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# IN-SILICO PREDICTIVE BINDING AFFINITY AND ADMET OF NOVEL N-[5-(2-FLUOROPHENYL)-1, 3, 4-OXADIAZOLE-CARBOXAMIDE DERIVATIVES TOWARDS PROTEIN KINASE G OF MYCOBACTERIUM TUBERCULOSIS

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**Abstract**

The present study experimentally investigated the nitro-substituted heteroaromatic carboxamidesas effective against PKnG of Mycobacterium tuberculosis. Here we designed 15 heteroaromatic carboxamides [A1-B5]. The activities of the compounds can be explained in terms of docking results and biological activity by ADMET prediction. Protein Kinase G is a thioredoxin-fold containing eukaryoticlike serine/threonine Protein Kinase is a virulence factor in Mycobacterium tuberculosis. In present study the compounds A7, A2, A5& A6 are the candidates that shows the good results in Molecular Docking and these are tested against the reference compound that is stand Anti-TB agent Isoniazid.



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## Introduction

In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form a stable complex [1]. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using, for example, scoring functions.

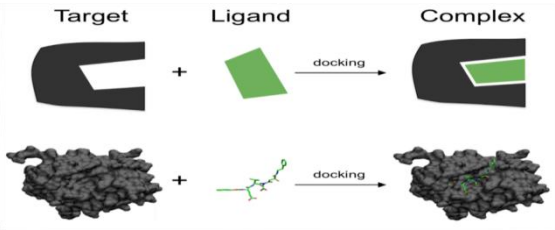



Figure 1: Molecular Docking

## Docking assessment (DA)

Procedure to quantify the predictive capability of a docking protocol.

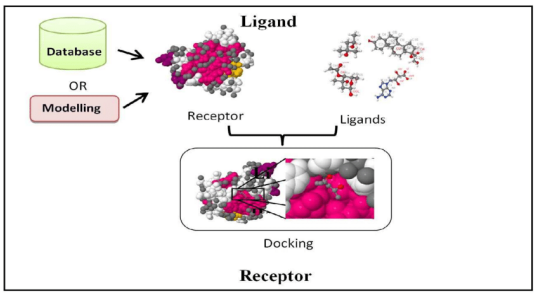



Figure 2: Molecular Docking Flow chart

The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism vs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced.

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterization of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes [2, 3].

## Stages of Docking

### i. Pose generation

Place the ligand in the binding site generally well solved. Rigid docking with a series of conformers most techniques use this approach and then techniques will generate the conformers internally rather than using conformers as inputs. Incremental construction (Flexx): Split ligand into base fragment and side-chains place base add side chains to grow, scoring as you grow.

### ii. Pose selection/scoring

Where most of the current research focused more sophisticated scoring functions take longer. Balance need for speed vs. need for accuracy. Virtual screening needs to be very fast. Studies on single compounds can be much slower. It can do multistage studies.

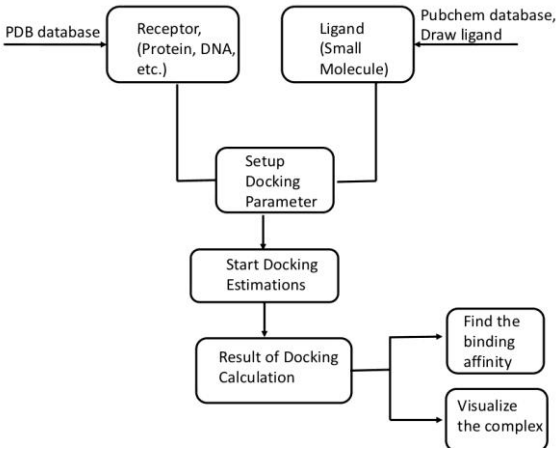



Figure 3: Stages of docking

**Tuberculosis** Tuberculosis (TB) is caused by an Mycobacterium Tuberculosis an etiological agent leading cause of morbidity and mortality all over the world. The tuberculosis death rate has dropped significantly in the past due to an extensive implementation of DOTS and stop TB strategy by world health organization [4].

### Carboxamides

An amide of a carboxylic acid having the structure RC (=O) $NR_2$. The term is used as a suffix in systematic name formation to denote the –C(=O) $NH_2$ group including its carbon atom [5].

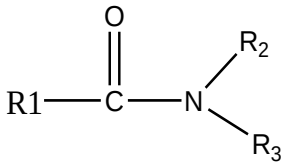



Figure 4: General structure of Carboxamides

### Oxadiazole

Oxadiazole or furadiazole is a five membered heterocyclic molecule and is considered to be derived from furan by replacement of two methane (-CH2) groups by pyridine type nitrogen [6].

