Synthesis and Characterization of Light-Triggered Metal Complexes for Cancer Treatment

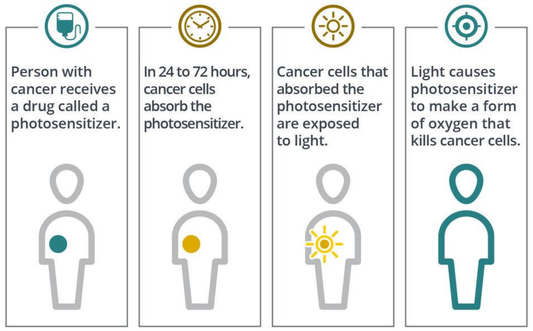
Dalton Lucas [a], Alisher Talgatov [a], Joshua Rahmon [a], Broderick Nelson [a], Ge Shi [a], Gurleen Kaur [a], Debby Sunday [a], Abbas Vali [a], Colin G. Cameron [a], Sherri A. McFarland [a†]

[a] Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, Texas, United States [†] Principal Investigator

Abstract

Photodynamic therapy (PDT) offers a controlled approach to cancer treatment by confining cytotoxicity to tumors and sparing healthy tissue. PDT employs a photosensitizer (PS), light, and oxygen to generate reactive oxygen species (ROS) that destroy tumors and tumor vasculature and to induce an antitumor immune response. PDT can be combined with standard therapies or used when such approaches are not effective. Over the past decade, there has been an interest in exploiting the rich photophysical properties of transition metal complexes derived from ruthenium (Ru) to address certain limitations of PDT. Our own TLD1433 is one example that is showing promise in phase II clinical trials for treating non-muscular invasive bladder cancer. Similar to other Ru PSs being explored in the context of phototherapy, TLD1433 is a tris-diimine complex. Its distinguishing and function-determining feature is an imidazo-phenanthroline appended terthienyl unit. Herein, we explore a different Ru scaffold that incorporates tridentate polypyridyl ligands and oligothiophenes. We systematically investigate the effect of the number of thienyl groups on various chemical, biological, and photophysical properties.

Photodynamic Therapy

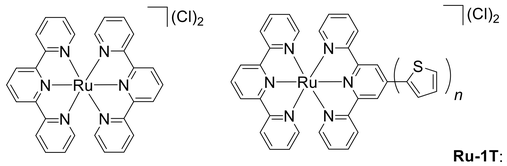


cancer.gov/about-cancer/treatment/types/photodynamic-therapy

Objectives

- Synthesize, characterize, and evaluate a new class of Ru(II) terpyridine oligothiophene complexes.
- Determine the effect of oligothiophene chain length and co-ligand identity on biological activity.

Target Structures



Ru(tpy)$_2$

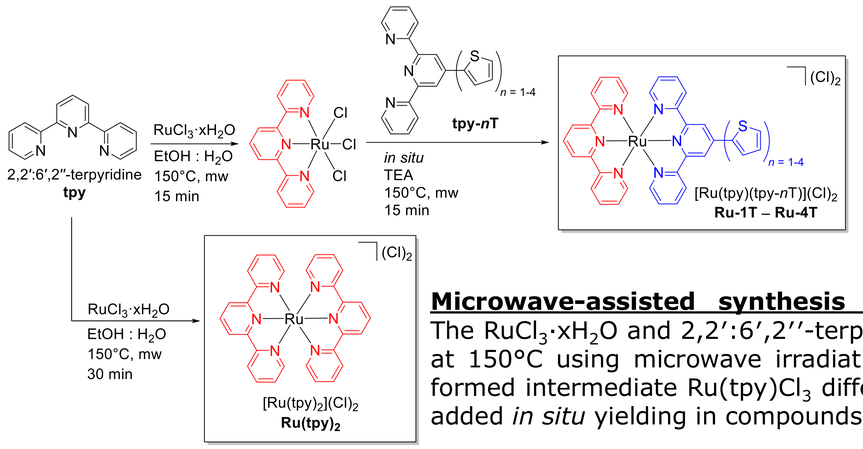
[Ru(tpy)$_2$](Cl)$_2$

Ru-*n*T

[Ru(tpy)(tpy-*n*T)](Cl)$_2$

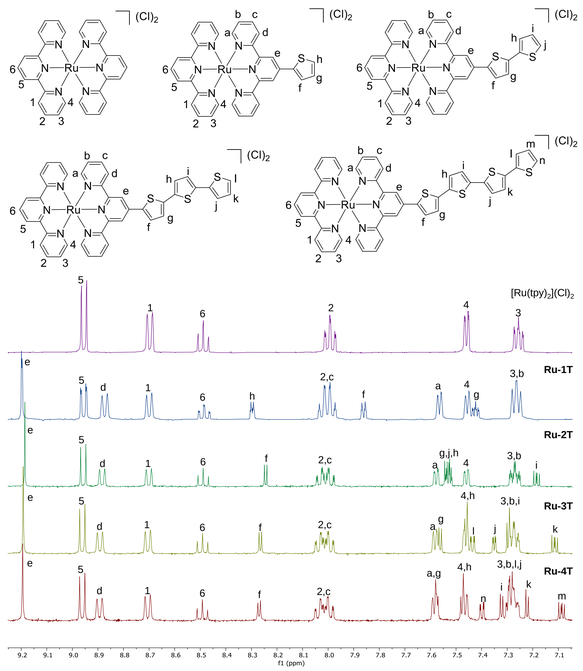
Ru-1T: *n* = 1
Ru-2T: *n* = 2
Ru-3T: *n* = 3
Ru-4T: *n* = 4

