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Structure-Based Drug Design and Development for Potential Anti-Diabetic Activity



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ABSTRACT

Alanine aminotransferase (ALT) and Aspartate transaminase (AST) are the enzymes that are increased, benzopyrimidine derivatives are widely used to decrease their activity and are used in the treatment of Diabetes Mellitus. 68 different ligands were used for the docking study. Alanine aminotransferase was obtained from Protein Data Bank 1xi9. Docking analysis was performed using AutoDock Vina. The interaction between the ligands and the protein was analyzed and its affinity was observed. The results obtained exhibited that benzopyrimidine derivatives containing methyl, ketone, and heterocyclic rings had a greater affinity.

INTRODUCTION

DIABETES MELLITUS (DM)

Diabetes Mellitus is the inadequate control of blood glucose levels. The name of the disease ‘Diabetes Mellitus’ is taken from the Greek word ‘*diabetes*’, meaning siphon i.e. to pass through and the Latin word ‘*Mellitus*’ meaning sweet.

The human body has the pancreas, the organ which is responsible for regulating blood sugar levels with the help of its endocrine part. This organ has cells called Islets of Langerhans which have two main endocrine cells (a) Insulin which is responsible for producing beta cells and (b) Glucagon which is in charge of secreting alpha cells. Based on the glucose environment in the human body, both, beta and alpha cells are continuously balancing their levels of hormone secretions, without which the glucose levels are badly influenced.

What happens in Diabetes Mellitus?

Insulin is either completely absent which means it’s not produced by the human body and/or there is insulin resistance i.e. the function of insulin is impaired, which leads to hyperglycemia (increased levels of blood glucose).

In Type I Diabetes Mellitus, there is the destruction of beta cells hence insulin is extremely low or absent whereas in Type II of Diabetes Mellitus the functions of insulin or insulin sensitivity are greatly impaired which is due to aging or obesity.

BENZOPYRIMIDINES

Quinazoline is a fused six-member aromatic ring i.e. a benzene ring joined with a pyrimidine ring. Quinazoline is 1,3-diazanaphthalene. It is also called 5,6-benzopyrimidine or benzo[*a*]pyrimidine. It is a fused bicyclic compound that was earlier known as benzo-1,3-diazine. It is reported for its diversified biological activities and when substituted with different groups it brings together knowledge of how the molecule might interact with the target receptors and affords to have a promising biological potential. It is a large class of biologically active compounds that exhibit a broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, etc.

Based on the substitution patterns of the ring, quinazolinones are classified into five categories. There are 2-substituted-4(3H)-quinazolinones, 3-substituted-4(3H)-quinazolinones, 4-substituted-quinazolines, 2,3-disubstituted-4(3H)-quinazolinones and 2,4-disubstituted-4(3H)-quinazolinones. Also, depending upon the position of the keto or oxo groups, they can be classified into three types. They are 2(1H)quinazolinones, 4(3H)quinazolinones, and 2,4(1H,3H)quinazolinone, out of which 4(3H)-quinazolinones are most commonly used as intermediates or as naturals products in many biosynthetic pathways.

MATERIALS AND METHODS

DOCKING

Molecular docking research focuses on computationally simulating the molecular recognition process. It aims to achieve an optimized confirmation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces. The second approach simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated. The methods are fast enough to allow virtual screening of ligand libraries containing tens of thousands of compounds. Docking experiments are useful for exploring the function of the target, and virtual screening, where a large library of compounds is docked and ranked, may be used to identify new inhibitors for drug development.

DIFFERENT DOCKING SOFTWARE

1. AUTODOCK
2. AUTODOCK VINA
3. RACOON2

1. AUTODOCK

AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates bind to a receptor of known 3D structures. Current distributions of AutoDock consist of two generations of software. AutoDock 4 and AutoDock Vina. AutoDock-4 consists of two main programs. AutoDock performs the

docking of the ligand to a set of grids describing the target protein. Auto grid pre-calculates these grids. In addition to using them for docking, the atomic affinity grids can be visualized. This can help, for example, to guide organic synthetic chemists design better binders. AutoDock is available for systems that require additional methodological enhancements.

2. AUTODOCK VINA-

AutoDock Vina was compiled and run under Windows 10 Operating System. All figures with representations were produced using Discovery Studio Visualizer. AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structures. For docking, all water molecules were removed and polar hydrogen atoms were added to the refined model using AutoDock Tools (ADT). The prepared protein was saved in PDBQT format. The ligands were downloaded from ChemSketch Database and converted to PDB file format by using OpenBabel software. In Auto Dock Vina that pdbqt files for protein and ligands preparation and grid box creation were completed using Graphical User Interface program Auto Dock Tool. ADT assigned polar hydrogens, united atom Kollman charges, solvation parameters, and fragmental volumes to the protein. AutoDock saved the prepared file in PDBQT format. AutoGrid was used for the preparation of the grid map using a grid box. AutoDock Vina is a new generation of docking software from the Molecular Graphics Lab. It achieves significant improvements in the average accuracy of the binding mode predictions.

The AutoDock Vina scoring function is highly approximate, with spherically symmetric hydrogen bond potentials, implicit hydrogens, and no electrostatic contribution. It has been demonstrated to perform well with ligands with typical biological size and composition. The AutoDock force field includes physically based contributions, including a directional hydrogen-bonding term with explicit polar hydrogens, and electrostatics. It is highly optimized to perform docking experiments using well-tested default methods. AutoDock Vina is fast and effective for most systems.

3.RACOON2

Virtual screening is rapidly becoming the primary application of computational docking methods, with many successes in the discovery of new lead compounds for pharmaceutical development. The idea is to screen a large library of available ligands to identify a small

subset for purchase and experimental testing. Raccoon is a graphical user interface designed to streamline the steps of performing a virtual screening and analyzing the results.

AIM AND OBJECTIVES

AIM: To do research-based drug design and development for potential anti-diabetic activity.

OBJECTIVES:

1. To check the anti-diabetic activity of synthetic compounds against Diabetes Mellitus. Based on Drug Design and Development using various software such as Auto Dock Vina, Discovery Studio Visualizer, ChemSketch, OpenBabel. In online mode, we have used Benzopyrimidines as a novel synthetic compound. Benzopyrimidines are investigated as antidiabetic in general. Molecular docking techniques aim to identify the best position for a substrate molecule to bind to a receptor molecule and predict the best matching binding mode of a ligand to a protein.

2. The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so, how strongly. We have designed the benzopyrimidines to predict the potential anti-diabetic activity against Diabetes Mellitus.

METHOD:-

Molecular docking is the study of how two or more molecular structures (e.g. drug and enzyme or protein) fit together. In a simple definition, docking is a molecular modeling technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands).

For docking purposes first, we drew structures by taking benzopyrimidine base as the main moiety, we added substituents this work was done on ChemSketch software. All the compounds were separately saved as a MOL file.

1) CHEMSKETCH:

ChemSketch is a molecular modeling program used to create and modify images of chemical structures. ChemSketch Freeware is a drawing package that allows you to draw chemical structures including organics, organometallics, polymer structures. With this program, it is

possible to write and perform chemical equations, diagrams laboratories, and chemical structures of various entities. Figure 1 shows ChemSketch software.

