**Course Code:** CH 406

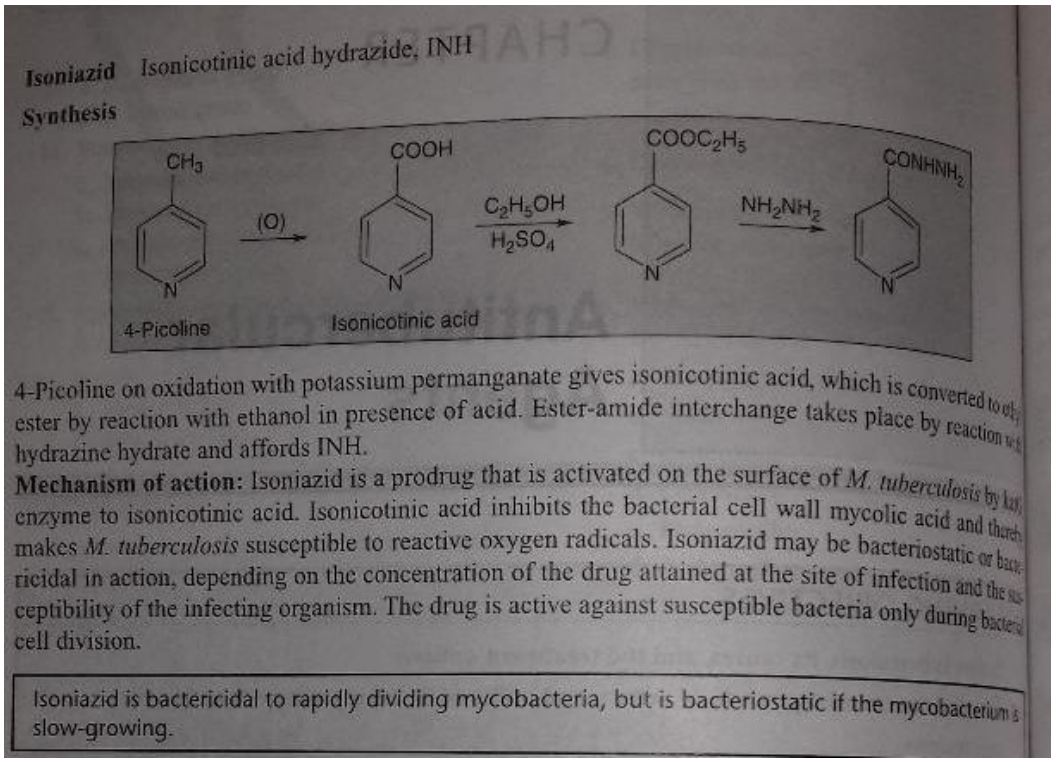
**Course Name:** Medicinal Chemistry- I

**Synthesis of Anticancer, Antivirals and Antibiotic drugs involving not more than three steps.**



**Book: Medicinal Chemistry (2nd edition) by D. Sriram and P. Yogeeswari**

## 1. Isoniazid:



**Isoniazid** Isonicotinic acid hydrazide, INH

**Synthesis**



4-Picoline on oxidation with potassium permanganate gives isonicotinic acid, which is converted to ethyl ester by reaction with ethanol in presence of acid. Ester-amide interchange takes place by reaction with hydrazine hydrate and affords INH.

**Mechanism of action:** Isoniazid is a prodrug that is activated on the surface of *M. tuberculosis* by katG enzyme to isonicotinic acid. Isonicotinic acid inhibits the bacterial cell wall mycolic acid and thereby makes *M. tuberculosis* susceptible to reactive oxygen radicals. Isoniazid may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. The drug is active against susceptible bacteria only during bacterial cell division.

Isoniazid is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if the mycobacterium is slow-growing.

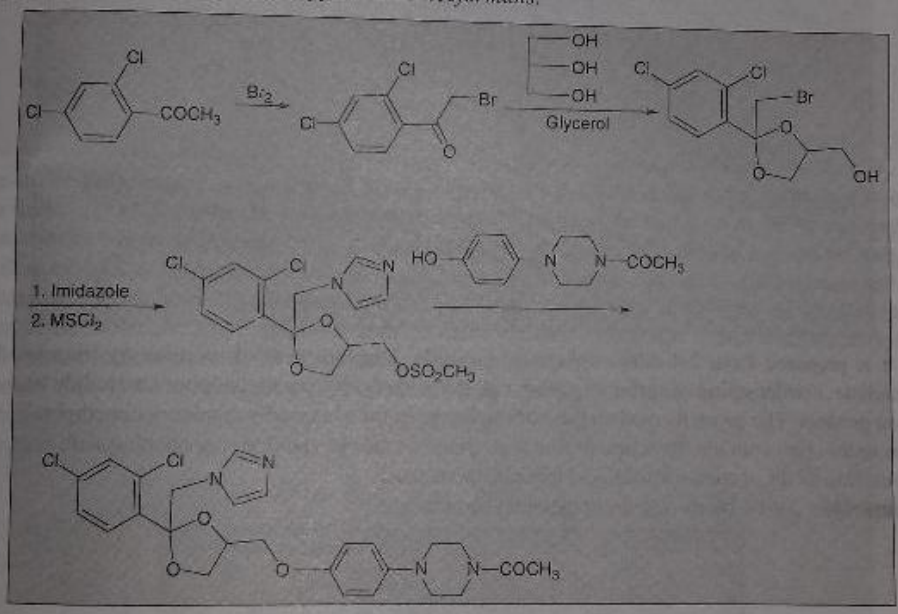
## 2. Ketoconazole:

28.4 AZOLE ANTIFUNGALS

**Mechanism of action:** Azole antifungals inhibit sterol-14-α-demethylase, a microsomal cytochrome p450-dependent enzyme system, and thus impair the biosynthesis of ergosterol for the cytoplasmic membrane and lead to the accumulation of 14-α-methyl sterols. These methylsterols may disrupt the close packing of acyl chains of phospholipids, impairing the functions of certain membrane-bound enzyme systems such as ATPase and enzymes of the electron transport system, and thus inhibiting the growth of the fungi.

