ANTIFUNGAL AGENTS

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Common ancestor?!

- About 1408 Million Years Ago, fungi and animals phyla split
- We are more closely related to fungi then plants!
- This will prove difficult for one to treat mycotic infections due to the similarities between the eukaryotic fungus and the eukaryotic host (us! ☹)

Human fungal infections have increased dramatically in recent years, owing mainly to advances in surgery, cancer treatment, and critical care accompanied by increases in the use of broad-spectrum antimicrobials and the HIV epidemic.

Fungal infections are usually more difficult to treat than bacterial infections, because fungal organisms grow slowly and because fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents.

Therapy of fungal infections usually requires prolonged treatment.

Superficial fungal infections involve cutaneous surfaces (skin, nails, and hair), and mucous membrane surfaces (oropharynx and vagina).

Deepseated or disseminated fungal infections caused by dimorphic fungi, the yeasts Cryptococcus neoformans, and various Candida spp.

*respond to a limited number of systemic agents:

-amphotericin B (a polyene),

-flucytosine (a pyrimidine antimetabolite),

-the newer azoles (ketoconazole, fluconazole, itraconazole, and voriconazole), and caspofungin (an echinocandin).

ANTIFUNGALS

1) Antifungal antibiotics

2) Imidazoles and triazoles (Azoles)

3) Allylamine derivatives

4) Other medicines
a) Systemic
b) Local

1. ANTİFUNGAL ANTİBİOTİCS

POLYENE ANTIBIOTICS

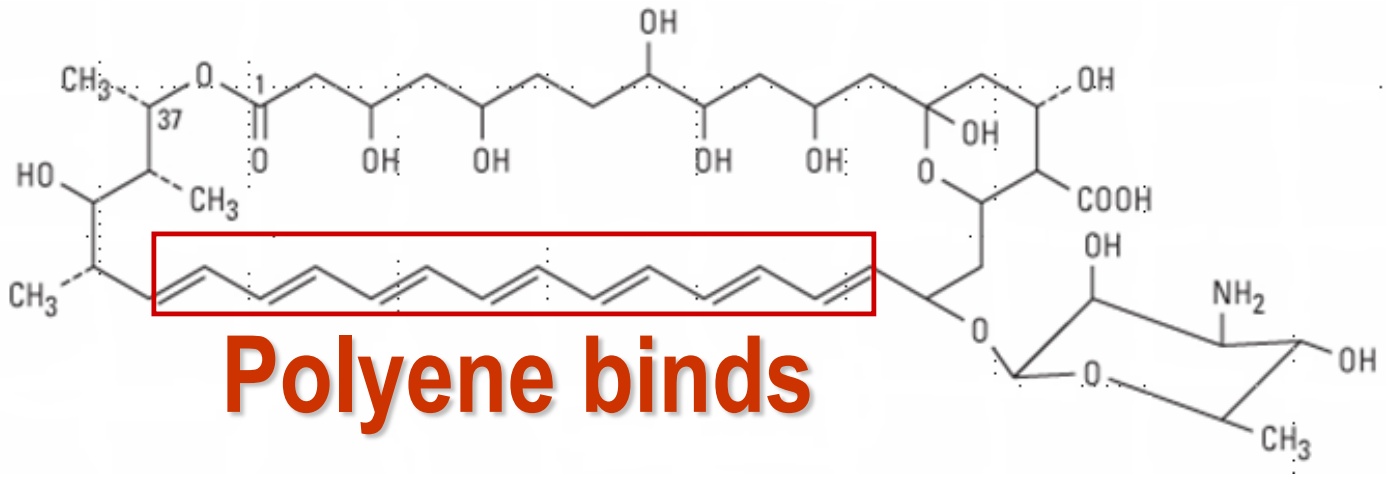
Amphotericin B and Nystatin bind to the fungal cell membrane component **ergosterol,** leading to *increased fungal cell membrane permeability* and the loss of intracellular constituents.

Amphotericin has a lesser affinity for the mammalian cell membrane component cholesterol, but this interaction does account for most adverse toxic effects.

Amphotericin B has activity against *Candida* spp., *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Sporothrix schenckii, Coccidioides immitis, Paracoccidioides braziliensis, Aspergillus* spp., *Penicillium marneffei, etc*.

Amphotericin B (Fungizone)

- Known as a polyene macrolide
  - 38 – Membered Ring
- Isolated 1955, market 1958
- Amphiphilic!



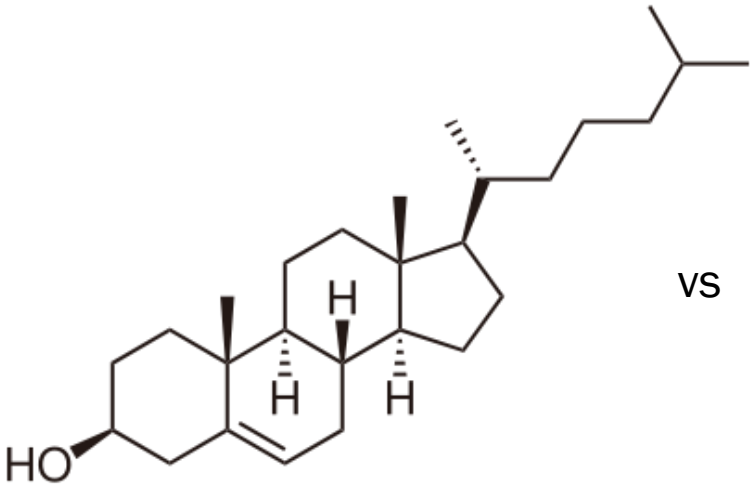
Amphotericin B

- **Mechanism of Action!**

Associates with the membrane and causes leakage of Na, K, and Ca across membrane. But how does it differentiate between fungal cells and human cells??

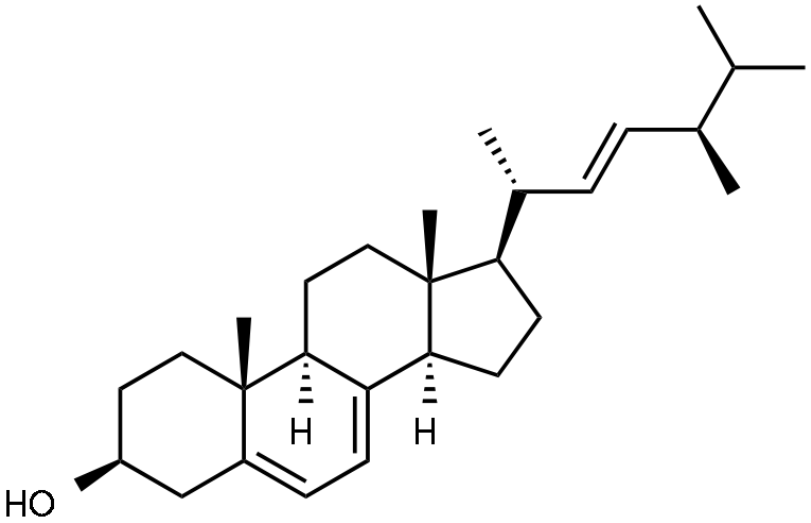
Amphotericin B

- Instead of cholesterol in the cell membrane, fungal cells have **ergosterol**. The heptaene portion of the ring interacts strongly with ergosterol instead of cholesterol.



Cholesterol

vs



Ergosterol

- Because of the amino sugar group in the molecule, it is a basic substance, salt can be made. The HCl salt is insoluble in water. It is given in dry complex with bile acid.

- Today, lipid-based amphotericin B formulations have been developed due to side effects and dose limiting toxicity.

- The antifungal spectrum is broader than nystatin. Used for the treatment of systemic fungal infections, especially systemic candidiasis

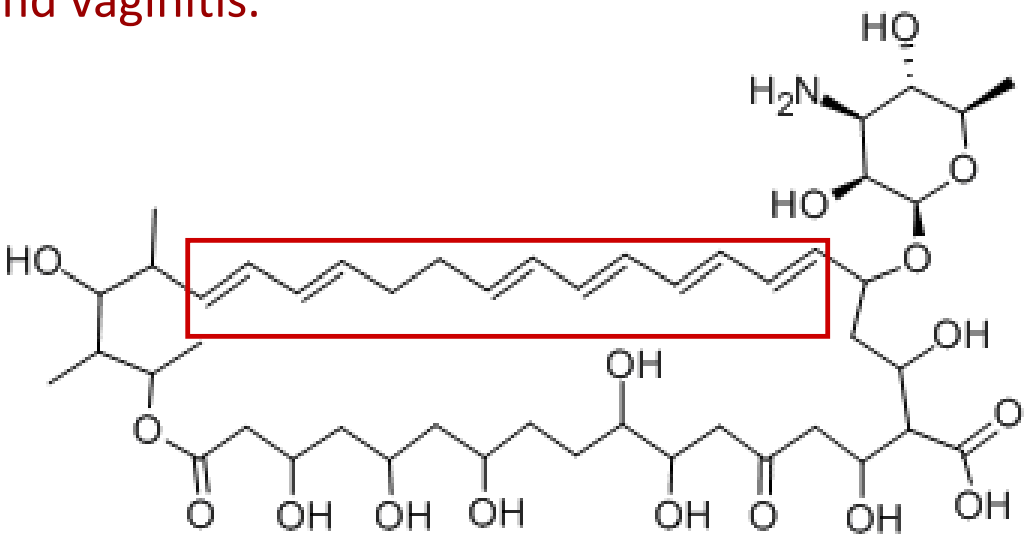
- Amphotericin B binds irreversibly to the sterol (ergosterol) found on the cell membrane of the sensitive fungus species (not on the mammalian cell membrane), impairing the permeability of the membrane and exhibiting fungicidal action. On the contrary, the low level of cholesterol affinity found in the human cell membrane explains the systemic use.

- There is little absorption from the gastrointestinal tract, which is why it is used parenterally in systemic fungal infections.

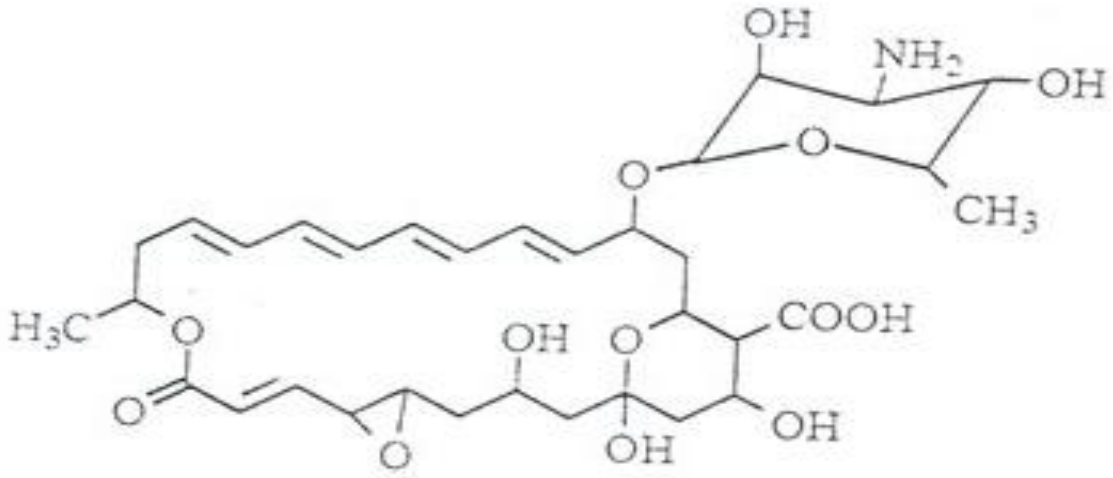
Nystatin is **a polyene** antifungal drug with a ring structure and a mechanism of action similar to that of amphotericin.

too toxic for systemic use, nystatin is limited to the **topical treatment of superficial infections caused by C. albicans**.

Infections commonly treated by this drug include oral candidiasis (thrush), mild esophageal candidiasis, and vaginitis.



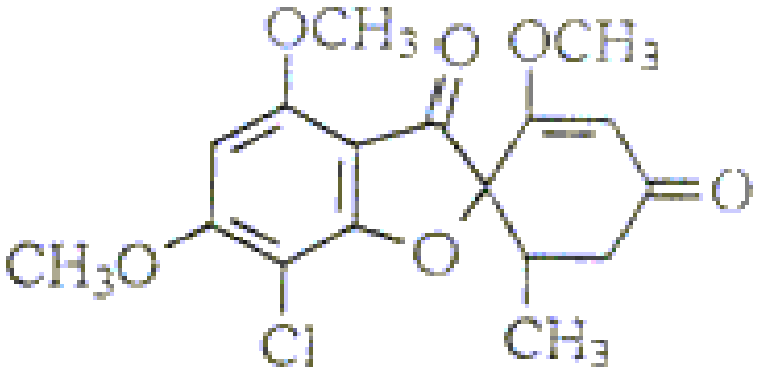
NATAMİSİN (=primarisin)



*It was isolated from Streptomyces natalensis.

*It consists of 26 member lactone ring.

GRİSEOFULVİN



7-chloro-4,6-dimetoksikumar-3-one-2-spiro-1 '- (2'-methoxy-6'-methylcyclohex-2'-en-4'-one

*It was isolated from Penicillium griseofulvum.

*It is effective against superficial infections caused by dermatophyte fungi such as Microsporum, Trichophyton and Epidermophyton.

2. ANTIFUNGAL AZOLES

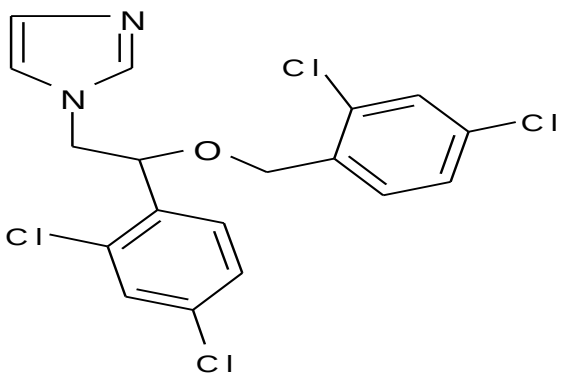
-synthetic drugs with broad-spectrum fungistatic activity.

-Azoles can be divided into two groups;

1) Older ***imidazole agents*** **(clotrimazole, ketoconazole, miconazole)** in which the five-member azole nucleus contains two nitrogens

2) Newer ***triazole compounds*** **(fluconazole, itraconazole, and voriconazole)**, in which the azole nucleus contains three nitrogens.

MİCONAZOLE

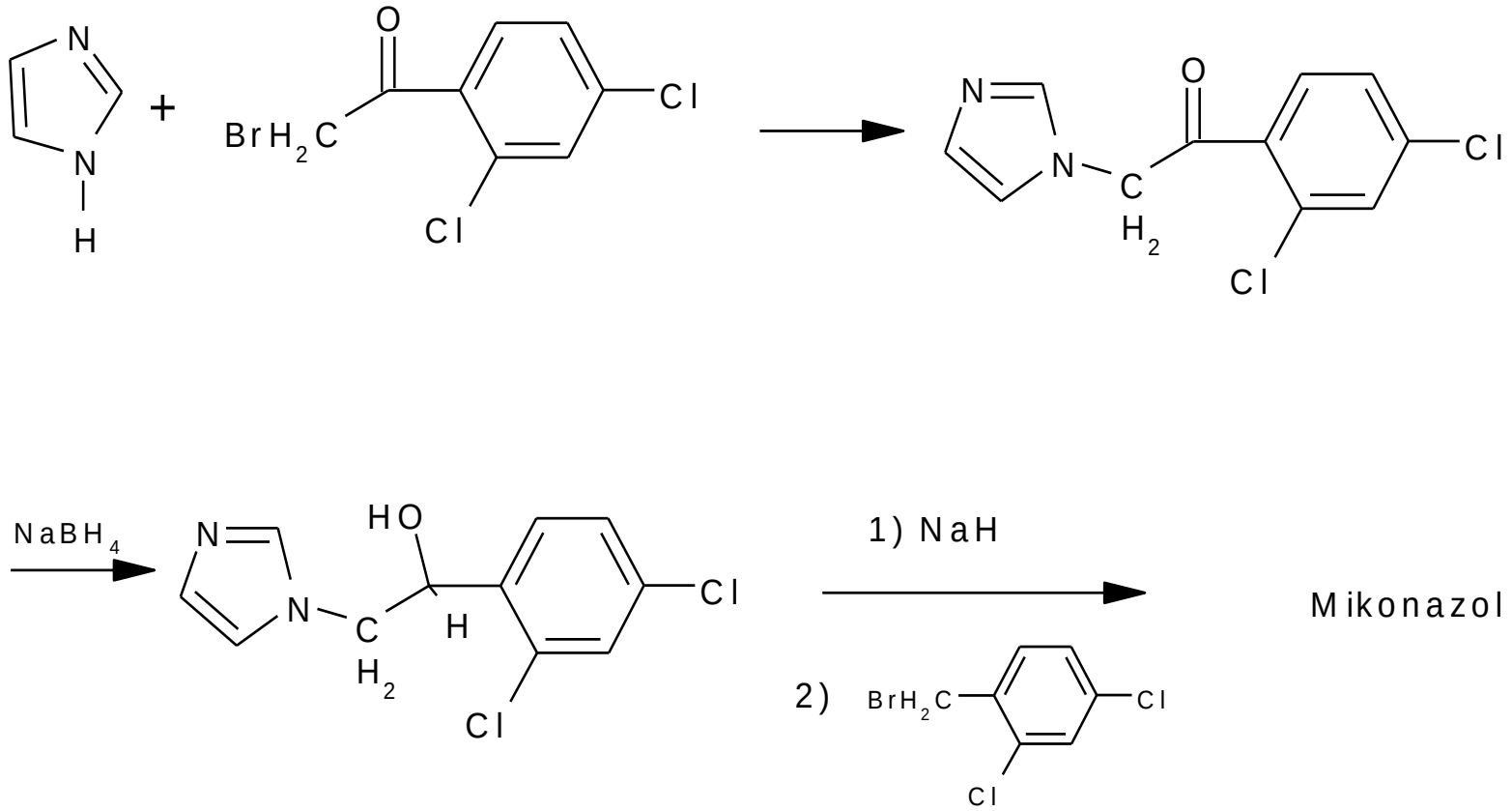


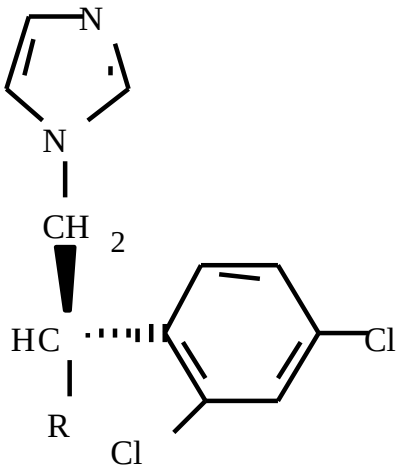
(±) 1- [2- (2,4-Dichlorophenyl) -2 - [(2,4-dichlorophenyl) methoxy] ethyl] -1H-imidazole

-It is effective against to maya mushrooms, candida and various dermatophytes.

-Local use in the form of 2% cream, lotion, spray or powder in tinea infections.

-Creams and suppositories are used in vaginal candidiasis.


N
H
+
O
BrH2C
Cl
Cl
N
N
C
H2
O
Cl
Cl
NaBH4
N
N
C
H2
HO
H
Cl
Cl
1) NaH
2)
BrH2C
Cl
Cl
Mikonazol



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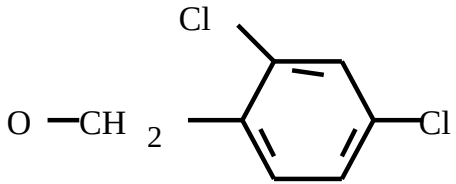
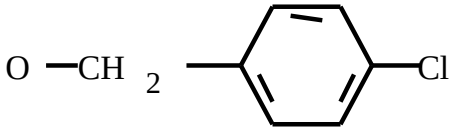
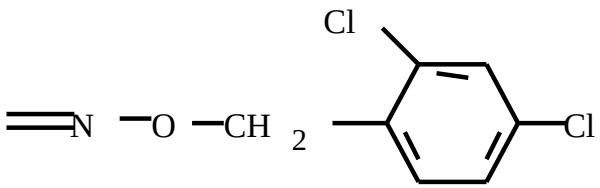


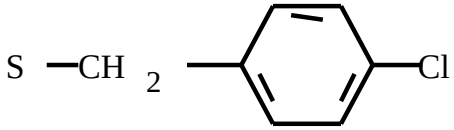
Miconazole



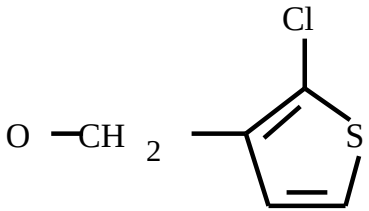
Econazole



Oxiconazole

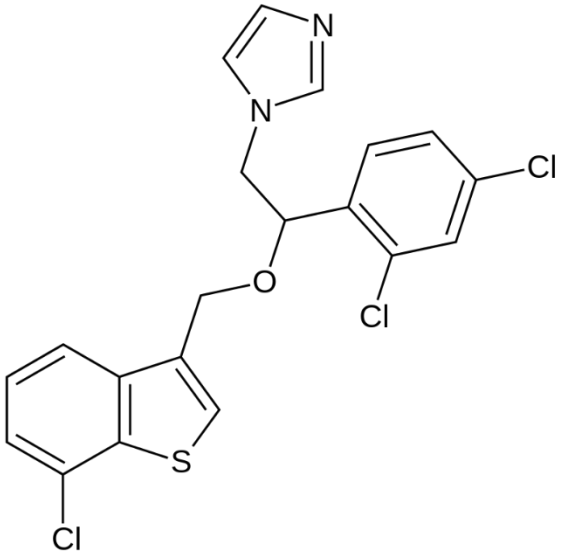


Sulconazole



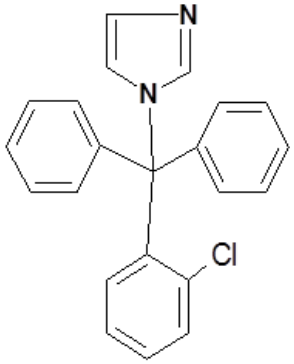
Tioconazole

Sertaconazole



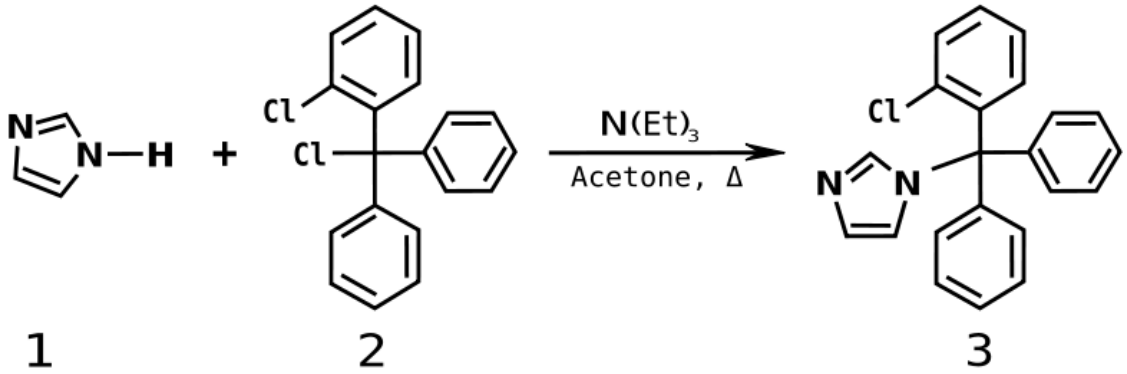
1- {2 - [(7-Chloro-1-benzothiophen-3-yl) methoxy] -2- (2,4-dichlorophenyl) ethyl} -1H-imidazole

KLOTRİMAZOL



Kandidalar gibi maya mantarlarına ve dermatofitlere etkilidir.
Trychomonas vaginalis'e karşı fungusid

1-[(2-Klorofenil)(difenil)metil]-1*H*-imidazol



Clotrimazole like the other azole antifungals inhibits the synthesis of ergosterol, one of the essential components of the cell membrane, by interacting with 14-α -demethylase, an enzyme that converts lanosterol to ergosterol.

Inhibition of ergosterol synthesis increases cell permeability, causing phosphorus compounds and potassium to escape from the cell.

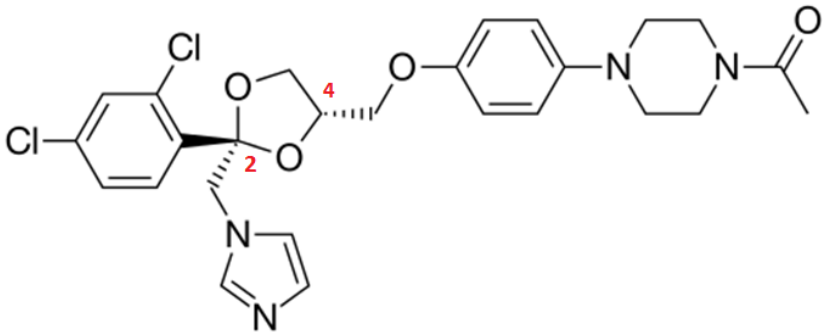
Clotrimazole does not show the same activity on human cholesterol synthesis.

Fungi have been shown to have very little resistance to clotrimazole.

Clotrimazole is not used systemically.

Preparations are available in pharmaceutical forms such as creams, topical lotions, and vaginal suppositories.

KETOCONAZOLE



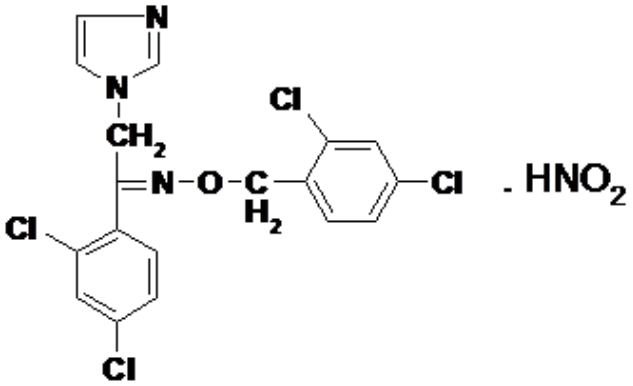
1- [4- (4 - {[(2R, 4S) -2- (2,4-Dichlorophenyl) -2- (1H-imidazol-1-ylmethyl) -1,3-dioxolan-4-yl] methoxy } phenyl) piperazin-1-yl] ethan-1-one

*It is fungistatic at therapeutic doses.

*It is effective on the fungi during the active reproduction period.

*It is absorbed quickly from the gastro-intestinal tract; It is a dibasic structure, stomach acidity is important in drug dissolution and increases absorption.

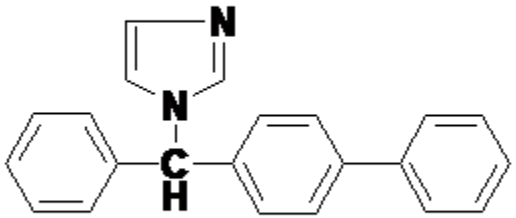
OKSİKONAZOL



I- 2',4'-Dikloro-2-(imidazol-1-il)asetofenon-O-(2,4-diklorobenzil)oksim

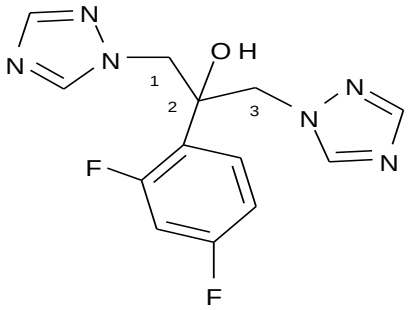
II- 1-(2,6-Diklorofenil)-2-(1H-imidazol-1-il)etanon-O-(2,4-diklorobenzil)oksim nitrat

BİFONAZOL



1- (p, α -diphenylbenzyl) imidazole

FLUCONAZOLE



2- (2,4-difluorophenyl) -1,3-bis (1H-1,2,4-triazol-1-yl) -2-propanol

*It is similar to ketoconazole in terms of antifungal spectrum and mechanism of action, but less toxic than it.

*Because it is sufficiently lipophilic and small molecule, it is distributed to Cerebrospinal fluid and other body fluids.

*It is as effective as amphotericin-B in fungal infections in AIDS patients

*Full abs from the GI track.

*Use as oral and parenteral (IV).

*It is indicated in local and systemic candidiasis, dermatophytosis and cryptococcal infections.

*It is also used for treatment of Cryptococcus caused meningitis

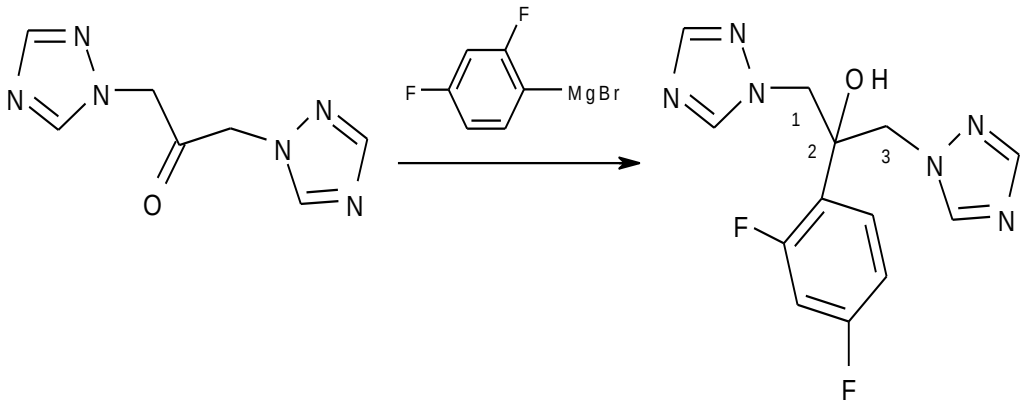
Mech of Action:

Specifically inhibits the cytochrome P450 fungal enzyme C-14(alpha) demethylase.

This enzyme is require in the 20 step pathway from lanosterol (intermediate in cholesterol synthesis) to ergosterol.

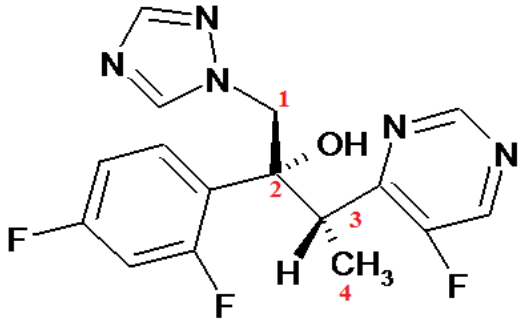
Fluconazole binds to the Fe center of the enzyme (one of the nitrogens coordinates to the Fe).

Synthesis;



flukonazol

VORİCONAZOLE

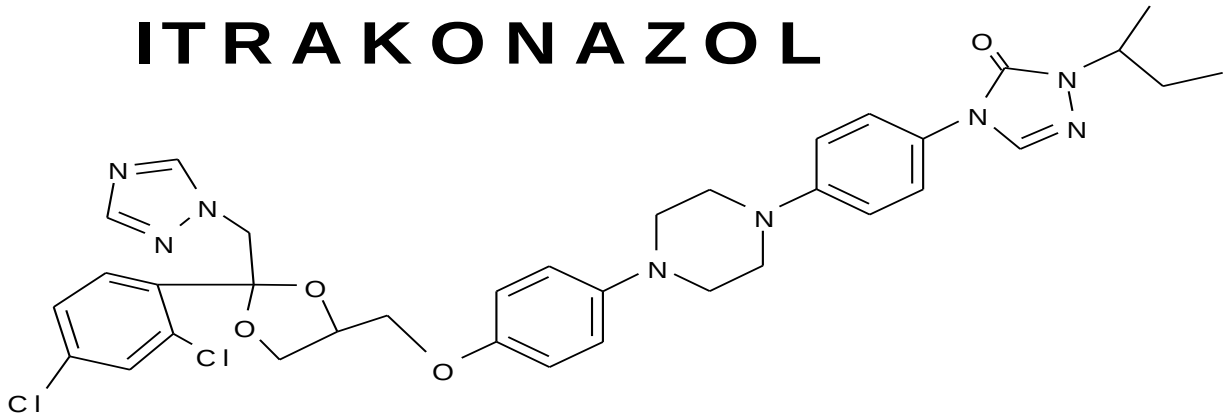


2R, 3S) 2- (2,4-difluorophenyl) -3- (5-fluoropyrimidin-4-yl) -1- (1H-1,2,4-triazol-1-yl)-butan-2-ol

It is effective against to ;

*Candidiasis that are susceptible or resistent to Flukonazole
*Cryptococcus neoformans
*Aspergillus
etc.

ITRAKONAZOL

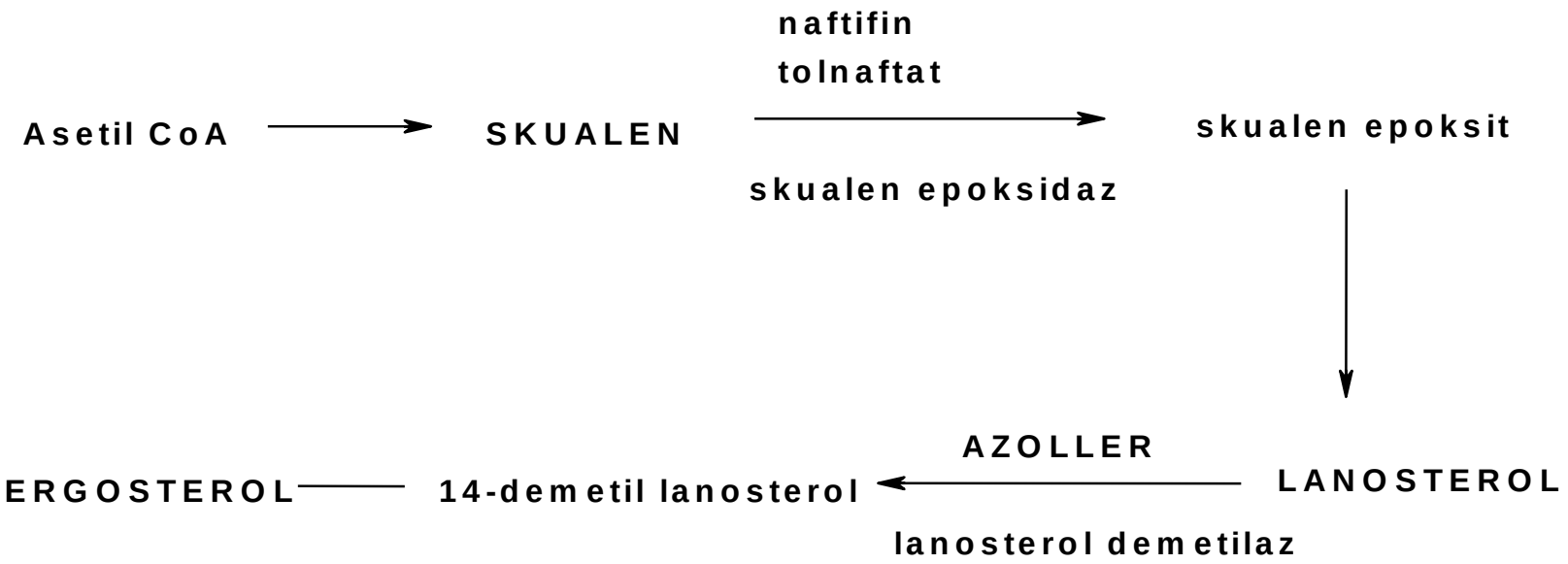


(2R, 4S) -1- (Butane-2-yl) -4- {4- [4- (4 - {[(2R, 4S) -2- (2,4-dichlorophenyl) -2- (1H- 1,2,4-triazol-1-ylmethyl) -1,3-dioxolan-4-yl] methoxy} phenyl) piperazin-1-yl] phenyl} -4,5-dihydro-1H-1,2,4 triazol-5-one

*Orally active.

*Systemic infections, including aspergillosis, candidiasis and cryptococcal meningitis

3. ALLILAMINE DERIVATIVES


naftifin
tolnaftat
Asetil CoA
SKUALEN
skualen epoksit
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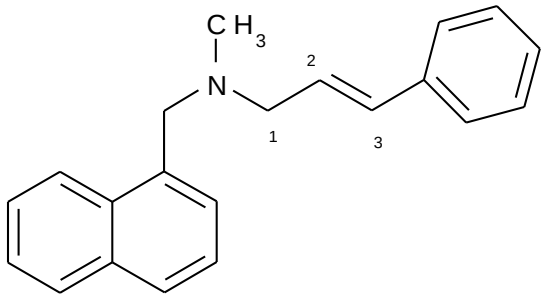
AZOLLER
ERGOSTEROL
14-demetil lanosterol
LANOSTEROL
lanosterol demetilaz

NAFTİFİNE



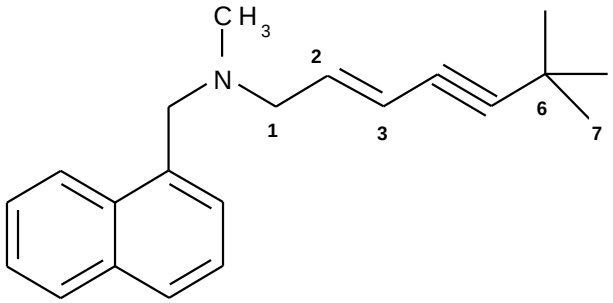
(E) -N-Methyl-N- (3-phenyl-2-propenyl) -1-naphthalene methanamide

*Uses at tinea infections like tinea pedis.

*Fungicide at low concentration against dermatophytes and fungustatic at high concentration against yeast fungi.

*It is a specific inhibitor of squalene epoxidase, an important enzyme in fungal ergosterol biosynthesis.

TERBİNAFİNE



(E) N- (6,6-dimethyl-2-hepten-4-in-yl) -N-methyl-1-naphthalene methanamine

*Oral (single dose per day) or topical use.

*Used in the treatment of onychomycosis (nail fungus) due to its fungicidal activity and its ability to concentrate in nails.

4- OTHER MEDICINES

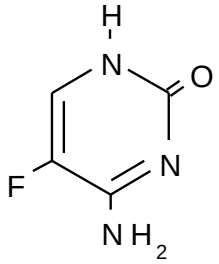
A- Systemically used

Flucytosine
Caspofungin acetate

B- Locally used

Fatty acids: Undecylenic, benzoic and salicylic Iodine (1-2% solution in alcohol)
tolnaftate
Cyclopirox olamine

FLUCYTOSINE (5-fluorocytosine)



4-amino-5-fluoro-2 (1H) -pyrimidinone

*Synthetic, very toxic

*Resistance develops

*Used orally in systemic fungal infections

*It has low effect and low toxicity than amphotericin B, so used in combination

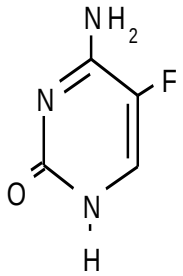
*Flucytosine was first developed as an antileukemic compound.

*It is effective against to candida, cryptococcus and aspergillus.

*Only fungus producing cytosine deaminase is sensitive to flucytosine.

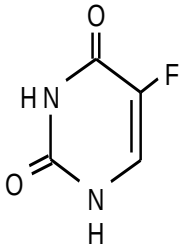
*Absorption from the GI channel is quite good.

flusitozin



sitozin deaminaz

5-fluorourasil
(antineoplastik)



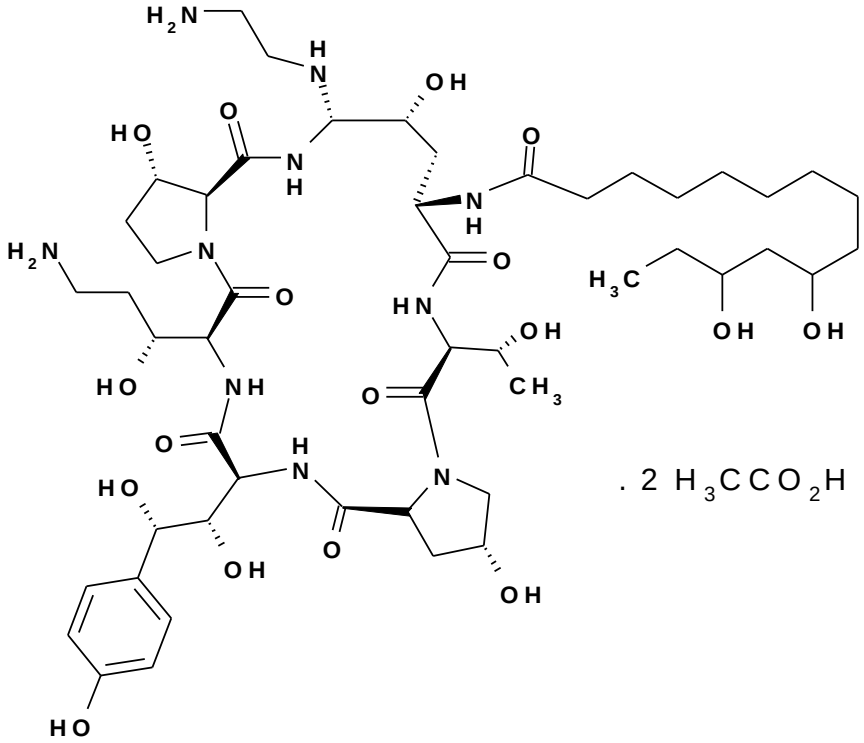
5-fluorodezoksi
urasil
(metabolit)

timidilat sentetazi inhibe eder.

RNA, DNA sentezi inhibe olur

insan dokuları çok az sitozin deaminaz içerir

KASPOFUNGİN asetat (**Cancidas** IV infüzyon için liyofilize toz)



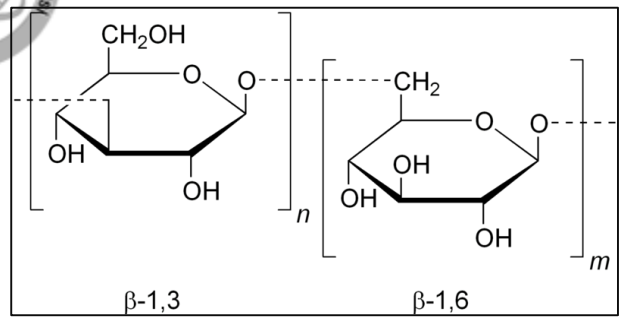
*Semisynthetic cyclic lipid-bearing polypeptide

*Belongs to class of antifungals: echinocandins – derived from the cyclic polypeptide.

*Large MW, low oral bioavailability => administered intravenously.

*Market 2001

CASPOFUNGIN



Mech of Action:

*Potent inhibitor of the fungal enzyme 1,3-(beta)-D glucan synthase.

*This enzyme catalyzes glucan polymerization (glucan is just a polymeric sugar molecule), which is essential in the synthesis of a fungi's cell wall.

*Human cells do not possess a cell wall, so the drug is effective.

*Cross-resistance between amphotericin B and azoles and caspofungin is not expected because the mechanism of action of caspofungin is unique.

*Effective against to Aspergillus and candida species.

*Not effective against Cryptococcus neoformans, but when used in combination with amphotericin B or fluconazole, it has a synergistic effect against C. neoformans.

b- Locally used

Fatty acids

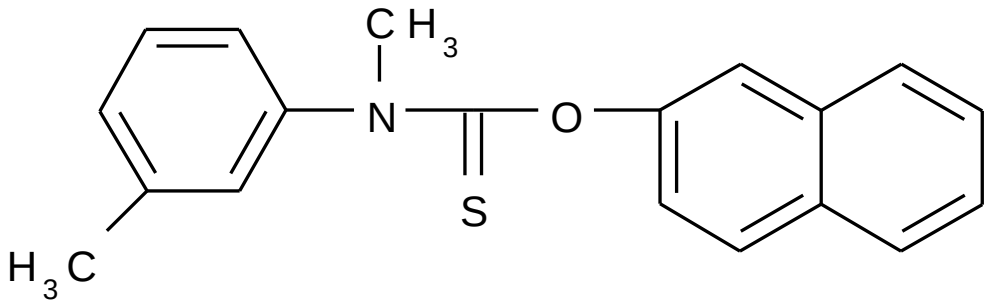
Propiyonik ac toksik ve irritan değil
CH_3CH_2COOH, Na, NH_4^+, Ca, Zn, K
fungustatik

Undesilenik asid fungusid
$CH_2=CH(CH_2)_8$-COOH (Zn tuzu %20 lik merhem
dietilamin tuzu)

*Undecylenic acid is the most effective acid derivative used for fungicidal purposes.

*It is prepared by distillation from Indian oil.

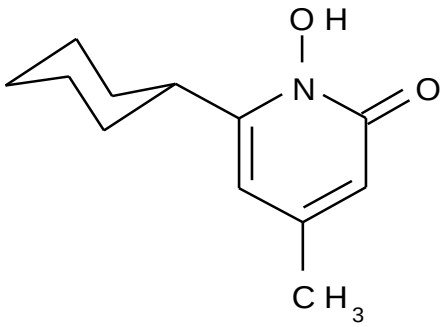
TOLNAFTATE



O-2-Naphthyl 3, N-dimethylthiocarbanylate

Topical 1% cream, powdered spray is used.

CYCLOPROXY olamine



$H_2NCH_2CH_2OH$

6-sikloheksil-1-hidroksi-4-metil-2-(1H)-piridinon etanolamin

*Broad spectrum

*At low concentrations, it affects the cell membrane and blocks the transfer of amino acids into the cell.

*Loss of cell components at high concentration

*Onychomycosis treatment.