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JAYPEE UNIVERSITY OF INFORMATION TECNOLOGY, WAKNAGHAT

T-3 EXAMINATION (JUNE 2016)

B.Tech. 6th Sem. (BI)

COURSE CODE: 16B11BI611 Max Marks: 35

COURSE NAME: Computer-Aided Drug Design Max Time: 2 Hrs

COURSE CREDITS: 4

Note: Attempt all parts of a question at one place.

Section A (Max. Marks: 10)

Q1. Each question carries 1 mark. Attempt any four.

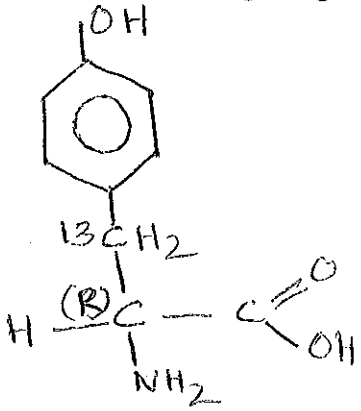
i. Fragments have more potential to become a drug candidate as compared to lead-like molecules, why? (Justify with example)

ii. How does ZINC database implement Tanimoto coefficient calculation? Why is this coefficient preferred over others for similarity calculation?

iii. Provide the SMILES representation of the structure provided at end.

iv. Suppose you have a pharmacophore and you would like to search a database using it. How do you score each of your searches? (Explain with example)

v. How do you refine lead molecules using database searching as well as analog design?



Q2. Each question carries 2 marks. Attempt any three.

i. What is the importance of conformation generation? How are the different principles implemented for diverse conformation generation? (0.5+1.5)

ii. When do you use the free energy perturbation method for lead refinement? How do you use multiple linear regression (MLR) method for calculating free energy and how do you validate this method?

iii. How does ensemble distance geometry method identify pharmacophore from a set of active molecules? What is the limitation of this and clique detection methods? (1.5+0.5)

iv. Most of the docking software use grid for calculating score of docking. Why are these grid values calculated prior to docking? How do you calculate grid values for any grid point using non-bonded interactions? How does grid points relate to active site of a protein? (0.5+1.0+0.5)

Section-B (Max. Marks: 25)

Q3. Each question carries 3 marks.

i. Against a particular protein target, the active and inactive molecules do not differ much w.r.t. molecular formulas. For development of a quantitative-structure activity relationship (QSAR) model, which types of descriptors do you prefer and why? How do you implement simultaneous and stepwise MLR method to develop the QSAR model? How do you evaluate the performance of the QSAR model? (1+1.5+0.5)

ii. Now-a-days, the partial least square (PLS) methods are preferred over MLR for the QSAR model development, why? Suppose you have molecular descriptors, how do you use the principal component analysis technique to design new potential lead molecules? Suppose you would like to improve the lead then which method are you going to be implemented and why? (1+1.5+0.5)

iii. Take any two molecules and calculate their Tanimoto, Dice and Cosine coefficients. For new drug discovery and lead refinement, how do you use the similarity criteria in database searching? (2+1)

iv. Are physico-chemical, biological and environmental properties of molecules good descriptors and discuss the applicability of these descriptors w.r.t. drug design? What are the important characteristics that need to be fulfilled by molecular descriptors and why? (1.5+1.5)

v. What is blood-brain permeability and discuss its significance w.r.t. drug design? How does each of the "Lipinski Rule of Five" correlate with oral bioavailability? (1.5+1.5)

Q4. Each question carries 5 marks.

i. Why do you need to study the computational basis of viral drug resistance? In the case study entitled "Molecular basis of ---------- HIV protease drug resistance", how the 'FV' value was calculated? Logically explains the significant findings of this study? How do you modify the existing FDA drugs (explain with example)? (1+2+1+1)

ii. How do you effectively implement the fragment-based approach for drug candidate development? What is the basis used in fragmenting database of potential drug molecules? Discuss the significant findings found from analysis of single and multiple chemical molecular databases, and how these findings can be incorporated for better drug candidate identification? (2+1+2)