



Research Article

# Drug repurposing of some US FDA-approved drugs using Binding strength Studies for the Treatment of Methicillin-resistant *Staphylococcus aureus* Infection



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## Abstract:

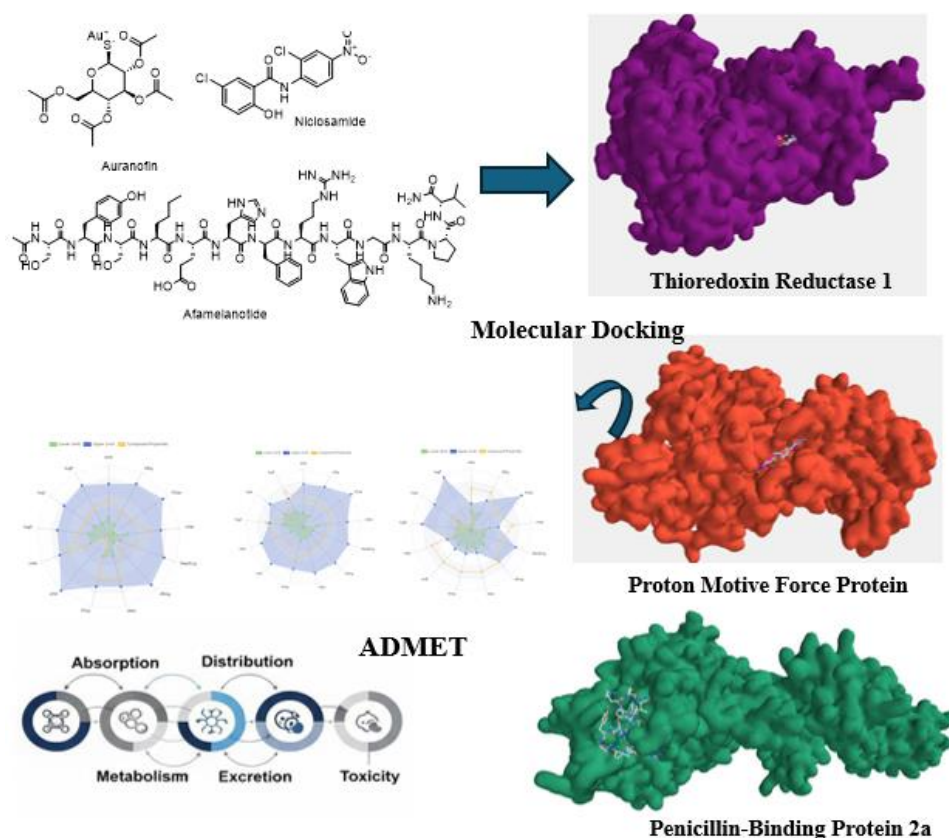
Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major multidrug-resistant bacterial pathogen responsible for severe infections worldwide. The increasing resistance of MRSA to conventional antibiotics has created an urgent need for new therapeutic strategies. Drug repurposing of US FDA-approved drugs offers a promising approach to identify alternative anti-MRSA agents while reducing the time and cost associated with traditional drug discovery. In this study, computational Binding strength analysis was performed to evaluate the inhibitory potential of selected compounds against important MRSA target enzymes, including thioredoxin reductase 1, proton motive force protein, and penicillin-binding protein 2a (PBP2a). Molecular docking results demonstrated strong interactions between the ligands and the active sites of the selected enzymes. The native ligand NL\_3QFB showed the strongest Binding strength toward thioredoxin reductase 1 with a docking score of -12.2 kcal/mol, while the reference drug Aurano fin exhibited -7.8 kcal/mol. For the proton motive force protein, NL\_9U6O displayed a docking score of -7.4 kcal/mol, comparable to Niclosamide (-7.5 kcal/mol). Similarly, NL\_6Q9N showed strong interaction with PBP2a with a docking score of -8.6 kcal/mol, whereas Afamelanotide showed weaker binding (-1.9 kcal/mol). ADMET analysis indicated acceptable physicochemical and pharmacokinetic properties for several compounds. Overall, the findings suggest that the investigated ligands demonstrate promising Binding capability and favorable drug-like properties against MRSA target enzymes. However, further experimental validation is required to confirm their therapeutic potential.

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## Graphical Abstract



## 1. Introduction

*Methicillin-resistant Staphylococcus aureus* (MRSA) is a serious antibiotic-resistant pathogen responsible for a wide range of infections in humans (1,2). MRSA has become a major public health concern worldwide because of its resistance to multiple classes of antibiotics, particularly  $\beta$ -lactam antibiotics, such as methicillin, penicillin, and cephalosporins (3,4). The emergence and rapid spread of MRSA strains in hospitals and community settings have significantly complicated the treatment of bacterial infections in these settings. These infections can manifest as skin and soft tissue infections, pneumonia, bloodstream infections, and surgical site infections, often leading to increased morbidity, mortality, and healthcare costs (5–8).

The resistance of MRSA primarily arises from the acquisition of the *mecA* gene, which encodes an altered penicillin-binding protein known as PBP2a (9,10). This protein exhibits reduced affinity for  $\beta$ -lactam antibiotics, allowing bacterial cell wall synthesis to continue even in the presence of antimicrobial agents (11,12). As a result, conventional antibiotics often fail to effectively inhibit MRSA growth (13,14). Although several antibiotics, such as Vancomycin, Linezolid, and Daptomycin, are currently used to treat MRSA infections, the increasing emergence of resistant strains highlights the urgent need for alternative therapeutic strategies (15–17). Drug discovery and development is a time-consuming and expensive process that typically requires years of research and substantial financial investment. In this context, drug repurposing (also known as drug repositioning) has emerged as a promising approach for identifying new therapeutic applications for existing drugs. Drug repurposing involves investigating already approved drugs for new medical indications beyond their original use. As the pharmacokinetic, safety, and toxicity profiles of these drugs have already been established, repurposing significantly reduces the time, cost, and risk associated with traditional drug development. Many repurposed drugs have successfully reached clinical application, demonstrating the effectiveness of this strategy in accelerating therapeutic discovery (18–21). Given the escalating resistance of

MRSA to conventional antibiotics, there is a growing shift toward computational approaches to accelerate the identification of effective therapeutic candidates for MRSA infections.

In recent years, computational methods such as molecular docking and binding capability studies have become powerful tools in drug repurposing research. These *in silico* techniques enable the prediction of interactions between small molecules and biological targets at the molecular level. By evaluating binding capabilities and interaction patterns, researchers can rapidly screen large numbers of compounds and identify potential inhibitors of specific proteins involved in disease pathways. Molecular docking helps determine how well a ligand fits into the active site of a target protein and provides insight into key interactions, such as hydrogen bonding, hydrophobic contacts, and electrostatic interactions, that contribute to binding stability. Several bacterial proteins involved in metabolic and resistance pathways are promising therapeutic targets for MRSA infections. These include enzymes responsible for bacterial redox balance and cell wall synthesis, such as thioredoxin reductase 1 and PBP2a, and proteins associated with energy metabolism, such as the proton motive force system. Targeting these proteins can disrupt essential bacterial processes and inhibit MRSA survival and proliferation.

Therefore, the present study focuses on the drug repurposing of selected US FDA-approved drugs through computational binding energy studies to identify potential inhibitors against MRSA-associated target proteins. Molecular docking analysis was employed to evaluate the interactions of the selected drugs with key MRSA proteins and to predict their binding stability and inhibitory potential. This approach may facilitate the identification of promising therapeutic candidates for MRSA treatment and contribute to the development of effective strategies to combat antibiotic-resistant bacterial infection. This study presents a novel computational drug repurposing approach by systematically evaluating selected US FDA-approved drugs against multiple MRSA-specific target proteins, integrating molecular docking and ADMET analysis to identify promising candidates with potential therapeutic applications.

## 2. Method Section

### 2.1 Molecular Docking

Molecular docking studies were conducted to evaluate the interactions between the synthesized ligands and selected target proteins to predict their potential binding energies and interaction patterns. Three US FDA-approved drugs, Aurano-fin, Niclosamide, and Afamelanotide, were selected for their interactions with the selected MRSA target proteins. Several computational tools, including ChemDraw, PubChem, the Protein Data Bank (PDB), BIOVIA Discovery Studio, and AutoDock Vina (version), were used during the docking procedure. The chemical structures of the synthesized compounds were drawn using ChemDraw. The generated structures were converted into three-dimensional (3D) formats and saved in the appropriate file formats for docking analysis. Ligand information and structural confirmation were obtained from the PubChem database (22). The ligand structures were then energy-minimized to obtain stable conformations that were suitable for docking studies. The three-dimensional crystal structures of the target proteins were obtained from the Protein Data Bank. The selected proteins were 3QFB, 9U6O, and 6Q9N. Protein preparation was performed using BIOVIA Discovery Studio. During this step, water molecules, co-crystallized ligands, and other heteroatoms were removed from protein structures. Hydrogen atoms were added to stabilize the protein structure and ensure proper protonation states for docking. The prepared proteins were saved in the required format for docking simulations. The docking grid box was defined around the active site of each protein based on binding pocket coordinates. The grid center coordinates used for docking were as follows: for protein 3QFB ( $X = 62.583472$ ,  $Y = -99.061774$ ,  $Z = 38.082736$ ), for protein 9U6O ( $X = 205.308704$ ,  $Y = 216.972259$ ,  $Z = 211.200852$ ), and for protein 6Q9N ( $X = -30.492278$ ,  $Y = -24.886944$ ,  $Z = 5.991556$ ). These coordinates ensured that the docking search space adequately covered the active binding regions of the proteins. Molecular docking simulations were performed using AutoDock Vina to predict ligand-protein binding modes and calculate binding scores. Multiple docking poses were generated for each ligand, and the best binding conformations were selected based on the lowest binding energy values. The docking results were further analyzed using BIOVIA Discovery Studio to visualize the ligand-protein interactions, including hydrogen bonding, hydrophobic interactions, and other non-covalent

interactions within the active site. The obtained docking scores and interaction profiles were used to assess the binding potential of the studied compounds to the selected protein targets (23). A 3D ribbon view of the active cavity of the enzymes with their native ligands is shown in Figure 1.

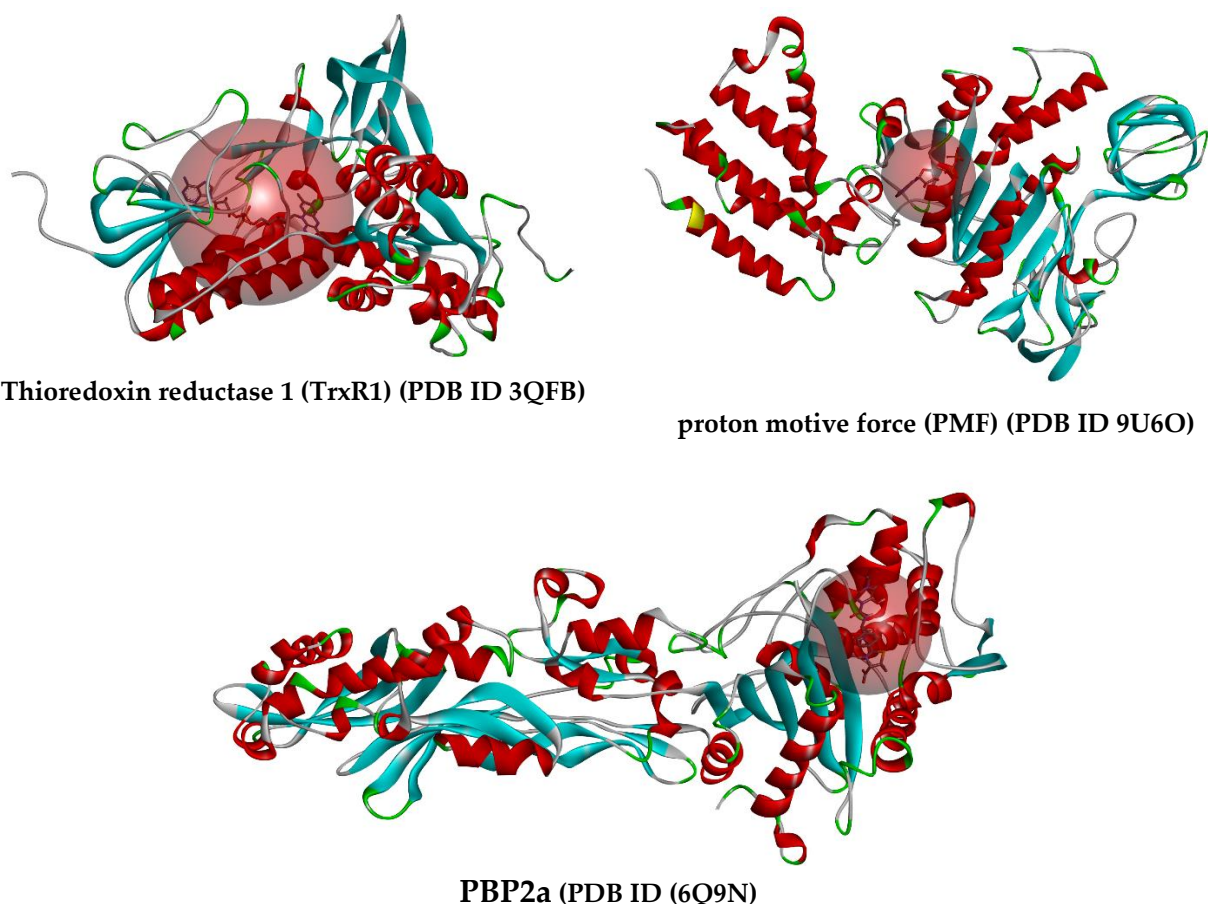


**Figure 1.** 3D ribbon view of the active cavities of enzymes with their native ligands.

## 2.2 ADMET Analysis

Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) analysis was performed to evaluate the pharmacokinetic properties and drug-likeness of the selected compounds using computational tools. The analysis was conducted using ChemDraw, PubChem, SwissADME, and ADMETLab 3.0 software. The chemical structures of the compounds were drawn using ChemDraw and converted into SMILES format for computational analysis. The molecular structures and related information were verified using the PubChem database to ensure their accuracy. The SMILES strings of the compounds were then submitted to SwissADME to predict the physicochemical parameters and pharmacokinetic properties, including molecular weight, lipophilicity (LogP), hydrogen bond donors and acceptors, topological polar surface area (TPSA), and gastrointestinal absorption. Drug-likeness was evaluated based on Lipinski's rule of five. Further ADMET predictions were performed using ADMETLab 3.0 to assess parameters such as human intestinal absorption, cytochrome P450 interactions, metabolism, clearance, and toxicity. These predictions helped identify compounds with favorable pharmacokinetic and safety profiles for further investigation (24–26).

## 3. Results and Discussion

### 3.1 Molecular Docking

Molecular docking analysis was performed to evaluate the binding energy and interaction pattern of the selected proteins with their respective native ligands (Table 1). The docking results were analyzed based on the binding energy (kcal/mol), ligand energy, and intermolecular interactions, such as hydrogen bonds and

hydrophobic interactions. The 2D and 3D interactions of the most potent compounds with Thioredoxin Reductase 1 (3QFB), Proton Motive Force Protein (9U6O), and PBP2a (6Q9N) are shown in Table 2-4.

### 3.1.1 Thioredoxin Reductase 1 (3QFB)

The docking interaction of 3QFB with the native ligand (NL\_3QFB) demonstrated a strong binding capability, with a docking score of -12.2 kcal/mol and ligand energy of 1859.01 kcal/mol. The ligand formed several conventional hydrogen bonds with amino acid residues, including ASP334, SER22, PHE43, GLY23, THR58, LYS67, and THR343, with bond lengths ranging from approximately 1.77–2.70 Å, indicating stable interactions within the active site. Additionally, carbon–hydrogen bonds were observed with ALA160, GLY57, and PRO344.

Other stabilizing interactions included  $\pi$ –sulfur interaction with CYS64 and  $\pi$ – $\pi$  T-shaped interaction with TYR200. Hydrophobic interactions, such as alkyl and  $\pi$ –alkyl interactions with VAL201, LEU342, and PHE184, further contributed to the stabilization of the ligand within the binding pocket. In comparison, the reference drug auranofin showed a docking score of -7.8 kcal/mol and ligand energy of 752.82 kcal/mol, which is significantly lower than that of the native ligand. Auranofin formed hydrogen bonds with GLY21, THR45, THR58, TYR131, and ARG164, along with a carbon hydrogen bond with GLY19 and a hydrophobic  $\pi$ –sigma interaction with TYR131. These results indicate that the native ligand exhibits a stronger binding capability with the 3QFB protein than auranofin.

### 3.1.2 Proton Motive Force Protein (9U6O)

Docking of 9U6O with the native ligand (NL\_9U6O) revealed a docking score of -7.4 kcal/mol and ligand energy of 1509.87 kcal/mol. The ligand formed several conventional hydrogen bonds with residues ASN498, GLY23, THR235, PRO22, GLY233, and LYS234, with bond lengths ranging from 1.93–3.20 Å. These hydrogen bonding interactions contribute significantly to the stabilization of the ligand in the active-binding region. The docking results were compared with the standard compound, niclosamide, which exhibited a docking score of -7.5 kcal/mol and ligand energy of 235.31 kcal/mol. Niclosamide formed hydrogen bonds with GLY231 and ARG258, along with hydrophobic interactions, such as  $\pi$ – $\pi$  stacked interactions with PHE419 and alkyl and  $\pi$ –alkyl interactions with VAL236 and PHE419. The docking scores of the native ligand and niclosamide were relatively comparable, indicating a similar binding score toward the 9U6O protein.

### 3.1.3 Penicillin-Binding Protein 2a (PBP2a) (6Q9N)

Docking analysis of 6Q9N with the native ligand (NL\_6Q9N) showed a docking score of -8.6 kcal/mol and a ligand energy of 1233.87 kcal/mol. The ligand formed multiple conventional hydrogen bonds with residues SER403, TYR441, ASN464, and THR600, with bond distances ranging from 1.87–2.80 Å, indicating strong and stable interactions. In addition, hydrophobic interactions, including  $\pi$ –sigma and  $\pi$ – $\pi$  T-shaped interactions with TYR446, contributed to the stability of the ligand within the binding pocket. For comparison, the peptide drug afamelanotide showed a relatively weaker docking score of -1.9 kcal/mol with a ligand energy of 1389.37 kcal/mol. Afamelanotide formed hydrogen bonds with TYR519, GLU602, and GLN613, along with carbon hydrogen bonding with THR444. Additional interactions, such as  $\pi$ –cation interactions with LYS604,  $\pi$ –sulfur interactions with MET641, and hydrophobic interactions, including  $\pi$ – $\pi$  stacked interactions with TYR446 and  $\pi$ –alkyl interactions with LYS430, were also observed.

### 3.1.3 Comparative Docking Analysis

Overall, the docking results indicated that the native ligands demonstrated strong binding affinities toward their respective protein targets. Among the studied systems, the NL\_3QFB–3QFB complex exhibited the strongest interaction, with a docking score of -12.2 kcal/mol, followed by NL\_6Q9N–6Q9N (-8.6 kcal/mol) and NL\_9U6O–9U6O (-7.4 kcal/mol). Compared with reference compounds such as Auranofin, Niclosamide, and Afamelanotide, the native ligands generally showed equal or stronger binding strengths and more extensive interaction networks within the active sites of the proteins. These findings suggest that the native ligands

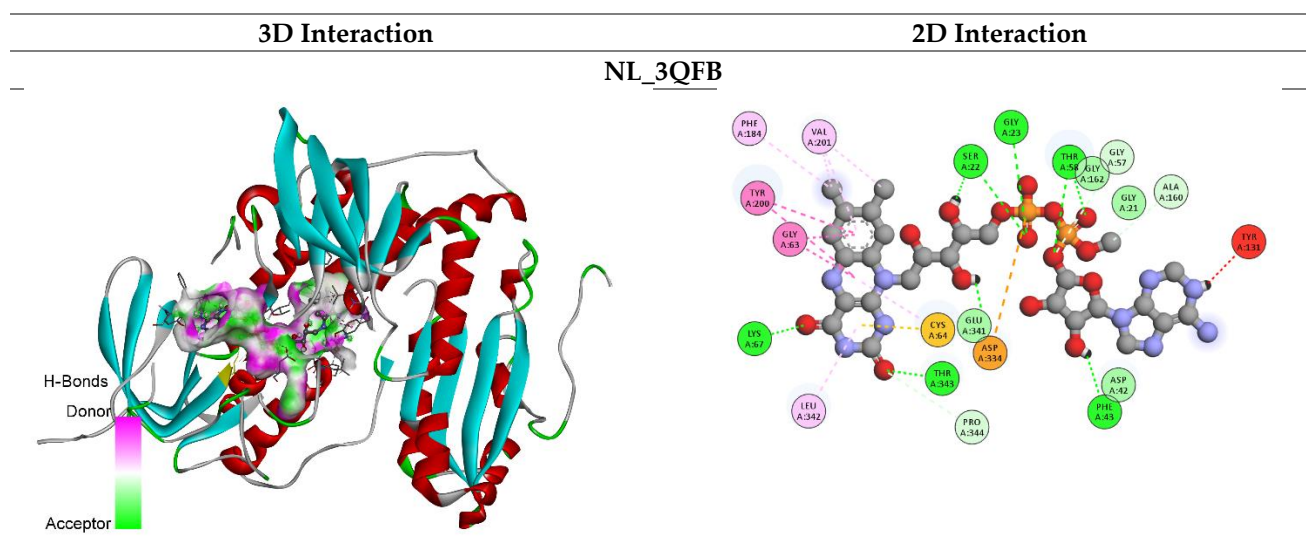
possess favorable interaction profiles and strong binding stability within the catalytic pockets of the selected target proteins, supporting their potential role in inhibiting the respective biological targets.

**Table 1.** Docking interaction of most potent compounds with Thioredoxin Reductase 1 (3QFB) Proton Motive Force Protein (9U6O) and PBP2a (6Q9N)

| Amino Acid | Bond Length | Bond Type     | Bond Category              | Ligand Energy | Docking Score |                      |
|------------|-------------|---------------|----------------------------|---------------|---------------|----------------------|
|            |             |               |                            | (Kcal/mol)    |               |                      |
| NL_3QFB    |             |               |                            |               |               |                      |
| ASP334     | 4.20249     | Hydrogen Bond | Conventional Hydrogen Bond | 1859.01       | -12.2         |                      |
| ASP334     | 2.09919     |               |                            |               |               |                      |
| SER22      | 2.69997     |               |                            |               |               |                      |
| PHE43      | 1.89598     |               |                            |               |               |                      |
| SER22      | 2.21559     |               |                            |               |               |                      |
| GLY23      | 2.64138     |               |                            |               |               |                      |
| THR58      | 2.07816     |               |                            |               |               |                      |
| LYS67      | 1.77901     |               |                            |               |               |                      |
| THR343     | 2.02036     |               |                            |               |               |                      |
| ALA160     | 2.84639     |               |                            |               |               |                      |
| GLY57      | 3.09714     | Other         | Carbon Hydrogen Bond       | 1859.01       | -12.2         |                      |
| PRO344     | 3.30273     |               |                            |               |               |                      |
| CYS64      | 3.44776     |               | Pi-Sulfur                  |               |               |                      |
| TYR200     | 5.27613     |               | Pi-Pi T-shaped             |               |               |                      |
| TYR200     | 5.41799     |               |                            |               |               |                      |
| GLY63      | 4.78539     |               |                            |               |               | Amide-Pi Stacked     |
| VAL201     | 3.69697     |               |                            |               |               | Alkyl                |
| VAL201     | 4.37092     |               |                            |               |               |                      |
| CYS64      | 4.32343     |               |                            |               |               |                      |
| VAL201     | 5.03305     |               |                            |               |               |                      |
| LEU342     | 5.24183     |               |                            |               |               |                      |
| PHE184     | 5.24025     |               |                            |               |               |                      |
| Auranofin  |             |               |                            |               |               |                      |
| GLY21      | 2.90157     | Hydrogen Bond | Conventional Hydrogen Bond | 752.82        | -7.8          |                      |
| THR45      | 2.20456     |               |                            |               |               |                      |
| THR58      | 2.12193     |               |                            |               |               |                      |
| TYR131     | 2.12164     |               |                            |               |               |                      |
| ARG164     | 2.66373     |               |                            |               |               |                      |
| GLY19      | 3.44982     |               |                            |               |               | Carbon Hydrogen Bond |
| TYR131     | 3.92952     | Hydrophobic   | Pi-Sigma                   |               |               |                      |
| NL_9U6O    |             |               |                            |               |               |                      |
| ASN498     | 2.66348     | Hydrogen Bond | Conventional Hydrogen Bond | 1509.87       | -7.4          |                      |
| ASN498     | 2.85155     |               | Conventional Hydrogen Bond |               |               |                      |
| GLY23:O    | 2.6283      |               |                            |               |               |                      |
| THR235     | 3.20531     |               |                            |               |               |                      |

|               |         |               |                            |         |      |
|---------------|---------|---------------|----------------------------|---------|------|
| PRO22:O       | 2.65793 |               |                            |         |      |
| GLY233        | 1.93485 |               |                            |         |      |
| LYS234        | 2.43033 |               |                            |         |      |
| LYS234        | 1.99942 |               |                            |         |      |
| THR235        | 2.3439  |               |                            |         |      |
| Niclosamide   |         |               |                            |         |      |
| GLY231        | 2.61234 | Hydrogen Bond | Conventional Hydrogen Bond |         |      |
| ARG258        | 1.8633  |               |                            |         |      |
| PHE419        | 3.6918  | Hydrophobic   | Pi-Pi Stacked              | 235.31  | -7.5 |
| VAL236        | 4.26535 |               | Alkyl                      |         |      |
| PHE419        | 4.99296 |               | Pi-Alkyl                   |         |      |
| NL_6Q9N       |         |               |                            |         |      |
| SER403        | 2.80131 |               |                            |         |      |
| TYR441        | 2.4287  | Hydrogen Bond | Conventional Hydrogen Bond |         |      |
| ASN464        | 1.87511 |               |                            | 1233.87 | -8.6 |
| THR600        | 2.19508 |               |                            |         |      |
| TYR446        | 3.92785 | Hydrophobic   | Pi-Sigma                   |         |      |
| TYR446        | 5.06669 | Hydrophobic   | Pi-Pi T-shaped             |         |      |
| Afamelanotide |         |               |                            |         |      |
| TYR519        | 3.02036 |               |                            |         |      |
| GLU602        | 2.54806 | Hydrogen Bond | Conventional Hydrogen Bond |         |      |
| GLN613        | 3.09455 |               |                            |         |      |
| GLN613        | 2.76893 |               |                            |         |      |
| THR444        | 3.71414 |               | Carbon Hydrogen Bond       | 1389.37 | -1.9 |
| LYS604        | 3.03728 | Electrostatic | Pi-Cation                  |         |      |
| MET641        | 5.59189 | Other         | Pi-Sulfur                  |         |      |
| MET641        | 4.99737 |               |                            |         |      |
| TYR446        | 5.5495  | Hydrophobic   | Pi-Pi Stacked              |         |      |
| LYS430        | 5.1879  |               | Pi-Alkyl                   |         |      |

**Table 2.** 2D and 3D docking interactions of the most potent compounds with Thioredoxin Reductase 1 (3QFB)



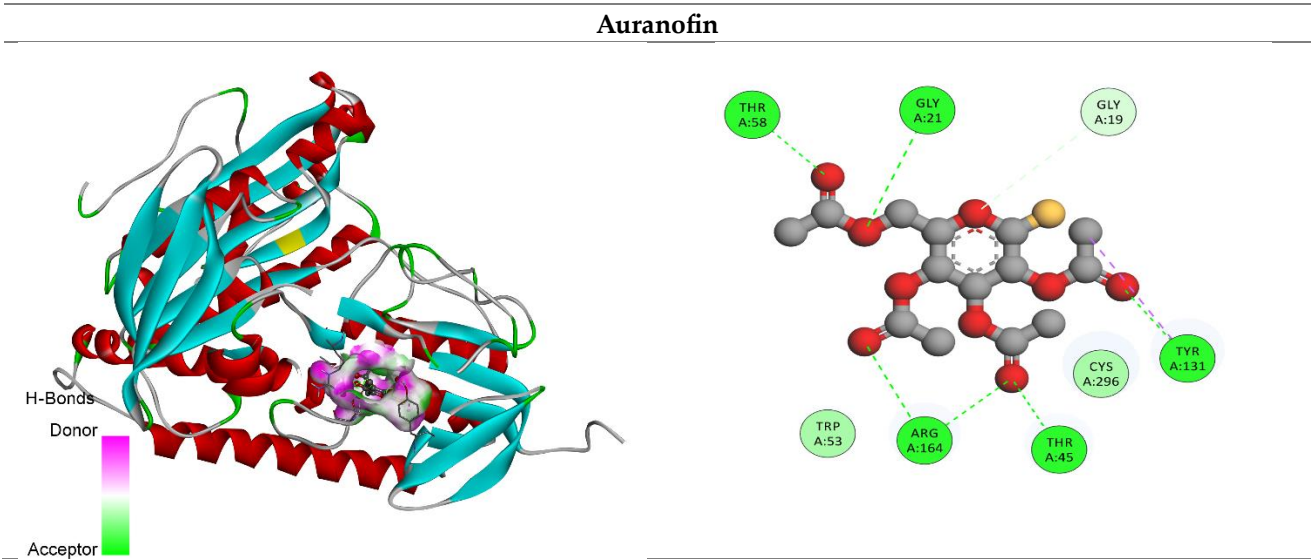


Table 3. 2D and 3D docking interaction of most potent compounds with Proton Motive Force Protein (9U6O)

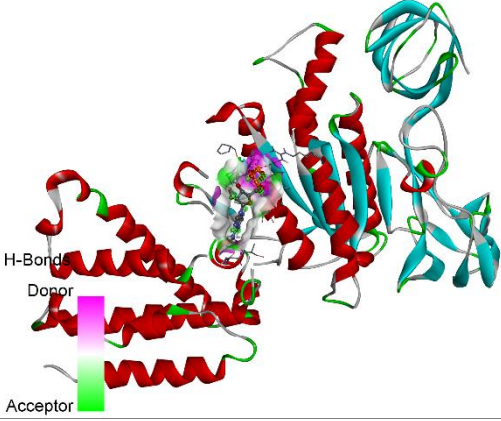
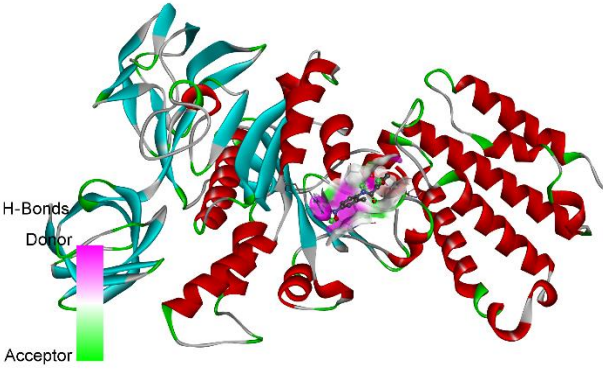
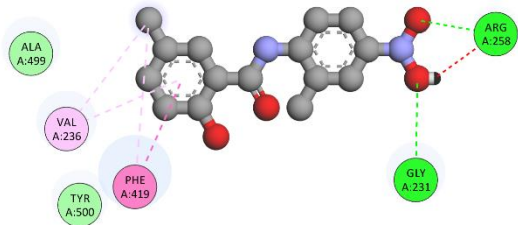
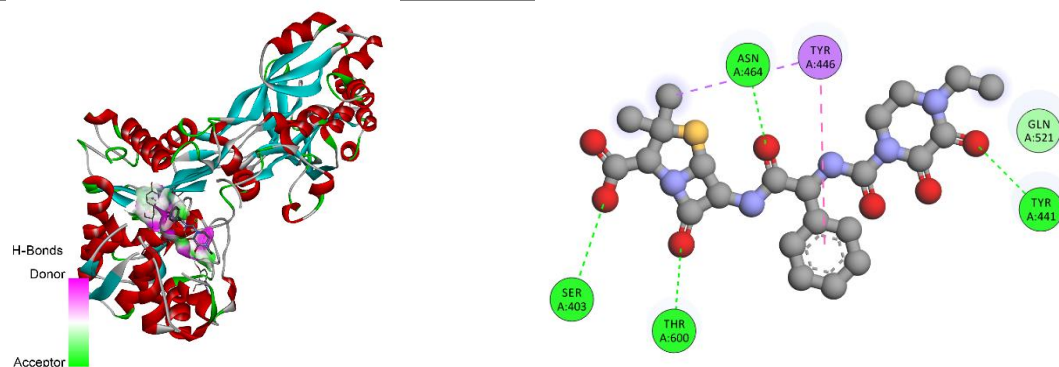
| 3D Interaction                                                                      | 2D Interaction                                                                       |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| NL_9U6O                                                                             |                                                                                      |
|   | The software did not create a 2D image of the compound.                              |
| Niclosamide                                                                         |                                                                                      |
|  |  |

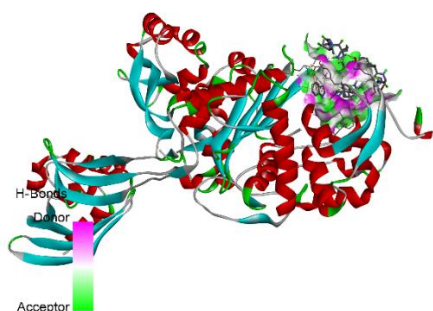
Table 4. 2D and 3D docking interactions of most potent compounds with PBP2a (6Q9N)

| 3D Interaction | 2D Interaction |
|----------------|----------------|
| NL_6Q9N        |                |



**Afamelanotide**

The software did not create a 2D image of the compound



### 3.2 ADMET Analysis

The pharmacokinetic behavior and safety profiles of the investigated molecules were evaluated through in silico ADMET prediction, including physicochemical characteristics, drug-likeness, absorption, distribution, metabolism, excretion, toxicity, and environmental toxicity parameters. The calculated results for all the compounds are summarized in Tables 4–10.

The physicochemical properties of these compounds showed considerable variation. NL\_3QFB has a molecular weight (MW) of 785.16 g/mol, volume of 665.68 Å<sup>3</sup>, density of 1.18, TPSA of 351.93 Å<sup>2</sup>, and logP of -1.89, indicating high polarity and hydrophilicity. In comparison, auranofin presented a lower MW (363.08 g/mol) with TPSA 114.43 Å<sup>2</sup> and logP 1.24, suggesting better membrane permeability. NL\_9U6O displayed a MW of 427.03 g/mol, TPSA of 232.60 Å<sup>2</sup>, logP of -2.67, and logS of -1.92, whereas NL\_6Q9N showed a MW of 517.16 g/mol, TPSA of 156.43 Å<sup>2</sup>, and logP of 0.89. Niclosamide demonstrated the highest lipophilicity (logP 4.62) with a TPSA of 92.47 Å<sup>2</sup>, while afamelanotide exhibited an extremely large molecular size (MW 1645.84 g/mol) and TPSA 646.14 Å<sup>2</sup>, reflecting its peptide nature.

Drug-likeness analysis indicated QED values of 0.048 (NL\_3QFB), 0.281 (NL\_9U6O), 0.345 (NL\_6Q9N), 0.363 (auranofin), 0.661 (niclosamide), and 0.003 (afamelanotide). NL\_3QFB, NL\_9U6O, NL\_6Q9N, and afamelanotide satisfied one Lipinski criterion violation, whereas Auranofin and Niclosamide showed no violations but differed in other medicinal chemistry filters. The NP-scores ranged from -1.824 (niclosamide) to 1.388 (NL\_9U6O), indicating differences in natural product-like characteristics.

Absorption analysis revealed moderate permeability across the intestinal cell models. The Caco-2 permeability values ranged from -5.88 to -4.89, whereas the MDCK permeability ranged from -5.25 to -4.55. NL\_9U6O (HIA 0.949) and NL\_6Q9N (0.9996) showed higher predicted human intestinal absorption than NL\_3QFB (1.19×10<sup>-7</sup>). The bioavailability probability values (F30% and F50%) were also higher for NL\_9U6O (0.993 and 0.875) and NL\_6Q9N (0.999 and 0.999) than for NL\_3QFB.

The distribution parameters showed plasma protein binding (PPB) values of 57.50% (NL\_3QFB), 24.44% (NL\_9U6O), 39.33% (NL\_6Q9N), and 99.31% (niclosamide). The BBB permeability values were generally low, such as 1.9×10<sup>-11</sup> for NL\_3QFB and 0.0065 for NL\_9U6O, indicating limited central nervous system

penetration. The fraction unbound (Fu) ranged from 39.65% to 66.79%, suggesting moderate systemic distribution. Metabolic prediction indicated low interaction probabilities with major CYP450 enzymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4.

Excretion parameters showed plasma clearance values of 1.29 (NL\_3QFB), 1.96 (NL\_9U6O), 3.66 (NL\_6Q9N), and 4.82 (niclosamide), with half-life values ranging from 0.75 to 3.80 h. Toxicity assessment indicated relatively low Ames mutagenicity probabilities for NL\_9U6O (0.119) and NL\_6Q9N (0.098) compared with auranofin (0.868) and Niclosamide (0.863). Hepatotoxicity probability values were high for several compounds, including 0.999995 for NL\_3QFB and 0.999495 for NL\_6Q9N, which is common in predictive toxicity models.

Environmental toxicity analysis showed relatively low bioaccumulation potential for NL\_3QFB (BCF 0.0798) and NL\_9U6O (0.0167), whereas niclosamide exhibited a higher BCF value (1.6837). The aquatic toxicity parameters showed IGC50 values of 2.59 (NL\_3QFB), 2.37 (NL\_9U6O), and 3.19 (NL\_6Q9N). The LC50 values for fathead minnows were 3.65, 3.41, and 4.08, while LC50 values for *Daphnia magna* were 4.42, 3.76, and 4.91, respectively, indicating moderate environmental toxicity.

