https://doi.org/10.48047/AFJBS.6.13.2024.6035-6068

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

DESIGN, SYNTHESIS, AND HYPOGLYCEMICEVALUATION OF SULFONYL UREA AND GUANIDINE DERIVATIVES

Shahnawaz[1]*, Preeti Anand[1], Rajat Saini[1]

[1]*IIMT College of Pharmacy, IIMT University, 'O' Pocket, Ganga Nagar Colony, Mawana Road, Meerut (U.P.).*

***Corresponding Author*:** *Shahnawaz, (M.Pharm., Research Scholar), IIMT College of Pharmacy, IIMT University, 'O' Pocket, Ganga Nagar Colony, Mawana Road, Meerut (U.P.).*

Volume 6, Issue 13, Aug 2024

Received: 15 June 2024

Accepted: 25 July 2024

Published: 15 Aug 2024

doi:10.48047/AFJBS.6.13.2024.6035-6068

ABSTRACT

Diabetes Type 1 diabetes is a notable condition impairing the body's control over blood sugar levels, in this condition, the body lacks the production of insulin, an essential hormone for maintaining normal In type 2 diabetes, the cells in the body become resistant to insulin, resulting in higher blood glucose levels, a condition known as hyperglycemia. Prolonged hyperglycemia is associated with severe Long-term complications such as retinopathy (damage to the eyes) and neuropathy, affecting both small and large blood vessels. Finding new, safe, and effective treatments for diabetes remains a major challenge for researchers. Based on an extensive review of existing studies, we chose to design and synthesize new anti-diabetic agents. Using the iGEMDOCK program, we performed docking, screening, and analysis of the compounds targeting the 5TWV protein.

Keywords: Diabetes mellitus, Glipizide, iGEMDOCK, Streptozotocin (STZ)

INTRODUCTION

1.1 Definitions

The world is facing an epidemic of Diabetes mellitus is a group of metabolic disorders characterized by high blood sugar levels due to problems with insulin secretion, insulin action. Prediabetes, marked by reduced ability to tolerate glucose or reduced glucose levels after fasting, occurs when Blood glucose levels are high above normal but do not meet the threshold for classification as type 2 diabetes [1]. These glucometabolic deviations are linked to cardiovascular morbidity and mortality. Prediabetes denotes a transitional stage of disrupted glucose metabolism between normal levels and diabetes. Currently, over currently, 250 million individuals worldwide have diabetes, a IMAGE projected to double in a little over 20 years. [2–3].

Diabetes mellitus is a condition characterized by persistent endocrine disorder marked by high

blood sugar levels due to a complete lack of insulin. [4].

Diabetes mellitus, among the oldest known diseases, was documented in an Egyptian manuscript around 3000 years ago [5]. Scientific trials show that lifestyle changes such as diet, physical activity, and Losing weight can postpone or even prevent the development of type 2 diabetes in individuals vulnerable [6].

Type 1 diabetes occurs because of the autoimmune destruction of insulin-producing pancreatic β-cells, leading to a shortage of insulin and hyperglycemia, affecting 10-15%of diabetics. Type 1 diabetes develops due to the autoimmune destruction of insulin- producing cells. Pancreatic β-cells, causing, is characterized by abnormal insulin secretion and peripheral resistance. The onset of type 1 diabetes typically occurs in youth, while type 2 often manifests later in life, though diagnosis can be complex in some cases.

In uncontrolled diabetes of both types, there is increased liver glucose production and reduced glucose uptake by muscles and adipose tissue. Individuals with type 1 diabetes are susceptible to significant lipolysis, which can lead to diabetic ketoacidosis, while type 2 diabetics are less prone to ketoacidosis due to residual insulin inhibiting ketone production, but they may develop a hyperosmolar, non-ketotic state.

Globally, diabetes prevalence continues to increase due to rising diabetes associated with lifestyle changes, particularly in developing nations. As of In 2011, approximately 366 million people were estimated to have diabetes, with type 2 constituting about 90% of cases [7-8]. The rate of type 2 diabetes is increasing globally, especially in low- and middle-income countries, where 80% of diabetics reside.

Physical exercise offers numerous physiological and psychological benefits for diabetic patients, playing a crucial role in managing type 1 diabetes and promoting overall well- being.

1.2 History of diabetes mellitus

The chronicle of diabetes mellitus spans thousands of years and reflects our evolving understanding of this chronic condition. Here's a brief overview:

1. Ancient Discoveries: Diabetes was first described in ancient texts dating back to ancient Egypt, where symptoms resembling diabetes were noted in manuscripts around 1550 BCE. These descriptions included excessive urination (polyuria) and thirst (polydipsia), characteristic symptoms of diabetes.

2. Early Observations: Throughout ancient history, similar symptoms were observed in various cultures, including ancient Greece and India. However, it wasn't until much later that

diabetes was distinguished as a specific disease entity.

3. Naming and Understanding: The term The term "diabetes" comes from word that means "siphon" or "to pass through," refered to the excessive urination seen in the condition. The term "mellitus" was added later to distinguish it from diabetes insipidus, another condition with similar symptoms but different causes.

4. 19th Century Advances: Significant progress in understanding diabetes occurred in the 19th century. This led to the recognition of the pancreas' role in diabetes and the discovery that insulin production was crucial for managing the disease.

5. Discovery of Insulin: One of the most significant crucial advancements in thehistory of diabetes was the identification of insulin by Frederick Banting, and John

Macleod in 1921-1922. This breakthrough allowed for effective treatment of diabetes, turning it from a fatal condition into a manageable chronic disease.

6. Advancements in Treatment: Since the discovery of insulin, there have been continuous advancements in diabetes management, including the development of oral medications, improvements in blood glucose monitoring technology, and the emphasis on lifestyle interventions such as diet and exercise.

7. Epidemiological Trends: In recent decades, diabetes has become a global health challenge, with the rising prevalence can be ascribed to factors such as inactive lifestyles, poor dietary habits, and an aging demographic.

Understanding the history of diabetes mellitus provides insights into how medicalknowledge and treatments have evolved over time, leading to better outcomes and quality of life for individuals living with this condition today.

1.3 Diabetes Prevalence in India

India, once leading the world in diabetic population according to the International Diabetes Federation, possesses now been surpassed by China. Currently, India has 61.3 million diabetics, a number projected to reach 103 million by 2030 [10]. Almost 1 million Indians succumb to diabetes each year. As of 2015, India had 69.1 million individuals with diabetes, ranking it as the country with the second-highest number of cases after China [11].

The Indian Heart Association predicts that India will have 109 million people areprojected to have diabetes by 2035, as indicated by a study from the American Diabetes Association, India is expected to experience the highest increase in diagnosed cases of diabetes by 2030.

This high prevalence is due to a combination of genetic factors predisposition and the shift towards a high-calorie, low-activity lifestyle, especially among India's expanding middle class.

1.4 Type 2 Diabetes

t has yet to fully comprehend why some individuals with Prediabetes or type 2 diabetes experience complications while others do not.

Weight: Increased fat tissue leads to greater insulin resistance in cells.
Inactivity: Lack of physical activity contributes to weight gain, reduces glucose utilization as energy, and decreases insulin responsiveness in cells.

Family History: Having a parent or sibling with type 2 diabetes, your risk increases.
Age: Advancing age often correlates with reduced Physical activity, loss of muscle mass, and weight gain are factors contributing to the rise in diagnoses of type 2 diabetes.

Gestational Diabetes (GD): Developing during pregnancy, gestational diabetes raises risk, especially.

1.5 Gestational Diabetes

Gestational diabetes can develop during pregnancy, with certain women being at higher risk compared to others.

1.5.1 Factors Increasing the Risk of Gestational Diabetes

1.5.1.1 **Age:** Women over the age of 25 are at an increased risk.

1.5.1.2 **Personal History:** The risk is higher if you have had Prediabetes. (a precursor to type 2 diabetes) or if a close family member, such as a parent, has type 2 diabetes. You are also at greater risk if you had gestational diabetes during a previous pregnancy.

1.5.1.3 **Weight:** Being obese prior to pregnancy heightens the risk.

1.6 Various Classes of Hypoglycemic Agents

Table 1.1 lists various types of hypoglycemic agents. Table 1.2 details first and second generation sulfonylureas.

1.7 Mechanisms of Sulfonylurea Hypoglycemia

Sulfonylureas induce hypoglycemic effects through two primary mechanisms, broadly classified as pancreatic and extra-pancreatic:

1.7.1 Pancreatic function:

Sulfonylureas block the outward flow of potassium ions (K+ channel blockers that is closely linked to ATP-sensitive potassium channels. This inhibition results in depolarization ß-cell

membrane. Subsequently, voltage- dependent calcium channels in the beta - cell membrane open, enabling calcium ions (Ca+2) to enter the cell. The increased intracellular concentration of Ca+2 activates kinases linked to secretory granules, facilitating the release of insulin-containing granules through exocytosis.

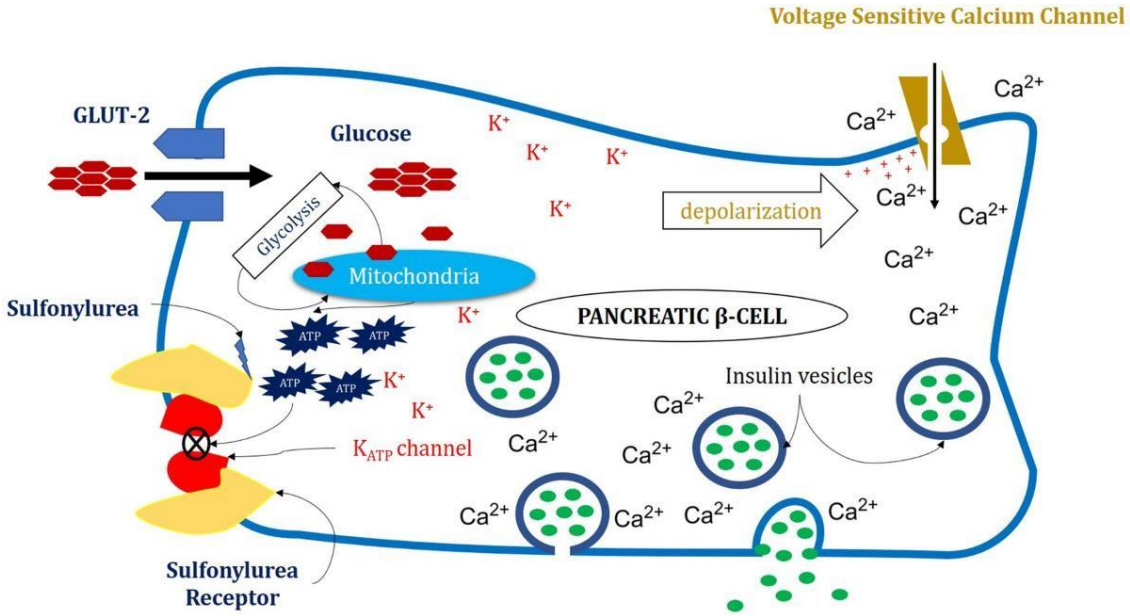


IMAGE 1.1 Pancreatic Mechanism of sulphonylurea

1.7.2 Mechanisms outside the pancreas:

Sulfonylureas additionally reduce serum glucagon levels, potentially contributing to their hypoglycemic effects. The precise mechanism of this action is not fully understoodbut may involve indirect inhibition through increased secretion of both somatostatin and insulin. Sulfonylureas may also improve insulin action at target tissues through drug- specific mechanisms.

1.8 Insulin

1.8.1 Chemistry and Biosynthesis

Insulin's hormone secreted by the β cells in the pancreas. It is of biological origin and. Introduced for clinical use in 1922, insulin is typically administered before each main meal with an additional injection at night; often around [13-16].

1.8.2 Pharmacodynamics of Insulin

Insulin promotes the uptake of glucose. Activation of the insulin receptor's inherent tyrosine kinase leads to increased tyrosine phosphorylation; it also suppresses hepatic glucose production. [17].

1.8.2.1 Distribution

Upon release once released from the pancreas, insulin quickly disperses throughout extracellular fluids without binding to plasma proteins.

1.8.2.2 Metabolism

Insulin metabolism primarily occurs in the liver, with minor contributions from Insulin is distributed to the kidneys. Glutathione transhydrogenase breaks the disulfide bonds between molecules between the A and B chains. It has a brief half-life of around 5-6 minutes, with approximately half of the insulin in circulation metabolized thrugh the liver during every circulation cycle.

1.8.2.3 Excretion

Insulin is filtered by the glomeruli of the kidneys and nearly fully reabsorbed (98%) in the proximal tubules for subsequent use. In healthy individuals.

1.8.3 Pros and Cons of Insulin

Insulin therapy involves recommended when dietary adjustments or oral medications fail to adequately manage sugar levels, particularly after pancreatectomy. Insulin analogues offer advantages such as a lower the risk of hypoglycemia, particularly nocturnal episodes. Challenges associated with insulin therapy include local discomfort, the inconvenience of frequent injections, and insulin-induced edema, lipohypertrophy, insulin allergies, resistance, and notably, weight gain [18-20].

1.8.4 Mode of Action

Insulin facilitates the entry of glucose into adipose tissue, muscles, and the liver by stimulating various enzyme responses initiated at receptors for insulin. Activation of theinsulin receptor's intrinsic tyrosine kinase leads to increased membrane phosphorylation, enhancing glucose membrane permeability through a intricate series ofintracellular events.

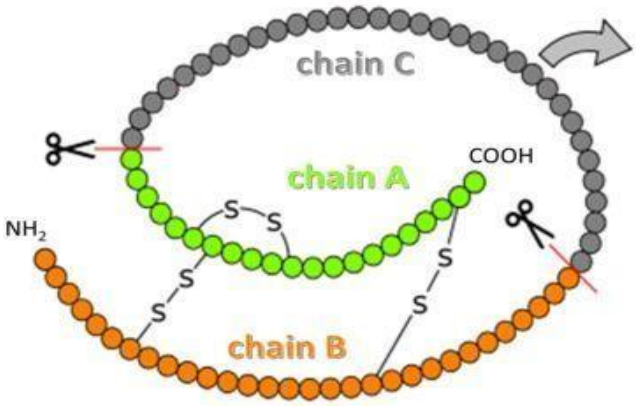
1.8.5 Insulin Resistance

Insulin resistance contributes to negative metabolic alterations involving insulin, lipids, blood pressure, lipoproteins, and cardiovascular diseases glucose. It occurs although it is rare in type 1; if present, Resistance can be caused by both immune and non-immune factors.

It manifests as tissue insensitivity to the hormone, characterized by either a decrease in insulin receptor quantity or reduced insulin's binding affinity to its receptors. It iscategorized as either acute or chronic: acute resistance may arise from toxins, stress, while it immune-mediated and

develops after the development of antibodies against insulin. Resistance frequently manifests in patients undergoing prolonged insulin treatment.

IMAGE 1.2 Insulin Structure



1.8.6 Pharmaceutical Insulin Preparations

Injection remains the established method for administering insulin due to the peptide nature of insulin, which prevents its oral use. However, clinical trials are ongoing to evaluate various oral insulin formulations for their effectiveness in regulating glycemia in diabetic patients. Additionally, efforts continue to explore insulin delivery via inhalation and other novel routes such as intra-peritoneal devices.

Commercially, insulin can be administered subcutaneously, intravenously, or intramuscularly administration. While animal and human insulin preparations perform similarly in terms of action, there is a heightened risk of allergic reactions associated with animal-derived insulin. Which correlates with their zinc content? Preparations containing lower zinc levels, like regular insulin, usually exhibit rapid onset and brief duration of effect. In contrast, insulin with higher zinc content.

1.8.6.1 Fast-Acting Insulin Formulations

Rapid-acting insulin formulations are typically composed of water for injection. This category includes regular insulin, lispro insulin, insulin aspart, and glulisine insulin.

1.8.6.2 Standard Insulin

Standard insulin consists insulin dissolved in water for injection or a phosphate buffer solution with a low concentration of zinc chloride (0.01-0.04 mg/100 Units). Zinc ions interact with insulin, facilitating the production of insulin hexamers. Upon injection, these hexamers dissociate into dimers and then into monomers, which rapidly enter circulation, resulting in a

quick onset of action.

1.8.6.3 Lispro insulin

Lispro insulin is the initial synthetic human insulin analog created through genetic engineering technology employing targeted mutation. It distinguishes itself from regular insulin by substituting amino acids produce lyspro in place of the prolys structure typically found in standard human insulin. This structural change in lispro insulinpromotes faster dissociation into monomers in subcutaneous tissues. Consequently,lispro insulin has a quicker onset of action compared to regular insulin.

1.9 Polyol Pathway

The polyol pathway contributes to the formation of sugar cataracts and involves glucose metabolic imbalance in diabetic patients. a member of the aldo-ketoreductase family, is the initial and pivotal enzyme in this pathway. It converts glucose is converted to sorbitol with nicotinamide adenine dinucleotide phosphate as a cofactor. Sorbitol is subsequently metabolized to fructose by sorbitol dehydrogenase, which uses NAD+ as acofactor[21].

Aldose reductase and sorbitol are implicated in kidney osmoregulation, with AR reducing NADPH levels during glucose metabolism. NADPH also functions as a cofactor in glutathione reductase, which converts oxidized glutathione into its reduced form. Excess sorbitol is further oxidized to fructose. Increased glucose Activity within the polyol pathway contributes to the production of Advanced Glycation End Products, along with their interaction with receptors, are known to induce oxidative stress.

1.10 Inositol 1, 4, 5-Trisphosphate Pathway

Over the past 25 years, my scientific focus has centered on inositol 1,4,5-trisphosphate and calcium. The relationship between these two messengers has progressed through two distinct phases. Initially, research led to the finding that IP3 functions as a second messenger that mobilizes calcium. Subsequently, a second phase of interest emerged, revealing that the IP3/Ca2+ signaling pathway serves as a crucial regulator of various cellular control mechanisms.

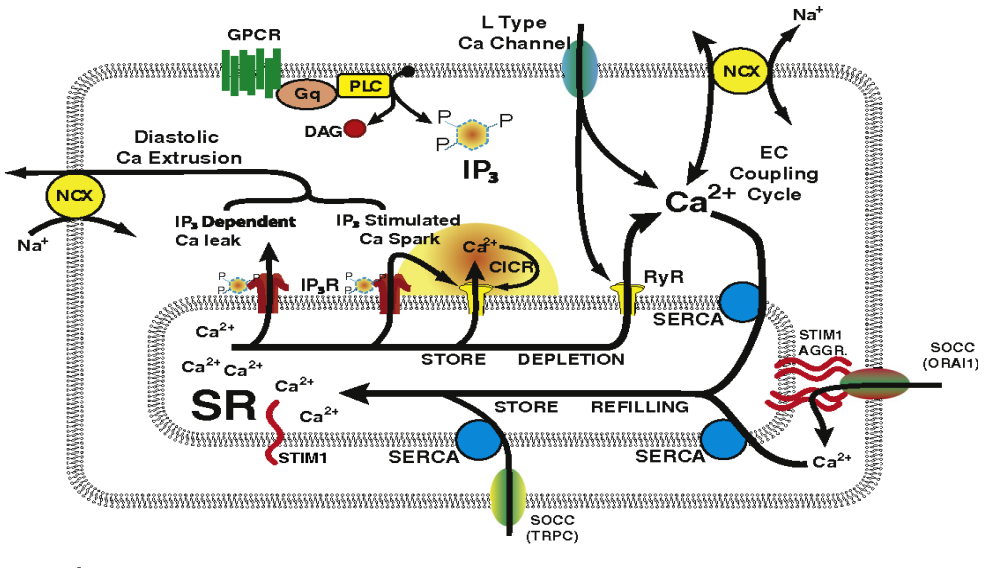


IMAGE 1.3: Inositol 1, 4, 5-trisphosphate pathway

1.11 Need for study

The need for studying the design, synthesis, and hypoglycemic evaluation of sulfonylurea and guanidine derivatives arises from several key reasons associated with the treatment and management of diabetes mellitus:

1. **Development of New Therapeutic Agents**: Diabetes mellitus, particularly type 2 diabetes, is a persistent condition that necessitates lifelong management. While existing medications like sulfonylureas and guanidines are effective, there is a continuous need to develop new therapeutic agents that can offer improved efficacy, safety, and tolerability profiles.

2. **Enhancing Potency and Selectivity**: By designing and synthesizing new derivatives, researchers aim to enhance the potency and selectivity of these drugs. This can lead to medications that have improved management of blood glucose levels with reduced side effects.

3. **Addressing Drug Resistance**: Over time, some patients develop resistance to existing diabetes medications, which reduces their effectiveness. New derivatives may overcome these resistance mechanisms, providing alternative treatment options for such patients.

4. **Minimizing Side Effects**: Existing drugs like sulfonylureas can sometimes cause side effects such as hypoglycemia (low blood sugar) or weight gain.Through careful design and synthesis, researchers can aim to minimize these adverse effects while maintaining therapeutic benefits.

5. **Exploring Mechanisms of Action**: Studying new derivatives allows researchers to explore different mechanisms of action. This can lead to a betterunderstanding of how these

compounds interact with biological targets related toglucose metabolism and insulin regulation.

6. **Personalized Medicine**: The development of new derivatives may contribute to personalized medicine approaches, where treatments can be customized for eachindividual patient needs based on genetic and metabolic profiles.

7. **Global Health Impact**: Diabetes is a growing a worldwide health issue, particularly in low- and middle-income countries where access to effective

MATERIALS AND METHODS

4.1 Materials

All chemicals and reagents were obtained in LR grade from Sigma Aldrich, Merck, Chemco, and Acros Organics. Reactions were tracked for completion using thin-layer chromatography on silica gel 60 F254 plates, with n-hexane acetate (7:3) chosen as the mobile phase solvent.

4.2 Experimental Section

4.2.1 Molecular Docking Study

4.2.1.1 Steps of Ligand Docking [44]

Docking is a technique used to predict the favored positioning of a ligand when boundto an active site to form a stable compound.

Step 1 –Ligands Preparation

- Use Marvin Sketch, a Java-based program, for drawing molecule structures, which simplifies molecule drawing with a wide range of editing tools andtemplates.
- Automatically establish rotatable bonds and atom categories or adjust themmanually.
- Arrange ligands into folders defined by the user.

Step 2 –Proteins Preparation

Import protein structures from files or obtain them from the Protein Data Bankby using the Docking.

- Specify the heteroatoms, ligands, protein chain and water molecules foundwithin the protein PDB file for docking calculations.
- Here is a revised version:
- Choose a phenomenon binding site using a co-crystallized ligand.
- Determine the protein's center of mass molecules.
- Define the coordinates of the box center and the amino acid residues thatdelineate the binding site.

Step 3 – Prepare Ligand-Protein Calculations

- Choose a protein and a ligand from your collection.
- Customize advanced simulation parameters, such as the number of runs and

evaluations.

Step 4 – Evaluation's Results

- Select an image from the gallery or render it within the Molecular Docking Server interface.
- Examine additional interactions between the protein & ligand.
- This process outlines the systematic approach to conducting molecular docking studies for evaluating the interactions between ligands and protein targets.

4.2.1.2 Ligand Docking

The crystal structure of the pancreatic ATP-sensitive K+ channel SUR1/Kir6.2 bound with ATP and Glipizide (PDB ID: 5TWV) was utilized for the docking investigation. [45]. Docking, The screening and subsequent analysis of the designed molecules were performed using the iGEMDOCK program with the protein target **5TWZ**. The binding sites of the ligands were specified, and the energy-minimized molecules were prepared for docking. During the docking process, parameters such as Bond orders, explicit hydrogens, charges, and flexible torsions were assigned to both the protein and ligands without plagiarism.

The docking protocol involved selecting the wizard ligand and employing the iGEMDOCK scoring function. Hydrogen bonding feasibility was evaluated, and the docking score incorporated energy contributions from hydrogen bonds, penalizing deviations from ideal bonding angles to refine results and optimize internal electrostatic interactions.

The search algorithm employed was iGEMDOCK, with 70 runs and a maximum of 2000 interactions, using a population of 200 and an energy threshold set at 100. At each step, the algorithm verified minimal twists, shifts, and rotations, selecting configurations that minimized energy. Additional positions were tested if initial configurations yielded positive energy results. A Root Mean Square Deviation (RMSD) threshold ensured diverse pose solutions by penalizing poses similar to previouslyidentified ligands, enhancing the variety of returned docking solutions.

This meticulous approach in ligand docking aimed to predict and optimize the binding interactions between the designed molecules and the protein target, facilitating the exploration of potential therapeutic candidates for hypoglycemic activity.

The docking procedure involved setting an energy penalty of 100 and an RMSD threshold of 2.00 for standard docking calculations. Protein-inhibitor docking was executed to

determine binding strengths measured in kcal/mol. Parameters for Both the hydrophobic preference and electrostatic preference were set to 1.00 for the binding site of the target. Protein was defined within an 8 Å radius.

This scoring function integrated these components to assess the overall suitability or compatibility of the ligand in the protein's binding site, guiding the selection of promising docking poses for further analysis and evaluation.

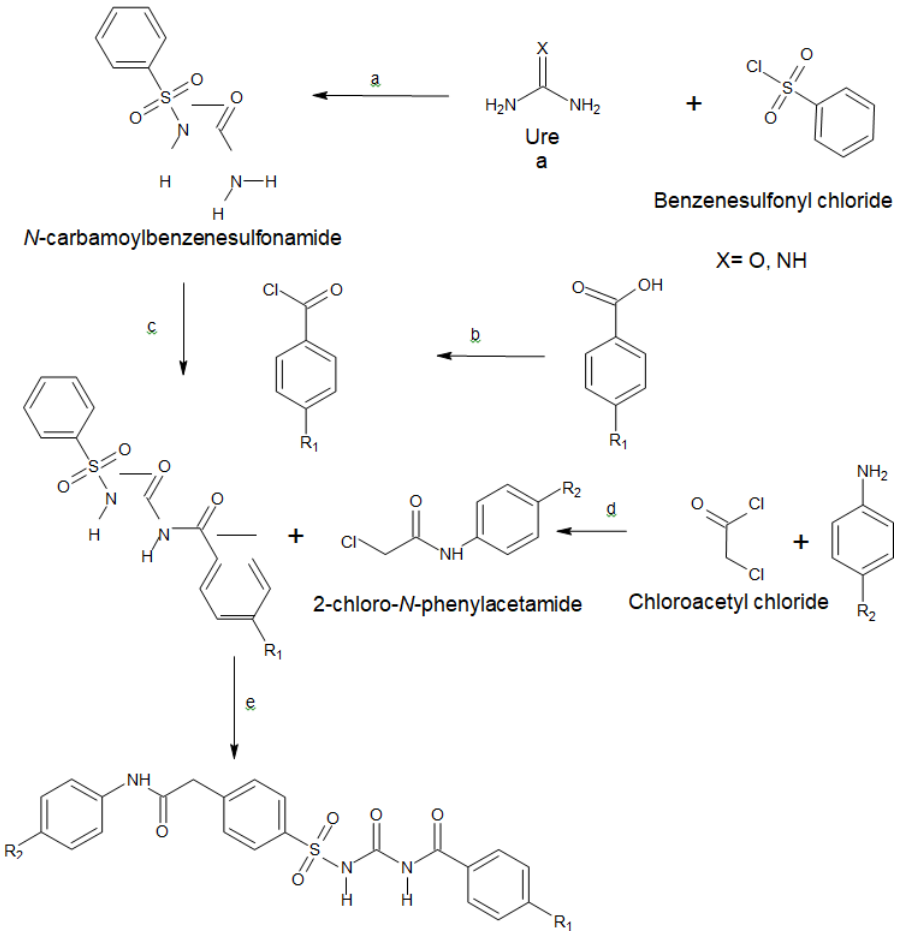
In silico toxicity studies aim to evaluate the physicochemical properties crucial for the long-term feasibility of molecules, alongside gathering biological data on characteristics and distribution volumes. Based on these findings, efforts are directed towards optimizing similar physicochemical properties. Emphasis is often based on easily calculable. One seminal study in this field is the work by Lipinski and colleagues, who highlighted potential challenges. Recent research has improved these guidelines, and this review focuses on a subset of these advancements.

4.2.2 SciFinder Report [47]

SciFinder, developed provided by the Chemical Abstracts Service is an extensive resource for accessing chemical substances, and reactions. It provides search options for topics, authors, substances by name or CAS Registry Number, and allows users to draw chemical structures, substructures, or reactions using an editor.

All designed compounds were evaluated using SciFinder software to assess their novelty. Chapter 4 includes some images illustrating the analysis conducted with SciFinder.

4.2.3 Synthesis Scheme



Scheme 1: Synthesis Pathway for the Preparation of Sulfonylureas Derivatives

Reagents and Conditions:

(a) Triethylamine (TEA), ethanol (CH3CH2OH), reflux (yield >70%)

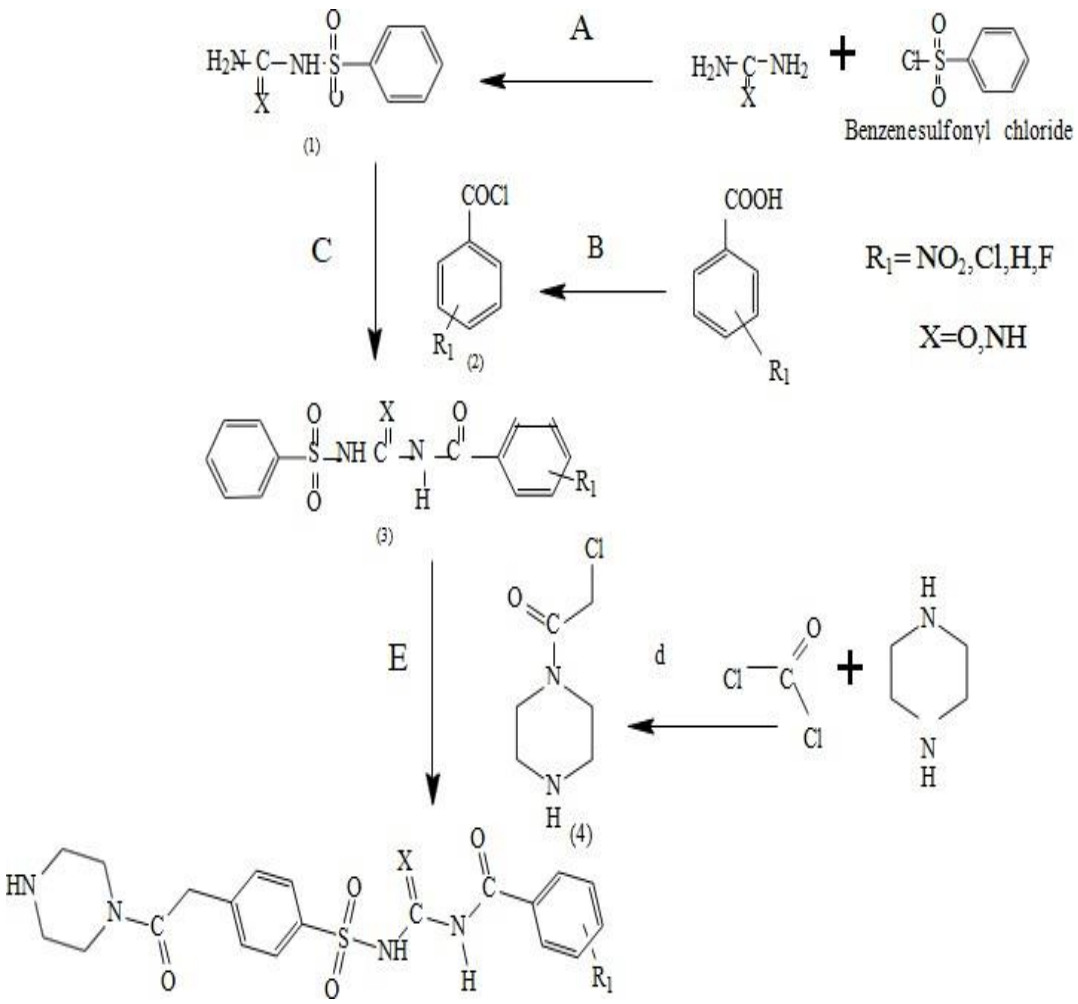
(b) Thionyl chloride (SOCl2), reflux, 3 hours (yield >60%)

(c) Triethylamine (TEA), ethanol (CH3CH2OH), reflux (yield >80%)

(d) Dry tetrahydrofuran (THF), room temperature (RT), stirring, 4 hours (yield >85%)

(e) Nitrobenzene, ferric chloride (FeCl3), reflux, 7 hours

This scheme outlines the sequential reactions and conditions used to synthesize sulfonylureas and guanidine derivatives, ensuring high yields suitable for subsequent applications such as hypoglycemic evaluation.



