MEDICINAL CHEMISTRY-II

(B.PHARMACY 5th SEMESTER)

MOST IMPORTANT QUESTIONS & SOLUTIONS

QUE 1. Define and classify antihistaminic agents with examples. Explain the synthesis, mechanism of action, and uses of Diphenhydramine.

ANSWER:

Definition of Antihistaminic Agents

Antihistaminic agents are drugs that block the effects of histamine, a chemical involved in allergic reactions, thus helping reduce symptoms like itching, swelling, and congestion.

Classification of Antihistaminic Agents

Type	Description	Examples
H1-Receptor Antagonists	Primarily used to treat allergies	Diphenhydramine, Chlorpheniramine
H2-Receptor Antagonists	Used to reduce gastric acid secretion in the stomach	Ranitidine, Famotidine

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Mechanism of Action (MOA) of Diphenhydramine

1. **H1 Receptor Blockade**: Diphenhydramine is a first-generation H1 receptor antagonist.
2. **Competitive Inhibition**: It competes with histamine for binding to the H1 receptors on cells in smooth muscle, blood vessels, and the respiratory tract.
3. **Prevention of Histamine Action**:

- By blocking these receptors, it prevents histamine from causing typical allergic symptoms like vasodilation, bronchoconstriction, and increased capillary permeability.

4. **Central Sedative Effect**: As a first-generation antihistamine, it crosses the blood-brain barrier, leading to sedative effects by inhibiting central histaminergic neurons.

Synthesis of Diphenhydramine

1. **Starting Materials**: Benzhydrol and 2-dimethylaminoethyl chloride.
2. Steps:
   - **Step 1**: **Benzhydrol** reacts with **2-dimethylaminoethyl chloride** in the presence of a base (such as sodium or potassium hydroxide).
   - **Step 2**: The reaction proceeds through an alkylation reaction where the hydroxyl (-OH) group on benzhydrol is replaced by the 2-dimethylaminoethyl group.

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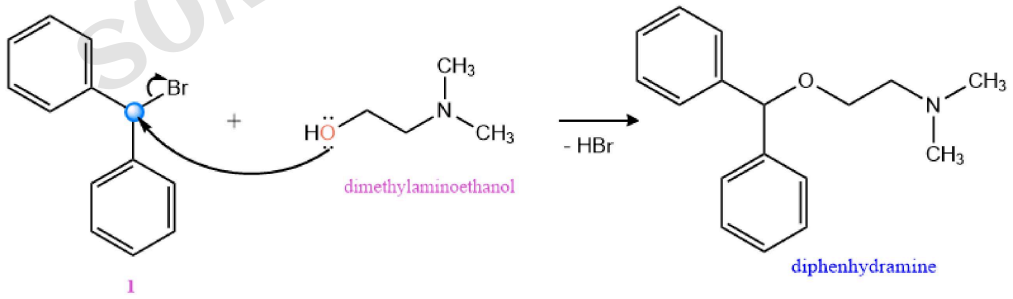

Uses of Diphenhydramine

- **Allergy Relief**: Effective for symptoms like sneezing, runny nose, and itchy eyes.
- **Motion Sickness**: Helps reduce nausea and dizziness.

- **Sedative**: Often used as a mild sleep aid due to its sedative properties.

QUE 2. Classify diuretics with examples. Explain the synthesis, mechanism of action, and uses of Chlorothiazide.

ANSWER:

- **Diuretics** are medications that promote the excretion of water and salts from the body through urine.
- By reducing fluid buildup, they help lower blood pressure and treat conditions like hypertension, heart failure, and edema.
- Diuretics work by acting on the kidneys to enhance urine production, thus reducing the volume of fluid in blood vessels and tissues.

Classification of Diuretics

Type	Description	Examples
Thiazide Diuretics	Act on the distal convoluted tubule to inhibit sodium reabsorption	Chlorothiazide, Hydrochlorothiazide
Loop Diuretics	Act on the ascending limb of the loop of Henle; most potent diuretics	Furosemide, Bumetanide
Potassium-Sparing Diuretics	Inhibit sodium reabsorption without potassium loss	Spironolactone, Amiloride
Osmotic Diuretics	Increase osmolarity of filtrate in the kidney tubules, drawing water into urine	Mannitol, Urea

Carbonic Anhydrase Inhibitors	Reduce hydrogen ion concentration and decrease bicarbonate reabsorption	Acetazolamide

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Mechanism of Action (MOA) of Chlorothiazide

1. **Inhibition of Sodium and Chloride Reabsorption**: Chlorothiazide acts on the distal convoluted tubule, specifically inhibiting the sodium-chloride symporter.
2. **Increased Urine Output**: By preventing sodium and chloride reabsorption, it increases the osmotic pressure in the tubule, drawing water into the urine and increasing urine output.
3. **Reduction in Blood Pressure**: This diuretic effect reduces blood volume, thereby lowering blood pressure.
4. **Additional Calcium-Sparing Effect**: Chlorothiazide increases calcium reabsorption, which can be beneficial in conditions requiring calcium conservation.

