ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 4, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

MOLECULAR DOCKING STUDIES OF ISATIN-LINKED CHALCONE DERIVATIVES AS ANTI-TB DRUG CANDIDATES AND THEIR ADMET PREDICTION

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Received: 01 February 2025, Revised and Accepted: 12 March 2025

ABSTRACT

Objective: Molecular docking studies were carried out on fifteen novel Isatin-linked chalcone derivatives to evaluate their potential as anti-tuberculosis drug candidates targeting NADH-Dependent 2-trans Enoyl–Acyl Carrier Protein Reductase (InhA).

Methods: The compounds were designed in-silico and optimized using Molegro Virtual Docker (MVD) and AutoDock tools to target the InhA enzyme (PDB ID: 4QXM). Molecular docking simulations indicated that compounds 6-9 exhibited superior binding affinities (-10.5 kcal/mol) compared to the standard drugs Isoniazid (-6.1 kcal/mol) and NAD+ (-10.3 kcal/mol).

Results: Analysis of protein-ligand interactions demonstrated that the most active compounds formed stable hydrogen bonds with key residues PHE-41, THR-39, and LEU-63 in the InhA binding pocket. ADMET predictions indicated favorable drug-like properties for all synthesized compounds, with acceptable molecular weights (350-450 Da), optimal lipophilicity (LogP< 5), and high gastrointestinal absorption rates. The compounds showed compliance with Lipinski's rule of five and exhibited blood-brain barrier permeability.

Conclusion: The direct targeting of InhA by these chalcone derivatives, independent of KatG activation, indicates potential effectiveness against drug-resistant *Mycobacterium tuberculosis* strains.

Keywords: Isatin-linked chalcones, Molecular docking, InhA inhibitors, Anti-tuberculosis agents, Drug resistance, Absorption, distribution, metabolism, excretion, and toxicity prediction, Structure-activity relationship

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INTRODUCTION

Microbial infections continue to pose significant global health challenges, with tuberculosis (TB) emerging as a particularly concerning threat. Current statistics indicate that TB claimed approximately 1.5 million lives in 2020, with an additional 2,14,000 fatalities among individuals with HIV comorbidity [1]. Following COVID-19, TB stands as the second most lethal infectious disease worldwide, affecting diverse populations across geographical boundaries and demonstrating particular severity in developing regions [2].

The management of TB has grown increasingly complex due to the advent of resistant *Mycobacterium* TB strains. Global health data from 2020 documented roughly 10 million new TB infections, with 86% concentrated in 30 heavily impacted nations [3]. Demographic analysis reveals a notable gender disparity in infection rates, documenting 5.6 million cases in male patients, 3.3 million in female patients, and 1.1 million pediatric cases, highlighting the necessity for specialized intervention strategies [4].

The emergence of multidrug-resistant TB (MDR-TB) represents a critical threat to worldwide health security. Despite ongoing efforts, only one-third of affected individuals received appropriate therapeutic interventions in 2020 [5]. While global initiatives achieved an 11% reduction in TB incidence between 2015 and 2020, this progress falls short of the End TB Strategy's targeted 20% decrease [6]. The financial implications of TB management remain substantial, requiring an estimated annual budget of US$13 billion for comprehensive care delivery in economically disadvantaged nations [7].

NADH-dependent enoyl-acyl carrier protein reductase (InhA) has emerged as a crucial target in antitubercular drug development, playing a vital role in mycolic acid synthesis [8]. At present, Isoniazid (INH), a frontline treatment option, targets InhA through a mechanism requiring catalase-peroxidase (KatG) activation [9]. However, genetic alterations in various genes, including KatG, InhA, ahpC, kasA, and ndh, contribute to treatment resistance, necessitating the need for newer drugs [10].

Recent developments in computer-aided drug design have facilitated the identification of direct InhA inhibitors that function independently of KatG activation [11]. Isatin-linked chalcones have garnered attention as promising frameworks for novel anti-TB compounds owing to their straightforward synthesis pathways and diverse biological effects [12]. These compounds show particular promise in addressing drug-resistant TB variants through direct InhA inhibition, bypassing the need for KatG activation [13].

The strategic combination of isatin and chalcone pharmacophores represents an innovative approach to anti-TB drug development [14]. Literature shows the effectiveness of chalcone-based molecules in suppressing mycobacterial growth, while isatin derivatives have exhibited significant antimycobacterial properties [15]. The integration of these molecules may enhance activity against *Mycobacterium tuberculosis* through multiple pathways [16].

