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? (↔ primary metabolites)

essential and universal

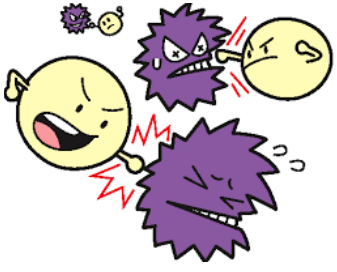
- They are organic compounds generated in organisms (metabolites) that are not essential in the reproduction, development, or normal growth.
- They often provide evolutionary advantages for the producing organisms.

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

spider venom

frog toxins

anti-bacterials



What is natural product?

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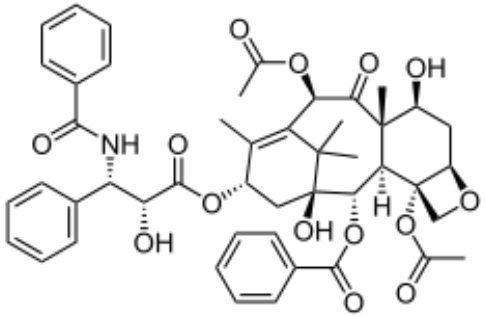
- It is a chemical compound produced by a living organism—that is, found in nature
- In a narrow sense, natural products often means secondary metabolites that have intriguing bioactivities.

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

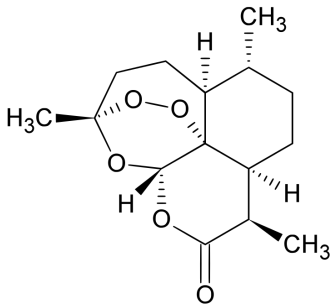
e.g.)



Paclitaxel

anti-cancer drug

isolated from a plant (*Taxus brevifolia*)

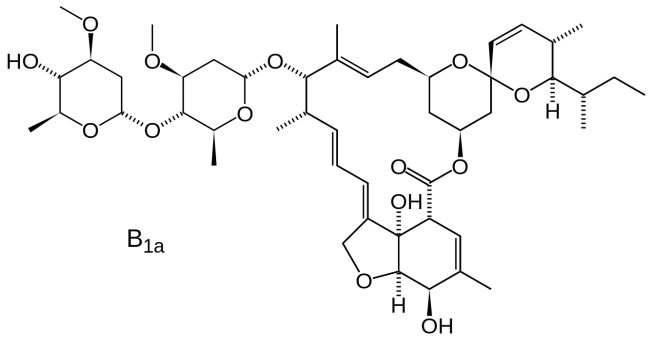


Artemisinin

anti-malarial drug

isolated from a plant (*Artemisia annua*)

Physiology/Medicine, 2015



Avermectin

anti-parasitic worm drug

produced by a bacterium (*Streptomyces avermitilis*)

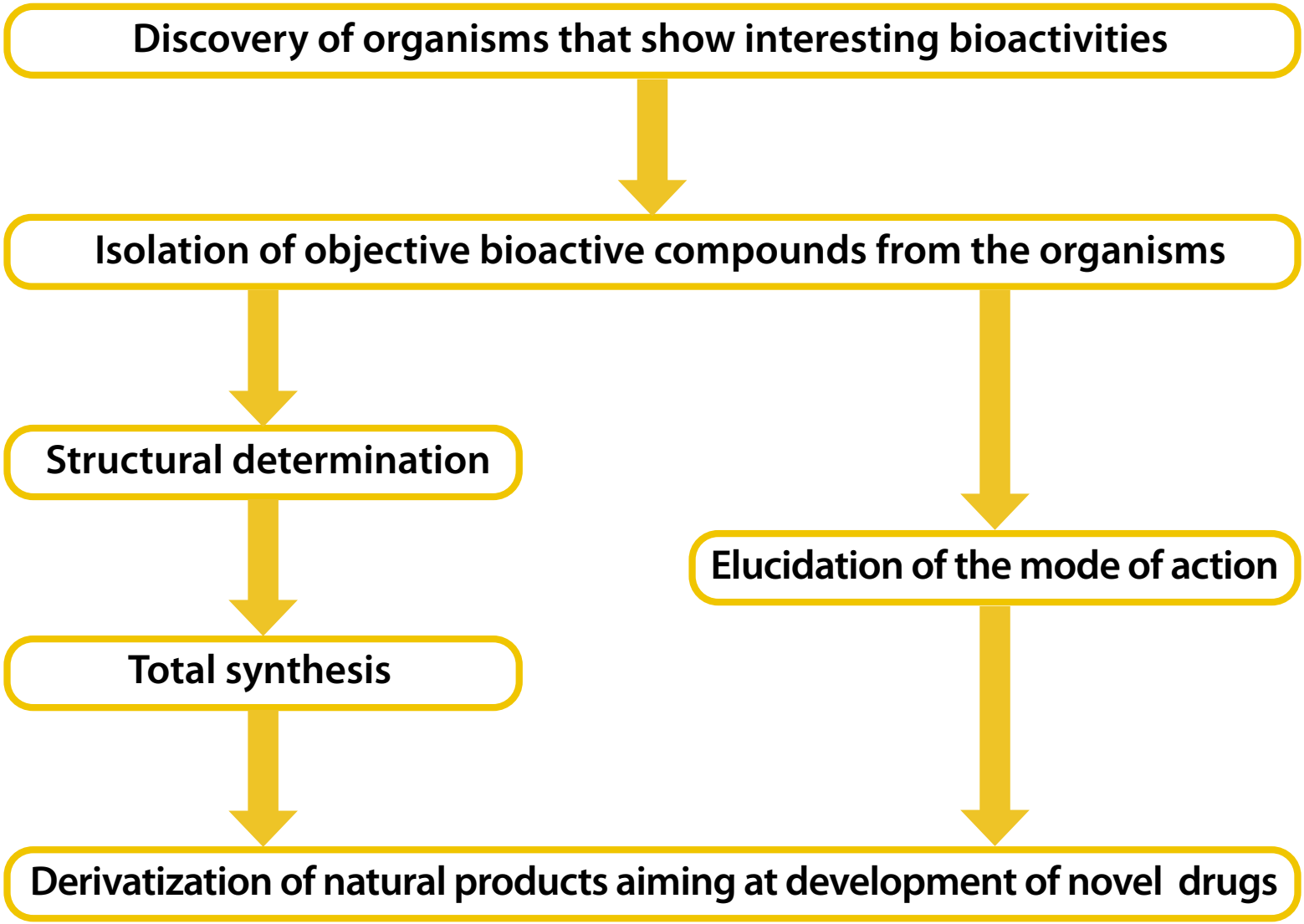
Physiology/Medicine, 2015

What is natural products chemistry?

What is natural products chemistry?

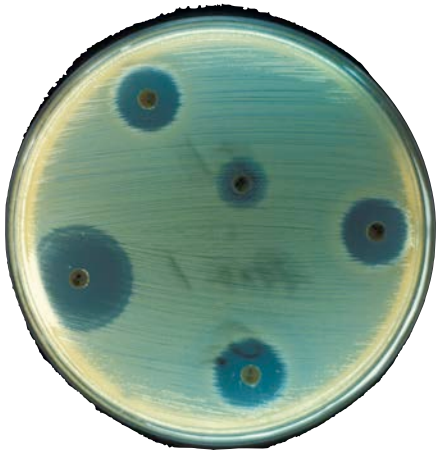
- A field of organic chemistry that deals with “natural products”.
- It is related to various chemistry fields such as medicinal chemistry, synthetic chemistry, and agricultural chemistry.
- Japanese scientists have historically shown large presence.

