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Molecular Docking, Synthesis and Anti-diabetic Studies of Pyrimidine Derivatives

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Abstract

Pyrimidines are essential for the treatment of type-II diabetes and a variety of other diseases. The inhibition of the concentration of α-amylase enzyme is necessary for preventing starch breakdown. The primary objective of the study is to develop successful *in silico* protocol for the designing, synthesis and bio evaluation of pyrimidines derivatives. Five different pyrimidines derivatives were designed. Molecular docking studies were performed in order to see the binding mode of these designed pyrimidine derivatives in active site of anti-diabetic target. Based on binding interaction and stable docked energies, hits were identified. These designed and identified pyrimidine derivatives were further synthesized through the Claisen-Schmidt Condensation (CSC) of Aldehydes, 1,3-dicarbonyl compounds, and substituted urea. After their synthesis and characterization these were further evaluated for *in vitro* anti-diabetic behavior. Pyrimidine derivatives appear to be effective against diabetes type-II. *In vitro* studies have shown that all synthetic chemicals exhibit good anti-diabetic activity. Molecular docking studies were performed to investigate the anti-diabetic behavior of these synthesized compounds. Pyrimidines derivatives showed strong Hydrogen binding with target complex 1HNY. Both Docking and *in vitro* analysis of synthesized molecules showed that these compounds may be further used for detailed analysis of anti-diabetic behavior.

Keywords: Pyrimidine derivatives; Molecular docking; Diabetes mellitus; Anti-diabetic assay

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Introduction

Diabetes is a metabolic disorder with multifunctional dysfunctions and is characterized by the high level of glucose in the blood [1,2]. Humans can acquire one of two forms of diabetes: Type-I in which the body does not produce enough insulin, type-II diabetes can develop insulin resistance, which regulates the amount of glucose in the body. In some cases, the human body possessing diabetes type-II produces insulin, but it could not consume properly in certain patients. The question is open why some patients fail to respond to insulin while others do. However, several factors may involve, including excess weight and being physically inactive can have an impact. Diabetes Mellitus (DM) type-II patients are more likely to have various forms of health issues (it could be short- or long-term complications) and may lead to serious consequences including premature death [3]. Therefore, it is challenging to achieve and maintain adequate lifestyle changes. Consequently, the risk of diabetes still exists; even the weight loss is attained effectively [4]. DM type-II patients also have other risk factors including dyslipidemia, obesity, hypertension, and chronic kidney disease [5]. For the treatment of diabetes mellitus, one of the most reliable remedial methods is to reduce the catalytic activity of alpha-amylase, which catalyzes alpha-D-glucopyranose. For efficient inhibitors to interact with the active pocket of the α-amylase enzyme and have adequate inhibitory effect, the chemical structures must be adequate. Table 1 shows some alpha-glycosidase inhibitors with chemical structures that are often prescribed [6].

Clinical investigation for DM type-II have proposed multiple anti-diabetic medications,

including metformin, Thiazolidinediones (TZDs), insulin, Glucagon-Like Peptide (GLP-1) compounds, Sulfonylurea compounds (Sus), and Dipeptidyl Peptidase–4 (DPP4) inhibitors. Despite the fact that all available diabetic medications have recognized side effects, many patients are still unable to attain their desired glycemic control. Hence, there is a serious need for new medications that are both safer and more effective in treating diabetes [7]. Heterocyclic compounds of pyrimidines offer therapeutic agents due to the wide range of structural diversity and have proven economical [8]. Pyrimidine occupies a unique role in medicinal chemistry, being a part of nucleic acids. Pyrimidine derivatives have considered as most important inhibitors of the enzymes responsible for the treatment of diabetes. Dihydropyrimidines (DHPMS) and pyrimidine are fused as heterocyclic structures and identified as specific alpha-glycosidase inhibitor [9]. Pyrimidines alliance with thiazole has a greater impact on medicinal chemistry [10]. The production of Pyrazolo[3,4-d]-pyrimidine derivatives has also gained attention recently due to their potential application in medicine like anti-bacterial, anti-tumor, and anti-diabetic agent [11].

