CHEM 4580 Winter 2020
Natural Products Chemistry and Biosynthesis

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Required Text:

Medicinal Natural Products: A biosynthetic approach 3rd Edition by Paul M. Dewick, John Wiley & Sons, 2009

Available: University of Manitoba Bookstore (order desk) or on-line.

This will be the primary text for the course and will form the basis for most of the lecture material.

Strongly Recommended Reading:

Natural Product Biosynthesis: Chemical Logic and Enzymatic Machinery by C.T. Walsh and Y. Tang RSC Press 2017. Available: Online from RSC

The Organic Chemistry of Enzyme Catalyzed Reactions Revised Edition by Richard B. Silverman, Academic Press 2002

Available: University of Manitoba Library.

Suggested Reading:

The Organic Chemistry of Drug Design and Drug Action 2nd Edition by Richard B. Silverman Elsevier Academic Press, 2004

Available: University of Manitoba Library

This book provides an excellent resource for anyone that expects to face a job interview in a biotech or pharmaceutical company. There is an overview of some of the strategy involved in developing a drug for market.

Additional Resources:

Comprehensive Natural Products Chemistry

Editors-in-Chief: Lew Mander and Hung-Wen (Ben) Liu.

Available on-line through library:

http://www.sciencedirect.com.proxy2.lib.umanitoba.ca/science/referenceworks/9780080453828

Chemical Aspects of Biosynthesis by John Mann Oxford University Press 1994

Available: From OUP (£11) or Amazon ($25CDN)

Murder Magic and Medicine by John Mann Oxford University Press 1992

Available: University of Manitoba Library

An entertaining overview of the use of natural products for the stated purposes throughout history and in modern times.

Journals: A number of journals including *Natural Products Reports*, *Journal of Natural Products* and *Natural Product Communications* are excellent resources for this course. NPR provides comprehensive reviews of recent developments in Natural Products Chemistry. *NPC* is a good source for recent discoveries of new natural products.

Course Organization:

Class Time:

Class will meet every Tuesday at 2:30 pm for ~ 2.5 - 3 hours in Biological Sciences Building 401

Class Work:	
PROBLEM SETS:	10 points
TERM PROJECT:	20 points
MID-TERM:	20 points
FINAL EXAM:	50 points
TOTAL:	100 points

Problem Sets:

Will be assigned throughout the term and will be designed to further develop the concepts presented in class.

Mid-Term Exam:

The mid-term exam for this class is scheduled for **Tuesday March 3rd, 2020** during class time.

The format of the mid-term will be written-answer, problem-solving questions based on the material covered up to and including the previous lecture and will be 2 hours in duration.

Term Project:

The term project for this course will consist of a literature-based research proposal on a natural product of your choice. A more detailed description of the expectations for the project will be made available in the first few days of class. In brief, the term project will be composed of a research proposal to investigate the biosynthesis of a newly discovered natural product. There will be a *brief* **written paper** where the planned experiments are described.

The due date for the term project is **Tuesday March 31st, 2020**.

Final Exam:

The date for the final exam is will be finalized after the exam schedule is released by the registrar's office.

The format for the final exam will be written answer, problem solving questions based on the cumulative knowledge of the class.

Course Outline:

Overview:

This class is designed to serve as a comprehensive overview of secondary metabolism and the origin of small molecule natural products from sources such as plants, fungi and bacteria. Emphasis in this course will be on the organic chemistry behind the various molecular transformations that occur during the biosynthesis of each important class of molecule. A mechanistic approach will be used to understand the chemical basis of each transformation. Although there is no specific course prerequisite for this class a strong mechanistic background in organic chemistry will be assumed. While previous biochemistry will be an asset, the basic biochemistry needed to complete the course will be thoroughly covered, and a previous biochemistry course is not required. Although descriptive chemistry will be used to place biological relevance of the various natural products in context it will not form a major part of the formal instruction of the class.

By the conclusion of the course a student will be familiar with the biosynthetic origins of the major classes of secondary metabolites and the biological relevance of each. A student that completes this class will be able to examine a natural product not previously encountered and be able to propose a biosynthetic origin for that molecule. In addition, a student that completes this course will have the skills necessary to propose experiments that would confirm the above proposal.

Section 1. An Introduction to Secondary Metabolism (*ca. 2 hours*)

An overview of the basic concepts of secondary metabolism will be presented, including a brief history of some of the major developments in our understanding of the production of small molecules in Nature. The role of secondary metabolites in Nature will also be examined from a chemical ecology viewpoint.

Included will be a description of the basic biochemical transformations that are necessary for an understanding of secondary metabolism. The building blocks used in secondary metabolism will be described and will be related to fundamental transformations in organic chemistry. The various enzymes and cofactors employed for these reactions will be related to the organic transformations that they carry out. Emphasis will be placed on understanding the organic mechanism that each enzyme carries out. Little emphasis will be placed on the sequence or structure of the enzyme itself.

Section 2. Fatty Acids and Polyketides (*ca. 6 hours*)

The biosynthesis of the fatty acids will be outlined and a description of the enzymes responsible for their formation will be given. The biological relevance of fatty acids and their related metabolites (such as the prostaglandins and leukotrienes) will be described. This information will serve as the basis for a description of the polyketide (acetate derived) natural products.

Section 3. The Terpenes (*ca. 6 hours*)

The biosynthesis of di-, tri-, and tetra-terpenes as well as similar molecules will be described. A more detailed description of the biosynthesis of the steroids will be given and the biological relevance of the steroids such as testosterone and cholesterol will be emphasized in this section. A comparison of mevalonate and non-mevalonate biosynthetic pathway that leads to the terpenes will be discussed in detail. An examination of the skeletal rearrangements that are common in trpenoid biosynthesis will also be covered.

Section 4. Shikimic Acid Derived Metabolites (*ca. 4 hours*)

Aromatic amino acids and other shikimic-derived metabolites will be detailed in this section. In particular the biosynthesis of phenylalanine, tyrosine and tryptophan will be covered in detail. In addition, the biosynthesis of other metabolites such as lignans and coumarins will be covered in this section.

Section 5. Alkaloids (*ca. 4 hours*)

Nitrogen containing natural products such as morphine, nicotine and curare will be covered in this section. Emphasis will be placed on the biotransformations that the parent amino acid undergoes on the way to a more complex metabolite. Molecules that are derived from a mixture of more than one type of pathway, such as strychnine and ergotamine will be discussed as well.

Section 6. Non-ribosomal Peptides (*ca. 2 hours*)

Amino acid derived metabolites such as the clinically important vancomycin will be covered in this section of class. Included will be the biosynthesis of the penicillins and related β-lactam antibiotics as well as a description of some of the biotransformation experiments that have been conducted. We will be able to examine some similarities between the biosynthesis of the non-ribosomal peptides and polyketides.

Section 7. Current developments and future directions (*ca. 2 hours time permitting*)

This will serve as a review period where we can take a look at some of the current ‘hot areas’ in the field of natural products chemistry. We will look at the recent developments in the area such as new techniques for linking natural products to the genes that code for their biosynthesis. In addition other potential applications, such as altering the biosynthetic pathways will be examined. Other areas, such as the application of enzymes to organic synthesis, or the use of whole-cell reactions in materials chemistry will be briefly examined. An introduction to chemical ecology will also provide insights into the utility of further research into natural systems.