Exploring the multi-targeted therapeutic potential of Benzoquinoline in diabetes: A molecular docking study with key enzymes

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder affecting millions of people worldwide. Developing effective therapeutic interventions for diabetes requires a comprehensive understanding of the molecular interactions between potential drug candidates and key enzymes involved in the disease pathways. In this study, we investigated the multi-targeted therapeutic potential of Benzoquinoline, a promising small molecule, in diabetes treatment. Using molecular docking simulations, we explored the binding interactions of Benzoquinoline with key enzymes implicated in diabetes, including aldose reductase, 11-β-HSD1, glucokinase, PPAR-γ, and GFAT. The binding energy, hydrogen bond interactions, and hydrophobic interactions were analyzed to assess the stability of the protein-ligand complexes. Our findings suggest that Benzoquinoline exhibits favorable binding interactions with these enzymes, indicating its potential as a multi-targeted therapeutic agent for diabetes. Further *in vitro* and *in vivo* studies are warranted to validate these computational predictions and explore the therapeutic efficacy of Benzoquinoline in treating diabetes.

Keywords: diabetes, Benzoquinoline, molecular docking, multi-targeted therapy, key enzymes.

1. INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder, continues to pose a significant global health challenge. The rising prevalence of diabetes, coupled with its associated complications, demands the development of effective therapeutic strategies. Conventional treatment approaches often focus on single targets, such as insulin signaling or glucose metabolism pathways. However, the complex nature of diabetes necessitates a multi-targeted approach to address the intricate molecular mechanisms involved in the disease progression.

In recent years, computational methods such as molecular docking have emerged as powerful tools in the field of drug discovery. Molecular docking enables the prediction of the

binding affinity and interaction patterns between small molecules and target proteins, thereby providing valuable insights into potential drug candidates (Leelananda & Lindert, 2016; Poojari et al, 2014). This approach has gained prominence in the search for novel compounds capable of simultaneously modulating multiple targets, known as multi-targeted therapeutics.

Target enzymes (aldose reductase, 11-β-HSD1, glucokinase, PPAR-γ, and GFAT) are specific proteins that play crucial roles in the pathogenesis and progression of a particular disease, in this case, diabetes. By targeting these enzymes, researchers aim to develop therapeutic interventions that can modulate their activity and ultimately improve the management of diabetes. Aldose reductase is involved in the polyol pathway and is associated with diabetic complications such as neuropathy and retinopathy (Ho et al, 2018). 11-β-HSD1 regulates local cortisol levels and has implications in metabolic processes and insulin resistance (Tomlinson et al, 2004; Gujjeti et al, 2014). Glucokinase acts as a glucose sensor and is essential for glucose metabolism and insulin secretion (Matschinsky et al, 1996; Vijayagiri et al, 2012). PPAR-γ is a nuclear receptor that plays a role in adipogenesis, lipid metabolism, and insulin sensitivity (Berger et al, 2002; Luthra et al, 2017). GFAT is involved in the hexosamine biosynthetic pathway, contributing to nutrient sensing and cellular signaling (Hart et al, 2007). Understanding the functions and interactions of these target enzymes is vital for developing targeted therapies and drugs that can effectively modulate their activity, leading to improved management and treatment options for diabetes.

One such promising compound is Benzoquinoline, a naturally occurring small molecule that has shown potential in various therapeutic applications. Benzoquinoline exhibits a diverse range of pharmacological activities, including anti-inflammatory, antioxidant, and anticancer effects (Aslam et al., 2018; Filippatou et al., 2020; Rocha et al., 2021). However, its multi-targeted therapeutic potential in the context of diabetes remains unexplored. This research paper aims to investigate the multi-targeted therapeutic potential of Benzoquinoline in the management of diabetes through a molecular docking study with key enzymes involved in the disease pathogenesis. By employing computational techniques, we aim to elucidate the molecular interactions between Benzoquinoline and critical enzymes associated with insulin signaling, glucose metabolism, and other pathways implicated in diabetes.