Since pyrimidines have variety of unique biological properties and play significant role in medicine as illustrated in Figure 1, including antimicrobial [12] anticancer activity [13]. The structure of pyrimidine is a crucial component of nucleic bases and alkaloids, in addition to the large number of pharmacophores with a wide range of potential biological effects. Cell cycle-specific pyrimidine derivatives only kill rapidly proliferating cells. Further, these functions prevent the production of nucleic acid (DNA and RNA) [14]. There are several pyrimidine derivatives including thiazolidinedione [11], pyrimidine-fused heterocyclic inhibitor [10], 6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylicacid derivatives [15], thiazolopyrimidine carboxylates [16] pyrazoles, fused pyrazolo[3,4-d]-pyrimidine, 1,2-dihydroimidazo-[2,1-c][1,2,4] triazin-6-one derivatives [11], and pyrimido[1,6-a] pyrimidine derivatives [17] are reported in literature as anti-diabetic inhibitors. However, with the significant increase in DM-type-II patients worldwide, researchers are performing to build up new anti-diabetic agents and attempting to find out the performance mechanism by using both dry and wet labs approaches [17]. Computer Aided Drug Design (CAAD) is an interdisciplinary field that uses computational methods and techniques to discover and design new drugs [18]. It involves the use of computational tools, such as molecular modeling, docking, virtual screening and molecular dynamics simulations to study the interactions between drugs and their biological targets [19,20]. CADD plays an essential role in the drug discovery process by accelerating the identification and optimization of potential drug candidates. The pharmacokinetic characteristics of medicine, such as clinical effectiveness, and safety are greatly influenced by the plasma binding characteristics of the drug. When a drug binds to serum proteins, the rate of clearance is affected due to target tissues only taking the unbound drug [21]. *In silico* methods are useful to foresee pharmacophore for the prediction of the biological activity of the compound [22], pharmacophore models are used to identify lead structure design. Ligand information predicts the activity by ligand-based methods; however, it depends on how much the novel ligand is similar/dissimilar to standard active ligands. The knowledge of standard molecules bind to the target molecule of interest is necessary to build a pharmacophore model that demonstrates the minimum structural properties required [23]. In order to identify the Structure-Activity Relationship (SAR) of novel drugs, a ligand-based pharmacophore model is developed. Designing new active molecules is the most consistent method for designing novel active compounds, sharing similarities with scaffolds by employing their computational prediction data. SAR profiling is followed by docking investigations. It predicts the optimal binding sites and inhibitory mechanism for newly synthesize drug derivatives. However, it is preferred to take a reference compound and docked it with the active site of the target protein before docking. These new derivatives potencies are computationally measured in dock scores. The negative score implies more favorable interactions between the compound and the target protein [24]. Molecular modeling has improved the understanding of the bioactivity mechanism of these pyrimidine derivatives.

This study is based on the identification, synthesis, and bio-evaluation of dihydropyrimidines by using computational and wet lab approaches of chemical synthesis and *in vitro* analysis. In order to elucidate the potential mechanism of action for the novel active candidates, molecular modeling study used *in silico* methods to identify and dock onto certain target proteins [25]. The chemical computing group created the software package MOE to support cheminformatics, molecular docking, bioinformatics, virtual testing, and structural-based formats can be utilized to generate new SVL (Scientific Vector Language) programs.

Materials and Methods

Molecular docking protocol

Five different pyrimidines derivatives were designed on basis of Lipinski rule of five. Pharmacokinetics studies were performed by using online PKCSM tool. Molecular docking was conducted after studying pharmacokinetics behavior of synthesized compounds activity. The three-dimensional chemical structure was drawn using Chem Draw Ultra 8.0. The Molecular Operating Environment (MOE) has implemented these structures using a power gradient with a convergence threshold of 0.0001 kcal/mol. The cellular data file contained properties were retained for accounting and configuration investigations. RCSB PDB (Protein Data Bank) provided protein PDB ID 1HNY with anti-diabetic action. Targets were adjusted to the Molecular Operating Environment (MOE) by following steps: To clean the crystal protein structure, energy was reduced to a power gradient of 0.0001 kcal/mol, and 3D protonate and water molecules were eliminated. Active site was identified using site finder tool of MOE.

Chemical synthesis

All the solvents and reagents were pure and according to international standards. The technique of infrared spectroscopy was conducted by using infrared spectrometer, which produces an infrared spectrum. In IR spectra, reciprocal centimeters (also known as wave numbers) with the sign cm^{-1} were a common unit of frequency. Agilent Technologies' 6890N inert mass selective detector was used to record mass spectra. The melting points in open capillaries were measured using Gallenkamp Melting Point apparatus (6MP-D). Thin Layer Chromatography (TLC) was used to track the development of each reaction on aluminum sheets that were 2.0 cm by 5.0 cm and had been pre-coated with silica gel that was 170.25 mm thick.

General procedure for the synthesis of Dihydropyrimidines (1-5)

Dihydropyrimidines were synthesized by using three components of Biginelli reaction. Aldehydes, 1,3-dicarbonyl compounds and urea were reacted in a test tube under ultrasonic irradiation by using $SnCl_2$

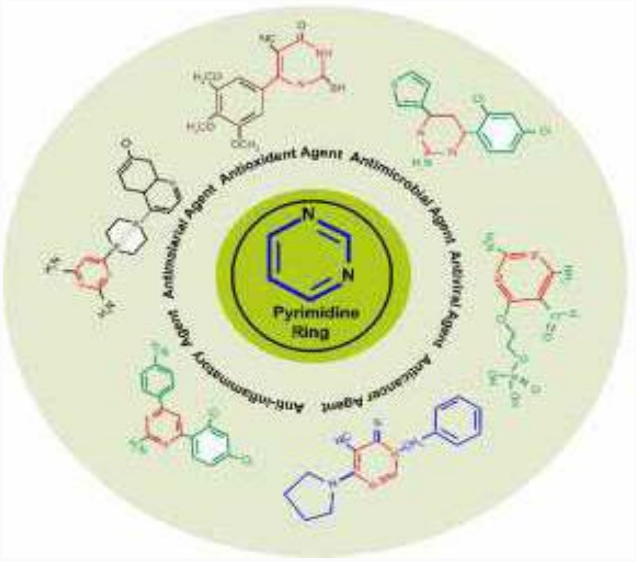


Figure 1: Pharmacological applications of pyrimidines derivatives.

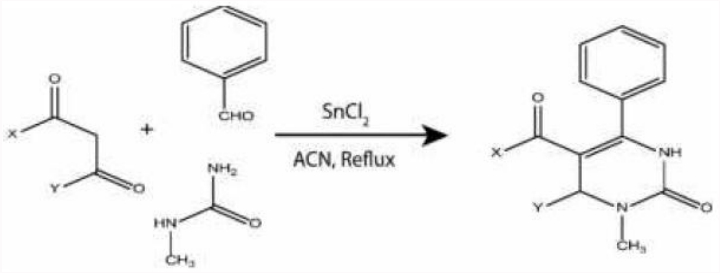


Figure 2: Chemical synthesis of Pyrimidines derivatives SA-1 to SA-5.

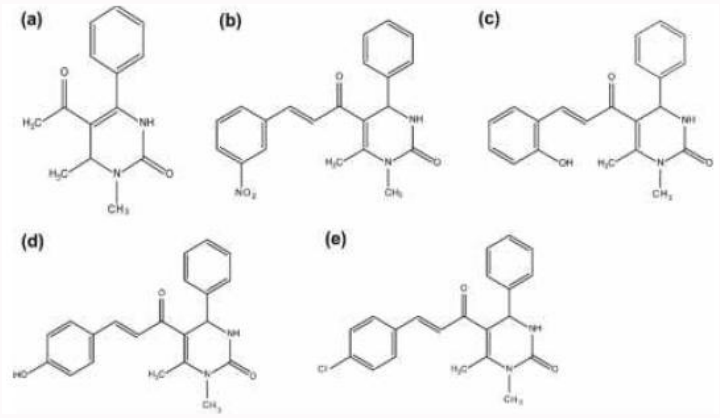


Figure 3: 2D structures of synthesized Dihydropyrimidines (a-e).

as catalyst and Acetonitrile (ACN) as solvent. The reaction mixture then treated with right aldehydes, dihydropyrimidine molecules containing an acetyl group at position C-5 were synthesized due to Claisen-Schmidt condensation reactions as shown in Figure 5. Five different dihydropyrimidine derivatives were synthesized by using different 1,3-dicarbonyle compounds as shown in Figure 6.

In vitro anti-diabetic studies

By employing the previously described technique of Nazli et al. an assay for the inhibition of alpha-amylase was carried out to test the synthetic compounds anti-diabetic efficacy. Enzyme (α–amylase) acts on the starch and breakdown it into maltose sugar. In the presence of enzyme inhibitors, the starch will not be degraded and yields blue color. In a 96 well plate, all the reagents for the assay including α–amylase enzyme (25 µL, 0.0175 U/mL), phosphate buffer (15 µL, pH 6.8), starch solution (40 µL, 2 mg/mL potassium phosphate buffer) and test sample (10 µL, 4 mg/mL DMSO) were transferred to their respective wells. The 96 well plates with reaction mixtures were kept at 50°C for 30 min. After 30 min of incubation period, HCl (20 µL, 1M) and iodine reagent (90 µL) were added in all the wells, and absorbance

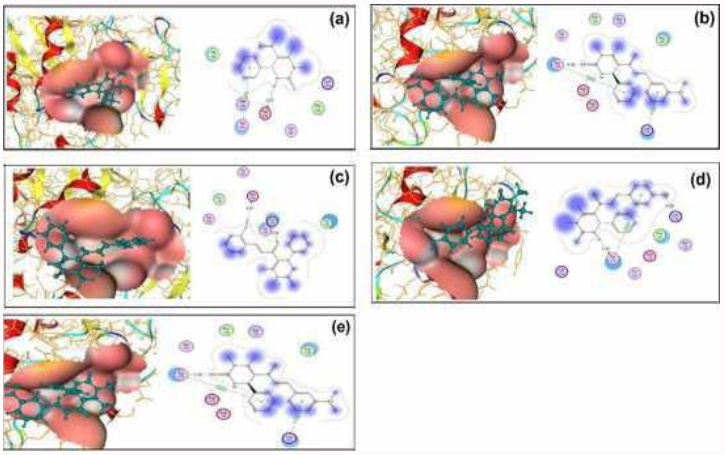


Figure 4: (a). 3D and 2D docking posture of ligand **SA-1** in the active spot of protein1HNY, showing H-bonding with Asp 135 and π-π connections with Tyr 174. (b). Ligand **SA-2**(viewing H-attachment with Tyr173 and π-π collaborations with Tyr174 and Lys172. (c). Ligand **SA-3** pointing H-interactions with Asp135 and Lys136 (d). Ligand **SA-4** showing H-bonding with Tyr174, Lys172 and π-π interactions with Tyr174. (e). Ligand **SA-5** shows H-bonding with Tyr174, Lys172 and π-π interactions with Tyr174.

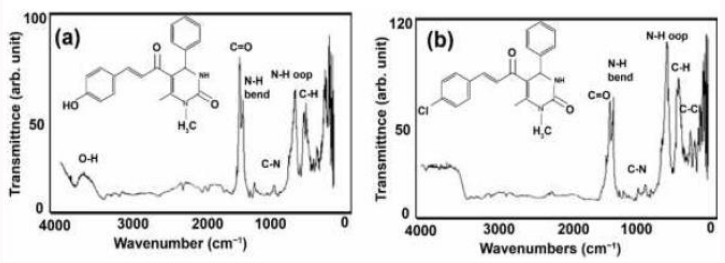


Figure 5: FTIR spectra of (a) SA-3 pyrimidine derivative. (b) FTIR peaks for SA-4 pyrimidine derivative.

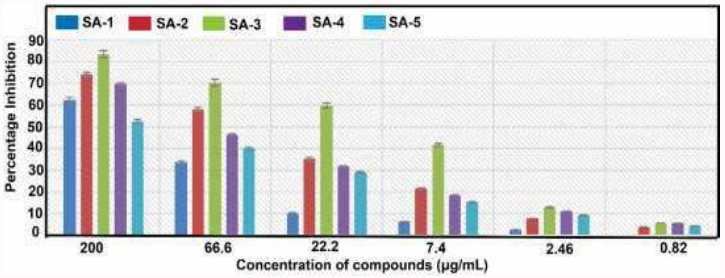


Figure 6: *In vitro* Anti-diabetic behavior of synthesized compounds.

was checked at 540 nm by using micro plate reader. For positive and negative control, similar protocol was by substituting the test sample with a similar volume of acarbose and DMSO, respectively. Moreover, a blank solution was prepared by adding an equal quantity of buffer rather than test samples and α–amylase enzyme solution.

% α–amylase enzyme inhibition was calculated as: % α–amylase enzyme inhibition = [(Abs – Abn)/(Abb – Abn) × 100]

where, Abs: Absorbance of test sample; Abb: Absorbance of blank; Abn: Absorbance of negative control

Results

Pharmacokinetics & Docking studies

Pharmacokinetic behavior of synthesis compounds was studied by using PKCSM in order to check toxic effect. Table 3 showed ADMET properties of these pyrimidines' derivatives.

Spectroscopic analysis discussion

All the solvents and reagents were purchased from commercial sources and were used without any further purification. The melting points were determined in open capillaries using Gallenkamp Melting Point Apparatus (MP-D).

Different pyrimidine derivatives were synthesized by using reported experimental method. These compounds were further characterized by using spectroscopic techniques *i.e.* LCMS and FTIR. The FTIR spectra are shown in Figure 2.

In vitro anti-diabetic studies

α- amylase inhibition assay: Graph (Figure 6) evaluates the in vitro anti-diabetic activity of SA-1, SA-2, SA-3 and SA-4 with α- amylase enzyme. *In vitro* studies have shown that all synthetic chemicals exhibit good anti-diabetic activity. The anti-diabetic activities of these compounds were predicted by using molecular

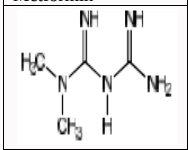
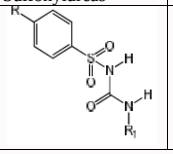
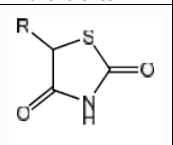
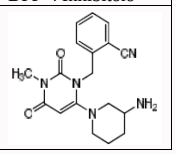
Metformin	Sulfonylureas	Thiazolidiones	DPP-4 Inhibitors
			

Table 1: Standard drugs used for DM type-II.

Table 2: FTIR and LCMS peaks of SA-1-SA-5 synthesized pyrimidine derivatives.

Peaks	C=O cm^{-1}	N-H cm^{-1}	C-N cm^{-1}	C-OH	C-H cm^{-1} (Ar)	C-NO^2 cm^{-1}	C=C cm^{-1} (Ar)	C-Cl	LCMS M^+
SA-1	1712	1590	1159	--	793	--	1560	--	244
SA-2	1715	1560	1160	--	830	1440	1525	--	377
SA-3	1723	1556	1154	3250	694	--	1456	--	348
SA-4	1723	1556	1154	3396	680	--	1470	--	348
SA-5	1730	1562	1162	--	678	--	1530	743	338

Table 3: ADMET properties of anti-diabetic derivatives SA1- SA5.

S. No	Compounds	Absorption	Distribution	Metabolism	Excretion	Hepatoxity/Oral toxicity
1	SA-1	92.723	0.272	No	0.32	No/1.169
2	SA-2	90.149	0.43	No	0.409	No/2.414
3	SA-3	90.066	0.069	No	0.409	No/2.108
4	SA-4	89.731	0.289	No	0.366	No/2.094
5	SA-5	87.372	0.22	No	0.322	No/2.109

Table 4: Hydrophobic and hydrophilic binding interaction of derivatives with target.

S. No	Compounds	H-Bonding	π-π interactions		Binding energy (KJ/mol)
		Distance Å	Nitrogen base		
1	SA-1	2.03	Asp 135	Tyr 174	–9.3322
2	SA-2	3.03	Tyr 174	Tyr 174 Lys 172	–8.6748
3	SA-3	2.22 3.27	Lys 172 Asp 136	---	–10.5361
4	SA-4	1.37 2.28	Tyr 174 Lys 172	Tyr17	–9.5480
5	SA-5	2.05	Asp 135	Tyr174	–9.3449

docking studies.

Discussion

Computational studies

All synthesized compounds were found to be not hepatotoxic as shown in Table 3 by using theoretical pharmacokinetics studies. Anti-diabetic behavior of these five compounds was also studied by using molecular docking findings. Thus, entire *in silico* findings for these complexes indicated that compounds show excellent constraining energies and the essential functional group needed for the binding in the active spot. All derivatives were found to be deeply anchored in the active sites of target 1HNY. Both hydrophilic and hydrophobic interactions were observed in these docked complexes with target site as shown in Table 4.

The essential residues in the process of used 1HNY proteins are Lys195, Lys199, Gln 196, Tyr150, Ser192, Glu153, Ala291, Glu292, His288, Phe157, Tyr150. The remaining 9 chemicals were placed 21 in the active site of the protein located in the data bank of the protein containing PDB ID 1HNY (Figure 3), and active compounds were discovered following drug resemblance and ADMET analysis. All synthesized DAP were docked in active site of 1HNY.

Wet Lab Synthesis

Five different pyrimidines derivatives as shown in Figure 6 were synthesized and characterized by using spectroscopic analysis.

FTIR spectral data of pyrimidines derivative SA-3 Figure 2a showed the typical aromatic C=O peak at 1723 cm^{-1}. (C-N) at 1154, (N-H) bending at 1556 cm^{-1}, aromatic C-H at 694 cm^{-1}, and C-OH at 3250 cm^{-1}. Pyrimidine derivative SA-4 (Figure 2b) showed the specific C=O captivation at 1723 cm^{-1}. Further, crests were noticed as aromatic N-H bending at 1556cm^{-1}, C-N at 1154 cm^{-1} and aromatic C-H expanding at 680 cm^{-1}.

The summary of the FTIR and LCMS peaks of SA-1-SA-5 synthesized pyrimidine derivatives are shown in Table 2.

Anti-diabetic Analysis Discussion

Graph (Figure 4) evaluates the in vitro anti-diabetic activity of SA-1, SA-2, SA-3 and SA-4 with α- amylase enzyme. The alpha-amylase inhibitory activities of all samples were correlated well with the increase of concentrations. At the concentration of 2000 µg/mL,

the alpha-amylase inhibitory activities for SA-1, SA-2, SA-3, SA-4, and SA-5 were 62.3%, 74.1%, 83.5%, 69.8% and 52.4% respectively.

Conclusion

Five different derivatives of pyrimidines were designed and synthesized by using molecular docking and reported synthetic procedure. Spectroscopic data confirm the synthesis of these compounds. All these synthesized compounds were further evaluated for α–amylase inhibition assay. Both *in silico* and *in vitro* findings for these complexes have demonstrated that these compounds have great binding potential and may be further used for detailed analysis of anti-diabetic behavior.

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