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.

Article Information

DOI: 10.9734/JPRI/2021/v33i44B32650

Editor(s):
(1) Dr. Juan Carlos Troiano, University of Buenos Aires, Argentina.

Reviewers:
(1) Azibanasaamesa D. C. Owaba, Niger Delta University, Nigeria.
(2) Amit Gupta, Invertis University Bareilly, India.

Complete Peer review History: https://www.sdiarticle4.com/review-history/73863

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 docking.

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dockings 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**

| Acronym | Abbreviation |
|---------|--------------|
| 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 GKA 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 GKA 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], acylamides [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.

**Step-I:**

\[
\text{Benzoic acid} \xrightarrow{\text{N,N'-Dicyclohexylcarbodiimide (DCC)}} \text{N-(4-chlorophenyl)benzamide}
\]

**Step-II:**

\[
\text{Ethyl 3-oxobutanoate} + \text{Aldehyde} + \text{Thiourea} \xrightarrow{\text{Ethanol/HCl, Reflux, \(4-5\text{ hrs}\)}} \text{1,2,3,4-tetrahydropyrimidine-2-thiol}
\]

**Step-III:**

\[
\text{N-(4-chlorophenyl)benzamide} + \text{1,2,3,4-tetrahydropyrimidine-2-thiol} \xrightarrow{\text{H2O:Acetone (2:1), 50-60°C, 45 min}} \text{methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidin-5-carboxylate Derivatives}
\]

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

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

| Code | Structure | IUPAC Name |
|------|-----------|------------|
| A1   | ![Structure A1](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidin-5-carboxylate |
| A2   | ![Structure A2](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-phenylpyrimidin-5-carboxylate |
| A3   | ![Structure A3](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)pyrimidin-5-carboxylate |
| Code | Structure | IUPAC Name |
|------|-----------|------------|
| A4   | ![Structure A4](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A5   | ![Structure A5](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A6   | ![Structure A6](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A7   | ![Structure A7](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-p-tolylpyrimidine-5-carboxylate |
| A8   | ![Structure A8](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A9   | ![Structure A9](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A10  | ![Structure A10](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)pyrimidine-5-carboxylate |
| Code | Structure | IUPAC Name |
|------|-----------|------------|
| A11  | ![Structure A11](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(3-hydroxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A12  | ![Structure A12](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(2,3,4-trihydroxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A13  | ![Structure A13](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(4-hydroxy-3-methoxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A14  | ![Structure A14](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4-(2-methoxyphenyl)-6-methylpyrimidine-5-carboxylate |
| A15  | ![Structure A15](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-cinnamyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A16  | ![Structure A16](image) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(naphthalen-1-yl)pyrimidine-5-carboxylate |
| A17  | ![Structure A17](image) | 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  | ![Image](image1.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-(4-(methylsulfonyl)phenyl)pyrimidine-5-carboxylate |
| A19  | ![Image](image2.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-((4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A20  | ![Image](image3.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-((4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A21  | ![Image](image4.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-4,6-dimethylpyrimidine-5-carboxylate |
| A22  | ![Image](image5.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-4-ethyl-1,2,3,4-tetrahydro-6-methylpyrimidine-5-carboxylate |
| A23  | ![Image](image6.png) | methyl 2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methyl-4-propylpyrimidine-5-carboxylate |
| A24  | ![Image](image7.png) | methyl 4-((dimethylamino)cinnamyl)-2-((4-(benzamido)phenyl)sulfanyl)-1,2,3,4-tetrahydro-6-methylpyrimidine-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 = 31.68Å; size_y = 3.7901Å; size_z = 64.27Å) 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 (2.21Å), LYS-169 (2.60Å), and ASP-78 (2.04Å); one carbon hydrogen bond with GLY-81 (3.75Å); Pi-Anion bond with ARG-85 (3.57Å), ASP-409 (3.71Å), Pi-Cation bond with ASP-205 (3.95Å) 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 ARG63 (2.38753Å) and hydrophobic interactions with the target. Molecule A3 exhibited -9.3 kcal/mol binding free energy and formed one conventional hydrogen bonds with ARG63 (2.17618Å) and hydrophobic interactions with the target. Molecule A8 showed -9.2 kcal/mol binding free energy and formed one conventional hydrogen bond with LYS296 (2.41616Å) and one electrostatic bond with GLU331 (5.02607Å). 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 (2.41616Å) and one electrostatic bond with GLU331 (5.02607Å). It has developed many

![Fig. 2. The identified active cavity with native ligand present in human GK (PDB ID: 1V4S)](image-url)
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 (3.02994Å), THR228 (2.71297Å), and LYS296 (2.72134Å). 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 SER411 (3.02994Å), THR228 (2.71297Å), and LYS296 (2.72134Å). It has developed many hydrophobic interactions with GLU300, THR332, ARG333, and VAL277. Molecule A13 exhibited -9.4 kcal/mol binding free energy with LYS296 (2.57884Å). 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 (2.48334Å) and one carbon hydrogen bond with GLY328 (3.29691Å). 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 (2.53866Å), GLU442 (2.00919Å), ASP409 (3.09435Å), GLU443 (1.88481Å, 2.22894Å), GLY444 (2.6412Å), and SER445 (1.99286Å, 1.8802Å). It has formed Pi-anion bond with ASP409 (3.64706Å). Compound A18 exhibited -9 kcal/mol binding free energy and formed two conventional hydrogen bond with THR228 (2.40684Å) and LYS296 (3.00479Å). It has formed one carbon hydrogen bond with GLY295 (3.72558Å). 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 (Å) | 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               |
| ILE159                   | 5.14365         | Hydrophobic        | Pi-Alkyl               |
| VAL452                   | 4.87776         | Hydrophobic        | Pi-Alkyl               |
| VAL455                   | 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 (Å) | 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                   | 4.68555         | 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           | 4.85956         | 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 (Å) | 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                          |
| ARG333                  | 4.21676       | 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 (Å) | 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                     | 2.16085         | 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 (Å) | 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                             |
| 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              | ![3D-docking pose](image1) | ![2D-docking pose](image2) |
| A3              | ![3D-docking pose](image3) | ![2D-docking pose](image4) |
| A8              | ![3D-docking pose](image5) | ![2D-docking pose](image6) |
| A10             | ![3D-docking pose](image7) | ![2D-docking pose](image8) |
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

ACKNOWLEDGEMENTS

The authors are thankful to the principal, S.N.J.B’s S.S.D.J. College of Pharmacy, Neminagar, Chandwad, Nashik, Maharashtra, India-423101 for providing necessary facilities to perform this research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73863