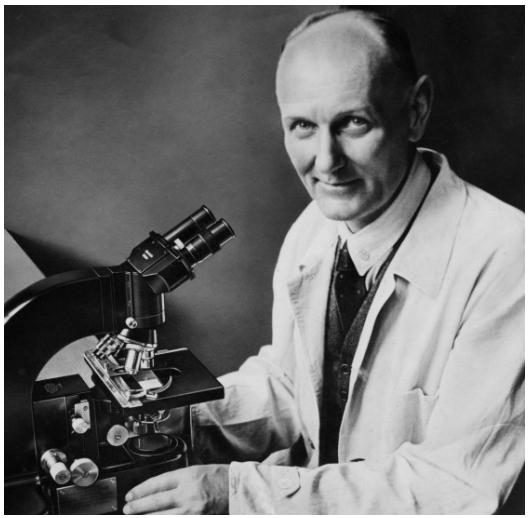
# Antibiotics

Sulfa Drugs

# Sulfa Drugs

Sulfanilamide

Comes from dye industry



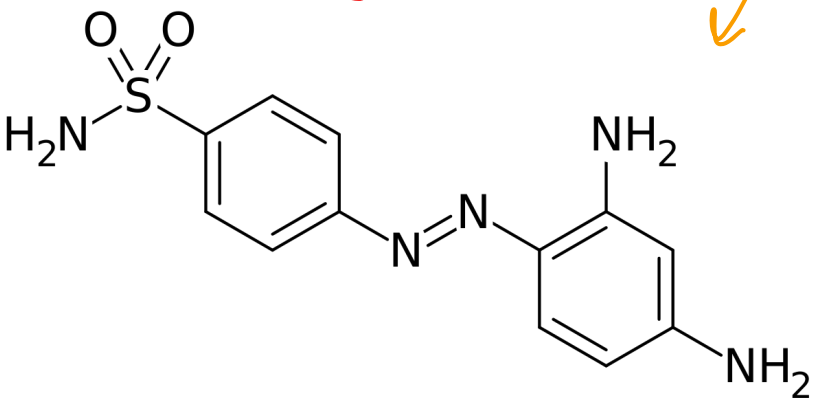
Dr. Gerard Domagk

Prontosil

Prontosil Rubrum

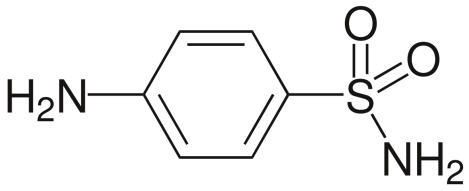
Red Dye

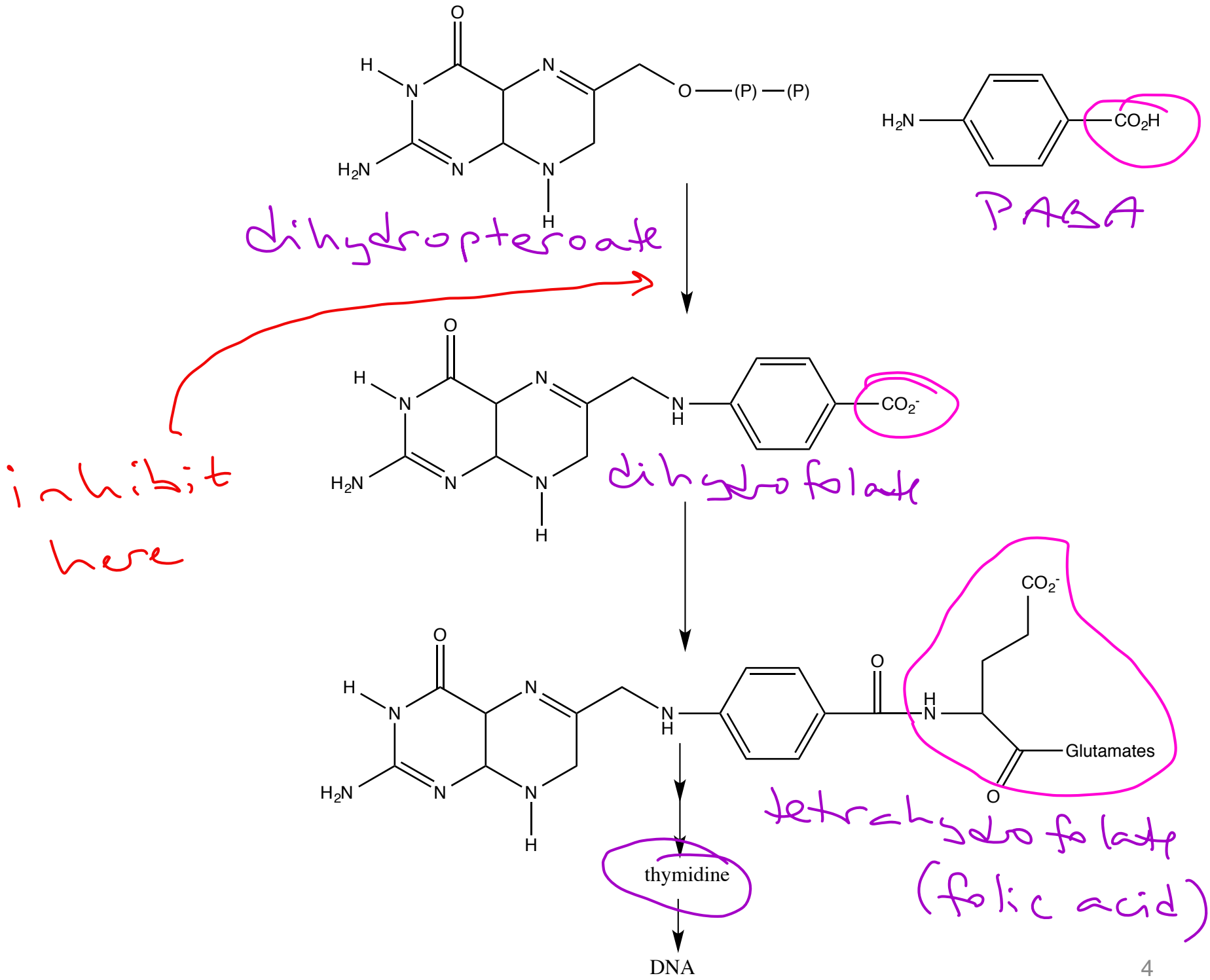
active in vivo but not in vitro

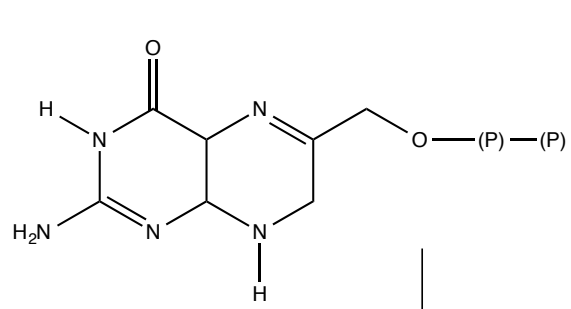


