(Syllabus): ORGANIC PHARMACEUTICAL CHEMISTRY (elective)

Code number:
ΝΠ46

Cycle:
Undergraduate

Semester:
8th semester

Course type

	Background/General knowledge
X	Scientific area (pharmacy)

Credit Units (ECTS):
4
Lectures (hours/week):
2

Tutorial (hours/week):
-
Laboratory work (hours/week):
2

Course coordinator:
Vasilis Demopoulos, Professor

Tutors:
1) Vassilis Demopoulos, Professor
Room 408A & 409B, 4th floor Biology/Pharmacy building.
Collaboration with students: Every day 11-12 am.
Communication: e-mail (vdem@pharm.auth.gr)

2) Eleni Rekka, Professor
Room 409, 4th floor Biology/Pharmacy building.
Collaboration with students: Every day.
Communication: e-mail (rekka@pharm.auth.gr)

3) Ioannis Nicolaou, Assistant Professor
Room 404, 4th floor Biology/Pharmacy building.
Collaboration with students: Every day 12-1 pm.
Communication: e-mail (inikolao@pharm.auth.gr)

Assisting personnel:
Dr. Antony Gavalas, ΕΔΙΠ

Aims of the course:
The course is an expansion and in depth analysis of the required course (code number: ΝΠ-38) of the same semester and its aim is the application of modern aspects of medicinal chemistry in drug design and in the successful confrontation of pathologic conditions using contemporary approaches of medicinal chemistry & chemical biology. Specifically:
- Scaffolds and physicochemical properties of drug-like molecules. Principles of identification, optimization and production of new chemical entities.
- Oxidative stress, antioxidant pharmacotherapy. Oxidative stress and biologic stress in pathologic conditions. Pharmacochemical aspects of biological stress, relations between biological and oxidative stress. Indices of oxidative and biologic stress and their interrelationships. Consequences of oxidative and of biologic stress on health.

Skills:
By the end of this course, the students will have a working knowledge of:
- The three dimensional graphical depiction of compounds using a molecular modeling software.
- The structural energy minimization implementing molecular & quantum mechanism.
- The two dimensional drawing of compounds and the calculation of distribution & partition coefficients.
- The involvement of oxidative stress in pathologic conditions and diseases and the response of the organism to xenobiotics
- The physiologic defensive mechanisms as stress response

Teaching methods:
Lectures and laboratory work. The material is covered by textbook & notes as well as laboratory notes.

Contents of the course:
1) Vassilis Demopoulos
Chemical biology in medicinal chemistry, with focus on:
a) stereo-chemical factors and biological activity (optical isomerism, spatial isomerism, conformational space)
b) physical & chemical properties important in biological activity (lipophilicity, hydrophobicity, ionization, solubility, molecular polar surface area)
c) bioisosterism
d) thermodynamic analysis of ligand-receptor interactions
e) permeability through biological membranes

2) Eleni Rekka
In this course, pharmacochemical aspects of oxidative and biologic stress, their indices and their relationships are analysed. Importance of oxidative and of biologic stress in diseases of the modern society, e.g. Alzheimer's and Parkinson's diseases, development of biologic stress and other pathologic conditions is examined. Xenobiotic toxicity connected to free radical formation, toxic metabolites, antioxidant intervention are presented.

3) Ioannis Nicolaou
Pharmacochemical approach for the management of the lack of selectivity toward tumor cells and low therapeutic index of the antineoplastic agents, via two primary strategies:

a) through the design of targeted anticancer prodrugs for tumor site-specific activation, and
b) through a tumor-targeting drug delivery system which consists of a tumor recognition moiety (as monoclonal antibodies, polyunsaturated fatty acids, folic acid, hyaluronic acid, and oligopeptides) and a cytotoxic warhead connected directly or through a suitable linker to form a conjugate.

Proposed literature:

1) Vassilis Demopoulos

-«Βασικές αρχές σχεδιασμού και ανάπτυξης φαρμάκων» Β. Ι. Δημόπουλος και Α. Τσαντίλη-Κακουλίδου, ISBN: 978-960-603-190-8, 2015. Αθήνα: Σύνδεσμος Ελληνικών Ακαδημαϊκών Βιβλιοθηκών. Διαθέσιμο στο: http://hdl.handle.net/11419/5881. ID **Ευδόξου**: 59303610

- Richard B. Silverman "The Organic Chemistry of Drug Design and Drug Action", Academic Press, 2004, ISBN-10: 0126437327

-Joseph J. Cannon "Pharmacology for Chemists", Oxford University Press, 2007, ISBN-10: 0841239274

- Jonathan M. Goodman "Chemical Applications of Molecular Modelling", The Royal Society of Chemistry, 1998, ISBN: 0854045791

- M. P. Edwards and D. A. Price, "Role of Physicochemical Properties and Ligand Lipophilicity Efficiency in Addressing Drug Safety Risks". *Ann. Rep. Med. Chem.*, 45: 381–391 (2010)

- A. Avdeef, "Physicochemical profiling (solubility, permeability and charge state)", *Curr. Top. Med. Chem.*, 1, 277-351 (2001)

- N. A. Meanwell "Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design", *J. Med. Chem.*, 54, 2529–2591 (2011)

- J. Clayden, S. R. LaPlante et. al. "The Challenge of Atropisomerism in Drug Discovery" *Angew. Chem. Int. Ed.*, 48, 6398 – 6401 (2009)

2) Eleni Rekka

1. E.A. Rekka, P.N. Kourounakis, "Organic Pharmaceutical Chemistry: Topics in Medicinal Chemistry-Drug Design", F. Hatzipantou, Ed., 2010 (ISBN 978-960-98594-3-1) (in Greek) **(Εύδοξος).**
2. R. Rodrigo, "Oxidative Stress and Antioxidants: Their Role in Human Disease", 2009, Nova Science Pub Inc.

3) Ioannis Nicolaou

- Journal **of Medicinal** Chemistry **(ACS Publications)**
- Bioorganic & Medicinal Chemistry Letters **- Elsevier**
- Bioorganic & Medicinal Chemistry **(ISSN 0968-0896)**

Educational activities:

Lectures, discussion with the students in every lecture, problem solving and practical work in the laboratory.

Evaluation process and methods:

- The evaluation of knowledge and skills which have been acquitted by the students from the course work is attested with written examinations (80% of the final grade + 20% of experimental aptitude) which are conducted in a fixed date. The written examinations have duration of 3.5h, and consist of approximately ten (10) composite

questions spherically covering the tough subjects. Grading is proportionally allocated to the tutors.

- 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.
- During the laboratory work, students hand over a report of their results and are evaluated. Successful termination of the laboratory course permits their participation to the final examination.

Use of TIC / Electronic distribution of the lectures:

Lectures, notes, statements etc. are presented in the corresponding place of the website of the School of Pharmacy or at the website: http://users.auth.gr/vdem/.

Teaching

Teaching of this course is accomplished through lectures, special supportive lectures and laboratory work.

A total of 26 lectures (13 weeks x 2 hours) are given in the lecture room Δ12 implementing power point projection and/or overhead projection, as well as with chalk and a blackboard.

α) Lectures:

Lecture	Title	Tutor
1	Molecular size/shape, optical & geometric isomerism and biological activity	V. Demopoulos
2	Atropoisomerism-conformers and biological activity	V. Demopoulos
3	Quantitative relationships stereo-structure & activity, polar surface area of molecules	V. Demopoulos
4	Lipophilicity & determination of coefficients of distribution	V. Demopoulos
5	Determination of coefficients of partition	V. Demopoulos
6	Permeation through biological membranes	V. Demopoulos
7	Biopharmaceutical classification of new chemical entities	V. Demopoulos
8	Ligand-receptor interactions and physicochemical properties	V. Demopoulos
9	Classical and non classical isosterism	V. Demopoulos

10	Bioisosterism	V. Demopoulos
11-14	Design of targeted anticancer prodrugs for tumor site-specific activation	I. Nicolaou
15-16	Tumor-targeting drug delivery system which consists of a tumor recognition moiety (as monoclonal antibodies, polyunsaturated fatty acids, folic acid, hyaluronic acid, and oligopeptides) and a cytotoxic warhead connected directly or through a suitable linker to form a conjugate	I. Nicolaou
17-18	OXIDATIVE STRESS AND XENOBIOTIC TOXICITY: Ethanol, carbon tetrachloride, polyhalogenated hydrocarbons, dipyridyl compounds, iron and other heavy metal ions, clofibrate, paracetamol	E. Rekka
19-20	OXIDATIVE STRESS AND PATHOLOGIC CONDITIONS: Hypercholosterolemia, Angiopathies, Hypertension, Cardiovascular diseases, Diabetes mellitus complications	E. Rekka
21-22	OXIDATIVE STRESS AND PATHOLOGIC CONDITIONS: Inflammation, Rheumatoid arthritis, Drugs used in inflammatory conditions, Autoimmune diseases	E. Rekka
23-24	OXIDATIVE STRESS AND PATHOLOGIC CONDITIONS: Neuronal degeneration and oxidative stress, Defense of the brain against oxidative insult, Interaction of iron in the brain, Senile dementia - Alzheimer's disease, Pathobiochemistry of Alzheimer's disease, Cellular death, Cellular damage in Alzheimer's disease, Possible causes of Alzheimer's disease, Aspects of rational drug design in Alzheimer's disease, Parkinson's disease, Causes of Parkinson's disease	E. Rekka
25-26	BIOLOGICAL STRESS AND RESPONSE TO DRUGS: Homeostasis, Biological stress, Manifestations and determination of biologic stress, effect of benzodiazepines, Stress and response to drugs and other xenobiotics, Biologic and oxidative stress interrelationships.	E. Rekka

Laboratory Work:

Students are notified on February of each year to enroll for laboratory work. Students who neglect to enroll in time will perform the laboratory work next proper semester.

The laboratory work will be performed in groups, because the aim of this work, with students in an advanced semester, is the accomplishment of collective, complete experimental work, where the interest is stimulated, the initiative is stressed, the routine work is avoided, and, mainly, the idea of a constructive application of acquired knowledge, as well as of new methods and techniques is materialized.

Laboratory	Title	Tutor
1-3	3D structural drawing of apomorphine & three chemical derivatives of apomorphine	V. Demopoulos
4-7	Structural energy minimization invoking molecular mechanism & quantum mechanism subrutines	V. Demopoulos
8-9	Listing of results (energies & intramolecular distances)	V. Demopoulos
10-12	2D structural drawing of apomorphine & three chemical derivatives of apomorphine. Calculation of lipophilicity coefficients	V. Demopoulos
13-14	Conformers & Boltzman's distribution. Calculated structural results & reported *in vivo* activity	V. Demopoulos
15-18	Synthesis and identification of paracetamol	E. Rekka
19-22	Induction of hepatotoxicity to rats by the administration of high doses of paracetamol, study of the effect of compounds with different mechanism of action, aiming to the protection of the organism against oxidative insult	E. Rekka
23-26	Determination of the effect of the above treatments, with analysis of indices in blood and liver of the experimental animals.	E. Rekka