BP601T Medicinal Chemistry III (Theory)

UNIT I

Prepared by-

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Unit I 10 Hours

Antibiotics

Historical background, Nomenclature, Stereochemistry, Structure activity relationship Chemical degradation classification and important products of the following classes

β-Lactam antibiotics: Penicillin, Cephalosporins, β-Lactamase inhibitors, Monobactams

Aminoglycosides: Streptomycin, Neomycin, Kanamycin.

Tetracyclines: Tetracycline, Oxytetracycline, Chlortetracycline, Minocycline, Doxycycline.

Antibiotics

Antibiotics, also known as antimicrobial agents, are medications that destroy or slow down the growth of other species of microorganisms. They include a range of powerful drugs and are used to treat diseases caused by bacteria, fungi, actinomycetes, etc.

History of Antibiotics

Antibiotics began with the growing acceptance of the germ theory of disease (Louis Pasteur was one of the first recognized physicians who observed that bacteria could be used to kill other bacteria).

1871= The surgeon Joseph Lister found urine contaminated with mould could not kill the bacteria

1890's = German doctors Rudolf Emmerich, Oscar low made Pyocyanse from microbes. It was the first antibiotic used in hospitals but the drug did not work

1909 = First modern chemotherapeutic agent Salvarsan for the treatment of syphilis (Paul Ehrlich)

1928 = Scottish bacteriologist Sir Alexander Fleming discovered enzyme lysozyme and the antibiotic substance penicillin

1932= Gerhard Domagk discovered Prontosil a prodrug.

1936= Sulfanilamide the first synthetic sulfonamide in human medicine

1940 = Invention of Modern Drug Discovery: Ehrlich & The Magic Bullet means compound that selectively targets a disease causing organism while having no Negative effect on human tissue.

1940 = First therapeutic use of penicillin by Floury.

1944 Selman Waksman made Streptomycin from soil bacteria.

1948 = Chlortetracycline.

1957= Nystatin (fungal infections)

1970s= a New quinolone (pipemidic acid, oxolinic acid, cinoxacin)

1980= Norfloxacin the first fluoroquinolone.

1980= Enrofloxacin

1998= Smithkline Beecham patented Amoxicillin/ clavulanate potassium

Classification

Antibiotics are classified in many ways based on chemical structure, source, its spectrum of activity and mechanism of action (MOA).

Based on the chemical structure

1. B-lactam antibiotics: Penicillins, Cephalosporins, carbapenams, monobactams.

2. Amino glycoside antibiotics: Streptomycin, Neomycin, Kanamycin, Gentamycin, Tobramycin, Amikacin.

3.Tetracyclines: Tetracycline, Chlortetracycline, Oxytetracycline, Doxycycline, Minocycline, Methacycline, Meclocycline.

4. Macrolide antibiotics: (i.e. large macrolide structure): Erythromycin, Clarithromycin, Azithromycin, Roxithromycin.

5. Polypeptide antibiotics: Actinomycin, Bacitracin, Colistin, Polymyxin B, tyrothricin.

Based on the sources

- **Natural**

Sr. No.	Microorganism	Isolated antibiotics
1.	*Penicillium chrysogenum*	Penicillin
2.	*Bacillus subtilis*	Bacitracin
3.	*Bacillus polymyxa*	Polymyxin
4.	*Stryptomyces griseus*	Stryptomycin
5.	*Streptomyces aureofaciens*	Chlortetracyclines
6.	*Streptomycers erythreus*	Erythromycin
7.	*Streptomyces venezulae*	Chloramphenicol

- **Semisynthetic**
  These antibiotics are commercially synthesized from natural antibiotics. Examples include- Ampicillin, Methicillin, Cloxacillin, Oxacillin, etc.
- **Synthetic**
  These antibiotics are synthesized commercially. Examples include- Chloramphenicol

Based on spectrum of activity

Narrow-spectrum antibiotics target a few types of microorganisms. Examples of narrow-spectrum antibiotics are the older penicillins (penG), the macrolides and vancomycin.

Broad-spectrum antibiotics target many types of microorganisms. Examples of broad-spectrum antibiotics are the aminoglycosides, the 2nd and 3rd generation cephalosporins, the quinolones and some synthetic penicillins.

Both types work well to treat infections. But using broad-spectrum antibiotics when they're not needed can create antibiotic-resistant bacteria that are hard to treat.

Antibiotic activity

Based on their activity against different mechanism of action they are divided in to

(a) Antibacterial antibiotics: The chemotherapeutic agents which kill or inhibit the growth of bacteria are called antibacterial antibiotics (penicillins, cephalosporins, tetracyclines, aminoglycosides).

- Bactericidal antibiotics: These are more effective in killing harmful microorganisms particularly bacterial species (Kill the bacteria directly). Examples: Penicillins, Cephalosporins, Aminoglycosides, Flouroquinolones, Metronidazole.
- Bacteriostatic antibiotics: These are effective in abolishing or preventing the growth of bacterial species (stop the bacteria from growing): Examples: Tetracyclines, Chloramphenicol, Clindamycin.

(b) Antifungal antibiotics: Griseofulvin, (c) Anthelmintic agents: Ivermectin, Amphoterisin B, Nystatin.

(d) Anticancer antibiotics: Bleomycin, Dactinomycin, Doxorubicin.

Based on Mechanism of Action (MOA)

Cell wall synthesis inhibitors: Penicillins, Cephalosporins, Carbapenams. Aztreonam.

Microbial cell membrane inhibitors: Polymyxin B and E, Colistin, Polyene, Imidazole.

Protein synthesis inhibitors: Amine glycosides, Macrolides, Tetracyclines.

β-Lactam Antibiotics

β-Lactam Antibiotics are majorly divided into four categories-

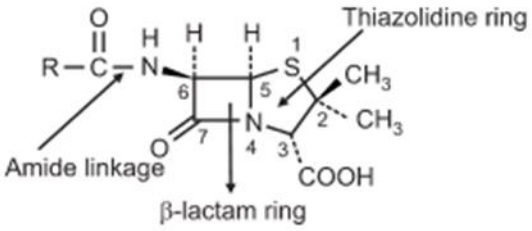
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

1. Penicillins

- Penicillin is derived from the Penicillium mould.
- Penicillin is a group of antibiotics that are commonly used to treat different types of gram positive and gram negative bacterial infections.
- In their structure, beta-lactam ring is located due to this reason these drugs are also called as beta-lactam antibiotics.
- Biological Source- Penicillium notatum and Penicillium chrysogenum

Structure

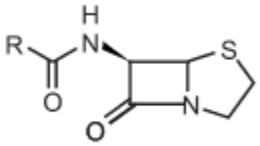
- It contains two rings fused with each other- Thiazolidine ring and β-Lactam ring



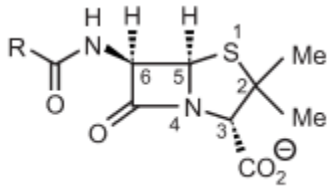
Nomenclature

(a) There are two types of numbering for the fused bicycling system of penicillin: whether which atom is number one Sulfur or Nitrogen.

(b) Penam nucleus is used in naming which comprise bicyclic system with the amide carbonyl group. Penicillin is named as 6-acylamino-2,2-dimethylpenam-3-carboxylic acid.

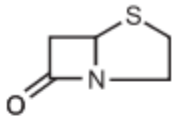


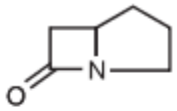
(c) Penicillanic acid nucleus: Which includes the 2,2-dimethyl and 3-carboxyl groups. Penicillin is named as 6-carbonylaminopenicillanic acid.

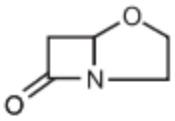


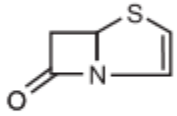
Penicillanic acid

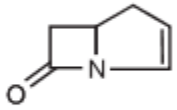
(d) Penicillin nucleus: Which includes 6-carbonyl aminopenicillanic acid. So Penicillin G is named benzylpenicillin if R is benzene ring.

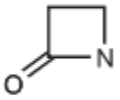

(1) Penam

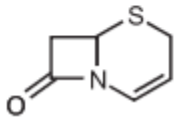

(2) Carbapenam

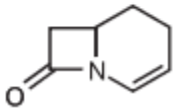

(3) Oxapenam

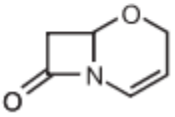

(4) Penem


(5) Carbapenem


(6) Monobactam


(7) Cephem


(8) Carbacephem


(9) Oxacephem

Stereochemistry

a. The penicillin molecule contains three chiral carbon atoms at C-3, C-5 and C-6
b. All natural and synthetic penicillins have the same absolute configuration about these three centers
c. The 6 carbon atom bearing the acyl amino group has the L-configuration, whereas the carbon to which the carboxyl group was attached has the D-configuration.
d. The acyl amino group and carboxyl group are trans to each other, with the former and latter in the β orientation relative to penam ring.
e. The absolute stereochemistry of the penicillins is designated as 35: 5R: 6R.
f. The atoms composing the 6-aminopenicillanic acid are biosynthetically derived from two amino acids, L-cysteine and D-valine

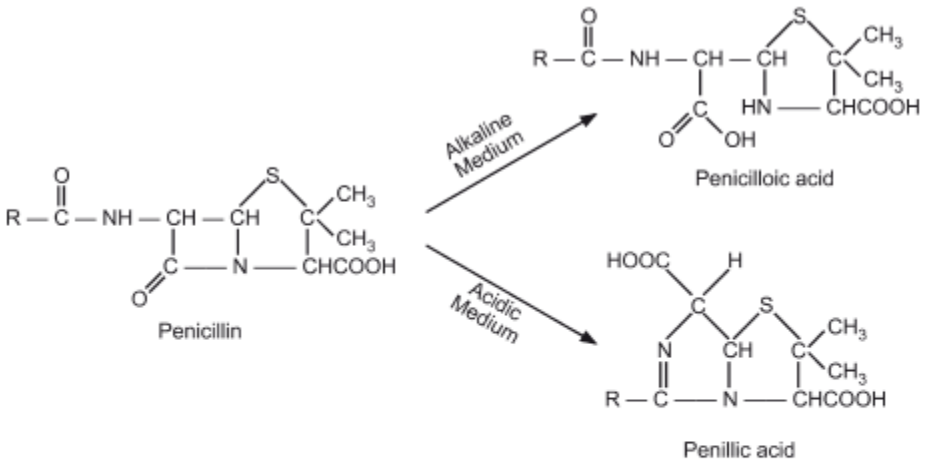
Mechanism of action

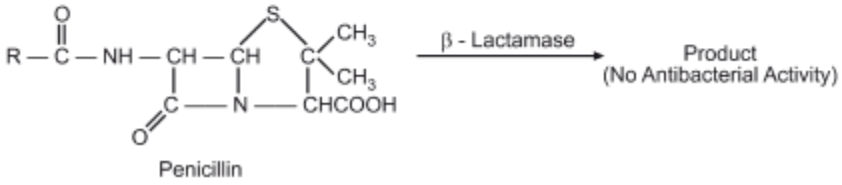
It destroys bacteria by inhibiting the enzyme- transpeptidase responsible for the formation of the cell wall and cross-linking in the bacterial cells.

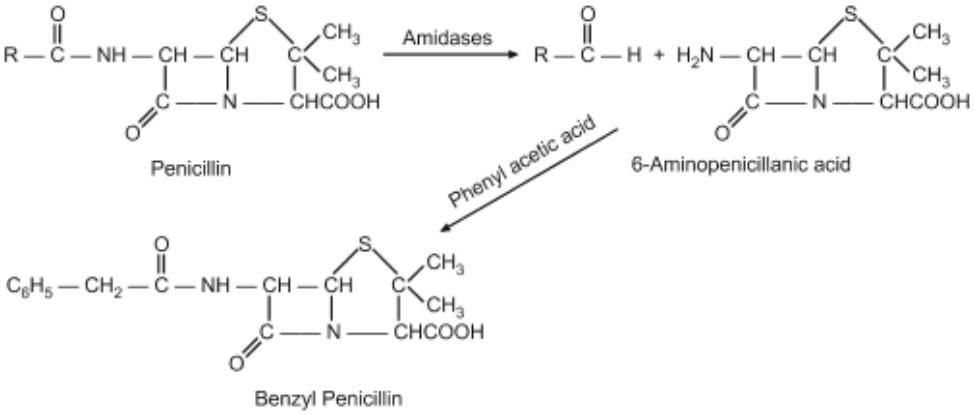
Chemical Degradation

The Penicillins gets degraded under the acidic and basic conditions as well as in the presence of β-lactamases.

The degradation is shown below.







Classification

A. Natural penicillins (narrow-spectrum, β-lactamase susceptible penicillins)

1) **Parenteral administration:** Benzylpenicillin (penicillin 'G')
2) **Oral administration:** Phenoxymethylpenicillin (penicillin 'V')

B. Semi-synthetic penicillins

1. **Very narrow-spectrum, β-lactamase resistant penicillins** (Antistaphyloccal)
   - Oxacillin
   - Dicloxacillin
   - Flucloxacillin
2. **Broad spectrum, β-lactamase susceptible penicillins**
   a) **Aminopenicillins**
      - Ampicillin
      - Amoxycillin

b) Mecillinam (active to gram-negative (G-) flora, inefficient against pseudomonads)
   - Pivmecillinam

c) Carboxypenicillins (antipseudomonal)
   - Carbenicillin
   - Ticarcillin

d) Ureidopenicillins (antipseudomonal)
   - Azlocillin
   - Mezlocillin
   - Piperacillin

3. Other β-lactam drugs
   - Monobactam (aztreonam)
   - Carbapenems (imipenem and meropenem)
4. β-lactamase inhibitors
   - Sulbactam
   - Tazobactam
   - Sodium or potassium clavulanate
5. Combined drugs of penicillin and β-lactamase inhibitors
   - Amoxiclav (amoxicillin + potassium clavulanate)
   - Unasin (ampicillin + sulbactam)

Structure activity relationship

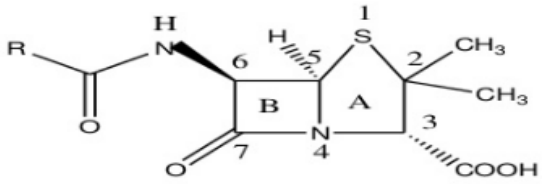
Position 1 – When the sulfur atom of the Thiazolidine ring is oxidized to a sulfone or sulfoxide, it improves acid stability, but decreases the activity of the agent.

Position 2 – No substitutions allow at this position, any change will lower activity. The methyl groups are necessary

Position 3 – The carboxylic acid of the Thiazolidine is required for activity. If it is changed to an alcohol or ester, activity is decreased.

Position 4 – The nitrogen is a must.

Position 5 – No substitutions allowed.



Uses

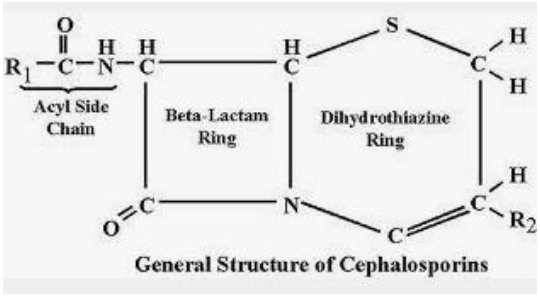
a. Abscesses
b. Beta-hemolytic streptococcus
c. Meningitis
d. Otitis media
e. Pneumonia
f. Respiratory infections
g. Tooth and gum infections
h. Venereal diseases (syphilis and gonorrhea)
i. Endocarditis due to streptococci

2. Cephalosporins

- The cephalosporins are β-lactam antibiotics isolated from Cephalosporium spp. or prepared semisynthetically. Most of the antibiotics introduced since 1965 have been semisynthetic cephalosporins.

Structure

- Cephalosporin nucleus consists of a β-Lactam ring fused with dihydrothiazine ring (7-Aminocephalosporanic acid)



General Structure of Cephalosporins

Classification

First generation cephalosporins	
Parenteral	*Oral*
Cephalothin*	Cephalexin
Cefazolin	Cephradine
	Cefadroxil
Second generation cephalosporins	
Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil
Third generation cephalosporins	
Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	Ceftamet pivoxil
Fourth generation cephalosporins	
Parenteral	
Cefepime	
Cefpirome	

Nomenclature

- The chemical nomenclature of the cephalosporins is slightly more complex than even that of the penicillins because of the presence of a double bond in the dihydrothiazine ring.
- The fused ring system is designated by Chemical Abstracts as 5-thia-1-azabicyclo[4.2.0]oct-2-ene.
- In this system, cephalothin is 3-(acetoxymethyl)-7-[2- (thienylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

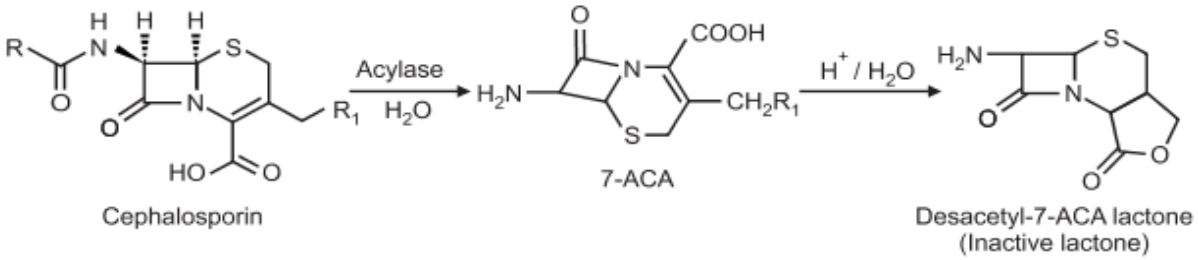
Chemical Degradation

The pathway depends on structure of Cephalosporin:

- 3-acetoxylmethyl group is most reactive (nucleophilic displacement, acid solvolysis)
- The lactonize products are inactive.
- The broken β-lactam products are inactive.