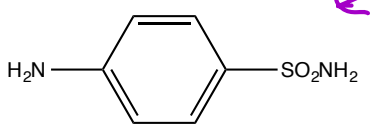

liver enzymes

Sulfanilamide

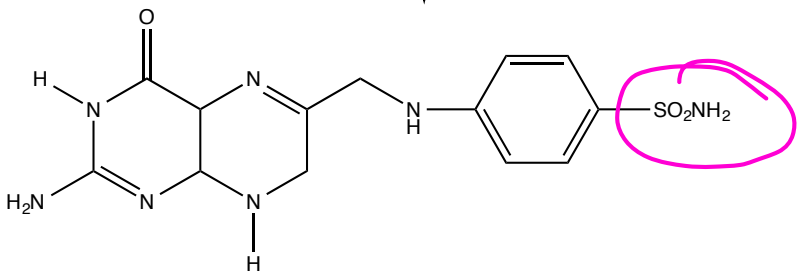



dihydropteroate
PABA
inhibit here
dihydrofolate
Glutamates
tetrahydrofolate (folic acid)
thymidine
DNA





looks like PABA

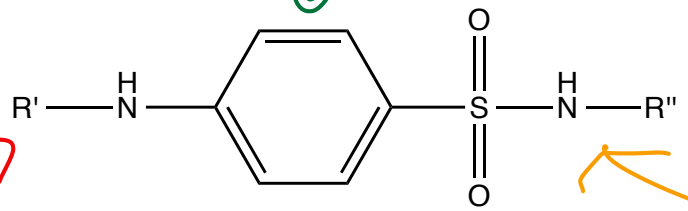


nothing to attach to can't continue pathway

Antimetabolites – an artificial compound that replaces a metabolite in a reaction

In some organisms it acts as a competitive inhibitor

SAR




need para substituted ring

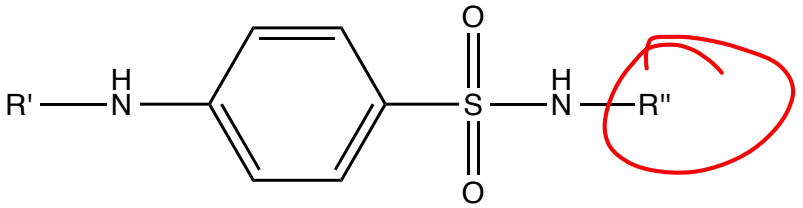
H or { acyl group

need to be removed in vivo to make active compound

need sulfonamide

1° or 2° amine

SAR



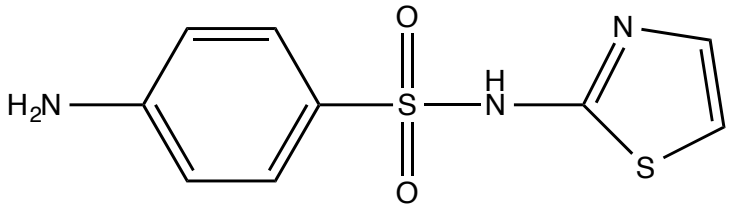

most changes here

(1) improve solubility
low [Drug] in water
can crystallize in kidneys

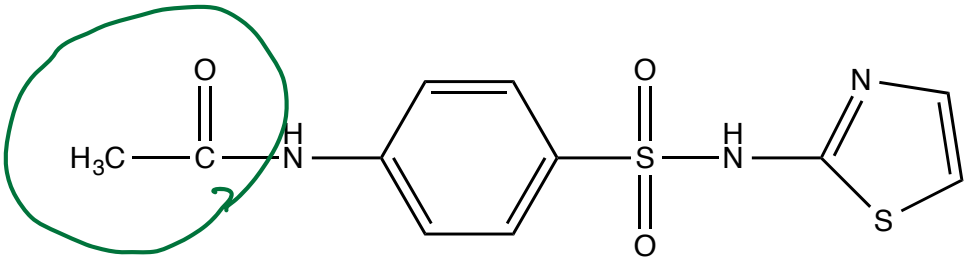
(2) make more lipophilic
improve binding to the proteins in blood that carry them

(3) improve antimicrobial properties

Toxicity (Sulfamethiazole)



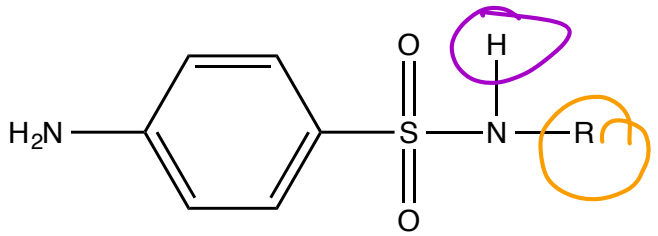

N-acetylation in vivo




Insoluble
Can block
Kidney tubules

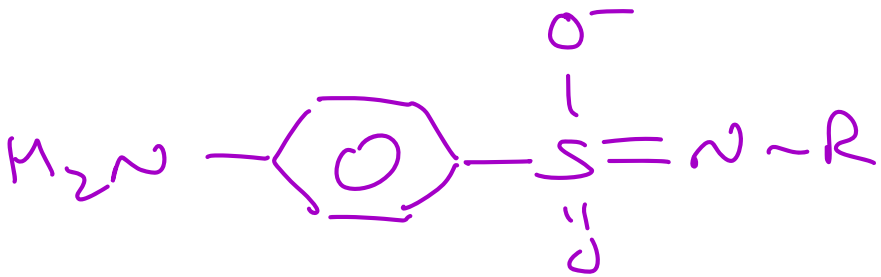
Japanese + Chinese descent
do this faster
more prone to toxic effects

$pK_a = 10$ $pH = 7$




HA

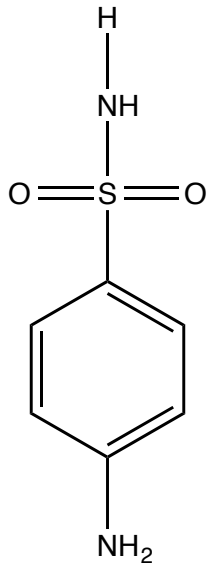
7L

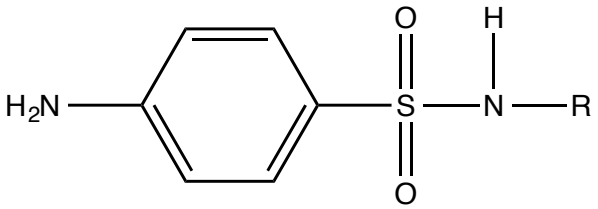



$A^-$ more $H_2O$ soluble

Want a low pKa

pH > pKa deprotonated


H
NH
O
S
O
NH2

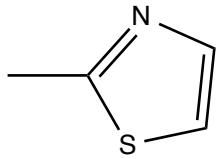



To have an ionized (soluble) molecule we want the pKa less than the pH

Decreasing the pKa decreases risk of crystalluria

R

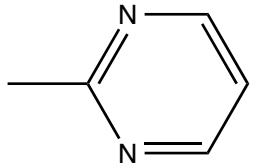
Sulfathiazole




pKa = 7.2

$10^{7-7.2} = 0.631$ ratio $\frac{A}{HA}$

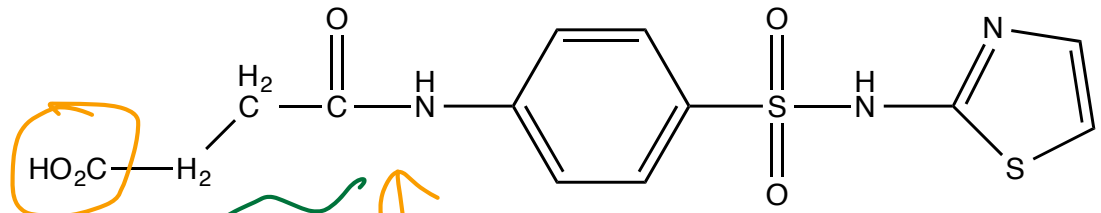
Sulfadiazine




pKa = 6.5

$10^{7-6.5} = 3.16$

$pK_a = 8.5$



Succinyl sulfathiazole

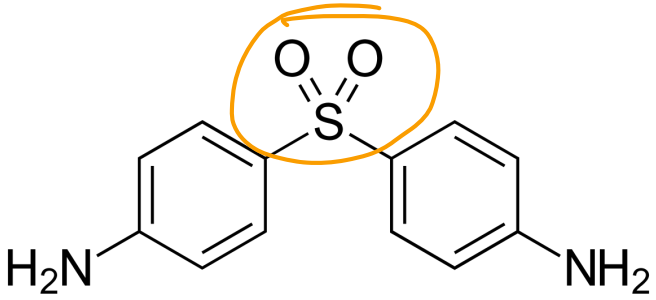
to be active hydrolyze here

at pH = 8

$-CO_2^-$

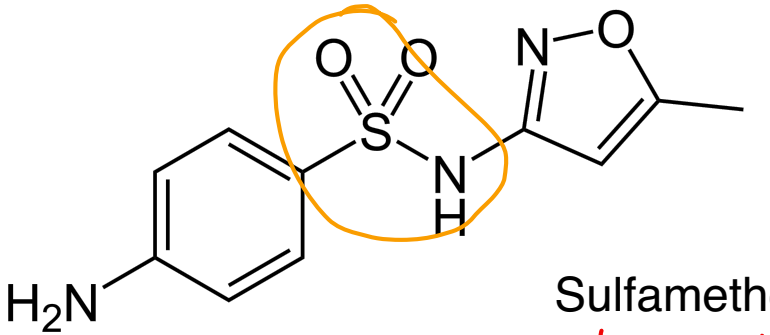
don't absorb

used for GI infections



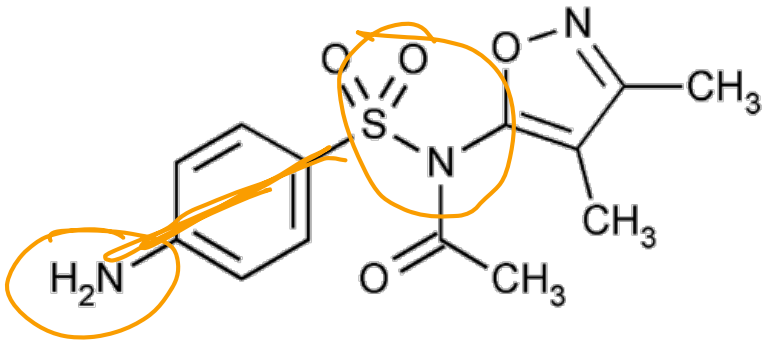
Dapsone

leprosy malaria pneumonia

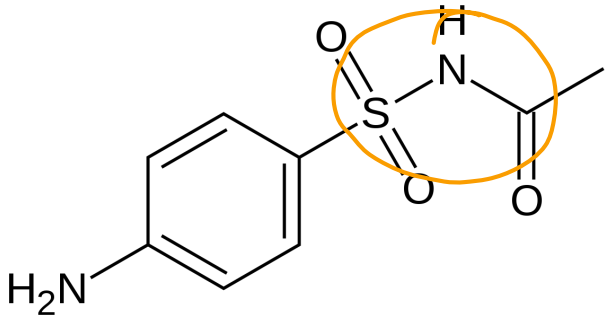


Sulfamethoxazole

combined with trimethoprim for UTI's

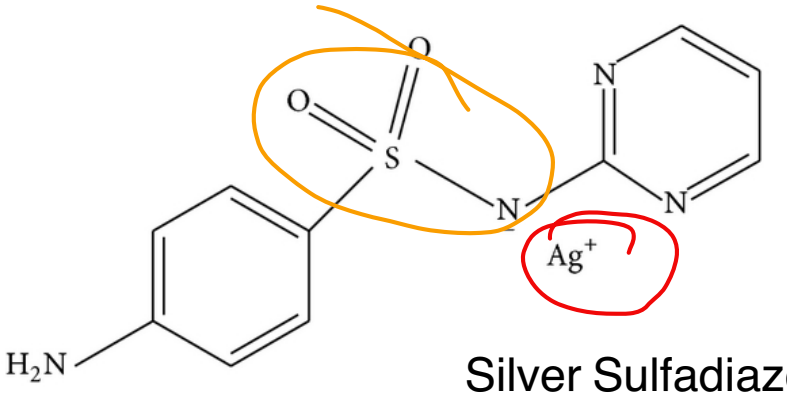


Acetyl Sulfisoxazole



Sulfacetamide

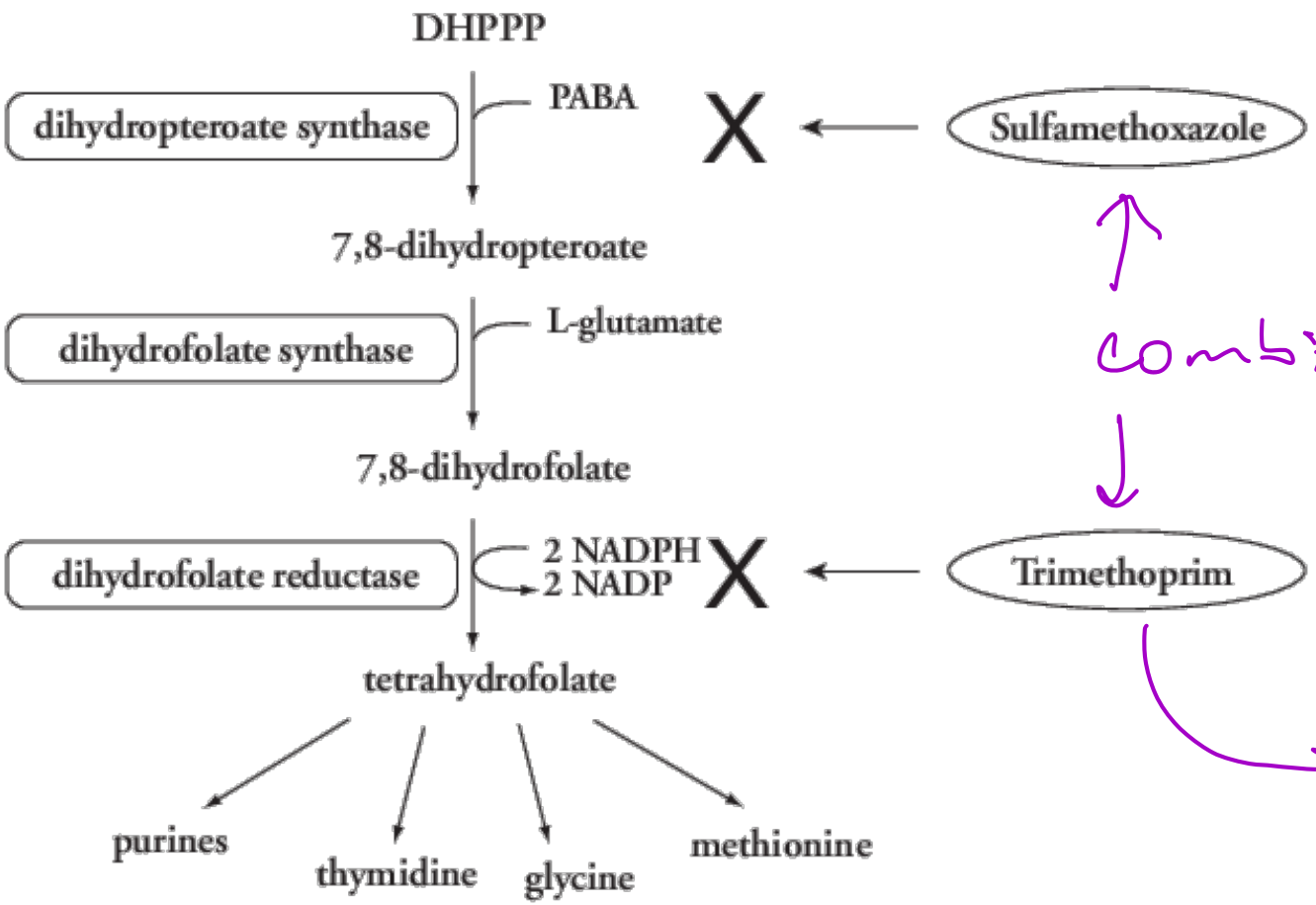
eye + skin infections



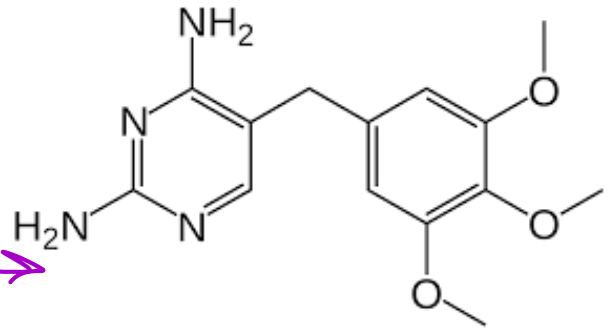
Silver Sulfadiazene

burns

Ag has antibacterial properties



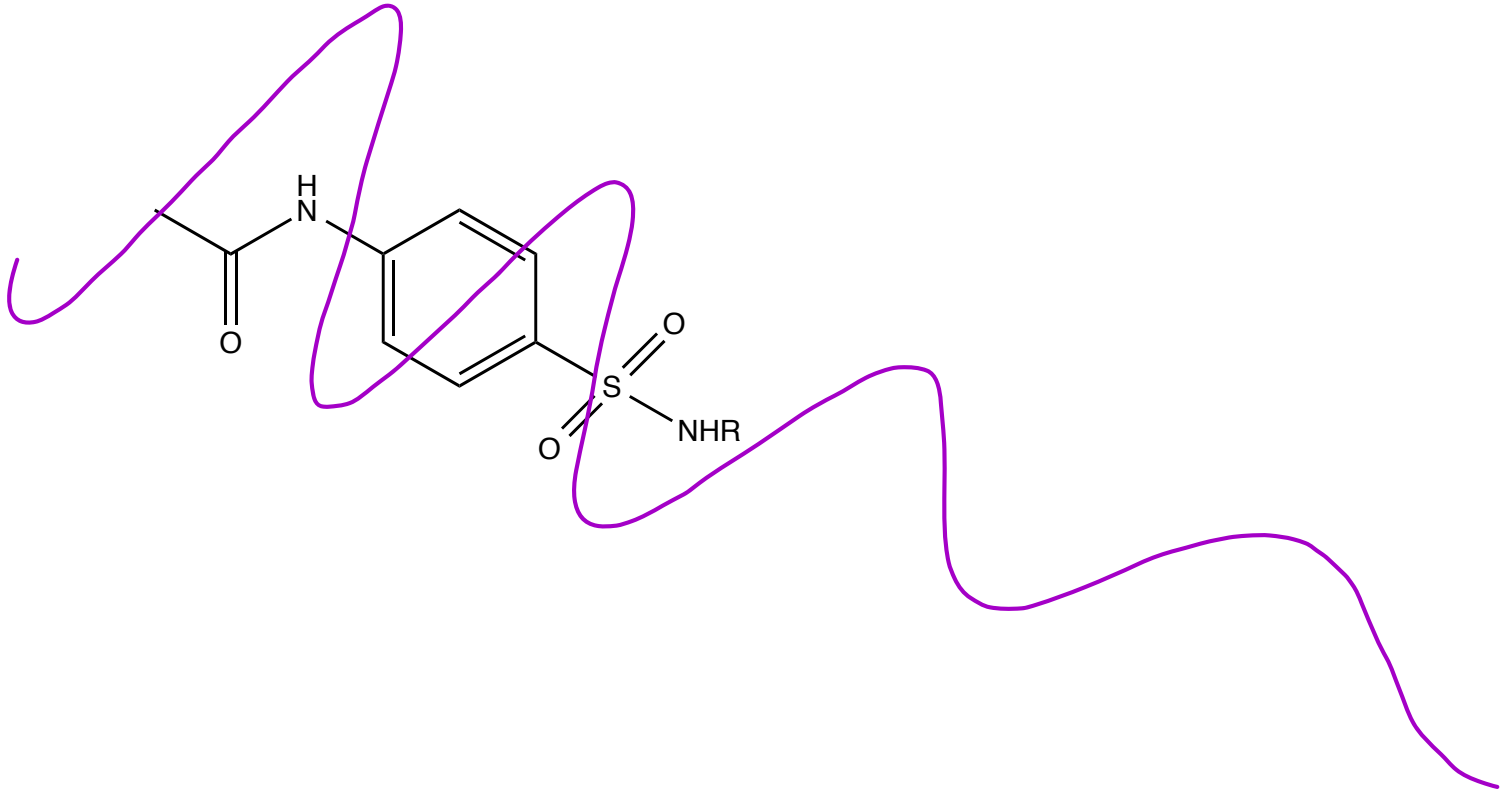

combine to make bactrim



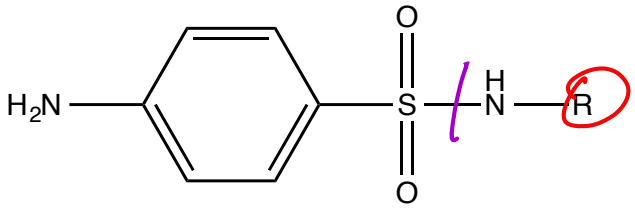

Sequential blocking

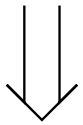
inhibit multiple steps in a pathway

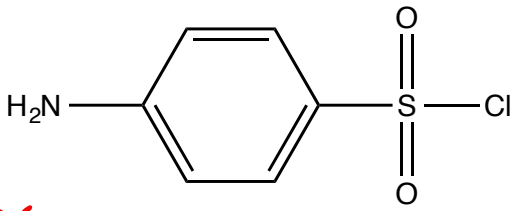
# Phamacokinetics of Sulfonamides



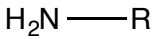
# Synthesis of Sulfa Drugs : Retrosynthesis

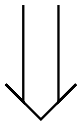


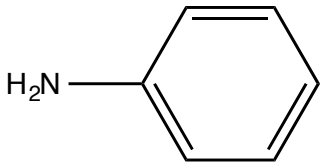






Sulfonyl chloride






aniline

Synthesis of Sulfa Drugs : Forward Synthesis