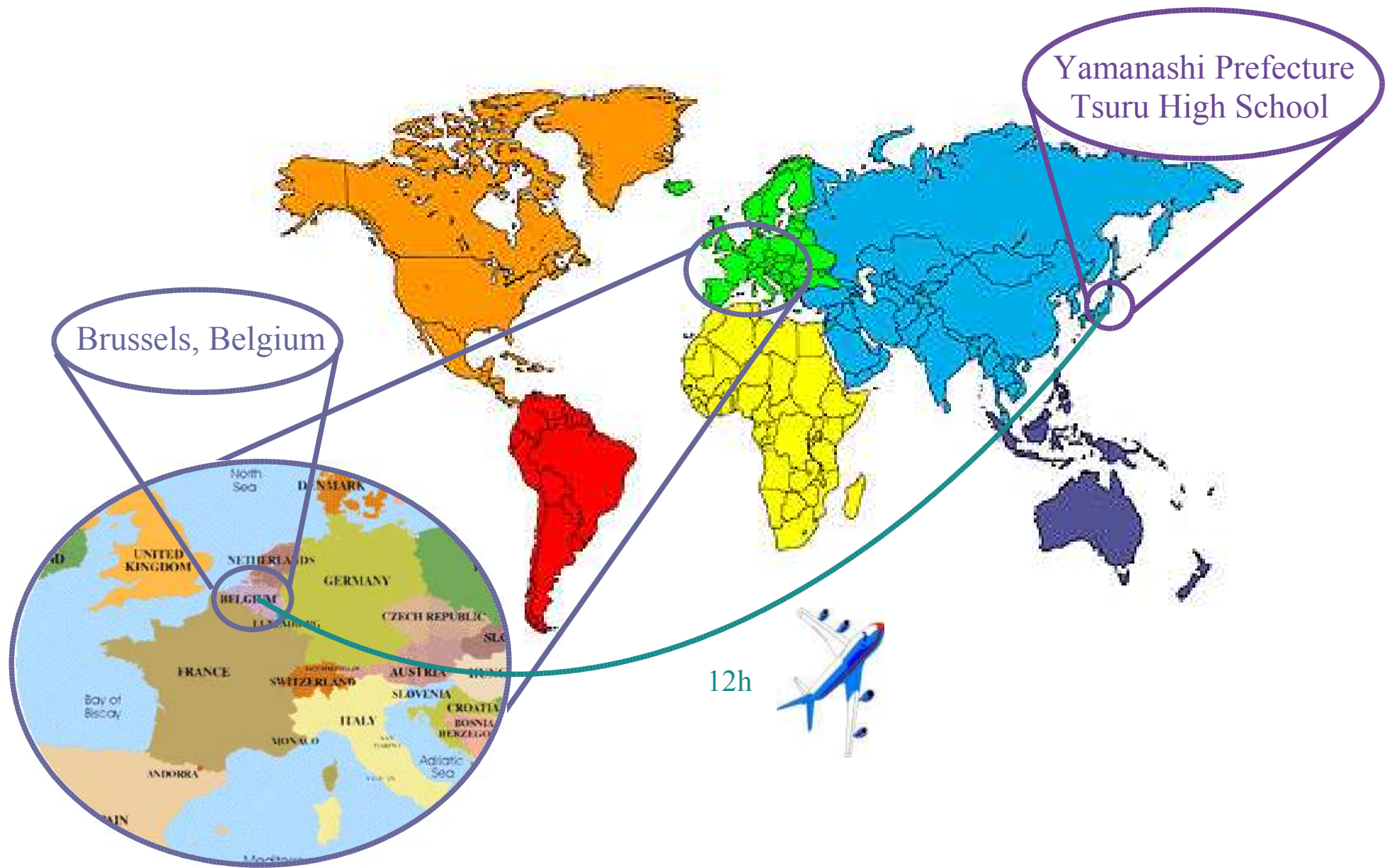
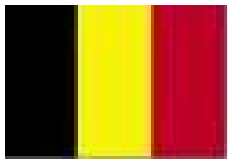


Science Dialogue
Yamanashi Prefecture Tsuru High School
2005/10/25

Introduction to Natural Products and Medicinal Chemistry

David LEMIN, PhD.
JSPS Post-Doctoral Fellow
Pharmaceutical Sciences Faculty
Chiba University





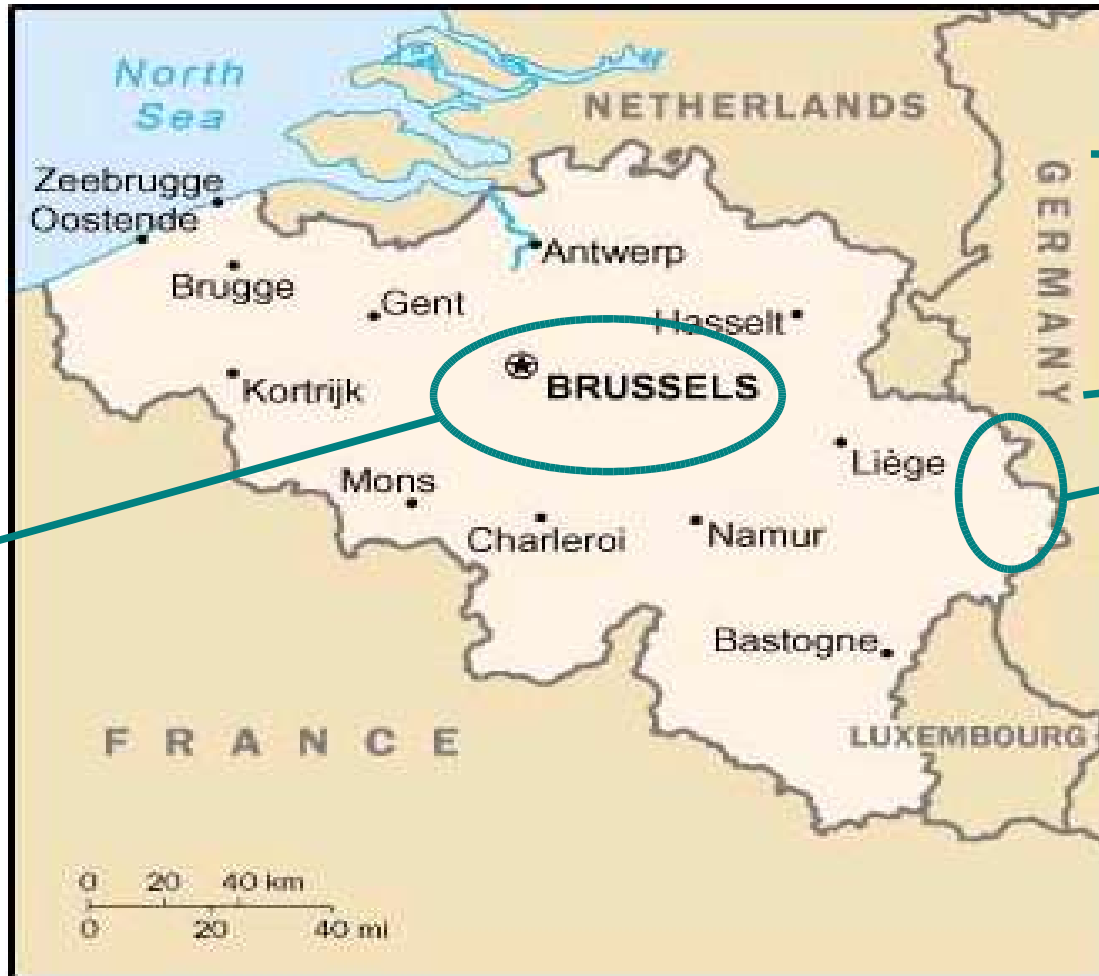
3 Regions : Flandria, Wallonia and Brussels.