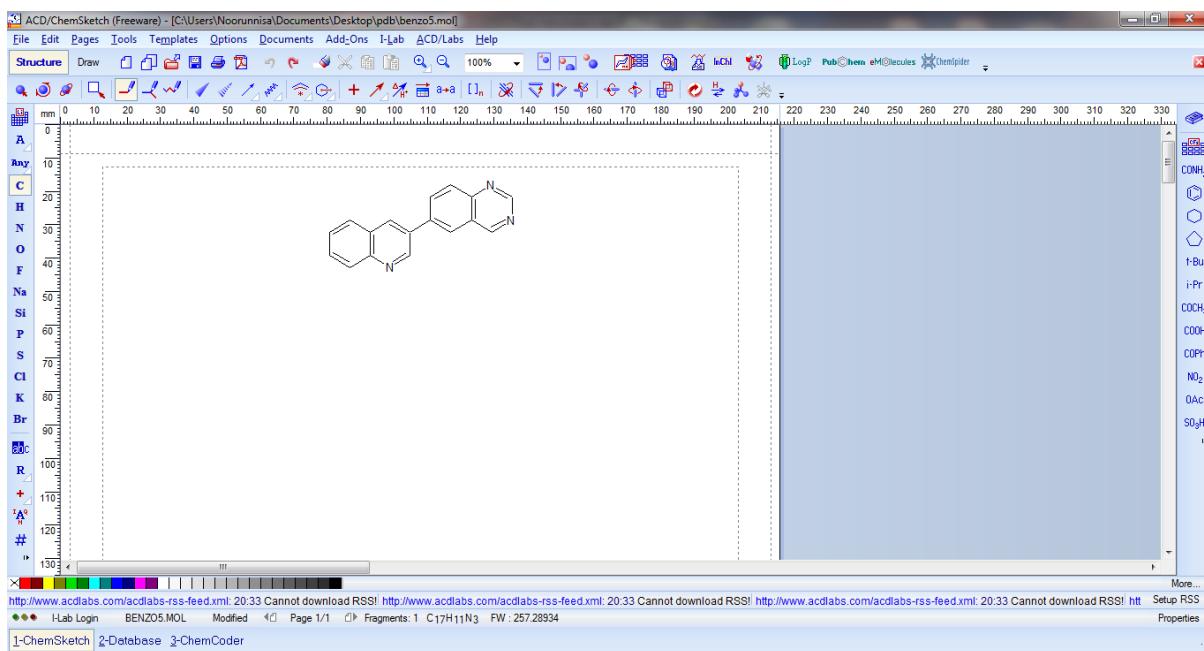


Figure 1 :- ChemSketch

After drawing the structures, the MOL files were converter to PDB format with the help of OpenBabel for further docking.

2) OPEN BABEL:

OpenBabel, an open-source chemical toolbox that speaks the many languages of chemical data. Open Babel version 2.3 interconverts over 110 formats. OpenBabel supports 111 chemical file formats in total. It can read 82 formats and write 85 formats. These encompass common formats used in Cheminformatics (SMILES, InChI, MOL, MOL2), input and output files from a variety of computational chemistry. OpenBabel identifies all linear and ring substructures in the molecule of lengths 1 to 7 (excluding the 1-atom sub structures C and N) and maps them onto a bit-string. Figure 2 shows OpenBabel software.

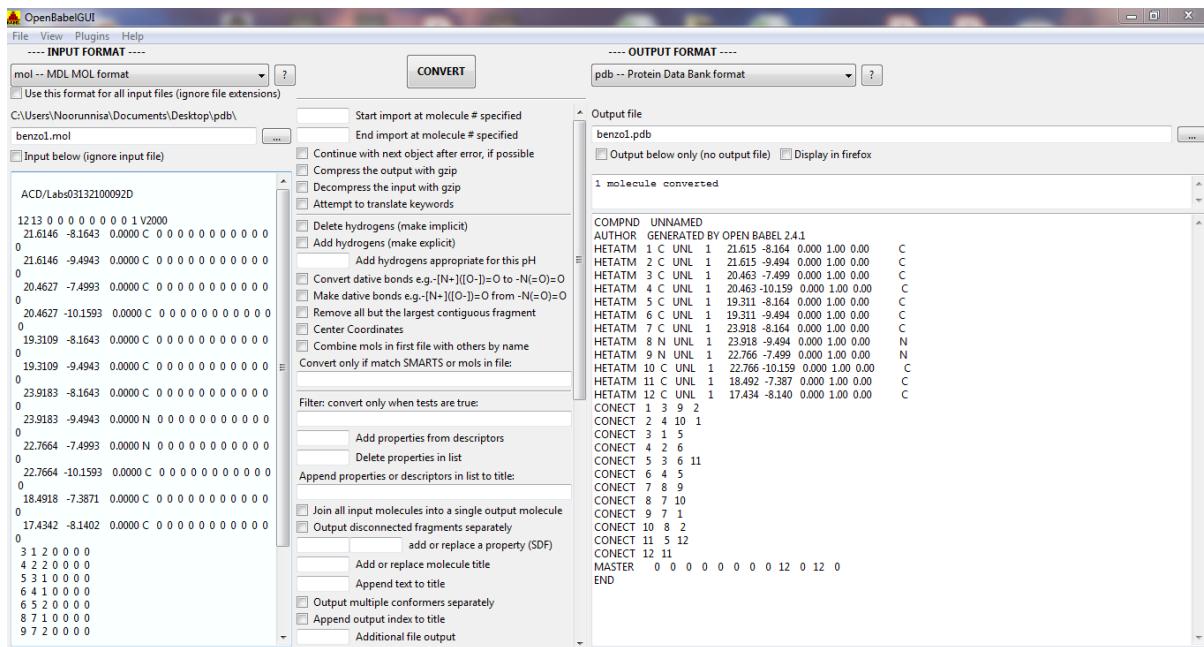


Figure 2 :- OpenBabel conversion of .mol to .pdb

After the conversion, we had to take a look at the properties of the compound (i.e. physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness). The compounds that are selected are following “**Lipinski’s rule of five**” which states that an orally active drug has no more than one violation.

3) SWISSADME (online tool):

SwissADME is a web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness. “Lipinski’s rule of five” is used to evaluate the drug-likeness of a chemical compound. It states that an orally active drug has no more than one violation of the following criteria:

- a) less than 5 hydrogen-bond donors,
- b) less than 10 hydrogen-bond acceptors,
- c) a molecular mass less than 500 Da, and
- d) log *P* not greater than 5.

All ligands of the present study met the requirements of “Lipinski’s rule of five”. Figure 3 shows the result obtained by Swiss ADME.

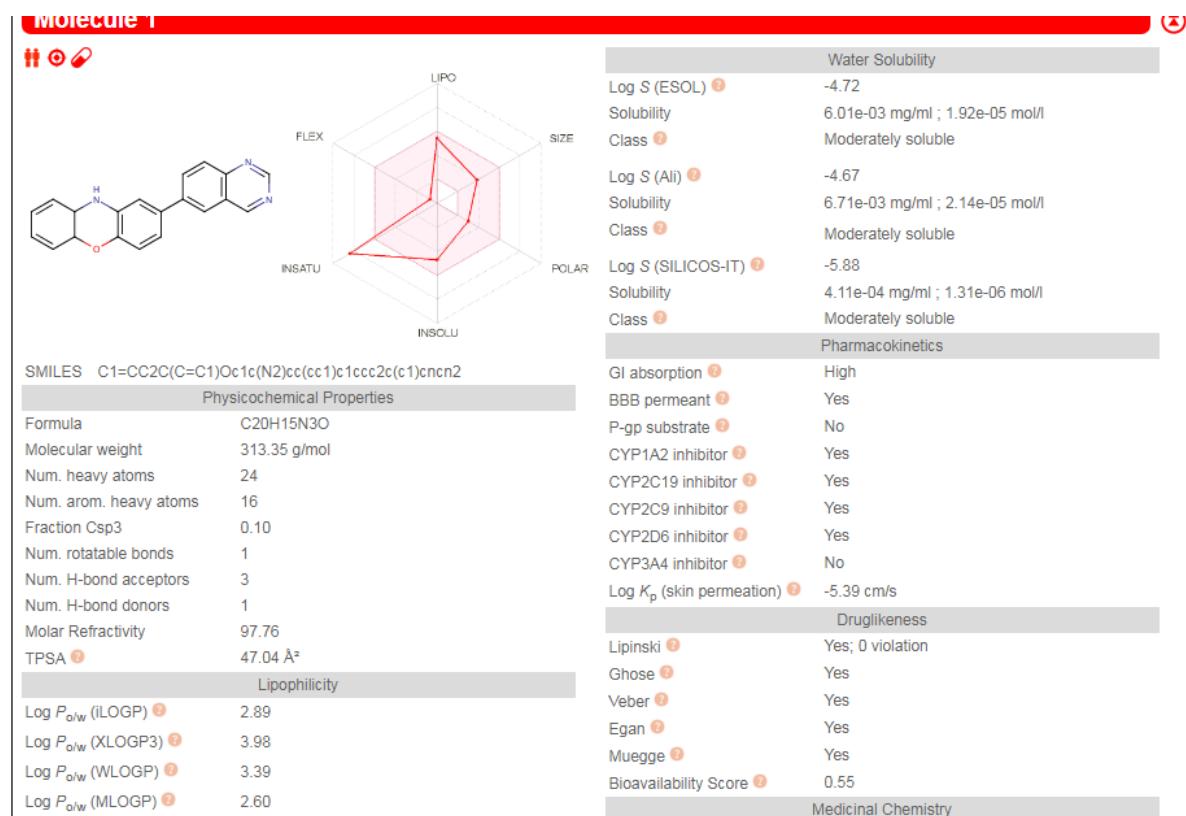


Figure 3:- Result obtained by SwissADME

After the clearance of compounds from SwissADME, we downloaded the proteins, Name for the protein as given in Table Number 1. the proteins were downloaded from the following site: <https://www.rcsb.org/> Figure 4 & Figure 5 shows protein structures obtained from Protein Data Bank.

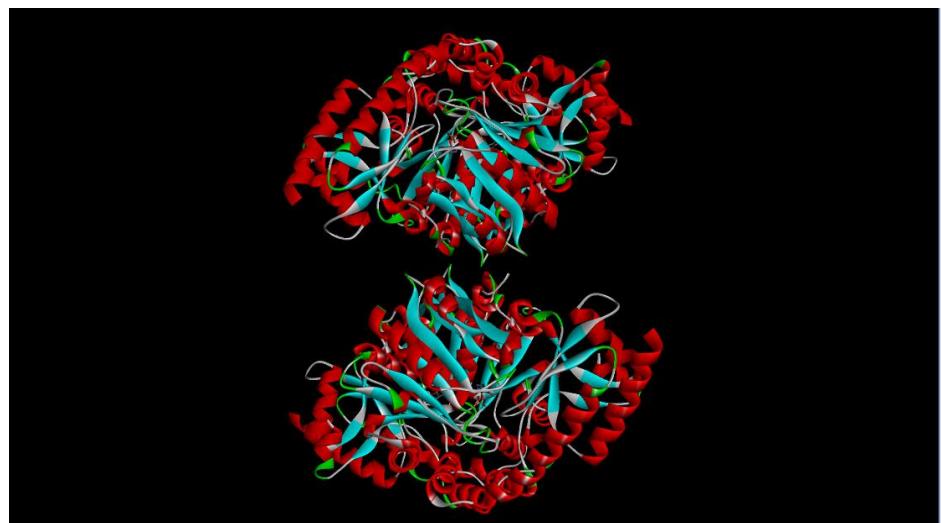


Figure 4:- 1xi9

4) DISCOVERY STUDIO VISUALIZER:

Discovery Studio is a suite of software used for preparing protein for docking, viewing Interactions of ligand and Protein, simulating small molecule and macromolecule design, and validation by Dassault System BIOVIA.

5) AUTODOCK TOOLS:

Molecular modeling is a very much investigated technique for recognizing the potent compound without putting excessive exertion and investment in research. AutoDock Tool (ADT) 1.5.6 software is used by us to investigate the activity in terms of binding affinity (Kcal/mol), and thereafter the outcomes are compared in binding affinity score for best-docked conformation. The outcomes of results were analyzed by AutoDock Vina result which reveals close contact, hydrogen bond, hydrophilic, and hydrophobic interactions. By using ADT one can easily find the affinity of their compound with protein. Figure 5 shows the ligand view in the AutoDock image. Figure 6 Docking result obtained by command prompt.