Synthesis of Chlorothiazide

1. **Starting Materials**: Chlorosulfonic acid, 3,4-dihydro-2H-1,2,4-benzothiadiazine.
2. Steps:
    - **Step 1**: **3,4-dihydro-2H-1,2,4-benzothiadiazine** is treated with chlorosulfonic acid.
    - **Step 2**: This reaction introduces a sulfonamide group to the benzothiadiazine ring.
    - **Step 3**: A cyclization reaction forms the thiazide structure.

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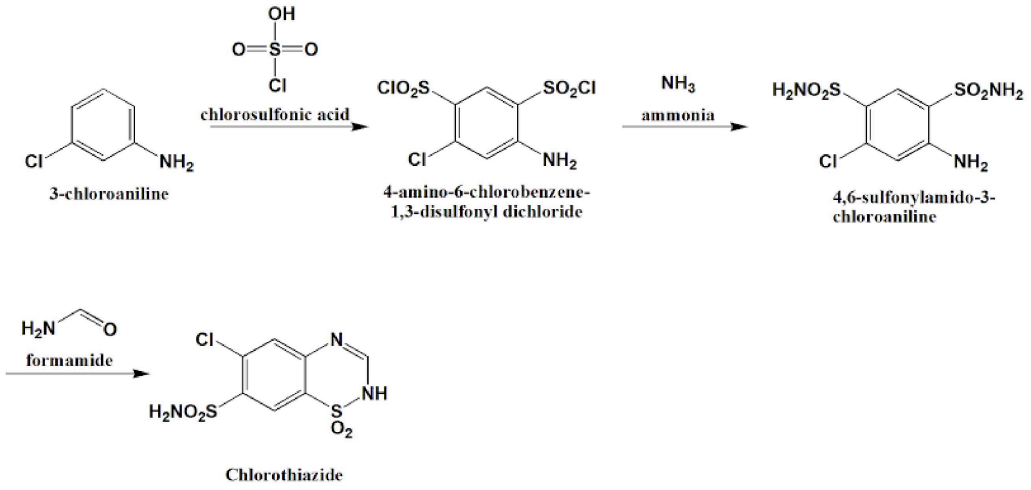


Uses of Chlorothiazide

- **Hypertension**: First-line treatment to reduce blood pressure.
- **Edema**: Used to treat fluid retention due to heart failure, liver cirrhosis, or renal disease.
- **Calcium Conservation**: Beneficial for patients at risk of osteoporosis or kidney stones by reducing calcium loss.

QUE 3. Classify antidiabetic agents, especially sulfonylureas. Describe the SAR, mechanism of action, and synthesis of Tolbutamide.

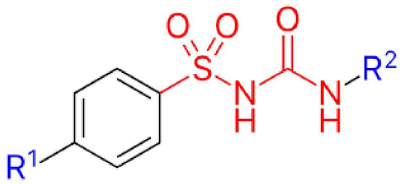
ANSWER:

Classification of Antidiabetic Agents

Type	Mechanism of Action	Examples
Insulin and Insulin Analogues	Replace or supplement endogenous insulin	Insulin glargine, Insulin lispro

Sulfonylureas	Stimulate insulin secretion by acting on pancreatic beta cells	Tolbutamide, Glibenclamide
Biguanides	Decrease hepatic glucose production	Metformin
Thiazolidinediones (TZDs)	Increase insulin sensitivity in peripheral tissues	Pioglitazone, Rosiglitazone
DPP-4 Inhibitors	Prolong action of incretin hormones	Sitagliptin, Saxagliptin
SGLT2 Inhibitors	Increase urinary glucose excretion	Dapagliflozin, Canagliflozin

Structure-Activity Relationship (SAR) of Sulfonylureas



1. **Aromatic Ring**: An aromatic ring is essential for binding affinity. Substituents on this ring can alter potency and duration.
2. **Sulfonamide Group**: The -SO2-NH- group is crucial as it contributes to the drug's interaction with the ATP-sensitive potassium channels in beta cells.
3. **Alkyl Chain**: Modifications in the alkyl chain (particularly branching) can impact drug binding and half-life.
4. **Amide Linkage**: Essential for interaction with the receptor site in the pancreas.

Mechanism of Action of Tolbutamide

1. **Binding to Beta Cells**: Tolbutamide binds to the ATP-sensitive potassium channels on the pancreatic beta cells.
2. **Closure of Potassium Channels**: This binding blocks the potassium channels, leading to cell depolarization.
3. **Calcium Influx**: The depolarization triggers calcium influx, stimulating the release of insulin.
4. **Increased Insulin Levels**: The increased insulin reduces blood glucose levels by promoting glucose uptake in tissues.

Synthesis of Tolbutamide

1. **Starting Materials**: p-Toluenesulfonyl chloride and ethyl acetate.
2. Steps:
   - **Step 1**: p-Toluenesulfonyl chloride reacts with ethyl acetate to form an intermediate.
   - **Step 2**: The intermediate undergoes hydrolysis to yield Tolbutamide.

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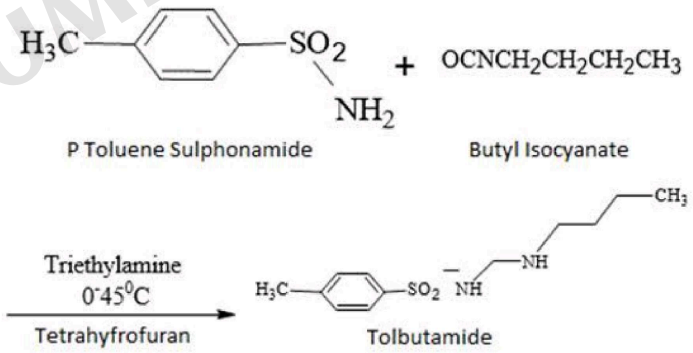


Uses of Tolbutamide

- **Type 2 Diabetes Mellitus**: Effective in lowering blood glucose levels in patients with mild to moderate Type 2 diabetes.
- **Short-acting Sulfonylurea**: Suitable for patients requiring shorter duration therapy.

QUE 4. Classify anti-hyperlipidemic agents and explain the mechanism of action of HMG-CoA reductase inhibitors.

ANSWER:

- **Anti-hyperlipidemic agents** are a class of drugs used to lower lipid levels in the blood, specifically targeting elevated levels of cholesterol, triglycerides, or both.
- These agents help reduce the risk of cardiovascular diseases, such as atherosclerosis, heart attack, and stroke, by managing lipid levels and improving blood vessel health.

Classification of Anti-Hyperlipidemic Agents

Type	Mechanism	Examples
HMG-CoA Reductase Inhibitors	Inhibit cholesterol synthesis in the liver	Atorvastatin, Simvastatin
Bile Acid Sequestrants	Bind bile acids, increasing cholesterol excretion	Cholestyramine, Colesevelam
Fibrates	Increase lipolysis of triglycerides	Fenofibrate, Gemfibrozil
Niacin	Reduces VLDL and LDL levels	Niacin (Vitamin B3)
PCSK9 Inhibitors	Increase LDL receptor activity	Alirocumab, Evolocumab

Mechanism of Action of HMG-CoA Reductase Inhibitors

1. **Inhibition of HMG-CoA Reductase**: These drugs inhibit the enzyme HMG-CoA reductase, which is the rate-limiting step in cholesterol biosynthesis.

2. **Reduced Cholesterol Synthesis**: Blocking this enzyme reduces cholesterol synthesis in the liver.
3. **Increased LDL Receptor Expression**: Lower intracellular cholesterol levels trigger upregulation of LDL receptors on liver cells.
4. **Enhanced LDL Clearance**: More LDL receptors increase clearance of LDL from the bloodstream, lowering blood LDL levels.

