SulphonamidesandSulfones

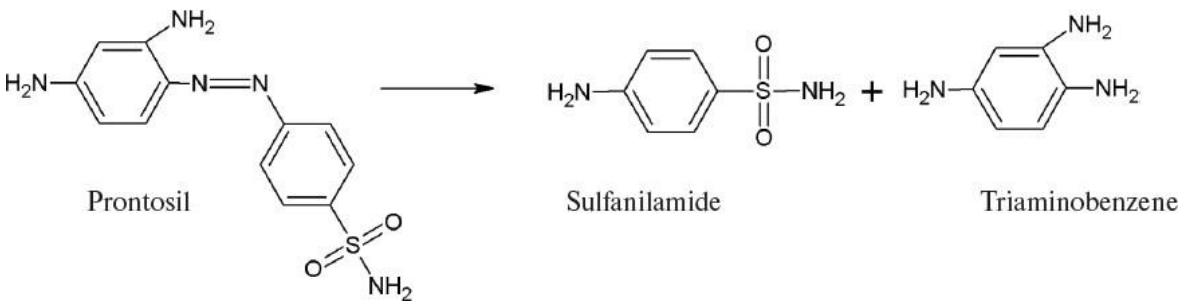
Historicaldevelopment,chemistry,classification,andSARofSulfonamides:Sulphamethizole,Sulphaisoxazole,Sulfamethazine, Sulfacetamide*, Sulphapyridine, Sulphamethoxazole*, Sulphadiazine, Mafenide acetate, Sulfasalazine.

Folatereductaseinhibitors:Trimethoprim*,Cotrimoxazole.

Sulfones:Dapsone*.

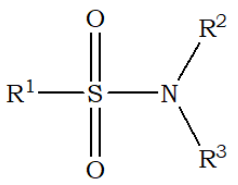
❖ Introduction

- Sulfonamides (Sulphonamides) are a group of man-made (synthetic) medicines that contain thesulfonamidechemicalgroup.Theymayalsobecalledsulfadrugs.
- Some sulfonamides are also devoid of antibacterial activity, e.g., the anticonvulsant (**Sultiame**). The sulfonylureas and thiazide diuretics are newer drug groups based upon the antibacterial sulfonamides.
- The first sulfonamide was trade named Prontosil, which is a prodrug Prontosil, the first commercially available antibacterial with a relatively broad effect (against Gram-positive cocci but not against enterobacteria).

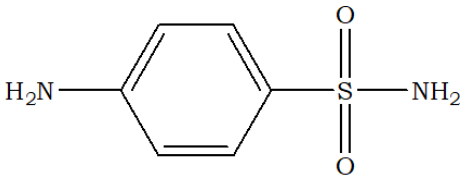


Azoreductionofprontosilisoneexample,whereintestinalbacteriaconvertinactivetherapeuticsinto theirpharmacologicallyactiveform.**Bacterial*azoreductases***presentinthedistalgutcleavetheN-N doublebondandproduceactivemetabolitesulfanilamide.

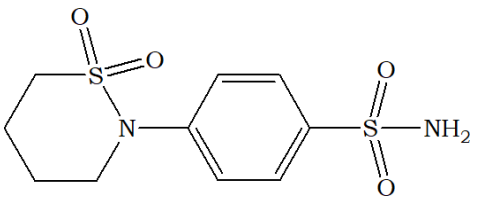
- Allergiestosulfonamidesarecommon.Theoverallincidenceofadversedrugreactionstosulfa antibiotics is approximately 3%, close to penicillin.
- Thegeneralstructureof Sulfonamides.



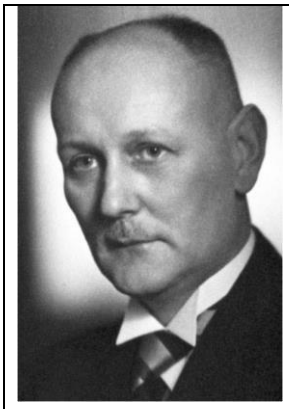
Sulfonamide functional group



Sulfanilamide



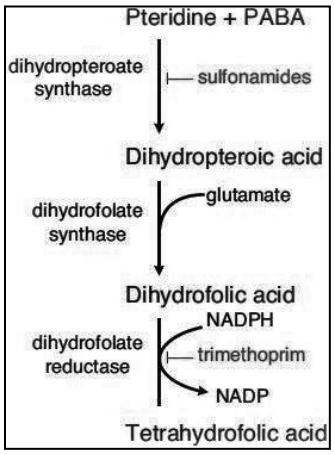
Sultiame

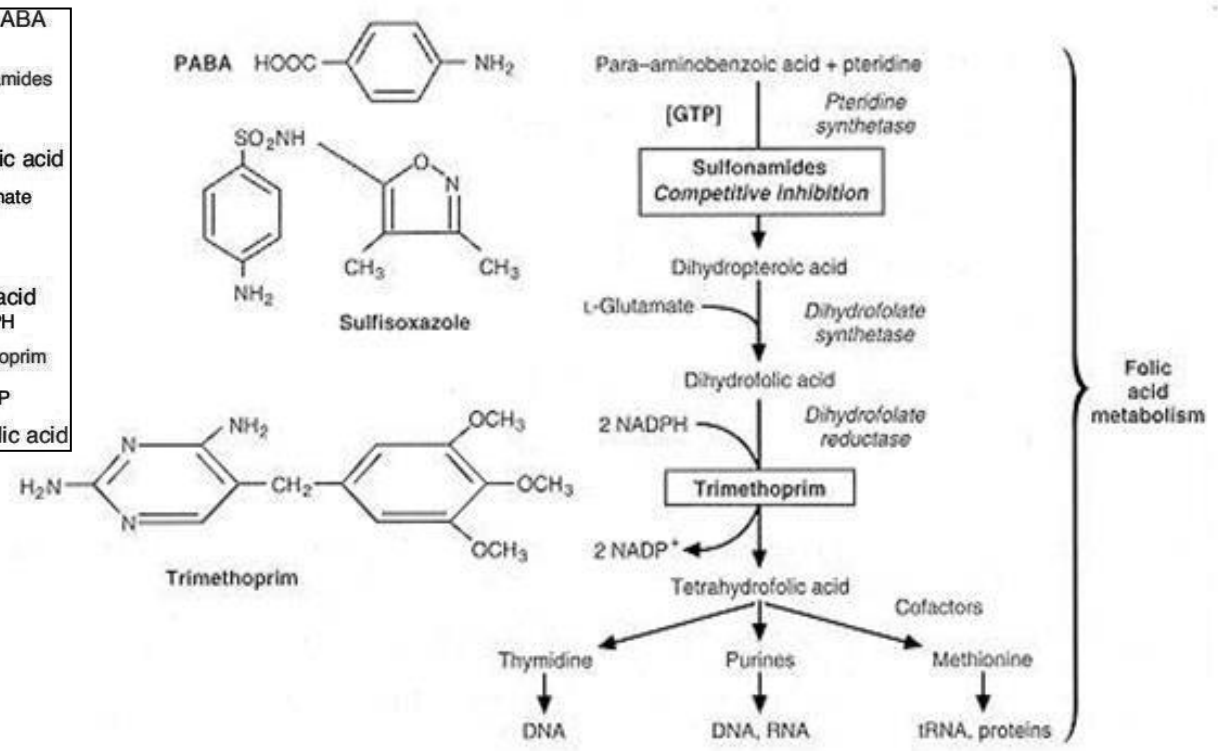


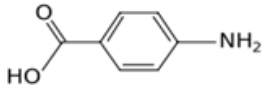
SirGerhardDomagk,(bornOctober30,1895,Lagow,Brandenburg,Germany-diedApril24,1964,Burgberg,nearKönigsfeld,Germany),Germanbacteriologist andpathologist whowas awardedthe1939**NobelPrize**forPhysiology or Medicine for his discovery (announced in**1932**) of the antibacterial effects of**Prontosil**, the first of the **sulfonamide** drugs.

❖ Mechanismofaction:Sulfonamides&Trimethoprim

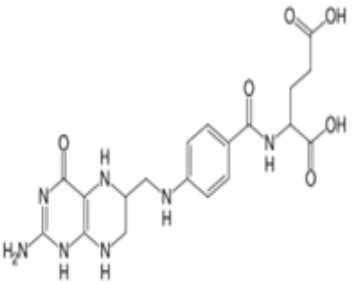
- **Sulfanilamide**is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase. This enzyme normally uses para-aminobenzoic acid (PABA) for synthesizing the necessary folic acid. The inhibited reactionisnormallynecessaryintheseorganismsforthesynthesisoffolicacid.Withoutit,bacteria cannot replicate.
- **Trimethoprim**is a**reversible inhibitor**of***dihydrofolate reductase***, one of the principal enzymes catalyzing the formation of**tetrahydrofolic acid**(**THF**) from**dihydrofolic acid**(**DHF**).**Tetrahydrofolic acid**isnecessaryforthebiosynthesisofbacterial**nucleicacids**and**proteins**andultimatelyfor continued bacterial survival-inhibiting its synthesis, then, results in bactericidal activity. Trimethoprimbinds with a much stronger affinity to bacterial dihydrofolate reductase as compared to its mammalian counterpart,allowingtrimethoprimtoselectivelyinterferewithbacterialbiosyntheticprocesses.
- **Trimethoprim**exertsa**synergisticeffect**with**sulfonamides**.
- **Trimethoprim**isoftengivenincombinationwith**sulfamethoxazole**,whichinhibitstheprecedingstep in bacterial protein synthesis-given together, sulfamethoxazole and trimethoprim inhibit two consecutive steps in the biosynthesis of bacterial nucleic acids and proteins. As a monotherapy trimethoprimisconsideredbacteriostatic,butincombinationwithsulfamethoxazoleisthoughttoexert bactericidalactivity.



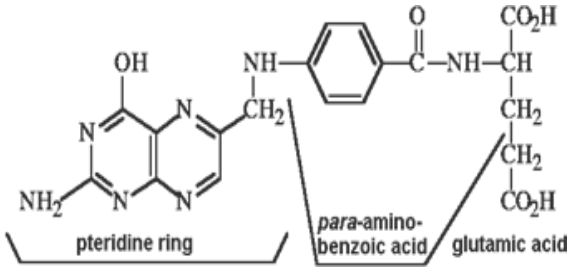




4-Aminobenzoic acid (PABA)



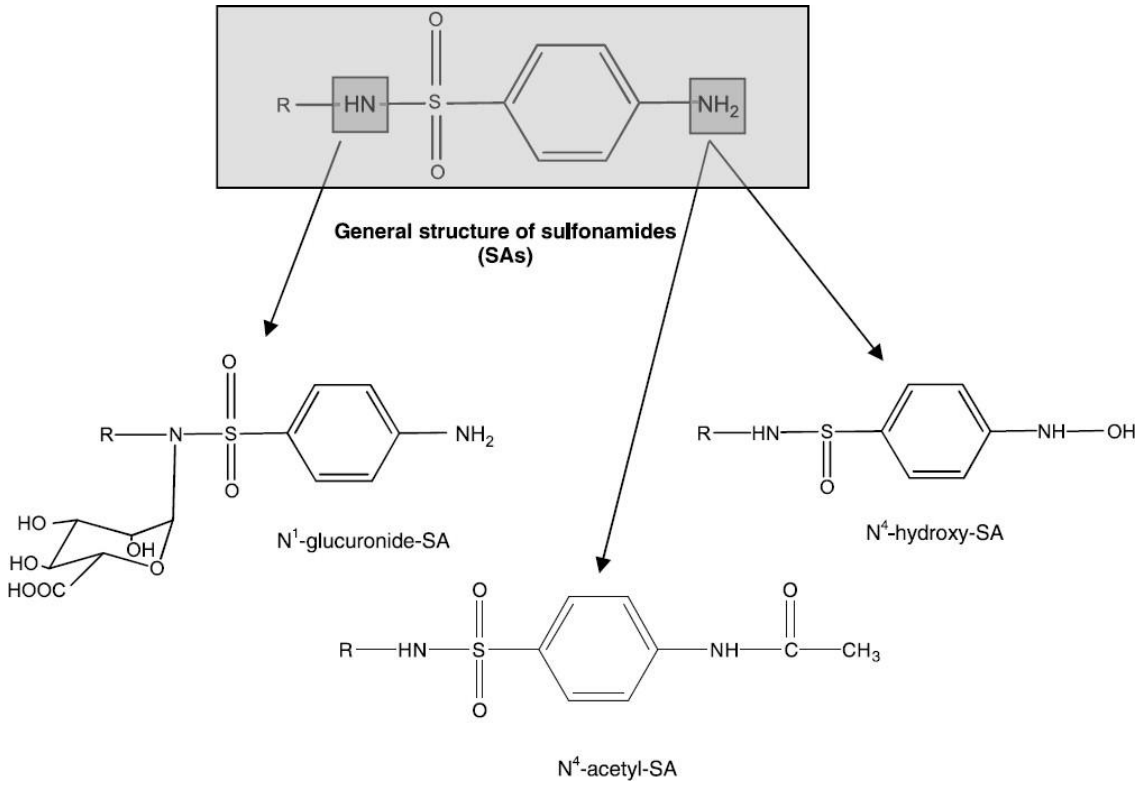
Tetrahydrofolicacid



Folicacid

❖ Absorption,Distribution,Metabolism&Excretion

- Sulfonamidesclass ofdrugsisabsorbedrapidly fromtheGItract.
- Approximately70-100%ofanoraldoseisabsorbed,andsulfonamidecanbefoundintheurinewithin 30 min of ingestion.
- Peakplasmalevelsareachievedin2-6h,dependingonthedrug.
- The small intestine is the major site of absorption, but some of the drug is absorbed from the stomach. Absorption from other sites, such as the vagina, respiratory tract, or abraded skin, is variable and unreliable.
- Allsulfonamidesareboundinvaryingdegreetoplasmaproteins,particularlytoalbumin.
- Sulfonamides are metabolized in the liver. The major metabolite is the**N⁴-acetylated sulfonamide**. Acetylation results in products that have no antibacterial activity but retain the toxic potential of the parent substance.
- Sulfonamides are eliminated from the body partly as the unchanged drug and partly as metabolic products. The largest fraction is excreted in the urine, and the $\mathbf{t_{1/2}}$ depends on renal function.
- In acid urine, the older sulfonamides are insoluble and crystalline deposits may form. Small amountsare eliminated in the feces, bile, milk, and other secretions.



Majormetabolitesofsulfonamideantibiotics.

❖ Sideeffects

- Sulfonamideshavethepotentialtocauseavarietyofuntowardreactions,includingurinarytract disorders,haemopoietic disorders,and hypersensitivityreactions.
- When used in large dose, it may develop a strong allergic reaction. One of the most serious is*StevensJohnson syndrome* (or toxic epidermal necrolysis).
- Some of the original sulfonamide drugs were derived from azo dyes and had the interesting effect of temporarily turning the patient red.
- **N.B-Stevens-Johnsonsyndrome**(SJS)isalife-threateningconditionaffectingtheskin,inwhichdue tocell death theepidermis separates from thedermis. The syndrome is thought to be ahypersensitivity complexaffectingtheskinandthemucousmembranes.

❖ Adversereactions

i) The most common manifestation of ahypersensitivity reaction to sulfa drugs are rash and hives. However, there are several life-threatening manifestations of hypersensitivity to sulfa drugs, includingStevens-Johnson syndrome,toxic epidermal necrolysis,agranulocytosis,hemolyticanemia,thrombocytopenia, andfulminant hepatic necrosis, among others

ii) The sulfonamide antibiotic chemical structures are implicated in the hypersensitivity reactions associated with the class.

- Thefirstisthe**N^1heterocyclicring**,whichcausesatypeIhypersensitivityreaction.
- Thesecondisthe**N^4aminonitrogen**that,inastereospecificprocess,formsreactivemetabolitesthat cause either direct cytotoxicity or immunologic response.

➢ NoteBy:

- **Folic acid:**Folic acid and folate(theanionform)areformsofthewater-solubleVitamin B_9.Theseoccur naturallyinfoodandcanalsobetakenassupplements.FolategetsitsnamefromtheLatin word *folium*.

- **Biologicalrolesoffolate**

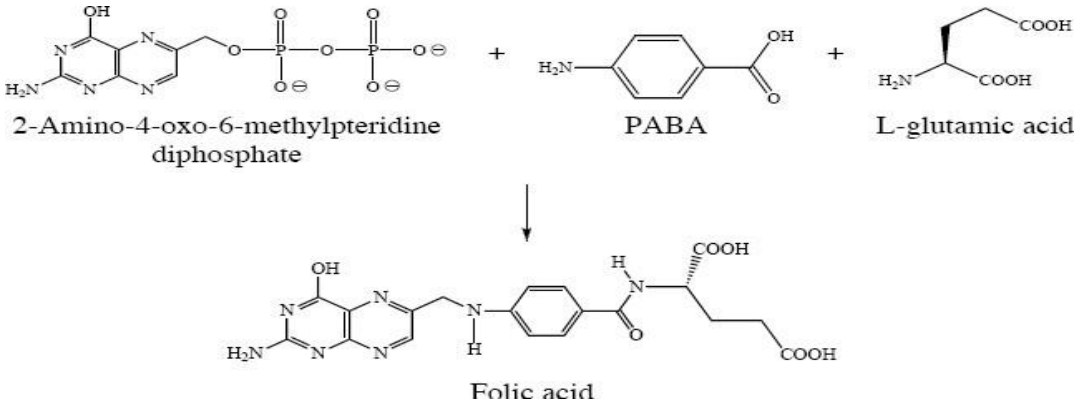
i) Folateisnecessaryfortheproductionandmaintenanceofnewcells.Thisisespeciallyimportant during periods ofrapid cell division and growth such as infancy and pregnancy. Folate is needed to synthesizeDNA bases (most notably thymine, but alsopurine bases) needed for DNA replication. Thus folatedeficiencyhindersDNAsynthesisandcelldivision,affectingmostnotablybonemarrowand cancer,bothofwhichparticipateinrapidcelldivision.

ii) In the form of a series of**tetrahydrofolate**(**THF**) compounds, folate derivatives aresubstratesin a number of single-carbon-transfer reactions, and also are involved in the synthesis of**dTMP**(**2′- deoxythymidine-5′-phosphate**) from**dUMP**(**2′-deoxyuridine-5′-phosphate**). It is a substrate for an importantreactionthatinvolves**vitaminB_{12}**anditisnecessaryforthesynthesisof**DNA**,requiredfor all dividing cells.

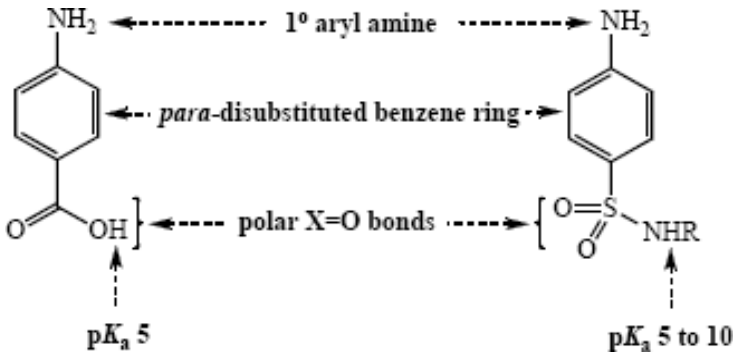
- The pathway leading to the formation of**tetrahydrofolate**(**FH_4**) begins when**folate** (**F**) is reduced to **dihydrofolate**[**DHF**;**FH_2**],whichisthenreducedto**THF**.***Dihydrofolatereductase***catalysesthelast step.**VitaminB_3**intheformof**NADPH**isanecessarycofactorforbothstepsofthesynthesis.

❖ *Whysulfonamideorsulfonamideinhibitfolicacidsynthesismechanism?*

- Cells use folic acid as a single-carbon atom building block for the construction of nucleic acids and other biologicalmolecules.Inhibitionofthisprocesspreventsgrowthandreproductionbutdoesnotdirectly lead to cell death. Bacteria synthesize folic acid from 2-amino-4-oxo-6-methylpteridine diphosphate,*p*-aminobenzoicacid(PABA),andL-glutamicacid.Becausesulfadrugsarestructuralmimicsof PABAthey may bind to dihydropteroate synthetase, one of the enzymes necessary for folic acid synthesis (reversibleandcompetitive inhibition).Withthis enzyme inhibited,folicacidsynthesis isprevented,andcellgrowth and reproduction are halted.



- Inaddition, the twomolecules are ofnearlyidenticallength(6.7Å forPABA versus 6.9Å forsulfanilide), bothareroughlyflat,andbothhaveanequaldistributionofcharge(δ⁺ontheNH₂groupandδ⁻onthe COOH or SO_2NHR groups). This effect can be seen more clearly by examining the electrostatic potential surfaces of these molecules.

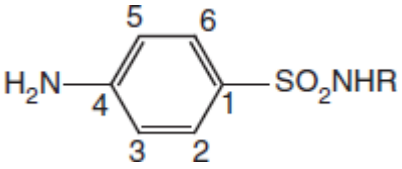


❖ *Why bacterial dihydrofolate reductase is many times more sensitive to Trimethoprim than is equivalent enzyme in humans?*

- Inmicroorganismhumanoneofthekeyenzymes*dihydrofolatereductase*whichreducesdihydrofolate to tetrahydrofolate is many more sensitive to folate antagonist trimethoprim in bacteria than in human becauseof**IC_{50}**values(theconcentrationcausing50%inhibition).

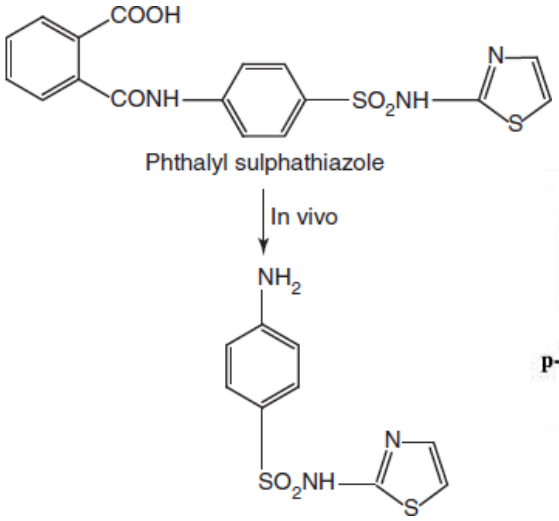
Inhibitor	**IC_{50}(micromol/lit)for*dihydrofolatereductase*enzyme**		
	Human	***Protozoal***	***Bacteria***
Trimethoprim	260	0.07	0.005
Pyrimethamine	0.7	0.0005	2.5
Methotrexate	0.001	0.1	Inactive

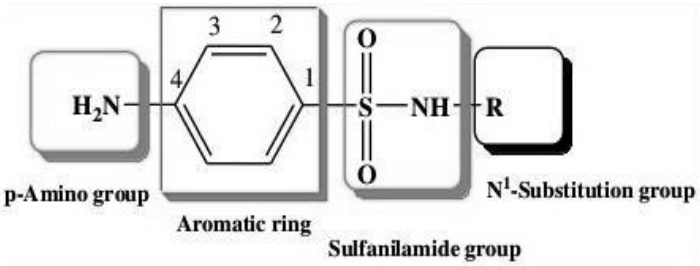
❖ SARofSulphonamides



- ThemajorfeaturesofSARofsulphonamidesincludethefollowing:

- Sulphanilamideskeletonistheminimumstructuralrequirementforantibacterialactivity.
- Theamino-andsulphonyl-groupsonthebenzeneringareessentialandshouldbein**1**and**4position**.
- The**N-4**aminogroupcouldbemodifiedtobeprodrugs,whicharecon*v*ertedtofreeaminofunction *in-vivo*.





- Sulphuratomshouldbedirectlylinkedtothebenzenering.
- Replacementofbenzeneringbyotherringsystemsortheintroductionofadditionalsubstituentsonit decreases or abolishes its activity.
- Exchangeofthe**–SO_2NH**groupby**–CONH**reducestheactivity.
- On**N-1**-substituted sulphonamides, activity varies with the nature of the substituent at the aminogroup. With substituents imparting electron-rich characters to**SO_2group**, bacteriostatic activity increases.
- Heterocyclic substituents lead to highly potent derivatives, while sulphonamides, which contain a single benzeneringat**N-1position**,areconsiderablymoretoxicthanheterocyclicringanalogues.
- Thefreearomaticaminogroupsshouldresideparatothesulphonamidegroup.Itsreplacementat orthoormetapositionresultsincompoundsdevoidofantibacterialactivity.
- Theactiveformofsulphonamideistheionized,maximumactivitythatisobservedbetweenthepKa values **6.6–7.4.**
- Substitutionsinthebenzeneringofsulphonamidesproducedinactivecompounds.
- Substitution of free sulphonic acid**(–SO_3H)** group for sulphonamido function destroys the activity, but replacementbyasulphinicacidgroup**(–SO_2H)**andacetylationof**N-4**positionretainsbacktheactivity.
- *Meta-Sulphonamides*bind to the basic centres of arginine, histidine, and lysine sites of proteins. The binding groups are alkyl, alkoxy, and halides. The binding affects the activity of sulphonamides; protein binding appears to modulate the availability of the drug and its half-life.
- The lipid solubility influences the pharmacokinetic and antibacterial activity, and so increases the half-life and antibacterial activity in vitro.

❖ Sulphonamidescanbeclassifiedinavarietyofways:

1. Onthebasisofthesiteofaction

(i) ***Sulphonamides for general infection:***Sulphanilamide, Sulphapyridine, Sulphadiazine, Sulphamethoxacine, Sulphamethoxazole.

(ii) ***Sulphonamidesforurinarytractinfections***:Sulphaisoxazole,Sulphathiazole.

(iii) ***Sulphonamides for intestinal infections:***Phthalylsulphathiazole, Succinyl sulphathiazole, Sulphasalazine.

(iv) ***Sulphonamidesforlocalinfections:***Sulpahacetamide,Mafenamide,Silversulphadiazine.

(v) ***Sulphonamidesfordermatitis:***Dapsone,Solapsone.

(vi) ***Sulphonamidesincombination:***TrimethoprimwithSulphamethoxazole.

2. Onthebasisofthepharmacokineticproperties

(i) ***Poorly absorbed sulphonamides (locally acting sulphonamides)*****:** Sulphasalazine, Phthalylsulphathiazole, Sulphaguanidine, Salicylazo sulphapyridine, Succinyl sulpha thiazole.

(ii) ***Rapidly absorbed and rapidly excreted (systemic sulphanamides):***Sulphamethoxazole, Sulphaisoxazole, Sulphadiazine, Sulphadimidine, Sulphafurazole, Sulphasomidine, Sulphamethiazole, Sulphacetamide Sulphachlorpyridazine.

(iii) ***Topicallyusedsulphonamides:***Sulphacetamide,Mafenide,Sulphathiazole,Silversulphadiazine.

3. Onthebasisofthepharmacologicalactivity

(i) ***Antibacterialagents:***Sulphadiazine,Sulfisoxazole.

(ii) ***Drugsusedindermatitis***:Dapsone.

4. Onthebasisofthedurationofaction

(i) ***Extra-long-acting sulphonamides*****(half-life greater than 50 h):**Sulphasalazine, Sulphaclomide, Sulphalene.

(ii) ***Long-acting sulphonamides*****(half-life greater than 24 h):**Sulphadoxine, Sulphadimethoxine, Sulphamethoxy pyridazine, Sulphamethoxydiazine, Sulphaphenazole, Sulphamethoxine.

(iii) ***Intermediate-actingsulphonamides*****(half-lifebetween10–24h):**Sulphasomizole, Sulphamethoxazole.

(iv) ***Short-actingsulphonamides*****(half-lifelessthan20h):**Sulphamethiazole,sulphaisoxazole.

(v) ***Injectable*****(solublesulphadrugs):**Sulphafurazole,Sulphadiazine,Sulphamethoxine.

5. Onthebasisofthechemicalstructure

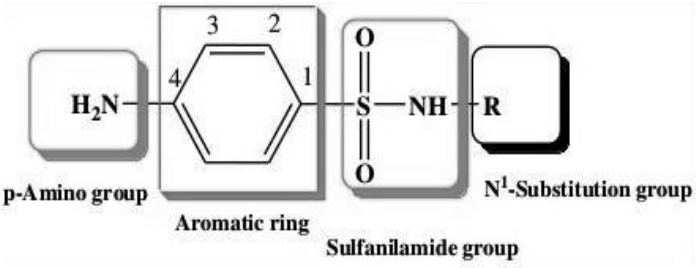
(i) ***N-1substitutedsulphonamide:***Sulphadiazine,Sulphacetamide,Sulphadimidine.

(ii) ***N-4substitutedsulphonamides(prodrugs):***Prontosil.

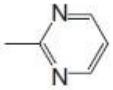
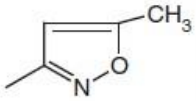
(iii) ***BothN-1andN-4substitutedsulphonamides***:Succinylsulphathiazole,Phthalylsulphathiazole.

(iv) ***Miscellaneous:***Mefenide sodium.

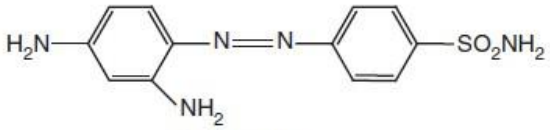
❖ StructuresofSulfonamidederivatives:



N-1 Substituted sulphonamides

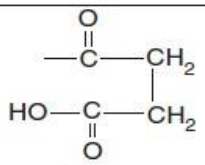
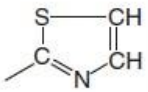
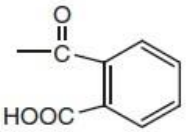
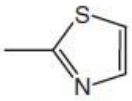
Name	R	R^1
Sulphanilamide	–H	–H
Sulphacetamide	–H	$-COCH_3$
Sulphadiazine	–H	
Sulphamethoxazole	–H	

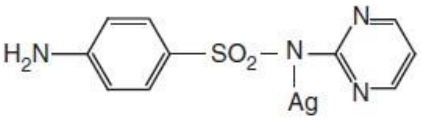
N-4 substituted suphonamides



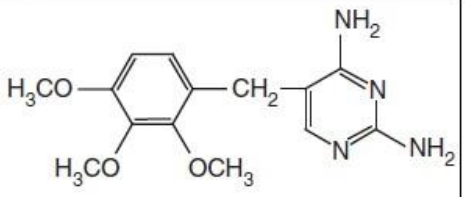
Prontosil

N-1 and N-4 substituted suphonamides

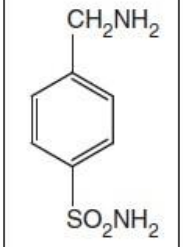
Name	R	R_1
Succinyl sulphathiazole		
Phthalylsulphathiazole		



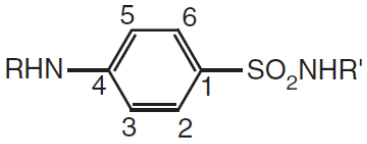
Silver sulphadiazine

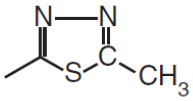
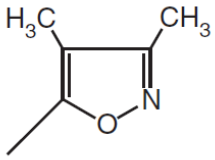
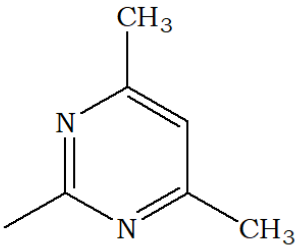
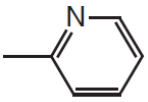


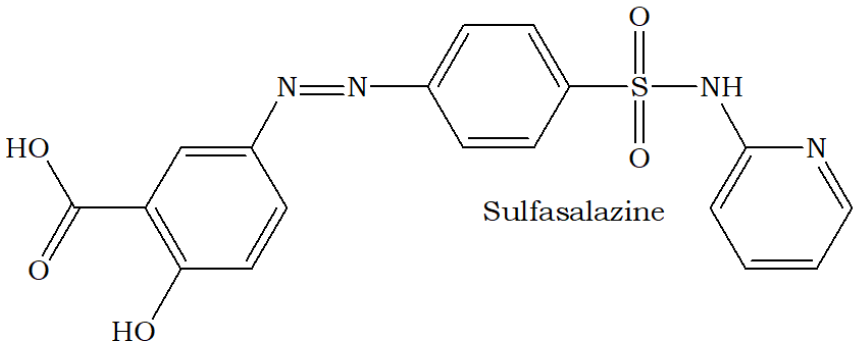
Trimethoprim



Mafenide



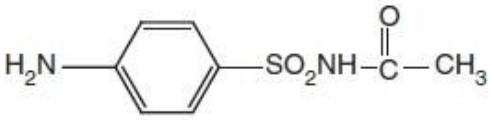
Name	R	R¹
Sulphamethizole	–H	
Sulphaisoxazole	–H	
Sulfamethazine	–H	
Sulphapyridine	–H	



Sulfasalazine

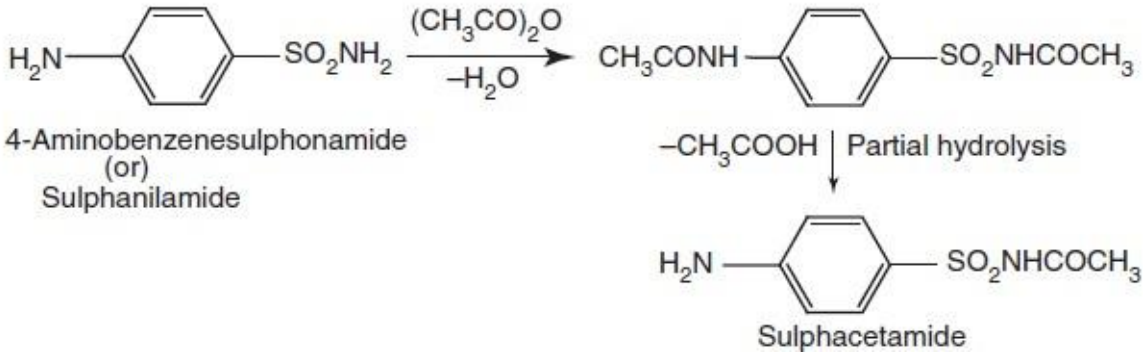
❖ SynthesisofSulphacetamide

Sulphacetamide



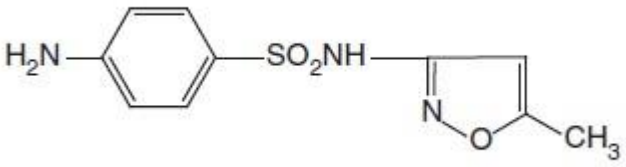
N-Sulphanilyl acetamide

Synthesis



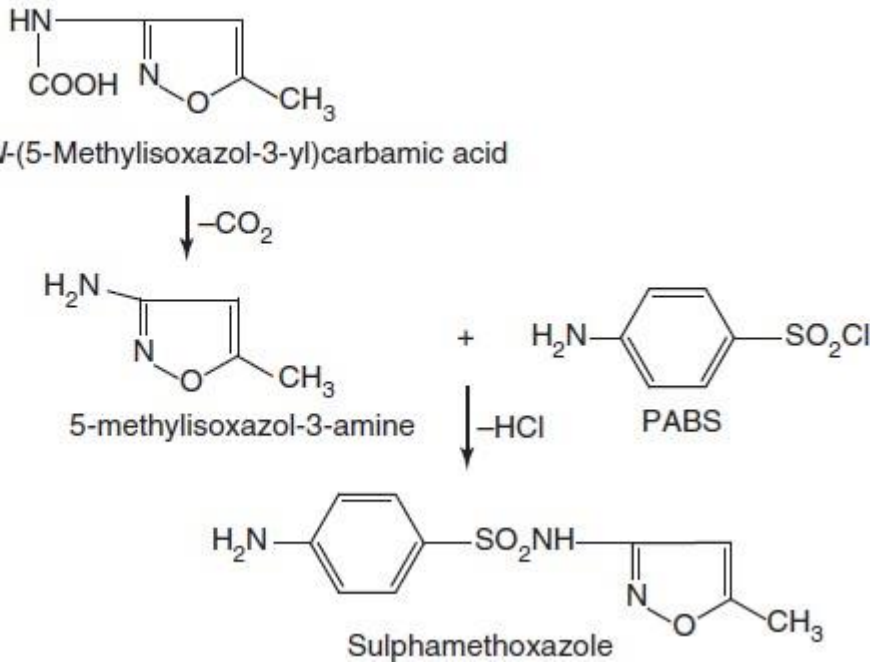
❖ SynthesisofSulphamethoxazole

Sulphamethoxazole

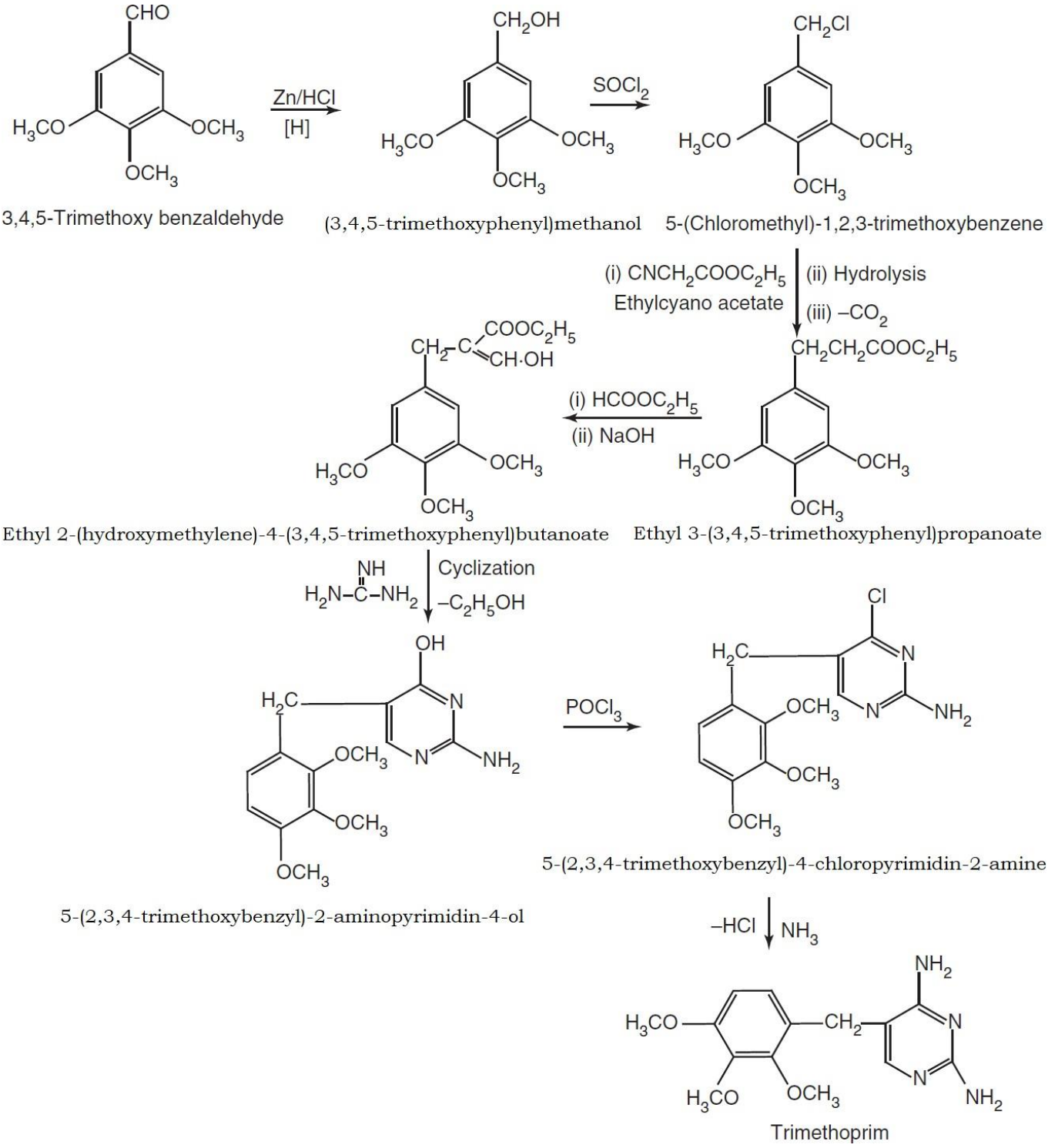


3-(4-Amino benzene sulphamido)-5-methyl isoxazole

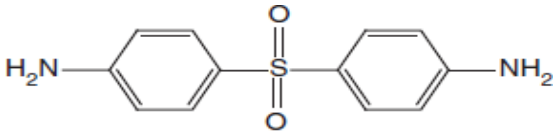
Synthesis



❖ Synthesisof Trimethoprim

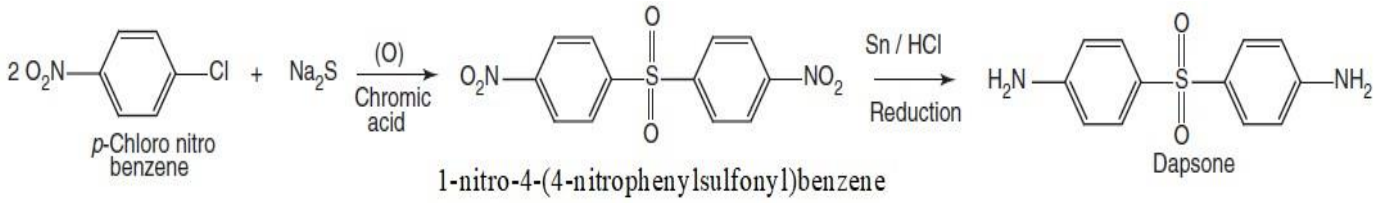


❖ Dapsone(DDS,Diaminodiphenylsulphone)



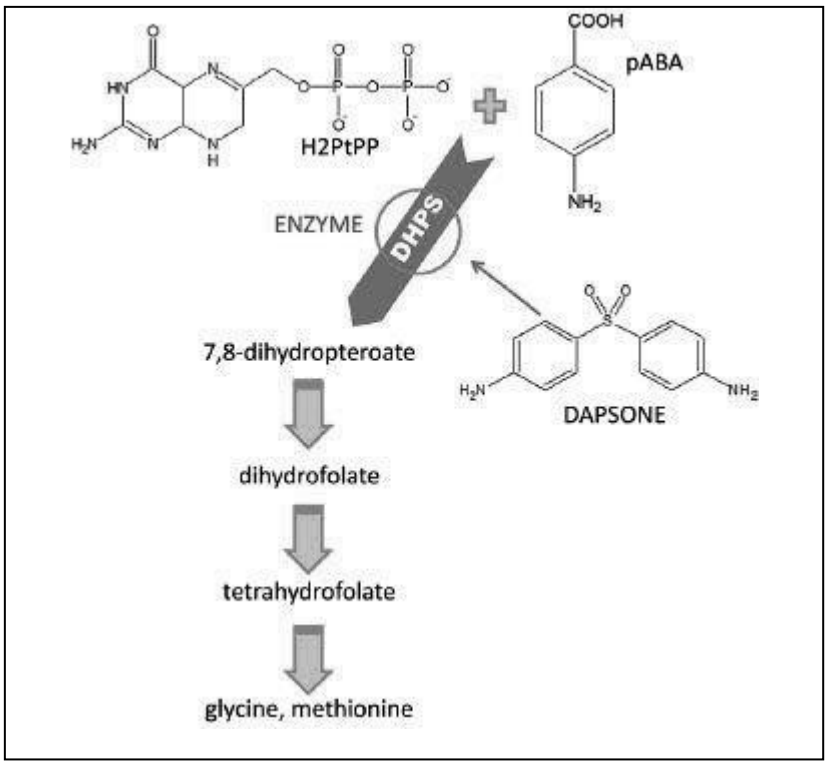
4-(4-Aminophenylsulfonyl)benzenamine

• Synthesis



• Mechanismof action

- Asanantibacterial,Dapsoneinhibitsbacterialsynthesisof**dihydrofolicacid**,viacompetitionwith **para-aminobenzoate**fortheactivesiteof***dihydropteroatesynthase***.
- Asananti-inflammatory,Dapsoneinhibitstheenzyme***myeloperoxidase***.Aspartoftherespiratory burst that neutrophils use to kill bacteria



• Adverseeffects

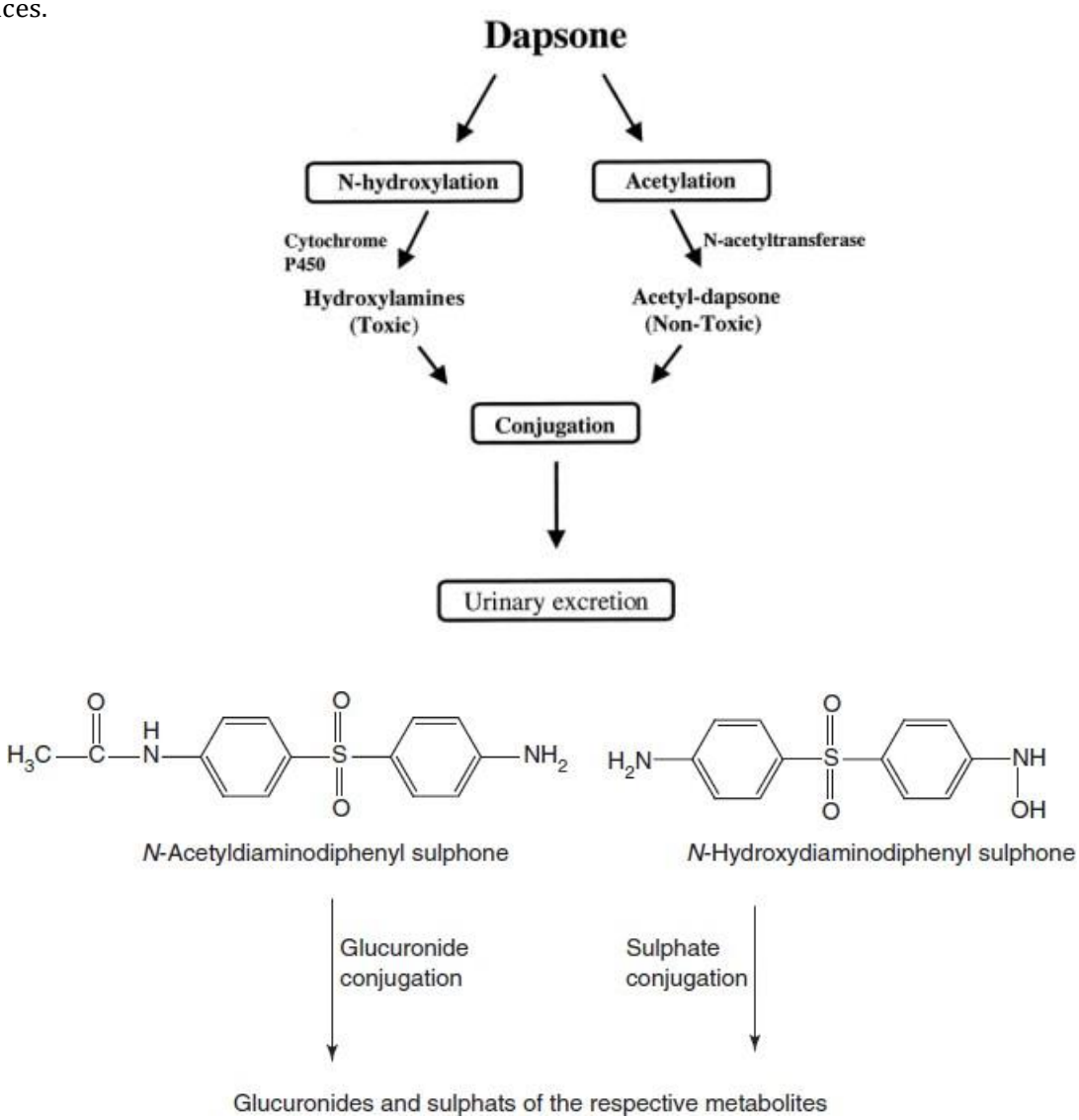
- Themostprominentside-effectsofthisdrugaredose-related**hemolysis**(whichmayleadtohemolyticanemia) and**methemoglobinemia**.
- Toxichepatitisandcholestaticjaundice.
- Otheradverseeffectsincludenausea,headache,andrash(whicharecommon),andinsomnia, psychosis, and peripheral neuropathy.

• Dosage

- Thedoseastabletsis25or100mg.Foradultsthedoseconsumedis50mgperdayorally.For lepromatousleprosy,100mgDapsone+600mgRifampinand/orclofazimine100mgdailyforatleast 2 years followed by Dapsone monotherapy. For borderline tuberculoid disease, Dapsone 100 mg daily + Rifampin600 mg once monthly for 6months.

- **Pharmacokinetics**

- ThemajormetabolicproductofDapsoneresultsfrom**N-acetylation**intheliverby***N- acetyltransferase***.
- Italsoundergoes**N-hydroxylation**to**hydroxylaminederivative**.Thesemetabolicreactionsare catalyzed by**CYP3A4** isoforms.
- Theurineconsistsofsmallamountsof Dapsoneandthemetabolites,thatis,**N-acetyldiamino- diphenyl sulphone**and**N-hydroxy-diamino-diphenyl sulfone**, as well as glucuronide and sulphate ofeach of these substances.

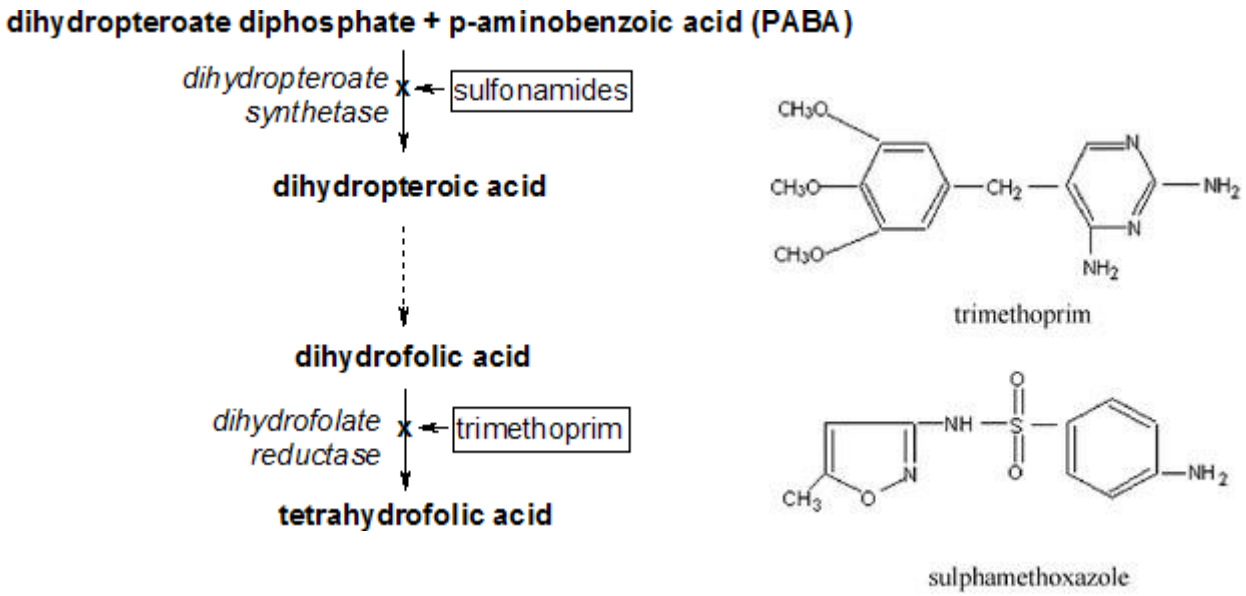


- **Uses**

- Dapsoneiscommonlyusedincombinationwithrifampicinandclofazimineforthetreatmentof **leprosy**.
- Itisalsousedtobothtreatandprevent**pneumocystispneumonia**and**toxoplasmosis**.
- Dapsonebymouthwasoneofthefirstmedicationsusedtotreatmoderatetosevere**acnevulgaris** andusefulinthepreventionofmalaria.
- DapsonealsousedtotreatAutoimmunedisease(likeCutaneouslupuserythematosus,Idiopathic thrombocytopenicpurpura,Chronicspontaneousurticaria,Relapsingpolychondritis).
- DapsonealsousedintreatmentofDermatitisherpetiformisandgeneralizedgranulomaannulare.
- Dapsonehasbeenusedasamonomerinthedesignofdyeadsorbentpolymers.

❖ Trimethoprim/Sulphamethoxazole

- **Trimethoprim/Sulphamethoxazole**(**TMP/SMX**),alsoknownas**Co-Trimoxazole**.
- Co-trimoxazoleisavailableinoralandintravenouspreparationswiththestandardsingle-strength tablet containing**80 mg of trimethoprim**combined with**400 mg of sulfamethoxazole**.
- Itisanantibioticusedtotreatavarietyofbacterialinfections.
- Itconsistsofoneparttrimethoprimtofivepartssulfamethoxazole.
- It is used for urinary tract infections, skin infections, travellers' diarrhoea, respiratory tract infections, and cholera, among others. It may be used both to treat and prevent pneumocystis pneumonia in people with HIV/AIDS.
- **Co-Trimoxazolecanbeusedtotreatorprevent:**
  - Lunginfections(pneumoniaor PJP)caused bya bacteriumcalled*Pneumocystisjirovecii*(previously P. carinii).
  - It is usedforskin infections,travellers'diarrhoea,andcholera.
  - InfectionscausedbyabacteriumcalledToxoplasma(toxoplasmosis).
  - Urinarybladderorurinarytractinfections(waterinfections)
  - Respiratorytractinfectionssuchasbronchitis
  - Earinfectionssuchasotitismedia
  - Aninfectioncallednocardiosiswhichcanaffectthelungs,skinandbrain.
  - ItmaybeusedbothtotreatandpreventpneumocystispneumoniainpeoplewithHIV/AIDS.
- Itcanbegivenbyorallyorintravenously.
- Commonsideeffectsincludenausea,vomiting,rash,anddiarrhoea.
- Severeallergicreactionsand*Clostridiumdifficilediarrhoea*mayoccasionallyoccur.
- Itsuseneartheendofpregnancyisnotrecommended.
- Itappearstobesafeforuseduringbreastfeedingaslongasthebabyishealthy.
- TMP/SMXgenerallyresultsinbacterialdeath.Itworksbyblockingthemakingoffolatebythe bacteria.
- **MechanismofAction**



Drugs	*Uses*
Sulphamethizole	Cystitis,Genitaltractinflammation,Gonorrhea,Nephritis,Prostatitis,Urinary TractInfectionandVaginalInflammation
Sulphaisoxazole	Urinary Tract Infections, Meningococcal Meningitis, Acute Otitis Media, Trachoma, InclusionConjunctivitis,Nocardiosis,Chancroid,Toxoplasmosis,Malariaand OtherBacterialInfections.
Sulfamethazine	Forthetreatmentbacterialinfectionscausingbronchitis,prostatitis,Bacterial Conjunctivitis,Endometritis,Furuncle,StreptococcalSoreThroat,Ulcersand UrinaryTractInfections.
Sulfacetamide	ForthetreatmentofBacterialVaginitis,Keratitis,AcuteConjunctivitis,Acne Vulgaris,Conjunctivitis,Trachoma,SuperficialOcularInfectionsandBlepharitis.
Sulphapyridine	ForthetreatmentofDermatitisHerpetiformis,BenignMucousMembrane PemphigoidandPyodermaGangrenosum.
Sulphamethoxazole	Sulfamethoxazole is indicated in combination with trimethoprim, in various formulations, for the following infections caused by bacteria with documented susceptibility: urinary tract infections, acute otitis media in pediatric patients (when clinically indicated), acute exacerbations of chronic bronchitis in adults, enteritis caused by susceptible Shigella, prophylaxis and treatment of*Pneumocystisjiroveci*pneumonia,andtravelers'diarrheacausedbyenterotoxigenic *E.coli*.Additionalindicationsincludetheadjunctivetreatmentofcholera, treatmentofbacillarydysentery,nocardiosis,andsecond-linetreatmentof brucellosis incombinationwithgentamicin or rifampicin.
Sulphadiazine	For the treatment of rheumatic fever, Nocardiosis, Plague, Plasmodium Infections, Toxoplasmosis, Trachoma, Urinary Tract Infection, Wound Infections, Bacterial otitis media caused by Haemophilus influenzae, Prophylaxis of Rheumatic fever RecurrentRheumaticfeverandmeningococcalmeningitis.
Mafenide	Indicatedforuseasanadjunctivetopicalantimicrobialagenttocontrolbacterial infectionwhenusedundermoistdressingsovermeshedautograftsonexcised burn wounds (Second Degree Burns and Third-Degree Burns).
Sulfasalazine	ForthetreatmentofCrohn'sdisease,Crohn'sDisease(CD),Polyarticularjuvenile rheumatoidarthritis,chronicorunspecified,Proctitis,RheumatoidArthritis, SevereUlcerativeColitis,MildUlcerativeColitis,ModerateUlcerativecolitis