Applications of Photoactivated Metallodrugs for Cancer Therapy

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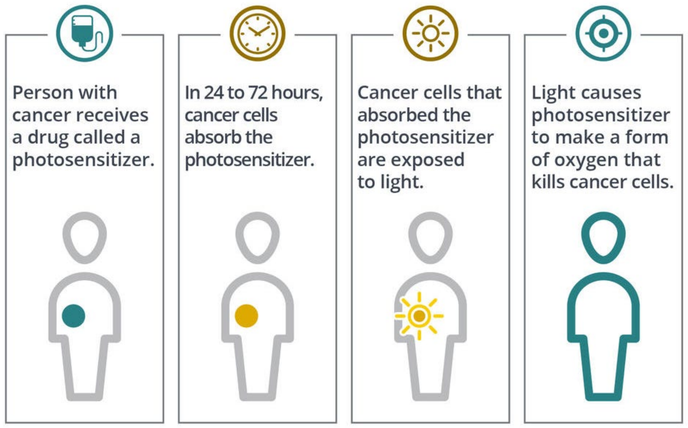
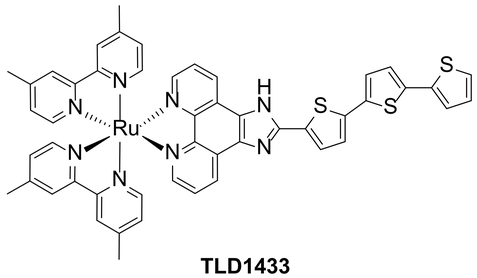
Photodynamic Therapy (PDT)



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



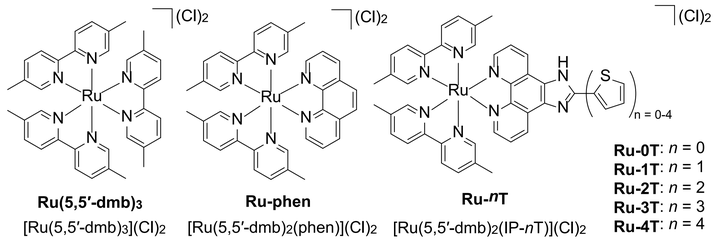
TLD1433
[Ru(4,4'-dmb)$_2$(IP-3T)](Cl)$_2$
ClinicalTrials.gov Identifier: NCT03945162
Chem. Rev. **2019**, *119*, 797-828.
DOI: 10.1021/acs.chemrev.8b00211

- **79 patients** are treated in Phase II clinical trials, Phase III is not needed

Objectives

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

Target Structures



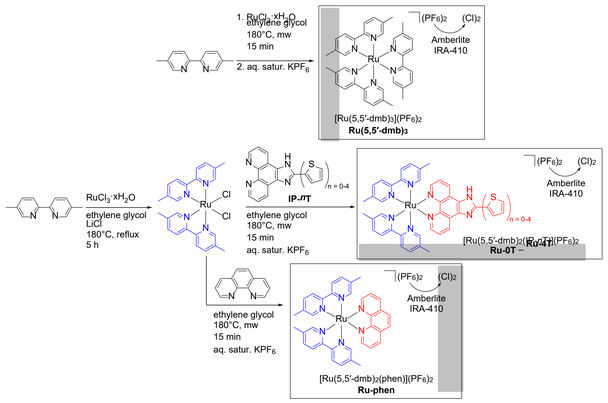
Ru(5,5′-dmb)3
[Ru(5,5′-dmb)$_3$](Cl)$_2$

Ru-phen
[Ru(5,5′-dmb)$_2$(phen)](Cl)$_2$

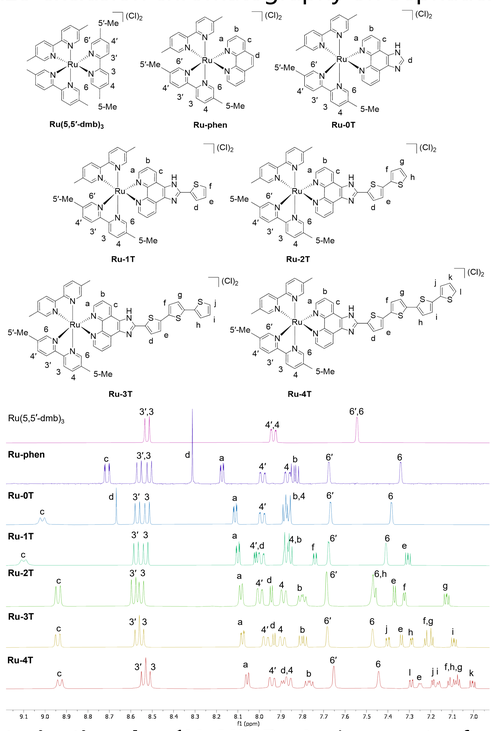
Ru-*n*T
[Ru(5,5′-dmb)$_2$(IP-*n*T)](Cl)$_2$

