex at the indicated drug concentrations. Percentage of viable (AV-/PI-), early apoptotic (AV+/PI-), apoptotic (AV+/PI+), and necrotic (AV-/PI+) cells are drawn.

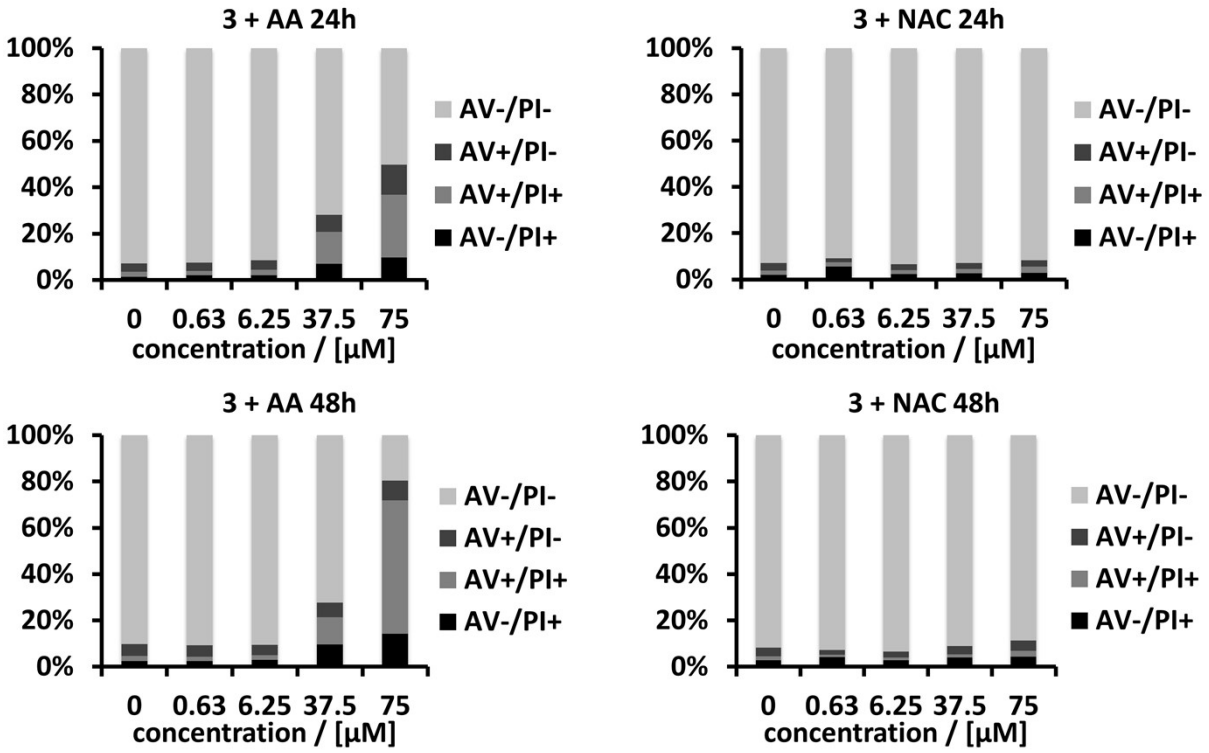

Figure S16: Induction of apoptosis of Pt^{IV} complex **3** in the presence of AA (25 µM) or NAC (200 µM). Annexin V/PI staining and FACS analyses were performed in A2780cis cells after 24 h or 48 h of exposure to the respective complex at the indicated drug concentrations. Percentage of viable (AV-/PI-), early apoptotic (AV+/PI-), apoptotic (AV+/PI+), and necrotic (AV-/PI+) cells are drawn.