INSILICO SCREENING OF SOME CHALCONE ISATIN COMPLEX ANALOGUES AGAINST ANTI-TUBERCULAR POTENTIAL

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ABSTRACT:
This in silico work aims to analyse the chemical properties of isatin-linked chalcones and identify their potential protein targets. Initially, we optimise the compounds for enhanced interaction with NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA), also known as protein 4QXM. We evaluate the efficacy of the synthesised chalcones in treating tuberculosis by comparing them to the standard isoniazid (INH). The best chalcone structures have an amazing dock score of -10.5, which means they have a strong affinity for binding to the target protein. In contrast, the docking score of the typical medication is -10.3. Compounds 6, 7, 8, and 9 demonstrate the greatest docking scores among the synthesized compounds, surpassing the traditional drug's score of -10.3. The docking scores for each synthesised chalcone range from -10.2 to -10.5. The standard tuberculosis treatment, isoniazid, possesses a dock score of -6.1 in this domain. These findings indicate that further in vitro These compounds require further in-vitro and in vivo evaluations due to their promising dock scores and potent properties.ial protein targets, they are suitable candidates for further investigation and advancement in tuberculosis medicine development.

Keywords: Molecular docking, Chalcones, Isatin, Isoniazid, Tuberculosis.

INTRODUCTION:

Despite advancements in medical knowledge, tuberculosis (TB), which is caused by Mycobacterium tuberculosis (Mtb), continues to be a major infectious illness that kills millions of people every year (1, 2). The development of extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains of Mtb has made it very hard to treat and control the disease. This necessitates the development of new therapeutic drugs with improved efficacy

