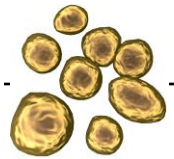
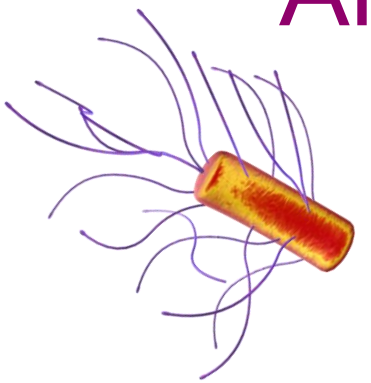
Drug Chemistry

By

Dr.Othman Ali Othman



Antibiotics and Antibiotic Resistance

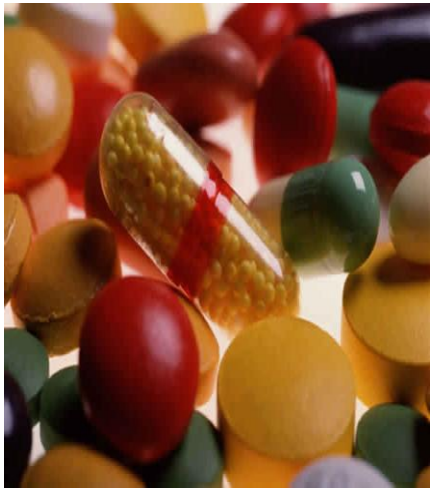


Antibiotics

Antibiotics are powerful medicines that fight bacterial infection

Literal translation

- *anti* – against
- *biotic* – living things



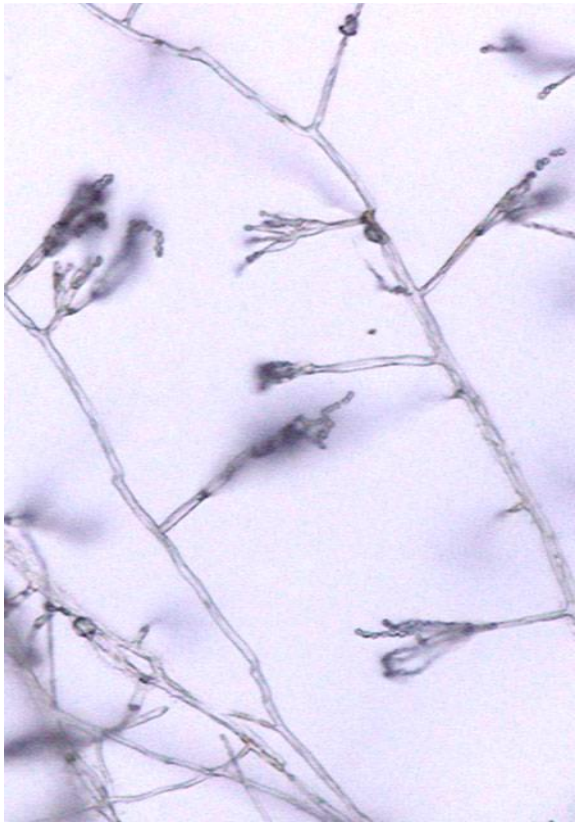
How antibiotics work

Antibiotics can be either

- Broad Spectrum
  - Kill a wide range of bacteria e.g. Penicillin
- Narrow Spectrum
  - Kill a specific type or group of bacteria e.g. Isoniazid

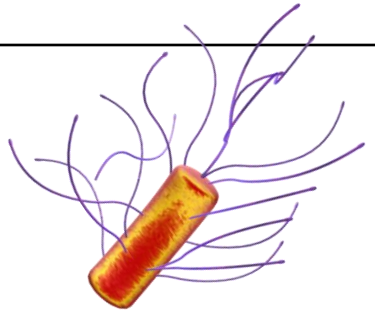
Antibiotics work in one of two ways

- Bactericidal
  - Kills the bacteria
- Bacteriostatic
  - Prevents the bacteria from dividing

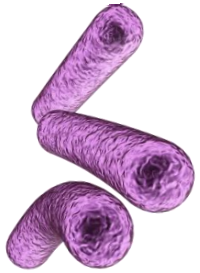


Antibiotic Resistance

The Causes

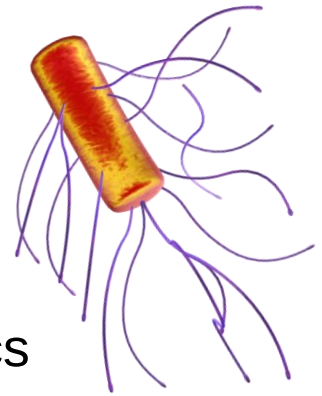


- Overuse
  - Antibiotics used to treat infections when they are not needed or not effective i.e. for the flu
- Misuse
  - Not completing a prescribed course
  - Using antibiotics not prescribed for you



How antibiotic resistance can be prevented

- Antibiotics should be the last line of defence NOT the first
  - Most common infections will get better by themselves through time, bed rest, liquid intake and healthy living.
- Only take antibiotics prescribed by a doctor
- If prescribed antibiotics, finish the course.
- Do not use other peoples or leftover antibiotics
  - they be specific for some other infection



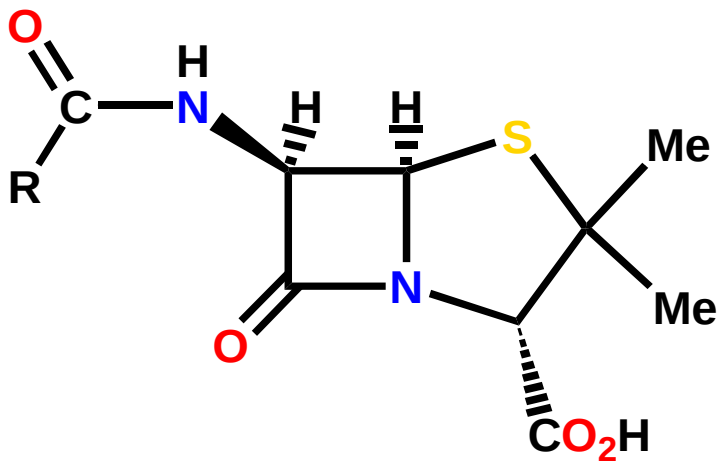
DEFINITION:

- are defined as chemical substances or compounds produced by various species of microorganisms such as bacteria and fungi, which in low concentrations destroy, kill or inhibit the growth of other species of microorganisms.”
- **Greek words anti = against ; bios = life**

characteristics of an antibiotic

- It should be **eliminated completely** from the body.
- -It should not side effects.
- -It should be highly effective in low concentrations.
- -It should be **nonallergenic** to the host.
- --It should be able to reach the part of the human body where the infection is occurring.
- -It should be inexpensive and easy to produce.
- -It should be chemically-stable

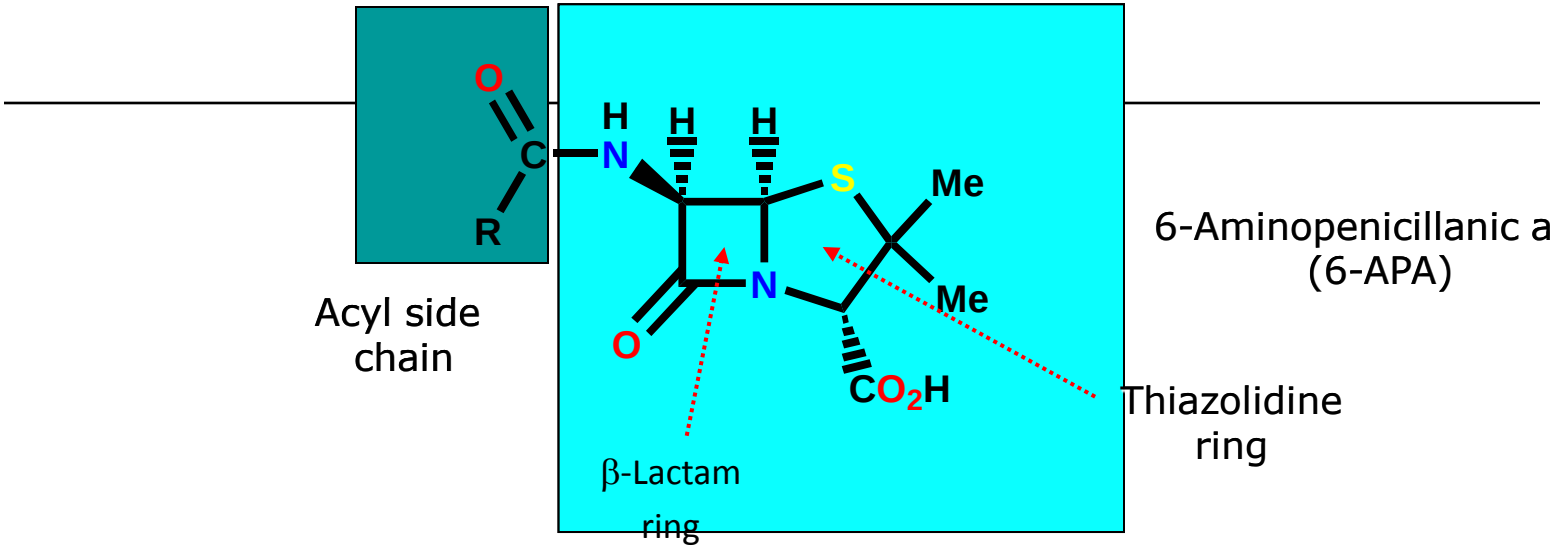
PENICILLINS



INTRODUCTION TO PENICILLINS

- Antibacterial agents which inhibit bacterial cell wall synthesis
- Discovered by Fleming from a fungal colony (1928)
- Shown to be non toxic and antibacterial
- Isolated and purified by Florey and Chain (1938)
- First successful clinical trial (1941)
- Produced by large scale fermentation (1944)
- Structure established by X-ray crystallography (1945)
- Full synthesis developed by Sheehan (1957)

STRUCTURE



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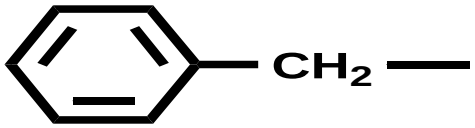

Benzyl penicillin (Pen G)

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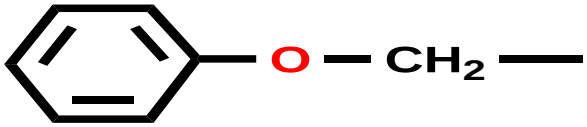
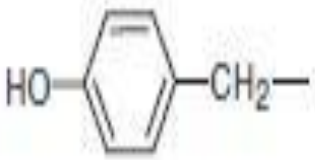


Phenoxymethyl penicillin (Pen V)



