UNIVERSIDADE DA CORUÑA USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA Universidade de Vigo

Master in Chemical Research and Industrial Chemistry

MEDICINAL CHEMISTRY

Course Guide

2014-15

1. Subject Description

Character: Optative

Call: First quarter

Credits: 3 ECTS

Teaching staff:

Concepción González Bello

Associate Professor,
Department of Organic Chemistry,
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS)
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Lectures, seminars and tutorials

Ricardo Riveiros Santiago

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Seminars and tutorials

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Profesor Contratado Doctor,
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Seminars and tutorials

Language: Spanish or English

2. Status, meaning and importance of the subject in the Master degree

2.1. Module to which the subject belongs in the Master. Related subjects.

Module 2: "*Chemical Biology*". It is mainly related to the subjects of this module.

2.2. Role of this subject in this module and in the Master

This subject aims that the students to acquire the basic concepts in the field of medicinal chemistry and drug design, and also to know the required steps for drug development, ranging from the discovery of an active compound in the laboratory to its integration into the market. The subject will also address the major current methodologies in finding lead compounds that are employed in both industrial and academic level, and its optimization for the development of a drug. This includes from structure-based design, virtual screening, to fragment-based design of compounds. The most relevant aspects in the quantification of the structure-activity relationships (QSAR) will be also described. Each of the contents of this subject will be illustrated by representative examples.

2.3. Prior knowledge (recommended/required) that students must have to study the subject

It is recommended to have previously completed the subject "Chemistry of Biomolecules". Basic knowledge in the visualization of the three dimensional structure of biomolecules using visualization programs such as Pymol, Mercury, etc. Management of databases such as Protein Data Bank (PDB), Expasy, etc. is also recommended.

3. Learning objectives and skills to be achieved by the student with the subject

3.1. Learning objectives

- Acquisition of advanced knowledge in medicinal chemistry and its most important applications in drug discovery.
- Understanding the required steps for drug development, ranging from the discovery of an active compound in the laboratory to its integration into the market.
- To know the main therapeutic targets used in drug discovery.
- To know the principal tools used in the identification and the design of hit compounds.
- Understanding the chemical basis for optimizing the activity of a hit compound.

3.2. General skills

- Acquire knowledge and understanding to provide a basis or opportunity for originality in developing and/or applying ideas, often within a research context.

- The students should apply their knowledge and ability to solve problems in new or unfamiliar environments within broader (or multidisciplinary) contexts related to their field of study.
- The students should communicate their conclusions, and the knowledge and the reasons that they support them, to specialist and non-specialists in a clear and unambiguous manner.
- The students should acquire the learning skills to allow them to continue studying in a way that will have to be largely self-directed or autonomous.
- Identify information from scientific literature by using appropriate channels and integrate such information to raise and contextualize a research topic.
- Use the scientific terminology in English to explain the experimental results in the context of the chemical profession.
- Apply correctly the new technologies of gathering and organization of the information to solve problems in the professional activity.

3.3. Specific skills

- Define concepts, principles, theories and facts of the various specialized areas of chemistry.
- Suggest alternatives for solving complex chemical problems of the different specialties in chemistry.
- Apply materials and biomolecules in innovative fields of industry and chemical engineering.
- Innovate in the synthetic methods and the chemical analysis related to different areas of chemistry.
- Promote innovation and entrepreneurship in industry and chemical research.

3.4. Transversal skills

Ability to work in groups on both the resolution and the discussion of problems.

4. Contents

4.1. Sections

4.2. Recommended bibliography

4.2.1. Basic (reference manual)

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013.
- "**Burger's Medicinal Chemistry, Drug Discovery and Development**", Donald J. Abraham & David P. Rotella Eds., 7ª Ed., Vol. 1, Wiley, 2010.

4.2.2. Supplementary

- "**Molecules and Medicine**", E. J. Corey, B. Czakó & L. Kürti, John Wiley & Sons, New Jersey, 2007.
- "**Molecules that Changed the World**", K. C. Nicolaou & T. Montagnon, Eds., WILEY-VCH, Weinheim, 2008.
- "**Structure-Based Drug Discovery, An Overview**", Roderick E. Hubbard Ed., RSC Publishing, Cambridge, 2006.
- "**Evaluation of Enzyme Inhibitors in Drug Discovery**", Robert A. Copeland, Wiley-Interscience, New Jersey, 2005.
- "**Fragment-Based Drug Discovery, A Practical Approach**", Edward R. Zartler & Michael J. Shapiro Eds., John Wiley & Sons, Chichester, 2008.
- "**Ligand Efficiency Indices for Drug Discovery**", Celerino Abad-Zapatero, Elsevier, Amsterdam, 2013.

CHAPTER 1. General Aspects, Definitions and Concepts

1. Introduction

This chapter begins with a historical perspective of drug discovery and development that will highlight the great progress that has experienced the area in recent years, particularly in terms of tools and methodologies. The required steps for the development of a drug - from the lab to the market - will be discussed. The basics of enzyme catalysis and its different behaviour in relation to receptors will be studied. The latter will define the basis of important concepts such as agonist, antagonist, reversible and irreversible inhibition, transition state analogs, etc. These concepts will be illustrated with representative examples.

2. Contents

Drug discovery: historical perspective. Drug activity phases. Enzymatic catalysis. Definitions and Concepts: agonist, antagonist, transition state analogs, reversible inhibition (competitive, non-competitive), irreversible inhibition, suicide substrates. Examples.

3. Bibliography

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008. Chapters 1-3.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013. Chapters 1 y 3.
- "**Burger's Medicinal Chemistry, Drug Discovery and Development**", Donald J. Abraham & David P. Rotella Eds., 7ª Ed., Vol. 1, Wiley, 2010.
- "**Evaluation of Enzyme Inhibitors in Drug Discovery**", Robert A. Copeland, Wiley-Interscience, New Jersey, 2005. Chapters 1-3.

4. Activities

The student will have to perform the exercises related to the chapter indicated by the professor on the date indicated in the subject activity schedule. In the seminars, students will solve the proposed exercises and questions and carry out oral presentations of papers, reviews etc. Those students who have difficulties with the exercises of the chapter should contact with the teacher during the tutorial schedule to receive the necessary support.

CHAPTER 2. Therapeutic Targets

1. Introduction

The major therapeutic targets will be studied. Special emphasis will be placed on the molecular basis of their relevance. Its usefulness in medicinal chemistry will be illustrated with several examples of drugs used clinically.

2. Contents

Therapeutic targets: classification and their main characteristics. Enzymes. Membrane transporters. Voltage-gated ion channels. Non-selective cation channels. Receptors with

intrinsic ion channels. Receptors with intrinsic enzymatic activity. Receptors coupled to various cytosolic proteins. G-protein-coupled receptors. Nuclear receptors.

3. Bibliography

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008. Chapter 4.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013. Chapters 4-6.

4. Activities

The student will have to perform the exercises related to the chapter indicated by the professor on the date indicated in the subject activity schedule. In the seminars, students will solve the proposed exercises and questions and carry out oral presentations of papers, reviews etc. Those students who have difficulties with the exercises of the chapter should contact with the teacher during the tutorial schedule to receive the necessary support.

CHAPTER 3. Strategies for Drug Discovery I. Structure-Based Design

1. Introduction

The evolution in the last years of the structure-based design approach in drug discovery will be first analyzed. The practical aspects of determining the three-dimensional structure of a target by X-ray crystallography, which is a key tool in the rational design, will be studied. Applications of Nuclear Magnetic Resonance to this area will be also addressed. The key concepts and basis of the computational tools widely used will be described. This includes docking, molecular dynamics simulations and QM/MM studies that allows the structure-based design of potential candidates, as well as to study in atomic detail the enzymatic mechanism, the transition states and which conserved residues and how are involved in the process. The usefulness of each of these tools in medicinal chemistry will be illustrated by representative examples.

2. Contents

Evolution of the structure-based design in drug discovery. Practical aspects of the determination of the three dimensional structure of a target - X-ray crystallography for the structure-based design. Applications of NMR spectroscopy in the rational design. Docking. Molecular dynamics simulations. QM/MM. Examples.

3. Bibliography

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013.

- "**Structure-Based Drug Discovery, An Overview**", Roderick E. Hubbard Ed., RSC Publishing, Cambridge, 2006.

4. Activities

The student will have to perform the exercises related to the chapter indicated by the professor on the date indicated in the subject activity schedule. In the seminars, students will solve the proposed exercises and questions and carry out oral presentations of papers, reviews etc. Those students who have difficulties with the exercises of the chapter should contact with the teacher during the tutorial schedule to receive the necessary support.

CHAPTER 4. Strategies for Drug Discovery II. Virtual Screening and Fragment-Based Design

1. Introduction

Two widely used strategies for identifying candidates, thus virtual screening and fragment-based design, will be studied. First, the utility of computational approaches for the identification of potential candidates of a target, as well as the potential targets for a given compound, will be addressed. Secondly, the principles of the fragment-based design, and the main biophysical techniques used for the analysis, such as X-ray crystallography, mass spectrometry, etc. will be described. These strategies will be illustrated by examples.

2. Contents

Basics of the virtual screening of candidates. Available databases. Applications: identifying ligands for a target or potential targets of a ligand. Basics of the fragment-based design. Screening of candidates by X-ray crystallography. Other biophysical screening methods. Examples

3. Bibliography

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008. Chapters 10 y 11.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013. Chapter 17.
- "**Fragment-Based Drug Discovery, A Practical Approach**", Edward R. Zartler & Michael J. Shapiro Eds., John Wiley & Sons, Chichester, 2008.

4. Activities

The student will have to perform the exercises related to the chapter indicated by the professor on the date indicated in the subject activity schedule. In the seminars, students will solve the proposed exercises and questions and carry out oral presentations of papers, reviews etc. Those students who have difficulties with the exercises of the chapter should contact with the teacher during the tutorial schedule to receive the necessary support.

CHAPTER 5. Hit Compound Optimization. QSAR Studies

1. Introduction

Once studied the principal methods for the discovery of hit compounds, the most important strategies to address and improve the initial activity obtained will be addressed. The most common chemical modifications for replacing pharmacologically unsuitable functional groups, which are based on isosterism, will be then studied. The relevance of the conformational restriction and/or steric hindrance in medical chemistry will be analyzed. Strategies based on the combination of two pharmacological units, as well as the development of prodrugs will be addressed. The bases and the importance for the optimization of compounds activity of quantifying the structure-activity relationships (QSAR) will be finally discussed.

2. Contents

Molecular modifications based on isosteric replacement. Conformational restriction and steric hindrance in medicinal chemistry. Homo and heterodimeric ligands. Prodrugs. Quantification of Structure-Activity Relationship (QSAR).

3. Bibliography

- "**The Practice of Medicinal Chemistry**", Camille Georges Wermuth Ed., 3ª Ed., Elsevier, Amsterdam, 2008. Chapters 15, 17 y 18.
- "**An Introduction to Medicinal Chemistry**", Graham L. Partrick, 5ª Ed., Oxford University Press, Oxford, 2013. Chapter 14.

4. Activities

The student will have to perform the exercises related to the chapter indicated by the professor on the date indicated in the subject activity schedule. In the seminars, students will solve the proposed exercises and questions and carry out oral presentations of papers, reviews etc. Those students who have difficulties with the exercises of the chapter should contact with the teacher during the tutorial schedule to receive the necessary support.

5. - Methodological guidelines and ECTS credits assignment

5.1. ECTS credits assignment

CLASSROOM WORK	HOURS	PERSONAL WORK	HOURS
Lectures in large groups	12	independent, individual or in a group study	29
Interactive class in small groups (Seminars)	7	Oral presentation of papers and exercises proposed by the teacher	21
Interactive class in very reduced groups (Tutorials)	2	Preparation of oral presentations, resolution of proposed exercises. Library work or similar.	4
Total classroom work hours	**21**	**Total personal work hours**	**54**
Total hours			**75**

5.2. Training activities in the classroom

A) *Lectures in large groups* ("L" in the timetable): It will be held 12 sessions of lectures in one group where the theoretical contents of the course will be associated with illustrative examples. It will consist mainly in PowerPoint presentations. Copies of these presentations will be available for the students in advance via the virtual campus of the course. This will allow the students to study ahead the contents of the course and to facilitate the monitoring of explanations.

B) *Interactive class in small groups* (*Seminars*, "S" in the timetable): 7 sessions in small group seminars where students will present the work proposed by the professor followed by a discussion section. Students will have in advance the proposed exercises and papers via the virtual campus of the course. Attendance at these classes is mandatory.

C) *Interactive class in very reduced groups (Tutorials,* "T" in the timetable): Tutoring scheduled by the professor and coordinated by the Centre. It will be 2 hours per student and will involve the supervision of proposed work, clarifying doubts, etc. Attendance at these classes is mandatory.

5.3. Recommendations for the study of the course

- Lecture attendance is more than recommended.

- It is essential to keep the study of course up to date.
- After the reading of a chapter in the reference manual, it is useful to summarize the key points (see summary of important concepts in the Reference Manual).
- Reading the specific biography for each chapter is encouraged for a better understanding of the key concepts.

5.4. Schedule

January 2015	Monday	Tuesday	Wednesday	Thursday	Friday
10-12 h	5	6	7	8	9
10-12 h	12	13	14	15	16
10-12 h	19	20	21	22	23

	Lectures
	Seminars
	Tutorials
	Holidays

6. Evaluation

6.1. Evaluation procedure

The evaluation of this course will be done by means of the continuous assessment and completion of a final exam. Access to the exam will be conditioned on the participation in at least 80% of the mandatory classroom teaching activities (seminars and tutorials). Continuous assessment (N1) will be 40% of the qualification and will consist of two components: interactive class in small groups (seminars) and interactive class in very small groups (tutorials). Seminars and tutorials include the following: resolution of exercises and practical cases (15%), realization of homework and reports (10%), oral presentations [(papers, reviews and practical cases), 10%] and oral questions during the course (5%).

The final exam (N2) will cover all the contents of the course.

The student's score will result of applying the following formula:

Final score = 0.4 x N1 + 0.6 x N2

N1 and N2 are the marks corresponding to the continuous assessment (0-10 scale) and the final exam (0-10 scale), respectively.

The repeaters will have the same system of class attendance than those who study the course for first time.

6.2. Recommendations

The students should review the theoretical concepts introduced in each chapter using the reference manual and the material provided by the professor. Those students, which have significant difficulties when working the proposed activities, should contact with the professor during the tutorials, in order to analyze the problem and to receive the necessary support.

The professor will analyze with those students who do not successfully pass the evaluation, and so wish, their difficulties in learning the course content. Additional material (questions, exercises, tests, etc..) to strengthen the learning of the course might be also provided.