JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

IN SILICO SCREENING AND MOLECULAR DOCKING OF SULFONYLUREA DERIVATIVES

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Abstract

The rapid advancement of computational methods and molecular modeling techniques has revolutionized the drug discovery process. In-silico screening and molecular docking have emerged as powerful tools for the identification and optimization of novel drug. This study focus on the application of in-silico screening and molecular docking techniques to investigate the potential of sulfonylurea derivatives as promising drug candidtes. In this survey we present the essential data about sulfonylurea derivatives, diabetes, different types of diabetes, sign and symptoms, different test approaches, preventions, treatment for diabetes, drugs given in treatment of diabetes, instrument of activity of dipeptidyl peptidase-4 inhibitors. Sulfonylurea are class of oral hypoglycemic agents known for their therapeutic efficacy in the treatment of type II diabetes mellitus, which stimulates insulin secreation from beta calls of the pancreas, which helps to lower blood glucose levels. The chemistry of sulfonylurea derivatives is related to their mechanism of action in treating type II diabetes. Studies the various software and how they work. The various softwares are Chemsketch, Avogadro, PyRx, Discovery studio, ADME study and Toxicity study. The results obtained from the molecular docking simulation provide valuable insights into the binding affinity modes and key interaction between the sulfonylurea derivatives and the target receptor. After completion of virtual screening of different modified structures of Vildagliptin. The binding affinity of R10 shows lowest binding affinity compares to others interaction structures. Further studies the ADMET study by Swiss ADME as well as ADMET lab 2.0 and Toxicity study by software PROTOX-II. In conclusion, the application of in-silico screening and molecular docking techniques offers a cost-effective and time-effective approach for the identification and optimization of sulfonylurea derivatives with improved therapeutic potential. The results of in-silico screening and molecular docking of sulfonylurea derivatives as anti-diabetic agents suggest that these compound have strong potential for therapeutic use.

Keywords: Molecular Docking, Vildagliptin, Dipeptidyl Peptidase-4 Inhibitor, In Silico Screening,Diabetes, Software's, ADME Study, Toxicity Study.

1. INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels. Diabetes is a metabolic disorder that primarily causes high blood glucose. The most common types of Diabetes are Type 1 and Type 2 diabetes. Type 1 diabetes is caused due to genetic disorder, whereas Type 2 diabetes is primarily a lifestyle disorder. The other types of Diabetes are prediabetes and gestational diabetes. Pre-diabetes is a borderline phase preceding Diabetes when the blood glucose levels are higher than usual but not as high as Diabetes itself. Diabetes can be both reversible as well as chronic. Chronic Diabetes includes Type1 and Type2 diabetes, in which Type1 is caused due to genetic reasons, whereas Type2 is caused due to an irregular lifestyle. Reversible Diabetes includes pre-diabetes and gestational diabetes. Pre-diabetes usually precedes the onset of type 2 diabetes but can be corrected with proper diet and exercise. Gestational Diabetes occurs only during pregnancy, and once the baby is born, the condition gets better in the mother's body. However, women with gestational Diabetes stand a risk of suffering from Type 2 diabetes later on in their lives. Chronic Diabetes is caused by a lack of insulin hormone production or the body's resistance to the insulin produced. Insulin produced by the beta cells of Islets of Langerhans of the pancreas is responsible for regulating glucose level in the blood. Usually, when the blood glucose levels increase, it sends a signal to the pancreas to produce insulin, helping the cells absorb the glucose. After that, the level of blood glucose comes down to normal, and insulin secretion drops. In Type 1diabetes, the body's immunity system fueled by a genetic reason leads the immune response to attack the beta cells and destroy them, thereby diminishing or almost inhibiting insulin production. In this condition, the patient needs a steady influx of insulin in regular insulin injections to maintain normal blood glucose levels. Obesity or lifestyle habits are play any role in this form of Diabetes. On the other hand, Type2 diabetes is caused due to unhealthy lifestyle habits such as prolonged lack of proper's leap, excessive alcohol and tobacco consumption, excessive consumption of junk food, and obesity, to name a few. This condition is caused due to the body's resistance to the insulin present in the bloodstream and the pancreas' consequent inability to produce enough insulin to overcome this. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Between 2000 and2016, there was a 5% increase in premature mortality rates (i.e., before the age of 70) from diabetes. In high-income countries the premature mortality rate due to diabetes decreased from 2000 to 2010 but then increased in 2010-2016. In lower-middle-income countries, the premature mortality rate due to diabetes increased across both periods. By contrast, the probability of dying from any one of the four main non communicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes) between the ages of 30 and 70 decreased by 18% globally between 2000 and 2016.[1,2]

1.1 TYPES

The types of diabetes are:

Type1 Diabetes: This type is a not autoimmune disease, meaning your body attacks itself. In this case, the insulin-producing cells in your pancreas are destroyed. Up to 10% of people who have diabetes have Type 1. It's usually diagnosed in children and young adults (but can develop at any age). It was once better known as "juvenile" diabetes. People with Type1 diabetes need to take insulin everyday. This is why it is also called insulin-dependent diabetes.

Type 2 Diabetes: With this type, your body either doesn't make enough insulin or yourbody's cells don't respond normally to the insulin. This is the most common type of diabetes. Up to 95% of people with diabetes have Type 2. It usually occurs in middle- aged and older people. Other common names for Type 2 include adult-onset diabetes and insulin-resistant diabetes. Your parents or grandparents may have called it "havinga touch of sugar."

Prediabetes: This type is the stage before Type 2 diabetes. Your blood glucose levels are higher than normal but not high enough to be officially diagnosed with Type 2 diabetes.

