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IN SILICO SCREENING AND MOLECULAR DOCKING OF ANALOGUES OF VILDAGLIPTIN AS A DIPEPTIDYL PEPTIDASE-4 INHIBITOR IN TREATMENT OF DIABETES

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Abstract

Computer aided drug design (CADD) is an evolving cascade of research area encompassing many facets. Computer-aided drug design (CADD) is an exciting and diverse discipline where various aspects of applied and basic research merge and stimulate each other. The theoretical basis of CADD involves quantum mechanics and molecular modelling studies like structure-based drug design; ligand-based drug design; database searching and binding affinity based on the knowledge of a biological target. In this present review we present the areas where CADD tools support drug discovery process. In this survey we present the essential data about diabetes, different kinds of diabetes; its impact on climate, its different signs and side effects, different ID test for diabetes, use and job of insulin in diabetes, its avoidances, Treatment for diabetes, drugs given in treatment of diabetes, different classes of medication used to treat diabetes, instrument of activity of dipeptidyl peptidase-4 inhibitor. Other than this audit likewise centers around in silico screening of vildagliptin and its analogs. Construction of vildagliptin, its property, its bioactivity examined with the assistance of molinspiration. Analogs of vildagliptin were made with the assistance of Chemsketch. Avogadro was utilized to change over .mol record to .pdb. With the assistance of protein information bank receptor was download in .pdb design. Pyrx was utilized to check binding liking of analogs with receptor and analogs are contrasted and primary medication. Furthermore, best medication's atomic mechanics, energy computation, and so forth and this is finished with BIOVIA revelation studio. In which R10 was found to tie with receptor more proficiently than that of vildagliptin, though some simple showed lower binding effinity than that vildagliptin.

Keywords: Molecular Docking, Vildagliptin, Dipeptidyl Peptidase-4 Inhibitor, In Silico screening, Diabetes

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. Hyperglycaemia, 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. Prediabetes 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 Type 1 and Type 2 diabetes, in which Type 1 is caused due to genetic reasons, whereas Type 2 is caused due to an irregular lifestyle. Reversible Diabetes includes prediabetes and gestational diabetes. Prediabetes 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 levels 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 1 diabetes, the body's immunity system fuelled 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 barely play any role in this form of Diabetes. On the other hand, Type 2 diabetes is caused due to unhealthy lifestyle habits such as prolonged lack of proper sleep, 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 and 2016, 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 noncommunicable 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:

- *Type 1 Diabetes:* This type is an 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 Type 1 diabetes need to take insulin every day. 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 your body'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 "having a 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 in life.[3]

1.2 SIGNS AND SYMPTOMS

Type 1 diabetes include:

- Bedwetting in children who previously didn't wet the bed during the night
- Irritability and other mood changes
- Fatigue and weakness
- Blurred vision

Type 2 diabetes includes:

- Increased thirst
- Frequent urination
- Increased hunger
- Frequent infections
- Numbness or tingling in the hands or feet
- Areas of darkened skin, usually in the armpits and neck

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]

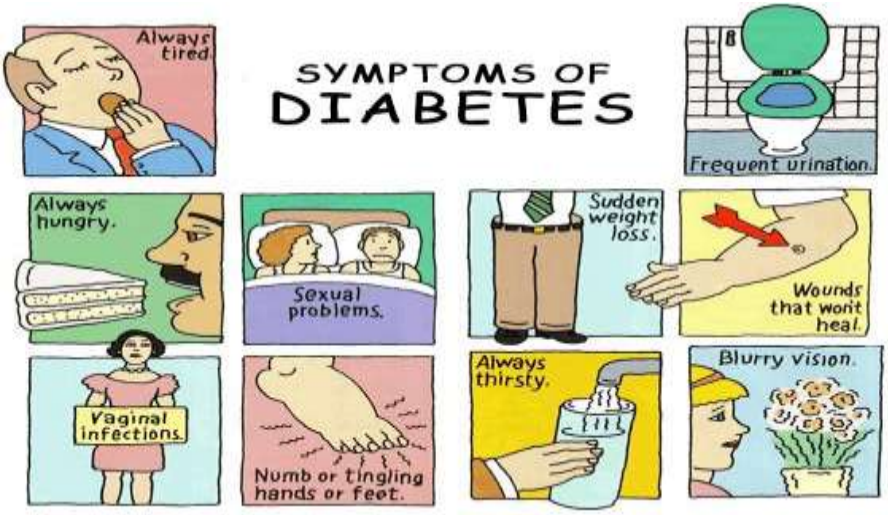


Figure No. 1 Symptoms of Diabetes [6]

