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MOLECULAR DOCKING STUDIES OF FEW 6-SUBSTITUTED QUINAZOLINE DERIVATIVES FOR GLUCOKINASE ACTIVATION

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ABSTRACT

Diabetes mellitus is a growing public health problem with increasing incidence and long-term complications. It results from insulin deficiency, resistance, or both, leading to high blood sugar levels and various metabolic disorders. One strategy to manage this is by activating glucokinase (GK) to enhance glucose use in muscles and insulin release from the pancreas. Researchers are testing quinazoline-based compounds to activate GK. In silico studies showed that several designed ligands could successfully bind and activate GK, suggesting potential for further development and clinical application.

KEYWORDS

International diabetes federation, Diabetes mellitus, Glucokinase activators and Side effects.

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INTRODUCTON

Diabetes mellitus is a group of metabolic disorders caused by insulin deficiency, resistance, or both, leading to high blood sugar levels (chronic hyperglycemia). This condition is a growing global health challenge. According to the International Diabetes Federation, the number of people with diabetes is expected to rise from 537 million in 2021 to 643 million by 2030, and further to 783 million by 2045[3,4]. This health problem and its financial burdens are significant worldwide[5,7]. Additionally, in 2021, over 6.7 million people aged 20-79 died from diabetes-related issues[3]. High fasting glucose levels (over 5.6mmol/l) are associated with a higher risk of death[8]. Fluctuating blood sugar levels are often linked to nerve damage, kidney disease, eye problems, and heart diseases[9,10].

Clinical trials show that over half of diabetic patients have one or more complications[11,12], this progressively leads to high risk of mortality[13,15]. Effective management and treatment of diabetes and its complications are crucial. Some people can control their blood sugar through weight loss, exercise and oral medications, but those with severe β-cell damage need insulin[16]. Even with strict glucose control strategies, diabetes is rarely reversed, and complications are likely to develop[17]. Recent strategies for diabetic complications aim to prevent or manage these issues based on known disease patterns[18]. Due to the limitations of current treatments, it's urgent to find new drugs and targets to fight diabetes and its complications.

Need of New drugs for treatment of Diabetes Mellitus

Several options of drugs available to treat T2DM including glucose-lowering agents like which suppress hepatic glucose production and increase glucose uptake, insulin secretagogues, like sulphonylureas and meglitinides, which enhance insulin secretion from pancreatic β-cells, peroxisome proliferator activated receptor-γ (PPAR-γ) activator-like thiazolidinediones, which enhance insulin sensitivity and α-glucosidase inhibitors which block glucose production in the gut, Sodium-Dependent Glucose Co-Transporter 2 (SGLT2) Inhibitors, glucagon-like peptide 1 (GLP1) Receptor agonist and DPP-4 inhibitors[77]. Those drugs act by different pharmacological actions; enhance insulin secretion, increase insulin sensitivity, suppress hepatic glucose production, and inhibit glucose reabsorption by the kidney[78]. Unfortunately, none of these antidiabetic agents used to manage hyperglycemia do not stop or reverse disease progression and even may have severe side effects and comorbidities. For example, treatment of T2DM patients with insulin, meglitinides and sulfonylureas associated with weight gain, hypoglycemia, and treatment with thiazolidinediones may cause osteoporosis, increased risk of heart failure, fluid retention, urinary bladder cancer, and hepatotoxicity. Besides, the Anti-diabetic agents like metformin, sulfonylureas, and GLP1 agonists lose their efficacy[79].

Glucokinase Activators

Glucokinase (GK), also known as hexokinase IV, is one of the Hexokinase families, which has a key role in glucose metabolism. In the liver, GK facilitates glucose uptake and glycogen synthesis. GK phosphorylates glucose to glucose- 6-phosphate, which may enter the mitochondrial to produce pyruvate or use as a substrate for glycolysis. These processes facilitate glucose clearance[112]. In pancreatic β cells, GK regulates glycolytic and oxidative ATP synthesis. GK increases ATP/ADP ratio, which closes the K+ channel, and makes the cell depolarized resulting in insulin secretion in Figure No.1.

METHODS AND MATERIAL

Computational Studies

The software used for carrying in silico studies during the project were

ACD Freeware 2018 (downloaded from the official website)

PyRx Virtual Screening tool (online) Version 1.1.1.2

Biovia discovery studio

SwissADME Software (online)

The RCSB Protein Data Bank entry *1V4S* (https://www.rcsb.org/structure/1V4S) contains the computational structure of Human GK. The protein was bound in its allosteric site by 5-(1-Methyl-1*H*-imidazol-2-yl-thio)-2-amino-4-fluoro-*N*-(thiazol-2-yl) benzamide, ATP and Mg^{++}. The protein was free from the native ligand, refined and made ready for docking studies in Discovery Studio Visualizer 2019.

As many as 250 protein structures, co-crystallized with Mg++ ion, ATP and the bound ligand (either *RO-28-1675*, Piragliatin, or any one of the several GKAs from the past) that were available on RSCB-PDB site to stand for the constitutional metalo-enzyme with kinase activity, *GK,* were downloaded and subjected to study by *Ramachandran Plot*[54,55]. This study allowed to have thorough insights regarding suitability of the orientations of amino acid residues in the computed protein co-

crystallized structures to select one out of many for the docking studies. Accordingly, co-crystals 5-(1-methyl-1H-imidazol-2-ylthio)-2-amino-4-fluoro-N-(thiazol-2-yl) benzamide of *GK* were obtained from the PDB site. PDB Site: https://www.rcsb.org/structure/1V4S. The structures of designed ligands were constructed using the *ChemSketch freeware* module of ACD Labs. The structures have represented by *Markush formula* in the Table No.1 of the Results and discussion section.

Docking Studies

In the CADD software, the shortlisted structures, used as ligands along with the standard *RO-28-1675*, were docked into the allosteric site of the crystal structure of the enzymes to study the interactions between them for selecting those designed structures with appropriate binding interactions for further studies. For the process, a grid was set measuring 5 Å radius around the amino acids constituting the allosteric site of the enzyme. The structures were docked, setting the Root Mean Square deviation at 2.0 tolerance. Binding energies (G score) were obtained, choosing the value with the lowest RMSD value. During each docking study, three interaction poses with lowest G score were considered for the final selection. The docking studies carried using protein interaction suit of *Autodock 1.5.6*, for 250 ligands. The obtained results were imported into *Discovery Studio* for visualizing the results of docking. The results of few of the ligands displayed acceptable G-score (-7.0127 to -7.1323) nearer to the G-score of standard ligand, *i. e.* RO-28-1675 (-.8.9124). The Figure No.2 shown in the results and discussion section depicts the dock pose of GK bound to one of the designed molecules in its allosteric cavity.

Screening through Molecular Docking

The combined view of all ligands actively docked in the allosteric site of the GK enzyme is given in Figure No.3 of the Results and Discussion Section. The Figure No.3 represents the ligand docked in the allosteric site of the GK enzyme. The images were obtained using PyRx virtual screening tool. All the designed derivatives were docked and only those which displayed expected interactions with the amino acid residues, viz. TYR215, TYR210, ARG63 and MET205. The ligands which were selected were further subjected to check the violation of Lipinski Rule of five, for better optimization of the study

Structures of the designed ligands that shows good docking score

The results of the application of Lipinski rule of five is given in Table No.2, the ligand binding energies of corresponding ligands with GK and the corresponding dock score are mentioned Table No.3 of the results and Discussion section.

SWISS ADME Study

The free softwares available online for assisting in ADME, *ca. SwissADME* and docking studies, *ca. Schrodinger 2020* and *AutoDOCK* tools (*ver. 1.5.7), Discovery Studio 2021* for studying the interaction between ligands and the selected protein structure[58]. The toxicity of these designed structures was studied by subjecting the SMILES formula of designed structures of quinazoline derivatives. This exercise strikes-off number of toxicity concerns[59] that would get generated if those structures with toxic profiles were to be synthesized in the laboratory. Parameters like aqueous solubility (Log *S*), membrane permeability (Log *Kp*), and synthetic accessibility scores (*SA*), percentage absorption, probable pharmacokinetics and drug-likeness properties of the designed molecules were thought worth to carried as, according to *Lipinski rule of five* assist in summarizing molecular properties of designed structures in hope to develop them as probable drug candidates with predicted therapeutic and pharmacokinetic and toxicity profiles. The rule implies considering molecules with molecular weights ≤ 500, hydrogen bond donors ≤ 5, hydrogen bond acceptors ≤10 and rotatable bonds ≤10, for further studies. Hence, significant drug-like molecules were shortlisted and studies further. The data obtained from *SwissADME* studies (The amino acid residues interacting with the docked ligands, their type of interactions, number of hydrogen bonds formed) have been displayed in Table No.3.

RESULTS AND DISCUSSION

This is the data of SwissADME studies carried on selected designed ligands which displayed apparent interactions with the AA residues of the enzyme GK and comparable *Gscore* with standard ligand (native). Followed by the 2D and 3D poses of docked ligands in Table No.4.

Table No.1: R and R^1 of the synthesized compound

S.No	Code	R	R1
1	Ki	-OH	$-C_6H_5NO_2$
2	Kiii	-OH	$- C_6H_5NH_2$
3	Kiv	-OH	$- C_6H_5CH_3$
4	Kvi	-OH	$- C_6H_4Cl_2$
5	Kix	$-CH_3$	$- C_6H_5NO_2$
6	Kxii	$-CH_3$	$- C_6H_5Cl$
7	Kxiv	$-CH_3$	$- C_6H_4Cl_2$
8	Kxvi	$-NH_2$	$- C_6H_5NO_2$
9	Kxviii	$-NH_2$	$- C_6H_5Cl$
10	Kxix	$-NH_2$	$- C_6H_4Cl_2$
11	Kxxi	$-NHCOCH_3$	$- C_6H_5NO_2$
12	Kxxii	$-NHCOCH_3$	$- C_6H_5CH_3$
13	Kxxiii	$-NHCOCH_3$	$- C_6H_5Cl$
14	Kxxiv	$-NHCOCH_3$	$- C_6H_4Cl_2$

Table No.2: The results of the application of Lipinski rule of five, the ligand binding energies of corresponding ligands with GK, and the corresponding dock score

S.No	Ligand	Log P values	Molecular weight	H-Bond donor	H-Bond acceptor	Lipinski Rule of Five	BBM
1	Ki	Log Po/w (iLOGP) 2.58 Log Po/w (XLOGP3) 4.55 Log Po/w (WLOGP) 4.65 Log Po/w (MLOGP) 2.51 Log Po/w (SILICOS-IT) 1.49 Consensus Log Po/w 3.16	358.35g/mol	2	5	Yes	No
2	Kii	Log Po/w (iLOGP) 2.58 Log Po/w (XLOGP3) 4.55 Log Po/w (WLOGP) 4.65 Log Po/w (MLOGP) 2.51 Log Po/w (SILICOS-IT) 1.49 Consensus Log Po/w 3.16	358.35g/mol	2	5	Yes	No
3	Kiii	Log Po/w (iLOGP) 2.48 Log Po/w (XLOGP3) 4.04 Log Po/w (WLOGP) 4.34 Log Po/w (MLOGP) 2.51	328.37g/mol	3	3	Yes	No

		Log Po/w (SILICOS-IT) 2.96 Consensus Log Po/w 3.27					
4	Kiv	Log Po/w (iLOGP) 3.10 Log Po/w (XLOGP3) 5.09 Log Po/w (WLOGP) 5.05 Log Po/w (MLOGP) 3.56 Log Po/w (SILICOS-IT) 4.20 Consensus Log Po/w 4.20	327.38g/mol	2	3	Yes	Yes
5	Kv	Log Po/w (iLOGP) 3.14 Log Po/w (XLOGP3) 5.35 Log Po/w (WLOGP) 5.40 Log Po/w (MLOGP) 3.96 Log Po/w (SILICOS-IT) 4.32 Consensus Log Po/w 4.43	347.80g/mol	2	3	Yes	Yes
6	Kvi	Log Po/w (iLOGP) 3.22 Log Po/w (XLOGP3) 5.98 Log Po/w (WLOGP) 5.05 Log Po/w (MLOGP) 4.45 Log Po/w (SILICOS-IT) 4.95 Consensus Log Po/w 4.93	382.24g/mol	2	3	Yes; 1 violatio: MLOGP >4.15	No
7	Kvii	Log Po/w (iLOGP) 3.41 Log Po/w (XLOGP3) 5.44 Log Po/w (WLOGP) 5.35 Log Po/w (MLOGP) 4.28 Log Po/w (SILICOS-IT) 4.70 Consensus Log Po/w 4.64	311.38g/mol	1	2	Yes; 1 violatio: MLOGP >4.15	Yes
8	Kviii	Log Po/w (iLOGP) 3.12 Log Po/w (XLOGP3) 5.27 Log Po/w (WLOGP) 5.26 Log Po/w (MLOGP) 3.27 Log Po/w (SILICOS-IT) 2.49 Consensus Log Po/w 3.88	356.38g/mol	1	4	Yes	NO
9	Kix	Log Po/w (iLOGP) 2.99 Log Po/w (XLOGP3) 4.76 Log Po/w (WLOGP) 4.94 Log Po/w (MLOGP) 3.70 Log Po/w (SILICOS-IT) 3.96 Consensus Log Po/w 4.07	326.39g/mol	2	2	Yes	Yes
10	Kx	Log Po/w (iLOGP) 3.64 Log Po/w (XLOGP3) 5.81 Log Po/w (WLOGP) 5.66 Log Po/w (MLOGP) 4.36 Log Po/w (SILICOS-IT) 5.21 Consensus Log Po/w 4.94	325.41g/mol	1	2	Yes; 1 violatio: MLOGP >4.15	Yes
11	Kxi	Log Po/w (iLOGP) 3.72	345.82g/mol	1	2	Yes; 1	No

