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Discovery of novel compounds to combat multi-drug resistant gonorrhoea

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Background

Treatment of *N. gonorrhoeae* (Ng) is a major public health challenge as it rapidly develops resistance to antibiotics used to treat it, with approximately half of reported cases today caused by drug resistant strains. In the absence of a vaccine to overcome the current and future threat of multi-drug resistant (MDR) Ng, this project focused on identification and development of novel therapeutics for Ng by investigating products from natural sources, which are often a valuable repository of bioactive compounds.

Aim/Methods

To identify novel anti-gonococcal therapeutics we have screened a library of natural products and natural product derived compounds using minimum inhibitory (MIC) and minimum bactericidal concentrations (MBC) assays and tested their efficacy to treat Ng infection in our in vitro cervical epithelial cell model.

Results

In our high throughput growth inhibition experiment we screened a library of 500 compounds and shortlisted 18 that were active against both susceptible (1291) and multi-drug resistant (WHO X) Ng strains. We determined that the MIC and MBC of these lead compounds ranged between 4 and 55 µg/mL against five Ng strains. The MIC of 15/18 compounds was equivalent for 3 MDR Ng strains (WHO K, Z and X) that have distinct antibiotic resistance profiles. Furthermore, the MIC of 13/18 compounds was equivalent between wild type and MtrE mutant strains, suggesting that these compounds are not susceptible to efflux by the via MtrE. We tested the effect of all compounds on metabolic activity of transformed cervical epithelial (tCX) cells and found that 10/18 compounds displayed no toxicity in tCX cells, while 7 weakly suppressed cellular respiration at the highest concentration tested and 1 was highly toxic. Finally, in our tCX cell infection treatment assay 2/10 non-toxic compounds were bacteriostatic and 8/10 were bactericidal, killing >80% of Ng after 3 hours at their MIC.

Conclusions

From our natural compound library screen we have identified 7 compounds with antibacterial activity against MDR Ng for further development as potential anti-gonococcal therapeutics.