1.3 TESTS FOR DIABETES AND PREDIABETES

- *Fasting **plasma glucose test**:* It measures your blood glucose after you have gone at least 8 hours 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 then checked at hours one, two and three.
- ***A1c test:*** This test, also called HbA1C or glycated haemoglobin test, provides your average blood glucose level over the past two to three months. This test measures the amount of glucose attached to haemoglobin, the protein in your red blood cells that 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]

1.4 PREVENTIONS

- Avoid sedentary lifestyle
- Control cholesterol levels
- Blood pressure control.
- Avoid beers and alcohol Losing extra weight
  - Exercise
  - Quit smoking
  - Avoid carbonated and sweetened drinks [12]

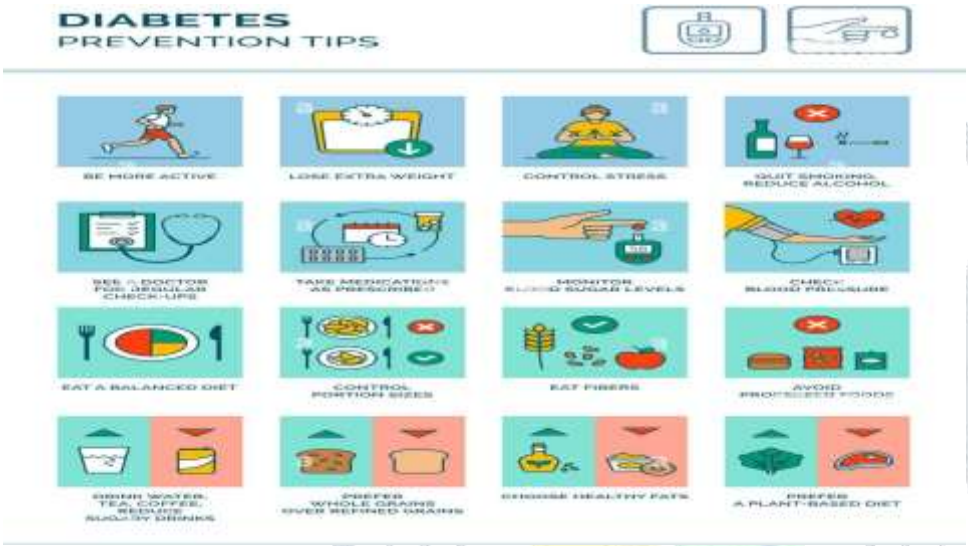


Figure No.2 Prevention from diabetes [13]

1.5 TREATMENT APPROACHES

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 always been saught. The early sulfonamides tested in 1940s produced hypo-glycaemia as side effect. 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. [14]

1.6 Dipeptidyl peptidase-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 the management 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]**

2. AIM

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

3. Work Flow

1. In silico screening of Vildagliptin
2. Downloading and Installing all the required Software Programmes
3. Preparation of the Ligands
4. Preparation of the Target
5. Virtual Screening

3.1 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 cyanopyrrolidine-based, orally bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4), with hypoglycaemic activity. Vildagliptin's cyano 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 are incretin 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 a thiazolidinedione in patients with inadequate glycemic control following monotherapy. It is marketed as Galvus. Vildagliptin is also available as Eucreas, 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]

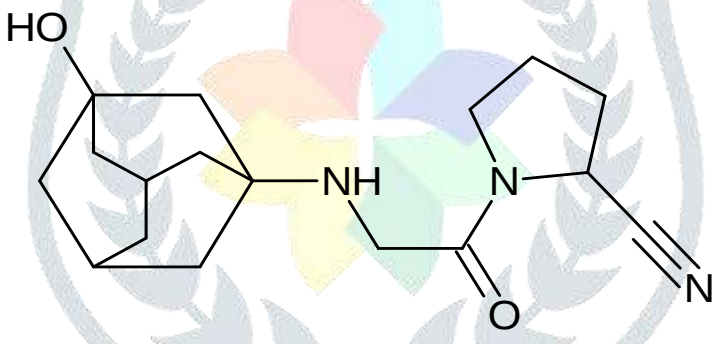


Figure No 3 Structure of vildagliptin [17]

