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### PHAR 421.01: Medicinal Chemistry I

David S. Freeman

*University of Montana - Missoula*

Charles M. Thompson

*University of Montana, Missoula*

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**INSTRUCTORS:**

David Freeman, Office: SB 308      Office Phone: 243-4772      Home Phone: 728-6551  
 E-mail: [dfreeman@selway.umn.edu](mailto:dfreeman@selway.umn.edu)  
 Internet Site: <http://skaggs-06.pharmacy.umn.edu/pharm-sci/Freeman/PHAR%20421/>  
 Chuck Thompson, Office: SB 383      Office Phone: 243-4643  
 E-mail: [cmthomp@selway.umn.edu](mailto:cmthomp@selway.umn.edu)  
 Internet Site: <http://www.umn.edu/medchem/teaching/part1syl.htm>

**EXAMS AND GRADING:**

First Exam:	Friday, Oct. 5 . . . . .	50 points
Second Exam:	Friday, Nov. 2 . . . . .	70 points
Third Exam:	Friday, Dec. 7 . . . . .	80 points
Final Exam:	Wednesday, Dec. 19 . . . . .	100 points
10 Point Quizzes:	Best 5 out of 6 scores . . . . .	50 points
Total Points: 350	90-100% = A      80-89 % = B      70-79 % = C      65-69 % = D	

- \* All EXAMS are comprehensive
- \* All exams and quizzes must be taken at scheduled times
- \* Instructor must be informed BEFORE missing a scheduled exam period and must be based on GOOD REASONS
- \* Missed exam periods must be made up within 2 days
- \* No make up quizzes

**STUDENT PERFORMANCE OBJECTIVES:**

- 1) Identify organic functional groups and know their polar/lipophilic and acid/base properties
- 2) Know the relationships between organic functional groups and biological activity
- 3) Know the possible modes of metabolism in the body for organic functional groups
- 4) Know the chemical structures of important neurotransmitters or hormones and the biochemical pathways for their syntheses and metabolism
- 5) Know the major biochemical events triggered by the activation of receptors important for drug action
- 6) Given the chemical structure of a drug, know its pharmacologic or therapeutic class
- 7) Given the chemical structure of a drug, know important chemical features (acid/base or lipophilic properties, chemical groups affecting absorption, distribution, or metabolism, chemical groups affecting potency or receptor interaction, chemical groups affecting storage or formulation) that contribute to the drug's pharmacological activity
- 8) Given the chemical structure of a drug, know important chemical changes that will predictably alter the pharmacological properties (potency, duration of action, etc.) of the drug
- 9) Given the chemical structure of a drug, know the important biological receptors it interacts with and the biochemical events produced by these interactions
- 10) Given the common or generic name of a drug, know its pharmacologic or therapeutic class, some of its important chemical properties (structural skeleton or chemical class, acid/base, etc.), the receptors it interacts with and the biochemical events produced by these interactions

**TEXTBOOK:** Goodman & Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition

**I. Physicochemical Properties of Drugs Related to Pharmacological Activity and Metabolism**

- A. Organic Functional Groups in Medicinal Chemistry
  1. Physicochemical Properties
  2. Metabolic Fate
- B. Acid/Base Review
  1. Equilibrium
  2. pKa values
- C. Quantitative Structure-Activity Relationships
  1. Concept of Linear Free Energy Relationships
  2. Hydrophobicity and Log P values
  3. Electronic Effects and Sigma values
- D. Problem Solving in Medicinal Chemistry

**II. Biochemical Processes Affecting Drugs and Pharmacological Activity**

- A. Processes Affecting Drug Distribution
  1. Non-specific binding sites and plasma protein binding
  2. Biotransformation reactions (metabolism)

- B. Processes Affecting Drug Action at the Active Site
  - 1. Structural families of receptors
  - 2. Binding events initiating the pharmacological response
    - a. Occupancy and conformational changes of receptor
    - b. Agonist vs. antagonist events
  - 3. Events propagating and amplifying pharmacological response
  - 4. Events terminating the pharmacological response

### III. Processes and Overview of Drugs Affecting Cholinergic Receptors

- A. Biochemical Events at the Cholinergic Synapse
  - 1. Synthesis and metabolism of acetylcholine
  - 2. Muscarinic and nicotinic receptors
  - 3. Processes following receptor activation
- B. Overview on Cholinergic Drugs

