

# Sulfonylureas As An Antidiabetic Agent

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**Abstract:** Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from inadequate insulin secretion, impaired insulin action, or a combination of both. It affects millions of individuals globally and remains a major public health concern due to its strong association with morbidity and mortality. This review provides an overview of the different categories of DM, including Type 1, Type 2, gestational diabetes, and several less prevalent forms. For decades, sulphonylureas (SUs) played a central role in the treatment of Type 2 Diabetes Mellitus (T2D), either as an alternative to or in combination with metformin. However, the introduction of newer oral anti-diabetic agents—initially DPP-4 inhibitors (gliptins) and more recently SGLT2 inhibitors (gliflozins)—has significantly transformed therapeutic strategies. Unlike SUs, these modern medications, though costlier, offer advantages such as a minimal risk of hypoglycaemia and favourable effects on body weight. Moreover, gliptins have demonstrated strong cardiovascular safety, while gliflozins provide both cardiovascular and renal protection in high-risk individuals. This article examines the evolving role of SUs in T2D management, considering the risks of hypoglycaemia and available evidence on cardiovascular outcomes. Although international recommendations differ due to varying economic factors, the relevance of SUs in current practice is gradually diminishing. Their use is still possible but should be carefully restricted, particularly in older adults with frailty and in patients prone to hyperglycaemia.

**Keywords:** Diabetes Mellitus, Gestational Diabetes, Insulin, Cardiovascular safety, Sulfonylureas, Hypoglycaemia

## 1. INTRODUCTION

Diabetes Mellitus (DM) is a long-term and progressive metabolic disorder marked by consistently high blood sugar levels (hyperglycaemias). This condition results from problems with insulin production, insulin function, or both. (1) Insulin, a hormone created by the pancreas, plays a crucial role in regulating glucose levels in the bloodstream. When the body either doesn't produce enough insulin or can't use it effectively, it leads to various health complications, both in the short and long term. Globally, DM is among the most prevalent hormonal disorders and poses a serious public health concern, contributing significantly to illness, death, and economic strain.

### 1.1 TYPES OF DIABETES MELLITUS

Diabetes Mellitus is primarily divided into four categories:

#### **A). Type 1 Diabetes mellitus (T1DM)**

This form is an autoimmune disorder in which the immune system wrongly targets and destroys the pancreas's beta cells that produce insulin. As a result, the body becomes insulin-deficient. Although Type 1 Diabetes can develop at any age, it is most frequently diagnosed in children, teenagers, and young adults.

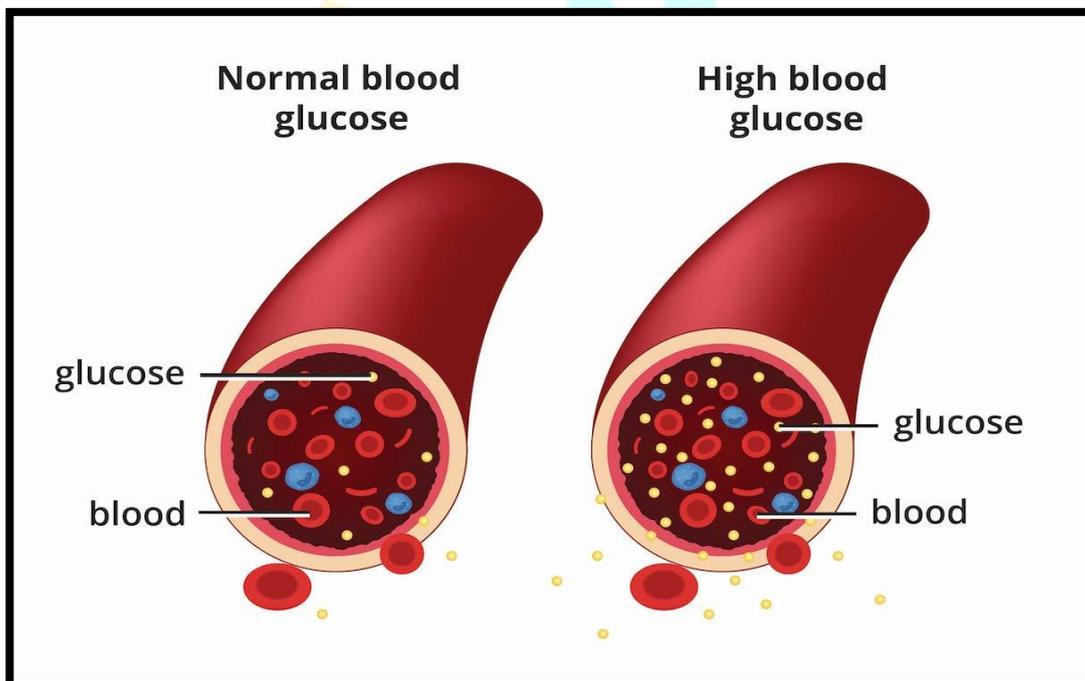
T1DM is a chronic autoimmune condition where the body's immune system destroys insulin-producing beta cells in the pancreas. As a result, individuals with T1DM are dependent on insulin therapy for life to maintain normal blood glucose levels

**b).Type 2 Diabetes Mellitus (T2DM)**

This is the most common form of diabetes, making up around 90% of all diagnosed cases. T2DM occurs when the body's cells become resistant to insulin, making it difficult for glucose to enter the cells. Over time, insulin production may decline as well. Risk factors include aging, obesity, sedentary behavior, and poor nutrition

**c) Gestational Diabetes Mellitus (GDM)**

GDM is a temporary type of diabetes that emerges during pregnancy and typically disappears after the baby is born. However, women who experience GDM are at a greater risk of developing type 2 diabetes in the future. GDM can also pose health risks to both mother and child (4).



**Fig.No.1: Diabetes Mellitus**

**d) Other Specific Types**

Other less common forms of diabetes include those resulting from genetic issues affecting insulin production or action, conditions affecting the pancreas (e.g., cystic fibrosis), or diabetes caused by certain drugs or chemicals (e.g., steroid-induced diabetes). These forms vary in severity and treatment approach.

