

Organic Chemistry of Natural Products

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佐竹 真幸 (Masayuki Satake, Natural Product Chemistry Lab.)

後藤 佑樹 (Yuki Goto, Bioorganic Chemistry Lab.)

加藤 敬行 (Takayuki Katoh, Bioorganic Chemistry Lab.)

Tentative lecture schedule:

date	No.	instructor	subject
9/26	1	Goto	overview of natural products
10/3	2	Goto	terpenes
10/10	3	Goto	terpenes
10/17	4	Katoh	amino acids and peptides
10/24	5	Katoh	amino acids and peptides
10/31	6	Satake	polyketides
11/14	7	Satake	polyketides
11/21	8	Satake	polyketides
11/28	9	Satake	chikimic acid pathway and its products
12/5	10	Satake	chikimic acid pathway and its products
12/12	11	Campbell	topic: protein engineering for diagnostics and therapeutics
12/19	12	Campbell	topic: protein engineering for diagnostics and therapeutics
12/26	13	Suga	topic: discovery and application of pseudo-natural peptides
1/9	14	Suga	topic: quorum sensing controlled by auto inducers

Grading:

Final exam + attendance

Suggested reference textbooks:

医薬品天然物化学（南江堂）、海老塚豊 監訳

マクマリー生化学反応機構（東京化学同人）、長野哲雄 監訳

Medicinal Natural Products: A Biosynthetic Approach, Paul M. Dewick

The Organic Chemistry Of Biological Pathways, John E. McMurry & Tadhg P. Begley

What is natural product?

What is natural product?

- It is a chemical compound produced by a living organism—that is, found in nature
- In a narrow sense, natural products often means secondary metabolites that have intriguing bioactivities.

What are secondary metabolites? (\leftrightarrow primary/metabolites)

- They are organic compounds generated in organisms (metabolites) that are not essential in the reproduction, development, or normal growth.
- They often provide evolutionary advantages for the producing organisms.

e.g.) "chemical weapon" agents against prey, predators, and competing organisms

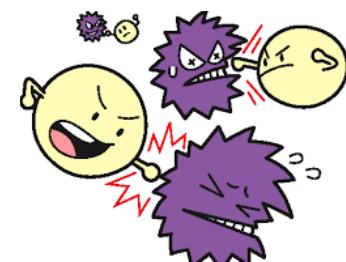
spider venom



frog toxins



anti-bacterials



essential and universal

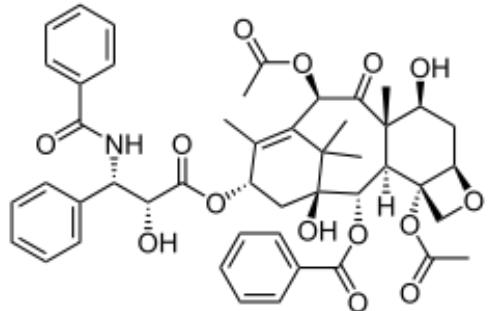
What is natural product?

What is natural product?

- It is a chemical compound produced by a living organism—that is, found in nature
- In a narrow sense, natural products often means secondary metabolites that have intriguing bioactivities.

Humans use secondary metabolites discovered from nature as medicines, agents, and flavorings.

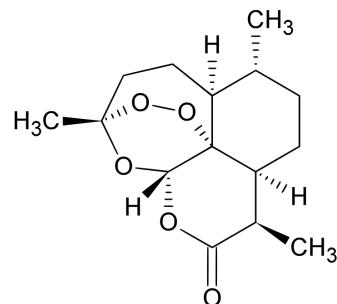
e.g.)



Paclitaxel

anti-cancer drug

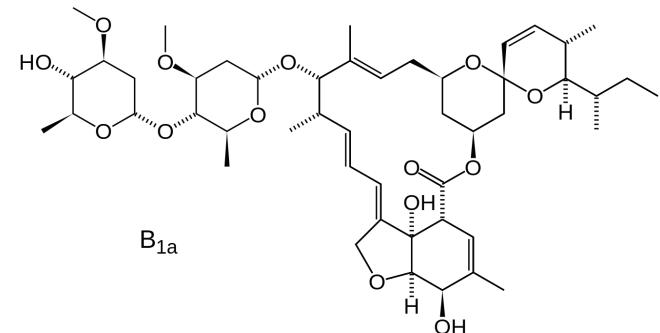
isolated from a plant
(*Taxus brevifolia*)



Artemisinin

anti-malarial drug

isolated from a plant
(*Artemisia annua*)



Avermectin

anti-parasitic worm drug

produced by a bacterium
(*Streptomyces avermitilis*)



Physiology/Medicine, 2015



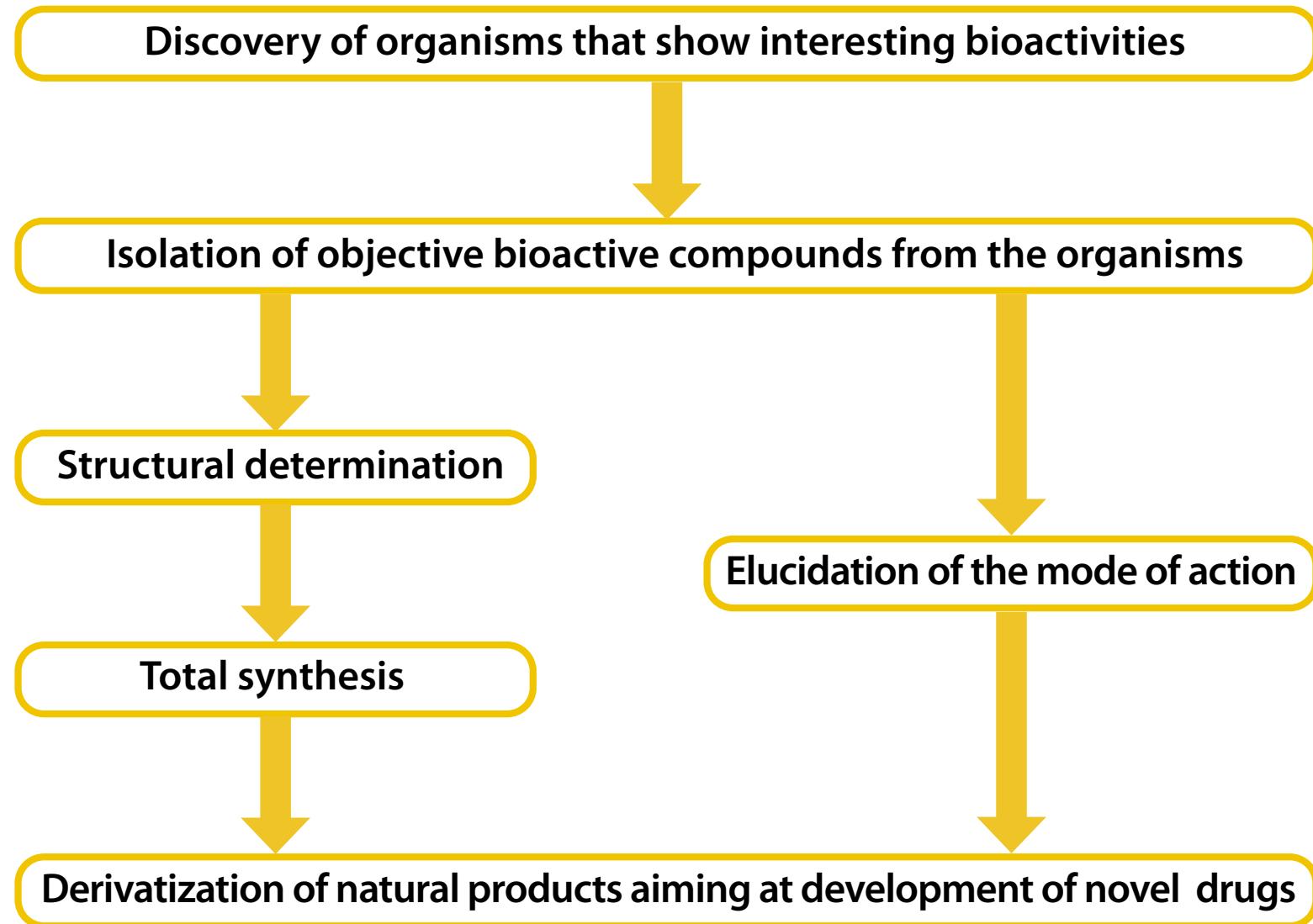
Physiology/Medicine, 2015

What is natural products chemistry?

📌 What is **natural products chemistry**?

