MEDICINAL CHEMISTRY

Semester-I Medicinal Chemistry

MC-510

Basics of Drug Action (2 credits)

1. **Structure:** Structure of drugs, structure of macro molecules and structures of their complexes. The importance of 3D Structure in Drug Action analysis. Electronic structure of drugs – metformin, omeprazole, Isoniazid, etc.

Electronic structure of ketenes and its importance in the generation of β-lactams. Conservation of orbital symmetry and Diels-Alder reaction. Group theory and Graph theory of drug molecules.

2. Energy concept and its importance in drug action. Energy of Drugs. Internal energy vs. thermodynamics. Interaction energy and free energy of drug – macromolecule interactions. First, Second and Third laws of thermodynamics and the principles derived from these laws which are of significance to drug action.

3. Free energy and Relationship between thermodynamics and statistics. Thermodynamic cycle. Statisticalt hermodynamics in predicting the structure of biomolecules and their interaction with drug molecules. Macromolecular vs. micromolecular correlation using thermodynamics and statistical thermodynamics**.**

4. Inter- and intramolecular interactions. Weak interactions in drug molecules. Covalent, ion-ion, ion-dipole, Hydrogen bonding, C-H hydrogen bonding, dihydrogen bonding, Van der Waals interactions and the associated energies. Charge transfer interactions, salt bridges, homolytic vs. heterolytic cleavage energies.

5. Receptors : Recogition and amplification components of Drug-receptor interactions, Receptor theories and drug action: Occupancy Theory, Rate Theory, Induced Fit Theory, Macromolecular perturbation theory,Activation-Aggregation theory. Topological and stereochemical consideration**.**

6. Enzyme Action : Enzyme – substrate interactions. Enzyme catalysis. Enzyme kinetics. Mechanisms of enzyme catalysis, Electrostatic catalysis and desolvation. Covalent catalysis, Acid-base catalysis, Strain / distortion in enzyme catalysis. Coenzyme catalysis.

7. Enzyme – inhibition : Enzyme – Inhibitor interactions, drug action through enzyme inhibition. Varieties of enzyme inhibition – inhibition at substrate binding domain, inhibition at allosteric binding domain, metals as inhibitors. Examples based on PDE4, GSK3, etc. Theories of enzyme inhibition and inactivation. Enzyme activation of drugs prodrugs.Mechanism based Inhibition (MBI) of cytochromes**.**

8. Nucleic Acids (NA) as targets for drug action. Structure of NA, topology of NA. NA as receptors. NA-interactive agents. Classes of drugs that interact with nucleic acids.Intercalation, NA-alkylation, NA-strand breaking and their importance in drug action.Topoisomerase inhibition via NA binding. DNA cleavage.

9. Drug likeness concept : DruLiTo and drug likeness property evaluation.Organic chemistry of Drug

metabolism, drug deactivation and elimination.Organic chemistry of drug toxicity. Enumeration methods, chemical property methods, Lipinski's rules, Weber rules, Ghoshe rules, etc.

10. Biotrasnformation and associated drug action: Phase I and Phase II transformations. Concept of hard and soft drugs. Role of cytochromes in oxidation of drugs. Consequences of drug oxidation reactions.

Radical reactions vs. ionic reactions.Recommended Books:

1. The Organic Chemistry of Drug Design and Drug Action by R.B. Silverman
2. Molecular Mechanism of Drug Action by C.J. Coulson , Taylor & Francis
3. A primer of Drug Action by R.M. Julien, Worth Publishers
4. Drug-Receptor Thermodynamics by R.B. Raffa,Wiley
5. Principles of Drug Action by W.B. Pratt, P. Taylor,Churchill Livingstone
6. Medicinal Chemistry How Drugs Act and Why by A. Gringauz
7. Principle of Molecular Recognition A.D. Buckingham, Springer-Science
8. Quantitative Molecular Pharmacology and Informatics by M. Lutz,Wiley
9. Physical Biochemistry by K.E.V Holde. Pearson/Prentice Hall
10. Free Energy calculations in Rational Drug Design by Rami Reddy, Kluwer Academic

MC-511

Spectral Analysis **(2 credits)**

1. **Ultra Violet (UV) and visible spectroscopy:**
   a) Energy levels and selection rules: Definitions, molecular orbital approach for energy absorption, various modes of transitions.
   b) Correlation of structural variation with UV absorption: Factors influencing the position and intensity of absorptions, Inductive and resonance effects, effect of ring size, influence of stereochemical factors.
   c) Predicting UV absorption: Woodward- Fieser, Fieser-Kuhn and Nelson rules;
   d) Other factors: Non-conjugative effect, solvent effect, *S-Cis* band.
2. **Infrared (IR)spectroscopy:**
   a) Characteristic regions of the spectrum: Various modes of vibrations, Energy levels
   b) Correlation of structure with IR spectra: Influence of substituents, ring size, hydrogen bonding, vibrational coupling and field effect on frequency.
   c) Applications: Determination of stereochemistry. Spectral interpretation with examples.
3. **Nuclear Magnetic Resonance (NMR) Spectroscopy:**
   a) Fundamentals: Physical basis, magnetic nuclei, resonance, relaxation processes, signal-sensitivity.
   b) Instrumentation: Continuous-Wave (CW) instrument, Pulsed Fourier Transform (FT) instrument, Functions, Relation with sensitivity, Sampling.

c) ^{1}H NMR, correlation of structure with spectra: Chemical environment and shielding, chemical shift and origin of its concept, reference compound, local diamagnetic shielding and magnetic anisotropy, relation with chemical shift, chemical and magnetic non-equivalence, spin-spin splitting and its origin, Pascal's triangle, coupling constant, mechanism of coupling, integral, NMR solvents and their residual peaks, protons on heteroatoms, quadrupole broadening and decoupling, effect of conformations and stereochemistry on the spectrum, Karplus relationship, diastereomeric protons, Heteronuclear coupling to ^{19}F and ^{31}P, virtual coupling, long range coupling-epi, peri, bay effects. Shift reagents-mechanism of action, spin decoupling and double resonance. Explanation of spectra of some compounds and drugs.

d) ^{13}C NMR, correlation of structure with spectra: Chemical environment, shielding and carbon-13 chemical shift, calculation, proton-coupled C Spetra, Proton-decoupled C spectra, Nuclear Overhauser Enhancement (NOE), Problem with integration, Distortionless Enhancement by Polarization Transfer (DEFT), Heteronuclear coupling for carbon to deuterium, carbon to ^{19}F, carbon to ^{31}P. Explanation of spectra of some compounds and drugs.

4. **Mass spectrometry (MS):** Molecular ion and metastable peak, fragmentation patterns, nitrogen and ring rules, McLafferty rearrangement, electron and chemical ionization modes, applications.

Recommended Books:

1. Spectroscopy by Donald L Pavia, Gary M Lampman, George S Kriz, James A Vyvyan
2. Organic spectroscopy by William Kemp
3. Spectroscopic Methods in Organic Chemistry by Dudley H. Williams & Ian Fleming
4. Spectrometric Identification of Organic Compounds by Robert M. Silverstein, Francis X. Webster & David J. Kiemie
5. Applications of Absorption Spectroscopy of Organic Compounds by Dyer
6. Fundamentals of Molecular Spectroscopy by Colin N. Banwell & Elaine M. McCash
7. Spectroscopy by Pavia, Donald L. Lampman, Gary M. Kriz, George S.

MC-520

Logic in Organic Synthesis-I **(3 credits)**

1. **Organic reaction mechanism:**
   a) **Methods of determining reaction mechanisms:** kinetic and non-kinetic methods; Energy profile diagrams, reaction intermediates, crossover experiments and isotopic labelling; order of reactions; Reversible, consecutive and parallel reactions; Solvent, ionic strength and salt effects; Acid-base catalysis.
   b) **Nucleophilic substitution reactions:** Uni- and bimolecular reactions; Attacking and leaving groups; Steric and electronic effects; Neighboring group participation; Formation and hydrolysis of esters, amides and acyl halides different mechanisms.
   c) **Electrophilic substitution reactions:** Aromatic electrophilic substitutions including Friedel-Crafts reactions.
   d) **Addition and elimination reactions:** Addition to C=C and C=O; Mechanism; Dehydrohalogenation, dehydration, etc; E1, E2 and *Syn*-elimination mechanism.

2. **Principles of synthetic planning:** Logic-centered molecular synthesis; Dislocation, synthetic tree, synthons, logical imposition of boundary conditions, direct associated approach; Structure-functionality relationships, functionality and unsaturation levels; Polar reactivity analysis; Control elements, consonant and dissonant circuits; Protocol for synthetic design.
3. **Alkylation:**
   a) **Enolates:** Regio- and stereo-selective enolate generation, "O" versus "C"-alkylation, effects of solvent, counter cation and electrophiles; Symbiotic effect; Thermodynamically and kinetically controlled enolate formations; Various transition state models for stereoselective enolate formation.
   b) **Enamines and metalloenamines:** Regioselectivity in generation, applications in controlling the selectivity of alkylation.
4. **Reaction of ylides:**
   a) **Phosphorous ylides**: Structure and reactivity, stabilized and Non-stabilized ylides, effects of ligands on reactivity, Wittig reaction, Schlosser modification, Wittig-Horner and Horner-Wadsworth-Emmons olefination reactions, Mechanism reactions and synthesis of various scaffolds.
   b) **Sulphur Ylides:** Stabilized and non-stabilized ylides; thermodynamically and kinetically controlled reactions with carbonyl compounds, regio- and stereo-selective reactions.
5. **Hydroboration:** Control of chemo-, regio- and stereo-selectivity, rearrangement of alkylboranes; Alkylboranes as organometallic reagents, e.g., 9-BBN, thexylboranes, siamylborane, chiral boranes- Ipc2BH IpcBH2 etc.

Recommended Books:

1. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure by Michael B. Smith, and Jerry March
2. Designing Organic Syntheses by Stuart Warren
3. Organic Synthesis: the Disconnection Approach by Stuart Warren
4. Advanced Organic Chemistry: Reactions and Synthesis, Part A: Structure & Mechanism by Francis A. Carey; Richard J. Sundberg
5. Advanced Organic Chemistry: Reactions and Synthesis, Part B: Reaction & Mechanism by Francis A. Carey; Richard J. Sundberg
6. Modern Synthetic Reactions by Herbert O. House
7. Modern Methods of Organic Synthesis by Carruthers, William Coldham, Iain
8. Mechanism and Structure in Organic Chemistry by Gould
9. Advanced Inorganic Chemistry by Cotton , Wilkinson, Murillo and Bochmann
10. Fundamentals of Medicinal Chemistry by Thomas ISBN047084307

In each case the treatment of the topic starts from the entry level discussion from the above text/reference books followed by relevant research articles from the original research work as well as review articles. Such suggested readings are provided along with the progress of the lectures.

