The University of Michigan
College of Pharmacy

Medicinal Chemistry 535
2 credits

Principles of Drug Design
Winter, 2019

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Andy White
Course Co-Director
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B. Course Information

Prerequisites: Medicinal Chemistry 532, or permission of instructor

Course Website: On CANVAS.
C. Course Schedule

General Course Information

Class Meeting Days: T-Th  
Time: 2-3 PM  
Room: 1567 N. University Building

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Section</th>
<th>Topic</th>
<th>Faculty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thu</td>
<td>Jan 10</td>
<td>Introduction</td>
<td>Overview of Drug Discovery and Class</td>
<td>Larsen</td>
</tr>
<tr>
<td>Tue</td>
<td>Jan 15</td>
<td>Lead Selection</td>
<td>Sources of Leads</td>
<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Jan 17</td>
<td>Lead Selection</td>
<td>Properties of Good Leads</td>
<td>Larsen</td>
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<tr>
<td>Tue</td>
<td>Jan 22</td>
<td>General Drug Design</td>
<td>Functional Groups and Bioisosterism</td>
<td>Kennedy</td>
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<tr>
<td>Thu</td>
<td>Jan 24</td>
<td>General Drug Design</td>
<td>Chirality and Conformational Restriction</td>
<td>Larsen</td>
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<tr>
<td>Tue</td>
<td>Jan 29</td>
<td>General Drug Design</td>
<td>Scaffold-Hopping (canceled; slides on Canvas)</td>
<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Jan 31</td>
<td>canceled</td>
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<tr>
<td>Tue</td>
<td>Feb 5</td>
<td>General Drug Design</td>
<td>Structure-based Design</td>
<td>White</td>
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<td>Thu</td>
<td>Feb 7</td>
<td>General Drug Design</td>
<td>Structure-based Design</td>
<td>White</td>
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<tr>
<td>Tue</td>
<td>Feb 12</td>
<td>General Drug Design (2 hr)*</td>
<td>NMR-based Design and Fragment-based Design</td>
<td>Cierpicki</td>
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<tr>
<td>Thu</td>
<td>Feb 14</td>
<td>Exam II*</td>
<td>Lead Selection and General Drug Design</td>
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<tr>
<td>Tue</td>
<td>Feb 19</td>
<td>Optimization for In Vivo (2 hr)***</td>
<td>Permeability</td>
<td>Barta</td>
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<tr>
<td>Thu</td>
<td>Feb 21</td>
<td>No class</td>
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<tr>
<td>Tue</td>
<td>Feb 26</td>
<td>Optimization for In Vivo</td>
<td>Solubility and Protein Binding</td>
<td>Kennedy</td>
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<tr>
<td>Thu</td>
<td>Feb 28</td>
<td>Optimization for In Vivo</td>
<td>Prodrugs</td>
<td>White</td>
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<td>Mar 2 - 10 Winter Break</td>
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<tr>
<td>Tue</td>
<td>Mar 12</td>
<td>No class, 533 1:00-3:00</td>
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<tr>
<td>Thu</td>
<td>Mar 14</td>
<td>Optimization for In Vivo</td>
<td>Drug metabolism</td>
<td>Larsen</td>
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<tr>
<td>Tue</td>
<td>Mar 19</td>
<td>Optimization for In Vivo (2 hr)*</td>
<td>Drug metabolism</td>
<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Mar 21</td>
<td>Optimization for In Vivo</td>
<td>Toxicity</td>
<td>Sliskovic</td>
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<tr>
<td>Tue</td>
<td>Mar 26</td>
<td>Optimization for In Vivo</td>
<td>Toxicity</td>
<td>Sliskovic</td>
</tr>
<tr>
<td>Thu</td>
<td>Mar 28</td>
<td>Optimization for In Vivo</td>
<td>Toxicity</td>
<td>Sliskovic</td>
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<tr>
<td>Tue</td>
<td>Apr 2</td>
<td>Team Project Presentations</td>
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<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Apr 4</td>
<td>Exam II*</td>
<td>Optimization for In Vivo</td>
<td>Larsen</td>
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<tr>
<td>Tue</td>
<td>Apr 9</td>
<td>Team Project Presentations</td>
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<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Apr 11</td>
<td>Team Project Presentations</td>
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<td>Larsen</td>
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<tr>
<td>Tue</td>
<td>Apr 16</td>
<td>Team Project Presentations</td>
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<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Apr 18</td>
<td>Team Project Presentations</td>
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<tr>
<td>Tue</td>
<td>Apr 23</td>
<td>Team Project Presentations</td>
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<td>Larsen</td>
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<tr>
<td>Thu</td>
<td>Apr 25</td>
<td>Team Project Presentations**</td>
<td></td>
<td>Larsen</td>
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*1:00-3:00, **Class in B022, ***2:00-4:00, #2:30-4:30 in Walgreen Lab

D. Course Description and Objectives

Course Description

This course surveys the strategies and selected techniques used to transform biologically active molecules into potential therapeutic agents. Topics include: sources of molecular leads, structure- and fragment-based design to enhance potency, improving physical and pharmacokinetic properties and reducing toxicity. The course concludes with team presentations of case histories of successful drug development illustrating the application of design principles taught in the class.

