Drugs and Pharmaceuticals

Lecture module -01

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What are Drugs ?

- The molecules /compounds which exert various physiological effects of therapeutic value.
- Ideally on administration a drug should be localized in its action and specifically should hit the areas where it is needed on our body.
- In reality, the drug molecules are distributed through out anywhere in the tissues of the host.

Are all biologically active agents drugs?

- There are compounds which are are biologically active (as drugs)
- These have the potential to destroy the microorganism and the host tissue cell at large
- These are not considered as therapeutic agents or drugs
- These compounds are applied externally
- These are termed as antiseptic or disinfectants . Examples are: Formaldehyde, Phenol, Iodine

Antiseptics and Disinfectants

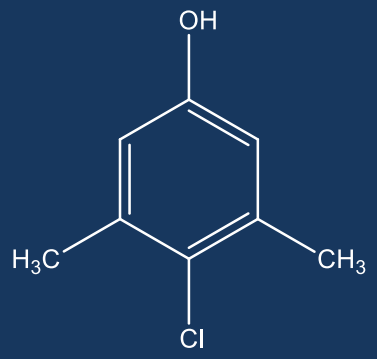
Antiseptics

- These are chemicals applied externally
- Prevents or kills the growth of micro organisms
- Directly applied on living tissues for wounds, cuts, ulcers
- Example: Dettol; widely used antiseptic composed of Chloroxylenol and alpha terpeneol

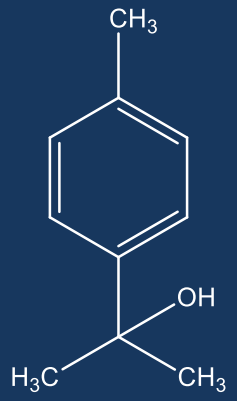
Disinfectants

- These are chemicals , more toxic in nature
- Prevents or kills the growth of micro organisms
- Directly applied on non living objects viz. on floor, drainage, instruments
- Example: Halazone used for water purification

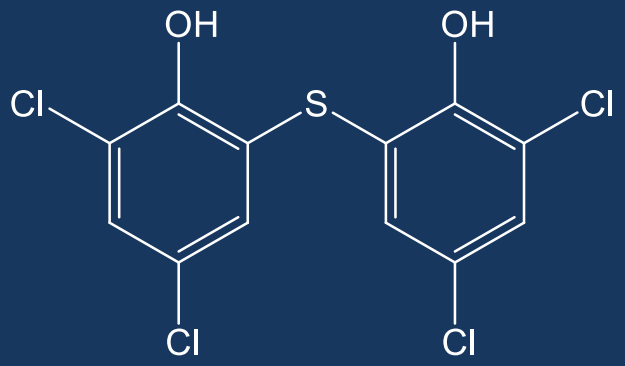
Antiseptics



Chloroxylenol: Used in Dettol

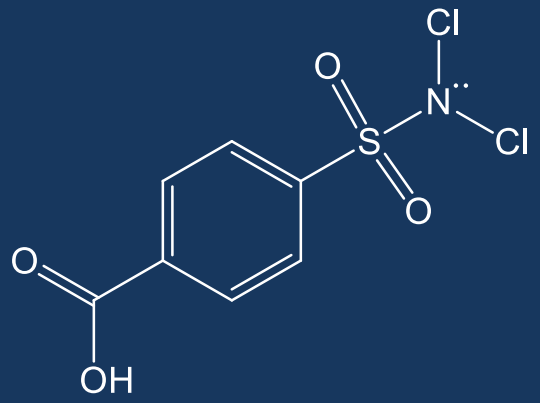


Alpha terpeneol: Used in Dettol

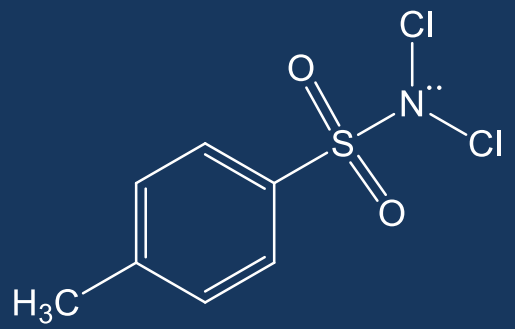


Bithiol: Used as antiseptic in soaps

Disinfectants



Halazone: Used for disinfecting water



Dichloramine T: Used for disinfecting instruments

How drugs are invented?

- **Trial and Error method: This involves the trial of all kinds of compounds, natural and synthetic. This is the most primitive one.**
- **By synthesizing bioactive mimic: The method with a complete knowledge of cell system and the compounds that interfere with it, and thereby synthesizing similar compounds.**
- **By synthesizing a compound of required activity: The method in which one starts with a compound known to have some required activity (information gained from previous methods: 1 and 2) and then the structural changes are done systematically. Each small change can bring enormous gain in curative activity of the drug. This method is the most fruitful in drug designing.**

Drugs Classification

- Anesthetics
- Neurologically active drugs
- Analgesic
- Anti Fertility drugs
- Non Steroidal Anti-Inflammatory drug
- Cardiovascular drug
- Antibiotics
- Vitamins

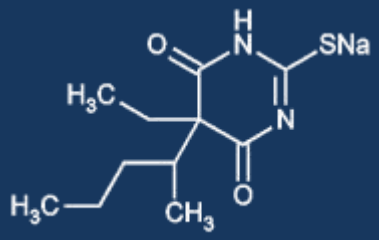
Anesthetic

These are chemical substances which produce insensibility to pain and other sensations.

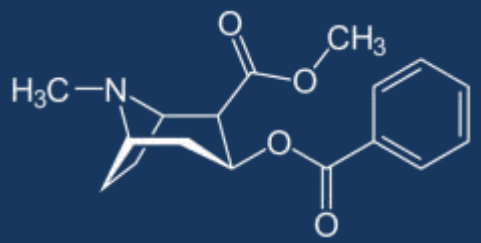
Classifications:

General anesthetic: These are mostly volatile in nature. and are used in minor surgeries. These are mostly muscle relaxants. Example: Ether, chloroform, trichloroethylene, ethyl chloride.

Non volatile anesthetic: These are liquid at room temperature. One very good example of this class is sodium thiopental "Fatal Plus" used in veterinary Euthanasia (a process to allow a suffering pet to death).



Local anesthetic: These anesthetics act locally, for example Cocaine.



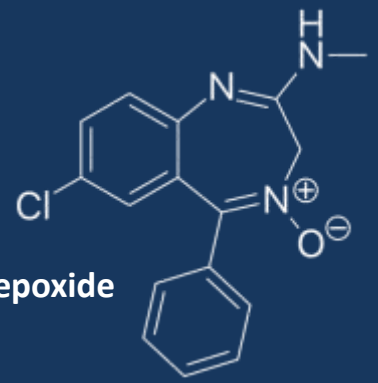
Neurologically active drugs

- These affect the message transfer mechanism from nerves to the receptor. There are two major classes:
- A) Tranquilizers B) Analgesics

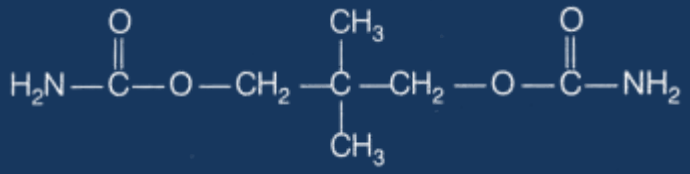
Tranquilizers

These are used for the treatment of stress, mild or severe mental disorder.

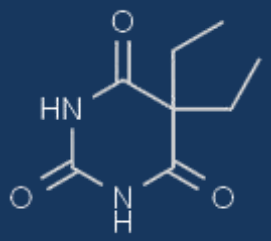
- Chlorodiazepoxide is a mild drug used to relieve tension. Equanil is used to control depression.
- Derivatives of barbituric acid viz. veronal , nembutal are important class of tranquilizers which are used to produce sleep and are termed as hypnotic drugs.



Chlorodiazepoxide



Equanil



Veronal

Neurologically active drugs

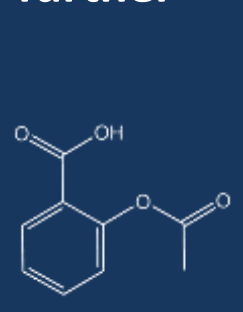
Analgesics

These reduce or abolish pain without causing unconsciousness or paralysis or other disturbances of the nervous systems. These are classified as non-narcotic and narcotic analgesic.

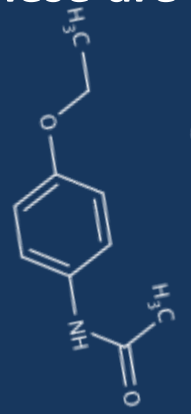
Non narcotic analgesic: These are non addictive drugs. These are further divided into following classes:

Anti -Rheumatic : To treat pains associated with rheumatism

Examples are Salicylic acid derivatives: Aspirin, Salicin



Aspirin

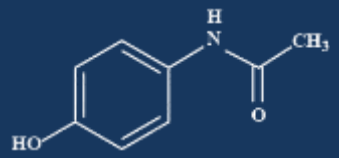


Phenacetin

Anti-Pyretic : To combat fever

Examples are 4-aminophenol derivatives:

Paracetamol, Phenacetin

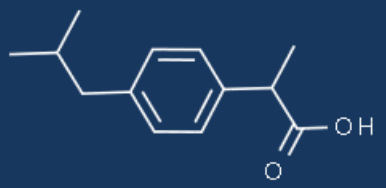


Paracetamol

Anti-Inflammatory: To reduce inflammation

Examples are Aryl acetic acid derivatives:

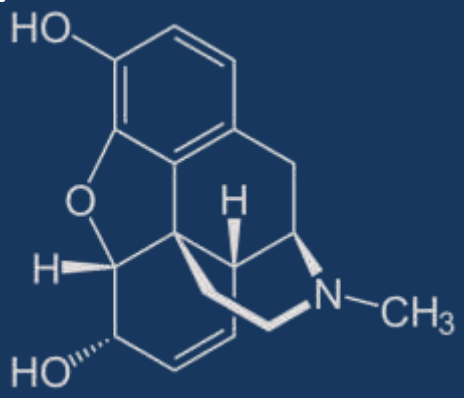
Ibuprofen (Brufen)



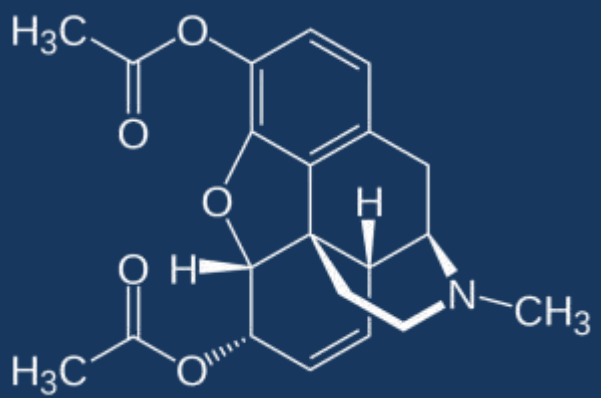
Ibuprofen

Analgesics

Narcotic analgesics: These are the analgesics when used in overdose, cause addiction. Morphine and its analogues (derivatives) fall in this class. Morphine once used before surgery during operation. Heroine, a derivative of morphine is infamous for its addictive power.



Morphine



Heroine

Aspirin

Aspirin falls in the class of non narcotic analgesic. It is anti-rheumatic.

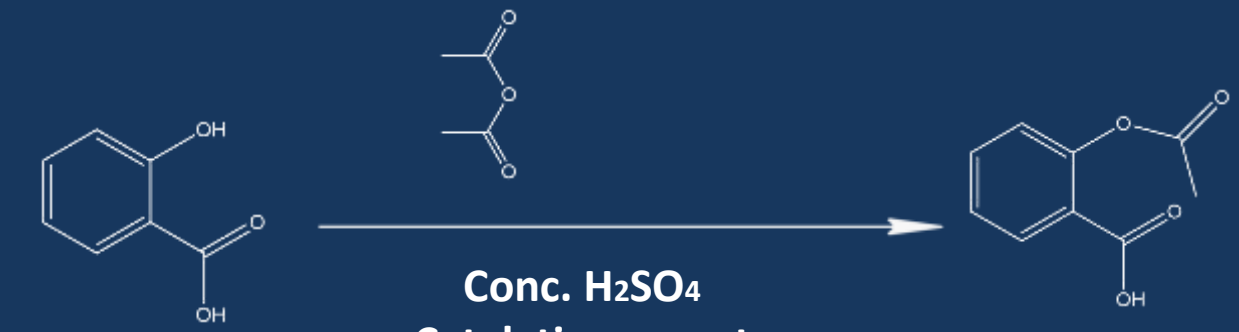
Preparation

Ortho hydroxy benzoic acid (salicylic acid) is reacted with acetic anhydride in presence of catalytic amount of concentrated sulfuric acid.

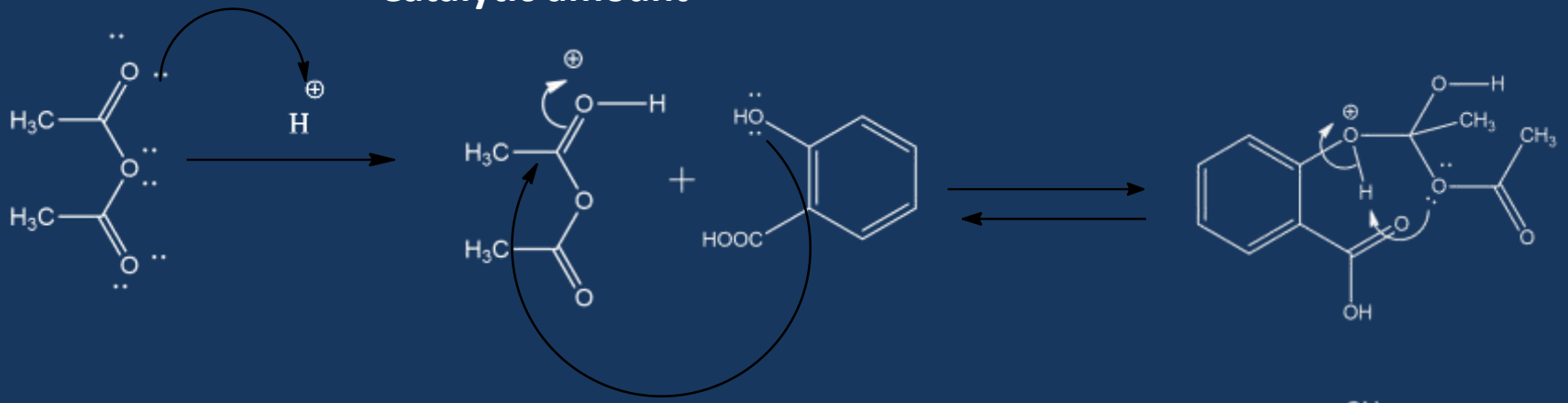
The temperature is maintained at 50-60 ^{o} C for about half an hour.
The reaction medium is continuously stirred.

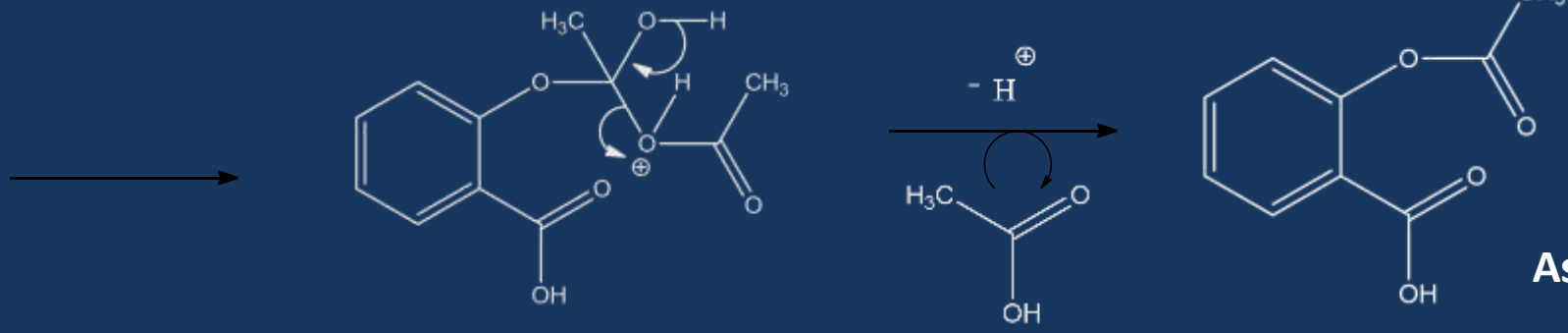
Aspirin is precipitated after pouring the medium in ice cold water.

