Anti-Microbial Agents:

Anti-Bacterial Agents: Sulfonamides

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SECTION 7

Drugs Impacting Infectious and Neoplastic Disease Processes

CHAPTER 29

Drugs Used to Treat Bacterial Infections

Elmer J. Gentry, E. Jeffrey North, and Robin M. Zavod

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Drugs covered in this chapter[a]:

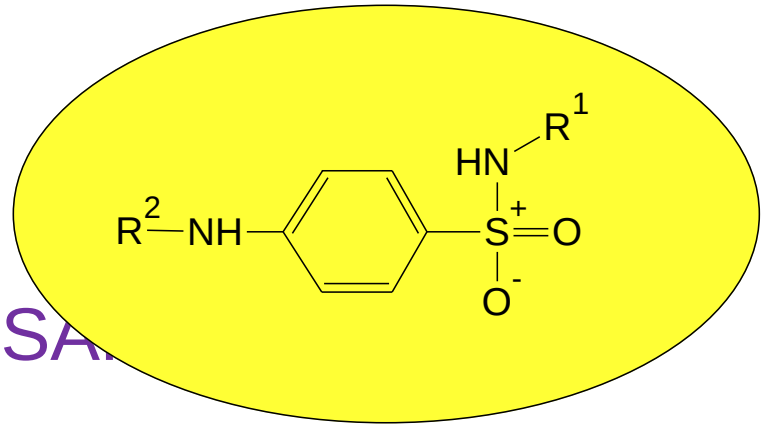
ANTIBACTERIALS

Sulfonamide class

- Silver sulfadiazine
- Sulfacetamide
- Sulfamethoxazole
- Sulfisoxazole
- Trimethoprim

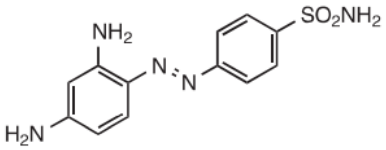
Sulfonamide

- Foundation
- Nomenclature
- Mechanism Of Action: MOA
- Structure Activity Relationship: SA
- Physicochemical properties
- Metabolism
- Sulfonamides in clinic



Foundation of Sulfonamides

- Prontosil rubrum: a red dye



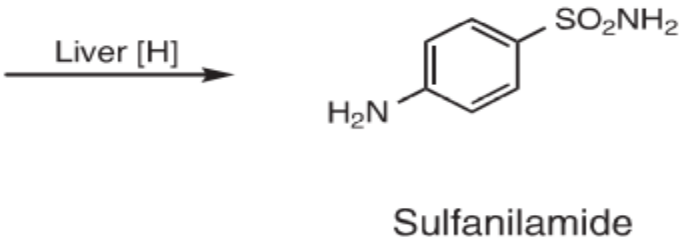
Prontosil rubrum

✓ examined by Gerhard Domagk in Bayer Co., Germany

✓ believed to affect selectively on pathogenic bacteria

✓ works selectively like Gram Stain

✓ against streptococcal infections



Sulfanilamide

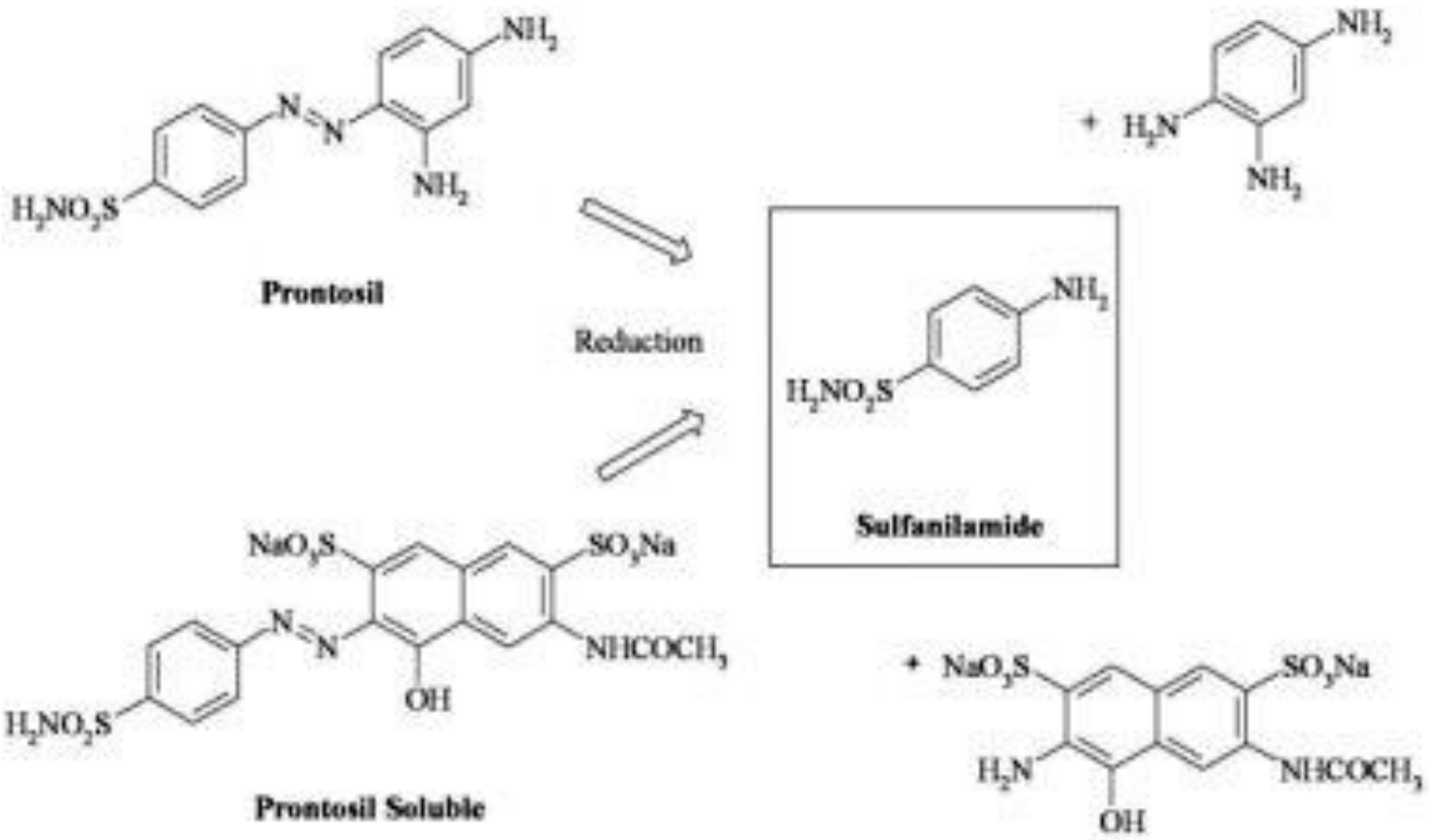
✓ not effective in-vitro

✓ As Prodrug: active metabolite: by liver reductase:

✓ identified as p-amino-benzene-sulfonic acid or sulfonamide:

✓ sulfanilamide: colourless

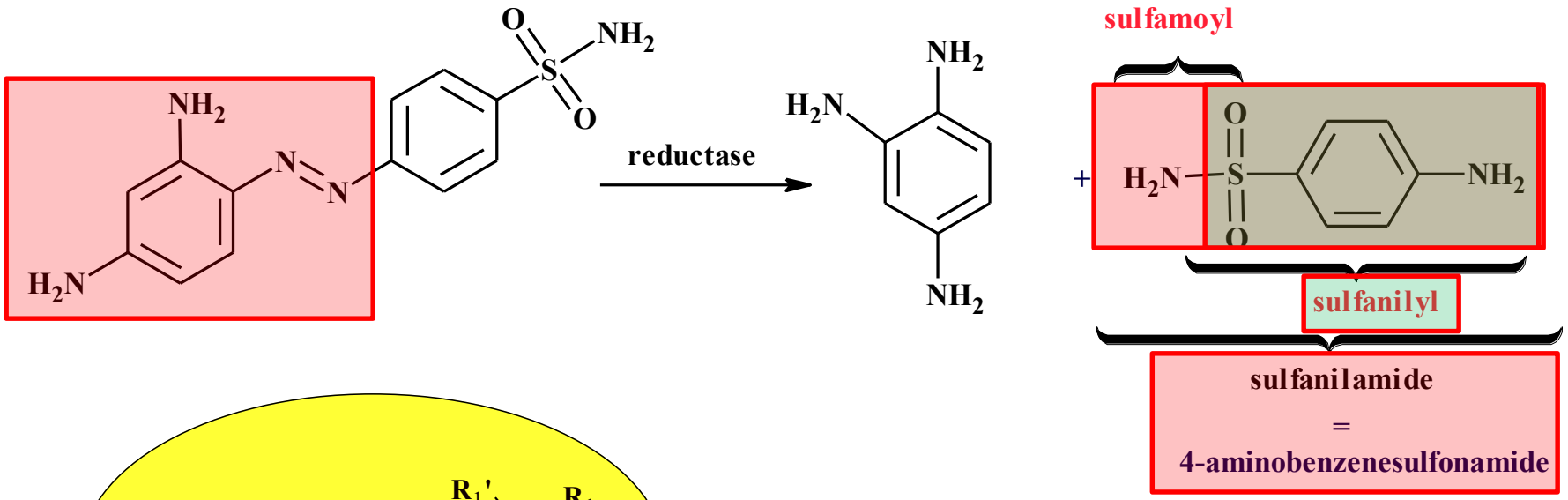
Foundation of Antimicrobial

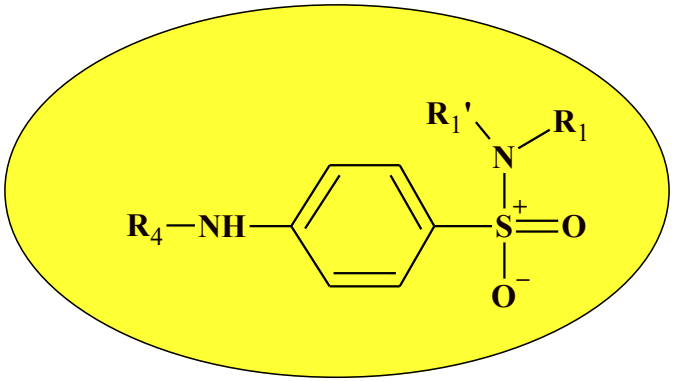


Nomenclature of Sulfonamide Scaffold

- Prontosil: 4-[(2,4-Di-amino-phenyl)-azo]-benzene-sulfonamide:

✓ as a Pro-Drug to produce sulfanilamide scaffold





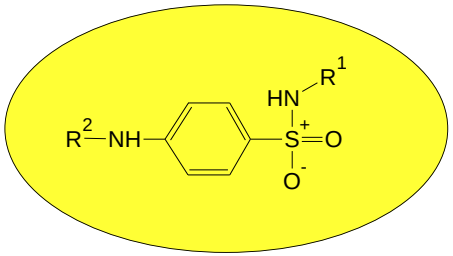
MOA for Sulfonamides

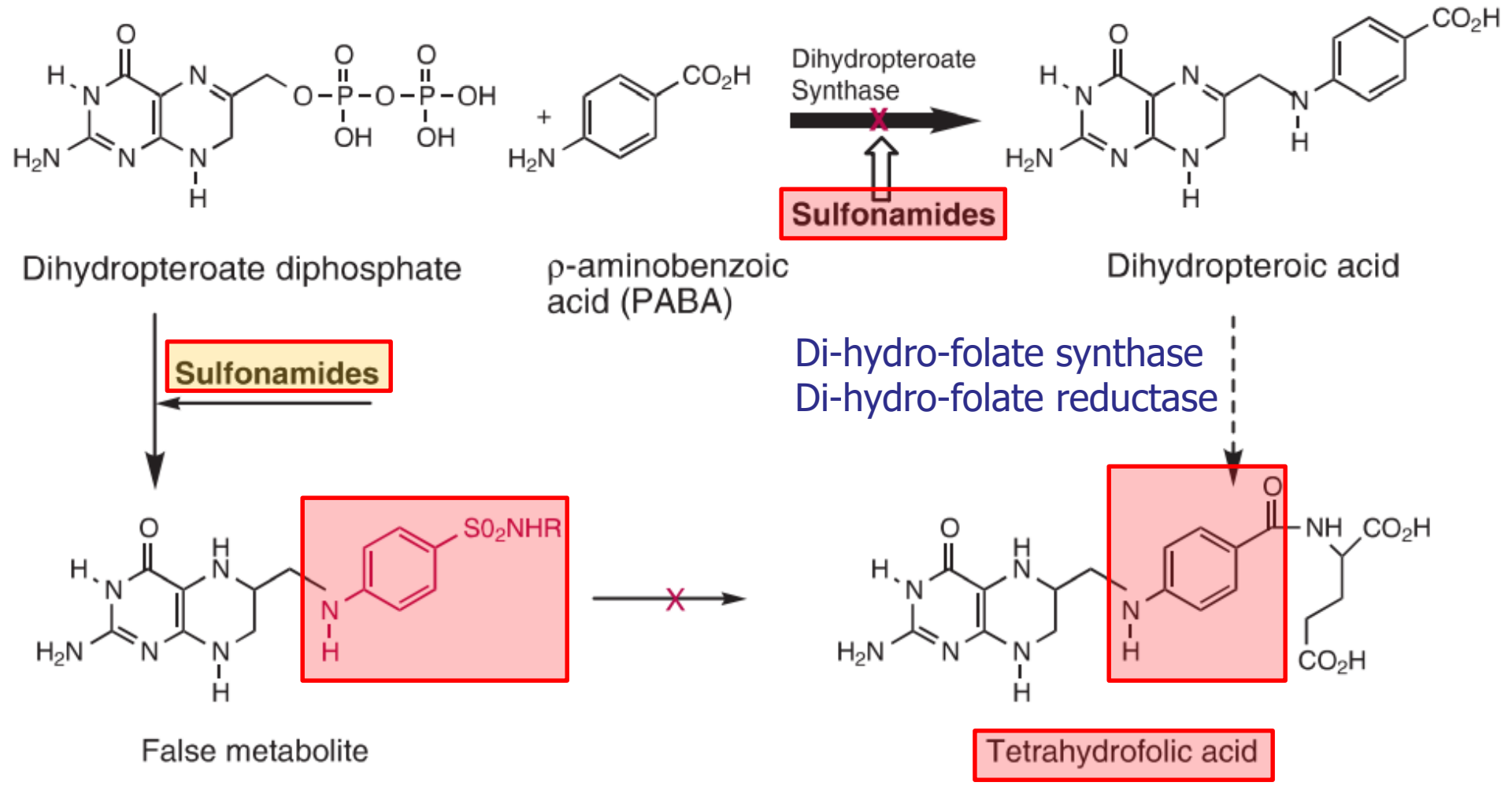
- Inhibitor of Dihydro-Pteroate synthase

✓ responsible enzyme in the biosynthesis of:

folic acid (dihydro-folic acid) & ultimately thymine

- Competing with PABA at the active site of the enzyme
- Might work as anti-metabolite: false metabolite
- Pharmacophore portion: will be given in SAR
- Can be reversed by adding/ prescribing PABA
- Consider against intrinsically resistant bacteria





- Involving enzymes in biosynthesis of tetrahydrofolate (THF):
  - ✓ Di-hydro-pteroate synthase
  - ✓ Di-hydro-folate synthase
  - ✓ Di-hydro-folate reductase

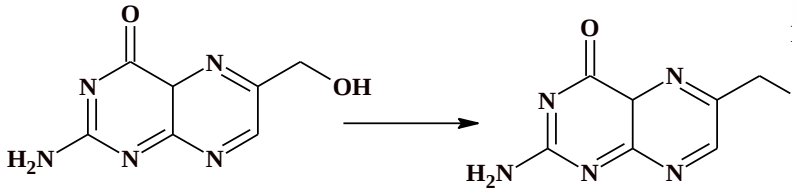
DNA ⟵ Thymidine

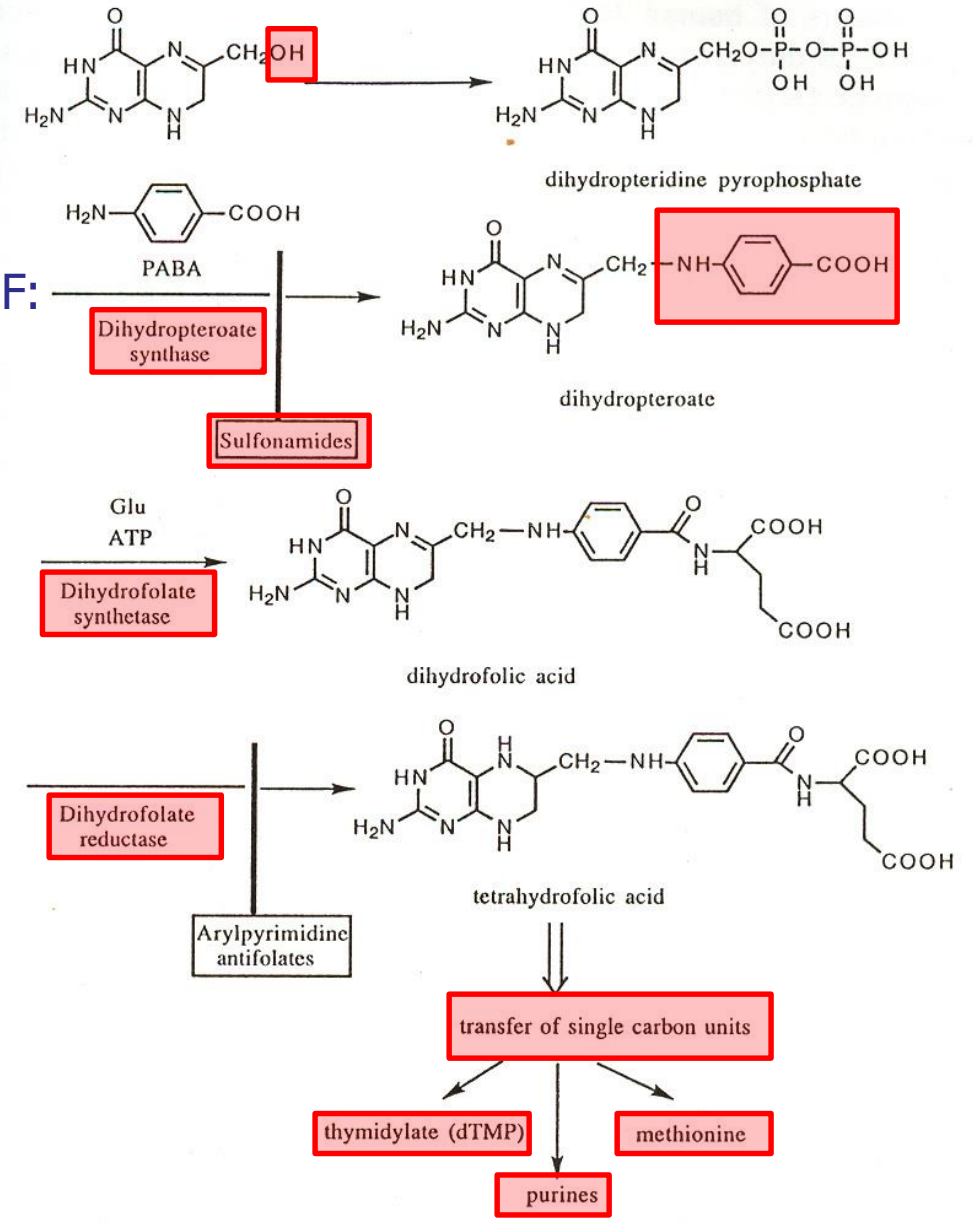
Figure 29.3 Microbial biosynthetic pathway leading to tetrahydrofolic acid synthesis and major site of action (⇧) of sulfonamides as well as site of action seen in some bacteria (←), resulting in incorporation of sulfanamide as a false metabolite.

Biosynthetic Site of Action for Sulfonamides

- As Anti-metabolite

- Involving enzymes in biosynthesis of THF:
  - ✓ Di-hydro-pteroate synthase
  - ✓ Di-hydro-folate synthase
  - ✓ Di-hydro-folate reductase





Comparing PABA versus Sulfonamides to Introduce SAR

- Compare distances of:

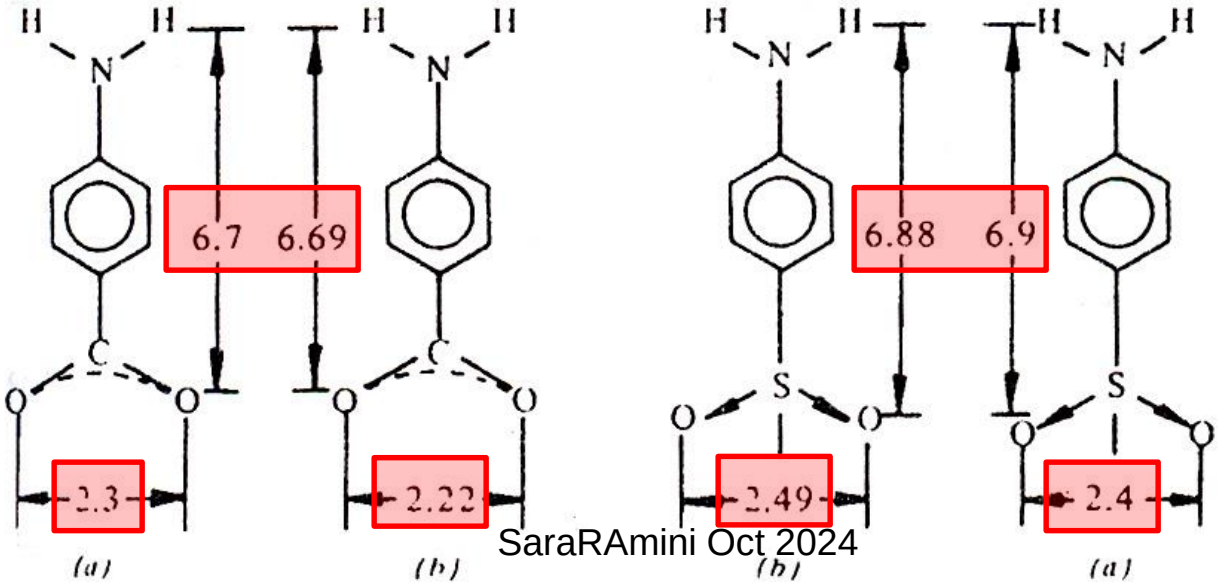
✓ "O-O in COO & H-N4 to O-C" to "O-O in SOO & H-N4 to O-S"

- Compare pk_a of PABA & sulfonanilic acid & sulfonanilamide:

✓ pk_a for PABA = 4.9 pk_a for sulfanilic acid = 10.4

✓ pk_a for optimum sulfonamide as antibacterial agent = 6.1-7.4

- Compare target interactions for both



Comparing PABA versus Sulfonamides to Introduce SAR- Contd.

- Compare three target interactions for both:

✓ hydrogen bond through p-amino group

✓ Van Der waals interactions through aromatic ring

✓ ionic bond through anionic carboxylate or sulfonamide

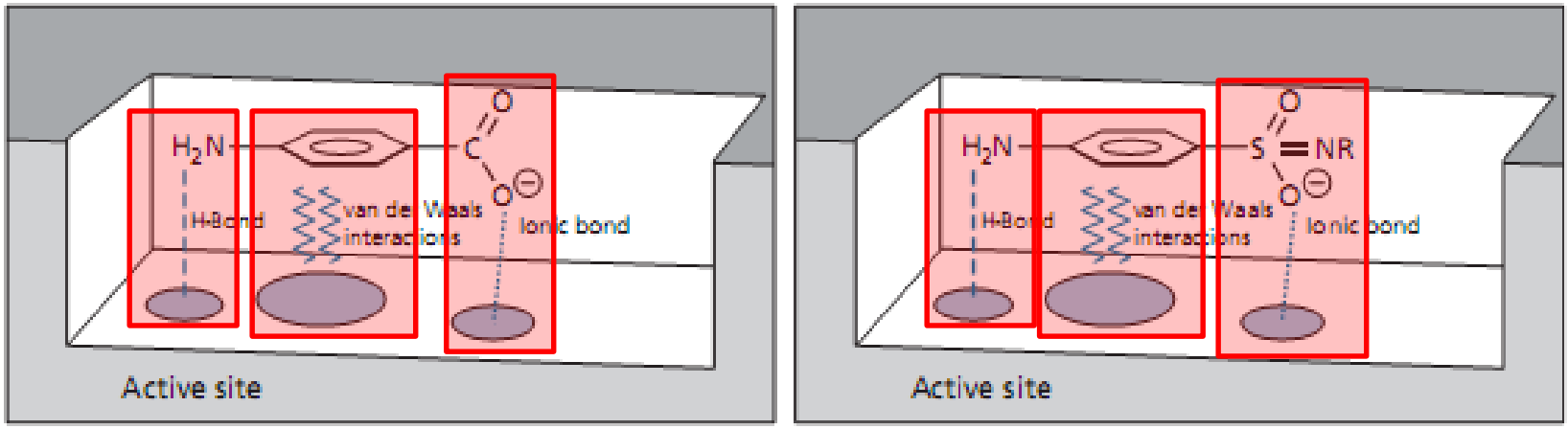
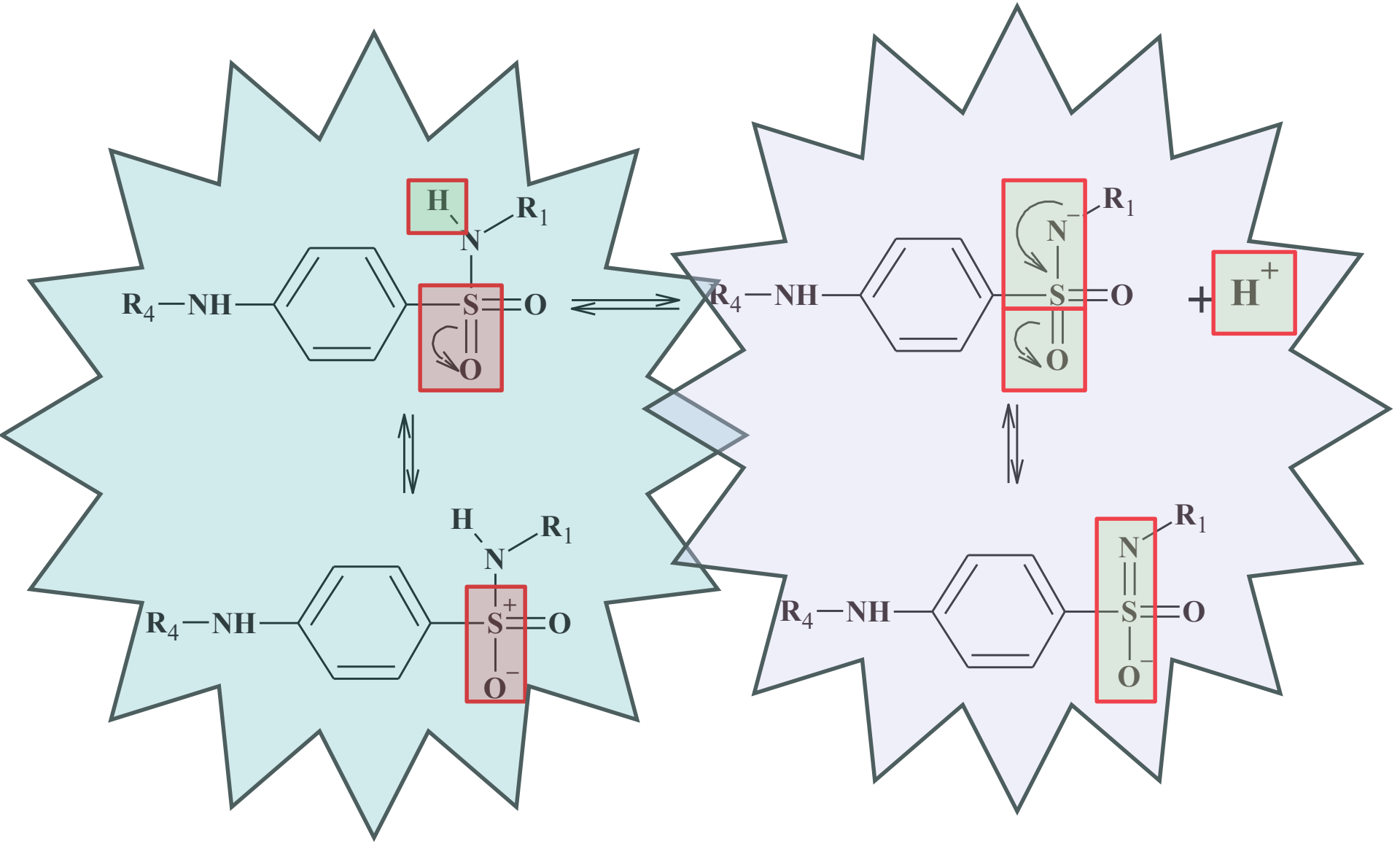


FIGURE 19.8 Sulphonamide prevents PABA from binding by mimicking PABA.

Electronic Characteristics of Sulfonamide in Sulfanilamides



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SAR for Sulfonamides

1. Chemistry scaffold: 4-amino-benzene sulfonamide
2. R1 & R1': provide appropriate pK_a to mimic PABA:

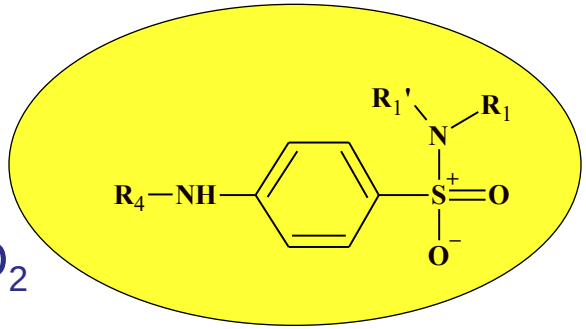
H or cation salt which is in equilibrium with H in biologic media

&

electron withdrawing hetero-aromatic azole (isoxazole / oxazole)

or diazine (pyrimidine)

3. R4: H or must be metabolizable to H



- Overall, consider distance of N_4-H to oxygens in SO_2

- Characteristics to consider:

✓ pK_a: related to Electron Withdrawing Groups (EWG) as R1 & R1'

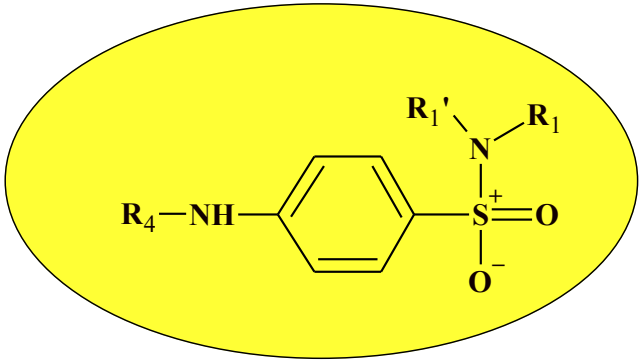
✓ water solubility: related to substitutes in R1 & R1'

✓ crystalluria: kidney damage: urine pH (about 6): pK_a related

✓ salt preparation: related to the acidity of acidic hydrogens: pK_a related

Pharmacokinetic for Sulfonamides

- GI absorption
- Distribution
- Protein Binding: PB: 30-70%
- Metabolism
- Excretion by kidney



- Plasma mediated resistance: ?

Metabolism for Sulfonamides

- Phase I: hydrolysis, …

✓ N4-hydroxylation: hydroxyl amine

✓ N4-oxidation

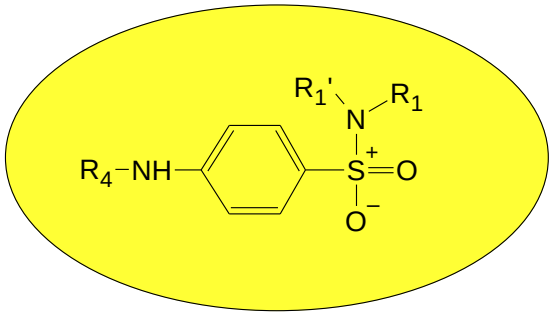
- Phase II: conjugation including:

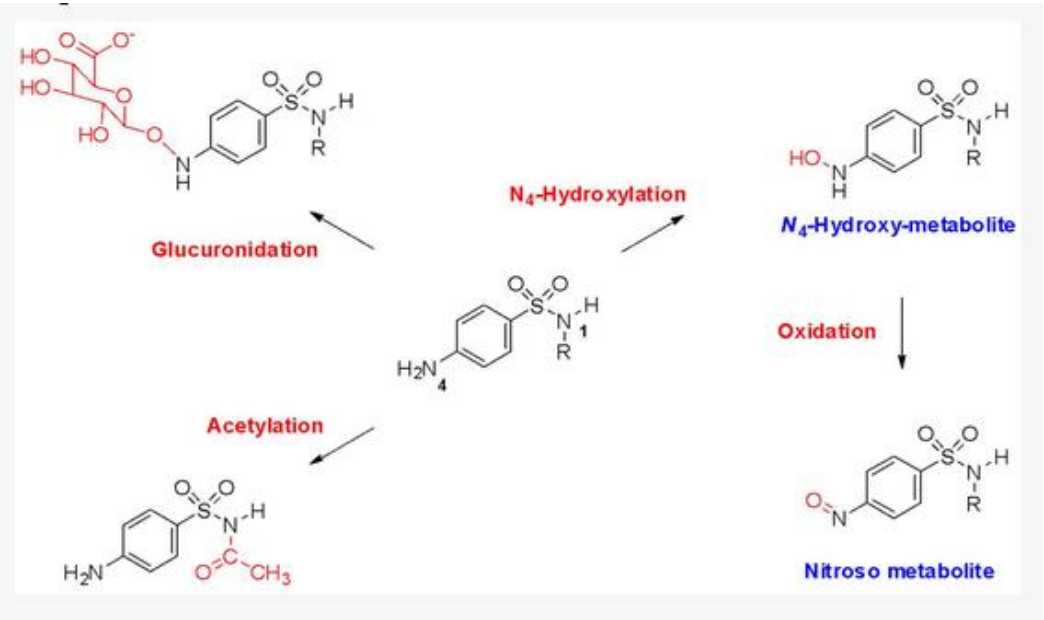
✓ N1-glucuronidation

✓ sulfonylation

✓ N1-acetylation

✓ N4-acetylation





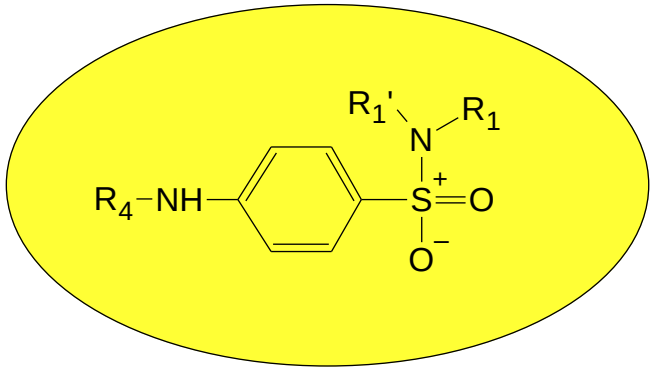
Clinical Characteristics for Sulfonamides

- Bacteriostatic
- Broad spectrum
- Therapeutic usages:

✓ UTI

✓ otitis

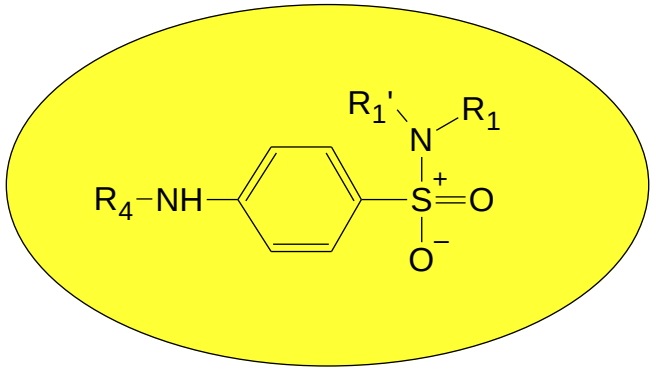
✓ ulcerative colitis



- Side Effects
- Allergic to sulfa

Side Effects of Sulfonamides

- Rash, vomiting, nausea, …



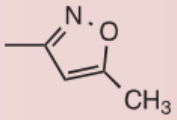
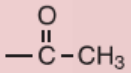
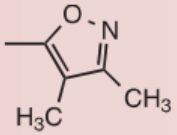
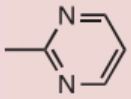
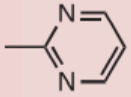
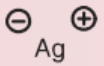
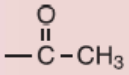
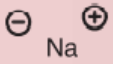
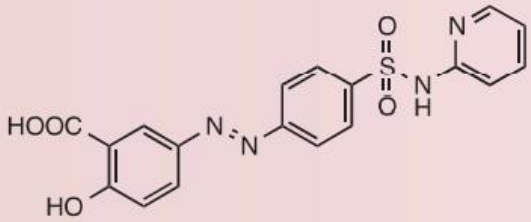
- Hematologic reactions: in G6PD deficient people
- Hypersensitivity reactions:

✓ Stevens Johnson syndrome

✓ photosensitivity

- Crystalluria: what is the solution?

Table 29.1 Clinically Relevent Sulfonamides

Drug: Generic Name	Product	R	R′	pK_a
Sulfisoxazole acetyl (prodrug)	In combination with erythromycin ethylsuccinate			5.6 after hydrolysis
Sulfamethoxazole	In combination with trimethoprim		—H	5.0
Sulfadiazine	Oral dosage form		—H	6.52
Silver sulfadiazine	Topical dosage form			
Sulfacetamide sodium	Opthalmic dosage form			5.4 free acid
Sulfasalazine	Gastrointestinal oral dosage form			

Common Sulfonamides in Clinic

- Sulfacetamide
- Sulfisoxazole
- Silver sulfadiazine
- Sulfadoxine: single & in combinational dosage
- Sulfasalazine: conjugational dosage form
- Triple sulfa: combinational dosage form

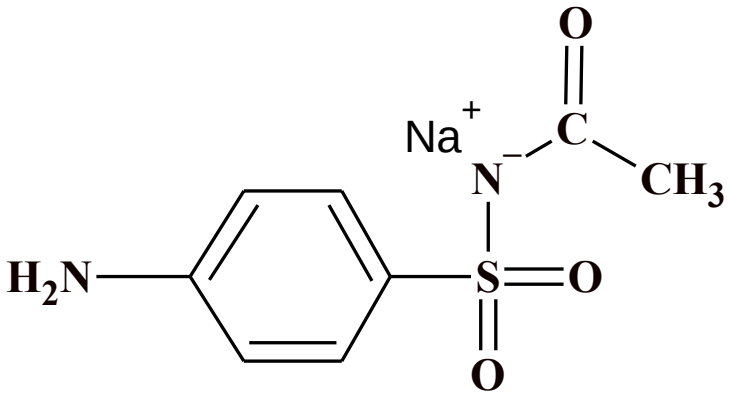
✓ what are the contents?

- Cotrimoxazole: combinational dosage form

✓ what are the contents?

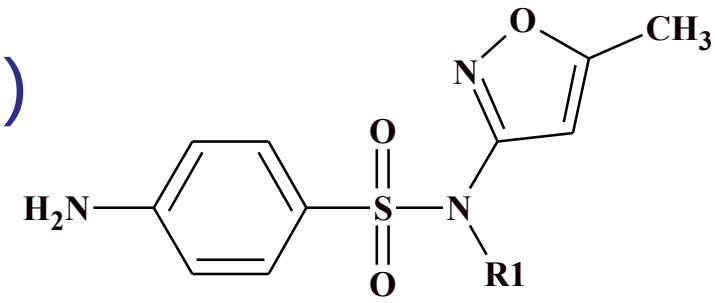
Sodium Sulfacetamide

- Follow SAR in this structure
- pK_a = 5.4 in free acid
- Therapeutic usage: against …
- Formulation: eye drop: ? %



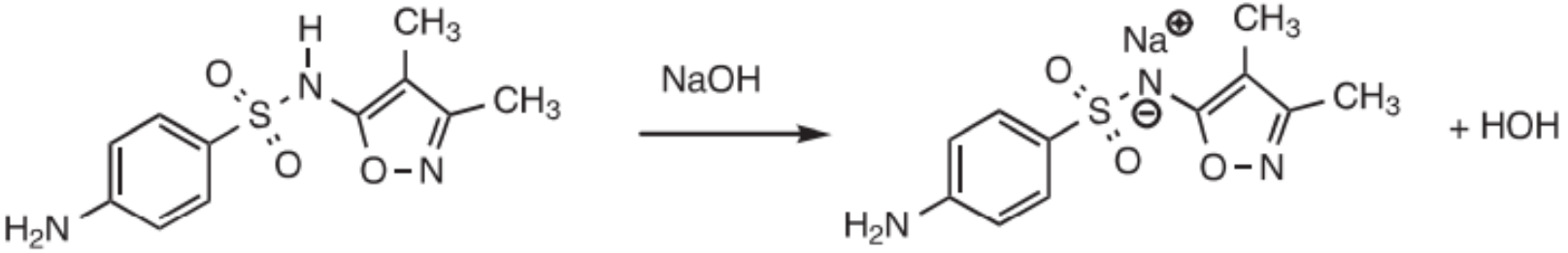
Sulfisoxazole & Sulfisoxazole Acetyl

- Follow SAR in this structure.
- pK_a = 5.6 after hydrolysis (R1= H)



- What is the commercial formulation?

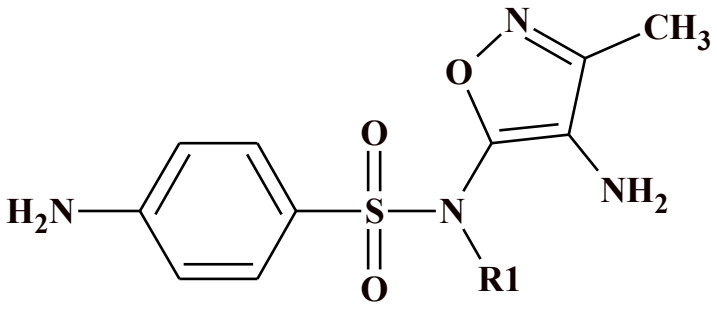
R1 = H ; Acetyl ($COCH_3$)



Sulfisoxazole $pK_a = 5$ Sodium sulfisoxazole

Sulfamethoxazole: R = H

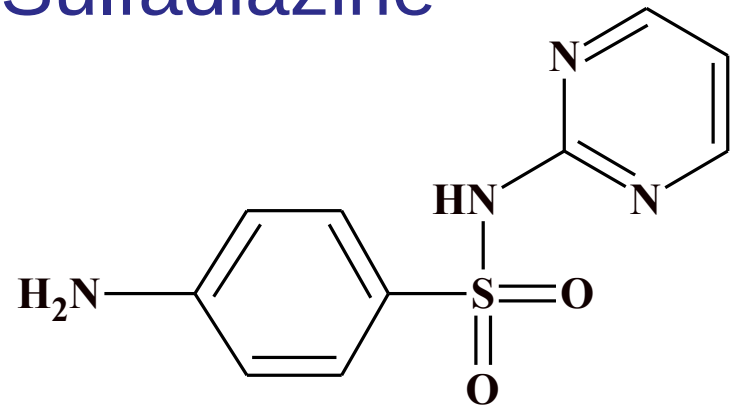
- Follow SAR in this structure.
- $pK_a = 5$



- What is the commercial formulation?

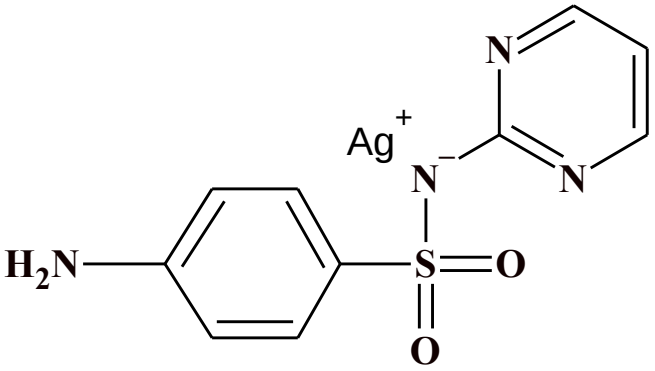
Sulfadiazine & Silver Sulfadiazine

- Follow SAR in this structure.
- $pK_a = 6.52$

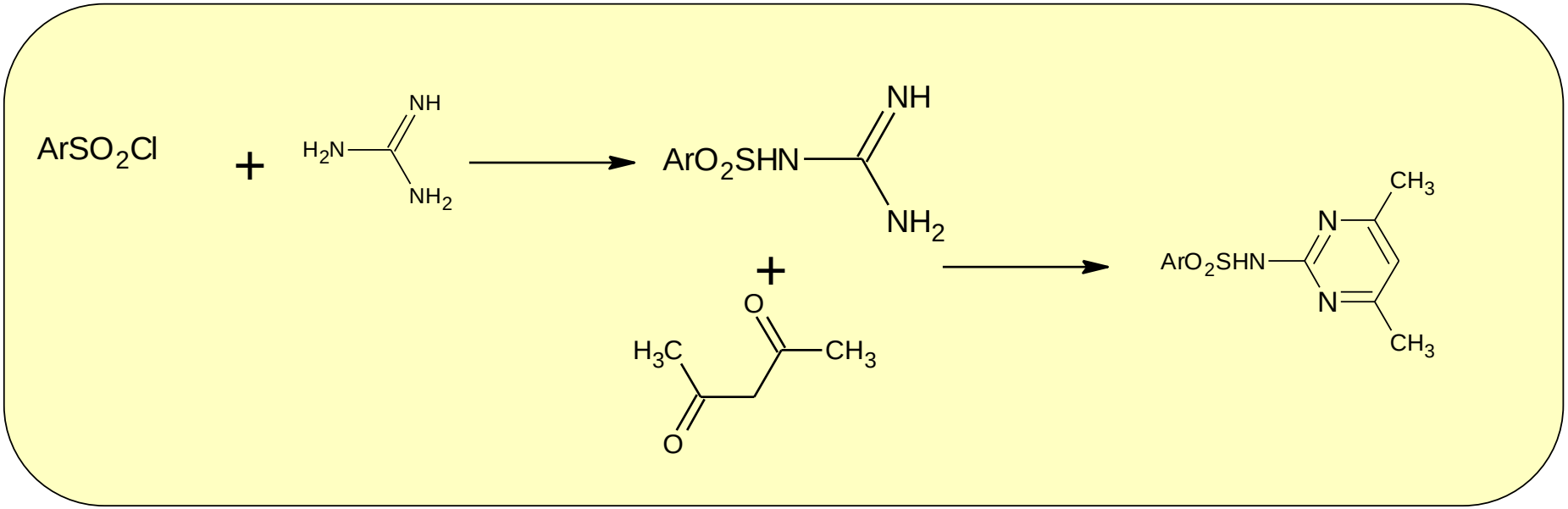


- Therapeutic usage: against pseudomonas

- Formulation: topical

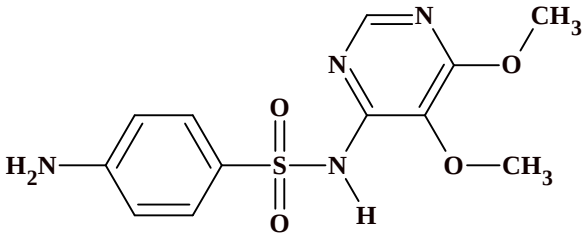


Synthesis of Sulfa-Pyrimidine Derivatives of Sulfonamides



Sulfadoxine

- Follow SAR in this structure.
- pK_a = 6.16 +/- 0.5 = 5.66 - 6.66



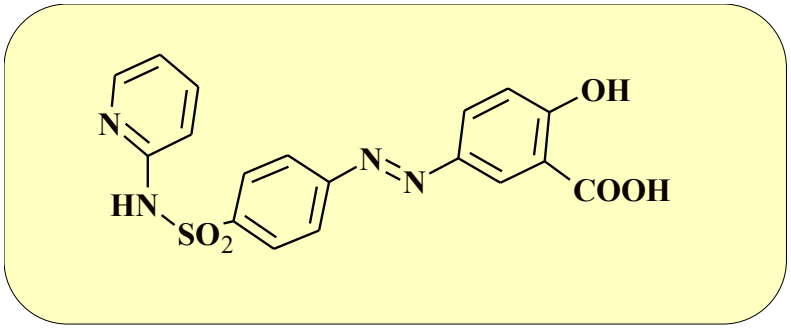
- What is the commercial formulation?

✓ single: not provided

✓ combinatorial dosage form: with pyrimethamine (DHFRI)

Sulfasalazine: Salicyl-azo-Sulfapyridine

- 2-hydroxy-5-{[4-(2-pyrdinyl-amino)-sulfonyl] phenyl] azo} Benzoic acid

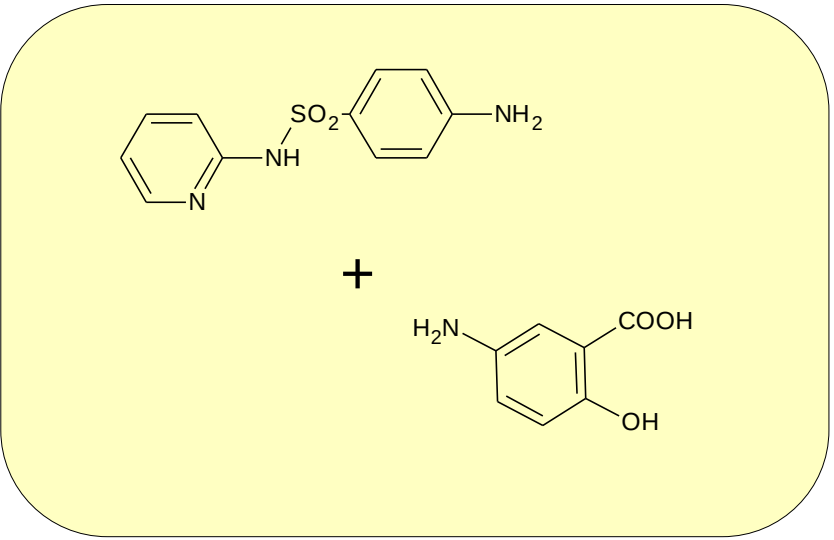


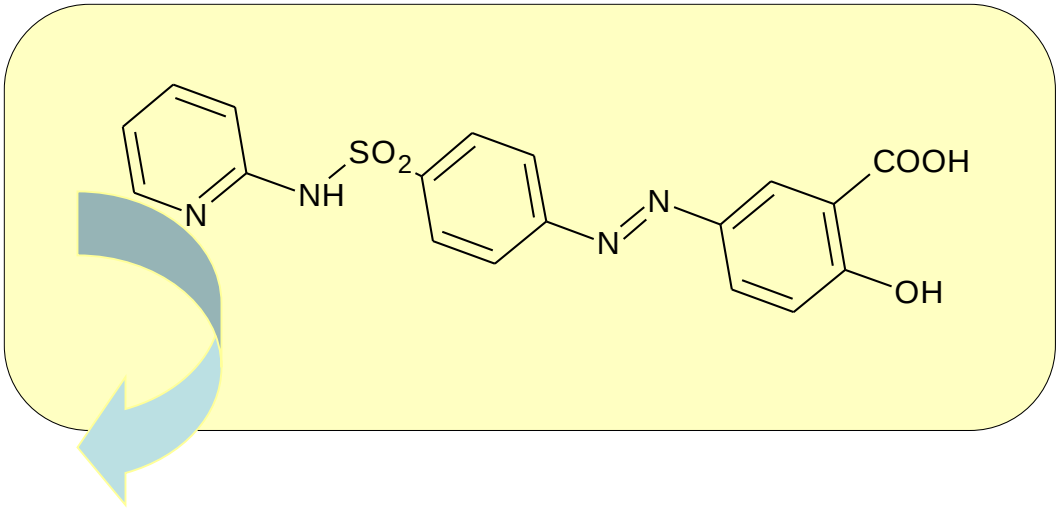
- Follow SAR in this structure.
- pK_a = ?
- Find the correlation of "sal" in the generic name to its structure.

- Therapeutic usage: against ulcerative colitis
- Formulation: topical
- What is the commercial formulation?

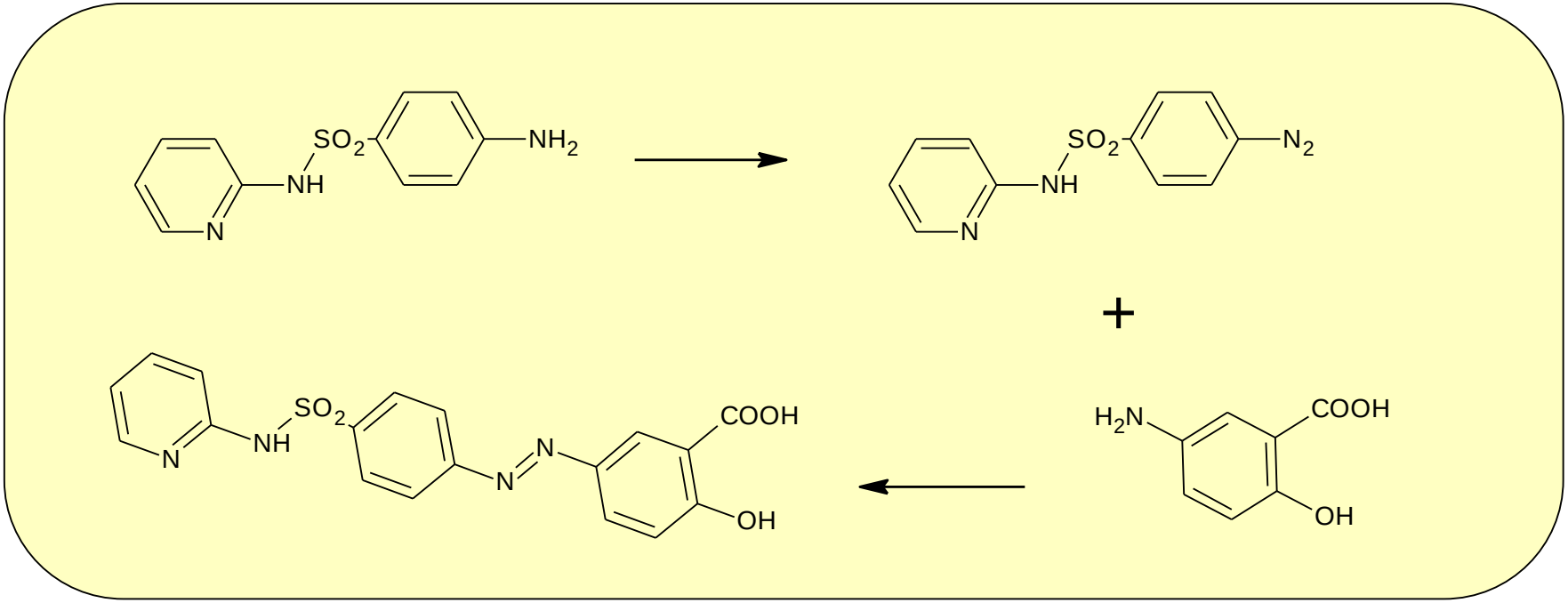
Bio-Activation of Sulfasalazine

- As a prodrug:
- Introduce active metabolites.





Synthetic Pathway for Sulfasalazine



Investigational Drug: Succinyl Sulfathiazole

- As a developing derivative
- Advantages & applications: ?

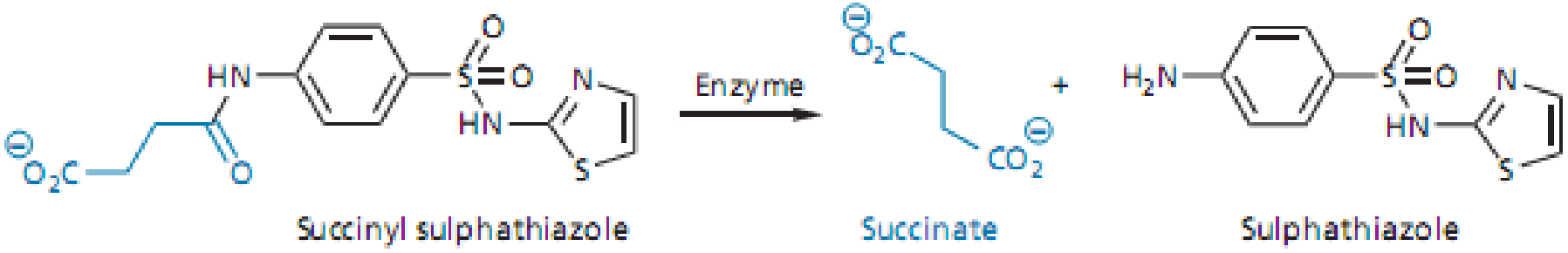


FIGURE 1 Succinyl sulphathiazole is a prodrug of sulphathiazole.

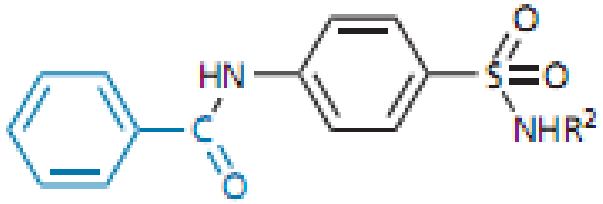
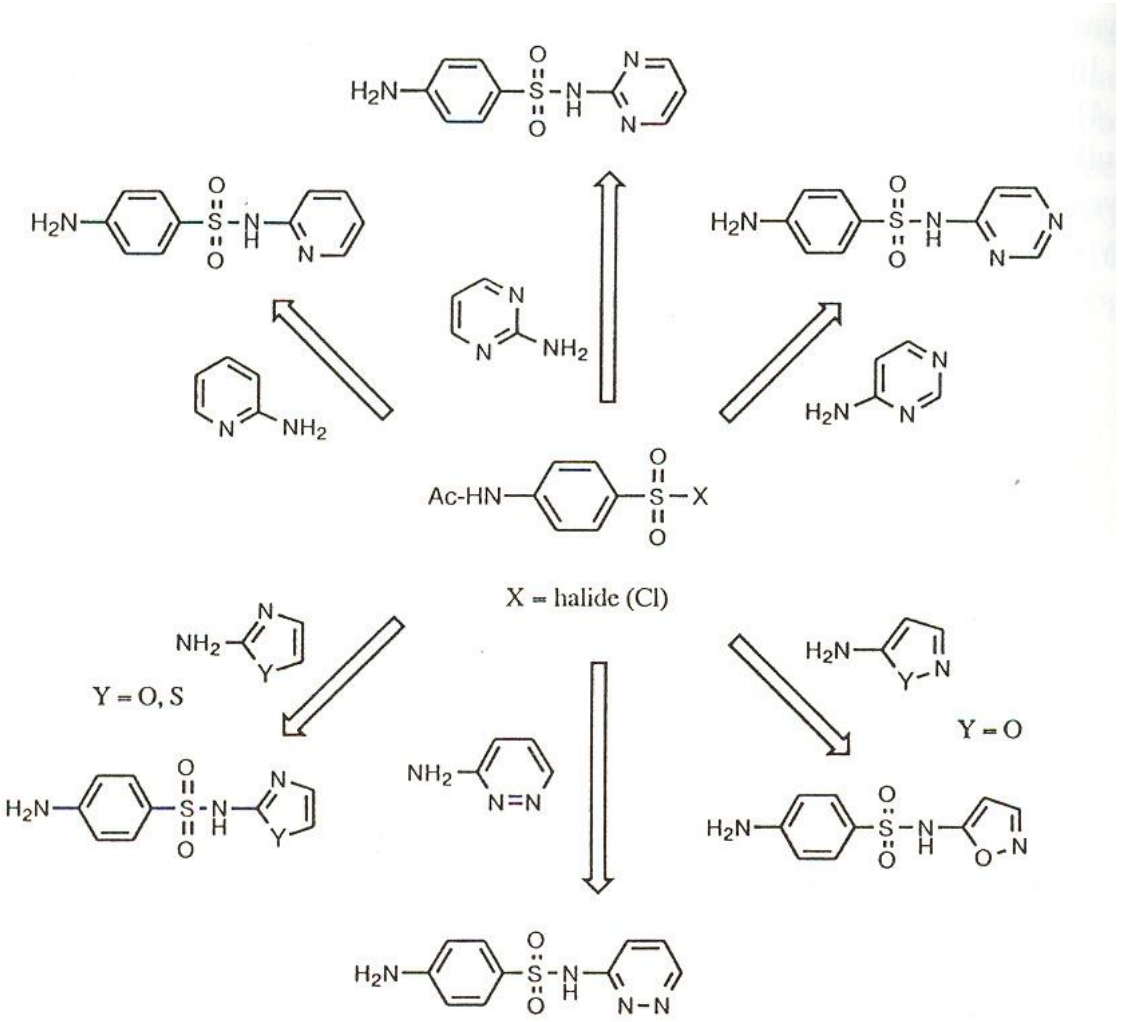


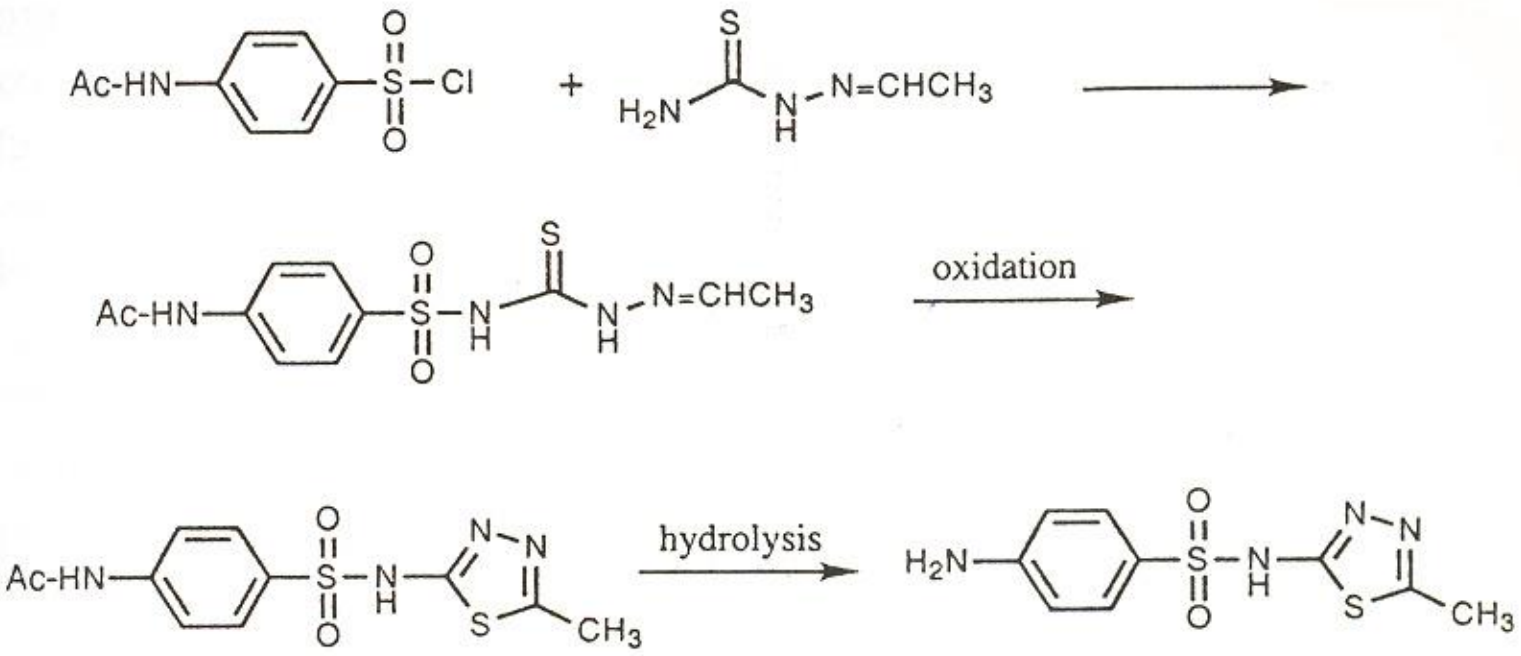
FIGURE 2 Substitution on the aniline nitrogen with benzoyl groups.

To synthesize Various Sulfonamides



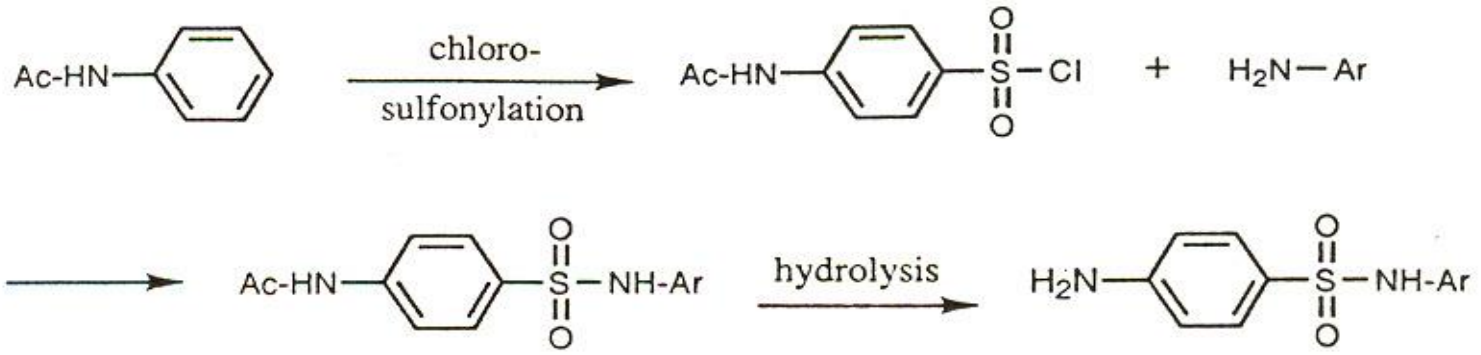
Most sulfonamides can be prepared by amine sulfonylation.

Synthetic pathway-1

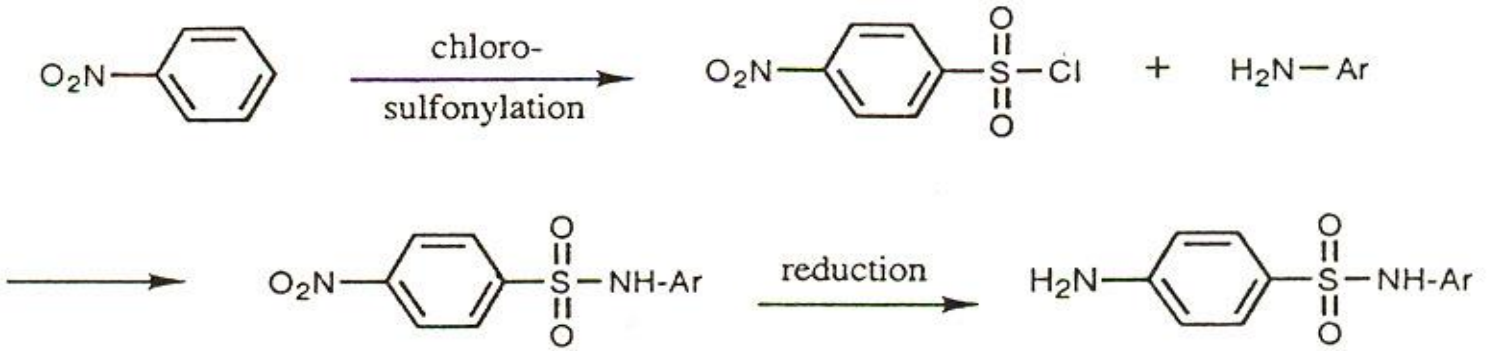


Sulfonamide synthesis with subsequent construction of an N-1 heterocyclic group.

Synthetic pathway-2

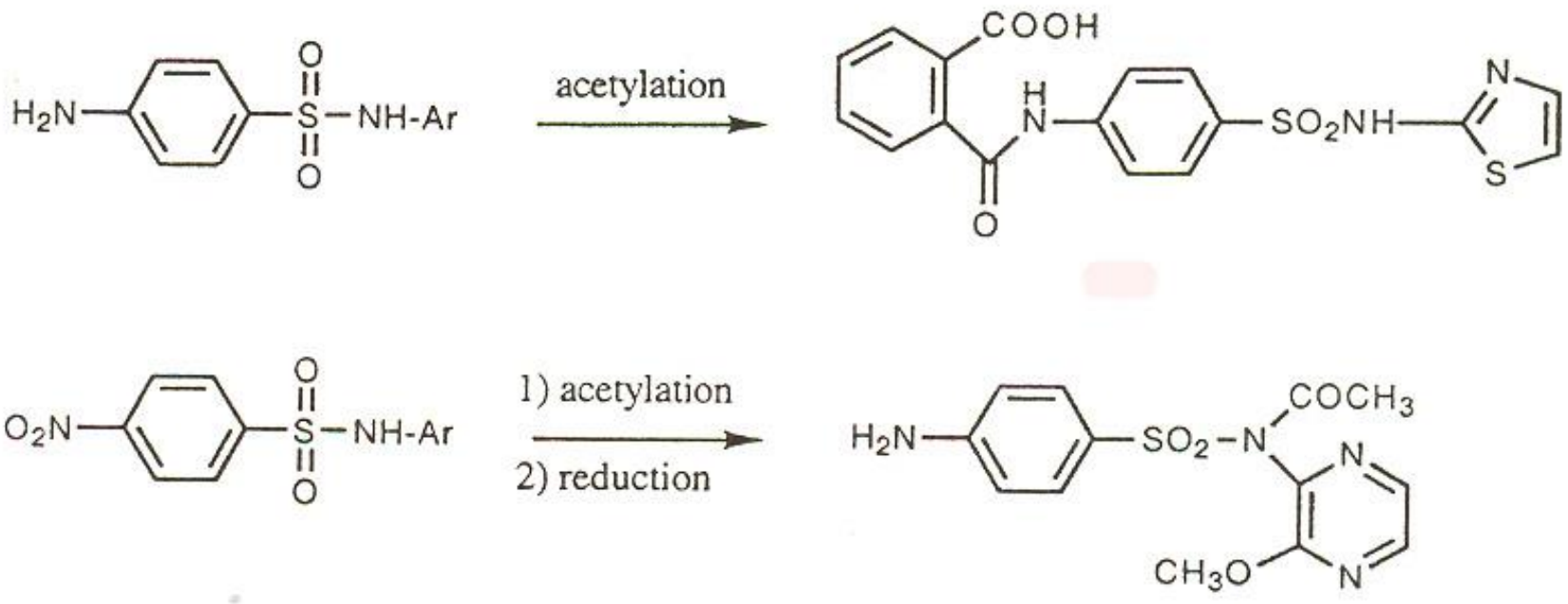


Chlorosulfonylation method for the preparation of sulfonamides.



Chlorosulfonylation method using nitrobenzene.

Synthetic pathway-3



Synthetic method for the synthesis of acylated sulfonamides