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Synthesis, antitubercular profile and molecular docking studies of quinazolinone-based pyridine derivatives against drug-resistant tuberculosis

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ABSTRACT

The promising quinazolinone-based pyridine derivatives (4a–j) were synthesized and subsequently tested for their antimycobacterial activities against the various drug-sensitive and drug-resistant *Mycobacterium tuberculosis* (Mtb) strains to combat infectious diseases and address growing concerns about the devastating effects of tuberculosis (TB). Utilizing ^{1}H NMR, ^{13}C NMR, and mass spectra, the structural and molecular confirmation of the synthesized compounds were deciphered. With minimum inhibitory concentration (MIC) values ranging from 0.31 to 19.13 μM, the results showed that compounds 4e and 4f showed promise anti-TB action against both drug-sensitive and drug-resistant TB strains. To study the cytotoxicity of synthesized molecules, normal Vero and mouse macrophage (RAW264.7) cell lines were utilized. Remarkably, it was revealed that at the highest concentration tested, none of the newly synthesized molecules were toxic to the Vero cell line. The binding patterns of the potent compounds 4b, 4e and 4f in the active site of the mycobacterial membrane protein Large 3 (MmpL3) protein are also revealed by molecular docking studies, which has contributed to the development of a structural rationale for Mtb inhibition. The physicochemical characteristics of the compounds were then predicted using theoretical calculations. Overall, the molecular docking results, physiochemical properties, and observed antimycobacterial activity all point to compound 4e with trifluoromethyl and compound 4f with nitro moiety as potential quinazolinone linked pyridine-based MmpL3 inhibitors.

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Quinazolinone; pyridine; tuberculosis; cytotoxicity; molecular docking

1. Introduction

Although it has been around for centuries, tuberculosis (TB), an infectious lung illness caused by *Mycobacterium tuberculosis* (Mtb), is still a danger to world health (Raghu, Pradeep Kumar et al., 2022; Raghu, Yogesh Kumar, et al. 2022). The causative agent of tuberculosis (TB), Mtb, is a highly contagious airborne infection. It primarily affects the lungs and has the power to subvert the immune system of the patient, frequently continuing for years without manifesting any signs (Malik et al., 2022). Although tuberculosis can be treated with antibiotic regimens, the current first line drugs such as isoniazid, rifampin, pyrazinamide and ethambutol have been used to treat tuberculosis for at least 50 years (Cinu et al., 2019). Unfortunately, there are a number of reasons why this first treatment for tuberculosis fails to provide a cure. The advent of TB strains resistant to several treatments is reason for grave worry since treatment with second-line therapies is both more difficult to get and more toxic and expensive than treatment with first-line drugs. Even though the first-line and second-line multi-drug examples of treatments for TB are still being used, they face real risks (Verma et al., 2021). The WHO estimates that 10 million people will get TB in 2021, making this illness the leading cause of premature death due to a single infectious agent (WHO, 2021). Treatment and control of the illness have been greatly hampered in recent years by the emergence and spread of widely and multidrug-resistant TB (Ying et al., 2022). Drug-resistant TB has emerged as a significant social health and safety risk concern as a result of the high death rate and socioeconomic burden (Pai et al., 2016). The creation of effective medicines, sensitive diagnostics, and potent chemotherapeutics is the present emphasis of attempts to manage TB. A novel method of action for next-generation chemotherapeutics that are compatible with current regimens is urgently required (Meena et al., 2020). To be effective against multidrug-resistant Mtb, the novel chemical entities must have a minimal toxicity profile. In light of this gloomy scenario, new anti-TB drugs to tackle drug-resistant infections are urgently needed.

Modern medicinal chemistry is built on heterocyclic molecules. With the help of this adaptable chemical class, drug

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