Platinum(II) and Ruthenium(II) Coordination complexes equipped with an anchoring site for binding the protein kinase enzyme pockets: synthesis, molecular docking and biological assays.

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^{1}H, ^{13}C NMR spectra and ESI-MS spectra of the synthesized complexes

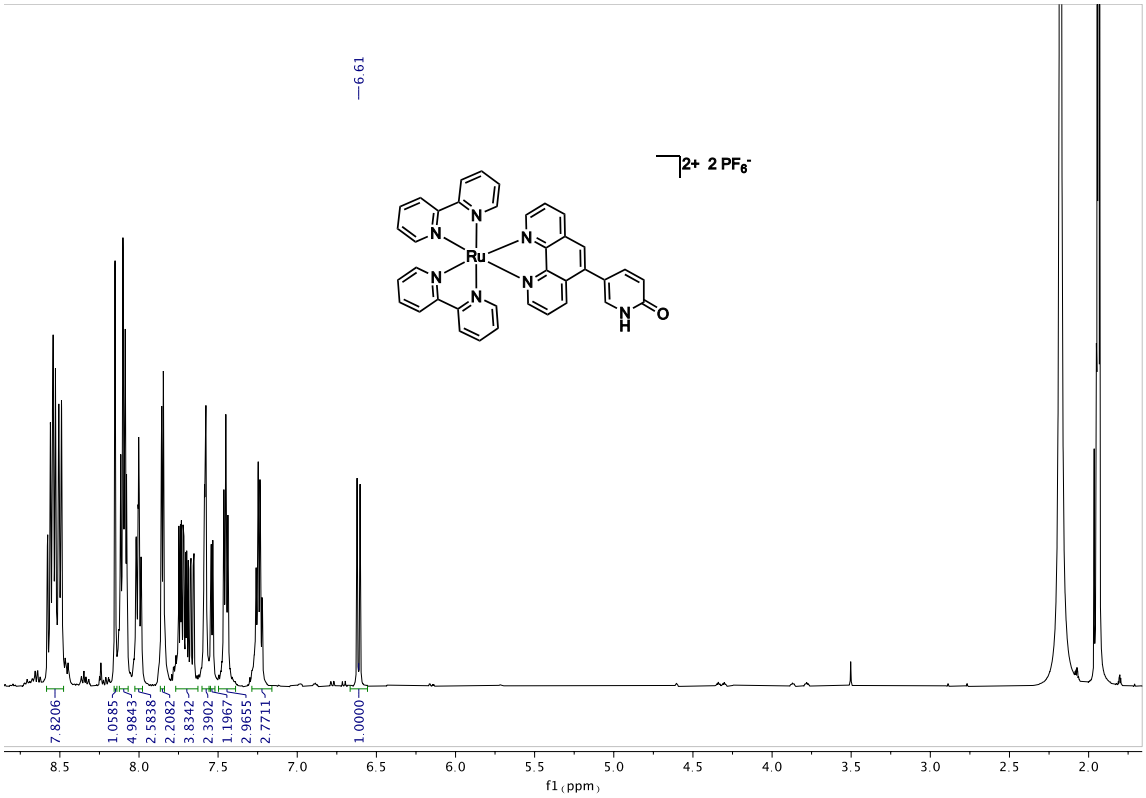


Figure S1. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Ru(1)**

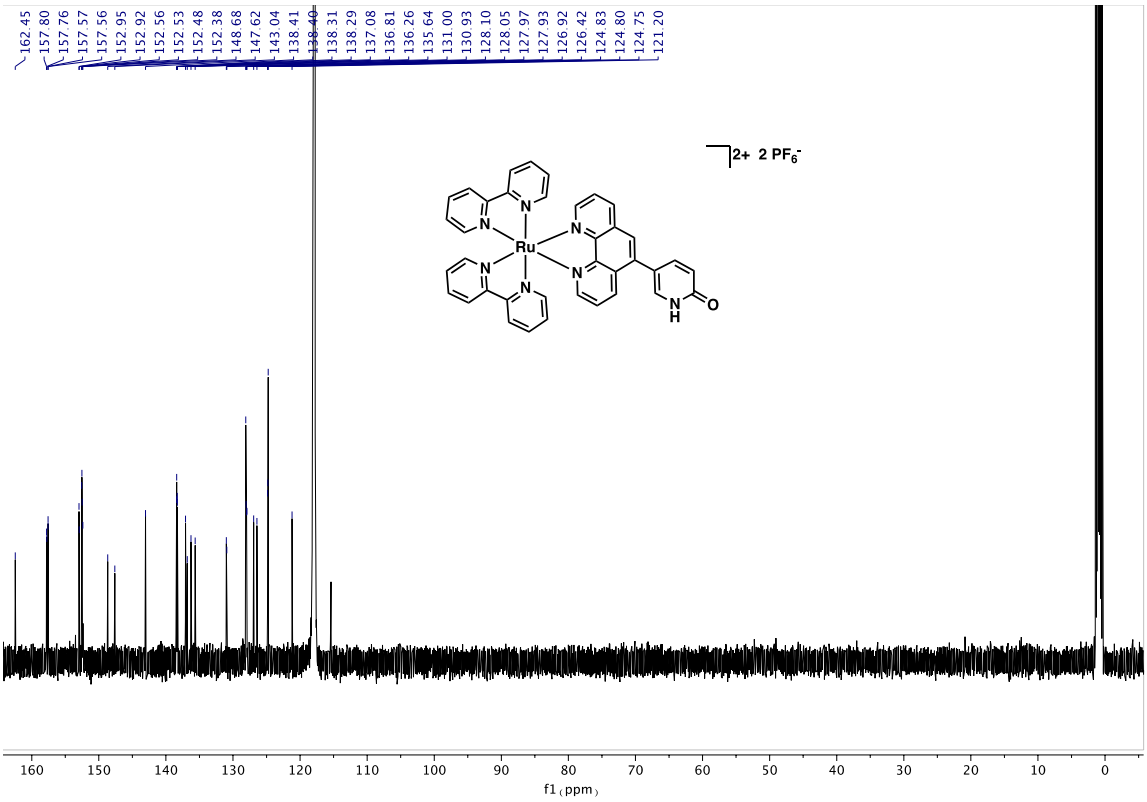


Figure S2. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Ru(1)**

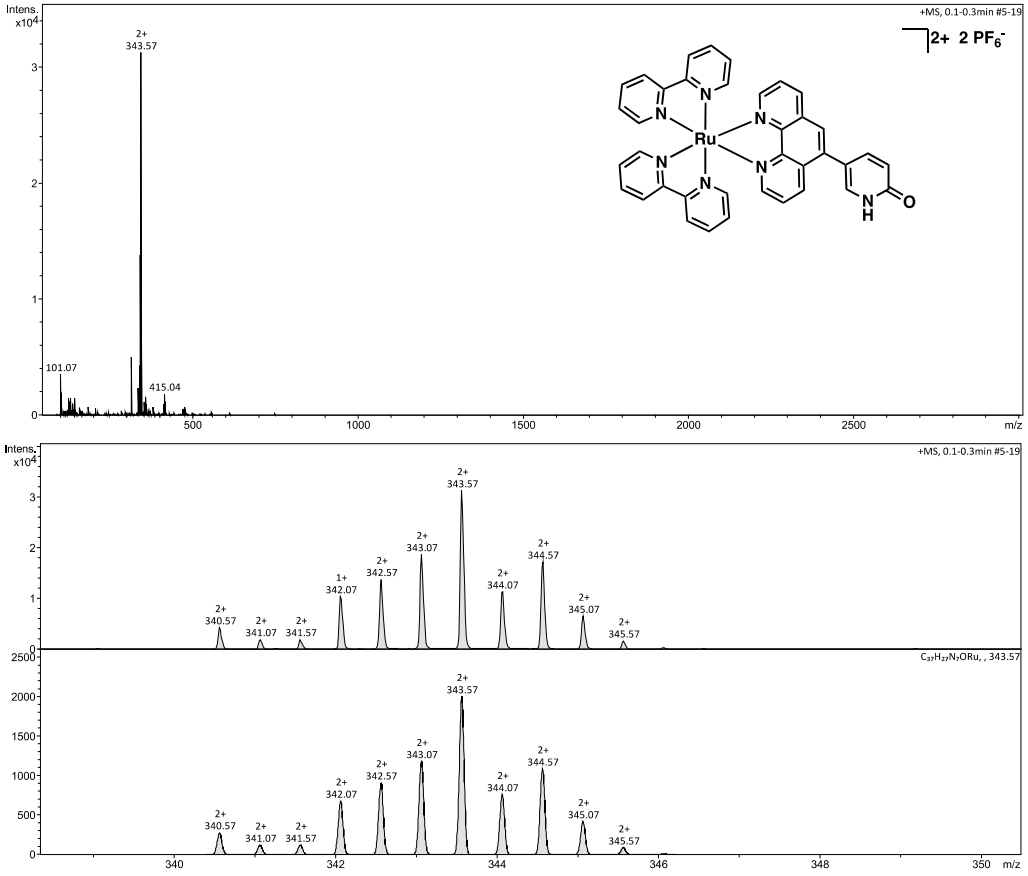


Figure S3. ESI-MS spectrum + simulated spectrum and close-up of **Ru(1)**

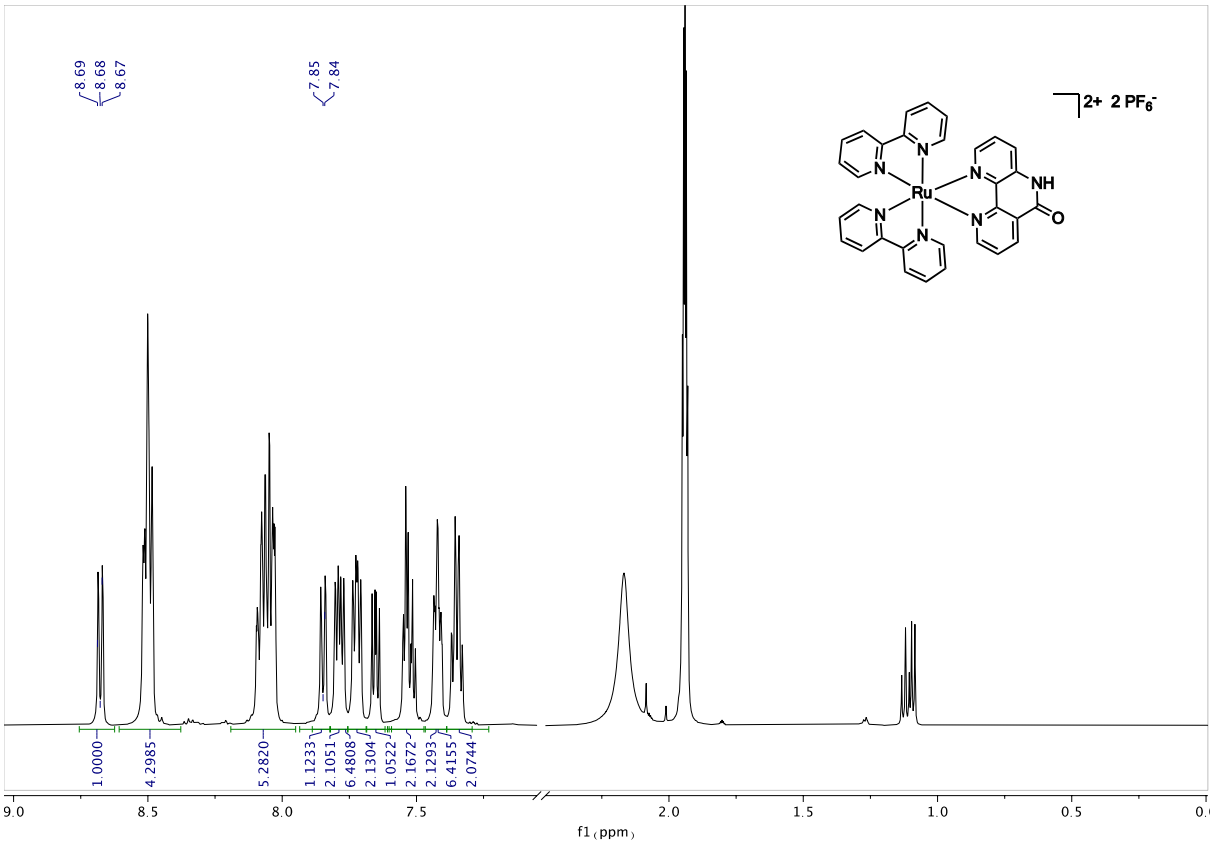


Figure S4. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Ru(2)**

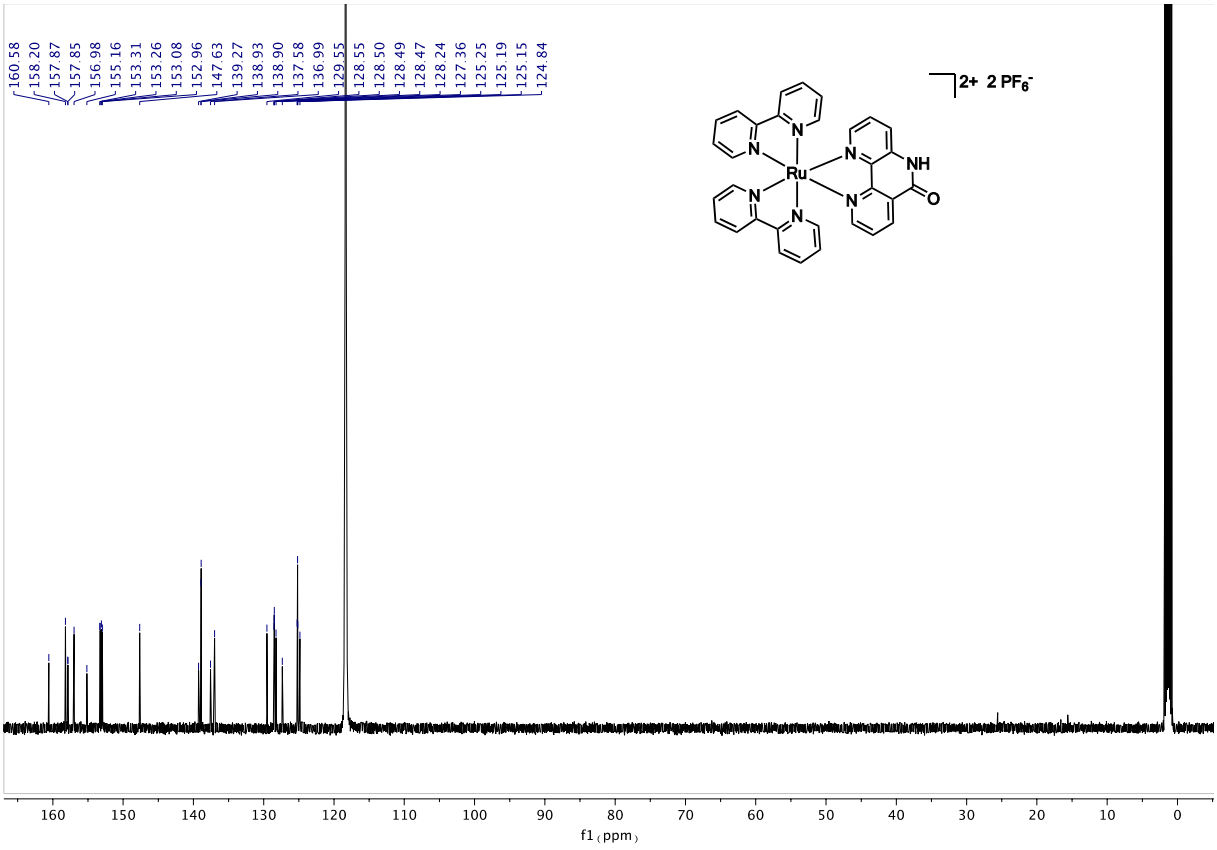


Figure S5. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Ru(2)**

