Medicinal Chemistry (MCH) 311 Outline

I. Historical Introduction to Drug Discovery/Development

A. Pharmacodynamic vs. Chemotherapeutic Drugs
B. Accomplishments/Challenges in Drug Development

II. Sources of Drugs

A. Drugs (Natural Products) from Natural Sources
  1. Plants
    a) Alkaloids
    b) Discovery
      i) Ethnopharmacognosy/Folklore
      ii) Toxicity Reports
      iii) Screening for Activity
    c) Role of Instrumentation in Drug Discovery & Development
  2. Animals
    a) Steroid, Peptide Hormones, Enzymes, Vitamins A/D, Prostaglandins
  3. Microorganisms (Fungi, Bacteria)
    a) Antibiotics
    b) Recombinant DNA Technology: Bacteria as Chemical Reactors
B. Drugs from Organic Synthesis
  1. Method
C. Drug Development
  1. Modification of a Lead Compound
  2. Rational Drug Design
  3. Structure-Activity Relationships
  4. Bioisosterism

III. The Chemistry of Drug Absorption, Distribution, and Receptors

A. Drug-Macrobiomolecule Complexes
B. Biomembranes and Drug Absorption
C. Receptors
  1. Historical Evidence for Receptors
  2. The Nature of Receptors
    a) Membrane-associated Receptors: Tyrosine Kinase, Ion Channels, G-Protein, c-AMP
    b) Enzymes
    c) Nucleic Acids
    d) Ribosomes
    e) Membranes
  3. Status of Receptor Knowledge
  4. Binding of Drugs to Receptors: Covalent, Hydrogen, Ionic, Hydrophobic Bonds; Fit of Drugs to Receptors
  5. Methods for Obtaining Knowledge About Structure
    a) Site-specific Labeling
    b) Mapping
    c) Isolation and Reconstitution, Composition Analysis

IV. The Chemistry of Drug Metabolism & Excretion

A. The Chemistry of Phase I Metabolism
B. The Chemistry of Phase II Metabolism
C. Consequences of Metabolism: Inactivation-Detoxication, Activation; New Drug Leads; Toxicity

V. The Relationship Between Molecular Structure & Biological Activity

A. Historical
B. Physicochemical Constants: Electronic & Lipophilicity Constants as Quantitative Measures of Drug Properties

VI. Drug Properties & Drug Action

A. Physicochemical Properties
1. Water Solubility
a) Generalizations
b) Water-soluble Prodrugs
c) Drug-Drug, Drug-Food Interactions: Chelation
d) Prescription Compounding Problems
e) Bioavailability
2. Partition Coefficients
a) QSAR's
b) Overton and Hansch Models
c) Data Evaluation
d) Interpretation and Uses of QSAR's
3. Ionization/Dissociation of Acidic Drugs
a) Carboxylic Acids
b) Amines/Ammonium Ions
c) Carbon Acids, Sulfonamido Acids & Imido Acids
d) Mole Fraction Calculations
e) Absorption & pH-pK Phenomena
f) Urinary Excretion & pH-pK Phenomena
i) The Nicotine Habit
ii) Mitigating Drug Toxicity via Control of Urinary pH
g) Ionization and Drug-Receptor Interactions
B. Chemical Structure & Electronic Effects
1) Inductive Effects
2) Resonance Effects
3) Electronic Effects & Anilino Mustard Reactivity,
4) From Functional Group Chemistry to Molecular Chemistry: Molecules Determine Pharmacology
i) Antibacterial, Hypoglycemic, & Diuretic Sulfonamides
ii) Phenyl Ethyl Amines
5) Fine Tuning with Halogens
C. Spatial Properties of Drugs
1. Drug-Receptor Complexes: Fit & Binding
2. Conformation of Drugs/Receptors
3. Configuration of Drugs

XI. Modification of Existing Drugs, Prodrugs.

A. Introduction/Rationale
B. Increased Chemical Stability: Epinephrinyl Borate
C. Altered Solubility: CAP Monosodium Succinate, Estradiol Valerate
D. Improved Taste & Compliance: EES, CAP Palmitate
E. Increased Absorption: Pivaloyl Epinephrine, Bacampicillin
F. Decreased Metabolism: Tolbutamide/Chlorpropamide, Prostaglandins and 15-methyl & 16-methyl Prostaglandins
G. Increased Selectivity: Sulfasalazine, Phenylalanine Mustard, Progabide, a GABA Prodrug

XII. Drug Incompatibility

A. Definition
B. Chemical Reactions
  1. Oxidation
  2. Nucleophilic Reactions: Aminolysis of β-lactams
  3. Hydrolysis
  4. Acid-base Chemistry and Solubility of Drug/Drug Salts

XIII. Drug Interactions

A. Definition, Polypharmacy, Patient Profiles, Pharmacokinetic vs. Pharmacodynamic Interactions
B. Drug Interactions at Absorption
  1. Anticholinergic Drugs & Decreased Peristalsis
  2. Metoclopramide & Increased Peristalsis
  3 Chelation: Tetracycline, Dicoumarol, Penicillamine
  4. pH Changes and Antacids, Weak Acids, Weak Bases
  5. Polymers and Drug Adsorption: Sucralfate & Quinolone Antibiotics (Ciprofloxacin, Norfloxacin)
C. Drug-Food Interactions
  1. Effect of Food on Peristalsis, Gastric Emptying
  2. Food, Gastric Secretion and Benzyl Penicillin Stability
  3. MAOIs and Contraindicated Foods: the Cheese Reaction
D. Drug Interactions at Excretion
  1. pH-Dependent Effects on Half-Life: Antacids, Foods, Weak Acids and Weak Bases
  2. Saluretics and Lithium Salts
  3. Probenecid and Drug Secretion
E. Drug Interactions in Blood
  1. Displacement of Potent, Highly Protein-Bound Drugs
F. Drug Interactions and Drug Metabolism
  1. Metabolic Enzyme Inducers (Barbiturates, Alcohol, Tolbutamide)
  2. Metabolic Enzyme Inhibitors (Cimetidine, Erythromycin, Verapamil)
G. Therapeutic (Pharmacodynamic) Drug Interactions
  1. MAOI's and OTC Phenyl Ethyl Amines
  2. 6-MP and Allopurinol: Desired vs. Undesired Drug Interaction

XIV. New Developments