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Original Article

LEAD IDENTIFICATION AND OPTIMIZATION OF PLANT INSULIN-BASED ANTIDIABETES DRUGS THROUGH MOLECULAR DOCKING ANALYSES

SHABANA BIBI[1], SAIMA KALSOOM[2], HAMID RASHID[3], KATSUMI SAKATA[1]*

[1]Department of Environment and Life Engineering, Maebashi Institute of Technology, Gunma, Japan, [2]Department of Chemistry, Quaid-e-Azam University, Islamabad, Pakistan, [3]Department of Bioinformatics, Mohammad Ali Jinnah University, Islamabad, Pakistan. Email: ksakata@maebashi-it.ac.jp

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ABSTRACT

Objective: Diabetes mellitus (DM) is a multifactorial disorder of the pancreas and the third leading cause of deaths in humans. Presence of plant proteins whose genomic sequences are similar to those of animal insulin has been demonstrated. We wished to discover anti-DM drugs having high inhibitory activity based on plant proteins.

Methods: Computer-aided molecular docking methods were applied using Auto Dock Vina software.

Results: We selected a plant protein with Uni Prot identification Q7M217 insulin in *Canavalia ensiformis* as the target protein for DM. We identified an active lead compound among eight candidate compounds on the basis of significant binding interactions with the target protein and half-maximal inhibitory concentration (IC_{50}) values. We designed four analogs of the lead compound. Molecular docking analyses showed that the four analogs could be used as anti-DM agents with suitable drug-like properties as compared with a standard compound for the treatment of DM (aleglitazar). These analogs can also be used for future studies.

Conclusion: We identified an anti-DM compound, a biphenyl derivative, based on plant insulin. We designed its analogs using a functional-group inter-conversion approach. Our computer-aided study provided information on binding energies and binding interactions of the analogs to predict their anti-DM activity.

Keywords: Diabetes mellitus, Plant insulin, Lead identification and optimization, Computer-aided drug design.

INTRODUCTION

Insulin is a hormone secreted by the pancreas that regulates glucose levels in the blood. In the absence of insulin, cells cannot use the energy from glucose to maintain metabolic activities within the body. Insulin was discovered from extracted protein from the pancreas tissues of dogs in 1921 by Frederick Grant Banting and Charles Best. This material was used later to keep dogs with diabetes mellitus (DM) alive. This material was introduced into a 14-year-old male with DM in 1922 for treatment of this disease.

Insulin was accepted by the US Food and Drug Administration in 1939 [1]. Insulin is involved in the homeostasis of glucose and lipids, the growth and development of tissue, and responds to elevated levels of glucose and amino acids in blood. It controls metabolism by tissue-specific actions such as the phosphorylation and changes in function of proteins, and shows differential gene expressions. Pathophysiology of type-2 diabetes mellitus (T2DM), in light of insulin resistance, involves pancreatic β-cells, the liver, skeletal muscles, and adipose tissues. A combination of a stimulus (higher post-prandial levels of glucose in blood) as well as secretion of insulin and suppression of glucagon is used by humans to sustain the plasma level of glucose at ≈5 mmol [2–4]. The mechanism of glucose-stimulated insulin secretion by ß-cells has been described [5].

β-cells of the pancreas respond to high levels of glucose in plasma by secreting insulin. Glucose transporter-2 on the membrane of β-cells has a high Michaelis constant. The maximum rate can be achieved by a system allowing rapid equilibration of glucose on both sides of the membrane. Glucokinase facilitates phosphorylation of glucose and its diversion into the glycolysis cycle, a key step in defining glucose-stimulated insulin secretion [5]. Released insulin attaches to the insulin receptor (IR). The IR is a transmembrane heterodimer of two α and two β subunits held by disulfide bonds. Two isoforms of the IR (IR-1 and IR-2) possess varying affinities for binding insulin to their extracellular domains. Varying affinity for insulin is a good basis for insulin resistance, but remains a controversial subject and is incompletely understood. Insulin binding results in the attachment and auto-phosphorylation of three tyrosine residues in the regulatory domains and increases the activity of tyrosine kinase. Then, the intracellular domains phosphorylate insulin receptor substrate (IRS)-1. IRS is an adaptor protein with four isoforms, of which IRS-1 and IRS-2 are implicated in glucose homeostasis and T2DM [6, 7].

Protein hormone insulin in the plant kingdom has not been acknowledged by researchers of plant science [8]. Insulin, the principal glucose-regulating hormone, was isolated originally from animal pancreatic tissue [9]. Plants do not possess pancreatic cells and glucose does not form their principal metabolite. Insulin was not considered to be present in plants even though studies showed that chemical substances similar to animal insulin existed in plants, and that extracts from these chemical substances modified the rate of seedling metabolism [10, 11]. Khanna *et al*. reported that the insulin-like material glucokinin was present in plant sources and microbes that exhibited similar functions to those of insulin in vertebrates [12]. Thereafter, some studies reported insulin-like peptides in other life forms such as bacteria and fungi [13, 14].

Additional work on the possible presence of an insulin-type molecule in *Momordica charantia* was done by Ng *et al*. [15]. They showed the related features of a protein of animal insulin in plants. The "genomics revolution" in the l990s permitted comparison of the sequences of nucleotides and amino acids through bioinformatic processes to identify common proteins that may exist across different life forms [16, 17].

Xavier-Filho *et al*. retrieved information that suggested insulin was present in plants. Their results suggested that a protein molecule with the same amino-acid sequence as bovine insulin was expressed in leguminous plants [18]. Koona *et al*. tested the hypothesis that plant genomes contain sequences similar to animal insulin by developing a phylogenetic tree of the different types of insulin. They evaluated protein domains, and demonstrated that insulin-like molecules are present in plants. Furthermore, domains common to sequences in insulin exist in cowpea, *Canavalia ensiformis* (jack bean), and *Bauhinia purpurea*. Insulin-like proteins may have roles in plant development and metabolic functions [19].

Bauhinia purpurea belongs to the class *Leguminosae*. It is a very popular medium-sized deciduous tree, the components of which are used in the treatment of dropsy, pain, rheumatism, convulsions, delirium, and septicemia [20]. The plant bark serves as an astringent in the treatment of diarrhea and its extract is useful for the treatment of ulcers. The plant has pharmacologic actions on the central nervous system, and has cardiotonic, lipid-lowering, anti-oxidant, hepatoprotective and hypoglycemic activities [21]. Leaves of *Bauhinia purpurea* have been used extensively for the treatment of abrasions and injuries [22].

Canavalia ensiformis DC belongs to the class *Leguminosae*. It is known as "horse bean" and is native to Central America and West Indian islands. It is also cultivated widely in the humid tropics of Asia and Africa. The seeds of *Canavalia ensiformis* DC have been reported to possess anti-hypercholesterolemic and hypoglycemic properties [23]. Its extracts have been tested on alloxan-induced DM rats, showed good activity against hyperlipidemia and hyperketonemia, and it has been shown to be potential anti-DM agents. Oral administration of an aqueous extract of the seeds of *Canavalia ensiformis* has been shown to reduce urinary and blood levels of glucose and to elevate levels of triacyl glycerol, ketone bodies and cholesterol associated with DM [24].

According to Singh *et al*., *Vigna unguiculata* (from the class *Leguminosae*), an ancient plant present in Asia and Africa [25], possesses a three-lobed leaf structure and long narrow pods. It reaches maturity 60 days after sowing. The amino-acid sequence of a protein in this plant was found to be similar to the sequence of bovine insulin and to the sequence of the insulin isolated from the seed coat of *Canavalia ensiformis* [26, 27].

These traditional medicines have a promising future in DM therapy. There is an urgent need to shift the focus towards a natural origin of insulin because it should elicit minimal side-effects compared with commercially used hypoglycemic agents [27]. In the present study, we carried out bioinformatics studies of molecular docking to identify new drugs for DM treatment using plant extracts with similar sequences to those of animal insulin.

We employed a ligand-based drug design and revealed diverse classes of small drug-like compounds to be potential candidates for DM treatment. Moreover, we completed molecular modeling and docking studies for the lead compound, which was identified from the test dataset of anti-DM compounds [28–31] and modified to optimize its activity. These results will provide deeper understanding of the inhibitory behavior of the compound and be valuable in the development of anti-DM drugs.

MATERIALS AND METHODS

Molecular docking analyses were undertaken to evaluate the most preferred geometry of protein–ligand complexes. Anti-DM compounds were analyzed with a target protein using Auto Dock v 4.0 and Auto Dock Vina (Scripps Institute, San Diego, CA, USA) [32]. The docking phase is, in general, meaningful with its two components: target protein and ligand. Docking results identify native or native-like configurations of protein–ligand complexes.

Docking steps were conducted in a specific sequence. Briefly, water molecules were eliminated from the target protein, after which an input was provided to the analytical software. Kollman and Gasteiger charges were computed for the macromolecule by Auto Dock v 4.0 [32]. Then, the macromolecule was checked for missing atoms. After repairing missing atoms, hydrogen atoms were added by keeping all the parameters at default settings. After these modifications, the macromolecule was obtained, and ligand preparation carried out. Kollman and Gasteiger charges were computed for the ligand [33]. Then, some of the torsions of the ligands were defined. To choose torsion for flexible docking, rotatable bonds were converted into non-rotatable bonds and *vice versa*. The number of active torsions was marked as the most atoms rather than the fewest. After preparation of a macromolecule and a ligand, a rigid residue was prepared using the GRID module provided in Auto Dock v4.0 [32]. A flexible macromolecule was then obtained. Auto Dock Vina [32] was used for molecular docking. This software outputs different energy models. Among the models, the lowest energy model against each ligand was selected, and docking results for the selected set generated.

For interpretation of docking results of a target protein and protein docked with the test dataset of compounds, the interactions between the "active pocket" of the protein and ligands must be found. There are three types of interactions: hydrogen bonding; ionic interactions; hydrophobic interactions. These interactions were evaluated using the Visual Molecular Dynamics (VMD) program (www.ksuiuc.e.d.u/Research/vmd/) [34]. Interaction results within a distance of 4 Å were considered. All possible binding interactions were evaluated in a docked complex of the target protein.

RESULTS AND DISCUSSION

Identification and selection of the most appropriate drug target is the major step to initiate drug design. Insulin protein was considered the target protein for this study. We extracted plant insulin structures from the MODBASE database (http://modbase.Compbio.ucsf.edu/modbase-cgi/index.cgi) [35] for testing as an alternative source to human insulin protein. The three-dimensional (3D) structure of plant insulin extracted from *Canavalia ensiformis* with accession number Q7M217 is shown in fig. 1 in two representations.

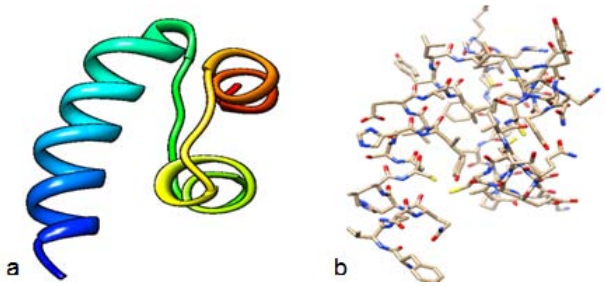


Fig. 1: Structure of plant insulin extracted from *Canavalia ensiformis*, accession number Q7M217 [a] protein in round ribbon and [b] stick representations

The insulin-like growth factor domains of human insulin are common to the insulin sequence in *Canavalia ensiformis, Vigna unguiculata* and *Bauhinia purpurea* [19]. These three plants belong to the same class: *Leguminosae*. We selected *Canavalia ensiformis* for testing as an insulin source because it has been tested in wet-laboratory experiments and because it has a highly identical homolog to human insulin protein (table 1). In a wet-laboratory experiment, this protein was recognized by anti-human insulin antibodies, lowered the blood glucose levels of alloxanized mice (suggesting that it possesses biologic potency against DM), and found to have evolutionary characteristics similar to those of human insulin [36]. Sequence alignment by Clustal Omega (Conway Institute UCD Dublin, Dublin, Eire) [37] of human insulin protein is shown in table 1 along with the plant homolog.

We used aleglitazar (Roche, Basel, Switzerland) with a half-maximal inhibitory concentration (IC50) value of 0.019 μM as a standard drug for DM. We collected data for aleglitazar from PubChem (https://pubchem.ncbi.nlm.nih.gov/), which provides validated chemical structures and detailed information of drugs, and which is organized by the US National Institutes of Health (Bethesda, MD, USA) [38]. Aleglitazar is a type of sensitizer used for T2DM treatment to reduce the complications of cardiovascular morbidity and mortality. In T2DM patients, aleglitazar can control levels of lipids and glucose in a synergistic manner while eliciting limited side effects and toxicity. [38] We designed and evaluated novel candidate compounds based on a comparison with aleglitazar.

We generated a test dataset of eight compounds (table 2) by perusing studies of anti-DM drugs in the literature [28–31]. These

compounds were considered highly active owing to their low IC_{50} values (μM). Lipinski's rule of five [39] was applied to evaluate their drug-like properties and to incorporate the pharmacokinetics of these compounds from a previous study [40]. Compound structures in the test dataset were made by Chem Draw Ultra v8.0 (chemdraw-ultra.software.informer.com/8.0/) [41]. Compounds and their IC_{50} values are shown in table 2.

We evaluated the binding interactions of the compounds with the target protein using Auto Dock and Auto Dock Vina [32]. By employing docking analyses, different conformations of compounds were provided as docked into the target protein. For each ligand, we generated the ten most active conformations, which were ranked on the basis of the binding affinities of the ligand with the target protein. Among these conformations, we selected the optimal conformation (with the smallest value of root-mean-square deviation) based on the binding energies of the compounds with the target proteins for interaction analyses.

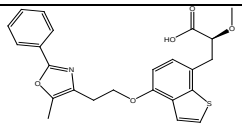
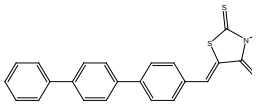
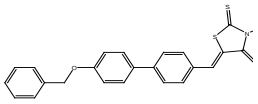
Furthermore, we analyzed the two-dimensional (2D) and 3D structures of the ligand and plant target protein. Amino acids involved in the interactions in the relevant binding pocket were studied. The test dataset was docked with the target protein. Amino acids in the active site were identified by looking in the vicinity of 10 Å. Residues that were significant for binding interactions and thus comprise the binding pocket of the target protein were: HIS4, HIS5, HIS10, ALA14, ALA30, PHE24, PHE25, VAL12, TYR16, TYR26, TYR49, THR27, CYS7, CYS36, CYS37, CYS41, CYS50, LYS29, LEU3, LEU11, LEU17, LEU43, LEU46, VAL40, GLN8, GLN35, GLN45, GLY8, GLY31, GLU13, ASN3, ASN48, and SER39 (table 2).

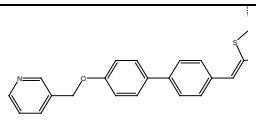
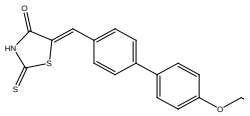
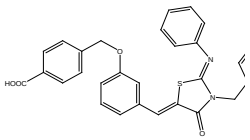
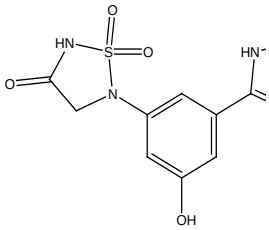
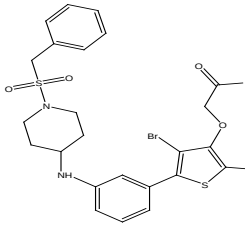
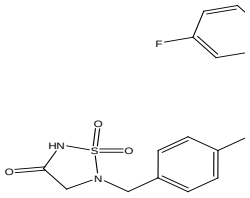
Table 1: Sequence alignment for human insulin

Upper row	Sequence length	Lower row	Sequence length	Alignment score	Alignment by Clustal Omega
Human insulin	110 aa	*Canavalia ensiformis*	51 aa	94.0	MALWMRLLPLLALLALWGPDPAAAFVNQHLCGSHLVEALYLVCGERGFFYTPKTRREAED ----------FVNQHLCGSHLVEALYLVCGERGFFYTPK------- ********** LQVGQVELGGGPGAGSLQPLALEGSLQKRGIVEQCCTSICSLYQLENYCN ----------AGIVEQCCASVCSLYQLENYCN *******:*:**********

aa* amino acid

Table 2: Structures and binding interactions of the standard drug aleglitazar and eight test compounds (T1–T8), including amino-acid data in the target protein pocket and binding energies

Name	Structure	IC_{50} (μM)	Hydrogen bonding		Ionic interaction		Hydrophobic interaction		Binding energy (Kcal/mol)
			Amino acids	Distance (Å)	Amino acids	Distance (Å)	Amino acids	Distance (Å)	
Aleglitazar		0.019	O-HIS10:NE2	3.21	None		C-HIS10:CD2 C-ALA14:CA C-ALA14:CB C-LEU11:CD2 C-LEU11:CD2 C-CYS7:CA C-SER39:C C-VAL40:CA C-VAL40:CA	3.82 3.93 3.71 4.03 3.83 3.82 3.90 3.94 3.73	–7.7
T1		0.53	S-GLN8:N	4.00	None		C-TYR26:CD2 C-TYR26:CB C-PHE24:CE2 C-PHE24:CZ C-PHE24:CZ C-TYR16:CB C-TYR16:CB C-TYR16:CD2 C-TYR16:CD2 C-TYR16:CE2 C-VAL12:CG1 C-VAL12:CG1 C-VAL12:CG2 C-VAL: C	3.95 3.85 3.95 3.75 3.89 3.45 4.00 3.90 3.75 3.69 4.00 3.94 3.71 3.75	–8.5
T2		0.48	O-SER39:N N-CYS37:O	3.95 3.55	None		C-GLU13:C C-ALA14:CA C-ALA14:CB C-LEU43:CD2 C-LEU46:CD2 C-LEU11:CD2 C-VAL40:CG1 C-VAL40:CB C-VAL40:CB C-VAL40:CG2	3.71 3.40 3.40 3.40 3.76 4.00 3.96 3.99 3.46 3.77	–7.8

T3		1.10	O-GLN45:NE2 S-ASN48:OD1 O-GLN45:NHN-TYR26:O	3.22 3.47 3.89	None		C-TYR49:CE1 C-TYR49:CE1 C-ASN48:CB C-ALA30:CA C-PHE25:CD2 C-GLN35:CD	3.75 3.75 3.29 3.80 3.84 3.96	–7.7
T4		1.24		3.91	None		C-TYR16:CD2 C-TYR16:CB C-GLU13:CG C-GLU13:CD C-VAL12:CB C-VAL12:CG1 C-TYR26:CB	3.58 3.78 3.51 3.97 3.66 3.85 3.75	–7.5
T5		0.22	O-CYS7:SG O-ASN3:ND2 H-ASN3:ND2	4.02 3.08 2.81	NH-GLU13:O	3.99	C-GLU13:CB C-ALA14:CB C-HIS10:C C-HIS10:CB C-LEU11:CD2 C-LEU46:CD2 C-CYS41:CB C-LEU11:CD2 C-LEU6:CD2	3.77 3.91 3.84 3.79 3.75 3.45 4.04 3.75 3.99	–8.1
T6		0.08	NH-TYR26:O O-SER9:NH S-CYS41:NH	4.04 3.24 3.81	NH-HIS5:0 NH-HIS5:ND1	1.97 3.06	C-HIS5:CA C-HIS5:ND1 C-TYR26:CB C-TYR26:CE C-VAL12:CB C-VAL12:CG1 C-VAL12:CG1 C-VAL12:CG2 C-TYR26:CB C-TYR26:CE C-PHE24:CE2 C-PHE24:CZ	3.88 4.00 3.06 3.81 3.71 3.67 3.86 4.00 3.94 3.67 3.67 3.90	–5.9
T7		0.005	O-LEU11:NH-ASN3:ND2 O-ASN3:ND2 H-ASN3OD1 H-CYS36:O H-SER39:O H-VAL40:N H-CYS41:N	3.73 2.62 3.15 3.74 3.47 3.55 3.71 3.95	None		C-LEU43:CD2 C-ALA14:CA C-ALA14:CB C-ALA14:CB C-VAL40:CG2	3.76 3.71 3.73 3.66 3.82	–7.6
T8		0.13	O-HIS5:NN-TYR26:OH	3.67 3.17	None		C-GLY8:C C-VAL12:CG1 C-VAL12:CG2 C-PHE24:CE2 C-PHE24:CZ C-TYR26:CB C-TYR26:CB C-TYR26:CB C-TYR26:CZ C-TYR26:CZ	3.84 3.87 3.79 3.78 3.56 3.65 3.90 3.64 3.92 3.92	–8.0

We considered most of the essential amino acids present in the binding pocket of the target plant protein that was similar to human insulin protein. One study reported insulin in the testa of *Canavalia ensiformis* [36]. Our docking results revealed that the amino acids present in the pocket of the target protein were involved in the binding interaction with the selected ligands for DM.

We selected the best conformation of the docked complex out of ten poses based on the criterion of minimum binding affinity, and identified and generated the interactions by VMD [34] (table 2). VMD software enables labeling and provides the computing distances between atoms of the selected ligand in a protein pocket. Important interactions identified in the test dataset included ionic (COOH-NH_3 or NH_2-COOH), hydrogen (N-O, O-N, O-O) and hydrophobic interactions (C-C). All interactions were calculated <4 Å of the distance between the active residues of the ligand and protein.

We selected a lead compound (T6 in table 2) from the eight compounds that had desired biologic activities on a validated molecular target.

In general, a lead compound can be modified to produce another compound with a better profile by removing unwanted properties to avoid unwanted side effects. Compounds used as potential leads can be synthetic and semi-synthetic compounds, as well as proteins in marine organisms, plants and animals [42]. The lead compound we selected was from the synthetic source in the test dataset (table 2). We conducted lead identifications in a computer-aided approach involving virtual screening, pharmacophore mapping, and molecular docking analyses [43].

In general, an appropriate potential drug candidate is a compound with fewer side effects or is more efficacious [44]. The lead compound may not necessarily become a drug candidate. To avoid such a situation, lead optimization can be advantageous in lead identification. One pharmaceutical company reported on the methods of the identification and optimization of lead compounds [45]. We identified a lead compound on the basis of a strong interaction, lowest value of IC_{50}, and binding energy. Fig. 2 shows the interactions of the lead compound docked in the target protein.

We made analogs of the compound to obtain the most active anti-DM drugs. Table 3 shows the analogs made by modifying the functional groups to make the compound more efficacious. The designed analog compounds from this study need to be tested for absorption, distribution, metabolism, excretion and toxicity in pharmacokinetics properties.

Four analogs were suggested after our study of lead compounds. Table 3 shows the analogs of the lead compound with their International Union of Pure and Applied Chemistry nomenclature generated by ChemDraw Ultra v8.0 [41]. These analogs were made by an introduction or removal of various functional groups, or by replacement of one group with another group present in the structure of the lead compound.

The first analog had a functional group comprising a sulfur atom and a hydrogen atom (-SH) at the position of (-OH). The second analog was made by a nucleophilic substitution (though its activity was dependent upon the electronic nature of the substituent). The third analog was made by the reduction of a ketone group. The fourth analog was made by removal of a steric blocker to improve the binding character of the compound.

This method of analog design improved binding interactions with the target protein. Table 3 also shows the maximum number of interactions and binding affinities of the analog set with an amino acid within 10 Å of the pocket of the target protein. The target protein (shown in table 1) showed a better binding interaction with our test dataset. Thus, we proposed it as a candidate to confirm its activity in future studies.

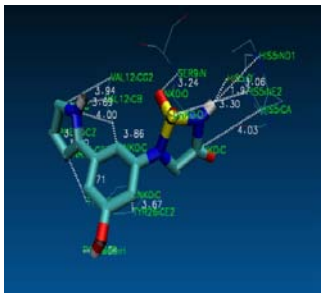
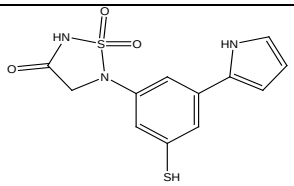
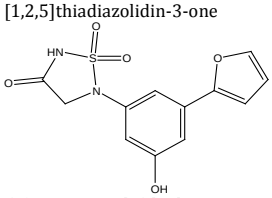
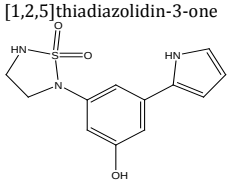
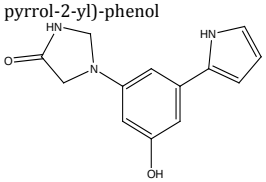


Fig. 2: Binding interaction of docked lead compound T6 with active-site residues with the lead compound represented in bond formation. Red shows the hydrogen-bond acceptor and blue shows the hydrogen-bond donor. White shows the hydrogen bond and yellow represents electronegative compounds such as halogens

Table 3: Analogs of the lead compound (T6) along with interactions and binding affinities of the analogs with those of the target protein pocket

No.	Functional group interconversion	Structure and IUPAC name	Hydrogen bonding		Ionic interaction		Hydrophobic interaction		Binding energy (Kcal/mol)
			Amino acids	Distance (Å)	Amio acids	Distance (Å)	Amino acids	Distance (Å)	
1	Functional group conversion	 5-[3-Mercapto-5-(1*H*-pyrrol-2-yl)-phenyl]-1,1-dioxo-1λ⁶-[1,2,5]thiadiazolidin-3-one	NH-CYS36:O O-CYS41:NH S-CYS41:NH	1.76 2.80 3.81	None		C-HIS10:CG C-HIS10:CG C-CYS7:CA C-CYS7:CA C-LEU11:CD2 C-ALA14:CB	3.90 3.81 3.66 3.78 3.88 3.63	–5.8
2	Nucleophilic substituent	 5-(3-Furan-2-yl-5-hydroxy-phenyl)-1,1-dioxo-1λ⁶-[1,2,5]thiadiazolidin-3-one	NH-SER39:O NH-CYS41:O NH-CYS41:SO	3.41 3.52 3.95	None		C-LEU3:CD2 C-ALA14:CB C-LEU11:CD2 C-CYS7:C C-CYS7:CA C-CYS7:CA	3.66 3.67 3.96 3.98 3.60 3.93	–5.9
3	Reduction of a ketone group	 3-(1,1-Dioxo-1λ⁶-[1,2,5]thiadiazolidin-2-yl)-5-(1H-pyrrol-2-yl)-phenol	NH-TYR25:O O-SER9:NS-CYS41:S	3.99 3.24 3.89	NH-HIS5:0	3.66	C-CYS7:CA C-CYS7:CA C-HIS5:CA C-HIS5:ND1 C-VAL12:CG1 C-VAL12:CG1 C-VAL12:CG2 C-TYR26:CB C-TYR26:CE	3.76 3.80 4.00 3.06 3.86 3.00 3.34 3.77 3.37	–5.9
4	Removal of steric blocker	 1-[3-Hydroxy-5-(1H-pyrrol-2-yl)-phenyl]-imidazolidin-4-one	NH-TYR49:O NH-CYS50:O	3.21 3.51	None		C-LEU3:CA C-ALA14:CB C-CYS7:CA C-CYS7:CB C-LEU11:CD2	3.22 3.51 3.76 3.52 3.99	–5.9

CONCLUSION

Natural products have been suggested to be the best sources of medicines for the treatment of DM [46]. Nearly 80% of the world population use traditional medicines: they prefer plant-based drugs for primary healthcare [47]. Safe and effective use of natural products can ensure that plant-based medicines are more harmonious with biologic systems.

We identified an anti-DM compound based on plant insulin: T6 (table 2). It is a biphenyl derivative and a potential lead candidate. We designed its analogs using a functional-group inter-conversion approach. Our computer-aided approach provided information on binding energies and binding interactions of the analogs to predict their anti-DM activities.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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