RESEARCH PAPER

In Silico Molecular Docking and ADMET Evaluation of Sulfonylurea Derivatives as Potential Antidiabetic Agents

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ABSTRACT

Background: Diabetes mellitus is a global metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Sulfonylureas are a widely used class of oral antidiabetic agents that act by stimulating insulin release from pancreatic β-cells through inhibition of the ATP-sensitive potassium (K_{ATP}) channel. Despite their clinical efficacy, sulfonylureas are associated with adverse effects such as hypoglycemia and weight gain, necessitating the development of safer and more potent derivatives.

Objective: To evaluate the binding affinity, drug-likeness, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of a series of sulfonylurea derivatives as potential antidiabetic agents using in silico molecular docking and computational ADMET prediction.

Methods: A library of sulfonylurea derivatives was subjected to molecular docking against the sulfonylurea receptor 1 (SUR1) subunit of the K_{ATP} channel using AutoDock Vina. The binding energies and interaction profiles of the derivatives were compared with those of glibenclamide and gliclazide as reference standards. Drug-likeness was assessed using Lipinski's Rule of Five, and ADMET properties were predicted using SwissADME and pkCSM online tools.

Results: Several sulfonylurea derivatives demonstrated binding affinities comparable to or better than the reference drugs, with binding energies ranging from −9.8 to −11.2 kcal/mol. Key interactions included hydrogen bonding with Arg306, Lys322, and Tyr323, and hydrophobic interactions with Phe310 and Leu315. All compounds satisfied Lipinski's Rule of Five, indicating good oral bioavailability. ADMET predictions suggested favourable absorption and distribution profiles, with moderate to low toxicity risks. Two derivatives (compounds 8 and 12) exhibited superior binding affinity and favourable ADMET profiles, making them promising candidates for further development.

Conclusion: The in silico analysis identified novel sulfonylurea derivatives with promising binding interactions and acceptable ADMET properties. These compounds warrant further in vitro and in vivo evaluation to confirm their antidiabetic potential and safety profile.

Keywords: Sulfonylurea; Molecular docking; ADMET; Diabetes; K_{ATP} channel; Antidiabetic agents.

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INTRODUCTION

Introduction In recent years, computational approaches have emerged as indispensable tools in modern scientific research, particularly in the fields of drug discovery, medicinal chemistry, and molecular biology. The term *in silico* refers to experiments performed using computer-based simulations, complementing traditional *in vitro* and *in vivo* methodologies. These approaches enable rapid screening of compounds, prediction of molecular interactions, and optimization of drug candidates, significantly reducing both time and cost associated with experimental research. The growing integration of computational tools into

pharmaceutical sciences has revolutionized the early stages of drug development, allowing researchers to analyze complex biological systems with high precision [1,2]. Recent studies have demonstrated that molecular docking combined with ADMET prediction plays a crucial role in accelerating drug discovery pipelines and improving candidate selection efficiency [3].

Advancements in bioinformatics, molecular modeling, and cheminformatics have further expanded the scope of *in silico* techniques. These methods facilitate the prediction of pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, excretion, and toxicity (ADMET), thereby improving the success rate of drug candidates in clinical development [4]. Several recent investigations have highlighted the integration of docking, molecular dynamics, and ADMET profiling as a comprehensive strategy for identifying bioactive compounds with high therapeutic potential [5]. Consequently, computational strategies are now widely adopted across academia and the pharmaceutical industry for rational drug design and target identification.

Among various therapeutic areas, diabetes mellitus remains a major global health challenge requiring continuous drug development efforts. Diabetes mellitus (DM) is a chronic, multifactorial metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [6]. Recent studies emphasize that diabetes is associated with severe long-term complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy, contributing significantly to global morbidity and mortality [7].

The global burden of diabetes has increased dramatically over recent decades, driven by factors such as urbanization, sedentary lifestyles, and dietary changes. Emerging research indicates that the prevalence of diabetes continues to rise rapidly, particularly in developing regions, highlighting the urgent need for novel therapeutic strategies [8].

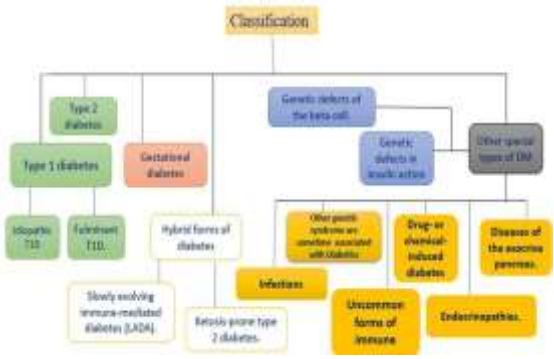
At the molecular level, insulin plays a critical role in maintaining glucose homeostasis by facilitating glucose uptake and utilization in peripheral tissues. Impaired insulin secretion or insulin resistance disrupts this balance, leading to chronic hyperglycemia. Prolonged hyperglycemia can result in metabolic complications, including ketone body formation and oxidative stress, which further aggravate disease progression [9].

Sulfonylureas are among the earliest and most widely used classes of oral antidiabetic agents. They exert their pharmacological action by stimulating insulin release from pancreatic β-cells through inhibition of ATP-sensitive potassium (K_ATP) channels [10]. Despite their therapeutic effectiveness, conventional sulfonylureas are associated with limitations such as hypoglycemia, reduced durability, and adverse metabolic effects, necessitating the development of improved derivatives [11].

In this context, *in silico* methods provide a powerful platform for the rational design and evaluation of novel drug candidates. Molecular docking enables the prediction of ligand–protein interactions at the atomic level, while ADMET analysis provides insights into pharmacokinetic behavior and toxicity profiles. Recent studies on antidiabetic compounds have successfully utilized these approaches to identify potential inhibitors targeting enzymes such as α-glucosidase and glucokinase [12]. Additionally, computational evaluation of sulfonamide and related derivatives has demonstrated promising binding affinity and drug-likeness properties, supporting their role in antidiabetic drug development [13].

Therefore, the present study aims to investigate the molecular docking interactions and ADMET properties of selected sulfonylurea derivatives to evaluate their potential as antidiabetic agents. This study contributes to ongoing efforts in developing safer and more effective therapeutic options for diabetes management using advanced computational drug design strategies.

1.2. CLASSIFICATION OF DM



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1.4. CLASSIFICATION OF ANTIDIABETIC DRUGS

1.2 Classification of Diabetes Mellitus

Diabetes mellitus (DM) is a heterogeneous metabolic disorder comprising multiple etiological subtypes characterized by chronic hyperglycemia. Based on pathophysiology and clinical presentation, DM is broadly classified into Type 1 diabetes, Type 2 diabetes, gestational diabetes, and other specific forms of diabetes [14].

1.2.1 Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus is a chronic autoimmune disorder characterized by the destruction of pancreatic β-cells, resulting in absolute insulin deficiency. It commonly manifests during childhood or adolescence, although it can occur at any age. The absence of insulin leads to impaired glucose utilization and accumulation of glucose in the bloodstream, resulting in hyperglycemia.

The pathogenesis of T1DM involves immune-mediated destruction of β-cells, primarily driven by autoreactive T lymphocytes. As β-cell mass declines, insulin secretion progressively decreases, ultimately leading to complete insulin deficiency. Consequently, individuals with T1DM require lifelong insulin therapy and continuous monitoring of blood glucose levels to prevent complications [15].

1.2.1.1 Idiopathic Type 1 Diabetes

Idiopathic T1DM represents a non-autoimmune form in which the exact cause of β-cell dysfunction remains unclear. The disease progression is marked by a gradual decline in insulin secretion, which may begin years before clinical diagnosis. Early metabolic changes, including alterations in glucose tolerance and C-peptide levels, can serve as predictive indicators of disease onset [16]. Following diagnosis, insulin secretion continues to decline over time, often exhibiting a biphasic pattern, with a more rapid decrease during the initial phase.

1.2.1.2 Fulminant Type 1 Diabetes

Fulminant Type 1 diabetes is a rare and rapidly progressive subtype first reported in Japan. Unlike classical T1DM, it is not primarily associated with autoimmune mechanisms. The condition is characterized by sudden onset of hyperglycemia and rapid development of diabetic ketoacidosis.

Patients typically exhibit near-complete β-cell destruction at diagnosis, with extremely low or undetectable serum C-peptide levels. Environmental and genetic factors, along with viral infections, have been implicated in disease pathogenesis [17,18].

1.2.2 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is the most prevalent form of diabetes and is characterized by insulin resistance combined with impaired insulin secretion. Insulin resistance reduces the ability of peripheral tissues to respond to insulin effectively, while β-cell dysfunction limits compensatory insulin production.

The interaction between insulin sensitivity and secretion is commonly assessed using the disposition index, which is reduced in individuals with T2DM, indicating impaired β-cell compensation [19]. Chronic hyperglycemia further exacerbates β-cell dysfunction and contributes to disease progression [20].

1.2.3 Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus is defined as glucose intolerance first recognized during pregnancy. It is associated with significant maternal and fetal complications, including macrosomia, preeclampsia, preterm delivery, and increased cesarean section rates.

Offspring of affected mothers are at higher risk of developing obesity and Type 2 diabetes later in life. Risk factors include obesity, advanced maternal age, family history of diabetes, and physical inactivity [21,22].

1.2.4 Hybrid and Intermediate Forms of Diabetes

1.2.4.1 Latent Autoimmune Diabetes in Adults (LADA)

LADA is a slowly progressive autoimmune form of diabetes characterized by the presence of pancreatic autoantibodies. Patients initially respond to oral therapy but eventually require insulin due to progressive β-cell failure [23].

1.2.4.2 Ketosis-Prone Type 2 Diabetes

Ketosis-prone diabetes presents with episodic diabetic ketoacidosis in the absence of autoimmune markers. Although patients may initially require insulin, many achieve temporary remission, though recurrence is common [24].

1.2.5 Other Specific Types of Diabetes

1.2.5.1 Genetic Defects of β-Cell Function (MODY)

MODY is a monogenic disorder caused by mutations affecting β-cell function [25].

1.2.5.2 Genetic Defects in Insulin Action

Mutations affecting insulin receptors can result in insulin resistance syndromes [26].

1.2.5.3 Diseases of the Exocrine Pancreas

Pancreatic disorders such as pancreatitis and pancreatic cancer can impair insulin secretion [27].

1.2.5.4 Endocrinopathies

Hormonal disorders including Cushing's syndrome and acromegaly can interfere with insulin action [28].

1.2.5.5 Drug- or Chemical-Induced Diabetes

Certain medications, such as glucocorticoids, can impair insulin sensitivity [14].

1.2.5.6 Immune-Mediated Diabetes

Rare autoimmune conditions can disrupt insulin signaling and contribute to diabetes [29].

1.2.5.7 Genetic Syndromes Associated with Diabetes

Genetic conditions such as Down syndrome and Turner syndrome are associated with increased diabetes risk [25].

1.2.5.8 Infections
Certain viral infections have been implicated in β-cell destruction [30].

1.3 Clinical Symptoms of Diabetes Mellitus
Diabetes mellitus presents with clinical manifestations associated with chronic hyperglycemia.

1.3.1 Polyuria and Polydipsia
Hyperglycemia leads to osmotic diuresis, resulting in excessive urination and thirst.

1.3.2 Unintentional Weight Loss, Impaired glucose utilization leads to breakdown of fat and muscle.

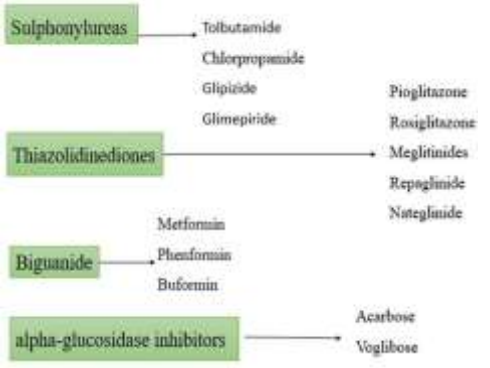
1.3.3 Blurred Vision, Hyperglycemia affects lens function.

1.3.4 Delayed Wound Healing, Microvascular damage slows tissue repair.

1.3.5 Increased Susceptibility to Infections, Elevated glucose impairs immune response.

1.3.6 Fatigue Reduced glucose uptake leads to decreased energy production [31].

CLASSIFICATION OF ANTIDIABETIC DRUGS



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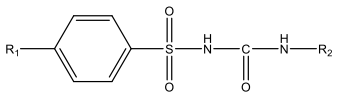
1.4.1. SULPHONYL UREA DERIVATIVES



Sulfonylurea derivatives constitute an important class of oral antidiabetic agents widely used in the management of type 2 diabetes mellitus. These compounds are broadly classified into first- and second-generation sulfonylureas, with the latter exhibiting greater potency, improved pharmacokinetic profiles, and reduced dosing requirements. Their primary mechanism of action involves stimulation of insulin secretion from pancreatic β-cells through inhibition of ATP-sensitive potassium (K_ATP) channels, leading to membrane depolarization, calcium influx, and subsequent insulin release. In addition to enhancing insulin secretion, sulfonylureas have been reported to exert modest effects on reducing hepatic glucose production, thereby contributing to improved glycemic control [32].

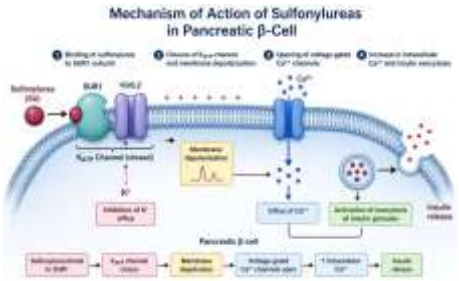
1.4.1.1. First Generation: Examples included
- Tolbutamide
- Tolazamide
- Chlorpropamide
- acetohexamide

1.4.1.2. Second Generation: Examples included
- Glyburide
- Gliclazide
- Glipizide
- glimepiride.

MECHANISM OF ACTION OF SULFONYLUREAS

Sulfonylureas are a class of oral hypoglycemic agents that function as **insulin secretagogues**, enhancing endogenous insulin release from pancreatic β-cells. Their pharmacological activity is mediated through **ATP-sensitive potassium (K_ATP) channels**, which play a critical role in coupling cellular metabolism to insulin secretion. These channels are hetero-octameric complexes consisting of four pore-forming **inwardly rectifying potassium channel (Kir6.x; Kir6.1 or Kir6.2)** subunits and four regulatory **sulfonylurea receptor (SUR; SUR1, SUR2A, or SUR2B)** subunits. The specific composition of K_ATP channels varies among tissues; however, pancreatic β-cells predominantly express the **SUR1/Kir6.2** isoform.

Sulfonylureas selectively bind to the **SUR1** subunit of pancreatic β-cell K_ATP channels, inducing channel closure and preventing potassium efflux. The resulting membrane depolarization activates **voltage-dependent calcium channels (VDCCs)**, leading to an influx of extracellular calcium ions. The consequent elevation in intracellular calcium concentration triggers the exocytosis of insulin-containing secretory granules, thereby increasing insulin release into the circulation. Through this mechanism, sulfonylureas effectively lower blood glucose concentrations in individuals with preserved β-cell function (MacDonald & Wheeler, 2003; Thompson & Satin, 2021).



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2. MATERIALS AND METHODS

In the present study, a combination of advanced computational tools and molecular modeling platforms was employed to facilitate rational drug design and in silico evaluation of sulfonylurea derivatives. These tools were utilized for ligand preparation, molecular docking, visualization of protein–ligand interactions, and structural analysis. The workflow integrated multiple software systems, including PyRx, PyMOL, Discovery Studio Visualizer, PubChem, ChemSketch, and ChemDraw, each serving a specific role in the drug discovery pipeline [35–39].

2.1 Molecular Docking Using PyRx

Virtual screening and molecular docking studies were performed using PyRx, an open-source platform that integrates AutoDock Vina for predicting ligand–protein interactions [35,36]. A library of designed sulfonylurea derivatives was subjected to docking against the selected target protein.

Protein structures were imported in PDB format and prepared by removing water molecules and adding hydrogen atoms where necessary. Ligand structures were converted into PDBQT format using the Open Babel module, followed by energy minimization to obtain stable conformations [37].

The docking grid box was defined around the active site of the target protein to ensure accurate binding predictions. The grid dimensions were set to 20 × 20 × 20 Å, with appropriate center coordinates (X, Y, Z). Default docking parameters of AutoDock Vina were maintained. Binding affinities (kcal/mol) and docking poses were recorded, and the best conformations were selected based on minimum binding energy and interaction profiles.

2.2 Molecular Visualization Using PyMOL

Three-dimensional visualization and structural analysis were conducted using PyMOL, developed by Schrödinger [38]. This software enabled detailed examination of protein structures and docking conformations.

Top-ranked ligand–protein complexes obtained from docking studies were analyzed to evaluate binding orientation, hydrogen bonding, hydrophobic interactions, and steric compatibility within the active site. Key amino acid residues involved in ligand binding were identified using PyMOL's selection and labeling tools. Additionally, high-resolution images were generated for graphical representation in the results section.

2.3 Interaction Analysis Using Discovery Studio Visualizer

Further interaction analysis was carried out using Discovery Studio Visualizer by BIOVIA [39]. This platform provided detailed insights into molecular interactions and pharmacophoric features.

Both 2D and 3D interaction diagrams were generated to identify key non-covalent interactions, including hydrogen bonds, van der Waals forces, π–π stacking, and hydrophobic contacts. These analyses were used to validate docking results and compare binding efficiencies among different ligands.

2.4 Ligand Retrieval from PubChem

Chemical structures of selected ligands were obtained from PubChem, a publicly accessible database maintained by the National Center for Biotechnology Information [40,41].

Ligands were downloaded in SDF format and selected based on criteria such as Lipinski's Rule of Five, structural diversity, and reported biological activity. Additional molecular descriptors, including SMILES notation, InChI keys, and physicochemical properties, were utilized for compound characterization and documentation.

2.5 Structure Design Using ChemSketch

Chemical structures not available in public databases were manually constructed using ACD/ChemSketch [42]. This tool enabled the generation of 2D molecular structures, calculation of molecular properties, and prediction of physicochemical parameters such as molecular weight and logP. The software also facilitated structural optimization and conversion into appropriate formats (e.g., MOL, SMILES) for further computational analysis.

2.6 Chemical Drawing Using ChemDraw

Advanced chemical structure design and annotation were performed using ChemDraw, developed by PerkinElmer [43]. Ligand structures were drawn and converted into three-dimensional formats using external tools such as CORINA [44].

ChemDraw was also used to generate publication-quality figures representing chemical structures, reaction pathways, and ligand design strategies. Structure validation was ensured using built-in IUPAC naming and structure-cleaning features.

3. SYNTHESIS OF NOVEL SULFONYLUREA DERIVATIVES

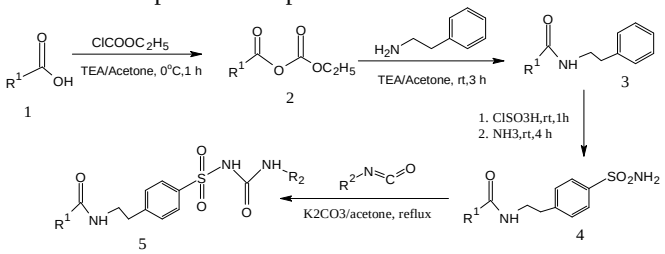
3.1 General Synthetic Procedure (Grunewald et al., 2006)

The synthesis of novel sulfonylurea derivatives was carried out using a multi-step reaction pathway involving sulfonamide intermediates and isocyanate coupling [43].

Initially, substituted carboxylic acids were reacted with 2-phenethylamine in the presence of ethyl chloroformate and triethylamine using anhydrous acetone as the solvent, resulting in the formation of corresponding amide intermediates.

Subsequently, the amide intermediates underwent chlorosulfonation to yield sulfonyl chloride derivatives (Intermediate 4, as shown in Scheme 1), followed by quenching with aqueous ammonia to produce sulfonamide intermediates.

