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# MEDICINAL CHEMISTRY - II

## UNIT 5

TOPIC :

- **Thiazolidinediones : Pioglitazone, Rosiglitazone.**

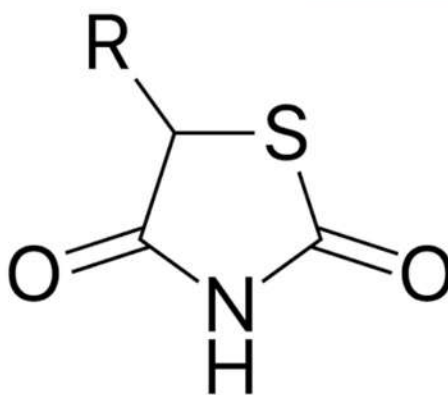


## Thiazolidinediones (TZDs)

- 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- $\gamma$  agonists: Activate peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) in adipose tissue, muscle, and liver
2. Gene transcription: Increases transcription of insulin-sensitive genes  
→  $\uparrow$  glucose uptake in muscle and adipose tissue
3. Effects on glucose:  $\downarrow$  hepatic glucose output,  $\uparrow$  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

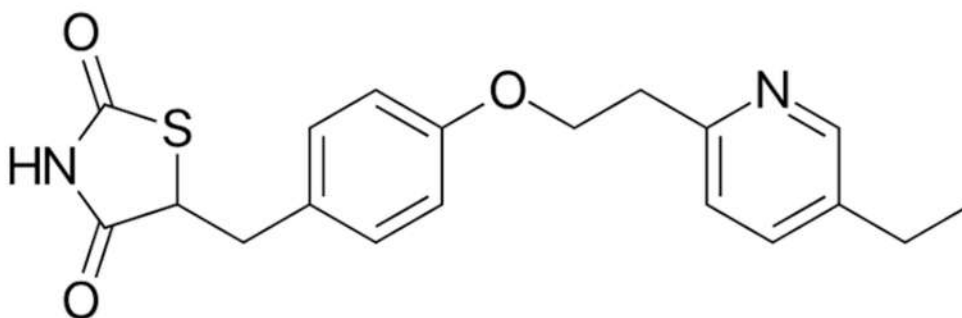


# Pioglitazone

- **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 (PPAR $\gamma$ ) in adipose tissue, liver, and skeletal muscle

### Stepwise Mechanism:

1. Pioglitazone **activates PPAR $\gamma$** , a nuclear receptor.

2. Activated PPAR $\gamma$  **modulates transcription of insulin-responsive genes**, increasing:
  - **Glucose transporter (GLUT<sub>4</sub>) 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

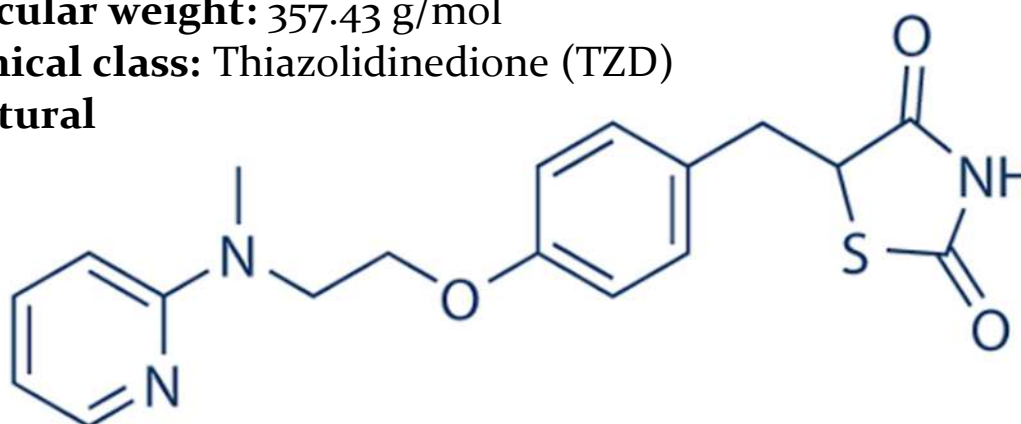
- **Therapeutic Uses:**
  1. **Type 2 diabetes mellitus** (monotherapy or combination therapy)
  2. Combined with **metformin, sulfonylureas, or insulin** if glycemic control is inadequate
  3. Improves insulin resistance in overweight or obese patients

# 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 (PPAR $\gamma$ ) in adipose tissue, liver, and skeletal muscle

### Stepwise Mechanism:

1. Rosiglitazone **activates PPAR $\gamma$** , a nuclear receptor.



2. Activated PPAR $\gamma$  **modulates transcription of insulin-responsive genes**, increasing:
  - **Glucose transporter (GLUT<sub>4</sub>) 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