Supplementary Materials

A Family of Rhodium Complexes with Selective Toxicity towards Mismatch Repair-Deficient Cancers

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Additional Methods:

Synthesis of $[Rh(L)(chrysi)(PPO)]^{2+}$ Complexes

For L = bpy

$RhCl_3 \bullet 3H_2O$ (270 mg, 1.0 mmol, 1 equiv.) and KCl (78 mg, 1.0 mmol, 1 equiv.) were refluxed in methanol (8 mL) for 2 hours at 98 °C. 2,2'-bipyridine (bpy, 160 mg, 1.0 mmol, 1 equiv) was added in a minimum volume of methanol and refluxed for 4 h, during which the deep red solution turned to golden precipitate. The solution was filtered over a medium fritted filter and rinsed with methanol and dried under vacuum (380 mg, 84% crude yield)

$[Rh(bpy)Cl_4]K$ (380 mg, 0.86 mmol, 1 equiv.) was added to an oven-dried 25 mL Schlenk flask and degassed under argon. Neat triflic acid (10 g, excess) was added to the flask under positive Ar pressure. The solution turned deep red upon triflic acid addition. The flask was purged to remove HCl gas and stirred for 12 h. The solution was then added dropwise to 300 mL cold, stirring ether at -78 °C to produce a yellow-brown precipitate. The precipitate was filtered over a medium frit, washed with cold ether, and dried under vacuum. $[Rh(bpy)(OTf)_4]K$ was combined with NH_4OH (28% w/v, 40 mL, excess) and stirred at 40 °C for 1 h, during which the solution became a foggy light yellow. The solvent was removed under vacuum (280 mg, 42% crude yield).

$[Rh(bpy)(NH_3)_4](OTf)_3$ (280 mg, 0.36 mmol, 1 equiv.) was combined with 5,6-chrysene-quinone (100 mg, 0.39 mmol, 1 equiv.) and 9:1 MeCN:H_2O (40 mL) and NaOH (1 M, 2 mL) and stirred for 1 h. The solution changed from the bright orange of the free ligand to a red-brown solution with no precipitate. The reaction was quenched with HCl (1 M, 2 mL), producing an even deeper red solution, and the solvent was removed under vacuum. The red product was purified over a C18 SepPak, pre-equilibrated with 0.1%TFA (aq) and eluted with 25% MeCN, 75% of 0.1% TFA (aq). (100 mg, 33% yield)

$[Rh(bpy)(chrysi)(NH_3)_2](TFA)_3$ (100 mg, 0.12 mmol, 1 equiv.) was combined with PPO (23 mg, 0.17 mmol, 1.4 equiv.) in 1:1 EtOH:H_2O (10 mL) and refluxed 12 h. The solvent was removed under vacuum and the product was purified by HPLC (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). The purified product was converted to the chloride salt using Sephadex QAE resin charged with $MgCl_2$. (24 mg, 30% purified yield).

For L = HDPA

$RhCl_3 \bullet 3H_2O$ (1.0 g, 3.8 mmol, 1 equiv.) was refluxed in concentrated HCl (38% w/v, 30 mL) for 3 h at 98 °C. 2,2'-dipyridylamine (HDPA, 1.3 g, 7.6 mmol, 2 equiv) was added in a minimum volume of HCl, followed immediately by boiling water (200 mL). The solution was refluxed for 12 h, then cooled to 4 °C. The golden precipitate was filtered over a Buchner funnel and dried under vacuum. (2.2 g, >100% crude yield)

$[Rh(HDPA)Cl_4][H_3O]$ (2.2 g, 1 equiv.) was added to an oven-dried 25 mL Schlenk flask and degassed under argon. Neat triflic acid (10 g, excess) was added to the flask under positive Ar pressure. The solution turned deep red upon triflic acid addition. The flask was purged to remove HCl gas and stirred for 12 h. The solution was then added dropwise to 200 mL cold, stirring ether at -78 °C to produce a yellow-brown precipitate. The precipitate was filtered over a medium fritted filter, washed with cold ether, and dried under vacuum.

$[Rh(HDPA)(OTf)_4][H_3O]$ was combined with NH_4OH (28% w/v, 100 mL, excess) and stirred at 40 °C for 45 min, during which the solution became a foggy light yellow. The solvent was removed under vacuum and the product was dissolved in a minimal amount of water and precipitated with 10:1 ether:EtOH, filtered over a medium fritted filter, and dried further under vacuum. (400 mg, 10% crude yield).

$[Rh(HDPA)(NH_3)_4](OTf)_3$ (400 mg, 0.51 mmol, 1 equiv.) was combined with 5,6-chrysene-quinone (140mg, 0.55 mmol, 1 equiv.) and MeCN (65 mL) and NaOH (1 M, 8 mL) and stirred for 12 h. The solution changed from the bright orange of the free ligand to a red-brown solution with no precipitate. The reaction was quenched with HCl (1 M, 8 mL),

producing an even deeper red solution, and the solvent was removed under vacuum. The red product was purified over a C18 SepPak, pre-equilibrated with 0.1%TFA (aq) and eluted with 25% MeCN, 75% of 0.1% TFA (aq). (220 mg, 51% yield)

$[Rh(HDPA)(chrysi)(NH_3)_2](TFA)_3$ (70 mg, 0.08 mmol, 1 equiv.) was combined with PPO (24 mg, 0.17 mmol, 2.1 equiv.) in 1:1 EtOH:H_2O (20 mL) and refluxed 7 d. The solvent was removed under vacuum and the product was purified by HPLC (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). The purified product was converted to the chloride salt using Sephadex QAE resin charged with $MgCl_2$. (6 mg, 10% purified yield).

For L = 4,7-DMP

$RhCl_3 \bullet 3H_2O$ (500 mg, 1.9 mmol, 1 equiv.) and KCl (150 mg, 2.0 mmol, 1 equiv.) were refluxed in methanol (10 mL) for 2 h at 98 °C. 4,7-dimethyl-1,10-phenanthroline (4,7-DMP, 400 mg, 1.9 mmol, 1 equiv) was added in a minimum volume of methanol and refluxed for 4 h, during which the deep red solution turned to golden precipitate. The solution was filtered over a medium fritted filter and rinsed with methanol and dried under vacuum (800 mg, 86% crude yield)

$[Rh(4,7\text{-}DMP)Cl_4]K$ (800 mg, 1.6 mmol, 1 equiv.) was added to an oven-dried 25 mL Schlenk flask and degassed under argon. Neat triflic acid (10 g, excess) was added to the flask under positive Ar pressure. The solution turned deep red upon triflic acid addition. The flask was purged to remove HCl gas and stirred for 12 h. The solution was then added dropwise to 250 mL cold, stirring ether at -78 °C to produce a yellow-brown precipitate. The precipitate was filtered over a medium frit, washed with cold ether. The product, $[Rh(4,7\text{-}DMP)(OTf)_4]K$ was combined with NH_4OH (28% w/v, 50 mL, excess) and stirred at 40 °C for 1 h, during which the solution became a foggy brown. The solvent was removed under vacuum and the product was suspended in EtOH (5 mL), filtered over a medium fritted filter, and rinsed with cold ethanol, and dried further under vacuum. (200 mg, 15% crude yield).

[Rh(4,7-DMP)$(NH_3)_4$]$(OTf)_3$ (200 mg, 0.24 mmol, 1 equiv.) was combined with 5,6-chrysene-quinone (70mg, 0.39 mmol, 1.6 equiv.) and 6:1 MeCN:H_2O (35 mL) and NaOH (1 M, 5 mL) and stirred for 1 h. The solution changed from the bright orange of the free ligand to a green-brown solution with no precipitate. The reaction was quenched with HCl (1 M, 5 mL), producing a deep red solution, and the solvent was removed under vacuum. The red product was HPLC purified (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). (100 mg, 46% purified yield)

[Rh(4,7-DMP)(chrysi)$(NH_3)_2$]$(TFA)_3$ (50 mg, 0.03 mmol, 1 equiv.) was combined with PPO (9 mg, 0.07 mmol, 2 equiv.) in 1:1 EtOH:H_2O (10 mL) and refluxed 12 h. The solvent was removed under vacuum and the product was purified by HPLC (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). The purified product was converted to the chloride salt using Sephadex QAE resin charged with $MgCl_2$. (4 mg, 10% purified yield).

