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ORIGINAL ARTICLE

Evaluation of Novel Quinoline-Thiadiazol Derivatives as Potent Anti-Tubercular Agents Through Docking Simulation Techniques.

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Abstract:
The Chemistry of Heterocyclic compounds has been an interesting field of study for a long time. The Quinoline - thiadiazol heterocyclic nucleus founds an important class for new drug development. Molecular Docking study is a key tool in Computer Aided Drug Designing. The main objective of this work is to perform preliminary docking screening using SAR studies, OSIRIS molecular property explorer, PASS prediction Activity spectra, and Rule of Five. This study is also an attempt to explore the Anti-Microbial activity of proposed Quinoline - thiadiazol derivatives by Molecular docking with ATP Synthase (PDB ID 7GJ4) via PYRX Autodock Vina wizard. This study also comprises of synthesis and characterization of the proposed Quinoline - thiadiazol derivatives and performed invitro anti-tubercular activity. Compound P1(E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylimino) methyl) phenol), had a significantly higher binding energy of -8.2 kcal/Mol and lowest RMSD value as compared to standard (Isoniazid), Compound P1 showed Vander Waals' interaction with Asp, Tyr, Phe and Ala..
Keywords: Quinoline - thiadiazol derivatives, Heterocyclic compounds, Anti-bacterial, Molecular Docking, Mycobacterium Tuberculosis.

Introduction

Tuberculosis (TB) is a persistent global health concern, with the emergence of drug-resistant strains posing a significant challenge to current treatment strategies. The search for novel therapeutic agents with improved efficacy and safety profiles remains a critical priority. In this context, quinoline-based compounds have garnered attention due to their diverse pharmacological activities, including antitubercular properties (Liu & Ren, 2006). pecifically, the synthesis and evaluation of 2-quinolin-4-amine derivatives have demonstrated promising anti-HIV-1 activity and low cell toxicity (Strękowski et al., 1991). Moreover, the incorporation of triazolyl moieties into quinoline scaffolds has led to the development of novel antileishmanial agents (Upadhyay et al., 2018). Quinoline-thiadiazole is fused with 1,3,4-thiadiazole ring attached to the basic quinoline nucleus as shown in Figure 1.

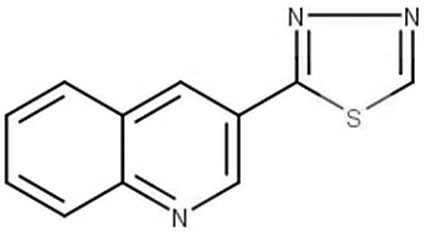


Figure 1. Quinoline-thiadiazole Nucleus

Molecular docking is a commonly employed technique in computer-assisted structure-based rational drug design. The evaluation involves assessing the compatibility between ligands, which are small molecules, and the target macromolecule, specifically ATP Synthase [Seeliger and Grootligand 2010; Norgan et. al,2011]. From the literature review it was revealed the ATP Synthase is responsible for inhibition of cell wall synthesis of M. tuberculosis.

Objective of this study - Building upon these observations, the present study focuses on the in silico docking analysis of quinoline-thiadiazol derivatives as potent antitubercular agents.

Methodlogy

Software used - Python language was downloaded from www.python.com, Chemdraw, Marvin sketch, OSIRIS Molecular property explorer, PASS Prediction was used for preliminary screening of proposed derivatives and BIOVIA drug discovery, PYRX docking software was used for this research study.Docking analysis is frequently employed to evaluate a compound's physical and chemical characteristics.

Pre-validation of compounds

The selected compounds were subjected to lead optimisation through the computation of drug similarity features. The pre-validation of all compounds was assessed using SAR investigations, Molecular property prediction (OSIRIS property explorer), Prediction of Activity Spectra for Substances (PASS), and Lipinski's rule.

1. **Structure Activity Relationship (SAR) Studies** – Following Positions can be modified for substitution to increase potential of quinoline. (Dine et al., 2023)

- Position 1 control the potency and pharmacokinetic properties. (Dine et al., 2023)
- Position 2 is essential for small group and activity. (Dine et al., 2023)
- Position 3 and 4 essentials for enzyme binding. (Dine et al., 2023)
- Position 6 & 7 enhances Gyrase affinity. (Dine et al., 2023)

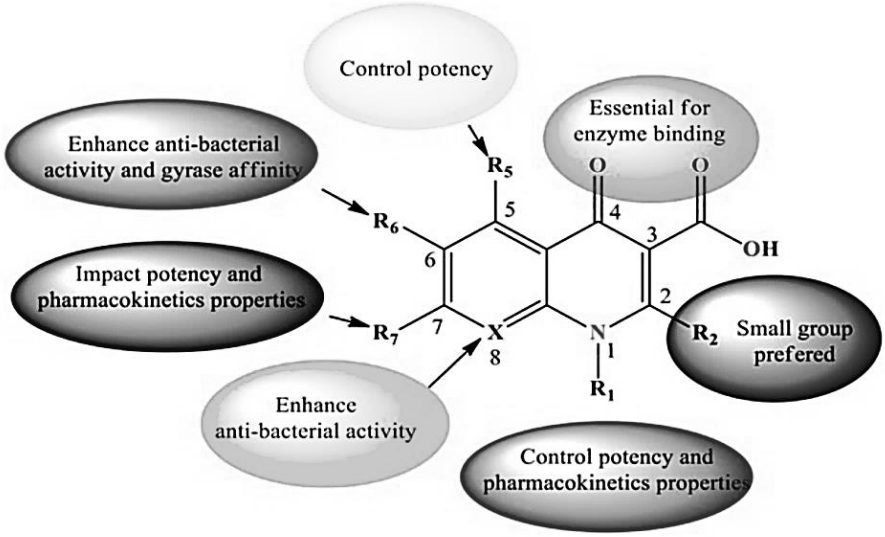
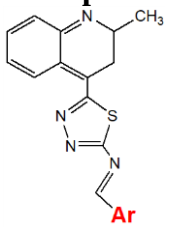


Figure 2. Structure Activity Relationship of Quinoline moiety.

OSIRIS Property Explorer - The OSIRIS Property Explorer is a drug discovery informatics system that has been built wholly in-house. This software enables the creation of chemical structures and provides real-time calculations of many attributes crucial to drugs, determining whether a structure is valid or not. The **Table 1** provides descriptions of the drug score, drug-likeness, solubility, and toxicity tests for all quinazoline derivatives.

Table 1. OSIRIS molecular property, PASS Prediction result and Lipinski rule of 5 of proposed compounds.



Basic Moiety of Quinoline – Thiadiazole

S. No.	Compound Name	OSIRIS (Molecular Property Explorer)						PASS Prediction Antimicrobial		Lipinski Parameters						
		Drug Score	Clog P	Drug Likeness	Solubility	TPSA	Toxicity Risk	Pa	Pi	Mol. Weight (dalton)	HBA	HBD	PSA (A2)	clog P	MR (m3/mol)	Obey Lipinski rule
1.	(E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylimino) methyl) phenol **(P1)**	0.68	2.92	4.07	-4.44	99.5	No risk	0,623	0,005	348.12	4	1	99.5	4.07	86.12	Yes
2.	(E)-phenyl N-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylformimidate **(P2)**	0.58	3.14	4.35	-4.75	88.5	No risk	0,288	0,078	348.12	4	1	88.5	4.35	82.38	Yes
3.	(E)-N-(furan-2-ylmethylene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-	0.64	2.9	3.6	-4.42	92.4	No risk	0,468	0,016	322.09	5	1	92.4	3.6	99.23	Yes

	2-amine **(P3)**															
4.	(E)-N-(4-chlorobenzy lidene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine **(P4)**	0.47	3.97	5.02	-5.47	79.2	No risk	0,412	0,028	366.07	6	1	79.2	5.02	80.24	Yes

Pa = probability "to be active, Pi= probability to be inactive, HBD =Hydrogen Bond Donor, HBA = Hydrogen Bond Acceptor, TPSA = Total Polar Surface Area, MR = Molar Refractivity

1. PASS Prediction - PASS prediction, also known as Prediction of Activity Spectra for Substances, is a specialised software designed to evaluate the overall biological potential of an organic chemical with drug-like properties. It employs the chemical composition of molecules to make predictions about many types of biological activity. The anticipated values for each element in Table 3 are transformed into antimicrobial activity, as denoted by the "*Probability of being active (Pa)*" being greater than the "*Probability of being inactive (Pi)*". The reference is from a publication by Filimonov DA et.al in 1995. Table 1 shows that the value of 'Pa' is greater than the value of 'Pi' for all compounds.
2. Rule of Five or Lipinski Rule - The parameters, including c logp, Molecular weight (MW), Hydrogen Bond Donor (HBD), Hydrogen Bond Acceptor (HBA), and Polar Surface Area (PSA), was determined using Chem draw and Marvin sketch software. The calculation and analysis of these properties are based on Lipinski's rule and its components. All compounds adhere to Lipinski's criterion, as seen in Table 1. The clogP values of these compounds were determined to be below 5, indicating that these compounds exhibit favourable permeability across the cell membrane. If the polar surface area is less than 140 Å², it indicates that the molecule readily binds to a receptor. Additionally, the molecular weight of all compounds is below 500, and the number of hydrogen bond donors (the total of OHs and NHs) is less than 5. Furthermore, the number of hydrogen bond acceptors (the sum of Os and Ns) is less than 10.

Docking Analysis

Molecular docking can be compared to a "lock-and-key" problem, in which the objective is to determine the proper relative orientation of the "key" that will open the "lock" (i.e., where the keyhole is on the lock's surface, which way to spin the key after it is inserted, etc.). In this case, the ligand functions as the "key" and the protein as the "lock." An optimisation problem that characterises the "best-fit" orientation of a ligand that binds to a certain protein of interest is what is known as molecular docking [Goh et al., 1985]. But rather than using the term "lock-and-key," a more fitting comparison would be "hand-in-glove," given the flexibility of both the ligand and the protein. The term "induced-fit" refers to conformational changes that result in overall binding and are made by the ligand and protein during the process to obtain an overall "best-fit" [Roth et al., 2000].

The ATP Synthase (PDB ID 7JG5) was used for docking analysis as ATP synthase well known for cell wall and mycolic acid inhibition of M. Tuberculi.

A typical method for determining the binding

orientation of drug candidates to their protein targets to estimate the affinity and activity is molecular docking, which involves matching the drug molecule with the receptor (target). This process provides valuable information regarding drug receptor interactions. Auto Dock 4.2 was used to carry out the docking studies. If a molecule in the docking research has a lower binding energy than the standard, this indicates a higher level of activity. Both the ranked list of docked ligands and their matching binding poses, as well as the docking poses, were rated based on their docking scores (Madeswaran et al, 2011). The compounds were ranked according to the energy at which they bound to the enzyme. All result and binding with Amoni acid are displayed in Table 2.

In figure 2 displayed docked pose of (E)-N-(Subsutitued benzylidene)5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine (**P1-4**) all derivatives with ATP Synthase (PDB ID 7JG5). The binding position of the ligand were displayed with dotted line shwing interaction between ligand and enzyme.

Table 2. Docking Score between ATP Synthase and ligands (Quinoline – thiadiazol derivatives)

