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Designing of some Novel Methyl 2-((4-(Benzamido)Phenyl)Sulfanyl)-1,2,3,4-tetrahydro-6-Methylpyrimidine-5-carboxylate Derivatives as Potential Glucokinase Activators through Molecular Docking

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Glucokinase (GK) is a cytoplasmic enzyme that metabolizes the glucose to glucose- 6-phosphate and supports the adjusting of blood glucose levels within the normal range in humans. In pancreatic β-cells, it plays a leading role by governing the glucose-stimulated secretion of insulin and in liver hepatocyte cells, it controls the metabolism of carbohydrates. GK acts as a promising drug target for the treatment of patients with type 2 diabetes mellitus (T2DM).
Study Design: In the current study, the goal is to identify new substituted benzamide derivatives and test them via molecular docking as possible anti-diabetic drugs.
Place and Duration of Study: The present work has been carried out at S.N.J.B's S.S.D.J. College of Pharmacy, Neminagar, Chandwad, Nashik, Maharashtra, India during the time period of December-2020 to February-2021.
Methodology: This work involved designing novel methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate derivatives and their screening by molecular

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docking studies to determine the binding interactions for the best-fit conformations in the binding site of the GK enzyme. Autodockvina 1.1.2 in PyRx 0.8 was used to perform the docking studies of all the designed novel derivatives and native ligand against the crystal structure of GK. Based on the results of docking studies, the selected molecules will be tested for their antidiabetic activity in the animal models.

Results: Amongst the designed derivatives, compounds A2, A3, A8, A10, A11, A13, A14, A16, A17, and A18 have shown better binding free energy (between -8.7 to -10.3 kcal/mol) than the native ligand present in the enzyme structure. In present investigation, many molecules had formed strong hydrogen bond with Arg-63 which indicate the potential to activate GK.

Conclusion: From above results it has been observed that these designed benzamide derivatives have potential to activate the human GK which enables us to proceed for the syntheses of these derivatives.

Keywords: Glucokinase activators; type 2 diabetes mellitus; Benzamide derivatives; 1V4S.

ABBREVIATIONS

GK : Glucokinase
GKA : Glucokinase Activators
T2DM : Type 2 Diabetes Mellitus
OGTT : Oral Glucose Tolerance Test
UFF : Universal Force Field
PDB : Protein Data Bank

1. INTRODUCTION

Diabetes is a metabolic condition categorized by malfunction of glucose metabolism [1]. It leads to other complications like cardiovascular, peripheral, vascular, ocular, neurologic and renal abnormalities etc [1,2]. The growing problem of diabetes has led to integrated research activities globally for the development of defensive and therapeutic strategies [1,3]. The World Health Organization (WHO) has estimated that ~1.6 and 2.5 million people may die from diabetes in 2015 and 2030 respectively [4,5]. It will be the 5th foremost reason of death worldwide by 2030 [6–8].

The glucose phosphorylating enzyme glucokinase (GK) is a monomeric protein having 465 amino acids (molecular weight =50kD) [9,10]. It maintains glucose homeostasis inside cells, acts as a glucose sensor in pancreatic β-cells and as a rate regulatory enzyme for hepatic glucose clearance and glycogen synthesis [11,12]. It has two binding sites, one for binding D-glucose and the other for a putative allosteric activator named glucokinase activator (GKA) [9]. The GKAs intermingle with the identical region of the GK enzyme that is normally affected by the naturally occurring mutations in humans. Newly, it has been reported that GKAs are extremely effective in patients with type 2 diabetes mellitus (T2DM) [13–17].

A wide range of compounds including benzamides [18–21], acetamides [22,23], carboxamides [22], acrylamides [24], benzimidazoles [25], quinazolines, thiazoles [23], pyrimidines [26], and urea derivatives [27–33] have been reported in recent decades to act as GK activators. Despite the fact that numerous chemical moieties are being discovered as GK activators by scholars, the maximum research efforts interrelated to GK activators had mainly focused on the benzamide derivatives owing to their alignment and thus binding configuration in the allosteric site of the enzyme.

As a glucokinase activator and in the treatment of T2DM, benzamide nucleus has been described in many publications. We chose the benzamide nucleus for the development of several new GK activators based on this literature. We had designed and developed some novel GK activators constructed on benzamide nucleus. The substitutions on benzamide nucleus were carried out in such a way that strong H-bond and hydrophobic interactions with residues in the allosteric site of GK protein can be targeted. Additionally, the molecules were designed so as to be orally bioavailable by introducing groups like aryl and/or alkyl in the benzamide nucleus.

2. MATERIALS AND METHODS

2.1 Designing of Novel Methyl 2-((4-(benzamido) phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-Methylpyrimidine-5-Carboxylate Derivatives

The novel derivatives have been designed as per the reaction scheme depicted in Fig. 1. In the first step, N-(4-chlorophenyl)benzamide has been designed by condensing with benzoic acid and 4-

chloroaniline in the presence of N,N'-Dicyclohexylcarbodiimide (DCC). In the second step, 1,2,3,4-tetrahydropyrimidine-2-thiol derivatives have been designed using modified Biginelli reaction by using different aromatic/aliphatic aldehydes. In the third step, product of first and second step were condensed to get final novel benzamide derivatives. The structures of the derivatives are shown in Table 1 with the IUPAC names.