Scheme 2: Synthetic Pathway for the Preparation of Guanidine Derivatives

Reagents and Conditions:

(a) Triethylamine (TEA), ethanol (CH3CH2OH), reflux (yield >70%)

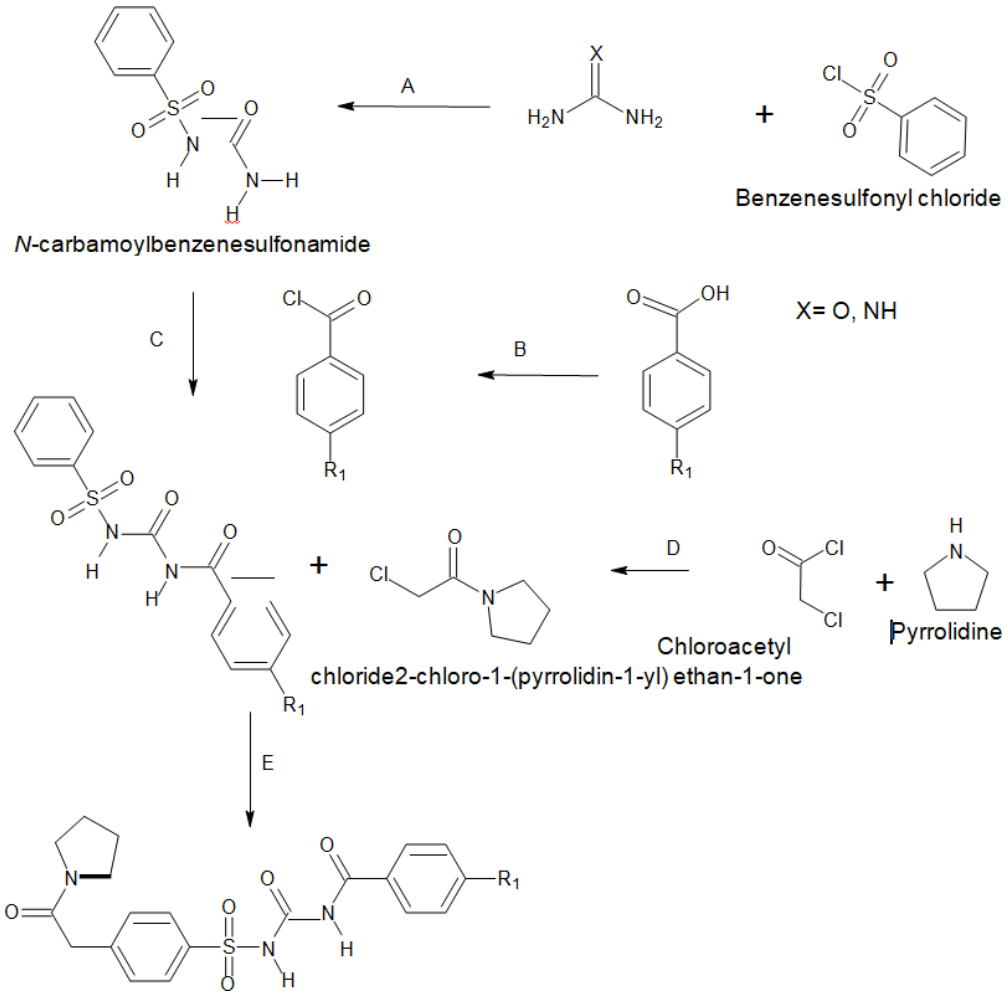
(b) Thionyl chloride (SOCl2), reflux, 3 hours (yield >60%)

(c) Triethylamine (TEA), ethanol (CH3CH2OH), reflux (yield >80%)

(d) Dry tetrahydrofuran (THF), room temperature (RT), stirring, 4 hours (yield >85%)

(e) Nitrobenzene, ferric chloride (FeCl3), reflux, 7 hours

This scheme illustrates the sequential reactions and optimal conditions used for synthesizing sulfonylureas and guanidine derivatives, ensuring high yields suitable forsubsequent applications, including hypoglycemic evaluation.



Scheme 3: Synthetic Pathway for the Preparation of Guanidine Derivatives

Reagents and Conditions:

(a) Pyridine, ethanol (CH3CH2OH), reflux (yield >75%)

(b) Thionyl chloride (SOCl2), reflux, 3 hours (yield >60%)

(c) Pyridine, ethanol (CH3CH2OH), reflux (yield >70%)

(d) Dry tetrahydrofuran (THF), 0°C to room temperature (RT), stirring, 4 hours (yield >85%)

(e) Nitrobenzene, ferric chloride (FeCl3), reflux, 7 hours

This scheme outlines the synthetic pathway employed for the production of sulfonylureas and guanidine derivatives, highlighting the specific reagents and optimized conditions utilized in each step to achieve high yields suitable for subsequent biological evaluations and applications.

4.2.4 Procedure and Spectral Characterizations

4.2.4.1 Synthesis of 1-Cyclohexanecarbonyl-3-[4-(2-(pyrazine-2-carboxamido) ethyl) phenylsulfonyl] guanidine (5a)

A reflux reaction was carried out between N-(2-chloroethyl) pyrazine-2-carboxamide (0.1 moles) and 1-cyclohexanecarbonyl-3-(phenylsulfonyl) guanidine (1 mole) for 7 hours in the presence of anhydrous FeCl3 using nitrobenzene as the solvent. After cooling, the liquid containing 1-Cyclohexanecarbonyl-3-(phenylsulfonyl)guanidine was isolated with a final yield of 60% and a boiling point of 100-102°C.The RF value was found to be 0.4 using a mobile phase of ethyl acetate (7:3).

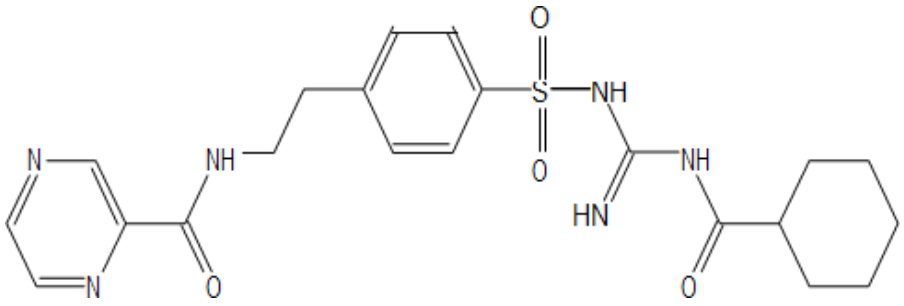


TABLE 4.3: Spectral data of 5a

Code	IR (KBr): ν (cm^{-1})	MASS (m/z)	^{1}H NMR (400 MHz)
5a	2977 (C-H) *str* Ar 1172 (S=O) *str* 2788 (C-H) *str* 2138(C=N) *str*	459 [M+1]	39.54 ($\underline{C}H_2CH_2Ar$), 38.28 ($CH_2\underline{C}H_2$,Ar), 141.12-145.05 (CH, pyrazine)

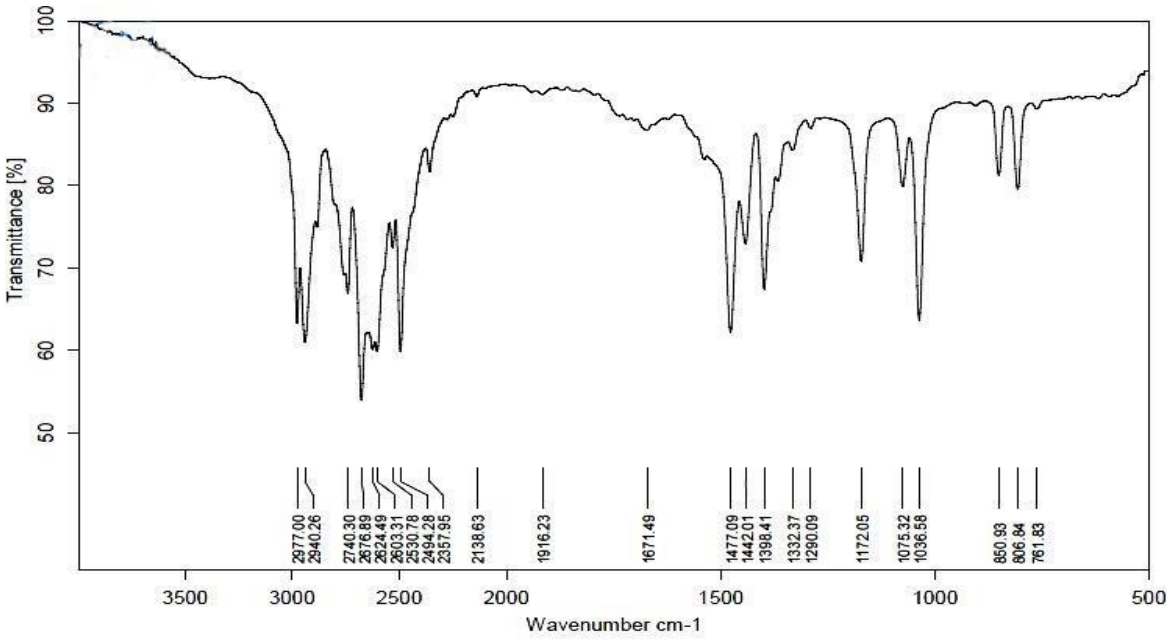


IMAGE 4.1: IR Spectra of 5a

Sample Name:	X			
Sample Type:	Unknown		Acquired By:	System
Vial:	72		Sample Set Name:	16002024_MASS_01
Injection:	1		Acq. Method Set:	MASS_METHOD
Injection Volume:	10.00ul		Processing Method:	MASSMETHOD_03
Run Time:	0.9 minutes		Channel Name:	MS TIC
			Proc. Chn. Descr:	ZQ F2 Scan MS TIC ZQ F4 Scan
Date Acquired:	19/06/2024	09:10:18 AM IST		
Date Processed:	19/06/2024	09:01:56 AM IST, 09:22:49 AM IST		

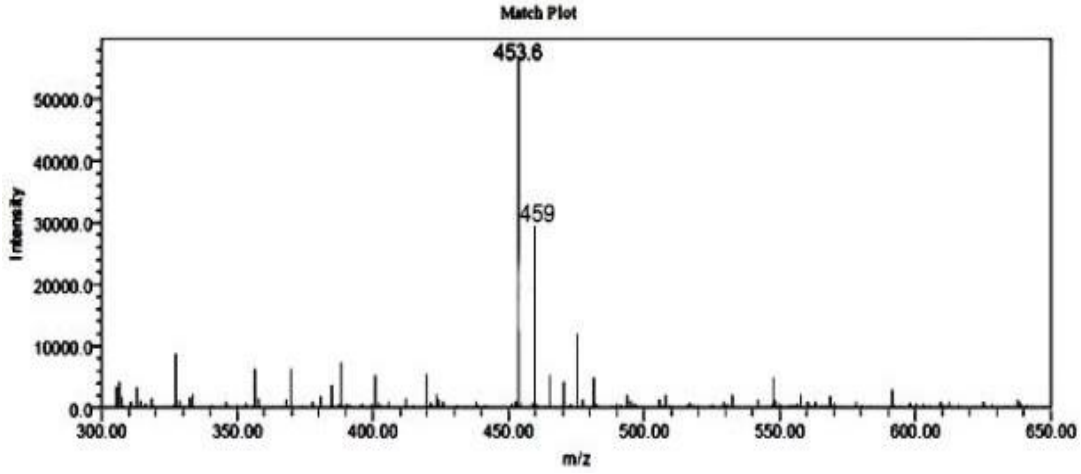


IMAGE 4.2: Mass Analysis report of 5a

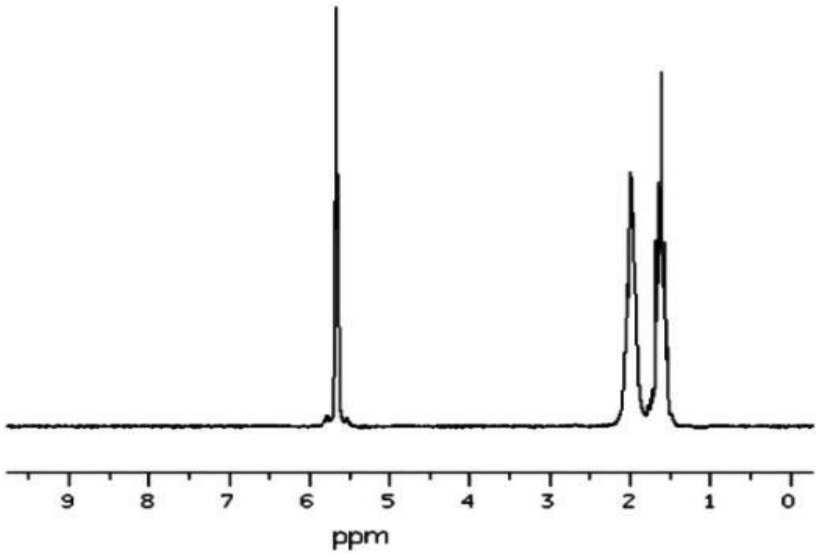


IMAGE 4.3: ^{1}H NMR of 5a

4.2.4.2 Synthesis of 1-(4-(2-Benzamidoethyl) phenylsulfonyl)-3-(cyclohexane carbonyl) urea (5b)

A reaction was conducted N-(2-chloroethyl)benzamide (0.1 mole) and 1-cyclohexanecarbonyl-3-(phenylsulfonyl)urea (0.1 mole) for 7 hours in the presence of FeCl3 using nitrobenzene as the solvent. After cooling, Solid white crystals were obtained with a yield of 75%. The melting point of the final product was recorded as 150-154°C. The Rf value was determined to be 0.5 using a mobile phase of ethyl acetate(7:3).

