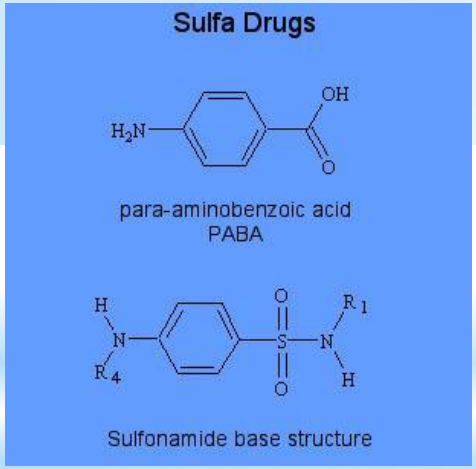
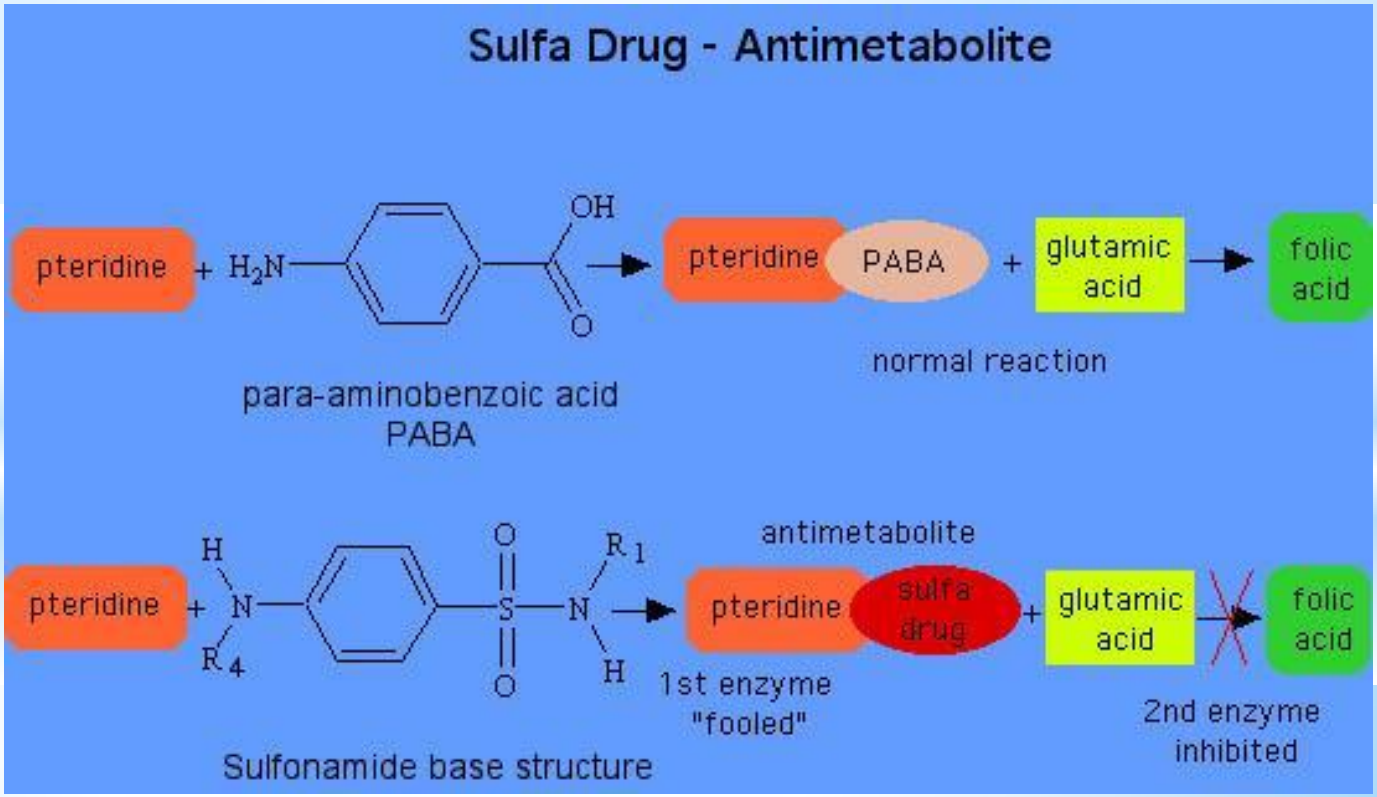
ZSMU Pharmacology Department

Lecture № 8

Sulfonamides, Fluoroquinolones, Oxiquinolines, Nitrofurans, Quinoxalines, Oxazolidinones and Antifungal Drugs



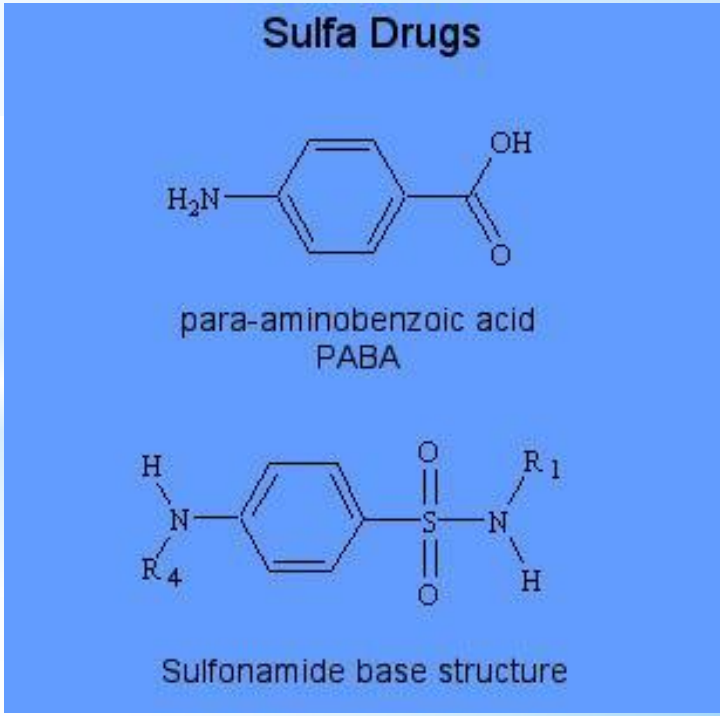


Sulfonamides – the synthetic antimicrobial agents, containing a sulfonamido (–SO_2–NH–) group.

This group is present in other compounds like antidiabetic sulfonylureas, diuretics like *thiazides*, *furosemide*, and *diacarb*.

The structure of the sulfonamides is similar to Para-Aminobenzoic Acid (PABA).

Sulfonamides tend to be much more soluble at alkaline than at acid pH. Solubility may be decreased in acidic urine, resulting in precipitation of the drug or its acetylated metabolites.



CLASSIFICATION of SULFONAMIDES

I. Oral, Absorbable (*Systemic Action*):

1. Short-acting (6-9 hours):

Sulfadimezine, Sulfazine, Ethazol, Urosulfane

2. Long-acting (24 hours) :

Sulfapyridazine, Sulfadimethoxine

3. Ultra-long acting (72 hours): *Sulfalen*

4. Combined preparations with:

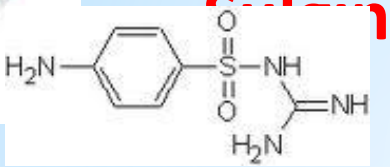
- Trimethoprim: *Co-trimoxazole* [*Biseptol*]
- Aminosalicylic acid: *Salazopyridazine, Sulfasalasine*

Salazodimethoxine

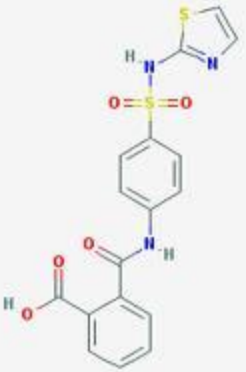
II. Oral, Non-Absorbable

(*acting the intestinal flora*):