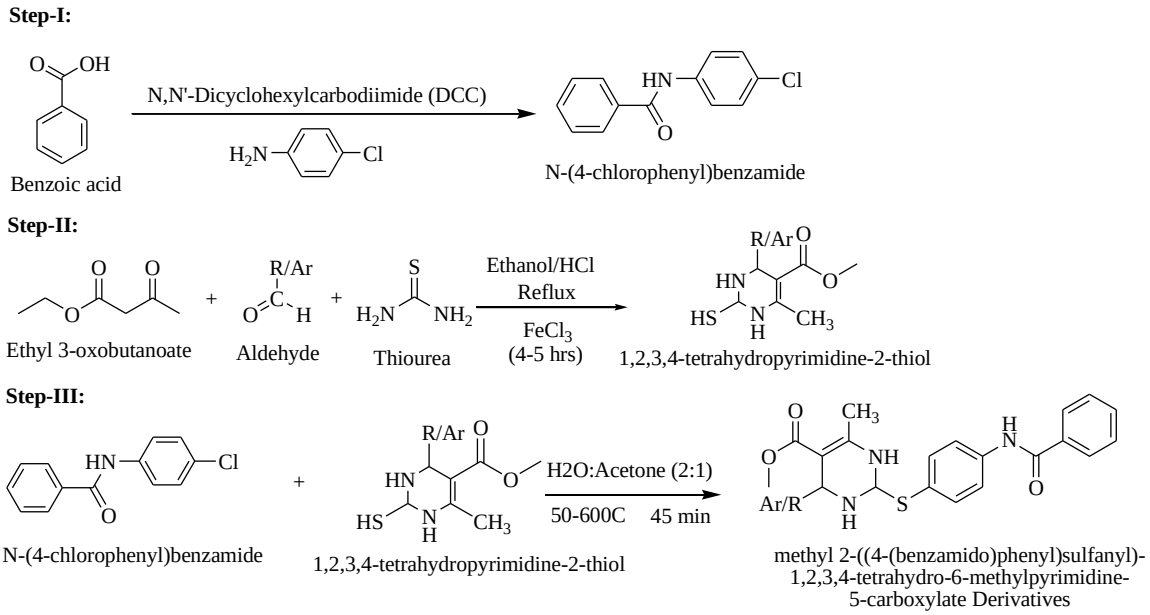
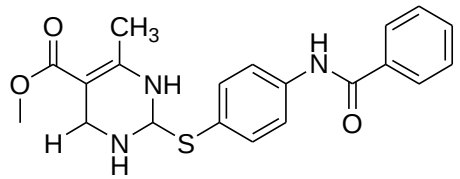
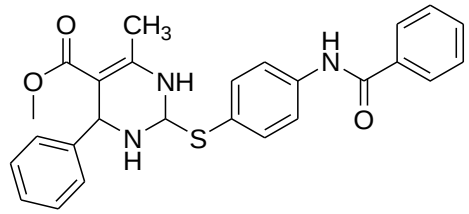
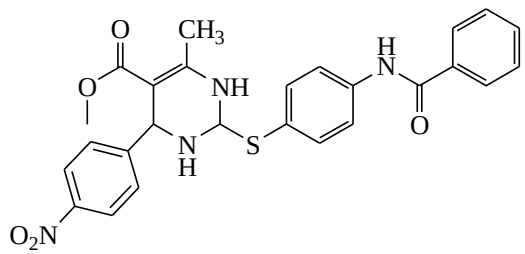
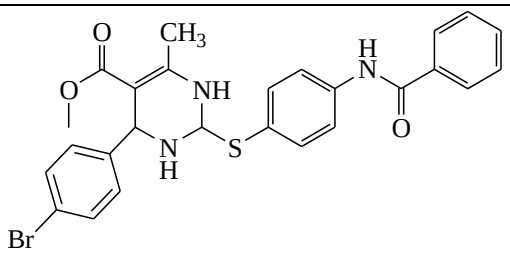
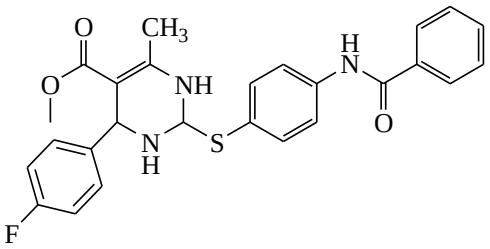
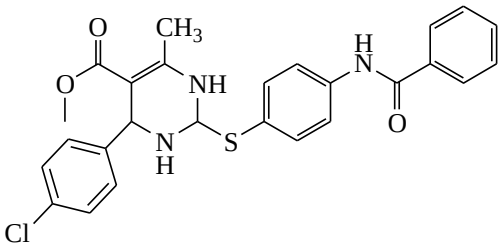
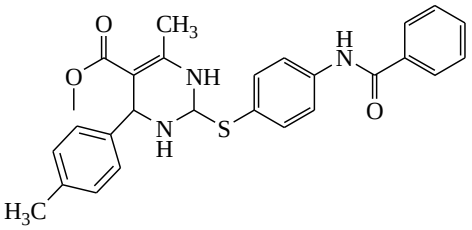
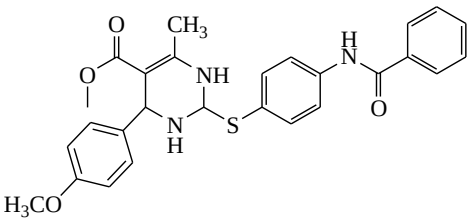
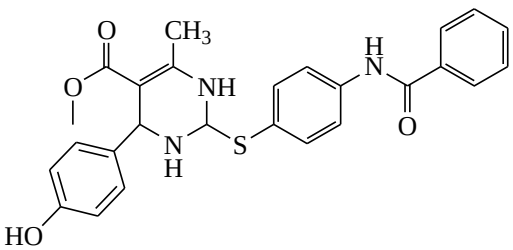
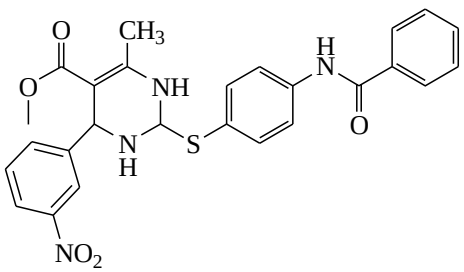
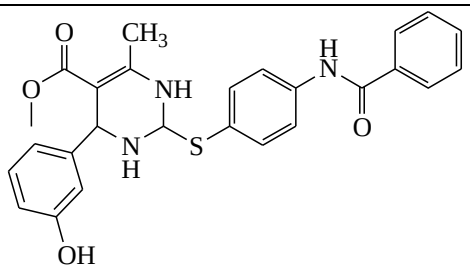
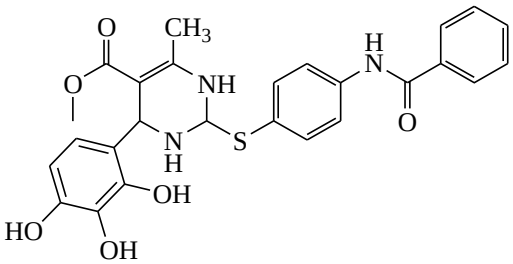
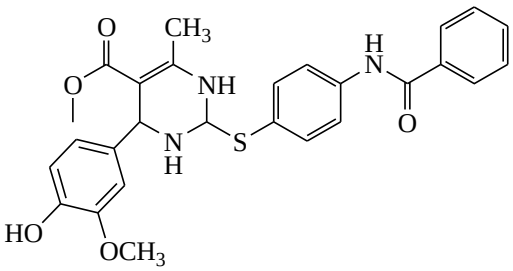
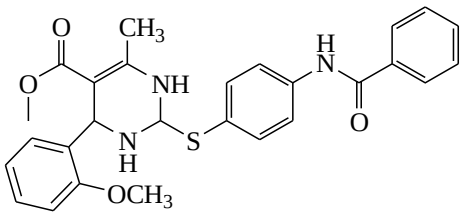
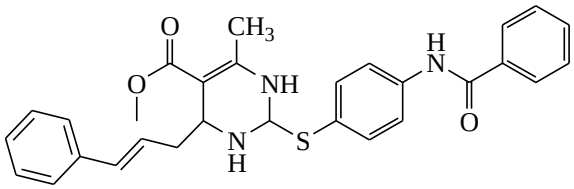
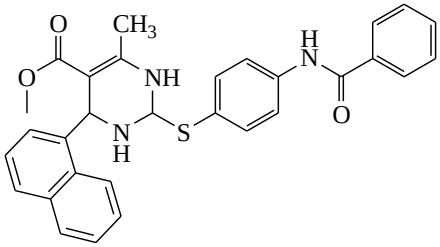
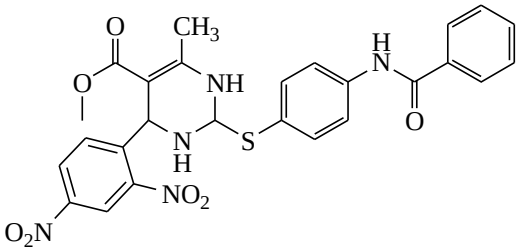


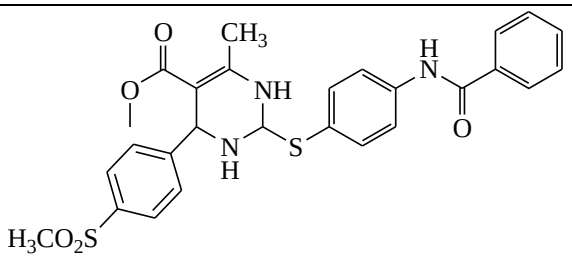
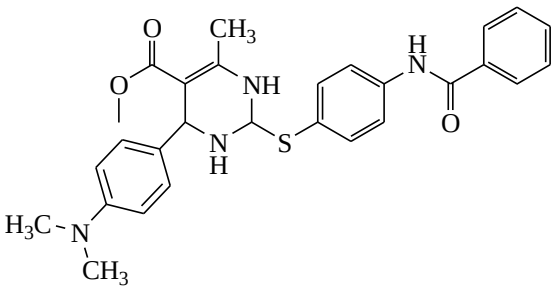
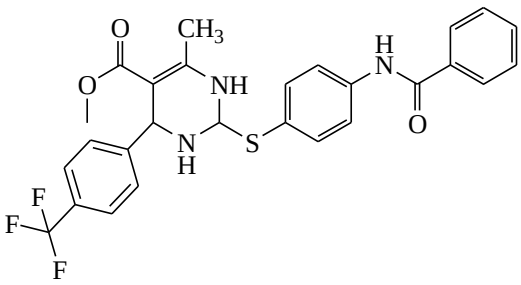
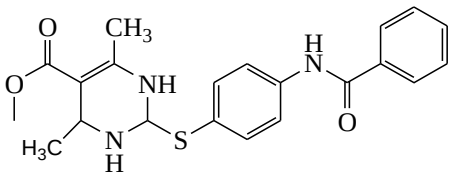
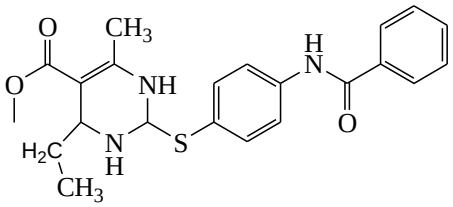
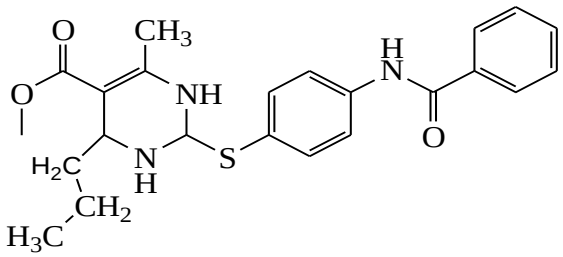
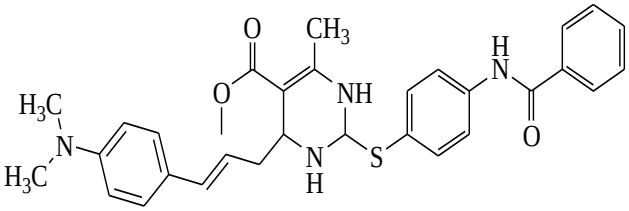
Fig. 1. The reaction scheme used for the designing of novel methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate derivatives

