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Investigation of novel alkynyl and alkynyloxy pyrimidine nucleoside analogs as antimycobacterial agents

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A rapid increase of the antibiotic resistance against microbial pathogens over the past several decades has become one of the most serious medical challenges to the world. Tuberculosis (TB) caused by *Mycobacterium tuberculosis* is the second leading cause of infectious deaths globally. In 2013, an estimated 9 million people developed tuberculosis and 1.4 million died from this disease. The resurgence of TB cases and the emergence of drug-resistant strains of mycobacteria necessitate the search for new antimycobacterial agents that are non toxic and distinct from the current drugs. We have designed, synthesized and evaluated novel pyrimidine nucleosides (1-20) for their antimycobacterial activities *in vitro*. The 3-N- and or 5-O-propynyl pyrimidine nucleosides (1-14) were synthesized by reacting 5-hydroxy and 5-hydroxymethyl pyrimidine nucleosides with propargyl bromide. 5-Acetylenic nucleosides (15-20) were prepared by coupling 5-iodo pyrimidine nucleosides with trimethylsilyl acetylene followed by de-protection with sodium methoxide. The antimycobacterial activity of compounds 1-20 alone and in combination with first line antituberculosis drug isoniazid was evaluated against *Mycobacterium tuberculosis* (*Mtb*), *Mycobacterium bovis* (*M. bovis*) and *Mycobacterium avium* (*M. avium*) using microplate alamar blue assay. Among alkynyl compounds 5-(2-propynyloxy) uridine (4) and N-3-propynylnucleoside analogs (5 and 12-14) exhibited modest activity against *Mtb* (H37Ra) and *M. bovis* with EC_{50}=160-180 μg/mL, however, they demonstrated strong synergistic interactions with isoniazid. C-5 Ethynyl substituted pyrimidine nucleosides analogs (15-20) were found to be inactive as antimycobacterial agents. Compounds 1-20 did not show cytotoxicity up to the highest concentration tested (CC50>200 μg/mL).

Biography

Saurabh Garg completed his PhD and is working at Laboratory Medicine and Pathology under Dr. Rakesh Kumar, Dr. Robert Rennie, University of Alberta Edmonton, Canada.

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