Medicinal Chemistry III (BP601T) I Sessional Examination Answer Key
Date: 23/06/2025
Duration: 1 Hour
Total Marks: 30

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

1. **(Analyzing) Discuss the structure-activity relationship (SAR) and mechanism of action of β-Lactam antibiotics, focusing on Penicillin and Cephalosporins. Explain how their chemical structure influences their antibacterial activity, including chemical equations for their synthesis.**
Answer:
β-Lactam antibiotics, such as Penicillin and Cephalosporins, inhibit bacterial cell wall synthesis by targeting penicillin-binding proteins (PBPs). The β-lactam ring in their structure forms a covalent bond with the active site of PBPs, inhibiting peptidoglycan cross-linking, leading to bacterial cell lysis.
SAR of Penicillin: The β-lactam ring is critical for activity; modifications at the acyl side chain (R-group) affect spectrum and stability. For example, Penicillin G has a benzyl group, effective against Gram-positive bacteria.
SAR of Cephalosporins: The cephem nucleus with a β-lactam ring is essential. Substitutions at C-3 and C-7 influence pharmacokinetics and resistance to β-lactamases.
Mechanism: Both inhibit transpeptidation in cell wall synthesis.
Synthesis of Penicillin: Fermentation of *Penicillium* mold produces Penicillin G. Chemical synthesis involves:

$$PhCH2COCl + 6 - APA - > PenicillinG$$

Synthesis of Cephalosporins: From 7-aminocephalosporanic acid (7-ACA):

$$7 - ACA + RCOCl - > Cephalosporin$$

Impact of Structure: The strained β-lactam ring mimics D-alanyl-D-alanine, enhancing binding to PBPs.

2. **(Evaluating) Evaluate the role of Quantitative Structure Activity Relationship (QSAR) in modern drug design. Provide examples of physicochemical parameters used in QSAR and explain how they contribute to predicting drug activity.**
Answer:
QSAR correlates physicochemical properties of molecules with biological activity, aiding drug design. It uses mathematical models to predict activity based on structural features.
Physicochemical Parameters:
- *Partition coefficient (log P):* Measures lipophilicity, affecting membrane permeability. Higher log P often enhances absorption but may reduce solubility.
- *Hammett's electronic parameter (σ):* Quantifies electron-withdrawing or donating

effects, influencing receptor binding.
- *Taft's steric parameter (Es):* Measures steric hindrance, affecting drug-receptor interactions.
- *Hansch analysis:* Combines log P, σ, and Es to predict activity.
Example: In designing antihistamines, QSAR predicts that increasing log P enhances CNS penetration.
Contribution: QSAR reduces experimental trials, optimizes lead compounds, and predicts toxicity, improving drug development efficiency.

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

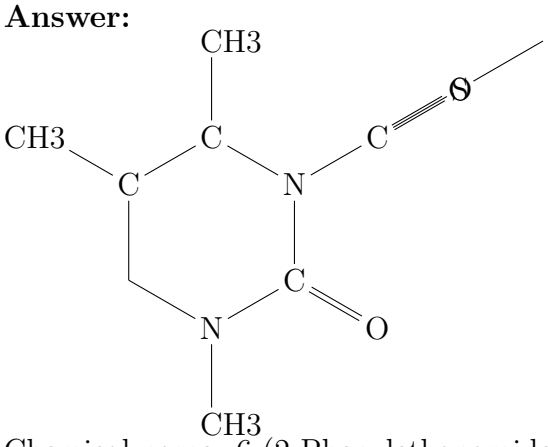
1. **(Understanding) Explain the historical background and classification of Tetracyclines, including their nomenclature and stereochemistry, with examples such as Tetracycline and Doxycycline.**
Answer:
Historical Background: Tetracyclines were discovered in the 1940s from *Streptomyces* species, with Chlortetracycline as the first.
Classification: Broad-spectrum antibiotics, divided into natural (e.g., Tetracycline) and semi-synthetic (e.g., Doxycycline).
Nomenclature: Named based on the tetracene core with functional group variations, e.g., 7-chlorotetracycline.
Stereochemistry: Tetracyclines have multiple chiral centers, influencing activity. Doxycycline's 5-hydroxy group enhances lipophilicity.
Examples: Tetracycline (natural, broad-spectrum) and Doxycycline (semi-synthetic, improved pharmacokinetics).

2. **(Applying) Describe the concept and applications of combinatorial chemistry in drug design, highlighting the differences between solid phase and solution phase synthesis.**
Answer:
Concept: Combinatorial chemistry generates large libraries of compounds by systematically combining building blocks to identify active molecules.
Applications: Used in lead discovery (e.g., identifying kinase inhibitors) and optimization.
Solid Phase Synthesis: Reactants are bound to a solid support (e.g., resin), allowing easy purification by washing. Example: Peptide synthesis.
Solution Phase Synthesis: Reactions occur in solution, suitable for small-scale libraries but harder to purify.
Differences: Solid phase is automated and scalable; solution phase is simpler but less efficient for large libraries.

3. **(Understanding) Discuss the mechanism of action and chemical degradation of Aminoglycosides, such as Streptomycin and Kanamycin, with emphasis on their structure-activity relationship.**
Answer:
Mechanism of Action: Aminoglycosides bind to the 30S ribosomal subunit, inhibiting protein synthesis by causing misreading of mRNA.
Chemical Degradation: Susceptible to hydrolysis and oxidation, especially at

amino and glycosidic bonds.
SAR: The aminocyclitol core (e.g., 2-deoxystreptamine in Streptomycin) is critical for ribosomal binding. Amino groups enhance activity; modifications reduce toxicity (e.g., Kanamycin).
Examples: Streptomycin (anti-tubercular) and Kanamycin (broad-spectrum).

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

1. **(Remembering) Draw the structure of Penicillin and write its chemical name.**
Answer:


Chemical name: 6-(2-Phenylethanamido)penicillanic acid.

2. **(Understanding) Explain why β-Lactamase inhibitors are used in combination with β-Lactam antibiotics.**
Answer:
β-Lactamase inhibitors (e.g., Clavulanic acid) block β-lactamase enzymes produced by resistant bacteria, which hydrolyze the β-lactam ring, restoring the efficacy of antibiotics like Penicillin.

3. **(Remembering) Define pharmacophore modeling and provide one example.**
Answer:
Pharmacophore modeling identifies key structural features responsible for a drug's activity. Example: The pharmacophore of opioids includes a tertiary amine and an aromatic ring.

4. **(Understanding) Describe the role of partition coefficient in QSAR studies.**
Answer:
Partition coefficient (log P) measures lipophilicity, influencing drug absorption and distribution. In QSAR, it predicts how well a drug crosses membranes, correlating with bioavailability.

5. **(Remembering) Write the chemical equation for the synthesis of Tetracycline.**
Answer:

$$Chlortetracycline- > [chemicalmodification]Tetracycline$$

(Note: Tetracycline is typically derived from natural fermentation, with semi-synthetic modifications.)

End of Answer Key