SOUTH VALLY UNIVERSITY

FACULTY OF SCIENCE
AT QENA

Chemotherapy

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العام الجامعي
٢٠٢٣

المحتوي :-

Chemotherapy

Paul ehrlich (1907 s) is the first scientist who introduced the term " chemotherapy “ . The higher plants made the earliest druge discovered , herbal remedies have been important throughout human history , crude plant product such as opium and belladonna have been valuable for centuries.

This field has changed when the antibiotics were discovered and change into drug biosynthesis.

In recent year the introduction of new synthesis pharmaceuticals has outpaced that of natural product . furthermore ,the isolated and purified active material superseded preparation of the parent crud drug.

These factors led to de-emphasis on chemotherapy in the pharmacy curriculum and often to its combination with medicinal chemistry.

Classification of drug on the basis of their origin

1-Drug from natural origin: Herbal or plant or mineral origin, some drug substances are of marine origin.

2-Drug from chemical as well as natural origin: Derived from partial herbal and partial chemical synthesis Chemical, example steroidal drugs

3-Drug derived from **chemical synthesis**.

4-Drug derived from animal origin: For example, hormones, and enzymes.

5-Drug derived from microbial origin: **Antibiotics**

6-Drug derived by biotechnology genetic-engineering, hybridoma technique for example

7-Drug derived from radioactive substances

A sampling of classes of medicine includes

1-Antipyretics: reducing fever (pyrexia/pyresis)

2-Analgesics: reducing pain (pain killers)

3-Antimalarial drugs: treating malaria

4-Antibiotics: inhibiting germ growth

5-Antiseptics : prevention of germ growth near burns, cuts

Definition of medicinal chemistry

Medicinal chemistry is the science which deals with the synthesis, chemistry of mode of action, chemical assay of drug substance.

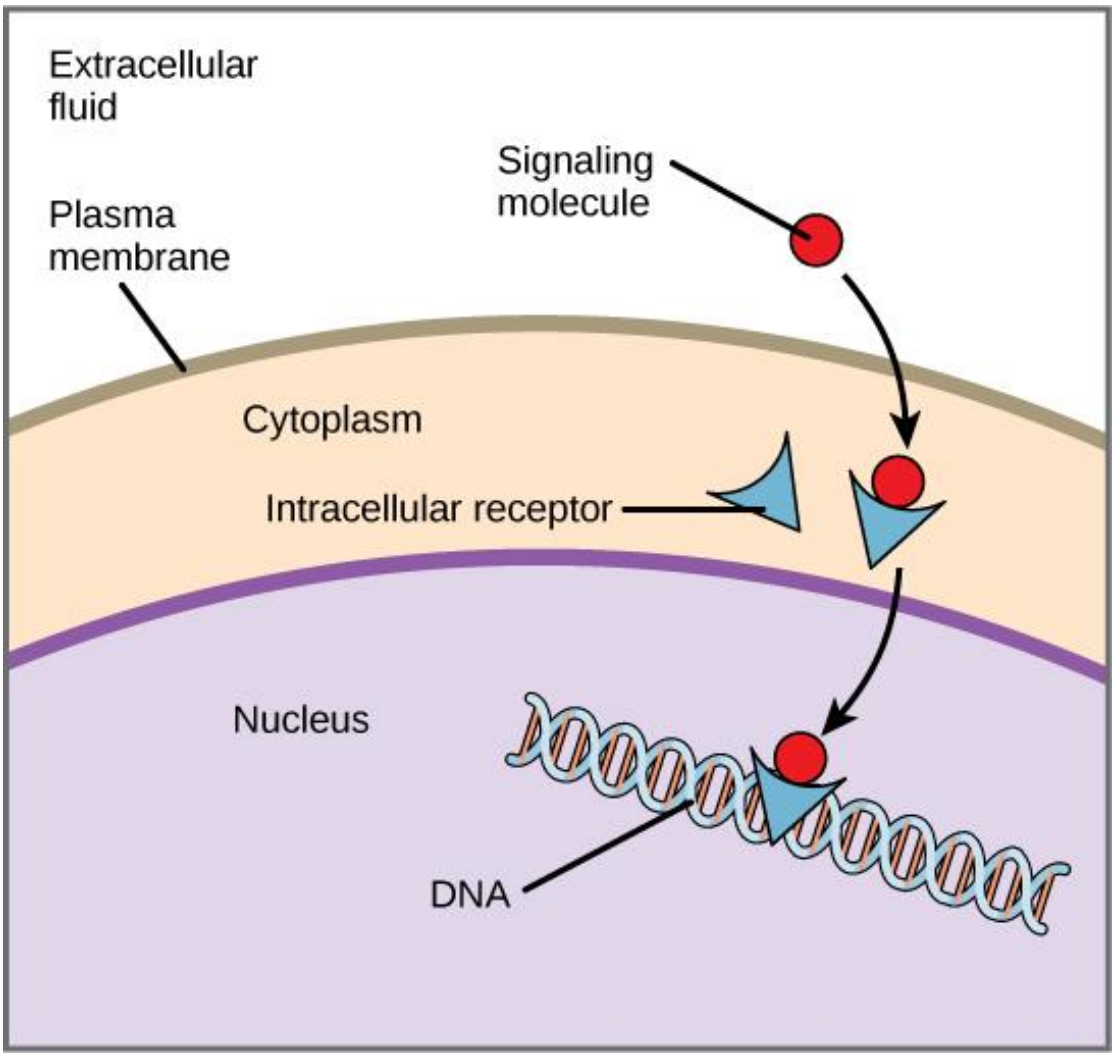
Definition of drug

Drug is any substance presented for treating, curing or preventing disease in human beings or in animals. It may also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions.

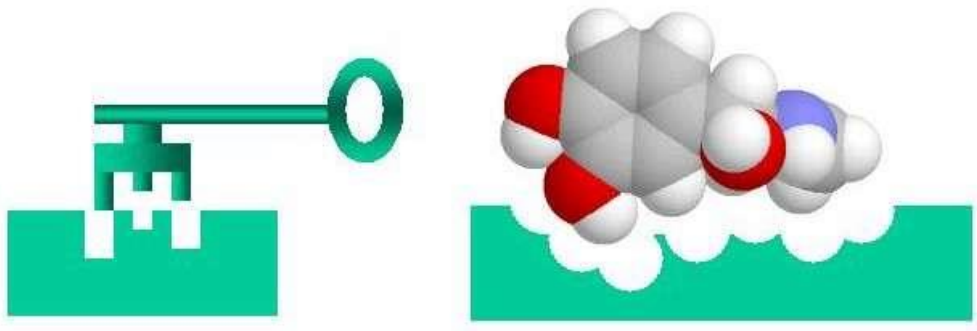



Definition of receptor

Receptor: It is a membrane bound or intracellular macromolecular protein which is capable of binding the specific functional groups of the drug with body.