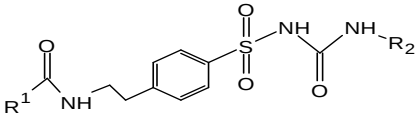
In the final step, these intermediates were reacted with appropriate isocyanates under controlled conditions to yield the target sulfonylurea derivatives (N1–N6), as **illustrated in Scheme 2.** The synthesized compounds were purified and characterized prior to computational evaluation.



Reaction scheme

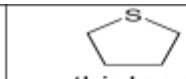
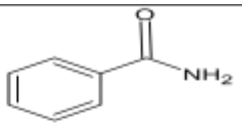
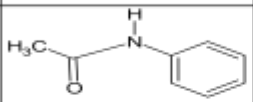
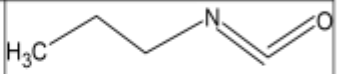
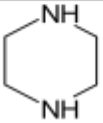
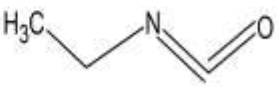
Sulfonylureas constitute a well-established class of oral antidiabetic agents characterized by a core **S-aryl sulfonylurea pharmacophore**. Structurally, these compounds typically contain a substituted phenyl ring—often bearing a para-substituent—linked to a sulfonylurea moiety, with diverse functional groups attached at the terminal N′-position. Structural variations at these positions significantly influence their pharmacokinetic and pharmacodynamic properties.

Pharmacologically, sulfonylureas are widely used in the management of **Type 2 diabetes mellitus** due to their ability to enhance endogenous insulin secretion. They exert their therapeutic effect by stimulating pancreatic β-cells, thereby increasing insulin release in response to elevated blood glucose levels. This insulinotropic activity makes them particularly effective in patients with residual β-cell function.



Different substitution in R1 and R2 group

Table: 1:

S N	R_1	R2
1		
2		
3		
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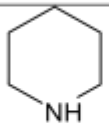
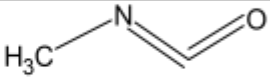
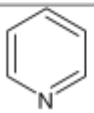
5		
6		

REPORTED HYPOGLYCEMIC DERIVATIVES OF SULFONYLUREA

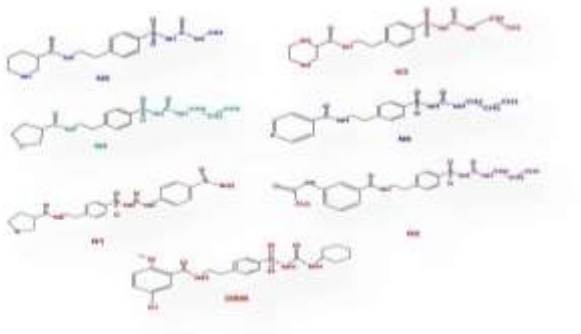


Figure: 4

Table: 2. IUPAC name and Smiles number of Sulfonylurea Derivatives

Code no	IUPAC	Smiles
Glibenclamide (GBM)	.5-chloro-*N*-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-2-methoxybenzamide.	COC1=C(C=C(C=C1)Cl)C(=O)NCCC2=CC=C(C=C2)S(=O)(=O)NC(=O)NC3CCCCC3
N1	.*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenethyl)piperidine-3-carboxamide.	O=[S@@](=O)(NC(=O)Nc1ccc(cc1)C(=O)N)c1ccc(CCNC(=O)C2CSCC2)cc1
N2	.3-acetamido-*N*-(4-(*N*-(propylcarbamoyl)sulfamoyl)phenethyl)benzamide.	O=[S@@](=O)(NC(=O)NCCC)c1ccc(cc1)CCNC(=O)c1cccc(NC(=O)C)c1
N3	*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenethyl)piperidine-3-carboxamide	O=S(=O)(NC(=O)NCC)c1ccc(CCNC(=O)C2NCCNC2)cc1
N4	*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenethyl)piperidine-3-carboxamide	O=S(=O)(NC(=O)NCCC)c1ccc(CCNC(=O)C2CCOC2)cc1
N5	*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenethyl)piperidine-3-carboxamide	O=S(=O)(NC(=O)NC)c1ccc(CCNC(=O)C2CCCNC2)cc1
N6	*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenethyl)piperidine-3-carboxamide	O=[S@@](=O)(NC(=O)NCCC)c1ccc(CCNC(=O)c2ccncc2)cc1

4. IN-SILICO MOLECULAR DOCKING STUDIES

4.1. TARGET PROTEIN SELECTION AND PREPARATION

Based on an extensive literature survey, the protein structure with **PDB ID: 4YVP** was selected as a relevant molecular target for antidiabetic investigation, as it represents the crystal structure of

human aldo–keto reductase 1C1 (AKR1C1) in complex with the hypoglycemic drug **Glibenclamide**. AKR1C1 is implicated in metabolic regulation and has been explored as a potential therapeutic target in diabetes-related pathways [35,36].

The FASTA sequence corresponding to the 4YVP structure was retrieved from the **National Center for Biotechnology Information (NCBI)** database. To validate sequence similarity and structural relevance, a **Basic Local Alignment Search Tool (BLAST)** analysis was performed against the **Protein Data Bank (PDB)**. The top 5–10 homologous protein sequences were shortlisted based on **query coverage, percentage identity, and E-value**, ensuring the selection of a structurally reliable and biologically relevant target [37].

The three-dimensional X-ray crystallographic structure of AKR1C1 (PDB ID: 4YVP) was downloaded from the PDB database and prepared using the **Protein Preparation Wizard** implemented in **Maestro (Schrödinger, version 14.1)**. The preparation protocol involved multiple steps, including the addition of missing hydrogen atoms, assignment of bond orders, and correction of structural inconsistencies. Water molecules located beyond 5 Å from the co-crystallized ligand were removed to avoid interference with ligand binding analysis.

Subsequently, the protein structure was subjected to **geometry optimization**, with a maximum root mean square deviation (RMSD) cutoff of 0.3 Å to minimize steric clashes and improve structural stability. Protonation states of ionizable residues were assigned using **Epik (v3.4)** at a physiological pH range of **7.0 ± 2.0**, ensuring biologically relevant ionization conditions [38].

4.2. Molecular Docking Studies

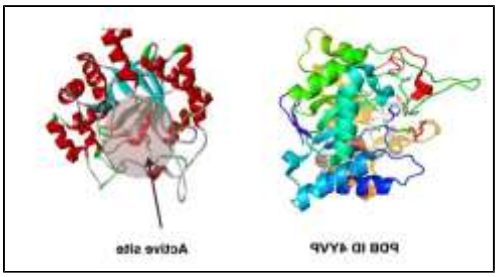
Molecular docking simulations were performed using the **Glide module** (Schrödinger Suite) to evaluate the binding affinity and interaction profiles of the designed sulfonylurea derivatives with the AKR1C1 target protein (PDB ID: 4YVP). The receptor grid was generated around the active binding site defined by the co-crystallized ligand.

