Modern Pharmaceutical Analysis (PCH 101)

1. UV- Ultraviolet/Visible Spectroscopy and Fluorimetry

Energy level and selection rules, effect of substituents, effect of conjugation, conformation and geometry, the Woodward-Fisher rules, the Fisher-Kuhn rules, applications of UV with reference to different electronic systems. Derivative spectroscopy and its applications. Fluorescence and chemical structure, fluorescence intensity, factors affecting fluorescence, instrumentation, comparison of fluorometry with spectrophotometry, applications of fluorimetry in pharmaceutical analysis.


3. Infra-Red spectroscopy:

The Hook’s law and calculation of stretching frequencies for different types of bonds and their bond strengths, coupled interactions, hydrogen bonding, examination of infrared spectrum, survey of important functional groups with examples, radiation source, detectors used, sample handling, quantitative applications, qualitative applications with special reference to stereochemical aspects and hydrogen bonding, Near-IR spectroscopy, absorption and reflectance spectrophotometry, instrumentation, applications, Far Infrared spectroscopy. Introduction to FTIR and its applications. Raman spectroscopy Introduction, theory and polarization measurement, rules of selection and polarization, instrumentation, applications in pharmaceutical sciences. Comparison of Infrared and Raman spectra.

4. Optical Rotatory Dispersion:


5. Nuclear Magnetic Resonance spectroscopy:

Nuclear Magnetic Resonance Spectroscopy 1H-NMR spectroscopy Magnetic equivalence, failure of the N+1 rule, chemical shifts, local diamagnetic shielding, hybridization effects, magnetic anisotropy, mechanism of spin-spin coupling, the origin of spin-spin splitting, Pascal’s triangle, the coupling constant, protons on oxygen, nitrogen and sulphur, diastereomeric protons, chemical shift reagents, long range coupling, spin decoupling methods, nuclear over Hauser effect. Correlation NMR spectrometry: introduction to 1H-1H cosy and 1H-13C cosy and its applications. Introduction and applications of 2D NMR; solid state NMR. 13 C-NMR spectroscopy.
Introduction, peak assignments, off resonance decoupling, selective proton decoupling; chemical shift equivalence; chemical shifts; spin coupling. Spectrometry of other important nuclei
Introduction to 15N, 19F, 31P, basic concepts.

Electron Spin Resonance Spectroscopy

Introduction, derivative curves, g values, hyperfine splitting, ESR instrumentation, ESR spectra of free radicals, applications.

6. Mass spectrometry:
Basic principle and theory involved; instrumentation, type of ions; various ion sources, electron impact source, chemical ionization sources, field ionization sources, desorption sources, mass analysers, double focusing, quadripole, time of flight, ion trap analyzer, ionization, fragmentation, rearrangements, mass spectra of representative compounds, recognition of molecular ion peak, metastable peak, isotopic peaks, applications.

7. X-ray Crystallography: Production of X rays, Different X ray methods, Braggs law, Rotating crystal technique, X ray powder technique, Types of crystals, Interpretation of diffraction patterns and applications of X-ray diffraction

8. Chromatographic methods, Introduction, classifications,

   a) Liquid chromatography, instrumentation, materials, column selection, resolution optimization and efficiency parameters. HPLC detectors, modes of HPLC, Ion–pair, Ion exchange, Size exclusion, Supercritical, gel-permeation, flash chromatography, applications.

   b) High Performance Liquid Chromatography: Partition, adsorption, ion exchange, size exclusion; pharmaceutical applications of HPLC and LC-MS. Super critical fluid chromatography; brief introduction to HPTLC.

   c) Gas Chromatography: Gas liquid chromatography, gas solid chromatography, instrumentation and applications (GC-MS and GC-FTIR). Column parameters, Resolution, Liquid Phases Derivatisation and detectors, Derivatization as a means of sampling of thermosensitive compounds.

   d) Capillary electrophoresis.: Introduction, methods and applications.

9. Radio Immuno Assay and ELISA for some drugs.

Practical

1. Practical based on instrumental methods of analysis. A sufficient training will be given through exercises using different kinds of spectral analysis.

