

PRINCIPLES AND APPROACHES TO DRUG DESIGN AND DISCOVERY

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OBJECTIVES

The problems developed for this course offer students the opportunity for self-directed learning in the area of drug design. This course explores the fundamental concepts, principles, and processes underlying the design, discovery, and development of selected drug classes, with special emphasis on the molecular mechanisms and structure-activity relationships of some of the most important drug classes on the market today. Within each problem, students investigate disease and/or pathogen processes to understand the rationale for choosing a particular drug target, explore the molecular structure of drug binding sites on target molecules, and understand how the chemical structure of a drug relates to its biological activity. Small molecule drugs are emphasized, but students also have the opportunity to explore new therapies and research areas, such as antibodies and siRNA. Each problem provides historical context to the discovery and development of the drug classes studied and encourages students to explore contemporary approaches to drug design that are applied across successive stages of the design and development of new drugs.

In addition to “personal” objectives, there are **minimal learning objectives** that every student is expected to attain.

MINIMAL LEARNING OBJECTIVES

By the end of the course, you should be able to:

- 1) Discuss the molecular mechanism of action of **at least four** of the following types of drugs:
 - a. β -lactam antibiotics
 - b. DNA synthesis inhibitors
 - c. HIV protease inhibitors
 - d. Receptor-tyrosine kinase inhibitors
 - e. Adenosine receptor agonists/antagonists
 - f. Excitatory amino acid receptor agonists/antagonists
 - g. Angiotensin converting enzyme inhibitors
- 2) Demonstrate an understanding of the concepts involved in designing drugs for selected target sites, including:
 - a. Cell membrane receptors
 - b. Intracellular or extracellular enzymes
 - c. Receptor-coupled signal transduction pathways
 - d. Bacterial cell wall synthesizing enzymes
 - e. Viral proteases and viral nucleic acid synthesizing enzymes
- 3) Demonstrate an understanding of the physiochemical principles involved in drug action by being able to discuss how the following parameters influence drug action:
 - a. Stereochemistry and conformation
 - b. Electronic structure
 - c. Nature of chemical bonding

- 4) Demonstrate an understanding of the concepts and principles of drug design by being able to discuss approaches employed in the design of new drugs, such as:
- Discovery of lead compounds – natural products as pathfinders
 - High-throughput screening – a tool for drug discovery
 - Identification of drug targets – application of molecular biology and bioinformatics
 - Structure modification – the generation of combinatorial libraries
 - Structure-based drug design – the process of iterative optimization

Students should understand how computer-assisted drug design and computational methods can be applied through successive stages of drug development to accelerate candidate discovery and optimization, and how AI and machine learning can drive advances in drug discovery.

- 5) Apply these concepts to novel systems in your Written Term Paper.

EVALUATION

Final marks for this course will be awarded according to the following scheme:

1) Participation in Tutorials	20 %
2) Problem Summaries	30 %
3) Written Term Paper	30 %
4) Presentation of Term Paper	15 %
5) Publicity for BioPharm Program	5 %

1) Participation in Tutorials

Each student will complete a **Tutorial Self-Evaluation Sheet** at the end of each tutorial and a record will be kept by the student. A **mid-course evaluation** will be performed **on a date TBA** during which each student and the tutor will assess all students in the group in the categories: Responsibility, Information gathering, Communication, Critical Sense and Self-Assessment. As a result of the discussion the tutor will assign a grade to each student in each category. The tutor will keep a record of the grades, but the purpose of this evaluation is strictly formative.

A final **evaluation** will be performed exactly as described for the mid-course evaluation **on a date TBA**. In this case the evaluation will be summative, and grades will be used to compute the overall mark.

2) Problem Summaries

A problem summary must be submitted to the tutor for every problem **two weeks** after the group completes that problem. It should be neat, free of spelling and grammatical errors, and contain your name, and the title of the problem. The problem summary should have two components:

Part A: Tutorial Summary (5 marks)

In this section answer the following questions (point form is sufficient):

1. What learning objectives did the group generate around this problem?
2. Which of the course objectives were met during your study of this problem?

Part B: Course Objective Discussion (20 marks)

In this section choose **any one** of the major issues from Part A, **consistent with the overall objectives of the course**. Write a concise summary of your current knowledge of this issue. Do not exceed **four double-spaced pages** (excluding references, figures, and tables).

3) Written Term Paper

A **Written Term Paper** based on the course objectives listed above will be submitted by each student at the end of the course (**due date April 19, 2024 at 11:59 pm**). This Term Paper should be a fully referenced discussion paper of no more than 2,500 words in length (excluding any tables, figures, or references). The topic for this paper will be selected by the student, in consultation with the tutor. Detailed guidelines for this paper will be circulated by **January 30, 2024**.

4) Oral Presentation of Term Paper

At the end of the term, each student will give a 20 min oral presentation of their Written Term Paper. Each presentation will be evaluated by all students and the tutor according to a marking scheme to be circulated.

Presentations will take place **on a date TBD**.

PROBLEMS

There are six problems for this course, four of which will be completed by the tutorial group, which deal with the following general areas:

1. Mechanism of action and structure-activity relationships of **β -lactamase inhibitors** and **quinolones** (antimicrobial agents).
2. Mechanism of action and structure-activity relationships of **DNA replication inhibitors** (antineoplastic and antiviral agents) and **viral protease inhibitors** (anti-HIV drugs).
3. Molecular mechanism of action and structure-activity relationships of **receptor tyrosine kinase inhibitors** (anti-cancer agents).
4. Molecular mechanism of action and structure-activity relationship of **angiotensin converting enzyme inhibitors** (antihypertensive drugs).
5. Structural basis of drugs, which act on **adenosine receptors** (anti-ischemic drugs).
6. Molecular mechanism of action and structure-activity relationships of drugs, which act on the **excitatory amino acid receptors** (anticonvulsants and neuroprotective agents).

TUTORIALS

Tutorials will be held on **Tuesdays, January 9–April 9, 2024.**

Time: 2:30–5:30 pm

Place: TBD

CONDUCT EXPECTATIONS

As a McMaster student, you have the right to experience, and the responsibility to demonstrate, respectful and dignified interactions within all of our living, learning and working communities. These expectations are described in the Code of Student Rights & Responsibilities (the “Code”). All students share the responsibility of maintaining a positive environment for the academic and personal growth of all McMaster community members, whether in person or online.

It is essential that students be mindful of their interactions online, as the Code remains in effect in virtual learning environments. The Code applies to any interactions that adversely affect, disrupt, or interfere with reasonable participation in University activities. Student disruptions or behaviours that interfere with university functions on online platforms (e.g. use of Avenue 2 Learn, WebEx or Zoom for delivery), will be taken very seriously and will be investigated. Outcomes may include restriction or removal of the involved students’ access to these platforms.

ACADEMIC INTEGRITY

You are expected to exhibit honesty and use ethical behaviour in all aspects of the learning process. The academic credentials that you earn are rooted in the principles of honesty and academic integrity. **It is your responsibility to understand what constitutes academic dishonesty.**

Academic dishonesty is to knowingly act or fail to act in a way that results or could result in unearned academic credit or advantage. This behaviour can result in serious consequences, e.g. the grade of zero on an assignment, loss of credit with a notation on the transcript (notation reads: “Grade of F assigned for academic dishonesty”), and/or suspension or expulsion from the university. For information on the various types of academic dishonesty please refer to the Academic Integrity Policy. Important and helpful information can be found here.

The following illustrates only three forms of academic dishonesty:

- plagiarism, e.g., the submission of work that is not one’s own or for which other credit has been obtained.
- improper collaboration in group work.
- copying or using unauthorized aids in tests and examinations.

AUTHENTICITY/PLAGIARISM DETECTION

Some courses may use a web-based service (Turnitin.com) to reveal authenticity and ownership of student submitted work. For courses using such software, students will be expected to submit their work electronically either directly to Turnitin.com or via an online learning platform (e.g. A2L, etc.) using plagiarism detection (a service supported by Turnitin.com) so it can be checked for academic dishonesty. Students who do not wish to submit their work through the plagiarism detection software must inform the Instructor before the assignment is due. No penalty will be assigned to a student who

does not submit work to the plagiarism detection software. **All submitted work is subject to normal verification that standards of academic integrity have been upheld** (e.g. on-line search, other software, etc.). For more details about McMaster's use of Turnitin.com, please go to www.mcmaster.ca/academicintegrity.

ACADEMIC ACCOMMODATIONS

For Students with Disabilities

- Students with disabilities who require academic accommodation must contact Student Accessibility Services (SAS) at 905-525-9140 ext. 28652 or sas@mcmaster.ca to make arrangements with a Program Coordinator. For further information, consult McMaster University's Academic Accommodation of Students with Disabilities policy.

For Religious, Indigenous, or Spiritual Observances (RISO)

- Students requiring academic accommodation based on religious, indigenous or spiritual observances should follow the procedures set out in the RISO policy. Students requiring a RISO accommodation should submit their request to their Faculty/Program Office normally within 10 working days of the beginning of term in which they anticipate a need for accommodation or to the Registrar's Office prior to their examinations. Students should also contact their instructor/coordinator as soon as possible to make alternative arrangements for classes, assignments, and tests.

COURSES WITH AN ONLINE ELEMENT

Some courses may use online elements and platforms. Students should be aware that, when they make use of these platforms, information such as first and last names, usernames for the McMaster email accounts, and program affiliation may become apparent to all other students in the same course. The available information is dependent on the technology used. Continuation in a course that uses on-line elements will be deemed consent to this disclosure. If you have any questions or concerns about such disclosure, please discuss this with the course instructor.

COPYRIGHT AND RECORDING

Students are advised that lectures, demonstrations, performances, and any other course materials provided by an instructor include copyright protected works. The Copyright Act and copyright law protect every original literary, dramatic, musical, and artistic work, including lectures by University instructors. Students must not disseminate these materials to others not registered in the course, or post to third-party websites. The recording of lectures, tutorials, or other methods of instruction may occur during a course by the instructor for instructional purposes; students may make recordings for the purpose of personal study, but these must not be disseminated in any form. Students should be aware that their voice and/or image may be recorded by others during the class. Please speak with the coordinator if this is a concern for you.

EXTREME CIRCUMSTANCES

The University reserves the right to change the dates and deadlines for any or all courses in extreme circumstances (severe weather, labour disruptions, etc.). Changes will be communicated through regular McMaster communication channels, such as McMaster Daily News, Avenue to Learn, Microsoft Teams and/or McMaster email.

HEALTH AND WELLNESS RESOURCES FOR STUDENTS

As a signatory on the Okanagan Charter, McMaster University is committed to enhancing mental health and wellness and provides various resources for students to manage their well-being. Students are encouraged to seek support as necessary; the following are several campus- and community-based resources that you may find helpful. For more resources and additional information, please visit <https://wellness.mcmaster.ca/resources/>

ON-CAMPUS RESOURCES

- **Student Wellness Centre:** Provides counselling, medical services, wellness education, guided self-help, and other relevant resources. PGCLL 210; 905-525-9140, x27700; <https://wellness.mcmaster.ca>
- **Sexual Violence Support:** An on-campus resource where students, staff, and faculty of all backgrounds and social identities can find support and information about sexual, intimate partnership or family violence. UH 104; 905-525-9140 x20909; <https://svpro.mcmaster.ca>
- **Faculty/Program Office:** Feel free to contact an Academic Advisor in your Faculty/Program Office who can connect with academic advising and connect you with other resources.

OFF-CAMPUS RESOURCES

- **Good2Talk:** Free, confidential helpline providing professional counselling and information and referrals for mental health, addictions and well-being to post-secondary students in Ontario, 24/7/365; 1-866-925-5454; <https://good2talk.ca>
- **Big White Wall:** Online peer-to-peer chat-based service that provides mental health and wellbeing support, 24/7/365. <https://www.bigwhitewall.com>
- **SACHA (Sexual Assault Centre - Hamilton Area):** Confidential, anonymous 24-hour nonjudgmental telephone support for adults who have experienced sexual violence. 905-525-4162; <http://sacha.ca>

If you have immediate safety concerns for yourself or others, call **Campus Security** who will respond with the **MSU Emergency First Response Team (EFRT)** at 905-522-4135 or call 911 if you are off campus.

LAND ACKNOWLEDGEMENT

McMaster University recognizes and acknowledges that it is located on the traditional territories of the Mississauga and Haudenosaunee nations, and within the lands protected by the Dish With One Spoon wampum agreement.

NOTE

The instructor and the university reserve the right to modify elements of the course during the term. The university may change the dates and deadlines for any or all courses in extreme circumstances. If either type of modification becomes necessary, reasonable notice and communication with the students will be given with explanation and the opportunity to comment on changes. It is the responsibility of students to check their McMaster email and course websites weekly during the term and to note any changes.