Ph.D. SYLLABUS

1. Medicinal Chemistry
2. Pharmaceutics
3. Pharmacology & Toxicology
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 stereoselectivity, concept of enantio/diastereo-differentiation, methods of inducing stereos-electivity, strategies for stereoselective synthesis, kinetics and thermodynamics of stereoselective reactions.

4. **Approaches 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, hydroxylation, hydrcynation, stereoselective oxidation enantio / diastereo-selective epoxidation 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. **Steroselective C-C bond formation:** Nucleophilic addition to C=X(X=C, O, S, N), Stereoselective hydroformylation, Pericyclic reaction asymmetric induction in [3+2] and [2+2] cycloaddition , stereoselective 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. **Retroynthetic 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, 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 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 and its modification, and nucleophilic ring opening of epoxide and aziridine.

9. **Alkyne-azide click chemistry in the drug discovery research**: Synthetic and medicinal chemistry advantageous 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, Kabachnik-Fields 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.
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.
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 830 - Advanced Topics in Drug Action and Drug Design (2 Credits)

1. **Molecular basis of drug action:** Receptor specificity and signal transduction, Channel containing 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, Glutathione 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 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.
7. **Drug action of some agents:** Steroid biosynthesis and action, neurotransmitter action and metabolism, membrane-active agents, hormonal modulators, microtubule action.
8. **Case study 1:** PdFHFR-Thymidylate 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 Glycogen Synthase Kinase (GSK), seven different methods of lead action on GSK3, drug design strategies for anti-diabetic drugs acting at GSK3.
# PE 710 - Implications of Solid State Properties in Drug Delivery (2 Credits)

{Prerequisite to course PE-660}

1. **Barriers to Drug Delivery:** Aqueous solubility, permeability, first pass metabolism.

2. **Solid State Properties and Biopharmaceutics:** Implications of molecular level and particle level solid state properties on aqueous solubility, permeability, first pass metabolism.

3. **Molecular level of Solid State and Drug Delivery:**
   a) Polymorphs-thermodynamic properties, solubility advantage.
   b) Co-crystals-crystal engineering aspects, synthons exploited in pharmaceuticals, phase behavior, solubility behavior.
   c) Amorphous phase-thermodynamic and kinetic properties, physical stability, solubility advantage, challenges in use of amorphous phase, stabilization strategies and surface behavior of amorphous form.

4. **Particle level of solid state and drug delivery:**
   a) Particle size reduction to micron and nano size-Nanocrystals, polymeric nanocrystalline solid dispersions, small molecule assisted nano-crystalline solid dispersions.
   b) Crystal habit-surface anisotropy and its impact on dissolution behavior.
**PE 810 - Novel Approaches for Targeted Drug Delivery (2 Credits)**

1. **Principles of drug targeting and molecular basis of targeted drug delivery:** Receptor mediated endocytosis; Different levels of targeting-first order, second order and third order targeting; Different types of targeting-active and passive targeting.

2. **Disease based targeting approaches:** Novel approaches to target diseases and disorders such as cancer and infectious diseases, exploitation of disease environment for the targeted delivery of therapeutics.

3. **Organ based targeting:** Novel strategies for CNS, pulmonary, liver, and colon targeting.

4. **Cell/Organelles based targeting:** Mitochondria, Nuclear targeting, lymphatics/M cells, liver parenchymal cells/macrophages, hepatocytes and bone marrow cells.

5. **Physico-chemical approaches of targeting:** Stimuli responsive: Magnetically, thermal and pH assisted drug delivery systems, Chemical drug delivery (prodrugs), Lipid-drug/Polymer drug conjugates.

6. **Carrier based approach for targeted drug delivery:** Functionalized liposomes, polymeric and lipid nanoparticles, liquid crystalline nanoparticles, polymeric micelles, functionalized carbon nanotubes and inorganic nanoparticles.

7. **Gene Delivery:** Barriers to gene delivery, novel approaches based on viral and non viral vectors for site specific gene delivery, their advantages and limitations, siRNA delivery.

8. **Advanced characterization techniques for nanocarriers:** Nanoscale characterization techniques, Biophysical characterization of nanoparticles and in vivo imaging techniques Fluorescence Gamma scintigraphy, X rays.

9. **Miscellaneous Topics:** Emerging roles of Emulsomes, transferosomes, ethosomes, bilosomes, virosomes etc. for drug/macromolecule delivery.

