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Synthetic analogues of pyridine-N-oxide disulfides from *Allium stipitatum* demonstrate potent anti-tubercular activities and inhibit mycobacterial drug efflux pumps

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Tuberculosis (TB), having been declared a global emergency since 1993, is still an issue of great public health concern because of the emergence of multi- and extensively- drug-resistant strains of *Mycobacterium tuberculosis*. New molecules with pleiotropic modes of action are urgently required to tackle this challenging menace. Pyridine-N-oxide alkaloids possessing disulfide functional groups were isolated from the bulbs of *Allium stipitatum*, belonging to the genus *Allium* with common members like garlic, onion, leeks and chives. From this discovery, a series of methyl disulfides were synthesized based on the structure of the natural product disulphides isolated from the bulbs of *Allium stipitatum*. The synthetic analogues were produced by adopting the method of Kitson and Loomes, briefly, the appropriate aromatic thiol purchased from Sigma Aldrich was S-methylthiolated using S-methyl methanethiosulphonate and back extracted with dichloromethane.

Antibacterial activities using various high-throughput whole cell phenotypic assays were carried out. A selection of five compounds of that chemical class showed antimycobacterial activities at clinically relevant concentrations when tested against *M. aurum*, *M. bovis* BCG, *M. tuberculosis* H37Rv and multi-drug resistant strains of TB-clinical isolates. In addition, the synthetic compounds inhibited mycobacterial drug efflux mechanism as we report for the first time for this class of compounds.

These studies suggest that synthesized methyl disulfides are novel chemical scaffolds, which potentially can lead to the design of new drugs against TB. The inhibition of efflux pumps by these compounds is promising as it would be a way to improve the efficacy and/or extend the clinical utility of existing antibiotics.

Biography

Cynthia Amaning Danquah is a third year PhD student working on an interdisciplinary research between UCL school of Pharmacy and the Institute of Structural and Molecular biology, ISMB, Birkbeck University of London. Supervised by Prof. Simon Gibbons (Department of Pharmaceutical and Biological Chemistry, UCL school of Pharmacy) and Dr Sanjib Bhakta (Mycobacteria Research Laboratory, ISMB, Birkbeck, University of London). Her PhD is sponsored by the Ghana Education Trust fund.

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