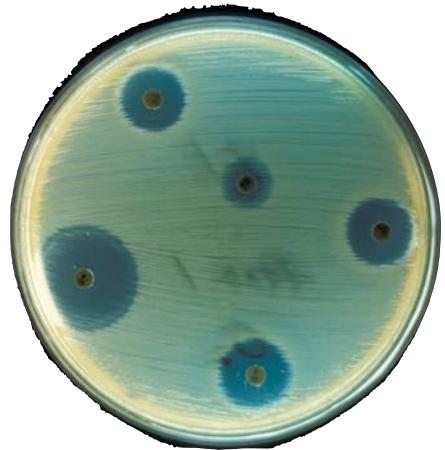
- A field of organic chemistry that deals with “natural products”.
- It is related to various chemistry fields such as medicinal chemistry, synthetic chemistry, and agricultural chemistry.
- Japanese scientists have historically shown large presence.

Typical flow in natural products chemistry



Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities



A fungus kills microbials



Willow bark can be used for suppression of toothache



Morays sometimes cause food poisoning

Isolation of objective bioactive compounds from the organisms

Structural determination

Total synthesis

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities

Isolation of objective bioactive compounds from the organisms

culture medium of fungi

willow bark

meat of morays
(e.g. 850 morays, 4 tons!)

(0.3 mg of final compound)

Purifying the natural samples by means of various separation methods,
and hunting the fractions that shows the objective bioactivity



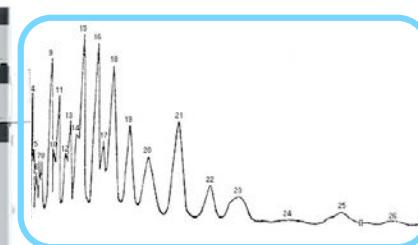
extraction



liq.-liq. separation



chromatography



crystallization

Structural determination

Elucidation of the mode of action

Total synthesis

Derivatization of natural products aiming at development of novel drugs

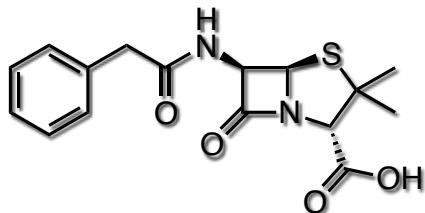
Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities

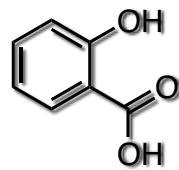
Isolation of objective bioactive compounds from the organisms

Structural determination

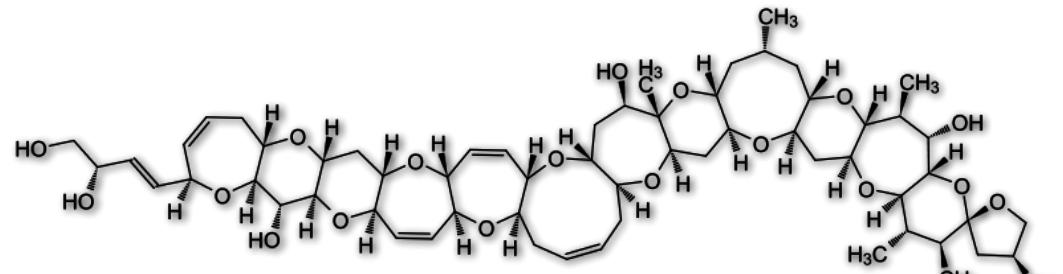
Determination of the structure of the bioactive compound by means of elementary analysis, crystal structure analysis, and comprehensive spectrum analyses (e.g., MS, MS-MS, IR, NMR, etc.)



benzylpenicillin



salicylic acid



ciguatoxin

Total synthesis

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

Typical flow in natural products chemistry

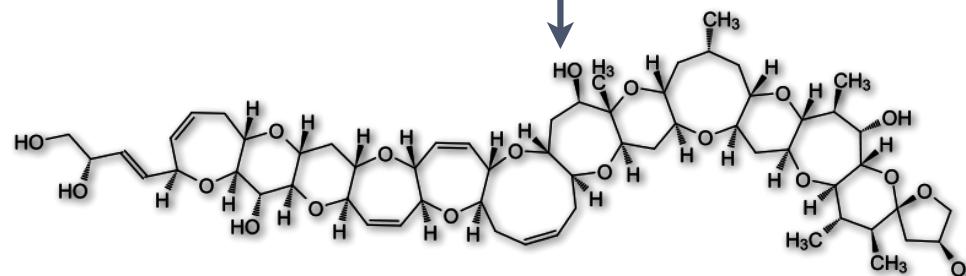
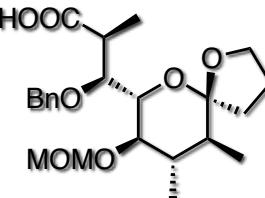
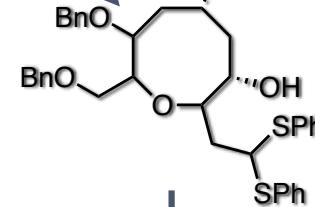
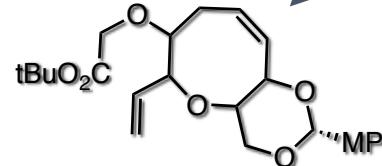
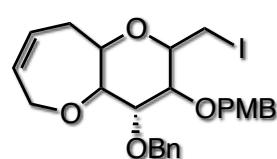
Discovery of organisms that show interesting bioactivities

Isolation of objective bioactive compounds from the organisms

Structural determination

Total synthesis (de novo chemical synthesis of natural products)

available reagents



Science, 294, 5548 (2001)

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities

Isolation of objective bioactive compounds from the organisms

Structural determination

Total synthesis (de novo chemical synthesis of natural products)

- Purpose/motivation:
- Confirmation of proposed structures
 - Mass supply of useful natural products
 - Derivatization of natural products
 - Artistic synthesis of sophisticated structures

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

Typical flow in natural products chemistry

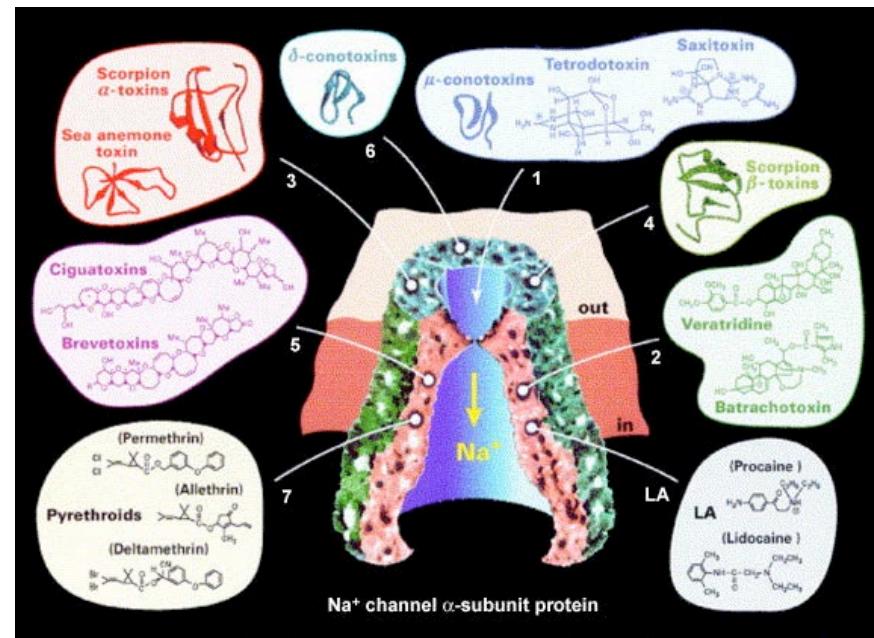
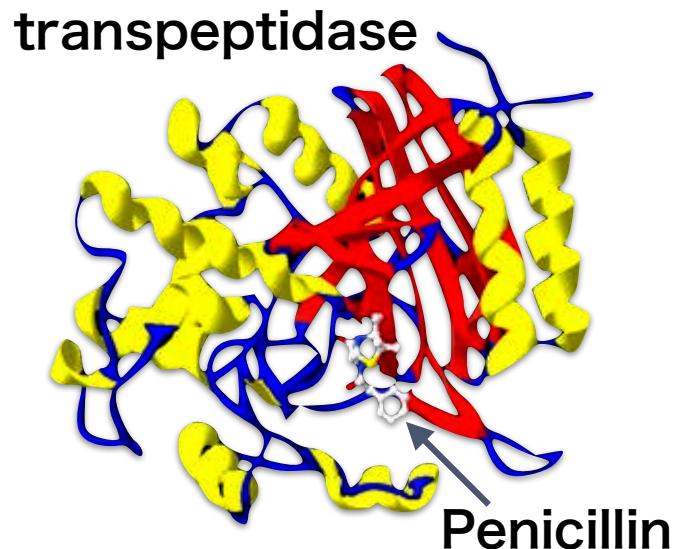
Discovery of organisms that show interesting bioactivities

Isolation of objective bioactive compounds from the organisms

Structural determination

Total synthesis

Elucidation of the mode of action



Derivatization of natural products aiming at development of novel drugs

Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities

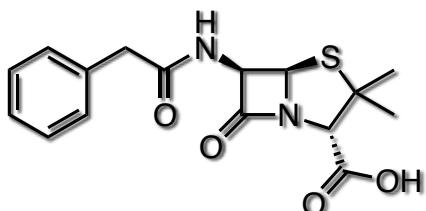
Isolation of objective bioactive compounds from the organisms

Structural determination

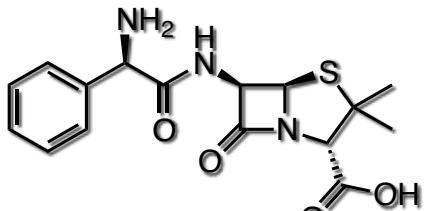
Total synthesis

Elucidation of the mode of action

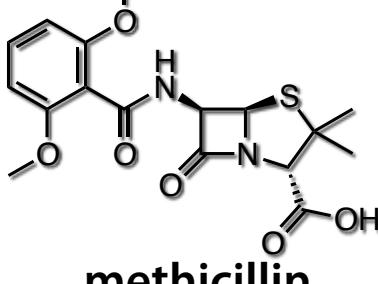
Derivatization of natural products aiming at development of novel drugs



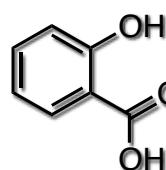
benzylpenicillin
(penicillin G)



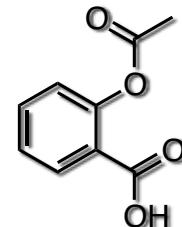
Ampicillin



methicillin

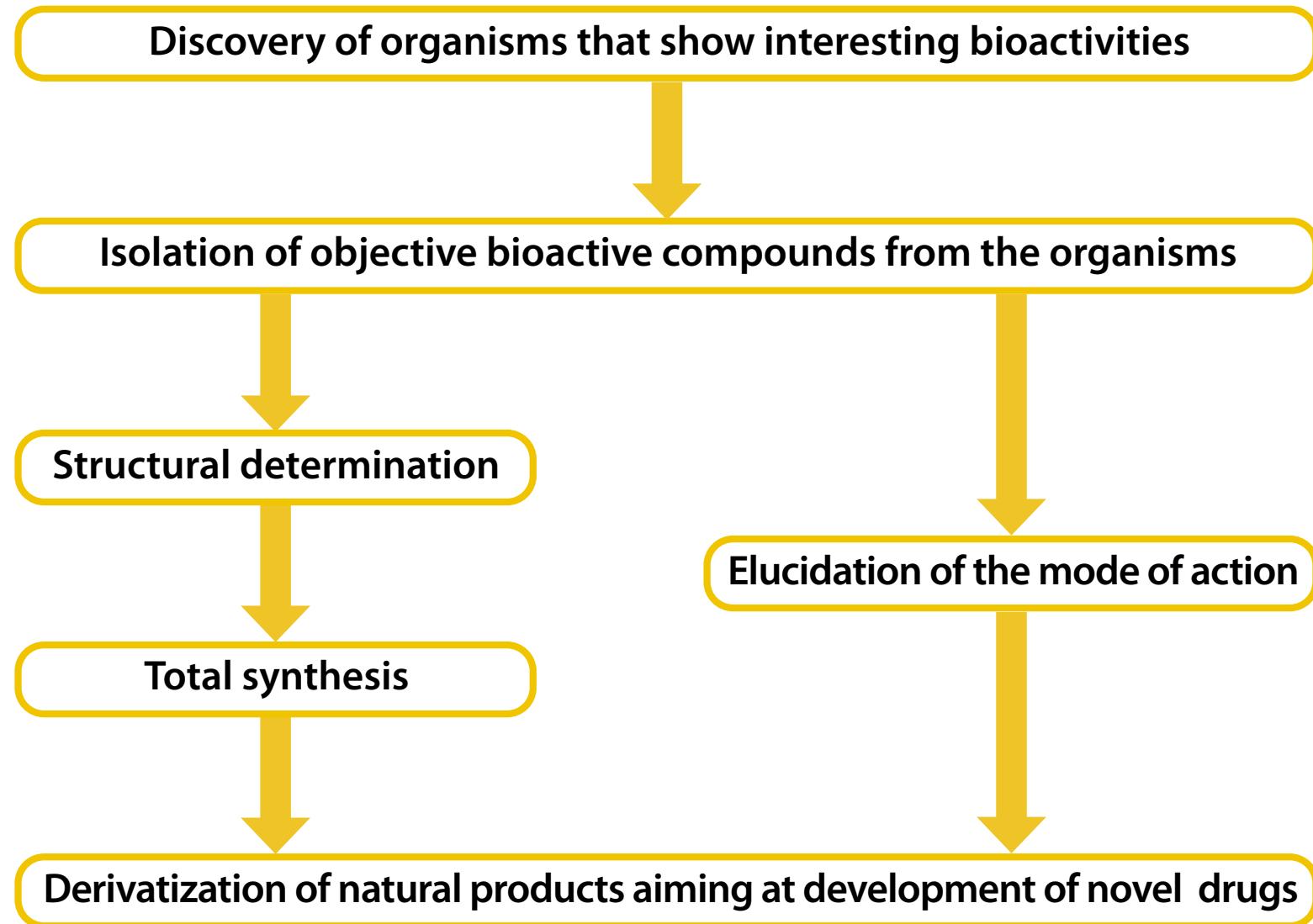


salicylic acid



acetylsalicylic acid
(aspirin)

Typical flow in natural products chemistry



An example of drug development based on natural products

1985: Uemura *et al.*



600 kg of sea sponge (*Halichondria okadai*)
from Miura Peninsula

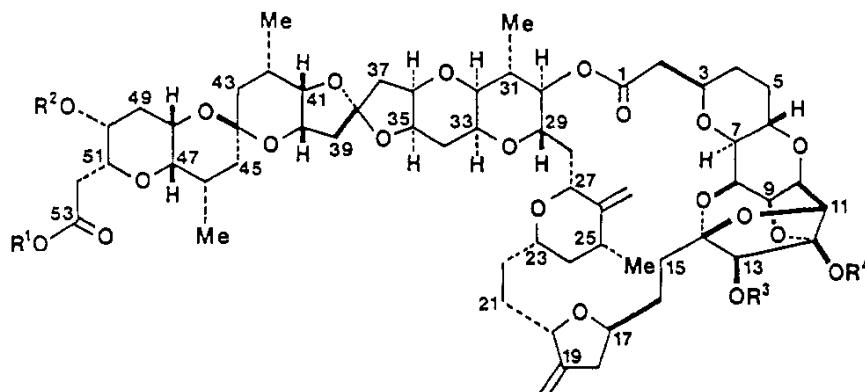


homogenization, extraction,
liq.-liq. separation, chromatography



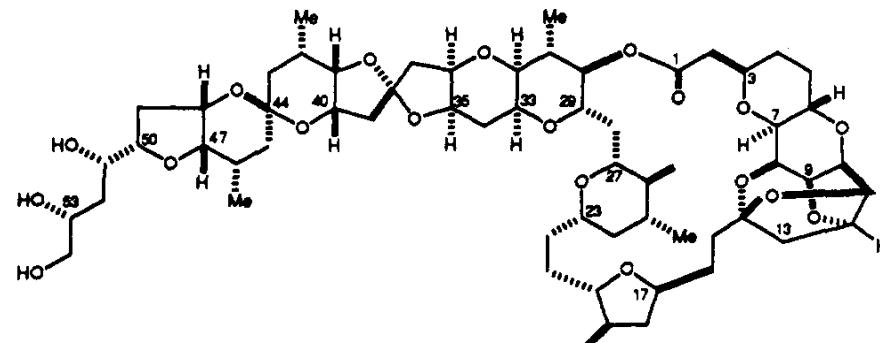
**Discovery and identification of novel compounds
with potent cytotoxicity
(named halichondrins)**

Pure Appl. Chem. **58** (5): 701–710



norhalichondrin A

isolation yield: 35 mg
0.00005% of the original sample!



halichondrin B

cytotoxicity against B-16 melanoma cells
 $IC_{50} = 0.093 \text{ ng/mL} (= 80 \text{ pM})$

Mode of action: Inhibition of cell division via targeting tubulin

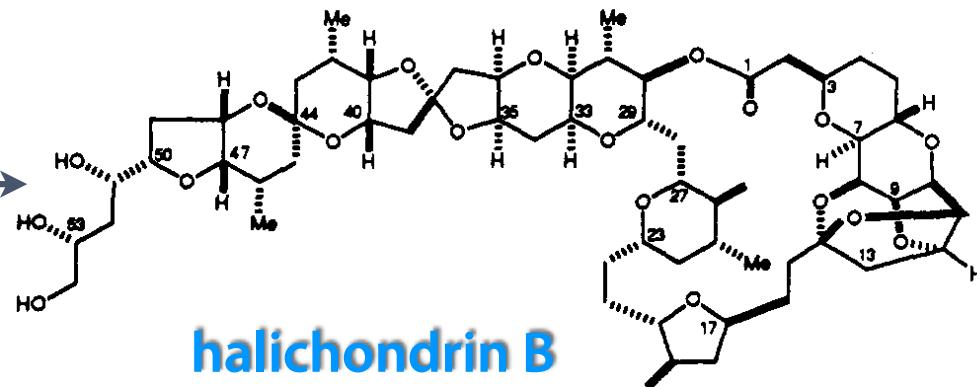
J. Biol. Chem. **266** (24): 15882–9

An example of drug development based on natural products

1992: Kishi *et al.*

Total synthesis of halichondrin B

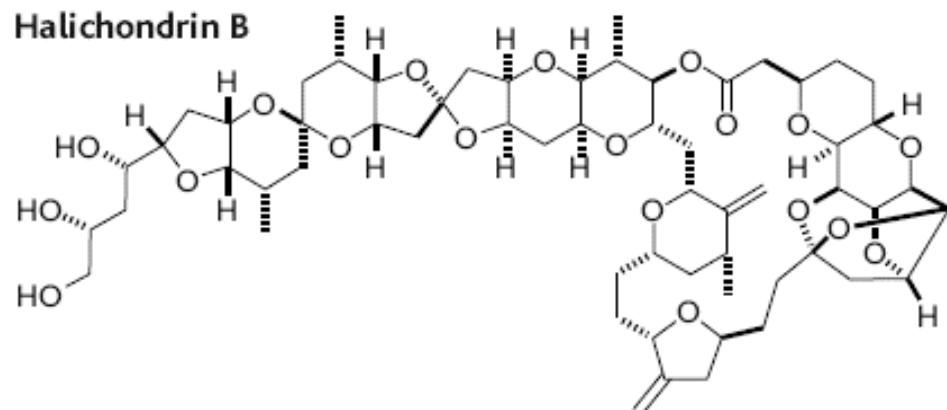
commercially available reagents → over 160 steps chemical reactions



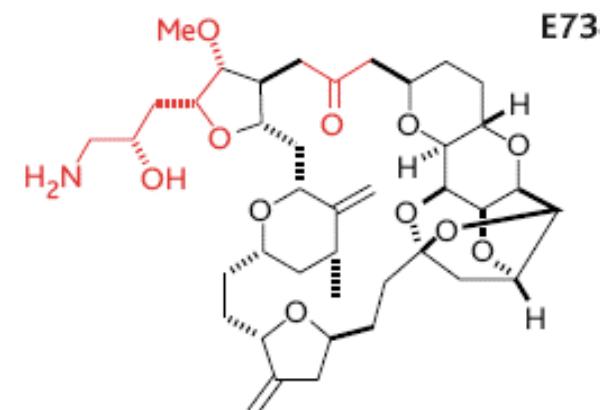
J. Am. Chem. Soc. 114 (8): 3162–3164.

2004: Eisai Co., Ltd.

Simplification of halichondorins - development of E7389



Structural deletion
Macrolactone → ketone



2/3 molecular weight and chiral centers

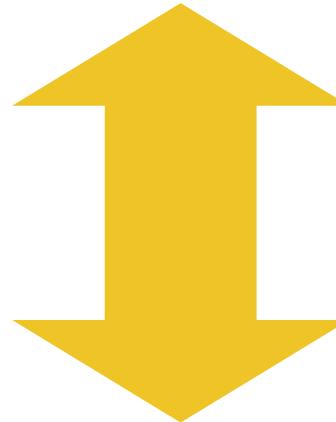
improved in vivo stability

FDA approval in 2010!

Drug development using artificial compounds

Drug development based on natural products chemistry

- Discover the “seeds” of objective drugs from nature,
and brush them up to develop desirable drugs