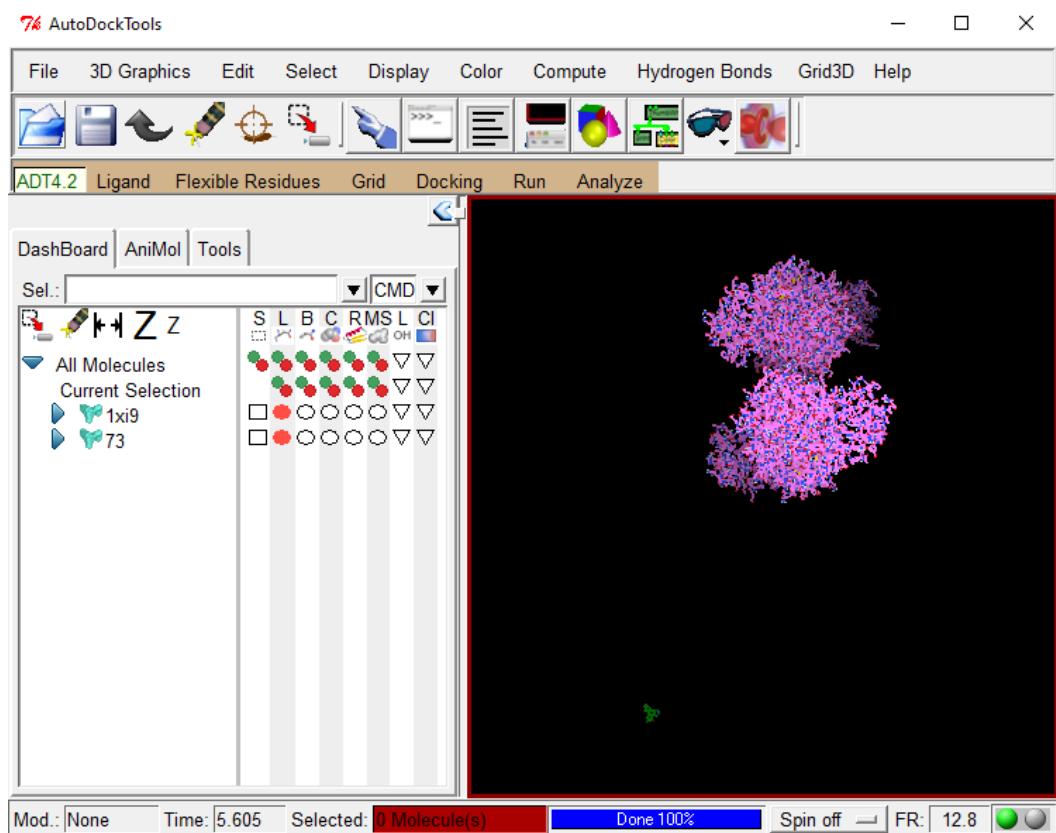


Figure 5:- Ligand view in Autodock

```
Command Prompt
# Please see http://vina.scripps.edu for more information.      #
#####
Detected 2 CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: 2074529296
Performing search ...
0% 10 20 30 40 50 60 70 80 90 100%
|----|----|----|----|----|----|----|----|----|
*****done.
Refining results ... done.

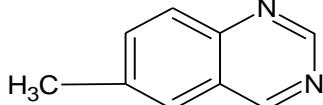
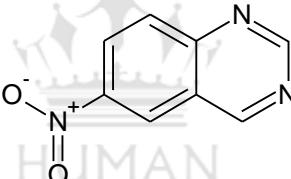
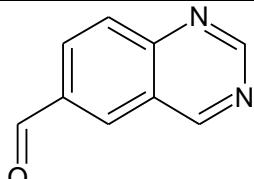
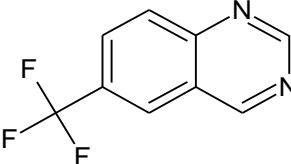
mode | affinity | dist from best mode
| (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+-----+-----+
 1     -8.4      0.000      0.000
 2     -8.3      3.721      5.871
 3     -8.1     12.864     14.863
 4     -7.9     11.754     13.588
 5     -7.8      8.134      9.427
 6     -7.8     10.132     12.291
 7     -7.8      6.580      8.956
 8     -7.8      4.564      8.143
 9     -7.7      7.729      9.952
Writing output ... done.
```

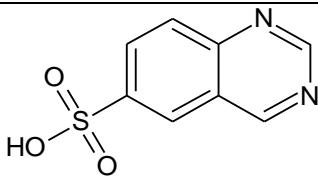
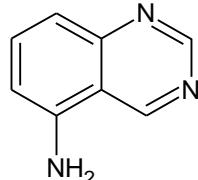
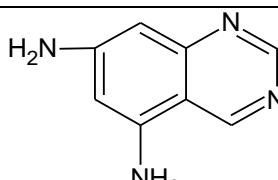
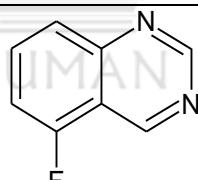
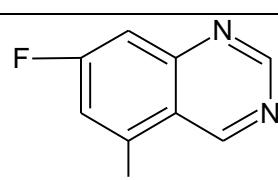
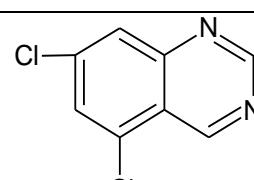
Figure 6:- Docking result obtained from Command Prompt

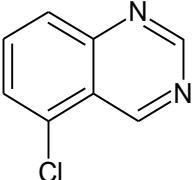
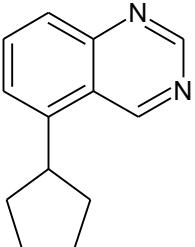
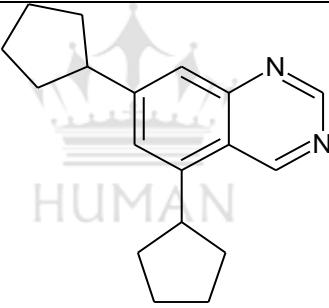
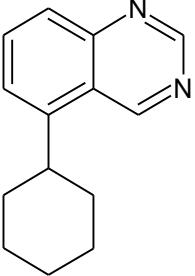
RESULTS AND DISCUSSION

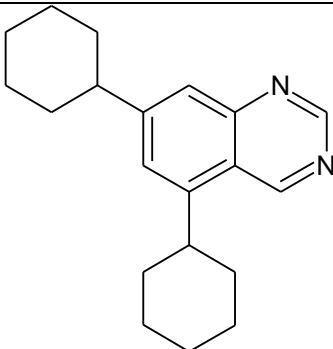
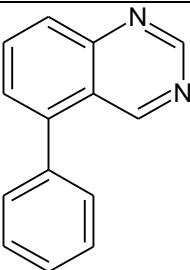
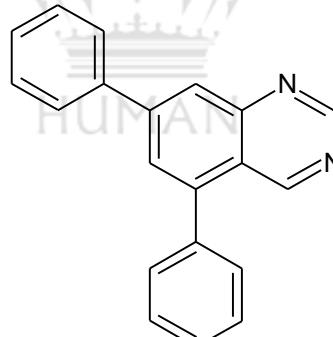
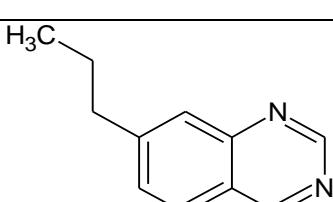
Designed the Novel Synthetic Compounds that are Benzopyrimidines from the Quinazoline class of compounds based on - Research-Based Drug Design and Development to find out the anti-diabetic activity against Diabetes Mellitus. For the design of novel molecules, various structural changes were made on the novel compounds that were interacted against alanine aminotransferase proteins. Table Number 01 shows the compounds docked and docking score concerning proteins.

Table Number 01:- Docking scores of ligands concerning proteins

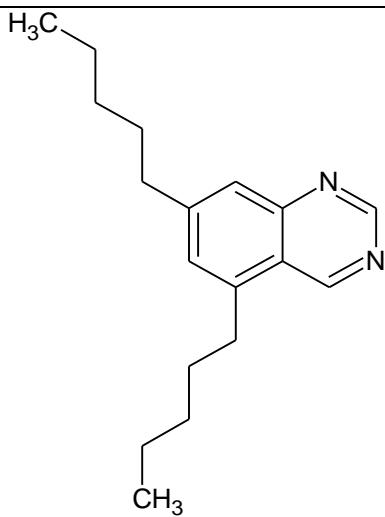
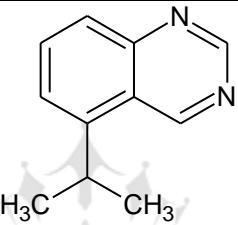
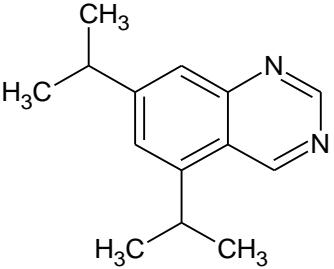
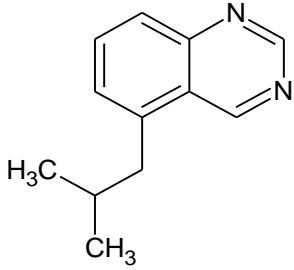
Sr No		Structure	Affinity
1	1		-5.3
	IUPAC	6-methylquinazoline	
2	2		-5.7
	IUPAC	6-nitroquinazoline	
3	3		-5.4
	IUPAC	quinazoline-6-carbaldehyde	
4	4		-6.3
	IUPAC	6-(trifluoromethyl)quinazoline	