**Ketoconazole** (*cis*-1-Acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]phenyl]piperazine)

Ketoconazole is an imidazole antifungal agent. Ketoconazole is a highly lipophilic compound. This property leads to high concentrations of ketoconazole in fatty tissues and purulent exudates. Ketoconazole is active against *Candida* sp. and *Cryptococcus neoformans*.

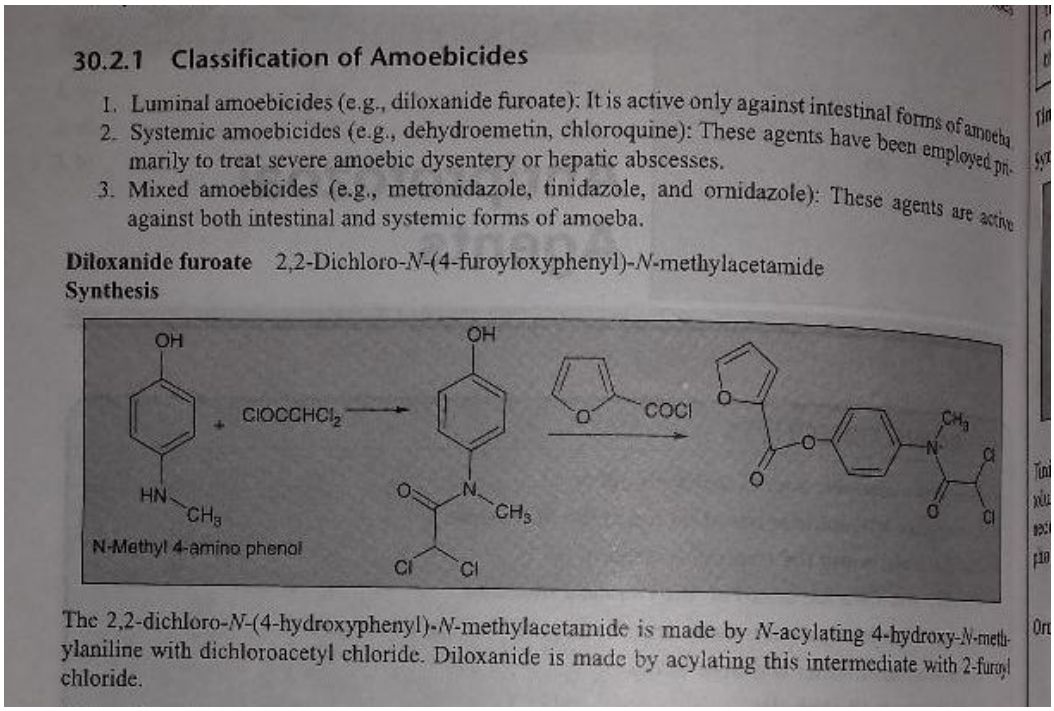



Ketoconazole is synthesised from 2,4-dichlorophenacyl bromide, the ketalization of which using glycerol gives *cis*-2-(2,4-dichlorophenyl)-2-bromoethyl-4-hydroxymethyl-1,3-dioxolane. Alkylating the resulting compound with imidazole gives the derivative, which on reaction with methanesulphonyl chloride gives a mesylate. Finally, alkylating with 1-acetyl-4-(4-hydroxyphenyl)piperazine gives ketoconazole.

A study in mice indicated that ketoconazole may have a stimulatory effect on hair growth. Nizoral shampoo has shown to be beneficial in men suffering from androgenic alopecia. One 1998 study showed that Nizoral 2% worked just as well as minoxidil 2% (brand name Rogaine) in men with androgenic alopecia. Both medicines increased hair thickness and increased the number of anagen-phase hair follicles on the scalp

## 3. Diloxanide:

**Diloxanide** is a medication used to treat amoeba infections.



30.2.1 Classification of Amoebicides

1. Luminal amoebicides (e.g., diloxanide furoate): It is active only against intestinal forms of amoeba
2. Systemic amoebicides (e.g., dehydroemetin, chloroquine): These agents have been employed primarily to treat severe amoebic dysentery or hepatic abscesses.
3. Mixed amoebicides (e.g., metronidazole, tinidazole, and ornidazole): These agents are active against both intestinal and systemic forms of amoeba.

