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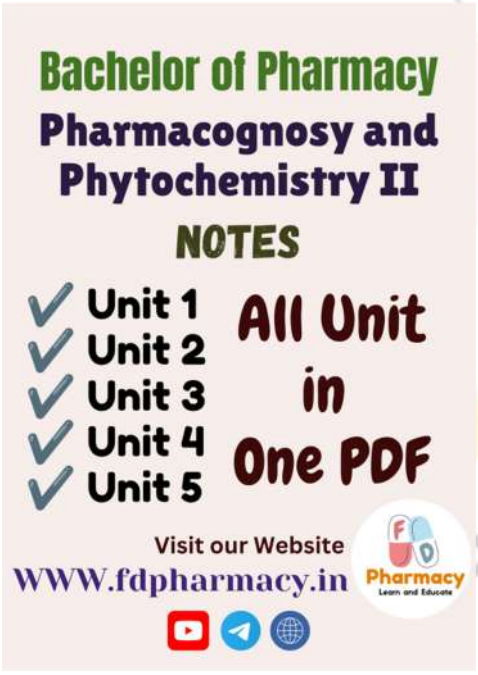
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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

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

Sulfonylureas

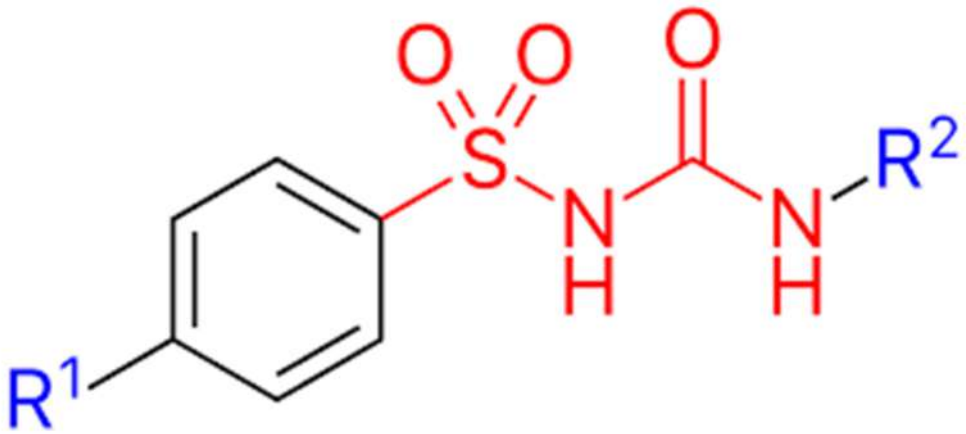
- Sulfonylureas (SUs) are a class of oral hypoglycemic agents used in Type 2 Diabetes Mellitus (T2DM).
- They stimulate insulin secretion from pancreatic β-cells, hence are insulin secretagogues.
- Useful in patients with residual β-cell function.
- Classified based on generation:

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

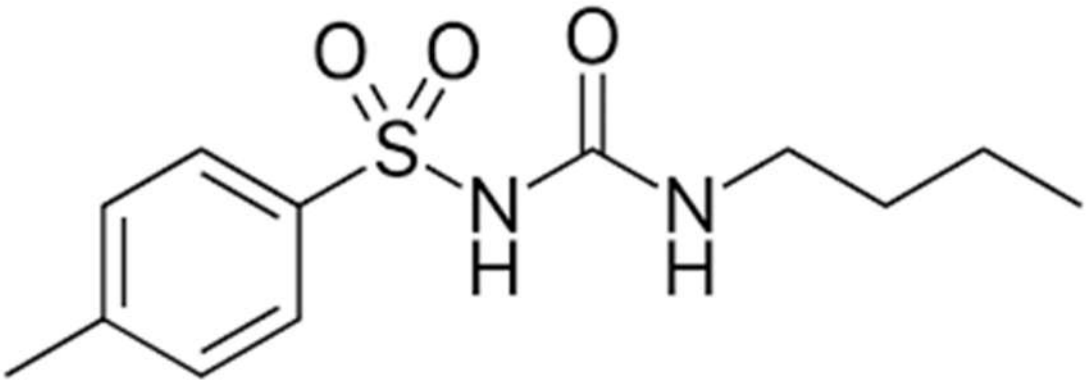
- Type 2 Diabetes Mellitus (especially overweight or elderly patients with residual β-cell function)
- May be used in combination with Metformin or other oral agents for additive effect