Synthesis, Purification and Characterization



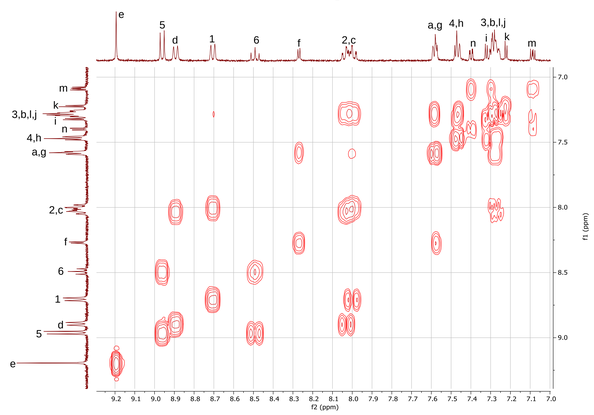
Microwave-assisted synthesis of target complexes. The RuCl$_3$·xH$_2$O and 2,2′:6′,2′′-terpyridine (tpy) were heated at 150°C using microwave irradiation for 15 minutes. To a formed intermediate Ru(tpy)Cl$_3$ different tpy-*n*T ligands were added *in situ* yielding in compounds **Ru-1T** – **Ru-4T**.

Column chromatography. Crude products were isolated as Cl$^-$ salts and purified using silica gel flash column chromatography (solvent gradient: MeCN – 10% H$_2$O in MeCN – 0.5% KNO$_3$, 7.5% H$_2$O in MeCN). To remove residual mixture of NO$_3^-$ and Cl$^-$ salts, compounds were converted to their corresponding PF$_6^-$ salts via addition of aqueous saturated solution of KPF$_6$. Anion metathesis was performed on the Amberlite IRA-410 resin using ion-exchange chromatography. Finally, the Cl$^-$ salts were further purified using size-exclusion chromatography on Sephadex. Purity >95% was confirmed by HPLC.

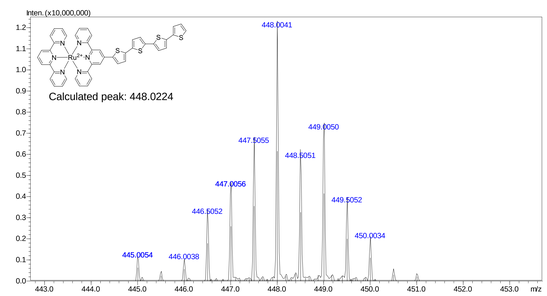


Characterization by ^{1}H NMR. Assignment of all ^{1}H signals was confirmed by correlation spectroscopy (COSY) (^{1}H-^{1}H) NMR. ^{19}F NMR was also performed to confirm removal of the PF$_6^-$ ions.

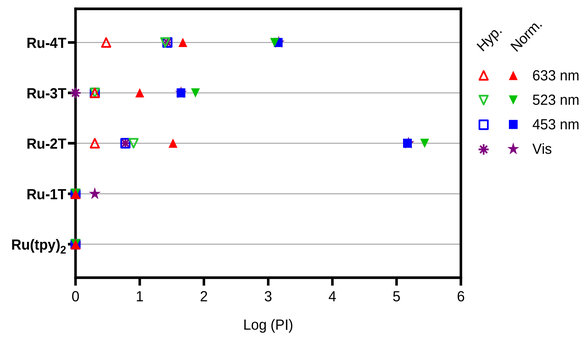
^{1}H–^{1}H COSY NMR Spectrum of Ru-4T

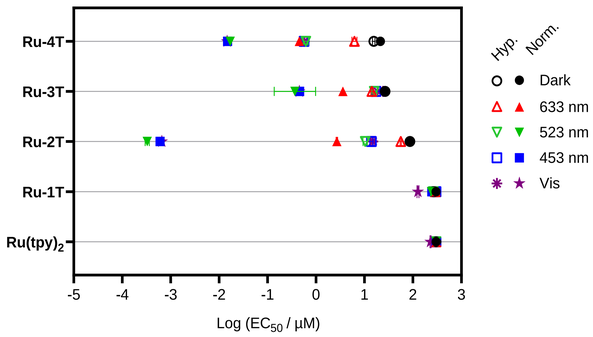


High-resolution ESI$^+$ MS Spectrum of Ru-4T



Photobiological Evaluation





SKMEL28 cells. Fluence: 100 J cm^{-2}. Irradiance: ~20 mW cm^{-2}. Normoxia = 18.5-20% O$_2$. Hypoxia = 1% O$_2$.

Conclusions

- A new family of Ru(II) terpyridine complexes were synthesized, characterized, and evaluated for photobiological efficacy against cancer cells
- **Ru-2T** showed the highest potency (in normoxia) compared to the other complexes in the family

References

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