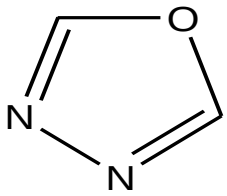



Figure 5: General structure of Oxadiazole

## Materials Method and Methodology

### Software used

A Software is a set of instructions, data or programme used to operate computers ans execute specific tasks. Here it describes about the software that used in the docking process to obtain the effective results.

- MCULE
- Protein Data Bank (https://doi.org/10.2210/pdb4Y0X/pdb)
- Swiss ADMET Programme
- Chemdraw 8.0

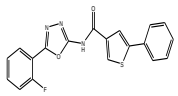
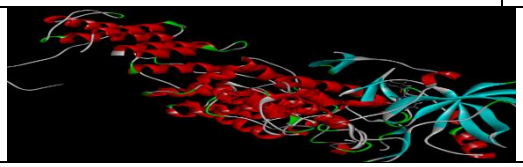
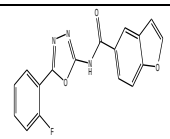
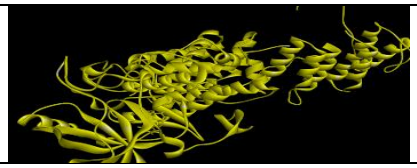
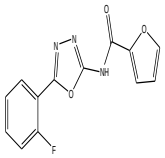
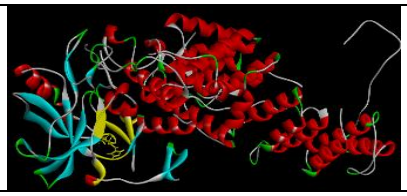
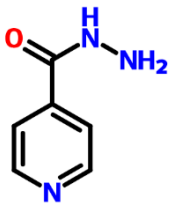
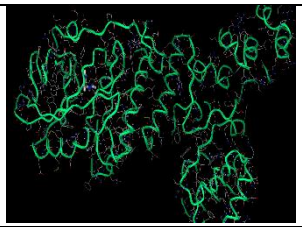
### Protein Profile

### Protein Kinase G (PKnG)

Protein kinase G (PknG), a thioredoxin-fold-containing eukaryotic-like serine/threonine protein kinase, is a virulence factor in *Mycobacterium tuberculosis*, required for inhibition of phago-lysosomal fusion [7].

PknG acts as an unusual ubiquitinating enzyme to remove key components of the innate immunity system, thus providing a potential target for tuberculosis treatment. Among eleven Mtb STPKs, the mycobacterial serine/threonine protein kinase G (PknG) is of particular interest due to its critical role in Mtb intracellular survival and pathogenicity.PknG promotes the intracellular survival of Mtb by inhibiting host phagosomal maturation.

Table 1: Binding Interactions of Possible aryl halides in R position

| CODE | COMPOUND | BINDING INTERACTION | IUPAC NAME |
|---|---|---|---|
| A1 |  |  | *N*-(5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl)-5-phenylthiophene-3-carboxamide |
| Figure 6:Binding Interaction of A1 with PKNG | | | |
| A2 |  |  | *N*-(5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl) benzofuran-5-carboxamide |
| Figure 7:Binding Interaction of A2 with PKnG | | | |
| A3 |  |  | *N*-(5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl) furan-2-carboxamide |
| Figure 8:Binding Interaction of A3 with PKnG | | | |
| Isoniazid |  |  | Pyridine-4-carbohydrazide |
| Figure 9:Binding Interaction of Isoniazid with PKnG | | | |

## Results

The results of Designed molecules with PknG were obtained as docking score are mentioned in following table. The entire Designed molecules have shown a good binding affinity with PknG in comparison with standard Isoniazid.

Table 2: Moleculardocking results representing Docking Scores

| S.NO | CODE | DOCKING SCORE (1) | DOCKING SCORE (2) | DOCKING SCORE (3) | DOCKING SCORE(4) |
|---|---|---|---|---|---|
| 1. | A1 | -8.7 | -8.5 | -8.3 | -8.2 |
| 2. | A2 | -9.7 | -8.9 | -8.6 | -8.4 |
| 3. | A3 | -7.5 | -7.3 | -7.3 | -7.3 |
| 4. | A4 | -7.9 | -7.7 | -7.5 | -7.4 |
| 5. | A5 | -9.1 | -8.8 | -8.8 | -8.7 |
| 6. | A6 | -9.1 | -8.5 | -8.3 | -8.1 |
| 7. | A7 | -10.0 | -9.1 | -9.0 | -8.9 |
| 8. | A8 | -9.1 | -8.3 | -8.0 | -7.8 |
| 9. | A9 | -9.0 | 8.7 | -8.2 | -8.2 |
| 10. | B0 | -8.3 | -7.9 | -7.9 | -7.8 |
| 11. | B1 | -8.3 | -8.1 | -7.9 | -7.5 |
| 12. | B2 | -7.7 | -7.6 | -7.5 | -7.3 |
| 13. | B3 | -7.9 | -7.9 | -7.7 | -7.7 |
| 14. | B4 | -8.1 | -7.8 | -7.7 | -7.0 |
| 15. | B5 | -8.7 | -8.5 | -8.4 | -8.3 |
| 16. | Isoniazid | -5.7 | -5.0 | -4.9 | -4.7 |