Properties of vildagliptin

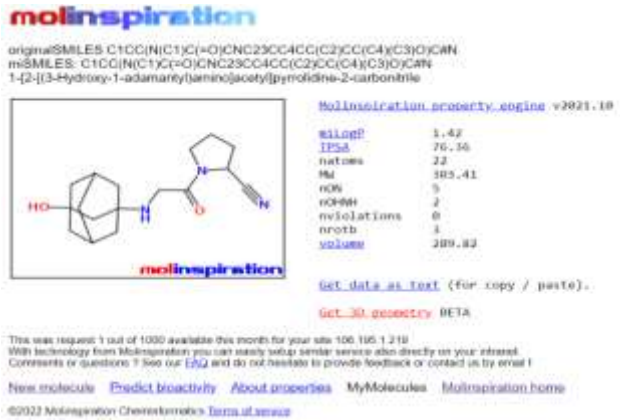


Figure No 4 Properties of vildagliptin

Bioactivity of vildagliptin

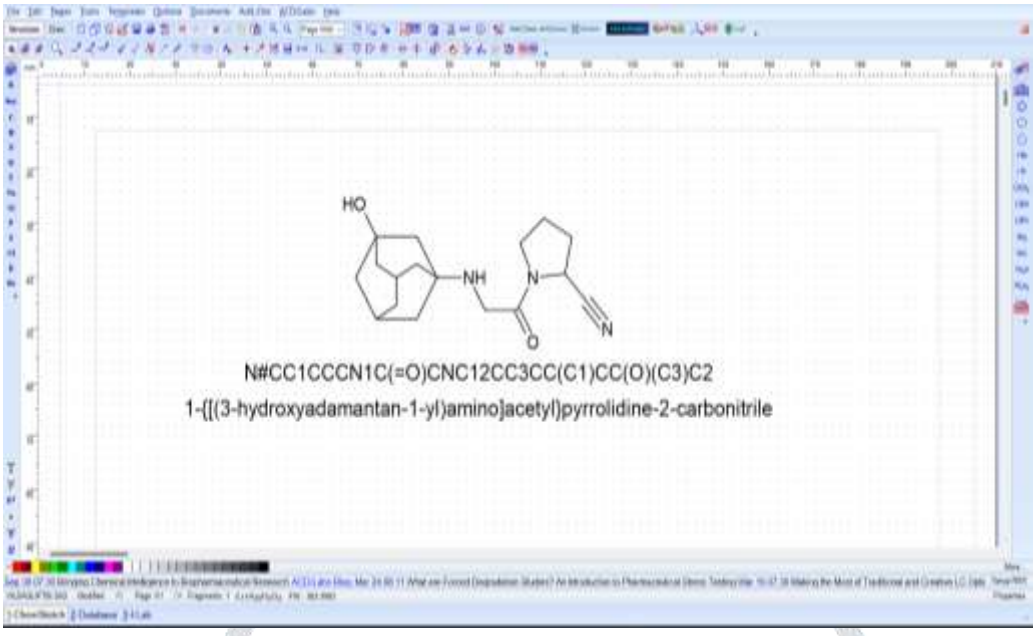


Figure No 5 Bioactivity of vildagliptin

3.2 Downloading and Installing all the required Software Programmes

a) Chemsketch
b) Avogadro
c) Pyrx
d) Discovery Studio

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 three dimensions, 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 allows molecules 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]

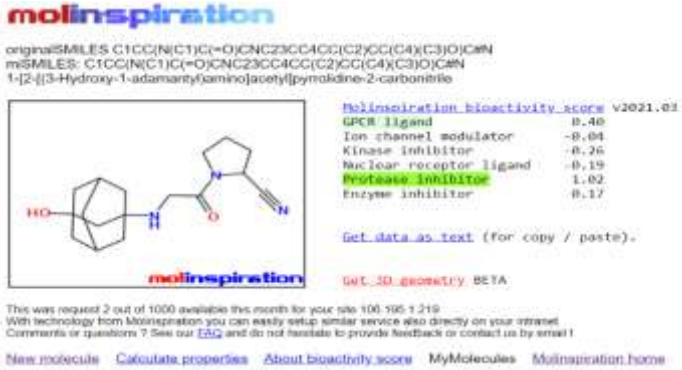


Figure No. 6 Chem Sketch

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]

