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PHARMAKEFTIKI, 36, I, 2024 | 27-39 RESEARCH ARTICLE

Application of Molecular Docking and Drug-Likeness Prediction for the Discovery of New Antidiabetic Agents

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ABSTRACT

Type 2 diabetes mellitus is a severe and increasingly prevalent disease that is considered as a serious public health. The purpose of this study was to identify novel and more efficient alpha glucosidase inhibitors using molecular docking approach and to determine the mode of interaction during the binding of those inhibitors to the enzyme.

The molecular docking method using the active site of alpha glucosidase and the drug likeness prediction were successful in identifying new products that were predicted to have a high negative binding energy to the target protein compare to the reference drug, acarbose. The compounds 6-O-[4-O-[4-[[(1S)-4beta,5alpha,6beta-Trihydroxy-3-(hydroxymethyl)-2-cyclo-hexene-1beta-yl]amino]-4,6-dideoxy-alpha-D-glucopyranosyl]-alpha-D-glucopyrano-syl]-L-ascorbic acid (CID101184779) and methyl alpha-R-acarviosinide (CID102067844) are the best, they showed excellent in silico activity with energy interaction of -49.1218 kJ/mol and -45.8468 kJ/mol respectively. The interactions that govern the complexes alpha glucosidase-proposed products stability are principally hydrogen bonds. These compounds were predicted to have satisfying drug likeness properties, they can serve as leads for further type 2 diabetes treatment.

1. Introduction

Type 2 diabetes is a major public health problem worldwide. Current World Health Organization statistics indicate that this disease will affect 642 million people by the year 2040[1-3]. Persistently high blood sugar levels can lead to severe complications, like blindness, kidney failure, neuropathy, heart attacks and lower-extremity amputation[2-9].

Treatment of type 2 diabetes involves diet and physical activity along with lowering of blood sugar[10,11]. Essential medications listed by World Health Organization to treat this disease and its complications are sulfonylureas and biguanides[6,12]. Those treatments simulate insulin secretion even at hypoglycaemia. In contrast, alpha glucosidase inhibitors retard the absorption of glucose and decrease the postprandial blood glucose levels by delaying the digestion of carbohydrates that are transformed into simple sugars and absorbed by the intestines[13-16]. Therefore, the alpha glucosidase inhibitors can be developed into effective therapeutic drugs to treat this disease.

The purpose of this study was to analyze the interactions involved in the inhibition of the alpha glucosidase by the acarbose, the first approved drug in alpha-glucosidase inhibitor[17-20], and a collection of its analogues by means of applying the molecular docking method followed by a computational drug likeness prediction, with a view to discover novel and more efficient alpha glucosidase inhibitors as new antidiabetic agents.

2. Materials and methods

Molecular docking approach has become an essential tool for drug development[21-23]. It can be used to screen the interactions between a variety of small compounds and proteins at the atomic level[24,25], which allow to characterize the behavior of small compounds in the binding site of target proteins[26-28].

2.1. Program used

Affinity and binding interactions between ligands and target proteins play an important role in bioactive compounds' discovery[29,30]. FlexX is a fast calculation program suited for molecular docking (https://www.biosolveit.de/). It is able to dock ligands in an environment consisting of amino acids with good accuracy[31,32]. The resulting poses were given as a binding free energy (ΔG, kJ/mol).

2.2. Molecular structures preparation

In this study we selected the alpha glucosidase as target; its three dimensional structure was retrieved from the Protein Data Bank (PDB ID: 3W37)[33]. This enzyme has one chain. In the structure preparation, the co-crystal inhibitor (acarbose) was used to identify the active site. The amino acids Asp232, Ile233, Ala234, Ser235, Phe236, Asn237, Leu240, Tyr243, Cys327, Arg328, Trp329, Asp357, Ile358, Ile396, Asp398, Trp432, Trp467, Asp469, Met470, Glu472, Ser474, Phe476, Arg552, Trp565, Gly567, Asp568, Asn569, Asp597, Phe601, Ala602, Arg624, His626, Ser627, Ala628 and four water molecules (HOH1117, HOH1166, HOH1171 and HOH1324) were found to be present in the ligand-binding site of the proposed target protein.

The three dimensional structures of 239 analogues compounds to acarbose, a potent alpha glucosidase inhibitor[17,18], were downloaded in the SDF file format from PubChem database (https://pubchem.ncbi.nlm.nih.gov/), an open chemistry library.

2.3. Drug Likeness and Toxicity Prediction

The physico-chemical and pharmacokinetic properties of the best alpha glucosidase inhibitors obtained in the molecular docking study were predicted using SwissADME at http://www.swissadme.ch/ and PreADMET at https://preadmet.bmdrc.kr/. These properties consist of Lipinski's rule, gastrointestinal absorption (GI), blood-brain barrier permeability (BBB), Cytochrome P450 (CYP) inhibition, cell permeability (COCA-2) [34,35] and toxicity[36,37]. The same proprieties of acarbose, the reference

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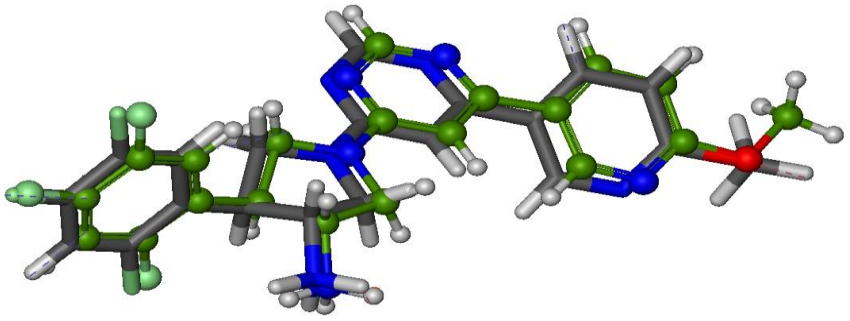

Figure 1. *Overlay of co-crystal ligand PZF conformation extracted from 2QJR (in grey) with the best predicted pose (in green) (RMSD = 0.4886 Å).*

inhibitor, were also studied for comparison.

