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# Oxidative Stress and Insulin Resistance: Correlation, *In-Silico* Design, and Alpha-Glucosidase Inhibition of Benzimidazole Derivatives

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**ABSTRACT**

This study aims to design benzimidazole derivatives and evaluate their alpha-glucosidase inhibitory activity using *In-silico* approaches. The *in-silico* modeling, oral bioavailability, and toxicity prediction were carried out using online web servers. The compounds were optimized using Spartan14 and Chimera. Molecular docking of the compounds against alpha-glucosidase enzyme was carried out using AutoDock Vina. All the ligands passed Lipinski's rule of five which means that they are all druggable. The ligands revealed a good interaction with the enzyme's active site residues while the most notable interactions were hydrogen bonding and another interaction type with ASP352, GLU277, ASP69, TRY72, and ARG442. The binding score of all the ligands is better than the native ligand but slightly lower than Acarbose. Therefore, the study suggested that the ligands have the potential to be utilized as a lead molecule for the synthesis of new orally available diabetic drugs.

**Keywords**: Oxidative stress, Diabetes, Alpha-glucosidase, Benzimidazoles.

## INTRODUCTION

Reactive oxygen species (ROS), also known as oxygen-containing reactive species, comprises the following; singlet oxygen, hydrogen peroxide, superoxide anion, peroxynitrite, hydroxyl radical, and hypochlorous acid [1]. Though they are a byproduct of oxygen metabolism, reactive oxygen species are important for normal cellular processes [2,3]. However, an imbalance between the generation of reactive oxygen species and antioxidant capacity results in the

accumulation of ROS, which causes chemical changes in DNA, proteins, and lipids, ultimately leading to oxidative stress, or damage to cells [1,3].

Type 2 diabetes is among the many disorders that are closely associated with oxidative stress [3]. Insulin resistance is a crucial link between the obesity pandemic and the aging population, which are the two main causes of the rise in type-2 diabetes worldwide. It is well recognized that an important risk factor for type-2 diabetes as well as other chronic illnesses including cancer and cardiovascular disease is insulin resistance [4].

Hypoglycemia in diabetic patients is known to lead to serious complications by enhancing oxidative stress in the heart, kidneys, and eyes. It has also been proposed recently that oxidative stress contributes to insulin resistance [5,6]. *In vivo,* glucose metabolism is largely regulated by the insulin-mediated signaling pathway, which also helps to reduce blood glucose levels. Insulin resistance is the biological term for a reduction in the biological impact of insulin, whereby tissues that are sensitive to insulin such as skeletal muscle, adipose tissue, and the liver cannot use blood glucose as an energy source as efficiently [1]. β-cells generate more insulin in an attempt to overcome this state, but ultimately, this results in β-cell exhaustion [7]. Type 2 diabetes is brought on by elevated blood glucose levels due to a decrease in insulin secretion brought on by β-cell exhaustion [1].

Diabetes is a global health disorder as a result of hyperglycemia and glucose intolerance, caused by insulin malfunction, defective insulin secretion, or both [8]. It is reported that long-term diabetes can result in other health issues such as cardiovascular disease, kidney malfunction, and neuropathy [9].

Inhibition of α-glucosidase, an enzyme that catalyzes starch hydrolysis to simple sugars, to maintain glucose levels in the blood, is one of the known effective ways to cure diabetes type-2 [10]. Side effects in the gastrointestinal (GI) tract such as abdominal discomfort, flatulence, and diarrhea are said to be caused by the enzyme, α-glucosidase inhibitors such as acarbose, miglitol, and voglibose [11]. These side effects are caused by the carbohydrates which are not absorbed and thus remain in the gut. Later on, the bacteria will digest the carbohydrates in the colon, and then produce gas [12,13]. Another way to manage diabetes mellitus is by inhibiting the deterioration of pancreatic β-cells caused by oxidative stress. Therefore, antioxidant activity

can also help in the treatment of diabetes [14,15]. It is also indicated that the compounds with high affinity to α-glucosidase inhibition are likely to have antioxidant activity [11]. Due to the side effects of clinically used α-glucosidase inhibitors [11], the design and development of effective, safer, and specific α -glucosidase inhibitors to treat diabetes mellitus is essential.

