Dr. C. Rout

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY, WAKNAGHAT
END SEMESTER EXAMINATION-2015
B.Tech. (BI) VI Semester

COURSE CODE: 10B11BI613 MAX. MARKS: 45
COURSE NAME: DRUG DESIGNING TECHNIQUES
COURSE CREDITS: 04 MAX. TIME: 3 HRS

Note: *All questions are compulsory. Carrying of mobile phone during examinations will be treated as a case of unfair means. Provide example and schematic diagram wherever applicable.*

Section A (9 Marks)

1. Each question carries 1 mark.
   a. Why do economical factors drive R & D in drug development and how is the neglected disease treated?
   b. Why do you calculate docking score as non-covalent interactions between drug target and ligand? How do you calculate covalent interaction computationally?
   c. How does the triad potency, solubility and permeability influence drug candidate selection?
   d. How does physicochemical lead profile help to identify lead molecules in a traditional setting?
   e. How did the high throughput screening (HTS) drive the synthesis of lead molecules towards high molecular weight in Pfizer Company?
   f. When do you use polarized basis function for an atom? For 2nd row of periodic table (B to Ne), how many polarization functions is used for each atom and why?
   g. How do you optimize the basis function (explain with examples) in atom?
   h. Why and how do you consider limited flexibility in a receptor protein?
   i. How do you guess the possible time requirement for the completion of geometry optimization job using quantum mechanical method? (Take any example and explain)

Section B (13.5 Marks)

2. Each question carries 4.5 marks.
   a. How was "FV" value calculated in the case study entitled "Molecular basis of drug resistance ------- HIV-1 protease"? Discuss the basis suggested in this study to modify already existing FDA drugs and how do you implement it for new drug design? (2.5+2)
   b. Suppose cyclooxygenase (COX) enzyme in human is present in five or more isotypes, and you have IC_{50} values for many inhibitors/potential drugs against this enzyme. Few isotypes structures of this enzyme are available, and few drugs are specific while others are non-specific. How do you determine the basis of selectivity of the specific drug using molecular modeling (visualization, docking and simulation) methods?

P.T.O.

c. In quantum mechanics methods, how do you determine atomic and molecular orbitals and discuss the significance of Born-Openheimer and Hartree-Fock assumptions? How do you optimize geometry of a molecule quantum mechanically using Schrodinger equation (Hamiltonian basis function, etc.), variational principle and self-consistent methods? (1.5+3)

Section C (22.5 Marks)

3. Each question carries 4.5 marks.
   a. What is combination therapy and why is this method in practice for the treatment against highly pathogenic microbe? How is this therapy carried out for the treatment against tuberculosis? How do you replace a drug in this therapy for new treatment regimen? (1.5+2+1)
   b. How do you identify a drug target against a pathogen and why should it be correlated with disease process? How do you refine computationally the lead candidates against a target (Explain at least three different methods)? (1.5+3)
   c. Most of the docking software use grid for score calculation and why? What are the values stored at each grid points and how are these values calculated? For a conformation, how do you calculate the docking score (explain with example) in grid method? (1+2.5+1)
   d. How do you optimize a lead using protein's temperature factor information determined from molecular dynamics (MD) simulation (explain with example) job? How do you use the anchor and grow method to determine binding mode of a ligand? How is configuration pruning used to determine diverse ligands against an active site? (1.5+1.5+1.5)
   e. How is free energy perturbation (FEP) method used to calculate free energy change of a reaction? How do you validate this method? How do you use this method to refine lead molecules against a particular receptor? Discuss the applications and limitations of this method from drug development point of view? (1+1+1.5+1)