Ru-0T: n = 0
Ru-1T: n = 1
Ru-2T: n = 2
Ru-3T: n = 3
Ru-4T: n = 4

Synthesis and Characterization

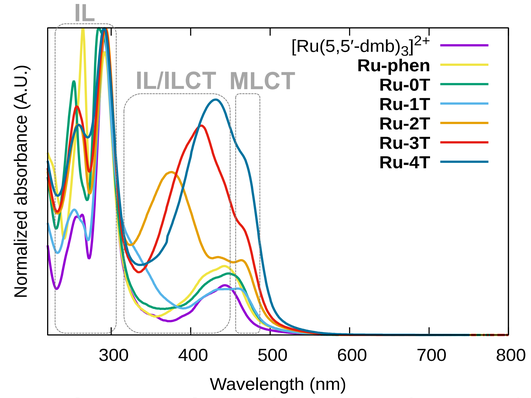


Microwave-assisted synthesis of target complexes. The Ru(5,5′-dmb)$_2$(Cl)$_2$ precursor, phen and different IP-*n*T ligands were heated at 180°C using microwave irradiation for 15 minutes. **Ru(5,5′-dmb)$_3$** was also synthesized by reacting $RuCl_3{\cdot}xH_2O$ and 5,5′-dmb under similar conditions. Crude products were isolated as PF_6^- salts and purified using silica gel column chromatography, followed by conversion to their corresponding Cl^- salt via anion exchange on Amberlite. Finally, the Cl^- salts were further purified using size-exclusion chromatography on Sephadex.



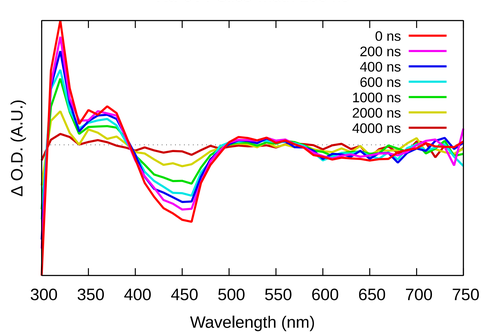
Characterization by ^{1}H NMR. Assignment of all ^{1}H signals was confirmed by 2D COSY (^{1}H-^{1}H) NMR. ^{19}F NMR was performed after purification to confirm that all PF_6^- ions were removed.

Photophysical Characterization



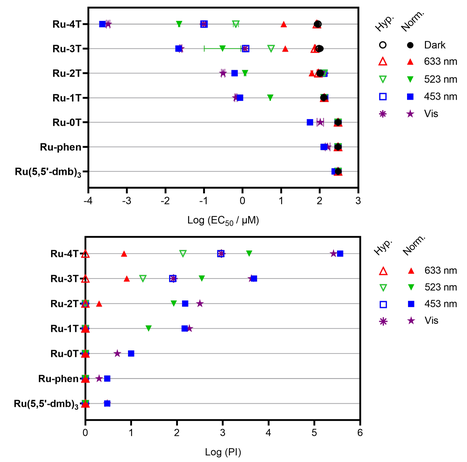
Steady-State Absorption Properties. UV-Vis absorption profiles major features:

- <300 nm intraligand (IL) ππ* transitions on coligands and phen/IP
- 330-450 nm IL or ILCT ππ* involve *n*T of the IP-*n*T. With increasing *n*: ↑ intensity, red shift →
- ~470 nm Ru(dπ) → phen(π*) metal-ligand charge transfer (MLCT) transitions



Excited-State Absorption Properties. The transient absorption (TA) spectra of **Ru-0T** and **Ru-4T** are compared above. Ground state bleach centred at 450 nm - depopulation of the ^{1}MLCT state. The ESA ~660 nm is due to the ^{3}ILCT state.

Photobiological Evaluation



Light-triggered activity in SKMEL-28 cancer cells. All of the complexes were relatively nontoxic in the dark (EC_{50} >100 µM). The light EC_{50} values decreased systematically with *n*, reaching low nM and a phototherapeutic index (PI) as large as $4{\times}10^5$ with **Ru-4T** in normoxia. **Ru-4T** was a notable hypoxia-active compound, with PIs >100 down to 1% hypoxia.

Conclusions

- ✓ A new family of Ru(II) polypyridyl oligothiophene based complexes has been synthesized, characterized, and evaluated for photobiological activity against cancer cells.
- ✓ The ^{3}ILCT state is key to achieving high photobiological activity.
- ✓ Increasing the number of thiophenes energetically positions the ^{3}ILCT state to be accessible upon photoexcitation.

References

- Monro, S. Chem. Rev. 2019, 119 (2), 797–828.
- McFarland, S. A. Curr. Opin. Chem. Biol. 2020, 56, 23–27.
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Acknowledgements

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