Yeast (single cell)
mold (many cell)

UNIT - 4
Antifungal Agents

Introduction —

=> Fungi are neither plants nor animals. & are classified as their own Kingdom.
- Fungi grow either as yeasts or as molds

=> many fungi including bread molds & mushrooms can be seen with the naked eye.
=> Fungal spores are present in the air or in soil, thus fungal infections begin mostly in the lungs or on the skin

Historical background :—

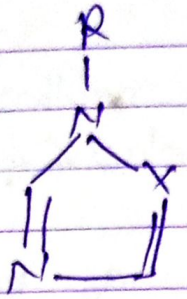
- The 1990 were the most productive period in antifungal development.

- In 1990 fluconazole was introduced that transformed antifungal development.
In 1992 itraconazole was introduced that expanded the activity.

SAR

SAR of Azoles :—

They are group of Synthetic anti-mycotic agent with broad spectrum of anti fungal activity.



X = C Imidazole
X = N Triazole

(i) A basic imidazole or 1,2,4 triazole is essential for anti-fungal activity.
(ii) N_3 of Imidazole & N_4 of triazole bind to P_{450} iron
(iii) The most active ones have two or three aromatic rings & atleast one ring is substituted with halogen or other non-polar groups (2,4-dichlorophenyl or 2,4-difluorophenyl).
(iv) The most active azoles have fluorine.
(v) Ring substitution at other position makes the azole inactive
(vi) The big non-polar resembles the steroid molecule in binding to the enzyme

SAR of Polyene Antifungals

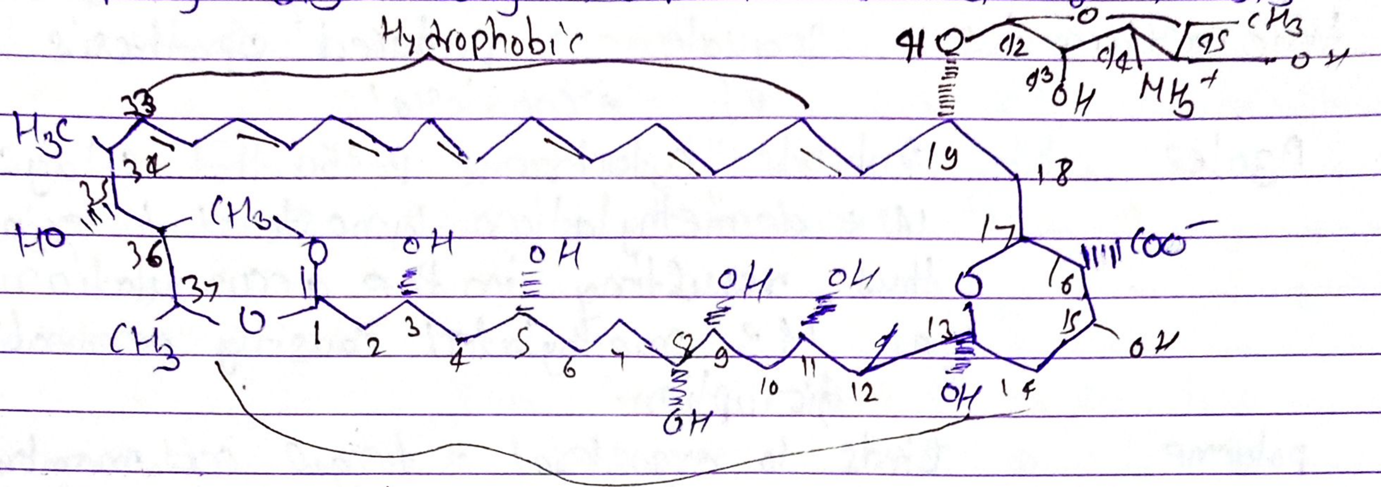
i) The polyene antibiotic probiotic produced by actinomycetes contains a large lactone ring with 4-7 unsubstituted conjugated double bonds
ii) Amphotericin B has 7 & nystatin has 6 conjugated double bonds thus the former is more active & more toxic
iii) The conjugated systems are in all trans configuration so that the ring contains a planner lipophilic segment and a less rigid hydrophilic portion.

(iv) ↑es in double bond conjugation will ↑es the activity & toxicity.

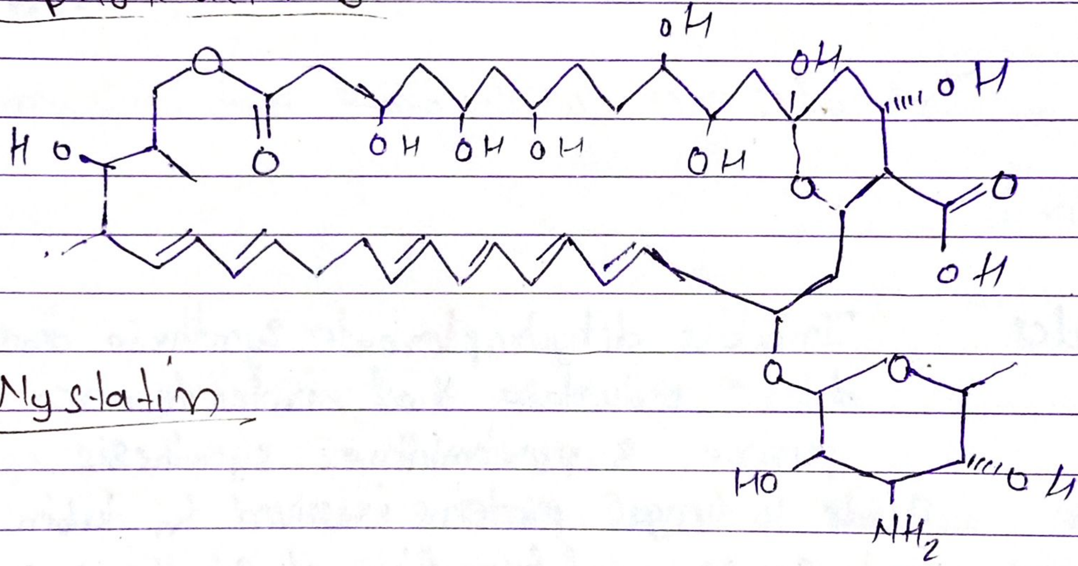
(v) polyenes have polyhydroxyl groups

vi) most polyene antifungal drugs are macrocyclic lactones

vii) Ring size vary from 12 - 37 atoms in size



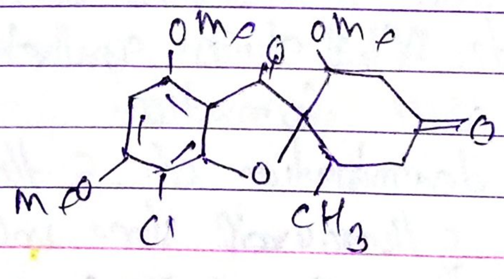
Amphotericin B



Nystatin

~~Mode of Action of Antifungal~~ Compound

Griseofulvin



MoA of Antifungal Compound

Compound	MoA
Allylamine and thiocarbamates	suppresses fungal squalene epoxide and results in the accumulation sequalene & reduced synthesis of ergosterol
Azoles	Inhibits cytochrome p-450 that catalyses 14 α demethylation lanosterol to ergosterol thus resulting in the accumulation of 14 α methylated causing permeability disruption.
polyene	Binds to ergosterol a fungal cell membranes and results in membrane disorganisation.

Interference with other metabolic processes

Compounds	MoA
Antifolates	Inhibits dihydropteroate synthase and dihydrofolate reductase that interference with purine & pyrimidine synthesis
Benzoluran cyclohexenes	Binds to fungal proteins involved in tubin assembly and cause malformation of spindle & cytoplasmic microtubules
Diamidines	Binds to DNA & interferes with its replication
Echinocandins	Inhibits β(1,3)-glucan synthetase & interferes with cell wall formation
Pyrimidines	causes deamination of 5 fluorocytosine by fungal cell to 5 fluorouracil since incorporated into RNA in place of uracil or is converted to 5-F-2' deoxyuridylic acid that inhibits thymidine Synthe

Antifungal Antibiotics

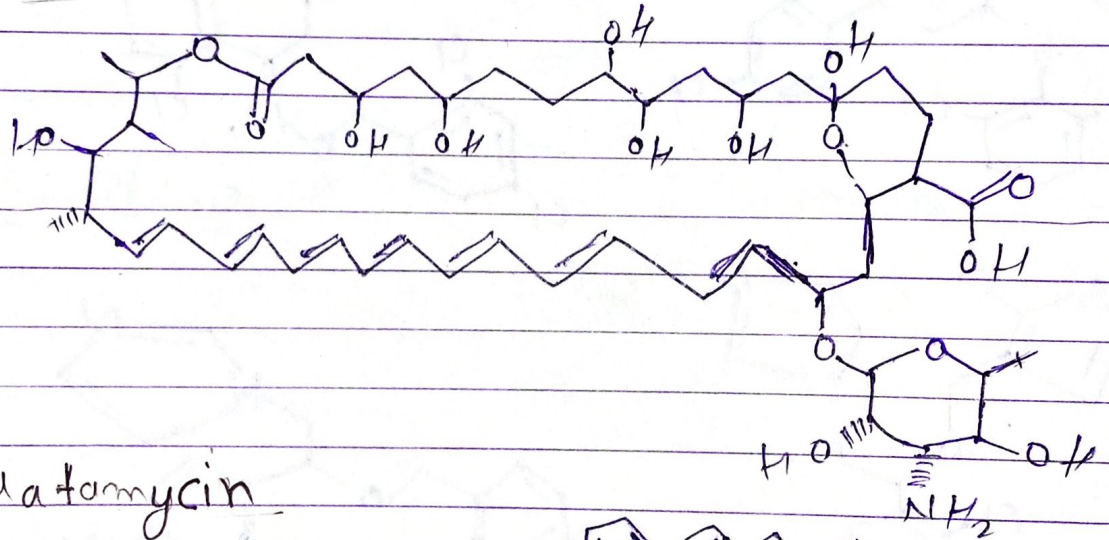
1) Amphotericin B
2) Nystatin
3) Natamycin
4) Griseofulvin

Use – 1) Athlete foot
2) Ring worm 3) Candidiasis
4) Serious systemic infections such as cryptococcal meningitis 5) mucocutaneous candidiasis
6) Systemic uses for dermatophytosis