		Log Po/w (XLOGP3) 6.07 Log Po/w (WLOGP) 6.00 Log Po/w (MLOGP) 4.77 Log Po/w (SILICOS-IT) 5.32 Consensus Log Po/w 5.18				violatio: MLOGP >4.15	
12	Kxii	Log Po/w (iLOGP) 3.80 Log Po/w (XLOGP3) 6.70 Log Po/w (WLOGP) 6.66 Log Po/w (MLOGP) 5.25 Log Po/w (SILICOS-IT) 5.95 Consensus Log Po/w 5.67	380.27g/mol	1	2	Yes; 1 violatio: MLOGP >4.15	No
13	Kxiii	Log Po/w (iLOGP) 2.76 Log Po/w (XLOGP3) 4.40 Log Po/w (WLOGP) 4.63 Log Po/w (MLOGP) 3.47 Log Po/w (SILICOS-IT) 3.46 Consensus Log Po/w 3.74	312.37g/mol	2	2	Yes	Yes
14	Kxiv	Log Po/w (iLOGP) 2.51 Log Po/w (XLOGP3) 4.23 Log Po/w (WLOGP) 4.54 Log Po/w (MLOGP) 2.51 Log Po/w (SILICOS-IT) 1.26 Consensus Log Po/w 3.01	357.37g/mol	2	4	Yes	No
15	Kxv	Log Po/w (iLOGP) 3.00 Log Po/w (XLOGP3) 4.76 Log Po/w (WLOGP) 4.94 Log Po/w (MLOGP) 3.56 Log Po/w (SILICOS-IT) 3.96 Consensus Log Po/w 4.04	326.39g/mol	2	2	Yes	Yes
16	Kxvi	Log Po/w (iLOGP) 3.03 Log Po/w (XLOGP3) 5.02 Log Po/w (WLOGP) 5.28 Log Po/w (MLOGP) 3.96 Log Po/w (SILICOS-IT) 4.08 Consensus Log Po/w 4.28	346.81g/mol	2	2	Yes	No
17	Kxvii	Log Po/w (iLOGP) 3.25 Log Po/w (XLOGP3) 5.65 Log Po/w (WLOGP) 5.94 Log Po/w (MLOGP) 4.45 Log Po/w (SILICOS-IT) 4.71 Consensus Log Po/w 4.80	381.26g/mol	2	2	Yes; 1 violatio: MLOGP >4.15	No
18	Kxviii	Log Po/w (iLOGP) 3.15 Log Po/w (XLOGP3) 4.25 Log Po/w (WLOGP) 4.81 Log Po/w (MLOGP) 3.42	354.40g/mol	2	3	Yes	Yes

		Log Po/w (SILICOS-IT) 3.81 Consensus Log Po/w 3.89					
19	Kxix	Log Po/w (iLOGP) 2.83 Log Po/w (XLOGP3) 4.08 Log Po/w (WLOGP) 4.72 Log Po/w (MLOGP) 2.50 Log Po/w (SILICOS-IT) 1.64 Consensus Log Po/w 3.15	399.40g/mol	2	5	Yes	No
20	Kxx	Log Po/w (iLOGP) 3.31 Log Po/w (XLOGP3) 4.62 Log Po/w (WLOGP) 5.12 Log Po/w (MLOGP) 3.64 Log Po/w (SILICOS-IT) 4.33 Consensus Log Po/w 4.20	368.43g/mol	2	3	Yes	No
21	Kxxi	Log Po/w (iLOGP) 3.45 Log Po/w (XLOGP3) 4.88 Log Po/w (WLOGP) 5.46 Log Po/w (MLOGP) 3.90 Log Po/w (SILICOS-IT) 4.45 Consensus Log Po/w 4.43	388.85g/mol	2	3	Yes	No
22	Kxxii	Log Po/w (iLOGP) 3.56 Log Po/w (XLOGP3) 5.51 Log Po/w (WLOGP) 6.11 Log Po/w (MLOGP) 4.38 Log Po/w (SILICOS-IT) 5.08 Consensus Log Po/w 4.93	423.29g/mol	2	3	Yes; 1 violatio: MLOGP >4.15	No

Table No.3: The interacting AAR, bond length (Å), type of interaction with the enzyme to bind with it

S.No	Ligand	AAR	Type of interaction	Bond type	Bond length (Å)	S.No	Ligand	AAR	Type of interaction	Bond type	Bind length (Å)
1	A1	TYR215	No interaction	Nil	--	73	G1	TYR215	Hydrogen	H-Donor	4.2
		TYR214	No interaction	Nil	--			TYR214	Hydrophobic	pi-pi stacking	4.5
		ARG633	H-Donor	Hydrogen	5.7			ARG633	Hydrogen	H-Acceptor	4.4
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil	--			PRO66	Hydrogen	H-Acceptor	4.7
2	A2	-				74	G2	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.5
		ARG633	H-Donor	Hydrogen	5.7			ARG633	Hydrogen	H-Acceptor	4.4
		VAL62	H-Acceptor	Hydrogen	5.7			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.7
3	A3	-				75	G3	- TYR215	Hydrogen	H-Donor	4.1
		TYR215	No interaction	Nil							
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.8
		ARG633	H-Donor	Hydrogen	5.7			ARG633	Hydrogen	H-Acceptor	4.6
		VAL62	H-Acceptor	Hydrogen	5.6			VAL62	Hydrogen	H-Donor	5.2

		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.8
4	A4	TYR215	No interaction	Nil		76	G4	- TYR215	Hydrogen	H-Donor	4.1
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.4
		ARG633	H-Donor	Hydrogen	5.6			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.8
5	A5	- TYR215	No interaction	Nil		77	G5	- TYR215	Hydrogen	H-Donor	5.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.9
		ARG633	H-Donor	Hydrogen	5.8			ARG633	Hydrogen	H-Acceptor	4.4
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.0
6	A6	-				78	G6	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	5.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	5.0
		ARG633	H-Donor	Hydrogen	5.8			ARG633	Hydrogen	H-Acceptor	5.2
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.2
7	A7	-				79	G7	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	5.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.8
		ARG633	H-Donor	Hydrogen	5.8			ARG633	Hydrogen	H-Acceptor	5.2
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.2
8	A8	-				80	G8	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	5.2
		ARG633	H-Donor	Hydrogen	5.9			ARG633	Hydrogen	H-Acceptor	4.8
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.3
9	A9	-				81	G9	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	5.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	5.2
		ARG633	H-Donor	Hydrogen	5.8			ARG633	Hydrogen	H-Acceptor	5.8
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	5.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.3
10	A10	-				82	G10	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	5.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	5.2
		ARG633	H-Donor	Hydrogen	5.6			ARG633	Hydrogen	H-Acceptor	5.8
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	5.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.3
11	A11	-				83	G11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi	4.2