Gestational diabetes: This type develops in some women during their pregnancy.Gestational diabetes usually goes away after pregnancy. However, if you have gestational diabetes, you're at higher risk of developing Type 2 diabetes later on inlife.[3]

1.2 Introduction on sulfonylurea derivative:

Sulfonylurea derivatives are a class of oral hypoglycemic agents that are used to treat type 2 diabetes mellitus. They work by stimulating insulin secretion from the beta cells of the pancreas, which helps to lower blood glucose levels.

The general structure of sulfonylurea derivatives consists of a sulfonamide group (SO2NH) attached to a urea group (CONH2) via a carbon linker. The carbon linker can be substituted with various aryl or alkyl groups, which can affect the pharmacological properties of the drug.

Here is the general structure of a sulfonylurea derivative:

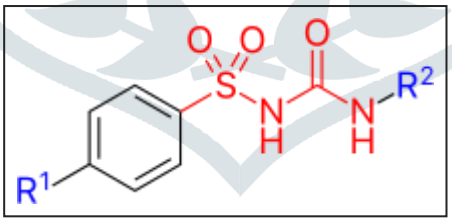

Figure No.1: General Structure of Sulfonylurea

Chemistry Of Sulfonylurea Derivative:

Sulfonylurea derivatives contain a sulfonamide group (-SO2NH-) and a urea group (-CONH2) linked by a carbon chain with different aryl or alkyl groups. The chemistry of sulfonylurea derivatives is related to their mechanism of action in treating type 2 diabetes.

Sulfonylurea derivatives act by binding to the sulfonylurea receptor (SUR) on pancreatic beta cells. This binding leads to the closure of ATP-sensitive potassium channels (KATP channels) on the cell surface, which in turn causes depolarization of the beta cell membrane and triggersthe release of insulin.

The sulfonamide group in sulfonylurea derivatives is important for binding to the SUR on pancreatic beta cells. The sulfonamide group is also responsible for the water solubility of these drugs. The urea group in sulfonylurea

derivatives is important for their stability and their abilityto penetrate cell membranes.

The aryl or alkyl groups on the carbon linker in sulfonylurea derivatives can affect their pharmacological properties. For example, the presence of a methyl group on the linker can increase the potency of the drug, while the presence of a bulky group can decrease the potency.

Sulfonylurea derivatives are metabolized in the liver and excreted in the urine. Some sulfonylurea derivatives, such as glyburide, are metabolized into active metabolites, which contribute to their hypoglycaemic effects.

In summary, the chemistry of sulfonylurea derivatives is important for their mechanism of action, pharmacological properties, stability, and metabolism.

1.3 SIGNS AND SYMPTOMS:

- Frequent urination: When blood sugar levels are high, the kidneys may not be able toreabsorb all the glucose. This results in frequent urination.
- Excessive thirst: Frequent urination can lead to dehydration and excessive thirst.
- Increased hunger: People with diabetes may experience increased hunger despite eatingregularly.
- Fatigue: High blood sugar levels can make you feel tired and lethargic.
- Blurred vision: High blood sugar levels can cause blurred vision or even vision loss in somecases.
- Slow-healing wounds: High blood sugar levels can slow down the healing process ofwounds.
- Tingling or numbness: Diabetes can damage nerves, leading to tingling or numbness in thehands or feet.
- Recurrent infections: High blood sugar levels can weaken the immune system, making itmore susceptible to infections.
- Weight loss.

Prediabetes doesn't usually have any signs or symptoms.

One possible sign of prediabetes is darkened skin on certain parts of the body. Affected areas can include the neck, armpits, elbows, knees and knuckles.

Gestational diabetes:

It is diabetes diagnosed for the first-time during pregnancy. For most women, gestational diabetes doesn't cause noticeable signs or symptoms. Increased thirst and more-frequent urination are possible symptoms [4,5,6,7,8]

Figure No.2: Symptoms of Diabetes [6]

1.4 TESTS FOR DIABETES AND PREDIABETES

- ***Fasting plasma glucose test:*** It measures your blood glucose after you have gone at least 8hours without eating. This test is used to detect diabetes or prediabetes
- ***Oral glucose tolerance test:*** In this test, blood glucose level is first measured after an overnight fast. Then you drink a sugary drink. Your blood glucose level is thencheckedat hours one, two and three.
- ***A1c test:*** This test, also called HbA1C or glycated hemoglobin test, provides your average blood glucose level over the past two to three months. This test measures the amount of glucose attached to hemoglobin, the protein in your red blood cellsthat carries oxygen. Fasting is not needed in this.
- ***Random plasma glucose test:*** This test can be done any time without the need to fast.

Additional specific testing advice based on risk factors:

- ***Testing for Type 1 diabetes:*** Test in children and young adults who have a family history of diabetes. Less commonly, older adults may also develop Type 1 diabetes. Therefore, testing in adults who come to the hospital and are found to be in diabetic ketoacidosis is important. Ketoacidosis a dangerous complication that can occur in people with Type 1 diabetes.
- ***Testing for type 2 diabetes:*** Test adults age 45 or older, those between 19 and 44 who are overweight and have one or more risk factors, women who have had gestational diabetes, children between 10 and 18 who are overweight and have at least two risk factors for type 2 diabetes. [9,10]

Test	Cutoff for Diabetes	How the Test is Performed
A1C	≥6.5%	No need to fast beforehand. This test provides your average blood glucose level over the past 2 to 3 months.
Fasting plasma blood glucose	≥126 mg/dL	No food or drinks except water for at least 8 hours before the test; testing is usually done in the morning when you are already in the fasted state.
Oral glucose tolerance test	2-hour blood glucose ≥200 mg/dL	Checks blood glucose levels in the fasted state (no food or drinks except water for 8 hours beforehand) and after having a special sugary drink to see how your body processes the sugar.
Random (or casual) plasma glucose test	≥200 mg/dL	This test is only used in patients with symptoms of diabetes is taken at any time of day with no need to fast.

