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In search of new potent α-glucosidase inhibitors: molecular docking and ADMET prediction

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Abstract

Diabetes mellitus has become one of the most problematic diseases in the world. Thus, the identification of new drugs for diabetes mellitus is an important requirement. In this study, we have selected a dataset of twelve 1,2,3-triazole derivatives previously synthetized by Gonzaga et al and has been studied for α-glucosidase inhibitory activity. The twelve selected molecules were undergone to molecular docking simulation and *in silico* ADMET prediction. Molecular docking outcomes demonstrated that all 1,2,3-triazole derivatives interacted well in the active pocket of α-glucosidase receptor (PDB: 5NN8). Most of the 12 triazole derivatives exhibited a conventional hydrogen bond interaction with amino acid residue Ser924 and/or pi-alkyl interaction with amino acid residue Val 923 and also formed a carbon hydrogen bond interaction with amino acid residue Asn925. Docking outcomes revealed that the molecules N° **1**, **3**, **6** and **10** have more types and number of interactions and exhibited high binding energy value, thus, they have high stability in the active pocket of 5NN8 receptor. Moreover, the 12 studied molecules and Miglitol, used as reference drug, were further subjected to *in silico* ADMET prediction. The results showed that the triazole derivatives: **M1**, **M3**, **M6** and **M10** have high absorption, permeation, good metabolism, found to be no toxic and they were in excellent accordance with the most important rules of drug likeness e.g. Lipinski, Ghose, Viber, Egan and Muegge compared to Miglitol. These findings suggest that the triazole derivatives **M1**, **M3**, **M6** and **M10** can be adopted as potential new candidates for the treatment of diabetes mellitus.

Keywords: *α-Glucosidase, Triazole, Molecular docking, ADMET, Drug discovery*

1. Introduction

Diabetes mellitus is the most frequent disease as far as metabolic disorder is concerned [1-3]. In 2010, the number of diabetes cases was 210 million and this number could increase to 300 million by 2025 [4]. There are two main types of diabetes, type-1 and type-2. Type-2 diabetes is also called non-insulin dependent diabetes or juvenile diabetes. In this case, the body does not produce insulin or insufficient quantities [5]. This type of diabetes represents approximately 90% to 95% of all diagnosed cases of diabetes [6]. Most patients with type-2 diabetes develop postprandial hyperglycemia for the main reason that α-glucosidase hydrolyzes carbohydrates in the small intestine [7]. Hence, α-glucosidase inhibitors may have a beneficial influence on the cure of diabetes mellitus [8,9] . The 1,2,3-triazoles are nitrogen-containing heterocyclic scaffolds, readily form hydrogen bonds that can increase solubility and promote binding of biomolecular targets [10]. They are showed significant importance in different fields like organic synthesis, medicinal chemistry and chemical biology [11]. Because of their unique properties, 1,2,3-triazoles are very interesting basic scaffolds in the field of drug discovery and development. 1,2,3-triazoles have been screened for important biological activities including anti-inflammatory [12,13], antifungal [14,15], anti-HIV [16] and α-glycosidase inhibition [17,18]. Molecular docking analysis is a modern technique widespread employed in medicinal chemistry in order to gain a deeper insight into the kinds and modes of interactions between a macromolecule called receptor and a small molecule called ligand [19-22]. Its application has grown in popularity throughout time, and it is now one of the most extensively utilized methods for the discovery and progress of biologically active entities. The rationale behind it is to minimize a simplified potential energy function which measures the interaction between a ligand and a target macromolecule [23-30]. The present work aimed to explore the interactions between the twelve 1,2,3-triazole derivatives and α-glucosidase receptor using molecular docking followed by ADMET (absorption, distribution, metabolism, excretion, toxicity) studies to identify their bioavailability and toxicity. Hence, select the candidate molecules that could be potent medicines for diabetes mellitus disease.

2. Material and methods

2.1. Data set

In this study, twelve 1,2,3-triazole derivatives were taken from literature (Figure 1 and Table 1) [31], these molecules were synthetized by Gonzaga et al from simple substrates and methods . The computational techniques including molecular docking and *in silico* ADMET investigations were applied on the 12 triazole molecules.

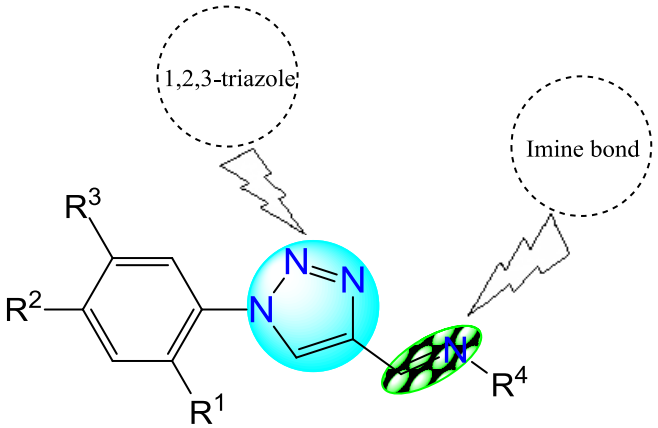

Figure 1. General chemical structure for 1,2,3-triazole derivatives with different R groups.

Table 1. Chemical structures of the twelve 1,2,3-triazole derivatives.

Compound N°	R^1	R^2	R^3	R^4
1	H	H	H	NH-C_6H_5
2	H	H	H	NH-3,5-Cl-C_6H_3
3	H	H	H	NH-4-F-C_6H_4
4	H	H	H	NH-4-Cl-C_6H_4
5	H	H	H	NH-4-Br-C_6H_4
6	H	H	H	NH-3,5-CH_3-C_6H_3
7	H	H	H	NH-2,4-NO_2-C_6H_3
8	H	H	H	CO-4-pyridyl
9	H	Cl	H	NH-C_6H5
10	H	Cl	H	NH-4-Br-C_6H_4
11	H	H	H	OH
12	H	Cl	H	OH

2.2. Ligand preparation

In this work, all chemical structures of 1,2,3-triazole derivatives studied were sketched with the sketch module in SYBYL and minimized by applying the Tripos force field [32] with the Gasteiger-Huckel charges [33]. Minimization of structural energy was effectuated by using Powell gradient algorithm with a convergence criterion of 0.005kcal/mol [34].

