MEDICINAL CHEMISTRY-II

UNIT 5 NOTES

- Antidiabetic Agents
- Local Anaesthetics
- Benzoic Acid Derivatives
- Amino Benzoic Acid Derivatives
- Miscellaneous

IMPERFECT PHARMACY

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DIABETES MELLITUS

- Diabetes Mellitus is a chronic metabolic disorder characterized by high levels of Glucose in Blood.
- It occurs either due to inadequate production of Insulin by Pancreas or body's inability to effectively use Insulin.
- Insulin is a Hormone produced by Pancreas that helps to regulate Blood Sugar Level by facilitating absorbtion of Glucose into cells to be used for Energy.

TYPES OF DIABETES MELLITUS

Diabetes Mellitus can be mainly classified into 3 types

① Type 1 Diabetes Mellitus
② Type 2 Diabetes Mellitus
③ Gestational Diabetes

TYPE 1 DM

- Earlier it was known as Insulin Dependent Diabetes Mellitus.
- It constitutes about 10% cases of Diabetes Mellitus.
- It occurs because of destruction of β cells of pancreas due to Autoimmune Disorders.
- It leads to deficiency of Insulin that leads to increase in Blood Glucose Level.
- Type 1 Diabetes often develops during Childhood or Adult Age.

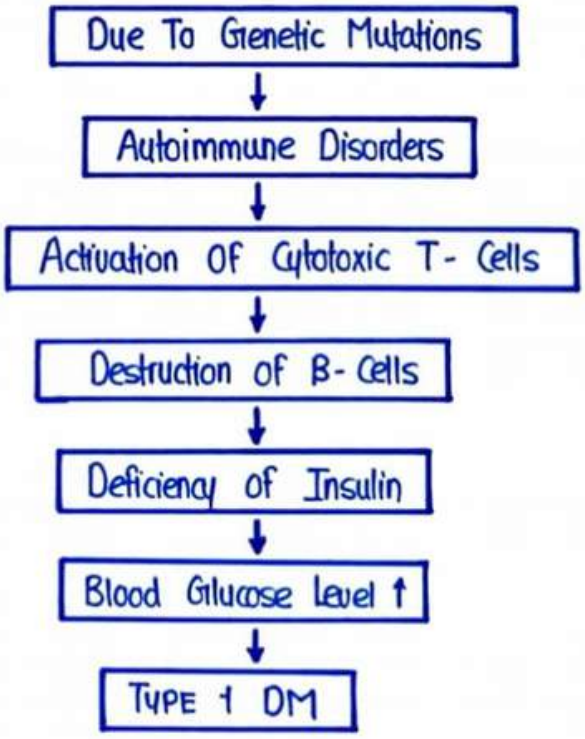
CAUSES

- Type 1 Diabetes Mellitus primarily occurs due to an Autoimmune Disorder, where body's immune system mistakenly attacks & destroys insulin producing β cells in pancreas.
- The exact cause of this autoimmune response is not fully understood, it is beleived to involve a combination of Genetic & Environmental factors.
- There are following factors that can be responsible for this AIR.

① Genetic Mutations
② Viral Infections
③ Early Childhood Exposures
④ Geographical & Seasonal Patterns

PATHOGENESIS

The pathogenesis of Type 1 Diabetes can be explained as follows :



Symptoms

- Increased Thirst
- Frequent Urination
- Extreme Hunger
- Weight Loss
- Fatigue
- Weakness

Complications

- Diabetic ketoacidosis
- Diabetic Neuropathy
- Diabetic Nephropathy
- Diabetic Retinopathy
- Depression & Anxiety

Treatment & Management

- Insulin Therapy
- Blood Sugar Monitoring
- Physical Activity
- Management of Other Health Conditions
- Carbohydrate Counting

TYPE 2 DM

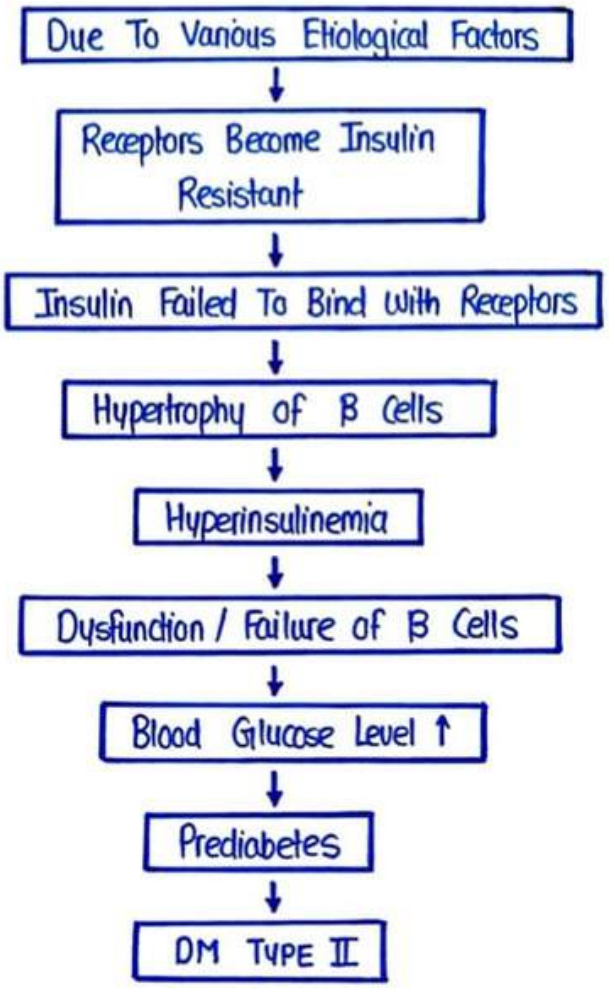
- Earlier it was known as Non Insulin Dependent Diabetes Mellitus.
- It constitutes about 90% cases of Diabetes.
- It generally occurs when cell doesn't respond to properly.
- In Type 2 Diabetes receptor on cells becomes Insulin Resistance.
- Type 2 DM, if maintained for a long period of time can also leads to Insulin Deficiency
- It generally occurs later (mostly after 30) due to physical inactivity, obesity & poor dietary habits.

