Unit-4
Medicinal Chemistry - III

B.Pharma 6th Sem Notes

Unit: 4

Antifungal agents:

- **Antifungal antibiotics:** Amphotericin-B, Nystatin, Natamycin, Griseofulvin.
- **Synthetic Antifungal agents:** Clotrimazole, Econazole, Butoconazole, Oxiconazole Tioconozole, Miconazole*, Ketoconazole, Terconazole, Itraconazole, Fluconazole, Naftifine hydrochloride, Tolnaftate*.
- **Anti-protozoal Agents:** Metronidazole*, Tinidazole, Ornidazole, Diloxanide, Iodoquinol, Pentamidine Isethionate, Atovaquone, Eflornithine.
- **Anthelmintics:** Diethylcarbamazine citrate*, Thiabendazole, Mebendazole*, Albendazole, Niclosamide, Oxamniquine, Praziquantal, Ivermectin.

Sulphonamides and Sulfones

- **Historical development, chemistry, classification and SAR of Sulfonamides:** Sulphamethizole, Sulfisoxazole, Sulphamethizine, Sulfacetamide*, Sulphapyridine, Sulfamethoxaole*, Sulphadiazine, Mefenide acetate, Sulfasalazine.
- **Folate reductase inhibitors:** Trimethoprim*, Cotrimoxazole.
- **Sulfones:** Dapsone*.

Antifungal Agents

Introduction

- Antifungal agents are drugs used to treat fungal infections (mycoses) caused by pathogenic fungi.
- Fungal infections can be **superficial** (skin, hair, nails, mucous membranes) or **systemic/deep** (affecting internal organs, often in immunocompromised patients).
- Compared to bacteria, fungi are **eukaryotic organisms** and share many cellular processes with humans, making selective toxicity harder to achieve.

OR

- Antifungal agents are drugs used to treat fungal infections (mycoses), which range from superficial skin conditions to life-threatening systemic diseases.
- These infections are particularly problematic in immunocompromised individuals.
- Fungi are eukaryotic organisms with complex cell structures, making selective toxicity a challenge in antifungal drug development.

Classification of Antifungal Agents:

Antifungal drugs classified into 5 types

1. Antibiotics
2. Antimetabolites
3. Azoles
4. Allylamine
5. Topical Agents

1. Antibiotics Antibiotics also classified into 3 types.

A. Polyenes
B. Echinocandins
C. Heterocyclic benzofuran

A. Polyenes

- Amphotericin B
- Nystatin
- Hamycin

B. Echinocondins

- Caspofungin
- Micafungin
- Anidulafungin

C. Heterocyclic Benzofuran

- Griseofulvin

2. Antimetabolites

- Flucytosine

3. Azoles Azoles having 2 types

A. Imidazoles
B. Triazoles
C. Imidazoles Having

2 Subtype

a. Topical

- Clotrimazole
- Econazole
- Miconazole
- oxiconazole

b. Systemic

- Ketoconazole

B. Triazoles

- Fluconazole
- Itraconazole
- voriconazole
- posaconazole

4. Allylamine

- Terbinafine

5. Topical Agents

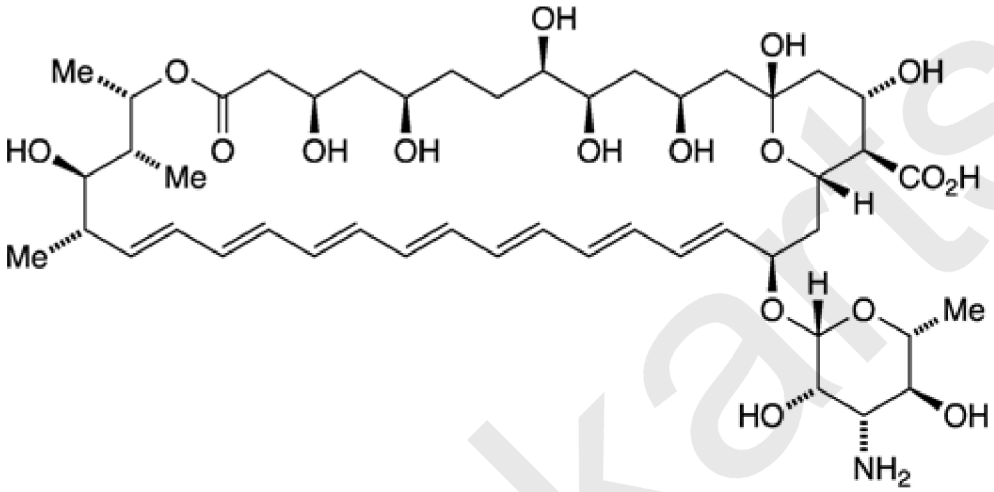
- Tolnaftate
- Undecylenic acid
- Benzoic acid
- Cicloplrox olamine
- Butenafine
- Quiniodochlor
- Sod. thiosulfate

Antifungal antibiotics:

Amphotericin-B

- **Source:** *Streptomyces nodosus*

Structure:



Mechanism of Action:

- Binds to **ergosterol** in fungal cell membrane → forms pores → leakage of **cellular contents** → fungal cell death.
  (Fungicidal action)

Uses:

- **Systemic fungal infections** like:
  - Candidiasis
  - Cryptococcosis
  - Aspergillosis
  - Histoplasmosis
  - Mucormycosis
- Used in **immunocompromised patients** (HIV, organ transplant).

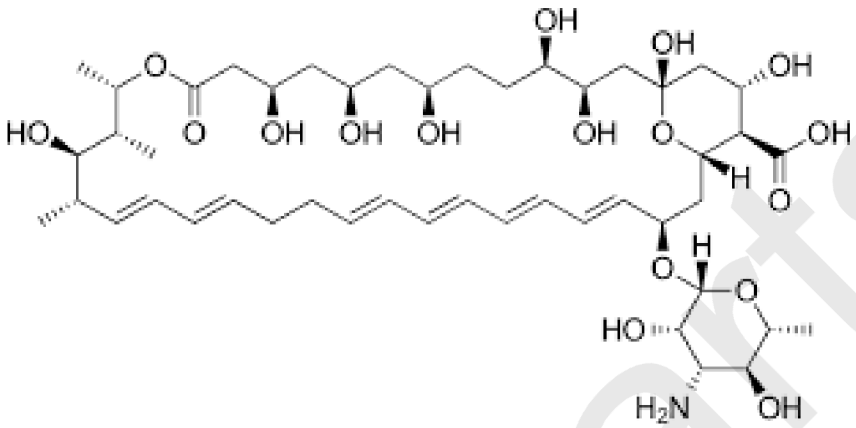
Adverse Effects:

- Fever and chills (infusion-related reactions)
- **Nephrotoxicity** (kidney damage)
- Hypotension
- Hypokalemia (low potassium level)
- Anemia

Nystatin

- **Source:** *Streptomyces noursei*

Structure:



Mechanism of Action:

- Similar to Amphotericin-B → Binds to **ergosterol**, forms pores, and causes leakage of fungal cell contents.

Uses:

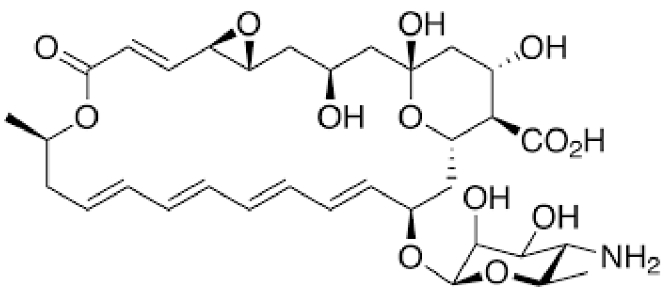
- **Topical or oral use only** (too toxic for systemic use)
  - Oral candidiasis (*thrush*)
  - Vaginal candidiasis
  - Skin fungal infections caused by *Candida albicans*.

Adverse Effects:

- Nausea, vomiting, diarrhea (when swallowed)
- Local irritation or allergic reaction (topical use)

Natamycin

Structure:



Mechanism of Action:

- Binds to **ergosterol** in fungal cell membrane → inhibits growth by **blocking membrane transport**.

Uses:

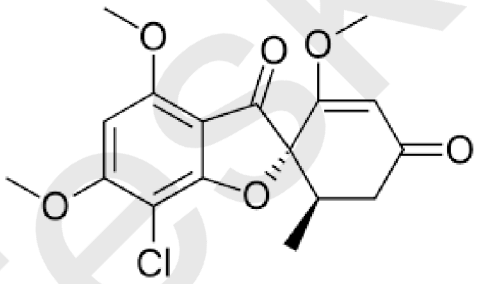
- Mainly for **ocular fungal infections** (eye drops/ointment)
  - Fungal keratitis
  - Conjunctivitis
- Used in **food industry** as a preservative to prevent fungal growth.

Adverse Effects:

- Mild eye irritation or redness
- Rare hypersensitivity reactions

Griseofulvin

- **Structure:**



Mechanism of Action:

- Binds to **fungal microtubules**, inhibits **mitosis** (cell division).
- Deposits in keratin of skin, hair, and nails → prevents fungal invasion.

Uses:

- **Dermatophyte infections** like:
  - Tinea infections (ringworm, athlete's foot)
  - Onychomycosis (nail infection)
  - Fungal infections of hair and scalp.

Adverse Effects:

- Headache, dizziness
- Nausea, vomiting
- Skin rash or photosensitivity
- Rarely **hepatotoxicity** (liver damage)

Azole Antifungals

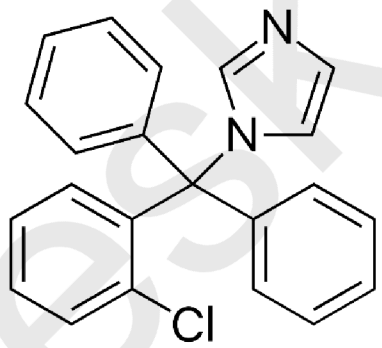
These drugs have an **azole ring** in their chemical structure and are classified into:

- **Imidazoles (2 nitrogen atoms):**
  Clotrimazole, Miconazole, Econazole, Butoconazole, Oxiconazole, Tioconazole, Ketoconazole.
- **Triazoles (3 nitrogen atoms):**
  Fluconazole, Itraconazole, Terconazole.

Mechanism of Action (All Azoles):

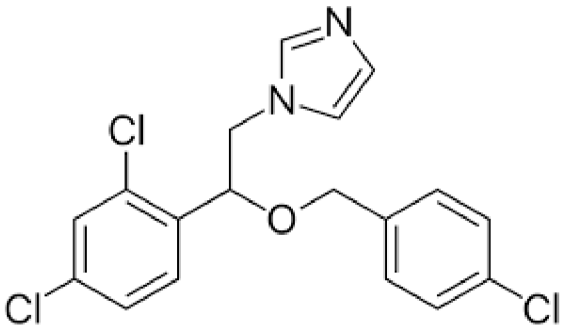
- Inhibit the enzyme **lanosterol 14-α-demethylase** →
  prevents **ergosterol synthesis** (important component of fungal cell membrane).
- Results in **disruption of cell membrane** → fungal cell death.
  (Fungistatic or fungicidal depending on concentration)

A. Clotrimazole



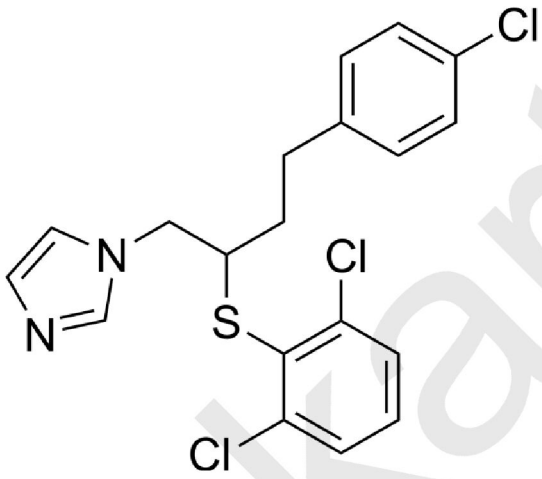
- **Uses:**
  - Oral thrush (*Candida infections in mouth*)
  - Vaginal candidiasis
  - Skin fungal infections (*ringworm, athlete's foot*).
- **Adverse Effects:**
  Local irritation, burning, redness, mild GI upset (when used orally).

B. Econazole



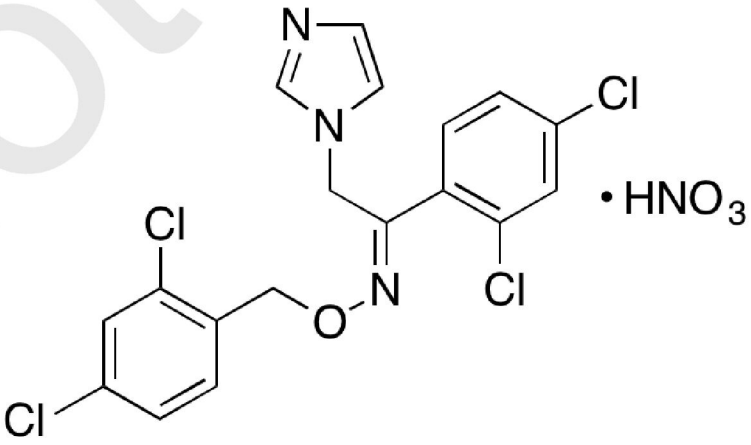
- **Uses:**
  - Topical treatment of **dermatophyte infections** like tinea pedis, tinea corporis.
  - Vaginal candidiasis.
- **Adverse Effects:**
  Local redness, itching, irritation.

C. Butoconazole



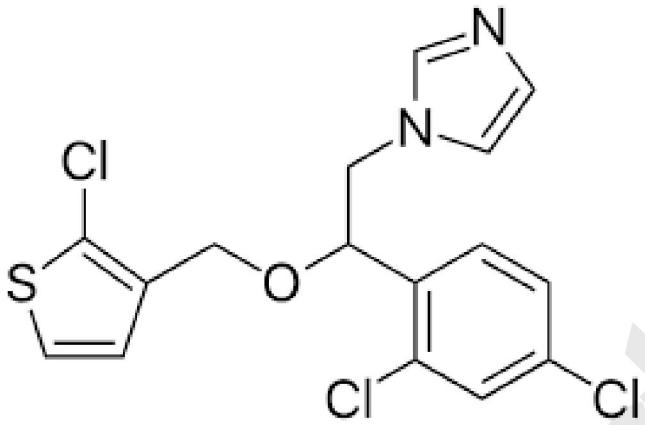
- **Uses:**
  - Vaginal cream for **vaginal yeast infections**.
- **Adverse Effects:**
  Burning sensation, mild irritation.

D. Oxiconazole



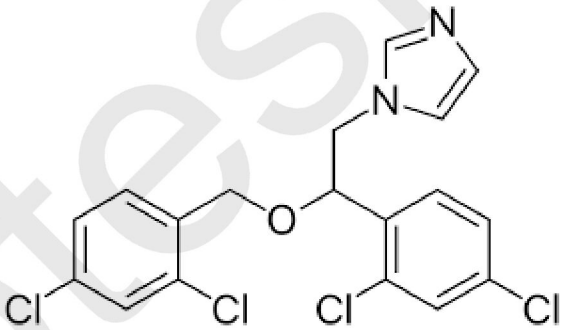
- **Uses:**
  - Skin fungal infections: athlete's foot, ringworm, jock itch.
- **Adverse Effects:**
  Mild itching, stinging, redness.

E. Tioconazole



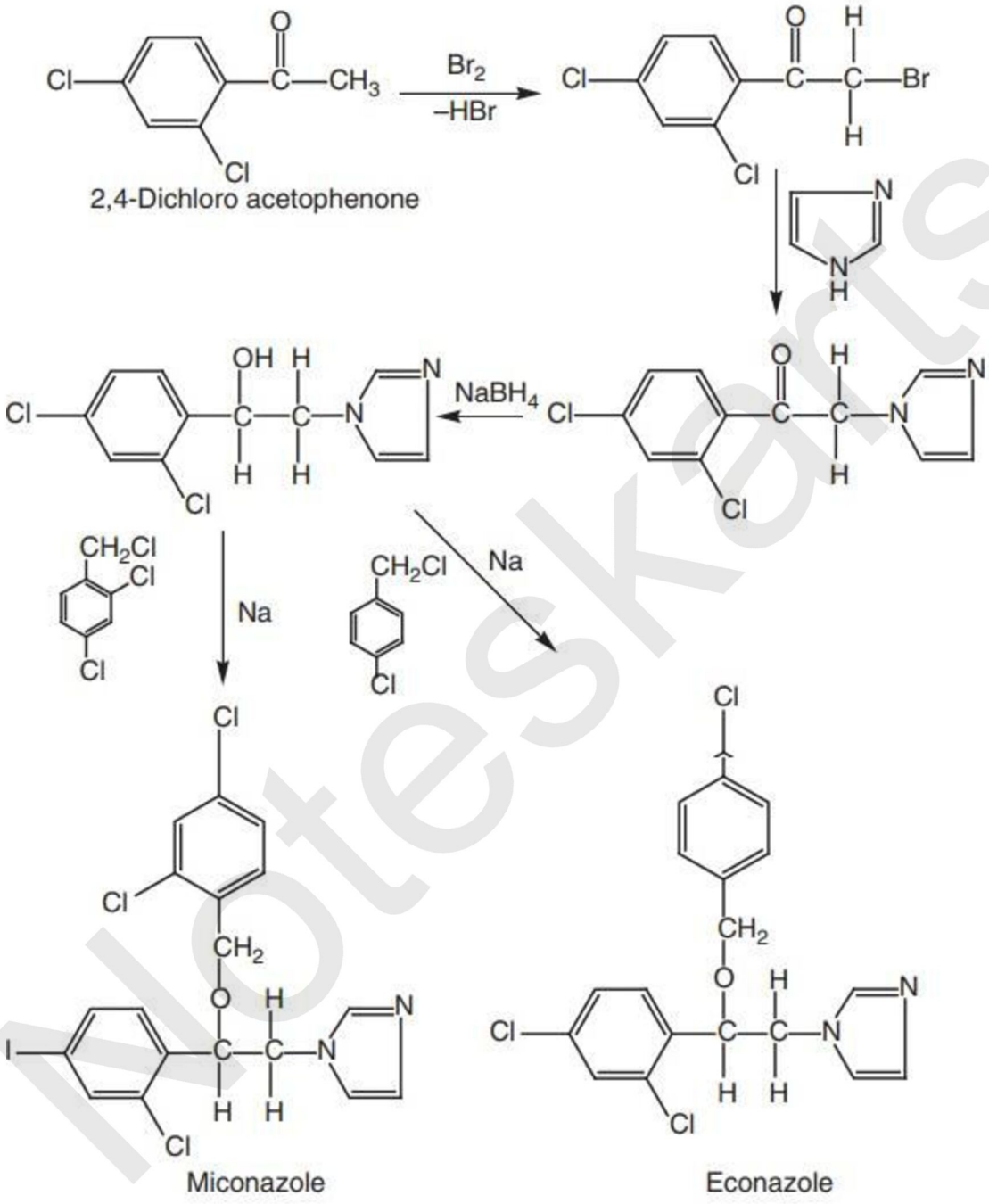
- **Uses:**
  - Vaginal candidiasis (single-dose vaginal preparation).
  - Onychomycosis (fungal nail infection).
- **Adverse Effects:**
  Local burning, swelling, irritation.

