In-silico design and ADMET predictions of some new imidazo[1,2-a]pyridine-3-carboxamides (IPAs) as anti-tubercular agents

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A R T I C L E   I N F O
Keywords:
In-silico design
Tuberculosis
Binding affinity
Pharmacokinetics
Molecular interactions
Hydrogen bond

A B S T R A C T

Tuberculosis (TB) is one of the leading infectious diseases worldwide even with the ravaging COVID-19 pandemic in recent times. This mandated further search and exploration of more possible anti-TB drug candidates against M. tuberculosis strains. As an extension of our previous work on the homology modeled cytochrome b subunit of the bc1 complex (QcrB) of Mycobacterium tuberculosis, an in-silico design was carried out in order to further explore more newly potential anti-TB compounds. Ligand 26 was selected as the lead template (scaffold A) based on our previous docking results and its less bulky structure. Successively, eight (8) new ligands (A1–A8) were designed with better binding affinities in comparison to the scaffold template (~6.8 kcal/mol) and isoniazid standard drug (~6.00 kcal/mol) respectively. In addition, three (3) designed ligands namely, A6, A2, and A7 with higher binding affinities were validated via ADME and toxicity prediction analysis, and the results showed zero violations of Lipinski rules with similar bioavailability, and high rate in gastrointestinal absorption, while toxicity parameters such as carcinogenicity and cytotoxicity were all predicted as non-toxic (inactiveness). The designed IPA compounds in the present study could serve as a promising gateway that could help the medicinal and synthetic chemist in the exploration of a new set of derivatives as anti-TB agents. Therefore, this research strongly recommends further experimental consideration of the newly designed IPA compounds through synthesis, in-vitro and in-vivo studies to validate the theoretical findings.

1. Introduction

Mycobacterium tuberculosis is the organism that causes one of the chronic infectious diseases popularly known as Tuberculosis (TB) responsible for the global high mortality rate [1]. The emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the cursor of the COVID-19 pandemic has continued to dominate the scientific research community and other media outlets in recent times [2,3]. Scientific evidence based on clinical perspective indicates that COVID-19 materializes regardless of TB manifestation, either after, during, or before an active diagnosis [2]. Therefore, TB should be given utmost attention even with its global declining rate of cases [1]. An imidazo [1, 2-a] pyridine-3-carboxamide (IPA) candidate (Q203) was reported to exhibit robust inhibitory activity against extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains and it is currently in clinical trials [4]. Researchers are currently developing a keen interest in the synthesis of diverse series of compounds as anti-TB agents. Recently, benzo[d]imidazole-2-carboxamides and benzimidazo-zoquinazoline derivatives as new anti-TB agents were designed, synthesized, and tested for biological responses respectively [5,6]. Hence, the rapid increase in the occurrences of TB drug resistance attracts the need to find new therapeutics as well to discover novel drug targets that could effectively kill M. tuberculosis when exploited. Some of the promiscuous targets inhibited by more than one compound include DprE1, MmpL3, QcrB, etc [7]. The novel derivatives of Q203 (IPAs) as anti-TB agents were also reported to have the ability to block the growth of MDR and XDR strains of M. tuberculosis by targeting the respiratory cytochrome bc1 complex (QcrB) [7]. The QcrB subunit is an important component of the electron transport chain necessary for the synthesis of ATP as it catalyzes the transfer of an electron from the ubiquinol to the cytochrome c [8]. However, the interaction of bonded ligand to the QcrB subunit receptor remains unclear and the crystal structure is not

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https://doi.org/10.1016/j.jctube.2021.100276

Available online 20 September 2021
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available in the Protein Data Bank (PDB) [9]. The search for more potent compounds is very tedious, costly, and time-consuming [10]. As such, the use of computational chemistry tools based on theoretical insights could come in handy with the aim to modify and design new compounds with better bioactivities. Some of the computational methods employed in computer-aided drug design include homology modeling, molecular docking simulation, pharmacokinetic predictions, and QSAR analysis amongst others. These computational approaches have been employed over the years to improve existing anti-tubercular agents through virtual screening for the identification and modification of potential hits [11,12]. Structure-based drug design (SBDD) solemnly depends on the knowledge and information of the 3D crystal structure of the targeted protein to design the ligands that can serve as better inhibitors [13]. In the case where the 3D experimental structure of the targeted protein is not reported, the experimental amino acid sequence can be used to build a homology model [14]. The homology modeling technique predicts the 3D structure of the targeted protein sequence based on the alignment of an experimentally known homologous protein as a template [15]. In our previous report, homology modeling and molecular docking studies were carried out on some IPAs anti-TB agents targeting the QcrB subunit. The homology modeling of the receptor built and predicted a new 3D structure of QcrB target in M. tuberculosis using QcrB subunit of M. smegmatis as template [12,16]. Furthermore, the results of molecular docking in the study further revealed the binding profiling of the 35 IPA

