BIOCHEMISTRY AND MOLECULAR BIOLOGY SEMINAR SERIES

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Screening marine-derived compounds as potential inhibitors of key bacterial enzymes and pathogens

Infections of the respiratory tract are increasingly prevalent and drug-resistant. Tuberculosis is one such example. A third of the world's population is infected with tuberculosis, which can become active if the host becomes immune compromised. There is an alarming increase in the number of drug-resistant and extensively drug-resistant strains of tuberculosis. Our study uses the target-specific and whole-cell approach in screening for potential anti-tubercular agents. Our whole-cell approach uses Mycobacterium smegmatis as a model (in lieu of the more pathogenic M. tuberculosis) and the target-specific approach focuses on the seventh enzyme of the shikimate pathway, shikimate kinase (SK). Substrate-dependent fluorescence binding assays showed a K_D of 0.05 ± 0.01 mM. for shikimate and 0.12 ± 0.04 mM for ATP. A K_D of 0.26 ± 0.01 mM was recorded for the binding of the inhibitor avarone to shikimate kinase. Chromatograms of the avarone-SK complex showed decreasing intensities over a 24 hr incubation period and the appearance of shoulder peaks, suggesting possible covalent modification of the enzyme. Whole-cell screens with M. Smegmatis showed an IC_{50} of 11.89 ± 0.01 and 15.93 ± 0.38 μM for inhibitors avarone and hymenidin, respectively after a 9 hr incubation period. Our data show promising activity for these inhibitors as potential lead compounds and further mechanistic investigation is performed.

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