Ch 8C: ANTIFUNGAL AGENTS

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❖ INTRODUCTION

➢ Fungal infections are divided into either superficial or systemic mycoses.

-Superficial mycoses affect the skin, nails, scalp and mucous membranes.

-Systemic mycoses affect internal tissues and organs.

➢ Fungal infections sometimes is due to medical treatments, such as antibiotics, radiotherapy, immunosuppressant drugs and steroids.

➢ Fungal microorganisms are believed to damage the cell membrane, leading to a loss of essential cellular components.

-This may result in inflammation of the infected tissue.

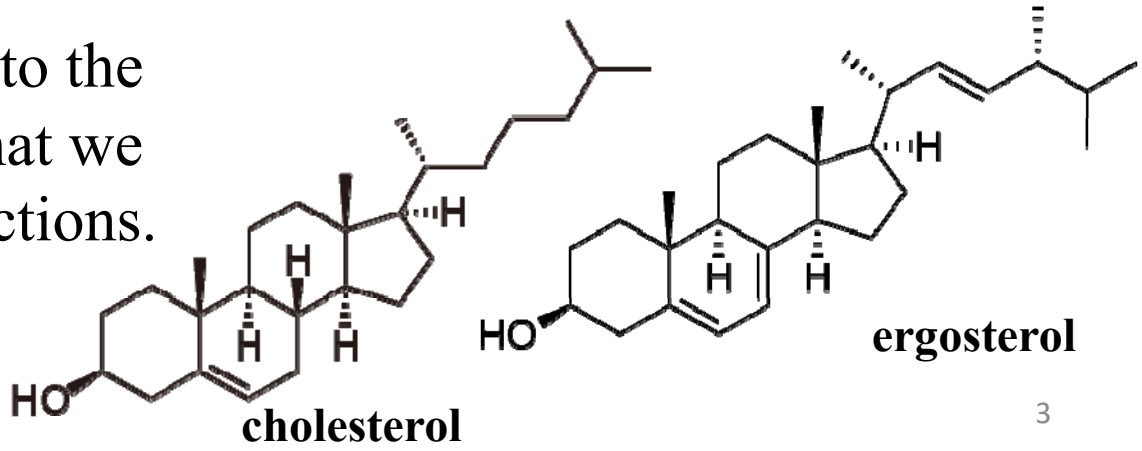
- Antifungal agents can be a fungistatic “action occurs when a drug prevents the fungi reproducing, then it dies out naturally” or fungicidal action “kills the fungi”.

- Fungal microorganisms have chemical structures and biochemistry are similar to those of humans.

- Thus it is more difficult to design drugs that would selectively target these fungi.

- A slight difference exists in the cell membranes. In human cells the cell membrane contains cholesterol but the fungi contains ergosterol.

- this difference accounts to the only source of selectivity that we have in treating fungal infections.



➢ Antifungal Classes

1. Fatty acids

2. Phenols

3. Nucleoside antifungals

4. Antifungal antibiotics

5. Other antifungal antibiotics

6. Allyamines

7. Azoles

1) FATTY ACIDS

- Adults have an acidic fatty substance in and on the skin called **sebum:** It functions as a natural antifungal agent.

- Fatty acids have been used for years with the idea to have a substance similar to sebum.

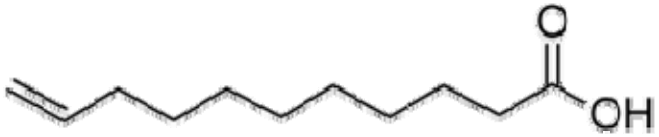
  -When applied to the infected area, the effect of the sebum would be augmented and fungi could be eradicated.

- The application of fatty acids or their salts does in fact have an antifungal effect.

- The higher-molecular-weight fatty acids have the advantage of having lower volatility.

- Salts of fatty acids are also fungicidal and provide nonvolatile forms for topical application

❑ Undecylenic Acid (10-undecenoic acid)



➢ Undecylenic acid is one of the better fatty acids for use as a fungicide.

➢ It can be used in concentrations up to 10% in solutions, ointments, powders and emulsions for topical administration.

➢ The preparation should never be applied to mucous membranes because it is a severe irritant.

➢ Undecylenic acid has been one of the agents traditionally used for athlete's foot (Tinea pedis).

2) PHENOLS & THEIR DERIVATIVES

➢ We saw them previously in the anti-infective agents

3) NUCLEOSIDE ANTIFUNGALS

❑ **Flucytosine**

➢ 5-Fluorocytosine is an orally active antifungal agent with a very narrow spectrum of activity.

➢ It is indicated only for the treatment of serious systemic infections caused by susceptible strains of *Candida* and *Cryptococcus* spp.

- **mechanism of action**

➢ The drug enters the fungal cell by active transport on ATPases that normally transport pyrimidines.

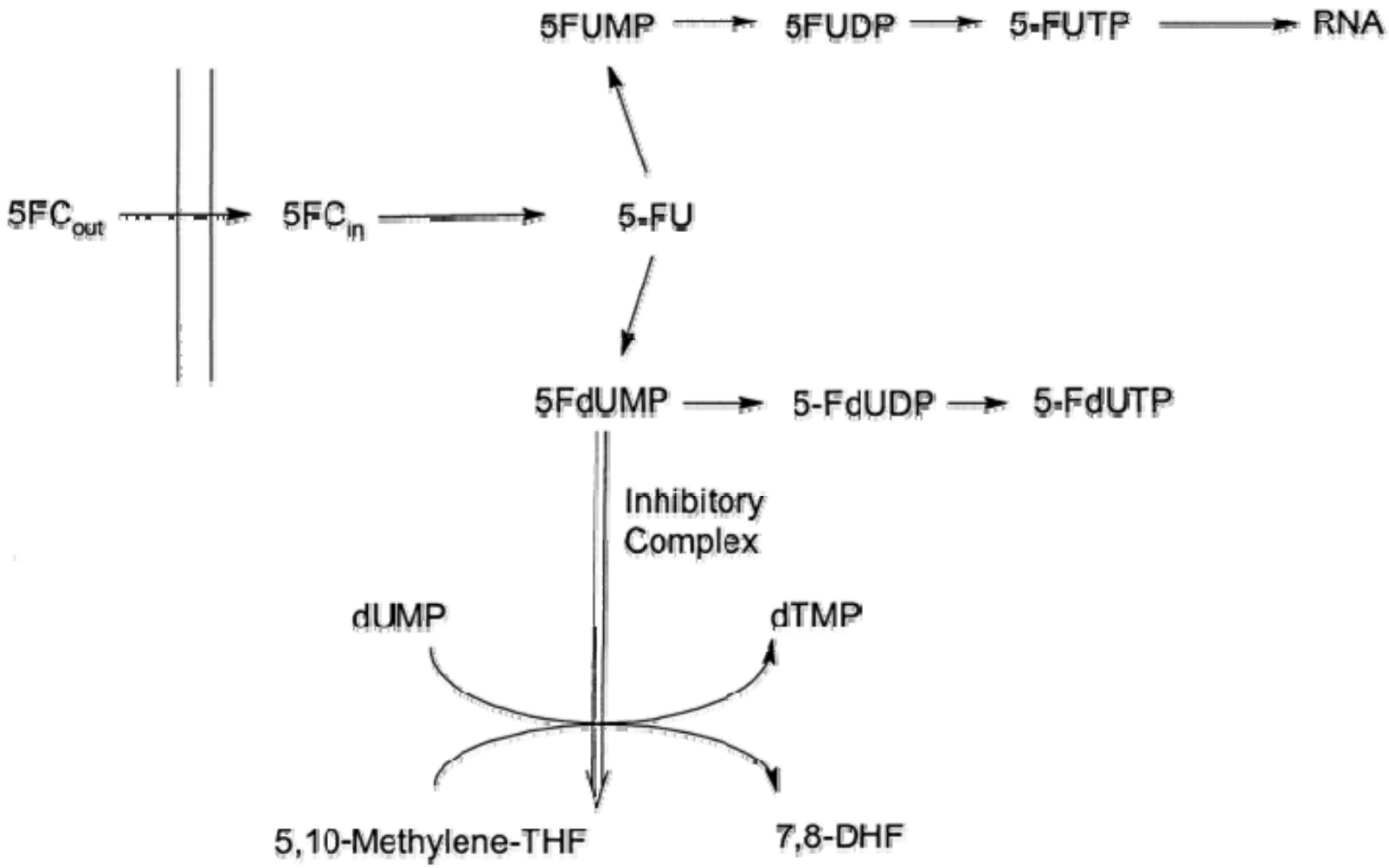
➢ Once inside the cell, 5-fluorocytosine is deaminated in a reaction catalyzed by cytosine deaminase to yield 5-fluorouracil (5-FU). It is the active metabolite of the drug.

➢ 5-Fluorouracil enters into pathways of both ribonucleotide and deoxyribonucleotide synthesis & block the synthesis of RNA & DNA.

➢ Resistance to 5-FC is very common, and it occurs at several levels.

-A main one is the transport the drug into the fungal cell. The transport system simply becomes impermeable to 5-FC.

-The cytosine deaminase step is another point at which resistance occurs.


5FUMP
5FUDP
5-FUTP
RNA
5FC$_{out}$
5FC$_{in}$
5-FU
5FdUMP
5-FdUDP
5-FdUTP
Inhibitory
Complex
dUMP
dTMP
5,10-Methylene-THF
7,8-DHF

4) antifungal antibiotics "polyenes-isolated from *Streptomyces*"

- The antifungal antibiotics make up an important group of antifungal agents. All of the antibiotics are marked by their complexity.

- The compounds are similar, in that they contain a system of conjugated double bonds in macrocyclic lactone rings.

- The clinically useful polyenes fall into two groupings on the basis of the size of the macrolide ring: **1)** The 26-membered–ring polyenes, such as natamycin, form one group, **2)** the 38-membered macrocycles, such as amphotericin B and nystatin, form the other group.

- The antifungal polyenes usually have: **1)** Series of hydroxyl groups & **2)** A glycosidically linked deoxyaminohexose called ***mycosamine***.

- Polyenes are used mainly in topical preparations for superficial fungal infections.

- The use of the polyenes for the treatment of systemic infections is limited by the toxicities of the drugs, their low water solubilities, and their poor chemical stabilities.

- Amphotericin B, the only polyene useful for the treatment of serious systemic infections, must be solubilized with a detergent.

- The number of double bonds in the macrocyclic ring differs: Natamycin the smallest macrocycle has a pentene, Nystatin is a hexene, Amphotericin B is a heptene.

- **MOA**: Because their three-dimensional shape, a barrel-like nonpolar structure capped by a polar group "sugar":
  - They penetrate the fungal cell membrane
  -Act as false membrane components causing membrane disruption
  -Cessation of membrane enzyme activity
  -loss of cellular constituents, especially potassium ions.

❑ Amphotercin B

➢ The drug is fungistatic at low concentrations and fungicidal at high concentrations

➢ Amphotecrin B can be administered parentally using micelle formulations

➢ It binds to the ergosterol found in the cell membranes of fungi to form a transmembrane channel that allows the leakage of the cell contents.

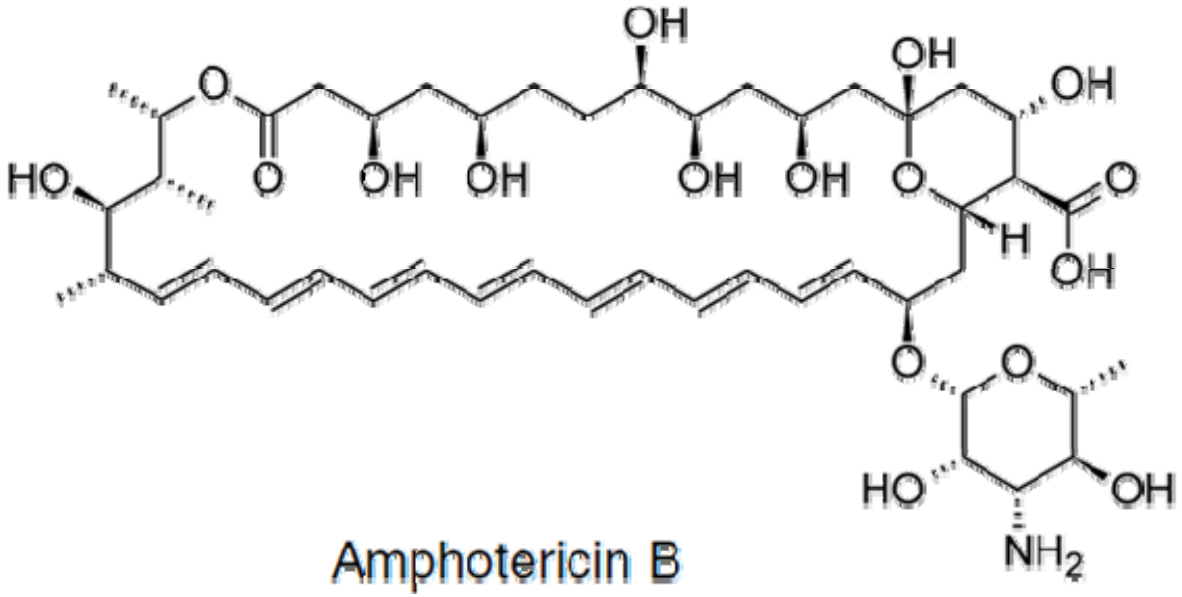
➢ It acts in the same way with the cholesterol found in human cell membranes, which accounts for its toxicity.

➢ The usefulness of amphotericin B is limited by a high prevalence of adverse reactions.

- Nearly 80% of treated with amphotericin B develop nephrotoxicity.

- Fever, headache, anorexia, gastrointestinal distress, and muscle and joint pain are common.

- Pain at the site of the injection. The drug must never be administered intramuscularly.



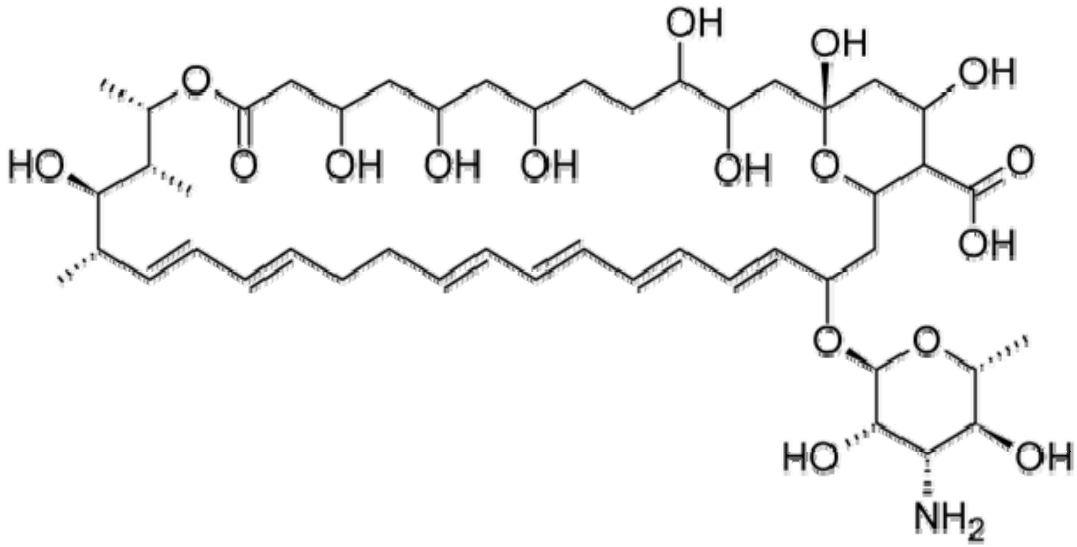
Amphotericin B

❑ Nystatin

➢ Nystatin is a polyene antibiotic was first isolated in 1951 from a strain of the *Streptomyces noursi*.

➢ It is too toxic to be administered parenterally. It is used only as a topical agent.

➢ Nystatin is a valuable agent for the treatment of local infections caused by *Candida* species.



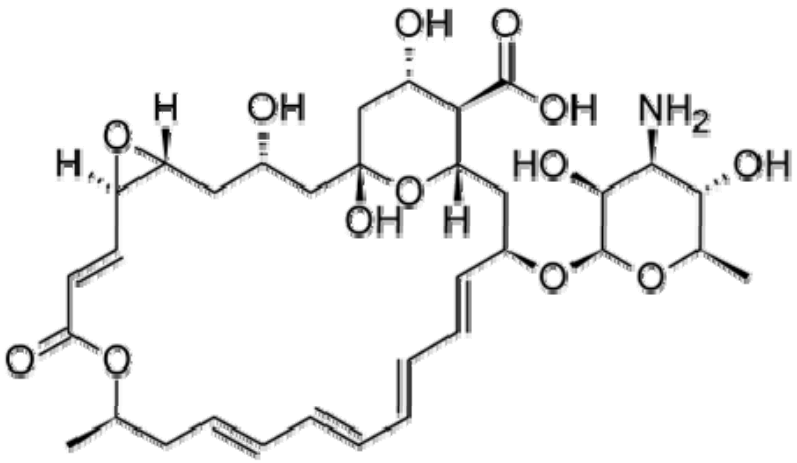
Nystatin

❑ Natamycin

➢ Natamycin is a polyene antibiotic obtained from cultures of *Streptomyces natalensis*.

➢ The natamycin structure consists of a 26-membered lactone ring containing a tetraene chromophore.

➢ The **MOA** of the smaller polyenes differs from that of amphotericin B and nystatin. The 26-membered–ring polyenes cause both potassium ion leakage and cell lysis at the **same concentration**, whereas the 38-membered–ring polyenes cause potassium leakage at low, fungistatic concentrations and cell lysis at high, fungicidal concentrations



5) Other Antifungal Antibiotics

❑ Griseofulvin

➢ Griseofulvin was first reported in 1939 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.

➢ After systemic absorption, griseofulvin is carried by the systemic circulation and capillary beds to the skin, nails, and hair follicles, where it concentrates in keratin precursor cells, which are gradually exfoliated and replaced by healthy tissue.

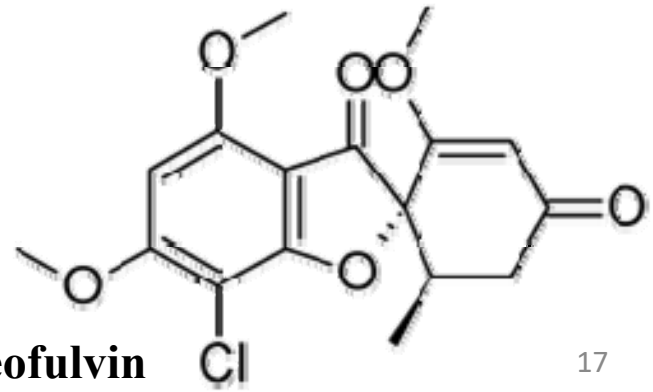
➢ Griseofulvin is a fungistatic agent. Treatment must be continued until all of the infected tissue has been exfoliated, because old tissues will still support and harbor fungal growth. Therapy in slow growing tissues, such as the nails, must be continued for several months.

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

➢ Griseofulvin is a mitotic spindle poison. It rapidly arrests cell division in metaphase.

➢ It causes a rapid, reversible dissolution of the mitotic spindle apparatus, probably by binding with the tubulin dimer that is required for microtubule assembly.

➢ The selective toxicity to fungi is probably because of the propensity of the drug to concentrate in tissues rich in keratin, where dermatophytes typically establish infections.



Griseofulvin

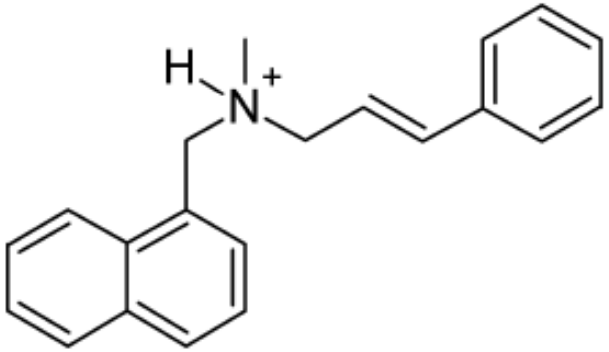
6) ALLYLAMINES AND RELATED COMPOUNDS

- They are weak bases, the allylamine group is essential for activity.

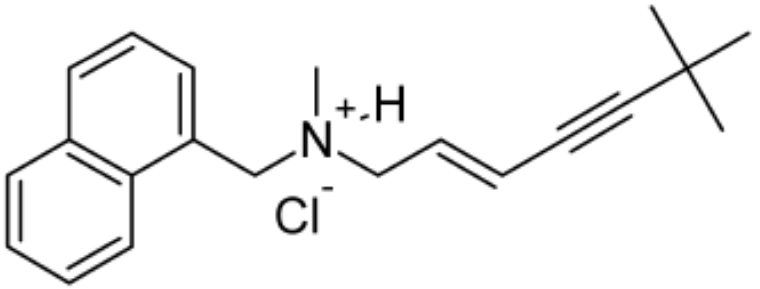
- Allylamines are believed to act by inhibiting squalene epoxidase.
  -The enzyme for the squalene epoxidation stage in the biosynthesis of ergosterol in the fungal membrane.
  -This leads to an increase in squalene concentration in the membrane
  -This leads to loss of membrane integrity which allows loss of cell contents to occur.

- Allylamines do not significantly inhibit the mammalian cholesterol biosynthesis.

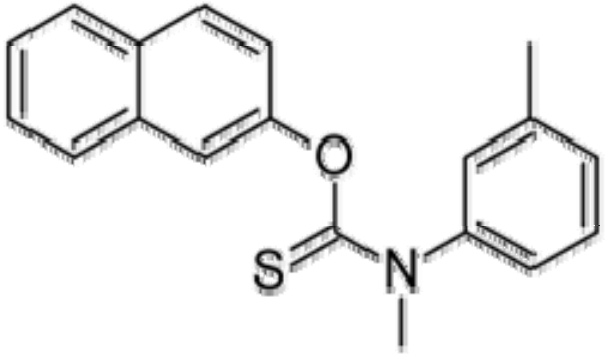
- Tolnaftate, although it is not an allylamine but it act in a similar fashion.



Naftifine



Terbinafine "lamisil®"
More potent than naftifine



Tolnaftate

7) AZOLE ANTIFUNGAL AGENTS

- The first members of the class were highly substituted imidazoles, such as clotrimazole and miconazole.

- Structure–activity studies revealed that the imidazole ring could be replaced with a bioisosteric 1,2,4-triazole ring without adversely affecting the antifungal properties of the molecule.

- Hence, the more generic term azoles refers to this class of antifungal agents.

- Depending on the azole drug used, one can treat infections ranging from simple dermatophytoses to life-threatening, deep systemic fungal infections.

- They exhibit fungistatic activity at nanomolar concentration & fungicidal activity at higher micromolar concentrations.

❖ Mechanism of action

➢ The **fungicidal effect** is clearly associated with damage to the cell membrane, with the loss of essential cellular components such as potassium ions and amino acids.

➢ The **fungistatic effect** associated with inhibition of membrane-bound enzymes. A cytochrome P450-class enzyme, lanosterol 14-demethylase, is the likely target for the azoles.

➢ P450 possesses a heme moiety as part of its structure, and the basic electron pairs of the azole rings can occupy a binding site on P450, preventing the enzyme from turning over.

➢ The function of lanosterol 14-demethylase is to oxidatively remove a methyl group from lanosterol during ergosterol biosynthesis.

- Lanosterol 14-demethylase is also required for mammalian biosynthesis of cholesterol, and the azoles are known to inhibit cholesterol biosynthesis.

- In general, higher concentrations of the azoles are needed to inhibit the mammalian enzyme. This provides selectivity for antifungal action.

- The 1,2,4-triazoles appear to cause a lower incidence of endocrine effects and hepatotoxicity than the corresponding imidazoles, possibly because of a lower affinity for the mammalian cytochrome P450 enzymes involved.

❖ Structure-activity relationship

➢ The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKa of 6.5–6.8) bonded by a nitrogen–carbon linkage to the rest of the structure.

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

➢ The most potent antifungal azoles possess two or three aromatic rings, 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, although functional groups such as sulfonic acids have been shown to do the same.

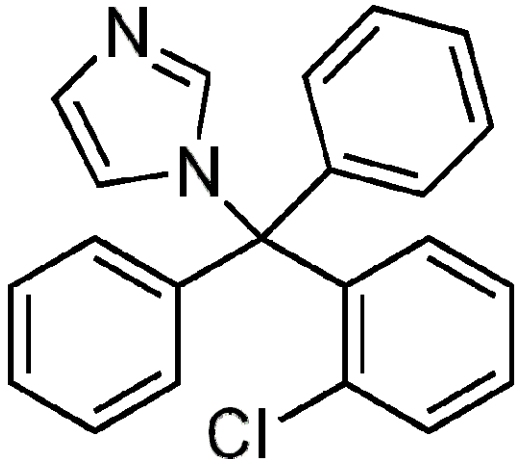
- Substitution at other positions of the ring yields inactive compounds.

- Presumably, the large nonpolar portion of these molecules mimics the nonpolar steroidal part of the substrate for lanosterol 14-demethylase, in shape and size.

- The nonpolar functionality confers high lipophilicity to the antifungal azoles. The free bases are typically insoluble in water

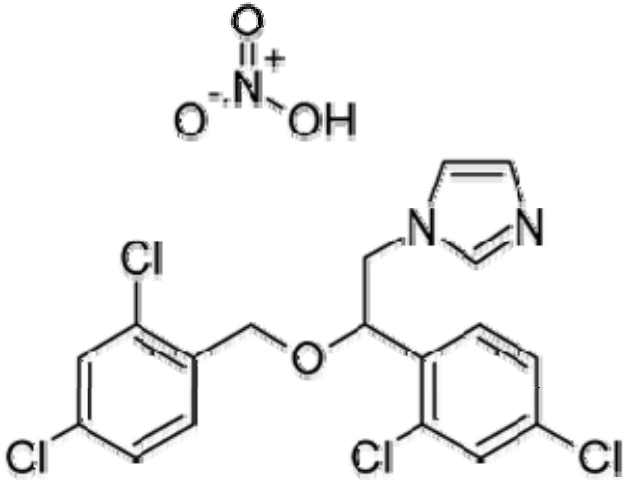
- Fluconazole, which possesses two polar triazole moieties, is an exception, in that it is sufficiently water soluble to be injected intravenously as a solution of the free base.

❑ Clotrimazole



➢ It is a broad-spectrum antifungal drug that is used topically for the treatment of tinea infections and candidiasis.

❑ Miconazole Nitrate



➢ It is a weak base with a pKa of 6.65. The nitric acid salt occurs as white crystals that are sparingly soluble in water and most organic solvents.

➢ it is intended for the treatment of serious systemic fungal infections

❑ Ketoconazole

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

➢ It is a weakly basic compound that occurs as a white crystalline solid that is very slightly soluble in water.

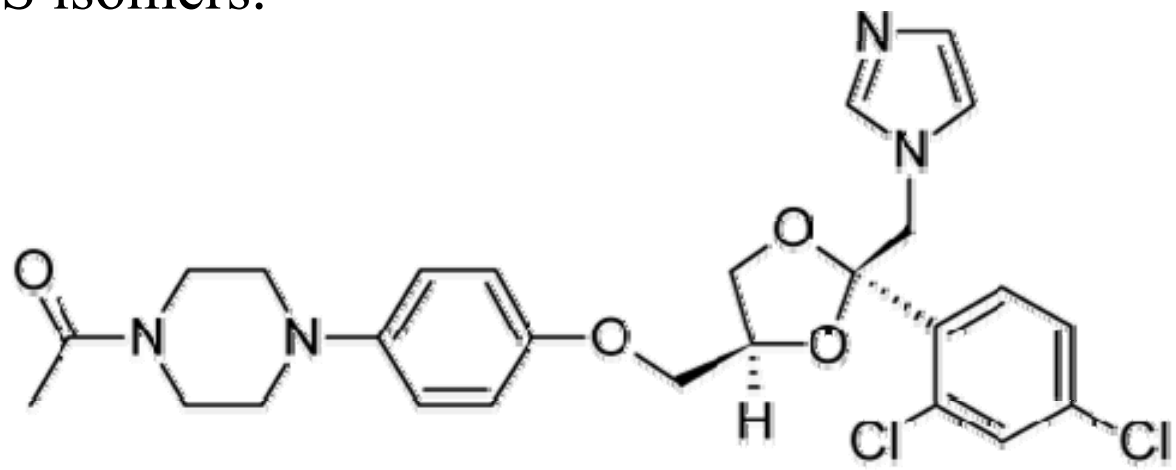
➢ Hepatotoxicity, primarily of the hepatocellular type, is the most serious adverse effect of ketoconazole. Ketoconazole is known to inhibit cholesterol biosynthesis.

➢ High doses have also been reported to lower testosterone and corticosterone levels, reflecting the inhibition of cytochrome P450-requiring enzymes involved in human steroid hormone biosynthesis.

➢Cytochrome P450 oxidases responsible for the metabolism of various drugs may also be inhibited by ketoconazole to cause enhanced effects.

➢ Thus, ketoconazole causes clinically significant increases in plasma concentrations of cyclosporine, phenytoin, and terfenadine. It may also enhance responses to sulfonylurea hypoglycemic and coumarin anticoagulant drugs.

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



❑ Itraconazole

➢ It is a unique member of the azole class that contains two triazole moieties in its structure, a weakly basic 1,2,4-triazole and a nonbasic 1,2,4-triazol-3-one.

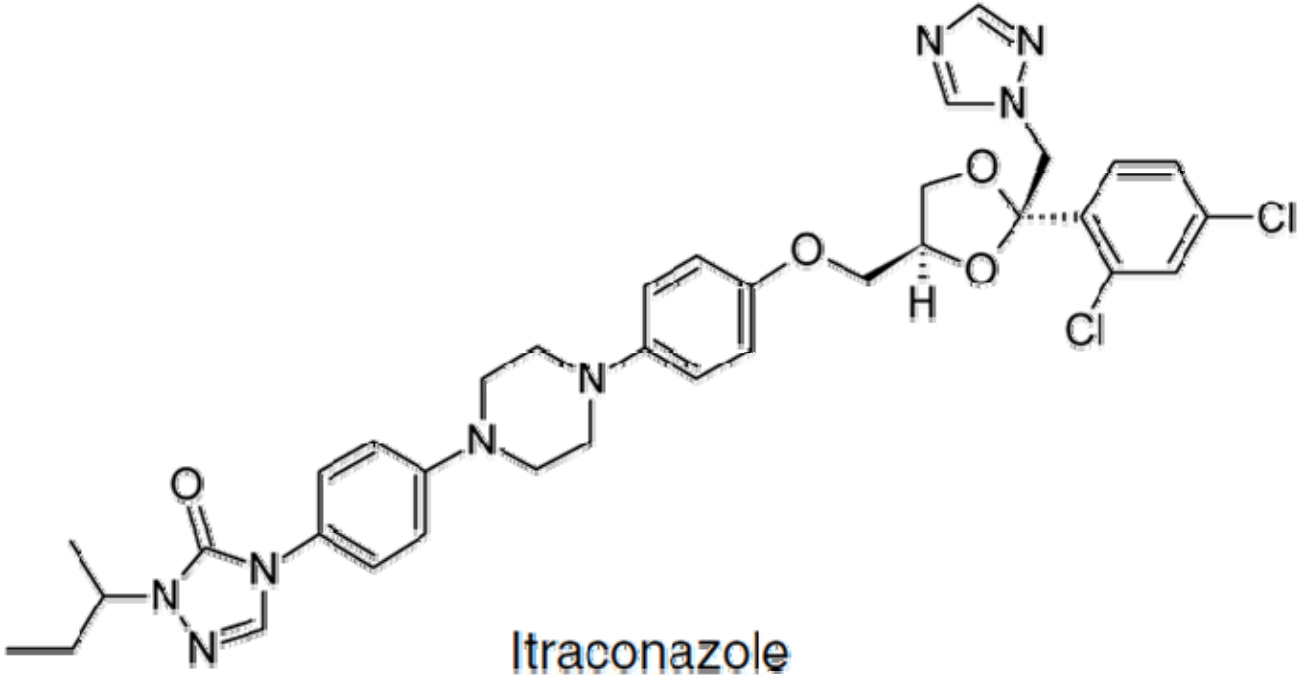
➢Itraconazole is an orally active, broad-spectrum antifungal agent that has become an important alternative to ketoconazole.

➢ An acidic environment is required for optimum solubilization and oral absorption of itraconazole.

➢ Drugs such as H_2-histamine antagonists and antacids, which reduce stomach acidity, reduce its gastrointestinal absorption.

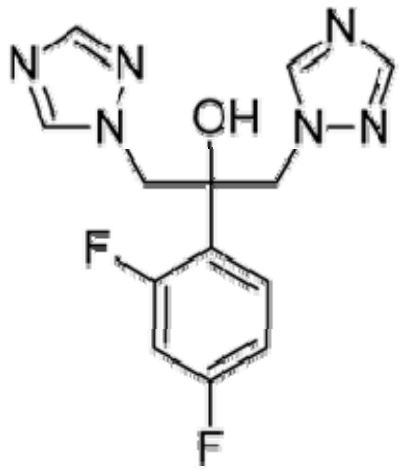
➢ itraconazole is more effective and better tolerated than is ketoconazole. Unlike ketoconazole, it is not hepatotoxic and does not cause adrenal or testicular suppression in recommended therapeutic doses.

➢ Nonetheless, itraconazole can inhibit cytochrome P450 oxidases involved in drug metabolism and is known to increase plasma levels of the antihistaminic drugs terfenadine and astemizole.



Itraconazole

❑ Fluconazole



➢ the presence of two weakly basic triazole rings in the molecule confers sufficient aqueous solubility to balance the lipophilicity of the 2,4-difluorophenyl group.

➢ The oral absorption of fluconazole, in contrast to the oral absorption of ketoconazole or itraconazole, is not affected by alteration in gastrointestinal acidity or the presence of food.

➢ Fluconazole has a relatively long elimination half-life, ranging from 27 to 34 hours.

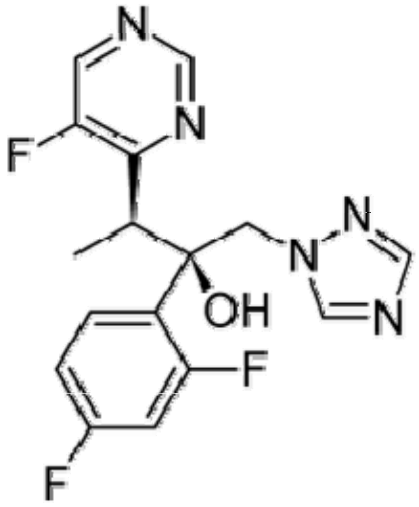
➢ Inhibition of cytochrome P450 oxidases by fluconazole can give rise to clinically significant interactions involving increased plasma levels of cyclosporine, phenytoin, and the oral hypoglycemic drugs (tolbutamide, glipizide, and glyburide).

➢ It is not appear to interfere with corticosteroid or androgen biosynthesis in dosages used to treat systemic fungal infections.

➢ Because of its efficient penetration into CSF, fluconazole is an agent of choice for the treatment of cryptococcal meningitis and for prophylaxis against cryptococcosis in AIDS patients.

❑ **voriconazole**

➢ It is a new azole, has potent activity against a broad variety of fungi, including the clinically important pathogens and used against some of the newer and rarer fungal pathogens.



Topic 8D: Antiprotozoal Agents

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- Protozoal diseases are highly prevalent in tropical third World countries.

- Protozoal diseases include: malaria, amebiasis, Giardiasis, trichomoniasis, toxoplasmosis, Leishmaniasis and trypanosomiasis

- Amebiasis: is caused by *Entamoeba Histolytica*, can invade the wall of the colon or other parts of the body (e.g., liver, lungs, skin).

- Protozoal species that colonize the intestinal tract and cause enteritis and diarrhea include: *Giardia lamblia* & *Crvptosporidium* spp.

- Trichomoniasis: is venereal "تناسلي" disease caused by the flagellated protozoan *Trichomonas vaginalis*, is common throughout the world and cause serious physical discomfort.

➢ *Toxoplasma gondii* is an obligate intracellular protozoan can cause blindness in neonates.

➢ The lymphatic system, skeletal muscles, heart, brain, eye, and placenta may be affected. It is increasingly prevalent in association with HIV infection.

➢ Leishmaniasis is a chronic tropical disease caused by various flagellate protozoa of the genus *Leishmania*.

➢ Various forms of trypanosomiasis chronic tropical diseases caused by pathogenic members of the family *Trypanosomidea*.

- occur both in humans and in livestock.

-The principal disease in humans, sleeping sickness (African sleeping sickness).

❑ Metronidazole "Flagyl®"

➢ 2-Methyl-5-nitroimidazole-1-ethanol is the most useful of a group of antiprotozoal nitroimidazole derivatives that have been synthesized throughout the world.

➢ Metronidazole was first marketed for the topical treatment of T. vaginalis vaginitis.

➢ The drug possesses useful amebicidal activity and is, in fact, effective against both intestinal and hepatic amebiasis.

➢ It has also been found of use in the treatment of such other protozoal diseases as giardiasis and balantidiasis.

➢ More recently metronidazole has been found to efficacy against obligate anaerobic bacteria.

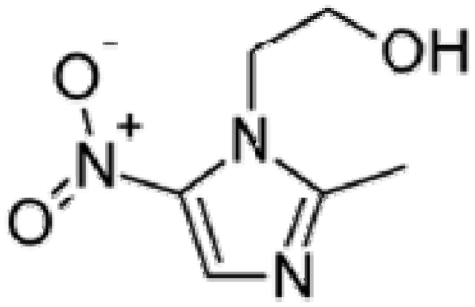
➢ The suggested mechanism:

• the generation of a reactive intermediate in the microbe reduction of the 5-nitro group of metronidazole covalently binds to the DNA of the microorganism, triggering the lethal effect.

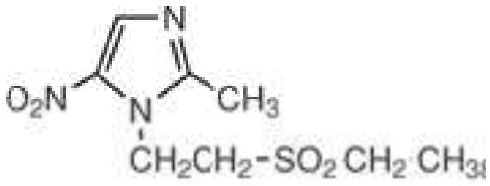
• Potential reactive intermediates include the nitroxide, nitroso, hydroxylamine, and amine.

➢ The 2-hydroxy metabolite is active, other metabolites other are inactive.

➢ Metronidazole can be given orally or parentally.



❑ Tinidazole (Fasigyn®, Tinogyn®):



Tinidazole

- It is used in the treatment of amebiasis, giardiasis, and trichomoniasis.
- Basically, tinidazole appears to mimic the actions of metronidazole.
- There are reports that it is effective against some protozoa which are resistant to metronidazole.

❑ Melarsoprol

➢ It is prepared by reduction of a corresponding pentavalent arsanilate to the trivalent arsenoxide.

➢ It has become the drug of choice for the treatment of the later stages of both forms of African trypanosomiasis.

➢ Melarsoprol has the advantage of excellent penetration into the CNS and, therefore, is effective against meningoencephalitic forms.

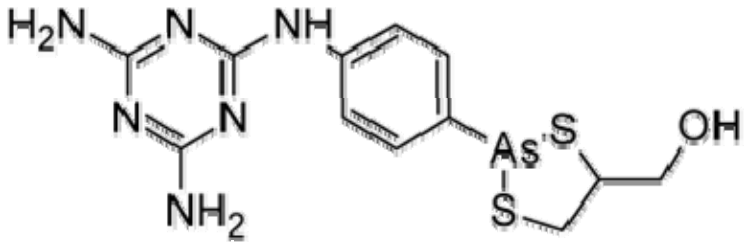
➢ Trivalent arsenicals tend to be more toxic to the host (as well as the parasites) than the corresponding pentavalent compounds.

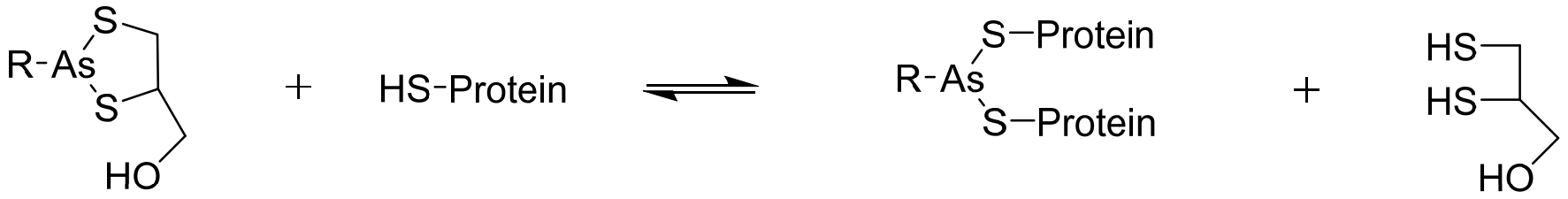
➢ The bonding of arsenic with sulfur atoms tends to reduce host toxicity, increase chemical stability (to oxidation), and improve distribution of the compound to the arsenoxide.

➢ It is known that trivalent arsenic reacts rapidly and reversibly with sulfhydryl-containing proteins

➢ The enzyme with which melarsoprol reacts is an enzyme involved in glycolysis.

➢ Blockage of glycolysis would be expected to lead to loss of motility and cell lysis.



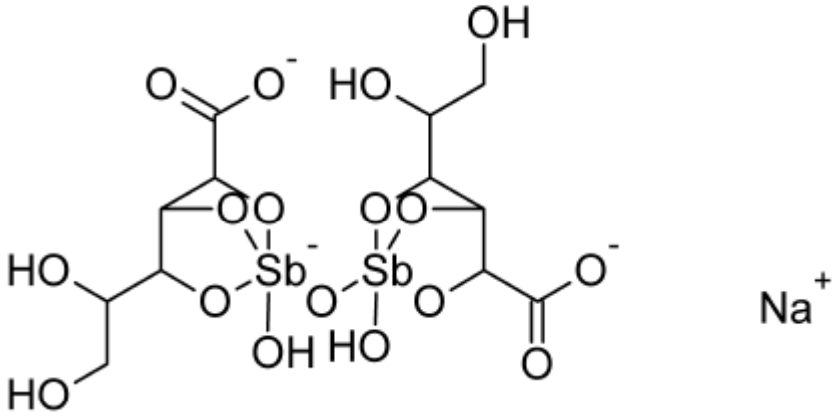


❑ Sodium Stibogluconate “Pentostam®”

➢ It is a pentavalent antimonial compound intended primarily for the treatment of various forms of leishmaniasis “DOC”.

➢ Pentavalent antimony compounds: They inhibit the bioenergetic processes in the pathogen, and they inhibit the catabolism of glucose. This in turn results in inhibition ATP formation.

➢ It is available for administration by injection



Topic 8E: Anthelmentics

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➢ Anthelmentics are drugs that have the capability of ridding the body of parasitic worms or helminths.

➢ The prevalence of human helminthic infestations is widespread throughout the globe

➢ It represents a major world health problem, particularly in Third World countries.

➢ Helminths that infect human hosts are divided into two categories:

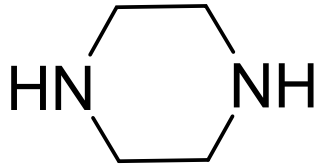
1) Platyhelminths (flatworms):

- include Cestode (tapeworms)
- and Trematode (flukes or schistosomes).

2) Nemathelminthes (The nematode) (roundworm), These worms are cylindrical in shape it includes:

- Hookworm (الدودة الشصية)
- Pinworm :(الشعرية) also known as threadworm
- Whipworm :(دودة سوطية)
- Ascaris spp.

❑ Piperazine



➢ Piperazine is still used as an anthelmintic for the treatment of pinworm and roundworm (Ascaris lumbricoides) infestations.

➢ Piperazine blocks the response of the ascaris muscle to acetylcholine, causing flaccid paralysis in the worm, which is dislodged from the intestinal wall and expelled in the feces.

❑ Pyrantel Pamoate

➢ It is a depolarizing neuromuscular blocking agent that causes spastic paralysis in susceptible helminths.

➢ It is used in the treatment of infestations caused by pinworms and roundworms (ascariasis).

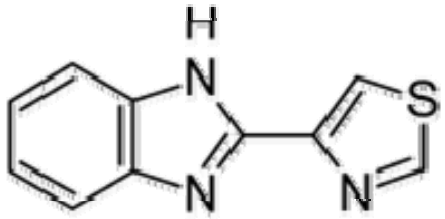
➢ Because its action opposes that of piperazine, the two anthelmintics should not be used together.

❑ Thiabendazole

➢ Benzimidazole anthelmintic drugs such as thiabendazole and mebendazole arrest nematode cell division in metaphase by interfering with microtubule assembly.

➢ They exhibit a high affinity for tubulin, the precursor protein for microtubule synthesis.

➢Thiabendazole has broad-spectrum anthelmintic activity.



❑ Mebendazole “Vermox®”

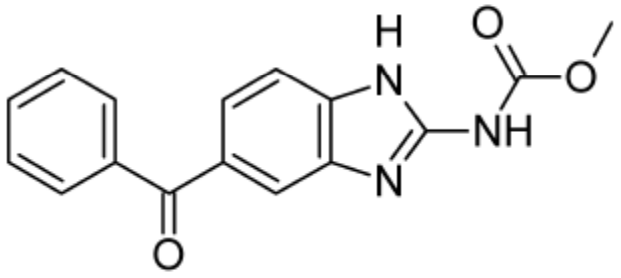
➢ It is a broad-spectrum anthelmintic that is effective against various nematode infestations.

➢ Mebendazole irreversibly blocks glucose uptake in susceptible helminths, thereby depleting glycogen stored in the parasite. It apparently does not affect glucose metabolism in the host.

➢ It also inhibits cell division in nematodes.

➢ Adverse reactions are uncommon and usually consist of abdominal discomfort.

➢It is teratogenic in laboratory animals and, therefore, should not be given during pregnancy.

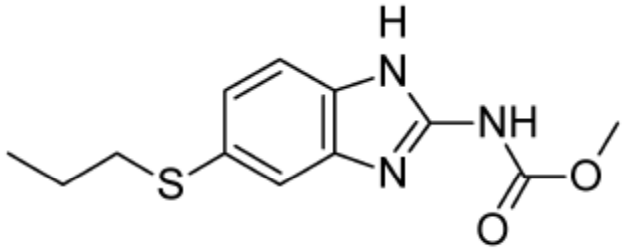


❑ Albendazole

➢ Albendazole is widely used throughout the world for the treatment of intestinal nematode infection.

➢ The oral absorption of albendazole is enhanced by a fatty meal.

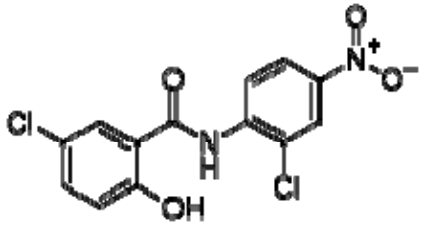
➢ The drug undergoes rapid and extensive first-pass metabolism to the sulfoxide, which is the active form in plasma. The elimination half-life of the sulfoxide ranges from 10 to 15 hours

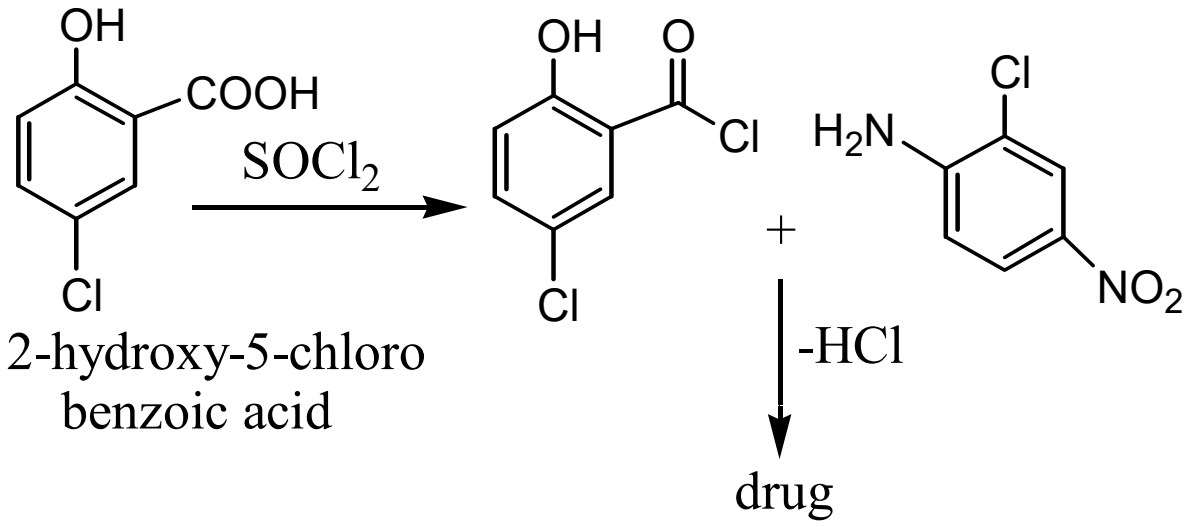


❑ Other Anthelmitics:

Niclosamide (Yomesan®)

- Niclosamide is a chlorinated salicylanilide





- It is specially effective against cestodes that infect humans.
- Niclosamide is used to treat tapeworms
  - It is not effective against pinworms or roundworms.
  - It works by blocking the uptake of sugar by the worm

Topic 8F: ANTI MALARIAL AGENTS

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Department of pharmacy
Faculty of Medicine & Health sciences

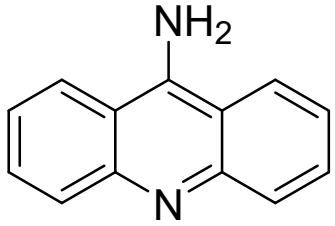
➢ Malaria is a mosquito-borne infectious disease of humans and other animals caused by genus *Plasmodium*.

➢ The disease results from the multiplication of Plasmodium parasites within red blood cells, causing symptoms:

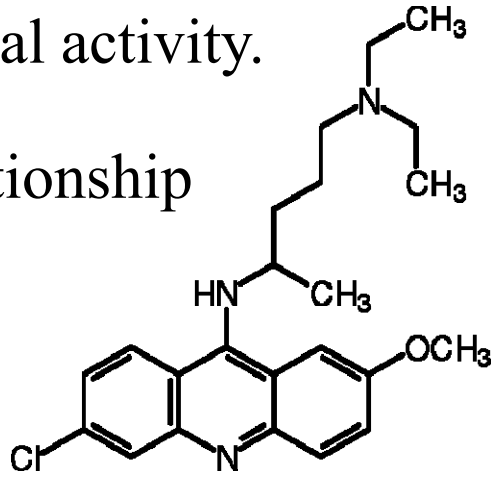
- including fever and headache,
- in severe cases progressing to coma or death.

➢ Quinine, was the first known anti malarial. The use of quinine in Europe began in the seventeenth century after being isolated from the cinchona bark.

➢ 9-aminoacridine was synthesized in 1934



➢ quinacrine, was found to possess weak antimalarial activity.

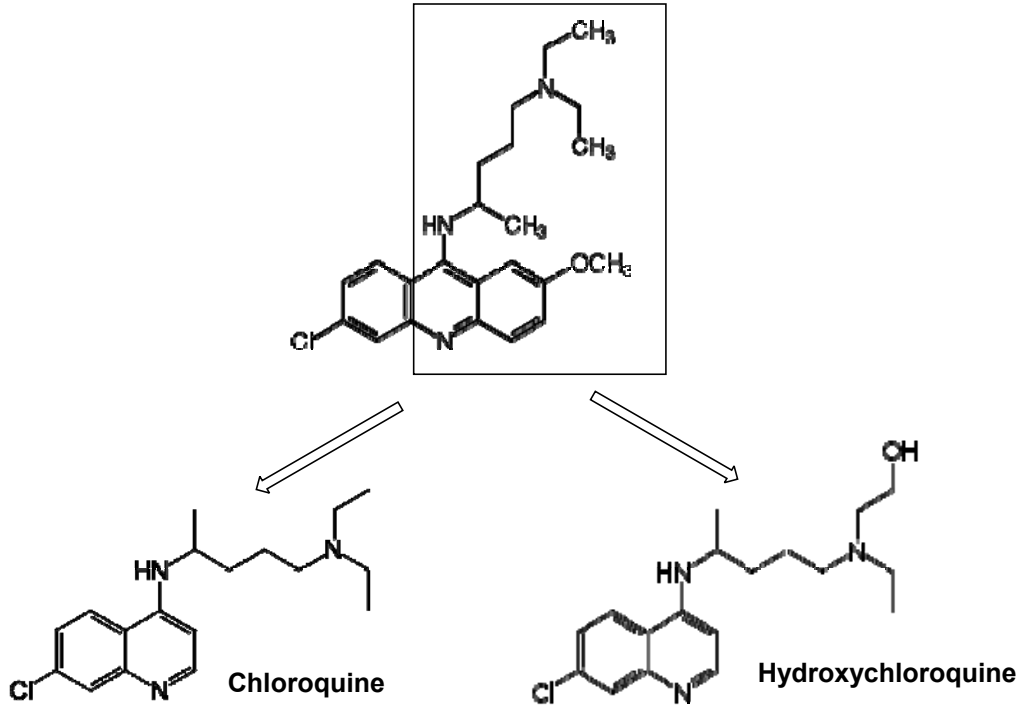


➢ With understanding of the structure–activity relationship of quinine and quinacrine

➢ The 4-aminoquinolines:

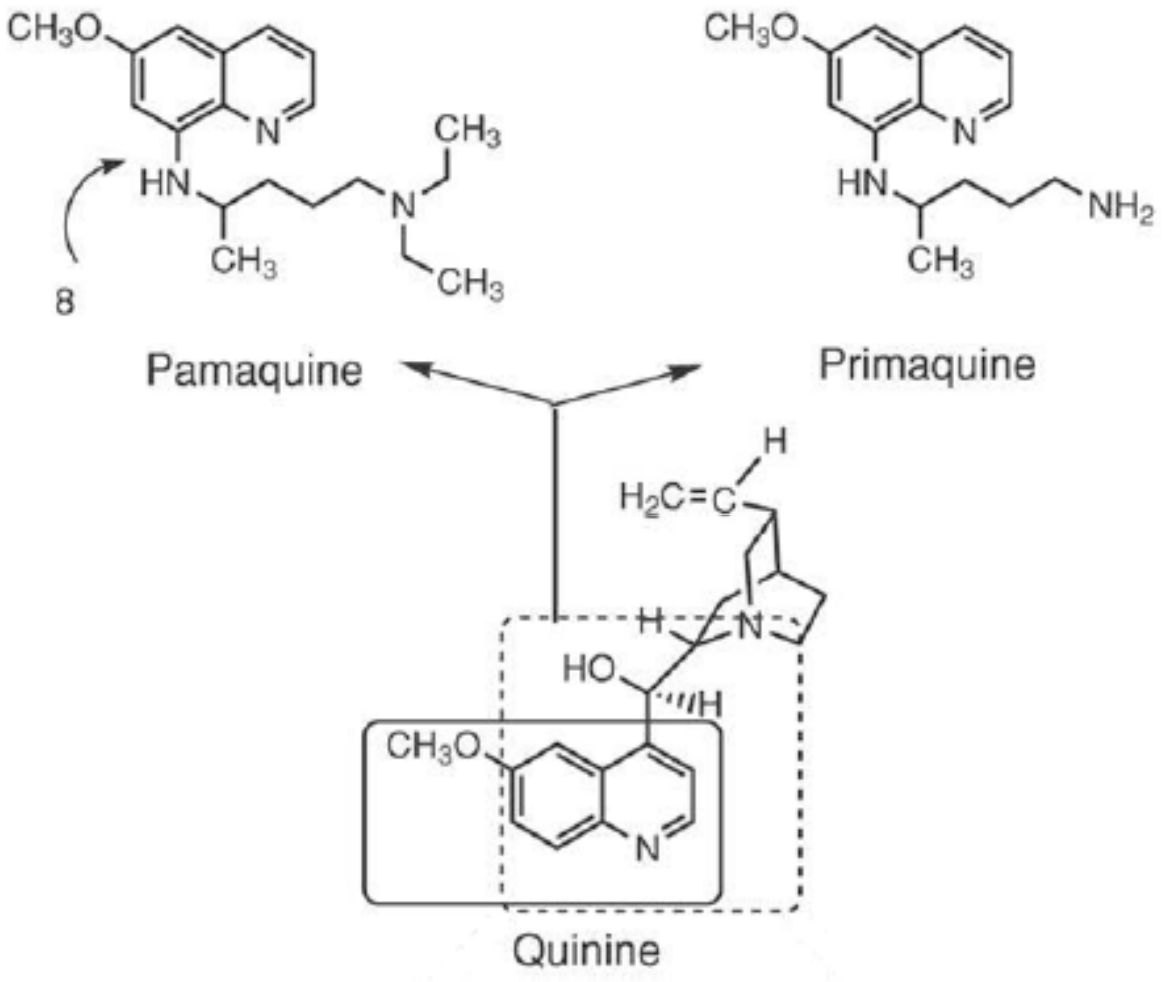
- Chloroquine and hydroxychloroquine

-They are structurally similar to the right half of quinacrine .



➢ The 8-aminoquinolines: like pamaquine and primaquine

➢ They retain the methoxyquinoline nucleus of quinine and quinacrine.



Mechanism of action

- It is known that hemoglobin is transported into the food vacuoles of the plasmodium

- Hemoglobin supplies the organism with a source of amino acids.

- In the plasmodium vacuole is polymerized to hemozoin (called malaria pigment).

- It has been demonstrated that the quinolines bind to hemozoin through a drug–heme complex.

- This drug–heme complex caps the growing hemozoin polymer, thus blocking further extension of the polymer.

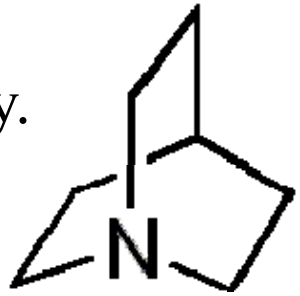
- The result of this complexation is that newly formed, free toxic heme is now present, which leads to the death of the plasmodium.

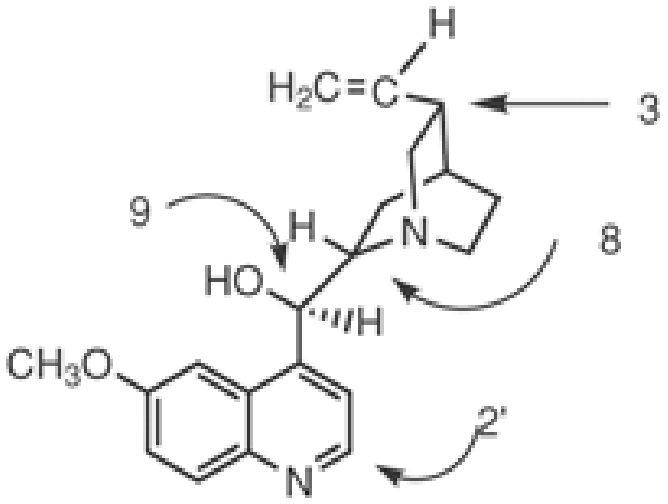
❑ Quinine

➢ Quinine is the most prevalent alkaloid present in the bark extracts (~5%) of cinchona.

➢ Modification of the secondary alcohol at C-9, through oxidation, esterification, or similar processes, diminishes activity.

➢ The quinuclidine portion is not necessary for activity.





Quinine

- A quinine overdose causes: tinnitus and visual disturbances; these side effects disappear on discontinuation of the drug.

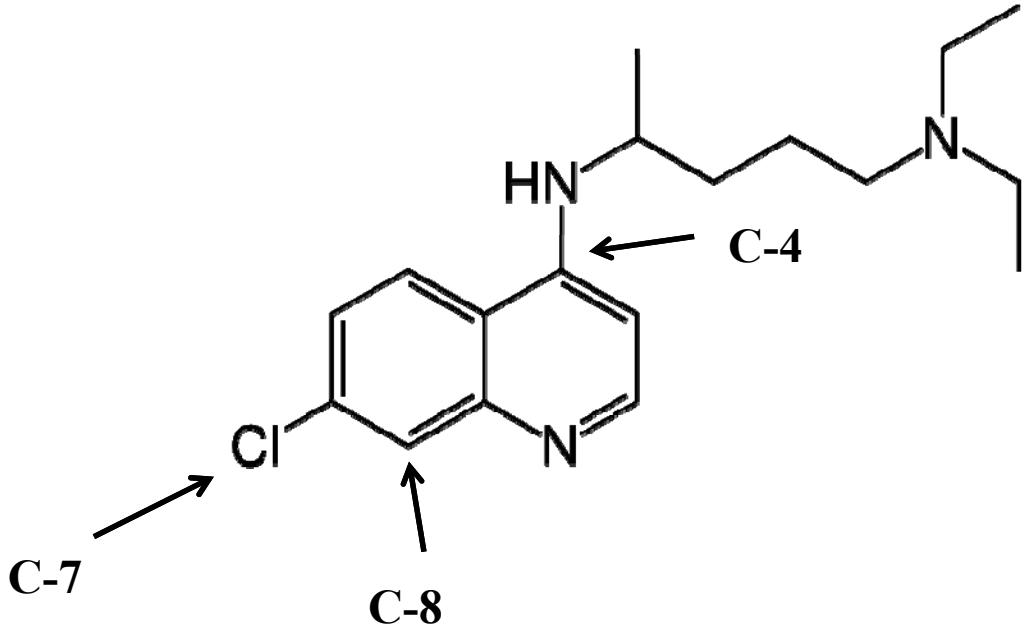
- Quinidine, the isomer of quinine, has been shown to be more effective in combating the disease, but it has undesirable cardiac side effects.

❑ Chloroquine

- Chloroquine is commonly administered as the racemic mixture.

- Structure–activity relationships demonstrated that:

  -The chloro at the 7-position increased activity,
  -Alkylation at C-3 and C-8 diminished activity.

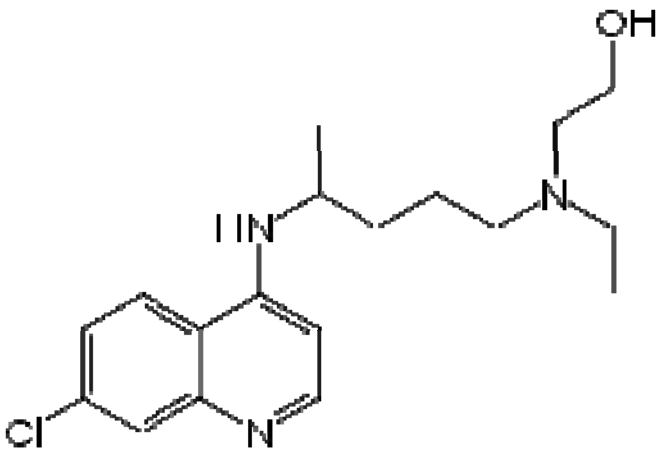


❑ Hydroxychloroquine

➢ The replacement of one of its N-ethyl groups of the Chloroquine with a hydroxyethyl produced hydroxychloroquine.

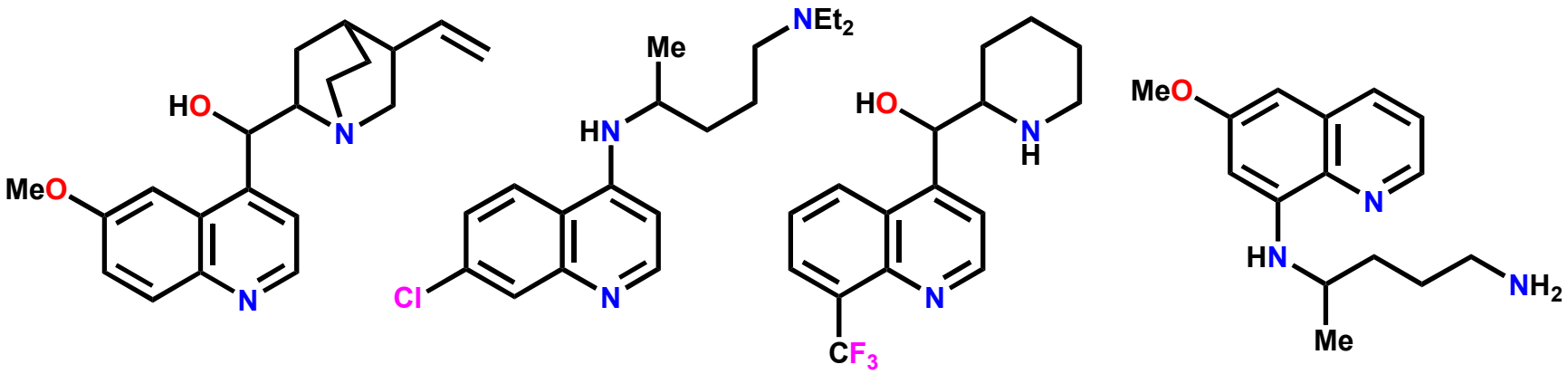
➢ The compound has a reduced toxicity

➢ it is used today in cases of rheumatoid arthritis.



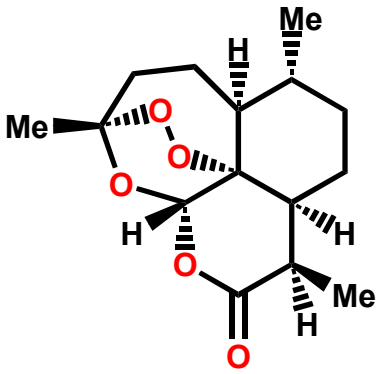
1. Malaria

- Responsible for millions of deaths
- Caused by protozoal parasite - Plasmodium genus
- *Plasmodium falciparum* is the most dangerous
- Conventional therapy - quinine and quinine-based drugs
- Problem of increasing drug resistance in many countries
- Need for novel agent with different mechanism of action



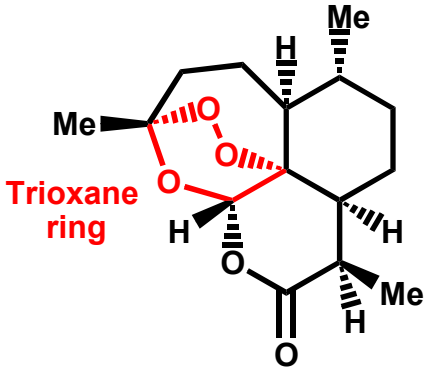
Quinine Chloroquine Mefloquine Primaquine

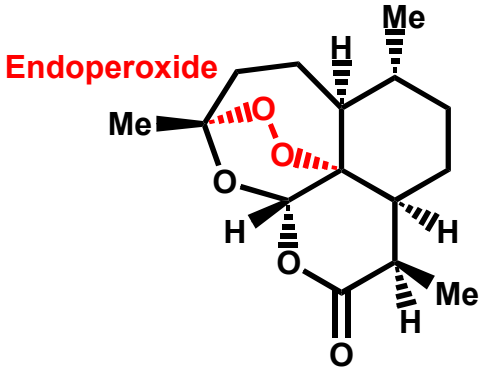
2. Artemisinin

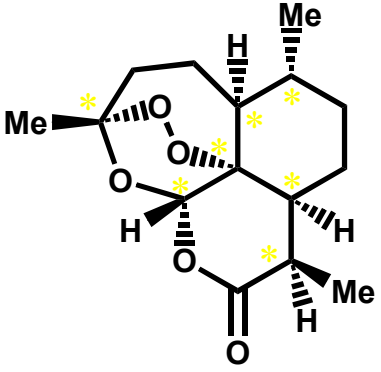


Notes

- Natural product from Chinese plant isolated in 1972.
- Crude extract used for many centuries
- Multicyclic structure, 7 asymmetrical centers
- Contains unstable looking trioxane group



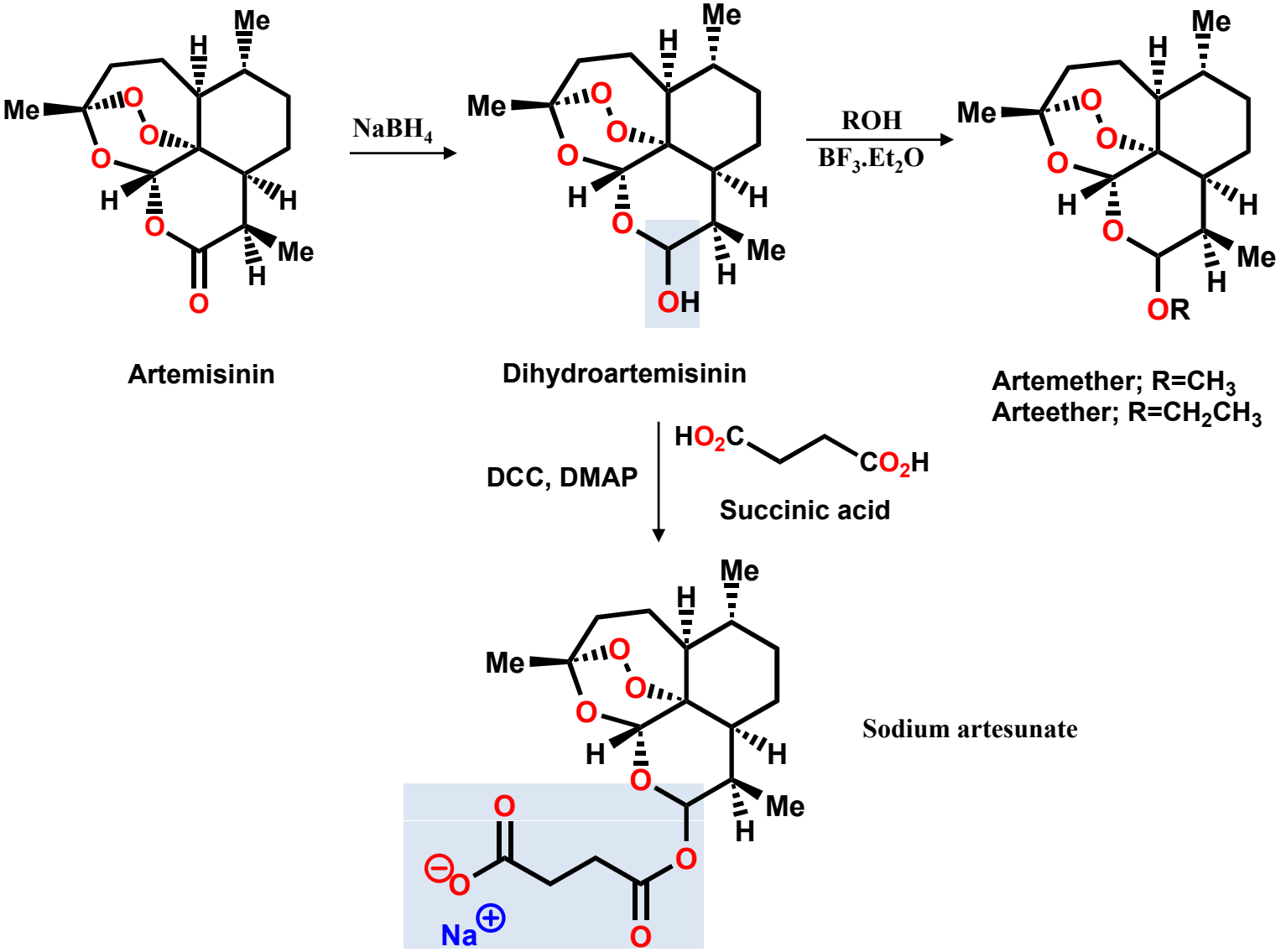




Asymmetric centres

3. Synthesis of analogues

Prepared from artemisinin



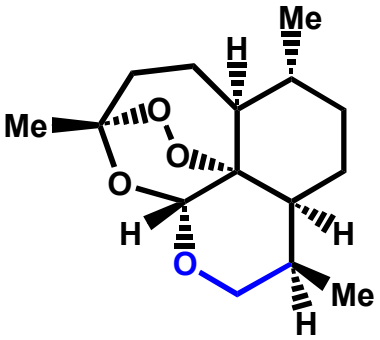
Artemisinin

Dihydroartemisinin

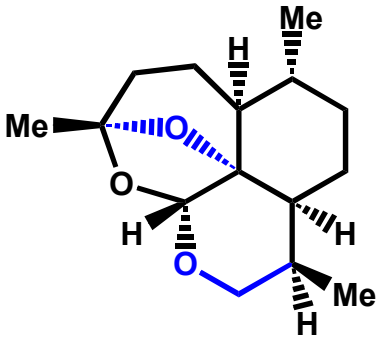
Artemether; R=CH_3
Arteether; R=CH_2CH_3

4. Structure-activity relationships

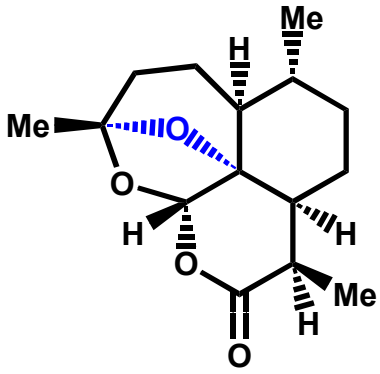
- **Trioxane group is essential for activity**
- **Dihydroartemisinin, artemether, artether and sodium artesunate are more active than artemisinin**
- **Deoxoartemisinin is as active as artether**
- **Lactone group is not essential**
- **Analogues lacking trioxane group have poor activity (deoxodeoxyartemisinin and deoxyartemisinin)**



Deoxoartemisinin

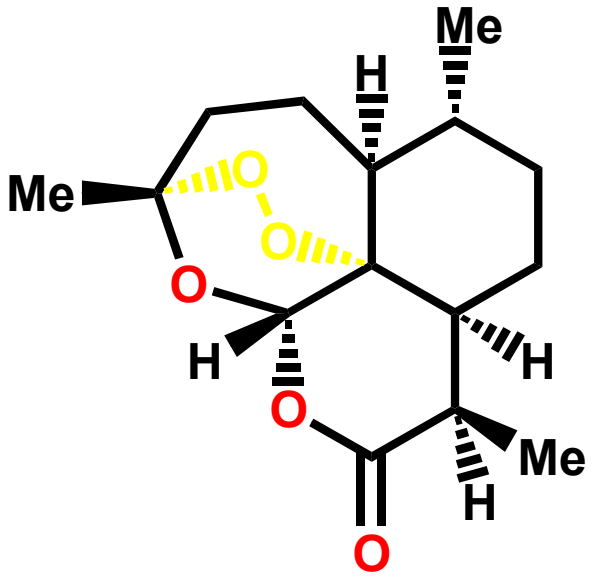


Deoxodeoxyartemisinin



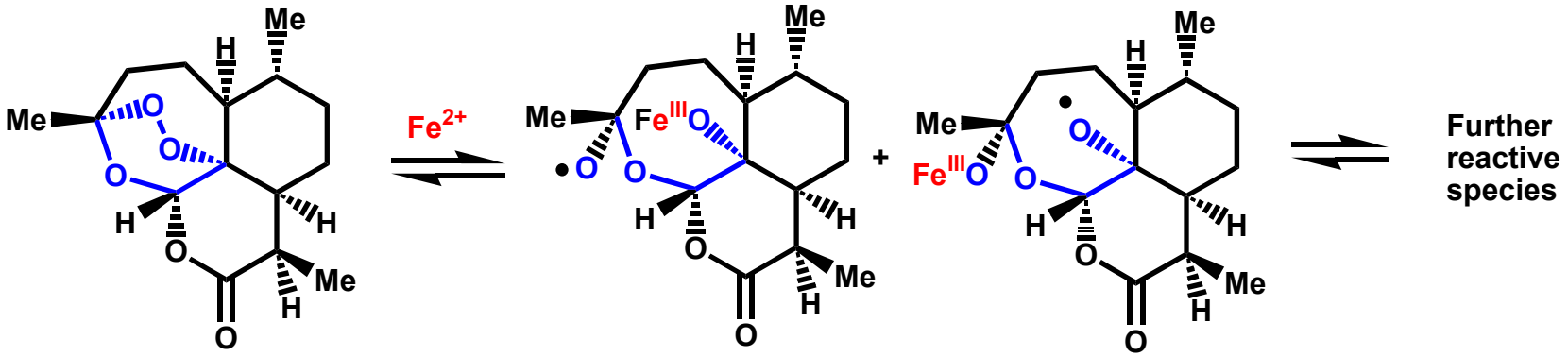
Deoxyartemisinin

5. Pharmacophore



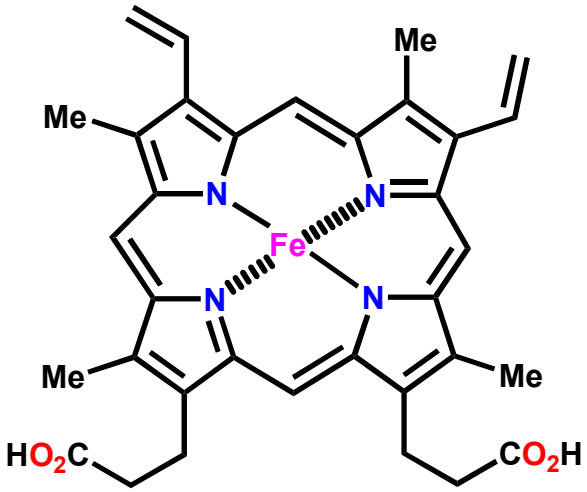
6. Mechanism of action

- Endoperoxide group acts as a ‘molecular trigger’
- Molecule activated by ferrous ions
- Endoperoxide reacts to produce radical species
- Radicals react with biomacromolecules leading to cell death



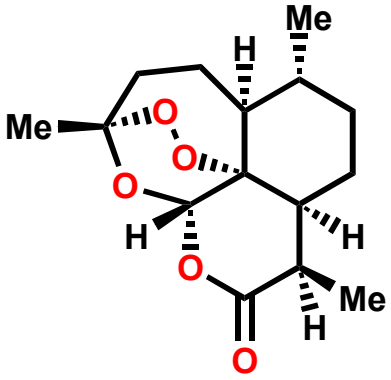
6. Mechanism of action

- Parasite invades red blood cells
- Breaks down haemoglobin as a ‘food source’
- Releases heme and associated iron
- Iron reacts with artemisinin
- Artemisinin not activated in uninfected red blood cells

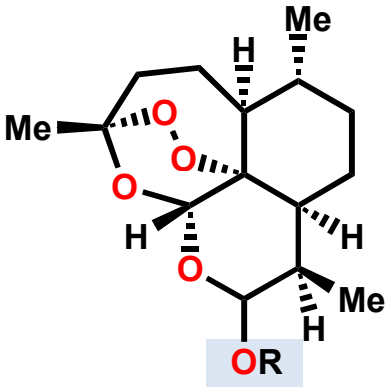


Haem

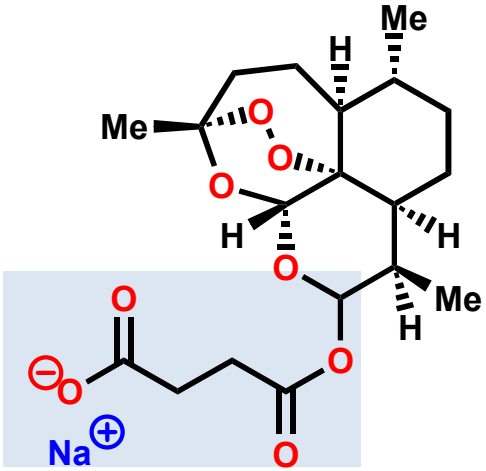
7. Drug Design and Development



Artemisinin



Artemether; R=CH_3
Arteether; R=CH_2CH_3



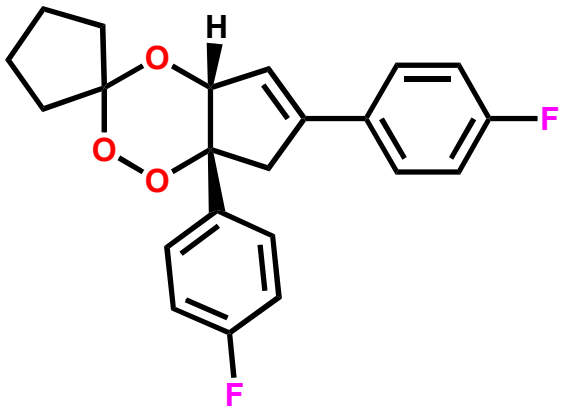
Sodium artesunate

- Artemisinin is poorly soluble in water or oil
- Artemether and arteether are more hydrophobic and more soluble in oil
- Sodium artesunate is ionised and more water soluble

7. Drug Design and Development

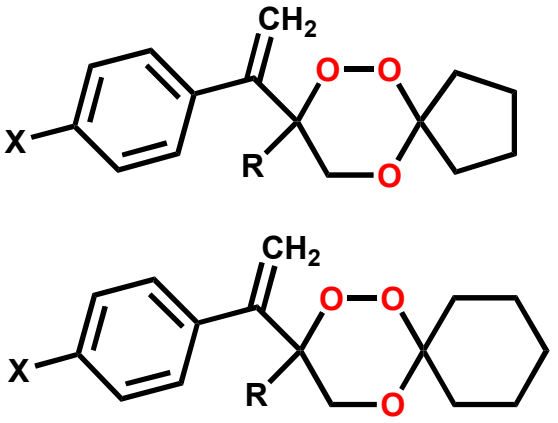
Simplification

- **Design analogues that are easier to synthesise**
- **Retain pharmacophore (trioxane group)**



Fenozan

Comparable activity to artether and sodium artesunate



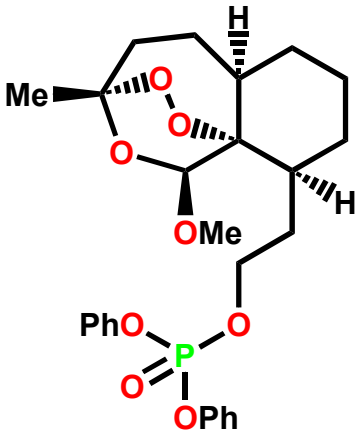
Spiroalkyl trioxanes

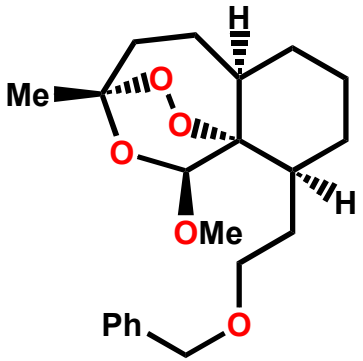
Comparable activity to artemisinin

7. Drug Design and Development

Simplification

- **Design analogues that are easier to synthesise**
- **Retain pharmacophore (trioxane group)**





Trioxanes

Comparable activity to artemisinin