										stacking	
		ARG633	H-Donor	Hydrogen	5.6			ARG633	Hydrogen	H-Acceptor	4.3
		VAL62	H-Acceptor	Hydrogen	5.8			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.3
12	A12	-				84	G12	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	5.3
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	5.3
		ARG633	H-Donor	Hydrogen	5.6			ARG633	Hydrogen	H-Acceptor	5.3
		VAL62	H-Acceptor	Hydrogen	5.7			VAL62	Hydrogen	H-Donor	5.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	5.3
13	B1	-		Nil		85	H1	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	3.9
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	Hydrogen	6.2	Hydrogen			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	Hydrogen	6.2	Hydrogen			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.5
14	B2	-		Nil		86	H2	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.7
		ARG633	H-Donor	Hydrogen	6.8			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	H-Acceptor	Hydrogen	6.9			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.6
15	B3	-		Nil		87	H3	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	3.7
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.4
		ARG633	H-Donor	Hydrogen	6.9			ARG633	Hydrogen	H-Acceptor	3.5
		VAL62	H-Acceptor	Hydrogen	6.7			VAL62	Hydrogen	H-Donor	3.4
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.5
				Hydrogen							
16	B4	-	No interaction	Hydrogen		88	H4	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.3
		TYR214	H-Donor	Nil				TYR214	Hydrophobic	pi-pi stacking	3.4
		ARG633	H-Donor	Hydrogen	5.9			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	3.4
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Acceptor	3.5
				Nil							
17	B5	-		Nil		89	H5	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.5
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Hydrogen	6.4			ARG633	Hydrogen	H-Acceptor	3.6
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	3.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.7
				Nil							
18	B6	-				90	H6	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	3.9

		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Nil	6.7			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	H-Acceptor	Nil	6.7			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	3.5
19	B7	-		Nil		91	H7	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.7
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.8
		ARG633	H-Donor	Hydrogen	6.4			ARG633	Hydrogen	H-Acceptor	3.9
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.8
				Nil							
20	B8	-		Nil		92	H8	-			
		TYR215	No interaction	Hydrogen				TYR215	Hydrogen	H-Donor	3.3
		TYR214	No interaction	Hydrogen				TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Nil	6.5			ARG633	Hydrogen	H-Acceptor	3.3
		VAL62	H-Acceptor	Nil	6.3			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.6
21	B9	-				93	H9	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.3
		ARG633	H-Donor	Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	3.6
		VAL62	H-Acceptor	Hydrogen	6.5			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Acceptor	3.4
				Nil							
22	B10	-		Nil		94	H10	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.4
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	H-Acceptor	Hydrogen	6.0			VAL62	Hydrogen	H-Donor	3.4
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.4
				Nil							
23	B11	-		Nil		95	H11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.6
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.8
		ARG633	H-Donor	Hydrogen	6.0			ARG633	Hydrogen	H-Acceptor	3.7
		VAL62	H-Acceptor	Hydrogen	6.0			VAL62	Hydrogen	H-Donor	3.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.4
24	B12	-		Nil		96	H12	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	3.9
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.6
		ARG633	H-Donor	Hydrogen	6.1			ARG633	Hydrogen	H-Acceptor	3.6
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.5
25	C1	-				97	II	-			

		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	3.4
		VAL62	H-Acceptor	Hydrogen	6.3			VAL62	Hydrogen	H-Donor	3.5
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	3.5
26	C2	-		Nil		98	I2	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.5
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	4.6
		ARG633	H-Donor	Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	4.5
		VAL62	H-Acceptor	Hydrogen	6.3			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.5
				Nil							
27	C3	-		Hydrogen		99	I3	-			
		TYR215		Nil				TYR215	Hydrogen	H-Donor	4.2
		TYR214		Nil				TYR214	Hydrophobic	pi-pi stacking	4.3
		ARG633		Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62		Hydrogen	6.3			VAL62	Hydrogen	H-Donor	4.5
		PRO66						PRO66	Hydrogen	H-Acceptor	4.5
28	C4	-		Nil		100	I4	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.8
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	4.7
		ARG633	H-Donor	Hydrogen	6.4			ARG633	Hydrogen	H-Acceptor	4.6
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.5
29	C5	-				101	I5	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	4.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.6
		ARG633	H-Donor	Hydrogen	6.6			ARG633	Hydrogen	H-Acceptor	4.8
		VAL62	H-Acceptor	Hydrogen	6.6			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	4.7
30	C6	-		Nil		102	I6	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.7
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.6
		ARG633	H-Donor	Hydrogen	6.5			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Hydrogen	6.8			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.7
				Nil							
31	C7	-		Nil		103	I7	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	4.7
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	4.3
		ARG633	H-Donor	Hydrogen	6.6			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Hydrogen	6.5			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.6
32	C8	-				104	I8	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.7

		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.7
		ARG633	H-Donor	Nil				ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Hydrogen	6.7			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Hydrogen	6.7			PRO66	Hydrogen	H-Acceptor	4.7
				Nil							
33	C9	-		Nil		105	I9	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.6
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	4.4
		ARG633	H-Donor	Hydrogen	6.8			ARG633	Hydrogen	H-Acceptor	4.8
		VAL62	H-Acceptor	Hydrogen	6.8			VAL62	Hydrogen	H-Donor	4.7
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.6
34	C10	-				106	I10	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	4.4
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.8
		ARG633	H-Donor	Hydrogen	6.6			ARG633	Hydrogen	H-Acceptor	4.6
		VAL62	H-Acceptor	Hydrogen	6.6			VAL62	Hydrogen	H-Donor	4.9
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	4.6
35	C11	-		Nil		107	I11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.7
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.2
		ARG633	H-Donor	Hydrogen	6.0			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	4.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.7
36	C12	-		Nil		108	I12	-			
		TYR215	No interaction	Hydrogen				TYR215	Hydrogen	H-Donor	4.2
		TYR214	No interaction	Hydrogen				TYR214	Hydrophobic	pi-pi stacking	4.8
		ARG633	H-Donor	Nil	6.3			ARG633	Hydrogen	H-Acceptor	4.6
		VAL62	H-Acceptor	Nil	6.4			VAL62	Hydrogen	H-Donor	4.5
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.6
				Hydrogen							
37	D1	-		Hydrogen		109	J1	-	Hydrogen	H-Donor	4.4
		TYR215	No interaction	Nil				TYR215	Hydrophobic	pi-pi stacking	4.4
		TYR214	No interaction	Nil				TYR214	Hydrogen	H-Acceptor	4.4
		ARG633	H-Donor	Nil	6.3			ARG633	Hydrogen	H-Donor	4.4
		VAL62	H-Acceptor	Hydrogen	6.1			VAL62	Hydrogen	H-Acceptor	4.5
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Donor	4.5
				Nil							
38	D2	-		Nil		110	J2	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.3
		TYR214	No interaction	Hydrogen				TYR214	Hydrophobic	pi-pi stacking	4.5
		ARG633	H-Donor	Hydrogen	6.5			ARG633	Hydrogen	H-Acceptor	4.4
		VAL62	H-Acceptor	Nil	6.5			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.4
				Nil							
39	D3	-		Hydrogen		111	J3	-			