**1.2 Epidemiology**

Diabetes Mellitus has become a major public health concern globally, with its prevalence rising at an alarming rate. According to the International Diabetes Federation (IDF), as of 2021, about 537 million adults aged 20–79 had diabetes, which equates to 10.5% of the global adult population. Projections suggest this figure may rise to 643 million by 2030 and 783 million by 2045 if current trends continue. A disproportionate number of cases occur in low- and middle-income nations, where diagnosis and treatment are limited. Nearly half of all individuals with diabetes are unaware of their condition, underscoring the importance of early detection and screening initiatives.

### 1.3 Risk Factors

Multiple factors contribute to an individual's risk of developing diabetes: Genetics: Family history plays a significant role; those with close relatives who have diabetes are more susceptible. Excess Body Weight: Obesity, particularly abdominal fat, contributes significantly to insulin resistance, a key factor in T2DM. Lack of Exercise: Inactivity is strongly linked to the onset of type 2 diabetes. Aging: The risk increases notably after the age of 45. Unhealthy Diet: Diets rich in processed foods and sugary drinks, and low in fibre, elevate the risk. Ethnic Background: Higher rates of diabetes are observed in African American, Hispanic,

Native American, and Asian American, populations. Previous Gestational Diabetes Women who had GDM are more likely to develop T2DM later on. Chronic Stress Mental Health: Ongoing stress and psychological issues may lead to poor lifestyle choices and hormonal imbalances, raising diabetes risk.

### 1.4 Complications

When not adequately managed, diabetes can result in numerous severe health complications. These complications are typically divided into three main categories:

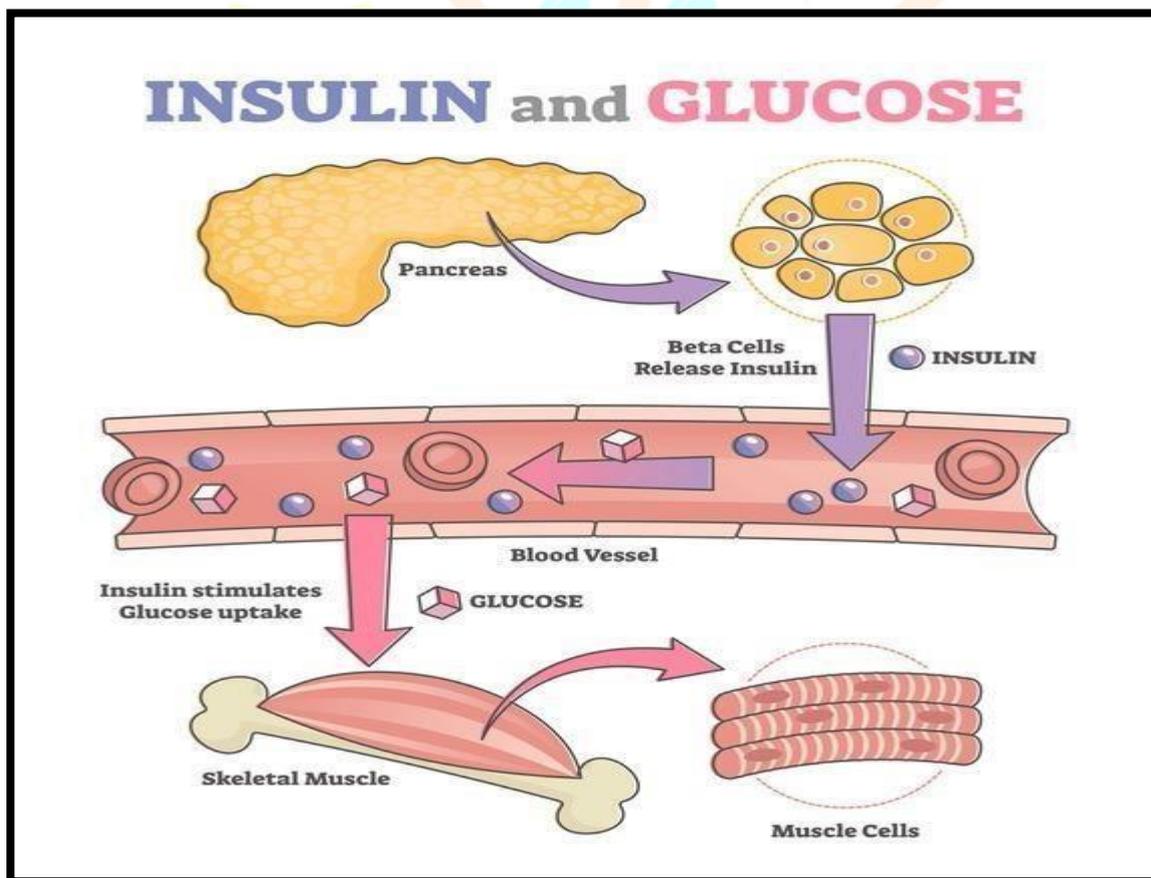


Figure 1 : Insulin and Glucose

### 1.3 Micro vascular Complications

**1.3.1 Diabetic Retinopathy:** This involves damage to the small blood vessels in the retina, potentially leading to visual disturbances and, in severe cases, blindness

**1.3.2 Diabetic Nephropathy:** This refers to damage to the kidneys caused by prolonged high blood sugar levels, which can progress to chronic kidney disease and possibly end-stage renal failure.

**Diabetic Neuropathy:** This condition involves nerve damage, most commonly in the peripheral nerves, and can cause pain, numbness, and muscular weakness, particularly in the limbs.