CAUSES

Type 2 diabetes is mainly a lifestyle disorder in which body becomes resistant to the effect of Insulin. Several factors contribute to the development of Type 2 DM as follows :

- Genetic Factors
- Obesity
- Physical Inactivity
- Unhealthy Diet
- Age
- Gestational Diabetes
- Polycystic Ovary Syndrome (PCOS)

Pathogenesis



Symptoms

- Excessive Thirst
- Frequent Urination
- Increased Hunger
- Weight Loss
- Fatigue
- Slow Healing

Complications

- Diabetic Neuropathy
- Diabetic Nephropathy
- Diabetic Retinopathy
- Cardiovascular Diseases
- Depression / Anxiety

Treatment / Management

- Healthy Diet
- Regular Exercise
- Weight Management
- Certain Medications :
  - Sufonyl Urea
  - Metformin
- Blood Sugar Monitoring

ANTIDIABETIC AGENTS

- Antidiabetic Agents are used for treating Diabetes Mellitus by decreasing blood glucose levels.
- Some of these drugs are administered orally and termed Oral Hypoglycaemic or Oral Antihyperglycaemic Agents
- Different classes of anti-diabetic drugs exist and they are selected based on nature of diabetes, individual's age, situation and other factors

INSULIN

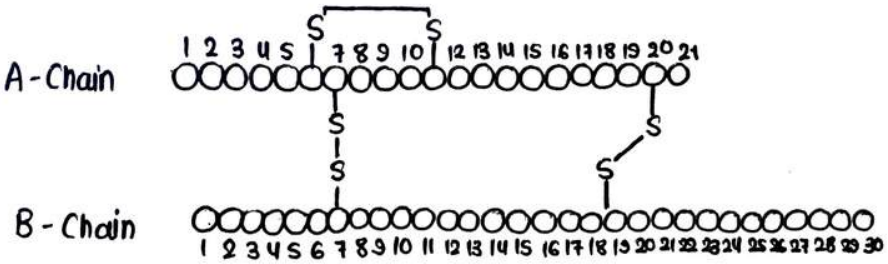
- Insulin is a peptide hormone that plays a central role in regulating various metabolic processes, particularly the regulation of blood glucose levels.
- It is produced & secreted by beta cells of islets of Langerhans in pancreas.
- Insulin is essential for proper utilization, storage and regulation of glucose and other nutrients in the body.

Structure Of Insulin

- Insulin is a protein hormone composed of 51 amino acid arranged in two polypeptide chains:

① A Chain (21 amino acids)
② B Chain (30 amino acids)

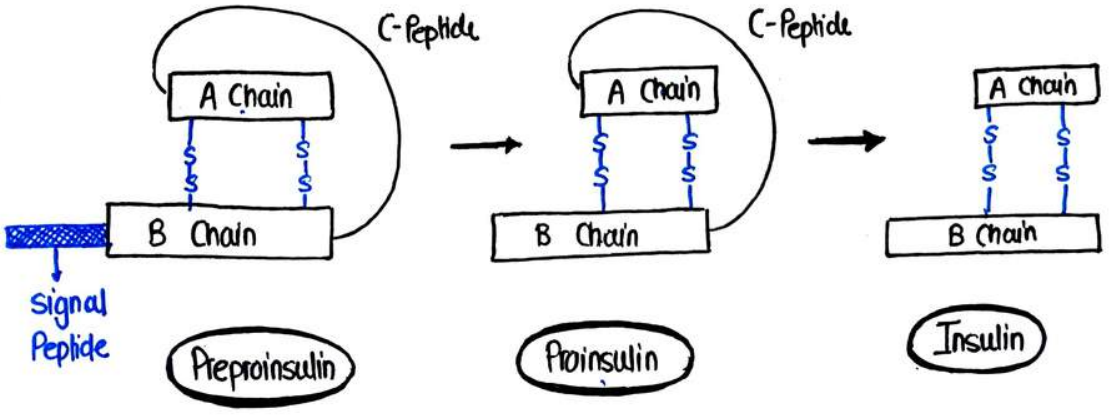
- These chains are connected by disulfide bonds, crucial for maintaining its functional 3 dimensional structure.



INSULIN

SYNTHESIS

- Synthesis of Insulin refers to process by which Insulin, a peptide hormone, is produced in pancreas, specifically by the beta cells of islets of Langerhans.
- The insulin mRNA is translated as a single chain precursor, known as pre-pro-insulin.
- The signal peptide is removed from Pre-pro-insulin, forming proinsulin
- In Golgi Apparatus, proinsulin is processed into Mature Insulin. by removing C peptide.



Insulin Preparation

Types	Onset	Peak	Duration
Short Acting Insulin			
(i) Crystalline Soluble Insulin	0·30-1	2	5-8
(ii) Amorphous Insulin Zinc Suspension (Semilente)	0·30-1	8	12-16
Intermediate Acting			
(i) Globin Zinc Insulin	1-4	6-10	16-24
(ii) Insulin Zinc Preparation (Lente)	1-4	6-8	24-30
(iii) Isophane Insulin Suspension	1-2	10-12	24-30
Long Acting Insulin			
(i) Protamine Zinc Suspension	8	14-16	30-36
(ii) Extended Insulin Zinc Crystalline (Ultralente)	7	14-16	34-36

CLASSIFICATION OF ORAL HYPOGLAECEMIC AGENT

Oral Hypoglaecemic agents can be classified as follows :

① Sulfonyl Ureas

- Tolbutamide *
- Chlorpropamide
- Glipizide
- Glimepiride

② Biguanides

- Metformin

③ Thiazolidinediones

- Pioglitazone
- Rosiglitazone

④ Meglitinides

- Repaglinide
- Nateglinide

⑤ Glucosidase Inhibitors

- Acrabose
- Voglibose

① SULFONYL UREAS

- Sulfonylureas are a class of oral hypoglycemic agents primarily used to treat Type 2 Diabetes Mellitus
- They stimulate insulin secretion from pancreatic β cells, thereby lowering blood glucose levels.

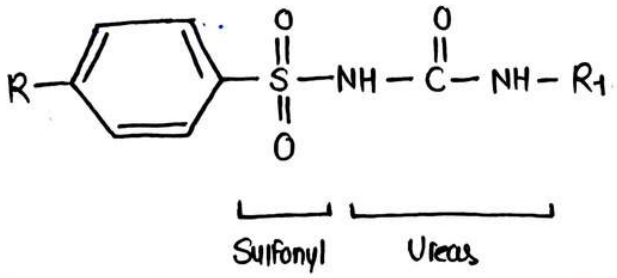
MOA

- Sulfonylureas binds to and inhibit the ATP-sensitive potassium channels on β cell membrane of pancreas.
- This inhibition causes membrane depolarization, leading to opening of voltage gated calcium channels.
- The resulting influx of calcium triggers the exocytosis of insulin granules, increasing insulin secretion.