LOCK & KEY" model of RECEPTORS



Four types of binding takes place between the receptor and the drug molecule

1. Van der Waals forces
2. Hydrogen bonding
3. Ionic interaction
4. Dipole- dipole bonding
5. Covalent bonding

1. Van der Waals Attraction

■weakest intermolecular force (0.5-1.0 kcal/mole)

■electrostatic

■occurs between nonpolar groups (e.g. hydrocarbons)

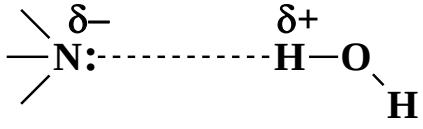
■highly distance and temperature dependent

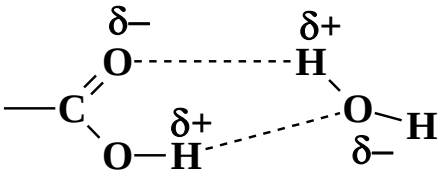
2. Dipole-Dipole Bonding

■stronger (1.0 to 10 kcal/mole)

■occurs electrostatically between electron deficient and electron excessive /ric atoms (dipoles)

■hydrogen bonding is a specific example of this bonding and serves as a prime contributor to hydrophilicity



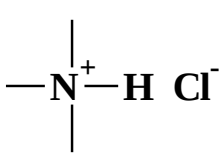


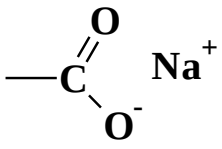
3.Ionic Bonding

■electrostatic attraction between cations and anions

■common in inorganic compounds and salts of organic molecules

■relatively strong (5 kcal/mole)





4.Ion-Dipole Bonding

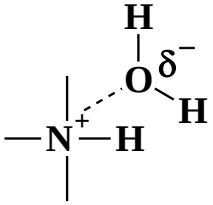
■electrostatic between a cation/anion and a dipole

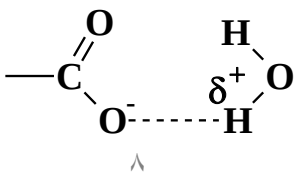
■relatively strong (1-5 kcal/mole)

■low temperature and distance dependence

■important attraction between OMAs**(organic medicinal agents**) and H2O

- **hydrophilic.....water loving**
- **lipophobic.....lipid hating**
- **lipophilic.....lipid loving**
- **hydrophobic.....water hating**

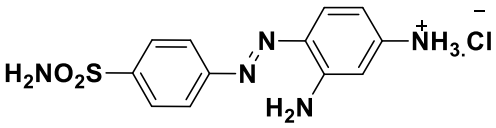




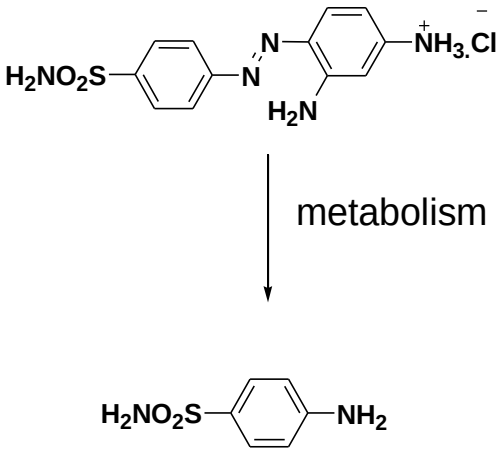
Sulpha drugs

Sulfonamides:-

The sulfonamide are synthetic ,not of natural origin which called " antimicrobials " and not antibiotics. They were the first antibacterial drugs that were not overtly toxic to human.

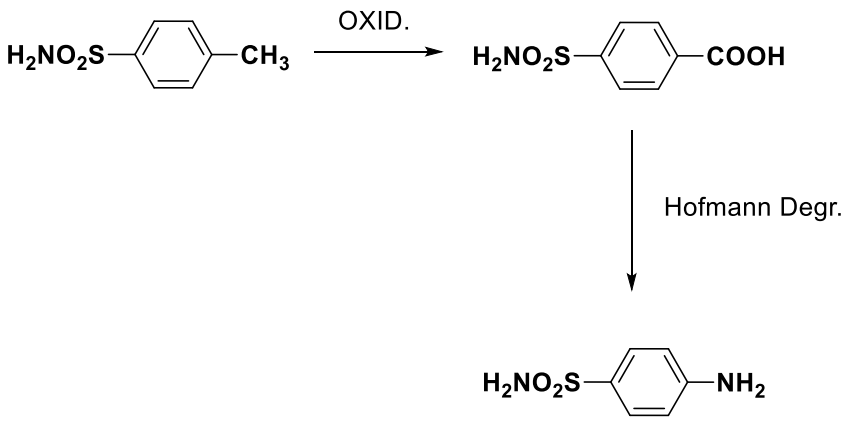


Prontosil which is 2,4-diamino-4-sulphamyl azobenzen hydrochloride was the first sulpha drug to be used in medicine ,it is red dye and metabolized in the body to p-aminobenzene sulphonamide.



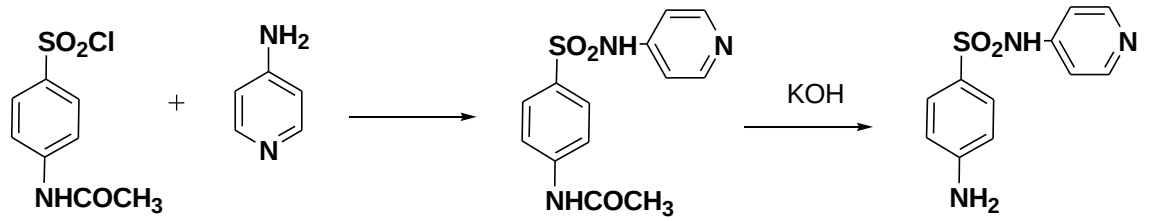
Synthesis of sulphanilamides derivative :-

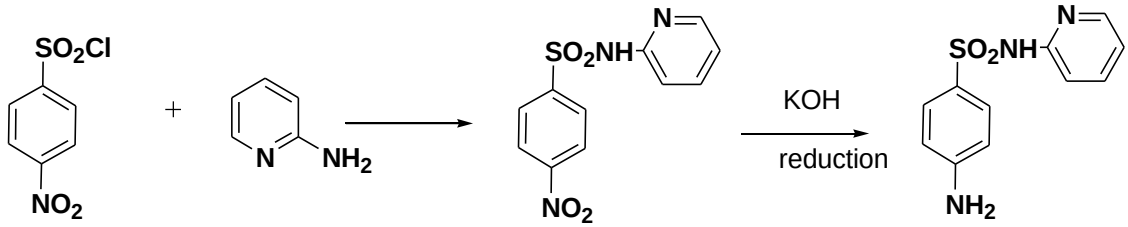
Oxidation of p-toluenesulphonamide to p-sulphamidobenzoic acid fallowed by Hoffmann degradation.



Sulpha pyridine

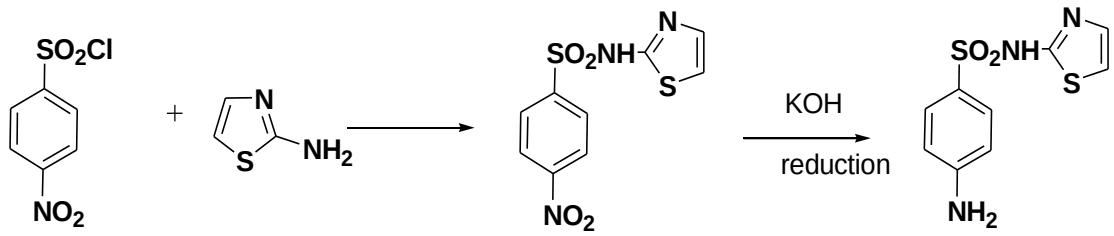
Used to treatment the cocci pneumonia ,but it high toxicity in men ,it is rarely used any longer.





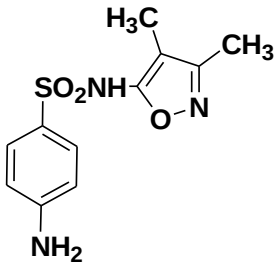
Sulpha thiazole

2-thiazolyl sulponilamide is more patent than sulphapyridine and less toxic ,it most highly bacteriostatic drug which has a permanent place in the pharma.



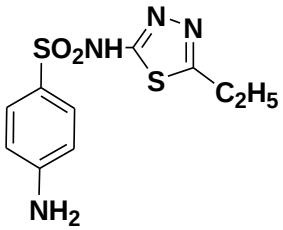
Sulphaisoxazole

Is soluble over a wide pH range ,which have highest bacteriostatic activity and rapid excretion through the kidney.



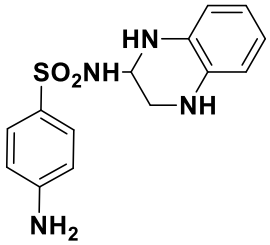
Sulphathiadiazole :-

2-sulphanilamide-5-ethyl-1,3,4-thiadizole is highly soluble and rapidly excretion from the kidney in urine so it consider the most suitable for urinary tract infection.