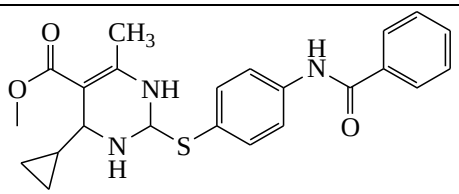
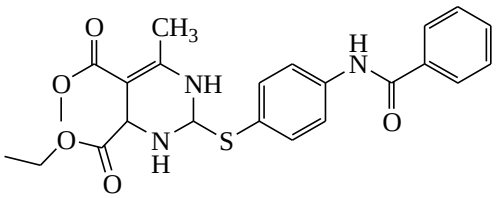
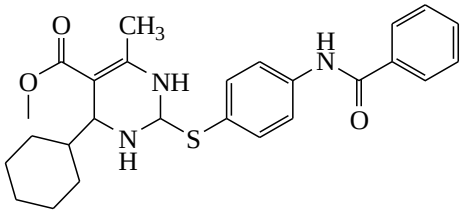
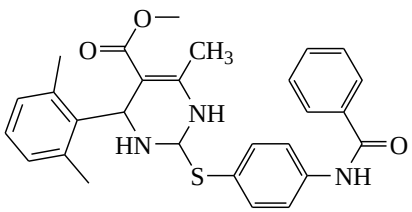
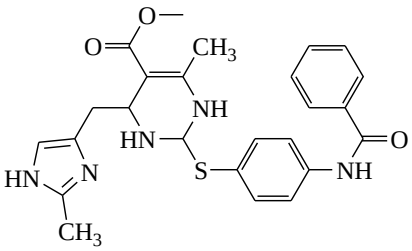
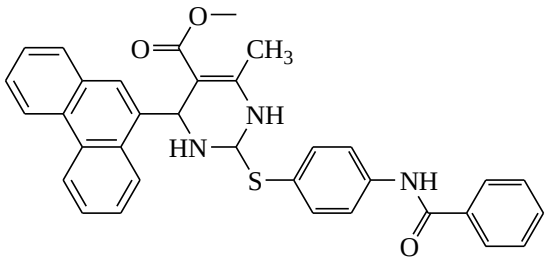
Table 1. The structures of methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate derivatives with their IUPAC names

Code	Structure	IUPAC Name
A1		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A2		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-phenylpyrimidine-5-carboxylate
A3		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)pyrimidine-5-carboxylate

Code	Structure	IUPAC Name
A4		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A5		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A6		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A7		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-p-tolylpyrimidine-5-carboxylate
A8		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate
A9		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-methylpyrimidine-5-carboxylate
A10		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)pyrimidine-5-carboxylate

Code	Structure	IUPAC Name
A11		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(3-hydroxyphenyl)-6-methylpyrimidine-5-carboxylate
A12		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(2,3,4-trihydroxyphenyl)-6-methylpyrimidine-5-carboxylate
A13		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-6-methylpyrimidine-5-carboxylate
A14		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(2-methoxyphenyl)-6-methylpyrimidine-5-carboxylate
A15		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-cinnamyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A16		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(naphthalen-1-yl)pyrimidine-5-carboxylate
A17		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(2,4-dinitrophenyl)pyrimidine-5-carboxylate

Code	Structure	IUPAC Name
A18		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(methylsulfonyl)phenyl)pyrimidine-5-carboxylate
A19		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A20		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A21		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4,6-dimethylpyrimidine-5-carboxylate
A22		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-ethyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A23		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-propylpyrimidine-5-carboxylate
A24		methyl 4-(4-(dimethylamino)cinnamyl)-2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate

Code	Structure	IUPAC Name
A25		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-cyclopropyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A26		4-ethyl 5-methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-4,5-dicarboxylate
A27		methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-cyclohexyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate
A28		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(2,6-dimethylphenyl)pyrimidine-5-carboxylate
A29		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-((2-methyl-1H-imidazol-4-yl)methyl)pyrimidine-5-carboxylate
A30		methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(phenanthren-10-yl)pyrimidine-5-carboxylate

2.2 Molecular Docking

Molecular docking was performed on Lenovo ThinkPad with 64-bit operating system, Processor: Intel(R) Core(TM) i5-4300M CPU @2.60 GHz 2.59 GHz, RAM: 4GB by using PyRx-Virtual Screening Tool. The structures of all the designed novel derivatives (A1-A30) and native ligand (mole. File format) were drawn in ChemDraw Ultra 8.0. The energy minimization (optimization) was performed by Universal Force Field (UFF) [34]. The elucidated crystal structure of human GK was obtained from the RCSB Protein Data Bank (PDB) as entry 1V4S (https://www.rcsb.org/structure/1V4S). The native ligand present in 1V4S was 5-(1-methyl-1H-imidazol-2-ylthio)-2-amino-4-fluoro-N-(thiazol-2-yl)benzamide. Autodockvina 1.1.2 in PyRx 0.8 was used to perform the docking studies of all the designed novel derivatives and native ligand against the crystal structure of GK [35]. The enzyme structure was optimized, purified and

prepared for docking with the help of Discovery Studio Visualizer 2019 [36].

The binding affinity studies were performed by using Vina Wizard Tool in PyRx 0.8. Molecules (PDBQT Files), both ligands as well as target (human GK) were selected for docking study. For molecular docking simulation, the three-dimensional grid box (size_x = 31.68A^{o}; size_y = 3.7901A^{o}; size_z = 64.27A^{o}) was designed using Autodock tool 1.5.6 with exhaustiveness value of 8 [35]. The active amino acid residues in the protein were identified and noted using BIOVIA Discovery Studio Visualizer (version-19.1.0.18287) [36]. The complete molecular docking procedure, identification of cavity and active amino acid residues was performed as per the procedure described by S. L. Khan *et al.*,[37–40]. The identified cavity of the enzyme with co-crystallize ligand molecule is represented in Fig. 2.

3. RESULTS AND DISCUSSION

The ligand energy (kcal/mol) and binding free energy (kcal/mol) of the derivatives are illustrated in Table 2. The molecular interactions of the derivatives are tabulated in Table 3. The 3D- and 2D-docking poses of the best 10 molecules with GK enzymes are depicted in Table 4.

All the designed novel derivatives were docked on human glucokinase enzyme and the docking results were compared with native ligand present in enzyme (PDB ID 1V4S). The formation of hydrogen bonds with the target can cause more effective conformational changes. Many derivatives showed better binding interactions at allosteric site than the native ligand with the formation of more hydrogen bonds. The native ligand has formed 3 conventional hydrogen bonds with THR-228 (2.21A^{0}), LYS-169 (2.60A^{0}), and ASP-78 (2.04A^{0}); one carbon hydrogen bond withGLY-81 (3.75A^{0}); Pi-Anion bond with ARG-85 (3.57A^{0}), ASP-409 (3.71A^{0}), Pi-Cation bond with ASP-205 (3.95A^{0}) and binding free energy of -7.2 kcal/mol.

Amongst the designed derivatives, compounds A2, A3, A8, A10, A11, A13, A14, A16, A17, and A18 have shown better binding free energy (between -8.7 to -10.3 kcal/mol) than the native ligand present in the enzyme structure. Molecule A2 exhibited -9.2 kcal/mol binding free energy and formed one conventional hydrogen bond with LYS296 (2.38753A^{0}) and one carbon hydrogen bond with SER411 (3.7174A^{0}). It has developed electrostatic interaction with GLU300 (4.22325A^{0}) and hydrophobic interactions with ARG333, THR332, VAL277, and ARG327. Molecule A3 exhibited -9.3 kcal/mol binding free energy and formed two conventional hydrogen bonds with ARG63 (2.17618A^{0}) and GLY68 (2.8237A^{0}). It has developed many hydrophobic interactions with the target. Molecule A8 showed -9.2 kcal/mol binding free energy and formed one conventional hydrogen bond with LYS296 (2.41616A^{0}) and one electrostatic bond with GLU331 (5.02607A^{0}). It has developed many

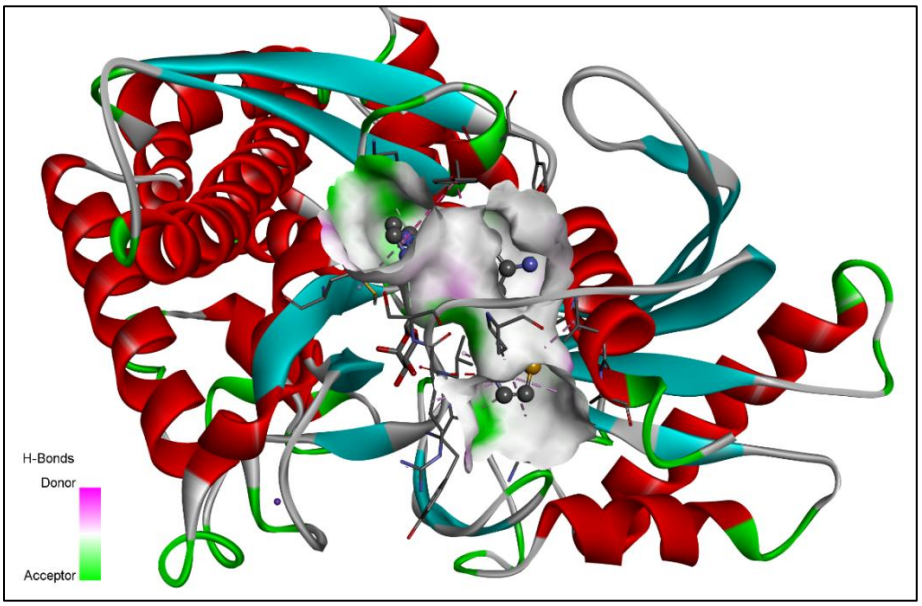


Fig. 2. The identified active cavity with native ligand present in human GK (PDB ID: 1V4S)

