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In Silico Drug-Likeness/ADME-T Studies and Molecular Docking of Compounds from *Tephrosia bracteolata* Leaves against some Targets of Diabetic Complications

Precious Idakwoji [1,*], Endaline Madu [2], Claribel Okorie [3], Ijeoma Nwafor [4], Aanuoluwa Iyiola [5], Emmanuel Iyiola [6], Hannah Nsude [7], Micheal Adeyeye [8,10], Racheal Chinweuba [2], Okpanachi Oyibo [2], Josiah Aderinto [9]

[1] Department of Biochemistry, Faculty of Natural Sciences, Prince Abubakar Audu University, Anyigba, Kogi State, Nigeria; precious.ia@ksu.edu.ng;
[2] Department of Biochemistry, Faculty of Biological Sciences, University of Nigeria, Nsukka, Enugu State, Nigeria; endaline.madu@unn.edu.ng;
[3] Department of Medical Biochemistry, College of Medicine, Godfrey Okoye University, Ugwuomu-Nike, Enugu State, Nigeria; claribel@gouni.edu.ng;
[4] UNESCO International Center for Biotechnology, Nsukka, Enugu State, Nigeria; princesss.ijeoma05@gmail.com;
[5] Department of Biochemistry, Federal University of Technology, Minna, Niger State, Nigeria; aanuoluwaiyiola94@gmail.com;
[6] Department of Microbiology, University of Ilorin, Ilorin, Kwara State, Nigeria; iyiolaemma247@gmail.com;
[7] Department of Biochemistry, Renaissance University, Ugbawka, Enugu State, Nigeria; nsudehannah@gmail.com;
[8] Department of Biochemistry, College of Natural and Applied Sciences, Salem University, Lokoja, Kogi State, Nigeria; adeyeyemicheal714@gmail.com;
[9] Department of Plant Breeding and Seed Technology, Federal University of Agriculture, Abeokuta, Ogun State, Nigeria; seunaderinto07@gmail.com;
[10] Department of Science and Laboratory Technology (Biochemistry Option), School of Natural and Applied Sciences, Federal Polytechnic, Bida, Niger State, Nigeria; adeyeyemicheal714@gmail.com;
* Correspondence: idakwojipa@gmail.com;

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Abstract: Diabetes mellitus often leads to severe complications such as neuropathy, nephropathy, and retinopathy primarily due to hyperglycemia. Identifying and targeting the molecular mechanisms underlying these complications is crucial for developing effective therapeutic strategies. This study focused on molecular docking and drug-likeness/ADME-T tests of some compounds (Myo-Inositol, 2-methoxy-4-vinyl phenol, 1-D-thioglucitol, and 4-Piperidone) identified through GC-MS analysis of *Tephrosia bracteolata* leaves. These compounds were docked against key molecular targets associated with diabetic complications, such as Angiotensin Converting Enzyme (ACE), Dipeptidyl-Peptidase IV (DPP-IV), Sodium-Glucose Co-transporter-2 (SGLT-2), Aldose reductase (AR), and Alpha-amylase (α-amylase). 3D Structures of the compounds were obtained from the Protein Data Bank. The SDF structures of the ligands were obtained from the PubChem database. Site-specific auto-docking was carried out, and the binding affinities (Kcal/mol) were determined using AutoDock Vina. Drug-likeness and ADME-T analyses of the ligands were carried out using the SwissADME Tool. The docking results revealed that methoxy-4-vinyl phenol exhibited strong binding affinities towards ACE, DPP-IV, SGLT-2, and AR, while Myo-Inositol exhibited strong binding affinity towards α-amylase. ADME-T analysis revealed that the compounds possess favorable ADMET profiles. It was concluded that the compounds, after further *in vitro* and *in vivo* validation, could be useful in managing diabetic complications, making them suitable candidates for further drug development processes.

Keywords: drug-likeness; ADME-T studies; molecular docking; myo-inositol; 2-methoxy-4-vinyl phenol; DPP-IV; SGLT-2.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistently elevated blood glucose levels resulting from abnormalities in insulin secretion or utilization [1, 2]. The global prevalence of diabetes is high. About 537 million adults aged 20–79 years are living with diabetes, with 75% of these cases in low- and middle-income countries. It has been predicted that these numbers may reach 643 and 783 million by 2030 and 2045, respectively [3,4]. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. The first category is type 1 diabetes, which results from an absolute deficiency of insulin secretion, while the second category is type 2 diabetes, which results from a combination of insulin resistance and an inadequate compensatory insulin-secretory response [5]. Type-2 diabetes mellitus (T2DM) is currently the most dominant type of diabetes worldwide, and it is associated with debilitating complications such as neuropathy, nephropathy, retinopathy, and cardiovascular diseases [6,7]. The global burden of diabetes continues to rise, necessitating an urgent need for effective therapeutic strategies, particularly those targeting its long-term complications [8].

Controlling blood glucose levels is essential for preventing diabetic complications and improving the health of people with diabetes [9]. The current pharmacological management of diabetes includes the use of oral hypoglycaemic agents (biguanides, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, DPP-1V inhibitors) and insulin therapy [10]. However, as a result of the inability of these pharmacological interventions to effectively manage all the pathophysiological mechanisms underlying diabetic complications, in addition to the clinically significant adverse effects associated with their use, safer and cheaper strategies are often sought as substitutes [11]. Recently, efforts have shifted to medicinal plants and their bioactive compounds as substitutes for the management of diabetes [9]. Globally and in Nigeria specifically, many medicinal plants have been shown to be reservoirs of phytochemicals with antidiabetic potential [12]. *Tephrosia bracteolata* is one of such plants used traditionally in the management of diabetes. The antidiabetic potential of *Tephrosia bracteolata* has also been scientifically proven by [9, 13–15]. However, the potential of its bioactive compounds to target molecular pathways associated with diabetic complications has not been extensively explored.

The plant *Tephrosia bracteolata* Guill. & Perr. (Leguminosae-Papilionoideae) It is a common tree around the tropics and sub-tropics. It usually grows to a height of 2 to 8 ft, with long, straight, thinly silky branches and flowers that are usually bright pink or purple. The fruits are linear in appearance and usually measure 5 to 6 cm long and 4 mm broad. The seeds are housed in pods about 4 to 8 cm long and 3 to 5 cm broad [16]. The plant is popular in African folklore medicine. The roots are used in the treatment of syphilis in pregnant women. The leaves of the plant have also been reported to possess analgesic, anti-inflammatory, and antipyretic properties [17]. According to Egharevba *et al*. [13], the leaves of *Tephrosia bracteolata* are rich in phytochemicals such as alkaloids, steroids, tannins, and flavonoids. Several studies have revealed that some of these phytochemicals are responsible for the antidiabetic activities of many medicinal plants.