2. Microbial analysis of Vitamins and Anti-biotics

3. Pharmacological Bioassay of some drugs.

Reading Material Recommended

10. Gordy, W., Theory & Applications of Electron Spin Resonance, Willy.
14. Beckett and Stenlake, Practical Pharmaceutical Chemistry, CBS.
16. Giddings, J.C., Principles and Theory- Dynamics of Chromatography, Marcel Dekker.
20. Gross - Mass Spectrometry
24. Haffmann, Chromatography.
25. Sethi and Charegankar, Identification of Drugs in Pharmaceutical Formulations by TLC.
29. George, S., Steroid Analysis in Pharmaceutical Industry.
30. Higuchi, Pharmaceutical Analysis.
31. Bidingmeyer, Practical HPLC Methodology and Applications.
33. Scott, Techniques and Practice of Chromatography.
34. Wilkins, Identification of Microorganism by Mass Spectrometry.
1. Acids and Bases

Bronsted and lewis concepts, acidic and basic catalysis, hard and soft acids and bases, effect of structure on the strength of acids and bases, effect of medium on the acidic and basic strength.

2. Mechanisms and Methods for Determination Thermodynamic requirements for reaction, kinetic requirements for reaction, basic mechanistic concepts, kinetics versus thermodynamic control. Methods for determining mechanisms:

(a) Non-kinetic: Identification of products, determination of the presence of intermediate, isolation of an intermediate, detection of an intermediate, trapping of an intermediate and addition of suspected intermediate, study of catalysis, isotopic labelling stereochemical evidences and crossover experiments.

(b) Kinetic studies: First order reactions, second order reactions, third order reactions, determination of the order of reaction and reversible reactions.

2. Stereochemistry

Elements of symmetry: Plane of symmetry and center of symmetry, alternating axis of symmetry, simple axis of symmetry. Kinds of molecules displaying optical activity: compounds with a chiral carbon atom, compounds with other quadrivalent chiral atoms, compounds with tervalent chiral atoms suitably substituted adamantanes. Optical isomerism in compounds containing no chiral atom: biphenyls, allenes, compounds with exocyclic double bonds, spiranes, chirality due to a helical shape, chirality caused by restricted rotation of other types. Cis-trans isomerism: resulting from double bonds, monocyclic compounds, fused ring systems, out-in isomerism. Enantiotopic and diastereotopic atoms, groups and faces. Chirality and importance of chiral drugs, techniques for preparing chiral drugs (chirality pool, enzymatic transformation and asymmetric synthesis).

3. Aromatic Substitution Reactions

Electrophilic aromatic substitution: Nitration, halogenation, Friedel-crafts alkylations and acylations. Nucleophilic aromatic substitution: aromatic diazonium ions as synthetic intermediates, substitution by the addition-elimination mechanism, substitution by the elimination-addition mechanism, substitution by the Sn1 mechanism.
4. Reactions of Carbon Nucleophiles with Carbonyl Groups

Aldol condensation: The general mechanism, mixed aldol condensation with aromatic aldehydes, control of regiochemistry and stereochemistry of mixed aldol condensation of aliphatic aldehydes and ketones, intramolecular aldol condensations and the robinsons annulation. The Mannich reaction, aminecatalyzed condensation reactions. Acylation of carbanions, the Wittig and related reactions, nucleophilic additioncyclization. Functional Group Interconversion by Nucleophilic Substitution


5. Alkylation of Nucleophilic Carbon, Enolates and Enamines

Generation of carbanions by deprotonation, regioselectivity and stereoselectivity in enolate formation, other means of generating enolates, alkylation of enolates, oxygen versus carbon as the site of alkylation, alkylation of aldehydes, esters, amides and nitriles. The nitrogen analogs of enols and enolates enamines and imine anions.

6. Electrophilic Additions to Carbon-Carbon Multiple Bonds

Addition of hydrogen halides, hydration and other acid-catalyzed additions, oxymercuration, addition of halogens to alkenes, electrophilic substitution alpha to carbonyl groups, addition of allenes and alkynes. Addition at double bonds via organoboranes: hydroboration, reactions of organoboranes, enantioselective hydroboration, hydroboration of alkynes.

7. Rearrangements Carbon to carbon migration:


Nitrogen to carbon, oxygen to carbon migrations: Steven’s rearrangement, Witting rearrangement.
8. Photochemistry and Pericyclic Reactions


9. Reactive Intermediates

Generation of carbocation, carbanions, carbenes, nitrenes/nitrenium ions and free radicals, stability, structure and reactivity of these intermediates.

Elimination Reactions

E2, E1 and E1cb mechanisms, orientation effects in elimination reactions, stereochemistry of E2 elimination reactions, elimination not involving C-H bonds. Reaction Mechanism and method of determining them, Aliphatic nucleophilic (SN1, SN2, SN’1, SN’2) and Aromatic nucleophilic substitution (SNAr and benzyne mechanism) reactions.