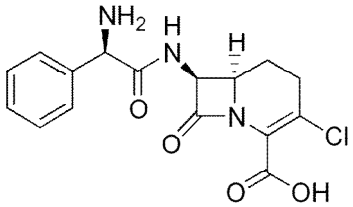
**Diloxanide furoate** 2,2-Dichloro-*N*-(4-furoyloxyphenyl)-*N*-methylacetamide
**Synthesis**



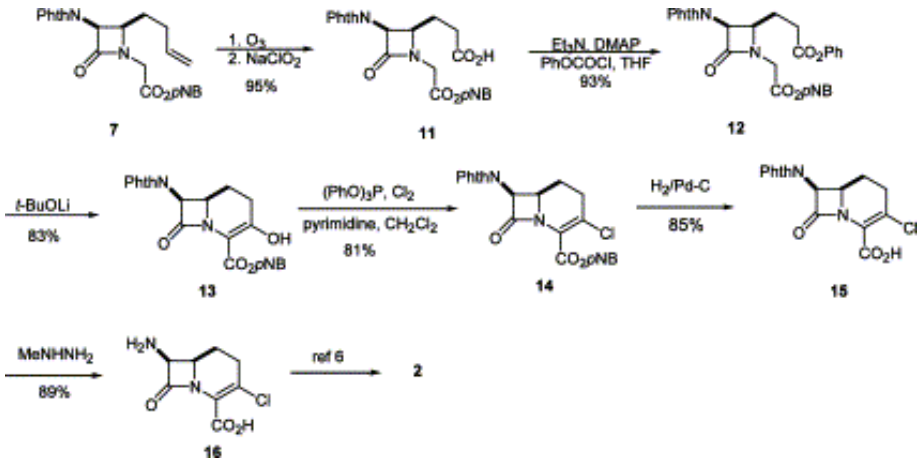
The 2,2-dichloro-*N*-(4-hydroxyphenyl)-*N*-methylacetamide is made by *N*-acylating 4-hydroxy-*N*-methylaniline with dichloroacetyl chloride. Diloxanide is made by acylating this intermediate with 2-furoyl chloride.

## 4. Loracarbef:

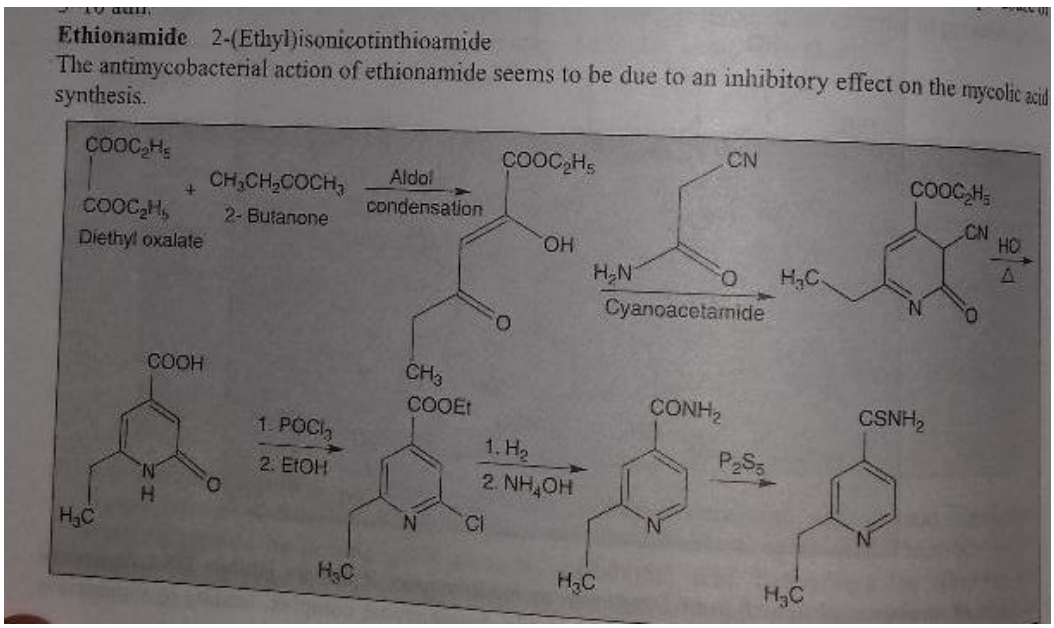
Loracarbef is a beta-lactam antibiotic of the carbacephem class. Chemically, carbacephems differ from cephalosporin-class antibiotics in the dihydrothiazine ring where a methylene group has been substituted for a sulfur atom. Loracarbef is an antibiotic It is a carbacephem, but it is sometimes grouped together with the second-generation cephalosporin antibiotics. Loracarbef is a synthetic "carba" analog of cefaclor, and is more stable.



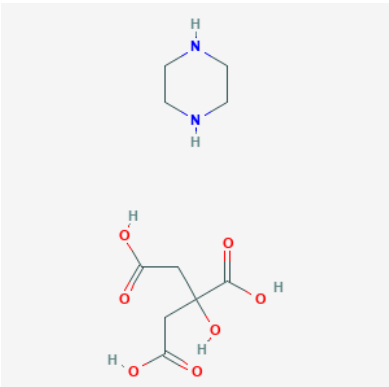

Synthesis:




## 5. Ethionamide:



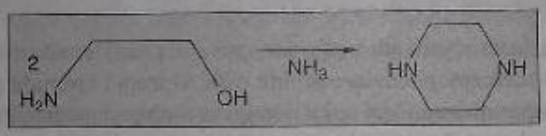

## 6. Piperazine Citrate:



## Piperazine derivatives

**Piperazine citrate** It is highly effective against both *Ascaris lumbricoides* (roundworm) and *Enterobius vermicularis* (pinworm). Piperazine blocks the response of worm muscle to acetylcholine, apparently by altering the permeability of the cell membrane to ions that are responsible for the maintenance of the resting potential. The drug causes hyperpolarization and suppression of spontaneous spike potentials with accompanying paralysis that result in the expulsion of the worm by peristalsis.

**Synthesis**




It is made from ethanolamine by heating it in ammonia at a temperature of 150°C–220°C and a pressure of 100 atm–250 atm. It is used as a drug in the form of a salt, and as a rule, in the form of adipate orcitrate.

## 7. Pamaquine:

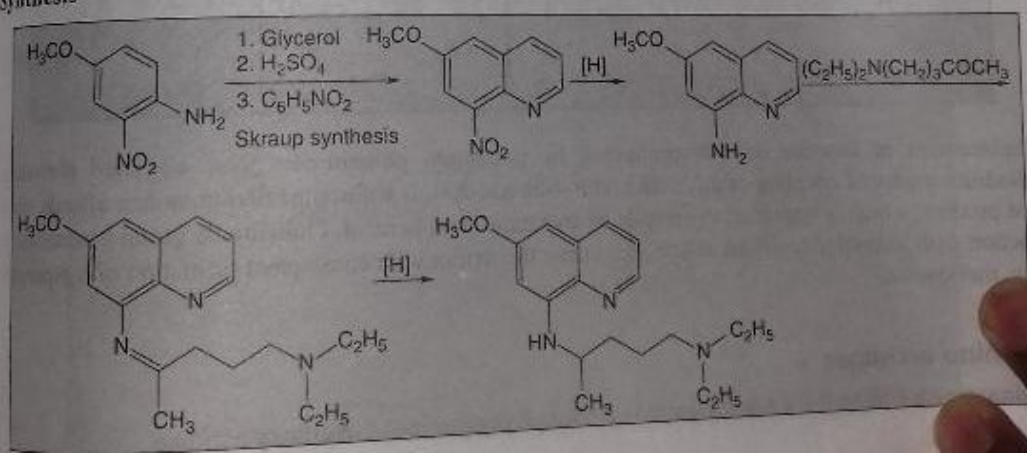
afford amodiaquine.

**Pamaquine** 8-[(4-Diethylamino-1-methylbutyl) amino]-6-methoxy quinoline

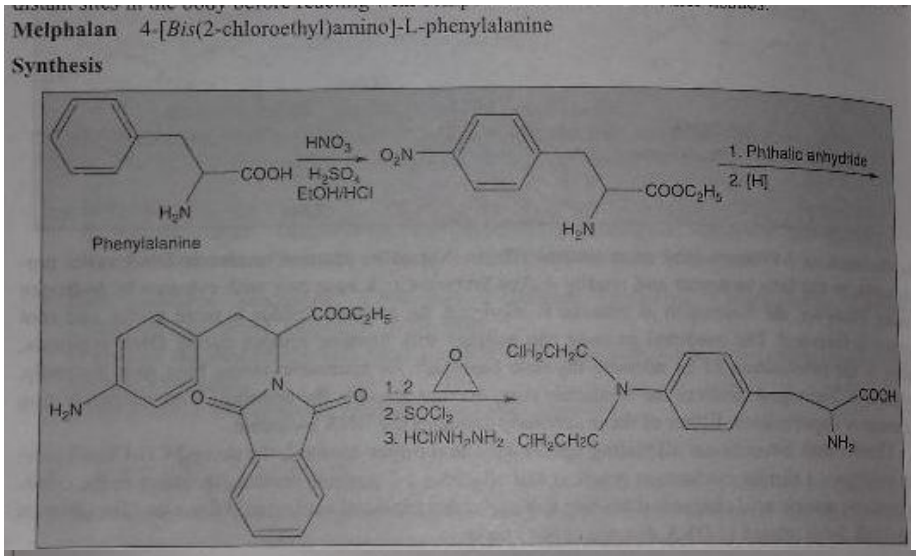
Pamaquine is an 8-aminoquinoline drug used for the treatment of malaria. It is closely related to primaquine (de-diethylamino derivative).

Moving the side-chain from the fourth position of the quinoline ring to the eighth position completely changes the compound's spectrum of activity. Unlike the 4-substituted aminoquinolines, primaquine and pamaquine has practically no effect on erythrocyte forms of the malaria parasite. Its activity is limited to tissue forms of the parasite in mammals and in the mosquitoes themselves. This makes primaquine and pamaquine an especially valuable drug, allowing radical recovery and simultaneous prevention, which is usually not achieved by using erythrocyte drugs.

**Synthesis**



## 8. Melphalan:

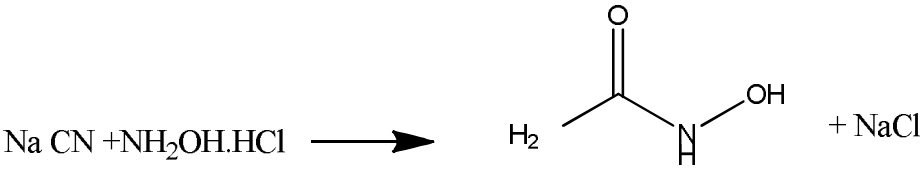



It is synthesised from L-phenylalanine, the nitration of which with nitric acid gives 4-nitro-L-phenylalanine. Reacting this with an ethanol in the presence of hydrogen chloride gives the hydrochloride of 4-nitro-L-phenylalanine ethyl ester, the amino group of which is protected by changing it to phthalimide by a reaction with phthalic anhydride. The nitro group in this molecule is reduced to an amino group using palladium on calcium carbonate as a catalyst. The resulting aromatic amine is then reacted with ethylene oxide, which forms a *bis*-(2-hydroxyethyl)-amino derivative. The hydroxyl groups in this molecule are replaced with chlorine atoms upon reaction with thionyl chloride, after which treatment with hydrochloric acid and hydrazine removes the ethyl ester and phthalamide protection, respectively, giving melphalan.