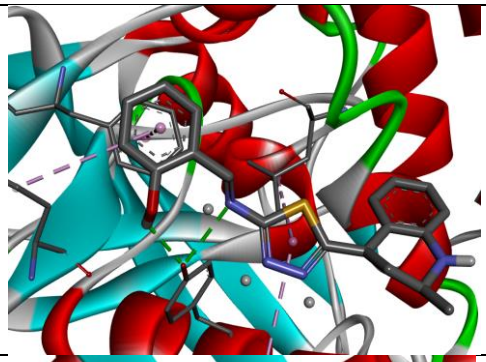
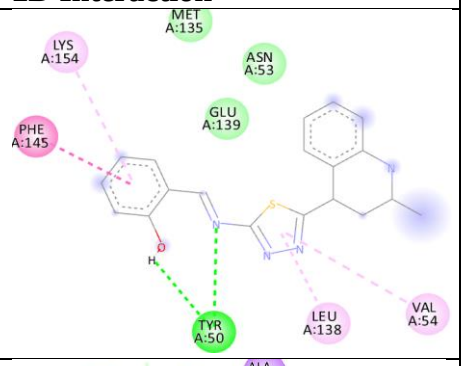
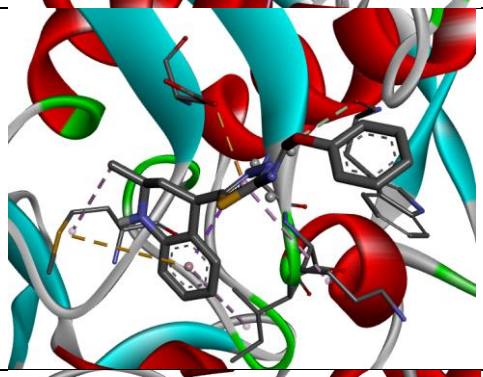
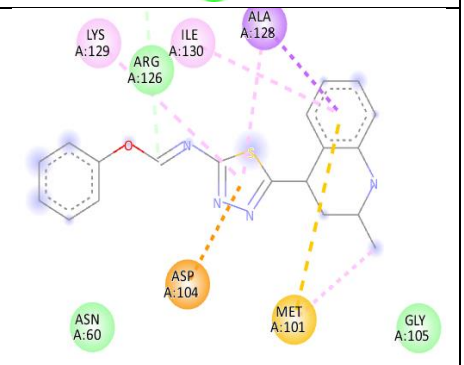
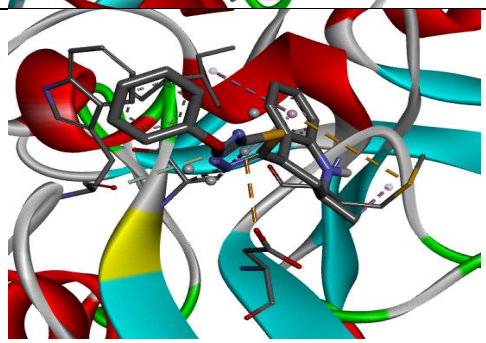
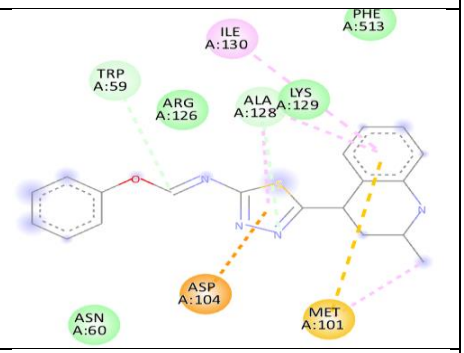
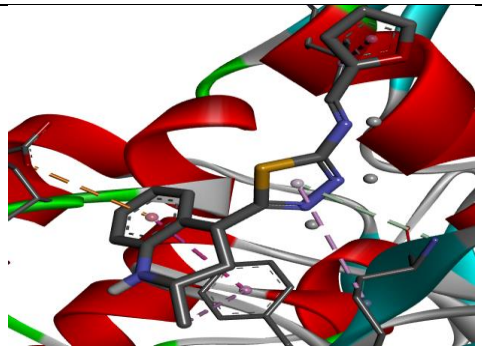
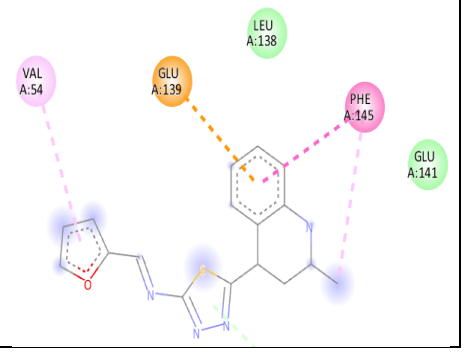
S. No	Compound Name & ID	Binding affinity (Kcal/Mol)	RMSD	Interacting amino acid
1	(E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylimino) methyl) phenol **(P1)**	-8.2	0.023	PHE, LYS, MET, ASN, GLU, LEU, VAL, TYR
2	(E)-phenyl N-5-(2-methyl-2,3-dihydroquinolin -4-yl)-1,3,4-thiadiazol-2-ylformimidate **(P2)**	-7.6	0.098	LYS, ALA, ILE, MET, ASP, ASN, GLY
3	(E)-N-(furan-2-ylmethylene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine **(P3)**	-7.2	0.234	ASP, MET, GLY, VAL, ARG, TRP
4	(E)-N-(4-chlorobenzylidene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine **(P4)**	-7.0	0.890	PHE, VAL, GLU, LEU
5	Standard (Ligand)	-9.8	0.011	ALA, LYS, ARG
5	Standard (Ligand)	-9.8	0.011	ALA, LYS, ARG

