Antibiotics

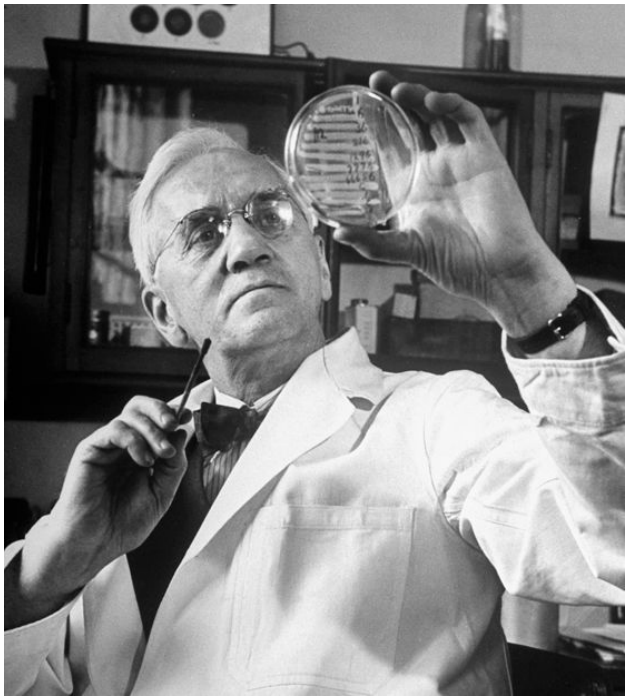
Lactam Antibiotics

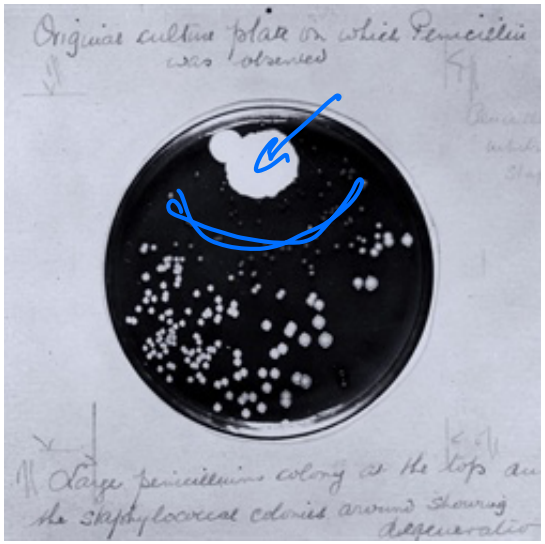
Penicillins

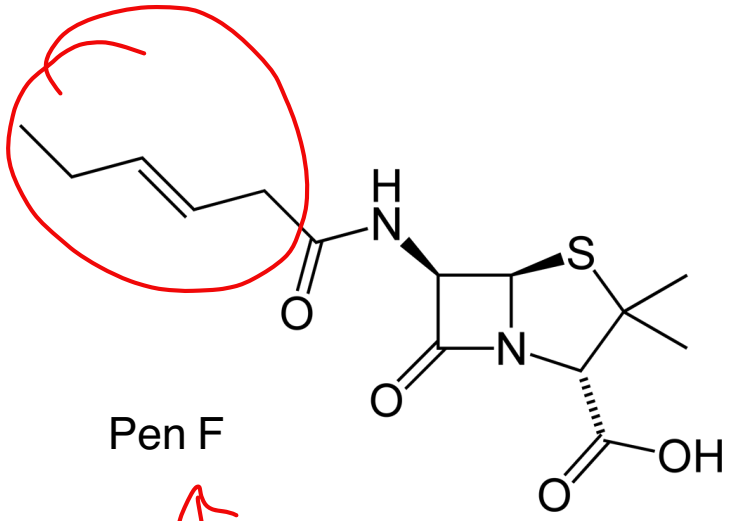
1928 Alexander Fleming

1941 Florey + Chain trials for Staph + Strep

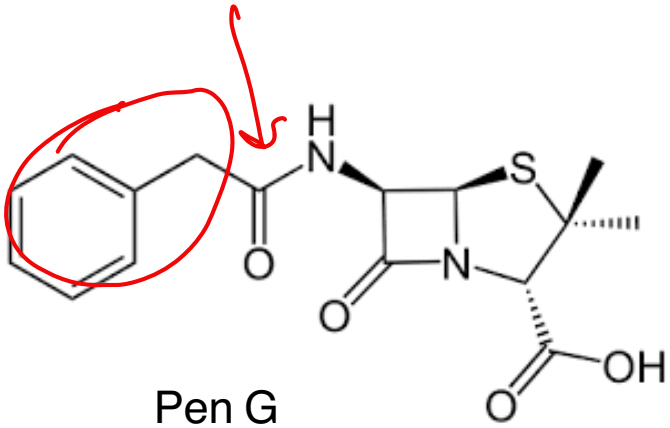
1945 Nobel prize







Pen F



Pen G

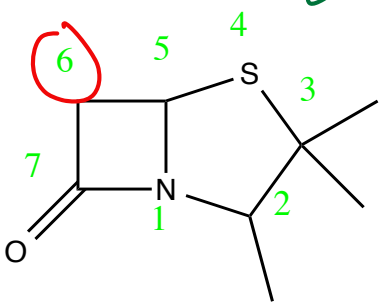
Initial studies at Oxford the critters made this

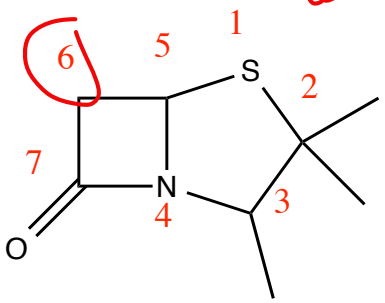
made this when moved to Ill

different media produce different side chains

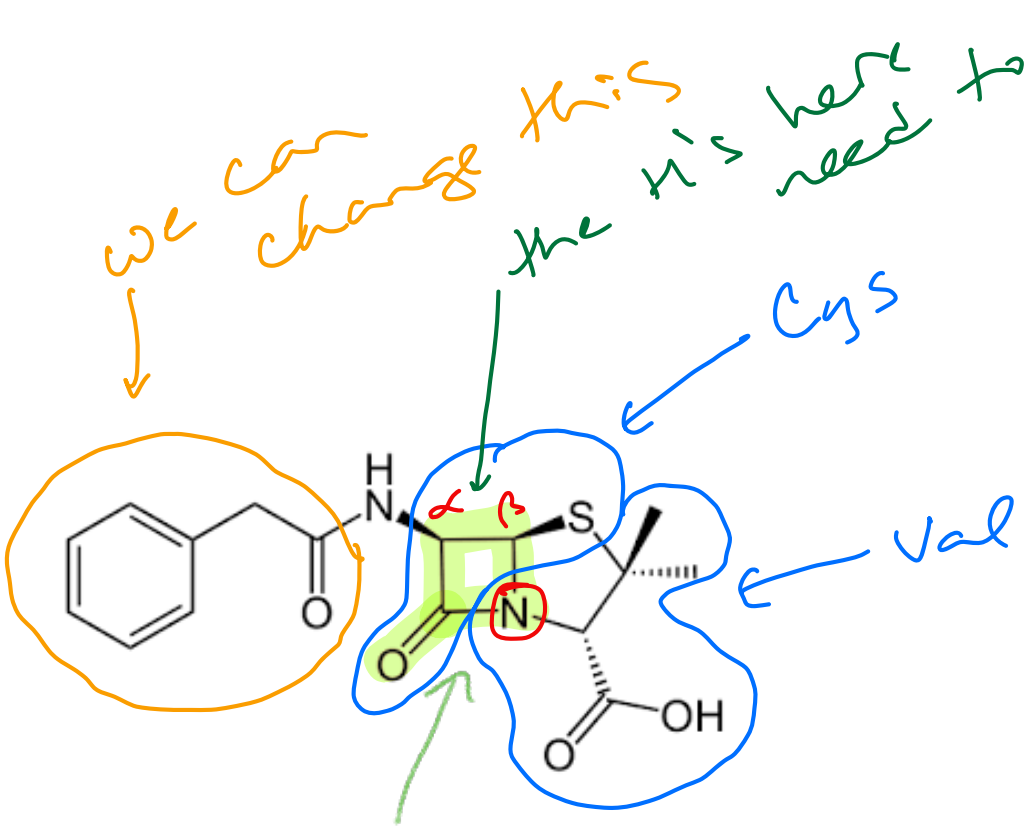
chem d Abstracts

USP #'s





Penicillin G (Benzylpenicillin)



* β lactam ring
* free carboxylic acid
* bicyclic (provides more strain to β-lactam rings)

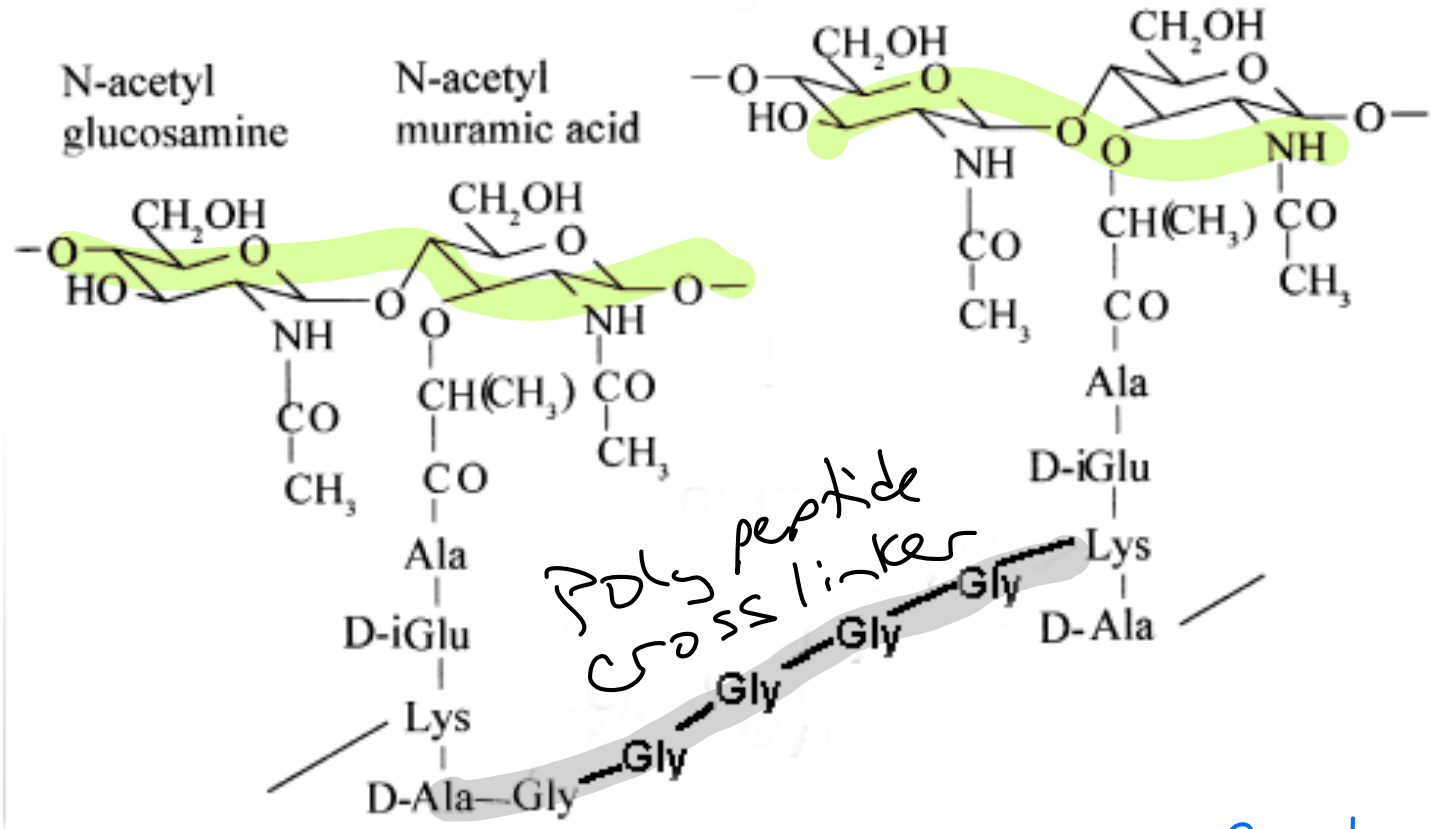
(move ↓)

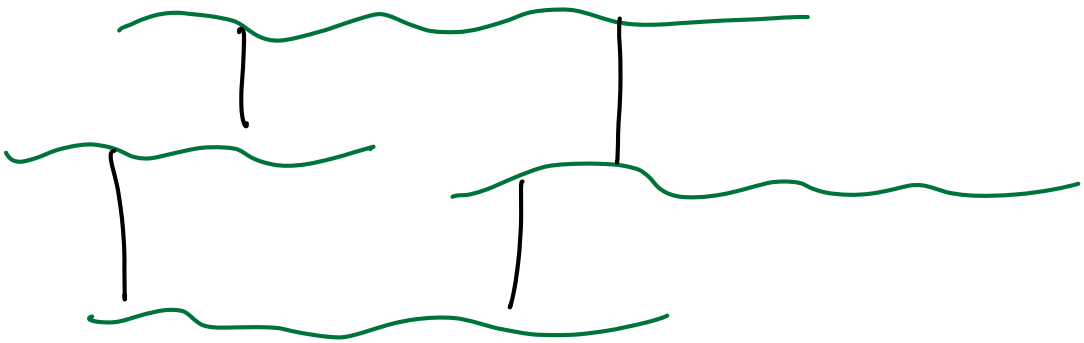
Pen G Modifications

1) ineffective orally
   has to be injected
   broken down by stomach acid

2) sensitive to β-lactamases

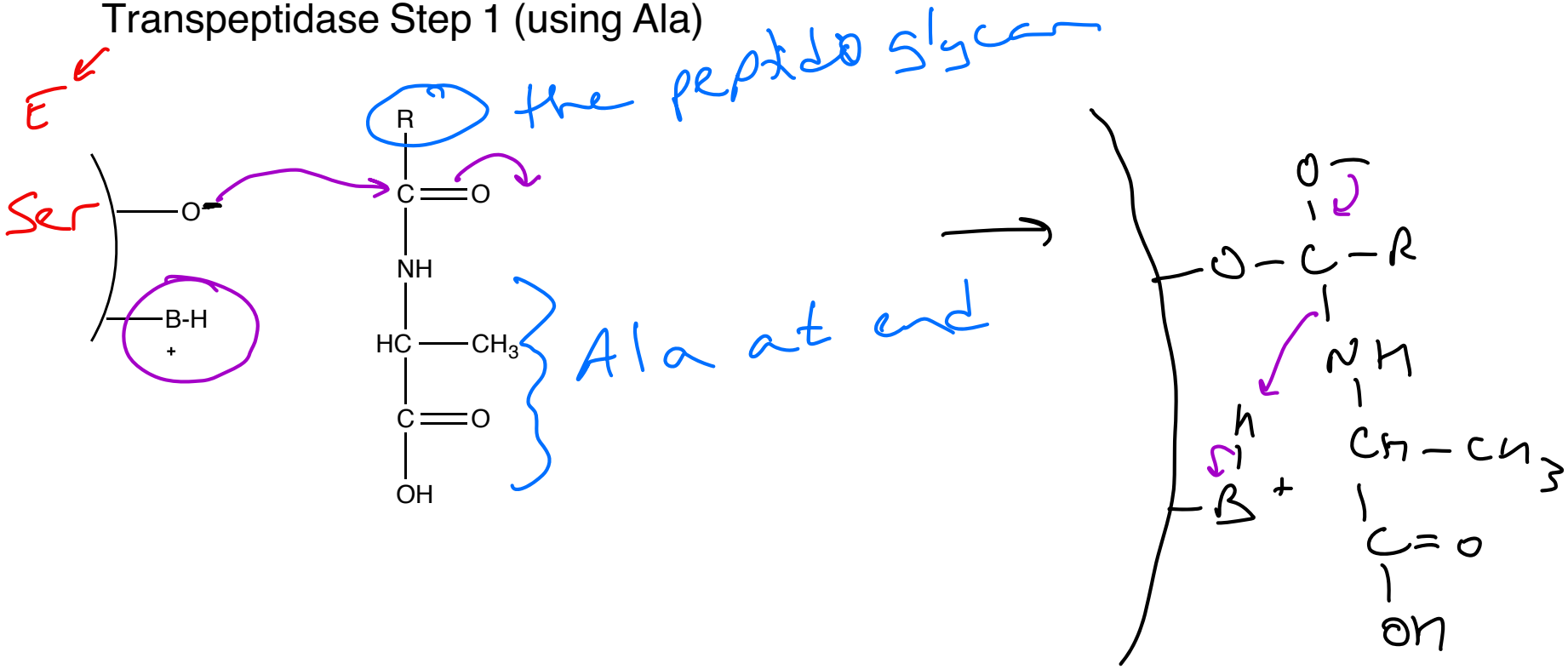
Structure of Peptidoglycan

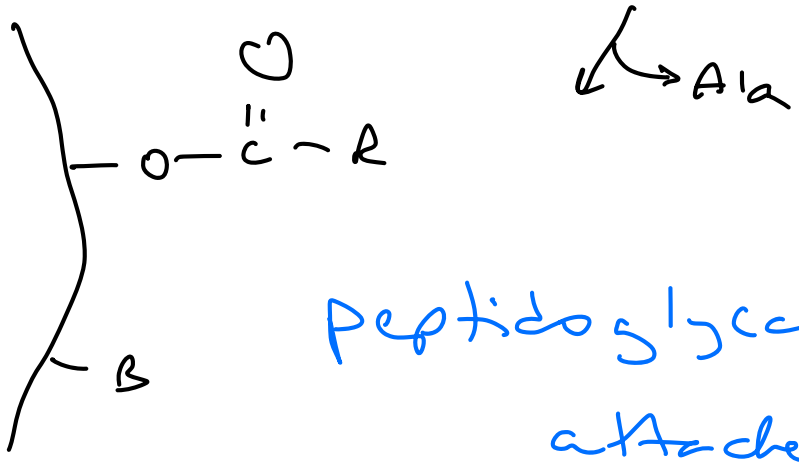




β-lactams inhibit the crosslinking

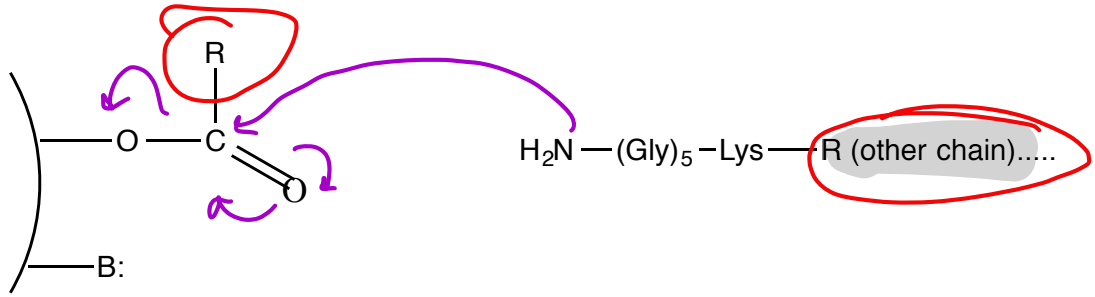
Transpeptidase Step 1 (using Ala)

