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IN SILICO MOLECULAR DOCKING, DRUG-LIKENESS AND ADMET STUDIES OF QUINAZOLINE DERIVATIVES AGAINST PTR1 ENZYME (PDB ID: 1E7W) FOR ANTILEISHMANIAL ACTIVITY

Mr. Rahul Meena[1]*, Mr. Shashank Saxena[2], Ms. Ghazala Qureshi[3], Mr. Ashish Khandvi[4], Ms. Muskan Soni[5], Mr. Jeevan Singh Bodana[6]

[1,2]Department of Pharmaceutical Chemistry, Assistant Professor, Ujjain Institute of Pharmaceutical Sciences, Ujjain (M.P.)

[3,4,5,6]Department of Pharmaceutics, Assistant Professor, Ujjain Institute of Pharmaceutical Sciences, Ujjain (M.P.)

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***Corresponding Author**

Mr. Rahul Meena

Department of Pharmaceutical Chemistry, Assistant Professor, Ujjain Institute of Pharmaceutical Sciences, Ujjain (M.P.)

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ABSTRACT

Leishmaniasis is a neglected tropical disease caused by protozoan parasites of the genus *Leishmania*, posing a significant global health burden. The emergence of drug resistance and the limitations of current therapeutic agents necessitate the discovery of novel antileishmanial compounds. In the present study, an in silico approach was employed to evaluate the antileishmanial potential of selected quinazoline derivatives targeting Pteridine Reductase 1 (PTR1), a key enzyme involved in the parasite's folate metabolism pathway. The three-dimensional crystal structure of PTR1 (PDB ID: 1E7W) was obtained from the Protein Data Bank and used for molecular docking studies. A series of quinazoline derivatives were designed and docked into the active site of PTR1 using molecular docking software to investigate their binding affinity and interaction patterns. The docking results revealed that several derivatives exhibited favorable binding energies and formed stable interactions with crucial active-site amino acid residues, suggesting strong inhibitory potential against PTR1. Furthermore, drug-likeness properties were evaluated based on Lipinski's Rule of Five, indicating that the majority of the compounds possessed

desirable physicochemical characteristics for oral bioavailability. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was performed to assess pharmacokinetic behavior and safety profiles. The selected lead compounds demonstrated acceptable ADMET parameters, including good intestinal absorption, low toxicity risk, and favorable pharmacokinetic properties. Overall, the findings suggest that quinazoline derivatives may serve as promising lead molecules for the development of novel antileishmanial agents targeting PTR1. Further in vitro and in vivo investigations are recommended to validate their therapeutic efficacy and safety.

KEYWORDS: Leishmaniasis, Quinazoline Derivatives, Pteridine Reductase 1 (PTR1), Molecular Docking, Drug-Likeness, ADMET, In Silico Studies, Antileishmanial Activity.

1. INTRODUCTION

Leishmaniasis is a neglected tropical disease caused by *Leishmania* parasites and transmitted through infected female sandflies. Despite significant advances in treatment, the disease continues to pose a major public health challenge, particularly in developing countries. The currently available therapies, including pentavalent antimonial, amphotericin B, miltefosine, and paromomycin, are often associated with toxicity, high cost, prolonged treatment duration, and increasing drug resistance, highlighting the need for novel antileishmanial agents.[1,3,4,5]

Pteridine Reductase 1 (PTR1) is a key enzyme involved in the folate and pterin metabolic pathways of *Leishmania* and plays a crucial role in parasite survival. Its ability to compensate for the inhibition of Dihydrofolate Reductase-Thymidylate Synthase (DHFR-TS) makes PTR1 an attractive target for antileishmanial drug discovery.[1,2,4,5,7,8,11,13]

Quinazoline derivatives are an important class of heterocyclic compounds known for their diverse pharmacological activities, including antimicrobial, antimalarial, and antiparasitic properties. Their structural diversity and biological potential have made them promising candidates for the development of new therapeutic agents.[9]

Recent advances in in silico drug discovery have accelerated the identification of potential lead molecules through molecular docking, drug-likeness evaluation, and ADMET prediction. These computational approaches provide valuable insights into ligand–protein interactions and pharmacokinetic behavior while reducing the time and cost of drug development.[6,10,12,14,15]

Therefore, the present study investigates the binding affinity of selected quinazoline derivatives against PTR1 (PDB ID: 1E7W) through molecular docking analysis, along with drug-likeness and ADMET assessments, to identify potential lead compounds with promising antileishmanial activity.

