

# Chemistry of Drugs (20346)

**Qualification/course:** Bachelor's Degree in Human Biology

**Year:** 2

**Term:** 3

**ECTS credits:** 6

**Study hours:** 150

**Course languages:** Catalan, Spanish, English

**Teaching staff:** David Andreu (coordinator), Beatriz G. de la Torre, Ricardo Gutiérrez.

## 1. Presentation

Chemistry of Drugs is an obligatory subject in the degree course in Human Biology, with a value of 6 ECTS credits. Taught in the third term of the second year by David Andreu (coordinator), Beatriz G. de la Torre and Ricardo Gutiérrez.

## 2. Competences to be achieved

The goal of the course, as defined in the syllabus, is to provide Human Biology students with a chemical view of pharmaceuticals enabling them to recognize structural features in biomolecules and drugs, and to understand how these relate to relevant biological function.

Skills referred to above involve the following general objectives:

- a) Relating concepts of molecular structure of organic compounds (acquired in Basic Sciences II) with properties such as ionization state, solubility in water/lipids, passage through membranes, etc.
- b) Ability to interpret substituent effects or other modifications on molecular properties of a drug.
- c) Understanding the basic workings and applications of HPLC and gas chromatography; interpreting chromatograms of simple separations.
- d) Understanding the foundations and applications of  $^1\text{H}$ -NMR and mass spectrometry. Ability to interpret, using appropriate tables,  $^1\text{H}$ -NMR spectra of simple (drug) structures. Ability to interpret mass spectra of simple molecules (EI or MALDI-TOF).
- e) Understanding the basic stages in drug design and development processes.
- f) Understanding the main strategies of drug molecular modification, in particular those involving metabolism and pharmacokinetics. Ability to identify and interpret practical cases in drug development.
- g) Becoming acquainted with the main techniques currently available for drug

design using computational methods (2D- and 3D-QSAR, CoMFA, etc.).

h) Interpreting the main features (design, data analysis) of a standard paper in medicinal chemistry.

i) Perfecting experimental skills acquired in Basic Sciences II, particularly in relation to separation techniques, both manual and instrumental.

### **3. Contents**

Course subject matter will be presented through lectures (emphasis on basic concepts), seminars (emphasis on learning by problem-solving), and group presentations (emphasis on biomedical relevance) mostly focusing on:

- Organic chemistry relevant to medicinal chemistry: electronic structure, acid/base equilibria, substituent effects on molecular properties (solubility, hydrophobicity), stereochemistry, etc.
- Analytical techniques (separation, identification) relevant to medicines: HPLC, GC,  $^1\text{H}$ -NMR, mass spectrometry.
- Lead discovery, development and validation.
- Conventional SAR and quantitative (QSAR) approaches to drug design and modification.
- Pharmacokinetic/metabolic aspects of drug design and development.

#### ***Lectures (24 h)***

**1.** Review (I). Covalent bonds, skeleton and functional groups. Lewis structures, arrows for depicting electron pair movement. Resonance.

**2.** Review (II). Solubility and hydrophobicity: relationship with structure and substituent effects. Acid-base chemistry. Hendersson equation. Ionic state of drugs in physiological media.

**3.** Review (III). Inductive and resonance effects and their impact on the acidity of phenols, carboxylic acids, etc.

**4.** Stereochemistry (I). Basic concepts: constitution, conformation, configuration. Conformational equilibria of simple molecules. Projection systems: wedge, zigzag, sawhorse, Newman, Fischer.

**5.** Stereochemistry (II). Chirality. Enantiomers. Configurational notation of chiral centers: the R/S system.

- 6.** Stereochemistry (III). Structures with more than one chiral center. Diastereomers. Monosaccharides as an example. Meso forms.
- 7.** Separation techniques: chromatography, general concepts. HPLC and GC.
- 8.** Mass spectrometry: principles and instrumental aspects.
- 9.** Interpretation of mass spectra of simple drugs.
- 10.** Nuclear magnetic resonance (I). Magnetic properties of nuclei.  $^1\text{H}$ -NMR. Chemical shift.
- 11.** Nuclear magnetic resonance (II). Factors influencing chemical shift. Using tables to estimate  $^1\text{H}$  chemical shifts.
- 12.** Nuclear magnetic resonance (III). Spin-spin  $^1\text{H}$  coupling. Analysis of simple spin systems. Spectra of simple drugs.
- 13.** Introduction to medicinal chemistry (I). Objectives, terminology, relationship with other disciplines. Main types of therapeutic targets. Stages and strategies in drug development. Intellectual property issues.
- 14.** Introduction to medicinal chemistry (II). Strategies for lead identification. High-throughput screening of natural and synthetic compound libraries. The growing role of biologicals in the pharma industry. Generics and biosimilars.
- 15.** Drug-target interactions (I). Types of bonding and other structural aspects in drug-target interactions Chirality in drug-target interactions. Impact of chiral switch in drug development.
- 16.** Drug-target interactions (II). Solubility and distribution: pharmacokinetic implications. Drug-likeness: Lipinski's rule of five. Virtual screening.
- 17.** Structure-activity relationships (I). Structural manipulation toward lead optimization.
- 18.** Structure-activity relationships (II). Disjunctive approaches. Pharmacophore concept.
- 19.** Structure-activity relationships (III). Modulative approaches: ring opening, expansion and contraction; homology, isomerization, vinilogs.
- 20.** Structure-activity relationships (IV). Modulative approaches: bioisosteric replacement. Peptidomimetics. Conjunctive approaches: twin drugs.
- 21.** Structure-activity relationships (V). QSAR methods.
- 22.** Drug metabolism: phase I and II processes. Chemo-, regio- and stereoselectivity in xenobiotic transformations.

**23.** Drug design based on pharmacokinetic criteria (I). Structural manipulation for pharmacokinetic purposes: solubility, permeability, toxicity and metabolic stability. Hard and soft drugs.

**24.** Drug design based on pharmacokinetic criteria (II). Prodrugs and strategies for their design. Other aspects: targeting, synergism, administration and formulation.

### ***Seminars (13 h)***

- 1.** (1 h). Computer tools for molecular representation.
- 2.** (2 h). Problems: structure, bonding, acid-base and other molecular properties.
- 3.** (2 h). Problems: stereochemistry.
- 4.** (2 h). Problems: mass spectrometry.
- 5.** (2 h). Problems:  $^1\text{H}$  NMR.
- 6.** (2 h). Problems: drug development and modification (I).
- 7.** (2 h). Problems: drug development and modification (II).

### ***Group presentations***

Students will give 50-min presentations on topics related to medicinal chemistry proposed by the teaching staff. Each presentation will be prepared and delivered by a group of 5-6 students, as described below.

### ***Practical laboratory sessions (24 hours in total)***

Session 1. HPLC determination of paracetamol in plasma.

Session 2. Determination of paracetamol, acetylsalicylic acid and caffeine in a medicine by liquid chromatography.

Session 3. Separation of a mixture of drugs by liquid-liquid extraction.

Session 4. Spectrophotometric determination of thiocyanate in saliva as an indicator of tobacco consumption.

## 4. Evaluation

### *Methods*

Evaluation will be done by multiple-choice tests (following Faculty criteria), written essay exams, problem solving, group presentations, lab performance and a laboratory log-book.

### *Type and number of evaluations*

1. In problem-based seminars 2-7, students in front of the class will solve pre-assigned problems; this activity will be evaluated.
2. Presentations involve several (usually 2-3) preparatory sessions with the assigned tutor plus the actual public presentation; all these activities will be evaluated.
3. Half-way through the term a formative evaluation will be conducted, including topics covered so far in lecture classes. Students who score  $\geq 5/10$  in this test will add 5% of this score to their final grade.
4. In laboratory practicals, evaluation will include attitude and performance in the laboratory, lab book management, and interpretation of results obtained.
5. End-of-course tests will include ten multiple-choice questions (10% of the total grade) and an "essay test" (55% of the total grade) with several questions, mostly of applied nature, related to the various course topics, including those of group presentations (pre-selected by teaching staff, with full access by students to the presentation file during the exam) and also questions related to laboratory sessions. Evaluation will prioritize the ability to analyze data rather than memorization.

### *Contribution of various types of evaluation to the final grade*

#### *A. End-of-course exams:*

Multiple choice test= 10%

Essay test= 55%

#### *B. In-course continuous evaluation:*

Laboratory practicals= 15%

Problem seminars= 10%

Group presentations= 10%

All evaluations will be on an individual basis, except group presentations, for which the group will be globally scored by the teaching staff on the basis of their preparation and delivery of the presentation.

Additionally, students scoring  $\geq 5/10$  in the formative evaluation test will add 5% of this score to their final grade.

### *Pass criteria*

In order to pass the subject, students must:

- a) Participate in the planned activities. There will be **attendance checks** for problem seminars, group presentations and laboratory practicals.
- b) Turn in laboratory log-books within the specified deadline.
- c) Obtain a  $\geq 5/10$  final grade.

**Please note:** Copying or cheating of any type will cause the student to fail the course.

### *Repeat exams*

Students who have sat for the final exams but failed to obtain a  $\geq 5$  grade can sit for a repeat exam at the end of the academic year (July). These exams will be in essay format (see #5 in "Type and number of evaluations" above) and their score will contribute 65% to the final grade, the other 35% being the grades from laboratory practicals (15%), problem seminars (10%) and group presentations (10%).

Students will be allowed to sit for the repeat exam only if they have previously taken and failed the final exam as required in pass criterion (c) above. If, after this repeat exam, final grade does not meet condition (c), the student will have to take again the course the following academic year.

## **5. Bibliography and teaching resources**

### *5.1. Basic bibliography*

Vollhardt, K. P. C.; Schore, N. E. *Química orgánica*. 5a ed. Barcelona: Ediciones Omega, 2007. ISBN 978-8428214315.

Avendaño, M. C. (coord.). *Introducción a la química farmacéutica*. 2a. ed. Madrid: McGraw-Hill-Interamericana de España, 2001. ISBN 8448603613.

Delgado, A.; Minguillón, C.; Joglar, J. *Introducción a la Química Terapéutica*, 2a. ed. Madrid: Díaz de Santos, 2004. ISBN 84797-86019

Patrick, G.L. *An Introduction to Medicinal Chemistry*, 5<sup>th</sup> edition. Oxford: Oxford University Press, 2013. ISBN 9780199697397.

Skoog, D. A.; West, D. M. *Principles of Instrumental Analysis*. 5a. ed. Belmont, CA: Brooks Cole, 2006. ISBN 9780030012297.

## 5.2. Supplementary bibliography

Raviña, E. *The Evolution of Drug Discovery*. Weinheim: Wiley-VCH, 2011. ISBN 9783527326693

Wermuth, C. G. (ed.). *The Practice of Medicinal Chemistry*. 3a. ed. Amsterdam: Elsevier-Academic Press, 2008. ISBN 978-0123741943.

## 6. Methodology

### *Lectures*

Theoretical contents will be taught in 24 sessions of 1 h each.

### *Seminars*

Seminars are of two types: (i) Seminar 1, where programs for molecular representation (ChemSketch, Rasmol) will be presented, and (ii) seminars 2-7, focused on problem solving. Attendance to all seminars is obligatory. Seminars will be conducted in groups of 10. For seminars (2-7) each student will be assigned a problem that he/she must solve and present individually at the blackboard, as an **evaluable activity**.

### *Students' presentations*

Presentations will be conducted in groups of 6 students, on a topic relating to pharmacological chemistry assigned by the teaching staff and prepared by the group with a lecturer acting as tutor. Each student will have 2-4 tutorial hours (in group format) to prepare the presentation. Presentations are approximately 40-50 min long; **attendance is obligatory**.

### *Laboratory practical sessions*

Practical sessions will be conducted in groups consisting of a quarter of the students on the course. It will be emphasised that students must take a responsible and serious attitude in the laboratory, acting with initiative, independence and a critical spirit, over and above the mere following of an experimental plan. **Attendance is obligatory**.

Students will compile **during laboratory practicals** a log-book where records in sufficiently detailed and understandable form will be entered on

the experimental procedures performed, together with results obtained and conclusions arrived at.

### *Individual study*

Students must dedicate 78 h (non-presential) to study and solving questions related to the content of the course.

## **7. Program of activities**

Included in the official schedule of the course issued by the Faculty.