Chapter 17. Antidiabetic Drugs

Syllabus:

- Insulin and its preparations
- **Sulfonyl Ureas**: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride.
- **Biguanides**: Metformin.
- **Thiazolidinediones**: Pioglitazone, Rosiglitazone.
- **Meglitinides**: Repaglinide, Nateglinide.
- **Glucosidase inhibitors**: Acrabose, Voglibose

Pharmacology Lectures:

Diabetes Meletus: https://youtu.be/G_1QrQDMouM

Oral antidiabetic Drugs: https://youtu.be/s1eiqxdkZrg

Sulphonylureas: https://youtu.be/p9ZJeWyTHoQ

DPP4 Inhibitors and Thiazolidinedione: https://youtu.be/vK3TQ0MvRmQ

Biguanides and Acarbose: https://youtu.be/cWUwBGqUOwY

17.1. DIABETES MELETUS

- Diabetes mellitus (DM), is a group of heterogenous metabolic diseases in which there are high blood sugar levels (hyperglycemia) over a prolonged period due to defect in insulin formation, secretion, and action.
- DM is also known as Metabolic syndrome, Syndrome X or Insulin resistance syndrome.
- Characterized by:
  - Hyperglycemia (fasting blood glucose >7 mmol/L; >120 mg/dL
  - Altered carbohydrate metabolism
  - Altered protein and Lipid metabolism
- Symptoms:
  - Polyurea (Frequent Urination)
  - Glycosuria (Glucose in Urine)
  - Polydipsia (Excessive Thirst)
  - Polyphagia (Excessive Hunger)
  - Lethargy, Fatigue

- **Types**
  - **I. TYPE 1 DIABETES MELLITUS (10%)**
    - (Earlier called Insulin-dependent (IDDM), or juvenile-onset diabetes)
    - *Type IA DM:* Immune-mediated
    - *Type IB DM:* Idiopathic
  - **II. TYPE 2 DIABETES MELLITUS (80%)**
    - (earlier called non-insulin-dependent (NIDDM), or maturity-onset diabetes)
  - **III. GESTATIONAL DIABETES MELLITUS (4%)**
  - **IV. OTHER SPECIFIC TYPES OF DIABETES (6-10%)**

TYPE 1 DIABETES

- Earlier called **Insulin-dependent (IDDM),** or **juvenile-onset diabetes (JOD)**
- Account for 10% cases
- Usually Occurs in non-obese person before the age of 30 Years
- They are absolute requirement of insulin replacement as a treatment.
- Lake of both insulin release phase
- Beta-cells fails to respond to normal stimuli for insulin release
- As per new classification, neither age nor insulin dependence are considered as absolute criteria. So further Type I DM is can be classified into two subtypes: **A. Type IA and B. Type IB**

A. Type IA (Immune Mediate) Diabetes Mellitus:

- This type is characterized by **Autoimmune Destruction of Beta-Cells** which usually leads to Insulin Deficiency (Reduction in Insulin Production)

B. Type IB (Idiopathic Mediated) Diabetes Mellitus

- This type is characterized by insulin deficiency with tendency to develop ketosis but these patientsvare negative for autoimmune markers.

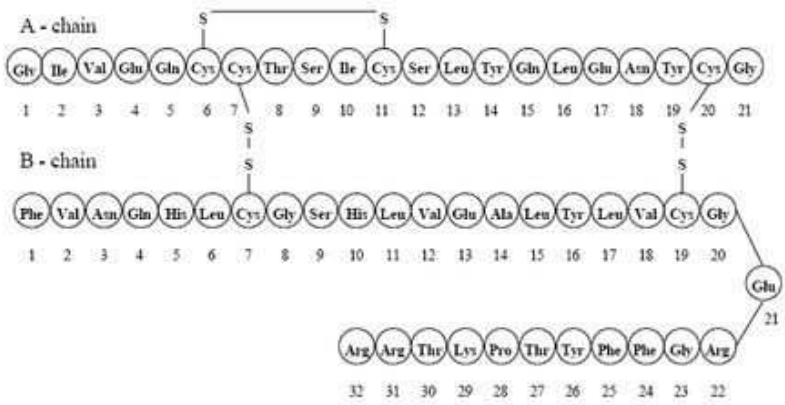
TYPE 2 DIABETES

- Earlier called **non-Insulin-dependent (NIDDM),** or **maturity-onset diabetes (MOD)**
- Account for 80% cases
- Usually Occurs in older individuals and obese adolescent children.

