

Topics in Organic Chemistry: Modern Medicinal Chemistry (CHEM 515)

updated 9/1/26

Fall 2026

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Educational Goals:

- develop a knowledge base of medicinal chemistry concepts
- understand structure-activity principles in a variety of chemical structures
- become proficient with reading and understanding the scientific literature
- develop fundamental critical thinking skills, including pattern recognition and analogous reasoning
- understand common and basic approaches to the synthesis of small molecule drugs

Class meetings: Mon. and Wed. 11:40-1:00 PM in Dalton 300.

Office Hours: Tues. 3:00-4:00 PM, Fri. 3:30-4:30 PM and by appointment in Park 270

Textbook:

None! The course will depend on articles from the scientific literature, wisdom from the most highly paid individual in the classroom and about 7 presentations of practicing pharmaceutical scientists.

Week	Tuesday	Thursday
1	<u>8/31 Introduction</u> Concepts: basic understanding of medicinal chemistry and stages of drug development; pharmacophores <i>Lecture reference:</i> Divine inspiration	<u>9/2 Where do new drugs come from today?</u> Concepts: basic medicinal chemistry structural parameters; current examples of drug development <i>Lecture reference:</i> D. G. Brown et al., Where Do Recent Small Molecule Clinical Development Candidates Come From? , J. Med. Chem. 2018 , 61, 9442–9468.
2	<u>9/7 Labor Day-No class</u> PS#1 due 9/8	<u>9/9 Lead development (continued)</u>
3	<u>9/14 Molecular interactions</u> Concepts: intermolecular forces in biology; thermodynamics of drug interactions <i>Lecture reference:</i> M. Stahl et al., A Medicinal Chemist's Guide to Molecular Interactions , J. Med. Chem., 2010 , 53, 5061–5084. PS#2 due	<u>9/16 ADMET and Drug metabolism</u> Concepts: absorption, distribution, metabolism (Phase I and II reactions), excretion and toxicity <i>Lecture reference:</i> Currie GM., Pharmacology, Part 2: Introduction to Pharmacokinetics , J Nucl Med Technol. 2018 Sep;46(3):221-230.
4	<u>9/21 Protease drugs</u>	<u>9/23 Case study: Paxlovid</u>

	Concepts: protease enzyme mechanisms; peptidomimetic drug design; irreversible inhibition; target selectivity <i>Lecture reference:</i> M. Drag & G. S. Salvesen, Emerging principles in protease-based drug discovery, Nature Reviews Drug Discovery 2010, Vol. 9, pp. 690–701. and P. S. Dragovich et al., Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors. 4. Incorporation of P1 Lactam Moieties as L-Glutamine Replacements J. Med. Chem. 1999, 42, 1213-1224. PS#3 due	Concepts: rational drug design, irreversible enzyme inhibition, protease enzyme mechanism and pharmacokinetics (PK) principles <i>**Lecture reference:</i> D. Owen, C. M. Allerton, Jisun Lee '06 et al., An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19, Science 2021, 374, 1586-1593.
5	<u>9/28 Case study: Paxlovid (continued) and synthesis of nirmatrelvir</u> Concepts: Medicinal chemistry synthetic techniques <i>Lecture reference:</i> Supporting Information (SI) for D. Owen, C. M. Allerton et al. Science 2021, 374, 1586-1593. PS#4 due	<u>9/30 COVID-19 drugs: RNA polymerase inhibitors</u> Concepts: nucleoside metabolism, “anti-metabolites”, isosteric groups, pro-drugs <i>Lecture reference:</i> Review article: Ashleigh Shannon and Bruno Canard, Kill or corrupt: Mechanisms of action and drug-resistance of nucleotide analogues against SARS-CoV-2 - PMC Antiviral Res. 2023 Feb; 210: 105501. Molnupiravir: Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis Nature Structural & Molecular Biology, C. Hobartner, P. Cramer et al., Nature Structural Biology 2021, 28, 740-6. also B. Malone and E. Campbell, Molnupiravir: coding for catastrophe Nature Structural & Molecular Biology, Nature Structural Biology 2021, 28, 706-8. <i>Pro-drug lecture reference:</i> The expanding role of prodrugs in contemporary drug design and development, J. Rautio et al. Nature Reviews Drug Discovery 2018, 17, 559–587.
6	<u>10/5 Midterm Exam 1</u>	10/7 <u>Drugs and Receptors</u> Concepts: receptor types, ligand types (agonist, partial agonist, inverse agonist, antagonist) <i>Lecture reference:</i> Divine inspiration
Fall break	10/12	10/14
7	<u>10/19 OPEN or</u>	<u>10/21 OPEN or....</u> <u>Microdosing psychedelics</u>

	Case study: <u>Xanomeline (Cobenfy) for schizophrenia</u> "Classics in Chemical Neuroscience: Xanomeline" ACS Chemical Neuroscience, 2017, Vol. 8, pp. 435-443. Craig W. Lindsley et al. https://pubs.acs.org/doi/10.1021/acscchemneuro.7b00001	A non-hallucinogenic psychedelic analogue with therapeutic potential Nature 2021, Vol. 589, pp. 474–479 D. E. Olson et al. https://www.nature.com/articles/s41586-020-3008-z
8	10/26 OPEN or Case study: <u>K-Ras inhibition K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions Nature</u> <i>Reading:</i> K. M. Shokat et al. Nature 2013, 503, 548-551. PS#5 due	10/28 OPEN or.... <u>Antibiotics: Old and New</u> <u>Penicillin</u> <i>Lecture reference:</i> divine inspiration <u>Cresomycin</u> <i>Lecture reference:</i> “<u>An antibiotic preorganized for ribosomal binding overcomes antimicrobial resistance Science</u>” <i>Science</i>, 15 Feb 2024; Vol 383, Issue 6684 pp. 721-726. A. G. Myers et al.
9	11/2 OPEN or <u>Heteroaromatics: structures, properties, and synthesis</u> <i>Lecture reference:</i> N. A. Meanwell, <u>A Synopsis of the Properties and Applications of Heteroaromatic Rings in Medicinal Chemistry - ScienceDirect</u>, <i>Advances in Heterocyclic Chemistry</i> 2017, Vol. 123, pp. 245-361 PS#6 due	11/4 Dr. Chris Adams, Novartis: <u>Discovery of 4-((2S,4S)-4-Ethoxy-1-((5-methoxy-7-methyl-1H-indol-4-yl)methyl)piperidin-2-yl)benzoic Acid (LNP023), a Factor B Inhibitor Specifically Designed To Be Applicable to Treating a Diverse Array of Complement Mediated Diseases Journal of Medicinal Chemistry ACS Publications - J. Med. Chem. (2020) 63 (11): 5697–5722.</u>
10	11/9 Dr. Trevor Sherwood, Bristol-Myers Squibb: <u>TBA</u> PS#7 due	11/11 OPEN
11	11/16 Dr. Shorouk Badir '16, Merck: <u>An improved synthetic route to Caldasib, a breakthrough therapy for Metastatic KRAS G12C-Mutant Non-Small Cell Lung Cancer</u> PS#8 due	11/18 OPEN
12	11/23 Dr. Hu Li, Ph.D. '96: <u>Antibody drug conjugates (ADC's)</u> PS#9 due	11/25 OPEN
13	11/30 : <u>Midterm Exam 2</u>	12/2 Dr. Kelly Bleasby, Bristol Myers Squibb: “Optimizing Blood-Brain-Barrier Penetration: Considerations for Drug Design, Delivery and Translation” (remote via TEAMS)

		<i>Lecture reference:</i> N. C. Patel et al. Harnessing Preclinical Data as a Predictive Tool for Human Brain Tissue Targeting ACS Chemical Neuroscience , ACS Chem. Neurosci. 2021 , 12, 6, 1007-1017. (embellished with some machine learning SAR topics)
14	<u>12/7 OPEN or...</u> <u>Glioma treatment</u> Mechanism-based design of agents that selectively target drug-resistant glioma Science 2022, Vol. 377, pp. 502-511 R. Bindra, S. Herzon et al. https://www.science.org/doi/10.1126/science.abn7570	<u>12/9 OPEN</u> PS#10 due
Finals week	12/13-12/18 Comprehensive Final Exam	

Potential guest lectures:

- Dr. Davis Chase HC '21, Yale University, PROTACS
- Dr. Hu Li BMC Ph.D. '96, Eight Roads in Shanghai, ADC's
- Dr. Shorouk Badir BMC '16, Merck, Process chemistry
- Dr. Kelly Bleasby, Bristol Myers Squibb: "Optimizing Blood-Brain-Barrier Penetration: Considerations for Drug Design, Delivery and Translation"
- Dr. Trevor Sherwood, Bristol-Myers Squibb: TBD
- Dr. Mike Visser, Novartis, Discovery of DKY709 Helios Degradar
- Dr. Chris Adams, Novartis, LNP023
- Dr. Rachel Lagiakos, Novartis, AI's Impact on Modern Drug Discovery.

Class participation: Up to 50 pts. will be awarded based on questions and answers during class discussions. I recognize this risks rewarding loudmouth behavior.

Problem Sets: There will be ten 15-point take-home problem sets which will be collected at the beginning of class on the date shown on the schedule above. You may work with classmates to complete the problem sets, but you should submit your own version of the problem set solutions. You may use artificial intelligence to help you with the answers, but you should understand the concepts as you'll be tested on them; without the assistance of AI. Your two lowest problem set grades of the semester will be dropped in calculating your final grade.

Midterm Exams: Two midterm exams will be given on October 5 and November 30 in class and will be a joyous celebration of knowledge.

Final Exam: There will be a scheduled comprehensive final exam during the exam period, 12/13-12/18/26.

Course Grading:

Class participation	50 pts.
Problem Sets	120
Midterm Exam (100 pts.) x 2	200
Final Exam	150
Total Points	520 pts.

Approximate Grading Scheme: *The grading scheme may be modified if I consider it necessary.*

100-93%	4.0, A	81-79%	2.7, B-	67-64%	1.3, D+
92-89%	3.7, A-	78-76%	2.3, C+	63-60%	1.0, D
88-86%	3.3, B+	75-72%	2.0, C	<60%	0.0, F
85-82%	3.0, B	71-68%	1.7, C-		

Students with Disabilities: Bryn Mawr College is committed to providing equal access to students with a documented disability. Students needing academic accommodations for a disability must first speak with Access Services. Students can email accessservices@brynmawr.edu to request an appointment to begin this confidential process. If eligible for accommodations as per Access Services, students should schedule an appointment with the professor as early in the semester as possible to share their verification form and make appropriate arrangements. Please note that accommodations are not retroactive and require advance notice to implement. More information can be obtained at the Access Services website. (<http://www.brynmawr.edu/access-services/>)