I. SUMMARY

Heterocyclic compounds are highly important building blocks for pharmaceutical substances. The top worldwide best-selling drugs contain an aromatic heterocyclic ring in their structure. Developing skills in the synthesis and structural modification of aromatic heterocycles is of utmost importance in an organic synthesis / medicinal chemistry career. In each module, following a flipped-classroom approach, selected examples of best-selling heterocyclic drugs will be used to show the essentials of the synthesis of heterocycles and their most relevant reactivity. A brief discussion of their therapeutical mode of action will also be included.

II. OBJECTIVES

By the end of the course, the student must be able to understand the current methods used for the synthesis of heterocyclic drugs and must be able to design the synthesis of target molecules.

III. TABLE OF CONTENTS

Module	Description	Time (h)
1	**Atorvastatin** Synthetic methods: Paal-Knorr synthesis, Robinson-Gabriel synthesis, Feist-Benary synthesis, Hantzsch synthesis of pyrroles, Huisgen synthesis of pyrroles. Reactivity concepts: Functionalization of the imine-type nitrogen, heterocyclic carbenes and the Stetter reaction, [3+2]-cycloaddition reactions and click chemistry.	2
2	**Nifedipine, Amlodipine, Moxifloxazin** Synthetic methods: Hantzsch pyridine synthesis, Krönke reaction, Bohlmann-Rahtz pyridine synthesis, synthesis of pyrilium salts, Grohe – Heitzer synthesis. Reactivity concepts: Structure of pyridones and pyrones, S_NAr in benzenes, hydrogenation of heterocycles.	1
3	**Celecoxib, Leflunomide, Risperidone, Allopurinol** Synthetic methods: Knorr synthesis, Claisen synthesis. Reactivity concepts: S_NAr in heterocyles.	1
4	**Trimethoprim, Cefdinir, Risperidone** Synthetic methods: Pinner synthesis, Hantzsch synthesis of thiazoles, Blümlein-Lewi synthesis. Reactivity concepts: The “OH” group as leaving group in S_NAr, hydrodehalogenation reactions	1
5	**Methotrexate** Synthetic methods: Gabriel-Isay synthesis. Reactivity concepts: Reactions of azines with electrophiles, functionalization of N-oxides, Bakke nitration.	1
6	**Clopidrogel, Tadalafil** Synthetic methods: Fiesselmann synthesis, Kenner synthesis, Bischler-Napieralski, Pictet-Gams and Pictet-Spengler syntheses, diastereoselective Pictet-Spengler synthesis. Reactivity concepts: S_EAr on π-excessive compounds.	1

7	**Sumatriptan** Synthetic methods: Fischer indole synthesis. Reactivity concepts: Japp-Klingemann reaction, Buchwald synthesis of arylhydrazones, decarboxylation reactions.	1
8	**Clopidrogel, Etoricoxib** Reactivity concepts: Metalation of heterocycles, transition-metal-catalyzed C-C couplings	1
9	**Exam**	1
TOTAL		10

IV. GRADING

- Summary of a paper chosen by the student from the primary literature (Angewandte Chemie, Journal of the American Chemical Society, Organic Letters, Journal of Organic Chemistry, Journal of Medinal Chemistry, ACS Medicinal Chemisty Letters), 60%.
- Written exam, 40%.