- Many Type II DM patients require Insulin to prevent hyperglycemia, and ketosis and thus are not truly non-insulin dependent
- The basic metabolic defect in type II DM is either impaired insulin secretion and or insulin resistance.

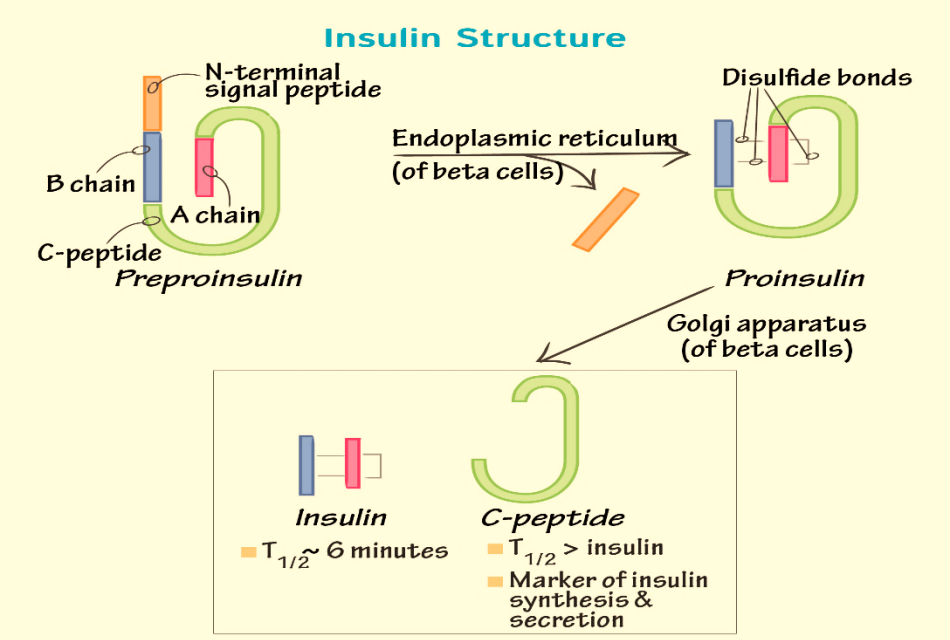
17.2. INSULIN AND ITS PREPARATIONS

- Isolated in 1921 by Banting & Best and used clinically in 1922.
- Amino acid sequences of insulin (51 amino acid) were determined by Sanger's Group in Cambridge in 1955.
- Made up two polypeptide chains-
  - A chain (Acidic)- 21 amino acid
  - B Chain (Basic)- 30 amino acids
- Chain A and B are linked together by two disulphide bridge [A7 Cys-B7 Cys and A20 Cys-B19 Cys]



- **Biosynthesis**: synthesis within the pancreatic beta cell from propreinsulin (single chain 86 amino acids).

Propreinsulin (RER)→Preinsulin (Golgi apparatus)→Insulin



Effects on Metabolism

Type of metabolism	Liver cells	Fat cells	Muscle
Carbohydrate metabolism	↓ Gluconeogenesis ↓ Glycogenolysis ↑ Glycolysis ↑ Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat metabolism	↑ Lipogenesis ↓ Lipolysis	↑ Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis	–
Protein metabolism	↓ Protein breakdown	–	↑ Amino acid uptake ↑ Protein synthesis

Preparations

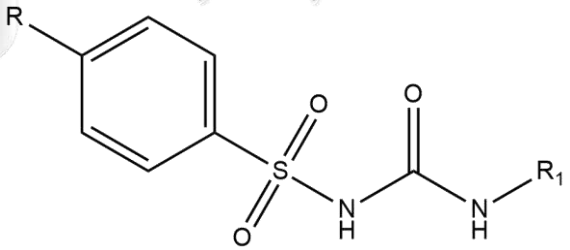
Category/Name of Insulin	Brand Name (manufacturer)	Preparation(s)
Rapid-Acting		
Insulin Lispro	Humalog (Lilly)	Vial, cartridge, disposable pen
Insulin Aspart	Novolog (Novo Nordisk)	Vial, cartridge, disposable pen
Insulin Glulisine	Apidra (Sanofi-Aventis)	Vial, disposable pen
Technosphere insulin	Afreeza	Inhaler
Short-Acting		
Regular Human	Humulin R (Lilly) Novolin R (Novo Nordisk)	Vial
Intermediate-Acting		

Category/Name of Insulin	Brand Name (manufacturer)	Preparation(s)
NPH Human	Humulin N (Lilly) Novolin N (Novo Nordisk)	Vial, disposable pen Vial
Long-Acting		
Insulin Detemir	Levemir (Novo Nordisk)	Vial, disposable pen
Insulin Glargine	Lantus (Sanofi-Aventis) Basaglar (Lilly) Toujeo (Sanofi-Aventis)	Vial, cartridge, disposable pen Basaglar is only available as a disposable pen Toujeo is only available as a disposable pen
Insulin Degludec	Tresiba (Novo Nordisk)	Disposable pen
Insulin Mixtures		
NPH/Regular (70%/30%)	Humulin 70/30 (Lilly) Novolin 70/30 (Novo Nordisk)	Vial, disposable pen Vial
Protamine/Lispro (50%/50%)	Humalog Mix 50/50(Lilly)	Vial, disposable pen
Protamine/Lispro (75%25%)	Humalog Mix 75/25(Lilly)	Vial, disposable pen
Protamine/Aspart (70/30)	Novolog Mix 70/30 (Novo Nordisk)	Vial, disposable pen

17.3. MEDICINAL CHEMISTRY OF ORAL ANTIDIABETIC DRUGS

1. Sulfonylureas

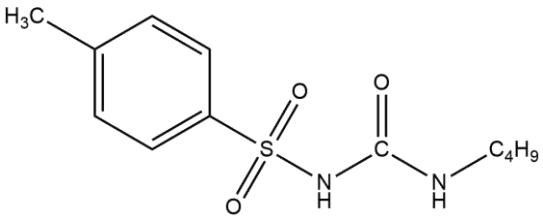
SAR:



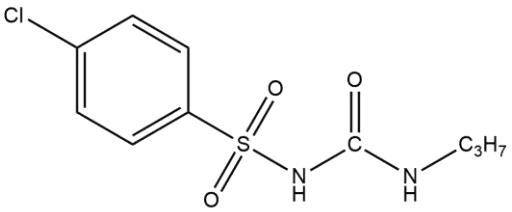
Basic Ring of Sulfonylureas

Benzene ring contain substitution at para position.

- **R-** $-CH_3$, $-COCH_3$, $-NH_2$, -Cl, -Br, $-CF_3$, and dithiomethyl enhance the antihyperglycemic activity. Eg. Chlorpropamide> Tolbutamide