Table 1
Chemical structures of the designed imidazo[1,2-a] pyridine-3-carboxamides (IPAs).

| Compound code | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> |
|---------------|--------------|--------------|--------------|
| A1            | Cl           | Me           |              |
| A2            | Cl           | Me           |              |
| A3            | H            | Me           |              |
| A4            | H            | Et           |              |
| A5            | H            | Me           |              |
| A6            | H            | n-Pr         |              |
| A7            | H            | OMe          |              |
| A8            | H            | c-Pr         |              |

Template scaffold A (-6.8kcal/mol)
labeled docked with the modeled protein. In the current study, the same 3D crystal structure of the QcrB modeled protein in *M. tuberculosis* was used to analyze the binding profiling and ADMET prediction of some newly designed compounds as potential hits of anti-TB candidates.

2. Methodology

2.1. Template selection and structural modifications

In our previous report, we have successfully carried out virtual screening of thirty-five (35) N-(2-phenoxy) ethyl imidazo[1,2-a] pyridine-3-carboxamides (IPAs) synthesized by Wang et al., (2019) with our homology modeled QcrB protein as the active target in the *Mycobacterium tuberculosis* [7,16]. As such, ligand 26 was selected as the template scaffold for further structural modification and rigorous molecular docking simulation. The structure of the newly designed ligands was drawn (Table 1) and optimized accurately at the density functional level of theory (B3LYP/6-31G**) in a vacuum using Spartan 14 [17].

2.2. Molecular docking, ADME analysis, and toxicity prediction

Molecular docking is the most preferable technique in structure-based drug design to predict the binding free energy and the binding mode of the protein and ligand compound [18]. Therefore, molecular docking simulation was carried out to determine the binding affinities and the residual interactions when the ligand molecules bind with the active pockets of the protein as macromolecule using AutoDock 4.2 module implemented in PyRx 0.8. Blind docking was performed for all the designed ligand molecules to predict the active binding pockets of the modeled QcrB protein as the targeted macromolecule [19]. To ensure that all ligand molecules are properly docked, the 3D grid box dimensions were adjusted as X: 203.60, Y: 177.43, Z: 211.23 for grid spacing of 1.875 Å on the whole protein structure to predict the best outcome of the docking task. Furthermore, the docking algorithm used was the Lamarckian Genetic Algorithm at default parametrized settings. After docking, protein and the ligands were obtained in PDBQT format, and complexes were formed using UCSF Chimera software while the visualization of residual interactions was done using Discovery Studio. Conventional drug was the Lamarckian Genetic Algorithm at default parametrized settings. Blind docking was performed for all the modeled QcrB protein as the targeted macromolecule [19].

