

Model answer

(Code-AR-7495)

GURU GHASIDAS VISHWAVIDYALAYA
DEPARTMENT OF PHARMACEUTICAL SCIENCES
B. PHARMACY (FINAL SEMESTER)
SUB-PHARMACEUTICAL CHEMISTRY-VIII

Time: Three Hours]

[Max. Marks: 80

Note: Section 1. is compulsory. Attempt any four questions from section –B.

SECTION- A (Objective type questions)

12×02= 24

1. A) Ans; Chemical Name: Tris (1-aziridinyl) phosphine sulfonate

B). Ans: It is Quantitative Structure Activity Relationship, involves the mathematical and statistical analysis of SAR- data.

C). Ans:

- i) **Mefenide:** It has been mainly employed for burn dressing to prevent infection and pus.
- ii) **Sulfasalazine:** it has been used in ulcerative colitis and rheumatoid arthritis.

D)Ans: Rational drug design is the logical inventive process of finding new drug/medication(s) based on the knowledge of a biological target.

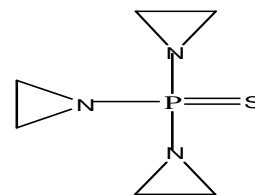
E)Ans; The drugs or chemical agents which are used in the treatment of cancer or neoplasm are called anticancer or antineoplastic or antineoplasm or cytotoxic drugs (An agent or process that is toxic to cells). Cancer chemotherapy is generally nonspecific. This means that drugs kill not only cancerous cells, but also normal cells. Because of the fact that it is nonspecific special strategies are developed to increase the potential of destroying cancerous cells and lessing toxic effect of normal tissue. Eg. Chlorambucil, Cyclophosphamide, cisplatin etc.

F) Ans: i) **Ototoxicity** (means 8th cranial nerve damage of eyer)

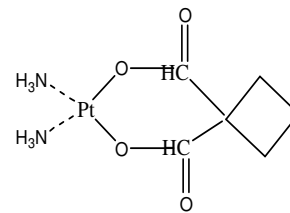
- ii) **Nephrotoxicity** (means it manifests as tubular damage resulting in loss of urinary concentrating power)

G) Ans: antimetabolites are the compounds that prevent the biosynthesis or use of normal cellular metabolite such as folic acid, pyrimidines and pyrines which after being introduced in the body, begin to imitate the structure of primary metabolite. They complete with metabolites to block important reaction leading to formation of DNA/RNA.

eg. Methotrexate, Mercaptopurine, Thioguanine.



H) ANS:



Chemical Name: Cis-di-amino-(1, 1-cyclobutadicarboxylate) platinum

H) Ans: SAR is Structure Activity Relationship, indicating the effect of structure of molecule/drug on the Biological activity. QSAR is Quantitative Structure Activity Relationship, involves the mathematical and statistical analysis of SAR- data.

J)Ans: The name of two causative organism of malaria: (Any two)

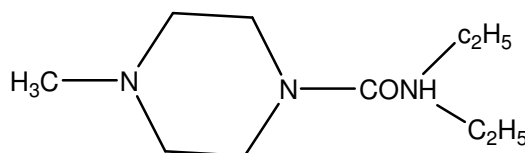
I) *Plasmodium falciparum*

II) *Plasmodium vivax*

III) *Plasmodium oval*

IV) *Plasmodium malariae*

K) Ans;



Chemical name: N N-diethyl-4-methyl-1-piperazinecarboxamide

L) Ans:

Alopecia: complete removal of hair follicle due used of antineoplastic agents.

Gastritis: G I T problem due to use of antineoplastic agents specially ulceration and bleeding.

SECTION- B

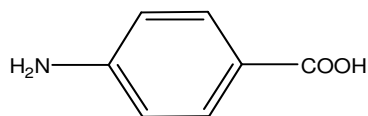
Q2 to Q.7 (Descriptive type, may contain subquestions)

14X4= 56

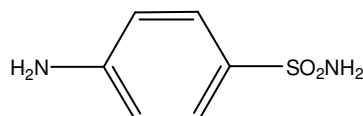
1.Ans:

Sulfonamide drugs are a group of synthetic antimicrobial drugs that have a broad spectrum of use with respect to Gram-positive as well as Gram-negative microorganisms (including *Staphylococcus aureus*, nonenterococcal types of *Streptococcus*, *Listeria monocytogenes*, *Nocardia*, *Neisseria*, *Haemophilus influenzae*, enteric Gram-negative types of *E. coli*, *Proteus mirabilis*, and a few forms of anaerobic bacteria. Sulfonamides are used for treating uncomplicated infections of the urinary tract, infections caused by *Nocardia asteroides*, *streptococcal pharyngitis*, *meningococcal* diseases, *toxoplasmosis*, and others.). They were introduced into medical practice even before the discovery of penicillins. Sulfonamide drugs are derivatives of sulfanilamide (p-aminobenzenesulfonamide), which is a structural analog of p-aminobenzoic acid (component necessary in bacteria for synthesizing folic acid), the precursor of purine, nucleic acids, and especially DNA.

The presence of an additional substituent in the N^1 and N^4 positions of the benzene ring of sulfanilamide reduces the activity of the given series of compounds as antibacterial agents. Here N^4 substituents are responsible for antibacterial properties and N^1 substituents are responsible for solubility, potency and pharmacokinetic properties.



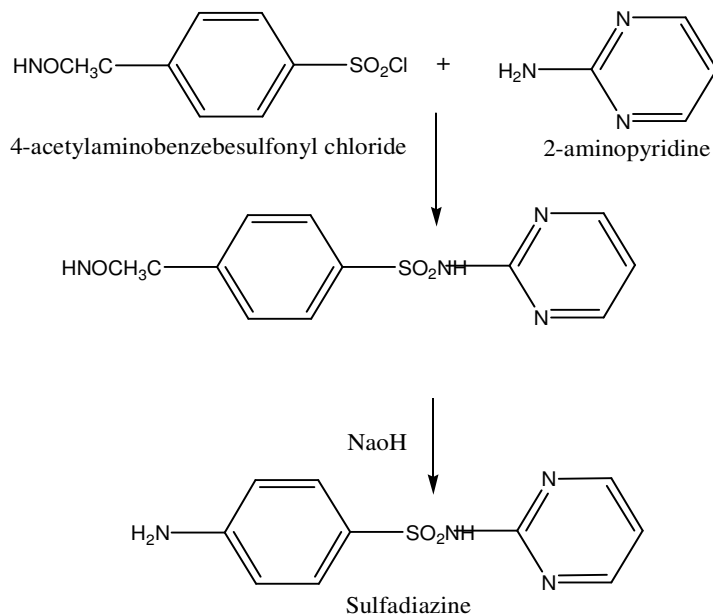
P-Amino-benzoic acid



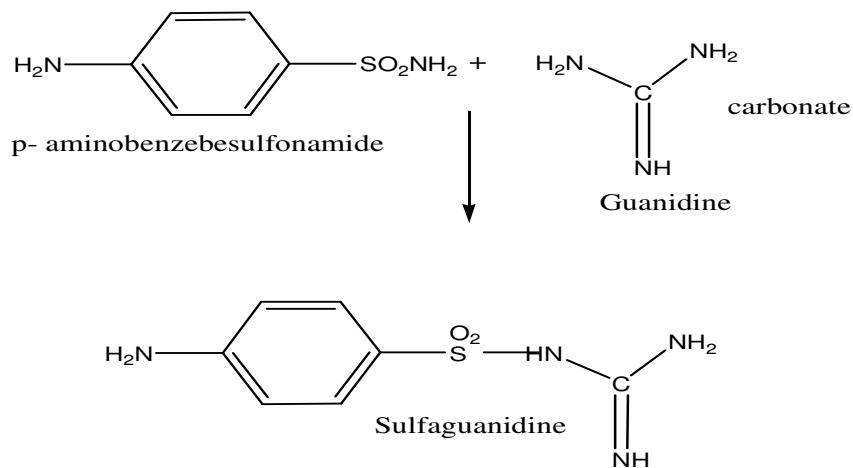
Sulfanilamide

Synthetic route of the following Sulfonamide:

