SEMESTER –IV

DRUG DESIGN AND DRUG DISCOVERY

THEORY

Programme: M.Sc. **Max.Hours : 60**
Course Code: P20/CHE/DSC/401 **Hours per week : 4**
Course Type: DSC – 1
No. of credits : 4

COURSE OBJECTIVES

- The drug design and discovery imply random evaluation of synthetic as well as natural products in bioassay systems, creation of newer drug molecules based on biologically-active-prototypes derived from either plant or animal kingdom (lead compound).

- Structure activity relationship (SAR) is a powerful concept in drug discovery research that allows the selection and optimization of ideal drug candidates.QSAR models summarize a relationship between chemical structures and biological Activity in a data-set of molecules and also predicts the activities of new molecules.Computer aided drug design deals with the relationship between molecular structure and biological activity, and thus essential in the process of rational drug design.

- Combinational chemistry is a new technique developed in pharmaceutical industry, which involves synthesis of large number of compounds in a short period of time.

COURSE OUTCOMES:

CO1: Explain the stages involved in drug discovery.
CO2: Discuss the various Lead modification strategies and also how these can be used in drug development process with examples
CO3: Discuss the Structure-Activity Relationship studies in sulfa drugs, benzodiazepines, and taxol analogs
CO4: Identify the various physicochemical properties of drug molecules and the relationship. between these and biological activity
CO5: Explain the various tools used in QSAR studies and how these are applied in the design of drugs using examples.
CO6: Outline the principles of Computer aided drug design.
CO7: Describe the principles of Combinatorial Chemistry.
CO8: Discuss the Combinatorial approach in the process of drug discovery and plan and design combinatorial synthesis

MODULE 1: PRINCIPLES OF DRUG DESIGN AND DRUG DISCOVERY (15 Hrs)

Introduction to drug discovery. Folklore drugs, stages involved in drug discovery- disease, drug targets, bioassay. Discovery of a lead- screening of natural products and synthetic compound libraries. Existing drugs as leads (me too drugs). Pharmacokinetics (ADME), pharmacodynamics. Nature of drug – receptor interactions and their theories – Occupancy theory, Induced – fit theory, Macromolecular purturbation theory and Two-state model of receptor activation. Natural products as lead structures in drug discovery – Pharmacophore - structure pruning technique e.g. morphine.Discovery of lead structure from natural hormones and neurotransmitters.Principles of design of agonists (e.g.Salbutamol), antagonists e.g. cimitidine) and enzyme inhibitors (e.g. captopril).Drug discovery without lead – serendipity- Penicillin and Librium as examples. Principles of prodrug design. Introduction to drug patents and Clinical trials.

MODULE 2: LEAD MODIFICATION AND SAR STUDIES (15 Hrs)

SAR: Lead modification strategies, Bioisosterism, variation of alkyl substituents,chain homologation and branching, variation of aromatic substituents,extension of structure, ring expansion and ring contraction, ring variation, variation and position of hetero atoms, ring fusion, simplification of the lead, rigidification of lead.Discovery of oxaminquine, salbutamol, cimitidine and captopril Structure-Activity Relationship studies in sulfa drugs,benzodiazepines, and taxol analogs.

MODULE3: QSAR STUDIES AND COMPUTER AIDED DRUG DESIGN (15Hrs)

QSAR: Introduction, physicochemical properties - pKa, electronic effects and Hammettconstants(σ), lipophilicity constant(π), steric effects and Taft's constant, linear and nonlinear relationship between biological activityLipophilicity Substituent constants. Lipinski rule of five. Hansch analysis, Craig's plot,Topliss scheme, Free Wilson approach, cluster significant analysis. Two case studies (QSAR study on pyranenamine and design of Crizotinib).

Computer aided drug design: Introduction, active site, allosteric binding site,use of grids indocking , rigid docking , flexible docking and induced fit docking of ligands. Basic principles and difference between structure and ligand based drug design, denovo drug design and utility to optimize the lead structure.