Recently, medicinal chemists have developed a strong interest in nitrogenous heterocyclic compounds. A significant number of these possible heterocyclic medications are benzimidazole scaffolds. Benzimidazole derivatives are important as chemotherapeutic agents because of their isostructural pharmacophore of naturally occurring active biomolecules [16]. Benzimidazoles are a class of heterocyclic, aromatic compounds that share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety [17]. The pharmacological application of benzimidazole analogs found potent inhibitors of various enzymes involved and therapeutic uses including as antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and also neurological, endocrinological, and ophthalmological drugs [17]. Structure-activity relationship implies that methoxy and methyl substitutions on the phenyl ring between Schiff-base linkage and benzimidazole moiety favor the α-glucosidase inhibition [18].

This study employs *in-silico* design and molecular docking approaches to identify novel benzimidazole derivatives as potential inhibitors of alpha-glucosidase, an enzyme responsible for diabetes and other metabolic disorders. Structural modification and optimization of the lead compound were utilized to improve the binding affinity. This will reduce time, and cost and enhance efficacy and safety in new antidiabetic drug discovery as it was reported by the International Diabetes Federation (IDF) [19] that the number of diabetic patients is expected to rise to 783.7 million by 2045. Therefore, the need for a computational method of antidiabetic drug discovery is worthy. This expands the collection of available alpha-glucosidase inhibitors.

This research aims to investigate the relationship between oxidative stress and diabetes based on reported literature and to design and evaluate novel benzimidazole derivatives as potential alpha-glucosidase inhibitors for the management of type 2 diabetes through an *in-silico* approach. The objectives of this study are: To design and optimize a series of benzimidazole derivatives using in-silico modeling; to evaluate pharmacokinetic and pharmacodynamic properties using

computational methods; and to identify potential lead compounds with favorable drug-like properties and ideal inhibitory activity.

## MATERIALS AND METHODS

### Materials

HP EliteBook 830 G6, Intel(R) Core(TM) i5-8365U CPU @ 1.60GHz  1.90 GHz.

Software utilized are; ChemDraw ultra version 12.0.2, Spartan 14v 114, UCFS chimera version 1.17.3, AutoDockTool version 1.5.6, Autodock Vina, Cygwin64 terminal and Discovery studio visualizer version 20.1.0.

### Ligand preparation

The 2D structures were generated using ChemDraw ultra version 12.0.2 and Spartan 14v 114 was used to convert the 2D structure to 3D structures. The ligands were optimized and saved as mol2 files.

### Receptor preparation

The crystal structure of alpha-glucosidase enzyme (PDBs: 3A4A) protein was downloaded from 6Protein Data Bank (PDB, http://www.rcsb.org)  at a resolution of 1.6 Å. The crystal structure was deposited on 07-01-01 and released on 14-07-2010. It has a unique ligand, Oligo-1,6-glucosidase abbreviated as GLC [20]. The enzyme was prepared by removing all non-residues followed by the addition of hydrogen atoms and Gasteiger charges to the amino acid residues, using UCFS chimera version 1.17.3 [21].

### Molecular docking

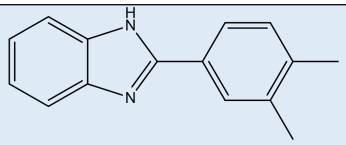
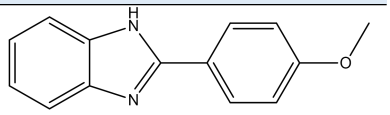
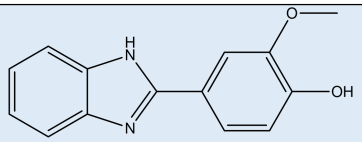
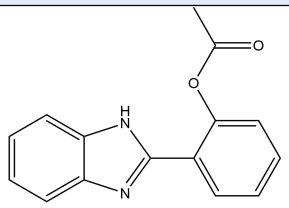
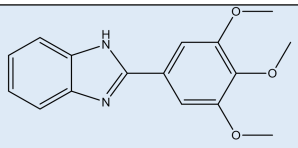
Both the prepared 3D ligands and the receptor were converted to pdbqt by utilizing AutoDockTool version 1.5.6 [22]. The grid box for the alpha-glucosidase was placed at the center of the native ligand (GLC) with x, y, and z coordinates of 17.7786, -8.7537, and 19.7425. The number of sizes in x, y and z dimensions was 16, 14 and 16 respectively. The molecular docking of the ligands and target enzyme was carried out using Autodock Vina [22] with the aid of Cygwin64 terminal. The docking calculations were viewed using UCFS chimera version 1.17.3 [21] and were saved in pdb format. The saved pdb files were viewed using Discovery Studio visualizer version 20.1.0 for receptor-ligand interactions.