a) Sulfadiazine Chemical name: N^1 -pyrimidinylsulfanilamide

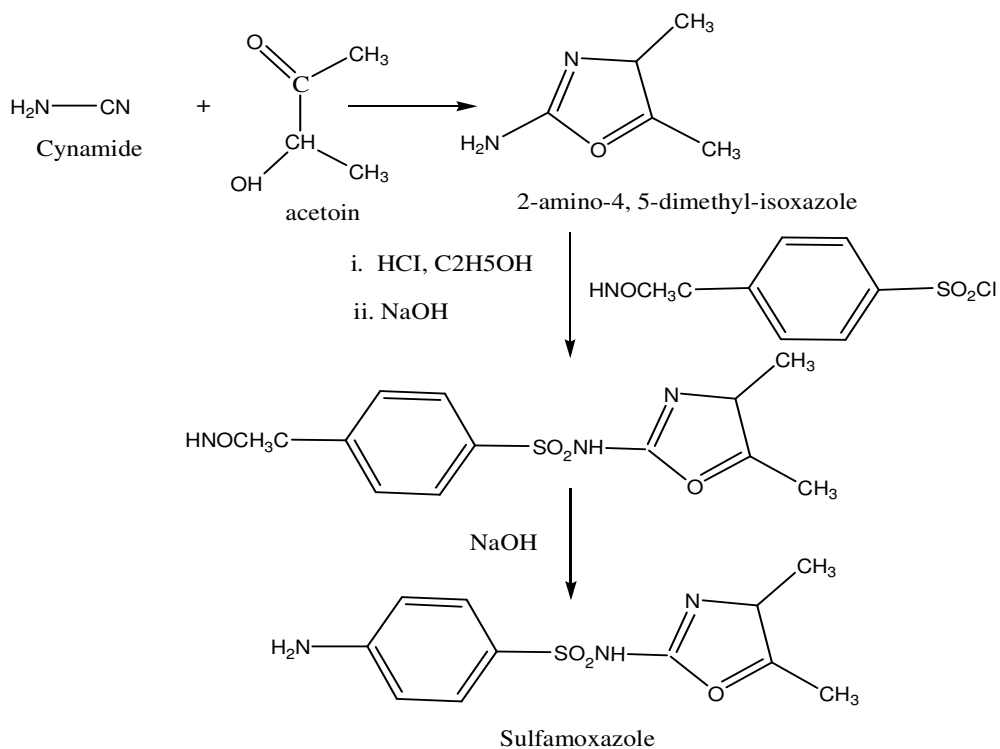


b) Sulfaguanidide. Chemical name; 4- amino- N- (amino imino methyl)benzene sulfon amide.



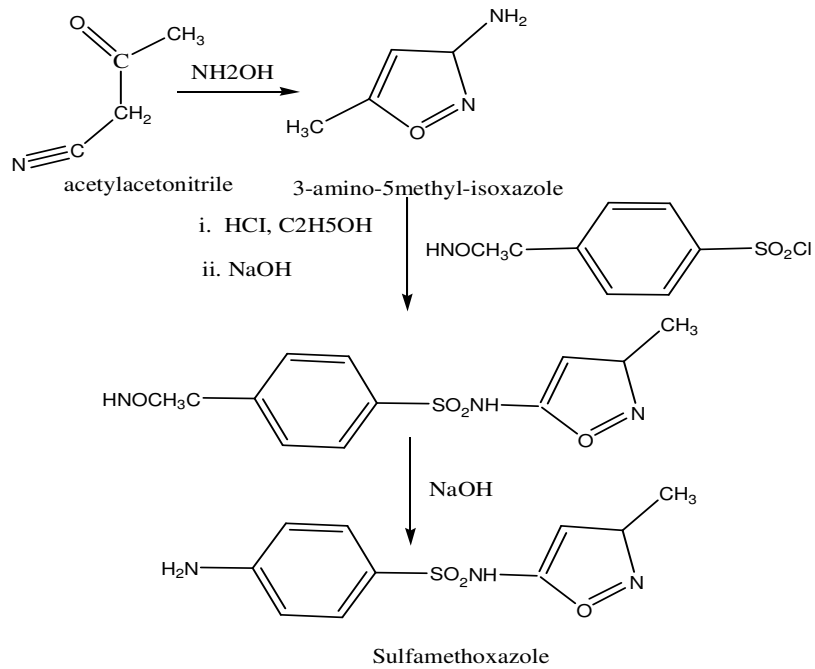
c) Sulfamoxazole

Chemical name: 4-amino-N-(4, 5-dimethyl-2-oxazolyl)benzensulfonamide

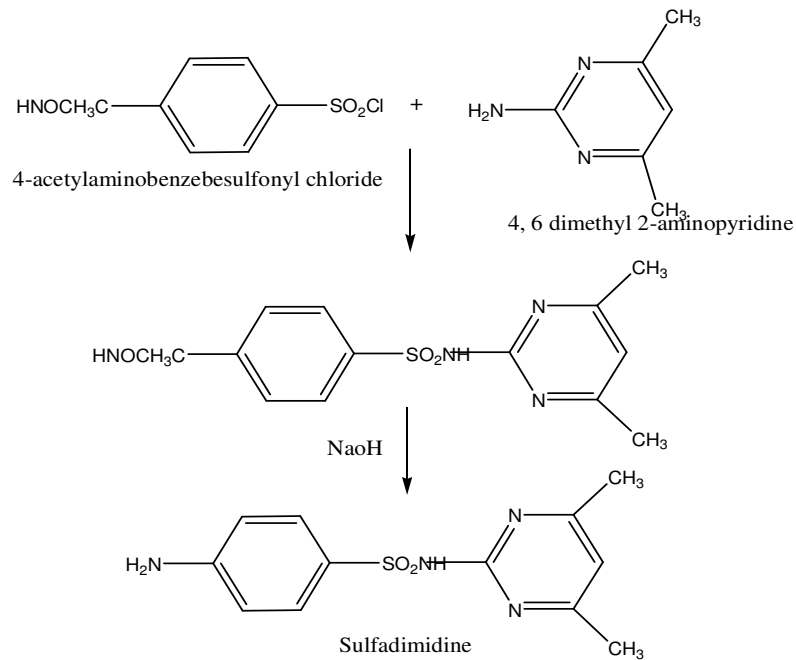


d) Sulfamethoxazole

chemical name: *N*¹ (5-methyl-3-isoxazolyl) sulfanilamide

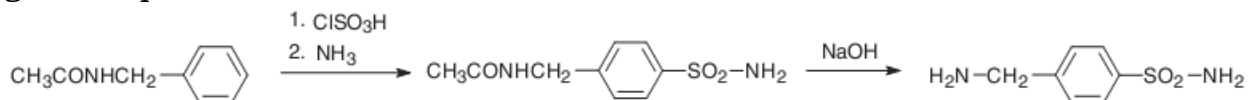


e) Sulfadimidine. Chemical Name: *N*¹-(4,6-dimethyl pyrimidinyl) sulfanilamide



Maphenide: N-(aminomethyl)-benzenesulfamide.

