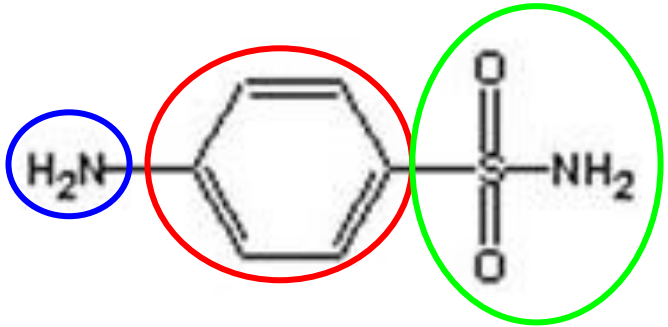
Folic Acid Biosynthesis Inhibitors

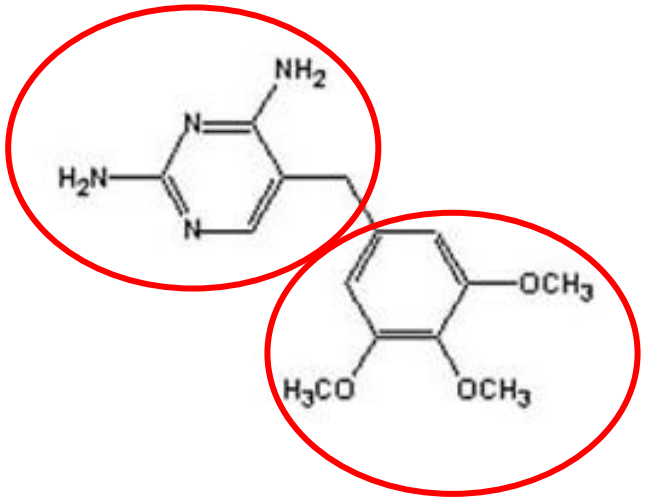
SAR Learn Tool



- **SAR requirements**
  - **Sulfonamides**
    - PABA mimic
    - **Benzene ring is essential**
    - **Amine is essential**
      - Must be un-substituted
      - Must be para to the sulfonamide
    - **Sulfonamide is essential**
      - Must be un-ionized to cross bacterial cell membrane
      - Must be ionized to interact with DHPS active site
      - Mono-substitution allowed (EWG & heterocycle are favorable)
      - Di-substitution abolishes activity
      - Must be para to the amine

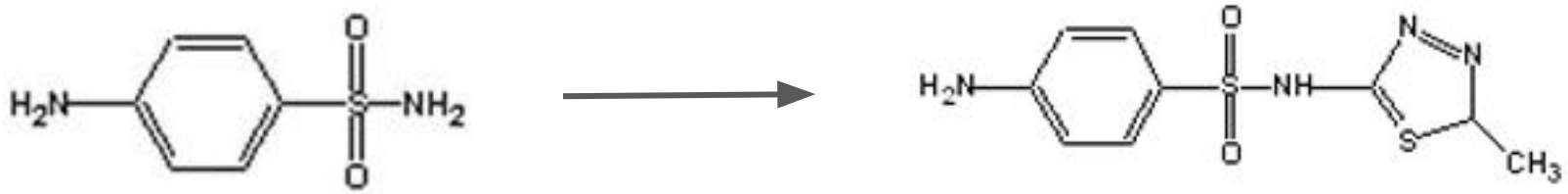
SAR Learn Tool

- **SAR requirements**
  - **Trimethoprim**
    - Circled parts are characteristic of this compound



SAR Learn Tool

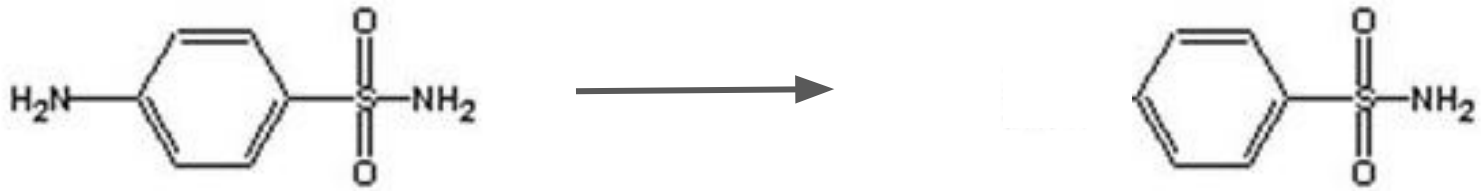
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**



  - **ANSWER: Increase**
    - **Addition of heterocycle to sulfonamide is favorable and decreases pH to optimal range**

SAR Learn Tool

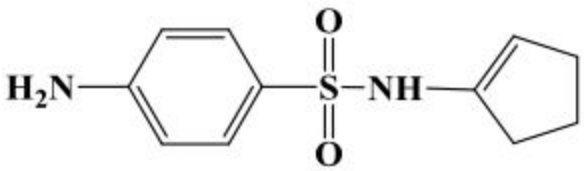
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**

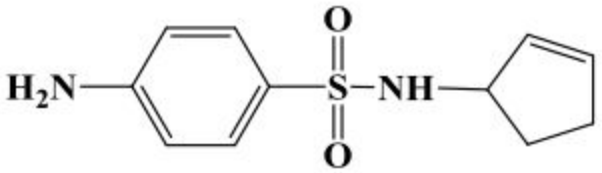


  - **ANSWER: Decrease**
    - **Amine essential for activity**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the two compounds has greatest antimicrobial activity?**

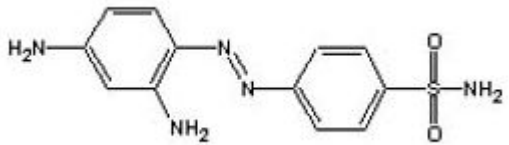


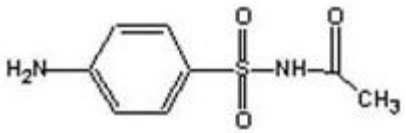


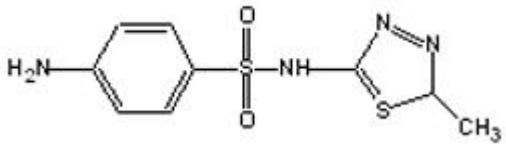
  - **ANSWER: Compound 1**
    - **The negative charge on the sulfonamide can be stabilized by resonance with the ring**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which is a prodrug?**



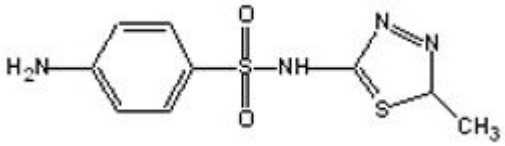


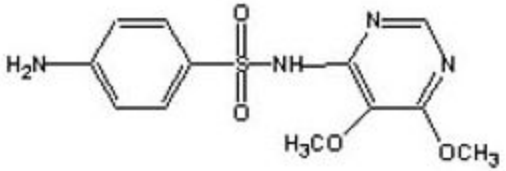


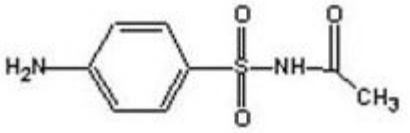
  - **ANSWER: Compound 1 (prontosil)**
    - **Metabolized by reductases to give active form of sulfonamide**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which is the longest acting sulfonamide?**



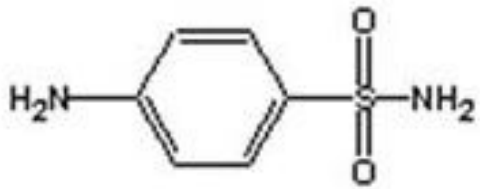




  - **ANSWER: Compound 2 (sulfadoxine)**
    - **Has a half life of 150 hours**

SAR Learn Tool

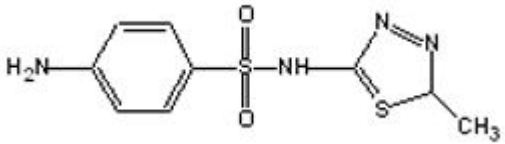
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which characteristics, at physiological pH, would provide the most effective sulfonamide?**
    - **Low lipophilicity, unionized**
    - **High lipophilicity, unionized**
    - **Low lipophilicity, ionized**
    - **High lipophilicity, ionized**

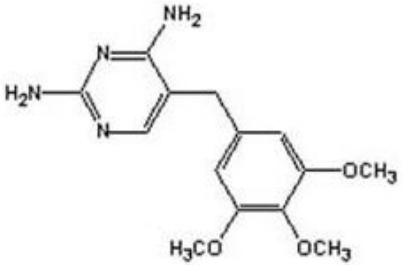


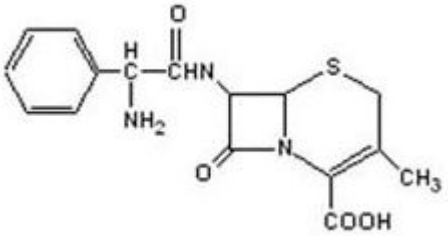
  - **ANSWER: High lipophilicity, ionized**
    - **Lipophilicity is needed to enter the cell and ionization is required to bind to enzyme**

SAR Learn Tool

- **PRACTICE PROBLEM: Mechanism of Action**
  - **Which of the following inhibits DHPS?**



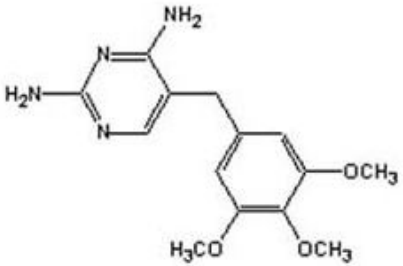


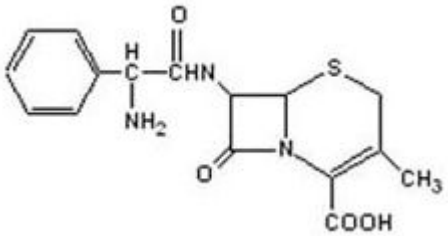


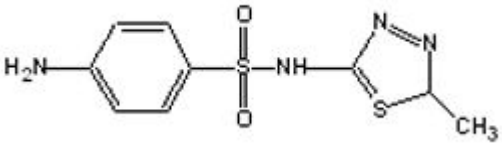
  - **ANSWER: Compound 1 (sulfamethoxazole)**

SAR Learn Tool

- **PRACTICE PROBLEM: Mechanism of Action**
  - **Which of the following inhibits DHFR?**



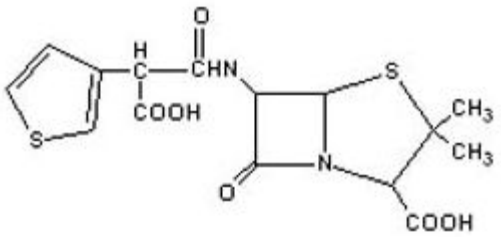


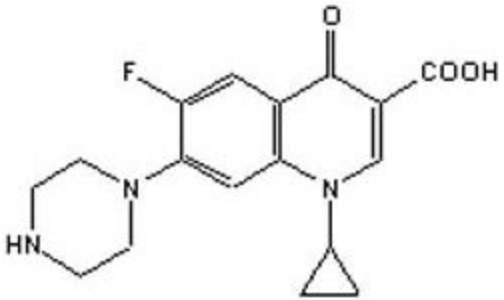


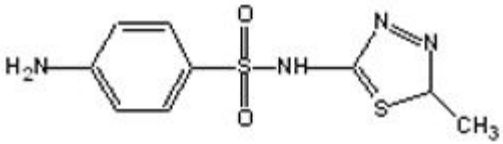
  - **ANSWER: Compound 1 (trimethoprim)**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **KT has a history of Steven Johnson Syndrome, which antibiotic is best avoided in her?**





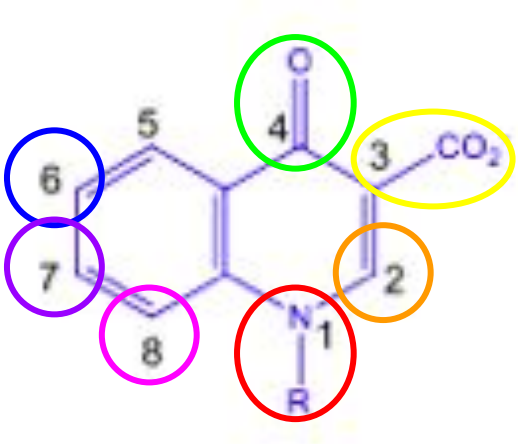


  - **ANSWER: Compound 3 (sulfamethoxazole)**
    - **Sulfonamides can to this life-threatening rash**

DNA Topoisomerase Inhibitors

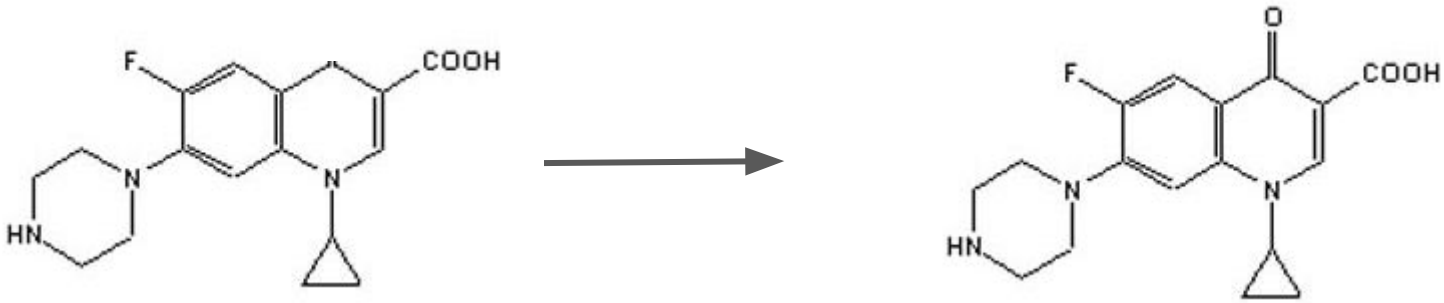
SAR Learn Tool

- **SAR requirements**
  - **Quinolones**
    - **Position 1:** nitrogen can allow substitutions of alkyl (Me, Et, cPr) or aryl (2,4-difluorophenyl) groups
    - **Position 2:** can be either a carbon or nitrogen
    - **Position 3:** must be unsubstituted carboxylic acid
    - **Position 4:** must be ketone
    - **Position 6:** fluorine substitution increases activity and broadens spectrum
    - **Position 7:** substitution with nitrogen containing heterocycles (piperazine ring) broadens spectrum; potential for zwitterion
    - **Position 8:** substitution with small polar groups (OCH_3, F, Cl) increases activity



SAR Learn Tool

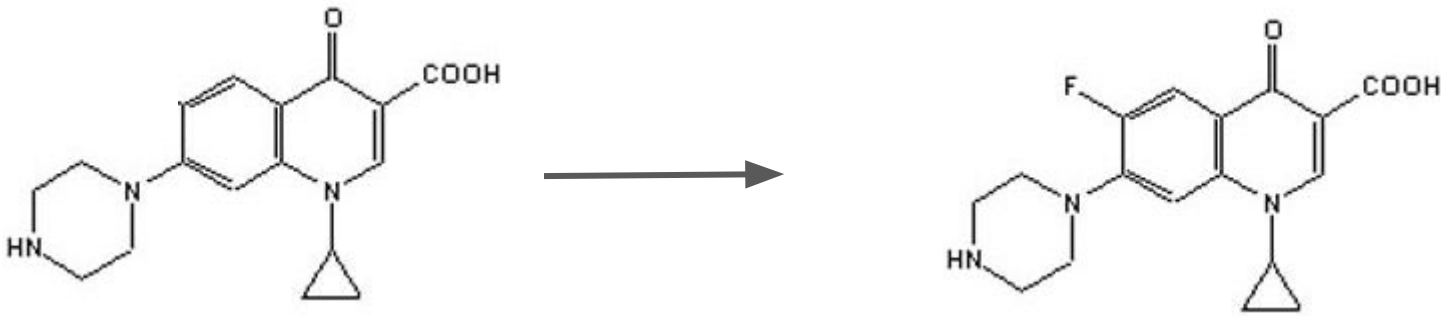
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**