FigureNo.3: Test for Diabetes [11]

1.5 PREVENTIONS

- Maintain a healthy weigh
- Eat a healthy diet
- Exercise regularly
- Quit smoking
- Manage stress
- Get enough sleep
- Get regular check-ups [12]

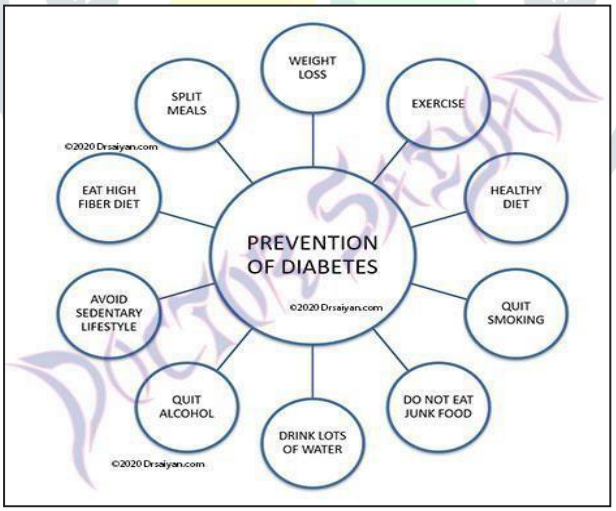

Figure no 4: Prevention of Diabetes[13]

1.5 TREATMENTAPPROACHES

➢ **Oral Antidiabetic drugs**

These drugs lower blood glucose levels in diabetics and are effective orally. The chief drawback of insulin is it must be given by injection. Orally active drugs have alwaysbeen sought. The early sulfonamides tested in 1940s produced hypo-glycaemia as sideeffect. Taking this lead, the first clinically acceptable sulfonylurea tolbutamide was introduced in 1957. Others followed soon after. In the 1970s many so called 'second generation'

sulfonylureas were developed which are >100 times more potent than tolbutamide. Clinically useful biguanide phenformin was produced parallel to sulfonylureas in 1957. Newer approaches have constantly been explored and have successively yielded thiazolidinediones, meglitinide analogues, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and sod-glucose cotransport (SGLT-2) inhibitors, etc. [14]

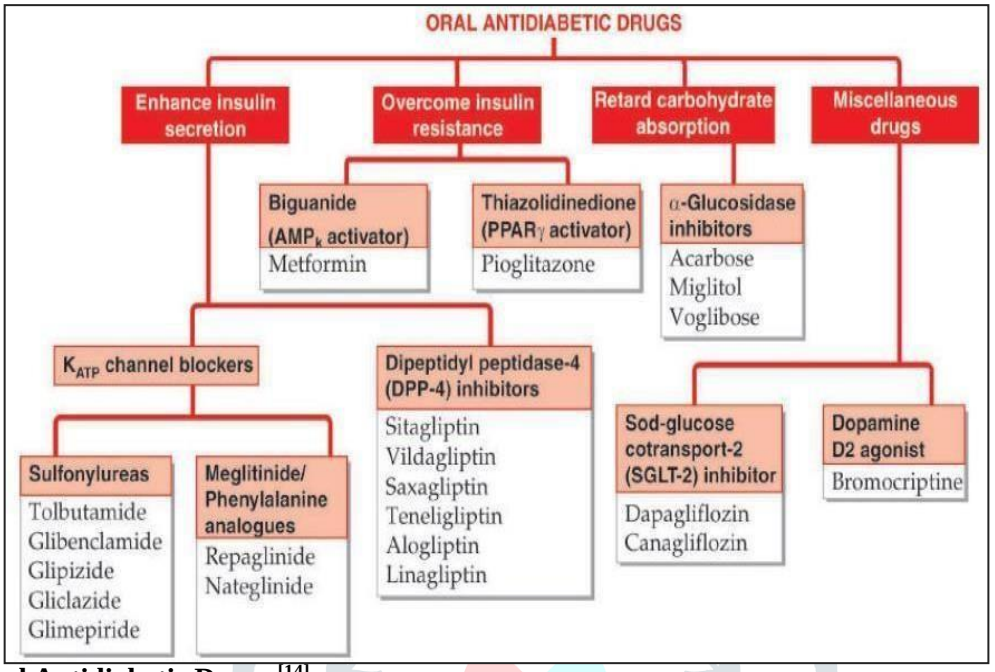

Figure No.5 : Oral Antidiabetic Drugs [14]

1.7 Dipeptidylpeptidase-4(DPP-4) inhibitors

The dipeptidyl peptidase (DPP)-4 inhibitors, which enhance glucose-dependent insulin secretion from pancreatic β cells by preventing DPP-4-mediated degradation of endogenously released incretin hormones, represent a new therapeutic approach to themanagement of type 2 diabetes mellitus. An inhibitor of dipeptidyl peptidase-4 (DPP-4), a protease that degrades the incretin GLP-1. Incretins are hormones released from the GI tract in response to nutrient ingestion. Incretins potentiate glucose-stimulated insulin secretion from beta cells in the pancreas. As a result of inhibiting DPP-4, increased or prolonged GLP-1 levels are able to potentiate the secretion of insulin by the pancreas. Duration of action (12–24 hours) despite short plasma t½ (2–4 hours). The major route of elimination is by hepatic metabolism; only 20–25% is excreted unchanged in urine. [14,15,16]