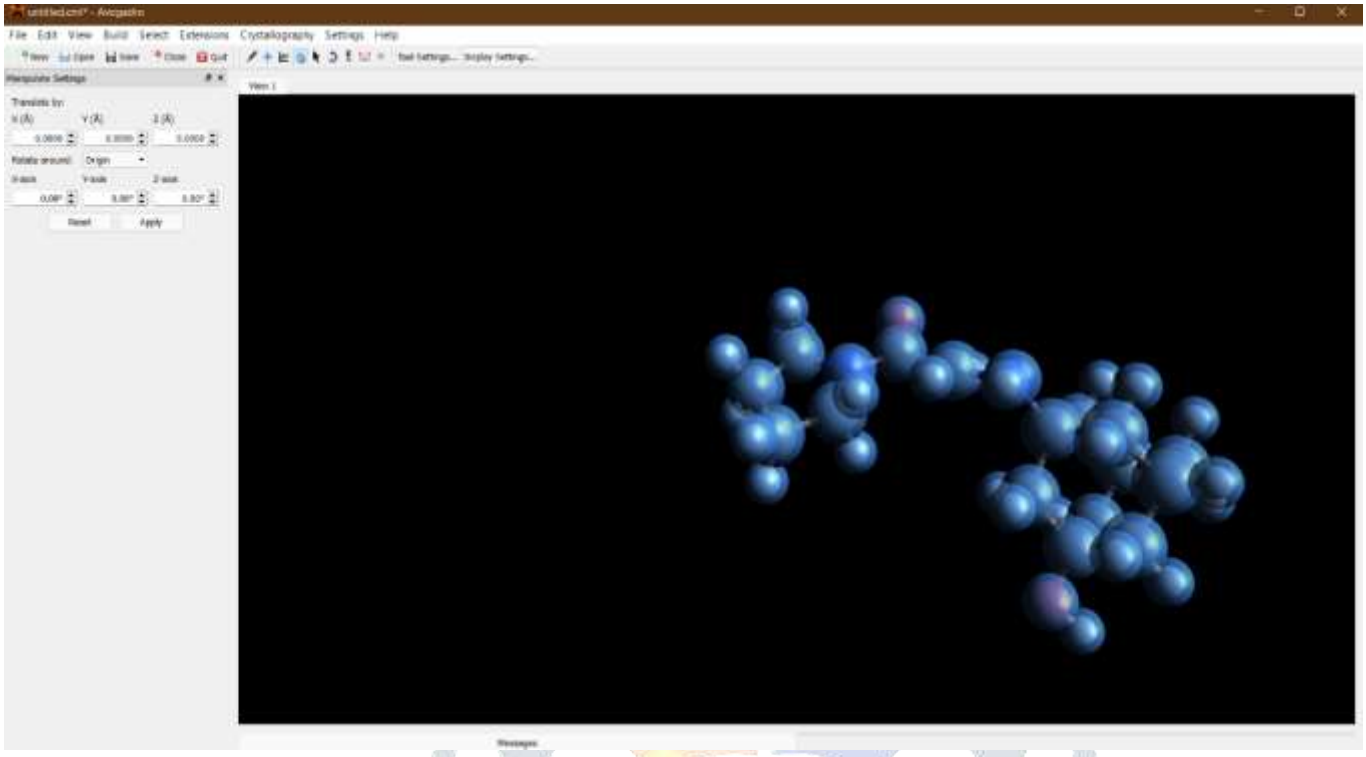


Figure No. 7 Avagadro

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 molecules to a target and segregate the best fit molecules from the library. The tool includes a 4 step 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]

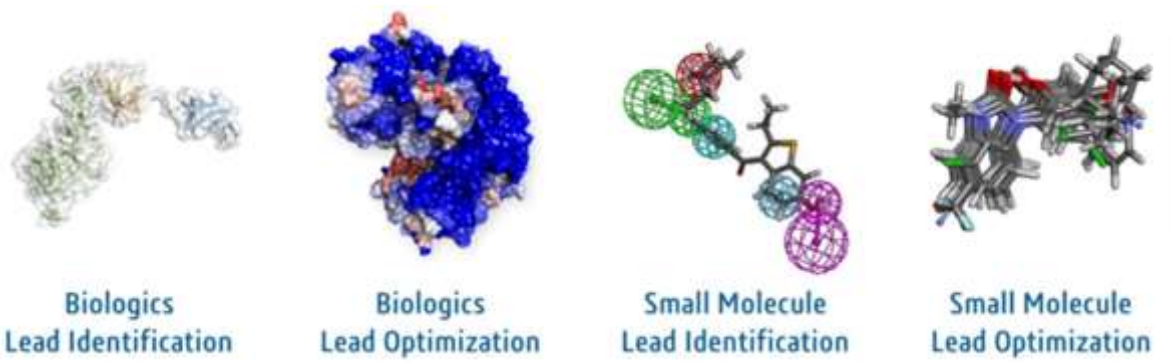


Fig. No. 8 Applications of discovery studio

With Discovery Studio you can:

• Investigate and test hypotheses in silico prior to costly experimental implementation, thus reducing the time and expense involved in bringing products to market

• Drive scientific exploration from target identification to lead optimization with a wealth of trusted life science modeling and simulation tools

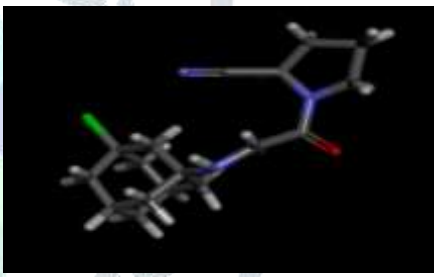
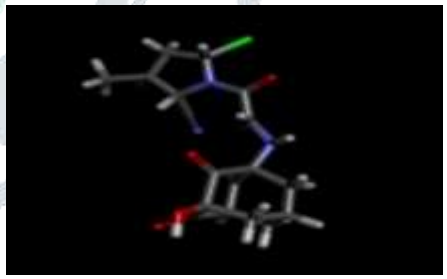
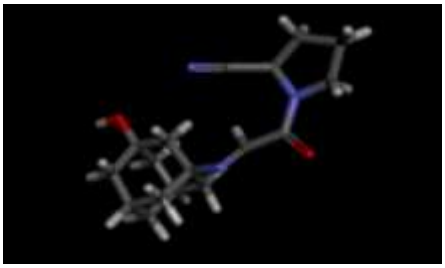
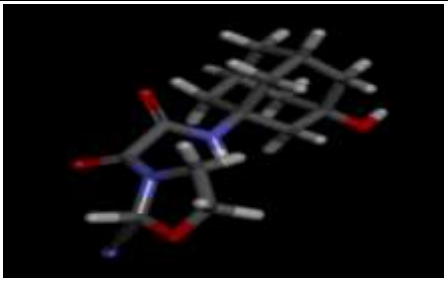
• Leverage BIOVIA Pipeline Pilot to automate processes, create and deploy custom workflows, and integrate data types, databases, and third-party or in-house tools

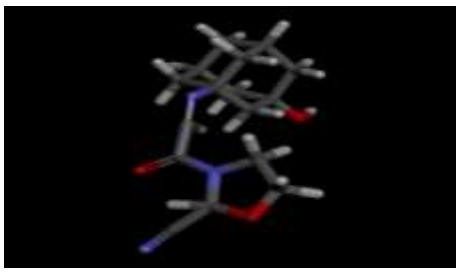
• Enhance personal productivity and boost team collaboration by enabling researchers to share data and make better informed decisions

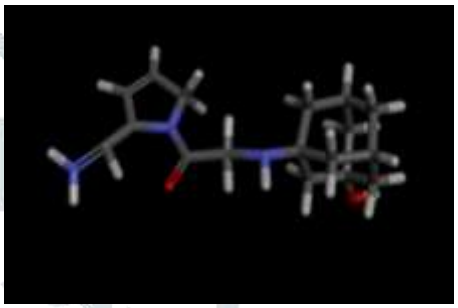
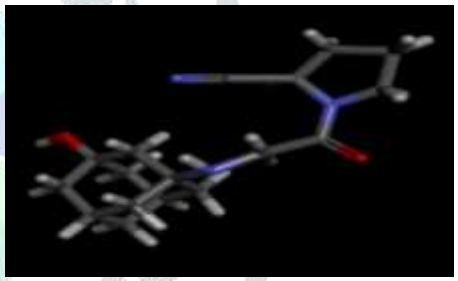
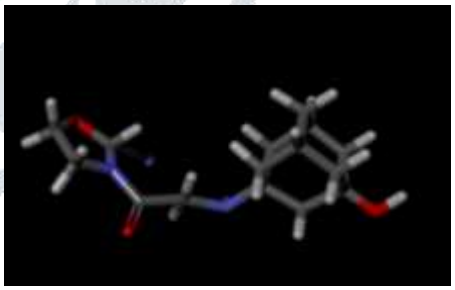
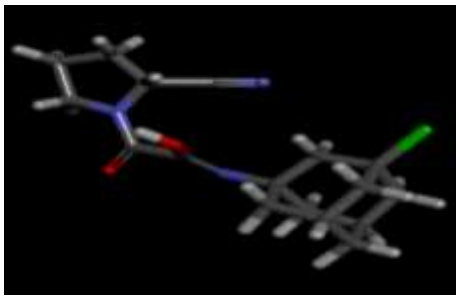
3.3 Preparation of ligand (structurally similar design derivatives)

