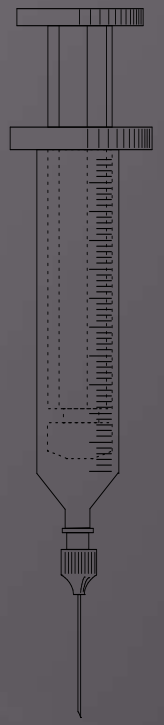
UNIT-V
ANTIDIABETICS



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DIABETES MELLITUS

- Diabetes Mellitus - A chronic disease resulting from deficient glucose metabolism, caused by insufficient insulin secretion from the beta cells high blood sugar (hyperglycemia). 3 P's
  1. Polyuria - inc. urine output
  2. Polydipsia - inc. thirst
  3. Polyphagia - inc. hunger
- Mainly2 forms of diabetes
  1. Insulin-dependent diabetes mellitus (IDDM) or type I - was refereed to as juvenile-onset w/ no insulin secretion

CONTINUE....DIABETES MALLITUS.

2. Non-insulin-dependent diabetes mellitus (NIDDM) or type II - was referred to as maturity-onset or adult-onset diabetes w/ some insulin secretion

- Unknown how lack of insulin causes diabetes - poss. = infection, heredity
- Insulin - Released from the beta cells of the islets of Langerhans in the pancreas in response to an increase in bld. glucose

- Promotes the uptake of glucose, amino acids, & fatty acids & converts them to substances stored in body cells

- **Other types include**

Gestational Diabetes-Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly shown diabetes

Specific types of diabetes due to other cause-Neonatal diabetes, maturity –onset diabetes of the,disease of the exocrine pancreas and drug or chemical induced diabetes.

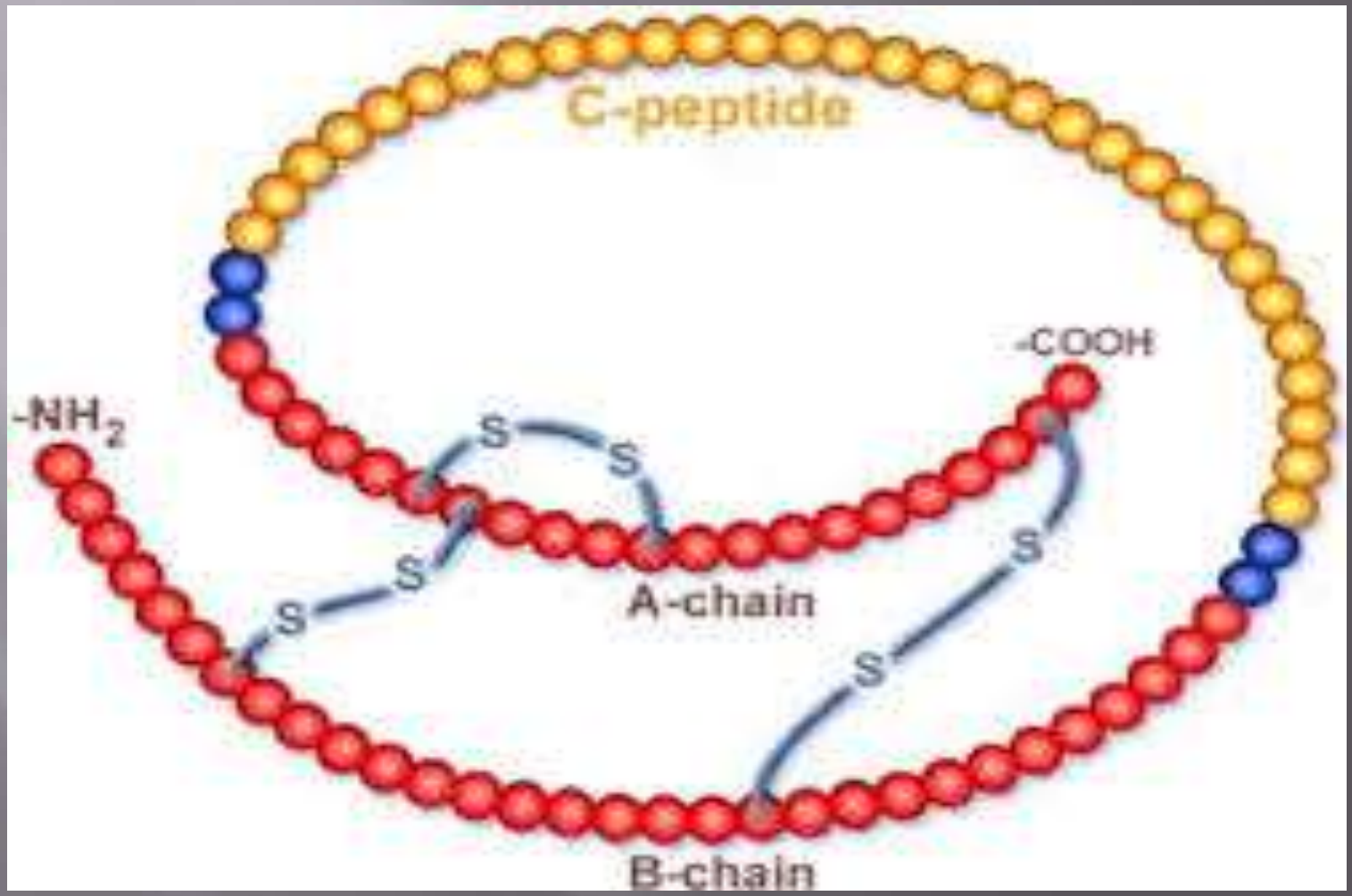
CONTINUE……DIABETES MALLITUS

- Glucose is converted to glycogen for future glucose needs in the liver & muscle = lowers bld. glucose level (range for bld. glucose is 70 - 110 mg/dl)

 * bld. glucose > 180 = sugar in urine = diuretic effects = polyuria

- Insulin can be animal (pork or beef), or human (using DNA technology)
- Concentration of insulin is 100 U/ml, & insulin packaged in a 10 ml vial. For accurate dosing, insulin can be given in insulin syringes ONLY.

