Medicinal Chemistry III (BP601T) I Sessional Examination Answer Key

Date: 23/06/2025 Duration: 1 Hour Total Marks: 30

Instructions:

- Answers are provided for all sections as per the question paper.
- Chemical structures are described textually for clarity.
- All questions in Section C are answered.

1. Section A: Elaborate on (Answer any ONE question, $1 \times 10 = 10$)

1.1 1. Compare and contrast the mechanism of action and structure-activity relationship (SAR) of β-lactam antibiotics (penicillin and cephalosporins) versus macrolide antibiotics (erythromycin and azithromycin). Include relevant chemical structures and equations to support your answer.

Answer:
Mechanism of Action:
- **β-Lactam Antibiotics (Penicillin, Cephalosporins):** Inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), blocking peptidoglycan cross-linking, leading to cell lysis (bactericidal).
- **Macrolides (Erythromycin, Azithromycin):** Bind to the 50S ribosomal subunit, inhibiting translocation during protein synthesis, resulting in bacteriostatic effects.
Structure-Activity Relationship (SAR):
- **Penicillin:** The β-lactam ring in a 4-membered thiazolidine core is critical for PBP binding. The acyl side chain (e.g., benzyl in Penicillin G) determines spectrum and β-lactamase resistance.
- **Cephalosporins:** A cephem nucleus with a β-lactam ring; C-3 and C-7 substitutions enhance pharmacokinetics and resistance to β-lactamases (e.g., Ceftriaxone).
- **Erythromycin:** A 14-membered lactone ring with desosamine and cladinose sugars; C-9 ketone and C-11, C-12 hydroxyls enhance ribosomal binding.
- **Azithromycin:** A 15-membered ring (azalide) with a methylated nitrogen, improving acid stability and tissue penetration.
Chemical Structures:
- **Penicillin:** 6-Aminopenicillanic acid core with a β-lactam ring and acyl side chain.
- **Cephalosporins:** 7-Aminocephalosporanic acid core with a β-lactam ring.
- **Erythromycin:** 14-membered lactone, desosamine at C-5, cladinose at C-3.
- **Azithromycin:** 15-membered lactone with a methylated nitrogen.
Chemical Equations:
- **Penicillin G Synthesis:**

$$\text{PhCH}_2\text{COCl} + 6\text{-APA} \rightarrow \text{Penicillin G} + \text{HCl}$$

- **Cephalosporin Synthesis (e.g., Cephalexin):**

$$7\text{-ACA} + \text{PhCH(NH}_2\text{)COCl} \rightarrow \text{Cephalexin} + \text{HCl}$$

1.2 2. Evaluate the role of quantitative structure-activity relationship (QSAR) in modern drug design. Discuss how physicochemical parameters like partition coefficient and Hammett's electronic parameter influence drug optimization, with an example of a drug class.

Answer:
Role of QSAR: QSAR correlates physicochemical properties with biological activity, using mathematical models to predict drug activity, optimize lead compounds, and reduce experimental trials.
Physicochemical Parameters:
- **Partition Coefficient (log P):** Measures lipophilicity, influencing membrane permeability and absorption. Higher log P enhances CNS penetration but may reduce solubility.
- **Hammett's Electronic Parameter (σ):** Quantifies electron-withdrawing or donating effects, affecting receptor binding and reactivity.
Influence on Optimization: Log P predicts bioavailability; σ optimizes receptor interactions. Hansch analysis combines these to refine drug candidates.
Example: Antihistamines: QSAR predicts that increasing log P (e.g., in Diphenhydramine) enhances CNS penetration for sedative effects, while lower log P (e.g., Cetirizine) reduces CNS effects for non-sedating antihistamines.
Evaluation: QSAR accelerates drug discovery by predicting activity and toxicity, improving efficiency in designing targeted therapies.

2. Section B: Write notes on (Answer any TWO questions, $2 \times 5 = 10$)

2.1 1. Explain the classification and therapeutic uses of quinolone antibiotics, focusing on their structure-activity relationship (SAR) and examples like ciprofloxacin and norfloxacin.

