

7.4. MACROLIDES - ERYTHROMYCIN

7.4.1. Introduction

Macrolides are compounds with a macrocyclic lactone ring (containing 14 or 16 atoms) with attached deoxy sugars. Erythromycin is the prototype drug which was obtained in 1952 from *Streptomyces erythreus*. It consists of two sugar moieties attached to a 14-atom lactone ring. Clarithromycin and azithromycin are semi-synthetic derivatives of erythromycin.

7.4.2. Classification

Following are the drugs included under the class of macrolides:

- | | |
|--------------------|-------------------|
| 1) Erythromycin, | 2) Telithromycin, |
| 3) Clarithromycin, | 4) Oleandomycin, |
| 5) Azithromycin, | 6) Tylosin, and |
| 7) Dirithromycin, | 8) Spiramycin. |

7.4.3. Mechanism of Action

Macrolides act by inhibiting the bacterial protein biosynthesis and by preventing peptidyltransferase from attaching the growing peptide to tRNA to the next amino acid. They also inhibit ribosomal translation and causes premature dissociation of the peptidyl-tRNA from the ribosome.

Macrolide antibiotics reversibly bind to the P site on the 50S subunit of the bacterial ribosome. This action is bacteriostatic. Macrolides get actively concentrated in the leukocytes, and are transported to the infection site. Macrolide inhibit translocation by binding to 50S subunit of ribosome. Figure 7.2 depicts the mechanism of action of macrolide antibiotics:

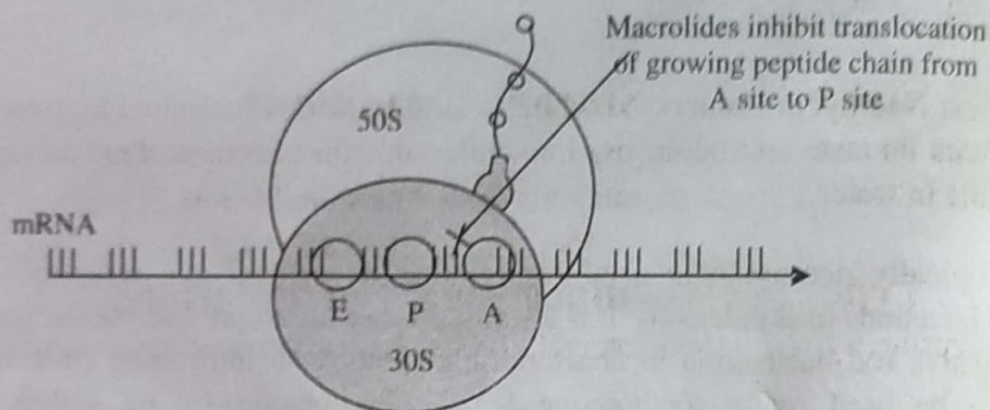


Figure 7.2: Mechanism of Action of Macrolide Antibiotics

7.4.4. Properties

Macrolides occur as white to slightly yellow coloured crystalline powder with a bitter taste and no odour. They are freely soluble in alcohol, chloroform, acetonitrile, acetone, ethyl acetate; and moderately soluble in ether, amyl acetate, and ethylene dichloride.

7.4.5. Uses

Macrolides can be used in the following cases in patients allergic to penicillin:

- 1) **Orodonal Infections:** Erythromycin is used to prevent and cure orodental infections, post-extraction infections, periapical abscesses, and other infected periodontal lesions.
- 2) **Atypical Pneumonia:** This condition is caused by *Mycoplasma*, *Chlamydia*, and *Legionella*. Erythromycin is used in doses of 500mg 6 hourly via oral or intravenous route in atypical pneumonia caused by *Mycoplasma pneumonia*.
- 3) **Legionnaire's Pneumonia:** This condition is treated in 10-14 days with erythromycin via intravenous route. However, at present azithromycin is the drug of choice.
- 4) **Whooping Cough:** Erythromycin, clarithromycin, and azithromycin are used for the treatment and post-exposure prophylaxis of close contacts.
- 5) **Streptococcal Infections:** Erythromycin is used for pharyngitis, tonsillitis, and scarlet fever.
- 6) **Staphylococcal Infections:** Erythromycin is used for minor infections.

- 7) **Diphtheria:** Erythromycin is used in acute stage as well as in the carrier stage of diphtheria.
- 8) **Syphilis and Gonorrhoea:** These conditions can also be treated with erythromycin.
- 9) **Campylobacter Gastroenteritis:** Erythromycin is used as an alternative to fluoroquinolones.
- 10) **Tetanus:** Erythromycin eradicates the carrier state.
- 11) **Anthrax:** Erythromycin is used as an alternative to penicillin.
- 12) Erythromycin ointment is used for skin infections and boils; while the lotion is used for acne vulgaris.

7.4.6. Stability and Storage Conditions

Macrolides should not be exposed to heat and open flames. They should be stored at 15-30°C and topical ointments should be stored below 27°C.

7.4.7. Types of Pharmaceutical Formulations

Tablet, capsule, syrup, suspension, gel, ointments, and intravenous injections.

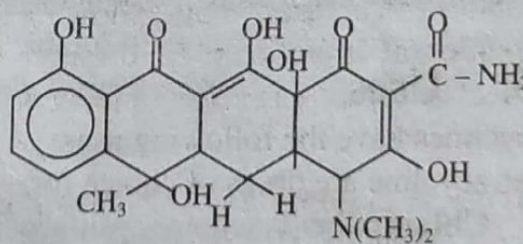
7.4.8. Brand Names

Althrocin, Citamycin, Emthrocin, and Etomin.

7.5. TETRACYCLINE

7.5.1. Introduction

Tetracycline is a potent, broad-spectrum antibacterial agent with activity against a host of gram-positive and gram-negative aerobic and anaerobic bacteria. Therefore, they are the drugs of choice or well-accepted alternatives for various infectious diseases. They are also used in the treatment of sexually transmitted and *Gonococcal* diseases, urinary tract infections, bronchitis, and sinusitis.



Tetracycline

Most of the marketed tetracyclines (tetracycline, chlortetracycline, oxytetracycline, and demeclocycline) occur naturally and are obtained by the fermentation of *Streptomyces spp.* broths. The duration of antibacterial action of semi-synthetic tetracyclines (methacycline, doxycycline, and minocycline) is longer. They also have a similar profile in terms of antibacterial potency. The activity encompasses many strains of gram-negative organisms (*E. coli*, *Proteus*, *Klebsiella*, *Enterobacter*, *Niesseria*, and *serratia spp.*) and gram-negative organisms (*Streptococci* and *Staphylococci*). The potency of tetracyclines against *Haemophilus*, *Legionella*, *Chlamydia*, and *Mycoplasma* is of great importance.

7.5.2. Classification

Tetracyclines are classified as follows:

- 1) **Short Acting (Half-Life 6 Hours):** Chlortetracycline and Oxytetracycline.
- 2) **Intermediate Acting (Half-Life 16 Hours):** Demeclocycline and Methacycline.
- 3) **Long Acting (Half-Life 18-24 Hours):** Doxycycline and Minocycline.

7.5.3. Mechanism of Action

Tetracyclines are bacteriostatic in nature. They inhibit protein synthesis by binding to 30S ribosomes in susceptible organisms. After this binding, the attachment of aminoacyl-t-RNA to the mRNA-ribosome complex is hindered, and thus the peptide chain fails to grow.

7.5.4. Properties

Tetracyclines are the first antibiotic and are derived from *Streptomyces aureofaciens*. They occur as a bright yellow coloured crystalline powder. They are sparingly soluble in water. They are stable in air but turns dark when exposed.

Tetracycline Hydrochloride (I.P. and B.P.): It is a hydrochloride salt of tetracycline.

Chlortetracycline Hydrochloride (I.P., B.P., and U.S.P.): It differs from tetracycline in having an extra chloro group at position 7. The compound is of a bright-yellow colour (hence was formerly called aueromycin. It is water soluble. It is different from tetracycline as it contains an extra chloro group at 7th position. It occurs as a bright yellow coloured, water-soluble powder.

Oxytetracycline (I.P.): It occurs as a yellow coloured, crystalline, powder with a bitter taste and no odour. It is slightly soluble in water; and sparingly soluble in alcohol. Its hydrochloride salt (official in B.P. and U.S.P.) is a pale yellow coloured crystalline powder with a bitter taste and soluble in water and alcohol. Alkali hydroxide can deactivate both oxytetracycline and its salt.

7.5.5. Uses

Tetracyclines have the following uses:

- 1) Tetracycline are drugs of choice for:
 - i) **Chlamydia:** Trachoma, psittacosis, and lymphogranuloma venereum,
 - ii) **Mycoplasma Pneumoniae:** Pneumonia,
 - iii) **Rickettsia:** Typhus fever and Q fever,
 - iv) **Spirochaetes (Borrelia):** Relapsing fever, Lyme disease, and
 - v) **Gram (-) Infections:** With aminoglycosides in brucellosis, tularaemia, plague, and cholera.
- 2) They are used for intestinal amoebiasis, actinomycosis, and *P. falciparum* malaria.
- 3) Minocycline (200mg of oral dose taken daily for 5 days) is used to treat meningococcal carrier state.
- 4) Demeclocycline is used in chronic hyponatraemia as it inhibits the action of ADH in renal tubules.

- 5) Tetracyclines are also a part of combination therapy for *H. pylori* induced gastric/duodenal ulcers. The widespread and indiscriminate use of tetracyclines for trivial illnesses have led to emergence of resistance in previously highly susceptible groups, viz., *Pneumococci*, *Staphylococci*, and group A *Streptococci*.

7.5.6. Stability and Storage Conditions

Tetracyclines are stable in air but darkens when exposed.

Tetracycline Hydrochloride (I.P., B.P.): Its stability and solubility in water are the reasons for its therapeutic use.

Chlortetracycline Hydrochloride (I.P., B.P., U.S.P.): It is also stable in air.

Oxytetracycline (I.P.): It is stable in air but darkens on exposure to light.

7.5.7. Types of Pharmaceutical Formulations

Tetracyclines are used for treating various infectious diseases in the form of oral suspensions (official in I.P.) in a standard dose of 1-4gm (in divided doses). Tetracycline Hydrochloride (I.P., B.P.): It is used as capsules, eye ointment, injections, and tablets. For parenteral purposes, its standard dose is 1-4gm/day and the solutions are prepared aseptically or sterilised by filtration method; while 1% ointment or 0.05-0.1ml of 1% suspension is suitable for external use.

Chlortetracycline Hydrochloride (I.P., B.P., U.S.P.): It is commonly used as capsules because it has a bitter taste. However, to reach the blood circulation rapidly, it is given through parenteral route.

Oxytetracycline (I.P.): It is administered orally as capsules because it gets absorbed well from the GIT. Its salt is water-soluble so it is administered intravenously in 0.1% w/v as infusion in dose of 1-2gm/day or intramuscularly in concentration not more than 5% w/v for adults in dose of 0.2-0.4gm/day. For children, the dose should be 5mg/kg of body weight daily.

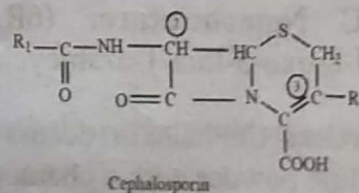
7.5.8. Brand Names

Sumycin, Acromycin, Hostacycline, Idilin, Indacycline, and Subamycin.

7.6. CEPHALOSPORINS

7.6.1. Introduction

Cephalosporins are semi-synthetic antibiotics derived from cephalosporin-C, which is obtained from *Cephalosporium* (fungus). Their nucleus consists of a β -lactam ring fused to a dihydrothiazine ring (7-aminocephalosporanic acid). A large number of semi-synthetic



compounds are produced by adding different side chains at position 7 of β -lactam ring (this alters the spectrum of activity) and position 3 of dihydrothiazine ring (this affects the pharmacokinetic profile). Cephalosporins are categorised into 4 generations. This categorisation has a sequence of development, and also considers the overall antibacterial spectrum and potency.

7.6.2. Classification

Cephalosporins are classified as follows according to their stages of development:

First Generation	
Parenteral	Oral
Cephalothin	Cephalexin
Cefazolin	Cephadrine Cefadroxil
Second Generation	
Parenteral	Oral
Cefuroxime	Cefaclor
Cefoxitin	Cefuroxime axetil
Third Generation	
Parenteral	Oral
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Caftazidime	Ceftibuten
Cefoperazone	
Fourth Generation	
Parenteral	
Cefepime	
Cefpirome	

7.6.3. Individual Compounds

The following drugs are studied in detail:

- 1) Cephalexin,
- 2) Cephaloridine, and
- 3) Cephalothin.

7.6.3.1. Cephalexin

Cephalexin is a semi-synthetic cephalosporin having antimicrobial activity, but less potency than cephaloridine or cephalothin. It acts against both gram-positive and gram-negative organisms.

Molecular Formula: $C_{16}H_{17}N_3O_4S$

IUPAC Nomenclature: (6R,7R)-7-[(2R)-2-amino-2-phenylacetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid

Properties: Cephalexin occurs as a white or cream coloured, water-soluble crystalline powder with a characteristic odour. It is slightly soluble in alcohol and chloroform.

Uses: Cephalexin is used for treating respiratory tract infections due to *Streptococcus pneumoniae* and *Streptococcus pyogenes*. It is also used for treating otitis media caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Moraxella catarrhalis*. It is used in skin and skin structure infections due to *Staphylococcus aureus* and/or *Streptococcus pyogenes*. It is also useful in bone infections produced by *Staphylococcus aureus* and/or *Proteus mirabilis*. Genitourinary tract infections, such as acute prostatitis, caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* are also treated with this drug.

Stability and Storage Conditions: Cephalexin is hygroscopic in nature and gets affected by light, thus should be stored at room temperature in tightly-closed light-resistant containers away from heat and moisture.

Types of Pharmaceutical Formulations: Tablet, capsule, and suspension.

Brand Names: Acelex, Alsporin, Suprax, Neocof, and Cefaxin.

7.6.3.2. Cephaloridine

Cephaloridine is derived from cephalosporin C and is also its first generation semi-synthetic derivative. It is different from other cephalosporins as it exists as a Zwitter ion.

Molecular Formula: $C_{19}H_{17}N_3O_4S_2$

IUPAC Nomenclature: (6R,7R)-8-oxo-3-(pyridin-1-ium-1-ylmethyl)-7-[(2-thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

Properties: Cephaloridine occurs as a white coloured crystalline powder which may be odourless or have a slight odour of pyridine. It is soluble in water; and insoluble in most organic solvents.

Uses: Cephaloridine is used for treating lower respiratory tract infections. It is highly effective for curing pneumococcal pneumonia. It is highly successful clinically and bacteriologically in *Staphylococcal* and *Streptococcal* infections.

Stability and Storage Conditions: Cephaloridine loses its colour when exposed to light. Therefore, it should be stored in tightly-closed, sterile, light-resistant, sealed containers (to protect from microorganisms) at a cool place. It should have a label indicating whether it is α -form or δ -form.