In silico techniques such as drug-likeness prediction, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling, and molecular docking offer rapid, cost-effective approaches for screening natural compounds for drug potential [18, 19]. These computational tools can help prioritize lead molecules based on pharmacokinetic properties and binding affinity to disease-relevant proteins, thereby accelerating early-stage drug discovery [18, 19]. This study aims to evaluate the drug-likeness, ADMET properties, and molecular docking interactions of selected compounds from *Tephrosia bracteolata* leaves against some key molecular targets involved in diabetic complications. The targets considered in this study include Angiotensin Converting Enzyme (ACE), Dipeptidyl Peptidase IV (DPP-IV), Sodium-Glucose Co-transporter-2 (SGLT-2), Aldose reductase (AR), and Alpha-amylase (α-amylase). These targets were selected based on their critical roles in glucose homeostasis, insulin regulation, and vascular function. By identifying, through in silico analysis, compounds with promising antidiabetic properties in Tephrosia bracteolata leaves, this research may contribute to the development of novel drugs for the management of diabetes and its associated complications.

2. Materials and Methods

2.1. Protein target retrieval.

3D Structures of Angiotensin Converting Enzyme, ACE (PDB ID: 1O86), Dipeptidyl peptidase-IV, DPP-IV (PDB ID: 3WQH), Sodium-Glucose Co-transporter 2, SGLT-2 (PDB ID: 7VSI), Aldose reductase, AR (PDB ID: 3S3G), and α-amylase (PDB ID: 1B2Y) were obtained from the Protein Data Bank (www.rcsb.org). These protein structures were refined using Discovery Studio software

2.2. Test ligand.

From our study that evaluated the fractions of the extract of *Tephrosia bracteolata* leaves against an experimental model of diabetes, four of the GC-MS- identified active principles- Myo-Inositol, 2-methoxy-4-vinyl phenol, 1-D-thioglucitol, and 4-Piperidinone were selected for this study. The GC-MS details of the compounds are presented in Table 1 below.

Table 1. GC-MS details of the test ligands.

Peak No.	R. Time	Area	Area%	Name of compound
1	8.811	441042	0.11	4-piperidinone
2	11.908	841673	0.21	2-methoxy-4-vinylpheno
3	15.993	2413208	0.61	1-thio-d-glucitol
4	18.088	252100743	63.43	Mome inositol

2.3. Ligand retrieval.

The 3D format of Myo-Inositol, 2-methoxy-4-vinyl phenol, 1-D-thioglucitol, 4-Piperidinone, and the standard drugs (Lisinopril, Anagliptin, Empagliflozin, Alrestatin, and Acarbose) were downloaded from the PubChem database in SDF format. These SDF files were converted to PDB using Pymol software prior to molecular docking studies [20].

2.4. Molecular docking profile.

The targets and ligands were prepared prior to molecular docking using AutoDock tools, which involved adding charges and polar hydrogens and generating a grid box. The active site investigation was performed using the Site Finder of Molecular Operating Environment [21]. Molecular docking was performed using AutoDock Vina Software [22]. Docking was performed using a grid box defined around the known active site of each protein to ensure accurate targeting of ligand binding. Each grid box was sized at 40 x 40 x 40 Å with a spacing of 1.0 Å, centered on the ligand-binding pocket of the target protein. AutoDock Vina's scoring function, based on empirical free energy estimation, was used to rank binding affinities in kcal/mol. For validation of docking accuracy, re-docking of co-crystallized ligands into their respective protein binding sites was conducted, and the root mean square deviation (RMSD) between the docked pose and crystal conformation was evaluated. An RMSD value of ≤ 2.0 Å was acceptable for reliable reproduction of the binding mode.

Visualization of protein-ligand interactions was performed using Discovery Studio and Pymol, producing both 2D interaction diagrams and 3D surface renderings of binding poses [20].

2.5. Drug-likeness/ ADMET analysis using the SwissADME tool.

The Physicochemical, lipophilicity, solubility, pharmacokinetics, and Lipinski drug-likeness of compounds and standard drugs were determined using SwissADME Server [23].

3. Results and Discussion

Table 2 shows the binding energies of the ligands against the molecular targets. Among the ligands, 2-methoxy-4-vinyl phenol had the highest binding affinity (-6.2 kcal/mol) with ACE, which was comparable to that of the standard drug- lisinopril (-7.4kcal/mol), while 4-piperidone had the lowest binding affinity (-4.5kcal/mol) with ACE. 2-methoxy-4-vinyl phenol also had the highest binding affinity (-5.8 kcal/mol) with DPP-IV, which was, however, not comparable to that of the standard drug, anagliptin (-8.2 kcal/mol), while 4-piperidone also had the lowest binding affinity (-4.4kcal/mol) with DPP-IV. Similarly, 2-methoxy-4-vinyl phenol had the highest binding affinity (-6.7 kcal/mol) with SGLT-2, which was not comparable to that of the standard drug- empagliflozin (-10.6 kcal/mol), while 4-piperidone had the lowest binding affinity (-4.7kcal/mol) with SGLT-2. For AR, 2-methoxy-4-vinyl phenol also had the highest binding affinity (-7.1 kcal/mol), which was comparable to that of the standard drug, alrestatin (-7.9 kcal/mol). In the case of alpha-amylase, myo-inositol had the highest binding affinity (-5.7 kcal/mol), which was not comparable to that of the standard drug, acarbose (-7.2 kcal/mol).

The results of the interactions of the ligands with ACE are presented in Figure 1. The standard drug, lisinopril, showed a unique set of interactions, viz. Pi-alkyl (ALA 354, VAL 380, GLU 411), conventional hydrogen bonds alkyl (TYR 523, HIS 513, GLU 336), and Van der Waals interactions. Myo-inositol showed similar interactions with lisinopril, while 2-methoxy-4-vinyl phenol and 1-D-thioglucitol interacted with ACE via only conventional hydrogen bonds and Van der Waals interactions. The interaction of 4-Piperidinone with the ligand was mainly via Van der Waals interactions (TRP 123, ALA 207, ALA 208) alone.

Figure 2 shows the results of the interactions of the ligands with AR. The standard drug, alrestatin, interacted with AR mainly via conventional hydrogen bonds and Van der Waals

interactions. 2-methoxy-4-vinyl phenol showed a unique set of interactions with AR via pi-alkyl (TRP 20, CYS 298), carbon-hydrogen bonds (SER 210, SER 214), and Van der Waals interactions. The interaction of myo-inositol with the ligand was mainly via conventional hydrogen bonds (TRP 20, TYR 48, SER 210, GLN 218). 4-Piperidinone and 1-D-thioglucitol interacted with the ligand mainly via conventional hydrogen bonds and Van der Waals interactions.

