Development of copper-dependent antimicrobial resistance breakers

Project Background Information/Introduction:

Antibiotics are life savers in the field of bacterial infectious diseases. However, several bacterial species are developing resistance against antibiotics, rendering an increasing threat to today's clinical settings and public health. Beta-lactam antibiotics are one of the most prescribed drugs for treating a variety of bacterial infections. Bacteria produces beta-lactamase enzymes in order to inhibit beta-lactam antibiotics. NDM-1, a metallo-beta-lactamase enzyme, has been found in New Delhi, India in 2008 and since then, several antibiotics have been reportedly failed due to this bacterial enzyme. Therefore, developing a resistance breaker is at an urgent need to stop this enzyme production and inhibitory action of bacteria.[1]

Research Aim/Objectives/Questions/Hypotheses:

Copper salts and the copper pyrithionate complexes have recently been shown to be effective in the fight against antibiotic resistance, due to their inhibitory action against the metallo-beta-lactamases.[2] Therefore, copper metal has quite good potential to break the bacterial resistance with help of proper carriers. With this objective, a small library of substituted pyrithione ligands (see figure below) have been aimed to be synthesised and characterised as potential carriers/ionophores. In particular, this project will focus on improving two major criteria of this ionophore: (i) lipophilicity to promote ease in membrane permeability, and (ii) stability of the copper coordinated complex (stable enough to avoid release of copper outside bacterial cell membrane but labile enough to release the copper inside the cellular environment of bacteria).

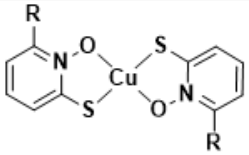

Figure: Substituted copper pyrithionate complex (R = substitution)

Data/Methods/Analysis:

With the objective of investigating structure-activity correlations, a small library of substituted pyrithione ligands with variation in the 6-position of the pyridine ring and respective copper complexes were synthesised (see figure below), purified and characterised. The methyl substituted pyrithione ligand was synthesised via a route of oxidation followed by nucleophilic substitution. The ligand was purified and stabilised as its sodium salt following three step procedure of an extraction in organic solvent, purification using solubility difference and another extraction in basic aqueous medium, respectively. The copper complex of this ligand has been synthesised and characterised using ASAP mass spectrometry, elemental analysis and crystallography data. Comparative discussion of the crystallographic packing structure data for single crystals of Cu(Py)2 and Cu(6-Me-Py)2 gives insight into the observable changes of their solubility. Considerable variation in geometry, as well as crystal-packing and probable types of different intermolecular bonding in the crystal structures of two isomers of Cu(6-Me-Py)2 was observed as hypothesised at the outset of this project, substitution at the 6-position led to a change in crystal packing and increased solubility in a range of solvents. Furthermore, trifluoromethyl substituted pyrithione ligand and the respective copper complex was synthesised and purified following the similar pathway of that for methyl substitution. Synthesis of tert-butyl- and methoxy-substituted pyrithione ligands was also done via similar route. Attempts towards the purification of tert-butyl and methoxy substituted ligands were made, however, the poor stability of these compounds in organic solvents meant that purification was unsuccessful. Most probable reasons behind the low stability could be the adverse steric hindrance and the high electron donating capability of tertiary butyl and methoxy groups, respectively. An attempt to use the impure ligands as precursors for the copper complex formation step was made, but no desired product has been observed in either case. In the upcoming time, we will investigate the physical properties of the complexes, such as solubility and lipophilicity, along with the antibacterial activity testing.

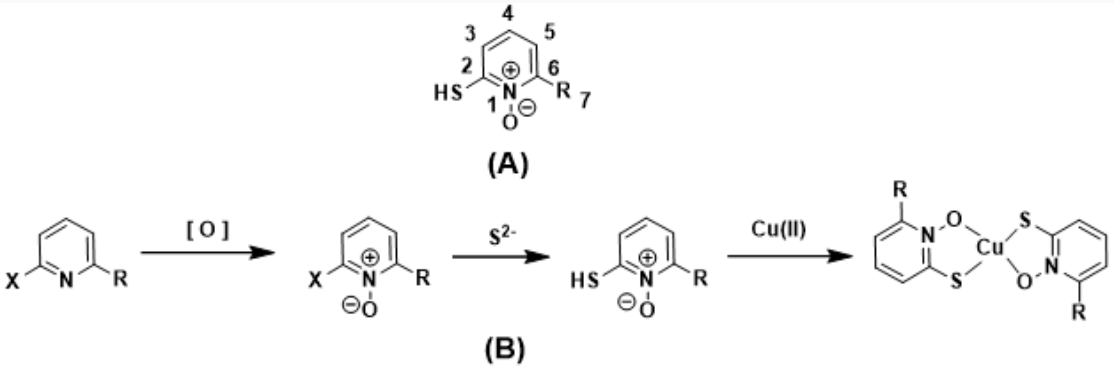

Figure: (A) Substituted pyrithione ligand, (B) general synthetic route for copper complex formation

Contributions to the SDGs:

This research contributes towards keeping antibiotics working. As such, it contributes significantly to SDG 3 on Good Health and Wellbeing, particularly target 3.b on research and development of medicice. This project aims to provide humanity with a solution towards bacterial resistance to antibiotic drugs, the life savers for several lethal diseases. Developing these resistance-breaker copper complexes can further contribute towards cancer research and the development and transfer of new science, knowledge, and technology (SDG 17).

Lessons learnt and key takes/reflections:

Working on this project since last one year has enriched the researchers with knowledge and skills in certain fields. However, it has also taught the meaning of being a postgraduate student; to learn how to attempt something eighth times even after failing seven times before, always striving towards the goal.

Project Information:

- Supervisors/partners
  - Dr. James W. Walton
  - Dr. Karrera Djoko
- Project Duration: 01/02/2019–31/01/2022 (3 Years)
- Project Resources (funded by): Durham University Centre for Doctoral Training Global Challenge Research Fund (GCRF-CDT)
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References:

1. G. L. Patrick, An Introduction to Medicinal Chemistry, 2013, vol. 5

2. K. Y. Djoko, M. E. S. Achard, M.-D. Phan, M. M. Alvin W. Lo, S. Prombhul, S. J. Hancock, K. M. Peters, et al., *Antimicrob. Agents Chemother*, 2018, 62, 1–10