3 Languages : French, Dutch and German.

Population : 10.3 Million (less than Tokyo)

Area : 30,528 sq km (about Kyushu)

Seat of both European Union (EU) and NATO.



Brussels,
bilingual.

Flandria,
Dutch speaking.

German speaking.

Wallonia,
French speaking.



Atomium, Brussels.

Grand-Place,
Brussels.



EU Parlement,
Brussels.

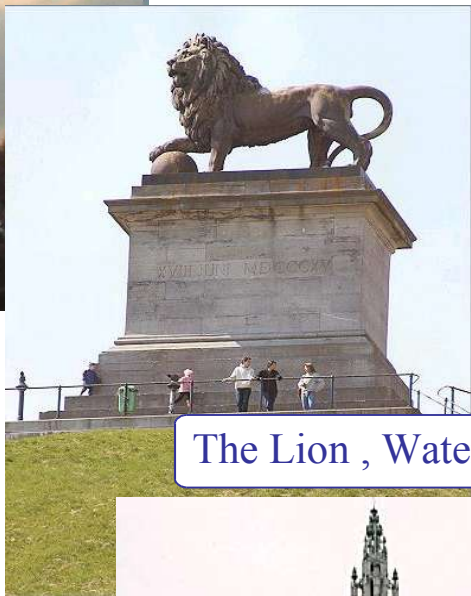


Famous places

Mannekenpis,
Brussels.



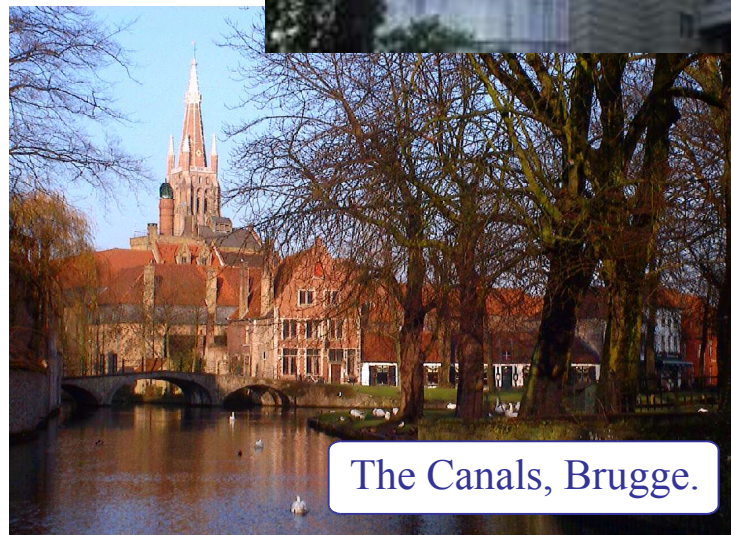
The Lion , Waterloo.



Onze Lieve Vrouw,
Antwerp.



The Canals, Brugge.

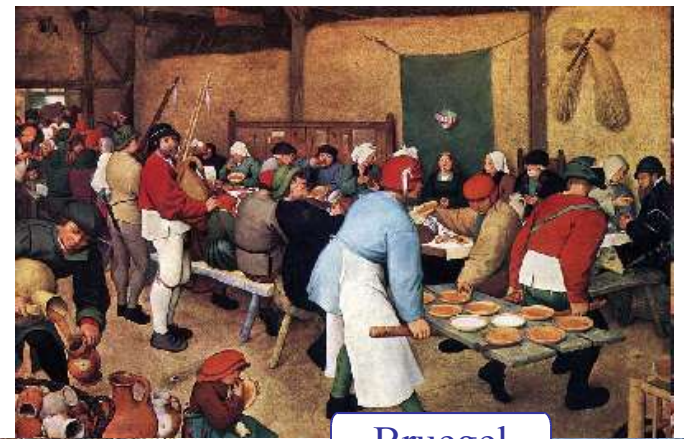




Magritte
1896-1967



Famous painters



Bruegel
1525-1569



Delvaux
1897-1994





Carnival, Binche.



Flowers drawing,
Grand-Place, Brussels.

Famous Events



Le Doudou, Mons.



Belgian Beers



Belgian Chocolates



Belgian Waffels

Famous Food



Mussels and
Potato Fries

A few things about me

David LEMIN

Born in 1975, Uccle, Brussels, Belgium.

High School Graduation, Sciences oriented, 1994.

Graduate Diploma in Chemical Sciences, Free University of Brussels, 1998.



Master Degree in Sciences , Free University of Brussels, 2001.

PhD. In Sciences , Free University of Brussels, 2004.



Japan Society for the Promotion of Sciences, Post-Doctoral Fellowship,
Chiba University, Octobre 2004 - Octobre 2006.



