WELCOME

TO

This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site http://www.fdspharmacy.in/

You tube https://www.youtube.com/c/FDSpharmacy

Telegram https://t.me/Fdspharmacy

App https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy

E-mail fdspharmacyinfo@gmail.com

MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

- **Sulfonyl ureas :** Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride.

Sulfonylureas

- **Sulfonylureas (SUs)** are a class of **oral hypoglycemic agents** used in **Type 2 Diabetes Mellitus (T2DM)**.
- They **stimulate insulin secretion** from pancreatic β-cells, hence are **insulin secretagogues**.
- Useful in **patients with residual β-cell function**.
- Classified based on **generation**:

Generations

Generation	Examples	Potency	Notes
First	Tolbutamide, Chlorpropamide, Acetohexamide	Lower	Rarely used now due to long half-life and side effects
Second	Glibenclamide (Glyburide), Glipizide, Gliclazide	Higher	Safer, more potent, shorter half-life
Third	Glimepiride	Very high	Once-daily dosing, fewer side effects

Chemical Structure

- **General formula:** $R–SO_2–NH–C_6H_4–R'$
- Contains a **sulfonylurea functional group** ($–SO_2–NH–CO–NH–$) attached to an **aromatic ring**
- Substitutions on aromatic ring influence **potency, duration, and pharmacokinetics**

Mechanism of Action

1. **Binding to sulfonylurea receptor (SUR1)** on pancreatic β-cells
2. **Closure of ATP-sensitive K^+ channels** → depolarization of β-cell membrane
3. Opening of **voltage-gated Ca^{2+} channels** → Ca^{2+} influx
4. **Stimulates exocytosis of insulin-containing vesicles** → ↑ insulin secretion

Additional effects (second-generation SUs):

- Some **extra-pancreatic action:** increase peripheral glucose utilization and decrease hepatic glucose production

Clinical Uses

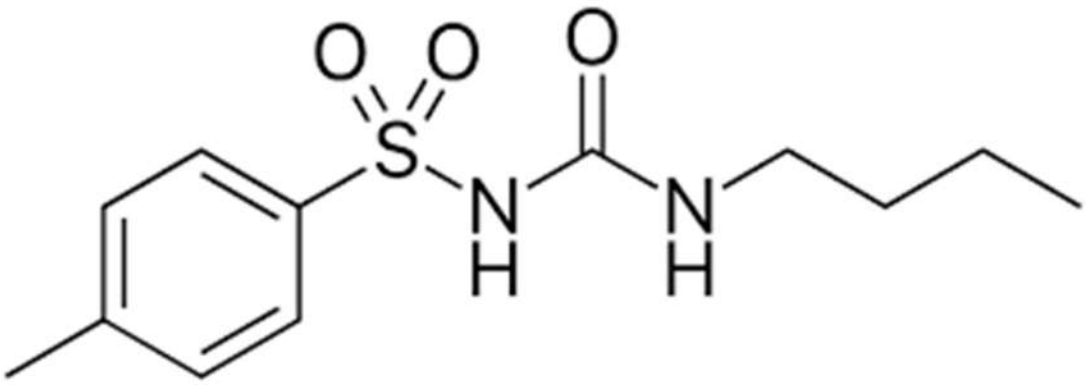
- **Type 2 Diabetes Mellitus** (especially overweight or elderly patients with residual β-cell function)
- May be used in **combination with Metformin or other oral agents** for additive effect

Tolbutamide

- **Tolbutamide** is a **first-generation sulfonylurea** oral hypoglycemic agent.
- It is used to **manage type 2 diabetes mellitus** in patients whose hyperglycemia is not controlled by diet and exercise alone.
- It works by **stimulating insulin release from pancreatic β-cells**.
- Administered **orally**, usually once or twice daily due to its **short duration of action** (about 6–12 hours).

