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Computational insight into synthetic alpha-glucosidase inhibitors: Homology modeling, docking, and molecular dynamics simulation

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ABSTRACT: Diabetes mellitus is a metabolic disorder with high prevalence. As hyperglycemia is the main manifestation of diabetes, controlling postprandial hyperglycemia by inhibiting carbohydrate digestion is important to treat the disease. α-glucosidase is one of the carbohydrate hydrolyzing enzymes that breaks carbohydrates into monosaccharides and thus causes hyperglycemia. Therefore, α-glucosidase is an attractive target to decrease blood glucose level by suppressing carbohydrate digestion. There are clinically available α-glucosidase inhibitor drugs. However, these drugs are associated with adverse effects. Therefore, novel drugs with high efficacy and low adverse effects are needed. Heterocyclic compounds are under investigation to this end.

In this study, active heterocyclic inhibitors were selected. The probable mode of action for these compounds was investigated through molecular docking and molecular dynamics (MD) simulation after the human α-glucosidase structure was built via homology modeling. The pharmacokinetic properties of the compounds were also assessed.

The docking study showed that some of them have high binding potential to the α-glucosidase. However, the compounds with high binding potential gave enzyme-compound complexes with moderate stability. Compound **5** gave a complex with relatively higher stability. The computational pharmacokinetic study revealed that the compounds except compounds **12** and **13** would have good absorption or permeability for oral administration. Understanding the mechanism of action for the existing active compounds will be helpful to pursue the research for further applications and to design novel compounds with similar scaffolds. The findings of this study need further investigation through *in vitro* and *in vivo* methods.

KEYWORDS: alpha-glucosidase; docking; homology modeling; MD simulation; pharmacokinetic.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose level [1]. Diabetes mismanagement can lead to serious health problems like cardiovascular diseases, hypertension, neuropathy, nephropathy, and retinopathy [2]. Diabetes management is a big global challenge as its prevalence was predicted to be 536.6 million people in 2021. Unless measures are taken to revert the prevalence, this figure is estimated to rise up to 783.2 million people by 2045 [3]. In addition, the rate of increase in developing countries has been high in relative to developed countries. Based on its manifestation mechanism, diabetes can be categorized into three major categories: Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) [4]. T2DM consists of nearly 90% of diabetes people around the globe.

Hyperglycemia is critical manifestation of all diabetes types [5]. In the early diabetes stage, reducing postprandial hyperglycemia is critical to control the blood glucose level and thus treating the disease [6]. This can be achieved by inhibiting carbohydrate digestion [7]. To this end, carbohydrate hydrolyzing enzymes on the brush border of intestine are inhibited so that glucose absorption would be hindered [8]. Among these enzymes, α-glucosidase is responsible for breaking α-glucopyranoside bond and hydrolyses oligosaccharides as well as disaccharides into monosaccharides that enter the bloodstream causing hyperglycemia [9]. Therefore, α-glucosidase is an attractive target to decrease blood glucose level by suppressing carbohydrate digestion [10]. α-Glucosidase inhibitors are considered as first line glucose reducing agents that are used to manage mild diabetics (Figure 1) [2].

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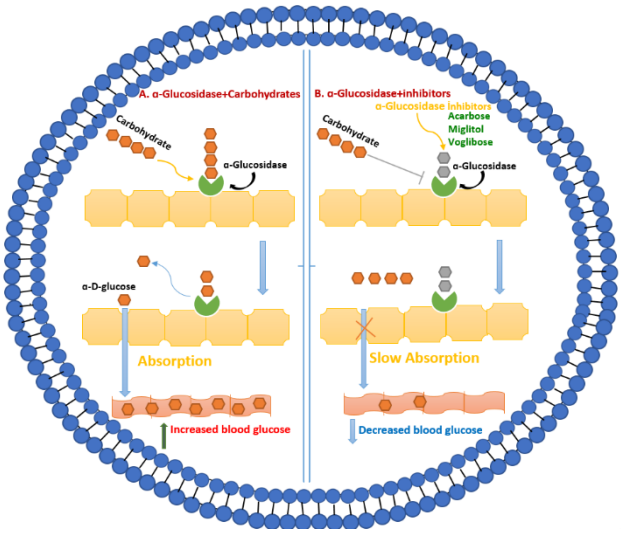

Figure 1. α–glucosidase inhibition mechanism and its effect

There are approved α-glucosidase inhibitors in the pharmaceutical market that mimic carbohydrates. Acarbose, miglitol, and voglibose are clinically available α-glucosidase inhibitors for diabetes treatment (Figure 2). As the molecular structure of these antidiabetic drugs is similar to disaccharides and oligosaccharides, they can hinder the binding of the carbohydrates to α-glucosidase binding site competitively [11,12]. Consequently, a delay in carbohydrate digestion followed by slow glucose absorption that leads to a reduced hyperglycemia is achieved. Nevertheless, they are associated with adverse effects like nausea, diarrhea, abdominal pain, bloating and flatulence [4]. Hence, researchers have been working to discover novel α-glucosidase inhibitors with high efficacy and low adverse effects.

