MCH 501 – Drug Discovery Principles

University at Buffalo Fall Semester 2017

Lecturer	*Location*	*Time*	*Days*
Michael Detty	Talbert 115	8:00 – 9:20 AM	Tu, Th

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Office Hours: 11:00 AM – noon, Tuesday; 1:00 – 2:00 PM, Thursday

Text

Erland Stevens, *Medicinal Chemistry: The Modern Drug Discovery Process*, Pearson, 2014. Hardcover available at UB Bookstore (approx.. $140 new, $100 used); e-book available from CourseSmart (as of Aug. 10, 2016, $53.99 for 180 days): http://www.coursesmart.com/medicinal-chemistry-the-modern-drug discovery/erland-stevens/dp/9780321768230

Academic Integrity

Individuals are expected to follow the principles of academic integrity set forth by the Graduate School. Graduate School policies for Academic Integrity can be found at:

http://grad.buffalo.edu/study/progress/policylibrary.html

During mid-term exams and the final examination, all students are expected to do their own work without assistance from others. Clear evidence of cheating or plagiarism will result in a grade of "0" for the examination. A second violation will result in a grade of "0" for the quiz or examination and an additional 50 points will be deducted from the students point total for the course. Students may not use or have visible any electronic device capable of transmitting or storing data. This includes, but is not limited to, i-pods or related devices, computers, tablets, calculators, cell phones including wrist phones. Violation of these rules will result in a grade of "0" for the examination with no warning. Unless given permission by the instructor, student may not be aided during quizzes and exams by notes, web-based data, or books.

Accessibility Resources

Students with disabilities may require accommodations to ensure full participation in class. A student requesting such accommodation at any time during the term should contact UB's Accessibility Resources Office where an assessment can be completed and appropriate accommodations determined and documented.

Lecture

Optimally, students should attend all lectures and read the text in advance of lecture to familiarize themselves with the material. Students are responsible for assigned materials and all materials presented in class whether they attend or not. **It is the students' responsibility to get class notes from a classmate in case of absence**, not from the instructor. The two midterm examinations will be given during class time, while the final exam will be given during exam week as it is scheduled by the University. The instructor reserves the right to give a take-home final examination that will be due no earlier than the scheduled time and date of the final.

Grading

There will be two midterm exams (combined 60% of course total) and a comprehensive final exam (40% of course total) based on the content of the entire course. **Your best midterm exam will be weighted more heavily than your poorer midterm score (35% vs. 25%).**

In class mid-term examination dates will be:
Mid-term 1: Thursday, October 5, 2017
Mid-term 2: Thursday, November 9, 2017

The comprehensive final exam will be at the scheduled exam date and place given to the course by Central Scheduling. At this time,

Final Exam: Tuesday, December 12, 2017 from 8:00 AM – 11:00 AM in NSC 205

The final course grade (A – F, including +/-) will be determined solely on the basis of total percentage accumulated. While grades will be assigned on a curve, students receiving 90% are assured of an "A"; students receiving 70% are assured of a "B"; students receiving 50% are assured of a "C".

Make up Quizzes/Exam

Students missing a midterm examination should provide valid documentation within 48 h of the examination to receive an excused absence. **Makeup exams must be completed within one week (7 days) of the scheduled exam or a grade of "0" will be entered.** Unexcused absences will result in a score of "0" being entered.

Students who are unavoidably absent from the final exam must present a valid, written excuse prior to or within 48 h of the final examination. Students should be prepared to document the absence if requested to do so.

Students with a documented, scheduling conflict for the final exam may schedule an alternative time for the final in advance. Students missing the final exam with an unexcused absence will be given a grade of "0" for the final examination. Students who present a valid, written excuse prior to or within 48 h of missing the final examination will be given a grade of "I" (incomplete) provided they have a passing average. Students with failing averages are not eligible for incompletes and will be given a grade of "F" if they miss the final exam. The default grade for an incomplete will be computed with the final examination counting as 0. Incompletes can be removed according to University guidelines.

Outline for MCH 501

The course will largely follow the text, but supplementary materials will be added.

Introductory Chapter: An Overview of Medicinal Chemistry
2.2 Terms used in medicinal chemistry
2.3 Drugs from plant sources
2.4 Modern drug discovery

Chapter 2: Drug Discovery Process (Overview)
2.2 Target Selection: druggability, assay development
2.3 Lead Discovery
2.4 Lead Optimization

Chapter 4: Enzymes as Drug Targets
4.1 Introduction: brief review of amino acids, protein structure, enzyme classes
4.2 Mode of Action: theory of enzyme catalysis, regulation
4.3 Kinetics: Michaelis-Menten equation, Lineweaver-Burk plots, multisubstrate mechanisms
4.4 Inhibitors: Reversible (competitive, noncompetitive, uncompetitive)
Supplement: Irreversible (covalent) inhibitors (inactivators)
4.5 Pharmaceutical Concerns: Ki and $IC50$, drug resistance

Chapter 5: Receptors as Drug Targets
5.1 Receptors: Introduction
5.2 Receptor Classification: ion channels, G-proteins, Tyr kinase, nuclear
5.3 Types of Ligands: agonists, antagonists, inverse agonists
5.4 Receptor Theories: occupancy, allostery, rate, residence time

Chapter 6: Oligonucleotides as Drug Targets
6.1 Nucleic Acids: brief review of DNA/RNA structure/function
6.2 Oligonucleotide Recognition: base pairing, electrostatics, intercalation, groove binding
6.3 Interference with Nucleic Acid Synthesis and Function: anti-HIV, antimetabolites

Chapter 3: A Trip Through the Body
3.2 Absorption: oral, injection, transdermal
3.3 Distribution: blood, membranes, blood-brain barrier
3.4 Pharmacodynamics
3.5 Metabolism and Elimination: kidneys, liver

Chapter 8: Metabolism
8.2 Metabolic Reactions: Phase I, Phase II
8.3 Metabolism Issues: metabolite activity, metabolic inhibition
8.4 Prodrugs

Chapter 9: Molecular Structure and Diversity
9.1 Determining Target Structure: X-ray crystallography, NMR, molecular modeling
9.2 Complementarity: intermolecular forces, molecular shape
9.3 Searching for Drugs: molecular space, privileged structures
9.4 Combinatorial Chemistry: parallel synthesis, split synthesis

Chapter 10: Lead Discovery
10.1 Searching for Hits: screening (library, fragment-based, virtual)
10.2 Filtering Hits to Leads: pharmacodynamics (PD), pharmacokinetics (PK), biological assays, Lipinski's Rules
10.3 Special Cases: serendipity, natural products

Chapter 11: Lead Optimization
11.1 Pharmacophore Determination
11.2 Functional Group Replacements: structure-activity relationships (SAR)
11.3 Alkyl Group Manipulation: chain homologation, ring-chain interconversion
11.4 Isosteres
11.5 Directed Combinatorial Libraries
11.6 Peptidomimetics

Chapter 12: Lead Optimization: Hansch Analysis
12.1 Background: quantitative SAR (QSAR), linear-free energy relationships (LFER)
12.2 Parameters: Hammett constants, Hansch constants, Taft steric parameter
12.3 Hansch Equations
12.4 Craig Plots

Student Learning Outcomes

Upon completion of this course, students will have an understanding of:

1) the covalent and non-covalent interactions of the building blocks (amino acids and nucleic acids) of biopolymers within proteins, DNA, and RNA and with small molecules such as drugs.

2) the various pathways to "drug discovery" and the qualities that a good drug candidate should possess. Critical thinking skills will allow students to predict good and poor candidates among several.

3) drug-receptor/active-site interactions and the various responses these interactions can induce. Critical thinking skills will allow students to differentiate the various pathways of drugreceptor interactions and to reconcile these interactions with theoretical and experimental models. 4) the mechanisms of bond making and bond breaking involved in covalent drugreceptor/ active-site interactions. Critical thinking skills will allow students to construct logical schemes for sequential movement of electrons in these processes.

Assessment Tools

The various elements of this course are used cumulatively and students will be expected to progress from an initial recognition of various concepts and processes to a synthesis of concepts and problem solving, using critical thinking skills.

1) Midterm I and the final examination will assess students' understanding of amino acids, their physical properties alone and in proteins, and their interactions with small drug-like molecules.

2) Midterm I and the final examination will assess students' understanding of enzyme and receptor function, inhibitor-enzyme and ligand-receptor interactions, and the theories describing these interactions. Students will use critical thinking skills to solve problems involving sequential movement of electrons in drug-receptor and drug-enzyme interactions.

3) Midterm II and the final examination will assess students' understanding of RNA and DNA structure and function and their interactions with small molecules (drugs).

4) Midterm II and the final examination will assess students' understanding of the metabolic fate of drugs.

5) Midterm II and the final examination will assess students' understanding of the relationship between target structure and ligand structure and of the strategies for diversifying ligand structure.

6) The final examination will assess students' understanding of various methods of drug discovery and the general concepts for lead-compound development including a descriptive understanding of theoretical models.

7) The final examination will be comprehensive and will also examine the students' critical thinking skills to propose solutions to problems involving multiple aspects of the course.