## RESULTS AND DISCUSSION

### *In-silico* ADME and Toxicity predictions

The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, as well as the drug-likeness of the benzimidazole derivatives, were studied with the help of ProTox-II (https://www.tox-new.charite.de/protox_II) and swissADME (https://www.swissadme.che). The designed compounds are coded and presented in Table 1, given their IUPAC names and chemical structures.

Table 1: designed compounds code, IUPAC name, and chemical structure.

| S/No. | Compound Code | IUPAC Name | Chemical Structure |
|---|---|---|---|
| 1 | BL8 | 2-(3,4-dimethylphenyl)-1H-benzo[d]imidazole |  |
| 2 | BL17 | 2-(4-methoxyphenyl)-1H-benzo[d]imidazole |  |
| 3 | BL19 | 4-(1H-benzo[d]imidazol-2-yl)-2-methoxyphenol |  |
| 4 | BL23 | 2-(1H-benzo[d]imidazol-2-yl) phenyl acetate |  |
| 5 | BL24 | 2-(3,4,5-trimethoxyphenyl)-1H-benzo[d]imidazole |  |

The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties, as well as the drug-likeness of the benzimidazole derivatives, were studied using online web server (ProTox-II and SwissADME) and presented in Table 2.

Table 2: ADME and Toxicity Prediction using *in-silico* model

| S/No | Code | Mw (g/mol) | GI Absorption | LogP | n-HBA | n-HBD | Lipinki's Violation | LD50 (mg/kg) | Toxicity Class |
|---|---|---|---|---|---|---|---|---|---|
| **1** | BL8 | 229.29 | High | 3.59 | 1 | 1 | 0 | 73 | 3 |
| **2** | BL17 | 224.26 | High | 2.91 | 2 | 1 | 0 | 800 | 4 |
| **3** | BL19 | 240.26 | High | 2.57 | 3 | 2 | 0 | 800 | 4 |
| **4** | BL23 | 238.24 | High | 2.88 | 3 | 1 | 0 | 3000 | 5 |
| **5** | BL24 | 284.31 | High | 2.88 | 4 | 1 | 0 | 3000 | 5 |

Mw: Molecular weight; GI: Gastrointestinal; n-HBA: Number of hydrogen bond acceptor; n-HBD: Number of hydrogen bond donor.

The molecular docking of the compounds against alpha-glucosidase enzyme was carried out using AutoDock Vina. The docking result was viewed for interaction using Discovery Studio. The results are presented in Table 3.

Table 3: Molecular Docking results, showing the binding energy, distance and interaction type with amino acid residues of the alpha-glucosidase enzyme.

| S/No | Compound | Amino acid Residue | Distance (Å) | Interactions | Binding Affinity (Kcal/mol) |
|---|---|---|---|---|---|
| **1** | GLC [a] | ARG442 | 2.7801 | Conventional HB | |
| | | GLU277 | 2.75128 | Conventional HB | |
| | | HIS351 | 3.0103 | Conventional HB | |
| | | ASP352 | 2.51611 | Conventional HB | **-5.7** |
| | | ASP69 | 2.63461 | Conventional HB | |
| | | HIS112 | 2.77084 | Conventional HB | |