### IV. Muscarinic Receptor Agonists

- A. Chemistry of Acetylcholine
  - 1. Important functional groups
  - 2. Conformations of acetylcholine
- B. SAR and Chemistry of Selected Agonists
  - \* **METHACHOLINE CARBACHOL BETHANECHOL PILOCARPINE CEVIMELINE** \*

### V. Anticholinesterase Agents

- A. Mechanism of Acetylcholine Hydrolysis
  - 1. Individual steps involved in hydrolysis
  - 2. Rates of reaction steps
- B. Mechanisms of Cholinesterase Inhibition
  - 1. Competitive binding at active site
  - 2. Covalent binding at active site
- C. SAR and Chemistry of Cholinesterase Inhibitors
  - 1. Natural product and model agent \* **PHYSOSTIGMINE** \*
  - 2. Competitive inhibitors \* **EDROPHONIUM** \*
  - 3. Carbamates - "reversible" inhibitors
    - \* **NEOSTIGMINE PYRIDOSTIGMINE** \*
  - 4. Organophosphates - "irreversible" inhibitors
    - \* **ECHOTHIOPHATE ISOFLUROPHATE PARATHION MALATHION** \*
- D. Reactivation of Inhibited Cholinesterase \* **PRALIDOXIME** \*

### VI. Cholinergic Antagonists

- A. Muscarinic Blocking Agents
  - 1. Natural product and model agent - atropine
  - 2. SAR and chemistry of selected antimuscarinic agents
    - a. Tertiary amines
      - \* **ATROPINE SCOPOLAMINE HOMATROPINE**
      - \* **DICYCLOMINE CYCLOPENTOLATE** \*
    - b. Quaternary amines
      - \* **GLYCOPYRROLATE METHANTHELINE** \*
      - \* **PROPANTHELINE IPRATROPIUM** \*

### VII. Agents Acting At Nicotinic Receptors

- A. Properties of the Nicotinic Cholinergic Receptor
- B. Neuromuscular blocking agents
  - 1. Natural product and model agent \* **TUBOCURARINE** \*
  - 2. Competitive agents \* **MIVACURIUM ATRACURIUM PANCURONIUM** \*
  - 3. Depolarizing agents \* **DECAMETHONIUM SUCCINYLCHOLINE** \*
- C. Ganglionic blocking agents
  - \* **HEXAMETHONIUM TRIMETHAPHAN MECAMYLAMINE** \*

## **VIII. Processes and Overview of Drugs Affecting Adrenergic Receptors**

- A. Biochemical Events at the Adrenergic Synapse
  - 1. Synthesis and storage of norepinephrine
  - 2. Termination and metabolism of catecholamines
  - 3. Alpha and beta receptors and subtypes
  - 4. Processes following receptor activation
- B. Overview on Adrenergic Drugs

## **IX. Adrenergic Receptor Agonists**

- A. Chemistry of Norepinephrine and Epinephrine
  - 1. Oxidative and acid/base properties
  - 2. Stereochemistry
- B. SAR and Chemistry of Selected Agonists
  - 1. Differentiating alpha and beta activity
  - 2. Decreasing metabolism
  - 3. Peripheral vs. CNS effects
  - 4. Direct and indirect effects
    - \* **DOPAMINE ISOPROTERENOL TERBUTALINE METAPROTERENOL \***
    - \* **ALBUTEROL SALMETEROL EPHEDRINE PHENYLPROPANOLAMINE \***
    - \* **RITODRINE CLONIDINE AMPHETAMINE TETRAHYDROZOLINE \***
    - \* **METHYLPHENIDATE DOBUTAMINE METHOXAMINE PHENYLEPHRINE**
    - \* **PHENTERMINE FENFLURAMINE METHYLPHENIDATE PEMOLINE COCAINE \***
  - 5. Physiological and biochemical mechanisms

## **X. Adrenergic Receptor Antagonists**

- A. Alpha Blocking Agents
  - 1. Chemistry of haloalkylamines \* **PHENOXYBENZAMINE \***
  - 2. Chemistry of imidazolines \* **PENTOLAMINE TOLAZOLINE \***
  - 3. Selective blockers \* **PRAZOSIN TERAZOSIN DOXAZOSIN \***
- B. Beta Blocking Agents
  - 1. Nonselective blockers
    - \* **PROPRANOLOL NADOLOL TIMOLOL PINDOLOL CARTEOLOL \***
  - 2. Selective blockers \* **METOPROLOL ATENOLOL ACEBUTOLOL ESMOLOL \***
  - 3. Blockers with intrinsic sympathomimetic activity (ISA blockers)
  - 4. Combined alpha and beta blocker \* **LABETALOL \***

