Exploration of Tunable Anti-Cancer Metallodrugs

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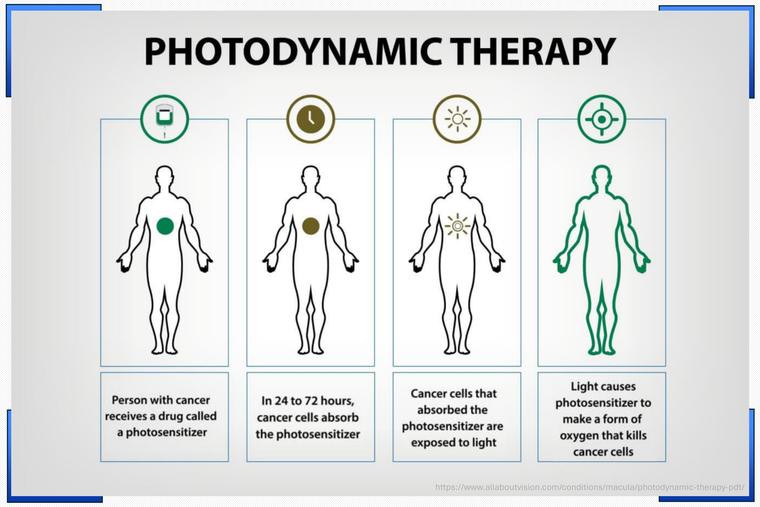
Background

Photodynamic therapy (PDT) is a complementary approach to conventional forms of cancer treatment, such as surgery, radiation, and chemotherapy. This highly selective therapy enables precise destruction of invasive cancer cells, while sparing the healthy tissue surrounding the targeted tumor. PDT, in its simplest definition, employs a nontoxic photosensitizer (PS) that is activated by a specific wavelength of light to destroy cancer cells via singlet oxygen or other reactive molecular species. Currently, the only FDA approved drug for PDT is Photofrin™, a porphyrin-based organic PS. Second and third generation PSs are also based on porphyrins as well and a few other tetrapyrrolic systems. We have a longstanding interest in utilizing highly tunable metallodrugs as PSs for PDT because they have a variety of excited state configurations, with interesting reactivities, that can be accessed with low energy light. Specifically, ruthenium(II) and osmium(II) PSs are showing promise, with our own TLD1433 in Phase II human clinical trials for treating non-muscle invasive bladder cancer. In this work, we report the synthesis and characterization of a ruthenium(II) terpyridine-based family of PSs and highlight some of their photobiological properties.

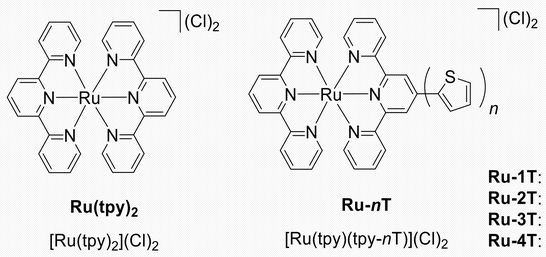
What is PDT?



Objectives

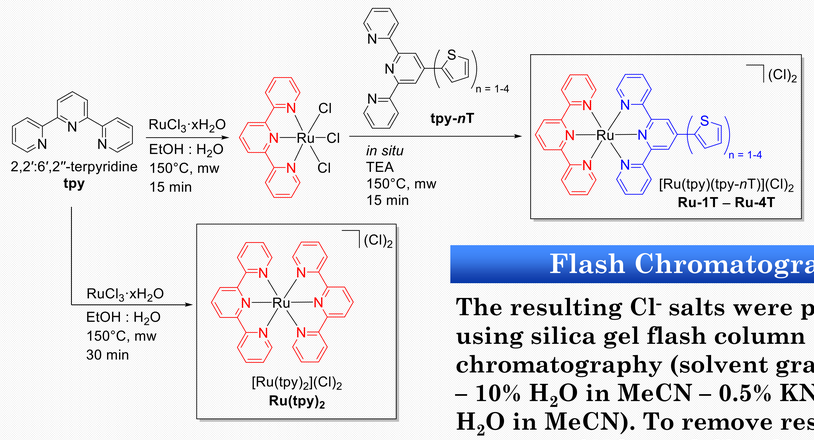
- Synthesize, characterize, and evaluate a new class of Ru(II) terpyridine oligothiophene complexes.
- Determine the effect of oligothiophene chain length and co-ligand identity on biological activity.