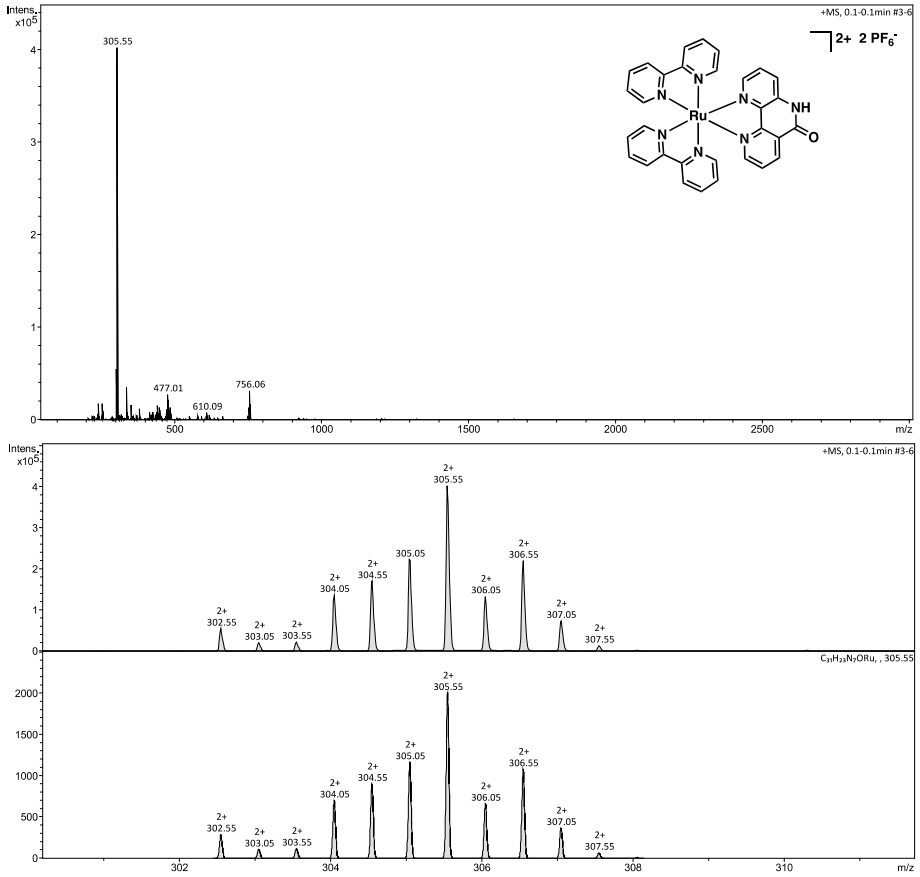


Figure S6. ESI-MS spectrum + simulated spectrum and close-up of **Ru(2)**

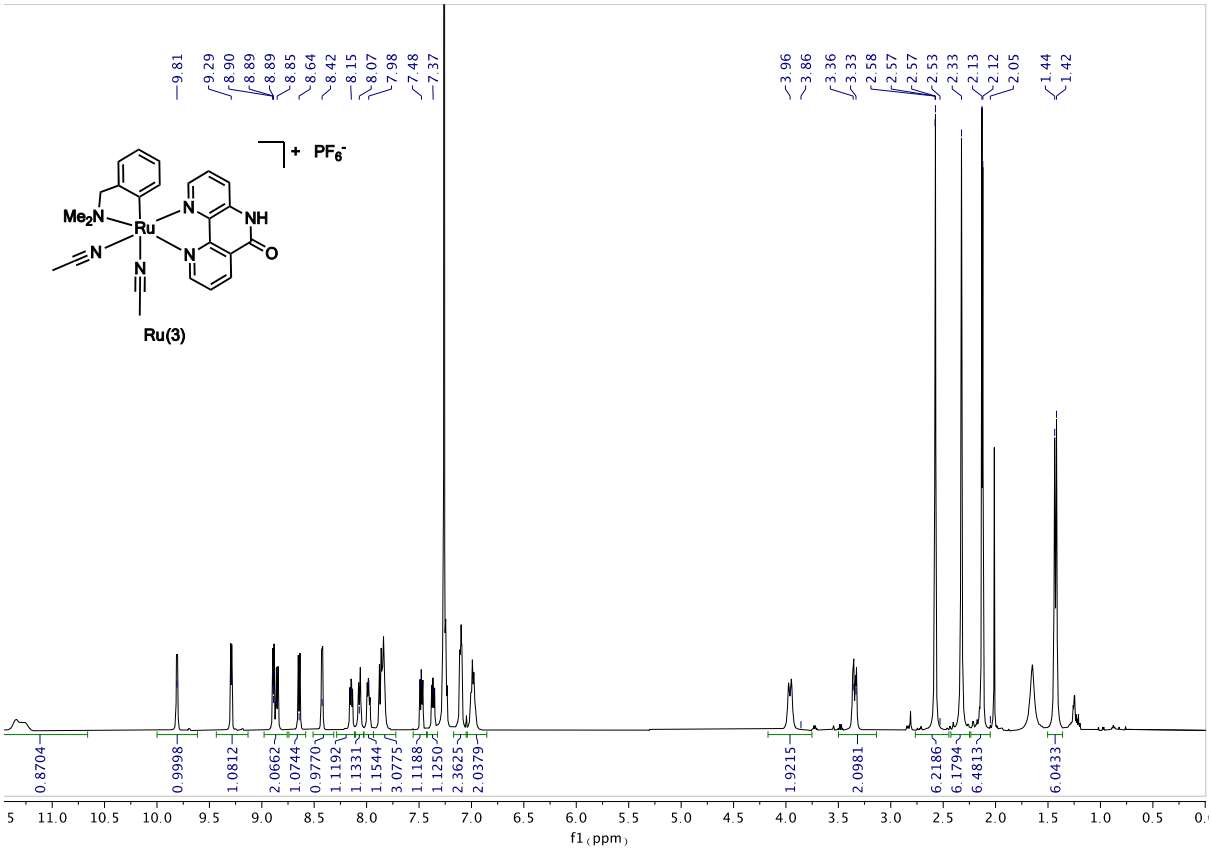


Figure S7. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of **Ru(3)**

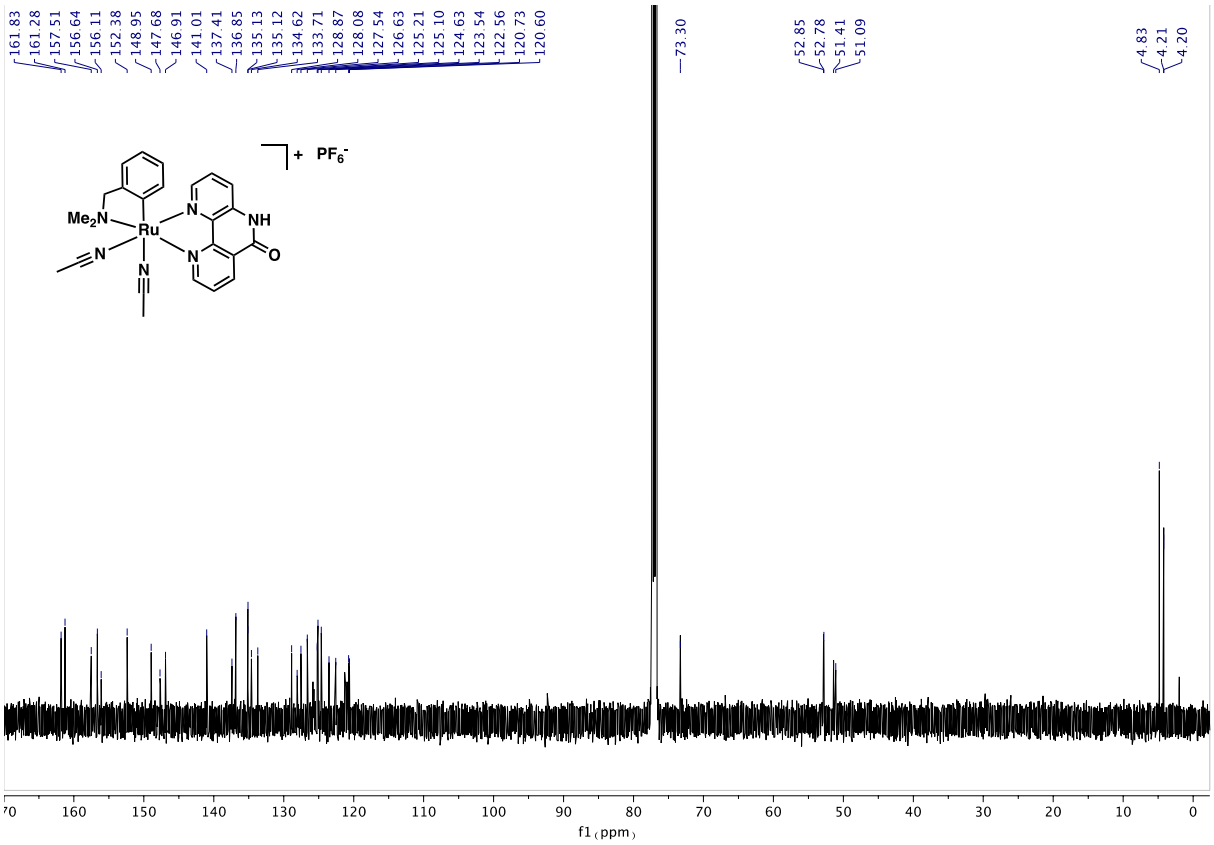


Figure S8. ^{13}C NMR spectrum ($CDCl_3$, 126 MHz) of **Ru(3)**

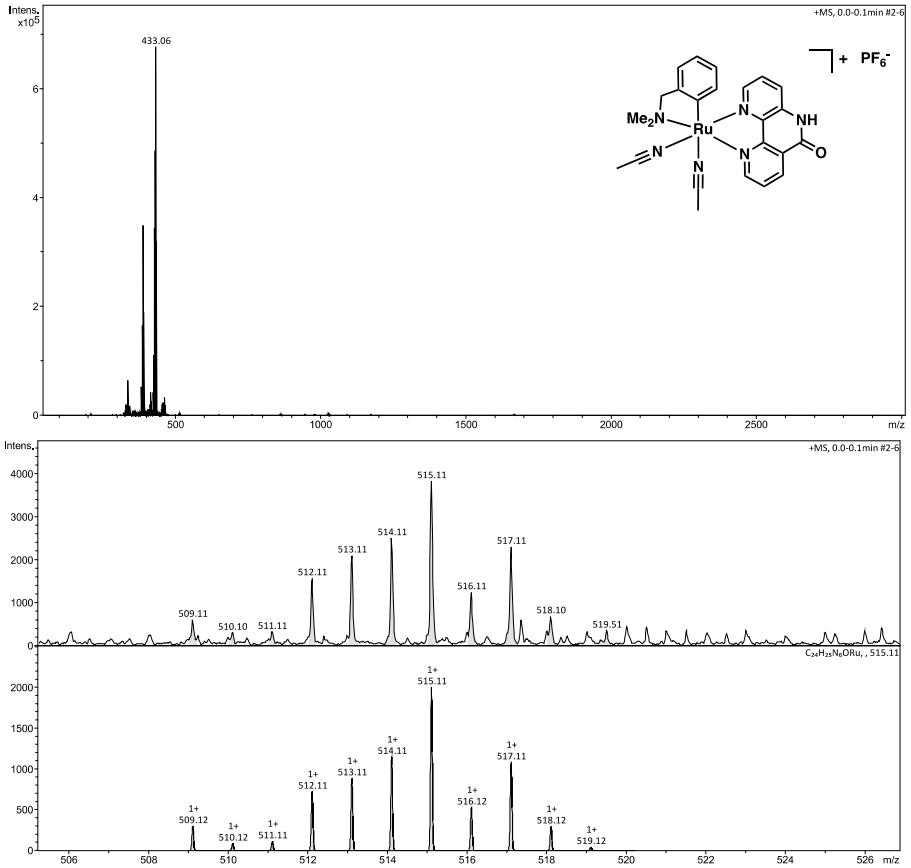


Figure S9. ESI-MS spectrum + simulated spectrum and close-up of **Ru(3)**

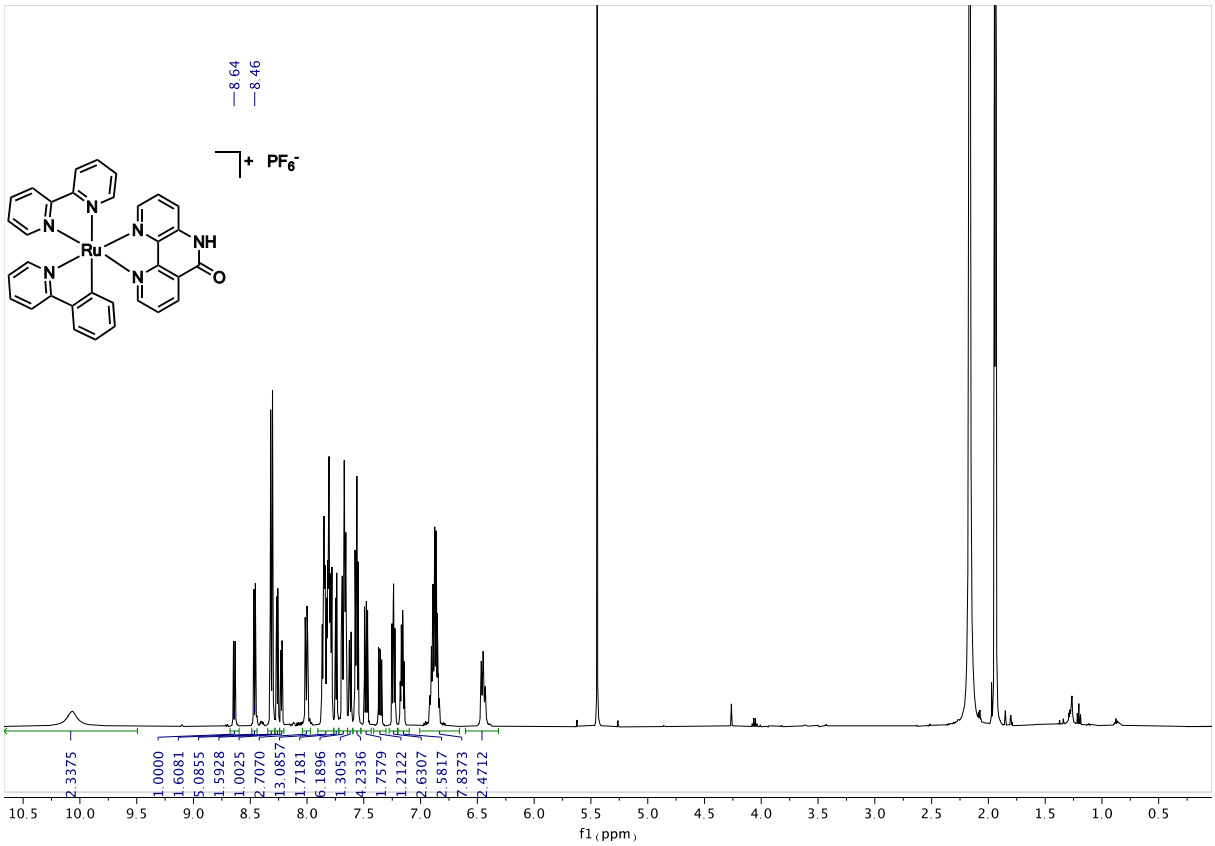


Figure S10. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Ru(4)**

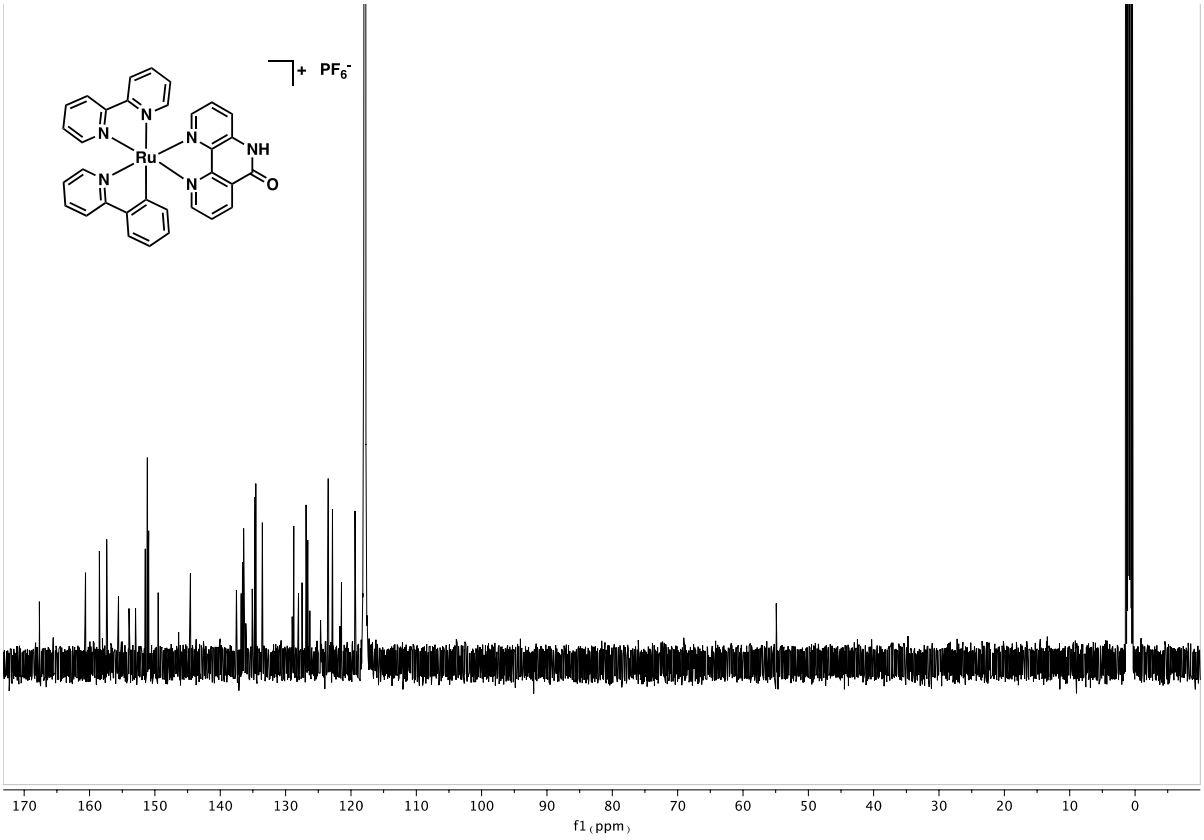


Figure S11. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Ru(4)**

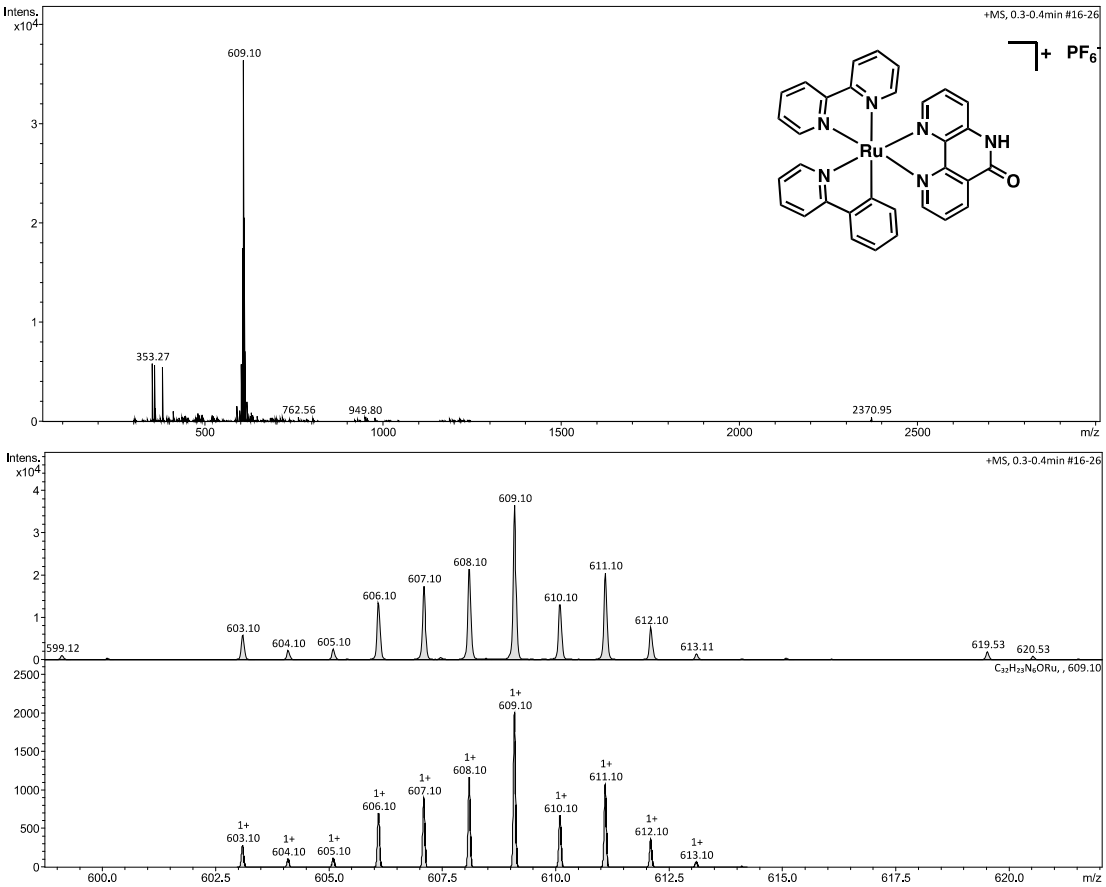


Figure S12. ESI-MS spectrum + simulated spectrum and close-up of **Ru(4)**

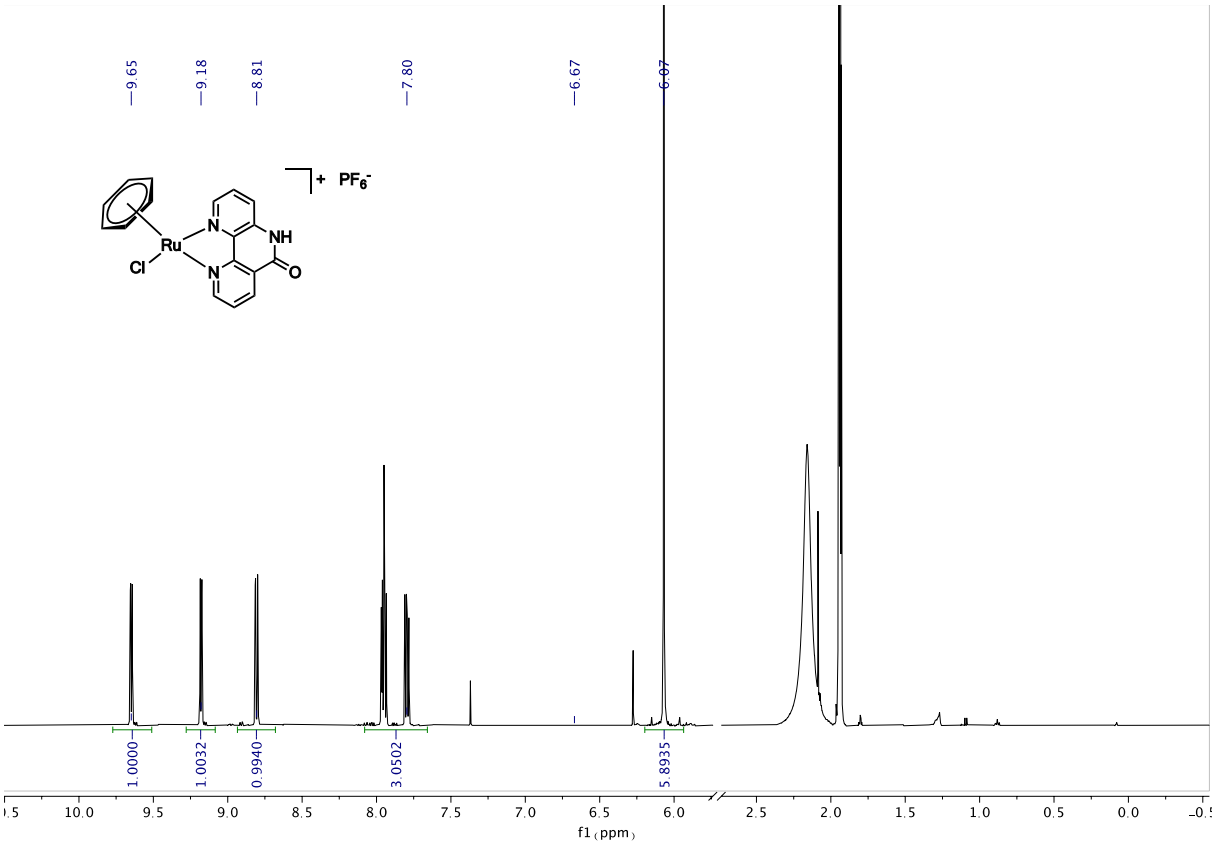