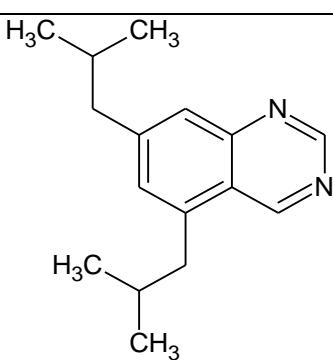
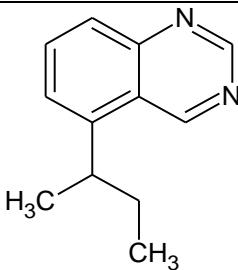
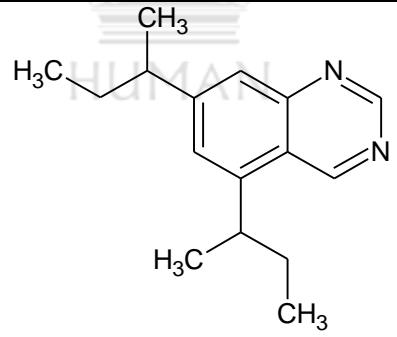
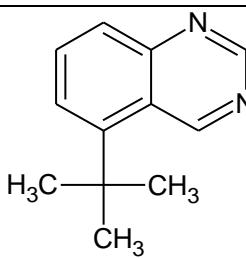
5	5		-6.0
	IUPAC	quinazoline-6-sulfonic acid	
6	6		-5.2
	IUPAC	quinazolin-5-amine	
7	7		-5.3
	IUPAC	quinazoline-5,7-diamine	
8	8		-5.4
	IUPAC	5-fluoroquinazoline	
9	9		-5.6
	IUPAC	5,7-difluoroquinazoline	
10	10		-5.6

	IUPAC	5,7-dichloroquinazoline	
11	11		-5.4
	IUPAC	5-chloroquinazoline	
12	22		-6.5
		5-cyclopentylquinazoline	
13	23		-7.7
		5,7-dicyclopentylquinazoline	
14	24		-6.9
		5-cyclohexylquinazoline	

15	25		-8.5
	IUPAC	5,7-dicyclohexylquinazoline	
16	26		-6.9
	IUPAC	5-phenylquinazoline	
17	27		-8.5
	IUPAC	5,7-diphenylquinazoline	
18	28		-5.9
	IUPAC	7-propylquinazoline	

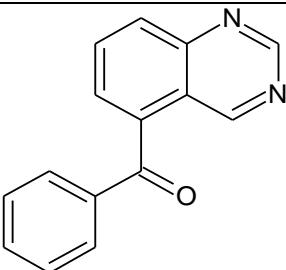
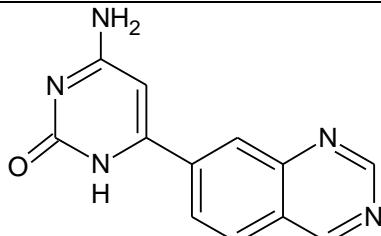
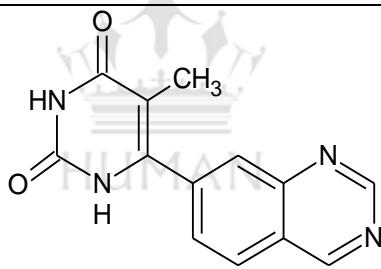
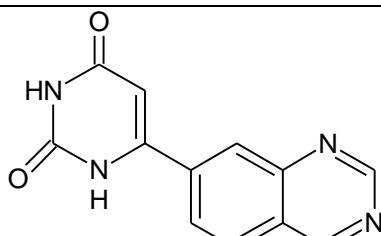
19	29	<p>5,7-dipropylquinazoline</p>	-6.3
	IUPAC		
20	30	<p>5-propylquinazoline</p>	-6.0
	IUPAC		
21	31	<p>5,7-dibutylquinazoline</p>	-6.9
	IUPAC		
22	32	<p>7-propylquinazoline</p>	-6.3
	IUPAC		

23	33		-7.0
	IUPAC	5,7-dipentylquinazoline	
24	34		-5.7
	IUPAC	5-(propan-2-yl)quinazoline	
25	35		-6.7
	IUPAC	5,7-di(propan-2-yl)quinazoline	
26	36		-6.1
	IUPAC	5-(2-methylpropyl)quinazoline	

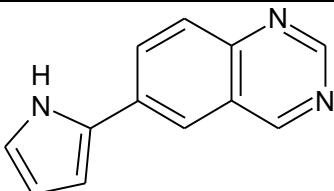
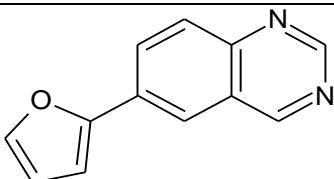
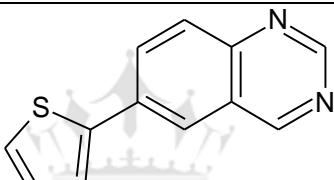
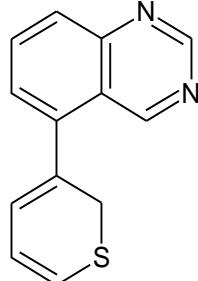
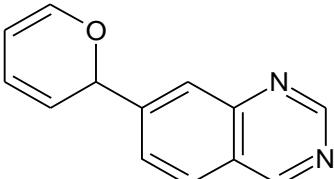
27	37	 <chem>C(C)CCc1cc2c(c1)ncnc2C(C)CC</chem>	-6.6
	IUPAC	5,7-bis(2-methylpropyl)quinazoline	
28	38	 <chem>C(C)CCc1cc2c(c1)ncnc2CC</chem>	-6.0
	IUPAC	5-(butan-2-yl)quinazoline	
29	39	 <chem>C(C)CCc1cc2c(c1)ncnc2CC(C)CC</chem>	-6.8
	IUPAC	5,7-di(butan-2-yl)quinazoline	
30	40	 <chem>C(C)(C)c1cc2c(c1)ncnc2C(C)(C)C</chem>	-6.5
	IUPAC	5- <i>tert</i> -butylquinazoline	

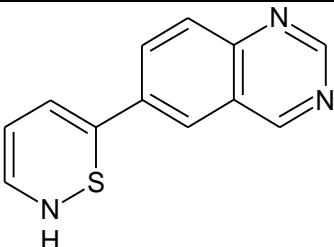
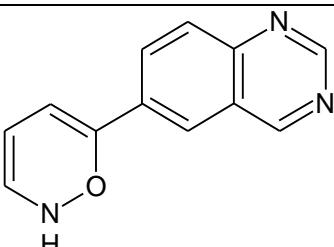
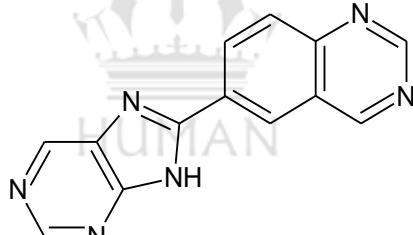
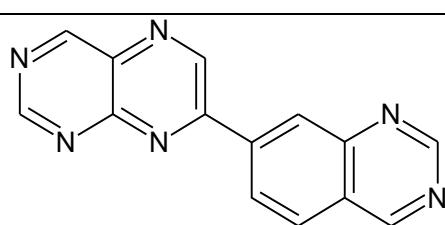
31	41	 5,7-di- <i>tert</i> -butylquinazoline	-7.9
	IUPAC		
32	42	 5-(3-methylbutyl)quinazoline	-6.4
	IUPAC		
33	43	 5,7-bis(3-methylbutyl)quinazoline	-7.3
	IUPAC		
34	44	 quinazoline-6-carboxylic acid	-5.6
	IUPAC		