10. **Nanotoxicology and regulatory issues:** Toxicity and regulatory hurdles of nanocarriers, Nanotoxicity in lungs.
PC 810 - Application of Biotechnology in Parasitic Disease Research (2 credits)

1. Biotechnology and parasitic disease research: An introduction: Role of genetic engineering in parasitic disease research, study of parasites and recombinant DNA technology, immuno technology and parasitology. Molecular biology of malaria parasites, leishmania donovani and entamoeba histolytica.

2. General techniques: Cultivation and cloning of plasmodium falciparum, leishmania donovani and entamoeba histolytica. Preparation of malaria parasites from experimental animals. Isolation of different stages of malaria parasites and synchronization; Identification, counting, cryopreservation and recultivation of parasites.


4. Recombinant DNA technology in parasitic disease research: Strategies for the use of rDNA technologies in the study of parasite antigens; Application of rDNA technology in the identification and exploitation of new drug targets in parasites; Biotherapy of parasitic diseases, detection and analysis of cytokine mRNA in cells and tissues using RT-PCR; Development of DNA probe based diagnostic tools for parasites; Construction of cDNA libraries and genomic DNA cloning and other related genetic engineering techniques.

5. Hybridoma technology and analysis of proteins: Basic principles of somatic cell hybridization; Production of monoclonal antibodies; Detection and characterization of monoclonal antibodies using immunofluorescence assay and ELISA; Applications of hybridoma technology in parasitic disease research; Metabolic and surface labelling of parasite antigens and SDS-PAGE and two-dimensional analysis of parasite antigens.

PC 820 - Pharmacological Interventions for Ischemic Brain Injury (2 Credits)

1. Pathophysiology of ischemic brain injury, clinical manifestations and laboratory evaluation.

2. Excitotoxicity of ischemic brain injury: Glutamate excitotoxicity, excitatory amino acid (EAA) receptors EAAantagonists.Problemswith EAAantagonists.


4. Potential neuroprotective approaches for ischemic brain injury: Calpain inhibitors, PARP inhibitors, MAP kinase inhibitors, apoptosis inhibitors etc.

5. Animal models for focal and global ischemia. Neuronal culture and brain slices for testing neuroprotective drugs.
PC 830 - Parasitology/Microbiology, Community & Pharmacy (2 Credits)

1. **Parasitic, microbial and viral infections, community and pharmacy:** The general perceptions, linkages and relevances; Basic principles of epidemiology; Epidemiology of infectious/tropical diseases; Community related issues involved in the epidemiological studies; Community participation in epidemiological studies; Role of epidemiological studies on disease treatment, control and prevention.

2. **Emerging and re-emerging infections:** Role of vectors and population migration; Impact of travel on the transmission patterns of infectious diseases; Mapping and managing of the drug-resistant pathogens.

3. **Biomedical and biocultural definitions of parasitic and microbial diseases:** The perceptions of community; Community or selected schools participation/involvement in the control and treatment of infectious diseases; Role of NGOs and media; Modern and traditional medicines for the treatment of tropical diseases.

4. **Mother's definition of malaria:** Mother's beliefs and behaviours in relation to malaria in children; Home management of childhood malaria, diarrhoea and respiratory infections; The decision-making dynamics in treatment seeking behaviours, antimalarials available in retail outlets and home; Impact of parasitic and microbial diseases on the education of children.

5. **Women and tropical diseases:** Introduction; Women's participation in the treatment and management of infectious diseases; The relationship between gender and tropical diseases: Risk factors of infection, social costs and access to care, knowledge and resources; Assessment of women's need as related to infectious diseases, their involvement in the identification of their own needs, setting their own goals and targets; Training of women to train themselves.

6. **Mass chemo and immunoprophylaxis against tropical diseases:** Evaluation of their impact and the understanding of the cost-effectiveness.

7. **Determination of disease burden, the disability-adjusted life years, and the understanding of the economical aspects of tropical diseases:** Details of studies the social and economic burden of malaria and tuberculosis.

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PC 840 - Regulatory Toxicology and Drug Safety Evaluation (2 Credits)

1. **Concept and development of regulatory toxicity testing models:** Bio assays and endpoints: Human pharmaceutical products; Exposure characterization; Routes of exposure; ADME profiles.

2. **Stages of drug development:** Drug laws, FDA, OECD, ICH, Schedule Y; Design of preclinical toxicity studies and clinical development, clinical risk/benefit analysis. Safety evaluation of medical devices and bio materials. Good Laboratory Practices (GLP), issues and implementation.

3. **Different methods in toxicity testing:** Dose determination, response characterization, NOAEL.