Synthesis



Conc. H_2SO_4
Catalytic amount





Aspirin

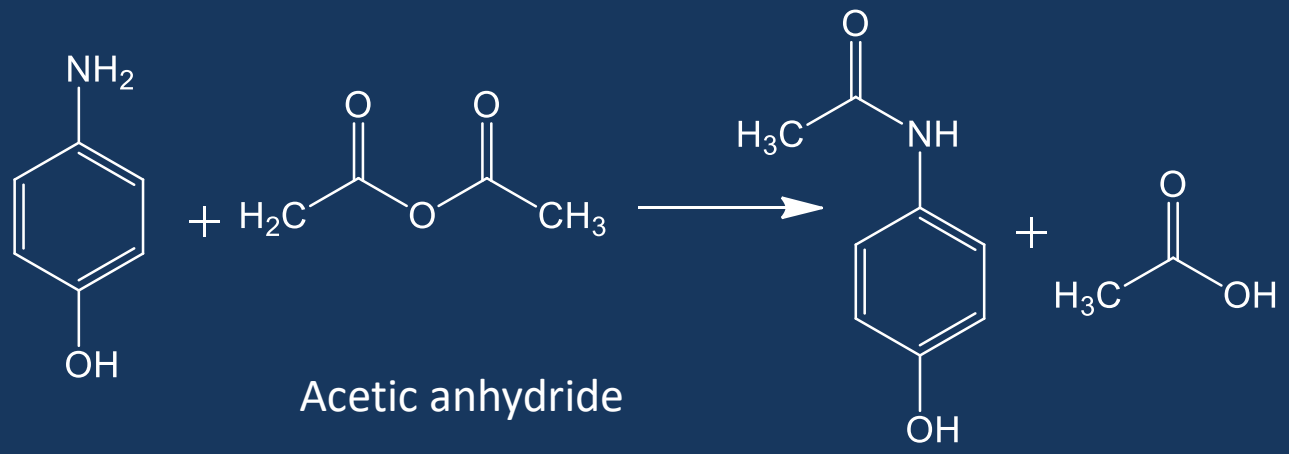
Mode of action of Aspirin

- Essentially helps to reduce fever with high temperature to bring it down to normal body temperature.
- It falls in the group of antipyretic analgesics.
- This NSAID inhibits the enzyme called cyclo oxygenase which is responsible for the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and or fever.

Paracetamol mode of action (Acetamenophen)

- **Paracetamol** (**acetaminophen**) is generally **not** considered an **NSAID.**
- It has only minor **anti -inflammatory** activity.
- **Acetaminophen** treats pain mainly by blocking Cyclooxygenase-2 and inhibiting endocannabinoid reuptake almost exclusively within the brain, but **not** much in the rest of the body.

Synthesis of Paracetamol



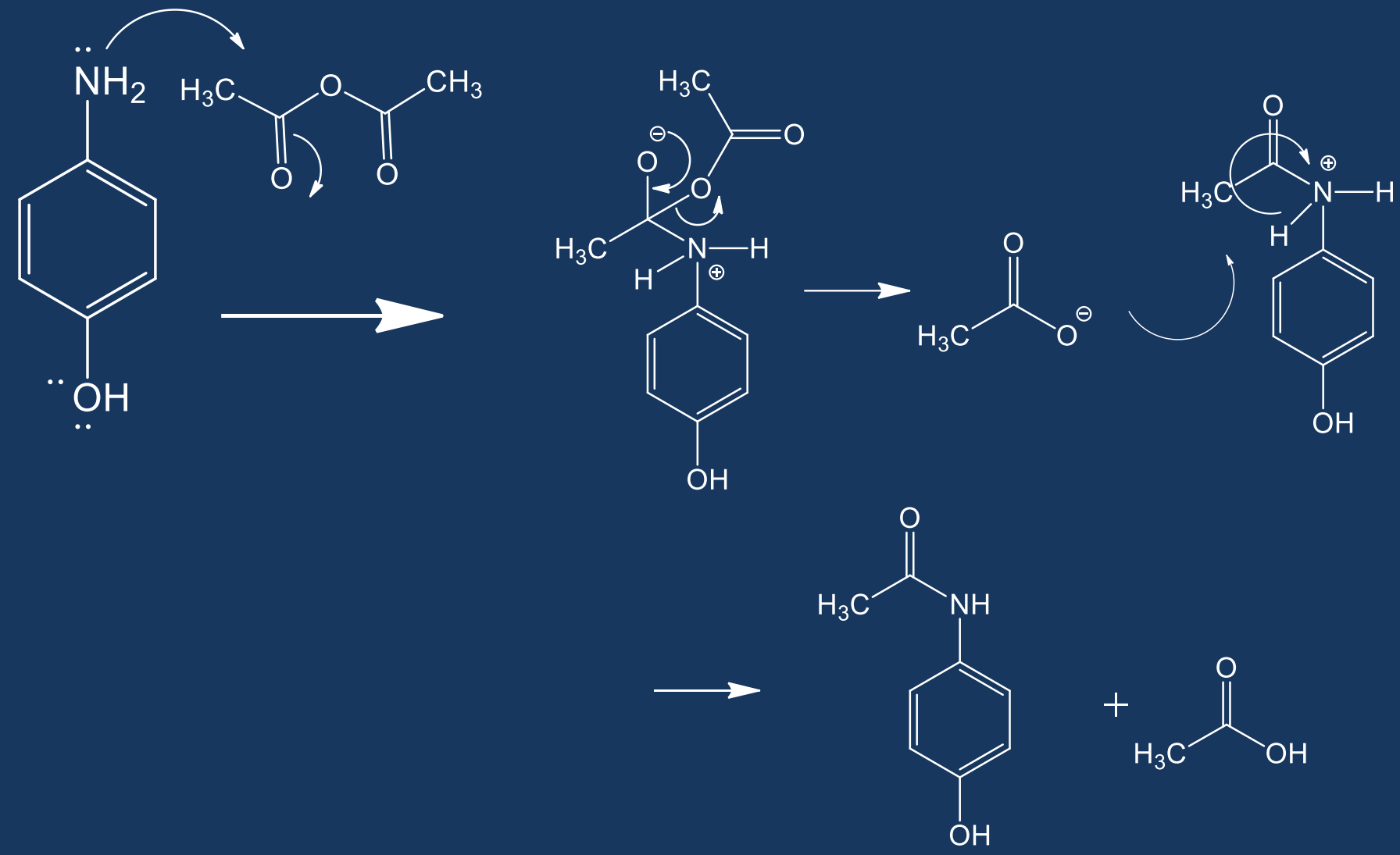
P-Aminophenol

Acetic anhydride

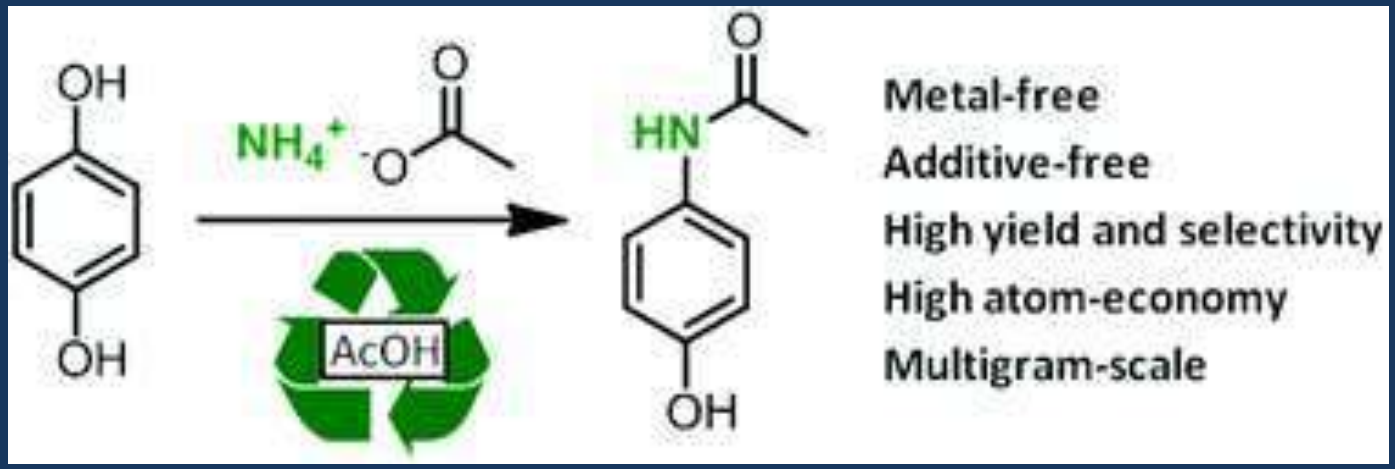
P-Acataaminophenol or
p-Hydroxy acetanilide

The widely used process of the synthesis of Paracetamol involves the acetylation of 4-amino phenol using equivalent amount of acetic anhydride and sodium acetate.

Mechanism


NH2
H3C
O
CH3
O
O
OH
H3C
O
O
O
H3C
N
H
H
OH
H3C
O
O
O
H3C
N
H
H
OH
O
H3C
NH
OH
+
O
H3C
OH

Synthesis of Paracetamol



Amidation of phenol derivatives: A direct synthesis from para quinol

Paracetamol mode of action (Acetamenophen)

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- It has only minor **anti -inflammatory** activity.
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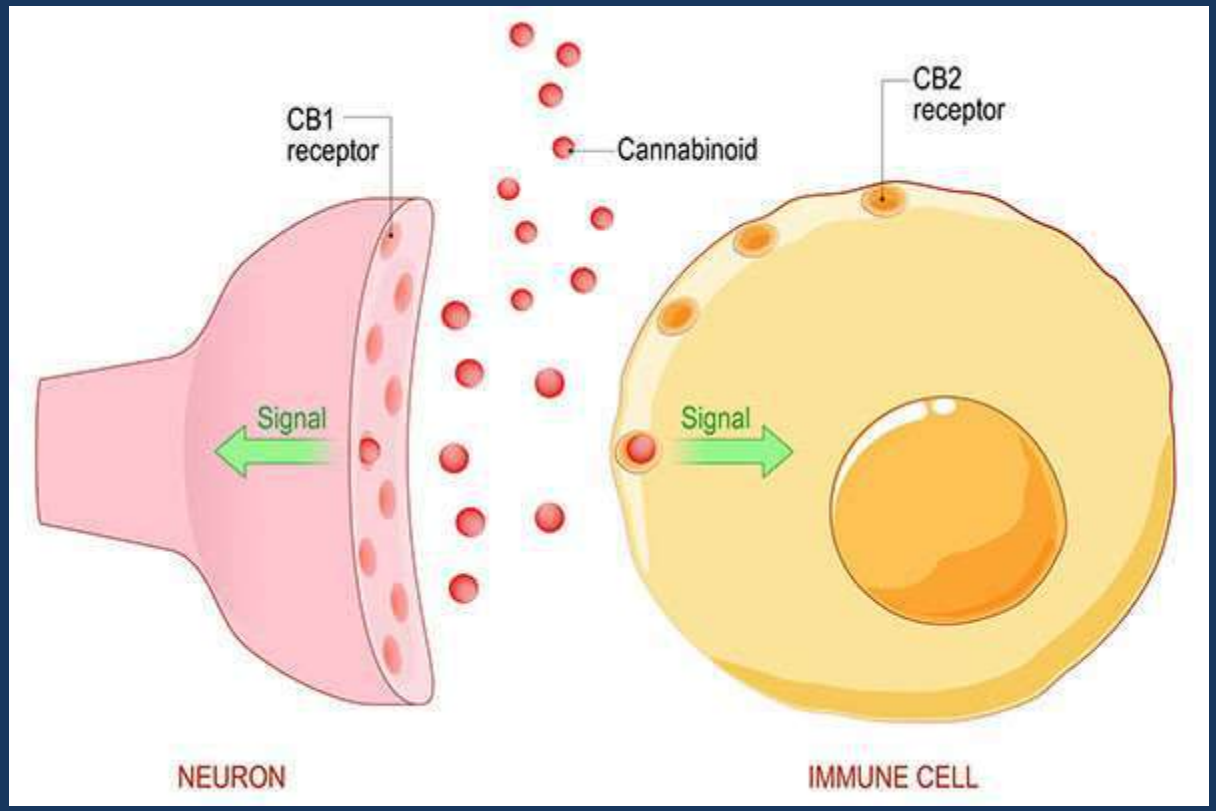
Endo Cannabinoid System (ECS): Responsible for Pain Feeling

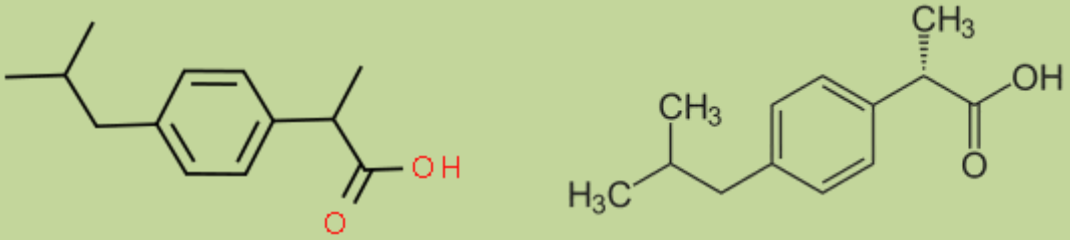
Endo genous cannabinoids or endocannabinoids are naturally occuring lipid based neurotransmitters. The ECS regulates and controls many of our most critical bodily functions such as learning and memory, emotional processing, sleep, temperature control, pain control, inflammatory and immune responses, and eating.



Source: Harvard University Archive (health.harvard.edu)

Synthesis of some drugs: Anti-Pyretic and analgesics (NSAID)

