HIGHLANDS IN CHEMISTRY SEMINAR SERIES

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"Hitting Malaria and Tuberculosis with the Same Bullet: Dxr Inhibitors as Antimicrobials"

Antibiotic resistance, improper drug administration, co-infection with multiple organisms, and other factors ensure our continued vulnerability to a diverse array of pathogens and necessitate the discovery and development of new drugs. Molecules with new mechanisms of action are especially needed to stem the tide of infectious diseases. 1-Deoxy-D-xylulose 5-phosphate reducto-isomerase (Dxr) catalyzes the first committed step in the methylerythritol phosphate (MEP) pathway of isoprenoid biosynthesis and is essential in most pathogens. Dxr is not found in humans and, thus, represents a promising opportunity for drug discovery. We have identified new inhibitors based on the structure of natural products fosmidomycin and FR900098. Termed MEPicides, these compounds specifically target Dxr. We determine the MEPicide SAR against several Dxr homologs and in a variety of whole cell assays. Our most active compounds display nM activity against P. falciparum parasites and in vivo efficacy against P. berghei-treated mice. MEPicides are on-target as MEPicide-treated P. falciparum is rescued by the addition of IPP (the product of the MEP pathway), and metabolite analysis shows a substantial reduction in MEP metabolites downstream of Dxr following MEPicide treatment. MEPicide prodrugs also display significant activity and an on-target mechanism against Mycobacterium tuberculosis. Toxicity profiles of these compounds are favorable, and our current synthetic work aims at improving key PK parameters. Collectively, our data demonstrate that these MEPicides potently and selectively inhibit Dxr of the MEP pathway, and support further exploration of MEPicides as promising leads in the search for new antimicrobials.

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2:30PM ET

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