For L = 5,6-DMP

$RhCl_3$•$3H_2O$ (1.0 g, 3.8 mmol, 1 equiv.) and KCl (290 mg, 3.9 mmol, 1 equiv.) were refluxed in methanol (15 mL) for 2 h at 98 °C. 5,6-dimethyl-1,10-phenanthroline (5,6-DMP, 790 mg, 3.8 mmol, 1 equiv) was added in a minimum volume of methanol and refluxed for 4 h, during which the deep red solution turned to beige precipitate. The solution was filtered over a medium frit and rinsed with methanol and dried under vacuum (1.7 g, 91% crude yield)

[Rh(5,6-DMP)Cl_4]K (1.7 g, 3.4 mmol, 1 equiv.) was added to an oven-dried 25 mL Schlenk flask and degassed under argon. Neat triflic acid (10 g, excess) was added to the flask under positive Ar pressure. The solution turned deep red upon triflic acid addition. The flask was purged to remove HCl gas and stirred for 12 h. The solution was then added dropwise to 200 mL cold, stirring ether at -78 °C to produce a beige precipitate. The precipitate was filtered over a medium fritted filter, washed with cold ether. The product, [Rh(5,6-DMP)$(OTf)_4$]K was combined with NH_4OH (28% w/v, 100 mL, excess) and stirred at 40 °C for 40 min. The solvent was removed under vacuum and the product was dissolved in

minimal EtOH and precipitated in ether, filtered over a medium fritted filter, and dried further under vacuum. (2.2 g, 77% crude yield).

$[Rh(5,6\text{-DMP})(NH_3)_4](OTf)_3$ (830 mg, 1.0 mmol, 1 equiv.) was combined with 5,6-chrysene-quinone (250 mg, 1.0 mmol, 1 equiv.) and 11:1 MeCN:H_2O (250 mL) and NaOH (1M, 4 mL) and stirred for 1 h. The solution changed from the bright orange of the free ligand to a green-brown solution with no precipitate. The reaction was quenched with HCl (1 M, 4 mL), producing a deep red solution, and the solvent was removed under vacuum. The red product was HPLC purified (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). (540 mg, 62% purified yield)

$[Rh(5,6\text{-DMP})(chrysi)(NH_3)_2](TFA)_3$ (40mg, 0.04 mmol, 1 equiv.) was combined with PPO (11 mg, 0.08 mmol, 2 equiv.) in 1:1 EtOH:H_2O (10 mL) and refluxed 12 h. The solvent was removed under vacuum and the product was purified by HPLC (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). The purified product was converted to the chloride salt using Dowex 1x2 500-100 mesh ion exchange resin. (8 mg, 23% purified yield).

For L = DIP

$RhCl_3 \bullet 3H_2O$ (770 mg, 2.9 mmol, 1 equiv.) and KCl (230 mg, 3.1 mmol, 1 equiv.) were refluxed in methanol (15 mL) for 2 hours at 98 °C. 4,7-diphenyl-1,10-phenanthroline (DIP, 970 mg, 2.9 mmol, 1 equiv) was added in a minimum volume of methanol and refluxed for 4 h, during which the deep red solution turned to beige-yellow precipitate. The solution was filtered over a medium frit and rinsed with methanol and dried under vacuum (1.7 g, 95% crude yield)

$[Rh(DIP)Cl_4]K$ (1.7 g, 2.8 mmol, 1 equiv.) was added to an oven-dried 25 mL Schlenk flask and degassed under argon. Neat triflic acid (10 g, excess) was added to the flask under positive Ar pressure. The solution turned deep red upon triflic acid addition. The flask was

purged to remove HCl gas and stirred for 12 h. The solution was then added dropwise to 200 mL cold, stirring ether at -78 °C to produce a beige precipitate. The precipitate was filtered over a medium fritted filter, washed with cold ether. The product, $[Rh(DIP)(OTf)_4]K$ was combined with NH_4OH (28% w/v, 100 mL, excess) and stirred at 40 °C for 40 min. The solvent was removed under vacuum and the product was dissolved in minimal EtOH and precipitated in ether, filtered over a medium fritted filter, and dried further under vacuum. (1.9 g, 72% crude yield).

$[Rh(DIP)(NH_3)_4](OTf)_3$ (510 mg, 0.54 mmol, 1 equiv.) was combined with 5,6-chrysene-quinone (140 mg, 0.55 mmol, 1 equiv.) and 11:1 MeCN:H_2O (250 mL) and NaOH (1 M, 4 mL) and stirred for 1 h. The solution changed from the bright orange of the free ligand to a green-brown solution with no precipitate. The reaction was quenched with HCl (1 M, 4 mL), producing a deep red solution, and the solvent was removed under vacuum. The red product was purified over a C18 SepPak, pre-equilibrated with 0.1%TFA (aq) and eluted with 25% MeCN, 75% of 0.1% TFA (aq). (620 mg, >100% crude yield)

$[Rh(DIP)(chrysi)(NH_3)_2](TFA)_3$ (52 mg, 0.05 mmol, 1 equiv.) was combined with PPO (15 mg, 0.11 mmol, 2 equiv.) in 9:1 EtOH:H_2O (10 mL) and refluxed 12 h. The solvent was removed under vacuum and the product was purified by HPLC (85:15 MeCN:0.1% TFA (aq) to 95:5 MeCN:0.1% TFA (aq) over 30 min). The purified product was converted to the chloride salt using Dowex 1x2 500-100 mesh ion exchange resin. (15 mg, 33% yield).

Radiolabeling of DNA

DNA was purchased from IDT DNA and purified by HPLC on a C18 reverse-phase column. The DNA was quantified using extinction coefficients provided by IDT DNA. A DNA hairpin (5'-GGCAGG**X**ATGGCTTTTTGCCAT**Y**CCTGCC-3', where XY=CG or CC for a well-matched or mismatched hairpin, respectively) was incubated with γ-^{32}P ATP and polynucleotide kinase at 37 ˚C for 2.5 h, then purified using two BioRad Micro Bio-Spin 6 columns following the manufacturer's instructions. Solvent was removed from the DNA, and the DNA was dissolved in 10 mM NaP_i, pH 7.1. A 2 μM solution of DNA was made in 100 mM NaCl and 20

mM NaP_i buffer containing approximately 1% ^{32}P-labeled DNA and 99% unlabeled DNA. To anneal, the DNA was heated on a 90˚C heat block for 10 min, cooled to room temperature over the course of 2.5 h, and then stored at 4 ˚C prior to use.

Table S1: Converted nuclear rhodium content values

	Compound	ng [Rh] / mg [nuclear protein]	ng [Rh] / nuclei × 10^{-8} [a]	[Rh] µM [b]	Increase over extracellular [Rh][c]
N Cells	**PHEN**	3.0	10.0	3.6	7.2
	BPY	1.8	5.8	2.1	4.2
	HDPA	6.5	21.3	7.7	15.5
	4,7DMP	4.1	13.3	4.8	9.6
	5,6DMP	4.1	13.5	4.9	9.8
	DIP	8.0	26.2	9.5	47.5
	RhBC	26.6	87.2	31.6	3.2
O Cells	**PHEN**	2.6	8.6	3.1	6.3
	BPY	3.5	11.6	4.2	8.4
	HDPA	7.3	23.8	8.6	17.2
	4,7DMP	5.0	16.4	5.9	11.9
	5,6DMP	6.8	22.4	8.1	16.2
	DIP	11.6	38.0	13.7	68.7
	RhBC	37.3	122.2	44.3	4.4

[a] a conversion factor of 3.28×10^{-8} mg nuclear protein / nuclei was determined in reference 1

[b] the nucleus was approximated as a sphere of radius 4µm following reference 2

[c] Increase taken as ratio between the nuclear rhodium concentration and the dosing concentration of each metalloinsertor.