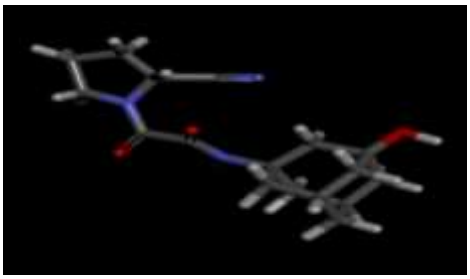
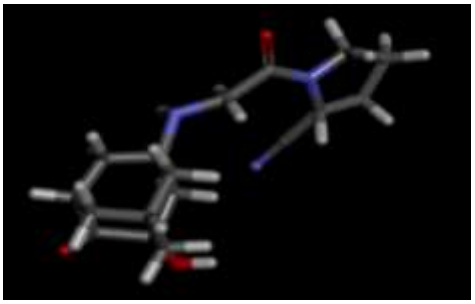
Ligand structure was drawn using Chemsketch software and the structure was cleaned using the clean structure tool. The structure was saved in the working folder as .mol file in a working folder. The .mol file present in working folder was then accessed in Avogadro software and structure was optimized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

Table No. List of derivatives design

Number and Code	**Name**	3D Structure
R0	Vildagliptin	
R1	1-{[(3-chloroadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile	
R2	5-chloro-1-{[(3-hydroxy-2,4,9-trioxoadamantan-1-yl)amino]acetyl}-3-methylpyrrolidine-2-carbonitrile	
R3	1-{(2*E*)-2-[(3-hydroxyadamantan-1-yl)imino]acetyl}pyrrolidine-2-carbonitrile	
R4	2-(2-cyano-1,3-oxazolidin-3-yl)-*N*-(3-hydroxyadamantan-1-yl)-2-oxoacetamide	

R5	3-{(2*E*)-2-[(3-hydroxyadamantan-1-yl)imino]acetyl}-1,3-oxazolidine-2-carbonitrile	

R6	2-(2-cyano-3,5-dihydroxypyrrolidin-1-yl)-*N*-(3-hydroxyadamantan-1-yl)-2-oxoacetamide	
R7	1-{[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidin-2-one	
R8	3-{[(3-hydroxyadamantan-1-yl)amino]acetyl}-1,3-oxazolidine-2-carbonitrile	
R9	(1*Z*)-*N*-(3-chloroadamantan-1-yl)(2-cyanopyrrolidin-1-yl)oxoethanimidic acid	

R10	2-(2-cyanopyrrolidin-1-yl)-*N*-(3-hydroxyadamantan-1-yl)-2-oxoacetamide	
R11	1-{[(3-hydroxy-4-oxoadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile	

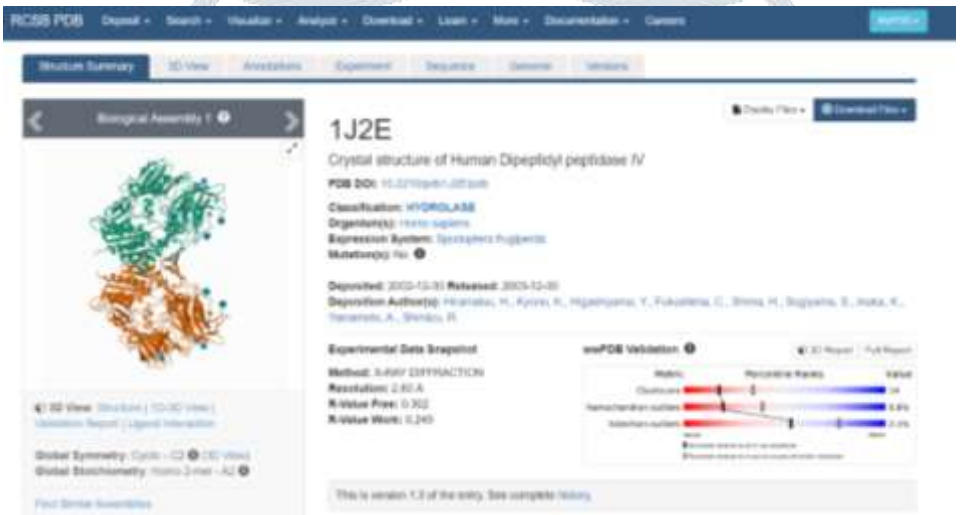


Figure no 9 Structure of 1J2E

3.4 Preparation of Protein Receptor

Open the Protein Data Bank site and Search for 1J2E and download in .pdb format from the online 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 and then saved in the working folder as .pdb file.

