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Design, synthesis and molecular dynamic studies of novel imidazo/pyrido-pyrimidine clubbed ethyl-1,2,3,4-tetrahydro-4-phenylpyrimidine-5-carboxylate derivatives as potent anti-tubercular agents

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ABSTRACT

A small library of substituted ethyl-1,2,3,4-tetrahydro-4-phenylpyrimidine-5-carboxylate was designed and synthesized. All the characterized molecules were screened for their anti-tubercular activity using the H37Rv strain of *Mycobacterium tuberculosis (Mtb)*. The compounds **5c, 5d, 5f,** 5h**, and 5k** showed equipotent activity (MIC 3.12 μg/mL), compounds **5b, 5e,** 5g**, 5i, and 5j** were more potent (MIC 1.6 μg/mL), whereas, **5a** and **5l** shown moderate activity (MIC 6.25 μg/mL). The potent inhibitory activity of screened compounds was rationalized with *in-silico* molecular modeling studies against the *Mtb*-dihydrofolate reductase (DHFR) enzyme. Compound **5i** displayed a good docking score of −8.56 Kcal/mole with H-bond and hydrophobic interactions. These interactions revealed the stability of the complex which in turn determined the potent inhibitory effect. To get in-depth mechanistic insight into the inhibitory effect and to assess the stability of the ligand–protein complex, a molecular dynamics (MD) simulation study was performed. The RMSD and RMSF values obtained by the MD simulation study were 2.39 Å and 0.92 Å, respectively. The obtained values suggested that the drug–ligand complex maintained the stability over entire 100 ns run and the molecule did not fluctuate. The H-bond and hydrophobic interactions displayed in molecular docking studies were found to be retained in the MD simulation run. The obtained MD simulation values indicate that the complex was stable and rationalize the potent inhibitory effect. The drug-likeliness properties of potent compounds were calculated and the values thus obtained suggested that the molecule 5i has drug-likeliness properties and complies with Lipinski's rule of five/Ro3. Hence, the identified compounds can be taken into further stages of drug discovery processes.

1. Introduction

Tuberculosis (TB) is a contagious illness that is a significant contributor to poor health and one of the leading causes of death worldwide from single infectious agents after COVID-19, rating higher than HIV/AIDS. The bacillus *Mycobacterium tuberculosis*, which causes TB, spreads when infected people release microorganisms into the atmosphere, such as when they cough. One-third of the entire human population is said to be affected by this illness. According to estimates, there were an additional 1.3 million HIV-negative deaths in 2020, up from 1.2 million in 2019, and 214, 000 HIV-positive deaths, up slightly from 209, 000 in 2019. All age groups and both sexes are affected by TB, although men (aged ≥15 years), bear the brunt of the disease, accounting for 53 % of all cases in 2020 [1]. Various drugs such as rifampicin, isoniazid, ethambutol, ethionamide, streptomycin, and pyrazinamide are used for the treatment of TB. These drugs take more than six months for the treatment of TB. Also, the increased multi-drug-resistant (MDR), extensively drug-resistant (XDR), and total drug-resistant (TDR) TB strains continue to pay attention for the synthesis of newer molecules as potent anti-tubercular agents. Various heterocyclic derivatives have proven to be promising anti-tubercular agents. Pyrimidine and its substituted derivatives are important pharmacophores and when clubbed with other heterocyclic compounds have shown potential

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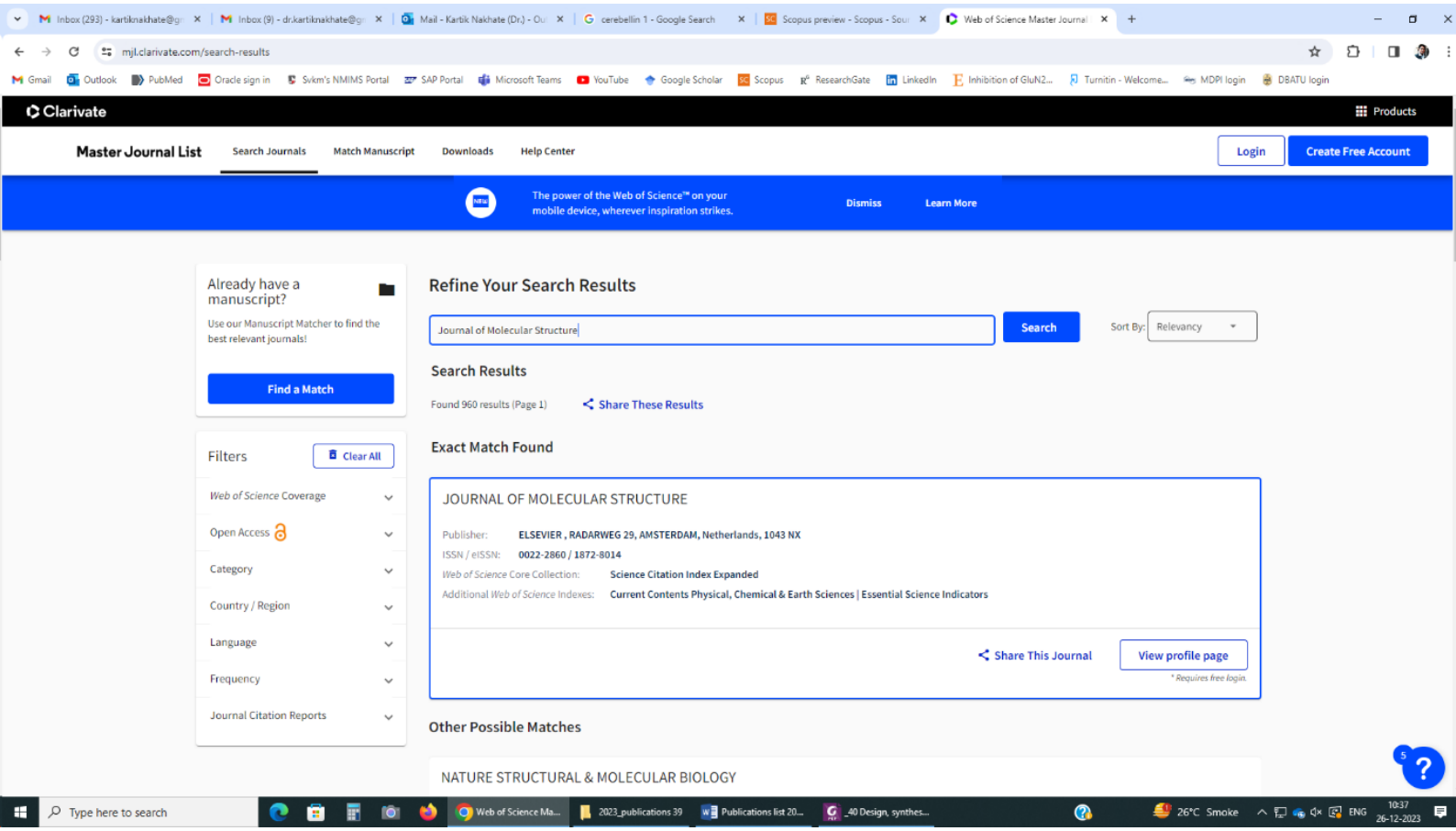
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