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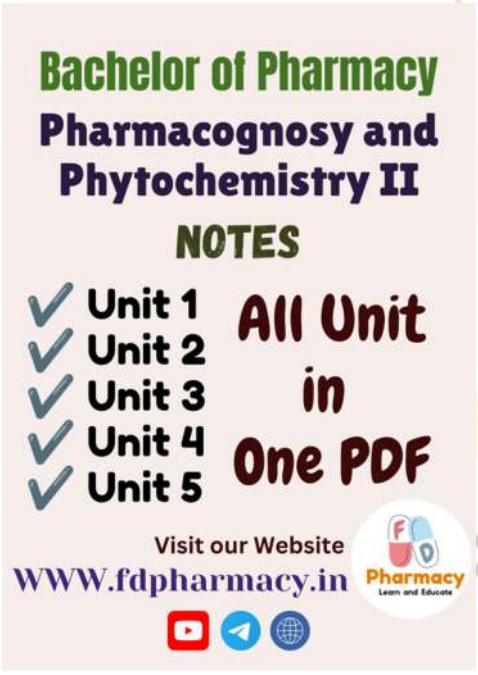
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# MEDICINAL CHEMISTRY - II

## UNIT 5

TOPIC :

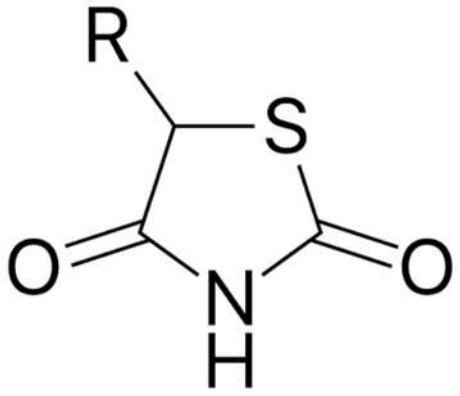
- **Thiazolidinediones :** Pioglitazone, Rosiglitazone.

# Thiazolidinediones (TZDs)

- Thiazolidinediones (TZDs), also called Glitazones, are oral antidiabetic agents used in Type 2 Diabetes Mellitus (T2DM).
- They act as insulin sensitizers, improving peripheral glucose uptake and reducing insulin resistance.
- Commonly used in obese patients with insulin resistance.

## Chemical Structure

- Contain a thiazolidinedione ring (five-membered ring with sulfur and nitrogen)
- Structure: R–C=O–N–C=S–R' (substitutions determine potency and pharmacokinetics)
- Examples: Pioglitazone, Rosiglitazone




## Mechanism of Action

1. PPAR-γ agonists: Activate peroxisome proliferator-activated receptor gamma (PPAR-γ) in adipose tissue, muscle, and liver
2. Gene transcription: Increases transcription of insulin-sensitive genes → ↑ glucose uptake in muscle and adipose tissue
3. Effects on glucose: ↓ hepatic glucose output, ↑ peripheral utilization
4. Effects on lipids: Redistributes fat from visceral to subcutaneous tissue → improves lipid profile

## Clinical Uses

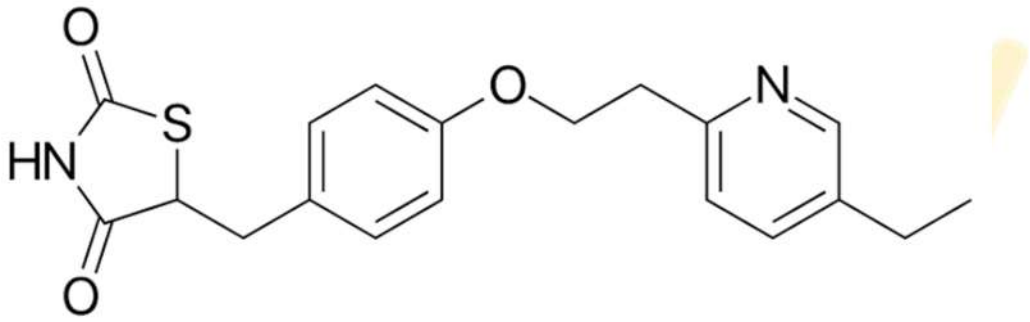
1. Type 2 Diabetes Mellitus (as monotherapy or combination therapy)
2. Insulin resistance syndromes
3. Polycystic Ovary Syndrome (PCOS) → improves insulin sensitivity and ovulation

# Pioglitazone

- Pioglitazone is a thiazolidinedione (TZD) class oral hypoglycemic agent.
- It is used to treat type 2 diabetes mellitus, especially in patients with insulin resistance.
- Unlike sulfonylureas, it does not directly stimulate insulin secretion, reducing risk of hypoglycemia.
- Administered orally, usually once daily.
- Additional benefits: improves insulin sensitivity, lowers fasting and postprandial blood glucose, favorable effect on lipid profile.

