Anti-tubercular drugs

OR

ANTI MYCOBACTERIAL DRUGS

Tuberculosis :

• Tuberculosis is a kind of *communicable chronic disease* caused by *M.tuberculosis* which can invade various *tissues* and organs of the whole body.

• The mycobacteria are *slow-growing intracellular bacilli* that cause tuberculosis.

Symptoms and Signs:

1. Malaise
2. Anorexia
3. Weight loss
4. Fever
5. Night sweats
6. Chronic cough, blood with sputum
7. Rarely, dyspnea

ANTI-TUBERCULOUS DRUGS

First-line

- Isoniazid
- Rifampicin
- Ethambutol
- Pyrazinamide
- Streptomycin

Second line drugs

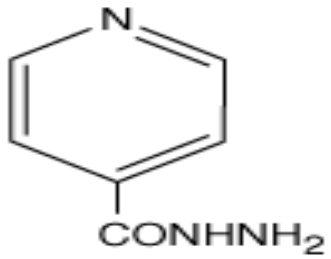
Thiacetazone (Tzn)
Paraaminosalicylic acid (PAS)
Ethionamide (Etm)
Cycloserine (Cys
Kanamycin (Kmc)
Amikacin (Am)
Capreomycin (Cpr)

Newer drugs :

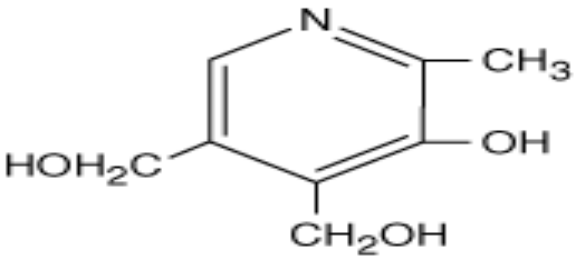
Ciprofloxacin
Ofloxacin
Clarithromycin
Azithromycin
Rifabutin

Isoniazid (INH)

- Most active drug
- Water soluble
- Similar to pyridoxine (Vit.B6)
- Good penetration to phagocytic cells



