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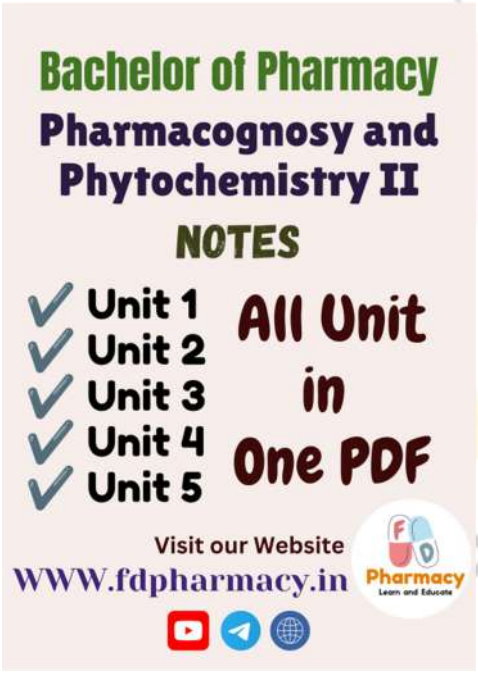
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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

- **Glucosidase inhibitors :** Acrabose,Voglibose.

α-Glucosidase Inhibitors

- α-Glucosidase inhibitors (AGIs) are oral antidiabetic agents used in Type 2 Diabetes Mellitus (T2DM).
- They reduce postprandial hyperglycemia by delaying the digestion of carbohydrates in the intestine.
- Commonly used in combination with other antidiabetic agents for better glycemic control.

Examples

Drug	Notes
Acarbose	Widely used, potent intestinal α-glucosidase inhibitor
Miglitol	Similar to acarbose but more rapidly absorbed
Voglibose	Used in some countries, less potent than acarbose

Mechanism of Action

1. Inhibit α-glucosidase enzymes in the brush border of small intestine.
2. Delay carbohydrate hydrolysis → slower glucose absorption.
3. Reduces postprandial blood glucose spikes.
4. No effect on insulin secretion or fasting glucose levels.

Clinical Uses

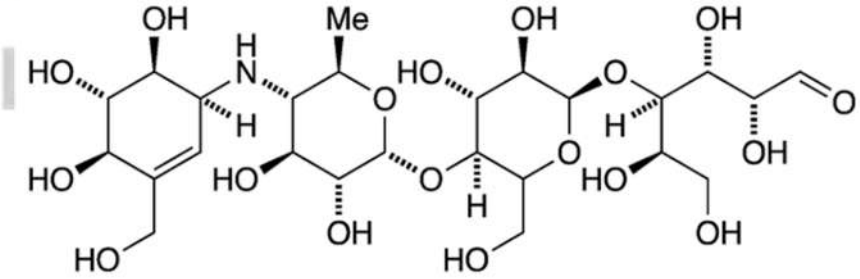
- Type 2 Diabetes Mellitus: Especially for postprandial hyperglycemia
- Combination therapy: With Metformin, Sulfonylureas, or Insulin
- Prediabetes: May delay progression to diabetes in high-risk individuals

Acarbose

- Acarbose is an oral antihyperglycemic (antidiabetic) drug used in the management of Type 2 diabetes mellitus.
- It belongs to the α-glucosidase inhibitor class of drugs.
- It is a complex oligosaccharide that delays the digestion and absorption of carbohydrates in the small intestine.
- Acarbose helps in reducing postprandial (after meal) blood glucose spikes.
- It does not stimulate insulin secretion and therefore does not cause hypoglycemia when used alone.
- Usually used as an adjunct to diet, exercise, and other oral hypoglycemics (e.g., metformin or sulfonylureas).

Chemical Structure

- Chemical Name: O-4,6-dideoxy-4-[[[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]methyl]-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl-(1→4)-D-glucose
- Molecular Formula: $C_{25}H_{43}NO_{18}$
- Molecular Weight: 645.6 g/mol
- Chemical Class: Pseudotetrasaccharide; α-glucosidase inhibitor
- Structural



Mechanism of Action

- Target: Intestinal brush border α-glucosidase enzymes and pancreatic α-amylase

Stepwise Mechanism:

1. After oral administration, acarbose remains in the intestinal lumen (not absorbed systemically).
2. It competitively inhibits α-glucosidase enzymes in the intestinal brush border.
3. These enzymes are responsible for converting complex carbohydrates and disaccharides (like maltose, sucrose) into glucose.
4. Inhibition delays the breakdown of carbohydrates → slower glucose absorption into the bloodstream.
5. This leads to reduced postprandial blood glucose levels.
6. Pancreatic α-amylase inhibition further slows starch hydrolysis.

Synthesis

The synthesis of Acarbose is complex and primarily biotechnological, involving fermentation by *Actinoplanes sp.* (a soil microorganism).

Steps Summary:

1. Fermentation: Acarbose is produced by *Actinoplanes utahensis* through microbial fermentation.
2. Isolation: The compound is extracted from the culture medium.
3. Purification: Carried out by crystallization and chromatographic techniques.

