BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE, Pilani
Pilani Campus
AUGS/ AGSR Division

SECOND SEMESTER 2020-21
COURSE HANDOUT

Date: 15.01.2021

In addition to part I (General Handout for all courses appended to the Time table) this portion gives further specific details regarding the course.

Course No : **PHA F416**
Course Title : **Chemistry of Synthetic Drugs**
Instructor-in-Charge : **Dr. Vaibhav A. Dixit**
Instructor(s) : **Dr. Vaibhav A. Dixit**
Tutorial/Practical Instructors: Dr. Vaibhav A. Dixit

1. Course Description:

Study of the physicochemical and biological properties of drugs and drug-likeness concepts and rules. Introduction to Green Chemistry and Toxicology Principles. Historical and modern methods of drug synthesis; mechanism of some heterocyclic drug synthesis; study of five and six-membered heterocyclic compound synthesis. Classification of C-C bond forming reactions and use in drug synthesis. Named reactions will be discussed in brief when appropriate.

2. Scope and Objective of the Course:

This course is designed to introduce important chemical and pharmaceutical concepts, and methodologies used in the design, synthesis, and development of drugs. The course is divided into four main sections: A) Physicochemical, biological and drug-like properties of molecules. B) Organic chemistry reactions used for drug synthesis. C) Classical methods of drug synthesis based on the chemical classification of drugs and D) Modern drug synthesis methodologies based on different carbon-carbon bond forming reaction types e.g. coupling reactions. Design principles, reaction mechanisms, role of catalysts, and solvents will be explained when appropriate. Green chemistry principles and the need for the development of environmentally friendly processes will be discussed. Representative examples of marketed drugs will be covered throughout the course. Students will be encouraged to solve problems in each unit and design their own synthetic methodologies for selected drugs. Case studies will be discussed when appropriate.

Prerequisite includes a basic knowledge of IUPAC nomenclature, organic compound classification, elementary organic reactions e.g. substitution (SN1 and SN2), elimination (E1 and E2), condensation, oxidations and reductions. Concepts like acids-bases, pH, pKa, nucleophile/electrophile, enzyme kinetics (Km, Vmax, Ki). Prerequisite courses are PHA F241, PHA F242.

Objectives of the course: After completion of this course the students are expected to:

1. List chemical, biological, and pharmacological properties of drugs and “drug-like” compounds.
2. Perform basic calculations related to like pH, pKa, log P/D, PK-PD properties, Ligand efficiency and toxicity metrics. Attempt to identify and prioritize drug-like compounds.
3. Recognize, classify and compare the reactions employed in drug synthesis.
4. List and illustrate basic principles of green chemistry and toxicology.

3. Text Books:

- Lednicer, Daniel & Lester A. Mitscher The Org. Chem. Of Drug Synthesis Wiley, Vol 1-6 , 1999.

4. Reference Books:

Synthetic Methods in Drug Discovery, Volume 1 and 2" Edited by David C. Blakemore, Paul M. Doyle and Yvette M. Fobian. RSC, Cambridge 2016. Vol. 1: 455 pp, ISBN 978-1-849-73803-3 and Vol. 2: 517 pp., ISBN 978-1-782-62786-9.

"Foye's Principles of Medicinal Chemistry" by Thomas L. Lemke, David A. Williams, Victoria F. Roche, S. William Zito, 7th Edition, 2013, Wolters Kluwer Health/Lippincott Williams & Wilkins. ISBN: 1609133455

Additional references are provided in the "Reference" column of the Course Plan table below. These must be consulted (read) by the students in the same week the topic is taught, and discussed in lectures.

5. Course Plan:

Module No.	**Lecture Session**		**Reference**	**Learning outcomes**
Introduction	1	Scope, objective, prerequisite and expectations for successful course completion.	Topics covered in PHA F241	Introduction to the course.
A) Physicochemical, and biological properties of drugs and drug-likeness measures and indices.	2-3	Chemical and druggable space. Molecular weight, acid-base properties, concept of pH, pKa, logP, and logD,	References in PHA F241	Physicochemical properties of organic compounds and drugs.
	4-7	Modulators of biochemical pathways and enzymatic reactions examples for agonist, antagonists, partial agonist, substrate, and inhibitor. Pharmacokinetic properties e.g. bioavailability, protein binding, Cmax, half-life, Vd, ADME(T).	Foye's Principles of Medicinal Chemistry and SwissADME paper and software.	Biological properties of drugs.
	8-10	Pharmacodynamics (PD) properties like IC50, Ki, Lipinski's rule of five (Ro5), Ro3, Ro2, LD50, on target and off target drug binding, Therapeutic index (TI), Drug Toxicity Index (DTI), LEI and LLE.	Foye's Ref book, Tox. Res. 2018, and J. Med. Chem., 2018, 61 (15), pp 6401–6420.	Concepts of drug-likeness, efficacy, ligand efficiency, therapeutic and Drug toxicity indices.
Quiz 1	**11**	**On section A**		
B) Organic chemistry reactions used for drug synthesis.	12-14	What is green chemistry and toxicology? Why it is required? 12-principles of green chemistry.	ACS website on green chemistry.	Green Chemistry and Green Toxicology principles.
	15-20	Reactions used by drug discovery teams in the 1980s vs 2010s. Overall frequency of usage and frequency in "production step". Suzuki–Miyaura, SNAr, Grignard, Horner–Wadsworth–Emmons, Wittig, alkylation, halogenation and reactions. "Click" and "cross-metathesis" chemistry.	J. Med. Chem., 2016, 59 (10), pp 4443–4458 and Organic Chemistry by Clayden, Greeves and Warren, Oxford Univ.	A historical and chemical classification of organic chemistry reactions used for drug synthesis.

			Press., and web animations.	
Quiz 2	21	Green chemistry and reaction quiz		
C) Classical methods of drug synthesis	22-25	Furans (Ranitidine), Pyrrole (Tolmetine), Thiophene (Duloxetine) and Imidazole (Metronidazole).	Text book and literature.	Drugs based on Five-Membered heterocycles.
	26-29	Pyridines (Chlorphenamine), Dihydropyidines (felodipine), Piperidine (Haloperidol), Triketo-Pyrimidines (Barbiturates), Pyrazines (Pyrazinamide).	Text book and literature.	Drugs based on Six-membered heterocycles.
	30-33	Indole (Sumatriptan), Benzimidazole (Thiabendazole), Quinolines (Chloroquine), Isoquinolines (Roxadustat),	Text book and literature.	Five and Six membered heterocycles fused to a benzene ring.
Quiz 3	34	Heterocyclic reaction quiz		
D) Modern drug synthesis methodologies	35	Importance of C-C bond forming reactions in natural product biosynthesis and drug synthesis. C-H activation and BDE. Matrix of C-C bond types (hybridization types) e.g. sp3-sp3, sp2-sp3.	Reference book, Chem. Rev., 2017, 117 (13), pp 8622–8648 and lecture notes.	Classification of C-C bond forming reactions.
	36-37	Aldol, Claisen, Knoevenagel and condensations. Cross-Couplings reactions and general mechanism. E.g. Alkyl-Alkyl Suzuki.		SP3-SP3 C-C bond forming reactions.
	38-39	Transition metal catalyzed cross coupling reactions, Pd, Cu, and Fe with at least one example each.		SP3-SP2, SP3-SP, SP2-SP and SP-SP C-C bond forming reactions.
Quiz 4	40	Section A, B, C, and D		
Course Review and discussion	41			

6. Evaluation Scheme:

Component		**Duration**	**Weightage (%)**	**Date & Time**	**Nature of component (Close Book/ Open Book)**
Mid term		90 min.	30	Date will be announced by AUGSD-AGSRD	Closed book
Continuous Assessment	Quizzes	30 min.	25	Will be announced in lectures.	Closed book/Open book
	Assignments	Expected submission deadline: within 1 week	10 /# of weeks taken for submission	Will be announced in lectures.	NA
Comprehensive exam		2 hr.	35	Date will be announced by AUGSD-AGSRD	Closed book/Open book

Students should note the following important points.

1) Students are strongly advised to prepare their own class notes using relevant information from lectures, text, reference books, and research/review articles given above. These notes are to be prepared/written in separate, dedicated notebook for this course and notebooks containing notes from other courses will not be allowed during closed book exam/quizzes. These handwritten notes and prescribed text would only be allowed for consultation during exams and will be used for assessments of open book components. Photocopies of any material (including research/review articles), written or printed will not be permitted. Stapled sheets, loose sheets of information written or printed, photocopies of slides used for discussion in class will not be allowed.
2) Slides, web-resources, educational/informative videos, multimedia resources and/or software/databases displayed during lectures provide key information for which additional supportive information is expected to be collected from these and aforementioned sources. The slides and selected material/information will not be shared and hence students are requested/advised to make their own notes during class hour. Recent developments in the area/topic will be discussed in class based on their significance to chemistry, biochemistry, synthesis and pharmacology of the drugs, besides others, and may differ from the information in text, reference material and hence students are expected to take note of such key discussions during lectures. Such discussions held in class will be considered as primary source of information in assessments.
3) Quiz(zes) may/will be conducted as a part of evaluation component, at random, during contact hours including lectures, tutorial hours, as convenient, with/without prior intimation and hence it is expected that the students come prepared to every class on topics covered in earlier lectures. Students are also requested to refresh their knowledge in basic organic reactions, chemical and biochemical concepts, and in topics and concepts covered in the prerequisite courses.
4) Mid-Sem. Grading would be done once at least 30-40 % evaluation components are completed.

5) For all evaluation components, information given during classroom instruction, aforementioned text books and reference books in the same order, will be considered as correct. Students are advised to follow the text, reference material as given in hand-out. All evaluation components are equally important, irrespective of weightage. Hence, students failing to attend scheduled classes, or absenting themselves in one or many of the evaluation components, may become ineligible for obtaining a valid grade at the end of the semester. Attendance in lectures, timely submission of assignments, and quizzes are all equally important as they are all integral components of learning, irrespective of weightage and may be taken into consideration, during grading.
*Hence, students are strongly advised to keep away from absenting themselves from all aforementioned contact sessions. Clearing the course would require adequate performance in written quizzes**, tests**, and examinations**, separately (i.e. earning low marks in evaluation components, aforementioned**, would not suffice, to clear the course).*
Any other adaptive changes in the handout, will be announced in class, if any.
Reading Assignments: Students are advised to read, collect additional information on the above mentioned topics as per given schedule.

7. Chamber Consultation Hour:

Students are advised to attend the majority of the classes (>95 %), read study material, given literature, textbooks and reference books on all topics within a week of the topic being covered in the lectures. They are also encouraged to ask clarification on major queries on the subject matter within the lecture hours and minor (non-urgent) queries can be reserved for consultation hours. Consultation hours will be announced in the lectures on weekly/fortnightly basis.

8. Notices:

Notices concerning this course will be displayed on Department of Pharmacy Notice Board. Students are advices to check notice board (and Nalanda account/BITS email) regularly.

9. Make-up Policy:

Generally make-up will be considered only for regular students (90% attendance) under very rare circumstances based on the **genuineness of the case** assessed on a case-to-case basis. No makeup will be granted for quizzes and all would be considered for evaluation.

10. Note (if any):

Instructor-in-charge
Course No. PHA F416