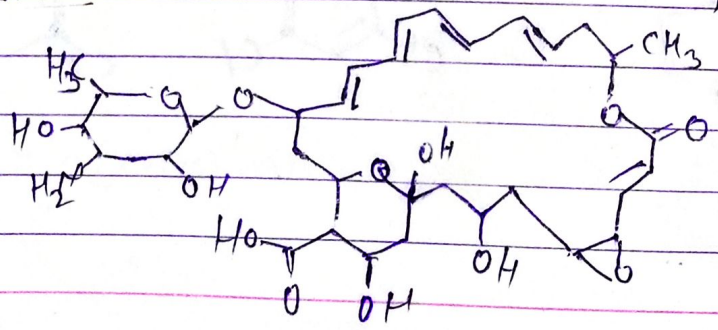
Adverse effects

Anti-fungal agents cause liver damage, affect estrogen levels & allergic reactions Ex- anaphylaxis

① Amphotericin –



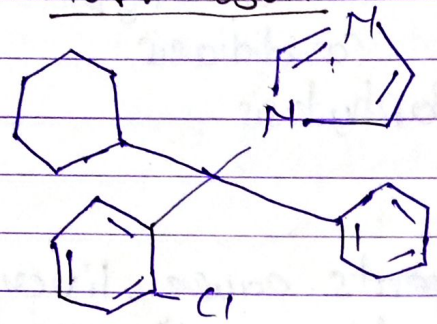
② Natamycin

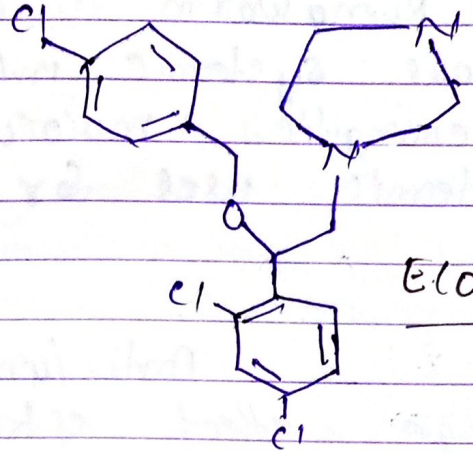


Synthetic Antifungal Agents —

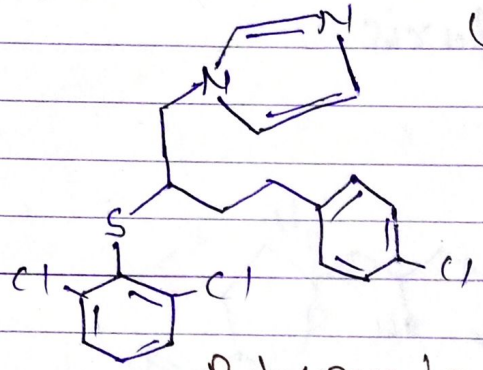
(1) clotrimazole (2) Econazole (3) Butoconazole (4) oxiconazole
(5) Tioconazole (6) miconazole (7) Ketoconazole (8) Terconazole
(9) Itraconazole (10) Fluconazole (11) Naftifine hydrochloride
(12) Tolnaftate

① clotrimazole –

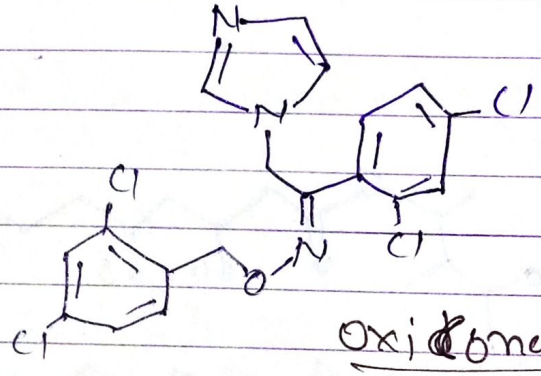


② 

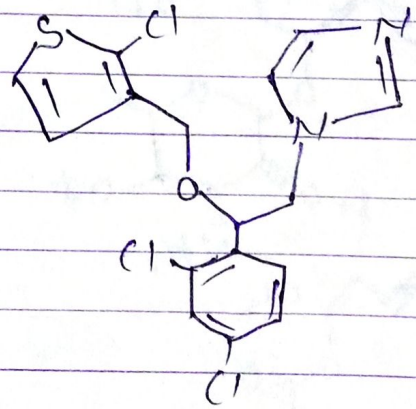
Econazole

③ 

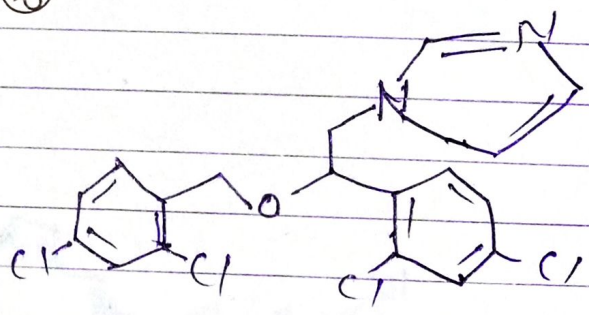
Butoconazole

④ 

oxiconazole

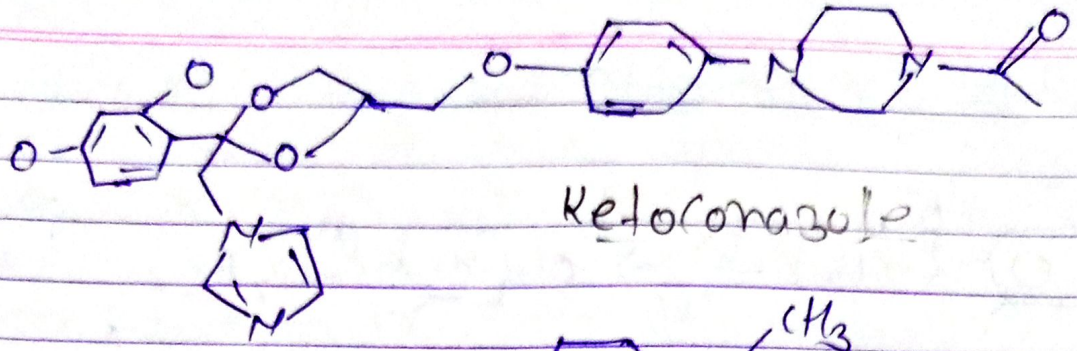
⑤ 

Tioconazole

⑥ 

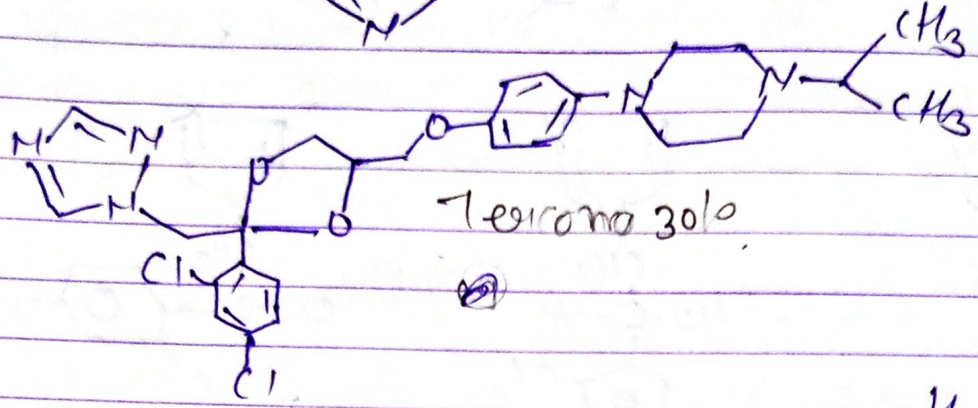
miconazole

(7)



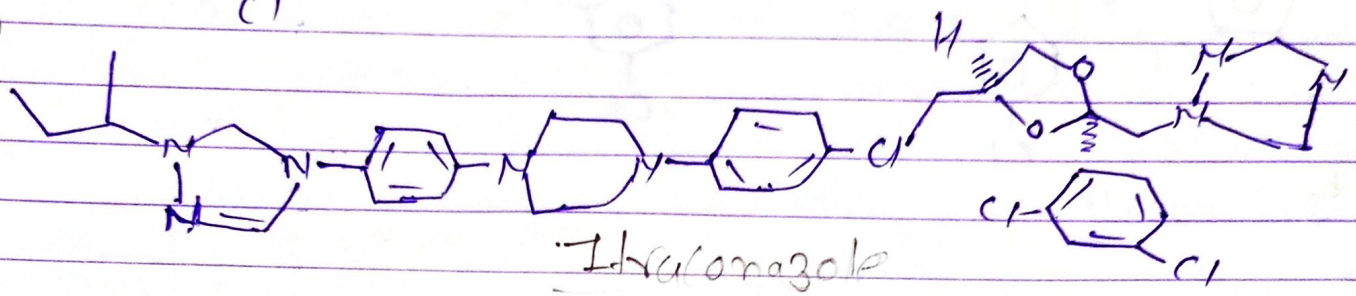
Ketoconazole

(8)



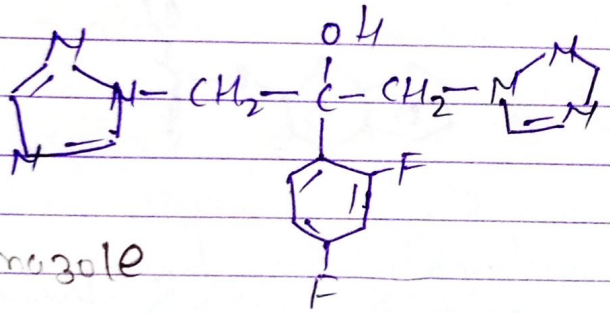
Terconazole

(9)



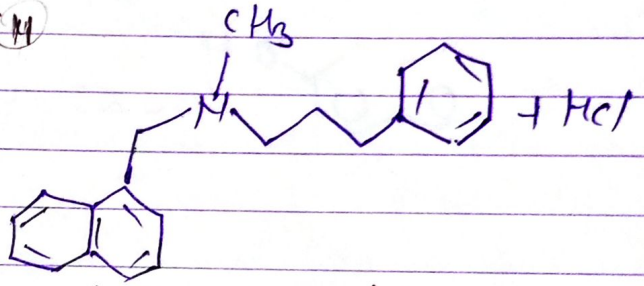
Itraconazole

(10)



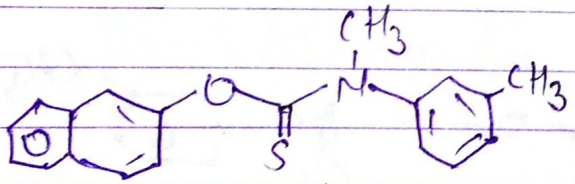
Fluconazole

(11)



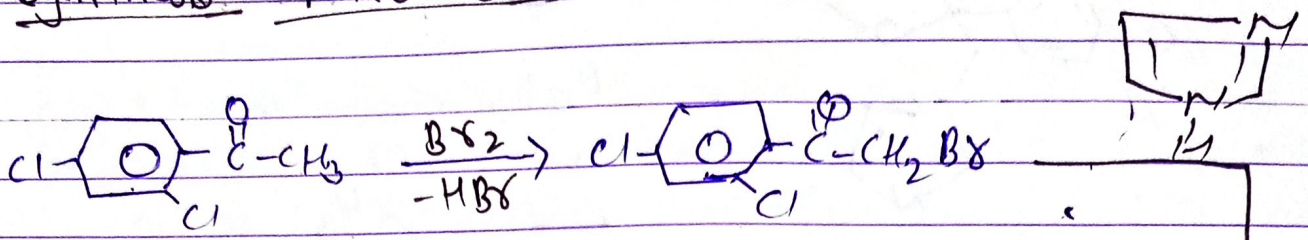
Naftifine Hydrochloride

(12)

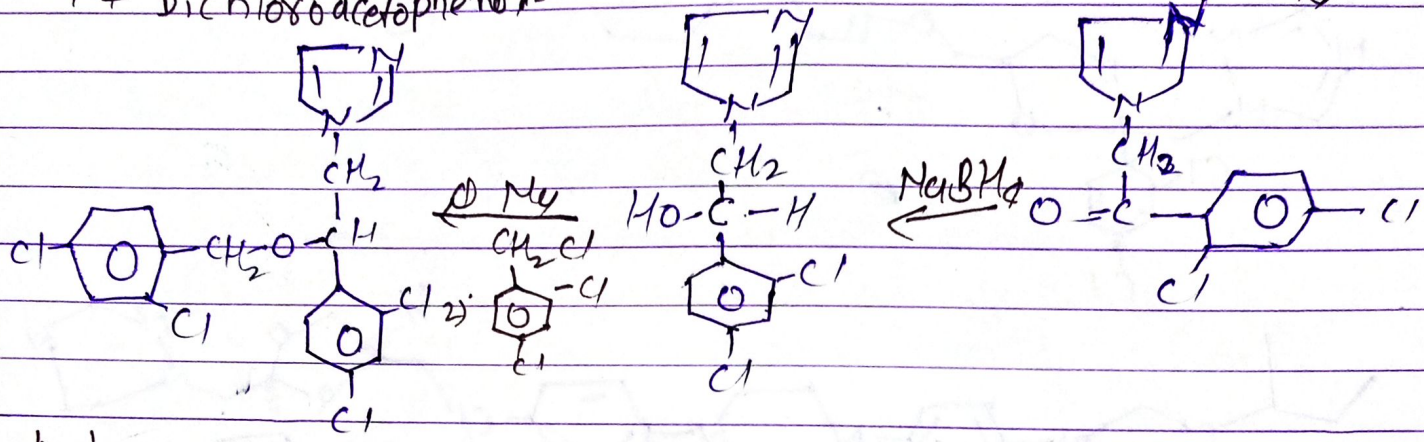


Tolnaftate

Synthesis - miconazole

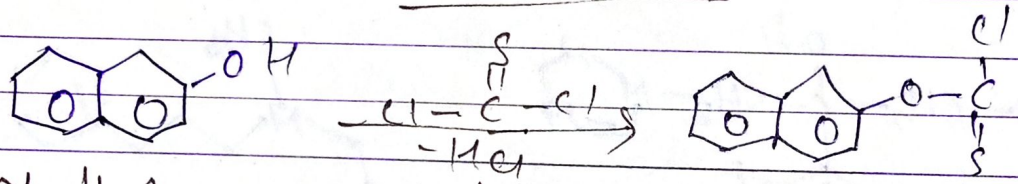


2, 4 Dichloroacetophenone



miconazole

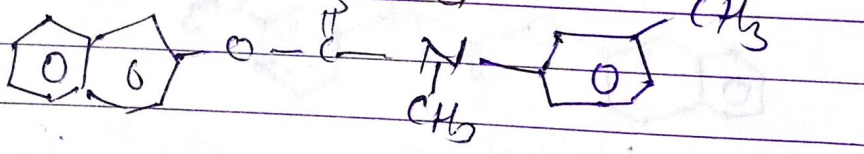
Tolnaftate



2 Napthol

Thiophosgene

N-methyl 3 toluidine

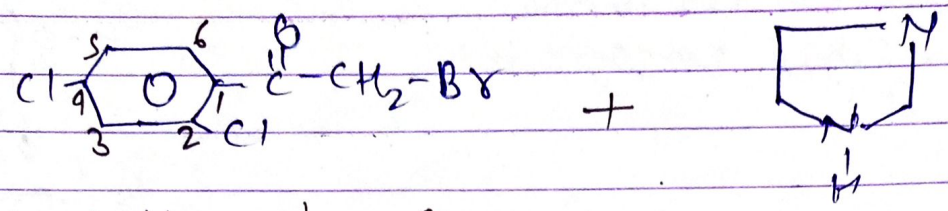


Tolnaftate

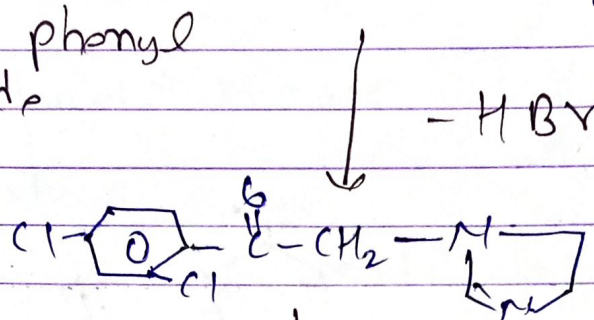
UNIT – 4 (Antifungal agent)

① Miconazole ② Tolnaftate

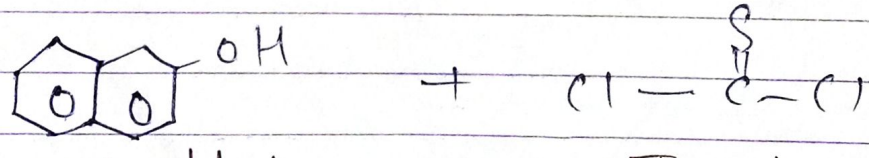
Miconazole

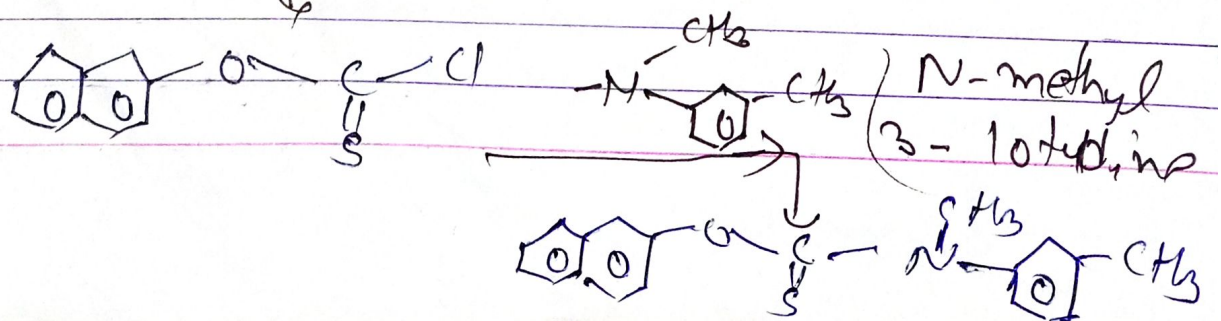


2-4 - Dichloro phenyl Bromide



Tolnaftate (Antifungal drug)

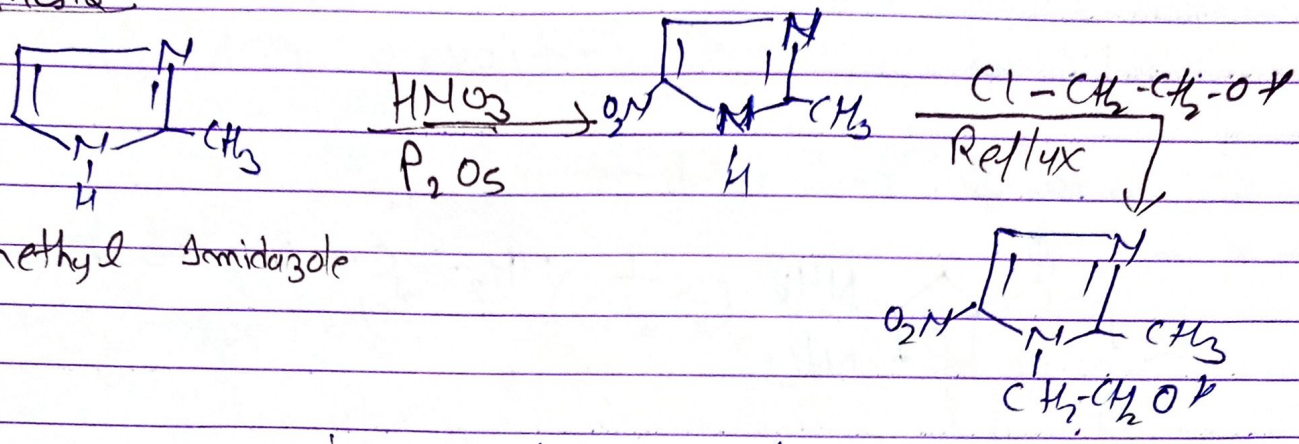




Use - ① use in treatment of skin infection
② Ringworm ③ Athelete's foot
④ Jock Itch

Metronidazole (Antiprotozoal drug)

Synthesis -

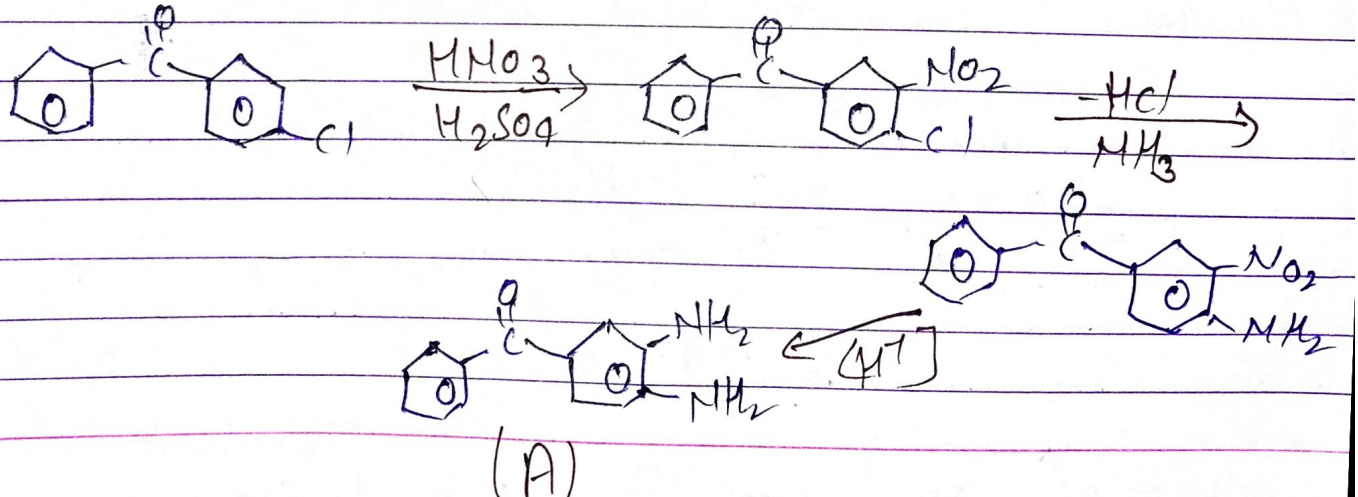


2-methyl 5nitroimidazole

Use - use in treatment of -
a - Trichomoniasis
b - Amoebiasis (Kills Entamoeba Histolytica
c - Anaerobic bacterial infection
d - Helicobacter Pylori