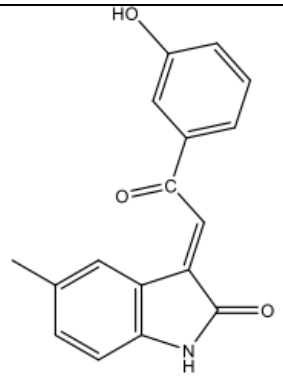
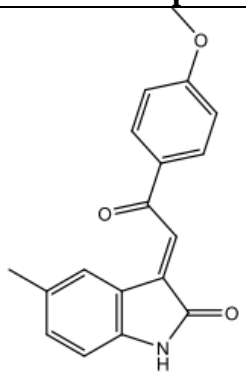
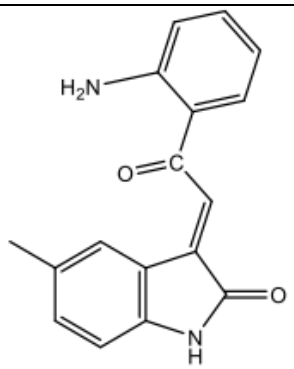
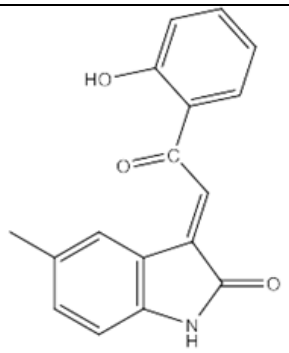
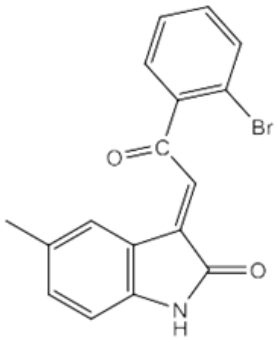
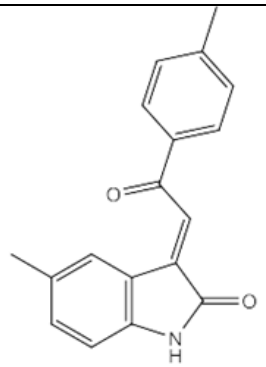
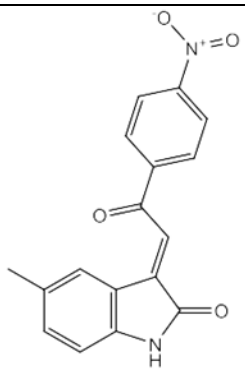
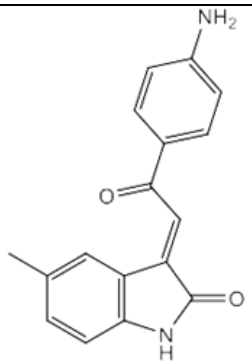
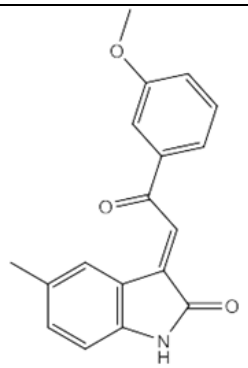
and reduced side effects (3, 4). Extensive study into the creation of alternative chemical entities with possible antibacterial action has been prompted by the demand for novel and potent anti-tubercular drugs.The chalcone-isatin complex analogues are one class of chemicals that has attracted a lot of interest lately (5, 6). A class of flavonoid derivatives known as chalcones has a variety of biological functions, such as antibacterial, anti-inflammatory, and anticancer effects (7). Because they are made up of a reactive α, β-unsaturated carbonyl system, it is easy to change and improve them to make them better bioactive agents (8). Indole produces isatin, a molecule that interacts with bacterial enzymes and cellular pathways, demonstrating promising efficacy against Mtb and other infections..Putting chalcone and isatin units together to make a single molecule is an intriguing way to improve the pharmacological profile of each part separately (9, 10). These different forms of the chalcone-isatin complex might work together to make the drugs more selective and effective against Mtb (11). Furthermore, because of their chemical diversity, their activity can be fine-tuned by structural alterations; potentially resulting in the development of next-generation anti-TB medicines with better pharmacological characteristics (12, 13). This project's goal is to use computers to test different versions of the chalcone isatin complex to see if they can fight tuberculosis (14). Using computer methods like molecular docking, we can guess how these drugs will bind to and interact with key targets in the M. tuberculosis bacterium. The findings from this in silico study will shed light on the most promising options for additional experimental verification and advancement as innovative anti-TB medications (15, 16). If you know what InhA stands for, you know that it is an important enzyme in the process by which M. tuberculosis makes fatty acids. InhA speeds up the process of reducing 2-trans-enoyl-ACP to its equivalent saturated acyl-ACP, which is an important step in the production of mycolic acids (17, 18). As a member of the short-chain dehydrogenase/reductase (SDR) superfamily, InhA is necessary to keep the integrity of the bacterial cell wall. This makes the bacteria more resistant to environmental stressors and more likely to spread (19). InhA has been identified as a particularly desirable target for the development of anti-TB drugs because of its crucial function in lipid metabolism (20). Recent years have seen a significant amount of research on InhA, particularly in relation to medication design. One of the most common first-line drugs for tuberculosis is isoniazid (INH). It works by blocking InhA, which stops the production of mycolic acid. Still, the discovery of Mtb strains that are not sensitive to INH has led to the search for new InhA inhibitors that can get around the mechanisms of resistance (21). Thus, the logical development of InhA inhibitors, aided by computational techniques like molecular docking and molecular dynamics simulations, may yield novel therapeutic possibilities for the management of drug-resistant tuberculosis (22).