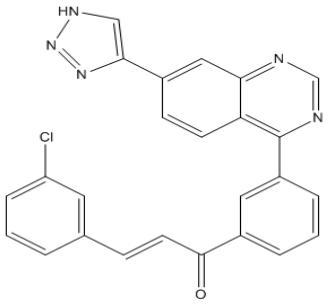
IN SILICO STUDIES

In silico studies have emerged as powerful tools in modern drug discovery and development, enabling researchers to evaluate the biological potential of compounds through computational techniques. These methods facilitate the prediction of molecular interactions between drug candidates and biological targets, thereby reducing the time, cost, and resources required for experimental screening. Molecular docking, virtual screening, and pharmacokinetic predictions are widely used in silico approaches that help identify promising lead molecules with favorable binding affinity and drug-like properties. Furthermore, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis provides early insights into the pharmacological and toxicological behavior of compounds, increasing the likelihood of successful drug development. Consequently, in silico methodologies have become essential components of contemporary medicinal chemistry and structure-based drug design research.[6,10,12,14,15]

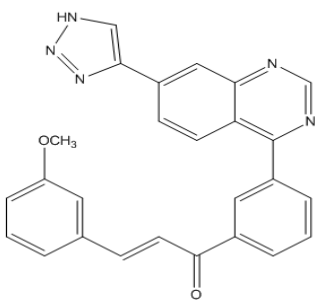
2. MATERIAL AND METHODS

2.1 Preparation of ligands

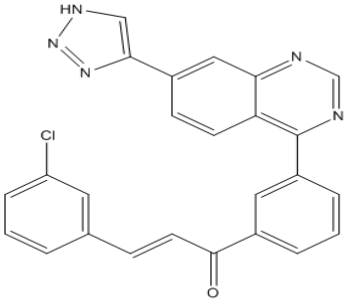
The chemical structures of the design ligands where first drawn using the ChemDraw ultra software. These 2D structures were then transfer to the Chem 3D ultra environment, were their 3D confirmations were generated and optimized using the MOPAC-based energy minimization protocol. The ligand confirmation displacing the lowest energy was considered the most stable and was selected for subsequent docking studies at the target protein active side.



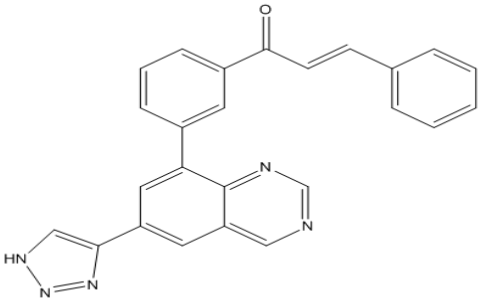
Compound 01 (MR10)



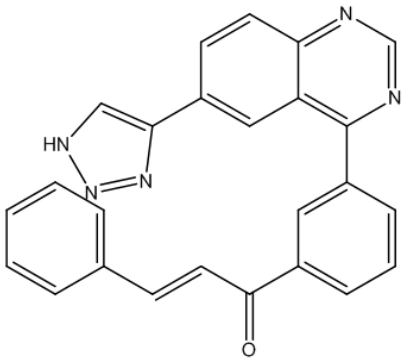
Compound 02 (MR09)



Compound 03 (MR08)



Compounds 04 (MR04)



Compound 05 (MR07)