NP-510

Separation Techniques **(1credit)**

1. **Separation Techniques:** Need for learning separation techniques, separation techniques in natural product research and drug discovery, extraction techniques.
2. **Chromatography:** General principles, classification of chromatographic techniques, normal and reverse phase, bonded phase chromatography, stationary phases, activity of stationary phases, elutropic series, and separation mechanisms.
3. **Column Chromatography and Short column chromatography:** Column packing, sample loading, column development, detection.
4. **Flash chromatography and Vacuum liquid chromatography:** Objectives, optimization studies, selecting column and stationary phases, selecting suitable mobile phases, automated flash chromatography, and reverse phase flash chromatography.
5. **High performance liquid chromatography:** Principles, instrumentation, peak shapes, capacity factor, selectivity, plate number, plate height, resolution, band broadening, pumps, injector, detectors, columns, column problems, gradient HPLC, HPLC solvents, trouble shooting, sample preparation, method development.
6. **Planar Chromatography - TLC/HPTLC/OPLC:** Basic principles, sample application, development of plates, visualization of plates, 2D TLC, densitometry, over pressure layer chromatography.
7. **Counter current chromatography:** Basic principles, droplet counter current chromatography, centrifugal partition chromatography, choice of solvents for SP and MP.
8. **Gas Chromatography:** Principles, instrumentation, split-splitless injector, head space sampling, columns for GC, detectors, quantification.
9. **Biochromatography:** Size exclusion chromatography, ion exchange chromatography, ion pair chromatography, affinity chromatography general principles, stationary phases and mobile phases.
10. **Hyphenated techniques:** Introduction to GC-MS and LC-MS techniques and their applications in natural products.

Recommended Books:

1. Methods in Biotechnology, Natural Product Isolation by Sarker, Latif, Gray
2. Methods in Biotechnology, Natural Product Isolation by Richard Canell
3. Various Reviews and Research Papers

PE-510

Pharmaceutical Preformulation - I **(1 credit)**

1. **Preformulation studies**: Preformulation studies of drug substances, proteins and peptides. Fundamental and derived properties in preformulation profiling. Preformulation work-sheet.
2. **Role of pre-formulation in drug discovery**: material properties in lead selection, 'drugability' of new chemical entities, in silico and high throughput pre-formulation studies.

3. **Role of preformulation in drug development**: Preformulation as a support for formulation development, identification of 'developmental challenges' during pharmaceutical development, dosage form specific studies.
4. **Salt selection:** Role of salt selection in drug discovery and development, theoretical concepts for selection of counter ions for salt formation, 'pKa rule' for salt formation, decision tree for salt selection, appropriate case studies.
5. **Solubilization:** Solubility and solubilization of non-electrolyte, drug solubilization in surfactant systems, use of co-solvents for development of liquid formulations, solid-state manipulations including use of metastable solid forms like amorphous state.

PT-510
Industrial Process and Scale up Techniques **(1 Credits)**

1. **Status of pharmaceutical industry:** Status of bulk drugs, natural products and formulations in India vis-a-vis industrialized nations.
2. **Scale-up Techniques:** Scale-up techniques for process optimization, maximization of productivity, in-process control techniques.
3. **Chemical technology of selected drugs:** Case studies with emphasis on rationale for selection of routes, raw materials, process control methods, pollution control procedures etc.
4. **Chemical technology of selected drugs:** Data collection during pilot plant trails, preparations of flow diagrams, material balance sheets and technical data sheets.
5. Process technologies for some selected natural products of commercial interest, e.g. 4-hydroxyisoleucine.
6. Scale-up techniques for industrial pharmacy, typical standard operating procedures for different dosage forms; In-process control procedures.
7. **Pharmaceutical manufacturing equipment:** Equipment used to manufacture bulk drugs.
8. **Pharmaceutical manufacturing equipment:** Equipment used in formulations.

Recommended books:

1. Process Chemistry in Pharmaceutical Industry by Kumar Gadamasetti, Vol I & II
2. Advanced Organic Chemistry by Jerry March
3. Pharmaceutical Process Chemistry for Synthesis: Rethinking the Routes to Scale-Up by Peter J. Harrington , Wiley
4. Practical Process Research and Development by Neal G. Anderson, Academic Press
5. Strategies for Organic Drug Synthesis and Design by Daniel Lednicer

GE-510
Biostatistics **(2 credits)**

1. **Statistics:** Introduction, its role and uses. Collection; Organization; Graphics and pictorial representation of data; Measures of central tendencies and dispersion. Coefficient of variation.
2. **Probability:** Basic concepts; Common probability distributions and probability distributions related to normal distribution.

3. **Sampling:** Simple random and other sampling procedures. Distribution of sample mean and proportion.
4. **Estimation and Hypothesis testing:** Point and interval estimation including fiducial limits. Concepts of hypothesis testing and types of errors. Student- t and Chi square tests. Sample size and power.
5. **Experimental design and analysis of variance:** Completely randomized, randomized blocks. Latin square and factorial designs. Post- hoc procedures.
6. **Correlation and regression:** Graphical presentation of two continuous variables; Pearson's product moment correlation coefficient, its statistical significance. Multiple and partial correlations. Linear regression; Regression line, coefficient of determination, interval estimation and hypothesis testing for population slope. Introduction to multiple linear regression models. Probit and logit transformations.
7. **Non-parametric tests:** Sign; Mann-Whitney U; Wilcoxon matched pair; Kruskal wallis and Friedman two way anova tests. Spearman rank correlation.
8. **Statistical techniques in pharmaceutics:** Experimental design in clinical trials; Parallel and crossover designs. Statistical test for bioequivalence. Dose response studies; Statistical quality control.

Recommended books:

1. Fundamentals of Biostatistics by Bernard Rosner
2. Pharmaceutical Statistics: Practical and Clinical Applications by Bolton and Bon
3. Statistical Misconceptions by Huck

GE-511 Seminars **(1 credit)**

LG-510

General Laboratory Experience - 15 hours / week **(3 credits)**

1. **Analytical techniques:** (75 hours)
   a) Spectral analysis workshop (45 hours)
   b) Separation Techniques (30 hours)
2. **Computer and application in pharmaceutical sciences (100 hours):** Introduction to computers, basic unit and functions, H/W and S/W, operating systems, word processing, spread sheet, graphic programs, dbase, windows, statistical S/W programs and packages. Steps involved in S/W development, computer languages with emphasis to FORTRAN language and programming, hands on experience in pharmaceutical software systems. Use of computers in information retrieval systems.
3. **Specialization (95 hours):** Two to three step synthesis. Purification by chromatographic technique and identification by IR, NMR, and MS.

Semester-II

MC-610

Drug Design **(2 credits)**

1. Wave function of drug molecules. Hamiltonian of Drugs. Absolute and relative energies of drug conformers. The importance of postulate 4 over postulate 3 in obtaining energy drugs. Energy minimization, comparison between global minimum conformation and bioactive conformation.
2. Manual and automated conformational search methods, their advantages and disadvantages. Implicit and explicit solvent effects on the structures of drugs. Conformational interconversion, transition-state determination and their role in designing rigid analogs. Molecular graphics. Computer methodologies behind molecular modeling including artificial intelligence methods.
3. Semi-empirical methods, molecular mechanical methods. Biguanides, nitreons in drugs, rapid racemization in glitazones, metabolism and toxicity of troglitazone, conversion of proguanil to cycloguanil.
4. QSAR: Steric and electronic effects: Hammett equation, lipophilicity effects. Hanschequation.Experimental and theoretical approaches for the determination of physico-chemical parameters, descriptors from Graph theory. Regression analysis, extrapolation versus interpolation, linearity versus nonlinearity. Descriptor calculation. The importance of biological data in the correct form; 2D QSAR; 3D-QSAR examples of CoMFA and CoMSIA. 4,5 and 6D QSAR methods
5. Molecular Docking: Rigid docking, flexible docking, manual docking, induced fit docking. Algorithms for molecular docking. Advantages and disadvantages of Glid, GOLD, Autodock and Dock software, with successful examples.
6. PharmacophorePerception :Unity in diversity; common minimum feature identification. Pharmacophore mapping techniques, methods of conformational search used in pharmacophore mapping. Comparison between the popular pharmacophore methods like Catalyst/HipHop, DiscoTech, GASP with practical examples.
7. Molecular Dynamics :Trajectories – structural, energy, interaction. Dynamics of drugs, dynamics of biomolecules, dynamics of drug-receptor complexes. Molecular dynamics in estimation of free energy from dynamical methods. Entropy and van der Waals vs. electrostatic component. Residuewise interaction energy estimation using MD simulations. Human vs. PfDHFR interaction energy difference with P218.
8. De novo Design : Active sites, allosteric sites, subpockets. Receptor/enzyme cavity size prediction. Predicting the functional components of cavities, designing drugs fitting into cavity. Trypanothione inhibitor Design using De novo design strategies.
9. Virtual Screening :Protocol development in virtual screening. Qualitative versus quantitative approaches- advantages and disadvantages. Random screening, Non-random screening, drug metabolism studies, clinical observations, rational approaches to lead discovery.
10. Case studies: Anti-malarial agent design using CADD methods (PfDHFR), Anti-diabetic agent design (GSK3), anti-cancer agent design (TopoisomeraseII), Anti-leishmanial agent design (TR inhibitors).

Recommended books:

1. Molecular Modelling, by A. R. Leach
2. Organic Chemistry of Drug Design and Drug Action, by R.B. Silverman
3. Practical Applications of computer aided drug design, by P.S. Charifson
4. Molecular modeling in Drug Design, by C. Cohen
5. Chemical Applications of Molecular modeling, by J. Goodman
6. Pharmacophore perception, by O.F. Guner

MC-620

Logic in Organic Synthesis-II (3 credits)

1. **Metal/ammonia reduction:** Reduction of mono-, bi- and tri-cyclic aromatic systems and various functional groups, reductive alkylation, regio- and stereoselectivity; Reduction of alkynes; Complex metal hydrides and selectrides.
2. **Reaction of electron-deficient intermediates:** Carbene, nitrene and free radical, their stabilities and modes of generation; Addition and insertion reactions of carbenoids and nitrenoids - regio- and stereoselectivity, role of the metal catalysts in the transitionmetalcatalyzed reactions, other types of reaction of carbenoids, e.g., ylide generation, 1,3- dipolar addition, rearrangement, etc.; Intra-molecular radical trapping process leading to ring annulation - Baldwin's rule.
3. **Organometallics:**
   Transition metal catalysis, heterogeneous catalysis, homogeneous catalysis; chelate effect and ligand nomenclature, hapticity and types of ligands, common coordination geometries, 18 electron rule, ligand charges and donor numbers, electron counting, reactivity of organometallic complexes,nomenclature of organometallic compounds; Preparation and reactions of organolithiums, Grignards, dialkyl lithium cuprates, organozinc reagents and acetylides, oxymercuration-demercuration of alkenes; Carbopalladation reaction, Heck reaction-Asymmetric Heck reaction, intramolecular Heck reaction, Heck reaction in heterocycle/natural product synthesis, reaction with unsymmetric alkenes, silicon-promoted Heck reaction, catalytic cycle and functional group tolerance in Heck reaction, Stille coupling and copper effect in Stille coupling, intramolecularStille coupling, reactivities of the triflates and the halides and sequential Stille coupling, Stille coupling in heterocycle/natural product synthesis, catalytic cycle in Stille coupling, Sonogashira coupling, application in enediyne synthesis, intramolecularSonogashira coupling, catalytic cycle in Sonogashira coupling, limitations of Sonogashira coupling, and, Suzuki coupling reaction, catalytic cycle in Suzuki coupling, and synthetic utility of Suzuki coupling.
4. **Umpolung and umpoled sythons:** Concept, acyl and glycine cation/anion, homoenolate anion, vicinyl dicarbonian, carbonyl dication equivalence, etc.
5. **Asymmetric synthesis:** Chiral induction-factors controlling facial selectivity; Chiral reagents/catalysts, auxiliaries, enzymes and antibodies; Kinetic resolution, double asymmetric induction, acyclic diastereoselection, asymmetric amplification; Asymmetric synthesis of amino acids and beta lactams.
6. **Concerted reactions and photochemistry:** Molecular orbital symmetry, frontier orbitals of 1,3-butadiene, 1,3,5- hexatrienes, allyl system, classification of pericyclic

reactions; FMO approach, Woodward-Hoffman correlation diagram method and PMO approach to pericyclic reactions; Electrocycli-creactions-conrotatory and disrotatory motions, [4n], [4n+2] and allyl systems, secondary orbiatl interaction; Cycloaddition-antarafacial and the suprafacial additions, [4n] and [4n+2] sytems with stereo chemical effects, 1,3 –dipolar cycloadditions, chelotropic reactions; Sigmatropic rearangements-supra and antarafacial shifts of H, sigmatropic shifts of carbon moiety, retention and inversion of configuration, [3,3] and [3,5] sigmatropic rearrangements, fluxional tautomerism, ene reactions; Franck-Condon principle, Jablonski diagram, singlet and triplet states, photosensitization, quantum effeciency; Photochemistry of carbonyl compounds, norish type-I and type-II cleavages, Paterno-Buchi reaction, photoreduction, photochemistry of enones and parabenzoquinones.

7. **Synthesis of complex molecules:**
   Various approaches for the synthesis of Taxol, Forskolin, FK-506, Gibberellines, Prostaglandins, Spatol, Aphidicolin, etc. andrecently developed important drugmoleculeson the basis of disconnection and direct associative approaches addressing the usefulness of the chemistries discussed under the headings 1-6 of this course and highlighting the new chemistries developed with respect to stereoselection and construction of the specific ring (structural framework).

Recommended books:

1. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure by Michael B. Smith, and Jerry March
2. Advanced Organic Chemistry: Reactions and Synthesis, Part A: Structure & Mechanism by Francis A. Carey; Richard J. Sundberg
3. Advanced Organic Chemistry: Reactions and Synthesis, Part B: Reaction & Mechanism by Francis A. Carey; Richard J. Sundberg
4. Modern Synthetic Reactions by Herbert O. House
5. Modern Methods for Organic Synthesis, W. Carruthers and Iain Coldham
6. Asymmetric Synthesis, Vol 3, Editor: J. D. Morrison Advanced Organic Chemistry by March
7. Mechanism and Structure in Organic Chemistry by Gould
8. Advanced Inorganic Chemistry by Cotton , Wilkinson, Murillo and Bochmann
9. Fundamentals of Medicinal Chemistry by Thomas
10. Web resources

    In each case the treatment of the topic starts from the entry level discussion from the above text/reference books followed by relevant research articles from the original research work as well as review articles published in peer reviewed journals of international repute. Such suggested readings are provided along with the progress of the lectures.

MC-630

Structure and Function of Biomolecules (2 credits)

1. **Properties of amino acids and peptide bond:** End group determination of peptides, sequencing of peptides using various chemical and analytical techniques; A techniques with case studies like LHRH and TRH peptides.
2. **Protein structure building block to quaternary structure of proteins:** Ramachandran plots; Peptidomimetics; Protein-ligand interactions; multiple binding modes.

3. Structure of lipoproteins and glycoproteins in relation to their function.
4. **Structure of lipids, polysaccharides and carbohydrates:** Relation-ship between their physico-chemical properties and their biological function.
5. **Detailed structure of nucleic acids and protein-nucleic acid interactions:** Nucleic acid and small molecule interactions;DNAdamage and repair.
6. **Structure and function of biomolecules pertaining to different thearapeutic areas:** Cancer- tubuline-role in cell proliferation, various binding sites, the chemistry and biology of tubuline inhibitors; farnesyl transferase- X-ray structure, ras protein and its role; Inflammation- COX-1 and COX-2 their structures and physiological role; Hyperlipidimia-HMG-CoAits structure and role in cholesterol manipulation.
7. **Biological crystallography:** Crystallisation data collection, refinement, identification of active site, phase determination heavy atom derivatives, electron density maps. Differences in the small molecule and biomolecule crystallography.
8. **Spectrofluorimetry and Optical methods:** Basic principles of fluorescence, intensity, fluoresent group, sensitivity of fluorescence to environment, biological applications. Optical activity measurements, ORD/CD applications to nucleic acids and proteins.
9. **Thermodynamical methods:** Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TA) of biomolecules, Isothermal Titration Calorimetry (ITC). Various thermodynamics based instrumental methods for estimation of structural features of biomolecules, enthalpy vs entropy contribution to free energy.

Recommended books:

1. Physical Biochemistry: Applications to Biochemistry and Molecular Biology by David Freifelder
2. Methods in Modern biophysics, by B. Nolting
3. Introduction to Biophysical methods in Protein and Neucleic Acid research, by J.A. Glasel
4. Monosaccharides. Their Chemistry and Their Roles in Natural Products
5. Essentials of Glycobiology by Varki
6. Carbohydrates by Osborn
7. Modern Methods in Carbohydrate Synthesis by Khan and O'Neill
8. Organic Synthesis with Carbohydrates by Boons and Hale
9. Enzymes in Synthetic Organic Chemistry by Wong and Whitesides
10. Methods in Modern Biophysics by B. Nolting
11. Introduction to Biophysical Methods in Protein and Neucleic Acid Research by J.A. Glasel.

MC-650

Stereochemistry and Drug Action **(2 credits)**

1. **Molecular isomerism:** Molecular motion, time scales and energy; Conformation of open chain and saturated cyclic systems.
2. **Chirality and molecular symmetry:** Nomenclature and representations; Macromolecular stereochemistry; Dynamic stereochemistry.
3. **Group theoretical interpretation of chirality group:** Laws of group theory, symmetry elements and operations, classification of symmetry operation into groups, chiral and achiral point groups, determination of molecular structures into symmetry point groups, platonic solids, disymmetrisation.

4. **Conformational analysis:**
   a) Definitions: Internal coordinates, distinction between conformation and configuration.
   b) Conformational analysis of cyclic compounds: carbocycles and heterocycles, bi- and tri-cyclic compounds.
   c) Conformational analysis of acyclic compounds: potential energy diagrams of various acyclic systems, gauch effect, generalized anomeric effect.
5. **Assignment of configuration:** Various projectional formulae, molecular with chiral center, axis and plane.
6. **Front on projectional formula of conformers and configurational isomers:** rational with specific examples.
7. **Resolution procedures:** Biological and chemical; Analytical chiral integrity determinations; Pfeiffer rule and its violations; Recent attempts to develop continuous scale for chirality; Chiral ligands.
8. **Chirality and drug action:** Realization that stereoselectivity is a pre-requisite for evolution; Role of chirality in selective and specific therapeutic agents; Case studies; Enantioselectivity in drug absorption, metabolism, distribution and elimination.

Recommended books:

1. StereoChemistry of Organic Compounds by Ernest L. Eliel, Samuek H. Wilen, Lewis N. Mander
2. StereoChemistry of Carbon Compounds by Ernest L. Eliel
3. Chemical Application of Group Theory by F. Albert Cotton
4. Relevant research articles as suggested time to time during the progress of class room teaching.

PC-610
Drug Metabolism **(1 credit)**

1. Biotransformation of drugs.
2. Enzymes responsible for bio-transformations, microsomal and non-microsomal mechanisms.
3. Factors influencing enzyme induction and inhibition.
4. Factors effecting drug metabolism.
5. Drug metabolism in fetus and new born.
6. Models to study drug metabolism.
7. Dose-effect relationships.
8. Excretion of drugs, biliary and fecal excretion.
9. Adverse drug reactions and drug interactions; Toxic reactions, allergic reactions, idiosyncracy.
10. Acute poisoning and its treatment.

Recommended books:

1. Introduction to Drug Metabolism, by G. Gordon Gibson and Paul Skett
2. Drug Metabolism Handbook Concepts and Applications Edited by Ala F. Nassar, Wiley

PE-660

Solid State Pharmaceutics (1 credit)

1. **Levels of solid state properties**: Molecular / particle / bulk level properties, interdependence of various levels on each other, role of different levels during pharmaceutical development and process development
2. **Molecular level**: Crystalline form, definition, concept of long range order, supramolecular arrangements, building blocks of crystals, unit cell, basic types of unit cells, demonstration of unit cells using crystal visualization softwares.
3. **Polymorphism**: Definition, significance of polymorphism in drug product performance, packing / conformational polymorphism, thermodynamics of polymorphs, enatiotropy / monotropy, concept of transition temperature, Burger and Ramberger rule.
4. **Crystallization process**: Molecular aggregation events in crystallization, energetic of crystallization, enthalpy entropy balance, types of nucleation, Ostwald's step rule, experimental protocols for polymorph screening.
5. **Implications of polymorphism in pharmaceutical development**: Regulatory concerns related to polymorphism, introduction to latest regulatory position on polymorphism.
6. **Amorphous state**: Definition, long range order versus short range order, disorder in the amorphous state, concept of glass transition temperature (Tg), thermodynamic necessity for Tg, entropy crisis.
7. **Role of amorphous state in drug delivery**: Solubility advantage, spring parachute effect during solubility studies, physical instability of the amorphous form, techniques for stabilization of amorphous form, amorphous solid dispersions.
8. **Co-crystals**: Introduction, synthons used for formation of co-crystals and applications in drug delivery
9. **Particulate level properties**: Crystal habit, generation of different crystal habits, implications of crystal habit on product performance and processing.
10. **Bulk level**: Bulk density, compressibility, flow properties, cohesivity, electrostatics,aggregation, agglomeration, role in formulation development and processing.

Books recommended:

1. Polymorphism in Pharmaceutical Solids Edited by Harry Brittain
2. Solid State Characterization of Pharmaceuticals Edited by Angeline and Mark Zarkrzewski
3. Crystal Engineering: A textbook, Edited by G. R. Desiraju, J. J.Vittal and A. Ramanan

GE-511 Seminars (1 credit)

LS-610

General Laboratory Experience 10 hours/week (2 credits)

Synthesis of a drug that includes 4 to 5 reaction steps; Isolation of each product by chromatographic and other techniques; Identification of structure of products by spectral and other analytical techniques; Report of yield; Understanding the correlation between theoretical and practical aspects of chemistry. Study of theoretical organic chemistry using computation methods for the same reactions and learning the techniques of molecular modeling.