Docking calculations were carried out under standard precision (SP) mode, and the resulting poses were ranked based on **Glide docking score (kcal/mol)**, which reflects the predicted binding affinity. In addition to docking scores, detailed interaction analyses were performed, including evaluation of:

- Hydrogen bonding interactions
- Hydrophobic contacts
- Electrostatic interactions
- van der Waals forces

These parameters provided insights into the stability and specificity of ligand–protein interactions. The best-performing sulfonylurea derivatives were identified based on their **binding energy, interaction patterns, and compatibility with key active site residues** of AKR1C1 [39,40].

Fig: 5. 3D structure of 4YVP



4.3 Virtual Screening Using PyRx

Virtual screening and docking optimization were performed using **PyRx**, incorporating the **AutoDock Vina (version 1.2.3)** engine to predict ligand–protein binding affinities. All designed sulfonylurea derivatives, along with the prepared target protein (PDB ID: 4YVP), were imported into the PyRx workspace for docking simulations.

Prior to docking, ligands were energy-minimized, and the receptor structure was prepared to ensure proper geometry and protonation states. The docking grid was defined around the active site of the enzyme to enable accurate prediction of ligand binding orientations. A grid spacing of **0.375 Å** was applied, and the grid box was centered on the active site to maximize coverage of potential interaction regions.

The grid parameters were configured using the following coordinates:

- **Center (X, Y, Z):** −52.746, −0.304, 43.450
- **Dimensions (Å):** X = 24.89, Y = 26.39, Z = 24.34

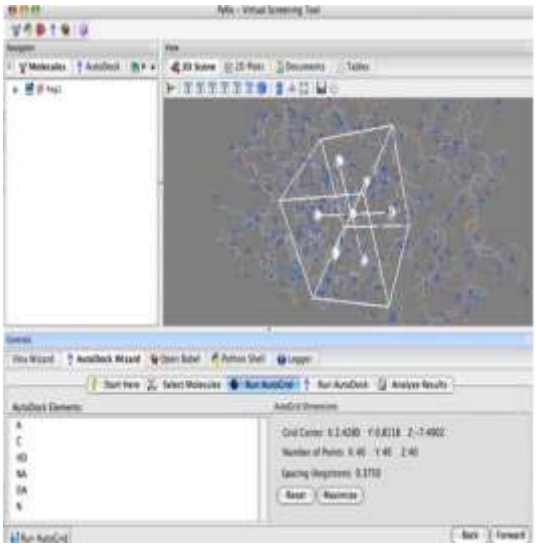
Additionally, a standardized grid box of **20 × 20 × 20 Å** was employed for comparative docking analysis. Default docking parameters of AutoDock Vina were maintained throughout the study. This setup enabled efficient exploration of ligand conformations and identification of energetically favorable binding poses.

Binding affinities were calculated in terms of **kcal/mol**, and the best docking conformations were selected based on minimum binding energy and optimal interaction profiles. The compact grid design ensured that the docking search space was restricted to the biologically relevant active site, thereby improving accuracy and computational efficiency.

The virtual screening library consisted of **six designed sulfonylurea derivatives**, which were evaluated for their binding potential against the

AKR1C1 enzyme. Post-docking analysis, including visualization of binding interactions and identification of key residues, was performed using **Discovery Studio Visualizer**, enabling detailed assessment of hydrogen bonding, hydrophobic interactions, and other non-covalent forces [41,42,43].

Fig: 6. Window of PyRx software with grid box



4.3. MOLECULAR.DOCKING STUDY

Docking is the process of estimating a derivative's activity and affinity for suitable protein targets. For docking investigations, AutoDock Vina, an open-source docking tool, was used. Protein preparation and visualization were done using PyMOL. Docking analysis was performed using PyRx.

STEP 1 – Preparation of ligands.

- Ligands may be submitted separately as files or drawn using a Java-based applet. Multiple ligands may also be uploaded in batches.
- In order to prepare ligands, structurally comparable derivatives have to be designed. ChemDraw Ultra 8.0 and ChemSketch 12.0 were used to generate the 3D chemical structures at first, and the Corina online tool was then used to convert them to PDB format.
- Ligands may be uploaded in MDL MOL, SYBYL MOL2, PDB, and SMILES, among other formats. It supports the SDF format for multiple ligands.
- Atom kinds and rotatable bonds may be manually or automatically allocated as necessary.
- Several formats, including MOL, PDB, MOL2, and PDBQT, are available for download as processed ligand files.
- To make project administration easier, ligands may be arranged into user-defined folders.

STEP 2 – Preparation of proteins.

- Protein structures may be directly uploaded or obtained using Docking Server by searching for keywords or providing the PDB ID from the Protein Data Bank (PDB).
- Chains, heteroatoms, ligands, and water molecules are among the PDB file components that users may choose to include in the docking calculations during protein setup.
- The following configuration options are available for the simulation box:

1. With a co-crystallized ligand, a known binding site may be found.
2. Through the selection of the protein molecule's center of mass.
3. By providing the box center's coordinates and the amino acid residues that define the binding pocket.

- The Molecular Docking Server prepares all the input data needed for docking simulations and creates the requisite map files for every kind of atom.

STEP 3– Setup ligand. Protein docking. Calculations

- From the generated molecular library, choose a protein and a ligand for docking study.
- Before running, advanced simulation parameters may be changed, including the number of runs, energy assessments, and other docking variables.

STEP 4 – Evaluation. of results

- The rendering capabilities of the Molecular Docking Server may be used to create visual representations, or they can be chosen from the gallery of existing images.
- Examine secondary interactions between the protein and ligand, such as π–π interactions, hydrophobic contacts, and hydrogen bonds, when the simulation is finished.

3.4. Lipinski rule of five:(Benet et al., 2016)

The Rule of Five, proposed by Lipinski, is a commonly used principle in pharmaceutical research to evaluate whether a compound has the potential to be orally active in humans. It predicts a drug's behavior in the body—covering aspects like absorption, distribution, metabolism, and excretion—by examining specific physicochemical traits.

1. Molecular weight > 500,
2. C log P > 5,
3. H-bond donors > 5
4. H-bond acceptors > 10.

Lipinski's Rule of Five states that a drug intended for oral administration should not violate more than one of its outlined criteria. The term 'Rule of Five' originates from the fact that each parameter in the rule involves values that are multiples of five.