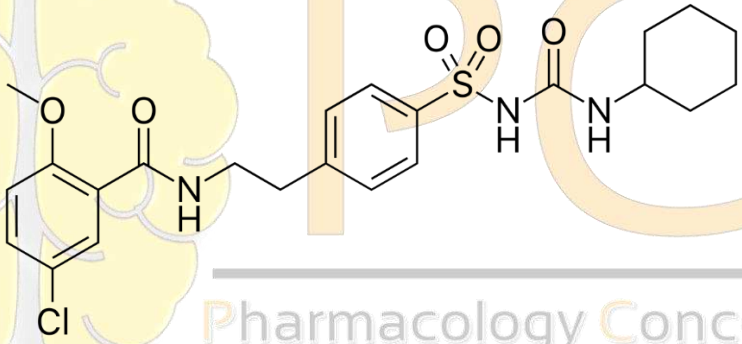


Tolbutamide

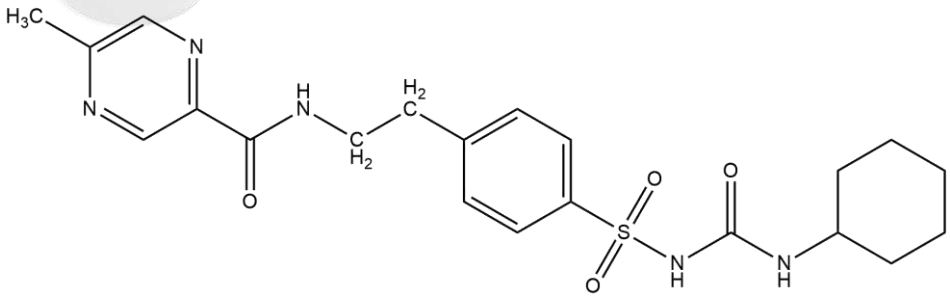


Chlorpropamide

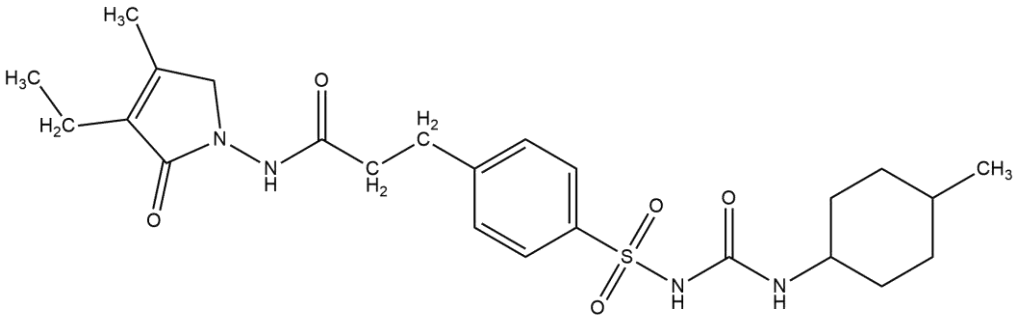
- **R-** aryl carboxamidoalkyl (second-generation sulphonylureas, such as glibenclamide), the activity was found to be enhanced further



Glibenclamide



Glipizide

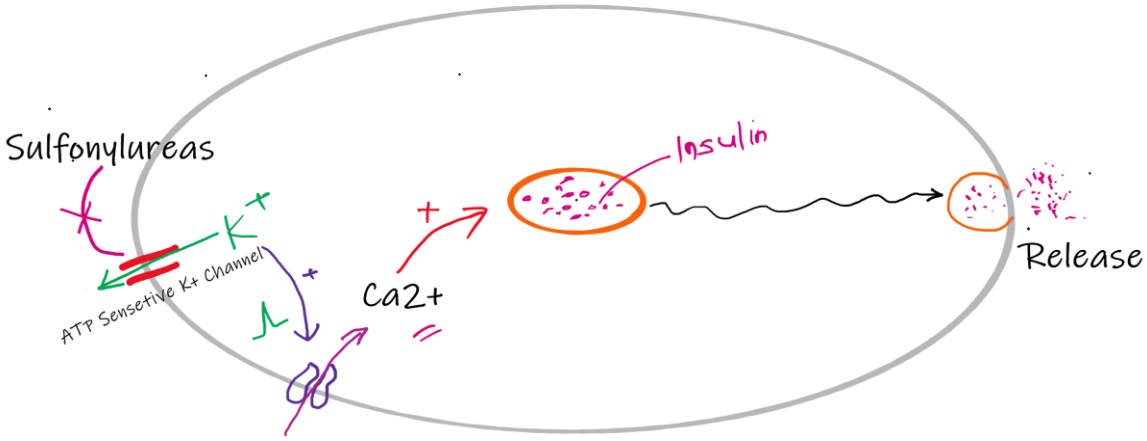


Glimepiride

- **R1-** the size of N-terminal is the most important for the lipophilicity and activity. N methyl or ethyl has show no activity, while N-propyl and higher homologues were found to be active upto 11-C atom. N-substitution contains more than 12-C atom lost their activity.