### 1.4 Macro vascular Complications

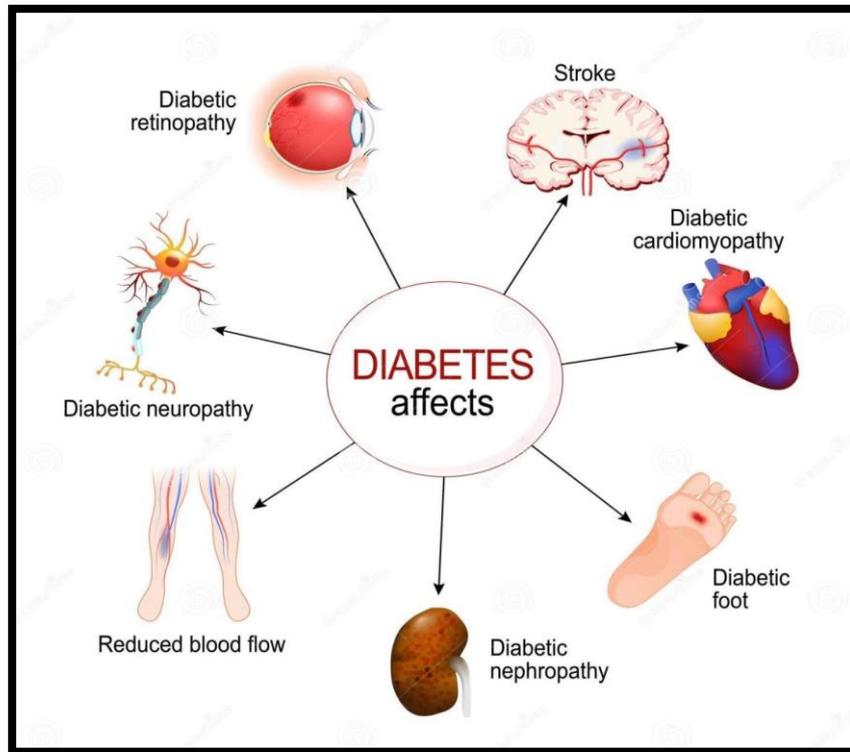
- **Cardiovascular, Disease:** Individuals with diabetes are at a substantially higher risk of developing heart disease, strokes, and peripheral artery disease.
- **Diabetic Foot:** Due to compromised blood flow and nerve impairment, diabetic patients face an elevated risk of foot ulcers, infections, and in severe cases, limb amputation.

### 1.5 Other Complications

**1.5.1. Infections:** Diabetes can weaken the immune response, increasing vulnerability to infections. For this reason, both diabetic and immunocompromised individuals are advised to monitor serum ferritin levels through laboratory tests. Research has shown that elevated ferritin levels are often seen in diabetic patients and may contribute to the development and severity of various complications, including those related to infections like COVID-19. Routine ferritin level monitoring is therefore recommended for individuals with prediabetes or diabetes.

**1.5.2. Inflammatory Conditions:** Elevated C-reactive protein (CRP) levels are associated with inflammation and are often higher in individuals with obesity. This is due to the secretion of inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6) from adipose tissue. CRP is considered a significant marker of inflammation and may play a role in the development and progression of type 2 diabetes mellitus (T2DM). Understanding the link between insulin resistance and inflammation is essential for improving treatment and prevention strategies.

- **Mental Health Concerns:** People living with diabetes are also at a greater risk of experiencing mental health challenges such as depression and anxiety.



**Figure 2 : Diabetes affects complications of diabetic mellitus.**

### 1.6 DIAGNOSIS

Diabetes is diagnosed using specific clinical tests that evaluate blood sugar levels. These include:

- **Fasting Plasma Glucose (FPG):** Measures blood glucose after an overnight fast. A result of 126 mg/dL (7.0 mmol/L) or higher confirms a diagnosis of diabetes.
- **Oral Glucose Tolerance Test (OGTT):** After fasting, the patient ingests a glucose containing drink, and blood sugar is measured two hours later. A result of 200 mg/dL (11.1 mmol/L) or higher indicates diabetes.
- **Hemoglobin A1c (HbA1c):** Provides an average of blood glucose levels over the past 2–3 months. A result of 6.5% (48 mmol/mol) or higher signifies diabetes.
- **Random Plasma Glucose Test:** Measures glucose levels at any point during the day, regardless of meals. A reading of 200 mg/dL (11.1 mmol/L) or more, along with symptoms such as excessive thirst or frequent urination, can also confirm diabetes.
- **Fructosamine Test:** This test measures glycated proteins in the blood and serves as an alternative to HbA1c. It reflects blood glucose control over a shorter period (2–3 weeks), making it useful in certain clinical scenarios where HbA1c is less reliable.
- **Fructosamine and Alternative Monitoring Methods** Fructosamine testing offers insights into short-term glucose regulation, reflecting average blood sugar levels over the past two to three weeks.

### 1.7 Emerging Cytological Technique:

A new microscopic method analyzes smears of oral epithelial cells. Research indicates a statistical correlation between glucose levels and the cellular count in the oral cavity (16). However, further studies are needed to validate its reliability for clinical laboratory use.

- **Oxidative Stress Markers:**

Two key indicators, total antioxidant capacity (TAC) and malondialdehyde (MDA) are commonly used to evaluate oxidative stress and damage in diabetic patients.

## 1.8 Diabetes Treatment

Diabetes management requires a comprehensive strategy that combines healthy lifestyle choices, medication, and continuous blood sugar monitoring.

### 1.8.1 Lifestyle Interventions

- **Nutrition:** A well-balanced diet tailored for diabetes involves controlled carbohydrate intake and emphasizes fruits, vegetables, lean proteins, and whole grains. **Exercise:** Engaging in regular physical activity enhances insulin sensitivity and supports weight control.
- **Weight Control:** Losing excess weight—especially for those who are overweight or obese—can lead to significant improvements in glycemic control.

### 1.8.2. Medications

- **Insulin:** Crucial for individuals with type 1 diabetes and may also be needed for those with advanced type 2 diabetes.
- **Oral Antidiabetic Drugs:** Multiple drug classes are available for type 2 diabetes management, including metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors.  
Injectable Therapies: Some patients may benefit from injectable GLP-1 receptor agonists to better regulate their blood glucose.

## 1.9 Monitoring Glucose Levels

Effective management also involves routine glucose monitoring, which may include self-testing, continuous glucose monitoring systems, and periodic HbA1c assessments. These tools help evaluate treatment success and guide any necessary modifications.