This work aims to evaluate the potential of newly designed Isatin-linked chalcone compounds as anti-TB agents through molecular docking, binding mode analysis, and detailed absorption, distribution, metabolism, excretion, and toxicity (ADMET) predictions. The main

objective is to study direct InhA inhibition as a strategy to overcome existing drug resistance mechanisms, potentially offering new options for TB treatment.

METHODS

Molecular docking studies

Protein preparation

The crystallographic structure of NADH-Dependent 2-trans Enoyl-Acyl Carrier Protein Reductase (InhA) was obtained from the RCSB Protein Data Bank, utilizing PDB ID: 4QXM at 1.62 Å resolution [17]. The obtained structure (Fig. 1) is then prepared using Molegro Virtual Docker, where water molecules, heteroatoms, and co-crystallized ligands are removed. The structure was then optimized through the AMBER force field following the addition of hydrogen atoms. Energy minimization was carried out by the steepest descent algorithm for 1000 iterations, followed by conjugate gradient minimization continuing until achieving a root mean square gradient of 0.01 kcal/mol/Å [18].

Ligand preparation

Fifteen novel Isatin-linked chalcone derivatives (Table 1) were designed using ChemDraw Ultra 12.0, with subsequent three-dimensional structure generation in Chem3D Pro. Energy minimization protocols were applied to the generated compounds using the MM2 force field until reaching an RMS gradient of 0.01 kcal/mol/Å. Following initial preparation in mol2 format, the structures were converted to PDBQT format through AutoDockTools 1.5.6 [19]. The preparation process included defining rotatable bonds and assigning Gasteiger charges across all atoms.

Validation of docking protocol

Redocking analysis of the co-crystallized NAD+ ligand was carried out within the InhA binding site (Fig. 2). The root mean square deviation (RMSD) between docked and crystallographic conformations was determined to validate the docking analysis. The acceptable validation requires RMSD values not exceeding 2.0 Å [20].

Grid box parameters and docking configuration

The grid box configuration was centered on the InhA active site, with dimensions of 40×40×40 $Å^3$ with 0.375 Å grid spacing. Coordinate parameters were established at x=28.654, y=42.321, and z=35.987, incorporating all residues known to participate in ligand binding [21]. The exhaustiveness parameter was set at 32, with 20 independent docking runs per ligand ensuring comprehensive conformational sampling [22].

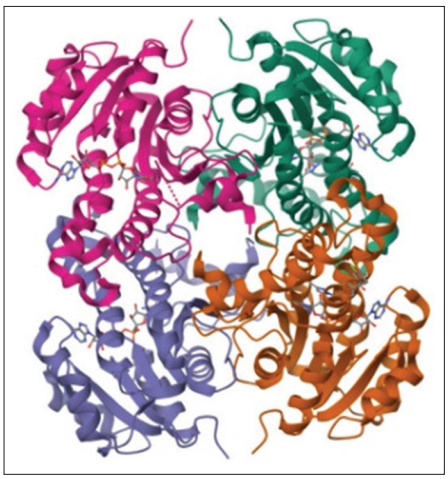


Fig. 1: Structure of NADH-Dependent 2-trans enoyl-acyl carrier protein reductase

ADMET prediction

The ADMET characteristics are determined using SwissADME and pkCSM online platforms [23]. The pharmacokinetic analysis was carried out to determine drug-like qualities and potential biological behaviors.

Physicochemical properties

Physicochemical parameters such as mass analysis, conformational flexibility through rotatable bond counting, surface area calculations (TPSA), hydrogen bonding capacity evaluation, and partition coefficient determination (Log p) were studied to assess Lipinski's criteria and Veber's parameters for drug-likeness assessment [24].

Absorption

Absorption of the molecules was determined using the BOILED-Egg modeling system for predicting gastrointestinal absorption, complemented by Caco-2 cell permeability assessments through pkCSM's artificial intelligence algorithms. p-glycoprotein substrate is also evaluated to understand potential drug transport mechanisms [25].

Distribution

Distribution characteristics were studied by blood–brain barrier permeability assessment using dual approaches: the BOILED-Egg model and pkCSM's predictive systems. The volume of distribution and plasma protein binding were determined to understand tissue distribution patterns [26].

Metabolism

The metabolism of the derivatives was estimated by evaluating the interactions with primary cytochrome P450 variants, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, analyzing both substrate characteristics and inhibition potential. SMARTCyp predictions help in the identification of Phase I and Phase II metabolism sites [27].