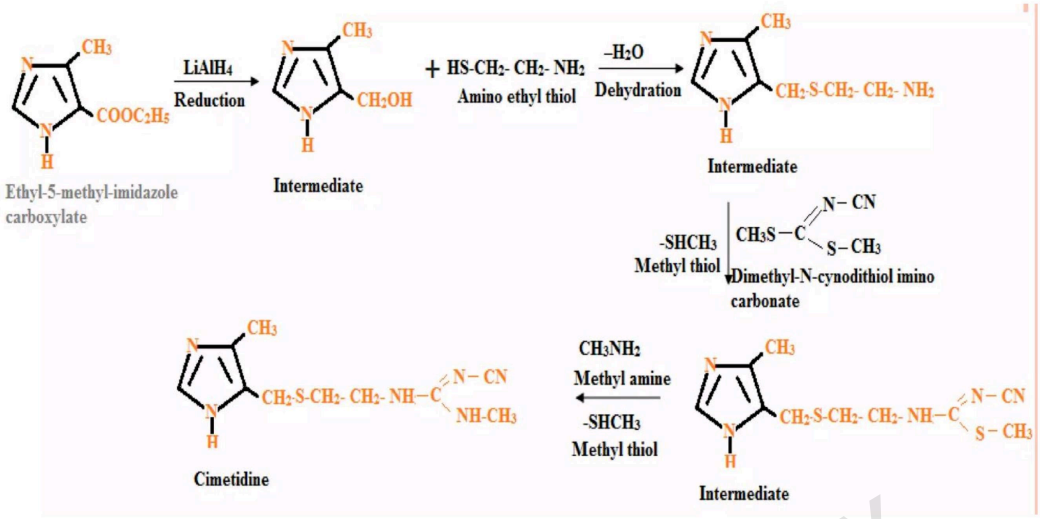
QUE 5. Outline the synthesis of Cimetidine.

ANSWER:

- **Cimetidine** is an **H2 receptor antagonist** used to reduce stomach acid production.
- It treats conditions like peptic ulcers, GERD, and Zollinger-Ellison syndrome by blocking histamine on H2 receptors in the stomach lining, thus decreasing acid secretion and promoting healing of the gastrointestinal tract.

1. **Starting Materials**: Cyanoguanidine and methyl isothiourea.
2. Steps:
   - **Step 1**: Cyanoguanidine reacts with methyl isothiourea to form a guanidine derivative.
   - **Step 2**: This derivative undergoes further reactions to introduce an imidazole ring.
   - **Step 3**: The final product is cimetidine, which includes an imidazole ring and a cyano group.

Reaction :



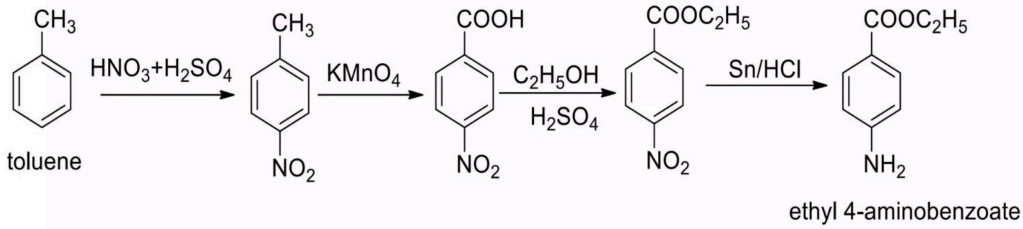
QUE 6. Outline the synthesis of Benzocaine.

ANSWER:

- **Benzocaine** is a **local anesthetic** commonly used to relieve pain and discomfort in minor skin irritations, sore throats, toothaches, and mouth ulcers.
- It works by blocking nerve signals in the body, temporarily numbing the area where it's applied.

1. **Starting Materials**: p-Aminobenzoic acid and ethanol.
2. Steps:
    - **Step 1**: p-Aminobenzoic acid is esterified with ethanol.
    - **Step 2**: This reaction produces benzocaine through a simple esterification process.

Reaction:



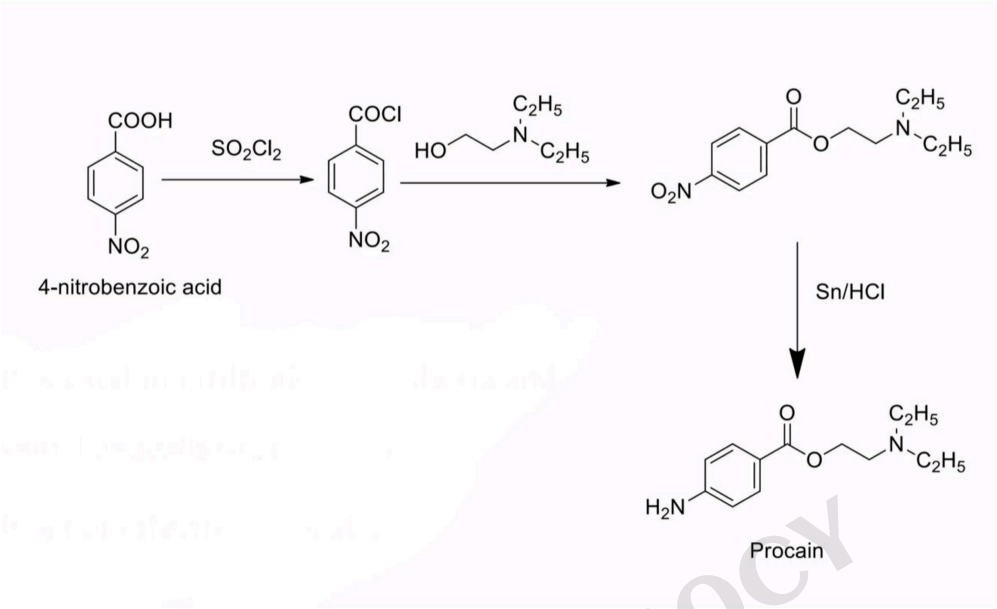
QUE 7. Outline the synthesis of Procaine.

