Research Article

Molecular docking assessment of N-heteroaryl substituted benzamide derivatives as glucokinase activators

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Abstract

Objective: Glucokinase (GK) activators are newer emerging class of therapeutic candidates, which activate GK in pancreatic β-cells and liver hepatocytes and show their hypoglycemic activity. The maximum drug discovery and development programmes linked to GK activators were primarily centered on the N-heteroaryl substituted benzamide derivatives. The present work was planned to predict the binding mode of a series of N-heteroaryl benzamide derivatives in the allosteric site of GK enzyme in a way to design newer GK activators. **Material and Methods**: A series of N-heteroaryl benzamide derivatives with reported high GK activity from literature were selected for the molecular docking studies. *In silico* molecular docking studies were performed for the selected derivatives in the allosteric binding site of GK protein using AutoDock Vina. **Results**: The superimpose of the docked poses of the selected benzamide derivatives with the GK-reference activator complex showed that the selected derivatives have the analogous binding pattern with the allosteric site residues of the enzyme as that of reference ligand. The results of the docking studies indicated that the amide group of the benzamide is required for the H-bonding interactions with Arg63 residue of GK protein and the aromatic rings are essential for the hydrophobic interactions with the residues in hydrophobic pocket in allosteric site of the GK protein. **Conclusion**: This information can be utilized to design novel potent, safe and effective GK activators based on benzamide scaffold for type 2 diabetes therapeutics.

Keywords: AutoDock, Benzamides, Docking, Glucokinase, GK activators, Type 2 diabetes

Introduction

Diabetes mellitus (simply known as diabetes) is a long-lasting disorder of food metabolism characterized by hyperglycemia, originating due to defect in insulin secretion, insulin function or both leading to tissue and vascular damage and resulting in a variety of complications including retinopathy, cataract, neuropathy, nephropathy, ketoacidosis, disorders of cardiovascular system and foot ulcers (Bastaki, 2005; Cade, 2008; Grewal et al., 2016). Type 2 diabetes (T2D) affecting more than 90% of all the diabetic patients, is a long-term disordered food metabolism caused by declined insulin action (Kohei, 2010; Olokaba et al., 2012). Despite the fact that various types of oral antidiabetic drugs are available for the treatment of T2D, no single drug is useful for achieving long-term control of normal blood glucose levels in majority of patients. Due to this reason, general practitioners prescribe combination of antidiabetic agents for T2D therapy and overdose of antidiabetic medicines could lead to severe hypoglycemia resulting in brutal toxic and side effects (Olokaba et al., 2012). The medicinal chemists are currently focusing on development of novel safe antidiabetic medicines with biologically new mechanism of action which can be used as single drug with improved efficacy. Results from several recent reports, including emerging clinical reports, have demonstrated that small-molecule allosteric glucokinase (GK) activators may be able to achieve these objectives (Pal, 2009).

Glucokinase (GK, EC 2.7.1.2) is a cytoplasmic enzyme

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which accelerates the breakdown of glucose to glucose-6-phosphate in presence of ATP and helps in the maintenance of the normal blood glucose levels in humans (Pal, 2009; Matschinsky and Porte, 2010). In pancreatic β-cells, it plays chief role by controlling glucose-stimulated insulin release and in liver hepatocyte cells, it controls the sugar metabolism. GK is an emerging target for the therapeutic management of T2D patients as it plays a key function in the regulation of carbohydrate breakdown. Animals that do not express GK enzyme die within days of birth with severe hyperglycemia whereas animals over expressing GK enzyme have shown better glucose tolerance. In addition, GK over expression in the liver hepatocytes of diabetic or non-diabetic animals demonstrated enhanced glucose tolerance. GK activators are novel class of therapeutic agents which activate GK enzyme and show their hypoglycemic activity (Coghlan and Leighton, 2008; Perseghin 2010; Verspohl, 2012; Castro, 2012). A wide range of chemically different compounds including benzamides, carboxamides, acrylamides, benzimidazoles, quinazolines, thiazoles, pyrimidines, and urea derivatives were developed recently to act as potent GK activators. The maximum drug discovery and development programmes linked to synthesis of GK activators were primarily focused on the substituted benzamide derivatives possibly due to their orientation and binding pattern in the allosteric site of GK protein (Johnson and Humphries, 2006; Grewal et al., 2014). Various N-heteroaryl substituted benzamide derivatives having best GK activity reported by different research groups recently were selected for the *in silico* evaluation through molecular docking studies (Figure **1**).