2.2 Energy minimization of ligands

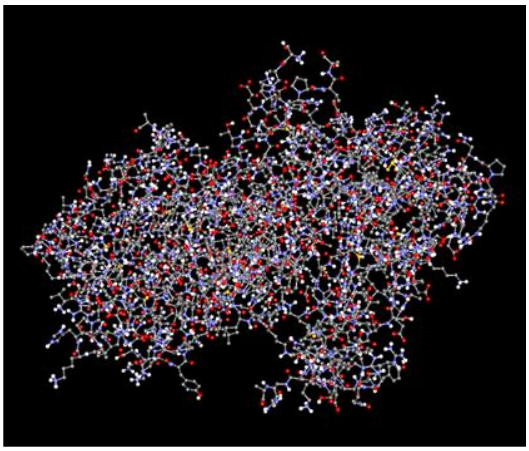
ChemDraw ultra 3D was used with the MM2 job to minimize energy. By ensuring that every ligand confirmation was in its lowest energy state, this step increased the precision of docking. The Pdb format was used to store the reduced ligand.

2.3 Protein Preparation

The three-dimensional crystal structure of Pteridine Reductase 1 (PTR1) from *Leishmania major* (PDB ID: 1E7W) was retrieved from the Protein Data Bank (PDB).[7] The protein structure was prepared prior to molecular docking studies to ensure its suitability for ligand binding analysis. All crystallographic water molecules, co-crystallized ligands, and other non-essential heteroatoms were removed from the protein structure using molecular visualization software. Missing hydrogen atoms were added to the protein, and appropriate bond orders were assigned.

The prepared protein structure was further optimized by correcting structural inconsistencies and assigning Kollman charges. The protein was then saved in the required format for docking analysis. The active binding site of PTR1 was identified based on the coordinates of

the co-crystallized ligand and reported active-site residues available in the literature. [1,2,4,7,13] Grid box parameters were defined to encompass the entire active site region and facilitate accurate ligand binding predictions. The final prepared protein structure was subsequently used for molecular docking studies with the selected quinazoline derivatives.



2.4 Receptor Grid Generation

To define the binding pocket for molecular docking, a receptor grid was generated around the active site of Pteridine Reductase 1 (PTR1) (PDB ID: 1E7W). The grid box was centered on the active-site region identified from the co-crystallized ligand and reported catalytic residues of the enzyme.[1,2,4,7] Grid parameters were adjusted to adequately cover the entire binding cavity and allow sufficient space for ligand flexibility during docking simulations.

The grid box center coordinates (X, Y, and Z) and dimensions were defined using AutoDock Tools/PyRx.[15] The selected grid dimensions ensured complete coverage of the active-site residues involved in ligand recognition and binding. The generated grid served as the search space for the AutoDock Vina docking algorithm, enabling the prediction of the most favorable binding conformations and interactions of the quinazoline derivatives within the PTR1 active site.

2.5 Molecular docking

AutoDock Vina was used for the docking process. Using a fixed grid box surrounding the ligand- binding site, each ligand was docked into 1RA1. Each ligand had ten binding poses produced by docking simulations; the optimal pose was chosen based on the lowest binding energy.[15]

2.6 Drug-Likeness and ADMET Prediction

The pharmacokinetic properties and drug-likeness profiles of the selected quinazoline derivatives were evaluated using the SwissADME web server. The chemical structures of the compounds were converted into SMILES format and submitted for analysis. Various physicochemical parameters, including molecular weight, lipophilicity (LogP), hydrogen bond donors, hydrogen bond acceptors, topological polar surface area (TPSA), and Lipinski's Rule of Five, were assessed to determine the drug-likeness characteristics of the compounds. Furthermore, gastrointestinal absorption, blood–brain barrier permeability, and bioavailability predictions were evaluated using the BOILED-Egg model available in SwissADME.[12,14]

2.7 Toxicity Prediction

Toxicological properties of the docked compounds were predicted using the ProTox-II web server. The SMILES structures of the selected compounds were submitted to the server to estimate toxicity endpoints, including LD50 values, toxicity class, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. The toxicity assessment was performed to identify compounds with favorable safety profiles for further drug development studies.[10]

