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Molecular Docking Studies Of Isatin-Linked Chalcone Derivatives As Anti-Tb Drug Candidates And Their Admet Prediction

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Abstract:

This in-silico study aims to examine the molecular properties of a group of compounds called Isatin-linked chalones and identify their potential protein targets. The compounds are first optimized to better interact with the protein 4QXM, NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA)[2]. The synthesized chalcones are compared to a standard Isoniazid (INH), focusing on their potential for treating Tuberculosis. Privileged structures of the chalcones exhibit a remarkable dock score of -10.5, indicating strong binding affinity to the target protein. In comparison, the docking score of the standard drug is -10.3. Among the synthesized compounds, Compound 6,7,8&9 demonstrates the highest dock score, surpassing even the standard drug's score of -10.3. All the synthesized chalcones exhibit dock scores ranging from -10.2 to -10.5. In this category, the standard drug of TB Isoniazid comprises a dock score of -6.1. These findings suggest that further testing of these compounds in in-vitro and in-vivo studies is warranted. The promising dock scores and potential protein targets make them potential candidates for future research and development in the field of TB drug development.

Keywords: Isatin-linked chalcones, NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA), Isoniazid (INH), Tuberculosis.

Introduction:

In 2020, approximately 1.5 million lives were tragically lost to tuberculosis (TB), with an additional 214,000 people affected by both TB and HIV. This makes TB the 13th leading cause of death worldwide and the second leading infectious killer, only surpassed by the COVID-19 pandemic. It's essential to note that TB doesn't discriminate, affecting individuals of all ages, and can be found in every country.

The good news is that TB is both preventable and curable. It's estimated that around 10 million people were diagnosed with TB in 2020. Among them, 5.6 million were men, 3.3 million were women, and sadly, 1.1 million were children. It's unfortunate that child and adolescent TB often goes unnoticed by healthcare providers, making diagnosis and treatment challenging. However, with increased awareness and proactive healthcare approaches, we can work towards ending the burden of TB. Let's join forces to ensure better detection, treatment, and prevention of TB, especially in children, paving the way for a healthier and brighter future for all.

In 2020, the majority of new TB cases, about 86%, were reported in the 30 countries with the highest burden. Among these countries, there are eight that contribute significantly, with India leading the list, followed by China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Dealing with multidrug-resistant TB (MDR-TB) remains a pressing public health concern and a threat to global health security. Astonishingly, only around one in three individuals with drug-resistant TB were able to access the necessary treatment in 2020.

Fortunately, there is some progress being made in the fight against TB. Globally, the incidence of TB has been declining at a rate of approximately 2% each year. Between 2015 and 2020, there was an overall reduction of 11%, which means we were more than halfway towards achieving the End TB Strategy milestone of a 20% reduction during that period. These efforts have resulted in an estimated 66 million lives being saved through TB diagnosis and treatment between 2000 and 2020.

It's clear that while there have been positive developments, there is still much work to be done to combat TB effectively. Did you know that despite significant efforts, the world fell short of achieving the milestone of 0% of TB patients and their households facing catastrophic costs due to TB disease by 2020? It's quite concerning, but there's hope! By 2022, an annual budget of US$13 billion is needed to effectively prevent, diagnose, treat, and care for TB globally, aligning with the target established at the UN high-level meeting on TB in 2018.

Unfortunately, funding in low- and middle-income countries (LMICs), which account for 98% of reported TB cases, is far from what is required. In fact, in 2020, global spending on TB fell short by a staggering US$5.3 billion, which is only 41% of the target. Moreover, there was an 8.7% decline in spending between 2019 and 2020, bringing us back to 2016 levels. However, it's important to remain optimistic and committed to ending the TB epidemic by 2030, which is one of the health targets of the United Nations Sustainable Development Goals (SDGs). With increased awareness, advocacy, and adequate funding, we can work towards a future where TB is no longer a threat to individuals and communities worldwide[1].

Enoyl acyl carrier protein reductase, also known as InhA, is an essential enzyme that plays a crucial role in the synthesis of fatty acids, particularly mycolic acid biosynthesis. This enzyme(4QXM) belongs to the family of NADH-dependent acyl carrier protein reductases[2].