Lowering the docking energy produced the optimal contact. The quantitative measure of binding strength, the Root Mean Square Deviation (RMSD), and the amino acids involved in the interaction are shown in Table 5. The interactions between the protein ATP synthase (PDB ID: 7JG5) and various ligands (Quinoline-Thiadiazol derivatives and isoniazid) were investigated in Figure 11 of Discovery Studio. The lengths of hydrogen bonds and their interactions were examined. The protein and ligand's usual sites of attachment are shown in the diagrams, and interactions are shown by dashed lines. Green dashed lines show the hydrogen bonding contacts; light pink shows alkyl connections; and magenta and pink show Pi interactions. An anonymous hydrogen donor is indicated by the presence of a red dashed line. All interaction was shown in Table 7.

The fundamental heterocyclic moiety that causes hydrophobic contact is Quinoline – thiadiazol derivatives. **Compound P1** (E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylimino) methyl) phenol interacted with Vander Waals forces with Leu, Gly, and Tyr as well as Pi-Pi bonds with phenylalanine (Phe). And binding affinities at -8.2 Kcal/mol.

Compound P2 (E)-phenyl N-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylformimidate was form vander wall forces interaction with lysine, Alanine and valine and

Compound P2 shown Binding affinities at -7.6 Kcal/mol. **Compound P3** (E)-N-(furan-2-ylmethylene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine showed binding affinities at -7.2 Kcal/Mol and showed hydrogen bonding interaction with Asparate, Methionine, Glycine and Valine. Compound **P4** (E)-N-(4-chlorobenzylidene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine showed binding affinities at – 7.0 Kcal/Mol and shown vander waal's interaction with Phenylalanine, Valine, & leucine. As compared to standard drug (Isoniazid) Compound P1 possess highest binding energies.

Compound Name	3D Docked POSE	2D Interaction
(E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-ylimino) methyl)phenol **(P1)**		
(E)-phenyl N-5-(2-methyl-2,3-dihydroquinolin -4-yl)-1,3,4-thiadiazol-2-ylformimidate **(P2)**		
(E)-N-(furan-2-ylmethylene)-5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine **(P3)**		
(E)-N-(4-chlorobenzylidene) -5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-amine **(P4)**		

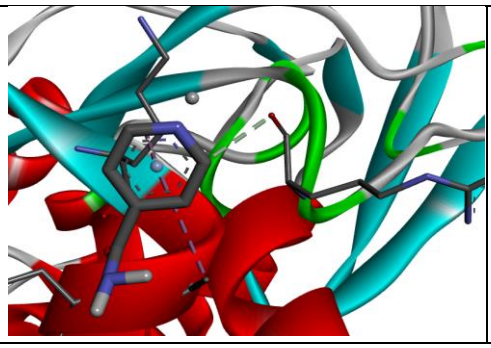
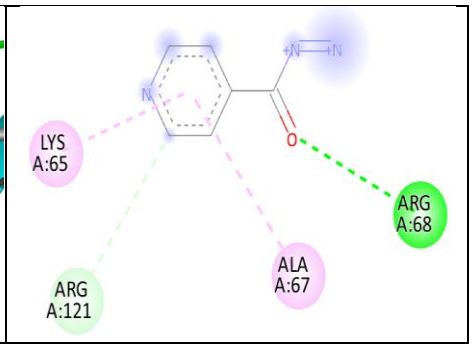
Standard (Isoniazid)		

Figure 3. 3D Docked Pose and 2D interaction between ATP Synthase (PDB ID 7JG5) and ligands (Isoniazid and Quinoline-thiadiazol derivatives).

Conclusion

CompoundP1(E)-2-((5-(2-methyl-2,3-dihydroquinolin-4-yl)-1,3,4-thiadiazol-2-yl imino)methyl)phenol), had a significantly higher binding energy of -8.2 kcal/Mol and lowest RMSD value as compared to standard (Isoniazid), Compound P1 showed Vander Waals' interaction with Asp, Tyr, Phe and Ala. Finally, it was concluded that all Quinoline - thiadiazol derivatives possess potent anti-tubercular activity. Further preparation and biological evaluation of quinazoline and some more derivatives may lead to the potent drug in near future.

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