3. RESULTS AND DISCUSSION

3.1 Energy Minimization of Ligands

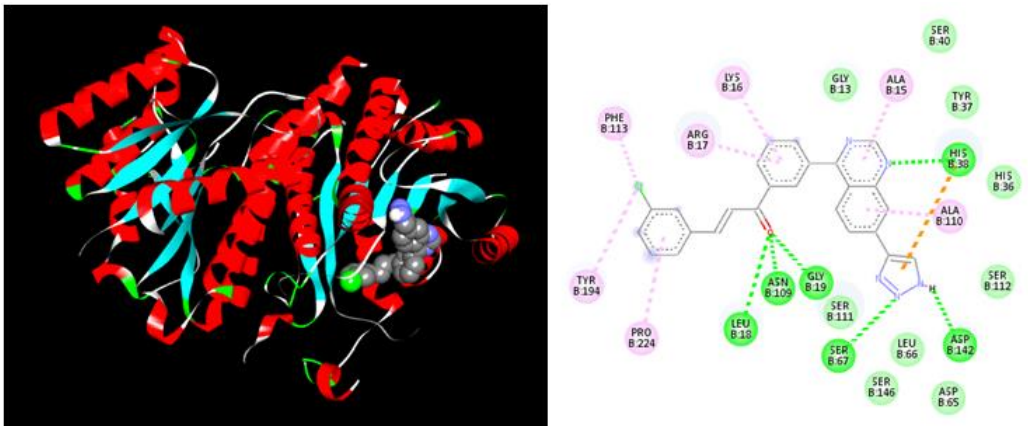
Table 1 presents the final total energy values of the compounds following energy minimization, expressed in kcal/mol. The resulting minimized structures were then employed as ligands for molecular docking studies with the PTR1 protein (PDB ID: 1E7W).

Table 01: Energy Minimization.

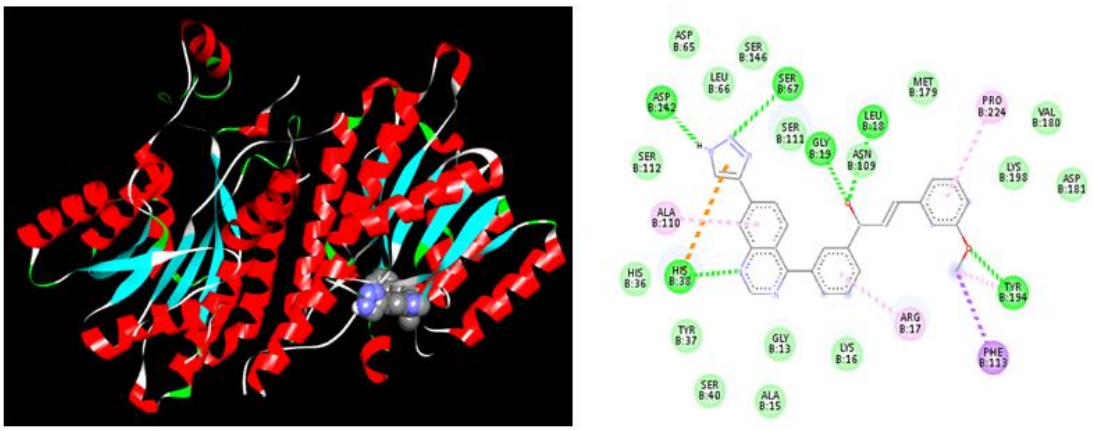
Compound ID	Ligand Name	Substituent Group	Substituent Position	Final Energy (Kcal/mol)
Compound 01	MR10	CHACLONE+TRIAZOLE+CL	R4,R7 AND R4' IN CHALCONE RING	21.7468
Compound 02	MR09	CHACLONE+TRIAZOLE+OCH3	R4,R7 AND R4' IN CHALCONE RING	22.5366
Compound 03	MR08	CHACLONE+TRIAZOLE	R4 AND R7	22.1148
Compound 04	MR07	CHACLONE+TRIAZOLE	R8 AND R6	23.322
Compound 05	MR04	CHACLONE+TRIAZOLE	R4 AND R6	19.4467
Quinazoline	QZ	NO	NO	4.8051