## 9. Hydroxy urea:

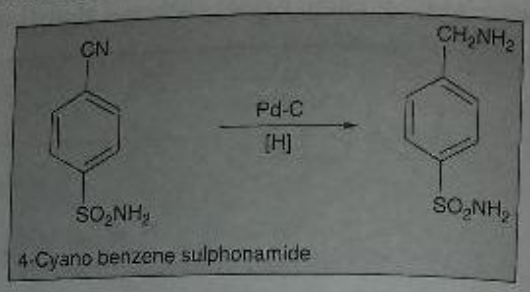
Hydroxyurea is also known as Hydroxycarbamide is an antineoplastic (anti-cancer) agent used to treat melanoma

Hydroxylamine hydrochloride (7.9 g, 1 mole) was dissolved in10 ml water in a RB and Sodium cyanate (8.9 g, 6 mole) also dissolved in 10ml water in a beaker then the mixture was stirred for 72 hours at room tempurture. The product is a mixture of hydroxylurea and sodium chloird salt. Water was removed from the reaction mixture by rotary evaporater at 55 $^{\circ}$C and the hydroxyurea was extracted from warm ethanol. After evaporation of the ethanol, the hydroxyurea was recrystalised with ethanol several times.



## 10 and 11. Mafenide and Sulfadoxine

**Mefenide** α-Amino-*p*-toluene sulphonamide

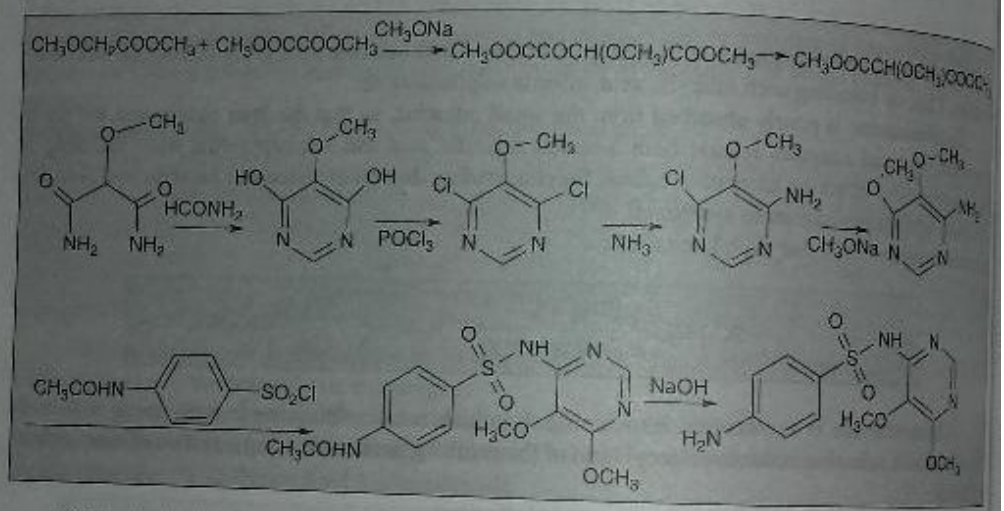



4-Cyano benzene sulphonamide

Mefenide is synthesised by reduction of 4-cyanobenzenesulphonamide.

It is applied locally for burn infections. Although it is a sulphonamide, the *para* substituent differ from the sulpha drug and its mechanism of action is much different.

**Sulphadoxine** $N^1$- (5,6- Dimethoxy-4-pyrimidinyl sulphanilamide)

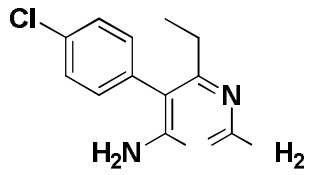



Sulphadoxine is synthesised by the standard scheme from 4-acetylaminobenzenesulphonyl chloride and 4-amino-5,6-dimethoxypyrimidine. However, 4-amino-5,6-dimethoxypyrimidine is synthesised from methyl ester of methoxyacetic acid. Interacting this with dimethyloxalate in the presence of sodium methoxide gives the methoxy derivative, and the pyrolysis of this compound gives the dimethyl ester of methoxymalonic acid. Reacting this with ammonia gives the diamide of methoxymalonic acid. Heterocyclization of the resulting product by a reaction with formamide in the presence of sodium ethoxide gives 4,6-dioxy-5-methoxypyrimidine, which is then transformed to 4,6-dichloro-5-methoxypyrimidine. The resulting 4,6-dichloro-5-methoxypyrimidine undergoes a reaction with ammonia to make 4-amino-6-chloro-5-methoxypyrimidine, and the resulting compound is then reacted with sodium methoxide to make the desired 5,6-dimethoxy-5-aminopyrimidine. Reacting this with 4-acetylaminobenzenesulphonyl chloride and subsequent hydrolysis of the acetyl group gives sulphadoxine.