Chemical Structure

- **Chemical name:** 1-(Butylsulfonyl)-3-methylurea
- **Molecular formula:** $C_{11}H_{16}N_2O_3S$
- **Molecular weight:** 240.31 g/mol
- **Chemical class:** Sulfonylurea; first-generation oral hypoglycemic
- **Structural**



Mechanism of Action

- **Target:** Pancreatic β-cells (ATP-sensitive K^+ channels)

Stepwise Mechanism:

1. Tolbutamide binds to **sulfonylurea receptor 1 (SUR1)** on β-cell plasma membrane.

2. This **closes ATP-sensitive K^+ channels**, causing **membrane depolarization**.
3. Depolarization **opens voltage-dependent Ca^{2+} channels**, increasing intracellular calcium.
4. Elevated calcium triggers **exocytosis of insulin-containing granules**.
5. **Overall Effect:**
    - Increased **insulin secretion**, lowering blood glucose levels

Synthesis

1. **Starting material:** Butylsulfonyl isocyanate or derivatives
2. **Step 1:** Reaction with methylamine → forms sulfonylurea moiety
3. **Step 2:** Purification → crystallization to obtain pharmaceutical-grade Tolbutamide

Uses

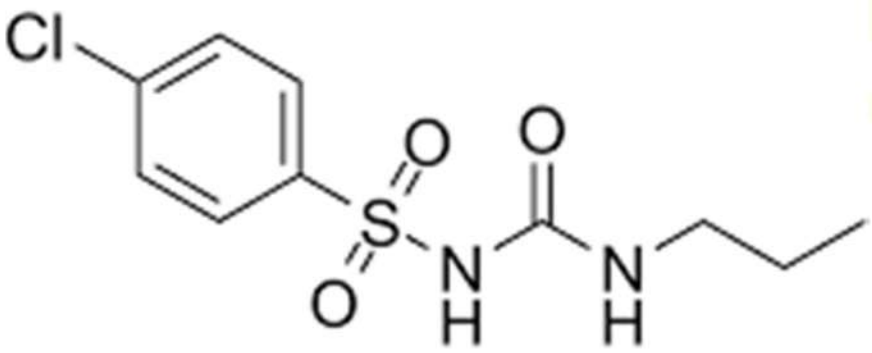
- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (as monotherapy or with diet/exercise)
    2. Occasionally used in **combination with other oral hypoglycemics** if glycemic control is inadequate
-

Chlorpropamide

- **Chlorpropamide** is a **first-generation sulfonylurea** oral hypoglycemic agent.
- Used primarily to **treat type 2 diabetes mellitus** in patients whose hyperglycemia is not controlled by diet and exercise alone.
- It has a **longer duration of action** (24 hours), making it suitable for **once-daily dosing**.
- Administered **orally**.

Chemical Structure

- **Chemical name:** 1-(4-chlorophenyl)sulfonyl-3-propylurea
- **Molecular formula:** $C_{10}H_{13}ClN_2O_3S$
- **Molecular weight:** 270.74 g/mol
- **Chemical class:** Sulfonylurea; first-generation oral hypoglycemic
- **Structural**



Mechanism of Action

- **Target:** Pancreatic β-cells (ATP-sensitive K^+ channels)

Stepwise Mechanism:

1. Chlorpropamide binds to **sulfonylurea receptor 1 (SUR1)** on β-cell plasma membrane.

2. This **closes ATP-sensitive K^+ channels**, causing **membrane depolarization**.
3. Depolarization **opens voltage-dependent Ca^{2+} channels**, increasing intracellular calcium.
4. Elevated calcium triggers **exocytosis of insulin-containing granules**.
5. **Additional Effect:** Chlorpropamide can **enhance the action of antidiuretic hormone (ADH)**, occasionally causing **water retention**.
6. **Overall Effect:** Increased **insulin secretion**, lowering blood glucose levels

Note: Does **not increase insulin sensitivity**; effect is purely secretagogue.