3.5 Virtual Screening through Pyrx

Now the PyRx software is used for virtual screening protocols. The Vina Wizard module was started, All the ligands and the enzyme were selected. Grid was selected and the Screening was carried out. Result was analysed using Discovery Studio Visualizer.

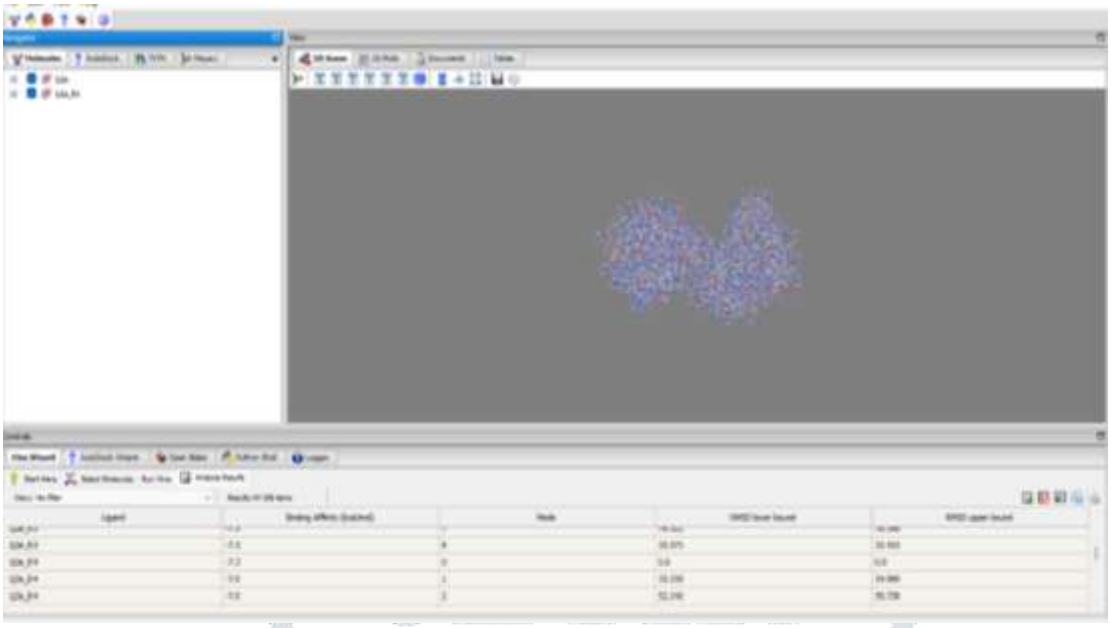


Figure No: 10. Virtual Screening of Vildagliptin and Derivatives

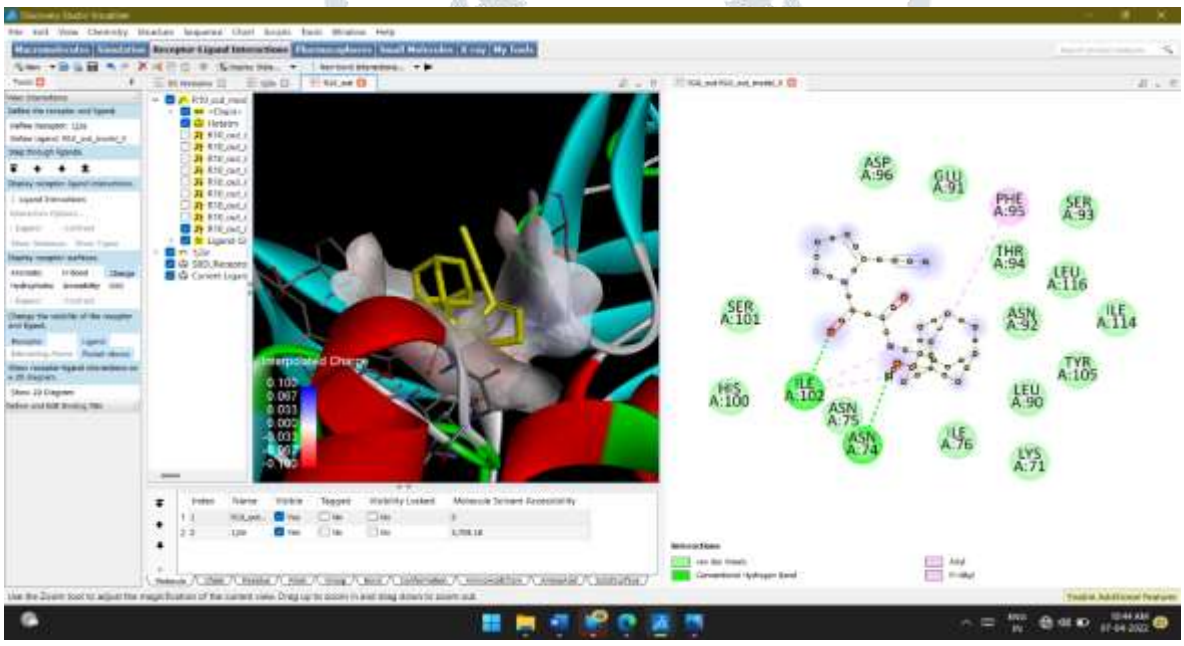


Figure No: 11. Visualisation of Drug Bonds

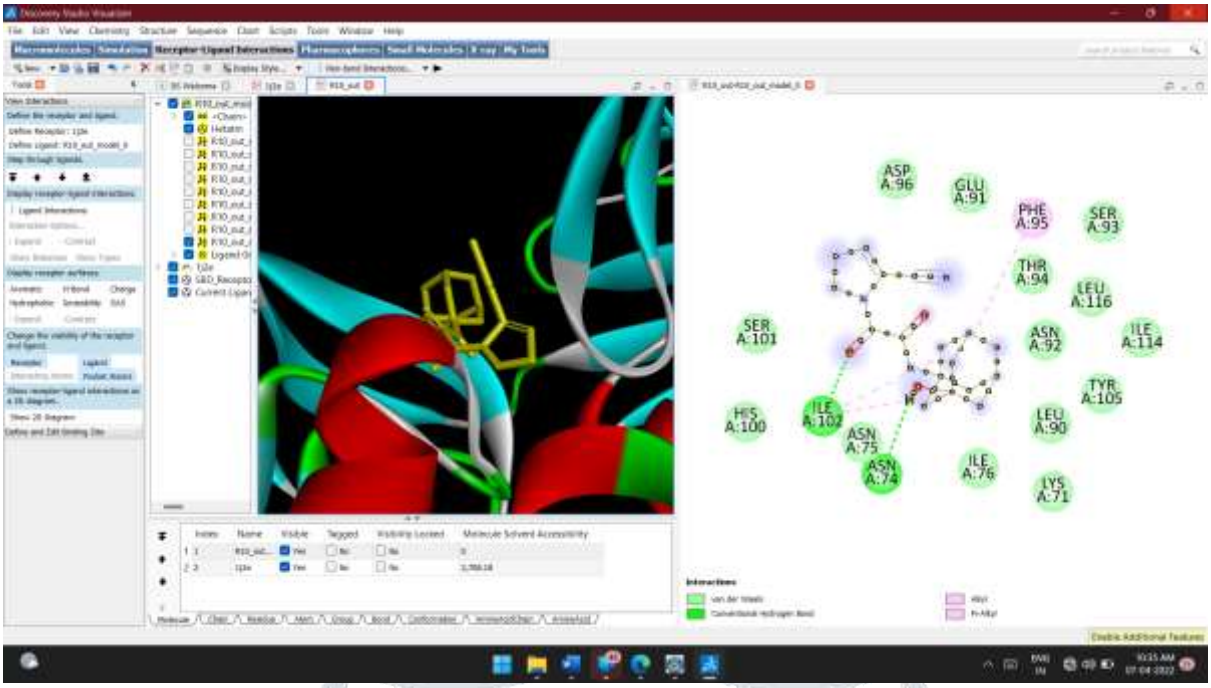


Figure No: 12. Receptor-Ligand Interaction

4. 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 affinity of -8 Kcal/mol.

Table. No:2. Result of Modified Ligand with Their Binding Affinity

Ligand	Binding Affinity
Vildagliptin	-8
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. CONCULSION

The Study showed that R10 (binding affinity = - 9.1 kcal/mol) showed best binding among all the change that were made on the Vildagliptin.R1, R3, R8, R11 likewise show preferred binding partiality over that of Vildagliptin. Other than that R2, R5, R6, R7 show slight low binding affinity than that of Vildagliptin. R4, R9 shows exceptionally low binding affinity than that of Vildagliptin.

Thus, from the above outcome we can say that R10 can be utilized as an option in contrast to Vildagliptin and further concentrate on R10 ought to be done to get it's Pharmacology in better manner.

6. REFERENCES

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