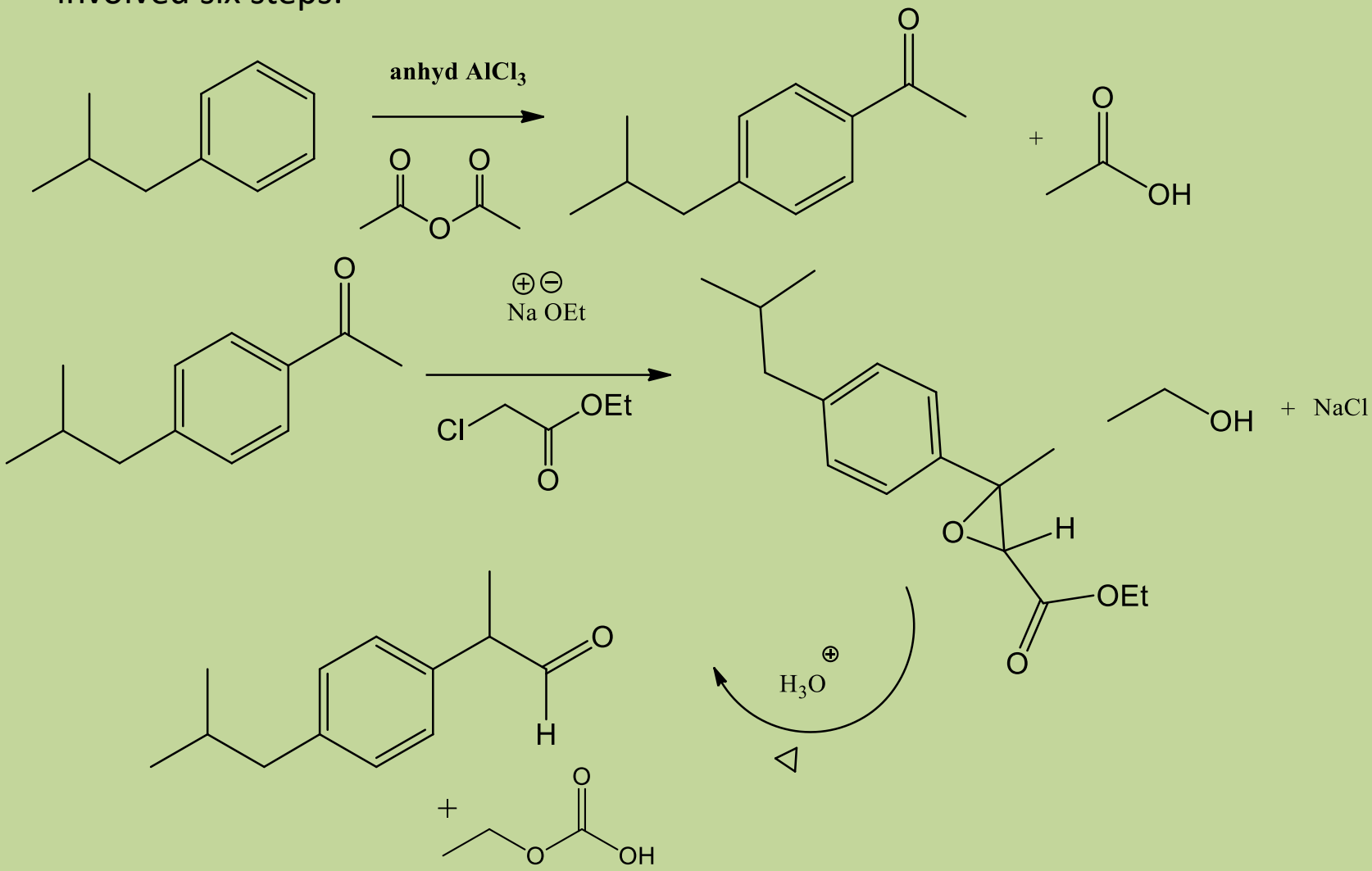
Ibuprofen



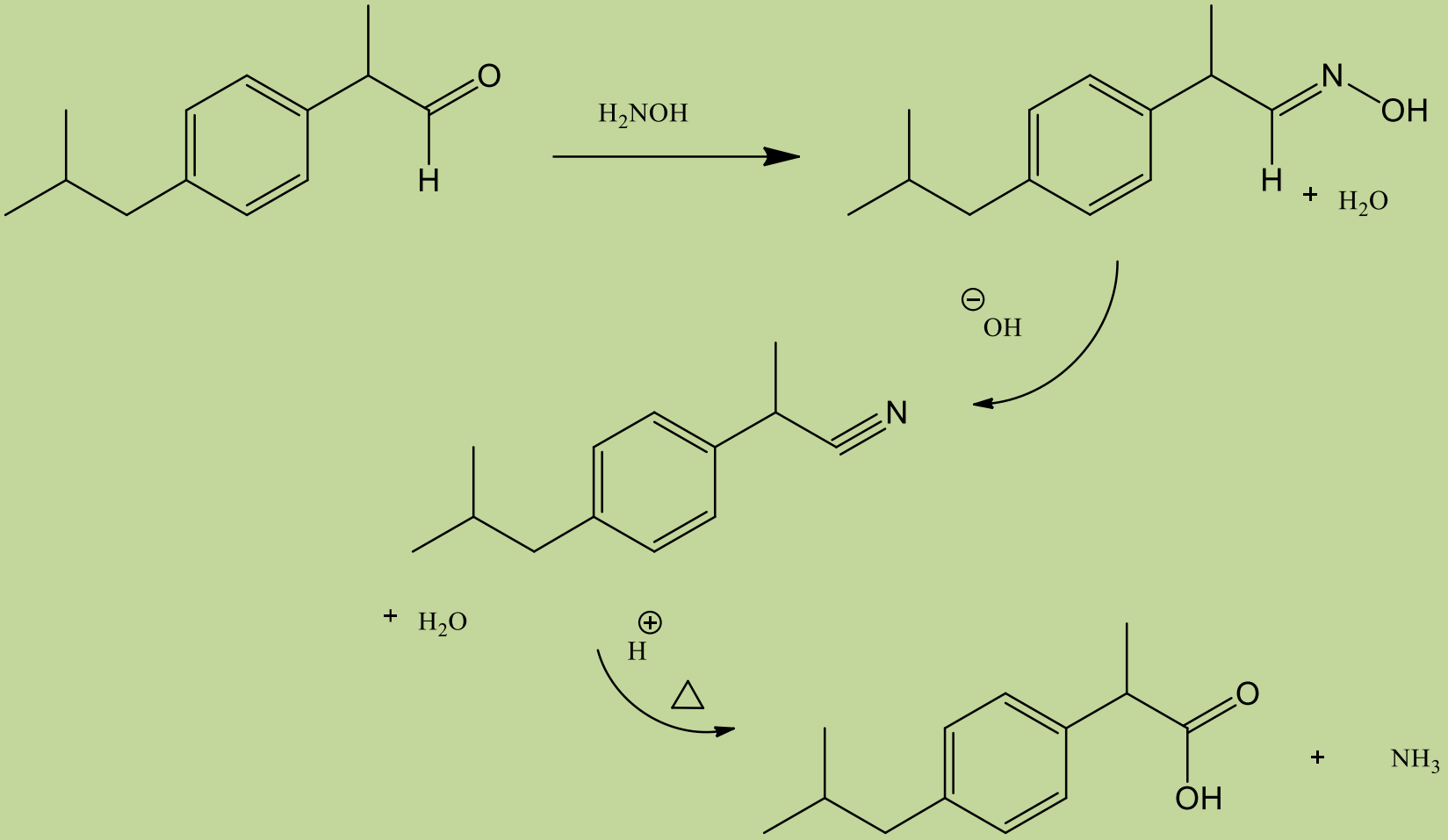
- Ibuprofen, industrially known as Brufen, is a non steroidal anti-inflammatory drug (NSAID).
- The racemic form is available in the market. However, the *S*-enantiomer is more biologically active.
- The synthesis of ibuprofen and its advancement from the traditional chemical route, the advanced greener route and the most advanced and the greenest pathway giving *S*-ibuprofen.

The Boot's synthesis

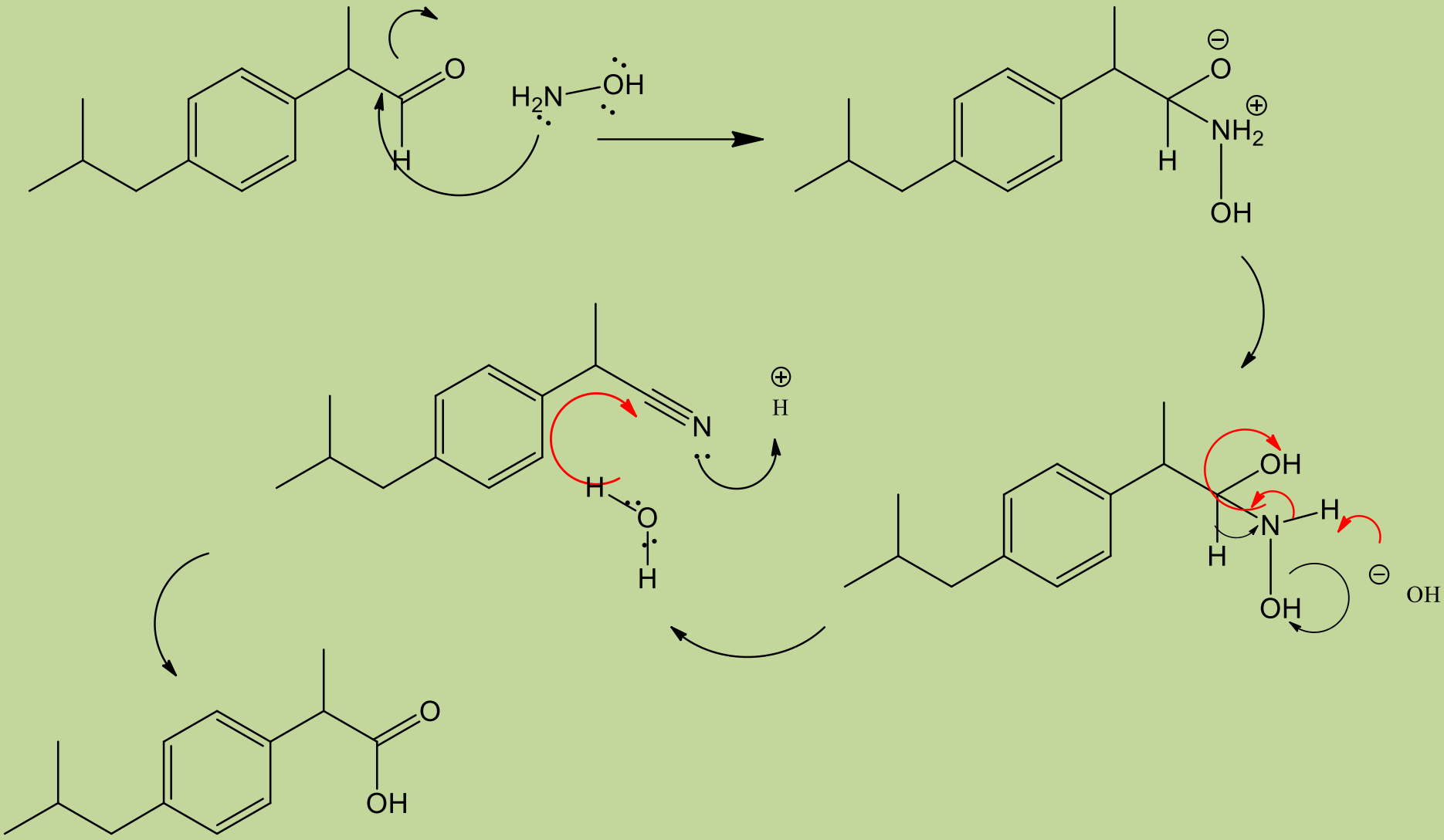
This was the most widely accepted process by industries till 1980. It involved six steps:



The Boot's Synthesis (Cont..)



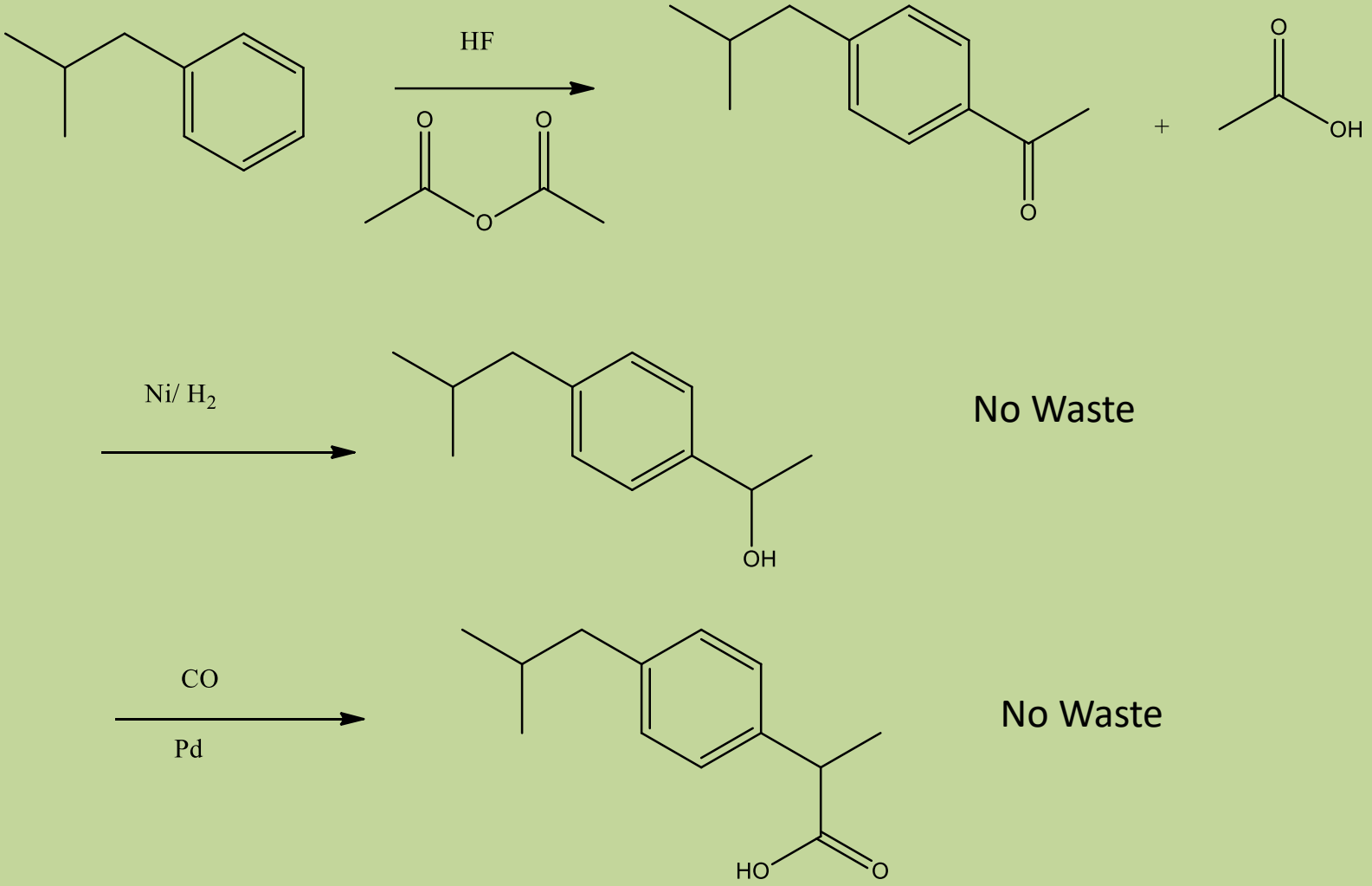
Mechanism



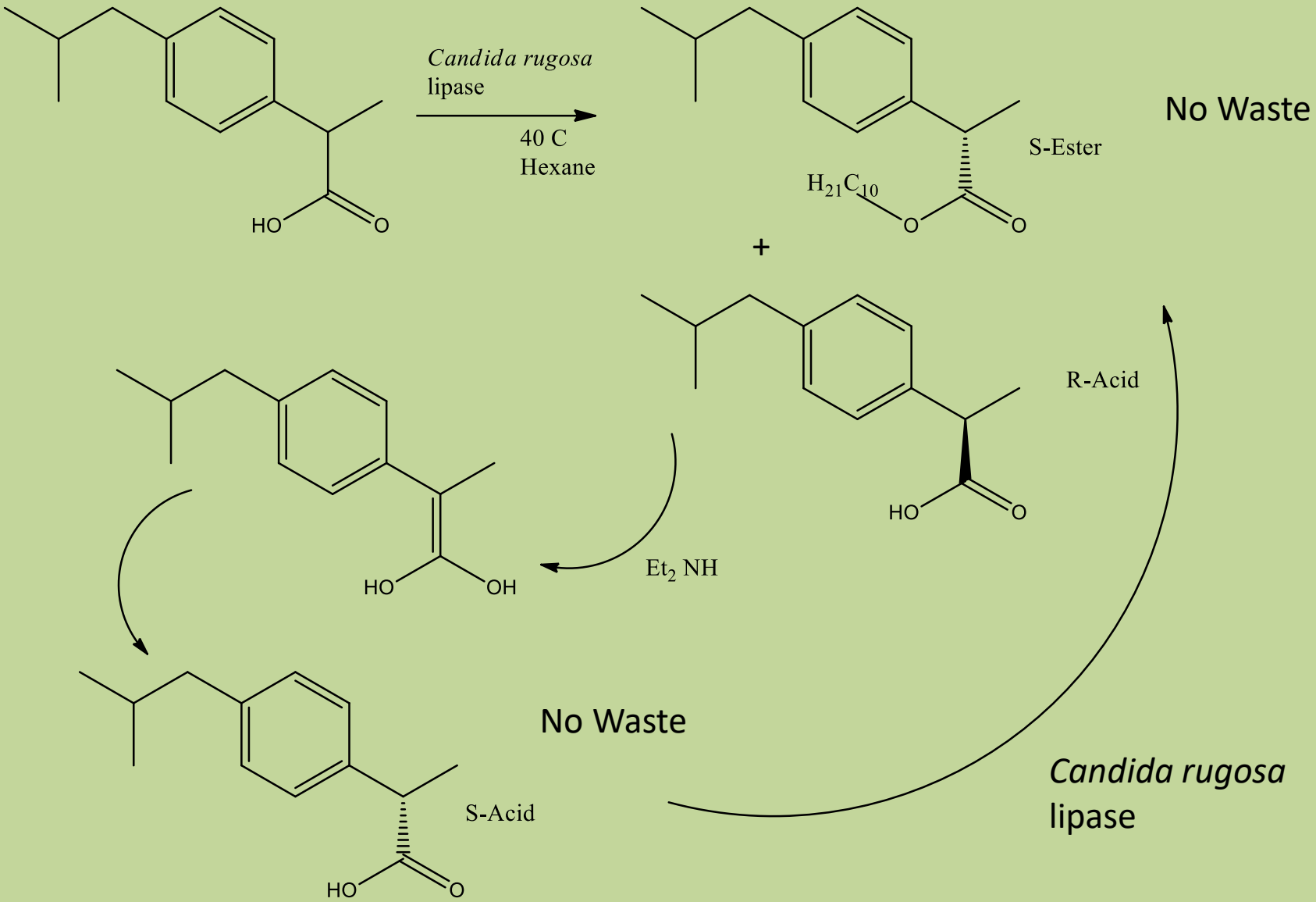
Disadvantage of Boot's process

- Large number of steps
- Large number of side products in each step.
- Poor Atom Economy
- Product is a Racemic mixture of *S*-Ibuprofen and *R*-Ibuprofen. That means 50% of the product remains biologically less useful or active.

Greener synthesis than Boot:
The Boots-Hoechst-Celanese



The Synthesis of *S*-Ibuprofen

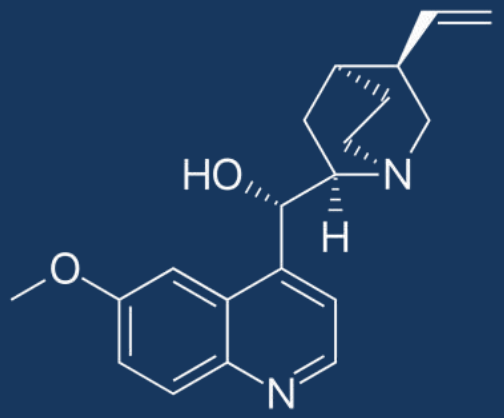


Cardiovascular drugs

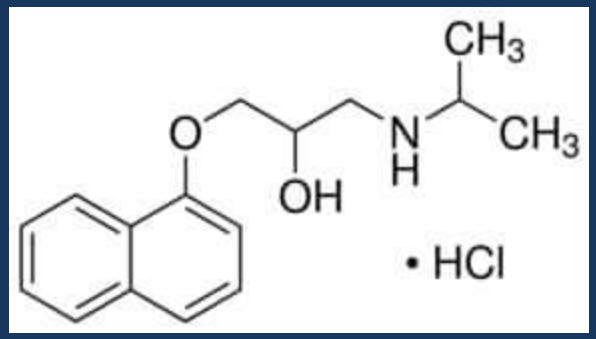
- Cardiovascular drugs are meant for better functioning of heart and or circulation of blood for oxygen transport. It consists of three subclasses

Anti arrhythmic drugs (Beta Blockers and ACE inhibitors) :
These are used to suppress abnormal rhythm.

Quinidine (blocks sodium ion influx causing slower heart rate)



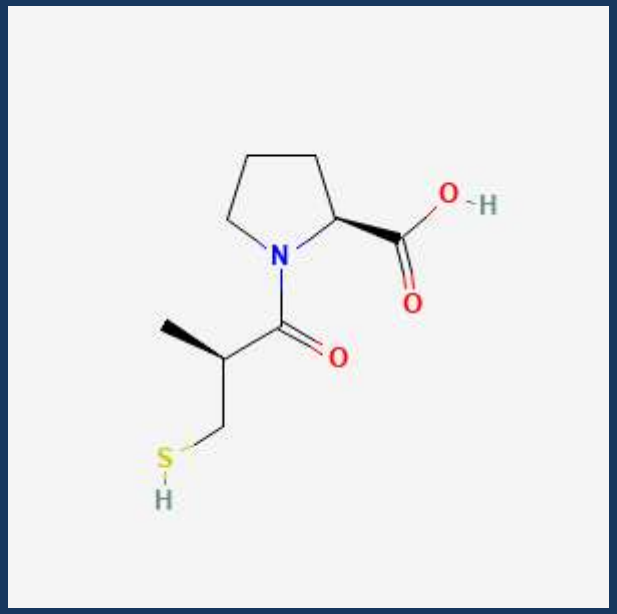
Beta Blocker



These block the function of hormones viz. adrenaline and nor adrenaline. These hormones are responsible for a very fast heart beat by forcing the heart muscle to pump with extreme rapidity

Propranolol: Beta Blocker

ACE (Angiotensin Converting Enzyme) Inhibitors



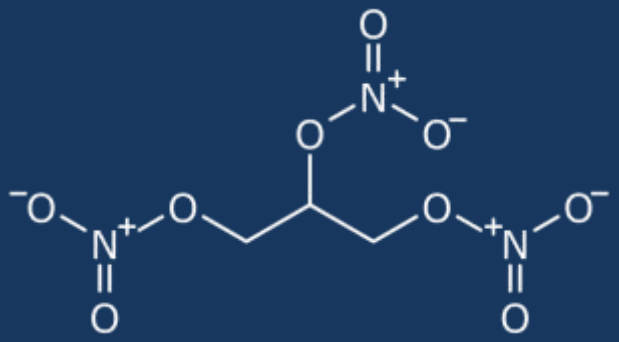
Captopril

ACE inhibitors **prevent an enzyme in the body from producing angiotensin II, a substance that narrows blood vessels**

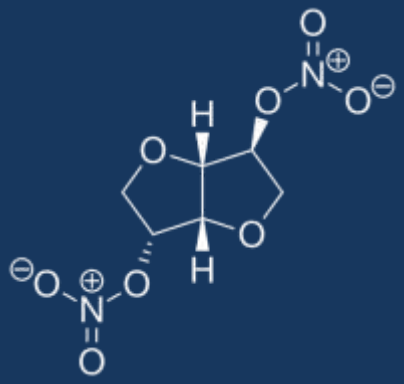
Cardiovascular drugs cont..

Anti-anginal drugs: These widen the blood vessels and help in better transport of oxygen.

Glyceryl nitrates fall in this category. Isosorbide dinitrate, marketed as Sorbitrate is a widely popular drug of this class.



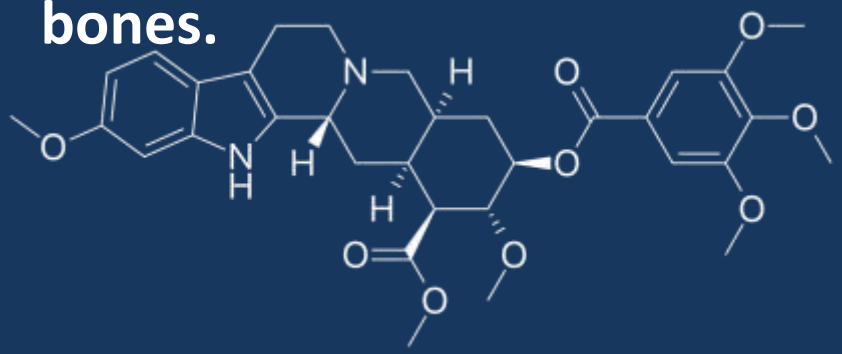
Glyceryl trinitrate



Sorbitrate

Cardiovascular drugs: cont..

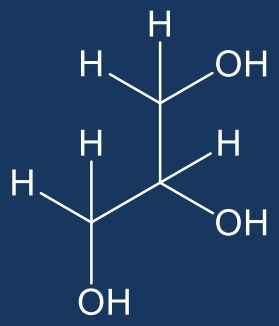
Anti hypertensive drugs: **These are used to reduce the blood pressure. A well known natural drug for this purpose is reserpine. Calcium channel blockers fall in this class. Calcium influx into the heart muscle cells and help those to contract with force. This class of drugs block calcium ion influx. Calcium ion comes into the blood stream from bones.**



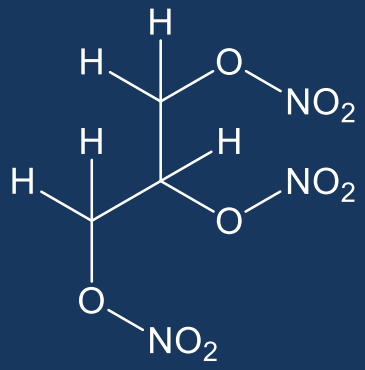
Reserpine

Cardiovascular Drugs cont..

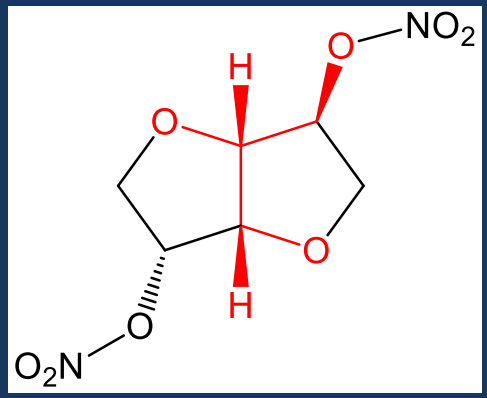
- Anti anginal agents: These widen the blood vessels and help in better oxygen transport preventing heart attack (angina pectoris). Glyceryl nitrates fall in this class.



Glycerin or Glycerol



Glyceryl trinitrate

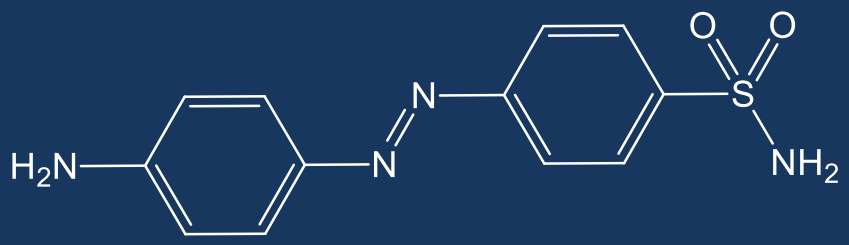


Sorbitrate
(isosorbid nitrate)

Anti Bacterial Drugs: The Sulphonamides

Sulphonamides were the first antibacterial drugs which were used systematically

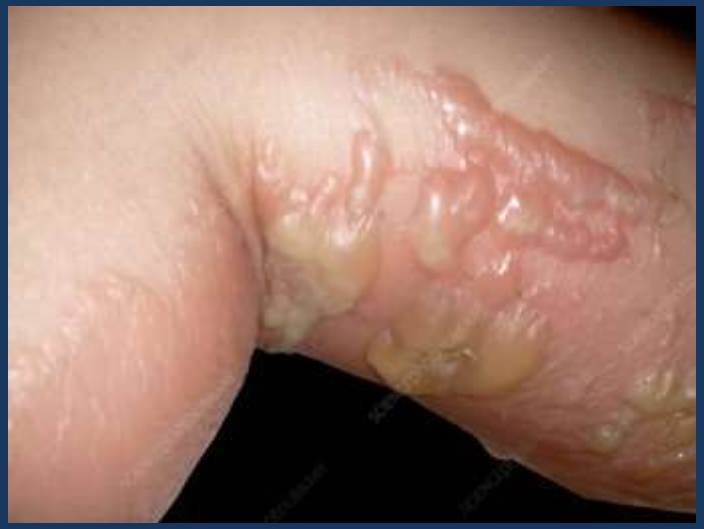
The first sulphonamide was " Prontosil" .



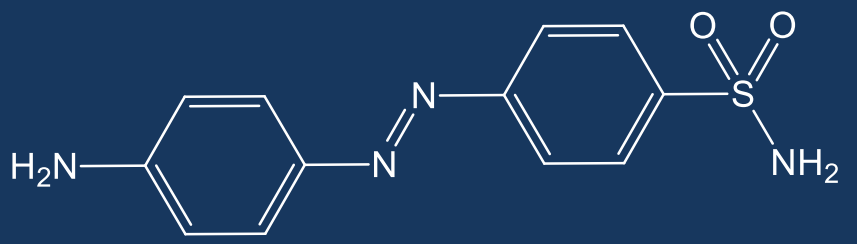
It was the first prodrug which could be used against a range of bacterial infections including streptococcus viz. blood infections , child bed fever and erysipelus

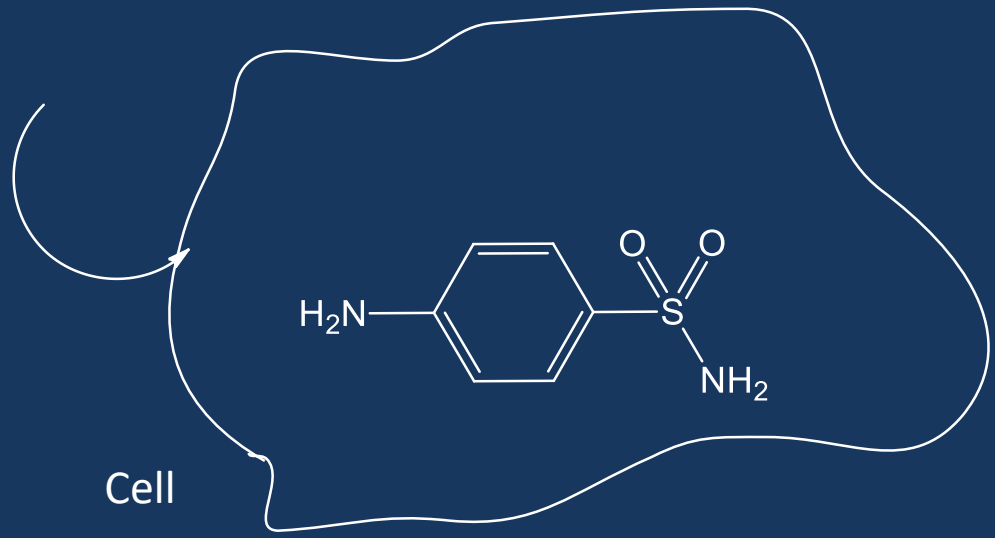
Prontosil is a pro drug

Inside the body the compound decomposes into sulphanilamide which is biologically most active.



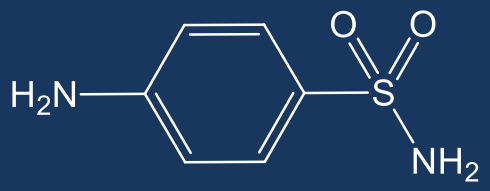
Erysipelus



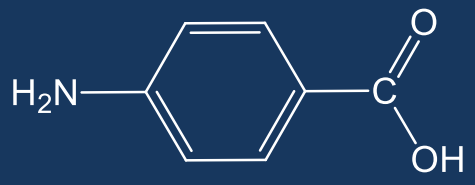


Sulphanilamide

Sulphonamides are structurally similar to p-amino benzoic acid



Suphanilamide



PABA

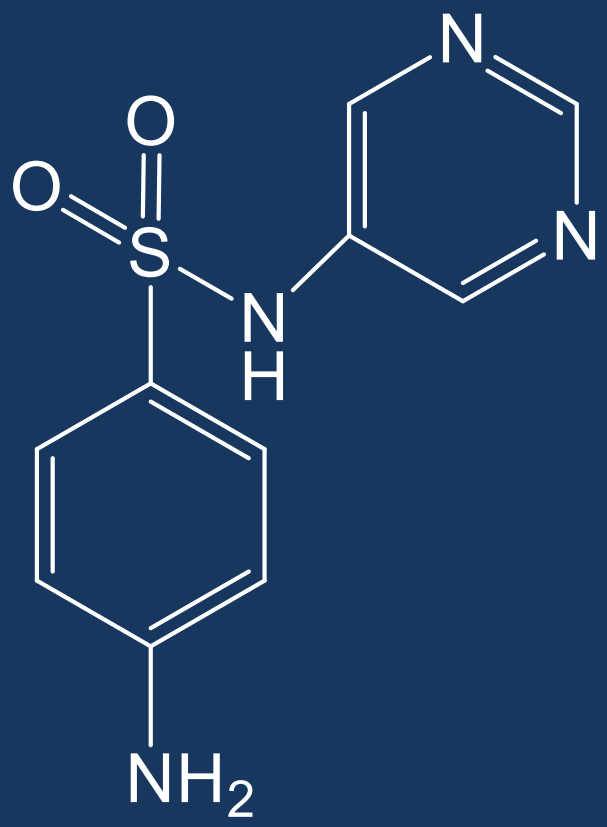
Thus sulphanilamides act as a mmic of PABA. Bacteria uses PABA to synthesise folic acid as a part of their metabolism. Sulphanilamides are taken up by bacteria and the process of folic acid synthesis by bacterial enzyme is inhibited.

Trimethoprim: Compound and use:

Trimethoprim

- Trimethoprim is a not a sulpha drug.
- It acts as a dihydrofolate reductase inhibitor.
- It prevents bacteria to form folic acid.
- Hence sulphonamides are given with it as a combination

Short acting **sulphonamides**



Sulpha diazines

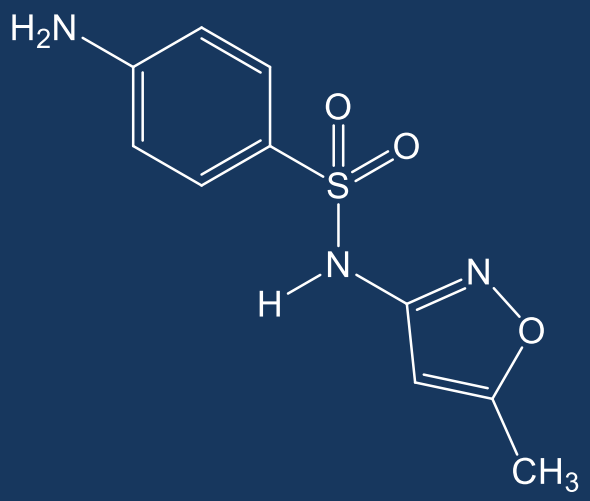
- **These are effective very soon after being administered.**
- **For a long treatment these are repeated periodically.**

- **Short acting suphonamides are used for urinarey tract infection as these are excreted in high concentration with urea.**

- **Urea binds it via H-bonding.**

Intermediate acting sulphonamides

Sulphamethoxazole is the main representative of this group

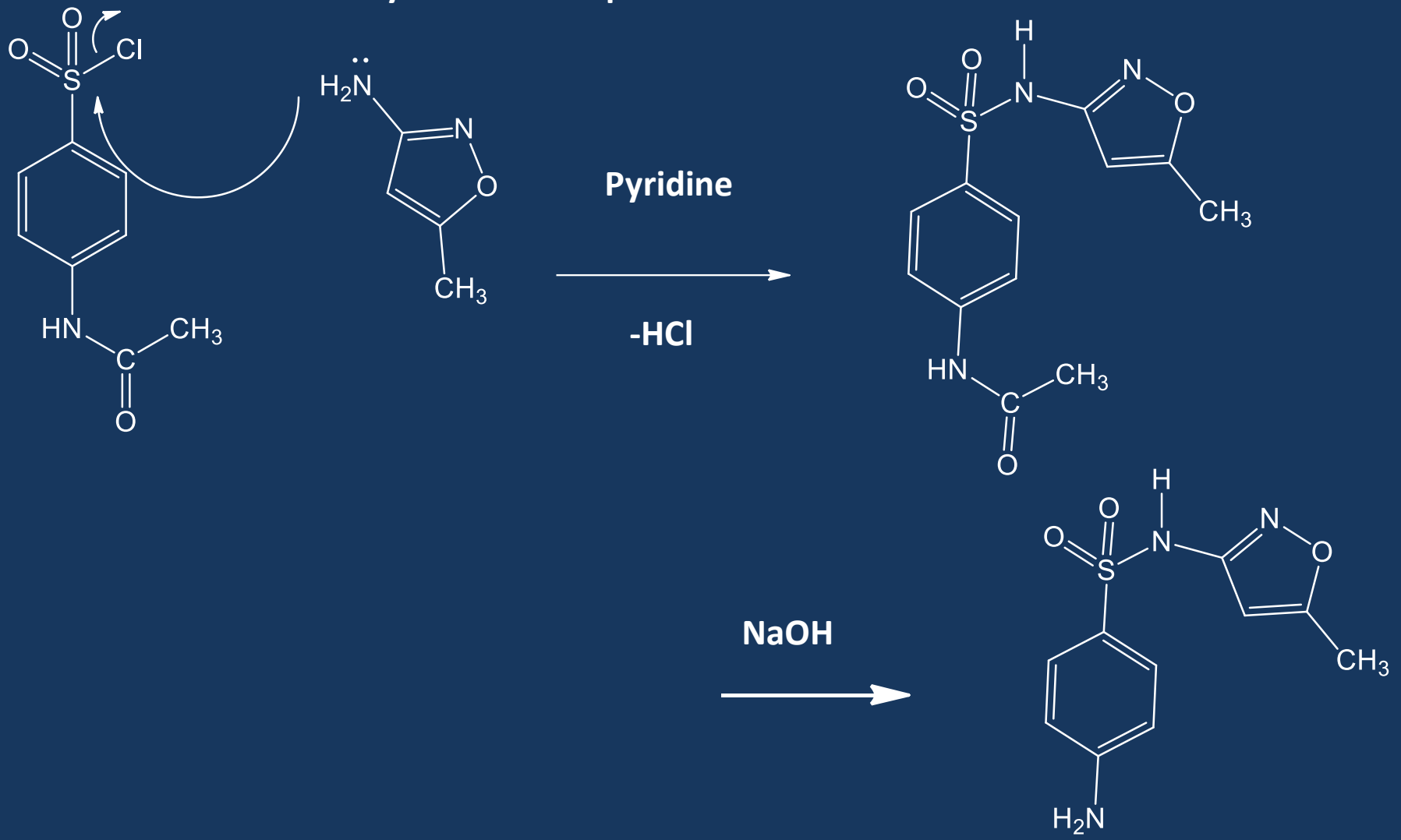


•Sulphamethoxazole with trimethoprim together produce a bacteriocidal effect against a wide range of gram positive and gram negative bacteria and protozoa. The combo is named as Co-trimoxazole (5:1) .

