Chemical classification of antibiotics

- Chemical classification of antibiotics is usually of limited value due to high variability.
- Structurally similar antibiotics derived from different microorganisms may have similar mechanism of action.

I. Sulfonamides
II. β-Lactams: include penicillins and cephalosporins
III. Aminoglycosides: amino sugars such as streptomycins, kanamycins, neomycins, gentamycins
IV. Polypeptides: such as tyrothricin and polymyxin
VI. Tetracyclines:
VII. Fused ring systems
VIII. Lincomycins
IX. Polyenes: Antifungal such as nystatin and amphotericins
X. Unclassified antibiotics
Sulfonamides (Sulfa or sulpha drugs)

- Diseases like pneumonia, meningitis, dysentry etc., could not be treated effectively until the discovery of **sulfa drugs** which were suitable for internal use against gram+ bacteria.

- **p-aminobenzenesulphonamide (sulfanilamide)** was initially synthesized in 1908 as intermediate for azo dyes, later on, it was observed that it is effective against streptococci.

- In 1935, a red dye (**4-sulfonamide-2′, 4′-diaminoazobenzene**) was prepared and showed curative properties against infections and named **Prontosil**.

- The inactivity of prontosil as antibacterial agents *in vitro* suggests that it should be converted to another metabolite to exert its antibacterial activity *in vivo*.

- Due to resistance development, only few sulfonamides are still in use such as (sul+trim).
**FIGURE 19.3** Metabolism of prontosil.
**FIGURE 19.7** Mechanism of action of sulphonamides.
• Sulfonamides inhibit DHPS by competing PABA.

• Some bacteria can resist sulfonamide competition by making more PABA, decrease cell membrane permeability to sulfonamide or by getting mutated DHPS.
Figure 6.8 - General nomenclature of the sulfonamides.
Any substitution in the ring abolishes activity.

Should not be substituted (i.e. $R^1 = H$), and if substituted should be metabolized back to 1° amine (i.e. act as prodrug).

Should be directly connected.

The only possible variable site. Electron withdrawing group improves ionizability of NH and thus activity and solubility.

Replacement of $-SO_2NH$ by $-CONH$ or by $-SO_3H$ reduces the activity.

Only para substitution is allowed.

The benzene ring and sulfonamide are critical and should be directly connected.

Should be 1° or 2° amine.
Sulfonamide group (SO₂NH₂) is unstable and get stabilized by losing a proton which results in negative charge being stabilized by resonance with sulfone group.

Therefore, the SO₂NH₂ group can be considered as HA acid similar to carboxyls (-COOH), phenols (benzene-OH) and thiols (-SH).

The R group in -SO₂-NH-R affects the ionizability of NH. If R is electron withdrawing group, the antibacterial activity and solubility of the drug is improved. Pyrimidine is more electron withdrawing than benzene and thiazole rings which produce toxic sulfonamide derivatives.

The lipid solubility influences the pharmacokinetic and antibacterial activity, and so increases the half-life and antibacterial activity in vivo.
Crystalluria and pKa of sulfonamides

- Despite the good ability to treat infections, the sulfanilamide are associated with sever renal damage due to crystallization in the kidneys.

- The pKa of sulfonamido group (-SO2NH-) of sulfanilamide is 10.4, therefore at urine pH of 6 only 0.004% of sulfanilamide is ionized (water-soluble) to be excreted in urine.

- The precipitated sulfanilamide in urine lead to crystalluria.

- Sodium bicarbonate was administered before each dose of sulfanilamide to improve solubility and thus excretion in urine.
Case study: Sulphathiazole (metabolism problem)

- Acetylation of N4 of sulfonamide $\rightarrow$↓ionization of N1 (NH)$\rightarrow$↓solubility

\[
\text{H}_2\text{N} - 4\text{S} - 1\text{NO}_2 - \text{NH}_2
\]
\[\text{pKa}=7.1\]  
Highly ionizable

\[
\text{HN} \xrightarrow{N-\text{Acetylation}} \text{Me-C} \xrightarrow{\text{Less ionizable}} \text{HN}
\]
\[\text{pKa}>7.1\]  
Insoluble

**FIGURE 1** Metabolism of sulphathiazole.

Electron withdrawing group (pyrimidine) Sulphadiazine. more soluble and less toxic

Impaired Oral bioavailability of sulfonamide offers advantage to locally treat gastrointestinal infection.

**Oral bioavailability (i.e. absorption through GIT) requires balanced hydrophobic/hydrophilic characters.**

- Too hydrophilic drug will not be absorbed as N4-succinyl derivatives

  ![Succinyl sulphathiazole](image)

  

  ![Succinate](image)

  ![Sulphathiazole](image)

- Too hydrophobic drug will not be absorbed as N4-benzoyl derivatives

  ![N4-benzoyl derivative](image)
Sulfamethazine naming options

4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamide;

N₁-(4,6-dimethyl-2-pyrimidinyl)sulfanilamide;

2-sulfanilamido-4,6-dimethylpyrimidine.

pKᵣ of 7.2
Classification of sulfonamides on the basis of Chemical structure

- N-substituted sulphonamide: Sulphadiazine, Sulphacetamide, Sulphadimidine.
- • N-4 substituted sulphonamides (prodrugs): Prontosil.
- • Both N-1 and N-4 substituted sulphonamides: Succinyl sulphathiazole, Phthalylsulphathiazole.
- • Miscellaneous: Mafenide sodium.
Classification of sulfonamides on the basis of Chemical structure:

A) N-substituted sulfonamides

<table>
<thead>
<tr>
<th>Name</th>
<th>R¹</th>
<th>R²</th>
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<tbody>
<tr>
<td>Sulphanilamide</td>
<td>−H</td>
<td>−H</td>
</tr>
<tr>
<td>Sulphapyridine</td>
<td>−H</td>
<td>[\text{Pyridine structure}]</td>
</tr>
<tr>
<td>Sulphathiazole</td>
<td>−H</td>
<td>[\text{Thiazole structure}]</td>
</tr>
<tr>
<td>Sulphacetamide</td>
<td>−H</td>
<td>−COCH₃</td>
</tr>
<tr>
<td>Sulphadiazine</td>
<td>−H</td>
<td>[\text{Diazine structure}]</td>
</tr>
<tr>
<td>Sulphadimidine</td>
<td>−H</td>
<td>[\text{Dimidine structure}]</td>
</tr>
</tbody>
</table>

[Chemical structures for R¹ and R² are shown as diagrams.]
Classification of sulfonamides on the basis of Chemical structure:

B) N-4 substituted sulphonamides (prodrugs)

Prontosil drug is inactive in vitro, but it is active in vivo since it is converted to sulphanilamide by *azo reductase* enzymes.

4-sulfonamide-2′, 4′ -diaminoazobenzene

Note: Pro-drugs of amines are occasionally prepared by incorporating them in to an azo linkage. By the action of *azo reductase* the amino compounds are released in vivo.
Classification of sulfonamides on the basis of Chemical structure:

B) N-4 substituted sulphonamides (prodrugs)

Sulphasalazine by the action of *azo reductase* releases the 5-amino salicylic acid (5-ASA) and sulphapyridine. The generation of anti-inflammatory salicylic acid prior to absorption prevents the systemic absorption of the agents and enhances the concentration of it in active site (intestine). Therefore, sulphaslazine is mainly used to treat inflammatory bowel syndrome due to the released 5-ASA.
Classification of sulfonamides on the basis of Chemical structure:

C) Both N-1 and N-4 substituted

<table>
<thead>
<tr>
<th>Name</th>
<th>R¹</th>
<th>R²</th>
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<tr>
<td>Succinyl sulphathiazole</td>
<td><img src="image1" alt="Chemical structure" /></td>
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<tr>
<td>Phthalylsulphathiazole</td>
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<td><img src="image4" alt="Chemical structure" /></td>
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</table>
Classification of sulfonamides on the basis of Chemical structure:

D) Miscellaneous

Mafenide

It is NOT a true sulfanilamide-type compound, as it is not inhibited by PABA. Its antibacterial action involves a mechanism that differs from that of true sulfanilamide-type compounds.

Silver sulphadiazine

Solapsone
Mechanisms of Microbial Resistance to Sulfonamides

- The indiscriminate use of sulfonamides has led to the emergence of resistance strains of bacteria.

- Resistance is likely through:
  - compensatory increase in biosynthesis of PABA.
  - Mutations at dihydropteroate synthase
  - Decrease cell membrane permeability to sulfonamides.
  - Active efflux of sulfonamides outside the cell
  - acquisition of another copy of DHPS through plasmid transfection.
<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
<th>Plasma Pr. binding</th>
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</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>4.8</td>
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</tr>
<tr>
<td>PABA</td>
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<td>Sulfisoxazole</td>
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<tr>
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