Uses

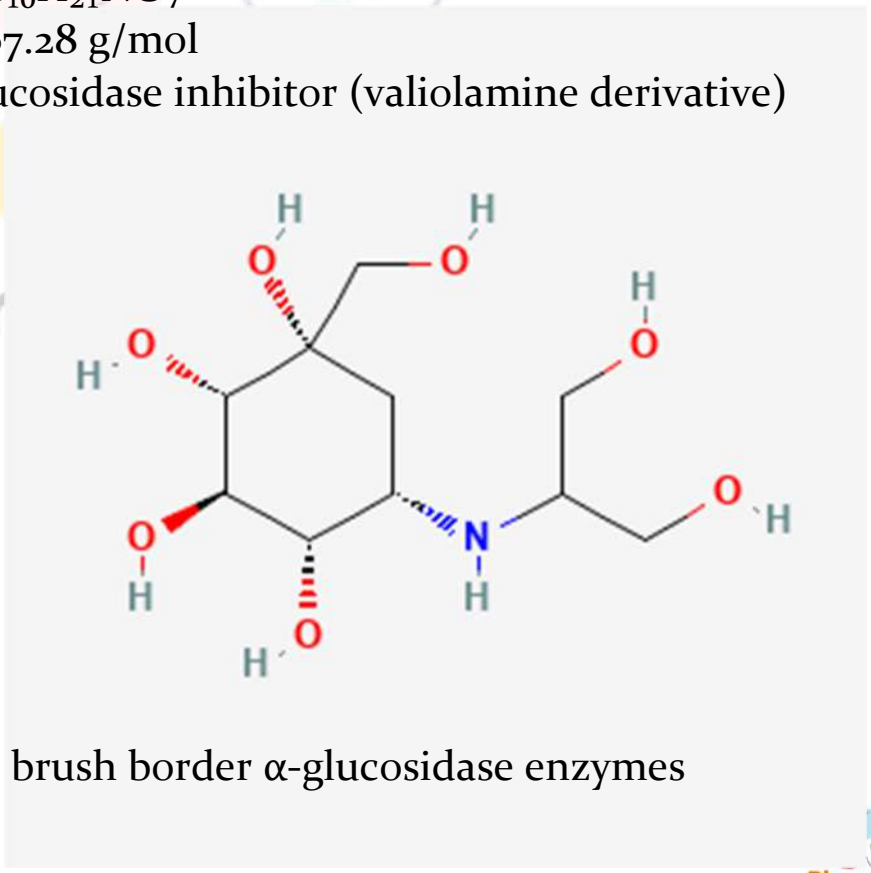
- Therapeutic Uses:
    1. Treatment of Type 2 Diabetes Mellitus (as monotherapy or in combination).
    2. Reduces postprandial hyperglycemia.
    3. Sometimes used in prediabetes to prevent progression to diabetes.

Voglibose

- Voglibose is an oral antihyperglycemic drug belonging to the α-glucosidase inhibitor class.
- It is mainly used for the management of Type 2 diabetes mellitus, either alone or in combination with other antidiabetic drugs.
- Voglibose acts locally in the intestine to delay the absorption of carbohydrates.
- It is a derivative of valiolamine, obtained from microbial sources.
- The drug is particularly effective in controlling postprandial (after-meal) hyperglycemia.
- It does not stimulate insulin secretion, and hence, it has a very low risk of hypoglycemia.

Chemical Structure

- Chemical Name: (1S,2S,3R,4S,5S)-5-[1,3-dihydroxypropan-2-ylamino]-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetraol
- Molecular Formula: $C_{10}H_{21}NO_7$
- Molecular Weight: 267.28 g/mol
- Chemical Class: α-Glucosidase inhibitor (valiolamine derivative)
- Structural



Mechanism of Action

- Target Site: Intestinal brush border α-glucosidase enzymes

Stepwise Mechanism:

1. After oral intake, Voglibose remains in the lumen of the small intestine (minimally absorbed).
2. It competitively inhibits α-glucosidase enzymes, such as sucrase, maltase, and isomaltase.
3. These enzymes normally break down complex carbohydrates and disaccharides into absorbable glucose.
4. Inhibition by Voglibose delays this breakdown → slower glucose absorption into the bloodstream.
5. Result: Reduced postprandial blood glucose spikes and improved glycemic control.

Synthesis

- Source: Voglibose is semi-synthetically derived from valiolamine, which is obtained by fermentation of microorganisms like *Streptomyces hygroscopicus*.

Steps:

1. Fermentation: Microbial production of valiolamine (a cyclitol amine compound).
2. Chemical modification: Introduction of hydroxyl and amino groups to increase α-glucosidase affinity.
3. Purification: Crystallization and isolation to yield pure Voglibose.

Uses

- Therapeutic Uses:
    1. Type 2 Diabetes Mellitus: To control postprandial hyperglycemia.
    2. As adjunct therapy with sulfonylureas, metformin, or insulin.
    3. In prediabetic conditions (Impaired Glucose Tolerance) to prevent diabetes onset.