COURSE OUTLINE FOR "ORGANIC SYNTHESIS OF DRUGS"

1. GENERAL

SCHOOL	NATURAL SCIENCES AND HEALTH SCIENCES		
ACADEMIC UNIT	CHEMISTRY AND MEDICINE		
LEVEL OF STUDIES	POSTGRATUATE (MSc)		
COURSE CODE	OSD 115	**SEMESTER**	FIRST
COURSE TITLE	ORGANIC SYNTHESIS OF DRUGS		

INDEPENDENT TEACHING ACTIVITIES	**WEEKLY TEACHING HOURS**	**CREDITS**
Lectures	4 (for a period of 6 weeks)	5

COURSE TYPE	Special Background (Semi-optional course)
PREREQUISITE COURSES:	There are not prerequisite courses. It is however recommended that students should at least have basic knowledge of Organic Chemistry and in particular Synthetic Organic Chemistry.
LANGUAGE OF INSTRUCTION and EXAMINATIONS:	Greek. The powerpoint material of the course is, however, in English. Teaching and examinations may be performed in English in case foreign students participate in the postgraduate program
IS THE COURSE OFFERED TO ERASMUS STUDENTS	Yes
COURSE WEBSITE (URL)	-

2. LEARNING OUTCOMES

Learning outcomes
At the end of this course student should be able to: • Understand the concept of chirality and its importance in the design and synthesis of drugs • Understand the approaches and the analytical techniques for the determination of enantiomeric and diastereomeric excess (ee/de) • Recognize chiral structural elements of chiral molecules and correlate them to potential chiral sustainable starting materials (amino acids, terpenes, sugars and other natural products • Know the most useful chiral reagents and catalysts which are suitable for basic transformations both in laboratory and industrial scale • Understand the mechanisms of the above and how the stereochemistry of the products is controlled in the transition state • Understand the advantages and the disadvantages of the various strategies of asymmetric synthesis: pools of chiral molecules-starting materials, chiral substrates, chiral reagents, asymmetric catalysis with metal ions/chiral ligands and organocatalysts • Suggest, depending on the case, the synthesis of chiral pharmaceutical molecules through resolution of racemetates, desymmetrization or application of the appropriate strategy of asymmetric synthesis • Recognize cycloaddition reactions and/or metal-mediated reactions in given synthetic schemes • Foresee the product(s) of a given cycloaddition reaction or a reaction mediated by metals when the reactants are provided • Choose appropriate reactants for the synthesis of a given target-molecule using the most

appropriate cycloaddition reaction or metal-mediated reaction

- Know the most important cycloaddition reactions or metal-mediated reactions and to incorporate them in non-familiar synthetic schemes
- Know the most important multicomponent reactions (MCR) and in particular those leading to important scaffolds of pharmaceutical interest
- Foresee the product of a given multicomponent reaction (MCR) when the reacting components are given
- Choose appropriate reactants for the synthesis of a given target-molecule using the most appropriate multicomponent reaction (MCR)
- Know the most important methods for activation of C-H bonds and their application to the formation of new C-C και C-heteroatom bonds
- Recognize reactions for the activation of C-H bonds in given synthetic schemes
- Incorporate reactions for the activation of C-H bonds in non-familiar synthetic schemes
- Recognize the reactions involved in multi-step syntheses of drugs and explain, through the knowledge of their mechanism, their stereochemical outcome
- Describe alternative synthetic pathways to drugs which allow their application in large scale in the Pharmaceutical Industry
- Understand the necessity of changing the synthetic course from industrial to industrial scale for the synthesis of drugs

General Competences

By the end of this course the student will, furthermore, have developed the following skills (abilities):

- Ability to demonstrate knowledge and understanding of the essential facts, concepts, theories and applications related to the Organic Synthesis of Drugs
- Ability to apply this knowledge and understanding to solve problems related to the Organic Synthesis of drugs of non-familiar nature
- Ability to apply this knowledge for understanding syntheses of other types of molecules of biological interest
- Ability to adopt and apply methodology for solving non-familiar problems
- Study skill needed for continuous professional development
- Ability to interact with others in solving problems of synthetic nature

Generally, by the end of this course the student will have developed the following general abilities:
Search for, analysis and synthesis of data and information, with the use of the necessary technology
Adapting to new situations
Decision-making
Working independently
Team work
Criticism and self-criticism
Production of free, creative and inductive thinking
Working in an interdisciplinary environment
Production of new research ideas

3. SYLLABUS

A. Asymmetric Synthesis [12 h]

- Importance of chirality in Nature and in the development of bioactive molecules
- Importance of asymmetric synthesis
- Chiral elements
- Diastereomers and meso-compounds
- Analytical techniques for the determination of the optical purity
- Strategy in asymmetric synthesis
- Classical and kinetic resolution of enantiomers

