NP-38 ORGANIC- AND RADIO-PHARMACEUTICAL CHEMISTRY III

Aims of the course: This course is an introduction to the applications of modern pharmacochemical aspects in drug design and in the successful confrontation of pathologic conditions (incurable, insufficiently cured diseases, toxicity of chemicals), using contemporary pharmacochemical methods. Relations of chemical structure, physicochemical properties and activity are studied. Another aim is the acquisition of satisfactory knowledge of the medicinal chemistry of free radicals, role of oxygen in life, free radical reactions in biological systems, reactive oxygen species and mechanisms of radical attack to lipids, proteins and DNA. Knowledge of physiological defensive mechanisms against free radicals, as well as explanation of oxidative stress are among the aims of this course. Comprehension of the blood-brain barrier, construction, function and physiologic role, in relation to drug action, is another aim.
Furthermore, the course aims at providing basic knowledge on the properties and medical applications of ionizing radiation, as well as the nuclear properties requirements of radionuclides used in radiopharmacy. In a deeper scope, this course covers the pharmaceutical radiochemistry of commonly used radionuclides in radiopharmacy. The design and mechanism of action of common radiopharmaceuticals at the target site is discussed. Finally, the course covers methods of evaluation of the radiochemical purity of radiopharmaceuticals.

Skills: By the end of this course, the students should be able to:
Relate structural features to biologic activity
Comprehend the structure, function and role of blood-brain barrier
Know the phenomenon of oxidative stress, role of free radicals and other active oxygen species in the organism
Comprehend oxidative attack, pharmacochemical confrontation and consequences in health.
The application of radionuclides for diagnosis or treatment based on the type of ionizing radiation emitted, γ, X, β^-, β^+, α.
The basic methods of radiolabeling with radionuclides used in radiopharmaceuticals, ^{99m}Tc, $^{186/188}$Re, $^{123/131}$I, ^{111}In, ^{11}C, ^{18}F.
Quality control methods of technetium radiopharmaceuticals.
Clinical applications of radiopharmaceuticals.

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

Contents of the course: This course presents some modern aspects in the broad field of bioactive molecules (drugs, poisons) and the molecular approach to pathologic conditions, aiming to a rational confrontation of them through drug design. The effect of the chemical characteristic groups on activity and toxicity of drug molecules is studied and an approximation in physicochemical properties/chemical structure/activity relationships is performed. Further topics are: Pharmacochemistry of free radicals. Role of oxygen in aerobic life, free radical reactions in biological systems. Reactive oxygen species. Mechanisms of radical attack on lipids, proteins, DNA. Defence of the body against radical offence, the involved mechanisms. Structure, function of blood brain barrier and drug permeability.

Radioactivity: Radioactive decay, α, β^-, β^+, particle emissions, electron capture, γ ray emission, isomeric transition, internal conversion, Auger electrons. Law of radioactivity, Half-life, Successive decay equations, transient and secular equilibrium. Interaction of radiation with matter: ionization, bremsstrahlung, annihilation, photoelectric effect, Compton scattering, pair production. Radiolysis of water, effect of radiation on macromolecules, DNA strand breaks, oxygen effect. *Radionuclide generator:* Principles of a generator. ^{99}Mo/^{99m}Tc generator. Yield of ^{99m}Tc. Radionuclide, radiochemical and chemical purity of ^{99}Mo/^{99m}Tc generator eluate. *Labeled compounds:* Radionuclide, radiochemical and chemical purity of labeled compounds. Methods of radiochemical yield calculation (radiochromatography). *Radiopharmaceuticals*: general principles, diagnostic and therapeutic

radiopharmaceuticals. Properties of ^{99m}Tc. Chemistry of ^{99m}Tc. Labeling with ^{99m}Tc (Labeling with reduced ^{99m}Tc, Formation of ^{99m}Tc-complexes by ligands exchange, reducing agents). Techentium(V), oxo core, isomerism. Methods of radioiodination of proteins (iodine chloride, iodogen, chloramin-T, enzymatic methods) *Radiopharmaceuticals of ^{99m}Tc and other radionuclides* (preparation, clinical applications, pharmacokinetic data). Sodium pertechnetate, technetium-sulfur colloid, technetium-human albumin macroaggregates, technetium-DTPA, technetium-glucoheptate, technetium-succimer, trivalent and pentavalent, technetium-methylendiphosphonate, technetium-iminodiacetic acid derivatives, technetium-hexamethylene amine oxime, technetium- ethyl cysteinate dimmer, technetium-mercaptoacetyltriglycine, technetium-hexacis(2-methoxy-isobutyl-isonitrile). [^{188}Re]-rhenium-(hydroxiethylidine diphosphonate). [^{111}In]-Indium-tris (oxine). [$^{123/131}$I]-Sodium Iodide, [$^{123/131}$I]-metaiodobenzyl-guanidine. [^{18}F]-2-fluorodeoxyglucose. Thallium-201. Labeling monoclonal antibodies-advantages and disadvantages. Direct labeling of mAbs with radio-iodine and technetium. Red blood cell labeling with technetium and indium.

Proposed literature:

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).
2. R. Rodrigo, "Oxidative Stress and Antioxidants: Their Role in Human Disease", 2009, Nova Science Pub Inc.
3. E. Chiotellis, "Radiopharmaceutical Chemistry" Ed. "Pigasos", 2000 (in Greek).
4. Gopal B. Saha, "Fundamentals of Nuclear Pharmacy", Springer, 5th Ed.2003.

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

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) of 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 3 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.
At the examination of the course, each instructor gives out separate exam forms.
To compute the final grade, the grade given by each tutor is weighted proportionately to the number of hours he/she has taught.
Final grade is calculated by addition of the course exam grade (90%) and the lab exam grade (10%).
Example: Supposing a course, where 60% of the hours are taught by tutor A and 40% by tutor B, the final grade is calculated by the following formula:

$$F.G.= 0.9(a+b) +0.1c,$$

Where, a the grade given by tutor A (in a scale of 0-6), b the grade given by tutor B (in a scale of 0-4), c the lab grade (the average of the lab book grade and the lab exam grade).

Use of TIC / Electronic distribution of the lectures

Lecture	Title	Tutor
1	Rational drug design. The main role of oxygen in aerobic life. Generation of free radicals in biologic systems.	E. Rekka
2-4	Important reactive oxygen species. Partially reduced oxygen, free radicals.	E. Rekka

Powerpoint presentation is used in the lectures (D. Papagiannopoulou) and the pdf files of the classes are available on Blackboard as well as on the website: user.auth.gr/papagd/Radiofarmaka

Teaching: Teaching of this course is accomplished through lectures and laboratory work.

A) **Lectures**. Lectures are given 2 hours per week in the lecture room D12 (located in the School of Natural Sciences)

5-7	Molecular mechanism of free radical attack. Lipid peroxidation. Protein oxidation. DNA oxidation.	E. Rekka
8-9	Effect of chemical characteristic groups on drug action.	E. Rekka
10-11	Relationships between physicochemical properties and drug action.	E. Rekka
12	Blood brain barrier, physiologic significance, pathologic conditions, drug transport.	E. Rekka
13	Review exercises and problem solving.	E. Rekka
14-15	Properties of Radionuclides	D. Papagiannopoulou
16	Diagnostic and Therapeutic radiopharmaceuticals	D. Papagiannopoulou
17	Radiopharmaceutical preparations and quality control	D. Papagiannopoulou
18	Production and nuclear properties of ^{99m}Tc-^{99}Mo/^{99m}Tc generator	D. Papagiannopoulou
19	Chemistry of technetium-preparation of technetium radiopharmaceuticals	D. Papagiannopoulou
20-22	Technetium Radiopharmaceuticals (renal, cerebral, myocardial, hepatobiliary, lung and bone imaging)	D. Papagiannopoulou
23	Iodine Radiopharmaceuticals	D. Papagiannopoulou
24	Cell Labelling	D. Papagiannopoulou
25	Labelling proteins and monoclonal antibodies	D. Papagiannopoulou
26	Cyclotron Radiopharmaceuticals	D. Papagiannopoulou

B) Laboratory work

Students must do laboratory work (2 hours each).

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.

Laboratory	**Title**	**Tutor**
1-8	Synthesis of sulfanilamide.	E. Rekka
9,10	Identification of an unknown compound by IR spectroscopy and melting point determination.	E. Rekka
11,12	Colourimetirc determination of procaine hydrochloride.	E. Rekka

13	Laboratory test	E. Rekka