Table: 3. Compound showing Lipinski's Rule parameter

Compound Code	Mo. Wet (g/mol)	H-bond donor	H-bond acceptor	Clog P	Drug likeness
Glibenclamide (GBM)	494.00	3	5	3.58	Yes
N1	493.70	4	5	1.23	Yes
N2	462.65	4	5	1.35	Yes
N3	383.47	5	6	-0.12	Yes
N4	383.46	3	5	1.21	Yes
N5	368.45	4	5	0.35	Yes
N6	390.46	3	5	1.51	Yes

INTERACTION OF SULFONYLUREAS DERIVATIVES WITH AMINO ACID RESIDUES WITH 4YVP

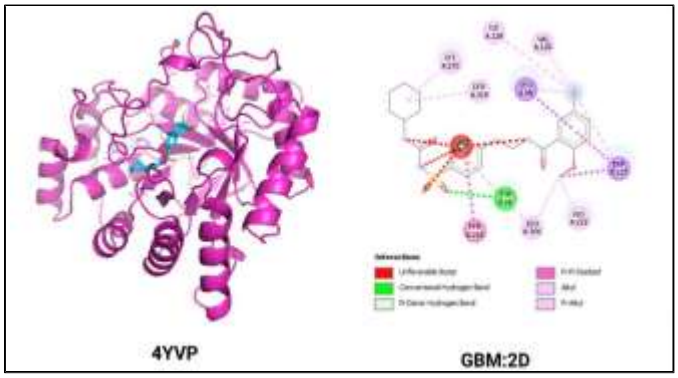


Fig: 7. Ligand GBM with Receptor 4YVP

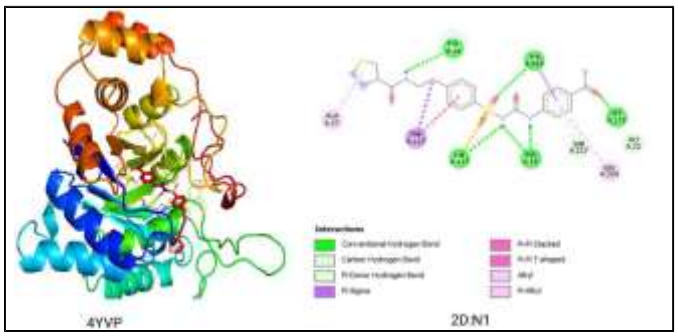


Fig: 8. Ligand N1 with Receptor 4YVP

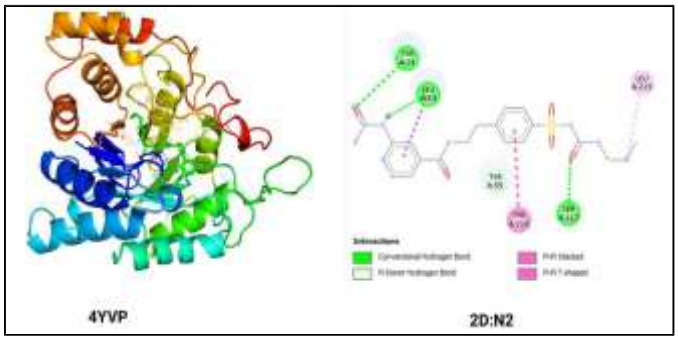


Fig: 9. Ligand N2 with Receptor 4YVP

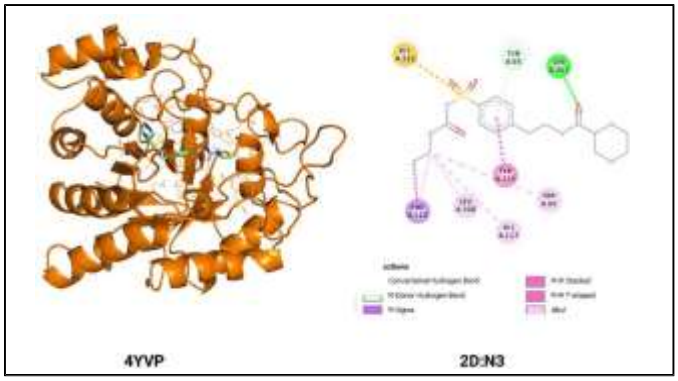
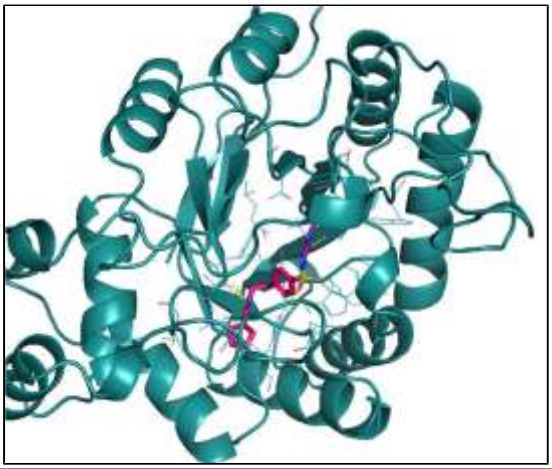
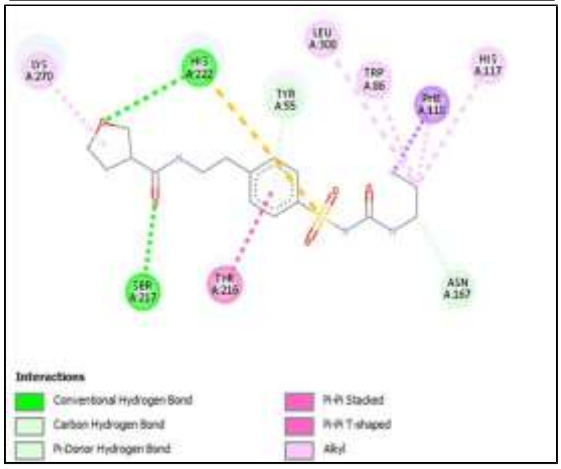
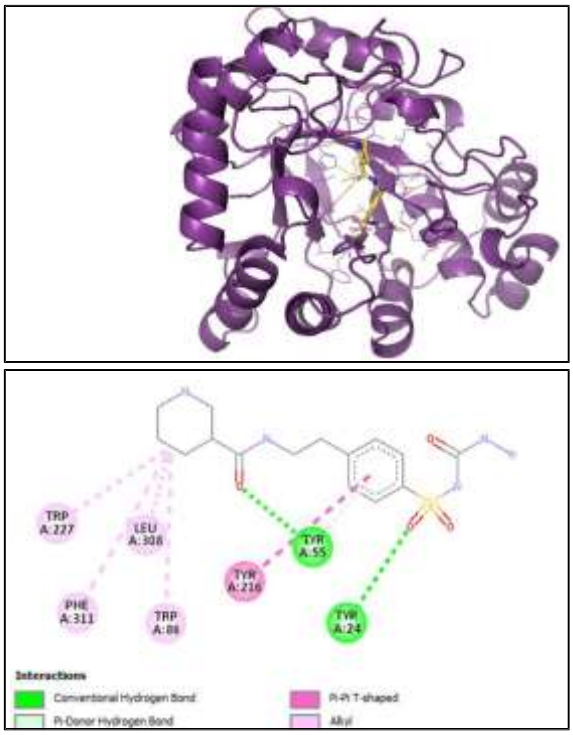