PHARMACOKINETICS

- Absorption : They rapidly absorbed from GIT.
- Distribution : They are highly protein-bounded.
- Metabolism : Metabolized in liver via CYP2C9 enzymes.
- Excretion : Excreted primarily in urine.

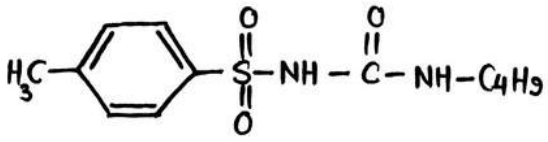
SAR Of Sulfonylureas



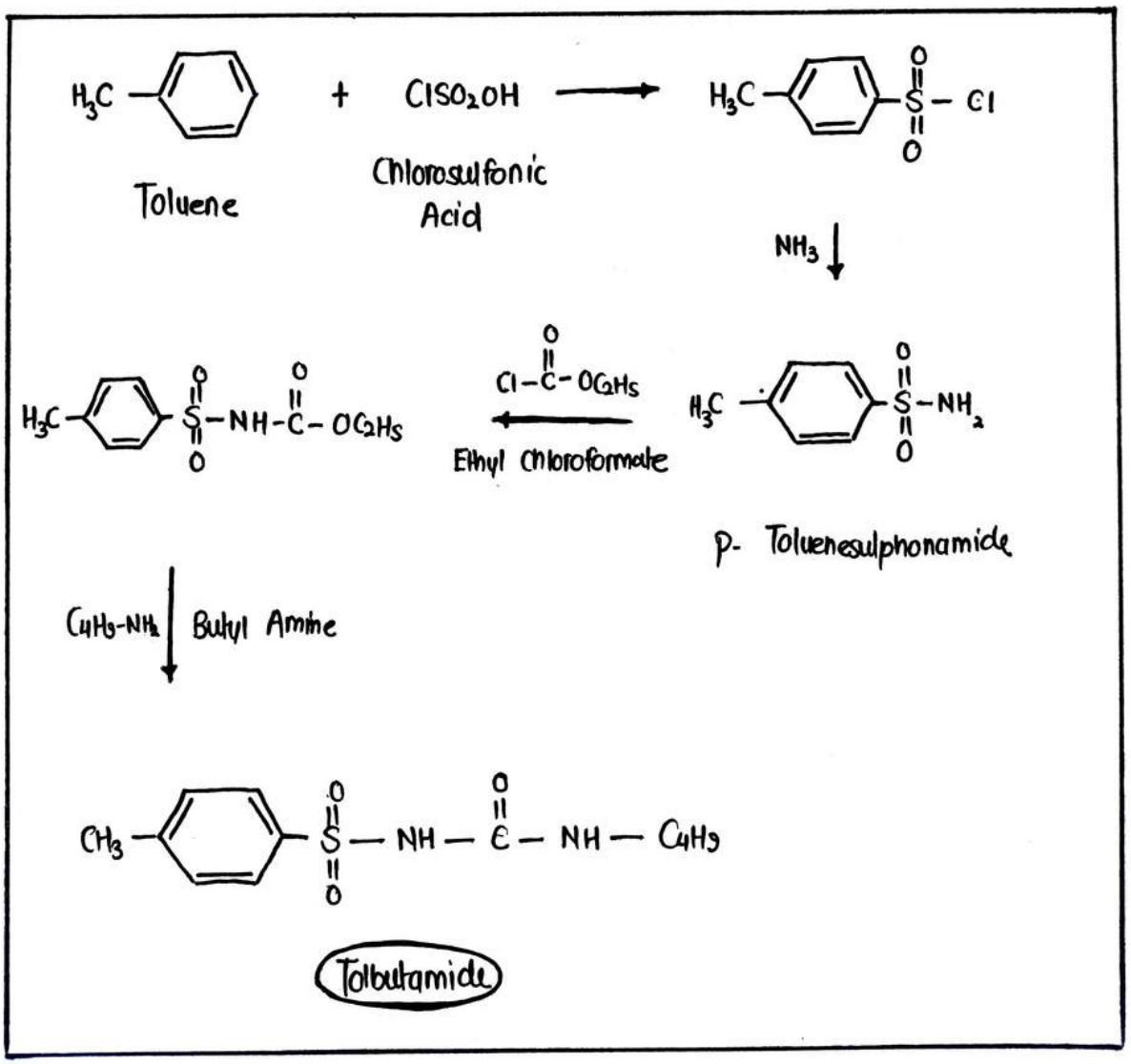
- The benzene ring should contain a substituent preferably in para position.
- The substituents such as methyl, amino, bromo, trifluoro methyl and dithiomethyl were found to enhance the antihyperglycaemic activity.
- Size of group attached to terminal nitrogen is essential for activity.
- Sulfonyl group is essential for binding to the ATP sensitive potassium channel on pancreatic β-cells.

@ Tolbutamide *

It belongs to class of sulphonylureas.



Synthesis



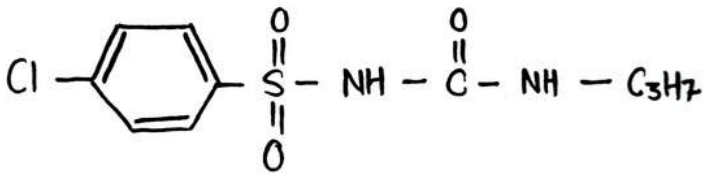
MOA

As mentioned in Sulfonylureas Introduction.

Uses

- Type - II Diabetes Mellitus

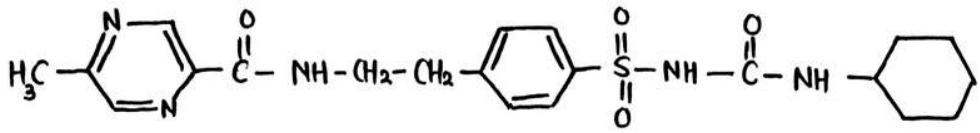
ⓑ Chlorpropamide



Uses

Type II DM

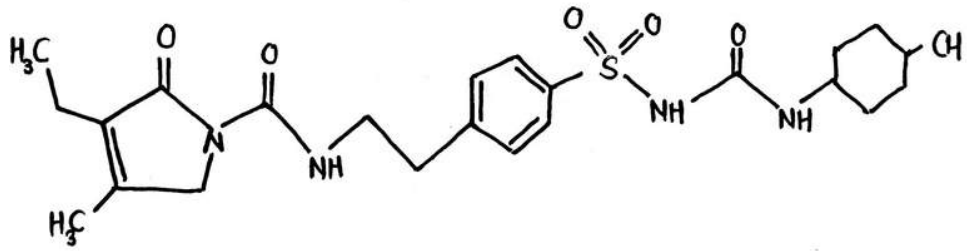
© Glipizide



Uses

- Type II DM

ⓓ Glimipiride



Uses

Type II DM

② BIGUANIDES

- Biguanides are class of oral antihyperglycemic agents primarily used in treatment of Type-2 diabetes mellitus.
- Metformin is most commonly used Biguanides.

MOA

- Biguanides inhibit gluconeogenesis and glycogenolysis in liver by suppressing complex-1 in ETC, leading to decreased ATP & activation of AMP dependent protein kinase AMP_K
- AMP_K activation reduces glucose production & increases Insulin sensitivity.
- It also slows down intestinal glucose absorption.

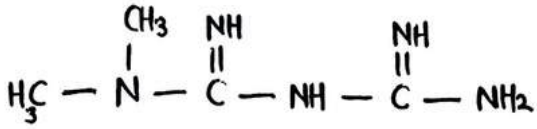
PHARMACOKINETICS

- Absorption : Well absorbed from GIT
- Distribution : Widely distributed in body tissues.
- Metabolism : It is not metabolized by liver
- Excretion : Excreted unchanged in urine

Adverse Effect

- Nausea
- Vomiting
- Diarrhoea
- Lactic Acidosis

ⓐ Metformin



Uses

Type II Diabetes Mellitus

③ THIAZOLIDINEDIONES

- Thiazolidinediones, also known as glitazones, are a class of medications primarily used to manage Type 2 DM.
- They function as insulin sensitizers, enhancing body's response to insulin, thereby improving glucose control.

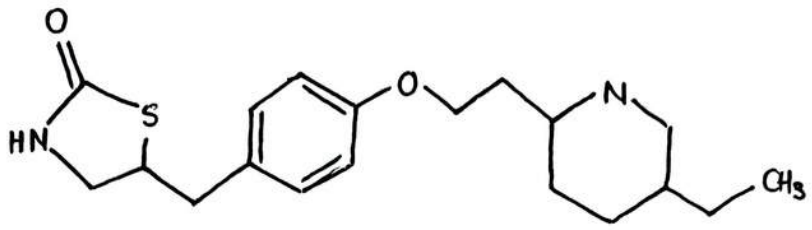
MOA

- Thiazolidinediones exert their effect by activating PPAR-γ (Proliferator-activated receptor gamma), a nuclear receptor found primarily in adipose tissue, muscle, and liver.
- When activated, PPAR-γ modulates the expression of genes involved in glucose & lipid metabolism.
- By activating PPAR-γ, TZDs increase the sensitivity of peripheral tissue (muscle & adipose tissue) to insulin, facilitating glucose uptake & reducing blood glucose levels.
- In liver, PPAR-γ activation leads to reduced hepatic glucose production, further lowering blood sugar levels.

PHARMACOKINETICS

- Absorption : They are well absorbed from GIT.
- Distribution : They are widely distributed in body.
- Metabolism : They are primarily metabolized in liver by CYTP450 enzyme.
- Excretion : They are excreted via kidneys.

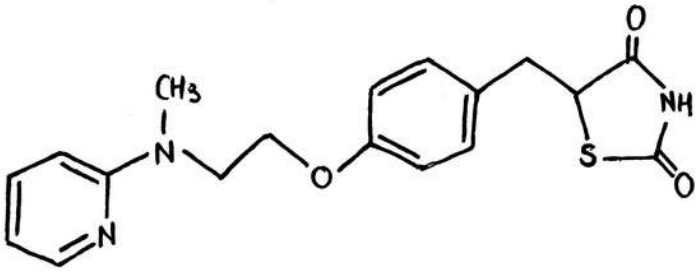
① Pioglitazone



Uses

- Type II Diabetes Mellitus

② Rosiglitazone



Uses

Type II Diabetes Mellitus

④ MEGLITINIDES

- Meglitinides are class of oral antidiabetic agents used to manage Type II Diabetes Mellitus by stimulating insulin secretion.
- They are generally short acting and primarily used to manage postprandial blood glucose levels.

MOA

- Meglitinides binds to specific sites on ATP-sensitive potassium channels on pancreatic beta cells.
- This binding causes closure of potassium channels, leading to cell depolarization.
- Depolarization opens voltage-gated calcium channels, allowing calcium influx, which triggers exocytosis of insulin.

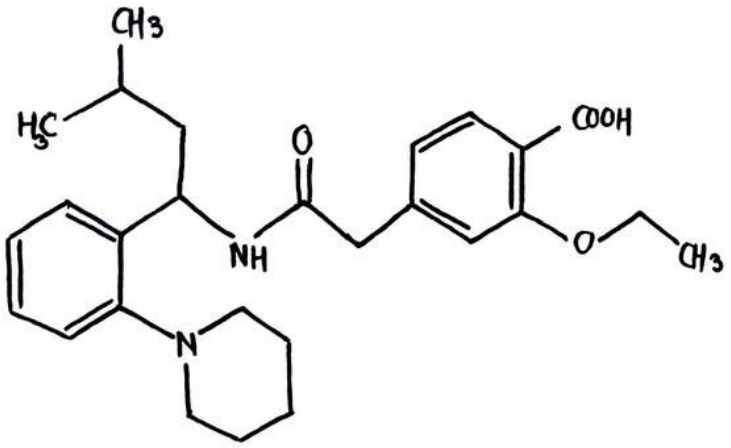
PHARMACOKINETICS

- Absorption : Rapidly absorbed from GIT.
- Distribution : Highly protein bounded.
- Metabolism : Metabolised in liver by CYP3A4 & CYP2C8 enzymes.
- Excretion : Mainly excreted via feces & urine.

Adverse Effects

- Hypoglycemia
- Weight Gain
- GIT Disturbances.

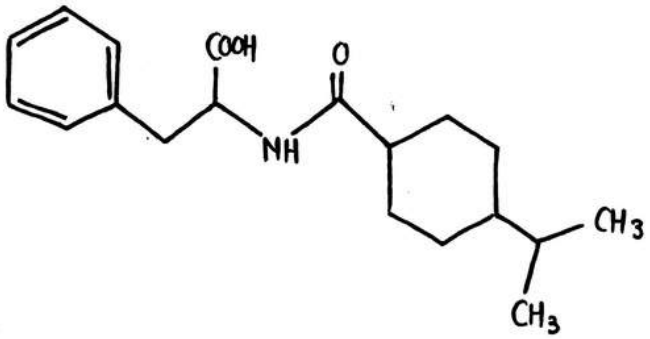
@ Repaglinide



Uses

Type 2 DM

ⓑ Nateglinide



Uses

Type 2 DM

⑤ α- Glucosidase Inhibitors

Alpha- Glucosidase Inhibitors are oral antidiabetic drugs that work by delaying carbohydrate digestion and glucose absorption, thereby reducing postprandial blood glucose levels.

MOA

- These drugs inhibit alpha- glucosidase enzymes located in brush border of small intestine
- These enzymes are responsible for breaking down complex carbohydrates (starch, oligosaccharides and disaccharides) into monosaccharides like glucose.
- By inhibiting these enzymes., AGIs slow the conversion of carbohydrates into glucose resulting in:

- A slower rise in blood glucose levels after meals.
- Lower postprandial blood glucose spikes.

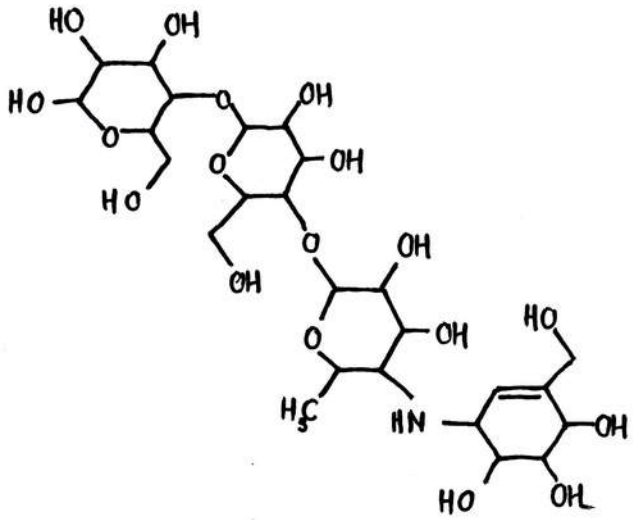
Pharmacokinetics

- Absorption : Acarbose poorly absorbed, Miglitol well absorbed
- Distribution : Generally low to moderate volume of distribution
- Metabolism : Partially or excreted unchanged
- Excretion : Excreted mainly in feces or unchanged in urine.

Adverse Effect

- Abdominal bloating & pain
- Diarrhea

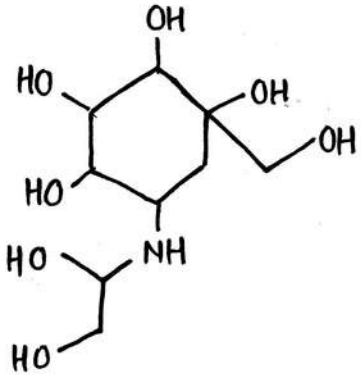
ⓐ Acarbose



Uses

- Type II Diabetes Mellitus

ⓑ Voglibose



Uses

- Type II Diabetes Mellitus

LOCAL ANAESTHETICS

- A Local Anaesthetic is a medication used to temporarily numb a specific area of the body, preventing pain sensation without affecting consciousness.
- It works by blocking nerve signals in the area where it is applied or injected.
- Local Anaesthetics are commonly used in minor surgical procedures, dental treatments and for pain management in specific areas.

CLASSIFICATION OF LOCAL ANAESTHETICS

① Benzoic Acid Derivatives

- Cocaine
- Hexylcaine
- Meprylcaine
- Cyclomethycaine
- Piperocaine

② Amino Benzoic Acid Derivatives

- Benzocaine *
- Butamben
- Procaine *
- Butacaine
- Propoxycaine
- Tetrocaine
- Benoxinate

③ Lidocaine / Anilide Derivatives

- Lignocaine
- Mepivacaine
- Prilocaine
- Etidocaine

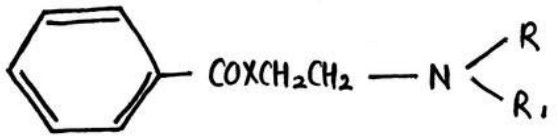
④ Miscellaneous

- Phenacaine
- Diperodon
- Dibucaine*

① BENZOIC ACID DERIVATIVES

- Benzoic acid derivatives are ester- linked local anaesthetics that include compounds such as procaine, cocaine & tetracaine.
- These agents are characterized by their ability to block nerve conduction, providing localized pain relief

SAR OF Benzoic Acid Derivatives



Lipophilic Group Intermediate Hydrophilic Group

① Aromatic Ring (Hydrophilic Group)

- The benzoic acid ring provides lipophilicity, allowing the molecules to penetrate the nerve membranes.
- Substituents on aromatic ring can influence potency
- Electron Donating Group : Enhance Activity
- Electron Withdrawing Group : May reduce activity

② Intermediate

- The ester bond connects the aromatic ring to alkyl chain
- The chain length & branching influence lipophilicity & potency.
- Increasing the chain length enhances lipid solubility & nerve membrane penetration.

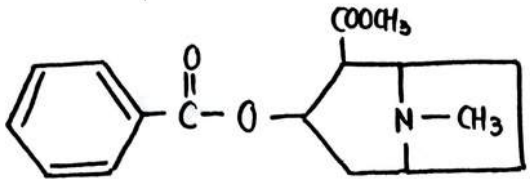
③ Amino Group (Hydrophilic Group)

- The terminal amine group is critical for solubility and interaction with sodium channel.
- Tertiary amines are more useful, secondary amines have longer duration, but they are more irritating, primary amines are not active.