		TYR215	No interaction	Hydrogen				TYR215	Hydrogen	H-Donor	4.6
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.8
		ARG633	H-Donor	Nil	6.3			ARG633	Hydrogen	H-Acceptor	4.7
		VAL62	H-Acceptor	Nil	6.1			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	4.7
40	D4	-		Nil		112	J4	-			
		TYR215	No interaction	Nil				TYR215			
		TYR214	No interaction	Nil				TYR214			
		ARG633	H-Donor	Hydrogen	6.6			ARG633			
		VAL62	H-Acceptor	Hydrogen	6.3			VAL62			
		PRO66	No interaction	Nil				PRO66			
41	D5	-		Nil		113	J5	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	4.6
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	4.5
		ARG633	H-Donor	Hydrogen	6.2			ARG633	Hydrogen	H-Acceptor	4.5
		VAL62	H-Acceptor	Hydrogen	6.1			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.5
42	D6	-		Hydrogen		114	J6	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.2
		ARG633	H-Donor	Hydrogen	6.4			ARG633	Hydrogen	H-Acceptor	4.4
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	4.4
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	4.4
43	D7	-		Nil		115	J7	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.1
		TYR214	No interaction	Hydrogen	6.3			TYR214	Hydrophobic	pi-pi stacking	4.1
		ARG633	H-Donor	Hydrogen	6.2			ARG633	Hydrogen	H-Acceptor	4.2
		VAL62	H-Acceptor	Nil				VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.5
				Nil							
44	D8	-				116	J8	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	4.6
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.5
		ARG633	H-Donor	Hydrogen	6.3			ARG633	Hydrogen	H-Acceptor	4.5
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	4.5
45	D9	-		Nil		117	J9	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	4.1
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	4.1
		ARG633	H-Donor	Hydrogen	6.2			ARG633	Hydrogen	H-Acceptor	4.2
		VAL62	H-Acceptor	Hydrogen	5.9			VAL62	Hydrogen	H-Donor	4.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	4.5
46	D10	-		Nil		118	J10	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	3.4
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Hydrogen	5.9			ARG633	Hydrogen	H-Acceptor	3.7

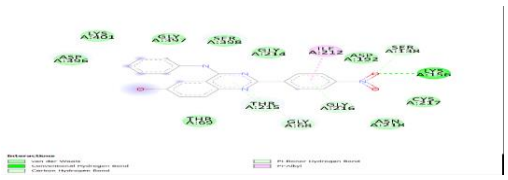
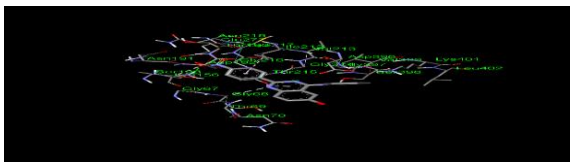
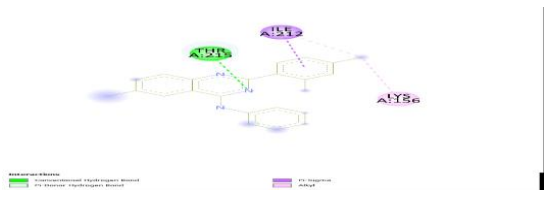
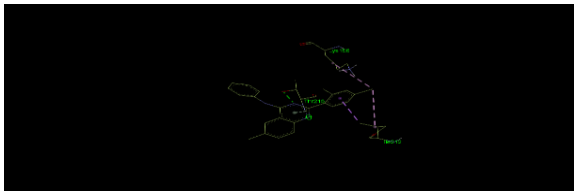
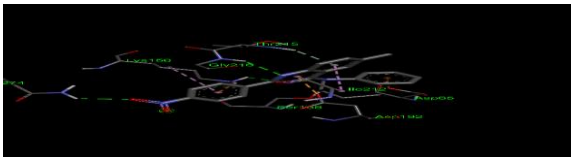
		VAL62	H-Acceptor	Hydrogen	6.1			VAL62	Hydrogen	H-Donor	3.4
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.4
47	D11	-				119	J11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.6
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	3.6
		ARG633	H-Donor	Hydrogen	5.9			ARG633	Hydrogen	H-Acceptor	3.6
		VAL62	H-Acceptor	Hydrogen	5.4			VAL62	Hydrogen	H-Donor	3.6
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Acceptor	3.6
48	D12	-		Nil		120	J12	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	3.9
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	3.5
		ARG633	H-Donor	Hydrogen	6.7			ARG633	Hydrogen	H-Acceptor	3.7
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	3.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	3.5
				Nil							
49	E1	-				121	K1	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	2.3
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.3
		ARG633	H-Donor	Hydrogen	6.2			ARG633	Hydrogen	H-Acceptor	2.3
		VAL62	H-Acceptor	Hydrogen	6.2			VAL62	Hydrogen	H-Donor	2.3
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Acceptor	2.6
50	E2	-	No interaction	Nil		122	K2	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.2
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.4
		ARG633	H-Donor	Hydrogen	6.5			ARG633	Hydrogen	H-Acceptor	2.3
		VAL62	H-Acceptor	Hydrogen	6.7			VAL62	Hydrogen	H-Donor	2.3
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.3
51	E3	-	H-Acceptor	Nil		123	K3	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Acceptor	Hydrogen	6.4			ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Donor	Hydrogen	6.1			VAL62	Hydrogen	H-Donor	2.6
		PRO66		Nil				PRO66	Hydrogen	H-Acceptor	2.5
52	E4	-	No interaction	Hydrogen		124	K4	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.2
		TYR214		Nil				TYR214	Hydrophobic	pi-pi stacking	2.3
		ARG633	H-Acceptor	Hydrogen	5.2			ARG633	Hydrogen	H-Acceptor	2.2
		VAL62	H-Donor	Hydrogen	5.1			VAL62	Hydrogen	H-Donor	2.2
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	2.4
53	E5	-	H-Acceptor	Nil		125	K5	-			
		TYR215	No interaction	Hydrogen				TYR215	Hydrogen	H-Donor	2.1
		TYR214		Hydrogen				TYR214	Hydrophobic	pi-pi stacking	2.2
		ARG633	H-Acceptor	Nil	5.3			ARG633	Hydrogen	H-Acceptor	2.5
		VAL62	H-Donor	Nil	5.5			VAL62	Hydrogen	H-Donor	2.2
		PRO66		Nil				PRO66	Hydrogen	H-Acceptor	2.2
54		-	No interaction	Hydrogen		126		-			