Penicillin X
p-Oxybenzylpenicillin

$CH_3CH_2CH{=}CH{-}CH_2{-}$

Penicillin F
2-Pentenylpenicillin

$CH_3(CH_2)_5CH_2{-}$

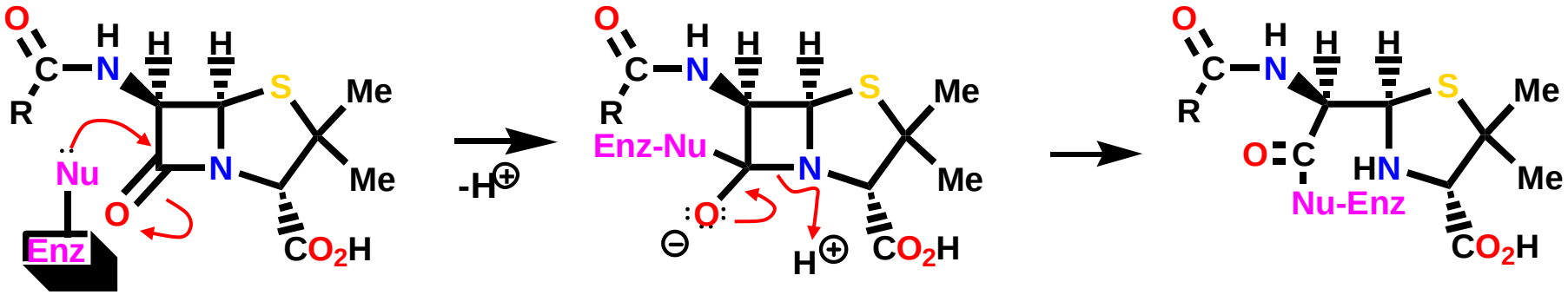
Penicillin K
p-Heptylpenicillin

$CH_2{=}CH{-}CH_2{-}S{-}CH_2{-}$

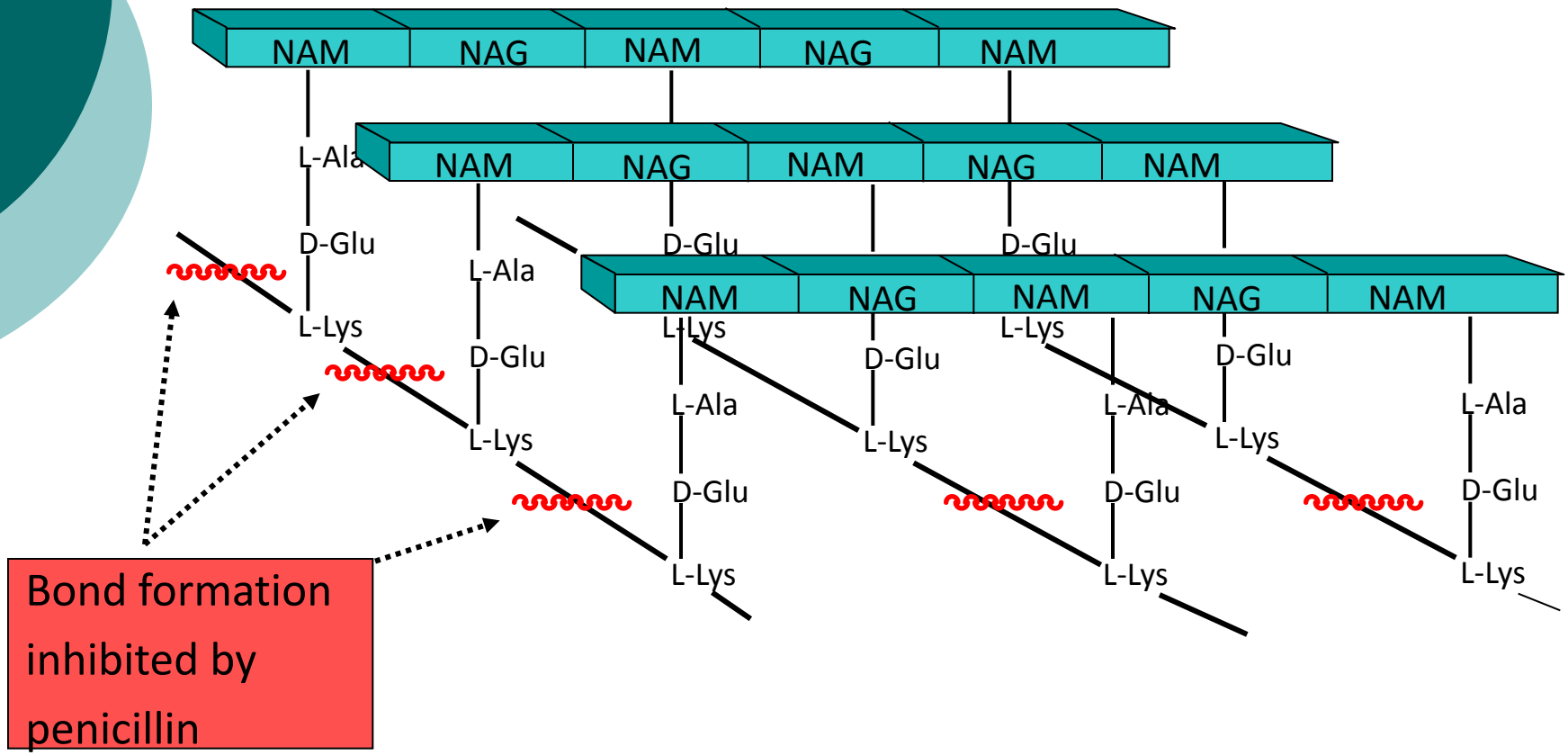
PenicillinO
Allylmercaptomethylpenicillin

Mechanism of action

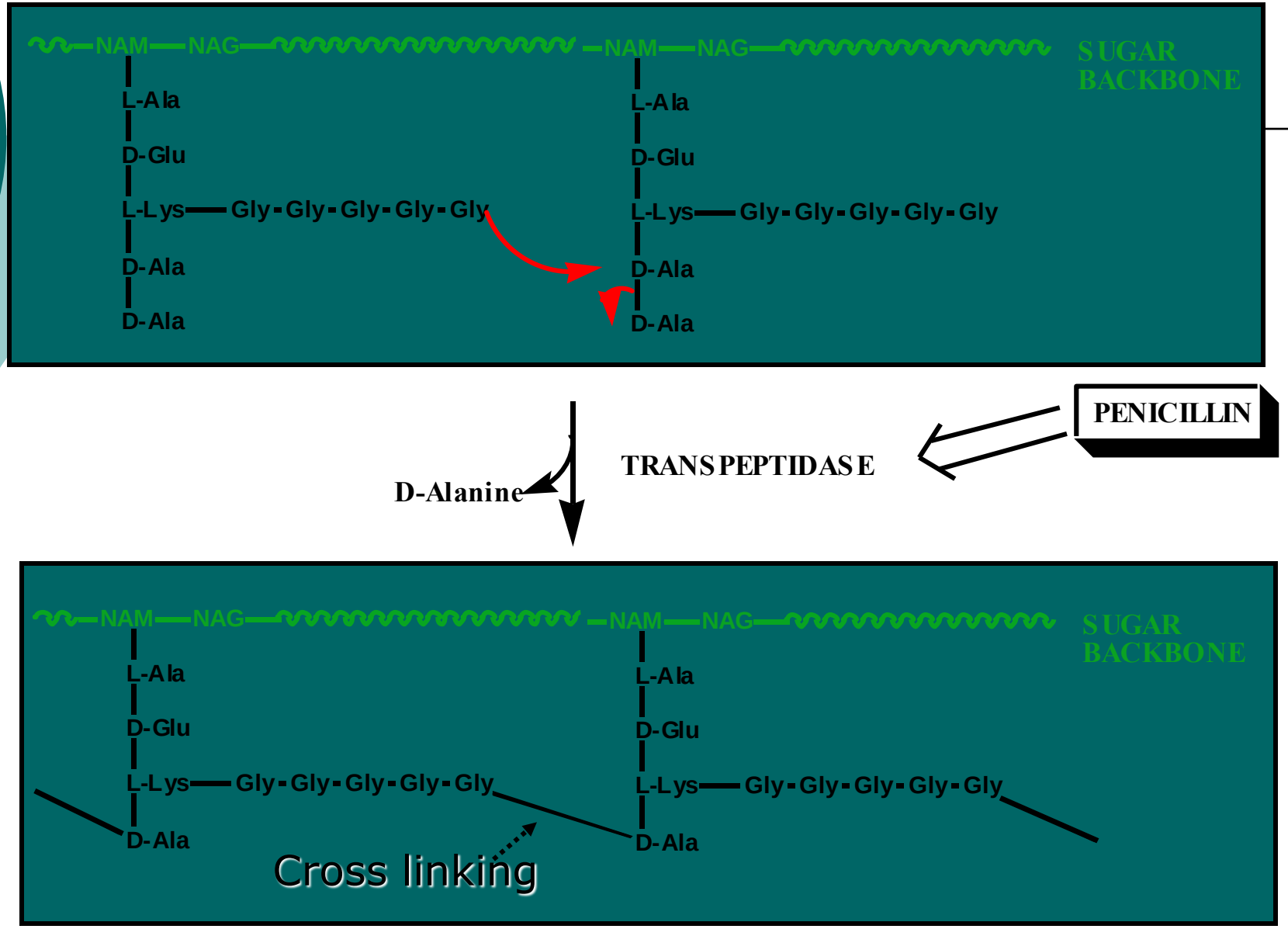
- Penicillins inhibit a bacterial enzyme called the transpeptidase enzyme which is involved in the synthesis of the bacterial cell wall
- The β-lactam ring is involved in the mechanism of inhibition
- Penicillin becomes covalently linked to the enzyme's active site leading to irreversible inhibition



Mechanism of action - bacterial cell wall synthesis



Mechanism of action - bacterial cell wall synthesis



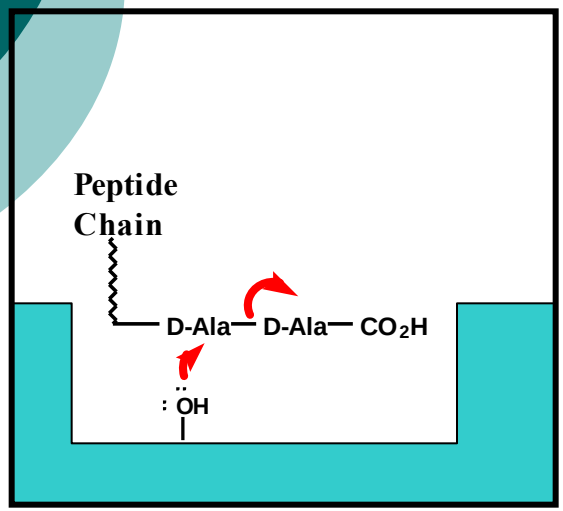
Mechanism of action - bacterial cell wall synthesis

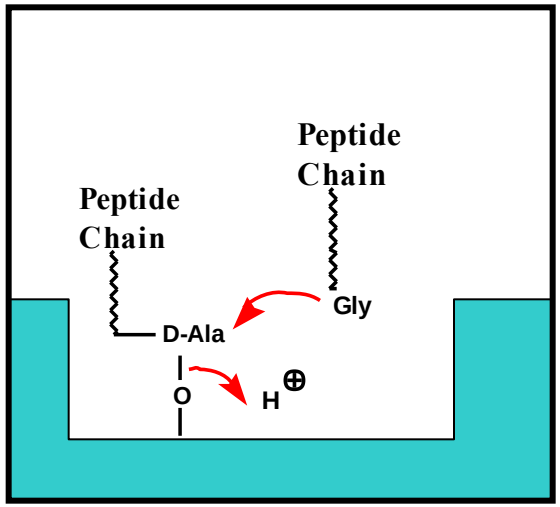
- Penicillin inhibits final crosslinking stage of cell wall synthesis
- It reacts with the **transpeptidase** enzyme to form an irreversible covalent bond
- Inhibition of transpeptidase leads to a weakened cell wall
- Cells swell due to water entering the cell, then burst (lysis)
- Penicillin possibly acts as an **analogue** of the L-Ala-γ-D-Glu portion of the pentapeptide chain. However, the carboxylate group that is essential to penicillin activity is not present in this portion

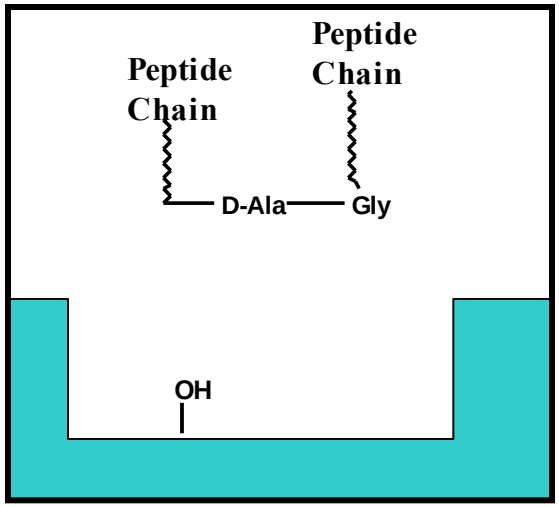
Mechanism of action - bacterial cell wall synthesis

Alternative theory- Pencillin mimics D-Ala-D-Ala.