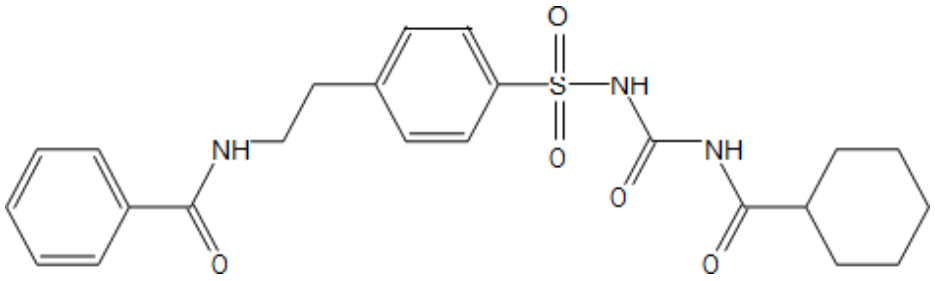


TABLE 4.4: Spectral data of 5b

Code	IR (KBr): ν (cm^{-1})	MASS (m/z)	^{1}H NMR (400 MHz)
5b	1669 (C=O) *str* 2994 (C-H) *str* 1247 (S=O) *str*	454.6 [M-2]	2.31 (s, 2H, CH_2), 3.48 (s, 2H, CH_2), 1.32 (s, 11H, CH_2) Cyclohexane, 8.16 (s, 1H, NH), 8.16-8.33(m,9H, Ar)

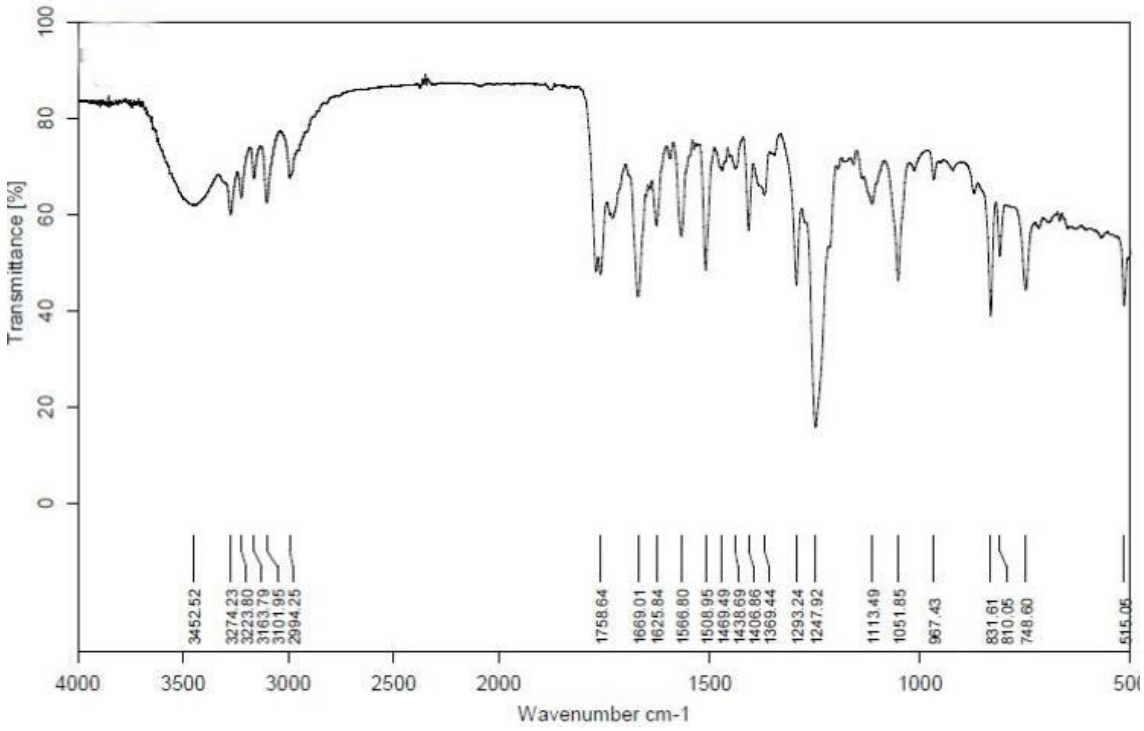


IMAGE 4.4: IR Spectra of 5b

Sample Name:	X			
Sample Type:	Unknown		Acquired By:	System
Vial:	72		Sample Set Name:	16022024_MASS_01
Injection:	1		Acq. Method Set:	MASS_METHOD
Injection Volume:	10.00ul		Processing Method:	MASSMETHOD_03
Run Time:	0.9 minutes		Channel Name:	MS TIC
			Proc. Chn. Descr:	ZQ F2 Scan MS TIC ZQ F4 Scan
Date Acquired:	19/06/2024	10:10:38 AM IST		
Date Processed:	19/06/2024	10:20:55 AM IST, 11:23:43 AM IST		

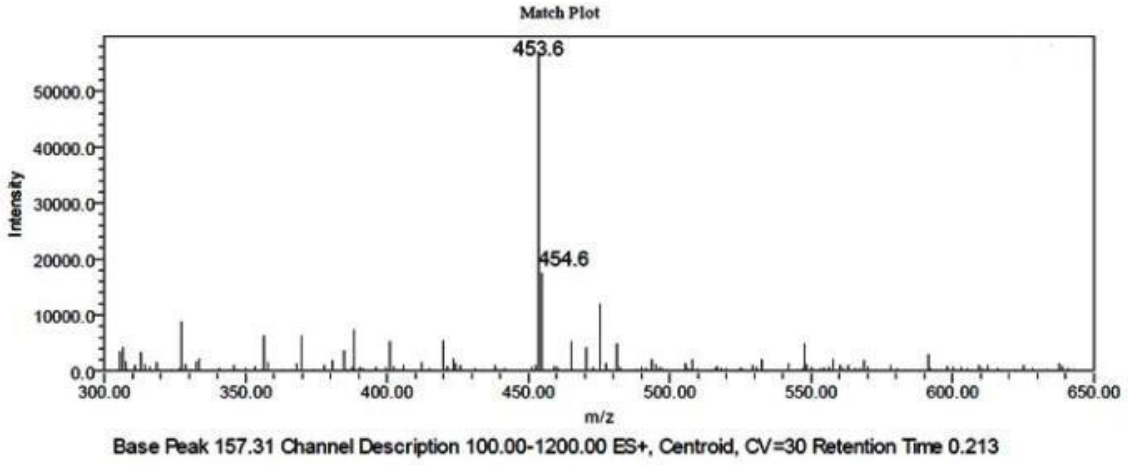


IMAGE 4.5: Mass Analysis report of 5b

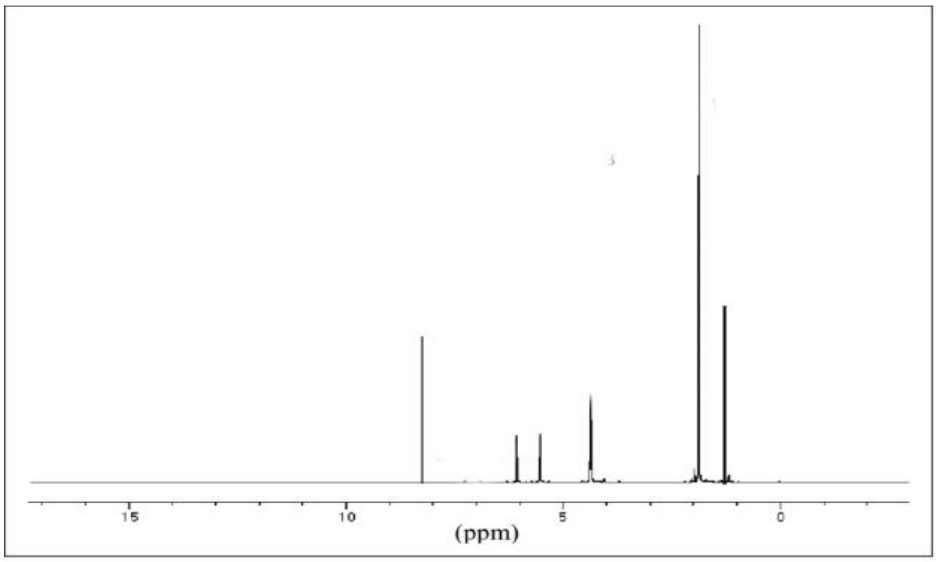


IMAGE 4.6: ^{1}H NMR of 5b

4.2.4.3 Synthesis of 1-(4-(2-(4-Fluorophenylamino)-2-oxoethyl) phenylsulfonyl)-3-(4-nitrobenzoyl) urea (5c)

The Friedel–Crafts alkylation reaction b/w 1-(4-nitrobenzoyl)-3 - (phenylsulfonyl) urea(0.1 mole) and 2 – chloro – N - (4-fluorophenyl) acetamide (1 mole) was conducted for 7 hours using anhydrous FeCl3 in nitrobenzene as the solvent. After cooling, crystals were isolated, yielding 65% of the product. The melting point of the obtained crystals was 116-118°C. The RF value was determined to be 0.6 using a mobile phase of ethyl acetate (7:3).

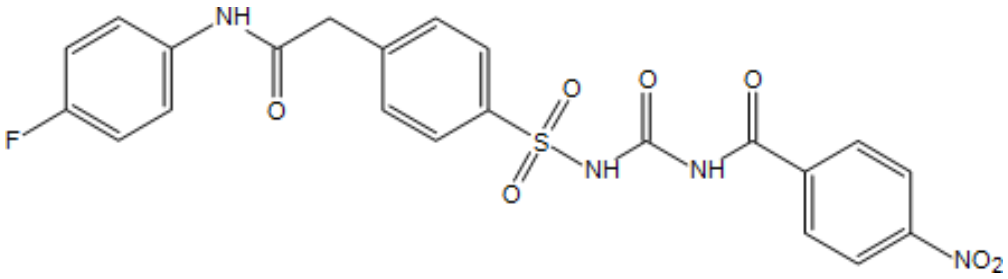


TABLE 4.5: Spectral data of 5c

Code	IR (KBr): ν (cm^{-1})	MASS (m/z)	^{1}H NMR (400 MHz)
5c	3701 (N-H) *str* 1670 (C=O) *str* 2988 (C-H) *str* Ar, 1278 (S=O) *str* 2950 (C-H) *str* 1568 (N-O) *str* *1350* (N-O) *str*	500.5 [M]	^{1}H NMR (δ rH),7.16(d,2H,ArH),7.60(d,6H,ArH),8.20(d,2H,ArH);

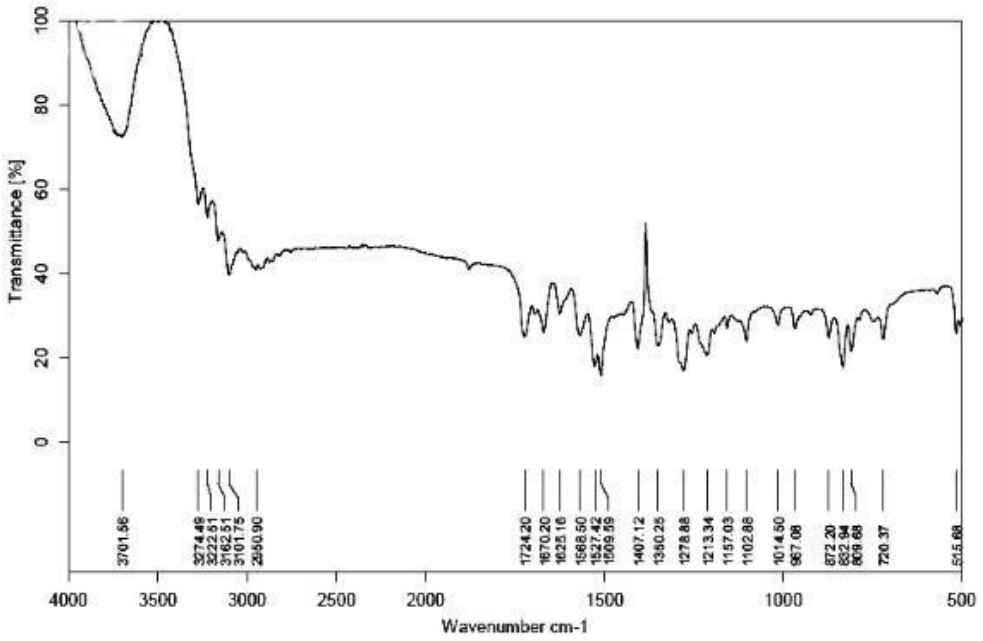


IMAGE 4.7: IR spectra of 5c

Sample Name:	X			
Sample Type:	Unknown		Acquired By:	System
Vial:	72		Sample Set Name:	17062024_MASS_01
Injection:	1		Acq. Method Set:	MASS_METHOD
Injection Volume:	10.00ul		Processing Method:	MASSMETHOD_03
Run Time:	0.8 minutes		Channel Name:	MS TIC
			Proc. Chn. Descr:	ZQ F2 Scan MS TIC ZQ F4 Scan
Date Acquired:	20/06/2024	11:40:37 AM IST		
Date Processed:	20/06/2024	11:41:54 AM IST, 11:42:43 AM IST		

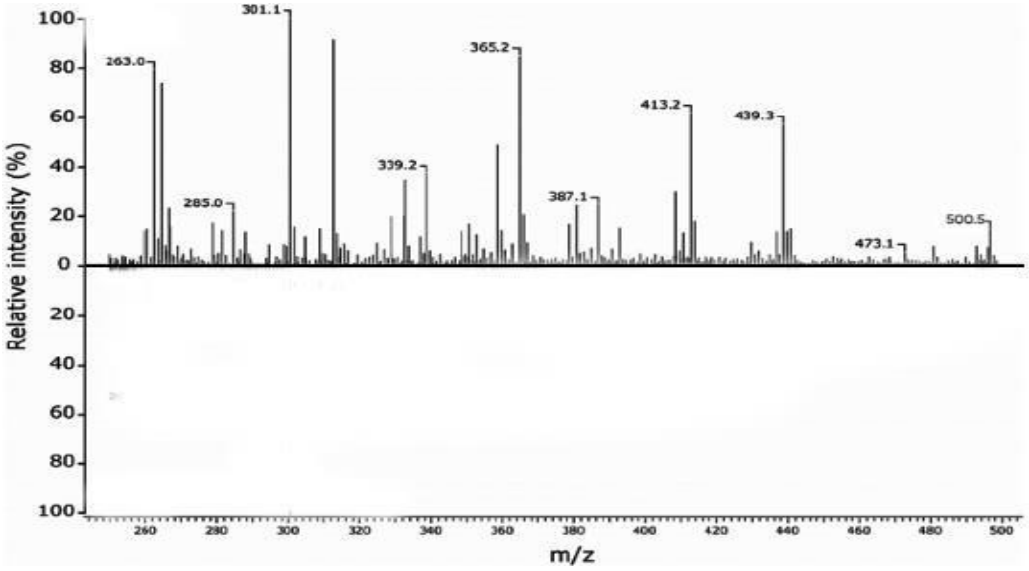
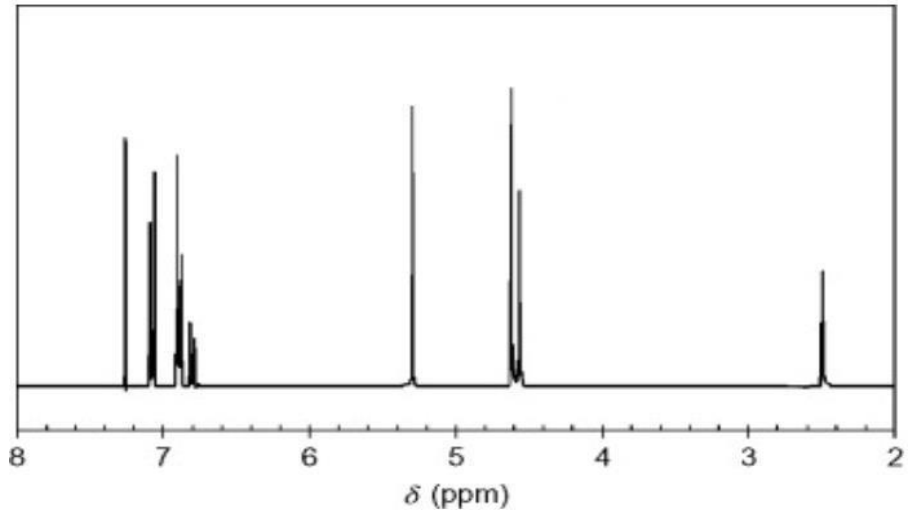


IMAGE 4.8: Mass Analysis report of 5c

IMAGE 4.9: ^{1}H NMR of 5c



4.3 In-vivo Biological Evaluation

4.3.1 Preparation of Diabetic Cell Cultures

1. **Cell Line Selection**: Use an appropriate pancreatic cell line or primary cells, such as insulin-producing beta cells, for the study. For diabetes research, a common choice is the **INS-1 cell line** or **RIN-5F cells** which are pancreatic beta-cell lines.
2. **Cell Culture**: Culture the selected cells in standard cell culture conditions (e.g., DMEM or RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics) until they reach the desired confluence.
3. **Induction of Hyperglycemia**:

- To simulate diabetes in vitro, treat the cells with high glucose concentrations (e.g., 25 mM glucose) to induce hyperglycemic conditions.

4. **Treatment Application**:

- After inducing hyperglycemia, apply the test compounds (Drug 5a, Drug 5b, Drug 5c) to the cell cultures. Dissolve the synthesized drugs in an appropriate solvent (e.g., dimethyl sulfoxide or sterile water) and add them to the cell cultures at the desired concentrations (e.g., 50 µM).

5. **Control Groups**:

- Include control groups for normal (non-diabetic) cells, hyperglycemic cells, and cells treated with a known standard (e.g., Glipizide).

4.3.2 Experimental Design

- **Control Groups**:

❖ **Normal Control**: Cells maintained in standard glucose conditions.

❖ **Hyperglycemic Control**: Cells exposed to high glucose conditionswithout drug treatment.

❖ **Standard Treatment**: Cells treated with Glipizide at a concentrationequivalent to the in-vitro dose.

- **Experimental Groups**:

❖ **Drug 5a Treatment**: Cells treated with synthesized Drug 5a at the in 1%CMC at 50 mg/kg body weight..

❖ **Drug 5b Treatment**: Cells treated with synthesized Drug 5b at the in1% CMC at 50 mg/kg body weight..

❖ **Drug 5c Treatment**: Cells treated with synthesized Drug 5c at the in 1%CMC at 50 mg/kg body weight..

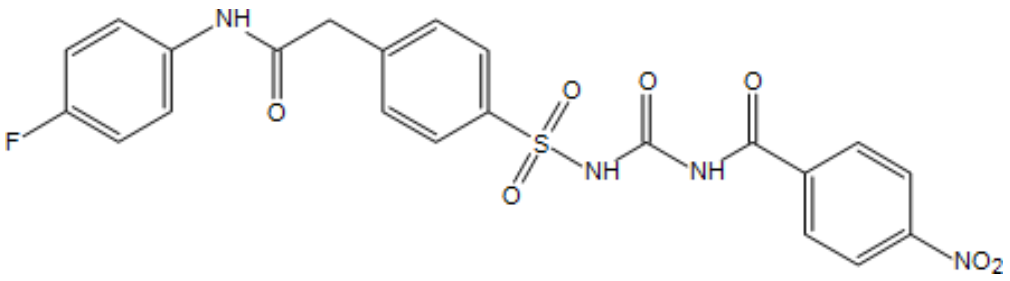
4.3.3 Statistical Analysis

- **Data Collection**: Measure relevant biological parameters such as cell viability, glucose uptake, insulin secretion, or other markers of interest.
- **Data Analysis**: Express the data as means ± standard error of the mean. Perform statistical analyses using one-way analysis of variance (ANOVA) followed by post-hoc Tukey's test, with $p < 0.01$ considered statistically significant.

RESULTS

5.1 Molecular Docking Analysis

The results are displayed as docking scores, indicating binding energies as listed inTable 4.1. All designed molecules exhibited favorable binding affinities compared tothe standard Glipizide. Among the 3 various substituted sulfonylureas and guanidine derivatives tested, compounds 5a, 5b & 5c demonstrated superior binding affinities compared to Glipizide. Notably, 1-(4-(2-(4-Fluorophenylamino)-2- oxoethyl)phenylsulfonyl)-3-(4-nitrobenzoyl)urea (5c) features NO2 and F groups at the para position of the benzene ring.



So, with the help of docking studies, we can say the electron withdrawing groups has significant effects on binding with receptor. As well as pyrrolidine ring does not have any notable affinity with binding pokect. **(5r-5w)**

The binding cavity and interactions of compounds 5a, 5b, and 5c with various amino acid residues are illustrated in IMAGE 4.1 to 4.5

TABLE 5.1: Docking outcomes for the synthesized compounds

Code	Docking score	Hydrogen bond energy	Van der Waals energy
5a	-112.311	- 16.3875	-95.9239
5b	-105.994	-13.5407	-92.4534
5c	**-120.836**	**-23.6739**	**-97.1619**
Glipizide	**-108.996**	**-91.48**	**-17.5158**

5.2 Computational Toxicity Analysis

Computational Toxicity Analysis profiles of the developed molecules were assessed using the ADME program. The application of Lipinski's The Rule of Five was crucial for assessing the analogs' drug-like properties. All designed and synthesized derivativesadhere to Lipinski's Rule of Five, indicating favorable drug-like characteristics. Most compounds exhibit good gastrointestinal (GI) absorption. Detailed results of the Computational Toxicity Analysis are summarized in Table 4.2.