INSULIN



Structure of Insulin

- Insulin has 51 amino acids and 6000 Da molecular weight in almost all species, including human.The human insulin molecule consists of two polypeptide chains, one A chain and one B chain containing 21 and 30 amino acid residues, respectively. These two chains are interconnected by SS (CysA7-CysB7 and CysA20-CysA19) with a disulfide bond, and an additional disulfide bond connects CysA6 and CysA11 in chain A .The amino acids of the two chains also participate in many non-covalent interactions.

Insulin receptor

- The insulin receptor is a member of the transmembrane signal proteins of the tyrosine kinase family and is synthesized as a single polypeptide.
- The formed polypeptide is glycosylated and divided into alpha-beta subunits, and a tetramer is formed, which is bound by disulfide bonds again.
- The hydrophobic part of each subunit is located within the plasma membrane. Alpha subunit contains the insulin binding site.
- The cytosolic part of the beta subunit is a tyrosine kinase and is activated by insulin. Binding of insulin to alpha subunits of the receptor causes positional changes .
- These changes are transmitted to beta subunits, and the tyrosine unit in these structures causes autophosphorylation. Consequently, insulin-receptor substrates (IRS-1 and IRS-2) activate phosphorylated phosphoidylinositol-3 kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways. Eventually, insulin acts on the target tissues.

Functions of insulin

- Insulin provides glucose homeostasis by keeping the plasma glucose value in an optimal range throughout the day.
- The main effects of insulin are:
- (i) In the liver, to stimulate glucose oxidation and storage of glucose (glycogenesis), as well as to convert glucose into triglycerides and protein synthesis
- (ii) in the muscle tissue, it provides glucose uptake into the cells, and be stored as glycogen,
- (iii) and in fat tissue, it provides glucose uptake and conversion to triglycerides for storage.

Antidiabetic Drugs

- Drugs used to control diabetes mellitus - a chronic disease that affects carbohydrate metabolism
- 2 groups of antidiabetic agents:
- Insulin & oral hypoglycemic agents

- Oral hypoglycemic agents = synthetic preparations that stimulate insulin release or alter metabolic response to hyperglycemia

- Insulin = a protein secreted from the beta cells of the pancreas - necessary for carbo metabolism & an important role in protein & fat metabolism

Antidiabetic Agents

Insulin

- Types of Insulin's - 3 standard types

1. Rapid-acting - Regular insulin - clear sol'n w/o added substances to prolong insulin action

   Onset = 1/2 to 1 h; Peak = 2 to 4 h; Duration = 6 to 8 h

2. Intermediate-acting - NPH, Lente - contain protamine (a protein that prolongs the action of the insulin)

   Onset = 1 to 2 h; Peak = 6 to 12 h; Duration = 18 to 24 h

3. Long-Acting - Ultralente - contain lg. crystals which dissolve slowly to prolong duration

   Onset = 4 to 8 h, Peak = 14 to 20 h; Duration = 24 to 36 h

CONTINUE....Antidiabetic Agents

Insulin

- Lispro Insulin (Humalog) - a new rapid acting insulin approved in 1996

  Action = 5 min.; Duration = 2 to 4 h - can be administered 5 min. before meal time
- Combination Insulin's - commercially premixed

  Humulin 70/30, Novolin 70/30, Humulin 50/50

  (70/30 = 70% NPH and 30% Reg)
- Reg can be mixed w/ NPH or Lente - Reg goes in first in the syringe *Clear to Cloudy*

Oral hypoglycemic Agents

- Used by persons w/ NIDDM - should NOT be used by persons w/ IDDM
- NIDDM has some degree of insulin secretion by pancreas
- These are administered orally and are thus also called as oral hypoglycemic agents or oral ant hyperglycemic agents.
- There are different class of antidiabetic drugs and their selection depends on nature of diabetes ,age ,and situation of the person as well as other factors

Several classes of oral hypoglycemic agents

1)SULPHONYLUREAS

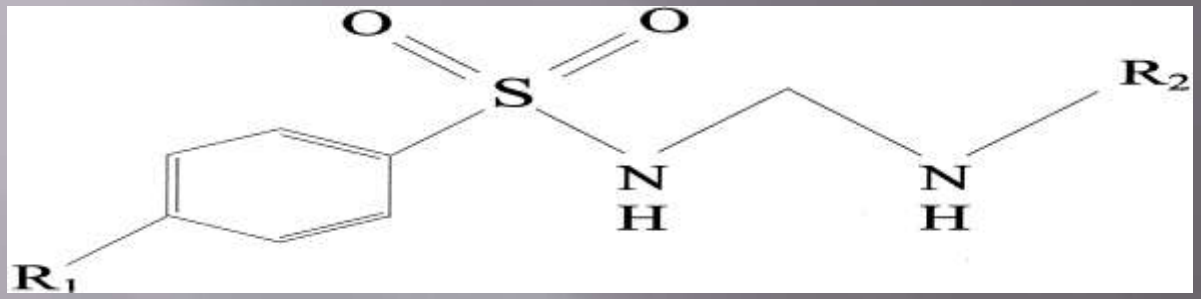
- **First generation**
  e.g Tolbutamide,Chlorpropamide