Normal Mechanism

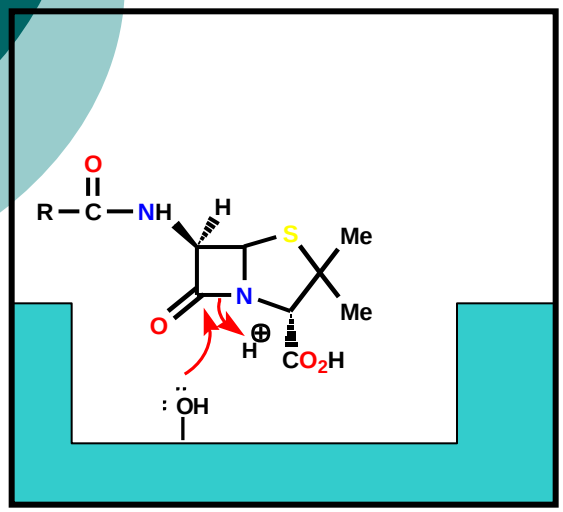


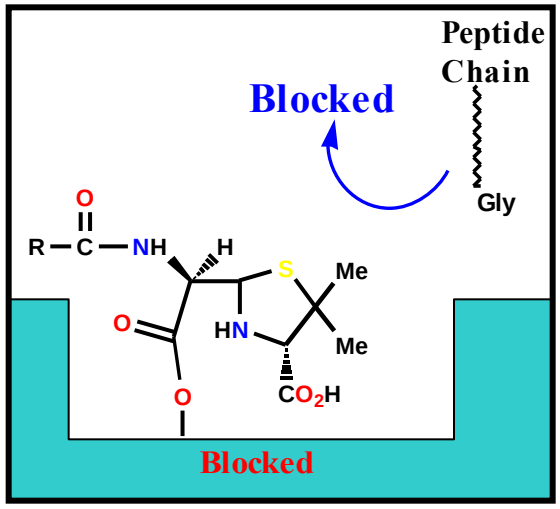


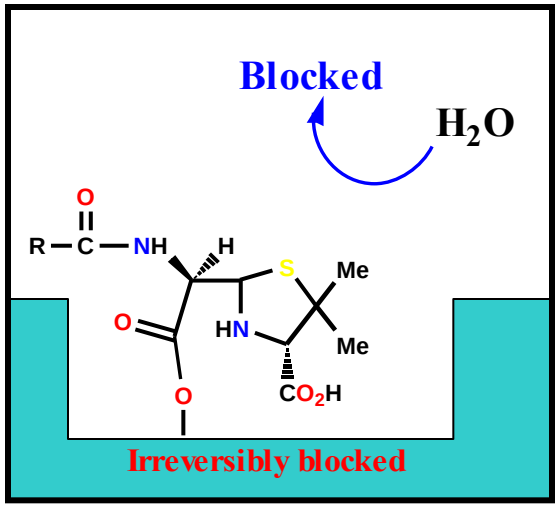


Mechanism of action - bacterial cell wall synthesis

Mechanism inhibited by penicillin

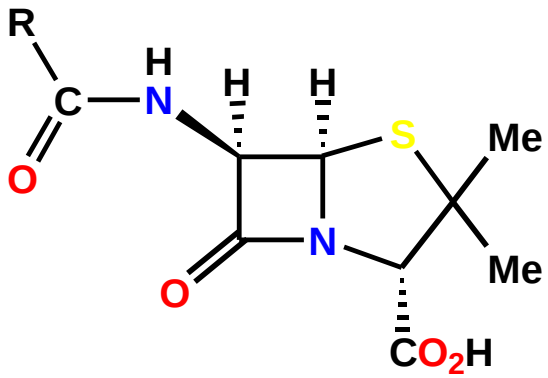




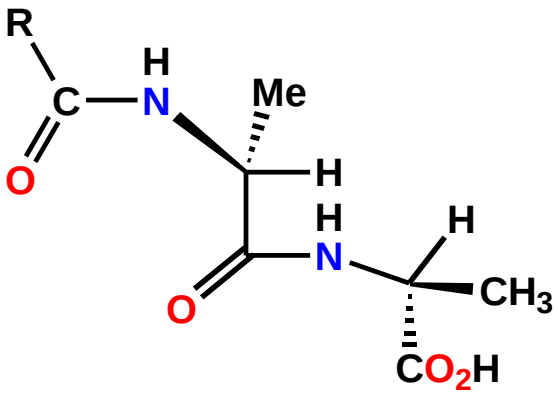


Mechanism of action - bacterial cell wall synthesis

Penicillin can be seen to mimic acyl-D-Ala-D-Ala

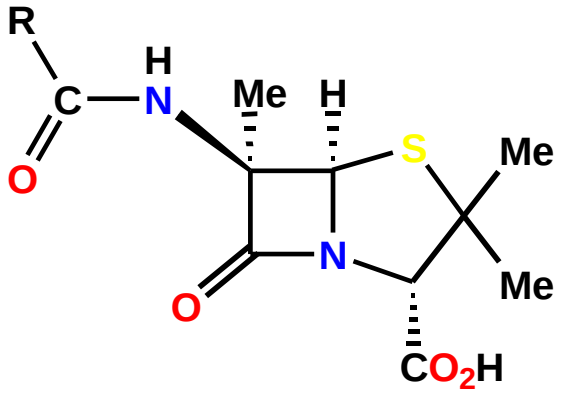


Penicillin

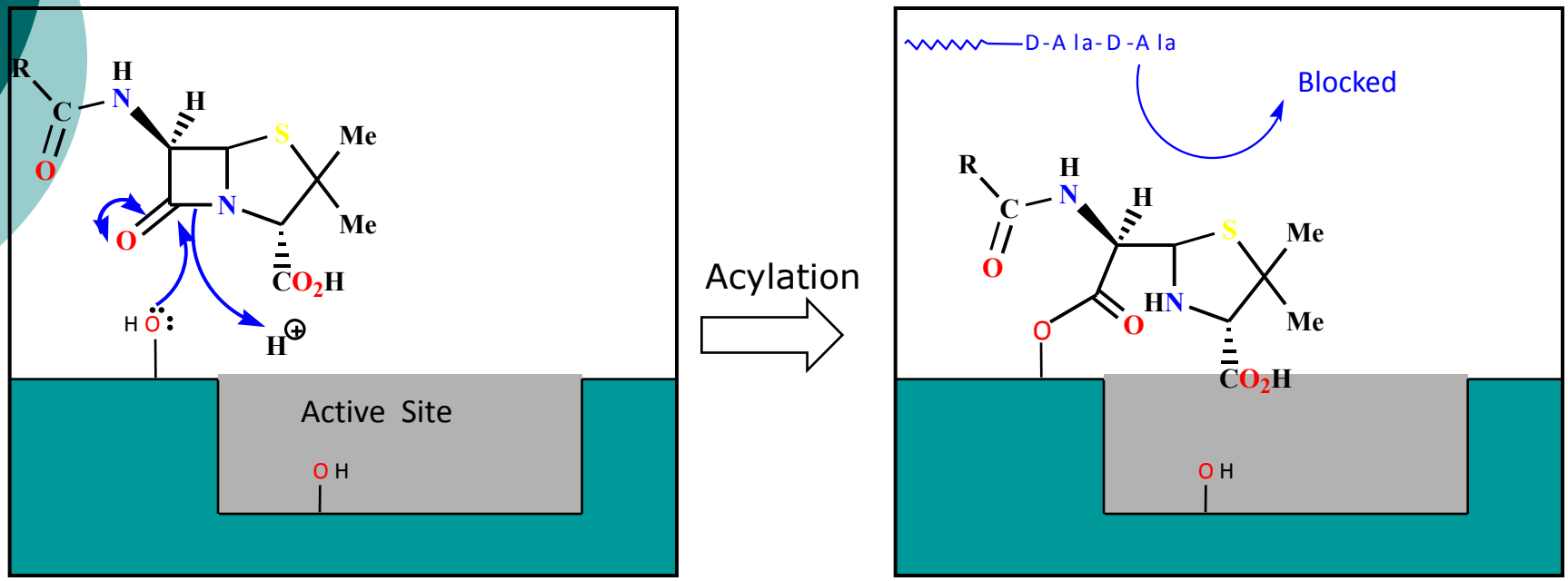


Acyl-D-Ala-D-Ala

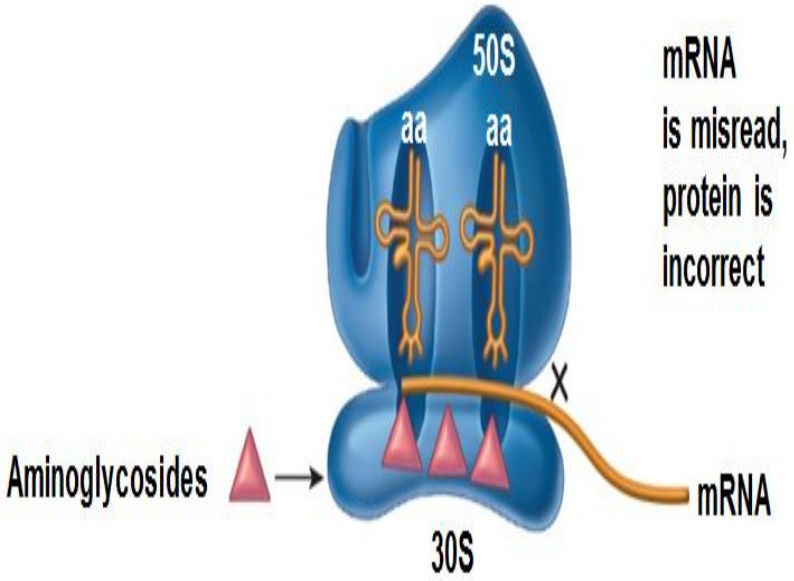
But 6-methylpenicillin is inactive despite being a closer analogue



Mechanism of action - bacterial cell wall synthesis



Aminoglycoside Antibiotics



- First member Streptomycin discovered by Waksman in 1944
- Natural and semi-synthetic antibiotics
- Produced from Actinomycetes
  - Those obtained from Streptomyces – Have suffix mycin (eg. Streptomycin)
  - Those obtained from Micromonospora – Have suffix micin (eg. Gentamicin,)

- **Structure characterized by**
  - **Two aminosugars joined to**
  - **One aminocyclitol moiety by**
  - **Glycosidic (-O-) bond**

In most of members aminoacyclitol moiety is 2-Deoxystreptamine .