  - **ANSWER: Increase**
    - Ketone at position 4 is essential to bind to target

SAR Learn Tool

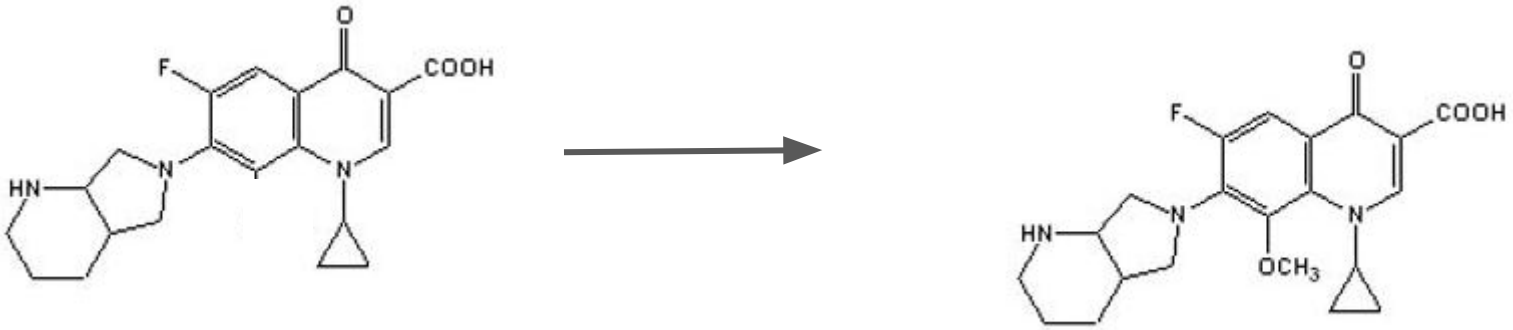
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**



  - **ANSWER: Increase**
    - F at position 6 increases activity and broadens spectrum

SAR Learn Tool

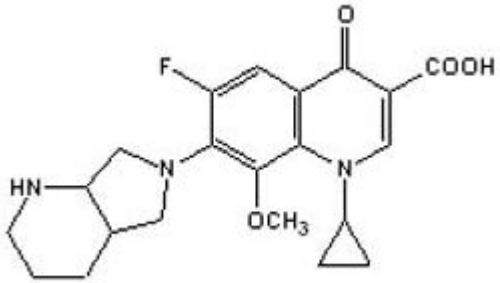
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease activity?**

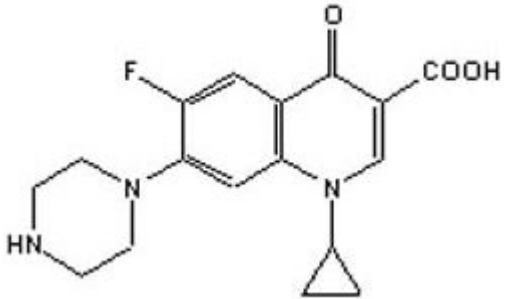


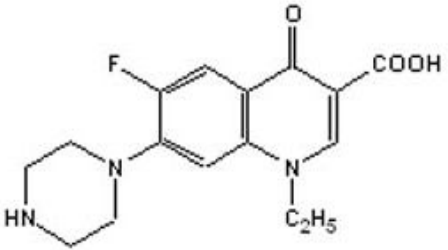
  - **ANSWER: Increase**
    - Methoxy substitution at position 8 increases activity

SAR Learn Tool

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



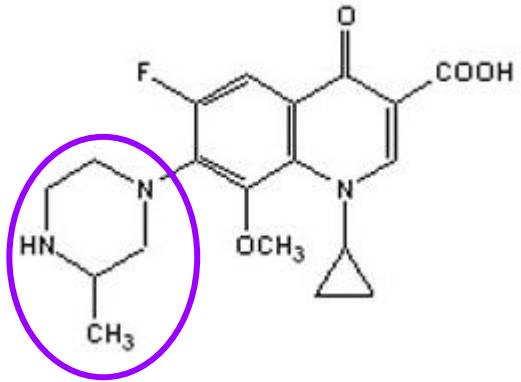




  - **ANSWER: Compound 1 (moxifloxacin)**
    - **Addition of methoxy at position 8 improves activity**

SAR Learn Tool

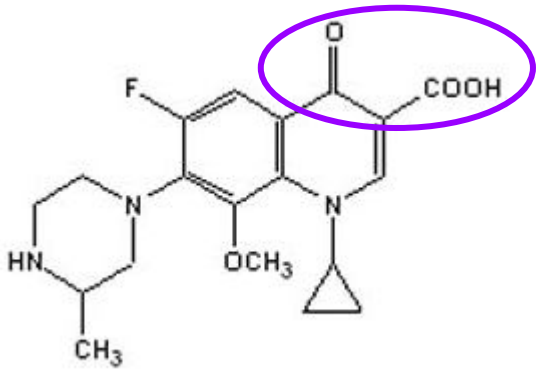
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **What is the importance of the circled group?**
    - **Improves activity**
    - **Increases half life**
    - **Broadens spectrum**
    - **Decreases resistance**



  - **ANSWER: Broadens spectrum**
    - **Increases activity against pseudomonas**

SAR Learn Tool

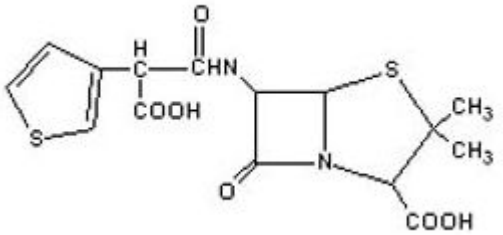
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **What is the circled group responsible for?**
    - **Broadening spectrum**
    - **Increasing half life**
    - **Decreasing resistance**
    - **Chelation with metals**

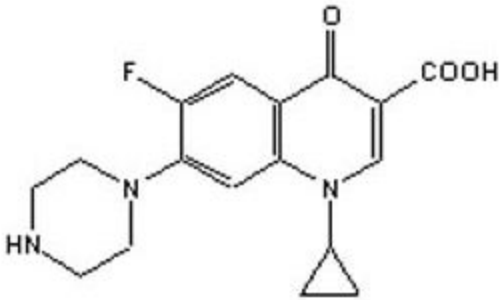


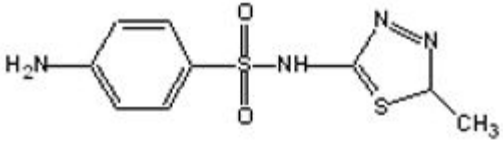
  - **ANSWER: Chelation with metals**
    - **Chelation with metals can reduce oral absorption; do not take with antacids, mineral supplements, or dairy products**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **JT is a 4-year-old boy diagnosed with a gram-negative infection, which antibiotic do you NOT recommend?**



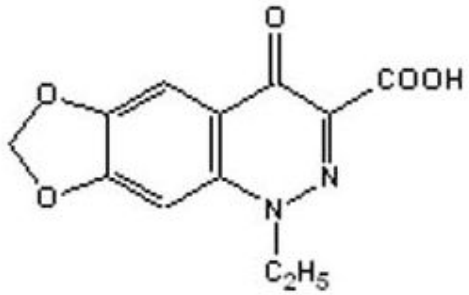


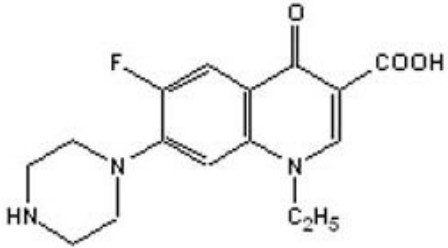


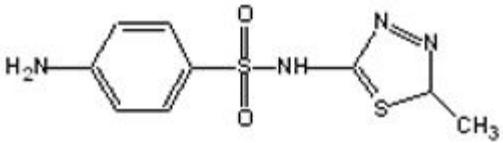
  - **ANSWER: Compound 2 (ciprofloxacin)**
    - **Quinolones can lead to tendon rupture in young children and should never be used first line**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **AM is diagnosed with a pseudomonal infection, which antibiotic do you recommend?**



