Chemistry 4DD3 – Mechanistic Biological Chemistry (Updated Feb. 08/2006)

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Office Hours: Tuesday and Wednesday 10:30am-11:30.
Lectures/tutorial: Tuesday, Wednesday and Friday at 9:30am BSB 145.

Outline: The course will cover a description of the basic building blocks and reaction mechanisms involved in the biosynthesis of naturally occurring compounds. The goal of the course is to provide students with a sound understanding of the structure and origin of these natural products and to introduce specific molecules that are of current interest in the field of chemical biology. We will also discuss the biological target and mechanism of action of these compounds as well as details of structure-determination and chemical synthesis where appropriate.

Prerequisites: CHEM 3D03 (Org. Chem) or 3F03 (Bio-organic).

Text:
There is no official course textbook. General introductory material can be found in the following two sources. More specialized books will be referenced in class however most of the latter material will be taken from the last few years of the chemical-biological literature.
Natural Products: the Secondary Metabolites, James R. Hanson, RSC (2003).
Chemical Aspects of Biosynthesis, John Mann, Oxford (1994).
Organic Chemistry, Clayden, Greeves, Warren, Wothers, Oxford (2001), Chapter 51.

Assessment

Assignments (2)	10%
Mid Term	25%
Literature research	25%
Presentation	10%
Final exam	30%

Assignments: A series of questions designed to apply the concepts presented in class. In order to insure that assignments are graded prior to tests and that answers to assignments can be posted quickly, LATE ASSIGNMENTS WILL ***NOT*** BE ACCEPTED.

	To be Handed In
Assignment 1	Wed. Oct. 27th 5:00pm
Assignment 2	Fri. Nov. 26th 5:00pm

Mid-Term: Fifty minutes duration to be held on Tuesday, Nov. 2nd during the regularly scheduled class. Students who miss a mid-term test for a valid reason AND who have

the Dean's permission (see below) will have their final exam increased by the value of the term test.

Missed Assignments and Tests: Failure to hand in an assignment or write a term test will result in a **zero** grade, unless a valid reason has been filed with and accepted by the Associate Dean's office. **It is the student's responsibility to ensure that medical slips, etc. are filed with the Dean**. The instructor will not make any exemption decisions under any circumstances.

Literature Research and Presentation: Students will select (or be assigned) a natural product from the recent literature that exhibits valuable biological properties. The review will cover the occurrence/isolation of the natural product, its known or postulated biosynthesis, a discussion on its mechanism of action at the molecular level and a discussion of its chemical synthesis. The format will become clear as the course progresses. The last two weeks of the course will involve an oral presentation (15 minutes) of this study.

Final: Scheduled examination to take place in December. A passing grade must be attained in the final examination to pass the course.

MORE DETAILS: CHEM 4DD3

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1) The building blocks and main reaction pathways of secondary metabolism.
   Systematic description of these building blocks (C1 to C6 building blocks).
   Reaction pathways (Walsh categories; redox, group transfer, C-C bond forming, isomerization/rearrangement reactions).

2) Glycolysis, citric acid cycle and redox co-factor cycling.
   Basically demonstrates where the building blocks come from and provides an appreciation of thermodynamics and the role of ATP in biochemistry.

3) Polyketides and lignans

4) Fatty acid derivatives

5) Mevalonate pathway leading to Terpenoids and Steroids.

6) Shikimate pathway

7) Ornithine and Lysine derived alkaloids

8) Phe and Tyr derived alkaloids, lignans in passing

9) Tryptophan derived alkaloids

10) Miscellaneous alkaloids

What can students do at the end of the course?

Identify the structural units in a given natural product and their origin. Propose a biosynthetic pathway for the biosynthesis of the target. This will develop an awareness of natural biosynthetic processes and what types of enzyme catalyzed reactions are involved.

Have a comprehensive understanding of major compounds of current interest in chemical-biology such as taxol, artemisinin, doxorubicin, pancratistatin, tamiflu etc. Have a good overview of the general uses of such natural products and derivatives as leads for anticancer, antibacterial, antiviral, antiparasitic and specific enzyme inhibitory properties (HMG-CoA reductase, COX, etc).

Two underlying developments:

Develop and gain appreciation for a new way of considering retrosynthetic analysis in the purely chemical case. Knowledge of the likely biosynthetic origin of a natural product often provides valuable clues in terms of “retro-biosynthetic” thinking and may allow the development of a short “biomimetic” synthesis of the target. Several recent examples described in the course will highlight the importance of this tactic.

A more general perception that will develop is the theme that Natural selection is significantly manifest at the secondary metabolic level. Changes (mutations) in DNA affect RNA and hence protein structure and function. The secondary metabolic reactions that these proteins catalyze will, on occasion, produce a new metabolite which bestows that organism with some evolutionary advantage. Organisms have thus evolved pathways to make particular compounds that give them a certain advantage. Hence we should not be surprised to find potent antibacterial, antifungal, cytostatic antiviral etc, etc, compounds in Nature. The course will also emphasize Nature’s use of “combination therapy” in battling pathogens and some valuable take home lessons in medicinal chemistry.