CBMS842

Advanced Medicinal Chemistry

S2 Day 2018

Dept of Chemistry & Biomolecular Sciences

Contents

General Information

Unit convenor and teaching staff
Lecturer
Joanne Jamie
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Contact via 98508283
4 Wally's Walk (F7B) room 231
Have an open door policy, but students are encouraged to arrange a meeting via email.

Lecturer in charge
Peter Karuso
peter.karuso@mq.edu.au
Contact via 9850 8290
F7B232
Wednesday 6-8 PM

Tutor and administrator
Vaughan Moon
vaughan.moon@mq.edu.au
Contact via 9850 8309
4 Wally's Walk (F7B) room 204
Wednesday 6-8 PM

Credit points
4

Prerequisites
(Admission to MBiotech or MBioBus or MLabQAMgt or MRadiopharmSc or MSc or GradCertLabQAMgt or GradDipLabQAMgt) and permission by special approval

Corequisites

Co-badged status

Unit description
This unit builds on the fundamentals of medicinal chemistry, including the discovery, design and development of new medicines. The aim of the unit is to integrate chemical biology and organic chemistry to reveal how these are used in medicinal chemistry to design and synthesise new drugs and to understand their mode of action. The unique aspect of this unit is the focus on computational chemistry in the field of drug design and development. This includes aspects of molecular modelling, molecular dynamics, docking, pharmacophore modelling and QSAR as they relate to the understanding of drug action and design of new drugs.

Important Academic Dates

Information about important academic dates including deadlines for withdrawing from units are available at https://www.mq.edu.au/study/calendar-of-dates

Learning Outcomes

On successful completion of this unit, you will be able to:

By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries

By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action

By the end of this unit, you should be able to design the structure of small molecules by combining the principles of drug design to create potential new drugs

By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

General Assessment Information

On line quizzes are multiple choice questions on the previous 2 weeks work.

The report and presentation is a major work that you will start preparing in week 5 and complete in week 13. It involves a written report and a powerpoint presentation (15 minutes)

The final exam is a 3 hr written exam

The weekly classes are a participation hurdle and failure to participate in at least 10 of the 13 weekly classes will result in you failing CBMS842. If you are unable to attend a class, please contact Peter Karuso (peter.karuso@mq.edu.au) immediately. In addition, you must submit a Special Consideration request at ask.mq.edu.au to justify your absence.

Your marks (in-class and online quizzes, report and presentation) will be placed on the CBMS842 web site.

Your final grade will be based on the mark from the aggregation of the individual assessments, **with 50% or greater needed overall for a pass.**

Medical certificates or official documents must be lodged as part of a disruption to studies request at ask.mq.edu.au as soon as possible if you are absent for any of the weekly classes, assessment tasks or miss the due date for any of the on-line tasks. If your reason is regarded as valid for missing the in-class quizzes, you will be given an average of the other quizzes done; with the on-line quizzes an extension of time will be provided if the disruption to studies request is approved. If you miss the final exam for a valid reason, a supplementary exam will be provided. Any assessment tasks not submitted on time that does not get approval through the disruption to studies request will get a 10% deduction of marks for every weekday late.

Final Examination Details: The examination timetable will be available in Draft form approximately eight weeks before the commencement of the examinations and in final form approximately four weeks before the commencement of the examinations. You are expected to present yourself for examination at the time and place designated by the University in the Examination Timetable. This could be any day after the final week of semester and up until the final day of the official examination period. It is Macquarie University policy to **not set early examinations** for individuals or groups of students. All students are expected to ensure that they are available until the end of the teaching semester, that is, the final day of the official examination period. **NOTE: If you apply for a supplementary examination, you must make yourself available for the week of Dec 4-8. If you are not available at that time, there is no guarantee an additional examination time will be offered. Specific examination dates and times will be determined at a later date.**

The only exception to sitting an examination at the designated time is because of documented illness or unavoidable disruption. Absence from the final exam will result in a grade of F except in the case of a genuine medical emergency or misadventure as defined by the University (see below). In these circumstances you should apply for a Supplementary Exam at ask.mq.edu.au.

