COMBINED MOLECULAR DOCKING AND 3D-QSAR STUDIES TO DESIGN NEW *Tc*CYP51 INHIBITORS

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Introduction

Chagas disease, a parasitic illness caused by *Trypanosoma cruzi* (*T. cruzi*), remains a significant public health challenge, particularly in Latin America [1]. Although nifurtimox and benznidazole are available therapies, their effectiveness is often limited in the advanced stages of infection, and they can cause severe side effects [1,2]. The lack of effective therapies for chronic Chagas disease has led to the search for novel therapeutic approaches [2]. One promising strategy involves inhibiting the enzyme *Tc*CYP51, essential for the parasite's ergosterol biosynthesis [3]. In a previous study, virtual screening identified a potential *Tc*CYP51 inhibitor, but its predicted activity was only moderate (pEC_{50} = 5.43) [4]. To design novel *Tc*CYP51 inhibitors with enhanced activity potential, we conducted a structural optimization study to propose new molecules with improved activity predictions.

Material and Methods

We generated a virtual library of new chemical structures by modifying a previously identified hit molecule [4]. The proposed modifications incorporated structure fragments from known *Tc*CYP51 inhibitors and considered synthetic feasibility. Open Babel 2.2.2 program was used to construct the 3D structures [5]. The generated library was subjected to a virtual screening using molecular docking simulation and QSAR-3D analysis [5].

Molecular docking studies were performed in GOLD 2020.1 employing the ChemScore scoring function. Molecular interactions were analyzed with the Discovery Studio program [6,7]. Docking scores for molecules from the generated library were evaluated for accuracy using ROC curve analysis. The molecules classified as active against the *Tc*CYP51 enzyme underwent 3D QSAR modeling to predict the biological activity and assess prediction reliability through application domain calculation.

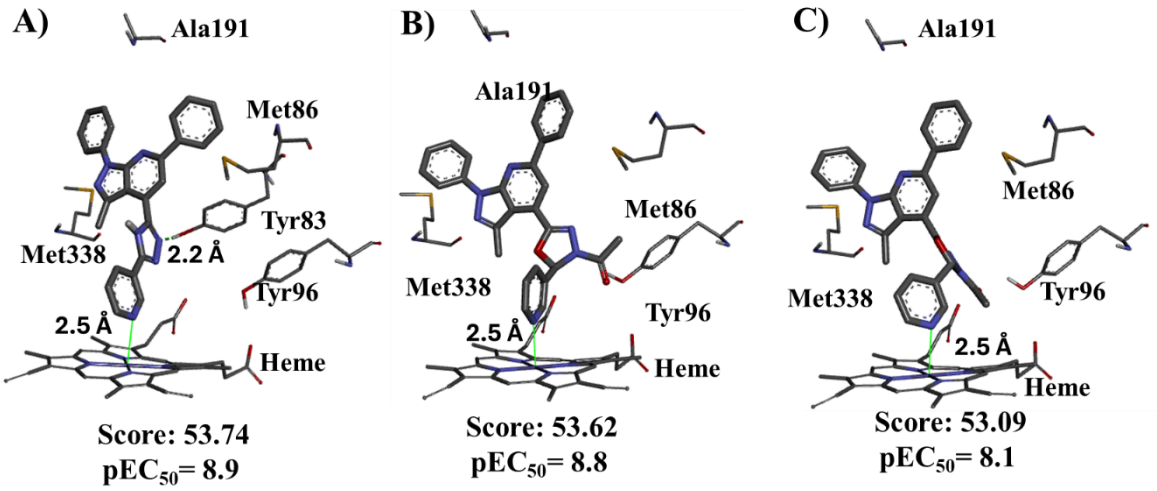
Results and Discussion

We created a virtual library of chemical structures comprising 13 proposed molecules structurally related to the hit molecule from our previous study [4]. The primary modification in these structures was the introduction of nitrogen heterocycles.

Molecular docking score analysis revealed that 9 of the 13 proposed structures had significant scores (> 52.3), suggesting their potential as *Tc*CYP51 inhibitors [6]. Analysis of these 9 structures indicated similar binding poses, and 3 of them exhibited improved predicted activity (pEC_{50} > 8.0) (**Fig. 1**) compared to the original hit molecule [4].

Analysis of the binding poses for these 3 top-performing molecules indicates Fe-N coordination bond at 2.5 Å, a known feature of *Tc*CYP51 inhibitors [8]. Structure 1, exhibiting the highest predicted activity, formed a hydrogen bond interaction with residue Tyr 83 (**Fig.1A**). In contrast, structures 2 and 3 lacked hydrogen bonding interactions despite their strong predicted activities **(Fig.1B** and **1C)**.

Fig. 1. Docking poses and intermolecular interactions of the proposed molecules 1 (A), 2 (B), and 3 (C) that show the best prediction for *Tc*CYP51 inhibitors.



Conclusion

Our structure-based drug design approach generated a virtual library of chemical structures with potential activity against *Tc*CYP51. Molecular docking simulations identified three proposed structures (1, 2, and 3) exhibiting high predicted *Tc*CYP51 inhibition ($pEC_{50} > 8.0$). These results demonstrated an improvement in the design of new *Tc*CYP51 inhibitors and provided a basis for optimizing and developing new anti-*T.cruzi* agents.

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