3.2 Molecular Docking Analysis

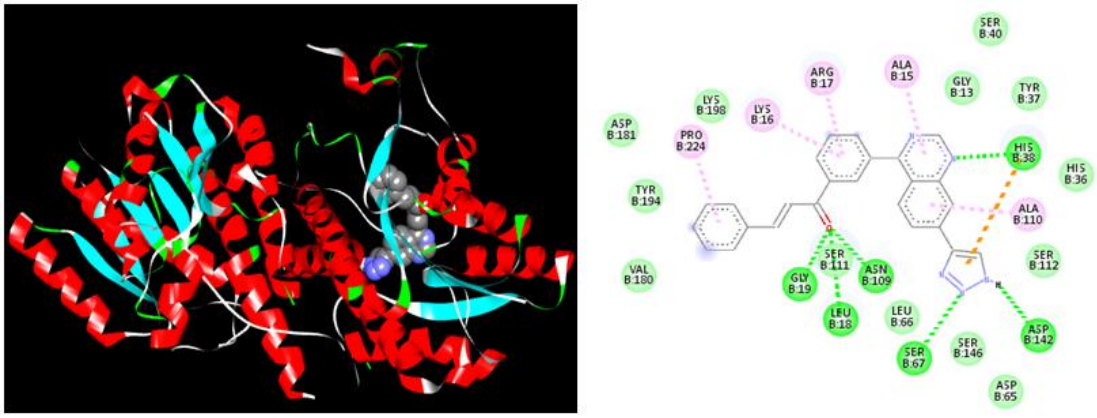
The molecular docking study was performed to evaluate the binding affinity of synthesized quinazoline–triazole–chalcone derivatives against the selected target protein. Among the ten screened compounds, MR10, MR09, MR08, MR04, and MR07 exhibited the most favorable docking scores and were therefore selected as lead candidates for detailed analysis.



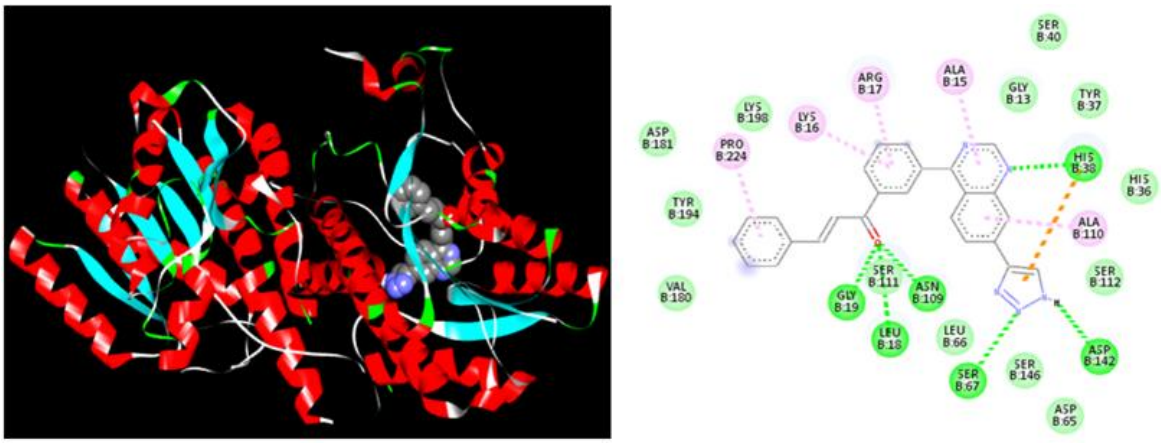
COMPOUND-1: (MR10) 3D AND 2D DOCKING POSE WITH PTR1 (1E7W).