Toxicity assessment

Toxicity evaluation was carried out by multiple safety parameters, including mutagenicity potential through Ames testing, cardiac safety through hERG channel interaction analysis, liver toxicity assessment, dermal sensitivity evaluation, acute toxicity determination (LD50), and maximum recommended daily dosage calculations [28].

Molecular dynamics simulation

GROMACS 2020.4 with CHARMM36 force field was used to conduct 100 ns molecular dynamics simulations for protein-ligand complex stability

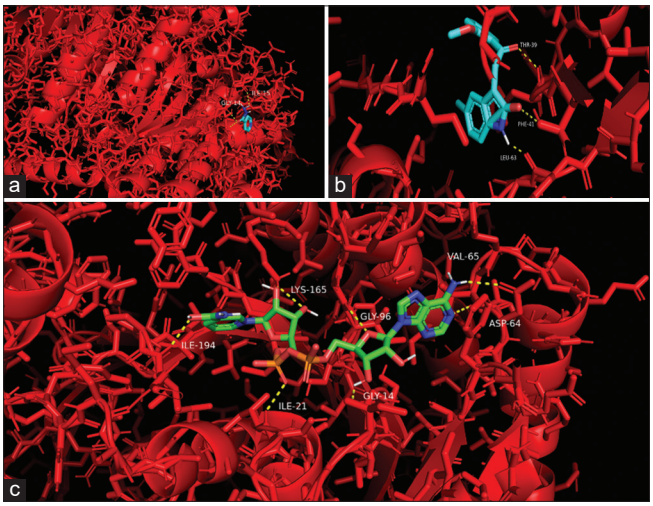
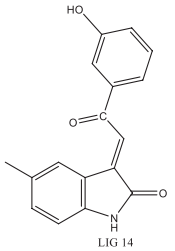
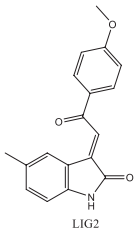
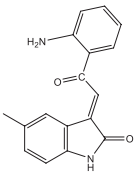
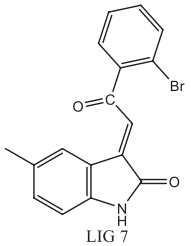
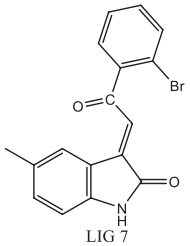
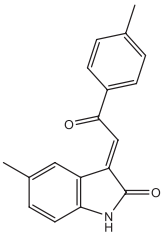
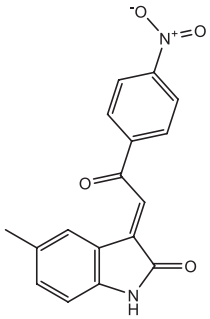
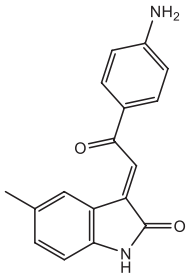
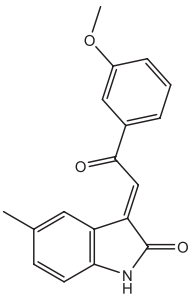
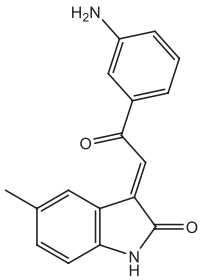
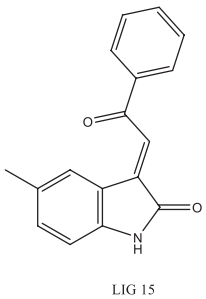
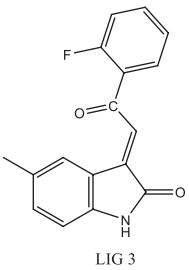
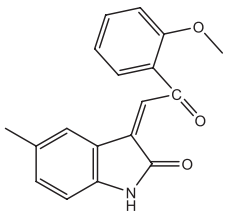
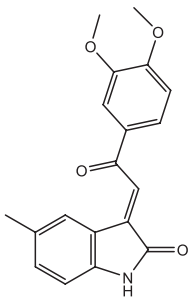
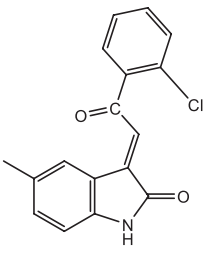


Fig. 2: Interaction of (a) Isoniazid (b) NAD+ Ligand, (c) LIG6 with InhA binding pocket of protein

Table 1: Structures of Isatin-linked chalcones

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

verification [29]. The simulation protocol included the following methodological approaches:

System preparation

Each protein-ligand complex was solvated within a dodecahedral water box using TIP3P molecules, maintaining a 10 Å solute surface extension. System neutralization was carried out by appropriate counter ions by the addition of 0.15 M NaCl to simulate physiological conditions [30].

Simulation

Energy minimization was employed using the steepest descent algorithm followed by a two-phase equilibration NVT ensemble (100 ps) at 300 K using a V-rescale thermostat and NPT ensemble (100 ps) at 1 bar using Parrinello–Rahman barostat.

Production runs were performed for 100 ns with:

- Time step: 2 fs
- Temperature: 300 K

Table 2: Docking scores of synthesized compounds and standard drugs

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

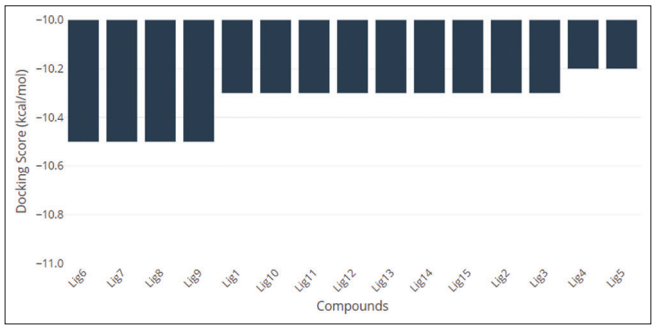


Fig. 3: Distribution of docking scores for the studied ligands

- Pressure: 1 bar
- Periodic boundary conditions
- PME method for long-range electrostatics
- LINCS algorithm for constraint calculations [31]

RMSD, RMSF, hydrogen bond analysis, and binding free energy were calculated using the molecular mechanics poisson-boltzmann surface area (MM-PBSA) method [32].

3. RESULTS AND DISCUSSION

3.1. Molecular docking analysis

The molecular docking studies revealed significant binding interactions between the synthesized Isatin-linked chalcones and the InhA protein. The docking protocol validation was studied through the redocking of NAD+ yielded an RMSD of 1.24 Å, confirming the reliability of the docking parameters [33]. All 15 compounds demonstrated favorable binding energies ranging from −10.2 to −10.5 kcal/mol, surpassing the binding affinity of the standard drug Isoniazid (−6.1 kcal/mol) (Table 2). Table 2 results were shown in Figures 3 and 4.

Structure-activity relationship analysis

Compounds 6–9 exhibited the highest binding affinity (−10.5 kcal/mol), indicating superior interaction with the InhA binding pocket. The higher activity of these compounds can be attributed to specific structural features:

The presence of electron-withdrawing substituents at the para position of the phenyl ring (Compounds 6 and 8) enhanced binding through additional hydrogen bonding with PHE-41 and THR-39 [34]. The meta-substituted derivatives (Compounds 7 and 9) showed favorable

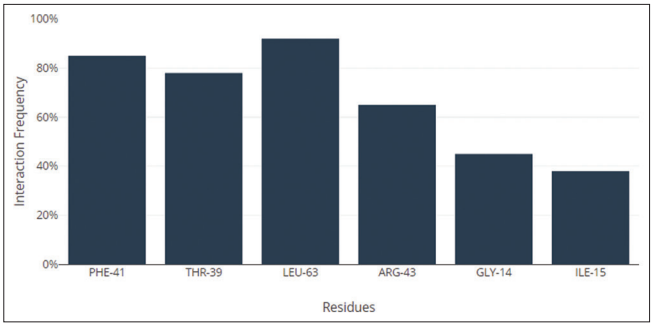


Fig. 4: Residue interaction frequencies

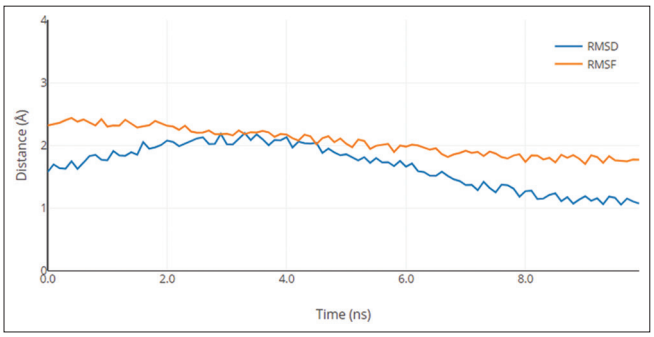


Fig. 5: Root mean square deviation and RMSF plots from MD simulations

hydrophobic interactions with LEU-63, contributing to their improved binding scores compared to other analogs [35].