Phthalazol



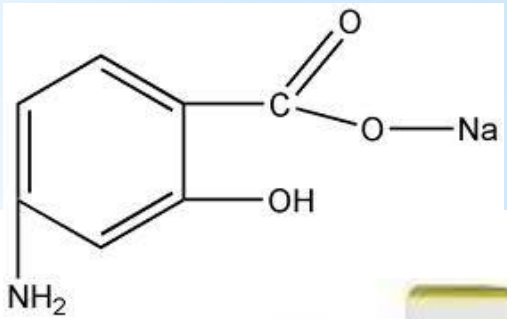
Sulgin

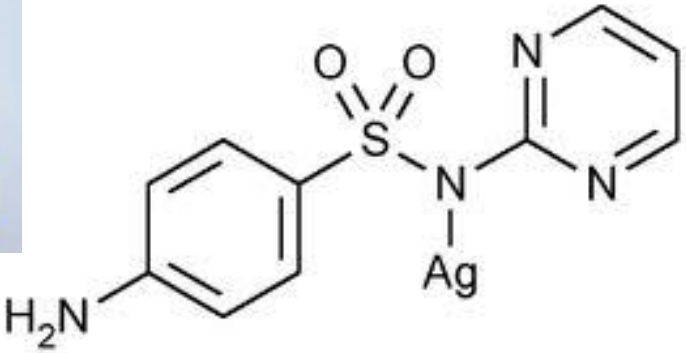


III. For Topical Use:

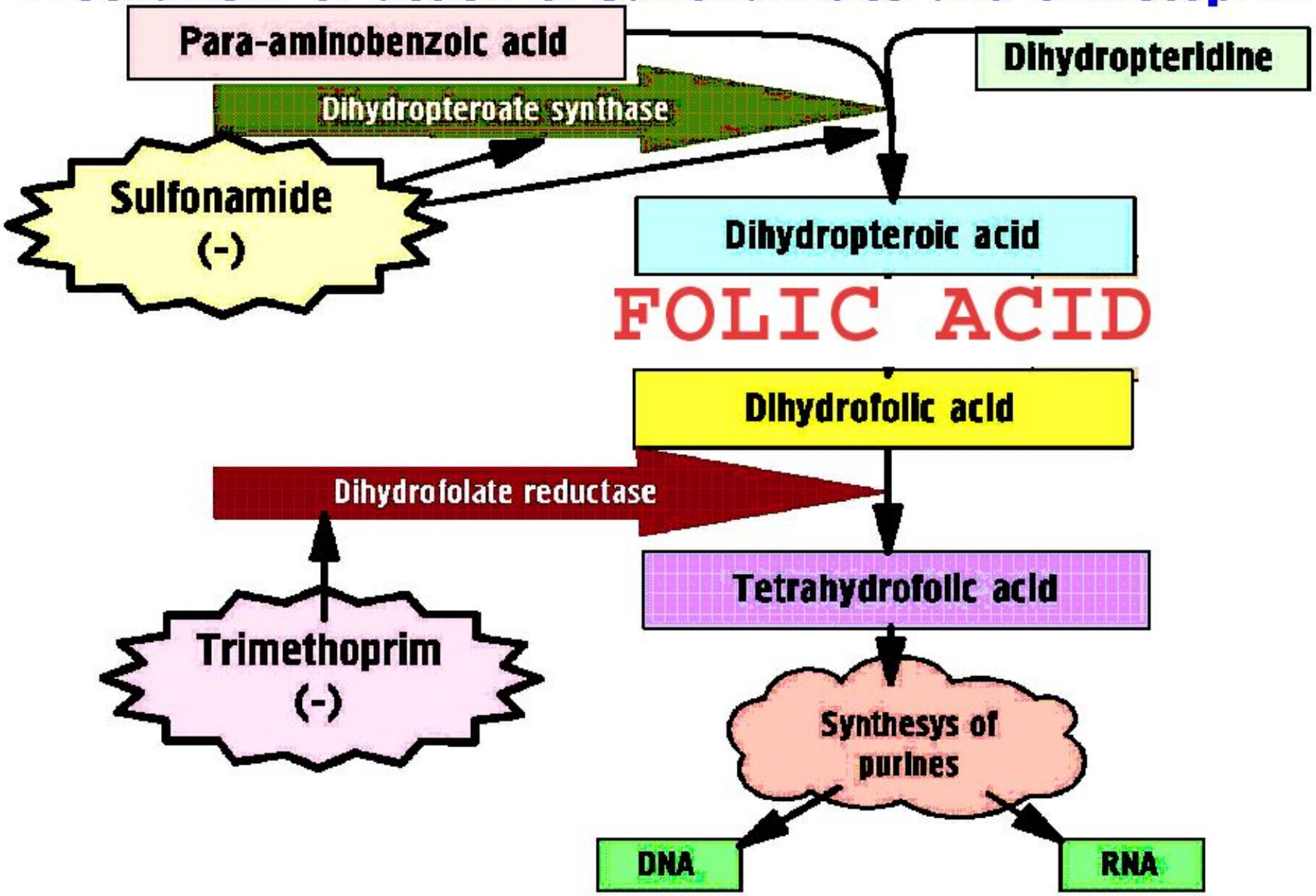
Sulfacil-natrium *(Albucid)*–

Silver Sulfadiazine (1% cream)





Mechanism of action of sulfonamides and trimetoprim



Clinical Uses of Sulfonamides :

- Respiratory infections
- Acute **urinary tract infection**: **Urosulfan**
- Combined with **Pyromethamine** –

  for drug-resistant ***malaria***, and for ***toxoplasmosis***
- Inflammatory bowel disease, non-specific ulcerative colitis

  - ***Sulfasalazine*** (*Sulfapyridine* + *Aminosalicylate*)
- Some sexually transmitted infections -

  trachoma, ***chlamydia***

Co-trimoxazole: the combination of

Sulfamethoxazole and **Trimethoprim**:

is generally bactericidal

- acts by sequential blockade of **folic acid** **enzymes** in the synthesis pathway:

Sulfamethoxazole inhibits formation of dihydrofolic acid from PABA,

Trimethoprim inhibits dihydrofolate reductase responsible for formation of tetrahydrofolic acid from dihydrofolic acid

Co-trimoxazole is effective against :

Escherihia coli

Klebsiella

Enterobacter

Streptococcus pneumoniae

Staphylococcus aureus

Salmonella

Shigella

Clinical uses: Chronic Bronchitis,

Urinary tract infections, Otitis media,

Pneumocytis carini pneumonitis, Traveller's Diarrhea, Pertussis, Cholera.

Adverse Effects of Sulfonmides:

- **Hypersensitivity Reactions: rashes, angioedema.**

All sulfonamides and their derivatives, including

Diacarb, Thiazides, Furosemide, Glibenclamide, Diazoxide are CROSS-ALLERGIC

- **Nephrotoxicity, Urinary tract disturbances:**

Sulfonamides precipitate in urine, esp. at **neutral** or **acid pH**, producing **crystalluria**, **haematuria**, or even **obstruction**.

Adequate HYDRATION and ALKALINIZATION of **urine prevent the problem**

- **Haemopoietic disturbances: hemolytic anemia, agranulocytosis, leukopenia, thrombocytopenia**

- **CNS: Depression, aseptic meningitis, seizures**

Acute Poisoning/Overdose with Sulfonamides

Sulfonamides are able to:

- form **methemoglobin** and **sulf-methemoglobine**,
- block the haemopoiesis and
- produce hepato- and nephrotoxicity.

Manifestation: dizziness, drowsiness, unconsciousness, anorexia, abdominal pain, nausea, vomiting, haemolytic anemia, acidosis, agranulocytosis, sensitivity reactions, jaundice, hepatomegalia

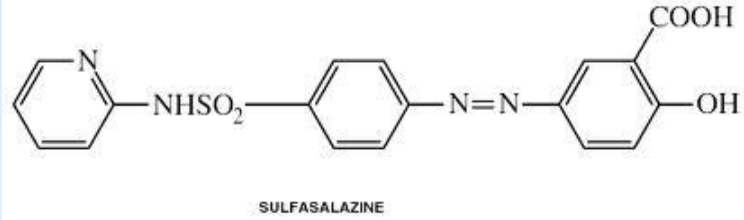
Treatment: gastric lavage, forced diuresis

ANTIDOTES:

* *Nicotinic acid IV 1% solution 2–5 ml* or *Nicotinamide*
* *Chromosmon* (1% *Methylene Blue* solution in 25% glucose) *IV 0.1 ml/kg*
* *Lipoic acid IV 0.5% solution 60-80 ml*
* *Folic acid PO 1 mg tid*

Sulfasalazine - Tab 0.5 g:

Sulfapyridine + *Aminosalicylic Acid* –



SULFASALAZINE

is split into its component parts by bacteria in the colon.

Clinical Uses:

- Ulcerative Colitis, Enteritis, Inflammatory Bowel Diseases
- **Rheumatoid diseases**: acts by **scavenging**

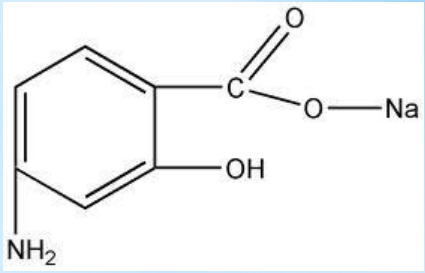
  the toxic **oxygen metabolites** produced by **neutrophils**
- ↓ ***IgA*** and ***IgM Rheumatoid Factor*** production
- **Suppression** of **T cell responses**
- **Inhibition** of **B cell proliferation**

- The absorption of *folic acid* is impaired –

  this can be countered by giving **Folic Acid** supplements

Sulfacyl-sodium (*Albucid*) –

10%, 15%, 30% **ophthalmic solution** or **ointment** - effective for:



- **Bacterial Conjunctivitis** and as **adjunctive therapy** for **Trachoma**.
- **Ocular gonorrheal infection** in ***newborns*** and **adults**.

It acts by **inhibiting the uptake of PABA**, which is required in the synthesis of **Folic Acid** needed for **bacterial growth**.


New Born Baby with Gonorrhoea Eye Infection

Naphthyridine derivatives: Nalidixic acid

Quinolone derivatives: Oxalinic acid

Mechanism of action: inhibition of DNA-gyrase and supression of protein synthesis and cell division.

The type of action - bactericidal.

The action spectrum - gram(-) bacteria.

Side effects: dyspeptic disorders, headache, transitory photodermatoses.

Fluorquinolone derivatives:

- First generation - Ofloxacin, Ciprofloxacin, Pefloxacin, Norfloxacin, Lomefloxacin, Fleroxacin, Enoxacin, Levofloxacin.
- Second generation - Sparfloxacin, Moxifloxacin,
- Third generation - Tosufloxacin, Rufloxacin, Sitafloxacin,

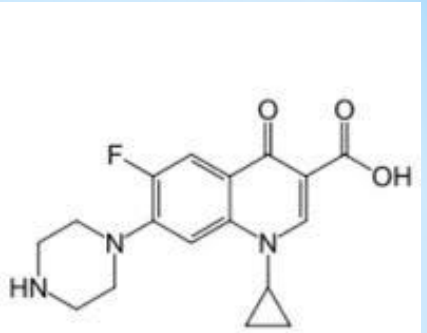
Mechanism of action: inhibition of DNA-gyrase and supression of protein synthesis and cell division.

The type of action - bactericidal.

The action spectrum - extended: gram(+) and gram(-) bacteria (including Pseudomonas aeruginosa, obligate anaerobes, Chlamidia, Mycoplasma).

Side effects: dyspeptic disorders, headache, convulsions

Ciprofloxacin (Tab. 0.5 g; amp. 1%-10 ml) – a **synthetic, broad-spectrum, bactericidal antibiotic, effective against** both **Gr(+)** and **Gr(-) bacteria**.



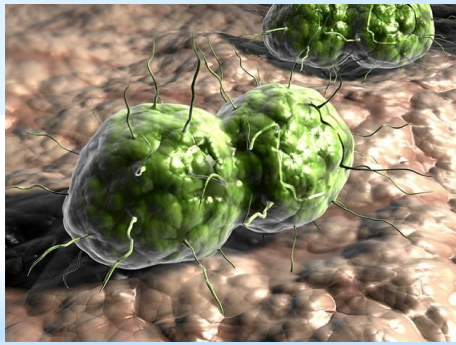
It has excellent activity against:

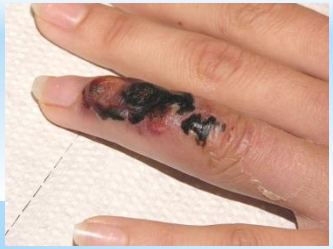
- ***Enterobacteriaceae***
- Enteric **coliform bacilli**, including **resistant to Penicillins**, **Cephalosporins** and **Aminoglycosides**
- ***Haemophilus influenzae,***
- **Penicillinase-producing *Neisseria gonorrhoeae*, *Campylobacter*** and ***Pseudomonads***.
- **Gr(+)** organisms, **streptococci** and **pneumococci** are **only weakly inhibited** and there is high incidence of ***staphylococcal resistance***.

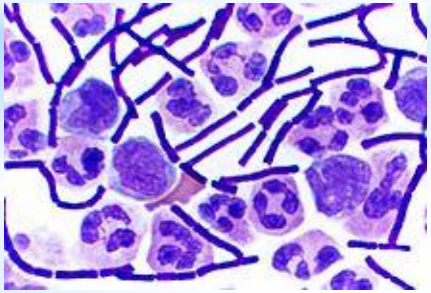
Clinical uses of Fluoroquinolones

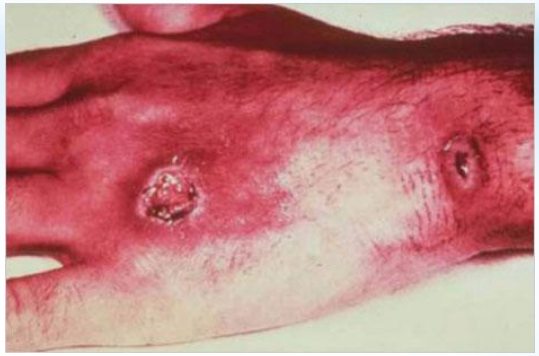
- **Urinary tract infections: Norfloxacin, Ofloxacin**
- Complicated **respiratory tract infections** - **Gr(-) flora**

  Pseudomonas aeruginosa respiratory infection
- **External otitis** caused by *P. aeruginosa*
- **Chronic Gr(-) bacillary osteomyelitis**
- **Eradication** of ***Salmonella typhi*** in carriers
- **Gonorrhoea: Norfloxacin, Ofloxacin**
- **Anthrax**

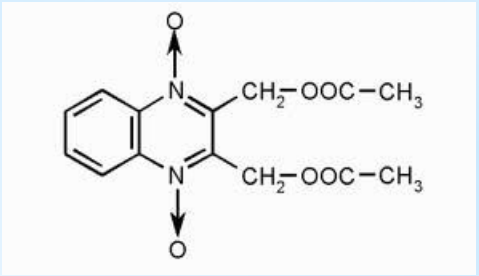


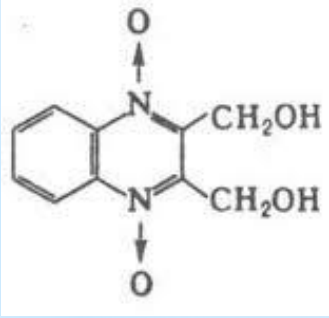






Quinoxalines





Chinoxydin

(***Quinoxydin*** – *tab. 0.25 g*)

Dioxydin (amp. 1%-10 ml for topical use;

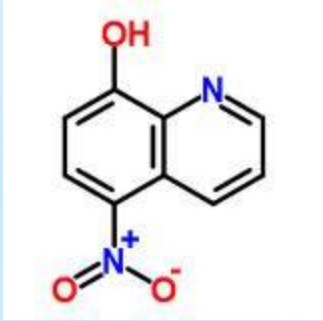
amp. 0.5%-10 ml IV).

- have **broad-spectrum** antibacterial effect including ***Proteus vulgaris***, **blue pus bacillus**, **pathogen anaerobes** and **others**.
- are used in **severe pyoinflammatory processes**.
- are toxic and adverse effects are not infrequent and include GIT upsets, headache, chill, seizures, allergic reactions.

Nitroxoline (*5-NOK, Nitrox)* – Tab. 0.05 g

a **Urinary Antiseptic** -

a **broad-spectrum**, **bacteriostatic agent**.



- blocks **replication** of **nucleonic acids**, forming **chelate complexes** with microelements (Fe, Cu)of **microbes**

=> enzyme systems inhibition.

- is **quickly absorbed** from GIT,

eliminates in **unmodified mode** with **urine**,

where it is **accumulated** in **bacteriostatic concentrations**.

Clinical uses: **urinary tract infections** (**Cystitis**, **Prostatitis**, **Pyelonephritis**, **Urethritis**), **prophylaxis** of **infections** after **kidney** and **urinary tract** surgery.

Side effects: GIT upsets. Urine is discolored **brightly yellow** during administration of drug.

Nitrofuran derivatives:

- Agents for treatment of the urinary tract infections - Furaginum *[Furazidin]*, Furadoninum *[Nitrofurantoin]*, Nifurtoinol, Nifuratel.
- Agents for treatment of the intestinal infections - Furazolidone, Nifuroxazide.
- Agents for local use - Furacillinum.

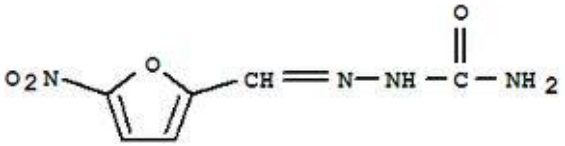
Mechanism of action: inhibition of enzymes of cell membranes of the micro-organisms.

The type of action - bacteriostatic, in high dose - bactericidal.

The action spectrum - extended.

Side effects: dyspeptic disorders, fever, allergic reactions.

Furacilin (***Nitrofurazone, Furacin***)



*0.02% **water solution**, **Tab**. 0.02 and 0.1 g*

is a **synthetic**, **broad-spectrum antibacterial nitrofuran derivative** used mainly for topic application as **ANTISEPTIC**:

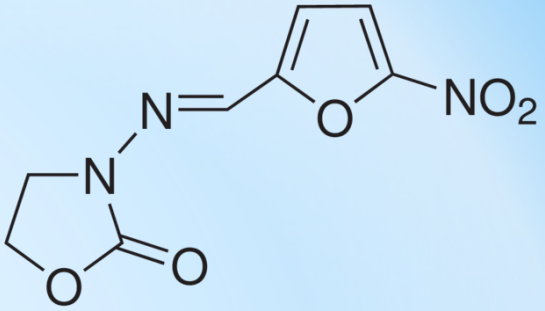
- Externally for the treatment and prevention of pyoinflammatory processes, major burns

(esp. when resistance to other antibacterial agents occurs);

- Prevention of skin graft infections.

0.02% *Furacilin Solution* is applied directly to **lesion** or to **dressing** used to **cover** the **affected area daily** or as **indicated**, **depending** on **severity** of **burn** or **injury**.

Furazolidone (Tab 0.05 g) is a nitrofuran compound active against many Gr(–) bacilli including ***Salmonella***, ***Shigella***, ***Giardia lamblia*** and ***Trichomonas***.



Clinical Uses:

- For **giardiasis** 100 mg tid for 5–7 days is inferior to **Metronidazole** or **Tinidazole**.
- **Intestinal infections**: **Bacterial Enteritis**
- **Food poisoning diarrhoeas, Bacillary Dysentery**
- **Trichomonad colpitis**

Furazolidone is partly absorbed from intestines and excreted in urine which **turns orange** – patients should be told about it.

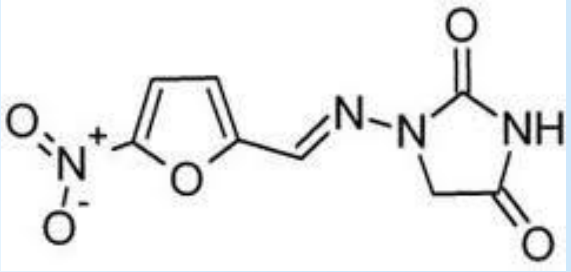
It is used **orally**, **intravaginally** and **rectally**.

Adverse effects are mild and infrequent – nausea, headache, dizziness.

Furadonin *(**Nitrofurantoin** – Tab. 0.05 g, Caps. 0.1 g) is* an effective urinary antiseptic.

- Is a **bacteriostatic** compound, but may be **cidal** at **higher concentrations** and in **acidic urine**:

its **activity** is **enhanced** at **lower** pH 5.5 or below.



- Ihibits many Gr(+) and Gr(–) bacteria.
- It antagonizes the action of Nalidixic acid.

Mechanism of action. Susceptible bacteria appear to **enzymetically reduce furadonin** to generate the **active form**:

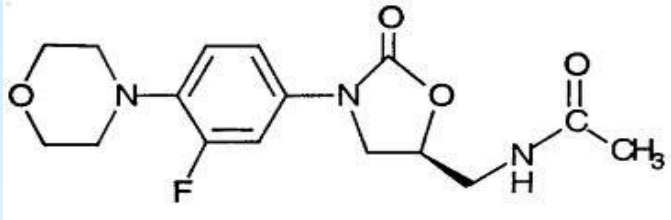
it **is highly reactive** and damages **DNA**.

Clinical uses: urinary tract infection.

Adverse reactions: **Interstitial changes** in the **lung**, **bronchoobstructive syndrome**, **cough**; **neuropathies** and **hemolytic anaemia** occur in **glucose-6-phosphate dehydrogenase** deficiency.

Rashes, **pulmonary infiltration** and other **hypersensitivity reactions** (**chills**, **fever**, **anaphylaxis**); **nausea**, **epigastric pain**, **diarrhoea**.

OXAZOLIDINONES



Linezolid *(Zyvox)* – tab. 0.6 g, amp. 15% - 2 ml

- a synthetic antibiotic for the treatment of resistant

  Gr(+) coccal (aerobic and anaerobic) and bacillary infections.

  Gr(–) bacteria ARE NOT INHIBITED!