3. Results and discussion

3.1. Test the reliability of the FlexX protocol.

Before starting molecular docking study of alpha glucosidase-inhibitors, the performance of FlexX protocol was validated by calculating the Root Mean Square Deviation (RMSD) value of 100 complexes protein-ligand crystal structures from PDB. It is a metric that measures distances between the experimental and the docking conformations of a ligand. The predicted interacting mode was considered correct if the RMSD was ≤ 2Å[38-40]. In our results, FlexX reproduced well the experimental data. Indeed, 74 % of RMSD values were less than 2Å (Table 1) which indicates the capacity of the FlexX protocol to reproduce the interaction mode and orientation of a co-crystal ligand[38,39,41].

For example, Figure 1 shows that there was a negligible deviation between docked pose (colored in green) and experimental conformation (colored in grey) of the ligand PZF from the complex 2QJR in the PDB.

3.2. Interactions between the alpha glucosidase and the acarbose.

Acarbose is an alpha glucosidase inhibitor used for the management of glycemic control in patients with type 2 diabetes mellitus[17,18].

Interesting interactions were detected between alpha glucosidase residues and acarbose with high number of matches (16 matches) and high interaction energies values (-51.0329 kJ/mol of the matched interacting groups, -11.0899 kJ/mol of the lipophilic contact area and -13.7975 kJ/mol of the lipophilic-hydrophilic contact area), but the effect of rotatable bonds has been carried out, they decreases the total score of the docking solution to -36.9770 kJ/mol. The interactions are represented in the figure 2.

The hydrophobic and hydrogen bonds play very important roles in the interactions between acarbose and alpha glucosidase[33,42], which were confirmed sufficiently by molecular docking (Figure 2).

Acarbose makes several hydrogen bonds with amino acid residues (Asp232, Ala234, Asn237, Asp357, Arg552, Asp568, His626) and water molecules (HOH1117, HOH1324) of the binding pocket. In particular, the hydroxyl functions are involved in twelve hydrogen bonds. The visual analysis shows that the acarbose is well placed in the active site of the enzyme.

3.3. Highlighting new alpha glucosidase-inhibitors.

In order to find new and more effective inhibitors

Table 1. List of 100 complexes protein-ligand used to test the reliability of the docking protocol.

Code	RMSD (Å)	Code	RMSD (Å)	Code	RMSD (Å)	Code	RMSD (Å)
1N1M	0.8030	3U7K	1.0179	2OQV	2.5090	2RIP	0.8829
1RWQ	1.6348	3SW8	2.0223	2P8S	1.7092	3K6L	0.8551
1X70	1.5342	2JID	0.8598	2QJR	0.4886	3C43	1.6716
2IIT	3.8011	4XPP	0.2931	2QOE	0.9268	3C45	1.8198
2GBI	2.0103	2OGZ	0.8708	2QT9	1.0875	3D4L	0.5575
2HHA	1.3248	2OLE	2.7875	2QTB	1.1471	3EIO	0.8963
2IIV	2.2418	2OPH	1.8343	2RGU	2.4373	3F8S	3.2153
3HAC	0.6211	3KWF	0.9773	3Q8W	1.8931	3SWW	4.8521
3HAB	0.9496	3KWJ	0.6746	3Q0T	5.2147	3SX4	4.9621
3E3U	1.2365	3NOX	4.5824	3QBJ	0.6197	3VJK	0.7595
5IED	0.3611	4DTC	1.1580	5J3J	0.7802	1OBB	3.3599
2EVC	2.7772	4J3J	2.8476	5Y7H	1.9666	5IEF	0.8339
3W2T	2.7145	5CWX	1.5747	5ZID	0.8169	7KRY	3.7367
3WQH	6.9625	1G2A	0.9587	5CX0	1.2762	7JTY	1.4977
2P98	0.5356	2AI7	1.5942	6DVV	2.6990	7K9O	3.0306
2P99	0.7963	4PV7	1.4821	2FH6	0.4470	1QXW	1.4071
2P9A	2.3450	5IEE	0.3061	2JKP	2.9075	1QXY	1.0411
2Q92	4.9934	1XNZ	0.9027	1WKM	1.6527	1YVM	1.6479
2Q93	0.6113	2EVM	0.4550	2GU4	5.7783	2P98	0.5356
2Q94	1.2446	2EVO	1.9830	2GU5	1.1365	2GU6	0.8152
2Q95	1.8514	4Z7M	2.7377	1LRU	1.0040	4E9A	0.8025
2Q96	2.0087	5YOI	0.9888	1LRY	1.1355	3U7N	1.2291
3D27	1.3443	5YPD	1.0600	1Q1Y	2.7251	5CY8	0.8709
5YOH	2.4179	5YXF	1.2702	2AI8	1.8357	3U7L	1.3475
1IX1	1.1419	5IED	0.3611	2AIE	4.9591	3U04	0.9670

of alpha glucosidase enzyme, we had taken compound acarbose as starting structure and we performed the molecular docking of a collection of 239 acarbose analogues from PubChem database using FlexX. The results are presented below in Table 2.

