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Synthesis and Antitubercular Activity of 4,5-Disubstituted N^1-(5′-deoxythymidin-5′-yl)-1,2,3-triazoles

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Synthesis of fifteen C^4-aroyl-C^5-aryl-N^1-(5′-deoxythymidin-5′-yl)-1,2,3-triazoles have been reported starting from azidation of 5′-*p*-toluenesulfonyloxythymidine followed by azide-alkene oxidative cycloaddition reaction of the resulted 5′-azido-5′-deoxythymidine with 1,3-diarylpropenones in dimethylformamide (DMF) in the presence of tetra-*n*-butylammonium hydrogen sulfate (*n*-$Bu_4N^+HSO_4^-$, TBAHS) as catalyst in 60 to 79% overall yields. Further, they were also synthesized by one pot sequential reaction of tosylated thymidine with sodium azide in DMF and then with 1,3-diarylpropenones in presence of *n*-$Bu_4N^+HSO_4^-$ in superior yield of 70 to 95% than 60 to 79% in two step procedure. All fifteen synthesized compounds were screened for their *in vitro* anti *Mycobacterium tuberculosis* activity against sensitive reference strain H37Rv and multi drug resistant (MDR) clinical isolate 591, and found to exhibit minimum inhibitory concentration (MIC) ranging from 2 to 15 μg/mL, which was equivalent to the MIC of first line anti-tubercular drug streptomycin. All compounds qualify for their drug likeness when their physicochemical parameters were assessed using online MolSoft and Lipinski filter software, except their molecular weight. The cytotoxicity of potent compounds evaluated human monocytic cell line THP-1 by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay was found to be less as compared to the first line drug, isoniazid.

Introduction

Tuberculosis (TB), predominantly caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) is one of the biggest health threat causing morbidity and mortality worldwide.[1] The current empiric therapy of combined use of four first-line anti-TB drugs (isoniazid, rifampicin, ethambutol and streptomycin) known as directly observed treatments (DOTS) launched by WHO requires 6–9 months of treatment and the cure rate is approximately 85%.[2] The situation of TB treatment has worsened with the emergence of new *M. tuberculosis* strains that are resistant to DOTS treatment. Cases of TB due to lethal drug-resistant strains (DR-TB), multidrug-resistant strains (MDR-TB) and extensively drug-resistant strain (XDR-TB) are on the rise, which has warranted discovery of new TB treatment regimens and chemotherapeutic agents.[3–6] Design of nucleoside based drugs capable of interfering with *mycobacterial* purine and pyrimidine metabolic pathways is a promising approach towards the future of anti-TB therapy.[4–9] Two 5′-modified lead nucleoside antibiotics, SQ641[5] and CPZEN-45[6] are currently undergoing preclinical testing as an anti-TB agent (Figure 1).

Substituted 1,2,3-triazoles have been considered as a privileged heterocyclic moiety owing to their indomitable biological potential[7] and ability to be linked to different pharmacophores to generate an array of new hybrid molecules with improved efficacy.[8–10] Herein, we describe facile synthesis of C^4-aroyl-C^5-aryl-N^1-(5′-deoxythymidin-5′-yl)-1,2,3-triazoles using two procedures, one by azidation of 5′-*p*-toluenesulfonyloxythymidine followed by condensation of azidothymidine with 1,3-diarylpropenones and the other by one-pot sequential reaction of tosylated thymidine with sodium azide in DMF and then with 1,3-diarylpropenones in presence of *n*-$Bu_4N^+HSO_4^-$ as catalyst involving oxidative azide-olefin [3 + 2] cycloaddition (OAOC) protocol in good to excellent yields. The synthesized 4,5-disubstituted N^1-(5′-deoxythymidin-5′-yl)-1,2,3-triazoles were evaluated for their *in vitro* anti-TB activity against sensitive reference strain H37Rv & MDR clinical isolate 591 and for cytotoxicity activity against human THP-1 cells by MTT assay.

Results and Discussion

The nucleoside precursor of 4,5-disubstituted N^1-(5′-deoxythymidin-5′-yl)-1,2,3-triazoles, *i.e.* 5′-azido-5′-deoxythymidine **2** was synthesized following literature procedure by selective mono-tosylation of thymidine with tosyl chloride followed by azidation of resulted 5′-*p*-toluenesulfonyloxythymidine with

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