2.3. Molecular docking study

In recent years, molecular docking analysis has received a lot of attention from many researchers in molecular modeling field because it gives a deeper insight into the binding modes and guesses the interactions between a small molecule called ligand and a macromolecule called receptor [35-38]. In this paper, surflex-dock available in Sybyl software was applied to investigate the ligand-receptor interaction. Before starting the molecular docking analysis, the X-ray crystallized complex of α-glucosidase (PDB: 5NN8) was extracted from Protein Data Bank (www.rcsb.org). Then, briefly followed the structure preparation step implemented in Discovery Studio 2016 program [39] by deleting water molecules and adding polar hydrogen atoms. Therefore, once the preparation of the protein is completed, we put into practice a molecular docking of 12 1,2,3-triazole molecules in the binding pocket of α-glucosidase receptor. Following that, the reached outcomes were examined using PyMol [40] and Discovery Studio 2016 [39] programs.

2.4. ADME and toxicity prediction

As mentioned earlier, molecular docking is a very important approach used to better understand the binding mode between the ligand and the protein, thus, determine the molecule that has the best interactions with receptor. Indeed, the candidate molecule can has a high stability in the binding pocket of receptor, but can has many issues e.g. absorption, permeation and toxicity. In view of the foregoing, ADMET study is considered a crucial phase in drugs development. As a result, we determined the pharmacokinetics properties of the twelve selected molecules and the reference medication (Miglitol) to known whether molecules have good or bad ADMET parameters on one hand and on other hand to make a comparison between them to select the best molecule that can be a candidate drug for diabetes

mellitus disease. The prediction of ADMET parameters was carried out by using pkCSM [41] and SwissADME [42] online servers.

3. Results and discussion

3.1. Molecular docking results

The twelve 1,2,3-triazole derivatives were molecularly docked with the X-ray crystallized complex of α-glucosidase receptor (PDB: 5NN8) using surflex-dock to acquire a deeper insight into the binding modes and scrutinize the types of interactions between these molecules and the receptor. Table 2 demonstrated the total scoring, binding energy and inhibition constant of the twelve 1,2,3-triazole molecules obtained through molecular docking analysis. Docking findings of the twelve triazole molecules with α-glucosidase receptor are illustrated in Figures 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13. From the findings of Table 2, we noted that the triazole derivatives N° **1**, **3**, **6** and **10** have good values of total scoring and binding energy, especially the compound **M10**. These preliminary outcomes could explain the good stability of these molecules in the active site of 5NN8 receptor. On the other hand, the inhibition constant (Ki) of a drug is defined as the concentration required reducing the activity of the cytochrome P450 (CYP) enzyme by half to cause its inhibition. Indeed, the smaller the Ki value the better the effectiveness of the medication. Findings of Table 2 indicate that the compounds **M3** and **M10** have smaller value of inhibition constant indicating the goof efficiency of these molecules. Thus, in the rest of the docking analysis will focus only on molecules N° **M1**, **M3**, **M6** and **M10**. The structures of the compounds that have the best total scoring and binding energy in the binding site of α-glucosidase receptor hint that the present of the phenyl group or phenyl with halogens atoms as F, Cl and Br in the structure give high stability to these molecules at the active site of 5NN8 receptor. The interaction findings of compound **M1** and 5NN8 receptor (Figure 2), present conventional hydrogen bond with Ser924 residue, pi-cation with Val939 residue, carbon hydrogen bond and pi-donor hydrogen bond with Ser918 and Asn925 residues, respectively and pi-alkyl interactions with Lys903, Val923, 939 residues. Docking study of molecule **M3** in the α-glucosidase 5NN8 (Figure 4), exhibits conventional hydrogen bond with Ser918, 924 residues, carbon hydrogen bond with Gln902 residue, pi-cation with Val939 residue, pi-sigma with Lys903 residue, pi-alky with val923 and Lys903 residues. Continuously, docking result of compound **M6** and 5NN8 receptor (Figure 7) shows conventional hydrogen bond with Gly908 residue, pi-sigma with Lys 933 residue, pi-alkyl with Ala797, Ala910, Lys933, Lys849 residues, and carbon hydrogen bond with Gly908 residue. In a similar vein, the molecule **M10** which has the best value of binding energy provides more types and number of interactions with α-glucosidase receptor like conventional hydrogen bond, carbon hydrogen bond, pi-cation, alkyl and pi-alkyl. The attendance of hydrogen bonding interactions could give to the molecule **M10** a pharmacological importance because hydrogen bonding plays a crucial role in ligand pharmacology.

Table 2. Total scoring, binding energy and inhibition constant results obtained during molecular docking of the 12 triazole derivatives.

N°	Total Scoring	Binding Energy (kcal/mol)	Inhibition constant (µM)	N°	Total Scoring	Binding Energy (kcal/mol)	Inhibition constant (µM)
1	**2.897**	**-7.238**	**4.882**	**7**	1.984	-6.904	8.584
2	2.183	-7.092	6.248	**8**	2.500	-7.053	6.673
3	**3.053**	**-7.550**	**2.881**	**9**	2.536	-7.181	5.375
4	1.817	-6.660	12.964	**10**	**3.739**	**-7.850**	**1.735**
5	1.667	-6.832	9.695	**11**	2.060	-6.976	7.601
6	**2.736**	**-7.233**	**4.923**	**12**	2.609	-7.062	6.573

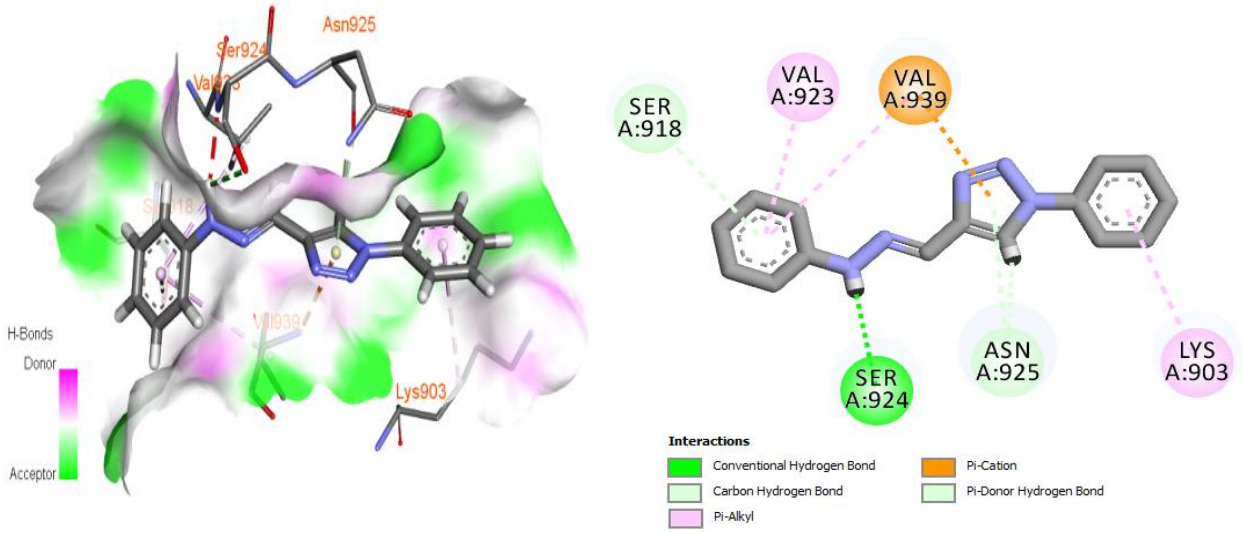

Figure 2. Docking finding of molecule N° **1** and the α-glucosidase receptor.

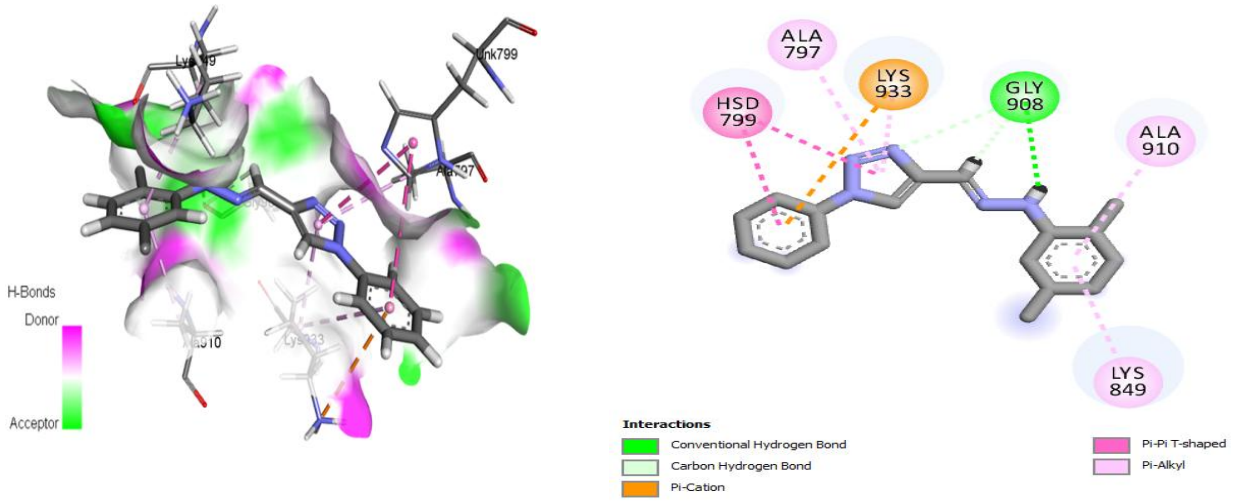

Figure 3. Docking finding of molecule N° **2** and the α-glucosidase receptor.

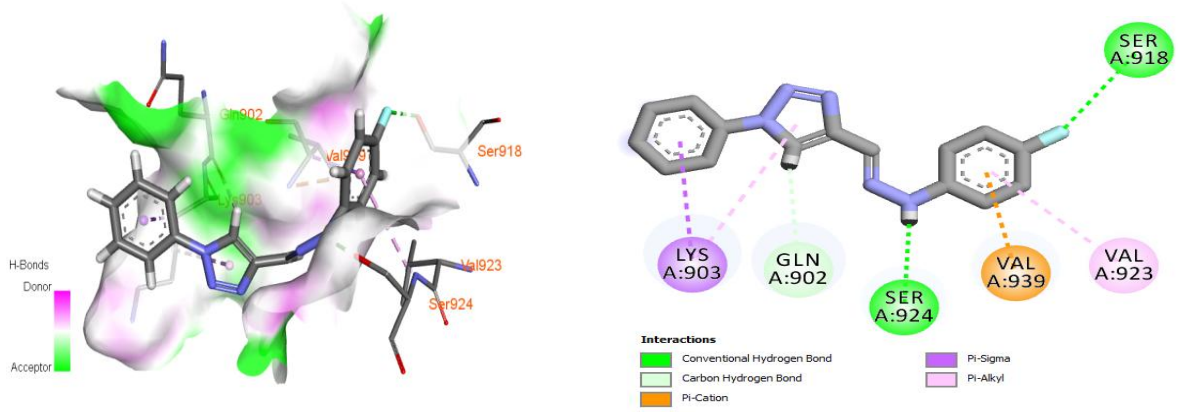

Figure 4. Docking finding of molecule N° **3** and the α-glucosidase receptor.