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

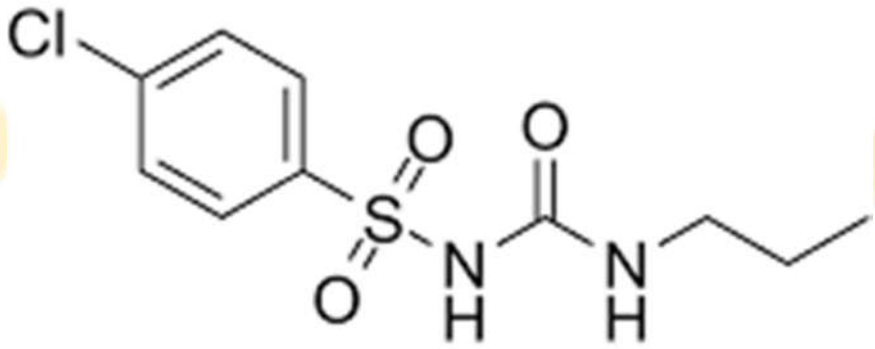
- Therapeutic Uses:
    1. Type 2 diabetes mellitus (as monotherapy or with diet/exercise)
    2. Occasionally used in combination with other oral hypoglycemics if glycemic control is inadequate
-

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

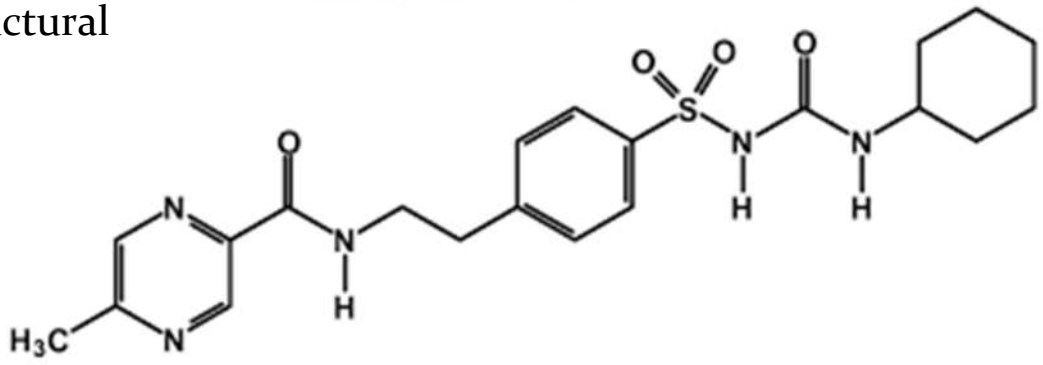
- Therapeutic Uses:
    1. Type 2 diabetes mellitus (monotherapy or combination therapy)
    2. Occasionally used in partial diabetes with diet and exercise
    3. Rarely, nocturnal polyuria due to ADH-potentiating effect

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

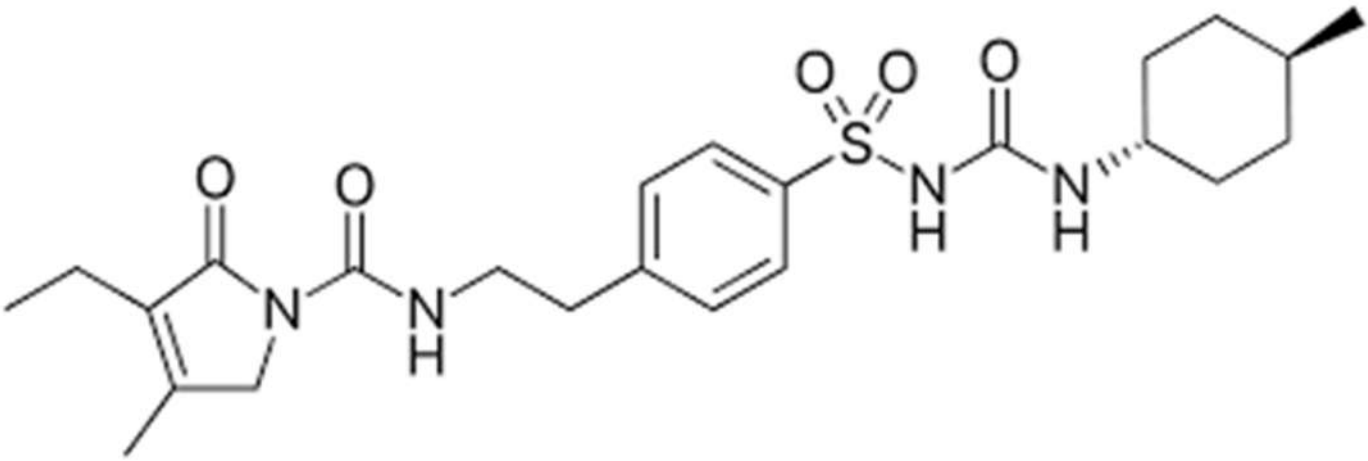
- Therapeutic Uses:
    1. Type 2 diabetes mellitus (as monotherapy or in combination with diet/exercise)
    2. Occasionally combined with metformin or other oral hypoglycemics if glycemic control is inadequate

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