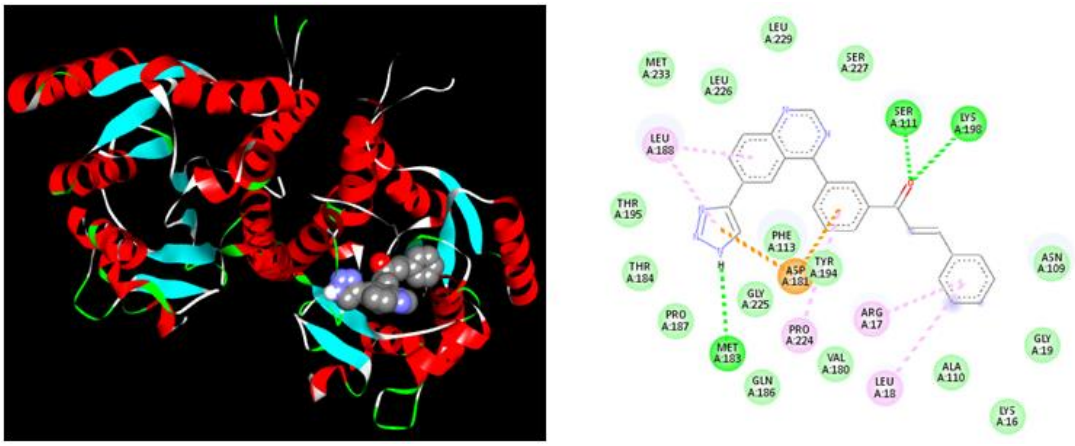
COMPOUND-2: (MR09) 3D AND 2D DOCKING POSE WITH PTR1 (1E7W).



COMPOUND-3: (MR08) 3D AND 2D DOCKING POSE WITH PTR1 (1E7W).



COMPOUND-4: (MR04) 3D AND 2D DOCKING POSE WITH PTR1 (1E7W).



COMPOUND-5: (MR07) 3D AND 2D DOCKING POSE WITH PTR1 (1E7W).

Table 02: Docking results of selected lead compounds.

Compound	Binding Energy (kcal/mol)	Difference from Best Compound	Relative Binding Strength
MR10	−14.1	0.0	Highest
MR09	−13.8	0.3	Very High
MR08	−13.7	0.4	Very High
MR04	−13.3	0.8	High
MR07	−13.3	0.8	High

Table 03: Comparative Binding Affinity Analysis.

Compound	Binding Energy (kcal/mol)	Difference from Best Compound	Relative Binding Strength
MR10	−14.1	0.0	Highest
MR09	−13.8	0.3	Very High
MR08	−13.7	0.4	Very High
MR04	−13.3	0.8	High
MR07	−13.3	0.8	High
Quinazoline	-5.9	-	Low

Table 04: Structure activity relationship analysis.

Compound	Structural Feature	Binding Energy (kcal/mol)	SAR Interpretation
MR10	Chlorine-substituted chalcone ring	−14.1	Strong hydrophobic interaction; highest affinity
MR09	Methoxy-containing chalcone ring	−13.8	Enhanced electronic interaction with receptor
MR08	R4 and R7 dual substitution	−13.7	Improved active-site accommodation
MR04	R8 and R6 substitution	−13.3	Moderate receptor stabilization
MR07	R4 and R6 substitution	−13.3	Stable binding orientation

3.3 Lead Compound Selection

Lead compounds were selected based on docking score, structural diversity, and predicted receptor interaction strength. Compounds exhibiting docking scores below −13.0 kcal/mol were considered highly promising candidates.

Table 05: Lead Optimization Potential of Top Compounds.

Compound	Docking Score	Lead Status
MR10	−14.1	Primary Lead
MR09	−13.8	Primary Lead
MR08	−13.7	Primary Lead
MR04	−13.3	Secondary Lead
MR07	−13.3	Secondary Lead

3.4 Statistical Evaluation of Docking Results

To evaluate the overall docking performance of the selected compounds, statistical parameters were calculated.

Table 06: Statistical Summary of Docking Scores.

Parameter	Value
Number of Lead Compounds	5
Highest Binding Energy	−14.1 kcal/mol
Lowest Binding Energy	−13.3 kcal/mol
Average Binding Energy	−13.64 kcal/mol
Range	0.8 kcal/mol
Standard Deviation	0.35 kcal/mol

3.5 Ranking of Lead Molecules

Based on docking affinity, the compounds were ranked in descending order of receptor binding strength.