- Chiral substrates – starting materials (Chiral Pool)
- Chiral reagents
- Chiral auxiliary groups
- Catalytic asymmetric synthesis with chiral organometallic complexes
- Applications to asymmetric reactions of epoxidation, dihydroxylation, aminohydroxylation, hydrogenation of various functional groups, sulfoxidation,
- Catalytic asymmetric synthesis with simple and biphasic organocatalysts,
- Applications to asymmetric reactions of epoxidation, sulfoxidation, reduction of various functional groups, alkylation, conjugate addition, Diels Alder and other cycloadditions, heteroatom introduction (oxidations), Henry/ Aza-Henry/ Mannich/ and aldol reactions,
- Examples from the syntheses of swainsonine, fluoxetine, efavirenz, (-)-frontalin, (-)-podorhizon, Indinavir, esomeprazole, naproxen, sugars, unnatural α-amino acids, β-amino acids, pregabalin and γ-amino acids, duloxetine, propranolol, damascene,metolachlor,
- Factors affecting the choice of strategy in asymmetric synthesis of a chiral drug in industrial scale
- Case-study: Development of the industrial asymmetric synthesis of Aliskiren

B. Topics of contemporary advanced Organic Synthesis with applications to the Pharmaceutical Industry [6 h]

- Cycloaddition reactions in the synthesis of a variety of compounds
- Metal-mediated reactions
- Multicomponent reactions (MCR) in the synthesis of a variety of compounds
- Activation of C-H bonds for C-C and C-heteroatom bond formation

C. Selected case-studies of organic synthesis of approved drugs

Selection from the following [6 h]:

- Darunavir (2nd generation inhibitor of the HIV-1 protease – Treatment of HIV)
- Aliskiren (Renin inhibitor – Treatment of hypertension)
- Sitagliptin (Dipeptyl-peptidase-4 inhibitor – Antidiabetic drug)
- Montelucast (Leucotriene receptor antagonist – Treatment of asthma/allergy)
- Sorafenib (Kinase inhibitor – Treatment of primary kidney cancer)
- MK4965 (Non-nucleoside reverse transcriptase inhibitor - Treatment of HIV-1)
- Tamiflu (Neuraminidase inhibitor – Treatment of influenza)
- Alogliptin [Dipeptidyl-peptidae-4 selective inhibitor 4 (DPP4) – Treatment of diabetes type 2]
- Bazedoxifen [Selecrive regulator of estrogen receptors (SERMs) – Treatment of ostmenopausal osteoporosis]
- Bilastine [Histamine H1 receptor (HRH1) antagonist - Treatment of allergic rhinoconjunctivitis and of urticaria]
- Zucapsaicin (Vanilloid receptor type 1 selective agonist – Treatment of muscle and joints pain)
- Dronedarone (Multiple channels blocker – Antiarrhythmic drug)
- Icotinib [Selective inhibitor of tyrosine kinase of epidermal growth factor (EGFR-TKI) -2nd or 3rd line drug for advanced or metastatic stage of non-small cell lung cancer (NSCLC)]

4. TEACHING and LEARNING METHODS – EVALUATION

DELIVERY	Face to face		
USE OF INFORMATION AND COMMUNICATIONS TECHNOLOGY	Use of ICT (powerpoint) in teaching Use of ICT in the communication with the students		
TEACHING METHODS	***Activity***	***Semester***	

		workload
	Lectures (4 hours / week for 6 weeks)	24
	Final examination	6
	Private study of the course material throughout the lecturing period Preparation of the team work and for the final oral examination	95
	Course total (25 hours total workload for each ECTS credit)	**125**
STUDENT PERFORMANCE EVALUATION	1. Team (groups of two students) work (40% of the final mark) 2. Individual oral examination (60% of the final mark) Greek grading scale: 1 to 10. Minimum passing grade: 5. Grades ≤ 3 correspond to ECTS grade F. Grade 4 corresponds to ECTS grade FX. For the passing grades the following equivalence normally holds with the ECTS passing grades: 5 = E, 6 = D, 7 = C, 8 = B and ≥ 9 = A 3. Teaching and examinations are delivered normally in Greek. Powerpoint slides are, however, in English. Instruction and examination may be given in English in case foreign students attend the course.	

5. ATTACHED BIBLIOGRAPHY

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2. Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, and Y. Zhang, 'Transition metal-catalyzed C-H bond functionalizations by the use of diverse directing groups', *Organic Chemistry Frontiers,* 2015, *2(9)*, 1107-1295 and references cited therein.
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Chemical Reviews, 2012, *112*, 3083-3135 and references cited therein.
14. A. Dömling, W. Wang, and K. Wang, 'Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry', *Chemical Reviews*, 2006, *106*, 17-89 and references cited therein.
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