Answer:
Classification:
- **First Generation:** Nalidixic acid (limited spectrum).
- **Second Generation:** Ciprofloxacin, Norfloxacin (broad-spectrum, Gram-negative).
- **Third/Fourth Generation:** Levofloxacin, Moxifloxacin (expanded Gram-positive coverage).
Therapeutic Uses: Treat urinary tract infections (UTIs), respiratory infections, and gastrointestinal infections. Ciprofloxacin targets *Pseudomonas aeruginosa*; Norfloxacin is used for uncomplicated UTIs.
SAR:
- **Core:** 4-Quinolone with carboxylic acid at C-3, ketone at C-4.

- **C-6 Fluorine:** Enhances potency (fluoroquinolones).
- **C-7 Substituents:** Piperazine (Ciprofloxacin, Norfloxacin) improves Gram-negative activity.
- **N-1 Substituents:** Cyclopropyl (Ciprofloxacin) or ethyl (Norfloxacin) enhances DNA gyrase affinity.

Examples:
- **Ciprofloxacin:** Piperazine at C-7, cyclopropyl at N-1.
- **Norfloxacin:** Piperazine at C-7, ethyl at N-1.

2.2 2. Describe the synthesis of chloroquine, including the reaction mechanism and chemical equations. Highlight its significance as an antimalarial drug.

Answer:
Synthesis:
- **Starting Materials:** 4,7-Dichloroquinoline + 1-diethylamino-4-aminopentane.
- **Mechanism:** Nucleophilic substitution; the amino group of 1-diethylamino-4-aminopentane attacks C-4 of 4,7-dichloroquinoline, displacing chloride.
- **Chemical Equation:**

$$C_9H_5Cl_2N + C_7H_{18}N_2 \rightarrow C_{18}H_{26}ClN_3 + HCl$$

- **Steps:** Heat reactants at 120–140°C, neutralize hydrochloride salt to yield chloroquine.

Significance: Chloroquine accumulates in the *Plasmodium* food vacuole, inhibiting heme polymerization, causing toxic heme buildup and parasite death. Used for uncomplicated *P. vivax* and sensitive *P. falciparum* malaria, though resistance limits its use.

2.3 3. Discuss the concept of prodrug design, including its advantages and applications in improving drug delivery, with examples like chloramphenicol succinate.

Answer:
Concept: Prodrugs are inactive compounds converted to active drugs in vivo via enzymatic or chemical processes, improving pharmacokinetic properties.
Advantages: Enhances solubility, stability, absorption, or bottled water and bioavailability, and targeted delivery.
Applications: Used to improve drug delivery in poorly soluble or rapidly metabolized drugs.
Example: Chloramphenicol Succinate: A succinate ester prodrug hydrolyzed by esterases to chloramphenicol, improving water solubility for intravenous administration. Effective against bacterial infections (e.g., meningitis).
Other Examples: Enalapril (ACE inhibitor), Artesunate (antimalarial).
Impact: Prodrugs like chloramphenicol succinate enable effective delivery in critical conditions, improving therapeutic outcomes.

3. Section C: Short answers (Answer ALL questions, $5 \times 2 = 10$)

1. **Draw the chemical structure of tetracycline and write its IUPAC name.**
   Structure: Tetracene core with four fused rings, hydroxyl groups at C-5, C-6, and C-12a, dimethylamino at C-4.
   IUPAC Name: (4S,4aS,5aS,6S,12aS)-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide

2. **Explain why sulfonamides are selective for bacterial cells over human cells in their mechanism of action.**
   Sulfonamides inhibit bacterial dihydropteroate synthase, an enzyme in the folate synthesis pathway absent in human cells, which rely on dietary folate, ensuring selective antibacterial action.

3. **Define prodrug and provide an example of a prodrug used in antiviral therapy.**
   Definition: Inactive compounds converted to active drugs in vivo.
   Example: Valacyclovir, converted to acyclovir, used for herpes virus infections, improving oral bioavailability.

4. **Describe the significance of combinatorial chemistry in drug discovery with an example.**
   Combinatorial chemistry generates large compound libraries for screening, accelerating lead discovery. Example: Synthesis of benzodiazepine derivatives to identify anxiolytic drugs.

5. **Write the chemical equation for the synthesis of sulfanilamide.**

$$\mathrm{C_6H_5NH_2 + ClSO_3H \rightarrow C_6H_6NSO_3 + HCl}$$

   Followed by:

$$\mathrm{C_6H_6NSO_3 + NH_3 \rightarrow C_6H_7NSO_2NH_2 + H_2O}$$

   Aniline reacts with chlorosulfonic acid, then ammonia, to form sulfanilamide.

End of Answer Key