Mebendazole (Antihelmentic)

① Synthesis of 3,4-Diaminobenzophenone -



(A)

(B) $NH_2-C(=NH)-SCH_3$ H_2SO_4 + $ClCOOCH_3$ methyl chloro formate

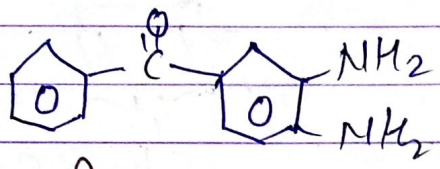
methyl Thiourea Sulphate

↓ - HCl

$NH_2-C(=N-COOCH_3)-SCH_3$ - (B)

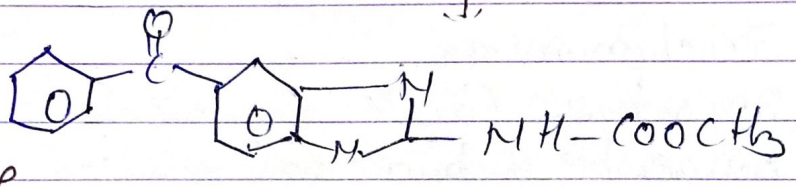
methyl - S - methyl thiourea carbonylate

Combination of A + B - ..



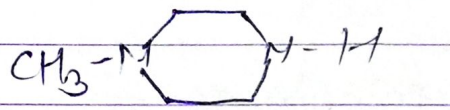
A + $NH_2-C(=N-COOCH_3)-SCH_3$ (B)

Cyclization | NaOH/HCl



Mabendazole

Diethyl carbamazine citrate (Antihelmenth drug)



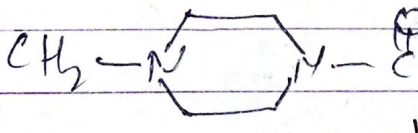
$Cl-C(=O)-N(C_2H_5)_2$

N - methyl piperazine

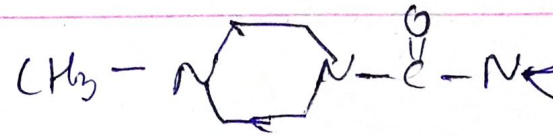
Diethyl carbonyl chloride

Condensation Reaction

↓ - HCl



↓ $HO-C(CH_2-COOH)(CH_2-COOH)-COOH$ citric acid

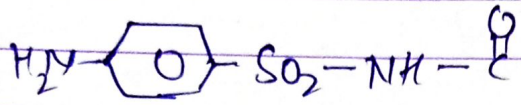


. $HO-C(CH_2-COOH)(CH_2-COOH)-COOH$

Use - ① use to treat infection caused by parasites is Round worm hook worm. flat worm etc.

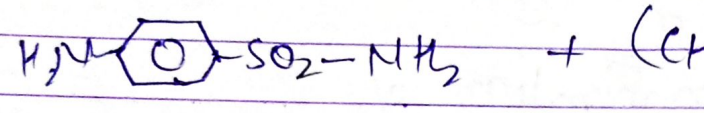
② Filoriasis

Sulphacitomide (Sulphonamide)



N- Sulphonyl Acetamide

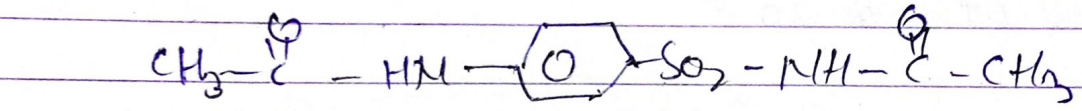
Synthesis -



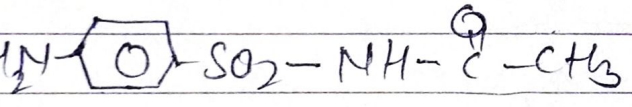
4 - amino benzene Sulphonamide

Acetic Anhydride

$-H_2O$



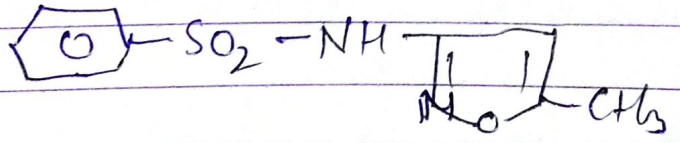
Partial hydrolysis $-CH_3COOH$



Use - ① ~~UTI~~ UTI

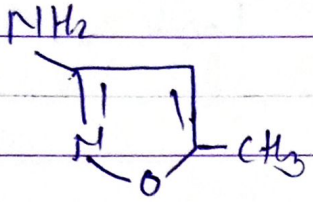
② use topically treat Ocular infection

Sulphomethoxazole (Sulphonamide) -



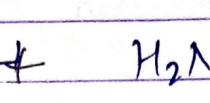
Sulpha methoxazole

Synthesis -



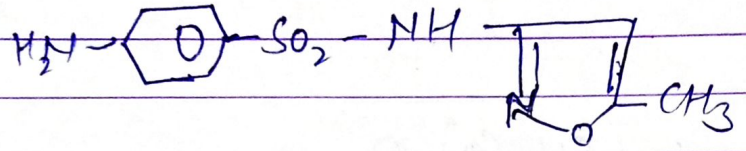
5 - methyl isoxazole amine

+



Para amino Benzene Sulphonyl chloride

$\downarrow$ -HCl



- It is given in combination of Trimethoprim + sulphomethoxazole

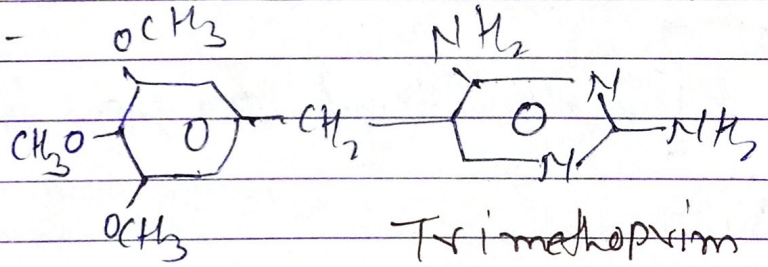
↓

cotrimoxazole

use - ① UTI ② Respiratory ③ Thyroid
④ Dysentary ⑤ Bacterial diarrhoea

Trimethoprim

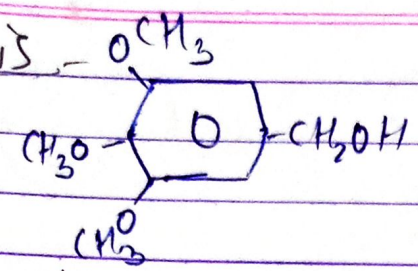
Structure -



Trimethoprim

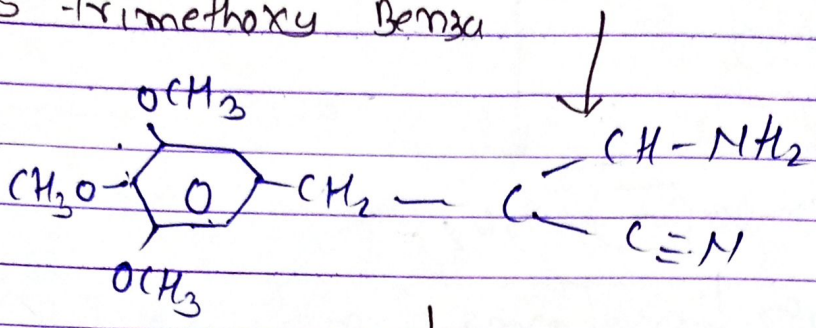
use :- - UTI
- Diarrhoea
- Bronchitis
- Pneumonia

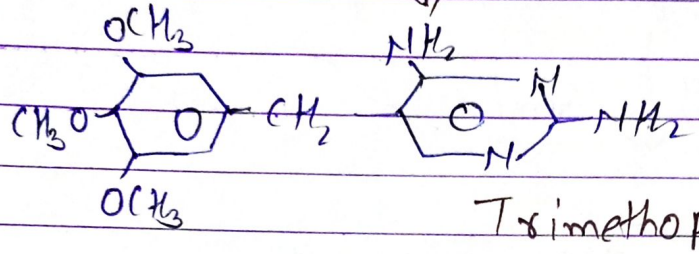
Synthesis -



+ $CH_2(C\equiv N)_2$ malonitrile

3,4,5 - trimethoxy Benza





Trimethoprim

Given as Trimethoprim + Sulphamethoxazole

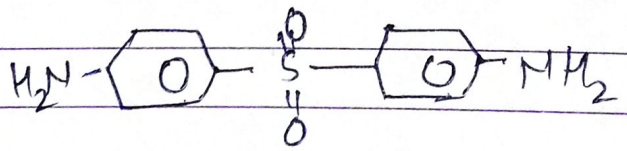
↓

Co-trimoxazole

Broad Spectrum activity against gm +ve & gm -ve bacteria

Dapsone

Structure -



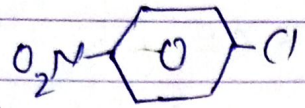
Use - Mycobacterium laprae infection (leprosy)

① Acne

② Dermatitis

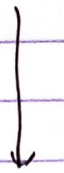
④ other skin infection

Synthesis –

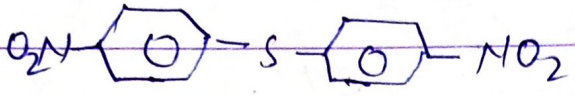


+ Na_2S Sodium sulphide

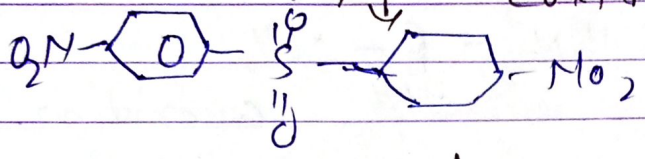
1-chloro 4 nitro benzene (2-molecule)



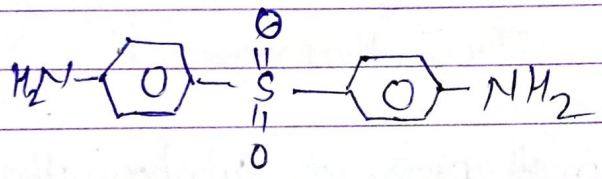
$-2NaCl$



$Cr_2O_7^{--}$ [oxidation]



Reduction [H] Sn/HCl



Dapsone

Anti proto-zoal Agent

Introduction:- protozoal infections commonly occur in people living in under developed tropical & sub tropical countries. However with increased world travel, protozoal diseases such as malaria, amoebiasis and giardiasis are no longs confined to specific geographic locales.