Course Objective

To explore in depth the rationale behind the selection of small molecule chemical leads and the process by which they are developed into effective therapeutics.
• **Lead Selection, General Drug Design and Optimization for In Vivo** - These sections will cover the entire “tool set” used by medicinal chemists to select and optimize small molecule leads. We will start with how to differentiate authentic biological activity from artifactual activity, desirable physical chemical properties for a lead, structures to avoid due to high potential for toxicity, etc. This will include the various possible sources for chemical leads, including natural products, high throughput screening and patent/literature reports. We will continue with how to optimize leads, including how functional groups affect protein binding and physical chemical properties, and the use of chirality and conformational restriction to enhance potency and selectivity. We will conclude with strategies for achieving in vivo activity without toxicity. Topics include optimizing cell permeability and intestinal absorption, major routes of drug metabolism and how to avoid them, impact of protein binding on in vivo activity, how to achieve good solubility without sacrificing activity, and mitigating toxicity through structural modifications.

• **Team Project Presentations** – The class will be divided into teams at the beginning of the course. The number and size of teams will be dependent on enrollment, but each team will consist of, at minimum, a student representing chemistry and one representing biology. Each team will be responsible for selecting a marketed drug in a specific therapeutic area, independently researching how it was developed, with a particular emphasis on challenges and roadblocks overcome, and the strategies employed to overcome them. Each team will then present their findings to the class during a one hour lecture period. An important problem-solving component of these presentations will be the proposal of reasonable alternate drug design strategies to overcome some of the roadblocks encountered. An example case history will be presented early in the course.

E. **Learning Objectives**

- Learn historical strategies for successful drug design
- Learn what state-of-the-art tools are currently available for rational drug design
- Develop an appreciation for the value of interdisciplinary collaboration in successful drug design
- Retrieve and interpret data from a critical reading of the academic and patent literature to define the development path and key hurdles overcome in the creation of a new marketed drug
- Work as an interdisciplinary team to critically analyze data from a drug discovery project and propose new directions by applying the design tools learned in the class
- Work effectively in a group (appreciate diversity and develop skills in communication, project planning, and time management )
- Organize and orally present a critical summary of a drug discovery project, with an emphasis on teaching the class what you have learned
F. Class Expectations

- **Academic integrity** - students are expected to abide by the College of Pharmacy Code of Conduct as it relates to all aspects of academic integrity. This includes, but is not limited to procedures expected of students while taking an in-class exam/quiz.

- **Special needs** - students with special needs are required to communicate with one of the course co-directors about special needs before classes begin.

- **Questions/concerns** - students should direct questions about a specific topic or exam/homework on that topic to the individual faculty teaching the subject. Questions or concerns such as absence from exams, illness, course logistics or other problems that the student may have in the course should be directed to one of the course co-directors.

- **Attendance** – class attendance is required, except for illness/emergency or prearranged absences.

- **Smart Phones** – are allowed, but should be set on silent/vibrate mode. Phone use during an exam is strictly prohibited.

- **Headphones** – are not allowed.

- **Laptop Policy** – are encouraged for note-taking, but not for other activities during class. Not allowed during exams.

G. Examinations and Grading

<table>
<thead>
<tr>
<th>Exams</th>
<th>Lead Selection and General Drug Design</th>
<th>Larsen, proctor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb 14</td>
<td>Exam I</td>
<td></td>
</tr>
<tr>
<td>Apr 2</td>
<td>Exam II</td>
<td>Optimization for In Vivo</td>
</tr>
</tbody>
</table>
The grade for the course will be determined by two (2) independent exams of 100 points each, along with a score (130 pts possible) for the team presentation.

**Exam Grading**

Exams will be graded as quickly as possible. Following the return of the graded exam, you will have one week to look over the exam and return it for re-grading if needed. Exams will not be re-graded if returned after the announced deadline. When returning exams for re-grading, indicate which questions you want re-graded and state clearly in writing why you feel the question was misgraded.

**Final Course Grades**

The letter grade for the course will be based on a curve, with the class average set near the border between B+ and A-.

**H. Recommended Text**

The following text is recommended for the course, but not required: