

UNIT-4

Antifungal Agents

Fungi are either yeasts (single round cells) or moulds (filamentous hyphae).

→ The fungi cell wall contains chitin and polysaccharides making it rigid and acts as a barrier to drug penetration.

→ The cell membrane of fungi contains ergosterol which influences efficacy of drug and may also be responsible for drug resistance.

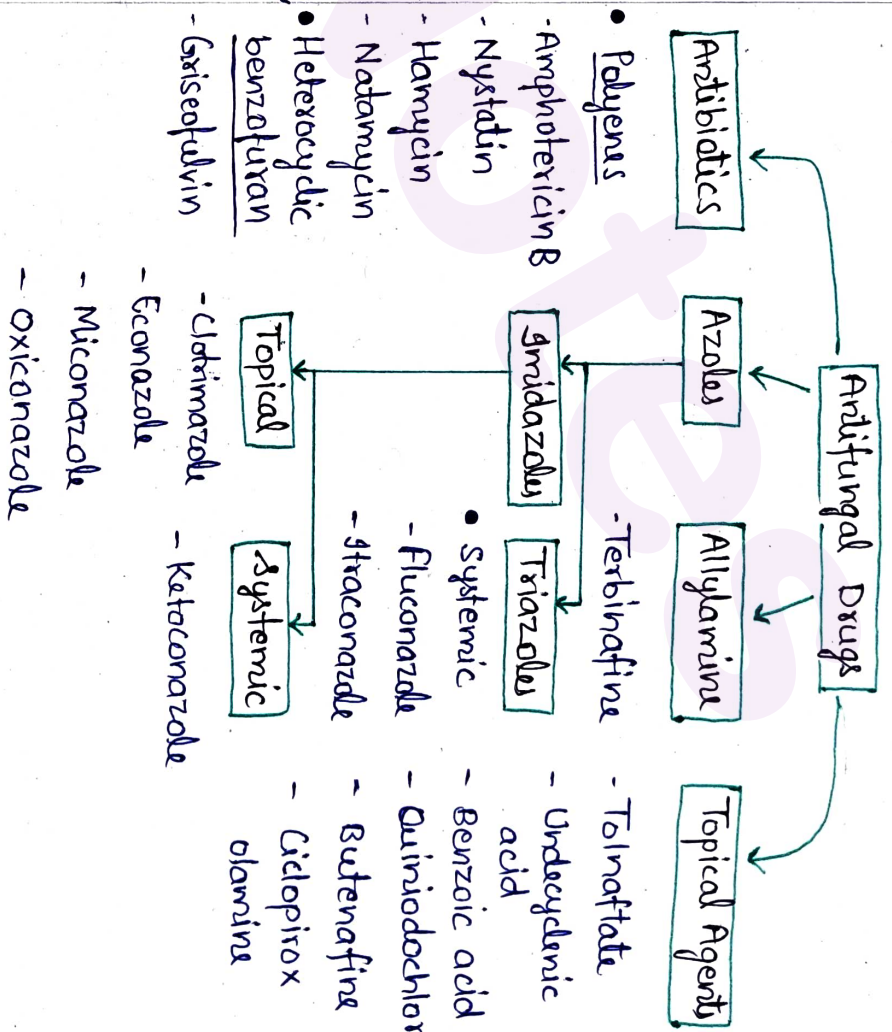
Antifungal agents are the drugs that treat the infections caused by fungi.

→ Most antifungal agents are fungistatic.

→ Fungal infections begin mostly in the lungs or on the skin. These infections progress slowly and are not serious.

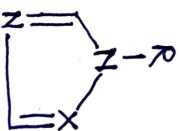
→ Nystatin was the first successful antifungal antibiotic.

Classification



SAR of Azoles

Azoles are a group of synthetic, broad-spectrum antifungal agents.



X=C → Imidazole
X=N → Triazole

- i) A basic imidazole or 1,2,4-triazole is essential for antifungal activity.
- ii) The most active azoles have fluoxina.
- iii) The most potent antifungal azoles possess two or three aromatic rings, at least one of which is halogen substituted (fluorine).
- iv) substitution at other positions of the ring yields inactive compounds.

Mechanism of Action

- 1) Allylamines :- reduce synthesis of ergosterol, which is a main component of fungi cell membrane. Reduced ergosterol increases the membrane permeability, which results in cell lysis and death.
- 2) Azoles :- Azoles inhibit cytochrome P-450 which catalyses the formation of ergosterol from lanosterol, causing permeability disruption of membrane.

- 3) Polynes :- They bind to ergosterol in fungal cell membrane and results in membrane disorganisation.

Uses of Antifungal Drugs

- 1) Athlete's foot, ringworm, candidiasis,
- 2) cryptococcal meningitis, mucocutaneous candidiasis
- 3) For seborrhoea dermatitis
- 4) systemic uses for dermatophytosis

Antifungal Antibiotics

The following drugs are antibiotics :

- 1) Amphoteriicin B
- 2) Nystatin
- 3) Natamycin
- 4) Griseofulvin

Amphoteriicin B

It shows inhibitory activity against many species of fungi, like *Histoplasma capsulatum*, *Candida* species, *Blastomyces dermatitidis*, *Rhodotorula*, *Cryptococcus neoformans* and *Aspergillus fumigatus*.

MOA

Amphotericin B acts as fungistatic or fungicidal depending on the concentration. It binds to ergosterol and changes the membrane permeability which results in leakage of intracellular components causing cell death.

Uses

- Used for treating serious fungal infections.
- Also used for suppressing oral or intestinal candidiasis.

Nystatin

Nystatin is used to treat fungal infections of the inside of the mouth and lining of the stomach and intestines. It is toxic if administered intravenously.

MOA

Nystatin binds to ergosterol in fungal cell membranes. This binding forms pores in the membrane through which potassium and other

cellular components leak and cause cell death.

Uses

- Used in the treatment of prophylaxis and candidiasis of skin and mucous membranes.
- Its tablets are used for treating intestinal and oesophageal candidiasis.

Natamycin

Natamycin is used for treating a variety of topical fungal infections. It is also used as an antifungal preservative on various food products like yogurt, Khao, sausages, juices, wines, etc.

MOA

Natamycin binds to sterols (ergosterol) and inhibits fungal growth.

Uses

Used in the treatment of fungal blepharitis, conjunctivitis and keratitis caused by *Fusarium solani*.

Griseofulvin

It is used for treating infections related to skin, nails, scalp, feet, groin and other body parts. Mostly, it is used for treating infections occurring from trinea strains of fungi.

MOA

Exact mechanism is not known. It inhibits fungal cell mitosis and nuclear acid synthesis.

Uses

Griseofulvin is used for treating ringworm infections of hair, skin, and nails, i.e., trinea corporis, trinea pedis, trinea cruris and other conditions caused by microsporum fungi.

Common side effects of griseofulvin include abdominal pain, chills, clay-coloured stools, confusion, trouble with daily activities, dark urine, diarrhea, dizziness, fatigue, fever, headache, insomnia, itching.

Synthetic Antifungal Agents

These are following drugs:

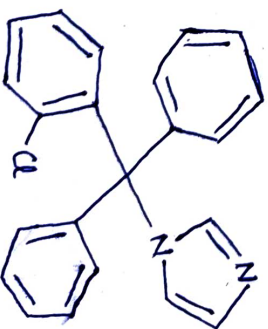
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| 1) Clotrimazole | 7) Ketoconazole |
| 2) Econazole | 8) Terconazole |
| 3) Butoconazole | 9) Atroconazole |
| 4) Oxiconazole | 10) Fluconazole |
| 5) Tioconazole | 11) Natifina hydrochloride |
| 6) Miconazole | 12) Tolnaftate |

Clotrimazole

It is an antifungal used in the treatment of fungal infections of humans and other animals, such as vaginal yeast infections and ringworm. It is also used to treat athlete's foot and jock itch.

MOA

Clotrimazole inhibits cytochrome P-450 enzyme that converts lanosterol to ergosterol.



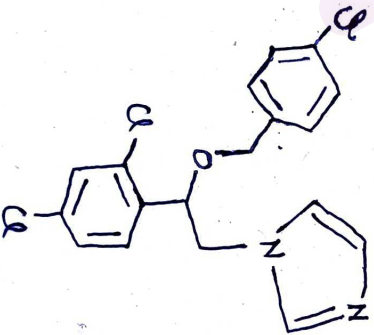
In this way, it inhibits ergosterol synthesis and increases cellular permeability.

Uses

- It is available as an OTC drug in various forms such as cream.
 - It is also available as ear drops for ear infection.
 - commonly found in conjunction with betamethasone to add steroid properties.
- side effects may include skin rash, hives, blistering, burning, itching, peeling, redness.

Econazole

Econazole is a broad-spectrum antifungal agent. It is topically used in dermatomycoses. It can also be used orally and parenterally.



MOA similar to clotrimazole.

Uses

- topically used in various infections.
- also used in cutaneous candidiasis and tinea versicolor.

Common side effects include burning, stinging, swelling, irritation, swelling, redness, skin flaking

Butoconazole

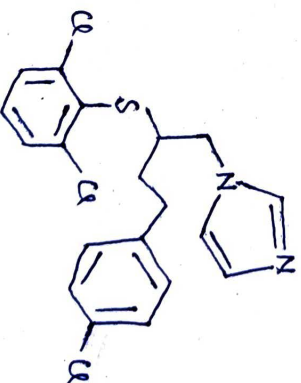
It is an imidazole antifungal used in gynaecology.

MOA

Exact mechanism is not clear but as it is an imidazole, its MOA is similar to clotrimazole.

uses → in local treatment of vulvovaginal candidiasis

Vaginal cream causes vaginal burning, itching, etc as side effects.



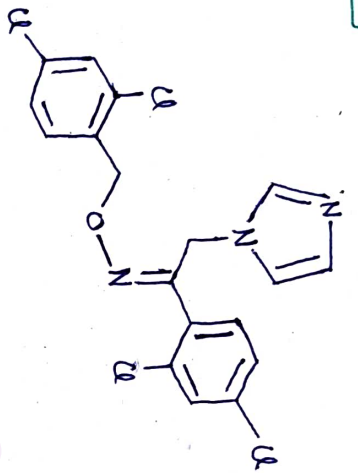
Oxiconazole

It is found in topical formulations.

MOA
similar to clotrimazole.

Uses

Used in the treatment of various skin infections such as athlete's foot, jock itch and ringworm. Common side effects like irritation, etc. occur.

**Tioconazole**

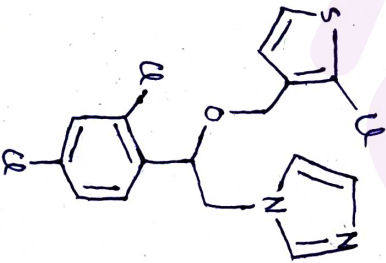
It is also an imidazole antifungal agent.

MOA
similar to clotrimazole.

Uses

ringworm, jock itch, athlete's foot, tinea versicolor, vulvovaginal candidiasis.

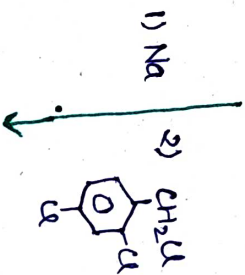
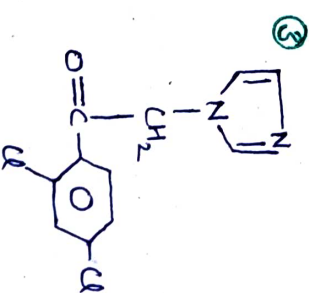
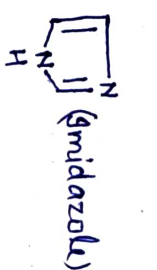
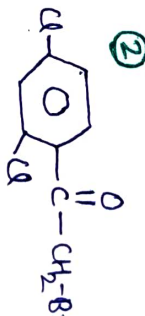
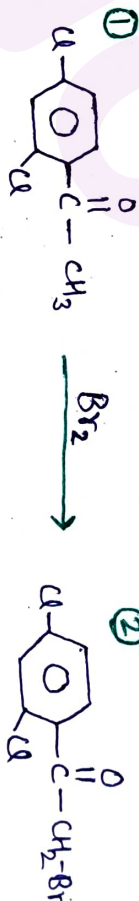
Common side effects include headache, vaginal burning, itching, pain or increased urination.

**Miconazole**

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It is an imidazole antifungal agent that is used topically and by intravenous infusion.

Synthesis

**Miconazole**

- ① 2,4 - Dichloroacetophenone
- ② 2,4 - Dichlorophenacyl bromide
- ③ 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone
- ④ 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanol

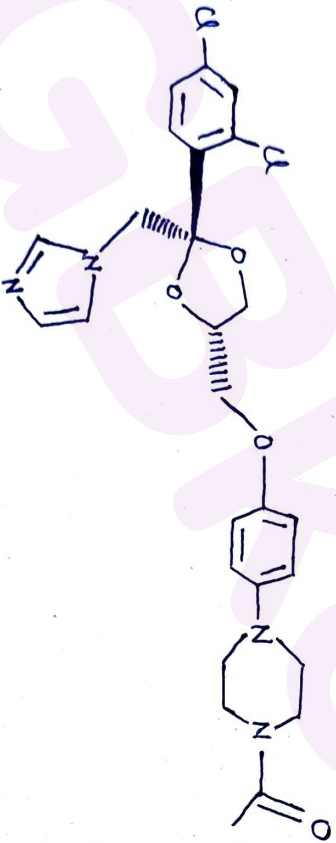
MOA

similar to clotrimazole

Uses

tinea pedis (athlete's foot), tinea corporis, cutaneous candidiasis and tinea versicolor.

Ketoconazole



It is an imidazole antifungal agent.

MOA

similar to clotrimazole

Uses → candidiasis, candiduria, blastomycosis, histoplasmosis, chromomycosis.

Terconazole

It is an antifungal that is used to treat vaginal yeast infections. It is a triazole ketal derivative. It is available as creams and suppositories.

Terconazole inhibits cytochrome P-450 14- α -demethylase in susceptible fungi, which leads to the accumulation of lanosterol and other methylated sterols and a decrease in ergosterol concentration.

This ergosterol depletion in fungal membrane disrupts the structure and function of fungal cell, thereby inhibiting fungal growth.

Uses

Used in the treatment of vulvar and vaginal candidiasis.

Itraconazole

It is used to treat onychomycosis of the toenails. This medicine works by killing the fungus and preventing its growth.

MOA

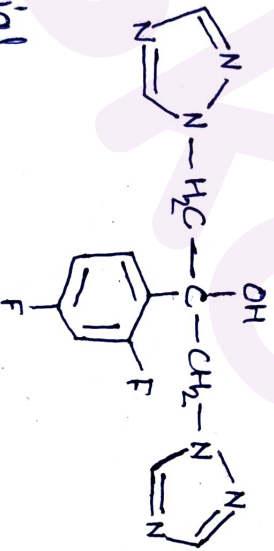
It inhibits cytochrome P-450-dependent enzymes, and impairs ergosterol synthesis, which increases cellular permeability, as a result of which the cellular contents leak out.

Uses

It treats fungal infections like pulmonary and extrapulmonary blastomycosis, histoplasmosis, aspergilliasis and cryptococcosis.

Fluconazole

Fluconazole is a triazole antifungal that is used in the treatment and prevention of superficial and systemic fungal infections.

MOA

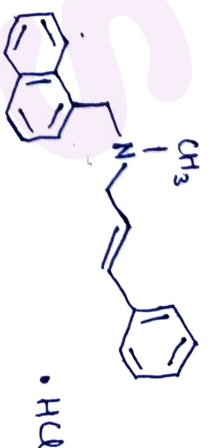
Similar to Itraconazole.

Uses

Used in the treatment of fungal infections.

Natifina Hydrochloride

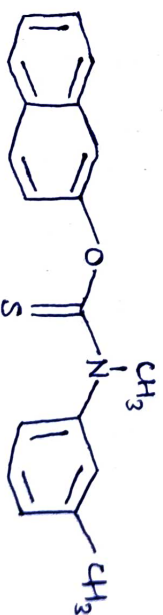
Natifina is a synthetic, broad spectrum, antifungal and allylamine derivative that is used topically.

MOA

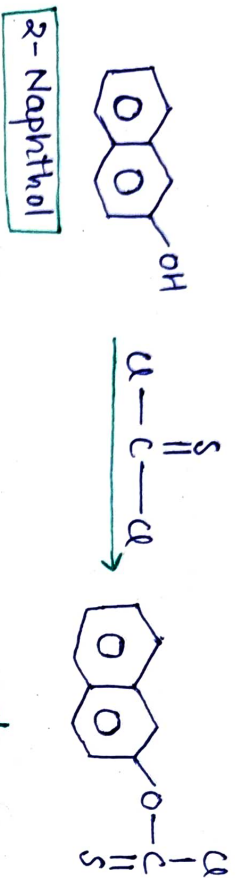
The exact mechanism of natifina is not known. But MOA is somewhat similar to itraconazole.

Uses

Used topically for the treatment of tinea pedis, tinea cruris and tinea corporis.

Tolnaftate*

Tolnaftate is a synthetic OTC anti-fungal. It is available as creams, powders, sprays or liquid aerosols. It is used to treat jock itch, athlete's foot and ringworm.

SynthesisMOA

Exact mechanism is not clear, but it is similar to itraconazole.

Tolnaftate also distorts the hyphae and inhibits mycelial growth in susceptible organisms.

Uses

→ Athlete's foot, jock itch and ringworm infections.

→ treat infections of nails, scalp, palm and soles of feet.

→ Its powder and powder aerosol formulation is used to prevent athlete's foot.

Adverse effects include mild itching, dryness, peeling of treated skin.

Anti-protozoal agents

Protozoal diseases are highly prevalent in tropical and sub-tropical countries, where sanitary conditions, hygienic practices and control of vectors of transmission are not maintained properly.

They infect both humans and animal population. Some of the protozoal diseases include malaria, amoebiasis, balantidiasis, giardiasis, trichomoniasis, Trypanosomiasis, Leishmaniasis, etc.

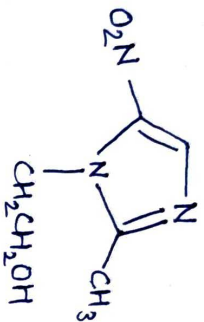
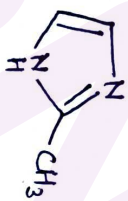
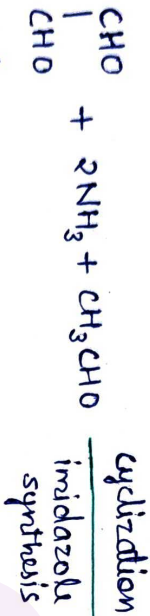
Anti-protozoal agents are drugs used in a wide range of diseases caused by protozoa.

Major Drugs

- | | |
|------------------|----------------------------|
| 1) Metronidazole | 5) Iodoquinol |
| 2) Tinidazole | 6) Pentamidine isethionate |
| 3) Oxidazole | 7) Atovaquone |
| 4) Diloxanide | 8) Eflornithine |

Metronidazole *

It is a nitroimidazole used for treating amoebiasis, vaginitis, trichomonas infections, giardiasis.

SynthesisMetronidazoleMOA

Metronidazole diffuses into the protozoal organism, inhibits protein synthesis by binding to DNA and causes a loss of radical DNA structure and strand breakage. Therefore, it causes cell death.

Uses

→ It is used in treating amoebic dysentery, amoebic hepatitis (caused by Entamoeba histolytica)
→ It is also used in giardiasis caused by Giardia lamblia.

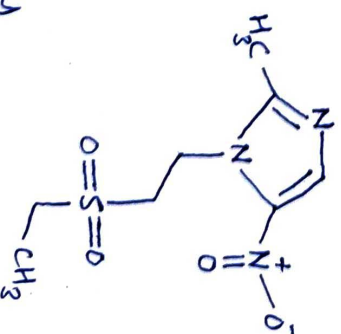
Adverse effects include nausea, diarrhoea or metallic taste in mouth.

Tinidazole

Tinidazole is a nitroimidazole agent that is effective against Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia infections.

MOA

The nitro group of Tinidazole is reduced in Trichomonas by a ferredoxin-mediated electron transport system. The free nitro radical generated as a result of this reduction is responsible for the antiprotozoal activity.

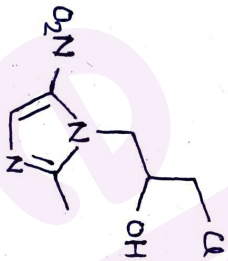


Uses

- used for the treatment of trichomoniasis caused by *T. vaginalis*.
- also used in giardiasis caused by *G. duodenalis*.
- it also helps in intestinal amoebiasis and amoebic liver abscess caused by *E. histolytica*.

Oxidazole

It is a synthetic nitroimidazole having a broad-spectrum activity against protozoa and some anaerobic bacteria.

MOA

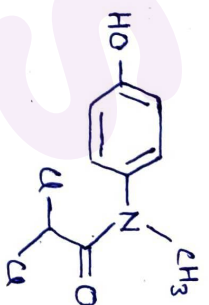
Oxidazole inhibits growth of protozoa by interacting with the DNA of the microorganism and inhibiting the protein synthesis, thereby leading to death of the microorganism.

Uses

- Treatment of giardiasis, trichomoniasis, etc.
- Treatment of diarrhea, dysentery, Crohn's disease.

Diloxanide

Diloxanide is an anti-protozoal that is used for treating infections caused by *Entamoeba histolytica* and other protozoa.



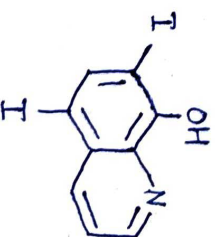
MOA
MOA of diloxanide is unknown. It is an amoebicide.

Uses

- Treat intestinal amoebiasis caused by *Entamoeba histolytica*.
- side effects include skin rashes, flatulence, nausea, abdominal cramps, anorexia and diarrhoea.

Iodoquinol

Iodoquinol is a quinoline derivative, also called as diiodohydroxyquinoline, is used in the treatment of amoebiasis. It is poorly absorbed from GI tract.



MOA → unknown

uses → amoebiasis

Pentamidine Isethionate

Pentamidine is an antiprotozoal, effective in trypanosomiasis, leishmaniasis and some fungal infections also.

MOA

It interferes with the nuclear metabolism, thus inhibit the synthesis of DNA, RNA, phospholipids and proteins.

uses

It is used in the treatment of pneumonia caused by *Pneumocystis carinii*.

Side effects

Pentamidine causes diabetes mellitus, CNS damage and other common side effects.

Atovaquone

Atovaquone is a hydroxynaphthoquinone.

It also has antifungal activity alongside being antiprotozoal.

MOA - unknown

But in *Plasmodium* species, it inhibits the mitochondrial electron transport chain at bc₁ complex (Complex III). Inhibition of bc₁ activity results in a loss of mitochondrial function, i.e., ATP synthesis.

uses

→ It is used in pneumonia caused by *Pneumocystis carinii*, and *Pneumocystis jirovecii* pneumonia (PCP).

Eflornithine

Eflornithine hydrochloride cream is applied topically in women suffering from facial hirsutism (hairs). It inhibits hair growth by inhibiting anagen phase of hair production by irreversibly binding to ornithine Decarboxylase (ODC).