Table 07: Ranking of Lead Molecules.

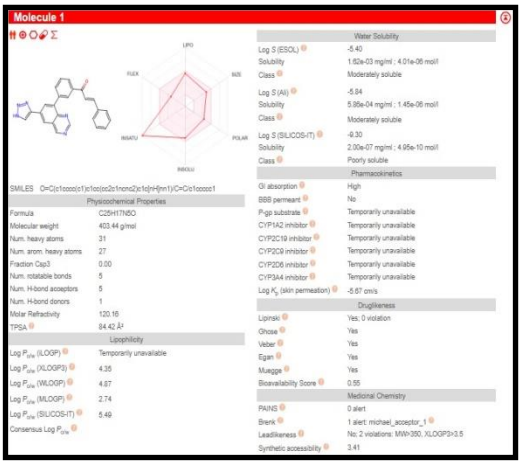
Rank	Compound	Binding Energy (kcal/mol)
1	MR10	−14.1
2	MR09	−13.8
3	MR08	−13.7
4	MR04	−13.3
5	MR07	−13.3

Table 08: Summary of Top Lead Compounds.

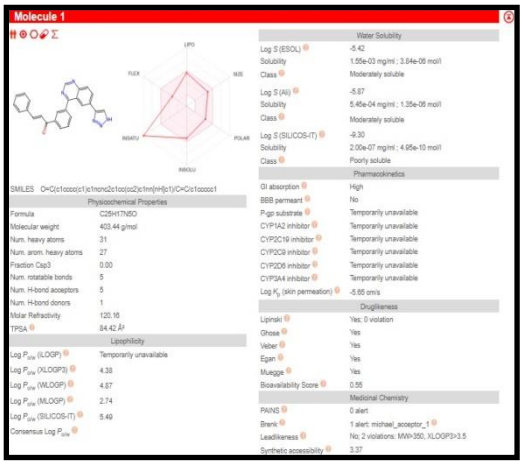
Compound	Minimized Energy	Binding Energy	Activity Level	Lead Status
MR10	21.7468	−14.1	Excellent	Lead-I
MR09	22.5360	−13.8	Excellent	Lead-II
MR08	22.1148	−13.7	Excellent	Lead-III
MR04	23.3220	−13.3	Very Good	Lead-IV
MR07	19.4467	−13.3	Very Good	Lead-V

3.6 ADMET and Drug-Likeness Profile of the Top Five Lead Compounds

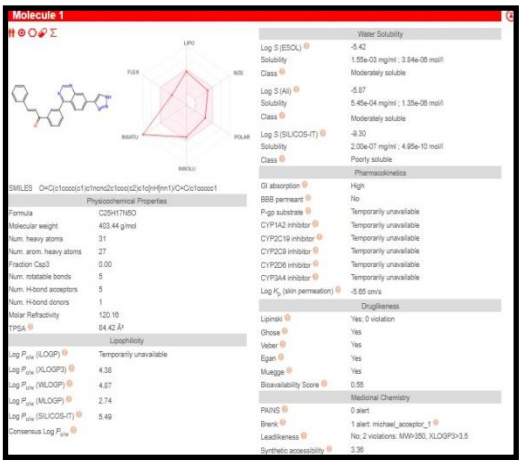
The pharmacokinetic, drug-likeness, and medicinal chemistry properties of the top five lead compounds were evaluated using the SwissADME web server. The predicted ADME parameters revealed favorable oral bioavailability, high gastrointestinal absorption, and acceptable drug-likeness profiles for all selected **compounds. The detailed results are presented in Table 09.**



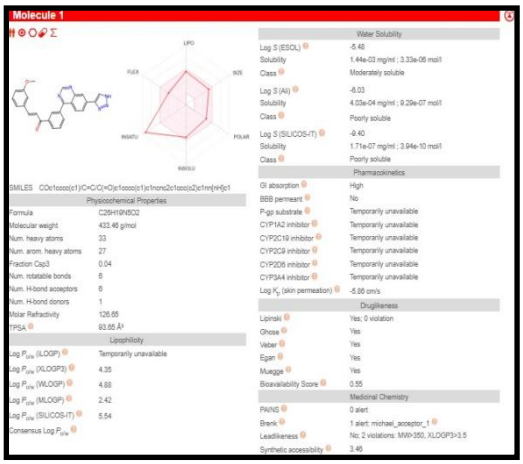
COMPOUND-5 (MR04)