Assessment Tasks

Name	Weighting	Hurdle	Due
Five on-line assessments	25%	No	Weeks 3, 5, 7, 9, 11
Final Exam	50%	No	Week 15
Research presentation	25%	No	Week 13
Class participation	0%	Yes	weeks 1-13

Five on-line assessments

Due: **Weeks 3, 5, 7, 9, 11**
Weighting: **25%**

5 on-line quizzes, worth 5% each

On successful completion you will be able to:

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action
- By the end of this unit, you should be able to design the structure of small molecules by combining the principles of drug design to create potential new drugs

Final Exam

Due: **Week 15**
Weighting: **50%**

This is a 3 hr final exam

On successful completion you will be able to:

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action
- By the end of this unit, you should be able to design the structure of small molecules by combining the principles of drug design to create potential new drugs
- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Research presentation

Due: **Week 13**
Weighting: **25%**

Using what you have learnt, pick a drug target, research what is known about this target and summarise the relevant literature and design your own library of compounds to test. Present this review and design task to the rest of the class in week 13 and hand in a written report.

On successful completion you will be able to:

- By the end of this unit, you should be able to apply the principles of rational drug design

for the creation of drug libraries
- By the end of this unit, you should be able to design the structure of small molecules by combining the principles of drug design to create potential new drugs
- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Class participation

Due: **weeks 1-13**
Weighting: **0%**
This is a hurdle assessment task (see assessment policy for more information on hurdle assessment tasks)

Participation in the weekly classes is a hurdle and you are expected to attend all classes. In the event of illness or misadventure, you can justify your absence from a class by submitting a special consideration request.

On successful completion you will be able to:
- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action

Delivery and Resources

This is a self taught unit using the "molecular conceptor" and MOE software. Each week a set number of tasks are assigned and assessed. There is no text book set for this unit but the material in the CBMS606 text book (Patrick, "Medicinal Chemistry", 5th Ed) is assumed knowledge.

Unit Schedule

WEEK 1 – Introduction to drug design

Introduction to Drug Discovery

1. From the Origin of Medicines to Today
2. Revolutions that Changed Drug Discovery
3. In-Silico Technologies
4. The Drug Discovery Process
5. Rational Drug Design Strategy

Principles of Rational Drug Design

1. Rational Drug Design
2. Pharmacophore-Based Design
3. Receptor-Based Design
4. Integration in a Global Perspective
5. Challenge of the Genomics Era
6. Typical Projects

WEEK 2 – Molecular basis of drugs

Molecular Geometry

1. 2D/3D
2. Conformers
3. Torsion Angles
4. Conformational Complexity
5. Ratio of Conformers

Molecular Energies

1. Introduction
2. Thermodynamics
3. Kinetics
4. Modelling in Drug Design
5. How to Calculate Energies
6. Quantum Mechanics
7. Molecular Mechanics

Molecular Graphics

1. Visualisation
2. Editing and Manipulation
3. Surfaces and Volumes
4. Visualising Interactions

WEEK 3 – Library design

Library Design

1. Introduction

2. The Basis of a Good Scaffold
3. Scaffold Selection and Design
4. Focused and Diverse Strategies
5. Measuring Distances Between Molecules
6. Increasing the Quality of a Library
7. Example of Library Analysis

Case Studies in Library Design

1. Case Study-1: CDK2 Inhibitors
2. Case Study-2: DHFR Inhibitors

WEEK 4 - Structural bioinformatics and protein structure

Protein Structure

1. Structural and Functional Diversity of Proteins
2. Amino Acids: Building Blocks of Proteins
3. From Amino Acids to Proteins
4. Geometry of Proteins and Peptides
5. Protein Structure Overview
6. Primary Structure
7. Secondary Structure
8. Tertiary Structure
9. Quaternary Structure
10. Structural Classification of Proteins

Structual Bioinformatics

1. Introduction to Structural Bioinformatics
2. Biomolecular Properties
3. Assembly of Biomolecules

WEEK 5 – Structure-activity relationships (SAR)

Structure Activity Relationships (SAR)

1. Introduction
2. Probing H-Bond Interactions
3. Probing Ionic Interactions
4. Probing Hydrophobic Interactions

5. Probing Other Interactions
6. Modifications to Alter the Geometry of the Ligand
7. Complexity of SAR Analyses

WEEK 6 – SAR case studies

Case Studies in SAR Analyses

1. Case Study-1: Banyu Example
2. Case Study-2: Dioxobenzothiazole Example
3. Case Study-3: EGF-R Kinase Inhibitors
4. Case Study-4: Nifedipine Example
5. Case Study-5: Carbonic Anhydrase Example
6. Case Study-7: Anilino-Quinazoline Example