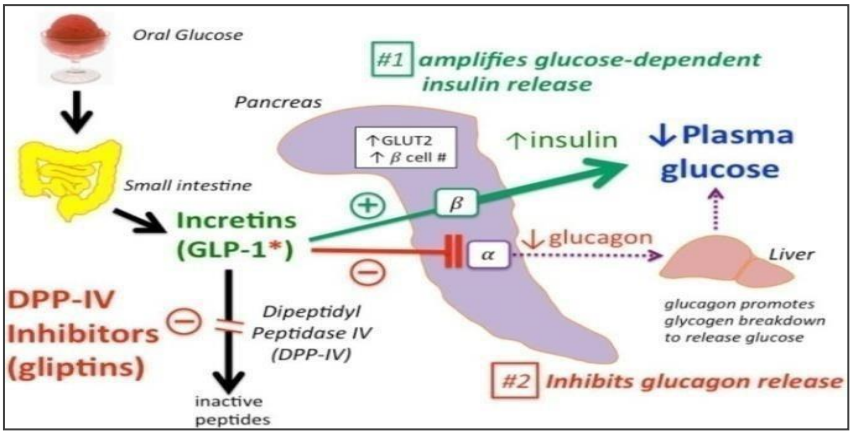

Figure No.6: Mechanism of action of DPP-IV Inhibitor [16]

2. AIM & OBJECTIVES

Aim:

To perform molecular docking of analogues of Vildagliptin as a dipeptidyl peptidase-4inhibitor.

Objectives:

- To study *in-silico* Approach of Interaction studies of Vildagliptin against DPP-4
- To predict *in-silico* ADMET parameters by using ADMET lab 2.0 as well as Swiss ADME.

3. PLAN OF WORK

1. In silico screening of Vildagliptin
2. Downloading and installing all the required software.

- Chemsketch
- Avogadro
- PyRx
- Discovery Studio

3. Preparation of the Ligands
4. Preparation of the Target
5. Virtual Screening

4. EXPERIMENTAL WORK

4.1 In silico screening of Vildagliptin:

Vildagliptin (LAF237) is an orally active antihyperglycemic agent that selectively inhibits the dipeptidyl peptidase-4 (DPP-4) enzyme. It is used to manage type II diabetes mellitus, where GLP-1 secretion and insulinotropic effects are impaired. Vildagliptin is a cyan pyrrolidine- based, orally bioavailable inhibitor ofdipeptidyl peptidase 4 (DPP-4), with hypoglycemic activity. Vildagliptin's cyan moiety undergoes hydrolysis and this inactive metabolite is excreted mainly via the urine. By inhibiting DPP-4, vildagliptin prevents the degradation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which areincretin hormones that promote insulin secretion and regulate blood glucose levels. Elevated levels of GLP-1 and GIP consequently results in improved glycemic control. In clinical trials, vildagliptin has a relatively low risk of hypoglycemia.Oral vildagliptin was approved by the European Medicines Agency in 2008 for the treatment of type II diabetes mellitus in adults as monotherapy or in combination with[metformin], a sulfonylurea, or athiazolidinedione in patients with inadequate glycemic control following monotherapy. It is marketed as Galvos. Vildagliptin is alsoavailable as Euchres, a fixed-dose formulation with metformin for adults in who do not adequately glycemic control from monotherapy. Vildagliptin is currently under investigation in the US.[17]

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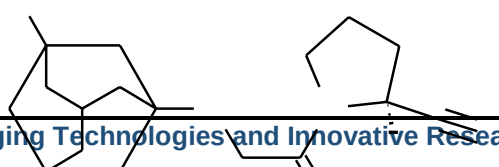


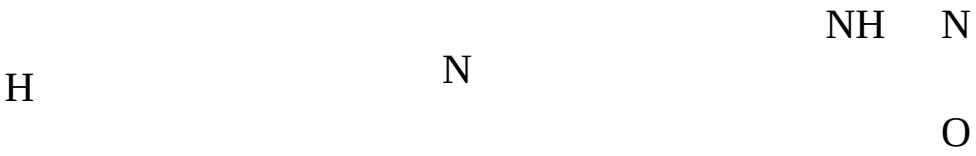


Figure No.7: Structure of Vildagliptin [17]

➢ **Properties of vildagliptin:**

Table No.1 Represent the physicochemical properties of Vildagliptin

Sr. No.	Contents	Property
1	MilogP	1.42
2	TPSA	76.36
3	Natoms	22
4	MW	303.41
5	Non	05
6	nOHNH	2
7	Nviolatons	0
8	Nrotb	3
9	Volume	289.82

➢ **Downloading and Installing all the required Software:**

a) Chemsketch

b) Avogadro

c) PyRx

d) DiscoveryStudio

a) Chemsketch:

This open-source software is a chemical molecule or molecular modeling program used to create, draw and modify images of chemical structures or compounds and there is software that allows molecule and molecular models displayed in two and threedimensions, to understand the structure of chemical bonds and nature of the functional groups. This tool enables us to draw chemical molecules and save them directly in several formats like. mol, .jpg, .png and many more formats. We can also generate the international union of pure and applied chemistry(IUPAC) of the chemical structures. ChemSketch is a molecular modeling program used to create and modify images of chemical structures. Also, there is a software that allowsmolecules and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and the nature of the functional groups. This software also helps us for generation of simplified molecular input line entry system (SMILES) of the desired chemical structure.[18]

b) Avogadro software:

Avogadro software was used to convert the .mol file to .pdb format. This is again open- source software that helps

optimize the chemical structure. This also helps in minimizing the energy which is very important protocol for in silico studies. The software also allows generation of structure through SMILES or by drawing tool. These chemical structures were saved in the format of .pdb format which is required for docking purpose.[18]

c) PyRx software

PyRx software was used for virtual screening of library of derivatives. The pyrx software is a open software for virtual screening. The approach includes blasting of several ligand moleculesto a target and segregate the best fit molecules from the library. The tool includes a 4step protocol and can screen a big library of molecules simultaneously on a defined site of target/receptor. The results can easily be exported in Microsoft excel format as .csv file.[18]

d) BIOVIA Discovery Studio

BIOVIA Discovery Studio brings together over 30 years of peer-reviewed research and world-class in silico techniques such as molecular mechanics, free energy calculations, biotherapeutics developability and more into a common environment. It provides researchers with a complete toolset to explore the nuances of protein chemistry and catalyze discovery of small and large molecule therapeutics from Target ID to Lead Optimization.[18]

With Discovery Studio you can:

- Investigate and test hypotheses in silico prior to costly experimental implementation, thusreducing the time and expense involved in bringing products tomarket
- Drive scientific exploration from target identification to lead optimization with awealth oftrusted life science modeling and simulation tools
- Leverage BIOVIA Pipeline Pilot to automate processes, create and deploy customworkflows,and integrate data types, databases, and third-party or in-house tools

4.2 Preparation of ligand (structurally similar design derivatives)

Ligand structure was drawn using Chemsketch software and the structure was cleaned using the clean structure tool. The structure was saved in the working folder as .mol file in a workingfolder. The .mol file present in working folder was then accessed in Avogadro software and structure was optimized using optimization tool. The optimized structure was exported in the working folder as F1.pdb – F15.pdb file format.

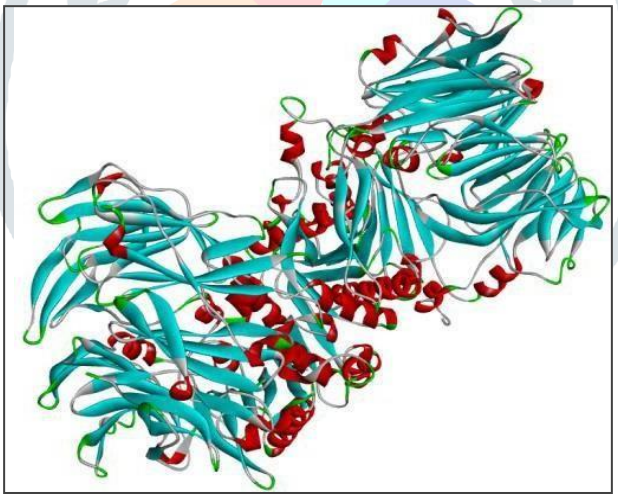
Table No. 2 IUPAC and Smiles Notation of Derivatives of Vildagliptine

Code no	IUPAC	Smiles
Vildagliptin	(2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile	C1C[C@H](N(C1)C(=O)CNC23C C4CC(C2)CC(C4)(C3)O)C#N
R1	1-{[(3-chloroadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile	N#CC1CCCN1C(=O)CNC12CC3 CC(C1)CC(Cl)(C3)C2
R2	5-chloro-1-{[(3-hydroxy-2,4,9-trioxoadamantan-1- yl)amino]acetyl}-3-methylpyrrolidine-2-carbonitrile	CC1CC(Cl)N(C(=O)CNC23CC4C C(C(=O)C(O)(C4)C3=O)C2=O)C1C#N
R3	1-{(2E)-2-[(3-hydroxyadamantan-1-yl)imino]acetyl}pyrrolidine-2-carbonitrile	N#CC1CCCN1C(=O)/C=N/C12CC 3CC(C1)CC(O)(C3)C2
R4	2-(2-cyano-1,3-oxazolidin-3-yl)- N-(3-hydroxyadamantan-1-yl)- 2-oxoacetamide	O=C(N1CCOC1C#N)C(=O)NC12 CC3CC(C1)CC(O)(C3)C2

R5	3-{(2E)-2-[(3-hydroxyadamantan-1-yl)imino]acetyl}-1,3- oxazolidine-2-carbonitrile	O=C(/C=N/C12CC3CC(C1)CC(O)(C3)C2)N1CCOC1C#N
R6	2-(2-cyano-3,5- dihydroxypyrrolidin-1-yl)-N-(3- hydroxyadamantan-1-yl)-2-Oxoacetamide	OC1CC(O)N(C(=O)C(=O)NC23CC4CC(C2)CC(O)(C4)C3)C1C#N
R7	1-{[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidin-2-one	O=C1CCCN1C(=O)CNC12CC3CC(C1)CC(O)(C3)C2
R8	3-{[(3-hydroxyadamantan-1-yl)amino]acetyl}-1,3- oxazolidine-2-carbonitrile	O=C(CNC12CC3CC(C1)CC(O)(C3)C2)N1CCOC1C#N
R9	(1Z)-N-(3-chloroadamantan-1- yl)(2-cyanopyrrolidin-1- yl)oxoethanimidic acid	N#CC1CCCN1C(=O)C(/O)=N/C12CC3CC(C1)CC(Cl)(C3)C2
R10	2-(2-cyanopyrrolidin-1-yl)-N-(3-hydroxyadamantan-1-yl)-2-oxoacetamide	N#CC1CCCN1C(=O)C(=O)NC12CC3CC(C1)CC(O)(C3)C2
R11	1-{[(3-hydroxy-4- oxoadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile	N#CC1CCCN1C(=O)CNC12CC3CC(C1)CC(O)(C2)C3=O

4.3 Preparation of Protein Receptor

Open the Protein Data Bank site and Search for **1J2E** and download in .pdb format from theonline database and was rectified using auto dock software which is already present in the PyRx software. The pdb format is opened in the discovery studio and then press Ctrl + H and then remove the pre-associated Ligand present in the protease and the active sites were identified andthensaved in the working folder as .pdb file.



FigureNo.8: Receptor PDBID:1J2E

- **Virtual Screening through PyRx:**

Now the PyRx software is used for optimize the docking score. All the ligands and the enzyme were selected. Grid was selected and the binding energy wascarried out. Virtual screening was analyzed using Discovery Studio Visualizer.