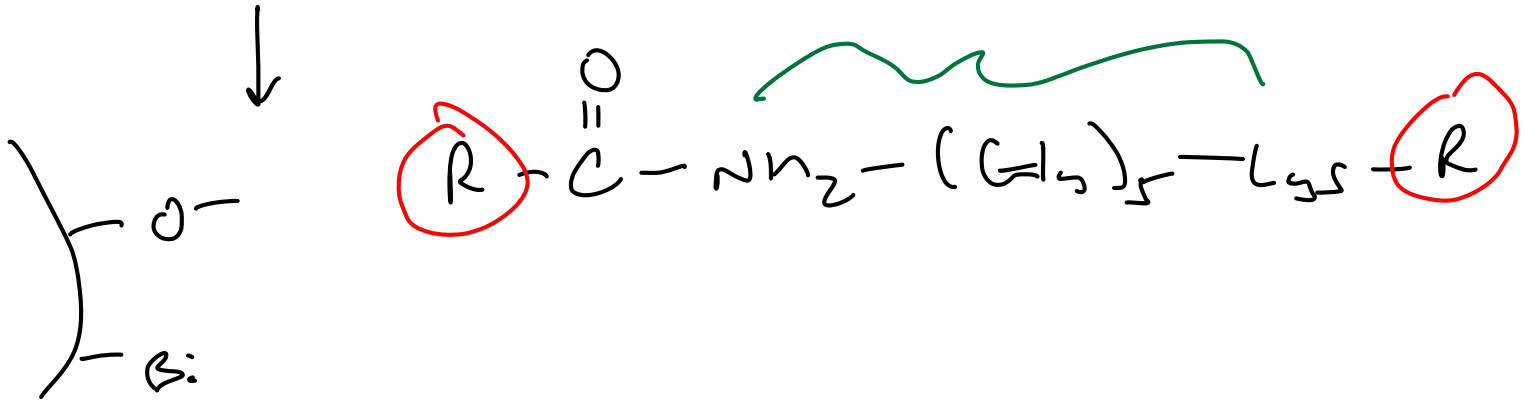


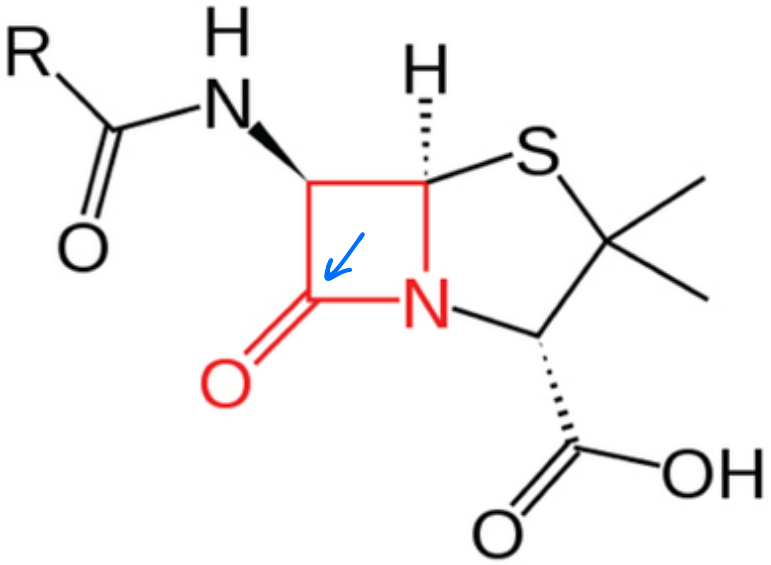


peptidoglycan now attached to enzyme

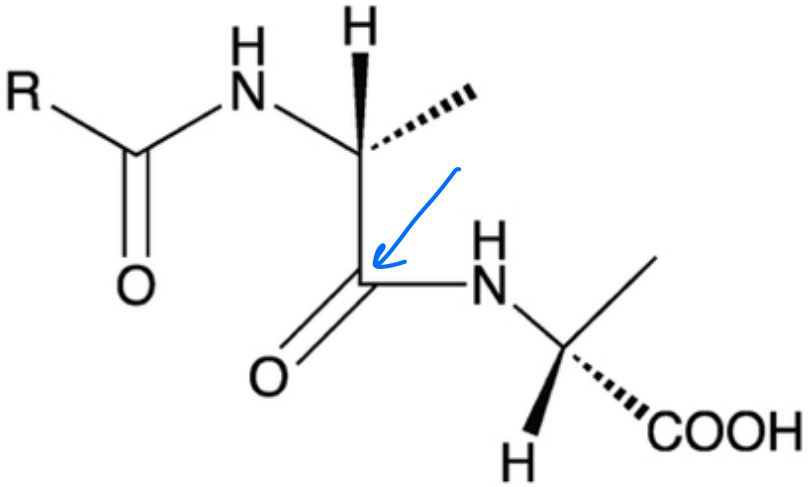
Transpeptidase Step 2 (attach to Gly)





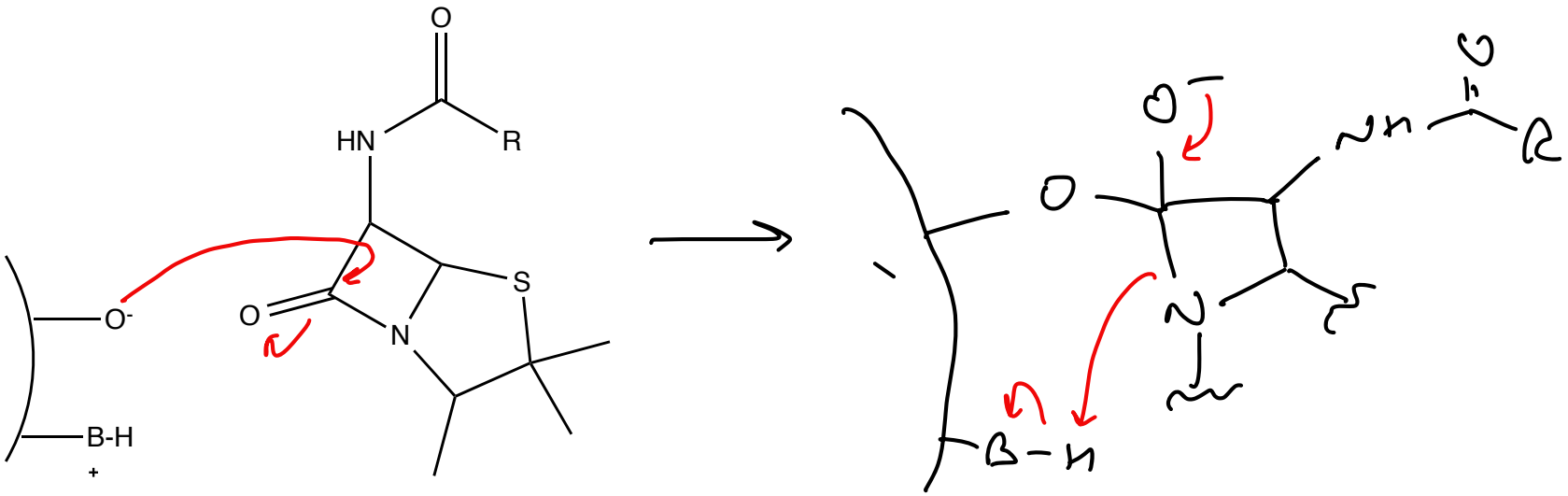


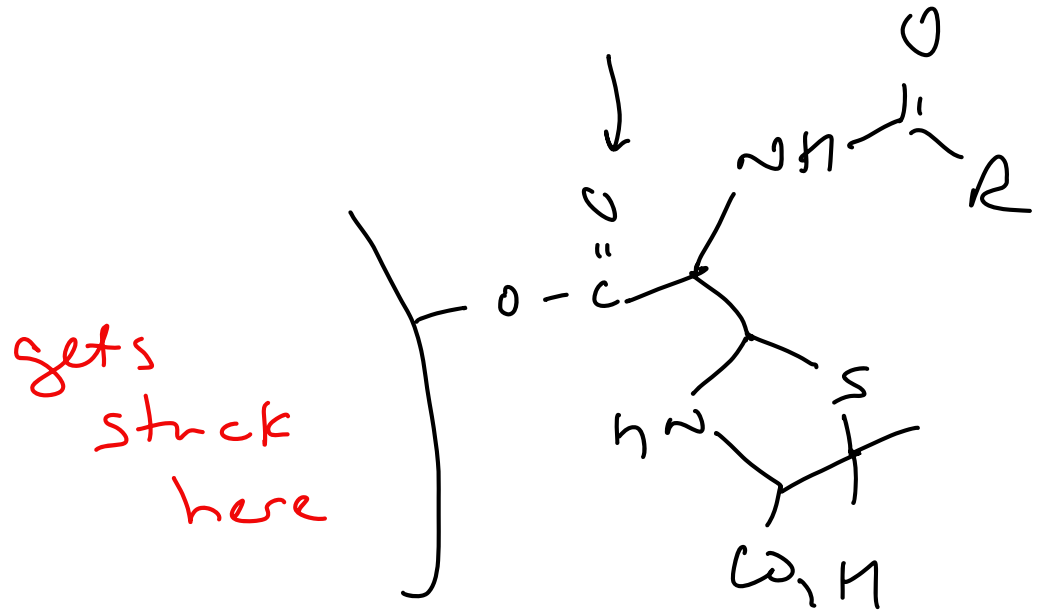
Penicillin



D-Ala-D-Ala

Transpeptidase with Penicillin





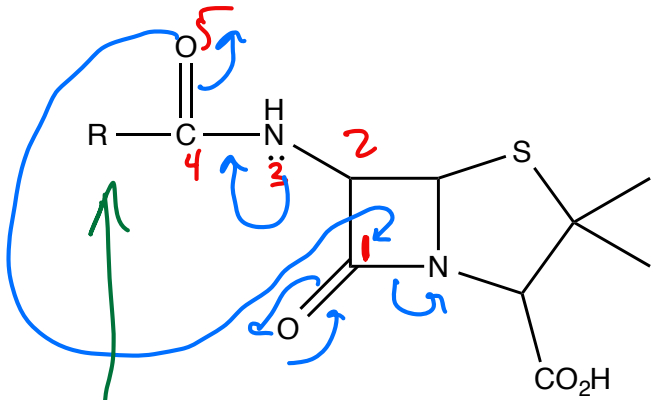
gets stuck here

acylated enzyme

Pen G is Sensitive to Acid

1. Ring strain
2. C=O is reactive
3. R group gets involved

Acid Hydrolysis



the C=O of the R group acts as the Nu: to hydrolyze the amide

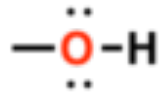
use R groups that make the O less Nu:

use EWD R groups

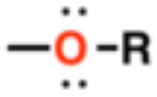
Activating and Deactivating Groups

Activating groups increase the rate of reaction in electrophilic aromatic substitution reactions, relative to H

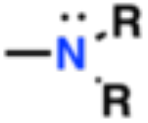
Examples



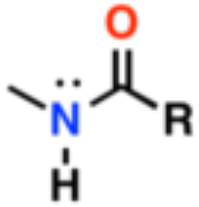
hydroxy



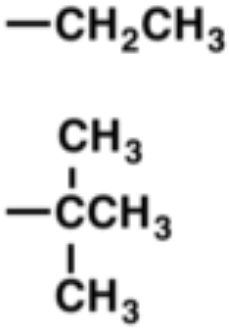
alkoxy



amine



amide

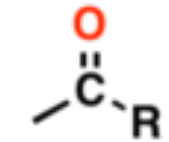


alkyl

Deactivating groups decrease the rate of reaction in electrophilic aromatic substitution reactions, relative to H

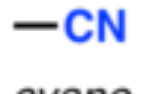
Examples

halo

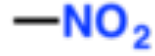


carbonyl

sulfonyl

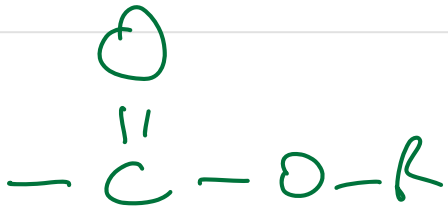


cyano



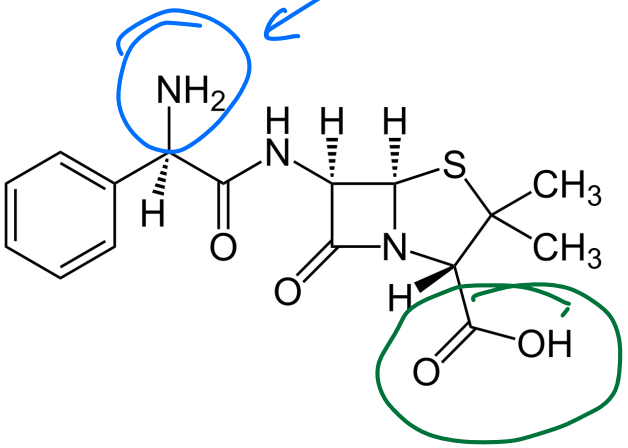
nitro

haloalkyl



protonated amines

Ampicillin

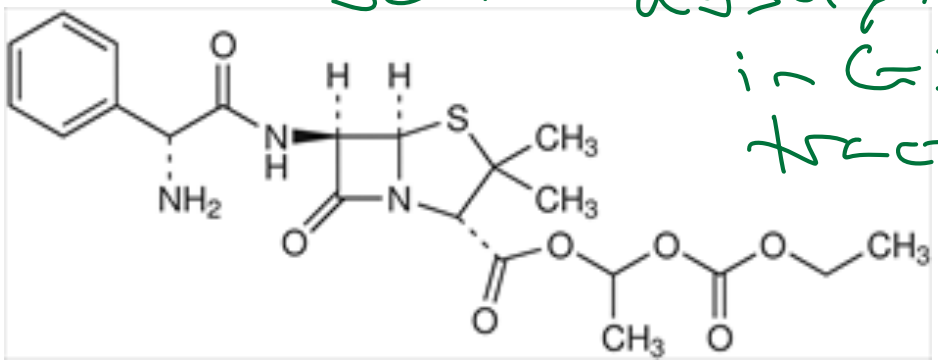


protonate!

Acid resistant
can be given orally
(not very resistant to
β-lactamases)

a prodrug
of ampicillin

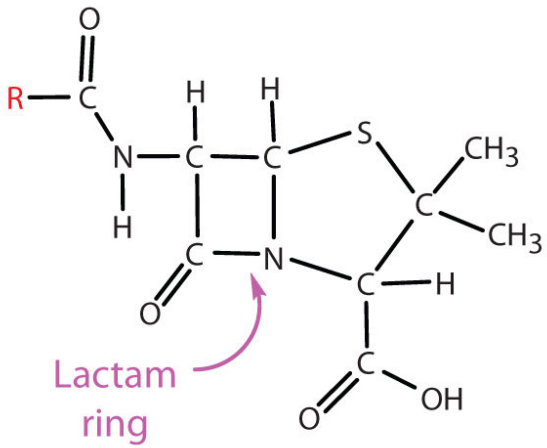
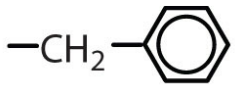
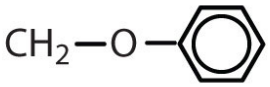
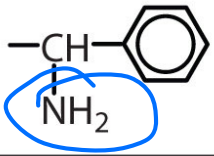
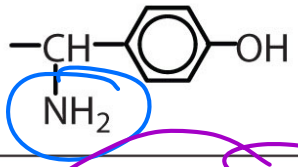
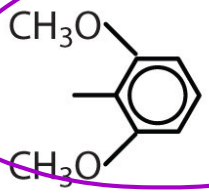
more lipophilic
better absorption
in GI
tract



bacampicillin

Inactive until

Side chain removed

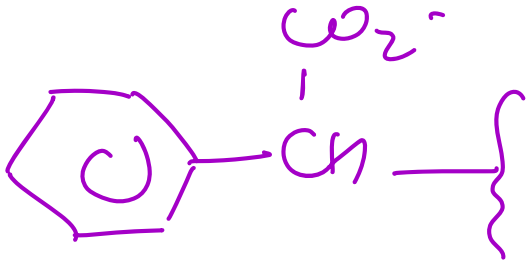
Penicillin Structure	R Group	Drug Name
		penicillin G
		penicillin V
		ampicillin
		amoxicillin
		methicillin

Bis Stuff

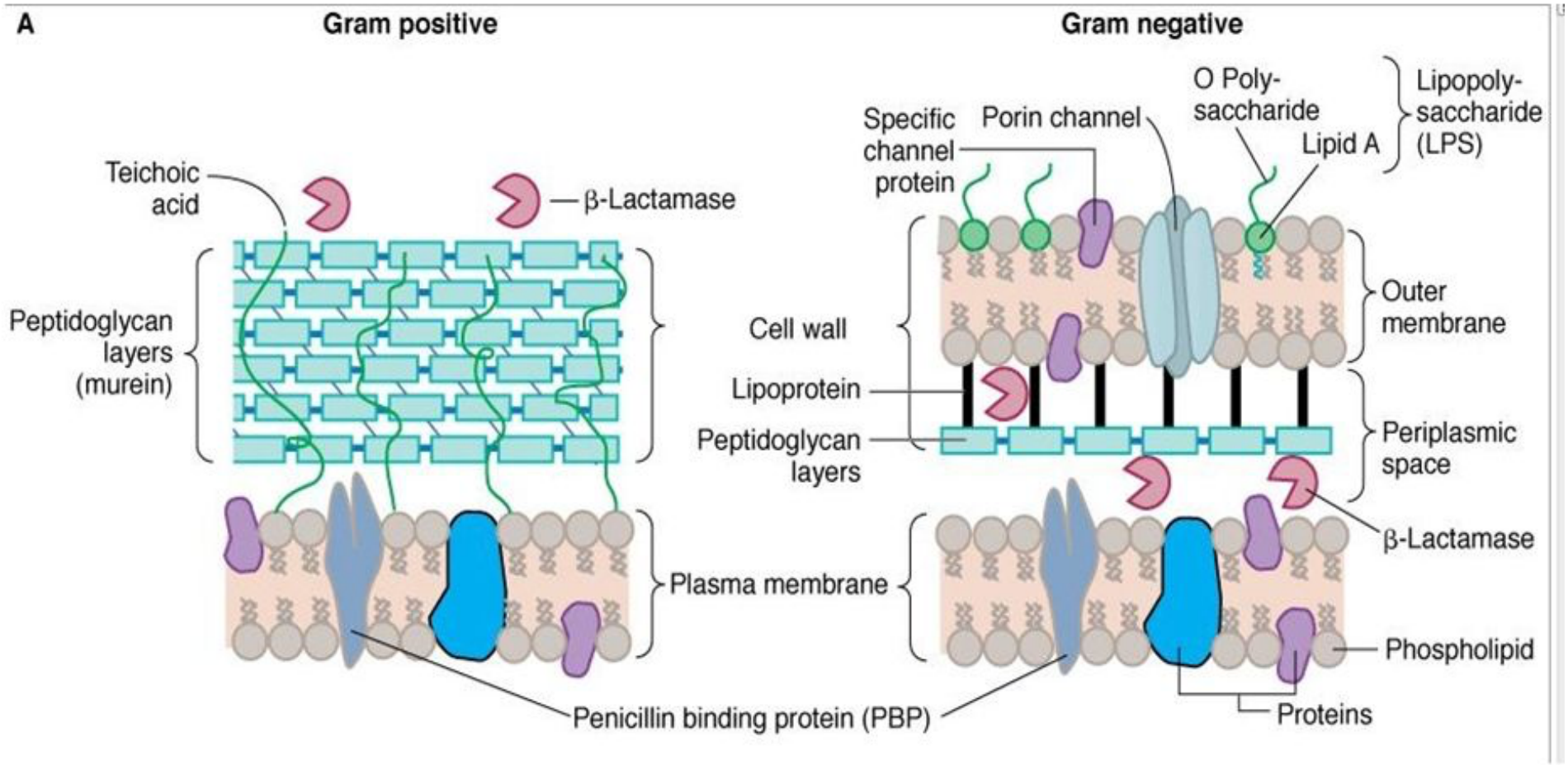
Increase side of R will improve β-lactamase resistance

Oxacillin

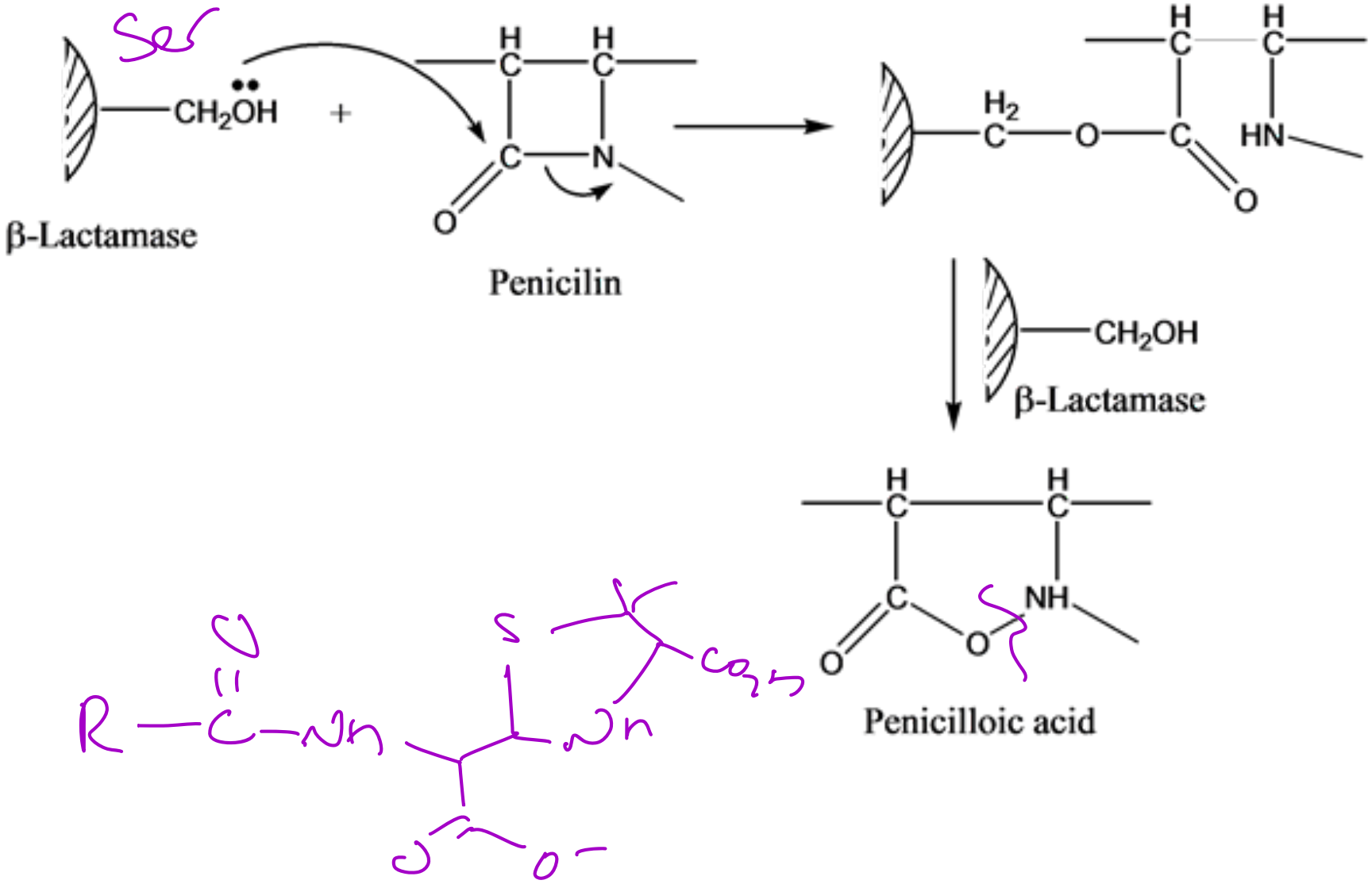
Carbenecillin

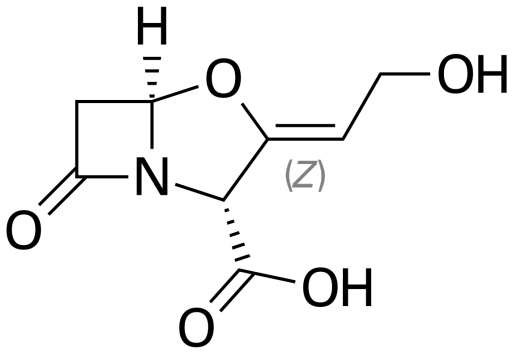


Antibiotic Resistance



Comparison of the structure and composition of gram-positive and gram-negative cell walls


Ser
CH2OH
β-Lactamase
Penicillin
H2
HN
O
CH2OH
β-Lactamase
NH
Penicilloic acid



Clavulanic acid

isolated from

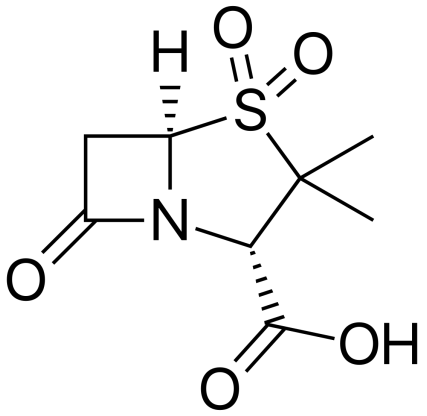
Streptomyces

clavuligerus

β-lactamase

inhibitor

Augmentin = Amoxicillin + this



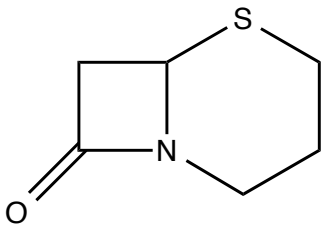
Sulbactam

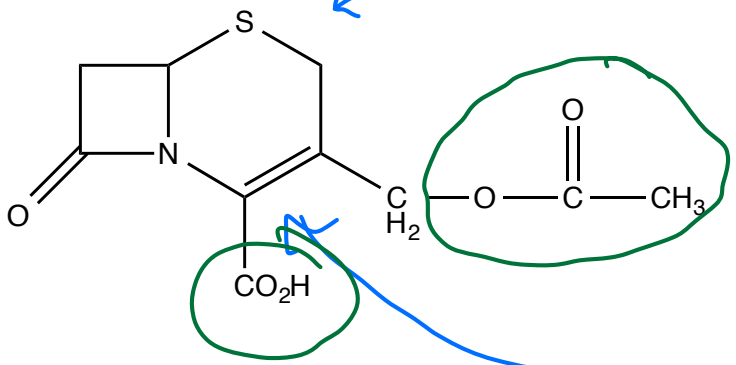
Unasyn = ampicillin
+
this one

Also
β-lactamase
inhibitor

Sentry Drugs : guards or protects the partner drug

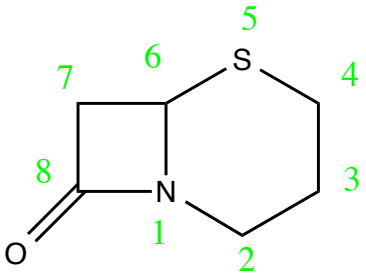
Cephalosporins

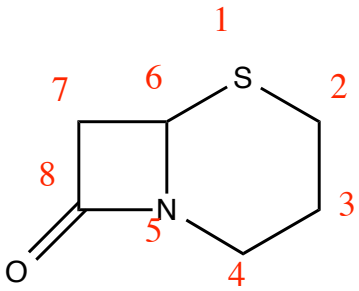




6-membered ring lose some strain

gain back with =

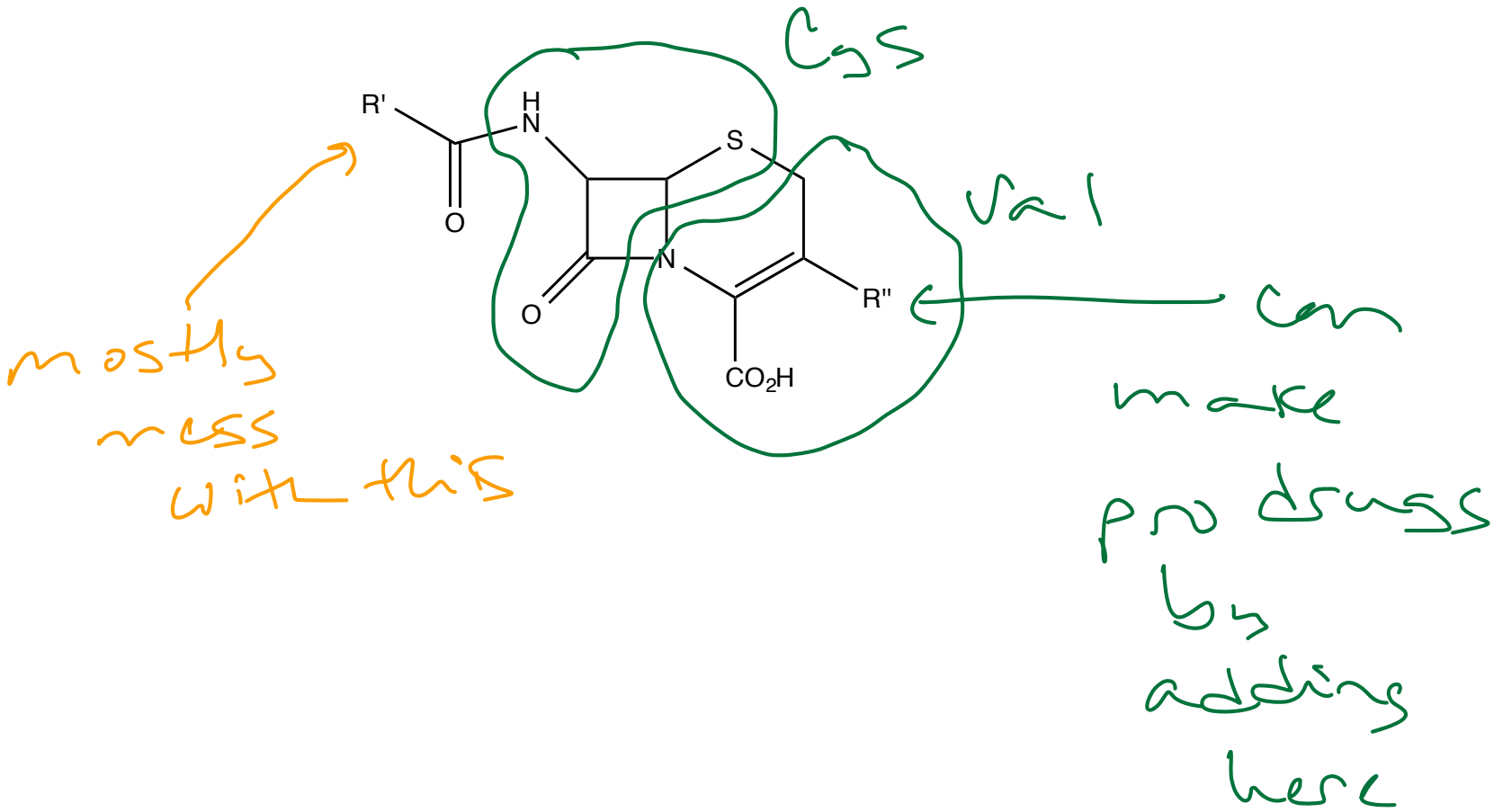




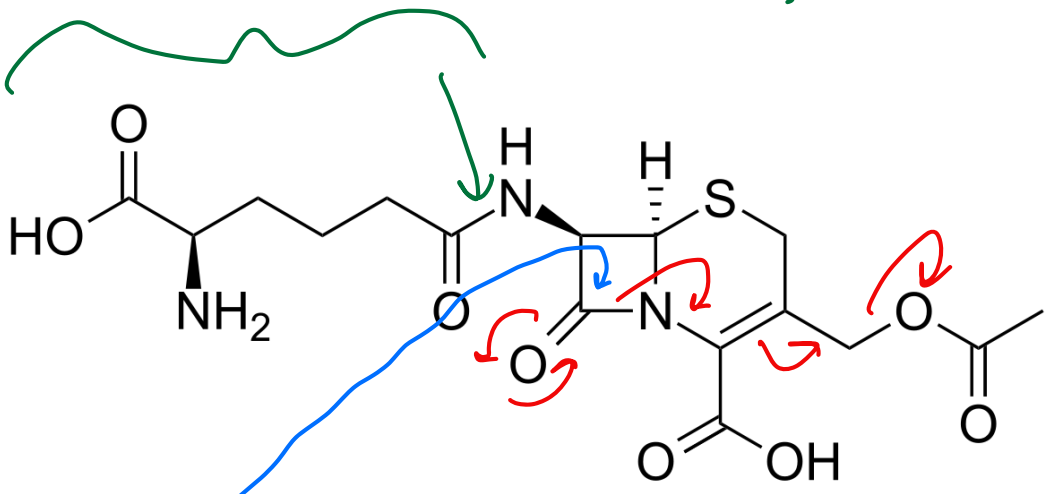
SAR

Similar to penicillin

SAR


R'
H
N
O
S
N
O
R''
CO_2H
Cys
Val
mostly
mess
with this
can
make
pro drugs
by
adding
here

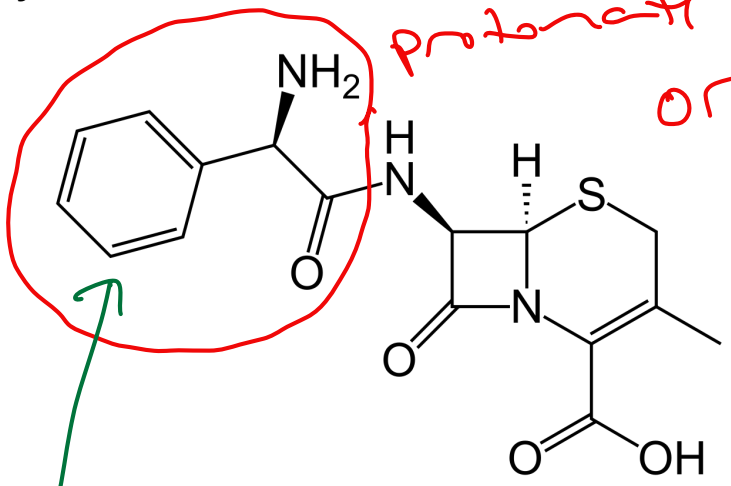
Cephalosporin C



First Generation Cephalosporins

Cefalexin

Primarily used for Gram + cocci



protonated

orally available

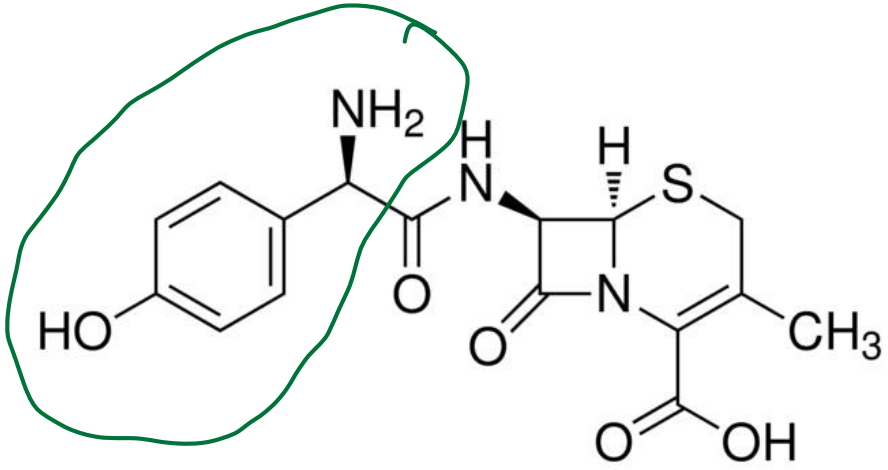
usually a phenylhere

looks like a dipeptide

carrier mediated transport to absorb

First Generation Cephalosporins

Cefadroxil



another orally available

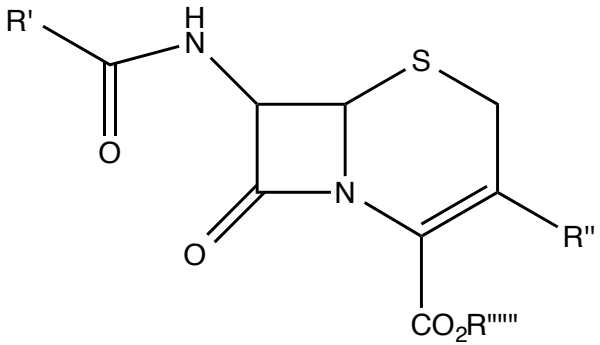
Second Generation Cephalosporins

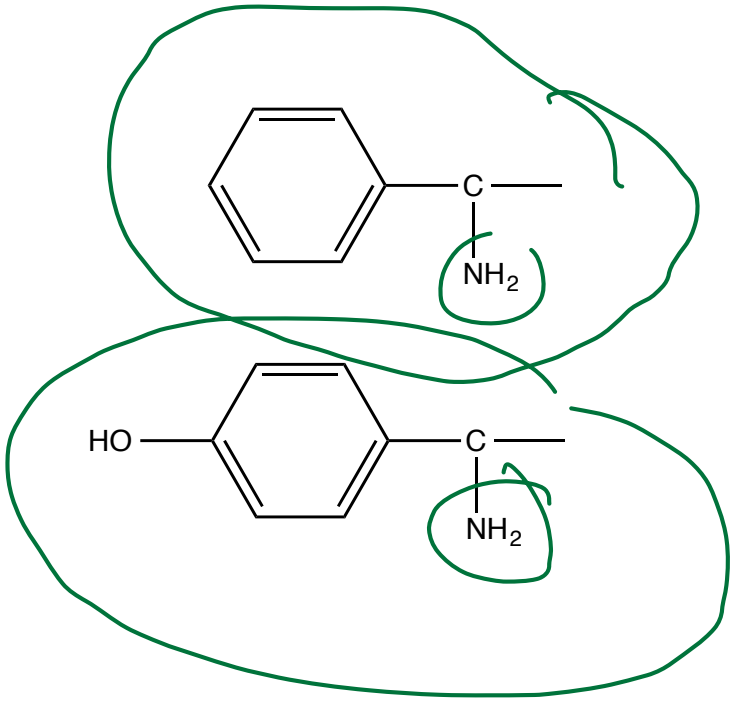
Increased activity against some Gram -

Third Generation Cephalosporins

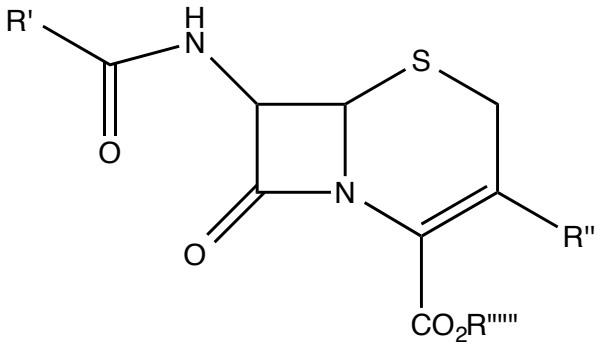
Good for Gram -, not very good for Staph

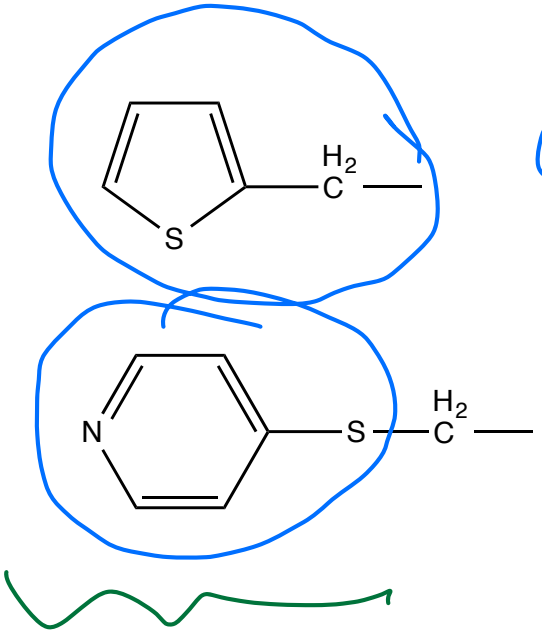
Oral vs Parenteral Cephalosporins





Oral vs Parenteral Cephalosporins



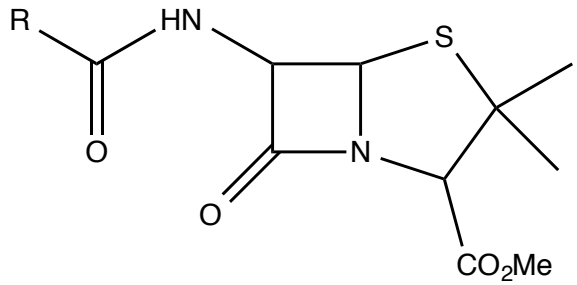


cephalothin
IM or IV

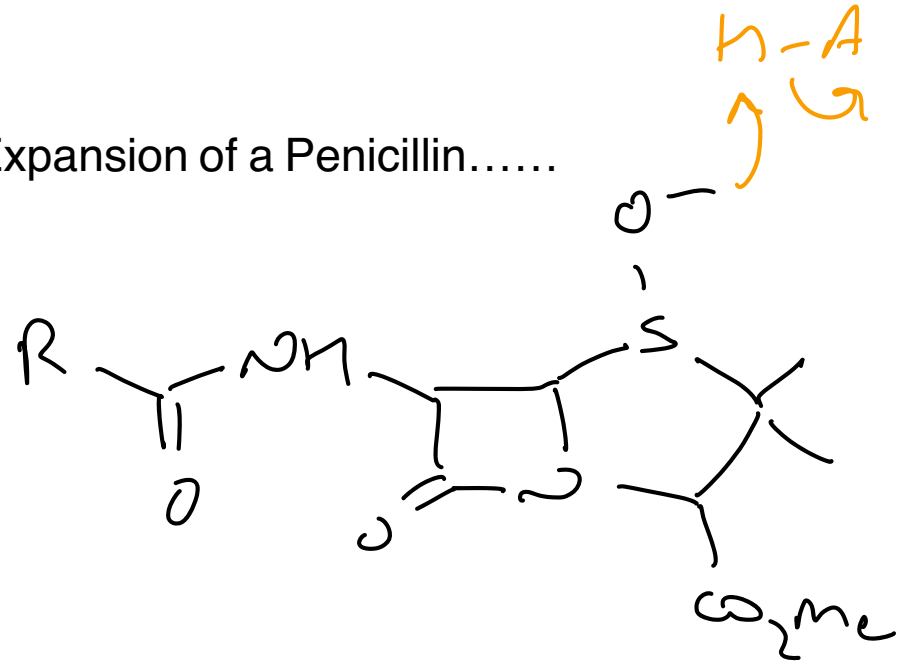
cephapirin

Synthesis of Cephalosporins

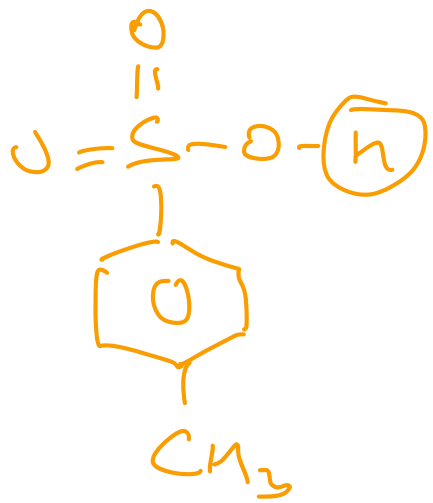
Ring Expansion of a Penicillin……

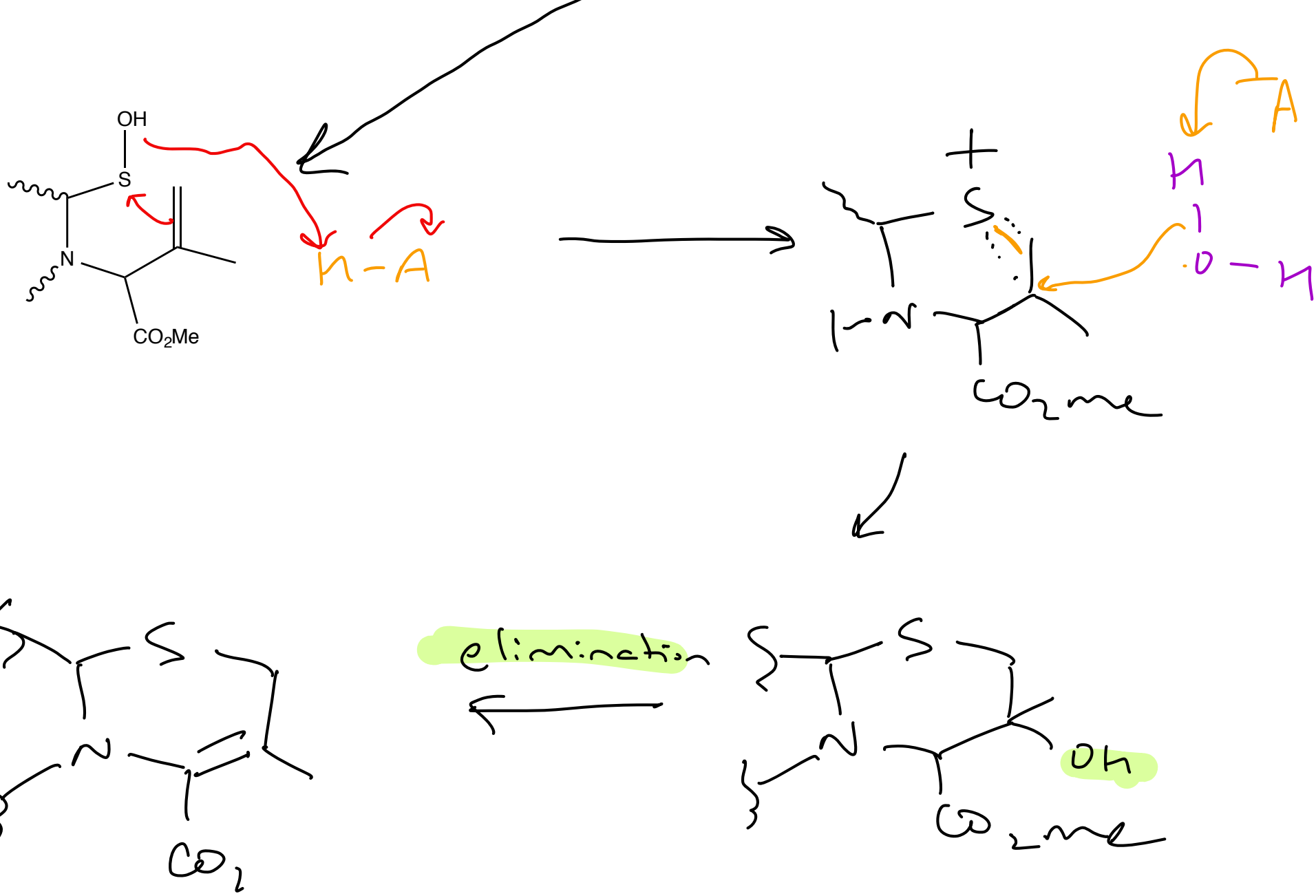


H_2O_2

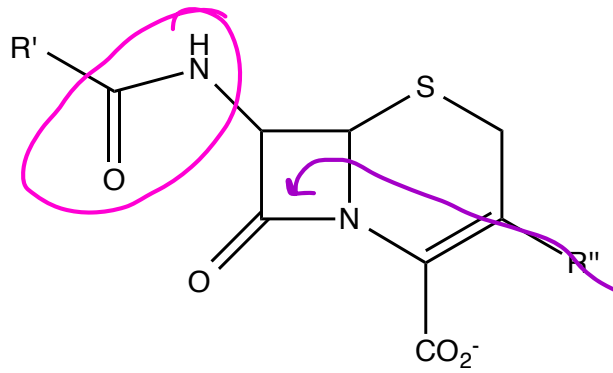


PTSA = HA




OH
S
N
CO2Me
H-A
A
H
O-H
elimination
OH

Modifying Cephalopsorins



to change the R need to hydrolyze this amide without hydrolyzing this amid

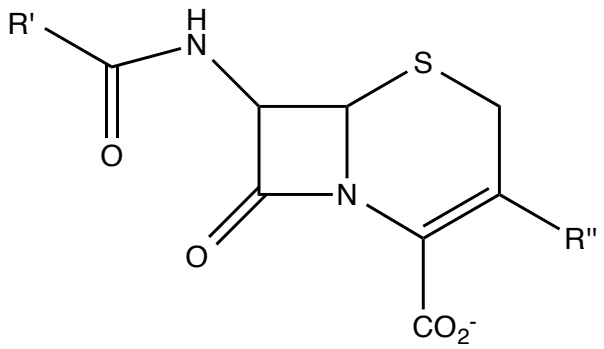
*make an imino ether

OR

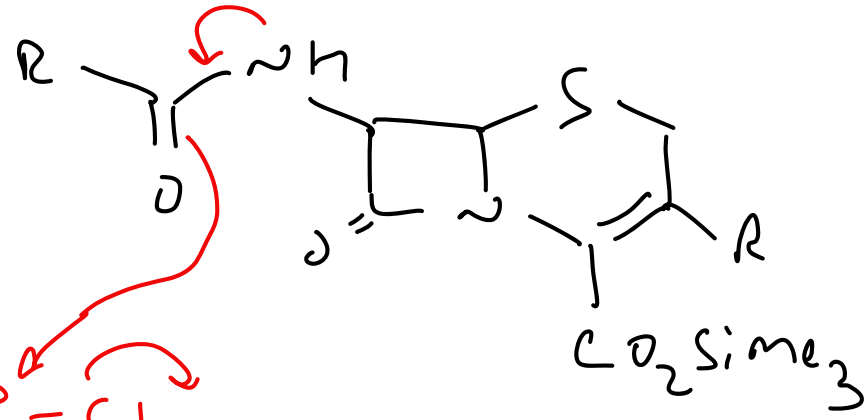
$-C=N-$

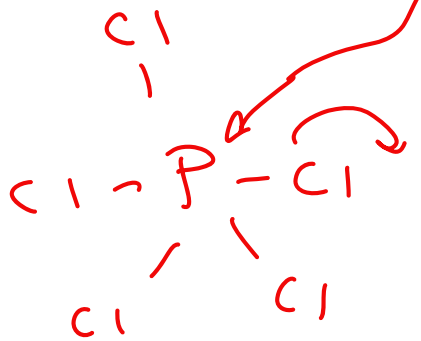
more susceptible to acid hydolysis

*can do same with penicillins

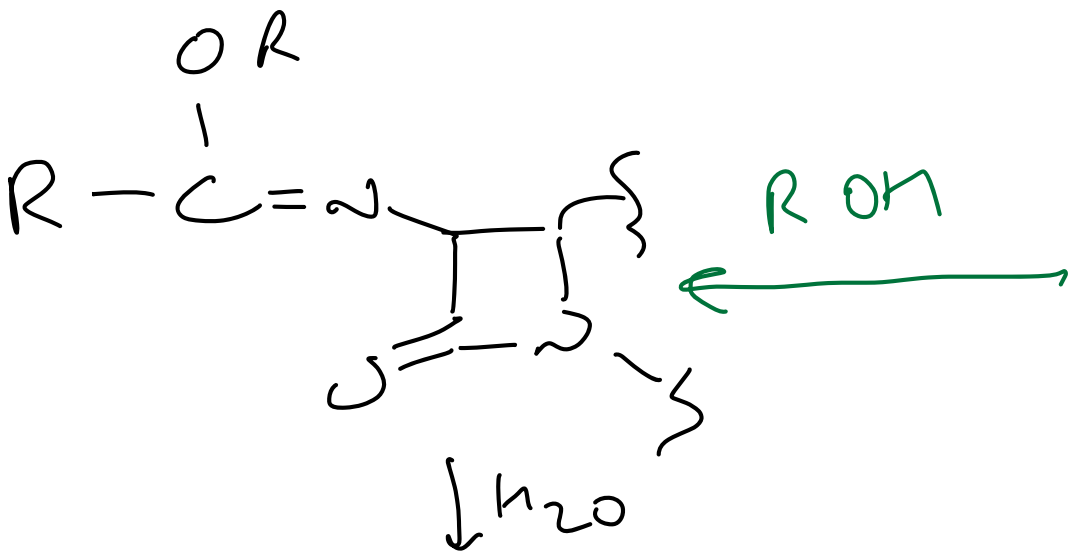


first cover the $-CO_2H$ with TMS

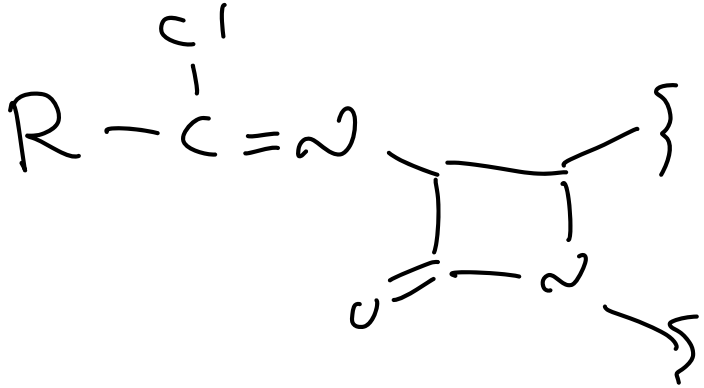




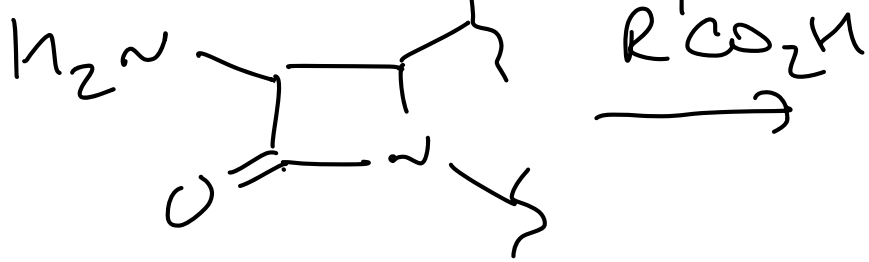
PCl_5

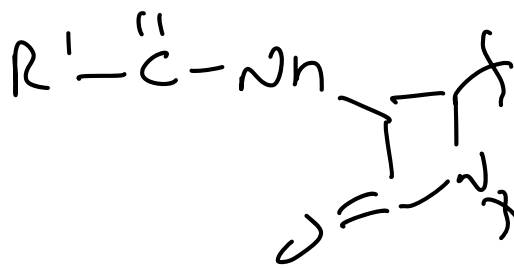


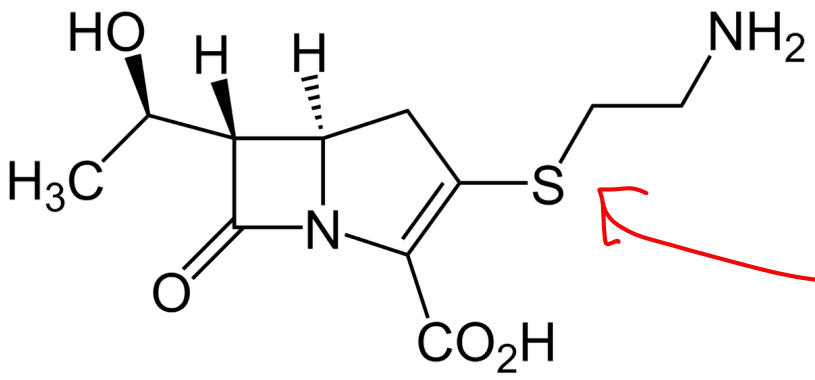
ROH



Carbapenems

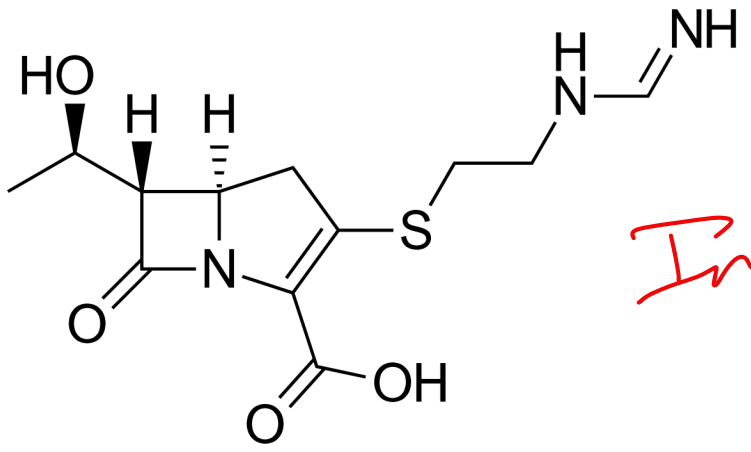




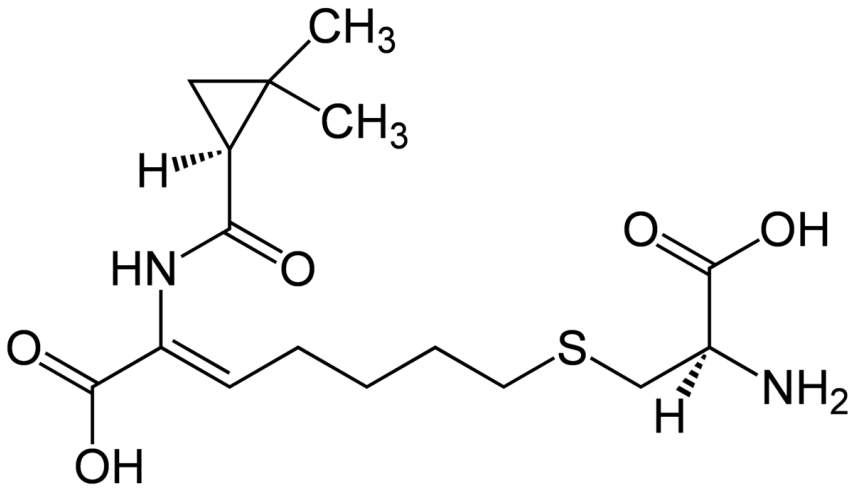


Similar to Cephalosporin

So on Outside



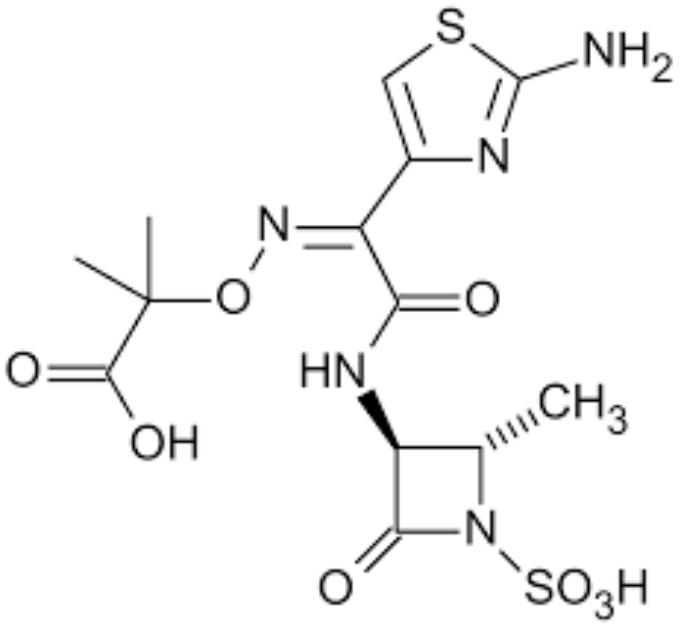
Imipenem



cilastatin

Sentry drug for carbapenems

Monobactams



Aztreonam

Antibiotic Nomenclature

-cillins — derived from fungi, penicillins

cef-
ceph- — derived from fungi cephalosporin

-floxacin — synthetic fluoroquinolones

-mycin — isolated from streptomyces

-micin — isolated from other soil microbes