ANSWER:

- **Procaine** is a local anesthetic commonly used to numb tissues during minor surgical or dental procedures.
- It works by blocking sodium channels in nerve cells, temporarily stopping pain signals from reaching the brain.
- Known by the trade name Novocain, it's favored for its effectiveness and low toxicity, though its use has declined with the development of newer anesthetics.

1. **Starting Materials:** p-Aminobenzoic acid and diethylaminoethanol.
2. Steps:
    - **Step 1:** p-Aminobenzoic acid undergoes esterification with diethylaminoethanol.
    - **Step 2:** The ester formed is procaine.

Reaction:



QUE 8. Discuss the SAR and uses of Thiazide diuretics like Chlorothiazide.

ANSWER:

- **Thiazide diuretics** are a class of medications that help reduce blood pressure and manage fluid retention by increasing urine production.
- They act on the kidneys, specifically inhibiting sodium and chloride reabsorption in the distal tubules, which leads to increased excretion of water, sodium, and potassium.
- Thiazides are commonly used to treat hypertension, edema, and certain cases of heart failure.

Structure-Activity Relationship (SAR) of Thiazide Diuretics

1. **Sulfonamide Group**: Essential for diuretic activity, allowing binding to the sodium-chloride symporter.
2. **Chlorine or Halogen Substitution**: Chlorine at the 6-position enhances diuretic effect.
3. **Electron-Withdrawing Group**: Improves binding to the target and enhances diuretic action.

4. **Sulfur-Containing Ring**: The presence of a sulfur group is characteristic of the thiazide structure.

Uses of Chlorothiazide

- **Hypertension**: Lowers blood pressure by reducing blood volume.
- **Edema**: Treats fluid retention in conditions like heart failure, liver disease, or kidney disorders.

QUE 9. Explain the SAR and uses of Sulfonylureas, specifically Tolbutamide.

ANSWER:

- **Sulfonylureas** are a class of **oral antidiabetic drugs** used to lower blood glucose levels in people with type 2 diabetes.
- They work by **stimulating insulin secretion** from pancreatic beta cells, which helps improve blood sugar control.
- Common examples include glipizide, glyburide, and tolbutamide.

Structure-Activity Relationship (SAR) of Sulfonylureas

1. **Aromatic Ring**: Essential for binding to the potassium channels on pancreatic beta cells.
2. **Sulfonamide Linkage**: The sulfonamide group contributes to the hypoglycemic effect.
3. **Substituent Groups**: Modifications in the R-group attached to the sulfonylurea backbone can affect the duration of action and potency.
4. **Chain Length**: Longer chain length generally results in longer action.

Uses of Tolbutamide

- **Type 2 Diabetes**: Effective for lowering blood glucose in patients with insulin resistance or insufficient insulin response.
- **Short Duration**: Suitable for managing blood sugar with a shorter duration of action, reducing the risk of hypoglycemia in some patients.

QUE10. Describe the mechanism of action of Digoxin and its role in treating congestive heart failure.

ANSWER:

- **Digoxin** is a **cardiac glycoside** used to treat heart conditions like **congestive heart failure** and certain types of **arrhythmias** (irregular heartbeats).
- It works by increasing the force of heart contractions and regulating heart rate, helping the heart pump blood more effectively.

Mechanism of Action of Digoxin

1. **Inhibition of Na+/K+ ATPase**:
    - Digoxin binds to and inhibits the Na+/K+ ATPase pump in the cell membranes of cardiac muscle cells.
    - This inhibition leads to an increase in intracellular sodium levels.
2. **Increased Intracellular Calcium**:
    - Higher intracellular sodium levels result in a reduced sodium-calcium exchange, leading to an accumulation of calcium within the cell.
    - The increased calcium concentration enhances the contractility of cardiac muscle fibers, a process known as positive inotropy.
3. **Vagal Stimulation**:
    - Digoxin also stimulates the vagus nerve, slowing down the heart rate (negative chronotropic effect).
    - This effect is beneficial in controlling heart rate in patients with heart failure, reducing the heart's oxygen demand.