Sulphaquinoxaline :-

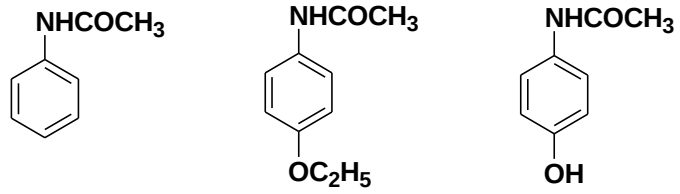
It is widely used in the treatment of coccidiasis infection caused by Eimeria tenella in chickens pheasants.



Antipyretic and analgesics

Aniline and p-aminophenol derivative :-

They have analgesic activity comparable to that of aspirin but don't have anti-inflammatory activity e.g. acetanilide , paracetamol and phenacetin .



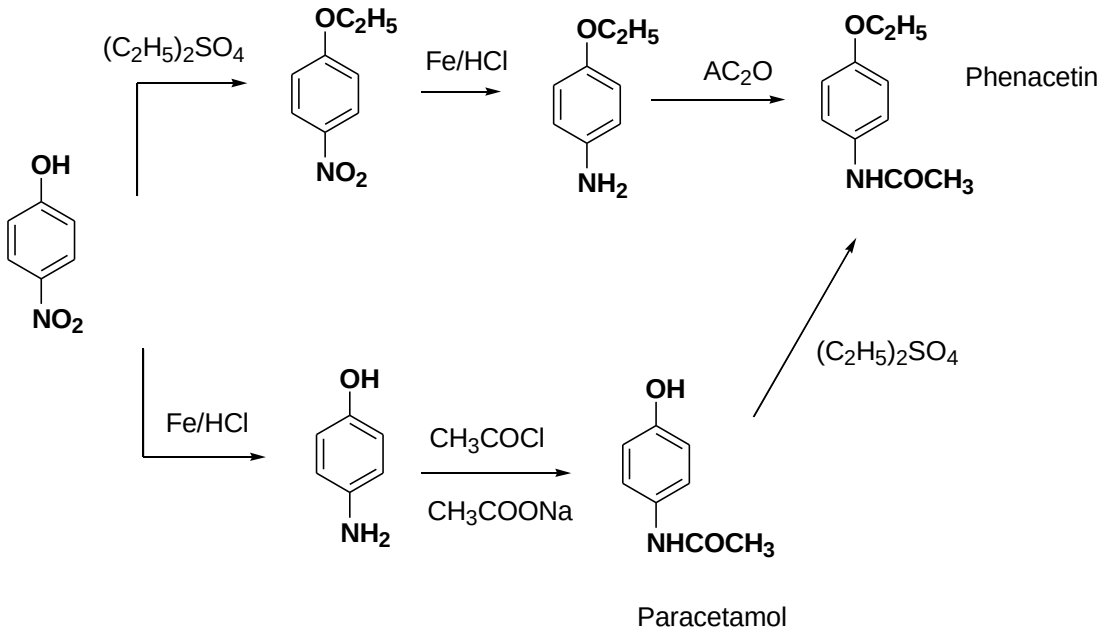
acetanilide phenacetine paracetamol

Acetanilide was introduced into therapy in 1886 as antipyretic-analgesic but it found later too toxic.

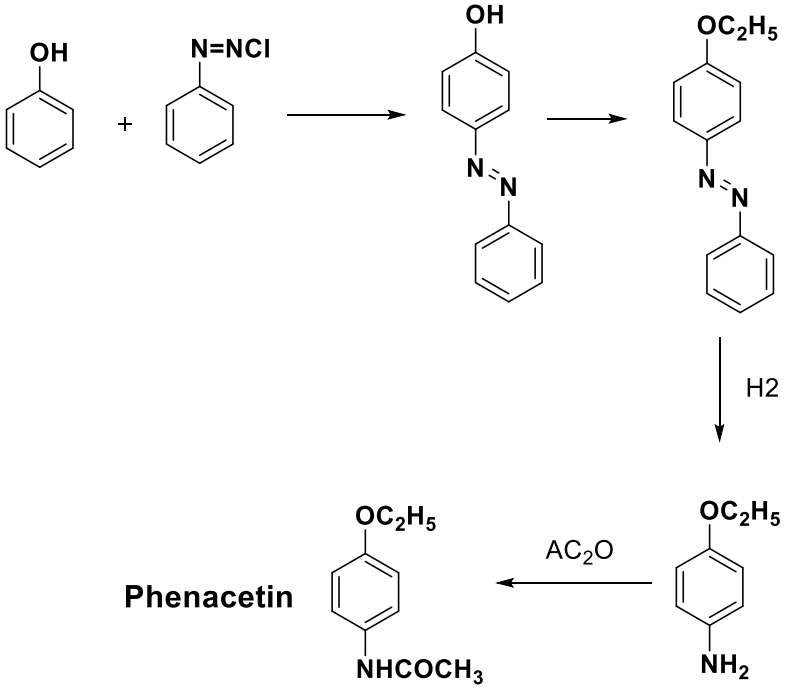
Phenacetin was introduced in the following year and it was widely used but recently it found nephrotoxicity.

Paracetamol is subseguently introduced in 1893 and it remains the only popular agent for this group.

Synthesis of paracetamol

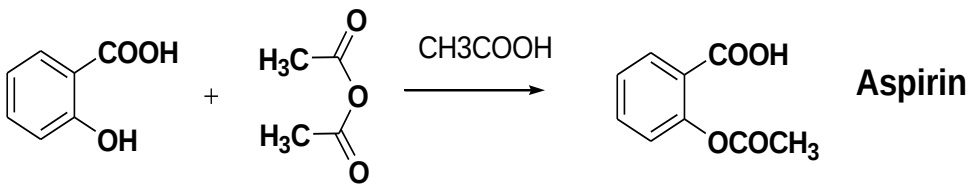


Industrial method for phenacetine



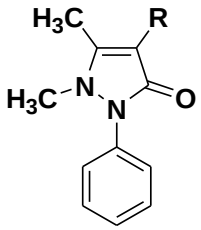
Salicylic acid derivatives

The major chemical classes of salicylates used in medicine are the ester ,the most common one is aspirin .

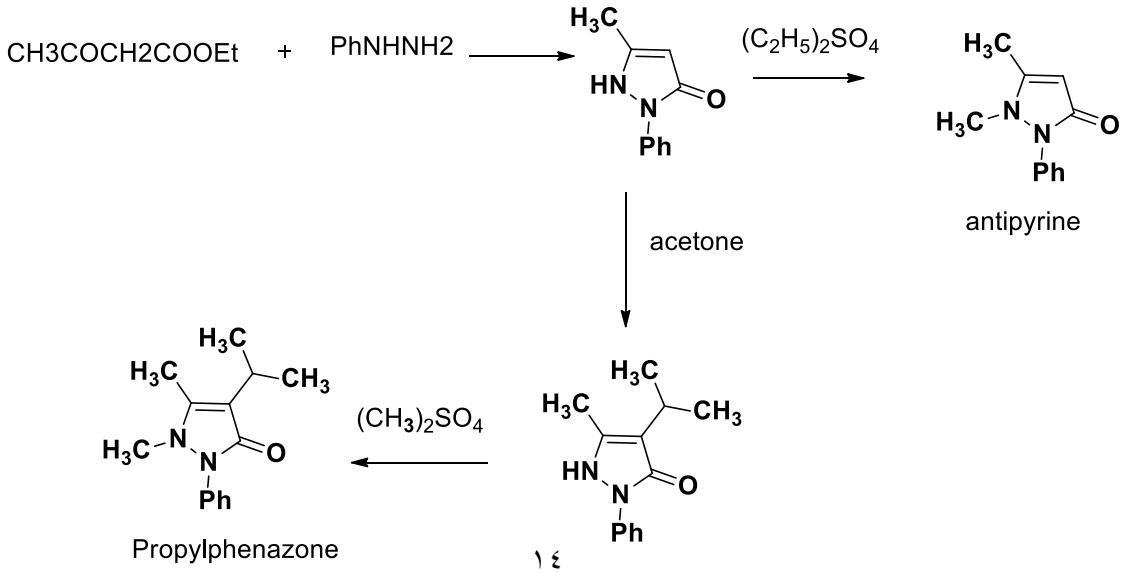


3-pyrazolone derivatives

Antipyrine(phenazone) and propylphenazone have analgesic, antipyretic and antirhumatic activities similar to those of aspirine and used for the same purpose.