The results of the simulation by FlexX of the compound acarbose and its similar are presented in Table 2. In 46 cases, the binding energy of the compounds acarbose derivatives was increased.

Of the 239 inhibitors tested, the similar 6-O-[4-O-[4-[[(1S)-4beta,5alpha,6beta-Trihydroxy-3-(hydroxymethyl)-2-cyclohexene-1beta-yl]amino]-4,6-dideoxy-alpha-D-glucopyranosyl]-alpha-D-glucopyranosyl]-L-ascorbic acid (CID101184779) forms the most stable complex alpha glucosidase-inhibitor and had the best inhibitory effect with a binding energy value of -49.1218 kJ/mol, followed

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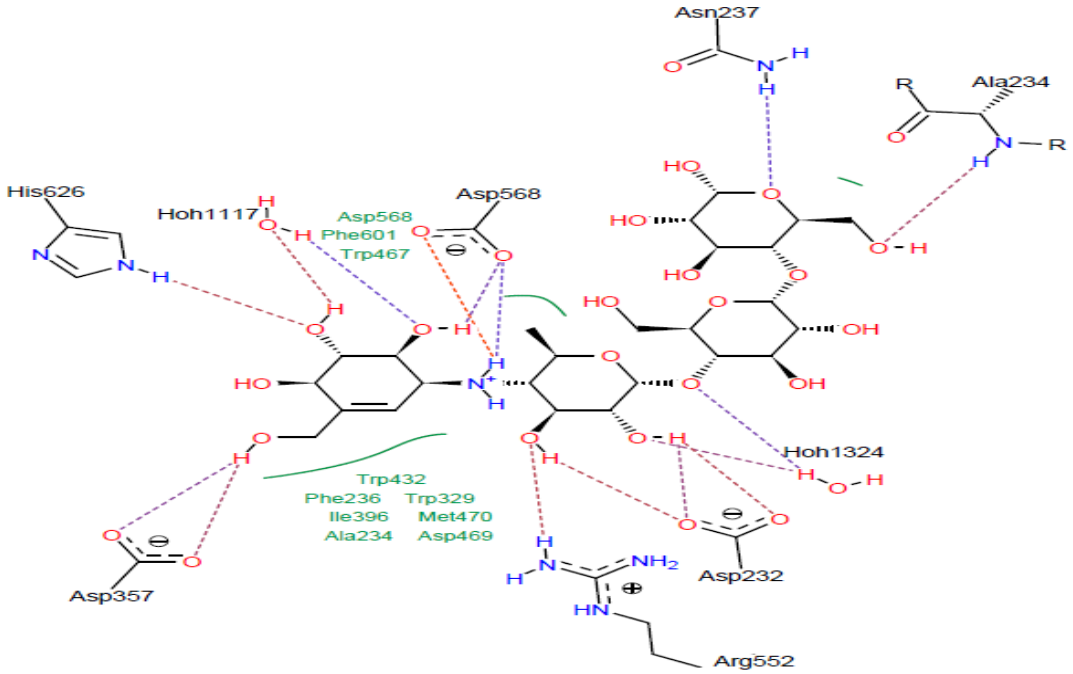

Figure 2. *Docking result for compound acarbose. Hydrogen bonding is represented by dotted lines and hydrophobic interactions are represented by green lines.*

Table 2. FlexX score of 239 acarbose derivatives in alpha glucosidase binding site.

PubChem ID	ΔG (kJ/mol)	PubChem ID	ΔG (kJ/mol)	PubChem ID	ΔG (kJ/mol)
Acarbose	-36.9770	CID156617917	-35.7313	CID90904637	-30.6920
CID163058885	-26.9460	CID156616906	-37.3103	CID90744171	-34.9396
CID101101475	-30.5559	CID156616596	-34.7068	CID90448344	-18.6382
CID70682078	-35.8019	CID156616595	-40.0248	CID90304936	-40.3799
CID197426	-31.0900	CID154702964	-28.8911	CID90304934	-32.3249
CID127767	-18.5236	CID163048502	-18.0257	CID89388686	-35.9863
CID131875583	-35.3560	CID154925673	-35.8364	CID89388654	-30.8778
CID101998608	-15.0282	CID141618198	-28.5518	CID87990761	-36.7845
CID86583399	-18.1523	CID134969637	-40.2381	CID78225312	-20.3393
CID449165	-14.4176	CID129837378	-34.7273	CID78225164	-26.4104
CID449164	-42.3869	CID125462883	-27.6094	CID73265284	-26.7620
CID163094043	-36.3991	CID122706040	-21.3319	CID71167118	-28.7956
CID145948806	-21.9028	CID122627482	-34.7818	CID71167117	-32.1001
CID131881950	-34.7627	CID9811704	-30.8392	CID71167116	-35.8606

Table 2, continued.