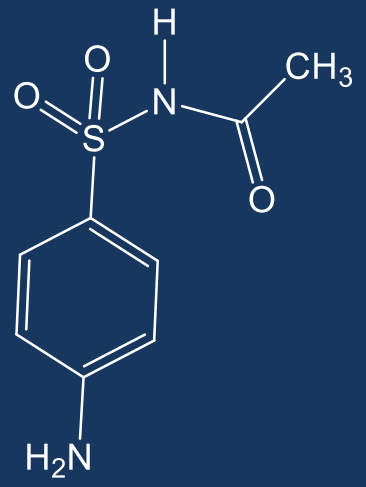
•The combo is used to treat infections of urinary, respiratory and gastrointestinal tracts.

Intermediate acting sulphonamides

Synthesis of sulphamethoxazole

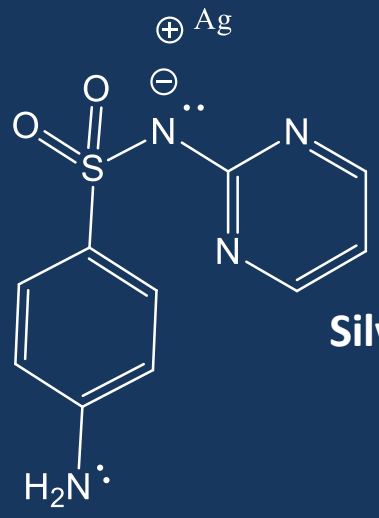


Sulphonamides For Topical Use

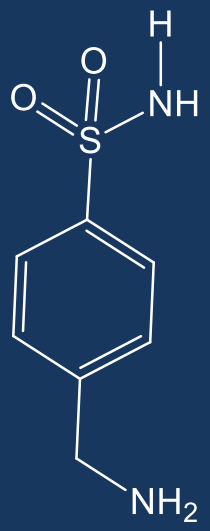


Sulphacetamide: Sulphacetamide sodium (a water soluble form) is exclusively used for opthalmic use as ointment

Silver sulphadiazine and Mafenide acetate is used in burns as antibacterial agents

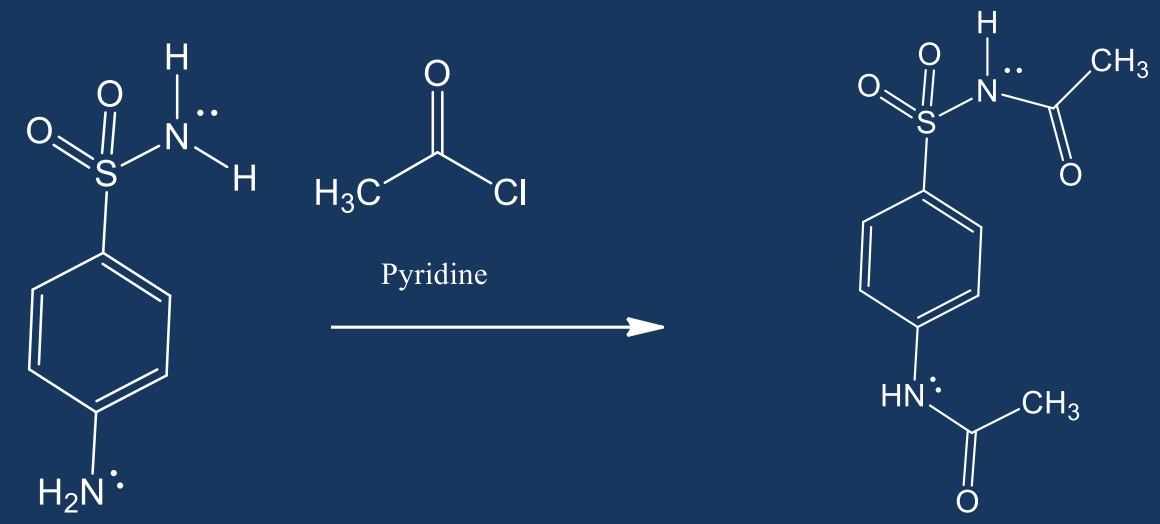


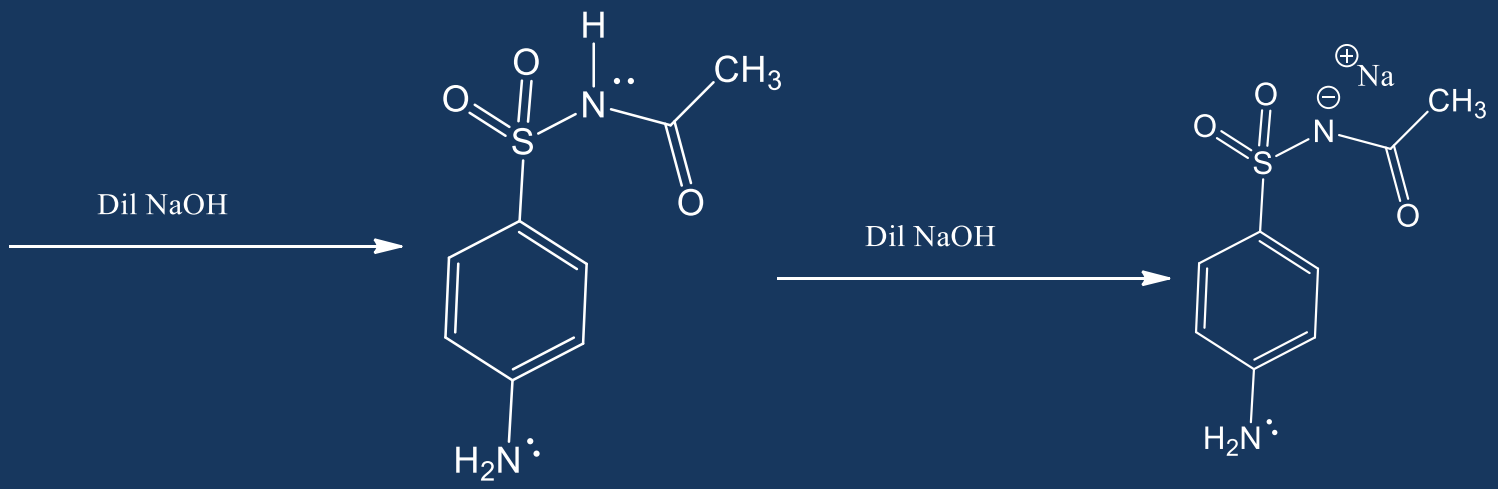
Silver sulpha diazine



Mafenide

Synthesis



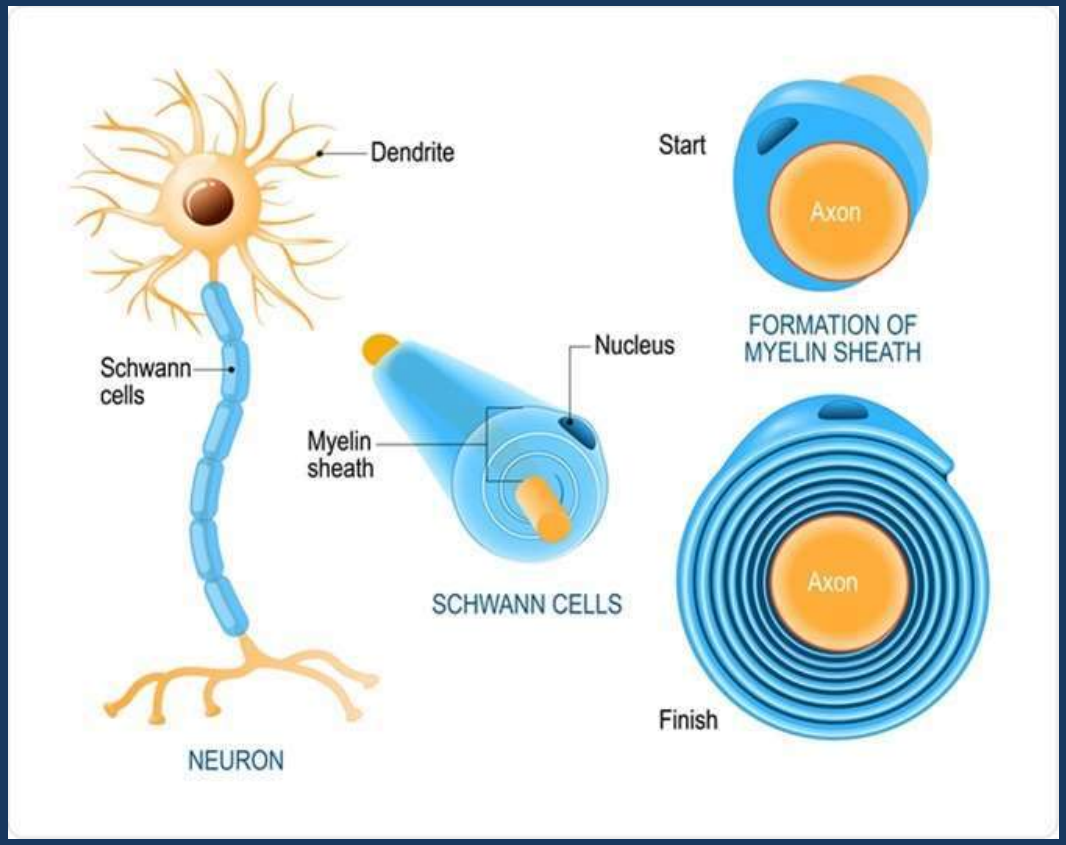


Anti Leprosy Drug

Micobacterium leprae (Leprosy bacillus or Hansen Bacillus**) is the microorganism responsible for human leprosy and has been reported to be infectious. It damages the peripheral nerves and targets skin, eyes, nose and muscle.**

Leprosy expression

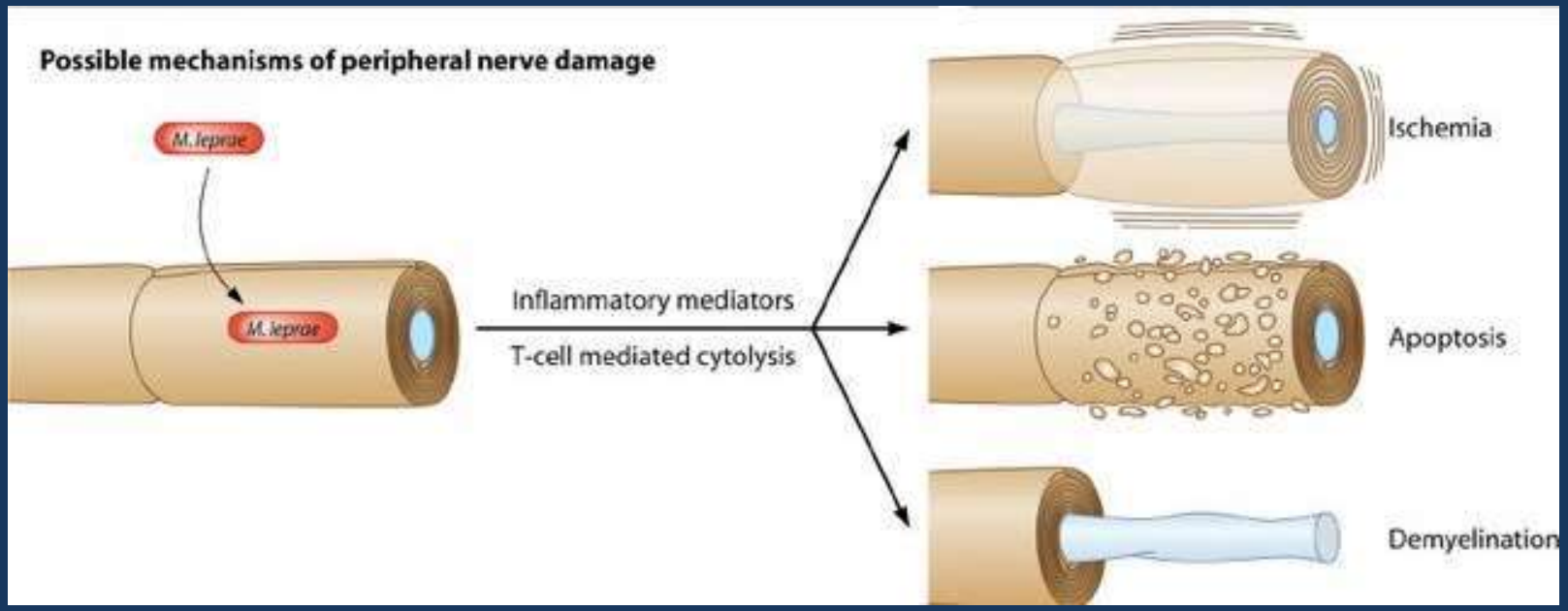
Action of *Micobacterium leprae*



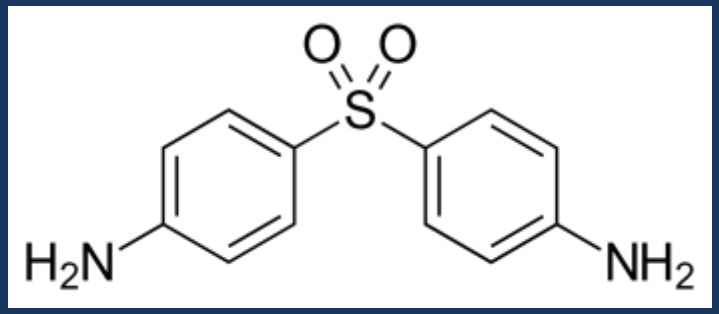
Primarily invades Schwann cells (SCs) in the peripheral nerves leading to nerve damage and the development of disabilities.

It damages the nerve cells via releasing exotoxins or through immune mechanism

Action of *M. leprae*



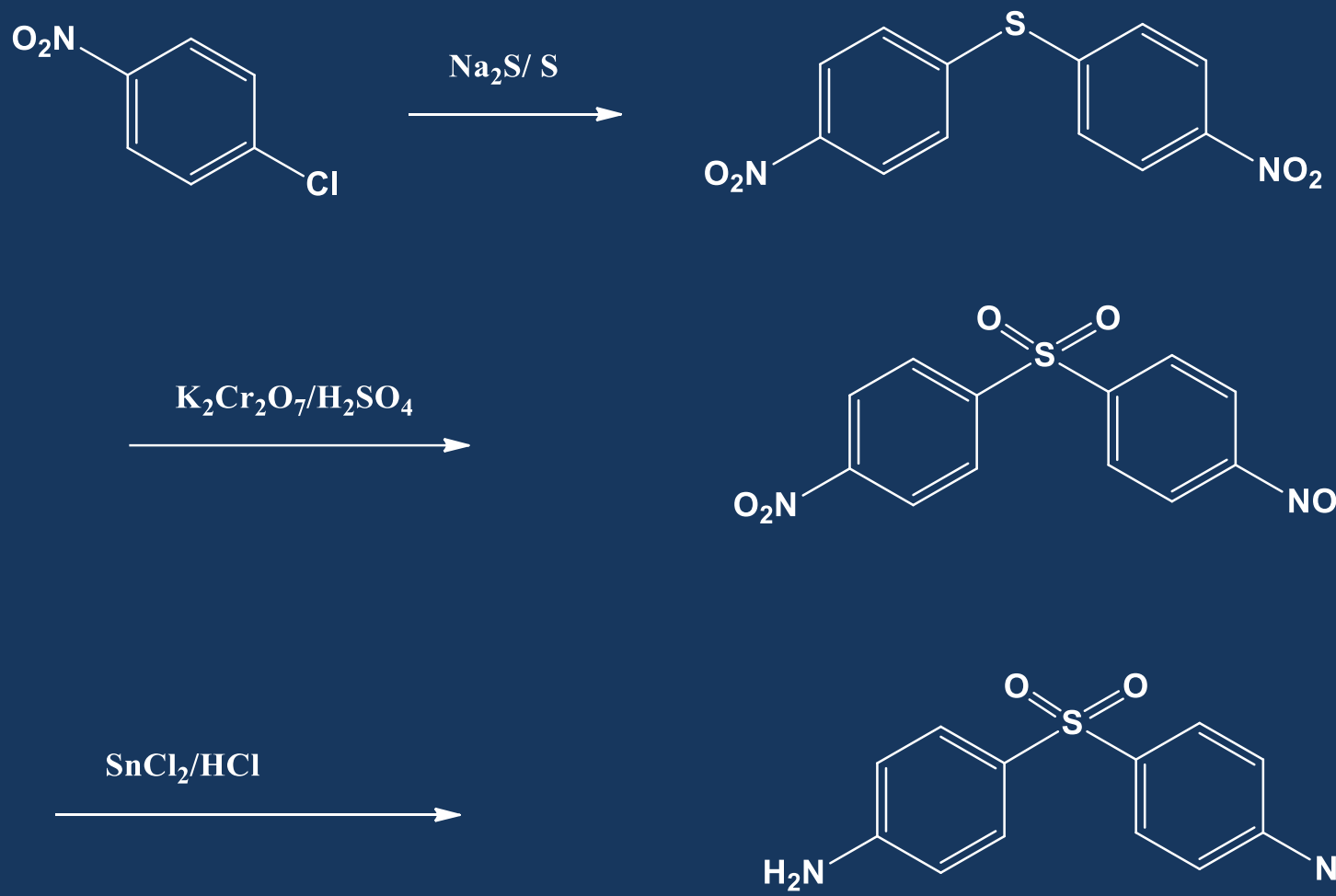
Use of sulpha-drug



Dapsone

Bis-(4 amino phenyl)sulphone, Dapsone became available since 1940 and has been used as the standard drug for the treatment of Leprosy.