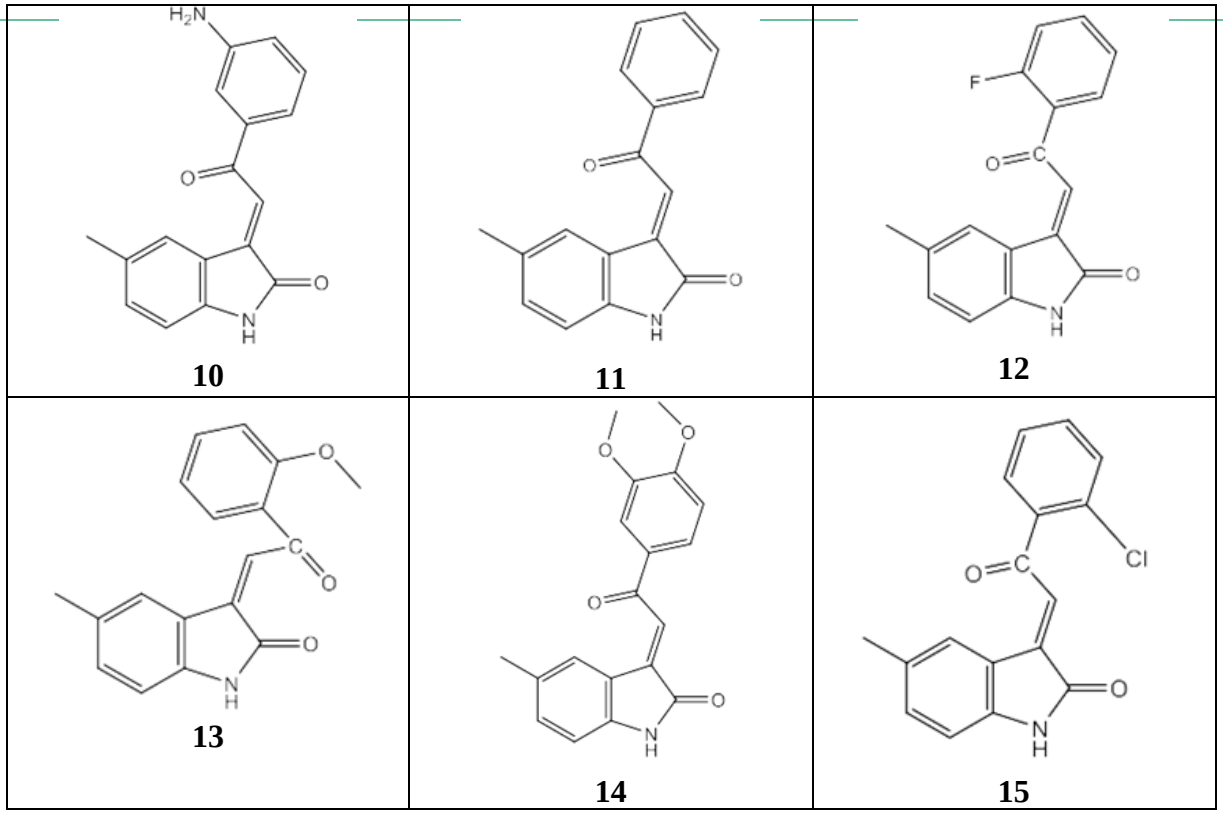
MATERIALS AND METHODS:

We figure out how a ligand attaches to its site by using 4QXM as a macromolecule and Molegro Virtual Docker (MVD), Autodock tools, and AU docker (23-25). The piecewise linear potential (PLP), a simplified potential with parameters calibrated to protein-ligand structures and binding data scoring functions, was augmented to incorporate additional hydrogen bonding terms and novel charge schemes to treat ligands and proteins as adaptable entities during docking simulations (26-29). The ligand NAD+, which has a nicotinamide ring that can cross the blood-brain barrier, and the protein 4QXM, which is known as NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA), were both found in the RCSB PDB protein database. A downloaded protein is imported into MVD (30). During importing, we remove all water molecules and cofactors. The preparation procedure eliminates the warnings and subsequently identifies the cavities. The Autodock tools open PDB files and export them as proteins and ligands. Prior to being saved as a PDBQT file, the

protein is initially imported and altered to include hydrogens, charges, and atoms. A ligand was inputted and stored as a PDBQT file with the protein to accommodate its binding location (31). Finally, AUdocker obtains the stored PDB QT files of the ligands and proteins. Using this program speeds up the docking process by providing quick and easy docking as MVD. It also creates files with the dock score for ligand accommodation within the protein binding site (32). The protein files and the individual ligand output files are loaded into the PyMOL software. The amino acids in the protein that interact with the ligand are then given labels. Interacting amino acids are discovered and documented using established labels (33, 34).

Table 1: Structures of Chalcones Isatin Complex

Chalcone Isatin Complex Structures		
 **1**	 **2**	 **3**
 **4**	 **5**	 **6**
 **7**	 **8**	 **9**



RESULTS AND DISCUSSION:

All molecules were molecularly analysed by docking with 4QXM, or NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA). We then arranged them according to their positions to examine their interactions with proteins. Elevated negative docking scores signify that a chemical exhibits greater activity compared to others.

Table 2: Docking Scores and amino acid sequence of the molecules

Molecule	Docking Score	Amino Acid Sequence
NAD+500 (Standard)	-10.3	GLY-14, ILE-21, ILE-194, LYD-165, GLY-96, VAL-65, ASP-64
Isoniazid (Standard)	-6.1	GLY-14, ILE-15
1	-10.3	PHE-41, THR-39, LEU-63
2	-10.3	PHE-41, THR-39, LEU-63
3	-10.3	PHE-41, THR-39, LEU-63, ARG-43
4	-10.2	LEU-63
5	-10.2	PHE-41, THR-39, LEU-63, ARG-43
6	-10.5	PHE-41, THR-39, LEU-63
7	-10.5	LEU-63
8	-10.5	PHE-41,THR-39, LEU-63
9	-10.5	LEU-63, ARG-43
10	-10.3	PHE-41, THR-39, LEU-63
11	-10.3	PHE-41, ASP-42, GLY-14
12	-10.3	PHE-41, THR-39, LEU-63
13	-10.3	PHE-41, ARG-43, GLY-14

