Subject: *Medicinal Chemistry-II* **Unit No:** I
Faculty: *Mrs. Sashmitha Samuel* **Lecture No:**
Topic: *Anti histaminic agents* **Reference Book:**

ANTI HISTAMINIC AGENTS

Histamine

Histamine is an organic nitrogenous compound involved in local immune responses, as well as regulating physiological function in the gut and acting as a neurotransmitter for the brain, spinal cord, and uterus.

Histamine is involved in the inflammatory response and has a central role as a mediator of itching.

It is an axial player in stimulating the development of allergic-related inflammatory diseases by regulating the maturation and activation of leukocytes and directing their migration to target sites where they cause chronic inflammation.

Histamine also exerts a various other immune regulatory function by modulating the functions of monocytes, T cells, macrophages, neutrophils, eosinophils, B cells, and dendritic cells.

Histamines start the process that hustles those allergens out of your body or off your skin.

Histamine receptors

Histamine and its receptors (H1R–H4R), all of which belong to the G protein coupled receptor family play a crucial and significant role in the development of various allergic diseases.

Mast cells are multifunctional bone marrow-derived tissue-dwelling cells that are the major producer of histamine in the body.

- H1R are expressed in many cells, including mast cells, and are involved in Type 1 hypersensitivity reactions.
- H2R are involved in lymphocyte cytokine production.
- H3R are mainly involved in blood–brain barrier function.
- H4R are highly expressed on mast cells where their stimulation exacerbates histamine and cytokine generation.

H1 ANTAGONISTS

H_1 antagonists, also called H_1 blockers, are a class of medications that block the action of histamine at the H_1 receptor, helping to relieve allergic reactions.

These agents are preferred for acute and chronic urticaria, with first-generation agents reserved for efractory cases.

THERAPEUTIC USES

H_1-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. These indications may include:

- Allergic rhinitis
- Allergic conjunctivitis
- Allergic dermatological conditions (contact dermatitis)
- Rhinorrhoea (Runny nose)

FIRST GENERATION (NON-SELECTIVE H1 BLOCKERS)

They are effective in the relief of allergic symptoms, but are moderately to highly potent muscarinic acetylcholine receptor (anticholinergic) antagonists as well. These agents also commonly have action at α-adrenergic receptors and/or 5-HT receptors.

They can be classified on the basis of chemical structure.

1. **Ethylenediamines**

They were the first group of clinically effective H1-antihistamines developed.

2. **Ethanolamines**

Diphenhydramine was the prototypical agent in this group. Significant anticholinergic adverse effects, as well as sedation, are observed in this group but the incidence of gastrointestinal adverse effects is relatively low.

3. **Alkylamines**

Alkylamines are considered to have relatively fewer sedative and gastrointestinal adverse effects, but relatively greater incidence of paradoxical central nervous system (CNS) stimulation.

4. Piperazines

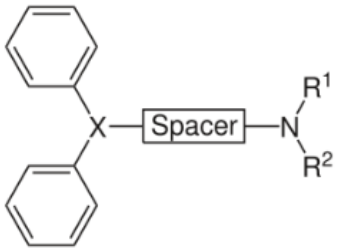
These compounds are structurally related to the ethylenediamines and the ethanolamines, and produce significant anticholinergic adverse effects.

5. Tricyclics and Tetracyclics

They are also structurally related to the tricyclic antidepressants (and tetracyclics), explaining the H1-antihistaminergic adverse effects of those three drug classes and also the poor tolerability profile of tricyclic H1-antihistamines.

General structure

- Two aromatic rings, connected to a central carbon, nitrogen or CO
- Spacer between the central X and the amine, usually 2–3 carbons in length, linear, ring, branched, saturated or unsaturated
- Amine is substituted with small alkyl groups, e.g., CH_3



X = N, R1 = R2 = small alkyl groups

X = C

X = CO

- Chirality at X can increase both the potency and selectivity for H1-receptors
- For maximum potency, the two aromatic rings should be orientated in different planes

SECOND GENERATION

Second-generation H_1-antihistamines are newer drugs that are much more selective for peripheral H_1 receptors as opposed to the central nervous system H_1 receptors and cholinergic receptors. This selectivity reduces the occurrence of adverse drug reactions, such as sedation, while still providing effective relief of allergic conditions. The reason for their peripheral selectivity is that most of these compounds are zwitterionic at physiological pH (around pH 7.4).

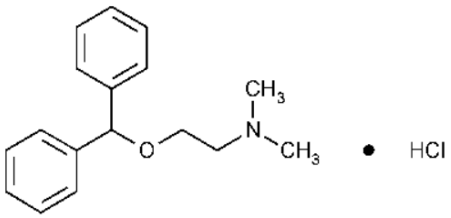
THIRD GENERATION

Third-generation H_1-antihistamines are second-generation antihistamines informally labelled third-generation because the active enantiomer (levocetirizine) or metabolite (desloratadine and fexofenadine) derivatives of second-generation drugs are intended to have increased efficacy with fewer adverse drug reactions.

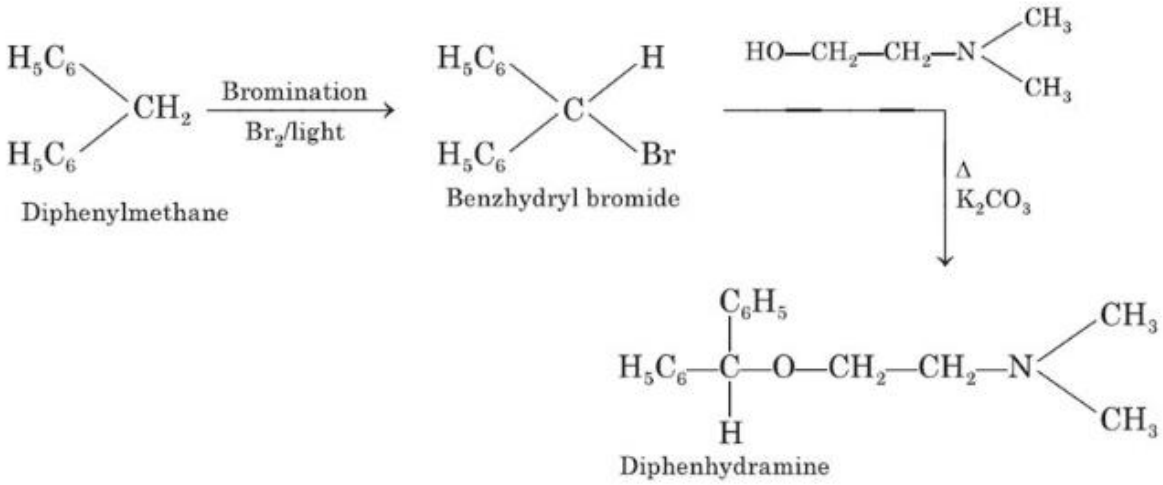
TOXICITY

The most common adverse effect is sedation; this "side-effect" is utilized in many OTC sleeping-aid preparations. Other common adverse effects in first-generation H_1-antihistamines include dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, increased appetite leading to weight gain, insomnia, tremor, nausea and vomiting, constipation, diarrhoea, dry mouth, and dry cough.

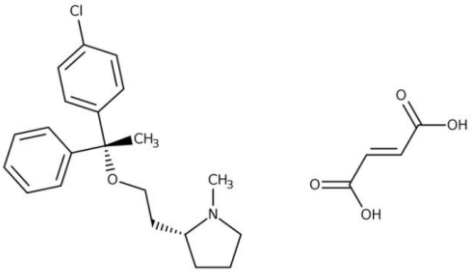
DIPHENHYDRAMINE HYDROCHLORIDE



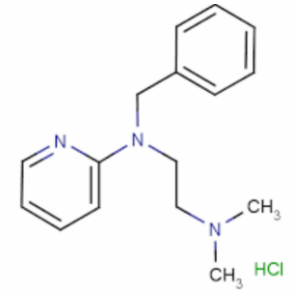
Synthesis:



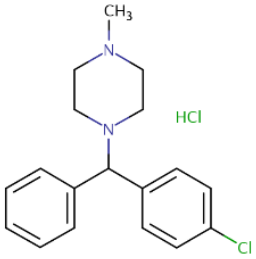
CLEMASTINE FUMARATE



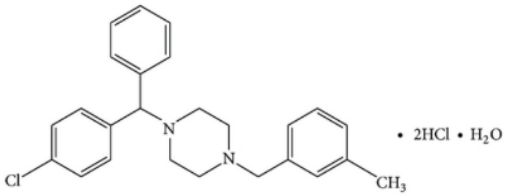
TRIPELENAMINE HYDROCHLORIDE



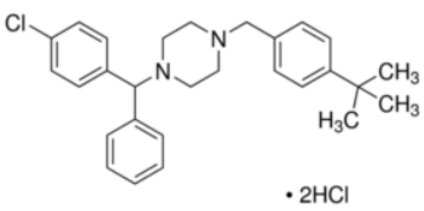
CHLORCYCLIZINE HYDROCHLORIDE



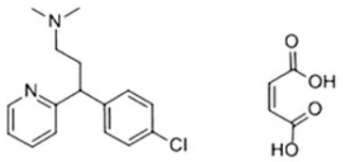
MECLIZINE HYDROCHLORIDE



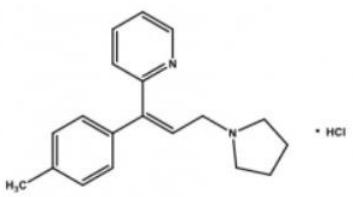
BUCLIZINE HYDROCHLORIDE



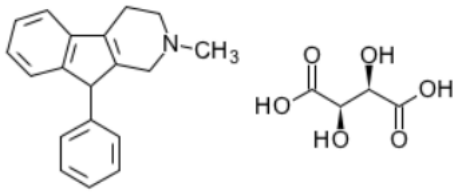
CHLORPHENIRAMINE MALEATE



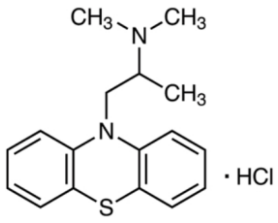
TRIPROLIDINE HYDROCHLORIDE



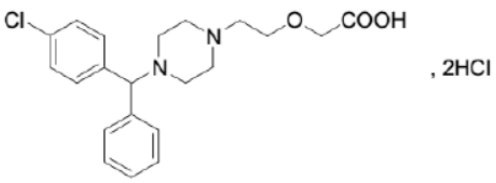
PHENIDAMINE TARTRATE



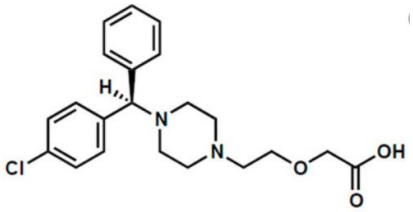
PROMETHAZINE HYDROCHLORIDE



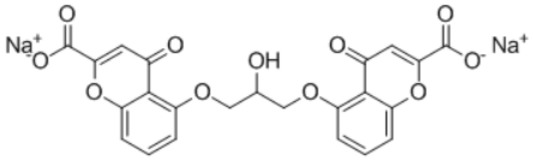
CETRIZINE



LEVOCETRAZINE



CROMOLYN SODIUM

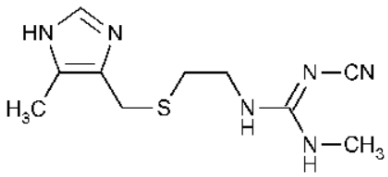


H2 ANTAGONISTS

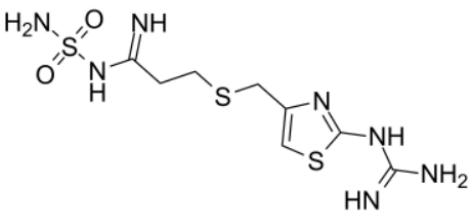
H2 blockers are a group of medicines that reduce the amount of acid produced by the cells in the lining of the stomach. They are also called 'histamine H2-receptor antagonists' but are commonly called H2 blockers.

H_2 antagonists can be used in the treatment of dyspepsia, peptic ulcers and gastroesophageal reflux disease. They have been surpassed by proton pump inhibitors (PPIs); the PPI omeprazole was found to be more effective at both healing and alleviating symptoms of ulcers and reflux oesophagitis than the H_2 blockers ranitidine and cimetidine.

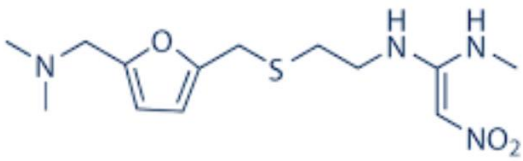
CIMETIDINE



FAMOTIDINE



RANITIDINE



THERAPEUTIC USES

- Peptic ulcer disease (PUD)
- Gastroesophageal reflux disease (GERD/GORD)

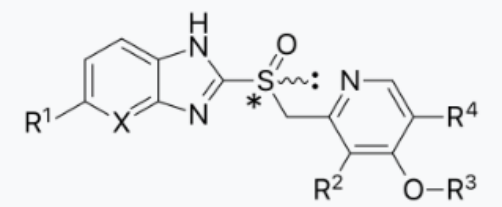
- Dyspepsia
- Prevention of stress ulcer (a specific indication of ranitidine)
- Prevention of aspiration pneumonitis during surgery.

TOXICITY

This class of agents are well tolerated and rare adverse effects include headache, tiredness, dizziness, confusion, diarrhoea, constipation, and rash.

GASTRIC PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are a group of medications whose main action is a pronounced and long-lasting reduction of stomach acid production. They block the **gastric** H, K-ATPase, **inhibiting gastric** acid secretion.



General structure of a proton-pump inhibitor

Therapeutic uses

These medications are used in the treatment of many conditions, such as:

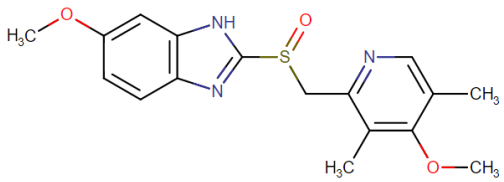
- Dyspepsia
- Peptic ulcer disease including after endoscopic treatment for bleeding
- Gastroesophageal reflux disease (GERD or GORD) including symptomatic endoscopy-negative reflux disease and associated laryngopharyngeal reflux causing laryngitis and chronic cough

Adverse Effects

Common adverse effects include headache, nausea, diarrhoea, abdominal pain, fatigue, and dizziness. Infrequent adverse effects include rash, itch, flatulence, constipation, anxiety, and depression.

OMEPRAZOLE

This drug was the first clinical useful drug in its class.



Therapeutic uses:

• Treatment of active duodenal ulcer in adults

• Eradication of Helicobacter pylori to reduce the risk of duodenal ulcer recurrence in adults

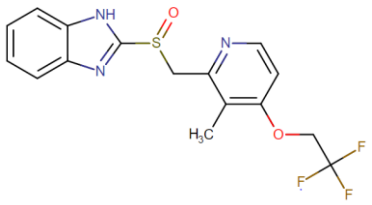
• Treatment of active benign gastric ulcer in adults

Toxicity:

Symptoms of overdose include confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, and dry mouth.

LANSOPRAZOLE

Lansoprazole marketed under the brand Prevacid, is structurally classified as a substituted benzimidazole.



Therapeutic uses:

It is used to reduce gastric acid secretion and is approved for short term treatment of active gastric ulcers, active duodenal ulcers, erosive reflux oesophagitis, symptomatic gastroesophageal reflux disease, and non-steroidal anti-inflammatory drug (NSAID) induced gastric and duodenal ulcers.

It may be used in the maintenance and healing of several gastric conditions including duodenal ulcers, NSAID related gastric ulcers, and erosive esophagitis.

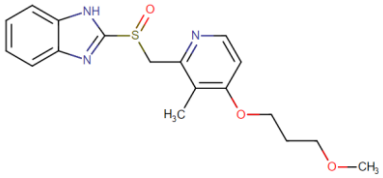
Toxicity:

Abdominal pain, constipation, diarrhoea, and nausea.

Toxic epidermal necrolysis (TEN) is a rare but very serious cutaneous reaction.

RABEPRAZOLE

Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. It is a prodrug - in the acid environment of the parietal cells it turns into active sulphonamide form.

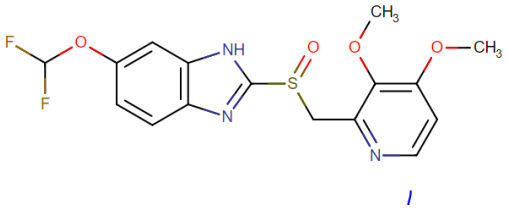


Therapeutic uses

For the treatment of acid-reflux disorders (GERD), peptic ulcer disease, H. pylori eradication, and prevention of gastrointestinal bleeds with NSAID use. It belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties but suppress gastric acid secretion by inhibiting the gastric H^+/K^+ATPase.

PANTOPRAZOLE

Pantoprazole is a first-generation proton pump inhibitor (PPI).



Therapeutic uses

It is used for the management of gastroesophageal reflux disease (GERD), for gastric protection to prevent recurrence of stomach ulcers or gastric damage from chronic use of NSAIDs, and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome.

ANTI NEOPLASTIC AGENTS

The antineoplastic agents or anticancer drugs represent a large and diverse class of medications that inhibit or prevent the proliferation of neoplasms. These are a group of specialized drugs used primarily to treat cancer. Antineoplastic drugs are also called anticancer, cytotoxic or hazardous drugs.

Cancer is an extremely common disease, which impacts an untold number of people (and animals) each year. The abnormal cell division caused by cancers can impact virtually any body system, unlike other diseases that may only impact a single organ. In many cases, multiple systems are impacted at the same time.

Antineoplastic agents can be administered to patients alone or in combination with other antineoplastic drugs. They can also be given before, during or after a patient receives surgery or **radiation therapy**.