10. Rearrangement reactions:


10. Dakin reaction, Reformatskey, Chichibabin reaction, Birch reduction, Wittig reaction, Oppensuer oxidation, Ozonolysis and Jourdan Ullmann reaction, Stork enamine reaction, Ene reaction, Barton reaction, Shapiro reaction.
Practical

Preparation: (Minor experiments)

a) Study of experimental technique such as solvent purification, distillation (vacuum, fractional, steam and simple), preparative, column and TLC, Crystallization and filtration.

b) Carryout the preparations of organic compounds by conventional as well as microwave assisted methods along with their purity, percentage yield, physical and spectral data (UV/IR) for the following:

1) Preparation of benzanilide from benzophenone (Beckmann rearrangement)
   Benzophenone ——— Benzophenone oxime —— Benzanilide

2) Preparation of 2-Phenyl indole from acetophenone (Fischer indolisation)
   Actophenone ——— Acetophenone phenylhydrazine ——— 2-Phenylinodole

3) Preparation of 2,5-dihydroxy acetophenone from hydroquinone (Fries rearrangement)
   Hydroquinone——— Hydroquinone diacetate———2,5-Dihydroxy acetophenone

4) Preparation of Diethyl fumarate from maleic acid (conversion of cis isomer to trans isomer)
   Maleic acid ———— Fumaric acid ———— Diethyl fumarate

5) Preparation of 2, 2'-Dihydroxy –1, 1'-binapthyl from 2-naphthol (oxidation of 2-naphthol and free radical coupling)

6) Preparation of Benzilic acid from Benzoin (Benzilic acid rearrangement)

7) Preparation of 2-amino-3-cyano-4,5-tetrahydro(b)thiophene

8) Preparation of 2-amino-3-carbethoxy-4,5-diphenylfuran

9) Preparation of thiazolidine-2, 4-dione.

c) Carryout at least two experiments on protection and de-protection of functional groups like hydroxyl, amino etc using Fmoc/BOC
Part-II Qualitative Analysis (Major experiment)
A minimum of six organic binary mixtures and four ternary mixtures should be analyzed systematically by ether/aqueous separation technique with the preparation of at least one derivative in each compound.

Reading Material Recommended

MEDICINAL CHEMISTRY-I (DRUG DESIGN)-(PCH 103)

1. Theoretical aspects of Drug Design
Introduction to drug design and discovery. Conventional methods of drug design. Lead, discovery of lead, lead optimization, objectives of lead optimization, pharmacophore identification and analog approach of drug discovery

2. Targets in Drug Discovery and Development

3. History and development of QSAR.
Theoretical compartment model for relationship between physical properties and biological activity(Hammet, Taft)
Mathematical methods for the analysis of QSAR
   i) Diagnosis mechanism
   ii) Prediction of activity
   iii) Optimization
   iv) Refinement of synthetic Targets
Application of Hansh Analysis
Application of Free-Wilson Analysis

4. In-silico and Computer Aided Drug design
Molecular Mechanics, force fields (Potential energy function), Energy Minimization Methods, Conformational Analysis, Concepts of Virtual Screening, Drug likeness, Screening-Counting Schemes, Functional Group Filters, Topological Drug Classification-Pharmacophore Point Filter-Focused Screening Libraries for Lead Identification, Pharmacophore Screening, Structure-Based Virtual Screening, Protein Structures, Computational Protein-Ligand Docking Techniques, Rigid Docking, Flexible or induced fit Docking, in silico De Novo design.

5. Designing and applications of Prodrugs
Basic concept, Prodrugs of functional group, Prodrug design to improve Patient acceptability, Drug solubility, Drug absorption and distribution, site specific drug delivery, and sustained drug action. Rationale of prodrug design and practical consideration of prodrug design.

6. Rational design of enzyme inhibitors
Enzyme inhibitors- Reversible, irreversible, Kcat inhibitors, transition state analogs and their application with respect to drug design.
Enzyme inhibitors of ACE, leukotrienes, Lipoxygenase, Cyclooxygenase, Aromatase, Xanthine oxidase, Cytochrome P-450 Inhibitors, DHFR Inhibitors, and Gastric proton pump Inhibitors.
HIV-Protease / Reverse Transcriptase, Integrase and DNA polymerase Inhibitors.

7. Recent advances in the development of Immuno modulators

Recombinant DNA technology
Introduction; New drugs from Recombinant DNA technology
Protein engineering and site directed mutagenesis. Development of t-PA as a therapeutic agents
Epitope mapping and Human growth hormone.
Screening of recombinant DNA libraries and development of HIV-tat inhibitor.

Practical

Synthesis of the following important medicinal compounds involving more than one step and characterization using TLC. M.P. and IR spectroscopy.

