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Computational screening of novel therapeutic and potent molecules from bioactive trehalose and it's eight derivatives by different insilico studies for the treatment of diabetes mellitus

Shopnil Akash*

Department of Pharmacy, Daffodil International University, Sukrabad, Dhaka-1207, Bangladesh

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Abstract: Diabetes mellitus represents a set of disorders that impact how your body utilizes sugar levels (glucose), and it is a chronic disease. Every year, a huge portion of people have diagnosed with this disease globally. So, it is an urgent and required effective treatment to manage this disease. Trehalose is a potent biomolecule, So in this research, bioactive Trehalose and its derivatives have been studied to find potent molecules and inhibitors. Numerous studies have been included to make them as potent medications, such as Pass perdition, molecular docking, ADMET, and Pharmacokinetics experiment. When the pass prediction value has been satisfied, the docking studies were then conducted to determine how actively binds with the targeted protein. The docking score was seen as -7.0 kcal/mol to -9.1 kcal/mol against *Human Maltase-Glucoamylase* (PDB ID 2QMJ), and -7.0 kcal/mole to -9.8 kcal/mol was found against Human CYP3A4 bound to metformin PDB ID 5G5J. At the same time, standard FDA-approved Metformin Hydrochloride was also studied, and it provided -5.3 kcal/mole and -5.0kcal/mol. So, it is visualized that newly generated molecules are better scores than the standard.In the overall investigation, all drugs have satisfied and obtained Pass prediction score, excellent binding affinities, ADMET, and Pharmacokinetics profiles, and it could be concluded that all the medicines could be used as potent drugs.

Keyword: Diabetes mellitus; pass prediction; molecular docking; ADMET; drug-likeness.

1. Introduction

Diabetes mellitus (DM) is a chronic physiological condition[1] caused by the deficit with insulin production[2], reduced activity or insulin resistance[3], or both. This Chronic hyperglycemia leads to glucose, fat, and protein metabolism abnormalities from insulin deprivation[4]. The most prevalent endocrine condition is DM globally, among other chronic diseases[5]. Type 1 and Type 2 are the two most prevalent types of Diabetes[6]. There are a few oral medications available now that are used chiefly for survival and symptom alleviation of DM[7], such as Metformin[8], Thiazolidinediones[9]. To prevent long-term diabetes problems and enhance lifespan by eradicating numerous adverse outcomes, the use of parenteral insulin treatment has been implemented for patients of type 1 DM[10]. Insulin may be required in type 2 diabetes when blood glucose levels cannot be managed with proper diet, weight reduction, physical activity, or oral drugs[11]. Although insulin is the most potent medication towards diminishing blood glucose than other diabetes medications, such as increasing the chance of hypoglycemia[12], most consumers could be apprehensive regarding administering parenterally[12]. However, it

* E-Mail: shopnil29-059@diu.edu.bd ; Phone: +8801935567417

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has several significant limitations. To mitigate problems of conventional and parenteral drug delivery. So, we have fascinated to developed potent and biologically active molecules by modification of Trehalose which is a non-reducing sugar[13]. In that case, most widely acceptable and authentic technique computer AIDED drug design has been applied and added some new side chain by substitute with hydroxyl in Aromatic ring of Trehalose.

Trehalose is major glucose derivatives that have traditionally been regarded to serve as glucose reserve substances[14]. There are numerous other roles for Trehalose, such as: safeguarding proteins and membranes from stress; and, (ii) operating as an allosteric inhibitor of glycogen synthesis and a transcriptional controller; (iii) representing as an integral part of mycobacterial cell membrane; and (iv) as a donor of mycolic acid to the mycobacterial cell wall[15].

So, metformin binding receptor protein Human Maltase-Glucoamylase PDB ID 2QMJ and human CYP3A4 bound to metformin PDB ID 5G5J have been studied against the mention drugs molecules and analysis different parameter to established as better drugs than standard.