4. **MTD and threshold limitations:** Hormesis, lower dose extrapolation, in vitro and in vivo correlation, animal to human extrapolation; Flow chart.

5. **Mechanism of toxicity:** Evaluation across different models: Target organs, cell death, necrosis, apoptosis, oxidative stress, chromosome and DNA damage.

6. **Acute and chronic toxicity, genetic toxicity:** Types of genetic toxicity testing; Principles of detection; Genotoxicity of marketed drugs, test batteries, Salmonella test, micronucleus test, chromosome aberration test, Comet assay, New-bio assays.

7. **Reproductive toxicity:** Germ cell toxicant, effect on gonads, F1 generation study. Neonatal toxicity; Transplacental mutagenesis and carcinogenesis.

8. **Carcinogenicity, carcinogen identification:** Carcinogenesis process, drug induced carcinogenicity, lifetime carcinogenicity bio assays, neonatal mouse models; Short and medium term bio assays, limitations and impacts.

9. **Regulations, discovery-development gap:** Risk characterization; Management and Communication.

PC 850 - Cellular and Molecular Parasitology (2 Credits)

1. **Ultrastructure of parasites/microbes/viruses:** Plasmodium, leishmania, entamoeba, mycobacterium, candida, HIV, hepatitis B virus; Basic principles related to structure and function of the cell membranes; Biology of the cell membranes of plasmodium, leishmania and entamoeba; Cell wall of mycobacterium tuberculosis and its unique features; Structure of HIV.

2. **Disease processes and the definition of pathogenesis:** Modern concepts of the pathogenetic mechanisms with special reference to the underlying genetic basis; Mechanisms of virulence; Acute-phase response and proinflammatory mechanisms during infections; Mechanisms of mimicry; Cerebral malaria (CM) and mechanisms of sequestration; Experimental models of CM; Hematopoiesis and anaemia in malaria; Genetic factors that determine the susceptibility and resistance to malaria. *E. histolytica:* Mechanisms of encystations and excystation; Macrophage-mycobacteria interaction, and the mechanisms of latency during M. tuberculosis infection.

3. **Bioimmunotherapy of infectious diseases and the development of protein drugs:** Brief introduction to carbohydrate, protein, lipid and nucleic metabolism in parasitic infections (plasmodium, leishmania and M. tuberculosis); Studies on some known potential drug targets in plasmodium,leishmania, M. tuberculosis and HIV. genes and antigens/proteins of plasmodium, leishmania, M. tuberculosis in the development of vaccines and drugs.

4. **Drug-resistance:** The definition; Drug-resistance in parasites and microbes; General mechanisms of drug-resistance; Detailed studies on mechanisms of resistance of (1) Plasmodium to chloroquine, artemesinin derivatives and pyrimethamine; (2) M. tuberculosis to isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin; Reversal of drugresistance; Experimental selection of drug-resistant strains of Plasmodium berghei (in vivo) and P. falciparum (in vitro); Role of cloning in experimental selection of drug-resistant strains.

5. **Basic principles of vaccinology:** Conventional (whole cell live, killed and attenuated), subunit and molecular vaccines. nucleic acid vaccines; Prime-boost vaccination; Adjuvants and the mechanisms of their action; Experimental models of vaccination against malaria and tuberculosis; Latest knowledge in the human vaccine development against malaria, leishmania, tuberculosis and HIV.

6. **Fundamentals of the immunodiagnosis with special reference to tropical diseases; Immunodiagnosis:** Approaches, practices and research needs; Impact of immunodiagnosis on the disease control. Various serological tests (ELISA, IFA, IHA etc.); Studies on presently used diagnostic kits for malaria, tuberculosis and HIV; Molecular diagnosis: Weaknesses and strengths.

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PC 860 - Epigenetics and Diseases (2 Credits)

1. Toxigenomics, pharmecogenomics, pharmecognetics and personalized medicine.

2. **Proteomics in Drug Discovery:** Two dimension gel electrophoresis; in-gel digestion etc.

3. **Microarray technology:** Hybridization and types of arrays, tilling array, protein arrays.

4. **Chromatin structure and functions:** The Nucleosome, euchromatin & heterochromatin, regulation and alteration of chromatin higher order structure.

5. **Chromatin Immunoprecipitation:** Chip on chip technology.

6. **Epigenomics, Histone modifications:** Acetylation, methylation, phosphorylation, Ubiquitination, ribosylation etc.

7. Role of histone modifications in diseases in diabetes.

8. Role of histone modifications in cancer.