Figure S13. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Ru(5)**

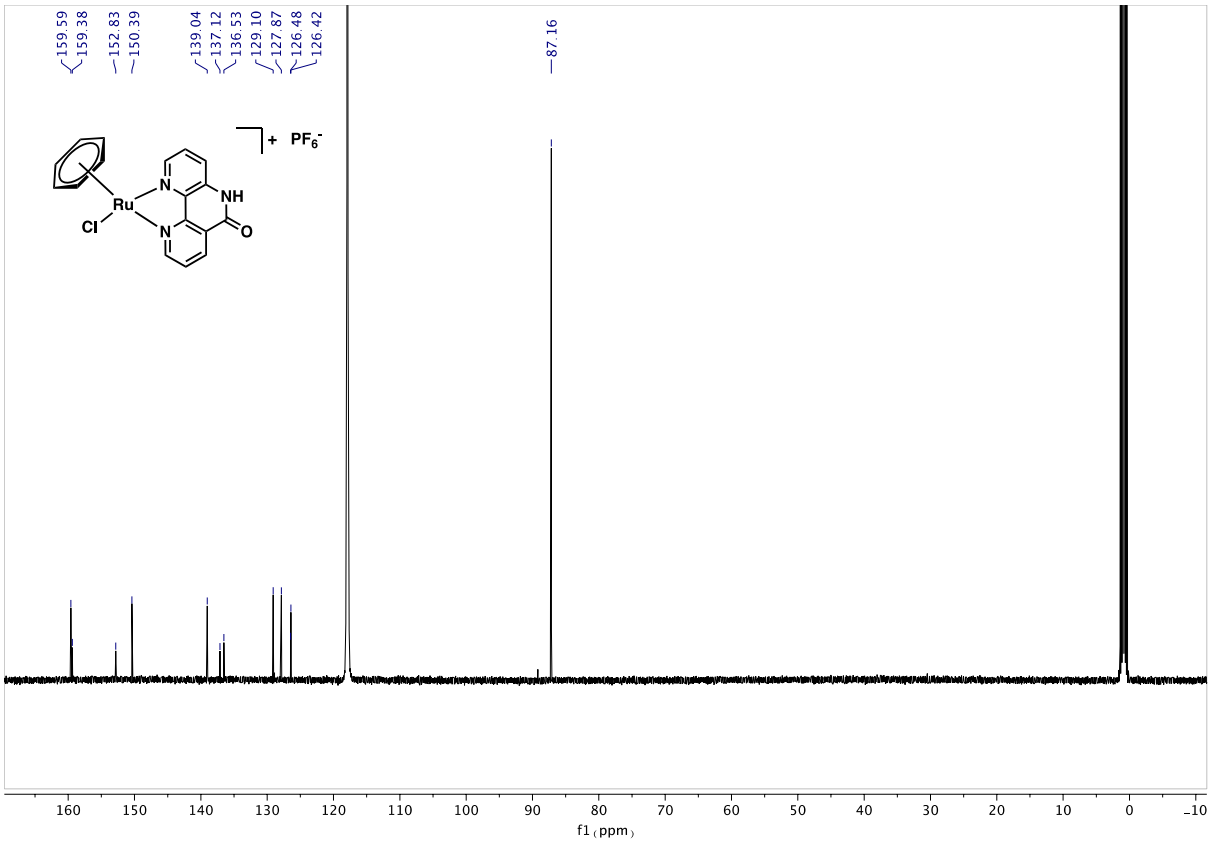


Figure S14. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Ru(5)**

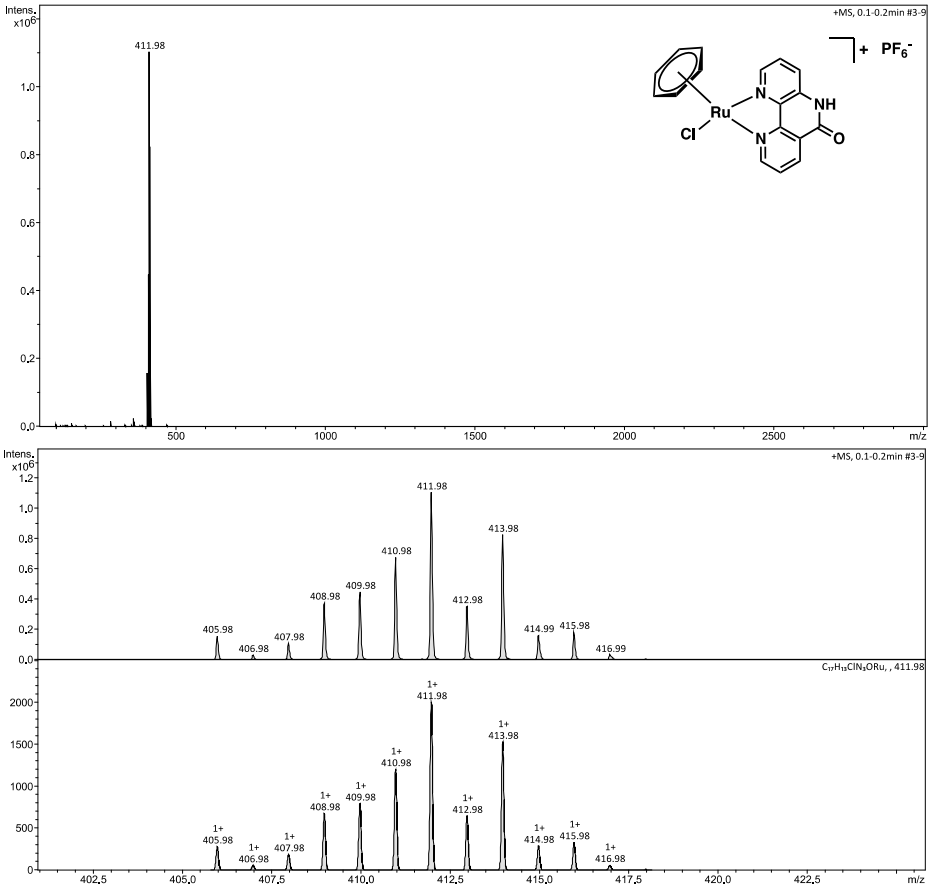


Figure S15. ESI-MS spectrum + simulated spectrum and close-up of **Ru(5)**

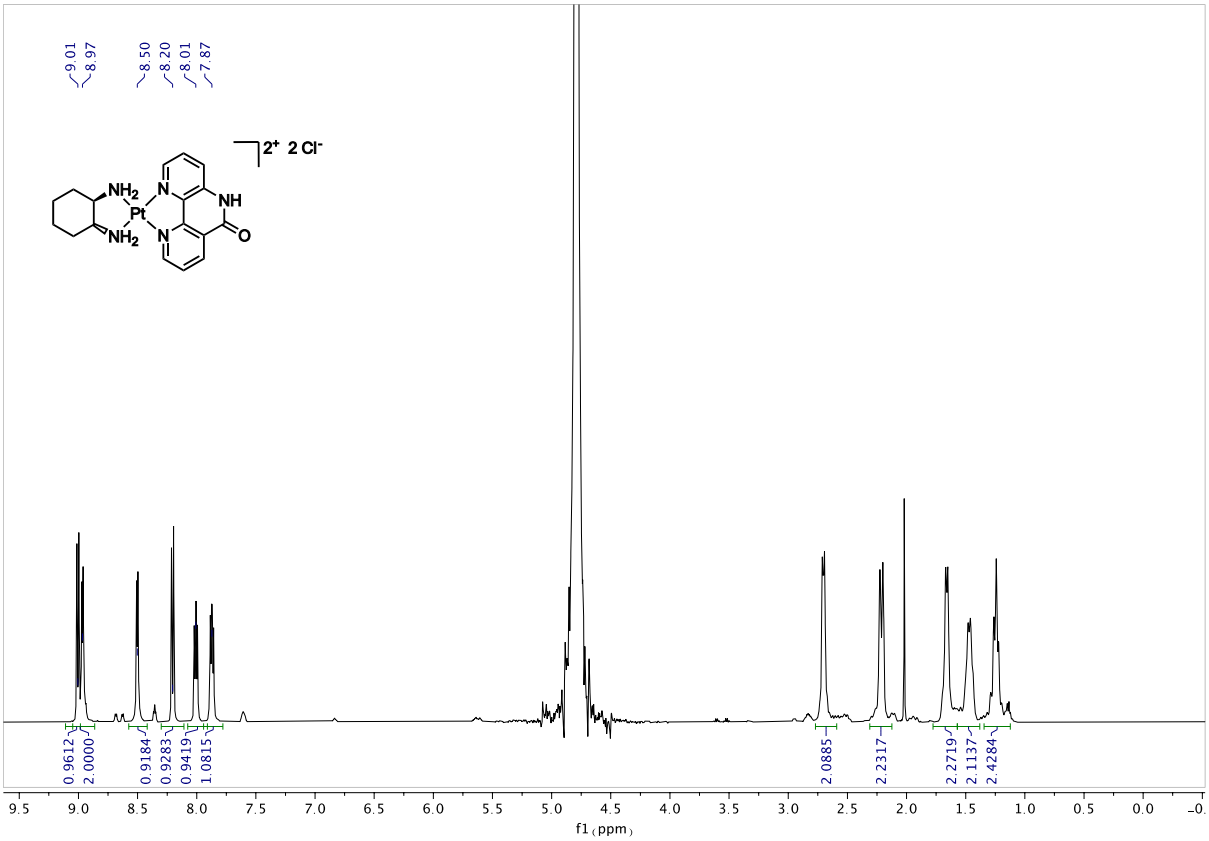


Figure S16. ^{1}H NMR spectrum (D_2O, 500 MHz) of **Pt(1)**

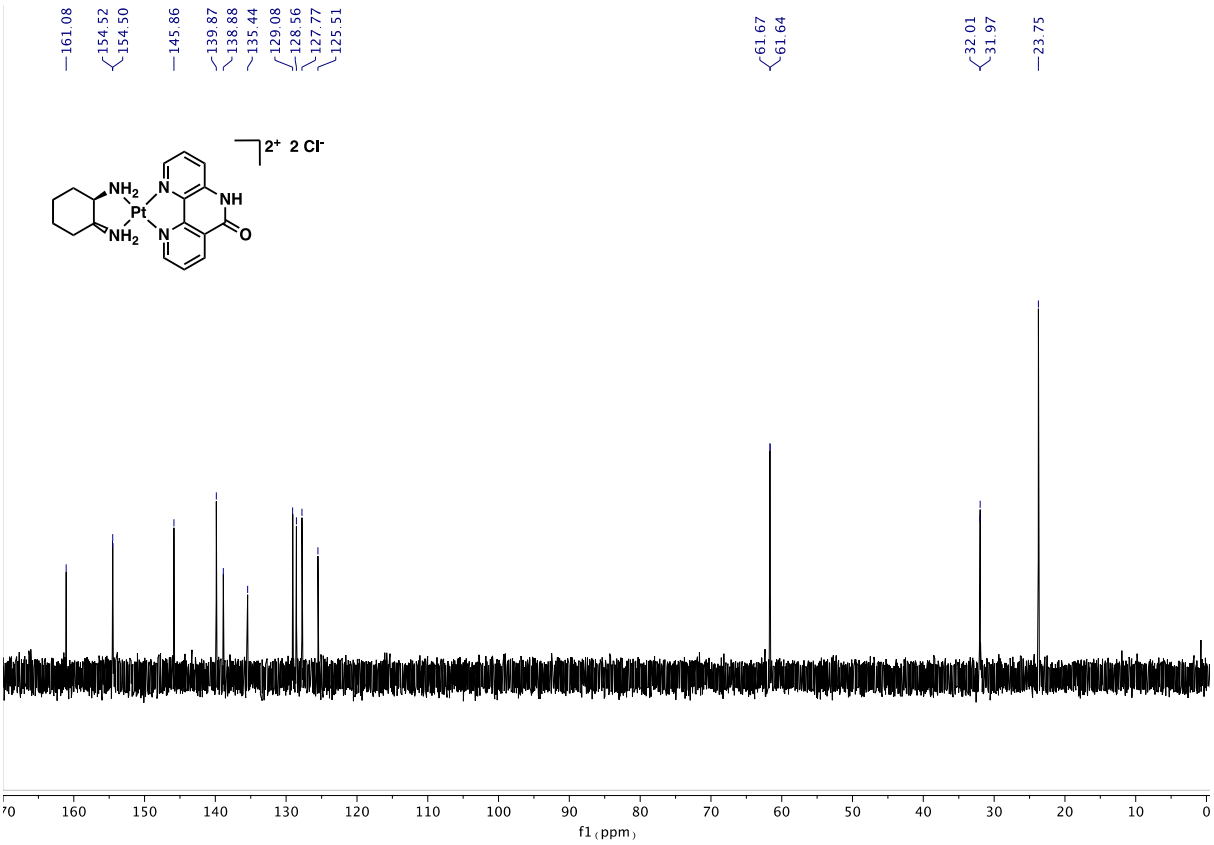


Figure S17. ^{13}C NMR spectrum (D_2O, 126 MHz) of **Pt(1)**

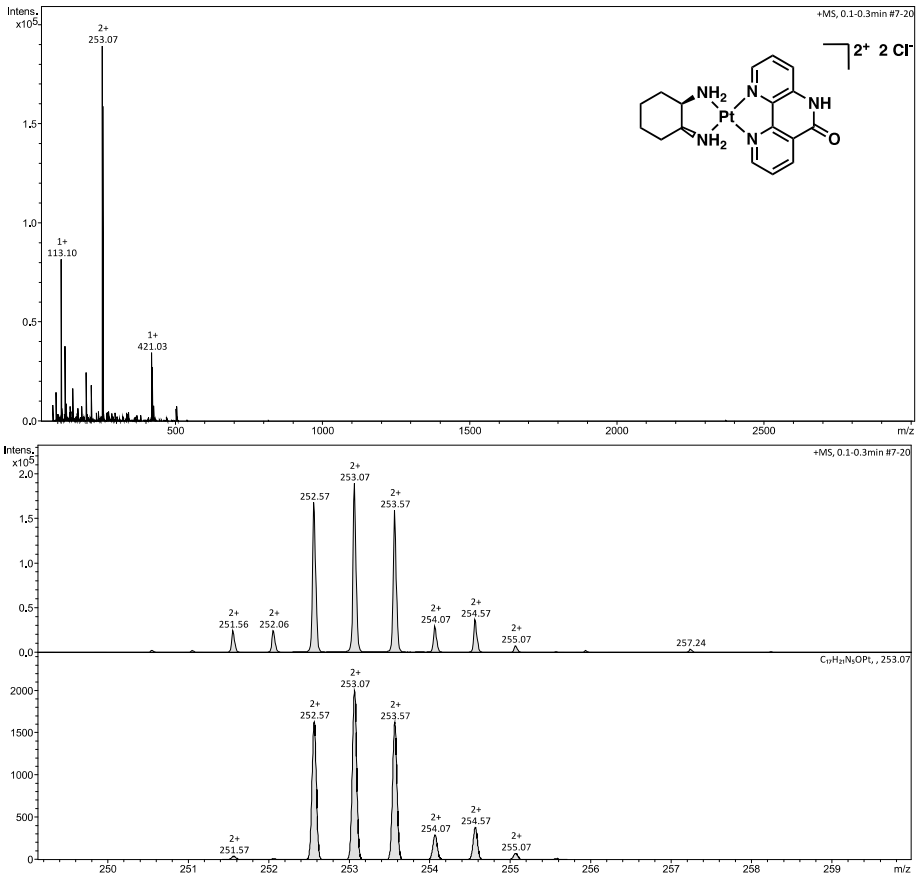


Figure S18. ESI-MS spectrum + simulated spectrum and close-up of **Pt(1)**

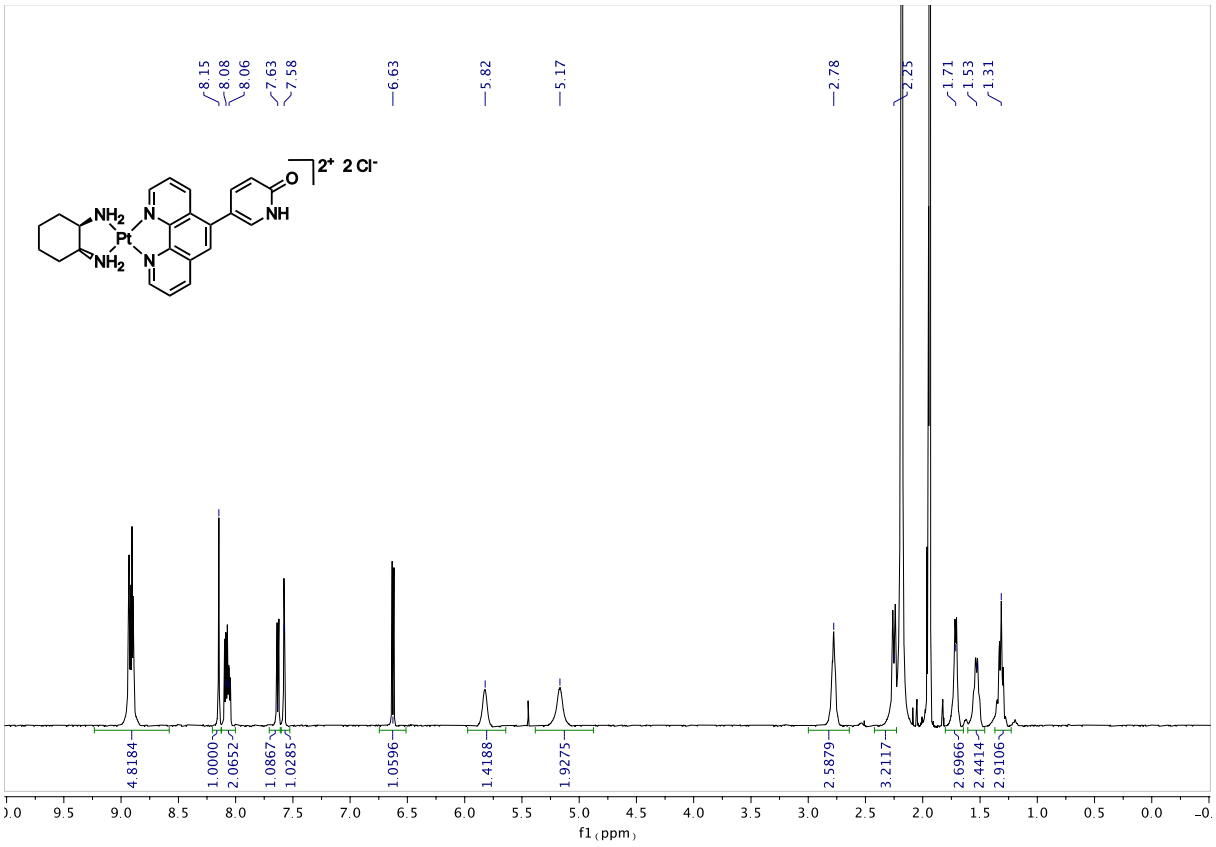


Figure S19. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Pt(2)**

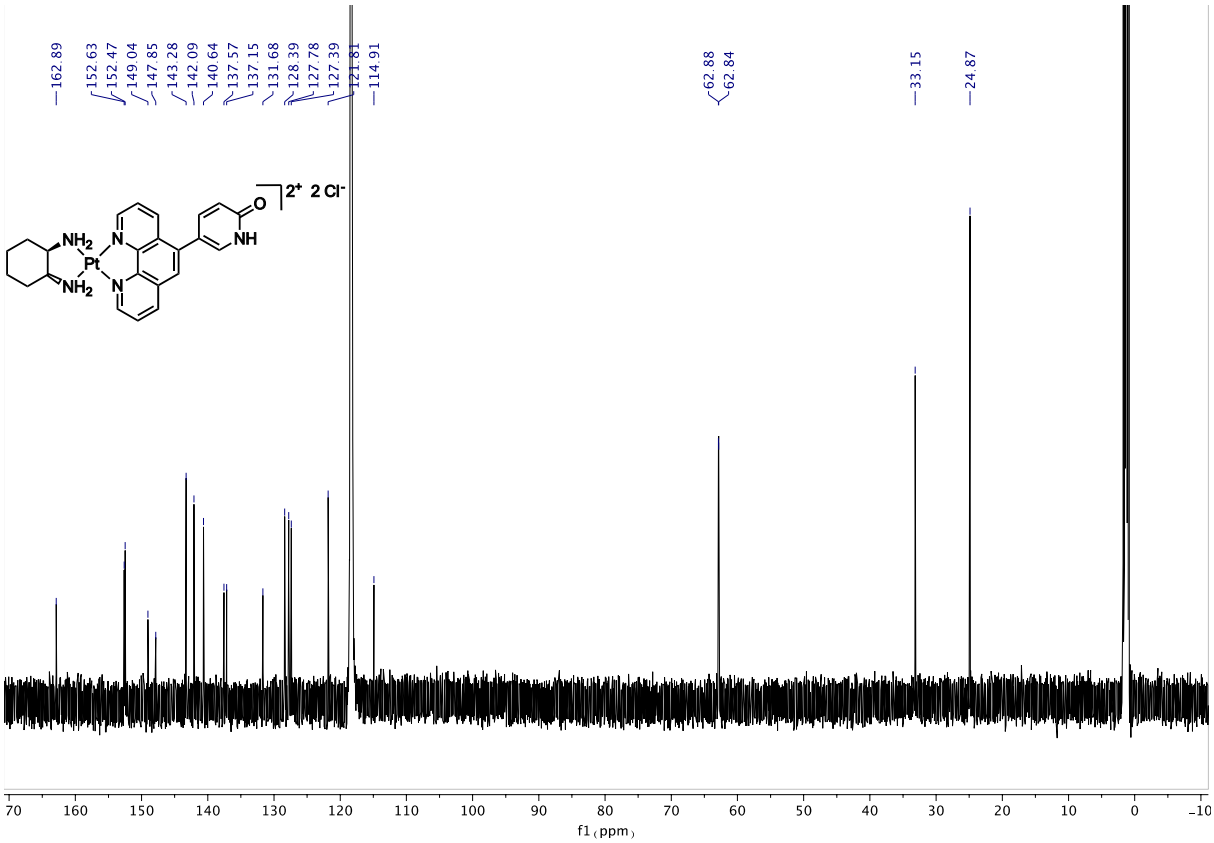


Figure S20. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Pt(2)**

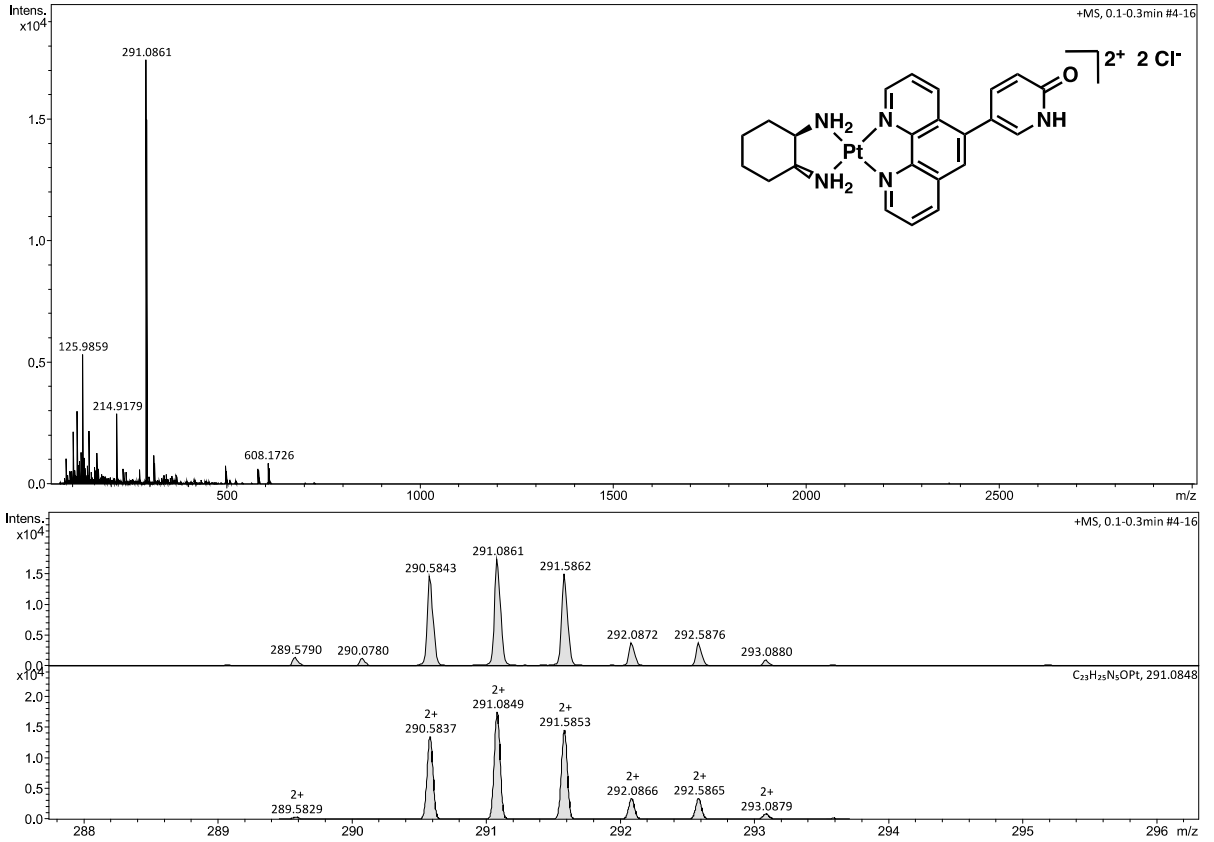