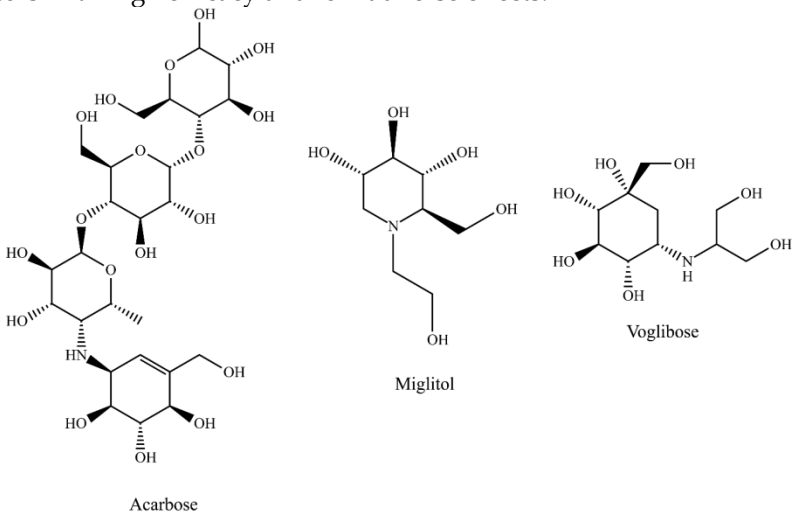

Figure 2. α–glucosidase inhibitors under clinical use

Heterocyclic compounds have been reported as potential α-glucosidase inhibitors [9]. These scaffolds are promising inhibitor candidates as they are accessible, easy to synthesize, high efficacy, and less adverse effects [13]. Among these heterocyclic compounds, benzimidazole (1), oxindole (2), oxidiazole (3), pyrido-pyrrolidine (4), quinazoline (5), thiazole (6), iminothiazoline (7), thiazolidienedione (8), pyrimidine (9), coumarin-linked thiazole (10), furan (11), betulinic acid (12), and thiadiazole (13) containing various compounds have been found to have potential α-glucosidase inhibitor activity (Figure 3) [2]. Hence, these compounds may pave the way towards novel α-glucosidase inhibitors with high efficacy and low side effects. Understanding the mechanism of action for the active compounds will facilitate the search for relevant modifications on them towards better potency.

Computational approaches have been applied to drug design and discovery process to minimize the cost and time required [14]. Among these approaches, molecular docking is utilized to understand the

mechanism of binding for drug candidate compounds [15,16]. Thereafter, molecular dynamics (MD) simulation is performed to measure the stability level of the resulting target-compound complexes obtained from the docking.

In this study, molecular modeling for synthetic α-glucosidase inhibitors was undertaken. To this end, the most active α-glucosidase inhibitors available in the literature were selected. Thereafter, homology modeling of human α-glucosidase was performed first. Then, molecular docking of all the selected compounds to the generated model and MD simulation of compounds with the highest binding potential to the human α-glucosidase was performed. A computational pharmacokinetic study of these compounds was also performed. The study showed that some of the compounds have high binding potential to the enzyme. However, the stability of the complexes obtained from the docking was found to be low. Among these compounds, compound **5** gave a complex with relatively moderate stability. This study aimed at elucidating the binding mode of the active compounds to the human α-glucosidase unlike the reported studies, which were performed on non-human sourced enzyme. Further *in vitro* and *in vivo* investigations are recommended to confirm the results in the *in silico* study.

2. RESULTS AND DISCUSSION

2.1. Homology Modeling

The 3D structure of human α-glucosidase was built through homology modeling. First, the best model among I-TASSER and SWISS-MODEL models was determined by using SAVES validation parameters. The best model was the SWISS-MODEL generated model. The model had ERRAT, Verify3D, and Ramachandran plot values of 92.1412, %92.98, and %99.793, respectively (Figure 4). Similarly, ERRAT, Verify3D, and Ramachandran plot values of the AlphaFold model were 93.7215, %91.31%, and %99.3, respectively. The Verify3D and Ramachandran plot values of the model generated in this study were better than the AlphaFold model. On the other hand, the AlphaFold model had a better ERRAT value. The SAVES evaluation implicated that the model built might have better quality than the AlphaFold model.

MD simulation study of the two models was performed to assure the quality of the structure built in relative to the AlphaFold model. RMSD (root mean square deviation) is used to evaluate the fluctuations of protein structures from reference structures in a simulation period [17]. In the first 40 ns simulation period, the two structures had high fluctuations. Thereafter, the structures attained stability and retained it till the end of the simulation period. The model built attained stability earlier. In addition to this, the model had lower RMSD value than the AlphaFold model that implied a better stability for it (Figure 5).

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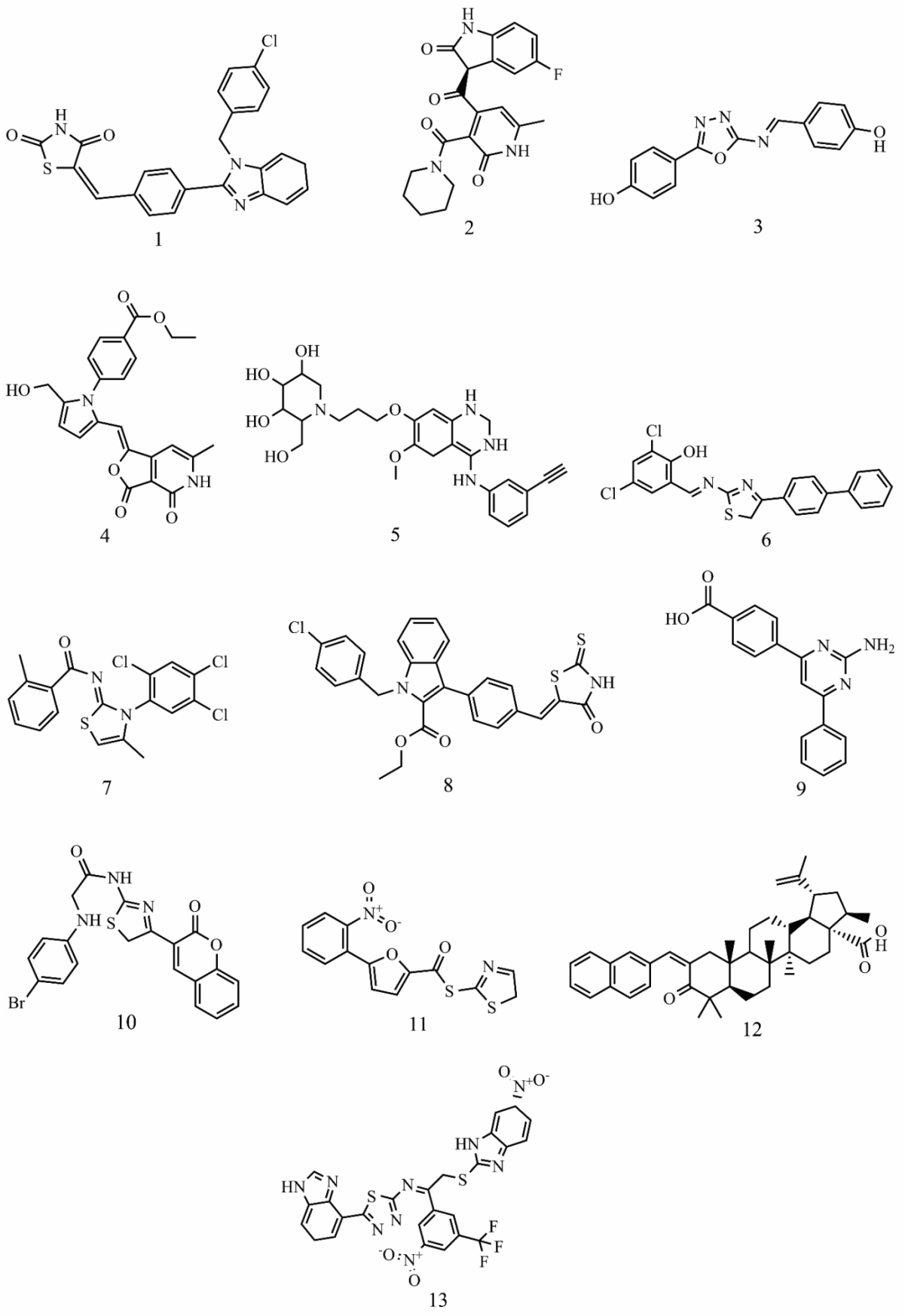

