DOCKING STUDIES OF 1,2,4-TRIAZOLES

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Heterocycles are the largest class in organic chemistry. Most agrochemicals, pharmaceuticals, and additives used in industrial applications are heterocyclic in nature (Katritzky et al., 1996). Organic chemists have succeeded in discovering and developing a wide variety of heterocyclic compounds for the benefit of humanity by far. A notable structural feature of heterocycles that continues to be investigated is their ability to host substituents around a central structure. Since their first use in agriculture nearly a century ago, the chemistry of sulfur- and nitrogen-containing heterocycles has made significant advances (Katritzky et al., 2008; Maddila et al., 2013). 1,2,4-triazole is a crucial nucleus present in many compounds (Aktaş Yokuş et al., 2017; Beytur et al., 2019; Yüksek et al., 2022). The 1,2,4-triazole nucleus, which is stable against metabolism, acts as a hydrogen acceptor and donor at the active site of the receptor. Since the triazole core is polar, it can increase the solubility of the ligand and in this way significantly improve the pharmacological structure of the drug. A wide range of their derivatives are noted to have a wide spectrum of biological applications including anti-cancer activity (Kaur et al., 2016).

Molecular docking is computer-based tool that enables for prediction of whether and how small molecules bind to a macromolecular target (de Azevedo, 2019). The docking techniques, by selecting the appropriate binding position of a protein-ligand complex, complements and optimize variables such as hydrophobic, steric, and electrostatic and thus calculating their binding free energy (Adelusi et al., 2022). Due to the high time and financial needs associated with obtaining a commercial drug for the market, the computer-aided application of drug design has been accepted as a strong technology in drug discovery. In the drug discovery process, molecular modeling applications have undergone significant changes in computational abilities over the last decade. For lowering the cost and time needed for the discovery of an effective drug academic research organizations and pharmaceutical companies are using diverse

computational modeling approaches (Adelusi et al., 2022). In this chapter, we focus on reviewing molecular modeling, its applications, and its limitations in 1,2,4-Triazoles.

Characterization, molecular docking studies, and antibacterial potential assessment of the novel compounds containing the 1,2,4-triazole ring in their structure were reported by Mermer and co-authors in 2019. The synthesized derivative interaction ability with DNA gyrase was determined. To reveal the interaction mode of fluoroquinolone-1,2,4-triazole hybrids to receptors, a molecular docking application was performed. All tested compounds were seen to have excellent inhibitory potentials against DNA gyrase (E. coli) (Figure 1) (Mermer et al., 2019).

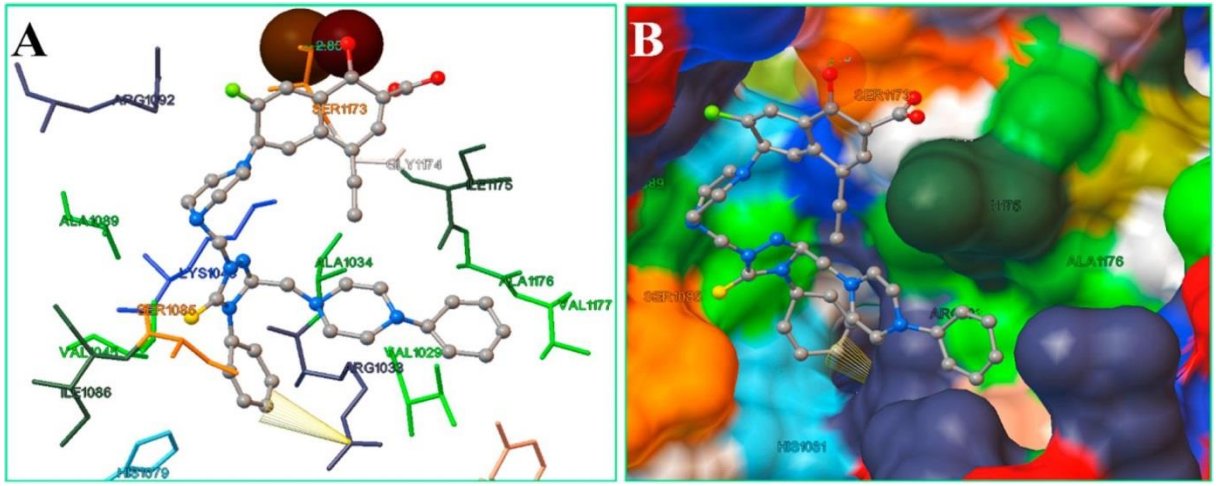

Figure 1. Interaction of most active compound to DNA Gyrase (PDB: 2XCT). and B. To DNA Gyrase (PDB: 2XCT) binding pocket (Mermer et al., 2019).

In a study, 1,2,4-Triazole-containing fifteen compounds were tested for their potential antimicrobial activities. For this, a molecular docking study was successfully applied against the topoisomerase II enzyme (PDB: 5bs8). All synthesized compounds binding energy scores were calculated between (−6.31 to −16.11 Kcal/mol) and compared with the reference moxifloxacin. Relatively lower binding interactions were observed compared to the reference moxifloxacin (Mohammed et al., 2019).

Stingacia and co-authors reported that as antimicrobial agents new vinyl-1,2,4-triazole derivatives eight compounds molecular docking studies have been performed at the active sites of E. coli DNA GyrB (PDB code: 1KZN), Thymidylate kinase (PDB code: 4HOF) and E. coli MurB (PDB code: 2Q85). The binding scores revealed that E. coli DNA GyrB 24-kDa domain in complex with clorobiocin is the most proper enzyme. For E. coli MurB 2Q85, the binding

score was changed in the range of (−5.29, −8.56 kcal/mol).The best binding score was (−8.56 kcal/mol) with compound 8 (Figure 2) (Stingaci et al., 2020).

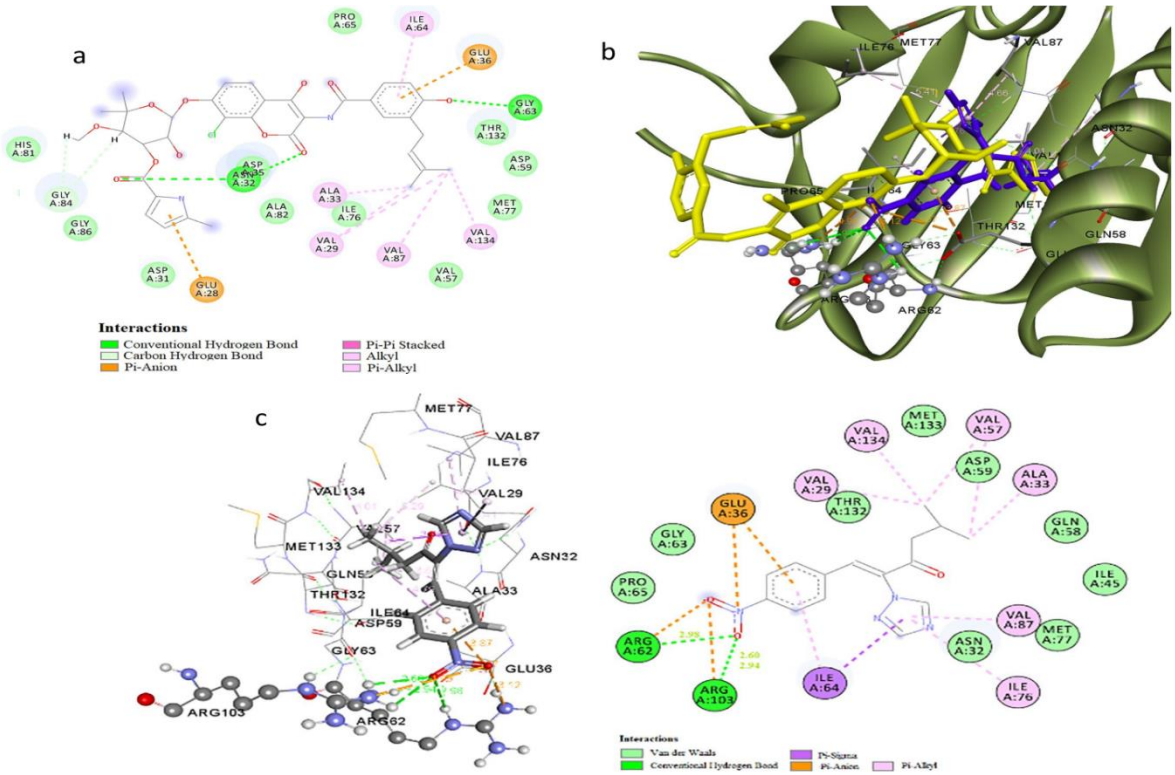

Figure 2. Docked conformation a) Clorobiocin in *E. coli* DNA GyrB, b) Compound 8 (blue) and clorobiocin (yellow) in *E. coli* DNA GyrB c) Compound 8 in *E. coli* DNA GyrB (Stingaci et al., 2020).

In 2022, Medetalibeyoğlu and co-authors applied molecular docking interactions of a series of novel 4,5-Dihydro-1H-1,2,4-triazole-5-one derivatives with AChE (PDB ID:4EY7) as target enzyme using Chimera and AutoDock Vina softwares. -12.0 kcal/mol was calculated as the highest binding energy levels of the 4g compounds with AChE target enzyme were confirmed as the best binding affinities and molecular interactions (Medetalibeyoğlu et al., 2022).

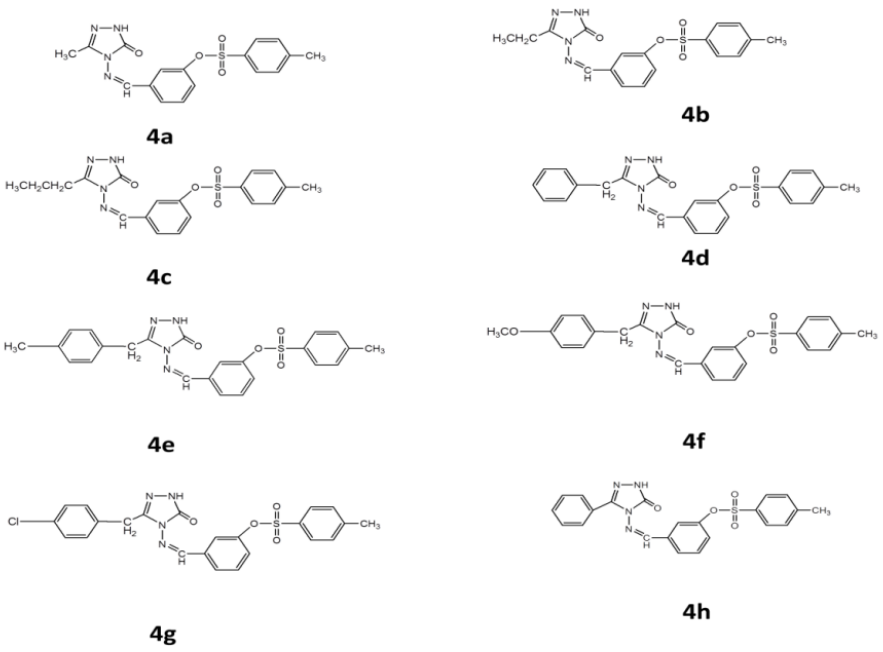

Figure 3. 4a-h compounds structures

Compounds 4a-4h binding energy scores with AChE were calculated as -10.2 kcal/mol, -10.6 kcal/mol, -10.7 kcal/mol, -12.0 kcal/mol, -11.3 kcal/mol, -8.7 kcal/mol, -12.0 kcal/mol, -11.2 kcal/mol respectively. Two compounds (4d and 4g) were firmly bound with the optimal conformation of the AChE enzyme, and their binding energy levels exceeded 12.0 kcal/mol.

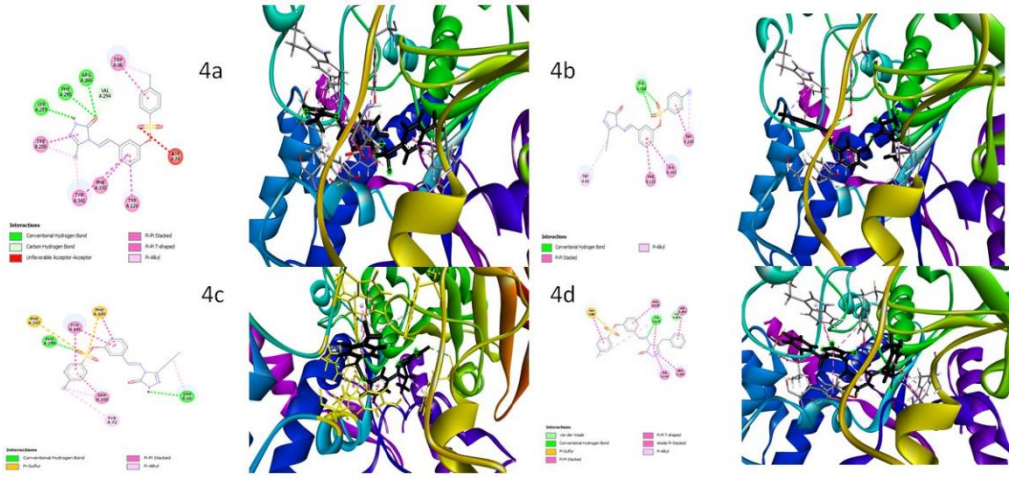

Figure 4: The interaction mode between **4a**, **4b**, **4c**, and **4d** and AChE enzyme, 3D ribbon models, and 2D view of ligand-binding residues (Medetalibeyoğlu et al., 2022)

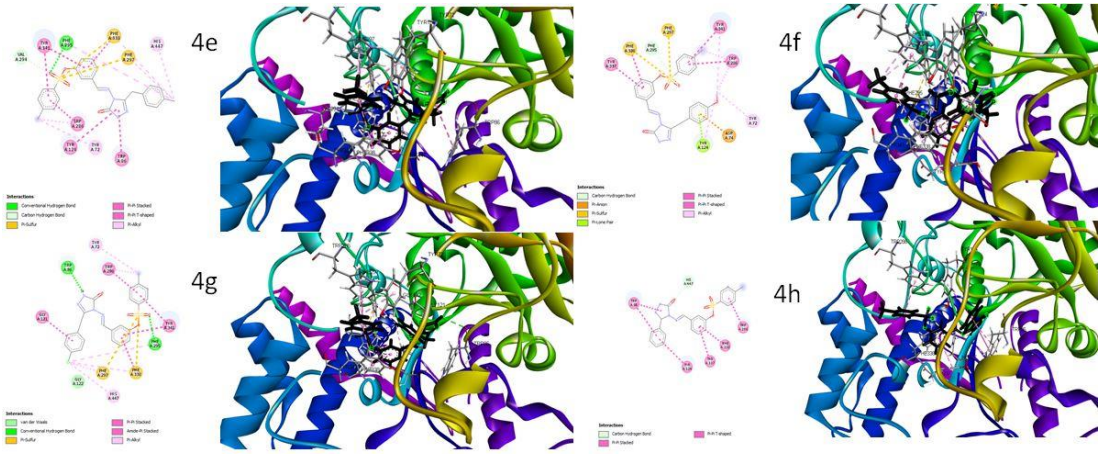

Figure 5: The interaction mode between **4e**, **4f**, **4g**, and **4h** and AChE enzyme, 3D ribbon models, and 2D view of ligand-binding residues (Medetalibeyoğlu et al., 2022)

Carbon Hydrogen, Pi-anion, conventional hydrogen bonds, Pi-Alkyl, Pi-Pi, van der Waals, Pi-sulfur, and other bonds of the compounds with enzyme-used residues were shown in the 2D views and 3D ribbon models in the Figures 4-7 (Medetalibeyoğlu et al., 2022). All novel synthesized compounds (4a-h) showed good enzyme inhibition results on AChE receptors.

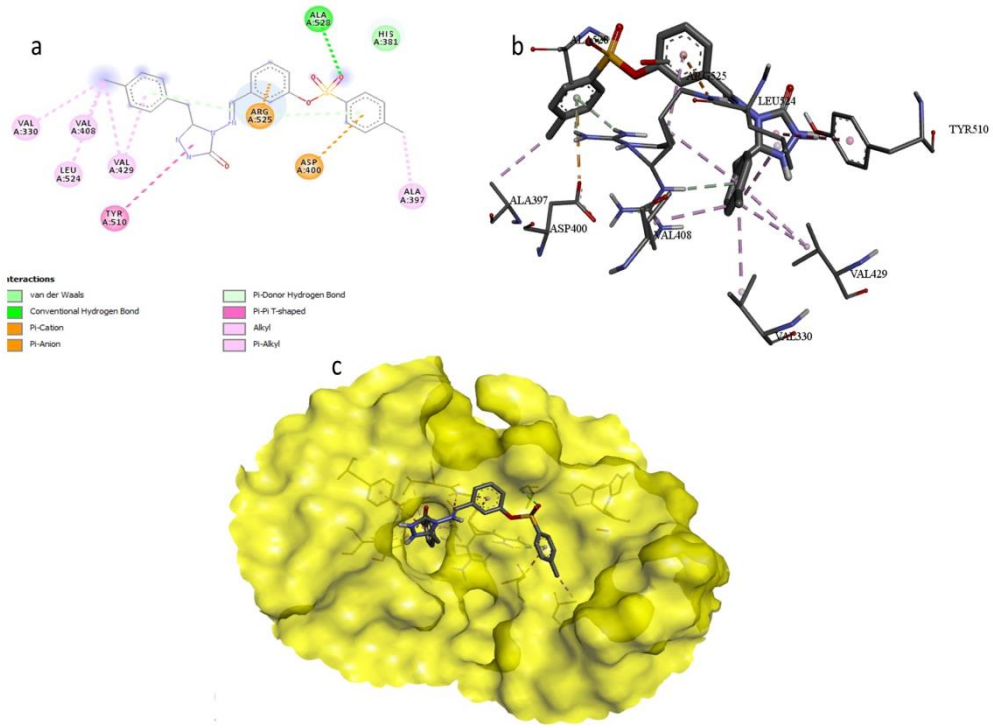

Figure 6: The interaction mode between one of most active compound **4e** and AChE enzyme

The result data have shown that inhibitor 4e formed conventional hydrogen bond, Pi-donor hydrogen bond, Pi-donor hydrogen bond, Pi-cation, Pi-anion, Pi-Pi T-shaped, alkyl, and pi-alkyl with Ala528, Arg525, Asp400, Tyr510, Ala397, Val330, Leu524, and Val429. The inhibitor 4g formed conventional hydrogen bond, Pi-cation, Pi-Sulfur, Pi-Pi Stacked, and pi-alkyl with Tyr124, Trp286, Tyr341, and His447.

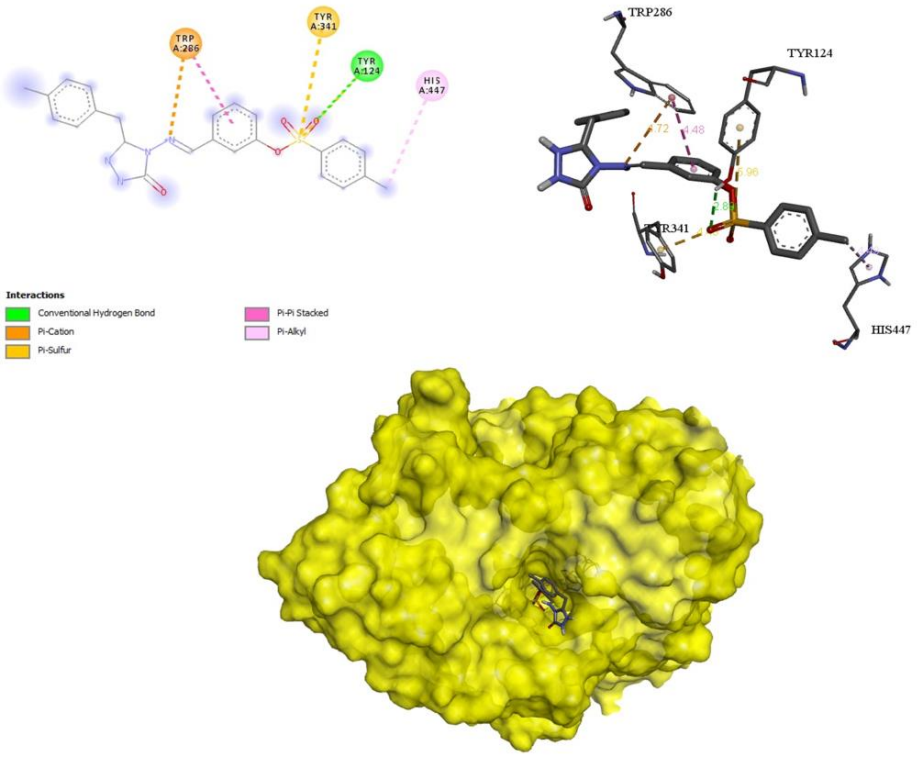

Figure 7: The interaction mode between one of most active compound **4g** and AChE enzyme

Previously, a study reported molecular docking interaction of a series novel morpholine-derived Mannich bases containing 1,2,4-triazoles with acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and glutathione S-transferase (GST) enzymes. For the performing of the molecular docking studies, catalytic active sites of three GST, AChE, and BChE enzymes were determined and chosen sites were utilized for the docking process and assessment of the best pose of the inhibitors. By using the induced-fit docking (IFD) method, inhibitors were docked into the catalytic active site of the three enzymes.

The indication diagrams have shown that inhibitor 4e formed two hydrogen bonds with His287 and Tyr124. The triazole oxygen has accepted hydrogen, while hdroxybenzyldene oxygen has donated hydrogen to the AChE enzyme residues. Metoxybenzyl and the hydroxybenzyldene aromatic ring interacted with Trp286 and Tyr72 through π-π interaction. compound 1 inhibitor

formed an aromatic hydrogen bond with four aromatic rings with Tyr124, Tyr72, Ser293, Val282, Tyr341, and Phe338. AChE enzyme active site consists of acyl and choline-binding sites. Interactions of 4e are with residues of the active sites of AChE. The enzyme was inhibited by the inhibitor by interacting with Trp286 and Tyr72 via parallel π-π interactions. Enzyme activity has been affected through the steric blockade interactions with the residues. Hydrogen bonds with His287 and Tyr124 affected enzyme inhibition (Figure 8) (Boy et al., 2021).

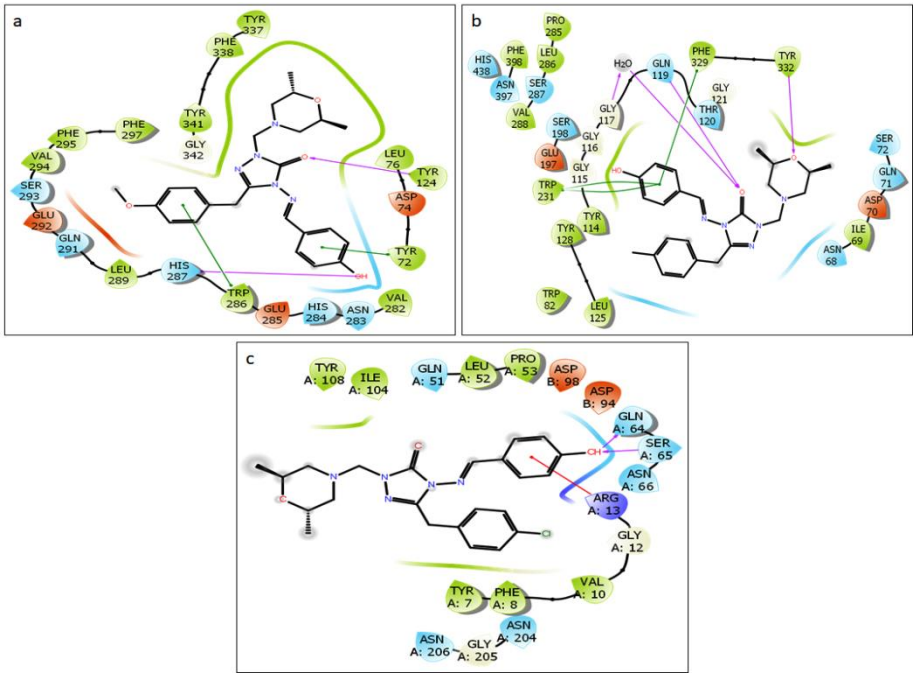

Figure 8. 2D interaction mode of most active inhibitors. a) Compound 1-AChE, b) Compound 2-BChE, andc) Compound 3-GST. Hydrogen bonds were represented as a purple arrow, π-π interactions were represented as a green line, and π-cation was represented as a red line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article) (Boy et al., 2021).

As seen in Figure 8 c, hydroxybenzyldene through π-cation, the aromatic ring made an interaction with Arg13 and it is oxygen moiety interacted by a hydrogen bond with Ser65 and Gln64 residues of GST enzyme. Through a water bridge, a hydrogen bond was formed between chlorobenzyl moiety and Tyr108 (Figure 8c). Compound 6 as a inhibitor binding modes with GST have shown that hydroxybenzyldene moiety has participated in interactions. This result has revealed that the compound structure is a little bit big for the GST active site. Diverse G-site inhibitors showed parallel interaction with compound 4 inhibitor. Docking Scores of compounds 4-6 inhibitors with AChE, BChE, and GST enzymes were detected as -10.294 kcal/mol, -9.562 kcal/mol, and -7.112 kcal/mol, respectively (Figure 9) (Boy et al., 2021).

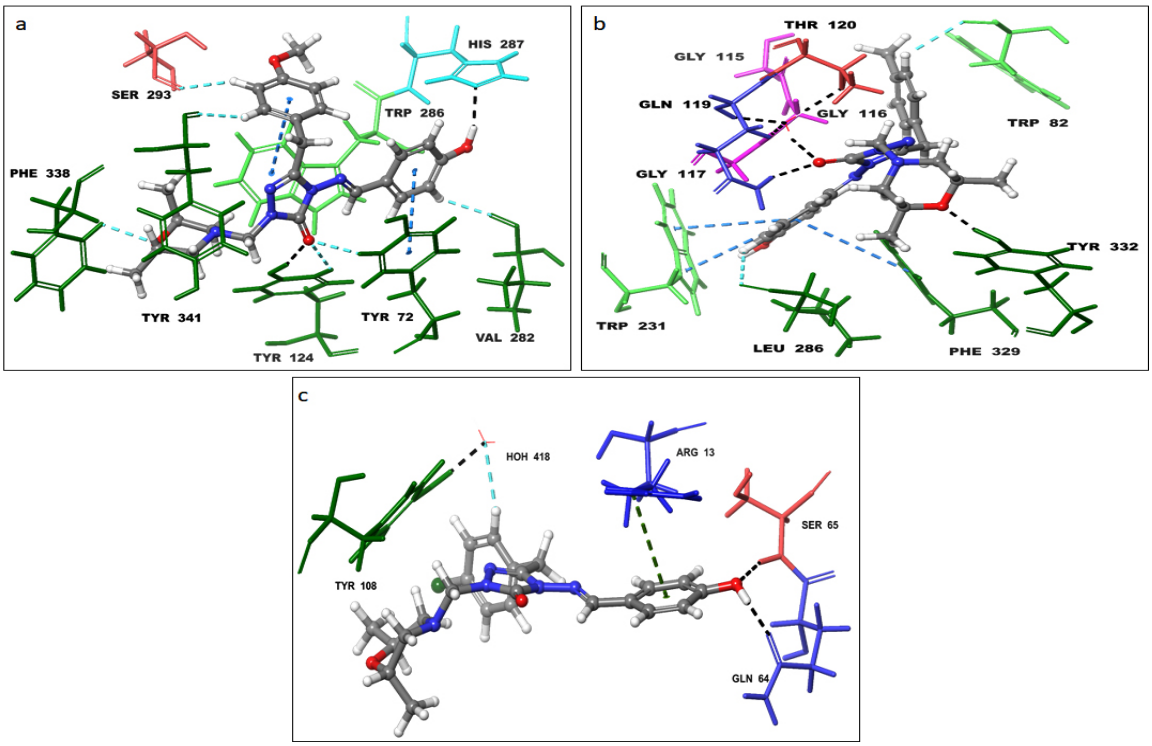

Figure 9. Detailed binding mode of most active compounds. a) Compound 5-AChE, b) Compound 4-BChE, and c) Compound 6-GST. Hydrogen bonds were represented as a black dashed line, π-π interactions were represented as a blue dashed line, π-cation was represented as a green dashed line, and aromatic hydrogen bonds were represented as a turquoise dashed line (Boy et al., 2021).

In 2019, Akın and co-workers reported Molecular docking studies of novel 2,4,5-trisubstituted-1,2,4-triazole-3-one derivative against the mushroom tyrosinase enzyme crystal structure. For analyzing the binding affinity AutoDock Vina was applied. Docking studies results indicate that the using compound as a inhibitor with the highest affinity score (−6.2 kcal/mol) strongly binds to the enzyme. The interaction of different groups in the structure of the inhibitor used with the amino acid side chains in the appropriate position in the enzyme three-dimensional structure is also important in the formation of the enzyme-inhibitor complex (Figure 10). Some of the interactions of the inhibitor compound with the enzyme active site were as follows; conventional interactions of triazole ring with His244, p-alkyl interaction of bromo phenyl ring with Val283, and p-alkyl with Val283 (Akın et al., 2019).

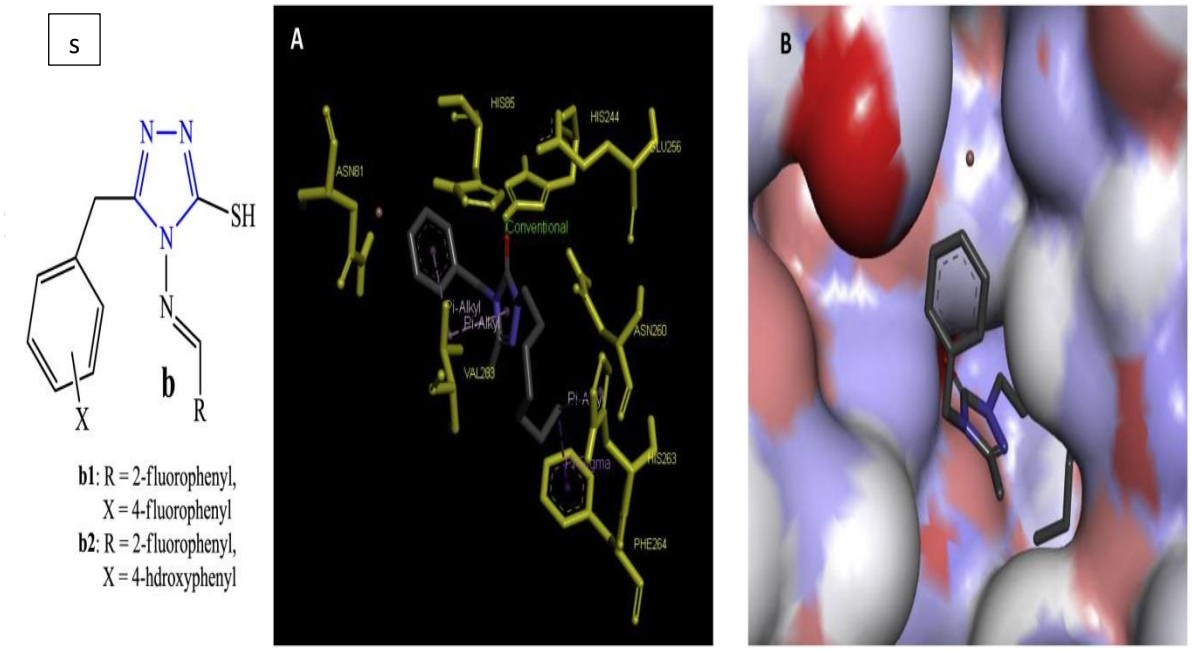

Figure 10. S) Molecular structure of 1,2,4-triazole based tyrosinase inhibitor. A) Interactions of the compounds atoms with the amino acid residues B) general projection (Akın et al., 2019).

Mohassab et al. applied a docking studies of a series of novel quinolines including 1,2,4-triazole/oxime hybrids towards the cyclooxygenases (COX-1 and COX-2) enzymes to explain compounds' possible anti-inflammatory effects. Docking applications were performed using MOE 2014 software. Inhibitors demonstrated effective anti-inflammatory properties with a low incidence of gastric ulceration, similar to that of celecoxib and indomethacin. Most of the 22 tested inhibitors revealed remarkable inhibition of COX-1 and maintained normal stomach tissue integrity. Also, docking analysis results were in agreement with promising anti-inflammatory activity when compared to indomethacin (Mohassab et al., 2017).

In 2018, Sherief and co-authors synthesized two new compounds containing 1,2,4-triazole and applied a molecular modeling study to obtain structural insights into the potential binding and possible interactions of the active compounds inside the tubulin active sites by operating Molecular Operating Environment (MOE) software. Tubulin (PDB ID: 1sa0) 3D crystal structures in complex with colchicine, were employed for docking simulation study. The overlay of the top docking poses tubulin proteins binding pockets were given in Figure 11. Docking results showed that the two compounds against tubulin set properly inside the ATP-active site engaging in two hydrogen bonds with Ser 178 and Thr 179 residues. The triazole core was extended towards the hinge region forming hydrophobic interaction with Ala 12, Lys

254, Leu 248, and Tyr 224 amino acids. Due to the high similarity of the two structures, they were in the same orientation inside the Tubulin active pocket (El-Sherief et al., 2018).

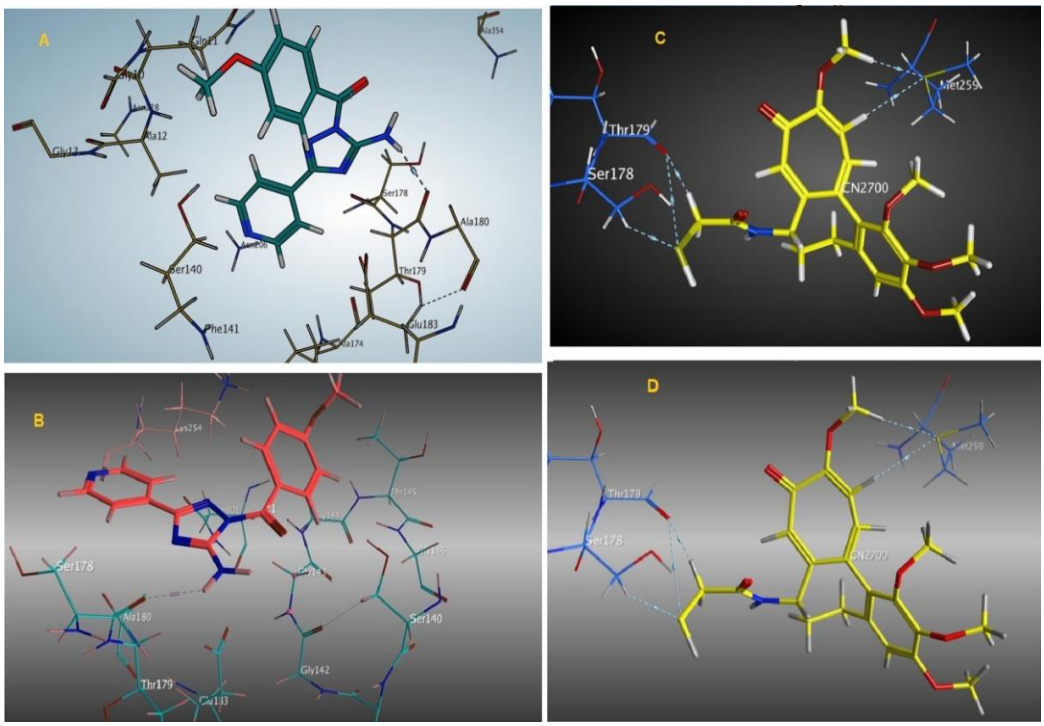

Figure 11. (A, B, C, and D) 3D overlay of the top docked poses (El-Sherief et al., 2018).

Tariq et al. tested some novel 1,2,4-Triazole-based benzothiazole/benzoxazole derivatives on p38 mitogen-activated protein kinases (MAPK) by using molecular docking studies (Tariq et al., 2018). p38 MAPK activation plays an important role in the inflammatory response. Some MAP kinase isoforms are the key regulator of the pro-inflammatory cytokines biosynthesis including TNF-α and IL-1β (Kumar et al., 2003). Also, inhibition of p38α MAP kinase blocks the production of COX-2 thereby avoiding tissue inflammation (Dean et al., 1999).

The docking scores of the newly synthesized fourteen compounds against p38α MAP kinase are calculated. All the compound's docking scores were in the range of −4.870, and −7.944. The molecules can be housed more effectively in the p38α MAP kinase active binding site because eNHCOeCH2Se (linker) flexibility. Compound 2 interacts by a hydrogen bond with hinge region MET 109 which provides the strong inhibitory activity. In the binding of compound 2 to p38α MAPK, the hydrogen bond with MET 109 seems to play an anchor role as 107–110 Amino acid residues are located at the ATP-binding site entrance. Complex 2 binding with p38α MAP Kinase, revealed that the carboxyl group and amino group which is placed between

benzothiazole and triazole ring led to two hydrogen bond interactions with LYS 53 and ASP 168 respectively (Figure 12) (Tariq et al., 2018).

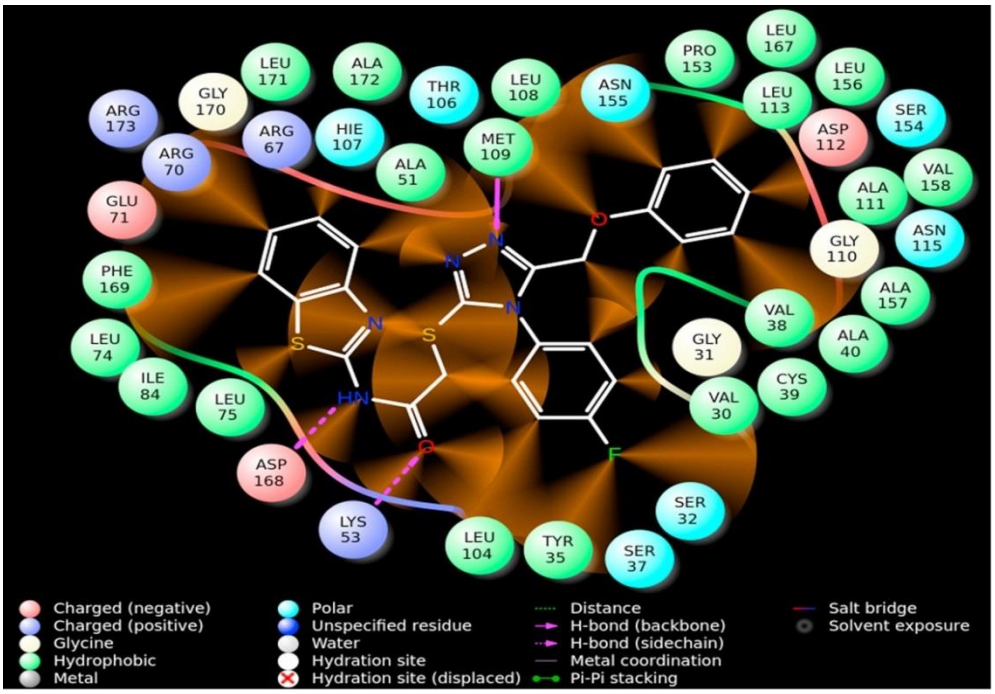

Figure 12. 2D LigPlot diagramme of compound 5b (Tariq et al., 2018).

The data detected by docking showed that electron-withdrawing para substitution on aryl moiety can result in ideal docking scores. The fluorine atom Incorporation resulted in an increase in binding affinity to the target protein receptor because it is the most electronegative element that can modify the polarity. When compared to Cl and Br, fluorine is smaller in size thereby adjusted properly at the p38α MAP Kinase receptor binding site. Compound 2 and 9 with promising molecular docking outcomes indicated that derivatives with electron-attract groups such as F at the para position can interact perfectly in the p38α MAP kinase active region (Figure 13).

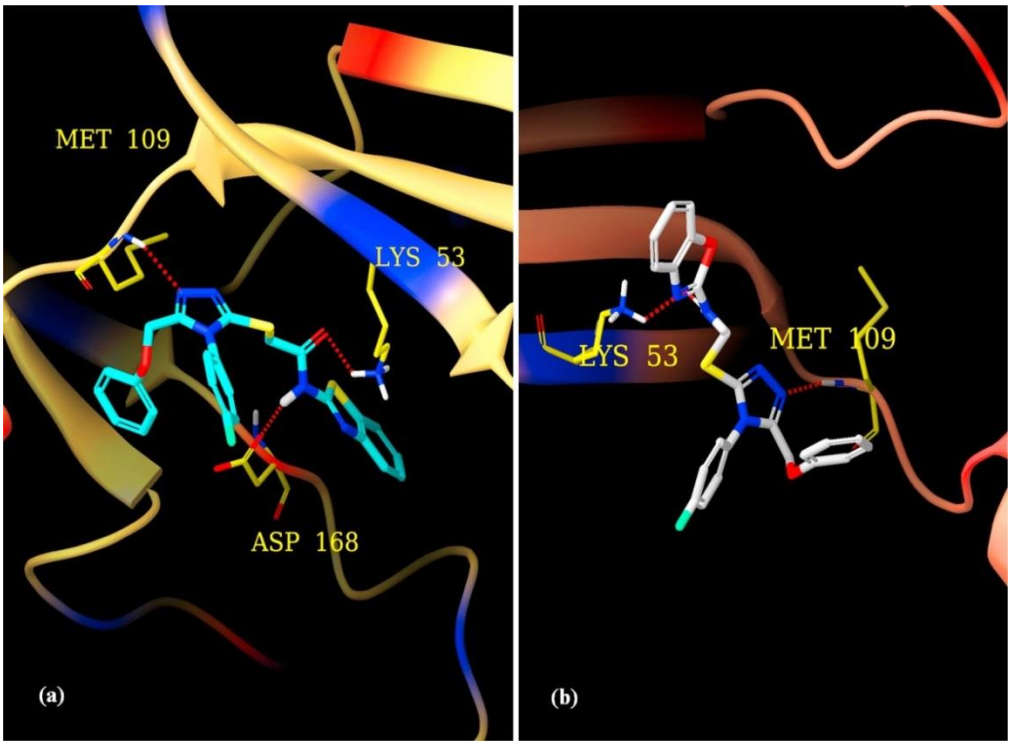

Figure 13. 3D Docked conformer of (a) Compound 2, (b) Compound 9, presented the binding site of p38α MAP Kinase receptor observing hydrogen bond interactions(Tariq et al., 2018).

In 2017, Thakkar and co-workers investigated antimalarial and antimicrobial activities analogs containing 1,2,4-triazole as DHFR inhibitor by using molecular docking interaction. To explain the binding energies potential of the active compounds containing 1,2,4-Triazole as antimalarial agents were docked against P. falciparum dihydrofolate reductase (PDB ID: 4DPD). Interactions were evaluated between the tested molecules and the Pf-DHFR enzyme. The 3D diagrams displayed the binding sites of the ligands within the receptor 4DPD. The molecules interacted with the amino acids of receptor 4DPD in the active sites through conventional carbon-hydrogen bond, van der Waals, p-sigma, hydrogen bonds, p-cation, p-anion, p-donor hydrogen bonds, p-alkyl, p-sulfur, and etc. The binding energies of these molecules were found in the range of -7.20, and 9.06 kcal/mol (Thakkar et al., 2017).

In 2021, Boy et al. reported molecular docking study of eight novel piperidine derivatives heterocyclic Schiff-Mannich base towards AChE, BChE, and GST enzymes. The physicochemical properties of tested compounds were predicted and demonstrated that eight synthesized compounds are non-toxic as rtvFG values were less than 2. They are easily absorbable orally and octanol/water partition coefficient values are well for compounds. In the light of these results, we can state that the compounds can be easily distributed from the

extracellular fluid to the tissues in case of absorption as drugs. Also, related to their moderate logBB values the characteristics of the compounds allow them to cross the blood-brain barrier. The three most active compounds binding energy scores into the active side of the structures of the enzymes were calculated. The highest binding score in the negative was picked as the best pose. The compounds binding score was −12.775 kcal/mol compound 2 with BChE, −12.095 kcal/mol binding score compound 6 with AChE, and was −9.336 binding score compound 7 with GST respectively. Depending on the calculated scores, each compounds showed very good binding to the enzymes used. Compound 6 formed hydrogen bonds with Ser293, Asn283, Phe295 and Tyr124 residues with the residue of the AChE enzyme. Compound 6 formed hydrogen bonds with Ser293, Asn283, Phe295 and Tyr124 residues, Π-cation, salt-bridge, and halogen bond interactions with Try341, Asp74, and Ser293 residues, respectively.

AChE enzyme's catalytic active site consists of two peripheral and acylation sites (Rosenberry et al., 2017). Tyr124, Trp286, Tyr341, and Tyr72 aromatic residues of the site assists to fix acetylcholine into the choline-binding pocket by orienting the acylation site (Colletier et al., 2006). AChE enzyme activity may inhibited by compound 6 complex with embarrassed the orientation of acetylcholine to the choline-binding pocket. In BChE enzyme active side, compound compound 2formed hydrogen bonds (water-mediated) with Thr120 and Asn68 residues. Compound 2 phenol moiety formed Π-Π interactions over the aromatic ring with Phe329 and Trp231amino acid residues. In the GST enzyme catalytically active side, M7 compound formed hydrogen bonds with Gln51, Tyr7, Ser65, Gly205, and Asp98 amino acid residues. Beside, formed Π-cation interaction and Π-Π interaction and with Arg13 and Phe8 residues, respectively (Figure 14-16) (Boy et al., 2021).

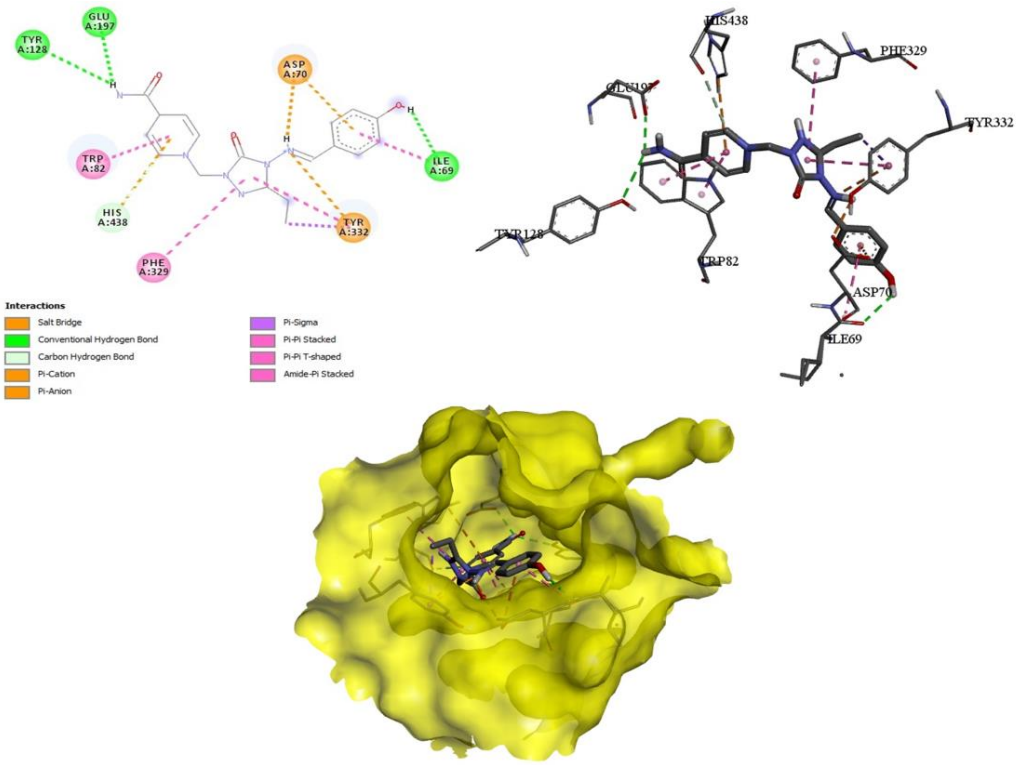

Figure 14: The interaction mode between one of most active compound 2 and BChE enzyme

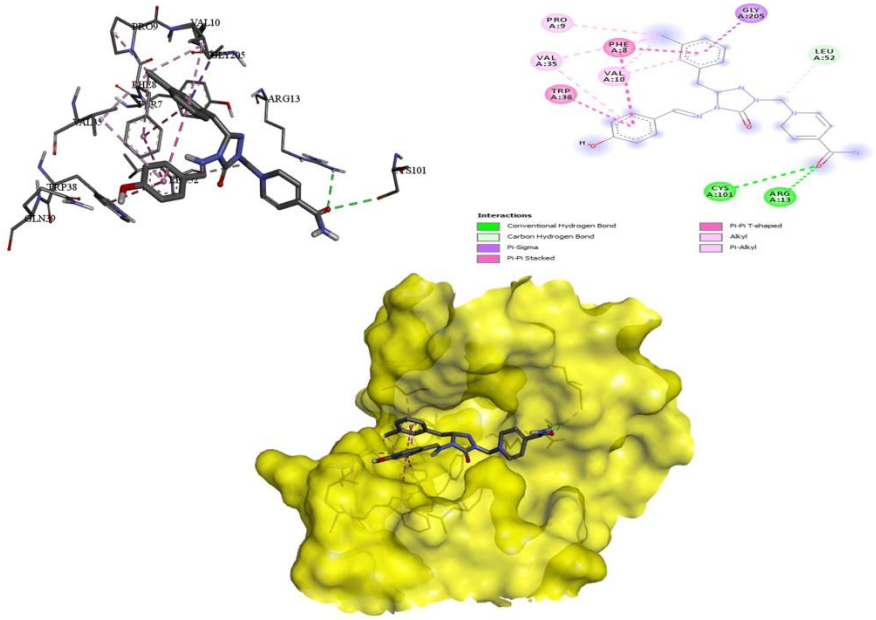

Figure 15: The interaction mode between one of most active compound 6 and GST enzyme

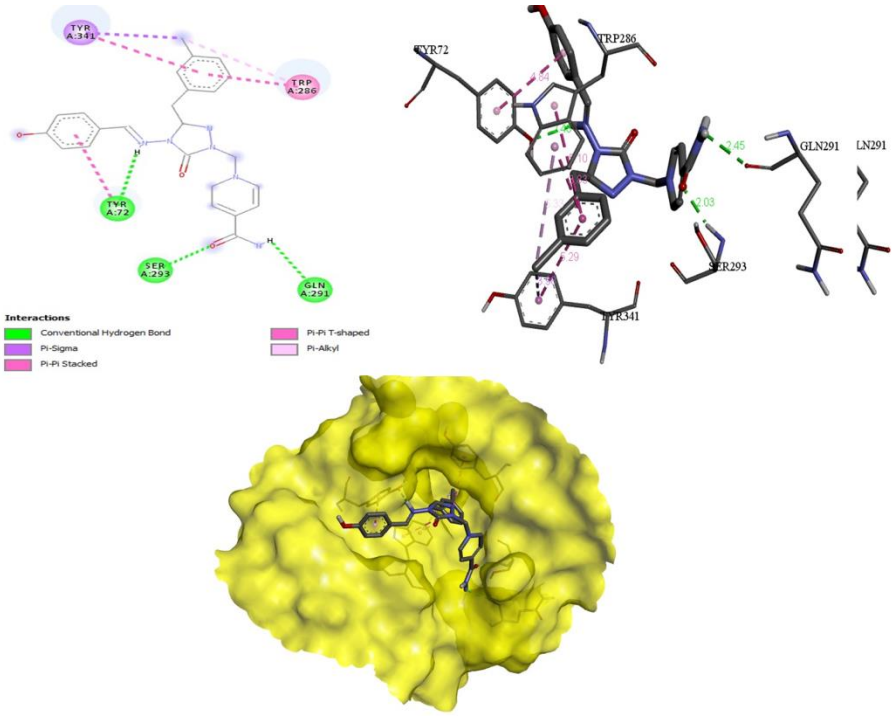

Figure 16: The interaction mode between one of most active compound 7 and AChE enzyme

Multiple computational techniques such as molecular docking protecting a vast range of time, is effectively seizing information across biological scales (Aminpour et al., 2019). Experiments; It assumes a fundamental role in science, especially in the field of drug discovery. Rich experimental results form the basis for understanding the chemistry of life. But still experiments only make sense together with models and theories. Depending on the dynamic and complex nature of chemical systems, biological systems are also complex structures. Because of these complex structures of biological systems, computer methods have become important in health and science. In the analysis of such complex structures, it is possible to understand memory and graphical features, such as computers, by using advanced tools. Computer simulations act as a bridge between processes (theory) theory and the laboratory world (experiment) (Eren and Yalçın). The core triazole ring structures with higher stabilization energies act as bridges between the interacting binding site of the enzyme and various pharmacophores. Therefore, fragment-based drug design is known to play vital roles in a wide variety of biological activities (Matin et al., 2022).

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together with their Benzo and other Carbocycl.-fused Deriv. V4 Five-memb. Rings with Two Heteroat., each with their Fused Carbocycl. Deriv. (pp. 1-13718): Elsevier.

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