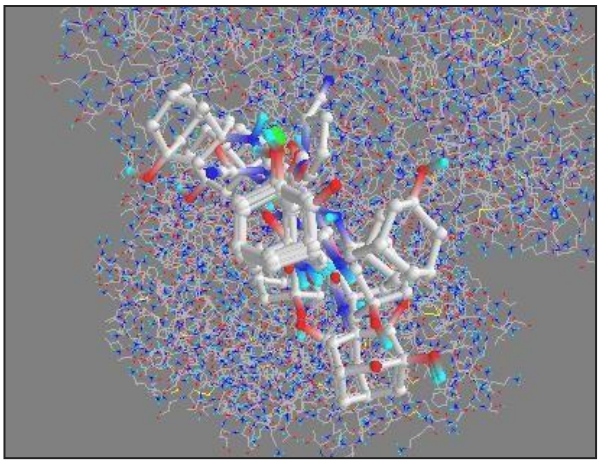


Figure No.9: Docking of Vildagliptin, Derivatives with IJ2E

5. Result and Discussion

After the completion of virtual screening of different modified structures of Vildagliptin. The structure modified as R10 Showed the Binding Affinity of -9.1 Kcal/mol which means it has the best binding among all modifications and Vildagliptin which has the binding affinityof-8 Kcal/mol.

Table No.3. Ligands with their Binding Affinity

Ligand	Binding Affinity(Kcal/mol)
Vildagliptin	-8.0
R1	-8.2
R2	-7.8
R3	-8.7
R4	-7.3
R5	-7.9
R6	-7.8
R7	-7.8
R8	-8.4

