Fall 9-1-2005

BMED 421.01: Medicinal Chemistry I

David S. Freeman
University of Montana - Missoula

Todd G. Cochran
University of Montana - Missoula

BIOMEDICAL & PHARMACEUTICAL SCIENCES 421 (MEDICINAL CHEMISTRY I) AUTUMN, 2005

INSTRUCTORS:
David Freeman, Office: SB 308 Office Phone: 243-4772 Home Phone: 728-6551
E-mail: david.freeman@umontana.edu
Todd Cochran, Office: SB 353 Office Phone: 243-4941
E-mail: todd.cochran@umontana.edu

EXAMS AND GRADING:

First Exam:	Friday, Sept. 30	. . . . . 60 points
Second Exam:	Friday, Nov. 4	. . . . . 80 points
Third Exam:	Friday, Dec. 2	. . . . . 80 points
Final Exam:	Wednesday, Dec. 14, 10 a.m.	. . . . . 100 points
10 Point Quizzes:	Best 5 out of 6 scores	. . . . . 50 points

Total Points: 370 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
* Corrections to exams or quizzes must be requested within 7 days after returning

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

Reading in TEXT	
	I. Acid-Base Partitioning and Solubility of Drugs
3-4	A. Distribution ratio for acid/base drugs between two membrane bound compartments
	B. Altering urinary pH to avoid crystalluria, uric acid kidney stones, or drug toxicity
	C. Producing inorganic and organic salts of drugs for parenteral administration

Reading in TEXT	

II. Protein Structure and Function

A. Polar/lipophilic properties of amino acids
B. Types of intramolecular interactions determining the tertiary structure of proteins
C. General types of topography for proteins (e.g. transmembrane helices, beta-sheets, etc.)
D. General types of biochemical alteration of proteins (e.g. phosphorylation) that alter tertiary structure and control protein function

12-18 **III. Drug Metabolism**

A. Phase I biotransformations – Cytochrome P450
B. Phase II biotransformations
C. Pro-drugs
D. Variation in drug metabolism – pharmacogenetics

IV. Biochemical Processes Affecting Drugs and Pharmacological Activity

A. Processes Affecting Drug Distribution
3-4, 8-10 1. Non-specific binding sites and plasma protein binding
B. Processes Affecting Drug Action at the Active Site
31-36 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

V. Processes and Overview of Drugs Affecting Cholinergic Receptors

121-129 A. Biochemical Events at the Cholinergic Synapse
Table 6-2 1. Synthesis and metabolism of acetylcholine
2. Muscarinic and nicotinic receptors
3. Processes following receptor activation
B. Overview on Cholinergic Drugs

VI. Muscarinic Receptor Agonists

155-160 A. Chemistry of Acetylcholine
1. Important functional groups
2. Conformations of acetylcholine
B. SAR and Chemistry of Selected Agonists
*** METHACHOLINE CARBACHOL BETHANECHOL PILOCARPINE CEVIMELINE ***

VII. Anticholinesterase Agents

175-181 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 ***
185 D. Reactivation of Inhibited Cholinesterase *** PRALIDOXIME ***

Reading in TEXT

VIII. Cholinergic Antagonists

162-164 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 ***

IX. Agents Acting At Nicotinic Receptors

193-194 A. Properties of the Nicotinic Cholinergic Receptor

194-199 B. Neuromuscular blocking agents

1. Natural product and model agent *** TUBOCURARINE ***
2. Competitive agents *** MIVACURIUM ATRACURIUM PANCURONIUM ***
3. Depolarizing agents *** DECAMETHONIUM SUCCINYLCHOLINE ***

208-211 C. Ganglionic blocking agents *** HEXAMETHONIUM TRIMETHAPHAN MECAMYLAMINE ***

X. Processes and Overview of Drugs Affecting Adrenergic Receptors

129-142 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

XI. Adrenergic Receptor Agonists

216-220 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 METHYLPHENIDATE PEMOLINE COCAINE ***

5. Physiological and biochemical mechanisms

XII. Adrenergic Receptor Antagonists

242-246 A. Alpha Blocking Agents

1. Chemistry of haloalkylamines *** PHENOXYBENZAMINE ***
2. Chemistry of imidazolines *** PHENTOLAMINE TOLAZOLINE ***
3. Selective blockers *** PRAZOSIN TERAZOSIN DOXAZOSIN ***
   *** TAMSULOSIN ALFUZOSIN ***

249-253 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 CARVEDILOL ***

<u>Reading in TEXT</u>

XIII. Local and General Anesthetics

367-374 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

337-341 E. Structure and Chemical Properties of General Anesthetic Agents

*** DIETHYL ETHER NITROUS OXIDE HALOTHANE ISOFLURANE ***

XIV. Sedative/Hypnotic Agents

400-405 A. Benzodiazepines

Table 17-2 1. Structure, Chemical Properties, and SAR

409-412 2. Biochemical effects

*** DIAZEPAM CHLORDIAZEPOXIDE FLURAZEPAM OXAZEPAM ***

*** TRIAZOLAM MIDAZOLAM LORAZEPAM ZOLPIDEM ZALEPLON ***

412-416 B. Barbiturates

Table 17-4 1. Chemical properties and SAR of agents

2. Biochemical effects

*** PHENOBARBITAL PENTOBARBITAL SECOBARBITAL ***

*** BUTABARBITAL THIOPENTAL ***

420 C. Non-barbiturates *** CHLORAL HYDRATE ***

XV. Antineoplastic Agents

1389-1392 A. Chemistry and Mechanisms of Action for Alkylating and Cross-linking Agents

*** MECHLORETHAMINE CHLORAMBUCIL CYCLOPHOSPHAMIDE IFOSFAMIDE ***

*** BUSULFAN CARMUSTINE LOMUSTINE ***

1432-1434 *** CISPLATIN CARBOPLATIN OXALIPLATIN ***

B. Mechanisms of Action for Antimetabolite Agents

1399-1407 *** METHOTREXATE LEUCOVORIN FLUOROURACIL PEMETREXED ***

1408-1414 *** CYTARABINE GEMCITABINE CAPECITABINE MERCAPTOPURINE ***

C. Mechanisms of Action for Natural Products and Miscellaneous Agents

1417-1420 *** VINCRISTINE VINBLASTINE PACLITAXEL DOCETAXEL ***

1421, 1431 *** ETOPOSIDE ASPARAGINASE ***

D. Mechanisms of Action for Agents Inhibiting Enzymes

1422-1425 * **IRINOTECAN TOPOTECAN IMATINIB GEFTINIB ***

1435, 1439 *** HYDROXYUREA ANASTROZOLE LETROZOLE ***

E. Mechanisms of Action for Antibiotic Type Agents

1426-1430 *** DOXORUBICIN DAUNORUBICIN IDARUBICIN BLEOMYCIN ***