The results of the interactions of the ligands with SGLT-2 are presented in Figure 3. The standard drug, empagliflozin, showed a unique set of interactions, viz. Pi-Pi stacked, Pi-Pi T-shaped, Pi-alkyl, conventional hydrogen bonds, and Van der Waals interactions. 1-D-thioglucitol and 4-piperidinone interacted with SGLT-2 via conventional hydrogen bond and Van der Waals interactions only. The interaction of 2-methoxy-4-vinyl phenol and myo-inositol with the ligand was also mainly via conventional hydrogen bond and Van der Waals interactions, but with the presence of unfavorable donor-donor interactions.

Figure 4 shows the results of the interactions of the ligands with DPP-IV. The standard drug, anagliptin, showed a unique set of interactions, viz. Pi-alkyl (TYR 631, TYR 666), conventional hydrogen bonds (SER 630, LYS 554), and Van der Waals interactions. 2-methoxy-4-vinyl phenol showed Pi-Pi T-shaped (TYR 662, TYR 666), Pi-alkyl (VAL 656, HIS 740), conventional hydrogen bond (ARG 125), and Van der Waals interactions with DPP-IV. 1-D-thioglucitol, 4-piperidinone, and myo-inositol all interacted with the ligand mainly via conventional hydrogen bond and Van der Waals interactions.

The results of the amino acid interactions of the ligands with alpha-amylase are presented in Figure 5. The standard drug, acarbose, interacted with alpha-amylase through conventional hydrogen bonds and Van der Waals interactions. Myo-inositol showed interactions with the ligand, viz., carbon-hydrogen interactions (HIS 101, HIS 299), conventional hydrogen bonds (GLU 233, ASP 300), and Van der Waals interactions (LEU 162, LEU 165). 2-methoxy-4-vinyl phenol interacted with the ligand through alkyl, pi-alkyl, conventional hydrogen bond, and Van der Waals interactions. The interaction of 4-Piperidinone and 1-D-thioglucitol with alpha-amylase was mainly via conventional hydrogen bonds and Van der Waals interactions.

Table 3 shows pharmacokinetic (ADMET) and drug-likeness properties of the ligands. The compound possesses favorable ADMET profiles, indicating good oral bioavailability, solubility, metabolic stability, low toxicity, and also obeys Lipinski's rule.

Table 2. Binding affinities (ΔG (Kcal/mol) of compounds from *Tephrosia bracteolata* leaves and standard drugs against some targets of diabetic complications.

Compounds	Pubchem CID	ACE (1086)	DPP-IV (3WQH)	SGLT-2 (7VSI)	AR (3S3G)	α- amylase (1B2Y)
		ΔG energy (Kcal/mol)				
Lisinopril *	5362119	-7.4				
Anagliptin *	44513473		-8.2			
Empagliflozin*	11949646			-10.6		
Alrestatin *	2120				-7.9	
Acarbose*	41774					-7.2
Myo-Inositol	892	-5.7	-5.5	-6.4	-5.9	-5.7
2-methoxy-4-vinyl phenol	332	-6.2	-5.8	-6.7	-7.1	-5.6
1-D-thioglucitol	53785676	-5.1	-5.4	-5.7	-5.7	-4.9
4-Piperidone	33721	-4.5	-4.4	-4.7	-5.2	-4.0
RMSD value (Å)		1.2	1.8	1.5	1.2	1.4

* Standard ligands: Lisinopril for Angiotensin converting enzyme (ACE), Anagliptin for Dipeptidyl- peptidase-IV (DPP-IV), Empagliflozin for Sodium-Glucose Co-transporter 2 (SGLT-2), Alrestatin for Aldose Reductase (AR), and Acarbose for Alpha-amylase (α- amylase).

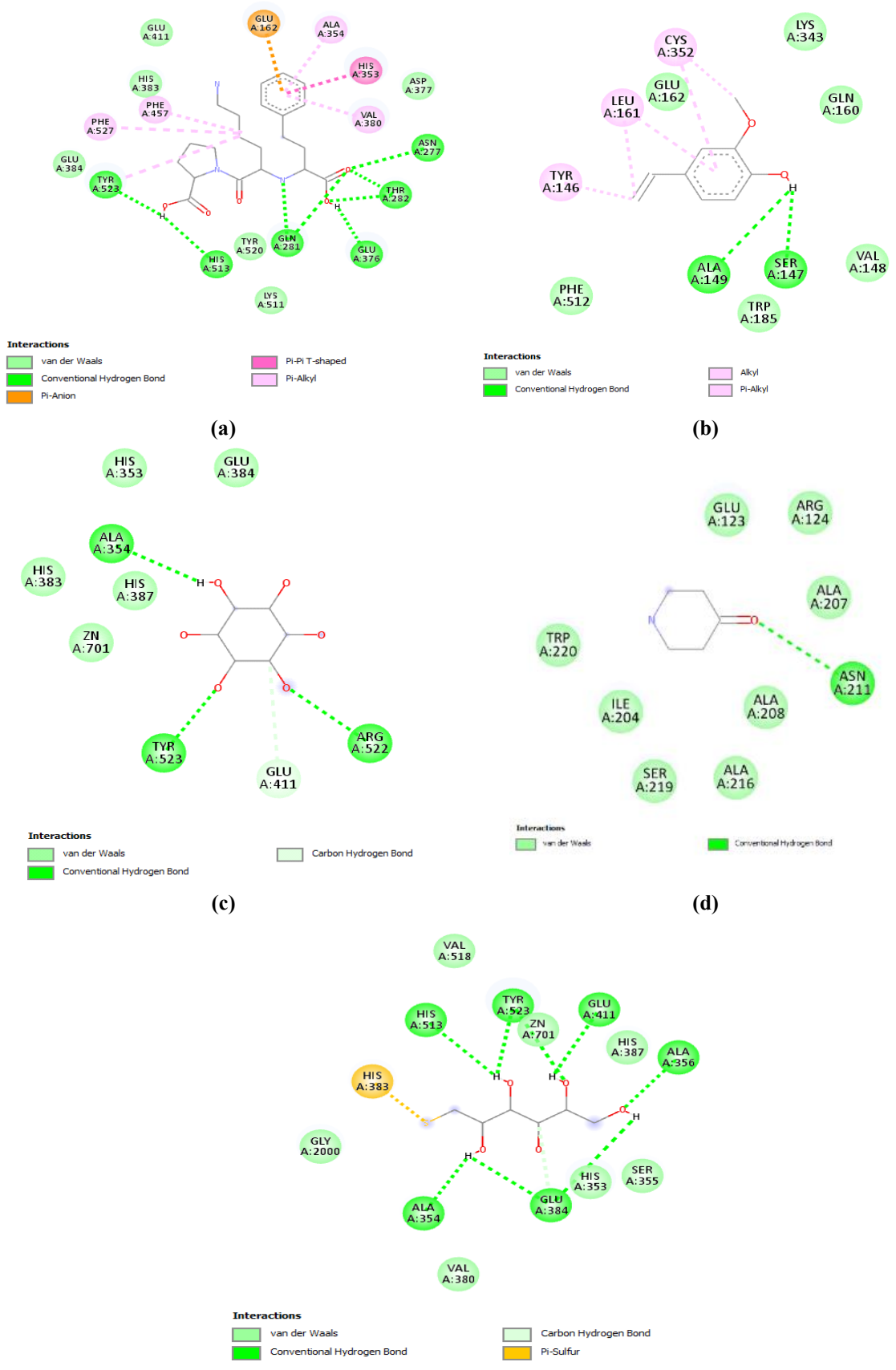

Figure 1. 2D structures of the potential molecular interactions of amino acid residues of angiotensin converting enzyme (ACE) with **(a)** Lisinopril; **(b)** myo-inositol; **(c)** 2-methoxy-4-vinyl phenol; **(d)** 4-Piperidinone; **(e)** 1-D-thioglucitol.

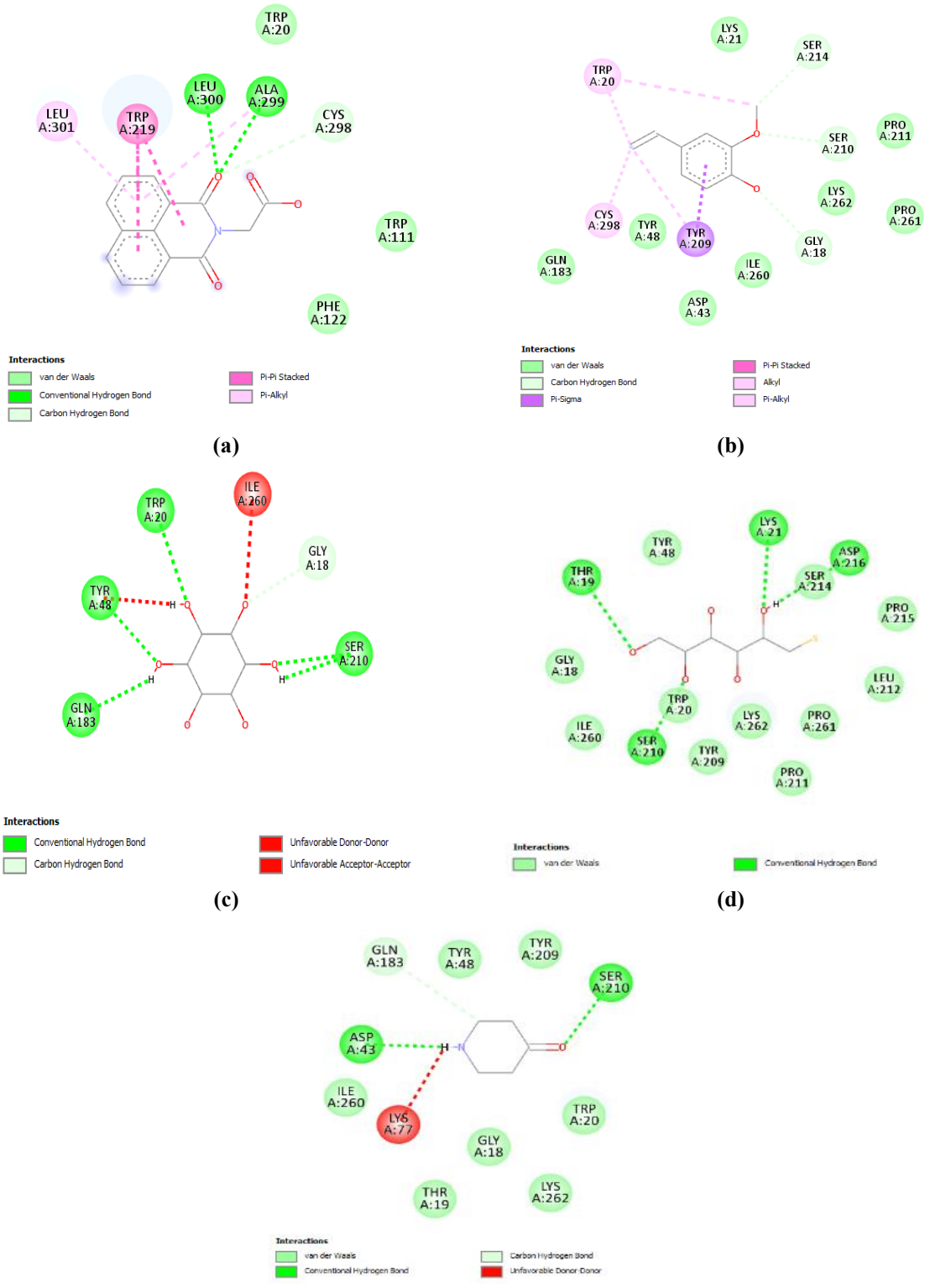

Figure 2. 2D structures of the molecular interactions of the amino acid residues of aldose reductase with **(a)** Alrestatin; **(b)** 2-methoxy-4-vinyl phenol; **(c)** myo-inositol; **(d)** 1-D-thioglucitol; **(e)** 4-Piperidinone.

