DISCIPLINE SPECIFIC ELECTIVE COURSE (BIOMED-DSE-) DRUG DESIGN AND DISCOVERY

CREDIT DISTRIBUTION, ELIGIBILITY AND PRE-REQUISITES OF THE COURSE

Course title & Code	Credits	Credit distribution of the course			Eligibility criteria	Pre-requisite of the course (if any)
		Lecture	Tutorial	Practical/ Practice		
Drug Design and Discovery	4	3	-	1	XII Pass with Physics, Chemistry & biology	Basic Knowledge of Medicinal Chemistry

Learning objectives

The Learning Objectives of this course are as follows:

1. The students will learn the fundamental computational techniques used in drug design and discovery that can be applied to study problems in biology.
2. The students will develop scientific and hands-on practical skills and abilities to plan and carry out drug design projects to design a druggable ligand using computer-aided drug design tools.
3. The students will develop skills that will be useful for higher studies in biomedical research.

Learning outcomes

Having successfully completed this course, students shall be able:

1. To use structural databases and computer programs to visualize three-dimensional structures of the proteins and to analyse the relationship between structure and function.
2. To describe molecular mechanics force fields, parameterization, and their limitations and procedure for energy minimization of simple systems.
3. To understand the principle and carry out basic steps involved in molecular dynamics simulations.
4. To interpret molecular dynamics results vis-a-vis their biological significance and limitations.
5. To understand the drug discovery process from molecules to new medicines, challenges encountered in the development, manufacturing, and regulatory approval.

SYLLABUS

Unit I: Structure of Proteins (08 hrs)

Basics of biomolecular structure- primary, secondary tertiary and quaternary protein structures, Ramachandran plot, various parameters of protein secondary structure, introduction to peptide planarity, chirality, side-chain packing.

Molecular structure databases and visualization, The PDB and mmCIF formats, structure classification databases (SCOP and CATH), structure comparison and alignment, structure and functional assignment; secondary structure assignment, identifying structural domains in proteins.

Unit II: Proteins as Drug Targets (08 hrs)

Chemical attributes of drug targets, candidate gene prioritization, experimental validation, practical aspects and case studies, structural bioinformatics in drug discovery, protein structure prediction (homology modelling, fold recognition and, *ab initio* methods).

Unit III: Ligand and Pharmacophore-based screening methods for Lead Discovery (07 hrs)

Traditional and rational drug discovery methods, SAR, drug discovery pipeline, , hit and lead discovery, chemical databases and 2D substructure searching, , molecular descriptors and fingerprints, molecular similarity (or diversity) and similarity searching, selecting 'diverse sets of compounds', ligands and targets, chemical libraries, Lipinski's rule of five, QSAR, deriving and using 3D pharmacophores, 3D database searching, strengths and limitations of pharmacophore-based virtual screening

Unit IV: Structure based drug design methods (07 hrs)

Introduction to structure-based drug design methods, , , library design, binding site prediction, virtual screening, , docking and scoring methods, rigid and flexible docking, induced fit methods, *de novo* drug design, calculation of binding free energies molecular affinities and assemblies, design against protein-protein interactions.

Unit V: Introduction to Molecular Mechanics (08 hrs)

Scope of computational chemistry, Potential energy surfaces and optimization methods, , Introduction of *ab initio* methods. Electrostatics for force fields, basics of molecular dynamics simulation, introduction to Monte Carlo methods, electrostatics and solvation in biomolecules; calculation of free energy, Poisson-Boltzmann surface area.

Unit VI: Overview of the Clinical Evaluation and Development Process (07 hrs)

Introduction to drug development pathway: how to go from molecule to medicine, pharmacological and toxicological evaluation (prediction as well as *in vitro/ in vivo* methods), preclinical evaluation methods, an overview of the clinical process, clinical safety and pharmacovigilance.

Practical (30 hrs)

1. To predict secondary e.g PSIPred, and tertiary structures of proteins e.g. Swiss Model.
2. To calculate the total energy of a biomolecule e.g Charmm-GUI, AMBER, Chimera.
3. To build a ligand- *ab initio* from similar ligands with and without a known macromolecular target. SWISS-DOCK
4. To perform virtual screening and molecular docking using Autodock, Chimera.
5. To calculate energy minimization (EM) through different EM methods. Charmm-GUI, Chimera
6. To calculate binding free energy/MMPBSA through tools/ servers. AMBER
7. To perform MD simulations e.g. Charmm GUI, NAMD

8. To design a druggable ligand using computer-aided drug design tools.

Essential readings:

- Stromgaard, K., Krogsgaard-Larsen, P., & Madsen, U. (Eds.). (2016). Textbook of drug design and discovery, Fifth Edition. United States: Taylor & Francis. ISBN: 9781315354545.
- Gu, J., & Bourne, P. E. (Eds.). (2011). Structural bioinformatics, Second Edition. John Wiley & Sons. ISBN: 9781118210567.

Suggested readings:

- Rostron, C. (2020). Drug Design and Development. United Kingdom: Oxford University Press. ISBN: 9780198749318.
- Jhoti, H., & Leach, A. R. (Eds.). (2007). Structure-based drug discovery. Springer Netherlands. ISBN: 9781402044076.
- Gasteiger, J., & Engel, T. (Eds.). (2006). Chemoinformatics: a textbook. John Wiley & Sons. ISBN: 9783527306817.
- Bajorath, J., (2013) Chemoinformatics for Drug Discovery, John Wiley & Sons, ISBN: 978-1-118-13910-3.
- Leach, A. R. (2001). Molecular modelling: principles and applications. Pearson Education. ISBN: 9780582382107.