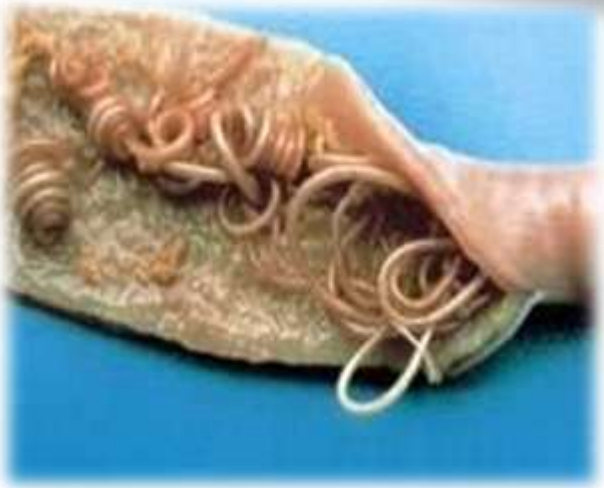
Anthelmintics OR Antihelmenthics



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Parasitic Infections

- Parasitic diseases is major health hazard world wide
- More wide spread in less developed countries
- Parasitic infections are due to different **protozoa** & **metazoa**
- **Protozoan infections:**

  amoebiasis, giardiasis, leishmaniasis, malaria etc
- Metazoan infections : **helminth**
- Parasitic worms are termed as helminths
- **Infections with worms are termed as helminthiasis**
- Worldwide 2 billion people are affected by helminthiasis

- Helminths (Worms)
  - Platyhelminths (Flatworm)
    - Cestode (Tapeworm)
    - Trematodes (Flukes or Schistosomes)
  - Ascheminths or Nematodes (Roundworm)
    - Roundworm
    - Hookworm
    - Pinworm
    - Whipworm

Helminths infections with drug therapy:

1) Cestode infections

Cysticercosis or tapeworm infection

Caused by Beef tapeworm (*Taenia saginata)*, pork tapeworm (*Taenia solium)*, dwarf tapeworm (*Hymenolepis nana)*, fish tapeworm (*Diphyllobothrium latum)*

Drugs:

Niclosamide, Praziquantel, Albendazole, Mebendazole

2) Trematode infections

Schistosomiasis or blood flukes

Caused by *Schistosoma hematobium, Schistosoma mansoni, and Schistosoma japonicum.*

Drugs:

Praziquantel, Oxamniquine, Bithionol, Niridazole

2) Nematode infections

- **Ancylostomiasis:**

  Caused by American hookworm (*Necator americanus)* *and the* "Old World" hookworm (*Ancylostoma doudenale)*
- **Enterobiasis or Pinwrom infection**

  Caused by *Enterobius vermicularis*
- **Ascariasis or Roundworm infections**

  Caused by *Ascaris lumbricoides*
- **Trichuriasis or Whipworm Infections**

  Caused by *Trichuris trichiura*
- **Trichinosis or Trichina Infection**

  Caused by *Trichinella spiralis*

Drugs:

Albendazole, Ivermectin, Piperazine, Mebendazole, Pyrantel pamoate

Anthelmintics and Antihelminthics

These are drugs used to destroy the parasitic worms or remove them from the infected host by killing them without causing significant damage to the host.

Anthelmintics acts against worms in GI tract, penetrated in tissues, & systemic infections

Also called as vermifuges (those that unconcious helminths) or vermicides (those that kill helminths)

Classification of antihelminthics

1) **Benzimidazoles**

   e.g. Mebendazole, Oxibendazole, Albendazole, Parbendazole, Ciclobendazole, Thiabendazole

2) **Quinolines & Isoquinolines**

   e.g. Praziquantel, Oxamniquine

3) **Piperazines**

   e.g. Piperazine citrate

4) **Vinyl pyrimidine**

   e.g. Pyrantel pamoate

5) **Amides**

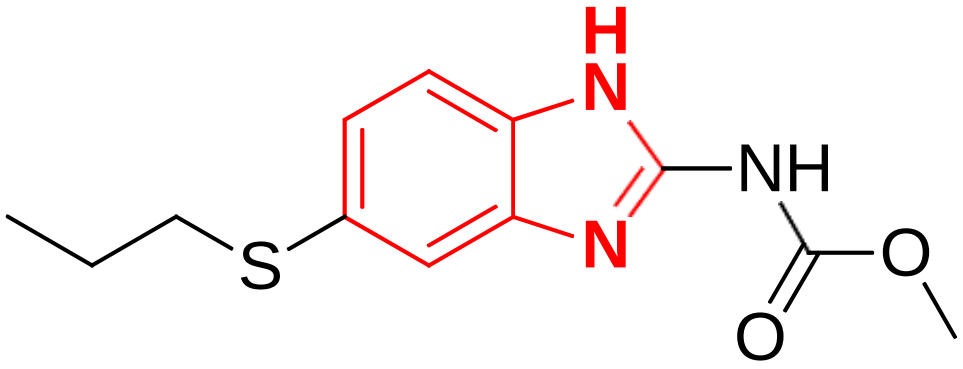
   e.g. Niclosamide

6) **Miscellanoues**

   e.g. Ivemectin, Niridazole, Levamizole

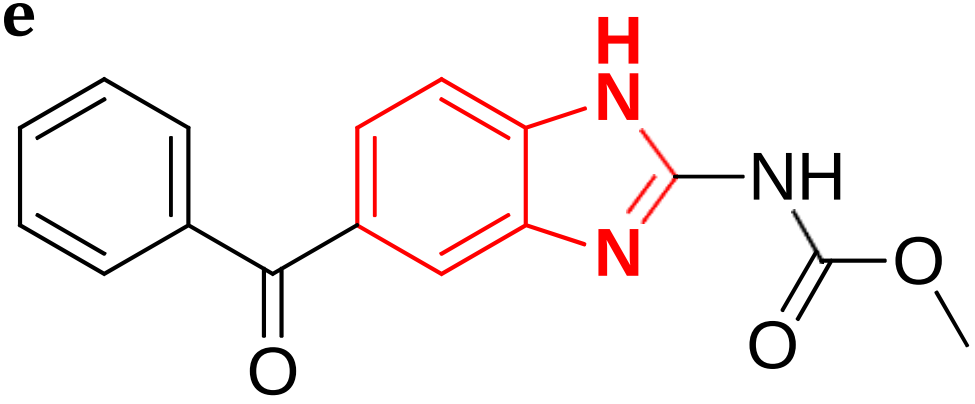
Benzimidaz ole

Albendazole



Methyl [5-(propylthio)-1H-benzoimidazol-2-yl]carbamate

Mebendazole



Methyl (5-benzoyl-1H-benzimidazol-2-yl)carbamate

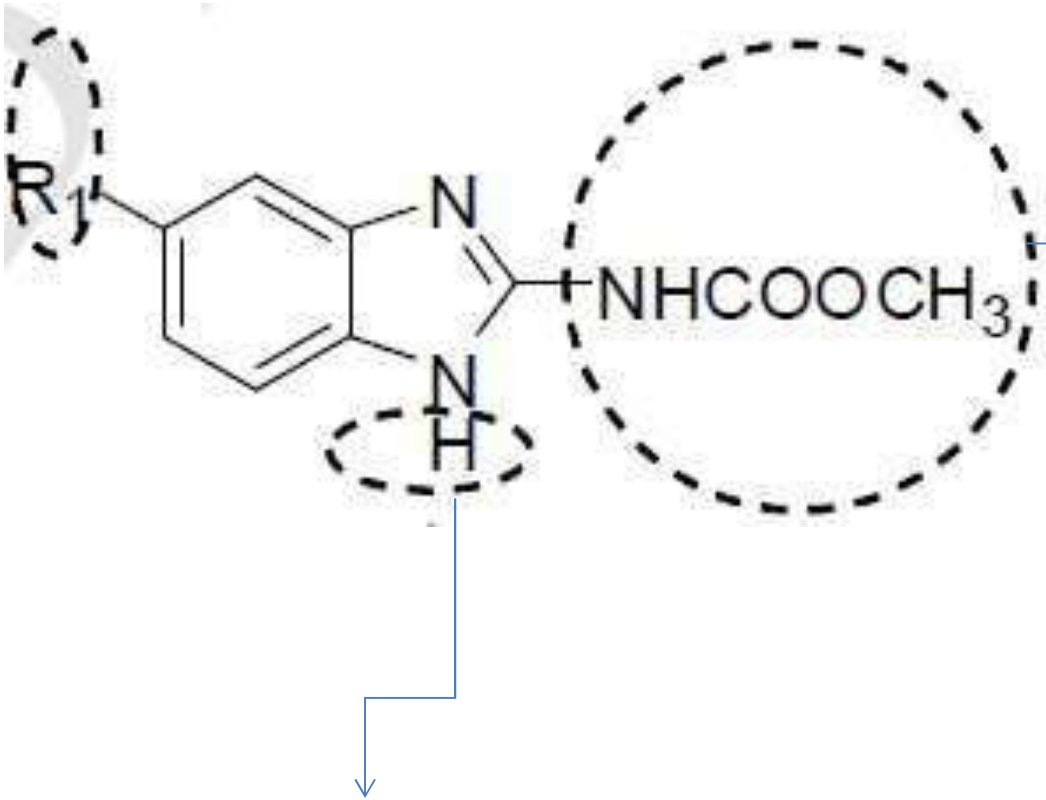
Mechanism of action

Two mechansim

1) *Inhibition of Fumarate reductase*: important in helminths for oxidation of NADH to NAD leads to uncoupling of oxidative phosphorylation.
2) Binds to protein tubulin and thus prevent tubulin polymerization to microtubules.

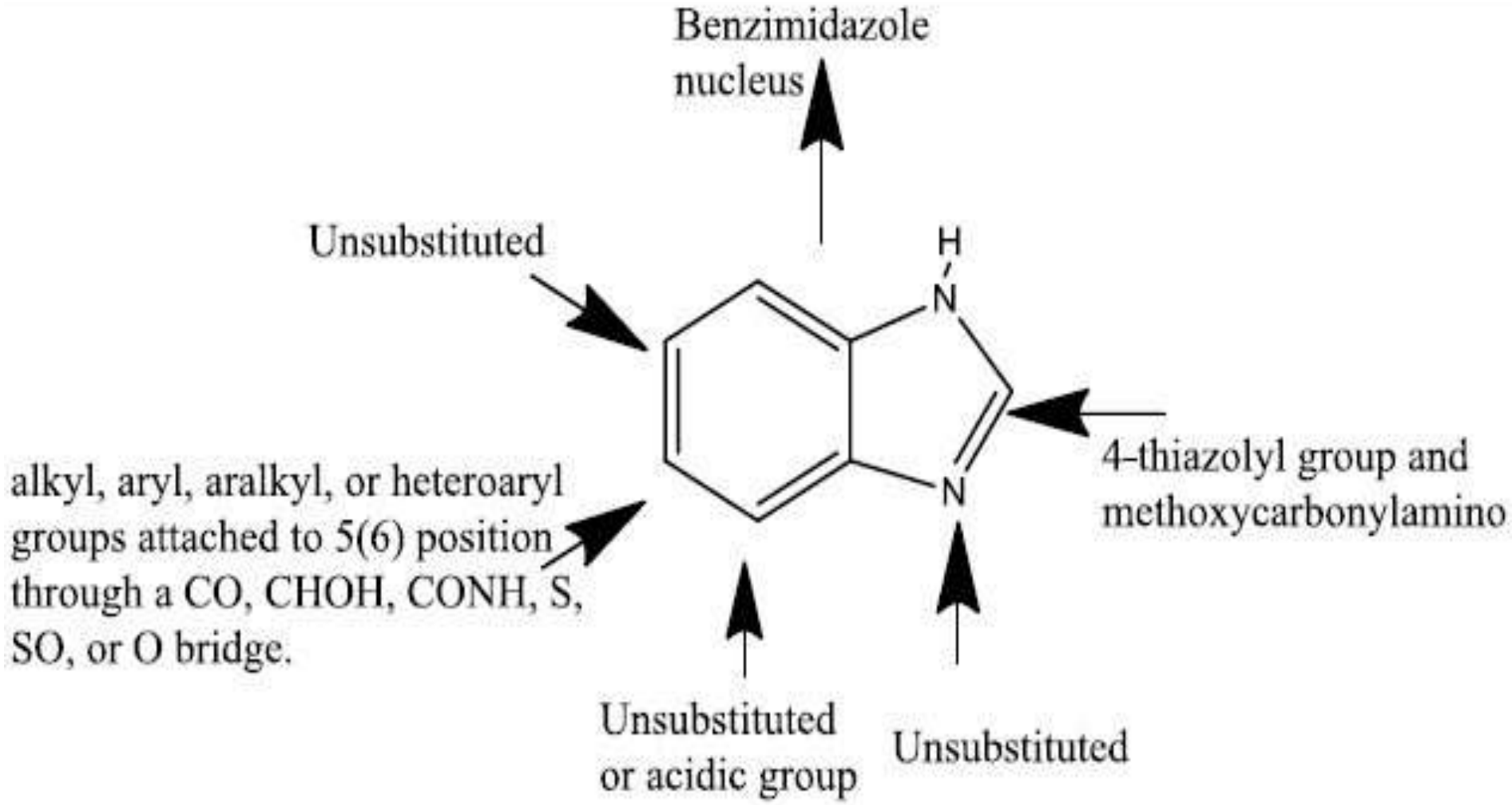
   Binding to the tubulin prevents the self-association of subunits and creates a "capping" of the microtubule at the associating end of the microtubule. The microtubulin continues to dissociate from the opposite end, with a net loss of microtubule length.

SAR of Benzimidazoles

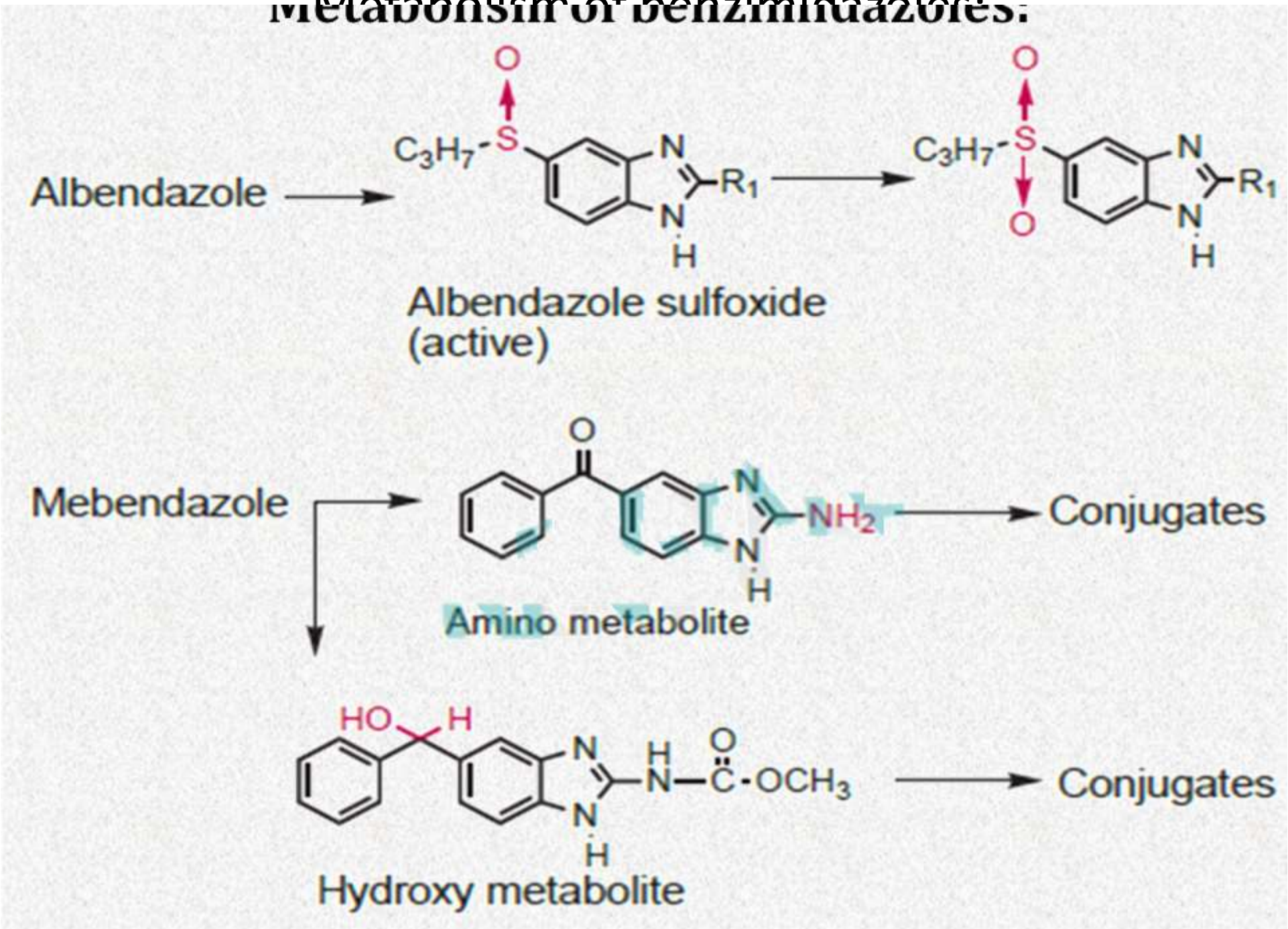


Methyl carbamate group is essential for Anthelmintic activity

For anthelmintic activity the molecule must have H group at 1-position of benzimidazole


Benzimidazole nucleus
Unsubstituted
H
N
N
4-thiazolyl group and methoxycarbonylamino
alkyl, aryl, aralkyl, or heteroaryl groups attached to 5(6) position through a CO, CHOH, CONH, S, SO, or O bridge.
Unsubstituted or acidic group
Unsubstituted

Metabolism of benzimidazoles:



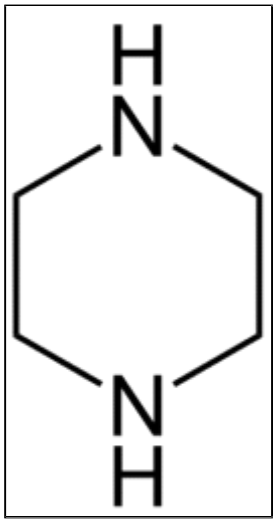
Albendazole

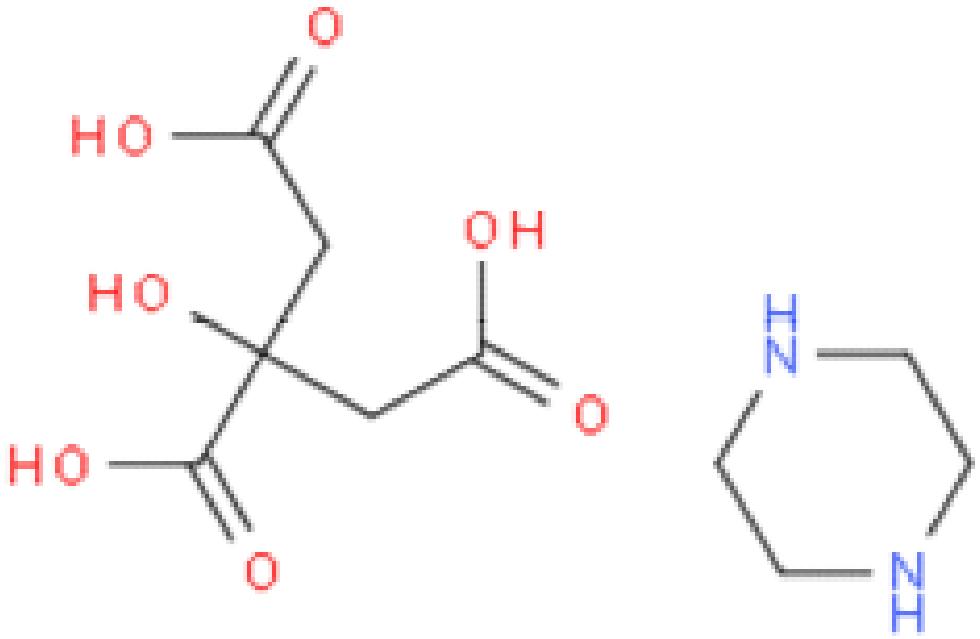
- It is effective as a single-dose treatment for ascariasis, hookworm infections and trichuriasis
- It undergoes rapid and extensive first-pass metabolism to the sulfoxide, which is the active form in plasma.
- The highdose, prolonged therapy adverse effects such as bone marrow depression, elevation of hepatic enzymes, and alopecia.

Mebendazole

- It also inhibits cell division in nematodes (interfering with microtubule)
- Mebendazole is poorly absorbed by the oral route.
- Adverse reactions are uncommon: abdominal discomfort
- It is teratogenic therefore, should not be given during pregnancy.

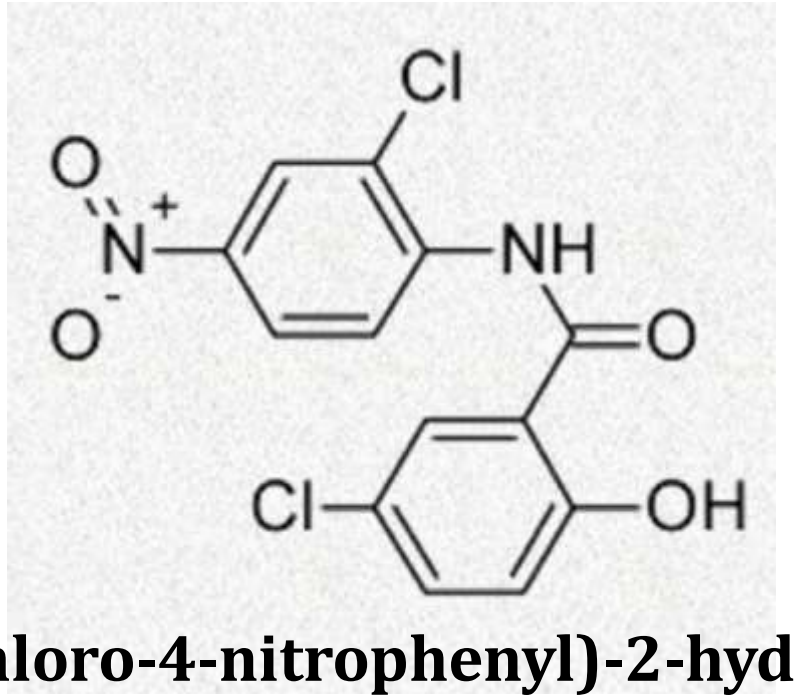
Piperazine citrate





- Piperazine is still used as an anthelmintic for the treatment of pinworm *and roundworm*
- It is available in various salt forms, including the citrate (official in the *USP)* in syrup and tablet forms.
- **Piperazine blocks the response of the ascaris muscle to acetylcholine, causing flaccid paralysis in the worm, which is forcefully removed from the intestinal wall and expelled in the faeces.**

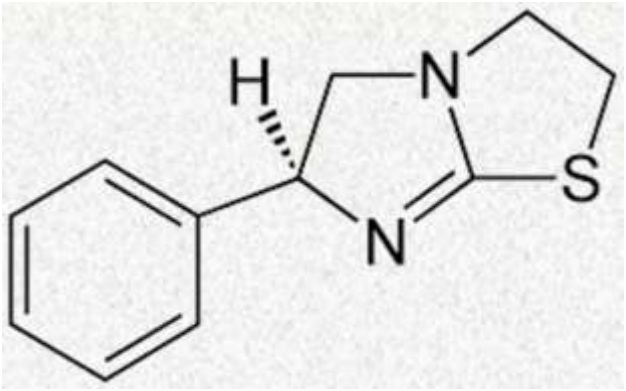
Niclosamide



5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

- It is a potent taeniacide (Kill tapeworms) that causes rapid disintegration of worm segments and the scolex (anterior end of tapeworm).
- Penetration of the drug into various cestodes is facilitated by the digestive juices of the host.

Levamisole



6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazole

- Levamisole works as a nicotinic acetylcholine receptor agonist that causes continued stimulation of the parasitic worm muscles, leading to paralysis
- One of the more serious side effects of Levamisole is depletion of the white blood cells

Antifungal Agents (Antimycotic Agents)

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INTRODUCTION

Treatment of fungal infections has lagged behind treatment of bacterial infections, because

•Fungal infections in humans have been superficial infections (skin and mucosal membrane).

•Due to normal functioning immune system (ward off effect) Potential lethal deep-seated infections were rare.

•Immuno compromised patients are susceptible to invasive fungal infections.

Fungal infections:

Superficial & Deep seated Mycoses

Fungal Kingdom include:

Yeasts, Molds, Rusts, & Mushrooms

Most fungi are **saprophytic** (live on dead organic matter in the soil or on decaying leaves or wood.

Cause **opportunistic infections** if introduced into humans through wounds or inhalation.

Most fungal infections are caused by **yeasts and molds.**

Yeasts Pathogens: *Candida albicans,* baker's yeast *Saccharomyces cerevisiae*
Grow in multicellular chains called hyphae

Molds Pathogen: *Trichophyton rubrum* causative agents of ringworm
Grow in clusters of hyphae called a mycelium

All fungi produce spores which may be transported by direct contact or through the air.

Fungal Diseases or Mycotic infections

Mycoses: a disease caused by infection with a fungus,

such as ringworm or thrush.

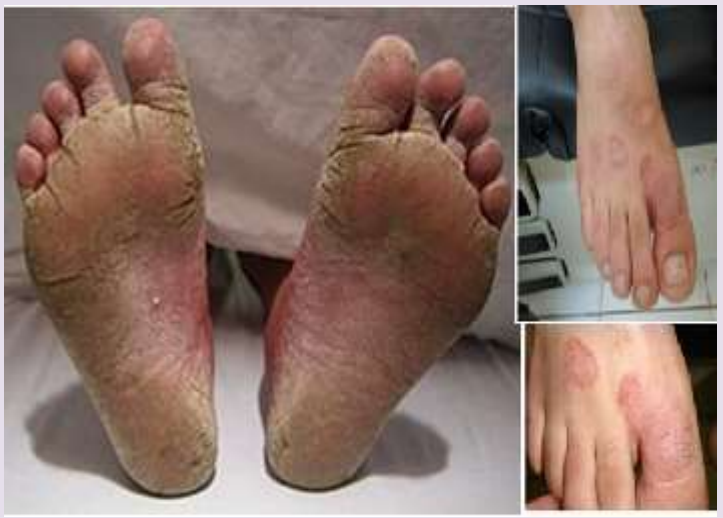
Dermatophytes: are fungi causing infections of skin, hair and nail.

Dematophytoses or cutaneous infection the most common types of human fungal diseases.

They obtain nutrition from keratin

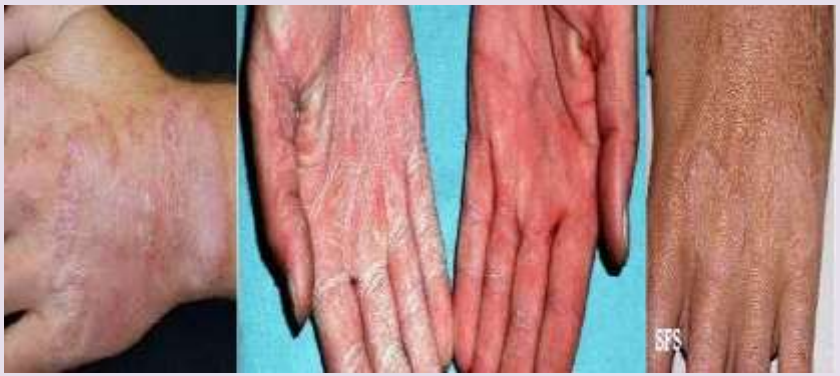
Known as **Tinea** caused by various species of three genera *(Trichophyton, Microsporum, and Epidermophyton)*

Infection of hair & scalp



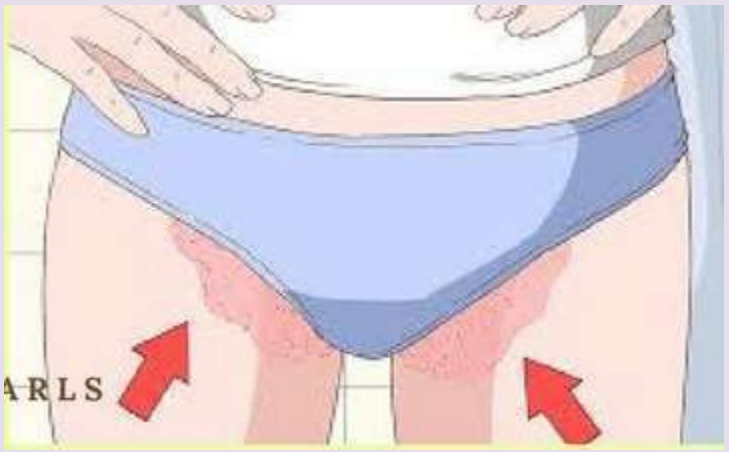
Tinea pedis

A severe case of athlete's foot



Tinea mannum

Infection of hands



Tinea cruris

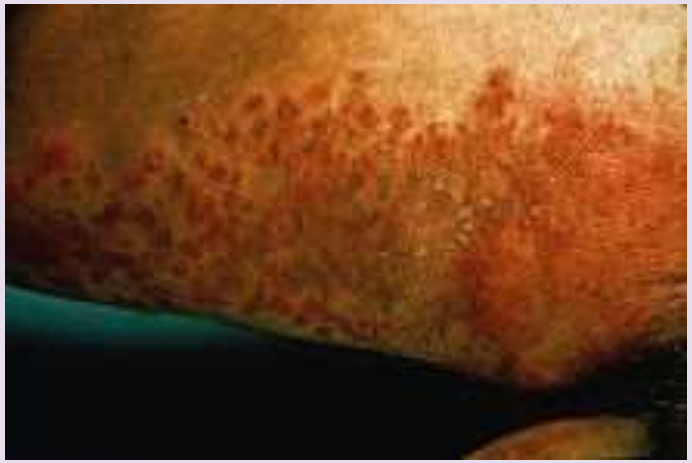
Infection of groin (jock itch)

Yeasts infections common cause is *candida albicans*
Resides in the oropharynx, gastrointestinal tract, vagina, and surrounding skin

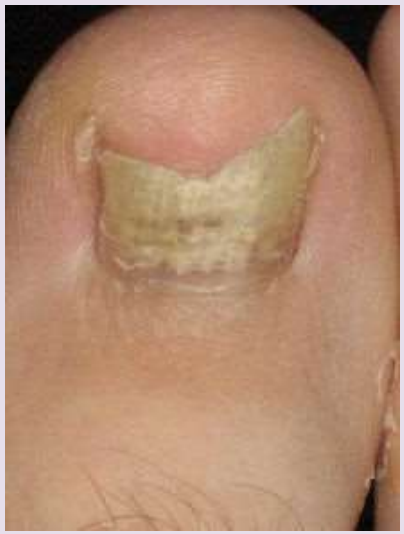
In persons with healthy immune systems, Candida infections are limited to superficial infections of the skin and mucosa.

Several other infections with Candida species occur, including *C. tropicalis, C. krusei, C. parapsilosis, and C. glabrata* (also known as Torulopsis glabrata).

Oral candidiasis



Skin candidiasis



Nail candidiasis

Thermally Dimorphic Fungi (Endemic Mycoses) infections:

That grow in one form at room temperature and in a different form in a human host at 37° C.

The common infections are **blastomycosis, aracoccidiomycosis, coccidiomycosis (valley fever), and histoplasmosis,** are due to Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis, and Histoplasma capsulatum respectively.

Molds infections

Various *Aspergillus* species causing diseases are

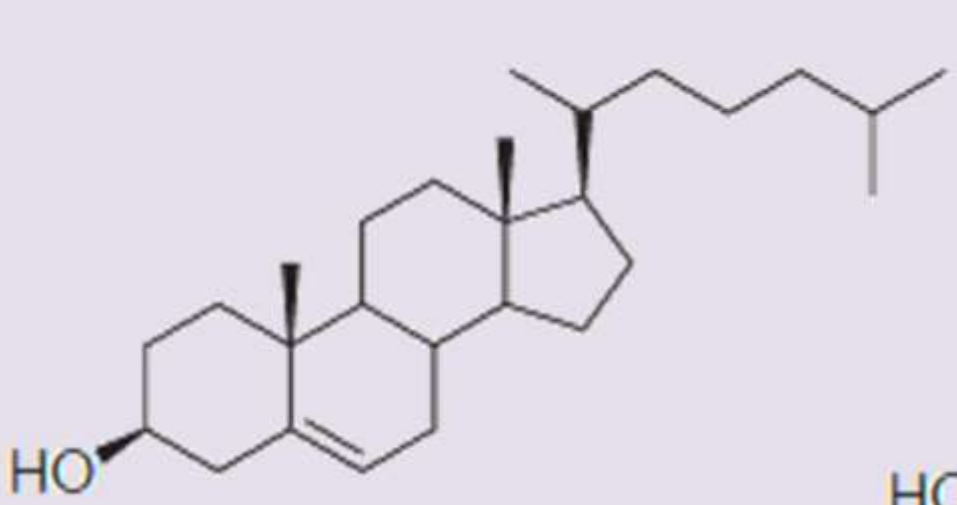
Aspergillus fumigatus, A. niger, and A. flavus

Aspergillus spp. very **rarely cause disease** in persons with **normal immune systems** but are **very dangerous** to persons with **suppressed immune systems**.

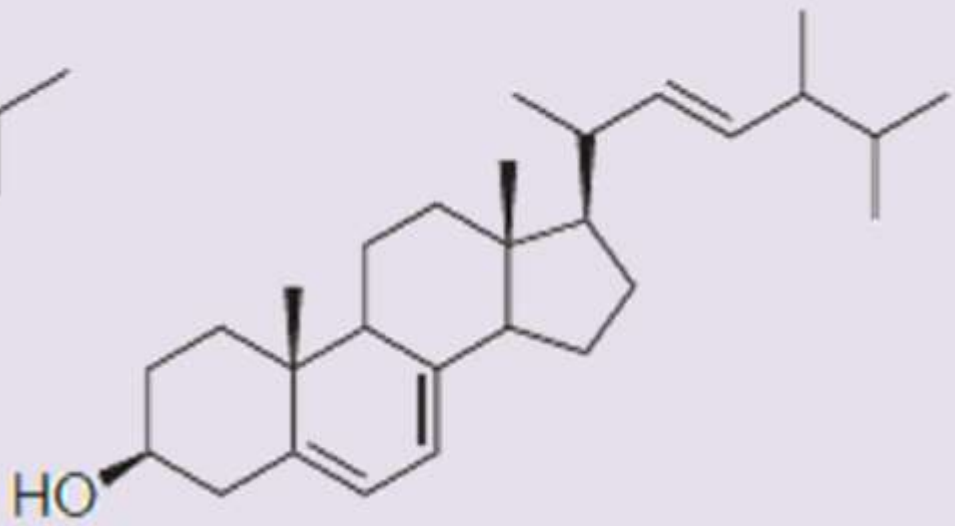
Because *Aspergillus* spores are everywhere, **inhalation is the most common route of inoculation**, but infection through wounds, burns, and implanted devices (e.g., catheters) also is possible.

Biochemical Targets for antifungal agents

- Anti-fungal therapy depends upon biochemical difference between fungi & mammals
- Bacteria are prokaryotes, while fungi & mammals are eukaryotes
- **Fungal cells have both cell membrane & outer cell wall**
- **Mammalian cells have only a cell membrane**
- Therefore, fungal cell wall is the logical target for drugs
- Other targets for antifungal agents: Inhibition of DNA biosynthesis, disruption of mitotic spindles
- **Cell membrane of fungi contains ergosterol**
- **Cell membrane of mammals contains cholesterol**



Cholesterol



Ergosterol

- **This difference in sterol component provides biochemical basis for selective toxicity of antifungal agents**

Prokaryotic Cells	Eukaryotic Cells
Very minute in size	Fairly large in size
Nuclear region (nucleoid) not surrounded by a nuclear membrane	Nuclear material surrounded by a nuclear membrane
Single chromosome present	More than one chromosome present
Nucleolus absent	Nucleolus present
Membrane bound cell organelles are absent	Membrane bound cell organelles are present
Cell division by fission or budding (no mitosis)	Cell division by mitosis or meiosis

Classification of Antifungal agents

On the basis of mode of action of drugs

I) Interference with Ergosterol

1) Allylamines & Thiocarbamated

e.g. Naftifine, Butanifine, Terbinafine, Tolnaftate

2) Azole

a) Imidazole

e.g. Clotrimazole, Flutrimazole, Econazole, **Miconazole**, Lanocazole, **Ketoconazole**, Sulconazole, Butoconazole

b) Triazole

e.g. Fluconazole, Itraconazole, Terconazole, Voriconazole, Genaconazole

3) Polyenes antibiotics

e.g. Amphotericin B, Nystatin, Natamycin

4) Morpholines

e.g. Amorolifine

II) Interference with other metabolic processes

1) Antibiotic

e.g. Griseofulvin

2) Pyrimidines / Nucleoside antifungal

e.g. 5-fluorocytosine (fluocytosine)

3) Miscellaneous agents (topical agents for dermatophytes)

e.g. Haloprogin, Clioquinol, Triacetin, Sodium caprylate

Ergosterol Biosynthesis Inhibitors

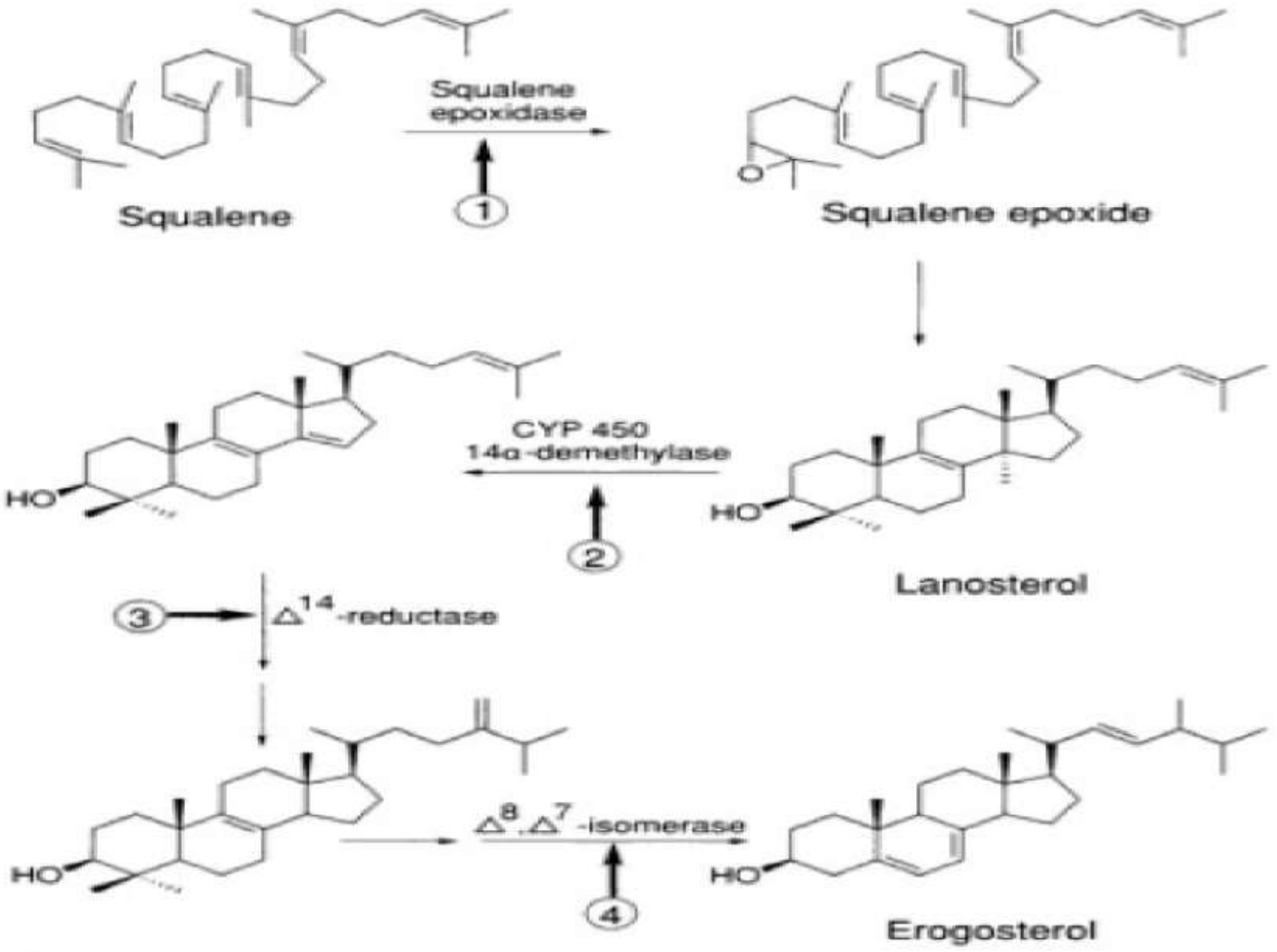


Fig. 40.1. Ergosterol biosynthesis from squalene, with key steps

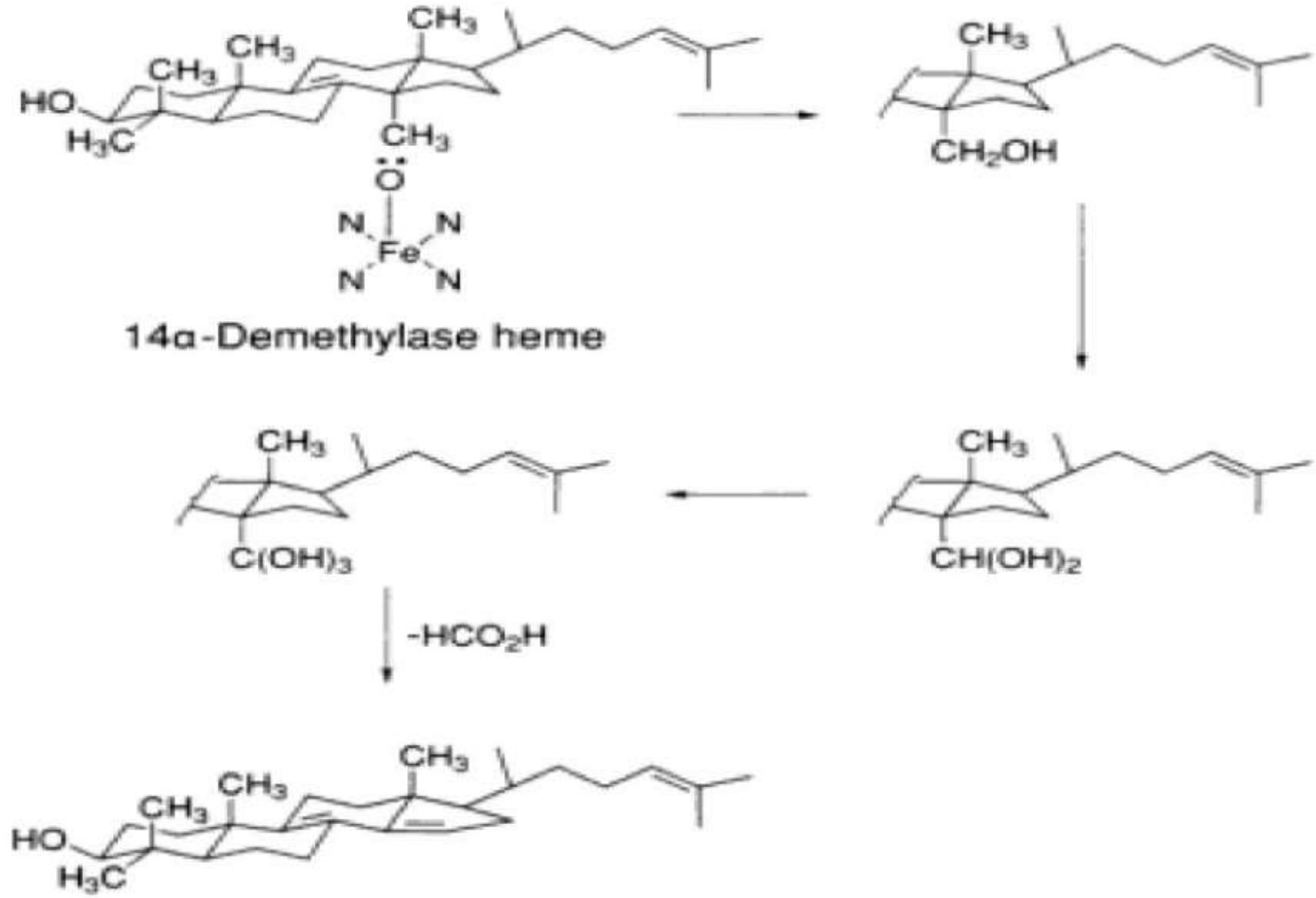


Fig. 40.2. Demethylation of the 14α-methyl group from lanosterol carried out by the cytochrome P450 enzyme sterol 14α-demethylase (CYP51). The mechanism involves three successive

Azoles-Imidazoles & Triazoles

- **Imidazoles...Clotrimazole, Miconazole, Ketoconazole, Econazole, Butoconazole**

- **Triazoles....Terconazole, Fluconazole, Voriconazole, Itraconazole**

Azole antifungal agents are the largest class of antimycotic available
More than 20 drugs on market

Some are used topically to treat superficial dermatophytic & yeast infections

Others are used orally to for treatment of systemic fungal infections

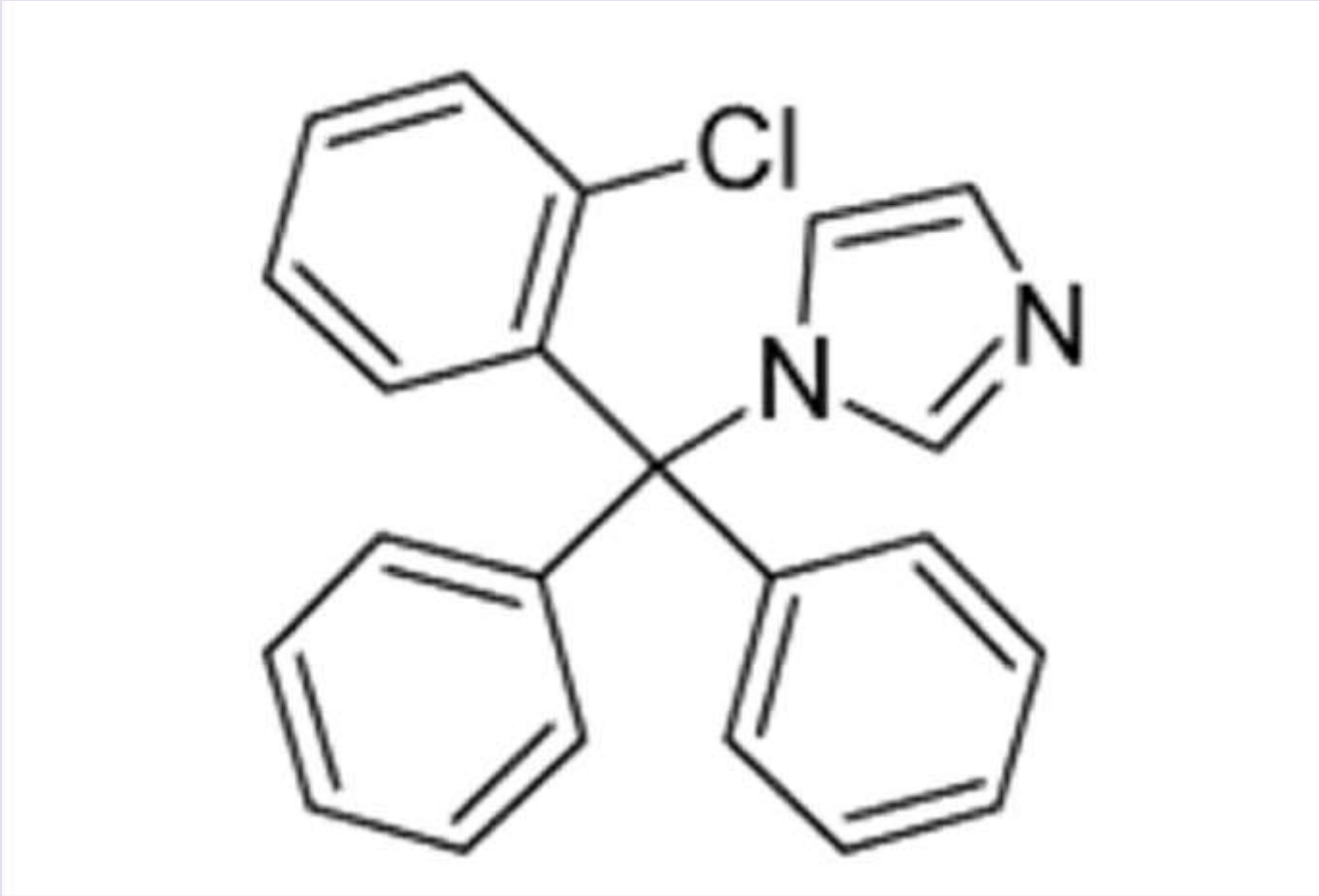
The **characteristic chemical feature of azoles** from which their name is derived is the **presence of a five-membered aromatic ring containing either two or three nitrogen atoms.**

Imidazole rings have **two nitrogens** and **triazoles three**.

In both cases, the azole ring is attached through N1 to a side chain containing at least one aromatic ring.

1*H*-imidazole

1*H*-1,2,3-triazole

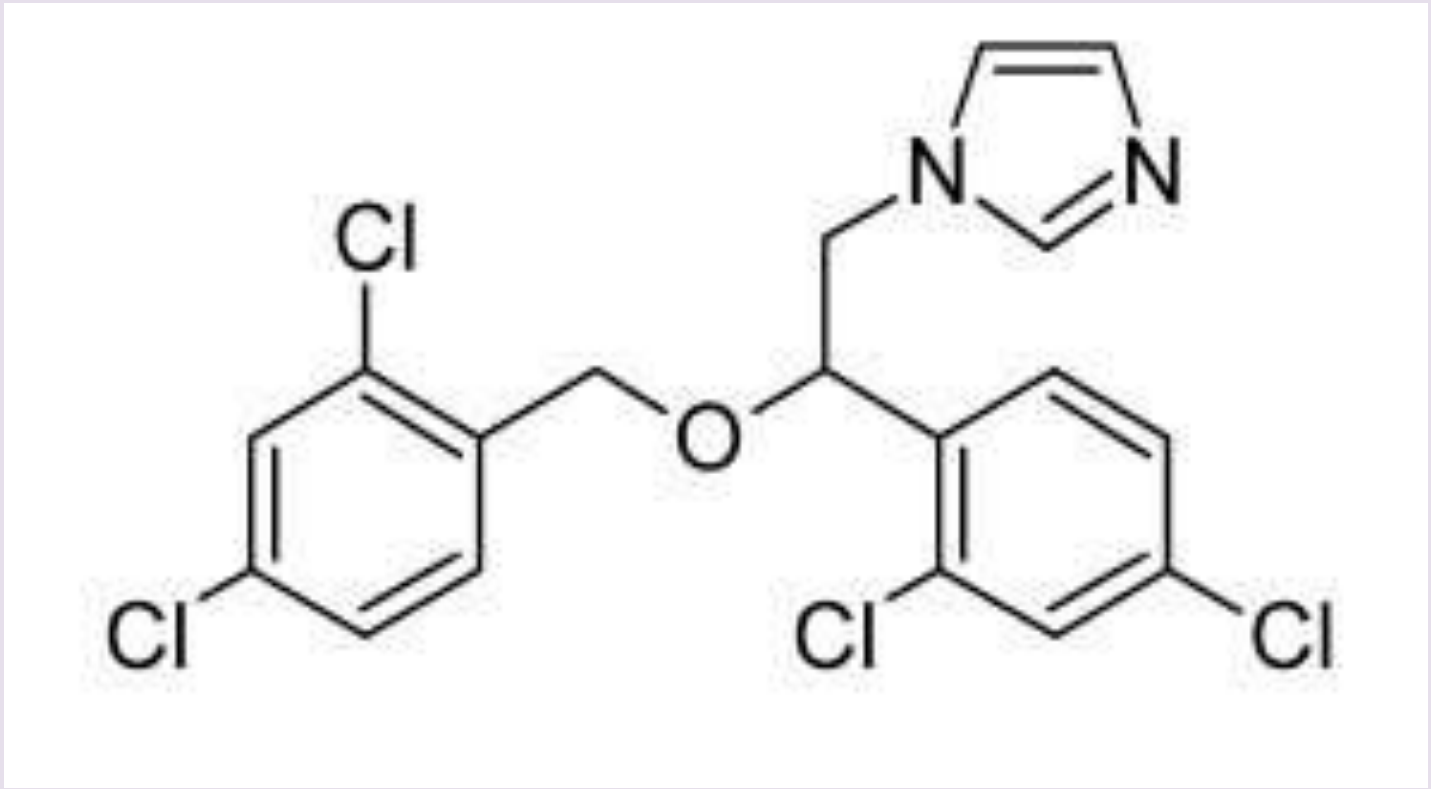


Clotrimazole

1-[(2-chlorophenyl)(diphenyl)methyl]-1H-imidazole

1-(o-Chloro-,-diphenylbenzyl)imidazole

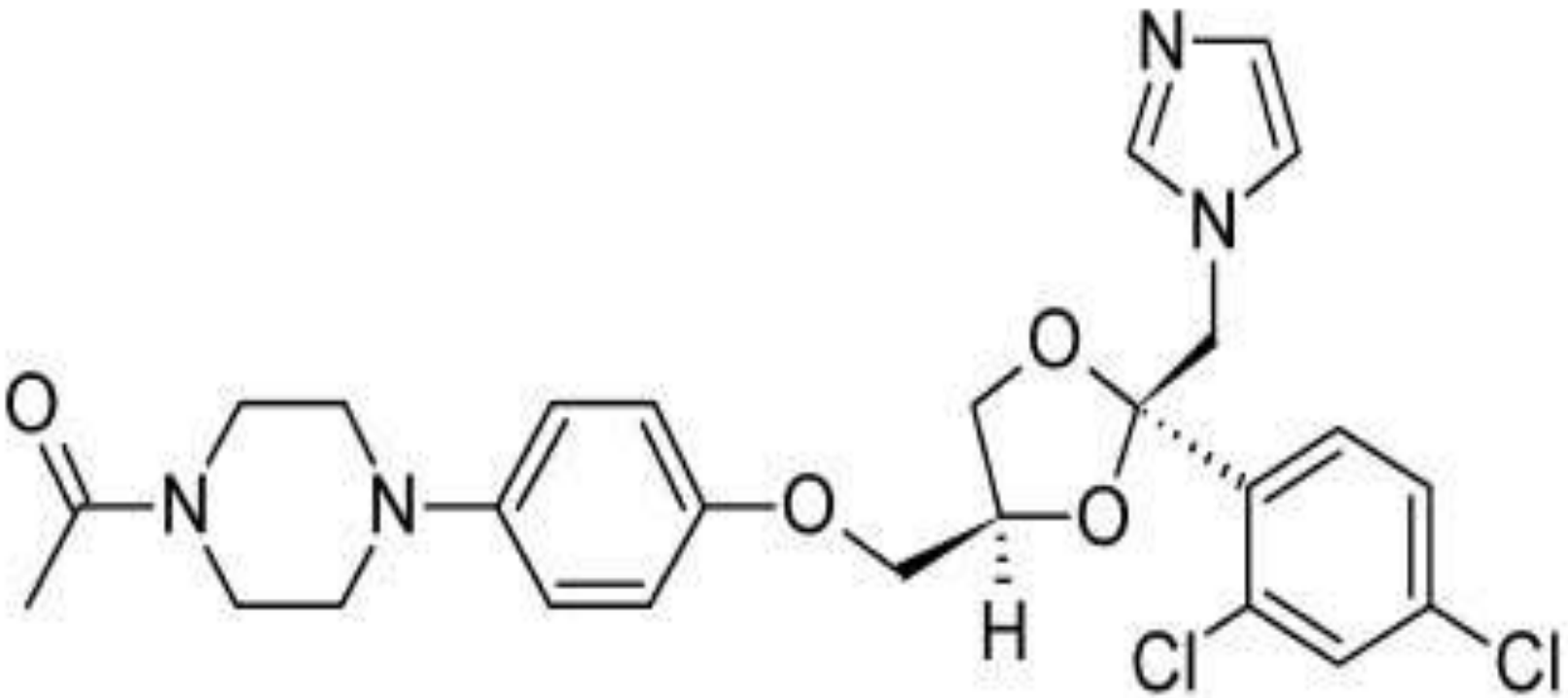
Ms. Rina P. Patil
(Assistant Professor)



Miconazole

1-[2-(2,4-Dichlorophenyl)-2-[2,4-dichlorophenyl]-methoxy]ethyl]-1*H-imidazole*

Ms. Rina P. Patil
(Assistant Professor)



Ketoconazole

1-[4-[4-[[2-(2,4-dichlorophenyl)-2-(imidazol-1-ylmethyl)-1,3-dioxolan-4-yl] methoxy]phenyl]piperazin-1-yl]ethanone

1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1H-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

MOA of Azoles

All azoles act by inhibiting ergosterol biosynthesis through inhibition of **cytochrome P450 14 α –demethylase**

At the molecular level, the nitrogen atom (N-3 in the imidazoles, N-4 in the triazoles) bind to the heme iron of enzyme-bound cytochrome P450. This inhibit activation of molecular oxygen and prevent oxidation of steroidal substrates.

When demethylation is inhibited, the 14 α-sterol accumulates in the membrane, causing destabilization

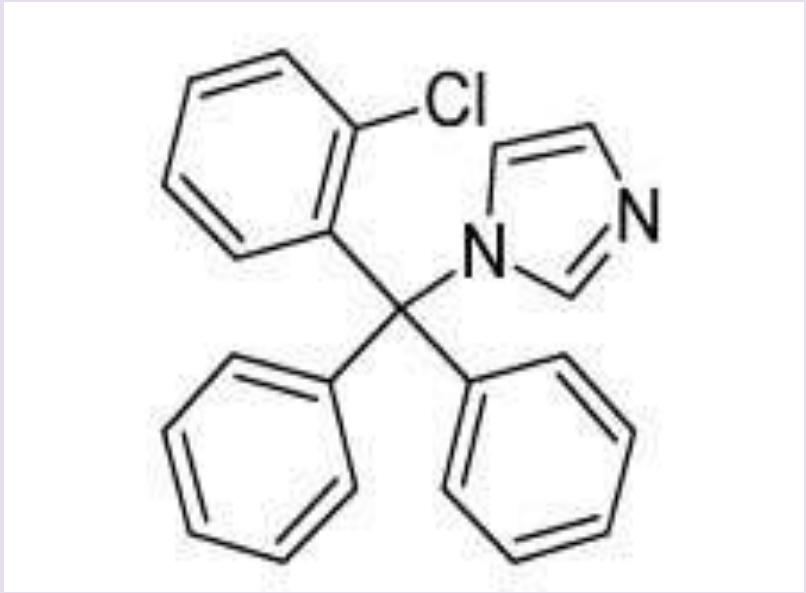
This leads to permeability changes, leaky membrane, & malfunction of membrane

All these effects leads to fungal cell death

STRUCTURE–ACTIVITY RELATIONSHIPS

The basic structural requirement for azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKa of 6.5–6.8).

The most potent antifungal azoles possess two or three aromatic rings.



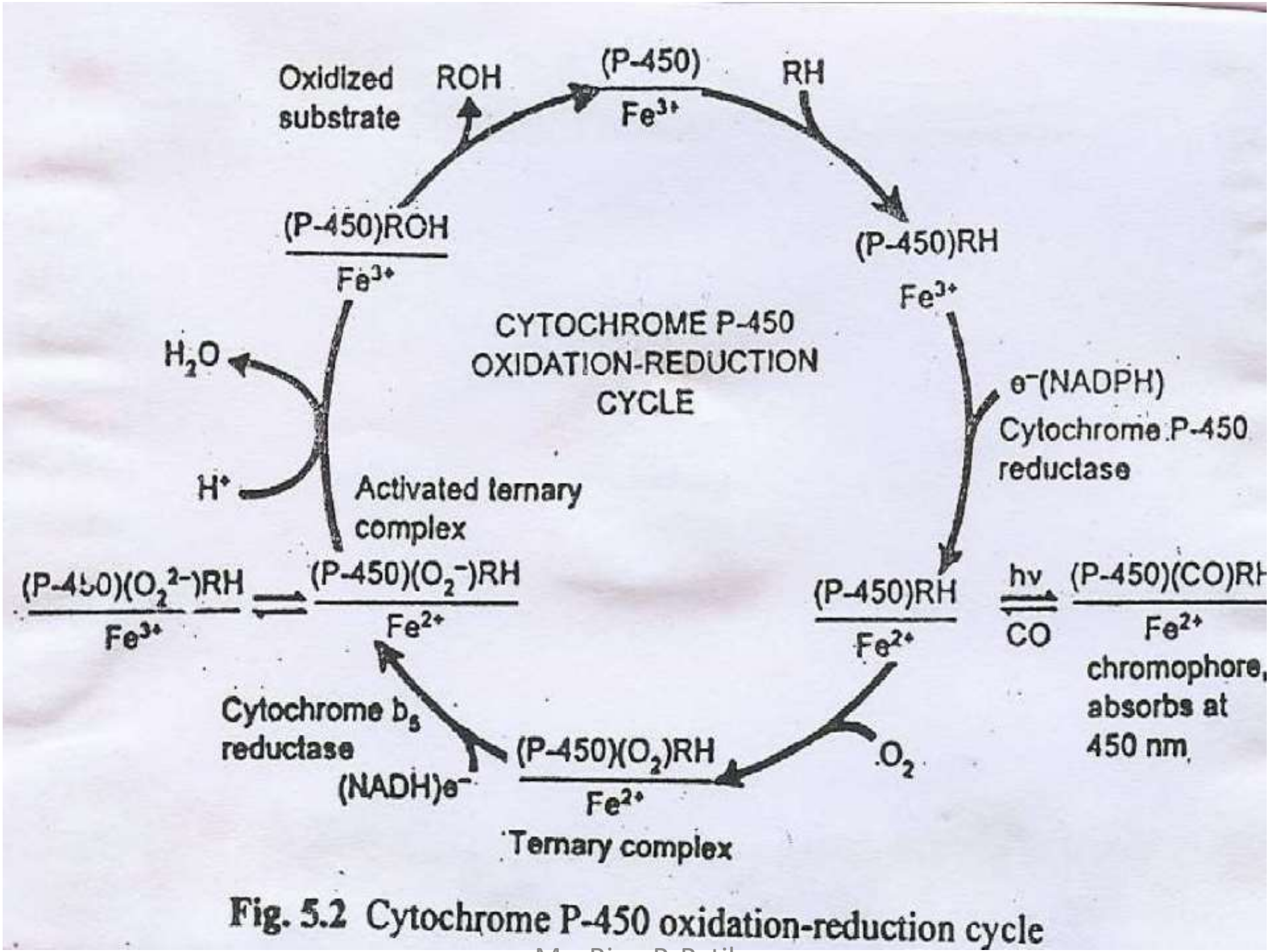
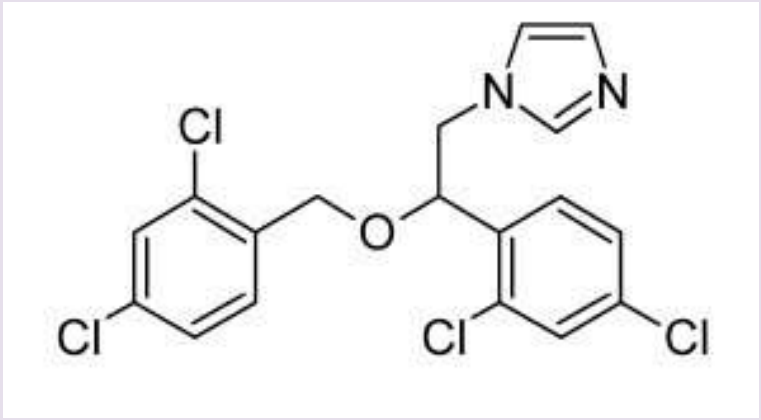
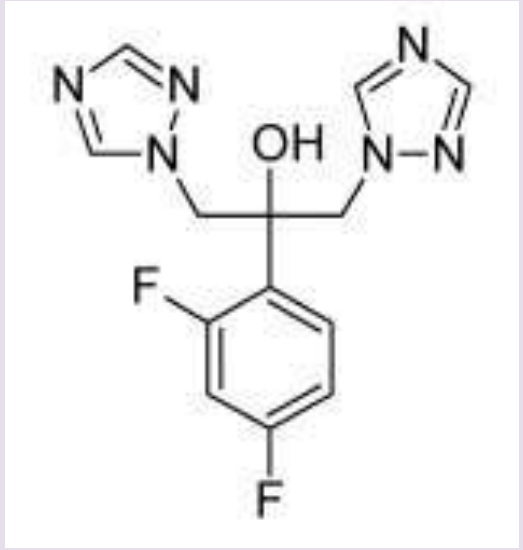


Fig. 5.2 Cytochrome P-450 oxidation-reduction cycle





At least one of which is halogen substituted (e.g., 2,4-dichlorophenyl, 4-chlorophenyl, 2,4-difluorophenyl), and other nonpolar functional groups.

Only 2, and/or 2,4 substitution yields effective azole compounds

The halogen atom that yields the most potent compounds is fluorine

Substitution at other positions of the ring yields inactive compounds

Clotrimazole (imidazole)
is a broad-spectrum antifungal drug.
used topically for the treatment of **tinea** infections and **candidiasis.**

Clotrimazole is available as a **solution**, **a lotion**, and **a cream** in a concentration of 1%.
1% vaginal cream and tablets of **100 mg and 500 mg** are available for vulvovaginal candidiasis.

Clotrimazole is effective against various pathogenic yeasts and is reasonably well absorbed orally.

Still not considered suitable for the treatment of systemic infections.

Because it causes severe gastrointestinal disturbances.

It is also extensively protein bound.

Miconazole (imidazole)

The free base is available in an injectable form and intended for the treatment of serious systemic fungal infections, **such as candidiasis, coccidioidomycosis, cryptococcosis, petriellidiosis** etc.

It may also be used for the treatment of chronic mucocutaneous candidiasis.

- **Serious toxic effects from the systemic administration of miconazole are comparatively rare**
- **Miconazole nitrate is supplied in various dosage forms (cream, lotion, powder, and spray) for the treatment of tinea infections and cutaneous candidiasis.**
- Vaginal creams and suppositories are also available

Ketoconazole

is a broad-spectrum imidazole antifungal agent that is administered orally for the treatment of systemic fungal infections.

Hepatotoxicity, is the most serious adverse effect of ketoconazole.

Ketoconazole is known to inhibit cholesterol biosynthesis suggesting that lanosterol 14α-demethylase is inhibited in mammals as well as in fungi.

High doses have also been reported to lower testosterone and corticosterone levels.

It inhibit Cytochrome P450 oxidases responsible for the metabolism of various drugs (cyclosporine, phenytoin).

Ketoconazole is a racemic compound, consisting of the *cis-2S,4R and cis-2R,4S isomers*

2S,4R isomer is more active

Ketoconazole is recommended for the treatment of : candidiasis (including oral thrush and the chronic mucocutaneous form), coccidioidomycosis, chromomycosis, etc

Other Antifungal Antibiotics

Griseofulvin

Griseofulvin was first reported in 1939 by Oxford et al. as an antibiotic obtained from the fungus *Penicillium griseofulvum*

In 1959, griseofulvin was introduced into human medicine for the treatment of *tinea* infections by the systemic route.

Griseofulvin is an example of a rare structure in nature, a spiro compound

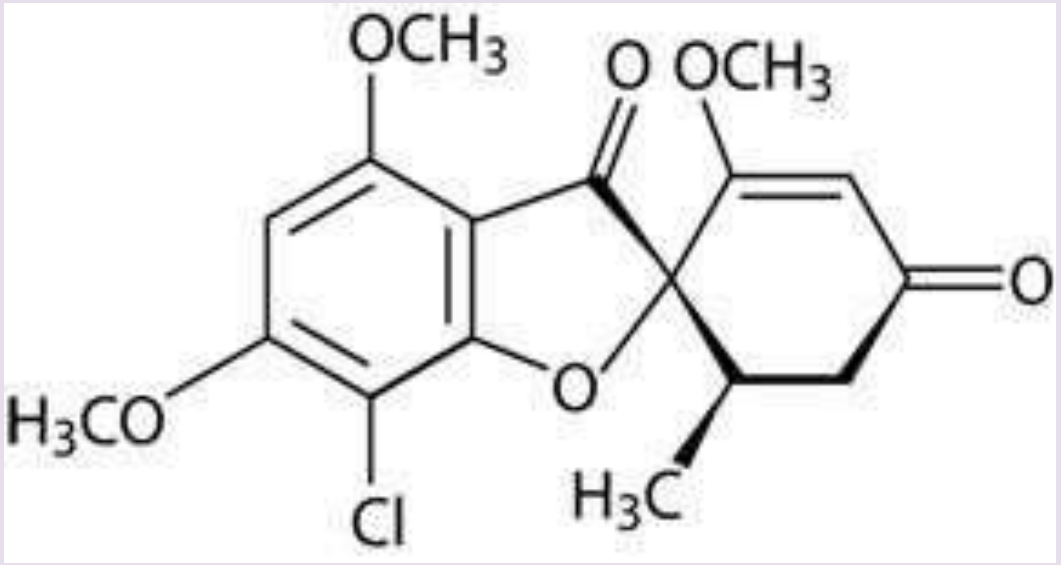
Griseofulvin has been used systemically for treatment of ringworm infections of the body, hair, nails, and feet caused by species of dermatophytic fungi including *Trichophyton, Microsporum* and *Epidermophyton*

Griseofulvin is a fungistatic agent, and as the new, healthy tissue develops, the drug prevents reinfection.

MAO of Griseofulvin

By binding to the protein tubulin, interferes with the function of mitotic spindle, thereby, inhibits cell division

It may also interfere directly with DNA replication



7-chloro-2',4,6-trimethoxy-6',β-methylspiro[benzofuran-2(3*H*)-*1'-[2]cyclohexene]*-3,4'-dione

Adverse effects:

The most common ones are allergic reactions such as rash and urticaria, gastrointestinal upset, headache, dizziness, and insomnia.

Sulfonamides

1935

Protosil

Sulfanilamide

Drug Name: Active form is Sulfanilamide
Trade Name: Prontosil
Use: Antiinfective

Introduction

- **Sulphonamideswere the first effectivechemotherapeutic agents to be employed systemically.**
- Their introduction led to a sharp decline in the morbidity and mortality of infectious diseases
- Soon widespread resistance developed to sulfonamides after their introduction
- And the increasing use of **the broader-spectrum penicillins** in the treatment of infectious disease diminished the usefulness of sulfonamides.
- Today, they occupy a rather small place in the list of therapeutic agents that can be used for infectious disease.
- Still they are not completely outmoded.
- **In the mid-1970s, the development of a combination of trimethoprim and sulfamethoxazole demonstrated usefulness in the treatment and prophylaxis of certain opportunistic microbial infections**

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History

- Fritz Mietzsch and Joseph Klarer systematically synthesized a series of azo dyes, containing the sulfonamide group, as potential antimicrobial agents.

- Sulfonamide azo dyes were included in the test series because they were readily synthesized and possessed superior staining properties

- In 1932, Domagk began to study a brilliant red dye, later named Prontosil.
- Prontosil was found to protect and cure, streptococcal infections in mice

- He recognized the antibacterial activity of an azodye, prontosil red.

- For this work, he was awarded Nobel Prize in Medicine in 1938.

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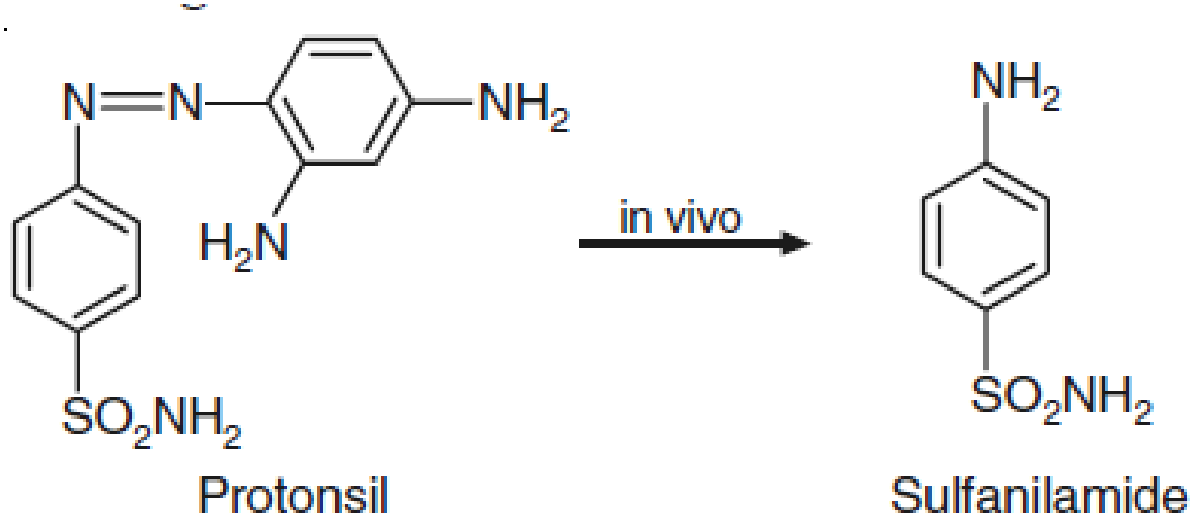
History

- Though synthesized first in 1908, sulfonamides did not receive much attention till 1937—when it was proved by some workers at Pasteur Institute in France that prontosil is a prodrug and the active drug, sulfanilamide gets released into the body after in vivo cleavage of the azo linkage.



These findings started modern era of chemotherapy and the concept of the *prodrug*

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History

- Following the dramatic success of Prontosil, several sulfanilamide derivatives was synthesized and tested.
- By 1948, more than 4,500 compounds had been evaluated.
- Of these, only about two dozen have been used in clinical practice.

Edit with WPS Office

Gerhard Domagk (1895-1964)

German bacteriologist and pathologist who was awarded the 1939 Nobel Prize for Physiology or Medicine for his discovery (announced in 1932) of the antibacterial effects of Prontosil, the first of the sulfonamide drugs.

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PHYSICAL PROPERTIES

•Sulfonamides are off white crystalline powders, mostly poorly soluble in water.

• Their sodium salts are usually used because of aqueous solubility.

•The solubility parameter is greatly influenced upon by the nature of the substituents on -SO_2NH_2- group.

•These substituent's modify the chemical features of the molecule. Hence they play an important role in governing the rates of absorption and excretion of sulfonamides.

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•The substitution of electron withdrawing heterocyclic rings lowers the pKa of sulfonamides.

•The sulfonamides and their metabolite are excreted almost entirely in the urine (pH – 6) and the sulfonamides which are not water soluble crystallize in kidney, thus damaging them (Crystallurea).

• One way to overcome this problem is to raise pH of the urine by
oral sodium bicarbonate closer to pH 10.4 (above pKa).
•
• The sulfonamides form salts that are water soluble.

•Many sulfonamides have been synthesized whose pKa is closer to pH of urine.

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- Sulfonamides can be considered as the derivatives of para-amino benzene sulfonamide (i.e. sulfanilamide) skeleton.

- Since the sulfamoyl (SO2NH2) group is the most important moiety for the antibacterial activity of sulfonamides, the amide nitrogen is designated as N1 while nitrogen of para-amino functional group is designated as N4.

- Most of the clinically used sulfonamides belong to the class of N'-substituted sulfonamides.

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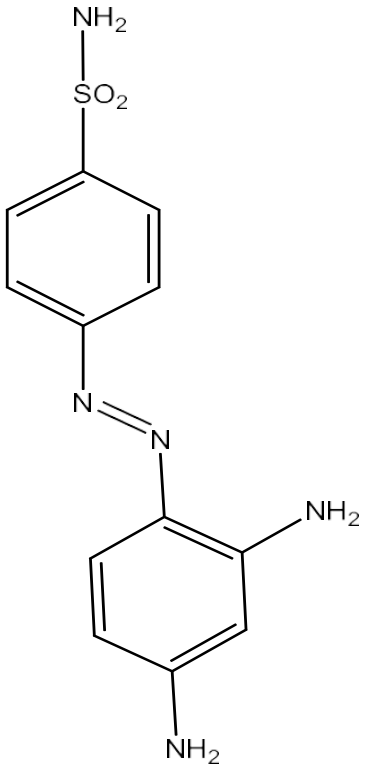
Classification of Sulphonamides

I. On the basis of chemical classification

i) N4 – substituted Sulphonamides (pro drugs):



Prontosil

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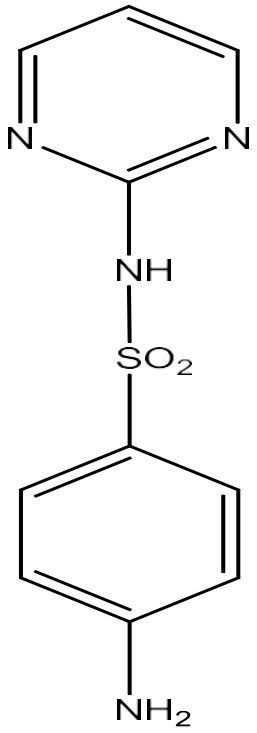
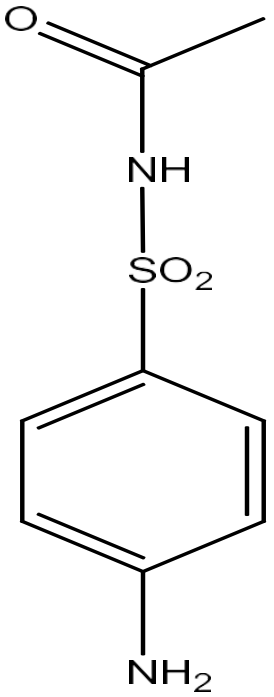
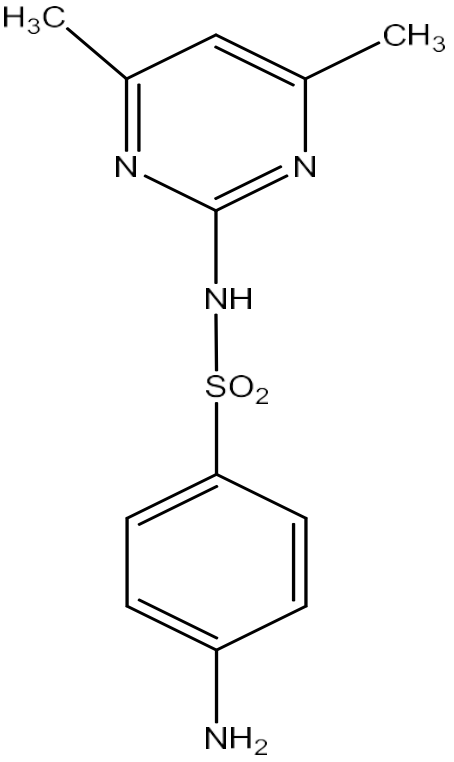
ii) N1 - substituted Sulphonamides:



Sulphadiazine



Sulphacetamide



Sulphadimidine

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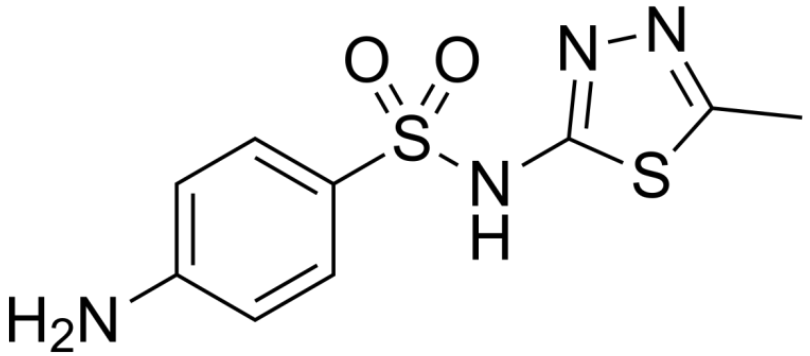
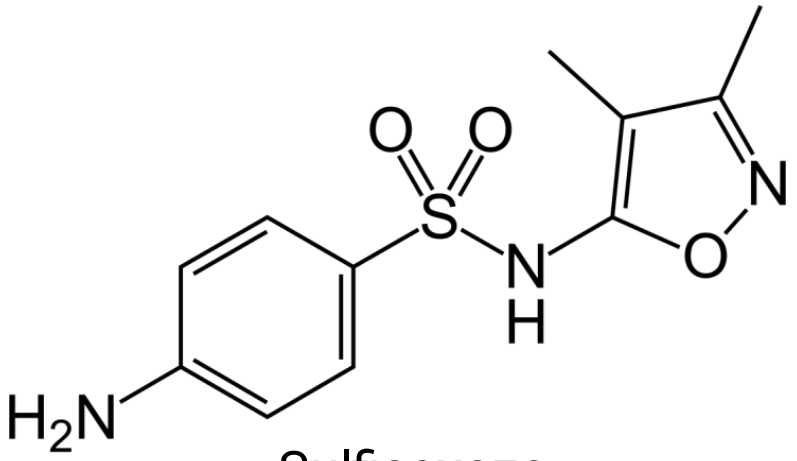
N1 - substituted Sulphonamides



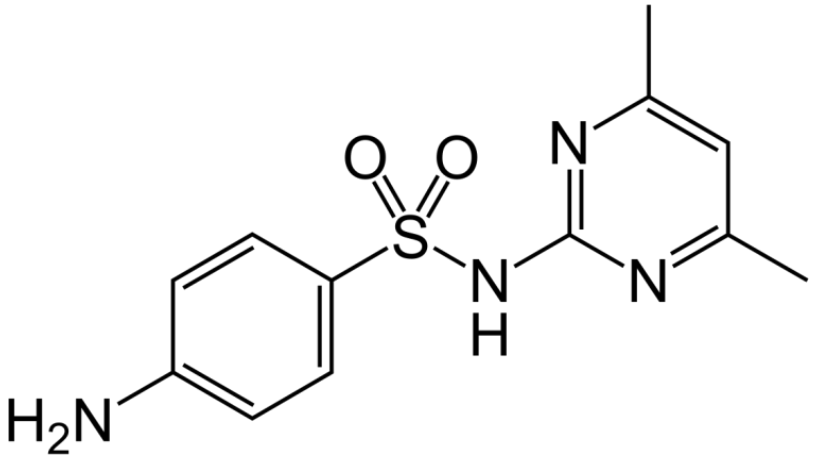
Sulphamethizole

4-amino-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)benzenesulfonamide

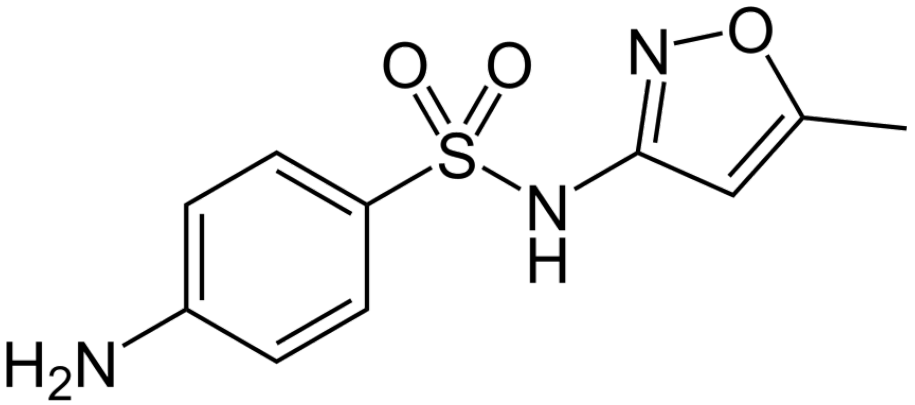


Sulfisoxazole

4-amino-*N*-(3,4-dimethyl-1,2-oxazol-5-yl)benzenesulfonamide



Sulfamethazine



Sulfamethoxaole

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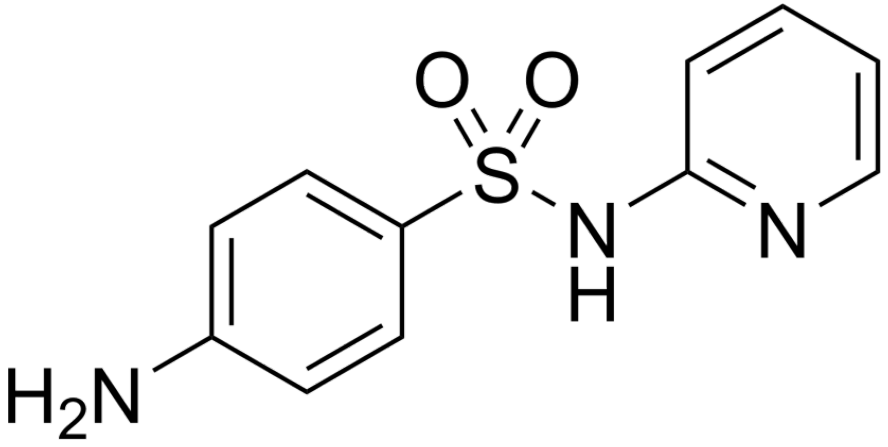
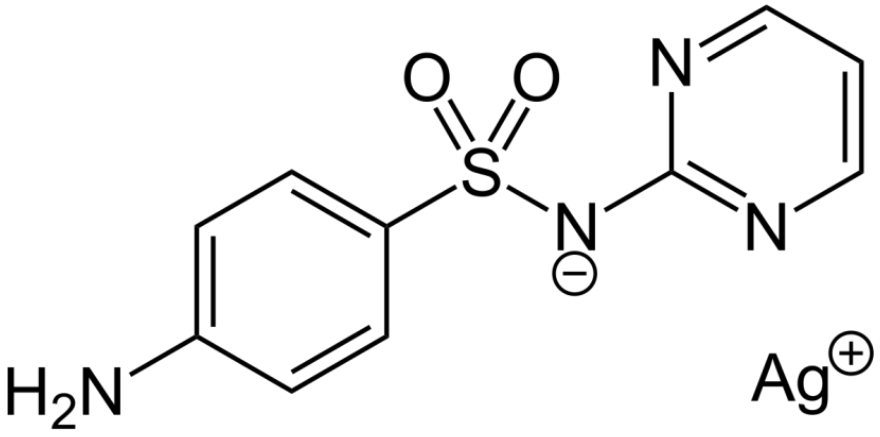
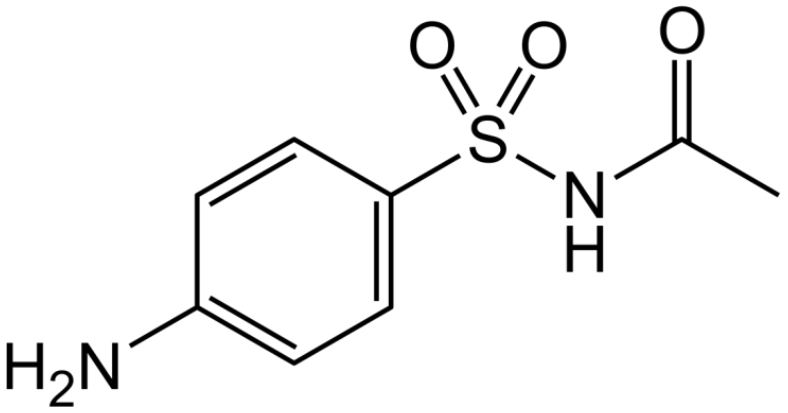
N1 - substituted Sulphonamides



Sulphapyridine



Sulphadiazine



sulphacetamide

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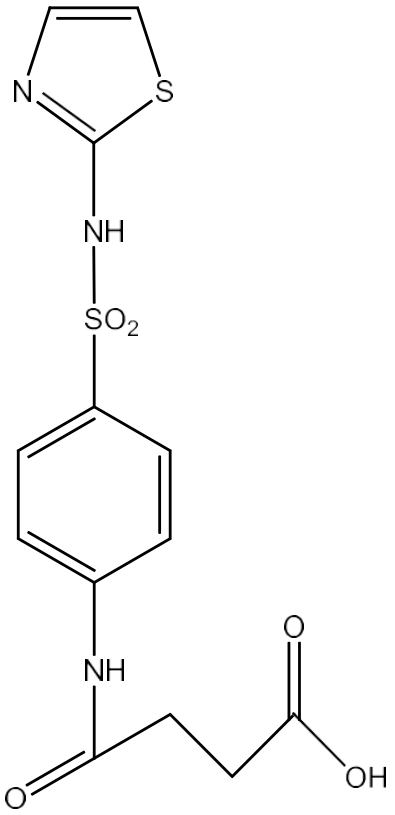
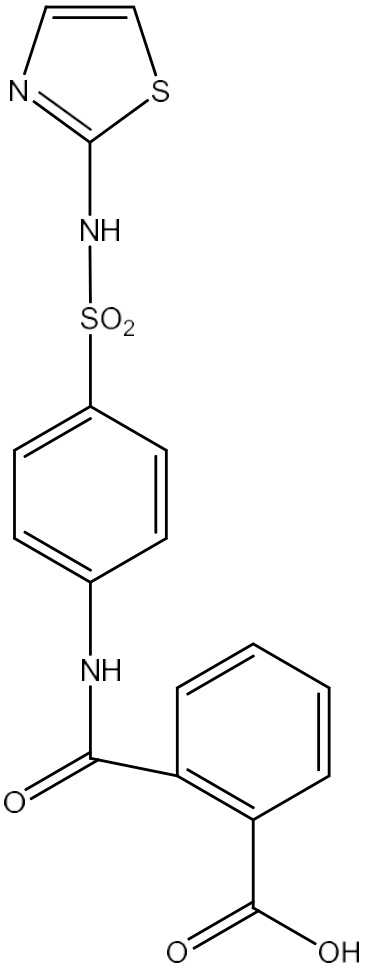
iii) Both N1 and N4 – substituted Sulphonamides:



Succinyl sulphathiazole



Phthalyl sulphathiazole

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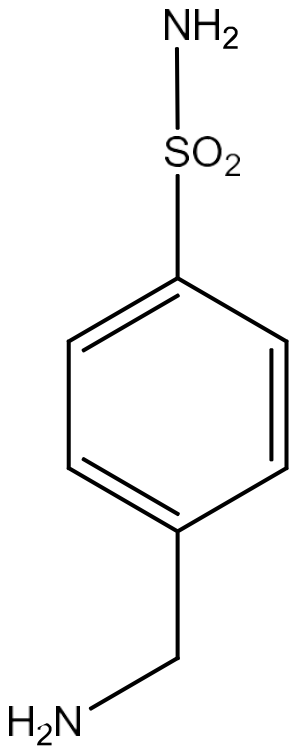
iv) Non-aniline Sulphonamides:



Mafenide sodium

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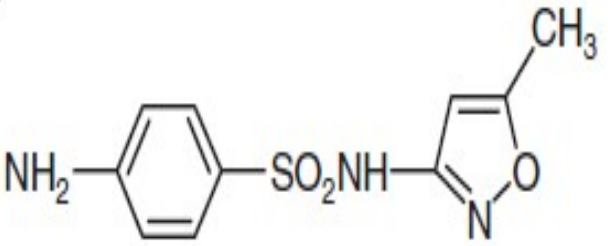
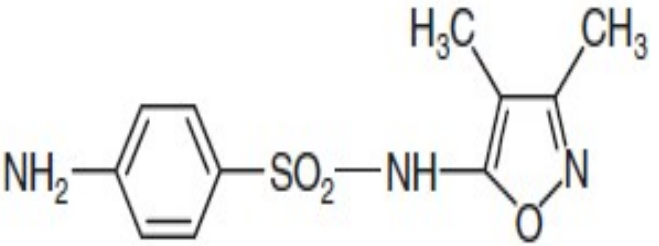
Based on Pharmacokinetic Parameter

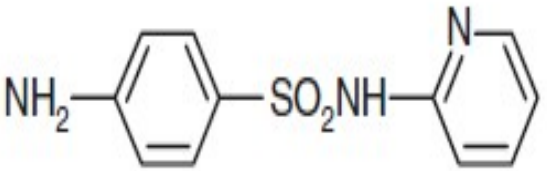
Agents which are rapidly absorbed



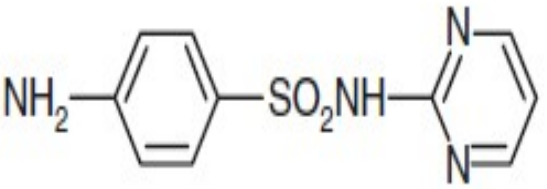
Sulfamethoxazole



Sulfisoxazole



Sulfapyridine



Sulfadiazine

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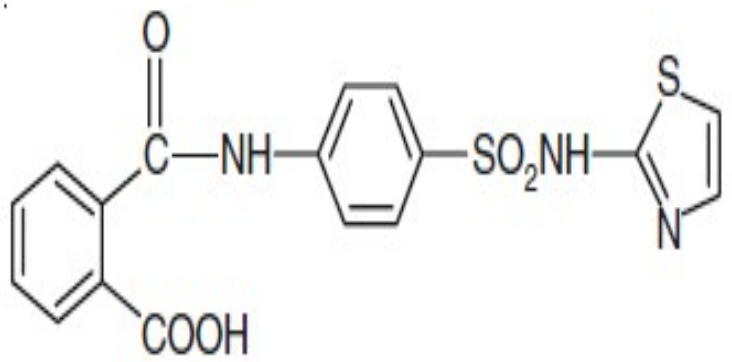
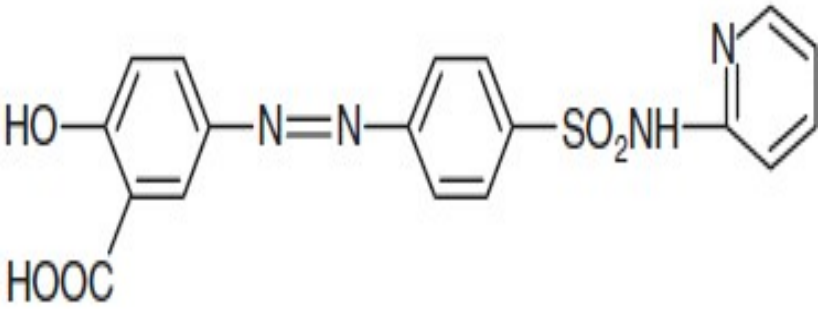
Agents which are poorly absorbed

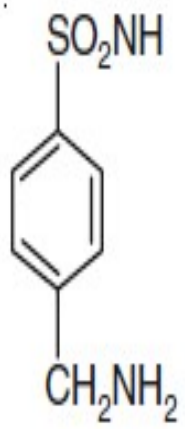


Phthalylsulfathiazole

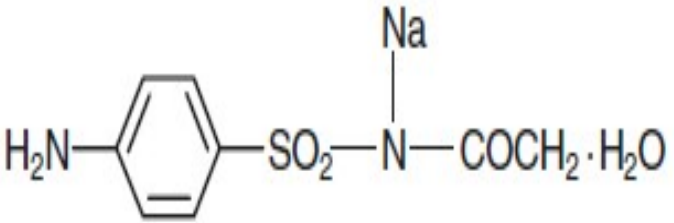


Sulfasalazine

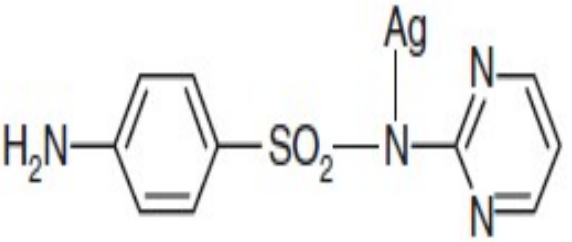
Agents which are applied topically



Mafenide



Sodium sulfacetamide



Silver sulfadiazine

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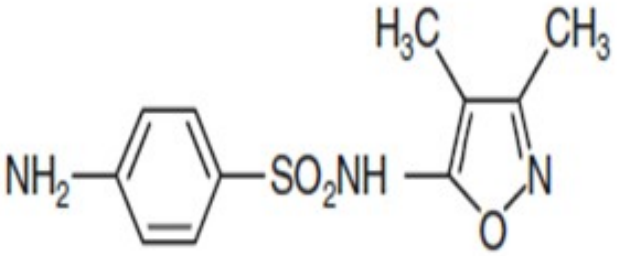
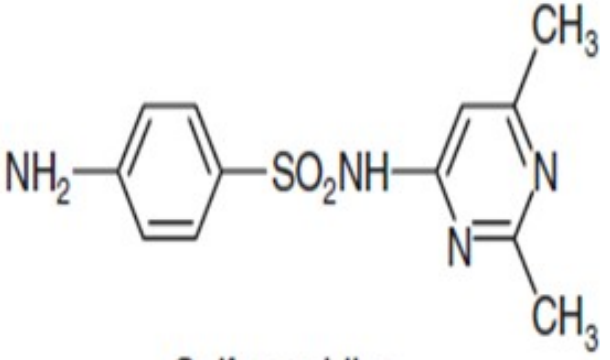
Based on Duration of Action

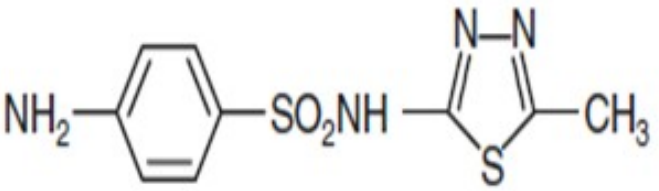
Short acting sulfonamides



Sulfisoxazole



Sulfasomidine



Sulfamethizole

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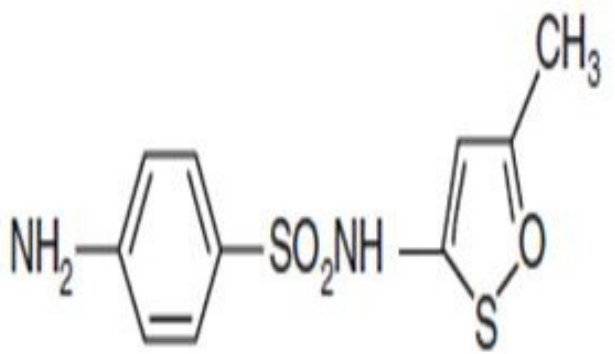
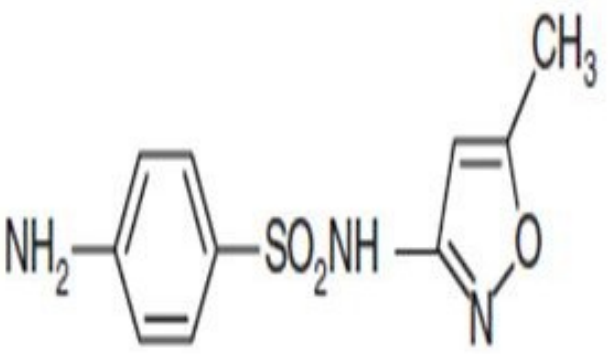
Intermediate acting



Sulfasomizol



Sulfamethoxazole

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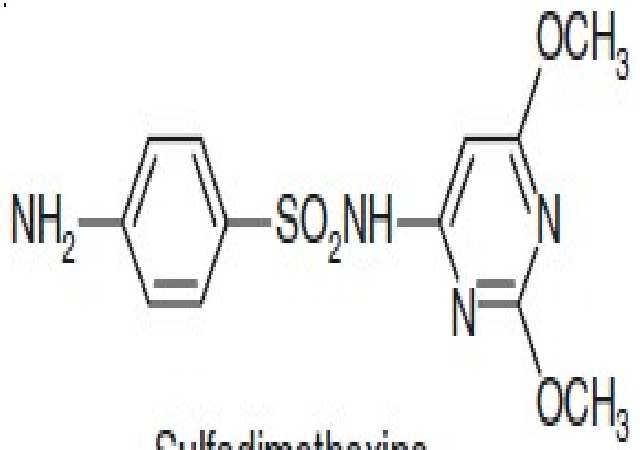
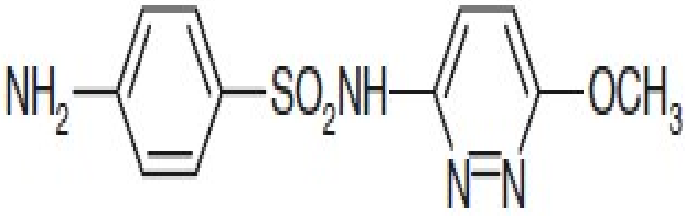
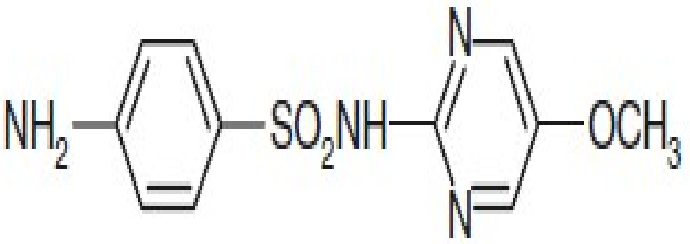
Long acting



Sulfadimethoxine



Sulfamethoxypyridiazine



Sulfamethoxydiazine

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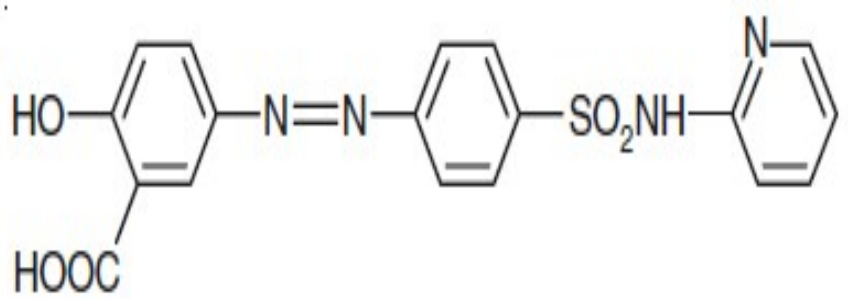
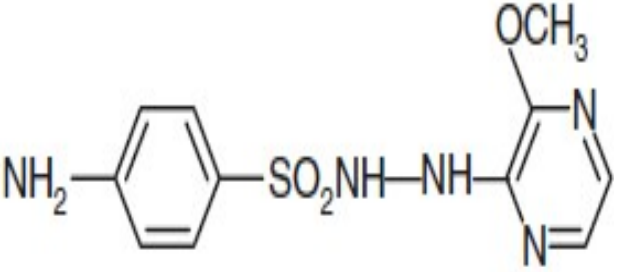
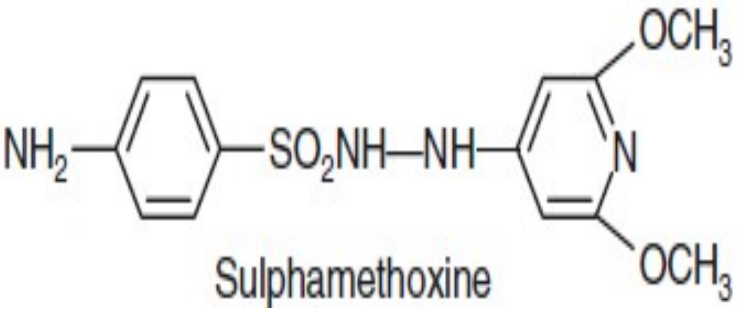
Ultralong acting



Sulphasalazine



Sulfalene



Sulphamethoxine

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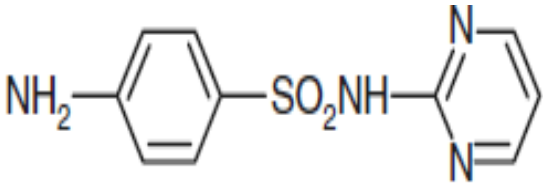
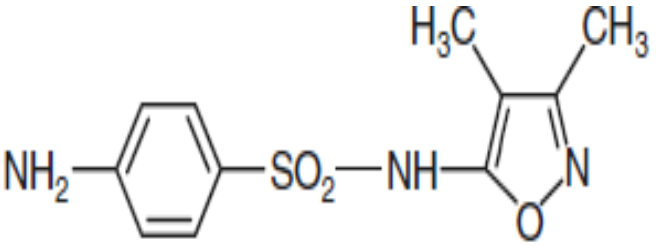
I. **On the basis of pharmacological activity**

i) **Antibacterial agents:**

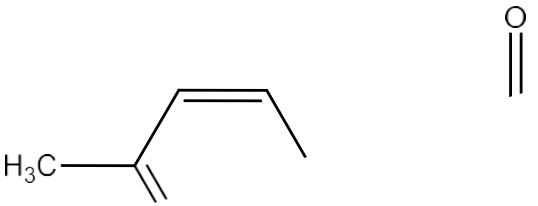


Sulfadiazine



Sulfisoxazole

ii) **Oral hypoglycemic agent:**



Tolbutamide

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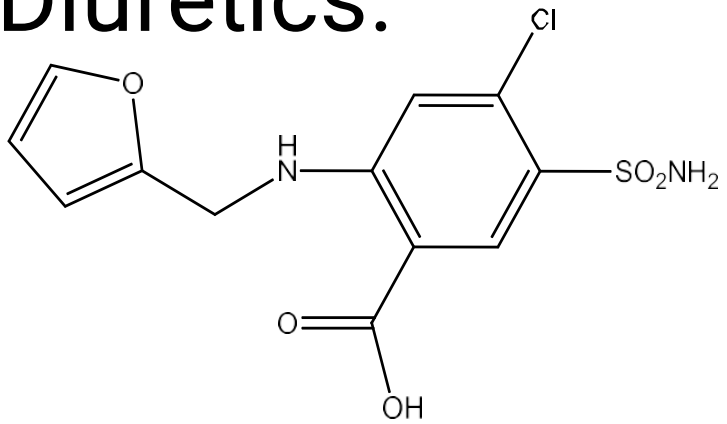
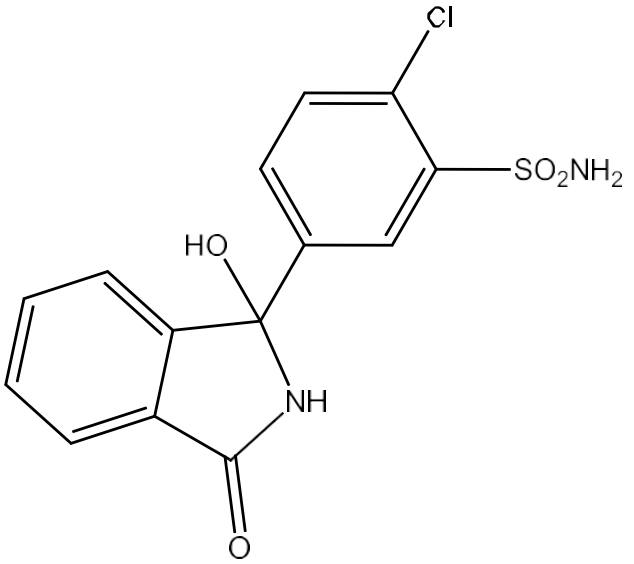
iii) Diuretics:



Furosemide



Chlorthalidone

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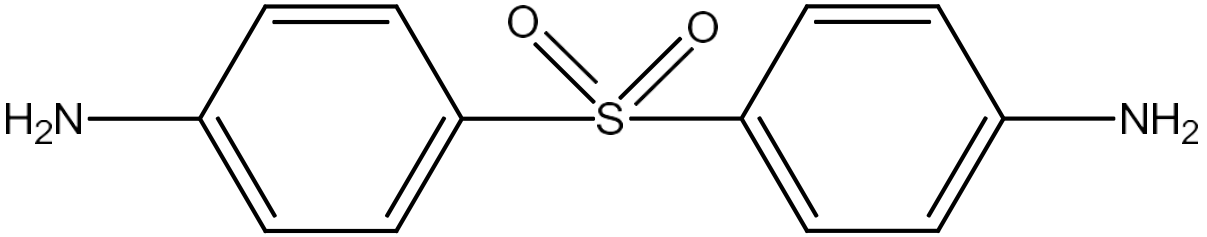
iv)
Dermatitis:



Dapson
e

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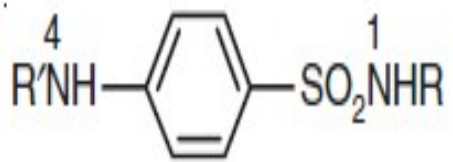
SAR STUDIES OF SULFONAMIDES

Sulfonamide being an important chemical class several thousand sulfonamides had been investigated for their activity on infective organisms. In antibacterial therapy, they are placed next to antibiotics, sometimes even preferred over the later. The major features of SAR of sulfonamides include:



1. Sulfanilamide skeleton is the minimum structural requirement for antibacterial activity.
2. Sulfur atom should be directly linked to the benzene ring.
3. In N^1-substituted, sulfonamides activity varies with the nature of the substituent at amido group. With substituents, imparting electron rich character to SO_2 group, bacteriostatic activity increases. Heterocyclic substituents lead to highly potent derivatives. While sulfonamides that contain a single benzene ring at N^1 – position, are considerably more toxic than heterocyclic ring analogs.

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4. N_1-disubstituted in general leads to inactive compounds. Because one hydrogen is essential for ionization of the ring.
5. The free aromatic group should reside para to the sulfonamido group. Its placement at ortho or meta position results in compounds devoid of antibacterial activity.
6. The presence of free amino group is very essential for the activity. Any substitution of amino group either result in prodrug nature or in the loss of activity.

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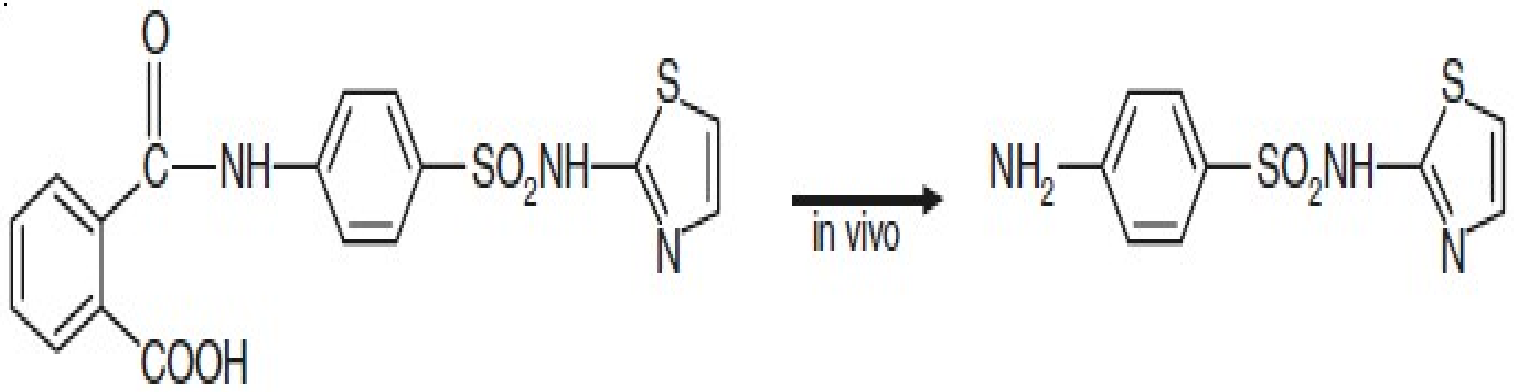
7. The free amino group could be modified to produce prodrug, which are converted to free amino function *in vivo*, e.g. phthalylsulfathiazole.



Phthalylsulfathiazole

8. The antibacterial activity of sulfonamides is related to pKa. Maximal activity would be found in those having a pKa value between 6.0–7.5.
9. Substitutions in the benzene ring of sulfonamides have also been tried. All attempts ended up in formation of inactive compounds.

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10. Substitution of free sulfonic acid ($-SO_3H$) group for sulfonamido function, destroys the activity but replacement by a sulfamic acid group ($-SO_2H$) and acetylation of N^4-position retains back the activity.
11. The lipid solubility influences the pharmacokinetic and antibacterial activity. In general, as the lipid solubility increases, so do the half-life and antibacterial activity.
12. The sulfonamides bind to the basic centers of arginine, histidine and lysine sites of protein. The binding groups are alkyl, alkoxy, and halo. The binding affects the activity of the drug and its half-life.

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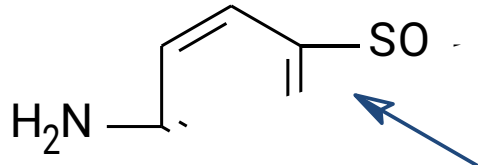
other aromatic rings or introducing other groups into the benzene ring will decrease or lose the antimicrobial activities

Mono substitution will enhenced the potency; heterocyclic rings have better activities, Bis substitution will lose their activites



unsubstituted or potential amino groupare essential for antimicrobial activities

sulfonic group must be in the 4 position of aniline; 2 or 3 position substitution will lose the other activities, 4 group will decrease the potency

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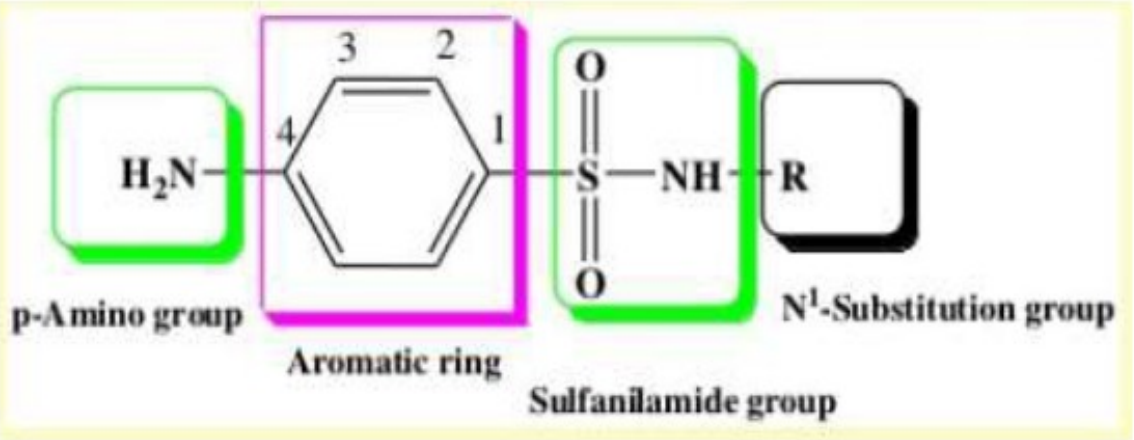

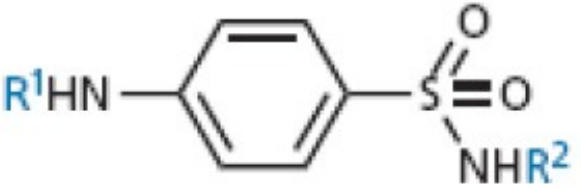

1. *Para -amino group : This is essential for activity and* must be unsubstituted The only exception is when R1 = acyl (i.e. amides).
2. The aromatic ring and the sulphonamide functional group are both required and both must be directly attached to the aromatic ring;
3. The aromatic ring must be *para -substituted only.*
4. *T*he sulphonamide nitrogen must be primary or secondary.
5. **R2 is the only possible site that can be varied in sulphonamides.**

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Crystallurea

- Sulfonamides, often cause severe kidney damage by forming crystal in kidney.
- Sulfonamides and their derivatives usually acylated at N-4 position
  because of which water solubility is decreased.
- On the other hand, sulfonamides and their metabolites are excreted entirely in the urine.
- Unfortunately, sulfonamides are not very water soluble, unless pH is
  above pKa, i.e. above pH 10.4.
- pH of urine is 6 and often slightly lowered during bacterial infection and that results all sulfonamides is in the insoluble non-ionized form in the kidney.

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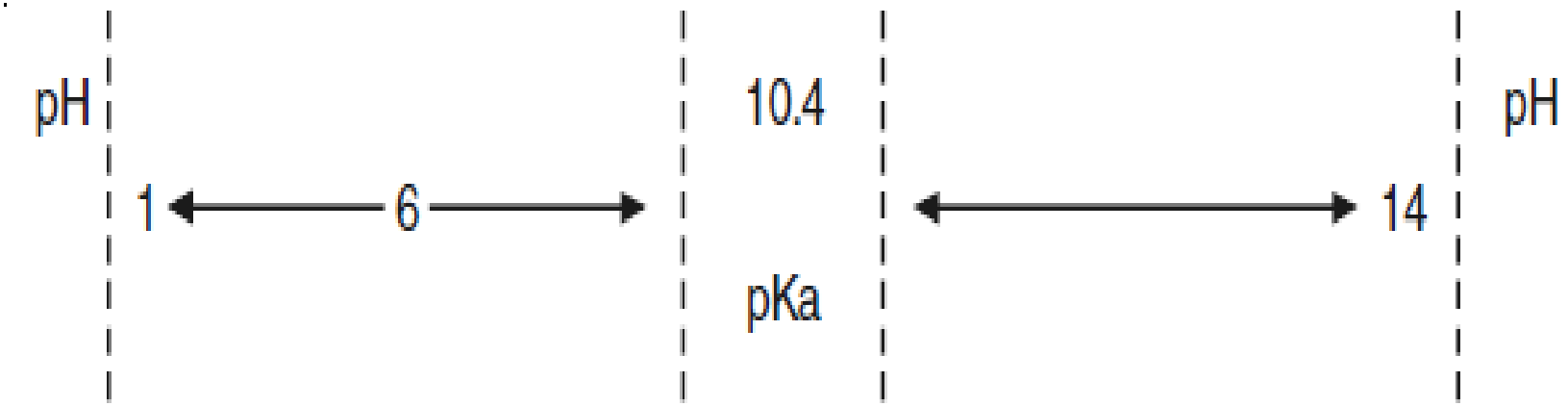

All sulfonamides are poorly water soluble and remain in non-ionized form

Nearly all sulfonamides are in highly water-soluble form

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- More effective sulfonamides are usually less soluble in acidic urine.

- This leads to the deposition of crystalline aggregates of parent drug
and/or its metabolites in the kidney, ureters or bladders.

- Oliguria, crystalluria and other renal complications may thus result.

- Such damagecan result in epithelial irritability, bleeding and/or
complete obstruction of kidneys.

Activate Windows
Go to Settings to activate Windows.

How to avoid Crystallurea

1. Greatly increased urine flow: During the early days of sulfonamides, patients were warned to take force fluids, with plenty of water.

2. Raise the pH of the urine: The closer the pH of the urine to 10.4, the more of the highly water soluble salt form will be present. Thus, sometimes oral sodium bicarbonate was, and occasionally still is, given to raise the urine pH.

3. Make derivatives of the sulfanilamide that have lower pKa values, closer to the pH of the urine.

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MECHANISM OF ACTION

- The para-amino benzoic acid (PABA) is essential in the biosynthesis of various folate enzymes and cofactors.
- The structural similarity of sulfonamides with PABA results into
competitive inhibition
- Sulfonamides inhibit the incorporation of PABA in dihydropteroic acid which is a precursor of folic acid needed for the synthesis of DNA
- This action arrests bacterial growth and cell division.

- Folate coenzymes are biosynthesized from dietary folic acid in humans and other animals. Bacteria and protozoa must biosynthesize them from PABA and pteridine diphosphate

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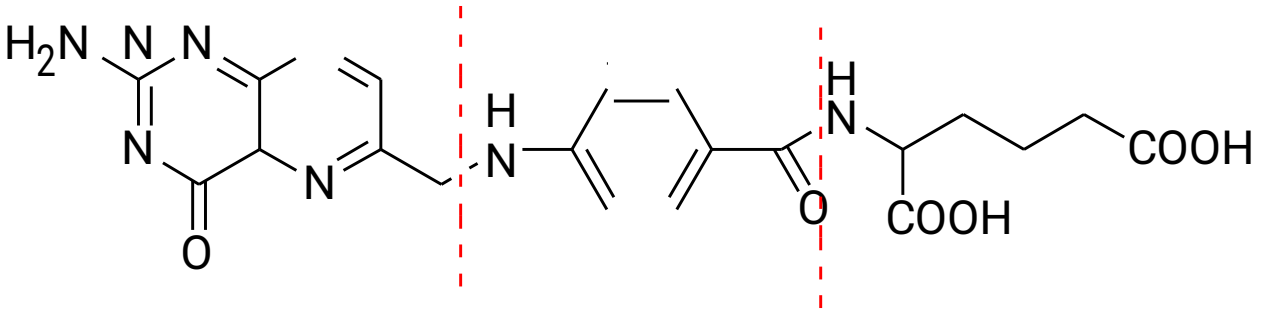
Folic acid



Pteridine Glutamic acid PABA

The structure of folic acid

Folate Raductase

Dihydrofolate Raductase

Folic aicd → Dihydrofolic acid → Tetrahydrofolic acid

Coezyme F

The biosynthesis of DNA/RNA

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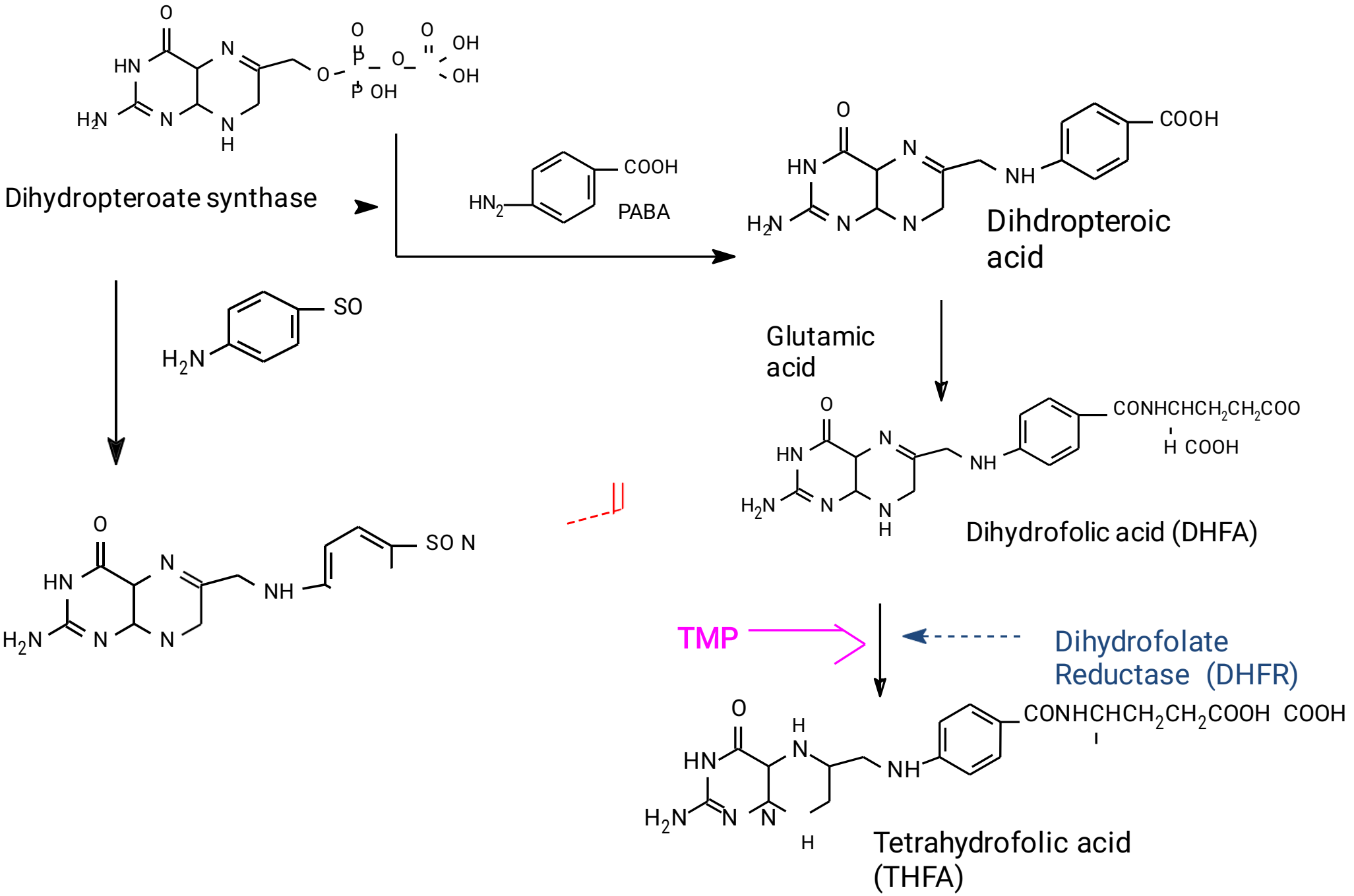

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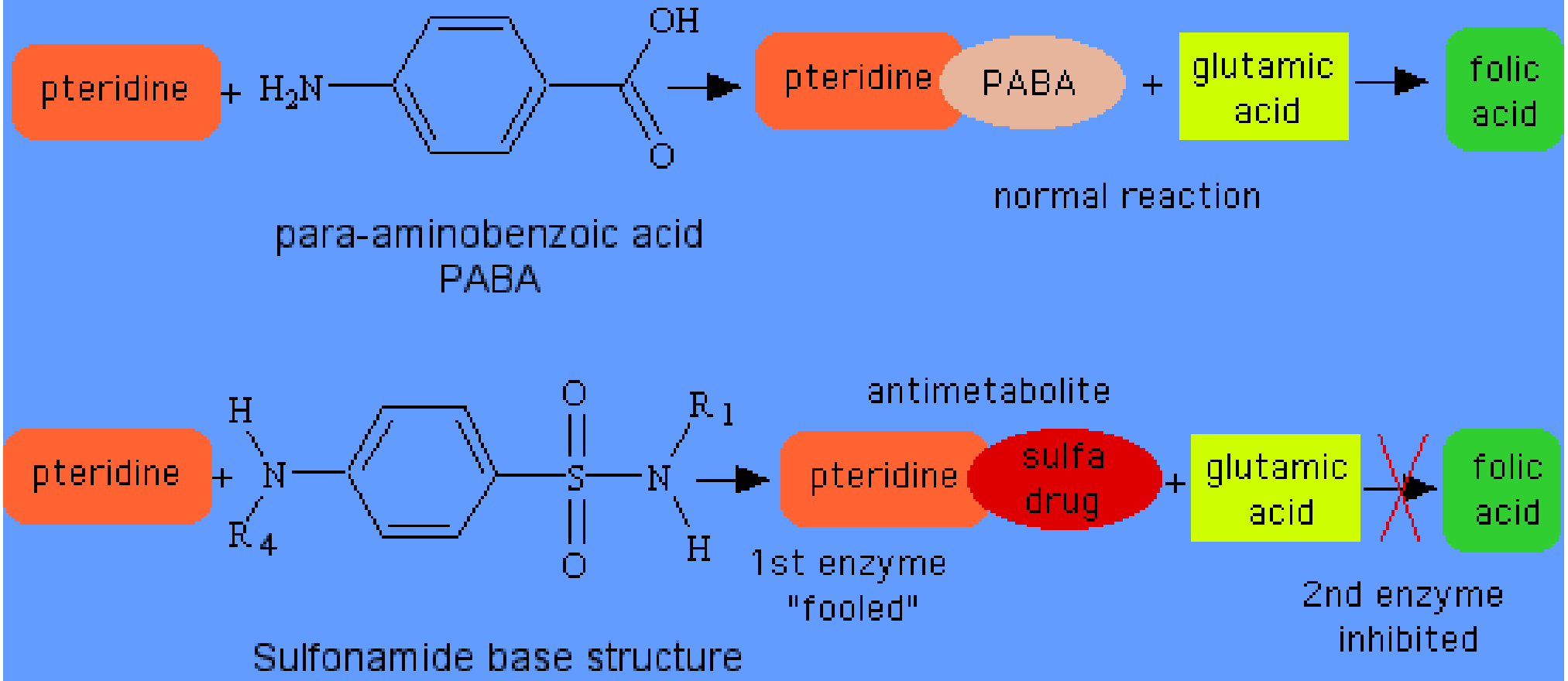
Sulfa Drug - Antimetabolite



C. Ophardt, c. 2003

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The antibacterial action of sulfonamides depends upon.

i. The form (ionized/unionized) in which they are circulated in the body and

ii. The dose of sulfonamide. Greater the concentration of drug in the plasma, greater will be the activity

- PABA has much greater affinity for the bacterial enzyme system. Since sulfonamide activity based on the principle of competitive antagonism it is necessary to maintain always a high concentration of sulpha drug in the tissue to achieve the desired effect. Hence certain drugs having PABA as the basic skeleton (e.g. procaine) will antagonize the action of sulfonamides *in vivo*.

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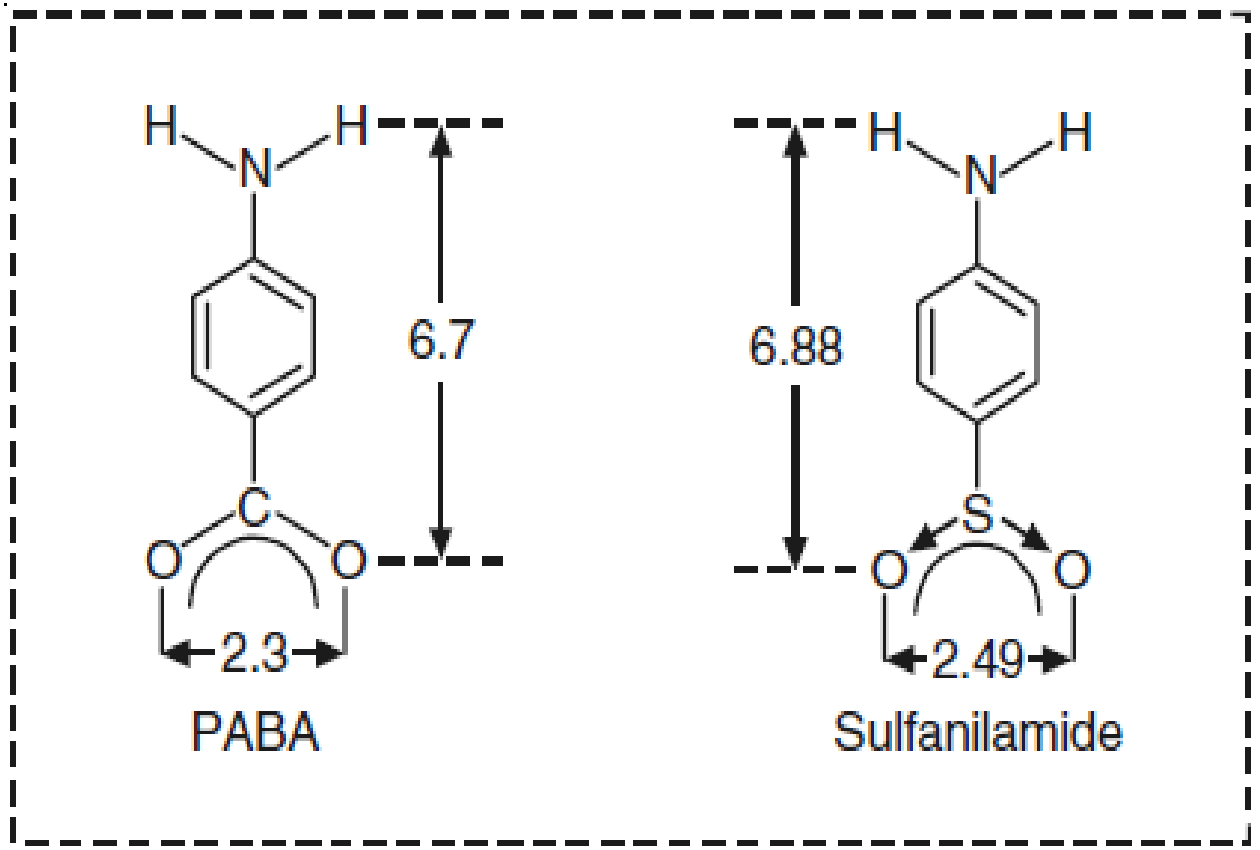

Fig. 57.1: Structural similarities between PABA and sulfanilamide

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TABLE 6.7 Therapy with Sulfonamide Antibacterials

Disease/Infection	Sulfonamides Commonly Used
Relatively Common Use	
Treatment and prophylaxis of *Pneumocystis carinii* pneumonia	Trimethoprim-sulfamethoxazole
Treatment and prophylaxis of cerebral toxoplasmosis	Pyrimethamine-sulfadiazine
First attack of urinary tract infection	Trimethoprim-sulfamethoxazole
Burn therapy: prevention and treatment of bacterial infection	Silver sulfadiazine and mafenide
Conjunctivitis and related superficial ocular infections	Sodium sulfacetamide
Chloroquine-resistant malaria (Chapter 9)	Combinations with quinine, others
	Sulfadoxine
	Sulfalene
Less Common Infections/Diseases	***Drugs of Choice or Alternates***
Nocardiosis	Trimethoprim-sulfamethoxazole
Severe traveler's diarrhea	Trimethoprim-sulfamethoxasole
Meningococcal infections	Sulfonamides, only if proved to be sulf otherwise, penicillin G, ampicillin, or chloramphenicol should be

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TRIMETHOPRIM – SULFONAMIDE COMBINATION (CO-TRIMOXAZOLE)

- The synergistic effect achieved by the combination of trimethoprim and sulfamethoxazole
- Bacteriostatic activity is observed due to the inhibition of two prominent steps in bacterial enzymatic pathway involved in folate synthesis.
- Sulfamethoxazole inhibits utilization of PABA in the formation of dihydrofolate,
- while trimethoprim is a potent and selective inhibitor of the enzyme that catalyzes the conversion of dihydrofolate to tetrahydrofolate.
- Thus a synergistic antimicrobial effect is observed due to the
double sequential effects on the bacterial metabolism.

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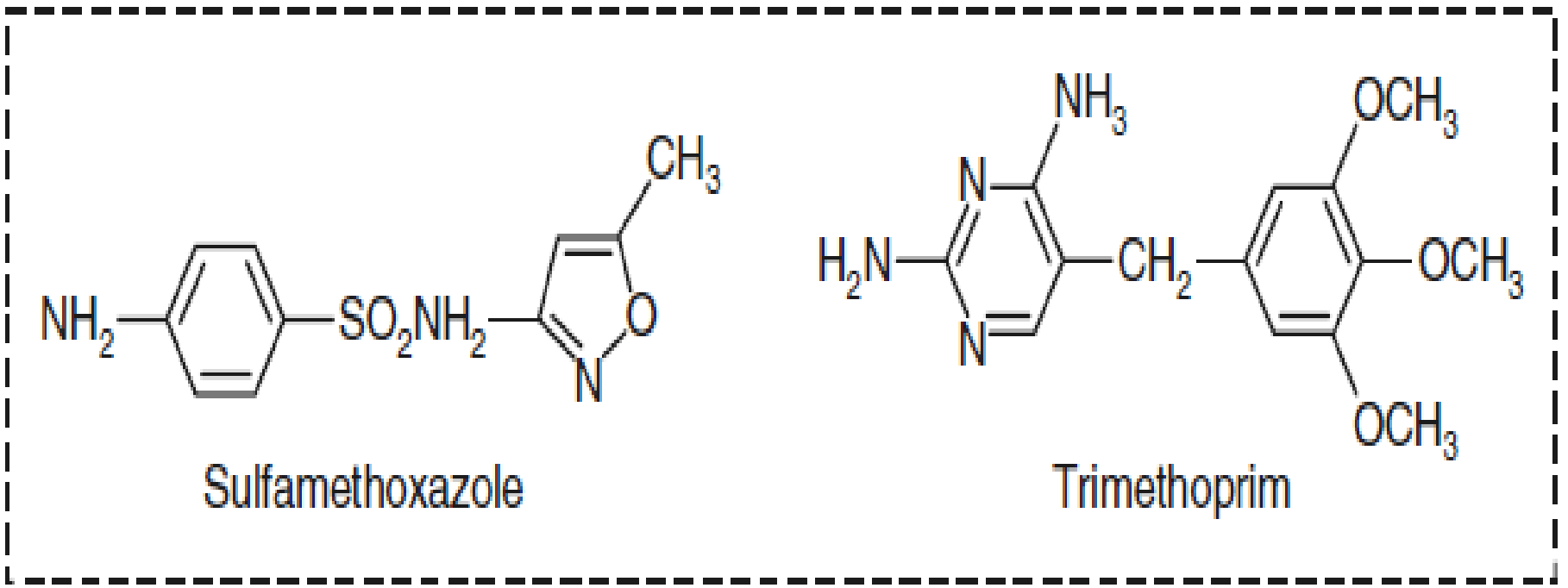
- Trimethoprim

  Originally, introduced as antimalarial agent, trimethoprim has also shown significant bacteriostatic activity. It is effective against most of gram-positive and gram-negative organisms with exceptions of *Pseudomonas aeruginosa and Enterococcus faecalis.*



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- Sulfamethoxazole was selected from systemic sulfonamide class on the basis that it has similar pharmacokinetic features (i.e. rates of absorption, and elimination) to that of trimethoprim.
- It is hence coadministered with trimethoprim in a fixed dose ratio of 5:1.
- This dose ratio yields a fairly constant plasma concentration of sulfamethoxazole – trimethoprim as 20:1 ratio
- which is found to be most effective concentration range to exhibit a synergistic effect against most of the pathogenic microorganisms.

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- Cotrimoxazole is thus effective against most gram positive cocci and gram-negative bacteria.
- *Neisseria meningitidis and gonococci are also susceptible.*
- *It is used in the treatment of* infections of urinary, intestinal and lower respiratory tracts.
- It is also effective in the treatment of chronic bacterial prostatitis, meningococcal infections (infections caused by the bacterium Neisseria meningitidis), gonorrhea

- Neisseria gonorrhoeae; symptoms are painful urination and pain around the urethra),
- nocardiosis (**Nocardiosis** is an infectious disease affecting either the lungs (pulmonary **nocardiosis**) or the whole body (systemic **nocardiosis**) and antibiotic resistant salmonellae and shigellae infections

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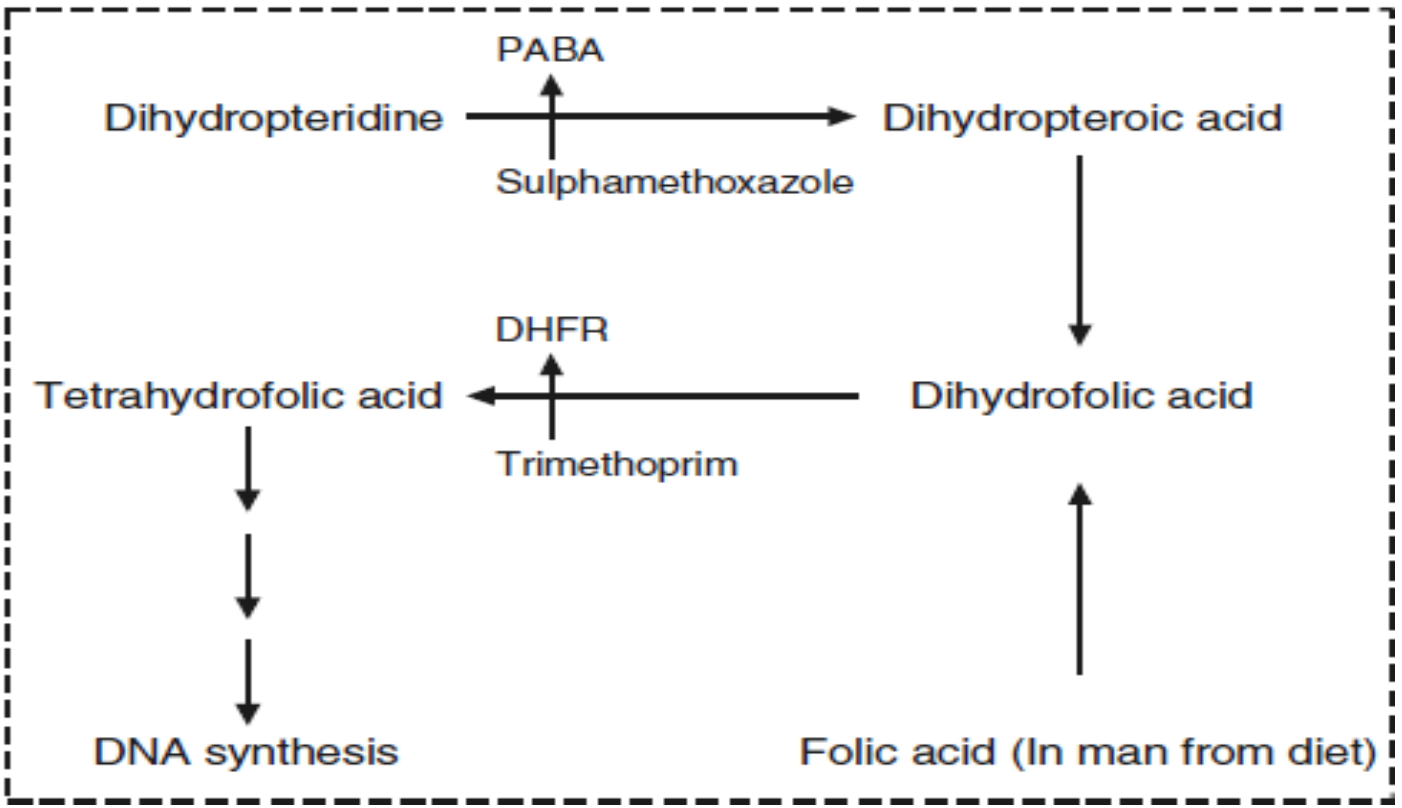
MAO of Combination



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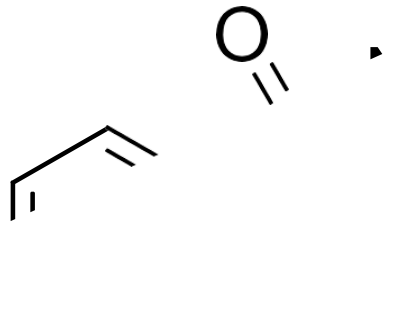
- **Topically Used Sulfonamides for burn therapy**

These agents are extremely useful in decreasing the bacterial colonization of burned skin and thereby preventing burn-wound sepsis. For antibacterial effect, they may also be applied topically to eye, ear, nose.

Examples include sulfapyridine, sulphacetamide, mafenide, silver sulfadiazine, sulfisoxazole and sodium



Mafenide

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Mefenide acetate

- It is a sulfonamide antibacterial agent effective against *Pseudomonas aeruginosa, an organism* that colonizes the burns.
- It is effective in the presence of necrotic tissue
- It is partly absorbed systemically upon topical application and is converted to P-carboxyl benzene sulfonamide.
- Adverse effects include skin rashes, eczema (Generic term for inflammatory conditions of the skin), urticaria (An itchy skin eruption); exfoliative dermatitis (The peeling off dead skin), metabolic acidosis, intense pain at the site of application and chances of super infection with Candida.
- It is available as a cream containing 85 mg/g of mafenide and is applied once or twice a day over burned skin

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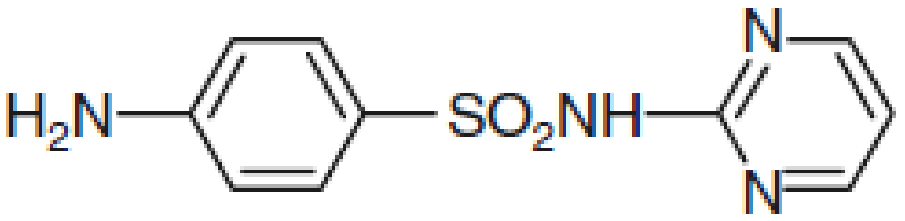
Silver sulfadiazine

- Silver ions are especially effective against gonococci and Pseudomonas species. Silver salts are highly germicidal. Silver sulfadiazine is available in microionized form. It may be used topically in the form of cream (10 mg/g) to inhibit the growth of most bacteria, yeast, some fungi and herpes simplex. It is effectively used to treat extensive burns and burn infections.



Sulfadiazine

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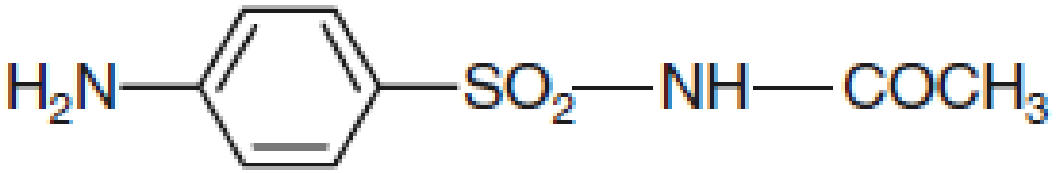
Ophthalmic infections

- Sulfacetamide



Sulfacetamide

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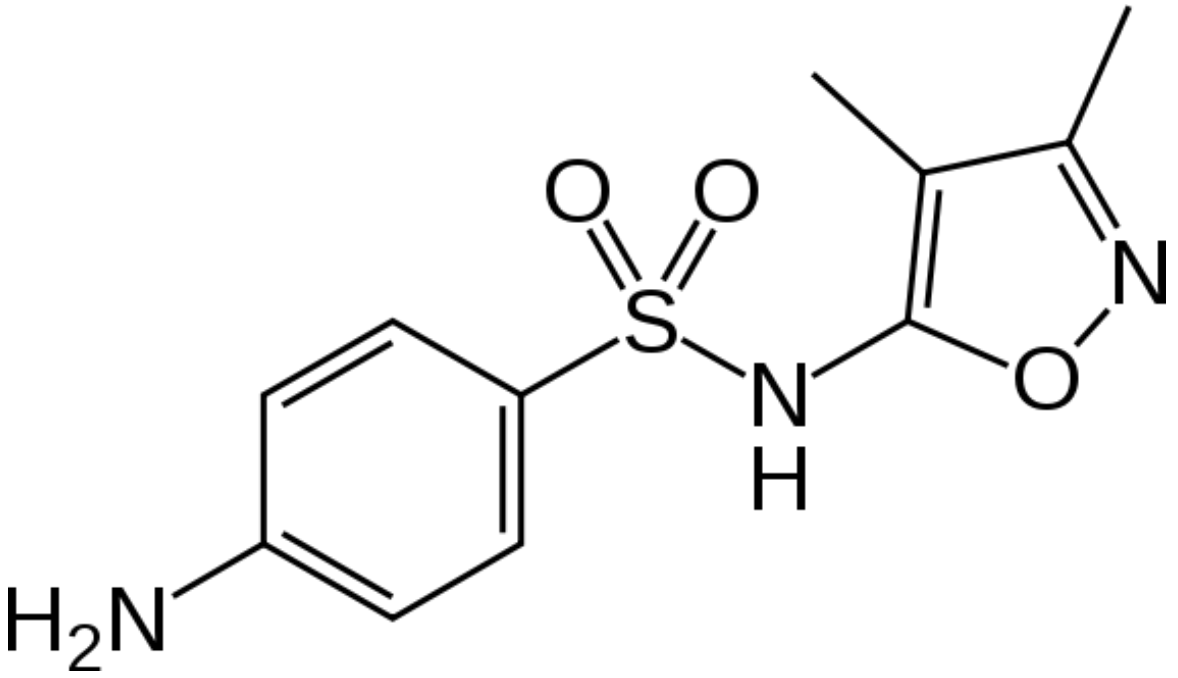
Sulfisoxazole



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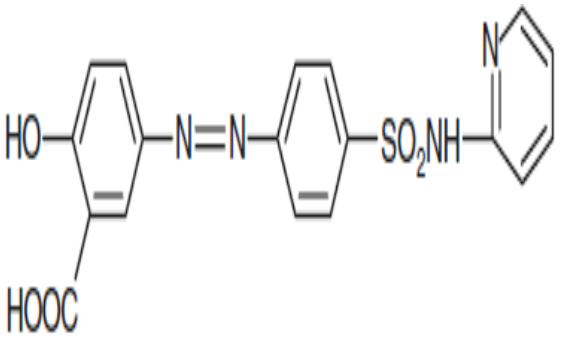
Sulfonamides for Intestinal Infections, Ulcerative Colitis, or Reduction of Bowel Flora

- Each of the sulfonamides in this group is a prodrug which is designed to be poorly absorbable, though usually, in practice, a little is absorbed.
- In the large intestine, the N^4-protecting groups are cleaved, releasing the free sulfonamide antibacterial agent. Today, only one example is used clinically, sulfasalazine.
- Sulfasalazine is broken down in the body to *m-aminosalicylic* acid and **sulfapyridine.** The drug is excreted through the kidneys and is detectable colorimetrically in the urine, producing an orange-yellow color when the urine is alkaline and no color when the urine is acid.



Sulfasalazine

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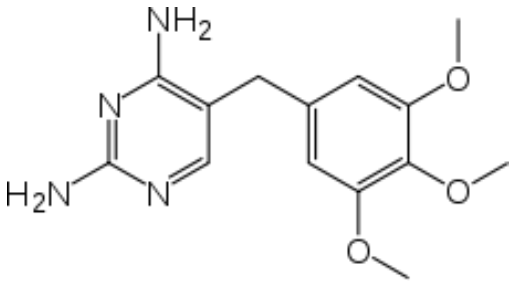
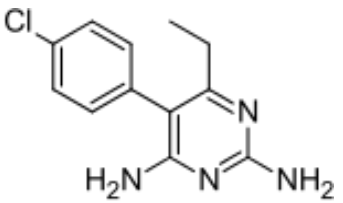
Dihydrofolate Reductase Inhibitors

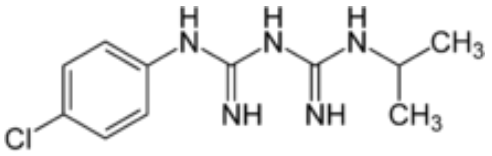
- Dihydrofolate reductase, DHFR, whose role is to regenerate folic acid into its reduced form tetrahydrofolate, is necessary for bacteria, Plasmodia and normal and cancerous human cells. Inhibitors of dihydrofolate reductase have **antibiotic, antimalarial** and **antineoplastic** properties.
- Inhibitors of DHFR must have a sufficient specificity for the DHFR of micro-organisms and that of cancerous cells for not inducing too many adverse effects in humans.



Trimethoprim (antibacterial)



Pyrimethamine (antimalarial)



Proguanil (antimalarial)

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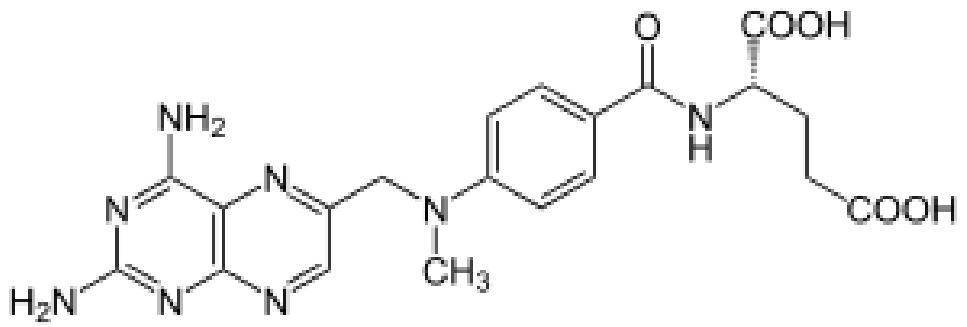

Methotrexate (antineoplastic)

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Sulfadiazine

4-Amino-*N-2-pyrimidinyl-benzenesulfonamide*

Sulfamethizole

4-Amino-*N-(5-methyl-1,3,4-thiadiazole-2yl)benzenesulfonamide*;

Sulfisoxazole

4-Amino-*N-(3,4-dimethyl-5-isoxazolyl)benzenesulfonamide*

Sulfamethoxazole

4-Amino-*N-(5-methyl-3-isoxazolyl)benzenesulfonamide*

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Sulfone
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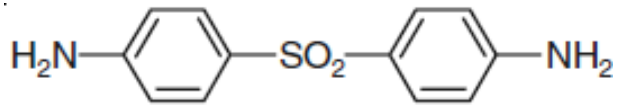
Sulfones are antibacterialagents having same mechanism of action as sulfonamides. They are less effective than sulfonamides

Several sulfones have proved useful in the treatment of leprosy, but among them only

dapsone is clinically used today.



Dapsone

The parent sulfone, dapsone (4,4-sulfonyldianiline), is the prototype for various analogs that have been widely studied. Four variations on this structure have given active compounds:

1. Substitution on both the 4- and 4-amino functions: Disubstituted derivatives are converted to dapson in vivo.

1. Monosubstitution on only one of the amino functions
2. Nuclear substitution on one of the benzenoid rings
3. Replacement of one of the phenyl rings with a heterocyclic ring

Monosubstituted and nuclear-substituted derivatives are believed to act as entire molecules.

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- Dapsone is used widely for all forms of leprosy, often in combination with clofazimine and rifampin. Initial treatment often includes rifampin with dapsone, followed by dapsone alone.
- Dapsone is also the drug of choice for dermatitis herpetiformis and is sometimes used with pyrimethamine for treatment of malaria and with trimethoprim for PCP (**Pneumocystis pneumonia** is a serious infection that causes inflammation and fluid buildup in the lungs).
- Serious side effects can include hemolytic anemia, methemoglobinemia
  (is a disorder characterized by the presence of a higher than normal level of methemoglobin), and toxic hepatic effects.

Thank You...

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