hydrophobic interactions with GLU300, THR332, VAL277, ARG327, and ARG333. Molecule A10 exhibited -9.3 kcal/mol binding free energy and formed three conventional hydrogen bonds with SER411 (3.02994A^0), THR228 (2.71297A^0), and LYS296 (2.72134A^0). It has developed many hydrophobic interactions with GLU300, THR332, ARG333, and VAL277. Compound A11 displayed -9.1 kcal/mol binding free energy and formed one conventional hydrogen bond with LYS296 (2.89683A^0) and one carbon hydrogen bond with SER411 (3.5354A^0). It has developed many hydrophobic interactions with GK. Molecule A13 exhibited -9.4 kcal/mol binding free energy with LYS296 (2.57884A^0). It has showed many hydrophobic interactions with GLU300, THR332, ARG333, VAL277, and ARG327. Molecule A14 demonstrated -8.3 kcal/mol binding free energy and exhibited many important interactions with the target such hydrogen bond and hydrophobic bonds. Molecule A16 exhibited -10.3 kcal/mol binding free energy and formed one conventional hydrogen bond with LYS296 (2.48334A^0) and one carbon hydrogen bond with GLY328 (3.29691A^0). It has formed hydrophobic interactions with GLU300, THR332, ARG333, and VAL277. Molecule A17 exhibited -8.7 kcal/mol binding free energy and formed 8 conventional hydrogen bond with ASP409 (2.53866A^0), GLU442 (2.00919A^0), ASP409 (3.09435A^0), GLU443 (1.88481A^0, 2.22894A^0), GLY444 (2.6412A^0), and SER445 (1.99286A^0, 1.8802A^0). It has formed Pi-anion bond with ASP409 (3.64706A^0). Compound A18 exhibited -9 kcal/mol binding free energy and formed two conventional hydrogen bond with THR228 (2.40684A^0) and LYS296 (3.00479A^0). It has formed one carbon hydrogen bond with GLY295 (3.72558A^0). It has developed many hydrophobic interactions with GLU300, THR332, ARG333, VAL277, and ARG327.

Table 2. The ligand energies (kcal/mol) and binding free energies (kcal/mol) of the derivatives

Ligand Code	Ligand Energy (kcal/mol)	Binding Free Energy (kcal/mol)
Native ligand	689.61	-7.2
A1	329.78	-8.4
A2	376.7	-9.2
A3	394	-9.3
A4	397.26	-9.2
A5	398.16	-9.4
A6	381.55	-9.5
A7	385.22	-9.4
A8	413.64	-9.2
A9	381.57	-9.2
A10	381.88	-9.3
A11	383.41	-9.1
A12	396.71	-8.9
A13	422.61	-9.4
A14	429.1	-8.3
A15	386.57	-7.6
A16	449.42	-10.3
A17	450.21	-8.7
A18	793.83	-9
A19	412.4	-9.2
A20	380.28	-8.5
A21	285.8	-8.4
A22	290.98	-8.3
A23	300.94	-8
A24	403.66	-8.8
A25	1340.52	-8.6
A26	308.53	-8.1
A27	352.53	-8.9
A28	467.74	-6.8
A29	626.29	-7.9
A30	509.66	-10.4

Table 3. The molecular interactions of the derivatives (active amino acid residues, bond length, bond type, and bond category)

Active Amino Acid Residue	Bond Length (A^0)	Bond Type	Bond Category
A1			
TYR61	2.51783	Hydrogen Bond	Conventional Hydrogen Bond
ASP158	3.6558	Electrostatic	Pi-Anion
ARG63	2.79401	Hydrogen Bond	Pi-Donor Hydrogen Bond
TYR214	3.70752	Hydrophobic	Pi-Sigma
VAL62	4.4804	Hydrophobic	Pi-Alkyl
ARG63	5.3723	Hydrophobic	Pi-Alkyl
PRO66	5.14365	Hydrophobic	Pi-Alkyl
ILE159	5.41538	Hydrophobic	Pi-Alkyl
VAL452	5.1178	Hydrophobic	Pi-Alkyl
VAL455	4.87776	Hydrophobic	Pi-Alkyl
ALA456	5.1916	Hydrophobic	Pi-Alkyl
ILE159	5.42528	Hydrophobic	Pi-Alkyl
A2			
LYS296	2.38753	Hydrogen Bond	Conventional Hydrogen Bond
SER411	3.7174	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.22325	Electrostatic	Pi-Anion
ARG333	3.63442	Hydrophobic	Pi-Sigma
THR332; ARG333	4.98907	Hydrophobic	Amide-Pi Stacked
VAL277	5.04113	Hydrophobic	Pi-Alkyl
ARG327	5.4274	Hydrophobic	Pi-Alkyl
A3			
ARG63	2.17618	Hydrogen Bond	Conventional Hydrogen Bond
GLY68	2.8237	Hydrogen Bond	Conventional Hydrogen Bond
LYS459	4.7061	Electrostatic	Pi-Cation
ARG63	2.72286	Hydrogen Bond	Pi-Donor Hydrogen Bond
ILE211	3.48273	Hydrophobic	Pi-Sigma
TYR214	4.95208	Hydrophobic	Pi-Pi T-shaped
VAL62	4.59387	Hydrophobic	Pi-Alkyl
ARG63	5.24925	Hydrophobic	Pi-Alkyl
PRO66	5.00381	Hydrophobic	Pi-Alkyl
ILE159	5.47971	Hydrophobic	Pi-Alkyl
VAL452	5.29494	Hydrophobic	Pi-Alkyl
VAL455	4.87526	Hydrophobic	Pi-Alkyl
ALA456	5.23048	Hydrophobic	Pi-Alkyl
PRO66	4.53813	Hydrophobic	Pi-Alkyl
LYS459	4.77597	Hydrophobic	Pi-Alkyl
A4			
LYS296	2.24111	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.35993	Electrostatic	Pi-Anion
ARG333	3.53206	Hydrophobic	Pi-Sigma
THR332; ARG333	4.84741	Hydrophobic	Amide-Pi Stacked
VAL277	5.18824	Hydrophobic	Pi-Alkyl
ARG327	5.48859	Hydrophobic	Pi-Alkyl
A5			
LYS296	2.42706	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.2021	Electrostatic	Pi-Anion
ARG333	3.58197	Hydrophobic	Pi-Sigma
THR332; ARG333	4.8609	Hydrophobic	Amide-Pi Stacked
VAL277	5.0831	Hydrophobic	Pi-Alkyl
ARG327	5.41511	Hydrophobic	Pi-Alkyl
A6			
LYS296	2.42807	Hydrogen Bond	Conventional Hydrogen Bond

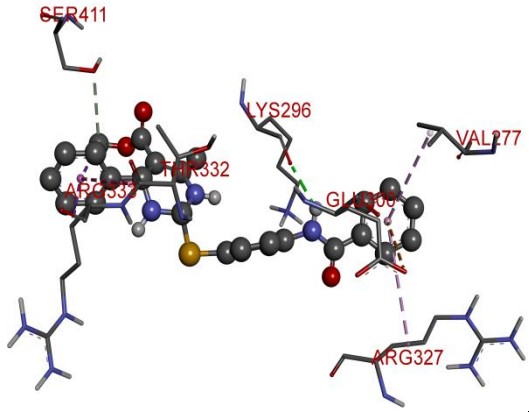
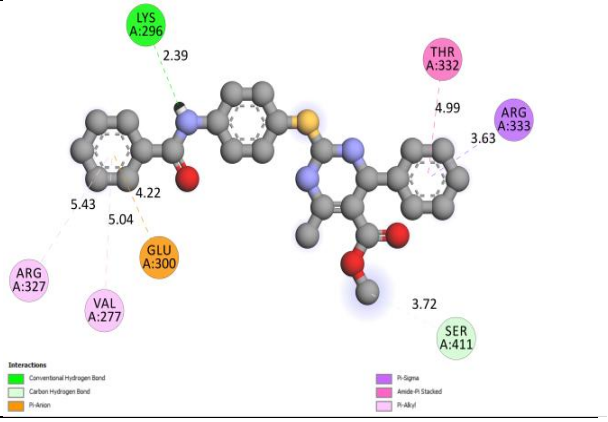
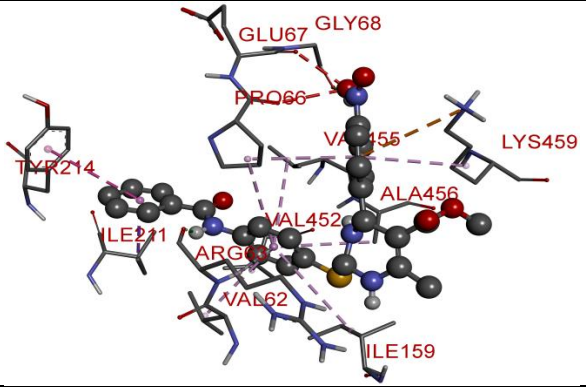
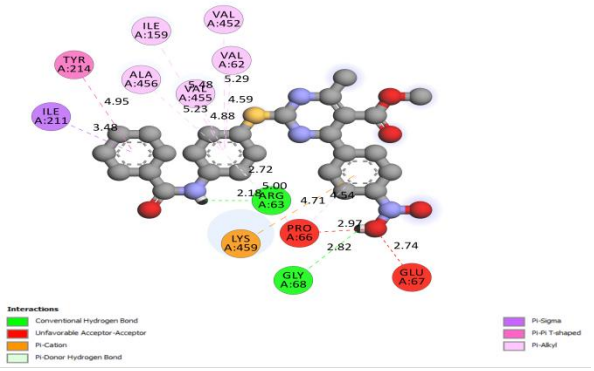
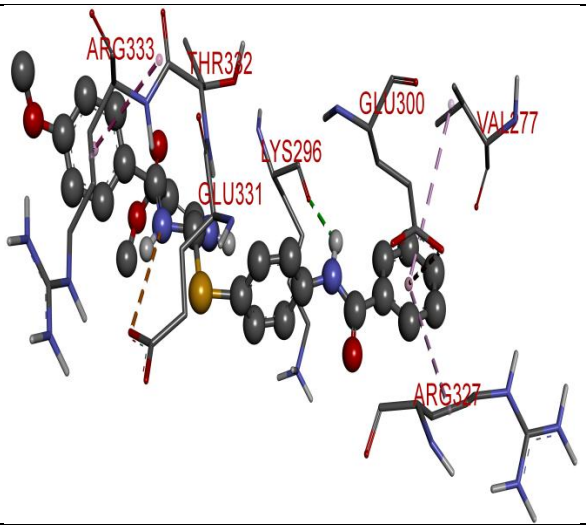
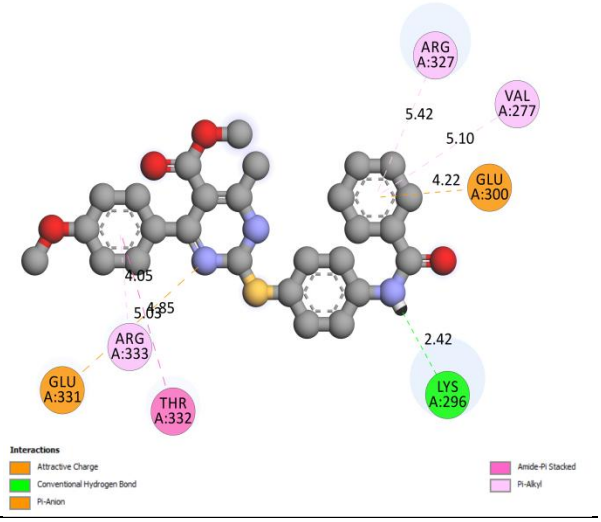
Active Amino Acid Residue	Bond Length (A^0)	Bond Type	Bond Category
GLU300	4.15736	Electrostatic	Pi-Anion
THR332; ARG333	4.84705	Hydrophobic	Amide-Pi Stacked
ARG333	4.83481	Hydrophobic	Alkyl
LEU415	4.83204	Hydrophobic	Alkyl
VAL277	5.12117	Hydrophobic	Pi-Alkyl
ARG327	5.36192	Hydrophobic	Pi-Alkyl
ARG333	4.115	Hydrophobic	Pi-Alkyl
A7			
GLU331	5.0865	Electrostatic	Attractive Charge
LYS296	2.49101	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.22872	Electrostatic	Pi-Anion
THR332; ARG333	4.85604	Hydrophobic	Amide-Pi Stacked
ARG333	4.68655	Hydrophobic	Alkyl
LEU415	4.92645	Hydrophobic	Alkyl
VAL277	5.11895	Hydrophobic	Pi-Alkyl
ARG327	5.41997	Hydrophobic	Pi-Alkyl
ARG333	4.15567	Hydrophobic	Pi-Alkyl
A8			
GLU331	5.02607	Electrostatic	Attractive Charge
LYS296	2.41616	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.22149	Electrostatic	Pi-Anion
THR332; ARG333	4.84631	Hydrophobic	Amide-Pi Stacked
VAL277	5.10166	Hydrophobic	Pi-Alkyl
ARG327	5.42355	Hydrophobic	Pi-Alkyl
ARG333	4.0533	Hydrophobic	Pi-Alkyl
A9			
LYS296	2.38413	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.28234	Electrostatic	Pi-Anion
ARG333	3.53907	Hydrophobic	Pi-Sigma
THR332; ARG333	4.85956	Hydrophobic	Amide-Pi Stacked
VAL277	5.20504	Hydrophobic	Pi-Alkyl
ARG327	5.39963	Hydrophobic	Pi-Alkyl
A10			
SER411	3.02994	Hydrogen Bond	Conventional Hydrogen Bond
THR228	2.71297	Hydrogen Bond	Conventional Hydrogen Bond
LYS296	2.72134	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.28815	Electrostatic	Pi-Anion
THR332; ARG333	4.71862	Hydrophobic	Amide-Pi Stacked
VAL277	5.46239	Hydrophobic	Pi-Alkyl
ARG333	4.57954	Hydrophobic	Pi-Alkyl
A11			
LYS296	2.89683	Hydrogen Bond	Conventional Hydrogen Bond
SER411	3.5354	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.19393	Electrostatic	Pi-Anion
THR332; ARG333	4.88459	Hydrophobic	Amide-Pi Stacked
VAL277	5.0867	Hydrophobic	Pi-Alkyl
ARG333	4.29412	Hydrophobic	Pi-Alkyl
A12			
LYS296	2.42659	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.15428	Electrostatic	Pi-Anion
THR332; ARG333	4.87249	Hydrophobic	Amide-Pi Stacked
VAL277	5.07907	Hydrophobic	Pi-Alkyl
ARG327	5.40245	Hydrophobic	Pi-Alkyl
ARG333	4.08635	Hydrophobic	Pi-Alkyl
A13			
LYS296	2.57884	Hydrogen Bond	Conventional Hydrogen Bond

Active Amino Acid Residue	Bond Length (A^0)	Bond Type	Bond Category
GLU300	4.16537	Electrostatic	Pi-Anion
THR332; ARG333	4.89846	Hydrophobic	Amide-Pi Stacked
VAL277	5.09333	Hydrophobic	Pi-Alkyl
ARG327	5.37448	Hydrophobic	Pi-Alkyl
ARG333	4.13497	Hydrophobic	Pi-Alkyl
A14			
THR228	2.37005	Hydrogen Bond	Conventional Hydrogen Bond
GLY295	3.30232	Hydrogen Bond	Carbon Hydrogen Bond
GLY328	3.1427	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.27203	Electrostatic	Pi-Anion
ARG327	5.47746	Hydrophobic	Pi-Alkyl
ARG333	4.76282	Hydrophobic	Pi-Alkyl
A15			
LYS459	4.47709	Electrostatic	Pi-Cation
VAL62	3.99617	Hydrophobic	Pi-Sigma
ILE159	4.75748	Hydrophobic	Pi-Alkyl
ALA456	4.332	Hydrophobic	Pi-Alkyl
PRO66	5.13293	Hydrophobic	Pi-Alkyl
VAL452	4.61165	Hydrophobic	Pi-Alkyl
VAL455	4.08878	Hydrophobic	Pi-Alkyl
PRO66	5.0076	Hydrophobic	Pi-Alkyl
LYS458	5.13973	Hydrophobic	Pi-Alkyl
LYS459	4.89602	Hydrophobic	Pi-Alkyl
A16			
LYS296	2.48334	Hydrogen Bond	Conventional Hydrogen Bond
GLY328	3.29691	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.20223	Electrostatic	Pi-Anion
THR332; ARG333	5.07541	Hydrophobic	Amide-Pi Stacked
THR332; ARG333	4.64702	Hydrophobic	Amide-Pi Stacked
VAL277	5.14875	Hydrophobic	Pi-Alkyl
ARG333	4.04289	Hydrophobic	Pi-Alkyl
ARG333	5.14717	Hydrophobic	Pi-Alkyl
A17			
ASP409	2.53866	Hydrogen Bond	Conventional Hydrogen Bond
GLU442	2.00919	Hydrogen Bond	Conventional Hydrogen Bond
ASP409	3.09435	Hydrogen Bond	Conventional Hydrogen Bond
GLU443	1.88481	Hydrogen Bond	Conventional Hydrogen Bond
GLU443	2.22894	Hydrogen Bond	Conventional Hydrogen Bond
GLY444	2.6412	Hydrogen Bond	Conventional Hydrogen Bond
SER445	1.99286	Hydrogen Bond	Conventional Hydrogen Bond
SER445	1.8802	Hydrogen Bond	Conventional Hydrogen Bond
ASP409	3.64706	Electrostatic	Pi-Anion
A18			
THR228	2.40684	Hydrogen Bond	Conventional Hydrogen Bond
LYS296	3.00479	Hydrogen Bond	Conventional Hydrogen Bond
GLY295	3.72558	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.16206	Electrostatic	Pi-Anion
THR332; ARG333	4.86504	Hydrophobic	Amide-Pi Stacked
VAL277	5.1355	Hydrophobic	Pi-Alkyl
ARG327	5.44564	Hydrophobic	Pi-Alkyl
ARG333	4.21676	Hydrophobic	Pi-Alkyl
A19			
LYS296	2.49003	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.20415	Electrostatic	Pi-Anion
THR332; ARG333	4.81795	Hydrophobic	Amide-Pi Stacked
VAL277	5.16318	Hydrophobic	Pi-Alkyl