Synthesis


O2N
Cl
Na2S/ S
S
O2N
NO2
K2Cr2O7/H2SO4
O
O
S
O2N
NO2
SnCl2/HCl
O
O
S
H2N
NH2

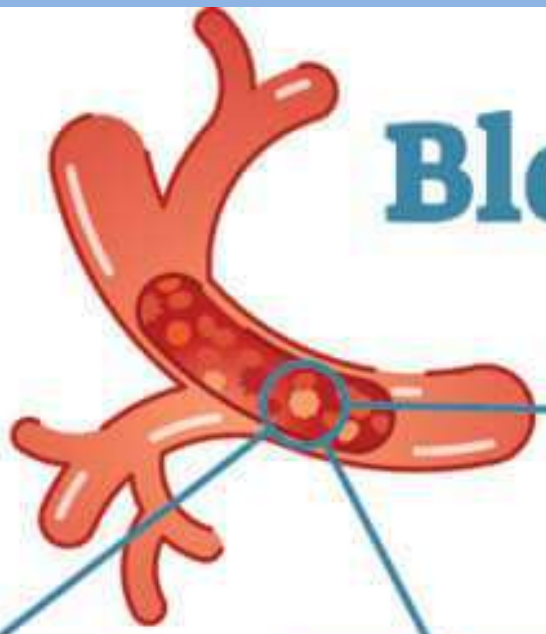
Mechanism of Action

- **It s action is similar to sulphonamides**
- **Bacteria use 4-amino benzoic acid (PABA) to form folic acid as a part of its metabolism**
- **Dapsone mimics 4-amino benzoic acid (PABA)**
- **Dapsone is absorbed by the bacteria and its enzyme action is inhibited.**

Anti-HIV drug

- The Human Immune Deficiency Virus infection causes AIDS (Acquired Immune Deficiency Syndrome)
- The infection causes the depletion of CD4 lymphocytes
- Lack of lymphocytes leads to immune deficiency

Blood Cells



Platelets

Thrombocytes

Red Blood Cells

Erythrocytes

White Blood Cells

Basophil

Neutrophil

Eosinophil

Monocyte

Lymphocytes

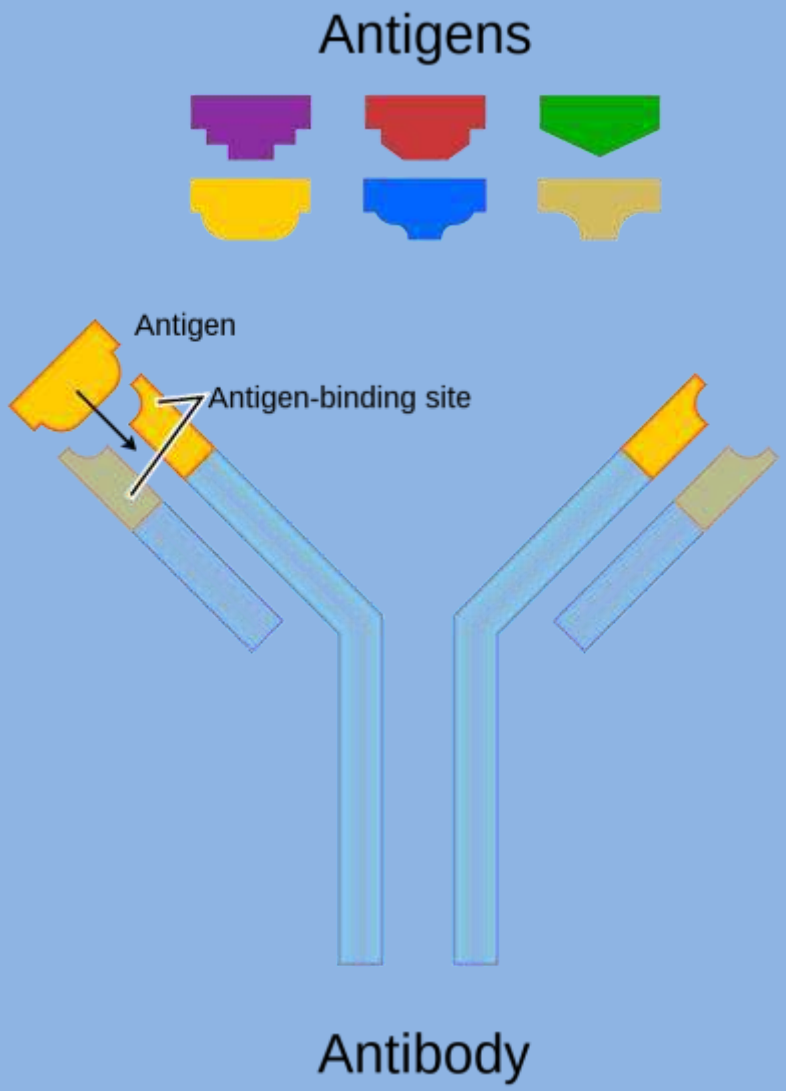
Antigen and Antibody

Antigen (**Ag**) is a molecule or molecular structure or any foreign particulate matter that can bind to a specific antibody or T-cell receptor.

The term *antigen* originally referred to a substance that is an antibody generator.

Antigens can be proteins, peptides (amino acid chains), polysaccharides (chains of monosaccharides/simple sugars), lipids, or nucleic acids, microorganisms including Virus, Bacteria.

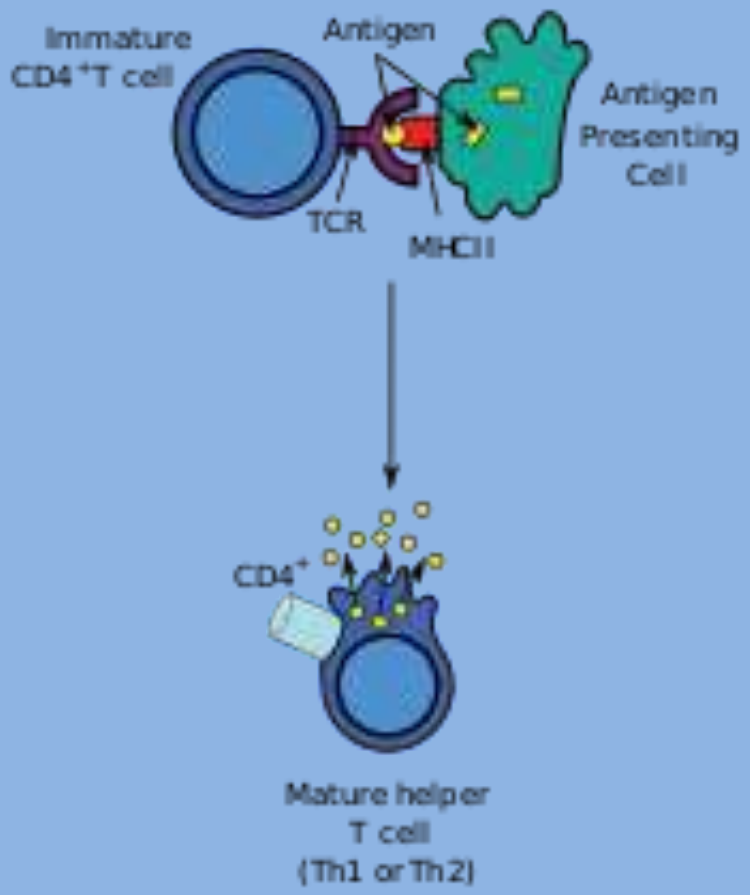
Immunity: Antigen and Antibody



Antigen-presenting cells present antigens in the form of peptides on histocompatibility molecules.
The T cells selectively recognize the antigens; depending on the antigen and the type of the histocompatibility molecule.

An **antibody** (**Ab**), also known as an **immunoglobulin** (**Ig**),[1] is a large, Y-shaped protein used by the immune system to identify and neutralize foreign objects such as pathogenic bacteria and viruses.

Immunity

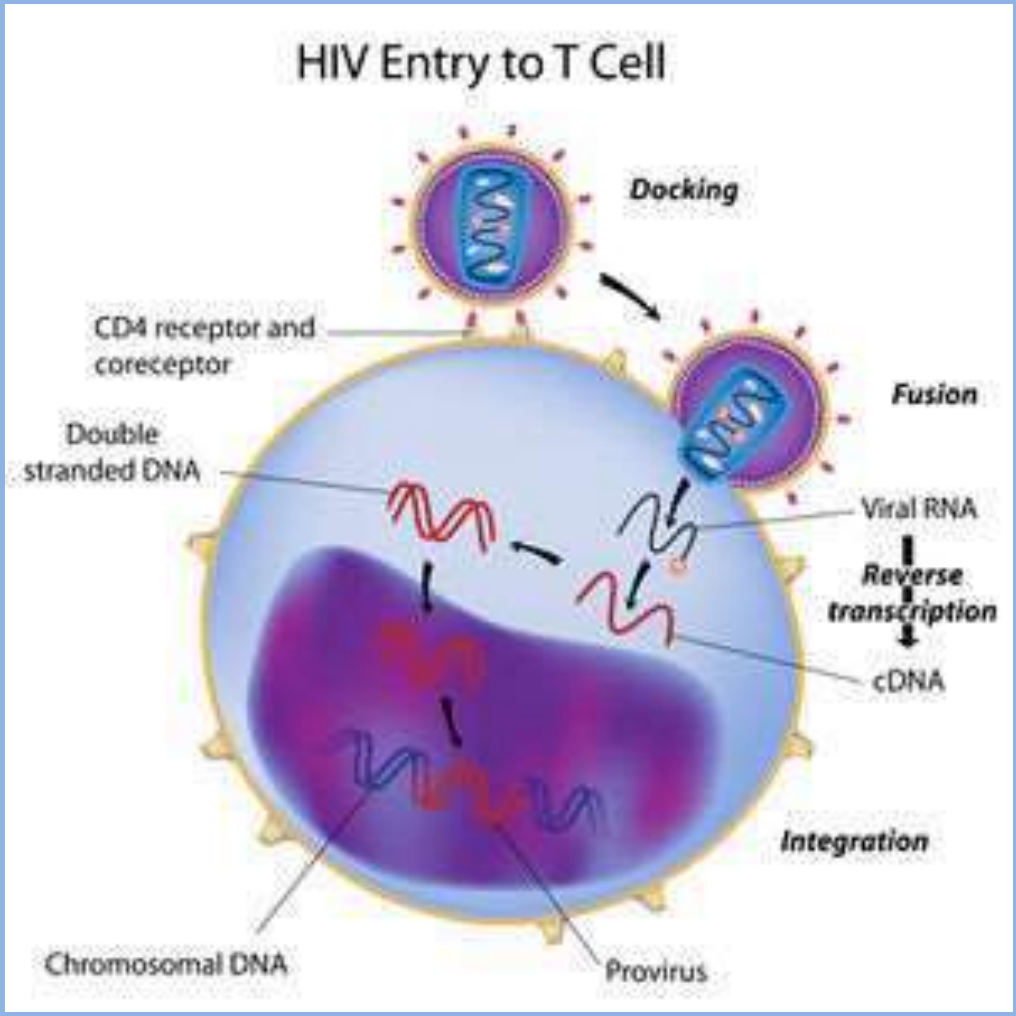


- **CD4 (cluster of differentiation 4) is a glycoprotein that serves as a co-receptor for the T-cell receptor (TCR).**

- **CD4 is a co-receptor of the T cell receptor (TCR) and assists the latter in communicating with antigen-presenting cells (APC).**

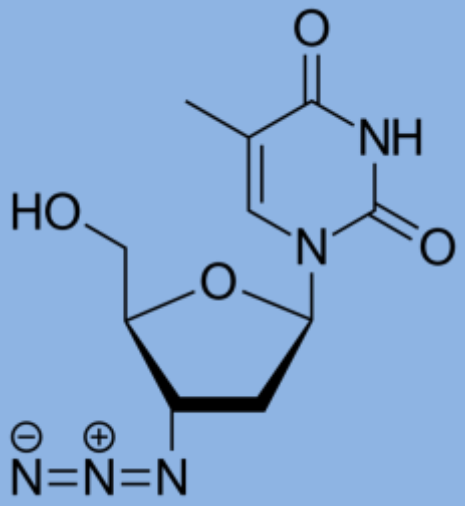
- **APCs process antigens and present them to T-cells.**

Types of HIV drugs

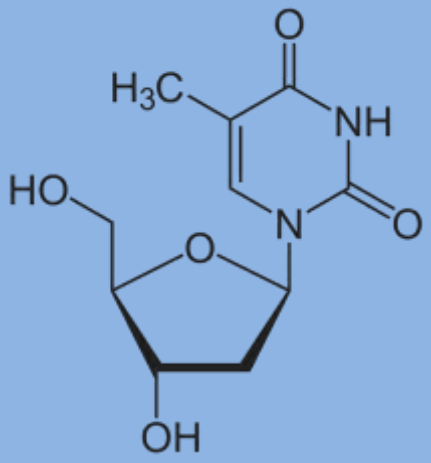


- Reverse Transcriptase Inhibitors
- HIV Protease Inhibitors

Anti HIV Drug: Zidovudine
AZidoThymidine (AZT)



Zidovudine

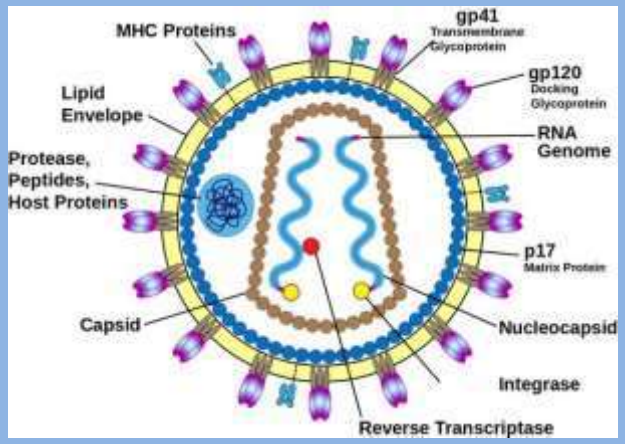


Thymidine

Zidovudine is structurally similar to Thymidine

Retro virus and RNA Virus

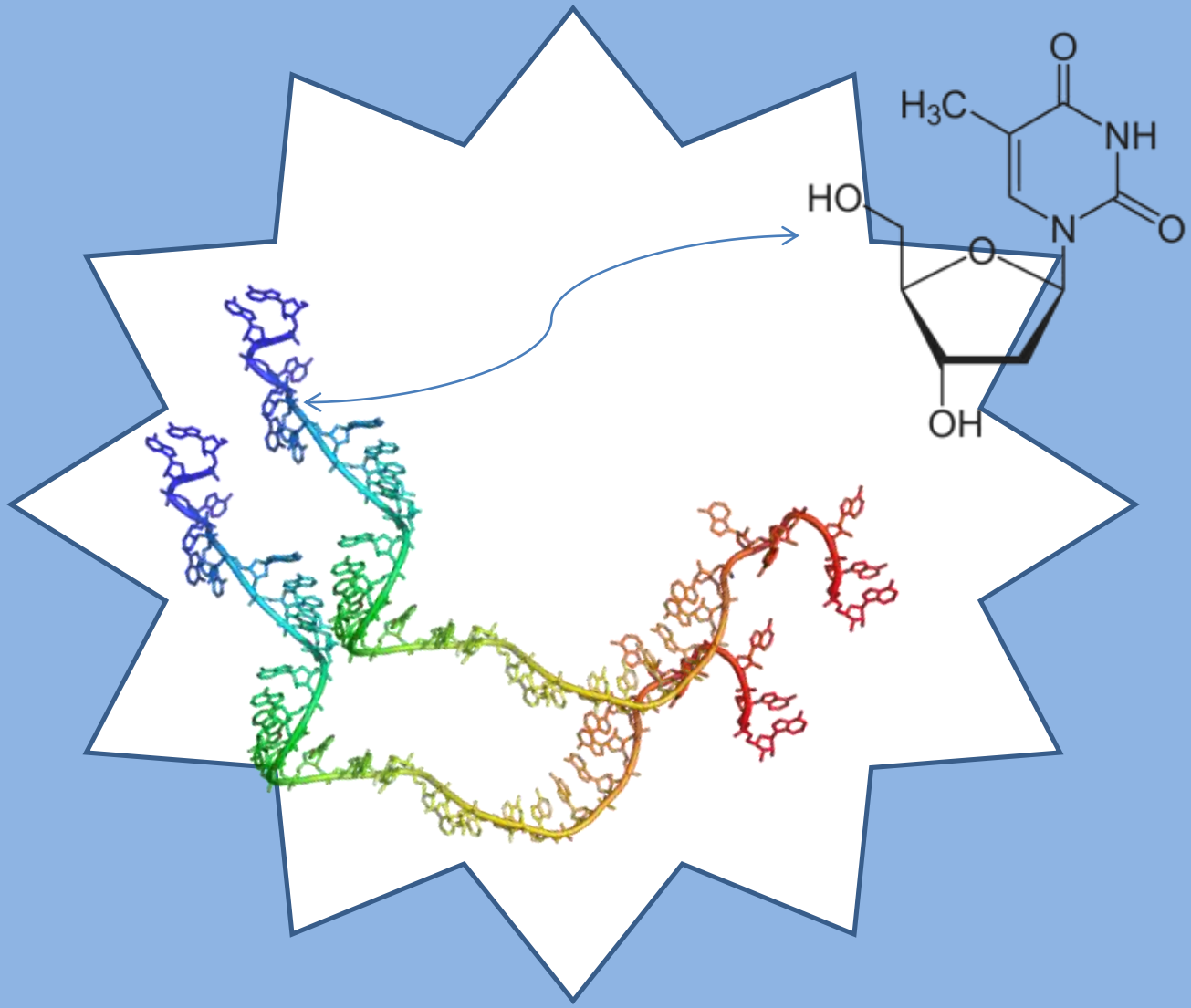
Most RNA viruses reproduce by inserting RNA into the host cell. The RNA contains the instructions for making copies of the virus.



