Q Classify anti-fungal agent with example. Give therapeutic uses and side effects of azole class of anti-fungal agent.

→

Anti-fungal agents are pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as athletes foot, ringworm, candidiasis, serious systemic infection such as cryptococcal meningitis
Are also called as an antimycotic agent.

Fungal diseases are those caused by pathogenic fungi, which are 100 species known to cause mycoses in human

Most fungal infections involve superficial invasion of the skin or mucous membrane of the body orifices

These diseases can usually be controlled by local application of the antifungal agents

They are eukaryotic organisms and possess cell wall.
Fungal cell wall is made up of chitin (N-acetylglutamate)
Cell membrane is made up of ergosterol

In 1950s the incidence of fungal infections were predominant.

Fungal infections are iatrogenic / drug induced

Infections majorly occur in immunocompromised people receiving immunosuppressant.

Human fungal infections can be divided into four groups:

1. Systemic or deep mycoses affect primarily internal organs and viscera. They are often extensively spread and involve many different tissues.

2. Subcutaneous myceses which involve bone fascia, skin and subcutaneous tissue, once fungi penetrate the skin remain localized in subcutaneous tissues

3. Cutaneous mycoses infest only epidermis and its appendages (hair and nail)

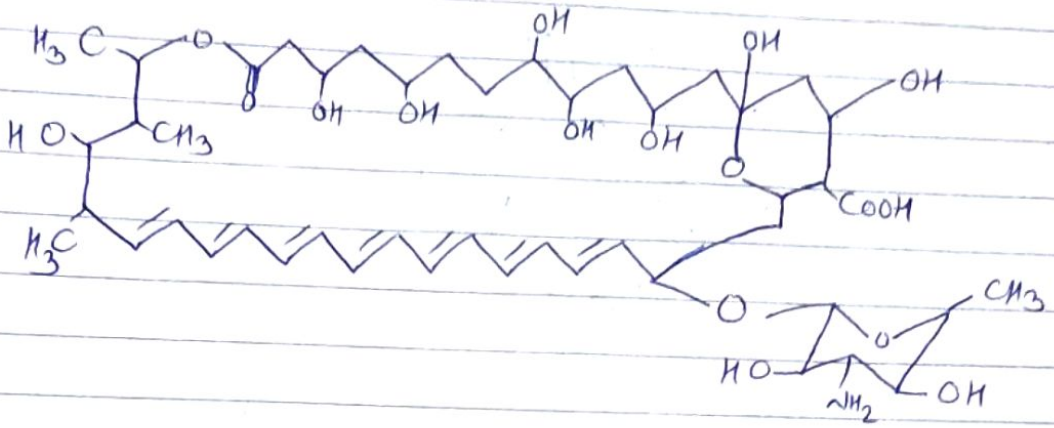
4. Superficial mycoses affect only hair and the most superficial layer of epidermis

Classification:

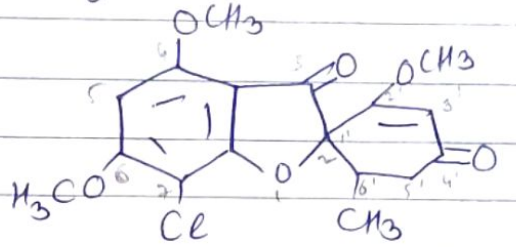
I Antibiotics
a) Polyenes
Eg: Amphotericin B*
Nystatin
Natamycin
Hamycin

DATE : / /20
PAGE : 03

☆ Amphotericin - B



b) Heterocyclic benzofuran
Eg: Griseofulvin

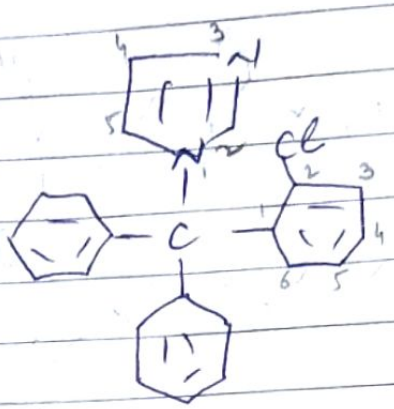


7-chloro-2',4,6-trimethoxy-6'-methyl-3H,4'H-spiro[1-benzofuran-2,1''-cyclohex-2-ene]3,4'-dione