CID100966752	-40.4070	CID3068765	-33.1258	CID71167077	-34.5229
CID70692640	-31.9477	CID90659860	-7.1240	CID71167075	-44.1107
CID131864693	-37.5345	CID46936908	-26.7290	CID71104404	-32.1565
CID70690487	-30.3509	CID160278855	-22.4250	CID71095954	-42.6304
CID70684192	-40.9240	CID162996640	-17.0996	CID71095952	-38.2795
CID66563683	-26.8012	CID121353418	-36.1876	CID66769438	-36.4586
CID46936699	-22.2351	CID91860852	-17.1377	CID145710693	-23.1081
CID46936518	-21.3846	CID91858193	-5.7402	CID147207264	-30.3563
CID46936324	-31.7483	CID91820480	-11.5324	CID68920480	-21.2490
CID17753825	-35.3533	CID91242099	-40.2636	CID68920478	-18.2420
CID5288404	-23.5093	CID91144966	-28.1567	CID68253726	-36.4393
CID444440	-40.8956	CID91109839	-30.5945	CID68023871	-25.3597
CID58960848	-23.6526	CID90995832	-39.9008	CID67969547	-38.1910
CID156618806	-36.3284	CID90941376	-34.3737	CID67718293	-36.4586
CID156618023	-29.6143	CID90928298	-31.1913	CID102033884	-14.1910
CID67363027	-35.4586	CID60040995	-21.9217	CID58618606	-42.2921
CID66769873	-35.4586	CID59701768	-31.2850	CID58618603	-23.6526
CID145710463	-26.9481	CID59701767	-21.3149	CID58618601	-27.5662
CID163058886	-21.1187	CID59366485	-21.9448	CID58618596	-37.9530
CID60041231	-25.4010	CID59366481	-24.4032	CID58618589	-18.6287
CID60041190	-26.3186	CID59366479	-23.9237	CID58618572	-37.2868
CID60041176	-24.0122	CID58960860	-28.2377	CID58618562	-19.2673
CID60041167	-32.5352	CID58960858	-20.6360	CID58618561	-30.7750
CID60041164	-26.4273	CID58960857	-21.7995	CID58618553	-37.6301
CID60041160	-25.3650	CID58960855	-23.6526	CID56672287	-28.5771
CID60041132	-21.3145	CID58960848	-23.6526	CID56668330	-31.0523
CID60041127	-26.0933	CID58960819	-21.5995	CID53386870	-28.7740
CID60041087	-36.5397	CID58960799	-18.9084	CID53386869	-28.4502
CID60041086	-43.4855	CID58618651	-37.2868	CID44629528	-34.9810
CID60041081	-31.7923	CID58618640	-18.8126	CID22800533	-37.2351
CID60041079	-32.5352	CID58618637	-20.6360	CID16052760	-35.3875
CID60041059	-21.9217	CID58618631	-27.3690	CID16040286	-39.0805
CID60041050	-36.7275	CID58618626	-21.5995	CID10689257	-28.2871
CID60041046	-25.0058	CID58618622	-21.6850	CID10403776	-40.0907
CID60041031	-21.6653	CID58618613	-25.9726	CID10042676	-40.0907
CID60041017	-26.4273	CID58618611	-31.2175	CID5288403	-22.1023

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Table 2, continued.

CID17754036	-21.8558	CID10614514	-30.7789	CID5288026	-43.8635
CID24830935	-7.7636	CID10627975	-25.5630	CID508375	-37.7810
CID24838414	-27.8225	CID10699545	-21.7142	CID448897	-40.9984
CID24971174	-38.1214	CID10770622	-24.5315	CID131704236	-42.3437
CID24971175	-40.6866	CID10815496	-38.6004	CID71604313	-23.6446
CID44561541	-36.6705	CID10883911	-26.5026	CID11968287	-27.6857
CID44891366	-37.7887	CID10927511	-23.7673	CID6852184	-26.1927
CID162984345	-27.7169	CID11215971	-11.5718	CID5287619	-41.6100
CID71421398	-16.1345	CID11779734	-32.9689	CID6917714	-22.8783
CID71481137	-36.7845	CID15144126	-22.7792	CID10055145	-33.4036
CID86301314	-379690	CID16052281	-32.9757	CID10070575	-15.4437
CID145710311	-23.6518	CID16052698	-34.0885	CID10085441	-34.7771
CID101005739	-42.3562	CID16052758	-39.8965	CID10258648	-23.5093
CID101184779	-49.1218	CID16057149	-35.3453	CID10381259	-30.5072
CID101184780	-39.3917	CID17753784	-24.3898	CID10403576	-33.1620
CID101343159	-11.7729	CID102404198	-30.7741	CID124905289	-30.3500
CID101343160	-14.7926	CID123133965	-21.0297	CID124905290	-18.1466
CID101343161	-0.6826	CID124710649	-26.8337	CID124905291	-20.0139
CID101343162	-31.1617	CID124710650	-13.7721	CID124905292	-29.1262
CID101343187	-26.4987	CID124710651	-17.2084	CID125462881	-15.0188
CID101343186	-24.0976	CID124710652	-19.7047	CID125462882	-19.1447
CID101343188	-23.9467	CID124744956	-23.0840	CID129539594	-37.6209
CID101343189	-24.5242	CID124744957	-13.7444	CID131632341	-27.7984
CID101596220	-25.5137	CID124744958	-18.3537	CID131707781	-22.3363
CID101596222	-28.7158	CID124744959	-17.5877	CID133636855	-7.5949
CID101748926	-40.8966	CID124903813	-14.0809	CID135121324	-42.9584
CID67372326	-36.4586	CID67372326	-36.4586	CID155294159	-24.4231
CID102067844	-45.8468	CID124903815	-16.7551	CID155294158	-37.3671
CID102355258	-37.1846	CID124903816	-28.1159	CID163099876	-10.4117
CID135121325	-40.5062	CID162926268	-18.4994	CID163285270	-21.4077
CID145710289	-26.8257	CID162955693	-30.9855	CID90659861	-15.0282