Figure 3. Reported active α-glucosidase inhibitor compounds

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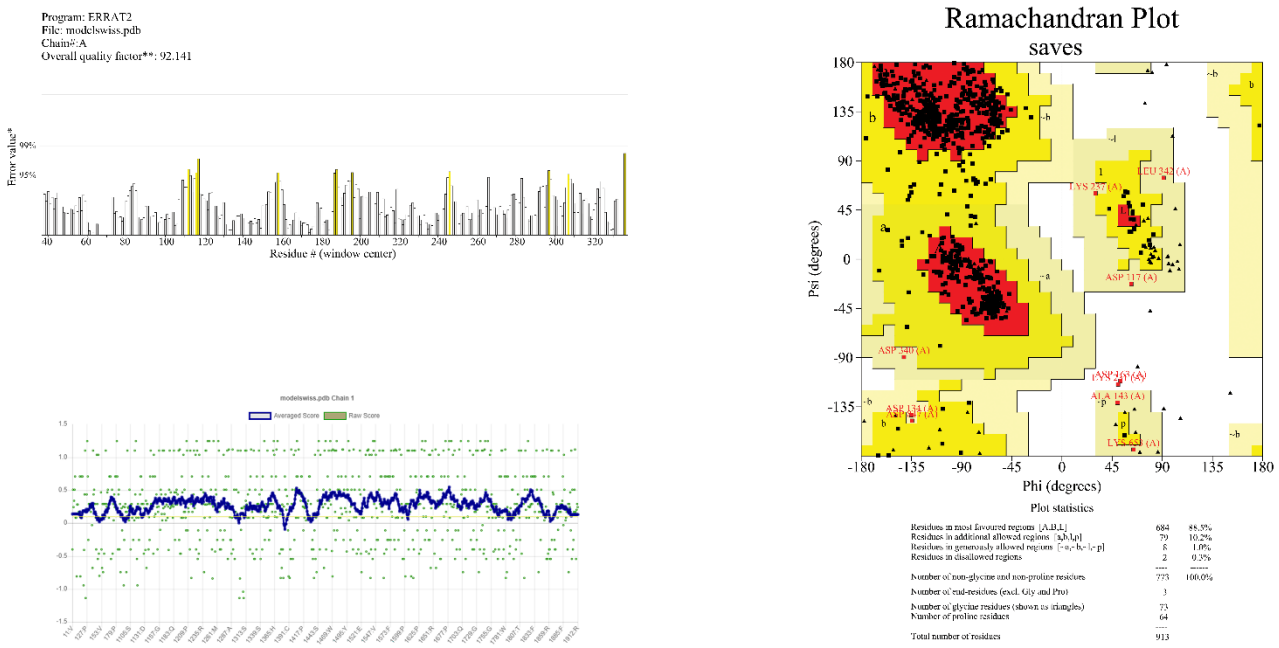


Figure 4. ERRAT, Verify3D, and Ramachandran plot value of the SAVES validation for the SWISS-MODEL

Rg (Radius of gyration) is used to evaluate compactness of a structure during the simulation period [18]. In the first 40 ns time interval, the generated model had higher compactness than the AlphaFold model. Thereafter, the AlphaFold model catched up the compactness of the built model (Figure 5). Therefore, the MD simulation study revealed that the SWISS-MODEL model generated had better stability than the AlphaFold model. Based on the SAVES and MD simulation evaluations, it is possible to infer that the model built has better qualities than the AlphaFold model. Hence, subsequent molecular docking and MD simulation studies were carried out by using the SWISS-MODEL model.