II Antimetabolites
Eg: Flucytosine

III Azole derivatives
a) Imidazoles
Eg: Clotrimazole*
Miconazole
Econazole
Oxiconazole
Ketoconazole
Bufoconazole

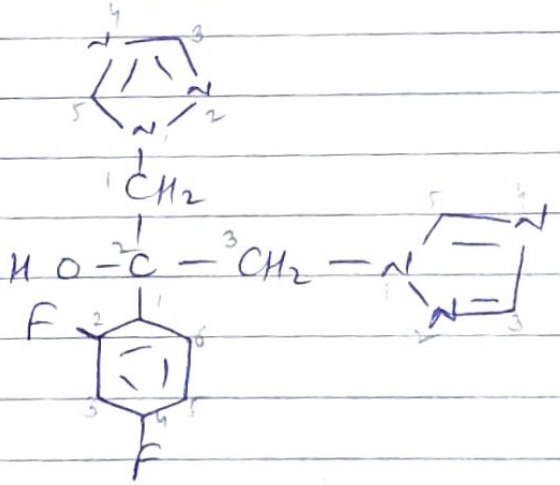
Clotrimazole



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

III b) Triazoles
Eg: Fluconazole *
Itraconazole
Terconazole

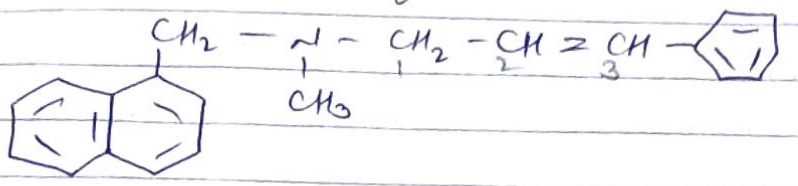
Fluconazole



2-(2,4- difluorophenyl)-1,3-bis [(1H)-1,2,4- triazol-1-yl] propan-2-ol

IV Allylamines
Eg: Naftifine *
Terbinafine
Butenafine

Naftifone

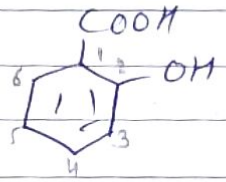


N-methyl-N-(naphthalen-1-yl methyl)-3-phenylprop-2-en-1-amine

V Acids and its derivatives

Eg: Salicylic acid
Benzoic acid
Propionic acid

Salicylic acid

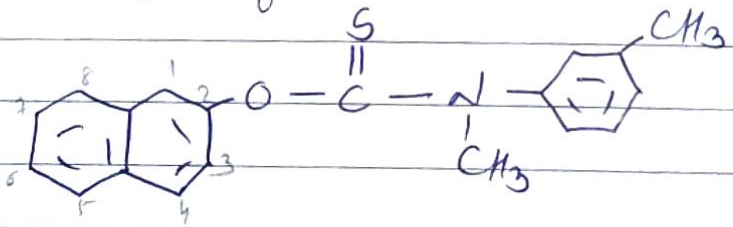


2-hydroxybenzoic acid

VI Miscellaneous agents

Eg: Tolnaftate
Ciclopirox
Parachlorometaxylenol

Tolnaftate



N-methyl naphthyl-2-yl-3-methylphenyl thiocarbamate.

Therapeutic uses of azole antifungals:

- Clotrimazole for treatment of topical infections like tinea, mucocutaneous candidiasis and vaginal candidiasis
- Miconazole - intravenously for treating systemic fungal infection.
  - Topically for treating tinea versicolor, mucocutaneous candidiasis, corneal infection.
- Ketoconazole - mucocutaneous and systemic mycoses, severe cutaneous dermatophytic infection.
- Fluconazole for treating mucocutaneous and systemic mycoses.

Side effects of azole antifungals:

Nausea, vomiting, Anorexia
Local discomfort.
Hepatotoxicity, edema, diarrhoea
Photosensitivity dermatitis, rash
Hypokalemia

Q Give mechanism of action of anti-fungal agents

→
- Anti-fungal agents are used to treat varieties of fungal infections.
- Most fungal infections involve superficial invasion of skin or mucous membrane of the body orifices.
- These diseases can usually be controlled by local application of the antifungal agents.

Mechanism of action:

I Polyene antibiotics.
Eg Amphoterican - B.

Amphoterican - B molecules bind to ergosterol on the plasma membranes of sensitive fungal cells

↓

They form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and sterol

↓

The pores disrupt membrane function, allowing electrolytes (K^+) and small molecules to leak from the cell resulting in cell death.

II Heterocyclic benzofuran
Eg: Griseofulvin

Griseofulvin arrests / inhibits cell division in metaphase

↓

The drug causes a rapid, reversible dissolution of mitotic spindle apparatus,

↓

apparently by binding with tubulin dimer required for microtubule assembly

III Azoles
Eg: Clotrimazole, Ketoconazole, Fluconazole

Azole antifungal inhibit sterol 14-α demethylase, a microsomal cytochrome P450-dependent enzyme system

↓

Thus impair the biosynthesis of ergosterol from lanosterol for cytoplasmic membrane

↓

Leads to accumulation of 14-α methyl sterols

↓

This methyl sterols may disrupt packing of aryl chains of phospholipids ie. functioning of certain membrane bound enzyme systems, such as ATPase & electron transport system

↓

Thus, Inhibiting the growth of fungi.

Allylamines.
Eg: Naftifine, Terbinafine, Butenifine

Naftifine inhibits ergosterol synthesis
↓
Inhibiting squalene epoxidase - enzyme that is part of fungal cell wall synthesis pathway
↓
Naftifine prevents conversion of squalene to lenosterol
↓
Thereby ergosterol synthesis does not take place.

Q Discuss about anti-HIV agent. Give synthesis of acyclovir.

→

Anti-HIV agents are agents used to treat AIDS and/or stop the spread of HIV infection.

Anti-viral agents are substances used on the treatment and prophylaxis of disease caused by viruses.

Viruses are obligate intracellular parasites, smallest of all self replicating organisms, able to pass through filter that retain the smallest bacteria

Virus conduct no metabolic process on their own. They invade the host cell which may be bacteria, animal or plant cell.

Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.

Anti-viral agents inhibits active replication so the viral growth resumes after drug removal

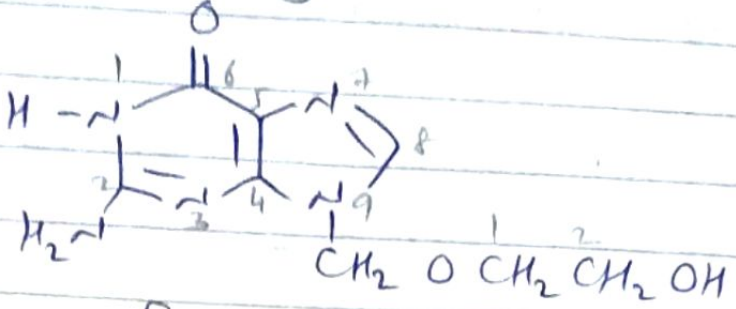
Key characteristics:

- Able to enter the cells infected with virus.
- Interfere with viral nucleic acid synthesis and/or regulation.
- Some drugs interfere with ability of virus to bind to cells
- Some drugs stimulate the body's immune system
- Best responses to antiviral drugs are in patients with competent immune systems.
- A healthy immune system works synergistically with the drug to eliminate or suppress viral activity.

Classification:

I Nucleoside Reverse Transcriptase inhibitors
a) Purine nucleoside and nucleotides.
Eg: Acyclovir
Gancyclovir
Didanosine

Acyclovir

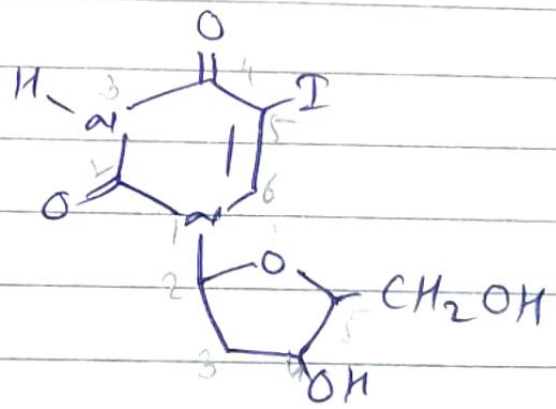


2-amino-9[(2-hydroxy ethoxy) methyl]-1H-purin-6-[9H]-one

b) Pyrimidine nucleoside and nucleotides

Eg: Idoxuridine
Zidovudine
Lamivudine

Idoxuridine



1-[4-hydroxy-(5-hydroxymethyl) oxalan-2-yl] 5-iodo-1,2,3,4-tetrahydro pyrimidin-2,4-dione

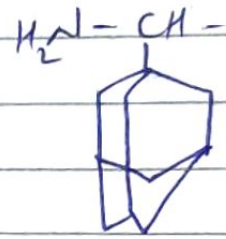
c) Thiosemicarbazones
Eg: Methisazone

d) Adamantane amines / derivatives.
Eg: Amantadine *
Rimantadine *
Somantadine

Amantadine

1-amino adamantane

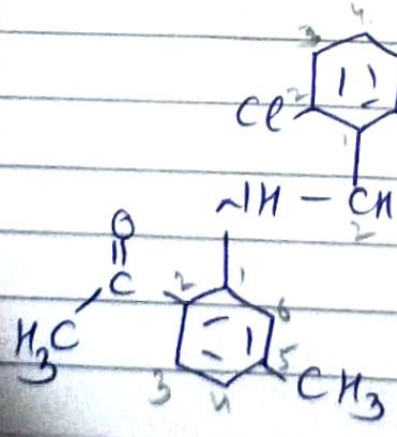
Rimantadine



α-methyl-1-adamantane methyl amine

II Non-nucleoside reverse transcriptase inhibitors.
Eg: Loviride *
Delavirdine
Troviridine

* Loviride

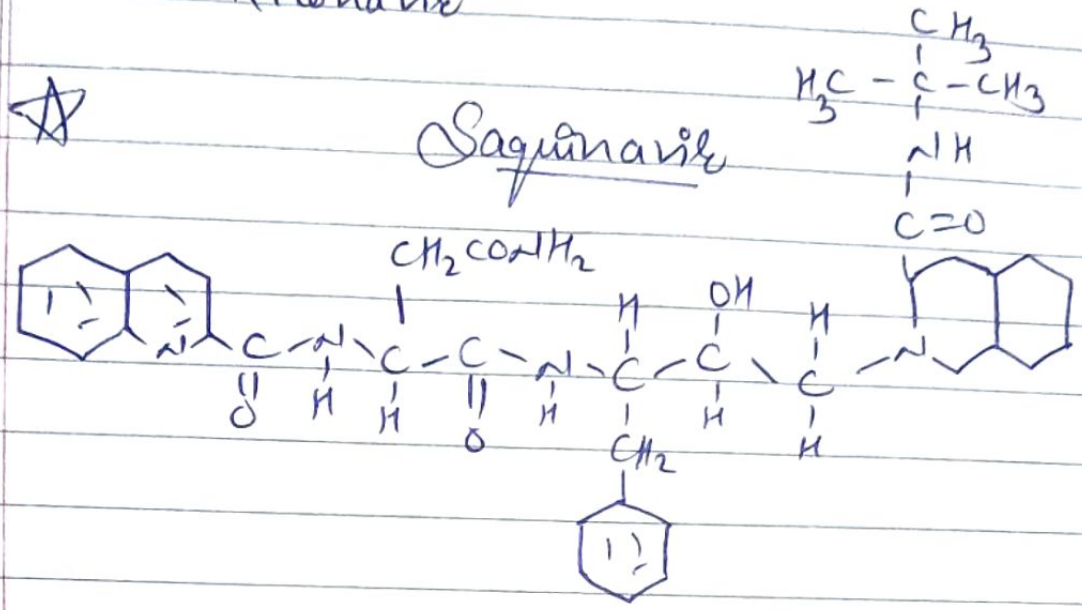


2-(2-acetyl-5-methyl anilino)-2-(2,6-dichloro phenyl) acetamide

III HIV protease inhibitor

Eg: Saquinavir
Indinavir
Ritonavir

Saquinavir

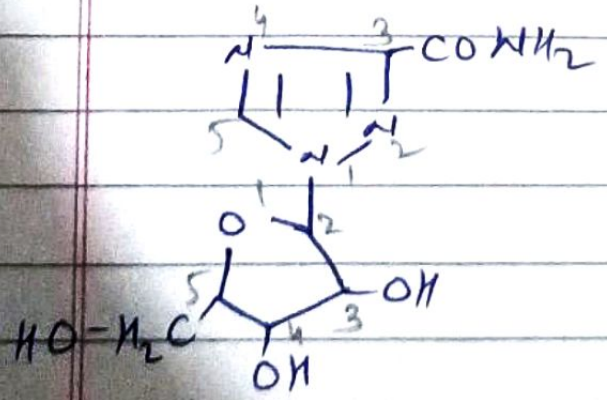


N-(4-(3-tert butyl carbamoyl)-octahydro, (1H) isoquinolin-2-yl)-3-hydroxy-1-phenyl butan-2-yl) 2-(quinoline-2-carbonylamino) butane diamide

IV Miscellaneous agents

Eg: Ribavirin
Foscarnet sodium

Ribavirin



1-[3,4-dihydroxy-5-(hydroxymethyl) oxalan-2-yl]-[1H]-1,2,4-triazole-3-carboxamide

Uses:

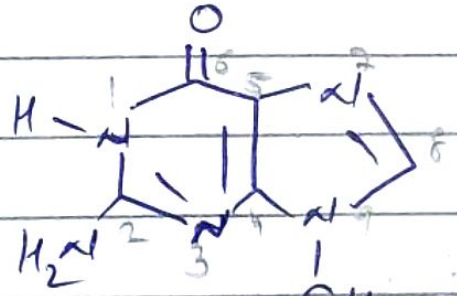
Acyclovir - treatment of herpes simplex virus, recurrent mucocutaneous herpes, primary and secondary genital herpes and herpes simplex encephalitis.

Idoxuridine - topical treatment of HSV infection of eyelid, conjunctiva & cornea.

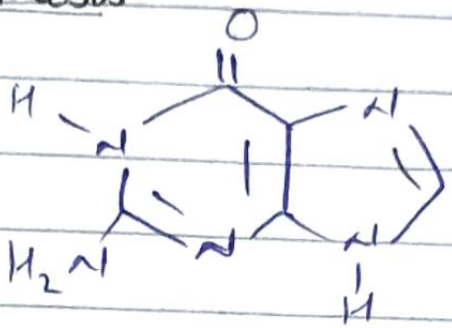
Side effects:

Hypersensitivity reaction.
Nausea, vomiting, abdominal pain
Peripheral neuropathy, Pancreatitis,
Increase in cholesterol
Risk of heart disease

✡ Acyclovir



Synthesis:



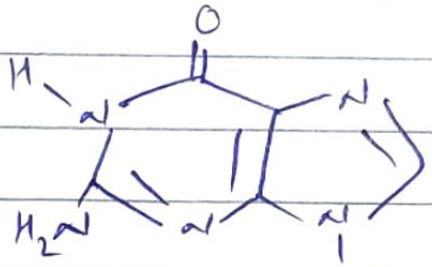
2-amino-1H-purin-6[9H]-one

(i) $(CH_3)_3Si_2NH$

(ii) $(C_2H_5)_3N$

(iii) $C_6H_5-COO-CH_2-CH_2-OCH_2-Cl$

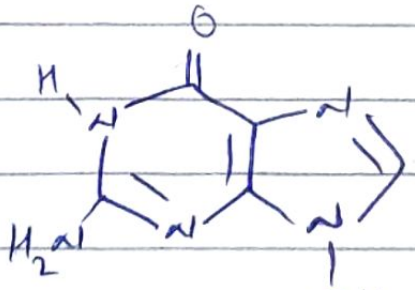
$-HCl$



$CH_2OCH_2CH_2OCOC_6H_5$

$NaOH$

$-C_6H_5COONa$



$CH_2OCH_2CH_2OH$

Acyclovir

Q Discuss various approaches used in drug design.

→

Drug design is the inventive process of finding new medications based on the knowledge of a biological target.

Drug design depends on computer modeling techniques. This type of modeling is referred as computer-aided drug design

Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design

Drug designing is challenging, expensive and time consuming process.
It is multidisciplinary approach

Principles of drug designing:
- Improving the selectivity
- Increasing the selectivity
- Reduce side effects.
- Arrangement functional groups and identification of a pharmacophore

There are two ways of drug designing:

- Development of ligands with desired properties of targets having known structure and functions.
- Development of ligands with predefined properties for targets whose structural information may be or may not be known

The concept of lead discovery predicts two investigational processes. They are:

1. Exploration of leads - search of new molecules.
2. Exploitation of leads - assessment, chemical modelling and extension of leads.

Approaches

I Approaches to lead discovery

a) Random screening

- The entire synthesized compounds or any chemical constituents obtained from natural products are evaluated in a series for their biologically active compound components.
- Thus, random screening may produce unexpected active medicines.

- Antibiotics such as streptomycin, tetramycins and fungal metabolites such as lovastatin and cyclosporine, were found through this method.
- This approach needs more manpower and it is expensive and time-consuming and the success rate is considerably low.

b) Non-random screening
In this method, only compounds that possess similar structural skeletons were evaluated from their particular properties.

c) Pharmacokinetic studies
- Biotransformation occurs as the fate by metabolizing enzymes.
- In order to develop new leads, the metabolites or biotransformed compounds are studied for their properties and such studies are expected to asses the activity from a comparison with the parent molecule
- For example, the discovery of sulphanilamide is reported through the metabolic studies of prontosil

d) Pharmacodynamic studies.

- The effects apart from the therapeutic actions, that is, effects may lead to the finding out of a new molecule with some appreciable structural modification
- For example, sulphonamide used specifically for treatment of typhoid, lowered the blood sugar levels drastically
- This exerted action led to the finding of aryl sulphonyl thiourea moiety responsible for the lowering of blood glucose level

II Rational approach to drug design

There are many approaches to drug designing in relation with physiochemical parameters and electronic features taken into consideration for designing a drug

(i) Approach with quantum mechanics.

- Quantum mechanics or wave mechanics contain certain vital principle derived from fundamental assumption, it describes natural phenomenon effectively
- The properties of proton, neutron, electron sufficiently explained under the quantum mechanics, and the electronic feature of molecules responsible for chemical alteration ≤ is basis for drug design

(ii) Approach with molecular orbital theory

- It is based on assumption of electron present in molecule is directly linked with orbital engulfing the entire molecule which set molecular orbital theory
- The molecular orbital approach shows dependence on electronic charge and also molecular conformation such as bond length, bond angle (including torsional angle).
- Molecular orbital calculation are done by using sophisticated computers and software and interprete the results of molecular structure with respect to structure activity.

(iii) Approach with molecular connectivity

- This approach establish in presence of structural features like cyclization, unsaturation, branching, position and presence of heteroatoms with a series of numerical indices.
- This approach has some limitation such as electronegativity variation b/w atoms. Do not distinguish b/w cis and trans isomerism.

(iv) Approach of linear free-energy

- This method establish link b/w proper selection of physicochemical properties with specific biological phenomenon
- Such correlation may not be guarantee and allow a direct interpretation with respective molecular structure but may offer possible clue towards selection of molecule (reactant) for synthesis.