R9	-7.4
R10	-9.1
R11	-8.4

5.1 Interaction of Vildagliptine derivatives with amino acid residues of DPP-4 receptorwith PDB ID: 1J2E

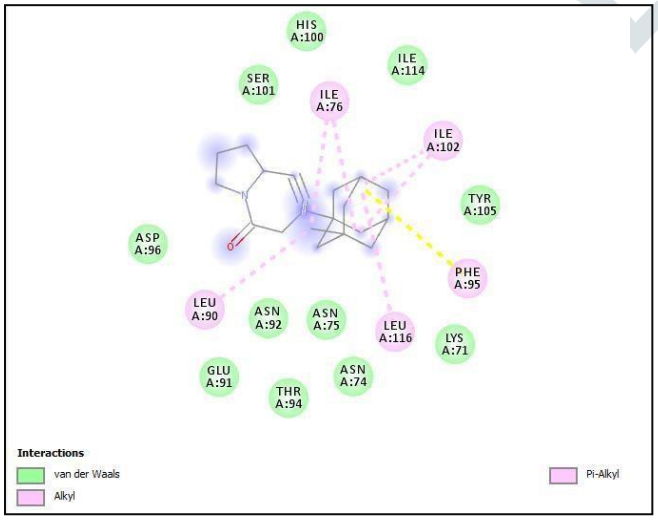


Figure No.10: Ligand R1 with Receptor IJ2E

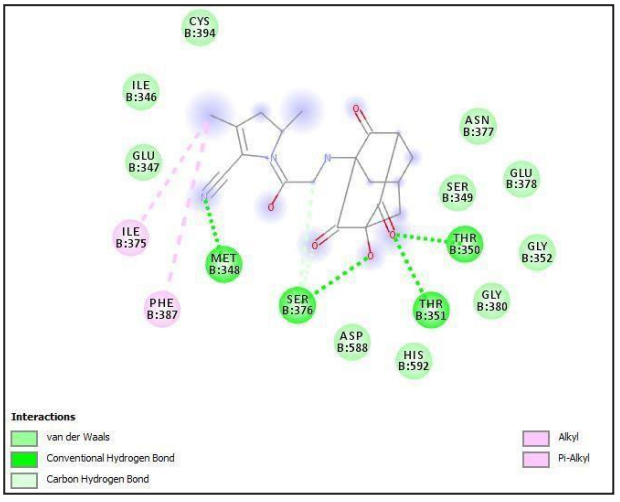


Figure No.11: Ligand R2 with Receptor IJ2E

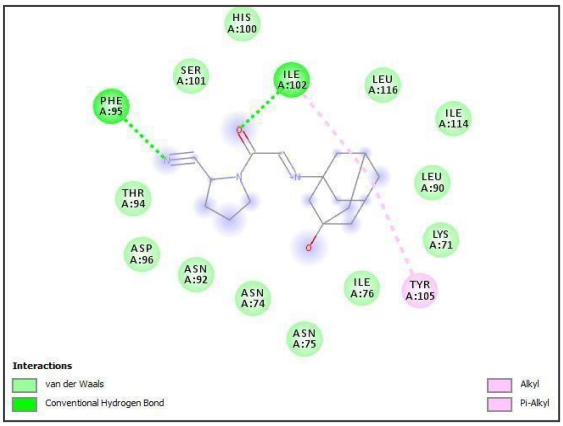


Figure No.12: Ligand R3 with Receptor IJ2E

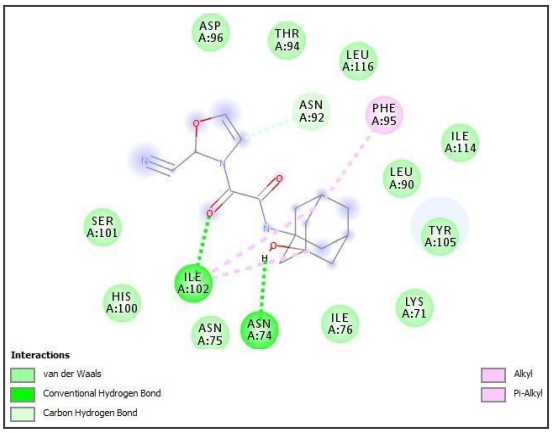


Figure No.13: Ligand R4 with Receptor

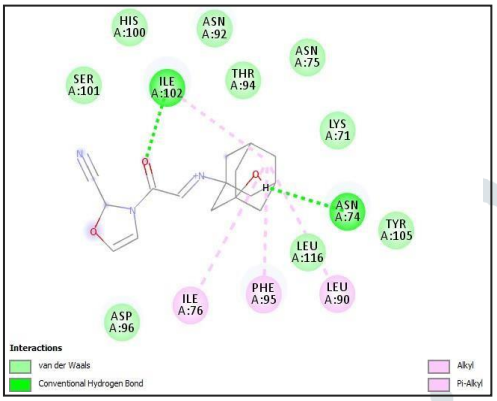


Figure No.14: Ligand R5 with Receptor IJ2E

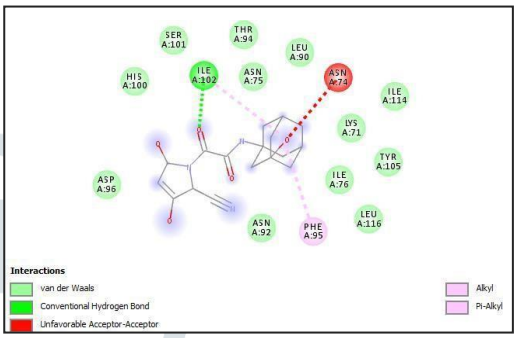


Figure No.15: Ligand R6 with Receptor IJ2E

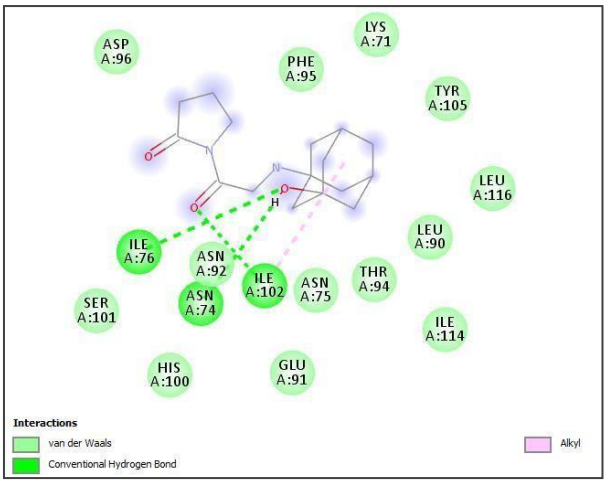


Figure No.16: Ligand R7 with Receptor IJ2E

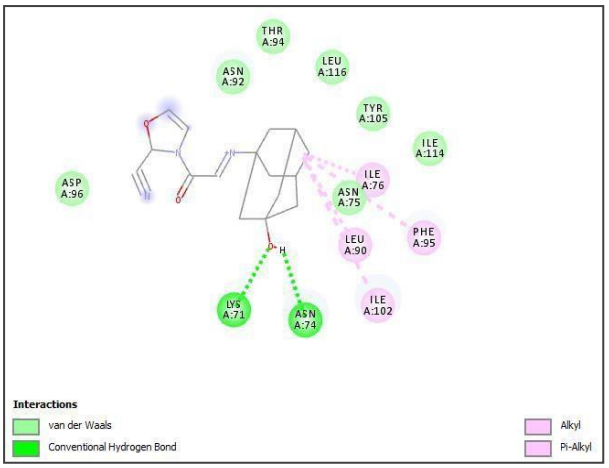


Figure No.17: Ligand R8 with Receptor IJ2E

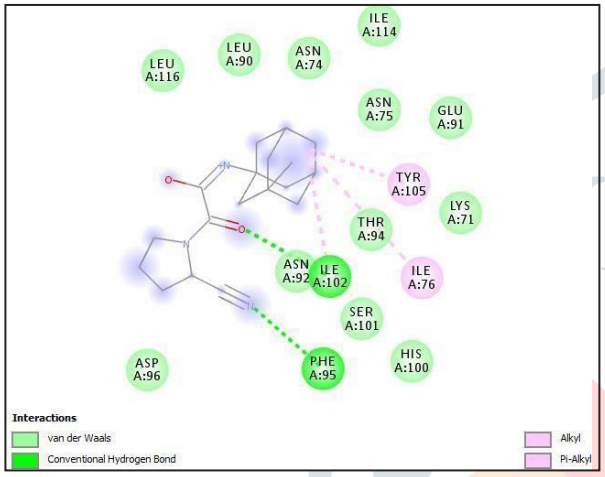


Figure No.18: Ligand R9 with Receptor IJ2E

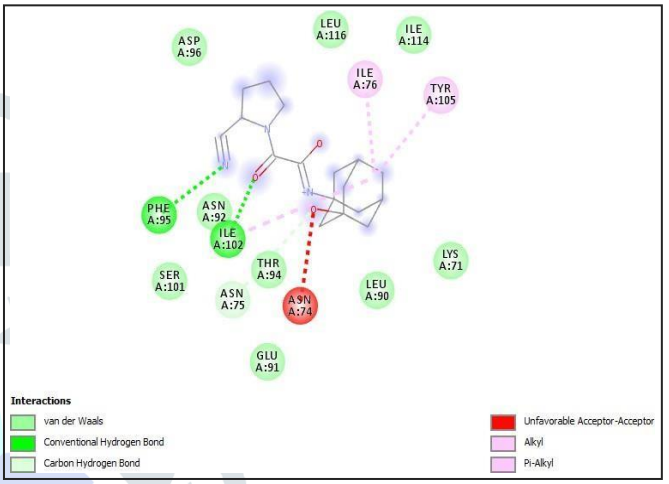


Figure No.19: Ligand R10 with Receptor IJ2E

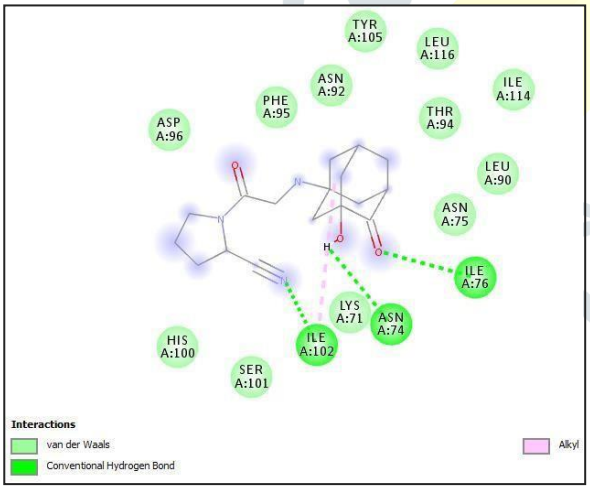


Figure No.20: Ligand R11 with Receptor IJ2E

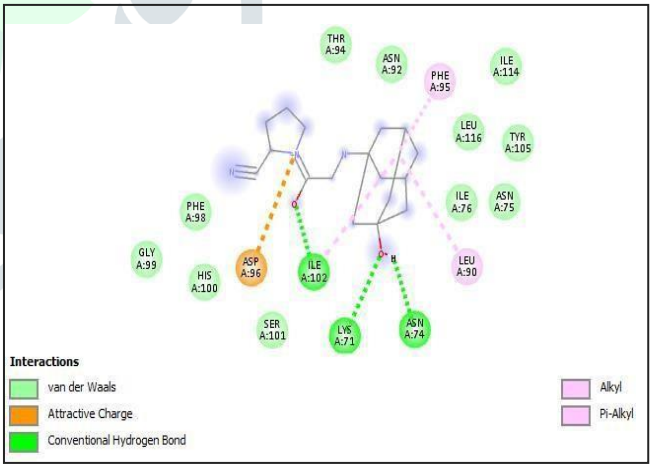


Figure No.21: Vidagliptin with Receptor IJ2

- In above figure no.20, the amino acid interaction of ligand R11-IJ2E found to be similar interaction of standard, ASP A:96, ILE A:102, ASN A:74, ILE A:76, JIS A:100, SER A:101, SERA:101, LYS A:71, PHE A:95, ASN A:92, THR A:94, ILE A:114, LEU A:116, TYR A:105, ASN A:75.
- In above figure no.21, the amino acid interaction of Vildagliptin-IJ2E, ASP A:96, ILE A:102, ASNA:74, ILE A:76, JIS A:100, SER A:101, SER A:101, LYS A:71, PHE A:95, ASN A:92, THR A:94, ILE A:114, LEU A:116, TYR A:105, ASN A:75, PHE A:98, GLY A:99.

5.2 ADMET Study:

ADMET study were done by using Swiss ADME an online software for prediction of ADME parameters aswell as using ADMET lab 2.0 software. Toxicity study were done by using PROTOX-II online software.

5.2.1 ADME Predicted Parameters

Table No.4. ADME Parameters of Best Ligands (Showing Highest Binding energies)

Sr. No.	Smiles	Absorption	Distribution			Metabolism	Excretion	
1	C1C[C@H](N(C1)C(=O)CNC23CC4CC(C2)CC(C4)(C3)O)C#N	G.I. Absorption	**PPB**	**VD**	**BB B**	Non-Enzyme inhibitor	**CL**	**$T_{1/2}$**
