
# Ph.D.
# SYLLABUS

## Medicinal Chemistry

# Ph.D - Medicinal Chemistry
# 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 and drug action:** Terminologies and definitions, significance of drug stereochemistry on drug action and metabolism.
3. **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.
4. **Approches for chiral synthesis:** Chiral pool approach, various chiral auxiliaries, self generation of chiral center.
5. **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.
6. **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.
7. **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.
8. **Applications:** Chiral auxiliary based and catalytic asymmetric synthesis of natural and unnatural amino acids and other bio-molecules.

## 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 interconver-sions, 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, 1,3 and 8 129 1,5-difunctional compounds.
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 :

| | | | |
|---|---|---|---|
| (a) Cholesterol | (b) Estrone | (c) Reserpine | (d) Penicillin |
| (e) Prostaglandin | (f) Progesterone | (g) Longifolene | (h) Taxol |

## 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 pharmaceuticallyrelevant compounds; Importance in the drug discovery research.
5. Metathesis: Grubbs (first and second generation) and Schrock catalysts,Advantages and disadvantages, Importance of Ru and molybdenumcatalysis;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 In situ 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, multiMCRs in synthesis, Diversity-oriented and convergent synthesis of pharmaceutically-relevant compounds. Interface.

# Ph.D - Medicinal Chemistry
# SEMESTER - II

## 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.

## MC 820- Carbohydrates: Occurances, 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- cholera, 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 and singnal 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, UDP- Glucuronosyl transferase.
3. **Resistance, Allergy, Tolerance :** Immunologic basis of drug allergy, origin of drug resistance,resistance to the b-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 metabolizersand 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.