Sulpha Drug: Sulphanilamide and Sulphadiazine

Learning Outcomes

Students will able to:

- **Explain Sulpha drugs**
- **Apply retrosynthetic approach to predict the method of Synthesis of Sulphanilamide and Sulphadiazine.**
- **Describe the Biochemical action of Sulpha drugs.**
- **Explain the uses and side effects of Sulpha drugs.**

Sulfa drug, also called sulfonamide, any member of a group of synthetic antibiotics containing the sulfanilamide molecular structure. Sulfa drugs were the first chemical substances systematically used to treat and prevent bacterial infections in humans.

Sulfonamides

- Sulfonamides were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in man.
- Sulfonamides or sulpha drugs are the basis of several group of drugs.This original anti-bacterial sulfonamide are synthetic antimicrobial agent that contain the sulfonamide group.
- Some sulfonamides are also devoid of antimicrobial activity e.g anticonvulsant sulfiamiame.

Chemistry of Sulfonamide

- Recognized since 1932.
- In clinical usage since 1935.
- First compounds found to be effective antibacterial agents in safe dose ranges.
- Chemically, it is a molecule containing the sulfonamido (sulfanilamide, SO_2NH2) functional group attached to an aniline.
- Structurally related to p-amino benzoic acid (PABA).
- This group is also present in other non-antibacterial compounds like

-Sulphonureas
-Benzothiazids
-Furosemide
-Acetazolamide

They act as antimicrobial agents by inhibiting bacterial growth and activity and commonly *called sulfa drugs*.

Classification

The sulfonamides still of clinical interest

(Tripathi)

A.	SHORT ACTING	(4-8 HOURS)	• Sulfadiazine
B.	INTERMEDIATE ACTING	(8-12 HOURS)	• Sulfamethoxazole
C.	LONG ACTING	(~ 7 DAYS)	• Sulfadoxine • Sulfamethopyrazine
D.	SPECIAL PURPOSE		• Sulfacetamide sodium • Silver sulfadiazine • Sulfasalazine • Mafenide

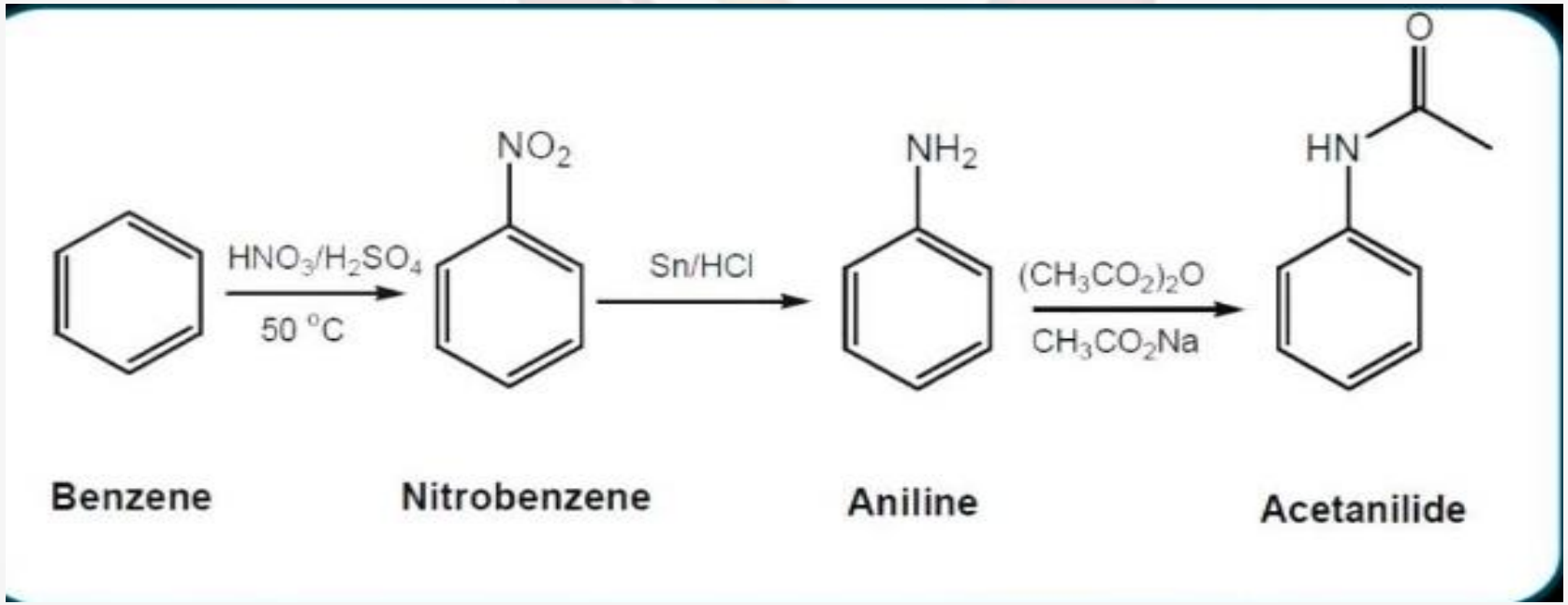
SULFANILAMIDE:

- They act as antimicrobial agents by inhibiting bacterial growth and activity commonly called as sulpha drugs.
- It is a molecule containing the sulfonamide group attached with aniline.
- Its molecular structure is similar to p-Amino benzoic acid (PABA)

Sulfanilamide

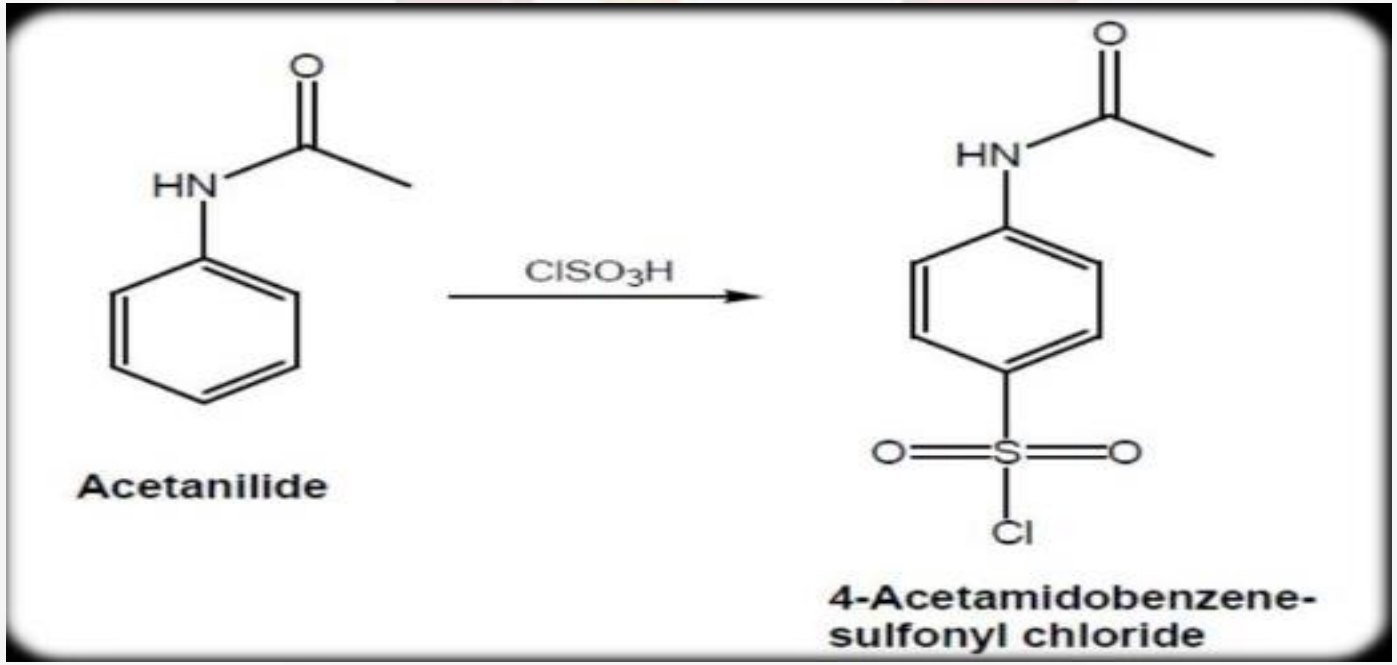
Synthesis Approach of Sulphanilamide

Synthesis of Sulphanilamide starts from benzene and involves different steps.
Step-1: Benzene upon nitration converted to nitrobenzene. Nitrobenzene undergoes reduction to form Aniline. Then aniline on acetylation converted into Acetanilide.