Selected Drugs: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride

Mechanism of Action

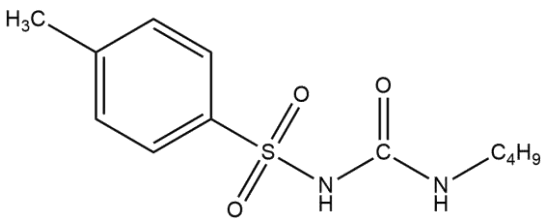


- Sulfonylureas stimulate the release of insulin form pancreas. They act on 'sulfonylurea receptors' (SUR1) on the pancreatic β cell membrane → cause depolarization by reducing conductance of ATP sensitive K+ channels→ enhances Ca2+ influx degranulation→ Stimulate the rate of insulin secretion at any glucose concentration.
- The sulfonylureas primarily augment the 2nd phase insulin secretion with little effect on the 1st phase

Uses:

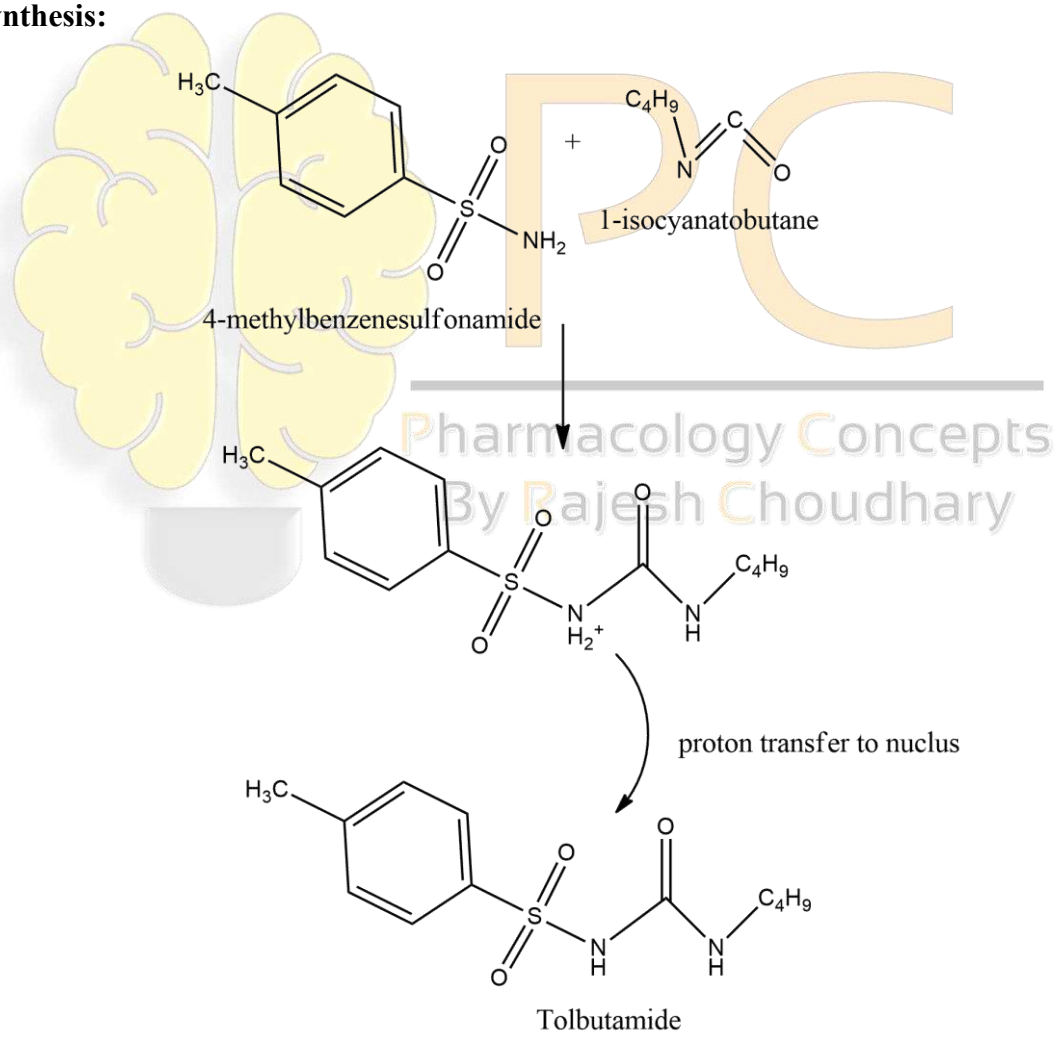
- ✓ Treatment of Type-2 Diabetes
- ✓ Tolbutamide has some diuretic action and tolbutamide can be used in the diagnosis of insulinoma