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

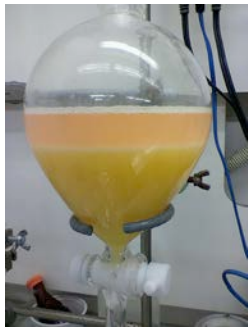
willow bark

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

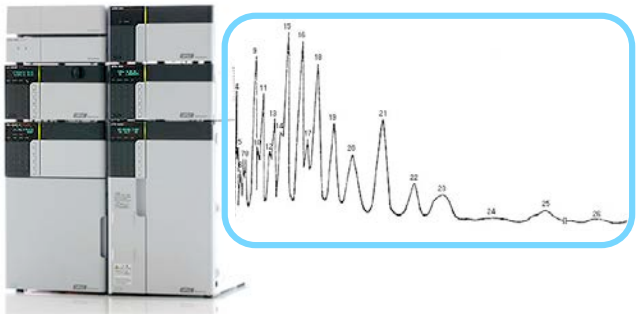
(0.3 mg of final compound)

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

Total synthesis

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

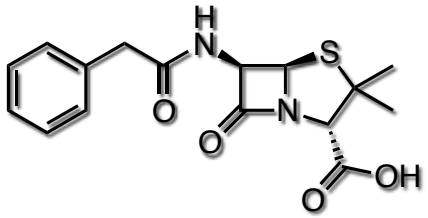
Typical flow in natural products chemistry

Discovery of organisms that show interesting bioactivities

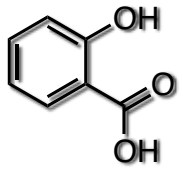
Isolation of objective bioactive compounds from the organisms

Structural determination

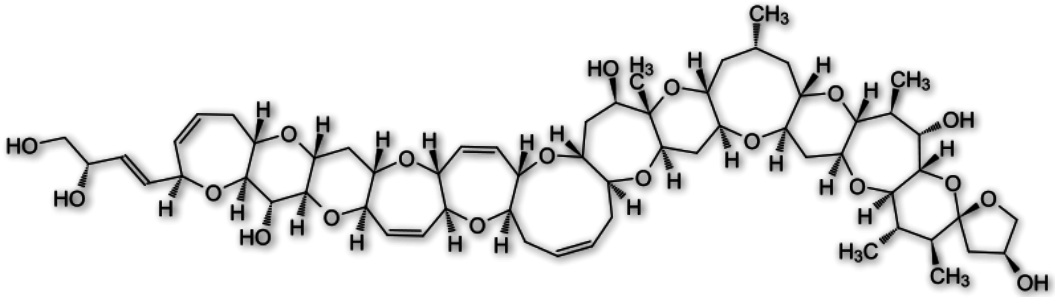
Determination of the structure of the bioactive compound
by means of elementary analysis, crystal structure analysis, and
comprehensive spectrum analyses (e.g., MS, MS-MS, IR, NMR, etc.)



benzylpenicillin



salicylic acid



ciguatoxin

Total synthesis

Elucidation of the mode of action

Derivatization of natural products aiming at development of novel drugs

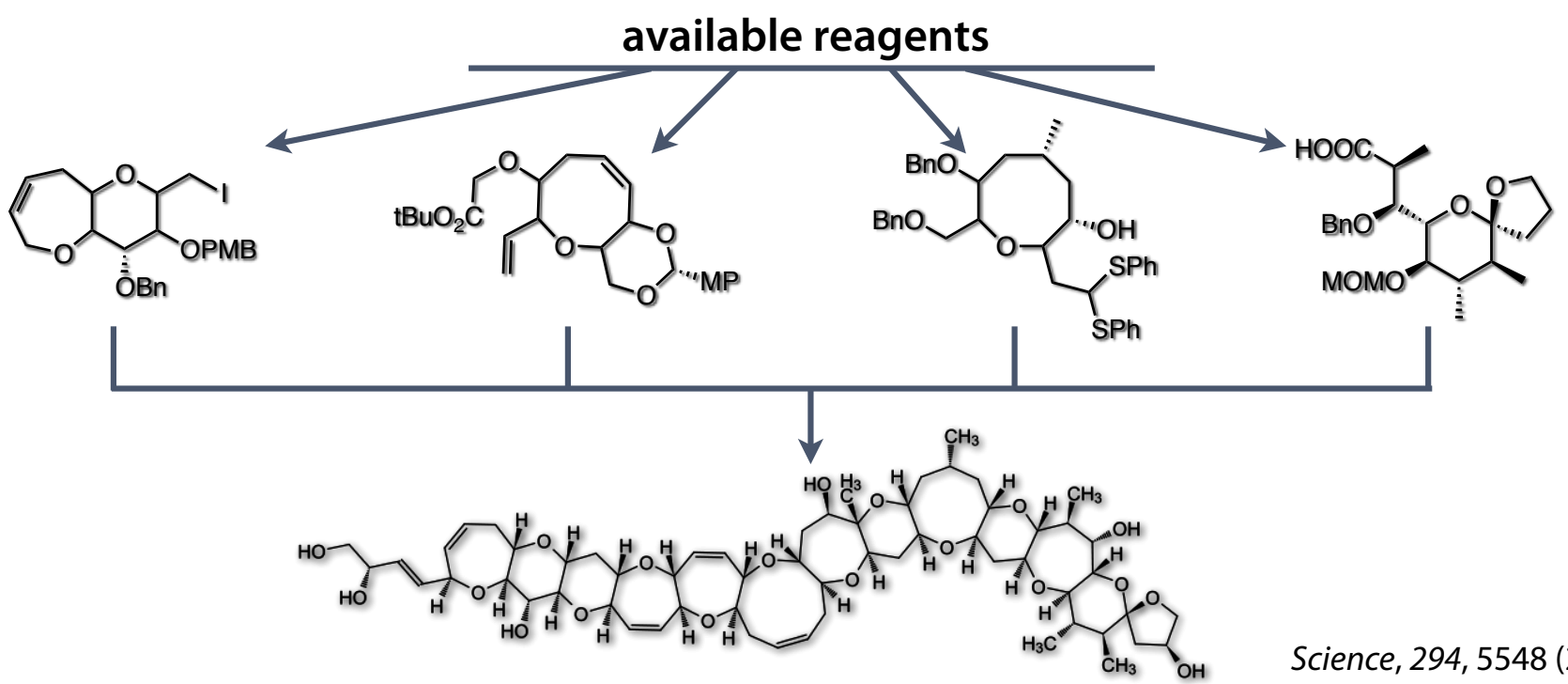
Typical flow in natural products chemistry

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)



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

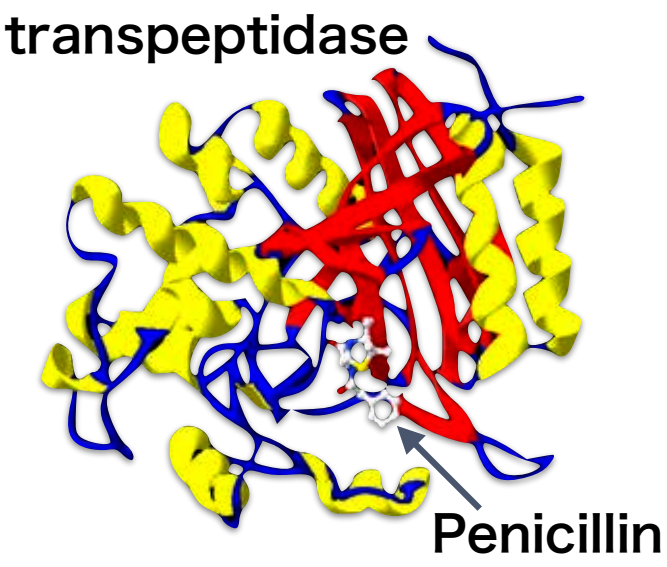
Discovery of organisms that show interesting bioactivities