Active Amino Acid Residue	Bond Length (A^0)	Bond Type	Bond Category
ARG327	5.3741	Hydrophobic	Pi-Alkyl
ARG333	4.00059	Hydrophobic	Pi-Alkyl
A20			
GLY328	3.15218	Hydrogen Bond	Carbon Hydrogen Bond
SER336	3.3413	Hydrogen Bond	Carbon Hydrogen Bond
SER411	3.3312	Hydrogen Bond	Carbon Hydrogen Bond
SER411	3.39819	Halogen	Halogen (Fluorine)
THR332; ARG333	4.83136	Hydrophobic	Amide-Pi Stacked
ARG333	4.95081	Hydrophobic	Alkyl
LEU415	4.58911	Hydrophobic	Alkyl
LYS296	5.40162	Hydrophobic	Pi-Alkyl
ARG333	4.32403	Hydrophobic	Pi-Alkyl
A21			
TYR61	2.51642	Hydrogen Bond	Conventional Hydrogen Bond
ARG63	2.71769	Hydrogen Bond	Conventional Hydrogen Bond
ARG63	2.92983	Hydrogen Bond	Pi-Donor Hydrogen Bond
VAL455	3.97413	Hydrophobic	Pi-Sigma
TYR214	4.94707	Hydrophobic	Pi-Pi T-shaped
VAL62	4.81623	Hydrophobic	Pi-Alkyl
ARG63	5.39556	Hydrophobic	Pi-Alkyl
PRO66	4.90175	Hydrophobic	Pi-Alkyl
VAL452	5.31344	Hydrophobic	Pi-Alkyl
ALA456	5.08513	Hydrophobic	Pi-Alkyl
ILE211	4.47564	Hydrophobic	Pi-Alkyl
A22			
ARG63	2.16085	Hydrogen Bond	Conventional Hydrogen Bond
ASP158	3.42329	Hydrogen Bond	Carbon Hydrogen Bond
ARG63	2.76111	Hydrogen Bond	Pi-Donor Hydrogen Bond
TYR214	4.97519	Hydrophobic	Pi-Pi T-shaped
VAL62	4.67229	Hydrophobic	Pi-Alkyl
ARG63	5.25922	Hydrophobic	Pi-Alkyl
PRO66	4.97003	Hydrophobic	Pi-Alkyl
ILE159	5.48068	Hydrophobic	Pi-Alkyl
VAL452	5.33675	Hydrophobic	Pi-Alkyl
VAL455	4.83569	Hydrophobic	Pi-Alkyl
ALA456	5.18458	Hydrophobic	Pi-Alkyl
ILE211	4.43483	Hydrophobic	Pi-Alkyl
A23			
ARG63	2.09009	Hydrogen Bond	Conventional Hydrogen Bond
ARG63	2.61633	Hydrogen Bond	Pi-Donor Hydrogen Bond
ILE211	3.46616	Hydrophobic	Pi-Sigma
TYR214	5.39648	Hydrophobic	Pi-Pi T-shaped
VAL62	4.8192	Hydrophobic	Pi-Alkyl
ARG63	4.99494	Hydrophobic	Pi-Alkyl
PRO66	5.0037	Hydrophobic	Pi-Alkyl
ILE159	5.28141	Hydrophobic	Pi-Alkyl
VAL455	5.12567	Hydrophobic	Pi-Alkyl
ALA456	5.15331	Hydrophobic	Pi-Alkyl
A24			
GLY295	3.01786	Hydrogen Bond	Conventional Hydrogen Bond
LYS296	2.35252	Hydrogen Bond	Conventional Hydrogen Bond
GLY328	3.4033	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.10946	Electrostatic	Pi-Anion
VAL277	5.15172	Hydrophobic	Pi-Alkyl
ARG327	5.36639	Hydrophobic	Pi-Alkyl
ARG333	4.28189	Hydrophobic	Pi-Alkyl

Active Amino Acid Residue	Bond Length (A^0)	Bond Type	Bond Category
LEU415	5.3197	Hydrophobic	Pi-Alkyl
A25			
ARG63	2.16097	Hydrogen Bond	Conventional Hydrogen Bond
ASP158	3.70495	Hydrogen Bond	Carbon Hydrogen Bond
ARG63	2.76564	Hydrogen Bond	Pi-Donor Hydrogen Bond
ILE211	3.51743	Hydrophobic	Pi-Sigma
TYR214	5.07202	Hydrophobic	Pi-Pi T-shaped
LYS459	4.73662	Hydrophobic	Alkyl
ALA456	4.59899	Hydrophobic	Alkyl
VAL62	4.73083	Hydrophobic	Pi-Alkyl
ARG63	5.23452	Hydrophobic	Pi-Alkyl
PRO66	4.9732	Hydrophobic	Pi-Alkyl
ILE159	5.43077	Hydrophobic	Pi-Alkyl
VAL452	5.39973	Hydrophobic	Pi-Alkyl
VAL455	4.86155	Hydrophobic	Pi-Alkyl
ALA456	5.13755	Hydrophobic	Pi-Alkyl
A26			
LYS296	2.83097	Hydrogen Bond	Conventional Hydrogen Bond
GLY295	3.64959	Hydrogen Bond	Carbon Hydrogen Bond
GLU300	4.15308	Electrostatic	Pi-Anion
VAL277	5.33024	Hydrophobic	Pi-Alkyl
ARG327	5.38373	Hydrophobic	Pi-Alkyl
A27			
LYS296	2.31586	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.26833	Electrostatic	Pi-Anion
ARG333	3.86974	Hydrophobic	Alkyl
VAL277	5.11942	Hydrophobic	Pi-Alkyl
ARG327	5.44961	Hydrophobic	Pi-Alkyl
A28			
SER151	3.52052	Hydrogen Bond	Carbon Hydrogen Bond
GLU442	4.84255	Electrostatic	Pi-Anion
LYS414	5.18575	Hydrophobic	Pi-Alkyl
LEU415	4.73616	Hydrophobic	Pi-Alkyl
A29			
ASP409	2.59435	Hydrogen Bond	Conventional Hydrogen Bond
ASN83	2.48714	Hydrogen Bond	Conventional Hydrogen Bond
THR228	2.37248	Hydrogen Bond	Conventional Hydrogen Bond
SER411	2.2424	Hydrogen Bond	Conventional Hydrogen Bond
ASP205	4.22522	Electrostatic	Pi-Anion
ILE225	5.20511	Hydrophobic	Pi-Alkyl
A30			
LYS296	2.61379	Hydrogen Bond	Conventional Hydrogen Bond
GLU300	4.09651	Electrostatic	Pi-Anion
THR332; ARG333	4.66401	Hydrophobic	Amide-Pi Stacked
THR332; ARG333	4.74735	Hydrophobic	Amide-Pi Stacked
VAL277	5.45997	Hydrophobic	Pi-Alkyl
ARG327	5.22541	Hydrophobic	Pi-Alkyl
ARG333	4.26989	Hydrophobic	Pi-Alkyl
ARG333	5.27053	Hydrophobic	Pi-Alkyl
LEU415	5.08417	Hydrophobic	Pi-Alkyl
ARG333	4.02585	Hydrophobic	Pi-Alkyl