Aminosugar	-O-	2-Deoxystreptamine	-O-	Aminosugar

- **In streptomycin the aminocyclitol is Streptidine.**

General character of Aminoglycosides group

Formulations are Sulfate or hydrochloric salts

Formulations are water soluble and stable } ***(Not absorbed from GIT)***

- **Highly polar basic drugs.**
- **Ionize during dissolution**
- **Distribution inside the cells is minimal**
- **Penetration through BBB is minimal**
- **Least metabolized by hepatic enzymes**
- **Excretion is mainly renal (unchanged form, through glomerular filtration)**

- Bactericidal in nature
- More active in alkaline pH
- MOA is by interfering with protein synthesis
- Attach with 30S ribosomal subunit (ATT)
- Concentration dependent (PAE)
- Mainly gram negative (plus tuberculosis by streptomycin, Kanamycin, Amikacin)
- Cross resistance is partial
- Therapeutic index is narrow

Have NONE side effects

- Nephrotoxic
- Ototoxic
- Neuromuscular blockage
- Etc.(Teratogenicity)

Nephrotoxicity

- Streptomycin is least nephrotoxic.
- Larger the number of NH2 more nephrotoxicity.
- Nephrotoxicity is caused by
  - Inhibition of an intracellular lysosomal phospholipase-A2 in renal brush border.
  - Leading to lysosomal distension,
  - Rupture and Release of acid hydrolases
  - Release of Free Aminoglycosides into cytosol.
  - This free drug binds to other cellular organelles (eg. In mitochondria it displaces Ca++ leading to mitochondrial degeneration and necrosis.)
- Nephrotoxicity is reversible
- Verapamil and Ca++ can
  - Reduce nephrotoxic potential But
  - Also reduce antibacterial effect

- **KAN (Kanamycin, Amikacin, Neomycin) mainly damage cochlea rest vestibular damage**

- **Al**

- **Neomycin and Framycetin have extreme systemic toxicity (only topically used)**

- **Amikacin has widest spectrum**

- **Avoid concurrent use of other Ototoxic drugs (Frusemide, Ethacrinic acid, Minocycline)**

- **Neomycin used orally for *Hepatic Encephalopathy)***

- **Avoid concurrent use of other nephrotoxic drugs (Amphotericin B, Vancomycin, Cephalothin, Cephradrine, Cyclosporin, Cisplatin)**

- **Be overcautious while using in extremes of age and renal compromised**

- **Be overcautious while using in operated patients (Received Curare)**

Don’t mix with any other drug (Pharmaceutical Drug Interaction)

Partially removed by peritoneal and haemodialysis

The excretion is proportional to creatinine clearance.

- Half life increases in renal insufficiency.
- Dose adjustment is needed in renal insufficiency
- Most precise method for calculating dose is using creatinine clearance

Daily dose of Aminoglycoside (in Renal compromised patients) = **Normal therapeutic dose** / **Serum Creatinine Value (mg/dl)**

calculated dose

Members

- ***Amikacin***
- ***Streptomycin***
- **Sisomicin**
- **Spectinomycin**
- ***Kanamycin***
- **Ispepamycin**
- **Netilmicin**
- ***Gentamicin***
- ***Tobramycin***

- **Ribostamycin**
- **Arbekacin**
- **Bekanamycin**
- **Dibekacin**
- **Hygromycin**
- **Verdamicin**
- **Astromicin**
- **Paromomycin**

MOA

Bactericidal (Gram Negative, No action on Anaerobes)

Initial entry of Aminoglycosides through bacterial cell wall to periplasmic space

- **Through porin channels by passive diffusion (1)**

- **Later on further Entry across cytoplasmic membrane is carrier mediated (linked to electron transport chain, energy and oxygen dependent)**
  - **Active transport (2)**
- **Advantage of adding Beta lactams**
  - **Beta Lactam antibiotics weaken the bacterial cell wall**

- **Penetration is dependent on**
  - **Maintenance of polarized membrane**
  - **Oxygen dependent active process**
    - **Not active in absence of oxygen**
    - **Not effective against anaerobes**
    - **Not effective in presence of big abscess**
  - **pH alteration. Alkalization favors penetration into cell**

Prevent polysome formation (accumulation of nonfunctional monosomes)

Inside the bacterial cell Aminoglycoside bind with 30S ribosome subunit (or at the interface of 30S and 50S)

- **Inhibit formation of initiation complex**
- **Inhibit protein synthesis**
- **Misreading of mRNA Codon**
- **Entry of wrong amino acid in the chain**
- **Formation of wrong peptide chain**

(Check the growth of bacteria, Bacteriostatic)

How Cidal action is achieved

Ans-

Defective proteins incorporated in cell membrane.

Due to secondary changes in the integrity of bacterial cell membrane. (Increase permeability for ions, amino acids, proteins- Leading to leaking of these out side)

- **Bonus of incorporation of defective protein in cell membrane**
- **More entry of antibiotic occurs in to the cell. Furthe**

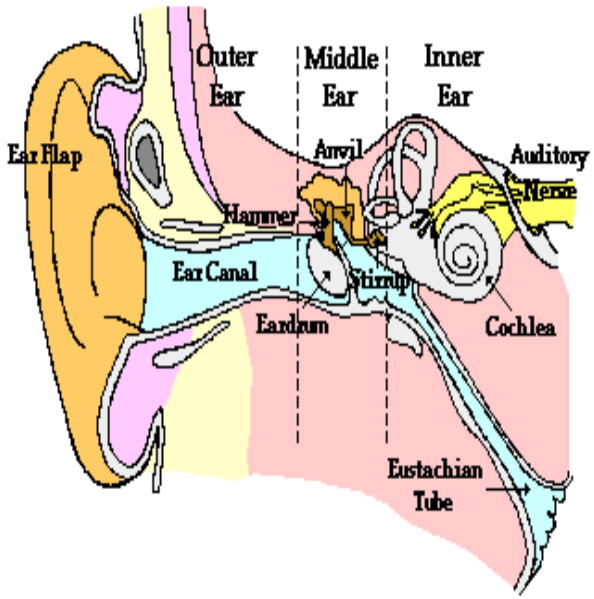
Death Of Bacteria

Resistance development (Conjugation and transfer of plasmid)

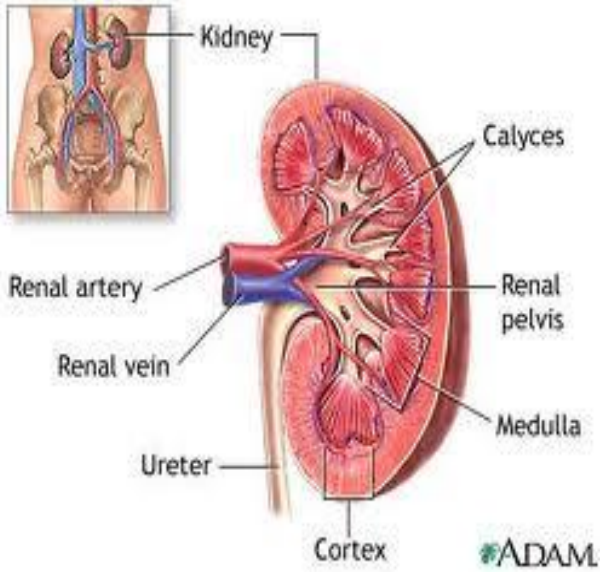
- Development and synthesis of plasmid mediated bacterial transferase enzyme (Acetyltransferase, Phosphotransferase, Adenylyltransferase), which inactivates Aminoglycosides.
- Impermeability of porins, Impaired active transport
- Inactivating enzymes in the cell membrane – Phosphorylate / Adenylate / Acetylate and inactivate Aminoglycosides
- Phosphorylated / Adenylated / Acetylated conjugates of Aminoglycoside can not bind at target ribosomal subunit and site.

Side effects and Toxicity

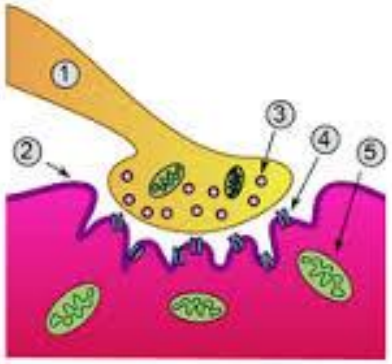
- **Ototoxic-**
  - Concentrated in labyrinthine fluid
  - Released from there when plasma concentration decreases.
  - Less seen in routine dose. (High dose, ... chance)
  - Damage of sensory and hair cells
- Vestibular-
  - Presents with Vertigo, Ataxia, Nysta
  - (Headache, Nausea, Vomiting, Dizz
  - Recover slowly (Least recovery in e
- Cochlear-
  - Starts from base spreads to apex.
  - High frequency affected first
  - Recovery is very poor.
  - Deafness may be permanent, more in elderly
  - Presents with tinnitus (reversible) followed by hearing



- **Nephrotoxicity-**
  - **More damage of cortical nephro**
  - **Related to total exposure**
  - **More in Elderly**
  - **More in pre-existing renal disea**
  - **Reversible**
  - **Tubular damage (Loss of concentrating mechanism)**
  - **Reduction in GFR (Interference with the prostaglandin production in kidney)**
  - **Urine contains albumin and casts**
  - **Nitrogen retention in body**
- **Nephrotoxicity- Reduced clearance of Aminoglycosides – High blood levels of Aminoglycosides – High chances of Ototoxicity**



- **Neuromuscular Blockade**
- **More with Neomycin and Streptomycin**
  - **Reduce Acetylcholine release from Motor E**
  - **Interfere with mobilization of synaptic ves**
  - **By antagonizing calcium**
  - **Decreased sensitivity of the muscle end plates to Ach.**
- **Non significant in otherwise normal cases in routine**
- **Dangerous in**
  - **Myasthenia gravis**
  - **Direct administration of Aminoglycosides into pleural and peritoneal cavities**
  - **If patient received curare like muscle relaxant during surgical procedure**



Partially antagonized by IV calcium

Streptomycin

Narrow spectrum (Gram negative + M. tuberculosis)

Uses

- **Tuberculosis (First drug to show antitubercular activity)**
  - **(PESRI-25,20,15,10,5 mg/kg)**
- **Acts against extracellular bacilli (due to poor penetration in the cell)**
- **Also active against Atypical Mycobacterium (M. kansasii and M. avium intracellulare.)**
- **Resistance develops fast (Never use streptomycin alone as antitubercular)**
- **SABE**
- **Plague – (Streptomycin {Tetracycline}**
- **Tularemia- (DOC {Tetracyclines alternate}**

- **Tularemia** (rabbit fever, deer fly fever, and Ohara's fever)is caused by the bacterium *Francisella tularensis* a gram-negative, nonmotile coccobacillus.