Isoniazid

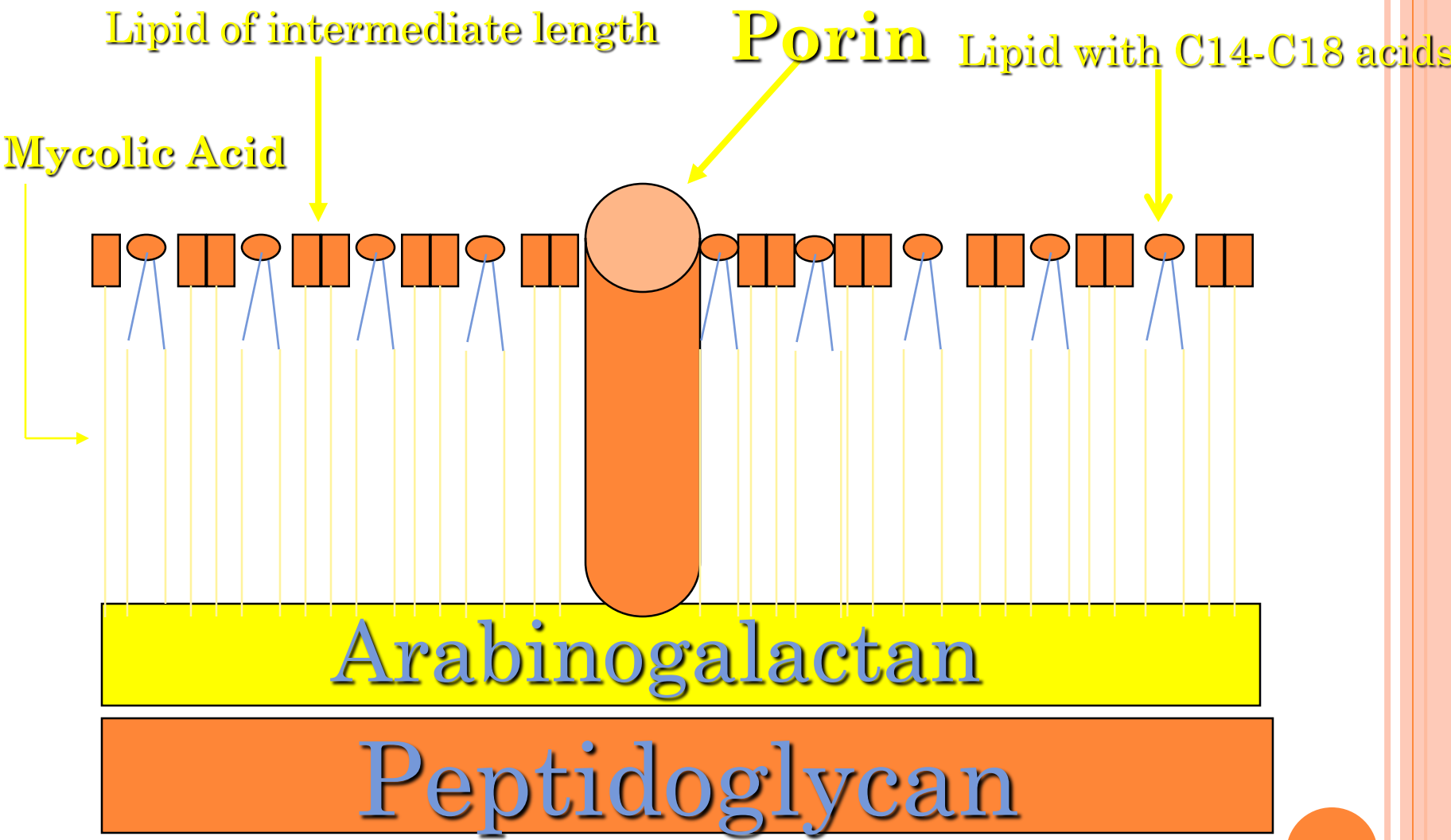


Pyridoxine

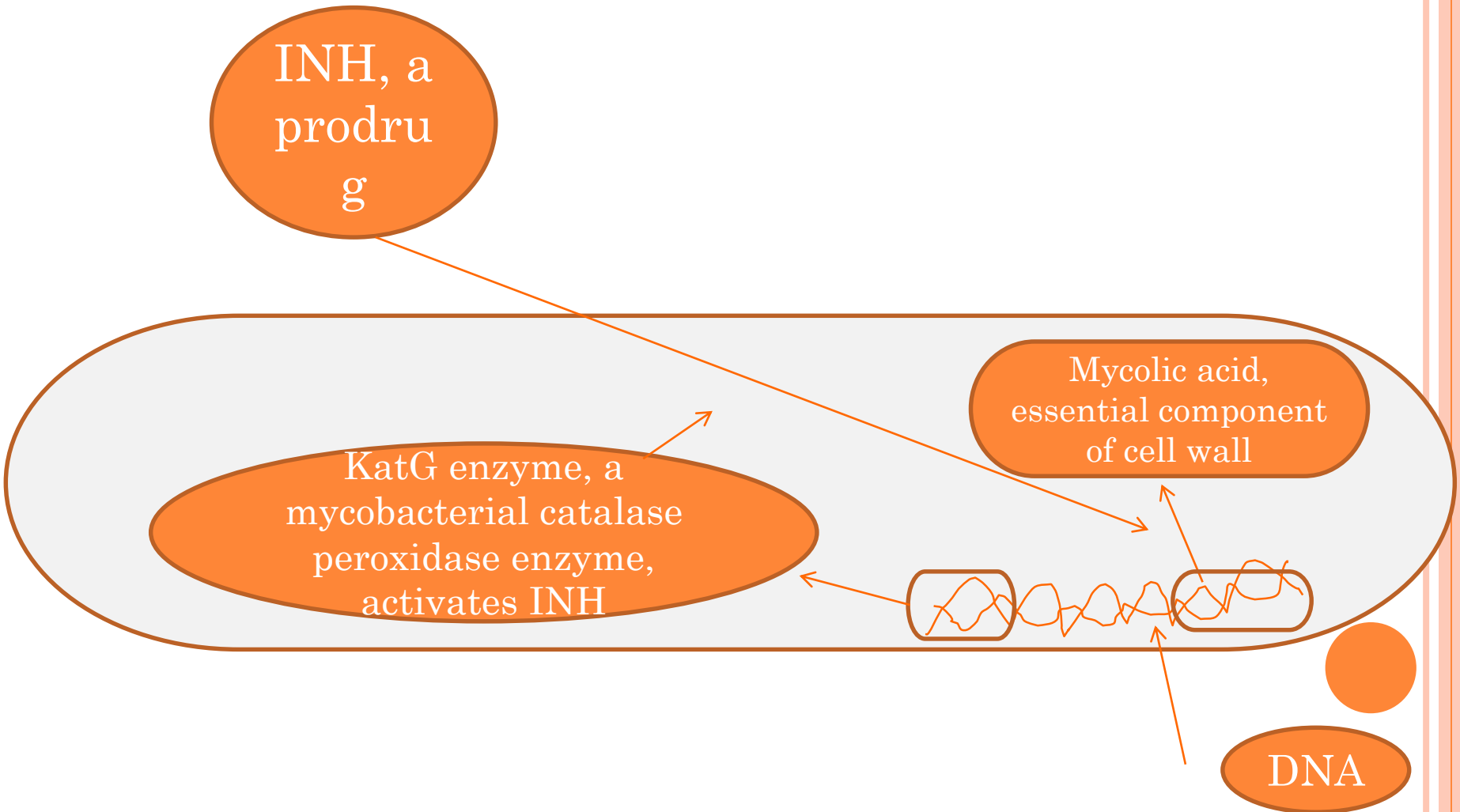
Isoniazid (INH): Mechanism of Action

- Prodrug: activated by KatG (Catalase proxidase)
- Active form bind to Acyl carrier protein (AcpM),and KasA (beta-ketoacyl carrier protein synthase), covalently
- Inhibits synthesis of mycolic acid (unique to mycobacterial cell wall)
- Mycolate depleted cell walls are structurally weak.

MYCOBACTERIAL CELL WALL



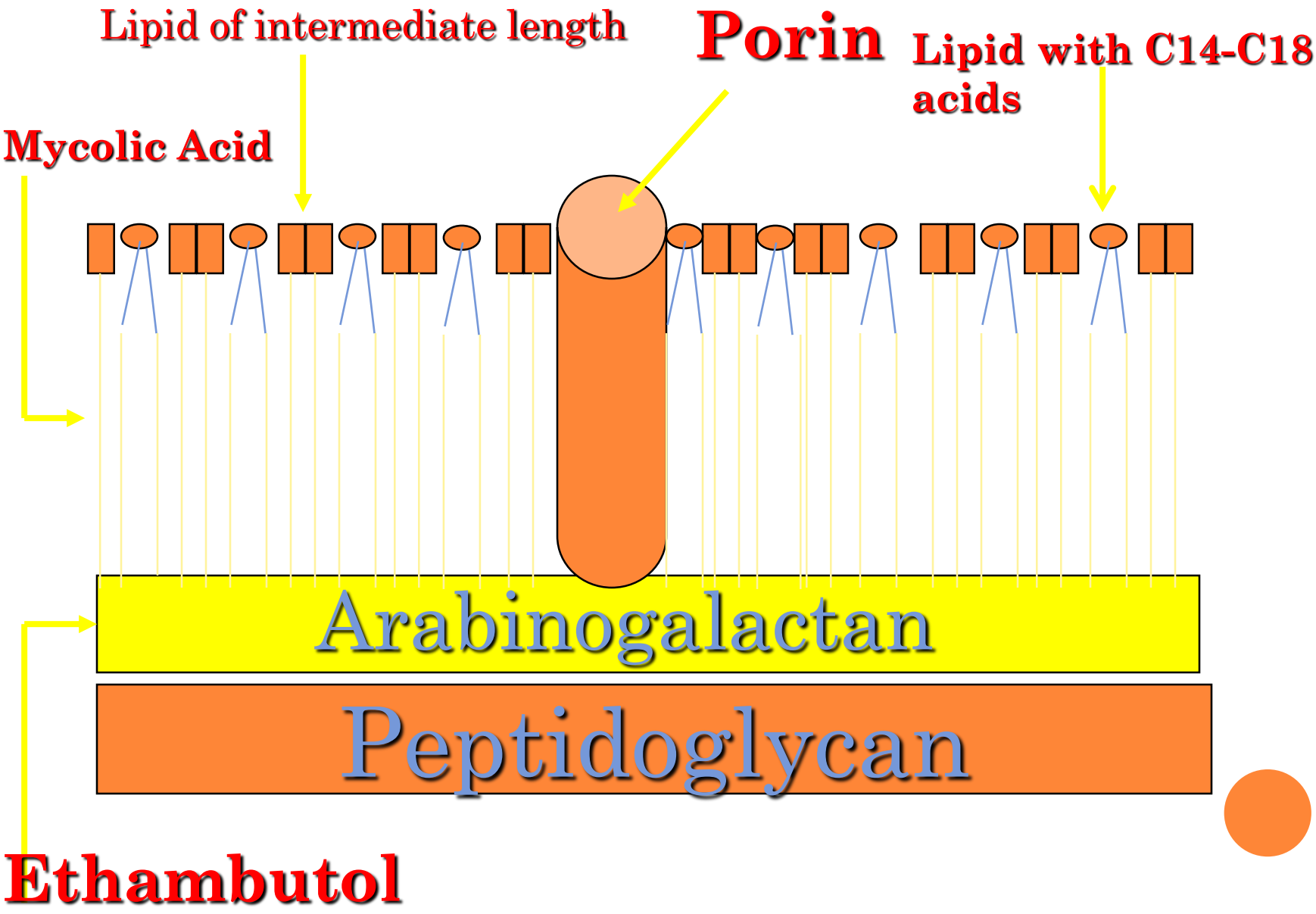
Isoniazid (Prodrug) → **katG** (**Catalase/Peroxidase**) → **Active Form**