14	-10.3	PHE-41, LEU-63, GLY-14
15	-10.3	THR-39, ILE-15

The standard interacts with the amino acids GLY-14, ILE-21, ILE-194, LYD-165, GLY-96, VAL-65, and ASP-64 in the protein. As previously stated, compounds with a significantly negative score exhibit greater activity. Among all the substances, compounds 6, 7, 8, and 9 exhibit the highest activity.

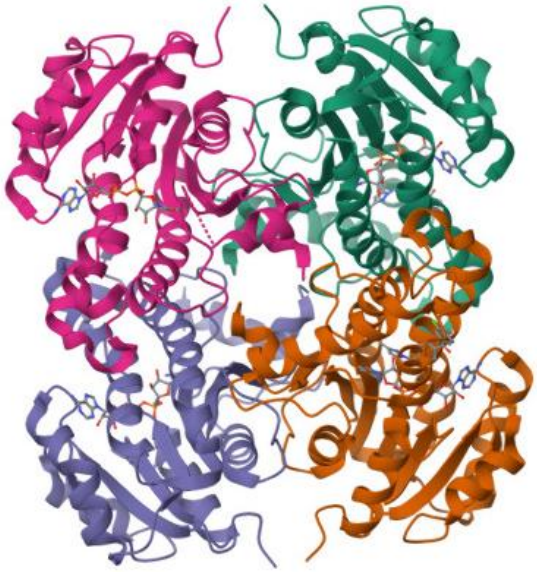
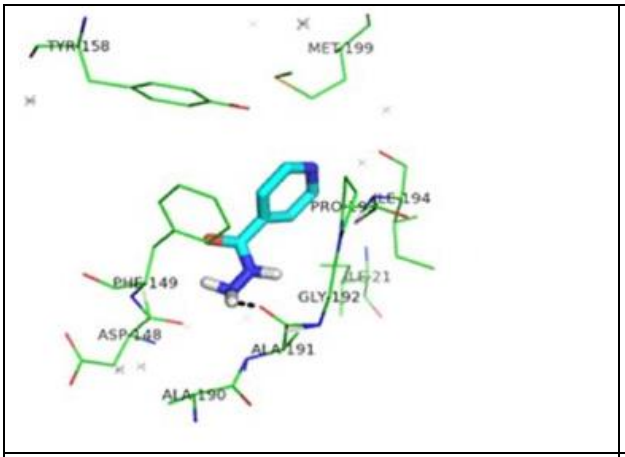
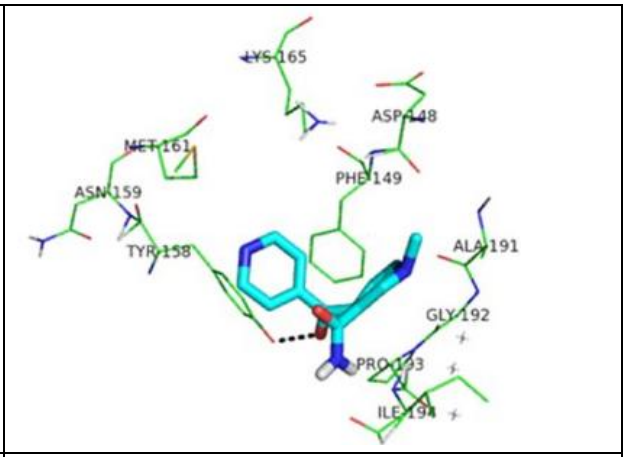