## 2.0 Sulfonylureas

Sulfonylureas (SUs) are powerful glucose-lowering medications that have been utilized in the management of type 2 diabetes (T2D) since the 1960s. They reduce blood glucose levels by promoting insulin release from the pancreatic  $\beta$ -cells through inhibition of the ATP-sensitive potassium (KATP) channels in the islets (Hellman & Taljedal, 1975). As some of the most commonly prescribed oral antidiabetic agents, SUs are effective but carry certain risks. One significant concern is the potential for severe hypoglycemia, which may lead to unconsciousness, coma, and in some cases, require emergency medical attention

Another common side effect associated with sulfonylureas is weight gain, typically ranging from 1 to 4 kilograms, often stabilizing after about six months of treatment. Over time, the effectiveness of SUs may decline due to the progressive reduction of  $\beta$ -cell mass in individuals with T2D. This often necessitates dose adjustments and may eventually result in treatment failure.

SUs are typically administered once or twice daily, either with or just before meals. In the event of a missed dose, it should be taken as soon as remembered. However, if it is close to the time of the next scheduled dose, the missed one should be skipped to avoid double dosing. In the United States, after metformin, the most frequently prescribed sulfonylurea is glipizide

## 2. Objective of the Study:

**Sulfonylureas (SUs)** are widely used second-line glucose-lowering agents in the management of Type 2 Diabetes (T2D), known for their effectiveness but also associated with a relatively high risk of hypoglycaemia. The primary objective of this study is to evaluate and discuss the use of Sulfonylureas in the treatment of T2D patients.

In addition to the main objective, the study also aims to:

## 2.1 Historical Background of Sulfonylureas

Sulfonylureas (SUs) were initially explored for their antibacterial properties before World War II. Their hypoglycemic potential was discovered in 1942 by French chemist Marcel Janbon and his team, who were investigating sulfonamide antibiotics, specifically p-amino sulfonamide-isopropyl-thiodiazole (2254RP), for the treatment of typhoid fever. During their research, they observed unexpected cases of severe hypoglycemia among patients

By August 1946, it was established that sulfa-based compounds could stimulate insulin release from the pancreatic islet  $\beta$ -cells, leading to lowered blood glucose levels. This discovery laid the foundation for the use of sulfonylureas in managing diabetes.

The first sulfonylurea drug, Tolbutamide, was introduced in Germany in 1956. It was soon followed by other first-generation SUs, including Chlorpropamide, Acetohexamide, and Tolazamide. A major advancement came in 1984 with the introduction of second generation sulfonylureas, such as Glipizide, Glyburide, and Glibenclamide

A significant contribution to understanding the mechanism of action came from French endocrinologist Auguste Loubatières. He demonstrated that the glucoselowering effect of sulfonylureas depended on the presence of a functional pancreas and was mediated through the stimulation of insulin secretion

1. Provide a brief historical background of Sulfonylureas,
2. Highlight the advantages and clinical benefits of Sulfonylureas, and
3. Examine the potential side effects and safety concerns associated with their use.

## 3. Mechanisms of Sulfonylureas :

Sulfonylureas (SUs) are a well-established and generally well-tolerated class of medications used in the management of type 2 diabetes (T2D). They are commonly prescribed when Metformin is contraindicated or not sufficient to maintain glycemic control. These agents can effectively reduce HbA1c levels by approximately 1–2%, making them a reliable option for improving blood glucose levels. Moreover, they are cost-effective and supported by long-term safety data (NICE, 2015; Mohajan & Mohajan, 2023v, w). An additional mechanism of action includes the reduction of hepatic insulin clearance, which leads to higher circulating insulin concentrations.

### 3.1 Sulfonylureas are categorized into three generations:

**1. First-Generation SUs:** Introduced in the 1950s, these include short-chain compounds such as Tolbutamide, Acetohexamide, Chlorpropamide, and Tolazamide).

**2. Second-Generation SUs:** Developed by modifying the side chain attached to the benzene ring, these drugs include Glyburide (introduced in 1984), Glipizide, Gliclazide, Glycopyramide, and Gliquidone. They offer enhanced efficacy, better membrane permeability, improved receptor selectivity, and a lower incidence of side effects compared to first-generation agents.

**3. Third-Generation SUs:** Glimepiride is the sole representative of this category, approved in 1995. Although sometimes grouped with second-generation agents, Glimepiride stands out due to its high potency and long-lasting action, allowing for once-daily administration

Among the most frequently prescribed SUs are Gliclazide and Glimepiride. Gliclazide is available in both immediate-release and modified-release formulations. These medications function by promoting the

secretion of endogenous insulin, making them effective only in patients with residual pancreatic beta-cell function. They are often used alongside Metformin or Glitazones for combined therapy.

All sulfonylureas act by enhancing insulin release and activity.

Common dosing includes: Glyburide (2.5–5 mg once daily), Gliclazide (80–320 mg, typically divided into two daily doses), and Glimepiride (1–8 mg once daily). It is recommended to take these medications approximately 30 minutes before meals to optimize their effects.

**4. Advantages of Sulfonylureas :** Sulfonylureas (SUs) play significant role in reducing microvascular complications associated with diabetes, including retinopathy, neuropathy, and nephropathy. They are widely utilized as a second-line treatment for type 2 diabetes (T2D), particularly when metformin therapy is no longer sufficient. Despite concerns over their association with an increased risk of hypoglycemic episodes—mainly due to their insulin-releasing mechanism—SUs remain a preferred option in many treatment plans. Physicians consider multiple factors such as effectiveness, safety profile, tolerability, and affordability when prescribing sulfonylureas for diabetes management.

Their low cost, widespread availability, and extensive clinical usage contribute to their continued relevance in diabetes care. As one of the earliest classes of antihyperglycemic agents, sulfonylureas remain among the most commonly prescribed for T2D. Their sustained popularity is largely attributed to their reliable glycemic control, low cost, and additional endocrine and metabolic benefits. Newer-generation sulfonylureas like glimepiride offer improved characteristics, including enhanced cardiovascular safety and more effective glucose regulation, making them suitable candidates in the era of precision medicine

**5. Classification of sulfonylureas**

Sulfonylureas are classified into two generations based on their chemical structure, potency, and duration of action:

- **First-Generation Sulfonylureas:** These are older drugs with a lower potency and a shorter duration of action. They have more drug– drug interactions due to high protein binding.