Synthesis of antipyrine



Aryl and hetroarylacetic acid derivative

(aryl alkanoic acid derivative)

This class of compounds represents the largest group of NSAIDS (Nonsteroidal anti-inflammatory drugs). They have the following general chemical structure .

Ar-CH(R)-COOH

(R = H,CH3,alkyl ….)

(Ar = Aryl or heteroaryl)

- The main type of NSAID include
- ibuprofen.
- naproxen.
- diclofenac.

Ketoprofene (Propionic acid derivatives)

- mefenamic acid.
- etoricoxib.
- indomethacin.
- high-dose aspirin (low-dose aspirin is not normally considered to be an NSAID)

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature.

They're often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain.

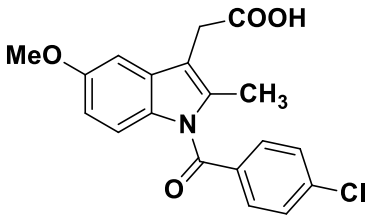
Although NSAIDs are commonly used, they're not suitable for everyone and can sometimes cause troublesome side effects.

Indoleacetic acid derivative

1- indomethacin

Indemethacin is one of the most potent non-steroidal anti-inflammatory agents.

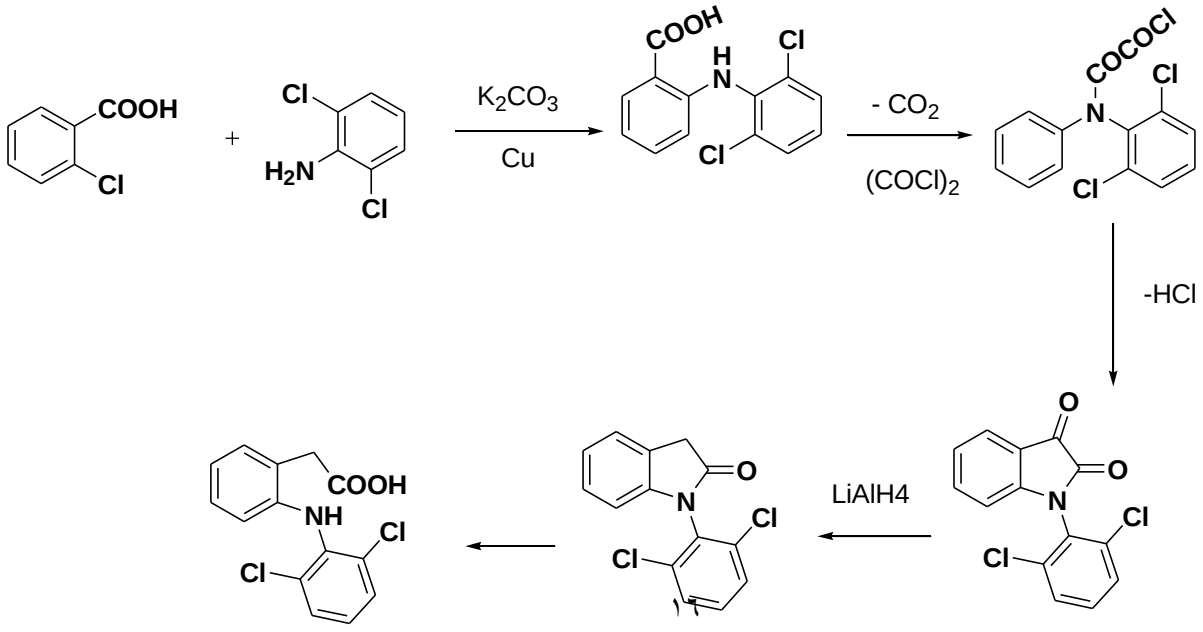
Substitution of a methyl group on the carbon atom separating the acid center from the aromatic ring tends to increase anti-inflammatory activity groups .



Phenylacetic acid derivatives (diclofenac sodium)

Diclofenac is available in 120 different countries and the most widely used NSAIDA in the world It is 6 time more potent than indomethacin and 40 time more potent than aspirin as antipyretic.