Classification

Historically, they are categorized as

(1) alkylating agents

(2) antimetabolites

(3) natural products

(4) hormones and antagonists

(5) miscellaneous.

1. ALKYLATING AGENTS

Examples include Cyclophosphamide, Ifosfamide, Chlorambucil, Busulfan and Melphalan.

MOA:

Classic alkylating agents interfere with DNA replication by crosslinking DNA strands, DNA strand breaking, and abnormal pairing of base pairs. They exert their lethal effects on cells throughout the cell cycle but tend to be more effective against rapidly dividing cells.

Because alkylating agents are active against cells in G0, they can be used to debulk tumours, causing resting cells to be recruited into active division. At this point, those cells are vulnerable to the cell cycle-specific agents.

Therapeutic uses:

These agents are active against lymphomas, Hodgkin's disease, breast cancer, and multiple myeloma.

Toxicity:

Major toxicities occur in the haematopoietic, gastrointestinal and reproductive systems. Individuals treated with these agents are also placed at a higher risk of developing secondary malignancies.

Classification:

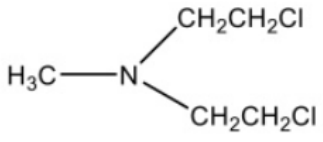
1. **Nitrosoureas**

   The nitrosoureas are a subgroup of the alkylating agents. They also interfere with DNA replication and repair. They are highly lipid soluble and readily cross the blood-brain barrier. An example is Carmustine.

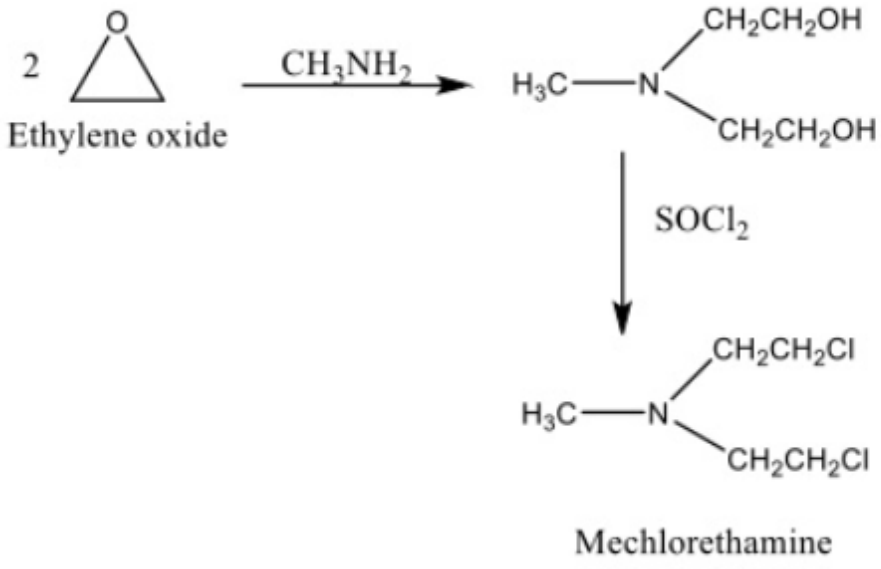
2. **Platinum-containing compounds**

   Another subgroup of alkylators called Platinum-containing compounds include agents such as Cisplatin, Carboplatin and Oxaliplatin. Their cytotoxic properties also extend to alteration of the cell membrane transport systems and suppression of mitochondrial function.

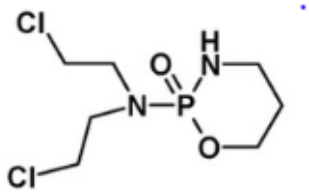
MECLORETHAMINE



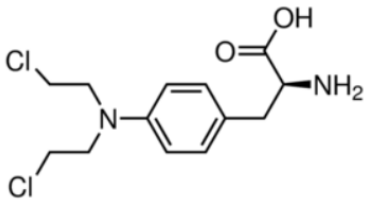
Synthesis:



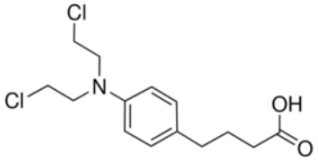
CYCLOPHOSPHAMIDE



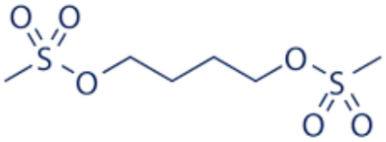
MELPHALAN



CHLORAMBUCIL



BUSULFAN

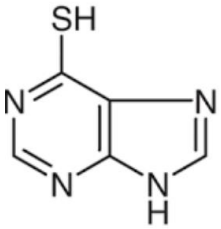


2. ANTIMETABOLITES

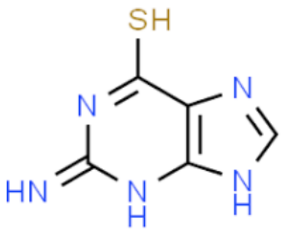
They interfere with DNA and RNA synthesis by acting as false metabolites, which are incorporated into the DNA strand or block essential enzymes, so that DNA synthesis is prevented. Most agents are cell cycle phase specific for S phase. These agents are most effective when used against rapidly cycling cell populations and are consequently more effective against fast-growing tumours than slow-growing tumours. Major toxicities occur in the haematopoietic and gastrointestinal systems.

Examples include Methotrexate, 5-Fluorourocil and Cytosine Arabinoside.

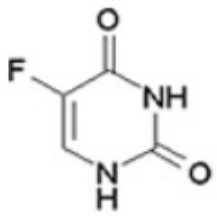
MERCAPTOPURINE



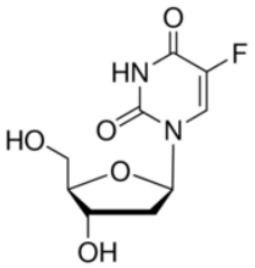
THIOGUANINE



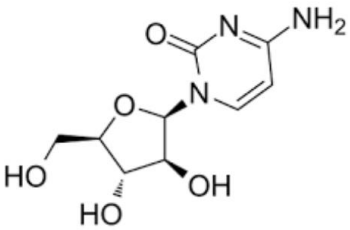
5-FLUORO URACIL



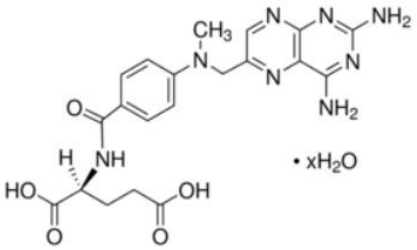
FLOXURIDINE



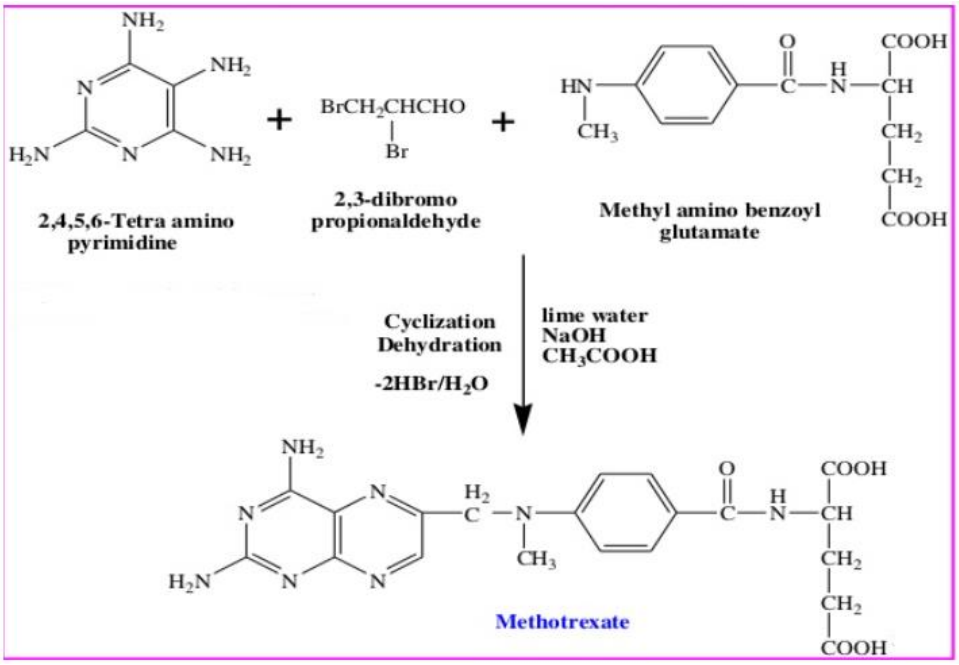
CYTARABINE



METHOTREXATE



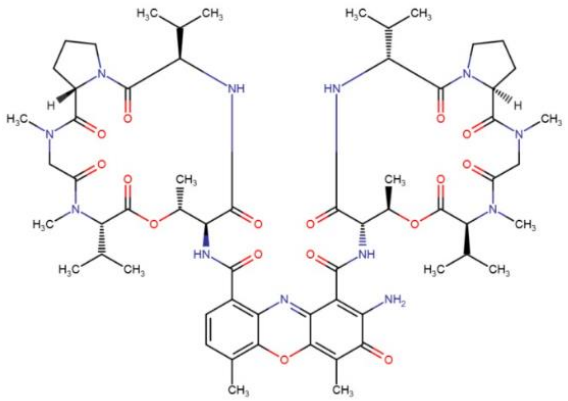
Synthesis:



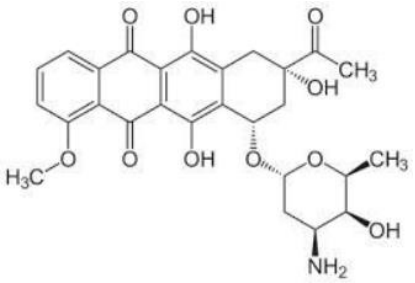
3. **ANTITUMOR ANTIBIOTICS** (also called Anthracyclines)

   These interfere with RNA and DNA synthesis. Most drugs are cell cycle non-specific. Major toxicities occur in the haematopoietic, gastrointestinal, cardiac and reproductive systems. Cardiac toxicity may be manifested as acute changes in the electrocardiograph (ECG) and arrhythmias. Individuals with pre-existing heart disease are most at risk. Examples include Bleomycin, Daunorubicin, and Doxorubicin.

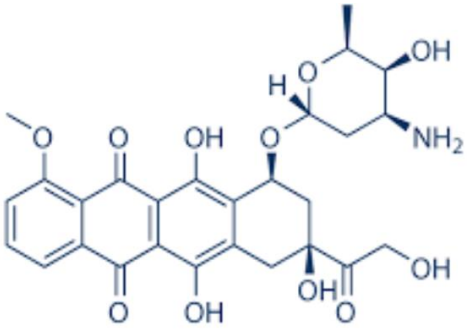
DACTINOMYCIN



DAUNORUBICIN



DOXORUBICIN

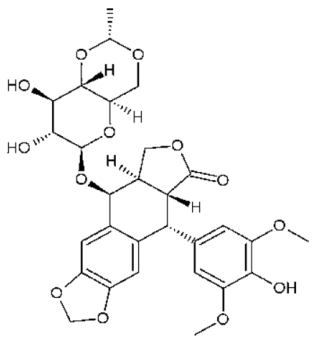


4. **PLANT ALKALOIDS**

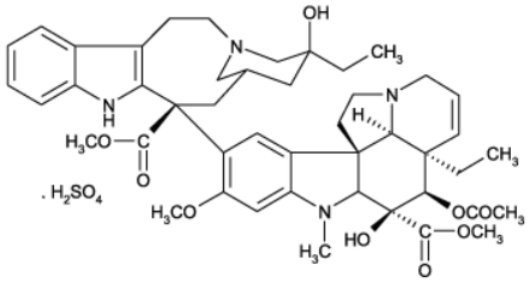
They bind to microtubule proteins during metaphase, causing mitotic arrest. The cell cannot divide and dies. This group is mainly cell cycle phase specific for M phase. Major toxicities occur in the haematopoietic, integumentary, neurologic and reproductive systems. Hypersensitivity reactions also may occur during administration of these agents. This group contains three subgroups:

- the vinca alkaloids e.g. vincristine and vinblastine
- the epipodophyllotoxins e.g. etoposide and teniposide
- the taxanes e.g. paclitaxel and docetaxel.

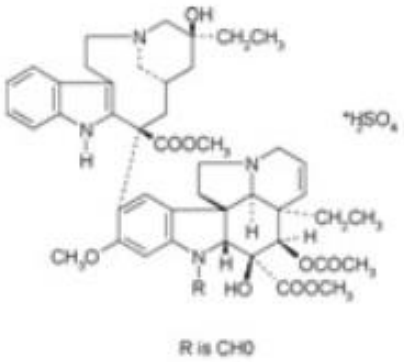
ETOPOSIDE



VINBLASTINE



VINCRISTINE



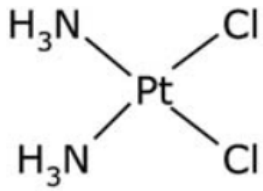
5. **MISCELLANEOUS AGENTS**

   They differ from any of the major classes of cytotoxic agents. Common miscellaneous agents are asparaginase and hydroxyurea.

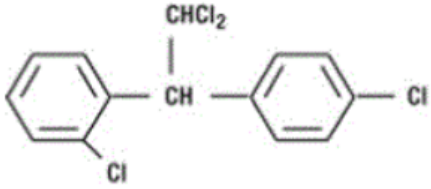
   Topoisomerase inhibitors prevent realigning of DNA strands and maintain single-strand breaks. Major toxicities occur in the haematopoietic and gastrointestinal systems.

   Examples include irinotecan and topotecan.

CISPLATIN



MITOTANE



6. **HORMONAL AGENTS alter the internal / extracellular environment**.

   Most agents are cell cycle phase non-specific. Breast, thyroid, prostate and uterine cancers are examples of tumours that are sensitive to hormonal manipulation. With these diseases, the action of

hormones or hormone antagonists depends on the presence of hormone receptors in the tumours themselves (i.e. oestrogen receptors in breast cancers). There are individual classifications of hormonal agents:

- adrenocorticoids, eg. prednisone
- androgens, eg. testosterone propionate
- oestrogens, eg. diethylstilboestrol
- selective oestrogen receptor modulators, eg. tamoxifen citrate
- selective aromatase inhibitors, eg. anastrozole
- progesterones, eg. megestrol acetate
- antitestosterone, eg. flutamide

Subject: ***Medicinal Chemistry II*** **Unit No: II**
Faculty: ***Mrs. Sashmitha Samuel*** **Lecture No:**
Topic: ***Anti anginal agents*** **Reference Book:**

ANTI ANGINAL AGENTS

An antianginal is a drug used in the treatment of angina pectoris, a symptom of ischaemic heart disease.

Angina results from a reduction in the oxygen supply/demand ratio. Therefore, in order to alleviate the pain, it is necessary to improve this ratio.

This can be done either

1. by increasing blood flow (which increases oxygen delivery or supply), or
2. by decreasing oxygen demand (i.e., by decreasing myocardial oxygen consumption).

Pharmacologic interventions that block coronary vasospasm (coronary vasodilators) or inhibit clot formation are used to treat variant and unstable angina, respectively.

Classification

Classes of drugs used in the treatment of angina and myocardial infarction are given below.

- **Vasodilators** (dilate arteries and veins)
  - calcium-channel blockers
  - nitro dilators
- **Cardioinhibitory drugs** (reduce heart rate and contractility)
  - beta-blockers
  - calcium-channel blockers
- **Anti-thrombotic drugs** (prevent thrombus formation)
  - anticoagulants
  - anti-platelet drugs

VASODILATORS

These drugs relax the smooth muscle in blood vessels, which causes the vessels to dilate.

Vasodilator drugs can be classified based on their site of action.

i) Arterial dilators

Some drugs primarily dilate resistance vessels and are called arterial dilators; e.g., hydralazine. These drugs are commonly used to treat systemic and pulmonary hypertension, heart failure and angina. They reduce arterial pressure by decreasing systemic vascular resistance.

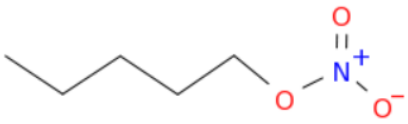
ii) Venous dilators

Some drugs primarily affect venous capacitance vessels and are called venous dilators; e.g., nitro glycerine. Venous dilators are very effective for angina.

iii) Mixed dilators

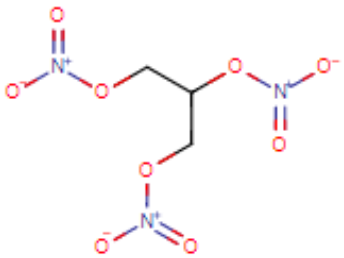
Most vasodilator drugs are mixed (or balanced) vasodilators in that they dilate both arteries and veins and therefore can have wide application in hypertension, heart failure and angina. e.g., alpha-adrenoceptor antagonists, angiotensin converting enzyme inhibitors).

1.Amyl nitrate



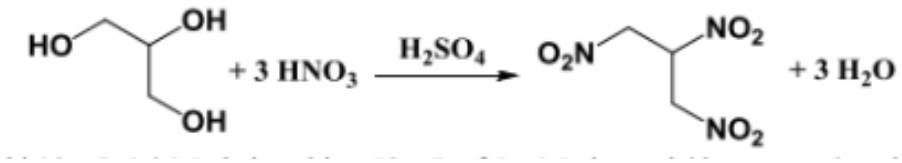
Amyl nitrite is employed medically to treat heart diseases such as angina and to treat cyanide poisoning

2.**Nitroglycerin**

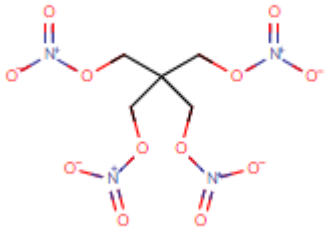


Nitroglycerin causes the relaxation of vascular smooth muscles, causing arteriolar and venous dilatation.

Synthesis

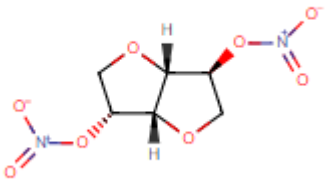


3.Pentaerythritol tetranitrate



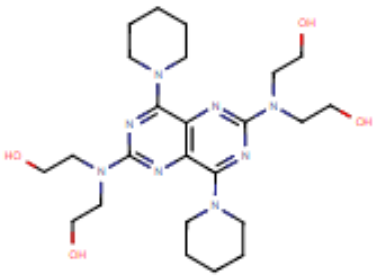
Pentaerythritol tetranitrate is the lipid soluble polyol ester of nitric acid belonging to the family of *nitro-vasodilators*.

4.Isosorbide dinitrite



A vasodilator used in the treatment of angina pectoris. Its actions are similar to nitroglycerin but with a slower onset of action.

5.Dipyridamole



It is a non-nitrate coronary vasodilator that also inhibits platelet aggregation. It is combined with other anticoagulant drugs.

CALCIUM CHANNEL BLOCKERS

Calcium-channel blockers (CCBs) bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes). Therefore, by blocking calcium entry into the cell, CCBs cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity within the heart, particularly at the AV node.

CCBs are used to treat hypertension, angina and arrhythmias.

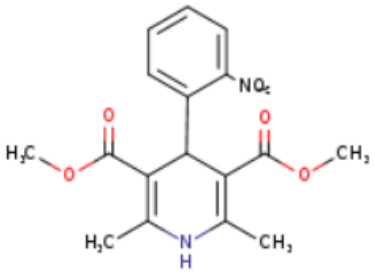
Classification

There are three chemical classes of CCBs. They differ not only in their basic chemical structure, but also in their relative selectivity toward calcium channels.

i) Dihydropyridines

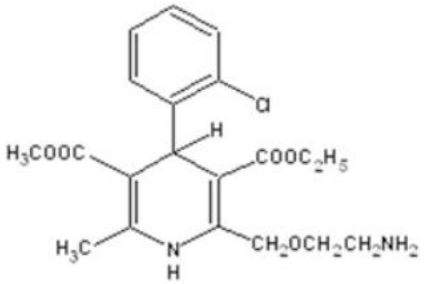
Because of their high vascular selectivity, these drugs are primarily used to reduce systemic vascular resistance and arterial pressure, and therefore are used to treat hypertension. long-acting compounds are used to treat angina and are particularly affecting for vasospastic angina.

Nifedipine



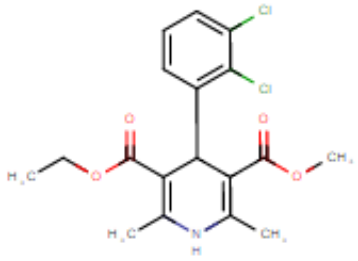
Nifedipine blocks voltage gated L-type calcium channels in vascular smooth muscle and myocardial cells.

Amlodipine



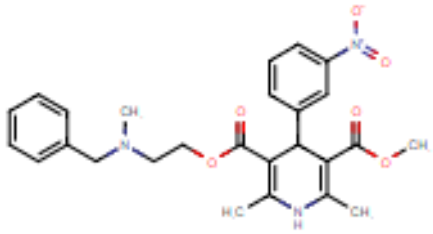
Dilatation of the main coronary arteries and coronary arterioles, both in healthy and ischemic areas causes an increase in myocardial oxygen delivery in patients experiencing coronary artery spasm (Printzmetal's or variant angina).

Felodipine



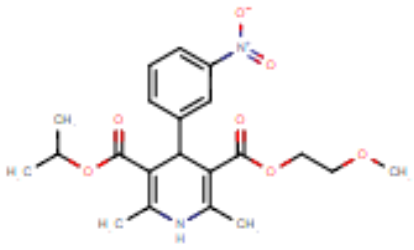
Felodipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ions through voltage-gated L-type calcium channels.

Nicardipine



Nicardipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes

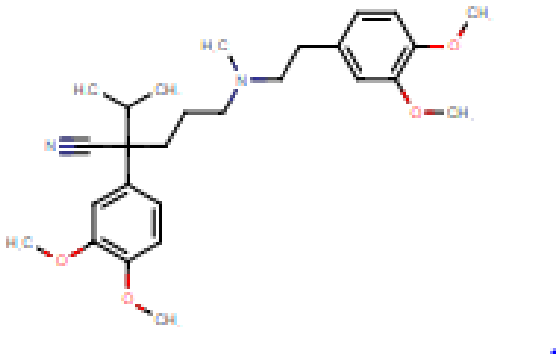
Nimodipine



By inhibiting the influx of calcium in smooth muscle cells, nimodipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction.

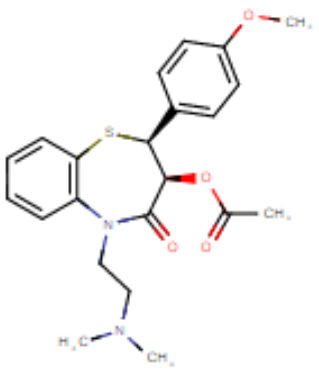
ii)Non dihydropyridines

a) Phenylalkylamines- **Verapamil**



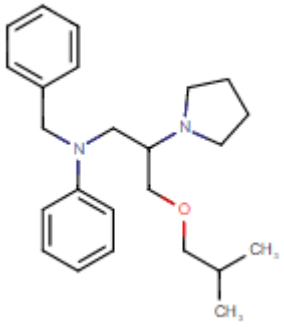
First calcium channel antagonist to be introduced into therapy in the early 1960s. Verapamil is indicated in the treatment of vasospastic (i.e. Prinzmetal's) angina, unstable angina, and chronic stable angina.

b) Benzothiazepines- **Diltiazem**



it primarily works by inhibiting the calcium influx into cardiac and vascular smooth muscle during depolarization.

Bepridil



A long-acting, non-selective, calcium channel blocker with significant anti-anginal activity.

It has antihypertensive and selective anti-arrhythmia activities and acts as a calmodulin antagonist.

DIURETICS

Diuretic drugs increase urine output by the kidney (i.e., promote diuresis).

Most diuretics produce diuresis by inhibiting the reabsorption of sodium at different segments of the renal tubular system.

Classification

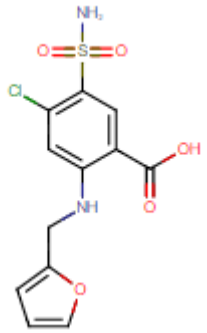
Based on their site of action

1. Loop diuretics
2. CAE inhibitors
3. Potassium sparing diuretics
4. Osmotic diuretics

LOOP DIURETICS

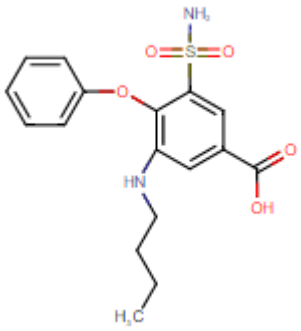
They inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb.

Furosemide



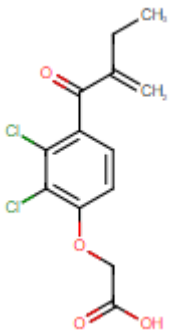
It is an anthranilic acid derivative. It mainly works by inhibiting electrolyte reabsorption from the kidneys and enhancing the excretion of water from the body.

Bumetanide



Bumetanide is a loop diuretic of the sulfamyl category to treat heart failure.

Ethacrynic acid

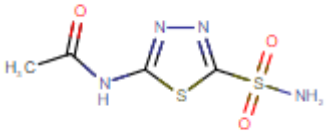


Ethacrynic acid is a monosulfonamyl loop or high ceiling diuretic. It inhibits symport of sodium, potassium, and chloride primarily in the ascending limb of Henle, but also in the proximal and distal tubules.

CARBONIC ANHYDRASE INHIBITORS

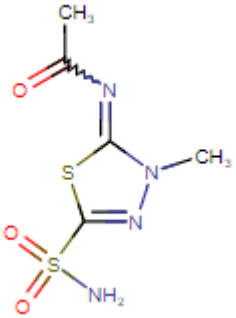
These drugs inhibit the transport of bicarbonate out of the proximal convoluted tubule into the interstitium, which leads to less sodium reabsorption at this site and therefore greater sodium, bicarbonate and water loss in the urine. These are the weakest of the diuretics and seldom used in cardiovascular disease. Their main use is in the treatment of glaucoma.

Acetazolamide



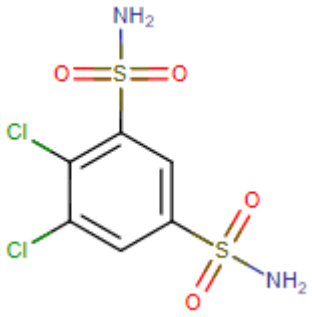
Acetazolamide is a potent carbonic anhydrase inhibitor, effective in the control of fluid secretion, in the treatment of certain convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention.

Methazolamide



It is a carbonic anhydrase inhibitor that is used as a diuretic and in the treatment of glaucoma.

Dichlorphenamide

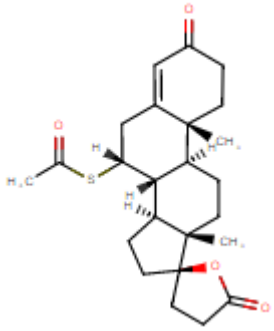


Dichlorphenamide is a carbonic anhydrase inhibitor that is used in the treatment of glaucoma.

POTASSIUM SPARING DIURETICS

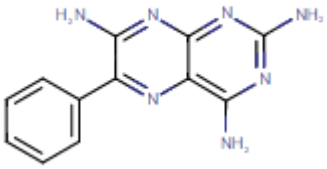
They are called K^+-sparing diuretics because they do not produce hypokalaemia like the loop and thiazide diuretics.

Spiranolactone



Spironolactone is structurally similar to progesterone and as a result is associated with progestogenic and antiandrogenic effects.

Triamterene



Triamterene (2,4,7-triamino-6-phenylpteridine) is a potassium-sparing diuretic that works by promoting the excretion of sodium ions and water while decreasing the potassium excretion in the distal part of the nephron in the kidneys by working on the luminal side.

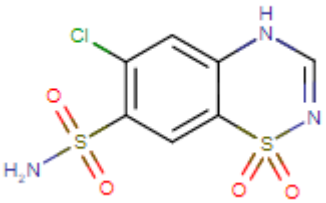
Amiloride

It is a pyrazine compound inhibiting sodium reabsorption through sodium channels in renal epithelial cells.

THIAZIDE DIURETICS

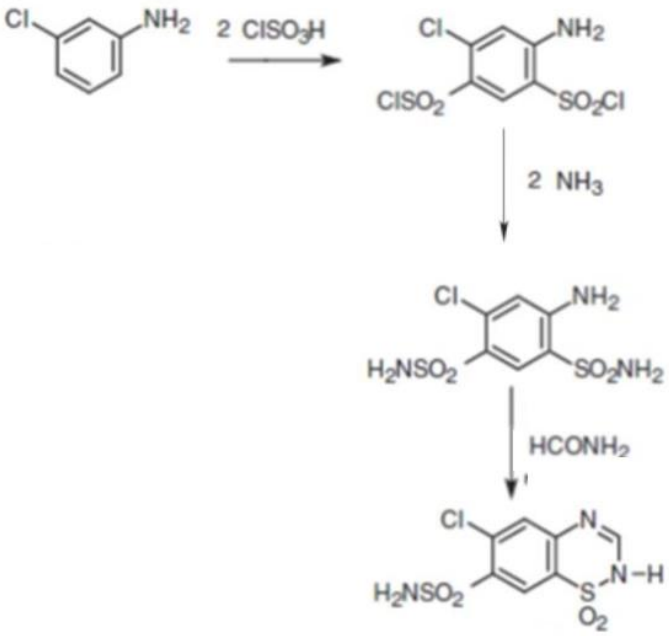
These are the most commonly used diuretic and they inhibit the sodium-chloride transporter in the distal tubule. Because this transporter normally only reabsorbs about 5% of filtered sodium, these diuretics are less efficacious than loop diuretics in producing diuresis and natriuresis.

Chlorthiazide

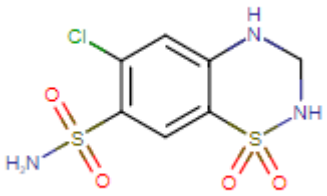


Like other thiazides, chlorothiazide promotes water loss from the body (diuretics). It inhibits Na^+/Cl^- reabsorption from the distal convoluted tubules in the kidneys.

Synthesis

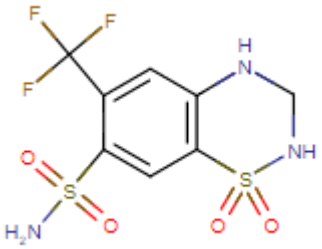


Hydrochlorothiazide



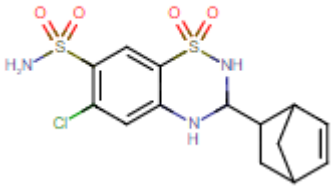
Hydrochlorothiazide is the most commonly prescribed thiazide diuretic. It is indicated to treat edema and hypertension. It prevents the reabsorption of sodium and water from the distal convoluted tubule, allowing for the increased elimination of water in the urine.

Hydroflumethiazide



It is a thiazide diuretic with actions and uses similar to those of hydrochlorothiazide. It is also used as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

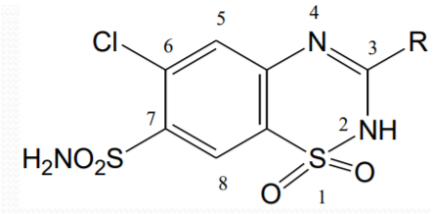
Cyclothiazide



It inhibits active chloride reabsorption at the early distal tubule via the Na-Cl cotransporter, resulting in an increase in the excretion of sodium, chloride, and water.

SAR of thiazides

General structure



1. The 2-position can tolerate small alkyl groups as CH3.

2. Substituents at the 3-position determine the potency and duration of action of the thiazides.

3. Saturation of C-C bond between the 3 and 4 positions of the benzothiadiazine-1,1-dioxide nucleus increases the potency of this class of diuretics approximately 3-10-fold.

4. Direct substitution of the 4-, 5-, or 8-position with an alkyl group usually results in diminished diuretic activity.

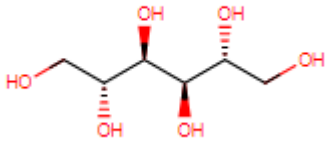
5. Substitution of the 6-position with an activating group is essential for diuretic activity. The best substituent includes Cl-, Br-, CF3 -, and NO2 - groups.

6. The sulfamoyl group in the 7-position is essential for diuretic activity.

OSMOTIC DIURETICS

An osmotic diuretic is a type of diuretic that inhibits reabsorption of water and sodium. They are pharmacologically inert substances that are given intravenously. They increase the osmolarity of blood and renal filtrate.

Mannitol



It is an osmotic diuretic that is metabolically inert in humans and occurs naturally, as a sugar or sugar alcohol, in fruits and vegetables.

ANTI HYPERTENSIVE AGENTS

Antihypertensives are a class of drugs that are used to treat hypertension. Antihypertensive therapy seeks to prevent the complications of high blood pressure, such as stroke and myocardial infarction.

Patients with primary hypertension are generally treated with drugs that

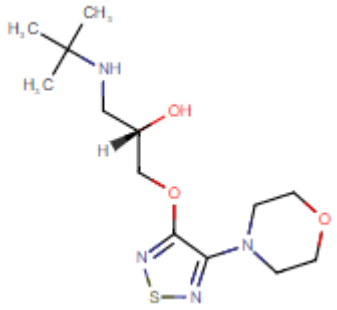
1) reduce blood volume (which reduces central venous pressure and cardiac output)

2) reduce systemic vascular resistance, or

3) reduce cardiac output by depressing heart rate and stroke volume.

Patients with secondary hypertension are best treated by controlling or removing the underlying disease or pathology, although they may still require antihypertensive drugs.

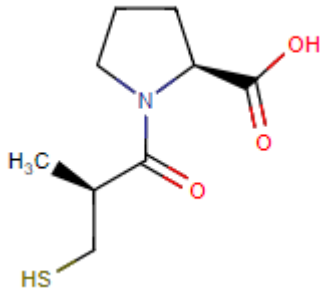
Timolol



Timolol is a nonselective beta-adrenergic antagonist given in an eye drop solution to reduce intraocular pressure, or pressure in the eyes.

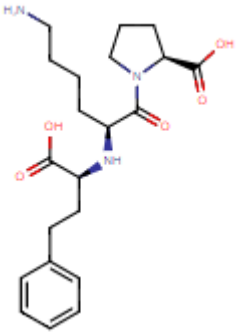
MOA: It competes with adrenergic neurotransmitters for binding to beta (1)-adrenergic receptors in the heart and the beta (2)-receptors in the vascular and bronchial smooth muscle. This leads to diminished actions of catecholamines, which normally bind to adrenergic receptors and exert sympathetic effects leading to an increase in blood pressure and heart rate. Beta (1)-receptor blockade by timolol leads to a decrease in both heart rate and cardiac output during rest and exercise, and a decrease in both systolic and diastolic blood pressure.

Captopril



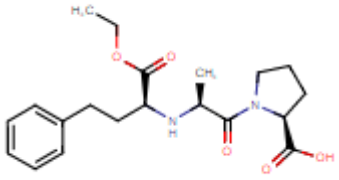
It is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Captopril may be used in the treatment of hypertension.

Lisinopril



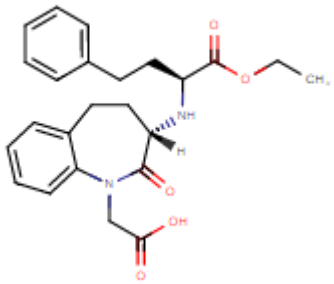
Lisinopril is an angiotensin converting enzyme inhibitor (ACEI) used to treat hypertension, heart failure, and myocardial infarction. It functions by inhibition of angiotensin converting enzyme as well as the renin angiotensin aldosterone system.It is indicated for the treatment of acute myocardial infarction, hypertension in patients ≥6 years, and as an adjunct therapy for heart failure.

Enalapril



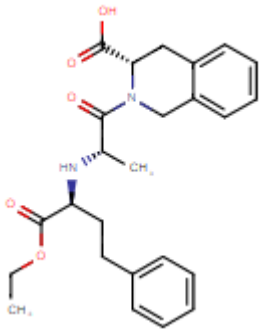
Enalapril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor drug class that works on the renin-angiotensin-aldosterone system, which is responsible for the regulation of blood pressure and fluid and electrolyte homeostasis.

Benazepril



It is used to treat high blood pressure (hypertension), congestive heart failure, and chronic renal failure.

Quinapril



Quinapril is the ethyl ester prodrug of the non-sulfhydryl angiotensin converting enzyme inhibitor quinaprilat. It is used to treat hypertension and heart failure. ACE inhibitors are commonly used as a first line therapy in the treatment of hypertension, along with thiazide diuretics or beta blockers.

SYMPATHOLYTIC DRUGS

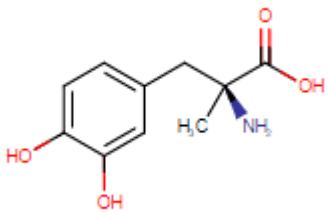
Sympatholytic drugs can block this sympathetic adrenergic system are three different levels.

1. **Peripheral sympatholytic drugs** block the influence of norepinephrine at the effector organ (heart or blood vessel).
2. **Ganglionic blockers** that block impulse transmission at the sympathetic ganglia.
3. **Centrally acting sympatholytic drugs** that block sympathetic activity within the brain.

Centrally acting sympatholytics block sympathetic activity by binding to and activating alpha$_2$ (α_2)-adrenoceptors. This reduces sympathetic outflow to the heart thereby decreasing cardiac output by decreasing heart rate and contractility. Reduced sympathetic output to the vasculature decreases sympathetic vascular tone, which causes vasodilation and reduced systemic vascular resistance, which decreases arterial pressure.

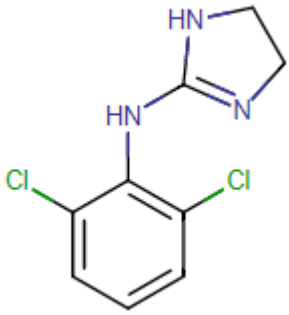
Side effects of centrally acting α_2-adrenoceptor agonists include sedation, dry mouth and nasal mucosa, bradycardia (because of increased vagal stimulation of the SA node as well as sympathetic withdrawal), orthostatic hypotension, and impotence. Constipation, nausea and gastric upset are also associated with the sympatholytic effects of these drugs. Fluid retention and edema is also a problem with chronic therapy; therefore, concurrent therapy with a diuretic is necessary.

Methyldopa



It is an alpha-2 adrenergic agonist that has both central and peripheral nervous system effects. Its primary clinical use is as an antihypertensive agent.

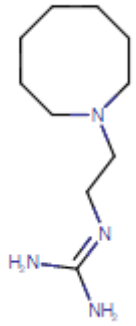
Clonidine



It is an imidazole derivate that acts as an agonist of alpha-2 adrenoceptors. This activity is useful for the treatment of hypertension, severe pain, and ADHD.

Symptoms of overdose include hypertension followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased reflexes, weakness, irritability, and miosis.

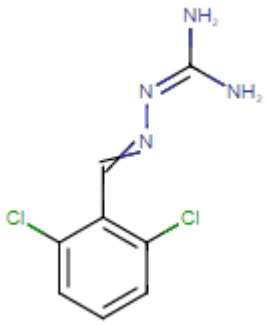
Guanethidine



It acts by inhibiting selectively transmission in post-ganglionic adrenergic nerves.

It is used in the treatment of moderate and severe hypertension, either alone or as an adjunct, and for the treatment of renal hypertension.

Guanabenz acetate

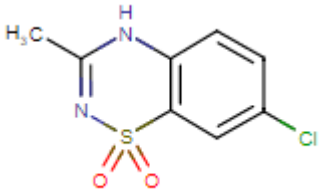


It is an alpha-2 selective adrenergic agonist used as an antihypertensive agent.

Sodium nitroprusside

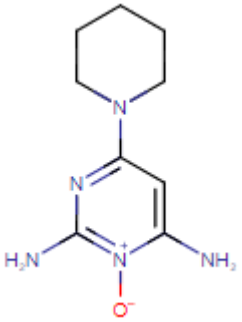
It serves as a source of nitric oxide, a potent peripheral vasodilator that affects both arterioles and venules (venules more than arterioles). It relaxes the vascular smooth muscle and produce consequent dilatation of peripheral arteries and veins.

Diazoxide



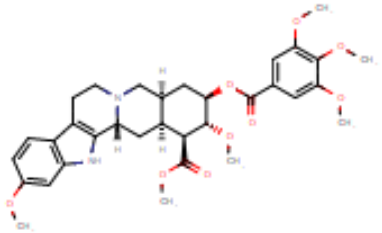
It is a benzothiadiazine derivative that is a peripheral vasodilator used for hypertensive emergencies. It lacks diuretic effect, apparently because it lacks a sulfonamide group. Diazoxide inhibits insulin release from the pancreas, by opening potassium channels in the beta cell membrane.

Minoxidil



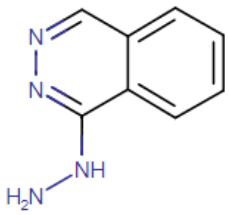
It is a potent direct-acting peripheral vasodilator (vasodilator agents) that reduces peripheral resistance and produces a fall in blood pressure. Minoxidil is an orally effective direct acting peripheral vasodilator that reduces elevated systolic and diastolic blood pressure by decreasing peripheral vascular resistance. Minoxidil is also used topically to treat androgenetic alopecia.

Reserpine



It is an alkaloid found in the roots of Rauwolfia serpentina and R. vomitoria. It is an adrenergic blocking agent used to treat mild to moderate hypertension via the disruption of norepinephrine vesicular storage. It has been used as an antihypertensive and an antipsychotic agent.

Hydralazine



Hydralazine is a hydrazine derivative vasodilator. It may interfere with calcium transport in vascular smooth muscle by an unknown mechanism to relax arteriolar smooth muscle and lower blood pressure. It is used alone or as adjunct therapy in the treatment of hypertension and only as adjunct therapy in the treatment of heart failure.

Subject: *Medicinal Chemistry II* **Unit No:** III
Faculty: *Mrs. Sashmitha Samuel* **Lecture No:**
Topic: *Anti-arrhythmic agents* **Reference Book:**

ANTI-ARRHYTHMIC DRUGS

Antiarrhythmic agents, also known as cardiac dysrhythmia medications, are a group of pharmaceuticals that are used to suppress abnormal rhythms of the heart, such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation. Antiarrhythmic drugs are used to:

- decrease or increase conduction velocity
- alter the excitability of cardiac cells by changing the duration of the effective refractory period
- suppress abnormal automaticity

Classification

Class I - Sodium-channel blockers.

Class II - Beta-blockers.

Class III - Potassium-channel blockers.

Class IV - Calcium-channel blockers.

Miscellaneous - adenosine. - electrolyte supplement (magnesium and potassium salts) - digitalis compounds (cardiac glycosides)

Class I - Sodium-channel blockers

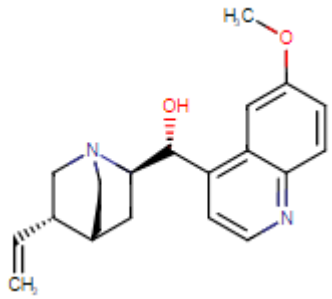
Sodium-channel blockers may also alter the action potential duration (APD) and effective refractory period (ERP).

The Vaughan-Williams classification of subclasses of Class I antiarrhythmic drugs is as follows:

1. Class IA - increase the ERP
2. Class IB- while others decrease the ERP
3. Class IC- have no effect on ERP

QUINIDINE SULPHATE

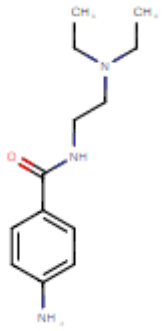
An optical isomer of quinine, extracted from the bark of the Cinchona tree and similar plant species. This alkaloid dampens the excitability of cardiac and skeletal muscles by blocking sodium and potassium currents across cellular membranes. It prolongs cellular action potential, and decreases automaticity. Quinidine also blocks muscarinic and alpha-adrenergic neurotransmission.



It acts on sodium channels on the neuronal cell membrane, limiting the spread of seizure activity and reducing seizure propagation. The antiarrhythmic actions are mediated through effects on sodium channels in Purkinje fibers.

PROCAINAMIDE HYDROCHLORIDE

A derivative of procaine with less CNS action.

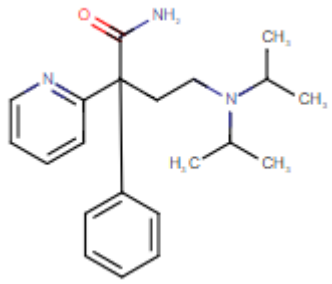


Procainamide is sodium channel blocker. It stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action. It is used for the treatment of life-threatening ventricular arrhythmias.

DISOPYRAMIDE PHOSPHATE

A class I anti-arrhythmic agent (one that interferes directly with the depolarization of the cardiac membrane

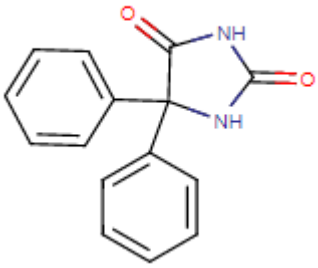
and thus serves as a membrane-stabilizing agent) with a depressant action on the heart similar to that of guanidine. It also possesses some anticholinergic and local anesthetic properties.



Disopyramide is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia that are life-threatening.

PHENYTOIN SODIUM

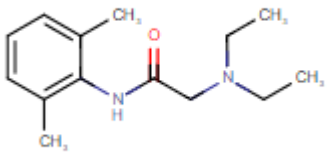
Phenytoin is classified as a hydantoin derivative



Phenytoin is often described as a non-specific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes.

LIDOCAINE HYDROCHLORIDE

Lidocaine is also considered a class IB anti-arrhythmic agent.

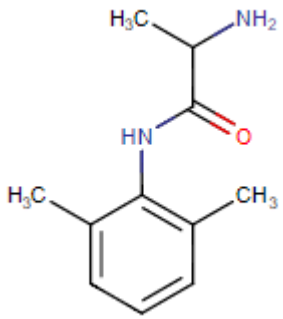


It ultimately elicits its numbing activity by blocking sodium channels so that the neurons of local tissues that have the medication applied on are transiently incapable of signalling the brain regarding sensations. In doing

so, however, it can block or decrease muscle contractile, resulting in effects like vasodilation, hypotension, and irregular heart rate.

TOCAINIDE HYDROCHLORIDE

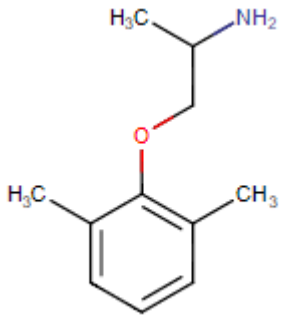
An antiarrhythmic agent which exerts a potential- and frequency-dependent block of sodium channels. It is a primary amine analog of lidocaine.



Tocainide acts on sodium channels on the neuronal cell membrane, limiting the spread of seizure activity and reducing seizure propagation in Purkinje fibres.

MEXILETINE HYDROCHLORIDE

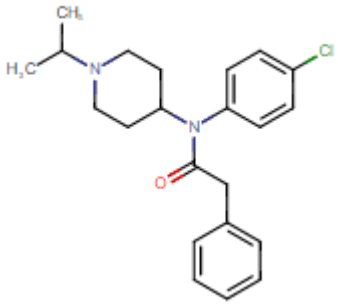
It is an antiarrhythmic agent pharmacologically similar to lidocaine. It may have some anticonvulsant properties.



Mexiletine, like lidocaine, inhibits the inward sodium current required for the initiation and conduction of impulses, thus reducing the rate of rise of the action potential, Phase 0.

LORCAINIDE HYDROCHLORIDE

This compound belongs to the class of organic compounds known as phenyl acetamides.



It is a Class 1c antiarrhythmic agent that is used to help restore normal heart rhythm and conduction in patients with premature ventricular contractions.

Class II - Beta-blockers

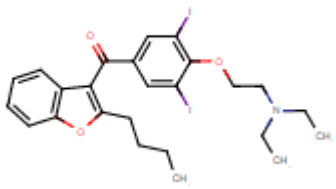
Beta-blockers are sympatholytic drugs. Some beta-blockers, when they bind to the beta-adrenoceptor, partially activate the receptor while preventing norepinephrine from binding to the receptor. These particular beta-blockers (partial agonists) are said to possess intrinsic sympathomimetic activity (ISA).

Class III - Potassium-channel blockers

These drugs bind to and block the potassium channels that are responsible for phase 3 repolarization. Therefore, blocking these channels slows (delays) repolarization, which leads to an increase in action potential duration and an increase in the effective refractory period (ERP).

AMIODARONE

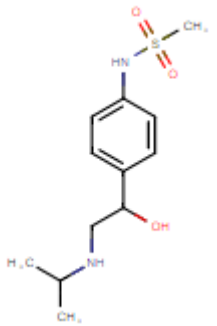
Amiodarone is a benzofuran derivative, anti-arrhythmic drug.



Amiodarone is considered a class III anti-arrhythmic drug. It blocks potassium currents that cause repolarization of the heart muscle during the third phase of the cardiac action potential.

SOTALOL

Sotalol is a methane sulfonanilide. It was the first of the class III anti-arrhythmic drugs.



It inhibits beta-1 adrenoceptors in the myocardium as well as rapid potassium channels to slow repolarization, lengthen the QT interval, and slow and shorten conduction of action potentials through the atria.

Class IV - Calcium-channel blockers

Calcium-channel blockers (CCBs) bind to L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue (sinoatrial and atrioventricular nodes).

These channels are responsible for regulating the influx of calcium into muscle cells, which in turn stimulates smooth muscle contraction and cardiac myocyte contraction.

Therefore, by blocking calcium entry into the cell, CCBs cause vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation (negative inotropy), decreased heart rate (negative chronotropy), and decreased conduction velocity within the heart (negative dromotropy), particularly at the atrioventricular node.

ANTIHYPERLIPIDEMIC AGENTS

Hyperlipidaemia involves abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. It is the most common form of dyslipidaemia (which includes any abnormal lipid levels).

Hyperlipidaemias are divided into two subtypes.

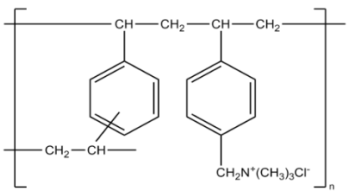
1. **Primary/Familial hyperlipidaemia:** It is usually due to genetic causes (such as a mutation in a receptor protein)
2. **Secondary/Acquired hyperlipidaemia:** It arises due to other underlying causes.

Antihyperlipidemic agents

They promote reduction of lipid levels in the blood. Some antihyperlipidemic agents aim to lower the levels of low-density lipoprotein (LDL) cholesterol, some reduce triglyceride levels, and some help raise the high-density lipoprotein (HDL) cholesterol. By reducing the LDL cholesterol, they can prevent both the primary and secondary symptoms of coronary heart disease.

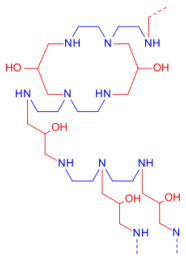
1. **Bile acid sequestrants**

   Bile acid sequestrants are used to reduce low density lipoprotein (LDL) cholesterol levels. After oral administration, they are not absorbed but bind to bile acids (which contain cholesterol) in the intestine and prevent their reabsorption into the body. The bound complex is insoluble and is excreted in the faeces. Decrease in bile acid leads to an increase in hepatic synthesis of bile acids from cholesterol. Depletion of cholesterol increases LDL receptor activity, therefore increases removal of LDL cholesterol from the blood.



typical structure of main polymeric groups

Cholestyramine

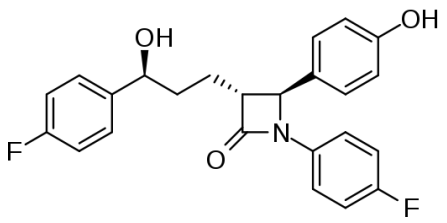


Colestipol

2. **Cholesterol absorption inhibitors**

   Cholesterol absorption inhibitors reduce the absorption of dietary and biliary cholesterol through the intestines. Therefore, it decreases the amount of intestinal cholesterol that is delivered to the liver.

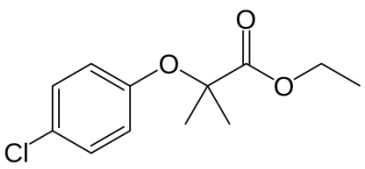
Reduced levels of cholesterol delivered to the liver results in increased hepatic LDL (low density lipoprotein) receptor activity, which leads to increased clearance of LDL cholesterol. Cholesterol absorption inhibitors are used to treat hyperlipidaemia, by lowering LDL cholesterol and total cholesterol.



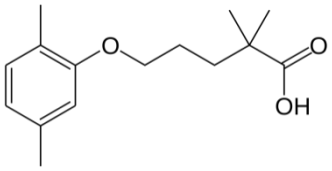
Ezetimibe

3. Fibrates

Fibric acid derivatives or fibrates are regarded as broad-spectrum lipid lowering drugs. Their main action is to decrease triglyceride levels but they also tend to reduce low density lipoprotein (LDL) cholesterol levels and help to raise high density lipoprotein (HDL) cholesterol.



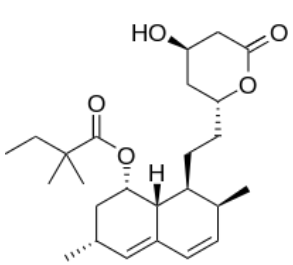
Clofibrate



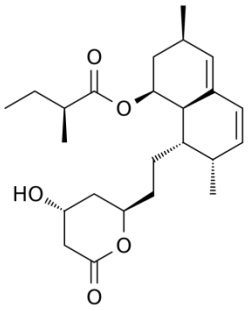
Gemfibrozil

4. HMG-CoA reductase inhibitors

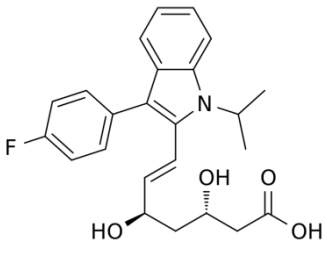
Statins, also known as HMG-CoA reductase inhibitors, inhibit HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase) an enzyme involved in the synthesis of cholesterol especially in the liver.



Simvastatin



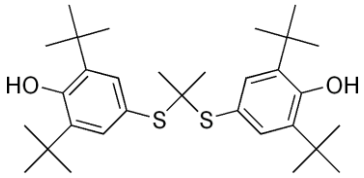
Lovastatin



Fluvastatin

5. LDL oxidation inhibitors

These lower the level of cholesterol in the bloodstream by increasing the rate of LDL catabolism. Additionally, they may inhibit cholesterol synthesis and delay cholesterol absorption. Probucol is a powerful antioxidant which inhibits the oxidation of cholesterol in LDLs; this slows the formation of foam cells, which contribute to atherosclerotic plaques.

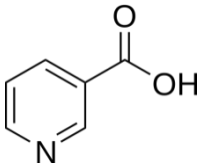


Probucol

6. Miscellaneous drugs

These agents are used to treat hyperlipidaemia. They help to decrease total cholesterol by lowering low-density lipoprotein (LDL) cholesterol and triglycerides and raising high-density lipoproteins (HDL) cholesterol.

Ex: **Niacin** (nicotinic acid): It is a water-soluble B vitamin, which inhibits the synthesis of cholesterol and triglycerides, therefore lowers total cholesterol and triglyceride levels, and raises HDL cholesterol levels.



COAGULANTS & ANTI COAGULANTS

Coagulation:

Coagulation, also known as clotting, is the process by which blood changes from a liquid to a gel, forming a blood clot. It potentially results in haemostasis, the cessation of blood loss from a damaged vessel, followed by repair.

Coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium lining the blood vessel. Exposure of blood to the subendothelial space initiates two processes: changes in platelets, and the exposure of subendothelial tissue factor to plasma factor VII, which ultimately leads to cross-linked fibrin formation. Platelets immediately form a plug at the site of injury; this is called ***primary haemostasis***. ***Secondary haemostasis*** occurs simultaneously: additional coagulation (clotting) factors beyond factor VII respond in a cascade to form fibrin strands, which strengthen the platelet plug.

BLOOD COAGULANTS

The three main types of drugs that are used to promote the formation of blood clots and to prevent or reduce abnormal bleeding are blood products, vitamin K, and antifibrinolytic drugs.

Blood products

Normal blood clotting depends on the presence in the blood of certain proteins called clotting factors.
For example, a blood product called **Factor VIII** is needed for the treatment of the inherited bleeding disorder haemophilia, in which a defective gene causes a deficiency of natural Factor VIII in the blood.
Another blood product, **fresh frozen plasma**, is given to counteract abnormally prolonged or severe bleeding due to causes such as an excessive dose of anticoagulants.

Vitamin K

This vitamin is essential for the production of several vital blood-clotting factors. Newborn babies (who are born with no stores of vitamin K) and people who are deficient in vitamin K may need a supplement, which is either given by injection or taken orally. Vitamin K is also used to reverse the effect of an excessive dose of oral anticoagulants. No side effects are known to be associated with its use.

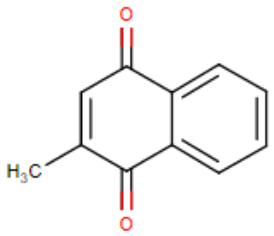
Antifibrinolytic drugs

These drugs may be used when bleeding is difficult to control, as may occur after surgery, or to reduce menstrual bleeding that is excessively heavy.

Some examples of antifibrinolytic drugs are aprotinin, tranexamic acid (TXA), epsilon-aminocaproic acid and aminomethylbenzoic acid.

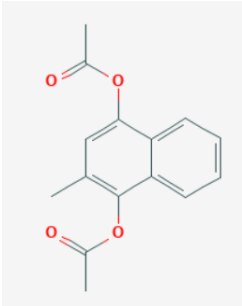
MENADIONE

A synthetic naphthoquinone without the isoprenoid side chain and biological activity, but can be converted to active vitamin K2, menaquinone, after alkylation in vivo.



ACETOMENADIONE

Acetomenadione is used for Coagulation disorders due to vitamin k deficiency, Anticoagulant-induced prothrombin deficiency and other conditions.



ANTI COAGULANTS

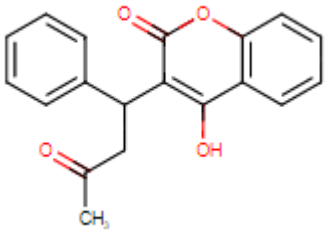
Anticoagulants are medicines that help prevent blood clots. They are given to people at a high risk of getting clots, to reduce their chances of developing serious conditions such as strokes and heart attacks. Anticoagulants work by interrupting the process involved in the formation of blood clots.

These drugs can also be classified as:

1. **Coumarins (vitamin K antagonists)**

   These oral anticoagulants are derived from coumarin, which is found in many plants.

WARFARIN



Warfarin is a vitamin K antagonist which acts to inhibit the production of vitamin K by vitamin K epoxide reductase.

2. Heparin and derivative substances

Heparin is a naturally occurring glycosaminoglycan. There are three major categories of heparin: unfractionated heparin (UFH), low molecular weight heparin (LMWH), and ultra-low-molecular weight heparin (ULMWH).

3. Directly acting oral anticoagulants

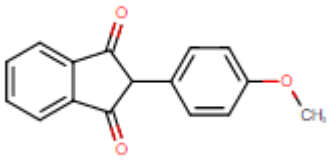
There are five DOACs - dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban.

They were also previously referred to as "new/novel" and "non-vitamin K antagonist" oral anticoagulants (NOACs).

4. Indanedione derivatives

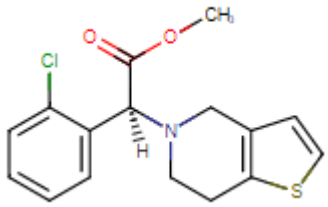
ANISINDIONE

Anisindione is a synthetic anticoagulant and an indanedione derivative. Its anticoagulant action is mediated through the inhibition of the vitamin K-mediated gamma-carboxylation of precursor proteins that are critical in forming the formation of active procoagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C and S, in the liver.



CLOPIDOGREL

Clopidogrel is a prodrug of a platelet inhibitor used to reduce the risk of myocardial infarction and stroke.



DRUGS USED IN CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) also known as Heart failure (HF), and congestive cardiac failure (CCF), is a chronic progressive condition that affects the pumping power of your heart muscles. CHF specifically refers to the stage in which fluid builds up around the heart and causes it to pump inefficiently. Heart failure can occur if the heart cannot pump (systolic) or fill (diastolic) adequately.

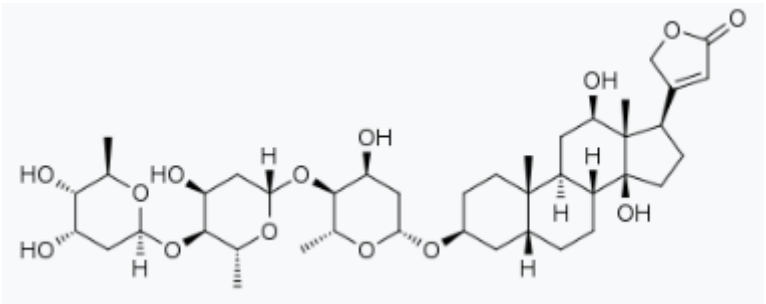
Causes of CHF

The major cause of heart failure is coronary artery disease (CAD). CAD reduces coronary blood flow and oxygen delivery to the myocardium. This leads to myocardial hypoxia and impaired function. Coronary artery bypass surgery and coronary stenting are frequently used in the treatment of coronary artery disease.

Another common cause of heart failure is myocardial infarction, which is the final and often fatal culmination of CAD. Arrhythmias such as severe bradycardia or tachycardia can also precipitate failure.

DIGOXIN

It is a common agent used to manage atrial fibrillation and the symptoms of heart failure.

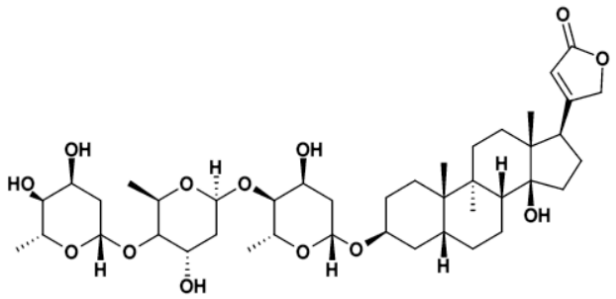


This drug originates from the foxglove plant, also known as the *Digitalis* plant.

It reversibly inhibits the Na-K ATPase enzyme, leading to various beneficial effects. The Na-K ATPase enzyme functions to maintain the intracellular environment by regulating the entry and exit of sodium, potassium, and calcium (indirectly).

DIGITOXIN

Digitoxin is a cardiac glycoside. It is a phytosteroid and is similar in structure and effects to digoxin. Unlike digoxin, it is eliminated via the liver, so could be used in patients with poor or erratic kidney function. It has a longer half-life than digoxin; toxic effects, which are similar to those of digoxin, are longer lasting.



It is used for the treatment and management of congestive cardiac insufficiency, arrhythmias and heart failure.

NESIRITIDE

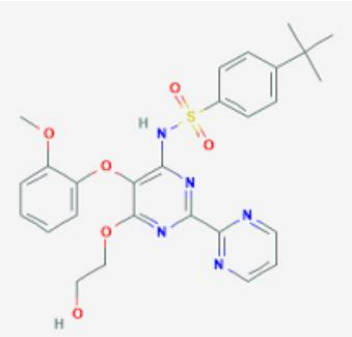
Nesiritide is a 32 amino acid recombinant human B-type natriuretic peptide. (Human BNP)

Nesiritide works by facilitating cardiovascular homeostasis through the negative regulation of the renin-angiotensin-aldosterone system. It promotes vasodilation, natriuresis, and diuresis.

It is used for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnoea at rest or with minimal activity.

BOSENTAN

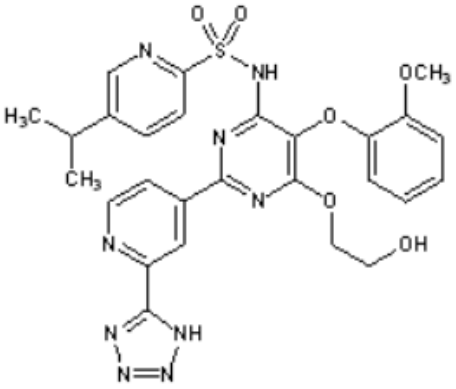
Bosentan is a dual endothelin receptor antagonist. It is used to treat pulmonary hypertension by blocking the action of endothelin molecules that would otherwise promote narrowing of the blood vessels and lead to high blood pressure.



Used in the treatment of pulmonary arterial hypertension (PAH), to improve exercise ability and to decrease the rate of clinical worsening (in patients with WHO Class III or IV symptoms).

TEZOSENTAN

Tezosentan is an intravenous endothelin receptor A/B antagonist. It was initially developed for vasodilation in patients with acute heart failure.



Investigated for use/treatment in congestive heart failure, liver disease, and heart disease.

Subject: *Medicinal Chemistry-II* **Unit No:** IV
Faculty: *Mrs. Sashmitha Samuel* **Lecture No:**
Topic: *Steroids* **Reference Book:**

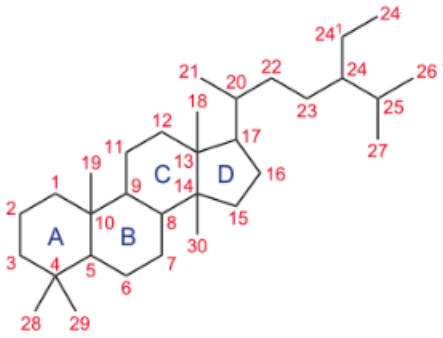
DRUGS ACTING ON ENDOCRINE SYSTEM

A steroid is a biologically active organic compound with four rings arranged in a specific molecular configuration. Steroids have two principal biological functions: as important components of cell membranes which alter membrane fluidity; and as signalling molecules

Chemistry of steroids

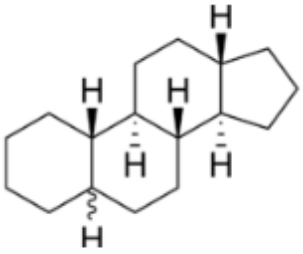
The steroid core structure is typically composed of seventeen carbon atoms, bonded in four "fused" rings: three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring).

General structure

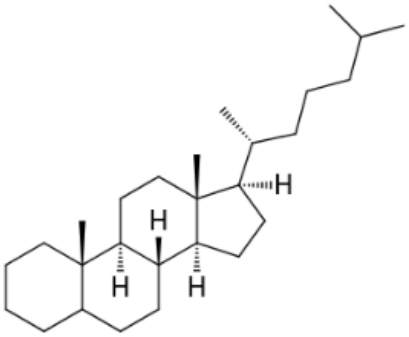


Nomenclature of steroids

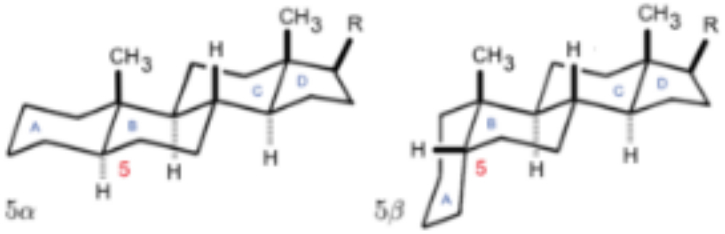
Gonane, also known as steran or cyclopentanoperhydrophenanthrene, the simplest steroid and the nucleus of all steroids and sterols, is composed of seventeen carbon atoms in carbon-carbon bonds forming four fused rings in a three-dimensional shape.



The three cyclohexane rings (A, B, and C in the first illustration) form the skeleton of a perhydro derivative of phenanthrene. The D ring has a cyclopentane structure. When the two methyl groups and eight carbon side chains (at C-17, as shown for cholesterol) are present, the steroid is said to have a cholestane framework.



The two common 5α and 5β stereoisomeric forms of steroids exist because of differences in the side of the largely planar ring system where the hydrogen (H) atom at carbon-5 is attached, which results in a change in steroid A-ring conformation.



Isomerisation at the C-21 side chain produces a parallel series of compounds, referred to as isosteroids.

In addition to the ring scissions (cleavages), expansions and contractions (cleavage and reclosing to a larger or smaller rings)—all variations in the carbon-carbon bond framework—steroids can also vary:

- in the bond orders within the rings,
- in the number of methyl groups attached to the ring (and, when present, on the prominent side chain at C17),
- in the functional groups attached to the rings and side chain, and
- in the configuration of groups attached to the rings and chain.[4]:2–9

Classification

- **Corticosteroids**:
    1. Glucocorticoids
    - Cortisol, a glucocorticoid whose functions include immunosuppression
    2. Mineralocorticoids
    - Aldosterone, a mineralocorticoid which helps regulate blood pressure through water and electrolyte balance
- **Sex steroids**:
    1. Progestogens:
        - Progesterone, which regulates cyclical changes in the endometrium of the uterus and maintains a pregnancy
    2. Androgens:
        - Testosterone, which contributes to the development and maintenance of male secondary sex characteristics
    3. Estrogens:
        - Estradiol, which contributes to the development and maintenance of female secondary sex characteristics

Metabolism of steroids

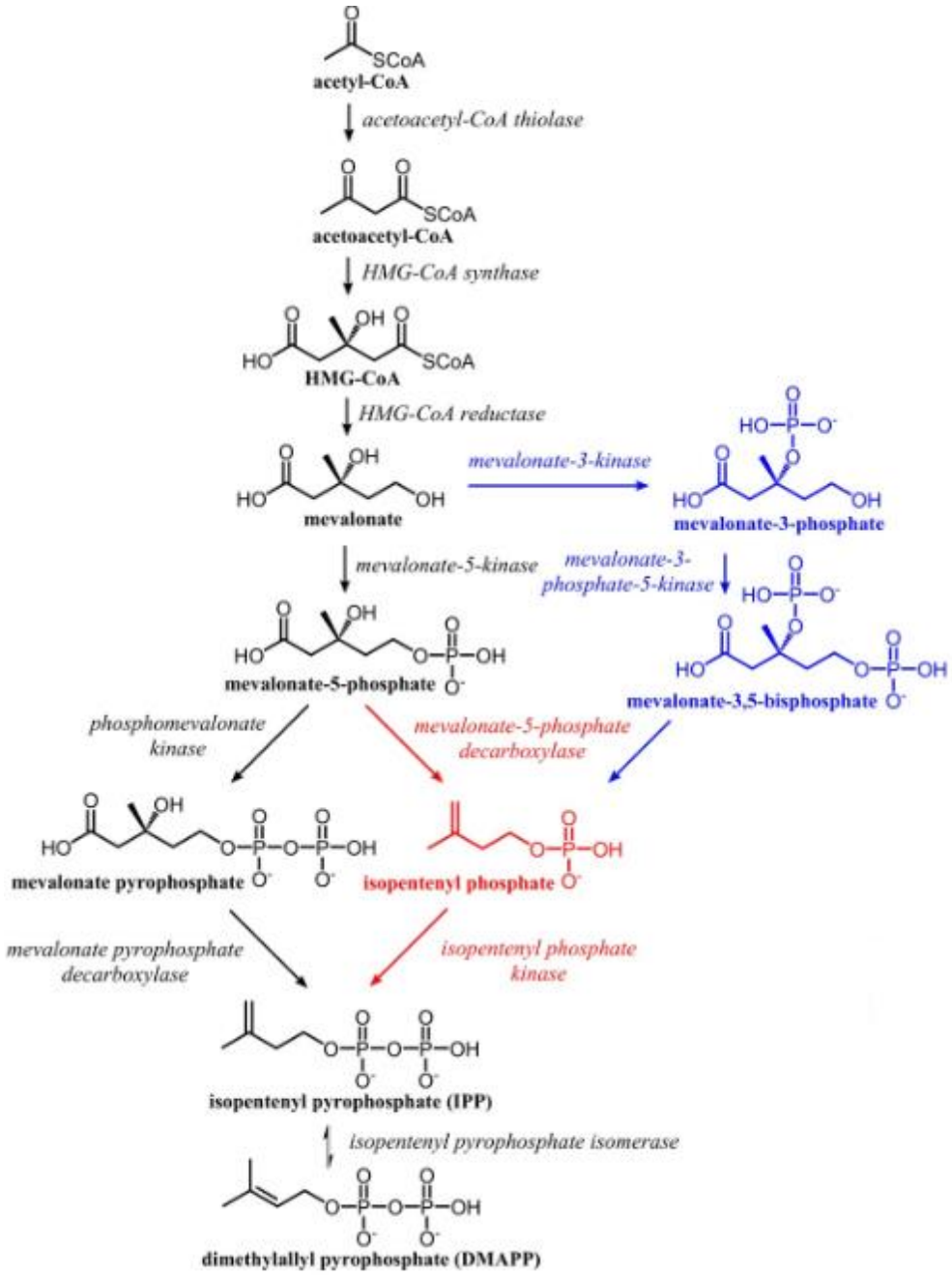
Steroid biosynthesis is an anabolic pathway which produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals (compared to many other organisms), making the pathway a common target for antibiotics and other anti-infection drugs. Steroid metabolism in humans is also the target of cholesterol-lowering drugs, such as statins.

In humans and other animals the biosynthesis of steroids follows the mevalonate pathway, which uses acetyl-CoA as building blocks for dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP).

In subsequent steps DMAPP and IPP join to form geranyl pyrophosphate (GPP), which synthesizes the steroid lanosterol. Modifications of lanosterol into other steroids are classified as steroidogenesis transformations.

Mevalonate pathway

The mevalonate pathway (also called HMG-CoA reductase pathway) begins with acetyl-CoA and ends with dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP).



SEX HORMONES

Sex steroids, also known as gonadocorticoids and gonadal steroids, are steroid hormones that interact with vertebrate steroid hormone receptors. The sex steroids include the androgens, Estrogens, and progestogens.

The two main classes of sex steroids are androgens and Estrogens, of which the most important human derivatives are testosterone and estradiol, respectively. Progestogens are considered as a third class of sex steroids, distinct from androgens and Estrogens. Progesterone is the most important and only naturally occurring human progestogen. In general, androgens are considered "male sex hormones", since they have

masculinizing effects, while Estrogens and progestogens are considered "female sex hormones" although all types are present in each sex at different levels.

FEMALE SEX HORMONES

The ovaries of sexually-mature females secrete both a mixture of *Estrogens (*of which 17 β-Estradiol is the most abundant and most potent) and *progesterone.*

Estrogens

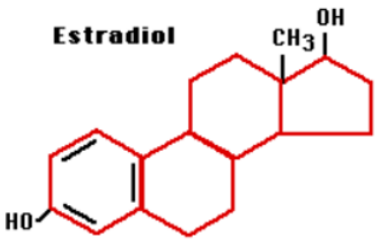
Estrogens are *steroids* and are primarily responsible for the conversion of girls into sexually-mature women including:

- development of breasts
- broadening of the pelvis
- participate in the monthly preparation of the body for a possible pregnancy
- participate in pregnancy if it occurs

Estrogens also have non-reproductive effects. For example, they antagonize the effects of the *parathyroid hormone*, minimizing the loss of calcium from bones and thus helping to keep bones strong. They also promote blood clotting.

OESTRADIOL

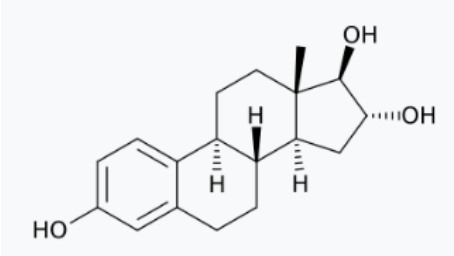
Estradiol (E2), or oestradiol, is an estrogen steroid hormone and the major female sex hormone. It is involved in the regulation of the estrous and menstrual female reproductive cycles.



Estradiol is responsible for the development of female secondary sexual characteristics such as the breasts, widening of the hips, and a female-associated pattern of fat distribution and is important in the development and maintenance of female reproductive tissues.

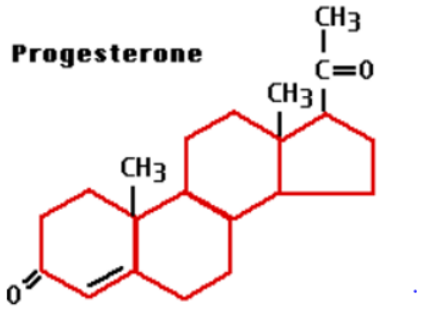
OESTRIOL

Estriol (E3), or oestriol, is a steroid, a weak estrogen, and a minor female sex hormone. It is one of three major endogenous estrogens, the others being estradiol and estrone.



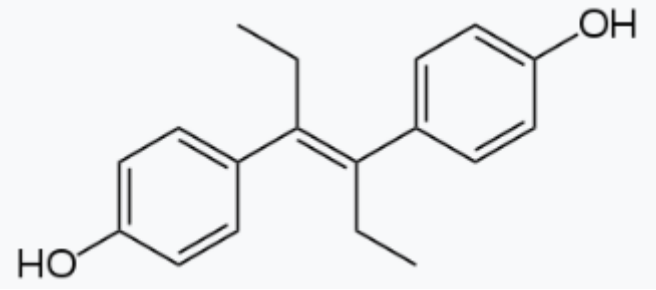
PROGESTERONE

Its production is stimulated by luteinizing hormone (LH), which is also stimulated by GnRH. Elevated levels of progesterone control themselves by the same negative feedback loop used by estrogen (and testosterone).



DIETHYL STILBESTROL

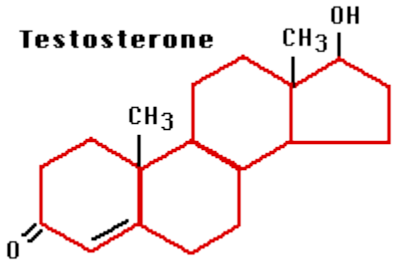
Diethylstilboestrol (DES), also known as stilbestrol or stilboestrol, is a nonsteroidal estrogen medication, which is rarely used.



It is only used in the treatment of prostate cancer and less commonly breast cancer.

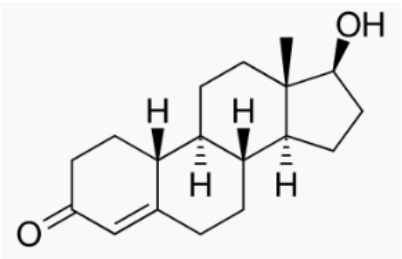
MALE SEX HORMONES

The principal androgen (male sex hormone) is testosterone. This steroid is manufactured by the interstitial (Leydig) cells of the testes. Secretion of testosterone increases sharply at puberty and is responsible for the development of the so-called secondary sexual characteristics (e.g., beard) of men.



NANDRALONE

Nandrolone, also known as 19-nortestosterone, is an androgen and anabolic steroid which is used in the form of esters such as nandrolone decanoate and nandrolone phenylpropionate. Nandrolone esters are used in the treatment of anaemias, cachexia, osteoporosis, breast cancer, and for other indications.



DRUGS FOR ERECTILE DYSFUNCTION

Erectile dysfunction (ED) is the inability to get or keep an erection firm enough to have sexual intercourse.

It is sometimes referred to as impotence, although this term is now used less often.

Erectile dysfunction can be a sign of a physical or psychological condition. It can cause stress, relationship strain and low self-confidence.

Patients suffering from erectile dysfunction should first be evaluated for any underlying physical and psychological conditions.

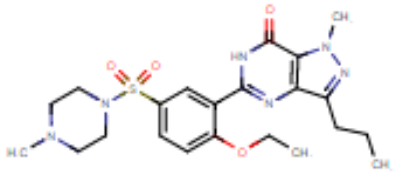
Therapy

The following oral medications stimulate blood flow to the penis to help treat ED:

- avanafil (Stendra)
- sildenafil (Viagra)
- tadalafil (Cialis)
- vardenafil (Levitra, Staxyn)

SILDENAFIL

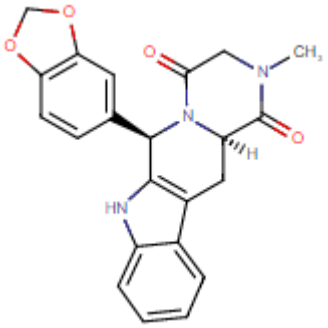
Sildenafil is an oral therapy for erectile dysfunction. It restores impaired erectile function by increasing blood flow to the penis.



MOA: Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP.Sildenafil has a peripheral site of action on erections.

TADALAFIL

Tadalafil is an orally administered drug used to treat male erectile dysfunction (impotence).



Tadalafil's distinguishing pharmacologic feature is its longer half-life (17.5 hours) compared with Viagra and Levitra (4-5 hours). This longer half-life results in a longer duration of action and is, in part, responsible for the Cialis nickname of the "weekend pill." This longer half-life also is the basis of current investigation for tadalafil's use in pulmonary arterial hypertension as a once-daily therapy.

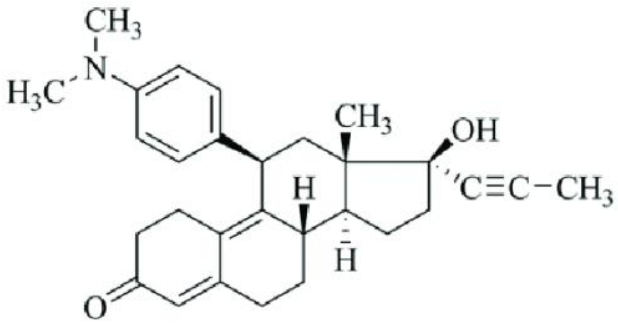
MOA: Tadalafil inhibits PDE5 and thereby enhances erectile function by increasing the amount of cGMP available.

ORAL CONTRACEPTIVES

The feedback inhibition of GnRH secretion by Estrogens and progesterone provides the basis for the most widely-used form of contraception. Their inhibition of GnRH prevents the mid-cycle surge of LH and ovulation. Hence there is no egg to be fertilized.

MIFEPRISTONE

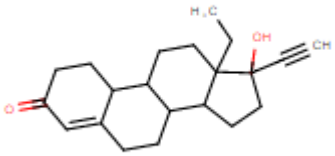
It is a synthetic steroid related to progesterone.



Use of mifepristone is generally limited to the first seven weeks of pregnancy. It has been used for many years in some countries.

NORGESTREL

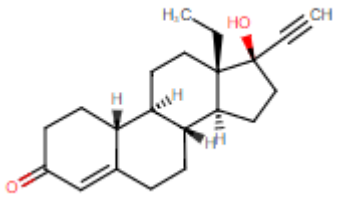
Norgestrel is a progestin, or a synthetic progestogen, and hence is an agonist of the progesterone receptor, the biological target of progestogens like progesterone. It has weak androgenic activity and no other important hormonal activity.



MOA: Norgestrel (and more specifically the active stereoisomer levonorgestrel) binds to the progesterone and estrogen receptors within the female reproductive tract, the mammary gland, the hypothalamus, and the pituitary. Once bound to the receptor, progestins like levonorgestrel will slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH (luteinizing hormone) surge. Loss of the LH surge inhibits ovulation and thereby prevents pregnancy.

LEVONORGESTREL

Levonorgestrel (LNG) is a synthetic progestogen similar to Progesterone used in contraception and hormone therapy. Also known as Plan B, it is used as a single agent in emergency contraception, and as a hormonal contraceptive released from an intrauterine device, commonly referred to as an IUD.



Oral contraceptives containing levonorgestrel suppress gonadotropins, inhibiting ovulation.

CORTICOSTEROIDS

Corticosteroids are a class of drug that lowers inflammation in the body. They also reduce immune system activity. Because they ease swelling, itching, redness, and allergic reactions, doctors often prescribe them to help treat diseases like: asthma. arthritis.

Therapeutic uses:

- **Addison's disease.** This occurs when your body doesn't make enough cortisol. Corticosteroids can make up the difference.
- **Organ transplants.** Corticosteroids help suppress the immune system and reduce the likelihood of organ rejection.
- **Inflammation.** In cases when inflammation causes damage to important organs, corticosteroids can save lives. Inflammation occurs when the body's white blood cells are mobilized to protect against infection and foreign substances.
- **Autoimmune diseases.** Sometimes the immune system doesn't work correctly, and people develop inflammatory conditions that cause damage instead of protection. Corticosteroids decrease the inflammation and prevent this damage. They also affect how white blood cells work and reduce the activity of the immune system.

Adverse effects

Side effects from oral steroids may include acne, blurred vision, water retention, increased appetite and weight gain, stomach irritation, difficulty sleeping, mood changes and mood swings, glaucoma, high blood pressure,

muscle weakness, delayed wound healing, stomach ulcers, Cushing syndrome, osteoporosis, depression, stunted growth in children etc.

Examples

Some common naturally occurring steroid hormones are cortisol , corticosterone , cortisone and aldosterone.

The main corticosteroids produced by the adrenal cortex are cortisol and aldosterone.

Classification

I. Based on administration

Corticosteroids can be systemic or localized. Localized steroids target a specific part of the body. These can be applied through:

- skin creams
- eye drops
- ear drops
- inhalers to target the lungs

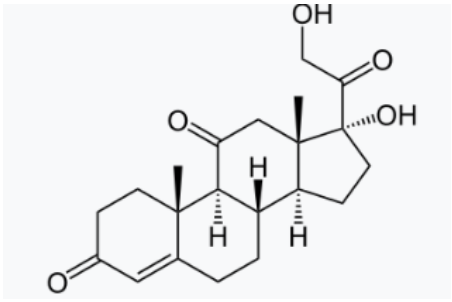
Systemic steroids move through the blood to assist more parts of the body. They can be delivered through oral medications, with an IV, or with a needle into a muscle. Localized steroids are used to treat conditions like asthma and hives. Systemic steroids treat conditions such as lupus and multiple sclerosis.

II. Based on function

- Glucocorticoids such as cortisol affect carbohydrate, fat, and protein metabolism, and have anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.
- Mineralocorticoids such as aldosterone are primarily involved in the regulation of electrolyte and water balance by modulating ion transport in the epithelial cells of the renal tubules of the kidney.

CORTISONE

Cortisone is a pregnane (21-carbon) steroid hormone. It is one of the main hormones released by the adrenal gland in response to stress. In chemical structure, it is a corticosteroid closely related to cortisol. It is used to treat a variety of ailments and can be administered intravenously, orally, intra-articularly (into a joint), or transcutaneously.



Cortisone, a glucocorticoid, and epinephrine (adrenaline) are the main substances released by the body as a reaction to stress. They elevate blood pressure and prepare the body for a fight or flight response.

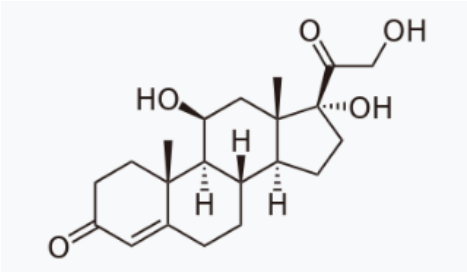
A cortisone injection can be used to give short-term pain relief and reduce the swelling from inflammation of a joint, tendon, or bursa in, for example, the joints of the knee, elbow, and shoulder and into a broken coccyx.

Cortisone is also used by dermatologists to treat keloids, relieve the symptoms of eczema and atopic dermatitis, and stop the development of sarcoidosis.

HYDROCORTISONE

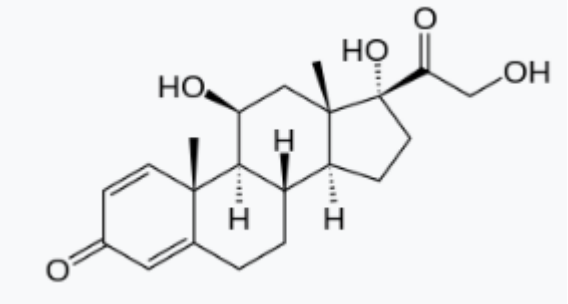
Hydrocortisone, also known as 11β,17α,21-trihydroxypregn-4-ene-3,20-dione, is a naturally occurring pregnane steroid.

It is the pharmaceutical term for cortisol used in oral administration, intravenous injection, or topical application.



PREDNISOLONE

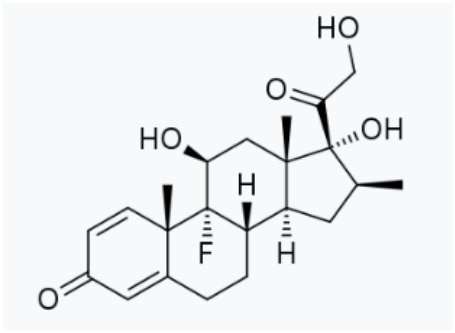
Prednisolone is a steroid medication used to treat certain types of allergies, inflammatory conditions, autoimmune disorders, and cancers.



It is used by mouth, injection into a vein, as a skin cream, and as eye drops. Common side effects with long term use include bone loss, weakness, yeast infections, and easy bruising. While short-term use in the later part of pregnancy is safe, long-term use or use in early pregnancy is occasionally associated with harm to the baby.

BETAMETHASONE

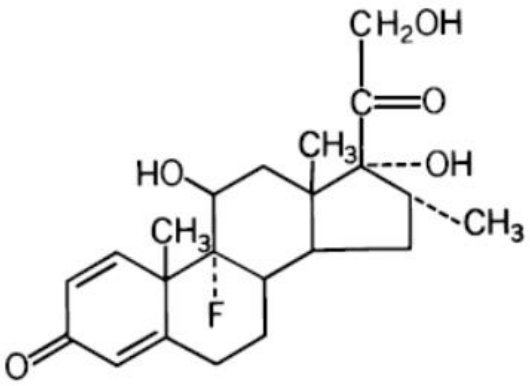
Betamethasone is a steroid medication used for a number of diseases including rheumatic disorders such as rheumatoid arthritis and systemic lupus erythematosus, skin diseases such as dermatitis and psoriasis, allergic conditions such as asthma and angioedema, preterm labour to speed the development of the baby's lungs, Crohn's disease, cancers such as leukemia, and along with fludrocortisone for adrenocortical insufficiency, among others.



DEXAMETHASONE

It is a steroid that prevents the release of substances in the body that cause inflammation.

It is designated chemically as 9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1, 4-diene, 3, 20-dione and the structural formula is:



Dexamethasone is used to treat many different conditions such as allergic disorders, skin conditions, ulcerative colitis, arthritis, lupus, psoriasis, or breathing disorders.

THYROID AND ANTI THYROID DRUGS

Thyroid gland is located in the middle of the neck and surrounds the trachea like a shield. It produces two hormones: thyroid hormone and calcitonin. The thyroid gland uses iodine to produce thyroid hormones that regulate body metabolism.

Thyroid agents either replace or remove hormones to prevent deficiency and excess. Thyroid agents include thyroid hormones (T_3, T_4, TSH) and antithyroid drugs **(**further classified as thioamides and iodine solution).

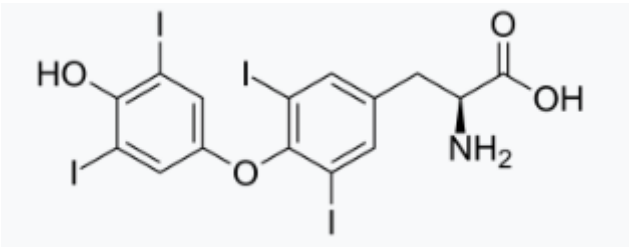
THYROID AGENTS OR HORMONES

Thyroid hormones are used to replace the low or absent levels of natural thyroid hormone and suppress the overproduction of TSH by the pituitary.

These can contain both natural and synthetic thyroid hormone.

L-THYROXINE

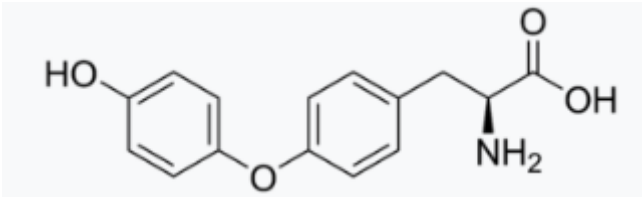
Levothyroxine, also known as L-thyroxine, is a manufactured form of the thyroid hormone thyroxine (T_4)



Adverse effects: Long-term suppression of TSH values below normal values will frequently cause cardiac side-effects and contribute to decreases in bone mineral density (low TSH levels are also well known to contribute to osteoporosis).

L-THYRONINE

Thyronine is a deiodinated form of thyroxine. It is chemically l-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl] alanine.



ANTI THYROID AGENTS

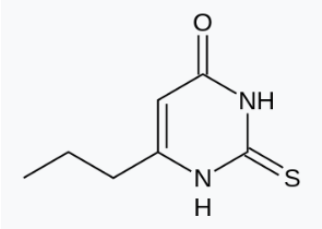
An antithyroid agent is a hormone antagonist acting upon thyroid hormones.

MOA:

The mechanisms of action are not completely understood. Some scientists believe that anti-thyroids inhibit iodination of tyrosyl residues in thyroglobulin. It is thought that they inhibit the thyroperoxidase catalysed oxidation reactions by acting as substrates for the postulated peroxidase-iodine complex, thus competitively inhibiting the interaction with the amino acid tyrosine.

PROPYL THIO URACIL

Propylthiouracil (PTU) is a medication used to treat hyperthyroidism. This includes hyperthyroidism due to Graves' disease and toxic multinodular goitre.

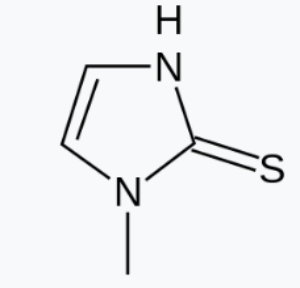


MOA: PTU inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis by oxidizing the anion iodide (I^-) to iodine (I^0), facilitating iodine's addition to tyrosine residues on the hormone precursor thyroglobulin. This is one of the essential steps in the formation of thyroxine (T4).

Adverse effects: Common side effects include itchiness, hair loss, swelling, vomiting, muscle pains, numbness, and headache. Other severe side effects include liver problems and low blood cell counts.

METHIMAZOLE

Methimazole, also known as **Thiamazole**, is a medication used to treat hyperthyroidism.



MOA: Thiamazole inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis.

Adverse effects: Common side effects include itchiness, hair loss, nausea, muscle pain, swelling, and abdominal pain. Severe side effects may include low blood cell counts, liver failure, and vasculitis.

ANTI DIABETIC AGENTS

Diabetes mellitus (DM) is one of the most prevalent chronic diseases and has been a leading cause of death in the last decades.

DM is described as a group of metabolic disorders characterized by chronic hyperglycaemia resulting from defects in insulin action, insulin secretion, or both.

This deficiency leads to disturbances in the metabolism of carbohydrates, fat and protein, which causes systemic complications and co-morbidities namely cardiovascular and renal failure. The most predominant types of DM are type 1 diabetes mellitus (T1DM) and T2DM.

1. T1DM is a chronic autoimmune disease caused by the pathogenic action of T lymphocytes on insulin-producing β-cells. Typically, the symptoms of T1DM appear in patients with less than 30 years, being known as juvenile-onset diabetes.
2. T2DM is characterized by hyperglycaemia that results from insulin resistance plus variable degrees of insufficient insulin secretion. The complexity of T2DM led to the establishment of an intermediate state, often called as pre-diabetes. In this prodromal stage of T2DM, the patients present glycaemic values higher than normal, but lower than T2DM thresholds.

Treatments include

(1) agents that increase the amount of insulin secreted by the pancreas

(2) agents that increase the sensitivity of target organs to insulin

(3) agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract

INSULIN AND ITS PREPARATIONS

Insulin is a hormone secreted by the pancreatic β-cells into the blood, in response to increased glucose concentration. Besides the direct involvement with glucose metabolism, insulin has a controlling influence on

the metabolism of fats and proteins. When the body is unable to produce insulin or develops insulin resistance, one of the possible treatments is the administration of an exogenous supply of this hormone.

Insulins are typically characterized by the rate at which they are metabolized by the body, yielding different peak times and durations of action. Faster-acting insulins peak quickly and are subsequently metabolized, while longer-acting insulins tend to have extended peak times and remain active in the body for more significant periods.

Examples of rapid acting insulins (peak time at ~1 hour) include:

- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)

Examples of short acting insulins (peak time between 2-4 hours) include:

- Regular insulin (Humulin R, Novolin R)
- Prompt insulin zinc (Semilente)

Examples of intermediate acting insulins (peak time between 4-10 hours) include:

- Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N)
- Insulin zinc (Lente)

Examples of long-acting insulins (duration ~24 hours, often with no peak) include:

- Extended insulin zinc insulin (Ultra Lente)
- Insulin glargine (Lantus)

INSULIN SECRETAGOGUES

SULFONYL UREAS

Sulfonylureas became the first pharmacological option to treat non-insulin-dependent DM, besides insulin injections.

First generation drugs- The first sulfonylureas developed were tolbutamide, chlorpropamide, acetohexamide and tolazamide.

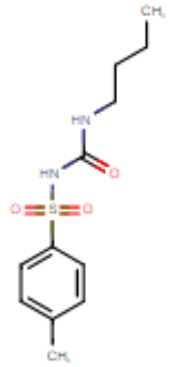
Second generation drugs- gliclazide, glipizide and glibenclamide (glyburide).

MOA: Sulfonylureas perform their secretagogue action by activating β-cell sulfonylurea receptor 1 (SUR 1), leading to closure of ATP-dependent potassium channels. Consequently, there is an uptake of extracellular

calcium, activating a cytoskeletal system, which causes translocation of secretory granules to the cell surface and extrusion of insulin through exocytosis.

TOLBUTAMIDE

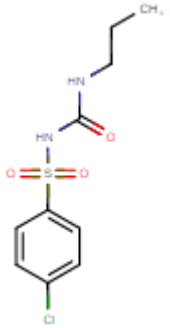
Tolbutamide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM).



Tolbutamide, a first-generation sulfonylurea antidiabetic agent, is used with diet to lower blood glucose levels in patients with diabetes mellitus type II.

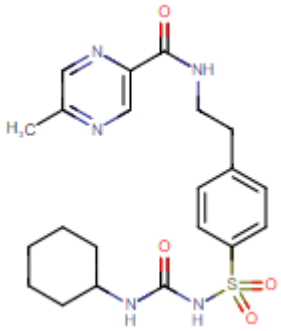
CHORPROPAMIDE

Chlorpropamide, a second-generation sulfonylurea antidiabetic agent, is used with diet to lower blood glucose levels in patients with diabetes mellitus type II.



GLIPIZIDE

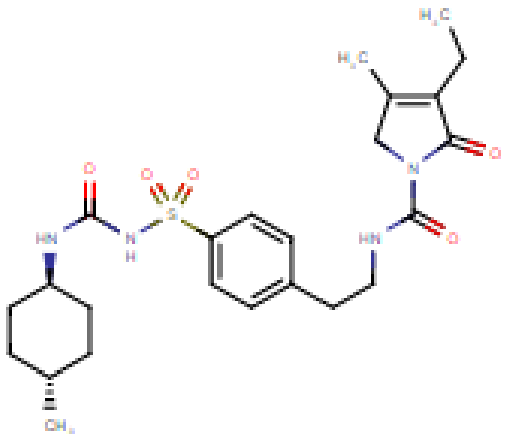
Glipizide is an oral hypoglycaemic agent in the second-generation sulfonylurea drug class that is used to control blood sugar levels in patients with type 2 diabetes mellitus.



Like other sulfonylureas, glipizide may work on pancreatic delta (δ) cells and alpha (α) cells to stimulate the secretion of somatostatin and suppress the secretion of glucagon, which are peptide hormones that regulate neuroendocrine and metabolic pathways.

GLIMEPIRIDE

Glimepiride is a member of the second-generation sulfonylurea (SU) drug class used for the management of type 2 diabetes mellitus (T2DM) to improve glycemic control.

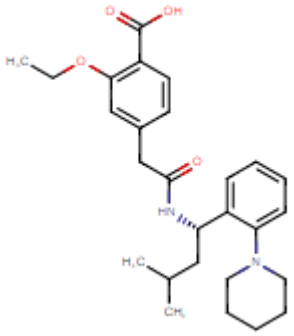


MEGLITINIDES

Meglitinides are insulin secretagogues with a similar mechanism of action to sulfonylureas, acting on ATP-dependent potassium channels. They offer an alternative to sulfonylurea treatment, but have almost the same disadvantages and a more complex dosing schedule. Three meglitinides have been used in clinical practice: nateglinide, repaglinide and mitiglinide.

REPAGLINIDE

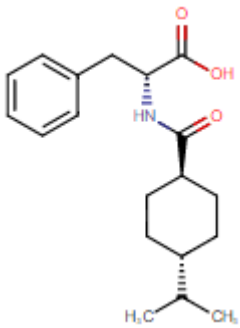
Repaglinide, a carbamoyl methyl benzoic acid derivative, was the first meglitinide analogue to become available for clinical use.



MOA: It promotes insulin secretion by closing ATP-dependent potassium channels in the membrane of pancreatic β- cells, but is ineffective in the absence of extracellular calcium. Repaglinide binds to a nearby location of the receptor site for sulfonylureas drugs, but generates a more rapid reaction.

NATEGLINIDE

Nateglinide, a D-phenylalanine derivative, quickly and reversibly binds to the SUR 1 like sulfonylureas and has specificity for pancreatic SURs. Thus, the binding site differs from that of repaglinide.



Nateglinide inhibits the ATP-dependent potassium channels faster than repaglinide but, on the other hand, there is a more rapid reversal of the inhibition of the channel when taking nateglinide in comparison with repaglinide. Like repaglinide, nateglinide is effective in combination with metformin or thiazolidinediones.

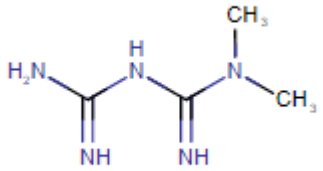
INSULIN SENSITISERS

Insulin sensitizers address the core problem in type 2 diabetes. They lead to a decrease in insulin resistance and a clinically significant reduction of plasma fasting insulin levels.

BIGUANIDES

METFORMIN

Metformin has been used to treat T2DM for over 50 years. It is usually described as the first line treatment to this disorder, along with diet and exercise.



MOA: Metformin is an insulin-sensitizing drug that exerts its antihyperglycemic effects by blocking liver gluconeogenesis through regulation of the gluconeogenic flux, rather than direct inhibition of gluconeogenic gene expression. It also increases skeletal muscle uptake of glucose and reduces the absorption of glucose in the intestinal mucosa.

Toxicity: Metformin decreases liver uptake of lactate, thereby increasing lactate blood levels which may increase the risk of lactic acidosis.

THIAZOLIDINE DIONES

Thiazolidinediones, also termed glitazones, are a class of oral antidiabetic agents that were originally developed in the early 1980s as antioxidants. The blood glucose-lowering potential of this class of drugs was observed after the synthesis of ciglitazone, the first thiazolidinedione.

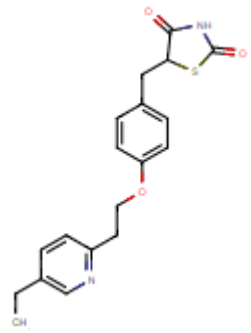
Two thiazolidinediones are available for clinical use: rosiglitazone and pioglitazone.

Adverse effects: An adverse effect of this class is fluid retention, making thiazolidinediones contraindicated in patients with heart failure, which is one of the leading causes of death among T2DM patients.

MOA: Thiazolidinediones are potent synthetic activators of the nuclear receptor peroxisome proliferator-activated receptor (PPAR). PPAR is abundantly expressed in key target tissues for insulin action such as adipose tissue, but is also present in muscle, liver, endothelium and pancreatic β-cells.

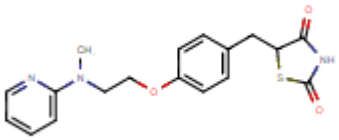
PIOGLITAZONE

Pioglitazone, a potent PPAR agonist, increases insulin stimulated glucose uptake in peripheral tissues as well as insulin sensitivity in hepatic and adipose tissue. It also causes a minor activation of PPARγ, which is related with anti-inflammatory effects, as well as with the decrease of plasma triglyceride levels.



ROSIGLITAZONE

Rosiglitazone acts as a highly selective and potent agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver.



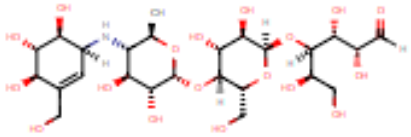
GLUCOSIDASE INHIBITORS

Complex carbohydrates are enzymatically degraded to monosaccharides by the action of α-galactosidases, α-amylase and α- glucosidases. Thus, inhibitors of intestinal α-glucosidase enzymes modulate the rate of digestion of complex carbohydrates and disaccharides by competitively and reversibly inhibiting α-glucosidases present in the brush border membrane of enterocytes that line the intestinal villi. Consequently, the digestion of carbohydrates and absorption of monosaccharides in the proximal jejunum are decreased or incomplete in the distal jejunum and ileum. Therefore, the rise in postprandial plasma glucose levels is diminished and/or delayed. α-glucosidase inhibitors allow the pancreatic β-cell more time to augment insulin secretion in response to the increase in plasma glucose level.

Adverse effects: The most common are flatulence, diarrhoea, and abdominal discomfort caused by altered bacterial metabolism of disaccharides in the colon.

ACARBOSE

Acarbose was the first α-glucosidase inhibitor described. It is a pseudotetrasaccharide of microbial origin (Actinoplanes utahensis) consisting of a maltose molecule linked to acarvosine with a nitrogen bound between

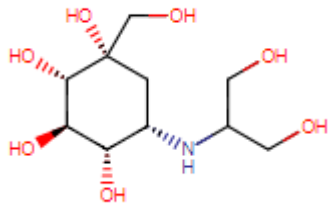


the first and second glucose unit.

It is used for treatment and management of diabetes type II (used in combination therapy as a second- or third-line agent).

VOGLIBOSE

Voglibose is a valiolamine derivative, which is produced by Streptomyces hygroscopicus.



It is specifically used for lowering post-prandial blood glucose levels thereby reducing the risk of macrovascular complications.

LOCAL ANAESTHETICS

Local anesthetics (LAs) are drugs that block the sensation of pain in the region where they are administered. LAs act by reversibly blocking the sodium channels of nerve fibers, thereby inhibiting the conduction of nerve impulses.

Loss of motor function and sensation of touch and pressure follow, depending on the duration of action and dose of the LA used.

Local anesthesia is used when:

- surgery is minor and does not require general or regional anesthesia
- the procedure can be done quickly and the patient does not need to stay overnight
- the operation does not need the muscles to be relaxed or for the patient to be unconscious

Examples include dental surgery, the removal of a verruca, a mole, or a cataract, and biopsies.

Classification

LAs are divided into two groups based on their chemical structure.

1. The amide group (lidocaine, prilocaine, mepivacaine, etc.) is safer and, hence, more commonly used in clinical practice.
2. The ester group (procaine, tetracaine) has a higher risk of causing allergic reactions or systemic toxicity and is, therefore, reserved for patients with known allergies to drugs of the amide group.

Adverse effects: Overdose or inadvertent injection of an LA into a blood vessel can cause systemic toxicity, which mainly affects the CNS (tinnitus, seizures, etc.) and the CVS (bradycardia, arrhythmias, etc.).

Factors that affect the efficacy of LA

- Use of vasoconstrictors (e.g., adrenaline) reduces bleeding and systemic absorption of LAs, leading to a prolonged anesthetic effect.
- Inflamed/infected tissue: decreased efficacy of LAs
- LAs are composed of a lipophilic group and a hydrophilic group, and permeability depends on which group is predominant.

Therapeutic uses

Topical application (lidocaine, tetracaine, prilocaine)

- Useful in children before performing minor invasive procedures (e.g., venipuncture, intravenous catheter placement)
- As a gel: prior to catheterizing the bladder (as a lubricant and as an LA)
- As a mouth gargle/spray: prior to performing indirect laryngoscopy, endoscopy, etc.;
  in pharyngitis with odynophagia

Infiltration

- Into the skin/subcutaneous tissue: for skin surgery (skin biopsy, suturing, foreign body extraction, etc.)
- Into the epidural space for epidural anesthesia
- Into the subarachnoid space for spinal anesthesia

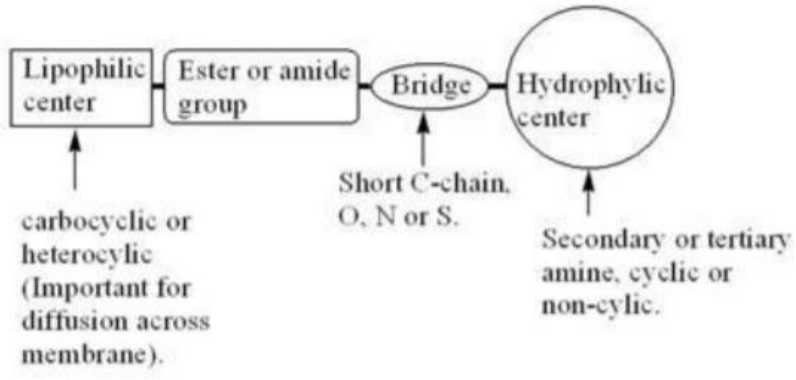
Adverse effects

- Complications are uncommon
- Allergy

  Acute: anaphylaxis (rare)

  Delayed: pruritic rash with blisters at site of LA injection within 72 hours of administration

SAR OF LOCAL ANAESTHETIC



Aryl group

- The clinically useful local anaesthetics of this series possess an aryl radical attached directly to the carbonyl group.

- Substitution of aryl group with substituents that increase the electron density of the carbonyl oxygen enhances activity.

- Favourable substituents in aryl ring include (electron-donating groups) alkoxy (propoxycaine), amino (procaine), and alkylamino (tetracaine) groups in the para or ortho positions.

- Aryl aliphatic radicals that contain a methylene group between the aryl radical and the carbonyl group result in compounds that have not found clinical use.

Bridge X

- The bridge X may be carbon, oxygen, nitrogen, or sulphur.

- In an isosteric procaine series, anaesthetic potency decreased in the following order: sulphur, oxygen, carbon, nitrogen.

• These modifications also affect duration of action and toxicity. In general, amides (X=N) are more resistant to metabolic hydrolysis than esters (X=O). Thioesters (X=S) may cause dermatitis.

Amino alkyl group

• The amino alkyl group is not necessary for local anaesthetic activity, but it is used to form water-soluble salts (HCl salts).

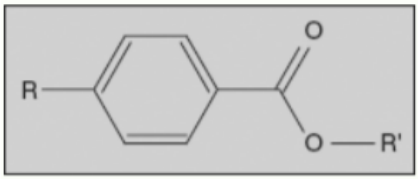
• Tertiary amines result in more useful agents. The secondary amines appear to be of longer activity, but they are more irritating; primary amines are not very active and cause irritation.

• The tertiary amino group may be diethylamino, piperidine, or pyrrolidino, leading to the products that exhibit essentially the same degree of activity.

• The more hydrophilic morpholino group usually leads to diminished potency.

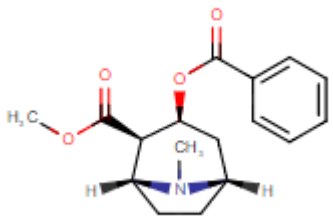
• Some analogues have no amino group at all, such as benzocaine. They are active but have poor water solubility.

BENZOIC ACID DERIVATIVES



COCAINE

An alkaloid ester extracted from the leaves of plants including coca. It is a local anesthetic and vasoconstrictor and is clinically used for that purpose, particularly in the eye, ear, nose, and throat. It also has powerful central nervous system effects similar to the amphetamines and is a drug of abuse.



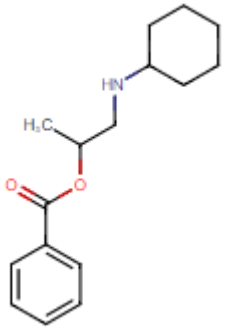
It is indicated for the introduction of local (topical) anesthesia of accessible mucous membranes of the oral, laryngeal and nasal cavities.

HEXYLCAINE

Hexylcaine hydrochloride is also known as cyclaine and osmocaine.

Hexylcaine is a local ester-class anesthetic.

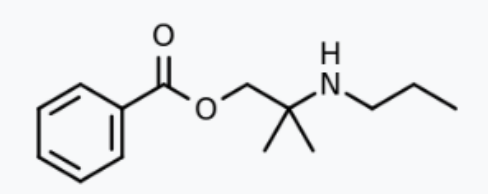
It is a short acting local anesthetic that acts through inhibition of sodium channels.



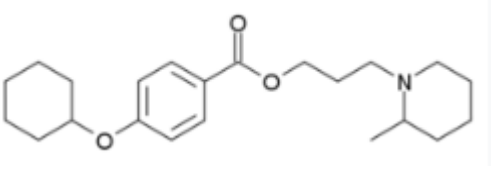
Symptoms of anesthetic overdose include headache, tinnitus, circumoral and tongue paresthesias, restlessness, talkativeness, facial twitching, convulsions, respiratory arrest, and cardiac depression.

MEPRYLCAINE

Meprylcaine (also known as **Epirocaine** and **Oracaine**) is a local anesthetic with stimulant properties that is structurally related to dimethocaine.



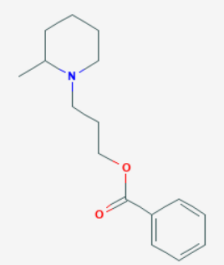
CYCLOMETHYCAINE



It is also known as Surfacaine.It is a benzoate ester.

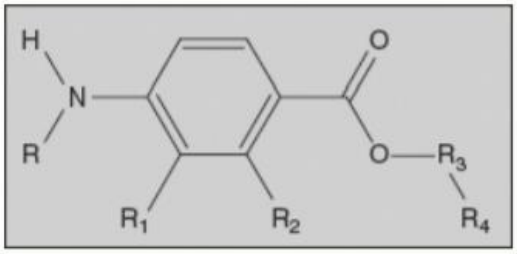
PIPEROCAINE

Piperocaine (Metycaine) is a local anesthetic drug. It is an ester and primarily is a sodium channel blocker. **Piperocaine** can partially inhibit dopamine. It is known as a alpha-1-proteinase inhibitor.



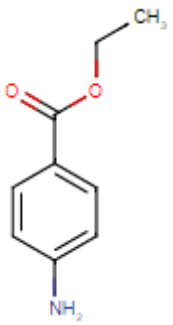
Used in the form of its hydrochloride as a local or spinal anesthetic and in dental anesthesia.

AMINO BENZOIC ACID DERIVATIVES



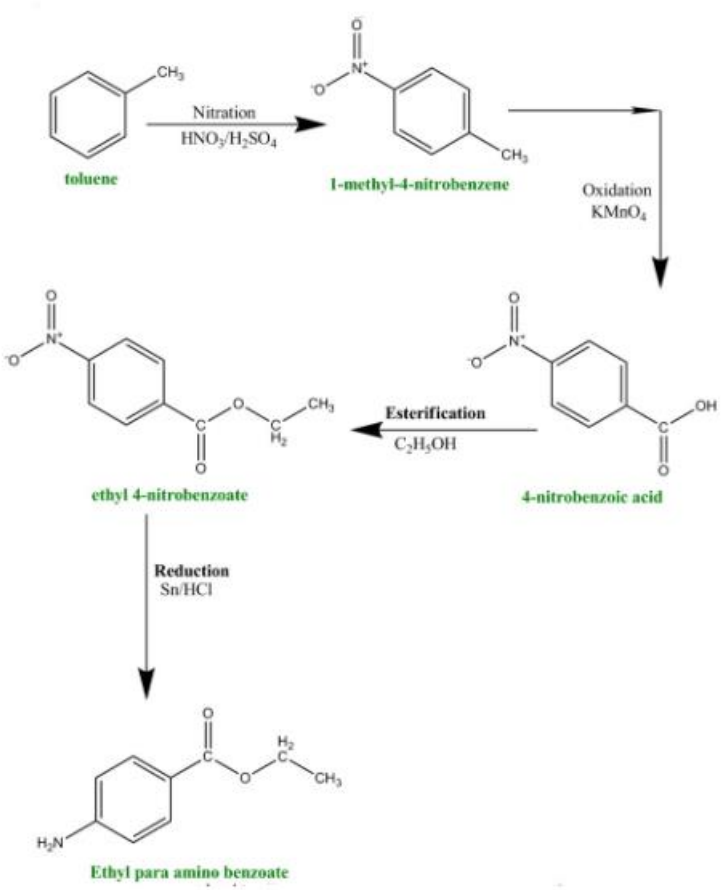
BENZOCAINE

A surface anesthetic that acts by preventing transmission of impulses along nerve fibers and at nerve endings.



Benzocaine binds to sodium channels and reversibly stabilizes the neuronal membrane which decreases its permeability to sodium ions. Depolarization of the neuronal membrane is inhibited thereby blocking the initiation and conduction of nerve impulses.

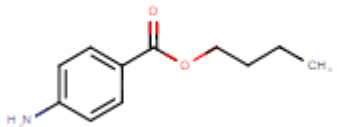
Synthesis



BUTAMBEN

Butamben is a local anesthetic in the form of n-butyl-p-aminobenzoate.

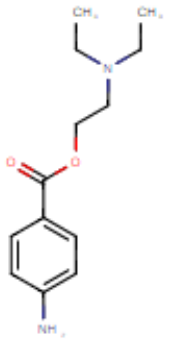
Due to its very low water solubility, butamben was considered of low usability as it is only suitable to be used as a topical anesthesia.



Butamben acts by inhibiting the voltage-gated calcium channels in dorsal root ganglion neurons.

PROCAINE

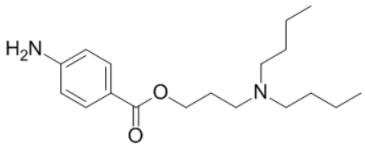
A local anesthetic of the ester type that has a slow onset and a short duration of action.



Procaine acts mainly by inhibiting sodium influx through voltage gated sodium channels in the neuronal cell membrane of peripheral nerves. Procaine has also been shown to bind or antagonize the function of N-methyl-D-aspartate (NMDA) receptors as well as nicotinic acetylcholine receptors and the serotonin receptor-ion channel complex.

Procaine is an anesthetic agent indicated for production of local or regional anesthesia, particularly for oral surgery. It is mainly used for infiltration anesthesia, peripheral nerve block, and spinal block.

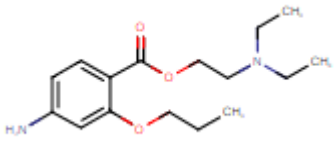
BUTACAINE



It is a local anesthetic that is an ester of para-aminobenzoic acid.

PROPOXYCAINE

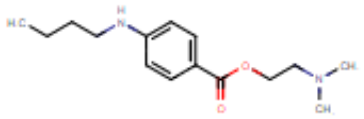
Propoxycaine is a local anesthetic of the ester type that has a rapid onset of action and a longer duration of action than procaine hydrochloride.



Propoxycaine binds to and blocks voltage-gated sodium channels, thereby inhibiting the ionic flux essential for the conduction of nerve impulses. This results in a loss of sensation.

TERRACAINE

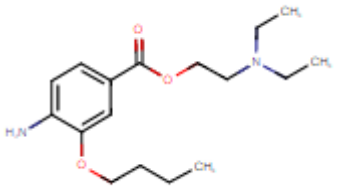
Tetracaine is an ester local anaesthetic currently available in combination with lidocaine as a cream and patch.



The most common adverse effects with the combination cream are localized reactions such as: erythema (47%), skin discoloration (16%), and edema (14%). Systemic adverse events were less common, occurring at a rate of <1% and included vomiting, headache, dizziness, and fever.

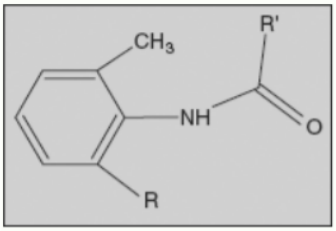
BENOXINATE

Oxybuprocaine (also known as Benoxinate) is a local anesthetic, which is used especially in ophthalmology and otolaryngology. Oxybuprocaine binds to sodium channels and reversibly stabilizes the neuronal membrane which decreases its permeability to sodium ions.



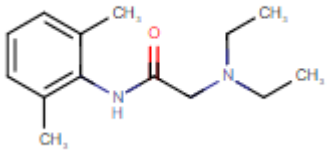
It is used to temporarily numb the front surface of the eye so that the eye pressure can be measured or a foreign body removed.

ANILIDE/LIDOCAINE DERIVATIVES



LIGNOCAINE

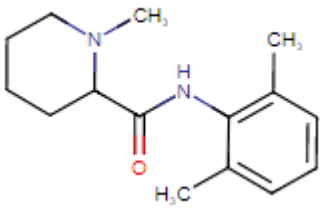
Its principal mode of action in acting as a local anesthetic that numbs the sensations of tissues means the agent is indicated for facilitating local anesthesia for a large variety of surgical procedures.



It is an anesthetic of the amide group indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks.

MEPIVACAINE

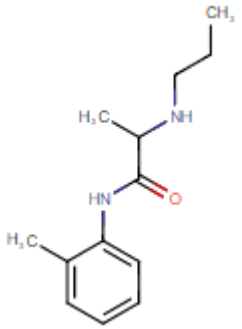
A local anesthetic that is chemically related to bupivacaine but pharmacologically related to lidocaine.



Mepivacaine is effective topically only in large doses and therefore should not be used by this route. It is used for production of local or regional analgesia and anesthesia by local infiltration, peripheral nerve block techniques, and central neural techniques including epidural and caudal blocks.

PRILOCAINE

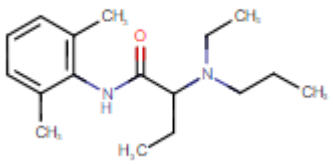
It is a local anesthetic that is similar pharmacologically to lidocaine.



Prilocaine binds to the intracellular surface of sodium channels which blocks the subsequent influx of sodium into the cell.

ETIDOCAINE

Etidocaine is marketed under the name Duranest.

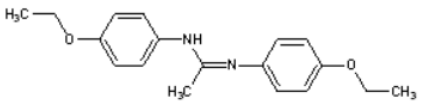


It is an injectable local anesthetic during surgery, labour, and delivery.

Etidocaine has a long duration of activity, but has the main disadvantage of increased bleeding during oral surgery.

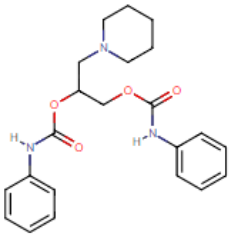
MISCELLANEOUS

PHENACAINE



It is approved for ophthalmic use.

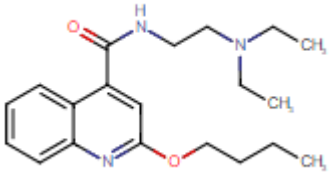
DIPERODON



Diperodon is one of several phenyl urethane derivatives of dialkyl amino alcohols which have demonstrated significant local anaesthetic activity.

DIBUCAINE

A local anesthetic of the amide type now generally used for surface anesthesia. It is one of the most potent and toxic of the long-acting local anesthetics and its parenteral use is restricted to spinal anesthesia.



It is used for production of local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks.