

FINAL EXAMINATION

INSTRUCTIONS: ANSWER ALL THE QUESTIONS

TIME: 3 HOURS

1. Discuss what you understand by the following terms as they have been used in rational drug design and Qsar. **(20 Marks)**
 - a) **Qsar** - Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable. In QSAR modelling, the predictors consist of physico-chemical properties or theoretical molecular descriptors of chemicals; the QSAR response-variable could be a biological activity of the chemicals. QSAR models first summarize a supposed relationship between chemical structures and biological activity in a data-set of chemicals. Second, QSAR models predict the activities of new chemicals.
 - b) **Drug** – any substance other than food which when taken is used in the diagnosis, cure, relief, treatment, prevention of disease or intended to affect the structure or functioning of the body. It is a combination of molecules that basically affect the body and its processes.
 - c) **Molecular docking** – Molecular docking is *in-silico* method which predicts the placement of small molecules or ligands within the active site of their target protein (receptor). It is mainly used to the accurate estimation of most favourable binding modes and bio-affinities of ligands with their receptor. Presently, it has been broadly applied to virtual screening for the optimization of the lead compounds.
 - d) **Comparative molecular movement analysis** – This is a unique alignment independent approach. The 3D Qsar analysis utilizes a succinct set of descriptors that would simply characterize the three-dimensional information contained in the movement descriptors of molecule mass and charge up to and inclusive of second order.

e) **COMFA (Comparative molecular field analysis)** – This is a grid-based technique, a most widely used tool for 3D structural activity relationship. It is based on the assumption that, since, in most cases, the drug receptor interactions are non-covalent, the changes in biological activities or binding affinities of sample compound correlate with the changes biological activities by partial least square (PLS) analysis.

2. List and discuss FIVE factors that affect drug discovery and development (**20 Marks**)

- a) **Medicinal objective:** Researchers and pharmaceutical industries are keen on fixing the medicinal objective. If the medicine is supposed to suppress pain such as a pain killer, it is comparatively supposed to have fewer or even no other effect on the body thus its only objective is to reduce pain unless stated otherwise.
- b) **The ability of medicinal chemist:** the role of the medicinal chemist includes identification, preparation of the therapeutic compound and evaluating the structure relationship for safety and efficacy.
- c) **Screening facilities:** Thorough knowledge of bio molecule screening and rapid mass screening techniques are potentially important to evaluate and detect the potentially active therapeutic molecule in a short span of time.
- d) **Drug development facilities:** State of the art facilities with interdisciplinary efforts in biology, chemistry and pharmaceutical research fields such as pharmacy are essential for drug development process.
- e) **The cost of a new drug:** This includes the cost involved in the synthesis of the drug, the nature of the active molecule in the drug, the cost involved in design, fabrication, packaging, storage and transportation of both raw materials and the finished drug.
- f) **Technology:** sometimes technology determines the effectiveness of drugs designed and the rate at which they are being developed. The involvement of computerized systems in the design of drugs has really reduced the time it takes to design and develop. Other forms of technological advancements include; storage (cold, warm storage), transportation (air, land, sea), technological sharing of information (science bodies that share research via the internet) etc.

3. Once a drug has been developed, it has to reach the consumers hand in the dosage form it should be formulated. State Four parameters that should be considered. **(10 Marks)**

- i. Dissolution characteristics of the drug from the dosage form
- ii. Solubility of the drug as a function of its physico-chemical characteristics
- iii. Intestinal effective permeability
- iv. Drug's pre-systematic metabolism

4. When building a new oral designer drug, there are basic requirements to adhere to. State Five **(10 Marks)**

- i. It must be safe and efficient
- ii. It should be well absorbed orally and bioavailable,
- iii. It should be metabolically stable and with a long half-life,
- iv. It should be nontoxic with minimal or no side pharmaceutical effects,
- v. It should have selective distribution to target tissues.

5. State FIVE purposes of QSAR **(10 Marks)**

- i. To calculate biological activity and physicochemical quality by rational means,
- ii. To comprehend and rationalize the activity of action within a group of chemicals,
- iii. Economic product amplification,
- iv. Predictions could lower the need for lengthy & expensive animal tests. Reduction of animal tests and discomfort to animals,
- v. Other areas for growth are green and greener chemistry increases efficiency and eliminates waste. Qsars are also models or mathematical relationship (often a statistical correlation), which relates a structure-related property to the presence or absence, or potency of another property or activity of interest

6. State FIVE advantages of computer aided drug design CADD. (10 Marks)

- I. Through it we can reduce the synthetic and biological testing efforts.
- II. It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy) through *in silico* filters.
- III. It is a Cost-effective, time saving, Rapid and automatic process.
- IV. Through it we can know about the drug-receptor interaction pattern.
- V. It gives compounds with high hit rates through searching huge libraries of compounds *in silico* in comparison to traditional high throughput screening.
- VI. This approach minimizes chances of failures in the final phase.

7. State FOUR principal steps of QSAR/ QSPR studies (10 Marks)

- i. Selection of data set and extraction of structural/empirical descriptors
- ii. Variable selection,
- iii. model construction and
- iv. validation evaluation.

8. What do you understand by molecular descriptors used in Qsar? (10 Marks)

This can be defined as a numerical representation of chemical information encoded within a molecular structure through a mathematical procedure. This mathematical representation has to be invariant to the molecule's size and number of atoms to allow model building with statistical methods. The information content of structure descriptors depends on two major factors; the molecular representation of compounds and the algorithm which is used for the calculation of the descriptor.