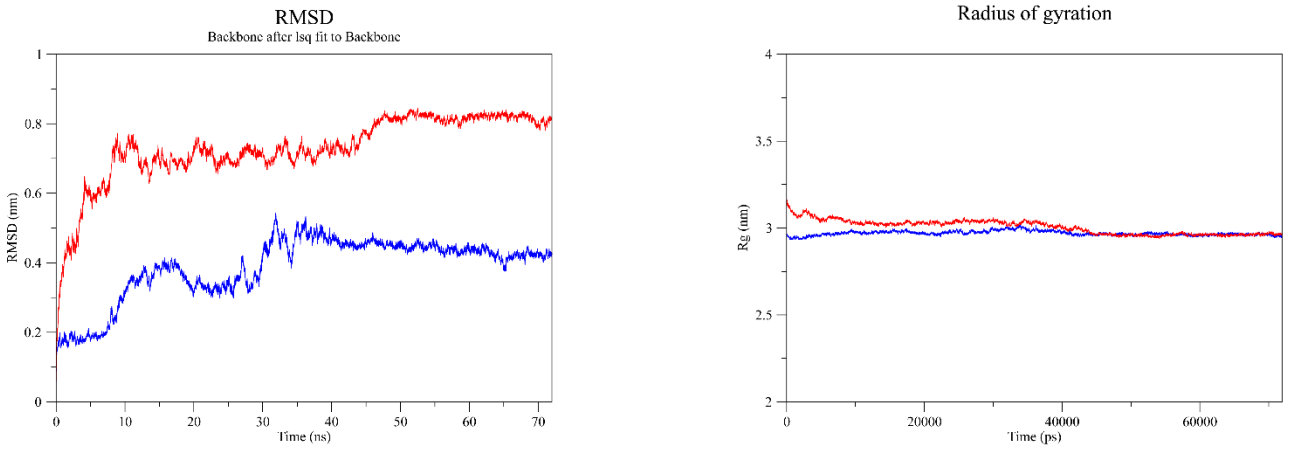
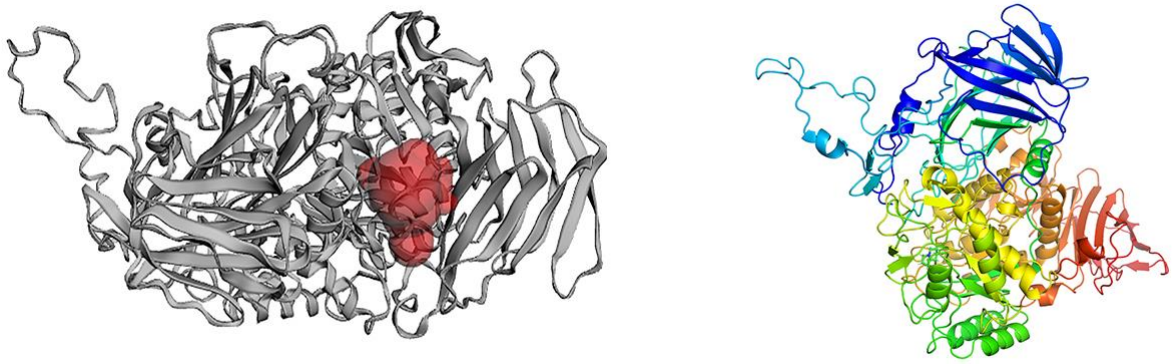


Figure 5. RMSD and Rg values of the two models (SWISS-MODEL model in blue, AlphaFold model in red)

The binding region of the model structure was predicted through CASTp 3.0 [19]. The grid box used in the molecular docking was specified in a manner that encompassed this region (Figure 6 A).



A B

Figure 6. Predicted binding region of the enzyme (A) and its 3D structure (B)

2.2. Molecular Docking

The interaction of the most active compounds against the generated model was investigated first. Prior to proceeding to docking of the active compounds with the selected model, the process was validated by docking the reference drug, acarbose, with the model. Acarbose interacted with the model very well through six conventional hydrogen bonds (Thr385(2), Arg518(2), Asp585, Arg610) (Table 1). This has implicated that the active compounds could also give a reliable interaction with the model.

Table 1. Interaction residues of the compounds with the model

Compounds	Binding Energy	Conventional Hydrogen Bonds	Other Interactions
1	-7.4	Thr385(2), Arg588	Val120(2)[a], Ala121[a], Arg377[a], Ala380(2)[a], Thr385[b], Ala387[a], Arg610[a]
2	-7.4	Tyr489, Asn514	Leu488[a], Lys491[a], Asn514[b], Gln561[c], His562[c], His562[d]
3	-6.9	Arg377, Ala380, Thr385	Val120[a], Ala380[d], Ala387[a], Arg610[a], His719[d]
4	-7.5	Arg100, Arg102(2), Arg114	Tyr113[a], Arg114(2)[a], Pro116[a], Leu119[a], Thr513[e], Trp566[d], Val571[a]
5	-7.6	Asp117, Leu119, Asp122	Pro116[f], Pro515[a], Tyr563[d]
6	-7.7	-	Pro108[a], Pro111[a], Tyr113[a], Arg114[a], Pro116[f], Pro515[a], Tyr563[a], Trp566[a], Val571[a]
7	-7.3	Arg727, Asp750	Phe710[a], Leu714[a], Ile723[a], Asp750[g], Ala751[a], Val810[a]
8	-7.6	Arg588, Gly592	Asp585[g], Arg588(2)[g], Arg610[a], Arg610[e], Phe852[d]
9	-7.0	Arg518(2)	Arg114[a], Pro116[a], Tyr563[d], Trp566[d], Trp566[e]
10	-7.8	Thr385 (2), His719, Arg720	Val120[a], Val120[f], Thr385[f], Arg610[e]
11	-6.5	Gln717, Arg727, Gln732	Gln717[e], Ile723[a], Ile723[f], Arg727[g], Asp750[g]
12	-8.8	Arg588, His719, Arg720	Met581(2)[h], Arg610(2)[g], Arg720[e]
13	-9.6	Arg112, Tyr113, Arg114(3), Thr513, Arg518, Tyr578	Arg114(2)[a], Pro116(3)[a], Asp117(2)[c], Thr513[c], Tyr563[d]
Acarbose	-7.1	Thr385(2), Arg518(2), Asp585, Arg610	-

[a]Alkyl/pi-alkyl, [b]pi-donor hydrogen bond, [c]halogen, [d]pi-pi, [e]carbon hydrogen bond, [f]pi-sigma, [g]pi-ion, [h]pi-sulfur

The most active compounds had good interactions with the human α-glucosidase. All the compounds except compound **6** formed at least two conventional hydrogen bonds with the enzyme. In addition to this, all of them interacted with at least three more other types of interactions (Figure S1, Figure 7, Table 1). The interaction residues for the compounds were concentrated mainly around similar sequences. Compounds **4** and **10** interacted with four conventional hydrogen bonds. Compound **13** had the highest number of conventional hydrogen bonds. The stability of model-compound complexes for the relatively highly

interacting compounds as well as compound **5**, which was one of the most effective in the *in vitro* assays and formed three conventional hydrogen bonds, was assessed through MD simulation.

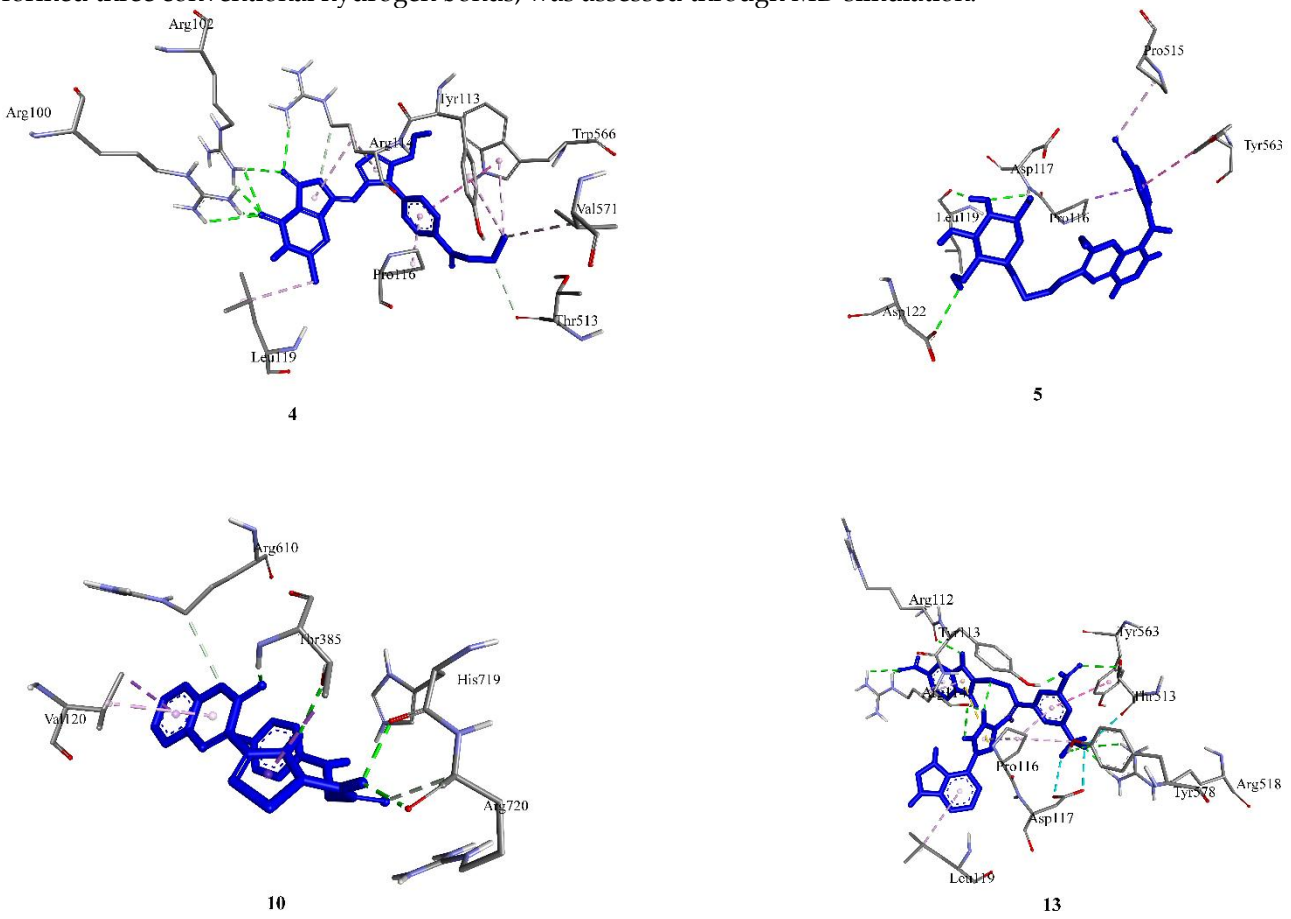


Figure 7. The 3D interaction of compounds with the generated model

In the literature, researchers have screened the effect of various novel compounds against α-glucosidase. In some of these researches, molecular docking of the compounds against homology model of the human α-glucosidase or its structure from other species was done. By doing molecular modeling, researchers endeavored to solve the structure-activity relationships of the compounds. In this regard, possible structure-activity relations of compound **3** was suggested through molecular docking. In that study, the inhibitory activity of the compound was correlated to its electron donating groups (OH) and electron availability in the phenyl ring moieties [20]. In this computational study, two of the hydrogen bonds were formed between an electron donating group of the compound and amino acid. In addition to this, most of the other interactions were formed with the phenyl ring and various amino acids (Figure S1). Therefore, the findings in this study were in line with the results reported earlier. In another study on the interaction of compound **4** with a homology modelled structure, four conventional hydrogen bonds were detected between the compound and the model [21]. Similarly, in this study four conventional hydrogen bonds were formed between compound **4** and the generated model. However, the interaction amino acid residues were different from each other as different templates were utilized in the homology modeling. In another study, binding potential of compound **6** to a homology model of α-glucosidase was analyzed. The interaction of compound **6** with the homolog structure was moderate [22]. In this study, compound **6** was the only compound that did not form conventional hydrogen bonding with the enzyme even if it had nine other types of interactions (Table 1). Hydrogen bonding is vital in the binding of a ligand to a target and keeping it inside the binding region. Therefore, the binding potential of compound **6** is expected to be moderate and thus it gave similar level of interaction to the previous study [22]. In a previous molecular docking study, interactions of amino acid residues of the enzyme with the oxygen of the carbonyl group and the hydrogen of the nitrogen at the bridge between the two aromatic rings was observed [23]. Similarly, in this study the two conventional hydrogen bonds were formed between the amino acids and the same atoms. Together with this, the rest interactions

were formed with the aromatic rings of the compound. In a molecular docking study of compound **8** to determine its binding potential with crystal structure of C-domain of α-glucosidase, it had three hydrogen bonds. This bonds were formed between the oxygen of the carboxyl group and oxygen of the group substituted to the indole ring and the amino acids of the enzyme [24]. In this study, two hydrogen bonds were detected. One of the hydrogen bonds was formed with the oxygen of the group substituted to the indole ring (Figure S1). In a previous computational study, compound **9** was found to have two hydrogen bond interactions with the oxygen of the carbonyl group and the proton of the hydroxyl group in the benzoic acid [25]. Similarly, in this study two hydrogen bonds were detected with the same oxygen and proton of the benzoic acid ring. The other interactions were formed with the aromatic and the heterocyclic rings. In another study, molecular docking study of compound **10** with crystal structure of an α-glucosidase was investigated. The interaction of compound **10** with the enzyme was achieved through a hydrogen bond and nine more other interactions [26]. In this study, four hydrogen bonds and four other interactions were detected. This was found to be a better interaction than the previous study that did not apply homology modeling. In a previous computational study, compound **11** had three hydrogen bonds. Similarly, in this study three conventional hydrogen bonds were observed. In addition to this, its interaction with the nitro group was found to be unique from other similar derivatives in the same study [27]. In this study, a hydrogen bond was formed with the nitro group that depicted the similarity between the two studies. In a previous molecular docking analysis, compound **12** had a single hydrogen bond and five interactions. The hydrogen bond was formed with its carboxyl moiety. In this study, three hydrogen bonds were detected [28]. One hydrogen bond was formed with the carboxyl moiety and the other with the proton next to it. Though the hydrogen bonding was observed in the same vicinity in the previous study, the number of hydrogen bonds in this study was higher that implicated a better interaction. In a previous computational study of the interaction of compound **13** to α-glucosidase from the PDB, it had four conventional hydrogen bonds and nine other interactions [29]. In this study, compound **13** had eight conventional hydrogen bonds and seven other interactions. Hence, stronger interaction of the compound with the homology model was achieved in relative to the interaction with the crystal structure.

2.3. Molecular Dynamics Simulation

The binding energy value, the number of conventional hydrogen bonds, and the *in vitro* potency level of the compounds were used as criteria to select the complexes for further MD simulation study. In this respect, the stability of the complexes formed with the binding of compounds **4**, **5**, **10**, and **13** to the built model was assessed through MD simulation. Compound **13** was selected as it gave the lowest binding energy and highest interaction though its IC_{50} value was 0.2 µM in the *in vitro* assay [29]. Compound **4** gave the highest number of interactions with the model next to **13**. The IC_{50} value for compound **4** was reported to be 0.56 µg/mL [21]. Compound **5** was selected as it was one of the compounds with the highest efficacy in the reported studies. The IC_{50} value for compound **5** was reported to be 0.09 µM in the wet-lab study [2]. Compound **10** had good interactions with the model in the docking and its IC_{50} value was found to be 0.14 µM [26]. After the MD simulation of the selected compounds was performed, the standard plots were drawn. The plots obtained were analyzed by comparing to the apo structure and with each other. As RMSD is used to evaluate the fluctuations of a structure in relative to reference structures during simulation, the RMSD plots of the compounds with the highest binding potential to the model was drawn [30]. In the first 40 ns, the apo structure had high changes but the structure was stabilized afterwards. The complex containing compound **4** had relatively stable trend in the first 50 ns interval but then its stability has decreased. Similarly, the complex containing compound **5** had relatively stable trend in the first 50 ns interval but then its stability has decreased. The complexes that contain compounds **10** and **13** had less stability than the other ligand bearing complexes and the apo structure. Among the ligand bearing complexes, compound **5** had relatively higher stability as the fluctuation of compound **4** complex was steeper after 50 ns interval (Figure 8). It is also important to note that all the investigated complexes depicted variations during the simulation period.

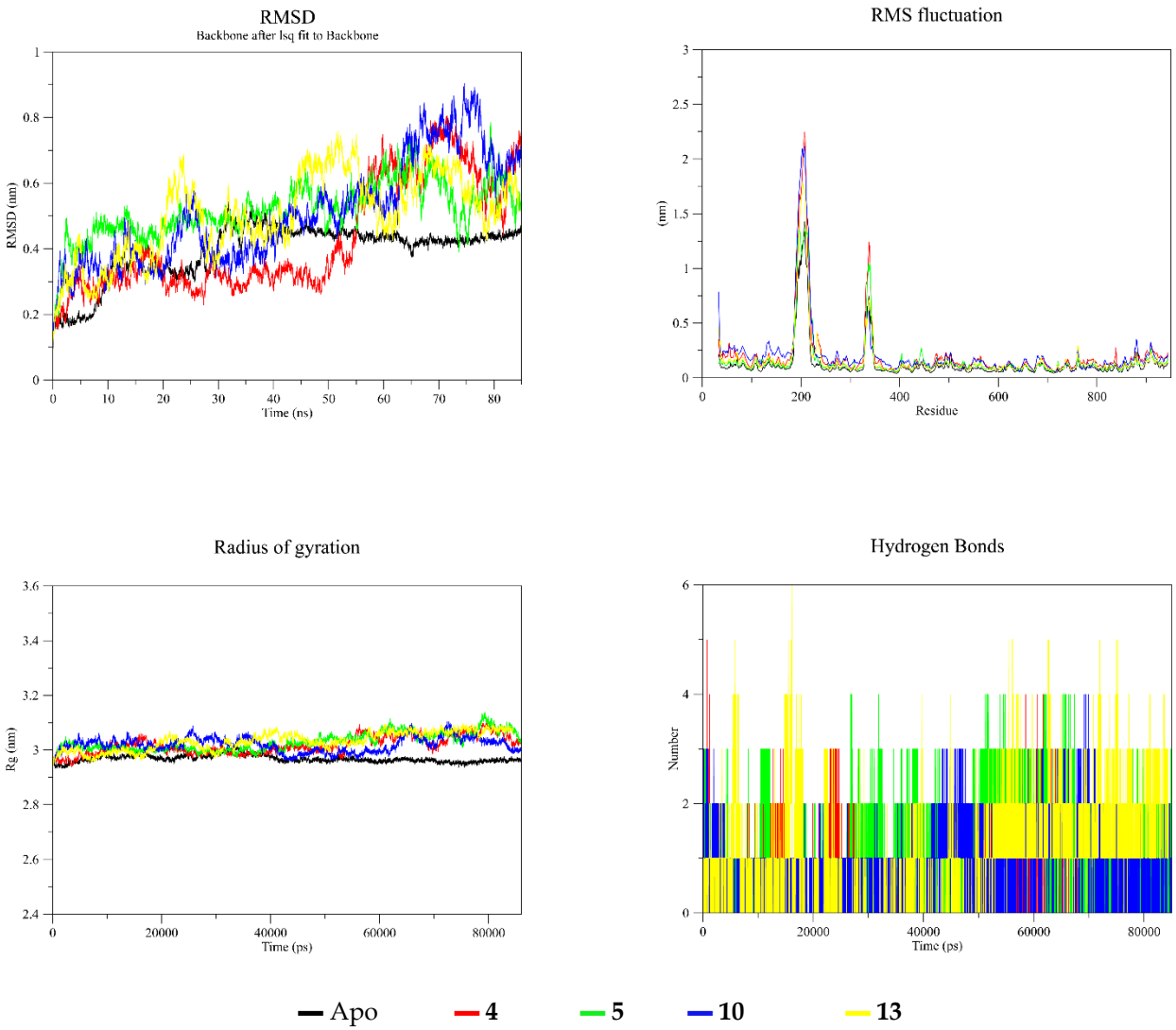


Figure 8. RMSD, RMSF, Rg, and ligand hydrogen bond plots of the compounds with the highest potential binding to the model generated obtained from the MD simulation

The RMSF plots of the compound containing complexes and the apo structure were drawn to evaluate changes in the model structure amino acid residues [31]. All the complexes and the apo structure depicted a similar trend of RMSF plots. There was a significant fluctuation that went up to 2.25 nm in 183-219 residue intervals. Similarly, a significant fluctuation that rose up to 1.24 nm was observed in 327-348 residue intervals (Figure 8). Rg plots of the compound bearing complexes and the apo enzyme were drawn to figure out the effect of the bound compounds on the overall secondary structure of the model [18]. The general Rg plots of the structures were similar with each other in the first half of the simulation but in the next half the apo enzyme had the highest compactness. The complex containing compound **10** had relatively the least compactness up to the first 37 ns and thereafter the complex containing compound **13** had the least compactness (Figure 8). The role of the intermolecular hydrogen bonding between the build structure and the compounds was investigated by drawing ligand hydrogen bonds during the simulation period [18]. Compound **4** formed single hydrogen bond intercalated with two hydrogen bonds and a sparse three hydrogen bonds. Compound **5** formed predominantly single and two hydrogen bonds intercalated with three hydrogen bonds and a highly sparse four hydrogen bonds. Compound **10** formed in general single hydrogen bonds. In some intervals, two hydrogen bonds intercalated with three hydrogen bonds were also observed. Compound **13** formed single and two hydrogen bonds generally. In addition to this, lesser number of three hydrogen bonds intercalated with four hydrogen bonds were observed in some intervals (Figure 8). The number of hydrogen bonds detected in the MD simulation was less than the number detected through molecular docking. In short, the MD simulation study revealed that some of the investigated model-compound complexes, for example **5**,

exhibited moderate level of stability but some others were expected to be unstable. The unbound model also found to be unstable in some time intervals.

2.4. Computational Pharmacokinetic Prediction

The *in silico* ADMET prediction demonstrated that the α-glucosidase inhibitors had good pharmacokinetic properties with some exceptions. PSA-2D values of all the compounds except compounds **4**, **5**, and **13** were predicted to be below one hundred (Table 2). This implies that most of the active compounds would have good oral absorption or membrane permeability [32]. More than half of the active compounds had AlogP98 values below five that implied an ideal lipophilic property (**2**, **3**, **4**, **5**, **9**, **10**, **11**) [33]. Compound **12** had high AlogP value that implied a non-ideal lipophilic property for it. The other active compounds resulted in AlogP values within an acceptable range as they had a value near to five (Table 2). In short, PSA-2D and AlogP value analysis implied good cell permeability for most of the compounds with some exceptions (Figure 9) [34].

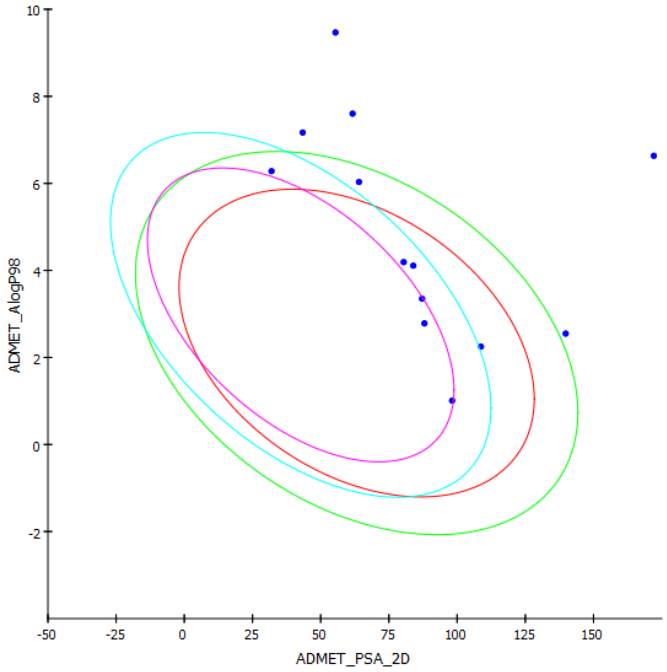


Figure 9. Prediction of the absorption properties through Discovery Studio (absorption 95 in red, absorption 99 in green, BBB 95 in purple, BBB99 in sky blue)