This drug is synthesized from N-benzylacetamide, subsequent reaction of which with chlorosulfonic acid and then with ammonia gives 4-(acetamidomethyl)-benzene-sulfonamide. Hydrolyzing this product with a base gives maphenid.



3.

Ans:

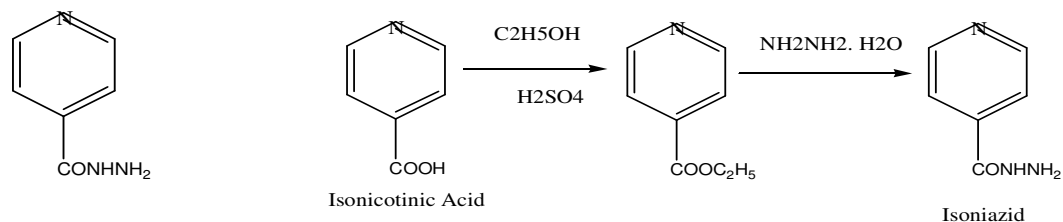
Tuberculosis is an infection caused by the mycobacteria *Mycobacterium tuberculosis*, which most often affects the lungs, and which is characterized by symptoms such as acute inflammation, tissue necrosis, and frequently by the development of open sores. In a few cases, the pathogen penetrates into the lymph or blood and the infection can spread to other body tissues. The modern therapy for tuberculosis is very effective, although it can be long and difficult. The pathogen quickly develops resistance to therapy using a single drug.

Moreover, many strains also developed resistance to bi- and even multi-drug therapy, and therefore antituberculosis drugs, as a rule, are used in the form of a combination of two or three drugs. They are divided into two groups.

1. **First Line drugs:** Isoniazide, Rifampin, Ethambutal, streptomycin, Pyrazinamide.
2. **Second line Drugs:** Thiacetazone, Para-aminosalicylic acid, Cycloserine, Capreomycin, Azithromycin, amikacin, Kanamycin, Ethionamide,

Isoniazide,

Chemical name: Isonicotinic acid hydrazide

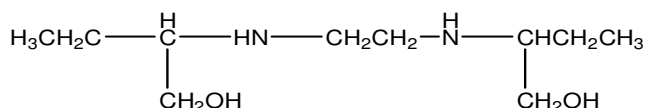


Mechanism ation: Isoniazide exhibits bactericidal action on *Mycobacterium tuberculosis*. It inhibits the synthesis of mycolic acid, an important component of the cell membrane of mycobacteria. mycolic acid is a specific only to mycobacteria. and it cause of the selective toxicity of the drugs with respect to these microorganisms.

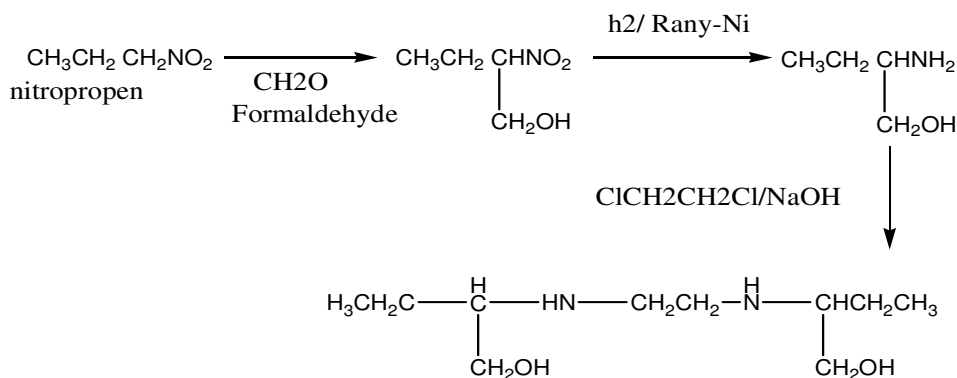
Properties: colorless crystal or white crystalline power. It is store in well closed, light resistant container. It is freely soluble in water.

Ethambutal:

Chemical name: bis (1-hydroxy-methylpropyl)ethylenediamine or N, N'-ethylenebis(2-aminobutan-1ol).



Synthesis:

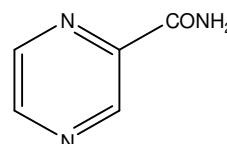


Mechanism ation: Ethambutol was discovered in 1961 and it is and aliphatic diamine. It possesses bacteriostatic action against *Mycobacterium tuberculosis*; however, the exact mechanism of its action is not known. It inhibits the diffusion of mycotic acid into cell membranes of *Mycobacterium smegmatis*, which also explains its selective toxicity. Ethambutol is active only against the *mycobac-teria Mycobacterium tuberculosis, Mycobacterium kansasii,*and *Mycobacterium scrofu-laceum .*

Properties: colorless crystal or white crystalline power. It is store in well closed, light resistant container. It is freely soluble in water.

Pyrazinamide:

Chemical Name: Pyrazine-2carboxamide



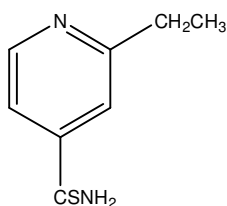
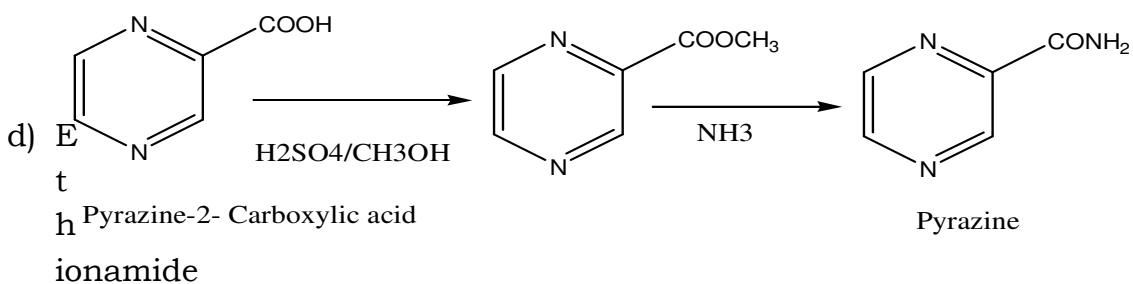
Mechanism action: Pyrazinamide was synthesized in 1952, and it is the nitrogen-analog of nicotinamide. It is weakly tuberculocidal but more active in acidic medium. It is more lethal to intercellularly located bacilli and to those sites showing an inflammatory response.

It inhibits mycolic acid synthesis, but by interacting with different fatty acid synthase encoding genes.

Toxicity: exhibits hepatotoxicity.

Properties: it is a white crystal or white crystalline powder. It is sparingly soluble in water, store well closed, light resistant container.

Synthesis;

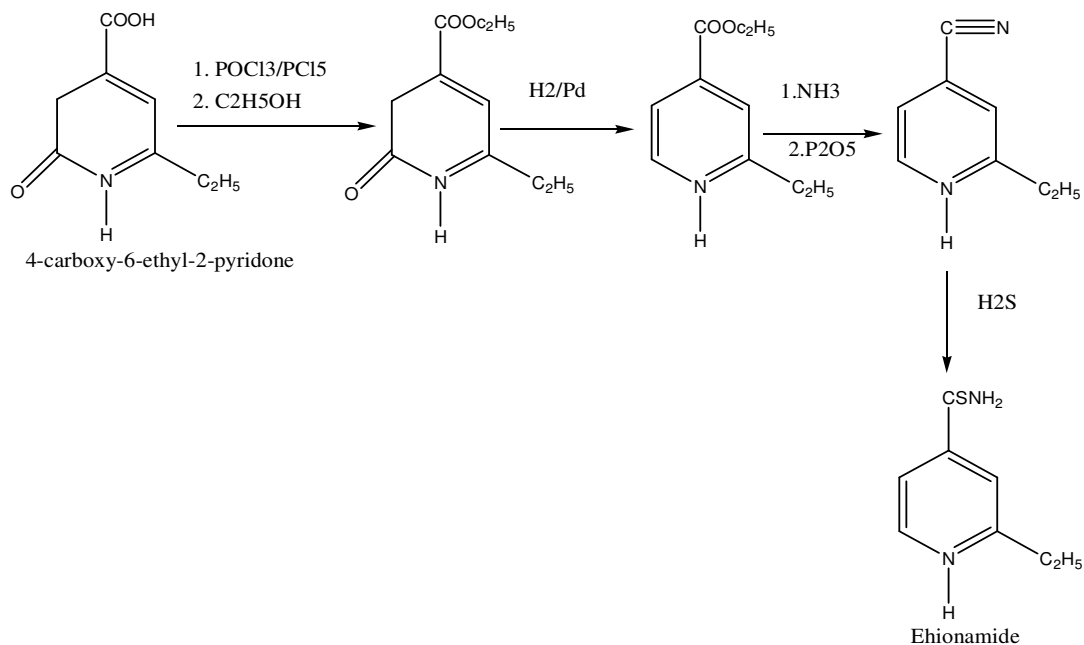


Chemical Name: (2-ethylpyridine-4-carboxamide)

Mechanism action: Ethionamide is active with respect to *Mycobacterium tuberculosis* and *Mycobacterium leprae*, but it does not have an effect on other microorganisms. It enhances phagocytosis at the center of tuberculous inflammation, which facilitates its decomposition.

Properties: it is a white yellow crystalline and yellow crystalline powder, darkening on exposure to light. It is practically insoluble in water, store well closed, light resistant container in a cool place.

Synthesis:



4.

Ans: Physico-chemical parameters used in QSAR can be broadly classified into three general types:

(I) Hydrophobic parameters:

- i. Partition coefficients: $\log P$, $(\log P)^2$
- ii. Pi substituent constants: π , π^2
- iii. R_M-chromatographic parameter: $\log R_M$
- iv. Solubility: δ
- v. Elution time in HPLC: $\log K'$
- vi. Parachor: [P]

- (Above point must be discuss and student may be write in his different way)

(II) Electronic parameters:

- i. Ionization constant: pK_a
- ii. Sigma substituent constants: σ , σ^2 , σ^- , σ^+
- iii. Spectroscopic chemical shift: ppm
- iv. Resonance effect: R
- v. Field effect: F
- vi. Ionization potential: I
- vii. Atomic charge densities: ϵ
- viii. Atomic net charge: q q^π
- ix. Energy of molecular orbit (E_{HOMO}) etc.

***(Above point must be discuss and student may be write in his different way)**

(III) Steric parameters

- i. Taft's steric substituent constant: Es
- ii. Van der Waal's radii: r
- iii. Inter atomic distances: B, L
- iv. Molar refractivity: MR
- v. Molar volume: MV

- **(Above point must be discuss and student may be write in his different way)**

Hydrophobic parameters:

Lipophilicity: In the drug discovery process, the lead candidates must have proper physicochemical properties, in addition to affinity and potency. Many pharmacologically active compounds fail to become drugs because of poor bioavailability, unacceptable pharmacokinetics, or unexpected safety problems, which sometimes are related to inappropriate physicochemical characteristics. As a result, physicochemical parameters have been incorporated into drug discovery programs, along with other properties, to rank the lead compounds and filter out unsuitable compounds. The pK_a , solubility, and lipophilicity are among the most fundamental physicochemical properties of a drug candidate, and their measurements are essential for both *in silico* and *in vitro* evaluation of drug-like properties. Similarly, the pharmacokinetic and pharmacodynamics properties are governed by lipophilic ($\log P$), electronic (σ) and steric feature (Es) of the drug molecules.

$$\log(BA) = a \log P + b \sigma + c Es + d$$

Where BA = Biological activity and a, b, c & d are the numerical values

Hansch established a model to measure the lipophilicity in term of partition coefficient.

Partition coefficient is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium.

$P = \text{Concentration of drug in organic phase} / \text{Concentration of drug in aqueous phase}$

Hansch proposed the lipophilicity measurement in term of partition coefficient "P"

$$P = [C]_{\text{octanol}} / [C]_{\text{water}}$$

It is called "Distribution coefficient"

$$\log P = -E \pi \quad (\text{additive free energy})$$

We can calculate the π value (effect of substituent) with this formula:

$$\pi = \log P_x - \log P_H$$

P_x denotes for substituted compound by "x"

P_H denotes unsubstituted "x = H"

Hydrophobic compounds will have a high P value, whereas hydrophilic compounds will have a

low P value. The hydrophobic character of a drug can be measured experimentally by testing the drug's relative distribution coefficient. Octanol is a suitable solvent for the measurement of partition coefficients.

Linear relationship between log P and biological activity:

$$\log (\text{BA or } 1/c) = a \log P + b$$

Non-linear relationship between log P and biological activity: Describe the parabolic relationship and reasons of non-linearity.

Other parameters:

$$R_M = \log (1/R_f - 1)$$

Parachor

(II) Electronic parameters: indicates the electronic effects of the substituent(s).

Hammett sigma substituent constants: σ , σ_m , σ_p , σ^2 , σ^- , σ^+ etc. with example.

(III) Steric parameters: steric features of the drug affect the drug-receptor interactions reflecting the change in onset and duration of action.

$$\text{Taft's steric substituent constant: } E_s = \log (K/K_0)$$

Where K = rate of acid hydrolysis of substituted ester and

K_0 = rate of hydrolysis of parent ester

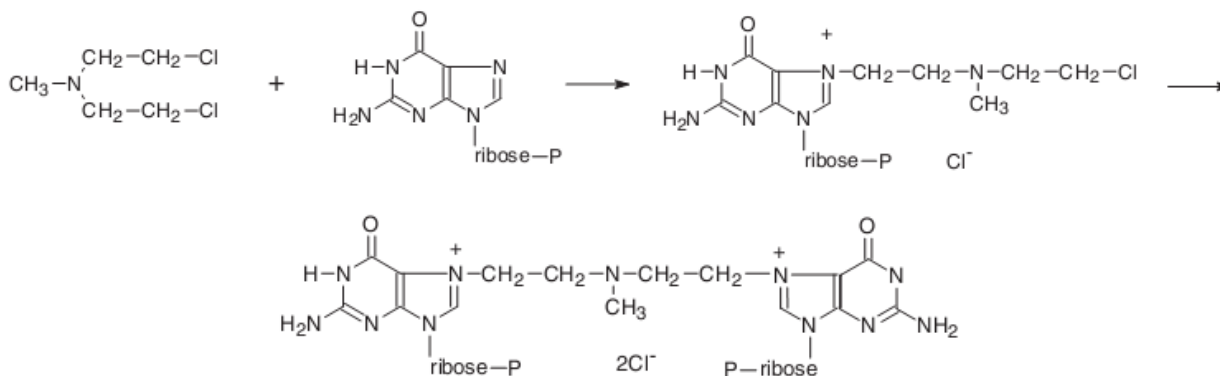
- (Above point must be discuss and student may be write in his different way)

5. Ans: ALKYLATING AGENTS are the drugs which are used in the treatments of neoplasm or cancer; they are cytotoxic agents because they are toxic for normal cells and neoplasm.

