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Multifunctional polycyclic amines as antimycobacterials: Exploring mechanism of action and resistance reversal possibilities in *Mycobacterium tuberculosis*

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Ever-increasing levels of drug resistance in *Mycobacterium tuberculosis* necessitate novel approaches in the search for new antimycobacterials. Early identification of likely mechanism of action and probability of successful accumulation of potential antimycobacterials within mycobacterial cells allow for triage of compounds that warrant further investigation. Early knowledge pertaining to novelty of mechanism of action, possible cross resistance to existing antimycobacterials as well as the risk of acquisition of genetic resistance brought on by efflux-mediated sub-therapeutic intracellular compound accumulation, promotes the likelyhood of identification of therapeutically viable antimycobacterials. Antimycobacterial activity as well as synergistic activity in combination with known antimycobacterials was evaluated for a range of polycyclic amine derivatives obtained from the School of Pharmacy compound library. Compounds were selected based on presence of pharmacophoric moieties for antimycobacterial activity, the inclusion of bulky lipophilic carriers to promote intracellular accumulation through increased cell wall penetration or alternatively reduced efflux as well as previously demonstrated bioactivity that may support accumulation of coadministered compounds within mycobacterial cells. The most active compound demonstrated a MIC_{99} of 9.6 µM against *Mycobacterium tuberculosis* H37Rv. Genotoxicity and inhibition of the problematic bc1 respiratory complex was excluded as mechanism for all compounds, with the two most active compounds likely inhibiting cell wall synthesis in a fashion similar to ethambutol. Synergism assays with known antimycobacterials are currently underway and preliminary results indicate possible synergistic activity with known antimycobacterials. Further structure activity relationship analysis will inform the development of compounds with increased potency and selectivity while exploring possible resistance reversal activity.

Biography

Erika Kapp is a Pharmacist and has completed her MSc in Pharmaceutical Chemistry at North-West University in 2005. From 2006 to 2011 she worked in the not-for-profit sector with the focus on health systems strengthening and sustainable access to antiretroviral and antimycobacterial treatment in the public sector in South Africa. She currently works as a Lecturer in Pharmaceutical Chemistry at the School of Pharmacy, University of the Western Cape, where she is in the process of completing her PhD. Her research interests center on the synthesis and utilization of polycyclic derivatives as resistance reversal agents in *Mycobacterium tuberculosis*.

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