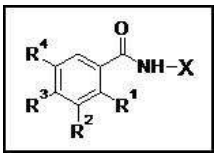


Figure 1. General structure of the N-heteroaryl substituted benzamide derivatives

The main objective of current investigation is the *in silico* evaluation of selected N-heteroaryl substituted benzamide derivatives in order to explore the binding modes of the selected compounds in allosteric site of GK protein and to establish the structural basis of their GK activity in order to design safe and effective GK activators using molecular docking.

Materials and Methods

The chemical structures of the benzamide derivatives selected for the molecular docking study are presented in table **1** along with their reported GK potency in terms of EC_{50} value (effective concentration causing 50% activation of GK).

Molecular docking studies

In silico molecular docking studies were carried out for the selected derivatives in the allosteric site of GK protein using AutoDock Vina (Trott and Olson, 2010) and AutoDock Tools (Morris et al., 2009). The 2-D chemical structures of all the ligands were prepared by MarvinSketch (MarvinSketch 18.5.0, 2018, ChemAxon) and transformed to 3-D by Frog2 server based on a graph decomposition of the compounds coupled with an identification of the stereo-centres for which the chirality is unspecified (Miteva et al., 2010). The ligands were converted to "pdbqt" files from "mol" format using AutoDock Tools. After assessing a numbers of co-crystallized structures for GK enzyme available in the protein data bank; the best ligand bound complex (PDB entry: 3IMX) was selected with complex having maximum resolution and best binding interactions between ligands and proteins. The PDB file of 3IMX was edited using PyMOL (PyMOL Molecular Graphics System, Version 1.7.4.5, Schrödinger) by removing the complexed activator, all the water molecules as well as all non-interacting ions. The "pdbqt" file of GK protein was generated from the PDB files using AutoDock Tools, grid parameters were calculated using "Grid" of AutoDock Tools and all the data regarding target protein, ligand, grid size and geometry were saved in "txt" file. The reference ligand was docked in the active site of 3IMX and compared with that of the co-crystallized activator of GK (PDB ligand of 3IMX) for determining the accuracy of the docking protocol. The 3-D optimized ligand molecules were docked in the active site of the refined GK model and scored by scoring function. The binding free energy (ΔG, kcal/mol) for each ligand was reported in log file and the binding interactions of the ligands in allosteric site of GK protein were analysed using PyMOL (Charaya et al., 2018).

Results and discussion

The drug-likeness properties including molecular weight, partition coefficient (log P), hydrogen bond acceptors (HBA) and hydrogen bond donors (HBD) were computed for all the molecules and all the compounds showed drug-like properties as contrived by Lipinski's rule of 5 (Table **2**). *In silico* studies were performed to explore the affinity and binding interactions of the selected benzamide derivatives in the allosteric binding site of GK protein. All the molecules were docked in the allosteric binding site, which was surrounded by the β1 strand and α5 helix of the large domain, the C-terminal α13 helix of the small domain, and the GK specific connecting region I (Ser64-Gly72). The allosteric binding site was comprised of Arg63, Tyr215, Met210, Tyr214, Val452 and Val455 residues. The docking simulations were carried out by energy minimization and optimization of selected benzamide ligands in the allosteric binding site of GK protein (PDB entry: 3IMX). The

Table 1. Structures of benzamide GK activators selected for molecular docking studies with their GK activity

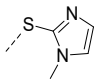
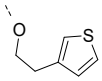
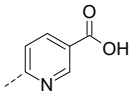
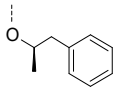
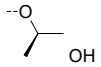
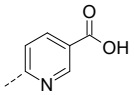
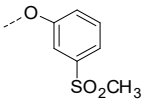
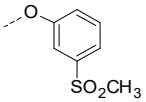
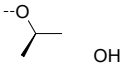
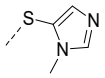
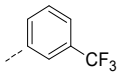
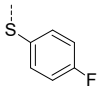
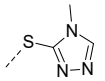
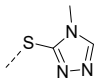
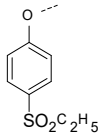
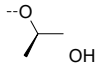
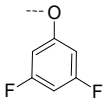
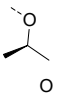
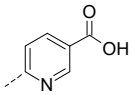
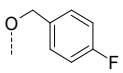
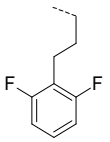
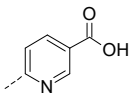
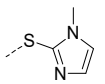
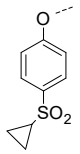
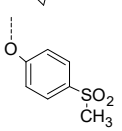
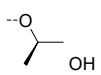
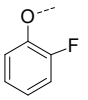
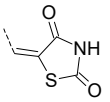
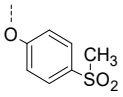
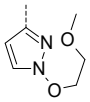
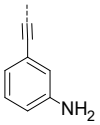
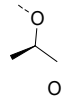
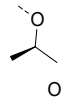
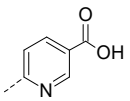
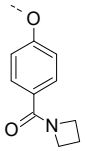
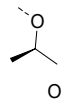
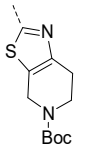
S. No.	R^1	R^2	R^3	R^4	X	EC_{50} (μM)#
1	NH_2	-H	F			0.067 (Kamata et al., 2004)
2	H		H			0.090 (McKerrecher et al., 2005)
3	H		H			0.030 (McKerrecher et al., 2006)
4	H		H			0.090 (Iino et al., 2009)
5	H		H			0.060 (Iino et al., 2009a)
6	NH_2	H	F			1.870 (Zhang et al., 2009)
7		H	H			0.970 (Mitsuya et al., 2009)
8	NH_2	H	H			0.140 (Nishimura et al., 2009)
9	H		H			0.065 (Eiki et al., 2011)
10	H		H			0.090 (Pike et al., 2011)
11		-H	H			1.4* (Li et al., 2011)
12	H		H			0.070 (Park et al., 2012)
13	NH_2	-H	H			0.230 (Jain et al., 2012)
14	H		H			0.283 (Mao et al., 2012)
15	H		H			0.045 (Ericsson et al., 2012)
16	H		H			0.056 (Park et al., 2013)

Table 1. Continue.....

17	NH_2	-H	H			0.026 (Jain et al., 2013)
18	H	-H	H			1.4* (Lu et al., 2014)
19	H		H			0.315 (Park et al., 2014)
20	H		H			0.027 (Park et al., 2015)
21	H		H			0.020 (Taha et al., 2015)
22	H		H			0.160 (Wang et al., 2017)

*Fold activation of GK at 10 μM; #EC_{50} for GK activation reported in literature

Table 2. Molecular properties, H-bond interaction and ΔG of the selected benzamide GK activators

S. No.	Mol. Wt.*	Log P*	HBA*	HBD*	H-bond distance (Å)	ΔG
1	349	3.74	4	2	3.4	-7.3
2	426	3.95	6	2	3.7, 3.1	-9.3
3	450	3.61	7	3	3.9, 3.3	-8.8
4	446	3.24	5	1	3.5	-7.9
5	462	2.03	6	2	4.0, 3.3	-8.8
6	410	4.39	3	2	3.8	-9.2
7	457	5.23	4	1	3.9	-8.6
8	346	2.45	5	2	3.7	-7.0
9	459	2.16	6	2	3.3, 4.1	-8.8
10	458	3.71	6	2	3.8, 3.3	-9.5
11	410	4.08	5	1	4.4, 3.4	-8.9
12	448	4.87	6	2	4.0, 3.4	-8.5
13	345	3.77	4	2	3.4	-7.4
14	484	4.20	5	1	3.6, 3.8	-8.7
15	445	1.69	6	2	3.1	-9.1
16	449	5.47	5	2	4.3	-7.9
17	343	3.97	3	2	3.3	-8.4
18	325	2.66	4	2	3.9, 3.3	-9.2
19	522	3.39	7	1	4.1, 3.6	-8.7
20	404	3.27	5	2	4.3, 3.9, 4.1	-8.8
21	388	2.50	7	2	3.6	-7.1
22	622	3.67	6	1	4.1	-8.7

*Mol. Wt., Log P, HBA, and HBD were calculated using MarvinSketch

reference ligand was docked into the active site of GK protein; and the docked reference activator of GK enzyme produced a similar binding pattern and superposition on the binding mode of co-crystallized activator with ΔG of -9.0 kcal/mol validating accuracy of docking methodology. Most of the compounds showed appreciable binding in the allosteric site of GK protein as established by analyzing their bonding interactions in terms of H-bond, hydrophobic interactions and ΔG of the best docked poses (Table 2).