| | | | | | |
|---|---|---|---|---|---|
| | | ASP69 | 3.40637 | Carbon HB | |
| | | TYR72 | 3.92966 | Pi-Donor HB | |
| **2** | BL8 | GLU277 | 2.26658 | Conventional HB | |
| | | ASP352 | 2.53159 | Conventional HB | |
| | | ARG442 | 3.7767 | Pi-Cation | **-8.2** |
| | | TYR72 | 5.11761 | Pi-Pi T-shaped | |
| | | PHE303 | 4.98576 | Pi-Alkyl | |
| **3** | BL17 | GLU277 | 2.32831 | Conventional HB | |
| | | ASP352 | 2.50332 | Conventional HB | |
| | | ARG315 | 3.01661 | Carbon HB | |
| | | ARG442 | 3.74666 | Pi-Cation | **-7.6** |
| | | ASP352 | 4.48418 | Pi-Anion | |
| | | TYR72 | 5.16514 | Pi-Pi T-shaped | |
| | | PHE303 | 5.44477 | Pi-Alkyl | |
| **4** | BL19 | GLU277 | 2.21725 | Conventional HB | |
| | | ASP352 | 2.47606 | Conventional HB | |
| | | ARG442 | 3.79122 | Pi-Cation | |
| | | ASP352 | 4.47533 | Pi-Anion | **-7.6** |
| | | TYR72 | 5.17214 | Pi-Pi T-shaped | |
| | | TYR158 | 4.75089 | Pi-Alkyl | |
| **5** | BL23 | GLU277 | 1.98617 | Conventional HB | |
| | | ASP352 | 4.95873 | Pi-Anion | |
| | | PHE303 | 4.63937 | Pi-Pi Stacked | |
| | | TYR72 | 5.84423 | Pi-Pi T-shaped | **-7.8** |
| | | VAL216 | 5.17149 | Pi-Alkyl | |

| | | | | | |
|---|---|---|---|---|---|
| **6** | BL24 | GLU277 | 2.56945 | Conventional HB | |
| | | ASP352 | 2.46096 | Conventional HB | |
| | | ARG315 | 2.75261 | Carbon HB | |
| | | TYR158 | 3.65501 | Carbon HB | |
| | | GLN353 | 2.87455 | Carbon HB | |
| | | ASP307 | 3.68217 | Carbon HB | **-7.3** |
| | | ARG442 | 3.80548 | Pi-Cation | |
| | | ASP352 | 4.46966 | Pi-Anion | |
| | | PHE303 | 5.3177 | Pi-Pi Stacked | |
| | | TYR72 | 5.07851 | Pi-Pi T-shaped | |
| | | TYR158 | 5.26162 | Pi-Alkyl | |
| | | HIS280 | 4.72842 | Pi-Alkyl | |
| **7** | Acarbose [b] | ASP352 | 2.13283 | Conventional HB | |
| | | GLU411 | 2.31122 | Conventional HB | |
| | | ARG315 | 2.3993 | Carbon HB | |
| | | GLU277 | 3.64276 | Carbon HB | **-9.0** |
| | | ASP215 | 3.49884 | Carbon HB | |
| | | ASP69 | 3.28237 | Carbon HB | |
| | | PHE303 | 2.85418 | Pi-Donor HB | |
| | | TYR72 | 3.7183 | Pi-Sigma | |

[a] Native ligand; [b] Standard drug; HB: Hydrogen bond

The native was prepared and viewed at enzyme's active site as presented in Figure 1. The docked native ligand (pink-red color) was superimposed to the undocked co-crystalized ligand (Blue color) to confirm the docking was carried out at the enzyme's active site as shown in Figure 2.

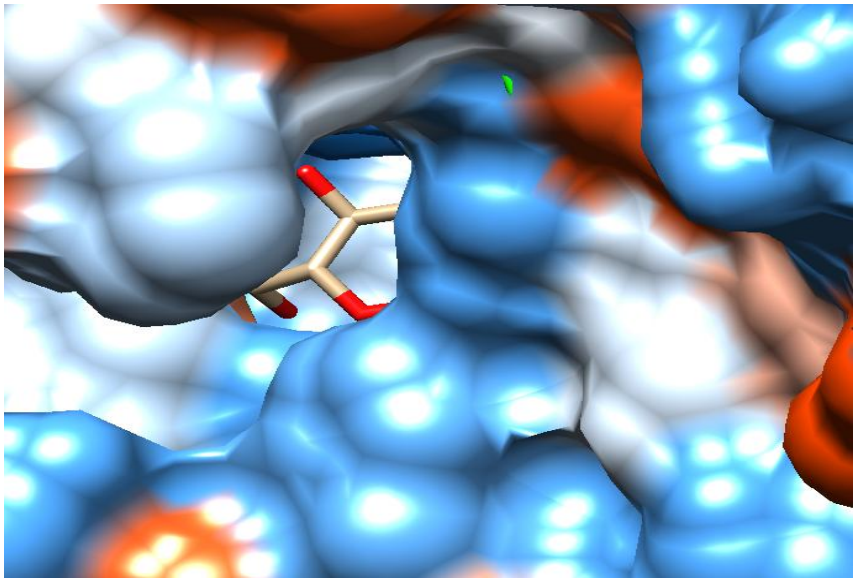


Figure 1: 3D binding poses and interaction of GLC at enzyme's active site

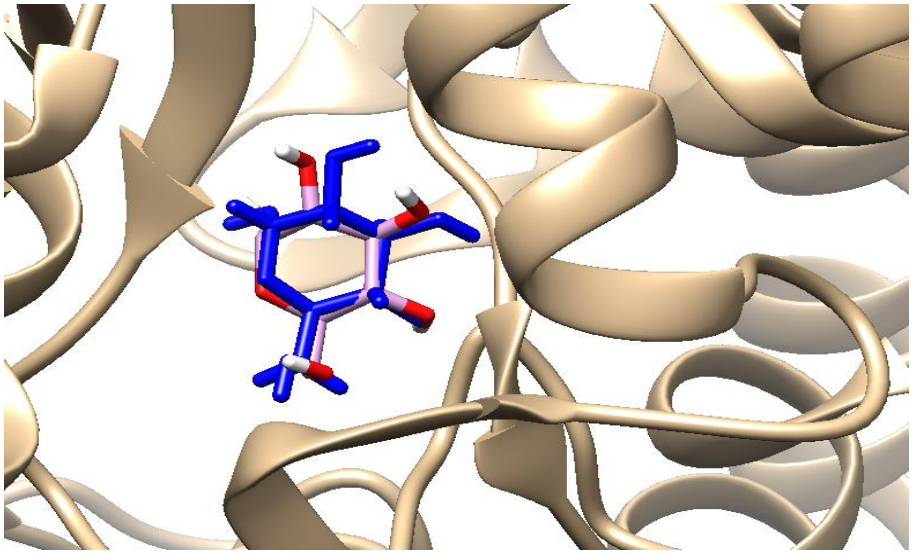
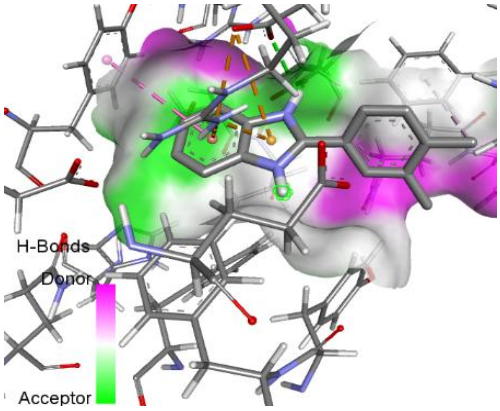
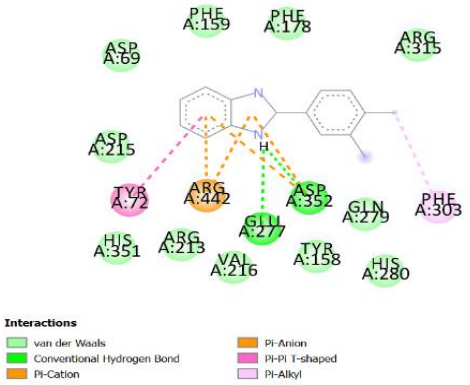


Figure 2: Docking Validation (Re-docked ligand and the native) ligand

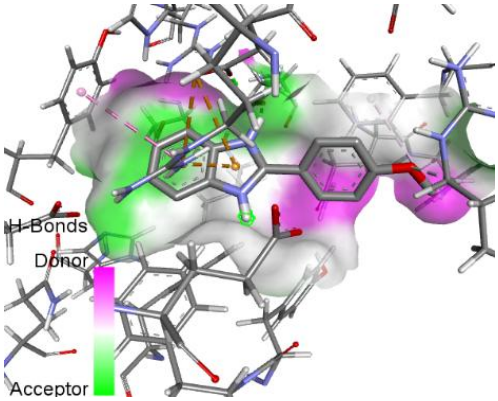
The 2D and 3D binding interactions of the ligands with the amino acid residues of the enzyme's active site are presented in Figure 3.



