Name : .....

Roll No. : .....

Invigilator's Signature : .....

CS/B.Tech(BT)/SEM-7/BT-703D/2012-13

2012

MOLECULAR MODELLING & DRUG DESIGNING

Time Allotted : 3 Hours *Full Marks* : 70

The figures in the margin indicate full marks.

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

GROUP – A

(Multiple Choice Type Questions)

1. Choose the correct alternatives for any *ten* of the following :

$10 \times 1 = 10$

i) A pharmacophore is defined as

a) a molecule that carries essential features responsible for a drug's biological activity

b) a molecule without biological activity

c) a molecule that carries non-essential biological information

d) a kinetically fast reacting molecule.

ii) ADME means

a) Addition Division Multiplication and Energy

b) Administration Distribution Metabolism and Excretion

c) About Drug Metabolism Effect

d) Additional Drug Mechanism Essential.

iii) SBDD means

a) Substrate Binding Data Determination

b) Structure Based Drug Determination

c) Structure Based Drug Designing

d) Substrate based Drug Development.

iv) IC_{50} means

a) concentration of a drug that is required for 50 per cent inhibition in an assay

b) concentration of a drug that is required for 50 per cent activation in an assay

c) 50 mg of drug that is required for 50 per cent inhibition in an assay

d) 50 µg of a drug that is required for 50 per cent activation in an assay.

v) MTD means

a) Minimum Tolerated Dose

b) Maximum Tolerated Drug

c) Maximum Tolerated Dose

d) Minimum Tolerated Drug.

vi) Which of the following statements is not true with respect to molecular dynamics simulation ?

a) Molecular dynamics calculates the 'real' dynamics of a molecular system

b) Molecular dynamics calculates time averaged properties of a molecular system

c) Molecular dynamics is a deterministic method

d) Molecular dynamics is a non-deterministic method.

vii) Which of the following sets of experimental techniques (any *one* set) use simulation methods widely ?

a) FT-IR and Resonance Raman

b) UV and steady state fluorescence

c) Single crystal biomolecular *X*-ray crystallography and *X*-ray diffraction

d) NMR and ESR.

viii) In a Monte Carlo simulation, the average of each conformational property <A> is given by which of the following expressions ?

a) <A> = 1/M £i = mi = 1 A (rN)

b) <A> = M2 £i = mi = 1A (rN)

c) <A> = M £i = mi = 1 A (rN)

d) <A> = 1/M2 £i = mi = 1A (rN).

ix) Most docking algorithms are characterized according to

a) the no. of degrees of freedom, *n*, that they include

b) the no. of degrees of freedom, *n*, that they exclude

c) the translational degrees of freedom only of the considered two molecules (biatomic system)

d) the rotational degrees of freedom only of the considered two molecules (biatomic system).

x) An example of an energy minimization algorithm is

a) steepest decent

b) OPLS

c) dielectric constant product

d) MOPAC.

xi) Denovo ligand design approaches include which one of the following ?

a) Top down, bottom up b) Outside in, inside out

c) Top down only d) Lateral and horizontal.

GROUP – B

(Short Answer Type Questions)

Answer any *three* of the following $3 \times 5 = 15$

2. Define the following :
   a) LC_{50}
   b) Prodrug
   c) Pharmacokinetics
   d) ED_{50}
   e) Pharmacodynamics.
3. Write short notes on any *one* of the following :
   a) Target Discovery
   b) Target Validation
   c) Assay Development.
4. a) Where is the Verlet algorithm widely applied to in simulation measurements ?
   b) Write down its integrated algebraic form clearly defining the terms and symbols.
   c) Cite one specific technical advantage and one specific technical disadvantage of this algorithm. 1 + 1½ + 2½
5. a) An early forerunner of the AUTODOCK docking portal was the DOCK algorithm/program. What was it originally designed to find ?
   b) What were the basic approximations of this and other early generation docking algorithms ?
   c) Use a simple cartoon diagram to illustrate the principles of DOCK. 1½ + 2 + 1½

GROUP – C

(Long Answer Type Questions)

Answer any *three* of the following. 3 × 15 = 45

6. a) What is drug ? Write the key steps of drug discovery.

   b) Write the use of willow bark and cinchona bark and write the chemical name and structure of the compound present in willow bark as drug.

   c) What is drug design and what are the names of earlier methods of drug discovery processes ?

   d) What is in-silico drug design and why is it significant ?

   e) Write cost and time line for drug discovery.

   3 + 3 + 3 + 3 + 3

7. a) How are chemicals selected for making drugs ?

   b) Explain steps of SBDD using a flow chart.

   c) Give three examples of drug designed using SBDD.

   5 + 6 + 4

8. a) What is combinatorial chemistry ? Write names of different approaches of it.

   b) Describe any one approach of combinatorial chemistry with example.

   c) Describe the Lipinsi's 'rule of five'. 3 + 7 + 5

9. a) Describe screening & hits to leads for drug designing.

   b) Describe lead optimization for drug designing.

   c) Describe clinical trials for drug designing. 5 + 5 + 5

10. a) How does a structure-activity relationship help in finding the in-vivo activity of a molecule ? Use a simple mathematical model to explain your answer. Give one early example of a structure-activity relationship.

    b) In the generalized QSAR expression,

    $\log(l/c) = k_1 \log P - k_2 (\log P)^2 + k_3 (sigma) + k_4$, define all the terms.

    c) What are the different steps necessary in setting up a 'good' QSAR equation ? 5 + 5 + 5

11. a) Briefly explain the configurational bias Monte Carlo (CBMC) method using two examples to illustrate its practical utility. What is the main physicochemical advantage of Gibbs Ensemble Monte Carlo method (GEMC) that establishes its practical computational utility.

    b) As a molecular modelling practitioner, you can exercise the choice of using either Monte Carlo or Molecular Dynamics simulation technique. What are some of the simple technical criteria used to make this computational choice ? Use example(s) to illustrate your answer. (4 + 3) + 8

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