Table 3: Insilico Absorption and Distribution studies of Derived Compounds

| Compound code | Absorption | P-gp substrate | BBB permeability | Bioavailability score | Skin permeation(cm/s) | | |
|---|---|---|---|---|---|---|---|
| | GI absorption | Lipophilicity Log p o/w | Solubility (Esol) | | | | |
| A1 | High | 2.74 | -4.07 moderately soluble | Yes | No | 0.55 | -6.29 |
| A2 | High | 3.41 | -4.93 moderately soluble | No | Yes | 0.55 | -5.76 |
| A3 | High | 2.20 | -2.96 soluble | No | No | 0.55 | -6.72 |
| A4 | High | 2.71 | -5.03 moderately soluble | No | No | 0.55 | -5.45 |
| A5 | High | 2.57 | -3.71 soluble | Yes | No | 0.55 | -6.68 |
| A6 | High | 2.46 | -3.52 soluble | No | No | 0.55 | -6.95 |
| A7 | High | 0.00 | -4.17 moderately soluble | Yes | No | 0.55 | -6.04 |
| A8 | High | 2.70 | -3.96 soluble | No | No | 0.55 | -6.18 |
| A9 | High | 3.23 | -5.73 moderately soluble | No | No | 0.55 | -5.50 |
| B0 | High | 2.42 | -3.97 soluble | No | No | 0.55 | -6.51 |
| B1 | High | 2.39 | -2.61 soluble | Yes | Yes | 0.55 | -7.13 |
| B2 | High | 1.70 | -2.32 soluble | No | No | 0.55 | -7.61 |
| B3 | High | 2.42 | -4.54 moderately soluble | No | No | 0.55 | -5.95 |
| B4 | High | 1.76 | -2.57 soluble | No | No | 0.55 | -7.16 |
| B5 | High | 2.42 | -3.97 soluble | No | No | 0.55 | -6.51 |
| Isoniazid | High | 0.03 | -0.56 very soluble | No | No | 0.55 | -7.63 |

Table 4: In-silico Metabolism and Excretion studies of Designed Derivative Compounds

| Compound code | CYP450 | | | | | Lipinski |
|---|---|---|---|---|---|---|
| | CYP1A2 | CYP2C19 | CYP2C9 | CYP2D6 | CYP3A4 | |
| **A1** | YES | YES | YES | NO | YES | YES,0 Violations |
| **A2** | YES | YES | YES | YES | NO | YES,0 Violations |
| **A3** | YES | YES | NO | NO | NO | YES,0 Violations |
| **A4** | YES | YES | YES | NO | NO | YES,0 Violations |
| **A5** | YES | NO | YES | YES | YES | YES,0 Violations |
| **A6** | YES | NO | YES | YES | YES | YES,0 Violations |
| **A7** | YES | YES | NO | NO | NO | YES,0 Violations |
| **A8** | YES | YES | YES | NO | NO | YES,0 Violations |
| **A9** | YES | YES | YES | NO | NO | YES,0 Violations |
| **B0** | YES | NO | NO | NO | NO | YES,0 Violations |
| **B1** | YES | NO | NO | NO | NO | YES,0 Violations |
| **B2** | YES | NO | NO | NO | NO | YES,0 Violations |
| **B3** | YES | YES | YES | NO | NO | YES,0 Violations |
| **B4** | NO | NO | NO | NO | NO | YES,0 Violations |
| **B5** | YES | NO | NO | NO | NO | YES,0 Violations |
| **Isoniazid** | No | No | No | No | No | YES,O Violations |

## Conclusion

All the compounds derivatives of novel carboxamides derivatives compounds were evaluated with the computational analysis by appropriate PknG were compared with carboxamide analogues standard drug respectively.The results of docking study revealed that the binding profile for derivatives A7, A2, A5, A6 was found significant interaction with PknG.The predicted ADMET properties revealed that all compounds fulfil drug like criteria and could be considered as good candidate for drug like ADMET properties.The further scope of this derivatives of novel carboxamide derivatives need to evaluation of various In-vivo pharmacological studies to bring potentially active molecules.

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Not Declared

**Conflict of interest:** No

**Informed Consent:** No

## Ethical Statement

Overall, the research study conducted adhered to ethical principles, maintaining integrity, respect, and responsibility in their pursuit of knowledge and understanding.

## Author contribution

All authors are contributed equally.

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