ETHAMBUTOL- MECHANISM OF ACTION

- It is not bactericidal.
- ***Ethambutol*** inhibits mycobacterial ***arabinosyl transferases***.
- Arabinosyl transferases are involved in the polymerization reaction of ***arabinoglycan***, an essential component of the mycobacterial cell wall.

MYCOBACTERIAL CELL WALL



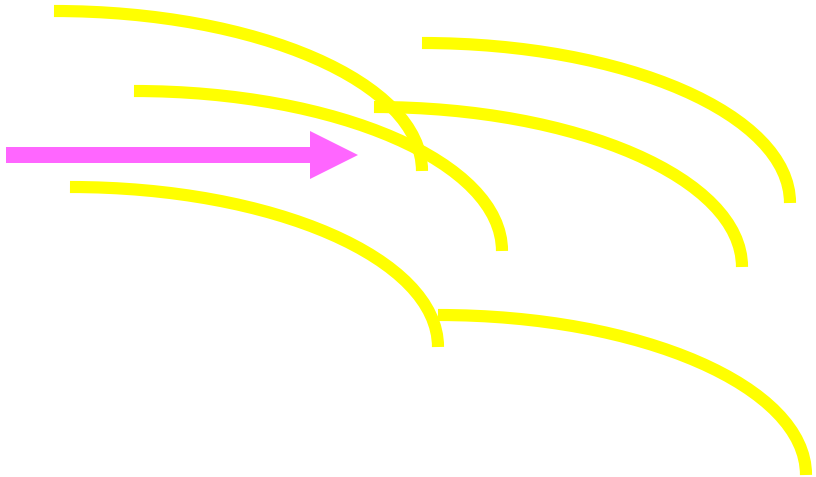
PYRAZINAMIDE
MECHANISM OF ACTION

- PZA **POA (pyrazinoic acid)**

pyrazinamidase

- Inhibits ***fatty acid synthetase I*** of Mycobacterium tuberculosis.

Pyrazinamide



Short chain fatty acid precursors

STREPTOMYCIN

Streptomycin was isolated from a strain of ***Streptomyces griseus.***

Mechanism of action:

- Like all Aminoglycosides, streptomycin irreversibly inhibits bacterial **protein synthesis**. Protein synthesis is inhibited in at least three ways:

1. interference with the initiation complex of peptide formation.
2. Misreading of mRNA, which causes incorporation of incorrect aminoacids into the peptide, resulting in a nonfunctional or toxic protein.
3. Breakup of polysomes into nonfunctional monosomes.

Note : Polyribosomes (or **polysomes**) also known as **ergosomes** are a cluster of ribosomes, bound to a mRNA molecule

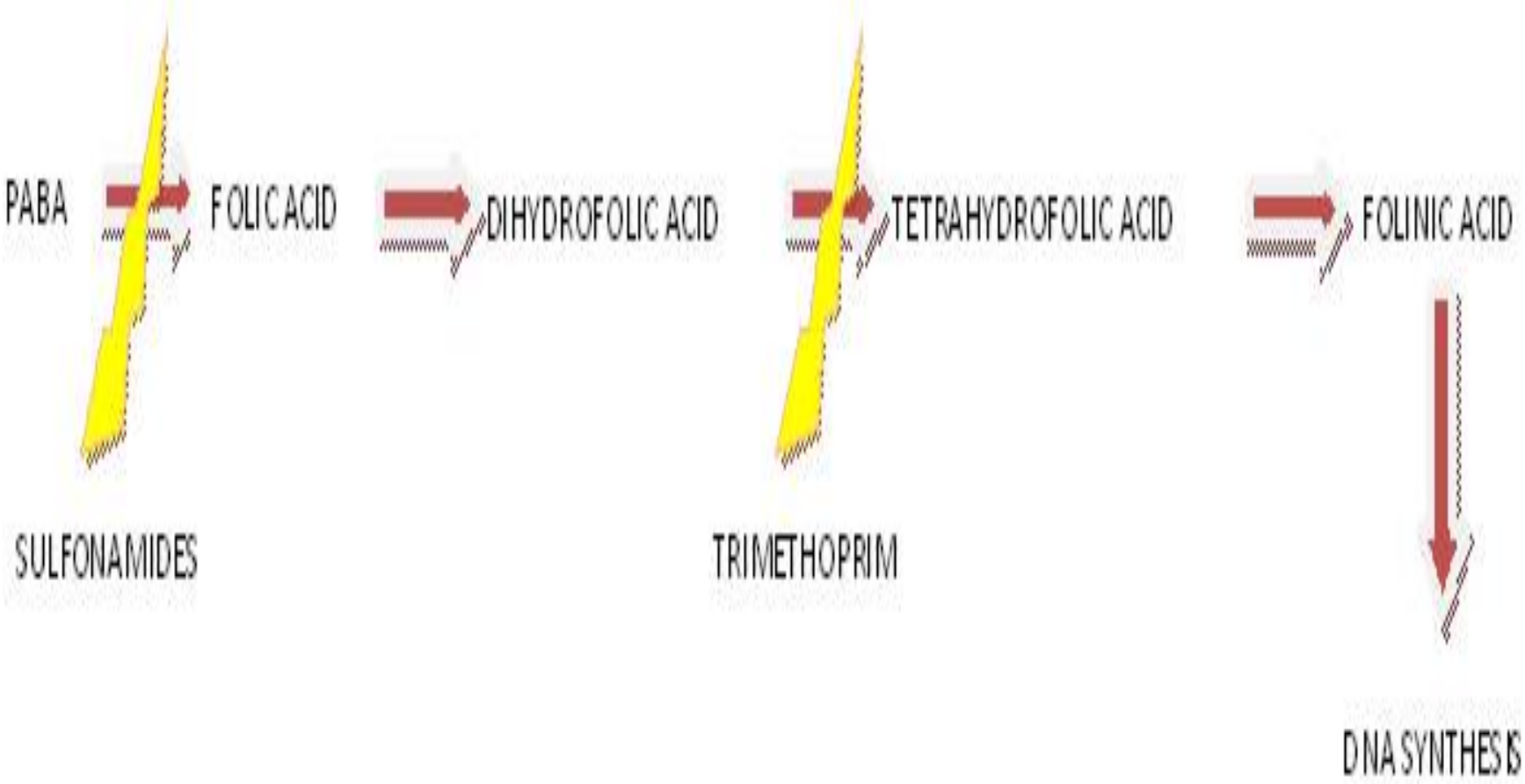
MECHANISM OF ACTION:

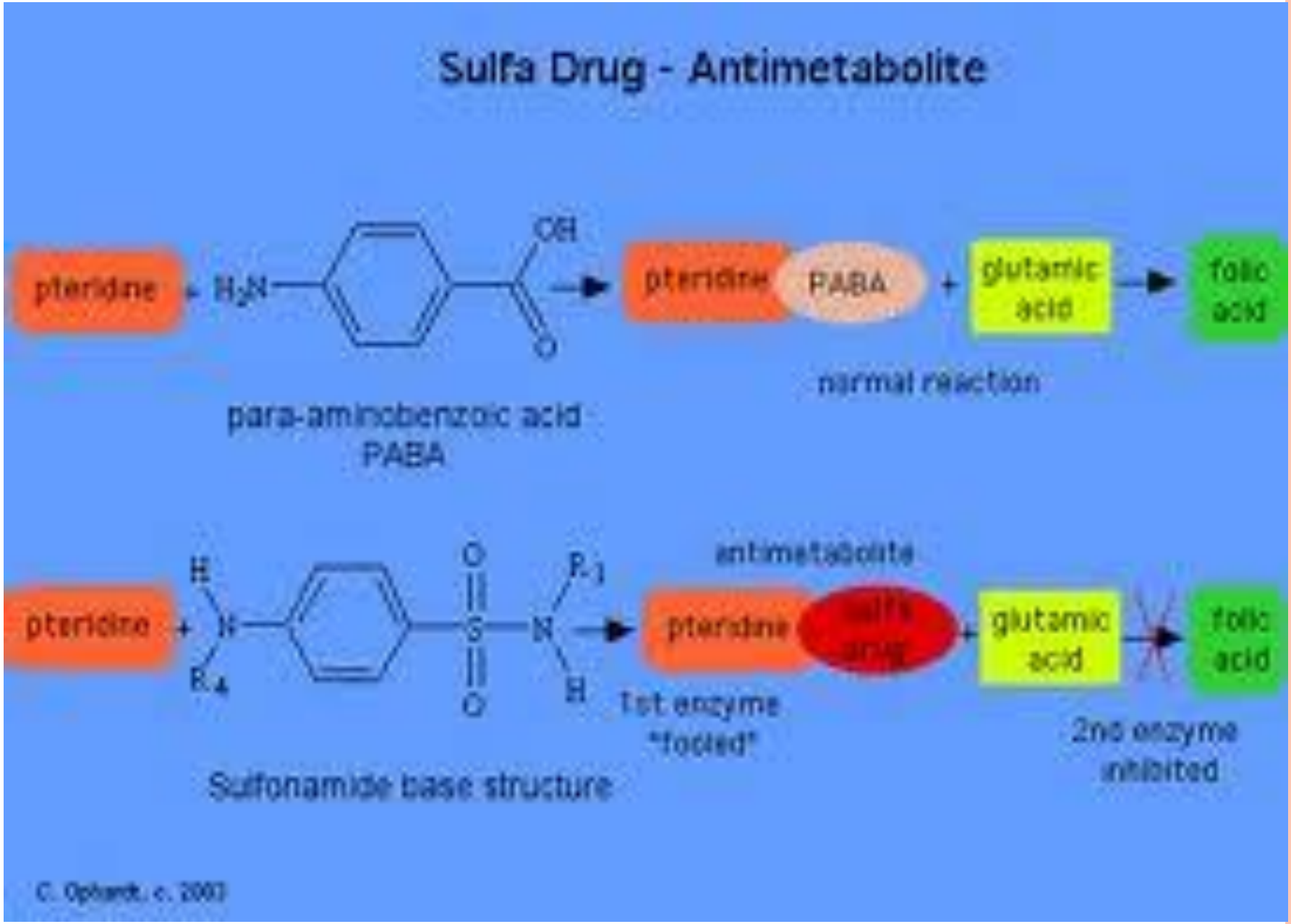
Ethionamide blocks synthesis of *mycolic acids* in susceptible organisms.

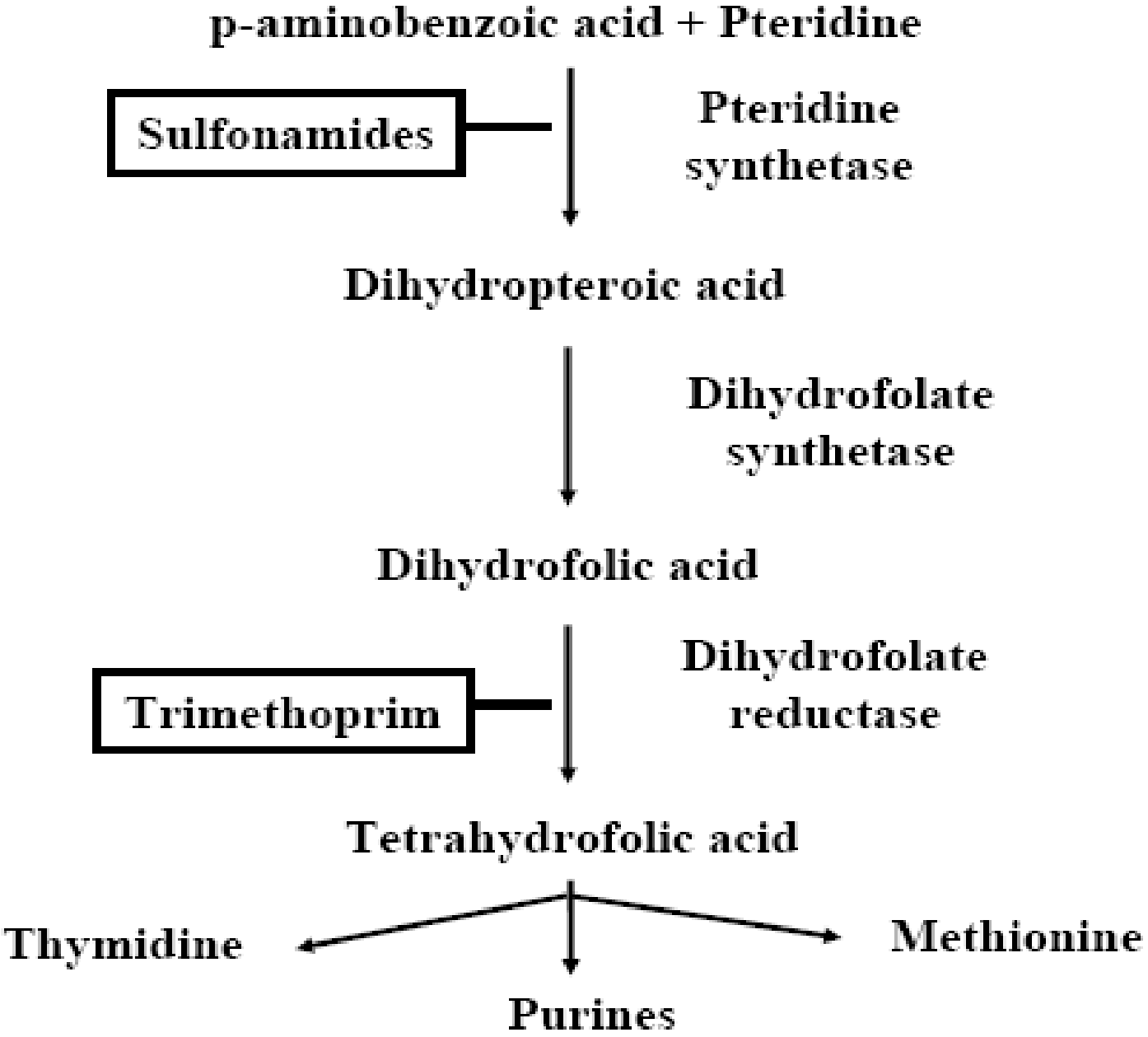
Aminosalicylic acid (PAS)

Aminosalicylic acid is a folate synthesis antagonist that is active almost exclusively against mycobacterium tuberculosis.

- it is structurally similar to p-aminobenzoic acid(PABA) and the sulfonamides.

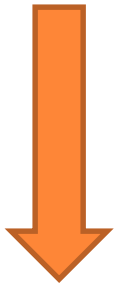

PABA
FOLIC ACID
DIHYDROFOLIC ACID
TETRAHYDROFOLIC ACID
FOLINIC ACID
SULFONAMIDES
TRIMETHOPRIM
DNA SYNTHESIS


Sulfa Drug - Antimetabolite
pteridine
H_2N
OH
O
para-aminobenzoic acid
PABA
pteridine
PABA
glutamic acid
folic acid
normal reaction
pteridine
H
N
R_4
O
S
O
N
R_1
H
Sulfonamide base structure
antimetabolite
pteridine
sulfa drug
1st enzyme "fooled"
glutamic acid
folic acid
2nd enzyme inhibited
C. Ophardt, c. 2003


p-aminobenzoic acid + Pteridine
Sulfonamides
Pteridine synthetase
Dihydropteroic acid
Dihydrofolate synthetase
Dihydrofolic acid
Trimethoprim
Dihydrofolate reductase
Tetrahydrofolic acid
Thymidine
Purines
Methionine

Rifampicin :

RFP binds strongly to the ß-subunit of *DNA-dependent RNA polymerase* *and* thereby inhibits RNA synthesis.



Inhibit protein synthesis


Thank you