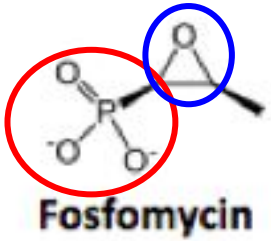
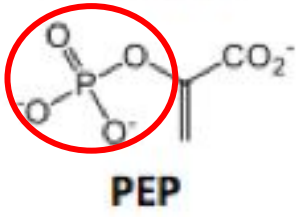
Cell Wall Biosynthesis Inhibitors

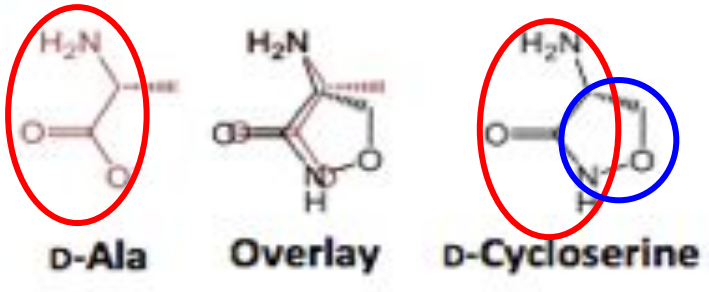
SAR Learn Tool

- **SAR Requirements**
  - **Fosfomycin**
    - 1. PEP mimic
    - 2. Reactive epoxide group



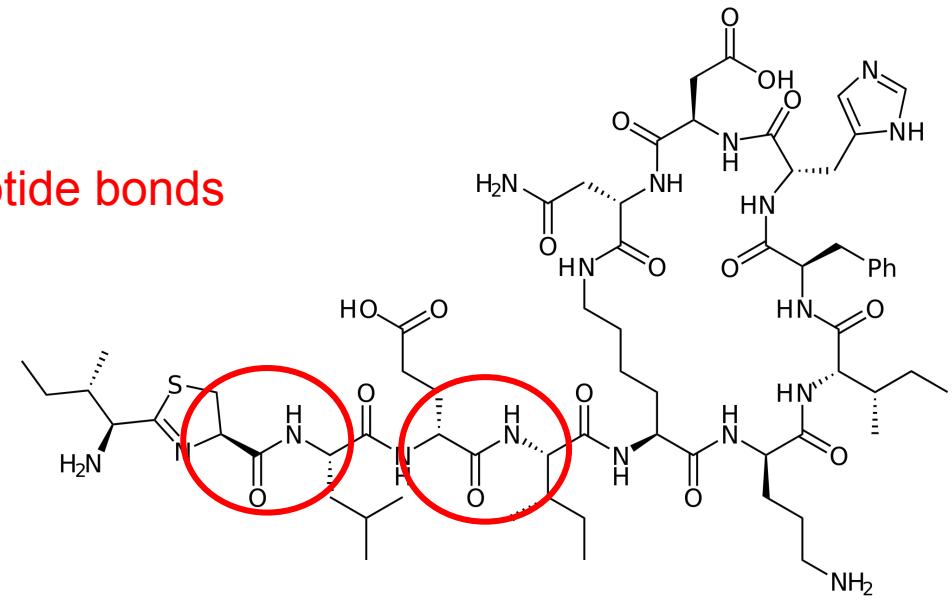


  - **Cycloserine**
    - 1. D-Ala analogue
    - 2. 5- membered ring



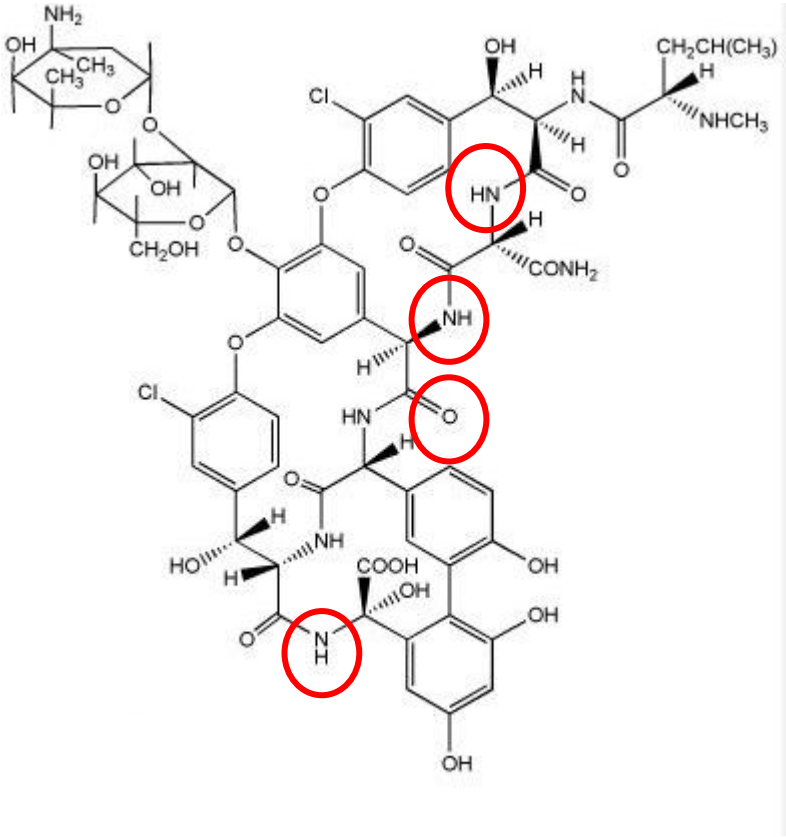
SAR Learn Tool

- **SAR Requirements**
  - **Bacitracin**
    - Large molecule
    - Contains many peptide bonds



SAR Learn Tool

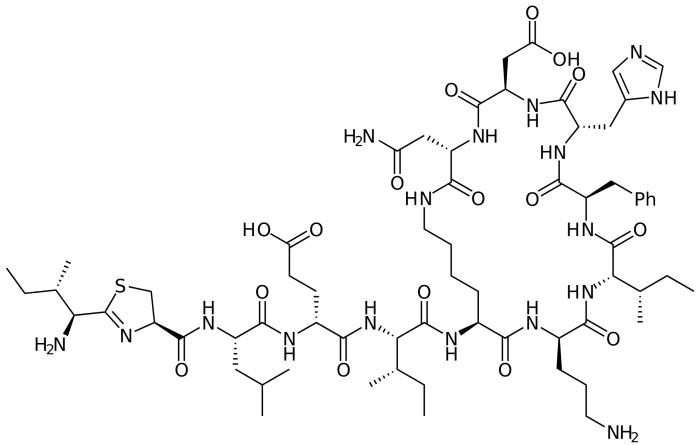
- **SAR Requirements**
  - **Vancomycin**
    - Large molecule
    - Contains many peptide bonds
    - Circled atoms form hydrogen bonds with D-Ala-D-Ala

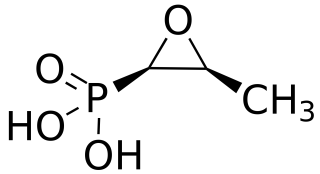


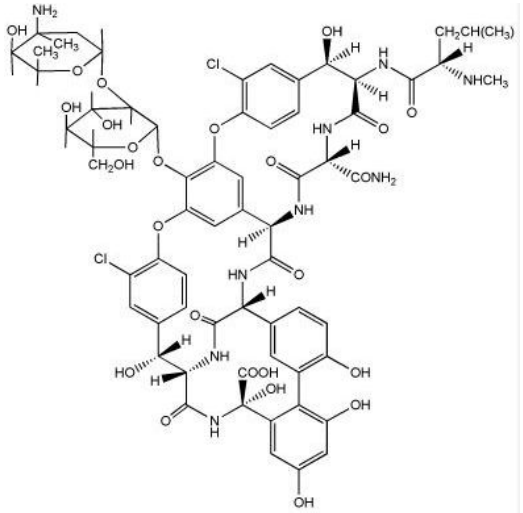
SAR Learn Tool

- **PRACTICE PROBLEM- Mechanism of Action**

Which compound below interferes with peptide cross-linking?





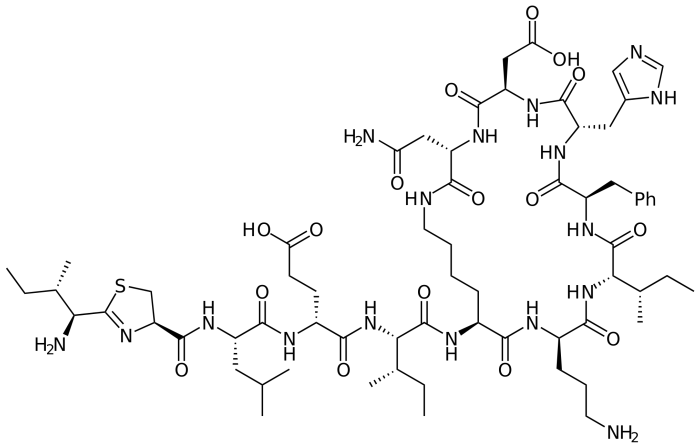


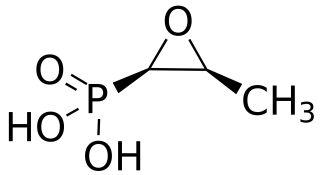
  - **ANSWER: Compound 3 (Vancomycin)**
    - Binds directly to the D-Ala-D-Ala terminal to prevent peptide cross-linking

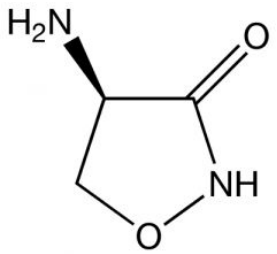
SAR Learn Tool

- **PRACTICE PROBLEM- Mechanism of Action**

Which compound below inhibits the conversion of UDP-NAG→ UDP-NAM?





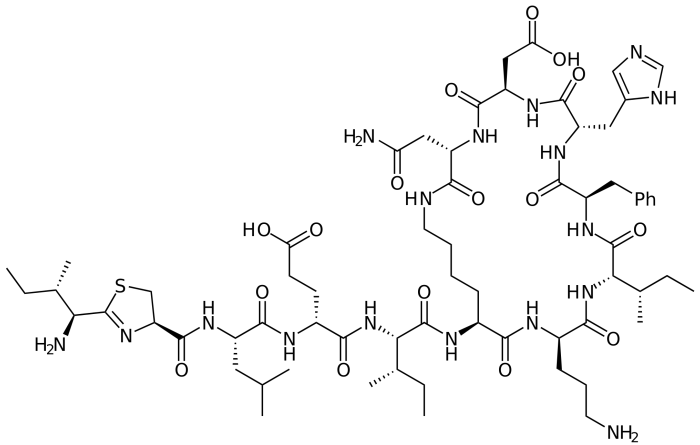


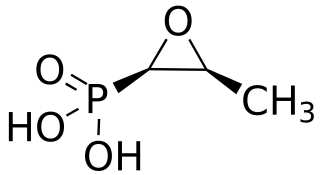
  - **ANSWER: Compound 2 (fosfomycin)**
    - Results in irreversible alkylation of the active cysteine on MurA

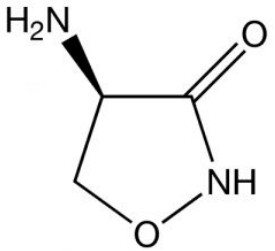
SAR Learn Tool

- **PRACTICE PROBLEM- Mechanism of Action**

Which compound below inhibits Ala racemase & D-Ala ligase?





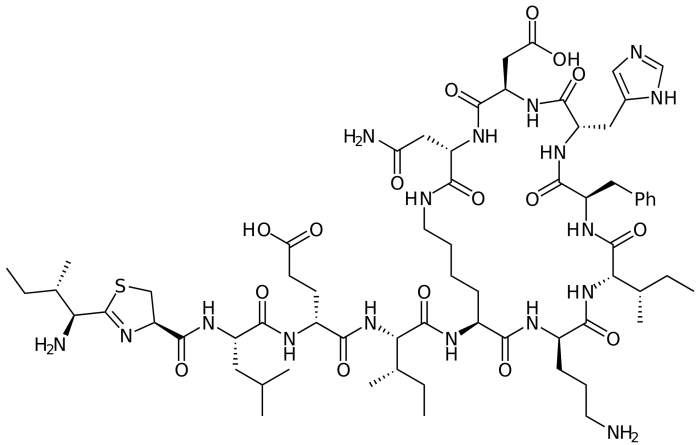


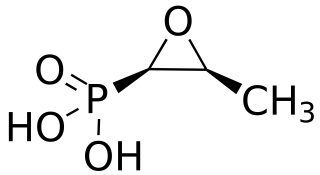
  - **ANSWER: Compound 3 (cycloserine)**
    - Prevents conversion of L-Ala→ D-Ala and the joining of D-Ala & D-Ala

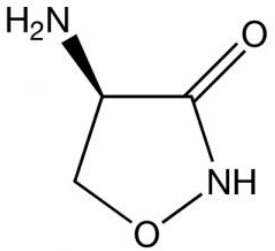
SAR Learn Tool

- **PRACTICE PROBLEM- Mechanism of Action**

Which compound below inhibits pyrophosphatase?



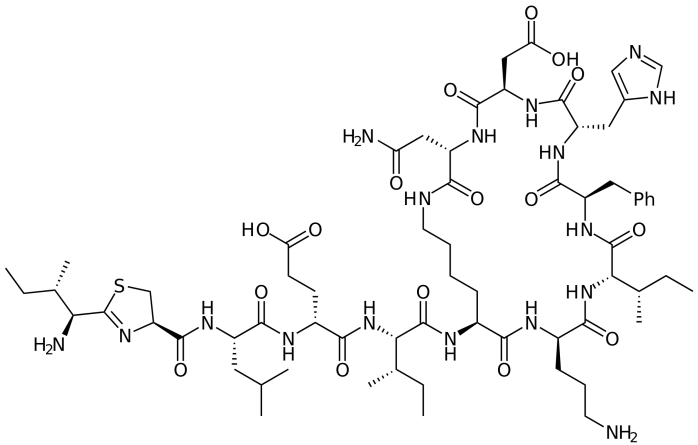


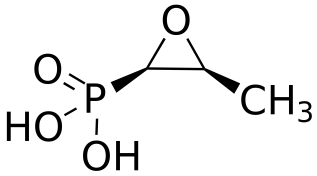


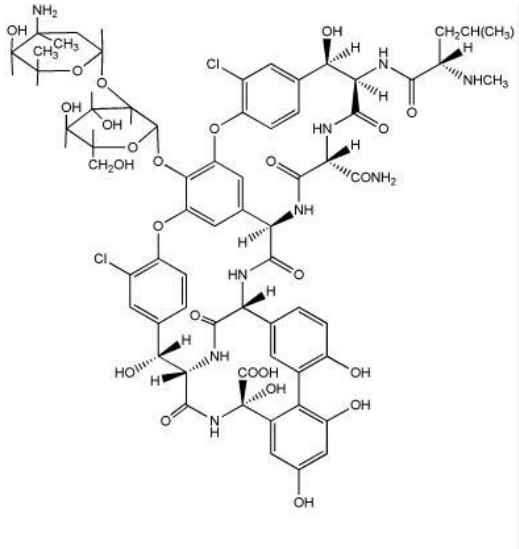
  - **ANSWER: Compound 1 (bacitracin)**
    - Inhibits the recycling of bactoprene molecule

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **GT is diagnosed with C. difficile. Which oral antibiotic would be best to treat his infection?**



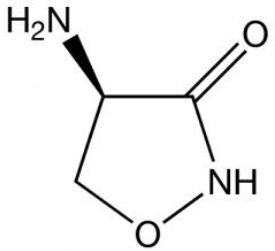


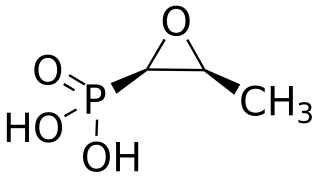


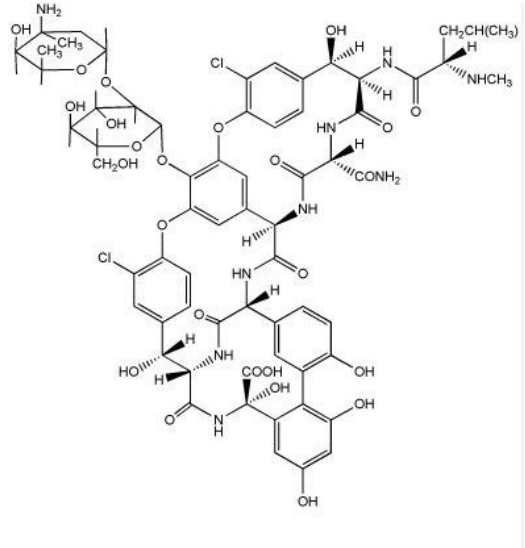
  - **ANSWER: Compound 3 (Vancomycin)**
    - Vancomycin is not orally absorbed, so it will stay in the gut to treat the infection in the large intestine

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **SM is diagnosed with a UTI infection. Which compound would be best to treat his infection and has few side effects?**



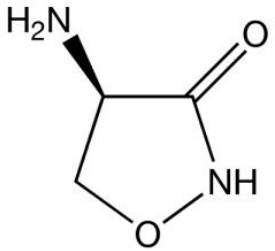


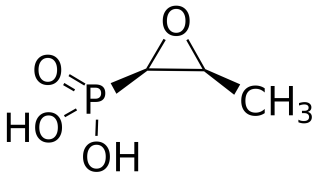


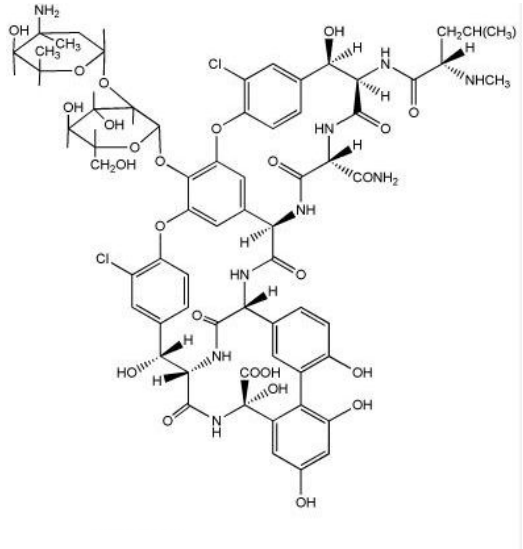
  - **ANSWER: Compound 2 (Fosfomycin)**
    - Fosfomycin is indicated for urinary tract infections, and is especially active against E. Coli

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **GT has a history of psychosis. Which antibiotic below is best avoided in this patient?**



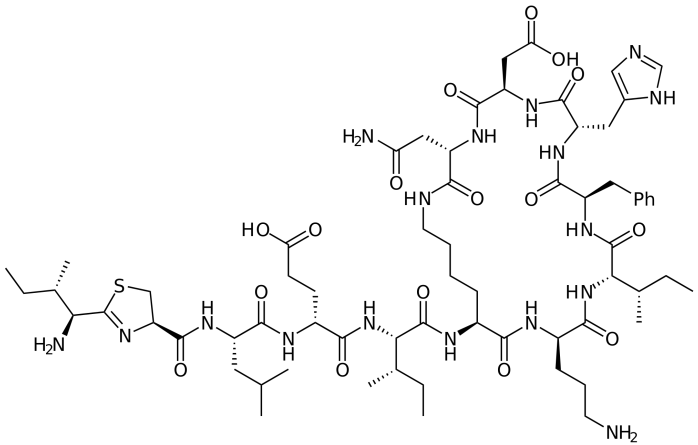


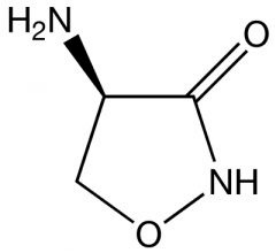


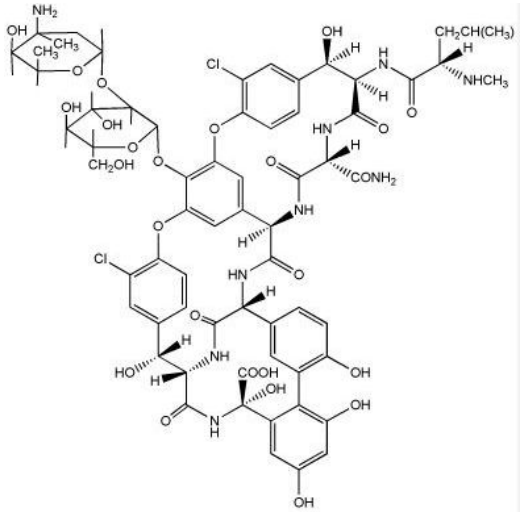
  - **ANSWER: Compound 1 (Cycloserine)**
    - Cycloserine acts as a partial agonist at the NMDA receptor can result in dose-dependent neurologic and psychiatric disturbances.

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **BK has kidney dysfunction. Which 2 antibiotics below have side effects that would be harmful to this patient?**



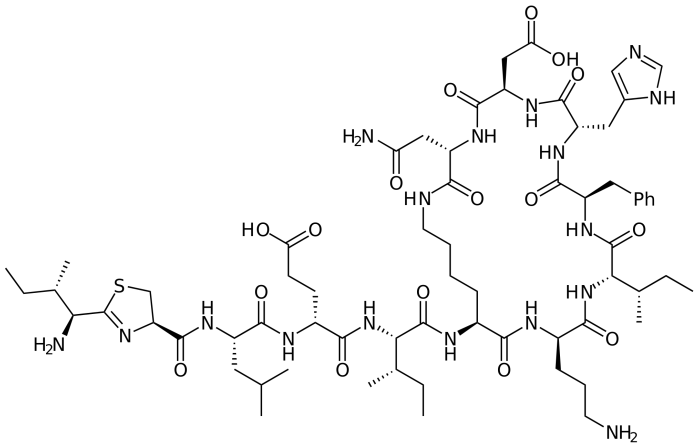


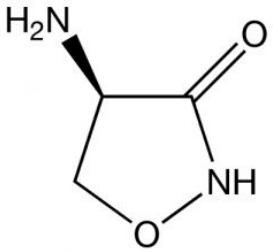


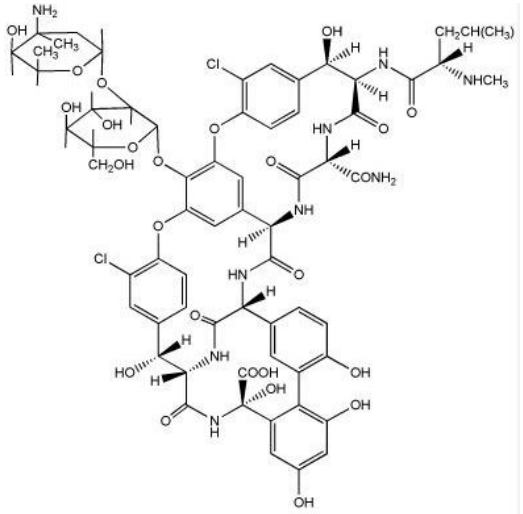
  - **ANSWER: Compound 1 & Compound 2**
    - Bacitracin and vancomycin can both result in nephrotoxicity

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **AM's bacterial infection is not responding to treatment. The bacteria in her body have become resistant to the antibiotic by producing D-Ala-D-Lac. Which of the antibiotics was she taking?**





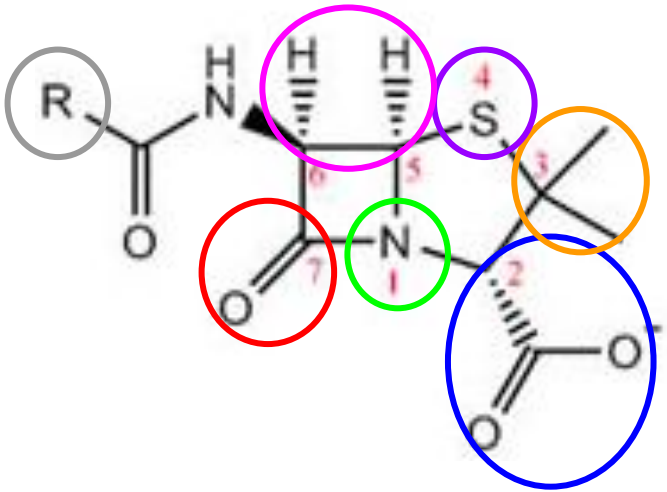


  - **ANSWER: Compound 3 (vancomycin)**
    - Vancomycin normally binds to D-Ala-D-Ala of the pentapeptide tail, but with this change to D-Ala-D-Lac, it can no longer bind

Beta Lactams

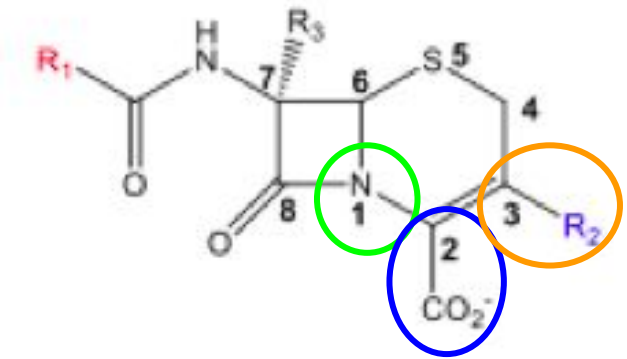
SAR Learn Tool

- **Penicillin SAR Requirements**
  - **B-lactam ring & fused bicyclic system: creates a strained system**
  - **Position 1: must be a nitrogen**
  - **Position 2: must be a carboxylic acid for activity; binds to charged nitrogen of a lysine residue in the binding site**
  - **Position 3: any change will lower activity**
  - **Position 4: sulfur is usual, but not essential**
  - **Position 5: no substitutions allowed; cis stereochemistry with hydrogens at position 5 & 6 is essential**
  - **R group**
    - **EWG: increases the acid stability of the compound**
    - **Bulky group: directly attached to the amide will make the compound more B-lactamase resistant**
    - **Polar group: broadens the spectrum as this allows the compound to pass through the porins of gram negative bacteria**
  - **Position 7: must be a carbonyl**



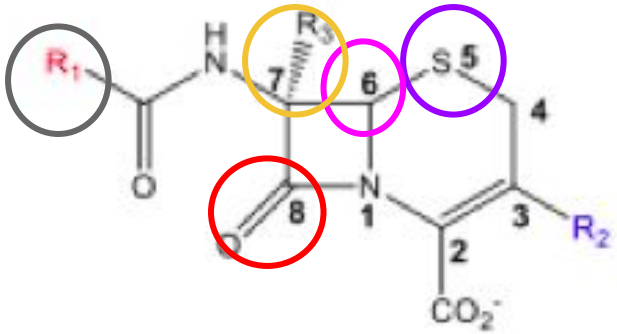
SAR Learn Tool

- **Cephalosporin SAR Requirements**
  - **B-lactam ring & fused bicyclic system: creates a strained system (but less strain than the penicillins, so less reactive)**
  - **Position 1: must be a nitrogen**
  - **Position 2: must be a carboxylic acid for activity; binds to charged nitrogen of a lysine residue in the binding site**
  - **Position 3: R2 group**
    - **Non-metabolized group: increases oral activity & acid stability**
    - **MTT group: extended spectrum, longer-half life, higher potency**
    - **Pyrimidine ring (positive charge): forms a zwitterion & increases solubility**
    - **1,3 thiazole ring: Anti-MRSA activity**



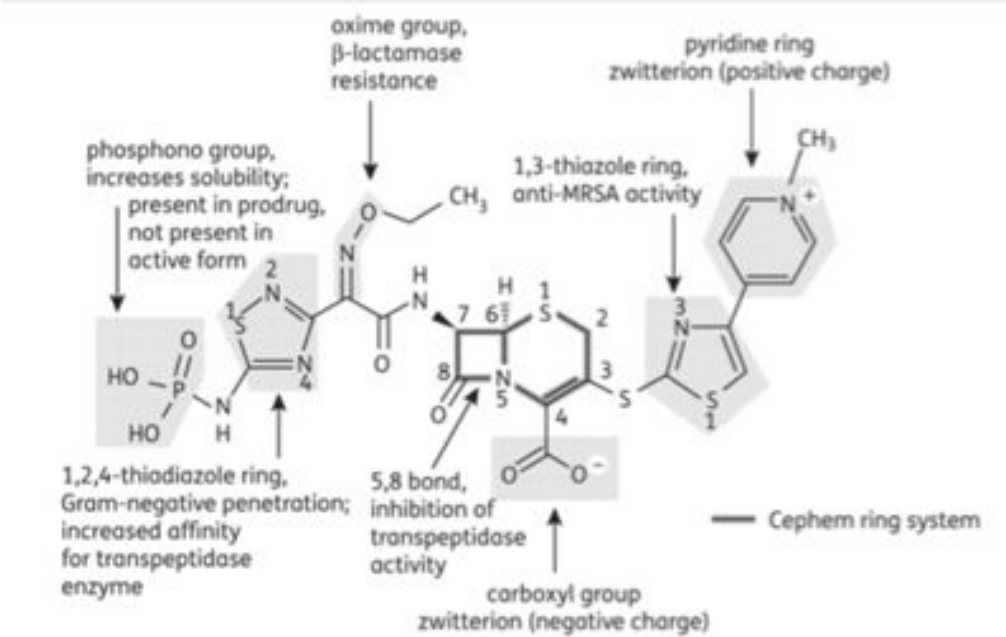
SAR Learn Tool

- **Cephalosporin SAR Requirements**
  - **Position 5: sulfur is usual, but not essential**
  - **Position 6: no substitutions allowed;**
  - **Position 7: R3 group- addition of OCH3 (7-alpha-methoxy) increases B-lactamase resistance**
  - **R1 group**
    - **EWG: increases the acid stability of the compound**
    - **Bulky group: directly attached to the amide will make the compound more B-lactamase resistant**
    - **Polar group: broadens the spectrum as this allows the compound to pass through the porins of gram negative bacteria**
    - **Oxime: increases B-lactamase resistance**
  - **Position 8: must be a carbonyl**



SAR Learn Tool

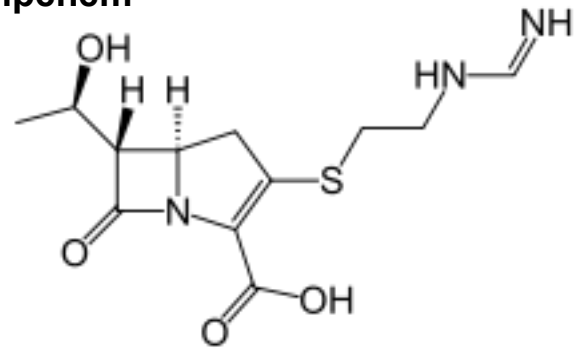
- **Cephalosporin SAR Requirements**
  - **Specific requirements for Ceftaroline (5th generation) to be aware of**



SAR Learn Tool

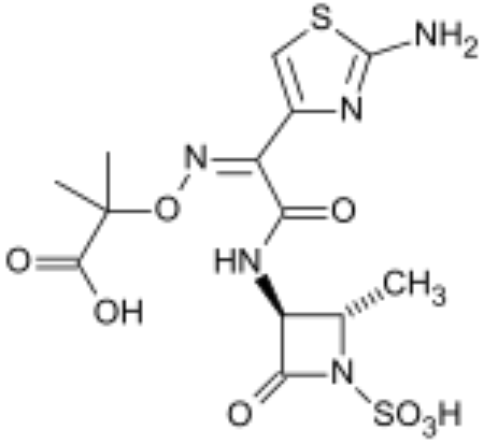
- **Other B-lactam classes:**
  - **Carbapenems**
    - **Unsaturated 5-membered ring connected to the B-lactam ring**

Imipenem



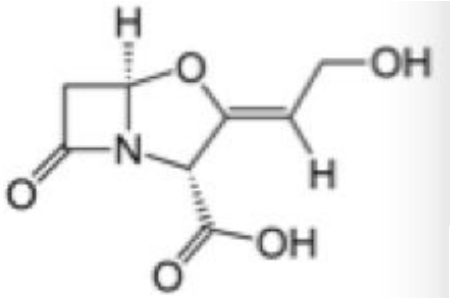
  - **Monobactams**
    - **Only a single B-lactam ring**

Aztreonam

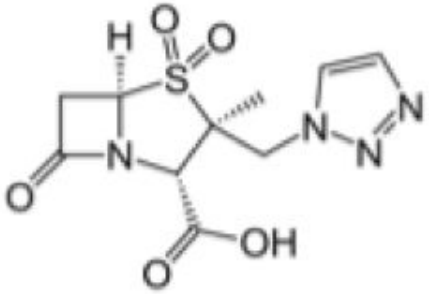


SAR Learn Tools

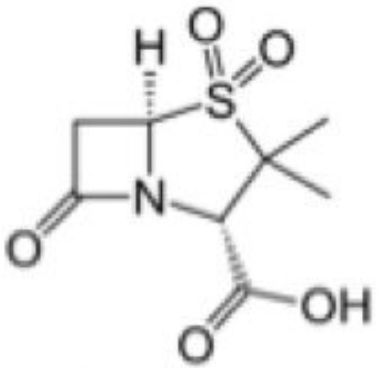
- **B-lactamase Inhibitors**



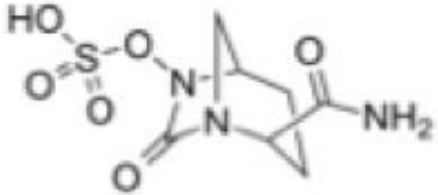
Clavulanic acid



Tazobactam



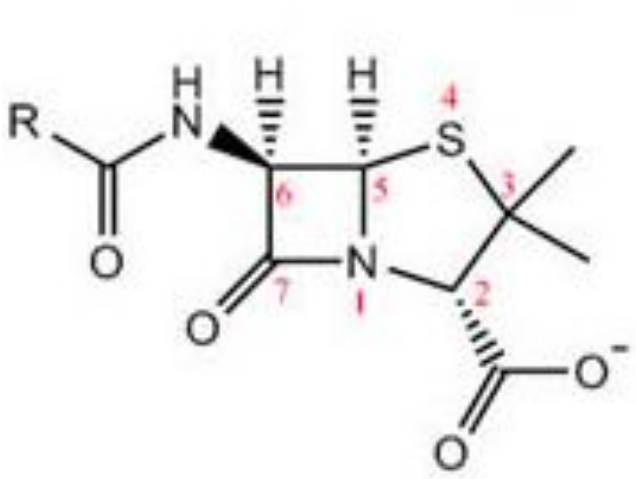
Sulbactam



Avibactam

SAR Learn Tool

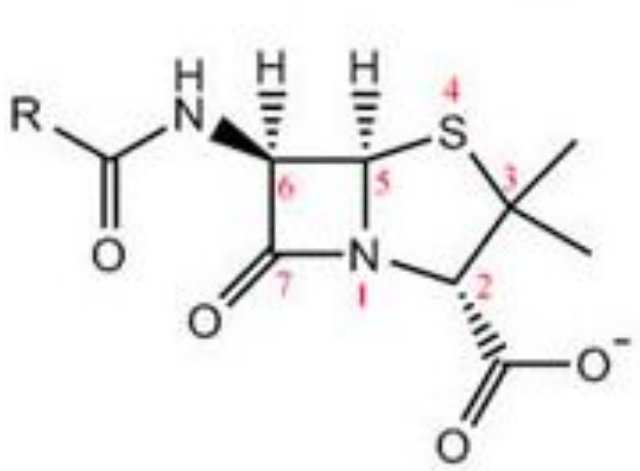
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which addition to amide side chain (R) broadens the spectrum of penicillins?**
    - **Bulky group**
    - **Heterocyclic ring**
    - **Polar group**
    - **Electron withdrawing group**



  - **ANSWER: Polar group**

SAR Learn Tool

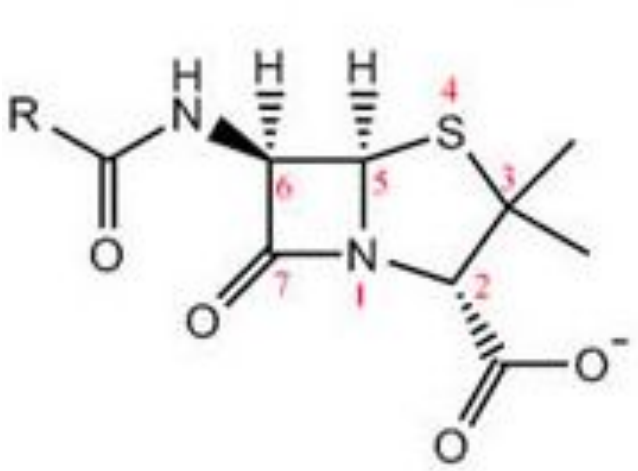
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which addition to amide side chain (R) makes penicillins more acid stable?**
    - **Bulky group**
    - **Heterocyclic ring**
    - **Polar group**
    - **Electron withdrawing group**



  - **ANSWER: Electron withdrawing group**

SAR Learn Tool

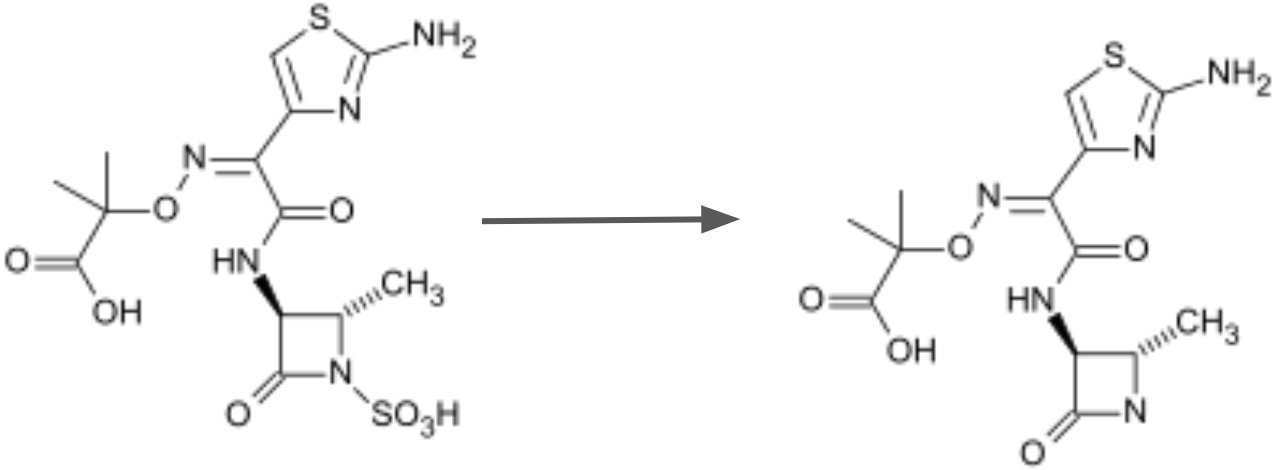
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which addition to amide side chain (R) makes penicillins less susceptible to B-lactamases?**
    - **Bulky group**
    - **Heterocyclic ring**
    - **Polar group**
    - **Electron withdrawing group**



  - **ANSWER: Bulky group**

SAR Learn Tool

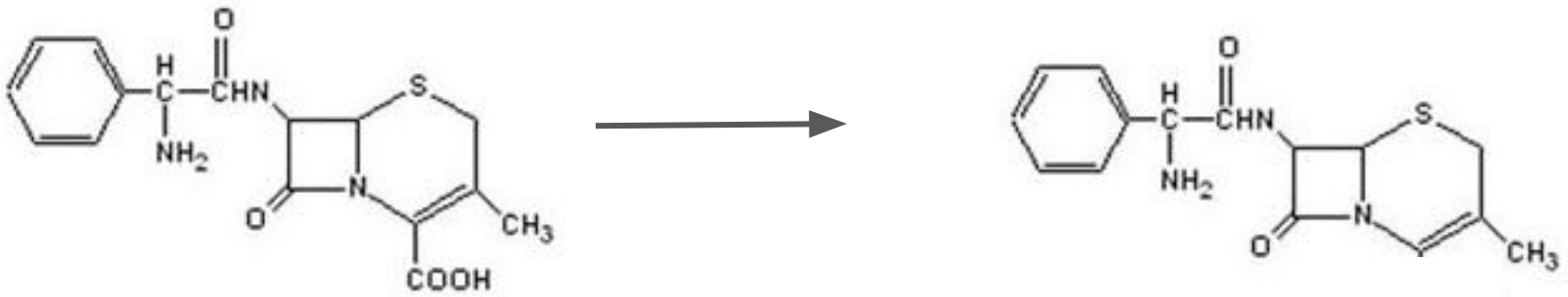
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**



  - **ANSWER: Decrease**
    - **Sulfate group essential for activity**

SAR Learn Tool

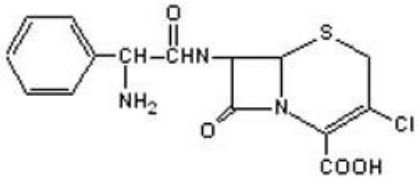
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**

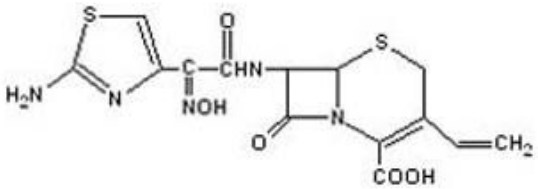


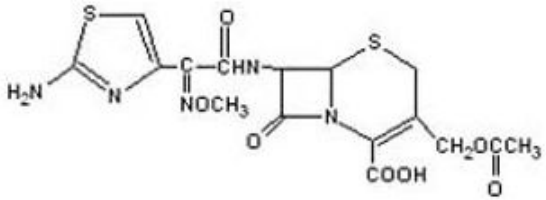
  - **ANSWER: Decrease**
    - **Carboxylic acid essential for activity**

SAR Learn Tool

- **PRACTICE PROBLEM: Choose the correct compound**
  - **Which compound(s) are acid stable and can be taken orally?**



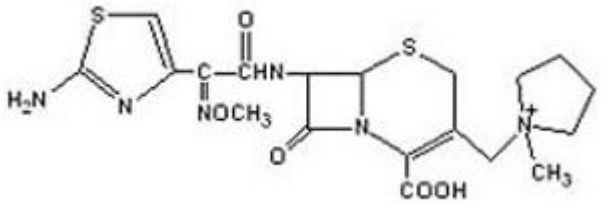


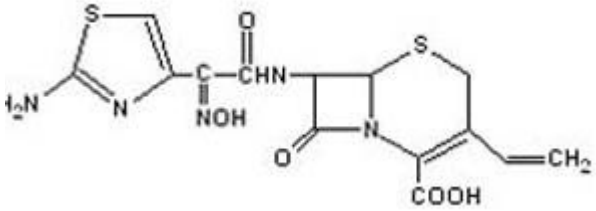


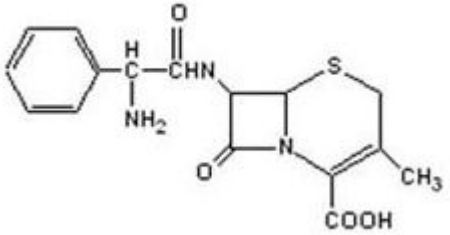
  - **ANSWER: Compound 1 (cefaclor) & compound 2 (cefdinir)**
    - **Both compounds contain non-metabolizable groups at position 3**

SAR Learn Tool

- **PRACTICE PROBLEM: Choose the correct compound**
  - **Which compound has increased B-lactamase resistance?**



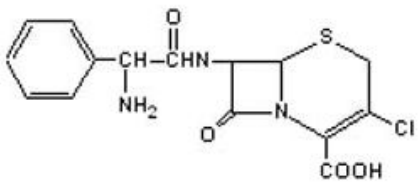


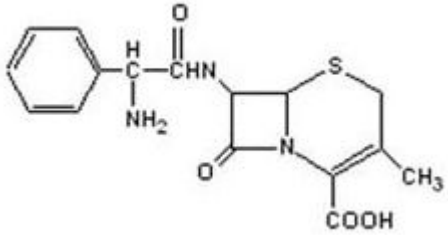


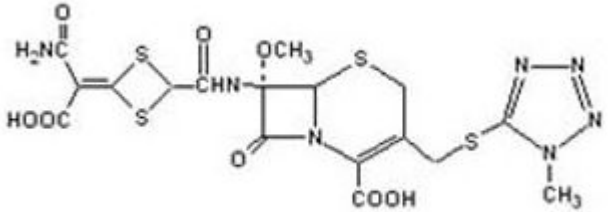
  - **ANSWER: Compound 1 (cefepime)**
    - **Contains oxime group as R1**

SAR Learn Tool

- **PRACTICE PROBLEM: Choose the correct compound**
  - **Which compound has increased B-lactamase resistance?**



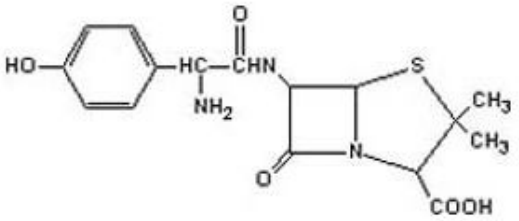


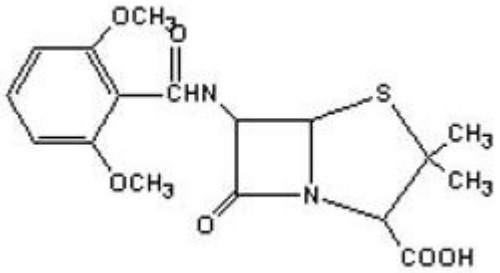


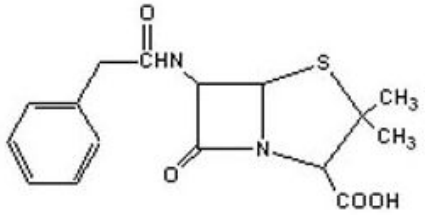
  - **ANSWER: Compound 3 (cefotetan)**
    - **Contains 7-alpha-methoxy group**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound is most active against staph?**



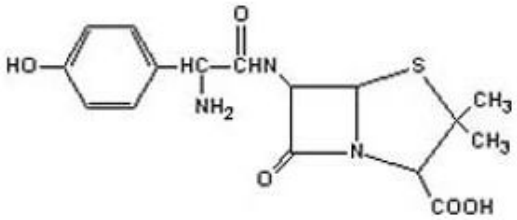


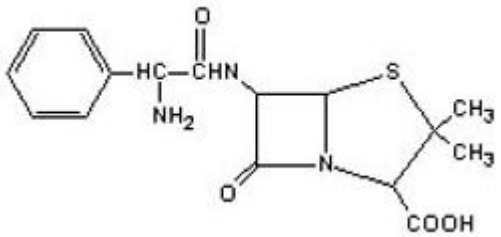


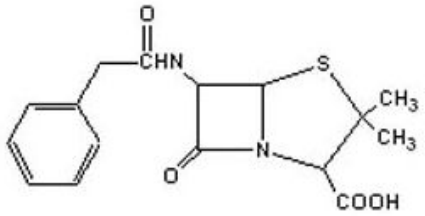
  - **ANSWER: compound 2 (methicillin)**
    - **Contains bulky R group directly attached to amide**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound is the most orally active?**



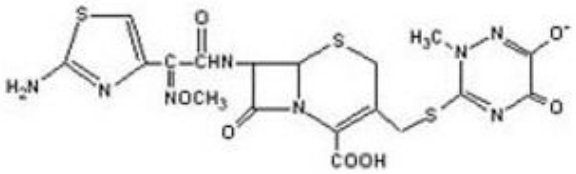


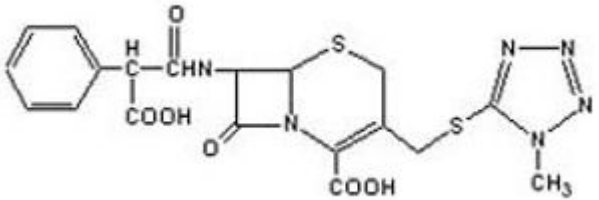


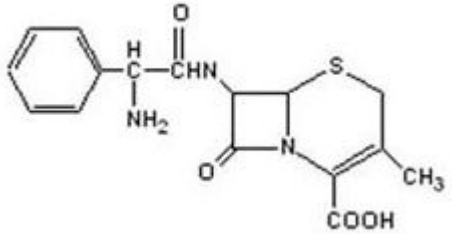
  - **ANSWER: Compound 1 (amoxicillin)**
    - **Contains polar R group**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound is associated with Disulfiram reaction?**



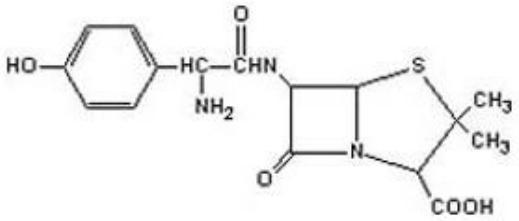


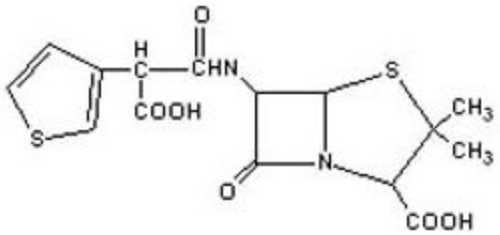


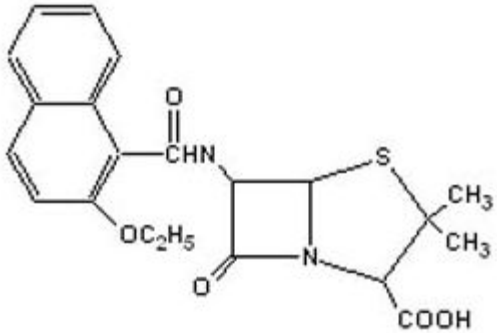
  - **ANSWER: Compound 2 (cefmandole)**
    - **R2- contains MTT ring**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound is NOT used with B-lactamase inhibitors?**



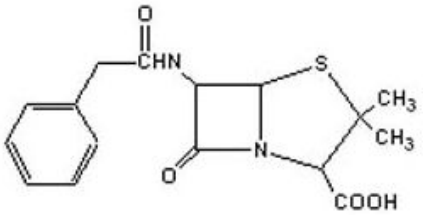


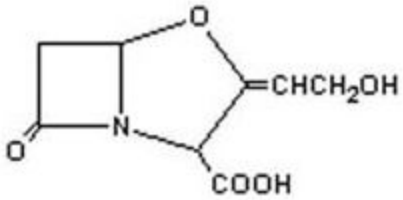


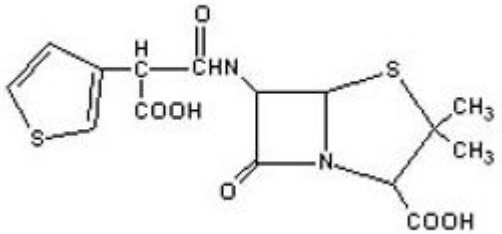
  - **ANSWER: Compound 3 (naficillin)**
    - **Contains bulky R group**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound shows the least amount of antimicrobial activity?**



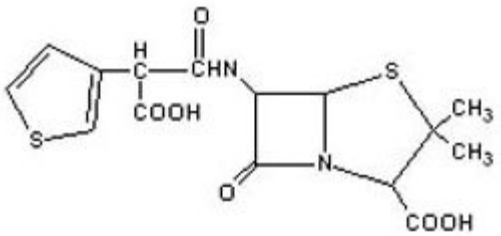


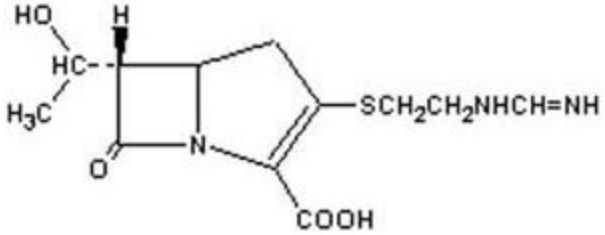


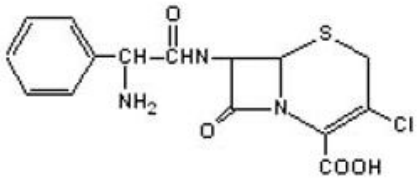
  - **ANSWER: Compound 2 (clavulanic acid)**
    - **B-lactamase inhibitor; no antimicrobial activity**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound must be used in combination with cilastin?**



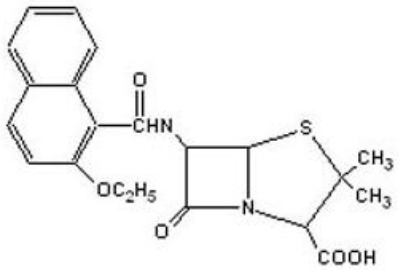


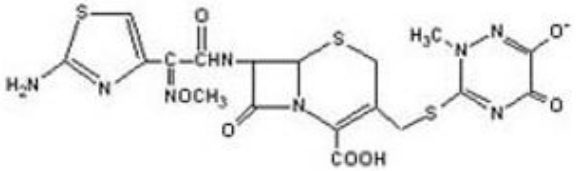


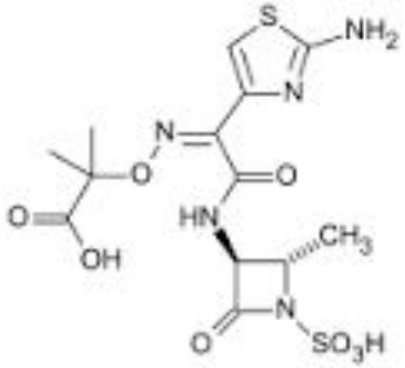
  - **ANSWER: Compound 2 (imipenem)**
    - **Imipenem is hydrolyzed by dehydropeptidase in the kidney to a nephrotoxic metabolite**
    - **Cilastin inhibits dehydropeptisdase**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **GM is experienced a life-threatening reaction from amoxicillin, which antibiotic is safe to use in him?**



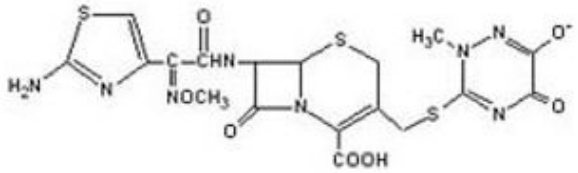


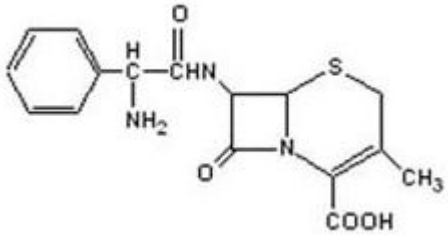


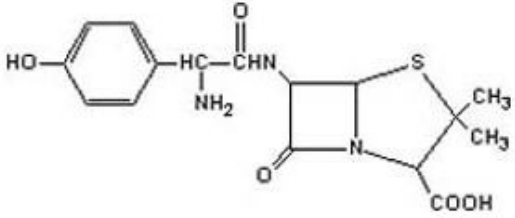
  - **ANSWER: Compound 3 (aztreonam)**
    - **No cross-allergic reactions with other B-lactams**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **RJ has a pseudomonal infection, which antibiotic do you recommend?**







  - **ANSWER: compound 1 (ceftriaxone)**
    - **Contains heterocyclic ring, which broadens spectrum and increases anti-pseudomonal activity**