It is active against *methicillin* resistant and *vancomycin* resistant

Staph. Aureus (VRSA), *vancomycin* resistant enterococci (VRE),

penicillin resistant *Strep. pyogenes, Str. viridans* and *Str. pneumoniae, Corynebacterium, Listeria, Clostridia* and *Bact. fragilis.*

Linezolid is primarily bacteriostatic, but cidal against some streptococci, pneumococci and *Bact. Fragilis*.

MOA: It binds to the 23S fraction of the 50S ribosomes and interferes with formation of the ternary tRNA-ribosome-mRNA complex and stops protein synthesis before it starts.

There is no cross resistance with any other class of antibiotics.

ANTIFUNGAL DRUGS

I. For the treatment of mycoses cause

by **Pathogenic Fungi**:

1. For **subcutaneous** and **systemic my**

Antibiotics:

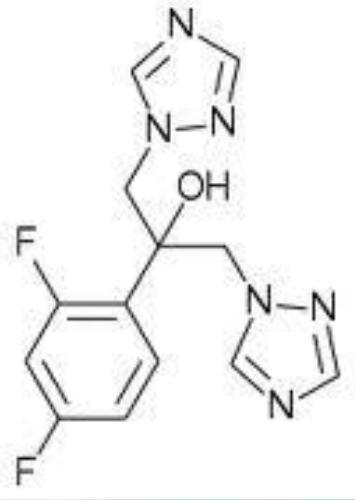
Amphoterici

Mycoheptin

Azole derivatives:

· **Imidazoles: Ketoconazole, Miconazo**

· **Triazoles: Itraconazole, Fluconazole**



2. Drugs for **Superficial Fungal Infections**:

Antibiotics: **Griseofulvin**

Methylnaftaline derivative:

Terbinafine (***Lamizyl*** – **Tab. 0.25 g; 1%** cream)

Imidazole derivatives:

Miconazole

Clotrimazole (1% cream, Tab. vaginal 0.1 g)

Nitrophenol derivatives:

Nitrofungin

Iodine preparations:

Iodide alcohol solution

Potassium iodide solution

II. Drugs for the treatment of mycoses caused by

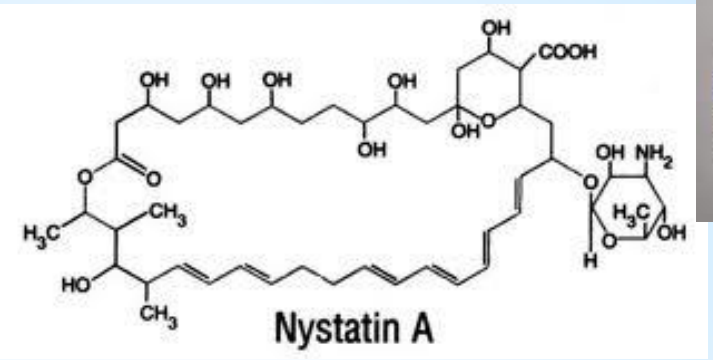
Conditional Pathogenic Fungi:

Antibiotics:

Nystatin

Amphotericin B

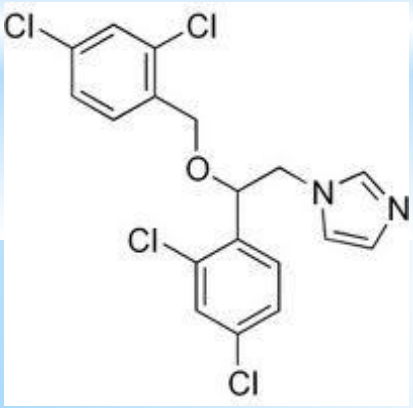
Levorin

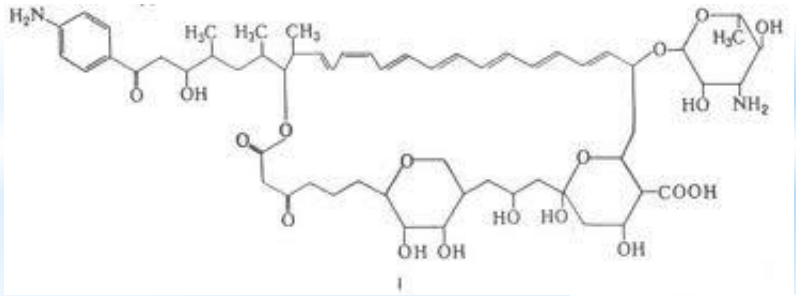


Imidazole derivatives:

Miconazole

Clotrimazole



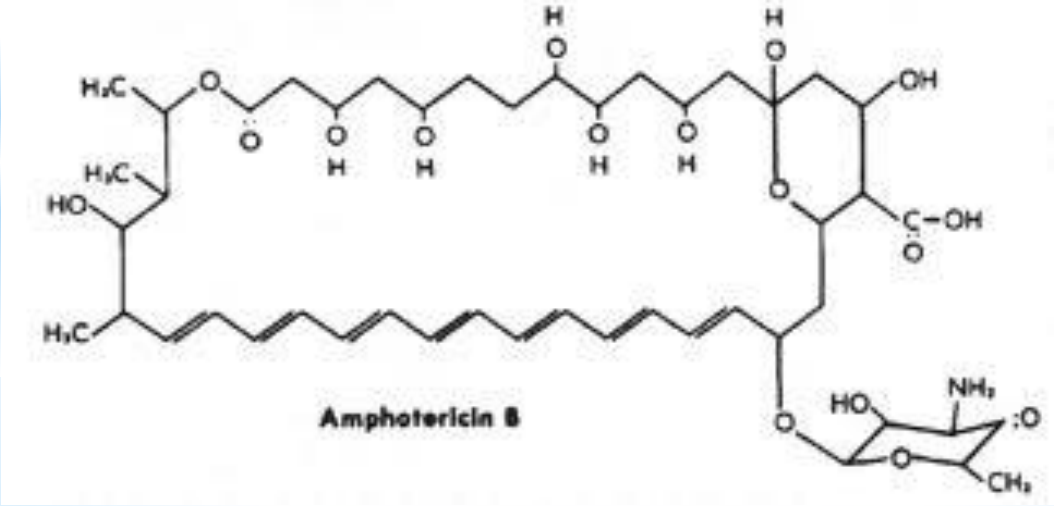


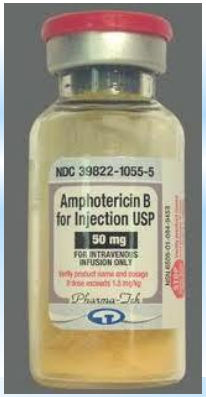
Amphotericin B **is a macrolide antibiotic, produced by**

Streptomyces nodosum**.**

the drug of choice in the treatment of the Systemic Mycoses.

MOA: Several polyene molecules bind to ergosterol in cell membrane of fungal cells to form pores disrupting membrane permeability and transport functions, allowing electrolytes (esp. K+) and small molecules to leak from the cell, leading to cell death.





Synthetic Antifungal Agents

Azoles: *Miconazole, Ketoconazole*

Triazoles: *Fluconazole, Itraconazole*

MOA: **produce inhibition of the fungal CYP-450 enzyme,**

lanosine 14α-demethylase which is responsible for converting lanosterol to ergosterol,

the main sterol in the fungal cell membrane.

The depletion of ergosterol =>

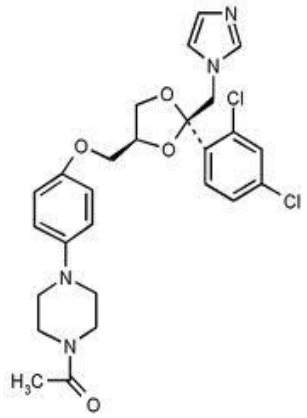
=> alters the fluidity of the membrane

=> interferes with the action of

the membrane-associated enzymes.

=> Inhibition of Replication.

Ketoconazole (*Nizoral*- Tab. 0.2 g, 2% cream, 1% Shampoo) is distinguished from *Fluconazole and Itraconazole* by its greater propensity to inhibit human CYP-450 enzymes



Inhibition of human CYP-450 enzymes:

- **Interferes** with **biosynthesis** of **adrenal** and **gonadal steroid hormones**, **producing significant endocrine effects** such as **gynecomastia**, **infertility**, and **menstrual irregularities**.
- ↓↓ **Metabolism** of other drugs, **leading** to **enhanced toxicity**

Clotrimazole – only for local administration

1% cream, lotion; Tab. vaginal 0.1 g –

a synthetic **imidazole derivative** for **dermatophytic infections**,

including ***Tinea corporis, Tinea pedis, Tinea cruris;***

Vulvovaginal and **Oropharyngeal Candidiasis, Keratitis**.

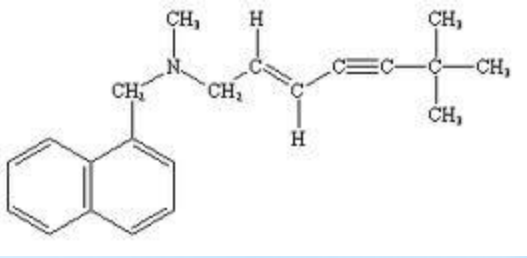
MOA: by binding with **phospholipids** in the fungal cell membrane,

alters cell **membrane permeability**

It inhibits or kills many fungi, including **yeast** and **dermatophytes**, and also is acting against **some Gr(+) bacteria**.

Pharmacokinetics: Absorption is negligible and adverse effects are rare.

Terbinafine (***Lamizil*** – Tab 0.25 g; 1% cream) -



Methylnaftaline derivative for

Superficial Fungal Infections –

a highly lipophilic keratophilic fungicidal compound

- Inhibits the enzyme **squalene epoxidase**, which is involved in the synthesis of **ergosterol** from **squalene** in the fungal cell wall.

The accumulation of squalene within the cell is toxic to the organism.

- Given **orally**, it is rapidly absorbed and is taken up by skin, nails and adipose tissue.
- Given **topically**, it penetrates **skin** and **mucous membranes**.
- 1 tab. PO for 12 weeks achieves a cure rate of up to 90% for onychomycosis (ringworm of nails)

Unwanted effects: GIT upsets, rashes, pruritus, joint and muscle pains, hepatitis.


Thank You for Attention!