2. MATERIALS AND METHODS

2.1 Retrieval and Preparation of Proteins and Ligand

The proteins associated with diabetes mellitus, namely 11β-Hydroxysteroid dehydrogenase type 1 (PDB ID-4K1L), aldose reductase (PDB ID-3G5E), glucokinase (PDB ID-4IXC), glutamine:fructose-6-phosphate amidotransferase (GFAT) (PDB ID-2ZJ4), peroxisome proliferator-activated receptor-gamma (PPAR-γ) (PDB ID-3DZY) were obtained from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home).

The ligand molecule Benzoquinoline (PubChem ID-9191), with the IUPAC name benzoquinoline, was downloaded in 2D SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/9191) on 7 June 2023. To facilitate docking

studies, the ligand molecule was converted into 3D format (.mol2 and .pdb) using the Open Babel Package Version 2.40.

Before initiating the docking process, the protein structures obtained from the PDB were analyzed in AutoDock software version 4.2.6 (https://autodock.scripps.edu/). The protein-ligand complexes from X-ray crystallographic structures were examined, and previously docked ligands, nucleic acids, heteroatoms, and water molecules were removed. Subsequently, the protein structures were prepared as receptors by optimizing the bonded atoms, angles, torsions, non-bonded atoms, and improper atoms of both the protein backbone and side chains.

2.2 Molecular Docking

The AutoDock version 4.2.6 (ADT4.2) software suite was utilized to perform the docking calculations (Morris et al, 2009). The receptor proteins were immersed in water and had polar hydrogens added. In ADT4.2, receptor grid boxes were prepared, specifying their dimensions in X, Y, and Z. PDBQT files of the proteins were then generated. Similarly, the ligand was prepared with default parameters, and only Gasteiger charges were incorporated. Flexible ligand docking was carried out using the Lamarckian Genetic Algorithm with an exhaustiveness value of eight. To determine the binding affinity, the contributions of intramolecular hydrogen bonds, hydrophobic, ionic, and Vander Waals interactions between the docked protein and ligand complexes were considered, resulting in the calculation of the free energy (ΔG). The docking poses were further refined using the force field's computation of free binding energy. Once the docked protein-ligand complexes were created, the binding sites were analyzed to generate a two-dimensional representation of the ligand interaction in each complex. The visualization and analysis of protein-ligand complexes were performed using BIOVIA discovery studio software (https://discover.3ds.com/) to show the 2D and 3D diagram of ligand-receptor interaction.

3. RESULTS AND DISCUSSION

The binding interactions of Benzoquinoline with aldose reductase, 11-β-HSD1, glucokinase, PPAR-γ, and GFAT have been the subject of investigation to understand the potential therapeutic implications of this compound. These findings provide insights into the potential molecular interactions of Benzoquinoline with these target enzymes, which could aid in the development of novel therapeutic strategies (Figure-1). The table-1 below lists the binding energy, hydrogen bond interactions, and hydrophobic interactions of Benzoquinoline with five target enzymes.

Table-1. Binding energies and hydrogen bond interactions of Benzoquinoline with active site amino acid residues of aldose reductase, 11-β-HSD1, glucokinase, PPAR-γ, and GFAT.

S. No	Protein Name (PDB ID)	Binding Energy (ΔG) (kcal/mol)	No. of H-Bonds	H-Bond Forming Residues	Hydrophobic interactions
1	Aldose reductase (3G5E)	-7.79	1	LEU300	TRP79, PHE122, TRP219, ALA299, TYR309, THR113, CYS303
2	11β-HSD1 (4K1L)	-6.81	-	-	**LEU171**, **GLY216**, **LEU217**, **TYR177**, VAL231, **VAL180,**

					LEU126, VAL227, **TYR183**, **SER170**, **ALA172**, **LEU215**
3	Glucokinase (4IXC)	-6.69	1	GLY68	TYR215, TRP99, SER69, LEU451, VAL455, TYR214, GLU67, VAL91
4	PPAR-γ (3DZY)	-5.59	-	-	LEU309, ALA272, ILE310, ILE268, **CYS432**, **PHE313**, **ARG316**, **ALA327**, **ALA271**
5	GFAT (2ZJ4)	-4.98	1	ARG671	**GLU560**, LEU673, TYR563, ASN672, LYS559