Synthesis

1. **Starting material:** 4-chlorobenzenesulfonyl isocyanate or derivatives
2. **Step 1:** Reaction with propylamine → forms sulfonylurea moiety
3. **Step 2:** Purification → crystallization to obtain pharmaceutical-grade Chlorpropamide

Uses

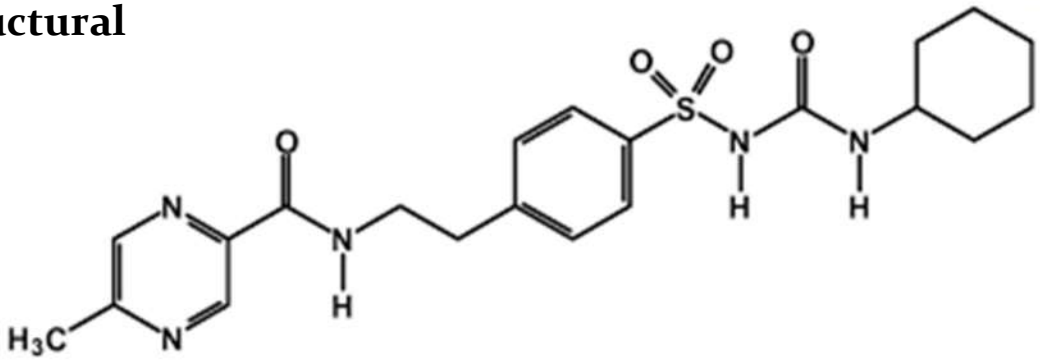
- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (monotherapy or combination therapy)
    2. Occasionally used in **partial diabetes** with diet and exercise
    3. Rarely, **nocturnal polyuria** due to ADH-potentiating effect

Glipizide

- **Glipizide** is a **second-generation sulfonylurea** oral hypoglycemic agent.
- Used to **treat type 2 diabetes mellitus** in patients whose hyperglycemia is not controlled by diet and exercise alone.
- **More potent** than first-generation sulfonylureas (e.g., tolbutamide, chlorpropamide) → lower doses required.
- Administered **orally**, usually **once or twice daily** depending on formulation.
- Rapid onset and relatively short duration of action, making it suitable for **controlling postprandial blood glucose**.

Chemical Structure

- **Chemical name:** 1-cyclohexyl-3-[[p-(2-(5-methylpyrazinecarboxamido)ethyl)phenyl]sulfonyl]urea
- **Molecular formula:** $C_{22}H_{27}N_5O_4S$
- **Molecular weight:** 445.56 g/mol
- **Chemical class:** Second-generation sulfonylurea; oral hypoglycemic
- **Structural**



Mechanism of Action

- **Target:** Pancreatic β-cells (ATP-sensitive K^+ channels)

Stepwise Mechanism:

1. Glipizide binds to **sulfonylurea receptor 1 (SUR1)** on β-cell plasma membrane.
2. This **closes ATP-sensitive K^+ channels**, causing **membrane depolarization**.
3. Depolarization **opens voltage-dependent Ca^{2+} channels**, increasing intracellular calcium.
4. Elevated calcium triggers **exocytosis of insulin-containing granules**.
5. **Overall Effect:**
    - Increased **insulin secretion**, lowering blood glucose levels
    - Does **not increase insulin sensitivity**

Advantages over first-generation sulfonylureas:

- Higher potency → lower dose required
- Shorter half-life → less risk of prolonged hypoglycemia

Synthesis

1. **Starting material:** Substituted arylsulfonyl isocyanate
2. **Step 1:** Reaction with cyclohexylamine → forms urea linkage
3. **Step 2:** Incorporation of pyrazine moiety via amidation
4. **Step 3:** Purification → crystallization to obtain pharmaceutical-grade Glipizide

