

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-Macrobimolecule 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

- a) Optical Isomerism: Ephedrine & Pseudoephedrine
- b) Geometric Isomerism: DES; Use of Rigid Molecules to Decide Bioactive Conformations of Drugs
- 4. Summary Points

VII. Molecular Mechanisms of Drug Action

- A. Modification (Inhibition) of Enzyme Action
 - 1. Classical Reversible Enzyme Inhibition
 - a) Competitive
 - b) Non-competitive
 - 2. Mechanism-Based Reversible Enzyme Inhibition
 - a) Transition State Analogs: Pentostatin
 - b) Reaction Coordinate Analogs: Elastinal
 - 3. Irreversible Inhibition
 - a) Affinity Labels: Penicillin
 - b) Mechanism-based Irreversible Enzyme Inhibition
 - 1. Irreversible Reaction Coordinate Inhibitors: Penicillin, 5-Fluorouracil
 - 2. Suicide Substrate Inhibition: Clavulanic Acid, Tranylcypromine
- B. Alteration of Nucleic Acids
 - 1. Intercalation: Amino Acridines
 - 2. Alkylation: Mustards, Nitroso Ureas, Antibiotics
- C. Reaction with Ribosomes: Streptomycin
- D. Interaction with Cell Membrane Receptors
- E. Alteration of Cell Membranes
- F. Non-receptor Mechanisms

VIII. Occupancy Theory of Drug Action at Membrane Receptors

- A. Michaelis-Menten Model
- B. Intrinsic Activity and Conformation Changes
- C. Log Dose- Response Curves

IX. The Basis of Selective Drug Action

- A. Accumulation of Drugs in Target Tissue
- B. Differences in Biochemical Pathways; Isoenzymes
- C. Differences in Cell Structures: the Bacterial Cell Wall

X. The Chemistry of Selected Drug Classes

- A. Pharmacodynamic Drugs
 - 1. The Chemistry of Allopurinol
 - 2. The Chemistry of Captopril
- B. Antibiotics/Antibacterial Agents
 - 1. D-Cycloserine: Alanine Racemase Chemistry; Mechanism of Inhibition; Stereoselectivity; Bioisosterism; Inhibition of Consecutive Enzyme Reactions, Trimethoprim & Sulfamethoxazole.
 - 2. D-2-Deuterio-3-fluoroalanine, a Mechanism-based Inhibitor of Alanine Racemase
 - a) Rationale for Drug Development
 - b) The High-dose Paradox

- c) The Basis of Selectivity
 - d) D-Cycloserine & D-Fluoroalanine: the "Universal Antibiotic"
 - e) The Rationale for Deuterium: Amino Acid Oxidase
 - f) Accumulation of Fluorolactate as a Metabolite & Withdrawal of the Drug from the Clinic.
 - g) The Cost of Research includes the Cost of the Failures
3. Beta-Lactams
- a) The Importance of a Knowledge of Structure of Natural Products & Degradation of Penicillin as a Method of Structure Determination
 - b) Sources of Penicillins
 - i) Microbiological
 - ii) Modified Microbiological
 - iii) From 6-Aminopenicillanic Acid
 - iv) From Total Synthesis
 - c) Rationale for Synthesis of Newer Penicillins
 - i) Increase Stability
 - ii) Overcome Resistance of Penicillinase- producing Bacteria
 - iii) Broaden Spectrum of Antibacterial Activity
 - d) Chemical Stability of Penicillin
 - i) Importance of Drug Stability
 - ii) Reactions with Solvent Species
 - iii) pH-Rate Profiles
 - iv) Nucleophilic Reactions
 - v) Electrophilic Reactions
 - vi) Stability vs. Structure: QSAR
 - e) Stability Toward Penicillinase
 - i) The Reaction
 - ii) Tritel Penicillin: QSAR
 - iii) Penicillins with Bulky 6-Side Chains
 - iv) Effect of Structure on Sensitive vs. Resistant *S. aureus*
 - v) Productive vs. Non-productive Binding
 - vi) Clavulanic Acid, Sulbactam
 - f) Modifications that Result in Broader Spectrum
 - i) Structural Features
 - ii) Carbenicillin: Stability, Esters
 - g) Other Beta Lactams
 - i) Monobactams
 - ii) Cephalosporins
- C. Antiviral Drugs
1. Description of Viruses
 2. Iododexyuridine: Isosteres, Tautomerization, DNA Alteration
 3. Acycloguanosine: Selectivity, Mechanism
 4. Human Immunodeficiency Virus (HIV)
 - a) The Cellular Infection Process
 - b) Drug Targets: gp120, Envelope, Proviral DNA Synthesis, HIV Protease, Protein Glycosylation
 - c) Zidovudine, Didanosine: DNA Chain Termination
 - d) Vaccines & Drugs: Prognosis for Preventative, Cure
- D. Antineoplastic Drugs
1. The Diseases
 2. Representative Anticancer Drugs, Focus on Chemistry of Action
 3. The Role of Steroid Hormones: Suicide Substrates of Aromatase; Estrogen Receptor Blockers (Tamoxifen); Estrogen Synthesis Inhibitors

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. MAOIs and OTC Phenyl Ethyl Amines
 - 2. 6-MP and Allopurinol: Desired vs. Undesired Drug Interaction

XIV. New Developments