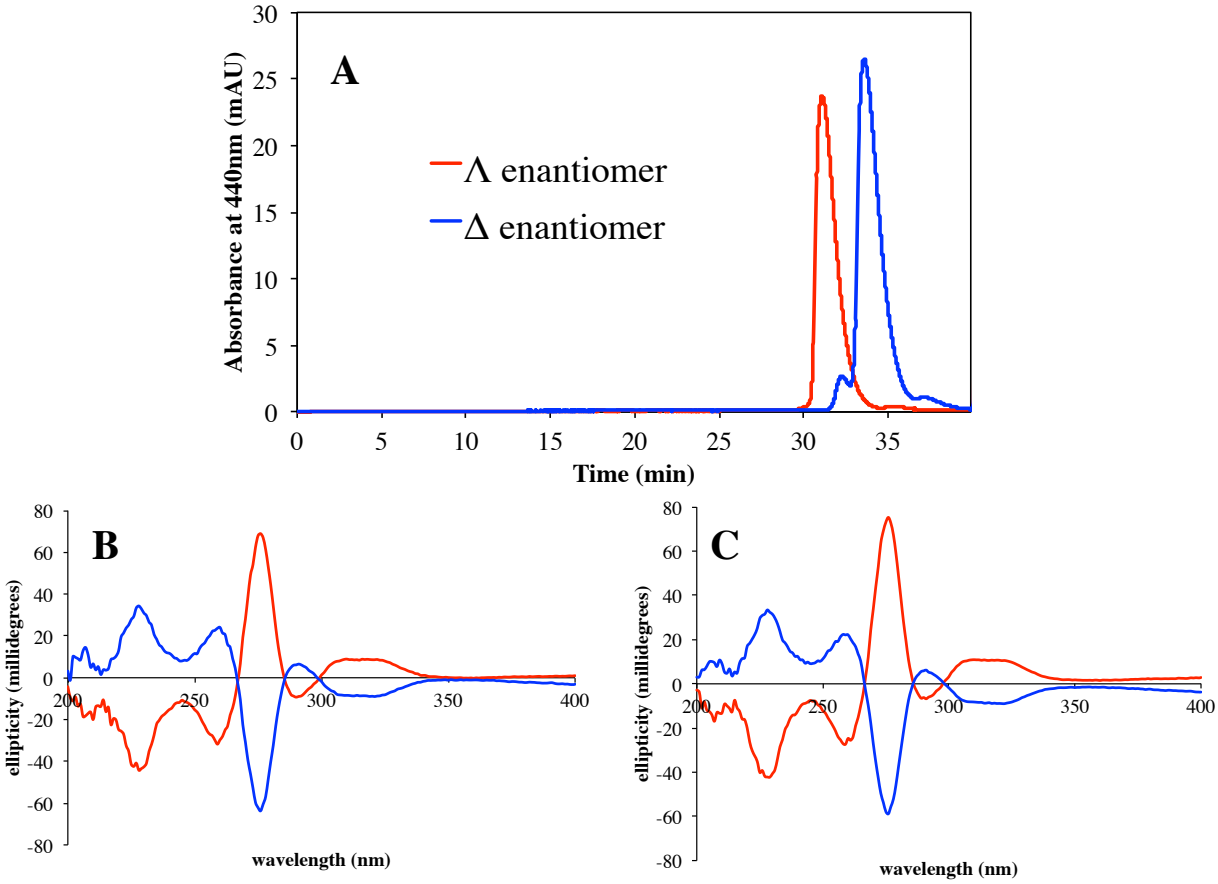

Figure S1: (A) HPLC trace of the purified Δ- and Λ-enantiomers of [Rh(phen)(chrysi)(PPO)]$^{2+}$, (B) a CD spectrum showing the enantiomeric nature of the two samples, and (C) a CD spectrum taken after one month of incubation at standard temperature and pressure, showing no racemization.

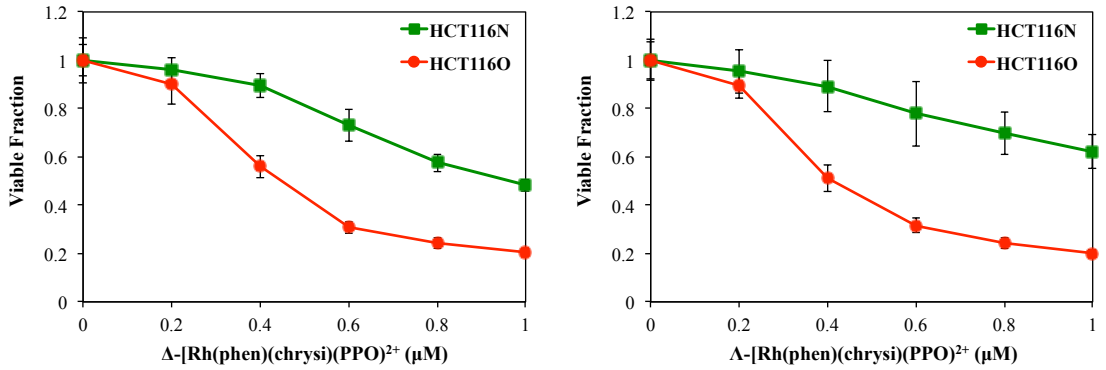

Figure S2: MTT assays of Δ- and Λ-[Rh(phen)(chrysi)(PPO)]Cl_2 with HCT116N (MMR proficient) and HCT116O (MMR deficient) cell lines. Both enantiomers show selective cytotoxicity towards the MMR deficient cell line at similar concentration ranges.

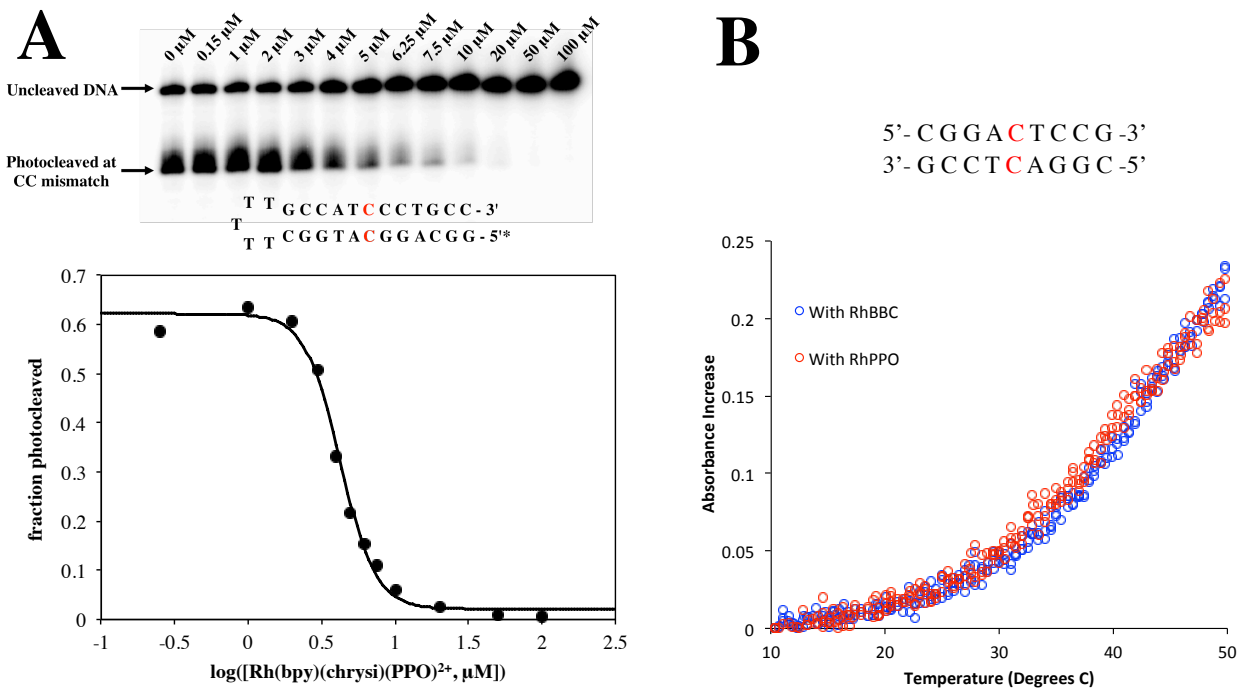

Figure S3: (A) A representative competition titration between $[Rh(bpy)(chrysi)(PPO)]^{2+}$ and $[Rh(bpy)_2(chrysi)]^{3+}$ to a hairpin DNA sequence containing a single CC mismatch. As the concentration of $[Rh(bpy)(chrysi)(PPO)]^{2+}$ is increased, $[Rh(bpy)_2(chrysi)]^{3+}$ is competed out of the mismatched site and the amount of DNA photocleavage decreases, as seen in the gel image. The photocleaved fraction of DNA is plotted against the log([Rh(bpy)(chrysi)$(PPO)^{2+}$,µM]) and fit with a sigmoidal curve. (B) Melting temperature analysis of a 9-mer containing a central CC mismatch in the presence of $[Rh(bpy)_2(chrysi)]Cl_3$ (RhBBC) or $[Rh(phen)(chrysi)(PPO)]Cl_2$ (RhPPO) showed comparable stabilization of the duplex with melting temperatures of 44.9 ± 0.6 and 41.3 ± 0.5 °C, respectively.

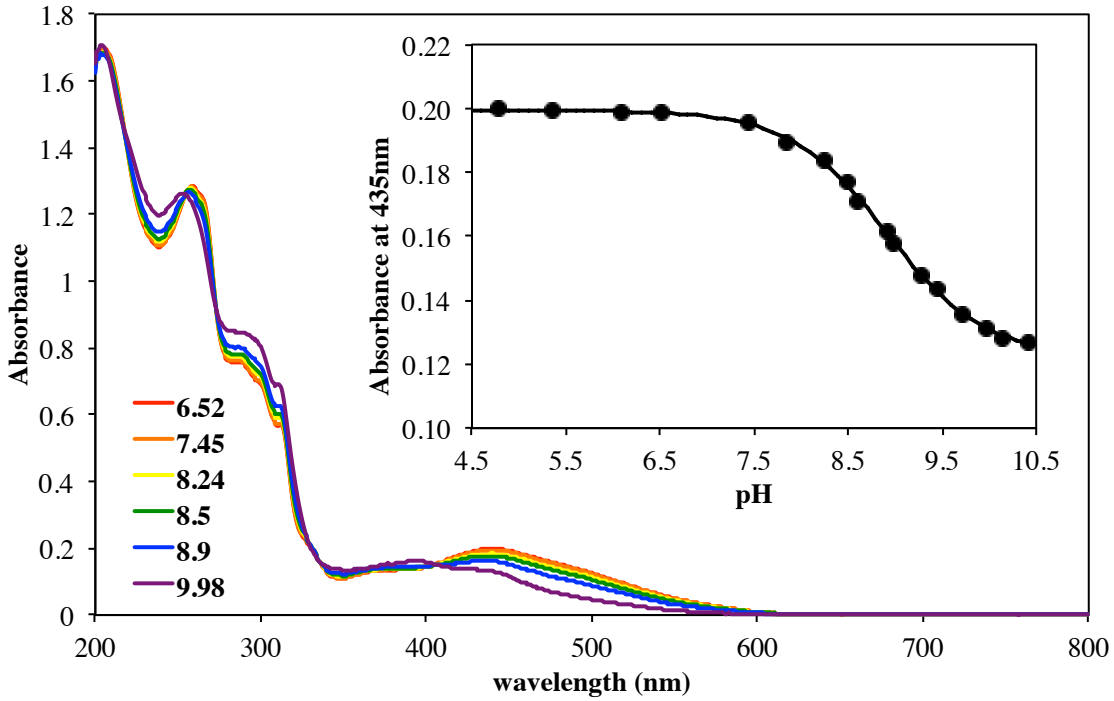

Figure S4: A pH titration of the metalloinsertor $[Rh(bpy)(chrysi)(PPO)]^{2+}$. Absorption spectra as the pH changes from 6.52 to 9.98 are shown, and the inset show the absorbance at 435nm vs pH and fit to a sigmoidal curve.

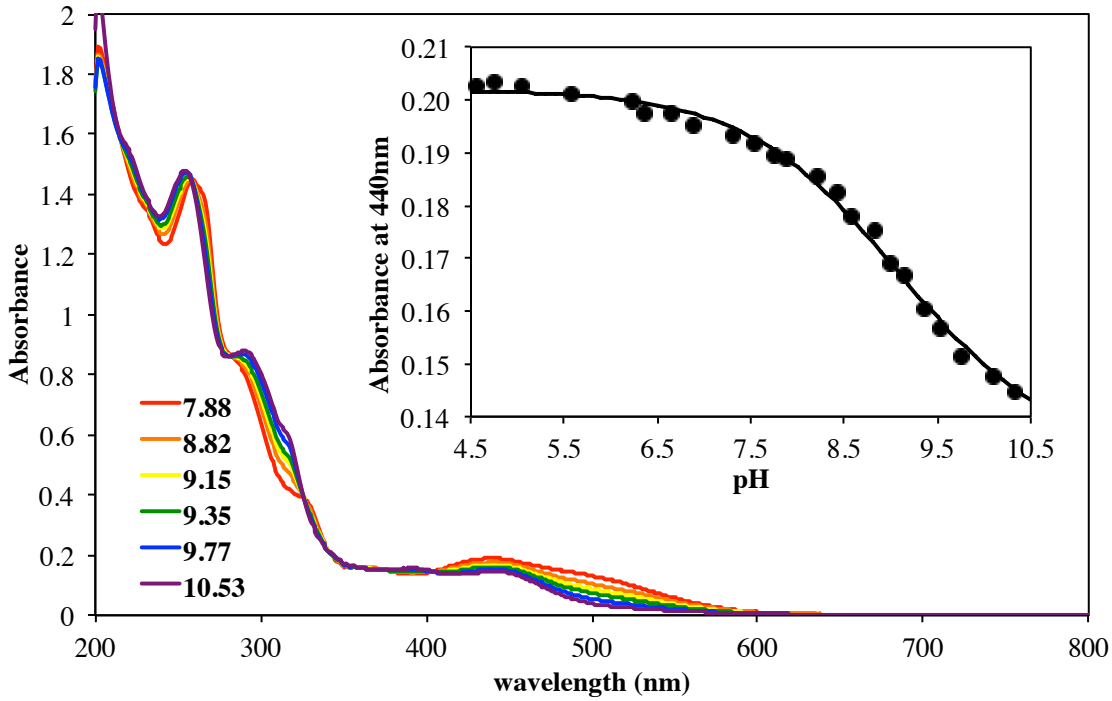

Figure S5: A pH titration of the metalloinsertor $[Rh(HDPA)(chrysi)(PPO)]^{2+}$. Absorption spectra as the pH changes from 7.88 to 10.53 are shown, and the inset show the absorbance at 440nm vs pH and fit to a sigmoidal curve.

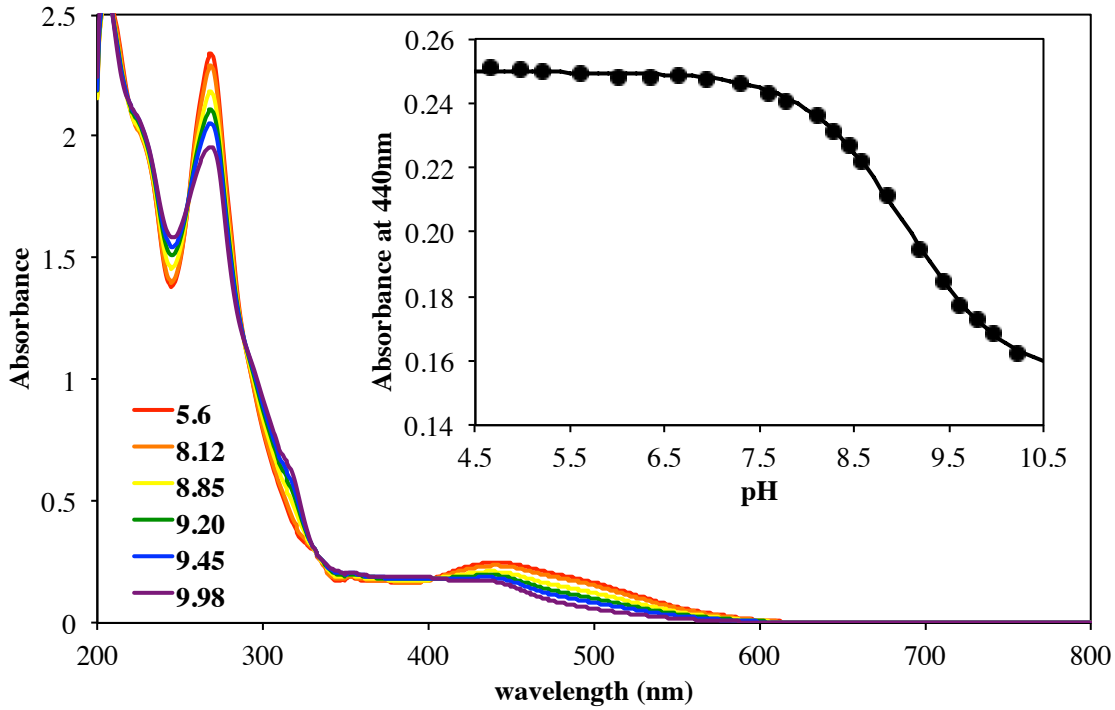

Figure S6: A pH titration of the metalloinsertor $[Rh(4,7\text{-}DMP)(chrysi)(PPO)]^{2+}$. Absorption spectra as the pH changes from 5.60 to 9.98 are shown, and the inset show the absorbance at 440nm vs pH and fit to a sigmoidal curve.

