MOLECULAR MODELING AND DRUG DESIGNING
(BTC3231)

Time Allotted : 2½ hrs **Full Marks : 60**

Figures out of the right margin indicate full marks.

Candidates are required to answer Group A and any 4 (four) from Group B to E, taking one from each group.

Candidates are required to give answer in their own words as far as practicable.

Group – A

1. Answer any twelve: **12 × 1 = 12**

Choose the correct alternative for the following

(i) What are the components of a pharmacophore feature?
(a) Chemical group, 3D orientation, tolerance, weight
(b) Chemical function, location, charge, weight
(c) Chemical function, location, orientation, tolerance
(d) Chemical group, 3D location, charge, weight.

(ii) Biomolecular simulation using molecular dynamics or Monte Carlo methods is one of the major fields of computational science nowadays. Which of the following statements is correct
(a) Modelling proteins is harder than modelling simpler systems such as liquid water, as the normal molecular dynamics method cannot be applied to biomolecules.
(b) Only small proteins such as crambin can be simulated, given the huge number of solvent and protein atoms present in larger proteins.
(c) Using state of the art codes and computers, it is possible to carry out simulations of systems containing many millions of atoms.
(d) Proteins are modelled using special forcefields describing secondary structure elements such as α-helices instead of the atoms making up the protein)

(iii) Which algorithm is commonly used for numerical integration in MD?
(a) Steepest Descent (b) Leapfrog
(c) Monte Carlo (d) Simulated Annealing.

(iv) The main objective of molecular mechanics is to find _____.
(a) lowest energy conformation of a molecule
(b) stable conformation of a molecule
(c) highest energy conformation of a molecule
(d) unstable conformation of a molecule

(v) Factors that affects rate of drug distribution in our body is
(a) blood perfusion (b) membrane permeability
(c) both (a) and (b) (d) pH

(vi) Which of the following statements is true?
(a) parallel synthesis involves the synthesis of a large number of compounds using the same reaction sequence, where there is a mixture of compounds in each reaction vessel
(b) parallel synthesis involves the synthesis of a large number of compounds using the same reaction sequence, where there is a different, single compound formed in each reaction vessel
(c) combinatorial synthesis involves the synthesis of a large number of compounds using a variety of different synthetic routes to produce a mixture of compounds in each reaction vessel
(d) a parallel synthesis carried out in a specified number of vessels will produce more compounds than a mixed combinatorial synthesis.

(vii) Which of the following major aims in drug design is not related to the pharmacodynamics of a drug?
(a) The reduction of side effects (b) The maximisation of activity
(c) The reduction of toxicity (d) The maximisation of oral bioavailability.

(viii) Which of the following method used for virtual screening?
(a) ADMET analyses (b) QSAR modeling
(c) Pharmacophore modeling (d) All of the above.

(ix) Identify the kind of interactions that are typically involved in binding a drug to the binding site of a protein.
(a) predominantly van der Waals interactions (b) predominantly ionic bonds
(c) predominantly hydrogen bonds (d) a combination of all of the above.

(x) The CHARMM program whose physico-chemical concepts are general, are applied to which one of the following simulations?
(a) energy maximization
(b) molecular dynamics simulations (MDS)
(c) simulations that apply only to solvation
(d) energy optimization techniques that apply to lipids only.

Fill in the blanks with the correct word

(xi) Lipinski's rule of five is used for _____.

(xii) The primary goal of CADD is to reduce the time and cost involved in traditional drug discovery by using _____ methods to predict the interaction between a small molecule and a biological target.

(xiii) The computational methodology that tries to find the best matching between two molecules, a receptor and ligand are called _____.

(xiv) High logP values generally indicate that a compound is more _____.

(xv) Name one free available energy minimization software _____.

Group - B

2. (a) "Molecular Dynamics simulations (MDS) can provide detailed information on fluctuations and conformational changes of proteins and nucleic acids". Explain this statement by

giving examples of (i) specific motions in biological molecules and their timescales and (ii) complex dynamic processes that occur in biological systems. *[(CO1)(Analyse/HOCQ)]*

(b) In MDS, the classical mechanical numerical solution of the integration algorithms assume that the positions, velocities and accelerations can be approximated by a Taylor series expansion. Write the corresponding algebraic expressions for $r(t+\Delta t)$, $v(t+\Delta t)$, $a(t+\Delta t)$ in such a generalized integration algorithm. What is the mathematical expression for the Verlet algorithm? What are its unique characteristics? Tabulate its advantages and disadvantages. *[(CO1)(Remember/LOCQ)]*

(c) Name three derivative minimization methods. Outline the essential mathematical characteristics of any one of them. Enumerate the general and specific applications of energy minimization. How can an energy minimization technique and associated analysis be used to study the binding of an anti-bacterial drug to an enzyme? *[(CO1)(Apply/IOCQ)]*

