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# Exploring Schiff bases as promising alternatives to traditional drugs in the *in silico* treatment of leishmaniasis

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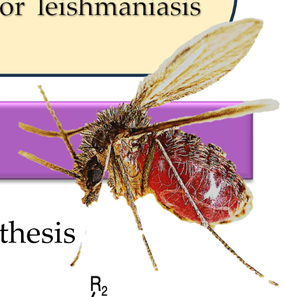
## INTRODUCTION & AIM

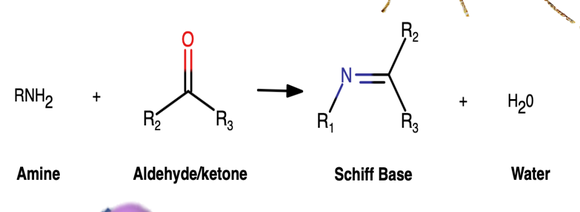
Leishmaniasis, caused by the protozoan *Leishmania* spp. and transmitted by sandflies, affects 2 million people worldwide annually, recognized as a global issue by the World Health Organization (WHO). Different forms of the disease exist, with visceral leishmaniasis being the most severe, characterized by fever, weight loss, and anemia, affecting internal organs and potentially leading to fatality if untreated. This condition poses a public health challenge, with preventive measures focusing on vector control and medical treatment for diagnosed cases. The concern lies in the observed side effects of conventional leishmaniasis treatments. Therefore, this study explores Schiff base compounds as potential alternatives, analyzing thirty-nine structures from the PubChem database using molecular docking methods. Promising Schiff base candidates (3-Quinolinamine, N-(2-quinolinylmethylene)-, 1,3-Bis[(E)-(2-Amino-4-Ethyl-5-Hydroxy-Phenyl)Methyleneamino]Urea, and Naphtaldehyde di-sulfide Schiff base) demonstrated significant affinities, outperforming commercial inhibitors. Hence, this study proposes computational-based alternatives for leishmaniasis treatment.

## Base Schiff Compounds



Schiff base compounds, also known as Schiff bases, refer to a class of organic compounds that contain an azomethine functional group (C=N) in their structure. These compounds are typically derived from the reaction of a primary amine with an aldehyde or ketone. The formation of the double bond between the carbon atom of the carbonyl group in the aldehyde or ketone and the nitrogen atom of the amine results in a characteristic structure.

**Figure 1.** Schiff base synthesis




## METHODS

1 Protein Selection and Preparation

SELECT STRUCTURE: Selection of a structure with satisfactory crystallographic quality and the presence of an inhibitor (RCSB PDB PROTEIN DATA BANK)

PREPARING FILE: Addition of Hydrogens and Gasteiger Charges (AutoDock 4)

OBTAIN FILE IN .PDBQT: Save file in .pdbqt format

2 Ligand Database Preparation

a Identify schiff base compounds

b Select on the pubchem platform

c Download compounds in .sdf format

d Add Hydrogens and Charges

e Save in .pdbqt format

3 Virtual Screening

Schiff Base Compounds

4 Select of Best Compounds

5 Comparison with commercial inhibitors

**Promissing Compounds**

## RESULTS & DISCUSSION

**Figure 2.** In (A), the enzyme (PDB: 2JK6) is depicted using the cartoon format overlaid with the surface, along with the Schiff base inhibitors. These inhibitors are shown in stick format and are colored according to the following legend: (B) Compound 21 (3-Quinolinamine, N-(2-quinolinylmethylene)-), (C) Compound 24 (2-((3-(1,3-Benzodioxol-5-yl)-2-methylpropylidene)amino)benzoic amethyl ester), and (D) Compound 39 (Benzoic acid, 2-((2-(phenylmethylene)octylidene)amino)-, methyl ester).

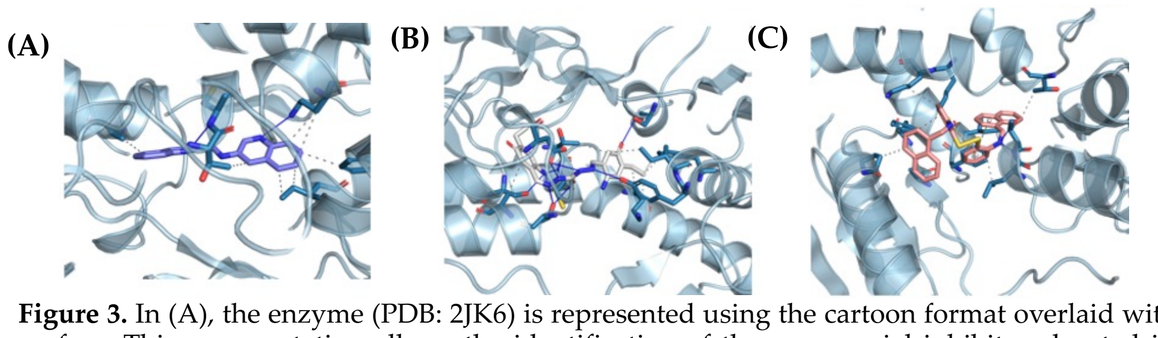



**Figure 3.** In (A), the enzyme (PDB: 2JK6) is represented using the cartoon format overlaid with the surface. This representation allows the identification of the commercial inhibitors located in the enzyme's active site. These inhibitors are shown in stick format and are colored according to the following legend: (B) Amphotericin B (Green), (C) Glucantime (Pool Blue), (D) Miltefosine (Pink), (E) Paromomycin (Yellow), and (F) Pentamidine (Orange).

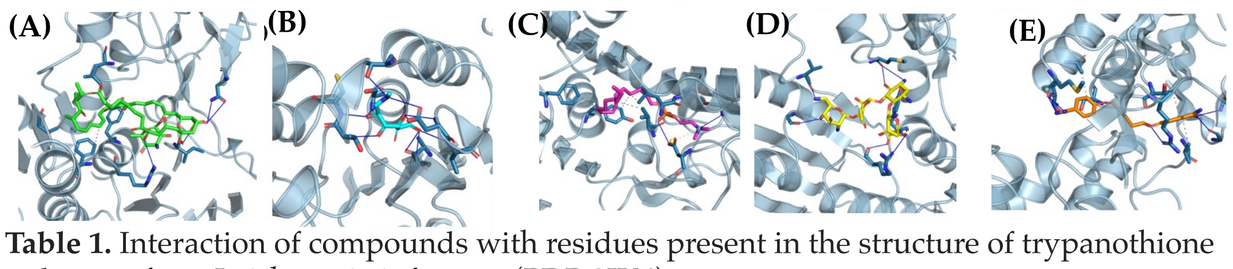



**Table 1.** Interaction of compounds with residues present in the structure of trypanothione reductase from Leishmania infantum (PDB:2JK6).

| Code | CID | Afinity (kcal/mol) | Interaction Type | Residues |
|---|---|---|---|---|
| **Promissing Compounds** | | | | |
| 21 | 265479 | -10,5 | Hydrophobic<br>Hydrogen | Thr51, Lys60, Ile199, Phe203 and Ala338<br>Ser14, Cys52, Ser178, Tyr198, Asp327 and Thr335 |
| 24 | 86573619 | -10,4 | Hydrophobic<br>Hydrogen | Thr51, Lys60, Ile199, Phe203 and Ala338<br>Ser14, Cys52, Ser178, Tyr198, Asp327 and Thr335 |
| 39 | 168349431 | -9,8 | Hydrophobic<br>Hydrogen<br>π-Perpendicular<br>π-Cation | Thr51, Lys61, Tyr198, Ile199, Leu334, Ala365, Phe367 e Pro435<br>Thr355<br>Tyr198<br>Lys60 |
| **Comercial Inhibitors** | | | | |
| A | Pentamidine | -8,8 | Hydrophobic<br>Hydrogen | Val36, Thr160 and Ala338<br>Ser14, Gly125, Gly127, Arg290, Met333 and Thr335 |
| B | Glucantime | -5,9 | Hydrogen | Ser14, Thr51, Cys52, Ala159, Gly161, Asp327, Val328 and Thr335 |
| C | Amphotericin B | -9 | Hydrophobic<br>Hydrogen | Tyr198, Phe230, Leu334 e Thr374<br>Arg228, Ile285 and Asn306 |
| D | Miltefosine | -5,8 | Hydrophobic<br>Hydrogen<br>Salt Bridges | Tyr198, Phe230, Val332 e Leu334<br>Ser14, Asp327 and Thr335<br>Asp327 |
| E | Paromomycin | -6,2 | Hydrogen | Tyr198, Arg228, Met333, Val362 and Gly376 |

## CONCLUSION

This study highlights the complexity and urgency associated with leishmaniasis as a significant challenge in public health. Current treatments, marked by toxicity, high costs, and resistance, reinforce the critical need to seek effective and affordable therapeutic alternatives. The innovative approach of Schiff Bases, exploring promising compounds, aims to improve the quality of life for patients and reduce the economic burdens associated with treatment. The convergence between natural and synthetic therapies stands out as a substantial strategy to overcome the limitations of conventional treatments, avoiding antimicrobial resistance and driving therapeutic innovations, highlighting the need for a global approach in addressing leishmaniasis. The results obtained through Molecular Docking simulations, especially with compounds 3-Quinolinamine, N-(2-quinolinylmethylene)- (Compound 21) with ΔG of -10.5 kcal/mol, 1,3-Bis[(E)-(2-Amino-4-Ethyl-5-Hydroxy-Phenyl)Methyleneamino]Urea (Compound 24) with ΔG of -10.4 kcal/mol, and Naphtaldehyde disulfide Schiff base (Compound 39) with ΔG of -9.8 kcal/mol, highlight the feasibility of this approach, suggesting possible efficacy against leishmaniasis. However, the caveat regarding the need for validation through rigorous laboratory analyses is emphasized as an essential step to consolidate these findings. If these compounds demonstrate effectiveness in subsequent analyses, the study envisions a significant advancement in the therapeutic field of leishmaniasis, offering renewed and hopeful options for the treatment and control of this debilitating disease. Therefore, this research contributes substantially to the evolution of therapeutic strategies against leishmaniasis, outlining a promising future of medical and scientific advancements, aligned with the objectives of understanding incidence, exploring types, conducting simulations, and highlighting the contributions of Schiff Bases in treating this illness.

## ACKNOWLEDGEMENTS

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