by compound methyl alpha-R-acarviosinide (CID102067844; ΔG = -45.8468 kJ/mol) (Tables 2 and 3). Hence, we propose that these compounds can interact efficiently with the enzyme. Further work was then undertaken to elucidate the mechanism of interaction of these two proposed compounds.

A representative interacting mode of the

Table 3. Docking scores of acarbose and the most promising alpha glucosidase inhibitors.

Compound	Score	Match	Lipo	Ambig	Clash	Rot	# Match
Acarbose	-36.9770	-51.0329	-11.0899	-13.7975	2.7434	30.8000	18
CID101184779	-49.1218	-66.3508	-10.6819	-16.6801	4.3910	30.8000	20
CID102067844	-45.8468	-49.6860	-8.3040	-8.9425	1.6858	14.0000	18

Score: Total score of the docking solution, **Match:** Contribution of the matched interacting groups, **Lipo:** Contribution of the lipophilic contact area, **Ambig:** Contribution of the lipophilic-hydrophilic area, **Clash:** Contribution of the clash penalty, **Rot:** Ligand conformational entropy score, **# Match:** Number of matches.

Table 4. The predicted pharmacokinetic and toxicity proprieties of the most promising compounds.

Properties	Acarbose	CID101184779	CID102067844
BBB penetration	0.0271005	0.0271294	0.0329973
GI absorption	Low	Low	Low
CYP inhibitor	None	None	None
COCA-2	9.44448	9.92867	18.8038
Lipinski's rule of 5	No; 3 violations: MW>500, NorO>10, NHorOH>5	No; 3 violations: MW>500, NorO>10, NHorOH>5	Yes
Toxicity	CR negative hERG_inhibition ambiguous	CR negative hERG_inhibition ambiguous	CR negative hERG_inhibition low_risk

COCA-2: human colorectal carcinoma 2 cell permeability (nm/sec), **MW:** molecular weight, **NorO:** Number of hydrogen bond acceptors, **NHorOH:** Number of hydrogen bond donors, **hERG inhibition:** human ether-ago-go related gene channel inhibition, **CR:** carcinogenicity in rat

compounds CID101184779 and CID102067844 with the binding site of alpha glucosidase is given in Figure 3. The figure 3 shows that the compounds CID101184779 **(a)** and CID102067844 **(b)** fit well into the binding pocket of the enzyme.

The FlexX software also helped to view the number and type of interactions involved in the CID101184779-alpha glucosidase, CID102067844-alpha glucosidase and acarbose-alpha glucosidase interactions. Interestingly, the present study revealed that the hydrogen bonding of CID101184779 with His626, Asp357, Asp568, Arg552, Asp232, Asn237 and Ala234 is similar to that of the binding orientation of acarbose in the alpha glucosidase binding pocket (Figures 2 and 4). This effect suggests that it can have a similar anti-diabetic propriety to acarbose.

Compounds CID102067844 and acarbose showed deep links within the alpha glucosidase binding pocket through their hydroxymethyl cyclohexane and methyloxane fragments. In addition, as acarbose, compound CID102067844, also demonstrated hydrogen-bonding interactions with Asp232, Asp357, Asp469, Arg552, Asp568 and His626 (Figures 2 and 5). These similarities in

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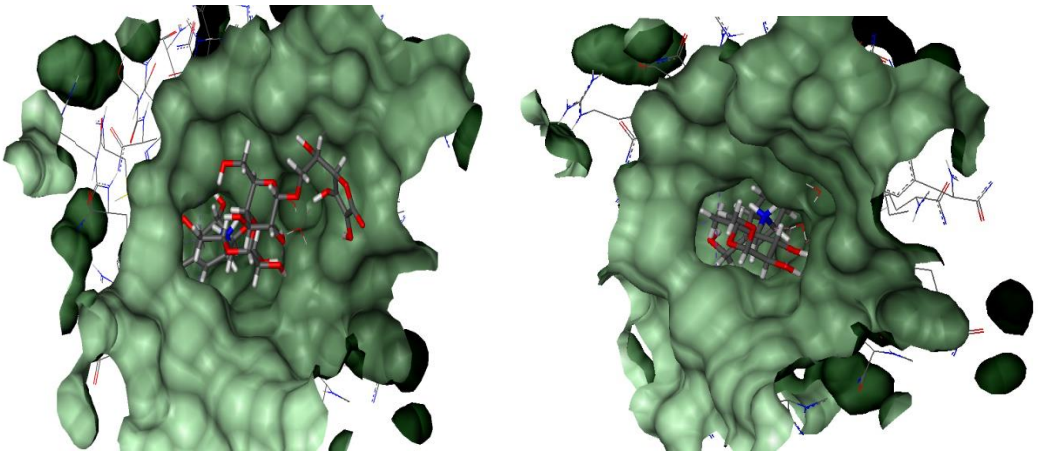

(a) **(b)**

Figure 3. *Illustration of the positioning of compounds CID101184779* ***(a)*** *and CID102067844* ***(b)*** *in the interacting site of alpha glucosidase.*

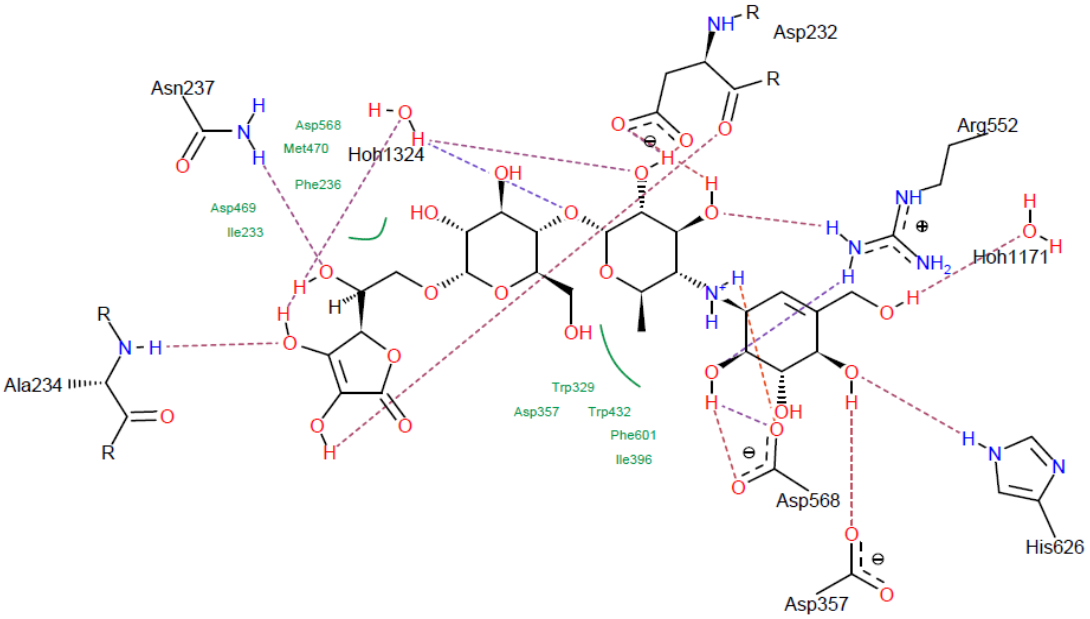

Figure 4: *Visual analysis of the interaction between the compound CID101184779 and alpha glucosidase binding site.*

interaction of compound acarbose to the catalytic pocket with the present studied compound, CID102067844, indicate that this compound is able to occupy the active site of alpha glucosidase and, hence, is involved in the inhibition of the enzyme.

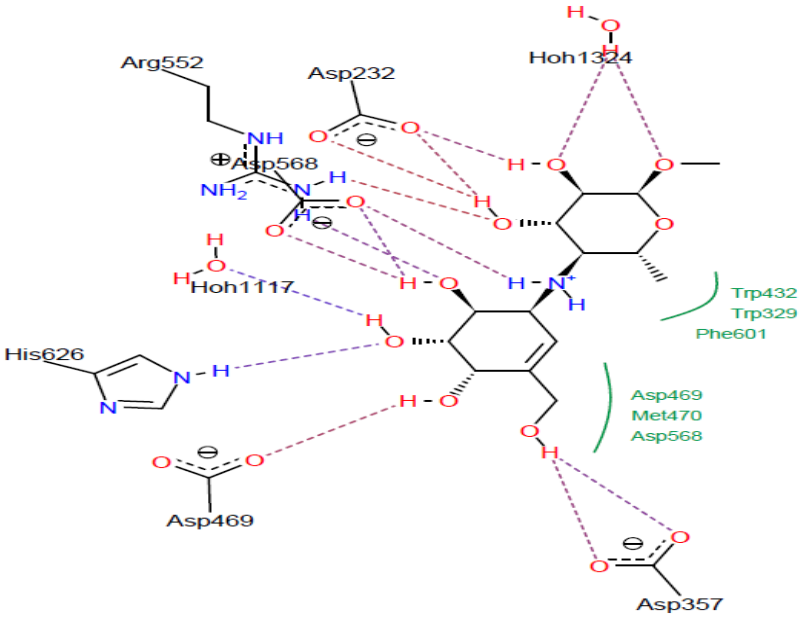

Figure 5: *Visual analysis of the interaction between the compound CID102067844 and alpha glucosidase binding site.*

Two hydrophobic pockets stabilize the compounds acarbose, CID101184779 and CID102067844 in the active site of alpha glucosidase. Moreover, hydrophobic interactions are carried out with residues Trp329, Asp469, Met470, Asp568 and Phe601 (Figures 2, 4 and 5).

3.4. Drug-likeness Prediction

In the subsequent part of our work, we verified the pharmacokinetic and toxicity proprieties of the most promising products (compounds CID101184779 and CID102067844) using SuissADME and PreADMET (Table 4). These properties consist of their blood-brain barrier (BBB) penetration, gastrointestinal absorption (GI), Cytochrome P450 (CYP) inhibition, Lipinski's rule of 5 categorization, cell permeability (COCA-2) and toxicity. The same parameters of acarbose were also studied for comparison.