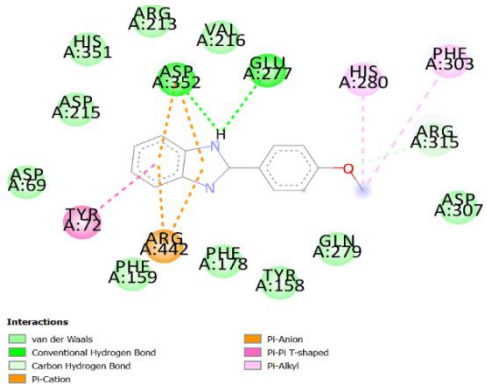

**BL8 (3D)**




**BL8 (2D)**



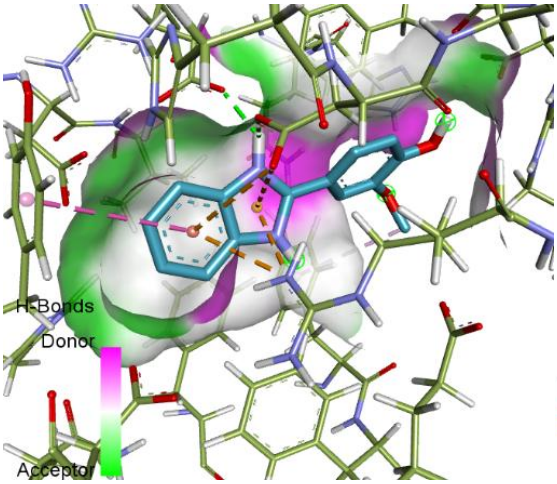

**BL17 (3D)**

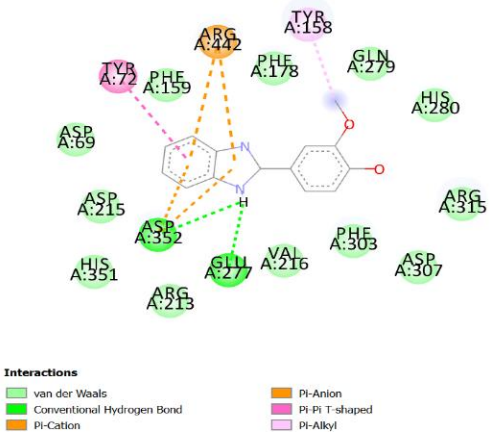



**BL17 (2D)**

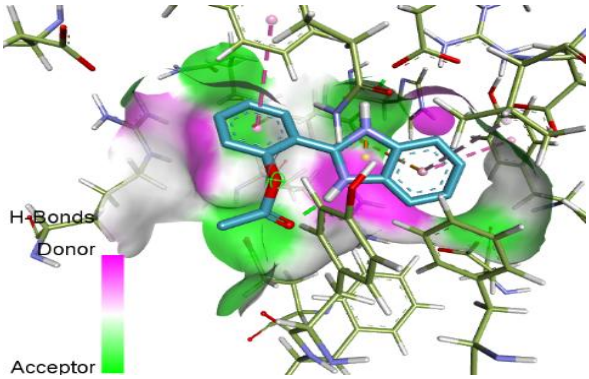
**BL19 (3D)**

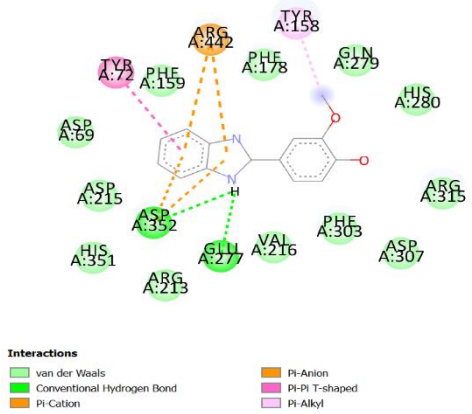
**BL19 (2D)**



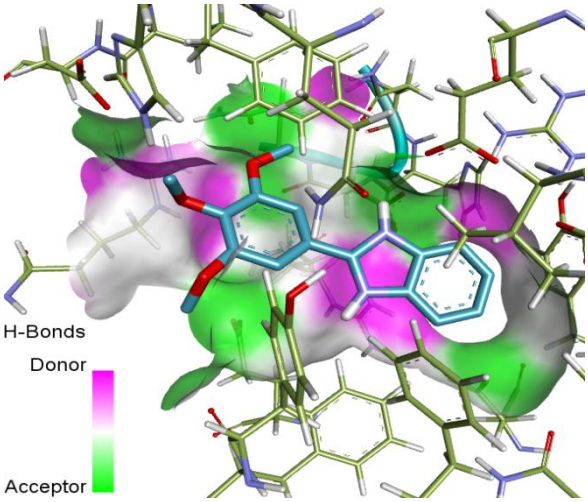