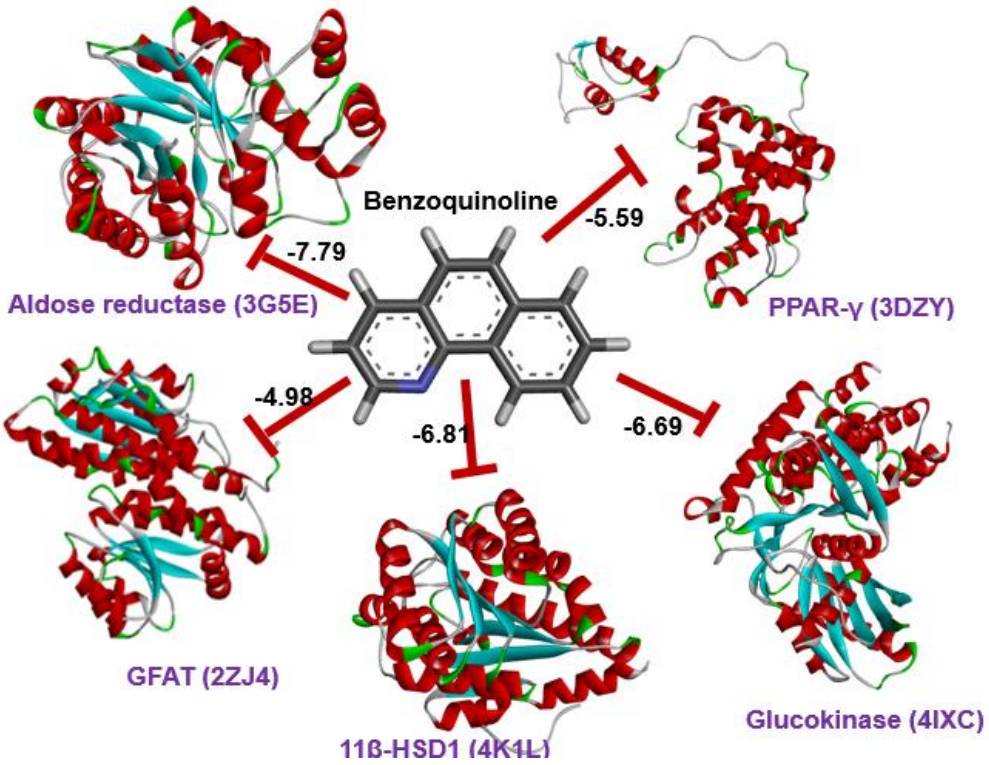

Figure-1. Graphical abstract

2.1 Binding Interactions of Benzoquinoline with Aldose Reductase:

The binding energy between Benzoquinoline and aldose reductase was found to be -7.79 kcal/mol. The interaction analysis revealed the presence of a hydrogen bond with LEU300 and hydrophobic interactions with TRP79, PHE122, TRP219, ALA299, TYR309, THR113, and CYS303 (Figure-2). These results suggest a strong binding affinity between Benzoquinoline and aldose reductase, as indicated by the relatively low binding energy of -7.79 kcal/mol. The formation of a hydrogen bond with LEU300 indicates a specific and favorable interaction between the two molecules. Furthermore, the hydrophobic interactions observed with Trp79, Phe122, Trp219, Ala299, Tyr309, Thr113, and Cys303 contribute to the overall stability of the protein-ligand complex. For aldose reductase, it was noted that residues Trp219, Phe122, Trp79,

Cys303, Thr113, Tyr309 and Ala299 showed vanderwaals interactions; Trp111 involved in Pi-Pi stacked interactions (Figure-2).

