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Structural Insights into Benzothiazole Derivatives as Modulators of Dehaloperoxidase: A Docking Study

Souvik Sur*

Author's Affiliations:
Research and Development Center, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh-244001, India

***Corresponding Author: Souvik Sur,** Research and Development Center, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh-244001, India
E-mail: drsouvik.engineering@tmu.ac.in

ABSTRACT

The aims of this work are the investigation of the docking interactions between DHP from Amphitrite ornata and a set of BTZ compounds to elucidate the effect of alterations in the chemical structure of the ligand on binding affinity. The docking results show the ability of binding strength from compound BTZ (-3.6) to BTZ-AC (-6.2). The improved binding shown in BTZ-M, BTZ-P, and BTZ-AC is due to the presence of extra van der Waals contacts and hydrogen interactions with critical residues including K58, L62, and V59. Here, again, polar interaction demonstrated a higher interaction energy than hydrophobic interaction, and BTZ-AC emerged as the best interacting ligand due to the presence of phenyl and carboxyl groups. These outcomes revealed the plan comprising of functionalized BTZ derivatives as enzyme modulators. In future work, similar results must be obtained through experiments along with the need for the development of better compounds for use in biocatalysis, environmental applications, and pharmaceuticals. This work lays a basis for the development of other DHP-targeting strategies employing derivatives of BTZ.

Keywords: Benzothiazole, dehaloperoxidase, molecular docking, docking score

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INTRODUCTION

DHP, derived from a marine worm '*Amphitrite ornata*' is a hemoglobin with multifunctional catalytic domain [1, 2] that will be discussed in this paper. Different to the other hemoglobin that are mainly involved in oxygen transport, the DHP has multiple enzymatic functions and thus represents a universal biocatalyst at the place of its natural occurrence. Its functional differentiation is presence of activity like peroxidase, oxidase, peroxygenase and oxygenase that allows the enzyme to perform both electron transfer and oxygen atom transfer. These abilities place DHP in an important role as a protector of the worm against toxic metabolites hence underlining its importance in the worm's ecology [3].

Of all the enzymatic activities attributed to DHP, peroxidase has been investigated and recorded in many scientific publications. Importantly, this function focused on scavenging of hypervalent halogen species can be viewed as the role of the enzyme in maintaining *A. ornata* against environmental toxicants. However, the four remaining activities; oxidase, oxygenase, peroxygenase have been somewhat overlooked

even though they are areas of interest in both natural and synthetic applications. The additional mechanisms presented here enlarge the functional dictionary of DHP, a mess which contributes to the understanding of structural plasticity and catalytic promiscuity of this protein. Since the original discovery of its functions, more research has been conducted on other aspects of the enzyme; thus, the aim of this article is to concentrate on these lesser-known attributes of the enzyme particularly the peroxygenase activity to add to the existing body of knowledge

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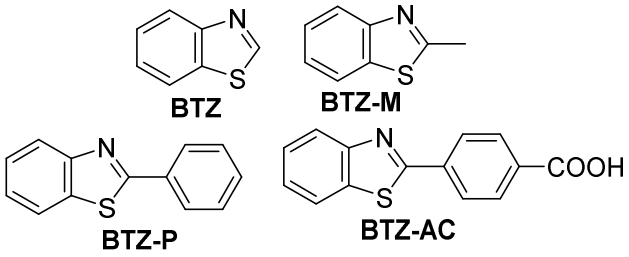


Figure 1: Chemical Structure

Among the molecules looked for in the modulation or enhancement of the enzymatic activities of DPH, the benzothiazole stands out as a promising drug. Benzothiazoles are heterocyclic compounds that possess a wide range of biological activity and represent one of the promising classes of enzyme probes [4-6]. Thanks to their structural means they can get into contact with remote biomolecular targets and modulate the activity of enzymes, for instance, through binding and electronic perturbation. From the perspective of DHP, benzothiazoles may be useful for further examination of the enzyme's mechanisms, including peroxygenase activity, where the combination of substrate binding and oxidation pathways is not fully understood yet. Due to the growing concern for green catalysts in industries and pharmacy, the knowledge regarding the action of small molecules like benzothiazoles on DHP will open new avenues.

The current article has the main objective to examine structural and mechanistic aspects of DHP's versatility from the viewpoint of interaction with benzothiazoles. Here we have taken three analogs of benzothiazole compounds along with parent one (**Figure 1**).

EXPERIMENTAL PROCEDURE

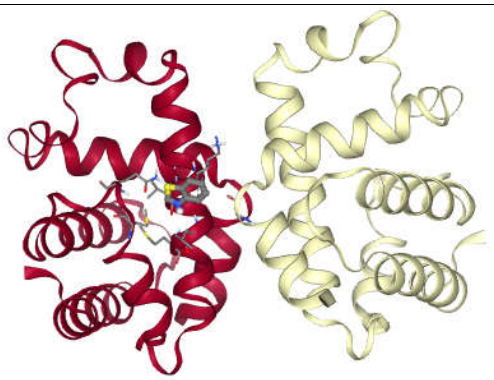
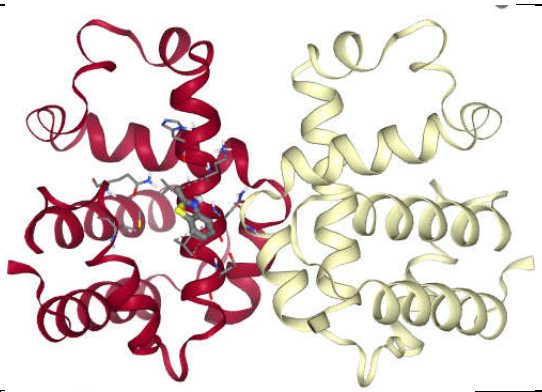
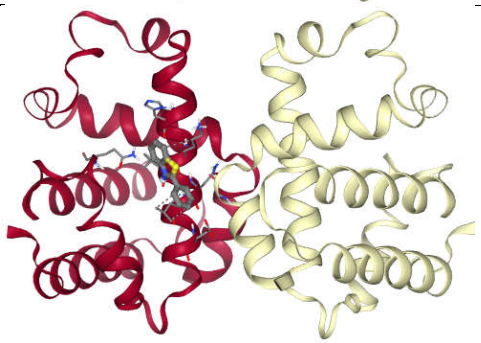
Our molecular docking experiment for the Benzothaizole analogs BTZ, BTZ-M, BTZ-P and BTZ-AC with Dehaloperoxidase-B was performed using AutoDock [7], a well-known non-commercial docking programme. The structure of PDB was obtained from protein data bank with PDB ID. 5K1L. To enhance the thermodynamic stability of ligand attached to the enzyme more we used stochastic Lamarckian genetic algorithm-based docking strategy along with minimization of scoring function. We docked the following medications using AutoDock Vina 4.2. Intermediary tasks, such as generation of grid boxes as well as pdbqt files for both enzyme and ligands, were performed, using the Graphical User Interface programme AutoDock Tools (ADT). The targeted enzyme sequences contained polar hydrogens and Kollman charges were added to the sequences by the authors during the manual process. The first set of the targeted Files for enzyme and drugs were stored in formats with PDBQT extension. AutoGrid was employed for generation of the grid to be used in the grid map using grid box was and the dimensions were set to 50 × 50 × 50 xyz points with a point spacing of 0.275 Å.

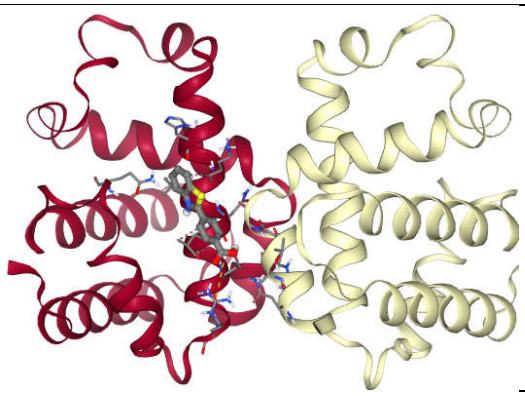
The docked structures that were acquired were examined using Biovia Discovery Studio [8]. The labelled amino acids, also known as the interacting residues, were in intimate contact with all four analogues. The presence of any potential interactions, such as H-bonding or other potential van der Waal interactions, in each docked complex was examined.

RESULTS AND DISCUSSION

The docking study assesses how the different BTZ-based compounds bind to DHP and whether the modifications alter the binding affinities and interaction patterns of the complex. The docking scores, which estimate the binding energy, varies between -3.6 for BTZ and -6.2 for BTZ-AC, a general increase observed with the incorporation of substituents. The parent compound, BTZ, shows the least interaction, which encompasses van der Waals (VdW) forces with residues K58(A) and L62(A) and the corresponding positions because of its less structural diversification. On the other hand, there rises slightly better docking score of -3.9 for the methyl substituted BTZ-M due to further hydrogen bonding interaction with the residue K58(A). This implies that increasing the steric hindrance of the substrate by the addition of a methyl group improves the hydrophobic and polar access to the enzyme.

Table 1: Docking Table

Compound	3D-Docked Structure	Docking Score and Interactive amino acids*
BTZ		Docking Score: -3.6 K58(A)-Vdw L62(A) -Vdw
BTZ-M		Docking Score: -3.9 K58(A) -Vdw L62(A) -Vdw K58(A) H-bonding
BTZ-P		Docking Score: -5.7 K58(A) -Vdw V59(A) -Vdw L62(A) -Vdw K58(A) H-bonding

BTZ-AC		Docking Score: -6.2 K58(A) -Vdw V59(A) -Vdw L62(A) -Vdw E65(A) -Vdw K58(A) H-bonding

*Docking scores are calculated in kcal mol^{-1}. K: Lysine, V: Valine, E: Glutamine. (A): Chain A, Vdw: through van der Waal interaction, H-bonding: Hydrogen bonding.

Higher results in binding are obtained from the phenyl-substituted BTZ-P and the phenyl-carboxyl-substituted BTZ-AC at a docking score of -5.7 and -6.2 respectively. Self-fit thanks to the phenyl group ability and spatial complementarity positioned in the binding site that forms VdW interactions with the crucial residue cluster, K58(A)/L62(A)/V59(A). The structure of the best compound, BTZ-AC, has both phenyl and carboxyl groups, and they are interacting effectively with each other to form strong interaction with the receptor through VdW interaction with L62(A), V59(A), E66(A) and K58(A) and hydrogen bonding interaction also with K58(A). It is also probable the presence of a carboxyl group in the centrally positioned molecule improves binding via further hydrogen bonding and polar forces. In conclusion these results depict that structural augmentation, and the incorporation of polar and hydrophobic functional groups raise the binding constant of benzothiazole with DHP considerably. In conclusion, this docking study reveals that functionalization of benzothiazole with specific substituents, such as methyl, phenyl, and carboxyl group, significantly enhances its binding affinity for DHP. These findings provide valuable insights for designing improved benzothiazole derivatives as potential modulators or inhibitors of DHP's enzymatic activities.

CONCLUSION

Exploring the docking analysis of benzothiazole (BTZ) derivatives with dehaloperoxidase (DHP) reveals that structural changes add value to binding interactions, and catalytic rectification. Among the tested compounds, BTZ-AC, with its phenyl and carboxyl substituents, demonstrated the strongest binding affinity, highlighting the critical role of both hydrophobic and polar interactions in stabilizing enzyme-ligand complexes. The gradual cumulative docking scores from BTZ to BTZ-AC indicate that the presence of functional groups like methyl, phenyl and carboxyl result in improved binding affinities through formation of more extensive van der Waals interactions and hydrogen bonds. These results underscore the possibility of benzothiazole derivatives as exciting lead structures for substrate-selective enzymatic intervention. Future studies could focus on experimental validation of these interactions and explore the impact of further substitutions to fine-tune specificity and activity. Additionally, the development of BTZ-based compounds could pave the way for novel applications in biocatalysis, environmental remediation, and pharmaceutical enzyme targeting.

Competing Interest

The Author declares no conflict of interest.

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REFERENCES

1. D'Antonio, J., D'Antonio, E. L., Thompson, M. K., Bowden, E. F., Franzen, S., Smirnova, T., & Ghiladi, R. A. (2010). Spectroscopic and

mechanistic investigations of dehaloperoxidase B from Amphitrite ornata. *Biochemistry*, *49*(31), 6600-6616.

2. Carey, L. M., Gavenko, R., Svistunenko, D. A., & Ghiladi, R. A. (2018). How nature tunes isoenzyme activity in the multifunctional catalytic globin dehaloperoxidase from Amphitrite ornata. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, *1866*(2), 230-241.
3. Rattray, R. M. (2007). Molecular characterization of bacterial populations implicated inthe anaerobic metabolism of toxic plant alkaloids from two different experimental and environmental sources.
4. Sur, S., & Khan, U. The Compatibility of Benzimidazole and Benzothiazole derivatives towards poly-A. poly-T DNA. *Indian Journal of Chemistry (IJC)*, 2024, 63(1), 65-71.
5. Khan, U., & Sur, S. Exploring DNA Binding of Benzothiazole-based Known Drugs: A Molecular Docking Investigation, 2023.
6. Khan, U., & Sur, S. (2024). Exploring the DNA Recognition of Compounds Based on Benzimidazole and Benzothiazole: A Concise Review. In *Macromolecular Symposia* 2024, 413(5), 2400111.
7. Huey, R., Morris, G. M., & Forli, S. (2012). Using AutoDock 4 and AutoDock vina with AutoDockTools: a tutorial. *The Scripps Research Institute Molecular Graphics Laboratory*, *10550* (92037), 1000.
8. Biovia, D. S. (2017). BIOVIA discovery studio visualizer. *Softw. version*, *20*, 779.

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