University of Fribourg / Faculty of Science and Medicine / Department of Chemistry

Therapeutic Applications of Rhenium(I) Complexes as Antimicrobial and Antimalarial Agents

Sara Nasiri Sovari

The threat of antimicrobial resistance to global public health is becoming more and more urgent as new resistance mechanisms emerge worldwide in infectious pathogens. Innovative solutions are needed to combat these new mechanisms of resistance. Most of the structural variations available in classic organic antibiotics have been exhausted, and the few compounds emerging from various industrial pharmaceutical pipelines appear unlikely to offer in the short run a new generation of agents with improved functions to deal with this urgent issue. A wide range of three-dimensional geometries in both inorganic and organometallic complexes can be exploited to discover and develop new antimicrobial agents. The antimicrobial efficacy of new series of Re(I) tricarbonyl complexes bearing mono- and bidentate coumarin-based ligands, and a series of *fac*-$[Re(CO)_3]^+$ complexes with different ligands, charges, and diimine (N^N) derivatives have been investigated in this study. A comprehensive antimicrobial potency assessment was performed on the metal complexes and their ligands against a panel of clinically relevant *Candida* and *Staphylococcus aureus* strains, and selected compounds were subsequently evaluated *in vivo* in Zebrafish. The results of our study allowed us to identify potent and non-toxic rhenium compounds effectively inhibiting antimicrobial infections and co-infection with *C. albicans* and MRSA. Moreover, in the last part of antimicrobial research, a series of rhenium(I) complexes coordinated to azole drugs, as known antifungal agents, were prepared, and tested for their antifungal activity. Based on the results, remarkable improvements in their activity compared to the free antifungal agents were found.

Malaria disease poses a serious threat to nearly half of the world's population. Approximately, 229 million cases of malaria were reported by the WHO in 2019 compared with 228 million in 2018. To control the danger caused by malaria parasite, first, malaria prevention medicines, and then, antimalarial medications can be options. As *P. falciparum* malaria parasites became resistant to previous generations of malaria medicines, such as chloroquine and sulfadoxine-pyrimethamine (SP), policies of malaria control were undermined. A crucial aspect of controlling and eliminating malaria is protecting the efficacy of antimalarial medicines. To evaluate and address drug resistance in malaria-endemic countries, regular monitoring of drug efficacy is highly required, accordingly, there is a constant call from WHO for discovering new antimalarial medicines with improved modes of action. In the second part of this research, the main target was to design and synthesize two groups of antimalarial agents conjugated to cobalamin and Re(I) tricarbonyl complexes, respectively, against *P. falciparum* strains.

Jury:

Prof. Dr. Fabio Zobi (thesis supervisor)

Prof. Dr. Christian Bochet (internal co-examiner)

Prof. Dr. Hendrik Visser (external co-examiner)

Prof. Dr. Marco Lattuada (president of the jury)