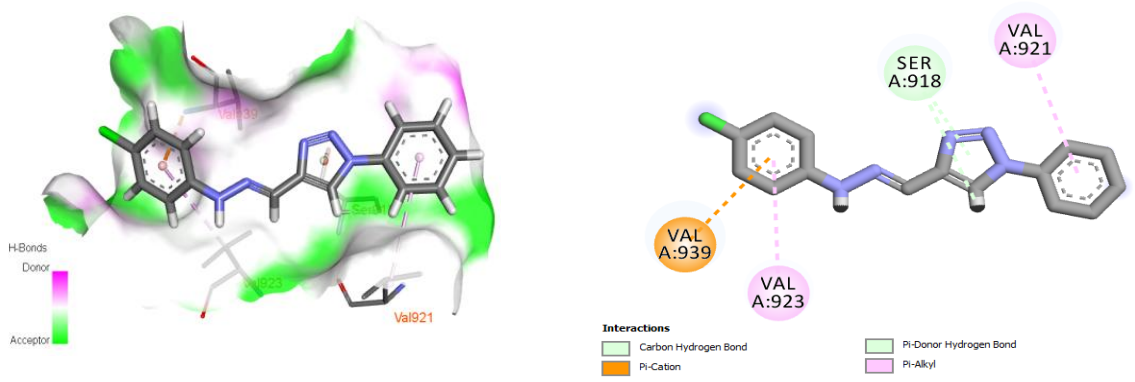

Figure 5. Docking finding of molecule N° **4** and the α-glucosidase receptor.

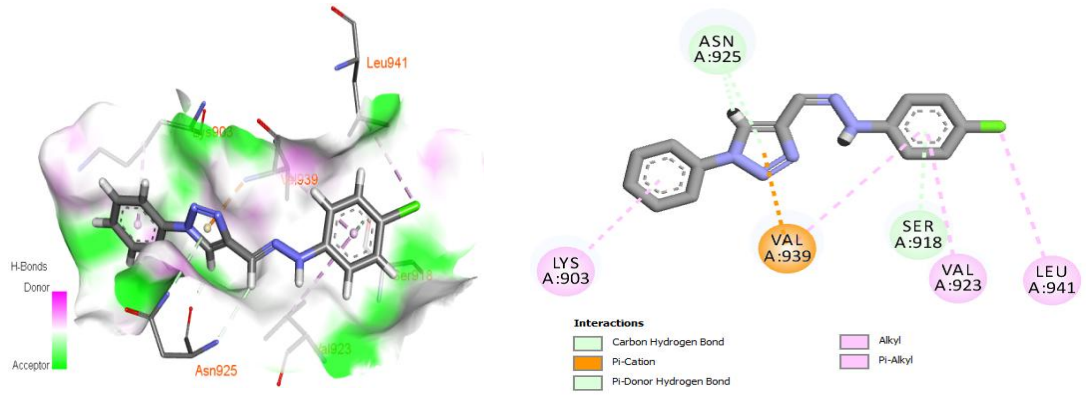

Figure 6. Docking finding of molecule N° **5** and the α-glucosidase receptor.

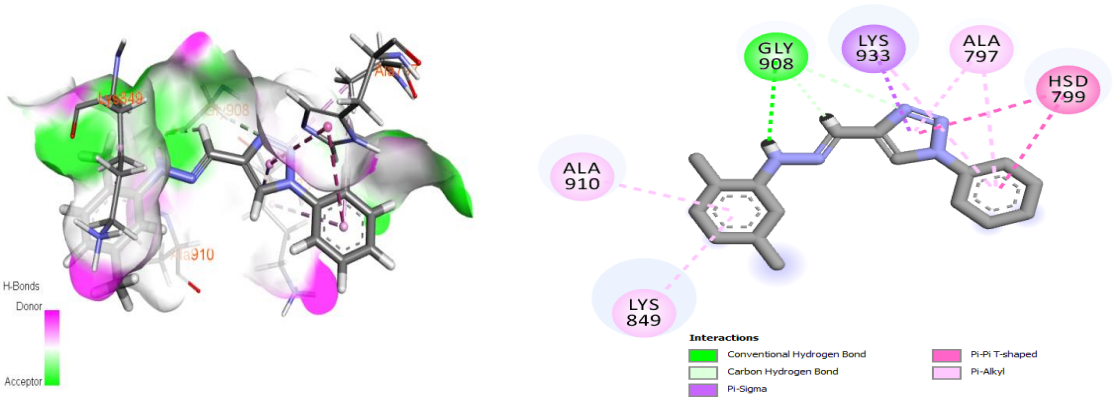

Figure 7. Docking finding of molecule N° **6** and the α-glucosidase receptor.

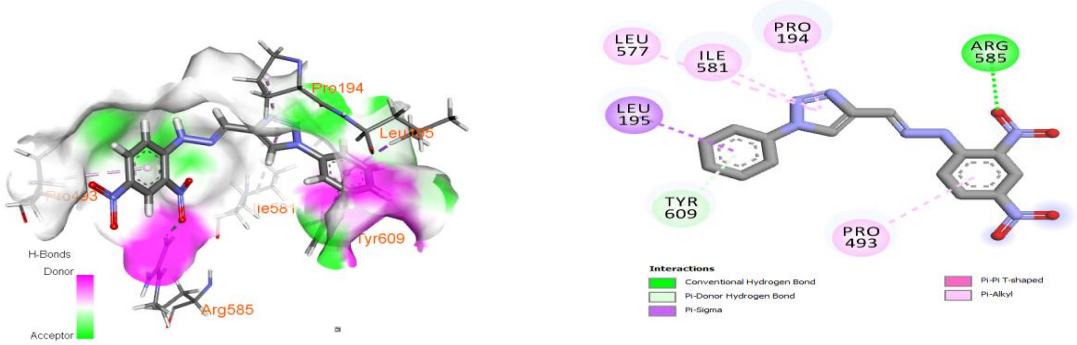

Figure 8. Docking finding of molecule N° **7** and the α-glucosidase receptor.