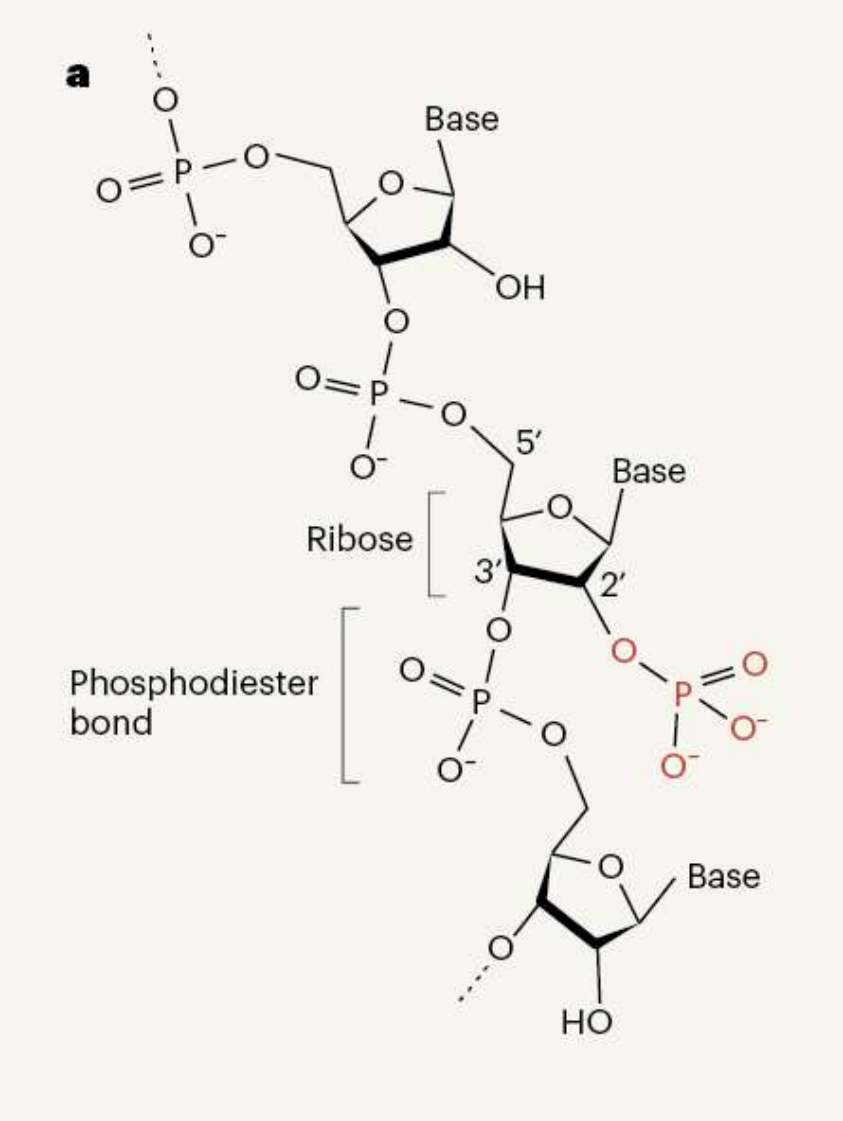
A retrovirus is an RNA virus, but instead of inserting the RNA directly into the cell, it first converts it into DNA.

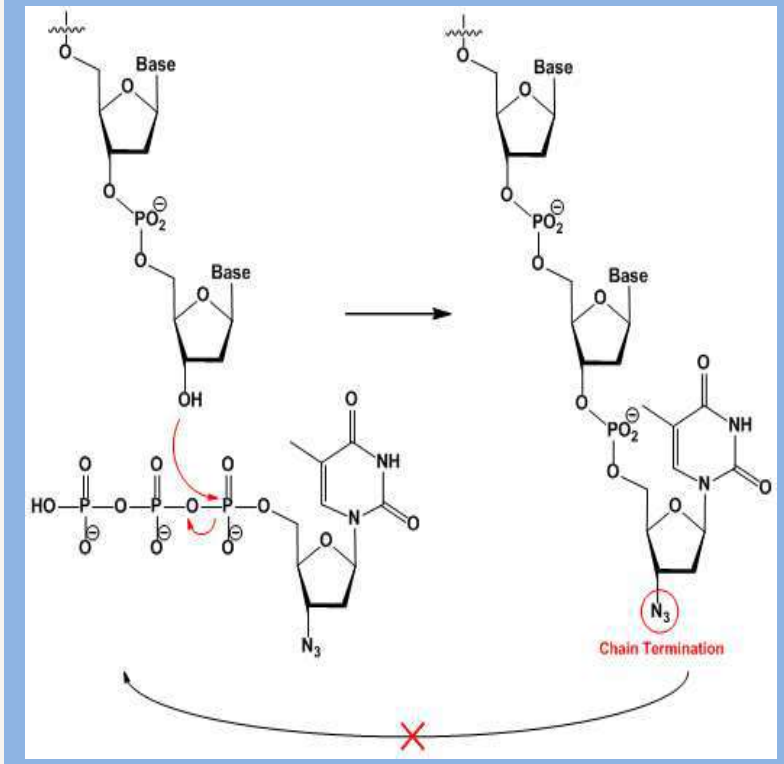
The HIV genome consists of **two identical single-stranded RNA molecules** that are enclosed within the core of the virus particle.

HIV virus structure

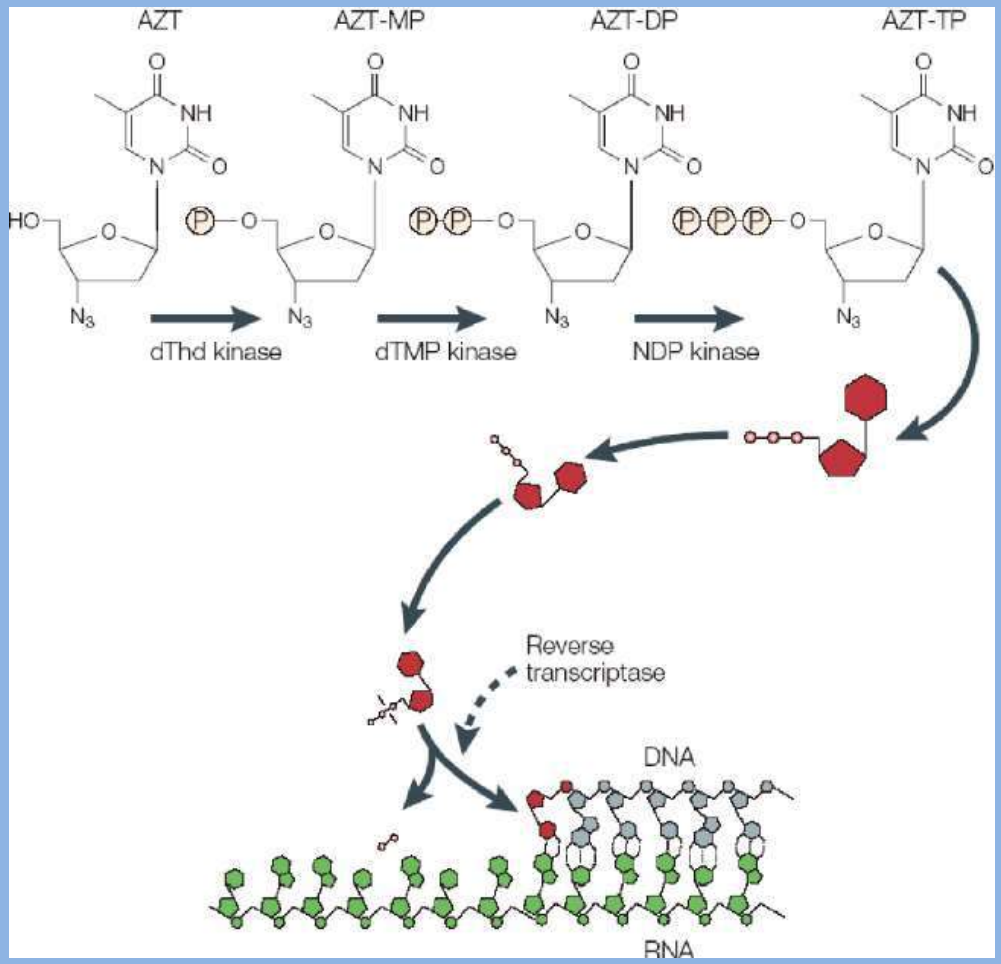


Chain growth of RNA





Mechanism of action of AZT Zidovudine

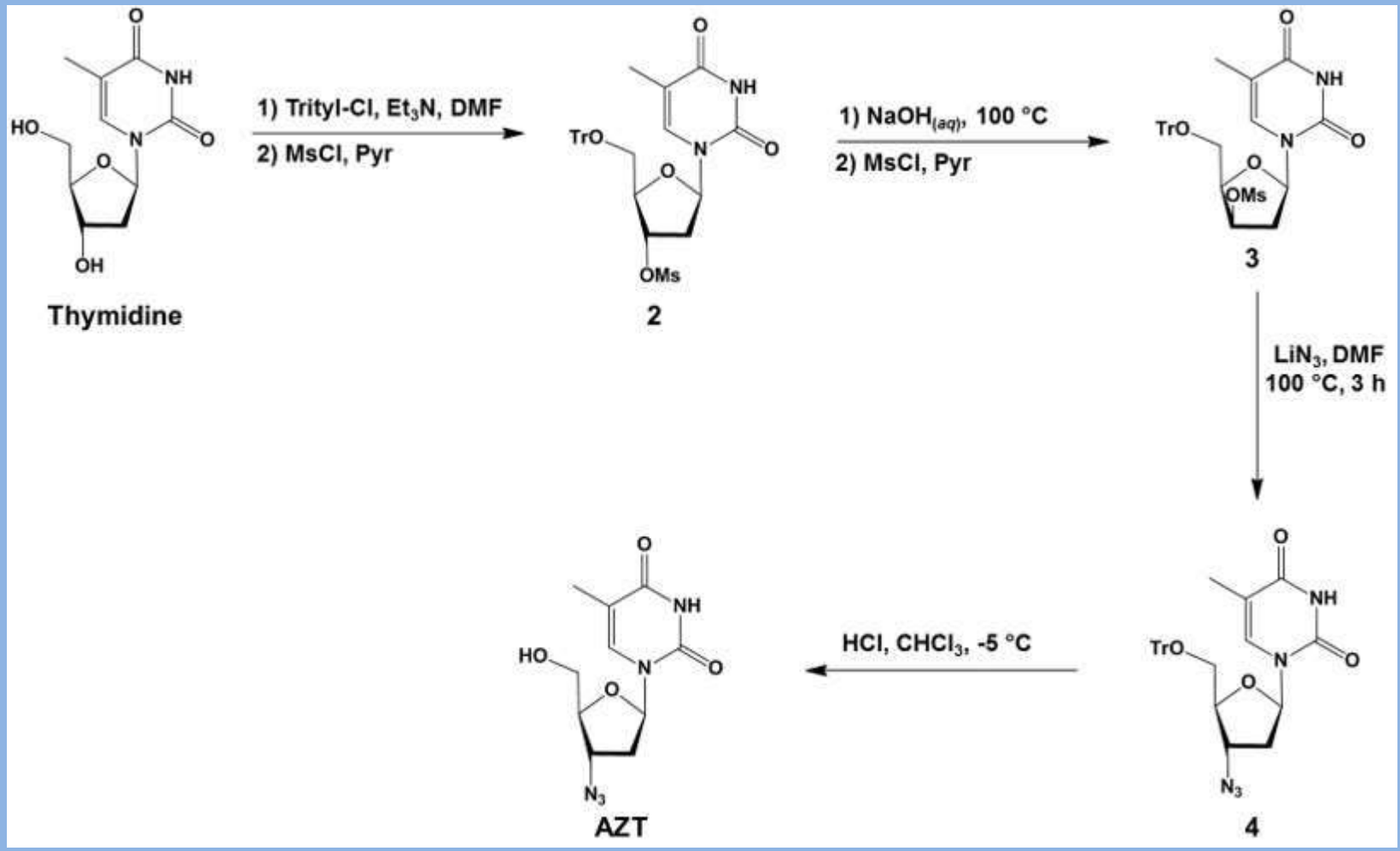


AZT is a thymidine analogue. It is well absorbed by oral intake and is converted to triphosphate.

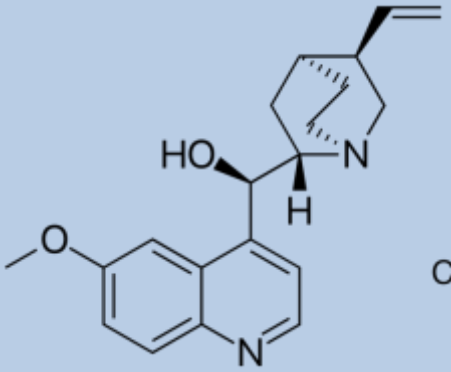
AZT works by **selectively inhibiting HIV's reverse transcriptase**, the enzyme that the virus uses to make a DNA copy of its RNA.

It halts the DNA synthesis

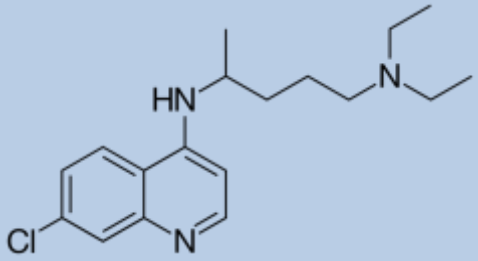
Synthesis


Thymidine
1) Trityl-Cl, Et3N, DMF
2) MsCl, Pyr
2
1) NaOH(aq), 100 °C
2) MsCl, Pyr
3
LiN3, DMF
100 °C, 3 h
4
HCl, CHCl3, -5 °C
AZT

Anti Malarial Drug



Quinine



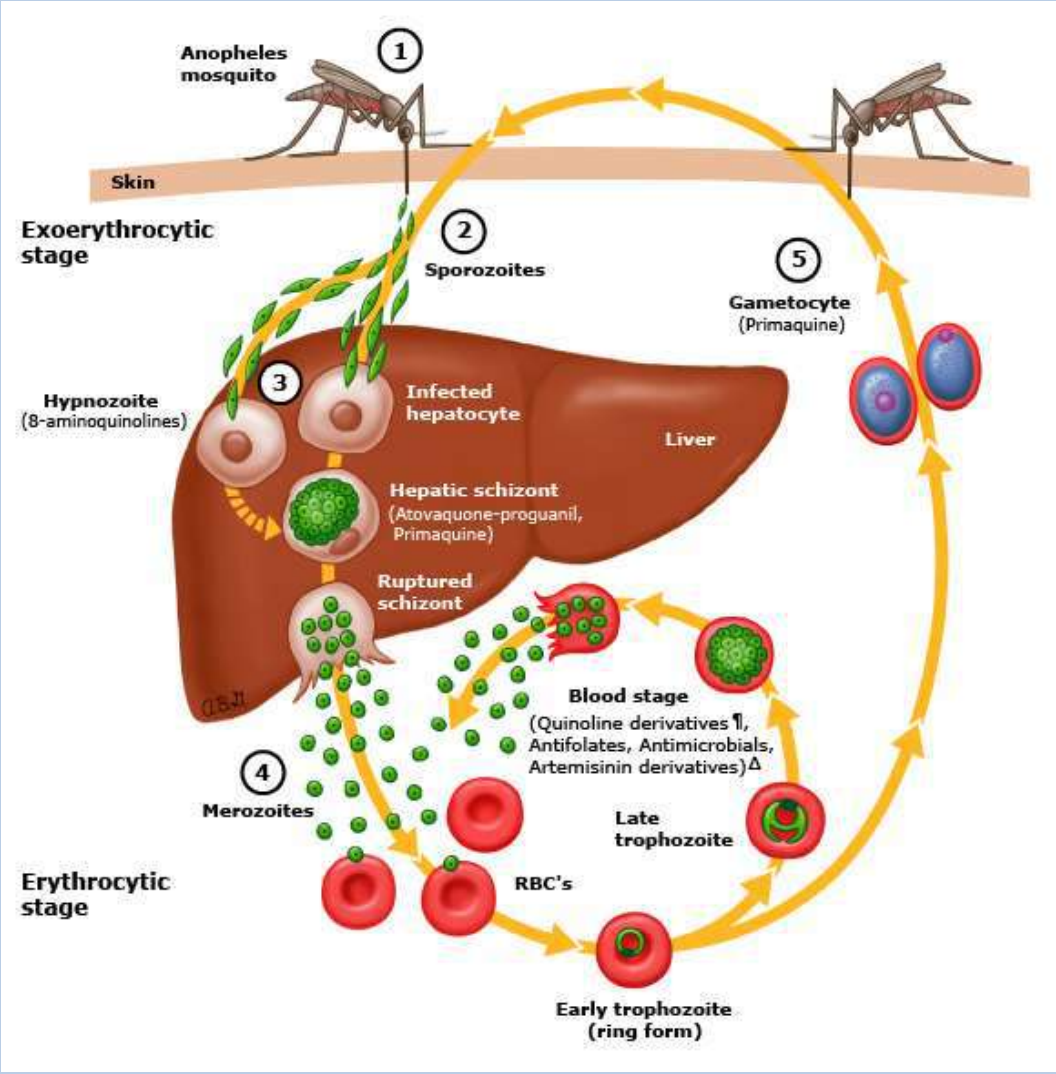
Chloroquinine

Quinine is **used to treat malaria caused by *Plasmodium falciparum*.** It is the only natural drug that can treat malaria.