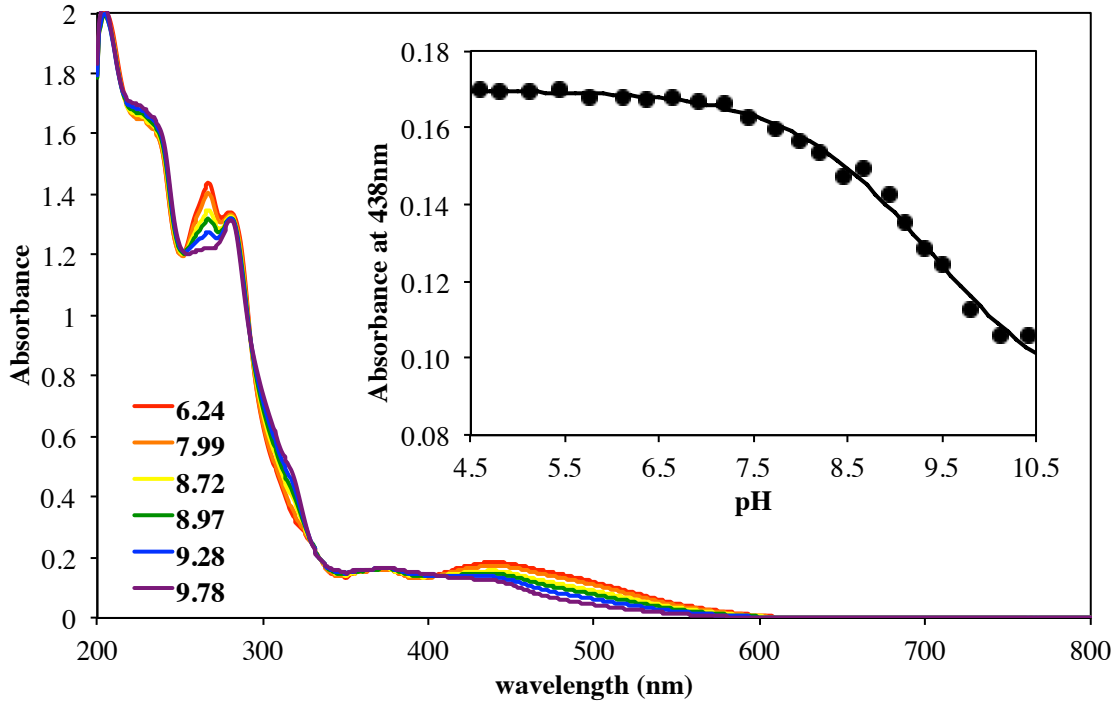

Figure S7: A pH titration of the metalloinsertor $[Rh(5,6\text{-}DMP)(chrysi)(PPO)]^{2+}$. Absorption spectra as the pH changes from 6.24 to 9.78 are shown, and the inset show the absorbance at 438nm vs pH and fit to a sigmoidal curve.

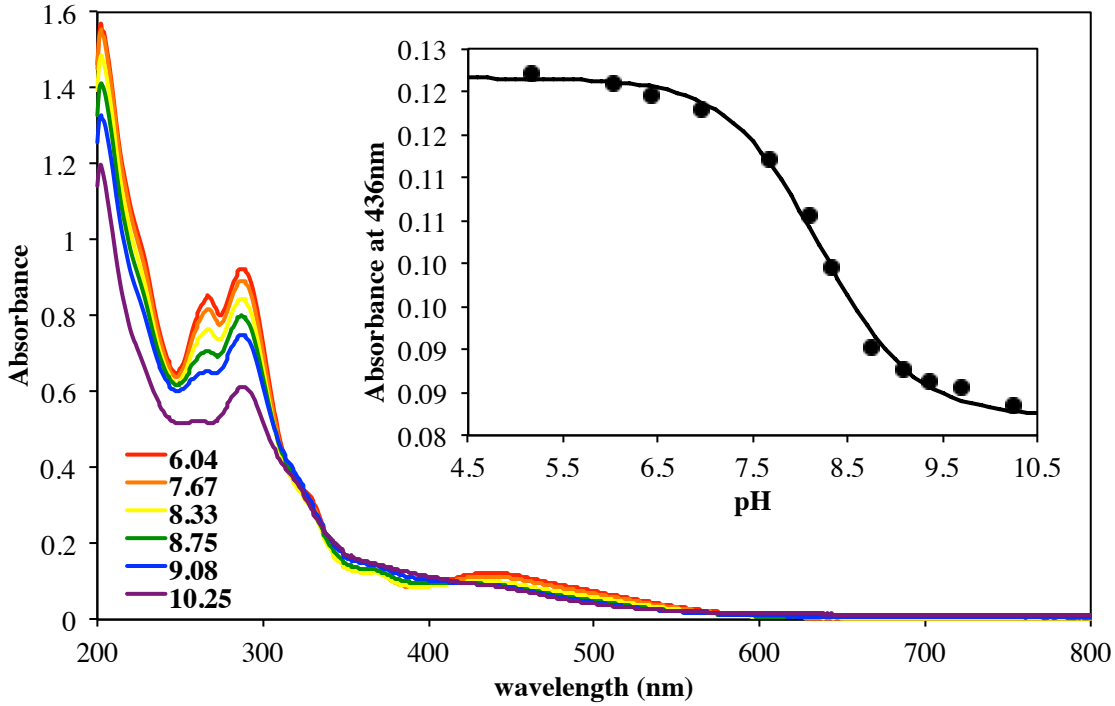

Figure S8: A pH titration of the metalloinsertor $[Rh(DIP)(chrysi)(PPO)]^{2+}$. Absorption spectra as the pH changes from 6.04 to 10.25 are shown, and the inset show the absorbance at 436nm vs pH and fit to a sigmoidal curve.

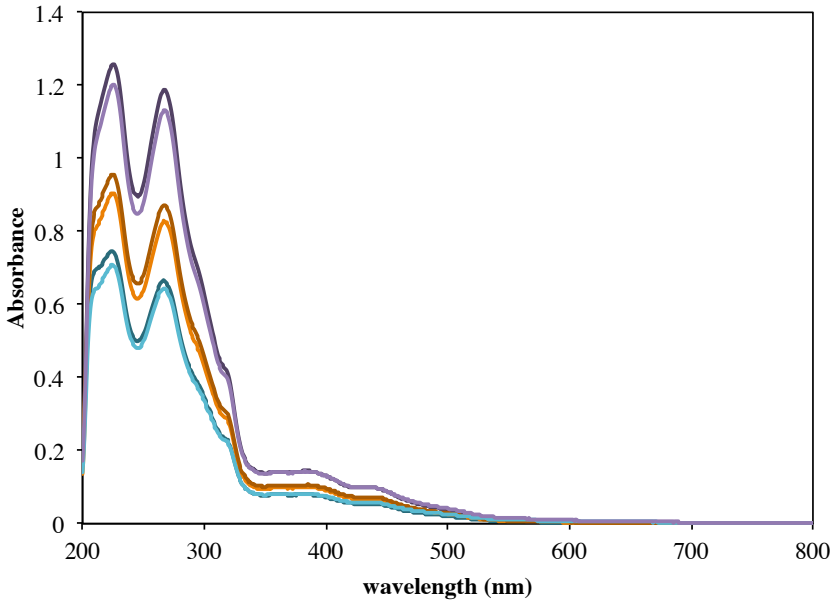

Figure S9: Absorption spectrum of $[Rh(phen)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade.

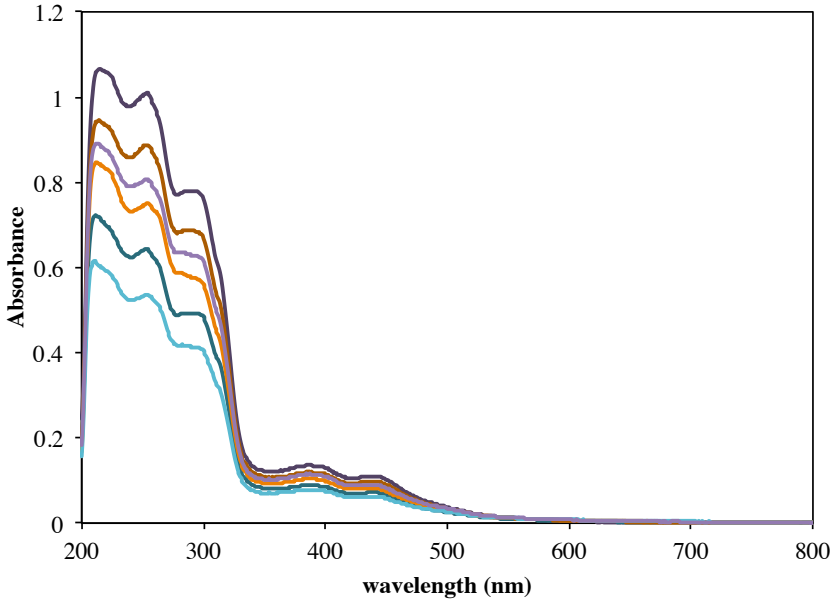

Figure S10: Absorption spectrum of $[Rh(bpy)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade.

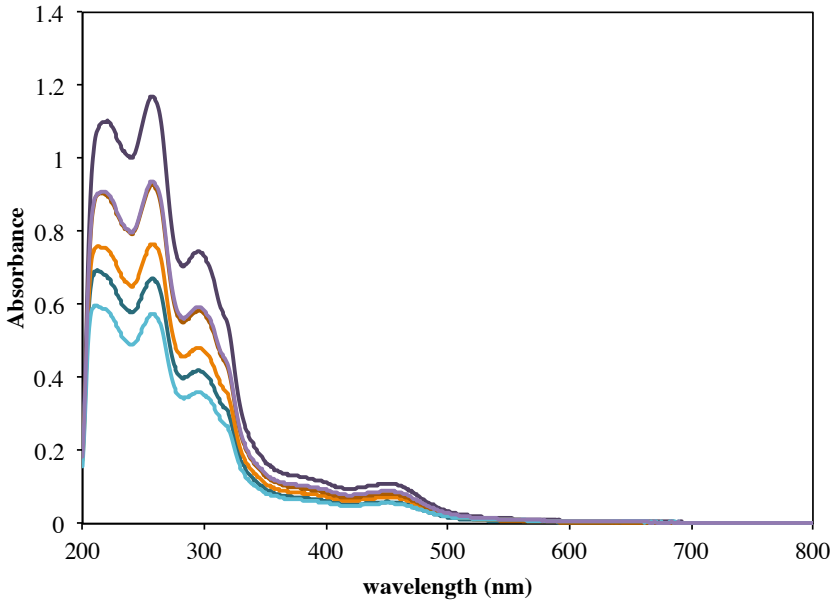

Figure S11: Absorption spectrum of $[Rh(HDPA)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade.

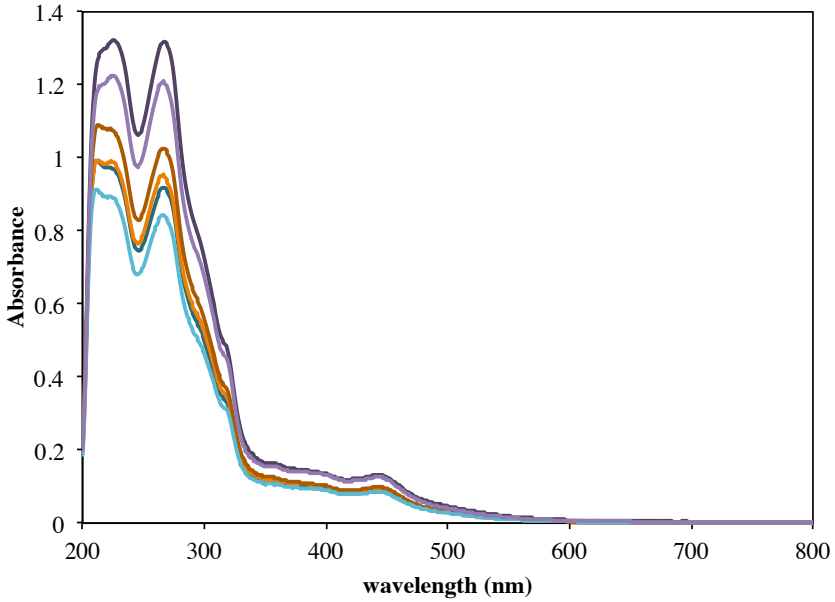

Figure S12: Absorption spectrum of $[Rh(4,7\text{-}DMP)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade.

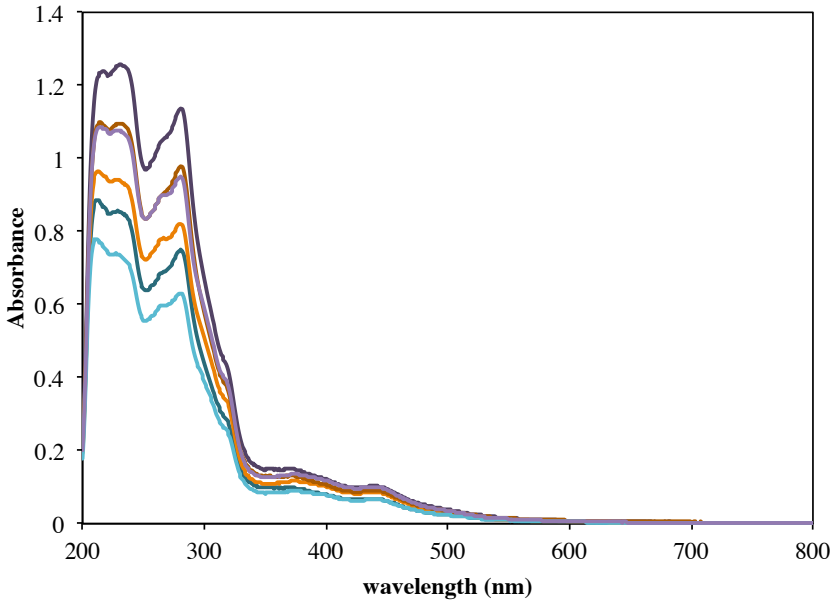

Figure S13: Absorption spectrum of $[Rh(5,6\text{-}DMP)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade.

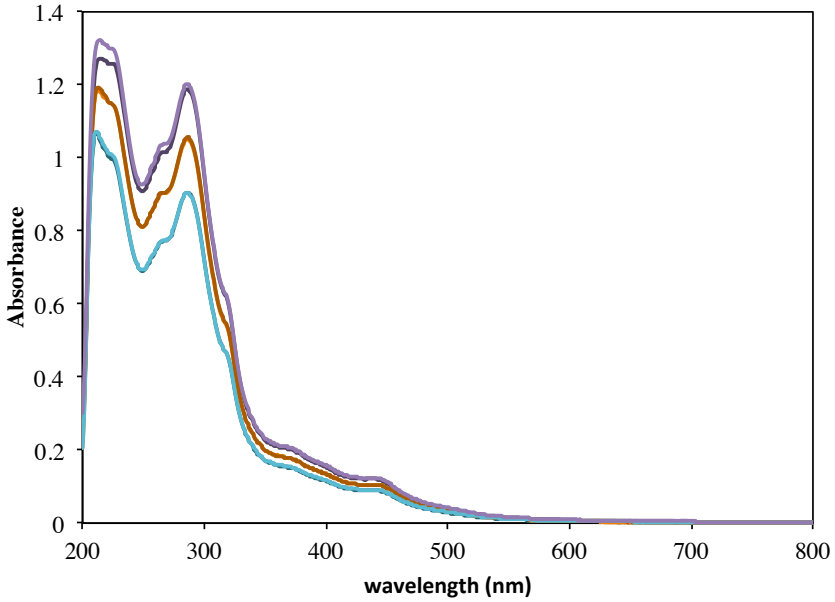

Figure S14: Absorption spectrum of $[Rh(DIP)(chrysi)(PPO)]^{2+}$ in 1-octanol before and after equilibration with aqueous solution (pH 7.4) with replicates taken at three different concentrations. Each replicate set (before and after trace) is shown as a different color (purple, orange, or blue) with the before trace shown in a darker shade and the after trace shown in the lighter shade. Note that the before and after spectra essentially overlap, therefore the log P value could not be accurately determined.

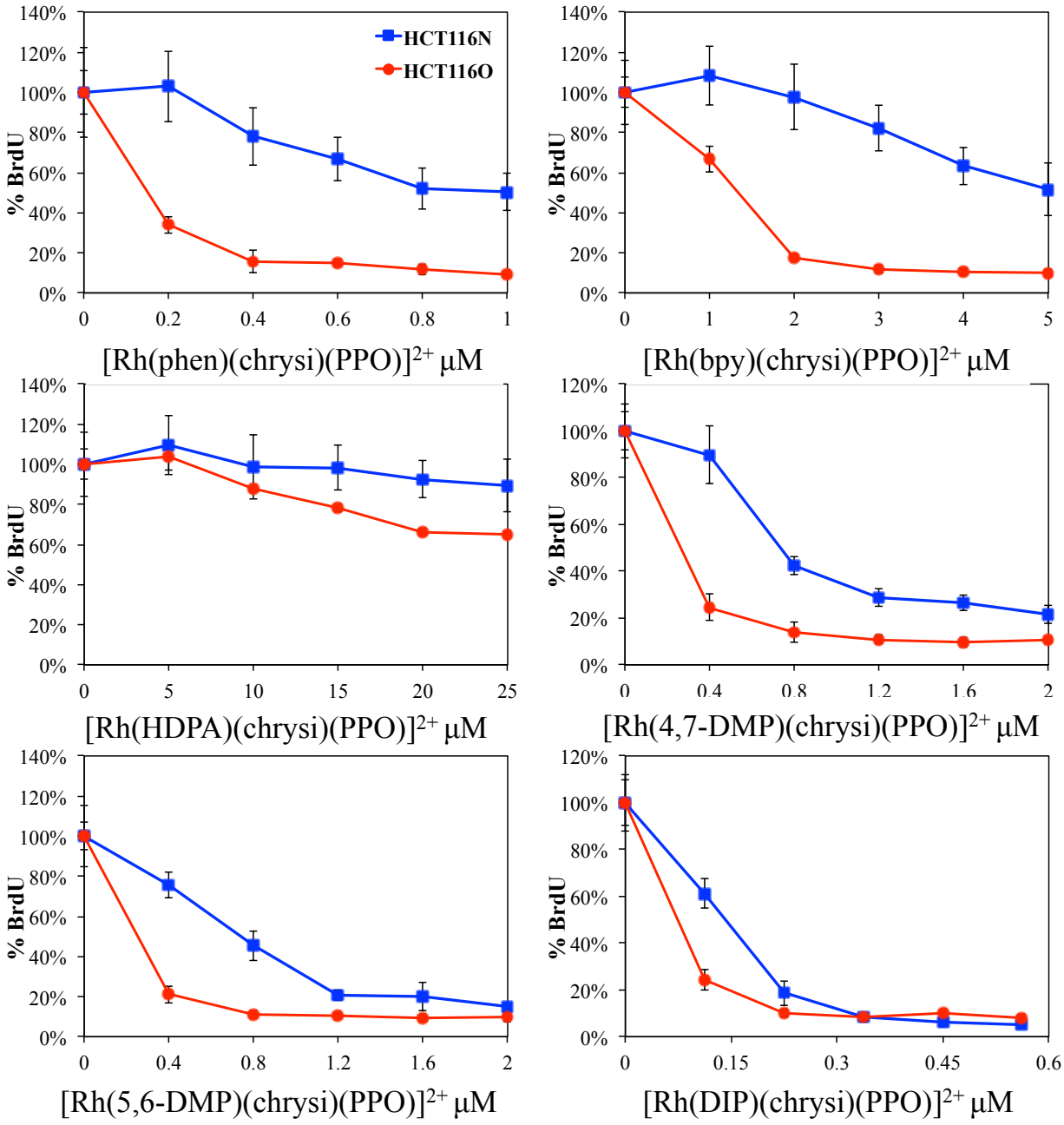

Figure S15: Cellular proliferation ELISA for the [Rh(L)(chrysi)(PPO)]$^{2+}$ metalloinsertors. Cells were incubated with various concentrations of metalloinsertor for 24 hours before treatment with BrdU. Cell proliferation is shown as %BrdU incorporated into DNA compared to untreated control cells. Error is shown as the standard deviation of 5 replicates.

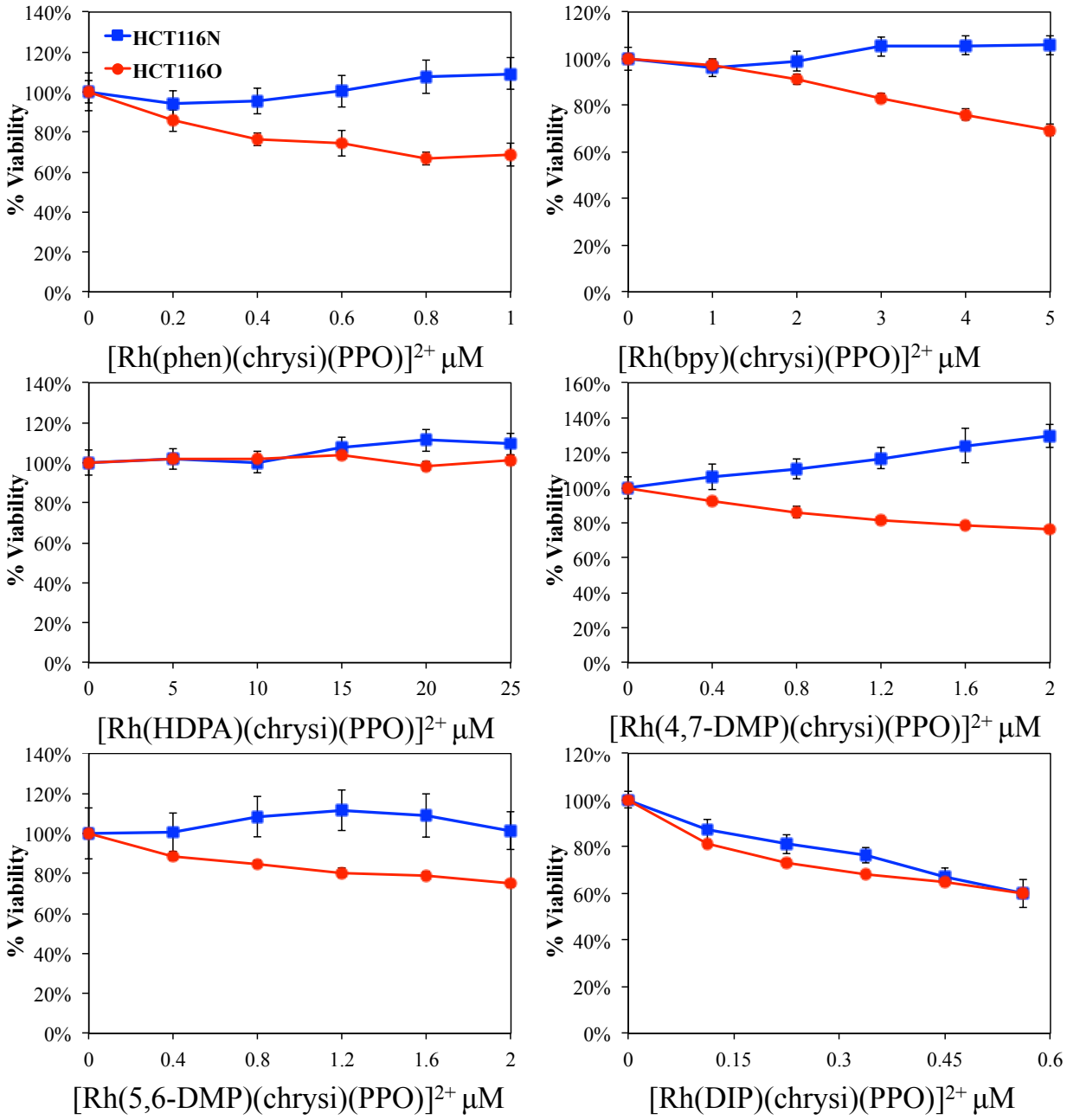

Figure S16: Cellular viability MTT assay for the [Rh(L)(chrysi)(PPO)]$^{2+}$ metalloinsertors. Cells were incubated with various concentrations of metalloinsertor for 24 hours before treatment with MTT. Cell proliferation is shown as %viability (from MTT metabolism), compared to untreated control cells. Error is shown as the standard deviation of 5 replicates.

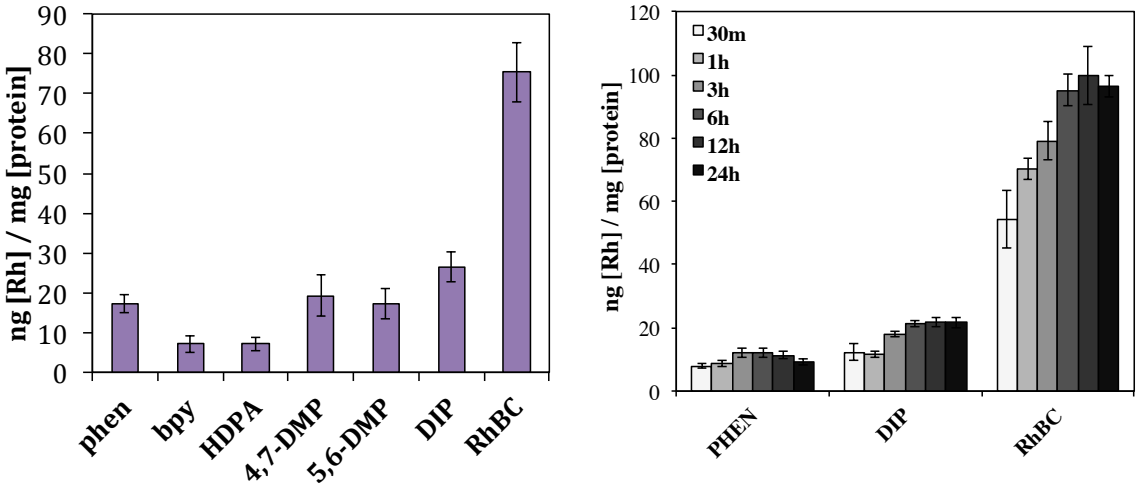

Figure S17: Whole-cell rhodium uptake assays. (*left*) Rhodium accumulation in HCT116N was measured by ICP-MS analysis after a 24 hour incubation with [Rh(**L**)(chrysi)(PPO)]$^{2+}$ metalloinsertors (where **L** = **phen**, **bpy**, **HDPA**, **4,7-DMP**, **5,6-DMP**, or **DIP**) or the parent metalloinsertor [Rh(bpy)$_2$(chrysi)]$^{3+}$ (**RhBC**). (*right*) Rhodium accumulation over time in HCT116N cells was measured by ICP-MS for three metalloinsertors, [Rh(phen)(chrysi)(PPO)]$^{2+}$ (**phen**), [Rh(DIP)(chrysi)(PPO)]$^{2+}$ (**DIP**), and the parent metalloinsertor [Rh(bpy)$_2$(chrysi)]$^{3+}$ (**Rh-BC**). Rhodium content was normalized to protein content determined by BCA assay, and the results of four independent trials were averaged with error shown as the standard deviation.