MECHANISM OF ACTION

- Benzoic Acid derivatives exert their effect by blocking voltage-gated sodium channels on neuronal membranes, specifically by binding to intracellular part of channel.
- This prevents sodium influx, inhibiting action potential generation and propagation, leading to localized numbness and loss of sensation

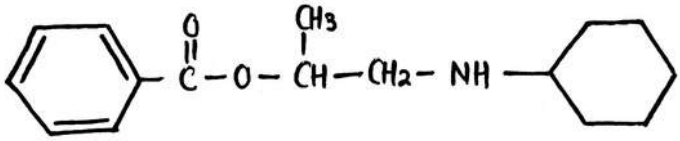
ⓐ Cocaine



Uses

- It is used as local anaesthetic primarily in ear, nose & throat surgeries
- Sometimes also used as opthalmic anaesthesia.

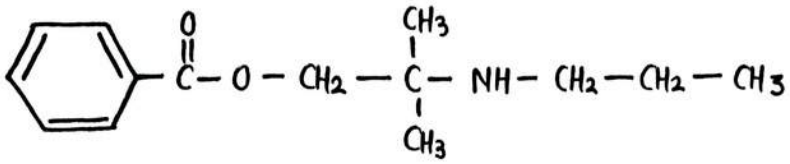
ⓑ Hexylcaine



Uses

- Mainly used as topical anaesthetic agent

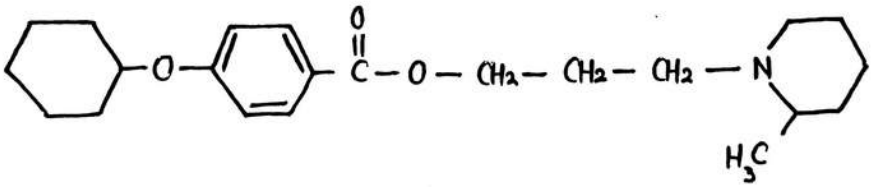
© MEPRYLCAINE



Uses

Dental Anaesthesia
Acute Pain
Topical Anaesthesia

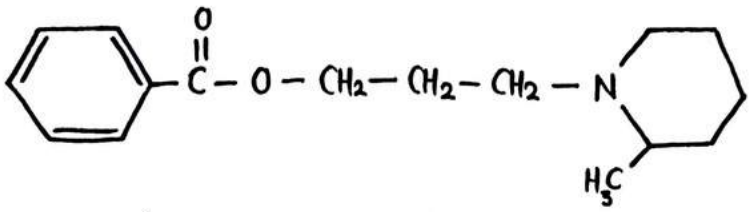
ⓓ CYCLOMETHYCAINE



Uses

- Topical Anaesthesia

© PIPEROCAINE



Uses

- Surface Anaesthesia
- Dental Anaesthesia

② AMINO BENZOIC ACID DERIVATIVES

- Amino benzoic acid derivatives have a benzene ring substituted with both an amino group ($-NH_2$) and a carboxyl group ($-COOH$)
- Common examples include procaine, benzocaine, Sulfonamides & furosemide.

MOA

Same as benzoic acid derivative.

Drugs

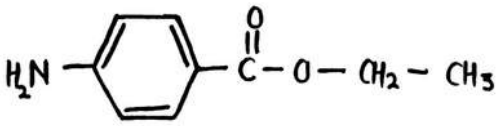
- Benzocaine *
- Butamben
- Procaine *
- Butacaine
- Poopoxycaine
- Tetracaine
- Benoxinate

SAR

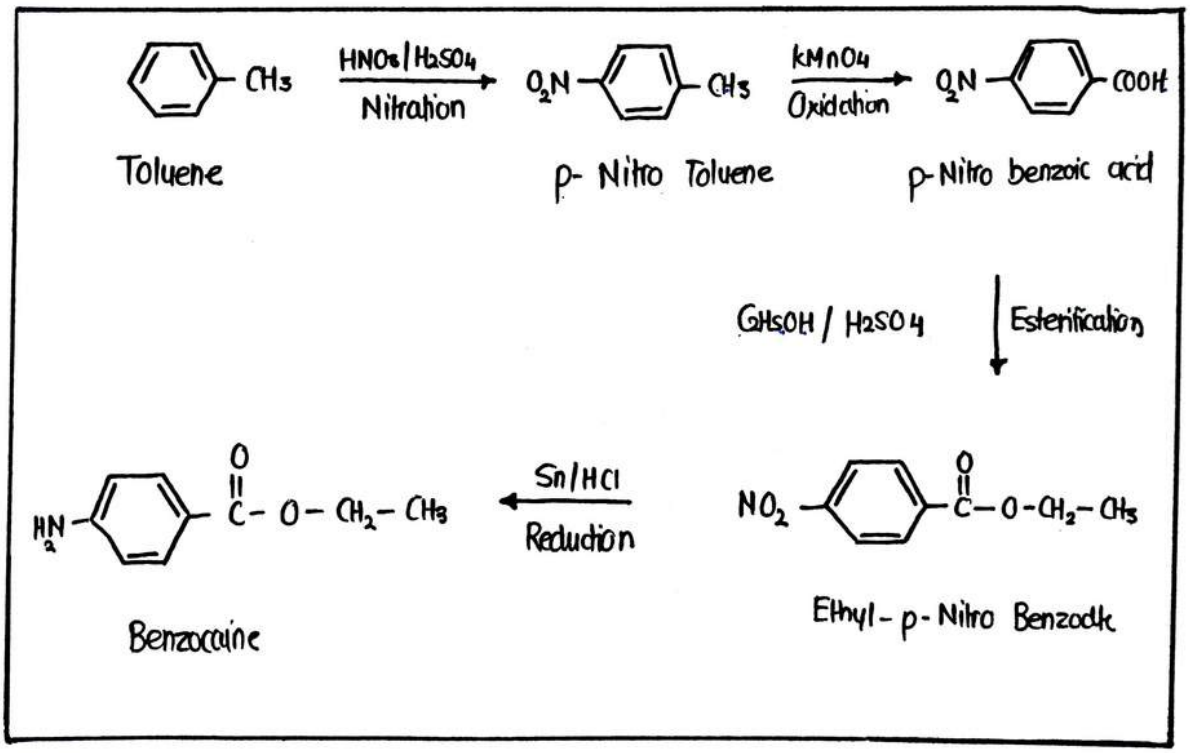
Similar to Benzoic Acid Derivatives

@ Benzocaine *

Benzocaine is a topical local anesthetic belonging to amino ester group of local anesthetics.