A) Tolbutamide

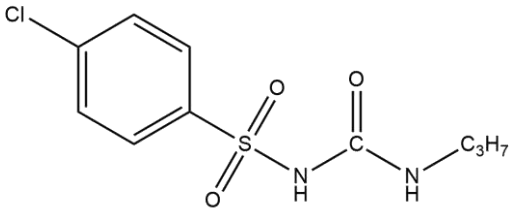


1-butyl-3-(4-methyl phenyl) sulfonyl urea

Synthesis:

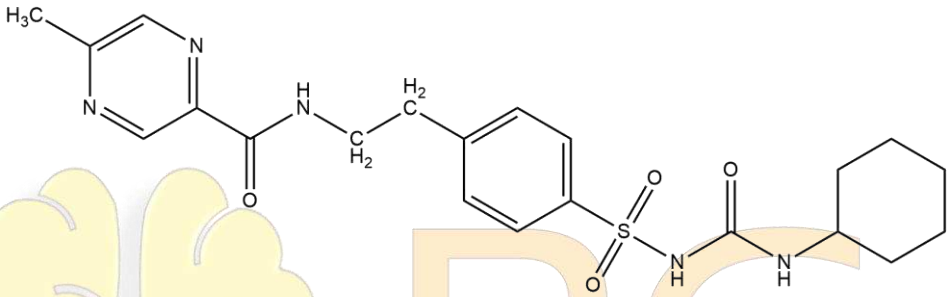


B) Chlorpropamide



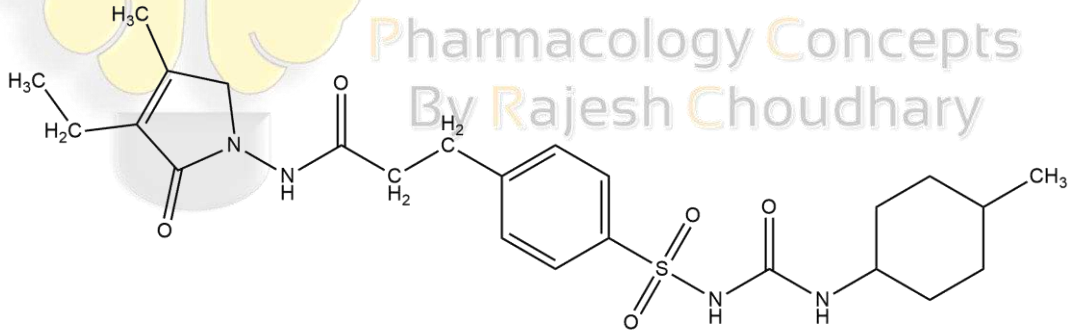
1-propyl-3-(4-chloro phenyl) sulfonyl urea

C) Glipizide



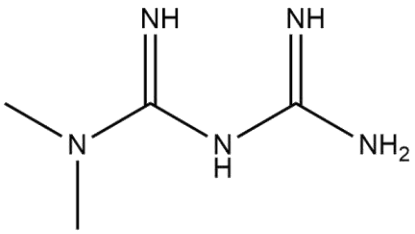
***N*-[2-[4-(cyclohexyl carbamoyl sulfamoyl) phenyl] ethyl]-5-methyl pyrazine-2-carboxamide**

D) Glimepiride

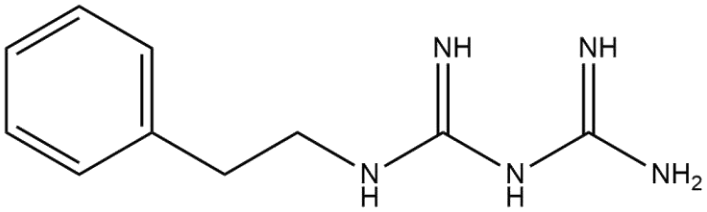


4-ethyl-3-methyl-*N*-[2-[4-[(4-methyl cyclohexyl) carbamoyl sulfamoyl]phenyl]ethyl]-5-oxo-2*H*-pyrrole-1-carboxamide

2. Biguanides



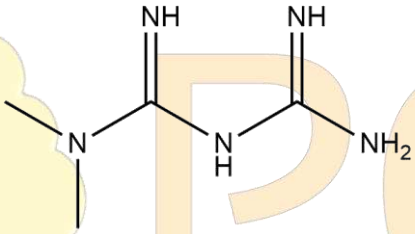
Metformin



Phenformin

*Phenformin is currently not in used due to high risk of lactic acidosis.