Overall, the ADMET evaluation suggests that NL\_9U6O and NL\_6Q9N demonstrate comparatively balanced physicochemical properties, absorption characteristics, moderate distribution, acceptable metabolism, and relatively low environmental toxicity, supporting their potential as promising candidates for further drug development.

**Table 4.** Physicochemical properties of selected derivatives

| Compounds         | MW          | Volum<br>e   | Density  | nH<br>A | nH<br>D | nRo<br>t | nRin<br>g | TPSA   | logS     | logP     |
|-------------------|-------------|--------------|----------|---------|---------|----------|-----------|--------|----------|----------|
| NL_3QFB           | 785.16      | 665.687      | 1.179473 | 24      | 9       | 13       | 6         | 351.93 | -3.27943 | -1.89177 |
| Auranofin         | 363.08      | 327.900<br>8 | 1.107286 | 9       | 0       | 9        | 1         | 114.43 | -2.77303 | 1.243957 |
| NL_9U6O           | 427.03      | 327.841<br>7 | 1.302549 | 15      | 7       | 6        | 3         | 232.6  | -1.92439 | -2.67001 |
| Niclosamide       | 325.99      | 282.776<br>2 | 1.15282  | 6       | 2       | 4        | 2         | 92.47  | -5.60546 | 4.622843 |
| NL_6Q9N           | 517.16      | 483.434<br>6 | 1.069762 | 12      | 3       | 9        | 4         | 156.43 | -2.23099 | 0.892164 |
| Afamelanoti<br>de | 1645.8<br>4 | 1630.43      | 1.009452 | 40      | 27      | 63       | 6         | 646.14 | -3.15863 | 0.12762  |

**Table 5.** Drug-likeness properties of designed derivatives

| Compounds     | QED   | NP<br>Score | Lipinski<br>rule | Pfizer<br>Rule | GSK<br>Rule | GoldenTria<br>ngle | Chelator<br>Rule |
|---------------|-------|-------------|------------------|----------------|-------------|--------------------|------------------|
| NL_3QFB       | 0.048 | 0.595       | 1                | 0              | 1           | 1                  | 1                |
| Auranofin     | 0.363 | 1.166       | 0                | 0              | 0           | 0                  | 0                |
| NL_9U6O       | 0.281 | 1.388       | 1                | 0              | 1           | 0                  | 1                |
| Niclosamide   | 0.661 | -1.824      | 0                | 0              | 1           | 0                  | 0                |
| NL_6Q9N       | 0.345 | 0.027       | 1                | 0              | 1           | 1                  | 0                |
| Afamelanotide | 0.003 | 0.088       | 1                | 0              | 1           | 1                  | 0                |

**Table 6.** Absorption parameter of selected compounds

| Compounds     | Caco-2<br>Permeability | MDCK<br>Permeability | Pgp-<br>inhibitor | Pgp-<br>substrate | HIA      | F20%     | F30%     | F50%     |
|---------------|------------------------|----------------------|-------------------|-------------------|----------|----------|----------|----------|
| NL_3QFB       | -5.78458               | -5.21795             | 2.62E-06          | 8.90E-09          | 0        | 1.19E-07 | 0.137074 | 0.004727 |
| Auranofin     | -5.3586                | -4.55966             | 0.978542          | 0.066019          | 0.157779 | 0.019422 | 0.985487 | 0.930521 |
| NL_9U6O       | -5.87245               | -5.16241             | 2.47E-06          | 7.54E-06          | 0.949439 | 0.035331 | 0.993356 | 0.875718 |
| Niclosamide   | -4.89217               | -4.72248             | 0.075977          | 0.001866          | 3.39E-05 | 0.000319 | 0.007878 | 0.07871  |
| NL_6Q9N       | -5.81263               | -5.1801              | 0.106056          | 0.009793          | 0.999619 | 0.999018 | 0.999998 | 0.999985 |
| Afamelanotide | -5.88006               | -5.25287             | 0.059016          | 0.999876          | 0.999966 | 1        | 1        | 1        |

**Table 7.** Distribution and metabolism parameter of selected molecules

| Compounds     | Distribution |          |          |          | Metabolism |           |           |           |           |           |           |           |           |           |
|---------------|--------------|----------|----------|----------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|               | PPB %        | VD       | BBB      | Fu       | CYP1A2     |           | CYP2C19   |           | CYP2C9    |           | CYP2D6    |           | CYP3A4    |           |
|               |              |          |          |          | Inhibitor  | Substrate | Inhibitor | Substrate | Inhibitor | Substrate | Inhibitor | Substrate | Inhibitor | Substrate |
| NL_3QFB       | 57.50264     | -0.42091 | 1.90E-11 | 39.65368 | 8.88E-06   | 2.98E-09  | 2.59E-13  | 3.28E-13  | 1.34E-09  | 0.000643  | 1.55E-09  | 9.06E-08  | 5.03E-06  | 2.89E-05  |
| Aurano fin    | 36.05272     | -0.42606 | 0.002069 | 59.41997 | 0.001042   | 1.61E-05  | 0.0001864 | 0.002959  | 5.30E-06  | 4.43E-05  | 0.95479   | 4.70E-06  | 0.000427  | 0.024885  |
| NL_9U6O       | 24.43912     | -0.44183 | 0.006512 | 62.15499 | 7.60E-18   | 3.04E-23  | 4.71E-18  | 9.24E-18  | 3.08E-11  | 0.246325  | 5.29E-09  | 1.14E-11  | 2.10E-11  | 3.19E-11  |
| Niclosamide   | 99.31344     | -0.38638 | 0.025711 | 0.316651 | 0.980366   | 0.023034  | 0.006578  | 1.37E-05  | 0.088964  | 0.170347  | 0.000883  | 0.015852  | 0.021878  | 0.005849  |
| NL_6Q9N       | 39.32546     | -0.56353 | 0.358732 | 58.9255  | 3.64E-10   | 0.105726  | 1.72E-06  | 0.999999  | 6.83E-08  | 2.54E-05  | 1.85E-06  | 1.85E-06  | 1.11E-05  | 0.005399  |
| Afamelanotide | 29.72657     | -0.46565 | 5.87E-16 | 66.7927  | 7.95E-35   | 1.05E-30  | 1.15E-21  | 7.30E-14  | 3.29E-28  | 3.14E-09  | 2.04E-10  | 0.002379  | 0.000344  | 1.46E-15  |