1. INH
2. Methaqualone
3. Saccharin Sodium
4. Dapsone
5. Phenytoin from Benzoin
6. Sulfanilamide
7. 2-Methyl Benzimidazole from OPDA (Phillips synthesis)
8. 2-Mercapto Benzimidazole/Benzimidazolyl-2-thiol
9. Antipyrine

Part 2:
1. Determination of Partition coefficient by shake flask method (Diazepam,Phenytoin and Caffeine)
2. Determination of $pKa$ value by potentiometric method (Phenobarbitone, Ibuprofen)
3. In vitro screening of medicinally important compounds for Anti-inflammatory, Antimicrobial and Antioxidant study.
4. In Silico QSAR based experiments (Three experiments)

Reading Material Recommended

1. A Biochemical basis – Medicinal chemistry by Thomas Nogrady
2. Introduction to quantitative drug design by Y.C.Martin
3. Selective Toxicity by Drein Albert
4. Comprehensive Medicinal Chemistry by Corwin and Hansch.
7. Drug design volumes by Ariens
8. Principles of Drug design by Smith
9. Strategy of Drug design by Brucell
10. The Organic Chemistry of the Drug design and Drug action by Richard B.Silverman
MEDICINAL CHEMISTRY–II (NATURAL PRODUCTS) (PCH 104)

   B) Structure elucidation of the following compounds based on chemistry, chemical degradation and synthesis of the compounds;
   Morphine alkaloids: Morphine, Papavine
   a) Cardiac glycosides: Lanatoside C, Ouabain
   b) Rauwolfia alkaloid: Reserpine
   c) Vinca alkaloids: Vinblastine and vincristine
   d) Ipecacuanha alkaloid: Emetine
   e) Microbial conversions as tools in the preparation of drugs

2. a) Introduction
   b) Practical aspects of microbial transformation
   c) Some theoretical aspects of microbial transformation
   d) Conversion by microorganism

3. A) General introduction and classification of steroids
   B) Hormones:
   a) Female and male sex hormones –development of antifertility agents.
   b) Adrenal cortex hormones and their derivatives
   c) Carotenoids and their therapeutic importance.
   d) Development of anabolic steroids and antifertility agents

4. a) Antibiotics :
   Penicillins and Cephalosporins:
   i) Early Penicillins and cephalosporins
   ii) AmidoPenicillins
   iii) Beta lactamase stable cephalosporins
   iv) Antipsuedomonalpenicillins and cephalosporins
   b) v) New oral compounds and future prospects
   Other beta lactam agents
   i) Nocardins and monobactams
   ii) Clavulanic acid analogs
   iii) Carbapenams
   Other fused Betalactam systems

5. a) Purine, Pyrimidines and their applications
   b) The metabolism of purines and pyrimidines, allopurinol and xanthine oxidase
   c) Purine and pyrimidine antimetabolites as antineoplastic agents
d) Purine and pyrimidine related Antiparasitic agents
Purine and pyrimidine related Antifungal agents
6. a) 
b) **Chemistry of vitamins**
Water soluble vitamins: Vitamin B$_1$, B$_2$, B$_6$ and Vitamin C
Fat soluble vitamins: Vitamin A, D, E and K

**Practical**

**Isolation and Characterization of following active constituents**
1. Eugenol from Clove
2. Curcumin from Turmeric
3. Sennosides from senna
4. Hesperidin from Orange Peel
5. Embelin from Embelia Ribes
6. Glycyrrhizin from Glycyrrhiza Glabra
7. Plumbagin from Plumbago Rosea
8. Solanine from potatoes
9. Naringen from Grape Fruit Peel
10. Trimeystin and Myristin from Nutmeg
11. Azylc acid from Castor Oil
12. Pectin from Orange Peel
13. Lycopene from Tomato Peel
14. Epicatechin from Cashew Kernel outer covering
15. Piperine from Black pepper

**Degradation reaction of following natural products and the identification of the degraded intermediates by micro TLC and qualitative tests.**
1. Atropine,
2. Caffeine,
3. Ephedrine,
4. Saponification of Trimeystin

**Reading Material Recommended**
1. Modern Methods of Plant Analysis- Peech and M.V. Tracey
2. Phytochemistry Vol-I and II by Miller, Jan Nostrant Rein Hold.
3. Recent Advances in Phytochemistry-Vol-I-IV Scikel Runecles
4. Chemistry of Natural Products Vol-I onwards IWPAC
5. Natural Products Chemistry Nakanishi Golo
7. The Alkaloid Chemistry and Physiology- Volumes RHF Manske
8. Introduction to Molecular Phytochemistry-CHJ Wells, Chapmannstall.
9. Comparative Phytochemistry edited by T.Swain
12. Elements of biotechnology by P.K. Gupta
15. Phytochemistry method by Harborne