Antiamoebic Agents -

Amoeba is a single celled organism which needs a host to survive & hence, it comes under protozoan category.

Historical Background :-

- Brazilian & central American Indians used ipecacuanha extracts in the treatment of diarrhoea
- Vedder established its anti amoebic activity in 1912.
  Ehrlich & Bertheim synthesised carbarsone in 1907.
- The anti-amoebic activity of chloroquine was reported by Conan in 1948.
- metronidazole was synthesised in 1954 in Rhone poulenc laboratories

Classification - ① Luminal Amoebicides - Act intes
② Systemic Amoebicides - treating amoebic dysenter
③ mixed Amoebicides - Act intestinal & systemic fo

Mechanism of Action:-

→ Anti-amoebic drugs act on artificial electron acceptor after accumulating in the cells as reduced compounds. This nitro group of the drugs accepts electrons This diverts electrons from normal pathways of the protozoan

→ The nitro group of the drugs accepts electrons (source of electrons may be reduced NADPH or sulphide) from electron-transport proteins (such as ferredoxins) & diverts them from normal energy yielding pathways. This reduction is catalysed by iron sulphur complexes.

→ metronidazole also impairs the ability of DNA to function as a template. The reduced metronidazole damages the helical structure of DNA. Cause strand breakage impairs DNA's function & ultimately cell death.

→ A disulfiram like reaction can occur when metronidazole is administered along with an alcoholic beverage.

Use - ① It is used to infections caused by anaerobic bacteria, amoeba & parasites in urinary tract, vagina & intestines
② Hepatic amoebas & off label for Crohn's disease

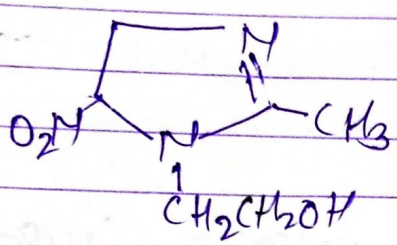
Adverse Effects -

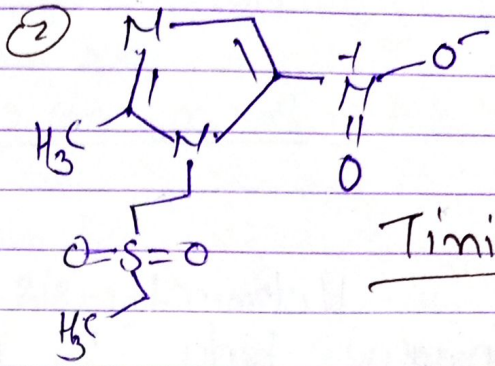
① Flatulence ② Loss of appetite ③ Nausea ④ Itching ⑤ Hives

Important products :—

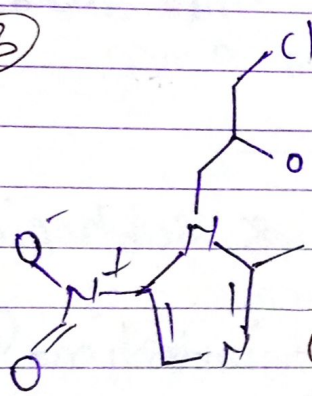
1) metronidazole 2) Tinidazole 3) ornidazole
4) Diloxamide 5) Iodoquinol 6) pentamidine isethionate
7) Atovaquone 8) Eflornithine

1) metronidazole

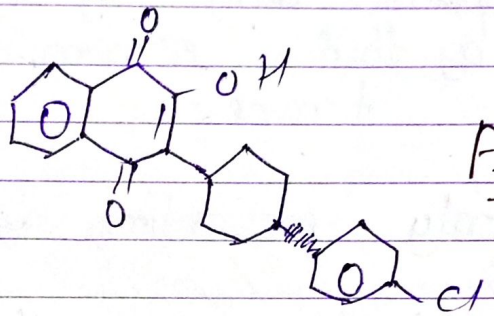


② 

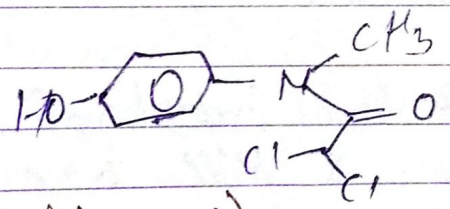
Tinidazole

③ 

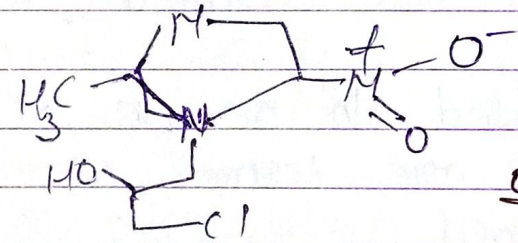
ornidazole

④ 

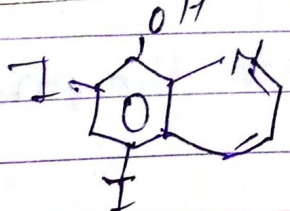
Atovaquone

⑤ 

Diloxamide

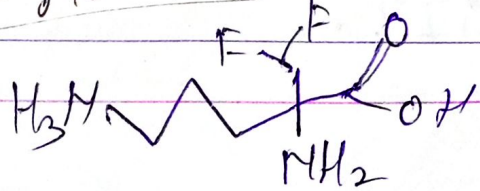


ornidazole

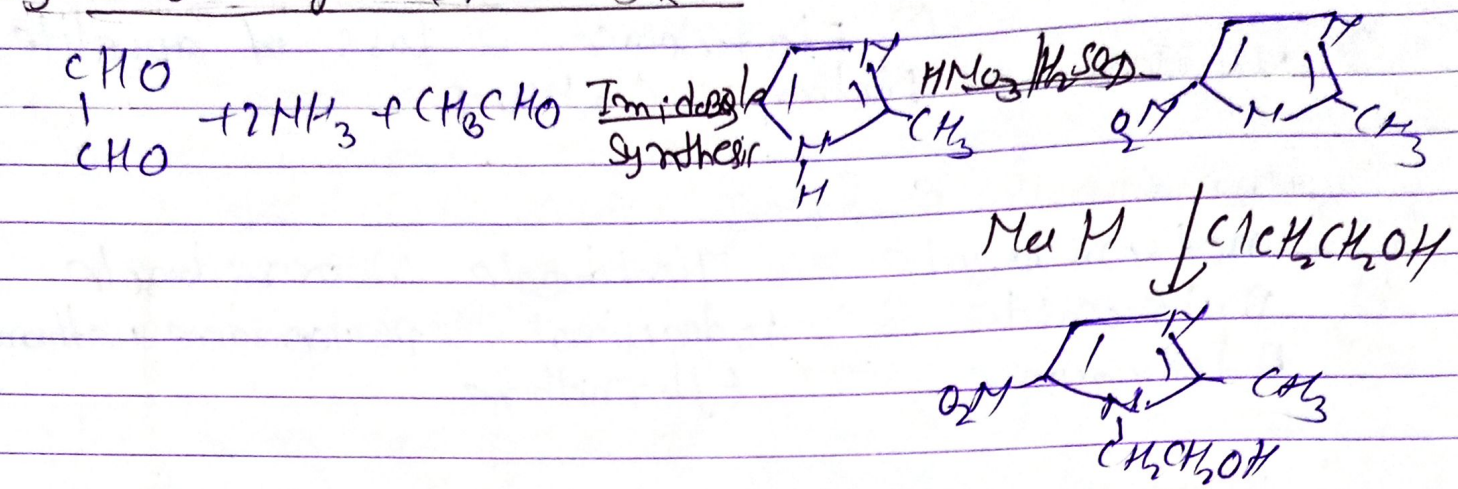


Iodoquinol

Eflornithine



Synthesis of metronidazole



Anthelmintics

Introduction -

- Helminthiasis is an infection caused to human body by helminths. This diseased caused by this worm are know since ancient times.

→ It mainly preventing in tropical & subtropical regions.

→ Drugs used to kill or eliminate the intestinal parasites are termed anthelmintics.

→ Drugs used to remove or expel the intestinal parasites are termed vermifuges. & Kill are termed vermicides.

→ Anthelmintics act locally to remove the parasite from GIT.

Historical Background :—

⇒ The first anthelmintics were some plant extracts, which are now outdated, but aspidium continues to be in use.

→ Anti-parasitic effects of Arsenic & antimony compds and lower toxicity of these heavy metal.

→ Based on the trypanocidal activity of aminidol violet, trypan blue, & trypan red dyestuffs.

→ Cloez synthesised piperazine in 1853. Giroud discovered its anthelmintic activity in 1942

→ It was discovered that some thioxanthenone derivatives have schistosomicidal activity. & several cyanine dyes posses anthelmintic activity.

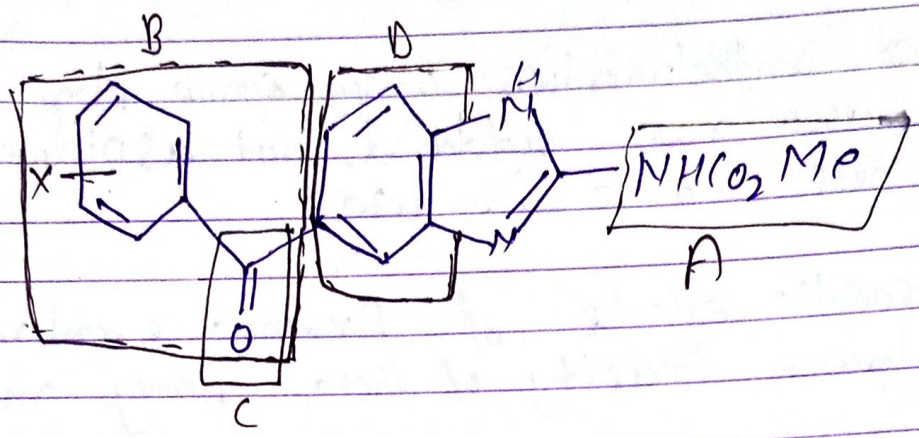
→ Barthel in 1951 first synthesised metrifonate as an intermediate in an organic reaction. It was synthesised by Lorenz in 1952

→ Thiabendazole is a product of investigation of several hundred substituted benzimidazoles.

→ Discovery of anthelmintic activity in Isothiuronium salt.

→ mebendazole was introduced in 1971.
Praziquantel was synthesised by Seubert in 1975.

SAR :—

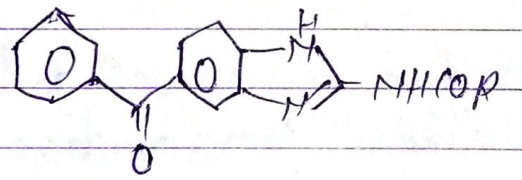


⇒ It studied by choosing the four possible sides.

1) Modification of 2-methyl carbamate group (A)
2) Modification of 5-benzoyl group (B)
3) Modification of keto group (C)
4) Modification of benzene ring (D) of the benzimidazole

(1) Modification of 2-methyl carbamate group A —

A series of benzimidazolyl ureas were synthesised to examine the anti filarial activity.
SAR Studies in this series showed rise in antifilarial activity against B Pahangi & Cairnii.

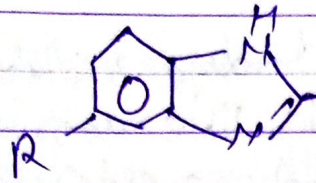


R = NMe_2
R = $PhNH$
R = $4FC_6H_4NH$

(2) Modification of 5-Benzoyl group (B) —

Substitution of NH group b/w the benzoyl group & benzimidazole moiety give rise to compounds that are 100% effective against adult B.

→ Pahangi in 100 mg/kg subcutaneous dose



R = 2-FC6H4CONH
R = 4-FC6H4CONH
R = 4-FC6H4NHCO
R = 3-CF3C6H4NHCO

③ Modification of keto Group (C) –

→ mebendazole & flubendazole metabolites ie. 2-amino-5-benzoylbenzimidazole.
→ It was of considerable interest that the compound retained the macrofilaricidal activity profile.
→ It is not show any antifilarial activity.

Mechanism of Action –

1) They inhibit fumarate reductase enzyme system of the worm & thus interfere with an important energy source
2) They inhibit nematode cell division in the metaphase by interfering with microtubule assembly.
3) They have high affinity for tubulin which is required for microtubule synthesis.
4) They irreversibly block uptake of glucose by susceptible helminths thus depleting the glycogen stores in the parasite. This fuel ATP production which is essential for survival & reproduction of helminths.

Classes	Example	moA
Benzimidazole	Albendazole	Tubulin binding & cellular disruption
Tetrahydropyrimidine	Levamisole	Nicotinic like agonists
organophosphates	Dichorvos	Acetylcholine esterase inhibitor
Piperazines	piperazine	GABA agonists
macrocyclic lactones	Ivermectin	GluCl-potentiators
	praziquantel	Enhance Ca^{++} permeability
salicylanilides	closantel	proton ionophores

Use

① The treatment of intestinal nematode infection and echinococcosis

② Treatment of schistosoma japonicum (blood fluke) & fasciolopsiasis (intestinal flukes), & liver flukes

③ The treatment of hookworm, pinworm & round worm infestations.

④ They are used in veterinary practice for controlling endoparasite & exoparasite in domestic animals.

Adverse Effects -

Common side effect - Dizziness, drowsiness, headed, sweeting, dryness, ringing ears.

Rare side effect - Appetite, diarrhoea nausea vomiting

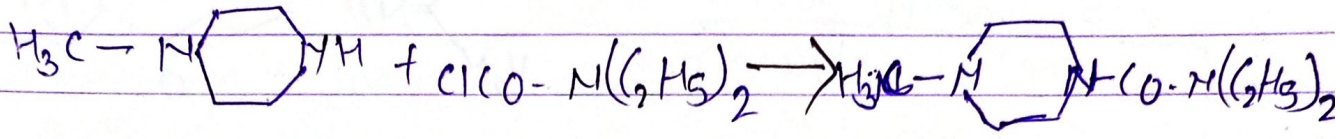
Serious side effect - fever, chills, confusion, extreme weakness, Nausea, vomiting, skin rashes, back pain

Important products -

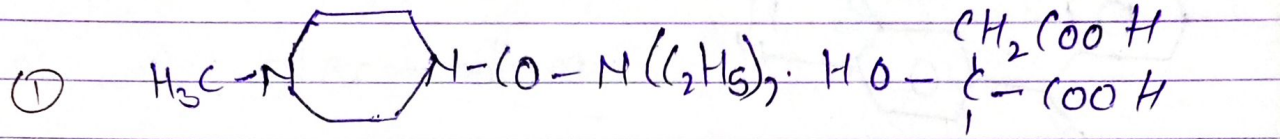
① Diethylcarbamazine citrate
⑤ Thiabendazole ② mebendazole ③ Albendazole
④ niclosamide ⑧ oxamniquine
⑥ praziquantel ⑦ Ivermectin

① Diethyl carbamazine citrate :-

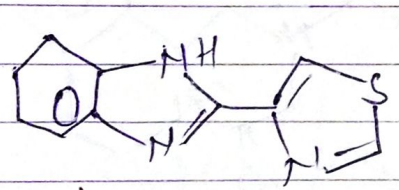
Synthesis -



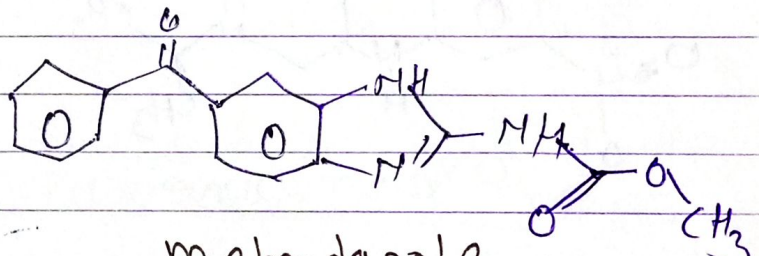
↓ citric acid



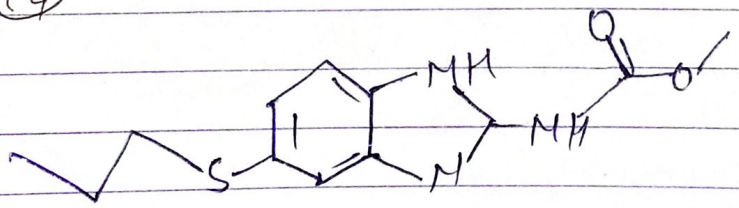
① Diethyl carbamazine citrate

② 

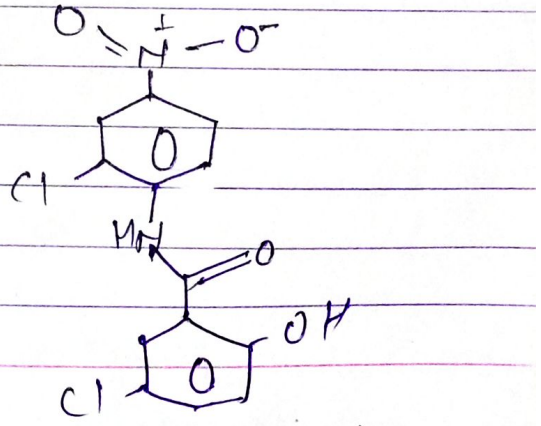
Thiabendazole

③ 

mebendazole

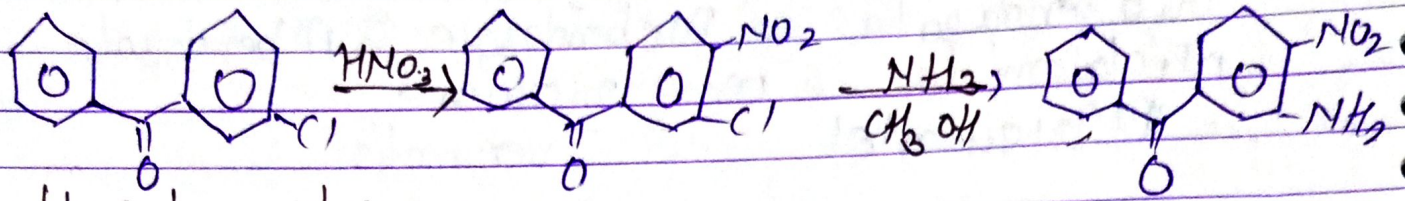
④ 

Albendazole

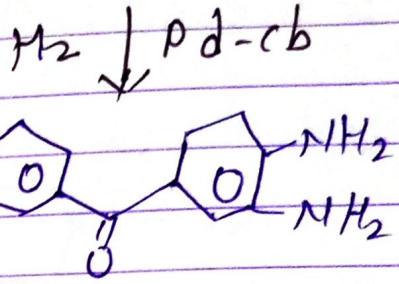


Niclosamide

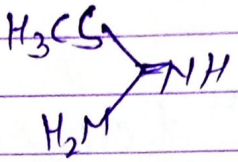
Synthesis mebendazole –

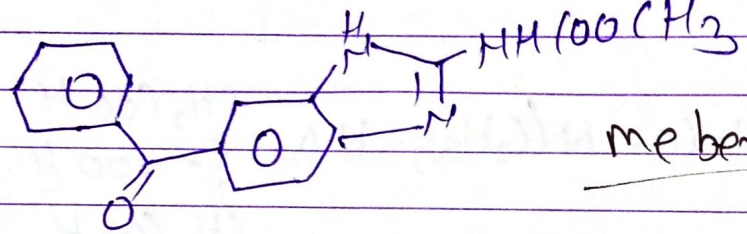


4-chloro benzophenone

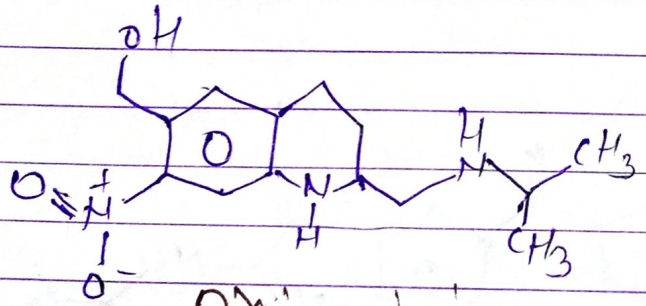


1) S-methylthiourea
2) methyl chloroformate

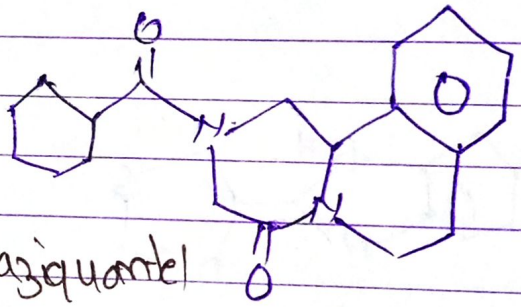




mebendazole



oxamniquine



praziquantel

Sulphonamides & Sulfones

Sulphonamides :-

Introduction :-

Several groups of drug are derived from sulphonamides. These are synthesis antimicrobial agent and anticonvulsant sultiame lack anti bacterial activity

- It is used to diabetics mellitus, oedema, hypertension & gout.

