IRSTI 31.21.15; 31.21.25; 31.21.27; 31.23.27 https://doi.org/10.26577/IJBCh2024v17.i2.12

D.B. Wadave *, S.C. Daswadkar

Dr. D. Y. Patil College of Pharmacy, Maharashtra, India
*e-mail: dishawadave1999@gmail.com
(Received 26 June 2024; received in revised form 21 July 2024; accepted 27 July 2024)

Molecular docking study of 2,4-disubstituted thiazole derivatives as antiulcer activity

Abstract. In this study, 2,4-disubstituted thiazole derivatives were used to create an antiulcer agent. These compounds were chosen based on molecular properties and a drug-likeness score, ensuring their suitability for oral absorption. The molecular docking of 2,4-disubstituted thiazole derivatives was performed using AutoDock Vina ver. 1.1.2. The thiazole derivatives were constructed using Cambridge's ChemDraw Ultra 8.0 software. The program Chem 3D Ultra 8.0 was used to convert 2D structures to 3D structures. Thiazole derivatives were docked into the H2 blocker, with nizatidine binding at the active site (PDB ID: 2XZB) as the target protein obtained from the protein data bank. The current study reported anti-ulcer activity of newly synthesized derivatives with electron releasing and electron withdrawing groups on thiazole derivative. The study provided potential derivatives exhibiting significant anti-ulcer activity with fast onset and extended duration of action, which is the most promising expectation of any anti-ulcer agent, especially when administered in conjunction with complaint-specific therapy.
Key words: Antiulcer, 2,4-disubstituted thiazole derivative, 2XZB, AutoDock Vina, ChemDraw.

Introduction

One of the most common chronic gastrointestinal disorders is peptic ulcer.causes resulting from an imbalance in blood flow, mucus, bicarbonate, prostaglandin, acid, pepsin, and bile. Factors related to heredity, alcohol, drugs, smoking, and *Helicobacter pylori* are causes of imbalance. A peptic ulcer is a lesion that appears on the mucosa of the stomach or duodenum and is caused by exposure of the mucosal epithelium to acid and pepsin. The continuous lining of the epithelium breaks when there is an imbalance between aggressive and protective to mucosal damage in peptic ulcers [1]. Around 10% of people worldwide suffer from peptic ulcers. Peptic ulcer disease is thought to affect 5-10% of the general population. Duodenal peptic ulcers account for about 19 of every 20 cases. An estimated 15,000 deaths are attributed to peptic ulcers annually. According to the most recent WHO data, 68,108 deaths in India were related to peptic ulcer disease in 2020, accounting for 0.80% of all deaths. India is ranked 42nd in the world with an age-adjusted death rate of 6.24 per 100,000 people [2]. The 2,4-disubstituted thiazole derivatives became important class in the field of medicinal chemistry due to their various pharmacological and biological activities such as antitumor [3], antiinflammatory [4], anticonvulsant [5], anticancer, antioxidant [6], anti-microbial [7], antibacterial, antifungal [8], antidiabetic [9].

Materials and methods

Preparation of target protein X-ray structure. The target protein was chosen to be the crystal structure of the H2 blocker in which nizatidine bound at the active site (PDB ID: 2XZB), which was obtained from http://www.pdb.org.

Design of 2,4 disubstituted derivatives. The three steps in the development of an innovative drug are (a) pharmacophore determination, (b) pharmacophore substituent variation, and (c) pharmacophore list determination. 2,4-disubstituted thiazole is the anti-ulcer agent used in this study and is pharmacophore-like. -F, -CF_3, -NO_2, -CH_3, -Br, -$N(CH_3)_2$, -NH_2, -OCH_3, and other substituents are among the several designated for the design of novel analogs (Figure 1).