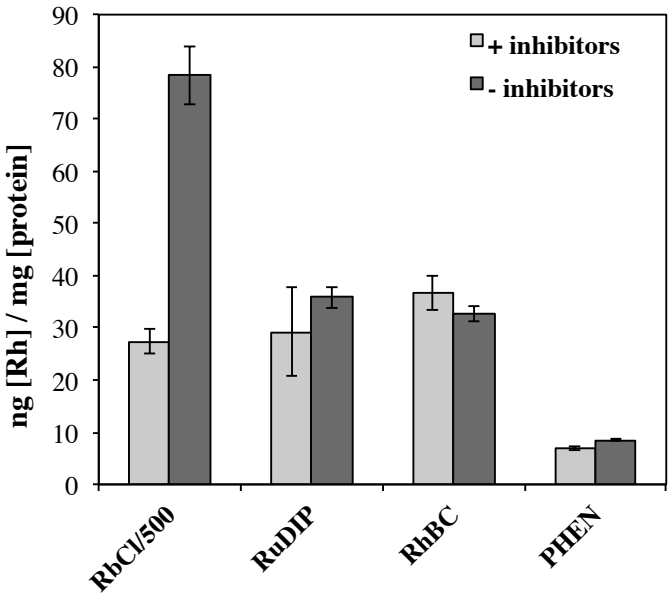

Figure S18: Uptake assay for rhodium metalloinsertors and controls. $[Rh(phen)(chrysi)(PPO)]^{2+}$ (**phen**), $[Rh(bpy)_2(chrysi)]^{3+}$ (**RhBC**), $[Ru(DIP)_2(chrysi)]^{2+}$ (**RuDIP**), and **RbCl** accumulation in HCT116N cells was measured by ICP-MS analysis after treatment with or without metabolic inhibitors (oligomycin and 2-deoxy-D-glucose). Rhodium, ruthenium, and rubidium contents were normalized to protein content determined by BCA assay. Each experiment was performed in triplicate and averaged, with error shown as the standard deviation. Each experiment was repeated three times with similar outcomes (not shown). RbCl/500 indicates that Rb concentrations for RbCl have been lowered by a factor of 500 in this graphic.

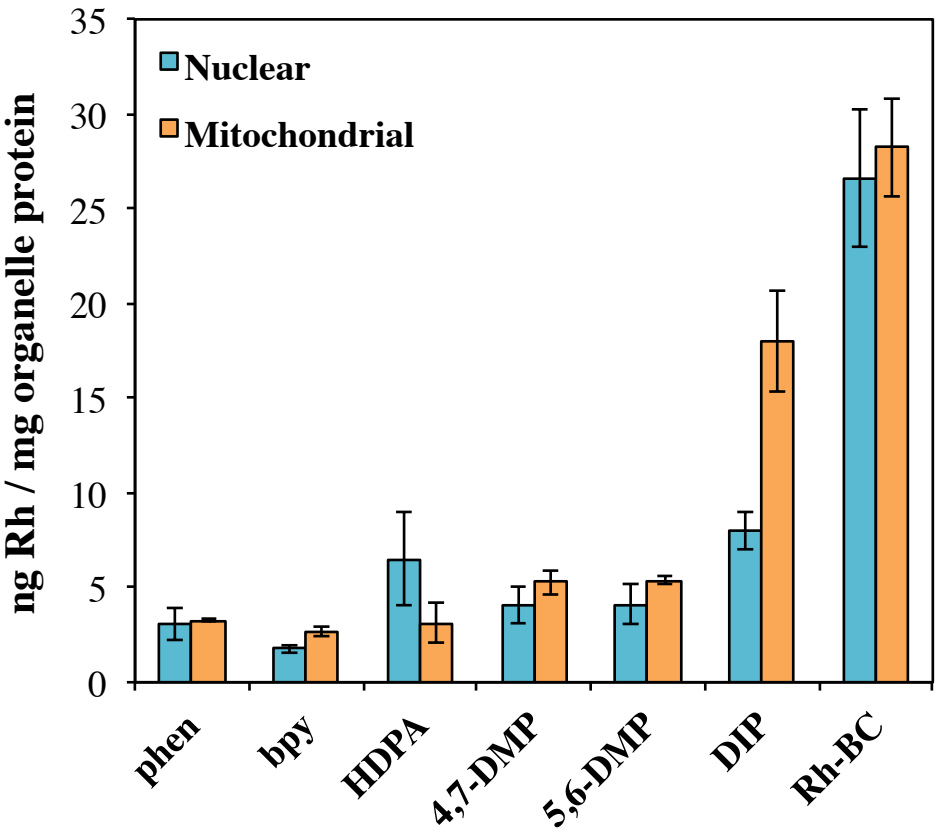

Figure S19: ICP-MS assay for nuclear and mitochondrial uptake of rhodium metalloinsertors. Rhodium accumulation in HCT116N cells was measured by ICP-MS analysis after a 24 hour incubation with $[Rh(\mathbf{L})(chrysi)(PPO)]^{2+}$ (where **L** = **phen**, **bpy**, **HDPA**, **4,7-DMP**, **5,6-DMP** or **DIP**) or the parent metalloinsertor $[Rh(bpy)_2(chrysi)]^{3+}$ (**Rh-BC**). Rhodium content was normalized to protein content of each organelle fraction determined by BCA assay. The results of 4 independent studies were averaged and error is shown as the standard deviation.

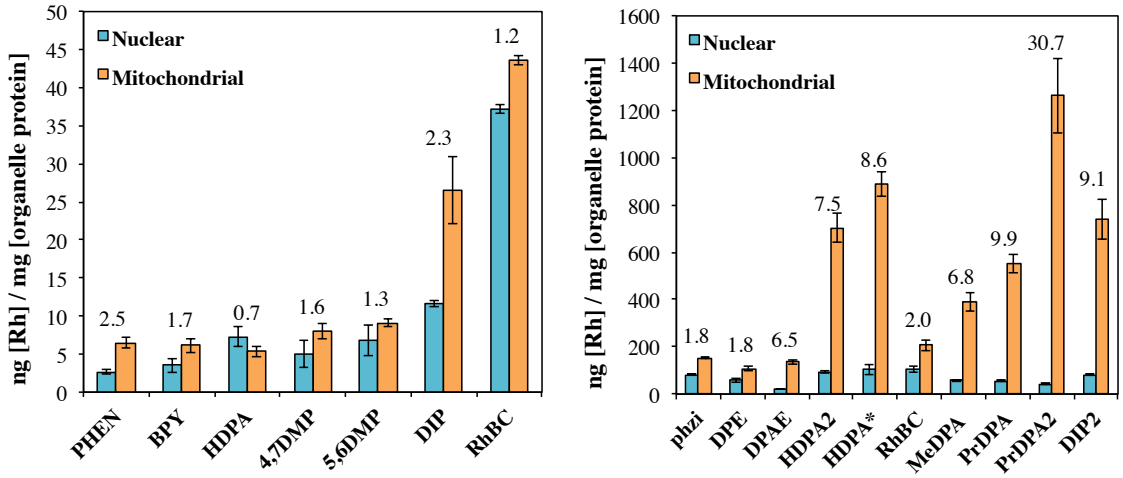

Figure S20: ICP-MS assay for nuclear and mitochondrial uptake or rhodium metalloinsertors. Rhodium accumulation in HCT116O cells was measured by ICP-MS analysis after a 24 hour incubation with $[Rh(\mathbf{L})(chrysi)(PPO)]^{2+}$ (where **L** = **phen**, **bpy**, **HDPA**, **4,7-DMP**, **5,6-DMP** or **DIP**) or the parent metalloinsertor $[Rh(bpy)_2(chrysi)]^{3+}$ (**RhBC**), a control (*left*) and comparison to a similar study on different metalloinsertors from reference [1] (dosed at 10 μM for all but DIP2, 2 μM for DIP2) (*right*). Rhodium content was normalized to protein content of each organelle fraction determined by BCA assay. The ratio of mitochondrial uptake (in ng[Rh]/mg[mitochondrial protein]) to nuclear uptake (in ng [Rh]/mg [nuclear protein]) for each complex is shown above each data set. The results of 4 independent studies were averaged and error is shown as the standard deviation.

References:

(1) Komor, A. C.; Schneider, C. J.; Weidmann, A. G.; Barton, J. K. *J. Am. Chem. Soc.* **2012**, *134*, 19223–19233.

(2) Fujioka, A.; Terai, K.; Itoh, R. E.; Aoki, N.; Nakamura, T.; Kuroda, S.; Nishida, E.; Matsuda, M. *J. Biol. Chem.* **2006**, *281*, 8917– 8926.