35	45	 1-(quinazolin-5-yl)ethanone	-5.7
	IUPAC		
36	46	 1,1'-quinazoline-5,7-diyl diethanone	-6.3
	IUPAC		
37	47	 5-benzylquinazoline	-7.2
	IUPAC		
38	48	 5,7-dibenzylquinazoline	-8.7
	IUPAC		

39	49		-7.4
	IUPAC	phenyl(quinazolin-5-yl)methanone	
40	76		-7.6
	IUPAC	4-amino-6-(quinazolin-7-yl)pyrimidin-2(1 <i>H</i>)-one	
41	77		-8.1
	IUPAC	5-methyl-6-(quinazolin-7-yl)pyrimidin-2,4(1 <i>H</i> ,3 <i>H</i>)-dione	
42	78		-7.6
	IUPAC	6-(quinazolin-7-yl)pyrimidin-2,4(1 <i>H</i> ,3 <i>H</i>)-dione	

43	79	<p>Chemical structure: 2-(2-amino-4H-pyrazin-1(2H)-yl)-8-(quinazolin-6-yl)quinoxalin-6-amine</p>	-7.8
	IUPAC	8-(quinazolin-6-yl)-5,9-dihydro-4H-purin-6-amine	
44	80	<p>Chemical structure: 2-amino-8-(quinazolin-6-yl)-1,9-dihydro-6H-purin-6-one</p>	-8.0
	IUPAC	2-amino-8-(quinazolin-6-yl)-1,9-dihydro-6H-purin-6-one	
45	82	<p>Chemical structure: 6-(isoquinolin-3-yl)quinazoline</p>	-8.5
	IUPAC	6-(isoquinolin-3-yl)quinazoline	
46	1	<p>Chemical structure: 6-(quinolin-3-yl)quinazoline</p>	-8.3
	IUPAC	6-(quinolin-3-yl)quinazoline	
47	2	<p>Chemical structure: 6-(pyridin-3-yl)quinazoline</p>	-6.9

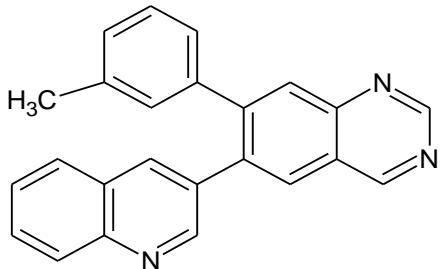
	IUPAC	6-(pyridin-2-yl)quinazoline	
48	3		-6.5
	IUPAC	6-(1 <i>H</i> -pyrrol-2-yl)quinazoline	
49	4		-6.5
	IUPAC	6-(furan-2-yl)quinazoline	
50	5		-6.5
	IUPAC	6-(thiophen-2-yl)quinazoline	
51	6		-6.7
	IUPAC	5-(2 <i>H</i> -thiopyran-3-yl)quinazoline - methane (1:1)	
52	7		-6.8

	IUPAC	7-(2 <i>H</i> -pyran-2-yl)quinazoline	
53	8		-6.8
	IUPAC	6-(2 <i>H</i> -1,2-thiazin-6-yl)quinazoline	
54	9		-7.1
	IUPAC	6-(2 <i>H</i> -1,2-oxazin-6-yl)quinazoline	
55	10		-7.5
	IUPAC	6-(9 <i>H</i> -purin-8-yl)quinazoline	
56	11		-8.0
	IUPAC	7-(quinazolin-7-yl)pteridine	

57	12		-10.0
	IUPAC	2-(quinazolin-6-yl)-10H-phenoxazine	
58	13		-10.3
	IUPAC	6-(4aH-xanthan-7-yl)quinazoline	
59	14		-7.8
	IUPAC	6-(1-benzofuran-2-yl)quinazoline	
60	15		-7.9
	IUPAC	6-(1H-indol-2-yl)quinazoline	

61	50	 quinazoline-5,7-diylbis(phenylmethanone)	-8.9
	IUPAC		
62	58	 phenyl quinazoline-5-carboxylate	-7.7
	IUPAC		
63	59	 diphenyl quinazoline-5,7-dicarboxylate	-9.2
	IUPAC		

64	68		-9.4
	IUPAC	7-[2,4-dimethyl-3-(propan-2-yl)pentan-3-yl]quinazoline	
65	69		-11.4
	IUPAC	7-tritylquinazoline	
66	72		-7.0
	IUPAC	2,2-dimethyl-1-(quinazolin-5-yl)propan-1-one	
67	73		-9.3
	IUPAC	1,1'-quinazoline-5,7-diylbis(2,2-dimethylpropan-1-one)	

68	16		-10.9
	IUPAC	7-(3-methylphenyl)-6-(quinolin-3-yl)quinazoline	

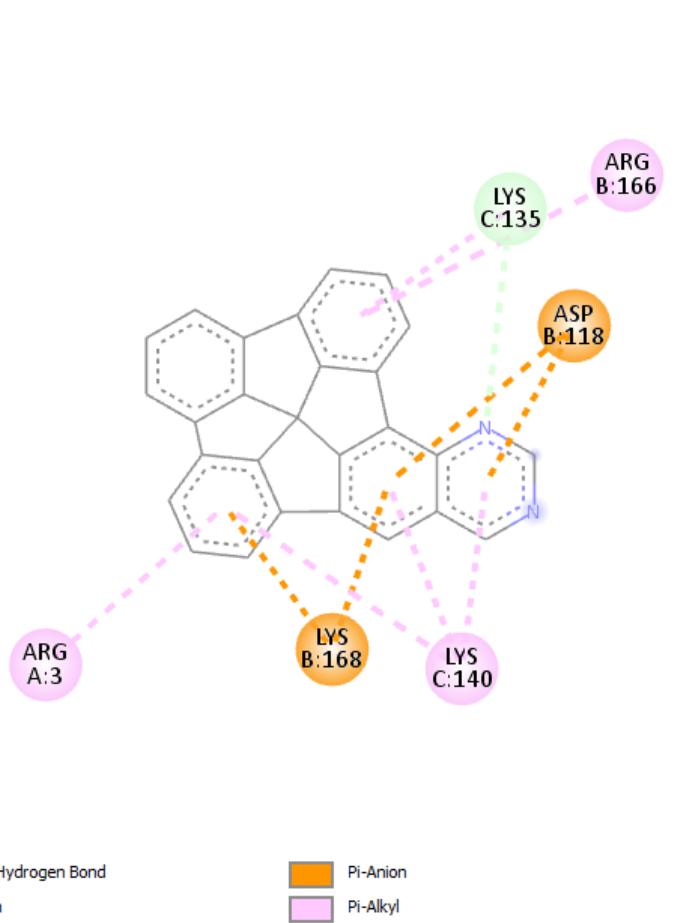


Figure 7:- Amino acid interactions of 69 with 1xi9

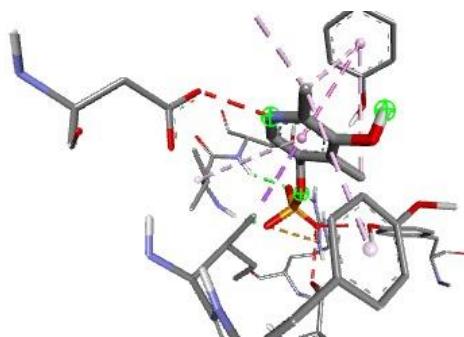


Figure 8:- Amino acid interactions of Benzopyrimidines with 1xi9

Table Number 02:- Amino acids interacted and some H-bonds formed with different classes of Benzopyrimidine derivatives

