Investigation of photoactive metallodrugs as antimicrobials

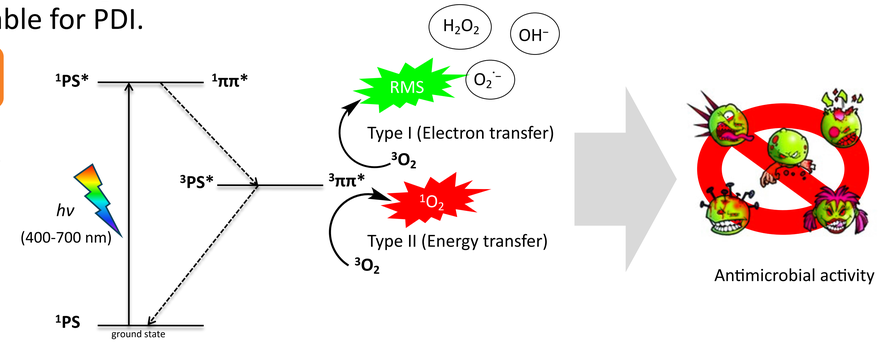
Gurleen Kaur, Debby Sunday, Alisher Talgatov, Ge Shi, Abbas Vali, Colin Cameron, Sherri A. McFarland*
Department of Chemistry and Biochemistry, The University of Texas at Arlington

Photodynamic Inactivation

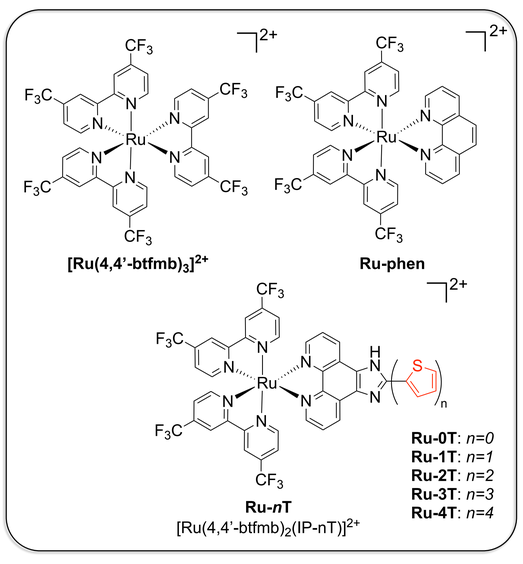
Photodynamic Inactivation (PDI) is a light-triggered therapy to treat antimicrobial infections where a photosensitizer (PS) is activated by light in the presence of oxygen to destroy microbial cells through the generation of singlet oxygen ($^1O_2$) and/or other reactive molecular species (RMS). A few key features of PDI include quick burst of cytotoxic species, multi-target approach followed by spatiotemporal selectivity, thus it is suitable as an alternative light-triggered antimicrobial treatment option compared to the use of conventional antimicrobial drugs. PDI produces cytotoxic RMS, such as $^1O_2$ that kill pathogens including antimicrobial resistant (AMR) strains. Therefore, PS with high $^1O_2$ quantum yields (ϕ_Δ) are desirable for PDI.

Objective

Conventional antimicrobial drugs rely on inhibiting/blocking steps in metabolic pathways that are crucial for survival of bacteria. Our objective is to develop PSs with longer triplet excited lifetimes for higher yields of cytotoxic $^1O_2$ and other RMS to overcome AMR acquired by bacteria through either natural or acquired resistance pathways.

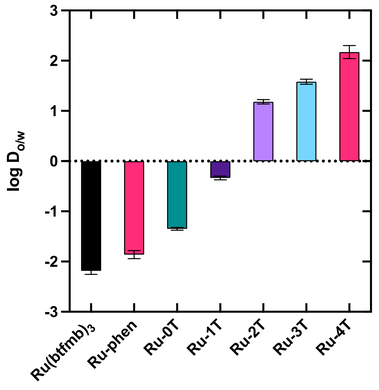


Complexes in this study



The Ru(II) polypyridyl complexes of Ru(4,4'-btfmb)$_3$, Ru-phen and Ru-0T—Ru-4T were studied as racemic mixtures of ***Δ/Λ*** enantiomers. The Cl^- and PF_6^- salts were used based on properties of the compounds under study.

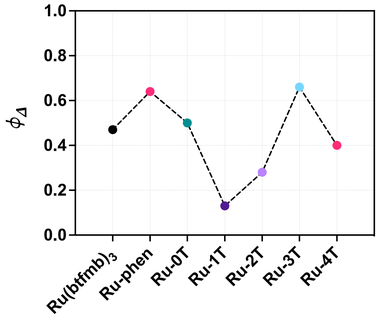
Pharmacokinetics

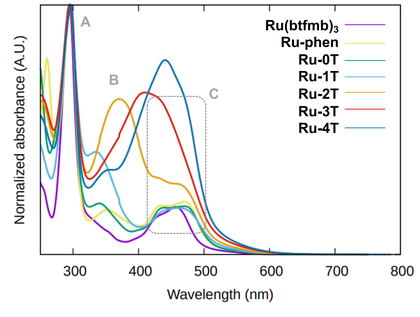


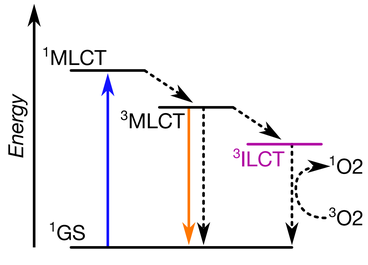
For lipophilicity determination, log $D_{o/w}$ (Distribution coefficient) were determined for Cl^- salts using shake flask method using saturated 1-Octanol and 10 mM Phosphate buffer. An increase in lipophilicity was observed with increasing number of thiophenes as expected.

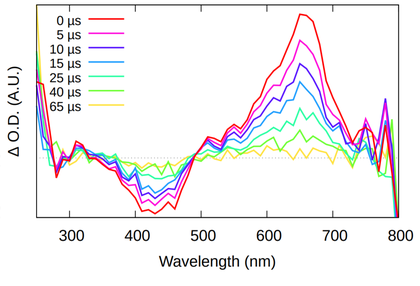
Photophysical characterization

The excited state PS undergoes either type-I (electron transfer) or type-II (energy transfer) reaction to produce $^1O_2$ and other RMS. The $^1O_2$ quantum yield (ϕ_Δ) of PF_6^- salts were calculated by actinometric method in an air-saturated acetonitrile system, taking $[Ru(bpy)_3](PF_6)_2$ as a standard (ϕ_Δ=0.56).







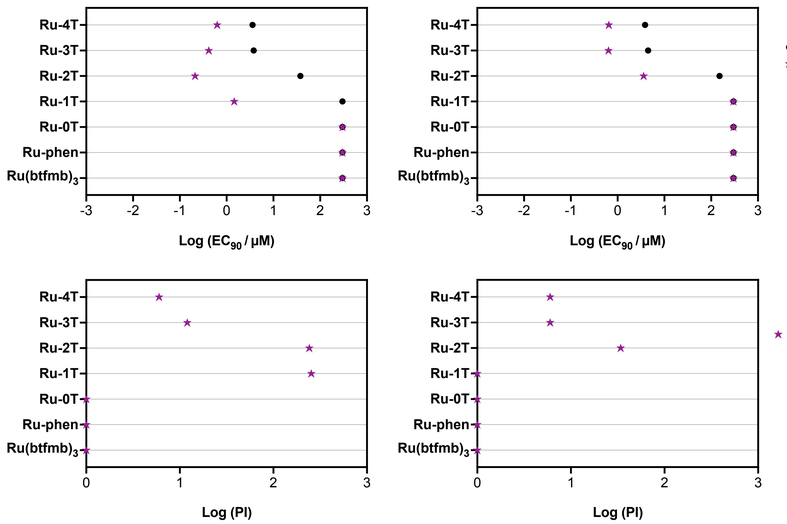


The photophysical model for **Ru-4T** involves excitation to the ^{1}MLCT state, which can then form two types of triplet states. The ^{3}MLCT state (t = 640 ns) is relatively short-lived and populates a much longer-lived ^{3}ILCT state (t = 20 µs) that can sensitize $^1O_2$ but also undergo photoredox reactions.

Photo(antibacterial) activity

Enterococcus faecalis

29212 vs. V587



The photobiological activities of Ru(btfmb)$_3$, Ru-phen and Ru-0T—Ru-4T were evaluated in antibiotic susceptible and resistant strains of *Enterococcus faecalis* under dark and broadband visible light (fluence = 100 J cm^{-2} and irradiance = 28—35 mW cm^{-2}). EC_{90} is the concentration of compound required to reduce cell viability by 90% whereas PI (Phototherapeutic Index) is the ratio of dark EC_{50} to Vis EC_{50}.

Future studies

These complexes will be further analyzed for localization and cell uptake studies. For the development of structure-activity relationship (SAR) library, various structural modifications are being designed for photophysical, photochemical, physicochemical and photobiological studies.

Acknowledgements

We thank the Department of Chemistry and Biochemistry at the University of Texas at Arlington. We also thank the National Science Foundation (NSF) (Award NSF 2102459)

References

1. Cole, H.D. *Inorg. Chem.* **2023**, *62* (51), 21181-21200.
2. Arenas, Y. *Photodiagnosis and Photodyn. Ther.* **2013**, *10* (4),615-625.
3. Monro, S. *Chemical Reviews* **2019**, *119* (2), 797-828.
4. Roque, J. A. *Inorg. Chem.* **2020**, *59* (22), 16341–16360.

UNIVERSITY OF TEXAS ARLINGTON
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

@McFarland_Labs