Figure S21. HR-MS spectrum + simulated spectrum and close-up of **Pt(2)**

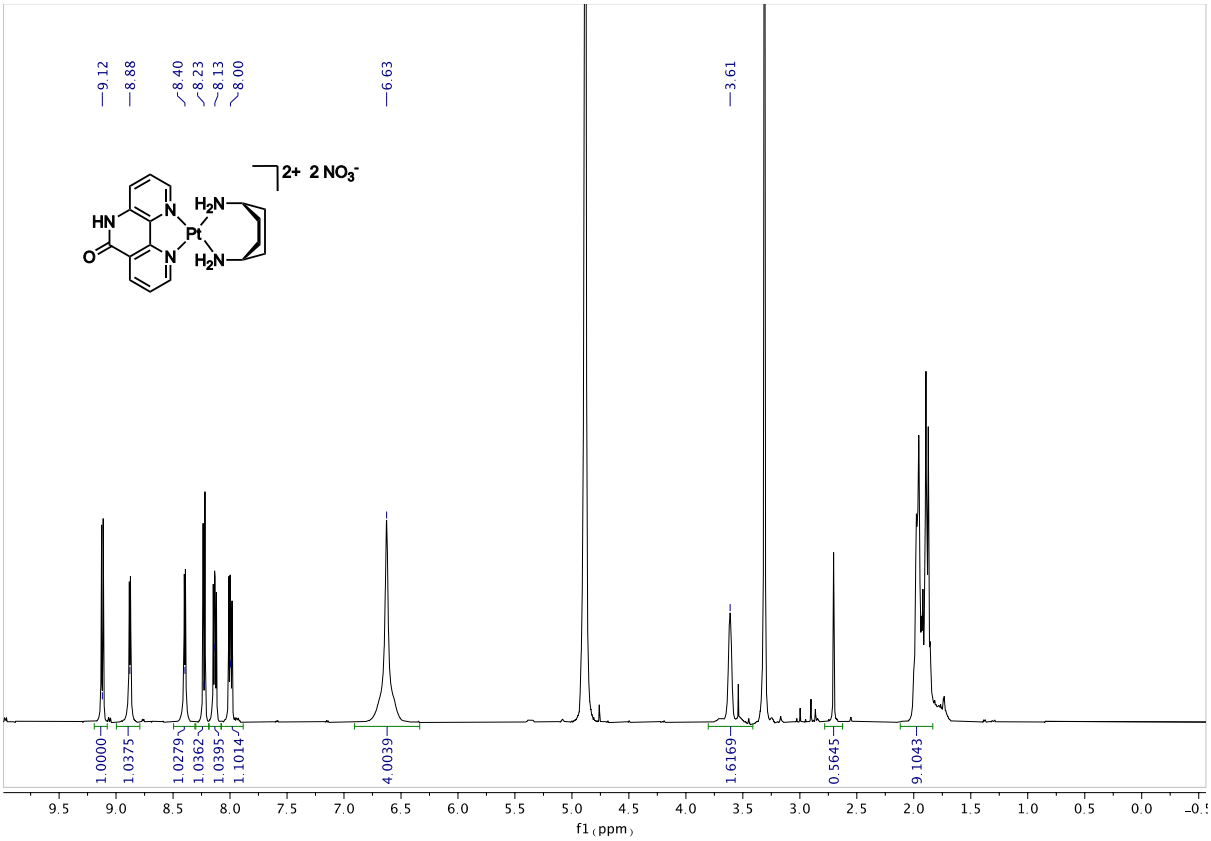


Figure S22. ^{1}H NMR spectrum (MeOD, 500 MHz) of **Pt(3)**

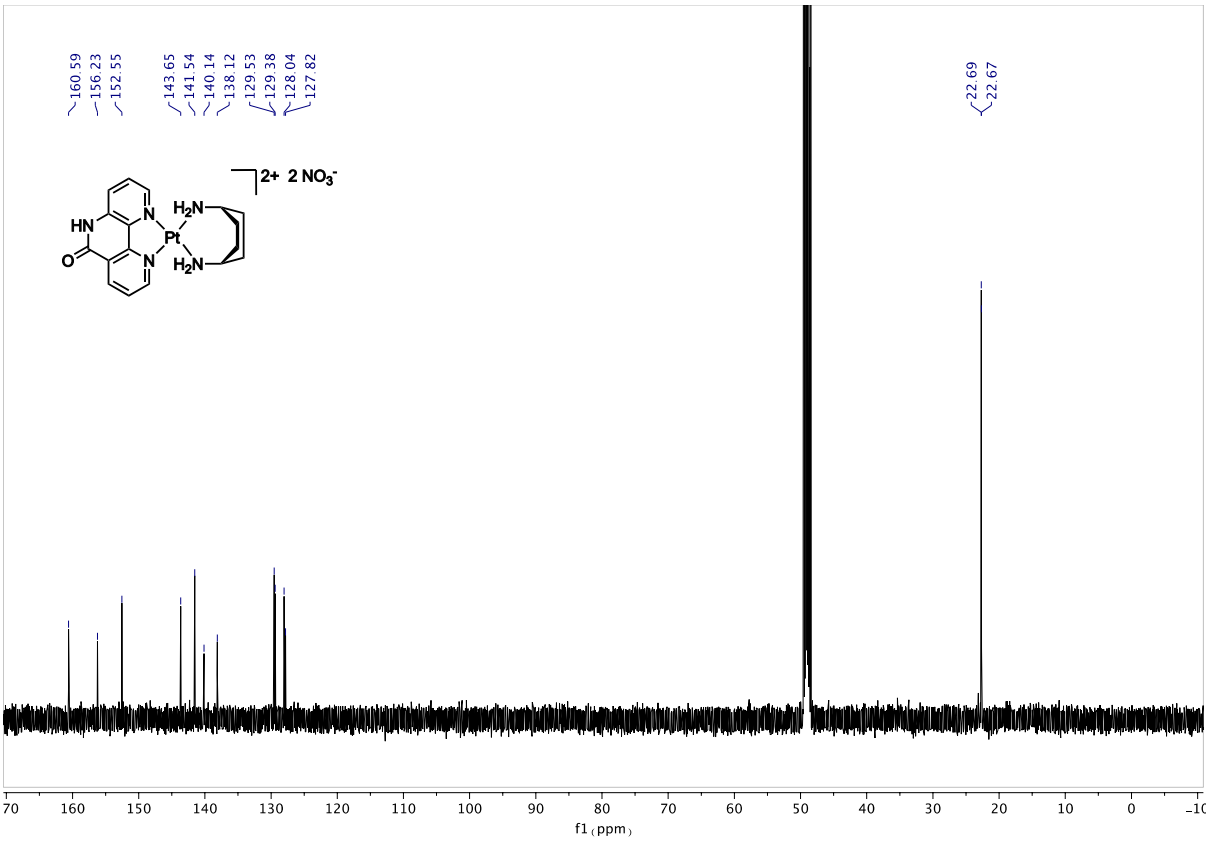


Figure S23. ^{13}C NMR spectrum (MeOD, 126 MHz) of **Pt(3)**

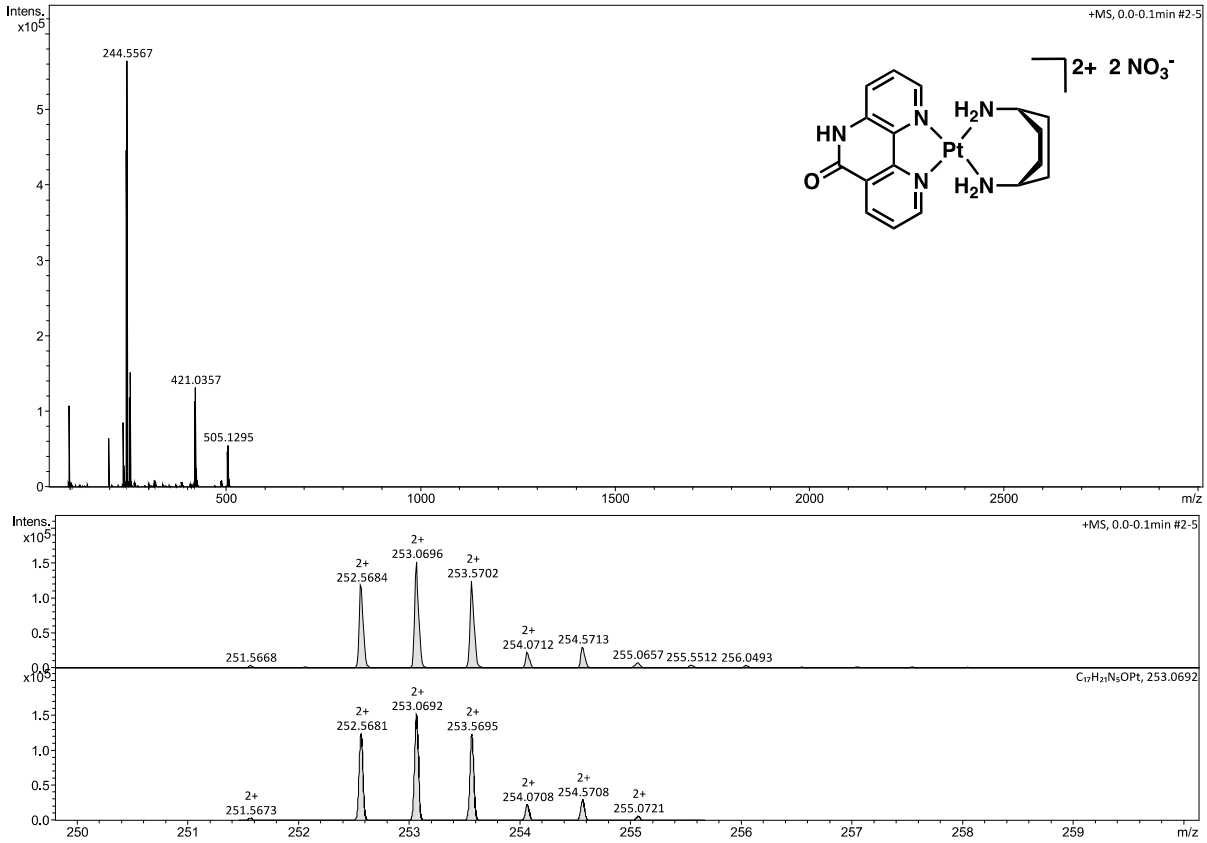


Figure S24. HR-MS spectrum + simulated spectrum and close-up of **Pt(3)**

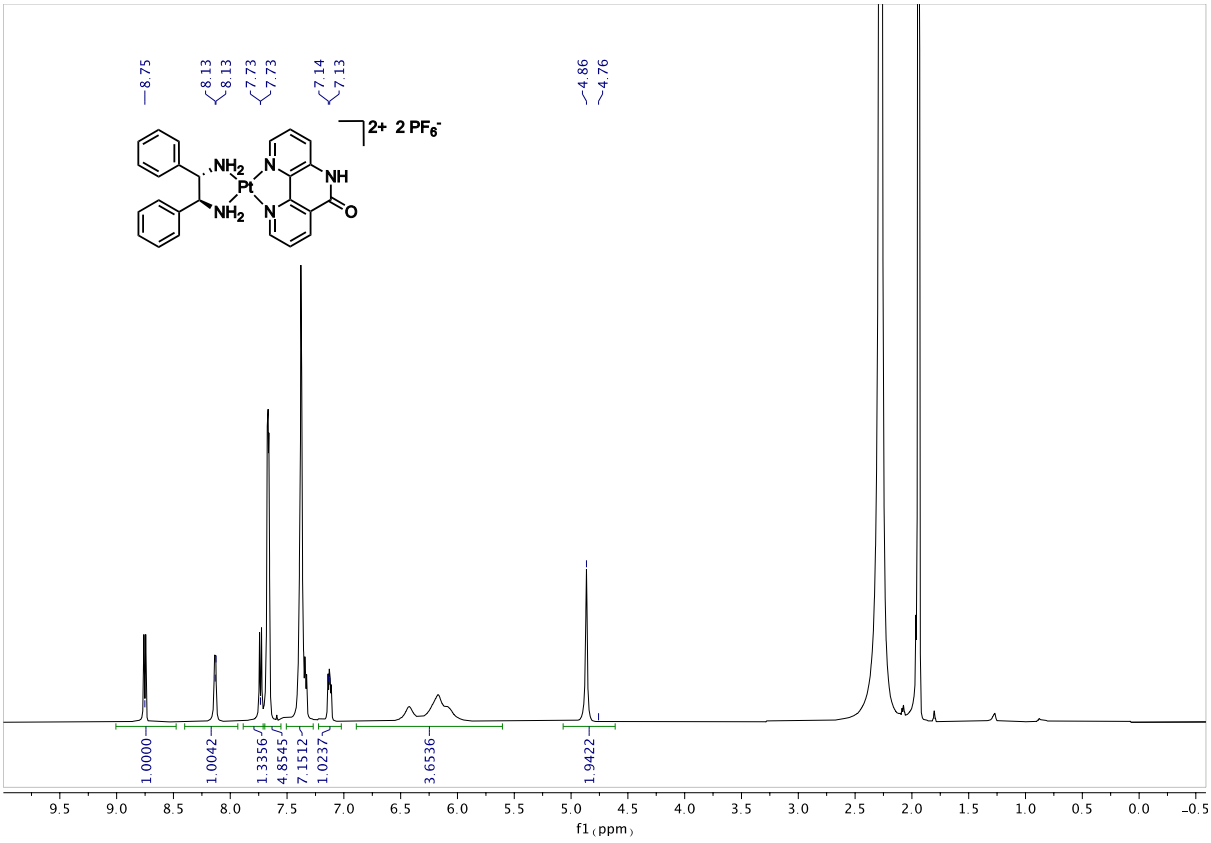


Figure S25. ^{1}H NMR spectrum (CD_3CN, 500 MHz) of **Pt(4)**

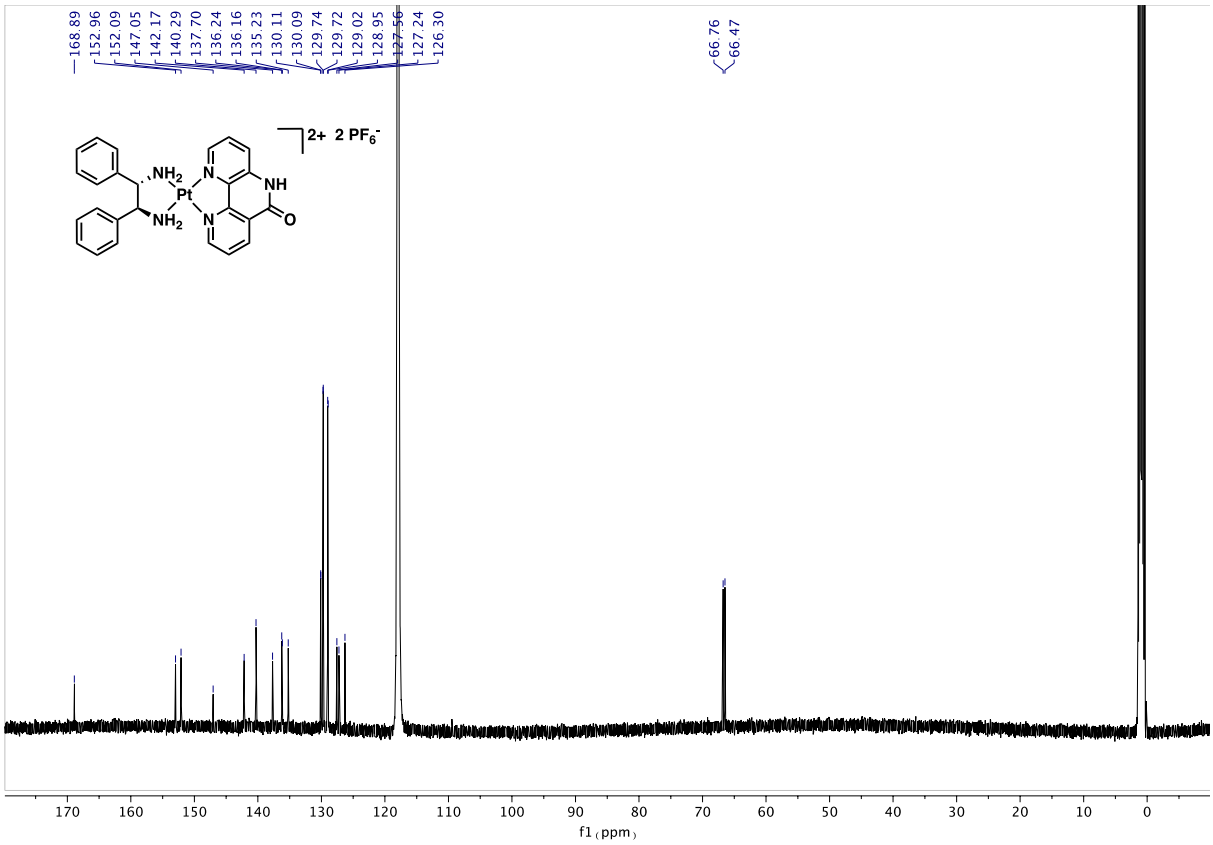


Figure S26. ^{13}C NMR spectrum (CD_3CN, 126 MHz) of **Pt(4)**

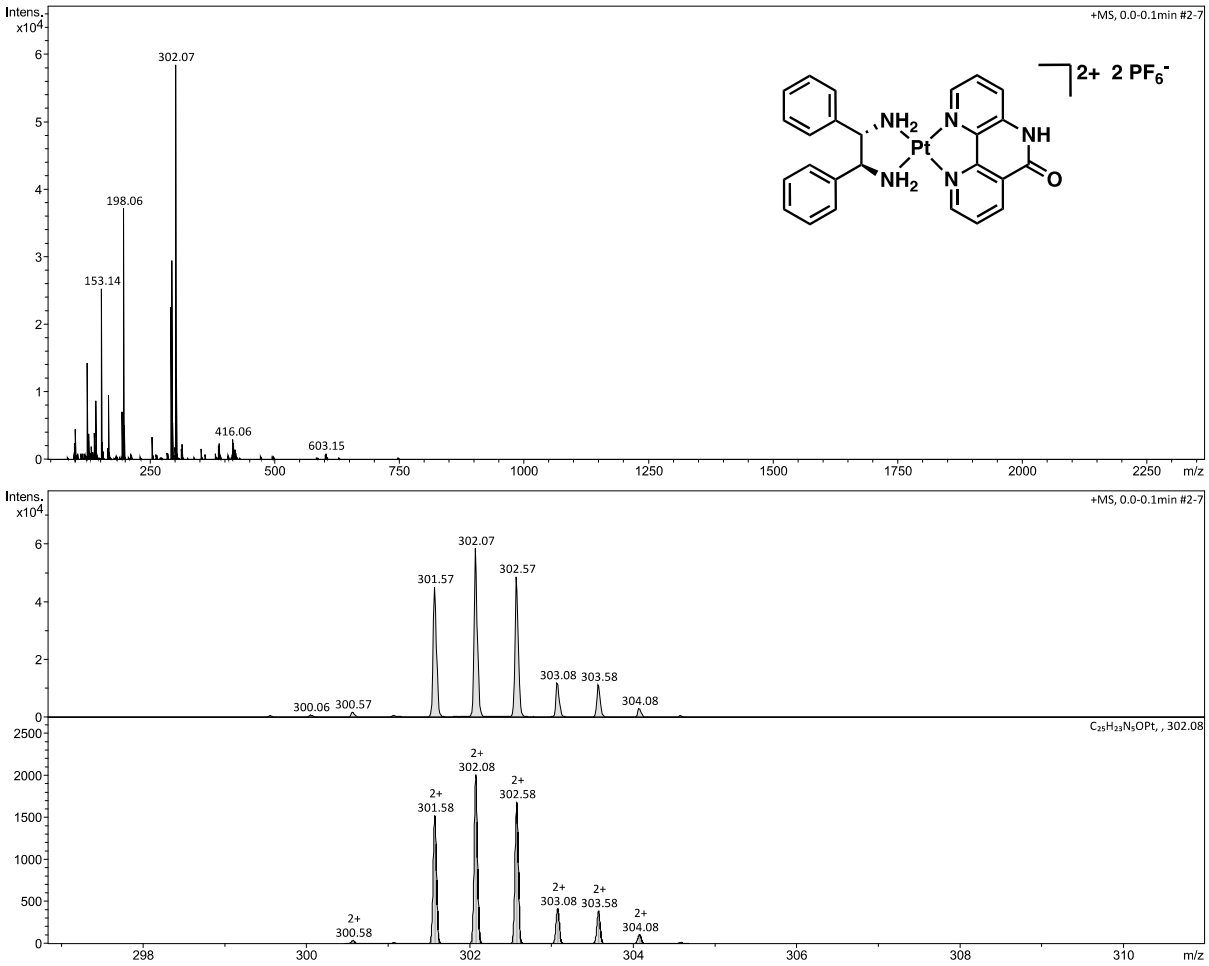


Figure S27. HR-MS spectrum + simulated spectrum and close-up of **Pt(4)**

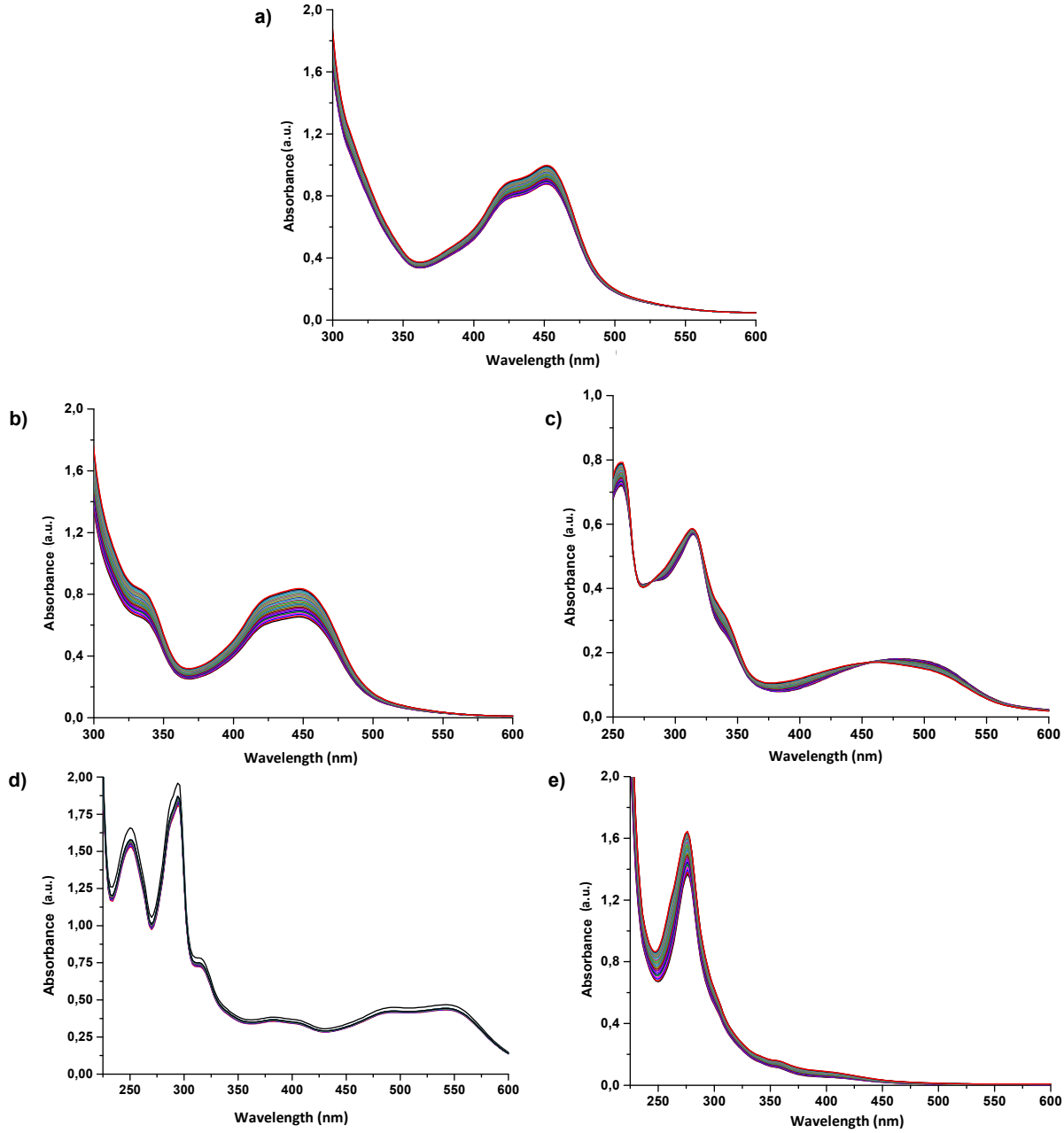


Figure S28: Hydrolysis kinetics of **Ru(1-5)** measured by UV-Vis absorption in a PBS buffer for 24 h (one spectrum every hour). A slight drop in intensity was observed for the analyzed complexes, which was explained by the medium evaporation. a) **Ru(1)**, b) **Ru(2)**, c) **Ru(3)**, d) **Ru(4)**, e) **Ru(5)**.

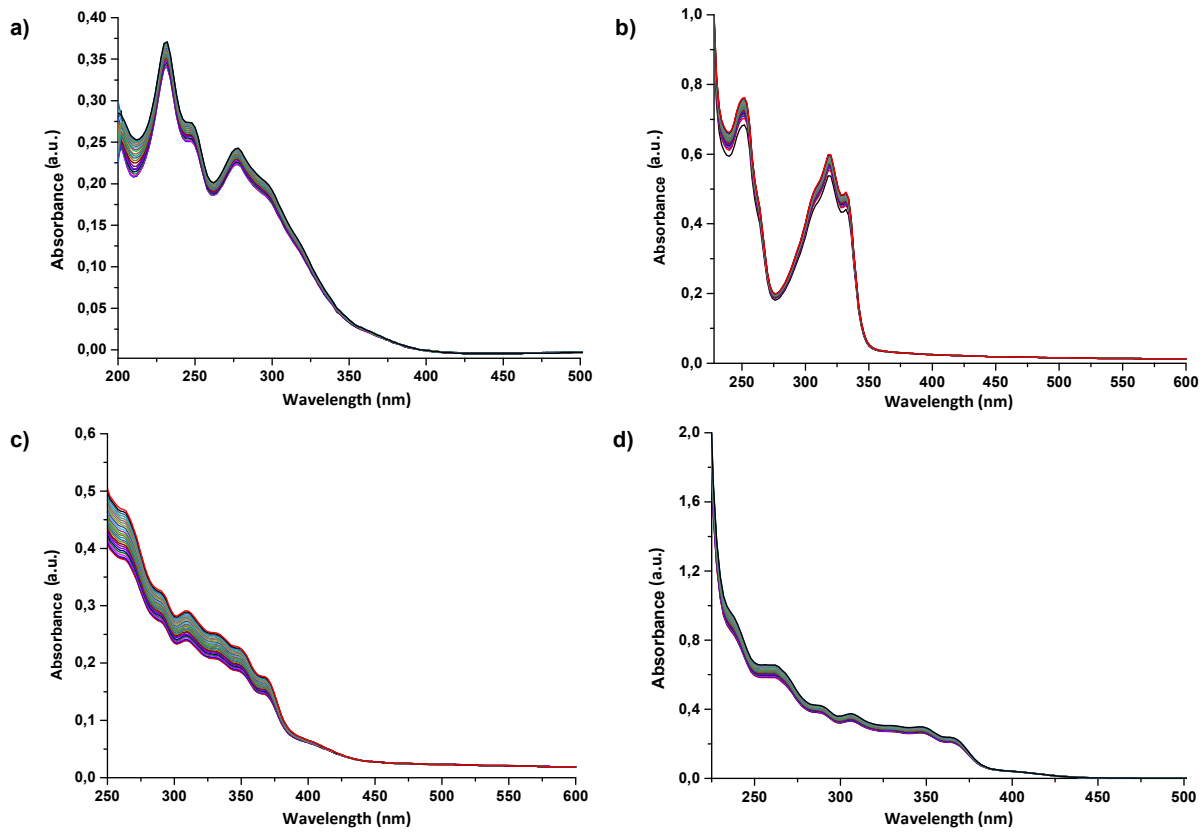


Figure S29: Hydrolysis kinetics of **Pt(1-4)** measured by UV-Vis absorption in a PBS buffer for 24 h (one spectrum every hour). A slight drop in intensity was observed for the analyzed complexes, which was explained by the medium evaporation. a) **Pt(1)**, b) **Pt(2)**, c) **Pt(3)**, d) **Pt(4)**.

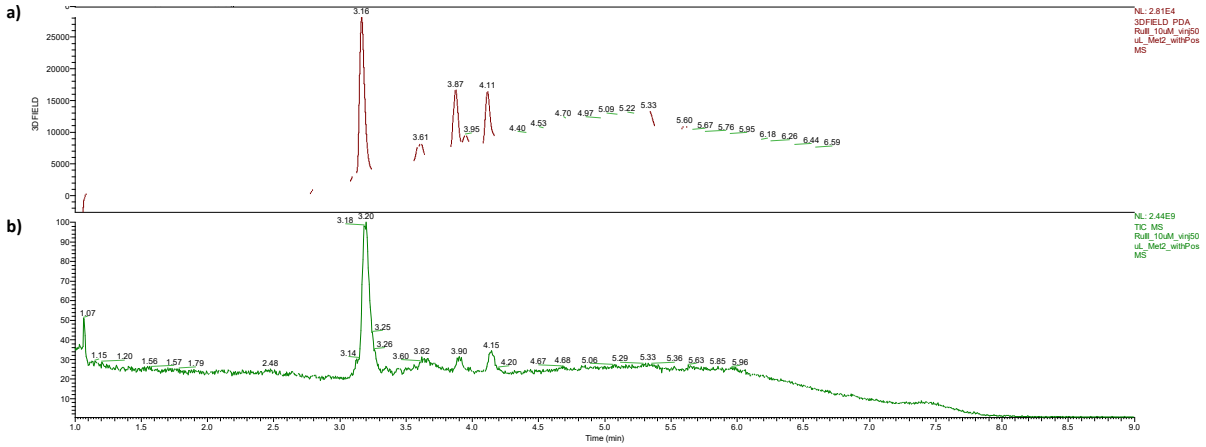
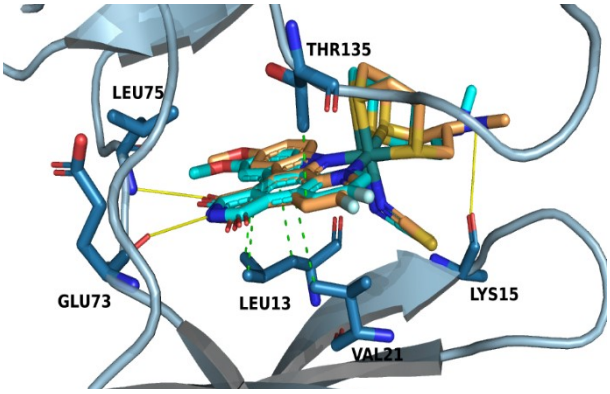


Figure S30: a) UV-Vis (260 nm) of the HPLC analysis of **Ru(3)** after 24 h in PBS. b) Total Ion Chromatogram.

a)



b)

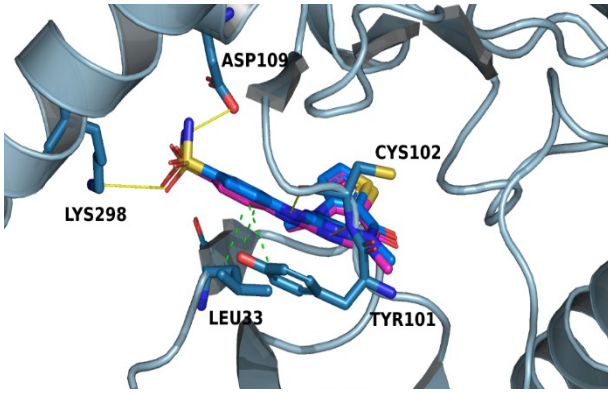


Figure S31: Panel A. re-docking of 72B in S6K1 (PDB code: 4rlp.pdb). In cyan is depicted the co-crystallized ligand and in orange the re-docked molecule. In green are highlighted the hydrophobic interactions and in yellow the hydrogen bonds. The docking score of this binding mode is -97.17. 72B in this binding pose establishes the same 3 H-bonds (with LEU75, GLU73 and LYS15) and hydrophobic interactions (with

THR135, LEU13 and VAL21) as the reference in the crystal structure. Panel B. re-docking of 5BS in MST2 (PDB code: 5dh3.pdb). In blue is depicted the co-crystallized ligand and in magenta the re-docked molecule. In green are highlighted the hydrophobic interactions and in yellow the hydrogen bonds. The docking score of this binding mode is -76.72. In this binding pose 5BS establishes both the same H-bonds (with CYS102, LYS298 and ASP109) and hydrophobic interactions (with LEU33 and TYR101) as the reference in the crystal structure.