As indicated in Table 4, compounds CID101184779 and CID102067844 are predicted to have low intestinal absorption and BBB penetration like that of acarbose. Moreover, they have high COCA-2 cell permeability, which insures their in vivo usage. Furthermore, the studied products do not inhibit CYP (essential enzymes for the metabolism of numerous medicaments in the liver). With no Lipinski's rule of 5 violation, CID102067844 follow the criteria for orally available drugs contrary to acarbose and CID101184779. However, these two promising compounds did not show potential toxicity, which guarantees their use in vivo.

Conclusion

In the present study, we used molecular docking approach to investigate the binding modes of a series of 293 acarbose derivatives selected from PubChem database with alpha glucosidase by the docking program FlexX. This approach allowed us to suggest products CID101184779 and CID102067844 as potential new alpha glucosidase

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inhibitors. These two compounds were predicted to have satisfying drug likeness properties, indicating that they might be promising lead compounds for further antidiabetic drug research. Nevertheless, it remains to test these inhibitors directly on our target, the alpha glucosidase. In this sense, work is currently underway on these two compounds as well as on many other acarbose derivatives, in order to find new antidiabetic agents.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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References

1. World Health Organization. Diabetes, [cited May 2022]. Available from Internet: https://www.who.int/news-room/fact-sheets/detail/diabetes.
2. Liu S.K., Hao H., Bian Y., Ge Y.X., Lu S., Xie H.X., Wang K.M., Tao H., Yuan C., Zhang J., Zhang J., Jiang C.S., Zhu K. Discovery of New α-Glucosidase Inhibitors: Structure-Based Virtual Screening and Biological Evaluation. *Front.Chem*. 9, 639279, 2021.
3. International Diabetes Federation. (2017). ATLAS du diabète de FID. 8eme *ed*. *Brussels, International Diabetes Federation.*
4. Al-Lawati J.A. Diabetes Mellitus: A Local and global public health emergency!. *Oman Med. J*. 32(3), 177-179, 2017.
5. Zeng Z., Yin X., Wang X., Yang W., Liu X., Hong Y. Synthesis of water soluble pentacyclic dihydroxyterpene carboxylic acid derivatives coupled amino acids and their inhibition activities on α-glucosidase. *Bioorg. Chem*. 86, 277-287, 2019.
6. World Health Organization, [cited May 2022]. Available from Internet: https://www.who.int/news-room/fact-sheets/detail/diabetes.
7. American Diabetes Association. Standards of Medical Care in Diabetes—2018 Abridged for Primary Care Providers. *Clin. Diabetes.* 36(1), 14–37, 2018.
8. Żuchnik M., Rybkowska A., Szczuraszek P., Szczuraszek H., Bętkowska P., Radulski J., Tomkiewicz M., Paluch M., Licak G., Olko P. Type 2 diabetes - factors of occurrence and its complications. *Quality in Sport*. 10(1), 32-40, 2023.
9. Kautzky-Willer A., Harreiter J., Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocr. Rev*. 37(3), 278–316, 2016.
10. Clement M., Harvey B., Rabi D.M., Roscoe R.S., Sherifali, D. Organisation des soins du diabète. *Canadian Journal of Diabetes*. 37, 381-387, 2013.
11. Kautzky-Willer A., Leutner M., Harreiter J. Sex differences in type 2 diabetes. *Diabetologia*. 66, 986–1002, 2023.
12. Butt S.M. Management and Treatment of Type 2 Diabetes. *International Journal of Computations, Information and Manufacturing*. 2(1), 15-27, 2022.
13. Bailey C.J., Day C. Treatment of type 2 diabetes: future approaches. *British Medical Bulletin*. 126, 123-137, 2018.