***Natural Product** : A chemical substance produced by a living organism; a term used commonly in reference to chemical substances found in nature that have distinctive pharmacological effects.*

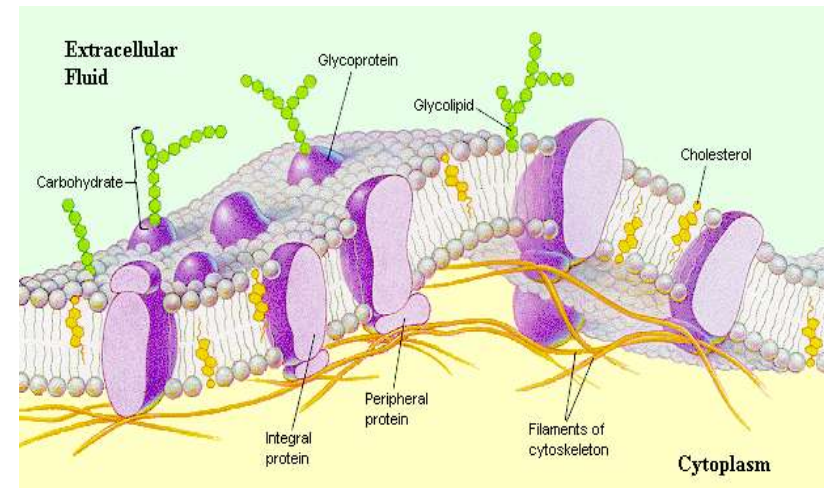
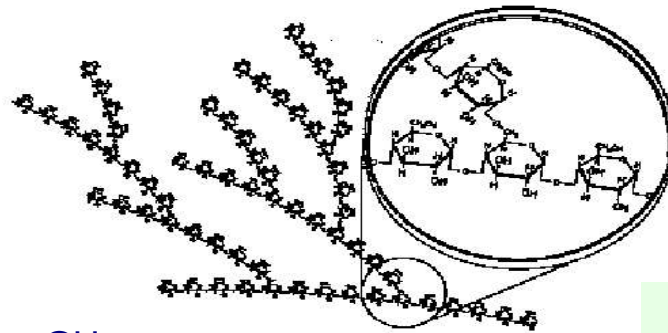
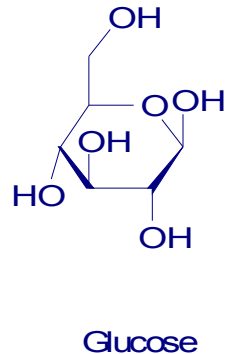
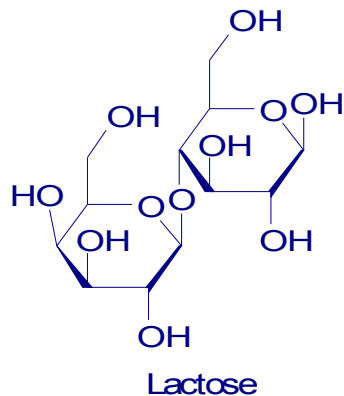
Main Classes of Natural Products:

- Carbohydrates
- Lipids
- Proteins
- Nucleic Acids

Carbohydrates

A broad category of chemical compounds, also referred to as Sugars. The most abundant class of bio-organic molecules on Earth. Although relatively low in human, it constitute about 75% by mass of dry plant materials.

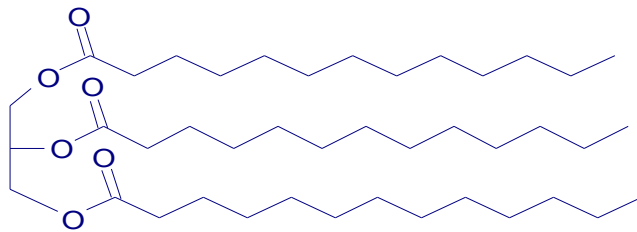
Main functions: Energy storage, structure element , source of carbon of the bio-synthesis of other substances, “Markers” on cell surface for cell-cell recognition.



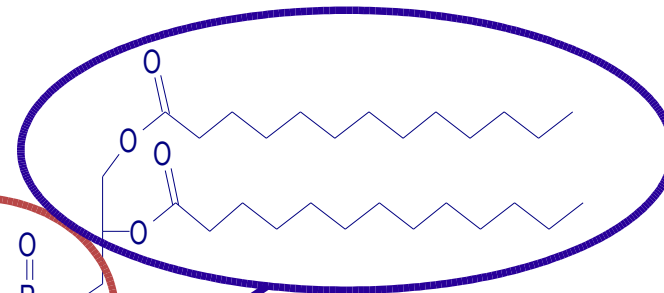
Lipids

A broad category of chemical compounds, also referred to as Fat. Most of those products are non polar fat, oil, or wax that does not (or poorly) dissolve in water.

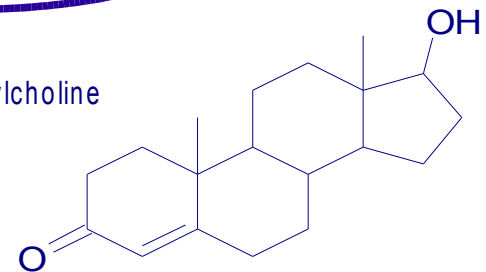
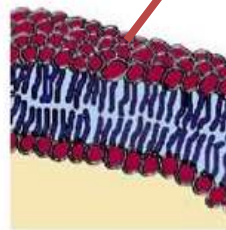
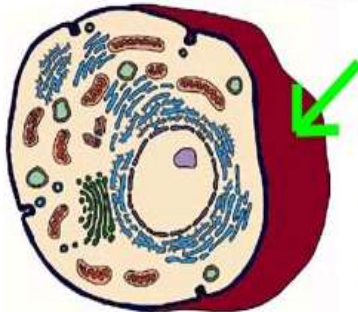
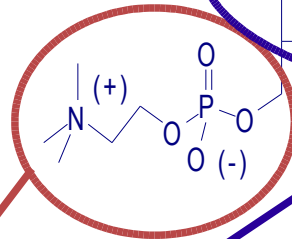
Main functions: Main component of cells membrane, energy storage, communication between cells (hormones).



Triglyceride



Phosphatidylcholine

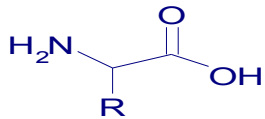


Testosterone

Proteins

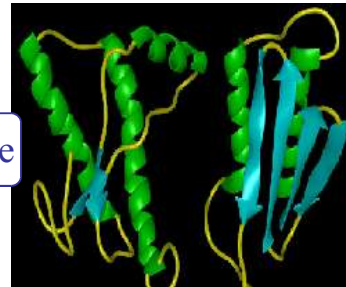
A broad category of chemical compounds composed of amino acids. Includes Aminoacids, polypeptides, Enzymes.

Main functions: Very large variety of functions, from maintenance or repairing of existing tissues and synthesis of new ones to the catalysis of all the bio-chemical reactions that take place in a living organism (Enzymes).

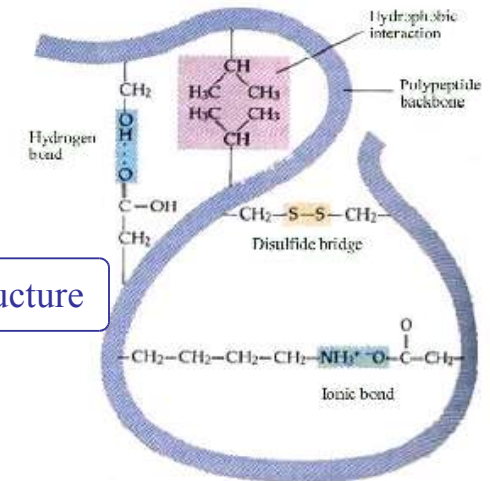


R = CH₂SH : Cys
R = CH₃ : Ala
R = CH₂COOH : Asp
R = (CH₂)₄NH₂ : Lys
....
....
....
....

