

ANTIFUNGAL AGENTS

- The fungal infections are superficial and systemic.
- SUPERFICIAL- The fungi causing infection of the hair , mucous membranes , nails or skin include candida (Candidiasis) ,dermatophyte fungi as epidermophyton microsporum and trichophyton (tinea , ringworm).
- SYSTEMIC–Thesystemic infections Aspergillus,Blastomyces,Candida,Cryptococcus.
- CUTANEOUS INFECTION (dermatophytoses) – One of the most common type of humen fungal disease are among the dermatophytoses . these are superficial infection of the Keratinized epidermis and Keratinized epidermal appendages (i.e. hair and nail).
- SUBCUTANEOUS FUNGAL INFECTIONS – Subcutaneous mycosis (fungal infection) refers to a group of fungal diseases in which both the skin and subcutaneous tissue are involved but typically dissemination to the internal organ occurs.

CLASSIFICATION

The antifungal agents can be divided into the following classes, based on their chemical structure , mechanism of action and sources.

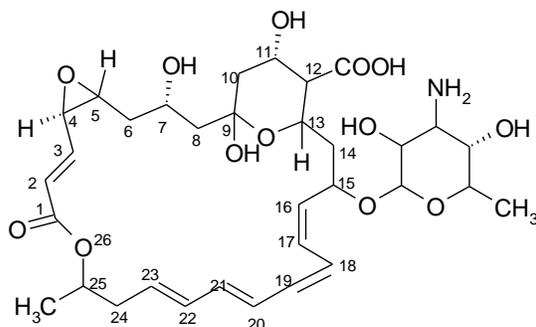
A) – POLYENES =>It has antifungal antibiotics have been isolated from soil bacteria of the genus Streptomyces.

The compounds are similar, in that they contain a system of conjugated double bonds in microcyclic lactone rings. They differ from the erythromycin type of structure , in that they are larger and contain the conjugated-ene system of double bonds.Hence they are called the polyene antibiotics.

Polyene divided into two groups.

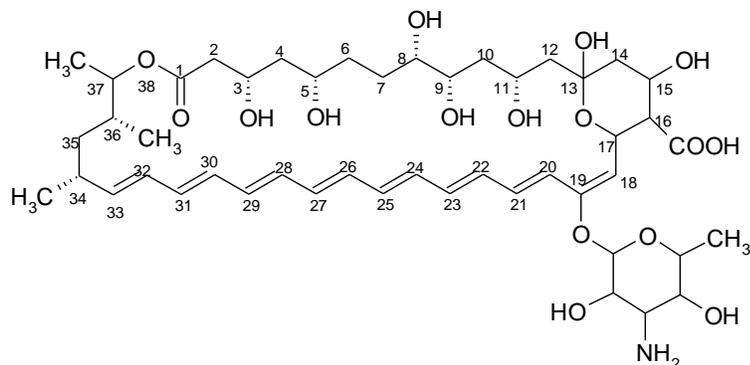
1)- 26-memberd-ring polyenes

Example - Natamycine



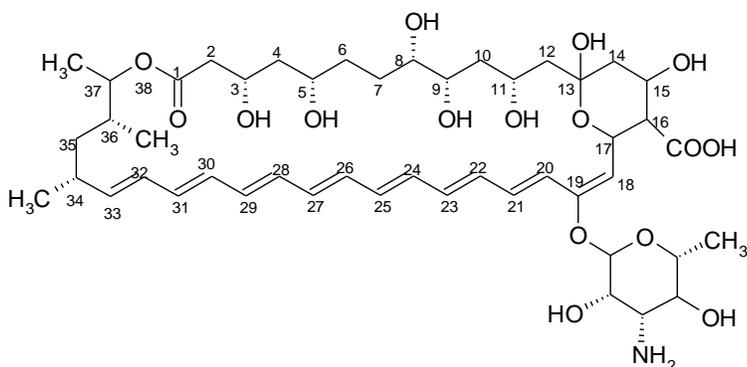
2)- 38- member macrocycles –

Example- Amphotericin B



- Amphotericin B (Fungizone) is produced by the growth of certain strain streptomyces nodosus. Which was isolated in Venezuela.
- It is a mixture of two compounds Amphotericin A and Amphotericin B But the Amphotericin B is most active .
- The Amino sugar mycosamine is glycosidically linked through position 19 of aglycone macrolide.
- Amphotericin B is an Amphoteric substances, with an primary amino group , attached to the mycosamine ring and carboxyl group on the macrocycle.
- Adverse effect – Nephrotoxicity

NYSTATIN



- Nystatin biologically active components are A1 , A2 and A3. The principal components of official product is Nystatin A1.
- Nystatin (Mycostatin) is a polyene antibiotic that was first isolated in 1951 from a strain of the actinomycete streptomyces noursei.
- Aglycon portion of nystatin is called nystatininollide . it also consist of a 38 – membered macrolide lactone ring containing single tetraene and diene moieties separated by two

methylene groups. The aglycone portion also contains hydroxyl groups. One carboxyl groups.

MECHANISM ACTION OF POLYENE =>

Polyenes is a three dimensional shape , a barrel- like nonpolar structure capped by a polar group (the sugar), they penetrate the fungal cell membrane acting as “false membrane components” and bind closely with ergosterol, causing membrane disruption, cessation of membrane enzyme activity and loss of cellular constituents, especially positive ions.

The drug is fungistatic at low concentration .At low concentration the polyenes bind to a membrane-bound enzyme component, such as an ATPase.

NATAMYCINE =>

Natamycin is a polyene antibiotic obtained from cultures of streptomyces natalensis. Natamycine structure consist of 26-membered lactone ring containing a tetraene chromophore,an α,β unsaturated lactone carbonyl group, three hydroxyl group , a carbonyl group, a transepoide and a glycosidically joined mycosamine. Mechanism action of the smaller polyenes differs from that of amphotericin B and nystatin. The 26- membered ring polyenes causes both potassium ion leakage and cell lysis at the some concentrating where as the 38-membered ring polyene causes potassium leakage at low fungistatics concentrations and cell lysis at high, fungicidal concentrations. The similar polyenes are fungicidal and fungistatic wiyhin the same concentration range.

B)-- AZOLES =>

Azoles represent a class of synthetic antifungal agents. The first members of the class were highly substituted imidazoles, such as Clatrimazole and Miconazole. Structure activity studies revealed that the imidazole rind could be replaced with a bioisosteric 1,2,3-trizole ring without adverse affecting the antifungal properties of the molecules. Hence, the more generic term azoles refers to this class of antifungal agents.

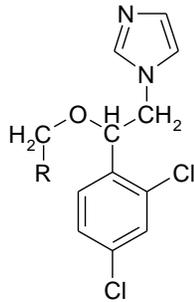
MECHANISM OF ACTION => At high concentration the azoles are fungicidal at low concentration , they are fungistatic. The fungicidal effect is clearly associated with damage to the cell membrane with the loss of essential cellular components such as potassium ions and amino acids . the fungistatic effects of the azoles at low concentration has been associated with inhibition of membrane-bound enzymes.

A cytochroms P-450-class enzyme, lanosterol 14 α -demethylase, is the target for the azoles. P-450 accus a here moiety as part of its structure and the basic electron pairs of the azole rings can occupy a binding site on P-450, preventing the enzyme from turning over.

The function of lanosterol 14 α -demethylase is to remove a methyl group from lanosterol during ergosterol biosynthesis. When demethylation is inhibited, the 14- α -sterol accumulates in the membrane, causing destabilization.

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

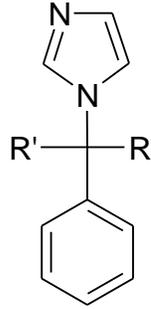
1)=> IMIDAZOLES



DRUG

R

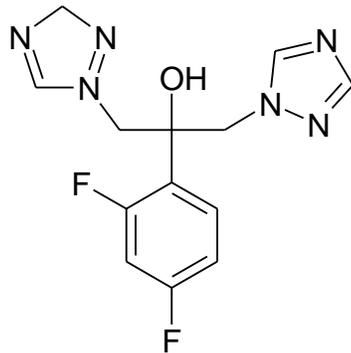
<p>➤ Miconazole</p>	
<p>➤ Econazole</p>	
<p>➤ Isoconazole</p>	



DRUG	R	\ddot{R}
➤ Clatrimazole		
➤ Flutrimazole		
➤ Bifonazole	H	

2) – TRIAZOLE =>

Example- Fluconazole =>

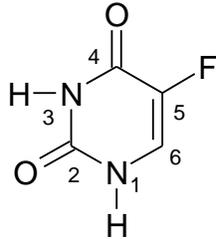


Itraconazole =>

Terconazole =>

C)- FLUORINATED PYRIMIDINES =>

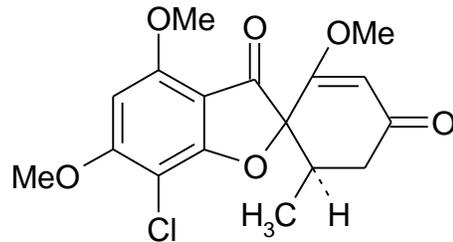
Example – Flucytosine



MECHANISM OF ACTION => Cytosine deaminase converts flucytosine to fluorouracil, than disrupting the protein synthesis.

D) – NATURAL PRODUCTS =>

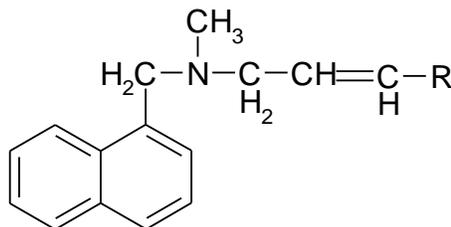
Example – Griseofulvin



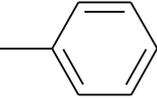
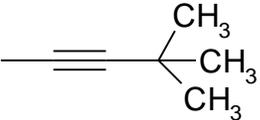
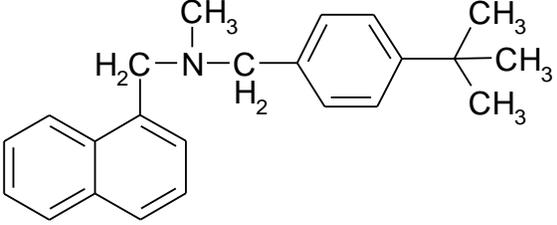
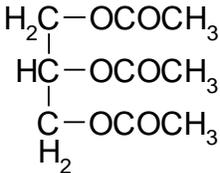
E) – CHITIN SYNTHETASE INHIBITORS =>

Example- Nikomycine.

F) –MISCELLANEOUS ANTI FUNGAL AGENT =>



DRUG	R
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<p>➤ Natifine</p>	
<p>➤ Terbinafine</p>	
<p>➤ Butenafine</p>	
<p>➤ Triacetin</p>	
<p>➤ Haloprogin</p>	
<p>➤ Ciclopirox</p>	