Lec 4 4th stage

Organic Pharmaceutical Chemistry III
2018-2019

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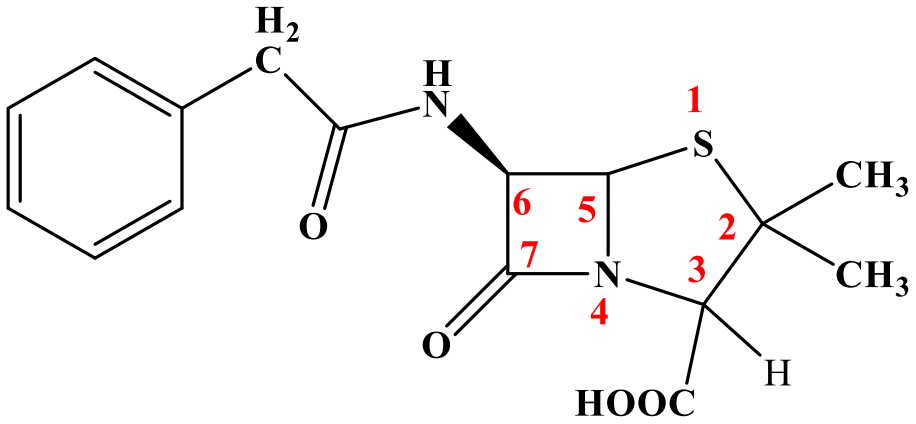
Textbook of Organic medicinal and pharmaceutical chemistry

Wilson and Gisvold's

Products

Penicillin G (benzylpenicillin)



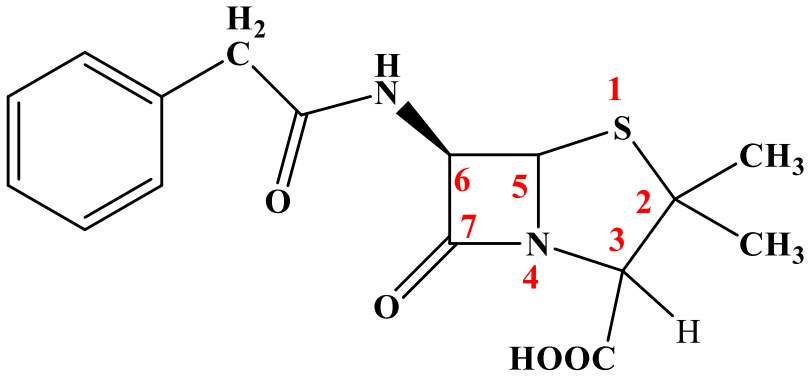
SAR :-

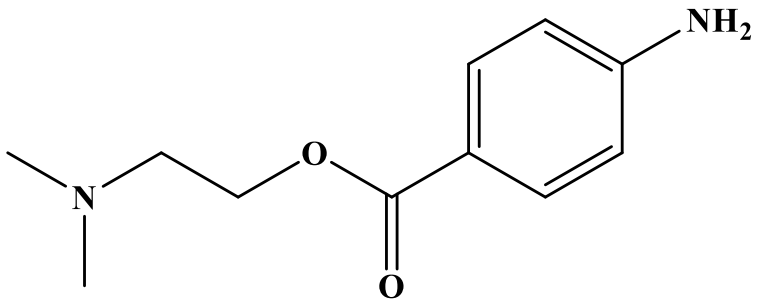
Unsubstituted Cα so the antibiotic acid liable, penicillinase sensitive, narrow spectrum.

Na+ and K+ salts of penicillin G→ water soluble and fast acting , used orally and parenterally to achieve high plasma concentrations of penicillin G rapidly.

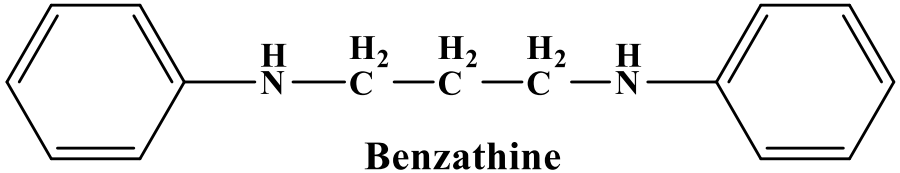
These salts of penicillin are inactivated by the gastric juice and are not effective when administered orally unless antacids, is added. Also, because penicillin is absorbed poorly from the intestinal tract, oral doses must be very large, about five times the amount necessary with parenteral administration.

Procaine penG (Crystacillin), and Benzathine PenG(bicillin)→ inj. In H_2O or oil, long acting



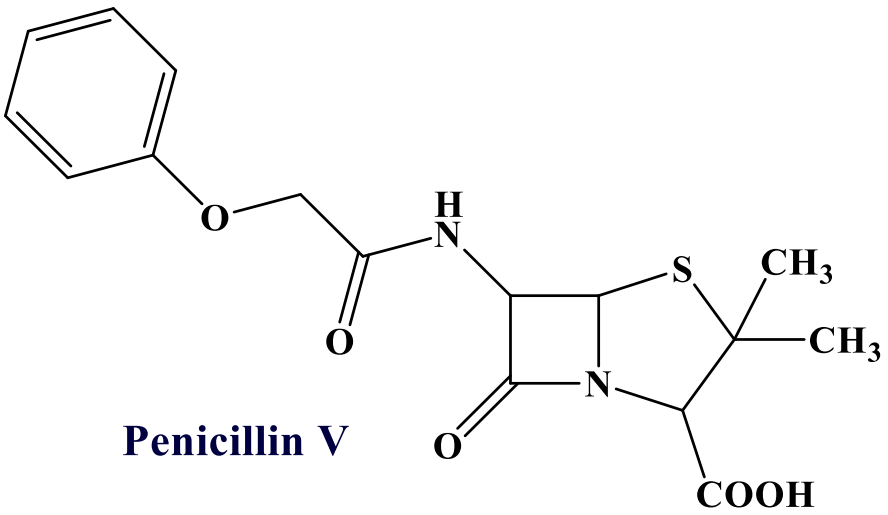


Procain



Benzathine

Penicillin V (Phenoxy methyl penicillin)

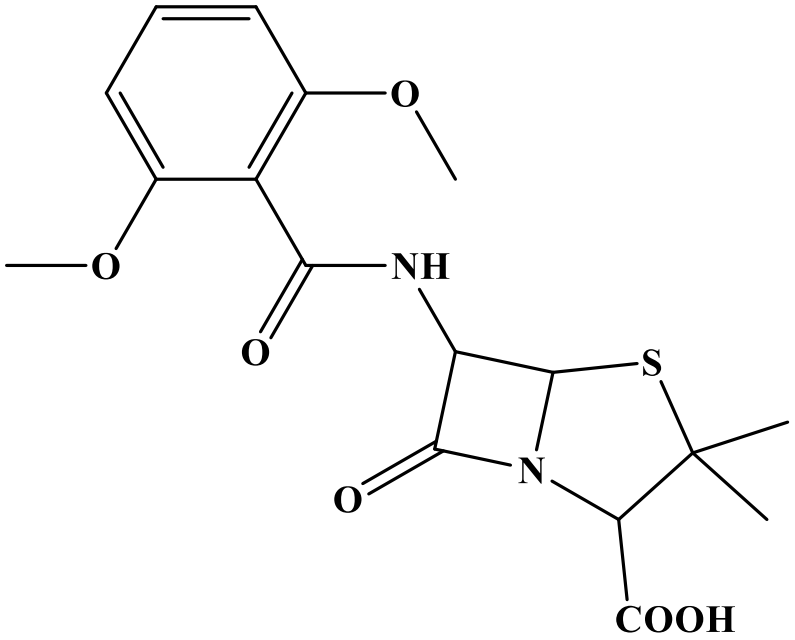


Penicillin V

SAR :-

- Electron withdrawing oxygen between Cα and benzene generate antibiotic with good acid stability and good oral activity.
- Cα is not substituted or remove so the antibiotic is penicillinase sensitive.
- narrow spectrum, lipophilic side chain, selective G+.
- K+ sat → water soluble, fast acting, organic salt, long acting as in compocillin V

Methacillin sodium



2,6-dimethoxyphenylpenicillin sodium

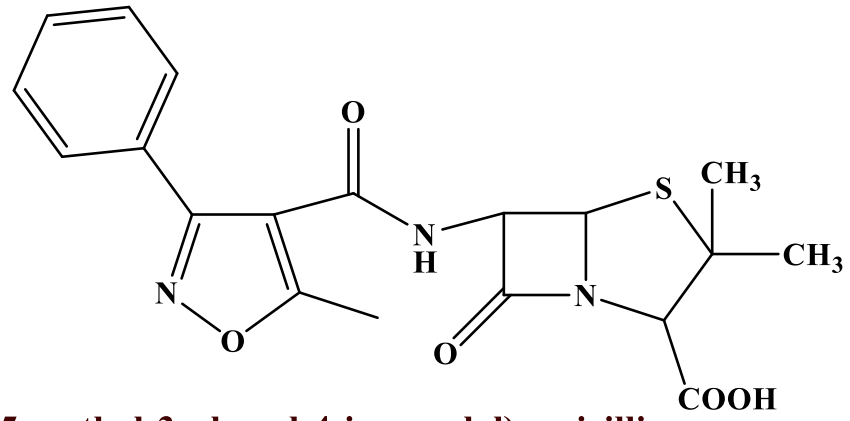
SAR:-

•Cα is removed and the carbonyl side chain is directly attach to aromatic ring so the antibiotic is penicillinase resistance.

•Narrow spectrum.

•OCH3 groups π e^- donors and are conjugated with acyl group so it increases δ^- character of side chain acyl oxygen result in poor acid stability, poor oral activity.

Oxacillin Sodium

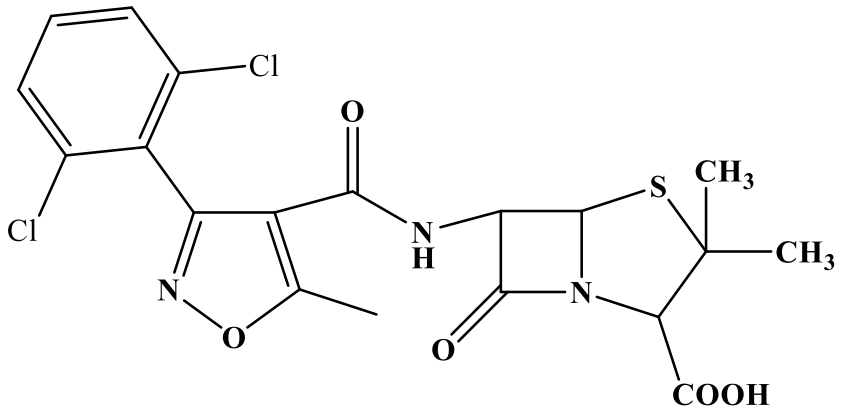


(5-methyl-3-phenyl-4-isoxazolyl)penicillin

SAR:-

- Cα is removed and the carbonyl side chain is directly attach 3-phenyl and 5-methyl groups of the isoxazolyl ring so the antibiotic is penicillinase resistance.
- It is also relatively resistant to acid hydrolysis and, therefore, may be administered orally with good effect.(e- withdrawing group isoxazole)
- Narrow spectrum.

Dicloxacillin sodium



[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]penicillin sodium

SAR :-

•Cα is removed and the carbonyl side chain is directly attach to arylheterocycle, so the antibiotic is penicillinase resistance.

•The dichloro substituent on benzene ring that is substitueted at C-3 of the isoxazole act as strong electron withdrawing groups results in decreases in the nucleophilicity of the oxygen of the acyl side chain and that lead to increase in acid stability and oral activity.

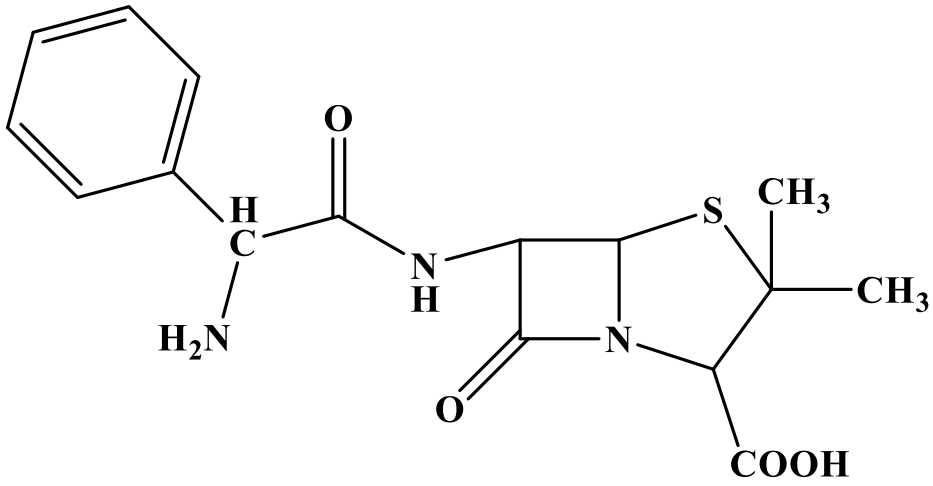
•Compound with only one chloro substituent on the benzene ring as in cloxacillin sodium is still with good oral activity but less than that for dicloxacillin.

•Compound with benzene ring only as in oxacillin this result in decrease in oral activity.

However oxacillin available in oral, IM and IV dosage form.

•Narrow spectrum→ Lipophilic group.

Ampicillin

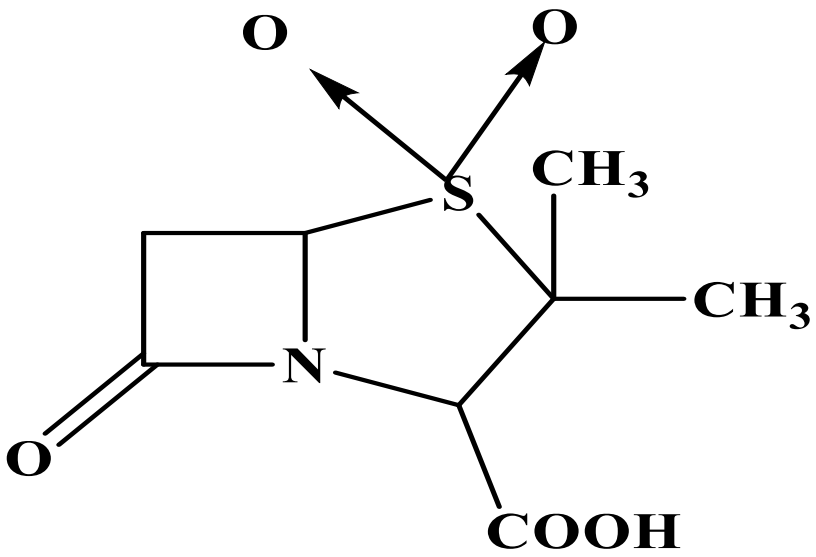


6-[D-α-aminophenylacetamido]penicillanic acid, D-α-aminobenzylpenicillin

SAR :-

- α –NH_2 ionizable at pH= 7.4, polar, with good inductive activity as electron withdrawing group result in good oral stability and activity and broad spectrum of activity.
- Penicillinase sensitive due to the presence of hydrogen on C-α.

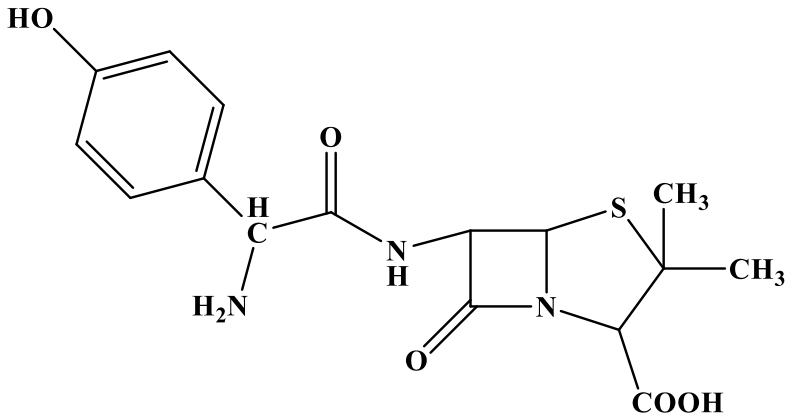
- Combination product with β-lactamase inhibitor such as Sulbactam sodium= provides penicillinase resistance drug, available for IM and IV use.



Sulbactam

Sulbactam sodium or potassium salts, selective inhibitor for β-lactamase because of greater affinity to with β-lactamase than penicillins. Thus protecting the antibiotics from destruction by the enzyme.

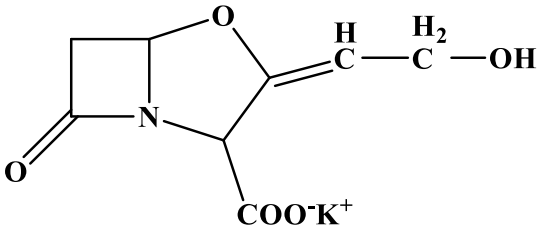
Amoxicillin



6-[D-(-)-α-amino-p- hydroxyphenylacetamido] penicillanic acid

SAR :-

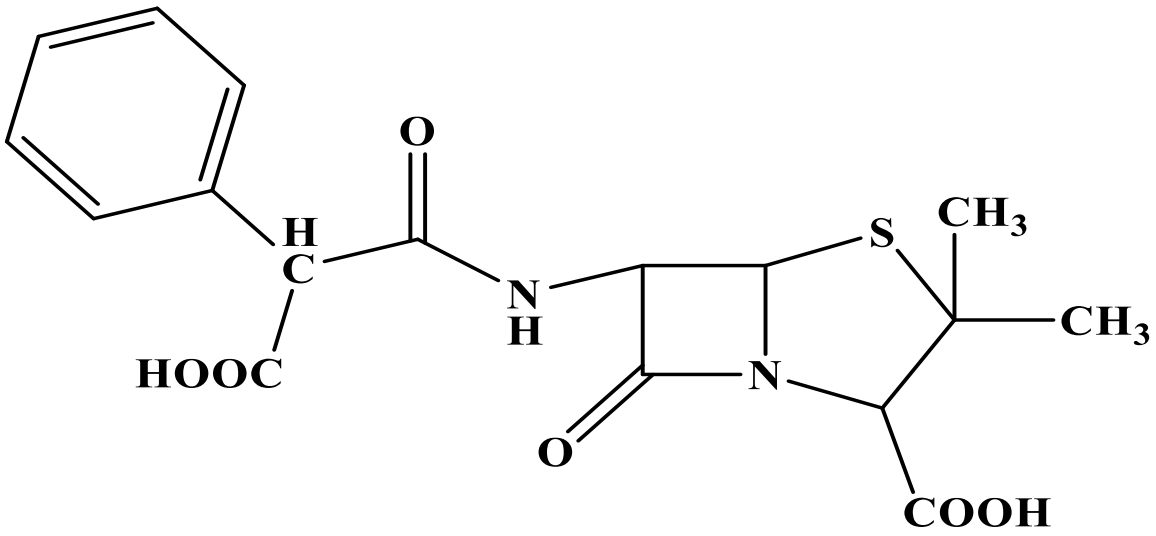
- Same spectrum of activity as that for ampicillin but has increase oral availability.
- Spent less time in the GI tract, result in decrease in GI upset.
- Sensitive to β-lactamase, given in combination clavulante (**Augmentin)**



Potassium Clavulante

Clavam derivative with higher affinity for β-lactamase than penicillin resulted in protection from destruction as discussed with sulbactam.

Carbenicillin Disodium•

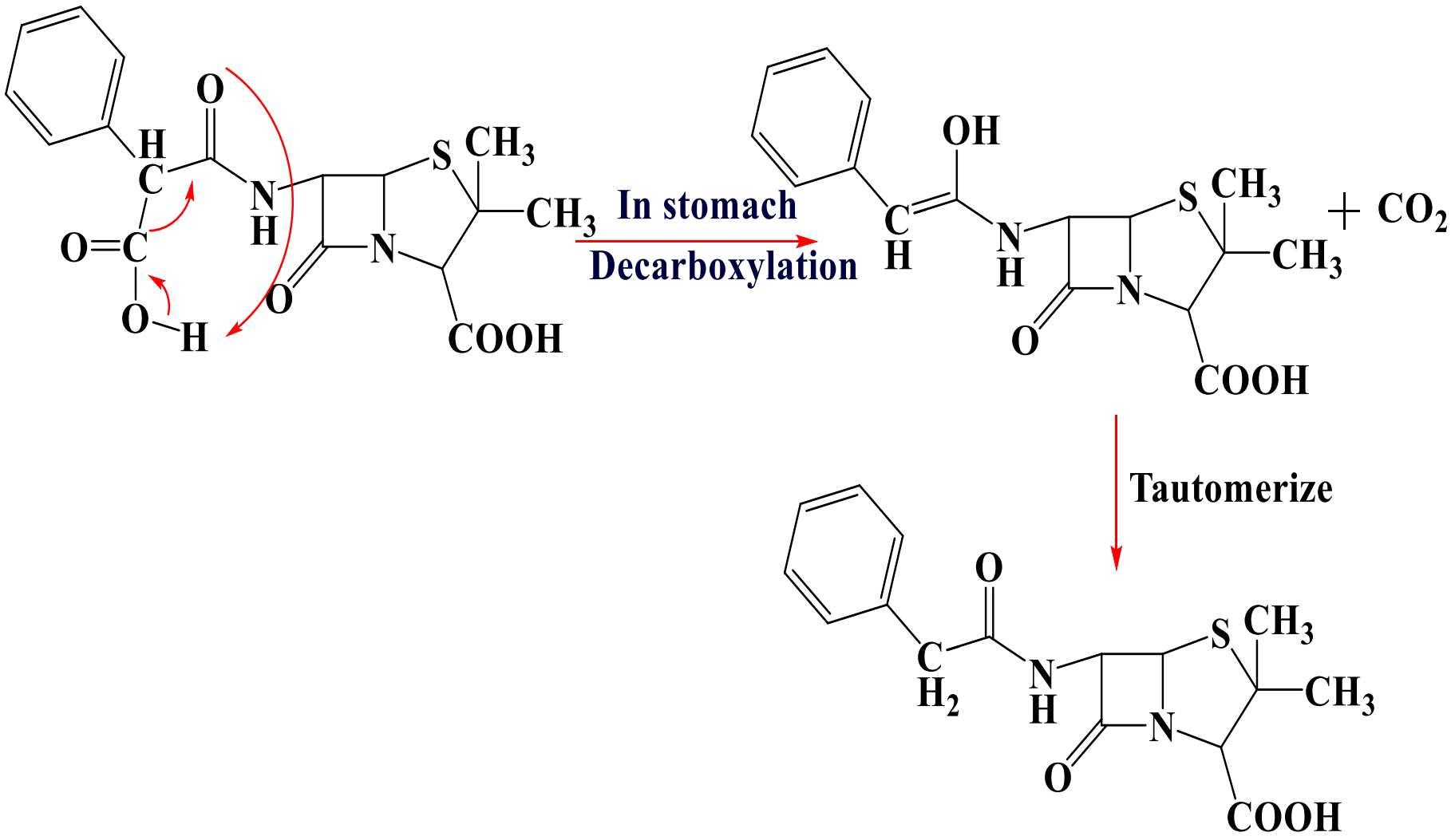


Adding polar functional group to C-α broadens spectrum of activity (drug is now able to penetrate through polar channels in G^- cell wall),this will increase G^- activity and decrease G^+ activity.

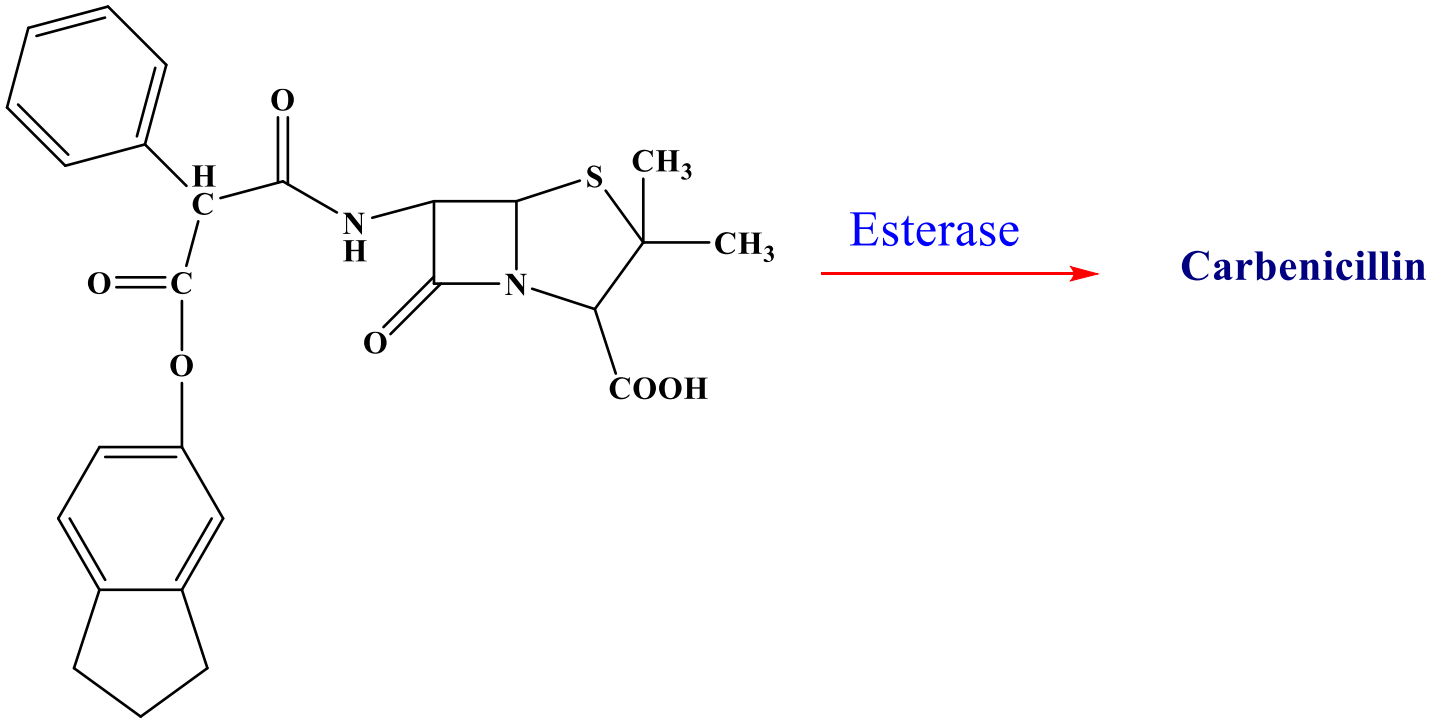
•α-COOH (most highly ionized).

•α-COOH gives drug extended spectrum (G^+, G^- anaerobes) broaden than ampicillin in activity.

•α-COOH is acid liable (COOH is electron withdrawing but undergoes acid catalyzed decarboxylation generating penicillin as shown below, for this reason cannot be given orally


In stomach
Decarboxylation
+ CO2
Tautomerize

to increase acid stability and retain broad spectrum, make an ester • (prodrug)out of the α-carboxyl group, hydrolysis then occurs by esterases in plasma to give carbenicillin as shown below.

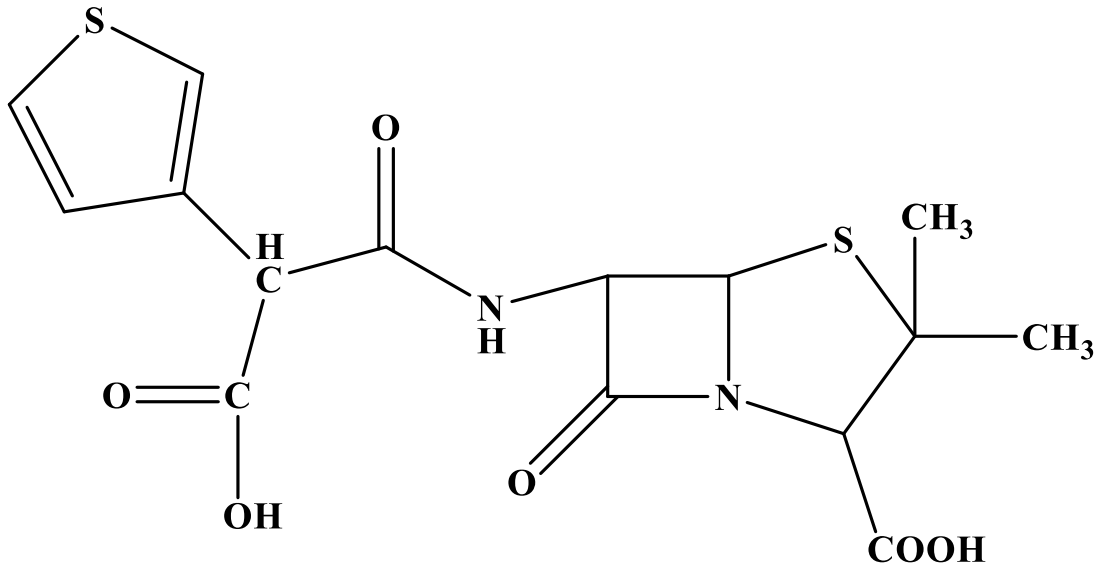


Indan ester of Carbenicillin

1. penicillinase sensitive (C-α- hydrogen present).

2. R- isomer = S-isomer in terms of potency.

Ticarcillin, Carbenicillin analog



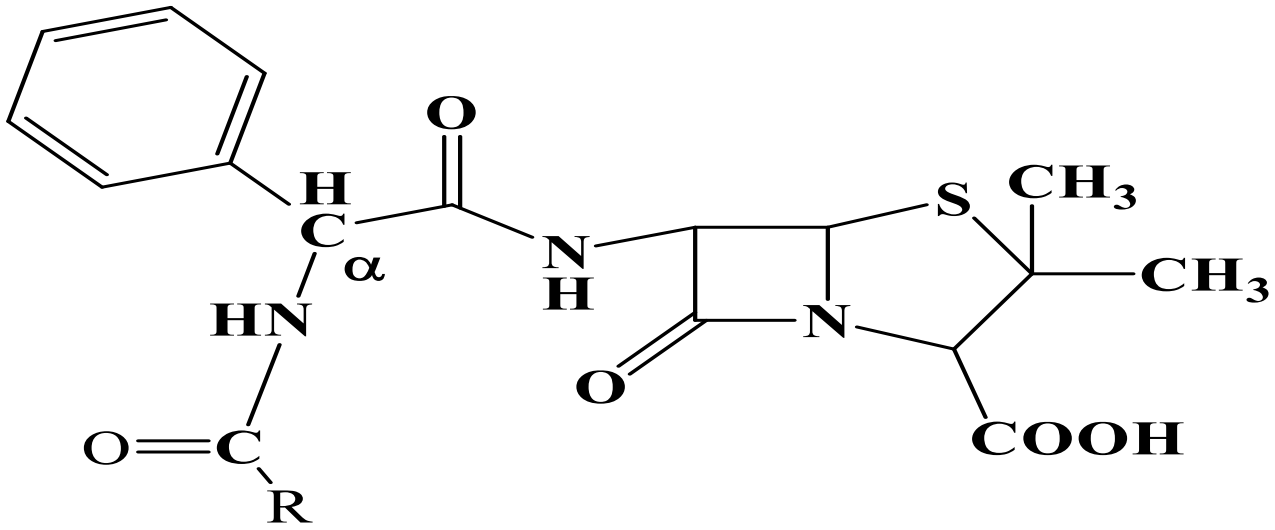
Benzene ring in carbenicillin replaced by aromatic thienyl ring

SAR:-

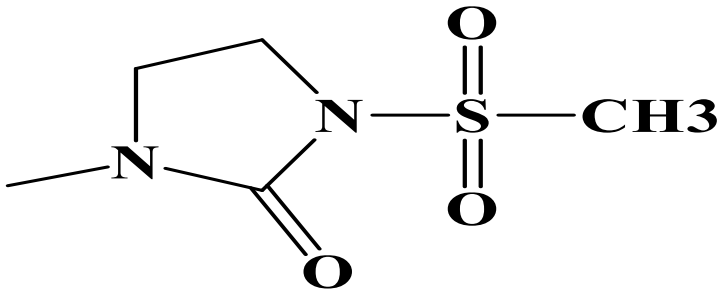
- Activity similar to carbenicillin but thienyl ring is more polar than benzene. Is active against more anaerobes.
- Available in combination with potassium Clavulanate (timentine).
- Available as disodium salt.

Extended spectrum of activity

- Series of antibiotics structurally related to ampicillin with a very broad spectrum (G+, G- and anaerobes).
- All have an amide linkage between the side chain acyl group and a N-containing heterocyclic aromatic ring.
- All are penicillinase sensitive.
- All are given orally, IM, IV, but their structure indicate that they should show acid stability.

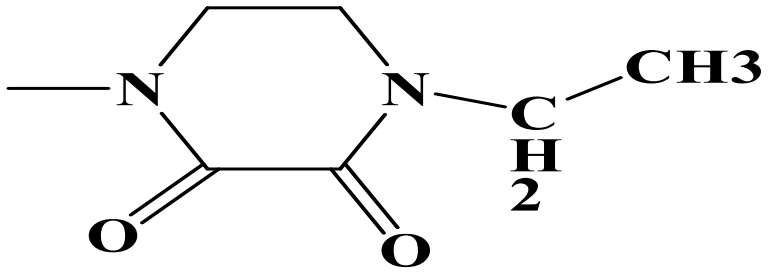


R=



Mezlocillin

R=



Piperacillin