Table 4. The 3D- and 2D-docking poses of best 10 molecules with GK enzymes

3D-docking pose	2D-docking pose
A2	
	
A3	
	
A8	
	
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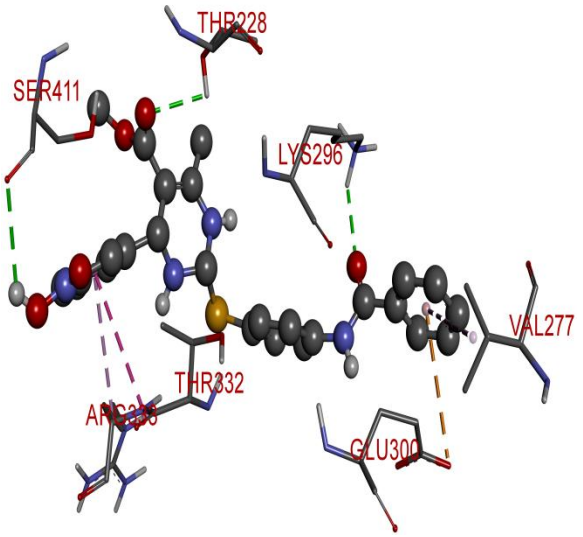
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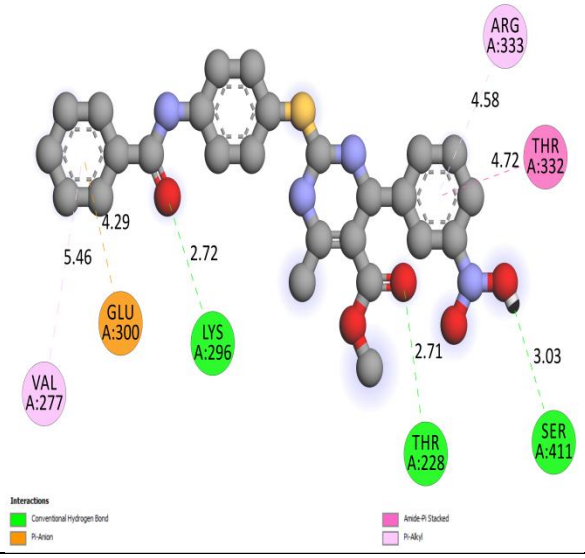
LYS296
VAL277
THR332
ARG333
GLU300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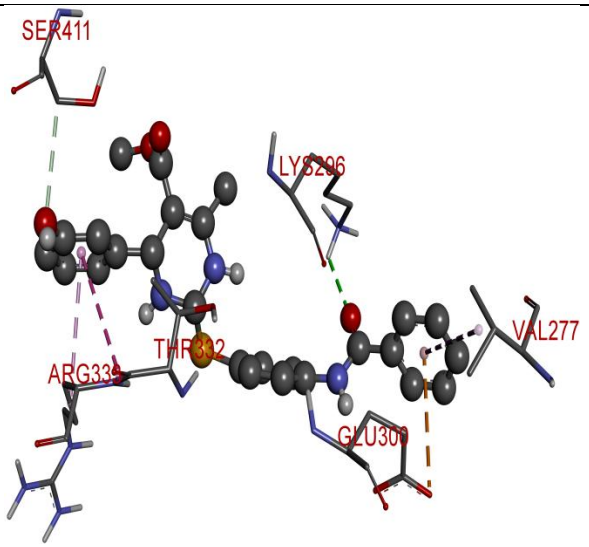
4.58
THR A:332
4.72
4.29
5.46
2.72
GLU A:300
LYS A:296
2.71
3.03
VAL A:277
THR A:228
SER A:411
Interactions
Conventional Hydrogen Bond
Pi-Anion
Amide-Pi Stacked
Pi-Alkyl

A11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VAL277
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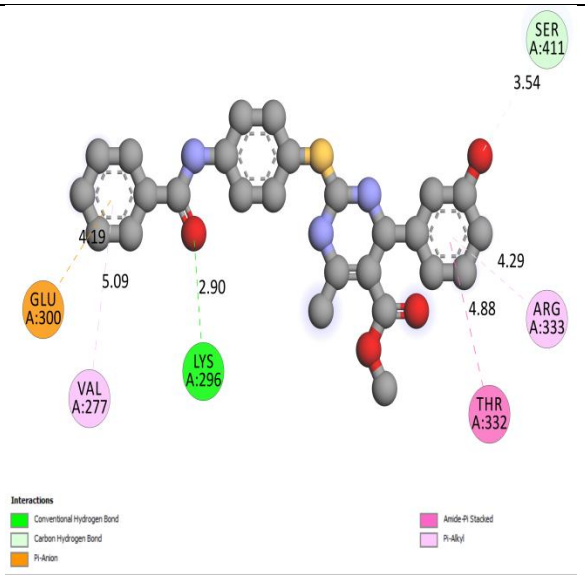
ARG333
GLU300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4.19
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5.09
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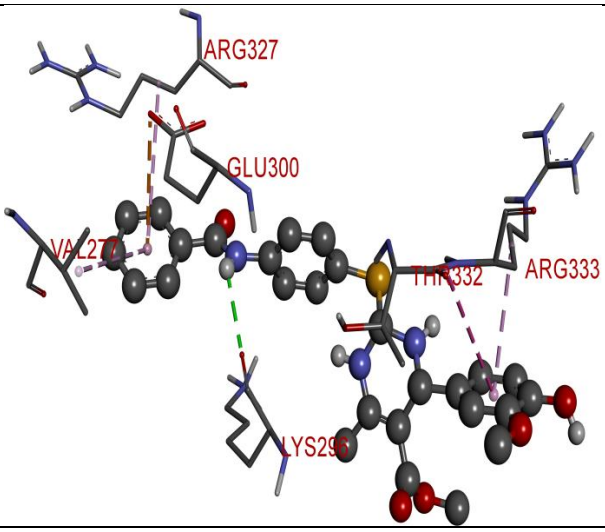
4.88
GLU A:300
ARG A:333
LYS A:296
VAL A:277
THR A:332
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Amide-Pi Stacked
Pi-Alkyl

A13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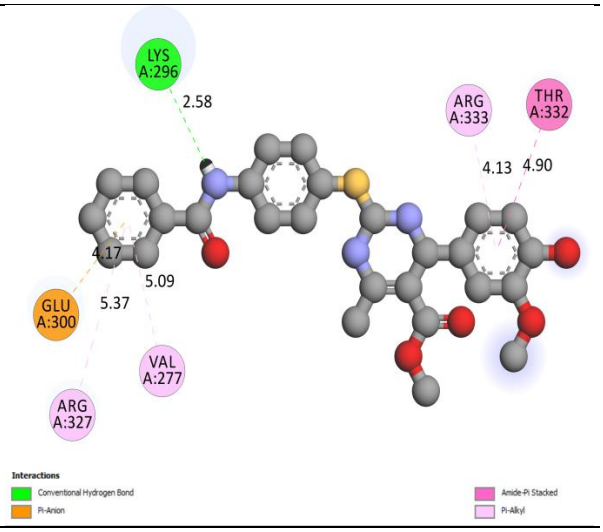
GLU300
VAL277
THR332
ARG333
LYS296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ARG A:333
THR A:332
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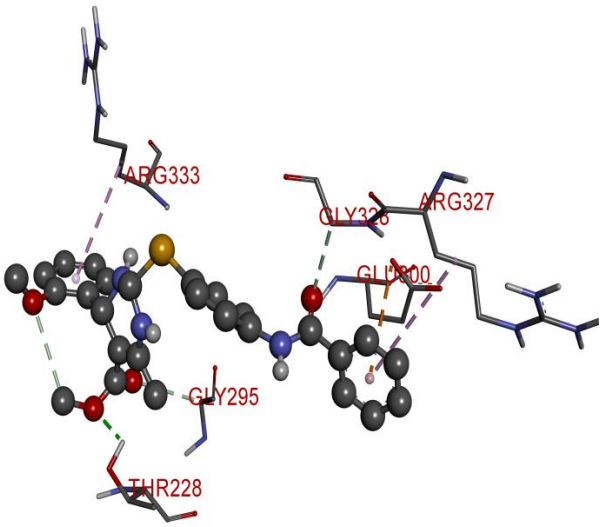
4.90
4.17
5.09
5.37
GLU A:300
VAL A:277
ARG A:327
Interactions
Conventional Hydrogen Bond
Pi-Anion
Amide-Pi Stacked
Pi-Alkyl

A14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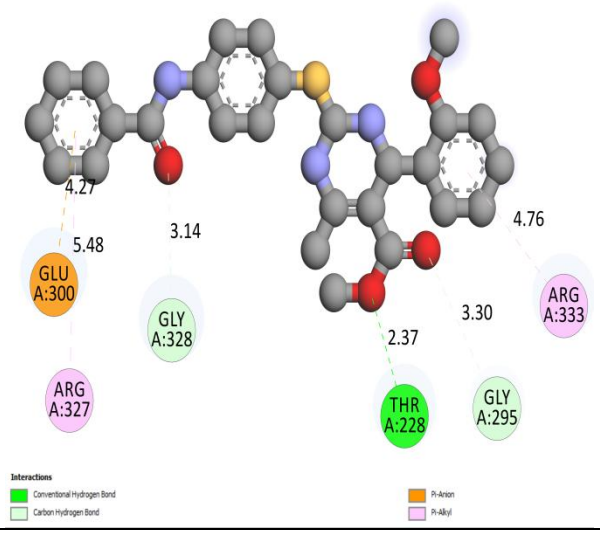
ARG327
GLU300
GLY295
THR228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3.14
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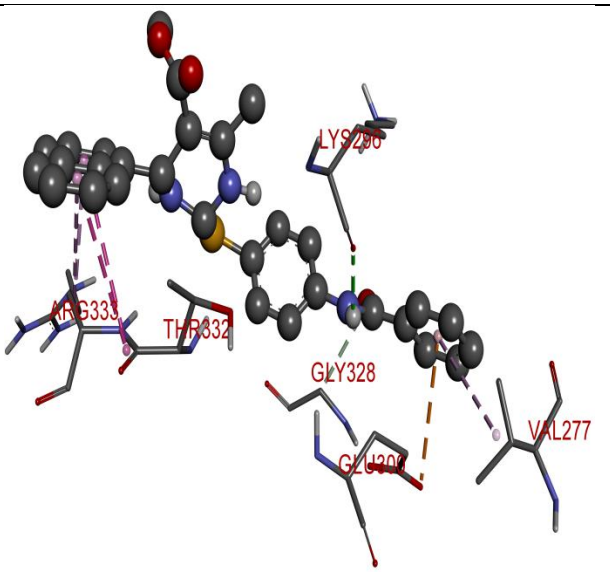
GLU A:300
GLY A:328
ARG A:333
3.30
2.37
ARG A:327
THR A:228
GLY A:295
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Pi-Alkyl

A16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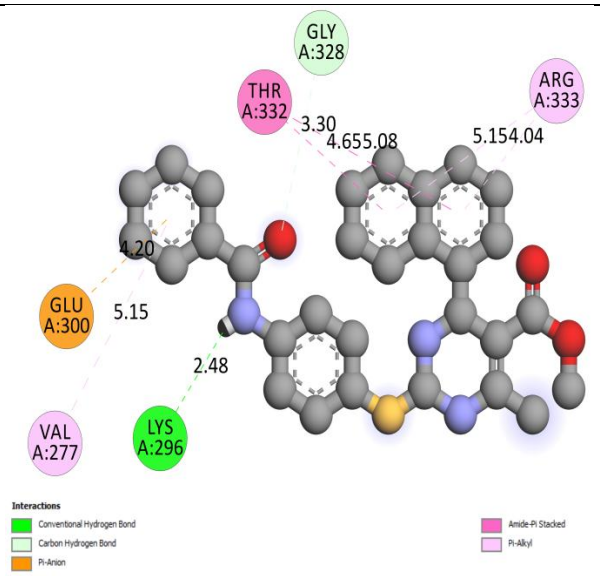
ARG333
THR332
GLY328
VAL277
GLU300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THR A:332
ARG A:333
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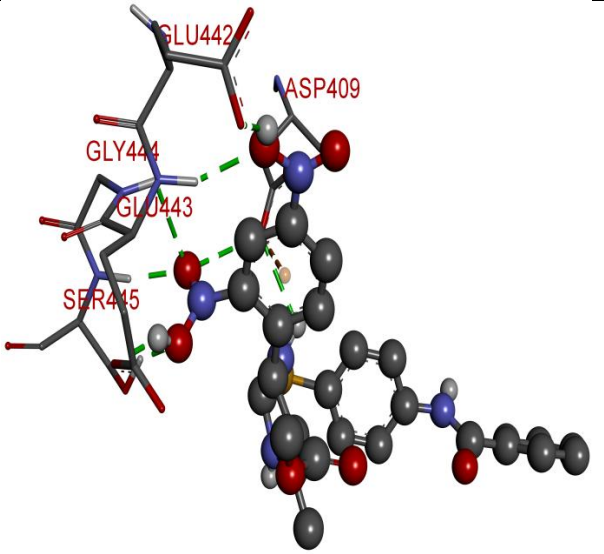
5.154.04
4.20
GLU A:300
5.15
2.48
VAL A:277
LYS A:296
Interactions
Conventional Hydrogen Bond
Carbon Hydrogen Bond
Pi-Anion
Amide-Pi Stacked
Pi-Alkyl

A17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GLY444
GLU443
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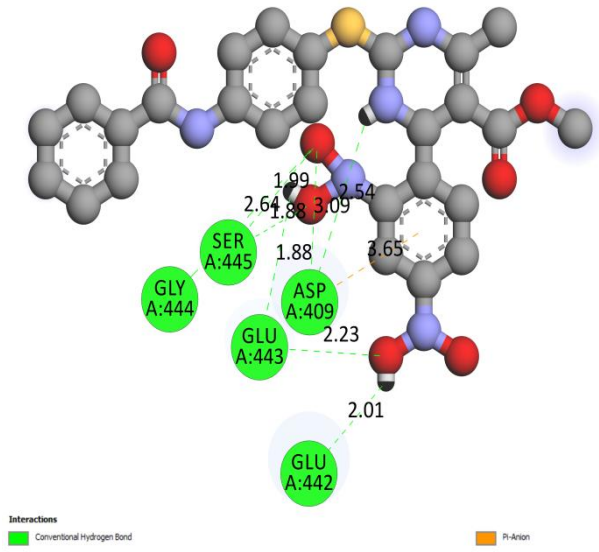
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2.54
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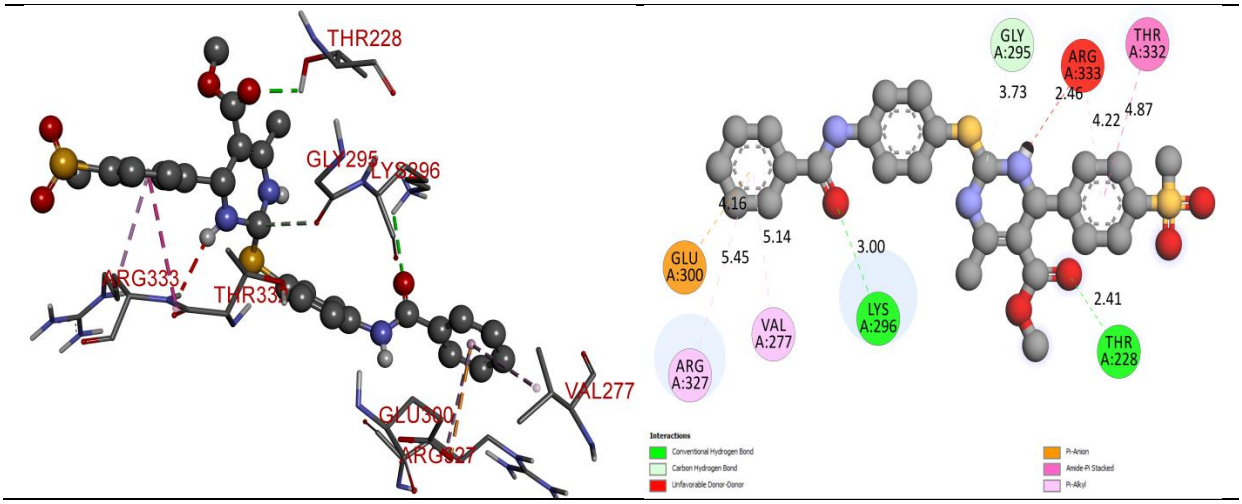
1.88
3.09
SER A:445
1.88
3.65
GLY A:444
ASP A:409
GLU A:443
2.23
2.01
GLU A:442
Interactions
Conventional Hydrogen Bond
Pi-Anion

A18



4. CONCLUSION

In the present work, we have designed and developed some novel benzamide derivatives as GK activators for treating T2DM. Neha Charaya *et al.* have designed, synthesized and evaluated some novel thiazol-2-yl benzamide derivatives as antidiabetic agents [18]. They have reported that this benzamide scaffold can be treated as the primary hits for the expansion of novel, safe, active, and orally bioavailable GK activators to treat T2DM. Saurabh C. Khadse *et al.* have designed, synthesized and evaluated the series of hetero-substituted sulphonamido-benzamide hybrids as GK activators and concluded that these are safe and could be explored further for better therapeutic efficacy in the treatment of T2DM. They have reported that the hydrogen bonding with Arg-63 amino acid residue is an essential interaction necessary for ideal binding [41]. Kaapjoo Park *et al.* have reported some novel heteroaryl-containing benzamide derivatives as GK activators. The strong hydrogen bonds with Arg-63, the hydrophobic pocket surrounded by Tyr-214, Tyr-215, Gly-97 and the solvent exposed region with hydrogen bonding to Arg-250 are important for GK activation [42]. In present investigation, many molecules had formed strong hydrogen bond with Arg-63 which indicate the potential to activate GK. From above results it has been observed that these designed benzamide derivatives have potential to activate the human GK which enables us to proceed for the syntheses of these derivatives.

All the designed novel derivatives were docked on the human glucokinase enzyme, and the docking results were compared with the native ligand present in the enzyme (PDB ID 1V4S). The formation of hydrogen bonds with the target can cause more effective conformational changes. Many derivatives showed better binding interactions at allosteric sites than the native ligand with more hydrogen bonds. Amongst the designed derivatives, compounds A2, A3, A8, A10, A11, A13, A14, A16, A17, and A18 have shown better binding free energy (between -8.7 to -10.3 kcal/mol) than the native ligand present in the enzyme structure. From current results, we have concluded that designed derivatives can effectively activate the human GK enzyme, which can be useful in treating T2DM. We will proceed with the syntheses, characterization and screening of these derivatives by oral glucose tolerance test (OGTT) as antidiabetic agents in animal models. In part two of this research work, we will report the synthesis of these derivatives and their pharmacological screening as antidiabetic agents in the animal model.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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