**Table 8.** Excretion and Toxicity parameters of selected compounds

| Compound<br>s | Excretion |      |      |      | Toxicity      |                |         |                    |                 |               |                |             |
|---------------|-----------|------|------|------|---------------|----------------|---------|--------------------|-----------------|---------------|----------------|-------------|
|               | CL-plasma | T1/2 | H-HT | DILI | Ames Toxicity | Rat Oral Acute | FDA MDD | Skin Sensitization | Carcinogenicity | Eye Corrosion | Eye Irritation | Respiratory |

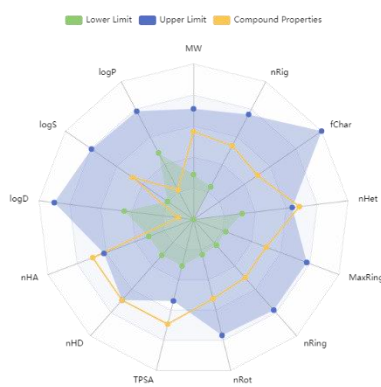
|                 | Toxi<br>city |              |              |              |              |              |              |              |              |              |              | Toxic<br>ity |
|-----------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| NL_3QFB         | 1.2922<br>58 | 3.80<br>2355 | 0.05<br>3156 | 0.99<br>9995 | 0.35<br>5883 | 0.13<br>2011 | 0.999<br>194 | 0.9685<br>47 | 0.28317<br>4 | 1.16E<br>-11 | 0.008<br>249 | 0.981<br>78  |
| Auranofin       | 4.7273<br>01 | 0.98<br>2555 | 0.99<br>999  | 0.99<br>9996 | 0.86<br>7905 | 0.89<br>4814 | 0.000<br>748 | 1            | 0.00896<br>9 | 0.005<br>141 | 0.978<br>982 | 0.013<br>934 |
| NL_9U6O         | 1.9641<br>15 | 2.11<br>9913 | 0.12<br>7048 | 0.98<br>0116 | 0.11<br>9637 | 0.03<br>6929 | 0.990<br>196 | 0.9934<br>79 | 0.70589<br>9 | 0.000<br>58  | 0.701<br>422 | 0.989<br>528 |
| Niclosami<br>de | 4.8178<br>37 | 0.75<br>6381 | 0.57<br>6958 | 0.99<br>8681 | 0.86<br>2506 | 0.38<br>6927 | 0.620<br>268 | 0.9949<br>56 | 0.14052<br>8 | 0.000<br>29  | 0.964<br>873 | 0.873<br>975 |
| NL_6Q9N         | 3.6562<br>55 | 1.05<br>644  | 0.84<br>5408 | 0.99<br>9495 | 0.09<br>8426 | 0.00<br>4609 | 0.000<br>348 | 0.9999<br>69 | 0.12776<br>3 | 5.27E<br>-08 | 0.143<br>134 | 0.000<br>236 |
| Afamelanotide   | 1.2907<br>76 | 1.68<br>2064 | 0.98<br>0255 | 0.06<br>1973 | 0.00<br>165  | 0.94<br>5933 | 1            | 0.9999<br>79 | 8.80E-<br>08 | 8.13E<br>-36 | 5.09E<br>-16 | 0.930<br>106 |

Table 9. Environmental toxicity profile of designed molecules

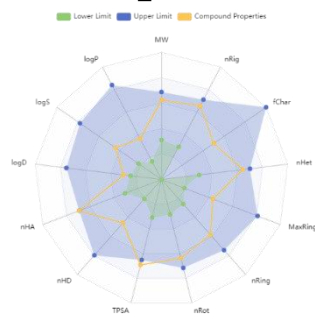
| Compounds     | BCF      | IGC50    | LC50FM   | LC50DM   |
|---------------|----------|----------|----------|----------|
| NL_3QFB       | 0.079785 | 2.592098 | 3.654612 | 4.421063 |
| Auranofin     | 0.644673 | 3.269557 | 4.402678 | 4.358058 |
| NL_9U6O       | 0.0167   | 2.367051 | 3.405481 | 3.761022 |
| Niclosamide   | 1.683747 | 4.984702 | 6.009206 | 6.224429 |
| NL_6Q9N       | 0.445678 | 3.194518 | 4.077341 | 4.910913 |
| Afamelanotide | 0.31539  | 3.439547 | 4.560843 | 5.448116 |

Table 10. ADMET Radar of Most Potent Compounds and All Native Ligands

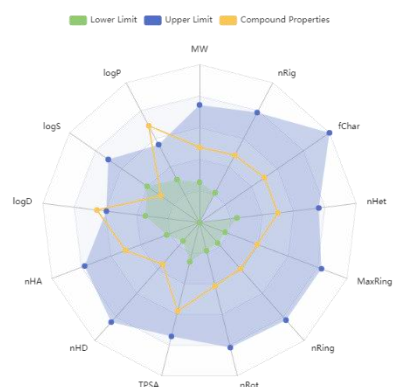




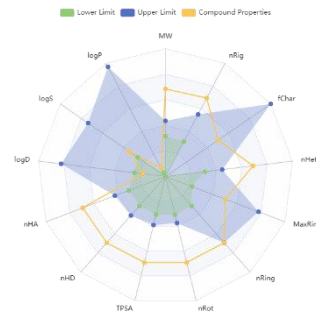
**NL\_9U6O**



**NL\_6Q9N**



**Niclosamide**



**Afamelanotide**

#### 4. Conclusion

MRSA continues to pose a significant therapeutic challenge owing to its evolving resistance mechanisms. In this study, a computational drug repurposing strategy was employed to identify potential inhibitors targeting key MRSA proteins, including thioredoxin reductase 1, proton motive force protein and PBP2a. The findings demonstrated that the selected US FDA-approved drugs exhibited favorable interaction profiles, indicating their potential to interfere with essential bacterial processes. Importantly, the integration of molecular docking with in silico ADMET evaluation provided a comprehensive assessment of both the interaction potential and pharmacokinetic suitability. Among the investigated compounds, certain candidates exhibited balanced properties, suggesting their potential for further development as anti-MRSA agents. This study highlights the effectiveness of computational approaches in accelerating the identification of alternative therapeutic options for resistant pathogens. Future studies should focus on experimental validation through in vitro and in vivo studies, along with structural optimization and mechanistic investigations to confirm efficacy and safety. These efforts may contribute to the development of more effective and accessible treatments for MRSA infections.

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None

#### Conflict of Interest

The authors declare no conflict of interest.

#### Authors' Contribution

Authors contribution includes "Conceptualization, and methodology, software, validation, and formal analysis investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration, Dibakar Roy. All authors have read and agreed to the published version of the manuscript.

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