The active compounds ability to cross the BBB was also assessed. The prediction demonstrated that compound **7** might have the highest probability to cross the BBB. The barrier might be permeant to compounds **9**, **10**, and **11** at moderate level. On the other hand, the barrier might be less permeant to the rest compounds (Table 2). Compounds **3** and **11** might be mutagenic according to the Ames mutagenicity prediction. Therefore, the necessary care should be taken in dealing with these compounds. Obeying to Lipinski's rule of five (RO5) manifests drug-likeness of compounds. All the active compounds except compounds **12** and **13** had drug-like properties according to the estimation made (Table 2). Compounds **12** and **13** violated the RO5 as they violated two of its rules. Therefore, all of the investigated active compounds except compounds **12** and **13** are anticipated to exhibit good absorption or permeability to be utilized as oral administrable α-glucosidase inhibitor drugs [35].

Table 2. ADMET Properties of the most active compounds

Molecule	AlogP98	PSA_2D	BBB Level	Bioavailability Score	RO5 Violation	Ames Prediction
1	6.031	64.021	4	0.55	0	Non-mutagen
2	1.007	98.176	3	0.55	0	Non-mutagen
3	2.783	88.03	3	0.55	0	Mutagen
4	2.248	108.736	4	0.55	0	Non-mutagen
5	2.548	139.806	4	0.55	0	Non-mutagen
6	7.168	43.399	4	0.55	0	Non-mutagen
7	6.28	31.976	0	0.55	1	Non-mutagen
8	7.602	61.69	4	0.55	1	Non-mutagen
9	3.349	87.178	2	0.55	0	Non-mutagen
10	4.19	80.413	2	0.55	0	Non-mutagen
11	4.109	83.939	2	0.55	0	Mutagen
12	9.467	55.417	4	0.85	2	Non-mutagen
13	6.634	172.123	4	0.17	2	Non-mutagen

3. CONCLUSION

In this study, comprehensive computational study for synthetic α-glucosidase inhibitors was conducted. First, the structure of human α-glucosidase was generated through homology modeling. A relatively reliable structure, among the models built, was chosen for further computational studies. Thereafter, molecular docking of all the selected compounds to the generated model and MD simulation of target-compound complexes with the highest binding potential to the human α-glucosidase was performed. The study showed that some of the compounds have high binding potential to the enzyme. However, the stability of the complexes obtained from the docking was not high. Among these compounds, compound **5** gave a complex with relatively high stability. The computational pharmacokinetic study revealed that all of the compounds with the exception of compounds **12** and **13** are expected to have good absorption or permeability for oral administration.

4. MATERIAL AND METHODS

4.1. Homology Modeling

The 3D structure of human α-glucosidase hasn't been determined and put into the protein data bank (PDB) yet. Therefore, its 3D structure was generated through homology modeling. The enzyme's amino acid sequence was obtained from UniProt (accession number: Q14697) [36]. The structure of the enzyme, which was generated through AlphaFold, was deposited into the UniProt [37]. More structures were generated through I-TASSER and SWISS-MODEL [38,39]. The quality of these structures was evaluated through the SAVES server [40]. The best structure among the I-TASSER and SWISS-MODEL generated ones was determined based on validation values. The best structure was then compared to the AlphaFold structure. Furthermore, the best model and AlphaFold model were subjected to MD simulation. The two structures were compared based on their RMSD and Rg values to assess their stability and compactness. In the final step, the structure to be used in further studies was selected by using the results obtained from the SAVES server and MD simulation.

4.2. Molecular Docking

Molecular docking of the α-glucosidase inhibitors was done on the homology model built. The binding site was predicted through CASPp 3.0 [19]. The center of binding for the docking was determined based on this result. The x, y, and z coordinates of the grid box utilized in the docking were -1.504, 50.300, and 72.988, respectively. The grid box has size of 25Å*25Å*25Å. The compounds were drawn through ChemDraw. Then,

the enzyme model generated and the compounds were made ready for the docking. The docking was performed with AutoDock Vina as described in previous studies [41,42].

4.3. MD Simulation

MD simulation of the compounds with the highest binding potential to α-glucosidase structure generated was performed by using the complexes obtained from the docking. The topology of the compounds was generated via CGenFF server. The topology of the model was generated by using the appropriate GROMACS (GROningen MAchine for Chemical Simulations) commands. The model-compound complexes and the model were put into a tricyclic box and solvated with TIP3P water. Thereafter, the system charge was neutralized with ions from NaCl salt. Then, energy minimization was undertaken through the steepest descent method for 50.000 steps. Next, system equilibration was undertaken by constant-volume ensemble (NVT)/constant-pressure ensemble (NPT) at a pressure of 100 kPa and temperature of 300 K. MD simulation was then run after the system requirements were ready. In the last step, RMSD, root mean square fluctuation (RMSF), Rg, and ligand hydrogen bond plots were drawn through qtgrace and analyzed accordingly [43].

4.4. Computational Pharmacokinetic Study

ADMET (absorption, distribution, metabolism, elimination, toxicity) properties of the α-glucosidase inhibitors were predicted with Accelrys Discovery Studio 3.5 and SwissADME server [44,45]. Then, estimation results were analyzed. The α-glucosidase inhibitors were evaluated by using AlogP98 (atomic logarithmic partition coefficient), PSA-2D (polar surface area-2 dimensional), blood-brain barrier (BBB) permeability, drug-likeness, and Ames toxicity [46].

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