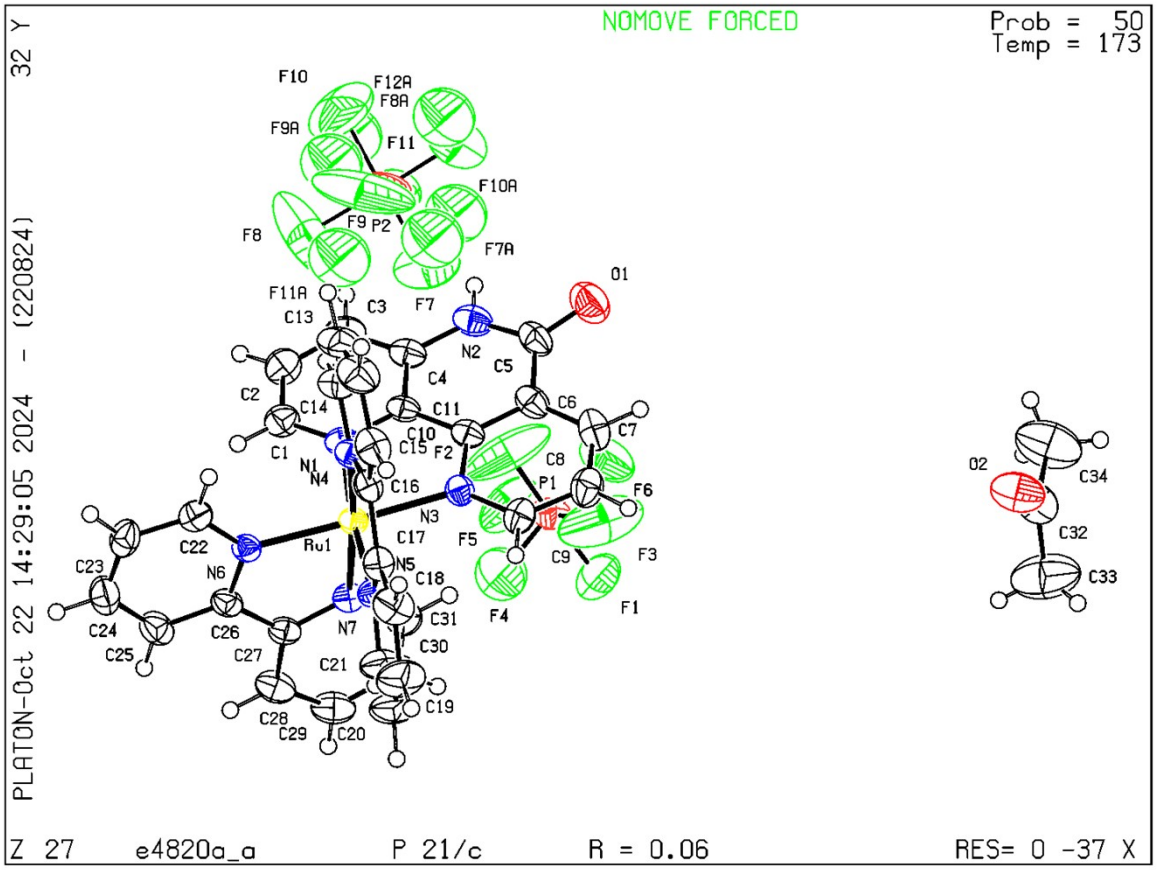


Figure S32: Ellipsoid plot of the Ru(2) crystal structure.

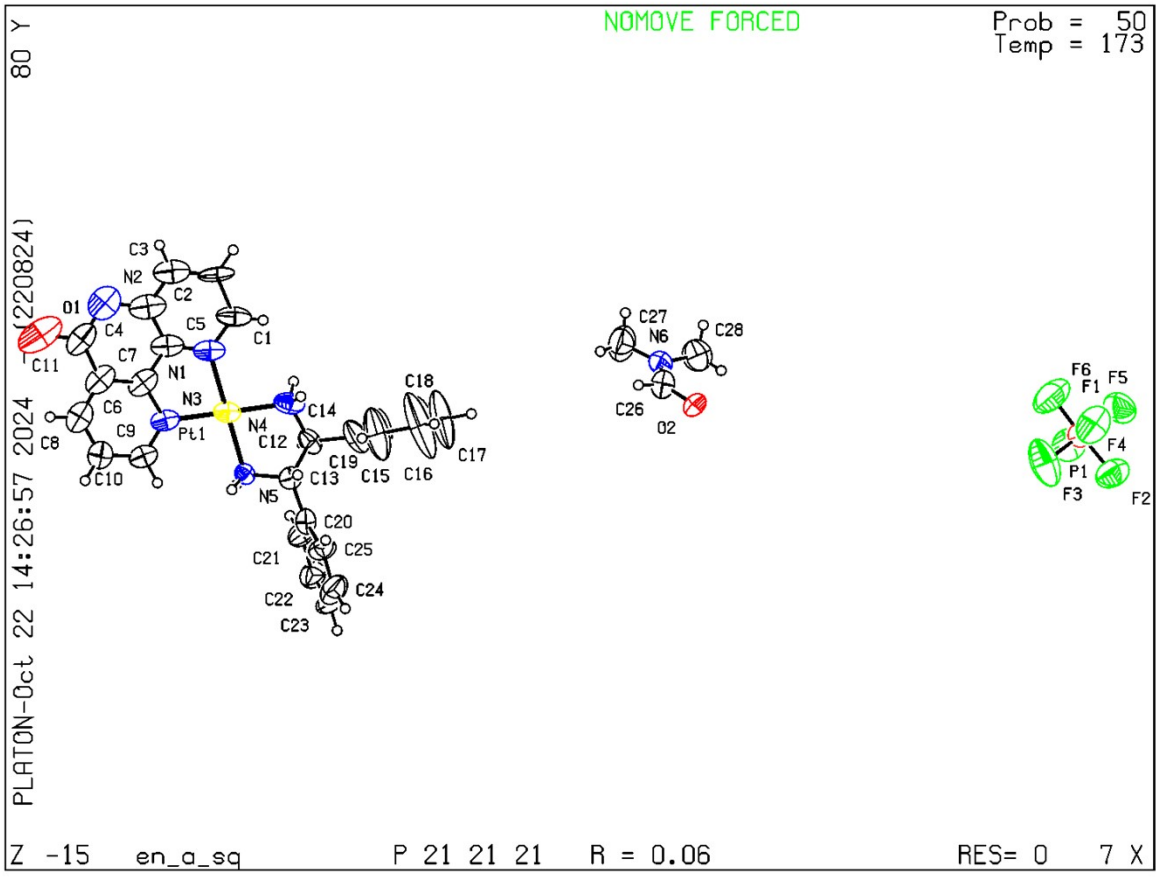
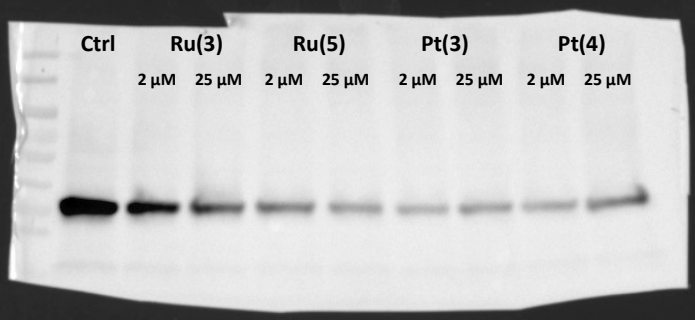


Figure S33: Ellipsoid plot of the Pt(4) crystal structure.

pS6 p-S235/236



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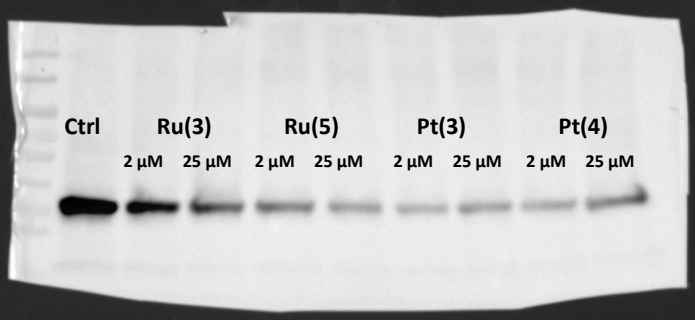

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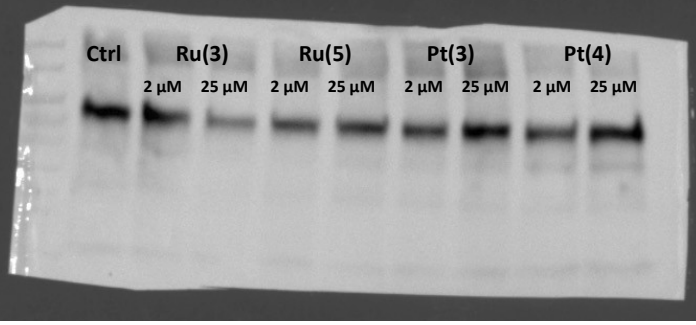
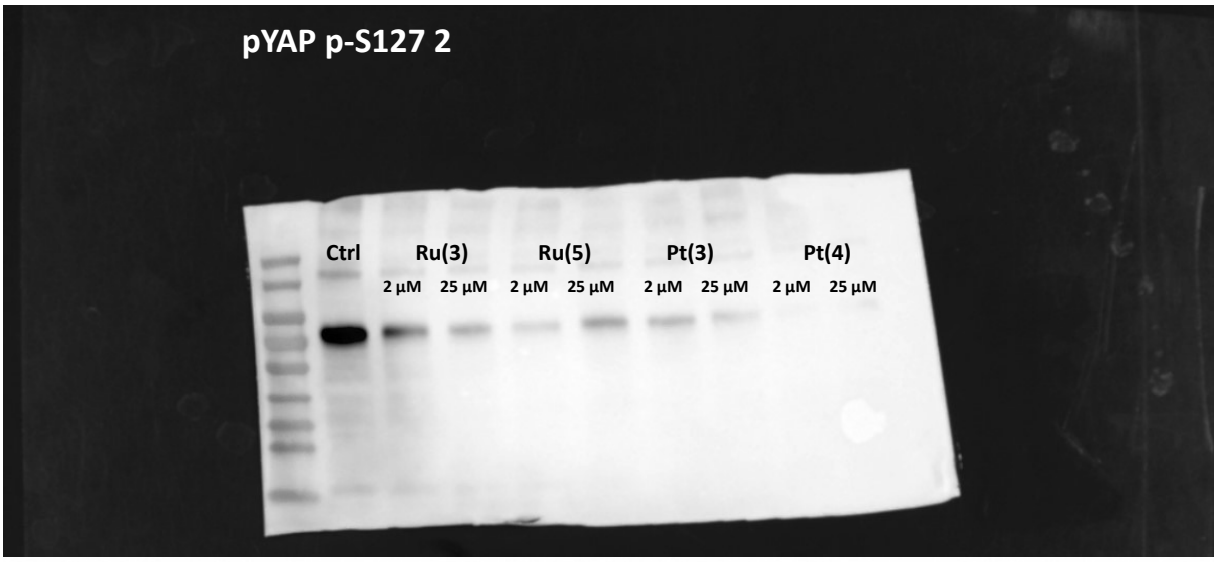
pYAP p-S127

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Ru(3)
Ru(5)
Pt(3)
Pt(4)
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25 µM
2 µM
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2 µM
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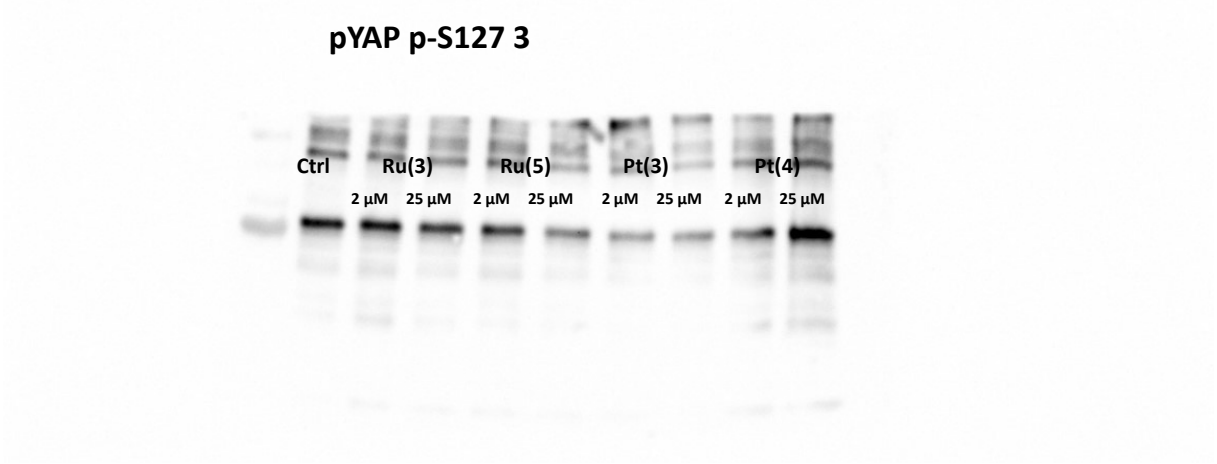
25 µM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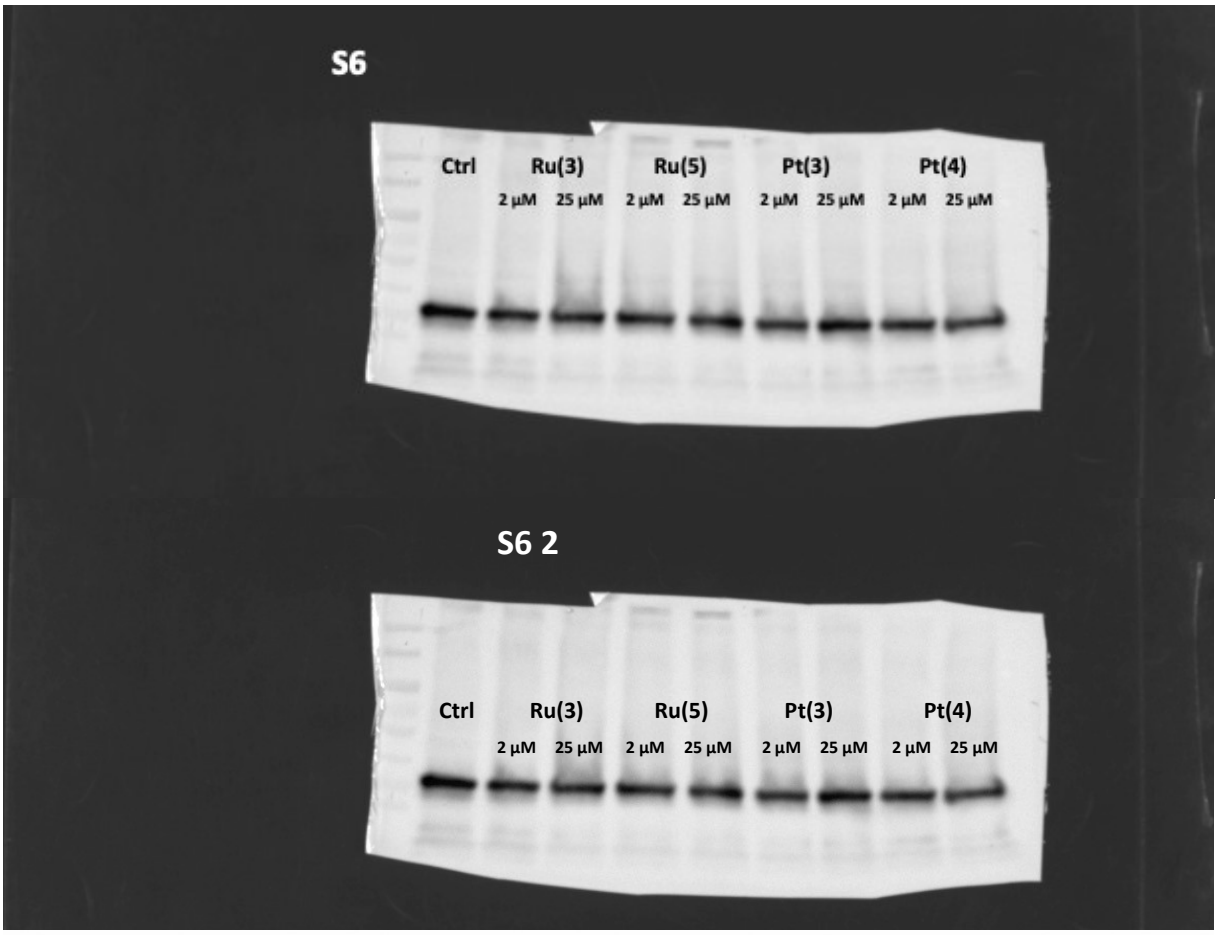
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S6 2
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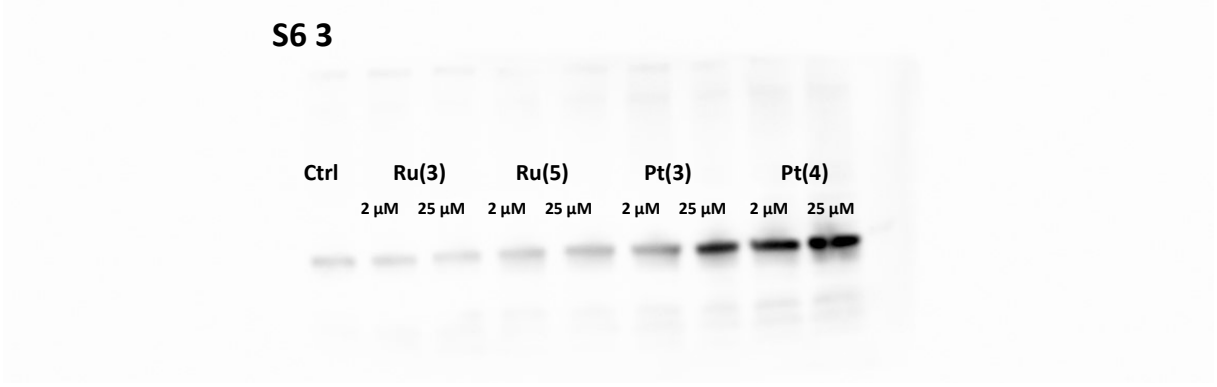
25 µM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Ru(3)
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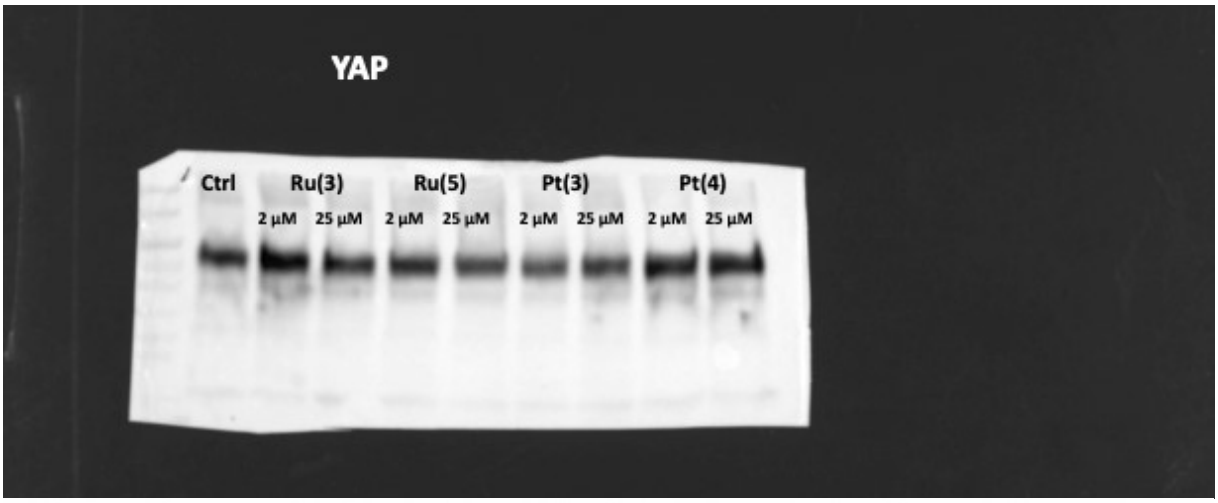
YAP
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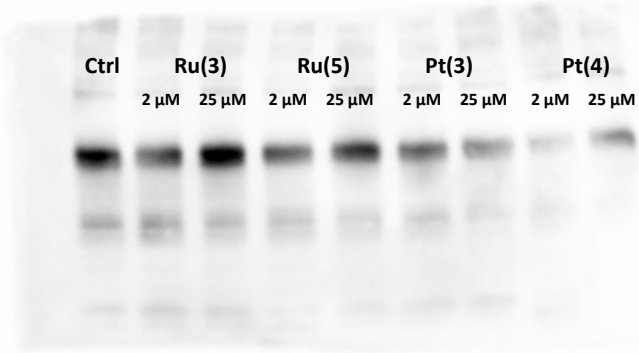
Ru(5)
Pt(3)
Pt(4)
2 µM
25 µM