COMPOUND-4(MR07)



COMPOUND-3(MR08)



COMPOUND-2(MR09)

COMPOUND-01(MR10)

Table 09: ADME, pharmacokinetic and drug-likeness properties of the top five lead quinazoline derivatives obtained from Swiss ADME analysis.

Parameter	MR04	MR07	MR08	MR09	MR10
Molecular Weight (g/mol)	403.44	403.44	403.44	433.46	437.88
H-Bond Acceptors	5	5	5	6	5
H-Bond Donors	1	1	1	1	1
Rotatable Bonds	5	5	5	6	5
TPSA (Å²)	84.42	84.42	84.42	93.65	84.42
Consensus LogP	5.49	5.49	5.49	5.54	6.12
GI Absorption	High	High	High	High	High
BBB Permeability	No	No	No	No	No
Lipinski Rule	Passed	Passed	Passed	Passed	Passed
Ghose Filter	Passed	Passed	Passed	Passed	Passed
Veber Filter	Passed	Passed	Passed	Passed	Passed
Egan Filter	Passed	Passed	Passed	Passed	Passed
Muegge Filter	Passed	Passed	Passed	Passed	Failed*
Bioavailability Score	0.55	0.55	0.55	0.55	0.55
PAINS Alert	0	0	0	0	0
Brenk Alert	1	1	1	1	1
Synthetic Accessibility	3.41	3.37	3.36	3.46	3.39

Table 10: ProTox-3.0 - Prediction of Toxicity of Compond-1 (MR10).

Category	Toxicity Parameter	Shorthand	Prediction	Probability
Organ Toxicity	Hepatotoxicity	DILI	Active	0.62
Organ Toxicity	Nephrotoxicity	Nephro	Inactive	0.58
Organ Toxicity	Cardiotoxicity	Cardio	Inactive	0.82
Toxicity Endpoints	Carcinogenicity	Carcino	Inactive	0.73
Toxicity Endpoints	Mutagenicity	Mutagen	Inactive	0.56
Toxicity Endpoints	Cytotoxicity	Cyto	Inactive	0.72
Metabolism	Cytochrome CYP1A2 Interaction	CYP1A2	Active	0.57
Metabolism	Cytochrome CYP2D6 Interaction	CYP2D6	Inactive	0.58
Metabolism	Cytochrome CYP3A4 Interaction	CYP3A4	Inactive	0.58

CONCLUSION

The present in silico study demonstrated that the designed quinazoline–chalcone–triazole derivatives possess promising antileishmanial potential against the target receptor. Molecular docking analysis revealed strong binding affinities for all selected compounds, with MR10 exhibiting the highest binding affinity, followed by MR09 and MR08. The enhanced activity of these compounds may be attributed to the presence of electron-withdrawing substituents, which facilitate favorable hydrophobic and non-covalent interactions within the active site.

Drug-likeness and ADMET evaluation indicated that the lead compounds possess desirable pharmacokinetic properties, including high gastrointestinal absorption, acceptable physicochemical characteristics, compliance with major drug-likeness filters, absence of PAINS alerts, and good oral bioavailability. Toxicity prediction further demonstrated a favorable safety profile, with no significant risk of carcinogenicity, mutagenicity, cytotoxicity, nephrotoxicity, or cardiotoxicity. Although a moderate hepatotoxicity alert was observed, the overall toxicity assessment remained within acceptable limits for early-stage drug discovery.

Collectively, the docking, drug-likeness, ADMET, and toxicity findings identify MR10 as the most promising lead candidate, while MR09 and MR08 also exhibited significant potential. These results support the quinazoline–chalcone–triazole scaffold as a valuable framework for the development of novel antileishmanial agents and warrant further in vitro and in vivo investigations.

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