MOLECULAR MODELING AND DRUG DESIGNING
(BIOT 3231)

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) The following potential energy expression, $V_{(r)} = 4\epsilon [(\sigma/r)^{12} - (\sigma/r)^{6}]$ represents
(a) an example of a potential where the r represents an infinite distance.
(b) a Beeman algorithm potential.
(c) an example of a periodic boundary condition (PBC).
(d) a Lennard-Jones potential.

(ii) Which one of the following is a 2nd order algorithm for energy minimization?
(a) Steepest Descent (b) Simplex
(c) BFGS/Newton-Raphson (d) Conjugate gradient/Powell.

(iii) In a Monte Carlo simulation, the minimum conformational energy is given by $\varepsilon(x)$, where the variable x could be
(a) Set of atomic coordinates (b) Mainchain torsion angles
(c) sidechain torsion angles (d) all of the above.

(iv) Which of the following statements best describes an induced fit?
(a) the process by which a binding site alters shape such that it is ready to accept a drug
(b) the process by which a drug adopts the correct binding conformation before entering a binding site
(c) the process by which binding of a drug to a binding site alters the shape of the binding site
(d) the process by which a binding site alters the shape of the drug into the binding conformation before binding.

(v) Which of the following terms is used to describe a drug that has the same effect on a receptor as the endogenous chemical messenger?
(a) agonist (b) antagonist
(c) partial agonist (d) inverse agonist.

(vi) Which of the following is a molecular descriptor for drug design
(a) clogP (b) molar refractivity MR
(c) topological indices (d) all of the above.

(vii) Ampicillin is eliminated by first-order kinetics. Which of the following statements best describes the process by which the plasma concentration of this drug declines?
(a) There is only 1 metabolic path for drug elimination
(b) The half-life is the same regardless of the plasma concentration
(c) The drug is largely metabolized in the liver after oral administration and has low bioavailability.
(d) The rate of elimination is proportional to the rate of administration at all times)

(viii) Which of the following is one of the rules in Lipinski's rule of five?
(a) a molecular weight equal to 500
(b) no more than five hydrogen bond acceptor groups
(c) no more than 10 hydrogen bond donor groups
(d) a calculated logP value less than +5

(ix) Which of the following approach is considered under the 'Ligand based drug designing'?
(a) Molecular docking (b) Pharmacophore modeling
(c) QSAR Modeling (d) (b) and (c) both

(x) Which of the following statement best describes a lead compound?
(a) A compound that contains the element lead
(b) A compound from the research laboratory that is chosen to go forward for preclinical and clinical trials
(c) A molecule that shows some activity or property of interest and serves as the starting point for the development of a drug.
(d) The first compound of a structural class of compounds to reach the market.

Fill in the blanks with the correct word

(xi) Procheck tool is used for _____.

(xii) A microsomal enzyme is _____.

(xiii) The simulated annealing is a consequence of _____.

(xiv) Name of one freely available molecular docking software is _____.

(xv) EC_{50} is calculated from a _____ response curve by dropping a line on the dose axis where 50% of the desired response is seen

Group - B

2. (a) What information is provided by radial distribution function (RDF) plots? Give a comparative overview of radial distribution function plots for a substance in solid, liquid and gaseous state. *[(CO1)(Analyse/HOCQ)]*

(b) How does the Verlet algorithm used in molecular dynamics simulation work? Give its advantages and drawbacks. How is Verlet algorithm different from Leap Frog algorithm? *[(CO1)(Remember/IOCQ)]*

(2 + 4) + (2 + 2 + 2) = 12

3. (a) Molecular mechanics is essentially empirical, while methods like PPP, CNDO, and AM1 are semiempirical. Give reason. Briefly mention the key features of the PPP, CNDO and AM1 semi-empirical methods. *[(CO1)(Analyse/IOCQ)]*

(b) Which of the following is more stable? Explain using Hückel Molecular Orbital theory (i.) allyl radical (ii) allyl cation (iii) allyl anion. *[(CO1)(Remember/IOCQ)]*

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

Group - C

4. (a) Explain the steps of one derivative and one non-derivative minimization method. *[(CO2)(Remember/LOCQ)]*

(b) Write the mathematical equation for the calculation of total molecular mechanics potential energy of a tetratomic molecule in the context of molecular modelling, explaining all the terms. *[(CO2)(Remember/LOCQ)]*

(c) The harmonic potential function of a bond stretching is expressed as $V_{bonds} = 0.8\ K_b\ (r_{AB} - r_{AB}^o)^2$

The stretching force constant for the bond A – B is 200 kcal/mol/A^2 and the equilibrium bond length r_{AB}^o is 1.2 A°.

(i) Sketch the potential as a function of A – B separation.

(ii) What is the energy if the bond is stretched by 60 A°?

(iii) What is the energy if the bond is compressed by 0.6 A°. *[(CO2)(Apply/HOCQ)]*

(3 + 3) + 3 + 3 = 12

5. (a) Describe the role of following physicochemical parameters in drug design: (i) solubility, (ii) partition Co-efficient. *[(CO2)(Analyse/HOCQ)]*

(b) What are principles, based on which, molecular mechanics (MM) methods are developed? What are the applications of MM? *[(CO2)(Remember/LOCQ)]*

(3 + 3) + (3 + 3) = 12

Group - D

6. (a) Based on two state receptor model explain the mechanism of action for an agonist and or an antagonist drug. *[(CO3)(Analyse/HOCQ)]*

(b) Explain how you will determine the ED_{50} and LD_{50} of a new drug experimentally when delivered orally into a mouse. *[(CO4)(Remember/LOCQ)]*

(c) Mr Jones has zero kidney function and is undergoing hemo-dialysis 3 days per week while awaiting a kidney transplant. He takes metformin for type 2 diabetes mellitus and was previously stabilized (while his kidney function was adequate) at a dosage of 500 mg twice daily, given orally. The plasma concentration at this dosage with normal kidney function was found to be 1.4 mg/L. He has had 6 dialysis procedures and metformin toxicity is suspected. A blood sample now shows a metformin concentration of 4.2 mg/L. What was Mr Jones' clearance of metformin while his kidney function was normal. *[(CO6)(Apply/IOCQ)]*

4 + (3 + 3) + 2 = 12

7. (a) Explain steps of LBDD using a flow chart and give example of successful drug developed by LBDD. *[(CO3)(Analyse/HOCQ)]*

(b) Explain the principle of one molecular descriptor with a example.
[(CO4)(Remember/LOCQ)]

(c) Describe mechanism of drug metabolism orally delivered in our body with a diagram.
[(CO4)(Apply/IOCQ)]

(4 + 1) + 4 + 3 = 12

Group - E

8. (a) Write out the mathematical expression for an all atom protein simulation force field that uses simple terms for bonded and nonbonded interactions to model the potential energy surface. Define and explain all the terms including the assumptions that are implicit for calculating non bonded interactions.
[(CO5)(Analyse/HOCQ)]

(b) What is the formal definition of a force field? Write out the mathematical expression for the AMBER force field defining all the terms. *[(CO5)(Remember/LOCQ)]*

(c) How is the molecular docking problem defined in terms of degrees of freedom?
[(CO6)(Apply/IOCQ)]

4 + (1 + 4) + 3 = 12

9. (a) Define the parameters of the following QSAR equation and explain their significance with respect to the above statement:
$\log (1/C) = k_1 \log P - k_2 (\log P)^2 + k_3\sigma + k_4$. *[(CO5)(Analyse/HOCQ)]*

(b) What properties of a potential drug does the hydrophobic component represent?
[(CO5)(Remember/LOCQ)]

(c) How can the above equation be re-parameterized with the term π? What are the physico-chemical implications of this newly parameterized equation?
[(CO5)(Apply/IOCQ)]

6 + 2 + (2 + 2) = 12

Cognition Level	LOCQ	IOCQ	HOCQ
Percentage distribution	33.33	31.25	35.42