Target Structures



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

Synthesis, Characterization, and Purification



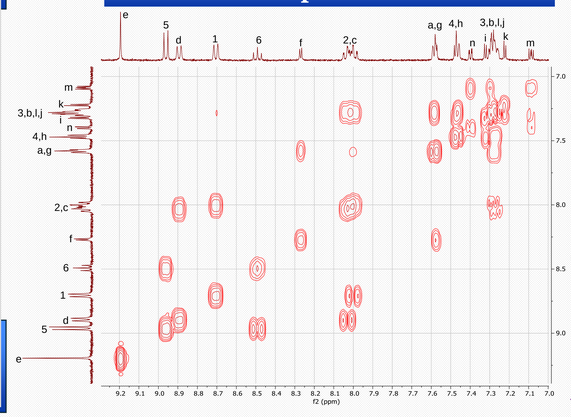
Microwave-Assisted Synthesis

$RuCl_3 \cdot xH_2O$ and 2,2′:6′,2″-terpyridine (tpy) were heated at 150°C using microwave irradiation for 15 minutes. The $Ru(tpy)Cl_3$ intermediate was then complexed with different tpy-*n*T ligands *in situ* yielding compounds Ru-1T – Ru-4T.

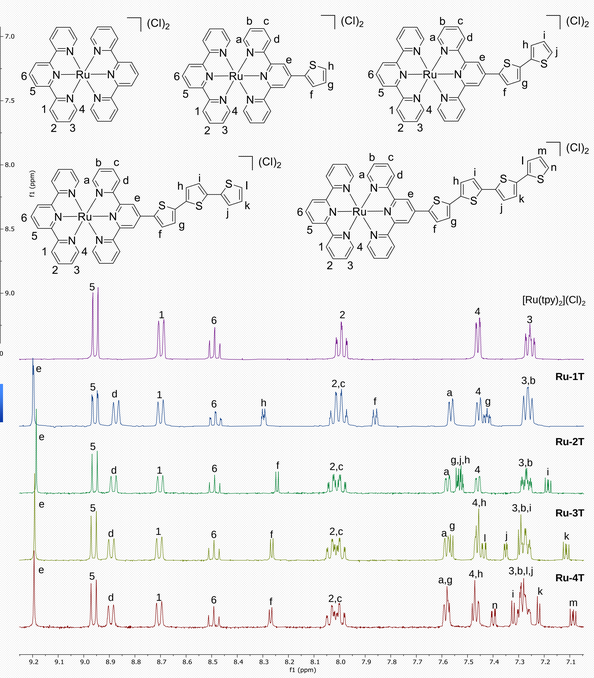
Flash Chromatography

The resulting Cl^- salts were purified using silica gel flash column chromatography (solvent gradient: MeCN – 10% H_2O in MeCN – 0.5% KNO_3, 7.5% H_2O in MeCN). To remove residual mixture of NO_3^- and Cl^- salts, all 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.

COSY NMR Spectrum of Ru-4T



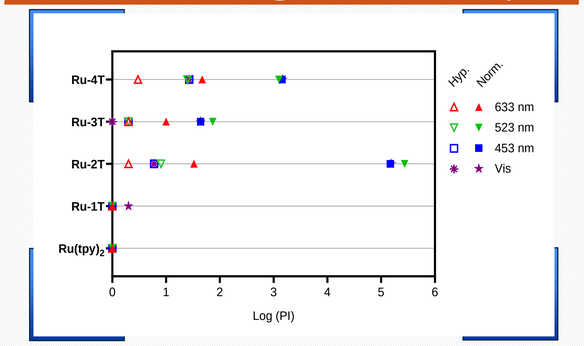
Characterization by ^{1}H NMR

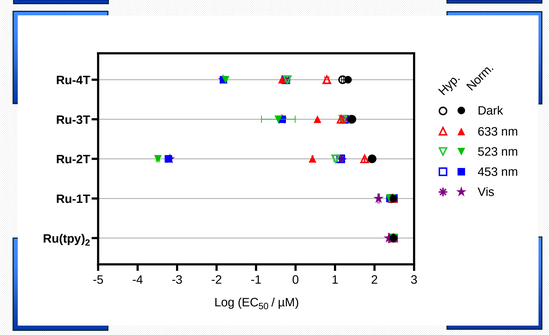


Characterization

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.

Photobiological Activity





Conclusion

- 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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