Role in Treating Congestive Heart Failure (CHF)

- **Improved Cardiac Output**: By increasing the force of myocardial contractions, Digoxin improves cardiac output, which is crucial in CHF, where the heart is unable to pump sufficient blood.
- **Symptom Relief**: It reduces symptoms such as fatigue, shortness of breath, and edema by promoting efficient circulation.

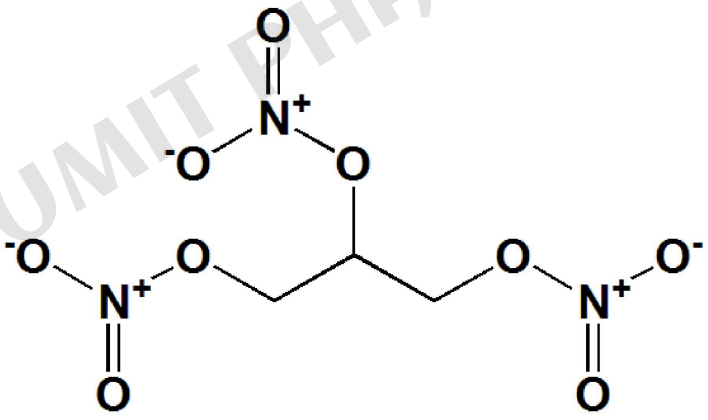
- **Heart Rate Control**: Particularly beneficial in patients with atrial fibrillation or flutter, where controlling heart rate helps prevent further complications.

QUE 11. Write the structure and uses of Nitroglycerin as an anti-anginal drug.

ANSWER:

- **Nitroglycerin** is a **vasodilator** commonly used to treat angina (chest pain) associated with heart disease.
- It works by relaxing blood vessels, which improves blood flow and oxygen supply to the heart, reducing its workload and alleviating pain.
- Nitroglycerin can be administered as tablets, patches, or sprays for quick relief of angina symptoms.

Structure of Nitroglycerin



Nitroglycerine

- **Chemical Formula**: C3H5N3O9
- **Structure**: Nitroglycerin contains three nitro (-NO2) groups attached to a glycerol backbone. It is a nitrate ester.

Uses of Nitroglycerin

1. **Angina Pectoris**: Nitroglycerin is primarily used to relieve chest pain associated with angina by dilating coronary arteries and improving blood flow to the heart.
2. **Acute Coronary Syndrome (ACS)**: It is used in emergencies to quickly relieve ischemic chest pain.
3. **Heart Failure**: In some cases, it helps reduce the workload on the heart by reducing preload and afterload.

Mechanism of Action

- Nitroglycerin is converted to nitric oxide (NO) in the body, which activates guanylate cyclase, leading to an increase in cyclic GMP (cGMP).
- This cascade results in smooth muscle relaxation, particularly in the coronary arteries and venous circulation, reducing cardiac oxygen demand and alleviating angina.

QUE 12. Discuss the mechanism of action and uses of Omeprazole as a proton pump inhibitor.

ANSWER:

- **Omeprazole** is a **proton pump inhibitor (PPI)** that reduces stomach acid production by blocking the H+/K+ ATPase enzyme **(proton pump)** in stomach lining cells.
- It is commonly used to treat acid-related conditions such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome by providing long-lasting acid suppression.

Mechanism of Action of Omeprazole

1. **Inhibition of H+/K+ ATPase**:
    - Omeprazole is a proton pump inhibitor that selectively and irreversibly binds to the H+/K+ ATPase enzyme on gastric parietal cells.
    - This enzyme is responsible for secreting hydrochloric acid in the stomach. By inhibiting it, omeprazole significantly reduces gastric acid production.
2. **Long-Lasting Effect**:

- Omeprazole forms a covalent bond with the proton pump, leading to prolonged suppression of acid secretion, even after the drug is no longer present in the bloodstream.
- This effect is beneficial in reducing acid-related damage to the stomach lining.