Synthesis



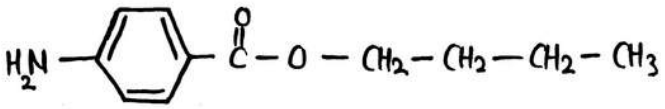
Properties

- It is white crystals or white odourless crystalline powder
- It is freely soluble in alcohol.

Uses

- Topical local anaesthetic agent.
- Pain Relievers

(b) Butambene

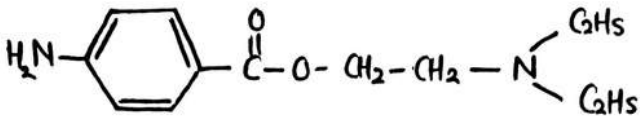


Uses

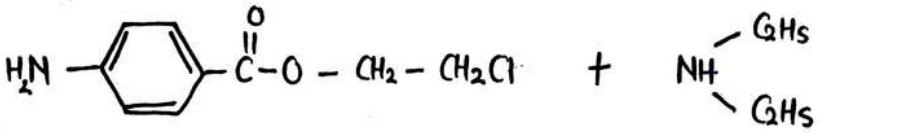
- local anaesthetic agent
- Anti - Inflammatory Agent
- Analgesic

© Procaine

Procaine is a local anaesthetic primarily used in medical & dental procedures to numb tissue before surgery.



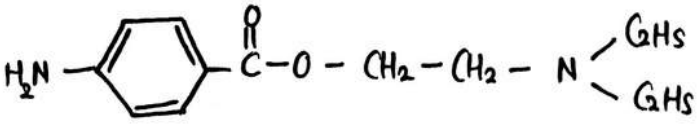
Synthesis



2- Chloroethyl- 4 aminobenzoate

Diethyl Amine

$-HCl$ ↓ Under Reduced Pressure



Procaine

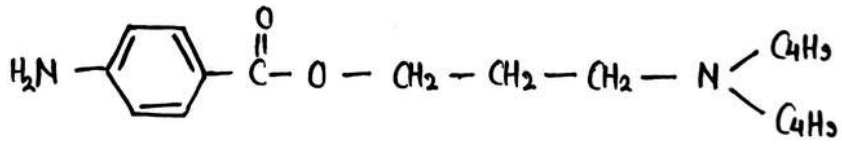
Properties

- It is odourless white crystalline powder.
- It is soluble in water.
- It should be protected from light.

Uses

- Dentistry
- Minor Surgical Procedures
- Pain Management

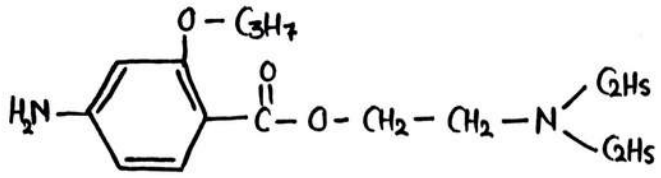
ⓓ Butacaine



Uses

- Topical Anaesthesia.

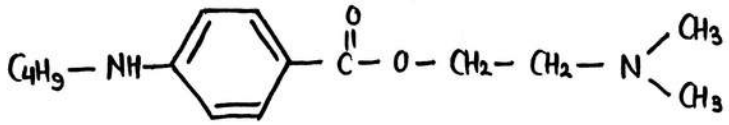
(e) Propoxycaine



Uses

- Local anaesthetic in minor surgical procedures
- Dental Procedures

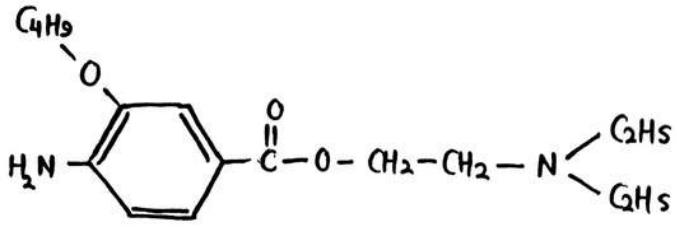
(f) Tetracaine



Uses

- Opthalmology
- Dentistry
- ENT Procedures

⑨ Benoxinate



Uses

- Opthalmic Poocedures

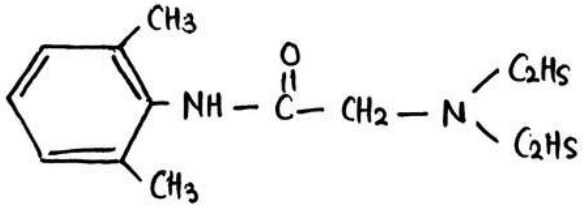
③ LIDOCAINE / ANILIDE DERIVATIVES

Lidocaine & other anilide derivatives are amide - type local anaesthetics widely used for their local anesthetic & antiarrythmic properties.

MOA

It blocks voltage - gated sodium channels in nerve membranes, preventing nerve impulse propagation & causing reversible anesthesia.

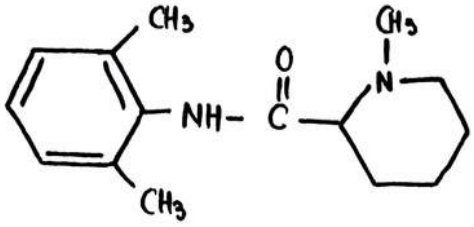
ⓐ Lignocaine



Uses

- Local anesthetic for minor surgical procedures
- Topical Anesthesia.

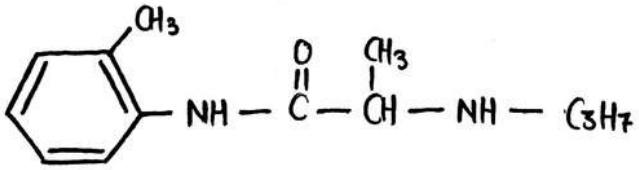
(b) Mepivacaine



Uses

- Local anesthetic for dental procedures
- Minor surgical procedures.