A) Metformin



3-(diamino methylidene)-1,1-dimethyl guanidine

MOA:

Biguanides do not cause insulin release, but for the action insulin is essential; thus they not effective in type-1 diabetes. Biguanides activate the **AMP-dependent protein kinase** (AMPK) to play a crucial role in mediating the actions of metformin, the key features of which are:

a) decrease the hepatic gluconeogenesis and glucose output from liver (MAJOR ACTION)

b) improve the peripheral glucose utilization by reducing insulin resistance.

c) enhance the cellular respiration

Uses: Preferred (1st choice drug) for treatment of type-2 diabetes.

3. Thiazolidinediones (PPARy Agonist)

Pioglitazone and Rosiglitazone are the thiazolidinediones derivatives. Rosiglitazone is currently banned in India since 2010 due to high risk of in risk of myocardial infarction, CHF, stroke and death

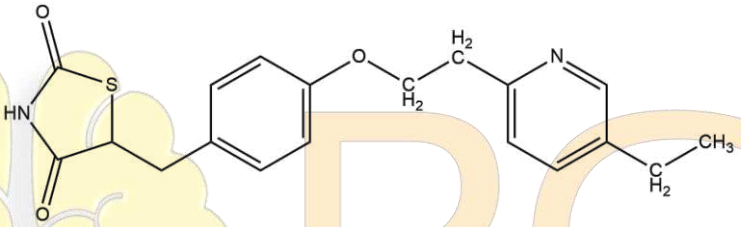
MOA: thiazolidinediones are the selective nuclear peroxisome proliferator-activated receptor (PPARy) agonist, which is expressed mainly in fat cells, but also in muscle and some other cells.

- It enhances the transcription of several insulin responsive genes.
- Reverse the insulin resistance by enhancing GLUT4 expression and translocation.
- Improve the Entry of glucose into muscle and fat cells.
- Supress the hepatic gluconeogenesis
- Lipolysis and plasma fatty acid levels are reduced. Fatty tissue is a major site of their action.

Uses:

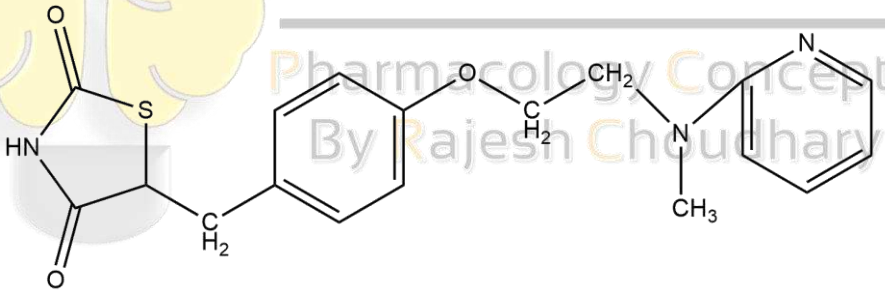
- ✓ Pioglitazone is indicated in type 2 DM, but not in type 1 DM.
- ✓ It reduces blood glucose and HbA1c (by 0.5–1.2%) without increasing circulating insulin

A) Pioglitazone



5-[[4-[2-(5-ethyl pyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione

B) Rosiglitazone.

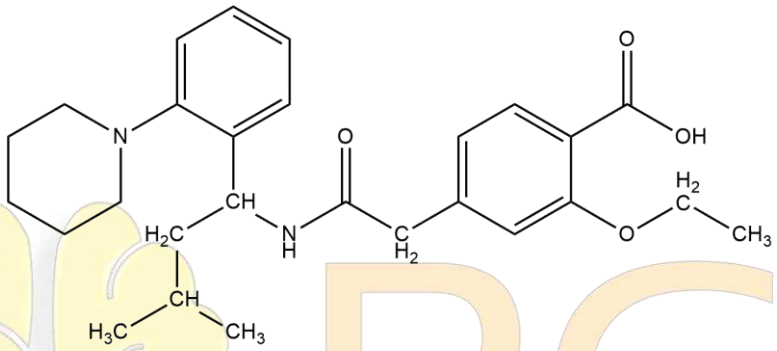


5-[[4-[2-[methyl(pyridin-2-yl)amino]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione

4. Meglitinides

Repaglinide and Nateglinide are meglitinide analogue oral hypoglycaemic is designed to normalise mealtime glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to SUR→ closure of ATP dependent K+ channels→depolarisation→insulin release. It is generally taken before each major meals to control postprandial hyperglycaemia.

A) Repaglinide

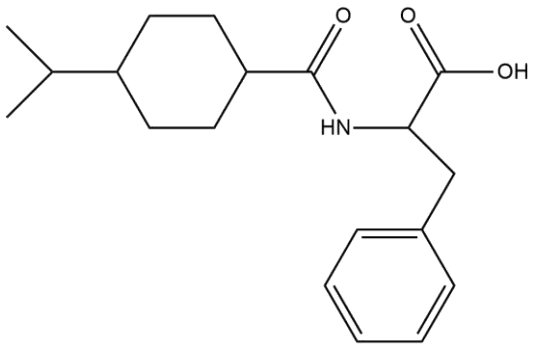


2-ethoxy-4-[2-[[(1*S*)-3-methyl-1-(2-piperidin-1-ylphenyl)butyl]amino]-2-oxoethyl]benzoic acid

MOA: KATP channel blockers

Uses: Treatment of type 2 diabetics who suffer pronounced post prandial hyperglycaemia, or to supplement metformin/long-acting insulin. It is contraindicated in liver disease condition.

B) Nateglinide



(2*R*)-3-phenyl-2-[(4-propan-2-yl cyclohexanecarbonyl)amino]propanoic acid

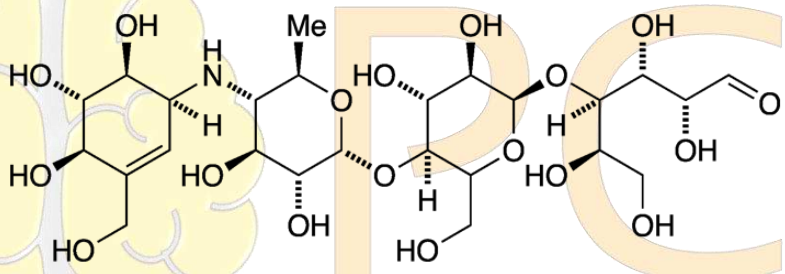
MOA: It is a D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion by closing β cell KATP channels resulting in faster onset and shorter lasting hypoglycaemia than repaglinide.

Uses: It is taken 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia.

5. Alfa Glucosidase inhibitors

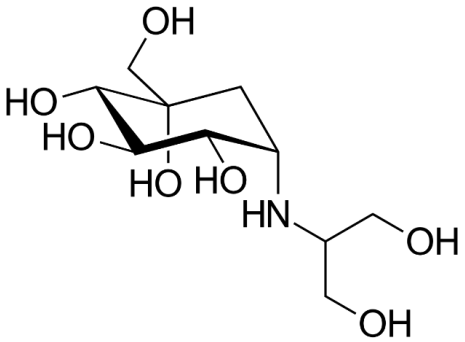
They reversibly inhibit α-glucosidases, which is responsible for digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose

A) Acarbose



Uses: Acarbose (25-50 mg/day, start with low dose) is used in the treatment of Type-2 diabeted used alone or along with other oral antidiabetic drugs and/or insulin.

B) Voglibose



3,4-dideoxy

(1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)- 1-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol

Uses: Used in the treatment of Type 2 diabetes mellitus (dose 200-300 ug three time in a day) alone or along with sulfonylureas or insulin.