## **XI. Antihistamines and Other Agents**

- A. Biochemistry of Histamine Synthesis, Metabolism, and Receptors
- B. H<sub>1</sub> receptor antagonists
  - \* **DIPHENHYDRAMINE CHLORPHENIRAMINE CYCLIZINE PYRILAMINE \***
  - \* **PROMETHAZINE TERFENADINE LORATADINE ASTEMIZOLE FEXOFENADINE \***
- C. H<sub>2</sub> receptor blocking agents
  - \* **CIMETIDINE RANITIDINE FAMOTIDINE NIZATIDINE \***
- D. Inhibitors of H<sup>+</sup>/K<sup>+</sup> ATPase
  - \* **OMEPRazole LANSOPRAZOLE RABEPRazole PANTOPRAZOLE \***
- E. Inhibitors of histamine release
  - \* **CROMOLYN SODIUM NEDOCROMIL SODIUM \***

## **XII. Local and General Anesthetics**

- A. SAR and Chemistry of Local Anesthetic Agents
  - 1. Natural product and model compound \* **COCAINE \***
  - 2. Synthetic esters and amides
    - \* **PROCAINE LIDOCAINE TETRACAINE ETIDOCAINE \***
    - \* **BENZOCAINE PRAMOXINE \***
- B. Nonspecific and Specific Effects on Neural Membranes
- C. Factors Affecting Activity of Agents
- D. Adverse effects and metabolism
- E. Structure and Chemical Properties of General Anesthetic Agents
  - \* **DIETHYL ETHER NITROUS OXIDE HALOTHANE ISOFLURANE \***

### **XIII. Sedative/Hypnotic Agents**

#### **A. Benzodiazepines**

1. Structure, Chemical Properties, and SAR
2. Biochemical effects

**\* DIAZEPAM CHLORDIAZEPOXIDE FLURAZEPAM OXAZEPAM \***

**\* TRIAZOLAM MIDAZOLAM LORAZEPAM ZOLPIDEM \***

#### **B. Barbiturates**

1. Chemical properties and SAR of agents
2. Biochemical effects

**\* PHENOBARBITAL PENTOBARBITAL SECOBARBITAL \***

**\* BUTABARBITAL THIOPENTAL \***

#### **C. Non-barbiturates      \* CHLORAL HYDRATE \***

### **XIV. Opioid Analgesic Agents**

#### **A. Biochemistry of Endorphins, Enkephalins, and Their Receptors**

#### **B. Natural Product and Model Agent      \* MORPHINE \***

#### **C. SAR, Stereochemistry, and Chemical Properties**

1. Chemical features of morphine
2. N-Substituents producing agonist, partial agonist, or antagonist effects
3. Synthetic agents

**\* HEROIN HYDROMORPHONE CODEINE MEPERIDINE LEVORPHANOL \***

**\* BUTORPHANOL METHADONE FENTANYL PENTAZOCINE ETORPHINE \***

**\* NALOXONE NALTREXONE DEXTROMETHORPHAN \***

### **XV. Antineoplastic Agents**

#### **A. Chemistry and Mechanisms of Action for Alkylating and Cross-linking Agents**

**\* MECHLORETHAMINE CHLORAMBUCIL CYCLOPHOSPHAMIDE IFOSFAMIDE \***

**\* BUSULFAN CARMUSTINE LOMUSTINE DACARBAZINE PROCARBAZINE \***

**\* CISPLATIN CARBOPLATIN \***

#### **B. Mechanisms of Action for Antimetabolite Agents**

**\* METHOTREXATE LEUCOVORIN FLUOROURACIL FLOXURIDINE \***

**\* CYTARABINE GEMCITABINE CLADRIBINE PENTOSTATIN MERCAPTOPURINE \***

#### **C. Mechanisms of Action for Natural Products and Miscellaneous Agents**

**\* VINCRISTINE VINBLASTINE PACLITAXEL ETOPOSIDE \***

**\* ASPARAGINASE HYDROXYUREA \***

#### **D. Mechanisms of Action for Antibiotic Type Agents**

**\* DAUNORUBICIN DOXORUBICIN IDARUBICIN BLEOMYCIN \***

**\* MITOXANTRONE MITOMYCIN DACTINOMYCIN \***