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Design, synthesis and docking studies of new molecular hybrids bearing benzimidazole and thiazolidine-2,4-dione as potential antitubercular agents

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ABSTRACT

Finding novel therapeutic medications to combat tuberculosis (TB) is crucial, as evidenced by the disease's growth as a worldwide health concern in recent decades and the rise of drug-resistant forms of *Mycobacterium tuberculosis* (Mtb). In this article, we describe the synthesis and design of a novel class of thiazolidine-2,4-dione derivatives (5a-i) based on 1*H*-benzo [*d*]imidazoles as antitubercular drugs. Spectroscopic techniques and elemental analysis were used to characterize each of the newly synthesized molecules. The antitubercular activity of all the newly synthesized title compounds was assessed against drug-sensitive Mtb H37Rv, multidrug-resistant (MDR-TB), and extensively drug-resistant (XDR-TB) tuberculosis. Compounds 5e and 5 h had the most antitubercular activity among all the newly synthesized hybrids against drug-sensitive, MDR-TB, and XDR-TB strains, with MIC values ranging from 0.21 to 47.84 μM. When it comes to drug-sensitive, drug-resistant, and XDR Mtb strains, compound 5 h with a trifluoromethyl group is 1.71, 10.86, and 3.50 times more potent, whereas compound 5e with a nitro group is 1.12, 8.50, and 2.61 times more active. Remarkably, the compounds' *in vitro* cytotoxicity test demonstrated good selectivity indices, highlighting their safety on the normal lung fibroblast (WI-38) cell line experiment. To further understand the interactions between potent hybrids and the target enzyme, molecular docking investigations were conducted against the decaprenyl-phosphoryl-ribose 2′-epimerase (DprE1) enzyme. The target protein exhibited preferentially positive interactions with the potent compounds 5e, 5f, 5 h, and 5i. Relationships between structure-activity as well as drug-likeness were used to connect the freshly synthesized compounds' physical and biological properties. When considered collectively, these results suggest that compounds 5e and 5 h might be promising candidates for the development of drug-sensitive and drug-resistant TB therapies in the future.

1. Introduction

Mycobacterium tuberculosis (Mtb) is the primary cause of tuberculosis (TB), an infectious illness that affects humans. Since it has been around for millennia, tuberculosis has been a serious health risk to people. It is believed that the TB bacterium infects around 25 % of people worldwide [1]. In 2022, an estimated 7.5 million people worldwide acquired tuberculosis (TB), and 1.3 million fatalities related to the disease were reported [2]. Despite being a disease that dates back to many years, money and effort are constantly put towards making tuberculosis obsolete. The death rate from tuberculosis is too high, even with several attempts to improve diagnostic and treatment protocols [3]. The

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