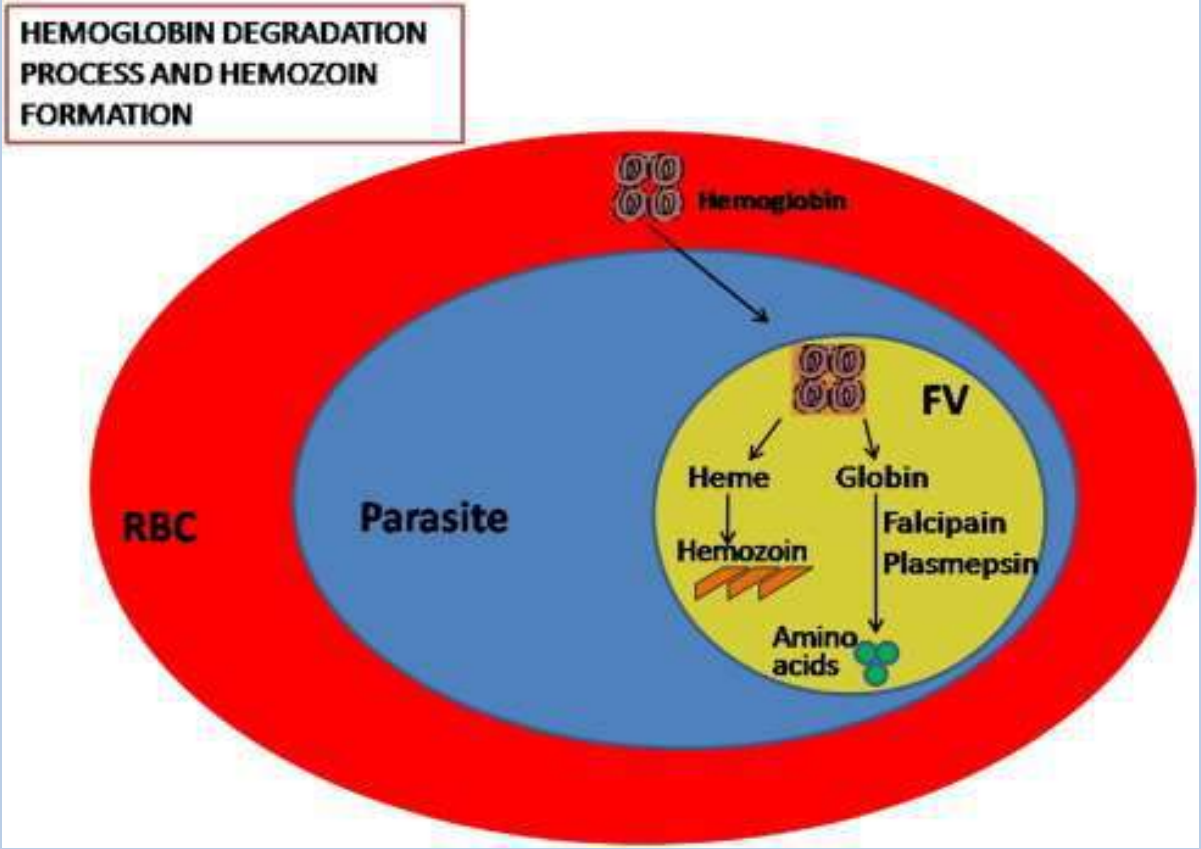
Plasmodium falciparum is a parasite that gets into the red blood cells in the body and causes malaria. Quinine works by killing the parasite or preventing it from growing.

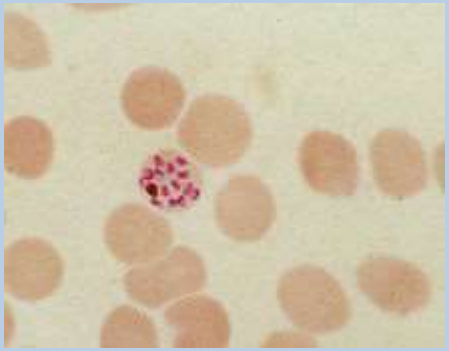
Parthenium integrifolium (wild quinine)

Malaria: How does it happen?



Degradation of Hemoglobin to Heme and Hemozoin formation



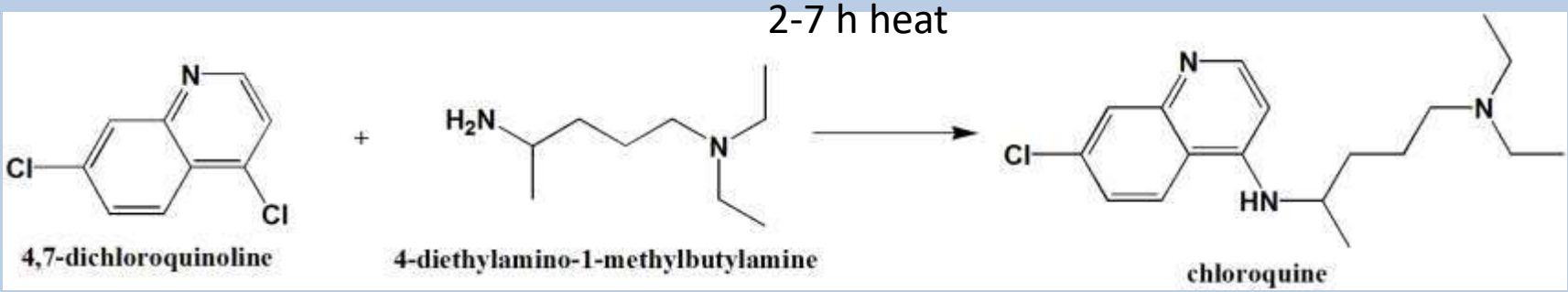


Quinine: Mechanism

- It enters red blood cells and binds with heme through complex formation
- This heme-quinine complex inhibits the metabolic process of the parasite.
- Chloroquine accumulates in the food vacuole of the Plasmodia parasite
- It prevents the conversion of Heme to Hemozoin
- Accumulation of Heme is toxic to the parasite and kills it

Chloroquine synthesis

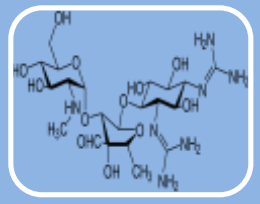
N-C Coupling reaction



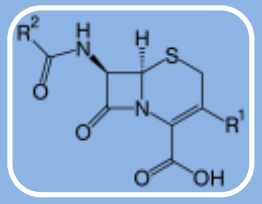
Antibiotics

Antimicrobial substance that can inhibit the growth or kill bacteria and in limited cases active against protozoa.

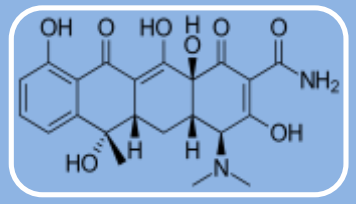
Antibiotics : Classification



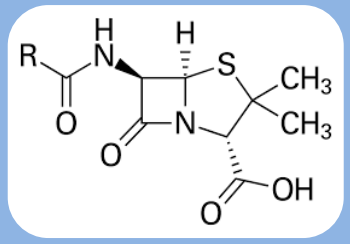
Aminoglycosides



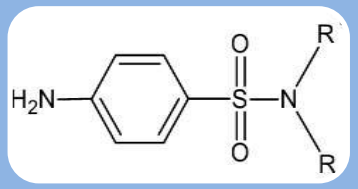
Cephalosporins



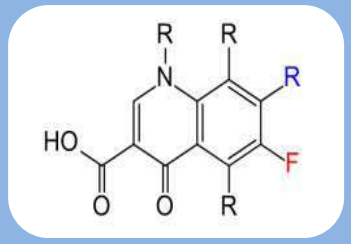
Tetracyclins



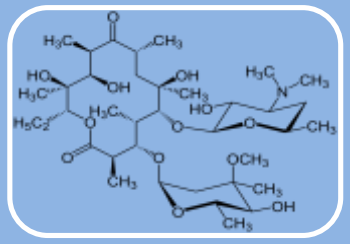
Penicillins



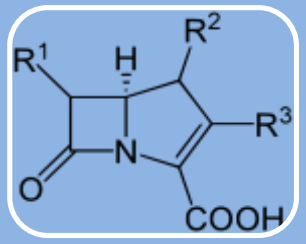
Sulphonamides



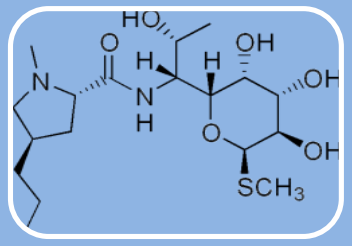
Fluoroquinolones



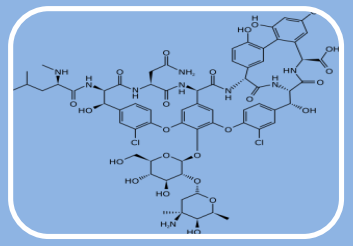
Macrolides



Carbapenems

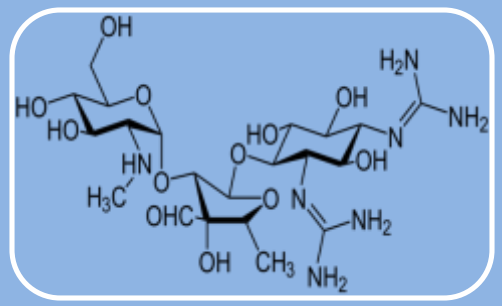


Lincosamides



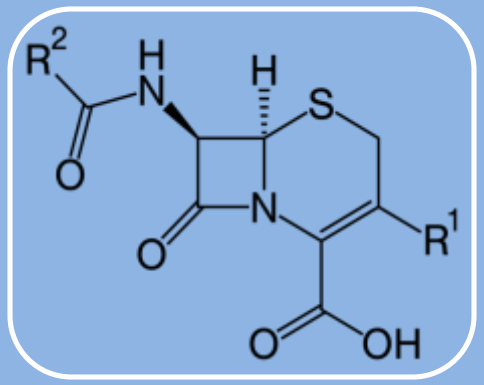
Glycopeptides

Aminoglycosides



- The name ends with “mycin”: e.g. Streptomycin, Gentamycin.
- Used for infection in blood streams and in severe abdominal infections: bacteremia
- These inhibit the protein synthesis in gram negative bacteria.
- It binds with the 30s subunit of the bacterial ribosome.

Cephalosporins



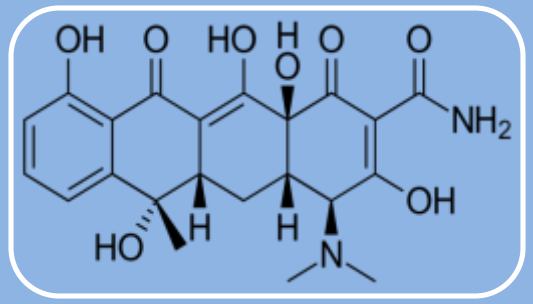
- The name of drugs starts with " ceph" of "Cef"
- For example: Cefixime

- Attacks both gram positive and gram negative bacteria.

- It inhibits cell wall synthesis of bacteria.

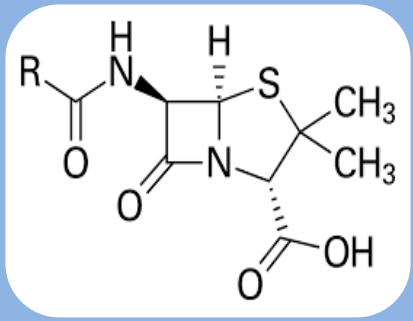
- Used for Skin, Urinary and respiratory infections.

Tetracyclins



- These drugs ends with the name " cycline" For Example: Doxycycline, Methacycline
- Attacks both gram negative and gram positive bacteria
- Acts like amino glycosides by inhibiting the protein synthesis of bacterial ribosome
- Used for Lyme Disease, Pulmonary inflammatory diseases and STDs (Sexually Transmitted Diseases)

Penicillins



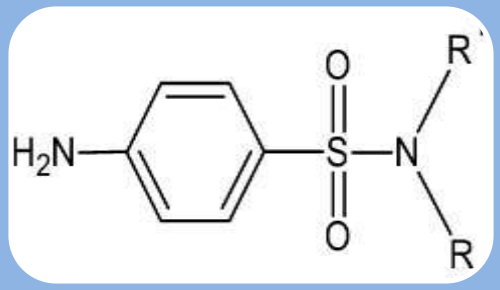
- These ends with the name " cillins" For example: Amoxycillin, Ampicillin

- Attacks both Gram positive and Gram negative bacteria

- Acts like Cephalosporins: inhibits cell wall synthesis of bacterial cell wall

- Used for ENT infections, Urinary Track Infections, Skin infections

Sulphonamides



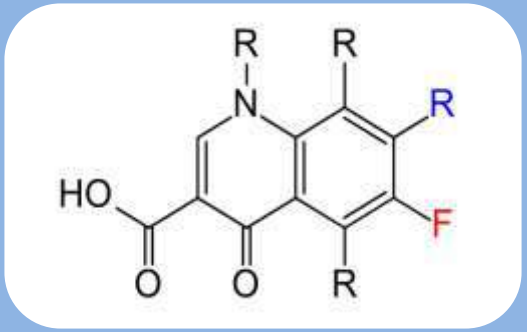
- Starts with “Sulpho”
- Examples: Sulphomethoxazole

- Covers both gram positive and gram negative bacteria

- Kills bacteria by inhibiting folate synthesis

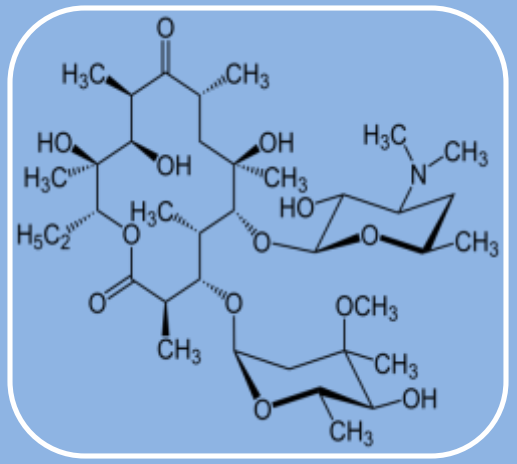
- Used for Urinary Tract Infection (UTI), Burns and Eye infections

Fluoroquinolones



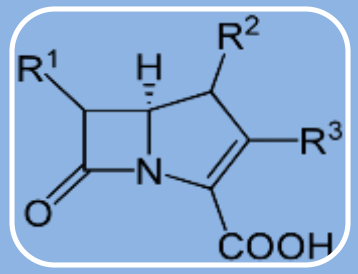
- Drug name ends with “floxacin”. For example: Ciprofloxacin, Levofloxacin
- Covers both gram positive and gram negative bacteria
- Inhibits bacterial DNA replication.
- Used for respiratory and UTI

Macrolides



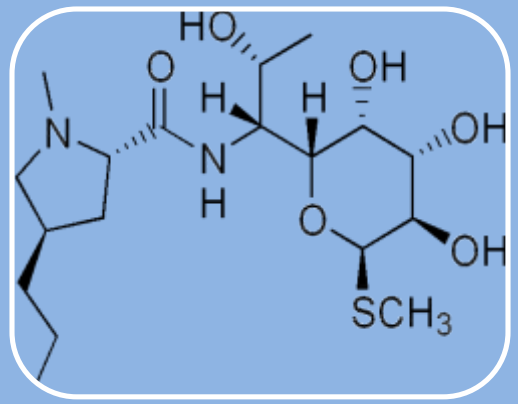
- Ends with the name : “thromycin”. For example , Azethromycin, Erythromycin
- Attacks only gram positive bacteria
- Inhibits bacterial protein synthesis by binding with 50 s subunit of ribosome.
- Used for pneumonia, sinucites, UTI, inner throat infection, STD.

Carbapenems



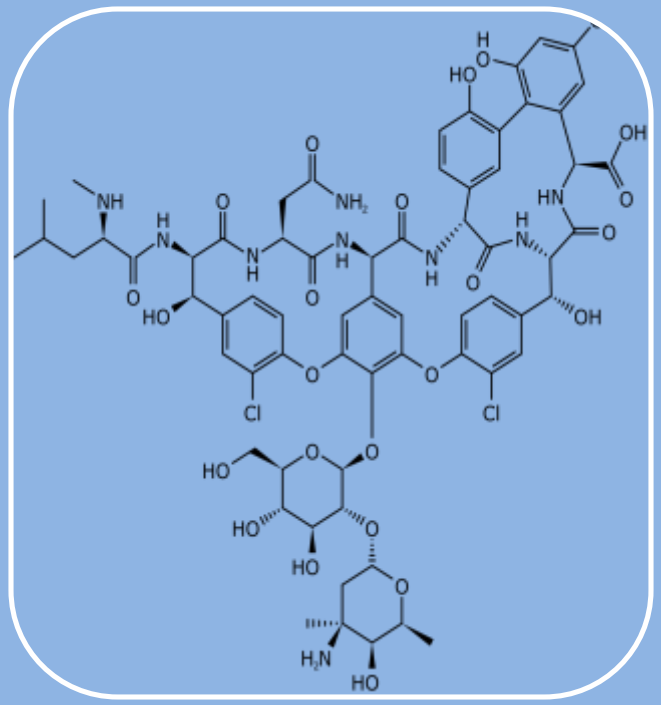
- Name ends with “penems”. Examples are like Meropenem, Ertapenem
- Covers both gram positive and gram negative bactera
- Inhibits bacterial cell wall synthesis
- Used for UTI and Abdomen infections

Lincosides



- Ends with mycin
- Only for gram positive bacteria
- Attacks the 50 s subunit of ribosome inhibiting bacterial protein sunthesis
- Used for skin, bone and lung infections

Glycopeptides



- This also ends with mycin:
- For example Vancomycin
- Used for only gram positive bacteria
- Inhibits bacterial cell wall synthesis
- Used for skin and cardioinfections