TABLE 4.2: In-silico Toxicity Studies

Code	M.W.	HBd	HBa	C Log P	Drug likeness
5a	459	**4**	**7**	**2.15**	Yes, 0 violations
5b	457	3	5	2.91	Yes, 0 violations
5c	500	4	5	2.20	Yes, 0 violations

4.3 SciFinder Report

The SciFinder report for some synthesized derivatives confirms the novelty of thecompounds. The report indicates that no existing candidates match our synthesized compounds, underscoring their novelty and uniqueness in the field.

5.4 Methods Section

5.4.1 Chemistry – Schemes 1, 2, 3

The synthesis of 1-(4-((4-substitutedphenyl) carbamoyl) phenylsulfonyl)-3-(4-substitutedbenzoyl)urea/guanidine derivatives followed a literature method [48]. Friedel-

Crafts alkylation involved reacting 1-(4-substitutedbenzoyl)-3-(phenylsulfonyl) urea (0.1 mmol) with N-(4-substitutedphenyl)-2-chloroacetamide (1 mmol) in the presence of anhydrous FeCl3. Nitrobenzene served as the solvent, and the reaction proceeded for 7 hours. After cooling, the The reaction mixture was rinsed with ice-cold water.

The preparation of compound 1began with the reaction of benzene sulphonyl chloride with an excess of urea/guanidine under reflux conditions for 5 hours. Pyridine (0.2 ml) acted as a catalyst, and The reaction progress was tracked using thin-layer chromatography. Various derivatives of benzene carboxylic acid (NO2, Cl, and F) were transformed into benzene carbonyl chloride 2.using SOCl2 under reflux conditions for 3 hours. To prepare N-(4-substitutedphenyl)-2-chloroacetamide 4, different 2nd and 4th substituted aniline derivatives (F, Cl, NO2), Pyrrolidine, and piperazine derivativeswere stirred with chloroacetyl chloride under cooling conditions for 4 hours in a fume hood. The mixture was then treated with ice-cold water was added to the reaction mixture, and solid crystals of N-(4-substitutedphenyl)-2-chloroacetamide Four wereseparated.

The one-step Friedel-Crafts alkylation technique was used to produce derivatives of 1- (4-substitutedbenzoyl)-3-(4-(2-oxo-2-(pyrrolidin-1-yl) ethyl) phenylsulfonyl)urea/guanidine (5a-5c), as illustrated in Schemes 1, 2, and 3. A suitable compound for this synthesis was 1-(4-substitutedbenzoyl)-3-(phenylsulfonyl) urea/guanidine and 2 N- (4-substitutedphenyl)-2-chloroacetamide were refluxed in nitrobenzene with anhydrous FeCl3 as the catalyst for 6 to After a duration of 7 hours, the reaction mixture was subsequently added to ice-cold water to obtain the final products 5. Compounds 5a-5c was purified by recrystallization. Thin-layer chromatography was used to monitor the reaction progress, employing Ethyl acetate and hexane in a 3:7 ratio were used as the mobile phase. Certain impurities closely co-eluted with most of the compounds, resulting in a lower percentage yield of the pure target compounds.

5.5 Biological Evaluation: Molecular Targets of Compounds

Insulin is a peptide hormone with an amide linkage, whereas sulphonylureas, including my products, contain an NHCONH linkage. Insulin receptors readily bind to compounds with NHCO groups due to the similarity in their chemical structure. Sulfonylurea receptors (SUR) are crucial elements of the cellular membrane. Targeted by anti-diabetic drugs of the sulfonylurea class. These drugs function by stimulating Insulin secretion from pancreatic beta cells involves the SUR proteins, which functionas subunits. of the Kir6.x (6.1 and 6.2)

inward-rectifier potassium ion channels. The assembly consisting of four Kir6.x subunits and four SUR subunits forms the KATP channel, which facilitates ion conduction.

The selection of compounds for biological evaluation was based on a literature reviewof hypoglycemic agents, referencing the work by S. Prakash, D. Maji, S. Samanta, and R.K. Sinha, who reported on the design, development, and evaluation of cinnamic acid- amino acid hybrid analogs for their antidiabetic properties in Medicinal Chemistry, 4(2),1-6. Plasma concentrations and bioavailability of the compounds were not measured in this study. Primary screening of synthesized compounds aimed to identify the most active derivatives. Further pharmacological evaluation was not conducted as it was outside the scope of this study. However, the fact that these compounds exhibited pharmacological action after oral administration suggests their bioavailability.

Streptozotocin (STZ) causes diabetes by harming insulin-producing cells in the pancreas, resulting in hyperglycemia. The capacity of our target molecules to bind to sulphonylurea receptors was assessed by evaluating them in albino Wistar rats to measure the reduction in blood sugar levels. Data analysis was conducted employing GraphPad Prism with one-way ANOVA and subsequent Tukey's test. Our research indicated that administering these compounds to diabetic rats resulted in a reversal of their blood glucose levels. The way in which they produce their hypoglycemic effect might involve enhancing insulin's effect by enhancing pancreatic secretion from β-cells in the islets of Langerhans or by releasing it from its bound form.

However, compounds 5c (50.88 ± 3.7), derivatives of sulfonylureas, demonstrated a higher percentage reduction in blood glucose levels (Table 4.3, 4.4, and IMAGE 4.4) compared to other derivatives. Compound 5c features an electronegative atom (NO2) at the 4th position of the benzene ring, respectively, in the 4th position of the sulfonylurea derivatives, showing superior blood sugar reduction compared to other derivatives.

Tukey's Multiple Compariso	**Mean Difference**	**Q Value**	**Significant? P < 0.01?**	**Summary**	**99% Confidence Interval of Difference**

n Test					
DC vs Gli	-57.26	9.552	Yes	***	-91.62 to -22.90
DC vs 5a	-35.28	5.885	Yes	**	-69.64 to 0.9166
DC vs 5b	-50.25	8.383	Yes	***	-84.61 to -15.89
DC vs 5c	-43.09	7.189	Yes	***	-77.46 to -8.733

TABLE 5.4: In-vivo biological activity

Groups	Mean± S.E.M
DC	0.6287±0.9512
GLI	57.89±4.905
5a	35.91±2.9
5b	50.88±3.7
5c	43.72±10.6

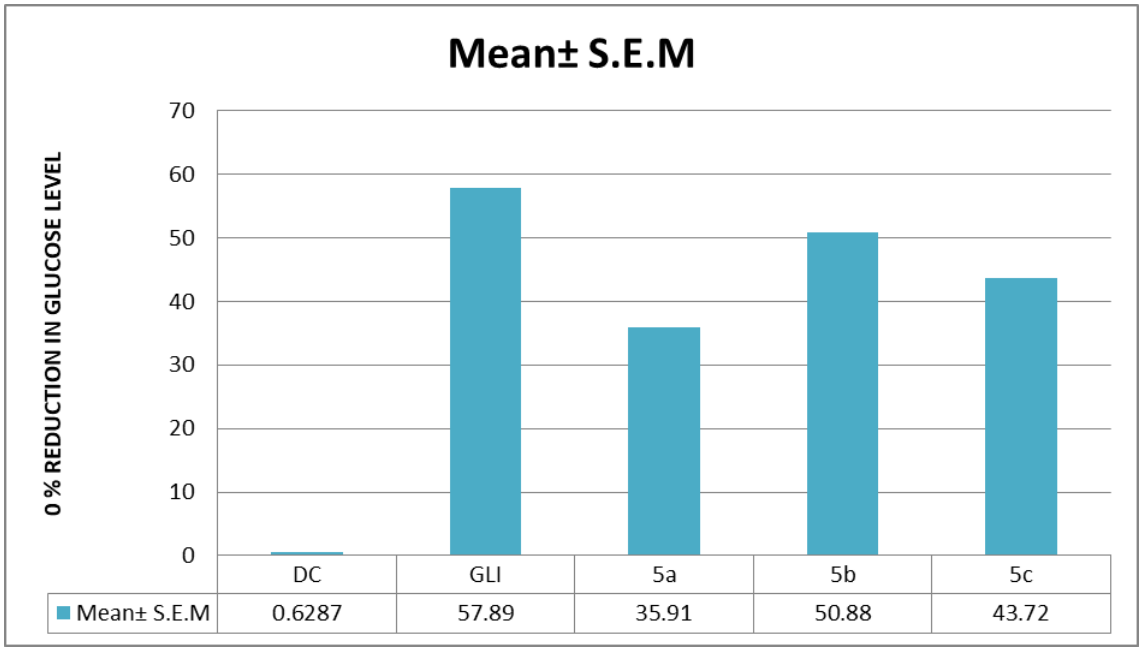


IMAGE 5.2 ***In vivo biological evaluations***

DISCUSSION

6.1 Overview of the Current Study

6.1.1 Molecular docking analysis (MDA)

MDA was conducted to assess the binding affinity of the designed compounds. The results, presented in Table 4.1, show the docking scores (binding energies) compared to the standard Glipizide. All designed compounds exhibited a favorable binding affinity. Notably, compounds 5c (-120.836) demonstrated superior binding affinities compared to Glipizide.

6.1.2 Computational Toxicity Analysis

Computational toxicity profiles of the designed compounds were assessed using the SWISS ADME program.

All targeted derivatives (5a-5ab) adhered to Lipinski's rule of five, indicating favorable properties related to absorption, distribution, metabolism, and elimination (ADME).

6.2 Experimental Section

All targeted derivatives underwent purification by recrystallization and were subsequently characterized using spectroscopic techniques including IR, Mass Spectroscopy, 1H NMR, and 13C NMR. The spectral analyses provided conclusive evidence supporting the elucidated structures.

6.2.1 In Vivo Biological Evaluation

Streptozotocin (STZ) causes diabetes by impairing insulin-producing cells in the pancreas, resulting in hyperglycemia. Compounds 5c (50.88±3.7) derivatives of sulfonylureas containing electronegative atoms (NO2, F, Cl) at the 4th position of the benzene ring, exhibited a superior percentage reduction in blood glucose levels compared to other derivatives.

6.3 Achievements with Respect to the Objectives

Diabetes mellitus is a long-term condition with a rising incidence and associated micro and macro vascular complications. Through literature review, molecular docking studies, and in-silico toxicity assessments, novel hypoglycemic agents were designed and synthesized. In vivo biological evaluation provided significant insights into blood sugar reduction in albino Wistar rats.

6.4 Recommendations for Future Research

The successful introduction of novel hypoglycemic agents derived from various Sulphonylureas/guanidine derivatives opens avenues for future research. Exploration of diverse heterocyclic such as pyrrolidine, Piperazine, oxazole, thiazole, pyrazine, and oxadiazole with different substitutions could be pursued. Additionally, there is scope for in

vitro biological evaluations to further enhance understanding in antidiabetic therapy. Development of an HPLC method for novel derivatives is also recommended.