Uses of Omeprazole

1. **Gastroesophageal Reflux Disease (GERD)**: Omeprazole is commonly used to treat acid reflux and heartburn by reducing stomach acid.
2. **Peptic Ulcers**: It helps heal gastric and duodenal ulcers by minimizing acidic irritation of the ulcerated area.
3. **Zollinger-Ellison Syndrome**: In cases of excessive gastric acid production due to tumors, omeprazole helps manage symptoms.

QUE 13. Describe the mechanism of action and uses of Metformin in diabetes treatment.

ANSWER:

- **Metformin** is an **oral antidiabetic medication** primarily used to manage type 2 diabetes.
- It works by **reducing glucose production in the liver** and **improving insulin sensitivity**, helping to lower blood sugar levels.
- Metformin is commonly prescribed due to its effectiveness, low risk of causing hypoglycemia, and potential benefits for weight management and cardiovascular health.

Mechanism of Action of Metformin

1. **Inhibition of Hepatic Glucose Production**:
   - Metformin reduces hepatic gluconeogenesis, which is a primary source of glucose in patients with Type 2 diabetes.
2. **Improved Insulin Sensitivity**:
   - It enhances insulin sensitivity in peripheral tissues, especially muscle and fat, thereby promoting glucose uptake.

3. **Reduced Intestinal Glucose Absorption:**
    - Metformin also decreases glucose absorption in the intestines, contributing to overall glycemic control.

Uses of Metformin

1. **Type 2 Diabetes Mellitus:** Metformin is a first-line treatment for managing blood glucose levels in Type 2 diabetes.
2. **Polycystic Ovary Syndrome (PCOS):** Sometimes prescribed to manage insulin resistance associated with PCOS.
3. **Prevention of Diabetes:** It may be used to delay the onset of Type 2 diabetes in high-risk individuals by improving metabolic parameters.

QUE 14. Explain the mechanism of action and uses of Sildenafil in the treatment of erectile dysfunction.

ANSWER:

- **Sildenafil** is a medication primarily used to treat **erectile dysfunction (ED)** and **pulmonary arterial hypertension (PAH)**.
- It works by inhibiting the enzyme **phosphodiesterase type 5 (PDE5)**, which leads to increased blood flow in certain areas, such as the penis for ED and the lungs for PAH, aiding in improved function and relief of symptoms.

Mechanism of Action of Sildenafil

1. **Phosphodiesterase-5 (PDE5) Inhibition:**
    - Sildenafil selectively inhibits PDE5, an enzyme found primarily in the corpus cavernosum of the penis.
    - PDE5 typically degrades cyclic GMP (cGMP), a molecule that promotes relaxation of smooth muscles.
2. **Increased cGMP Levels:**
    - By inhibiting PDE5, Sildenafil increases cGMP levels, leading to enhanced vasodilation and smooth muscle relaxation.

- This action increases blood flow to the penis, facilitating and maintaining an erection.

Uses of Sildenafil

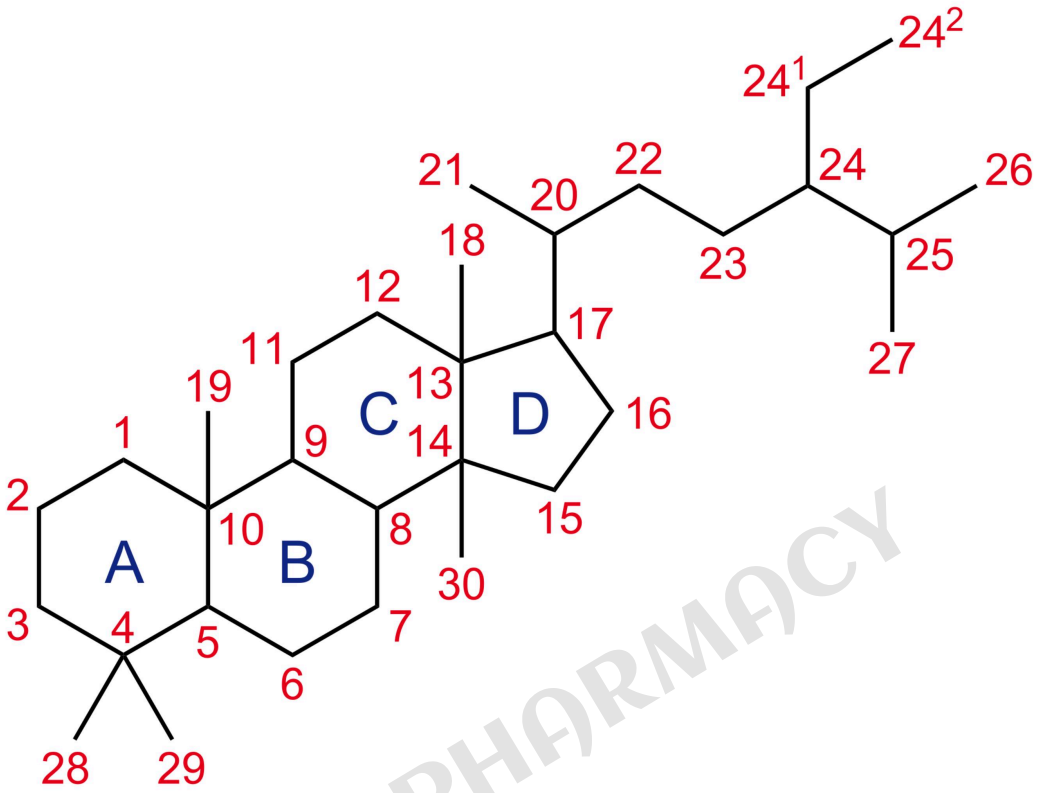
1. **Erectile Dysfunction**: Primarily used for the treatment of erectile dysfunction, helping men achieve and sustain an erection.
2. **Pulmonary Arterial Hypertension (PAH)**: Also approved for treating PAH by reducing blood pressure in the pulmonary arteries.