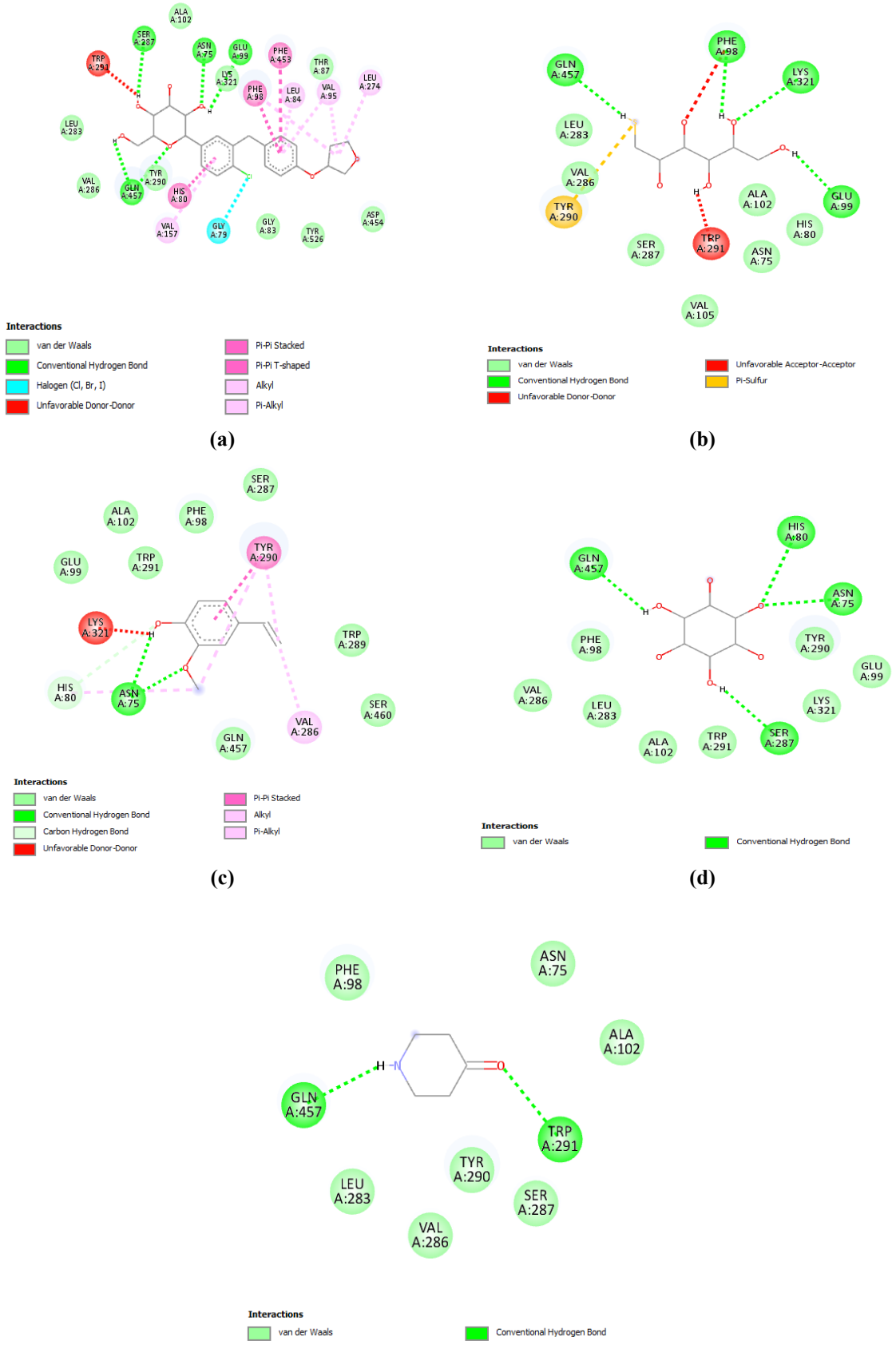

Figure 3. 2D structures of the molecular interactions of amino acid residues of sodium glucose cotransporter-2(SGLT-2) with **(a)** Empagliflozin; **(b)** 1-D-thioglucitol; **(c)** 2-methoxy-4-vinyl phenol; **(d)** myo-inositol; **(e)** 4-Piperidinone.

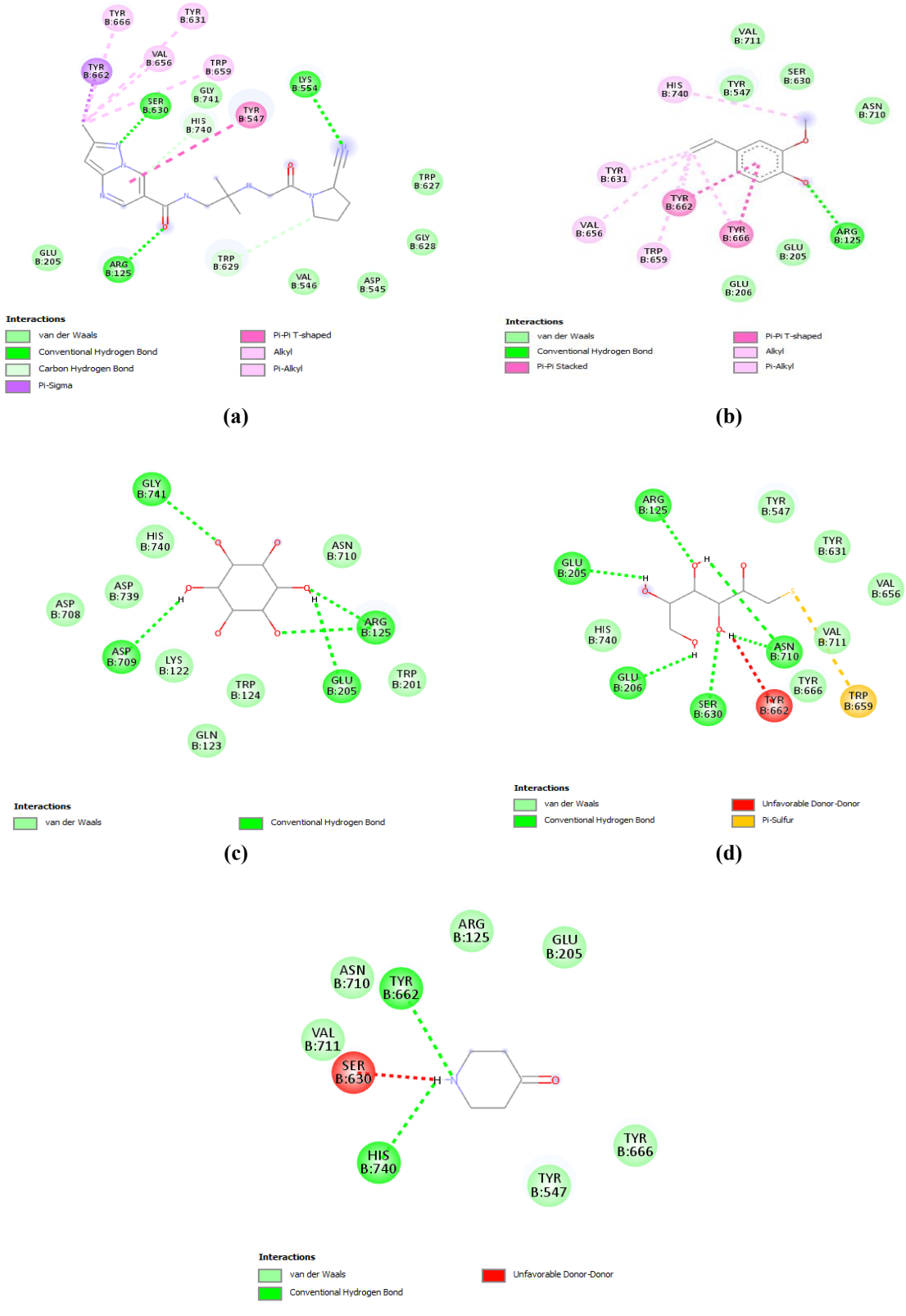

Figure 4. 2D structures of the molecular interactions of amino acid residues of dipeptidyl peptidase (DPP-IV) with **(a)** Anagliptin; **(b)** 2-methoxy-4-vinyl phenol; **(c)** myo-inositol; **(d)** 1-D-thioglucitol; **(e)** 4-Piperidinone.

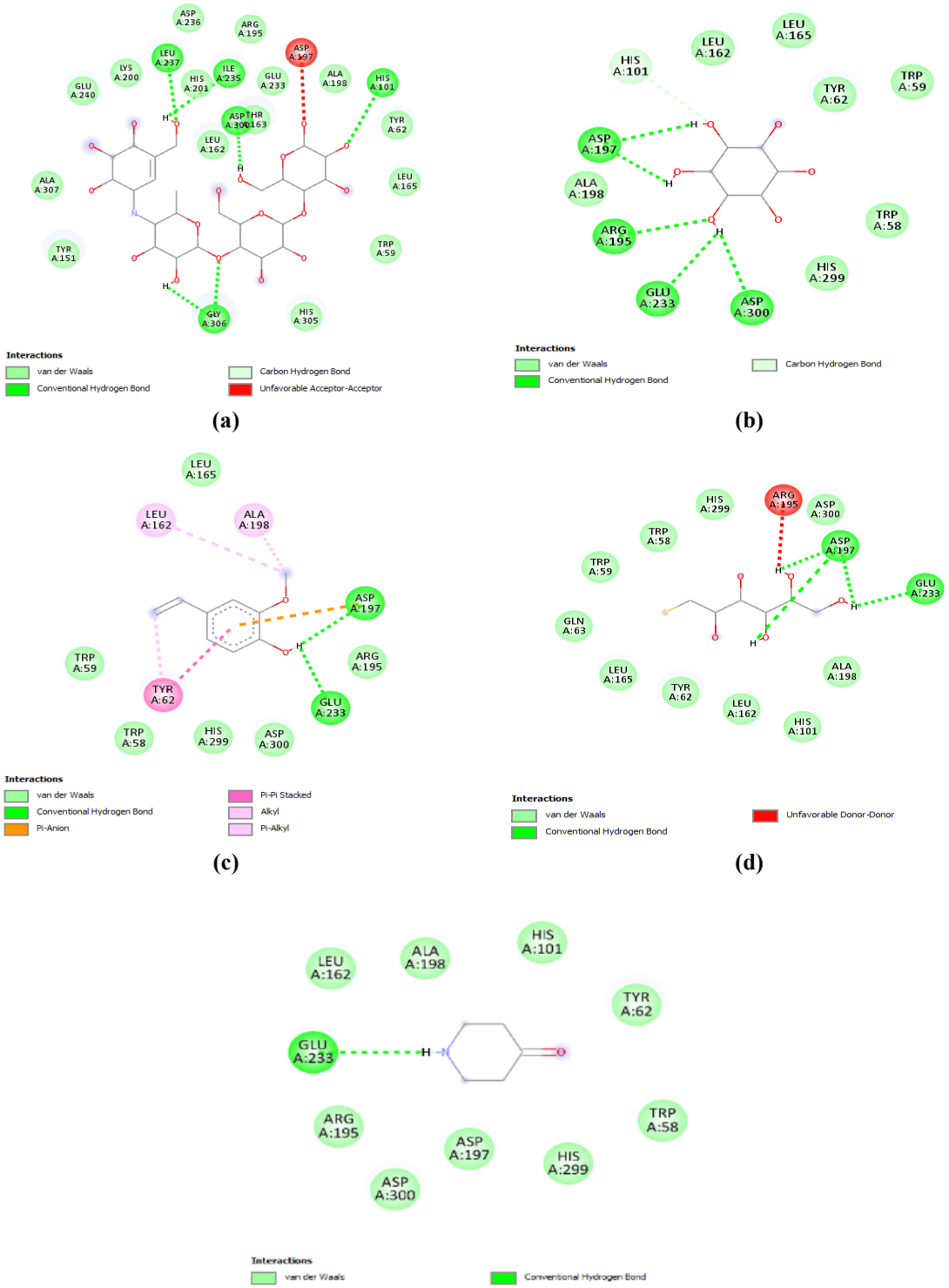

Figure 5. 2D structures of the molecular interactions of amino acid residues of alpha-amylase with **(a)** Acarbose; **(b)** myo-inositol; **(c)** 2-methoxy-4-vinyl phenol; **(d)** 1-D-thioglucitol; **(e)** 4-Piperidinone.

Table 3. Drug likeness and ADMET properties of the Test compounds.

Parameters	2-methoxy-4-vinyl phenol	Myo-Inositol	1-D-thioglucitol	4-Piperidinone
Molecular formular	C9H10O2	C6H12O6	C6H14O5S	C5H9NO
Molecular weight (g/mol)	150.17	180.16	198.24	99.13
H-Bond acceptor	2	6	5	2
H-bond donor	1	6	5	1
Molar Refractivity	45.05	35.81	44.69	30.95
Lipophilicity *CLog* $P_{o/w}$	2.14	-2.67	-1.64	0.20
Water solubility class (ESOL)	soluble	Highly soluble	Highly soluble	Highly soluble

Parameters	2-methoxy-4-vinyl phenol	Myo-Inositol	1-D-thioglucitol	4-Piperidinone
GI absorption	High	low	low	High
BBB permeant	yes	No	No	No
P-gp substrate	No	Yes	No	No
CYP3A4 inhibitor	No	No	No	No
Lipinski Drug-likeness	Yes; 0 violations	Yes; 1 violation: NH or OH>5	Yes; 0 violations	Yes; 0 violations
Veber drug likeness	yes	Yes	Yes; 0 violations	Yes
Bioavailability score	0.55	0.55	0.55	0.55
Predicted LD_{50} (mg/kg)	1560	10,000	15,900	338
Predicted toxicity class	4	6	6	4

One common metabolic pathway known to play a major role in the development of several diabetic complications is the polyol pathway [24]. The increased activity of the polyol pathway in conditions of persistently elevated blood glucose levels is a result of the diversion of the excess glucose towards the production of sorbitol. This is facilitated by aldose reductase, at the expense of cellular nicotinamide adenine dinucleotide phosphate (NADPH), which acts as a cofactor of aldose reductase [25, 26]. Given the importance of NADPH in the biosynthesis of glutathione, an intracellular non-enzymatic antioxidant, a reduction in NADPH concentration due to aldose reductase activity can jeopardize the cellular antioxidant defense mechanism. Subsequently, sorbitol is converted to fructose in a reaction catalyzed by sorbitol dehydrogenase. This is followed by the generation of nicotinamide adenine dinucleotide (NADH), which may increase reactive oxygen species (ROS) production via NADH oxidase. All these events, along with sorbitol accumulation and oxidative stress, are known to play a major role in the pathogenesis of diabetic complications [27]. Targeting the polyol pathway, typically by inhibiting aldose reductase activity, has emerged as a potential therapeutic strategy for managing diabetic complications [28].

The use of aldose reductase inhibitors (ARIs) such as sorbinil, tolrestat, and zopolrestat has been demonstrated and reported to reduce the occurrence of various diabetic complications, including nephropathy, neuropathy, atherothrombotic cardiovascular disease, retinopathy, and myocardial ischemia [29–32]. However, despite these promising preclinical data, the clinical effectiveness of ARIs remains uncertain, and concerns persist about adverse effects such as hepatic damage and neuropathy [29]. Natural compounds derived from plants, marine organisms, and microorganisms have been shown to possess a wide range of unique chemical properties and biological activities, making them a promising basis for the development of new drugs [33].