**Table 1 : Classification of first generation**

| Drug Name      | Brand Name | Half life          |
|----------------|------------|--------------------|
| Tolbutamide    | Orinase    | 4-8 hours          |
| Chlorpropamide | Diabinese  | 24-72 hours (long) |
| Acetohexamide  | Dymelor    | 6-12 hours         |
| Tolazamide     | Tolinase   | 10- 14 hours       |

**Table no :1 Classification of first generation**

2. **Second-Generation Sulfonylureas:** These are more potent, have longer durations of action, and fewer side effects than the first generation drugs.

**Table 2 : Classification of second generation**

| Drug Name                    | Brand name                   | Half life   |
|------------------------------|------------------------------|-------------|
| Glibenclamide<br>(Glyburide) | Daonil,Diabeta,<br>Micronase | 10-12 hours |
| Glipizide                    | Glucotrol                    | 2-4 hours   |
| Gliclazide                   | Diamicron,Reclide            | 10-12 hours |
| Glimepiride                  | Amaryl                       | 5-9 hours   |

**Table no:2 Classification of second generation**

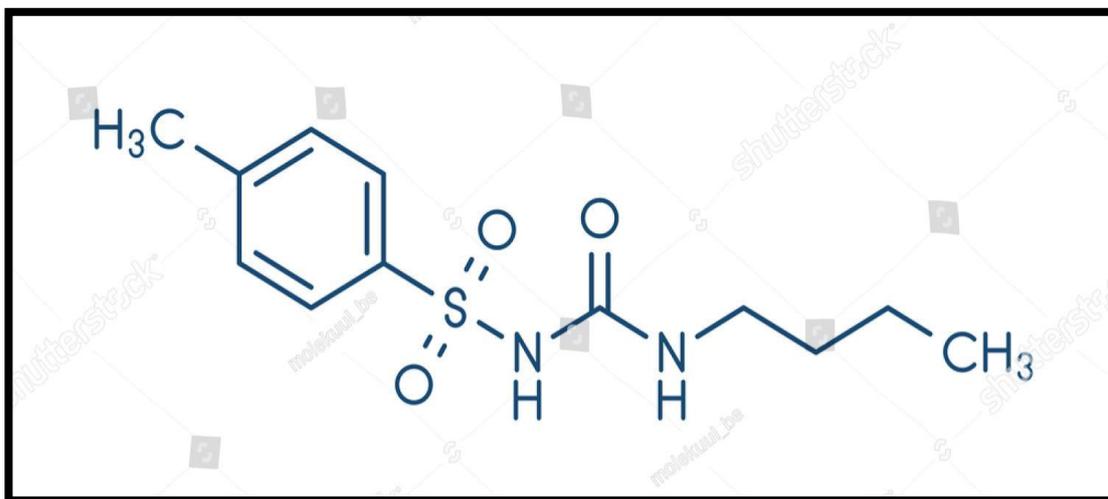
#### 4.1 Tolbutamide

Tolbutamide has a molecular formula of  $C_{12}H_{18}N_2O_3S$  and a molecular weight of 270.35 g/mol. Its structure consists of a butyl group attached to a urea moiety, which is linked to a p-methylbenzenesulfonyl (tosyl) group, forming an N-sulfonylurea structure. Molecular Formula & Weight

- **Molecular Formula:**  $C_{12}H_{18}N_2O_3S$
- **Molecular Weight:** 270.35 g/mol

#### Structure Composition

- **N-sulfonylurea:** Tolbutamide is an N-sulfonylurea compound.
- **Butyl Group:** A four-carbon butyl chain is attached to one end of the urea linkage.
- **Urea Linkage:** The central part of the molecule is a urea group (NH-CO-NH-).
- **Tosyl Group:** A p-methylbenzenesulfonyl (tosyl) group is linked to the other nitrogen



**Figure 3: Structure Of Tolbutamide**

#### ➤ SAR OF Tolbutamide

Tolbutamide SAR (Structure-Activity Relationship) is defined by its first generation sulfonylurea structure, which is key to its mechanism of action: it binds to a specific receptor on pancreatic beta cells, blocking ATPsensitive potassium channels, which leads to calcium influx, depolarization, and insulin release to lower blood sugar levels.

Key structural features include the sulfonylurea linkage and the ptoenesulfonyl group, with variations in the alkyl chain affecting properties like half-life

#### ➤ Uses of Tolbutamide :

1. **Providing a cost-effective treatment:** As a first-generation sulfonylurea, it is an established and generally affordable oral medication for type 2 diabetes.
2. **Used in combination therapy:** Tolbutamide can be combined with other antidiabetic agents, such as metformin, to achieve better glycemic control.
3. **Used in the tolbutamide test:** Historically, it has been used in a clinical test to evaluate the pancreas's ability to release insulin. This is not a common therapeutic use today.
4. **Stimulating insulin secretion:** It helps manage blood sugar by causing the beta cells in the pancreas to produce and release more insulin.
5. **Acting as an adjunct therapy:** It is used alongside diet and exercise when lifestyle changes alone are not enough to control blood sugar levels.
6. **Improving glycemic control:** By regulating insulin release, tolbutamide helps maintain overall glycemic control in patients with type 2 diabetes.
7. **Preventing diabetes complications:** Proper blood sugar management with tolbutamide can help reduce the long-term risk of serious complications, including nerve damage, kidney problems, eye issues, and cardiovascular disease.

#### 4.2. Chlorpropamide

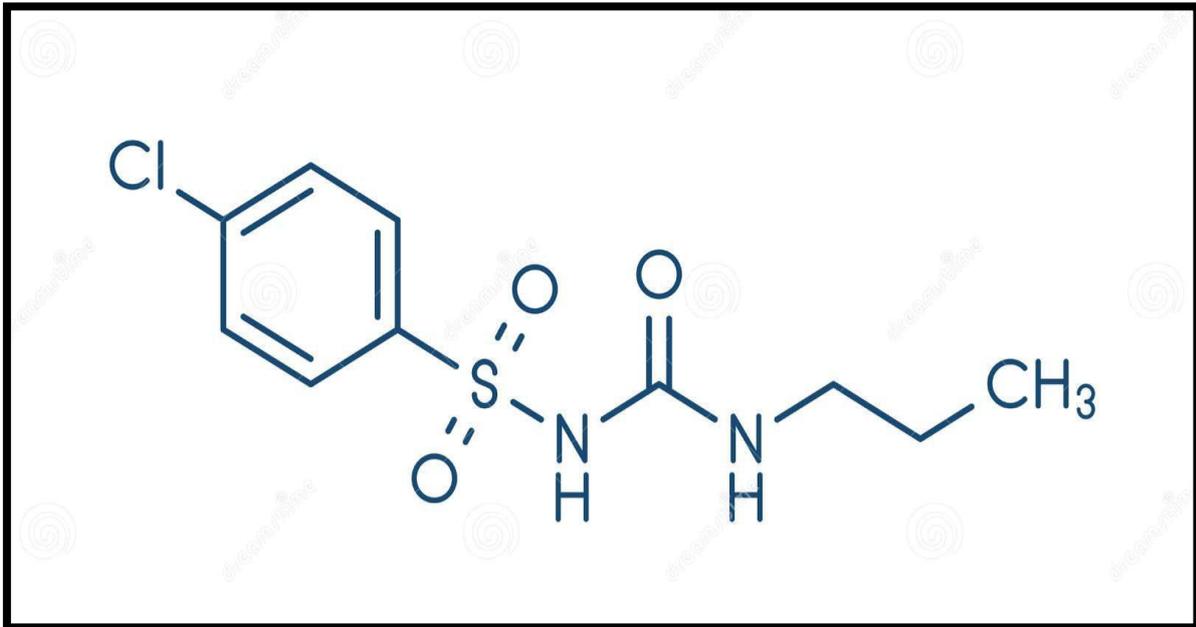
Chlorpropamide has a molecular formula of C<sub>10</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S and a molecular weight of approximately 276.74 g/mol. Its chemical structure is a substituted , specifically 1(pchlorobenzenesulfonyl)3propylurea, which is reflected in its formula and is available for viewing on various scientific databases like .

- **Molecular Formula:** C<sub>10</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>3</sub>S
- **Molecular Weight:** 276.74 g/mol

- **Structure:**

Chlorpropamide is characterized by:

- A benzenesulfonyl group (C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>) with a chlorine atom at the para (p-) position.



### Chlorpropamide

- A urea group (NH-CO-NH), where the nitrogen atoms are substituted. One of the urea nitrogens is attached to the sulfonyl group, and the other is linked to a propyl group (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>).

### SAR OF chlorpropamide

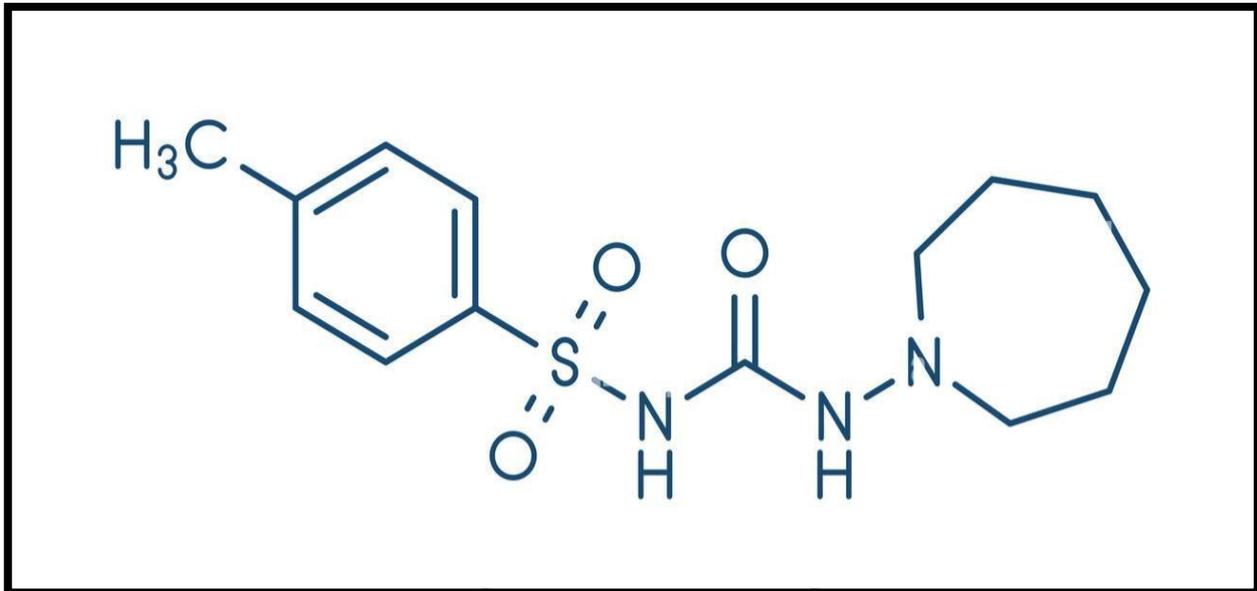
Chlorpropamide's SAR focuses on the sulfonylurea structure responsible for its antidiabetic action, which involves binding to ATP-sensitive potassium channels in pancreatic cells to increase insulin secretion. Key features include the sulfonylurea group (S(O<sub>2</sub>)NH), a substituted phenyl ring with a chlorine atom, and a propyl chain that influences its pharmacokinetics, half-life, and reduced protein binding compared to other sulfonylureas.

**Sulfonylurea Group (S(O<sub>2</sub>)NH)** Binding site:

### 4.3. Tolazamide

The chemical formula for tolazamide is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S, and its molecular weight is approximately 311.40 g/mol.

- **Formula:** C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S
- **Molecular Weight:** 311.40 g/mol
- **Structure :**



### Tolazamide

➤ **The SAR (Structure-Activity Relationship) for tolazamide**, a sulfonylurea, indicates that the drug's overall structure includes a p-toluenesulfonyl group linked to a urea moiety, which in turn is connected to an azepane ring. The p-toluenesulfonyl part of the molecule is crucial for its hypoglycemic effect, while the azepane ring influences the drug's pharmacokinetics, such as absorption and elimination, and contributes to its distinct properties compared to other sulfonylureas.

#### Key Structural Features and Their Significance

- **Sulfonylurea Moiety (p-toluenesulfonyl group):** This part of the molecule is a key pharmacophore common to all sulfonylureas and is essential for the drug's ability to stimulate insulin release from pancreatic beta cells.
- **Urea linkage:** The urea group connects the sulfonyl group to the heterocyclic ring.
- **Azepane ring:** The presence of the seven-membered azepane ring is a defining feature of tolazamide. This structural difference from other sulfonylureas, like tolbutamide with its butyl group, affects the drug's physicochemical properties, leading to different absorption, distribution, metabolism, and excretion (ADME) profiles.

#### ➤ Uses of Tolazamide

Tolazamide is an oral hypoglycemic medication used in the treatment of type 2 diabetes mellitus. It belongs to the first-generation sulfonylurea class of drugs and is used as an adjunct to diet and exercise to manage high blood sugar levels. The brand name for tolazamide, Tolinase, is discontinued in the United States, though generic versions may still be available.

1. Type 2 diabetes management: Tolazamide helps lower blood glucose levels in adults with type 2 diabetes when diet and exercise alone are not sufficient.
2. Combination therapy: It can be used as a second-line monotherapy or in combination with other oral antidiabetic drugs (except rapid-acting secretagogues) or insulin.
3. Transient glucose control: Tolazamide may be used for short term administration during periods of temporary loss of glycemic control in patients who are typically well-managed by diet.

#### 4.5. Glibenclamide

Glibenclamide has the molecular formula  $C_{23}H_{28}ClN_3O_5S$  and a molecular weight of approximately 494.00 g/mol. These are standard values used across chemical databases and scientific resources for this medication, which is also known by the name Glyburide.

- **Molecular Formula:**  $C_{23}H_{28}ClN_3O_5S$
- **Molecular Weight:** 494.00 g/mol
- **structure**

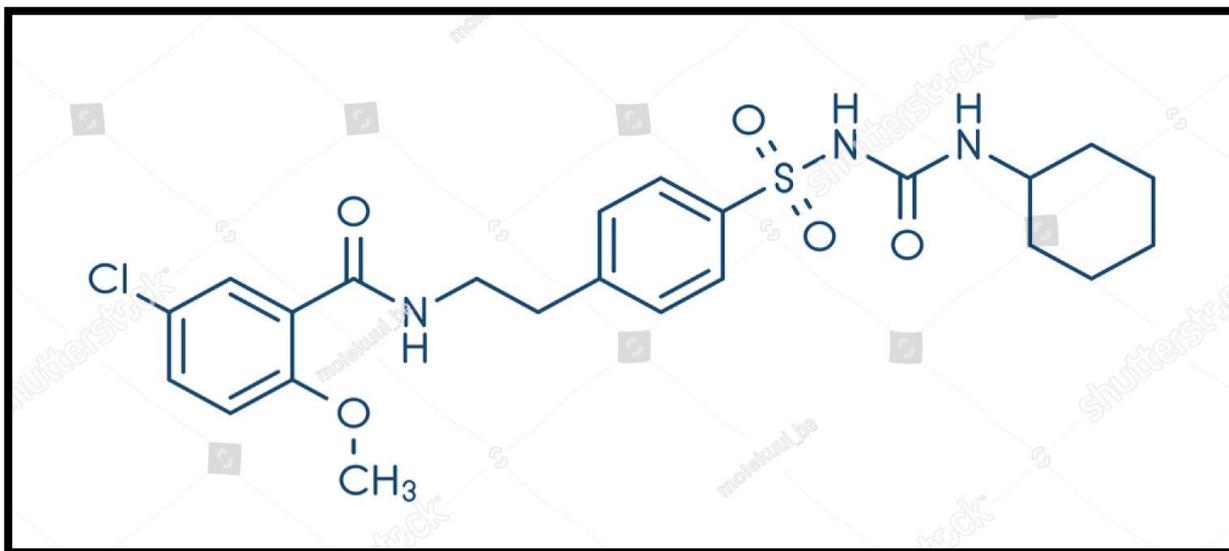


Figure 4 : Structure of Glibenclamide

##### ➤ SAR of Glibenclamide

Glibenclamide SAR refers to the structure-activity relationship of glibenclamide, which is a sulfonylurea antidiabetic drug used for Type 2 diabetes. Studies have analyzed its three-dimensional structural properties to understand how specific structural elements contribute to its potassium channel blocking activity, which is crucial for its ability to stimulate insulin secretion from the pancreas. Research in this area aims to design more effective compounds with better antagonistic activity by identifying key structural features responsible for its biological effects.

##### • Structure-Activity Relationship (SAR):

This term describes the relationship between the chemical structure of a molecule (like glibenclamide) and its biological or pharmacological activity.

##### • Glibenclamide's Mechanism:

As a sulfonylurea, glibenclamide's primary action is to increase the release of insulin from the pancreatic  $\beta$ -cells by blocking ATP-sensitive potassium channels (KATP).

##### • Research Focus:

Studies, such as those using comparative molecular field analysis (CoMFA), examine the effects of different structural modifications on glibenclamide's activity.

##### • Key Structural Elements:

Research has revealed that specific parts of the glibenclamide molecule are vital for its blocking action and subsequent insulin-stimulating effects.

### ➤ Applications in Drug Design:

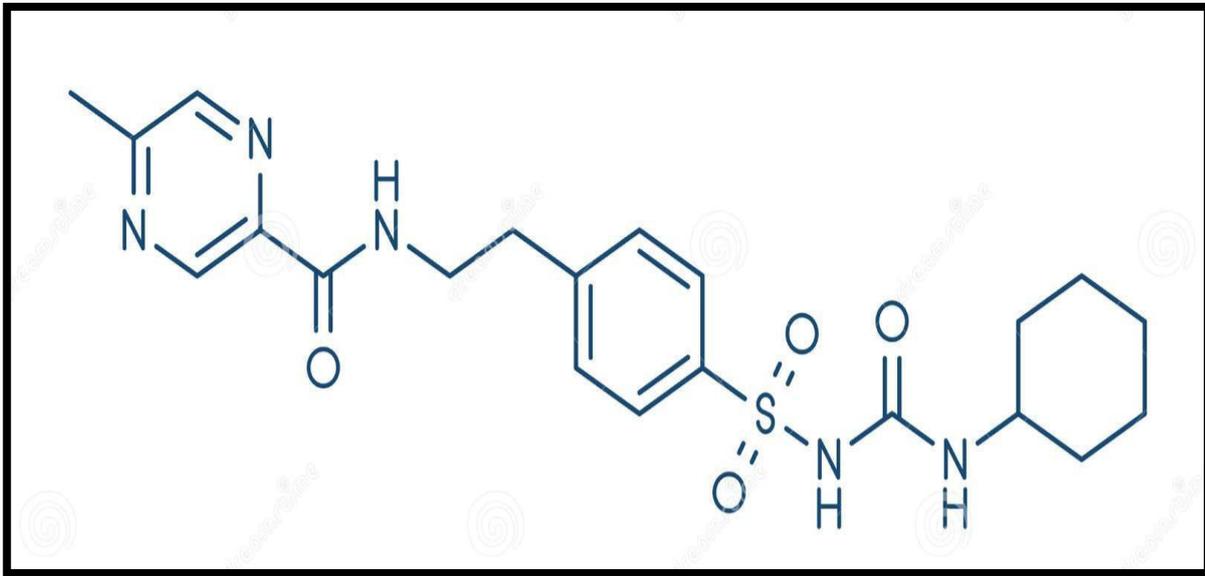
Understanding these relationships helps in developing new glibenclamide analogs or derivatives with improved activity, greater specificity, and potentially reduced side effects.

### ➤ Uses of Glibenclamide

1. Boosts insulin release: The main function of glibenclamide is to stimulate the beta cells in the pancreas to release more insulin.
2. Closes potassium channels: It does this by binding to and closing ATP-sensitive potassium channels on the beta cells. This causes the cell to depolarize, triggering the release of insulin containing granules.
3. Lowers blood sugar: The increased insulin helps to lower the glucose (sugar) level in the blood.
4. Other effects: Glibenclamide also has some effects outside the pancreas, including reducing glucose output from the liver and increasing the body's sensitivity to insulin.
5. Type 2 diabetes: Glibenclamide is used in adults with type 2 diabetes to help regulate blood sugar. It is sometimes combined with other medications, such as metformin, for better blood sugar control.
6. Gestational diabetes: It is sometimes used for managing gestational diabetes (diabetes during pregnancy) when blood glucose targets are not met with lifestyle changes and metformin. However, some studies suggest that babies of mothers treated with glibenclamide may have a higher birth weight compared to those treated with insulin.
7. Traumatic brain injury (TBI): Based on animal studies and early human trials, glibenclamide is being explored for its potential to reduce brain swelling (edema) after a TBI.
8. Spinal cord injury (SCI): Similar to its use for TBI, research is being conducted to evaluate glibenclamide's potential neuroprotective effects for patients with acute traumatic cervical SCI.

### 4.6 Glipizide

- **Molecular formula:**  $C_{21}H_{27}N_5O_4S$
- **Molecular weight:** 445.54 g/mol



**Figure 5 : Structure of Glipizide**

### SAR of Glipizide

- Structure-Activity Relationship (SAR) of Glipizide and Sulfonylureas
- The SAR of sulfonylureas (including glipizide) is key to understanding their biological activity. Here's a breakdown(33)
- **Region of the Molecule SAR Insight**
- **Sulfonylurea group (-SO<sub>2</sub>-NH-CO-NH-)** Essential for binding to the sulfonylurea receptor (SUR1) on pancreatic  $\beta$ -cells; triggers insulin release.
- **Para-substituted aryl ring** Enhances potency. A para-substitution is necessary for high activity.
- **Cyclohexyl group** A bulky lipophilic group on the terminal nitrogen increases binding affinity and potency.
- **Pyrazine ring with carboxamide** Improves binding to SUR1 and modulates pharmacokinetics; contributes to specificity and reduced side effects.
- **Alkyl/aryl substituents on urea** Adjust lipid solubility and duration of action. Larger, lipophilic substituents enhance cell membrane penetration.

### 6. Uses of Glipizide

1. **Monotherapy for type 2 diabetes:** Glipizide can be prescribed on its own for adults with type 2 diabetes whose blood sugar levels are not adequately controlled by diet and exercise alone.
2. **Combination therapy:** It is often used with other diabetes medications, such as metformin, to achieve better glycemic (blood sugar) control. This is typically done when a single medication is not sufficient.
3. **Adjunct to lifestyle changes:** Glipizide works alongside diet, exercise, and weight management to manage blood sugar. Medication is used to supplement, not replace, these healthy lifestyle habits.
4. **Managing glucose after meals:** The medication stimulates the pancreas to release more insulin, which is particularly effective for controlling the spike in blood sugar levels that occurs after meals.

## 7. Summary

Sulfonylureas are a class of oral antidiabetic drugs used primarily in the treatment of Type 2 Diabetes Mellitus (T2DM). They work by stimulating the pancreatic  $\beta$ -cells to release insulin, thereby lowering blood glucose levels. This insulin release is independent of blood glucose concentration, which increases the risk of hypoglycemia, especially in elderly patients or those with irregular eating patterns. Sulfonylureas are categorized into first-generation (e.g., chlorpropamide, tolbutamide) and second-generation (e.g., glipizide, gliclazide, glimepiride) drugs. Second-generation sulfonylureas are more potent, require lower doses, and have fewer side effects. These drugs are cost-effective, widely available, and can reduce HbA1c by 1–2%, making them effective for glycemic control. However, they may cause weight gain, hypoglycemia, and are not recommended in patients with Type 1 diabetes, pregnancy, or severe renal/hepatic impairment.

## 8. Conclusion

Sulfonylureas are a well-established class of oral medications used in the treatment of type 2 diabetes mellitus (T2DM). They function by stimulating insulin secretion from pancreatic  $\beta$ -cells, thereby helping to lower blood glucose levels. While sulfonylureas are effective at reducing blood glucose and HbA1c levels, their clinical use is often limited by important drawbacks, such as a high risk of hypoglycemia, weight gain, and diminished efficacy over time as  $\beta$ -cell function declines. These limitations are particularly relevant in long-standing diabetes or in elderly patients.

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