The drug targets InhA and its role in the fatty acid synthesis pathway in Mycobacterium tuberculosis[3]. the frontline antitubercular drug isoniazid (INH) interacts with InhA through the catalase-peroxidase enzyme KatG[4-6].

Resistance to INH is a concerning issue, and it's intriguing that it can be associated with multiple genes such as KatG, InhA, ahpC, kasA, and ndh. While the biochemical explanations for these findings may not be entirely clear yet, it's worth noting that defects in the KatG gene are often linked to resistance, sometimes accompanied by mutations in other genes[7]. Extensive research has been conducted to uncover and develop new inhibitors specifically designed to target InhA without relying on KatG activation. This breakthrough opens up the possibility of combating INH-resistant clinical isolates. To achieve this objective, a high-throughput screening campaign was executed to discover fresh and innovative direct inhibitors of InhA.

Isatin-linked chalcones were screened for the above-mentioned activity.

Materials and methods:

Molegro Virtual Docker (MVD), Autodocktools, and AU docker are used to determine the configuration in which a ligand will bind to a macromolecule's binding site, using 4QXM as a macromolecule. Treating ligands and proteins as malleable entities during docking simulations, a new hydrogen bonding term and new charge schemes were added to the piecewise linear potential (PLP), a simplified potential whose parameters were adapted to protein-ligand structures and binding data scoring functions.

Initially, a protein 4QXM, which is NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA)was downloaded from the RCSB PDB protein bank along with the ligand NAD+ which has a nicotinide ring that can cross the BBB. In **MVD** downloaded protein is imported. While importing all the cofactors and water molecules are removed. Then preparation is done by removing the warnings by optimising and followed by detecting cavities. Protein and ligand are exported as PDB files, which were opened in **Autodocktools**. First protein is imported and edited with hydrogens, charges, and atoms then saved as a PDBQT file. To fit in that protein's binding site, a ligand was input and saved as a PDBQT file along with the protein.

Finally, the saved PDBQT files of protein and ligands are given to **AU docker**. This program avails simple and efficient docking as MVD and also in less time consumed that runs the docking process to give the Dock score for ligand in fitting into the binding site of the Protein as out files. These out files of the individual ligands along with protein files are imported into **Pymol** software and labels are created for the amino acids that interact with the ligand in the protein. With created labels, interacted amino acids are detected and captured.

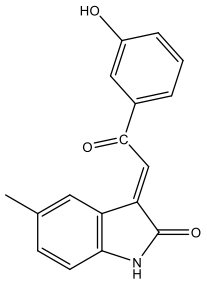
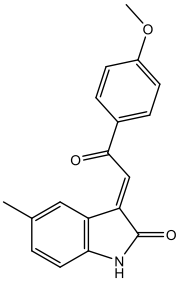
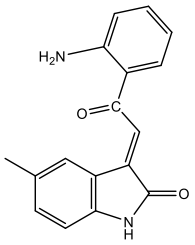
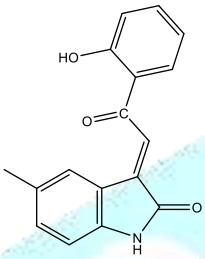
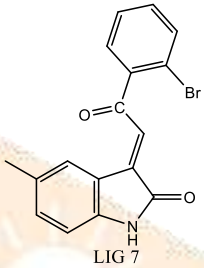
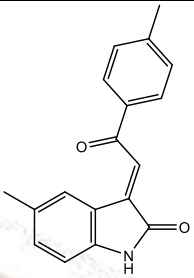
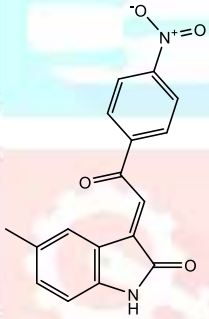
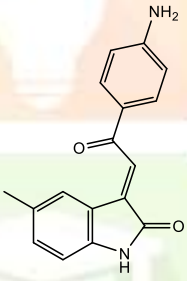
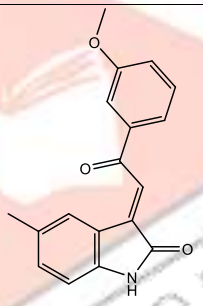
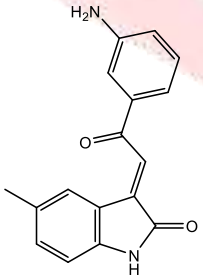
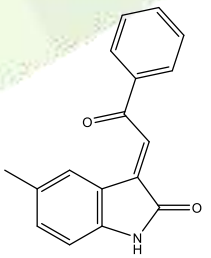
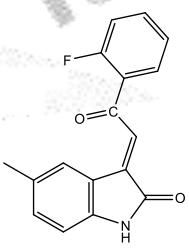
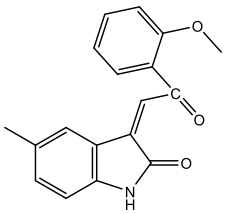
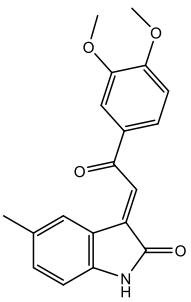
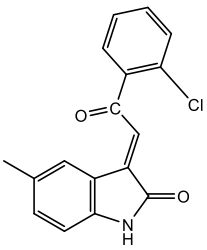
Isatin-linked Chalcone structures		
 LIG 14	 LIG2	 LIG 12
 LIG 13	 LIG 7	 LIG 1
 LIG 8	 LIG 10	 LIG 11
 LIG 9	 LIG 15	 LIG 3
 LIG 5	 LIG 4	 LIG 6

Table.1: Structures of Isatin-linked Chalcones

Results and Discussion:

All the compounds were studied molecularly by docking with 4QXM, which is NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA) and were sorted according to the poses to check their interactions with proteins. Compounds with high negative docking scores are more active than the other compounds.

Ligand	Dock score	Interactions
Lig6	-10.5	PHE-41, THR-39, LEU-63
Lig7	-10.5	LEU-63
Lig8	-10.5	PHE-41, THR-39, LEU-63
Lig9	-10.5	LEU-63, ARG-43
Lig1	-10.3	PHE-41, THR-39, LEU-63
Lig10	-10.3	PHE-41, THR-39, LEU-63
Lig11	-10.3	PHE-41, ASP-42, GLY-14
lig12	-10.3	PHE-41, THR-39, LEU-63
lig13	-10.3	PHE-41, ARG-43, GLY-14
Lig14	-10.3	PHE-41, LEU-63, GLY-14
lig15	-10.3	THR-39, ILE-15
Lig2	-10.3	PHE-41, THR-39, LEU-63
Lig3	-10.3	PHE-41, THR-39, LEU-63, ARG-43
Lig4	-10.2	LEU-63
Lig5	-10.2	PHE-41, THR-39, LEU-63, ARG-43
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

Table No.: 2: Dock Scores and Interactions of the Ligands

Standard interacts with the protein by GLY-14, ILE-21, ILE-194, LYD-165, GLY-96, VAL-65, ASP-64 amino acids. As we noted before, the compound with the high negative score is more active compounds 6,7,8 & 9 are highly active among all the compounds.

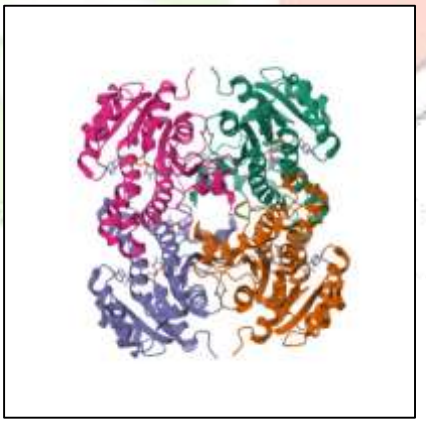
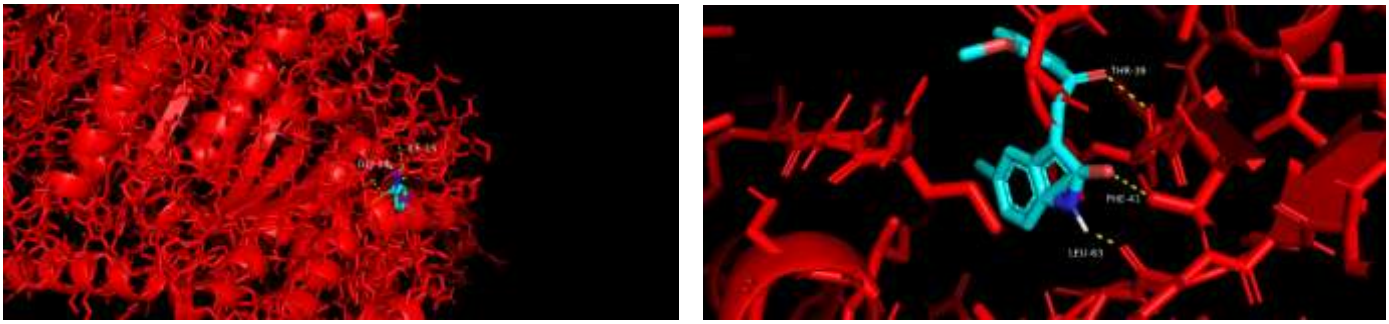
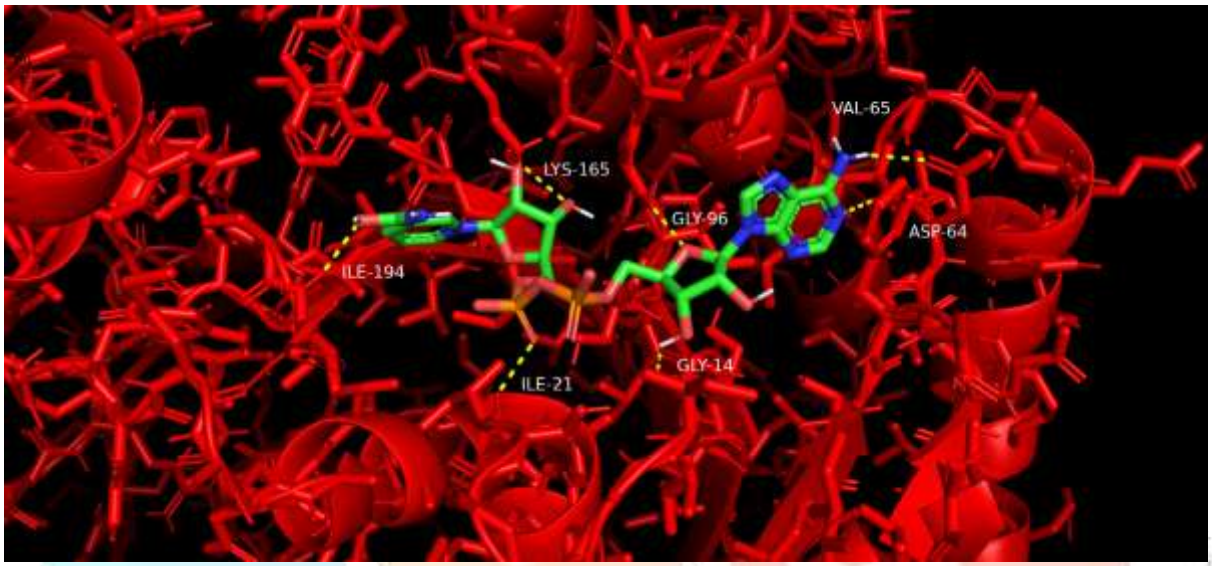


Figure no. 1: Structure of 4QXM protein.[6]



(a) (b)



(c)

Fig. no. 2: Interactions of Isoniazid(a), NAD+ Ligand(c) and LIG6(b) with 4QXM protein

Evaluation of ADMET Properties:

Drug candidates are evaluated for ADMET properties to see that they are preferably free from hazardous adverse and side effects. So, it is expected to get favorable ADME properties to propose the compounds as drug candidates.

Ligand	H-bond acceptors	H-bond donors	TPSA	I logP	X logP3	W logP	M logP	GI absorption	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

Table no.: 3: ADME Properties of the 15 Isatin-linked Chalcones

SWISS ADME is the software from which the above-mentioned ADME properties for the compounds are being taken and evaluated.

Conclusion:

These Chalcones are based on an Isatin-linked template and directly target the NADH-dependent 2-trans enoyl-acyl carrier protein reductase (InhA) enzyme, rather than relying on the activation by KatG enzyme like the traditional drug, isoniazid (INH). By circumventing KatG-related resistance, these compounds have the potential to be effective against multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of M. tuberculosis bacteria. It's exciting to see the development of new solutions to combat drug-resistant tuberculosis and provide hope for patients who may have limited treatment options.

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