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In silico Design and Synthesis of Some New Imidazole Derivatives for Tuberculosis

Ashutosh Jena[1], C. Prakashraj[1], Bharath Kumar Chagaleti[1], M. K. Kathiravan[2], B. Shantha Kumar[2]*

[1]Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM IST, Kancheepuram, Tamil Nadu, India
[2]APJ Abdul Kalam Research Lab, SRM College of Pharmacy, SRM IST, Kancheepuram, Tamil Nadu, India

ABSTRACT The present study involves designing a series of 3-(4,5-diphenyl-2-substituted aryl heteroaryl)-1*H* imidazole derivatives that were virtually screened, with the aim to overcome the growing antitubercular resistance and develop more potent antitubercular agents. The designed imidazole derivatives were subjected to *in silico* evaluation such as virtual screening, molecular docking, and ADMET analysis. The selection of synthesized compounds was based on their potent binding energies against the antitubercular target. The one-pot synthetic method was performed by refluxing benzil, aromatic aldehydes, and aromatic amines in ethanol using ceric ammonium nitrate as a catalyst. All six newly synthesized compounds were screened for ligand-receptor interaction of molecular docking. The compounds 1 (4-chloro-2-[1-(4-fluorophenyl)-4,5-diphenyl-1*H*-imidazol-2-yl] phenol) and 4-(2-(3-nitrophenyl)-1-(4-fluorophenyl)-4, 5-diphenyl-1*H*-imidazole) exhibited more binding affinity than the standard drug isoniazid. Finally, the synthesized compounds were screened for *in silico* biological evaluation using the prediction of activity spectra for substances and found to have prominent antitubercular activity.

KEYWORDS Arylaldehydes, Imidazole, Polyketide, Tuberculosis.

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INTRODUCTION

Over 10 million people were affected in 2019 by the second deadliest disease called tuberculosis caused by the common pathogen *Mycobacterium tuberculosis* and rarely by *Mycobacterium bovis*.[1] It is a well-known disease leading cause of death in most developing countries across the world. The main source of transmission in humans is droplets of nuclei. The lungs are the primary site of infection resulting in pulmonary tuberculosis.[2] In 2019, about 10 million people were infected and 1.4 million died of tuberculosis. An additional 1.9 million cases were reported in 2020 as a result of the COVID-19 pandemic. This would substantially rise up to a 20% increase in the tuberculosis burden worldwide over the next 5 years.[3,4] In contrast, 10% of the cases were reported from animals by *M. bovis*.[5] However, other species such as *Mycobacterium africanum* and *Mycobacterium avium* infections in humans are uncommon.[6] According to the WHO, every year more than 2 million people died from tuberculosis and the death toll is getting worse due to the rise of drug-resistant strains.[7] However, 20.8% of cases were found to be infected with a history of diabetes.[8,9] All these factors contribute to the researcher's to develop and introduction of several novel chemical entities against tuberculosis to control the infection.[10] Recent therapeutic targets that emerged from academic researchers and scientists would outline the potent drug targets that pave to develop of novel chemical entities in inhibiting the organism to a greater extent and completely eradicating infection in the future.[11]

Heterocyclic compounds play a peculiar role in the design and discovery of new chemical entities. Among various heterocycles, nitrogen, oxygen, and sulfur-containing heterocycles have been paid much attention

*Corresponding author: Email: ashokshantha0@gmail.com

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δ 7.48 (q, 4H, -CH), 7.32 (t, 4H, -CH), 7.22 (s, 2H, -CH), 7.2 (q, 2H, -CH),7 (q, 2H, -CH), 7.37 (s, 1H, -CH), 7.26 (s, 1H, -CH), 7.49 (s, 1H, -CH), 7.11 (s, 1H, -CH); MS (ESI) m/z:471 [M]+2; Anal. found C,68.35; H,4.24; N,5.94%. **Compound-5** Molecular formulae: $C_{27}H_{21}N_2BrFCl$.

2-(3-Nitrophenyl)-1-(4-fluorophenyl)-4,5-diphenyl-1H-imidazole (6):

m.p.156°C, yield 95.87%, IR (KBr,cm^{-1}): 1593(C-H), 640.22(C-F),569.2 (C-Cl);^{1}H NMR (400 MHz, DMSO): δ 7.48 (q, 4H, -CH), 7.32 (t, 4H, -CH), 7.22 (s, 2H, -CH), 7.33 (d, 2H, -CH),7.42 (d, 1H, -CH); MS (ESI) m/z:426 [M]+2; Anal. found C,76.05; H,4.69; N,6.57%. **Compound-6** Molecular formulae: $C_{27}H_{21}N_2FCl_2$.

Virtual screening

A series of substituted imidazole derivatives was designed as an inbuilt library and performed the virtual screening using PyRx a computational tool in drug discovery. In addition, PyRx has extensive visualization capabilities and chemical spreadsheet-like features that are crucial for rational drug design.[22] It is promising *in silico* technique that is extensively used to identify the hits and optimize the leads in a short period of time. It computationally evaluates a large library of compounds that targets the known structure and is tested experimentally to justify the prediction. Indirectly, this also screens the potential drug targets. It includes docking wizards that are easy-to-use user interfaces which makes it sophisticated for drug design and discovery.

Molecular docking

To find the ligand's binding affinity to the receptor, the molecules were subjected to molecular docking using the Maestro Schrodinger version (2020-1) 4. Their binding energies were calculated and analyzed.[23]

Ligand Preparation

Designed ligand structures were transferred into Maestro Schrodinger version 2020–21 using smiles notation and further subjected to required parameters such as ionization of compound.

Protein preparation

From PDB online database, the protein structure was imported and further processed for adding polar hydrogen, removal of water molecules, etc., Finally, the selected protein chain was optimized and minimized with the help of the reference tab.

Receptor-grid generation

Whole protein and ligands were covered with a grid box in X-, Y-, and Z-axis dimensions.

Ligand Docking

Ligand docking was chosen for docking. Grid files and ligand-out ZIP files were generated from the working directory.[24]

In-silico analysis

Selected top-score compounds from docking were subjected to *in-silico* analysis, namely, drug-likeness by Molinspirationlike molecular weight, hydrogen bond donors, acceptors, rotatable bonds, violations, volume, and mi logP.[25,26] ADME analysis was done by Swiss ADME, prediction of toxicity was by Protox-II[25,27] and *in silico* prediction of antitubercular activity was analyzed by PASS online.[27]

CONCLUSION

In the present study, a series of new six 2-(aryl)-1-(4-fluorophenyl)-4,5-diphenyl-1*H*- imidazole derivatives was synthesized utilizing CAN as a catalyst and screened for *in silico* evaluation for antitubercular activity using Isoniazid as a standard drug. All the synthesized compounds satisfied Lipinski's rule of five demonstrating intensified oral bioavailability, molecular weights, hydrogen bond donors, and acceptors, along with the log P values. Molecular docking results revealed that compounds **1 and 4 show** more interactions with the target with less binding energy. Therefore, compounds **1** and **4** can be further optimized to develop new leads in the future. The present investigation recommends that new imidazole derivatives can be utilized as lead for the advancement of novel anti-tubercular agents. Further studies are required to perform *in vitro, in vivo,* and molecular dynamic studies to know the stability of the drug.

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CONFLICTS OF INTEREST

No potential conflicts of interest were reported by the author(s).

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