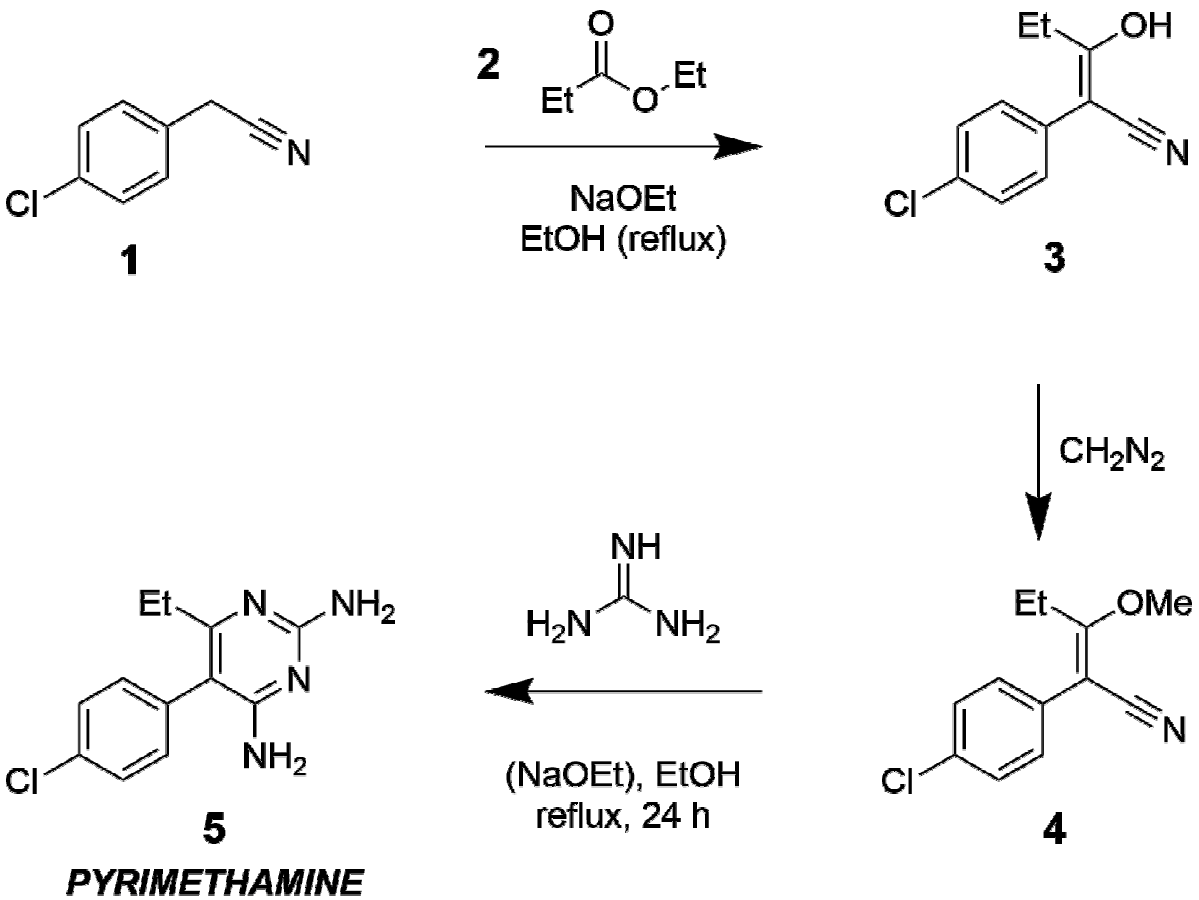
Its principal use is in the prophylaxis or suppression of malaria caused by chloroquine-resistant *P. falciparum*. It is used only in combination with pyrimethamine.

## 12. Pyrimethamine:

Pyrimethamine is a medication used to treat the parasite diseases toxoplasmosis and cystoisosporiasis.

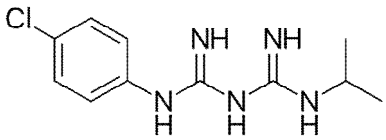



**Synthesis:**

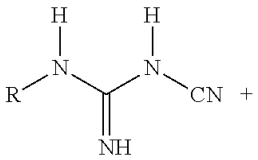


## 13. Proguanil:

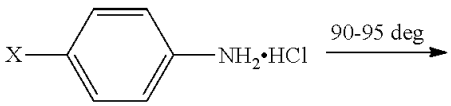
Proguanil is a prodrug that is metabolised in the liver to a diaminotrizine (cycloguanil), which acts as a dihydrofolate reductase inhibitor of plasmodium species and inhibits DNA synthesis.



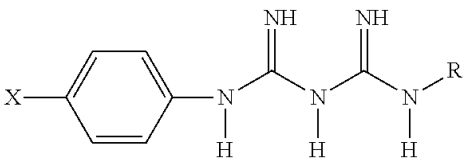

Synthesis method-I




Alkyldicyandiamide



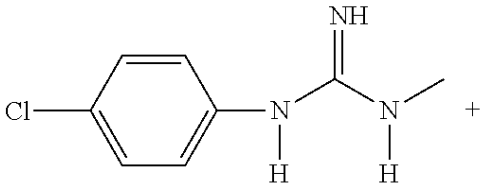

para-haloamiline hydrochloride




Biguanide

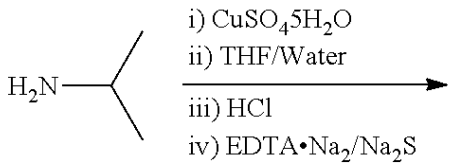
R = alkyl or aryl group and X = halogen

Synthesis method-II



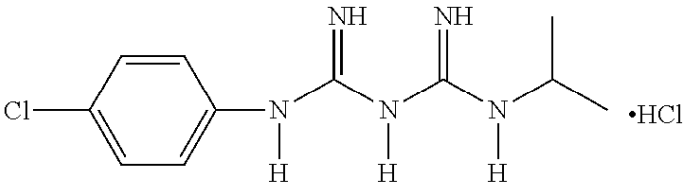

p-Chlorophenylcyano guanidine

(IV)