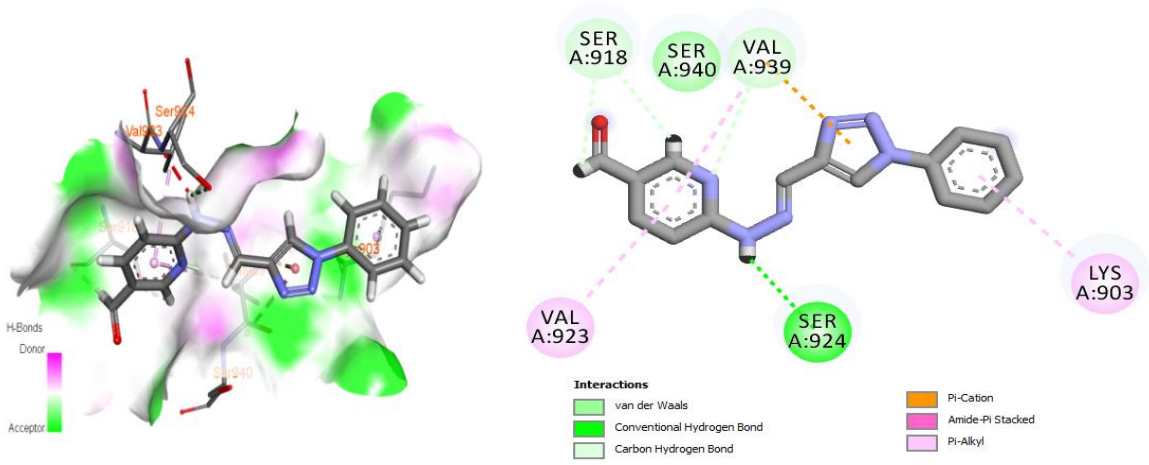

Figure 9. Docking finding of molecule N° **8** and the α-glucosidase receptor.

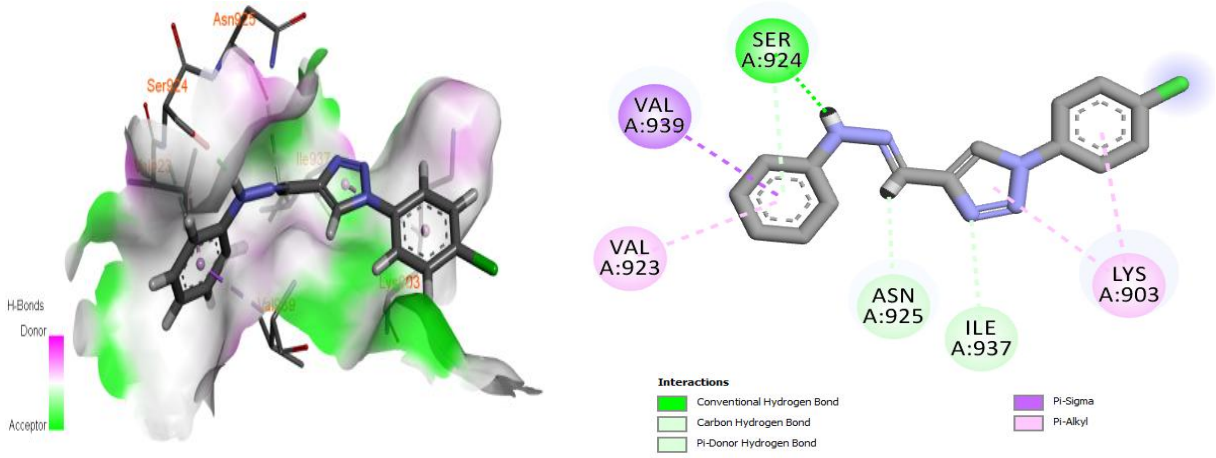

Figure 10. Docking finding of molecule N° **9** and the α-glucosidase receptor.

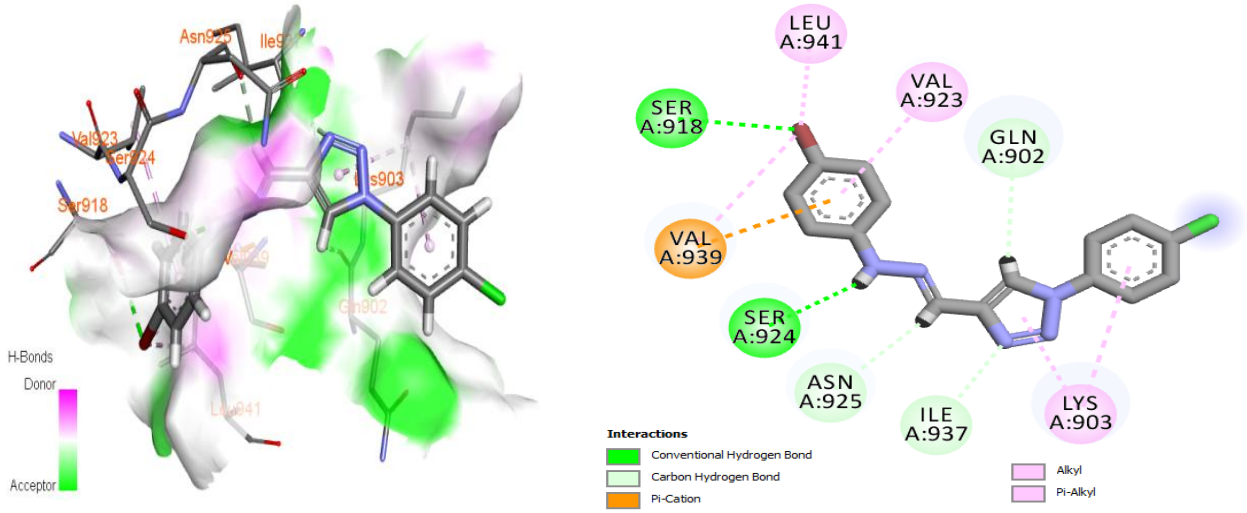

Figure 11. Docking finding of molecule N° **10** and the α-glucosidase receptor.

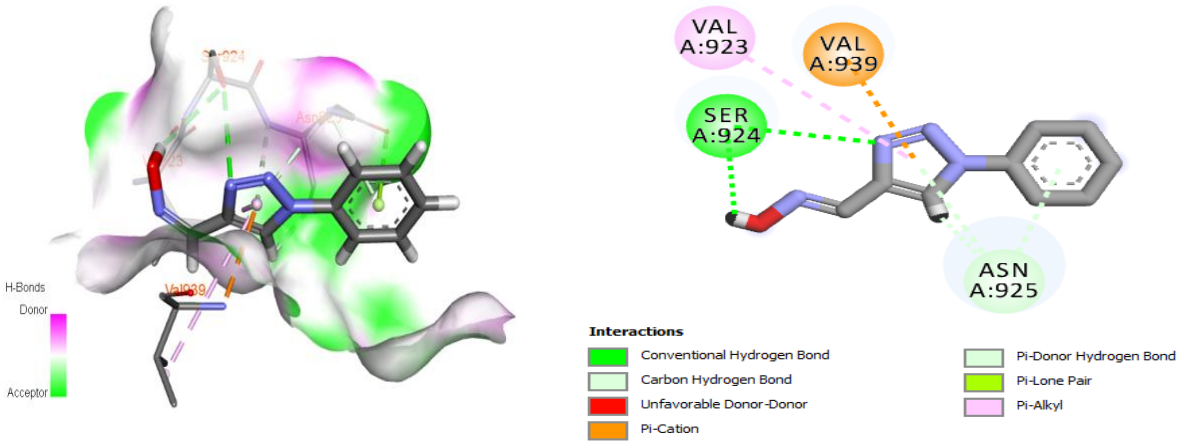

Figure 12. Docking finding of molecule N° **11** and the α-glucosidase receptor.

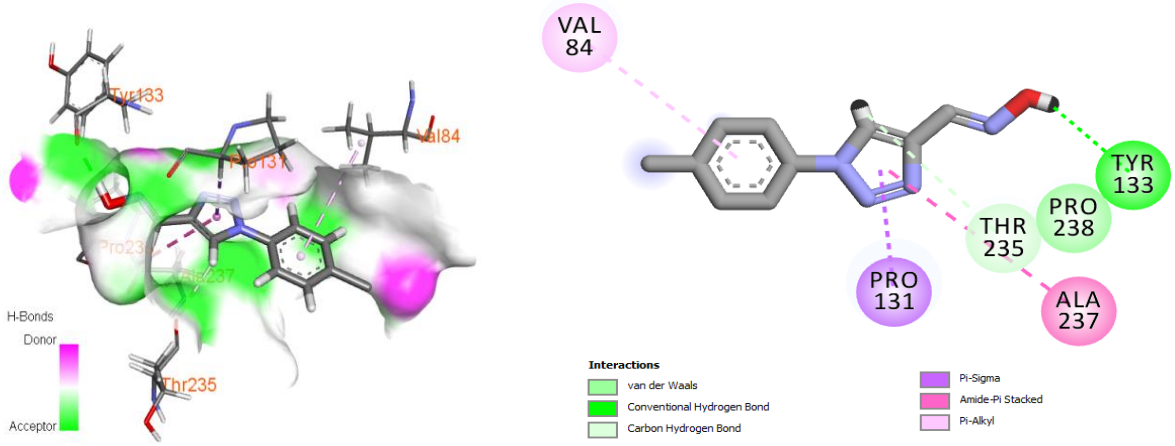

Figure 13. Docking finding of molecule N° **12** and the α-glucosidase receptor.

3.2. Drug-likeness and bioavailability

Drug-likeness is described as a complex equilibrium of numerous molecular properties and structural characteristics that identify whether a compound is a medication or not. Indeed, Lipinski's rule of five has held upper hand in this object which states that molecule with molecular weight (MW) < 500, logP < 5, hydrogen bond acceptor (HBA) number <10 and hydrogen bond (HBD) donor number < 5 have best oral absorption and permeation [43]. In this direction, we calculated numerous molecular properties of the 12 1,2,3-triazole derivatives by using pkCSM [41] and SwissADME [42] online servers to assess their drug-likeness, bioavailability and synthetic accessibility as clarified in Table 3. Results of MW, logP, HBA and HBD clearly evoked that all studied triazole molecules have good absorption and permeation (Table 3) compared to the reference drug (Miglitol) that has a negative logP value. Additionally, compound with total polar surface area (TPSA) not more than 140 $Å^2$ and number of rotatable bonds (nrotb) less than 10 reveals good bioavailability and happen more flexible for proficient interaction with a particular binding pocket [22]. From Table 3, all molecules have good bioavailability and more flexible at the binding site of the receptor, except the molecule N° **7** that has TPS over than 140 $Å^2$. Solubility deemed as an important molecular descriptor used for discovering of oral administrative drugs. Highly water solubility was advantageous for delivering sufficient quantity of active component in a small volume of such medicinal dose. These values were expressed by the decimal logarithm of the molar solubility in water (Log S). Results of Table 3 clearly stated that all triazole molecules, except

the molecule N° **7**, have good water solubility. High water solubility translates to high absorption and action. Furthermore, molecule with 250 ≤ MW (g/mol) ≤ 350, logP ≤ 3.5 and nrotb ≤ 7 considered as lead likeness. From the findings seem in the Table 3, it can be stated that the compounds N° **1**, **3** and **8** are lead likeness. On the other hand, the selected molecules have been subjected to drugs likeness rules. Findings of Table 4 expose that all studied triazole molecules (except the molecule N° **11**) were in excellent agreement with the most important rules of drug likeness as Lipinski, Ghose, Veber, Egan, and Muegge and they were exhibited a score of 55%; demonstrating good bioavailability. Therefore, these molecules have good drug likeness properties compared to the reference drug (Miglitol) that has violated rule of Ghose and Muegge.

Table 3. Prediction of molecular properties descriptors and lead likeness of the 12 triazole derivatives and Miglitol

N°	Property								
	Formula	MW	HBD	HBA	nrotb	LogP	TPSA	LogS	CSp^3	Lead-likeness
M1	$C_{15}H_{13}N_5$	263.30	1	5	4	2.71	55.10	-4.13	0.00	Yes
M2	$C_{15}H_{11}C_{l2}N_5$	332.19	1	5	4	4.02	55.10	-5.43	0.00	No
M3	$C_{15}H_{12}FN_5$	281.29	1	5	4	2.85	55.10	-4.24	0.00	Yes
M4	$C_{15}H_{12}ClN_5$	297.74	1	5	4	3.36	55.10	-4.79	0.00	No
M5	$C_{15}H_{12}BrN_5$	342.19	1	5	4	3.47	55.10	-4.85	0.00	No
M6	$C_{17}H_{17}N_5$	291.35	1	5	4	3.33	55.10	-4.89	0.12	No
M7	$C_{15}H_{11}N_7O_4$	353.29	1	9	6	2.52	146.74	-6.28	0.00	No
M8	$C_{15}H_{12}N_6O$	292.30	1	7	5	1.92	85.06	-3.43	0.00	Yes
M9	$C_{15}H_{12}ClN_5$	297.74	1	5	4	3.36	55.10	-4.79	0.00	No
M10	$C_{15}H_{11}BrClN_5$	376.64	1	5	4	4.12	55.10	-5.50	0.00	No
M11	$C_9H_8N_4O$	188.19	1	5	2	1.07	55.10	-2.33	0.00	No
M12	$C_9H_7ClN_4O$	222.63	1	5	2	1.72	55.10	-2.99	0.00	No
Miglitol	$C_8H_{17}NO_5$	207.22	5	6	3	-3.26	104.39	0.92	1.00	No

Table 4. Drug-likeness and bioavailability of the 12 studied molecules and reference drug

Compound	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
M1	Yes	Yes	Yes	Yes	Yes	0.55
M2	Yes	Yes	Yes	Yes	Yes	0.55
M3	Yes	Yes	Yes	Yes	Yes	0.55
M4	Yes	Yes	Yes	Yes	Yes	0.55
M5	Yes	Yes	Yes	Yes	Yes	0.55
M6	Yes	Yes	Yes	Yes	Yes	0.55
M7	Yes	Yes	Yes	Yes	Yes	0.55
M8	Yes	Yes	Yes	Yes	Yes	0.55
M9	Yes	Yes	Yes	Yes	Yes	0.55
M10	Yes	Yes	Yes	Yes	Yes	0.55
M11	Yes	Yes	Yes	Yes	No	0.55
M12	Yes	Yes	Yes	Yes	Yes	0.55
Miglitol	Yes	No	Yes	Yes	No	0.55

3.3. ADME and toxicity evaluation of the 12 triazole derivatives

The biggest challenge facing the researchers in drug discovery field is to find out new potent drugs without unwanted side effects e.g. absorption, metabolism, and toxicity. As a result, determining the ADMET properties of a given molecule became a topic of great significance. From this point of view and to avoid any pharmacokinetic issue related to the studied molecules, we examined the ADMET properties of the 12 triazole molecules using two famous online servers' pkCSM [41] and SwissADME [42]. We mentioned the reached findings in Table 5. The trip of a medication from the point of administration to the point of influence is named absorption [44]. In fact, a medication must be absorbed before any therapeutic benefits can occur, thus, absorption is a major emphasis in drug development and medicinal chemistry. Results of Table 6 demonstrate that all triazole molecules, except the molecule N° **7**, present high absorption compared to the reference medication (Miglitol). Along the same lines, the blood-brain barrier (BBB) may be defined as a supplementary boundary between circulating blood and the brain's extracellular space. In fact, a molecule with a logBB value more than 0.3 penetrates the BBB with ease [45]. From the outcomes seem in the Table 5, it can be stated that the distribution indices reported by the molecules N° **1**, **2**, **3**, **4**, **5**, **6**, **9** and **10** showed a better distribution capability than Miglitol. To predict brain penetration and gastrointestinal (GI) absorption of the twelve 1,2,3- triazole molecules and the reference medication (Miglitol), the boiled egg plot between TPSA and LogP was put into practice (Figure 14). From the plot, we can see that all studied molecules, except the molecules N° **7** and **8**, possess the BBB permeant (yellow region) but they are within the GI absorption region. The Miglitol, since it has a TPSA value of 104.39 and a negative log P value, is predicted as actively effluxed by P-gp substrates (PGP+). The CYP3A4 enzyme regarded as the most crucial of the CYP family of enzymes, metabolizing 50% of all medications by itself [46]. According to Table 5, all studied compounds inhibit CYP3A4 and are substrates of CYP3A4, except the molecules 11, 12 and the reference drug.

Table 5. Predicted ADME properties of the 12 studied molecule in comparison with the reference drug

N°	GI absorption	BBB permeant		P-gp inhibitor	CYP					CYP		Clearance
		Yes/ No	Numeric (Log BB)		1A2 Inhibitor	2C19	2C9	2D6	3A4	2D6 Substrate	3A4	
M1	High	Yes	0.426	No	Yes	Yes	Yes	No	No	No	Yes	0.180
M2	High	Yes	0.396	No	Yes	Yes	Yes	No	No	No	Yes	0.344
M3	High	Yes	0.376	No	Yes	Yes	No	No	No	No	Yes	0.275
M4	High	Yes	0.383	No	Yes	Yes	Yes	No	No	No	Yes	0.226
M5	High	Yes	0.381	No	Yes	Yes	Yes	No	No	No	Yes	0.205
M6	High	Yes	0.451	No	Yes	Yes	Yes	No	No	No	Yes	0.195
M7	Low	No	-1.45	Yes	Yes	Yes	Yes	No	No	No	Yes	0.157
M8	High	Yes	-0.903	No	Yes	No	No	No	No	No	Yes	0.570
M9	High	Yes	0.378	No	Yes	Yes	Yes	No	No	No	Yes	0.230
M10	High	Yes	0.330	No	Yes	Yes	Yes	No	No	No	Yes	0.075
M11	High	Yes	-0.245	No	Yes	No	No	No	No	No	No	0.217
M12	High	Yes	0.166	No	Yes	No	No	No	No	No	No	0.330
Miglitol	Low	No	-1.468	No	No	No	No	No	No	No	No	0.822

Table 5 clearly suggests that all molecules inhibit P-glycoprotein, with the exception of the compound N° **7**. Clearance is a parameter that defines the relationship between medication concentration in the human body and the degree of medication elimination [35]. Indeed, a lower value of the clearance index leads to a greater persistence of drugs in the body. The results appear in Table 5 showed that all studied molecules present lower value of the clearance index, especially the compound **M10** than the Miglitol. The studied 1,2,3-triazole molecules and the reference drug (Miglitol) were examined for their toxicity using four toxicological criteria namely mutagenicity, hepatotoxicity, skin sensitisation, and rat acute toxicity LD50 value. The mutagenicity criterion was assessed using Ames toxicity test to identify whether a molecule is mutagenic or not. This analysis was effectuated by using pkCSM online server and the results are clarified in Table 6. The compounds N° **1**, **2**, **3**, **4**, **5**, **6**, **8**, **9**, **10** and **12** were found to be no toxic unlike to Miglitol, respecting Ames criterion (Table 6). The all studied molecules and Miglitol are no-hepatotoxic, except the molecules N° **7** and **8**, as all compounds are poorly permeable to the skin. When comparing LD50 doses, a compound with a lower dose is more lethal than a compound with a higher LD50 dose. Results of Table 6 clearly hinted that compound **M10** that present good total scoring and has high stability in the binding pocket has higher LD50 dose than the reference medication.

Table 6. Toxicity prediction of the 12 studied compounds and reference drug

Compound	Ames toxicity test	Hepatotoxicity	Skin sensitisation	Oral Rat Acute Toxicity (LD50: mol/Kg)
M1	Non-toxic	Non-hepatotoxic	No	1.755
M2	Non-toxic	Non-hepatotoxic	No	2.085
M3	Non-toxic	Non-hepatotoxic	No	1.954
M4	Non-toxic	Non-hepatotoxic	No	1.924
M5	Non-toxic	Non-hepatotoxic	No	1.938
M6	Non-toxic	Non-hepatotoxic	No	1.862
M7	Yes-toxic	Yes-hepatotoxic	No	2.379
M8	Non-toxic	Yes-hepatotoxic	No	2.850
M9	Non-toxic	Non-hepatotoxic	No	1.922
M10	Non-toxic	Non-hepatotoxic	No	2.098
M11	Yes-toxic	Non-hepatotoxic	No	2.749
M12	Non-toxic	Non-hepatotoxic	No	2.766
Miglitol	Yes-toxic	Non-hepatotoxic	No	1.755

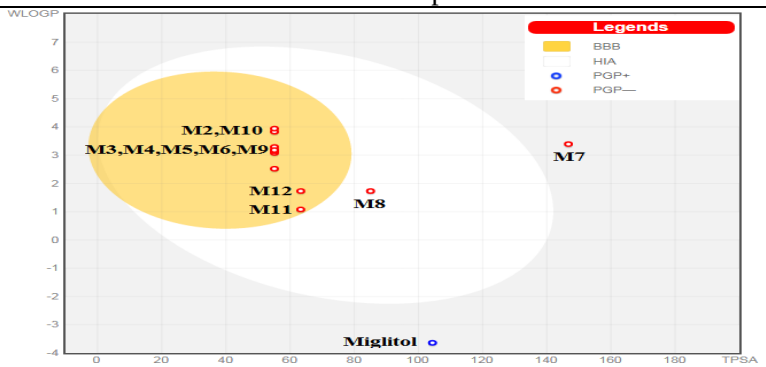

Figure 14. The Boiled-egg plot of the 12 studied molecules and reference drug.

4. Conclusion

In this paper, a set of twelve 1,2,3-triazole molecules was subjected to a molecular docking study to better understand the binding modes and explore the interactions between the α -glucosidase receptor (PDB: 5NN8) and these inhibitors. Outcomes of molecular docking revealed that the twelve studied molecules interacted well within active pocket of α-glucosidase receptor; the triazole compounds N° **1**, **3**, **6** and **10** demonstrated the high stability in its active site. These molecules also displayed good absorption, distribution, metabolism, have excellent pharmacokinetics properties and they are no toxic compared to the Miglitol. Extensive in vitro activity studies, supported by molecular docking and *in silico* ADMET results, strongly indicated that the triazole molecules: **M1**, **M3**, **M6** and **M10** can be adopted as treatments for diabetes mellitus in medicine.

In the next work, we will use the DFT approach to investigate the 1,3-dipolar cycloadditions of 1,2,3-triazole derivatives in order to determine the reaction's regiochemistry and regioselectivity. Hence, theoretically predict the preferred isomer and compare it to the experimental results.

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