Medicinal Chemistry 2
Sulfonamides (Sulfa drugs)

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Sulfonamides (Sulfa drugs)

Antibiotics

Definition

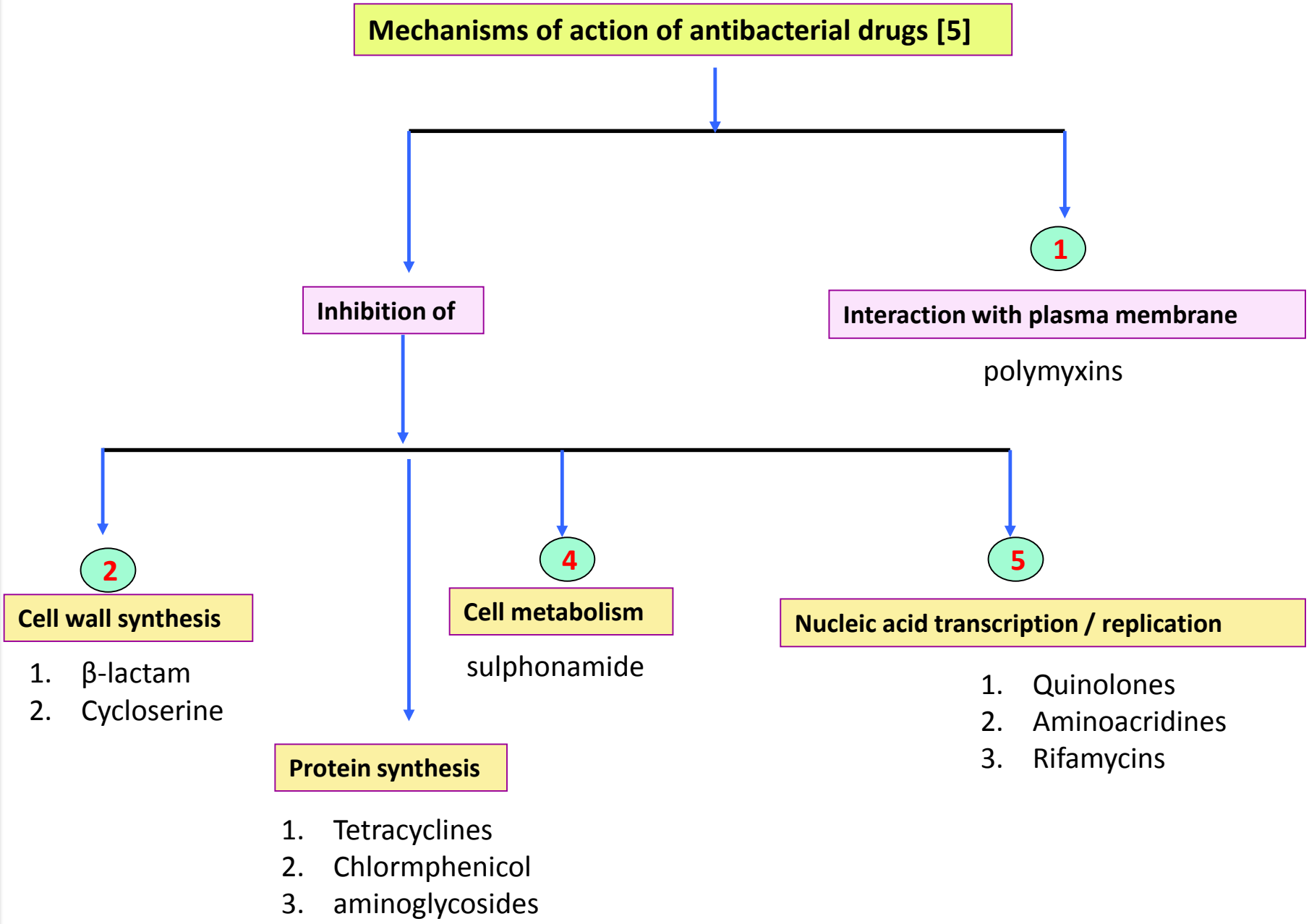
- 1942, Waksman "an antibiotic is a substance produced by microorganisms which has the capacity of inhibiting the growth & destroying other microorganisms".
- Later " any substance produced by a living organism that is capable of inhibiting the growth or survival of one or more species of microorganisms in low concs.
- medicinal chemists to modify the natural antibiotics to prepare new synthetic analogs so we now have ***semisynthetic*** & ***synthetic*** derivatives in the definition.

Classification of Antibiotics

β-Lactam	Penicillins & Cephalosporins
Non- β-Lactam	Aminoglycoside: Streptomycin & Kanamycin
	Tetracyclines
	Macrolides: Erythromycin & Oleandomycin
	Polypeptide: Polymixin
	Polyene: Amphotericin
	Miscellaneous : Chloramphenicol

Sulfonamides (Sulfa drugs)

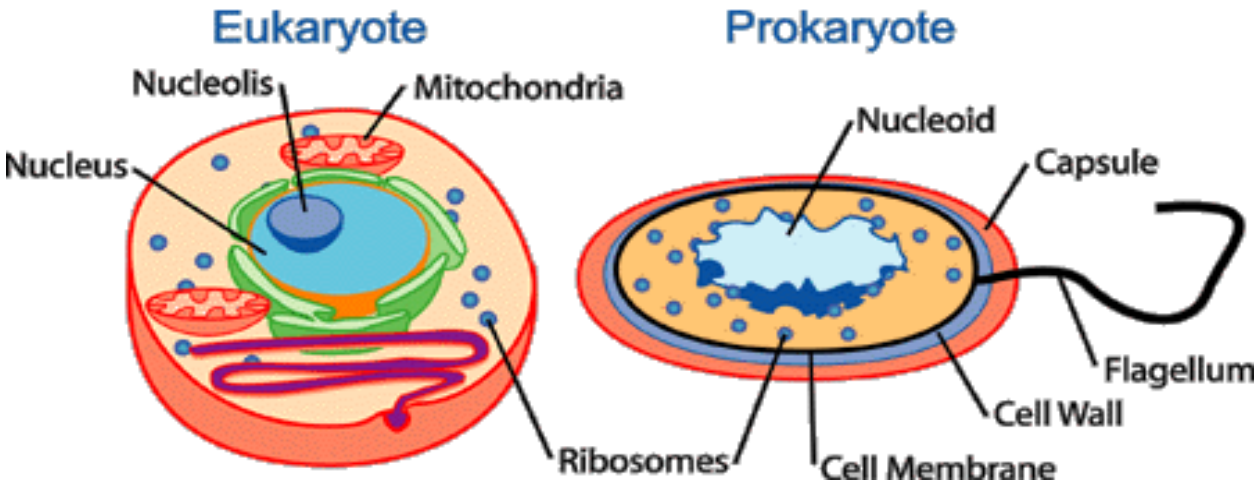
Sulfa drugs



Sulfonamides (Sulfa drugs)

Bacterial Cell Wall

Human cells have ***no cell wall***, but bacterial cells need a cell wall which composed of Peptidoglycan & Proteins. since they have a hypotonic environment in which the cell functions. If no cell wall, bacterial cells would rupture leading to cell death..

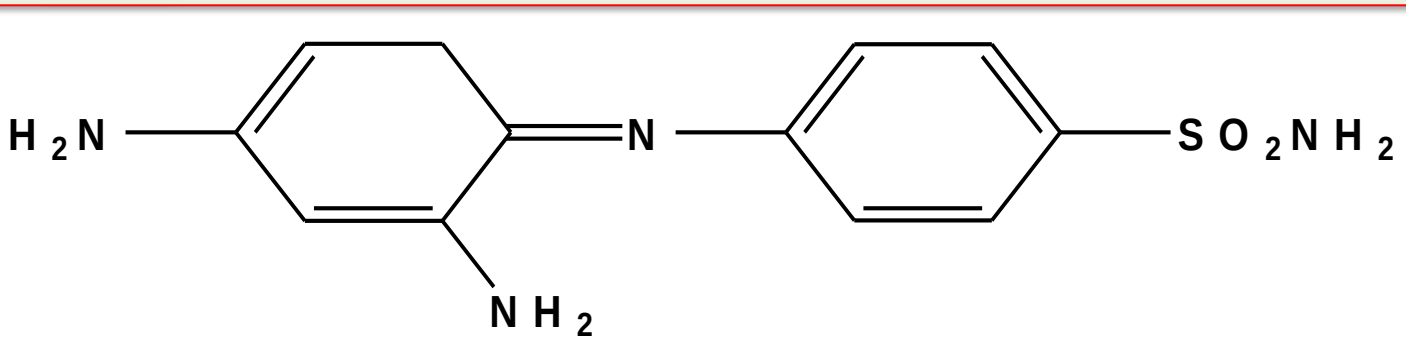


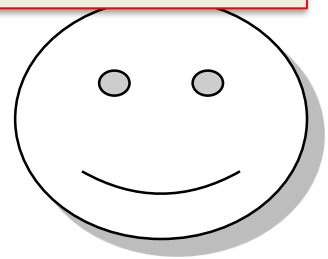
- **These differences are the key for treatment of bacterial diseases by use of antibiotics.**
- **Without such differences it would be difficult to target and kill bacterial cells once they get into human body.**

Sulfonamides (Sulfa drugs)

Discovery:

- In 1932: Domagk studied the antimicrobial effect of Prontosil Dye "brilliant red Dye" ➡ it was found to be active ≠ Streptococcal infection in mice [*in vivo*] but inactive on bacterial culture [*in vitro*].



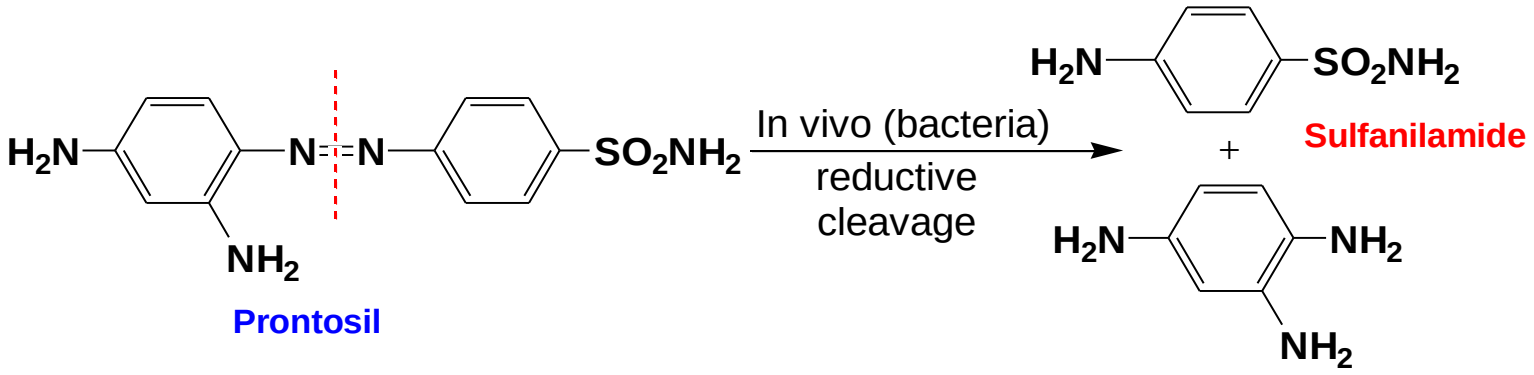


Prontosil Dye (prodrug)

Sulfonamides (Sulfa drugs)

Discovery:

- In 1935: Trefouel discovered the conversion of inactive prontosil dye -in vivo- into active Sulfanilamide "Lead cpd or Prototype". This finding was confirmed by isolating free sulfonamide from blood & urine of patients treated with Prontosil.



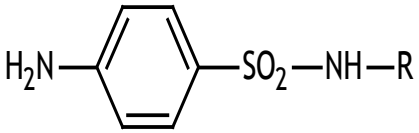
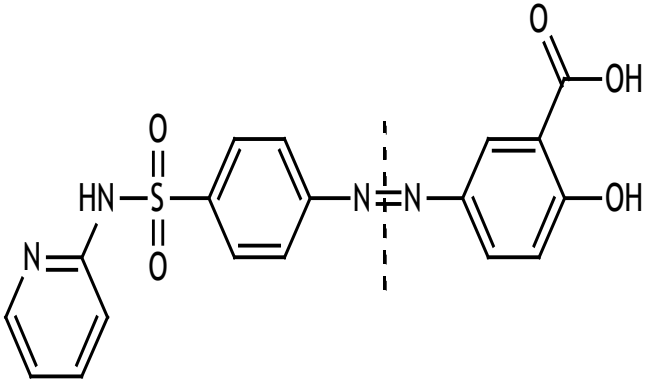
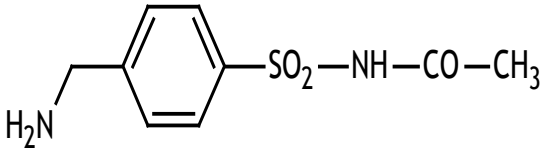
- Prontosil is inactive in vitro but in vivo → sulfanilamide (active form) by reductive cleavage
- This led to discovery of the first synthetic antibacterial agent

Sulfonamides (Sulfa drugs)

Sulfa drugs

Chemistry of sulfonamide

Chemistry of sulfonamide: they are classified as

[1] Aniline-substituted sulfonamide	[2] Prodrugs giving active sulfonamide	[3] Non-aniline sulfonamides
 Sulfanilamides	 Sulfasalazine	 Mafenide acetate

Sulfonamides (Sulfa drugs)

M. O . A of sulfonamide:

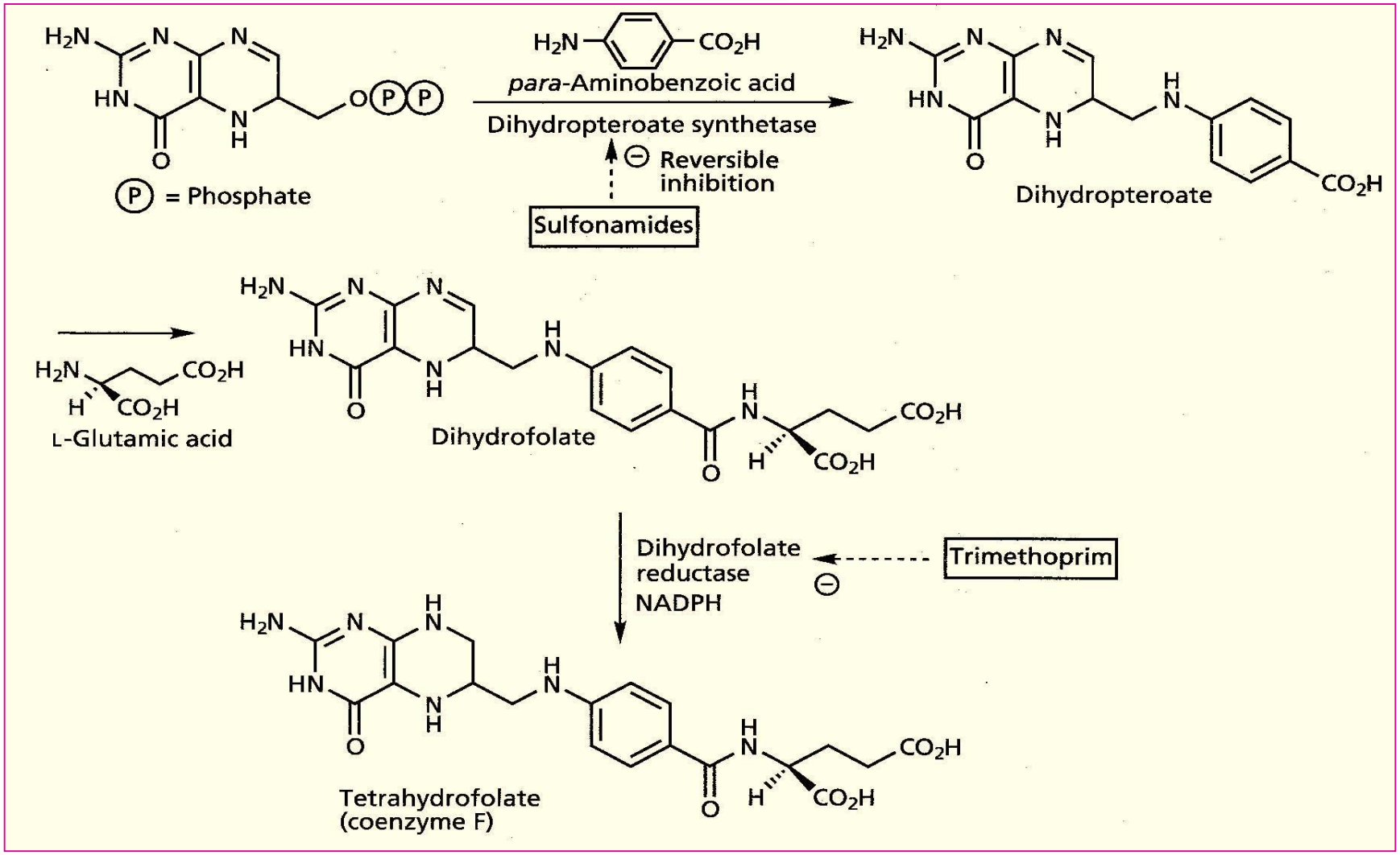
- Sulphanilamides are active BACTERIOSTATIC [so, eradication of m. o. is by normal immunity of body].
- Many bacteria are **impermeable** to folic acid, so they rely on their ability to synthesize folate from PABA "P-AminoBenzoic Acid" , Pteridine & Glutamate ≠ MAMMALS who can't synthesize folic acid, so obtained from diet & so not affected by sulfonamides [selective chemotherapy].
- Because of their structural similarity to PABA ,Sulphonamides act as competitive reversible inhibitor with this substrate for the enzyme DIHYDROPTEROATE SYNTHETASE ,thus ↓ synthesis of folic acid → ↓ thymidine, purine synthesis → ↓ synthesis of DNA → ↓ multiplication & growth of m.o.

Sulfonamides (Sulfa drugs)

Sulfa drugs

M. O . A of sulfonamide:

Biosynthesis of folate co-enzymes:

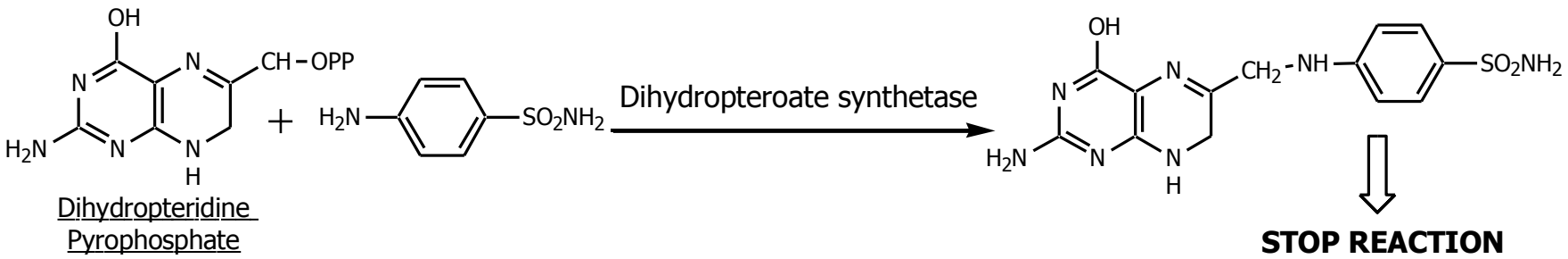


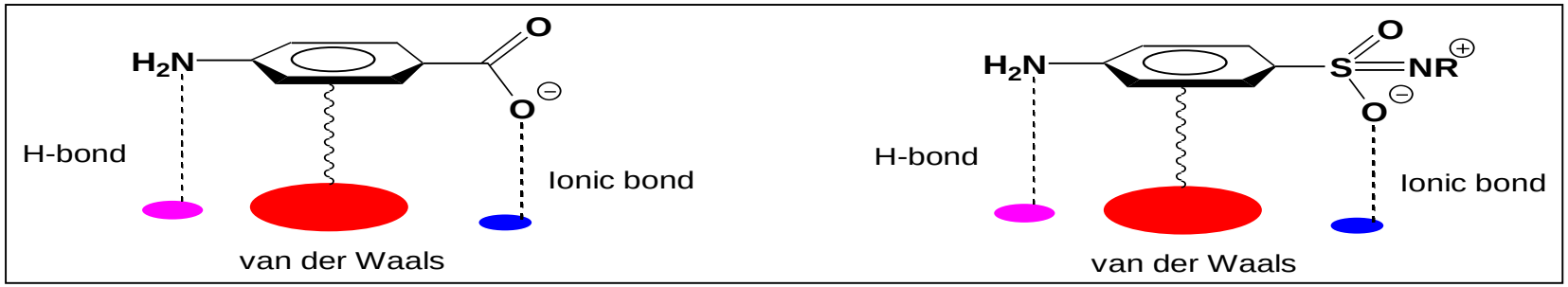
Sulfonamides (Sulfa drugs)

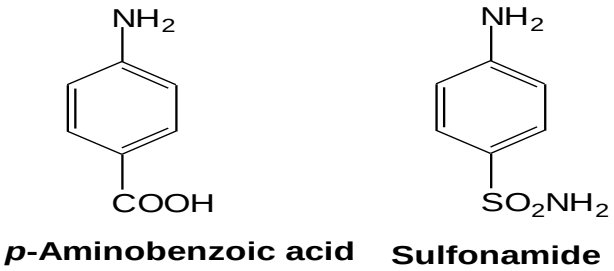
Sulfa drugs

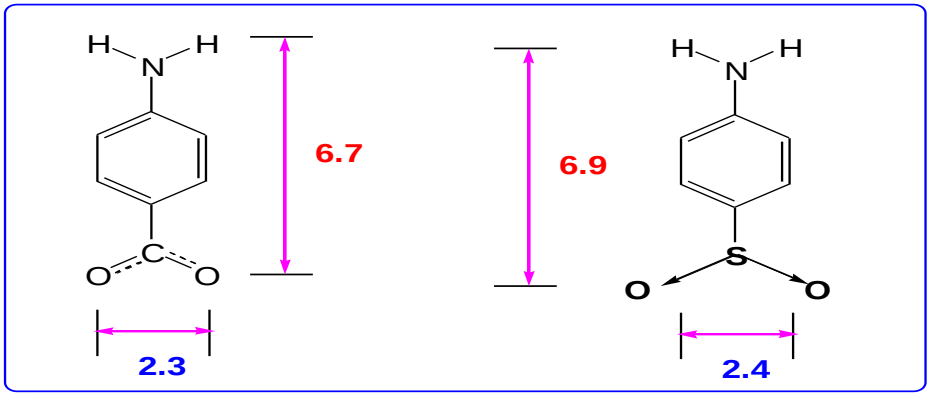
M. O . A of sulfonamide:

By using sulfonamides









Sulfonamides (Sulfa drugs)

M. O . A of sulfonamide:

This mechanism is supported by:

- 1. PABA added to culture media antagonizes effect of sulfonamides.
- 2. Man can't form folic acid ? so his cells are immune to sulfonamides.
- 3. M.O. which can utilize performed folic acid are less sulfonamides susceptible.

Sulfonamides (Sulfa drugs)

M. O . A of sulfonamide:

Resistance of m.o. to sulfonamide drugs by:

- 1. The bacterial cell wall becomes more permeable to folic acid.
- 2. The m.o. learn to utilize preformed folic acid.
- 3. The organism develop alternate pathway for synthesis of folic acid.
- 4. increase PAPA synthesis by m.o. to overcome inhibition of dihydropteroate synthetase.

Sulfonamides (Sulfa drugs)

Sulfa drugs

Structure Activity Relationship

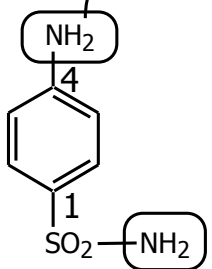
N.B: As structure become more close to PABA ⇨ more active.

The 2 functional gps must be para that other positional isomers [m- or o-] are inactive.

Other substitution on benzene ring → inactive

Other aromatic ring: decrease activity

Substitution of benzene ring with 5-membered ring cause inactivation. [due to different spacingbetween the two functional gps]



Free NH_2 gp is **ESSENTIAL** for activity:

[1] If substituted by another gp [as alkyl or alkoxy] → inactive

But, if substituted by a gp that will be converted to NH_2 gp in vivo [as NO_2,NO, N=N, NHCOR, NH-OH] → active

[2] Acylation of N with Dicarboxylic acid as succinic or phthalic acid, give slufonamide NOT absorbed from small intestine BUT hydrolyzed in large intestine into free sulfonamide [Local Intestinal action]

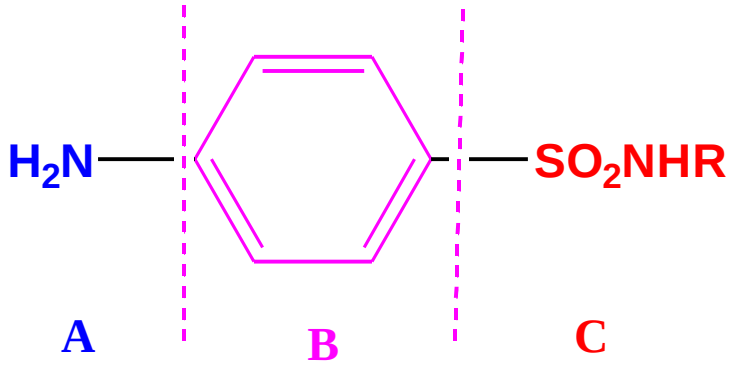
If di-substituted [$-SO_2NR_2$] → Inactive

If mono-substituted → ↑ activity

Sulfonamides (Sulfa drugs)

Structure Activity Relationship

N.B: As structure become more close to PABA ➡ more active.



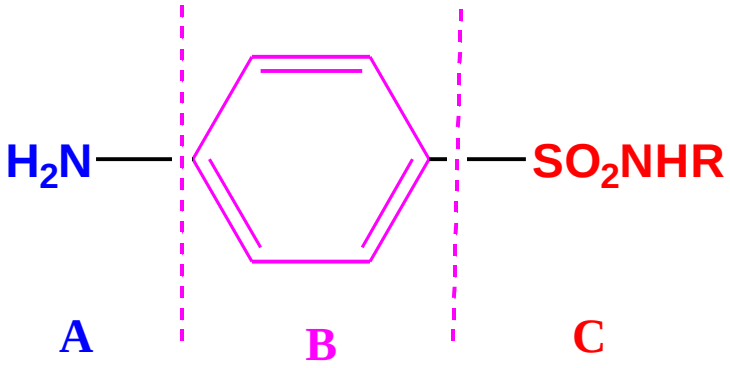
Change in A

- Free NH_2 is essential for activity.
- Removal of NH_2 → inactive compounds.
- Alkylation of NH_2 → inactive compounds.
- Shifting NH_2 gp to *m*- or *o*-position ▸ inactive compounds.
- Substitution with NO_2, NHOH, azo or acetylation ▸ prodrugs which upon reduction or hydrolysis in vivo ▸ free NH_2 (e.g. intestinal sulfa) still retain its activity.

Sulfonamides (Sulfa drugs)

Structure Activity Relationship

N.B: As structure become more close to PABA ➡ more active.



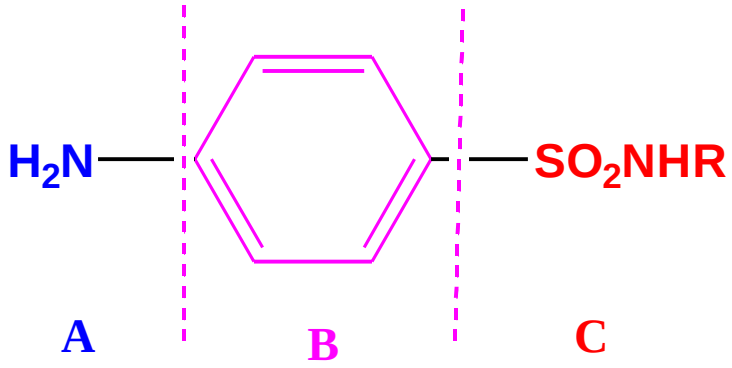
Change in B

1. Phenyl group is essential: replacement with naphthalene, anthracene, pyridine or by another heterocyclic rings or saturation to cyclohexyl → inactive compounds.
2. Substitution on benzene ring by halogen or any other group ▸ loss of activity.

Sulfonamides (Sulfa drugs)

Structure Activity Relationship

N.B: As structure become more close to PABA ➡ more active.



Change in C

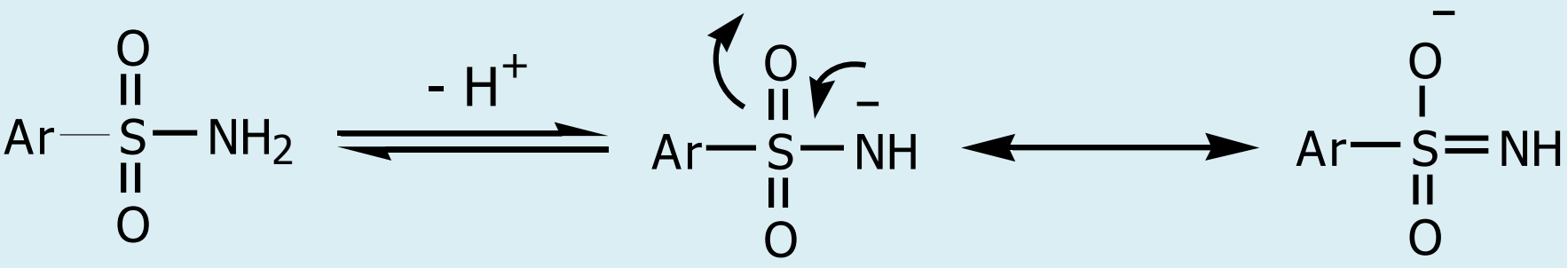
1. SO_2 must be directly attached to benzene ring.
2. R should be electron withdrawing group ▸ ↑ acidity ▸ ↓p*K*a ▸ ↑ionization ▸ ↑activity
3. N is best to be N-acyl "prodrug" this will help in;

- Mask the bitter taste (can be used orally as syrup).
- Hydrolyzed in vivo to give free active compound.

Sulfonamides (Sulfa drugs)

Physicochemical properties of sulfa drugs

[1] They are weak organic acids: due to SO_2NH_2 group [by loss of proton & stabilization of –ve charge by resonance], & this determine pka of the drug.

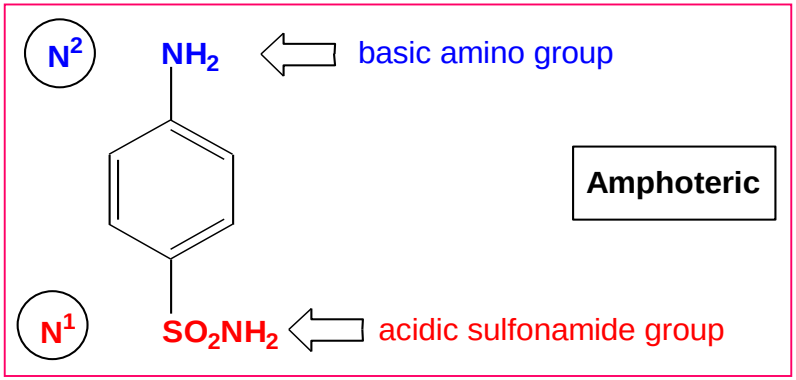


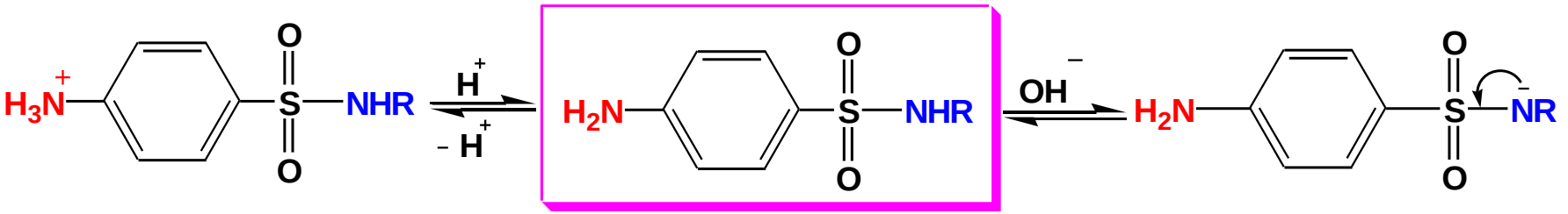
N.B: acidity increases by attachment of e-withdrawing group to N4

Sulfonamides (Sulfa drugs)

Physicochemical properties of sulfa drugs

2- Amphoteric characters: [with acidic & basic characters] React as acid & base





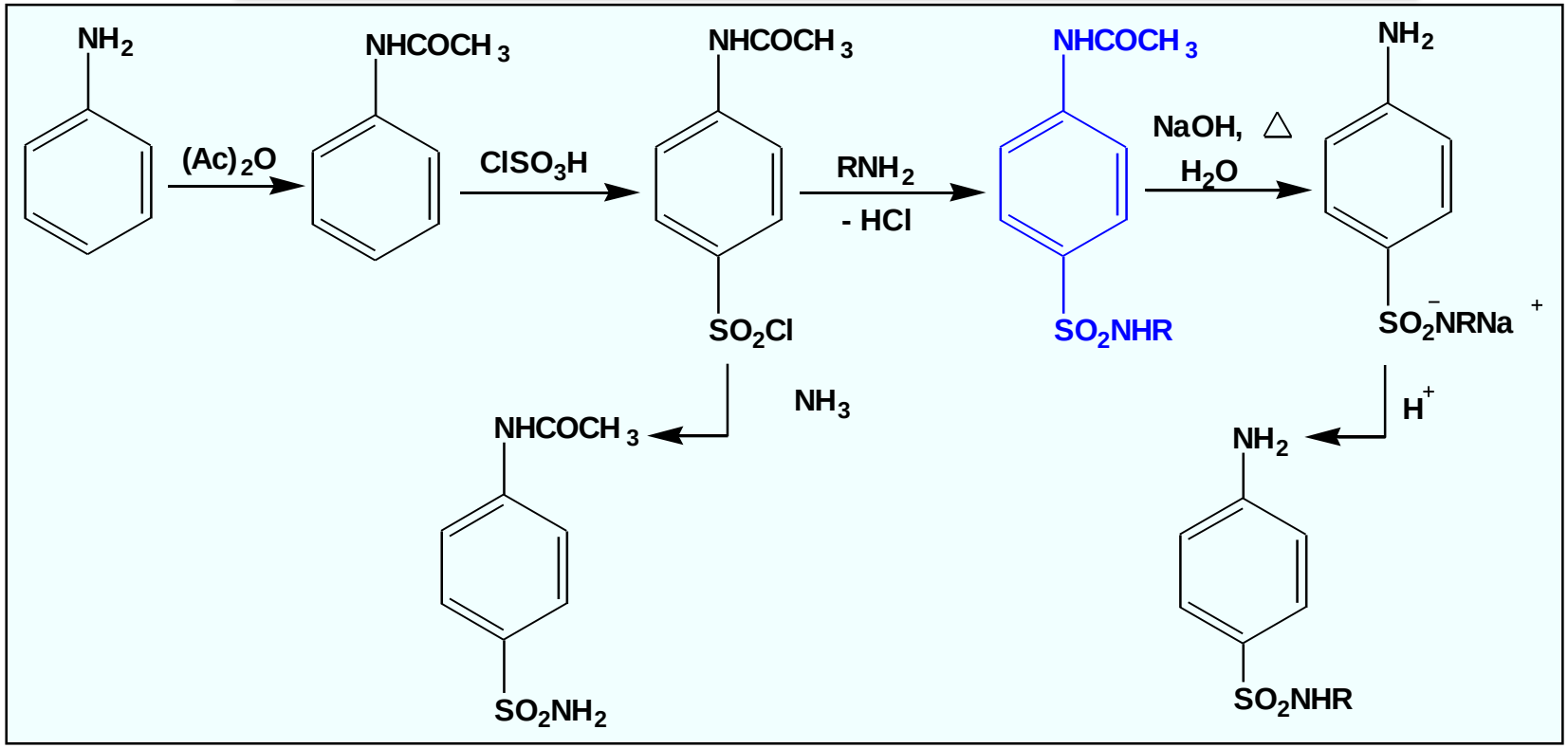
Resonance stabilized

The deprotonated form (in -OH medium) is more stable due to resonance stabilization

So, in when we make urine alkaline,we increase solubility [increase ionized form]

Sulfonamides (Sulfa drugs)

Synthesis of sulfonamides



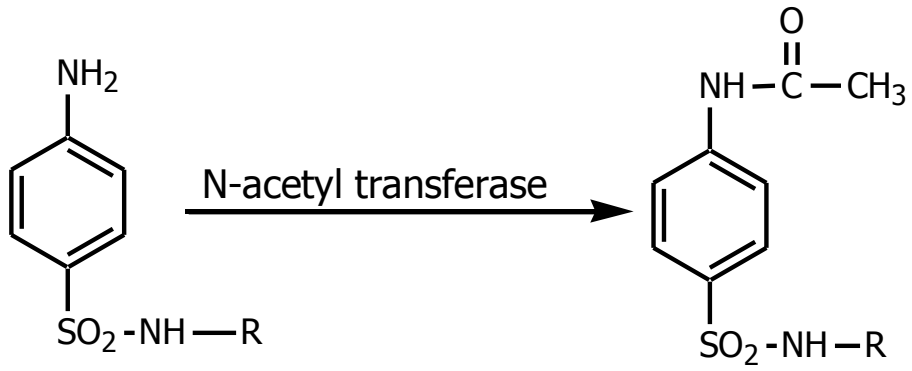
2- Solubility of sulfa drugs

All sulfonamides are insoluble in water except the sodium salts, on the other hand all sulfonamides are soluble in alkali except sulfaguanidine, while all sulfonamides are soluble in acids.

Sulfonamides (Sulfa drugs)

Metabolism:

- By N4-acetylation: sulfonamides excreted as it's + N4-acetate + glucuronide [both are inactive]
- N4-acetate is less water soluble than parent drug, which lead to increase tendency of crystalluria



[less water soluble than parent drug so, make crystalluria]

Crystallurea: precipitation of sulfonamide (has low water solubility) which may cause kidney damage

Sulfonamides (Sulfa drugs)

Crystallurea & PKa

- According to the following equation:

$$pka_{drug} = pH_{urine} + \log \frac{\text{Unionized form of the drug}}{\text{Ionized form of the drug}}$$

- If pH of urine = pka of drug ⟹ ionized/unionized = 1
- If pka of drug > pH of urine ⟹ unionized/ionized >1 ⟹ ↓ soublility
- If pka of drug < pH of urine ⟹ unionized/ionized <1 ⟹ ↑ soublility

Sulfonamides (Sulfa drugs)

Crystallurea & PKa

- According to the following equation:

$$pka_{drug} = pH_{urine} + \log \frac{\text{Unionized form of the drug}}{\text{Ionized form of the drug}}$$

- pH of urine is about 6 & pka of sulfanilamide is 10.4 → so present in urine in unionized form → ↓↓ solubility → crystalluria & bleeding.

Sulfonamides (Sulfa drugs)

Crystallurea & PKa

To solve problem of crystalluria:

- 1. Drinking large amount of water ⇒ ↑ urine flow by ↑ rate of glumerular filtration.
- 2. Combination therapy [triple therapy] : using mixed sulphonamides [3 sulpha drugs: Sulfadiazine + Sulfamerazine + Sulfamethazine] ⇒ only 1/3 of the amount of each drug is used giving the same bacterial action but each one is present in amount less that its solubility product ⇒ no precipitation.
- 3. ↑ pH of urine by alkalinization [using $NaHCO_3$]
- 4. ↓ pka of drug by N1-substitution with electron-withdrawing group [as heterocycle or acyl group]

Sulfonamides (Sulfa drugs)

Crystalluria & PKa

Question

if pka of sulfisoxazole is 5, determine its risk of crystalluria.

$$5 = 7 + \log \frac{\text{Unionized}}{\text{Ionized}}$$

$$\log \frac{\text{Unionized}}{\text{Ionized}} = -2 \quad \Rightarrow \quad \frac{\text{Unionized}}{\text{Ionized}} = \frac{1}{100}$$

- So, it's present mainly in ionized form ? more soluble ? ? risk of crystaluria.

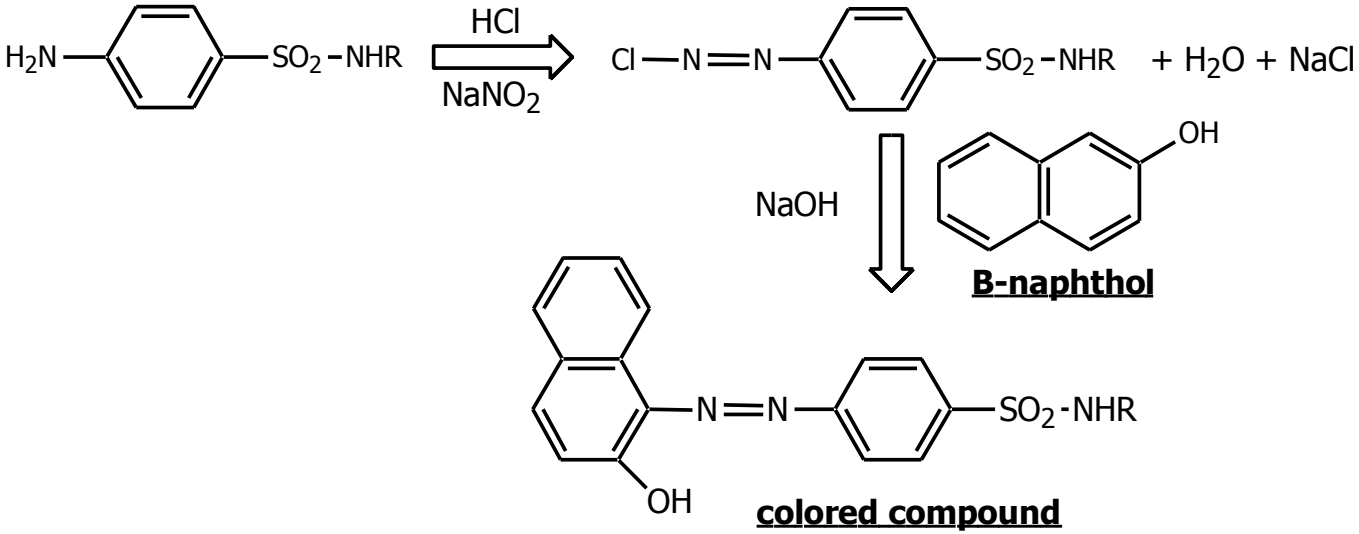
Sulfonamides (Sulfa drugs)

Assay of sulfonamide:

[1] Methods depends on aromatic amino group [N4] : Diazotization

1. Dissolve in dil.HCl & titrate ≠ M/10 $NaNO_2$ ⍰ diazonium salt.
2. E.p. is determined by ;

- KI/starch as external indicator.
- Potentiometrically.
- Colorimetrically ⍰ by coupling diazonium salt with ⍰-naphthol in NaOH ⍰ colored compound.

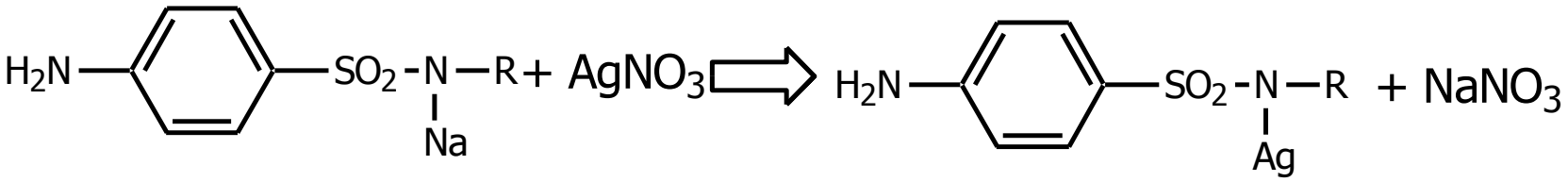


Sulfonamides (Sulfa drugs)

Assay of sulfonamide:

[2] Methods depend on acidity of sulphonamides [-SO2N1H2]

[a] Non-aqueous titration	[b] Argentometric method [Back titration]
• As they are weak acids → disslove in pyridine or DMF [basic solvent] & titrate ≠ $NaOCH_3$. • E.p. determined using thymol blue as indicator.	• Add known xss of std. $AgNO_3$ in NaOH → insol.Ag Salt + equivalent amount of HNO_3. • Ag salt is filtered out. • Either back titration of xss unreacted $AgNO_3$ in Filtrate ≠ NH_4SCN & ferric alum indicator [Volhard]



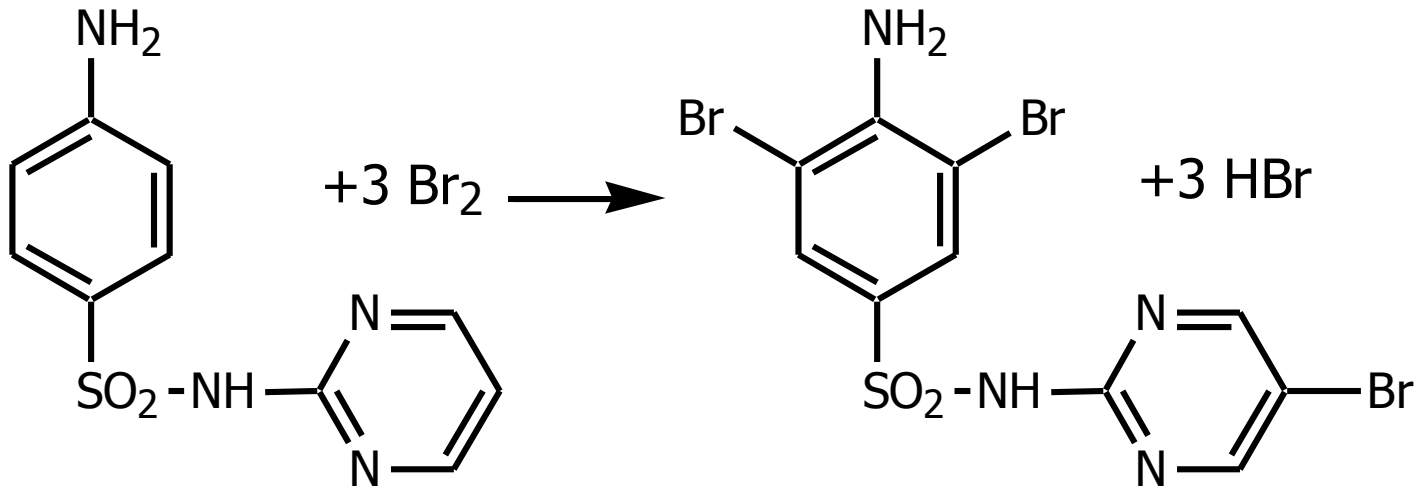
Sulfonamides (Sulfa drugs)

Assay of sulfonamide:

[3] Bromometric method

1. Add known xss of standard Br_2 solution in HCl → bromination of sulphonamides.
2. xss Br_2 determined by adding KI → I_2 → titrated ≠ std $Na_2S_2O_3$

e.g. Sulfadiazine



Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

- SYSTEMIC SULFONAMIDES [ORAL / ABSORBABLE]
- TOPICAL SULFONAMIDES [SKIN / EYE]
- INTESTINAL SULFONAMIDES [ORAL / NON-ABSORBABLE]

[i] Systemic Sulfoanmides

Used in treatment of systemic infections.
Classified according to rate of excretion [$t_{1/2}$] into:

SHORT ACTING	MEDIUM ACTING	LONG ACTING
Taken every 6 hrs	Taken every 8-12 hrs	Taken every 24 hrs
$t_{1/2}$ < 10 hrs	$t_{1/2}$ = 10-24 hrs	With slow excretion rate

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

- SYSTEMIC SULFONAMIDES [ORAL / ABSORBABLE]
- TOPICAL SULFONAMIDES [SKIN / EYE]
- INTESTINAL SULFONAMIDES [ORAL / NON-ABSORBABLE]

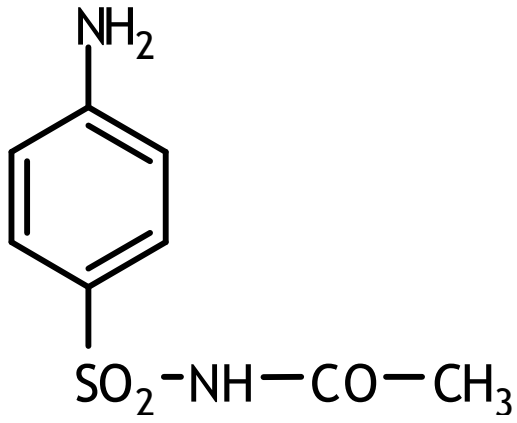
[i] Systemic Sulfoanmides

- N^1-ACYL DERIVATIVE
- N^1- HETEROATOMIC DERIVATIVE
  - PYRIMIDINE DERIVATIVES
  - PYRIDAZINE DERIVATIVES
  - ISOXAZOLE DERIVATIVES
  - THIADIAZOLE DERIVATIVES

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[1] N1-Acyl Derivatives



N-[(4-aminophenyl) sulfonyl] acetamide
OR [N^1-acetyl sulphanilamide]

- Water soluble, its solution with pka 5.4 [acidic] → ↓↓ risk of crystalluria.
- Its Na salt is less alkaline than Na salts of other sulfonamides → non-irritant to mucous membrane ⍰ used as eye drops till 30 % concentration.
- Can be used for urinary tract infection [why?] → it's highly soluble with t1/2 = 7 hrs [rapid excretion]

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative

[ii] Pyridazine Derivative

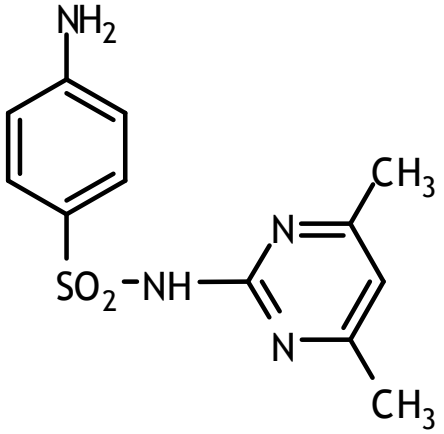
[iii] Isoxazole Derivative

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative (short acting)



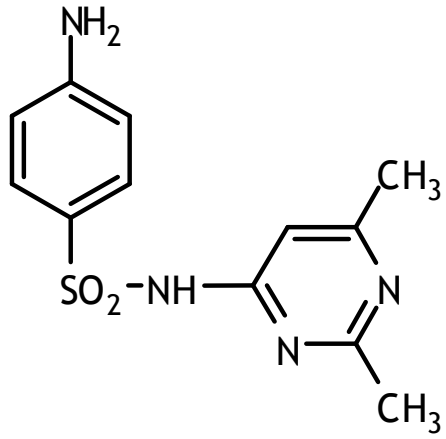
Sulfamethazine

$t_{1/2}$ = 7 hrs / pka = 7.2

More water soluble > sulfadiazine & sulfamerazine in acidic urine [pH=5.5], but lower activity in vitro & in vivo.

Used in **combination sulfa** [Tri-sulfapyrimidine therapy]

N^1(4,6-dimethyl- 2- pyrimidinyl) Sulphanilamide



Sulfisomidine

$t_{1/2}$ = 7.5 hrs

The most water soluble of pyrimidine derivatives → ↓↓ tendency of crystalluria.

N^1(**2**,6-dimethyl- **4**- pyrimidinyl) Sulphanilamide

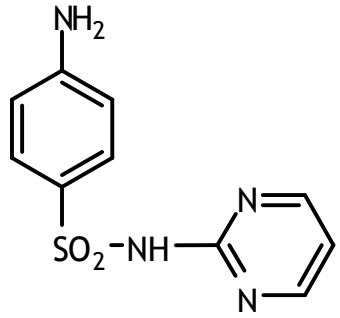
Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative (moderate or intermediate acting)

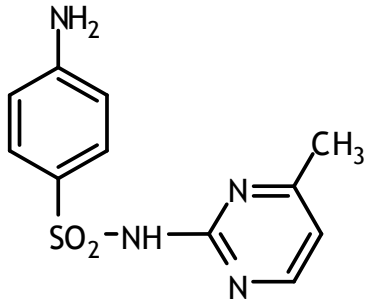
Sulfadiazine



$t_{1/2}$ = 17 hrs / pka = 6.3
Broad spectrum, the drug of choice in UTI.
$NaHCO_3$ is co-given [why ?]
Uses:
Na salt as 5 % solution(IV) : In Meningitis [penetrate into CSF].
Ag salt : topically in burns.

N^1(2- pyrimidinyl) Sulphanilamide

Sulfamerazine



$t_{1/2}$ = 27 hrs
Similar properties to sulfadiazine,but:
With more water solubility.
More absorbable.
Less excretion rate.
Higher blood level can be obtained with a similar dose.

N^1(4-methyl-2- pyrimidinyl) Sulphanilamide

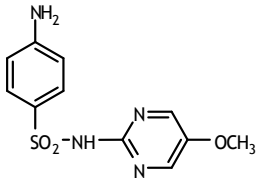
Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

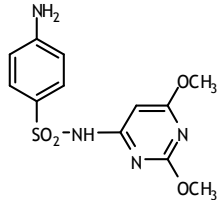
[i] Pyrimidine Derivative (long acting)

Sulfameter



N^1(5-methoxy -2- pyrimidinyl) Sulphanilamide

Sulfadimethoxine



N^1(2,6-dimethoxy-**4**- pyrimidinyl) Sulphanilamide

Long duration of action due to **presence of OCH_3** :

↑ plasma protein binding.

Drug-Plasma protein complex is too large to pass through kidney glumerular membrane → ↓ excretion → long duration.

This binding also ↓ free form of drug → ↓ metabolism → longer duration.

As a result of ↓ excretion → may cause **hypersensitivity** upon accumulation.

$t_{1/2}$ of Sulfameter is 37-48 hrs & for Sulfadimethoxine is 40 hrs.

sulfameter with **bitter taste** → not used in liquid preparations → **make N^1-acetyl derivative [Prodrug].**

Sulfonamides (Sulfa drugs)

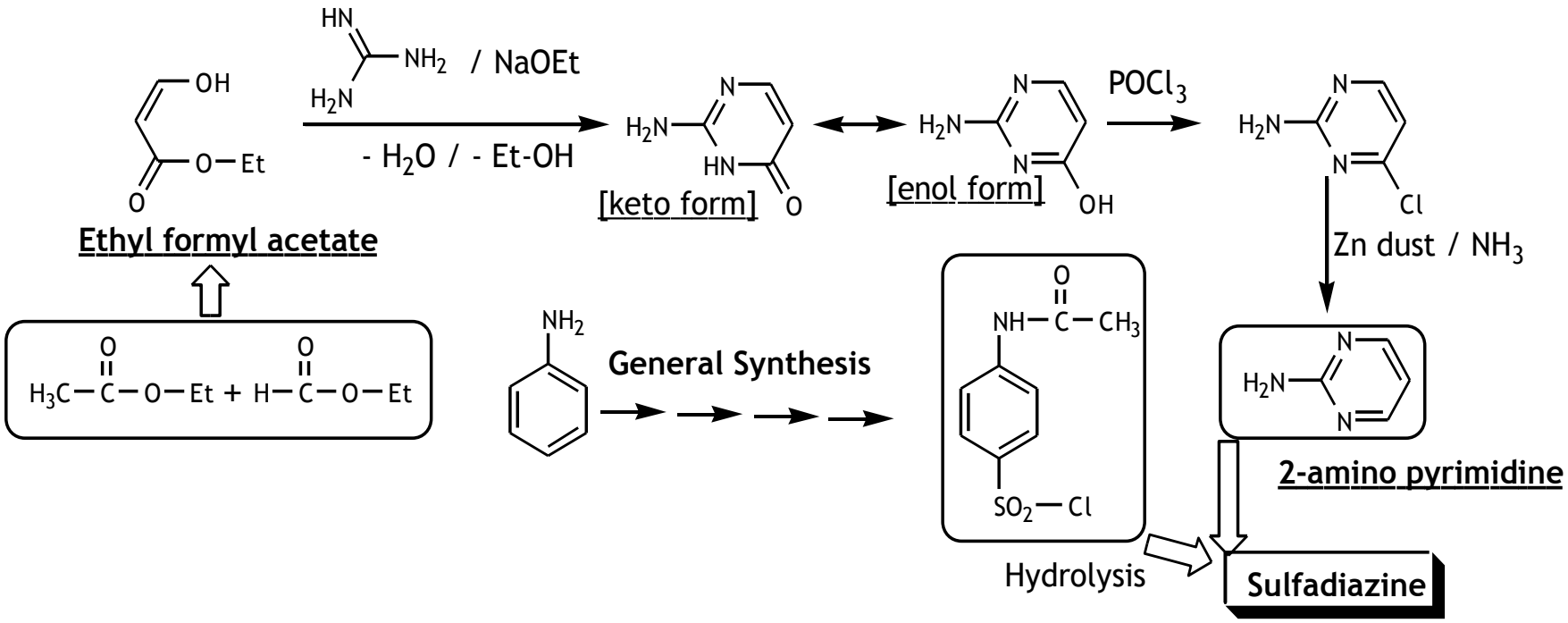
Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative

Synthesis of Pyrimidine derivatives:

Synthesis of Sulfadiazine



Sulfonamides (Sulfa drugs)

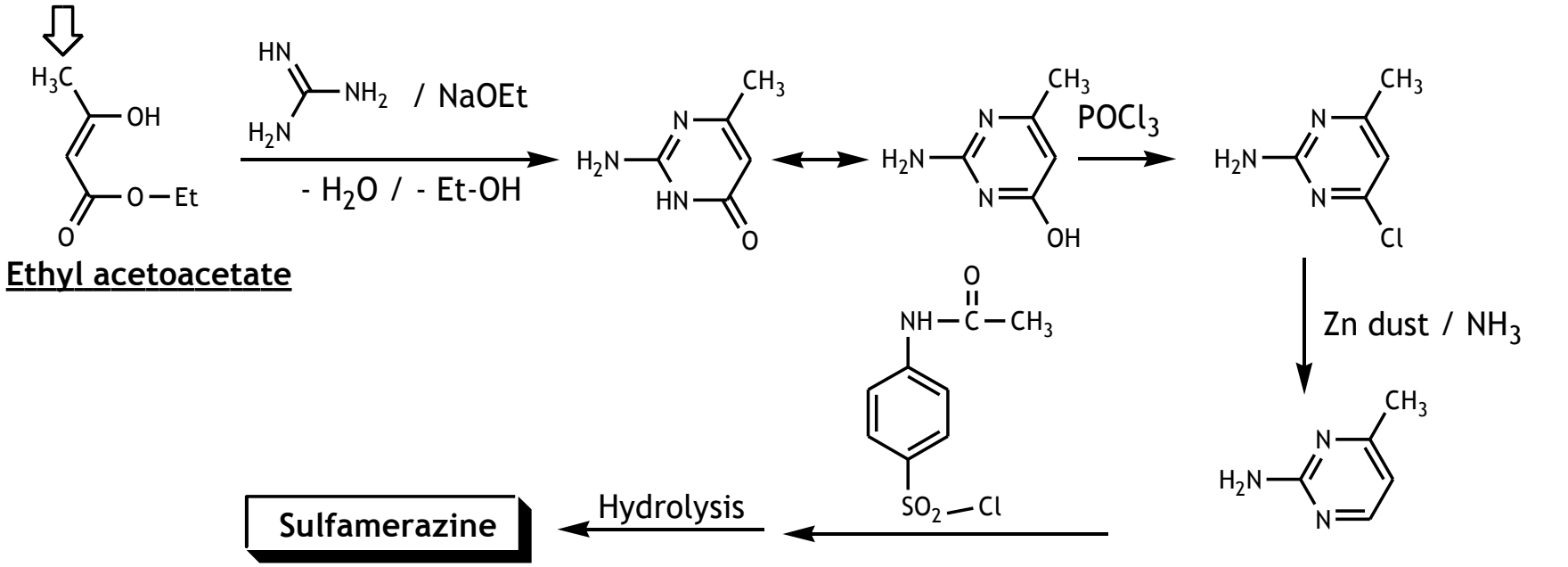
Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative

Synthesis of Pyrimidine derivatives:

Synthesis of Sulfamerazine



Sulfonamides (Sulfa drugs)

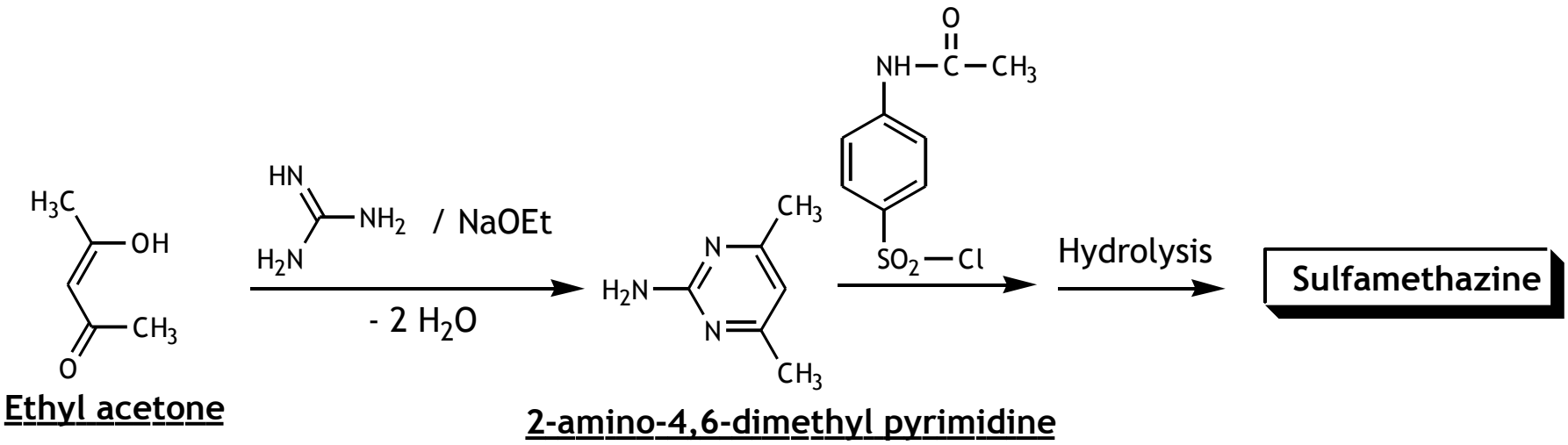
Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[i] Pyrimidine Derivative

Synthesis of Pyrimidine derivatives:

Synthesis of Sulfamethazine



Ethyl acetone

2-amino-4,6-dimethyl pyrimidine

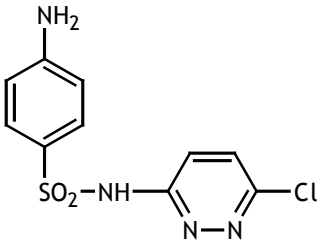
Sulfonamides (Sulfa drugs)

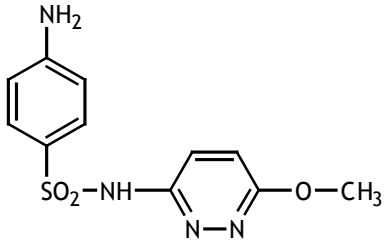
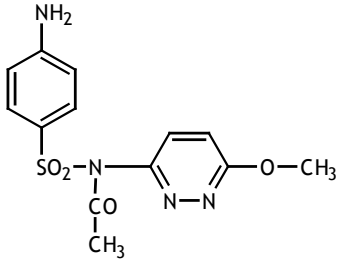
Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[ii] Pyridazine Derivative

[ii] Pyridazine Derivative

Sulfachloropyridazine	
 N^1(6-chloro-3-pyridazinyl) Sulphanilamide	• $t_{1/2}$ = 8 hrs → short acting. • Used in treatment of urinary tract infections.

Sulfamethoxypyridazine	Sulfamethoxypyridazine acetyl
 N^1(6-methoxy-3-pyridazinyl) Sulphanilamide	 N^1-acetyl-N^1(6-methoxy-3-pyridazinyl) Sulphanilamid
• $t_{1/2}$ = 37 hrs → long acting [why?] , due to presence of methoxy group. • With bitter taste.	• **PRODRUG** for sulfamethoxypyridazine → ↓ bitter taste → used for pediatrics. • Inactive in vitro → activated by deacetylation in intestine.

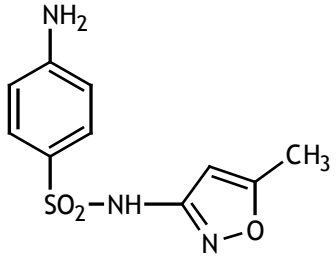
Sulfonamides (Sulfa drugs)

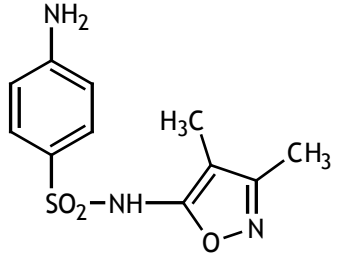
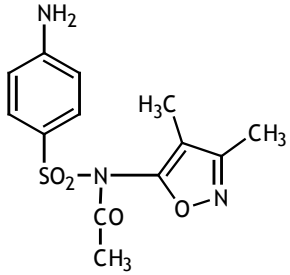
Classification of Sulfonamides

[2] N1-Heteroatomic Derivatives

[iii] Isoxazole Derivative

[iii] Isoxazole Derivative

Sulfamethoxazole	
 N^1(5-methyl-**3**-isoxazolyl) Sulphanilamide	• $t_{1/2}$ = 11 hrs → short acting. • Not rapidly absorbed as sulfisoxazole → its peak blood level is only about 50 %.

Sulfaisoxazole	Sulfaisoxazole acetyl
 N^1(3,4-dimethyl-**5**-isoxazolyl) Sulphanilamide	 N^1-acetyl-N^1(3,4-dimethyl-**5**-isoxazolyl) Sulphanilamide
• $t_{1/2}$ = 6 hrs → short acting. • Rapidly absorbed. • **Highly water soluble** → no need for using alkalinizing agent with it. • With bitter taste.	• **PRODRUG** for sulfaisoxazole → ↓ bitter taste → used for liquid oral preparations. • Inactive in vitro → activated by deacetylation in intestine. • Less soluble than sulfisoxazole.

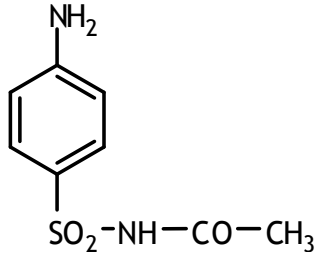
Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] topical Sulfoanmides

Sulfacetamide :

[1] N^1-Acyl Derivatives

Sulfacetamide	
 N-[(4-aminophenyl) sulfonyl] acetamide OR [N^1-acetyl sulphanilamide]	• Water soluble, its solution with pka 5.4 [acidic] → ↓↓ risk of crystalluria. • Its Na salt is **less alkaline** than Na salts of other sulfonamides → **non-irritant to mucous membrane** → used as **eye drops** till 30 % concentration. • Can be used for **urinary tract infection** [why?] → it's highly soluble with $t_{1/2}$ = 7 hrs [rapid excretion]

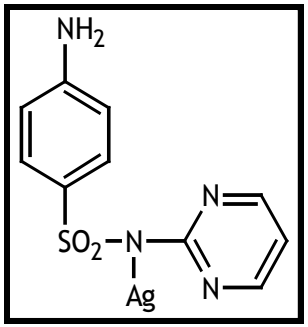
Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] topical Sulfoanmides

Sulfadiazine Silver [Silvadene]

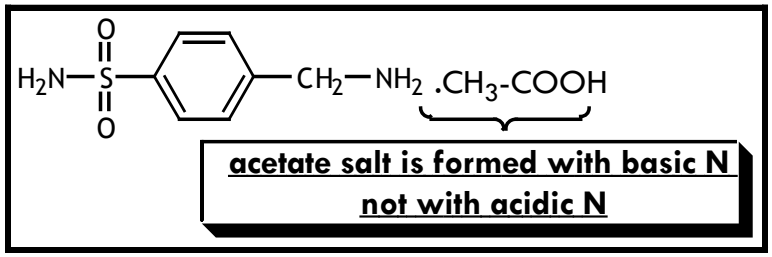
Mafenide acetate

Sulfadiazine Silver [Silvadene]	
	• Applied in <u>water-miscible cream</u> [**Dermazine®**] → active topically ≠ *Pseudomonas* species → used in **<u>burn therapy</u>** [that *Pseudomonas* is responsible for failure of therapy] • Slightly soluble, **<u>Not</u>** penetrate cell wall but <u>act on external cell structures</u>. • Prepared by mixing equimolar amount of **<u>$AgNO_3$</u>** & **<u>Na sulfadiazine</u>** [both dissolved in water].

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[2] topical Sulfoanmides

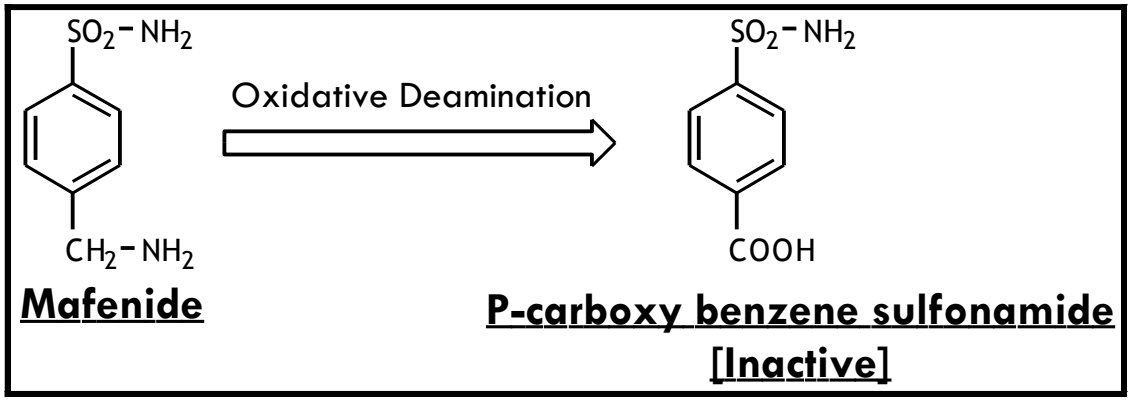
Mafenide acetate	
	• **NOT TRUE SULFONAMIDE COMPOUND [NOT TYPICAL SULFONAMIDE]** • Not inhibited by PABA [its M.O.A. involve different **unknown mechanism** than true sulfonamides]. • Not affected by pH. • Effective ≠ *Clostridium welchii* in topical use for infected wounds. • Not effective orally. • Used alone or with antibiotics in ttt of slow healing infected wounds. • If used in large quantities → **metabolic acidosis**. So, a series of new organic salts was prepared. • The **acetate derivative** in ointment base is the most efficient.

Classification of Sulfonamides

[2] topical Sulfoanmides

Mafenide metabolism

METABOLISM:



Both Mafenide & its metabolite [P-carboxy benzene sulfonamide] cause **INHIBITION OF CARBONIC ANHYDRASE ENZYME** → **METABOLIC ACIDOSIS**.

Sulfonamides (Sulfa drugs)

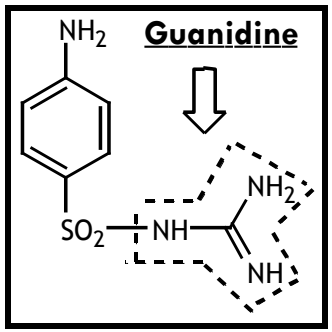
Classification of Sulfonamides

[3] non-absorbable Sulfoanmides

[i] Topical Sulfonamides : Sulfadiazine Ag & Mafenide acetate.

[ii] Intestinal Sulfonamides

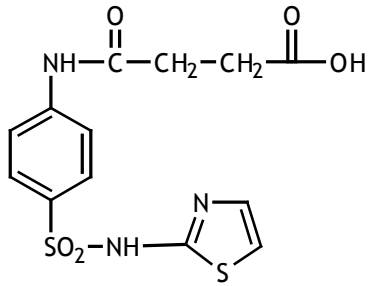
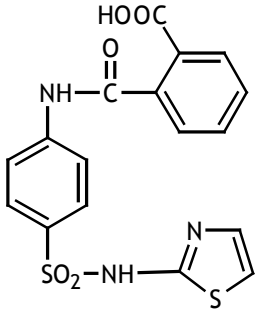
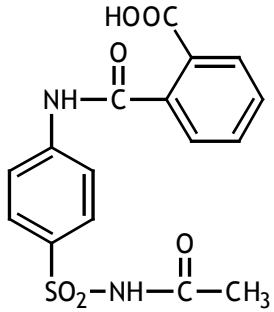
- They are **PRODRUGS** designed to be poorly absorbed, in large intestine → cleavaged → free sulfonamide "active".
- Used in treatment of intestinal infections, ulcerative colitis & reduction of bowel flora.

sulfaguanidine
 N^1-amidino sulfanilamide
• **Guanidine is a basic moiety that cause:** 1. ↓ absorption. 2. ↓ lipid solublility. • Poorly absorbed [with additional basic group] → not absorbed from GIT → high local concentration.

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

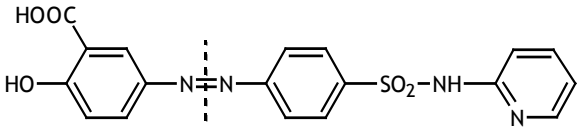
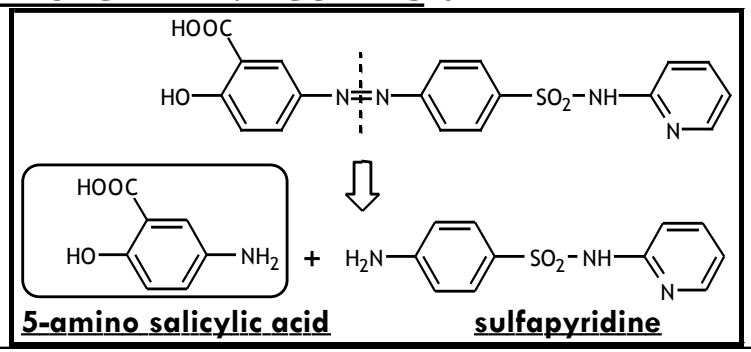
[3] non-absorbable Sulfoanmides

N^4-substituted Sulfonamides **[Acylation with Dicarboxylic acids "Succinic & Phthalic acids]**		
Succinyl sulphathiazole	Phthalyl sulphathiazole	Phthalyl sulphacetamide
 2-(N^4-succinyl sulfanilamide) thiazole	 2-(N^4-**phthalyl** sulfanilamide) thiazole	 N^4-**acetyl**-N^4-phthalyl sulfanilamide
They have additional acidic group → poorly absorbed from GIT.		
They are **PRODRUGS** → activated in vivo by slow hydrolysis giving ↑ local concentration.		
With little use now		

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

[3] non-absorbable Sulfoanmides

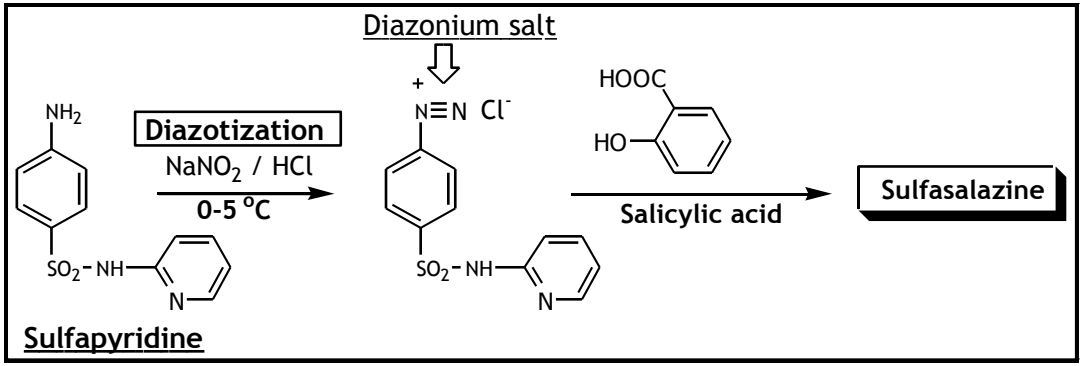
sulfasalazine	
 5-[4-(2-pyridyl sulfamoyl) phenyl azo] salicylic acid	**ONLY SULFAPYRIDINE DERIVATIVE.** **ONLY USED IN ULCERATIVE COLITITS.** • Water insoluble, broken in body giving: **m-amino saicyclic acid** [anti-inflammatory] + **Sulfapyridine** [anti-bacterial] → so,it acts as carrier for 5-amino salicylic acid → **USED IN ULCERATIVE COLITIS** it 

Sulfonamides (Sulfa drugs)

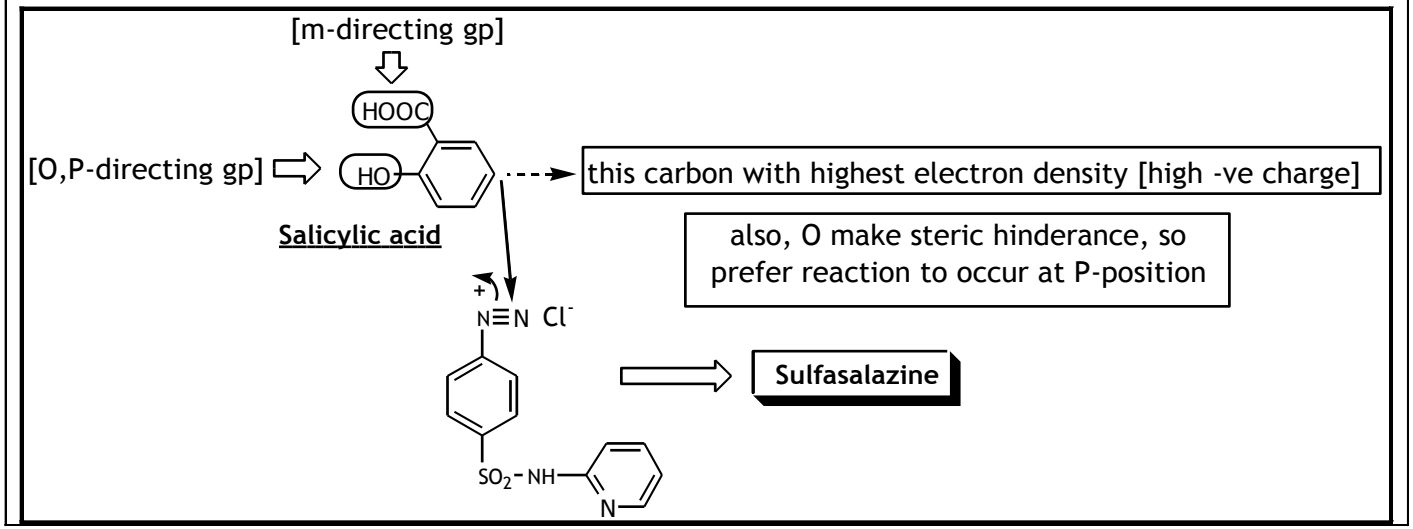
Classification of Sulfonamides

[3] non-absorbable Sulfoanmides

Synthesis:



It occurs by **electrophilic substitution reaction** at P-position of salicylic acid [why?]



Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

Adverse effects of sulfonamides therapy:

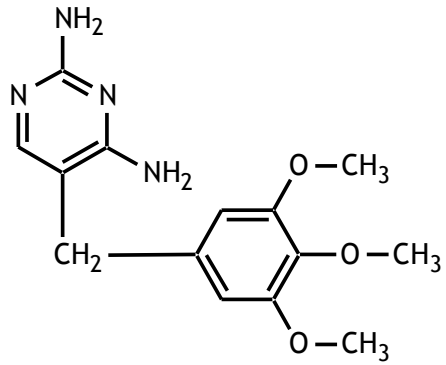
Gastrointestinal distress.
Hemolytic anemia.
Hepatitis.
Stevens-Johnson Syndrome [sever skin eruption].
Crystalluria.

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

Combination of sulfonamides with Dihydrofolate Reductase Inhibitor

Trimethoprim



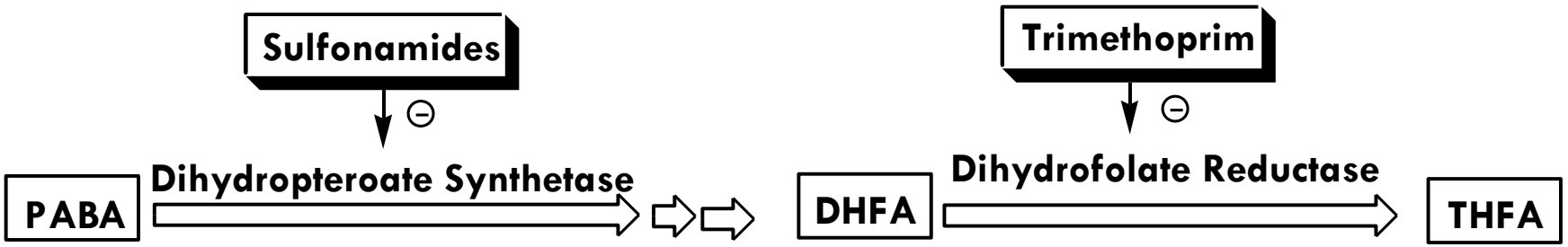
It's **potent anti-bacterial** by inhibition of DHFR enzyme → → stop bacterial growth.
Selective in action → 100.000 times more active ≠ bacterial DHFR relative to mammalian DHFR. [used for **UTI**]
Combined with **Sulfamethoxazole** as both have the same pharmacokinetic properties [t1/2 = hrs like that of sulfamethoxazole] → excreted at about the same time.[important condition for combination between two drugs]

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

Combination of sulfonamides with Dihydrofolate Reductase Inhibitor

M.O.A of combination:



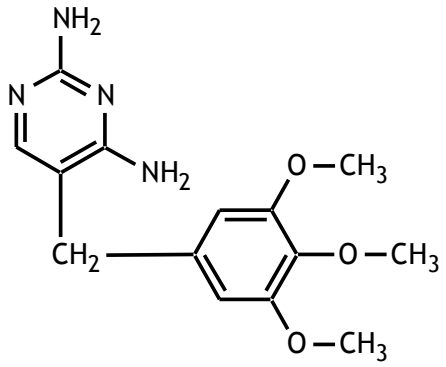
Remember☺ : ↓ THFA synthesis → ↓ purine & pyrimidine bases synthesis → ↓ DNA synthesis → stop growth of bacteria.

Sulfonamides (Sulfa drugs)

Classification of Sulfonamides

Combination of sulfonamides with Dihydrofolate Reductase Inhibitor

Trimethoprim



Trimethoprim combined with Sulfamethoxazole [Sutrim®][Septazole®][Septrin®]

<u>Advantages of this combination:</u>

1. Synergism due to sequential blockage.
2. Avoid development of resistance [if use sulfamethoxazole alone].
3. Broader spectrum of activity.
4. Bactericidal instead of Bacteriostaic.

Sulfonamides (Sulfa drugs)

Sulfa drugs

Important notes

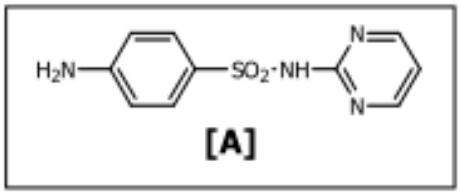
Sulfonamides
• Prototype is Sulfanilamide [from prontosil prodrug]. • Bacteriostatic NOT bactericidial • Act by competitive inhibition of dihydropteroate synthetase enzyme → inhibit folic acid synthesis → inhibit DNA synthesis. • Structurally similar to PABA → as structure more similar to PABA, it becomes more active. • Crystalluria → sulpha & acetyl metabolites are sparingly soluble in water. • ↑ pH or urine or ↓ pka of drug → ↓ risk of crystalluria. • ↓ pka → ↑ solubility → ↓ risk of crystalluria → UTI. • Assay: depend on acidity [non-aqueous/argentometry], basicity [diazotization] / bromometry. • Sulfacetamide Na salt is less alkaline than Na salts of other sulfa drugs → due to higher acidity → eye drops. • ↑ methyl groups on pyrimidine → ↑ solubility. • Methoxy group → bind to plasma proteins → long duration. • To overcome bitter taste of sulfa drugs → acetyl prodrug on N^1. • Ag sulfadiazine [act on external cell structure] & mafenide acetate [NOT true sulfa] → used topically for burns. • Additional basic or acidic moiety → intestinal sulfa. • Sulfasalazine → only pyridine derivative → only used in ulcerative colitits. • Best combination → Sulfamethoxazole [DHPS inhibitor] + Trimethoprim [DHFR inhibitor]

Sulfonamides (Sulfa drugs)

Sample questions

Questions

① **[a] Complete the following :**



[A]

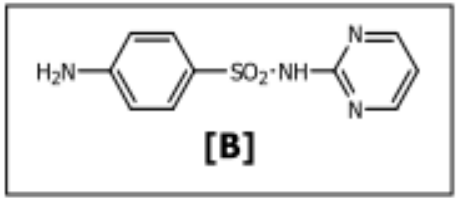
1. Compound A has generic name: ----------
Its chemical name is ----------
It's used for ---------- while its silver salt is used for ----------
It can be assayed by ----------

How can you synthesize compound A:

2. Sulpha triple therapy has the advantages of ----------
3. Sulfonamides are metabolized mainly by ----------
4. Sulfonamides are made more soluble in urine by ----------, ----------, ----------or ----------
5. Duration of action of ---------- [sulfa drug] is long due to ----------
6. Sulfacetamide is used for ---------- due to ----------

7. Sutrim is a combination of ---------- & ----------. Its advantages are ----------, -
---, ---------- & ----------

8. In the bromometric assay for determination of the compound B, it consumes -------- molecules of Bromine.



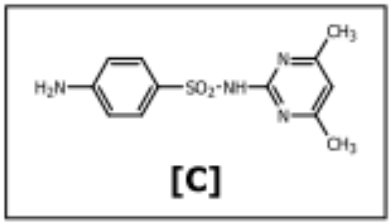
[B]

Sulfonamides (Sulfa drugs)

Sample questions

9. Compound C is more water soluble than sulfadiazine. T F

It has the advantage ----------



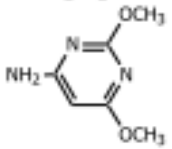
[C]

10. N^4-acylaiton with dicarboxlic acid yields a sulfonamide used in ----------

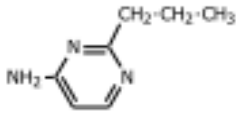
11. The following mechanisms may be seen in species resistant to sulfonamide therapy:
    1. ----------
    2. ----------
    3. ----------
12. The mode of action of sulfonamides involves ----------
13. Sulphonamides are assayed by :
    [a] ----------
    [b] ----------
    [c] ----------
14. The ---------- salt of sulfadiazine is used topically while ---------- salt is used I.V.
15. The basic intestinal sulfonamide is ---------- while the acidic intestinal sulfonamides are ----------, ----------, ----------

7. To design a long acting sulfonamide, the condensation step in preparation of sulpha can be done with:

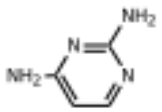
[a]



[b]



[c]



Sulfonamides (Sulfa drugs)

Sulfa drugs

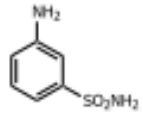
Sample questions

[b] In determination of activity of some sulfa drugs, the following data were reported:

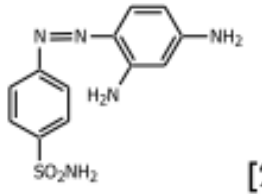
Drug	A) Sulfanilamide	B) Sulfacetamide	C) Sulfamethazine
pka	10.4	7.2	5.4

- Determine which one with the lowest risk of crystalluria [illustrate your answer with calculation].
- C is preferred over A for urinary tract infection. T F
- A is the best one used as eye drops. T F
- Starting from A, how can you synthesize B & C.

[c]



[1]



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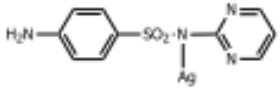

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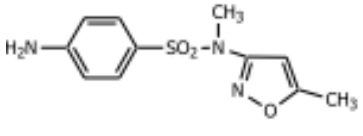

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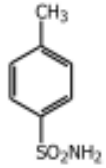

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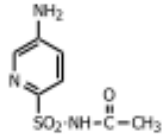


[6]

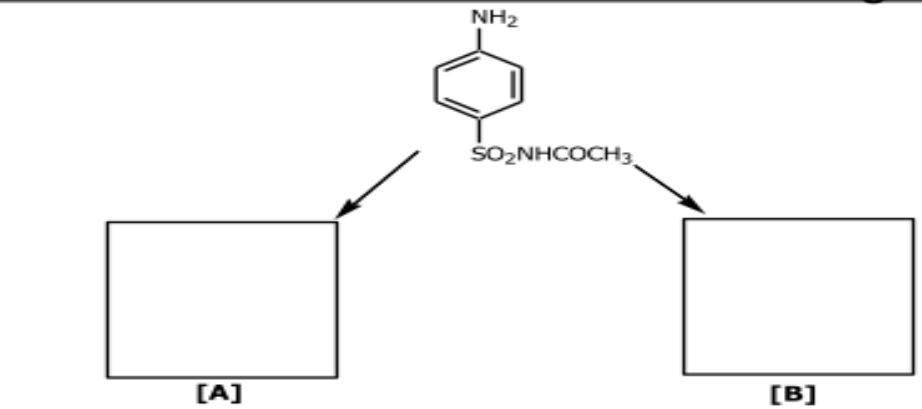
Compound	Active / Inactive	The reason
1		
2		
3		
4		
5		
6		

Sulfonamides (Sulfa drugs)

Sulfa drugs

Sample questions

[a] Modify the drawn structure into two derivatives acting locally :



Drug A : ----------
used as ----------
because ----------

Chemical name :----------

Drug B : ----------
used for ----------
because ----------

Chemical name :----------
---

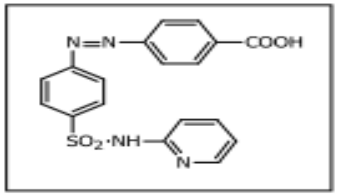
[b] Give a direct assays of sulfadiazine & another back titration.

[c] What's the effect of the following modifications on 4-aminobenzene sulfonamide?

[a] Replacing amino group by methyl amino.
[b] Replacing amino group by amino methyl.
[c] Addition of amidino group to N^1.
[d] Action of acetyltransferase.
[e] Increase pH of urine from 5 to 7.
[f] Substitution of acidic center with 4,6-dimethoxy-2-pyrimidinyl.

[d] A new product with the drawn structure was designed, it's expected to be active in: [Rationalize your answer]

[a] Intestianl infections & ulcerative colitis.
[b] Intestinal infections.
[c] Ulcerative colitis.
[d] Non of the above.



NSAIDS

The end

NSAIDS