Synthesis of diclofenac

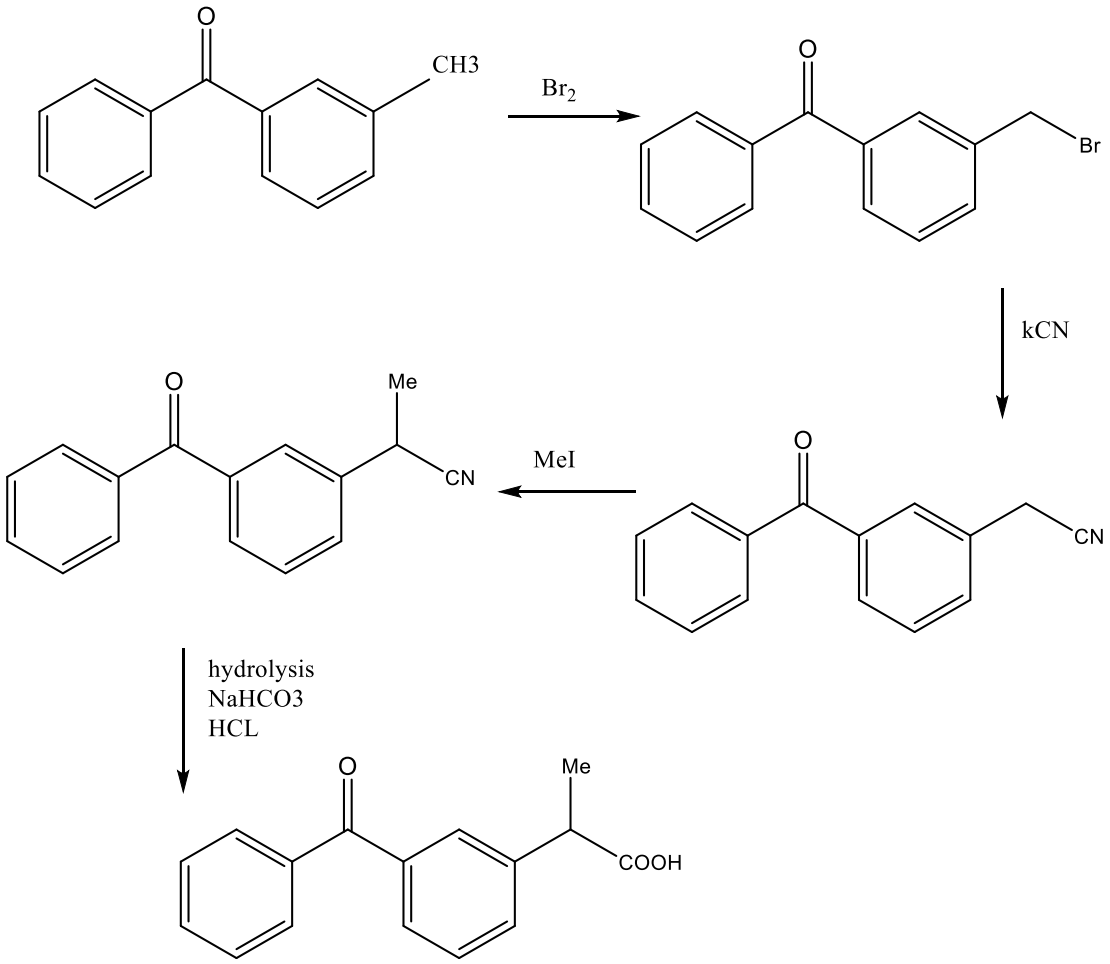


Ketoprofen

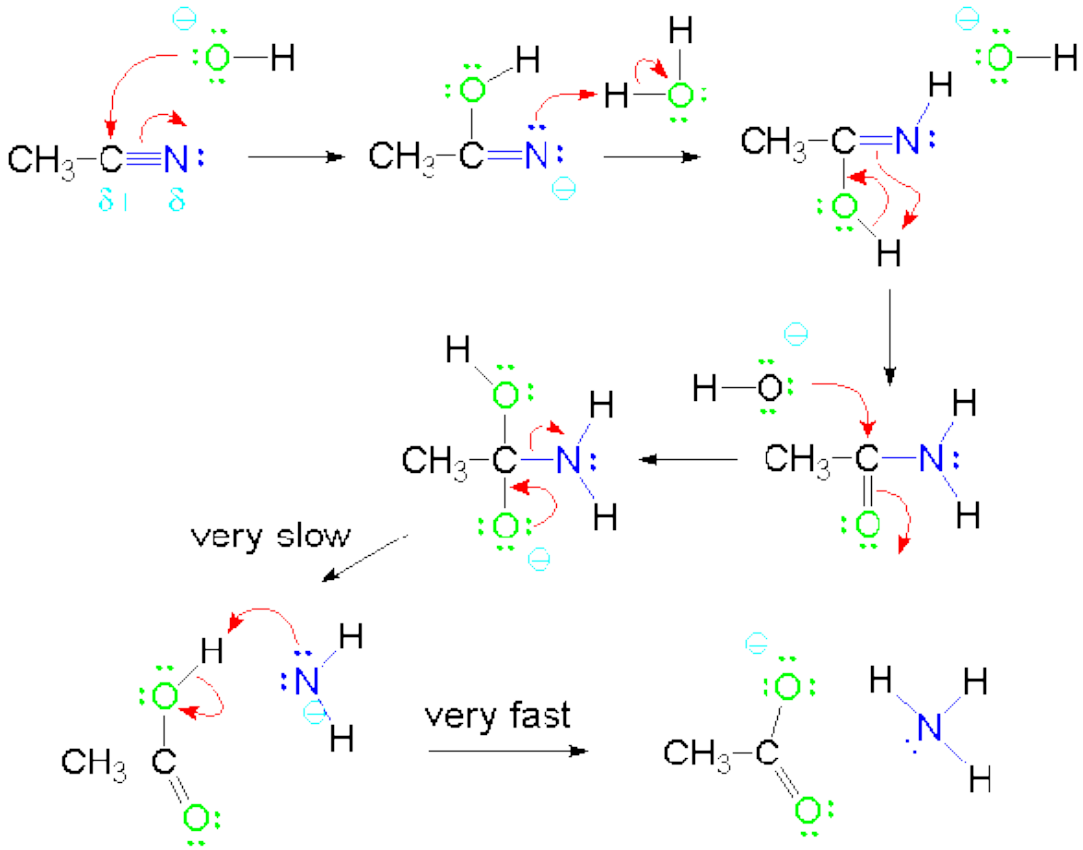
is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID)with analgesic and antipyretic effects It acts by inhibiting the body's production of prostaglandin.

(The prostaglandins are **a group of lipids made at sites of tissue damage or infection that are involved in dealing with injury and illness**. They control processes such as inflammation, blood flow, the formation of blood clots and the induction of labour)

Synthesis of ketoprofen

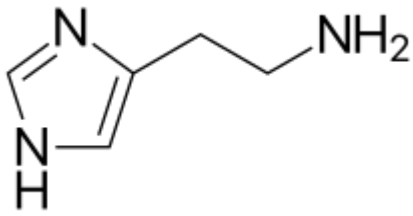

O
CH3
Br2
O
Br
kCN
O
CN
MeI
O
Me
CN
hydrolysis
NaHCO3
HCL
O
Me
COOH

Hydrolysis of cyanide group to carboxylic group



Antihistamine

Histamine



Histamine is an organic nitrogenous compound involved in local immune responses, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues.

The discovery of the H1and H2 antagonist burimamide in the early 1970 opened a new ear in the history of the attempt to explane histamine related physiologic processes

Antihistamine

Antihistamines are drugs which treat allergic rhinitis, common cold, influenza, and other allergies. Typically, people take antihistamines as an inexpensive, not patented (generic), drug that can be bought without a prescription and relieves from nasal congestion, sneezing, or hives caused by pollen, dust mites, or animal allergy with few side effects. Antihistamines are usually for short-term treatment.

Mechanism of action

1-Antihistamines are reversible blockers of histamine H1 receptor (**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.) on tissues, such as skin ,bronchi ,eye….etc.

2- Antihistamines are reversible blockers of histamine H2 receptor on tissues, such as stomach ,intestine….etc.

3-Many of antihistamines also possess adrenaline-antagonism which act as anesthetic

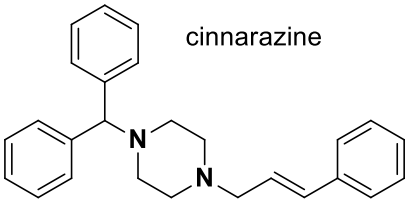
(The adrenal (suprarenal) glands are located at the top of both kidneys. The produce hormones that regulate the immune system, blood pressure, metabolism, and the stress response. In addition, also helps your body do the following:

- Promoting proper cardiovascular function
- Helps in how we respond to stress
- Properly utilizing carbohydrates and fats
- Helps distribute stored fat
- Gives you body odor and pubic hair
- Promotes healthy gastrointestinal functions

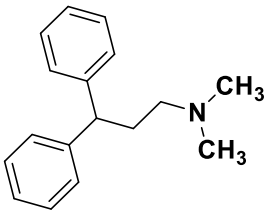
4- many of the traditional antihistamines (first generation) possess some sedative and antimuscarinic effects

5-Now developed antihistamines (second generation) free from these side effect which known as " non-sedating antihistamines "

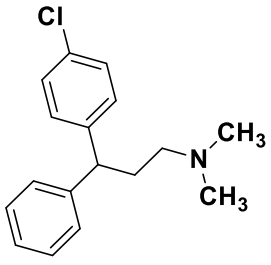
6-some like cinnarazine (second generation) act by inhibiting calcium ions transfer from the outside to inside of the cell so it is value in motion sickness and in vascular disorders



7- Substituents in one of the aryls influence the antihistaminic potency



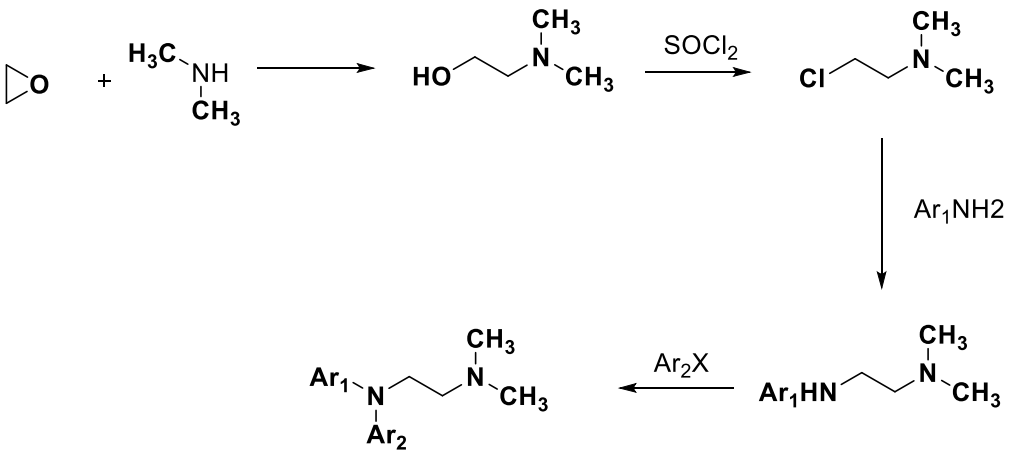
Pheniramine
Usual dose is 20-40mg
Three times daily

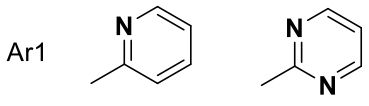


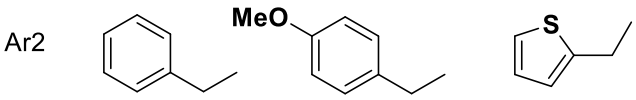
chlorpheniramine
Usual dose is 2-4mg
Three times daily

8- antazoline is a weak antihistamine but potent local anesthetic which used in the eye allergic condition.