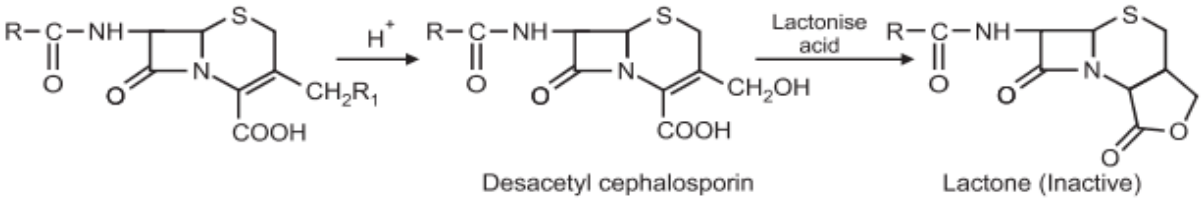
Step I : Degradation of Cephalosporins.

Step II : In the presence of acylase:



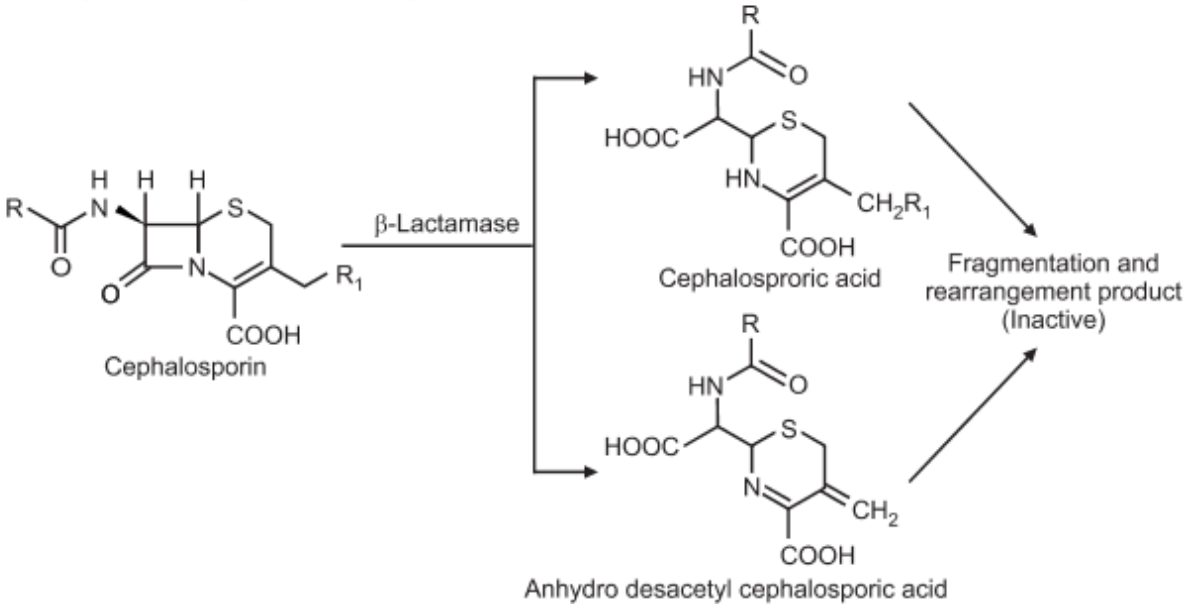
Cephalosporin — 7-ACA — Desacetyl-7-ACA lactone (Inactive lactone)

Step III: In the presence strong acid solutions:

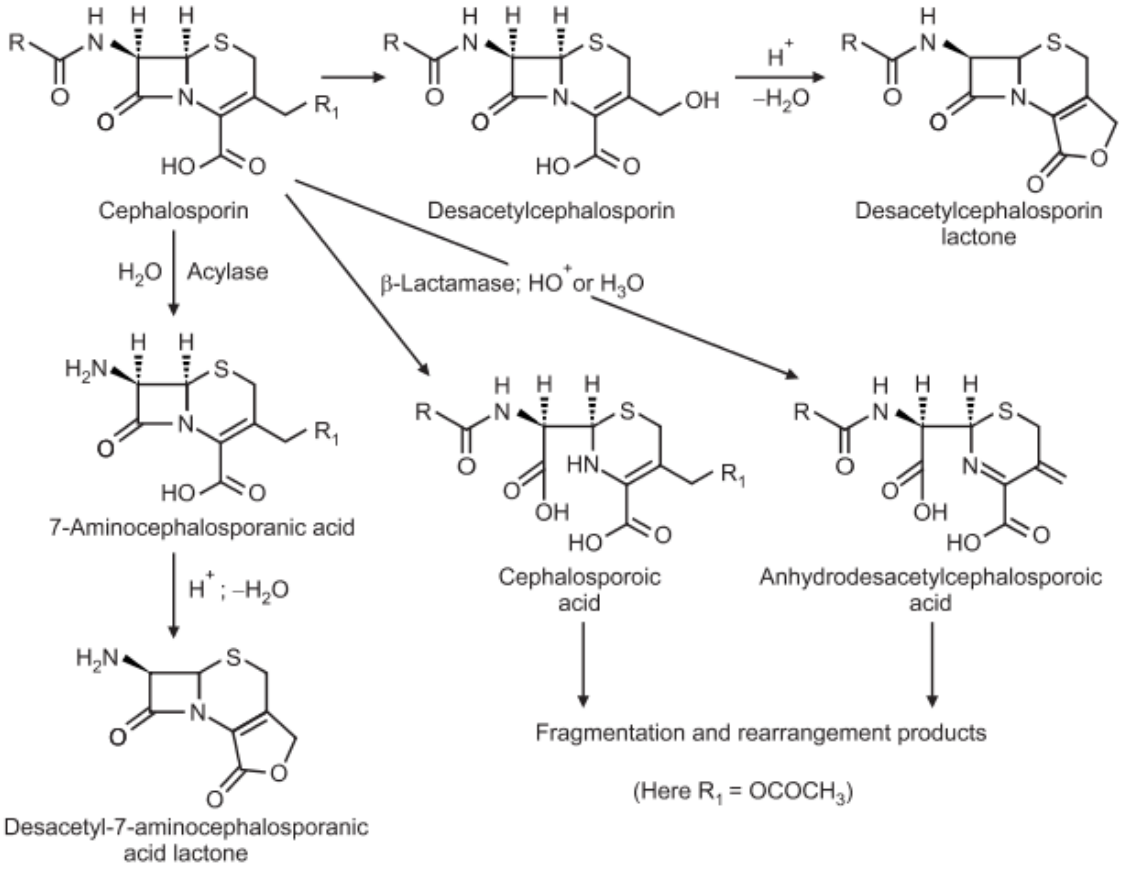


Desacetyl cephalosporin — Lactone (Inactive)

Step IV: In the presence of β-lactamase:



Cephalosporin — Cephalosproric acid — Anhydro desacetyl cephalosporic acid



SAR

1. 7-Acylamino substituents:

a) Acylation of amino group generally increases the potency against gram-positive bacteria, but it is accompanied by a decrease in gram-negative potency.

b) High antibacterial activity is observed only when the new acyl groups are derived from carboxylic acids for gram-positive bacteria.

c) Substituents on the aromatic ring that increases lipophilicity provide higher gram-positive activity and generally lower gram-negative activity.

d) The phenyl ring in the side-chain can be replaced with other heterocycles with improved spectrum of activity and pharmacokinetic properties, and these include thiophene, tetrazole, furan, pyridine, and aminothiazoles

2. C-3 substituents:

The nature of C-3 substituents influences pharmacokinetic and pharmacological properties as well as antibacterial activity. Modification at C-3 position has been made to reduce the degradation (lactone of desacetyl cephalosporin) of cephalosporins.

3. Pyridine and imidazole-replaced acetoxy groups show improved activity against P.aeruginosa. Displacement of acetoxy group by azide ion yields derivatives with relatively low gram-negative activity.

4. Displacement with aromatic thiols of 3-acetoxy group results in an enhancement of activity against gram-negative bacteria with improved pharmacokinetic properties.

5. Replacement of acetoxy group at C-3 position with —CH3, Cl has resulted in orally active compounds.

6. Oxidation of ring sulphur to sulphoxide or sulphone greatly diminishes or destroys the antibacterial activity.

7. Replacement of sulphur with oxygen leads to oxacepam (latamoxef) with increased antibacterial activity, because of its enhanced acylating power.

8. Replacement of sulphur with methylene group (loracarbef) has greater chemical stability and a longer half-life.

9. The carboxyl group of position-4 has been converted into ester prodrugs to increase bioavailability of cephalosporins, and these can be given orally as well. Examples include cefuroxime axetil and cefodoxime proxetil

10. Olefinic linkage at C 3-4 is essential for antibacterial activity. Isomerization of the double bond to 2-3 position leads to great losses in antibacterial activity

Mechanism of Action

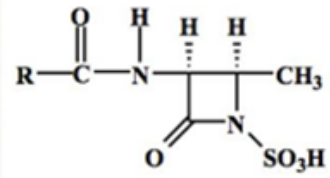
- Cephalosporins exert bactericidal effect in manner similar to that of Penicillins.
- Binding to specific PBPS
- Inhibition of cell wall synthesis by inhibiting transpeptidation of Peptidoglycan
- Activation of Autolytic enzymes: Autolysins or Murein Hydrolases

Uses

- Cephalosporins are widely used antibiotics. Unfortunately, overuse of these agents in situations where drugs with less broad spectrum activity would be more appropriate has led to the emergence of wide array of cephalosporin resistant bacteria.
- Cephalosporins are effective as both Prophylactically & Therapeutically.
- Alternative to Penicillins
- Respiratory tract infections caused by Klebsiella, Enterobacter, Proteus, Providencia, and Haemophilus species.
- Gonorrhoea
- Typhoid fever
- Meningitis

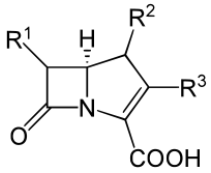
3. Monobactams

- They are resistant to β-lactamases and active against aerobic gram-negative rods.
- They have no activity against gram-positive bacteria or anaerobes.
- Aztreonam is the only commercially available monobactam.
- It is administered either IV or IM and can accumulate in patients with renal failure.
- Relatively nontoxic, but it may cause phlebitis, skin rash and, occasionally, abnormal liver function tests.
- Penicillin-allergic patients tolerate aztreonam without reaction.
- Monobactams have monocyclic beta lactam ring and are resistant to beta lactamses.



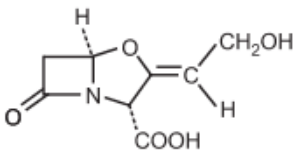
4. Carbapenems

- Synthetic β-lactam antibiotics differ in structure from the penicillins in that the sulfur atom of the thiazolidine ring has been externalized and replaced by a carbon atom.
- Penetrate body tissues and fluids well, including CSF.
- All are cleared renally, and the dose must be reduced in patients with renal insufficiency
- Broad spectrum of antimicrobial activity with bactericidal activity against most Gram-positive and Gram-negative aerobic and anaerobic pathogenic bacteria.
- They resist hydrolysis by most β- lactamases.
- Pseudomonas are naturally resistant

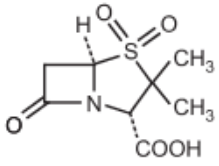


β-Lactamses inhibitors

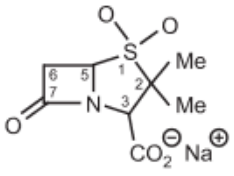
- β-lactamases are a family of enzymes involved in bacterial resistance to beta-lactam antibiotics.
- They act by breaking the beta-lactam ring that allows penicillin-like antibiotics to work.
- Strategies for combating this form of resistance have included the development of new beta-lactam antibiotics that are more resistant to cleavage and the development of the class of enzyme inhibitors called beta-lactamase inhibitors.
- Although β-lactamase inhibitors have little antibiotic activity of their own, they prevent bacterial degradation of beta-lactam antibiotics and thus extend the range of bacteria the drugs are effective against.



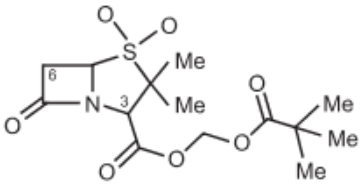
Clavulanic acid



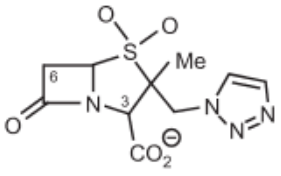
Sulbactam



Sulbactam



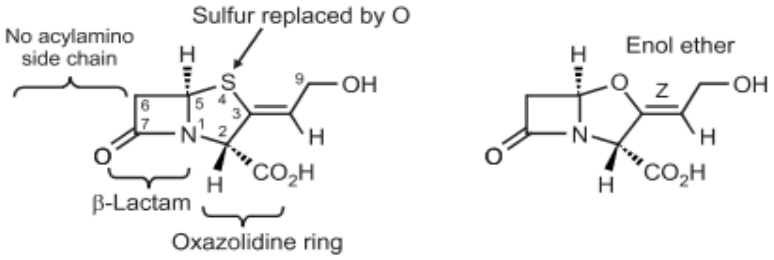
Sulbactam oral ester



Tazobactam

Essential requirements for β-lactamase inhibition are:

- Strained β-lactam ring.
- Enol ether.
- The double bond of the enol ether has the Z-configuration (Activity is reduced, but not eliminated if the double bond is E).
- No substitution at C-6.
- R-Stereochemistry at positions 2 and 5.
- Carboxylic acid group.



Uses

- In the treatment of infections known or believed to be caused by gram-negative bacteria, as β-lactamase production is an important contributor to beta-lactam resistance in these pathogens.
- Addition of clavulanic acid re-establishes the activity of amoxicillin against β-lactamase producing resistant E. coli, H. influenzae, Klebsiella, N. gonorrhoeae, Proteus, Staph aureus, Salmonella and Shigella.

Aminoglycosides

Introduction

- Streptomycin was isolated from Streptomyces griseus and neomycin was isolated from Streptomyces fradiae in the 1940's
- Gentamicin isolated from Micromonospora in 1963
- Others later developed amikacin, netilmicin tobramycin

History

Sr. No.	Antibiotic	Source	Year of Introduction
1.	Streptomycin	*Streptomyces griseus*	1944; Waksman
2.	Neomycin	*S. fradiae*	1949; Waksman
3.	Kanamycin	*S. kanamyceticus*	1957; Limezawa
4.	Gentamicin	*Micromonospora purpurea*	1964
5.	Tobramycin (nebramycin)	*S. tenebrarius*	1967; Higgins
6.	Framycetin, (soframycin)	*S. decaris*	
7.	Paromomycin	*S. rimosus formoparamomycinus*	1959
8.	Amikacin	Semisynthetic product from kanamycin	1972; Kawaguchi
9.	Sisomicin	M. inyoensis	1980
10.	Netilmicin (N-ethyl sisomicin)	Semisynthetic product from sisomicin	1963; Weinstein

Structure

- Consist of 2 or more amino sugars attached by glycoside linkage to hexose nucleus

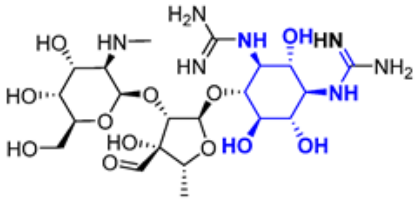
Classification

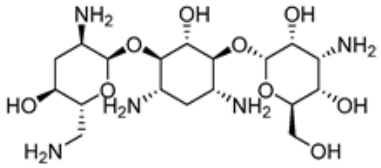
1. Systemic Aminoglycosides

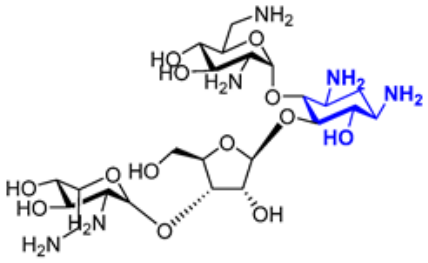
Streptomycin	Amikacin
Gentamicin	Sisomicin
Kanamycin	Netilmicin
Tobramycin	Paromomycin

