

70-ORGANIC PHARMACEUTICAL CHEMISTRY III

Aims of the course: This course is concerned with the discovery, design, synthesis and identification of biologically active compounds acting on the central nervous system (CNS), antiepileptics drugs: miscellaneous anticonvulsants, miscellaneous antiparkinson agents, NMDA receptor antagonists for the treatment of Alzheimer's disease, antimigraine agents, agonists/antagonists of Adenosine, Inhibitors of adenylyl-cyclase- Inhibitors of PDEs, Methylphenidate and analogues, Inhibitors of serineproteases, Statines, Agonists/Antagonists of CCK. Quantitative structure-activity relationships (SAR/QSAR). Finally, agents used illegally, such as opioids, cannabinoids and other drugs of addiction, with special pharmaco-sociologic interest, are studied.

Aims are the critical knowledge and thorough examination of synthesis, structure, correlation of structure with drug action, fate of the drugs in the organism, sites of loss, therefore duration of drug action. Aim is also to familiarise the students with relations governing molecules acting on CNS and the central nervous system site of action, as well as the involved neurotransmitters.

Skills: By the end of this course, the students should be able to: Know the synthesis of the important drug molecules used for pathologic conditions concerning CNS and cardiovascular system, the physical and chemical properties of these drugs, the biological properties that give the therapeutic potential to these groups of drugs, the structural changes (i.e. metabolism) and fate of these molecules in the organism, the duration of action, the possibility of biotransformation or biotoxication. Reach conclusions on the relationships between action and structural and physicochemical characteristics and examples are studied of characteristic molecules used illegally as narcotic and addictive agents, from the pharmacochemical point of view.

Teaching methods: Lectures and laboratory work. The material is covered by a textbook, text notes and laboratory notes.

Contents of the course:

1) Eleni A. Rekka

This course analyses synthetic pathways, extraction-isolation, physical, chemical, biological properties, purity and quality control, identification, quantitative determination, molecular mode of action, side effects, fate in the organism - drug metabolism, structure-activity relationships, therapeutic uses, adverse actions and doses of drugs acting on the Central Nervous System, i.e. hypnotics, anxiolytics, neuroleptics (drugs acting against mania and psychoses), antidepressants. Opioids and other centrally acting analgesic and antitussive agents. Opioid antagonists. Introduction to addiction. Agents used in detoxication and addiction therapy. Cannabinoids, psychotoxic and psychedelic drugs.

2) Ioannis Nicolaou

Pharmacochemical approach (as design, synthesis, physicochemical properties, target cell interactions, structure-activity relationships, pharmacochemical interpretation of toxicity, metabolism) of the below classes of drugs: miscellaneous anticonvulsants, miscellaneous antiparkinson agents, NMDA receptor antagonists for the treatment of Alzheimer's disease, antimigraine agents.

3) Dimitra Hadjipavlou-Litina

Stimulants-Analeptics -Agonists/antagonists of Adenosine, Inhibitors of adenylyl-cyclase- Inhibitors of PDEs, Methylphenidate and analogues, Inhibitors of serineproteases, Statines, Agonists/Antagonists of CCK. Quantitative structure activity relationships (SAR/QSAR). Examples of Quantitative structure activity relationshipsdetermination and chemical identifications.

Proposed Literature:

1) Eleni A. Rekka

- A. Korolkovas, "Essentials of Medicinal Chemistry", Wiley International Publications, John Wiley & Sons, 2003.
- J.M. Beale, J. Block, "Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry", Lippincott Williams & Wilkins; 12th ed., 2010

2) Ionnis Nicolaou

- ***Journal of Medicinal Chemistry* (ACS Publications)**
- ***Bioorganic & Medicinal Chemistry Letters* - Elsevier**
- ***Bioorganic & Medicinal Chemistry* (ISSN 0968-0896)**
- ***The Journal of Biological Chemistry***
- ***Chemical Research in Toxicology* (ACS Publications)**
- ***Drug Metabolism and Disposition***

3) D.Hadjipavlou-Litina

- Medicinal Chemistry Principles and Practice, Ed. F.D.King. 1994, The Royal Society of Chemistry, ISBN 0-85186-494-5
- Contemporary Drug Synthesis Li J.J, Johnson D., Sliskovic D., Roth B. Wiley-Interscience, 2004, ISBN 0-471-21480-9
- New Trends in Synthetic Medicinal Chemistry, Ed. F. Gualtieri, Wiley -VCH, Vol. 7, 2000
- Annual Reports in Medicinal Chemistry, Academic Press
- ***Journal of Medicinal Chemistry* (ACS Publications)**
- ***Bioorganic & Medicinal Chemistry Letters* - Elsevier**
- *Bioorganic & Medicinal Chemistry* (ISSN 0968-0896)
- "Practical Pharmaceutical Chemistry part I, II) The Athlone Press 1975
- "Principles of Medicinal Chemistry" W.O. Foye, ed. Lea & Febiger, 1995
- "Remington's Pharmaceutical Sciences", Osol A. ed. Mack Publishing Co., 1980
- « Goodman & Gilman's The Pharmacological Basis of Therapeutics » Goodman a., Hardman J., Limbird L., eds MacMillan Publishing Co 2001
- "Strategies for Organic Drug Synthesis and Design" Lednicer, D., ed. Wiley J. & Sons 2000
- "Essentials of Pharmacology" Theodoridis T. Little, Brown & Company 2nd edition, 1999
- Drug Actions, Basic Principles and Therapeutic Aspects, Mutschler/Devendorf
- Arch.Pharm 317, 183-185, 1984
- Arch Pharm 325, 483-90, 1992.
- Arch Pharm 328, 689-698, 1995
- Intensive Care Med. 18, 449-454, 1992
- Greenblatt et al. (1999) FEBS Letters **463**, p321
- Dvir et al. (2003) JACS **125**, p363
- Bar-On et al. (2002) Biochemistry **41**, p3555.
- Kryeger et al.,(1997) Structure 7,297
- Raves et al. (1997) Nature Structural Biology 4, p57
- National Formulary 2007, National Organization of Drugs

Educational Activities

Lectures, discussion with the students in every lecture, laboratory work and tutorials.

Evaluation process and methods:

Examination of the course can be done either by successful participation in two written mid-term exams (grade ≥ 5 in each mid-term exam) or by a final written examination at the end of the semester. Student eligibility to participate in the mid-term exams is gained by regular attendance of the lectures throughout the semester. The evaluation process is based on questions that the students are asked to answer based on their

knowledge obtained from the lectures as well as on the critical thinking and ability to combine, evaluate and handle the acquired knowledge and information.

The duration of the examination is 4 hours.

The examination at the end of the semester is performed at dates, time and place arranged by the department.

During the laboratory work, students hand over a report of their results and are evaluated. At the end of the laboratory work, there is a written examination on this. Successful termination of the laboratory course permits their participation to the final examination.

To compute the final grade: the grade given by each tutor is taken (E. Rekka = 4.5/ D. Hadjipavlou-Litina = 3.5 /I. Nicolaou = 2.5) and the final grade is calculated by addition of the course exam grade (80%) and the lab exam grade (20%).

Use of TIC / Electronic distribution of the lectures:

Tutors:

1) Eleni A. Rekka, professor

Relevant announcements are presented in the corresponding place of the website of the School of Pharmacy.

2) Ioannis Nicolaou, Lecturer

Lectures, notes, statements etc are presented in the corresponding place of the website of the School of Pharmacy

3) Dimitra Hadjipavlou-Litina, professor

Lectures, notes, statements etc are presented in the corresponding place of the website of the School of Pharmacy

Teaching (Lectures/Laboratory work/ Tutorial)

In general: Lectures, discussion with the students in every lecture, in the classroom, review of basic knowledge and practical work in the laboratory. Supportive teaching and discussions are provided when needed.

Powerpoint presentation is used in the lectures, as well as slides and blackboard.

E. Rekka (*especially*): Lectures, discussion with the students in every lecture, problem solving, homework and answers in the classroom, review of basic knowledge and practical work in the laboratory. Supportive teaching and discussions are provided when needed.

a) Lectures.

Lectures are given 3 hours per week (and additionally) in the lecture room D12 (located in the School of Natural Sciences)

Lecture	Title	Tutors
1	Hypnotics, Ethyl and methyl alcohols	E. Rekka
2-4	Neuroleptics-Phenothiazines, Butyrophenones, Newer	E. Rekka
5-7	Anxiolytics-Benzodiazepins, Newer	E. Rekka
8-10	Antidepressants-Tricyclic, Selective serotonin reuptake inhibitors, Newer	E. Rekka
11-13	Morphinomimetics-Natural, Semisynthetic, Synthetic	E. Rekka
14	Centrally acting antitussives, Opioid antagonists	E. Rekka
15-16	Cannabinoids, Psychotropics	E. Rekka

17	Non-therapeutic use of drugs (opioids, cannabinoids, psychotropics) - Addiction - Drugs used for detoxication	E. Rekka
18-19	Analeptics- synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
20-22	Analeptics-Agonists/antagonists of adenosine synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
23-24	Analeptics-Agonists/antagonists of adenosine - Inhibitors of adenylyl cyclase-synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
25-26	Inhibitors of PDEs- synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
27	Methylphenidate and analogues synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
28	Inhibitors of serinproteases - synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
29	Statins- synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
30-31	Agonist/antagonist of CCK- synthetic strategy and structure activity relationships	D. Hadjipavlou-Litina
32-35	Miscellaneous anticonvulsants	I. Nicolaou
36-38	Miscellaneous antiparkinson agents & NMDA receptor antagonists for the treatment of Alzheimer's disease	I. Nicolaou
39	Antimigraine agents	I. Nicolaou

b) Laboratory work

Students must do laboratory work (4 hours twice per week).

ATTENTION! The students who want to attend the lab have to fill out a participation form before the beginning of the semester at the Laboratory of Pharmaceutical Chemistry. There is an announcement, calling students to fill out the participation forms at the announcement board of the Laboratory of Pharmaceutical Chemistry. During the laboratory work, students report their results and are evaluated. At the end of the laboratory work, there is a written examination on this. Successful termination of the laboratory course permits their participation to the final examination.

Laboratory	Title	Tutor(s)
1-4	Synthesis of benzocaine	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou

5-6	Determination of saccharin sodium	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
7-8	Determination of chlordiazepoxide hydrochloride	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
9	Determination of nicotinamide	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
10	Spectroscopic identification (IR spectroscopy) of benzocaine (labs. 1-4)	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
11	Preparation and titration of standard solutions	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
12	Digestive decomposition of organic compounds (for the determination of nitrogen and chloride)	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou
13	Literature survey	E. Rekka - D.Hadjipavlou- Litina- I. Nicolaou