In this study, myo-Inositol, 2-methoxy-4-vinyl phenol, 1-D-thioglucitol, and 4-piperidone were docked against AR. Among these ligands, 2-methoxy-4-vinyl phenol had the highest binding affinity (-7.1 kcal/mol). 2-methoxy-4-vinyl phenol showed special interactions such as pi-alkyl (TRP 20, CYS 298), carbon-hydrogen bonds (SER 210, SER 214), and Van der Waals interactions with AR. Pi-Alkyl interactions are non-covalent in nature, and they occur between the π-electron cloud of an aromatic ring, such as benzene, and the electron density of an alkyl group, such as methyl or ethyl groups. Pi-alkyl interactions are very important in stabilizing protein-ligand binding [34]. Carbon-hydrogen interactions are also weak non-covalent interactions between a carbon-hydrogen bond and an electron-rich region or group, such as a lone pair or electronegative atom. Carbon-hydrogen interactions, though usually not pronounced, play an important role in the stabilization of protein–ligand interactions [34]. These interactions might have contributed to the strong binding affinity (-7.1

kcal/mol) that the ligand had with AR, which was comparable to that of the standard drug, alrestatin (-7.9 kcal/mol). The implication of this observation is that 2-methoxy-4-vinyl phenol could serve as a lead for the synthesis of a new AR inhibitor with a better safety profile than the already available AR inhibitors if its pharmacological relevance is confirmed through *in vitro* and *in silico* studies.

Diabetic Nephropathy (DN) is a dangerous complication of diabetes, and it is reported to be a leading cause of death in diabetic patients [35]. Recent studies revealed the important role of the ACE molecule in the pathogenesis of diabetic nephropathy [36, 37]. ACE is responsible for the production of angiotensin II, a key component of the renin-angiotensin system that plays a crucial role in blood pressure homeostasis by constricting blood vessels [38]. In individuals with diabetes, there is a sustained increase in angiotensin II production, leading to elevated oxidative stress, glomerular hyperfiltration, endothelial damage, thrombosis, inflammation, and vascular remodeling [39].

ACE inhibitors (ACEi) are usually administered as a first-line therapy in diabetics suffering from diabetic nephropathy due to their ability to protect the kidney [40]. ACEi acts primarily by inhibiting the biochemical conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates aldosterone release, leading to increased blood volume and pressure. By reducing angiotensin II biosynthesis, ACEi causes blood vessels to dilate, decreases blood volume, and consequently lowers blood pressure. Additionally, ACEi can increase bradykinin biosynthesis, leading to blood vessel dilation and decreased blood pressure. Among the commonly prescribed drugs for diabetic nephropathy treatment are lisinopril, ramipril, and captopril [41]. These drugs usually come with a wide range of side effects and adverse effects. Hence, there is a need for alternatives with better pharmacodynamic and pharmacokinetic profiles.

In this study, among the ligands, 2-methoxy-4-vinyl phenol had the highest binding affinity (-6.2 kcal/mol) with ACE. The ligand interacted with ACE via only conventional hydrogen bonds and Van der Waals interactions. Hydrogen bonds and Van der Waals interactions are the primary forces that stabilize ligand binding to the active site of an enzyme. Though 2-methoxy-4-vinyl phenol had a weaker binding affinity with ACE than lisinopril, further chemical modification, *in vitro*, and *in silico* screening of the ligand could qualify it as a lead compound for the synthesis of an ACEi with no or fewer side effects than those known with the ACEi currently in use.

Diabetic cardiomyopathy (DC) is another complication of poorly managed diabetes. In DC, the structure and function of the heart undergo various alterations, including increased left ventricular mass, myocardial fibrosis, and impaired heart muscle relaxation [42, 43]. The relationship between diabetes and heart failure is a two-way street. Anomalies in metabolic functions lead to cardiac dysfunction, while cardiac dysfunction leads to increased insulin resistance and poor glycemic control [44]. The DPP-IV is an enzyme that is widely secreted in endothelial cells, the immune system, and other tissues. It plays a key role in the metabolism of glucose by inactivating the incretin hormones, which include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [45].

DPP-IV inhibitors are a group of hypoglycaemic agents commonly referred to as gliptins. They prolong the activity of GLP-1, which increases insulin secretion and decreases glucagon release in a glucose-dependent manner. In addition to their effects on glucose homeostasis, DPP-IV inhibitors also enhance the cardioprotective properties of GLP-1 and GIP by improving endothelial function, reducing oxidative stress, and exerting anti-inflammatory

effects, which are potentially advantageous in heart failure management [46, 47]. In animal models, GLP-1 has been observed to improve myocardial contractility [48], reduce myocardial injury after ischemic events, and enhance endothelial function through increased nitric oxide availability, leading to vasodilation and improved blood flow [49].

In this study, 2-methoxy-4-vinyl phenol also had the highest binding affinity (-5.8 kcal/mol) with DPP-IV, which was, however, not comparable to that of the standard drug, anagliptin (-8.2 kcal/mol). 2-methoxy-4-vinyl phenol showed Pi-Pi T-shaped (TYR 662, TYR 666), Pi-alkyl (VAL 656, HIS 740), conventional hydrogen bond (ARG 125), and Van der Waals interactions with DPP-IV. As mentioned earlier, Pi-Alkyl interactions are non-covalent and very important in stabilizing protein-ligand binding [34]. Hydrogen bonds and Van der Waals interactions (though usually not pronounced) play an important role in stabilizing protein–ligand interactions [34]. Further chemical modifications of the ligand, such as the introduction of a functional group, could improve its binding affinity for the enzyme, providing an alternative to current DPP-IV inhibitors.

Distal symmetric polyneuropathy (DSPN) is another common microvascular complication of type 2 diabetes mellitus. It affects about 50% of people living with diabetes [50]. This pathophysiologic condition involves both metabolic and vascular abnormalities leading to nerve fiber damage, with hyperglycemia-driven oxidative stress, reduced nerve blood flow, and chronic subclinical inflammation contributing to its pathogenesis [51, 52]. The presence of DSPN impairs quality of life and is associated with increased mortality [53]. Even in conditions of optimal glycemic control, diabetic neuropathy frequently exists due to its multifactorial nature, including the presence of chronic oxidative stress and microvascular injury [54]. Orthodox therapies focus only on symptomatic relief, such as the management of pain with anticonvulsants or antidepressants and via the use of SGLT-2 inhibitors to slow the rate of disease progression by controlling hyperglycemia [55].