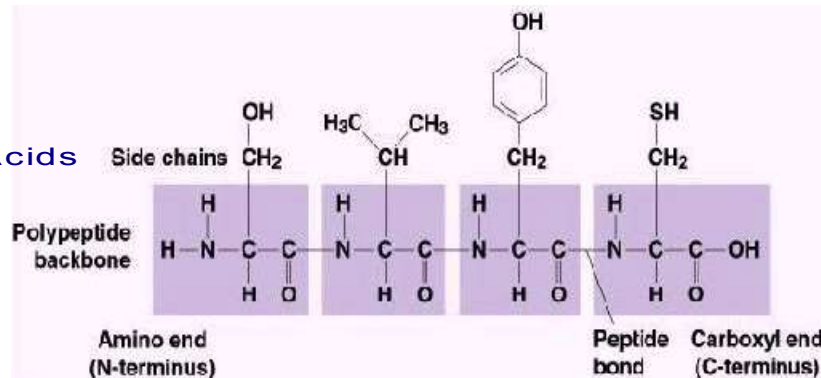
Secondary Structure



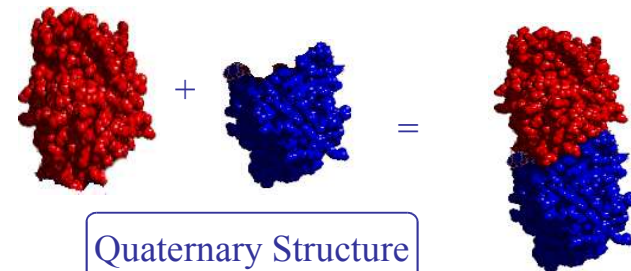
Tertiary Structure



Amino Acids



Primary Structure

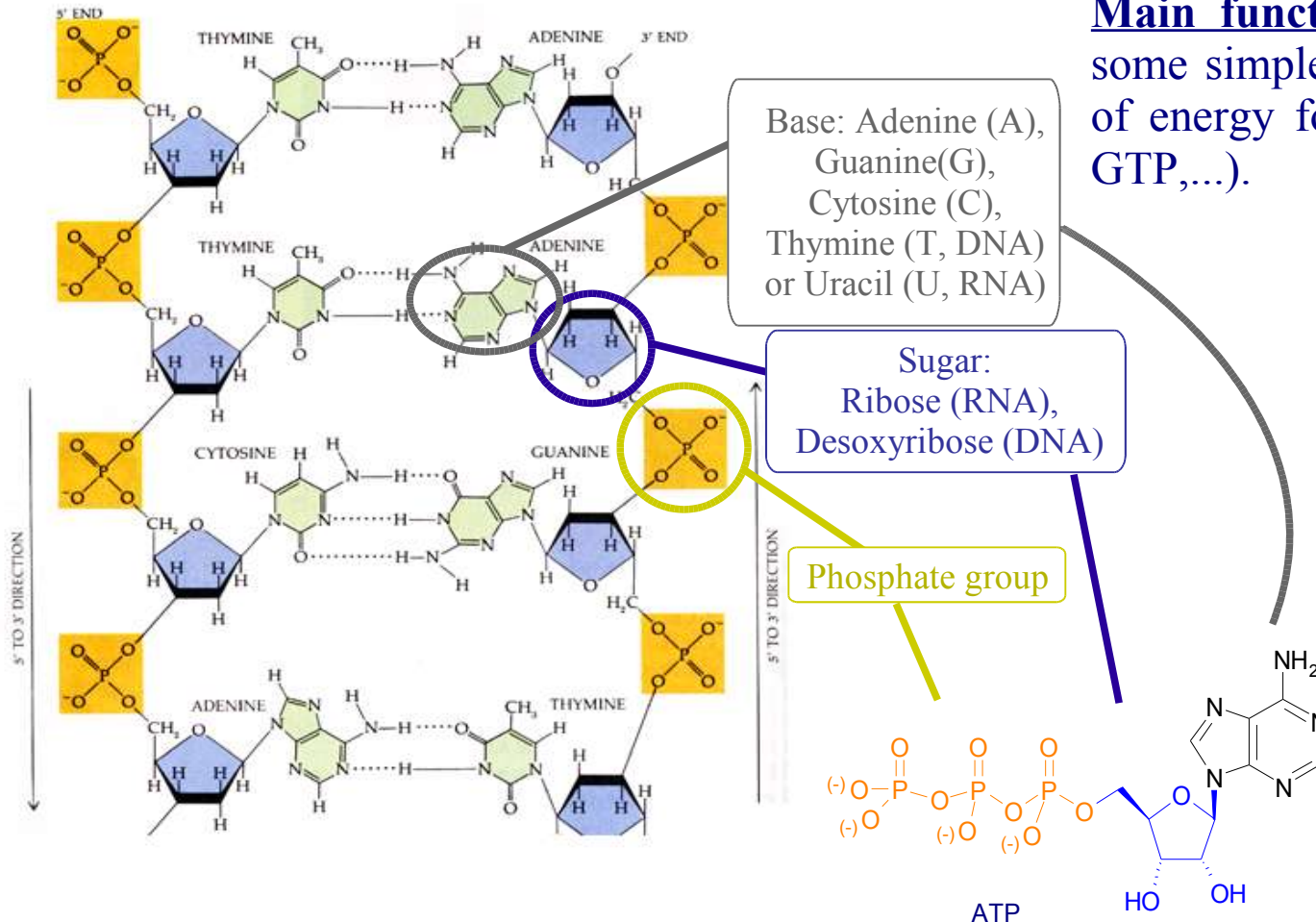


Quaternary Structure

Nucleic Acids

A category of complex chemical compounds involved in the transmission of genetic information (DNA) and its transfer as information to the cell (RNA).

Main functions: Genetic information, some simple nucleotides acts as source of energy for chemical reaction (ATP, GTP,...).



Metabolism

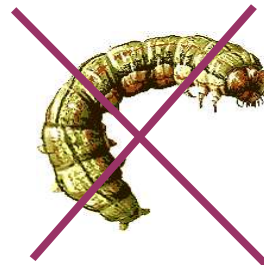
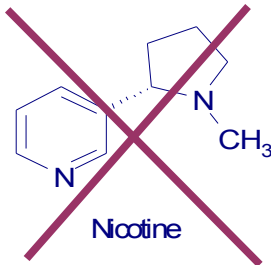
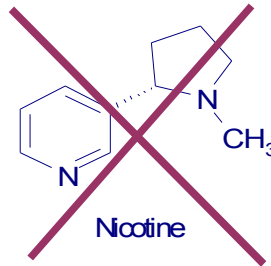
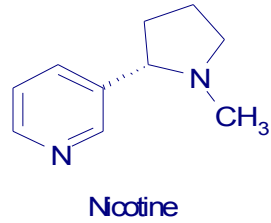
The Metabolism is the sum of all the chemical reactions that take place in a living organism.

Primary Metabolism: All the chemical reactions necessary for the live of the organism by itself.

Primary Metabolites: All the chemical products involved in the Primary Metabolism.

Secondary Metabolites: All the chemical products that are produced by the living organism but are NOT involved in the primary metabolism. Not necessary for the live of the organism by itself but usefull for interaction with others (chemical communication, chemical defences).

Tobacco Plant



Hormones, Pheromones and Allomones

Hormones: Chemical products use in the tranfer of information between tissues or organs within a Body, in order to coordinate their activity.

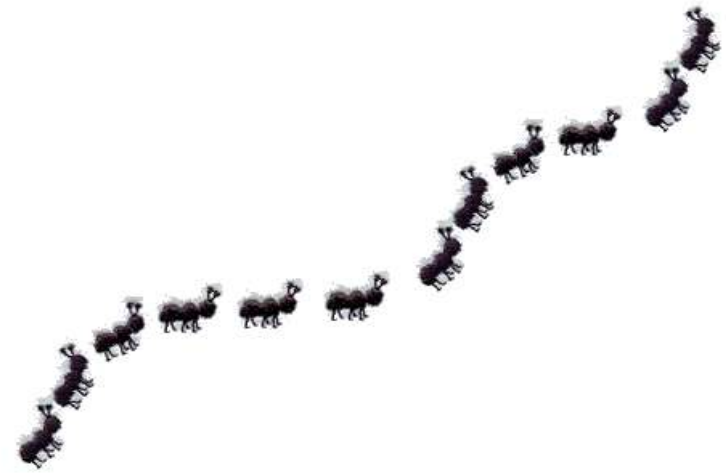
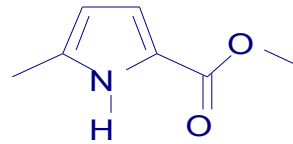
Pheromones: Chemical products used between individuals of the same specie in order to induce a specific behavior (Chemical communication).

Allomones: Chemical products released by an organism wich has a negative effect on another organism (Chemical defence).

Chemical Communication : Trail Pheromones

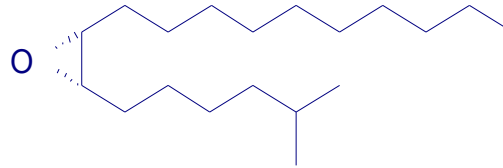


Nest

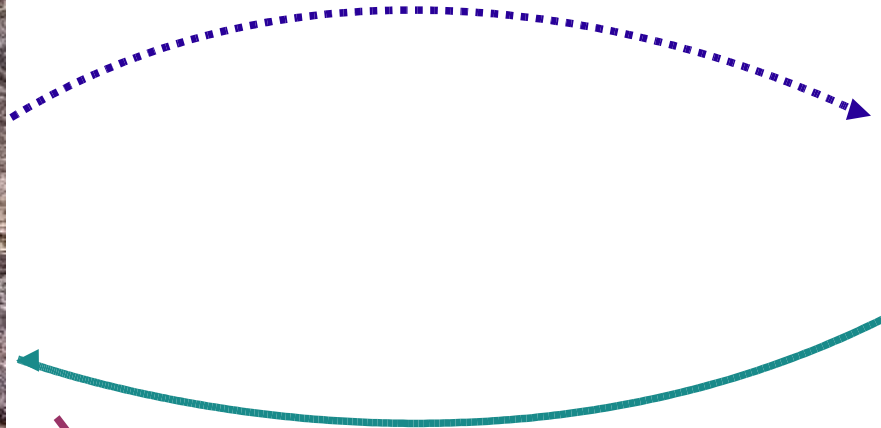


Food

Chemical Communication : Sexual Pheromones

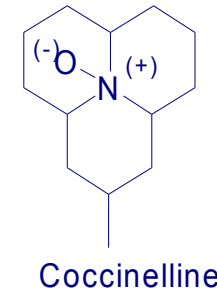


D i s p a r l u r e



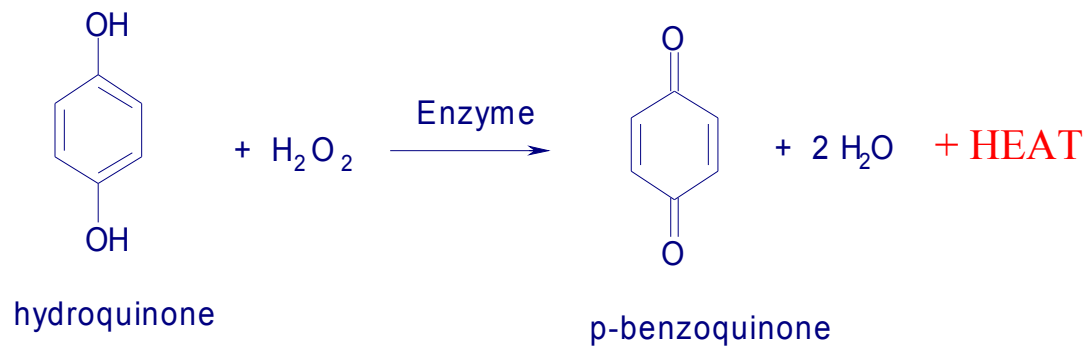
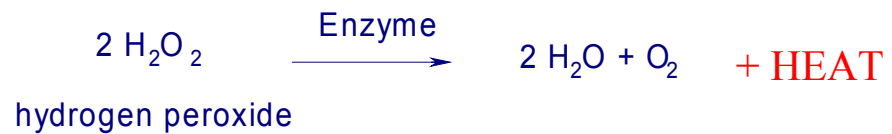
Reproduction

Chemical Defence : Ladybugs



Aposematism

Chemical Defence : Bombardier Beetle



Evolution gave different organism different “Chemical Tools” to communicate with individuals of the same specie or to defend themselves against predators.

Question : As we share the same kind of Primary Metabolism, doesn't those “Chemical Tools” have a effect on the human body?

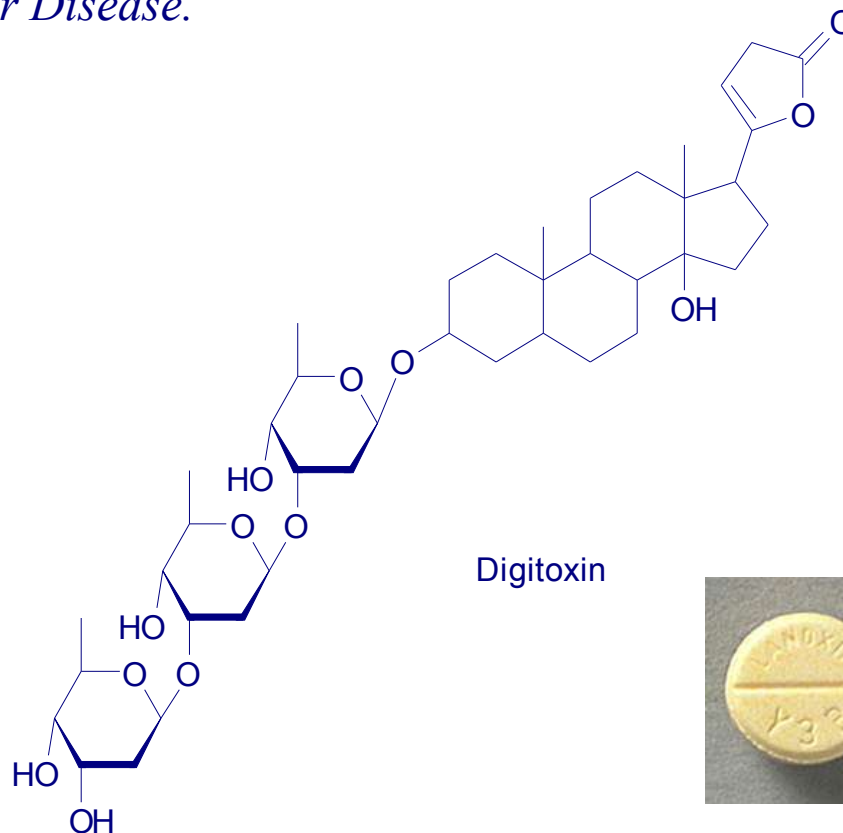
Answer : Yes, and some times those “Chemical Tools” can be used as Medicinal Drugs.

Pharmacologically active Natural Products : Digitoxin

Natural Products having a particular activity on the human body which is beneficial for the treatment of a particular Disease.



Digitalis purpurea



Digitoxin



Digitoxin strongly stimulates the contraction of the heart.
Treatment of heart deficiency.

Natural Products Derivatives : The Aspirin Story

Natural Products which are slightly modified in order to improve their activities or decrease the side-effects.

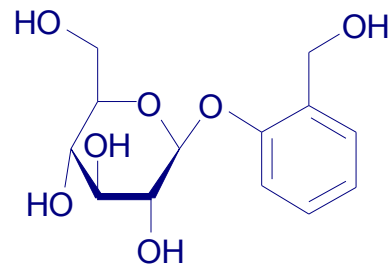


Willow tree

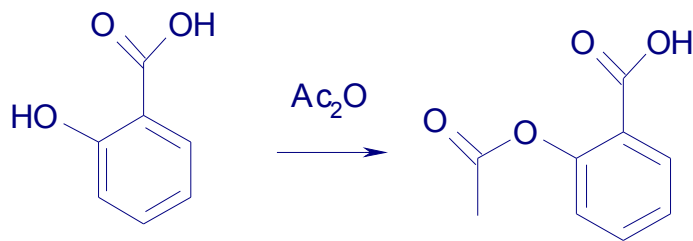
- 400 BC Use of the bark and leaves of willow tree to relieve pain and fever (Greece).
- 1758 Edward Stone (England) chew the bark of a willow tree \Rightarrow bitter $\Rightarrow \Rightarrow$ discovery of Salicin and Salicylic acid (side effect: stomach pain)
- 1897 Felix Hoffmann (BAYER, Germany) synthesise Aspirin.



Felix Hoffmann
1868-1946



Salicin



Salicylic acid

Aspirin



Total Synthesis vs Semi-synthesis : The Taxol Story



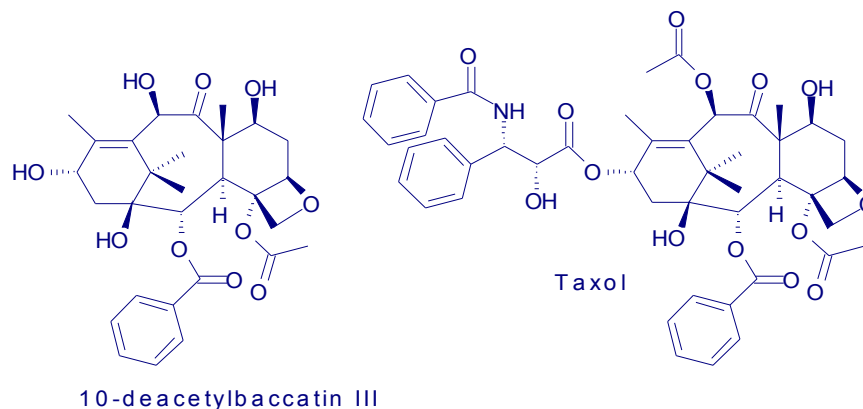
Pacific Yew Tree
Taxus brevifolia

- 1962 A. Barclay isolated Taxol from the bark of the Pacific Yew tree (*Taxus brevifolia*)
- Present in very small quantity :
100 year-old tree to isolate 300mg = a single dose \Rightarrow need to prepare it.

- *Total Synthesis starting from simple commercially available molecules* (more than 30 steps : less than 1% Total Yield)
- *Semi-synthesis starting from complex natural product* :
10-deacetylbaccatin III discovered from the needles of European Yew tree (*Taxus baccata*) : 3 Steps, 50 % Total Yield.



European Yew Tree
Taxus baccata



Natural Products Analogs

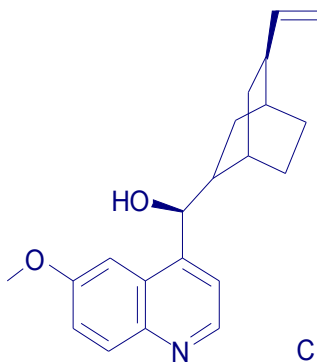


Cinchona tree

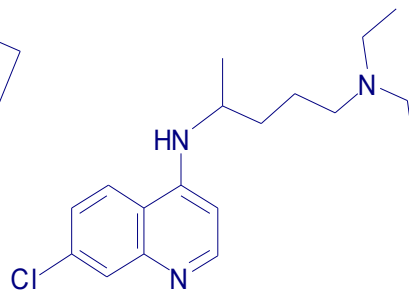


Synthetic Products that has a structure partially similar to a known Natural Product.

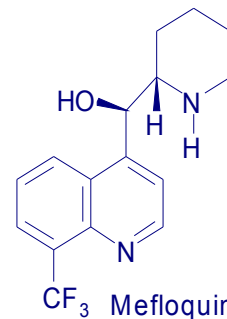
- Quinine was isolated in 1820 by Caventou and Pelletier (France), from the bark of the cinchona tree, brought back from south america by jesuit missionaries.
- Used for treatment of fever, pain and Malaria.
- 1934 I G Farben (Germany), synthesis of Chloroquine.
- 1978 (USA) synthesis of Mefloquine.



Quinine



Chloroquine



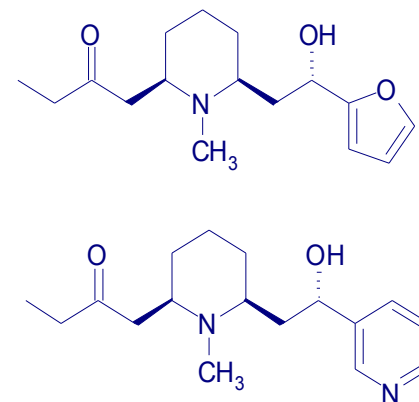
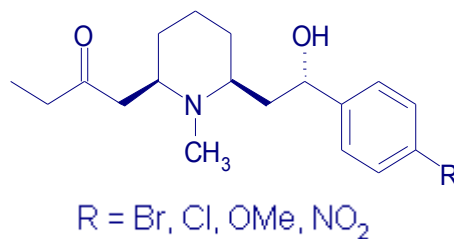
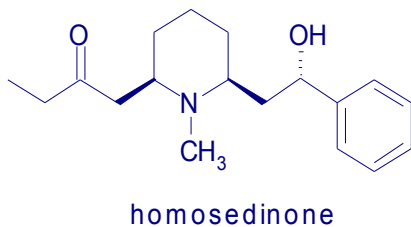
Mefloquine

Central Nervous System (CNS) and Homosedinone Analogs

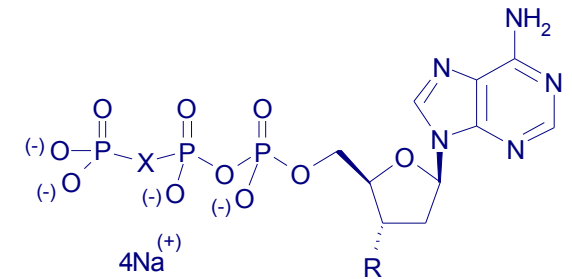
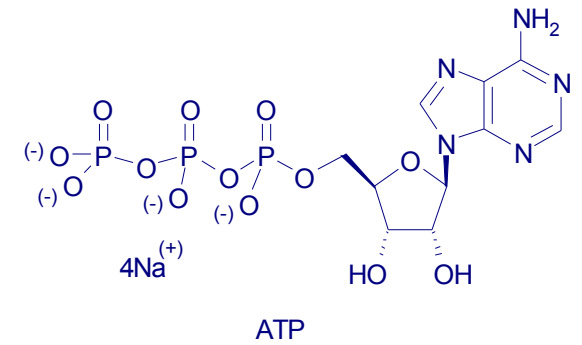
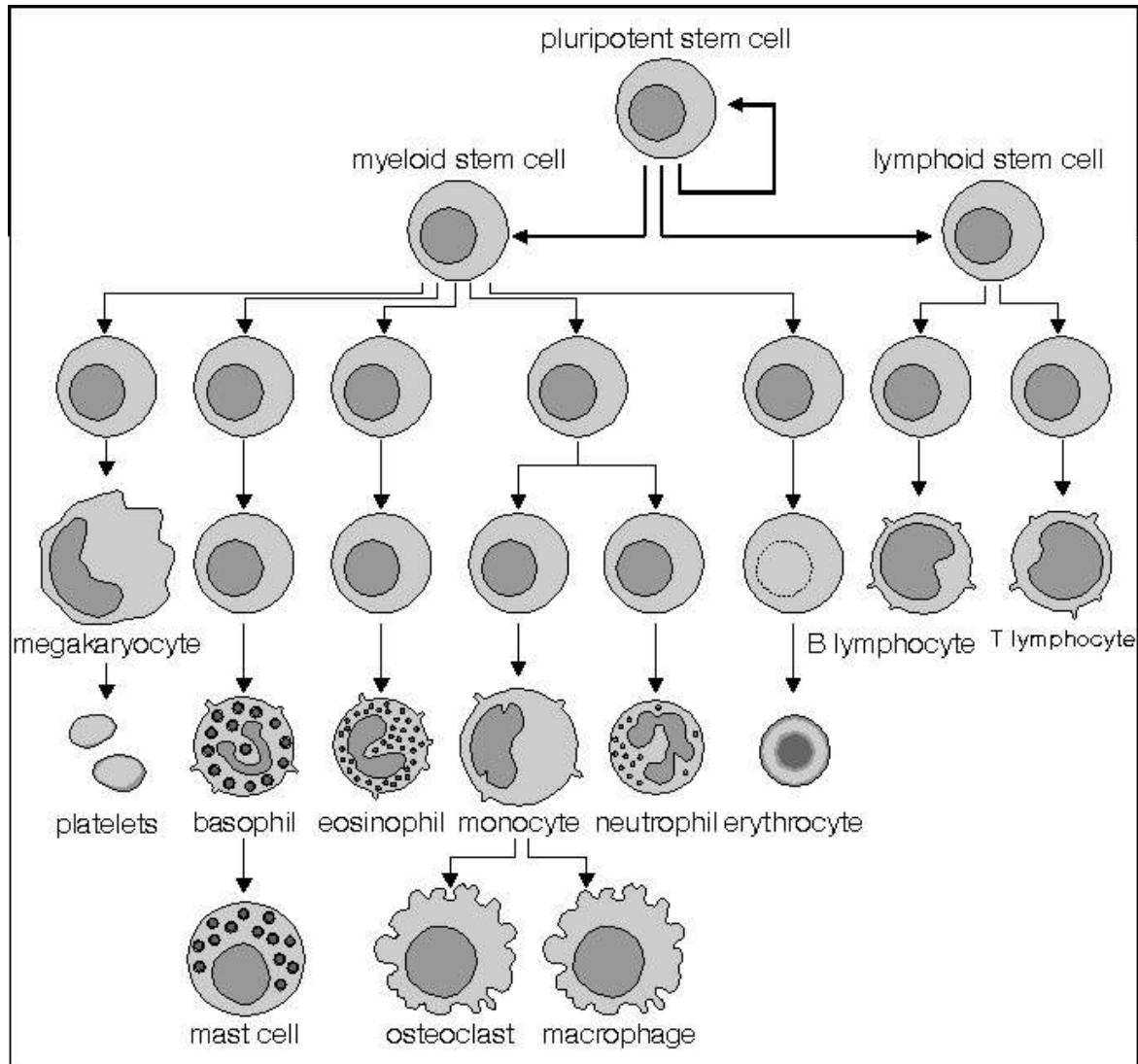


- Homosedinone was isolated from *Sedum acre* in 1988.
- Wide screening from Pharmaceutical French company Servier, for potential CNS Disease Therapeutics among naturally occurring products showed homosedinone has interesting activities.
- Collaboration between Servier and Free University of Brussels to prepare analogs of homosedinone and test their activity on CNS.

Sedum acre

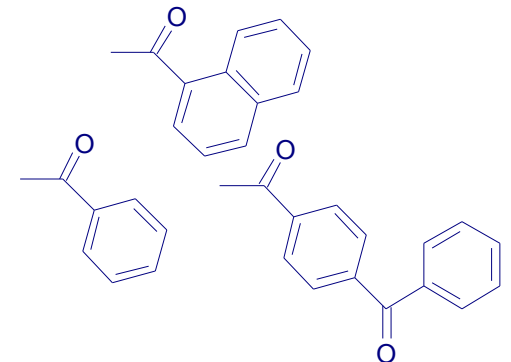


Leukemia and ATP Analogs



X = -CH₂-, -CCl₂-

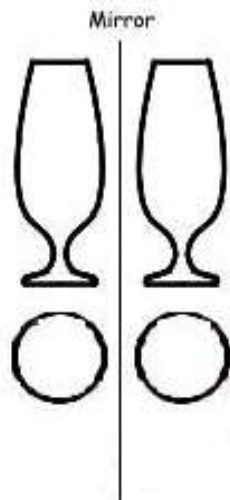
R = -O-H



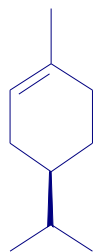
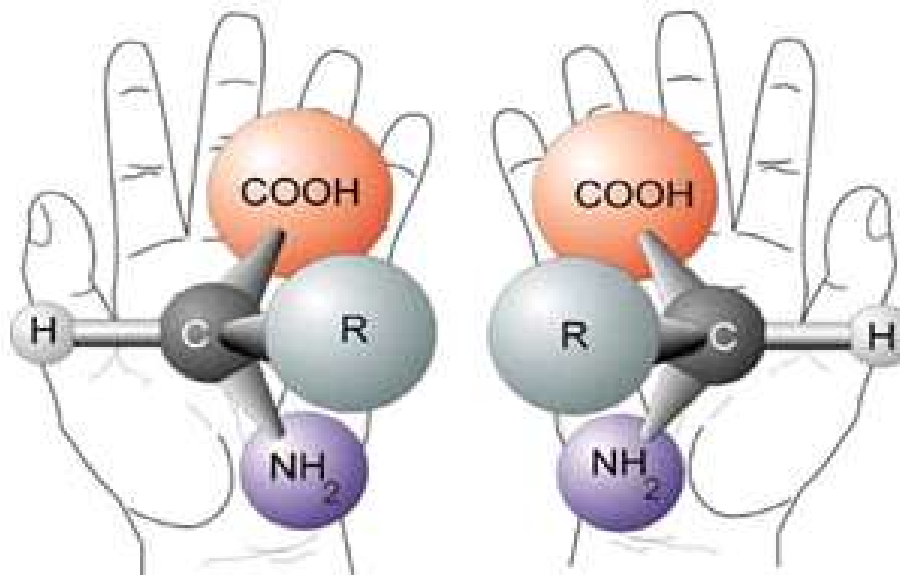
Chirality



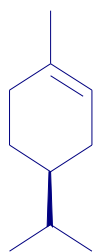
Chiral objects
Nonsuperimposable
mirror images



Nonchiral objects
Superimposable
mirror images

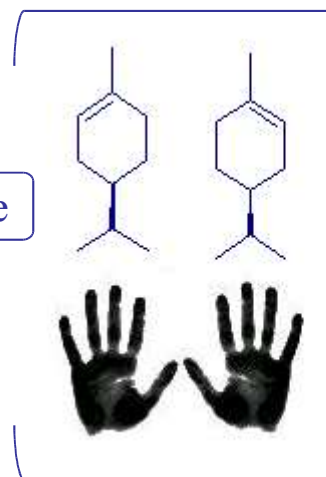


(R)-Limonene
smells orange



(S)-Limonene
smells lemons

Racemic mixture



One enantiomer

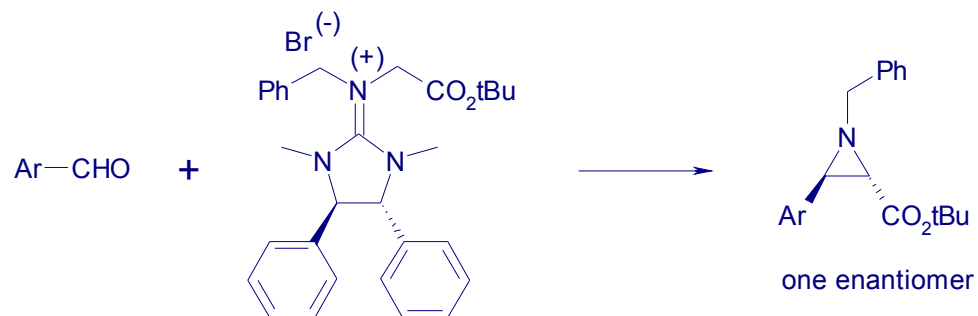
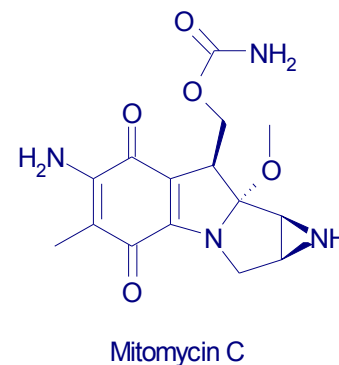


New Access to Mitomycin C Anti-Cancer Drug

- Isolated from *Streptomyces caespitosus* in 1958.
- Antibiotic and anti-cancer activity.
- Extensively used in combination chemotherapy treatment of cancer.



Streptomyces



Acknolegments

Japan Society for the Promotion of Sciences JSPS

- Post-Doctoral Fellowship for Foreign Researcher
- Science Dialogue Program



Prof. Tsutomu ISHIKAWA
and the members of the lab.

Ms. Kaori SHIMURA