Before started the investigation, metformin hydrochloride was applied and trial two patients 7 days and measured their oral glucose tolerance test before taking metformin hydrochloride and two hours after taking metformin hydrochloride. Then, this metformin hydrochloride considered as standard and studied with newly developed molecules.

2. Experimental

2.1. Preparation of Ligand and Structural Activity Relationship (SAR) Studies

An strategy to discovering correlations involving chemical composition (or structural-related attributes) and bioactivity (or target function) of researched substances by modification and substitution of certain functional is known as Structure-Activity Relationship (SAR)[16]. Trehalose has traditionally numerous bioactivity and pharmacological efficacy. So, the hydroxyl group of Trehalose has been substituted by benzene ring and COOH functional group. After that, their pharmacological and drug likeness has been analysis. The substitute configure and structure are presenting in Figure 1.

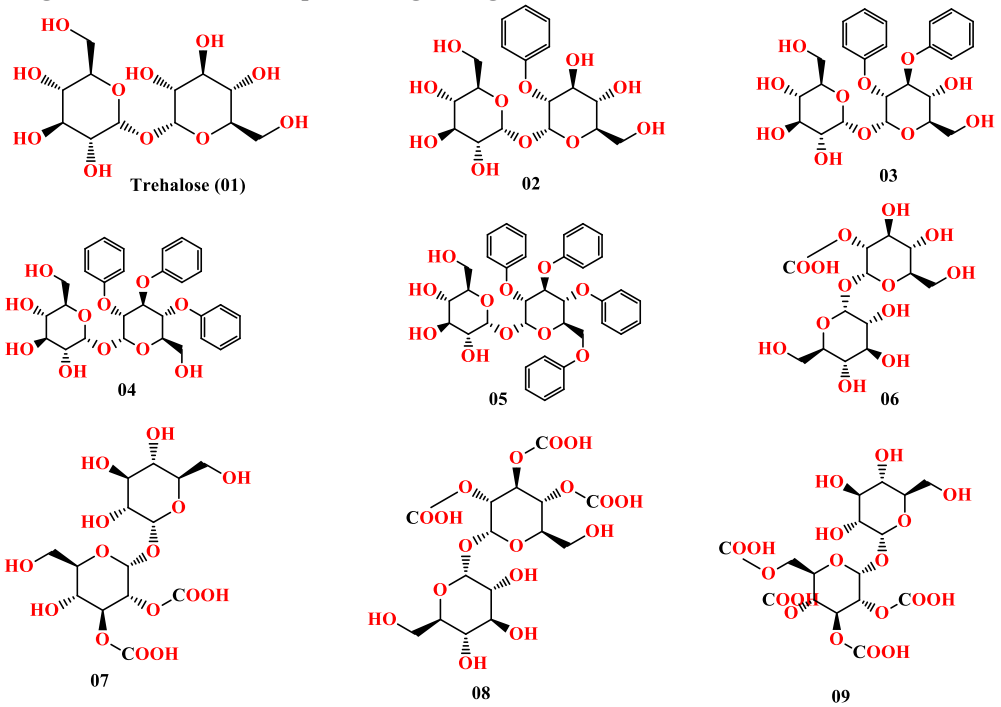


Figure 1. Chemical structure of Trehalose and its derivatives

2.2. Pass Prediction

Pass prediction data has been collected from pass online server (http://way2drug.com/PassOnline/predict.php) which provide more than 300 pharmacological effectiveness[17]. It has represented by Pa which means the probability of active and the probability of inactive (Pi). So, first of all entry the online server and upload the smile form of the reported compounds. Then, the server predicts the Pa and Pi values based on their chemical structure. Normally, Pa and Pi value vary from 0.0 to 1.0 and Pa will not equal to Pi. Although, 300 values could be predicted, but we have listed only four essential values for this research such as antiviral. antibacterial, antifungal and antidiabetics. showing in Table 1.

2.3. Determination of the Data of ADMET

Drug research and development are complicated by the fact that chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) are all involved. In this regards, ADMET measurement is fundamental requirement and important factors. So, the ADMET has been measured and determined by machine learning and web-based tool pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction)[18] and SwissADME (http://www.swissadme.ch/index.-php)[19]. These two websites provide various information related to designed and discovery new drug molecules such as AMES toxicity, blood-brain barrier (BBB), water solubility, total clearance, maximum tolerance rate, Hepatotoxicity, Oral Rat Acute Toxicity (LD50), Oral Rat chronic Toxicity and Skin Sensitization etc.

2.4. Protein Preparation and Molecular Docking Study and Visualization

The three-dimensional structure of Human Maltase-Glucoamylase PDB ID 2QMJ (https://www.rcsb.org/structure/2QMJ) and Human CYP3A4 bound to metformin PDB ID 5G5J (https://www.rcsb.org/structure/5G5J) have been picked up from protein data bank as PDB format. After that, the excess atom, water and ligand molecules were cleaned up by Pymol version 2021 and minimize their energy by swisspdbviwer[20]. Then, again they have been saved as PDB format and with the assist of PyRx virtual screening in AutoDock mode, molecular docking studies was conducted against the reported ligands. The protein information is given in Figure 2.

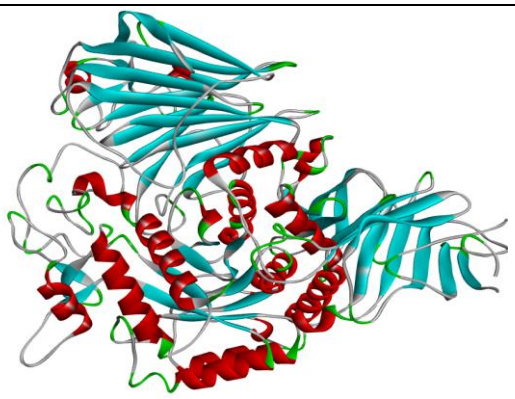
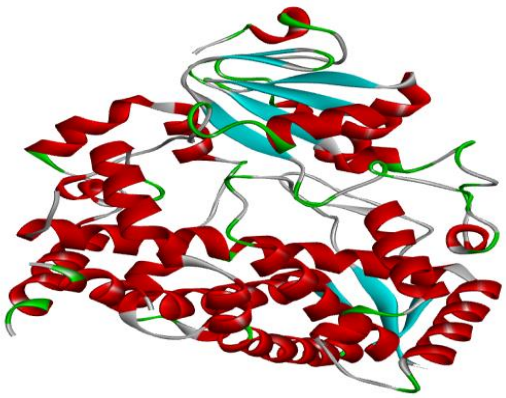
Title	**Human Maltase-Glucoamylase PDB ID 2QMJ**	**Human CYP3A4 bound to metformin PDB ID 5G5J**
Organism	Homo sapiens	Homo sapiens
Resolution	1.90 Å	2.60 Å
three-dimensional structure		
References	Ref.[21]	Ref.[22]

Figure 2. Three-dimensional protein structure of diabetes Mellitus

3. Results and Discussion

3.1. Optimized Structure of the Tested Ligand

The molecular geometry of a substance is established by its Optimized chemical structure, which depicts the configuration of molecules and chemical stability. This gives a crucial visual depiction of a chemical element, which is very beneficial for stability of molecules. The Avogadro application is used to complete the optimization and 3d visualization has been provided in Figure S1 (see Supporting Information)**.**

3.2. PASS Prediction

The biological activity spectrum (BAS) was established to explain the features of bioactive materials. The Internet-based version of the program PASS System component, includes approximately 31 000 bioactive substances can predicts physiological and biochemical spectra for 319 different kinds of therapeutic actions, active components, and particular adverse reactions[23]. It has been predict based on structural formula of a molecules, which may be effective and useful parameter to investigation of new targets molecules. Among 319 different kinds of therapeutic features, we have taken Antiviral, Antibacterial, Antifungal and Antidiabetic which is the key point of this investigation. The Pa value indicates the probability of active while the pa indicates the probability of inactive. In mentioned lead compounds, the ranges of Pa value for Antiviral are 0.294 – 0.422. Antibacterial 0.537-0.633, Antifungal 0.567- 0.704 and the Antidiabetic ranges is about 0.717 – 0.828, while the standard Metformin Hydrochloride has Pa value 0.414. So, it is cleared that these molecules have highest chances to effective against antidiabetic. Due to this high effectiveness spectrum against Antidiabetic, we have performed further studies against diabetes to check their efficacy and biological properties.

Table 1. PASS calculated data of Trehalose and its derivatives

Ligand No	Antiviral		Antibacterial		Antifungal		Antidiabetic	
	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pi
L01	0.422	0.012	0.577	0.010	0.658	0.013	0.808	0.005
L02	0.336	0.026	0.537	0.013	0.651	0.013	0.738	0.005
L03	0.332	0.032	0.557	0.012	0.669	0.012	0.733	0.005
L04	0.326	0.028	0.574	0.010	0.688	0.010	0.720	0.005
L05	0.294	0.039	0.555	0.012	0.704	0.009	0.717	0.005
L06	0.319	0.030	0.597	0.009	0.579	0.021	0.812	0.004
L07	0.321	0.030	0.620	0.008	0.599	0.018	0.828	0.004
L08	0.320	0.030	0.633	0.007	0.618	0.017	0.811	0.005
L09	0.332	0.027	0.616	0.008	0.567	0.022	0.815	0.005
Metformin Hydrochloride	0.373	0.048	0.288	0.040	N/A	N/A	0.414	0.030

3.3. Molecular Docking

Molecular docking research has long been acknowledged as among the most fundamental and crucial drug development strategies. Predicting interaction between a receptor and ligand in the coordination sphere is made possible by this method. Due to its inexpensive cost and apparent ease of use, molecular docking has grown in popularity among scientists, drug developer and researcher[24]. The general and standard value is considered -6.0 kcal/ mole to be a bioactive molecule[25,26]. In this study, the docking analysis is conducted by nine targeted drugs and one standard (Metformin Hydrochloride) against two receptor binding protein.

The maximum affinity for Human Maltase-Glucoamylase (PDB ID 2QMJ) has been found -9.0 (kcal/mole and -9.1 kcal/mole in ligand no 04 and 05 while the Metformin Hydrochloride has only -5.2 kcal/mole.

Similarly, the maximum affinity for Human CYP3A4 bound to metformin (PDB ID 5G5J) has obtained -9.1kcal/mole and -9.8 kcal/mole in same ligand 04 and 05. At the same time, the standard Metformin Hydrochloride has obtained only -5.0 kcal/mol. So, it is well understanding that the newly develop compounds is better in compare with standard Metformin Hydrochloride.

Table 2. Binding Affinity against Diabetes mellitus DM targeted protein

Drug Molecules No	Human Maltase-Glucoamylase (PDB ID 2QMJ)	Human CYP3A4 bound to metformin (PDB ID 5G5J)
	Binding Affinity (kcal/mol)	Binding Affinity (kcal/mol)
01	-7.0	-8.0
02	-7.3	-7.9
03	-8.0	-8.7
04	-9.0	-9.1
05	-9.1	-9.8
06	-7.3	-7.0
07	-7.0	-7.1
08	-6.8	-7.3
09	-7.3	-8.1
Metformin Hydrochloride	-5.2	-5.0

3.4. Trial Data and Result Analysis

In initial stages, 500 mg Metformin Hydrochloride (Brand Name: Bigmet) have been bought from Renata Pharmaceutical limited and every day 500mg tablet was administrated to the type -2 DM mellitus patients. The oral glucose tolerance test (OGTT) test has been conducted before administrated of the drugs and after administrated of the drugs by glucometer and the data has been noted. In each day, it is observed that the level of blood glucose is decreased after administrated of Metformin Hydrochloride. Since Metformin Hydrochloride can reduce the blood glucose and the binding affinity of our reported drugs is better than Metformin Hydrochloride. So, it is clearly said that the reported developed ligands could be better option for type-2 diabetes mellitus patients.

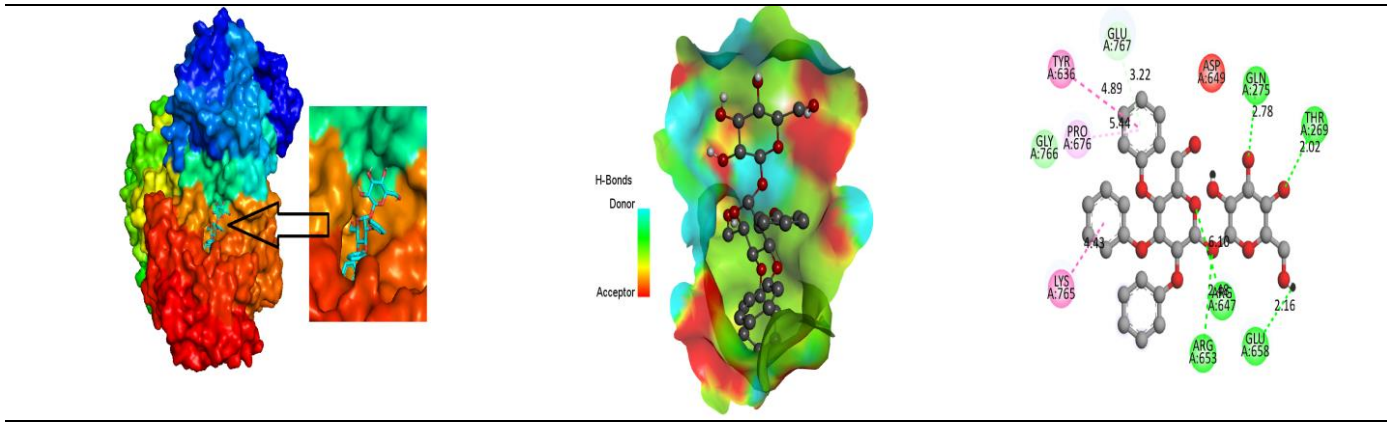
This study has been included to measured how much efficacy or potentiality is present when take them DM affected people and compare to the newly developed molecules (see Figure S2).

Table 3. Experimental oral glucose tolerance level

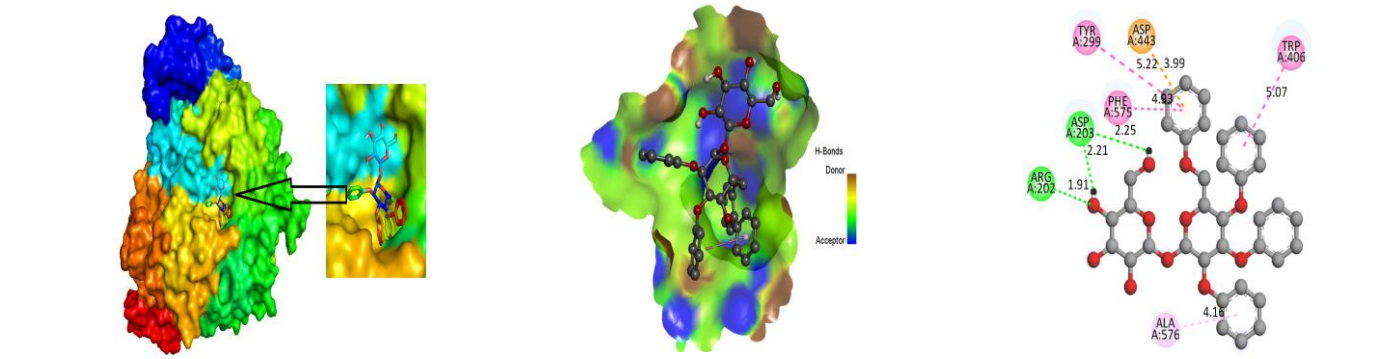
Date of test	Patients ID	Age	Before taken metformin mmol/L	One hour taken metformin mmol/L
01-03-2022	Patiant-01	Patient- 01 (45 years)	28.2	19.5
	Patiant-02		27.5	17.8
03-03-2022	Patiant-01		25.6	20.8
	Patiant-02		28.3	23.6
05-03-2022	Patiant-01		26.1	15.7
	Patiant-02		25.5	15.2
07-03-2022	Patiant-01	Patient- 02 (29 years)	22.3	17.1
	Patiant-02		24.0	19.5
09-03-2022	Patiant-01		20.5	12.8
	Patiant-02		22.1	16.4
11-03-2022	Patiant-01		21.8	12.1
	Patiant-02		25.6	19.5
13-03-2022	Patiant-01		16.5	9.4
	Patiant-02		23.5	18.1

3.5. Ligand-Protein Interaction and Molecular Docking Poses

Protein-ligand interaction has visualizer by Biovia discovery studio 2021. In this section, it is represented that how a targeted protein bind with develop molecules and how much active side present after molecular docking studies. In graphical illustration (Figure 4), two figures have been drawn. Besides, the 2d structure also drawn where it is clearly seen Hydrogen and Hydrophobic and electrostatic bond is present which is banded with ligand and show pharmacological efficacy.



Molecular docking poses of **2QMJ** with Ligand 04



Molecular docking poses of 2QMJ with Ligand 05

Figure 3. Molecular docking poses and 2d structure of protein of diabetes mellitus

3.6. ADME Studies

Web server pkCSM has been used to calculate the ADMET (absorption, distribution, metabolism, excretion, and toxicity) values for the reported compounds and showing in Table 4. According to the finding, around 40 percent to 60 percent of medications in development failed throughout clinical studies due to ADME/Tox inadequacies[27]. Virtual screening should not be limited to optimizing binding affinity and improving specificity; rather, the pharmacokinetic features of the compound should be considered as key factors throughout the virtual screening procedure. The present state of theoretical models for predicting drug absorption-related features, such as intestinal absorption, Caco-2 permeability, and blood-brain partitioning, is has been analysis. The significance of physicochemical parameters and forecasting in the assessment of passive medication absorption are highlighted.

Optimum value of Log S range from -4 to -6 and -2 to -4, respectively, for minimum and maximum solubility substances[28]. So, the obtaining result of water solubility is found under - 2 to -4 which indicates they are highly soluble in liquid medium where the maximum Caco-2 Permeability have obtained -1.394 in ligand 09. In G.I absorption rate, L02-L05 can absorb in intestinal and it has a correlation between Benzene ring and G.I absorption. Increasing number of benzene ring, also increasing percentage of G.I absorption and it is reported that Ligands 02-05 have been absorbed at GI tract moderately but the others molecules do not absorb. But the other compounds could not absorb in G.I tract due to highly Water soluble (or hydrophilic) in nature[29] as well as cannot reach the

BBB. The VDss level ranges is -0.123 to -1.125 when the maximum Total Clearance rate 1.491 ml/min/kg. In CYP 3A4 substrate, CYP450 1A2 Inhibitor, only ligand L05 has positive result and remaining drugs cannot Inhibitor or substrate the CYP 3A4, CYP450 enzyme. These enzymes mostly present in liver.

Table 4. ADME calculated data of Trehalose and its derivatives

	Absorption			Distribution		Metabolism		Excretion	
S/N	**Water solubility Log S**	**Caco-2 Permeability (10^{-6} cm/s)**	**G.I absorption (%)**	**VDss (human)**	**BBB permeability**	**CYP 3A4 substrate**	**CYP450 1A2 Inhibitor**	**Total Clearance (ml/min/kg)**	**Renal OCT2 substrate**
01	0.046	-0.287	No	-0.364	No	No	No	1.491	No
02	-2.621	-0.042	12.469	-0.123	No	No	No	1.278	No
03	-3.252	-0.774	27.602	-0.636	No	No	No	1.048	No
04	-3.137	-0.753	42.184	-0.997	No	No	No	0.887	No
05	-2.968	-0.965	56.466	-1.125	No	Yes	No	0.585	No
06	-2.907	-0.832	No	-0.656	No	No	No	1.337	No
07	-2.887	-1.005	No	-0.699	No	No	No	1.117	No
08	-2.892	-1.116	No	-0.283	No	No	No	0.889	No
09	-2.892	-1.394	No	-0.103	No	No	No	0.656	No
Metformin hydrochloride	-0.965	0.608	60.897	1.109	No	No	No	0.882	No

3.7. Aquatic and Non-Aquatic Toxicity

Aquatic and non-aquatic toxicity the study described by the impacts of a drugs substance to aquatic species and aquatic species[30]. Drugs are chemical in nature. So, they may degrade and mixed during production in pharmaceutical or drug manufacturer factory which may harmful to ecosystem. Besides, they may create carcinogenic or toxic impact in Human body after administration. So, this study is important.

In mentioned drugs, free from AMES toxicity, Hepatotoxicity and Skin Sensitization, but the standard Metformin hydrochloride may create AMES and Hepatotoxicity toxicity. The Max. tolerated dose is 1.327 mg/kg/day, the maximum Oral Rat Acute Toxicity level is 3.249 mol/kg and Oral Rat Chronic Toxicity 5.825 mg/kg/day. They all are indicates that these drugs are better physiochemical and pharmacokinetics properties.

Table 5. Aquatic and non-aquatic Toxicity prediction of Trehalose and its derivatives

S/N	**AMES toxicity**	**Max. tolerated dose (human) mg/kg/day**	**Oral Rat Acute Toxicity (LD50) (mol/kg)**	**Oral Rat Chronic Toxicity (mg/kg/day)**	**Hepatotoxicity**	**Skin Sensitization**	**T. Pyriformis toxicity (log ug/L)**
01	No	1.327	1.247	5.313	No	No	0.285
02	No	0.016	3.249	4.839	No	No	0.285
03	No	0.315	2.88	4.768	No	No	0.285
04	No	0.599	2.703	5.110	No	No	0.285
05	No	0.484	2.651	5.825	No	No	0.285
06	No	0.46	2.178	5.108	No	No	0.285
07	No	0.366	2.467	5.234	No	No	0.285
08	No	0.438	2.482	5.387	No	No	0.285
09	No	0.439	2.482	5.25	No	No	0.285
Metformin hydrochloride	Yes	1.321	2.76	0.647	No	Yes	0.294

4. Conclusion

In view of this investigation, the bioactive Trehalose and it's eight derivatives have been conducted different Insilico studies. The first investigation was Pass prediction score against Antiviral, antibacterial, antifungal and antidiabetic and it is about 0.717 – 0.828 for antidiabetic which is better while the standard Metformin Hydrochloride has Pa value 0. 414 than the Antiviral, antibacterial, antifungal. Thus, this value gave us further direction to continue these studies against Diabetes mellitus.

The most important and vital investigation was molecular docking. It was received that the mentioned compounds have effectively and tightly banned with Human Maltase-Glucoamylase (PDB ID 2QMJ) and Human CYP3A4 bound to metformin (PDB ID 5G5J). The highest docking result was found -9.1kcal/mol and -9.8 kcal/mol against Human CYP3A4 bound to metformin (PDB ID 5G5J) while -9.0 (kcal/mole and -9.1 kcal/mol have obtained in ligand no 04 and 05 against Human Maltase-Glucoamylase (PDB ID 2QMJ). Besides, all the drugs have outstanding soluble in water, do not show any AMES toxicity, Hepatotoxicity and Skin Sensitization. These, all are established them as effective oral medication.

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ORCID ID

Shopnil Akash: 000-0003-1751-705X

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