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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

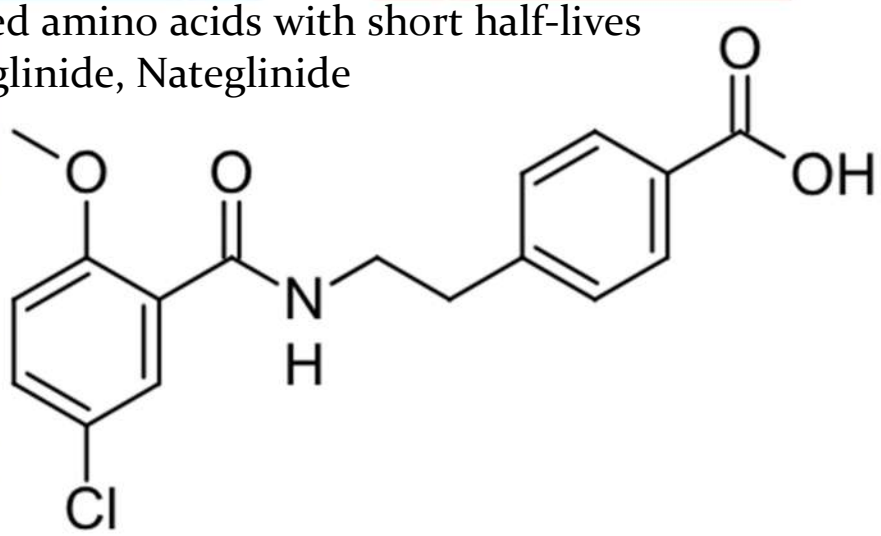
- **Meglitinides :** Repaglinide, Nateglinide.

Meglitinides

- Meglitinides are a class of oral antidiabetic agents used in Type 2 Diabetes Mellitus (T2DM).
- They are rapid-acting insulin secretagogues that help control postprandial hyperglycemia.
- Often used in patients who cannot tolerate sulfonylureas or have irregular meal schedules.

Chemical Structure

- Non-sulfonylurea insulin secretagogues
- C-aryl substituted amino acids with short half-lives
- Examples: Repaglinide, Nateglinide



Mechanism of Action

1. Bind to ATP-sensitive K^+ channels on pancreatic β-cells (different binding site than sulfonylureas)
2. Close K^+ channels → membrane depolarization
3. Opening of voltage-gated Ca^{2+} channels → Ca^{2+} influx
4. Stimulates rapid, short-duration insulin secretion in response to meals

Key point: Effect is glucose-dependent, so lower risk of hypoglycemia compared to sulfonylureas.

Clinical Uses

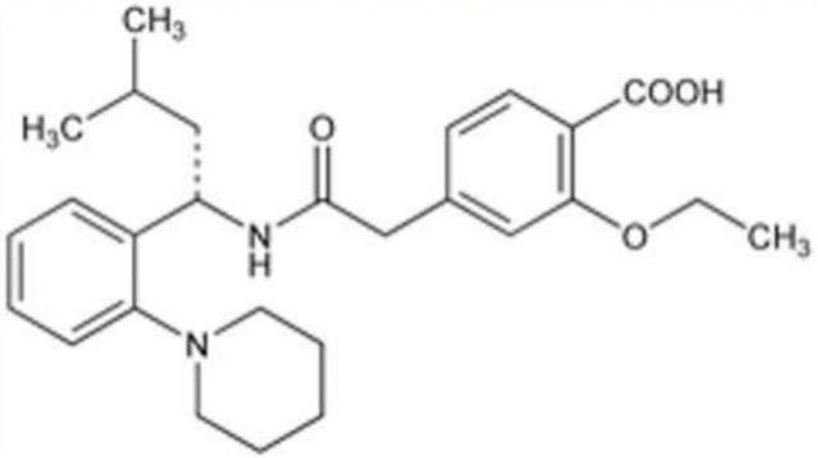
- Type 2 Diabetes Mellitus (particularly postprandial hyperglycemia)
- Combination therapy: Often used with Metformin for synergistic effect
- Useful in patients with irregular meals or risk of hypoglycemia with sulfonylureas

Repaglinide

- **Repaglinide** is a **meglitinide class oral hypoglycemic agent**.
- Used to **treat type 2 diabetes mellitus**, particularly **postprandial hyperglycemia**.
- It is **rapid-acting** with a short duration of action (about 4–6 hours), allowing dosing **before meals**.
- Administered **orally**, usually **0–30 minutes before a meal**.
- **Advantages:** Rapid onset, low risk of prolonged hypoglycemia, flexible dosing with meals.

Chemical Structure

- **Chemical name:** 2-ethoxy-4-[2-(3-methyl-1-(2-(1-piperidinyl)phenyl)butyl)phenyl]benzoic acid
- **Molecular formula:** $C_{22}H_{28}N_2O_4$
- **Molecular weight:** 452.48 g/mol
- **Chemical class:** Meglitinide; oral hypoglycemic agent
- **Structural**



Mechanism of Action

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

Stepwise Mechanism:

1. Repaglinide binds to **specific sites on SUR1 receptor** 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 **rapid exocytosis of insulin-containing granules**.
5. **Overall Effect:**
    - Rapid insulin release after meals → reduces **postprandial glucose**
    - **Short duration** minimizes prolonged hypoglycemia

Note: Unlike sulfonylureas, Repaglinide has **mealtime-specific action** with less risk of fasting hypoglycemia.

Synthesis

1. **Starting materials:** Substituted benzoic acids and phenylpropyl derivatives
2. **Step 1:** Formation of the central phenyl-propyl skeleton
3. **Step 2:** Introduction of piperidinyl moiety via amide formation
4. **Step 3:** Purification → crystallization to obtain pharmaceutical-grade Repaglinide

Uses

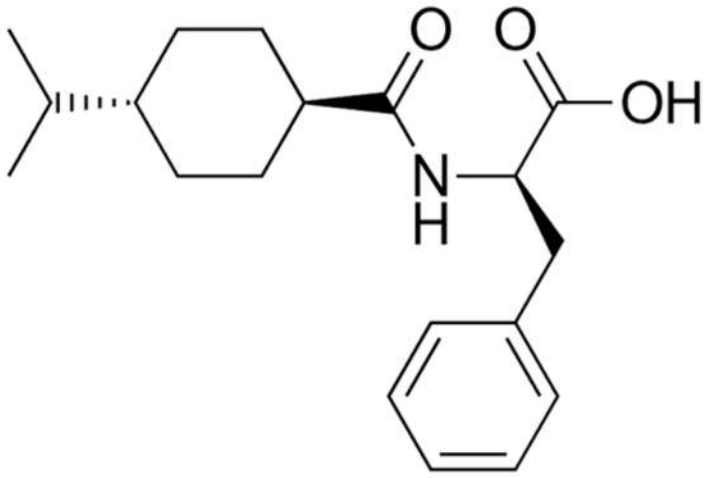
- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (especially postprandial hyperglycemia)
    2. Can be used **alone or in combination** with metformin

Nateglinide

- **Nateglinide** is a **meglitinide class oral hypoglycemic agent**, similar to repaglinide.
- Used for **type 2 diabetes mellitus**, specifically to control **postprandial hyperglycemia**.
- **Rapid-acting** with short duration (about 4–5 hours), taken **before meals**.
- It **stimulates insulin release** in a glucose-dependent manner, minimizing risk of prolonged hypoglycemia.
- Administered **orally**, usually 0–30 minutes before a meal.

Chemical Structure

- **Chemical name:** 2-cyano-3-(N-phenylacetamido)-N-(2-isopropyl-phenyl)propanamide
- **Molecular formula:** $C_{22}H_{24}N_4O_2$
- **Molecular weight:** 380.46 g/mol
- **Chemical class:** Meglitinide; oral hypoglycemic agent
- **Structural**



Mechanism of Action

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

Stepwise Mechanism:

1. Nateglinide binds to **specific sites on SUR1 receptor** 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-containing granules**.
5. **Overall Effect:**
    - Rapid insulin release after meals → reduces **postprandial glucose**
    - Short duration → minimal risk of prolonged hypoglycemia

Note: Glucose-dependent action reduces fasting hypoglycemia risk compared to sulfonylureas.

Synthesis

1. **Starting materials:** Substituted phenylpropyl derivatives and cyanoacetamide
2. **Step 1:** Formation of central phenylpropyl skeleton
3. **Step 2:** Amide bond formation with phenylacetamido group
4. **Step 3:** Purification → crystallization to obtain pharmaceutical-grade Nateglinide

Uses

- **Therapeutic Uses:**
    1. **Type 2 diabetes mellitus** (particularly postprandial hyperglycemia)

2. Can be used **alone or in combination** with metformin