## Chemical Structure

- Chemical name: 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
- Molecular formula: $C_{19}H_{20}N_2O_3S$
- Molecular weight: 356.44 g/mol
- Chemical class: Thiazolidinedione (TZD)
- Structural




## Mechanism of Action

- Primary Target: Peroxisome proliferator-activated receptor gamma (PPARγ) in adipose tissue, liver, and skeletal muscle

Stepwise Mechanism:

1. Pioglitazone activates PPARγ, a nuclear receptor.

2. Activated PPARγ modulates transcription of insulin-responsive genes, increasing:
    - Glucose transporter (GLUT4) expression → enhances glucose uptake in muscle and adipose tissue
    - Adiponectin levels → improves insulin sensitivity
3. Reduces hepatic glucose production and free fatty acids
4. Overall Effect:
    - Lowers fasting and postprandial blood glucose
    - Improves insulin sensitivity
    - Minimal risk of hypoglycemia when used alone

## Synthesis

1. Starting material: Thiazolidinedione derivatives and substituted phenyl alcohols
2. Step 1: Etherification of phenyl group with thiazolidinedione scaffold
3. Step 2: Substitution with pyridinyl ethyl group
4. Step 3: Purification → crystallization to obtain pharmaceutical-grade Pioglitazone

## Uses

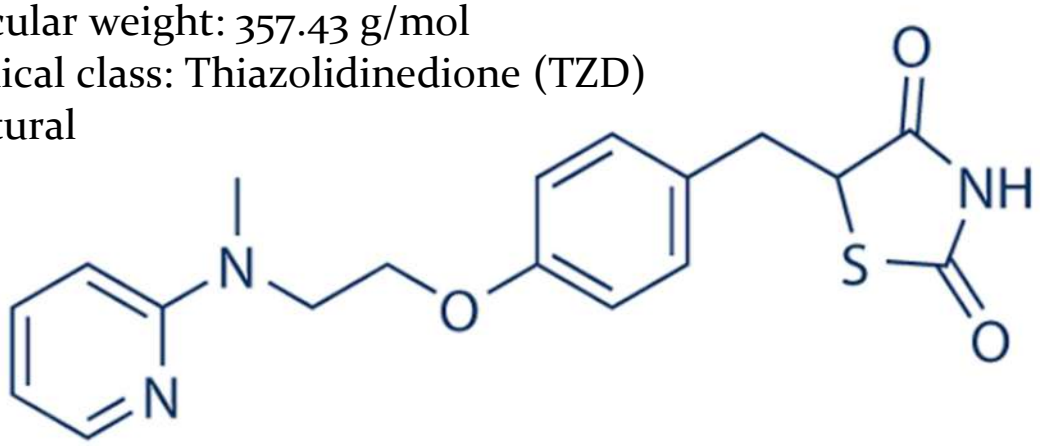
- Therapeutic Uses:
    1. Type 2 diabetes mellitus (monotherapy or combination therapy)
    2. Combined with metformin, sulfonylureas, or insulin if glycemic control is inadequate
    3. Improves insulin resistance in overweight or obese patients

# Rosiglitazone

- Rosiglitazone is a thiazolidinedione (TZD) class oral hypoglycemic agent.
- It is used to treat type 2 diabetes mellitus in patients with insulin resistance.
- Unlike sulfonylureas, it does not stimulate insulin secretion, reducing the risk of hypoglycemia.
- Administered orally, usually once or twice daily.
- Additional benefits: improves insulin sensitivity, lowers fasting and postprandial blood glucose, favorable effect on lipid profile.

## Chemical Structure

- Chemical name: 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
- Molecular formula: $C_{18}H_{19}N_3O_3S$
- Molecular weight: 357.43 g/mol
- Chemical class: Thiazolidinedione (TZD)
- Structural




## Mechanism of Action

- Primary Target: Peroxisome proliferator-activated receptor gamma (PPARγ) in adipose tissue, liver, and skeletal muscle

Stepwise Mechanism:

1. Rosiglitazone activates PPARγ, a nuclear receptor.

2. Activated PPARγ modulates transcription of insulin-responsive genes, increasing:
    - Glucose transporter (GLUT4) expression → enhances glucose uptake in muscle and adipose tissue
    - Adiponectin levels → improves insulin sensitivity
3. Reduces hepatic glucose production and circulating free fatty acids
4. Overall Effect:
    - Lowers fasting and postprandial blood glucose
    - Improves insulin sensitivity
    - Minimal risk of hypoglycemia when used alone

## Synthesis

1. Starting material: Thiazolidinedione derivatives and substituted phenyl alcohols
2. Step 1: Etherification of phenyl group with thiazolidinedione scaffold
3. Step 2: Introduction of pyridinyl amino group on phenyl moiety
4. Step 3: Purification → crystallization to obtain pharmaceutical-grade Rosiglitazone

## Uses

- Therapeutic Uses:
    1. Type 2 diabetes mellitus (monotherapy or combination therapy)
    2. Combined with metformin, sulfonylureas, or insulin if glycemic control is inadequate
    3. Improves insulin resistance in overweight or obese patients