14. Kim J.H., Kim H.Y., Jin C.H. Mechanistic investigation of anthocyanidin derivatives as α-glucosidase inhibitors. *Bioorg. Chem*. 87, 803-809, 2019.
15. Chiba S. (1988). Amyloglycosidase. Handbook of Amylases and related enzymes *ed*. *Oxford, U.K, The Amylase Research Society of Japan, Pergamum Press*.
16. Standl E., Schnell O. Alpha-glucosidase inhibitors 2012 - cardiovascular considerations and trial evaluation. *Diab. Vasc. Dis. Res*. 9, 163–169, 2012.
17. Chiasson J.L., Josse R.G., Gomis R., Hanefeld M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 359(9323), 2072-2077, 2002.
18. Hossain U., Das A.K., Ghosh S., Sil P.C. An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. *Food Chem. Toxicol*. 145, 111738, 2020.
19. Clissold S. Acarbose: A Preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. *Drugs*. 35(3), 214-43, 1988.
20. Dalsgaard N.B., Gasbjerg L.S., Helsted M.M., Hansen L.S, Hansen N.L., Skov-Jeppesen K., Hartmann B., Holst J.J., Vilsboll T., Knop F.K. Acarbose diminishes postprandial suppression of bone resorption in patients with type 2 diabetes. *Bone*. 170(5), 116687, 2023.
21. Zothantluanga J.H., Chetia D. A beginner's guide to molecular docking. *Sciences of Phytochemistry*. 1(2), 37-40, 2022.
22. Sagheer O.M., Ahmed M.S., Jwaid M.M., Alkhafaje Z., Al-hussaniy H.A., Al-Tameemi Z.S. The development of molecular docking and molecular dynamics and their application in the field of chemistry and computer simulation. *Journal of medical pharmaceutical and allied sciences*. 12, 5552–5562, 2023.
23. Aydın S.G. Review on molecular modelling and docking. *SAR Journal - Science and Research*. 5(4), 206-210, 2022.
24. Ahmad S., Singh S., Srivastava M.R., Shukla S., Rai S., Shamsi A.S. Molecular docking simplified: Literature review. *Adv.Med. Dental Health Sci.* 4 (4), 37-44, 2021.
25. Muhammed M.T., Aki-Yalcin E. Molecular docking: principles, advances, and its applications in drug discovery. *Lett. Drug Des.Discov*. 20, 1-16, 2022.
26. Kontoyianni M. Docking and virtual screening in drug discovery. *Methods Mol. Biol*. 1647, 255-266, 2017.
27. Zothantluanga J.H., Gogoi N., Shakya A., Chetia D., Lalthanzara H. Computational guided identification of potential leads from Acacia pennata (L.) Willd. as inhibitors for cellular entry and viral replication of SARS-CoV-2. *Futur. J. Pharm. Sci*. 7, 201, 2021.
28. Ferreira L.G., Dos Santos R.N., Oliva G., Andricopulo A.D. Molecular docking and structure-based drug design strategies. *Molecules*. 20(7), 13384-421, 2015.
29. Mohan V., Gibbs A.C., Cummings M.D., Jaeger E.P., DesJarlais R.L. Docking: Successes and challenges. *Curr. Pharm. Des.* 11(3), 323-333, 2005.
30. Gangwal R.P., Damre M.V., Das N.R., Dhoke G.V., Bhadauriya A., Varikoti R.A., Sharma S.S., Sangamwar A.T. Structure based virtual screening to identify selective phosphodiesterase 4B inhibitors. *J. Mol. Graph. Model*. 57, 89-98, 2015.
31. Rarey M., Kramer B., Lengauer T., Klebe G. A fast flexible docking method using an incremental construction algorithm. *J. Mol. Biol.* 261, 470-489, 1996.
32. Nagare S., Lokhande K., Swamy K.V. Docking and simulation studies on cyclin D/CDK4 complex for targeting cell cycle arrest in cancer using flavanone and its congener. *J. Mol. Model*. 29(4), 90, 2023.
33. Tagami T., Yamashita K., Okuyama M., Mori H., Yao M., Kimura A. Molecular basis for the recognition of long-chain substrates by plant & alpha-glucosidase. *J. Biol. Chem.* 288, 19296-19303, 2013.
34. Al Azzam K.M. SwissADME and pkCSM Webservers predictors: an integrated online platform for accurate and comprehensive predictions for in silico ADME/T properties of artemisinin and its derivatives. *Complex Use of*

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Mineral Resources. 325(2), 14-21, 2023.
35. Mvondo J.G.M., Matondo A., Mawete D.T., Bambi S.M.N., Mbala B.M., Lohohola P.O. In silico ADME/T properties of quinine derivatives using SwissADME and pkCSM Webservers. *Int. J.Trop.l Dis. Health*. 42(11), 1-12, 2021.
36. Pehlivan M. PreADMET supported in silico prediction results for possible drug characteristics, toxicity and ADME for flavocillin, [cited January 2023]. Available from Internet: https:// preadmet.webservice.bmdrc.org/ toxicity/.
37. Dandagvhal K., Chatpalliwar V. In silico Characterization, ADMET prediction and molecular docking studies of few 2/3 carboxylate-4/5/6-monosubstitued indole derivatives as potential GSK-3β inhibitors. *Int. J.Health Sci*. 6(S3), 12193-12212, 2022.
38. Hioual K.S., Chikhi A., Bensegueni A., Merzoug A., Boucherit H., Teniou S., Mokrani E.H., Merabti B. Successful challenge: A key step in infectious diseases treatment using computer-aided drug design. *Int. J. Biol. Sci. App*. 1(1), 11-14, 2014.
39. López-Camacho E., García-Godoy M.J., García-Nieto J., Nebro A.J., Aldana-Montes J.F. (2016) A New Multi-objective approach for molecular docking based on RMSD and binding energy. In: Boton-Fernandez M., Martin-vide C., Santander-Jimenez S., Vega-Rodriguez M. Algorithms for computational biology. eds. *Lecture Notes in Computer Science*. Springer, Cham, vol. 9702.
40. Buckley M.E., Ndukwe A.R.N., Nair P.C., Rana S., Fairfull-Smith K.E., Gandhi N.S. Comparative assessment of docking programs for docking and virtual screening of ribosomal oxazolidinone antibacterial agents. *Antibiotics*. 12(3), 463, 2023.
41. Grosdidier A. Conception d'un logiciel de docking et applications dans la recherche de nouvelles molécules actives. PhD Thesis, Joseph Fourier University: France, 2007.
42. Kimani N.M., Ochieng C.O., Ogutu M.D., Yamo K.O., Onyango J.O., Santos C.B.R. Inhibition kinetics and theoretical studies on *Zanthoxylum chalybeum* Engl. Dual inhibitors of α-glucosidase and α-amylase. *J. Xenobiot*. 13,102–120, 2023.