General Synthesis of Antazoline derivatives



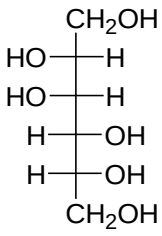


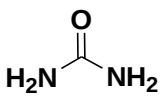


Diuretic

A diuretic is any substance that promotes the production of urine.

In medicine, diuretics are used to treat heart failure, liver cirrhosis, influenza, water poisoning, and certain kidney diseases.

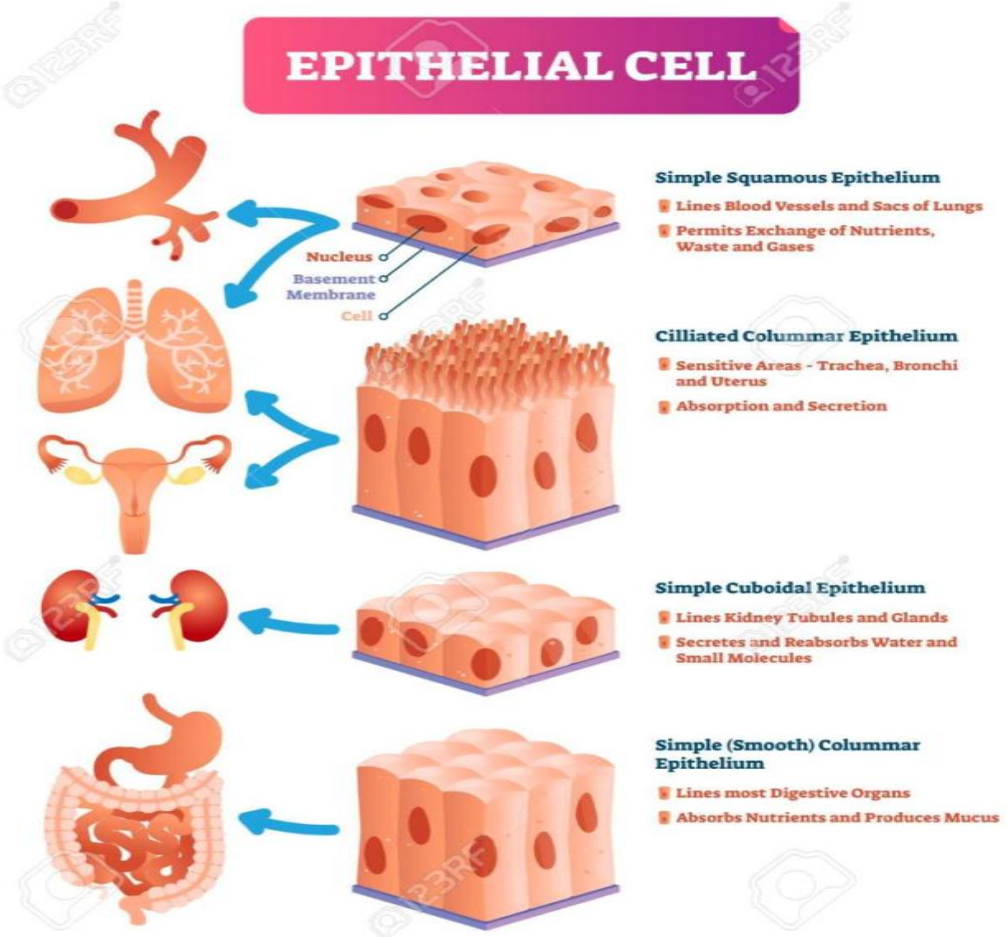




Osmotic diuretics

Osmotic diuretics (e.g. mannitol and urea) are substances that increase osmotlality but have limited tubular **epithelial cell** permeability.

They work primarily by expanding extracellular fluid and plasma volume, therefore increasing blood flow to the kidney.



Mechanism of action

1-Diuretics they effectively reduce blood pressure

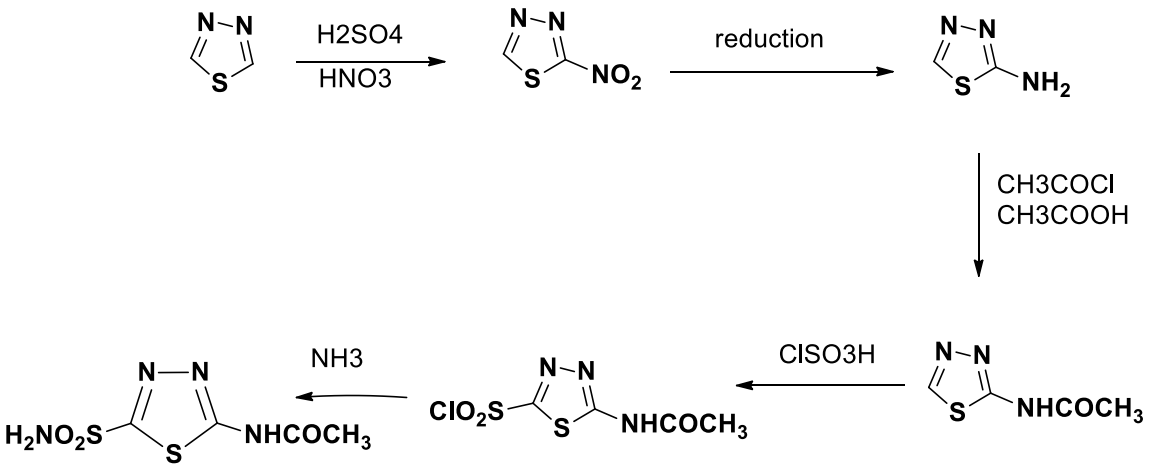
2- Diuretics are a diverse group of compounds that either stimulate or inhibit various hormones that naturally occur in the body to regulate urine production by the kidneys .

Carbonic anhydrase inhibitors: They increase the excretion of sodium, potassium, bicarbonate, and water. Some types of carbonic anhydrase inhibitors include:

Methazolamide .

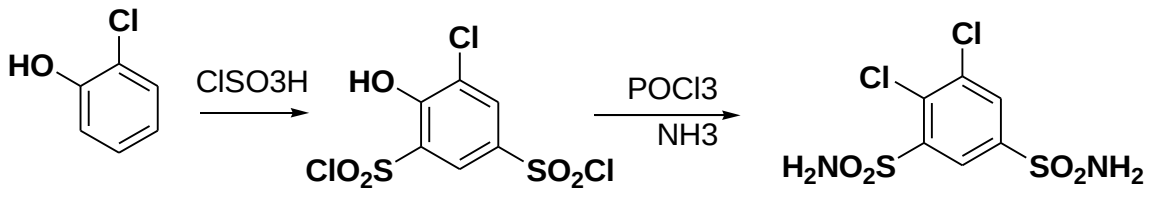
acetazolamide

carbonic anhydride inhibitors (acetazolamide)



2-acetylamino-1,3,4-thiadiazole-5-sulfonamide

dichlorphenamide (Daranide)