- **Second generation**
  e.g Glipizide,Glimepiride

2)NON-SULPHONYLUREAS

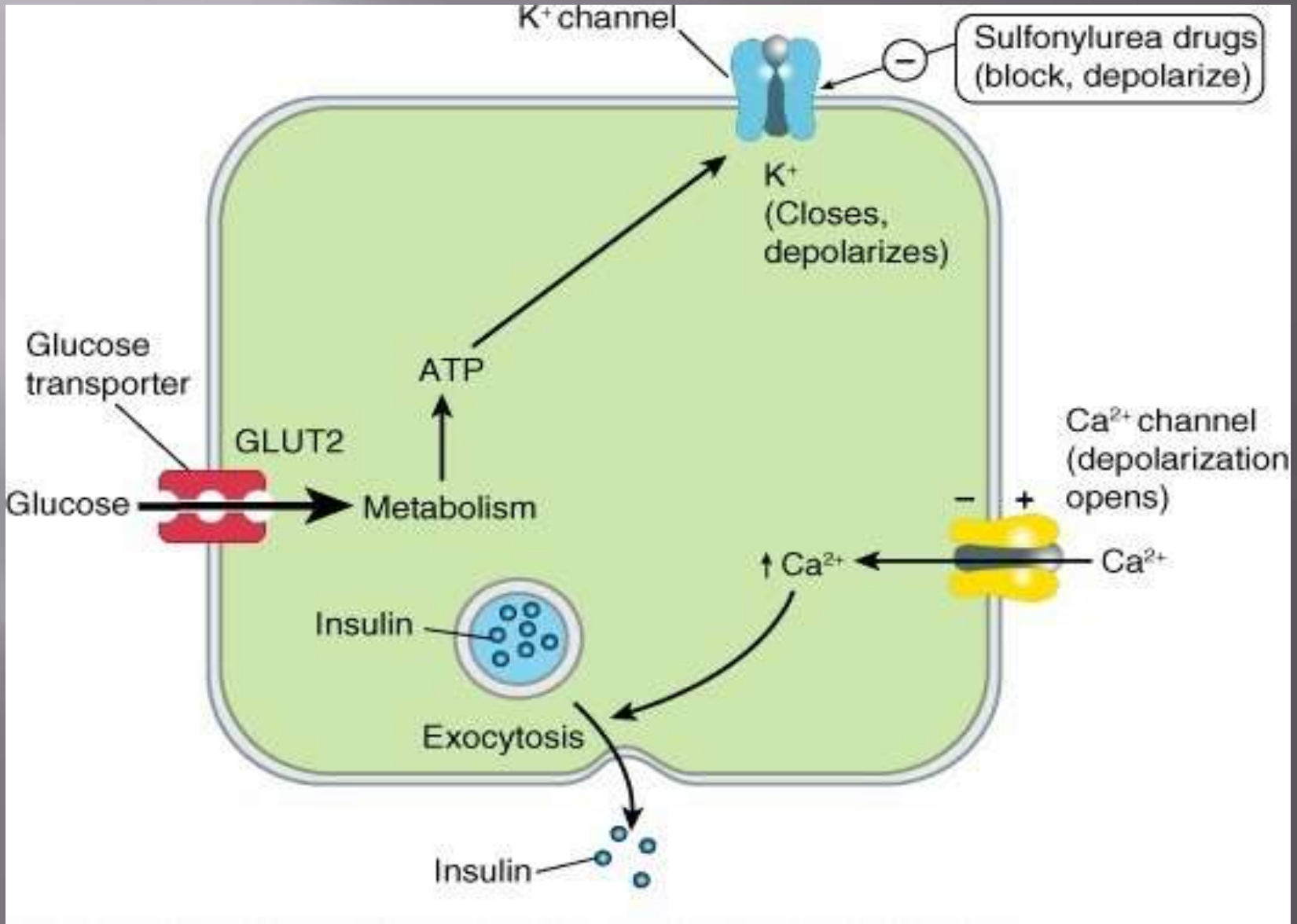
a) **MEGLITINIDES**
   e.g Rapaglinide, Nateglinide.
b) **THIAZOLIDINEDIONES**
   e.g Pioglitazone, Rosiglitazone.
c) **BIGUANIDE**
   e.g Metformin, Phenformin
d) ***ALPHA-GLUCOSIDASE INHIBITORS***
   e.g Acrabose, Voglibose

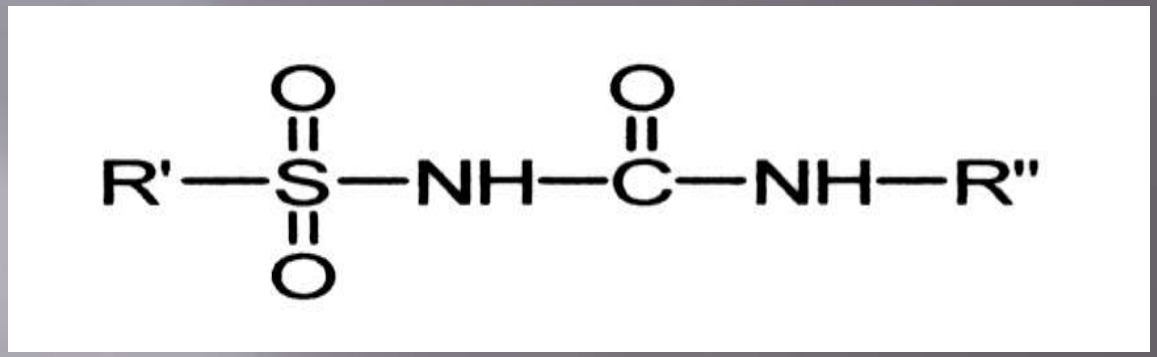
SULFONYLUREASE



- Contain sulphonyl and urea group
- The sulphonyl portion is very water soluble,it has am acidic amine and oxygen atoms for good hydrogen bonding
- R1 and R2 are very lipophilic and account for differences in overall potency,metabolism,duration and routes of elimination
- Overall drugs tend to be lipophilic and ionised at body pH
- They are weak acids with a pKa equivalent 5-6
- Second generation much more lipophilic than the first and hence more potent
- They stimulate secretion of insulin from the functioning β-cells of the intact pancreas
- Sulphonylureas are similar in chemistry to the sulphonamides and thus potentially share toxicities and allergies

MECHANISM OF SULFONYLUREASE





SAR:-

R1

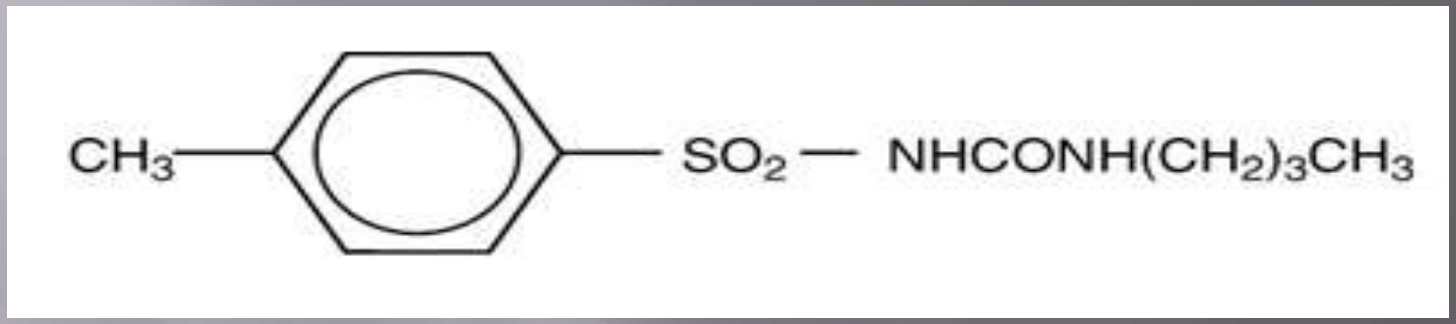
- **Must be lipophilic**
- **Must have an aromatic ring next to the sulfoxide groups have a phenyl ring**
- **Should have a substitutent at the para position. Methyl, amino, acetyl, chloro, bromo, metyithio and trifluorometyl enhance hypoglycemic activity.**
- **The larger, more complex, para substituents comprise the 2nd generation. The ethylcarboxamide appears to be very potent in these drugs which may be due to the distance from the carboxamide nitrogen to the sulfonamide nitrogen and how its binds to the receptor.**

R2

- **Must be lipophilic**
- **Has some size constraints: N-metyl is inactive, N-ethyl is low active, N-dodecyl and above are inactive**
- **N-propyl to N-hexyl are the most potent**

1st Generation:-

TOLBUTAMIDE

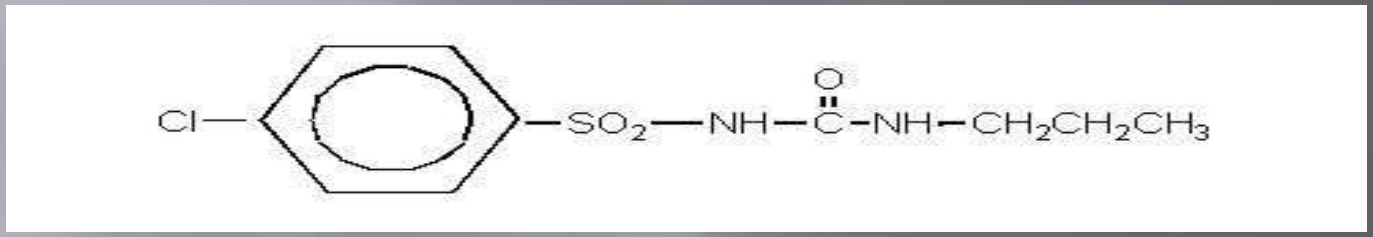


NAME:3-butyl-1-(4- methylbenzene sulfonyl) urea

- In general these are eliminated in the urine as some parent compound plus metabolites.

- **Tolbutamide** is one of the least potent oral hypoglycemics with short duration due to rapid hydroxylationof para methyl substituents followed by oxidation to the acid.

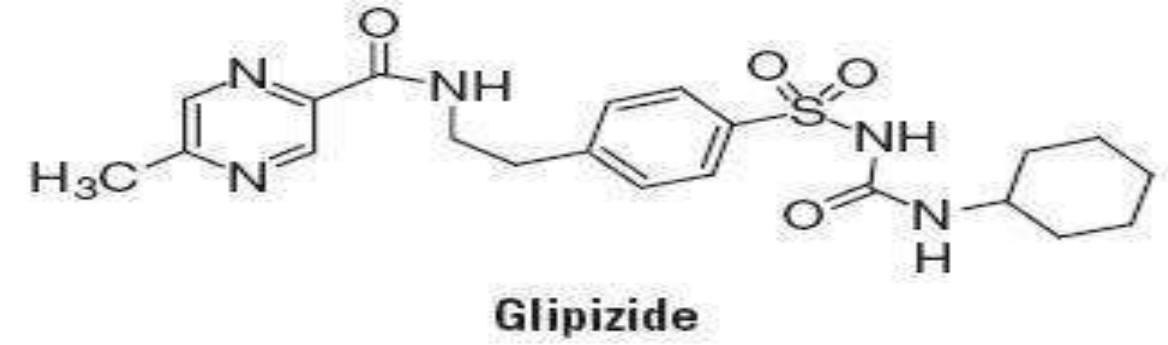
CHLORPROPAMIDE



IUPAC NAME:1-(4-chlorobenzenesulfonyl)3-propylurea

In **Chlorpropamide** the para chloro protect from oxidation and thus has a longer duration than tolbutamide. Also increases lipid solubility to increase potency.

2nd Generation:-Glipizide

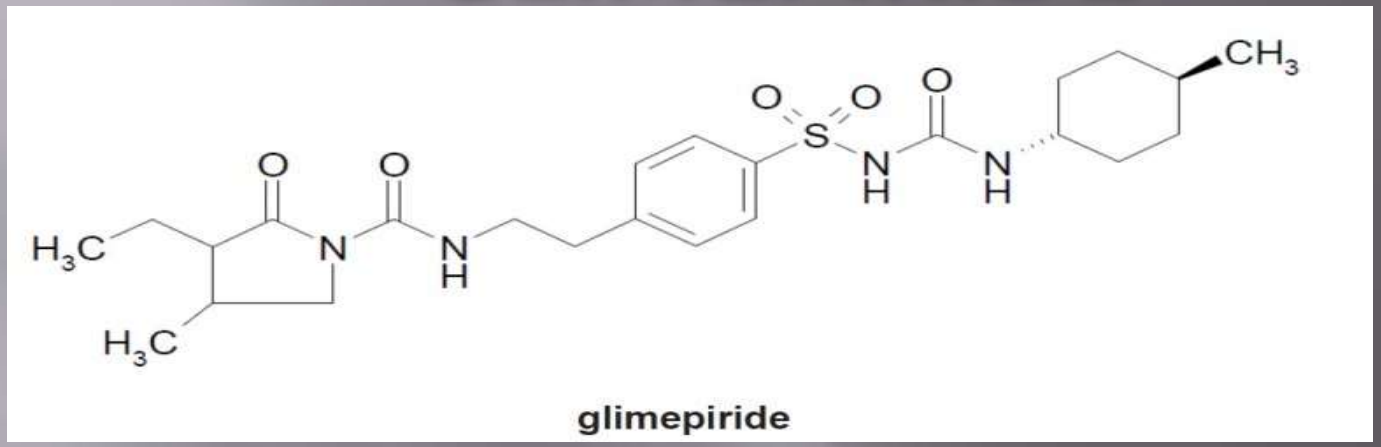


Glipizide

- IUPAC NAME:N-
- (2- (4-{[cyclohexylcarbamoyl)amino]sulfonyl)phenyl)ethyl]-5-methylpyrazine-2-carboxamide.

- **Glyburide and Glipizide are hydroxylated at the 3rd and 4th position on the cyclohexyl ring. Some metabolites are active so duration is longer than parent compound.**

GLIMEPIRIDE



IUPAC NAME: **3-ethyl-2,5-dihydro-4-methyl-N-[2-[4[[[[(trans-4methylcyclohexyl)amino-carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-1H-pyrrole-1-carboxamide.**

Glimepride, sometimes referred to as 3rd generation, is most potent of all sulfonylureas. The cyclohexyl metyl is hydroxylated then oxidized to the acid.

NON-SULFONYLUREAS :-

- The meglitinide are nonsulfonylurease oral hypoglycemic agents used in the management of type 2 diabetes (NIDDM).
- These agents tends to have rapid onset and short duration of action.
- Mechanism of action is similar to that of sulfonylurease.
- There are two major difference between these two classes

-- Meglitinide cause must faster insulin production than sulfonylurease

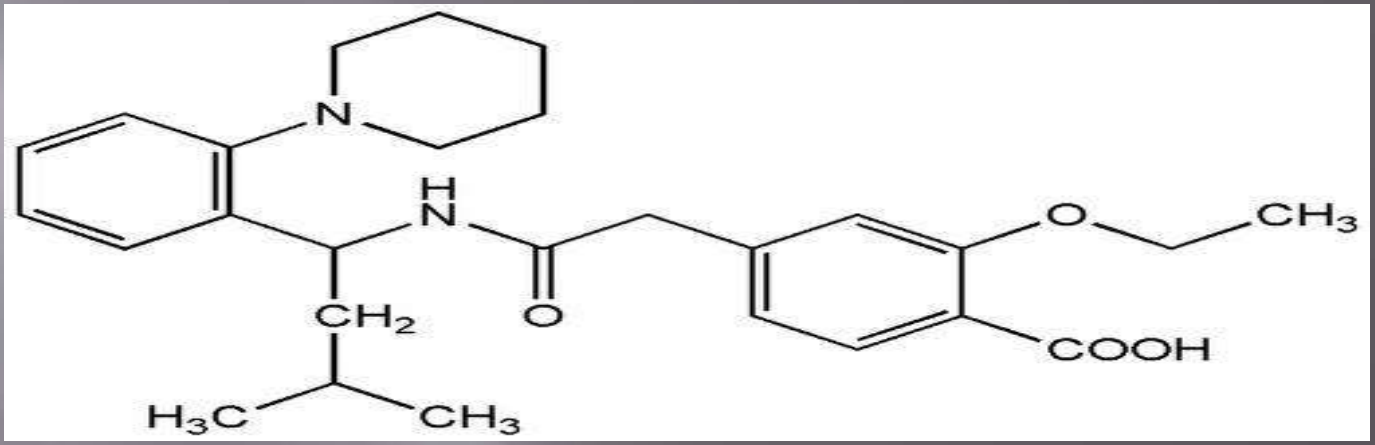
-- Effects of metaglinides do not last as long as the effect of sulfonylurease

-- The effect of these class appear to last less than one hrs while sulfonylurease continue to stimulate insulin productin for several hrs.

- As a result meglitinide should be taken 5 to 10 mins before meal.
- There is less risk of hypoglycemia due to short duration of action.
- Repaglinide excreted less than 0.2% by kidney which may be advantage for elderly patient who are renally impaired.

Examples:-

Repaglinide



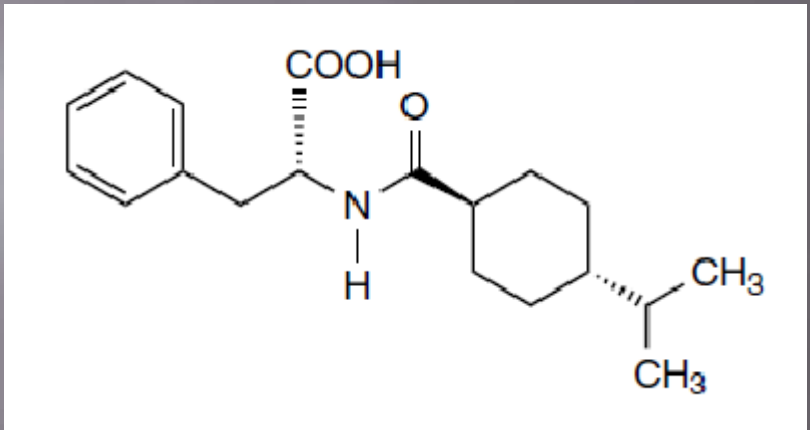
IUPAC NAME: 2-ethoxy-4-({[1S)-3-methyl-1-[2-(piperidin-1yl)phenyl]butyl]carbamoyl}methyl)benzoicacid.

Repaglinide is rapidly metabolized via oxidation and dealkylation by cytochrome P450 and 3A4.

Its metabolites do not possess appreciable hypoglycemic activity.

It has fewer side effects as it is rapidly onset and short duration of action as compared to other hypoglycemic drugs.

NATEGLINIDE



IUPAC NAME:(2R)-({hydroxy[1r,4r)-4(propan-2-yl)cyclohexyl]methylidene}amino)-3phenylpropanoic acid.

Metabolized in liver ,major metaboiltes are hydroxy derivative(CYP2C9,and CYP3A4) which are further conjugated to glucuronide derivatives.
Half life 1.5 Hr.

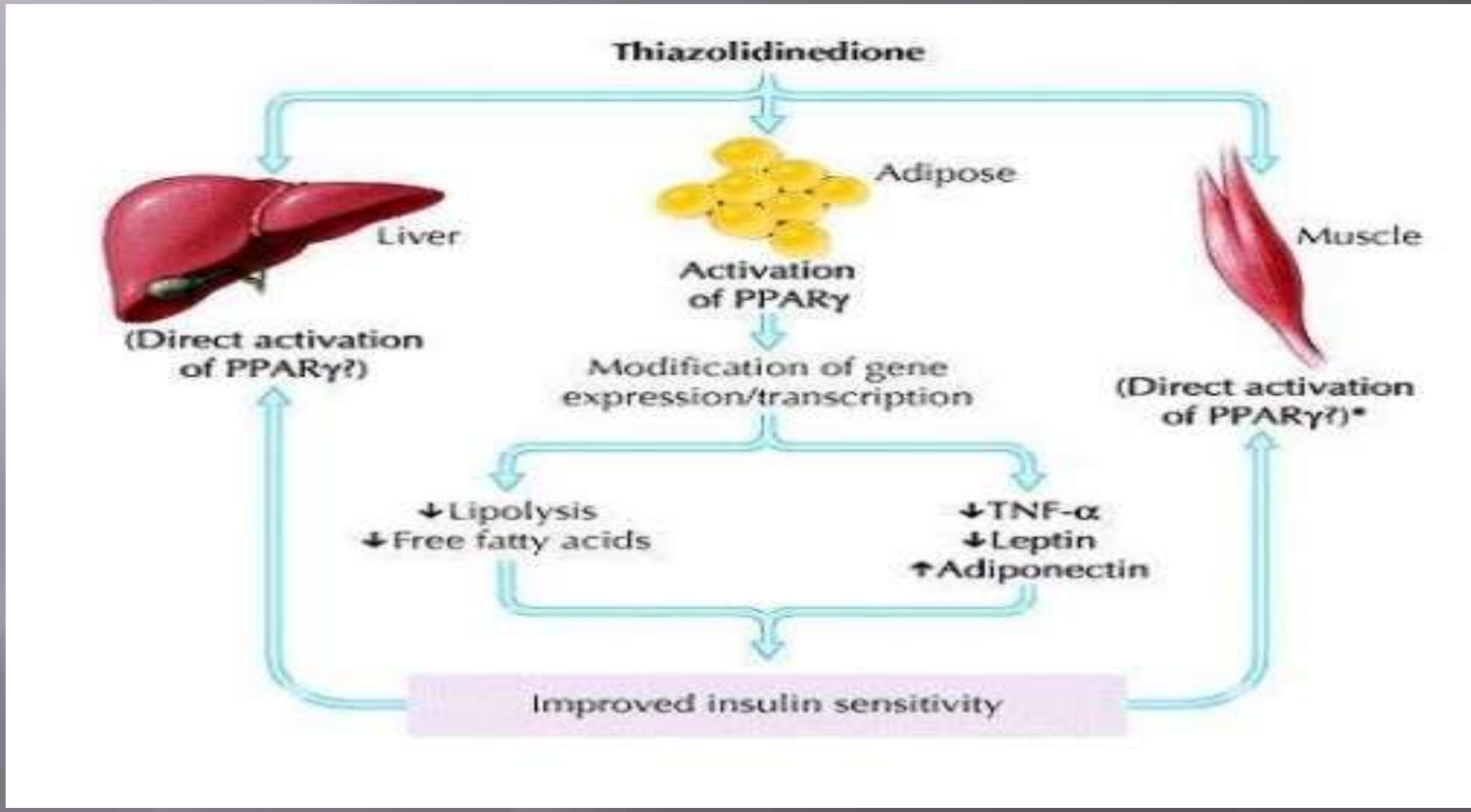
Thiazolindione:-

- The thiazolindione represent a novel nonsulfonylurease class of hypoglycemic agents for the treatment of NIDDM.

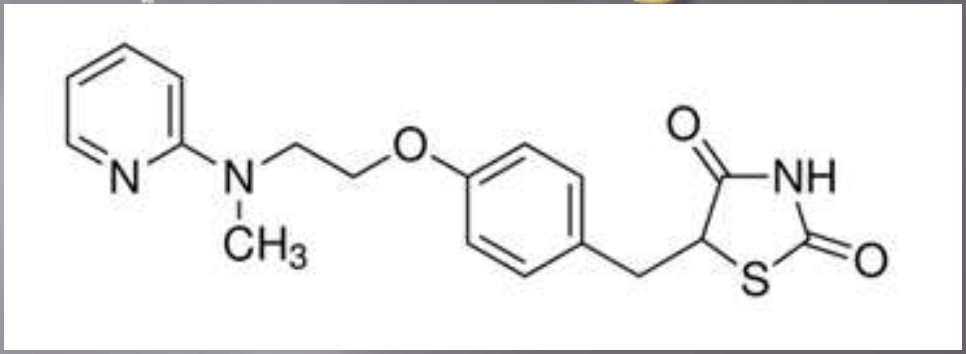
- Much like the sulfonylurease, the use of these agents requires a functioning pancreas that can successful secrete insulin from β-cell.

- The thiazolindindione are highly selective agonist for the peroxisome proliferator –activated receptor-gamma(PPARG), which is responsible for improving glycemic control, primarily through the improvement of insulin sensitivity in muscle and adipose tissue.

MECHANISM OF THIAZOLIDINEDIONE



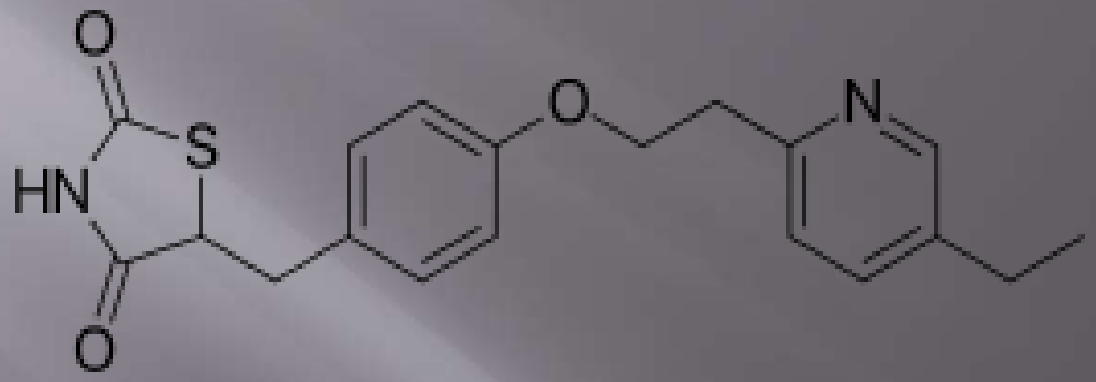
Examples:Rosiglitazone



IUPAC NAME: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione.

- It undergoes hepatic metabolism.it is extensively metabolised in liver to inactive metaboites via N-demethylation,hydroxylation, and conjugation with sulfate and glucuronic acid.
- In vitro data have shown that cytochrome(CYP)P450 isoenzyme 2C8(CYP2C8) and to a minor extent CYP2C9 are involved in the hepatic metabolism of rosiglitazone.
- Side effects include fluid retention,congestive heart failure(CHF), liver disease.

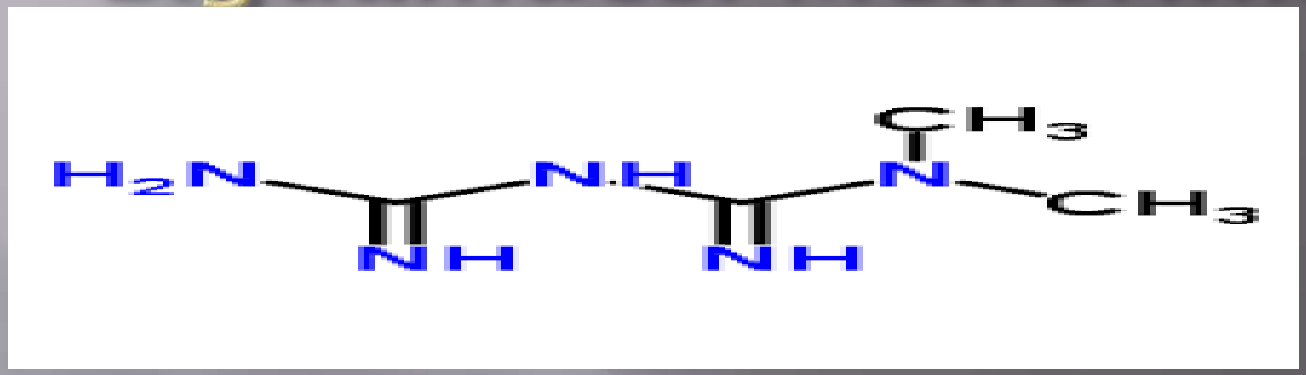
Pioglitazone



IUPAC NAME:5-({4[2-(5-ethylpyridin-2yl)ethoxy]phenyl}methyl)1,3-thiazolidine-2,4dione

Pioglitazone when metabolized the active metabolites M-III AND M-IV are Circulating in humans.

Biguanides: Metformin



IUPAC NAME: 1,1-Dimethylbiguanide

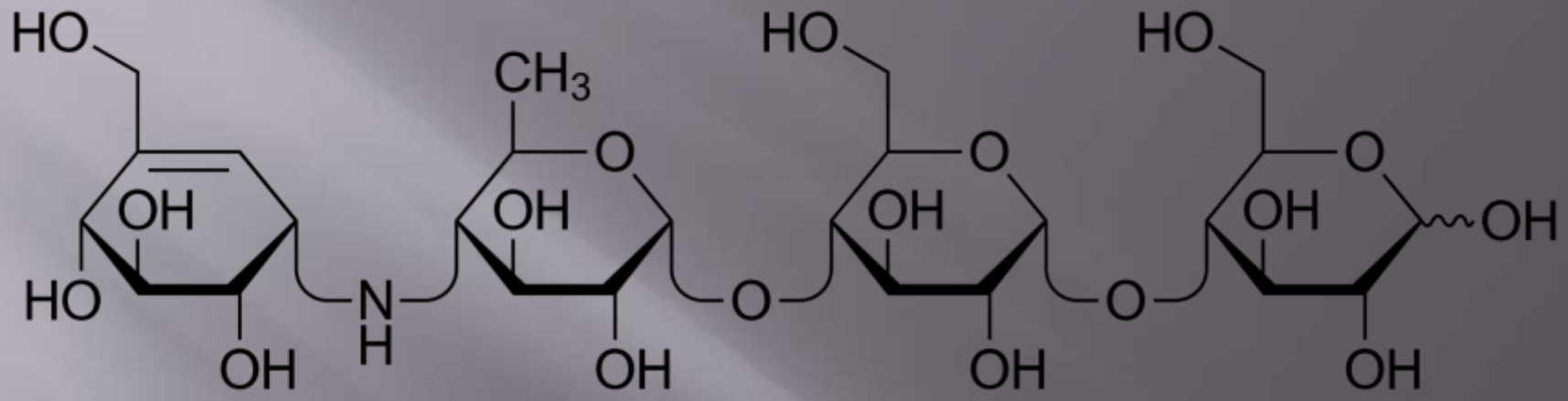
Metabolism:Intravenous studies using a single dose of metformin in normal subjects show that metformin is excreted as unchanged drug in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

- Metformin's mechanisms of action are unique from other classes of oral antihyperglycemic drugs. Metformin decreases blood glucose levels by decreasing hepatic glucose production (gluconeogenesis), decreasing the intestinal absorption of glucose, and increasing insulin sensitivity by increasing peripheral glucose uptake and utilization
- After ingestion, the organic cation transporter-1 (OCT1) is responsible for the uptake of metformin into hepatocytes (liver cells). As this drug is positively charged, it accumulates in cells and in the mitochondria .
- Metformin inhibits mitochondrial complex I, preventing the production of mitochondrial ATP leading to increased cytoplasmic ADP:ATP and AMP:ATP ratios
- . These changes activate AMP-activated protein kinase (AMPK), an enzyme that plays an important role in the regulation of glucose metabolism . Aside from this mechanism, AMPK can be activated by a lysosomal mechanism involving other activators. Following this process, increases in AMP:ATP ratio also inhibit *fructose-1,6-bisphosphatase* enzyme, resulting in the inhibition of gluconeogenesis, while also inhibiting *adenylate cyclase* and decreasing the production of cyclic adenosine monophosphate (cAMP) , a derivative of ATP used for cell signaling . Activated AMPK phosphorylates two isoforms of acetyl-CoA carboxylase enzyme, thereby inhibiting fat synthesis and leading to fat oxidation, reducing hepatic lipid stores and increasing liver sensitivity to insulin
- In the intestines, metformin increases anaerobic glucose metabolism in enterocytes (intestinal cells), leading to reduced net glucose uptake and increased delivery of lactate to the liver. Recent studies have also implicated the gut as a primary site of action of metformin and suggest that the liver may not be as important for metformin action in patients with type 2 diabetes. Some of the ways metformin may play a role on the intestines is by promoting the metabolism of glucose by increasing glucagon-like peptide I (GLP-1) as well as increasing gut utilization of glucose

Alpha glucosidase inhibitors

- Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates: specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine.
- Acarbose also blocks pancreatic alpha-amylase in addition to inhibiting membrane-bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine.
- Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels: the long-term effect is a small reduction in hemoglobin level.

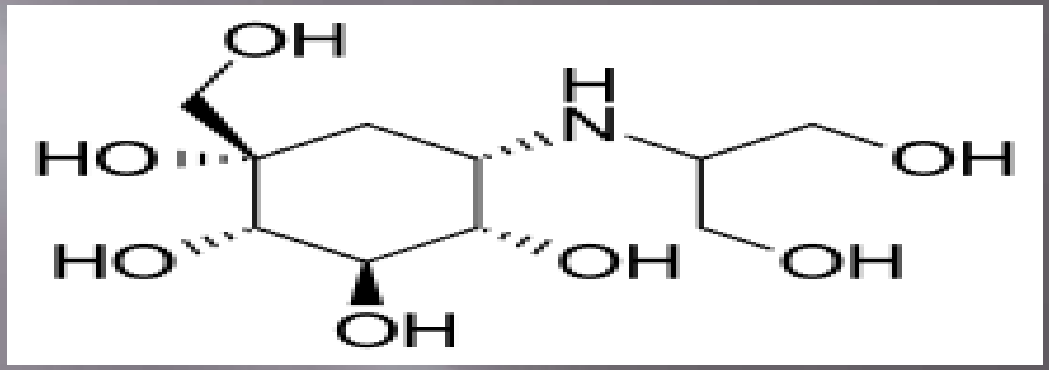
Acrabose



IUPAC NAME:O- 4didedoxy-4[[(1S,4R5S,6S)-4,56trihydroxy3-(hydroxymethyl)2-cyclohexen-1yl]amino] Ad glucopyranosyl(1—›4)-O α-D-glucopyranosyl-(1—›4)D-glucose.

Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, specifically, alpha-glucosidase enzymes in the brush border of the small intestines, and pancreatic alpha-amylase.
Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules.

VOGLIBOSE



IUPAC NAME: 1S,2S,3R,4S,5S)-5[(1,3 dihydroxypropan-2yl)amino]1(hydroxymethyl)cyclohexen 1,2,3,4tetrol.

- Voglibose is an alpha-glucosidase inhibitor used for lowering postprandial blood glucose levels in people with diabetes mellitus.

- Voglibose delays the absorption of glucose thereby reducing the risk of macrovascular complications.

THANK YOU