YAP 2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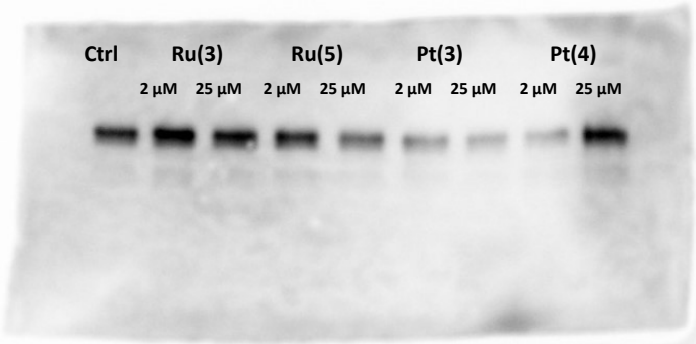
Ru(3)
Ru(5)
Pt(3)
Pt(4)
2 µM
25 µM

YAP 3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Ru(3)
Ru(5)
Pt(3)
Pt(4)
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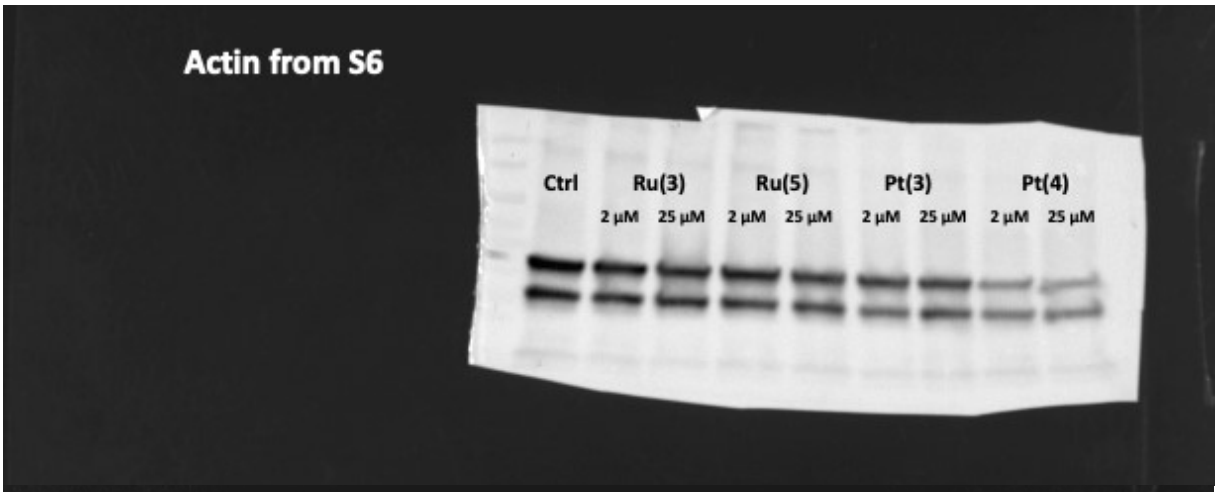
25 µM


Actin from S6
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Ru(3)
Ru(5)
Pt(3)
Pt(4)
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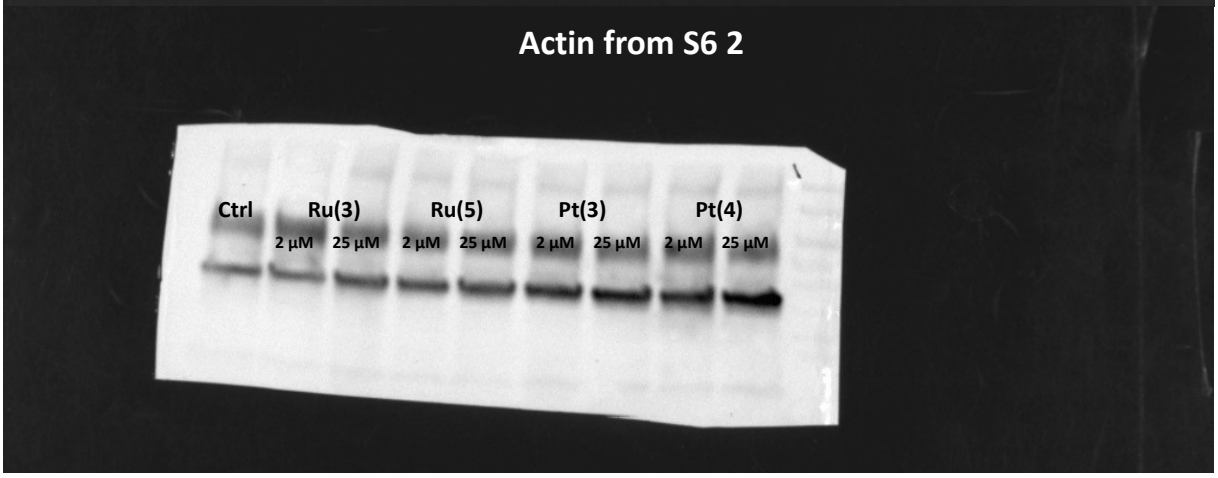
25 µM


Actin from S6 2
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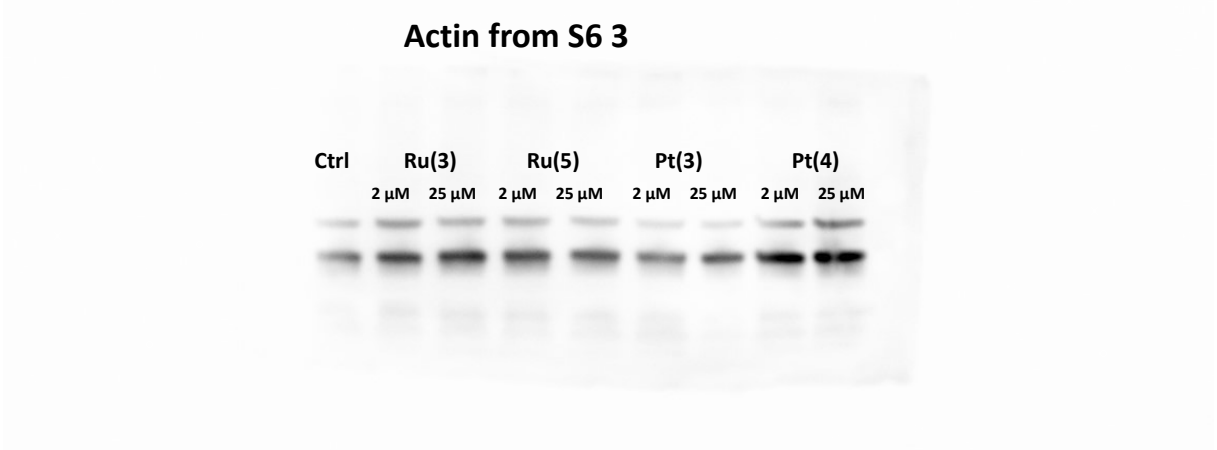
Ru(3)
Ru(5)
Pt(3)
Pt(4)
2 µM
25 µM


Actin from S6 3
Ctrl
Ru(3)
Ru(5)
Pt(3)
Pt(4)
2 µM
25 µM

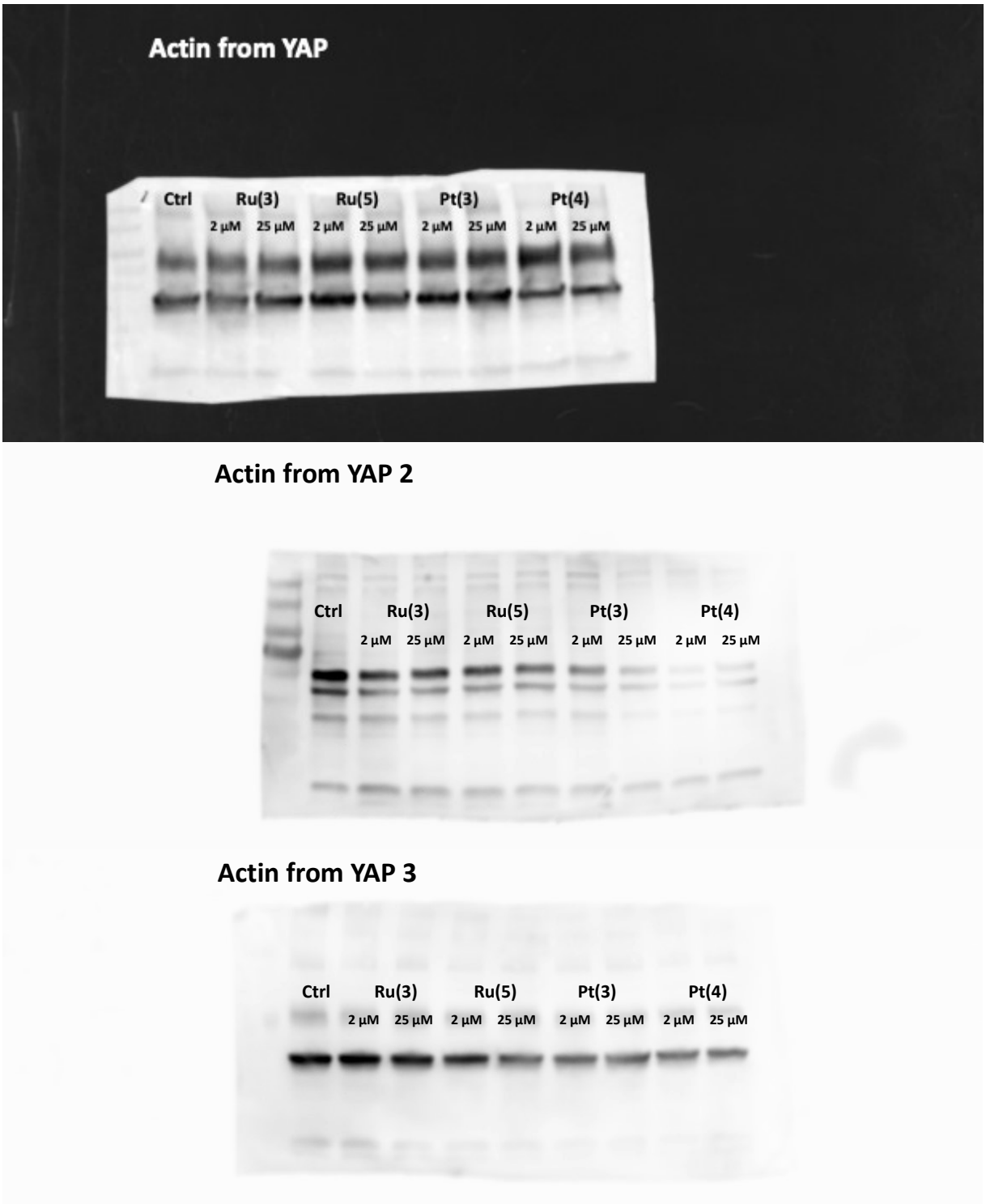


Figure S34: Western Blots

Residue (PDB:	Residue (this paper)	Interaction type	**Pt(3)**	**Pt(4)**	**Ru(3)**	**Ru(5)**

4RLP)						
E173/O	GLU-73	H bond	-	-	-	-
L175/N	LEU-75	H bond	✓	-	-	-
K99/O	LYS-99	H bond	-	-	-	-
Y174/OH	TYR74	H bond	-	✓	-	-
L97	LEU-13	VdW	✓	✓	-	-
V105	VAL-21	VdW	✓	-	✓	✓
A121	ALA-37	VdW	✓	✓	-	✓
T235	THR-135	VdW	✓	-	✓	✓

Table S1. Analysis of the interaction pattern of the ruthenium and platinum compounds at S6K1 as predicted by docking relative to the reference compounds FL772 solved in complex with the protein (PDB:4RLP). The interactions were analyzed using the software PLIP.[42] Green checks highlight when the interaction was detected in the lowest-energy binding mode by docking.

Residue (PDB: 5DH3)	Residue (this paper)	Interaction type	**Pt(3)**	**Pt(4)**	**Ru(3)**	**Ru(5)**
C102/O	CYS-102	H bond	✓	✓	-	-
C102/N	CYS-102	H bond	✓	-	-	-
D109/OD1	ASP-109	H bond	✓	-	-	-
L33	LEU-33	VdW	✓	✓	-	✓
V41	VAL-41	VdW	-	-	-	✓
Y101	TYR-101	VdW	-	-	-	✓

L153	LEU-153	VdW	✓	-	✓	✓

Table S2. Analysis of the interaction pattern of the ruthenium and platinum compounds at MST2 as predicted by docking relative to the reference compounds XMU-MP-1 solved in complex with the protein (PDB:5DH3). The interactions were analyzed using the software PLIP.[42] Green checks highlight when the interaction was detected in the lowest-energy binding mode by docking.

Antibodies List

β-Actin (anti-mouse) from Merck Millipore, anti-mouse (7076), anti-rabbit (7074), pS235/236-S6 Ribosomal Protein (anti-rabbit, D57.2.2E), S6 Ribosomal Protein (anti-rabbit, 5G10) and pS127-YAP (anti-rabbit, S127-D9W2I) from Cell Signaling technology and YAP (anti-mouse, sc-101190) from Santa Cruz Biotechnology and all antibodies were used at 1:1000 dilutions except for pS6 (1:2000), actin (1:15000), anti-mouse (1:2000), and anti-rabbit (1:10000).