  Depending on the site of infection, tularemia has six characteristic clinical symptoms: ulceroglandular , glandular, oropharyngeal, pneumonic, oculoglandular, and typhoidal.

  Brucellosis, also called Bang's disease, Crimean fever, Gibraltar fever, Malta fever, Mediterranean fever, rock fever, or undulant fever is a highly contagious zoonosis caused by ingestion of unsterilized milk or meat . Transmission from human to human, through sexual contact or from mother to child, is rare but possible.

- *Brucella* are small, gram-negative, non-motile, non-spore-forming, rod shaped (coccobacilli) bacteria. They function as facultative intracellular parasites .

- **Plague** is a deadly infectious disease that is caused by the enterobacteria *Yersinia pestis*. The symptoms of plague depend on the concentrated areas of infection in each person: such asbubonic plague in lymph nodes, septicemic

Tetracyclines:

Tetracyclines:

-a broad-spectrum antibiotics.

-It is commonly used to treat infection, and other infections caused by bacteria.

-The first of these compounds was chlortetracycline followed by oxytetracycline and tetracycline.

Tetracycline divided into:

a) Naturally occurring:

1-tetracycline 2-chlortetracycline

3-oxytetracycline

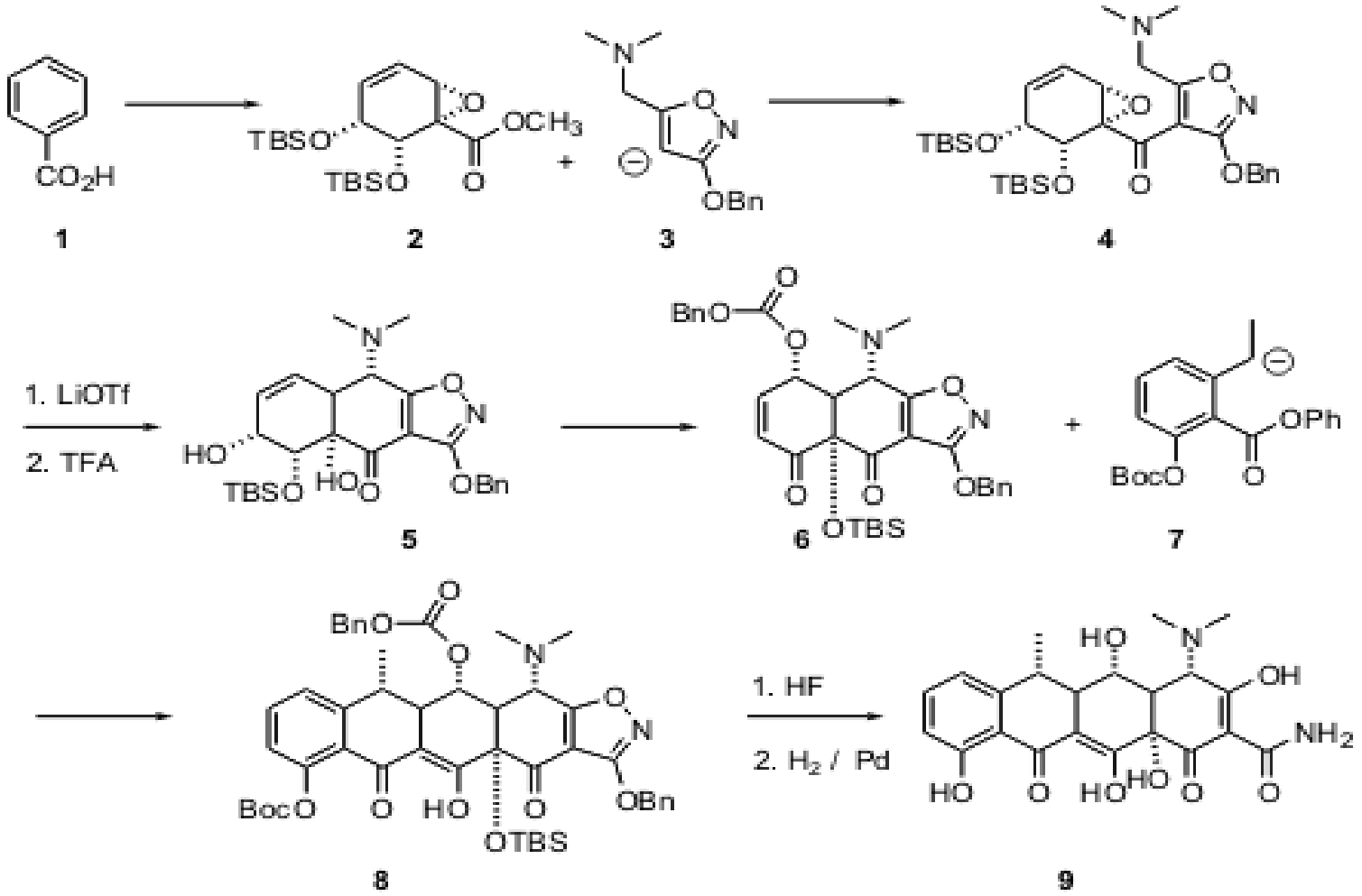
Semisynthetic occurring:

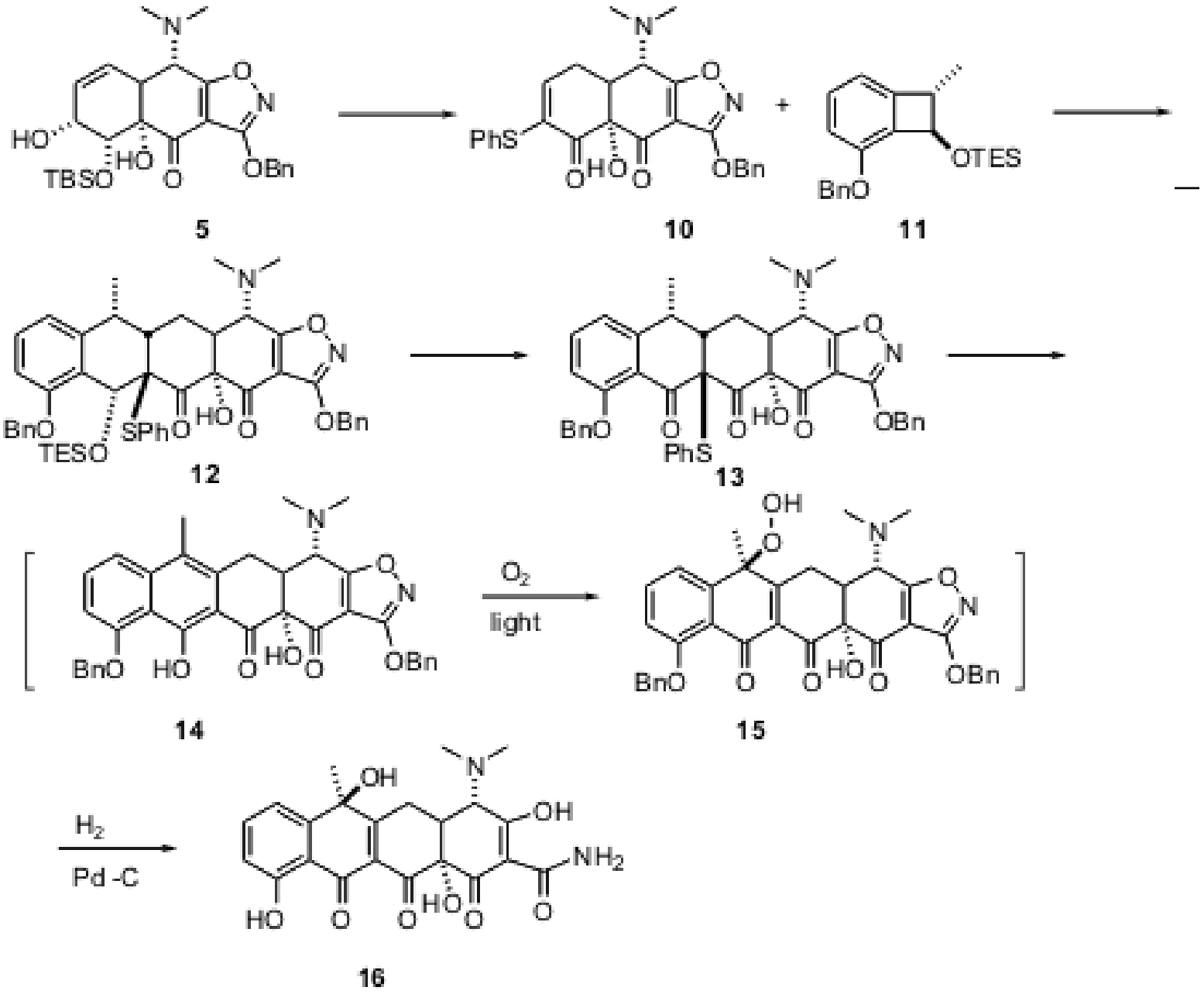
1-doxycycline

2-minocycline

3-methacycline

Total Synthesis of the Tetracyclines:

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TBSO
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BnO
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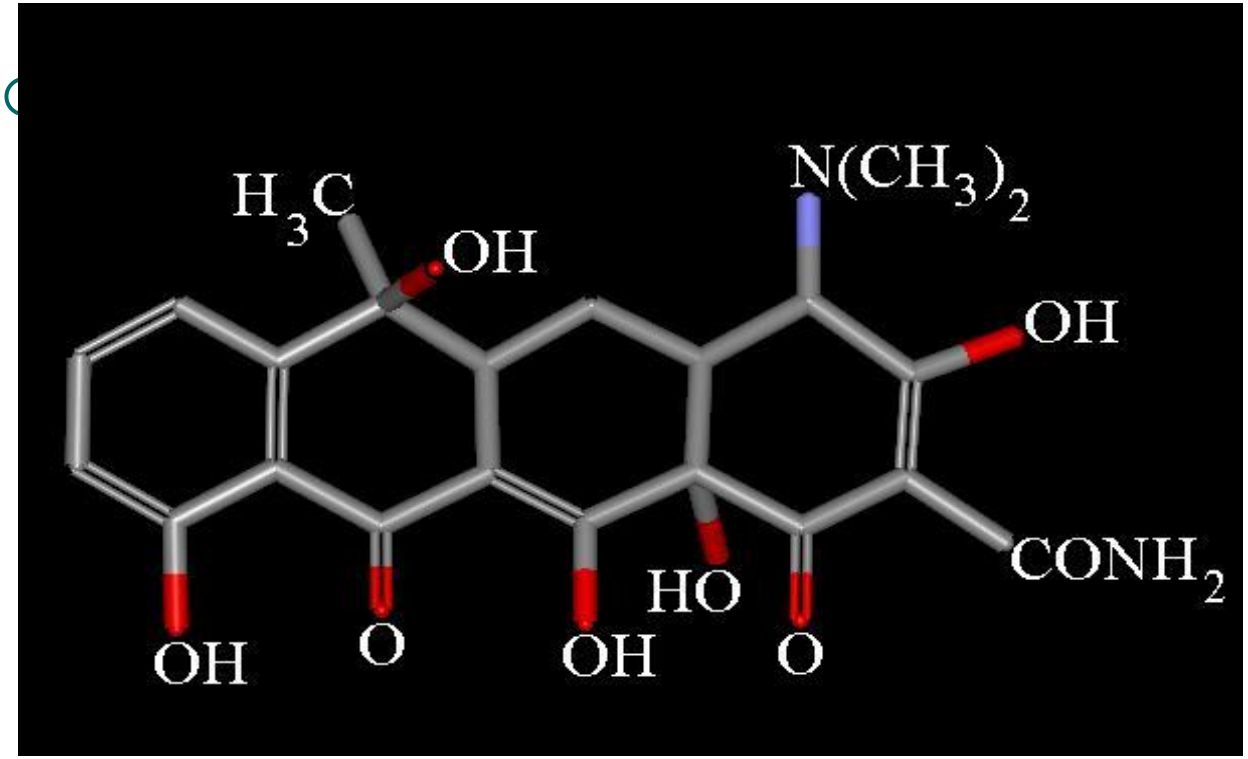
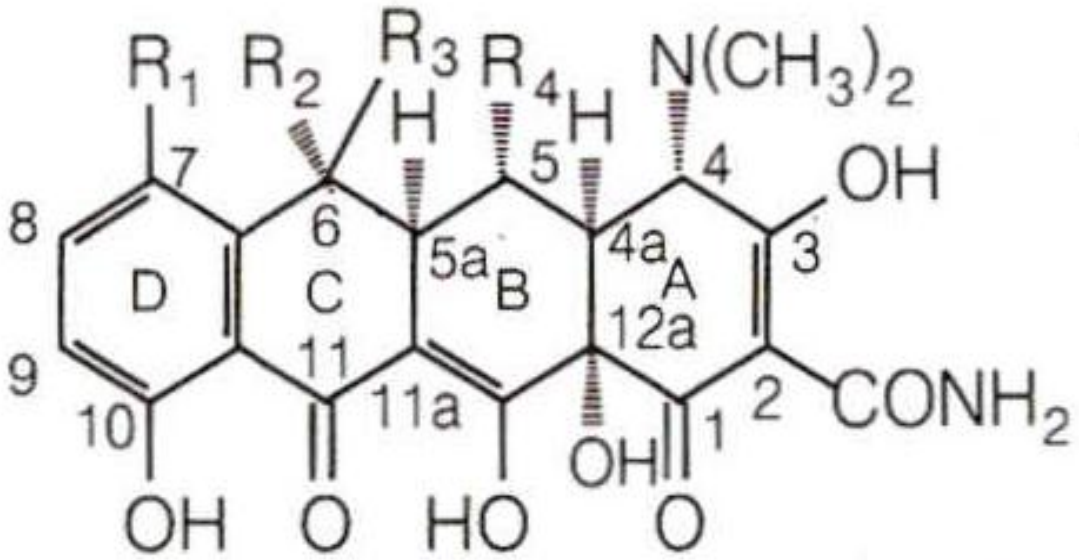
H_2
Pd -C
NH_2
16

Structure and chemical characteristics



Structure activity relationship

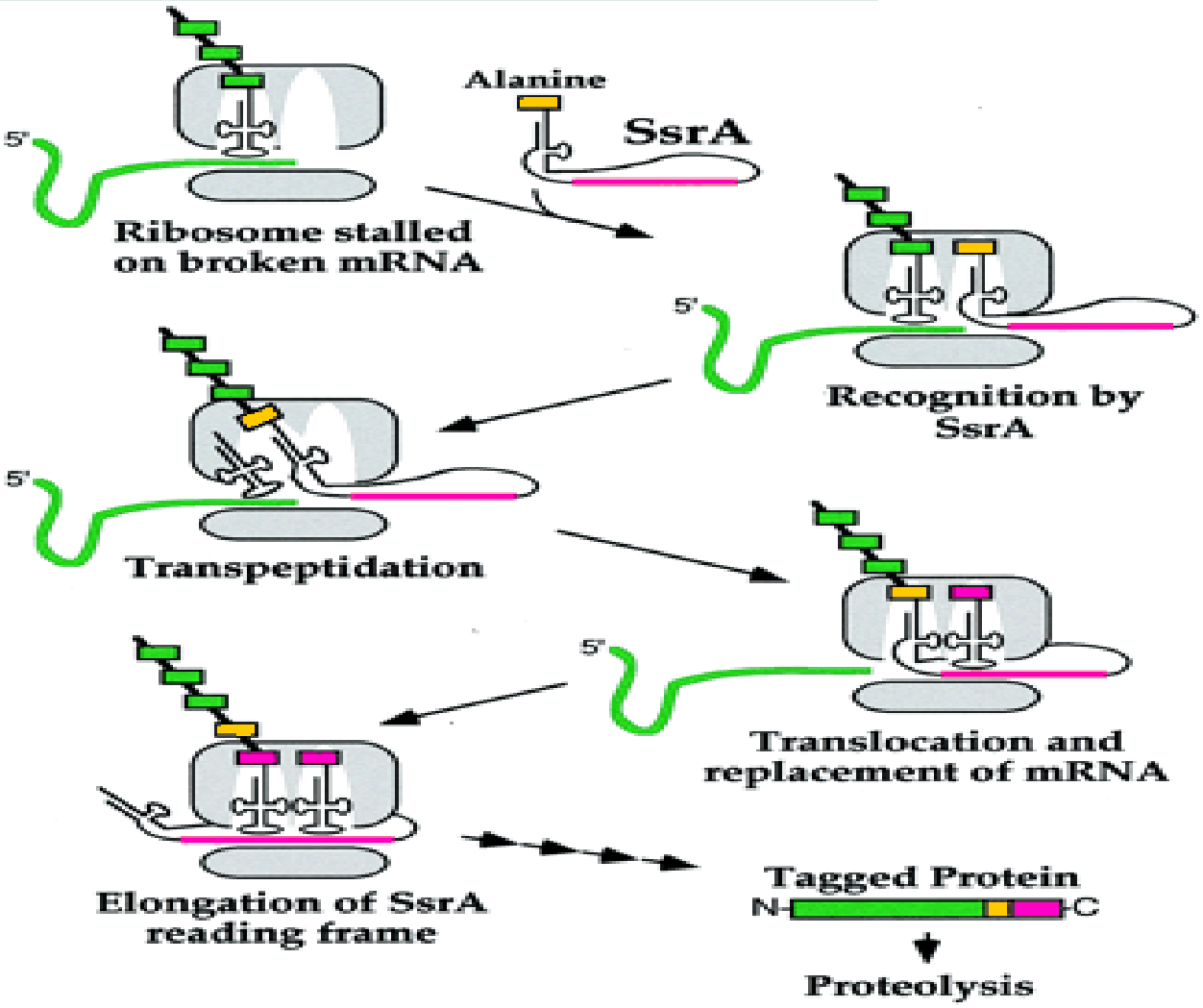


	R5	R4	R3	R2	R1.
Chlortetracycline	H	H	OH	CH3	Cl
Oxytetracycline	H	OH	OH	CH3	H
Tetracycline	H	H	OH	CH3	H
Demethylchlortetracycline	H	H	OR	H	CI
Rolitetracycline	H	H	OH	CH3	H
Metacycline	H	OH	CH2	H	H
Doxycycline	H	OH	H	CH3	H
Minocycline	H	H	H	N(CH3)2	H

Mechanism of action:

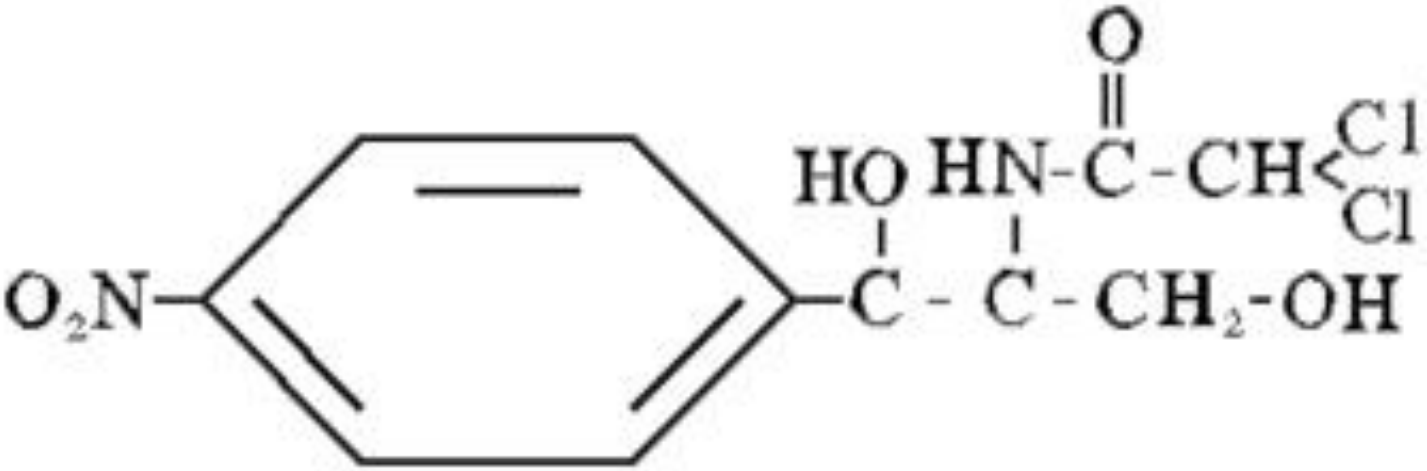
- Prevent the binding of aminoacyl tRNA with to mRNA and their for prevent synthesis of protein

Mechanism of action:



Chloramphenicol

- **Structure:**



- **Antimicrobial activity:**
- Broad spectrum.
- Effect on G^+ and G^- bacteria,
- ricketts organism,

- the drug appears to prevent the binding of the amino-acid-containing end of the aminoacyl tRNA. The interaction
- between peptidyltransferase and its amino acid substrate cannot occur, and peptide bond formation is inhibited

- **Mechanism action**
- ---
- **blocks Peptidyl transferase enzyme**
- **prevents formation peptide bound**
- **Prevents protein synthesis**

Quinolones

Dr. Othman Ali Othman

Synthetic antimicrobials

- Bactericidal
- ✓ Primarily gram negative bacteria

- **Quinolones - Antibacterial Spectrum**
- **● 1st generation (quinolones - nalidixic acid):**
- **limited to Gram negative enteric bacteria**
- **(UTIs)**
- **● 2nd generation (fluoroquinolones -**
- **norfloxacin, ciprofloxacin): improved Gram**
- **negative coverage with activity against *S.***
- ***aureus* (systemic infections) , pseudomonas**
- **and also against *B. anthracis***
- **– Addition of fluorine and piperazine derivative**

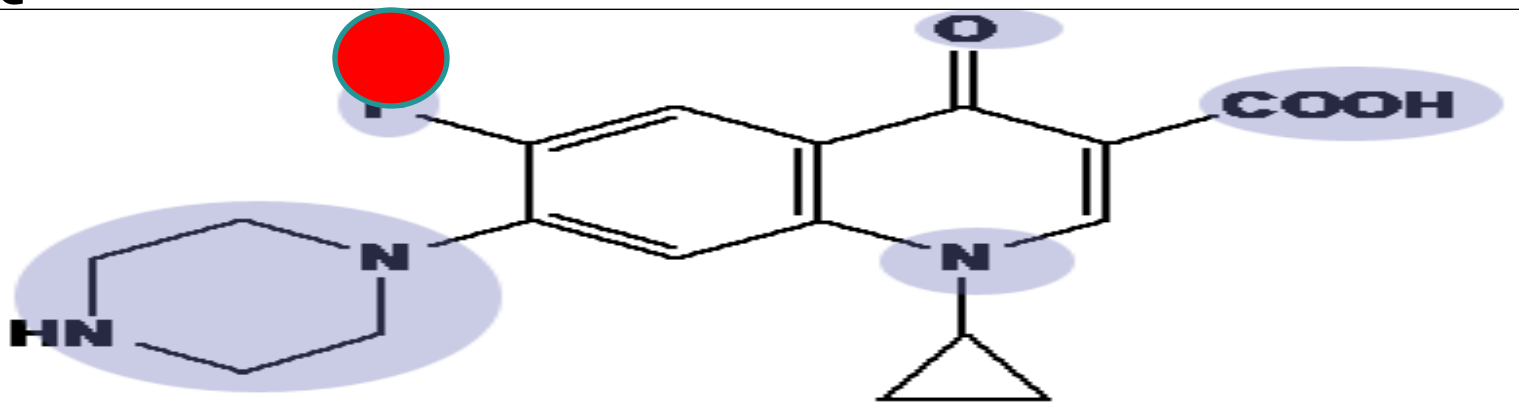
- **Quinolones - Antibacterial Spectrum**
- **• 3rd generation (fluoroquinolones - levofloxacin):**
- **Improved activity against Gram positives *e.g.***
- **staphylococci and pneumococci, also has activity**
- **against mycoplasma and legionella (systemic**
- **infections)**
- **– Longer half life**
- **– Increased structural complexity, greater antimicrobial**
- **spectrum but also increase in some toxicity**
- **• Gatifloxacin and moxifloxacin are two newer**
- **agents with extended half-lives and enhanced**
- **Gram positive activity**

Nalidixic acid

- First member

Quinolones and Fluoroquinolones

- **Have Quinolone structure**



- **Nalidixic acid is first member**
- **Fluorination of Quinolones - Fluoroquinolones**
- **Gram negative mainly**
  (Plus gram positive New FQs)

N to P

Members

Quinolones

- Nalidixic acid

Fluoroquinolones

First Generation

- Ciprofloxacin
- Norfloxacin
- Pefloxacin
- Ofloxacin

Fluoroquinolones

New Generations

- Lomefloxacin
- Levofloxacin — Second
- Prulifoxacin
- Sparfloxacin
- Gatifloxacin — Third
- Gemifloxacin
- Moxifloxacin
- Trovafloxacin
- Alatrofloxacin — Fourth
- Finafloxacin

MAN Can SPOT Good Life

- **M**oxifloxacin
- **A**latrofloxacin
- **N**orfloxacin

- **C**iprofloxacin
- **S**parfloxacin
- **P**efloxacin
- **P**rulifoxacin
- **O**floxacin
  - **T**rovafloxacin
  - **G**atifloxacin
  - **G**emifloxacin
  - **L**omefloxacin
  - **L**evofloxacin

M
A
N **C**an
S
P
O
T **G**ood
Life

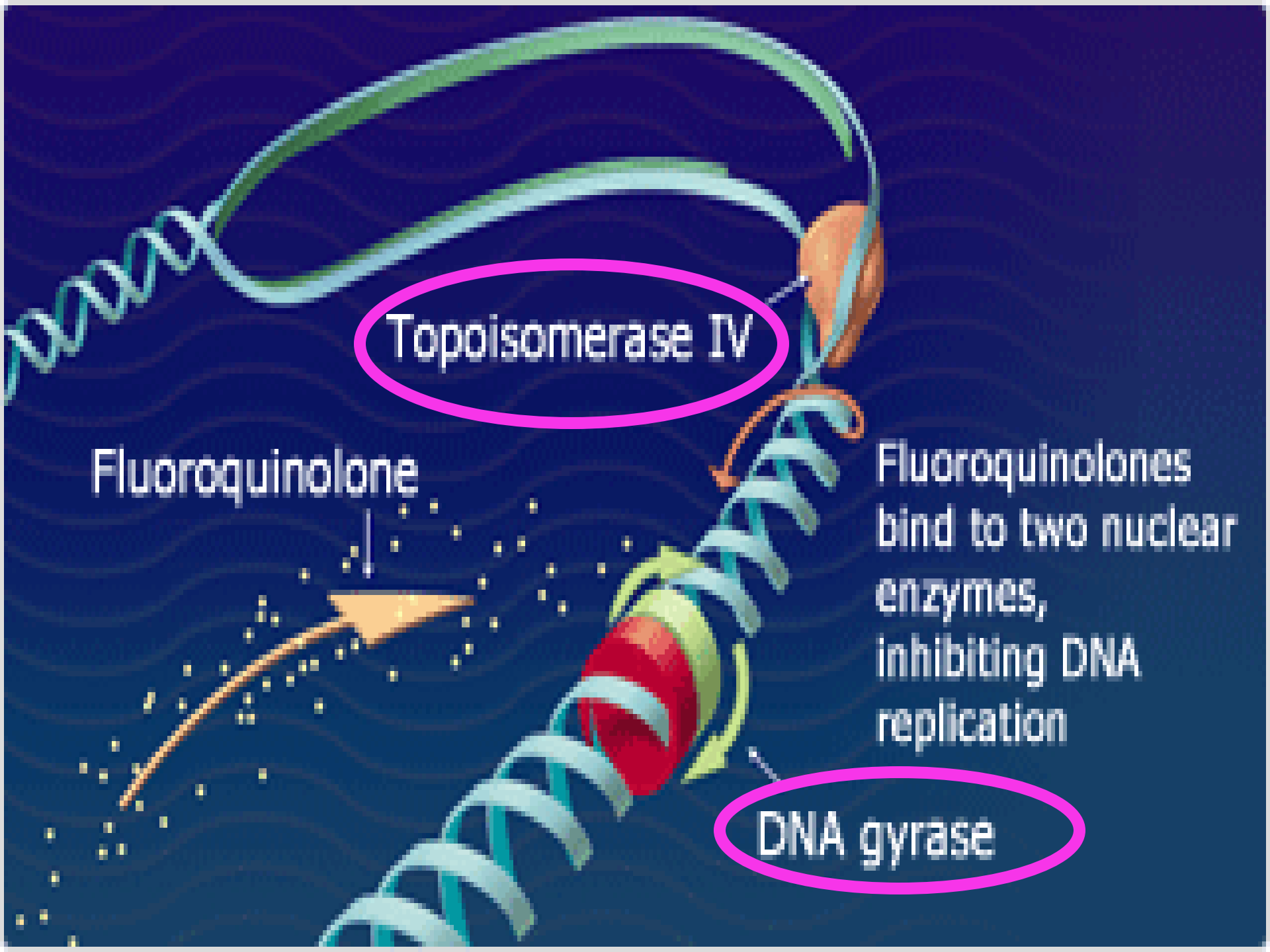
- **MOA-** ***(Queen stops gyrating dancers)***

- **In gram negative –**
  - **Inhibition of DNA gyrase enzyme (Inhibit negative super coiling)**

- **In gram positive –**
  - **Inhibition of Topoiosmerase IV – Inhibition of nicking and separation of daughter DNA strands after DNA replication (Inhibition of Decatenation)**

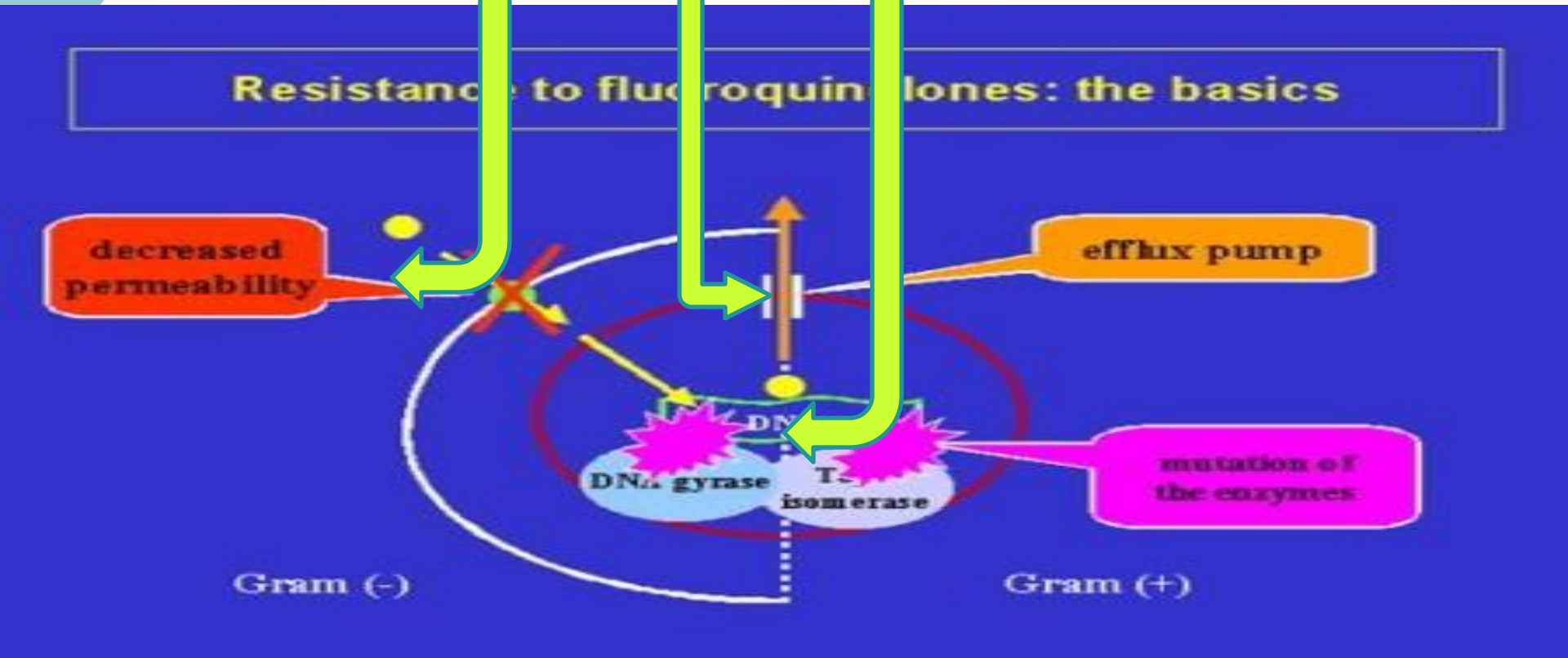
- **The malformed DNA is digested by Exonucleases**

Why not human cells affected ?


Topoisomerase IV
Fluoroquinolone
Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication
DNA gyrase

Resistance-Due to mutation in chromosomes

- Altered DNA gyrase and Topoisomerase IV
- Reduced permeability for drug
- Increased efflux of drug



Mechanism of action

Quinolones target bacterial DNA **gyrase** & **Topoisomerase IV**

- Gram negative bacteria - **DNA Gyrase**
- Gram positive bacteria - **Topoisomerase IV**

Mammalian cells

Topoisomerase II

Low affinity for flouroquinolones

Inhibited by quinolones only at much higher concentrations.