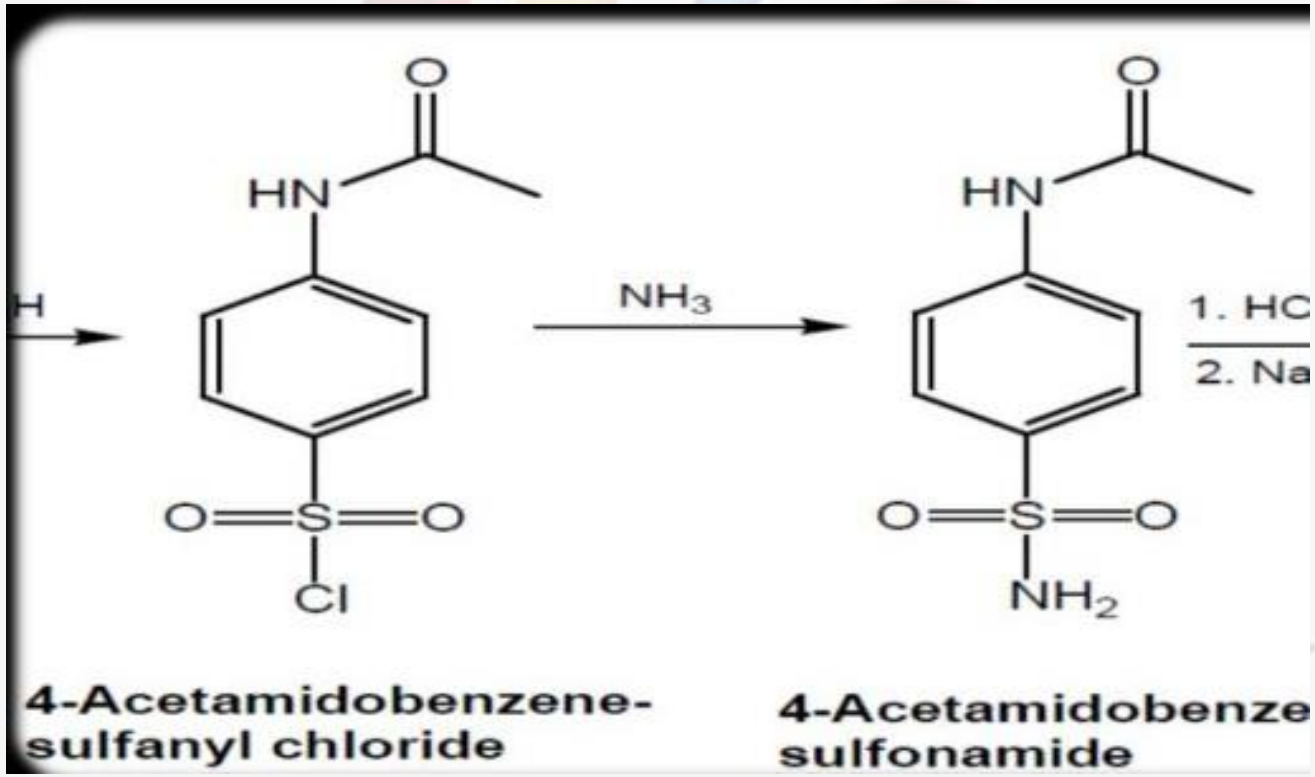
Method of Synthesis Cont.

Step-2: Reaction with Chlorosulfonic acid to form p-acetamidobenzenesulfonyl chloride.



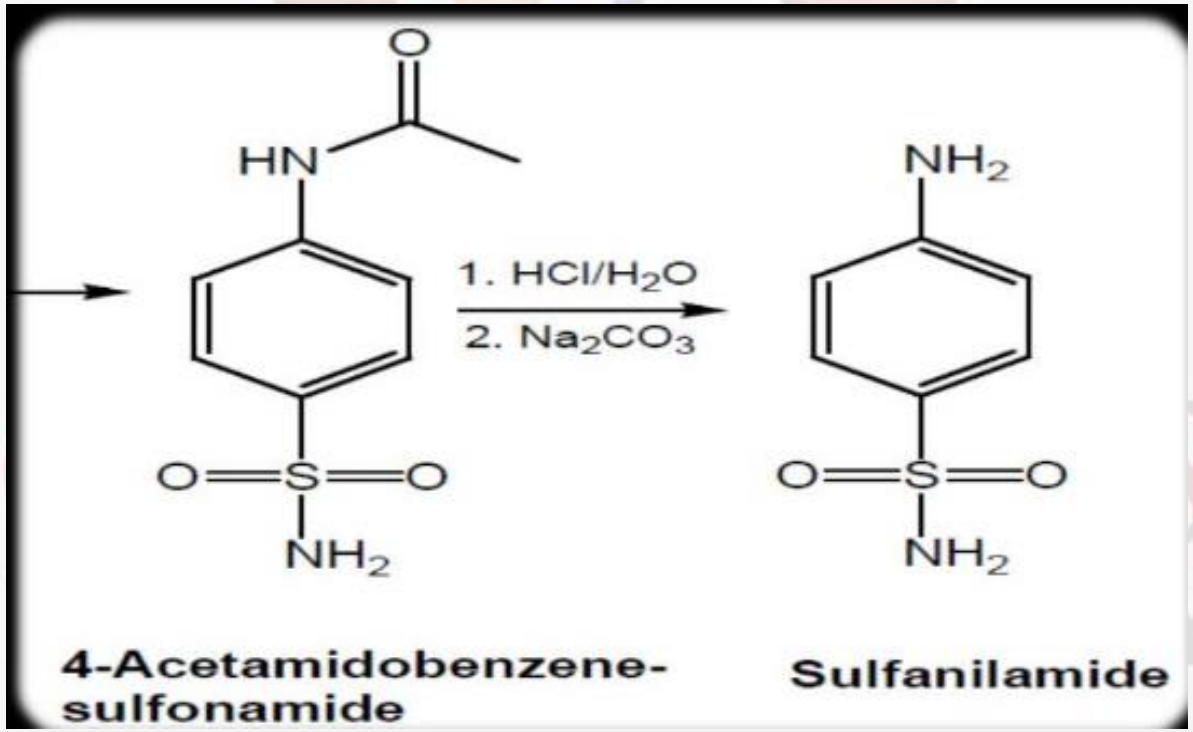
Method of Synthesis Cont.

Step-3: Reaction with NH3 to form p-acetamidobenzene sulfonamide.

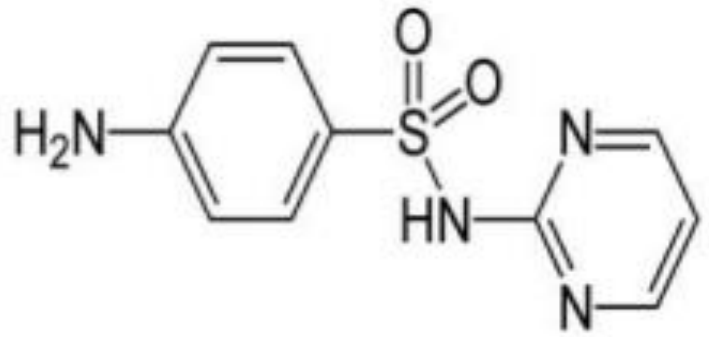


Method of Synthesis Cont.

Step-4: Acid hydrolysis of p-acetamidobenzene sulfonamide to form Sulphanilamide.



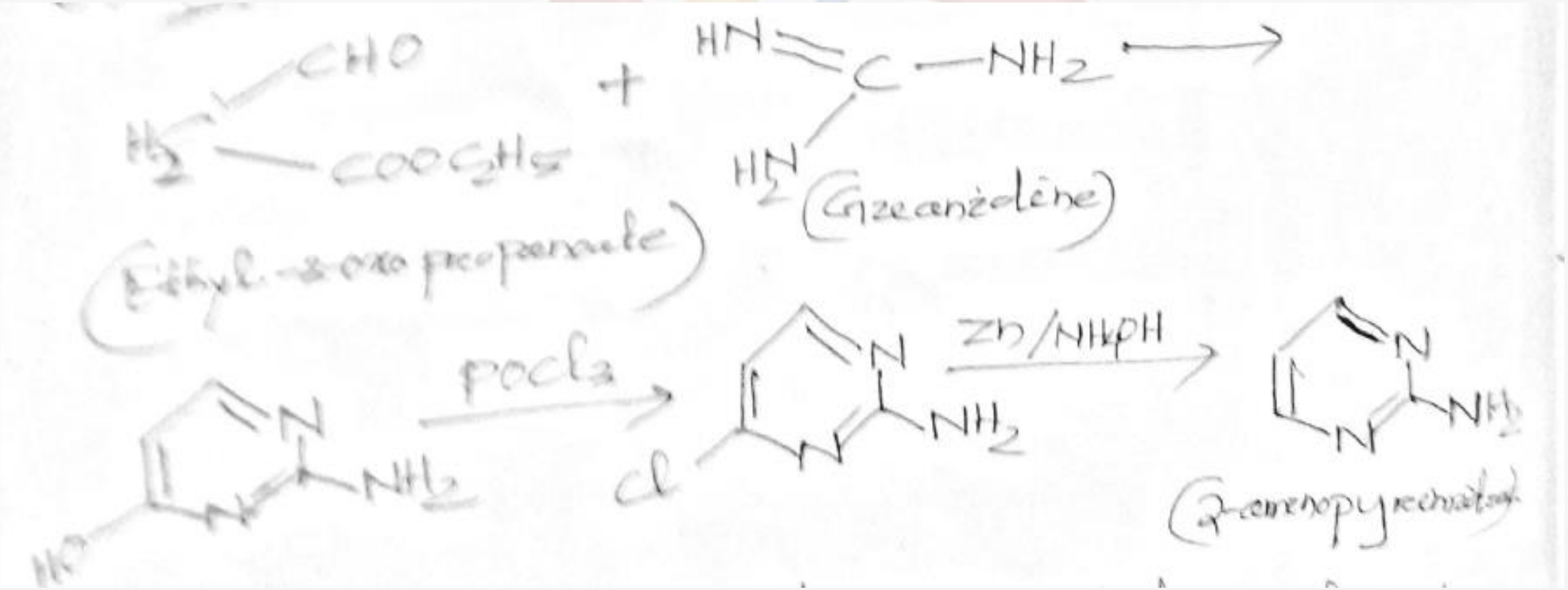
SULPHADIAZINE



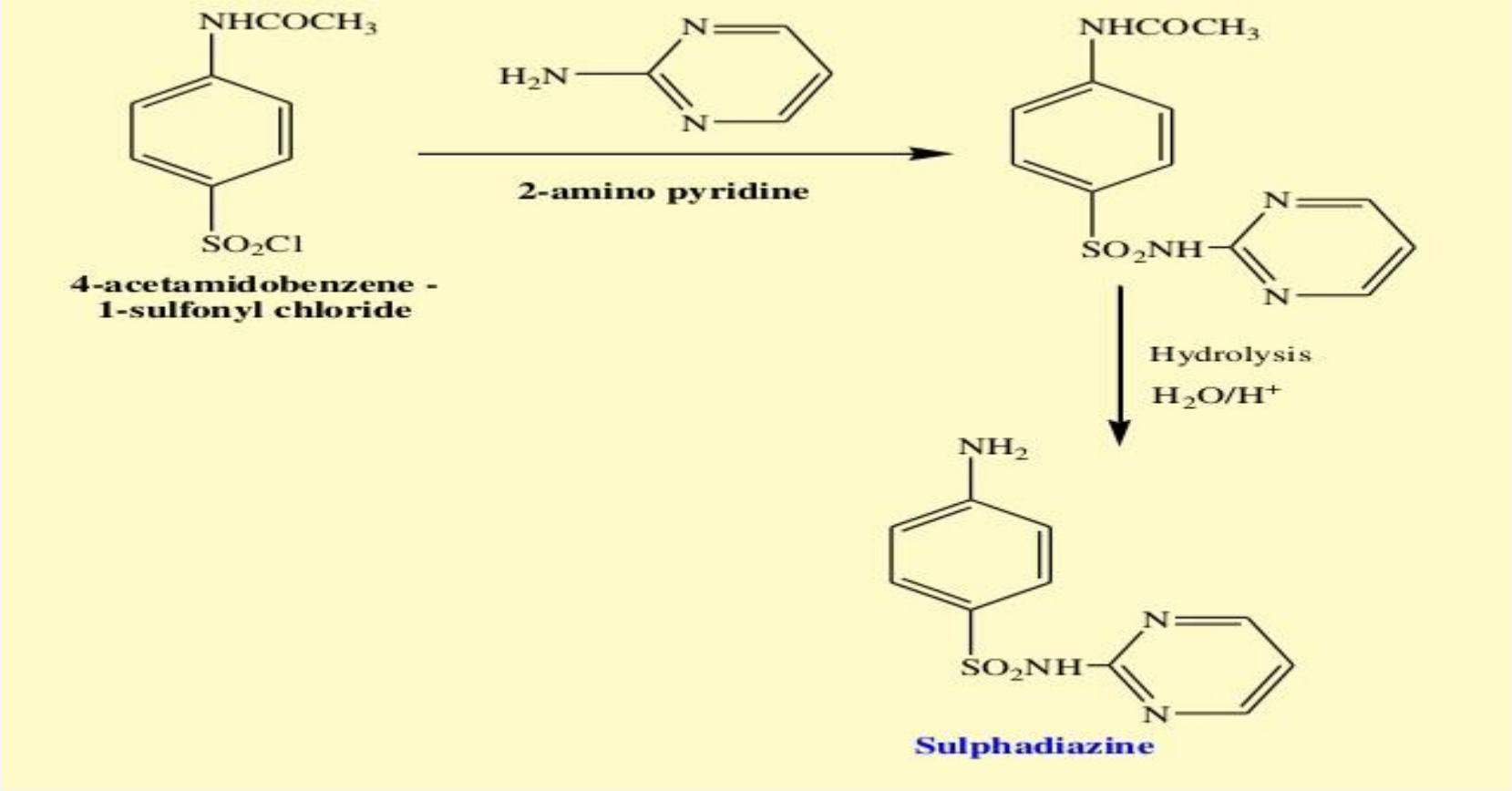
- Chemical formula:$C_{12}H_{14}N_4O_2S$
- IUPAC name:4-amino-N-(4,6-dimethylpyrimidin-2-yl)benzene-1-sulfonamide
- Indication :For the treatment bacterial infections causing bronchitis, prostatitis and urinary tract infections.
- Do not take calcium, aluminium, magnesium or iron supplements within 2 hours of taking this medication.

Synthesis of Sulphadiazine

It will synthesized by condensation of 2-aminopyrimidine with p-acetamidobenzene sulfonylchloride.

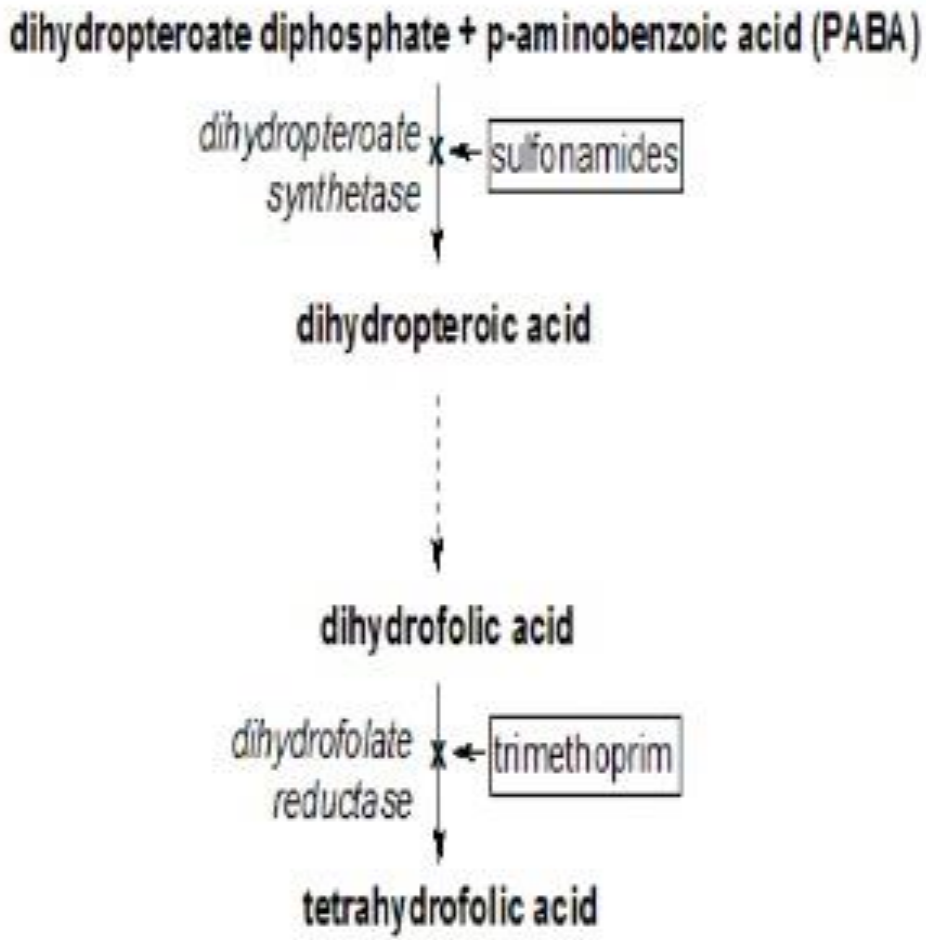


Synthesis of Sulphadiazine



BIOCHEMICAL ACTION:

- Dihydripteroate synthetase catalyses the condensation of dihydropteroate diphosphate + (PABA) to form dihydropteroic acid & convert into dihydrofolic acid.
- DHPS is the target of sulfonamides which are substrate analogues that compete with precursor p-aminobenzoic acid.
- Dihydrofolic acid converts into tetrehydrofolic acid & inhibited by trimethoprim

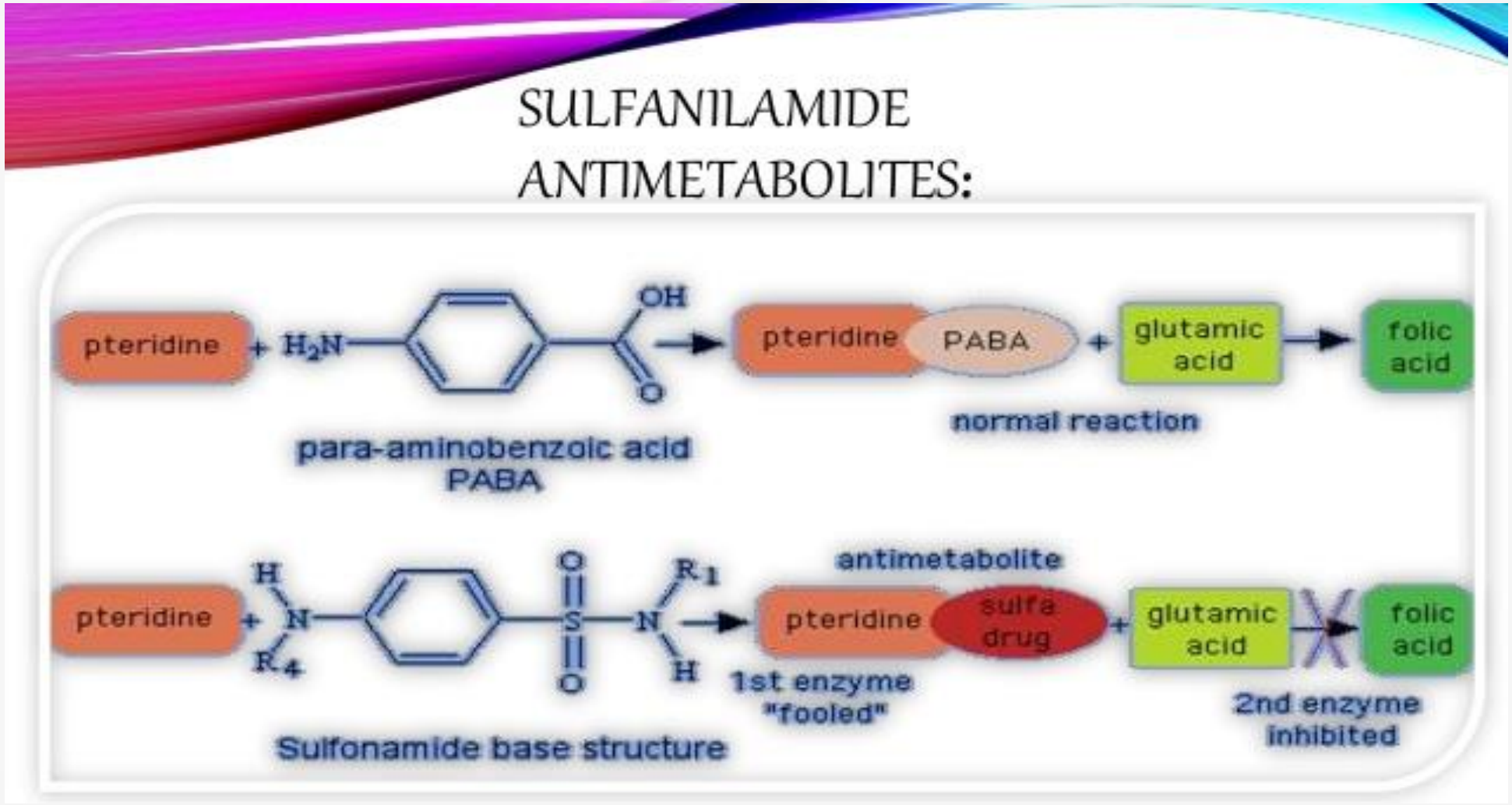


Mechanism of Action

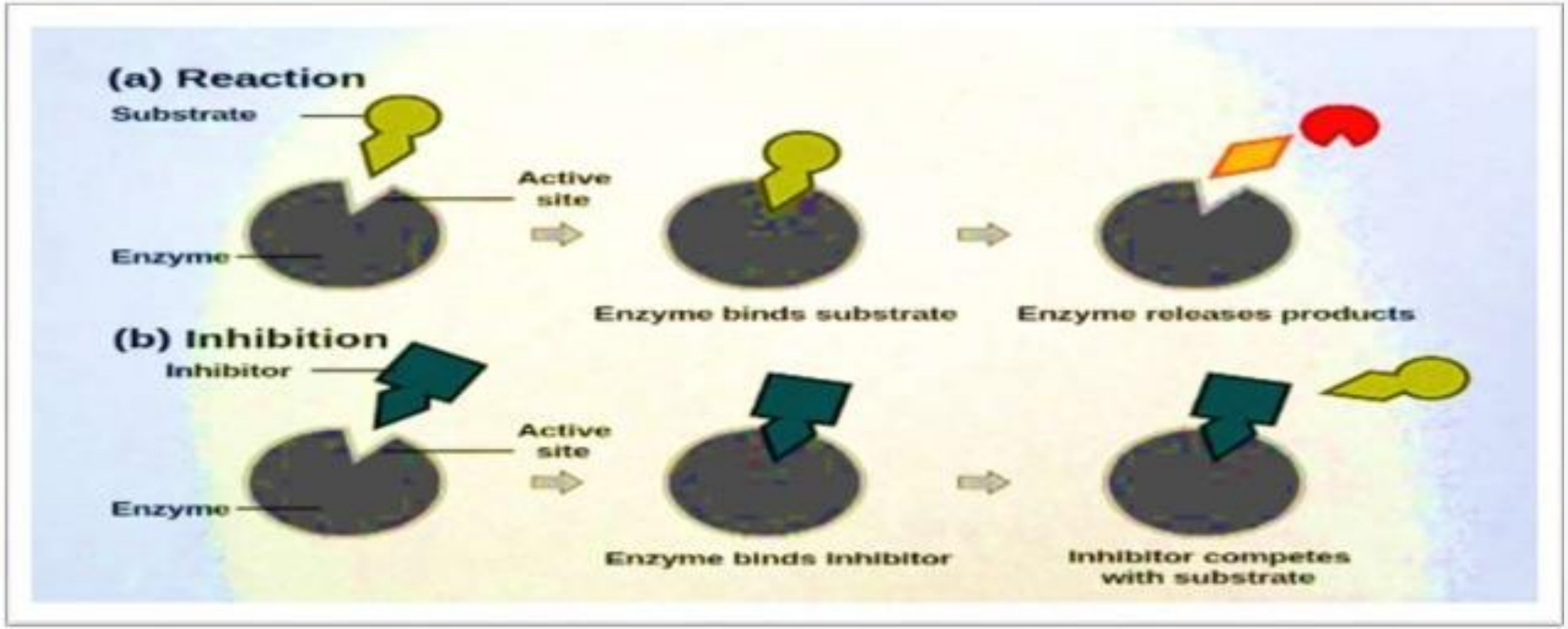
Folic acid is essential for the growth of bacteria. It is a precursor of purine, which is precursor of DNA&RNA. Para-amino benzoic acid(PABA) is a precursor of folic acid and sulfonamide has structural similarity to PABA.

Some bacteria synthesise their own folic acid from PABA. In this bacteria sulfanamide compete with the PABA for the enzyme folic acid synthetase and prevent the incorporation of PABA into folic acid, so folic acid is not synthesized.

As a result bacteria are deprived of folic acid and are unable to multiply.


SULFANILAMIDE
ANTIMETABOLITES:
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

COMPETITIVE INHIBITION:

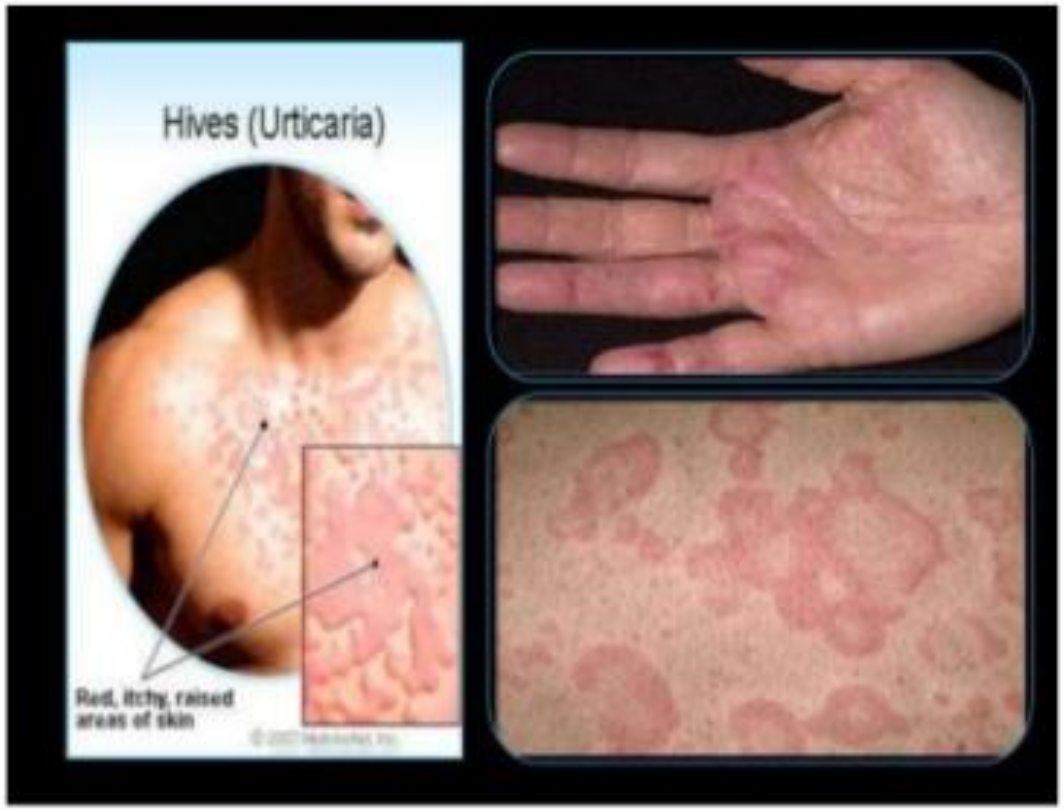


Uses of Sulpha drugs

- Treatment of Urinary tract Infections
- Treatment of Throat and Gum Infections
- Treatment of Eye Infection
- Silver salt of sulphadiazine is used for preventing infection in burnt surfaces.
- Sulpha drugs in combination with other drugs used for treatment of dysentery, typhoid, malaria, rheumatic fever and so on.

SIDE EFFECTS:

- Itching,rash
- Swelling of mouth,face and lips
- Fever,chills, sore throat etc.



References

Ashutosh kar, Medicinal Chemistry, 4th edition, New Age International Publisher, New Delhi, 2013.

https://www.youtube.com/watch?v=KMeawemUCiE

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