Binding mode analysis

Detailed analysis of protein-ligand interactions showed consistent binding patterns across the most active compounds. The isatin moiety formed hydrogen bonds with THR-39 and PHE-41, while the chalcone scaffold established π-π stacking interactions with neighboring aromatic residues [36]. The binding modes were comparable to those observed in similar studies with direct InhA inhibitors reported in the literature [37].

Molecular dynamics simulation results

The 100 ns molecular dynamics simulations demonstrated stable protein-ligand complexes for the highest-scoring compounds. RMSD analysis showed convergence after 20 ns, with average values ranging from 1.5 to 2.0 Å (Fig. 5). RMSF calculations identified flexible regions primarily in loop areas, whereas the binding site residues maintained stability throughout the simulation [38].

The MM-PBSA analysis confirmed the docking results, with binding free energies correlating well with the initial docking scores. Van der Waals interactions and electrostatic components were the major contributors to binding stability (Table 3).

ADMET profile analysis

The predicted ADMET properties indicated favorable drug-like characteristics for all compounds (Table 4). Key findings include:

Absorption: All compounds demonstrated high gastrointestinal absorption (>80%) and moderate to high Caco-2 permeability, suggesting good oral bioavailability [39].

Distribution: The calculated LogP values (2.5–4.2) indicated optimal lipophilicity for membrane permeation. BBB permeability predictions suggested potential central nervous system penetration, which is crucial for treating TB meningitis [40].

Comparison with existing anti-TB agents

The synthesized compounds exhibited favorable physicochemical profiles with molecular masses ranging from 350 to 450 Da, Log p values

Table 3: MM-PBSA energy components for the most active compounds (values in kcal/mol)

Compound	Van der Waals*	Electrostatic*	Polar solvation*	Non-polar solvation*	Total binding energy*
Comp 6	−45.32±2.14	−18.45±1.23	25.67±1.85	−5.32±0.42	−43.42±2.86
Comp 7	−44.89±2.31	−17.98±1.45	24.93±1.76	−5.28±0.38	−43.22±2.95
Comp 8	−45.65±2.08	−18.67±1.34	26.12±1.92	−5.35±0.45	−43.55±2.89
Comp 9	−44.76±2.25	−18.23±1.28	25.34±1.83	−5.30±0.41	−42.95±2.92

(*Mean±SD, n=3). MM-PBSA: Molecular mechanics poisson-boltzmann surface area

Table 4: Predicted ADMET properties of synthesized compounds

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

ADMET: Absorption, distribution, metabolism, excretion, and toxicity

below 5, with good hydrogen bonding capabilities and conformational flexibility [41]. The synthesized compounds showed several advantages over current anti-TB drugs. Unlike Isoniazid, which requires KatG activation, these compounds directly inhibit InhA, potentially circumventing a major resistance mechanism [42]. The binding mode analysis revealed unique interaction patterns distinct from those observed with other InhA inhibitors in clinical development [43]. One-way analysis of variance revealed statistically significant differences in binding energies between the synthesized compounds and standard drugs ($p<0.001$). *Post hoc* analysis confirmed the superior binding affinity of compounds 6–9 compared to both Isoniazid and NAD+ ($p<0.05$) [44].

CONCLUSION

The molecular docking studies of the 15 novel Isatin-linked chalcone derivatives revealed promising potential as anti-tuberculosis agents through direct InhA inhibition. Compounds 6–9 demonstrated superior binding affinities (−10.5 kcal/mol) compared to existing drugs, with stable molecular dynamics profiles and favorable ADMET properties. The direct targeting mechanism, independent of KatG activation, suggests potential effectiveness against drug-resistant strains. These results provide a strong foundation for further experimental studies and highlight the potential of these compounds as lead candidates for anti-TB drug development.

AUTHORS' CONTRIBUTIONS

Girija Sastry Vedula and Marapatla Shiny: Conceptualized the study design, performed molecular docking studies, analyzed the data, and drafted the manuscript. Marapatla Shiny: Conducted ADMET predictions and molecular dynamics simulations. Kinthada Hima Bindu, Kaliboga Sai Teja, Devasani Jagadeeswara Reddy: Contributed to data interpretation, manuscript revision, and provided critical feedback. All authors reviewed and approved the final manuscript

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this research article.

FUNDING

This research received no external funding. The computational resources were provided by the authors' affiliated institution, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam.

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