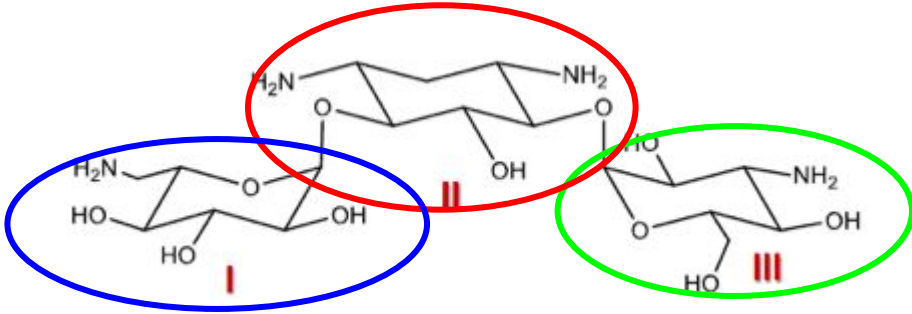




  - **ANSWER: Compound 2 (norfloxacin)**
    - **Contains piperazine ring, which gives it anti-pseudomonal activity**

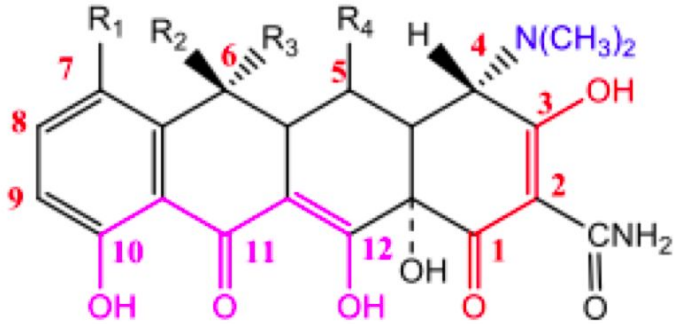
30S Protein Synthesis Inhibitors

SAR Learn Tool



- **SAR requirements**
  - **Aminoglycosides**
    - Polycationic at physiological pH
      - Poor oral absorption
    - **Ring I**
      - Crucial for broad-spectrum activity.
      - First target of inactivating enzymes.
      - The 2-, 3-, 4- hydroxyl groups are not essential for activity
      - Methylation of the amine will retain activity and will lower susceptibility to transferases.
      - All substitutions must be equatorial.
    - **Ring II**
      - Many modifications are possible, for example the 3- amine can be substituted or acylated
    - **Ring III:**
      - The amine can be methylated or changed to a hydroxyl group, but its removal will abolish activity

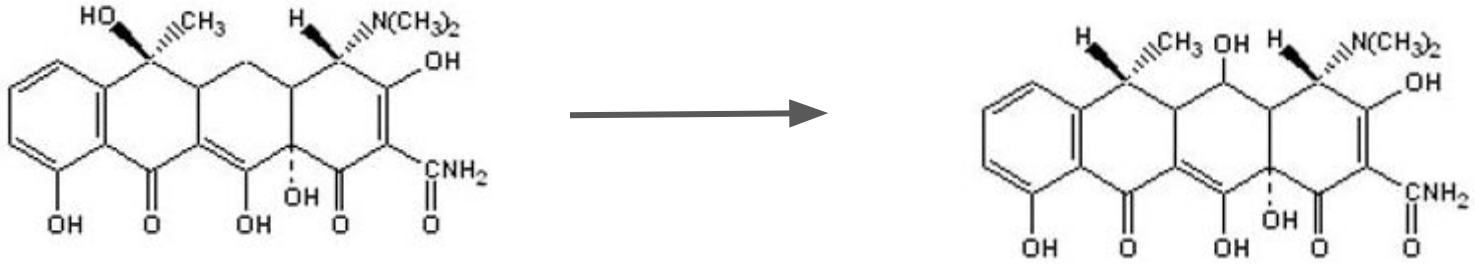
SAR Learn Tool



- **SAR requirements**
  - **Tetracyclines**
    - **Positions 1, 10, 11, 12 and 12a:** any changes will completely abolish activity, even changes in the stereochemical configuration.
      - Resonance between position 10 and 11 needed for activity
    - **Position 2:** any changes leads to decreased activity, even substitution to the amide
    - **Position 4:** amine in the α-position is essential, but monosubstitution is also active.
    - **Position 5:** R4 can be a hydroxyl, keto group or a hydrogen, and all are active
    - **Position 6:** both substitutions (R2 and R3) are not necessary.
    - **Position 7:** Cl, F, Br, NO2 and a tertiary amine are all active.
    - **Position 8:** any electron withdrawing or donating group is still active.
    - **Position 9:** bulky substitution decreases resistance

SAR Learn Tool

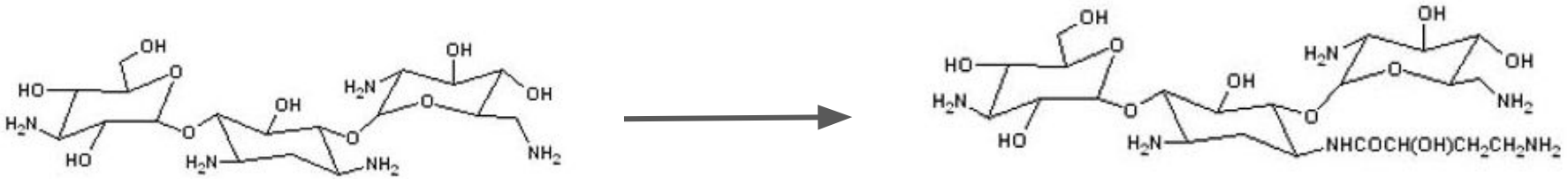
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease chemical stability?**



  - **ANSWER: Increase**
    - **Replacement of OH with CH3 at position 6 makes the compound more stable**

SAR Learn Tool

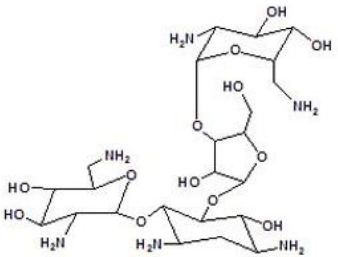
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease bacterial resistance?**

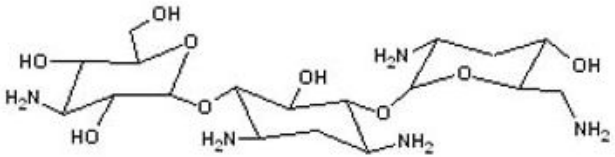


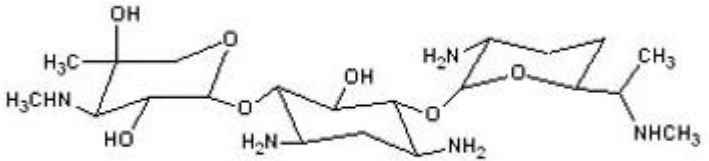
  - **ANSWER: Decrease**
    - **Addition of bulky group protects the compound from inactivating enzymes**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the following binds to both the 30S and 50S ribosomal units?**



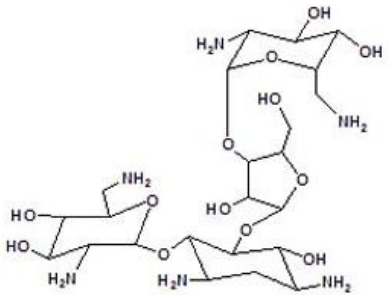


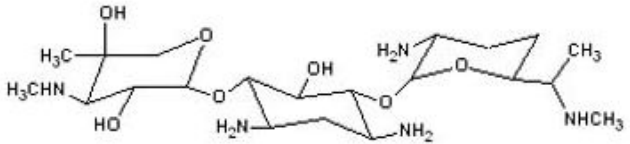


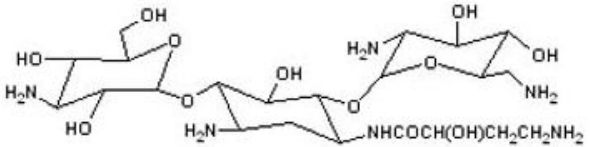
  - **ANSWER: Compound 2 (tobramycin)**
    - **Tobramycin is the only aminoglycoside that binds to both ribosomal units**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the following is only used topically?**



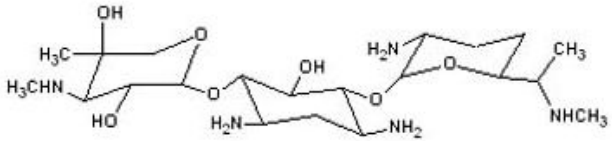


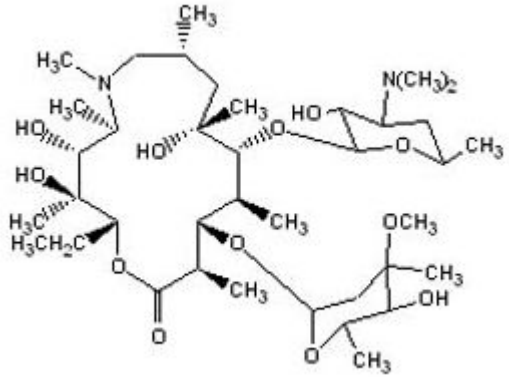


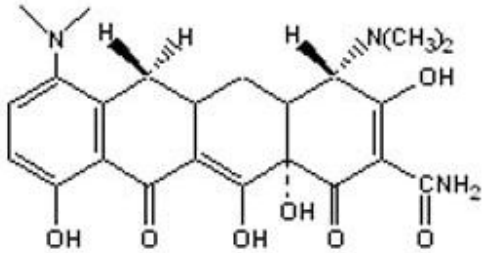
  - **ANSWER: Compound 1 (neomycin)**
    - **Only used topically due to nephrotoxicity**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the following does NOT bind to the 30S ribosomal unit?**



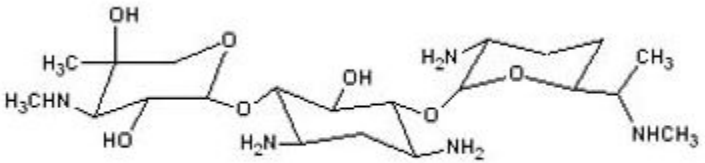


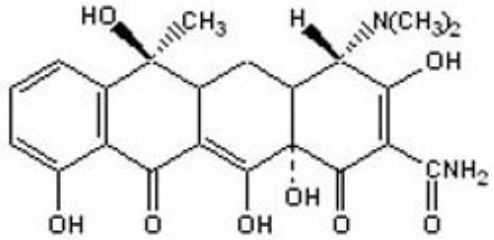


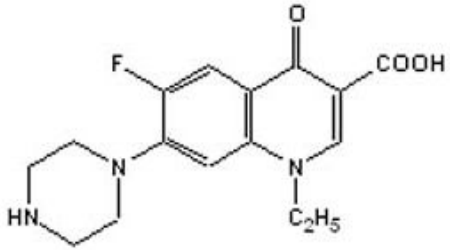
  - **ANSWER: Compound 3 (azithromycin)**
    - **Macrolides bind to the 50S ribosomal unit**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the following is NOT bactericidal?**



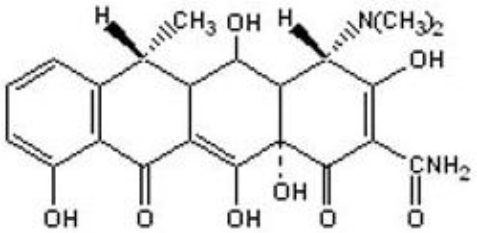


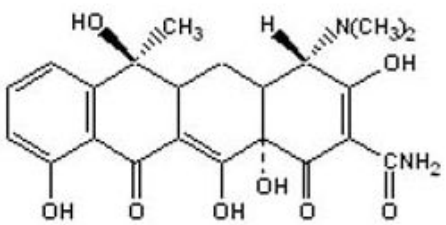


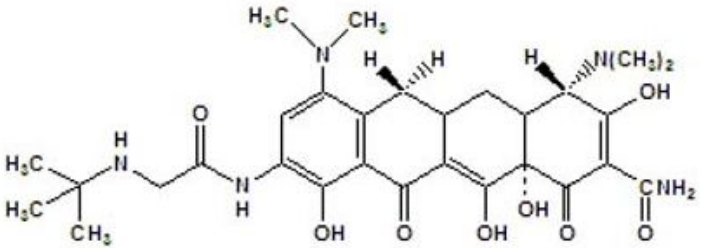
  - **ANSWER: Compound 2 (tetracycline)**
    - **Tetracyclines are bacteriostatic**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which is less susceptible to bacterial resistance?**



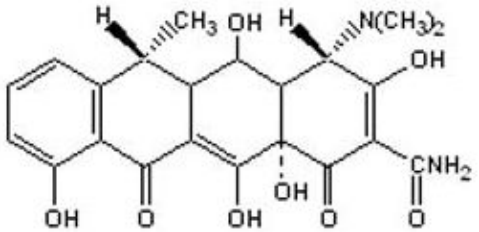


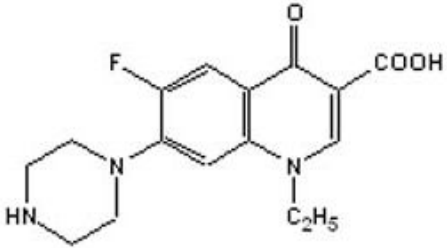


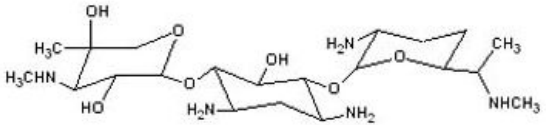
  - **ANSWER: Compound 3 (tigecycline)**
    - **Addition of bulky group to position 9**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which antibiotic is used primarily by IV injections?**



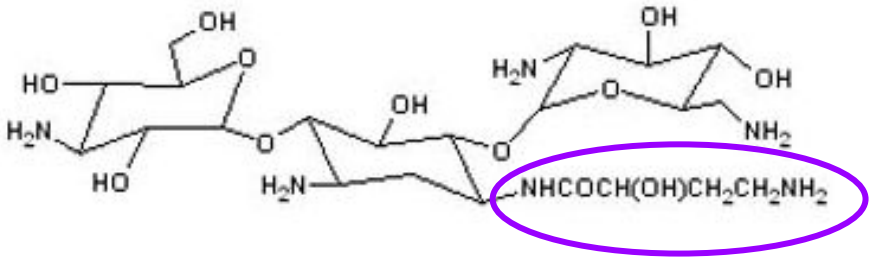




  - **ANSWER: Compound 3 (gentamicin)**
    - **Aminoglycosides are not orally absorbed**

SAR Learn Tool

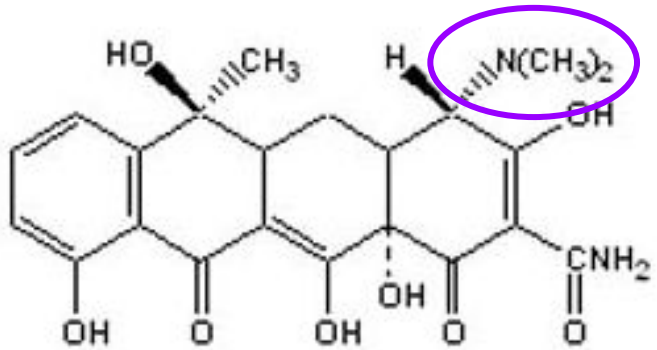
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **What is the main advantage of the circled group?**
    - **Retains activity**
    - **Increases half life**
    - **Broadens spectrum**
    - **Decreases resistance**



  - **ANSWER: Decreases resistance**
    - **Less spots for inactivating enzymes to act**

SAR Learn Tool

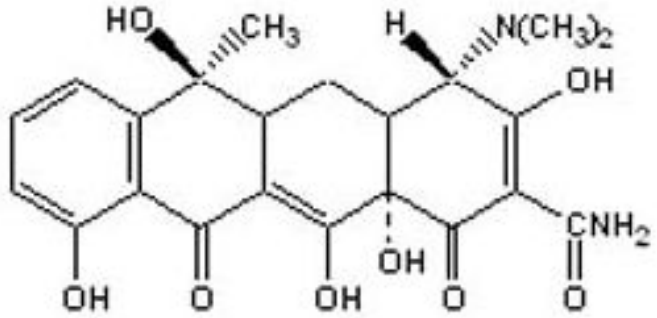
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **What is the importance of retaining the stereochemistry of the circled group?**
    - **Retains activity**
    - **Increases half life**
    - **Broadens spectrum**
    - **Decreases resistance**



  - **ANSWER: Retains activity**
    - **Essential for activity**

SAR Learn Tool

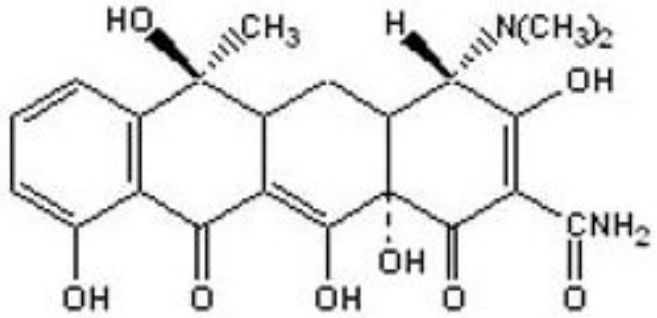
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which reaction of this compound leads to a toxic product?**
    - **Acidic medium**
    - **Basic medium**
    - **Chelation**
    - **Epimerization**



  - **ANSWER: Acidic medium**
    - **Nephrotoxic product**

SAR Learn Tool

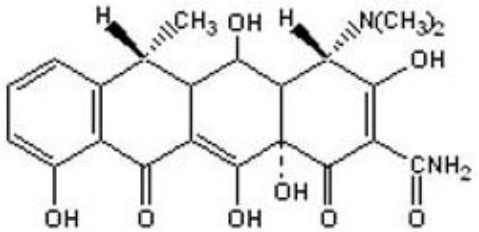
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Which reaction(s) inactivate this compound?**
    - **Acidic medium**
    - **Basic medium**
    - **Chelation**
    - **Epimerization**

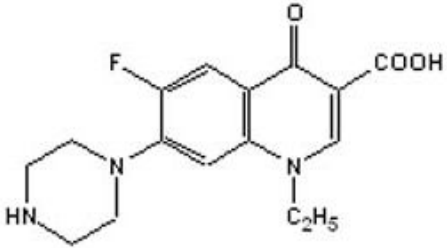


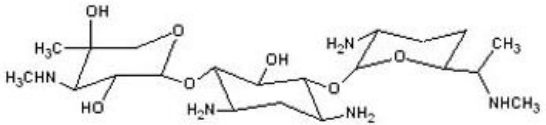
  - **ANSWER: Epimerization & Basic medium**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **CS is going on vacation to sunny florida, which antibiotic(s) should she avoid?**





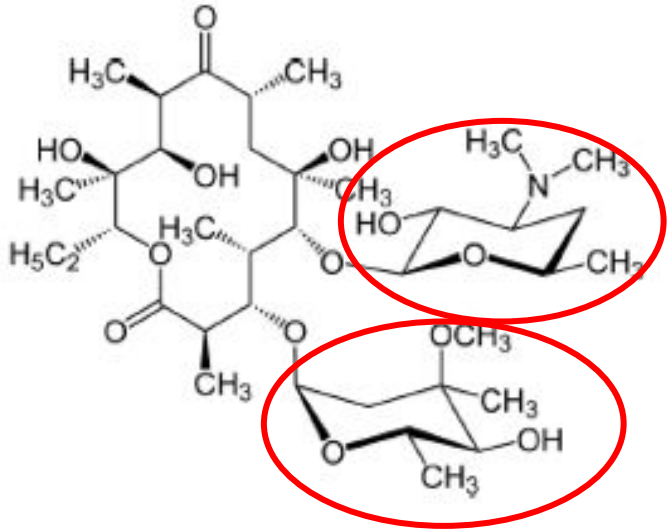


  - **ANSWER: Compound 1 (doxycline) & Compound 2 (ciprofloxacin)**
    - **Both tetracyclines and quinolones can lead to phototoxicity**

50S Protein Synthesis Inhibitors

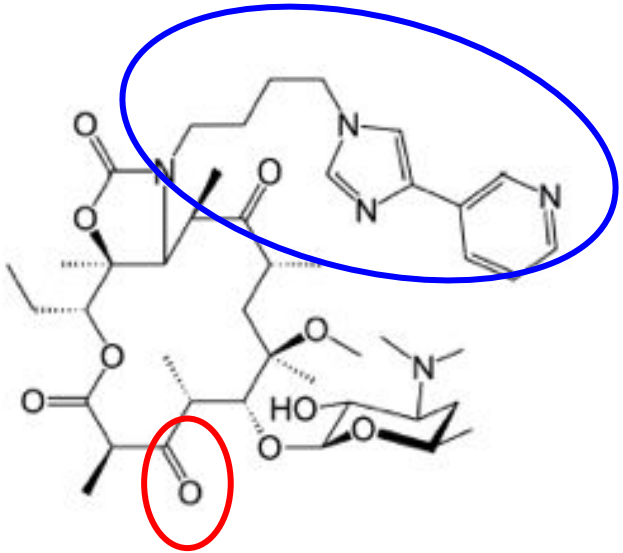
SAR Learn Tool

- **SAR requirements**
  - **Macrolides**
    - **Large lactone ring (12, 14, or 16 membered ring)**
    - **Contain one or two sugars usually desosamine and/or cladinose**



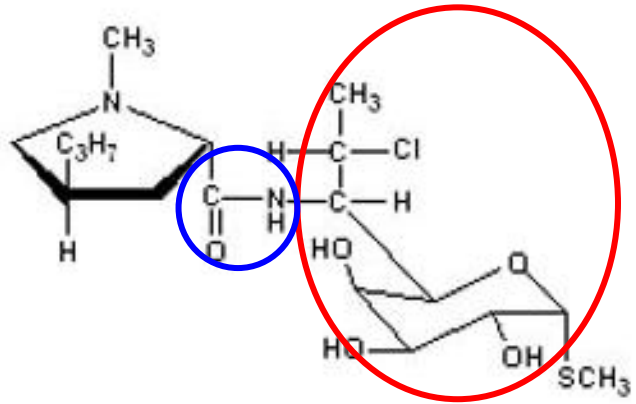
SAR Learn Tool

- **SAR requirements**
  - **Ketolides**
    - Replacement of the L-cladinose sugar of erythromycin A with a **3-keto functional group**
      - Restores activity against bacteria with inducible resistance mediated by Erm, and enhances activity against streptococci with Mef-mediated macrolide efflux
    - Addition of a **carbamate side chain**
      - Promotes activity against both erythromycin-sensitive and erythromycin-resistant bacteria by introducing an interaction with domain II of the 23S rRNA



SAR Learn Tool

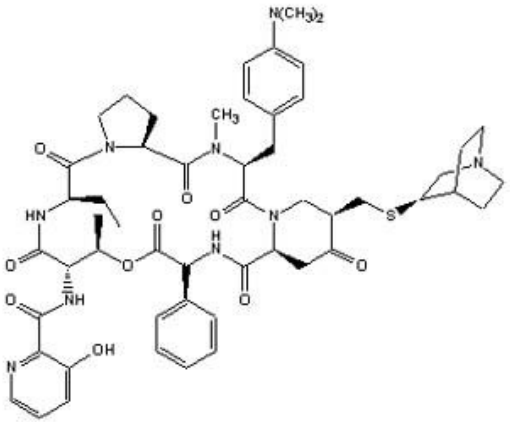
- **SAR requirements**
  - **Lincosamides**
    - **Eight carbon sugar**
    - **Amide bond**



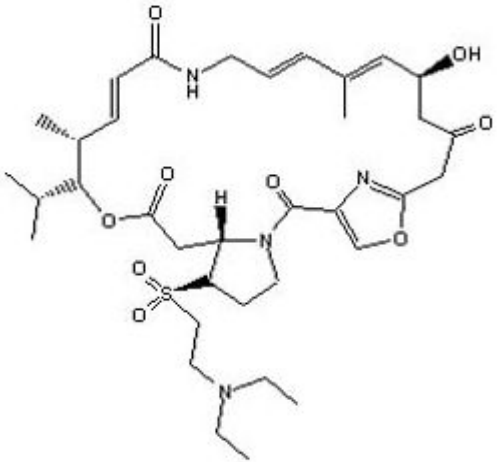
SAR Learn Tool

- **SAR requirements**
  - **Streptogramins**
    - Type A and Type B are used together synergistically

Type A: Quinupristin

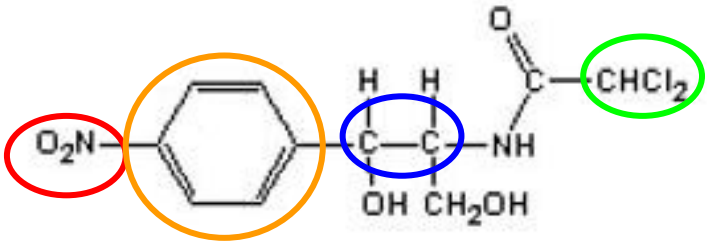


Type B: Dalfopristin



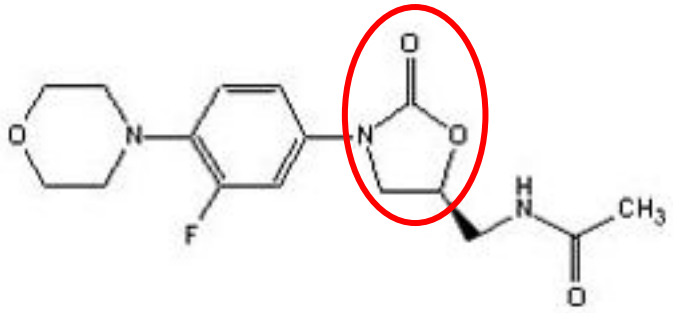
SAR Learn Tool

- **SAR requirements**
  - **Chloramphenicol**
    - **Nitro group:** can be replaced with other EWG, but activity decreases
    - **Aromatic ring:** essential for activity
    - **Chlorines**: can be removed or replaced with other halogens, but activity decreases
    - **R, R stereoisomer:** essential for activity



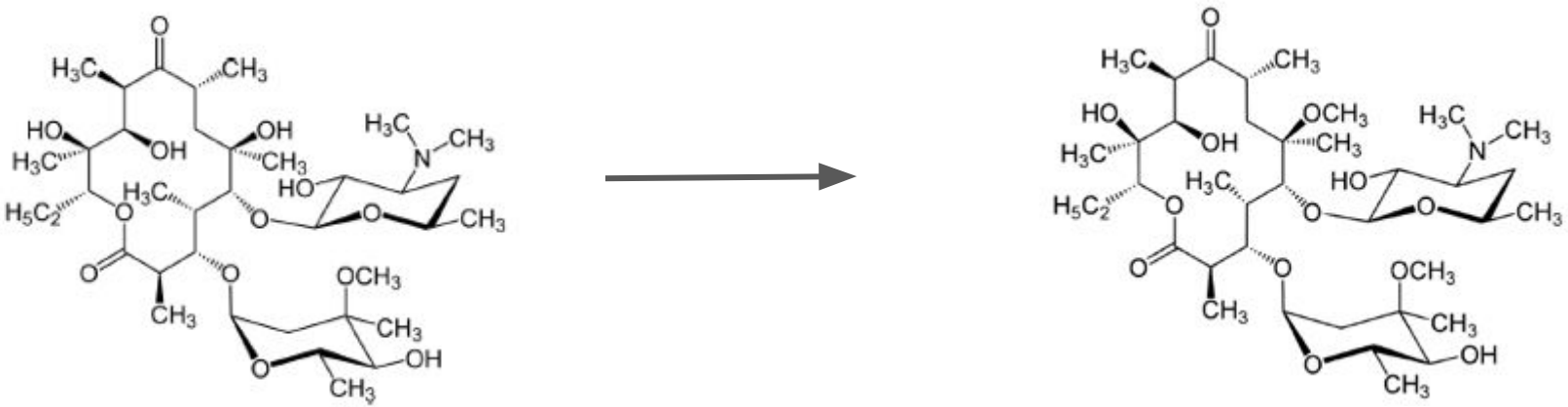
SAR Learn Tool

- **SAR requirements**
  - **Oxazolidinones**
    - **Oxazolidinone ring**



SAR Learn Tool

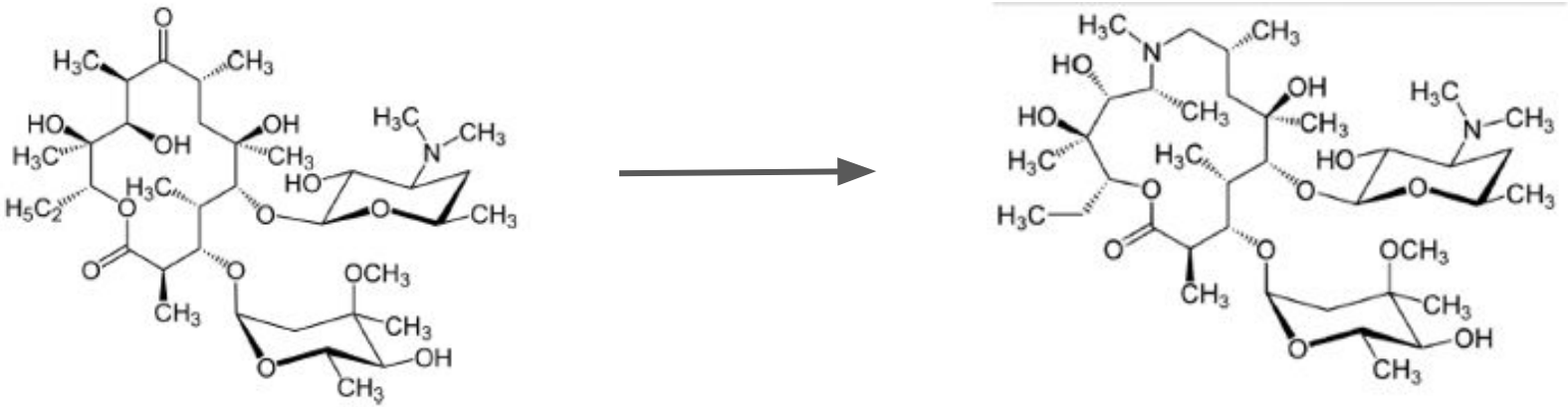
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease chemical stability?**



  - **ANSWER: Increase**
    - **Replacement of OH with OCH3 reduces acid-catalyzed degradation**

SAR Learn Tool

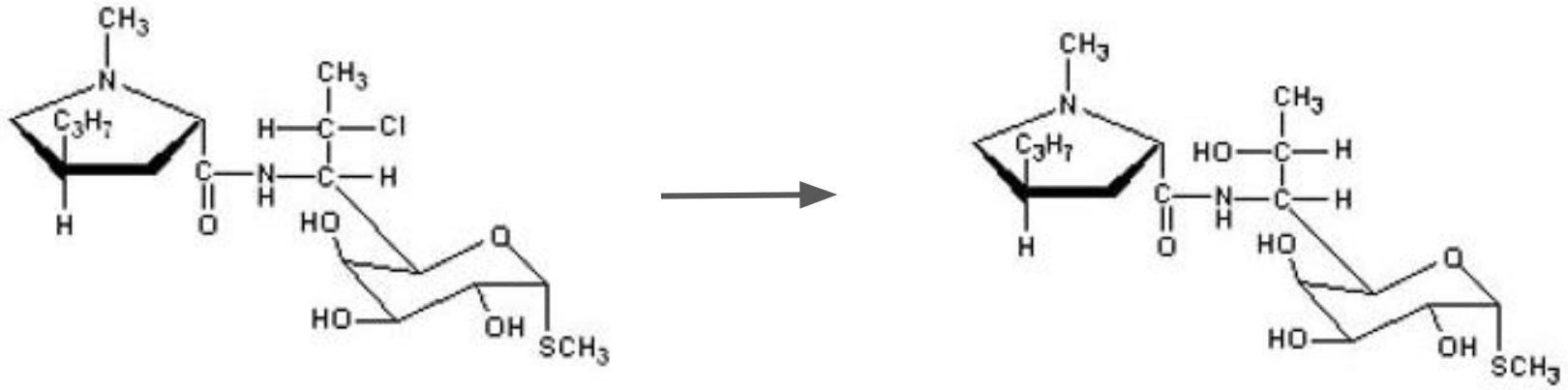
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or acid stability?**



  - **ANSWER: Increase**
    - **15 member ring (with no ketone) increases acid stability and permits accumulation of azithromycin in the cell**

SAR Learn Tool

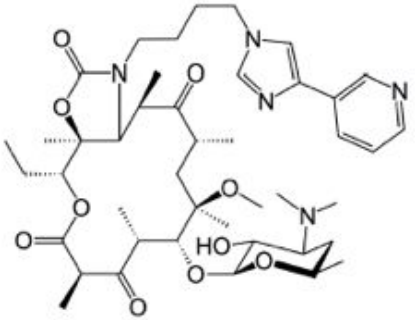
- **PRACTICE PROBLEM: Activity change**
  - **Will the following change increase or decrease chemical stability?**

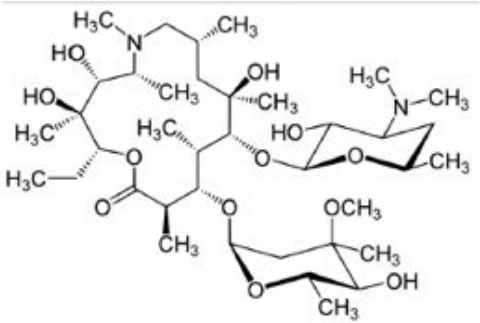


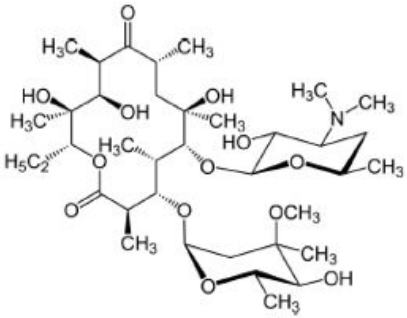
  - **ANSWER: Decrease**
    - **Cl increases lipophilicity and has better oral absorption**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which compound is less susceptible to bacteria resistance?**



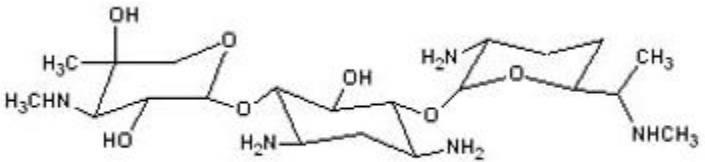


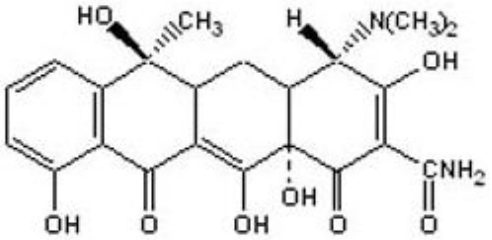


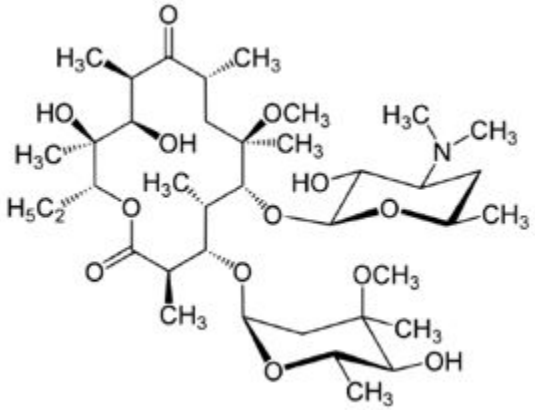
  - **ANSWER: Compound 1 (telithromycin)**
    - **Addition of 3-keto group and carbamate side chain**

SAR Learn Tool

- **PRACTICE PROBLEM: Compare Compounds**
  - **Which of the following is NOT bacteriostatic?**



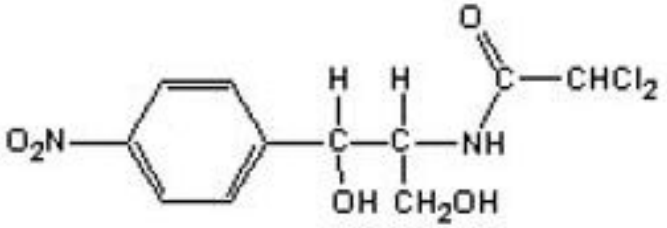




  - **ANSWER: Compound 1 (gentamicin)**
    - **Aminoglycosides are bactericidal**

SAR Learn Tool

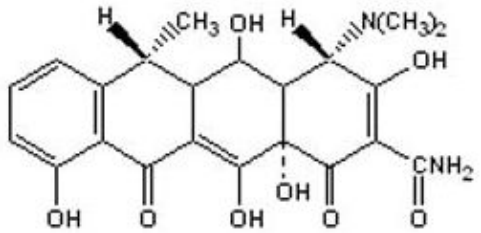
- **PRACTICE PROBLEM: Choose the Correct Answer**
  - **Gray Baby Syndrome results from inability to produce which metabolite?**
    - **Dechlorination**
    - **N-reduction**
    - **3-O-glucuronidation**

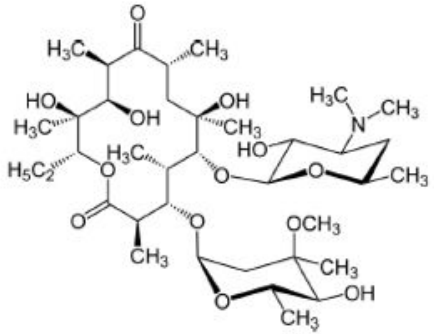


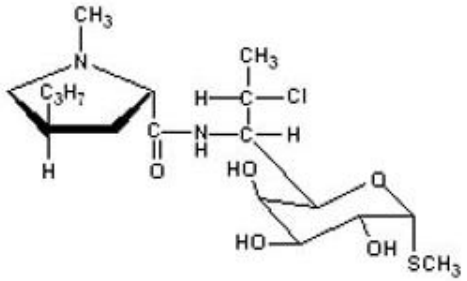
  - **ANSWER: 3-O-glucuronidation**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **LM is experiencing diarrhea after taking her antibiotic, which compound did she most likely take?**



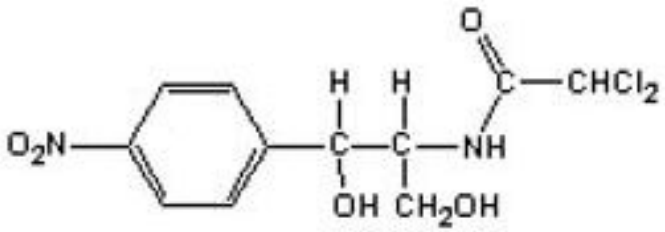


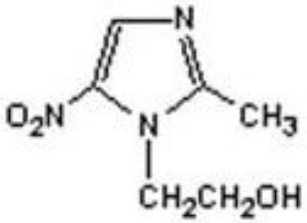


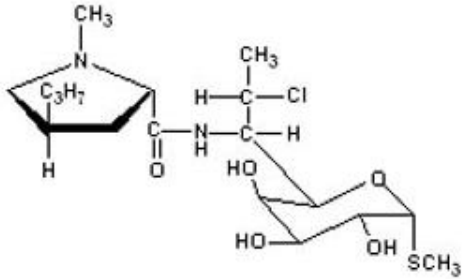
  - **ANSWER: Compound 3 (clindamycin)**
    - **Clindamycin has highest incidence of pseudomembranous colitis**

SAR Learn Tool

- **PRACTICE PROBLEM: SAR Clinical Case Study**
  - **LM is experiencing aplastic anemia, which antibiotic did she take?**







  - **ANSWER: Compound 1 (chloramphenicol)**
    - **Clindamycin has highest incidence of pseudomembranous colitis**