Analysis of the Binding Free Energy of TcDHODH Inhibitors using the MM/PBSA Method

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Introduction

Chagas disease is a parasitic disease caused by *Trypanosoma cruzi* transmitted to humans by insect vectors and is a public health problem in several endemic areas, mainly in Latin America. The disease is mostly asymptomatic, especially in the acute phase where the current treatment is effective; however, the life-lasting chronic phase does not have a successful antiparasitic treatment, and its progression can even lead to death.[1] It is essential to search for new drug candidates with fewer adverse effects and better therapeutic responses in the chronic phase of the disease. Among the therapeutic targets under investigation, the enzyme dihydroorotate dehydrogenase (*Tc*DHODH), responsible for the fourth step of pyrimidine biosynthesis, is essential for the parasite's survival and possesses greater selectivity.[2] Computer-aided drug design techniques have emerged as important tools in the search for new drugs. Among them, molecular dynamics can simulate atomic behavior through computational calculations based on molecular mechanics and can provide binding free energy values using the MM/PBSA tool. The aim of this work is to assist in the development of a more effective inhibitor by providing data that indicate which residues and interactions are more favorable and unfavorable for the binding free energy value.[3][4]

Material and Methods

We performed the molecular dynamics simulations in triplicate for 11 systems containing the *Tc*DHODH enzyme, its cofactor, and a co-crystallized ligand inserted into the active site, each with a duration of 100 ns. The MM/PBSA calculation was carried out from these trajectories, considering 500 continuous and representative frames after cluster analysis. We also extracted individual contribution values for each residue using the obtained binding free energy.

Results and Discussion

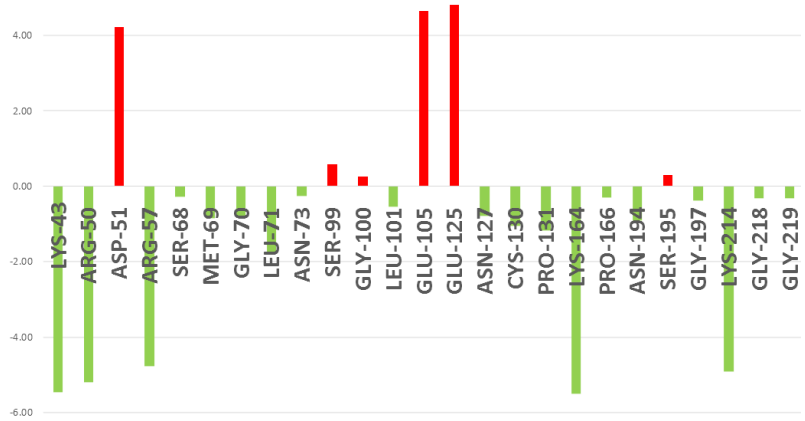
Our result showed that the investigated inhibitors exhibited negative binding free energy value (Table 1), including OXC (considering the standard deviation), which indicates a favorable interaction with the active site. The OXC ligand showed the highest binding free energy value, which can be attributed to its greater similarity to the natural substrate and the necessity to detach from the active site for the enzymatic action mechanism to occur. The results also suggest that electrostatic and solvation interactions had the most significant negative and positive contributions to the final binding free energy value. The results of the individual contribution values of each amino acid residue to the total binding free energy are in Figure 1. It was observed that residues with basic side chains favored the interaction with the inhibitor, while those with acidic side chains generated unfavorable interactions.

Table 1. Calculated energies for each *Tc*DHODH-Ligand complex.

LIGAND	ENERGY CHANGES – ΔE and ΔG * (Kcal/mol)				
	ΔE_{VDW}	ΔE_{ELECT}	ΔE_{SOLV}	ΔE_{SASA}	$\Delta G_{BINDING}$
OXC	-19.81 ± 2.65	-21.60 ± 2.47	44.75 ± 2.52	-2.06 ± 0.09	1.27 ± 2.56
FOT	19.50 ± 2.61	-125.14 ± 2.90	93.61 ± 2.46	-2.13 ± 0.10	-53.16 ± 3.07
5LL	-34.29 ± 2.73	-131.06 ± 3.29	115.90 ± 3.06	-3.57 ± 0.10	-53.01 ± 3.22
JDM	-30.88 ± 2.25	-111.63 ± 3.41	83.56 ± 3.26	-3.35 ± 0.14	-62.31 ± 2.96
QRO	-26.95 ± 1.85	-69.98 ± 2.89	50.52 ± 3.88	-3.39 ± 0.13	-49.80 ± 3.16
3RO	-33.00 ± 2.38	-97.98 ± 3.27	58.77 ± 2.97	-3.30 ± 0.15	-75.52 ± 3.30
XRO	-29.77 ± 2.19	-71.91 ± 2.82	53.04 ± 3.51	-3.64 ± 0.17	-52.29 ± 3.54
W86	-36.32 ± 2.67	-124.62 ± 3.81	105.25 ± 3.19	-4.28 ± 0.15	-59.98 ± 3.29
W87	-31.63 ± 2.03	-67.10 ± 3.10	50.42 ± 3.90	-3.98 ± 0.18	-52.29 ± 3.08
W75	-31.79 ± 2.32	-115.47 ± 4.15	94.80 ± 4.93	-3.68 ± 0.15	-56.14 ± 3.61
W7D	-27.45 ± 1.81	-66.91 ± 3.32	46.30 ± 3.10	-3.12 ± 0.11	-51.18 ± 2.14

*VDW: van der Waals; ELECT: electrostatic; SOLV: solvation; SASA: solvent-accessible surface area; BINDING: binding free energy.

Figure 1. Contribution of the amino acid residues to binding free energy.



Conclusion

The analysis of binding free energy demonstrated the presence of a favorable binding between the inhibitors and the enzyme and identified which residues are most significant for the energetic contribution of these interactions.

Acknowledgments

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