SR NO	PROTEIN NAME	FILENAME	NO. OF HYDROGEN BOND	AMINO ACID INTERACTED`
01	1xi9	F5	2H	C:ARG7:HH21 - :UNL1:N D: ARG7:HH21 -:UNL1:N : UNL1 - C: PRO116 : UNL1 - C: ARG7 : UNL1 - C: PRO116
02	1xi9	F6	1H	C:ARG7:HE - :UNL1:N :UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - C:PRO116
03	1xi9	F7	2H	C:GLY138:CA - :UNL1:N :UNL1:C - B:THR167:O :UNL1 - C:ARG7 :UNL1 - C:PRO116
04	1xi9	F8	1H	B:LYS168:HZ3 - :UNL1:O B:LYS168:NZ - :UNL1 A:ILE2:CA - :UNL1 :UNL1 - A:ARG3 :UNL1 - B:LYS168
05	1xi9	F9	1H	C:ARG7:HE - :UNL1:N

				:UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - C:PRO116
06	1xi9	F10	0H	:UNL1 - C:ARG7 :UNL1 - D:PRO116
07	1xi9	F11	1H	:UNL1:C - C:PHE136:O :UNL1 - C:PRO116 :UNL1 - C:ARG7
08	1xi9	F12	0H	
09	1xi9	F13	2H	:UNL1:C - B:ASP165:O :UNL1:C - A:ARG3:O B:LYS168:NZ - :UNL1 A:ILE2:CA - :UNL1 :UNL1 - A:ARG3 :UNL1 - B:LYS168
10	1xi9	F14	0H	B:LYS168:NZ - :UNL1 B:ASP118:OD2 - :UNL1 B:ASP118:OD2 - :UNL1 :UNL1 - C:LYS140 :UNL1 - C:LYS140
11	1xi9	F15	3H	C:ARG7:HE - :UNL1:N C:ARG7:HH21 - :UNL1:N A:ILE2:CA - :UNL1:N A:SER1:N - :UNL1 B:LYS168:HZ3 - :UNL1 :UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - C:PRO116 :UNL1 - A:ARG3 :UNL1 - B:LYS168
12	1xi9	F16	2H	B:LYS168:HZ3 - :UNL1:O C:ARG7:HE - :UNL1:N A:SER1:N - :UNL1

				A:SER1:N - :UNL1 B:LYS168:NZ - :UNL1 A:ILE2:CG2 - :UNL1 :UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - C:PRO116 :UNL1 - A:ILE2 :UNL1 - A:ARG3 :UNL1 - B:LYS168 :UNL1 - B:LYS168
13	1xi9	F17	2H	B:LYS168:HZ3 - :UNL1:O C:ARG7:HE - :UNL1:N A:SER1:N - :UNL1 A:SER1:N - :UNL1 B:LYS168:NZ - :UNL1 A:ILE2:CG2 - :UNL1 :UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - C:PRO116 :UNL1 - A:ILE2 :UNL1 - B:LYS168 :UNL1 - B:LYS168
14	1xi9	F18	2H	B:LYS168:HZ3 - :UNL1:O C:GLY138:CA - :UNL1:N B:LYS168:NZ - :UNL1 A:ILE2:CG2 - :UNL1 :UNL1 - C:PRO116 :UNL1 - C:PRO116 :UNL1 - A:ILE2 :UNL1 - B:LYS168 :UNL1 - B:LYS168
15	1xi9	F19	1H	:UNL1:C - B:ASP165:O A:SER1:N - :UNL1

				B:LYS168:NZ - :UNL1 A:ILE2:CG2 - :UNL1 :UNL1 - A:ILE2 :UNL1 - B:LYS168 :UNL1 - B:LYS168
16	1xi9	F50	1H	A:SER1:HT2 - :UNL1:O B:LYS168:NZ - :UNL1 C:PRO116:C,O;GLY117:N - :UNL1 :UNL1 - A:ARG3 :UNL1 - C:LYS140 :UNL1 - C:PRO116 :UNL1 - D:PRO116
17	1xi9	F58	2H	B:LYS168:HZ1 - :UNL1:N C:GLY138:CA - :UNL1:O B:LYS168:NZ - :UNL1 B:LYS168:NZ - :UNL1
18	1xi9	F59	1H	:UNL1:O - A:SER1:O A:SER1:N - :UNL1 B:LYS168:NZ - :UNL1 B:LYS168:NZ - :UNL1 A:ILE2:CA - :UNL1 :UNL1 - B:LYS168
19	1xi9	F68	1H	:UNL1:C - C:GLY138:O A:SER1:N - :UNL1 :UNL1 - A:ARG3
20	1xi9	F69	1H	C:LYS135:CE - :UNL1:N B:LYS168:NZ - :UNL1 B:LYS168:HZ1 - :UNL1 B:ASP118:OD2 - :UNL1 B:ASP118:OD2 - :UNL1 :UNL1 - C:LYS140 :UNL1 - C:LYS140

				:UNL1 - B:ARG166 :UNL1 - C:LYS135 :UNL1 - A:ARG3 :UNL1 - C:LYS140
21	1xi9	F72	3H	A:ARG3:HN - :UNL1:O :UNL1:O - A:ARG3:O C:LYS140:CE - :UNL1:N B:LYS168:NZ - :UNL1 :UNL1 - A:ARG3
22	1xi9	F73	2H	B:LYS168:HZ3 - :UNL1:N :UNL1:O - B:THR167:O A:SER1:N - :UNL1
23	1xi9	Fn1	0H	B:LYS168:NZ - :LIG1 B:LYS168:NZ - :LIG1 B:LYS168:HZ1 - :LIG1 B:ASP118:OD2 - :LIG1 B:ASP118:OD2 - :LIG1 :LIG1 - C:LYS140 :LIG1 - C:LYS135 :LIG1 - C:LYS140 :LIG1 - C:LYS140 :LIG1 - C:LYS135
24	1xi9	1xi976	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501