Alkylating agents are highly reactive compounds capable of forming covalent bonds with nucleophile regions of intracellular macromolecules, containing amino-, hydroxy-, sulfhydryl-, and carboxy- groups, as well as nitrogen heterocycles, such as nucleic acids, phosphates, aminoacids, and proteins. As a rule, alkylating drugs used in medicine alkylate position N₇ of guanine. In principle, however, alkylation can occur and occurs at O₆ or N₃ of guanine, at N₁, N₃, or N₇ of adenine, or at N₃ of cytosine. During this process, many parts of cells, including DNA, RNA, proteins, membrane components, and so on, are also alkylated. The main cytotoxic effect of these compounds can be explained by their ability to bind with DNA nucleotides themselves causing not only

alkylation, but also ring cleavage, abnormal base-pairing. This leads to an incorrect reading of information from DNA, and as a rule, cells die because of intervention in replication and mitosis. Bifunctional alkylating agents have the possibility of forming inter-chain bonds in DNA, causing cross-linking of two chains of DNA, and are considered more toxic than monofunctional alkylating agents.

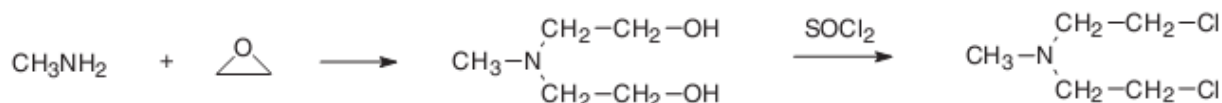
The schematic mechanism of the action of alkylating drugs, mechlorethamine for example



Classification of alkylating agents

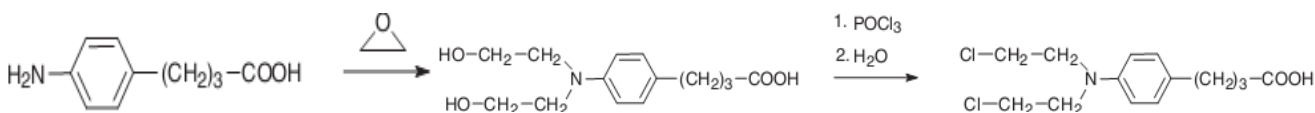
1. **Nitrogen mustards:** Mechlorethamine, Chlorambucil, Melphalan, Cyclophosphamide, Ifosfamide.
2. **Ethyleneimine:** Thiopeta
3. **Alkylsulfonate:** Busulfonate
4. **Nitrosourea:** Carmustine, Lomustine,
5. **Triazine:** Decarbazine

Mechlorethamine: bis-(2-chloroethyl) methylamine is made by reacting methylamine with ethylene oxide.



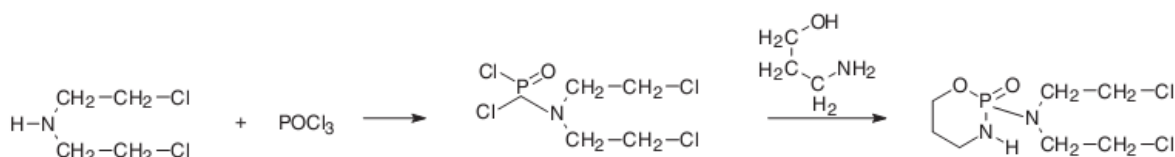
It is used to treat Hodgkin's disease, lymphosarcoma, leukemia, and bronchogenic carcinoma.

Chlorambucil: Chlorambucil, 4-[p-[bis-(2-chloroethyl)amino]phenyl]butyric acid synthesized from 4-(4-aminophenyl) butyric acid with ethylene oxide



It is used for chronic lymphatic leukemia and for multiple myelomas.

Cyclophosphamide: 2-[bis-(2-chloroethyl) amino]tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide is made by reacting bis(2-chloroethyl) amine with phosphorous oxychloride



It is used for chronic lymphatic leukemia, Hodgkin's disease, Burkitt's lymphoma, multiple myeloma, and cancer of the breast, neck, ovaries, and so on.

Ethylenimine derivatives

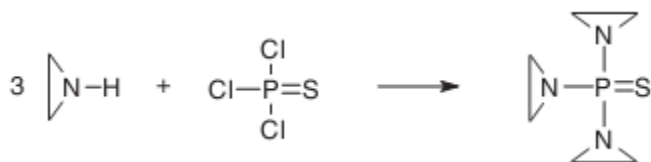
Thiotepa are used for breast and ovarian cancer, nonoperable tumors, and other recurrences and metastases.

Ethylenimines are highly reactive alkylating reagents. They alkylate DNA at position N7 Of guanine, analogous to mechlorethamine. Ethylenimines exhibit cytostatic action and suppress

Development of proliferating, as well as malignant tissues. They disrupt the metabolism of

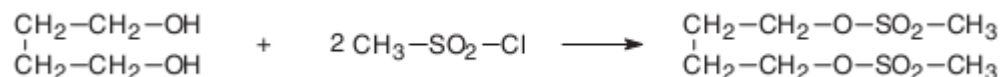
nucleic acids and block mitotic cell division. They are used for breast and ovarian cancer, nonoperable tumors, and other recurrences and metastases.

Thiotepa: tris(1-aziridinyl)phosphine sulfate is made by reacting ethylenimine with phosphorous sulfochloride.



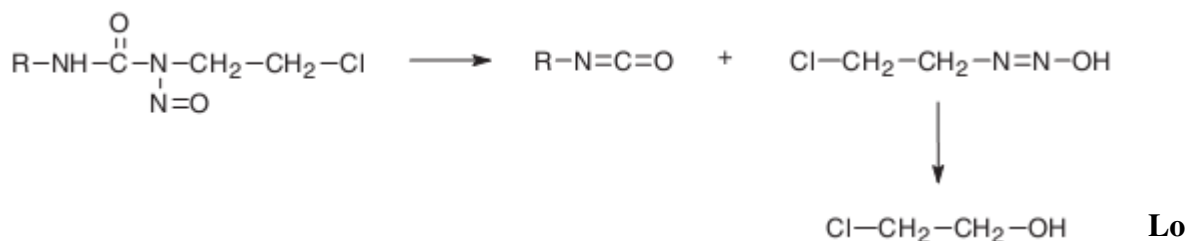
Alkyl sulfonates

Busulfan: 1,4-butandioldimethanesulfonate is made by reacting butandiol with methanesulfonyl chloride.

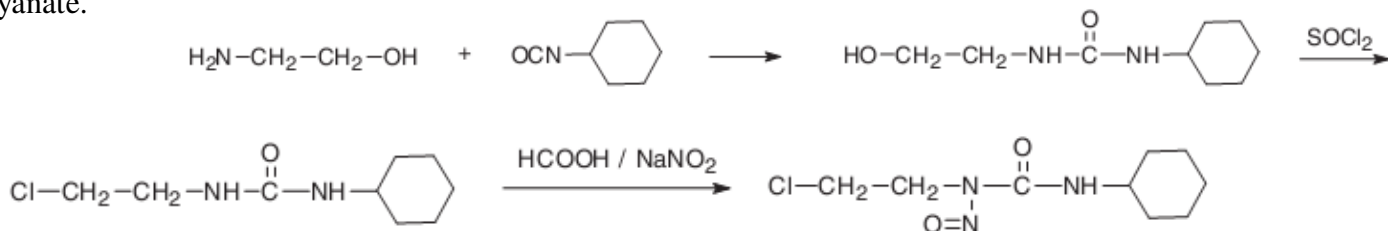


Nitrosoureas: antineoplastic drugs used in medicine is made up of nitrosoureas (lomustine, carbustine, streptozocin). There are also other drugs of this group (nimustine, semustine, and others), and they differ only in the presence of a different R group, which is shown in the scheme below. It is believed that in the body, nitrosoureas break down to β -chloroethanol and alkylisocyanate. The resulting β -chloroethanol is a highly reactive alkylating agent, and the alkylisocyanates are carbamoylating agents for proteins, which also exhibit certain cytotoxic activity.

The probable scheme of decomposition of nitrosourea in the body into active components is shown below.

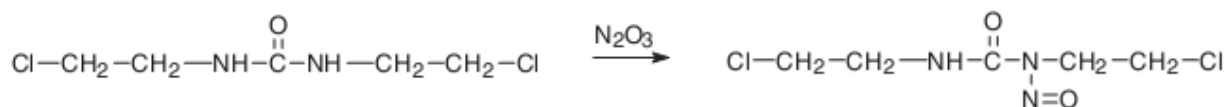


mustine: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea is made by reacting ethanolamine with cyclohexylisocyanate.



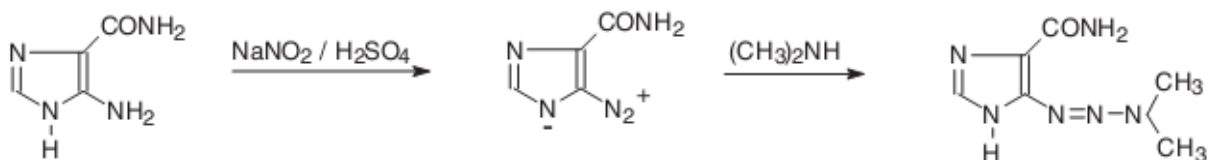
it is used for central nervous system tumors, brain, throat, and larynx tumors, lymphogranulomatosis, non-Hodgkin's lymphoma, and lung and gastrointestinal tract cancer.

Carmustin: 1,3-bis-(2-chloroethyl)-1-nitrosourea is made by nitrating 1,3-bis(2-chloroethyl)urea with nitrogen trioxide.



It is used for non-Hodgkin's lymphoma, multiple myeloma, and brain tumors.

Dacarbazine: 5-(3,3-dimethyl-1-triazeno)imidazol-4-carboxamide is made by diazotation of 5-aminoimidazol-4-carboxamide with nitrous acid, which results in the formation of 5-diazoimidazol-4-carboxamide. Reacting this with dimethylamine gives the desired dacarbazine



Dacarbazine is used intravenously for Hodgkin's disease, soft-tissue sarcoma, and metastatic melanoma.

***(Discussed the properties of all alkylating agents.)**

6.Ans: Malaria still continues to be a wide-spread infection disease. In man malaria may cause by four Species of *Plasmodium falciparum* (*malignant terian or subtertian*), *P. Vivax*, *P. ovale*, *P. malariae*.

All species of Plasmodium have to host, vertebrate and mosquito that act as both vector and definite host. Men get infected by the bite of infected mosquito which injects *sporozoates* into the circulation. The *sporozoates* get lodged in the parenchymal cells of the liver, where they grow, segment and sporulate. This continues the *pre-erythrocytic* stage of infection. On maturity *merozoite* are releases from the liver cells enter erythrocytes to start blood cycle. A proportion of parasite infects more tissues and this is term as *exoerythrocytic* stage(this happen in all species except *falciparum* species).Schizogony occurs in infected erythrocytes as a result of growth and segementation of the the *merozoites*. When the erythrocytes burst there is a feeling of chill fever follows, and liberate *merozoate* can infect more red -blood cells and start the cycle afesh.some merozoites differentiate into male and female parasites known as *gametocytes*. These gamatocytes can undergo *sporogony* (sexual cycle) in the gut of the female mosquito and give rise to infective sporozoates.

Antimalarial drugs that used for prophylaxis, treatment and prevention of relapses of malaria.

Classification of antimalarial drugs:

1. **4-aminoquinolines:** chloroquine, amodiaquine.
2. **Quinoline-methanol:** Mefloquine.
3. **Cinchona alkaloid:** quinine, quinidine
4. **Biguanide:** proguanil(Chloroguanide).
5. **Diaminopyrimidine:** pyrimethamine
6. **8-Aminoquinoline:** Primaquine, bulaquine.
7. **Sulfonamides and sulone:** Sulamethopyrazine, Dapsone.
8. **Tetracyclines:** tetracycline, Doxycycline.
9. **Sesquiterpene lactones:** Artesunate, Artemether, Arteether.
10. **Amino alcohols:** halofantrine Lumefantrine
11. **Mannich base:** Pyronaridine
12. **Naphthoquinone:** Atovaquone.

The antimalarial therapy given in the following form:

1. **Causal prophylaxis:** the pre-erythrocytic (in liver) which is the cause of malaria

Drugs used: Proguanil, Primaquine.

2. **Suppressive Prophylaxis:** the schizontocides which suppress the erythrocytic phase and thus attacks of malarial fever can be used as prophylactics.

Drugs used: chloroquine, primaquine, proguanil, mefloquine, doxycycline.

3. **Clinical cure:** the erythrocytic schizontocides to terminate an episode of malarial.

a. Fast-acting high-efficacy drugs; chloroquine, amodiaquine, mefloquine, halofantrine atovaquone, artemisinin.

b. slow-acting low efficacy drugs; proguanil, pyrimethamine sulfonamide, tetracycline.

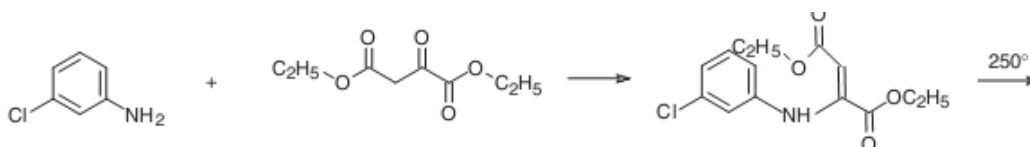
4. **Radical cure:** Drugs acts on exoerythrocytic stage

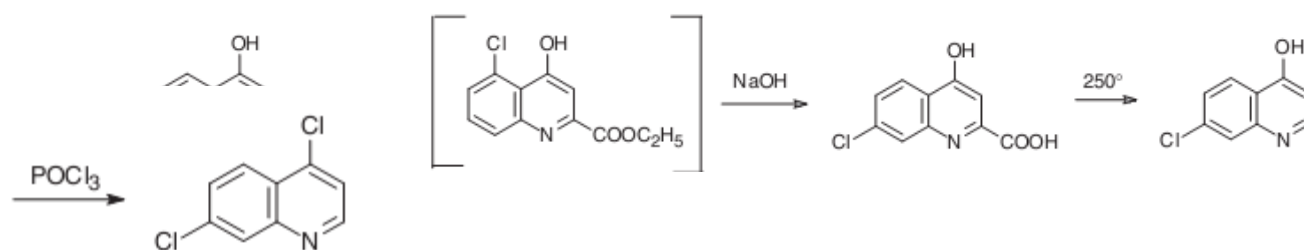
Drugs used; Primaquine

6. **Gametocidal:** this is for elimination of male female gametes of Plasmodia formed in the patients blood.

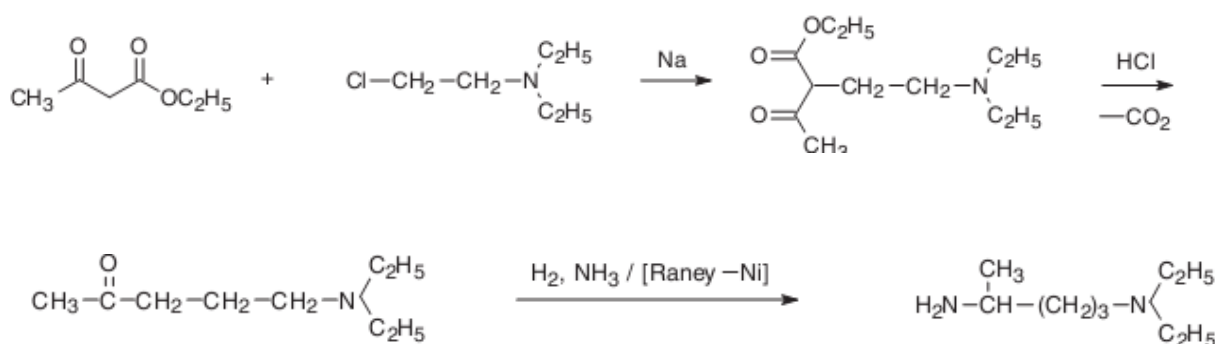
Drugs used: Primaquine, proguanil

Chloroquine: Chemical name: 7-chloro-4-(4-diethylamino-1-ethylbutylamino)-quinoline.



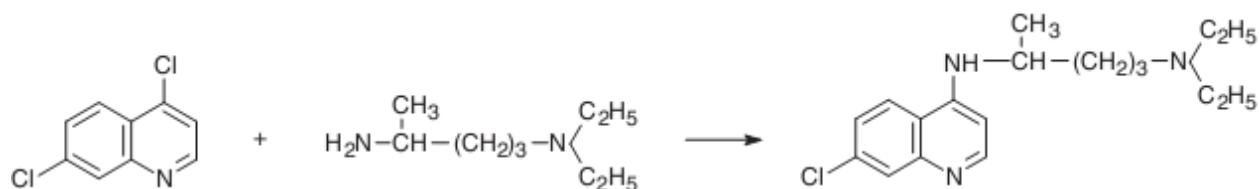


Synthesis starting material 3-chloroaniline and diethyl ester of oxaloacetic acid and final product 4,7-dichloroquinoline(**Step-1**)



The second component necessary for synthesizing of the chloroquine is 4-diethylamino-1-methylbutylamine (37.1.1.2), is also made in various ways and starting material are Alkylating acetoacetic ester with 2-diethylaminoethylchloride ion makes 1-diethylamino-4-pentanone and ultimate final product.(**step-II**)

Final step-



Properties: it is a white or slightly yellow crystalline powder. it is very slightly soluble in water and chloroquine sulphate is freely soluble in water, bitter in taste.

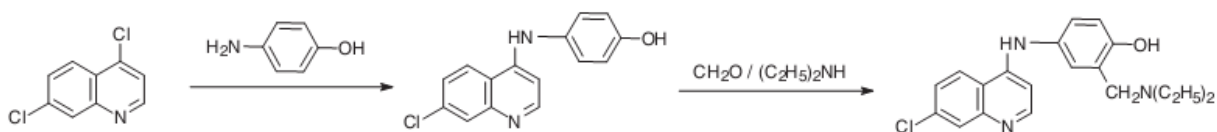
Mechanism action: The mechanism of action of chloroquine is not completely known. Polymerization of toxic haeme to nontoxic parasite pigment haemozoin is inhibited by formation of chloroquine-heme complex. Heme itself or its complex with chloroquine then damages the plasmidial membranes.

Used:

1. it killed the erythrocytic form of malaria parasite. When patient unable to swallow the phosphate salt are given by intramuscular or intravenous route. the solution are sterilized by autoclaving.
2. Chloroquine is also value in the treatment of amoebic hepatitis. It has been used in the treatment of systemic lupus erythematosus and rheumatoid arthritis.
3. It has been used in the treatment of giardiasis.

Adverse effects: Hypotension, cardiac depression, arrhythmia and CNS toxicity including convulsion, loss of vision due to retinal damage. Loss of hearing, photoallergy

Amodiaquine: 7-chloro-4-(4-hydroxyphenylamino)-quinoline



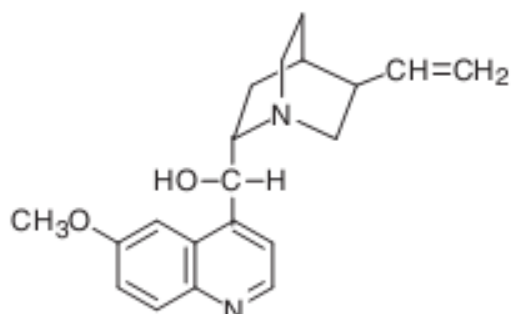
Synthesis starting material are 4, 7-chloroquinoline and 4-aminophenol and final product 7-chloro-4-(4-hydroxyphenylamino)-quinoline.

Properties: same as Chloroquine

Mechanism action: The mechanism of action same as chloroquine.

Used: same as chloroquine.

Quinine: (5-vinyl-2-quinuclidinyl)-(6-methoxy-4-quinolyl) methanol



Since the 17th century, cinchona bark was used in Europe as an antifever drug, and then as a drug for treating malaria. Two alkaloids were isolated from the bark of the cinchona tree as far back as the 1820s (**quinine** and **cinchonine**) which are noncondensed biheterocycles containing two heterocyclic nucleus, **quinoline** and **quinuclidine**. Quinine is a **methoxylated** derivative of cinchonine. Quinine is the levorotatory isomer of quinidine. Its structure consists of a quinoline ring, the fourth position of which is bounded by a hydroxy methylene bridge to a **quinuclidine** ring. The methoxy group at C₆ of the quinoline ring and the **vinyl** group in the quinuclidine ring enhance the activity of the compound; however, they are not absolutely necessary for the compounds of this group to express antimalarial activity.

Properties: quinine is a white, odorless, slightly efflorescent, flaky, granular or microcrystalline powder. It is very slightly soluble in water. Bitter in taste.

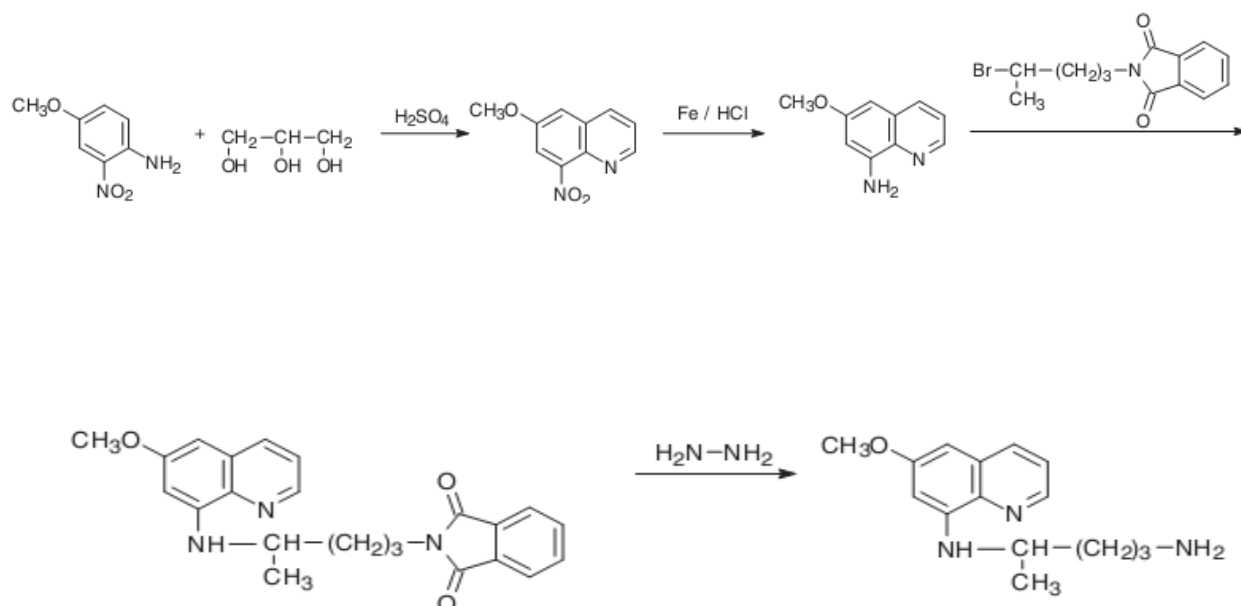
Mechanism action: Inhibits polymerization of heame to hemozoin, free heame or heame-quinine complex damages parasite membrane and kills it.

Used: Quinine is a highly active blood schizonticides and suppresses the asexual cycle of development of malaria parasite in the erythrocytic stage

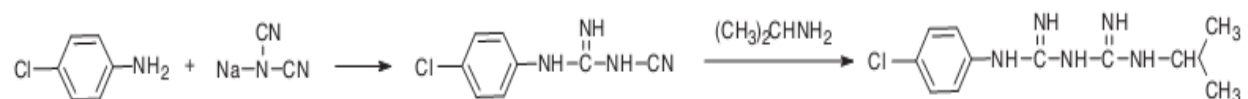
Adverse effect: Cinchonism(A large dose higher therapeutics dose taken a few days produce a syndrome called cinchonism), it consists of ringing in ears, nusea vomitintig, headache, mental confusion, vertigo, difficulty in hearing and efect, diarrhea, flushing and marked perspiration may also appear.

Quine occussionally causes haemolysisin case of pregnancy, Haemoglobinuria(Black water fever)

Primaquine: 8-[(4-amino-1-methylbutyryl)amino]-6-methoxyquinoline, this is the synthesis route of primaquine and must discuss in short properties , mechanism of action and use and adverse effect.



Chloroguanide: Chloroguanide, N¹-(4-chlorophenyl)- N⁵-isopropylbiguanide is made from 4-chloroaniline and sodium dicyanoamide, the interaction of which results in the formation of (4-chlorophenyl)dicyanodiamide. Reacting this with iso-propylamine gives the chloroguanide.



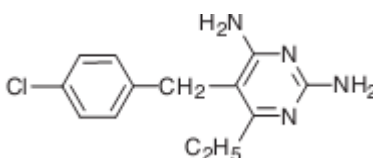
Properties: white crystalline powder, slightly soluble in water,

Mechanism action: is an antimalarial and dihydrofolate reductase inhibitor of parasites.

Used: it is used for causal prophylaxis of falciparum malaria, to other form of malaria.

Adverse effect; stomatitis, haematuria, rash and loss of hair.

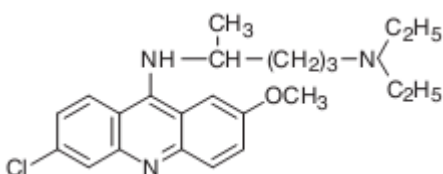
Pyrimethamine: 2,4-diamino-5-(4'-chlorophenyl)-6-ethylpyrimidine



Mechanism of action: This powerful inhibitor of dihydrofolate reductase is used for preventing and treating malaria caused by plasmodia *P. vivax*, *P. malariae*, *P. ovale*, including *P. falciparum*.

***(Discussed other properties, used, adverse effects)**

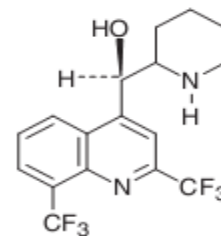
Quinacrine: 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxy-acridine



***(Discussed other properties, Mechanism of action, used, adverse effects)**

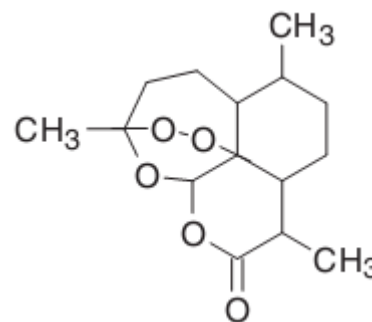
Mefloquine: D,L-erythro- α -2-piperidyl-2,8- bis-(trifluoromethyl)-4-quinolin-methanol

*(Discussed other properties, Mechanism of action, used, adverse effects)



Artemisinin): octahydro-3,6,9-trimethyl-3,12-epoxy-12H -pyrano-(4,3-di)-1,2-benzodioxepin-10-(3H)-one. Is isolated from the plant *Artemisia annua* .

*(Discussed other properties, Mechanism of action, used, adverse effects)



7. Ans. QSAR methods:

Hansch model

$$\log BA = a \log P + b \sigma + c E_s + d \dots \dots \dots \text{linear}$$

$$\log BA = a \log P \pm b (\log P)^2 \pm c \sigma \pm d E_s \pm e \dots \dots \dots \text{non-linear}$$

Where BA= Biological activity

Advantages of Hansch approach:(**need to be discuss**)

Disadvantages of Hansch approach: :(**need to be discuss**)

Free-Wilson model:

$$\log BA = \text{contribution of unsubstituted parent compound} + \text{contribution of corresponding substituent}$$

{Write Equation and explain}

Advantages of Free-Wilson approach:

Disadvantages of Free-Wilson approach:

Mixed approach:

Kubinyi has presented the combination of Hansch and Free-Wilson models as mixed approach.

{Write Equation and explain}

- Advantages of Mixed approach:
- Disadvantages of Mixed approach:

Students may be discuss every point by his own language