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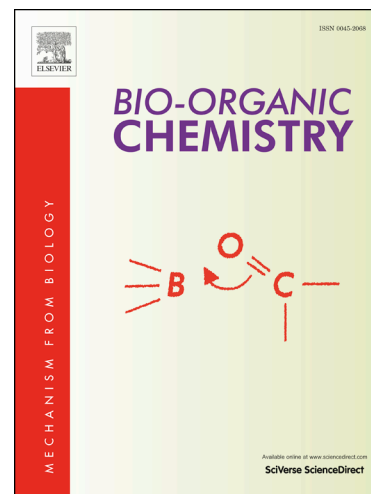
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## Structure-based design of some isonicotinic acid hydrazide analogues as potential antitubercular agents

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### ABSTRACT

New pyridine derivatives were designed and synthesized as Isonicotinic acid hydrazide (INH) analogues. The synthesized compounds were evaluated for their antitubercular activity against *Mycobacterium tuberculosis* strain H<sub>37</sub>R<sub>v</sub>. Ten compounds (**3c**, **3e-g**, **5a-c**, **6h**, **10** and **11b**) showed promising antitubercular activity with MIC range 7.30  $\mu$ M- 19.39  $\mu$ M. Compounds **3e**, **3g**, **5b** and **11b** were the most potent analogues, with MIC 7.30- 8.74  $\mu$ M. They were equipotent to the standard drug Ethambutol (MIC 7.64  $\mu$ M) and more active than the standard drug Pyrazinamide (MIC 50.77  $\mu$ M). They were further examined for cytotoxicity in human embryonic kidney (HEK) cell line at the concentration of 50  $\mu$ g/mL using MTT assay. Results declared that most compounds showed acceptable safety margin. Molecular Docking studies into 2-trans-enoyl-acyl carrier protein reductase, called InhA have been conducted for compounds **3e**, **3g**, **5b** and **11b** using Molecular Operating Environment software (MOE 2016.0802), where reasonable binding interactions have been identified and effective overall docking scores have been recorded. Their drug-likeness has been assessed using *Molinspiration* and *Osiris* software.

Keywords: Pyridine; Isoniazide; *Mycobacterium tuberculosis*; Cytotoxicity; Drug-likeness; Docking

### 1. Introduction

Tuberculosis is a fatal and infectious disease caused by various strains of mycobacteria, usually *Mycobacterium tuberculosis* [1]. It spreads through the air when people who have an active TB infection cough, sneeze, or otherwise air transmitted through respiratory fluids [2]. In 2004 there were about 4.8 million cases [3], most of which occurred in developing countries because of a poor immune system, largely due to high rates of HIV infection and the corresponding development of AIDS [4]. In 2014, there were an estimated 1.5 million deaths from TB, of them, 1.1 million deaths among people who were HIV negative and 390,000 deaths among people who were HIV positive. Tuberculosis is commonly a disease of the lungs (pulmonary tuberculosis) where it forms a localized infection after inhalation. It can affect extra pulmonary regions like lymph nodes, bone and joints [5].

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