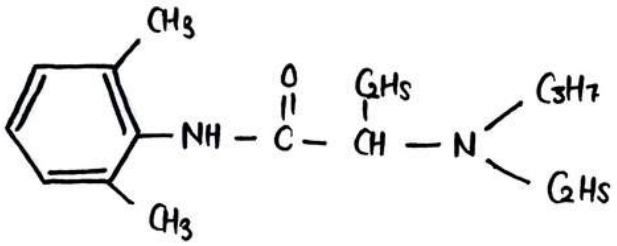
(c) Prilocaine



Uses

- Local anaesthetic in dentistry

⑥ Etidocaine

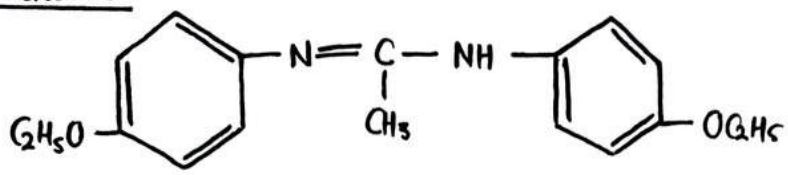


Uses

- Local anesthetic

④ MISCELLANEOUS

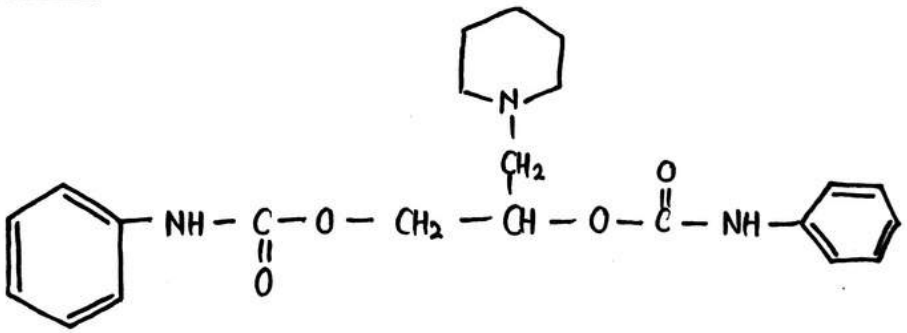
ⓐ Phenacaine



Uses

- Local Anesthetic
- Dental & other Minor surgical procedures.

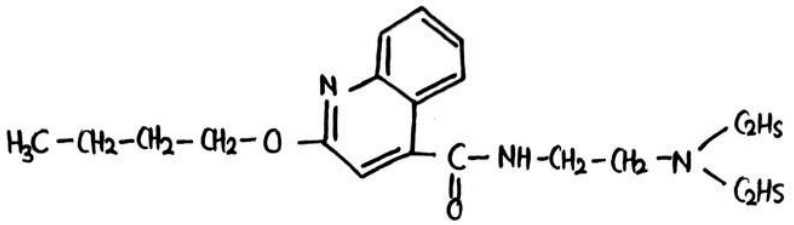
ⓑ Diperodon



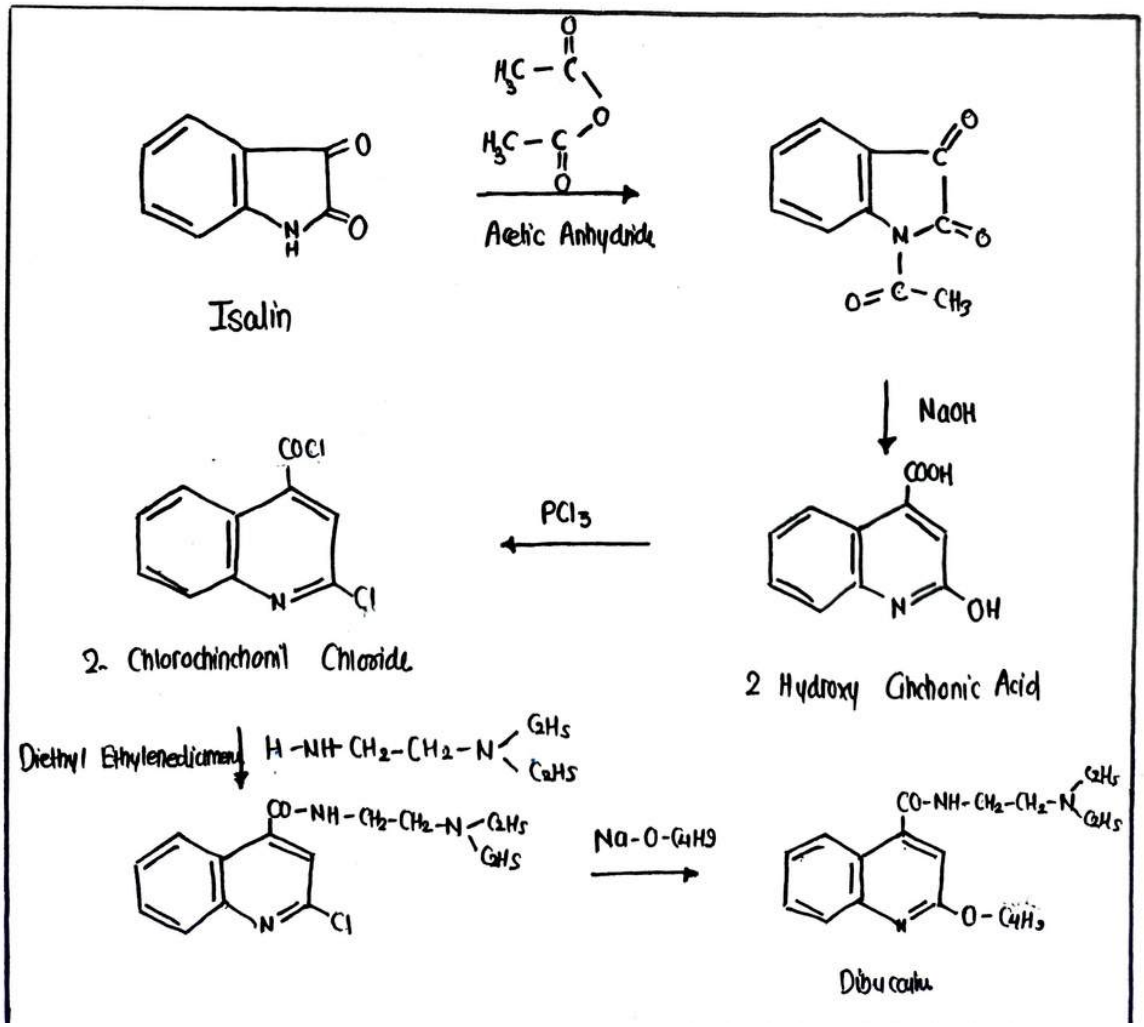
Uses

- Dentistry
- Analgesic

© Dibucaine



Synthesis



MOA

Dibucaine blocks sodium channels in nerve membranes, preventing nerve impulses and thus producing local anesthesia

Uses

Topical local anesthetics

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

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