QUE 15. Briefly explain the nomenclature and stereochemistry basics of Steroids.

ANSWER:

- **Steroids** are a class of **organic compounds** with a characteristic structure of **four carbon rings**.
- They include hormones like cortisol, testosterone, and estrogen, which play vital roles in regulating various body functions such as metabolism, immune response, and reproductive processes.
- Steroids are used medically to reduce inflammation, manage hormonal imbalances, and treat conditions like arthritis and asthma.

Basic Structure:



Nomenclature of Steroids

- **Basic Structure**: Steroids consist of a 17-carbon Ststructure arranged in four fused rings labeled as A, B, C, and D.
- **Ring System**: The structure includes three cyclohexane rings (A, B, and C) and one cyclopentane ring (D).
- **Substituents**: Different functional groups attached to the rings define specific steroids, such as hydroxyl (-OH) in cholesterol or ketone (C=O) in cortisol.

Stereochemistry of Steroids

1. **Chirality**: Steroids contain several chiral centers, especially at carbons 8, 9, 10, 13, and 14, giving them complex stereochemistry.
2. **Cis-Trans Configuration**: The orientation of substituents around rings A and B, or B and C, determines whether the configuration is cis or trans.

3. **Alpha (α) and Beta (β) Orientation**: In stereochemistry, groups attached to the steroid backbone can be in α (below the plane) or β (above the plane) orientation.

QUE 16. Give a basic classification and uses of Thyroid and Anti-thyroid drugs.

ANSWER:

- **Thyroid drugs** are medications used to supplement or replace thyroid hormones, primarily for treating **hypothyroidism**(an underactive thyroid).

They help regulate metabolism, energy, and growth by mimicking natural thyroid hormones, like **levothyroxine**.

- **Anti-thyroid drugs** are used to treat **hyperthyroidism** (an overactive thyroid) by inhibiting thyroid hormone production.

These include **methimazole** and **propylthiouracil**, which reduce excess hormone levels and manage symptoms like rapid heartbeat and weight loss.

Classification of Thyroid Drugs

Class	Mechanism	Examples
Thyroid Hormones	Replace deficient thyroid hormones	Levothyroxine (T4), Liothyronine (T3)
Anti-thyroid Drugs	Inhibit thyroid hormone synthesis	Methimazole, Propylthiouracil (PTU)

Uses of Thyroid Drugs

1. **Hypothyroidism:**

- **Levothyroxine (T4)**: Standard treatment for hypothyroidism to replace deficient T4 hormone.
- **Liothyronine (T3)**: Sometimes used in cases requiring rapid onset or in patients with poor T4 to T3 conversion.

Classification of Anti-thyroid Drugs

Type	Mechanism	Examples
Thionamides	Inhibit thyroid peroxidase to block hormone synthesis	Methimazole, PTU
Iodine and Iodide Compounds	Block thyroid hormone release	Potassium iodide
Radioactive Iodine (I-131)	Destroys thyroid tissue	Radioactive Iodine

Uses of Anti-thyroid Drugs

1. **Hyperthyroidism**:
   - **Methimazole and PTU**: Used to reduce thyroid hormone production in hyperthyroid conditions, such as Graves' disease.
   - **Radioactive Iodine**: Employed for definitive treatment by selectively destroying hyperactive thyroid tissue.