Fig: 10. Ligand N3 with Receptor 4YVP



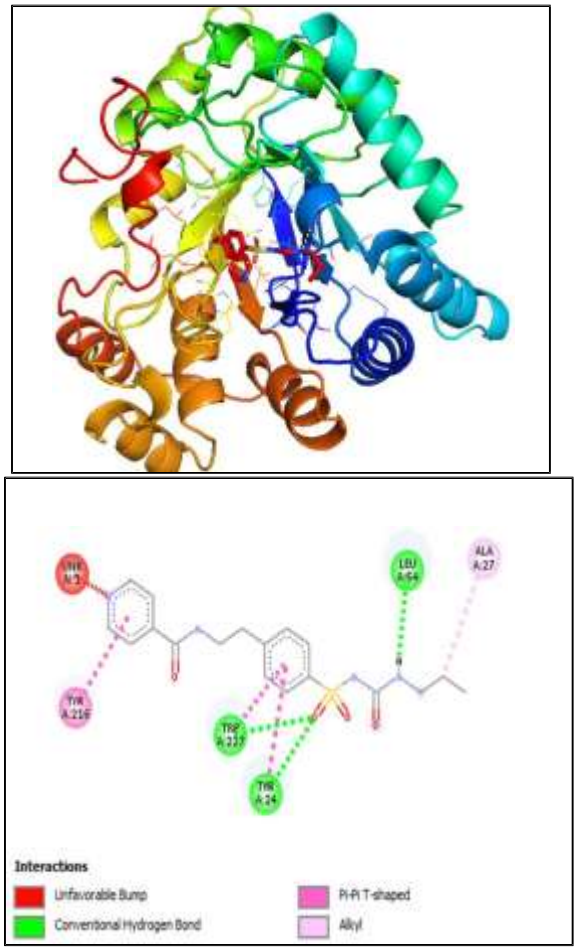


4YVP
2D:N4
Fig: 11. Ligand N4 with Receptor 4YVP



4YVP 2D:N5

Fig: 12. Ligand N5 with Receptor 4YVP



4YVP 2D:N6

Fig: 13. Ligand N6 with Receptor 4YVP

5. IN SILICO TOXICITY AND ADMET ANALYSIS

In addition to evaluating biological activity, comprehensive **in silico toxicity and pharmacokinetic (ADMET) analyses** were performed to assess the drug-likeness and safety profile of the designed sulfonylurea derivatives. These studies aimed to predict key parameters such as cytotoxicity, metabolic stability, efflux potential, cell permeability, oral bioavailability, central nervous system (CNS) penetration, plasma protein binding, brain tissue affinity, clearance, and volume of distribution.

The analysis further focused on correlating biological activity with essential physicochemical descriptors that influence drug performance. Parameters including **molecular weight (MW), calculated partition coefficient (CLogP), topological polar surface area (TPSA), number of hydrogen bond donors (HBD) and acceptors (HBA), aromatic ring count, and number of rotatable bonds** were systematically evaluated. These descriptors play a critical role in determining membrane permeability, solubility, and overall pharmacokinetic behavior of small molecules.

Drug-likeness of the synthesized compounds was assessed based on **Lipinski's Rule of Five**, which predicts oral bioavailability by considering key molecular properties such as molecular weight (≤ 500 Da), LogP (≤ 5), hydrogen bond donors (≤ 5), and hydrogen bond acceptors (≤ 10). Compounds satisfying these criteria are considered more likely to exhibit favorable pharmacokinetic profiles.

For further validation, toxicity risk and ADMET properties were predicted using the **SwissADME** web server. This platform provides detailed insights into gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeability, P-glycoprotein (P-gp) substrate recognition, cytochrome P450 enzyme inhibition, and bioavailability scores. Additionally, parameters such as synthetic accessibility and drug-likeness filters (e.g., Veber, Egan, and Ghose rules) were also analyzed.

The combined evaluation of physicochemical properties and ADMET parameters enabled the identification of promising sulfonylurea derivatives with optimal balance between efficacy, safety, and pharmacokinetic suitability. Compounds exhibiting favorable docking scores along with acceptable ADMET profiles were considered potential candidates for further experimental validation.

4. Results and Discussion

4.1. Results of Docking Analysis

Table: 4

Compound Code	Docking Score (K Cal/Mol)	H-Bond	
Glibenclamide (GBM)	-10.9	1	
N1	-11.2	5	
N2	-10.1	3	
N3	-9.8	1	
N4	-9.7	2	
N5	-9.5	2	
N6	-9.3	3	

The results generated by atomic docking are presented as docking scores, which reflect the medicinal activity or inactivity of a compound. Based on this, we can assess the compounds and also determine the activity of the compound by examining the binding energy listed in the table. All designed compounds exhibited better binding energy compared to standard Glibenclamide, while compound N1 demonstrated higher binding energy than Glibenclamide. The binding cavity and interactions with various amino acid residues for compounds N1 and N3 are shown below.

Table: 5. ACTIVE SITE RESIDUES OF TARGET DIABETIC PROTEINS

Protein	Drugs	Energy	Associated Amino Acid Residues
4YVP	GBM	-10.9	TYR-55, TYR-24, TRP-227, ILE-129, VAL-128, LEU-308, LEU-306, HIS-117, PHE-311, TRP-86, GLU-224, LEU-54
	N1	-11.2	TYR-55, TYR-55, TYR-24, TRP-227, LYS-270, LEU-268, HIS-117, TYR-216
	N2	-10.1	TYR-24, LEU-54, TYR-216, SER-217
	N3	-9.8	TYR-55, TYR-216, LEU-308, TRP-86, PHE-311, PHE-118, HIS-222, SER-217, TYR-55
	N4	-9.7	TYR-216, LEU-308, TRP-86, PHE-118, HIS-222, SER-217, HIS-222, SER-217, LYS-270, TYR-55
	N5	-9.5	TYR-55, TYR-24, LEU-308, TRP-86, PHE-311, TRP-227, TYR-216
	N6	-9.3	TYR-24, LEU-54, TRP-227, TYR-216

1. The amino acid interaction of ligand GBM-4YVP of standard, TYR-55, TYR-24, TRP-227, ILE-129, VAL-128, LEU-308, LEU-306, HIS-117, PHE-311, TRP-86, GLU-224, LEU-54.

2. The amino acid interaction of ligand N1-4YVP found to be similar interaction of standard, TYR-55, TYR-55, TYR-24, TRP-227, LYS-270, LEU-268, HIS-117, TYR-216.

3. The amino acid interaction of ligand N3-4YVP found to be similar interaction of standard, TYR-55, TYR-216, LEU-308, TRP-86, PHE-311, PHE-118, HIS-222, SER-217, TYR-55

There are many heterocyclic compounds which, when substituted at the R1 and R2 positions of sulfonylurea, can yield a variety of new compounds. Among these, several may exhibit greater activity than Glibenclamide and potentially lower toxicity levels. Similarly, we have synthesized different types of compounds and made extensive use of molecular docking in our work. We reviewed

numerous research papers where many derivatives were developed using docking techniques. Following a similar approach, we successfully developed compounds that are more effective than Glibenclamide and exhibit strong antidiabetic properties.

In the future, if further research is carried out on these compounds, the day may not be far when the world becomes free from diabetes.

Diabetes, as we know, is a disease that, once developed, cannot be cured without medication. Patients often require lifelong treatment to manage it. Currently, research is ongoing for all types of diabetes, and in the coming days, the world may indeed achieve freedom from this disease.

Table: 6. IN SILICO TOXICITY AND ADMET ANALYSIS RESULT

SN	MOLECULE	DRUG
1.	Molecule -1	**Glibenclamide (GBM)**
2.	Molecule -2	N1
3.	Molecule -3	N2
4.	Molecule -4	N3
5.	Molecule -5	N4
6.	Molecule -6	N5
7.	Molecule -7	N6

Fig: 14

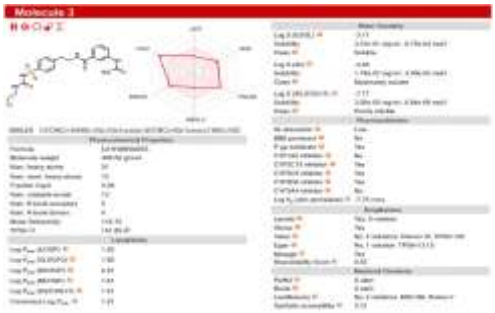


Fig: 15

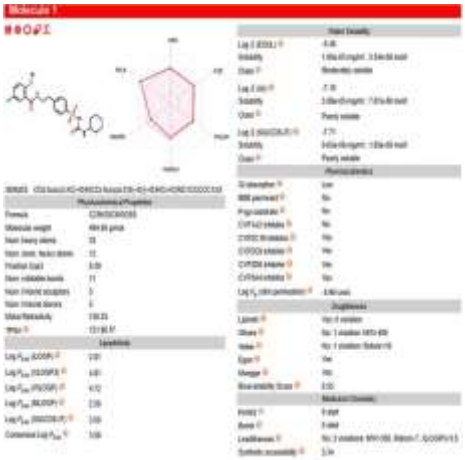


Fig: 16

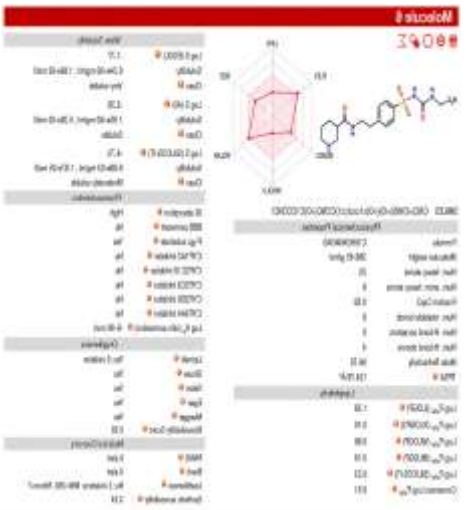


Fig: 17

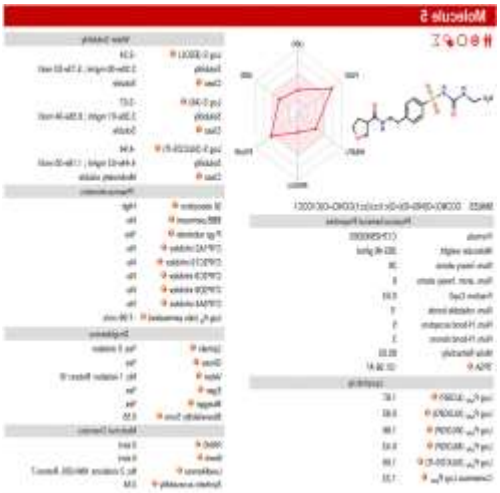


Fig: 18

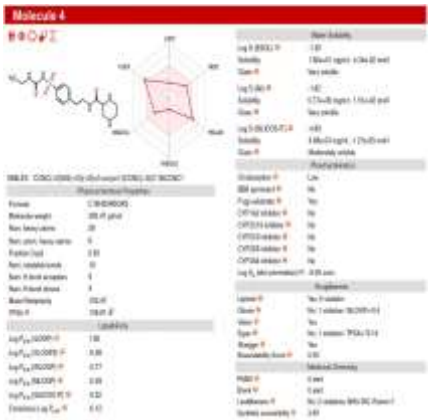


Fig: 19

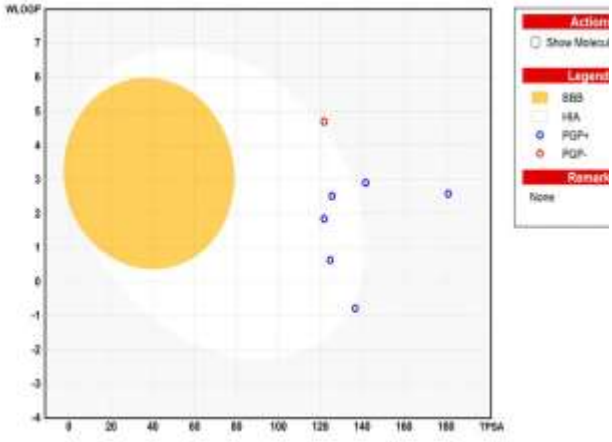


Fig: 20
BOILED-Egg model illustrating the predicted gastrointestinal absorption (HIA) and blood–brain barrier (BBB) permeability of the designed compounds based on ADME analysis.

5. CONCLUSION

If we talk about the conclusion of this research, the main objective is the modification of sulfonylurea to develop improved compounds that have minimal side effects and greater pharmacological activity than the standard drugs used in this experiment.

Sulfonylurea already exhibits strong antidiabetic effects. However, nowadays, people worldwide who suffer from diabetes are not getting complete relief, even though most diabetic patients are taking sulfonylurea derivative-based antidiabetic drugs. Glibenclamide, in particular, is a widely used and essential antidiabetic medication.

There are many heterocyclic compounds known to possess potent antidiabetic activity. In this study, various heterocyclic compounds were used as substituents at the R1 and R2 positions of sulfonylurea. As a result, numerous new derivatives were developed, potentially enhancing the antidiabetic effect of sulfonylurea derivatives.

Among these derivatives, some did not show better antidiabetic activity compared to the reference drug. However, the main goal of the research was to develop improved sulfonylurea-based antidiabetic drugs. According to the literature, heterocyclic compounds like piperazine, oxolane, piperidine, pyridine, thiolane, and N-phenylacetamide exhibit notable antidiabetic properties. Therefore, I substituted the R1 and R2 positions with these heterocyclic compounds, as well as with some carboxylic acid derivatives. Through this approach, we discovered several derivatives with significant antidiabetic effects.

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