REFERENCES

1. Ike SO, Rodney L., (2015). Prediabetes awareness, healthcare provider's advice, and lifestyle changes in American adults . *Int J of Dia Mell* , 3, 11-18. ISSN: 1877-5934

2. Zimmet P, Alberti KG, Shaw J.,(2001). Global and societal implications of the diabetes epidemic. *Nature* , 414, 782–7. ISSN: 0028-0836 (print); 1476-4687 (web)

3. Wild S, Roglic G, Green A, Sicree R, King H., (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27,1047–53. ISSN Print: 0149-5992; Online: 1935-5548

4. Kerner W, Brückel J.,(2014). Definition, Classification and Diagnosis of Diabetes Mellitus. *Exp Clin Endo Dia* ,122, 384–386. ISSN: 0947-7349

5. Ahmed AM., (2002). History of diabetes mellitus. *Saudi Med J,* 23, 373-378.

6. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA.,(2002). Diabetes prevention program research group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* , 346, 393–403.

7. Jumpup., (2007) Williams Textbook of endocrinology (12th ed.). Elsevier/Saunders, Philadelphia, USA 1371–1435.

8. Chen L, Magliano DJ, Zimmet PZ., (2014). The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nat Rev Endocrinol,* 8, 228-236. ISSN: 1759-5029 (print) and 1759-5037 (online).

9. Somanathan SS., (2016). The synergic antioxidant and antidiabetic activities of poly herbal preparation on streptozotocin induced diabetic rats. Jawaharlal Nehru Technological University, Anantapuram

10. Arun GG, Sumanth MM, Sonali S, Sitanshu SK, Gautam R, Ananthanarayanan PH, Das AK., (2013). Diabetes in rural Pondicherry, India: a population-based study of the incidence and risk factors. *WHO South-East Asia J of Public Health*
, 2, 3–4. ISSN**:** 2224- 3151, E-ISSN 2304-5272

11. Jaya PT, Gursimer J, Sohan C, Sanjay J, Arnab P, Rajendra P, Rajiv S.,(2017). Prevalence and risk factors of diabetes in a large community-based study in North India: results from a STEPS survey in Punjab, India. *Diab & Metabolic Syn* 9, 8, 1-8. ISSN: 1758-5996.

12. Danieal S, Luca R, Glan PC, Pamela M., (2015). Sulphonylureas and their uses in clinical practice. *Arch Med Sci*, 11 (4), 840-848. ISSN:1896-9151 (Online); 1734-1922 (Print).

13. Joshi SR, Parikh RM, Das AK.,(2007). Insulin - History, Biochemistry, Physiology and Pharmacology. *J Asso of Phy Ind* ,55, 19-25. ISSN 0004-5772

14. Bangstad HJ, Danne T, Deeb LC, Jarosz-Chobot P, Urakami T, Hanas R.,(2009). Insulin treatment in children and adolescents with diabetes. *Pedi Dia*, 10 (12), 82– 99. ISSN:1399-5448

15. Mane PB, Antre RV, Oswal RJ., (2012). Antidiabetic Drugs: An Overview. *Int JPharma and Chem Sci*, 1 (1), 301-306. ISSN: 2249-9504

16. Tasneem TS., (2013). Newer Insulins. *Int J of Pharm Chem and Bio Sci* 3 (2), 242- 246. ISSN: 2249-9504

17. Mehanna AS., (2005). Insulin and Oral Antidiabetic Agents. *Ame J Pharm Edu*, 69 (5), 1-11. ISSN: 1553-6467

18. Kinesh VP, Neelam DP, Punit BP, Bhavesh SB, Pragna KS.,(2010). NovelApproches for Oral Delivery of Insulin and Current Status of Oral Insulin Products. *Int J Pharm Sci And Nanot* 3 (3), 1057- 1064. ISSN: 0974-3278

19. Davis T, Edelman SV.,(2010). Insulin Therapy in Type 2 Diabetes. *The Medi Clini of North Amer* 88: 865–895. ISSN: 0025-7125 (Print), 1557-9859 (Electronic), 0025-7125 (Linking)

20. Kaur J, Badyal DK.,(2008). Newer Insulins. *Sci J of Med Edu & Res* 10 (3), 107-111.

21. Fahad A, Musad S., (2016). The Role and Prevalence of Polyol Pathway and Oxidative Stress Markers as Risk Factors for Diabetic Cataract in Adult Type-I Diabetic and Diabetic Cataract Saudi Patients. *J Clin Exp Ophthalmol*, 7(3), 1-8. ISSN: 2155-9570

22. Ananya S, Ajay T, Parminder S Moloy M.,(2011). Pharmacological and Pharmaceutical Profile of Gliclazide: A Review. *J of Appl Pharma Sci* 01 (09), 11-19.ISSN: 2231-3354

23. Alok KV, Himanshu S, Mavurapu S, Swayam PS, Priti T, Amar BS.,(2015). Flavone-Based Novel Antidiabetic and Antidyslipidemic Agents. *J Med Chem*, 55 (10), 4551– 4567. ISSN 0022-2623

24. Dhanaji VJ, Umesh RP, Neha R, Arvind KS, Ramrao AM, (2012). Synthesis and antihyperglycemic evaluation of new 2,4-thiazolidinediones having biodynamic aryl sulfonylurea moieties. *Bio & Med Chem Lett* ; 22, 436–439. ISSN: 0960- 894X

25. Satyanand T, Sachin K, Amit K, Mohit S., (2010). Synthesis of analouges of sulphonylureas as antidiabetic drugs and their structure activity studies. *Int J of Pharma world Res*, 1 (2), 1-16. ISSN: 0976-111X

26. Hermenegilda MD, Rafael VM, Rolffy OA, Daniel DC, Luis MF, Gabriel NV.,(2008). N-(6-substituted-1,3-benzothiazol-2-yl)benzene sulfonamideshaving antidiabetic activity. *Bio & Med Chem Lett* , 18, 2871–7. ISSN: 0960- 894X

27. Ameya AC, Nandini RP.,(2007). Synthesis and Biological Activity of Sulfonylureas having anti diabetic activity. *J Chinese Chem Soc*, 54, 771-7. ISSN:2192-6549

28. Wei Wei, Dandan C, Jingbo L, Yuxin L, Yi M, Yonghong L et al (2016). Design, synthesis and SAR study of novel sulfonylureas containing an alkenyl moiety. *Org and Bio Chem*, 21, 14 (35), 8356-66. ISSN: 1477-0520 (print), 1477-0539 (web)

29. Su X, Vicker N, Ganeshapillai D, Smithm A, Purohit A, Reed MJ, Potter B V.,(2006). *Mol Cell Endocrinol,* 248 (1-2), 214-217. ISSN: 1872-8057.

30. Santosh NM , Akash DP , Pritam ND, Nikhil SS, Pankaj BM.,(2016). Design, synthesis and in vivo screening of some novel quinazoline analogs as anti- hyperlipidemic and hypoglycemic agents. *Bioorg & Med Chem Lett*, 26, 272– 276. ISSN: 0960-894X

31. Hui-bin Z , Ya-an Z , Guan-zhong W, Jin-pei Z , Wen-long H, Xiao-wenH.,(2009). Synthesis and biological evaluation of sulfonylurea and thiourea derivatives substituted with benzenesulfonamide groups as potential hypoglycemic agents. *Bioorg & Med Chem Lett*, 19, 1740–1744. ISSN: 0960- 894X

32. HongWoo L, BokYoung K, Joong Bok A, Sung KK, Jung Hwa L ,Jae Soo S, Soon K A , Sang JL, Seung SY.,(2005). Molecular design, synthesis, and hypoglycemic and hypolipidemic activities of novel pyrimidine derivatives having thiazolidinedione. *Eur J of Med Chem*, 40, 862–874. ISSN: 0009-4374 (print); 0223-5234 (web)

33. Hassan MF, Khalid AK, Abdullah MA.,(2011). Synthesis and biological evaluationof new 3-trifluoromethylpyrazole sulfonylurea and thiourea derivatives as antidiabetic and antimicrobial agents. *J of Flu Chem*, 132, 131–137. ISSN: 0022-1139

34. Ji Xun, Xi Chunmei, J Wang, Su Mingbo, Lei Zhang, T Dong, Li Zeng.,(2014). Design, synthesis and biological evaluation of 4-fluoropyrrolidine-2- carbonitrile and octahydrocyclopenta[b]pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors. *Eur J of Med Chem*, 6, 242-256. ISSN: 0009-4374(print); 0223-5234 (web).

35. A Ahmadi, M Khalili, K Khatamia, M Farsadrooha, B Nahri-Niknafsa.,(2014). *Mini-Revi in Med Chem*, 14, 208-213. ISSN: 1875-5607

36. Bertrand C, Patrick T, Christophe M, Aline P, Jacques C.,(2002). Synthesis and Hypoglycemic Evaluation of Substituted Pyrazole-4-carboxylic Acids. *Bioorg &Med Chem Lett* , 12, 2105–2108. ISSN: 0960-894X

37. Koch W (1977). Benzazepinyl sulfonylureas and intermediates therefore. US Patent 19750549572.

38. Kuhla D, Sarges R (1973). Thiazolecarboxamide sulfonylurea hypoglycemic agents. US Patent 19730338965.

39. Dasseux Jean LH (2003). Cycloalkyl-hydroxyl compounds and compositions for cholesterol management, and related uses. US Patent 201615274436.

40. Basiard Z (1997). Derivatives of polyhydroxyalkylpyrazines, their synthesis and medicinal agents comprising thereof. RU Patent 19200103582.

41. Barnes D [Us]; Bebernitz GR [Us]; Coppola GM [Us]; Nakajima K [Us];StamsT [Us]; Topiol SW [Us] (2009).Thiadiazole derivatives as antidiabetic agents.WO2007067615A3

42. Schneider S, Ueberberg S, Korobeynikov, A, Schechinger, W, Schwanstecher C, Schwanstecher (2007). Synthesis and evaluation of a Glipizide glucose-conjugate:A potential new lead compound for substituted Glipizide derivatives as islet imaging agents. *Regulatory Peptides*, 139 (1-3), 122-7. ISSN: 0167-0115

43. Alok ST, Ravitas D, Arvind KJ, P. Sudhir K (2015). Synthesis and oral hypoglycemic effect of novel thiazine containing trisubstituted benzenesulfonylurea derivatives. *Sau Pharma J*,23, 475 – 82. ISSN: 1319-0164

44. Docking Server. [Online]. Virtual Drug research and development company.[Online]. Available: https://www.dockingserver.com/web/ [Accessed 1st August 2016]

45. GM Martin, C Yoshioka, EA Rex, JF Fay, Q Xie, MR Whorton, JZ Chen (2017). Cryo-EM structure of the ATP-sensitive potassium channel illuminates mechanisms of assembly and gating. *eLife*., 1-21. ISSN: 2050-084X

46. David T. Manallack, Richard J. Prankerd, Elizabeth Yuriev, Tudor I. Oprea, David K. Chalmers (2013). The Significance of Acid/Base Properties in Drug Discovery. *Chem Soc Rev* 21, 42 (2), 485–496. ISSN: 0306-0012 (print); 1460- 4744 (web)

47. Dhrubo JS, Ishan IP, Ashish DP (2017). Scifinder® As A Latest Tool In Innovative Research Within A New Dimension For Integrating Scientific Chemical Databases. *Eur J Pharma And Med Res, 3 (11), 01-19.* ISSN 2394- 3211

48. P Whalley. The comparison of Friedel-Crafts alkylation and acylation as a means to synthesise alkyl xylenes (2016). *Plymouth Student Sci*, 9 (1), 252-296. ISSN 1754-2383 [Online]

49. S Prakash , D Maji, S Samanta and RK Sinha (2014). Design, Synthesis and Antidiabetic, Cardiomyopathy Studies of Cinnamic Acid-Amino Acid Hybrid Analogs. *Med chem*, 4, 2, 1-6. ISSN: 2161-0444