Spring 2-1-2008

BMED 422.01: Medicinal Chemistry II

David S. Freeman
University of Montana, Missoula, david.freeman@umontana.edu

BMED 422 (MEDICINAL CHEMISTRY II) 2008 SPRING SEMESTER

INSTRUCTOR: David Freeman, Office – SB 308, Phone: 243-4772, E-mail: david.freeman@umontana.edu
Office Hours: Weekdays, NOON - 1:00 p.m. and Friday, 1:10 - 4:00 p.m.

EXAMS AND GRADING:

First Exam:	Friday, February 22	- 60 points
Second Exam:	Friday, March 21	- 80 points
Third Exam:	Friday, April 18	- 80 points
Final Exam:	Monday, May 5	- 100 points
10 Point Quizzes:	Best 5 or 6 out of 6 scores	- 50 or 60 points

Total Points: 370 or 380 A>92% A->90% B+>88% B>82% B->80% C+>78% C>72% C->70% D>65%

1. All EXAMS are comprehensive
2. All exams and quizzes must be taken at scheduled times
3. Instructor must be informed BEFORE missing a scheduled exam period for GOOD REASONS
4. Missed exams must be made up within 2 days
5. Corrections to exams or quizzes must be requested within 7 days after returning
6. Mistakes in marking scantrons will NOT be corrected

STUDENT PERFORMANCE OBJECTIVES:

1. Know the chemical structures of important neurotransmitters or hormones and the biochemical pathways for their syntheses and metabolism
2. Know the major biochemical events triggered by the activation of receptors important for drug action
3. Given the chemical structure of a drug, know its pharmacologic or therapeutic class
4. 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
5. 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
6. Given the chemical structure of a drug, know the important biological receptors it interacts with and the biochemical events produced by these interactions
7. 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", 11th Edition

Reading
In Text

I. Antihyperlipidemic Agents

933-940 A. Review of the Biochemical Processing of Lipids
1. Storage of cholesterol and triglycerides
2. Lipid transport and blood lipoproteins
3. Abnormal Lipid Metabolism and pathophysiology

B. Chemistry and Biochemical Mechanisms of Agents

948-952 1. Statins - Agents inhibiting cholesterol synthesis (HMG CoA Reductase Inhibitors)
LOVASTATIN PRAVASTATIN SIMVASTATIN FLUVASTATIN ATORVASTATIN ROSUVASTATIN

953-955 2. Bile acid binding resins
CHOLESTYRAMINE COLESTIPOL COLESEVELAM

955-958 3. Agents altering blood lipoprotein patterns
NICOTINIC ACID CLOFIBRATE GEMFIBROZIL FENOFIBRATE

959 4. Cholesterol absorption inhibition
EZETIMIBE

960 5. New agents in development

Reading
In Text

II. Antihypertensive Drugs

A. Overview of the Biochemical and Physiological Factors Responsible for Hypertension

B. Chemistry and Biochemical Mechanisms of Agents

850-852, 276 — 1. Alpha and Beta adrenergic blockers

855-856 — 2. Altering function of adrenergic neurons **GUANADREL**

852-855, 168 — 3. Altering sympathetic output from the central nervous system
METHYLDOPA CLONIDINE GUANABENZ GUANFACINE

858-860 — 4. Altering function of renin-angiotensin system

790-792 — a. Angiotensin converting enzyme inhibitors (ACE inhibitors)

800-804 — **CAPTOPRIL ENALAPRIL LISINOPRIL FOSINOPRIL BENAZEPRIL MOEXIPRIL PERINDOPRIL QUINAPRIL RAMIPRIL TRANDOLAPRIL**

796-798 — b. Angiotensin receptor antagonists

810-814 — **LOSARTAN CANDESARTAN IRBESARTAN VALSARTAN TELMISARTAN EPROSARTAN OLMESARTAN**

c. Renin inhibitor **ALISKIREN**

860-864 — 5. Vasodilators **HYDRALAZINE MINOXIDIL NITROPRUSSIDE**

III. Anticoagulant, Thrombolytic, and Antiplatelet Agents

1467-1470 — A. Biochemical Processes of the Blood Clotting Systems

1470, 1479 — B. Prothrombin time and clotting tests

C. Chemistry and Biochemical Effects of Agents

1. Calcium chelators **EDTA CITRATE**

1470-1474 — 2. Heparin and its derivatives
HEPARIN DALTEPARIN ENOXAPARIN TINZAPARIN FONDAPARINUX

a. Antagonist **PROTAMINE SULFATE**

1475 — 3. Direct Thrombin Inhibitors and other parenteral anticoagulants
LEPIRUDIN BIVALIRUDIN ARGATROBAN DANAPAROID DROTRECOGIN ALPHA

1475-1479 — 4. Oral Anticoagulants

a. Natural product and model agent
BISHYDROXYCOUMARIN

b. Synthetic agents
WARFARIN

1480-1481 — 5. Fibrinolytic agents
STREPTOKINASE t-PA UROKINASE

1481-1484 — 6. Antiplatelet/Antithrombotic agents
ASPIRIN TICLOPIDINE CLOPIDOGREL EPTIFIBATIDE DIPYRIDAMOLE TIROFIBAN ABCIXIMAB

7. Inhibitors of fibrinolysis
AMINOCAPROIC ACID APROTININ TRANEXAMIC ACID

IV. Agents Useful for Treating Heart Failure

886-887 — A. Cardiac Glycosides

1. Chemistry of cardiac glycosides

2. Cardiac ion channels and mechanism of action of Glycosides **DIGOXIN**

890 — B. Phosphodiesterase Inhibitors **INAMRINONE MILRINONE**

885-886 — C. New vasodilators **NESIRITIDE**

Reading
In Text

V. Antianginal Agents

824-829 A. Organic Nitrates - Chemistry and Mechanisms
NITROGLYCERIN ISOSORBIDE DINITRATE ISOSORBIDE MONONITRATE

832-836 B. Calcium Channel Blockers - Mechanisms
1. **VERAPAMIL DILTIAZEM BEPRIDIL**
2. Dihydropyridines
NIFEDIPINE NIMODIPINE NISOLDIPINE
AMLODIPINE NICARDIPINE FELODIPINE ISRADIPINE

VI. Diuretic Agents

740-742 A. Overview of the Biochemical Mechanisms of Transmembrane Transport in the Nephron

743-746 B. Chemistry and Mechanisms of Carbonic Anhydrase Inhibitors
ACETAZOLAMIDE DICHLORPHENAMIDE METHAZOLAMIDE

747-748 C. Chemistry and Mechanisms of Osmotic Diuretics **MANNITOL**

749-753 D. Chemistry and Mechanisms of "Loop" or High-Ceiling Diuretics
FUROSEMIDE BUMETANIDE TORSEMIDE ETHACRYNIC ACID

753-756 E. SAR and Chemistry of Thiazides
HYDROCHLOROTHIAZIDE CHLOROTHIAZIDE METHYCLOTHIAZIDE
QUINETHAZONE METOLAZONE CHLORTHALIDONE INDAPAMIDE

757-762 F. Potassium-sparing diuretics
TRIAMTERENE AMILORIDE SPIRONOLACTONE EPLERENONE

VII. Antihistamines and Other Agents

629-636 A. Biochemistry of Histamine Synthesis, Metabolism, and Receptors

636-640 B. H_1 Receptor Antagonists
DIPHENHYDRAMINE CHLORPHENIRAMINE CYCLIZINE
TRIPELENNAMINE PYRILAMINE PROMETHAZINE DOXEPIN
LORATADINE FEXOFENADINE CETIRIZINE

725-727 C. Inhibitors of histamine release
OMALIZUMAB CROMOLYN SODIUM NEDOCROMIL SODIUM

VIII. Agents Affecting Gastric Secretion

967-969 A. Biochemical Overview of Gastric Secretion

969-970 B. Proton Pump Inhibitors - Inhibitors of H+/K+ ATPase
OMEPRAZOLE ESOMEPRAZOLE
LANSOPRAZOLE RABEPRAZOLE PANTOPRAZOLE

971-972 C. H_2-Receptor Antagonists
CIMETIDINE RANITIDINE FAMOTIDINE NIZATIDINE

Reading
In Text

IX. Analgesic-Antipyretic-Antiinflammatory Agents

653-665 A. Chemistry, Biochemistry, and Overview of Eicosanoids

B. Nonsteroidal Antiinflammatory Drugs (NSAIDs)

671-681 1. Mechanisms of action

683-686 2. Adverse effects

687-690 3. Salicylates **ACETYLSALICYLIC ACID DIFLUNISAL OLSALAZINE SULFASALAZINE**

693-694 4. Para-aminophenols **ACETAMINOPHEN**

695-698 5. Acetic acid derivatives **INDOMETHACIN SULINDAC TOLMETIN KETOROLAC DICLOFENAC ETODOLAC**

699-700 6. Propionic acid derivatives **IBUPROFEN NAPROXEN FENOPROFEN KETOPROFEN OXAPROZIN FLURBIPROFEN**

700-701 7. Enolic Acids (Oxicams) and Other Agents **MECLOFENAMATE PIROXICAM MELOXICAM NABUMETONE**

702-705 8. Selective COX-2 Inhibitors **CELECOXIB ROFECOXIB VALDECOXIB**

973 9. Prostaglandin Agonist **MISOPROSTOL**

722-724 C. Inhibitors of Leukotriene Biosynthesis and Receptor Antagonists **ZILEUTON ZAFIRLUKAST MONTELUKAST**

X. Disease Modifying Antirheumatoid Drugs (DMARDs)

706 A. Gold compounds **AUROTHIOGLUCOSE AURANOFIN GOLD SODIUM THIOMALATE**

706 B. Other DMARDs **METHOTREXATE LEFLUNOMIDE ETANERCEPT INFLIXIMAB ADALIMUMAB SULFASALAZINE HYDROXYCHLORAQUINE PENICILLAMINE AZATHIOPRINE**

XI. Antigout agents

706-708 A. Agents that decrease granulocyte activity **COLCHICINE**

708-709 B. Agents that inhibit uric acid synthesis **ALLOPURINOL**

710-711 C. Uricosuric Agents **PROBENECID PHENYLBUTAZONE SULFINPYRAZONE**

710 D. Agents oxidizing uric acid **RASBURICASE**

XII. Opioid Analgesic Agents

547-552 A. Biochemistry of Endorphins, Enkephalins, and Their Receptors

555-556

563-565 B. Natural Product and Model Agent **MORPHINE**

565-567 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 CODEINE HYDROMORPHONE OXYMORPHONE OXYCODONE LEVORPHANOL TRAMADOL PENTAZOCINE NALBUPHINE

568-573 **MEPERIDINE FENTANYL SUFENTANIL REMIFENTANIL METHADONE**

574-578 **NALOXONE NALTREXONE BUPRENORPHINE BUTORPHANOL DEXTROMETHORPHAN**

XIII. Methylxanthines

727-729 A. Chemistry and Biochemical Mechanisms

B. Pharmacology of Methylxanthines **THEOPHYLLINE CAFFEINE THEOBROMINE**