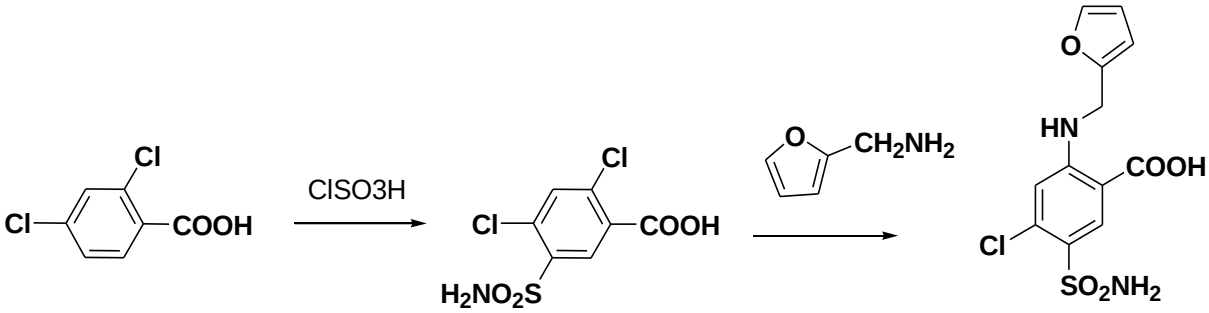


4,5-Dichloro-benzene-1,3-disulfonic acid diamide

Lasix

is a drug choice for urine secretion

(it reduce the body water content and the undesirable salts.)



Local anesthesia

is any technique to induce the absence of sensation in a specific part of the body by block the generation and the conduction of impulses analog a nerve fiber .

It uses :-

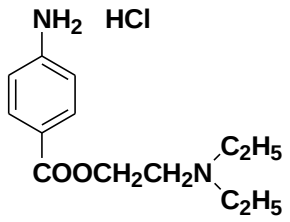
It allows patients to undergo surgical , spinal cord anesthesia and dental procedures with reduced pain and distress Reduced pain caused by minor burns, insect bites, allergic response .

Chemistry

1- ester derivatives e.g cocaine which dose not penetrate the skin ,but absorbed from mucous membranes

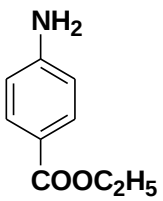
2- amino benzoic acid derivative

a- procaine.HCl



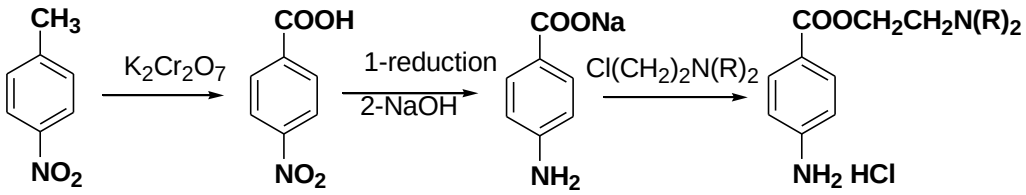
Effective in contact skin or mucous membrane

b- Ethyl p-aminobenzoate



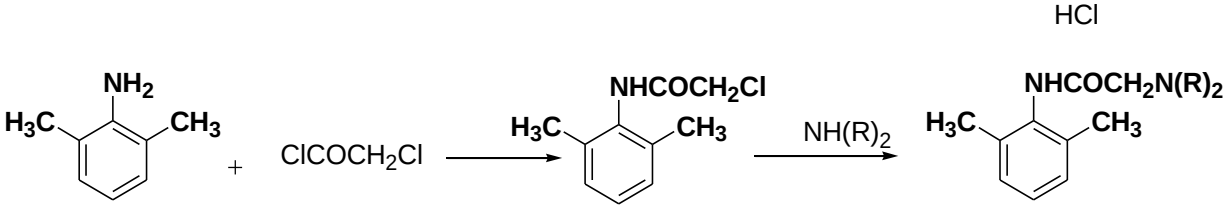
It used in the form of ointment and cream

synthesis of procaine and it's derivative



3-amide derivatives

lidocaine which used in injection, ointment, eye drop .



R= C_2H_5

Diabetes

Diabetes is a disease that occurs when your blood glucose, is too high. Blood glucose is your main source of energy and comes from the food you eat.

Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy.

Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Antidiabetics

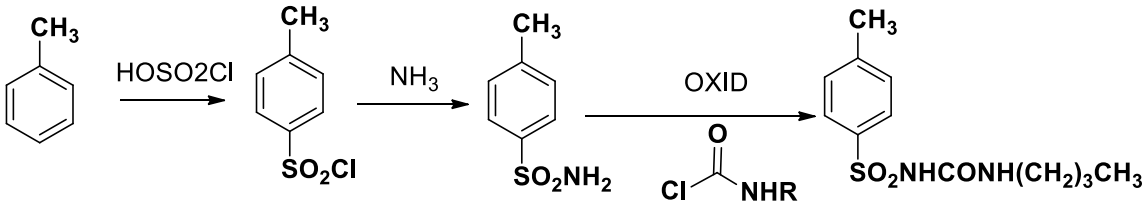
Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood for example :-

1- Type 1 diabetes is a condition in which your immune system destroys insulin-making cells in your pancreas. These are called beta cells. The condition is usually diagnosed in children and young people which treatment with insulin.

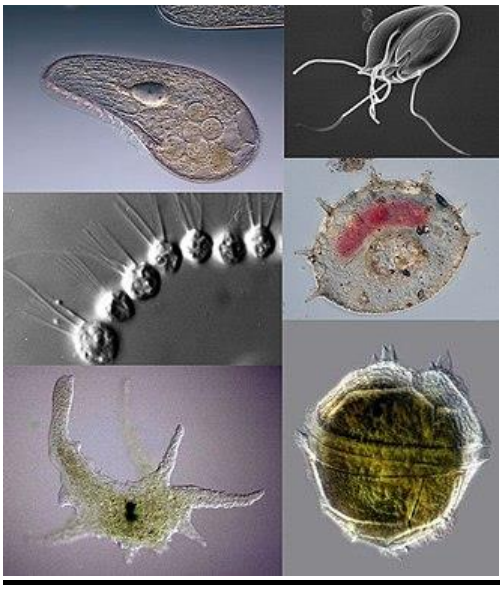
2- type 2 diabetes, in which your body doesn't respond to insulin which treatment with different kind of drug like

sulfonylurea (tolbutamide)

Synthesis of tolbutamide



Anti protozoa drugs

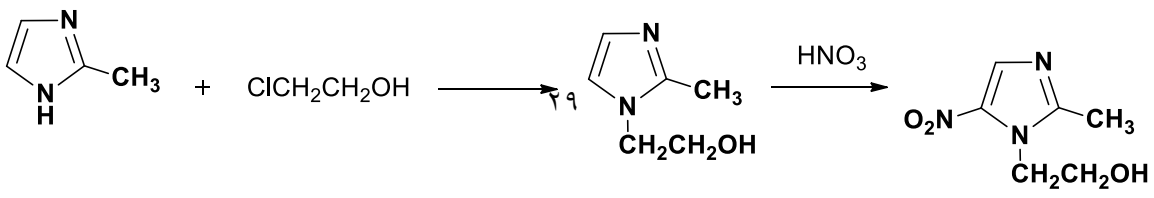


Protozoa Historically, the protozoa were regarded as "one-celled animals", either free-living or parasitic, which feed on organic matter such as other microorganisms or organic tissues

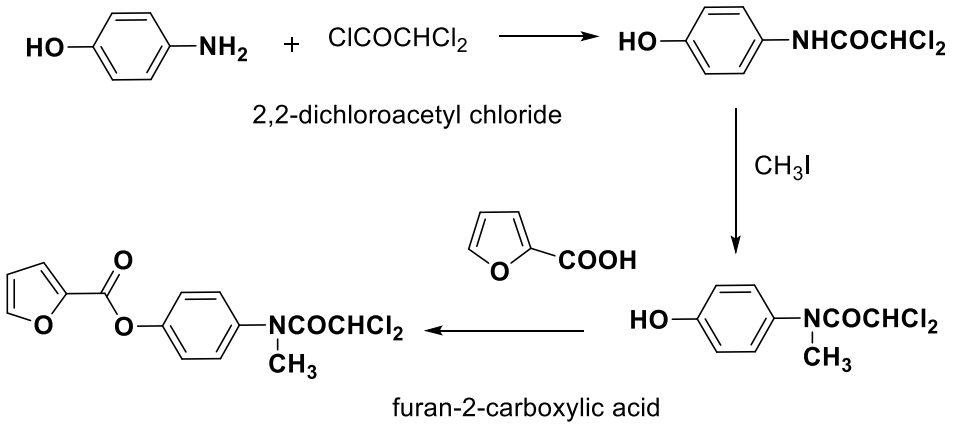
which considered a tropical disease

Treatment:-

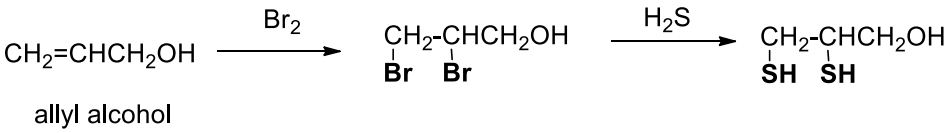
1-Metronidazole (M)



Diloxanide furoate



Dimercaptal



Antifungal agent

Fungi infect skin and lungs and cause diseases

Fungi treatment include:-

1- polyenes :- is a molecule with multiple conjugated double bonds

2- thiazole

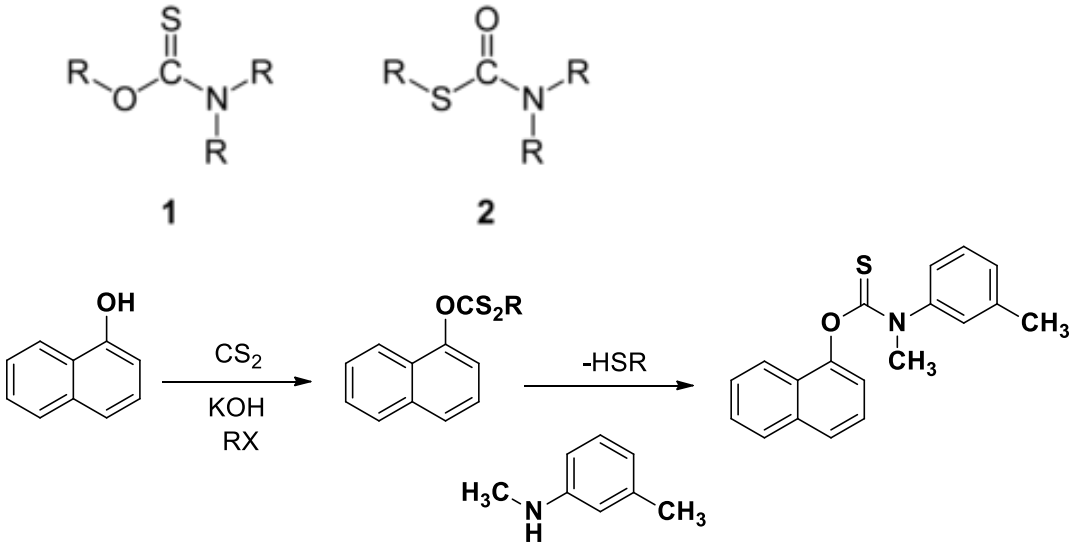
3- unsaturated fatty acid derived from natural castor oil

4-Imidazoles

5- tolnaftate – a thiocarbamate antifungal

synthesis of tolnaftate

Tolnaftate is a synthetic thiocarbamate



Antibiotics

Antibiotics or antibacterials are a type of antimicrobial used in the treatment and prevention of bacterial infection. They may either kill or inhibit the growth of bacteria. Several antibiotics are also effective against fungi and protozoans, and some are

toxic to humans and animals, even when given in therapeutic dosage. Antibiotics are not effective against viruses such as the common cold or influenza, and may be harmful when taken inappropriately

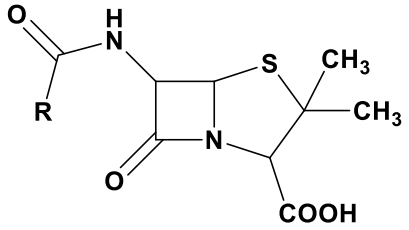
Penicillin (PCN or pen) is a group of antibiotics which include penicillin G (intravenous use), penicillin V (oral use), and benzathine penicillin (intramuscular use). They are derived from Penicillium fungi.

Penicillin antibiotics were among the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.

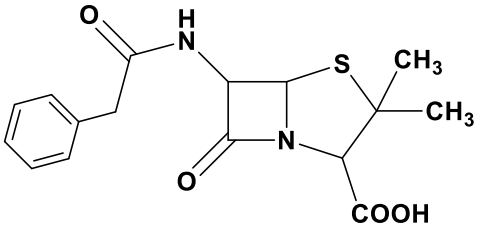
Penicillins are still widely used today, though many types of bacteria have developed resistance following extensive use. All penicillins are β-lactam antibiotics.

About 10% of people report that they are allergic to penicillin

Pencilline derivative

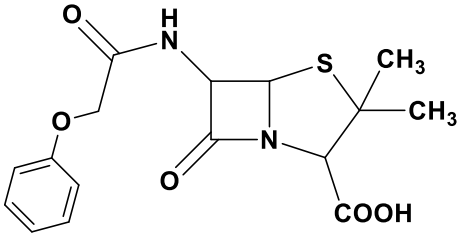


Pencilline G
Benzylpenicillin



As an antibiotic, Penicillin G is noted to possess effectiveness mainly against Gram-positive organisms. Some Gram-negative organisms

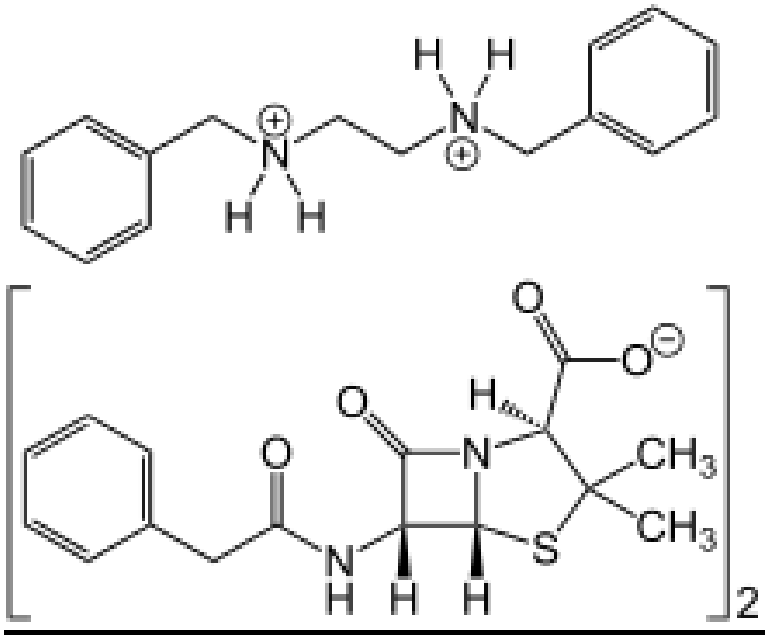
Pencilline v
Phenoxymethylpenicillin



penicillin V, is an antibiotic useful for the treatment of a number of bacterial infections. It is a penicillin that is orally

active. It is less active than benzylpenicillin (penicillin G) against Gram-negative bacteria.

benzathine penicillin
Benzathine benzylpenicillin



It is slowly absorbed into the circulation, after intramuscular injection, and hydrolysed to benzylpenicillin in vivo. It is the drug-of-choice when prolonged low concentrations of benzylpenicillin are required and appropriate, allowing prolonged antibiotic action over 2–4 weeks after a single IM dose

Medical uses for benzathine penicillin include: prevention of rheumatic fever