Uses

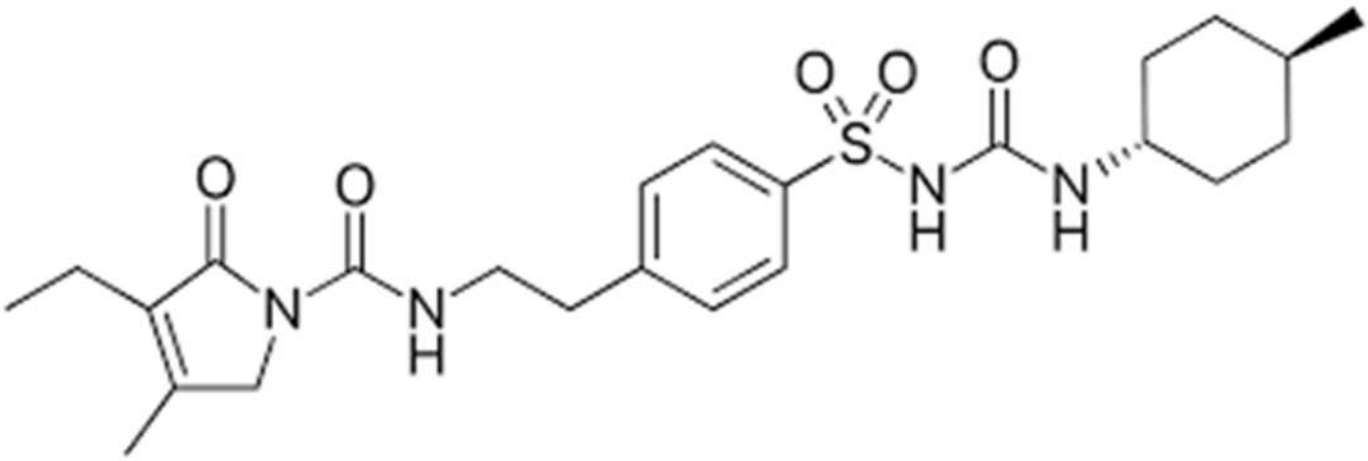
- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (as monotherapy or in combination with diet/exercise)
    2. Occasionally combined with **metformin or other oral hypoglycemics** if glycemic control is inadequate

Glimepiride

- **Glimepiride** is a **third-generation sulfonylurea** oral hypoglycemic agent.
- It is used to **manage type 2 diabetes mellitus** in patients inadequately controlled by diet and exercise.
- Compared to first- and second-generation sulfonylureas, it has:
  - **Longer duration of action** → once-daily dosing
  - **Lower risk of hypoglycemia**
  - **Additional extrapancreatic effects** improving insulin sensitivity
- Administered **orally**.

Chemical Structure

- **Chemical name:** 1-[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea
- **Molecular formula:** $C_{23}H_{31}N_3O_5S$
- **Molecular weight:** 490.6 g/mol
- **Chemical class:** Third-generation sulfonylurea; oral hypoglycemic
- **Structural**



Mechanism of Action

- **Primary Target:** Pancreatic β-cells (ATP-sensitive K^+ channels)

- **Secondary Effects:** Extrapancreatic actions (skeletal muscle, liver)

Stepwise Mechanism:

1. Glimepiride binds to **sulfonylurea receptor 1 (SUR1)** on β-cell plasma membrane.
2. **Closes ATP-sensitive K^+ channels**, causing **membrane depolarization**.
3. Depolarization **opens voltage-dependent Ca^{2+} channels**, increasing intracellular calcium.
4. Calcium triggers **exocytosis of insulin granules**, increasing insulin secretion.
5. **Extrapancreatic effects:**
    - Improves **peripheral insulin sensitivity**
    - Enhances **glucose uptake** in muscle and adipose tissue
6. **Overall Effect:**
    - Lowers **fasting and postprandial blood glucose levels**
    - Reduced hypoglycemia risk due to balanced action

Synthesis

1. **Starting materials:** Substituted arylsulfonyl isocyanates and cyclohexylamines
2. **Step 1:** Formation of urea linkage with cyclohexylamine
3. **Step 2:** Amidation with pyrroline-carboxamide derivative on aryl sulfonyl group
4. **Step 3:** Purification → crystallization → pharmaceutical-grade Glimepiride

Uses

- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (monotherapy or combination with diet/exercise)

2. Combined with **metformin or other oral hypoglycemics** if glycemic control is inadequate