Case Studies in Advanced Analog Design

1. Case Study-8: Salicylamide Mimics

WEEK 7 – Molecular docking

Molecular Docking: Principles and Methods

1. Introduction to Computational Docking
2. The Docking Problem
3. Scoring Methods
4. Uses of Docking in Research
5. Futures and Perspectives

WEEK 8 – Structure based design

Introduction to Protein-Ligand Binding

1. Introduction
2. Analytical Process
3. Principles of Analysis
4. Example of Tight Interactions
5. Receptor and Ligand Flexibility
6. Role of the Solvent
7. Prediction of Binding Modes

8. Methods for Analysing Binding
9. Conclusion

Principles of Structure-Based Design

1. Introduction
2. Eight Golden Rules
3. Four Design Methods
4. Analog Design
5. Database Searching
6. Manual Design
7. Another Iteration
8. Success Story
9. Conclusion

WEEK 9 – Structure based design & case studies

Case Studies in Structure-Based Design

1. Case Study-1: Phenyl Imidazoles
2. Case Study-2: BACE-1 Inhibitors
3. Case Study-3: Factor Xa Inhibitors
4. Case Study-4: Kinase Inhibitors

Case Studies of Docking in Drug Discovery

1. Case Study-1: Pyrimidin-4-yl-ureas for Kinase Inhibition
2. Case Study-2: Inhibition of CHK1
3. Case Study-3 Thrombin Inhibitors

Analyses of Protein-Ligand Complexes

1. Rotamase Inhibitors
2. Intercalating Antibiotics
3. Sialidase Inhibitors

WEEK 10 – Ligand based design A

Principles in Pharmacophore Elucidation

1. Introduction
2. Analytical Process

3. Simple Case
4. Typical Example
5. Complexity Levels
6. Principles of Analysis
7. Conformational Control
8. Managing Hypotheses
9. Receptor Mapping
10. Two Generations of Pharmacophores
11. Summary

Ligand-Based Approaches

1. Introduction
2. Four Design Methods
3. Chemical Modifications

WEEK 11 – Ligand based design B & case studies

Ligand-Based Approaches

1. Database Searching
2. De-Novo Design
3. Examples of Design
4. Conclusion

Examples of Pharmacophores

1. ACE Inhibitors
2. Serotonin Antagonists
3. Dopamine D-2 Antagonists
4. Beta-Lactam Antibiotics

Case Studies in Ligand-Based Design

1. Case Study-1: Aromatase Inhibitors
2. Case Study-2: Substance P Antagonists
3. Case Study-3: Tricyclic Antidepressants
4. Case Study-4: Morphinan Analgesics

WEEK 12 – QSAR (optional)

QSAR: Principles and Methods

1. Introduction to QSAR
2. The Foundations of QSAR
3. Design of a QSAR Model
4. Compounds Selection: Step 1
5. Descriptors Selection: Step 2
6. Deriving the Equation: Step 3
7. Validating the Model: Step 4

Case Studies in QSAR and 3d-QSAR

1. Case Study-1: QSAR of Capsaicin Analogs

MOE WORKSHOPS

1. Introduction to MOE
2. Building Molecules
3. 3D Visualisations
4. Structure based design
5. Docking
6. Ligand based design
7. Protein Ligand Interaction footprints

Policies and Procedures

Macquarie University policies and procedures are accessible from Policy Central (https://staff.mq.edu.au/work/strategy-planning-and-governance/university-policies-and-procedures/policy-central). Students should be aware of the following policies in particular with regard to Learning and Teaching:

- Academic Appeals Policy
- Academic Integrity Policy
- Academic Progression Policy
- Assessment Policy
- Fitness to Practice Procedure
- Grade Appeal Policy
- Complaint Management Procedure for Students and Members of the Public
- Special Consideration Policy *(**Note:** The Special Consideration Policy is effective from 4 December 2017 and replaces the Disruption to Studies Policy.)*

Undergraduate students seeking more policy resources can visit the Student Policy Gateway (https://students.mq.edu.au/support/study/student-policy-gateway). It is your one-stop-shop for the key policies you need to know about throughout your undergraduate student journey.

If you would like to see all the policies relevant to Learning and Teaching visit Policy Central (https://staff.mq.edu.au/work/strategy-planning-and-governance/university-policies-and-procedures/policy-central).

Student Code of Conduct

Macquarie University students have a responsibility to be familiar with the Student Code of Conduct: https://students.mq.edu.au/study/getting-started/student-conduct

Results

Results shown in *iLearn*, or released directly by your Unit Convenor, are not confirmed as they are subject to final approval by the University. Once approved, final results will be sent to your student email address and will be made available in eStudent. For more information visit ask.mq.edu.au.

Student Support

Macquarie University provides a range of support services for students. For details, visit http://students.mq.edu.au/support/

Learning Skills

Learning Skills (mq.edu.au/learningskills) provides academic writing resources and study strategies to improve your marks and take control of your study.

- Workshops
- StudyWise
- Academic Integrity Module for Students
- Ask a Learning Adviser

Student Services and Support

Students with a disability are encouraged to contact the Disability Service who can provide appropriate help with any issues that arise during their studies.

Student Enquiries

For all student enquiries, visit Student Connect at ask.mq.edu.au

IT Help

For help with University computer systems and technology, visit http://www.mq.edu.au/about_us/offices_and_units/information_technology/help/.

When using the University's IT, you must adhere to the Acceptable Use of IT Resources Policy. The policy applies to all who connect to the MQ network including students.

Graduate Capabilities

PG - Capable of Professional and Personal Judgment and Initiative

Our postgraduates will demonstrate a high standard of discernment and common sense in their professional and personal judgment. They will have the ability to make informed choices and decisions that reflect both the nature of their professional work and their personal perspectives.

This graduate capability is supported by:

Learning outcomes

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
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- By the end of this unit, you should be able to design the structure of small molecules by combining the principles of drug design to create potential new drugs
- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Assessment tasks

- Research presentation
- Class participation

PG - Discipline Knowledge and Skills

Our postgraduates will be able to demonstrate a significantly enhanced depth and breadth of knowledge, scholarly understanding, and specific subject content knowledge in their chosen fields.

This graduate capability is supported by:

Learning outcomes

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action
- By the end of this unit, you should be able to design the structure of small molecules by

combining the principles of drug design to create potential new drugs
- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Assessment tasks

- Five on-line assessments
- Final Exam
- Research presentation

PG - Critical, Analytical and Integrative Thinking

Our postgraduates will be capable of utilising and reflecting on prior knowledge and experience, of applying higher level critical thinking skills, and of integrating and synthesising learning and knowledge from a range of sources and environments. A characteristic of this form of thinking is the generation of new, professionally oriented knowledge through personal or group-based critique of practice and theory.

This graduate capability is supported by:

Learning outcomes

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action
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Assessment tasks

- Five on-line assessments
- Final Exam
- Research presentation
- Class participation

PG - Research and Problem Solving Capability

Our postgraduates will be capable of systematic enquiry; able to use research skills to create new knowledge that can be applied to real world issues, or contribute to a field of study or

practice to enhance society. They will be capable of creative questioning, problem finding and problem solving.

This graduate capability is supported by:

Learning outcomes

- By the end of this unit, you should be able to apply the principles of rational drug design for the creation of drug libraries
- By the end of this unit, you should be able to exploit structure activity relationships (SAR) and quantitative structure activity relationships (QSAR) principles to understand drug modes of action
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Assessment tasks

- Research presentation
- Class participation

PG - Effective Communication

Our postgraduates will be able to communicate effectively and convey their views to different social, cultural, and professional audiences. They will be able to use a variety of technologically supported media to communicate with empathy using a range of written, spoken or visual formats.

This graduate capability is supported by:

Learning outcome

- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Assessment tasks

- Final Exam
- Research presentation
- Class participation

PG - Engaged and Responsible, Active and Ethical Citizens

Our postgraduates will be ethically aware and capable of confident transformative action in

relation to their professional responsibilities and the wider community. They will have a sense of connectedness with others and country and have a sense of mutual obligation. They will be able to appreciate the impact of their professional roles for social justice and inclusion related to national and global issues

This graduate capability is supported by:

Learning outcome

- By the end of this unit, you should be able to communicate the above advanced medicinal chemistry concepts competently in oral presentations and in written format in the form of a report and a final exam

Assessment tasks

- Research presentation
- Class participation

Changes from Previous Offering

There are no major changes since last time.