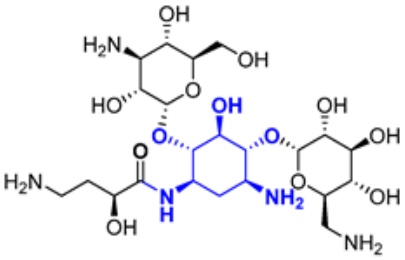
2. Topical Aminoglycosides

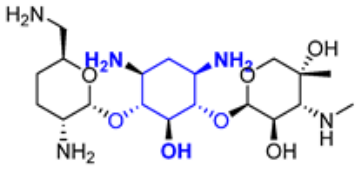
Neomycin
Framycetin

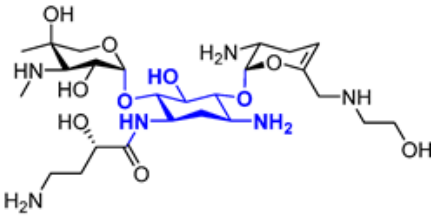

Streptomycin


Tobramycin


Neomycin B


Amikacin


Gentamicin


Plazomicin

SAR

- Natural aminoglycoside antibiotics share a non-sugar 2-deoxystreptamine scaffold connected to amino sugar substituents at the 4-, 5- and 6-positions.
- The two most important classes of aminoglycoside antibiotics are the 4, 5- and 4, 6-disubstituted 2-deoxystreptamine derivatives.
- The 4, 5-disubstituted 2-deoxystreptamine compounds include neomycin B whereas the 4,6-disubstituted 2 deoxystreptamine derivatives include gentamycin, kanamycin and streptomycin.
- Aminoglycoside antibiotics of these three groups, 4, 5- and 4, 6-disubstituted 2-DOS derivatives and apramycin, share in common a target site at the decoding center (A-site) of bacterial 16S ribosomal RNA (rRNA).

- 2-deoxystreptamine scaffold is the key pharmacophore required for the precise anchoring of the drugs at the RNA target.

1. Streptomycin

a. Streptomycin is the first aminoglycoside antibiotic to be discovered and was the first antibiotic to be used in treatment of tuberculosis.
b. It was discovered in 1943, in the laboratory of Selman Waksman at Rutgers University.
c. Streptomycin is derived from the bacterium Streptomyces griseus.
d. It inhibits bacterial growth by inhibiting protein synthesis.
e. Specifically, it binds to the 16S rRNA of the bacterial ribosome, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit.
f. It is chemically stable and rapidly bactericidal, with a broad spectrum of inhibitory activity (apart from anaerobic bacteria).
g. Streptose, the central moiety, is a C-3-formyl derivative of 5-deoxy-Llyxose.
h. Two major precursors of the streptidine portion of the molecule have nowbeen defined, n-arginine and n-glucose.

2.Neomycin

a. Neomycin, an aminoglycoside antibiotic, discovered on 1949 in the lab of Selman Waksman.
b. It has excellent activity against gram-negative bacteria, and has partial activity against gram-positive bacteria.
c. It is produced naturally by the bacterium Streptomyces fradiae. Most potent aminoglycoside translation inhibitors.

3.Kanamycin

a. Kanamycin is made up of 3 rings.
b. Ring II is sugar group,while ring I and III are non-sugar group.
c. Kanamycin B is a more potent antibiotic than either kanamycins A or C.
d. The presence of a diamino hexose, therefore, results in a compound that is a better inhibitor of protein synthesis than one containing only one amino group.Therefore, when only one amino group is present, an antibiotic that contains a 6-amino substituent is more active than one containing a 2-amino substituent
e. Antibiotic activity can be related to the number and location of amino groups in the hexose moiety glycosidically linked to the 4-position of deoxystreptamine as follows (in decreasing order of potency): 2', 6'-diamino > 6'-amino > 2'-amino > no amino

4.Gentamicin

a. There have 3 types of gentamicin in this class of aminoglycosides such as Gentamicin C1, Gentamicin C2 and Gentamicin C1a.
b. Gentamicin C1 exists when both R1 and R2 are CH3.
c. Gentamicin C2 exists when R1 is CH3 and R2 is H.

d. Gentamicin C1a exists when both R1 and R2 are H.
e. The structure of gentamicin is consistent with the aminoglycoside structural activity relationship(SAR), except few minor changes.
f. Gentamicin C1a binds in the major groove of the RNA.

Mechanism of Action

- Crosses outer bacterial membrane by passive diffusion via porin channels, then binds to 30s ribosomal subunit and thus inhibits protein synthesis
- Prevent the formation of an initiation complex of peptide formation
- Cause misreading of the messenger RNA message, leading to the production of nonsense peptides
- Increase membrane leakage
- Agents: Gentamicin, Tobramycin, Amikacin, Streptomycin
- MOA: binds to 30s ribosomal subunit; inhibits protein synthesis, bactericidal
- Dose dependent killing
- Post antibiotic effect

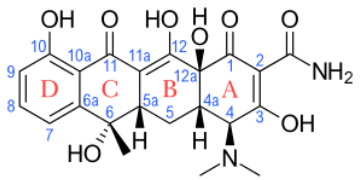
Clinical Uses

- Serious, life-threatening gram-negative infection
- Complicated skin, bone or soft tissue infection
- Complicated urinary tract infection
- Sepsis
- Peritonitis and other severe intra-abdominal infections
- Severe pelvic inflammatory disease
- Endocarditis
- Mycobacterium infection
- Neonatal sepsis
- Ocular infections (topical)
- Otitis externa (topical)

Tetracyclines

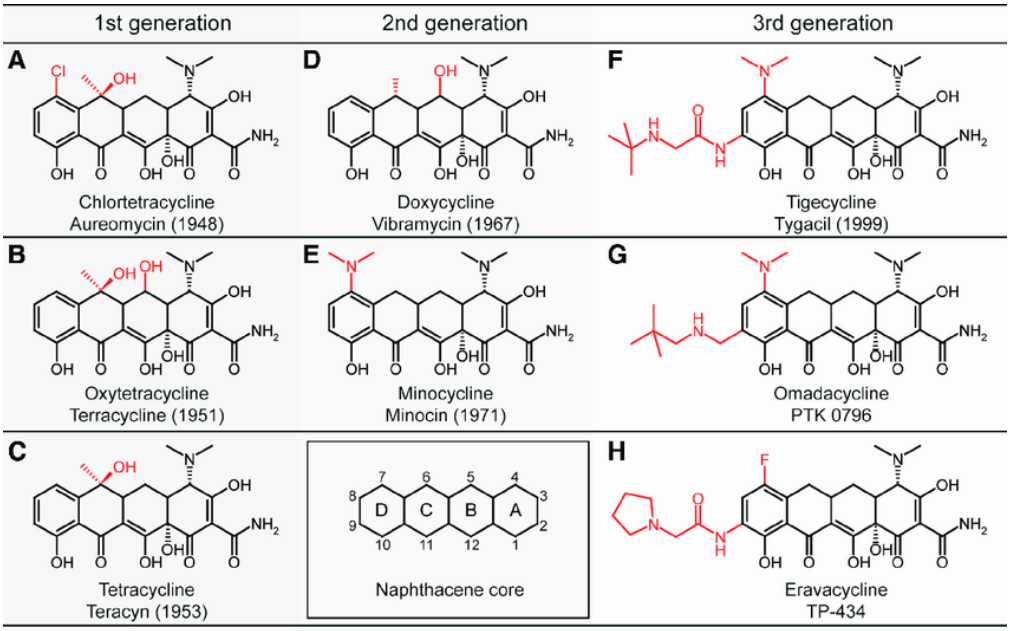
Tetracyclines are a class of antibiotics that may be used to treat infections caused by susceptible microorganisms such as gram positive and gram negative bacteria, chlamydiae, mycoplasmata, protozoans, or rickettsiae.

Structure



Classification

A) Naturally occurring:	B) Semisynthetic:
Eg.	Eg.
Tetracycline	Doxycycline
Chlortetracycline	minocycline
Oxytetracycline	meclocycline
Demeclocycline	methacycline
	rolitetracycline



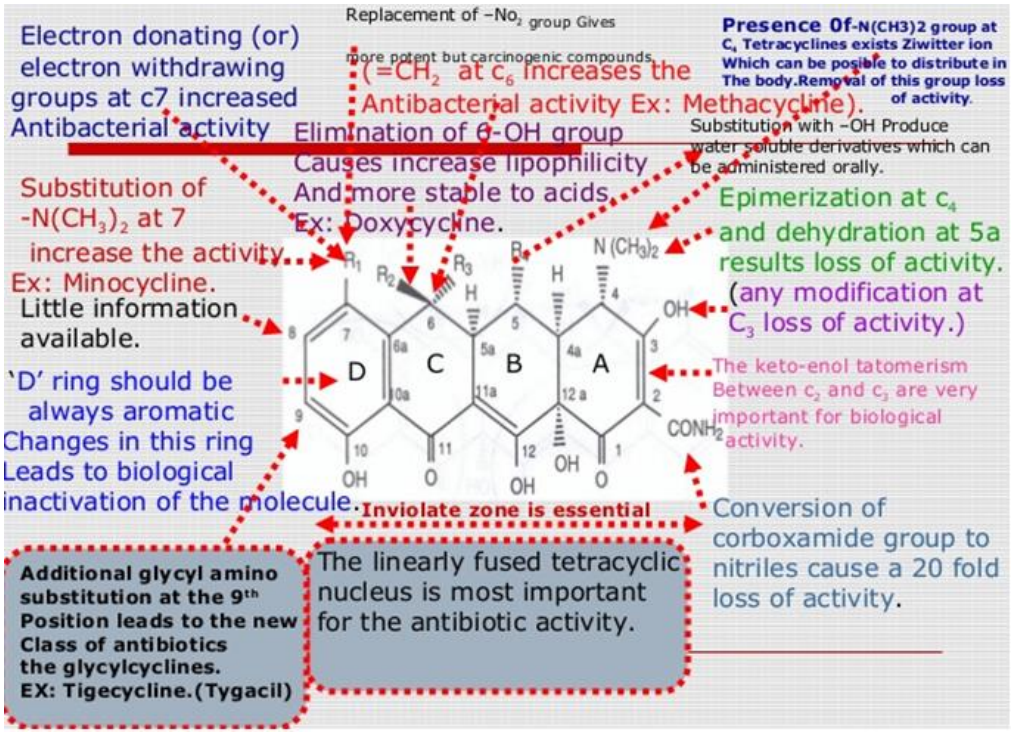
Mechanism of action

- Tetracycline antibiotics are protein synthesis inhibitors.
- They inhibit the initiation of translation in variety of ways by binding to the 30S ribosomal subunit, which is made up of 16S rRNA and 21 proteins.
- They inhibit the binding of aminoacyl-tRNA to the mRNA translation complex.
- They also have been found to inhibit matrix metalloproteinases. This mechanism does not add to their antibiotic effects, but has led to extensive research on chemically modified tetracyclines or CMTs (like incyclinide) for the treatment of rosacea, acne, diabetes and various types of neoplasms

Structure-activity relationship

- Tetracyclines are composed of a rigid skeleton of 4 fused rings.
- The rings structure of tetracyclines is divided into an upper modifiable region and a lower non modifiable region
- An active tetracycline requires a C10 phenol as well as a C11-C12 keto-enol substructure in conjugation with a 12a-OH group and a C1-C3 diketo substructure.
- Removal of the dimethylamine group at C4 reduces antibacterial activity.

- Replacement of the carboxylamine group at C2 results in reduced antibacterial activity but it is possible to add substituents to the amide nitrogen to get more soluble analogs like the prodrug lymecycline.
- The simplest tetracycline with measurable antibacterial activity is 6-deoxy-6-demethyltetracycline and its structure is often considered to be the minimum pharmacophore for the tetracycle class of antibiotics.
- C5-C9 can be modified to make derivatives with varying antibacterial activity



Uses

- Various gram-positive and gram-negative bacterial infections, including vibrio infections
- Drug of choice - rickettsiae
- Treat gastric and duodenal ulcer disease caused by Helicobacter pylori
- Most chlamydial infections, including sexually transmitted infections
- In combination with other antibiotics – plague, tularemia, and brucellosis
- No longer recommended for treatment of gonococcal disease because of resistance.
- Prophylaxis of protozoal infections