**BL23 (3D)**

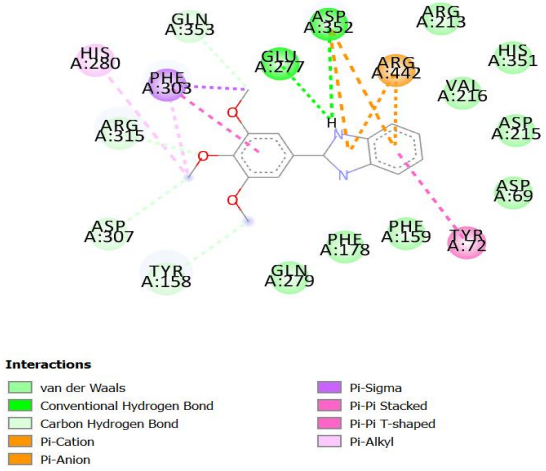



**BL23 (2D)**




**BL24 (3D)**




**BL24 (2D)**

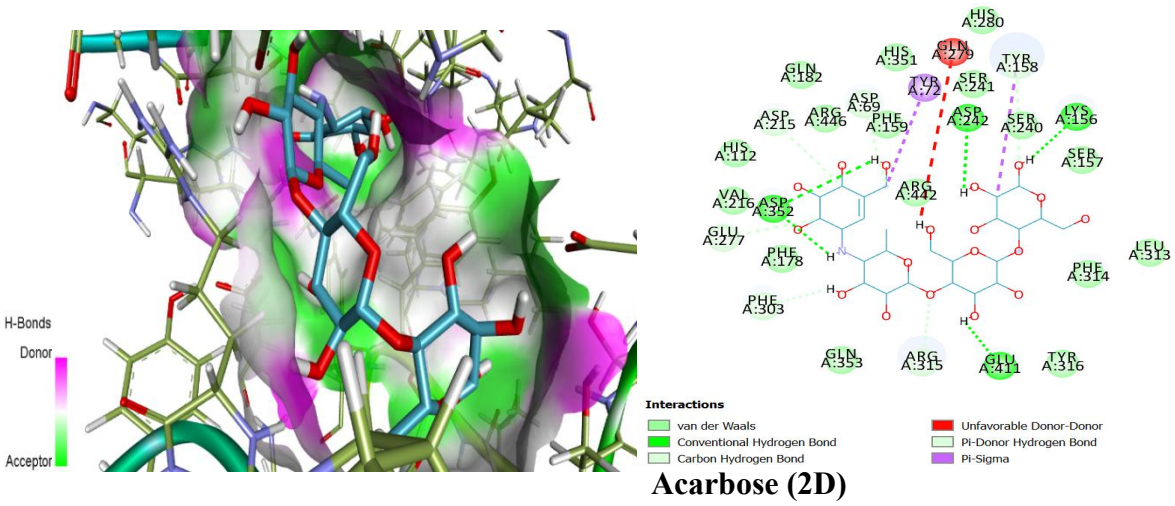



Figure 3: Showing 3D and 2D of Benzimidazole derivatives and Acarbose in the active site and interactions with amino acid residues of alpha-glucosidase

According to the ADMET predicted results in Table 2, all the compounds showed high GI absorption, with the predicted toxicity class of 3,4,4,5, and 5 for BL8, BL17, BL19, BL23 and BL24 respectively. All the compounds showed zero (0) Lipinski's violation. The ADMET properties of all the compounds have shown satisfactory results according Lipinski's rule. The Lipinski rule of five states that an orally active drug has at most one violation of the following criteria: molecular weight (Mw) less than 500, values of the octanol-water partition coefficient (log P) less than 5, the number of hydrogen bond donor less than 5 and number of hydrogen bond acceptor less than 10 [24]. From all these parameters, the compounds obeyed Lipinski's rule of five. Hence, based on the predicted data all compounds are likely to be orally active [25]. This is following the work of Bhandari et al., which shows benzimidazole scaffold to have a good ADME property [26].

The confirmation of the docking pose (active site) and docking validations were carried out and presented in Figure 1 and Figure 3 respectively. This was done before the docking of the designed ligand to ensure the ligands were docked at the right pocket of the enzyme.

The docking result in Table 3 shows that the native ligand, GLC exhibits a higher binding score (-5.7 Kcal/mol) than all the benzimidazoles compounds in this study (BL8, BL17, BL19, BL23

and BL24), with the standard drug, Acarbose, having the lowest binding score of -9.0 Kcal/mol, with BL8 having the best binding affinity (-8.2 Kcal/mol) of all the ligands. BL8 interacts with ARG442, GLU277, ASP352, PHE303, and TYR72. GLC displayed a hydrogen bond interaction with active site residues; ARG442, GLU352, ASP352, ASP69, and TYR72 among others. These interactions are similar to the work of Yamamoto *et al.*[20]. Acarbose revealed an interaction within the active site with amino acid residues forming hydrogen bonds, pi-donor and/or pi-sigma with ASP352, TRY72, GLU277, AS69, and PHE303 among others. This revealed that Acarbose interacts similarly as does GLC, with the amino acid residues of the alpha-glucosidase active site. The docking studies of compound BL8 revealed the ligand binds to the enzyme active site through a hydrogen bond, pi-cation, pi-pi and pi-alkyl as presented in Table 3 and Figure 3. Almost all the interacting amino acid residues are the same as in GLC and Acarbose. BL8 has the best docking score among all other benzimidazole compounds selected for this study as shown in Table 3. Other compounds; BL17, BL19, BL23 and BL24 showed a better binding score than the native ligand and also interacted with at least three amino acid residues of the enzyme target (Table 3).

The docking binding affinity values are higher than the native ligand which could be due to methoxy and methyl substitution on the phenyl ring at position-2 of benzimidazole moiety [18]. These ligands are capable of showing competitive inhibition as most of the interacting amino acid residues are found to be the same with interacting residues of the native ligand, GLC and Acarbose, the clinically used alpha-glucosidase inhibitor [27]. The overall interactions are similar to the work; Alpha-glucosidase inhibitory properties of a few bioactive compounds isolated from black rice bran [28]. This corresponds to the work of Dong and his co-researchers who reported that Hypericin as a Novel α-Glucosidase inhibitor binds to the enzyme in the same or similar way as acarbose [29].

## CONCLUSION

The *In-silico* modeling of benzimidazole hybrids showed their potential as alpha-glucosidase inhibitors. The ADME prediction and drug-likeness outcome shows that the ligands can be orally active, potent and safe. The docking score showed that the ligands have a better affinity to the target enzyme than the native ligand, as such the ligands have an inhibitory effect on the alpha-

glucosidase enzyme. The presence of the methoxy and methyl substituent on the phenyl ring at position-2 of the benzimidazole moiety is responsible for the alpha-glucosidase inhibition. It was also revealed from the reviewed literature that compounds with high affinity to alpha-glucosidase were likely to have antioxidant properties. Therefore, the study suggested that the ligands have the potential to be utilized as a lead molecule for the synthesis of new orally available diabetic drugs.

**Acknowledgment**

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