



SYLLABUS

Ph.D.

MEDICINAL CHEMISTRY

**NATIONAL INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH
GUWAHATI**

SilaKatamur (Halugurisuk), P.O.: Changsari
Dist: Kamrup, Assam, Pin: 781101, Assam, India
Website: www.niperguwahati.ac.in

Ph.D. Syllabus

MEDICINAL CHEMISTRY

Course No.	Course Name	Credits
Semester-I		
MC-710	Stereoselective and Stereospecific Synthesis	2
MC-730	Organometallic and Sustainable Chemistry in Synthesis of Pharmaceuticals	2
MC-810	Principles of Peptide Chemistry	2
*CS-701	Research Methodology (Compulsory)	2

Course No.	Course Name	Credits
Semester-II		
MC-720	Synthetic Strategies in the Total Synthesis of Complex	2
MC-820	Carbohydrates: Occurrence, Structure, Reactions, Syntheses, Functions and Applications in Present Day Drugs	2
MC-830	Advanced Topics in Drug Action and Drug Design	2
*CS- 801	Research and Publication Ethics (Compulsory)	2

***Detailed Syllabus is available at Page No. 39-40**

Ph.D. Syllabus 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 chirality constitutional 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 stereoselectivity, concept of enantio/diastereo-differentiation, methods of inducing stereoselectivity, 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, enantio/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, hydricylation, stereoselective oxidation enantio / diastereoselective 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. **Stereoselective 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.
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, Kumadacoupling reactions; Mechanistic aspects of these reactions, comparison in mechanism, relative reactivities of organometallic coupling partners; Palladium and other metalcatalysis, controlling parameters; Heck (α - and β -arylation) and Sonogashira coupling reactions; Palladium- and Coppercatalysis, mechanism; Synthesis of biaryls, multisubstituted 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.
- 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.
- 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, green 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 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, 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.

Ph.D. Syllabus 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, enediyne, 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 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, UDPG glucuronosyl transferase.
3. Resistance, Allergy, Tolerance: Immunologic basis of drug allergy, origin of drug resistance, resistance to the β -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 dependence.
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-entropy compensation.
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:** PfDHFR-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, epoxidereactivemetabolites, nitroso reactive metabolites, S-oxidation vs epoxidation inthiophene.
10. **Case study 3:** Drug action of agents acting at Glygogen Synthase Kinase (GSK), sevendifferent methods of lead action on GSK3, drug design strategies for anti-diabetic drugsacting at GSK3.

(Syllabus for Compulsory Courses)**Semester-I****CS- 701 :- Research Methodology****(2 Credits)**

Unit 1: **Objectives and types of research:** Motivation and objectives, research methods vs methodology. Types of research – descriptive vs analytical, applied vs fundamental, quantitative vs qualitative, conceptual vs empirical. Introduction to drug discovery & development research, objectives, flowchart from discovery to post-marketing research, overview of research methodology in various areas of drug discovery and development research.

Unit 2: **Research formulation and Literature review**– Defining and formulating the research problem, selecting the problem, the necessity of defining the problem, the importance of literature review in defining a problem, Literature review - primary and secondary sources, reviews, monographs, patents, research databases, web as a source, searching the web, critical appraisal of literature, identifying gap areas from literature review and research databases, and development of a working hypothesis.

Unit 3: **Research design and methods:** Research design – basic principles, need of research design, features of good design, important concepts relating to research design, observation and facts, laws and theories, prediction and explanation, research databases, development of models, developing a research plan – exploration, description, diagnosis, and experimentation.

Unit 4: **Execution of the research, data collection and analysis:** Aspects of method validation, observation and collection of data, methods of data collection, sampling methods, data processing and analysis strategies and tools, data analysis with statistical packages (GraphPad Prism, SPSS for Student t-test, ANOVA, etc), hypothesis testing, generalization, and interpretation.

Unit 5: **Safety measures in the laboratory: Handling of hazardous chemicals, incompatible chemicals, flammable solvents, toxic chemicals and forms of toxic materials.** Approaches for prevention and management of fire, electrical, chemical, biological, and gaseous hazards, good laboratory practices. General safety rules, waste minimization approaches and safety practices for disposal of chemical waste, biologicals and other laboratory waste.

(Syllabus for Compulsory Courses)**Semester-II****CS- 801 :- Research and Publication Ethics****(2 Credits)****Unit 1: Research Ethics:**

- a) Ethics – ethical issues, ethical committees (human & animal)
- b) Ethics with respect to science and research
- c) Intellectual honesty and research integrity
- d) Scientific misconducts: Falsification, Fabrication, and Plagiarism
- e) What is plagiarism? Similarity report software like iThenticate/ Turnitin/ Urkund.
- f) Redundant publications: duplicate and overlapping publications, salami-slicing
- g) Selective reporting, and misrepresentation of data

Unit 2: Publication Ethics:

- a) Publication ethics: definition, introduction, and importance.
- b) Best practices / standards-setting initiatives and guidelines: COPE, WAME, etc.
- c) Conflicts of interest
- d) Publication and Research misconduct: definition, concept, problems that lead to unethical behavior and vice versa, types
- e) Violation of publication ethics, authorship, and contributorship
- f) Identification of publication misconduct, complaints, and appeals
- g) Predatory publishers and journals.
- h) Journal finder/journal suggestion tools.

Unit 3: IPR and scholarly publishing:

Intellectual Property Rights (IPR) and patent law, commercialization, copyright, royalty, trade-related aspects of intellectual property rights (TRIPS)

Unit 4: Report and thesis writing:

- a) Structure and components of scientific reports, types of reports, technical reports, and thesis.
- b) Thesis writing – different steps and software tools (Word processing, etc) in the design and preparation of the thesis, layout, structure (chapter plan), and language of typical reports, Illustrations and tables, bibliography, referencing, and footnotes.
- c) Oral presentation – planning, software tools, creating and making an effective presentation, use of visual aids, the importance of effective communication
- d) Writing a research proposal and research grant
- e) Scholarly publishing – IMRaD concept and design of research paper, citation and acknowledgment, reproducibility, and accountability.
- f) Graphical Abstract and Artwork preparation

Unit 5: Databases and Research Metrics

- a) Indexing databases: PubMed, Embase, etc.
- b) Citation databases: Web of Science, Scopus, etc.
- c) Impact Factor of the journal as per Journal Citation Report, SNIP, SJR, IPP, Cite Score, etc.
- d) Metrics: h index, g index, i10 index, altmetrics