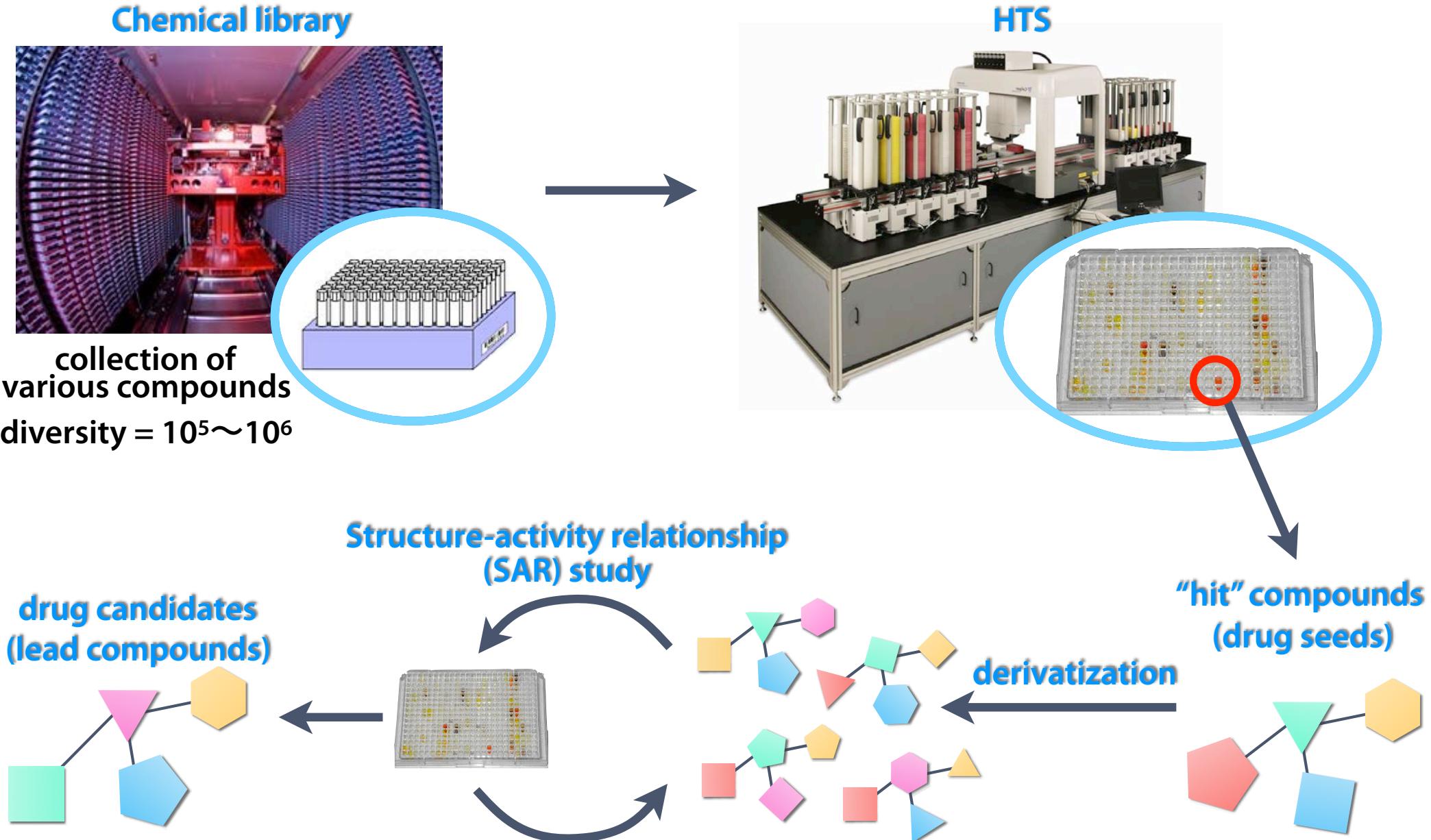


Drug development using artificial compounds

- de novo* development of drug seeds
using synthetic chemical approaches

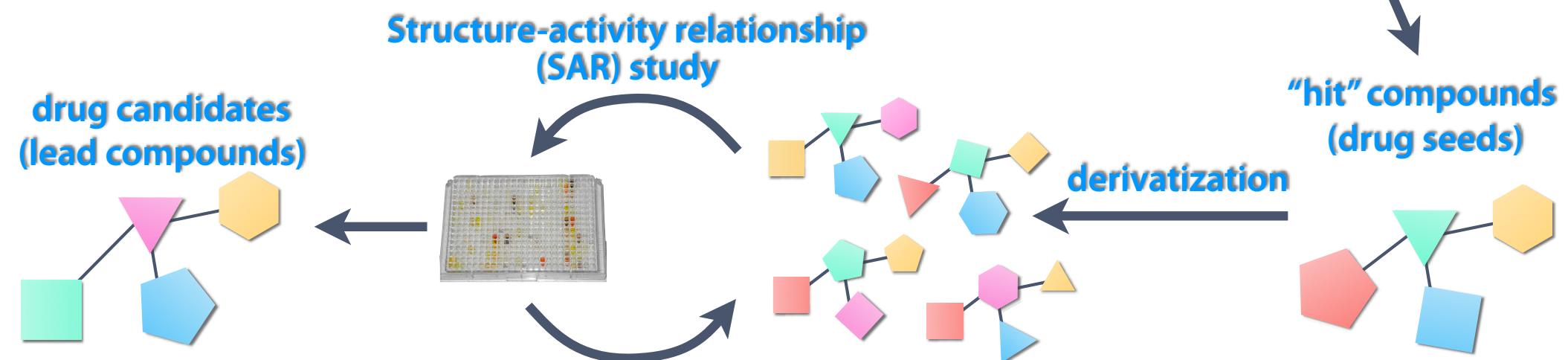
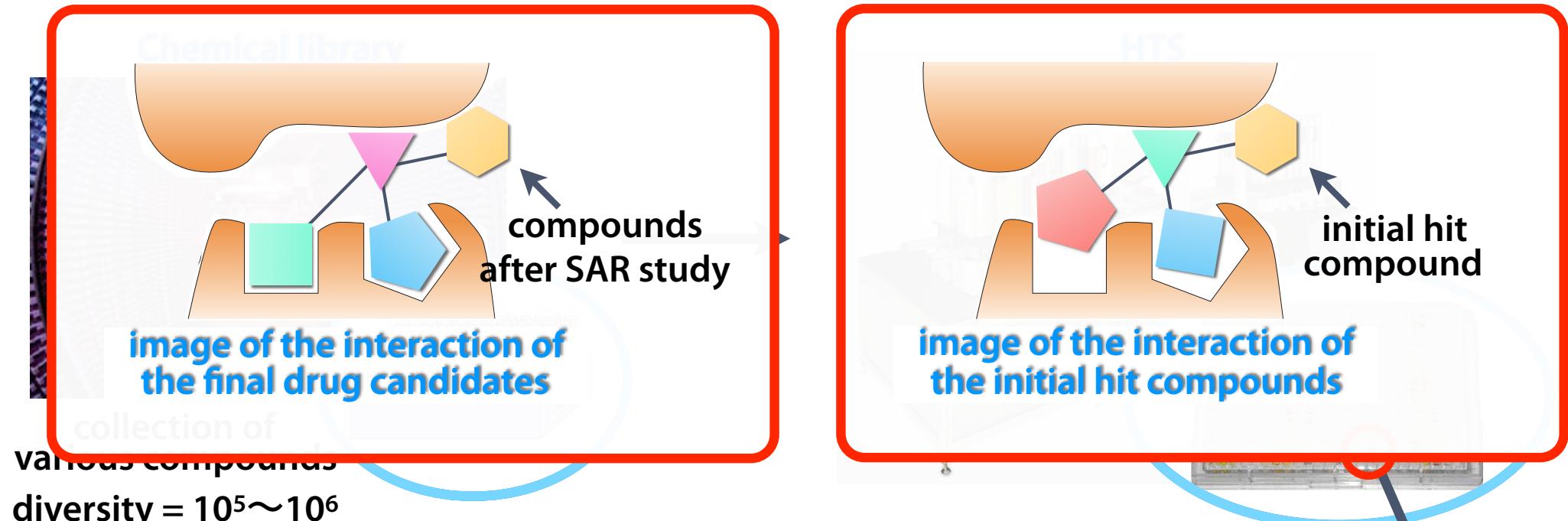
Drug development using artificial compounds

High-throughput screening (HTS) of chemical libraries



Drug development using artificial compounds

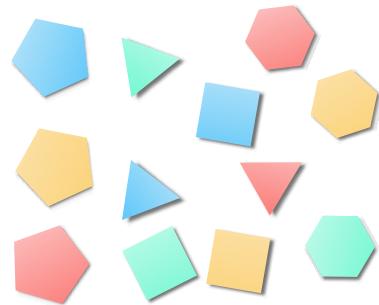
High-throughput screening (HTS) of chemical libraries



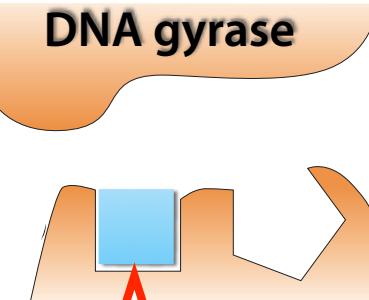
Drug development using artificial compounds

Fragment-based drug discovery (FBDD)

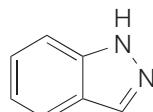
small compounds
(fragments)



monitoring the interaction
by NMR and/or crystallography

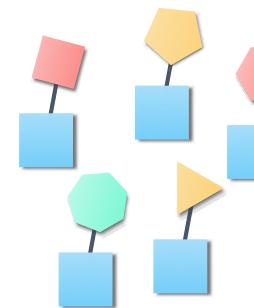


diversity = $10^2 \sim 10^4$

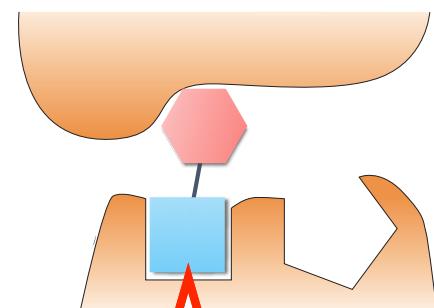


$K_d = 10 \text{ mM}$ (by NMR)
MNEC > 250 μg per ml

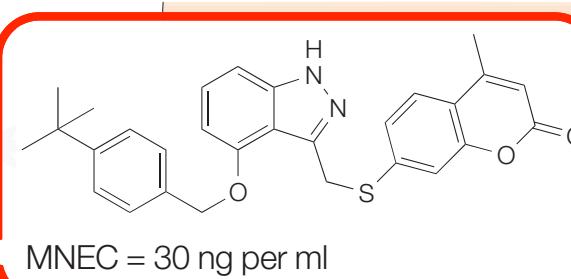
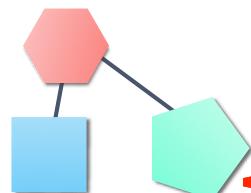
"extended"
fragment library



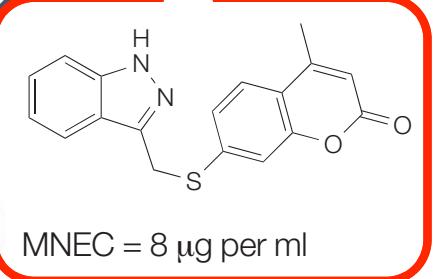
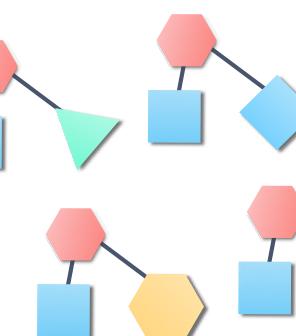
redesigned
chemical library



drug candidates
(lead compounds)



MNEC = 30 ng per ml



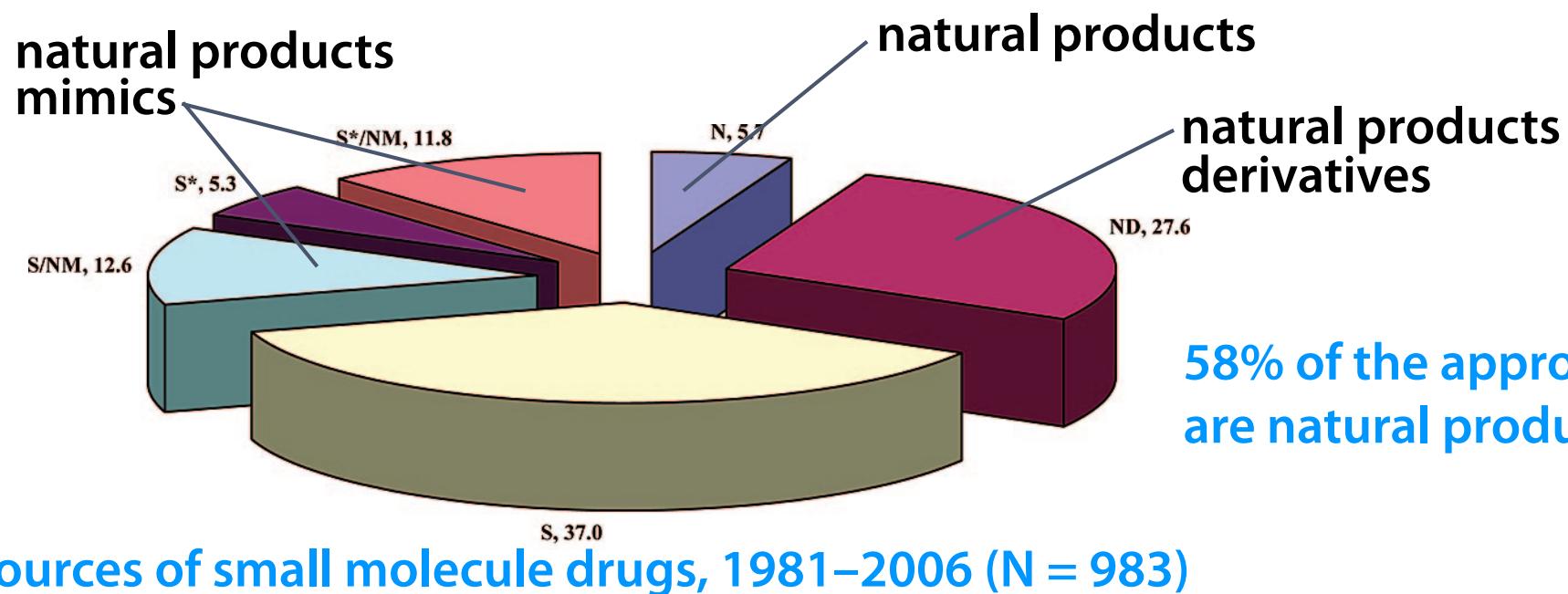
MNEC = 8 μg per ml

Natural products vs artificial compounds

Pros and cons of drug development approaches based on natural products

approach based on natural products	approach using artificial compounds
 Strong bioactivity obtained during the process of evolution	 Limitation in diversity of available chemical libraries
 Initial hit compounds are often drug-ready molecules	 Optimizations of hit compounds are generally required
 Highly rely on the compounds produced in nature	 Rational design strategies of novel compounds are possible
 Supply by chemical synthesis is sometimes challenging.	 The drugs can be readily supplied by chemically synthesis

Large presence of natural products in drug development



58% of the approved drugs
are natural products-related.

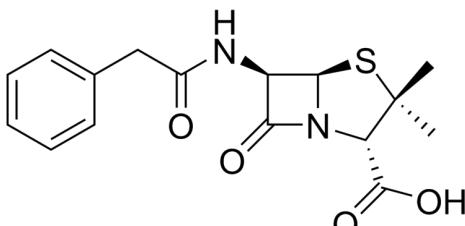
J. Med. Chem., 51, 2589–2599 (2008)

Power of natural products – 1

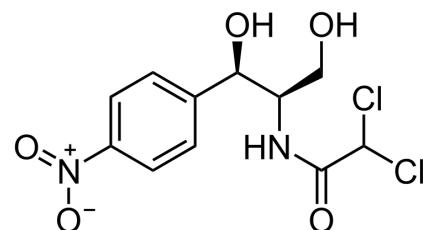
📌 Antibiotics

Antibiotics are compounds that kill bacteria or suppress bacteria growth

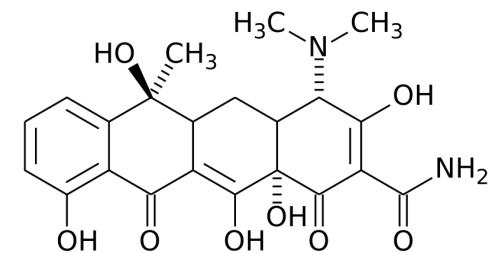
Many natural products exhibit antibiotic activities.



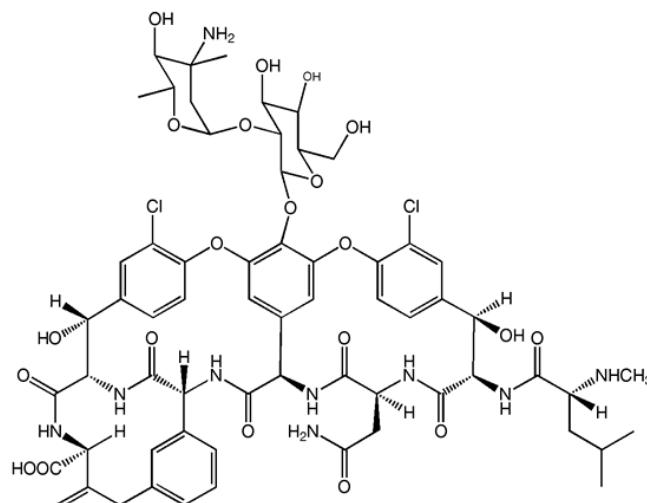
penicillin



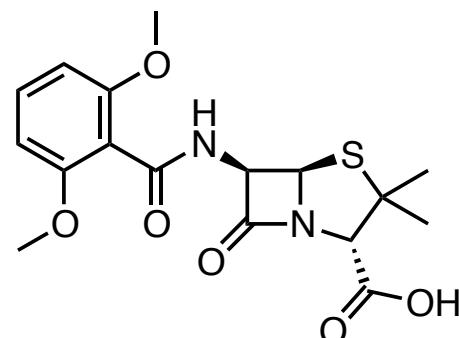
chloramphenicol



tetracycline



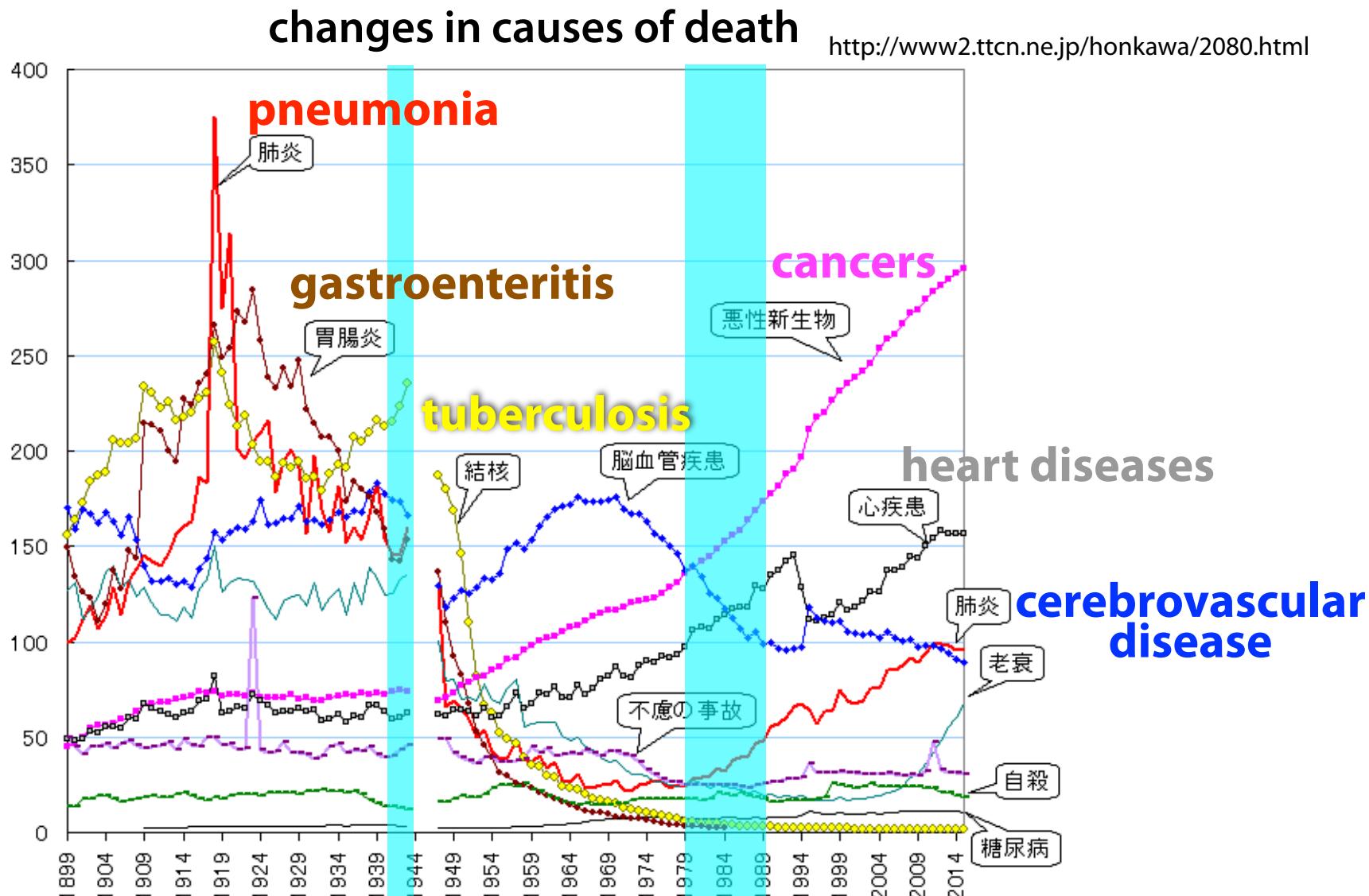
vancomycin



methicillin

Power of natural products – 1

Development of antibiotics changed the world.



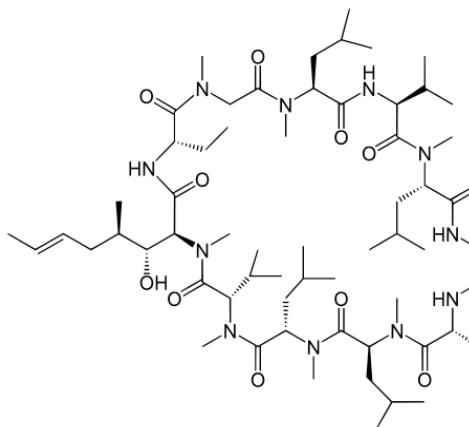
benzylpenicillin release in 1942

emergence of MRSA in 1980s

Power of natural products –2

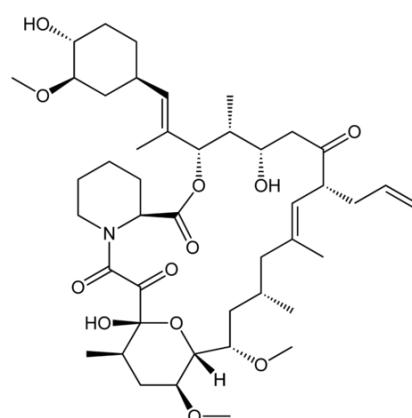
● Immunosuppressive drugs

- Immunosuppressive drugs are compounds that prevent the immune system.
- They drastically increased success rate of organ transplantation.



cyclosporin

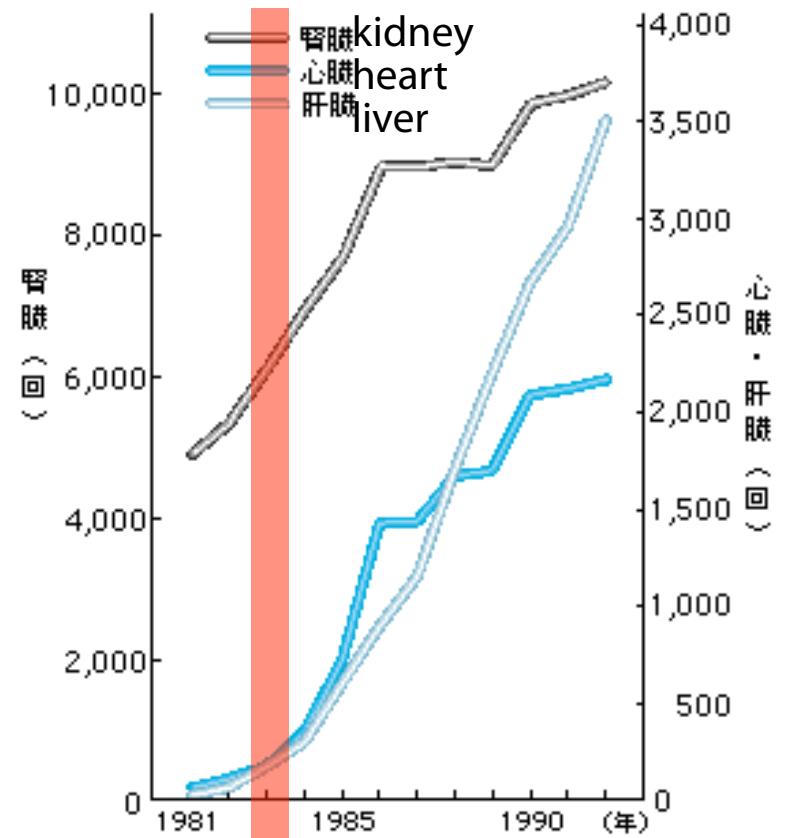
discovered by Sandoz (now Novartis)
approved in 1983



tacrolimus

discovered by Fujisawa (now Astellas)
approved in 1994

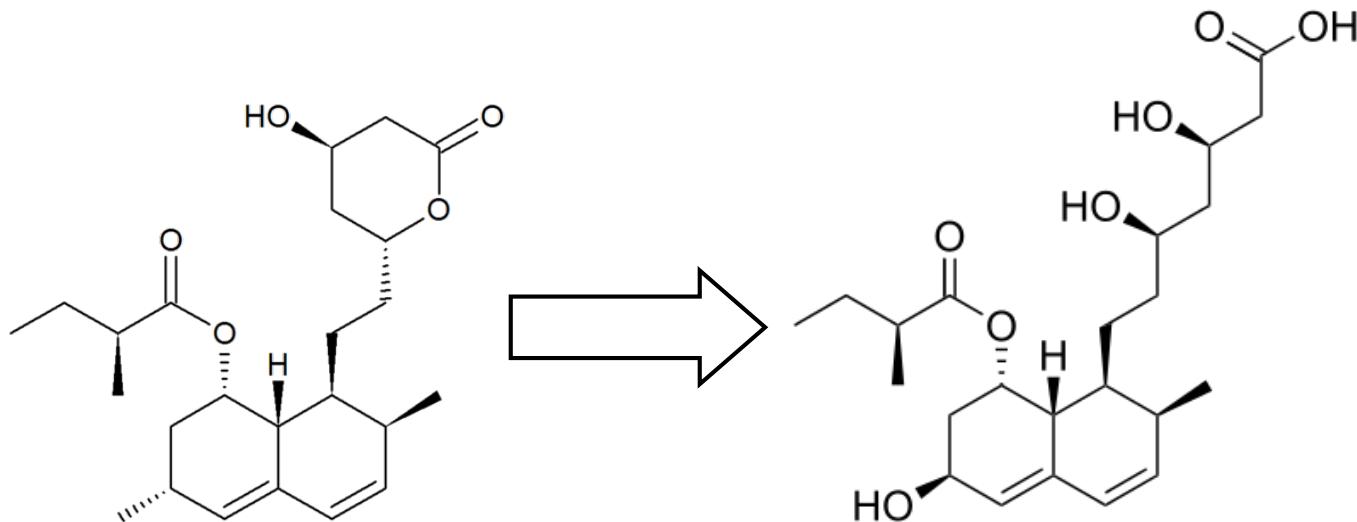
Number of transplantation in US



Power of natural products –3

Statins

- They reduce cholesterol in blood and are used for hyperlipidemia treatment.
- This class of drugs resulted in many blockbusters.



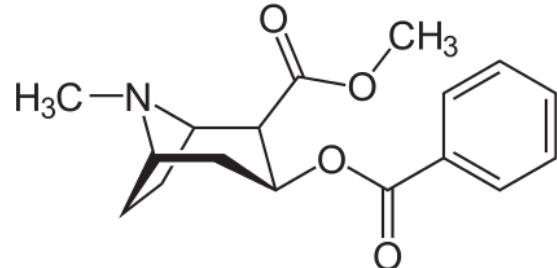
Mevastatin
natural product

Mevalotin
natural product derivative

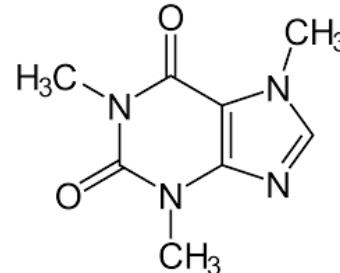
Daiichi-Sankyo/BMS
4,746 million \$ sales in 2003
(約5000億円)

Major categories of natural products

alkaloids (highly modified amino acids)

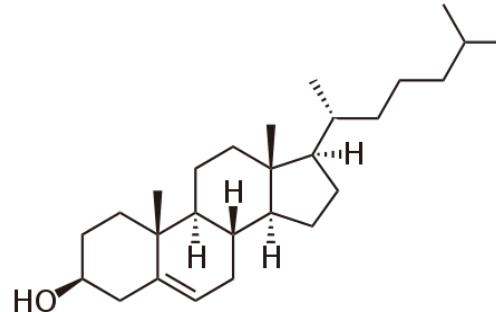


cocaine

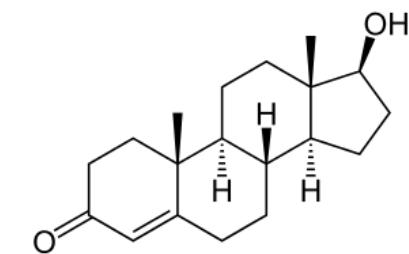


caffeine

steroids (terpenes with a specific ring system)

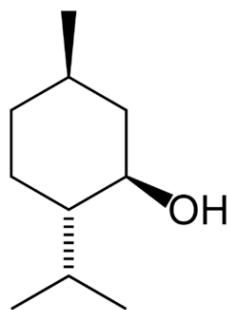


cholesterol

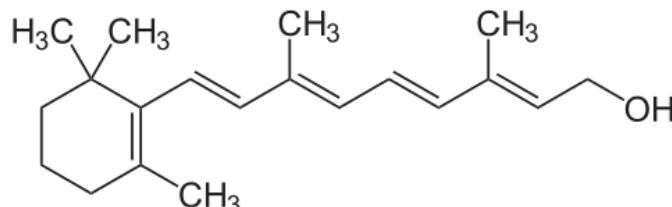


testosterone

terpenoids (oligomerized isoprenes)

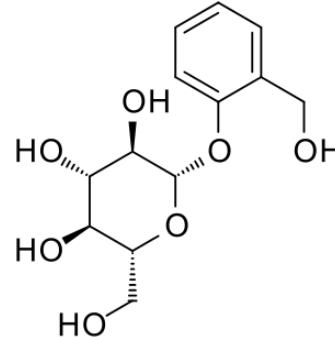


menthol

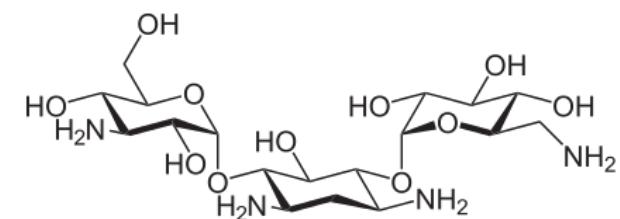


retinol

glycoside (highly modified sugars)



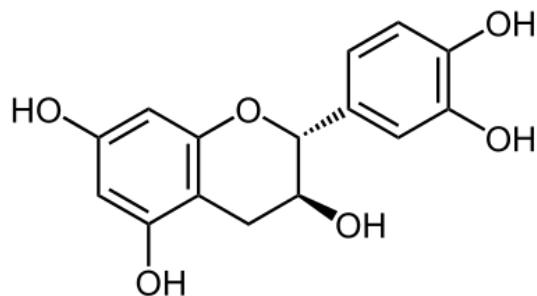
salicin



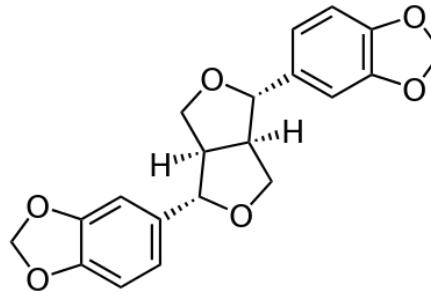
kanamycin

Major categories of natural products

polyphenol

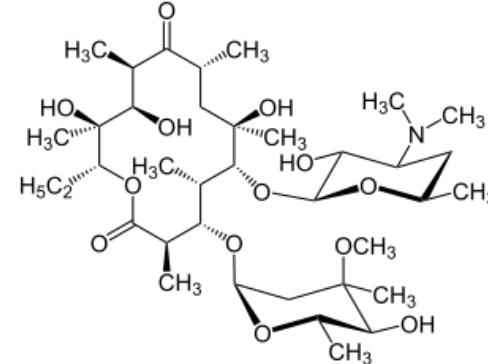


catechin

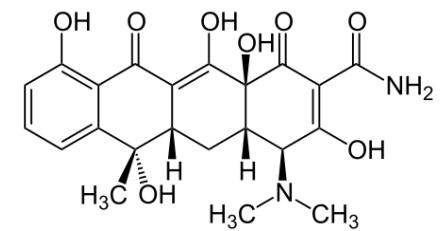


sesamin

polyketide (oligomerized malonic acid)

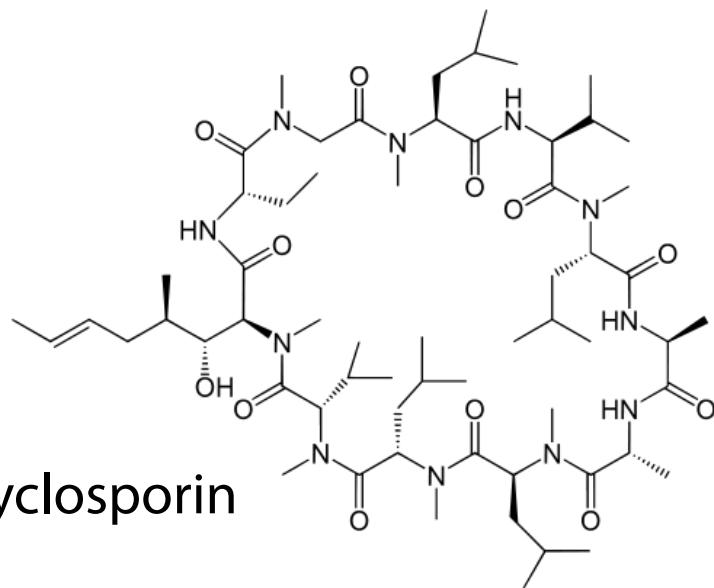


erythromycin

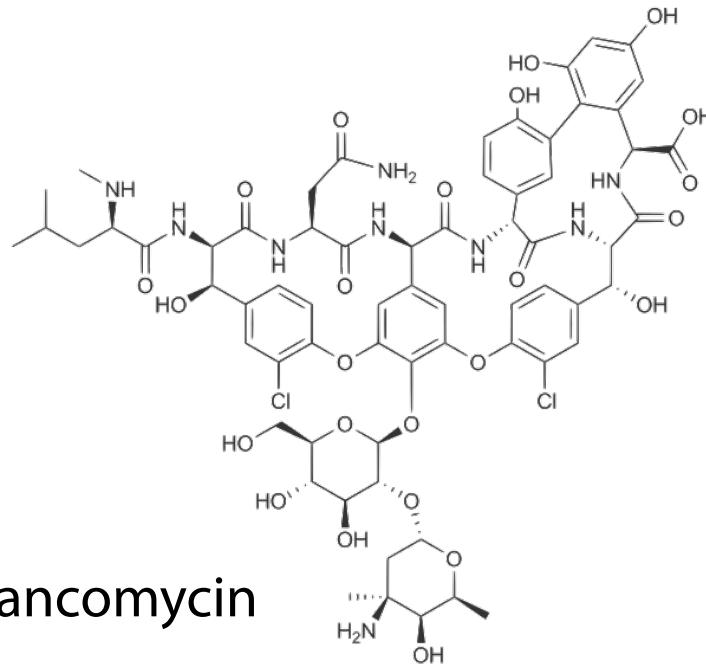


tetracycline

peptides (amino acid oligomers)



cyclosporin



vancomycin