Medicinal Chemistry Ph.D. Course

Semester-I

MC-710

Stereoselective and Stereospecific Synthesis (2 credits)

1. **General concept:** Differentiation of molecules, group selectivity,topicity and prochirality, substrate and product selectivities.
2. **Chirality:** Topological chirality and modifications of CIP classification of chiralityconstitutional properties of CIP system, continuous symmetry measure of chirality, degree of shape chirality.
3. **Chirality and drug action:** Terminologies and definitions, significance of drug stereochemistry on drug action and metabolism.
4. **Fundamentals of chirality generation:** Necessary conditions for streoselectivity, concept of enantio/diastereo-differentiation, methods of inducing stereos-electivity, strategies for stereoselective synthesis, kinetics and thermodynamics of stereoselective reactions.
5. **Approches for chiral synthesis:** Chiral pool approach, various chiral auxiliaries, self generation of chiral center.
6. **Enantioselective synthesis:** Multiplication of chirality-asymmetric hydrogenation, asymmetric alkylation, enatio/diastereo-selective protonation, asymmetric synthesis using chiral bases, dynamic kinetic resolution-mathematical treatment and implications.
7. **Asymmetric catalysis:** Stereoselective catalytic reduction- homogeneous hydrogenation (chiral ligands, effect of solvent/ pressure/ temperature/ addendum, substrate dependence of enantioselectivity, mechanistic aspects), stereoselective heterogeneous hydrogenation, transfer hydrogenation, hydrosilylation, hydricynation, stereoselective oxidation enantio / diastreoselective epoxydation and dihydroxylation.
8. **Concepts on catalytic asymmetric induction:** Ligand accelerated catalysis; Self replication of chirality- catalytic self-replicating molecules, control of chirality memory, P-stacking effect, selectivity and mechanism of catalytic asymmetric synthesis.
9. **Streroselective C-C bond formation:** Nucleophilic addition to C=X (X=C, O, S, N), Streoselective hydroformylation, Pericyclic reaction asymmetric induction in [3+2] and [2+2] cycloaddition, streoselective carbene addition, chirality transfer in sigmatropic rearrangements. Determination of enantiomeric purity: Various tools, chiral derivatising agents, chiral shift reagents, chiral solvating agents.
10. **Applications:** Chiral auxiliary based and catalytic asymmetric synthesis of natural and unnatural amino acids and other bio-molecules.

MC-730

Organometallic and Sustainable Chemistry in the Synthesis of Pharmaceuticals (2 credits)

1. **Carbon-carbon coupling reactions:** Suzuki, Hiyama, Stille, Negishi, Kumada coupling reactions; Mechanistic aspects of these reactions, comparison in mechanism, relative reactivities of organometallic coupling partners; Palladium and other metal

catalysis, controlling parameters; Heck (α- and β-arylation) and Sonogashira coupling reactions; Palladium- and Coppercatalysis, mechanism; Synthesis of biaryls, multi-substituted alkenes, alkynes, and various scaffolds.

2. **Carbon-heteroatom coupling reactions:** Ullmann, Chan-Lam, and Buchwald-Hartwig reactions. Mechanistic aspects, comparison; Synthesis of various amines, ethers, thioethers, and heterocycles.
3. **Cross-coupling of unactivated arenes:** Direct arene C-H bond arylation;oxidative couplings; two- and multi-fold C-H bond arylations; various approaches and mechanistic aspects; synthesis of biaryls and various scaffolds.
4. Application of coupling reactions (as mentioned in 1-3) in the synthesis of pharmaceutically-relevant compounds; Importance in the drug discovery research.
5. **Metathesis:** Grubbs (first and second generation) and Schrock catalysts, advantages and disadvantages, Importance of Ru and molybdenum catalysis; olefin, alkyne, ring closing, ring opening and multiple metathesis; Mechanism of these reactions, aspects of reaction conditions, and structural aspects of reactants.
6. Application of metathesis-reactions in the synthesis of various structural motifs including heterocycles, natural products, and pharmaceuticals; Importance in the drug discovery research.
7. **Green chemistry:** Principles, metrics, perspective of pharmaceutical industries; Green discoveries; greener reactions, catalysis, alternative reaction media, greener technologies; Sustainable synthesis of pharmaceuticals.
8. **Click chemistry:** Click reaction-criteria, water as solvent, various classes of reactions, thermodynamics; Huisgen cycloaddition andits modification, and nucleophilic ring opening of epoxide and aziridine.
9. **Alkyne-azide click chemistry in the drug discovery research:** Synthetic and medicinal chemistry advatgeous aspects of the reaction; Combinatorial, structure-based and approach of click chemistry in drug discovery research.
10. **Multicomponent reactions (MCR):** Ugi, Passerini, Biginelli, Hantzsch, Mannich, Petasis, Strecker, KabachnikFields reactions, Mechanism of these reactions, Conceptual discovery of MCR, Ugi-deprotection-cyclization (UDC) approach and synthesis of various biologically-relevant scaffolds, multi MCRs in synthesis, Diversity-oriented and convergent synthesis of pharmaceutically-relevant compounds. Interface

MC-810

Principles of Peptide Chemistry **(2 Credits)**

1. Importance of peptides in drug discovery.
2. **Protection and deprotection:** General aspects, need for protection, minimal versus global protection, protection of amino group by acid and base labile groups, protection of carboxyl group, concept of orthogonal protection in peptide synthesis.
3. Importance of side-chain functional group protection and details of protective groups used for masking individual amino acids, methods used for deprotection.
4. Various methodologies employed for coupling reaction.

5. **Side reactions in peptide synthesis:** Deletion peptides, side reactions initiated by proton abstraction, protonation, over-activation and side reactions of individual amino acids.
6. Segment and sequential strategies for solution phase peptide synthesis with case studies.
7. Principle of Merrifield solid phase peptide synthesis.
8. *t*-BOC and FMOC protocols.
9. Various solid supports and linkers, activation procedures, peptide bond formation.
10. **Deprotection and cleavage from resin:** Low and high HF cleavage protocols, formation of free peptides and peptide amides, purification and case studies, Site-specific chemical modifications of peptides.

Semester-II

MC-720

Synthetic Strategies in the Total Synthesis of Complex Organic Molecules **(2 credits)**

1. **Retrosynthetic analysis disconnections and reliability of reactions, synthons:** Donor and acceptor, functional group interconversions, one group carbon-heteroatom and carbon–carbon disconnections, two group carbon-heteroatom and carbon-carbon disconnections, chemo-, regio- and stereo-selectivity considerations, natural reactivity and umpolung.
2. **General synthetic reaction patterns and strategies:** Aliphatic nucleophilic and electrophilic substitutions, aromatic nucleophilic and electrophilic substitutions, addition to carbon–carbon and carbon-heteroatom multiple bonds, eliminations, rearrangements, oxidations and reductions.
3. **Chemistry of protecting groups:** Protection for alcohols, carbonyl groups, carboxylic groups and amino groups.
4. **Applications of synthetic strategies in the total synthesis of selected organic molecules:** Cholesterol (b) Estrone (c) Progesterone (d) Reserpine (e) Penicillin (f) Prostaglandin (g) Longifolene (h) Taxol.

MC-820

Carbohydrates: Occurrences, Structure, Reactions, Syntheses, Functions and Applications in Present Day Drugs **(2 credits)**

1. **Overview:** Introduction; importance of carbohydrates in food & nutrition and biology.
2. **Sources, Structure & Shape:** This will complement course # MC-630 in certain respects. Methods of structure elucidation.
3. **Recognition of carbohydrates by proteins:** Relevance in disease; discussion on the process of infection by microorganisms and possible methods of intervention; specific examples holera, flu, etc.
4. **Reactions at the anomeric centre:** Methods of glycosylation; details on the various types of glycosyl donors used; their preparation and methods of activation.

5. **Reactions at centres other than the anomeric centre:** Selective transformations; strategies for selective and global protection & deprotection of carbohydrates and their significance.
6. **Chemical synthesis:** Highlights on the need for synthesis; various approaches adopted for the chemical methods of oligosaccharide synthesis with examples.
7. **Enzymatic & chemo-enzymatic oligosaccharide syntheses:** Scope & limitation; discussion with examples relevant to medicinal chemists.
8. **Solid-phase oligosaccharide synthesis:** Relevance & its importance; different strategies used; applications.
9. **Carbohydrate-based drugs:** Discussion on various drugs (aminoglycoside antibiotics including glycopeptides, enediynes, macrolides, anthracyclines, etc; alkaloid, steroid and terpenoid glycosides; polyphenol glycosides etc.) that contain carbohydrate moiety (moieties) including polysaccharide therapeutics.
10. **Polysaccharide vaccines:** Relevance; discussion on the isolation and modification of bacterial polysaccharides, specifically capsular polysaccharides; protein conjugation.

MC-830

Advanced topics in Drug Action and Drug Design (2 Credits)

1. **Molecular basis of drug action:** Receptor specificity andsingnal transduction, Channelcontaining receptors, intracellular receptors, Receptor desensitization, Drug action in cell not mediated through receptors.
2. **Drug metabolism:** Inhibitions, induction, species and sex differences in drug metabolism, age on drug metabolism, CYP 450, Glutathone S-transferases, UDPGlucuronosyltransferase.
3. Resistance, Allergy, Tolerance: Immunologic basis of drug allergy, origin of drug resistance, resistance to the -lactam antibiotics, resistance via mutation and selection, resistance via gene transfer, resistance via gene amplification, biochemical mechanism of drug resistance, characteristics of tolerance and the dependence, tolerance by indirect mechanisms, cellular tolerance mechanisms, relationship between tolerance and ependence.
4. **Mutagenesis, carcinogenesis, teratogenesis:** DNA target for mutagenetic agents, mechanisms of chemical mutagenesis, types of mutations, biologic consequences of mutation, genetic reversion, mechanisms of chemical carcinogenesis, principal groups of chemical carcinogens, drug metabolizers and carcinogens, principles of teratogenesis.
5. **Lipophilicity and drug action:** Thermodynamics of van der Waals interactions, thermodynamics of hydrophobic interactions, Molecular lipophilicity potential. Physicochemical and biological factors that influence drug permeability by passive diffusion, lipophilicity of metabolites.
6. **Drug-Receptor thermodynamics:** Thermodynamic models of drug-receptor interactions, Effector-receptor interactions. Basics of correlations, relevance to enthalpy-entro compensation.
7. **Drug action of some agents:** Steroid biosynthesis and action, neurotransmitter action and metabolism, memberane-active agents, hormonal modulators, mictrotubule action.

8. **Case study 1:** PfDHFR-Thymedylate synthase, mechanism of protein synthesis, action of anti-folates, selective prevention of protein synthesis in *plasmodium falciparum*, enzyme action associated with dihydrofolate reduction.
9. **Case study 2:** Mechanism based inhibition, carbene reactive metabolites, epoxide reactive metabolites, nitroso reactive metabolites, S-oxidation vs epoxidation in thiophene.
10. **Case study 3:** Drug action of agents acting at Glygogen Synthase Kinase (GSK), seven different methods of lead action on GSK3, drug design strategies for anti-diabetic drugs acting at GSK3.