MODULE 4: COMBINATORIAL SYNTHESIS (15Hrs)

Introduction.Combinatorial approach. Combinatorial libraries, technologies. Solid phase synthesis, types of resins. Linkers.Reactants for solid phased synthesis. Methods of Parallel synthesis: Haughton's tea bag procedure. Automated parallel synthesis. Methods in Mixed combinatorial synthesis: general principles. Furkas mix and split combinatorial synthesis, Structure determination of active compounds-Deconvolution, Methods in deconvolution-recursive deconvolution, tagging and use of decoded sheets. Examples of Combinatorial Chemistry. Planning and designing of combinatorial synthesis, Spider like scaffolds, drug molecules. Automation in Combinatorial chemistry. High throughput screening.

Reference books

1. Burger's medicinal chemistry and drug discovery by Manfred E. Wolf.
2. Introduction to Medicinal chemistry by Patrick.
3. Introduction to drug design by R Silverman
4. Comprehensive medicinal chemistry. Vol 1-5 by Hanzsch.
5. Principles of medicinal chemistry. by William Foye
6. Biochemical approach to medicinal chemistry. by Thomas Nogrady.
7. Pharmaceutical Chemistry and Drug synthesis by Roth and Kleeman
8. Drug design by E.J.Arienes
9. Principles of Medicinal ChemisttyVol I & II by Kadam et al
10. Medicinal chemistry An introduction by Garreth Thomas
11. .Organic and Pharmaceutical chemistry By Delgrado
12. Organic Pharmaceutical chemistry By Harikishansingh
13. Medicinal Chemistry ByAshtoshkar
14. Medicinal Chemistry By Chatwal
15. Organic Drug synthesis By LedneicerVol 1-6
16. Strategies for organic drug synthesis and design By Daniel Ledneicer.
17. Top Drugs: Top synthetic routes By John Saunders
18. Chirotechnoiogy By Roger A. Sheldon
19. Burger's Medicinal Chemistry and Drug Discovery: Principles and Practices. Vol. 1.
20. Medicinal Chemistry by G. Patricks.
21. Text book of Drug Design and Discovery, Edited by PovlKrogsgaard – Larsen Tommy Liljefors.
22. Structure Based Drug Design of Crizotinib (PF-02341066), a Potent and Selective Dual Inhibitor of Mesenchymal–Epithelial Transition Factor (c-MET) Kinase and Anaplastic Lymphoma Kinase (ALK) Martin P. Edwards, J. Med. Chem., 2011, 54 (18), pp 6342–6363.

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MODEL QUESTION PAPER

THEORY

Course Code: **P20/CHE/DSC/401** **Max. Marks: 60**

TIME: 2 ½ Hrs

SECTION –A

I. Answer the following **4 x 10 = 40 M**

1. (a) Explain the various stages involved in drug discovery process. (CO1)
   (b) Discuss the development of Captopril from Lead molecule.(CO2)

   OR
2. (a) Discuss the lead modification by structure pruning technique with morphine as an example. (CO2)
   (b) Explain the occupancy theory in detail.(CO2)

3. (a)Explain the SAR in Sulfa drugs.(CO3)
   (b) Discuss the development and discovery of Oxaminquine(CO3)

   OR
4. (a) Discuss the concept of bioisosterism in the development of a lead. (CO3)
   (b) Explain the concept of structure extension, ring expansion and ring variation in the development of drugs.(CO3)

5. (a)Explain the linear and non linear relationship between log P and biological activity.(CO4)
   (b) How is Craig's Plot important in the Lead Development Programme. **(**CO5)

   OR
6. (a) Explain Topliss method of Lead Modification**.**(CO5)
   (b) What is CADD? Explain the difference between Structure based and ligand based drug design.(CO6)

7. (a)What is high throughput screening?(CO8)
   (b) Describe the planning and designing a combinatorial synthesis.(CO8)

   OR
8. (a) Outline the mix and split method of library synthesis.(CO7)
   (b) Write a note on Tagging method.(CO8)

SECTION –B

II Anwer any five **5 x 4 = 20 M**

9. What are Folkore drugs? (CO1)
10. Discuss about the Pharmacokinetics of the drug.(CO2)
11. Discuss the Binding role of Hydroxyl and aromatic ring. (CO3)
12. Explain in brief Chain Homologation(CO3)
13. What is Hansch Analysis? Explain its use in Drug Discovery.(CO4)
14. Write a short note on Docking Studies of Drug Molecules (CO6)
15. Describe Houghton's tea bag procedure.(CO8)
16. What are the common resins used in combinatorial synthesis.(CO7)