Table 2

| Compounds            | Binding affinity (kcal/mol) | Bonding types | Interacting amino acid residues | Distance (Å) |
|----------------------|----------------------------|---------------|---------------------------------|--------------|
| Standard drug        | −6.00                      | Conventional Hydrogen Bond | LEU58                         | 2.09388      |
| Hydrogen Bond        |                            | Conventional Hydrogen Bond | LEU59                         | 2.84072      |
| Pi-Anion             | GLU159                     | 3.32022       |
| Pi-Alkyl             | LEU58                      | 3.97204       |
| Pi-Alkyl             | PRO221                     | 5.18191       |
| Conventional Hydrogen Bond | A1                       | ALA385        | 2.52924                         |
| Halogen              | LEU348                     | 2.87618       |
| (Fluorine)           |                            |               |                                 |
| Pi-Sigma             | PHE133                     | 3.61502       |
| Pi-Alkyl             | ALA385                     | 3.67506       |
| Pi-Sigma             | ALA385                     | 3.60692       |
| Pi-Alkyl             | T-shaped                   | PHE133        | 4.99664                         |
| Amide-Pi Stacked     | ALA385                     | 4.12602       |
| Amide-Pi Stacked     | ILE386                     | 4.12602       |
| Alkyl                | LEU129                     | 5.40777       |
| Alkyl                | ILE386                     | 4.18797       |
| Alkyl                | VAL345                     | 3.40783       |
| Alkyl                | ALA385                     | 4.43333       |
| Alkyl                | ALA385                     | 4.32462       |
| Alkyl                | ILE386                     | 5.06303       |
| Alkyl                | LEU129                     | 5.19201       |
| Alkyl                | PHE133                     | 4.1159        |
| Alkyl                | PHE134                     | 4.35564       |
| Alkyl                | PHE388                     | 4.7971        |
| Alkyl                | TYR389                     | 4.48071       |
| Conventional Hydrogen Bond | A2                       | GLY56        | 2.08894                         |
| Halogen              | GLU159                     | 3.59989       |
| (Fluorine)           |                            |               |                                 |
| Pi-Alkyl             | GLU159                     | 4.31326       |
| Alkyl                | LEU59                      | 3.92938       |
| Alkyl                | PRO221                     | 4.39931       |
| Alkyl                | LEU65                      | 4.57881       |
| Alkyl                | ARG111                     | 4.54332       |
| Alkyl                | PRO167                     | 4.47863       |
| Alkyl                | LEU65                      | 4.48087       |
| Alkyl                | LEU166                     | 5.41423       |
| Alkyl                | PRO167                     | 5.16489       |
| Pi-Alkyl             | ILE217                     | 4.59328       |
| Pi-Alkyl             | PRO221                     | 4.71614       |
| Pi-Alkyl             | PHE69                      | 5.14437       |
| Pi-Alkyl             | PHE69                      | 4.72374       |
| Halogen              | HIS114                     | 3.36308       |
| (Fluorine)           |                            |               |                                 |
| Pi-Anion             | GLU159                     | 3.94788       |
| Alkyl                | LEU58                      | 3.81904       |
| Alkyl                | LEU59                      | 4.09035       |
| Alkyl                | PRO221                     | 4.4197        |
| Alkyl                | LEI65                      | 4.40346       |
| Alkyl                | LEU166                     | 4.97961       |
| Pi-Alkyl             | LEU58                      | 5.39169       |
| Pi-Alkyl             | LEU59                      | 5.27014       |
| Pi-Alkyl             | PRO221                     | 4.32695       |
| Pi-Alkyl             | PHE69                      | 4.72942       |
| Pi-Alkyl             | HIS114                     | 5.15802       |
| Pi-Alkyl             | HIS216                     | 5.28912       |
| Carbon Hydrogen Bond | GLY163                     | 3.31031       |
| Halogen              | GLY163                     | 3.31031       |
| (Fluorine)           |                            |               |                                 |
| Halogen              | HIS114                     | 3.68598       |
| (Fluorine)           |                            |               |                                 |
| Halogen              | HIS216                     | 3.05615       |
| (Fluorine)           |                            |               |                                 |
| Pi-Sigma             | LEU56                      | 3.7055        |
| Alkyl                | ALA97                      | 3.69526       |
| Alkyl                | ILE100                     | 4.33314       |
| Alkyl                | ARG111                     | 4.58662       |
| Alkyl                | PRO167                     | 4.85181       |

(continued on next page)
Fluorine), Pi-Anion, Alkyl, Pi-Alkyl were visualized in the complex with the amino acid residues of (GLY62, GLU159, LEU59, PRO221, LEU65, ARG111, PRO167, LEU65, LEU166, ILE217, PHE69) showed in Fig. 2. A7 as a ligand compound expressed (10.5 kcal/mol) binding affinity with the targeted modeled QcrB protein. Complex showed one Carbon Hydrogen Bond with the amino acid residue of (HIS216 at a distance of 3.78978 Å) and three different types of bonds such as Halogen Bonding. Table 2 (continued)