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25	1xi9	1xi977	1H	A:ILE2:CA - :UNL1:O B:LYS168:HZ3 - :UNL1 :UNL1 - A:ARG3 :UNL1 - B:LYS168
26	1xi9	1xi978	0H	B:LYS168:NZ - :UNL1 A:ILE2:CA - :UNL1 :UNL1 - A:ARG3 :UNL1 - B:LYS168
27	1xi9	1xi979	-	-
28	1xi9	1xi980	4H	B:ARG166:HE - :UNL1:O B:ARG166:HH21 - :UNL1:O C:LYS140:CA - :UNL1:N :UNL1:C - C:GLY138:O C:LYS135:NZ - :UNL1 C:GLY138:CA - :UNL1 :UNL1 - C:LYS135 :UNL1 - C:LYS135 :UNL1 - C:LYS140
29	1xi9	1xi982	1H	B:LYS168:HZ1 - :UNL1:N B:ASP115:OD1 - :UNL1 A:LYS6:CB - :UNL1 C:VAL142:CG1 - :UNL1 C:VAL142:CG2 - :UNL1 C:VAL142:CG2 - :UNL1 :UNL1 - C:LYS140 :UNL1 - C:LYS140 :UNL1 - A:LYS6

				:UNL1 - C:LYS140
30	1xi9	1xi91	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
31	1xi9	1xi92	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A

				A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
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34	1xi9	1xi95	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
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	1xi9	1xi920	0H	B:LYS168:NZ - :UNL1 B:ASP165:OD2 - :UNL1 :UNL1 - C:ARG7 :UNL1 - C:LYS135
41	1xi9	1xi922	-	-
42	1xi9	1xi923	1H	:UNL1:C - B:TYR198:O B:LYS168:NZ - :UNL1 C:TYR137:C,O;GLY138:N - :UNL1 :UNL1 - A:ARG3 :UNL1 - C:ARG7 :UNL1 - C:PRO116
43	1xi9	1xi924	-	-
44	1xi9	1xi925	1H	:UNL1:C - B:TYR198:O B:LYS168:NZ - :UNL1 :UNL1 - A:ARG3 :UNL1 - C:LYS140 :UNL1 - C:ARG7 :UNL1 - C:PRO116
45	1xi9	1xi926	3H	A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102

46	1xi9	1xi927	1H	:UNL1:C - B:TYR198:O B:LYS168:NZ - :UNL1 :UNL1 - A:ARG3 :UNL1 - C:LYS140 :UNL1 - C:ARG7 :UNL1 - C:PRO116
47	1xi9	1xi928	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
48	1xi9	1xi929	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P

				A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
49	1xi9	1xi930	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
50	1xi9	1xi931	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 -

				A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
51	1xi9	1xi932	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
52	1xi9	1xi933	0H	:UNL1 - B:ILE200 :UNL1:C - A:ILE2 :UNL1:C - B:LYS168 :UNL1:C - B:ILE200 :UNL1:C - B:PRO201 :UNL1:C - C:LYS135 :UNL1 - C:ARG7
53	1xi9	1xi934	3H	A:ARG245:HH22 -

				A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
54	1xi9	1xi935	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102

55	1xi9	1xi936	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
56	1xi9	1xi937	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A

				A:PLP501 - A:VAL102
57	1xi9	1xi938	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
58	1xi9	1xi939	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A

				A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
59	1xi9	1xi940	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
60	1xi9	1xi941	1H	B:LYS168:HZ3 - :UNL1:N
61	1xi9	1xi942	3H	A: ARG245:HH22 - A: PLP501:O3P A: ARG245:NH1 - A: PLP501:O1P A: VAL102:HN - A: PLP501:O1P A: THR103:HN - A: PLP501:O3P A: ARG245:HH12 - A: PLP501:O2P A: ILE207:CG2 - A: PLP501 A: TYR127 - A: PLP501

				A:PLP501:C2A - A:ILE173 A: TYR127 - A: PLP501:C2A A: TYR127 - A: PLP501:C4A A: TYR208 - A: PLP501:C2A A: PLP501 - A: VAL102
62	1xi9	1xi943	1H	A:SER1:HT3 - :UNL1:N :UNL1:C - A:ILE2 :UNL1:C - B:LYS168 :UNL1:C - A:ILE2 :UNL1:C - B:LYS168 :UNL1:C - B:ILE200 :UNL1:C - B:PRO201 :UNL1 - C:PRO116
63	1xi9	1xi944	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102

64	1xi9	1xi945	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A A:PLP501 - A:VAL102
65	1xi9	1xi946	3H	A:ARG245:HH22 - A:PLP501:O3P A:ARG245:NH1 - A:PLP501:O1P A:VAL102:HN - A:PLP501:O1P A:THR103:HN - A:PLP501:O3P A:ARG245:HH12 - A:PLP501:O2P A:ILE207:CG2 - A:PLP501 A:TYR127 - A:PLP501 A:PLP501:C2A - A:ILE173 A:TYR127 - A:PLP501:C2A A:TYR127 - A:PLP501:C4A A:TYR208 - A:PLP501:C2A

				A:PLP501 - A:VAL102
66	1xi9	1xi947	2H	C:ARG7:HE - :UNL1:N C:ARG7:HH21 - :UNL1:N :UNL1 - C:ARG7 :UNL1 - C:ARG7 :UNL1 - C:PRO116 :UNL1 - D:PRO116
67	1xi9	1xi948	2H	C:ARG7:HE - :UNL1:N C:ARG7:HH21 - :UNL1:N :UNL1 - C:ARG7 :UNL1 - C:ARG7
68	1xi9	1xi949	2H	C:ARG7:HE - :UNL1:N C:ARG7:HH21 - :UNL1:N :UNL1 - C:ARG7 :UNL1 - C:ARG7 :UNL1 - C:PRO116

Analysis of the docked results

The docking results predicted by AutoDock Vina showed that there were hydrogen bonds formed between Diabetes Mellitus proteins and the inhibitors used. The best lead compound was selected in terms of binding energy. Based on the analysis with AutoDock Vina, it was observed that the binding energies of the compounds were almost the same. Docking studies with AutoDock Vina showed that the novel synthetic benzopyrimidines showed the approvable readings. Based on these findings, these compounds can be further synthesized and studied further for their anti-diabetic activity to target Diabetes Mellitus proteins.

On analyzing the structures, it is observed that structures containing amino groups decrease activity to some extent, and structures containing methyl, ketone, and heterocyclic rings increase the activity to a greater extent.

CONCLUSION:

In this research paper, the novel classes of benzopyrimidines were docked to show anti-diabetic property via structure-based drug design like benzopyrimidine derivatives. These

compounds have been found to show marked binding activity which can lead to the synthesis and pharmacological activity of benzopyrimidines as a drug.

However, AutoDock Vina consistently outperformed as compared to other programs and was found to be relatively more useful in blind docking pose prediction. Moreover, analysis of the docked ligands with the protein brought into focus some important interactions operating at the molecular level. The results of the ligand docking showed that the binding pocket involves the amino acid residues ARG7, PRO116, GLY138, THR167, LYS168, ARG3, PHE136, ASP165, ILE2, ASP118, LYS140, SER1, LYS135, ARG166, TYR198, TYR137, GLY138, ILE200, PRO201, ASP115, LYS6, VAL142, ARG245, PLP501, VAL102, THR103, ILE207.

In conclusion, we have discovered highly potent lead compounds which will be useful for the design of novel less toxic, and highly efficient drugs for the treatment of Diabetes Mellitus.

Table Number 03:- Number of structures and their affinity

Range of Affinity	Number of structures
-5.0 to -5.9	13
-6.0 to -6.9	24
-7.0 to -7.9	15
-8.0 to -8.9	9
-9.0 to -9.9	3
-10.0 to -10.9	3
-11.0 to -11.9	1

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