→ Historical Development -

Sulfphonamides were the first antimicrobial drug that paved the way it antibiotic revolution in medicine

→ The first sulfonamide trade named prontosil was a prodrug. Experiments with prontosil began in 1932 in the laboratories of Bayer AG.

→ The first official communication about the discovery was not published & 1935 more than 2 years after Klarer & his research partner.

Classification -

① Based on their duration of Action

(i) Short Acting Sulphonamides -

4 - 8 hour duration

e.g sulphadiazine & sulphamethoxazole

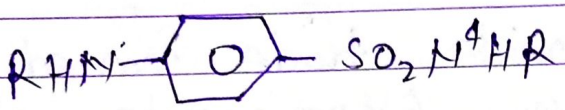
(ii) Intermediate Acting Sulph. :- 8-16 hour
e.g - Sulphaphenazole & Sulphamethoxazole

(iii) Long Acting :- 1-7 day
e.g - Sulphaphenazole & Sulphadimethoxine

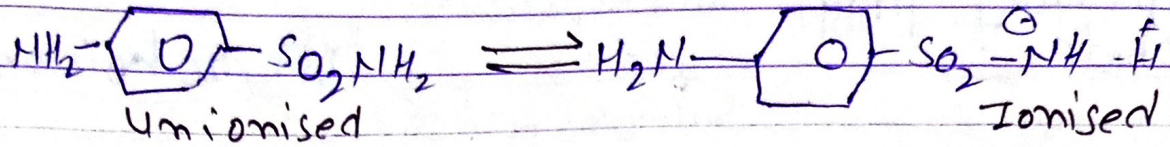
(2) Based on their pharmacological Action

i) used in systemic infection e.g Sulphadiazine
ii) used in eye infection e.g Sulphacetamide
iii) used in intestinal infection e.g. Sulphapyridine
iv) used in urinary tract infection e.g. Sulphamethaxazole

SAR of Sulphonamides



1) Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity
2) Sulphur atom should be directly linked to the benzene ring
3) In N' substituted sulphonamides, natures of the substituent at amide group influences the activity
4) Substituent that impart electron rich character to SO_2 group Yes bacteriostatic activity
5) Heterocyclic substituents give rise to highly potent derivatives.
6) Sulphonamides containing a single benzene ring at N' position are more toxic than the heterocyclic ring analogues



7) The free aromatic amino group should be present para to the sulphonamide group. Its substitution at ortho or meta position will give rise to compounds with no antibacterial activity

8) presence of free amino group is essential for activity. Any substitution of amino group either results in prodrug nature or in the loss of Activity

9) The sulphonamides are active in their ionised form. their maximum activity is observed b/w 6.6 - 7.4 pKa value

(10) Substitutions in the benzene ring of sulphonamides give rise to inactive compounds

11) substitution of free sulfonic acid ($-SO_3H$) for sulphonamide function destroys the activity however replacing with a sulfonic acid group ($-SO_2H$) & acetylation of N_4 position retains the activity

mechanism :—

Sulphonamides are bacteriostatic when administered to human in achievable dose. They inhibit dihydropteroate synthase enzyme which is essential for the biosynthesis of folic acid derivatives & ultimately thymidine which required for DNA

Dihydropteroate diphosphate + PABA → (Dihydropteroate Synthase, Sulfonamides) → Dihydrofolic acid

Dihydropteroate diphosphate → (Sulfonamides) → False metabolite

False metabolite → Tetrahydrofolic acid

Tetrahydrofolic acid → Thymidine → DNA

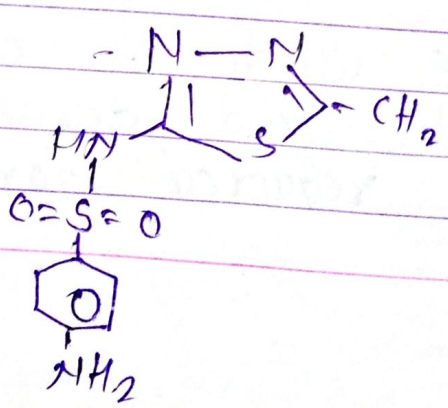
Use -
- Sulfisoxazole acetyl along with erythromycin ethylsuccinate
- UTI
- Crohn's disease
- eye infection

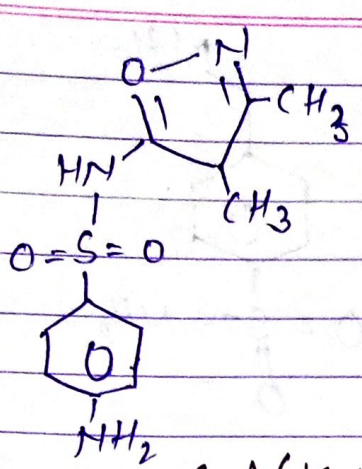
ADR - Common Side effect

Important product -

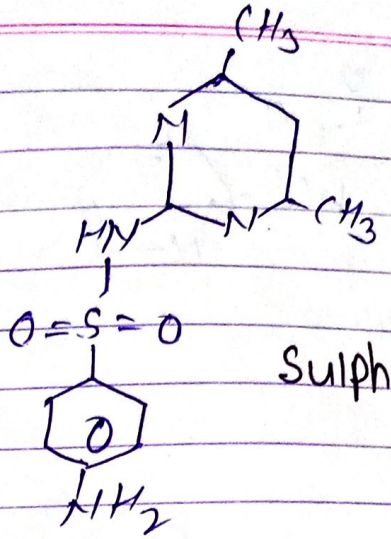
① Sulphamethizole ② Sulfisoxazole ③ Sulphamethazine ④ Sulfacetamide ⑤ Sulphapyridine ⑥ Sulfomethoxazole ⑦ Sulphadiazine ⑧ Mafenide acetate ⑨ Sulfasalazine

① Sulphamethizole



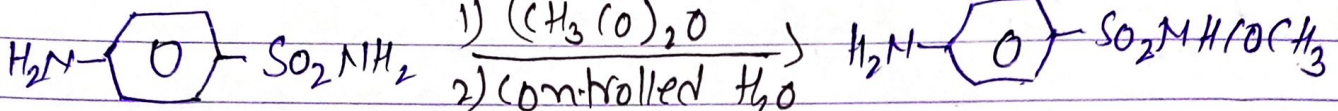


Sulfisoxazole

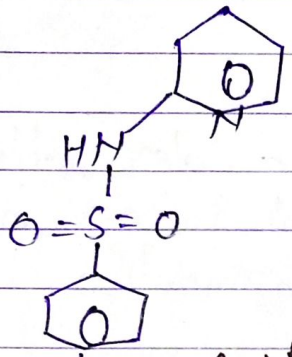


Sulphamethazine

Synthesis of Sulfacetamide

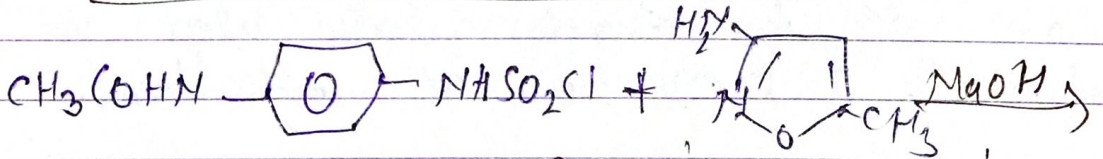


Sulfacetamide

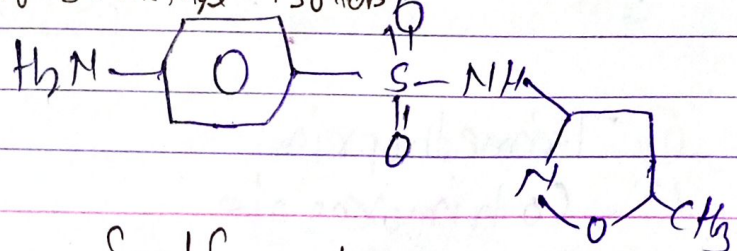


Sulphapyridine

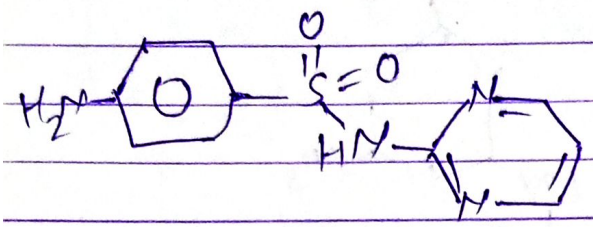
Synthesis of Sulfamethoxazole



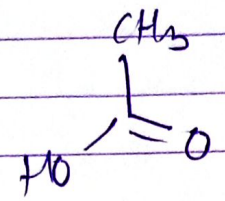
3 Amino-5-methyl isoxazole

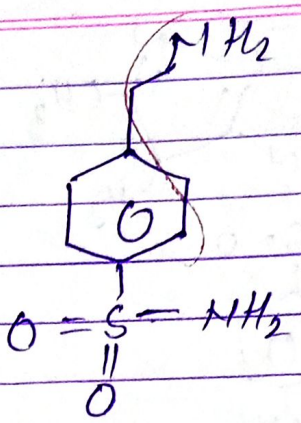


Sulfamethoxazole

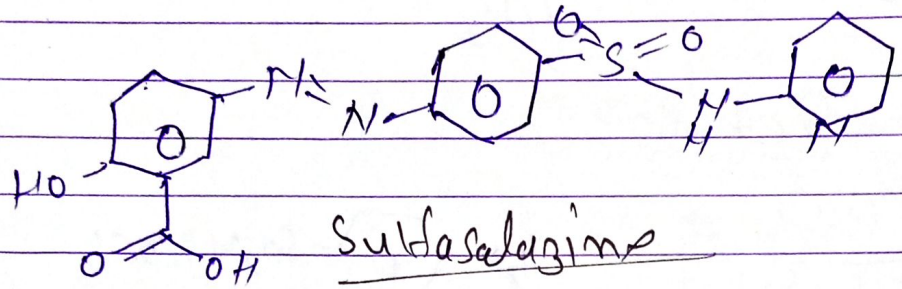


Sulphadiazine





mafenide Acetate



Sulfasalazine

Folate Reductase Inhibitors :-

Introduction

2,4 Diamino pyrimidine derivatives like trimethoprim and pyrimethamine inhibit DHFR enzyme of bacteria & plasmodium respectively.

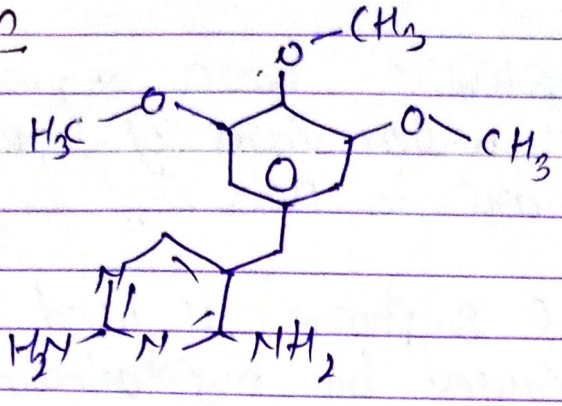
→ These drugs inhibit DNA Synthesis & cell division.

Sulphonamides & trimethoprim are used in the treatment & prevention of infections.

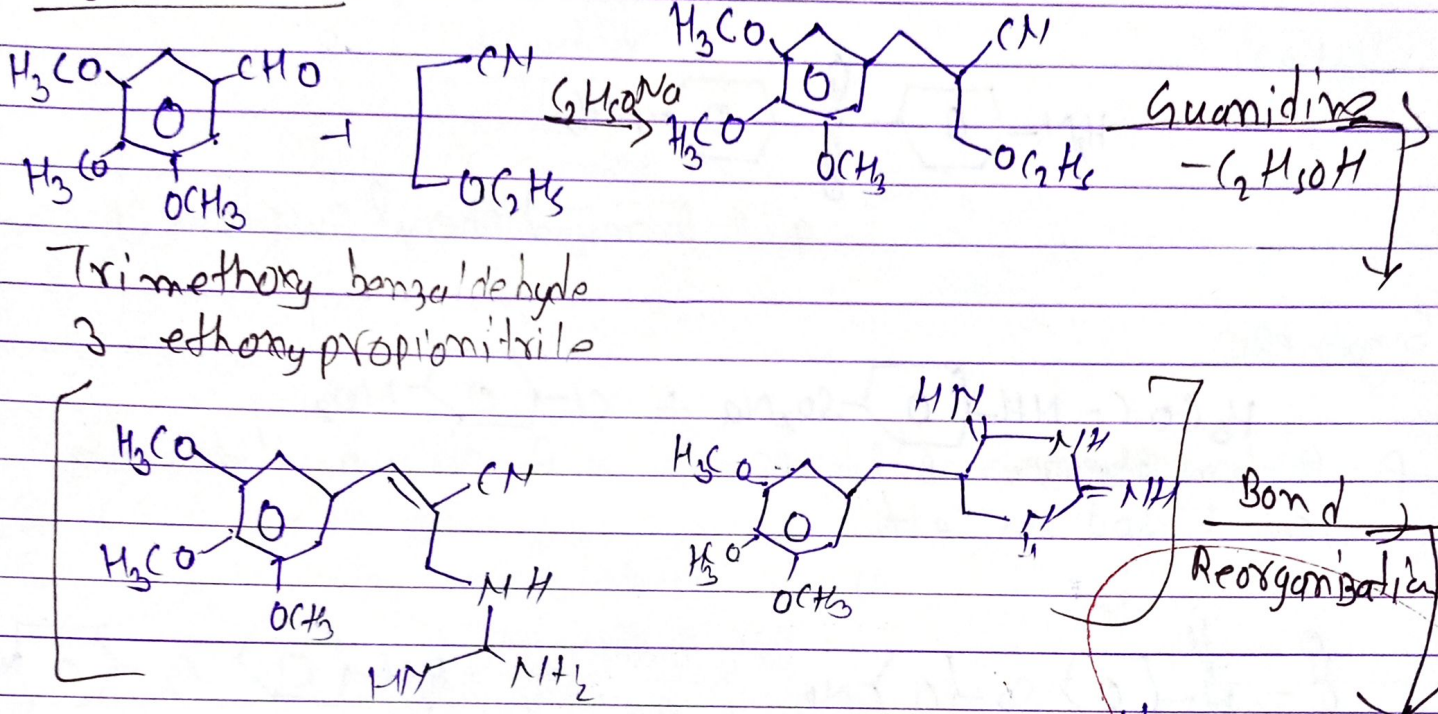
Important products -

1. Trimethoprim
2. Cotrimoxazole

① Trimethoprim



Synthesis –



MoA –

Dihydropteroate diphosphate + PABA

dihydropteroate synthetase ↓ Sulfonamide

Dihydropteroic acid

↓

dihydrofolic acid

dihydrofolate reductase ↓ trimethoprim

Tetrahydrofolic acid

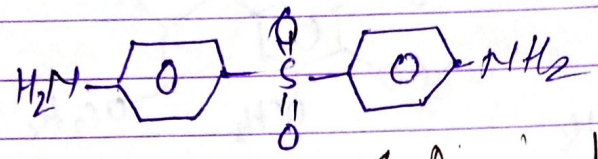
Sulfone

Introduction -

→ Studies have suggested that there are about 11 million cases of leprosy in world of which 60% are in Asia.

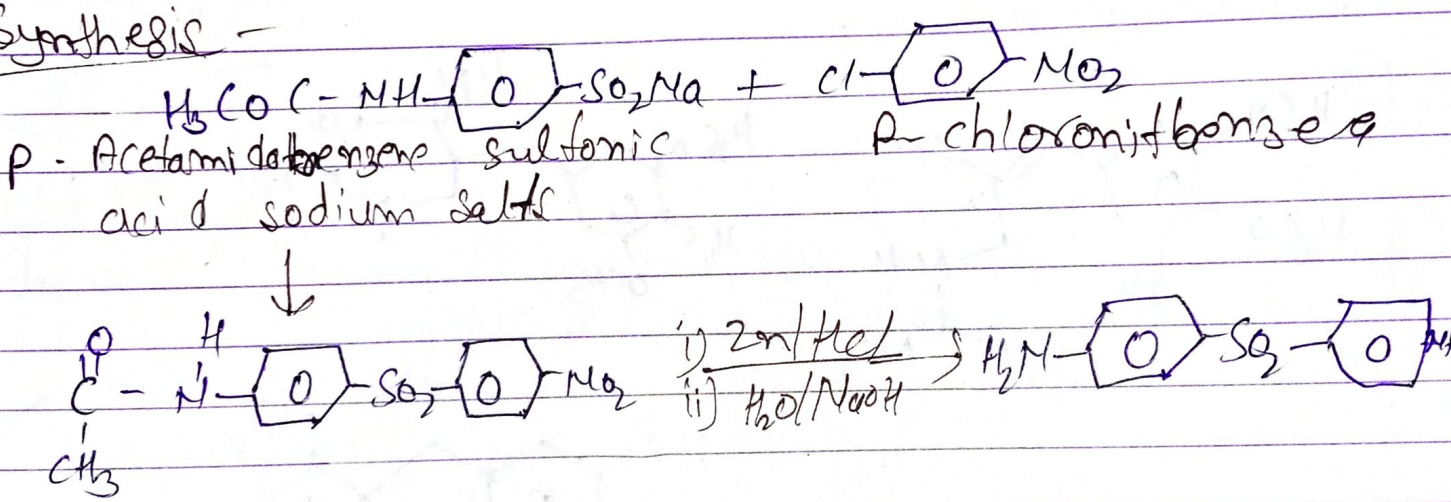
→ Diaminodiphenyl sulphone is used for the treatment of infection caused by myobacterium laprae.

Dapsone -



4, 4 Diaminodiphenyl sulphone (Dapsone)

Synthesis -



mechanism of Action -

PABA → pteridine

Dihydropteroate Synthetase | Dapsone

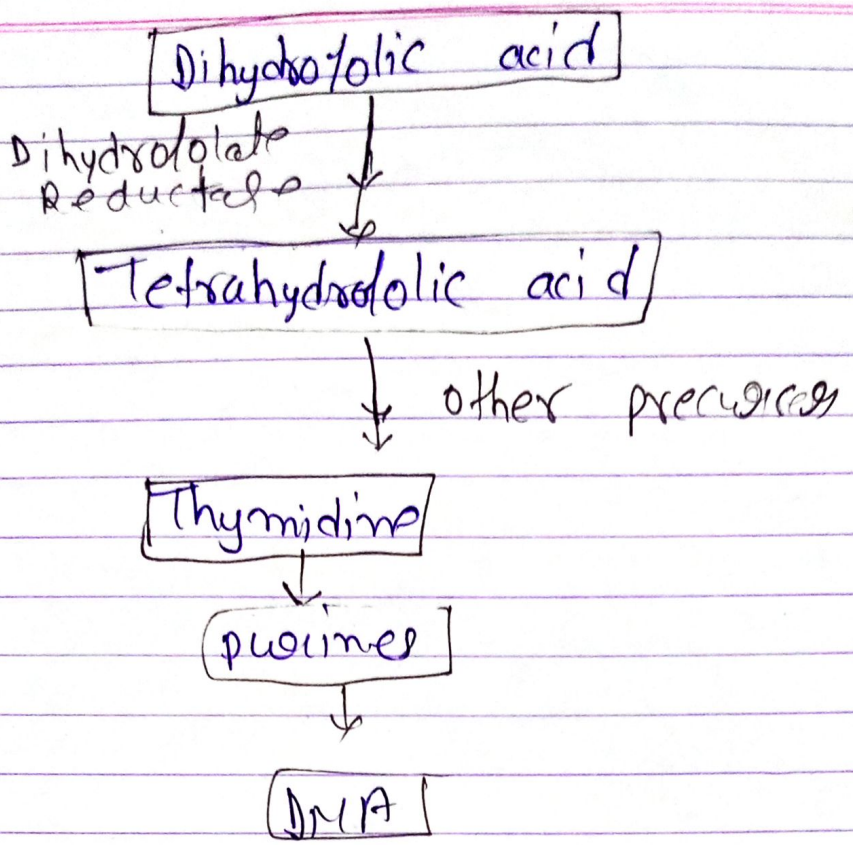
↓

Dihydropteroic acid

↓

Dihydrofolate Synthetase

↓



Use = used as dermatologic symptomes
- Antileprosy
- prevent malaria
- inflamatory condition

Chief editar –

Contact – 7905871310 (Whatapp) number).

Rajneesh Tiwari