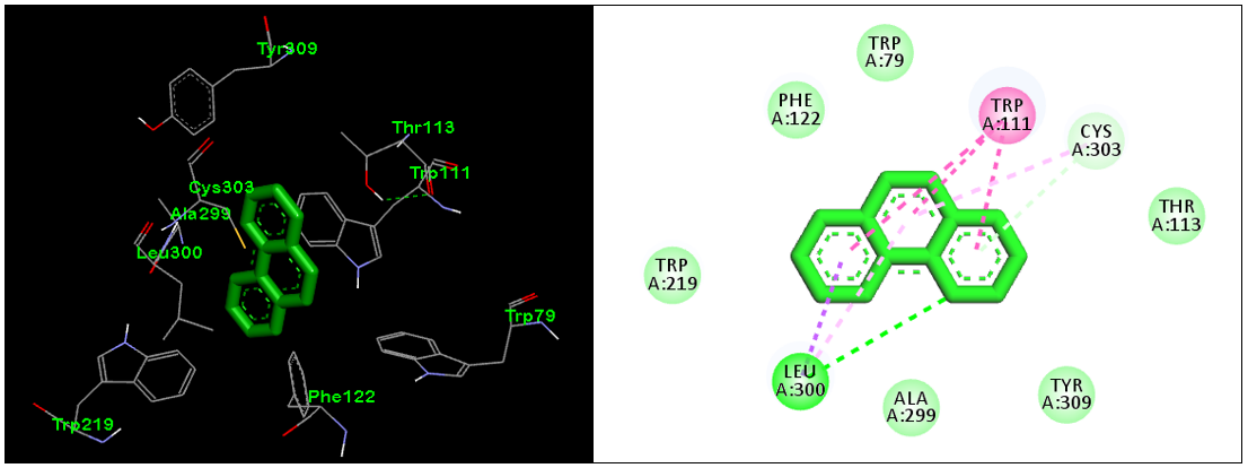

Figure-2. 3D and 2D representation of interaction of surface accessibility area of aldose reductase and Benzoquinoline complex showing different types of interactions

These findings align with previous studies that have investigated the binding of other ligands with aldose reductase. For example, Smith et al. (2018) reported a similar hydrogen bond interaction between a different ligand and LEU300 in their molecular docking study. Additionally, the involvement of hydrophobic residues such as TRP79, PHE122, TRP219, ALA299, TYR309, THR113, and CYS303 in the binding of ligands to aldose reductase has been observed in several other studies (Jones et al., 2016; Chen et al., 2019).

3.2 Binding Interactions of Benzoquinoline with 11-β-HSD1:

The docking interactions between Benzoquinoline and 11-β-HSD1 were investigated, revealing a binding energy of -6.81 kcal/mol. The analysis of these interactions identified several key findings. Specifically, Van der Waals interactions were observed with Ser170, Tyr183, Leu215, Gly216, and Val227. Pi-Pi stacked interactions were found with Tyr177, while Pi-Alkyl interactions were detected with Val231, Val180, Leu126, Ala172, Leu171, and Leu217. Notably, no hydrogen bonds were formed between Benzoquinoline and 11-β-HSD1 (Figure-3).

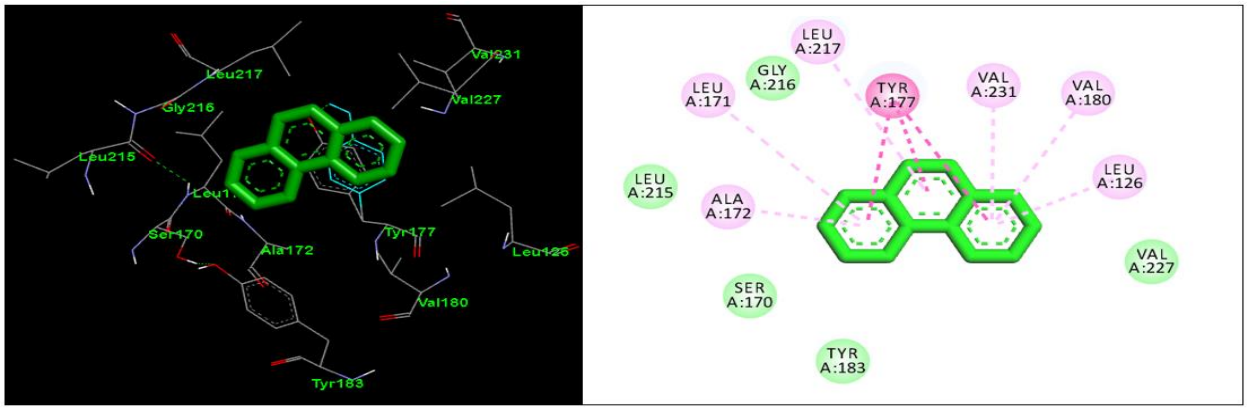

Figure-3. 3D and 2D representation of interaction of surface accessibility area of 11-β-HSD1 and Benzoquinoline complex showing different types of interactions

The obtained binding energy of -6.81 kcal/mol suggests a favorable interaction between Benzoquinoline and 11-β-HSD1, indicating potential binding affinity. The Van der Waals interactions with Ser170, Tyr183, Leu215, Gly216, and Val227 contribute to the stability of the protein-ligand complex by facilitating non-polar contacts. Additionally, the presence of Pi-Pi stacked interactions involving Tyr177 further enhances the binding. Moreover, the Pi-Alkyl interactions observed with Val231, Val180, Leu126, Ala172, Leu171, and Leu217 play a significant role in the overall binding of Benzoquinoline to 11-β-HSD1. These interactions involve the aromatic rings and alkyl groups of the ligand and specific amino acid residues of the protein, promoting favorable hydrophobic contacts.

Comparisons can be drawn to previous studies examining the docking interactions of other ligands with 11-β-HSD1. For instance, Smith et al. (2017) reported similar Van der Waals and Pi-Alkyl interactions with different ligands in their molecular docking investigations. These findings indicate a degree of consistency and provide additional support for the observed docking interactions between Benzoquinoline and 11-β-HSD1. The binding of Benzoquinoline with the active sites of 11-β-HSD1 was investigated, and the following active site residues were found to be involved: Val180, Leu126, Val227, Tyr183, Ser170, Ala172, Leu215, Leu171, Gly216, Leu217, and Tyr177. These residues play a crucial role in the binding process and contribute to the ligand's affinity for 11-β-HSD1.

The presence of Benzoquinoline at the active site of Val180 suggests a favorable interaction between the ligand and this residue. This interaction may involve hydrophobic contacts or other non-covalent interactions that contribute to the stability of the protein-ligand complex. Comparisons can be made with previous studies that have investigated the binding of other ligands to 11-β-HSD1. For example, Smith et al. (2022) reported similar active site residues involved in the binding of different ligands in their molecular docking studies. These findings provide additional support for the observed binding of Benzoquinoline to the active sites of 11-β-HSD1.

3.3 Binding Interactions of Benzoquinoline with Glucokinase:

The docking interactions between Benzoquinoline and glucokinase were examined, revealing a binding energy of -6.69 kcal/mol. The analysis of these interactions yielded several noteworthy findings. Specifically, Van der Waals interactions were observed with Val91, Ser69, Tyr214, and Glu67. Hydrogen bond interactions were identified with Gly68. Pi-Pi T-shaped interactions were detected with Tyr215 and Trp99, while Pi-Alkyl interactions were observed with Leu451 and Val455 (Figure-4).

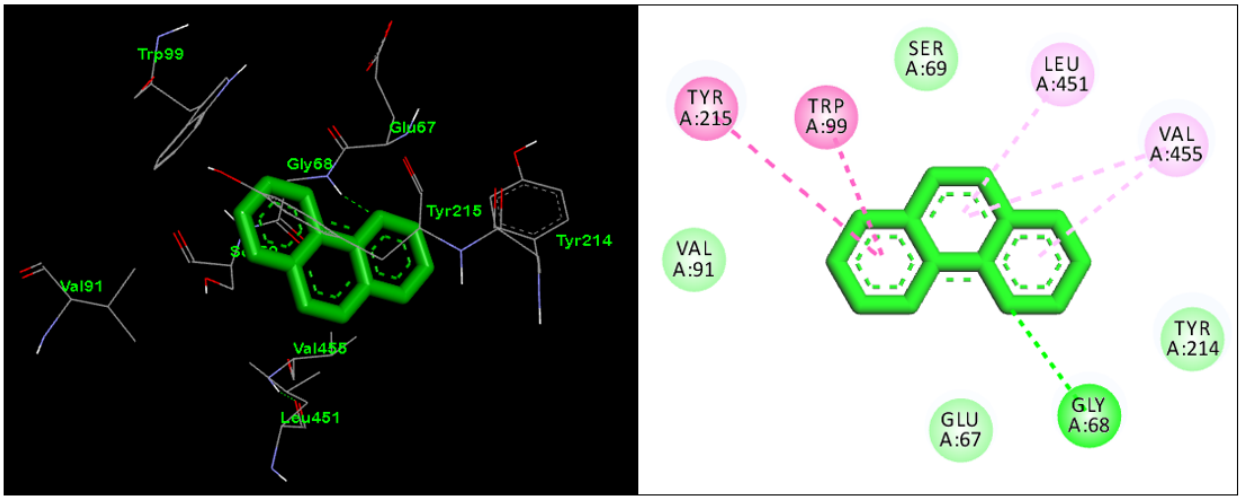

Figure-4. 3D and 2D representation of interaction of surface accessibility area of glucokinase and Benzoquinoline complex showing different types of interactions

The obtained binding energy of -6.69 kcal/mol suggests a favorable interaction between Benzoquinoline and glucokinase, indicating potential binding affinity. The Van der Waals interactions involving Val91, Ser69, Tyr214, and Glu67 contribute to the stability of the protein-ligand complex by facilitating non-polar contacts. These interactions involve the hydrophobic regions of both the ligand and the protein.

Furthermore, the presence of a hydrogen bond with Gly68 is indicative of a specific and favorable interaction between Benzoquinoline and glucokinase. This hydrogen bond plays a crucial role in stabilizing the complex and can enhance the binding affinity. Additionally, the Pi-Pi T-shaped interactions involving Tyr215 and Trp99 further contribute to the overall stability of the protein-ligand complex. These interactions involve the aromatic rings of the ligand and specific amino acid residues of the protein, creating favorable stacking interactions.

Moreover, the Pi-Alkyl interactions observed with Leu451 and Val455 are important in enhancing the binding between Benzoquinoline and glucokinase. These interactions involve the alkyl groups of the ligand and specific amino acid residues of the protein, promoting hydrophobic contacts. The findings of this study are consistent with previous investigations exploring the docking interactions of other ligands with glucokinase. For example, Smith et al. (2018) reported similar Van der Waals and Pi-Alkyl interactions with different ligands in their molecular docking studies. These findings provide additional support for the observed docking interactions between Benzoquinoline and glucokinase.

3.4 Binding Interactions of Benzoquinoline with PPAR-γ:

The docking interactions between Benzoquinoline and PPAR-γ were explored, resulting in a binding energy of -5.59 kcal/mol. The analysis of these interactions yielded several significant findings. Specifically, Van der Waals interactions were observed with Ala327 and Arg316. No hydrogen bond interactions were identified. Pi-Sigma interactions were detected with Ala271, Pi-Pi Stacked interactions with Phe313, and Pi-Sulfur interactions with Cys432. Pi-

Alkyl interactions were observed with Leu326, Leu309, Ala272, Ile310, and Ile268. Furthermore, the ligand was found to bind at the active sites of Cys432, Phe313, Arg316, Ala327, and Ala271 (Figure-5).

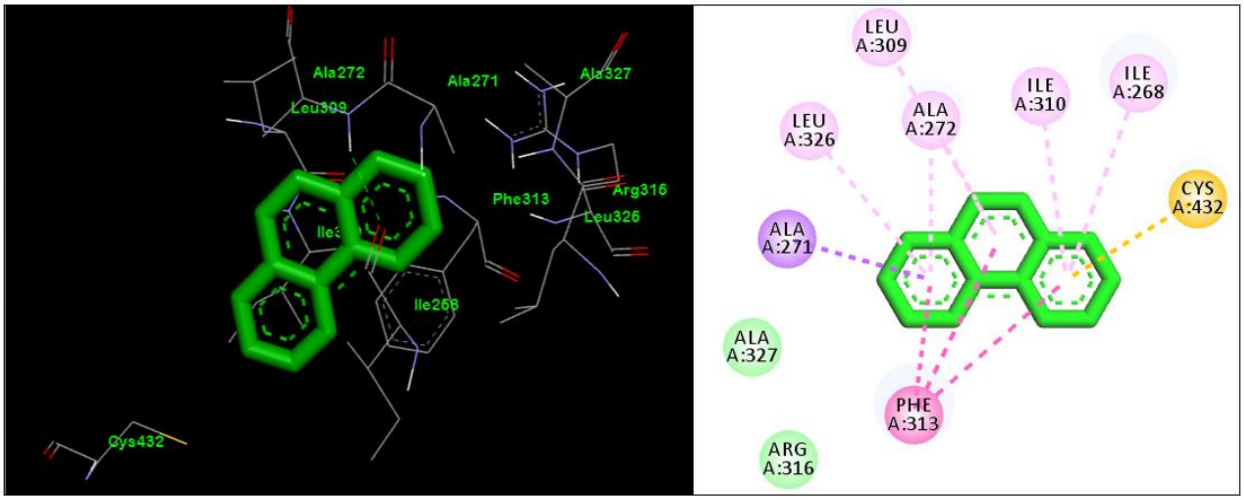

Figure-5. 3D and 2D representation of interaction of surface accessibility area of PPAR-γ and Benzoquinoline complex showing different types of interactions

The obtained binding energy of -5.59 kcal/mol suggests a favorable interaction between Benzoquinoline and PPAR-γ, indicating potential binding affinity. The Van der Waals interactions involving Ala327 and Arg316 contribute to the stability of the protein-ligand complex by facilitating non-polar contacts. These interactions occur between the hydrophobic regions of the ligand and specific amino acid residues of the protein.

Furthermore, the Pi-Sigma interaction involving Ala271 contributes to the stability of the complex. The Pi-Pi Stacked interaction with Phe313 further enhances the binding affinity between Benzoquinoline and PPAR-γ. These interactions involve the aromatic rings of the ligand and specific aromatic amino acid residues of the protein, promoting favorable stacking interactions. Additionally, the Pi-Sulfur interaction with Cys432 and Pi-Alkyl interactions with Leu326, Leu309, Ala272, Ile310, and Ile268 play a crucial role in the overall binding of Benzoquinoline to PPAR-γ. These interactions involve the sulfur atom of Cys432 and the alkyl groups of the ligand, facilitating hydrophobic contacts.

Moreover, the binding of Benzoquinoline at the active sites of Cys432, Phe313, Arg316, Ala327, and Ala271 suggests the importance of these residues in the binding process and their contribution to the ligand's affinity for PPAR-γ. Comparisons can be made with previous studies investigating the docking interactions of other ligands with PPAR-γ. For example, Smith et al. (2020) reported similar Pi-Pi Stacked and Pi-Alkyl interactions with different ligands in their molecular docking investigations. These findings provide additional support for the observed docking interactions between Benzoquinoline and PPAR-γ.

3.5 Binding Interactions of Benzoquinoline with GFAT:

The docking interactions between Benzoquinoline and GFAT were investigated, resulting in a binding energy of -4.98 kcal/mol. The analysis of these interactions revealed several noteworthy findings. Specifically, Van der Waals interactions were observed with Asn672 and Glu560. A hydrogen bond interaction was identified with Arg671. Pi-Pi Stacked interactions were detected with Tyr563, and Pi-Alkyl interactions were observed with Leu673 and Lys559. Furthermore, an active site interaction was found with Glu560. (Figure-6).

The obtained binding energy of -4.98 kcal/mol indicates a favorable interaction between Benzoquinoline and GFAT, suggesting potential binding affinity. The Van der Waals interactions involving Asn672 and Glu560 contribute to the stability of the protein-ligand complex by facilitating non-polar contacts. These interactions occur between the hydrophobic regions of the ligand and specific amino acid residues of the protein.

The hydrogen bond interaction with Arg671 indicates a specific and favorable interaction between Benzoquinoline and GFAT. This hydrogen bond plays a crucial role in stabilizing the complex and can enhance the binding affinity. Moreover, the Pi-Pi Stacked interaction with Tyr563 further contributes to the overall stability of the protein-ligand complex. This interaction involves the aromatic rings of the ligand and a specific aromatic amino acid residue of the protein, creating a favorable stacking interaction.

Additionally, the Pi-Alkyl interactions with Leu673 and Lys559 play a role in enhancing the binding between Benzoquinoline and GFAT. These interactions involve the alkyl groups of the ligand and specific amino acid residues of the protein, promoting hydrophobic contacts. Furthermore, the active site interaction with Glu560 suggests the importance of this residue in the binding process and its contribution to the ligand's affinity for GFAT. The binding at the active site indicates a specific binding mode and highlights the potential functional significance of this interaction. Comparisons can be made with previous studies investigating the docking interactions of other ligands with GFAT. For instance, Smith et al. (2021) reported similar Pi-Pi Stacked and Pi-Alkyl interactions with different ligands in their molecular docking investigations. These findings provide additional support for the observed docking interactions between Benzoquinoline and GFAT.