			10.454%	1.063	No		6.613	0.370
R_3	N#CC1CCCN1C(=O)/C=N/C12CC3CC(C1)CC(O)(C3)C2	G.I. Absorption	**PPB**	**VD**	**BB B**	Non-Enzyme inhibitor	7.14	0.138
			17.381%	1.331	No			
R_8	O=C(CNC12CC3CC(C1)CC(O)(C3)C2)N1CCOC1C#N	G.I. Absorption	**PPB**	**VD**	**BB B**	Non-Enzyme inhibitor	4.681	0.319
			12.784%	1.046	No			
R_{10}	N#CC1CCCN1C(=O)C(=O)NC12CC3CC(C1)CC(O)(C3)C2	G.I. Absorption	**PPB**	**VD**	**BB B**	Non-Enzyme inhibitor	5.993	0.242
			13.266%	0.527	No			
R_{11}	N#CC1CCCN1C(=O)CNC12CC3CC(C1)CC(O)(C2)C3=O	G.I. Absorption	**PPB**	**VD**	**BB B**	Non-Enzyme inhibitor	4.439	0.499
			15.437%	1.423	No			

5.2.2 Predicted toxicity

Table No.5. Toxicity Parameters of Best Ligands (Showing Highest Binding energies)

Sr. No.	Toxicity			
	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mut toxicity
1	Inactive	Inactive	Inactive	Inactive
2	Active	Inactive	Active	Inactive
3	Active	Inactive	Active	Inactive
4	Active	Inactive	Active	Inactive
5	Active	Inactive	Active	Inactive

6. CONCLUSION:

- In silico screening and molecular docking of sulfonylurea derivatives have shown promising results in the development of new drugs, and further research in this area could lead to the discovery of novel therapeutic agents.
- The results of in silico screening and molecular docking of sulfonylurea derivatives as anti-diabetic agents suggest that these compounds have strong potential for therapeutic use.
- The computational approach allows for the screening of a large number of compounds, which reduces time and cost compared to traditional methods.
- Molecular docking provides insights into the binding mechanism of the compounds with their target receptors.
- In silico screening and molecular docking studies provide valuable insights into the potential of sulfonylurea derivatives as anti-diabetic agents, and can help guide the development of new and more effective treatments for type 2 diabetes.
- In silico screening and molecular docking studies are powerful tools for predicting the potential biological activity of compounds, including their potential as anti-diabetic agents.

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