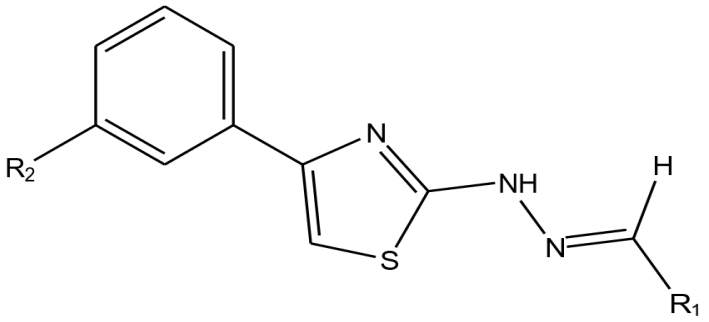

Figure 1 – Structure of 2,4-disubstituted thiazole derivative

Ligands preparation. Cambridge Soft's ChemDraw Ultra 8.0 program was used to haggard the structures of 2,4-disubstituted Thiazole derivatives like TZ6, TZ16, and TZ-17. By using the Chem 3D Ultra 8.0 tool, the 2D structures of the suggested ligand were transformed into a 3D structure. By applying a termination RMS gradient of 0.001 KCal/mol for extreme up to 1000 iterations, the semi-empirical PM3 technique was used to optimize the proposed ligand and minimize its energy. The resultant PBD arrangement was saved and could be read by the AutoDock Vina software. Following that, the Swiss ADME tool was used to determine the drug-likeness attribute.

Molecular docking studies. Molecular docking is the computational modeling of a ligand interacting with a receptor or target protein; it aids in predicting the ligand's binding to the target protein to determine its activity and affinity. A molecular docking method such as AutoDock Vina ver. 1.1.2 was used to evaluate the interaction between H2 blocker and thiazole derivatives. The target protein that we used was the X-ray crystal structure of the H2 blocker where nizatidine bound at the active site (PDB ID: 2XZB) [10], which was obtained from http://www.pdb.org. The ligands were redocked into their binding pocket within the H2 blocker x-ray crystal structure to obtain the docked pose and RMSD, which served as an authentication step for the docking procedure prior to ligand examination. The Discovery Studio software version 3.1.0.11157 was utilized to investigate the molecular interaction between the newly designed ligands and the target protein. Table 1 contains the tabulated interactions and docking scores. The ligands' active site of binding in an H2 blocker, in conjunction with the interacting amino acids.

Results and discussion

Molecular docking enables virtual screening, a computational method that finds new bioactive compounds in huge chemical libraries. By guiding drug-receptor interactions, these techniques help designers of new drugs by providing insight into the relationship between ligands and target proteins. Small molecules are identified with the help of computer-aided drug design, which places and scores them in the active site of the target protein. Using AutoDock Vina Version 1.1.2, molecular docking simulations were run for thiazole derivatives in this study, with the target protein being 2XZB. Based on the ligand binding position and fitness function scores, the program determined the optimal docking poses. The optimal ligand binding position was assessed using RMSD. The docking scores, which indicate the binding energy needed for the target protein to interact with ligands, demonstrated stability and were suggestive of compound activity (Figure 1).

Table 1 lists the thiazole derivatives' binding energy values. A total of twenty derivatives showed docking scores between -8.9 and -9.3 kcal/mol. When compared to the standard compound nizatidine, the thiazole derivatives displayed higher docking scores.

The proposed 2,4-disubstituted thiazole derivatives had an approximate docking score of -7.7–-9.3 kcal/mol. Ten derivatives of 2,4-disubstituted thiazole had higher docking scores than nizatidine (-8.2), which was used as the standard compound. The derivative TZ-16 had a higher binding energy (-9.3) than the other 2,4-disubstituted thiazole derivatives.

The interaction of probable derivatives with the target protein structure was determined and visualized using the Discovery Studio visualizer, as shown in Figures 2-3.

Table 1 – The thiazole derivatives' binding energy values

Ligand	Binding Affinity (kcal/mol)	Ligand	Binding Affinity (kcal/mol)
TZ-1	-9.8	TZ-11	-8.8
TZ-2	-8.5	TZ-12	-8.6
TZ-3	-9	TZ-13	-8.8
TZ-4	-9.2	TZ-14	-9.3
TZ-5	-8.6	TZ-15	-9
TZ-6	-8.8	TZ-16	-9.4
TZ-7	-9	TZ-17	-8.9
TZ-8	-8.4	TZ-18	-8.4
TZ-9	-9	TZ-19	-8.9
TZ-10	-8.5	TZ-20	-9.1
Std	-8.6	-	-