SGLT-2 inhibitors act primarily on the proximal tubule of the kidney by impeding the reabsorption of glucose and sodium. This results in glycemic control, which is independent of the action of insulin. This phenomenon induces a moderate osmotic diuresis and natriuresis, reducing blood volume and, consequently, leading to a significant decrease in blood pressure [56]. Additionally, SGLT-2 inhibitors have been reported to ameliorate oxidative stress and inflammation, a possible mechanism underlying the cardiovascular and renal protective effects observed [57]. SGLT-2 inhibitors are, however, not free of adverse effects, which include risk of diabetic ketoacidosis, dehydration, and, in some instances, Fournier's gangrene [58, 59]. Consequently, new interventions targeting these side effects could improve clinical outcomes in DSPN.

Results of this study showed that 2-methoxy-4-vinyl phenol had the highest binding affinity (-6.7 kcal/mol) with SGLT-2, which was not comparable to that of the standard drug-empagliflozin (-10.6 kcal/mol). The interaction of 2-methoxy-4-vinyl phenol with the ligand was mainly via conventional hydrogen bond and Van der Waals interactions. Hydrogen bonds and Van der Waals interactions are known to play an important role in stabilizing protein–ligand interactions [34]. Additional structural modifications of the ligand, such as the introduction of a functional group, could improve its binding affinity to the enzyme. With further *in vitro* and *in vivo* screening, the modified ligand could provide an alternative with fewer or no side effects compared to the currently available SGLT-2 inhibitors.

One key factor responsible for postprandial hyperglycemia is the fast uptake of glucose in the intestine by the action of glucosidases, a class of enzymes (α- amylase and α-glucosidase)

that help in the breakdown of complex carbohydrates (starch and oligosaccharides) into simple sugars such as maltose and glucose [60, 61]. Therefore, one important therapeutic approach to reduce postprandial hyperglycemia is to retard glucose absorption by inhibiting these carbohydrate-hydrolyzing enzymes.

At present, a number of conventional drugs are available that competitively and reversibly inhibit the α-glucosidase enzyme in the intestine and pancreas. These drugs include acarbose, miglitol, and voglibose. The use of these drugs is, however, limited due to a large number of side effects such as abdominal pain, flatulence, and diarrhea in the patients, which might be caused by excessive inhibition of pancreatic α- amylase resulting in fermentation of undigested carbohydrates in the colon by colonic flora [62, 63]. Therefore, a number of plants and plant-derived compounds with lesser side effects have been used to manage postprandial hyperglycemia through a mild inhibitory effect against α-amylase and strong inhibitory activity against α-glucosidase [64, 65].

It was observed in this study that in the case of alpha-amylase, myo-inositol had the highest binding affinity (-5.7 kcal/mol). Myo-inositol showed interactions with the target, viz., carbon-hydrogen interactions (HIS 101, HIS 299), conventional hydrogen bonds (GLU 233, ASP 300), and Van der Waals interactions (LEU 162, LEU 165). Hydrogen bonds and Van der Waals interactions are known to play an important role in stabilizing protein–ligand interactions [34]. The binding affinity of myo-inositol to α-amylase was not comparable to that of acarbose. The implication of this is that the inhibitory effect of myo-inositol on α-amylase might be milder than that of acarbose. Thus, myo-inositol might have fewer side effects, such as abdominal pain, bloating, and flatulence, that are usually associated with the use of acarbose.

Among the ligands tested, methoxy-4-vinyl phenol exhibited strong binding affinities towards ACE, DPP-IV, SGLT-2, and AR, while Myo-Inositol exhibited strong binding affinity towards *α*-amylase. 2-methoxy-4-vinylphenol is a naturally occurring phenolic compound. Different groups of phenolic compounds have different biological characteristics. However, they are usually known for their antioxidant properties. Many studies have shown that diabetes mellitus is associated with increased free radical formation and decreased antioxidant capacity, leading to oxidative damage to cellular components [66]. Studies have reported that 2-methoxy-4-vinylphenol is used as an anti-inflammatory, antioxidant, and antimicrobial agent [67–70]. Myo-inositol is a cyclitol present in animal and plant cells. It can be present in nine distinct stereoisomers, with myo-inositol being the most represented. D-chiro-inositol is an inositol isoform derived from myo-inositol through an epimerization process, and this reaction is insulin-dependent [71]. Both myo- and d-chiro-inositol showed insulin mimetic effects in animal models of insulin resistance [72, 73]. Inositol has been mainly used as a supplement in treating several pathologies, such as gestational diabetes (GDM) [74]. Consequently, a potential role for inositol as a treatment option could be hypothesized for type 2 diabetes, which is characterized by insulin resistance and reduced insulin secretion from the pancreas [75].

The pharmacokinetic properties and drug-likeness of the ligands were also investigated in this study. The compound possesses excellent ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties. The ligands also passed the drug-likeness test as they obeyed the five rules of Lipinski, which are- molecular weight (MW) of not more than 500 g/mol, hydrogen bond acceptors not more than 10, hydrogen bond donors not more than 5, LogP value less than 5, and number of rotatable bonds not less than 10 [76].

4. Conclusions

The docking results revealed that methoxy-4-vinyl phenol exhibited strong binding affinities towards ACE, DPP-IV, SGLT-2, and AR, while Myo-Inositol exhibited strong binding affinity towards α-amylase. ADME-T analysis revealed that the compounds possess favorable ADMET profiles, indicating good oral bioavailability, metabolic stability, and low toxicity. Furthermore, drug-likeness evaluation using Lipinski's rule of five and other criteria suggested that these compounds have promising drug-like properties. Conclusively, this study underscores the therapeutic potential of these compounds, especially methoxy-4-vinyl phenol and Myo-Inositol, for managing diabetic complications, making them suitable candidates for further drug development. However, this inference is based solely on *in silico* data and warrants further *in vitro* and *in vivo* studies to confirm the pharmacological relevance of these ligands.

Author Contributions

Conceptualization, P.I. and E.M.; methodology, P.I., C.O. and I.N.; software, E.M.; validation, P.I., E.M., and H.N.; formal analysis, M.A. and R.C.; investigation, T.I. and A.I.; resources, O.O., C.O. and J.A.; data curation, P.I.; writing—original draft preparation, P.I., I.N.and E.M.; writing—review and editing, H.N., T.I., A.I., O.O., and J.A.; visualization, E.M.; supervision, P.I.; project administration, P.I. and E.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
SGLT-2	Sodium-Glucose Co-Transporter 2
AR	Aldose Reductase

Abbreviation	Definition
DN	Diabetic Nephropathy
ACE	Angiotensin Converting Enzyme
DPP-IV	Dipeptidyl-Peptidase IV
ADA	American Diabetes Association
DSPN	Distal Symmetric Polyneuropathy
GC-MS	Gas Chromatography-Mass Spectrometry
MW	Molecular Weight
GLP-1	Glucagon-Like Peptide-1
GIP	Glucose-Dependent Insulinotropic Polypeptide
DC	Diabetic Cardiomyopathy
ARIs	Aldose Reductase Inhibitors

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