Low toxicity to host cells

Mechanism of action

- Double helical DNA
- Two strands must separate to permit DNA replication / transcription

- “over winding” / excessive positive supercoiling of DNA in front of point of seperation (mechanical hindrance)

- faulty protein synthesis
- Detrimental for bacterial growth.

DNA Gyrase has (A & B subunit)

A subunit - strand cutting function of DNA gyrase.

- B subunit - introduces negative supercoils

  DNA Gyrase - introduces negative supercoils into DNA (checks mechanical hindrance)

- A subunit reseals the strand

Quinolones

bind to **A - subunit** with high affinity & interfere with **strand cutting & resealing function**

- Prevent **replication of bacterial DNA** during bacterial growth & reproduction.

In addition bacterial DNA gyrase inhibition also leads to

extensive filamentation

vacuole formation

&

degradation of chromosomal DNA

All this confers **bactericidal** activity to FQ's

Mechanism of resistance

Chromosomal mutation

bacteria produce DNA Gyrase/ Topoisomerase IV with **reduced affinity** for FQs

-  **Efflux** of these drugs across bacterial membranes

- *No **quinolone modifying/inactivating enzymes** have been identified in bacteria*
- Resistance is **slow** to develop

Spectrum

Potent **bactericidal** against Gram negative bacteria:

- E.coli
- Salmonella
- Shigella
- Enterobacter
- Campylobacter & Neisseria

Ciprofloxacin is more active against

- Pseudomonas aeruginosa

Sulfonamides

Mechanism of action :

- Competitive inhibitor to dihydropteroate synthase enzyme .
- Inhibit bacterial growth by blocking folic acid synthesis .

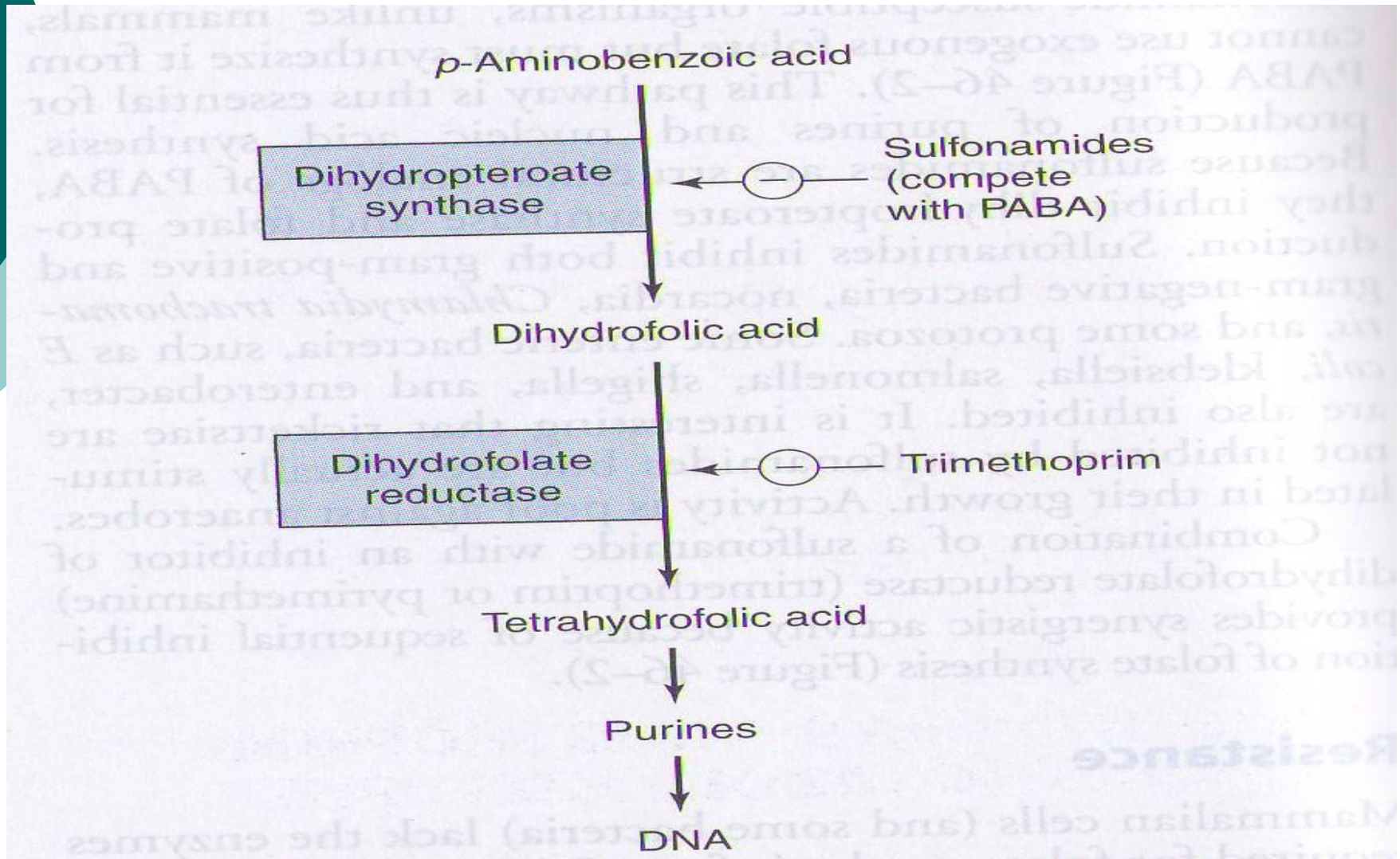


Figure 46–2. Actions of sulfonamides and trimethoprim.

Antibacterial activity

- Gram-positive and gram negative.
- Nocardia, chlamydia trachomatis, some protozoa.

Pharmacokinetics

1) Oral absorbable :

- Short acting e.g**. sulfisoxazole**
- Intermediate e.g. **sulfadiazine & sulfamethxazole**
- Long acting e.g. **sulfadoxine**
- They are absorbed from stomach & intestine
- Distributed widely including C.N.S.& placenta.

- Metabolized in liver to inactive metabolites .Excreted through kidney .
- Rate of excretion increases in alkaline urine.

2) Oral non-absorbable e.g. sulfasalazine

3)Topical. :sulfacetamide, mafenidic acid, silver sulfadiazine.

Therapeutic uses

- Urinary tract infections
- Upper respiratory tract infections
- Nocardiosis
- Sulfasalazine in IBD.
- Sulfacetamide in bacterial conjunctivitis & trachoma
- Silver sulfadiazine for prevention of infection of burn wounds .

Adverse effects

- Hypersensitivity reactions
- N.V.D.
- Crystalluria,hematuria,renal obstruction.
- Allergic nephritis
- Haemolytic anaemia,aplastic anaemia,thrombocytopenia.
- Kernicterus in new born

Trimethoprim-Sulfamethoxazole combination(Co-trimoxazole)

Mechanism of action:

- Sequential blocking of purine synthesis (synergism).
- Trimethoprim inhibits dihydrofolate reductase enzyme so inhibits tetrahydrofolic acid synthesis
- The combination is bactericidal

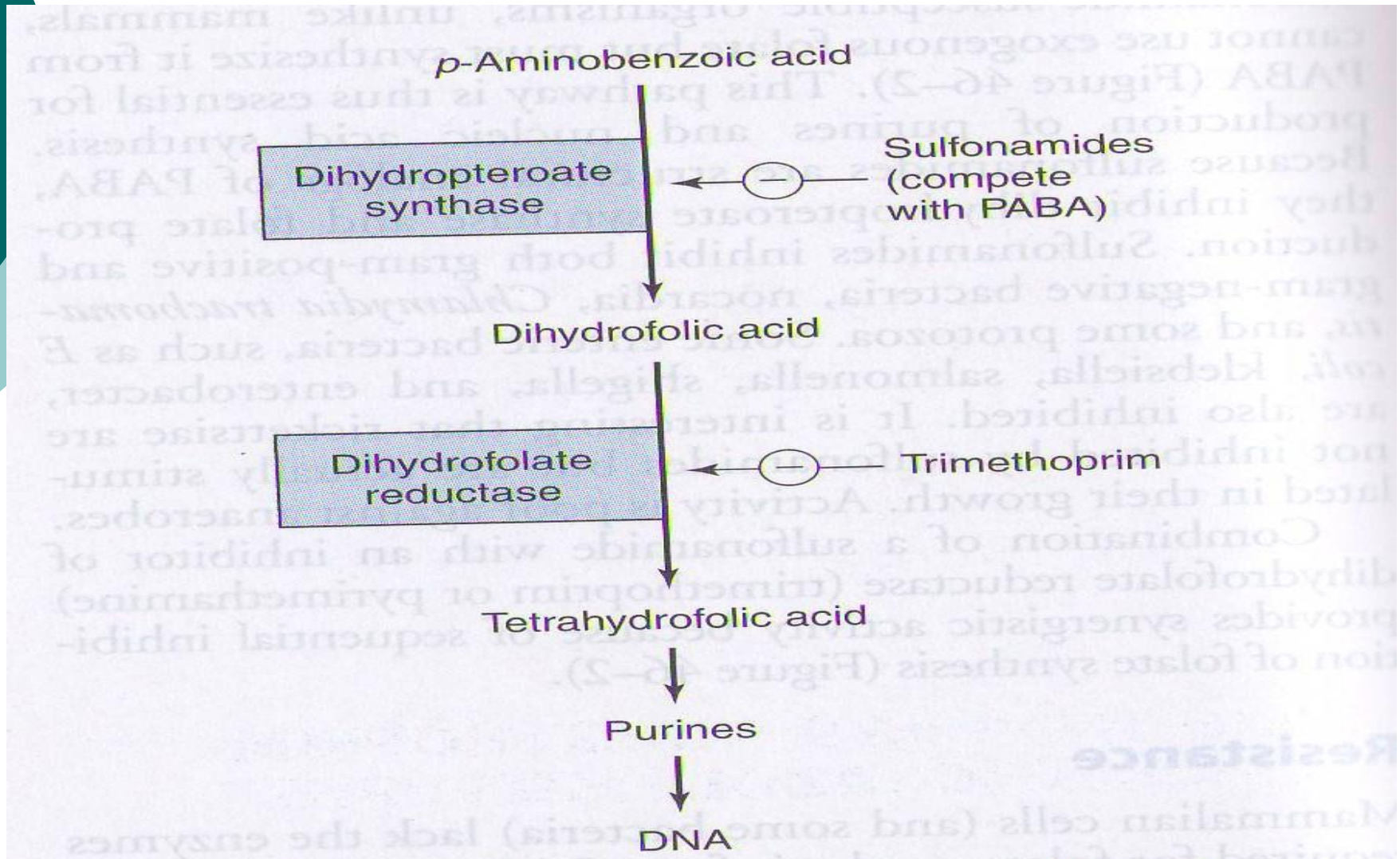


Figure 46–2. Actions of sulfonamides and trimethoprim.

Clinical uses

- Acute or Complicated or recurrent urinary tract infections especially in females
- Upper respiratory tract infections
- Pneumocystis jiroveci pneumonia
- Toxoplasmosis
- Shigellosis
- Nocardiosis

- Typhoid fever
- Salmonella infections
- Prostatitis
- Community –acquried bacterial pneumonia

Adverse effects

- Megaloblastic anemia , leukopenia & granulocytopenia (can be prevented by administration of folic acid)
- All side effects associated with sulfonamides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