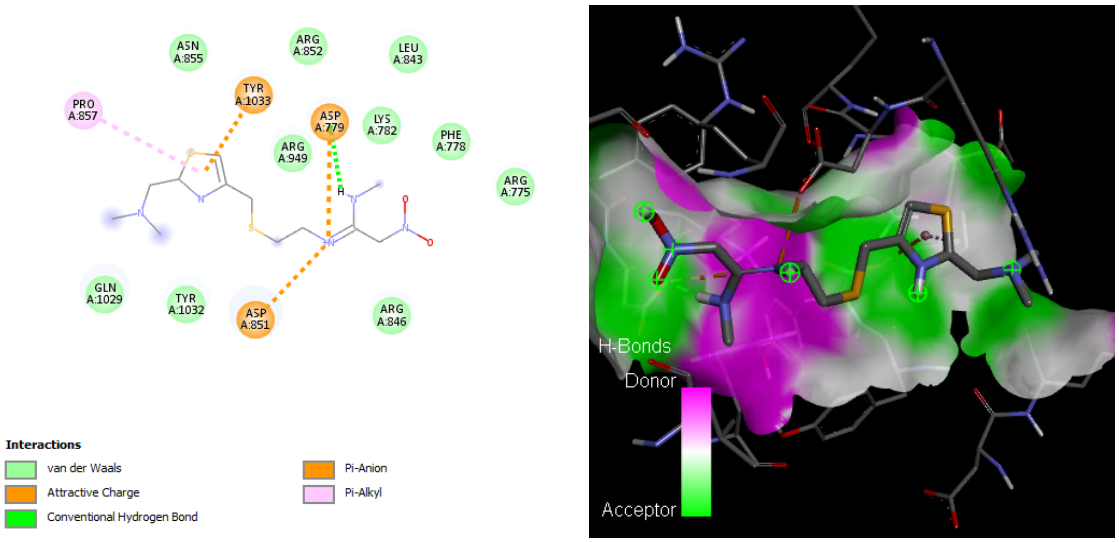

Figure 2 – 3D and 2D figures about the interaction of Nizatidine with 2XZB target protein

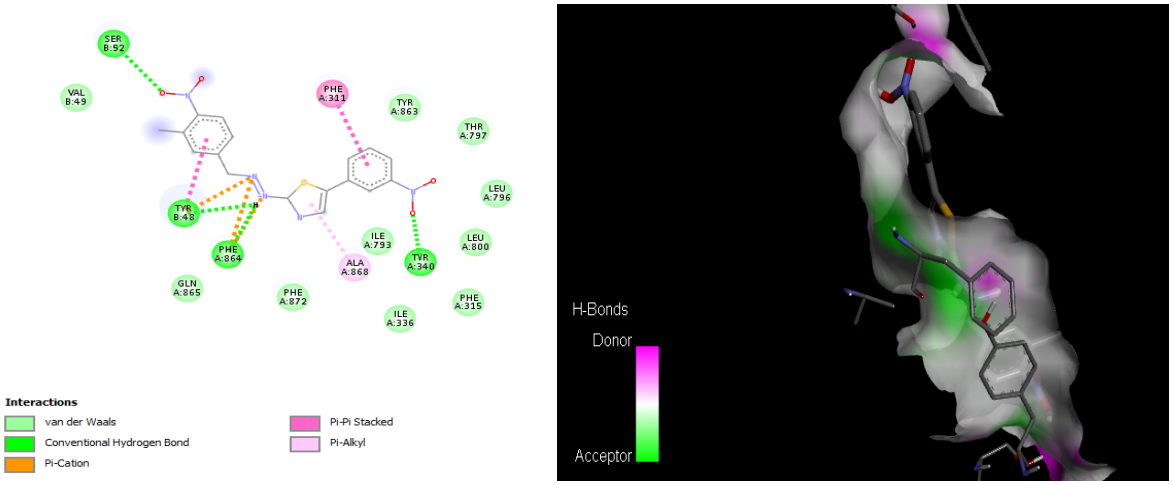

Figure 3 – 3D and 2D figures about the interaction of TZ-1with 2XZB target protein

Conclusion

This study analyzed 20 molecular structures of 2,4 disubstituted thiazole derivatives with aldehyde groups attached to their rings. These compounds were then docked to determine how they interact with the 2XZB protein structure. The docking scores were used to identify ligands that had a high affinity for 2XZB. The results showed that twenty derivatives had higher docking scores than nizatidine, indicating stronger binding energy and interaction with the target protein. As a result, these compounds have the potential to act as powerful antiulcer agents. However, additional studies involving synthesis and in vitro evaluations are required to determine their true antiulcer activity.

Conflict of interest

All authors are aware of the article's content and declare no conflict of interest.

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Information about authors:

Disha B. Wadave – (corresponding author) – master's student, Pharmaceutical Chemistry, Dr. D.Y. Patil College of Pharmacy, Akurdi Pune, India, e-mail: dishawadave1999@gmail.com

Shubhangi C. Daswadkar – PhD, Associate Professor, Dr. D. Y. Patil College of Pharmacy, Akurdi Pune, India, e-mail: shubhangidaswadkar@dyppharmaakurdi.ac.in