

## Research Techniques and Principles in Medicinal Chemistry

Fall 2021

Tues, Thurs 5:00-6:20 RM 249

Course Numbers: 16:663:501:01; 30:715:451:01

**Instructor:** Matthew Moschitto; Ernest Mario School of Pharmacy, William Levine Hall RM330.

**Email:** [m.moschitto@rutgers.edu](mailto:m.moschitto@rutgers.edu); I will strive to answer emails within 24 h. If I do not, please resend the email.

**Office Hours:** TBD, by appointment.

**Course Description:** This is an intensive course composed of medicinal and physical organic chemistry principles and techniques and will provide a basis for students to enter and succeed in a medicinal chemistry laboratory setting. The course is split into three parts. Part 1 covers physical organic principles, reaction mechanisms, and their interrelation with medicinal chemistry and enzymology. The organic chemical principles will cover the conceptual aspects of orbitals and bonding, stereochemistry, conformational analysis, acid/base theory, and substituent effects. Concepts surrounding elimination reactions, nucleophilic and electrophilic substitution using stereoelectronic and orbital theory, and general reaction mechanisms will be explored. Part 2 is based on enzymes, enzymatic mechanisms, and inhibitor design. Topics include cofactors, DNA interacting agents, and drug metabolism. The final part covers techniques needed in a medicinal chemistry laboratory including assay development and interpretation, as well as synthetic organic techniques and strategies. This course is designed as an introductory graduate course or an advanced undergraduate course for students who have completed two semesters of organic chemistry with an associated laboratory component.

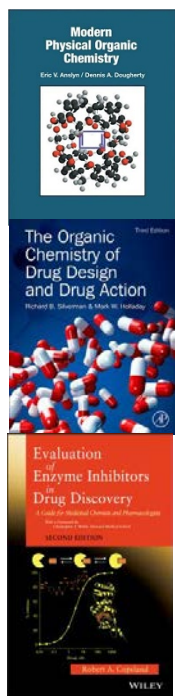
### Grading:

<b>3 Exams (including final)</b>	25% each (63 % total)
<b>Problem Sets</b>	20%
<b>Class Participation and Preparation</b>	5%

**Exams:** Two midterm exams and a final will be given. Each midterm exam will be 3h in length and be composed of the preceding sections' material. The final will be split between material from the first two exams and new material. Exam material will be based on lecture and problem set material only.

**Problem Sets:** Problem sets will be posted on Canvas. Their due date will be listed on canvas and in the syllabus. Problem sets should be placed on the table outside of Room 325 in EMSOP before 6pm on the day that they are due. Students should not share answers with each other. Copying another student's answers will be considered plagiarism (see below). It is permitted, however, to discuss the problems between students. It is in your best interest to work through the problems individually to understand the material. Students should not google or look up and copy answers from online sources either, this includes programs such as Reaxys and Scifinder.

**Books and Handouts:** The course generally follows three textbooks. The reading assigned are not required but are suggestions to supplement the lecture material. These textbooks are not required for purchase but are incredibly useful textbooks for any Medicinal Chemist. Handouts will be posted on the class canvas page and similarly are suggestions (unless otherwise noted in a problem set).



1. Anslyn EV, Dougherty DA. *Modern Physical Organic Chemistry*. Sausalito, CA: University Science; 2004.

2. Silverman RB, Holladay MW. *The Organic Chemistry of Drug Design and Drug Action*. Third edition. Amsterdam: Elsevier; 2014.

This book is available online free from Rutgers Library at:

<https://ebookcentral.proquest.com/lib/rutgers-ebooks/detail.action?docID=5754489>

3. Copeland, R. A. *Evaluation of enzyme inhibitors in drug discovery: A guide for medicinal chemists and pharmacologists*. Somerset: John Wiley & Sons, Incorporated, 2013.

This book is available online free from Rutgers Library at:

<https://ebookcentral.proquest.com/lib/rutgers-ebooks/detail.action?docID=1120975#>

**Computer Software:** This course will require the use of various software platforms. This software is available free of charge from the university and can be downloaded at [software.rutgers.edu](http://software.rutgers.edu) unless otherwise noted. If you need assistance, please ask. A computer lab is located in EMSOP room 323. Please email Elissa Glinn ([elissa.glinn@pharmacy.rutgers.edu](mailto:elissa.glinn@pharmacy.rutgers.edu)) if you require access. The following software will be used or discussed in class:

1. Chemdraw
2. Endnote
3. Origin Pro
4. Pymol (<https://pymol.org/2/>)

**Academic Integrity:** Rutgers University's policy on academic integrity will be strictly followed. If a student is found to be cheating during an exam or problem set, a grade of "F" will be given for the exam or problem set and the incident will be reported to the school. Details of Rutgers University's policy can be found at <http://academicintegrity.rutgers.edu/academic-integrity-policy/>.

Tentative Syllabus					
Date	Lecture Number	Topic	Specific topics	Readings	Problem Set # (lectures covered)
<b>PART I: Organic Mechanisms and Principles</b>					
Sept 2 <sup>nd</sup>	1	Mechanisms Chemical Bonding Stereochemistry	Orbitals Bonding Molecular Orbital Theory Chirality Atropisomerism	Anslyn Chap 1 Handout on Atropisomerism	
7 <sup>th</sup>	2	Conformational Analysis	Drawing chairs Strain Stable Conformers	Anslyn Chap 2	
9 <sup>th</sup>	3				
14 <sup>th</sup>	4	Acids and Bases	General Acid/Bases pKa of organics Lewis Acids Biological Acids Bases	Anslyn Chap 5	PS1 (1,2,3)
16 <sup>th</sup>	5				
21 <sup>nd</sup>	6	Additions and Eliminations Substitution reactions	C=O additions C=C additions E1 E2 Eliminations Fragmentations Nucleophilic substitution	Anslyn Chap 10	
23 <sup>th</sup>	7				
28 <sup>th</sup>	8	Pericyclic reactions	DA Rearrangements	Anslyn Chap 11	PS2 (4,5,6,7)
30 <sup>th</sup>	9				
Oct 5 <sup>th</sup>	10	Organometallics	Electron counting Oxidative Processes Reductive Processes Catalysis	Anslyn Chap 12	
7 <sup>th</sup>	11				PS3 (8, 9, 10)
12 <sup>th</sup>		<b>EXAM – Time TBD</b>	<b>Lectures: 1-11</b>		
<b>PART II: Enzymatic and Medicinal Chemistry Mechanisms</b>					
14 <sup>th</sup>		PACS Organic Symposium NO CLASS			
19 <sup>th</sup>	12	DNA agents	Intercalators Alkylators Strand Breakers	Silverman Chap 6	
21 <sup>nd</sup>	13	DNA agents Non covalent Binding		Anslyn Chap 7.1, 7.2,7.4,7.5,8.1,	
26 <sup>th</sup>	14	Non covalent Binding  Enzymes Mechanisms and Cofactors	$\pi$ -interactions H-Bonding Cofactors Oxidases, Reductases Kinases Phosphatases MBEIs	Anslyn Chap 3.2 Anslyn Chap 4.2, 4.3 Handout on $\pi$ - stacking Silverman Chap 4	
28 <sup>th</sup>	15	Drug Metabolism	CH/N/O oxidations Reductions Phase II transformations		PS4 (12,13, 14)
Nov 2 <sup>rd</sup>	16	Drug Metabolism		Silverman Chap 8	
5 <sup>th</sup>	17	Kinetics and Thermodynamics			PS5 (15, 16)

9 <sup>th</sup>		<b>EXAM – Time TBD</b>	<b>Lectures: 12-17</b>		
<b>PART III: Medicinal Chemistry Techniques</b>					
11 <sup>th</sup>	18	Inhibitor evaluation	Enzyme kinetics Reversible and Irreversible inhibitors	Copeland Chap 2.4-2.6, 3.1-3.6, 5.1-5.4, 6.1-6.4, 9.1-9.2	
13 <sup>th</sup>	19	Inhibitor evaluation			
18 <sup>th</sup>	20	Assay development	UV, Fluorescent, calorimetry assays Assay set up	Copeland Chap 4	
23 <sup>th</sup>	21				
30 <sup>th</sup>	22	Lit searching / Computer Programs	Lit. and Reaction Searching Citations Computer Programs	Handouts	PS6 (18-21)
<b>Dec 2<sup>nd</sup></b>	23	Laboratory Techniques and Safety	Purifications Chromatography Stereochemistry Safety procedures	Purification Chap 1 (handout)	
7 <sup>th</sup>	24				
9 <sup>th</sup>		<b>OPEN/Review</b>			PS7 (22, 23)
TBD	<b>FINAL</b>	<b>EXAM</b>	<b>40 % Lectures: 18-21</b> <b>60 % Lectures: 1-18</b>		