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BMED 421.01: Medicinal Chemistry I

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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  PANCRURONIUM *
   3. Depolarizing agents * DECAMETHONIUM  SUCCINYLCHOLINE *

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

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 *

Reading in TEXT

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
   * VINCRI STINE  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 *