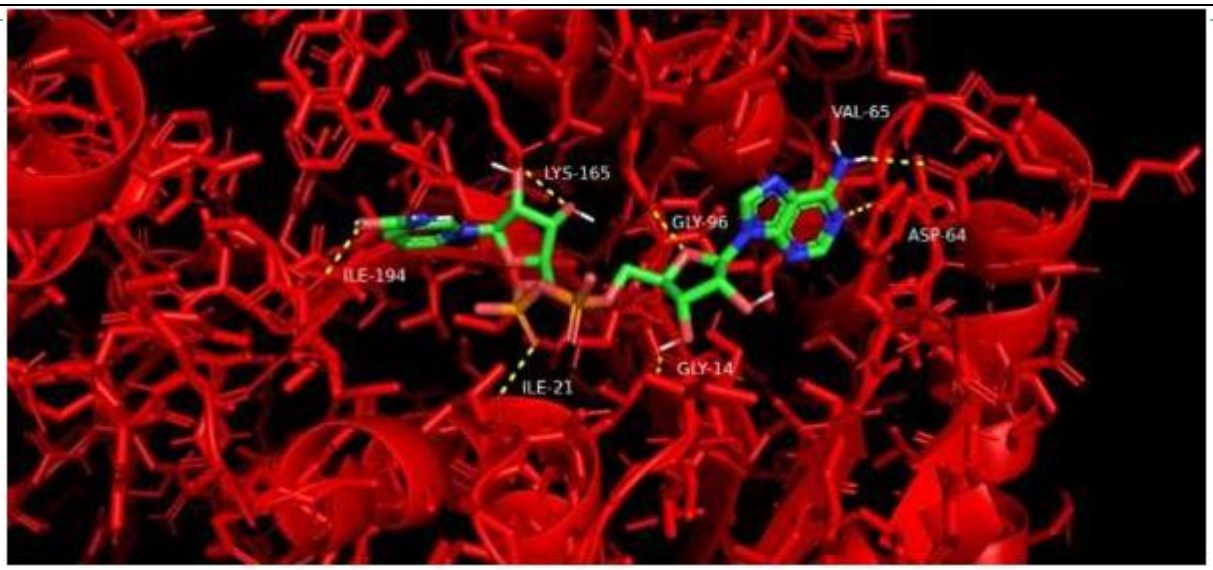
Figure 1: Structure of 4QXM Protein



(A)



(B)



(C)

Figure 2: Ligand receptor Interactions of (A) Isoniazid, (B) NAD + Ligand and (C) LIG6 with PDB ID: 4QXM of Protein

Prediction of ADMET Properties:

To make sure they are ideally free of detrimental side effects and unfavourable consequences, drug candidates are evaluated for ADMET characteristics. We expect the compounds to display favourable ADME characteristics before considering them as therapeutic candidates.

Table 3: ADME Properties of the Chalcone Isatin Complexes

Molecule	HBA	HBD	TPSA	I log P	X log P3	W log P	M log P	GI Abs	BBB permeation	Pgp substrate	Lipinski 's violations
1	2	1	46.17	2.37	2.76	2.64	2.33	High	Yes	No	0
2	2	1	46.17	2.38	3.12	2.95	2.57	High	Yes	No	0
3	3	1	55.4	2.28	2.73	2.65	1.99	High	Yes	No	0
4	3	1	46.17	2.19	2.86	3.2	2.72	High	Yes	No	0
5	4	1	64.63	2.84	2.7	2.66	1.66	High	Yes	No	0
6	3	1	55.4	2.51	2.73	2.65	1.99	High	Yes	No	0
7	2	1	46.17	2.29	3.39	3.3	2.84	High	Yes	No	0
8	2	1	46.17	2.41	3.45	3.4	2.95	High	Yes	No	0
9	4	1	91.99	1.71	2.59	2.55	1.32	High	No	No	0
10	2	2	72.19	2.23	2.63	2.23	1.75	High	Yes	No	0
11	3	2	66.4	2.11	2.4	2.35	1.75	High	Yes	No	0
12	2	2	72.19	2.04	2.08	2.23	1.75	High	Yes	No	0
13	3	1	55.4	2.72	2.73	2.65	1.99	High	Yes	No	0
14	3	2	66.4	1.7	2.96	2.35	1.75	High	Yes	No	0
15	2	2	72.19	2.04	2.08	2.23	1.75	High	Yes	No	0

The program used to extract and assess the aforementioned ADME characteristics for the substances is called SWISS ADME.

H-bond acceptors: HBA

H-bond donors: HBD

CONCLUSION:

Unlike the conventional medication isoniazid (INH), which depends on the activation by the Kat G enzyme, these chalcones are based on an isatin-linked template and directly target the NADH-dependent 2-trans enoyl-acyl carrier protein reductase (InhA) enzyme. They might be useful for fighting extensively drug-resistant (XDR) and multidrug-resistant (MDR) strains of M. tuberculosis bacteria because they don't cause Kat G-related resistance. The development of new approaches to combat drug-resistant TB is encouraging, as it offers hope to patients who may have limited other treatment options.

DISCLOSURE STATEMENT:

There is no conflict of interest financial or otherwise.

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