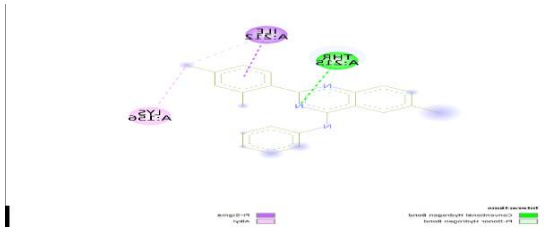
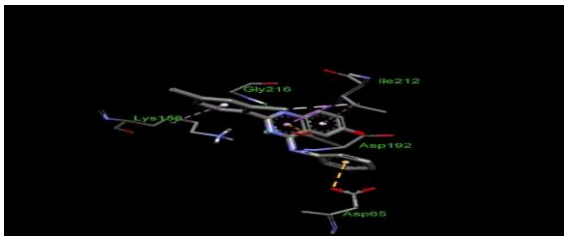
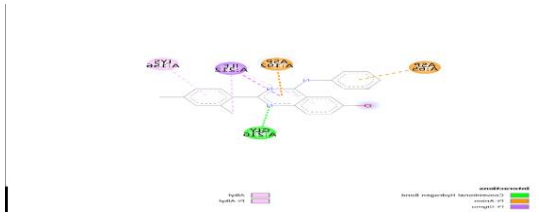
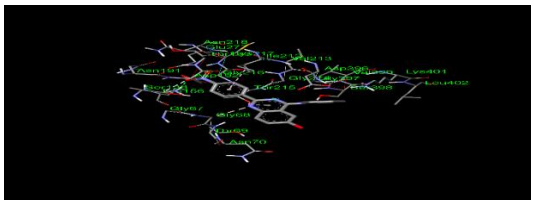
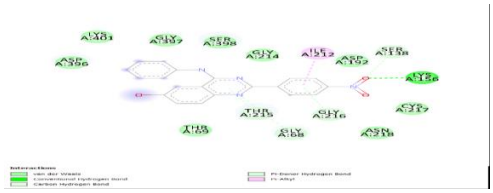
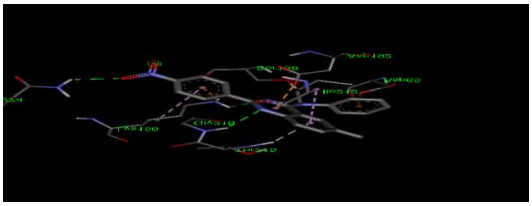
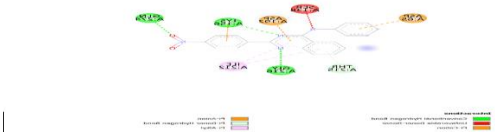
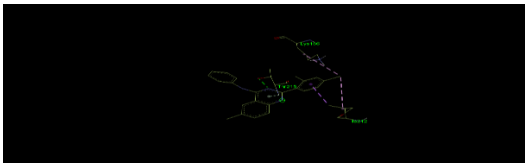
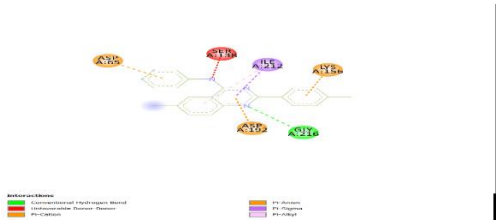
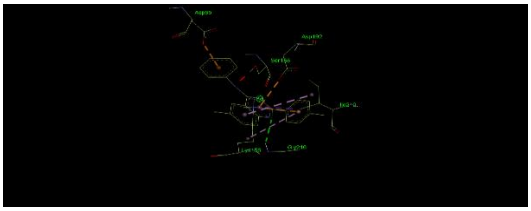
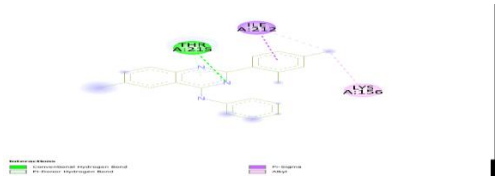
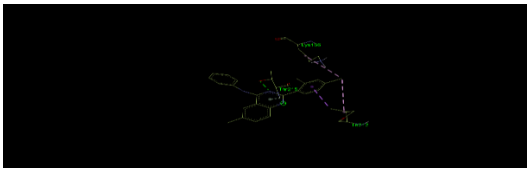
	E6	TYR215	No interaction	Nil			K6	TYR215	Hydrogen	H-Donor	2.0
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.0
		ARG633	H-Acceptor	Hydrogen	5.3			ARG633	Hydrogen	H-Acceptor	2.0
		VAL62	H-Donor	Hydrogen	5.3			VAL62	Hydrogen	H-Donor	2.0
		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	2.1
55	E7	-	H-Donor	Nil		127	K7	-			
		TYR215	H-Acceptor	Nil				TYR215	Hydrogen	H-Donor	2.0
		TYR214	No interaction		5.4			TYR214	Hydrophobic	pi-pi stacking	2.4
		ARG633	H-Donor	Hydrogen	5.5			ARG633	Hydrogen	H-Acceptor	2.0
		VAL62	H-Acceptor	Hydrogen				VAL62	Hydrogen	H-Donor	2.1
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.0
56	E8	-				128	K8	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	2.3
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Donor	Hydrogen	5.4			ARG633	Hydrogen	H-Acceptor	2.3
		VAL62	H-Acceptor	Hydrogen	5.4			VAL62	Hydrogen	H-Donor	2.2
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.1
57	E9	-	No interaction	Nil		129	K9	-			
		TYR215		Nil				TYR215	Hydrogen	H-Donor	2.0
		TYR214		Nil				TYR214	Hydrophobic	pi-pi stacking	2.6
		ARG633	H-Donor	Hydrogen	5.3			ARG633	Hydrogen	H-Acceptor	2.1
		VAL62	H-Acceptor	Hydrogen	5.4			VAL62	Hydrogen	H-Donor	2.1
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.4
58	E10	-	H-Acceptor	Nil		130	K10	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	2.2
		TYR214	No interaction					TYR214	Hydrophobic	pi-pi stacking	2.1
		ARG633	H-Acceptor	Hydrogen	5.1			ARG633	Hydrogen	H-Acceptor	2.3
		VAL62	H-Donor	Hydrogen	5.3			VAL62	Hydrogen	H-Donor	2.1
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.2
59	E11	-	No interaction			131	K11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.1
		TYR214	H-Donor	Nil				TYR214	Hydrophobic	pi-pi stacking	2.2
		ARG633	H-Acceptor	Hydrogen	5.1			ARG633	Hydrogen	H-Acceptor	2.2
		VAL62	No interaction	Hydrogen	5.3			VAL62	Hydrogen	H-Donor	2.2
		PRO66	No interaction	Hydrogen				PRO66	Hydrogen	H-Acceptor	2.2
			No interaction	Nil							
60	E12	-	H-Donor	Nil		132	K12	-			
		TYR215	H-Acceptor	Nil				TYR215	Hydrogen	H-Donor	2.3
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.4
		ARG633	No interaction	Hydrogen	6.8			ARG633	Hydrogen	H-Acceptor	2.3
		VAL62	No interaction	Hydrogen	6.8			VAL62	Hydrogen	H-Donor	2.3
		PRO66	H-Donor	Nil				PRO66	Hydrogen	H-Acceptor	2.3
61	F 1	-	No interaction			133	L1	-			
		TYR215	No interaction	Hydrogen				TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5

		ARG633	H-Donor	Nil	6.7			ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Acceptor	Nil	6.7			VAL62	Hydrogen	H-Donor	2.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.5
62	F 2	-		Nil		134	L 2	-			
		TYR215		Nil				TYR215	Hydrogen	H-Donor	3.0
		TYR214	No interaction	Hydrogen	6.7			TYR214	Hydrophobic	pi-pi stacking	2.9
		ARG633	H-Donor	Hydrogen	6.7			ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Acceptor	Nil				VAL62	Hydrogen	H-Donor	2.9
		PRO66	H-Donor	Nil				PRO66	Hydrogen	H-Acceptor	2.8
63	F 3	-	No interaction	Nil		135	L3	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.9
		ARG633	H-Donor	Hydrogen	6.8			ARG633	Hydrogen	H-Acceptor	2.9
		VAL62	H-Acceptor	Hydrogen	6.8			VAL62	Hydrogen	H-Donor	2.9
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.9
64	F 4	-	No interaction	Nil		136	L4	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.8
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Donor	Hydrogen	6.6			ARG633	Hydrogen	H-Acceptor	2.8
		VAL62	H-Acceptor	Hydrogen	6.4			VAL62	Hydrogen	H-Donor	2.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.5
			H-Donor	Nil							
65	F5	-	H-Acceptor	Nil		137	L5	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Acceptor	Hydrogen	6.6			ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Donor	Hydrogen	6.6			VAL62	Hydrogen	H-Donor	2.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.8
			No interaction	Hydrogen							
66	F6	-	No interaction	Hydrogen		138	L6	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.8
		ARG633	H-Acceptor	Hydrogen	7.3			ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Donor	Hydrogen	7.5			VAL62	Hydrogen	H-Donor	2.8
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.8
67	F7	-	H-Donor	Nil		139	L7	-			
		TYR215	H-Acceptor	Nil				TYR215	Hydrogen	H-Donor	2.8
		TYR214	No interaction	Hydrogen	6.9			TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	No interaction	Hydrogen	7.1			ARG633	Hydrogen	H-Acceptor	2.8
		VAL62	No interaction	Nil				VAL62	Hydrogen	H-Donor	2.6
		PRO66	H-Donor	Nil				PRO66	Hydrogen	H-Acceptor	2.8
68	F8	-	No interaction			140	L8	-			
		TYR215	No interaction					TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Donor	Nil	6.3			ARG633	Hydrogen	H-Acceptor	2.8
		VAL62	H-Acceptor	Nil	6.5			VAL62	Hydrogen	H-Donor	2.6

		PRO66	No interaction					PRO66	Hydrogen	H-Acceptor	2.5
69	F9	-	No interaction	Nil		141	L9	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.6
		TYR214	No interaction	Nil				TYR214	Hydrophobic	pi-pi stacking	2.6
		ARG633	H-Donor	Hydrogen	6.9			ARG633	Hydrogen	H-Acceptor	2.6
		VAL62	H-Acceptor	Hydrogen	6.8			VAL62	Hydrogen	H-Donor	2.6
		PRO66	No interaction	Nil				PRO66	Hydrogen	H-Acceptor	2.6
70	F 10	-				142	L10	-			
		TYR215	No interaction	Hydrogen	6.4			TYR215	Hydrogen	H-Donor	2.9
		TYR214	No interaction	Hydrogen	6.4			TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	No interaction	Nil				ARG633	Hydrogen	H-Acceptor	2.7
		VAL62	H-Donor	Nil	6.9			VAL62	Hydrogen	H-Donor	2.6
		PRO66	H-Acceptor	Nil	6.8			PRO66	Hydrogen	H-Acceptor	2.5
71	F11	-	No interaction			143	L11	-			
		TYR215	No interaction	Nil				TYR215	Hydrogen	H-Donor	2.9
		TYR214	H-Donor	Nil				TYR214	Hydrophobic	pi-pi stacking	2.5
		ARG633	H-Acceptor	Nil				ARG633	Hydrogen	H-Acceptor	2.4
		VAL62	No interaction	Hydrogen	6.7			VAL62	Hydrogen	H-Donor	2.5
		PRO66	No interaction	Hydrogen	6.8			PRO66	Hydrogen	H-Acceptor	2.5
			No interaction	Nil							
72	F12	-	H-Donor	Nil		144	L12	-			
		TYR215	H-Acceptor	Nil				TYR215	Hydrogen	H-Donor	2.7
		TYR214	No interaction	Hydrogen				TYR214	Hydrophobic	pi-pi stacking	2.8
		ARG633	No interaction	Hydrogen	6.9			ARG633	Hydrogen	H-Acceptor	2.8
		VAL62	No interaction	Nil	6.9			VAL62	Hydrogen	H-Donor	2.7
		PRO66	H-Donor	Nil				PRO66	Hydrogen	H-Acceptor	2.6

Table No.4: 2D and 3D poses of docked ligands that shows good results of docking and ADME

Compound Code	2D Structure	3D Structure
Ki		
Kiii		
Kiv		

Kvi		
Kix		
Kxii		
Kxiv		
Kxviii		
Kxix		

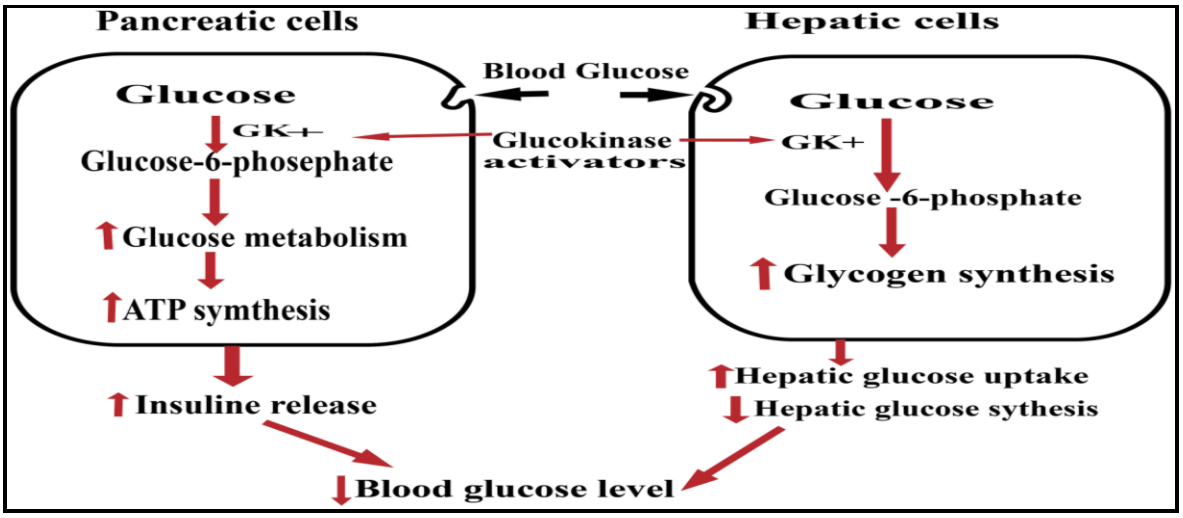


Figure No.1: The role of Glucokinase activators

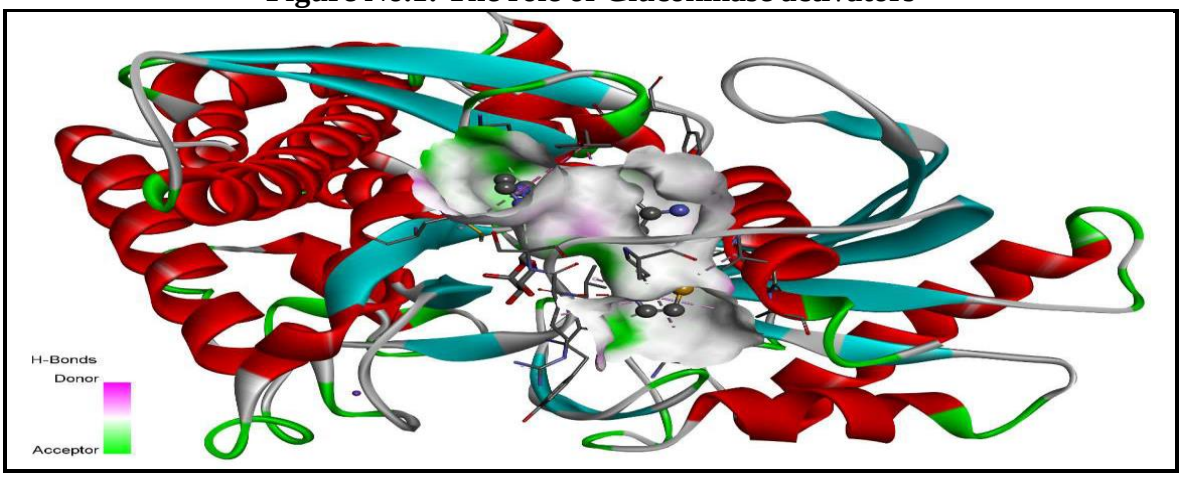


Figure No.2: Dock pose of GK bound to one of the designed molecules in its allosteric cavity

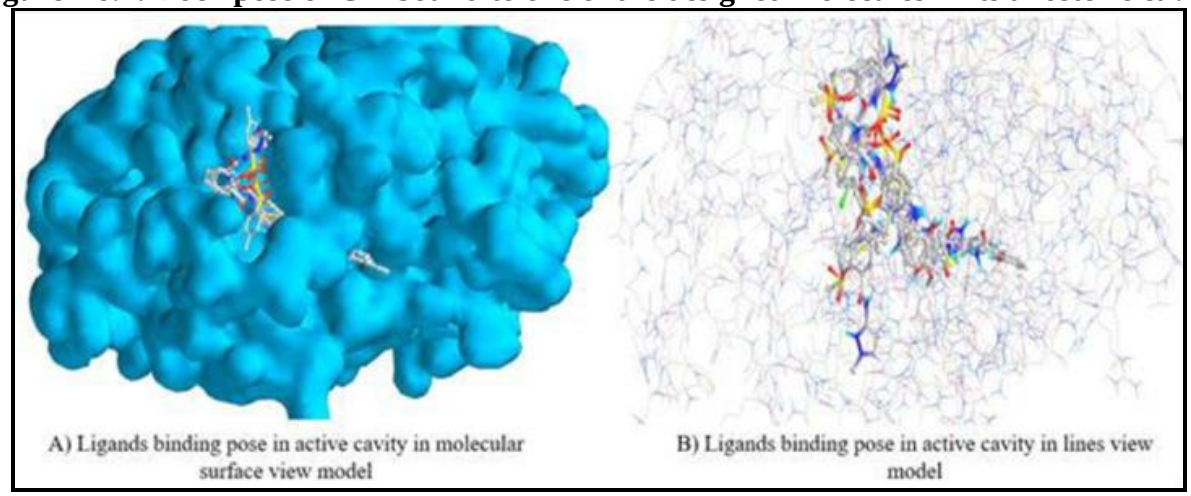


Figure No.3: Combined view of all ligands actively docked in the allosteric site of the GK enzyme

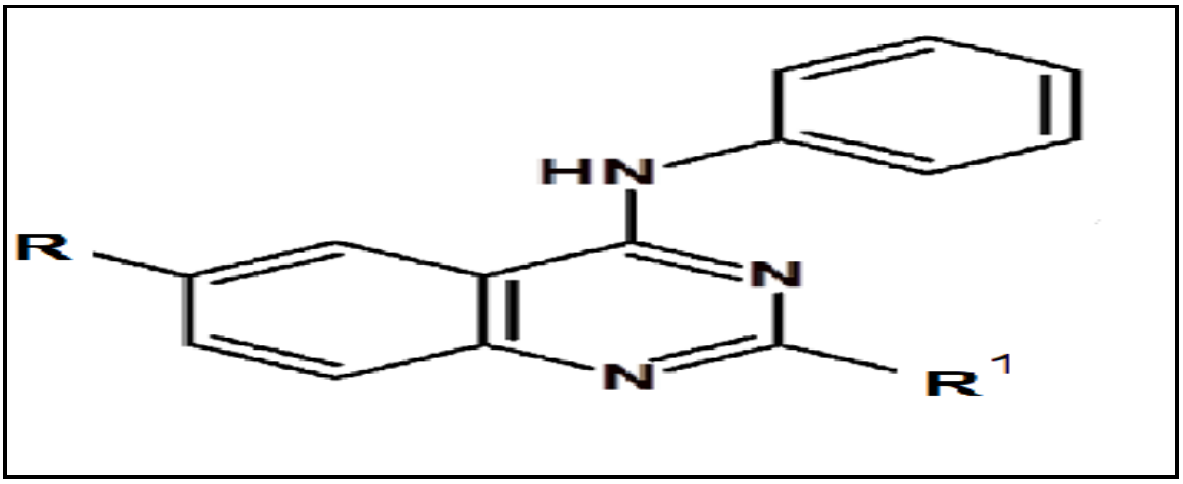


Figure No.4: Probable Pharmacophore

CONCLUSION

Taking into consideration the literature citations as Indole nucleus as a pharmacophore, substitutions shall form proton donor-acceptor action with the peptide linkage of VAL62-ARG63 to bind in the LBD to activate the enzyme Pocket 1. Substitutions on 1 position shall interact with Pro66 and Tyr215: Pocket 2 and substitutions on 5-position shall interact with Met210, Met235, Tyr 214: Pocket 3. The ligands that showed the foresaid bindings will be suitable to be synthesized and successful in binding with GK. The results strongly support the presence of hydroxyl group at the fifth position of the heterocyclic nucleus, as opposed to presence of other functional groups (-NH2, -CH3, -NHCO3), tried at the same position. The presence of 4-aminophenyl motif on second position of the heterocycle is well tolerated.

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AUTHOR CONTRIBUTIONS

Hamdani Kulsum reviewed the literature and prepared the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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