| Compounds | Binding affinity (kcal/mol) | Bonding types | Interacting amino acid residues | Distance (Å) |
|-----------|-----------------------------|---------------|---------------------------------|--------------|
| Alkyl     | ILE217                      | 4.56014       |
| Alkyl     | PRO221                      | 4.85313       |
| Pi-Alkyl  | PRO167                      | 5.10454       |
| Pi-Alkyl  | PHE69                       | 5.29162       |
| Pi-Alkyl  | HIS114                      | 4.68175       |
| Pi-Alkyl  | HIS216                      | 5.24304       |
| A5        | −10.3                       | Halogen (Fluorine) | HIS114 | 3.50679 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU58 | 4.04364 |
| A5        | −10.3                       | Halogen (Fluorine) | PRO221 | 4.89791 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU55 | 4.70392 |
| A5        | −10.3                       | Halogen (Fluorine) | ILE217 | 4.56661 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU55 | 4.52788 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU55 | 4.80007 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU166 | 4.60995 |
| A5        | −10.3                       | Halogen (Fluorine) | PRO221 | 5.42632 |
| A5        | −10.3                       | Halogen (Fluorine) | LEU59 | 5.39063 |
| A5        | −10.3                       | Halogen (Fluorine) | PRO221 | 4.44757 |
| A5        | −10.3                       | Halogen (Fluorine) | PHE69 | 4.87213 |
| A5        | −10.3                       | Halogen (Fluorine) | HIS114 | 5.14963 |
| A5        | −10.3                       | Halogen (Fluorine) | HIS114 | 5.12793 |
| A5        | −10.3                       | Halogen (Fluorine) | HIS216 | 5.28053 |
| A6        | −11.0                       | Conventional Hydrogen Bond | GLU159 | 3.66252 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU58 | 4.97455 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU59 | 4.97455 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU58 | 4.97241 |
| A6        | −11.0                       | Conventional Hydrogen Bond | VAL63 | 4.49813 |
| A6        | −11.0                       | Conventional Hydrogen Bond | ILE217 | 4.54423 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU55 | 4.95044 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU166 | 5.47454 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU55 | 4.41666 |
| A6        | −11.0                       | Conventional Hydrogen Bond | PRO2167 | 5.21434 |
| A6        | −11.0                       | Conventional Hydrogen Bond | PRO221 | 4.89313 |
| A6        | −11.0                       | Conventional Hydrogen Bond | LEU59 | 5.17173 |
| A6        | −11.0                       | Conventional Hydrogen Bond | PHE69 | 5.20022 |
| A6        | −11.0                       | Conventional Hydrogen Bond | PHE69 | 5.12895 |
| A6        | −11.0                       | Conventional Hydrogen Bond | TYR213 | 5.39932 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS216 | 3.78978 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS114 | 3.60387 |
| A7        | −10.5                       | Carbon Hydrogen Bond | LEU58 | 4.03498 |
| A7        | −10.5                       | Carbon Hydrogen Bond | LEU59 | 3.97007 |
| A7        | −10.5                       | Carbon Hydrogen Bond | LEU55 | 5.01233 |
| A7        | −10.5                       | Carbon Hydrogen Bond | LEU55 | 4.53948 |
| A7        | −10.5                       | Carbon Hydrogen Bond | PRO2167 | 5.11711 |
| A7        | −10.5                       | Carbon Hydrogen Bond | PRO221 | 5.46251 |
| A7        | −10.5                       | Carbon Hydrogen Bond | LEU59 | 5.39657 |
| A7        | −10.5                       | Carbon Hydrogen Bond | PRO221 | 4.5088 |
| A7        | −10.5                       | Carbon Hydrogen Bond | PHE69 | 5.20022 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS114 | 5.13828 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS114 | 4.95511 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS216 | 5.23027 |
| A7        | −10.5                       | Carbon Hydrogen Bond | HIS216 | 5.06078 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 2.16555 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 4.63904 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ILE386 | 4.63904 |
| A8        | −9.0                        | Conventional Hydrogen Bond | LEU129 | 4.97501 |
| A8        | −9.0                        | Conventional Hydrogen Bond | MET126 | 4.10023 |
| A8        | −9.0                        | Conventional Hydrogen Bond | VAL345 | 4.60088 |
| A8        | −9.0                        | Conventional Hydrogen Bond | VAL345 | 4.60002 |
| A8        | −9.0                        | Conventional Hydrogen Bond | LEU348 | 5.44256 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 4.26799 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 4.0649 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 4.75806 |
| A8        | −9.0                        | Conventional Hydrogen Bond | LEU129 | 5.14748 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ALA385 | 4.62964 |
| A8        | −9.0                        | Conventional Hydrogen Bond | ILE386 | 4.76785 |
| A8        | −9.0                        | Conventional Hydrogen Bond | PHE133 | 4.51775 |
| A8        | −9.0                        | Conventional Hydrogen Bond | PHE388 | 4.91468 |
| A8        | −9.0                        | Conventional Hydrogen Bond | TYR389 | 3.85255 |

Fig. 1. (a) Schematic representation of predicted A6 ligand with protein complex interactions in the 2D diagram. Interactions are colored depending on their type. (b) The three-dimensional representation of the binding pose, interactions, H bond donor, and acceptor surface of predicted A6 ligand with the protein complex. (c) Targeted protein is depicted in surface view and A6 ligand compound as the stick in the binding pocket.
(Fluorine), Alkyl, Pi-Alkyl with the amino acid residues of (HIS114, LEU58, LEU59, LEU65, PRO167, PRO221, LEU59, PHE69, HIS114, HIS216) showed in Fig. 3. Furthermore, A3, A4, A5, A8 ligand molecules as complexes with the targeted modeled QcrB protein also revealed higher binding affinity than the template molecule and standard drug respectively. Based on the highest molecular docking scores as binding affinity, non-bond interactions and in comparison with the binding affinity of the standard drug, three ligand compounds (A6, A2, and A7) were considered for further analysis.

3.2. ADME and toxicity prediction

Molecular weight (acceptable range: \(\leq 500\)), number of hydrogen bond acceptors (acceptable range: \(\leq 10\)), lipophilicity (Log P) \(\leq 5\), and molar refractivity (40–130) indicates the five rules of Lipinski, are crucial parameters for a successful drug candidate [20]. All the ADME parameters including drug-likeness, pharmacokinetic profile, and water solubility were analyzed for the selected ligand molecules showed in Table 3. All the ligand molecules as A6, A2, and A7 revealed 0 violations in Lipinski rules, similar bioavailability, and a high rate of gastrointestinal absorption. Only the A2 ligand molecule has glycoprotein permeability. Toxicity prediction was analyzed to determine the compounds were whether toxic or not. Predicted results were shown in Table 4. Determination of carcinogenicity and cytotoxicity of A6, A2, A7 were
template scaffold (Ligand 26) was selected for the in-silico design of IPA compounds as potential hits of anti-TB candidates. The Ethical statement showed zero violations of Lipinski rules with similar bioavailability, and addition, all docking results of designed ligands with the targeted protein showed binding affinities ranging from (−8.5 kcal/mol to −11 kcal/mol). The drug-likeness and pharmacokinetic profile prediction results for the selected ligands with higher binding affinities (A6, A2, and A7) showed zero violations of Lipinski rules with similar bioavailability, and high rate in gastrointestinal absorption, while toxicity parameters such as carcinogenicity and cytotoxicity were all predicted as non-toxic (inactiveness).

### 4. Conclusion

As an extension of our previous work, this research adopted the in-silico approach in analyzing the binding profiles of some newly designed IPA compounds as potential hits of anti-TB candidates. The template scaffold (Ligand 26) was selected for the in-silico design strategy and ligand compounds (A1–A8) were designed which exhibited better binding affinities when compared with that of the scaffold template (6.8 kcal/mol) and isoniazid standard drug (6.00 kcal/mol). In addition, all docking results of designed ligands with the targeted protein showed binding affinities ranging from (−8.5 kcal/mol to −11 kcal/mol). The drug-likeness and pharmacokinetic profile prediction results for the selected ligands with higher binding affinities (A6, A2, and A7) showed zero violations of Lipinski rules with similar bioavailability, and high rate in gastrointestinal absorption, while toxicity parameters such as carcinogenicity and cytotoxicity were all predicted as non-toxic (inactiveness).

### Ethical statement

Not applicable

### CRediT authorship contribution statement

**Mustapha Abdullahi**: Conceptualization, Methodology, Data curation, Formal analysis, Supervision. **Niloy Das**: Software, Visualization, Validation, Writing - original draft. **Ahmed Muhammad Sani**: Writing - review & editing.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this work reported in this paper.

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