The docking studies of these molecules suggested a complimentary fit in the allosteric site of GK protein. On the basis of their lowest binding free energy (kcal/mol) and docking interactions (including H-bond and hydrophobic interactions) in the allosteric site of GK protein, compounds **2, 10, 18** and **20** were further analyzed in details using PyMOL. Docked poses showing H-bond interactions for compounds **2, 10, 18** and **20** with amino acid residues of allosteric binding site of GK protein are presented in Figure

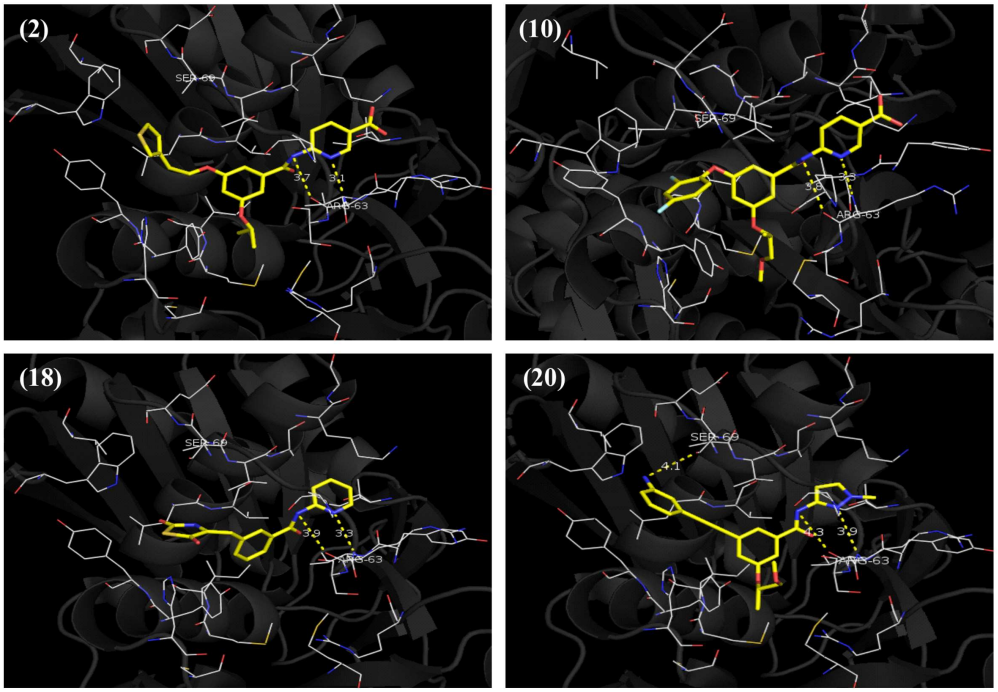


Figure 2. Docked poses showing H-bond interactions for compounds **2, 10, 18** and **20** with amino acid residues of the allosteric site of GK protein

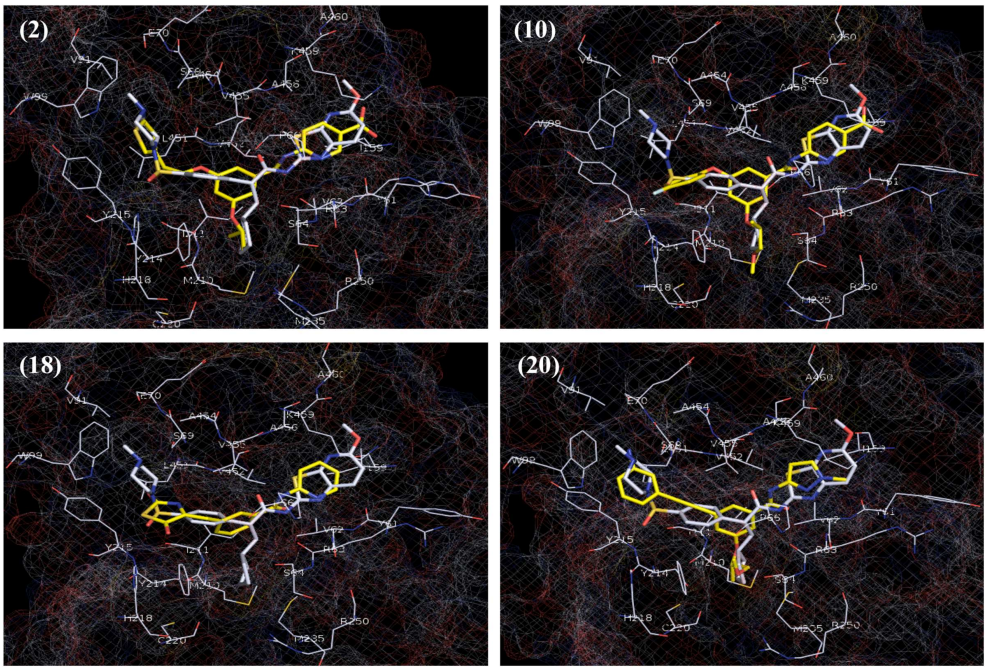


Figure 3. Overlay of the docked poses of compounds **2, 10, 18** and **20** (yellow stick) with that of PDB ligand of 3IMX (grey stick) in the allosteric site of GK protein

2. All the selected molecules were found to bind to an allosteric pocket of GK protein, which is about 20Å remote from the glucose binding site (Liu et al., 2012). The docked pose of compounds **2** and **10** showed the H-bond interaction between 'N' of pyridine-2-yl carboxylic acid group and 'NH' of benzamide with amide 'NH' and backbone 'carbonyl' of Arg63 residue on GK protein with H-bond distance of 3.7 Å and 3.1 Å; and 3.8 Å and 3.3 Å, respectively. Compound **18** showed the H-bond interaction between the 'N' of pyridine-2-yl ring and benzamide 'NH' with backbone 'carbonyl' and amide 'NH' with H-bond distance of 3.9 and 3.3 Å, respectively. Compound **20** showed the H-bond interaction between the 'N' of imidazole-2-yl ring, benzamide 'NH' and 'amino' group with amide 'NH' and backbone 'carbonyl' of Arg63 residue; and 'carbonyl' of Ser69 residue on GK protein with H-bond distance of 4.3 Å, 3.9 Å and 4.1 Å, respectively.

Overlay of the docked poses of compounds **2, 10, 18** and **20** with that of PDB Ligand 3IMX in the allosteric binding site of GK protein showed that the selected molecules had the similar orientation and binding pattern in the allosteric site of enzyme as that of co-crystallized ligand of PDB ID: 3IMX (Figure **3**). The substituted heteroaryl group of the selected compounds protruded in the hydrophobic pocket showing the interactions with Val455, Ala456, and Lys459 of the R13 helix, as well as Pro66 of connecting region I and Ile159 of the large domain, phenyl ring packs between Tyr214, Met210 and Val455. Overall the overlay of the docked poses of the selected compounds (**2, 10, 18 and 20)** with 3IMX ligand showed that these selected ligands had the similar orientation and binding pattern in the allosteric site of GK protein as that of co-crystallized ligand supporting the *in vitro* GK activity of these compounds.

Conclusion

In conclusion, the results of molecular docking studies performed on N-heteroaryl benzamide derivatives revealed that 3,5-disubstituted benzamide derivatives showed better binding interactions in the allosteric site of GK protein. The 'NH' of amide group of the benzamides and heteroatom of heteroaryl ring is required for the H-bond interactions with Arg63 residue of GK protein and the aromatic rings are essential for the hydrophobic interactions with the residues in hydrophobic pocket in allosteric site of the GK protein. This *in silico* docking study is actually an added advantage to screen the GK activators. Structural modifications and further studies on these substituted benzamide derivatives could help to develop safe, potent and orally bioavailable GK activators for the treatment and management of T2D.

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