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Synthesis, *in Vitro* Antibacterial, and Antitubercular Screening of Some New 4-(1*H*-pyrrol-1-yl)phenyl benzoates with Docking Studies

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ABSTRACT Some new 4-(1*H*-pyrrol-1-yl)phenyl benzoates (**4a-m**) were synthesized by the reaction of 4-(1*H*-pyrrol-1-yl)phenol (**2**) and substituted benzoyl chlorides (**3a-m**). All the synthesized compounds **4a-m** were studied for their antimicrobial and antitubercular activities using standard drugs. With minimum inhibitory concentration values ranging from 0.8 to 12.5 g/mL, all of the drugs demonstrated antitubercular activity. The tested compounds exhibited substantial synthetic accessibility, docking scores, and antimicrobial activities.

KEYWORDS ADMET studies, Antibacterial activity, Antitubercular activity, Molecular docking, Pyrrolyl benzoates.

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INTRODUCTION

Tuberculosis (TB) is a significant provider to morbidity and mortality worldwide.[1] In spite of being avertable and curable, TB still is a primary fatality causing infectious disease caused from *Mycobacterium TB*.[2-4] The World Health Organization (WHO) estimates over 35 million deaths in the coming years till 2025. TB is at present the chief killer among youths, women, and AIDS patients in the world.[5] In 28 different countries, a methodical assessment and meta-analysis of TB occurrence reported that gents have 2.21 times elevated occurrence of bacteriologically established TB compared to ladies.[6] The current standard of care for TB recommends drugs that are over 40 years old. Although steady short-course chemotherapy of aggressive drug-susceptible TB has been shown to be more potent in clinical studies,[7] it requires direct management to ensure better monitoring to prevent drug resistance. However, drugs that are preventing the development of resistant TB are less effective, have higher toxicity, and must be prescribed for a longer period of time. Over the past decades, even though quite a few anti-TB molecules are being developed, drug-resistance concern is the major issue to be looked into. Therefore, there is a huge need to develop novel anti-TB medications that process fewer and simpler regimens, are well-tolerated, effective against drug-susceptible and drug-resistant TB, and appropriate for the combined treatment of HIV and TB.[8] Inhibiting the growth of the *Mycobacterium* cell wall has been the subject of research along this route.[9] To prevent all forms of drug-resistant TB, a medicine must, therefore, work well on *Mycobacterium*'s concurrently acute and chronic developmental phases.[9,10] Due to this impression, numerous investigation has been conducted in aiming the *Mycobacterium* cell wall inhibition. Pyrrole analogs have exhibited anti-TB activity *in vitro*[11,12] and in recent times, a lot of their exploration has been done in designing along with *in silico* studies using pyrrole as a template for synthesis.[13-16] Due to its role as a basic ring

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Molecular docking using Surflex-Dock

The crystal structure of enoyl acyl carrier protein reductase InhA in conjunction with N-(4-methylbenzoyl)-4-benzylpiperidine was discovered using the Brookhaven Protein Database (PDB http://www.rcsb.org/pdb) (PDB ID 2NSD, 1.9 X-ray resolution). In our docking procedure, ligands and protein were prepared according to standard protocol of Sybyl-X 2.0. The docking complex was thought to represent ligand-receptor communication. D core, PMF score, G score, and Chem score scores were computed for a comparative analysis of the functional molecules using the C score package of Sybyl-X 2.0.

ADMET studies

Molecular ADME properties were calculated using *in silico* Swiss ADME online software and prediction of toxicities were calculated using ProTox-II.

Antitubercular activity

Using the MABA, all recently synthesized drugs were evaluated against MTB strain H37Rv. **Table 4** lists the outcomes along with their MIC values.[24]

Antibacterial activity

Using the broth microdilution method, antibacterial inhibition studies for all compounds were compared with the reference drug ciprofloxacin against *S. aureus* (Gram +ve) and *E. coli* (Gram-ve).[25] **Table 4** presents information on antibacterial activity along with MIC values.

CONCLUSION

The antimycobacterial efficacy of 13 new pyrrolyl-phenyl benzoates was investigated. With MICs ranging from 0.4 to 12.5 μg/mL, all the molecules, notably, showed considerable efficacy against the MTB strain. With inhibition values ranging from 0.4 to 1.6 μg/mL, the molecules **4c**, **4d**, **4g**, and **4k** revealed superior Gram -ve inhibition against *E. coli*. All the derivatives were studied for molecular docking analysis. The O- and H-bonding interactions between the TYR158 amino acid and the NAD+/cofactor were designed to be crucial for a drug-receptor binding interface. While, amino acids, LEU207, ALA206, GLY208, ILE215, GLY212, LEU218, ALA211, GLY205, PHE149, GLY204, ILE257, ALA201, MET199, ILE258, LEU188, ALA198, and VAL189 and HIS265, THR266, GLU219, ASP150, ASP256, ASP148, TYR259, and TYR158, played hydrophobic and hydrophilic interactions necessary for InhA enzyme activity inhibition. Based on molecular modeling studies, reported novel inhibitors have showed close fitting within the pocket of binding area of InhA in the similar way as that of 4TZK_ligand and standard drug pyrazinamide. Due to the potency of existing novel molecules to firm control of *M.* TB growth, additional modification of molecular fragment substitutions through molecular modeling, and additional QSAR evaluation, they might be categorized as new leads for the progression of candidate drugs.

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