F. Miconazole *(Important)*



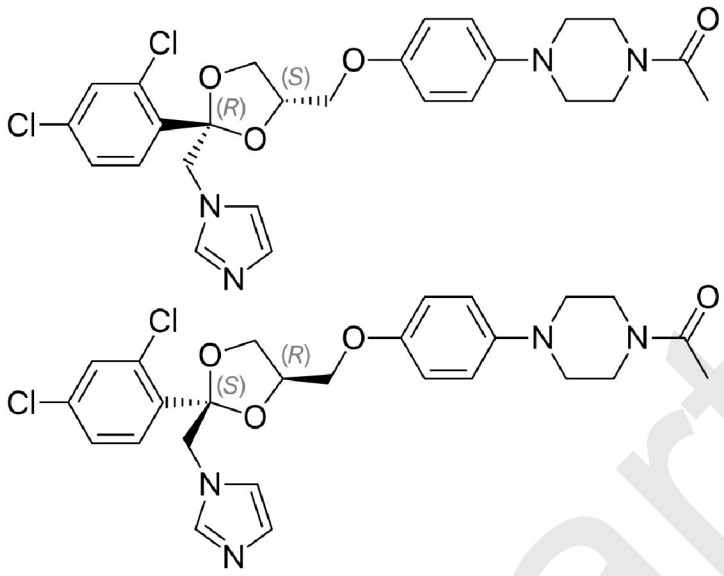
Synthesis

Synthesis of Miconazole and Econazole



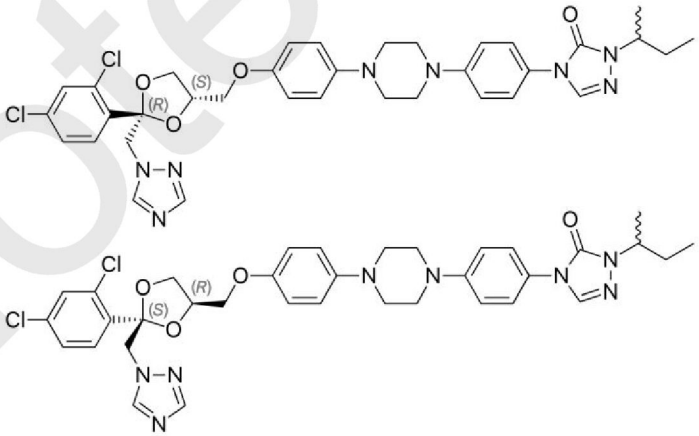
- **Uses:**
  - Oral and topical infections by *Candida albicans*.
  - Vaginal candidiasis.
  - Skin fungal infections.
- **Adverse Effects:**
  Nausea, vomiting (oral), skin irritation (topical).

G. Ketoconazole



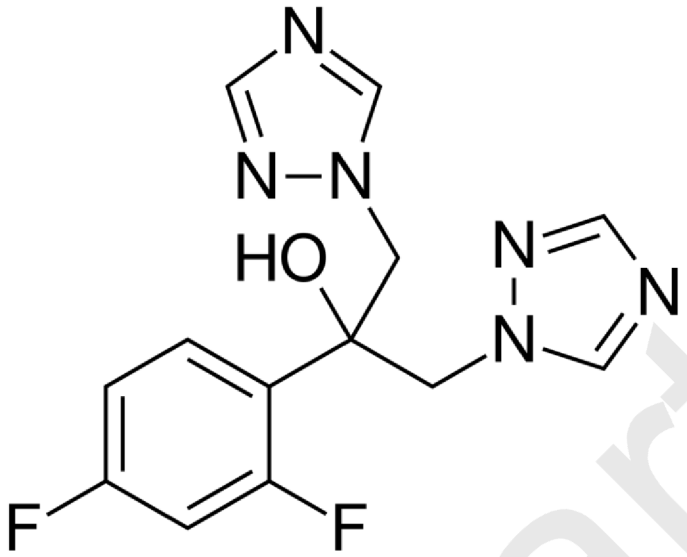
- **Uses:**
  - Systemic fungal infections (oral form).
  - Dandruff and seborrheic dermatitis (shampoo form).
- **Adverse Effects:**
  - **Hepatotoxicity** (liver damage) – important!
  - Endocrine effects: gynecomastia (breast enlargement in males).

H. Itraconazole



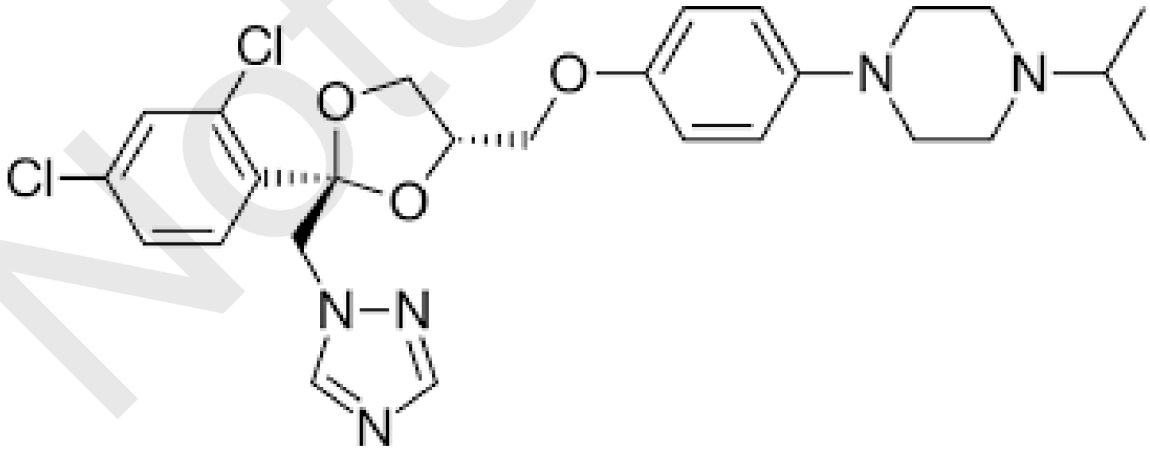
- **Uses:**
  - Aspergillosis
  - Histoplasmosis
  - Blastomycosis
  - Onychomycosis (nail infection).
- **Adverse Effects:**
  GI upset, liver toxicity, headache.

I. Fluconazole



- **Uses:**
  - **Cryptococcal meningitis** (drug of choice in HIV/AIDS patients).
  - Oral and vaginal candidiasis.
  - Systemic fungal infections.
- **Adverse Effects:**
  - Nausea, vomiting, abdominal pain.
  - Liver toxicity (rare).

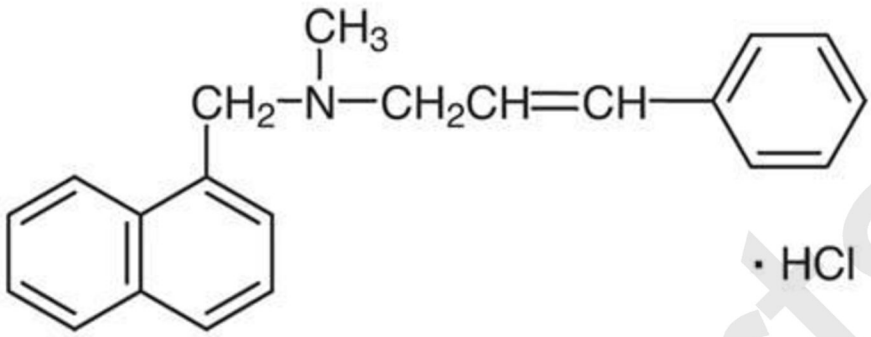
J. Terconazole



- **Uses:**
  - Vaginal cream for **vaginal yeast infections**.
- **Adverse Effects:**
  Vaginal irritation, itching, mild burning.

2. Allylamine Antifungals

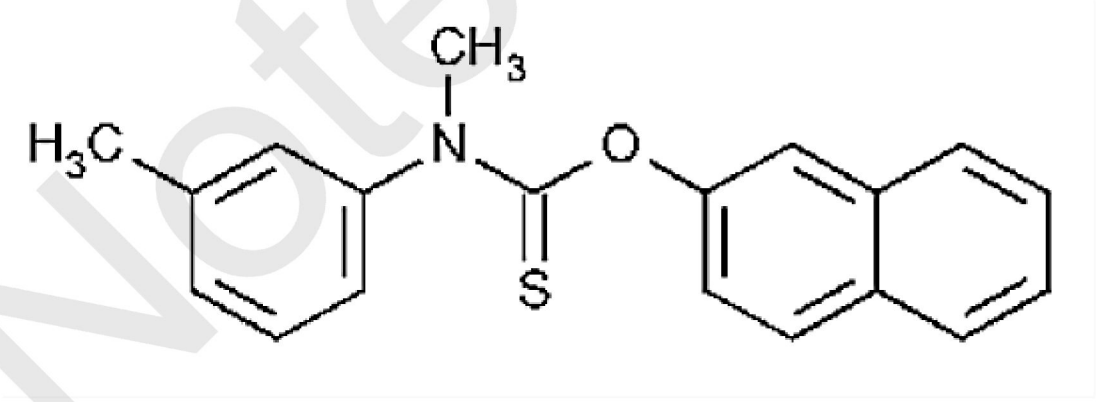
Naftifine Hydrochloride



- **Mechanism of Action:**
  Inhibits **squalene epoxidase** → decreases **ergosterol synthesis**, causing fungal cell death.
- **Uses:**
  - Topical treatment of **tinea infections** (athlete's foot, ringworm, jock itch).
- **Adverse Effects:**
  Mild burning, itching, skin redness.

3. Thiocarbamate Antifungals

Tolnaftate



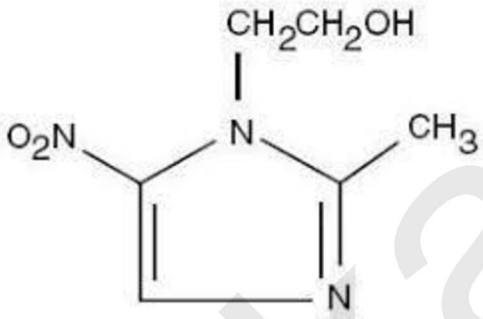
- **Mechanism of Action:**
  Inhibits **squalene epoxidase** (similar to allylamines), preventing ergosterol synthesis.
- **Uses:**
  - Superficial fungal infections like:
    - Athlete's foot (*tinea pedis*)
    - Jock itch (*tinea cruris*)
    - Ringworm (*tinea corporis*).
- **Adverse Effects:**
  Skin irritation, dryness, stinging.

Anti-Protozoal Agents

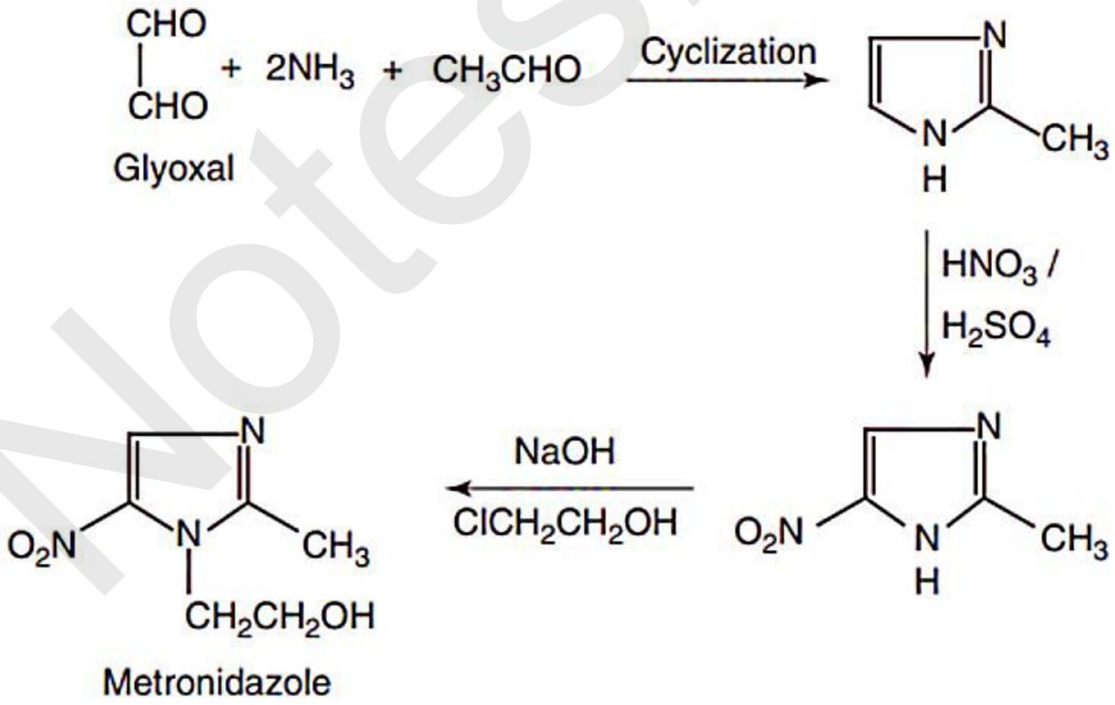
Definition:

Anti-protozoal agents are drugs used to **kill or inhibit protozoa**, which are single-celled parasites that cause diseases in humans.
These drugs are used to treat infections like **Amoebiasis, Malaria, Giardiasis, Leishmaniasis, African Sleeping Sickness**, etc.

1. Metronidazole ***(Important)***



Synthesis:

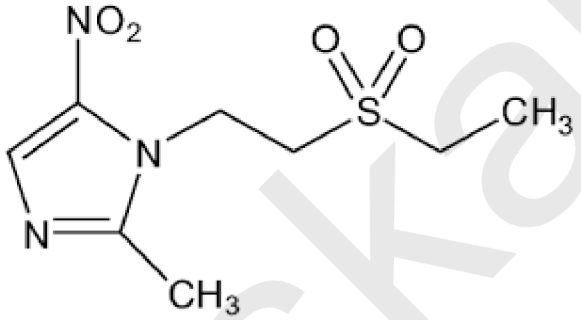


- **Class:** Nitroimidazole
- **Mechanism of Action:**
  - In anaerobic protozoa, metronidazole is **reduced to an active metabolite**.

- This active form **binds to protozoal DNA**, causing **strand breakage** and **inhibition of nucleic acid synthesis**, leading to cell death.

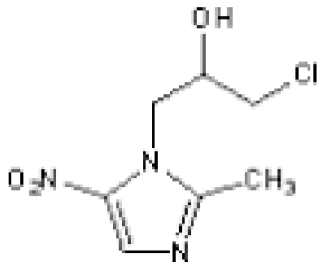
- **Uses:**
  - **Amoebiasis** (intestinal & extra-intestinal)
  - Giardiasis
  - Trichomoniasis
  - Anaerobic bacterial infections (e.g., *Clostridium difficile*).
- **Adverse Effects:**
  - Metallic taste in mouth
  - Nausea, vomiting, headache
  - **Disulfiram-like reaction** (avoid alcohol)
  - Neuropathy with long-term use

2. Tinidazole



- **Class:** Nitroimidazole
- **Mechanism of Action:** Same as metronidazole (DNA damage).
- **Uses:**
  - Amoebiasis
  - Giardiasis
  - Trichomoniasis
    (Longer half-life → given as once daily dose)
- **Adverse Effects:**
  Nausea, metallic taste, dizziness, alcohol intolerance.

3. Ornidazole

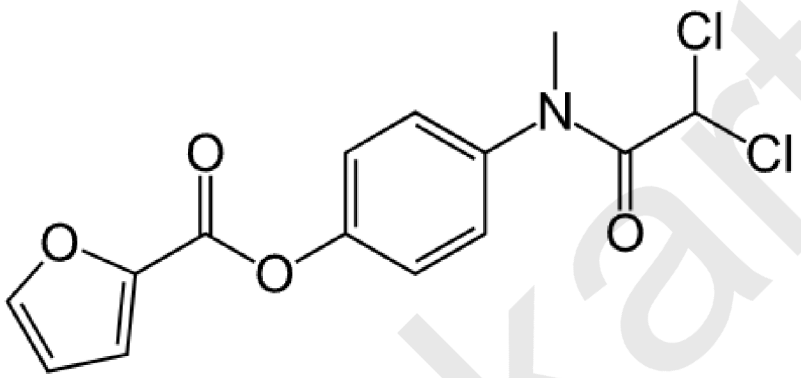


- **Class:** Nitroimidazole
- **Mechanism of Action:**

- Same as metronidazole – inhibits DNA synthesis in protozoa.

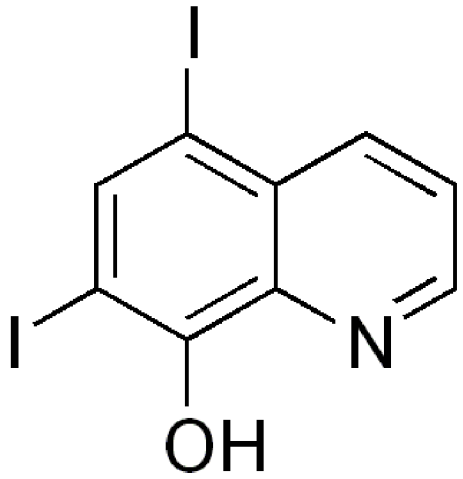
- **Uses:**
  - Amoebiasis
  - Giardiasis
  - Trichomoniasis
    (Better tolerated and fewer side effects than metronidazole)
- **Adverse Effects:**
  Nausea, headache, metallic taste.

4. Diloxanide Furoate



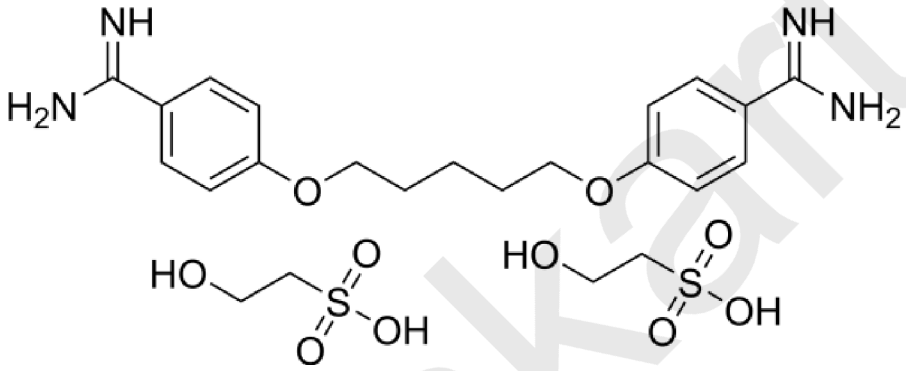
- **Class:** Luminal amoebicide
- **Mechanism of Action:**
  - Directly **acts on protozoa in the intestinal lumen**, but exact mechanism is unknown.
- **Uses:**
  - **Asymptomatic intestinal amoebiasis**
  - Used with metronidazole for **symptomatic amoebiasis**.
- **Adverse Effects:**
  - Flatulence, nausea, abdominal discomfort
  - Rare allergic rash.

5. Iodoquinol (Diiodohydroxyquin)



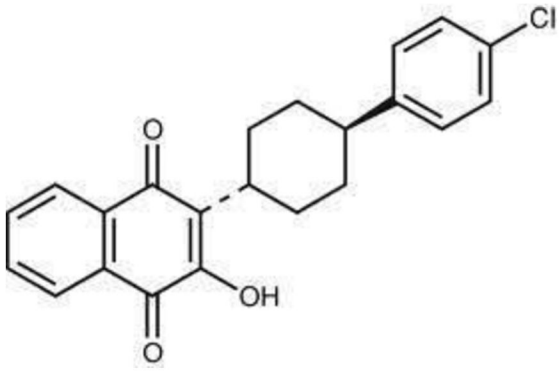
- **Class:** Luminal amoebicide
- **Mechanism of Action:**
  - Chelates iron and interferes with protozoal metabolism.
- **Uses:**
  - Intestinal amoebiasis (with or without symptoms).
- **Adverse Effects:**
  - Diarrhea, nausea
  - **Iodine toxicity** (skin rashes, thyroid problems)
  - Rare **optic neuritis** (damage to optic nerve).

6. Pentamidine Isethionate



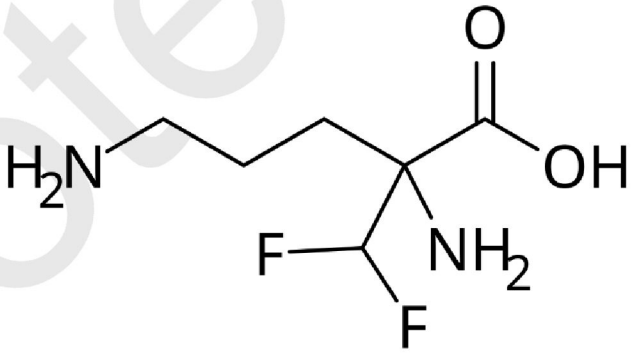
- **Class:** Aromatic diamidine
- **Mechanism of Action:**
  - Interferes with **DNA, RNA, and protein synthesis** in protozoa.
  - Disrupts mitochondrial function.
- **Uses:**
  - **African trypanosomiasis** (sleeping sickness)
  - Pneumocystis jirovecii pneumonia (PCP) in HIV patients
  - Leishmaniasis (second-line).
- **Adverse Effects:**
  - Hypotension
  - Hypoglycemia or hyperglycemia
  - Kidney toxicity
  - Arrhythmias.

7. Atovaquone



- **Class:** Hydroxyquinoline derivative
- **Mechanism of Action:**
  - Inhibits **mitochondrial electron transport** in protozoa → no ATP production → parasite death.
- **Uses:**
  - **Malaria** (used with proguanil in combination known as *Malarone*).
  - Pneumocystis jirovecii pneumonia (PCP).
  - Babesiosis.
- **Adverse Effects:**
  - Rash, fever
  - Abdominal pain, nausea, vomiting.

8. Eflornithine



- **Class:** Ornithine decarboxylase inhibitor
- **Mechanism of Action:**
  - Irreversibly inhibits **ornithine decarboxylase enzyme**, stopping cell growth and division in protozoa.
- **Uses:**
  - **Late-stage African trypanosomiasis** (sleeping sickness).
  - Topical form used for **excess facial hair (hirsutism)**.
- **Adverse Effects:**
  - Bone marrow suppression (anemia, leukopenia)
  - Diarrhea, seizures, headache.

Anthelmintic Drugs

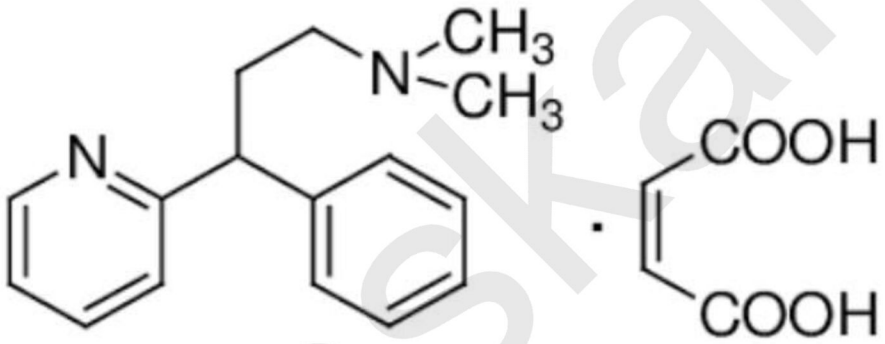
Definition:

Anthelmintics are drugs used to **kill or expel parasitic worms (helminths)** from the body by **stunning or killing them**, either in the **intestinal tract** or **tissues**.

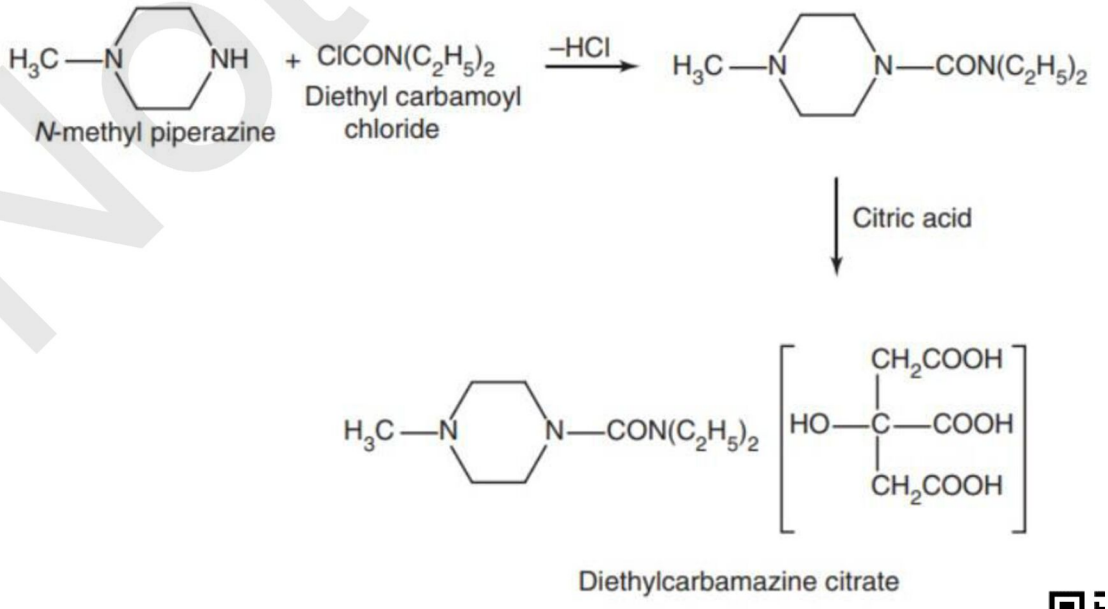
Types of Helminths:

1. **Nematodes (Roundworms)** – e.g., *Ascaris, Wuchereria bancrofti*
2. **Cestodes (Tapeworms)** – e.g., *Taenia solium*
3. **Trematodes (Flukes)** – e.g., *Schistosoma*

1. Diethylcarbamazine Citrate (DEC) ★



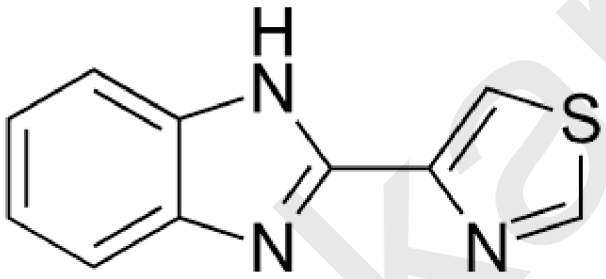
- **Class:** Anti-filarial drug
- **Synthesis:**



Diethylcarbamazine citrate

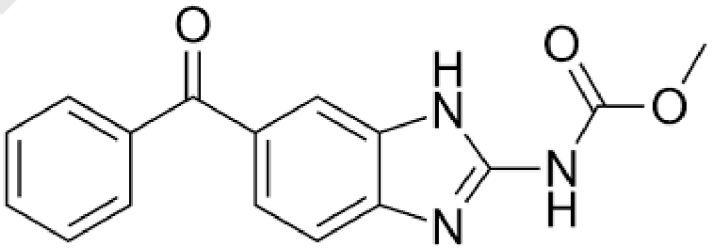
- **Mechanism of Action:**
  - Immobilizes **microfilariae and adult worms**, making them easier for the host immune system to destroy.
- **Uses:**
  - **Filariasis** (Wuchereria bancrofti, Brugia malayi)
  - Tropical eosinophilia
  - Loiasis (African eye worm)
- **Adverse Effects:**
  - Fever, headache, nausea
  - Allergic reactions due to death of microfilariae (Mazzotti reaction).
  - Joint pain.

2. Thiabendazole



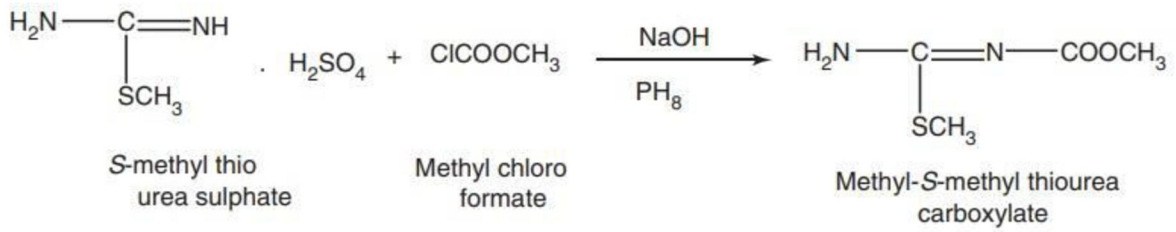
- **Class:** Benzimidazole derivative
- **Mechanism of Action:**
  - Inhibits **enzymes needed for energy production** in worms → paralysis and death.
- **Uses:**
  - Strongyloidiasis (*threadworm infection*)
  - Cutaneous larva migrans (*skin migrating larvae*).
- **Adverse Effects:**
  - Nausea, dizziness, vomiting
  - Liver toxicity (rare).

3. Mebendazole ★



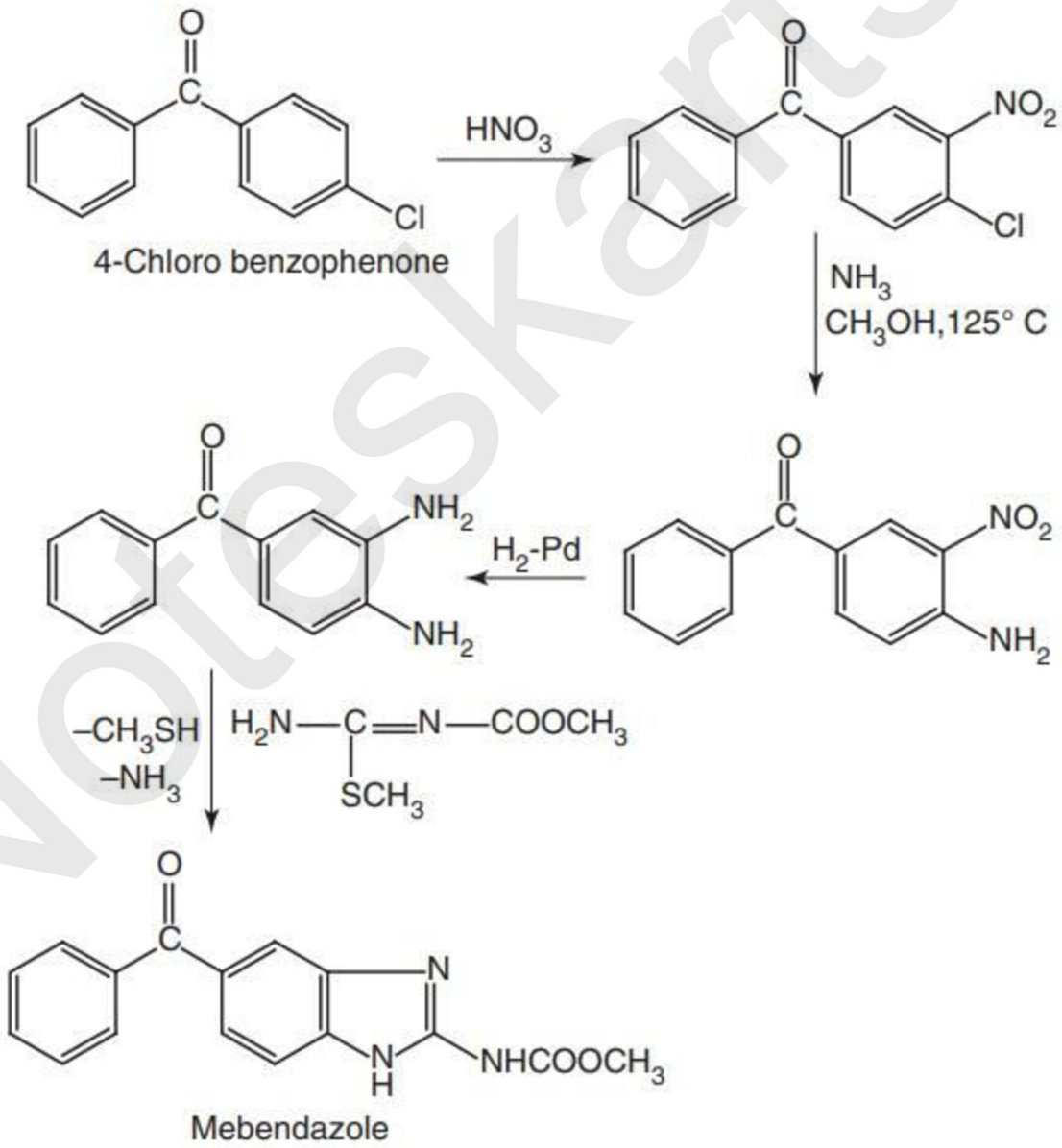
- **Class:** Benzimidazole
- **Mechanism of Action:**
  - **Inhibits microtubule formation** in worms → stops glucose uptake → energy depletion → worm death.

- *Step I.* Synthesis of an intermediate-S-methyl thiourea arboxylate



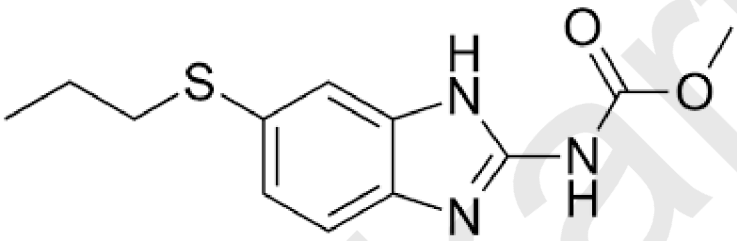
S-methyl thio urea sulphate | Methyl chloro formate | Methyl-*S*-methyl thiourea carboxylate

- *Step II.* Synthesis of Mebendazole



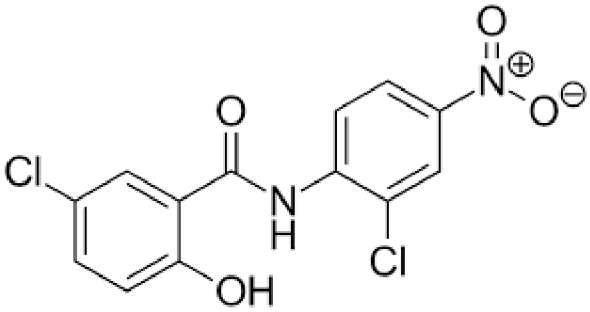
- **Uses:**
  - **Broad-spectrum:**
    - Roundworm (*Ascaris lumbricoides*)
    - Hookworm
    - Whipworm (*Trichuris trichiura*)
    - Pinworm (*Enterobius vermicularis*).
- **Adverse Effects:**
  - Abdominal pain, diarrhea
  - Rare liver toxicity
  - Teratogenic – **not used in pregnancy**.

4. Albendazole



- **Class:** Benzimidazole (similar to mebendazole)
- **Mechanism of Action:** Same as mebendazole – inhibits glucose uptake and depletes energy in worms.
- **Uses:**
  - Roundworm, Hookworm, Whipworm, Pinworm
  - **Hydatid disease (Echinococcus)**
  - Neurocysticercosis (*Taenia solium larvae in brain*).
- **Adverse Effects:**
  - Nausea, vomiting, abdominal pain
  - Liver toxicity
  - Avoid during pregnancy.

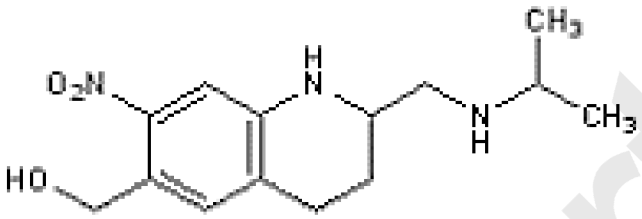
5. Niclosamide



- **Class:** Salicylamide derivative
- **Mechanism of Action:**
  - **Inhibits oxidative phosphorylation** in tapeworms → paralysis → expelled by intestine.

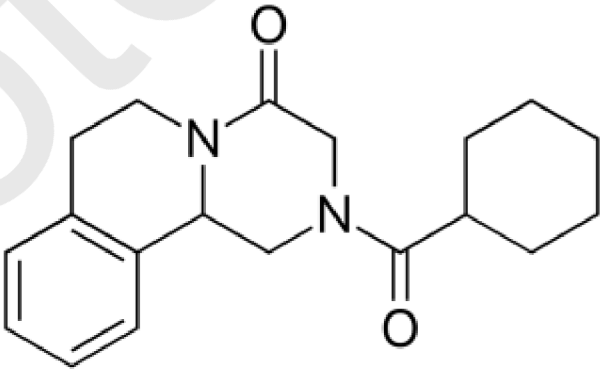
- **Uses:**
  - **Tapeworm infections** (Taenia solium, Diphyllobothrium latum).
- **Adverse Effects:**
  - Mild GI upset
  - **Alcohol must be avoided** → causes adverse reactions.

6. Oxamniquine



- **Class:** Quinoline derivative
- **Mechanism of Action:**
  - Causes **paralysis and death of schistosomes** by interfering with nucleic acid synthesis.
- **Uses:**
  - **Schistosomiasis** (*blood fluke infection*).
- **Adverse Effects:**
  - Headache, dizziness, seizures (rare).
  - GI upset.

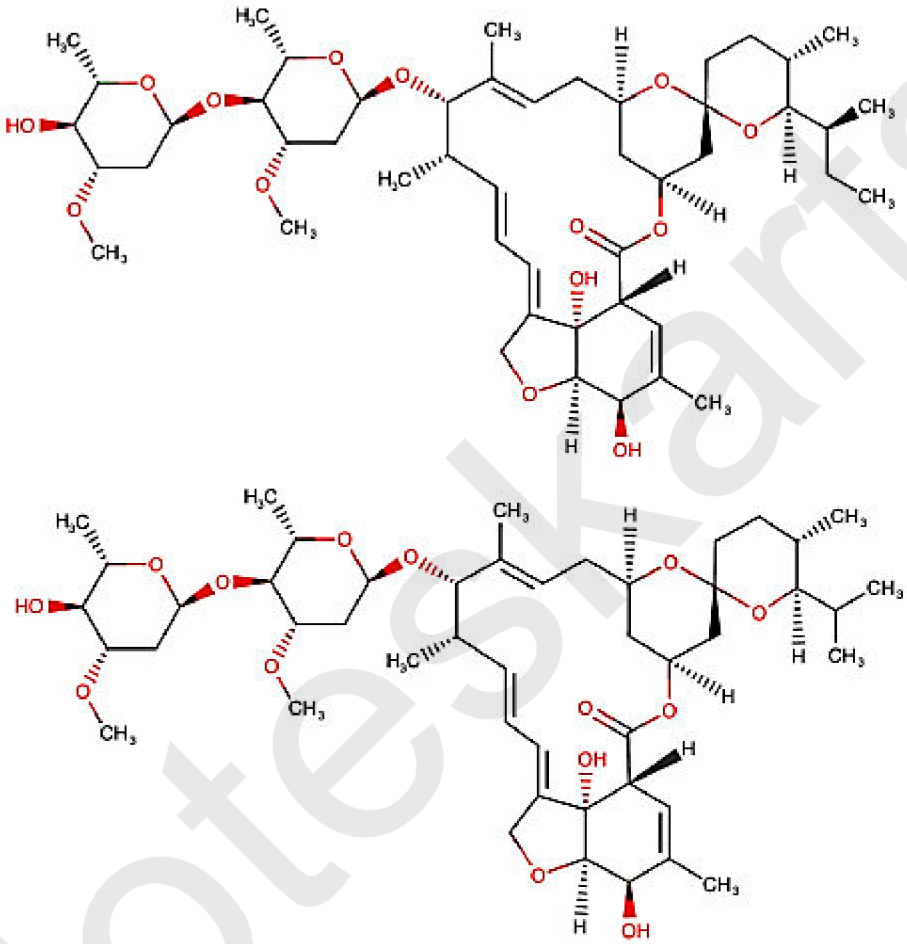
7. Praziquantel



- **Class:** Isoquinoline derivative
- **Mechanism of Action:**
  - **Increases calcium permeability** of worm's membrane → causes **muscle contraction and paralysis**, leading to worm death.
- **Uses:**
  - **Broad-spectrum:**
    - Schistosomiasis
    - Tapeworms

  - Liver flukes (*Clonorchis*).
- **Adverse Effects:**
  - Abdominal pain, dizziness, nausea
  - Headache and allergic reactions.

8. Ivermectin



- **Class:** Macrocyclic lactone
- **Mechanism of Action:**
  - Activates **GABA-gated chloride channels** in worms → hyperpolarization → **paralysis and death**.
- **Uses:**
  - **Onchocerciasis** (River blindness)
  - Strongyloidiasis
  - Scabies and lice (topical use).
- **Adverse Effects:**
  - Fever, joint pain
  - Mazzotti reaction (due to dying microfilariae).

Sulphonamides and Sulfones

Historical Development

- **1908** – *Paul Ehrlich* proposed the concept of **chemotherapy**.
- **1932** – *Gerhard Domagk* discovered **Prontosil**, the first sulfonamide drug, which was a red dye used to treat streptococcal infections.
- **1935** – Tréfouël and Bovet found that **Prontosil is a prodrug** → metabolized to **Sulfanilamide**, the active form.
- **Sulfanilamide** became the **first effective antibacterial drug** before penicillin.

Chemistry of Sulphonamides

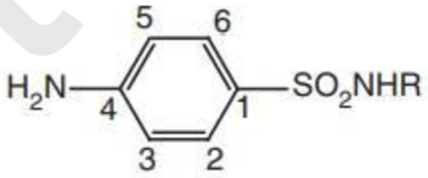
- Basic structure of sulphonamides resembles **p-aminobenzoic acid (PABA)**.
- General structure:

$$R{-}SO_2{-}NH{-}CO$$

Where:

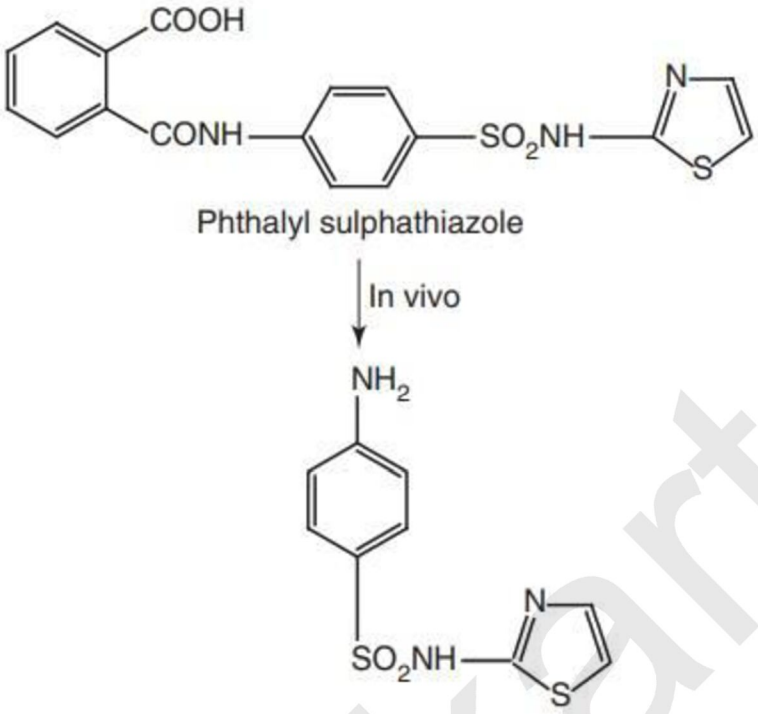
- **SO_2NH_2 group** = sulfonamide functional group.
- They act as **structural analogs of PABA**, allowing them to compete with PABA in folic acid synthesis.

SAR of Sulphonamides



The major features of SAR of sulphonamides include the following:

- Sulphanilamide skeleton is the minimum structural requirement for antibacterial activity.
- The aminoand sulphonyl-groups on the benzene ring are essential and should be in 1 and 4 position.
- The N-4 amino group could be modified to be prodrugs, which are converted to free amino function in vivo.



Phthalyl sulphathiazole

- Sulphur atom should be directly linked to the benzene ring.
- Replacement of benzene ring by other ring systems or the introduction of additional substituents on it decreases or abolishes its activity.
- Exchange of the $–SO_2NH$ group by –CONH reduces the activity.
- On N-1-substituted sulphonamides, activity varies with the nature of the substituent at the amino group. With substituents imparting electron-rich characters to SO_2 group, bacteriostatic activity increases.
- Heterocyclic substituents lead to highly potent derivatives, while sulphonamides, which contain a single benzene ring at N-1 position, are considerably more toxic than heterocyclic ring analogues.
- The free aromatic amino groups should reside *para* to the sulphonamide group. Its replacement at *ortho* or *meta* position results in compounds devoid of antibacterial activity.
- The active form of sulphonamide is the ionized, maximum activity that is observed between the pKa values 6.6–7.4.
- Substitutions in the benzene ring of sulphonamides produced inactive compounds.
- Substitution of free sulphonic acid ($–SO_3H$) group for sulphonamido function destroys the activity, but replacement by a sulphinic acid group (–SO2H) and acetylation of N-4 position retains back the activity.
- Sulphonamides bind to the basic centres of arginine, histidine, and lysine sites of proteins. The binding groups are alkyl, alkoxy, and halides. The binding affects the

activity of sulphonamides; protein binding appears to modulate the availability of the drug and its half-life.

- The lipid solubility influences the pharmacokinetic and antibacterial activity, and so increases the half-life and antibacterial activity in vitro.

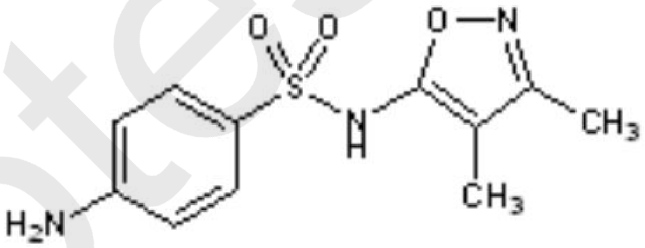
Mechanism of Action (MOA)

- Sulfonamides **competitively inhibit dihydropteroate synthase**, an enzyme that converts **PABA → dihydropteroic acid**.
- This blocks **dihydrofolic acid** and **tetrahydrofolic acid** formation → inhibition of **DNA, RNA, and protein synthesis**.
- **Effect:** *Bacteriostatic* (prevents growth, does not kill directly).

1. Sulphamethizole

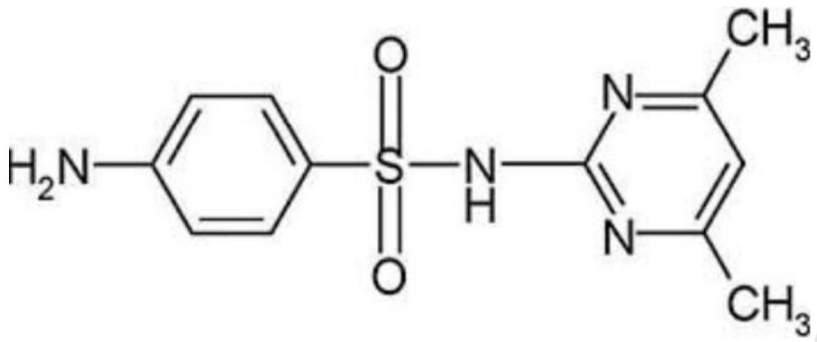
- **Use:**
  - Short-acting sulfonamide.
  - Used in **urinary tract infections (UTIs)**.
- **Adverse effects:** GI upset, hypersensitivity, crystalluria.

2. Sulfisoxazole



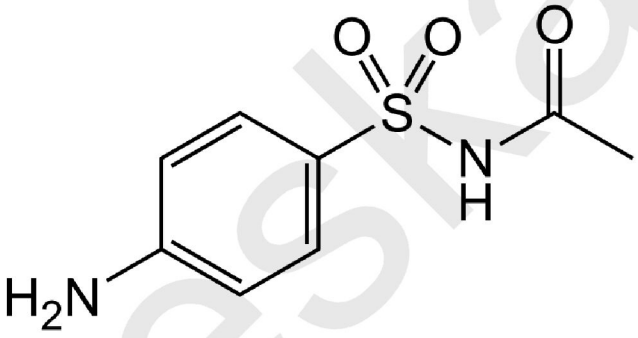
- **Use:**
  - Short-acting, well absorbed.
  - UTIs, otitis media (in children, often combined with erythromycin).
- **Adverse effects:** GI upset, rash, crystalluria (rare if well hydrated).

3. Sulphamethizine

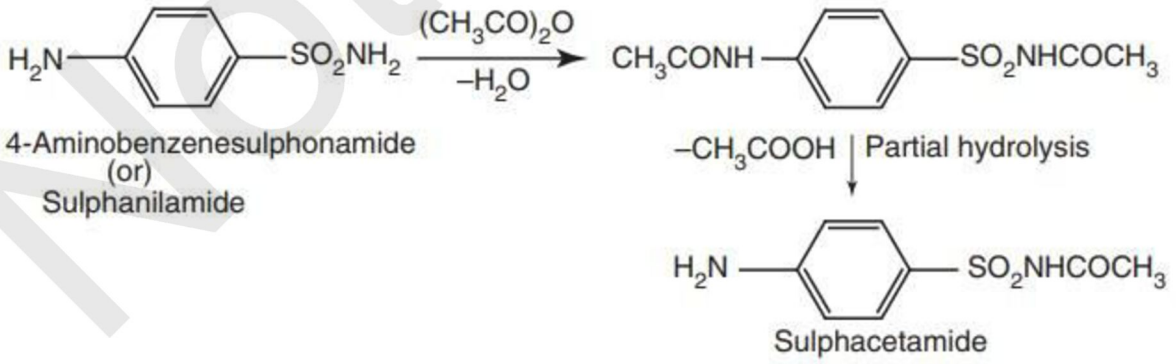


- **Use:**
  - Used in **respiratory tract infections** and sometimes in veterinary practice.
- **Adverse effects:** Rash, headache, GI upset, crystalluria.

4. Sulfacetamide*

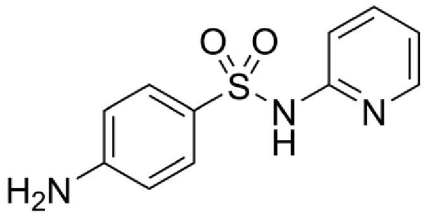


Synthesis



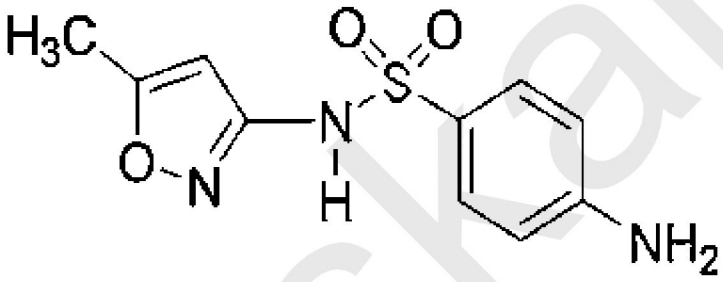
- **Use:**
  - Topical (ophthalmic) → **conjunctivitis, trachoma, corneal ulcer**.
  - Also used in acne (as lotion/cream).
- **Adverse effects:** Local irritation, hypersensitivity.

5. Sulfapyridine

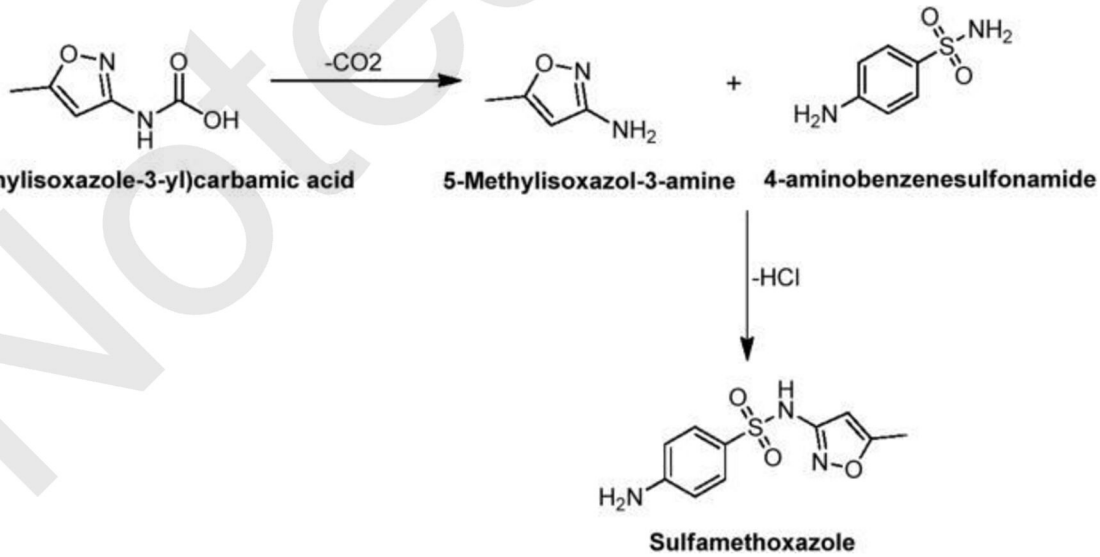


- **Use:**
  - Historically used in **leprosy** (before dapsone).
  - Rarely used now due to toxicity.
- **Adverse effects:** Severe skin rashes, hypersensitivity reactions, blood dyscrasias.

6. Sulfamethoxazole*

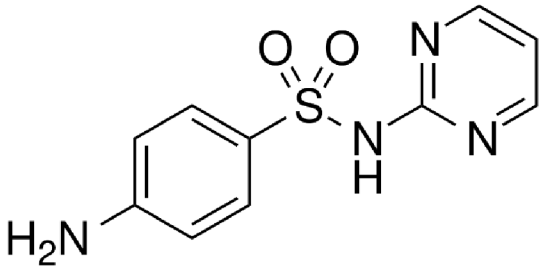


Synthesis of sulfamethoxazole:



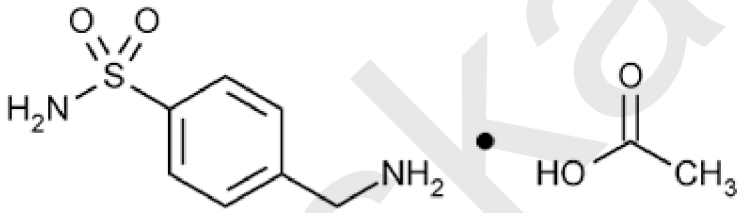
- **Use:**
  - Intermediate-acting sulfonamide.
  - Commonly used in combination with **Trimethoprim (Co-trimoxazole)** → for **UTIs, respiratory infections, Pneumocystis jirovecii pneumonia**.
- **Adverse effects:** GI upset, hypersensitivity, hematological effects (megaloblastic anemia).

7. Sulfadiazine



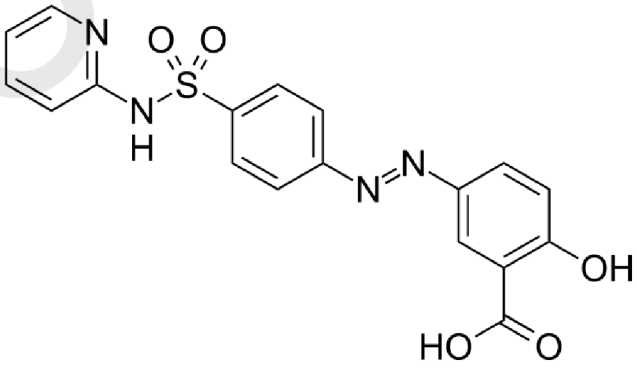
- **Use:**
  - **Toxoplasmosis** (with pyrimethamine).
  - **Meningococcal meningitis prophylaxis.**
- **Adverse effects:** Crystalluria, nausea, vomiting, hypersensitivity.

8. Mafenide acetate



- **Use:**
  - **Topical application for burns** to prevent bacterial infection.
- **Adverse effects:** Pain on application, metabolic acidosis (absorbed drug inhibits carbonic anhydrase).

9. Sulfasalazine



- **Use:**
  - Prodrug → split in colon to **sulfapyridine** and **5-aminosalicylic acid**.
  - Used in **ulcerative colitis, Crohn's disease, rheumatoid arthritis**.
- **Adverse effects:** Nausea, headache, reversible oligospermia, rash, bone marrow suppression.

Folate Reductase Inhibitors

Introduction

- These drugs inhibit **dihydrofolate reductase (DHFR)** enzyme.
- DHFR is essential for converting **dihydrofolic acid → tetrahydrofolic acid**, which is required for **purine & DNA synthesis**.
- Inhibition leads to impaired **bacterial DNA replication**.
- Selective toxicity: Bacterial DHFR is more sensitive than mammalian DHFR.

1. Trimethoprim*

Mechanism of Action (MOA)

- Inhibits **bacterial dihydrofolate reductase**.
- Blocks formation of **tetrahydrofolic acid** → inhibits **nucleic acid & protein synthesis**.

Uses

- Used **alone** in:
  - **Uncomplicated UTIs** (especially in women).
  - **Respiratory tract infections** due to *Haemophilus influenzae*.
- Often used in **combination with Sulfamethoxazole** (as Cotrimoxazole) for broader action & reduced resistance.

Adverse Effects

- Megaloblastic anemia, leukopenia, thrombocytopenia (due to folate deficiency).
- Nausea, vomiting.
- Skin rashes.
- Can be prevented by giving **folinic acid (Leucovorin)**.

2. Cotrimoxazole

(Combination of Sulfamethoxazole + Trimethoprim in 5:1 ratio)

Mechanism of Action

- **Sequential blockade** of folate pathway:
  - Sulfamethoxazole → inhibits **dihydropteroate synthase** (early step).
  - Trimethoprim → inhibits **dihydrofolate reductase** (late step).
- Together → **synergistic bactericidal effect** (while each alone is bacteriostatic).

Uses

- **Urinary tract infections (UTIs).**
- **Respiratory tract infections:** bronchitis, pneumonia, otitis media.

- **Pneumocystis jirovecii pneumonia (PCP):** drug of choice.
- **Toxoplasmosis (alternative to sulfadiazine + pyrimethamine).**
- Gastroenteritis, shigellosis, traveler's diarrhea.

Adverse Effects

- Same as sulfonamides + trimethoprim:
  - Hypersensitivity reactions (rash, Stevens–Johnson syndrome).
  - Hematological toxicity (megaloblastic anemia, leukopenia, thrombocytopenia).
  - GI upset, nausea, vomiting.
  - Crystalluria (rare with hydration).
  - Kernicterus in neonates (avoid in pregnancy & infants).

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