(2 + 2) + (2 + 1 + 1) + (2 + 1 + 1) = 12

3. (a) Compare and contrast the Monte Carlo and molecular dynamics simulation methods. *[(CO1)(Analyse/LOCQ)]*

(b) Outline the basic techniques involved in setting up and running a molecular dynamics simulation. *[(CO1)(Remember/LOCQ)]*

(c) Discuss the 'lattice dynamics' technique. For what types of problems would lattice dynamics methods typically be used? *[(CO1)(Apply/IOCQ)]*

4 + 4 + 4 = 12

Group - C

4. (a) Explain the significance of the following physicochemical properties of drug: (i) hydrophobicity, (ii) electronic effects. *[(CO2)(Analyse/HOCQ)]*

(b) Explain is the difference between local energy and global energy minimum graphically? *[(CO2)(Remember/LOCQ)]*

(c) Write rules of Lipinski's rule of five. Explain the significance of "Lipinski's rule of five". It contains four rules, then why is called rule of five? *[(CO2)(Apply/IOCQ)]*

(2 + 2) + 3 + (2 + 2 + 1) = 12

5. (a) What is molecular docking and how is it used in drug discovery? Explain the concept of QSAR (Quantitative Structure-Activity Relationship) and its applications. *[(CO2)(Analyse/HOCQ)]*

(b) What is the purpose of conformational analysis in molecular modeling? What are some common force fields used in molecular dynamics simulations? *[(CO2)(Remember/LOCQ)]*

(c) What is the role of molecular modeling in predicting drug absorption, distribution, metabolism, and excretion (ADME)? How can molecular modeling be used to identify potential drug targets. *[(CO2)(Apply/IOCQ)]*

(2 + 2) + (2 + 2) + (2 + 2) = 12

Group - D

6. (a) Explain kinetics of drug elimination. *[(CO3)(Explain/HOCQ)]*

(b) Describe the mechanism of drug metabolism. *[(CO4)(Remember/LOCQ)]*

(c) Describe the mechanism of drug interaction with different types of receptors present in a human cell with a diagram. *[(CO3)(Apply/IOCQ)]*

(d) Explain characteristics curve of drug concentration with time after administration of single dose. Morphine has an apparent volume distribution of 250 L, and half-life of elimination of 2 hours. In a 70 Kg man, what is its approximate rate of clearance? *[(CO3)(Apply/IOCQ)]*

3 + 3 + 3 + (1 + 2) = 12

7. (a) For a disease, the structure of the protein target is not present in the protein database. Explain steps of drug designing using that target, based on SBDD principle, using a flow chart with the names available free software (which will be used in each step). Write an example of successful drug name and its target name developed by SBDD. *[(CO3)(Analyse/HOCQ)]*

(b) What is bioavailability of a drug. It depends on which factors? Describe with experimentally how we can calculate this, with graph. *[(CO4)(Remember/LOCQ)]*

(c) A new drug is under study in phase 1 trials. It is found that this molecule is avidly taken up by extravascular tissues so that the final total amount in the extravascular compartment at steady state is 100 times the amount remaining in the blood plasma. What is the probable volume of distribution in a hypothetical person with 8 L of blood and 4 L of plasma? *[(CO6)(Apply/IOCQ)]*

(4 + 1) (1 + 1 + 3) + 2 = 12

Group - E

8. (a) What are some common software packages used for molecular modeling? How can molecular modeling be used to predict the binding affinity of a drug to its target. *[(CO5)(Analyse/HOCQ)]*

(b) What are some limitations of molecular modeling in drug discovery? How can molecular modeling be used to optimize drug structure for better efficacy and reduced toxicity? *[(CO5)(Remember/LOCQ)]*

(c) How can molecular modeling be used to identify new uses for existing drugs (drug repurposing)? What are some examples of how molecular modeling has been used to discover new drugs? *[(CO5)(Apply/IOCQ)]*

(2 + 2) + (2 + 2) + (2 + 2) = 12

9. (a) Define a scoring function with reference to a virtual screening experiment. What is the algebraic form of such a scoring function? Explain the terms used. Use a Score vs distance plot that can accurately represent such a scoring function. *[(CO5)(Analyse/HOCQ)]*

(b) A structure activity relationship (SAR) assumes that the biological activity of a chemical compound is determined by its physicochemical properties. Use this statement to define the terms in the following generalized QSAR equation: $\log (1/C) = b_0 + \sum_i b_i f(D_i)$, How are the coefficients b_i determined and why is this methodology adopted? *[(CO5)(Remember/LOCQ)]*

(c) What electronic factors stabilize the intercalator within the DNA double helix? Can all of these electronic factors be simulated by the commonly used force fields? Explain your answer. *[(CO5)(Apply/IOCQ)]*

4 + 6 + 2 = 12

Cognition Level	LOCQ	IOCQ	HOCQ
Percentage distribution	38.54	32.29	29.17