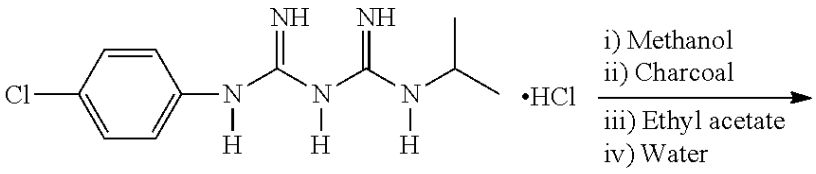



Isopropylamine

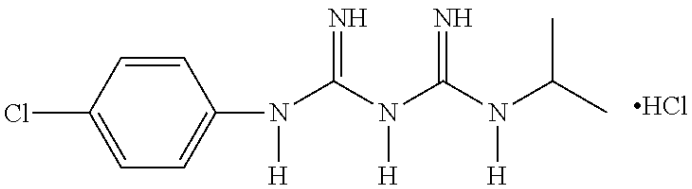
(V)




Proguanil HCl erude



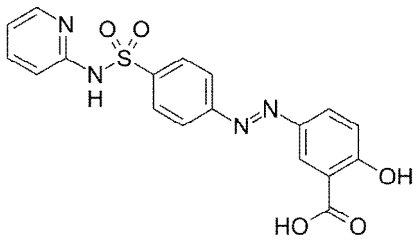

Proguanil HCl erude



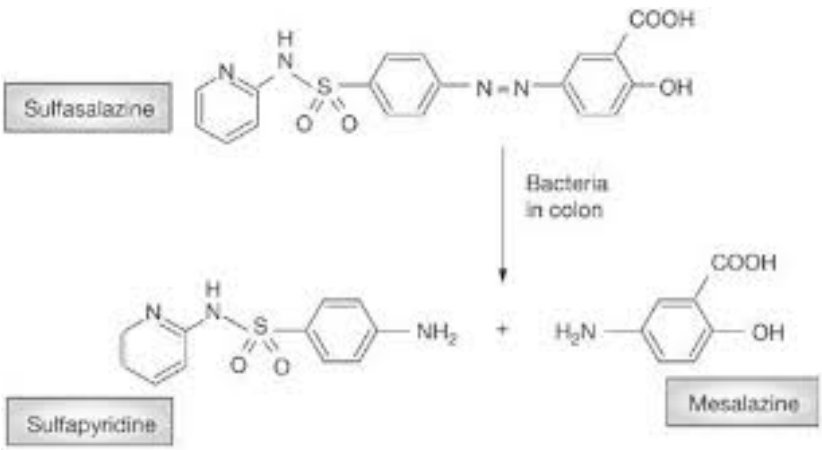

Proguanil HCl erude (EP)

(I)

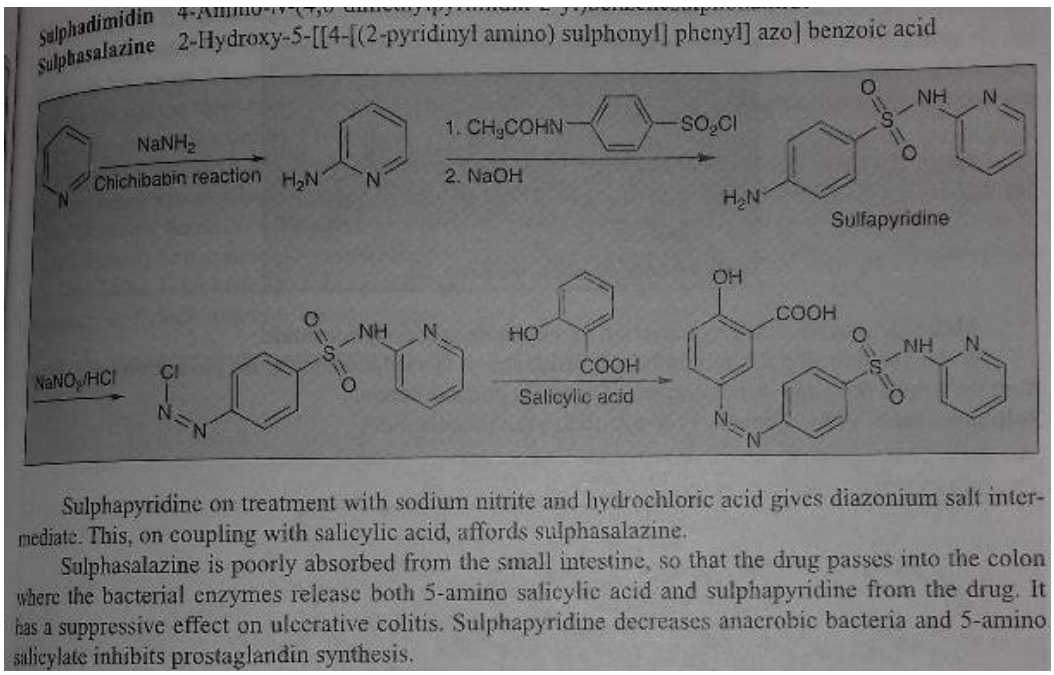
## 14. Sulfasalazine



Sulphasalazine is a bipartite mutual prodrg. In large intestines it gets activated to liberate 5-aminosalicylic acid, which in turn inhibits PG synthesis, and the sulphapyridine is is useful for the treatment of infection. Hence, sulphasalazine is used in the treatment of inflammatory bowel disease (ulcerative colitis). Anaerobic bacteria in the lower bowel metabolically reduces azo group of sulphasalazine to the therapeutic agents 5-aminosalicylic acid (which act as analgesic) and sulphapyridine (which act as antibacterial)



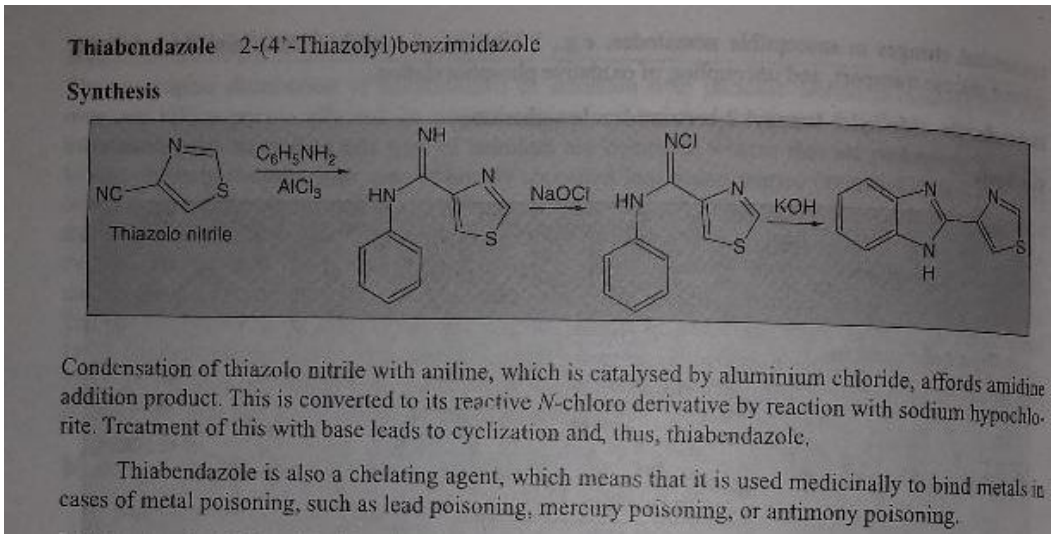

**Synthesis of Sulphasalazine**




Sulphapyridine on treatment with sodium nitrite and hydrochloric acid gives diazonium salt intermediate. This, on coupling with salicylic acid, affords sulphasalazine.

Sulphasalazine is poorly absorbed from the small intestine, so that the drug passes into the colon where the bacterial enzymes release both 5-amino salicylic acid and sulphapyridine from the drug. It has a suppressive effect on ulcerative colitis. Sulphapyridine decreases anaerobic bacteria and 5-amino salicylate inhibits prostaglandin synthesis.

## 15. Thiabendazole:

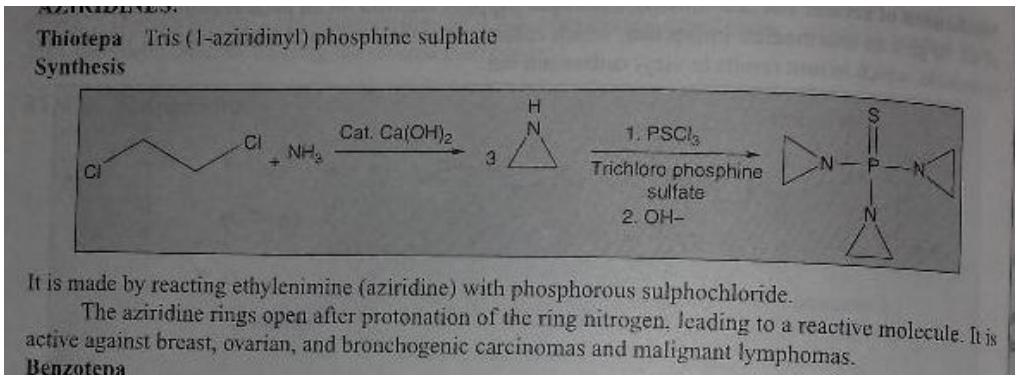



Condensation of thiazolo nitrile with aniline, which is catalysed by aluminium chloride, affords amidine addition product. This is converted to its reactive *N*-chloro derivative by reaction with sodium hypochlorite. Treatment of this with base leads to cyclization and, thus, thiabendazole.

Thiabendazole is also a chelating agent, which means that it is used medicinally to bind metals in cases of metal poisoning, such as lead poisoning, mercury poisoning, or antimony poisoning.

## 16. Thiotepa :

It is anticancer agents



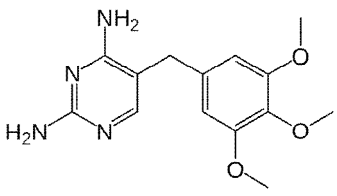

It is made by reacting ethylenimine (aziridine) with phosphorous sulphochloride.

The aziridine rings open after protonation of the ring nitrogen, leading to a reactive molecule. It is active against breast, ovarian, and bronchogenic carcinomas and malignant lymphomas.

**Benzotepa**

## 17. Trimethoprin:

**Trimethoprim** (**TMP**) is an antibiotic used mainly in the treatment of bladder infections. Other uses include for middle ear infections and travelers diarrhea. With sulfamethoxazole or dapsone it may be used for *Pneumocystis* pneumonia in people with HIV/AIDS.



Synthesis: