PHARM.D • YEAR 3

Medicinal Chemistry

CHAPTER 3

Sulphonamides and Sulphones

PPT CHAPTER COVER



Sulphonamides: the foundation

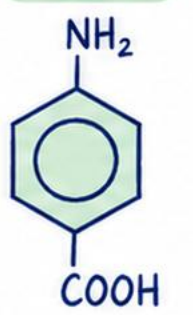
Origins and development

Sulphonamides are synthetic antibacterial agents developed from the Prontosil story in the 1930s.

Structural similarity

Their active scaffold resembles para-aminobenzoic acid (PABA).

PABA



Sulphonamide



Core scaffold: a para-amino benzene ring bearing a sulphonamide group.

Mechanism of action

They inhibit bacterial dihydropteroate synthase (DHPS), lowering folate synthesis and usually producing bacteriostasis.

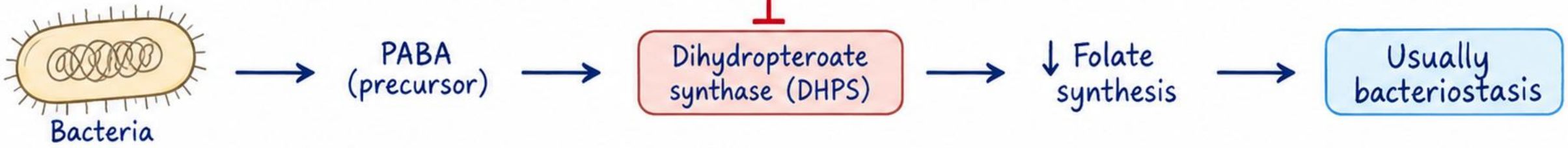
Selectivity

Humans obtain folate from food rather than using this bacterial pathway.

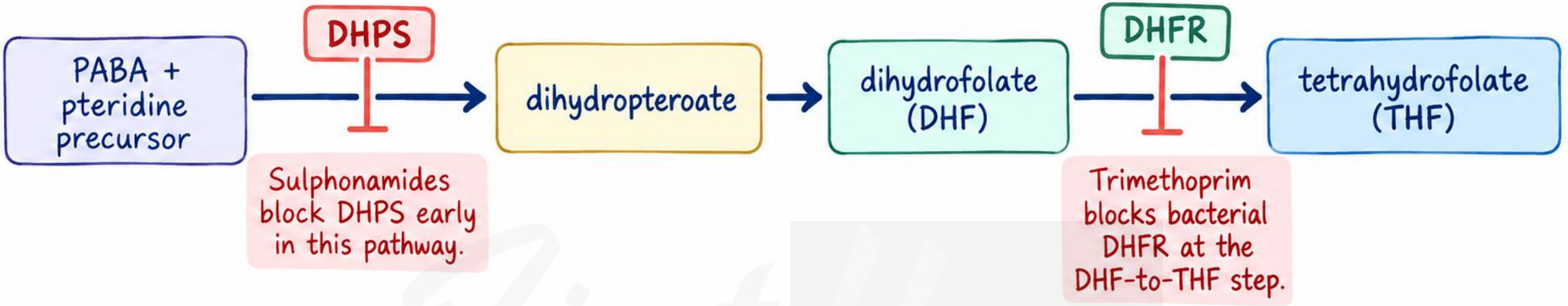
Activity and resistance

Activity depends on susceptibility, drug exposure and resistance; an old drug list is not a current treatment guideline.

From bacteria to folate (site of action)



The folate pathway: two targets



Role of THF

THF supports purine and thymidylate synthesis, so reduced folate supply impairs nucleic-acid production.



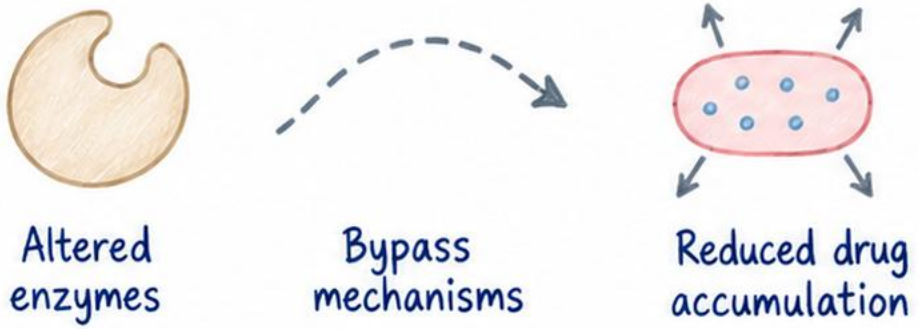
Co-trimoxazole

Co-trimoxazole combines the two targets: sequential blockade can strengthen activity against susceptible organisms.



Resistance

Sulphonamide and trimethoprim resistance can involve altered enzymes, bypass mechanisms or reduced drug accumulation.



Sulphonamide SAR: essential features

1. Para arrangement

Amino and sulphonamide groups are opposite on benzene; this supports PABA mimicry.

2. N4 amino group

The free aniline amino group is needed for classical antibacterial activity; some prodrugs release it in vivo.



3. N1 substitution

Heterocyclic substituents change acidity, solubility and disposition; electron-withdrawing groups can lower pKa.

4. Scope

These are classical antibacterial class trends, not universal rules for all sulphonamide medicines.

Classification and adverse effects

Systemic sulphonamides

Systemic sulphonamides have traditionally been grouped by duration of action; classifications may differ between textbooks.

Topical examples

Topical examples include sulfacetamide and mafenide.

Sulfasalazine

Sulfasalazine is mainly an anti-inflammatory prodrug, not a routine antibacterial.

Important adverse effects



Hypersensitivity and severe cutaneous reactions.



Blood dyscrasias.



Crystalluria.



Haemolysis is a concern in G6PD deficiency.



Protein binding and renal elimination influence interactions and exposure.



A sulphonamide allergy does not automatically establish cross-reactivity with every medicine containing a sulphonamide group.

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