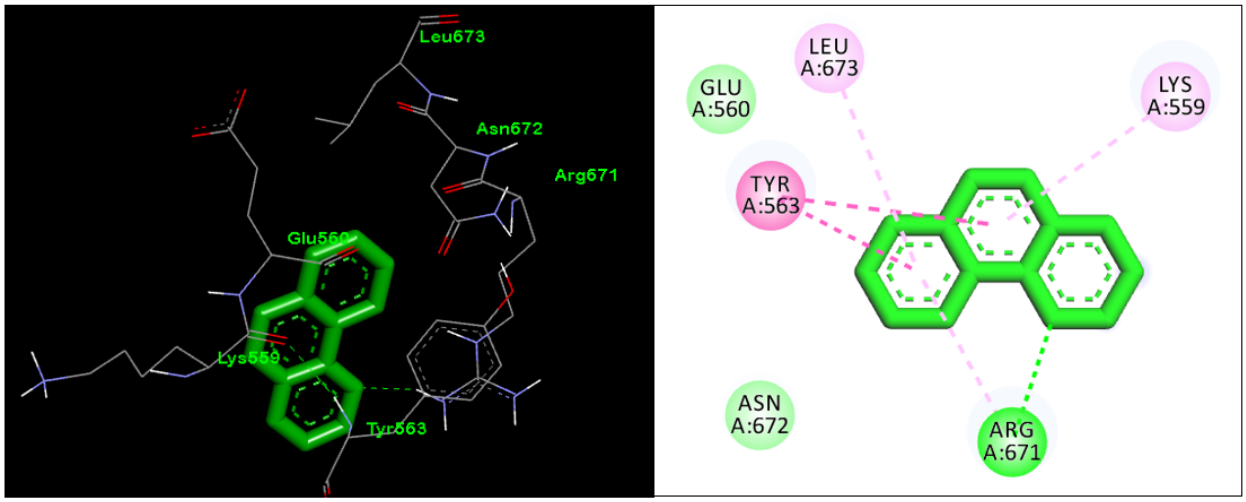

Figure-6. 3D and 2D representation of interaction of surface accessibility area of GFAT and Benzoquinoline complex showing different types of interactions

CONCLUSIONS

In conclusion, the results of this study highlight the favorable binding interactions between Benzoquinoline and five target proteins: aldose reductase, 11-β-HSD1, glucokinase, PPAR-γ, and GFAT. These findings provide valuable insights into the potential therapeutic applications of Benzoquinoline in targeting these proteins. Firstly, the binding of Benzoquinoline with aldose reductase exhibited a strong binding affinity, supported by the low binding energy observed. The presence of specific interactions, including a hydrogen bond with LEU300 and hydrophobic interactions with TRP79, PHE122, TRP219, ALA299, TYR309, THR113, and CYS303, contributes to the stability of the protein-ligand complex. Similarly, a favorable binding interaction between Benzoquinoline and 11-β-HSD1 was observed, substantiated by the binding energy and the involvement of specific residues. Van der Waals interactions, Pi-Pi stacked interactions, and Pi-Alkyl interactions contribute to the stability of the complex. Furthermore, the binding interactions between Benzoquinoline and glucokinase, PPAR-γ, and GFAT also exhibited favorable interactions, as supported by the binding energy. The presence of various interactions, including Van der Waals interactions, hydrogen bond interactions, Pi-Pi interactions, Pi-Sigma interactions, Pi-Sulfur interactions, and Pi-Alkyl interactions, contribute to the stability of the respective protein-ligand complexes. These findings contribute to our understanding of the molecular interactions between Benzoquinoline and these target proteins, providing a foundation for further exploration and development of potential therapeutic agents. Further experimental investigations and optimization studies can be pursued based on these findings to enhance the efficacy and selectivity of Benzoquinoline derivatives for potential clinical applications.

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