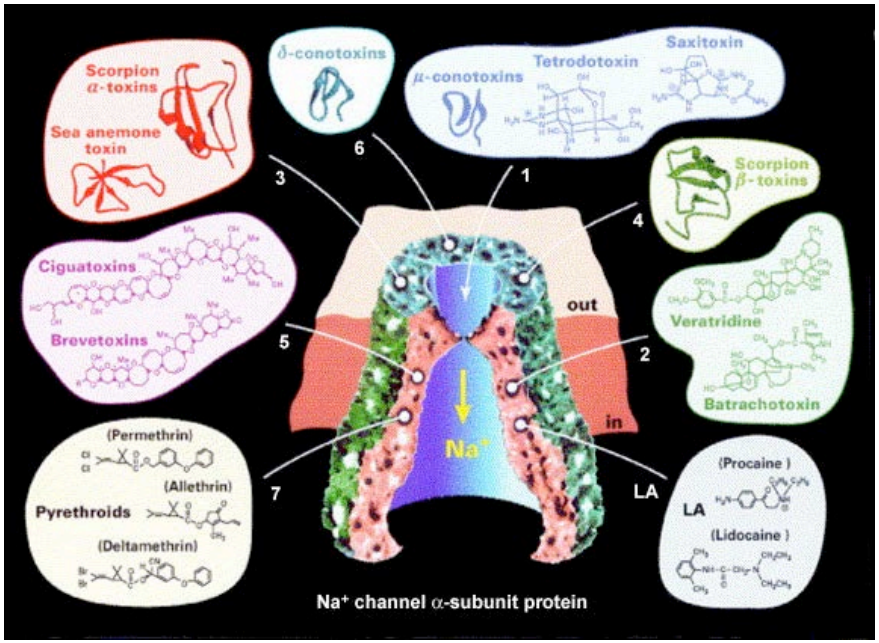
Isolation of objective bioactive compounds from the organisms

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

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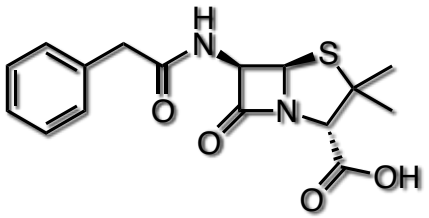
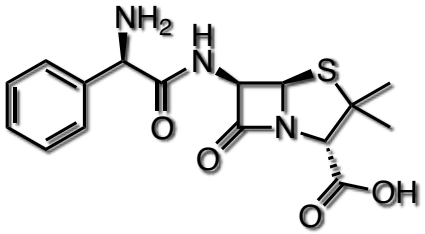
Total synthesis

Elucidation of the mode of action

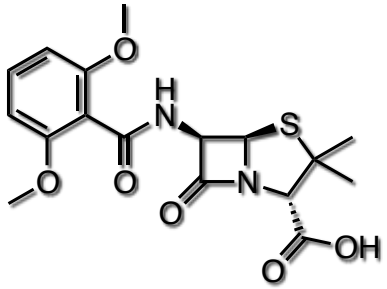
Derivatization of natural products aiming at development of novel drugs



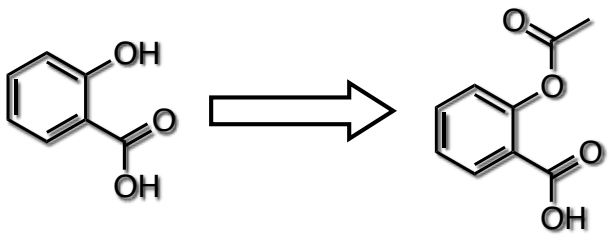
benzylpenicillin
(penicillin G)



Ampicillin



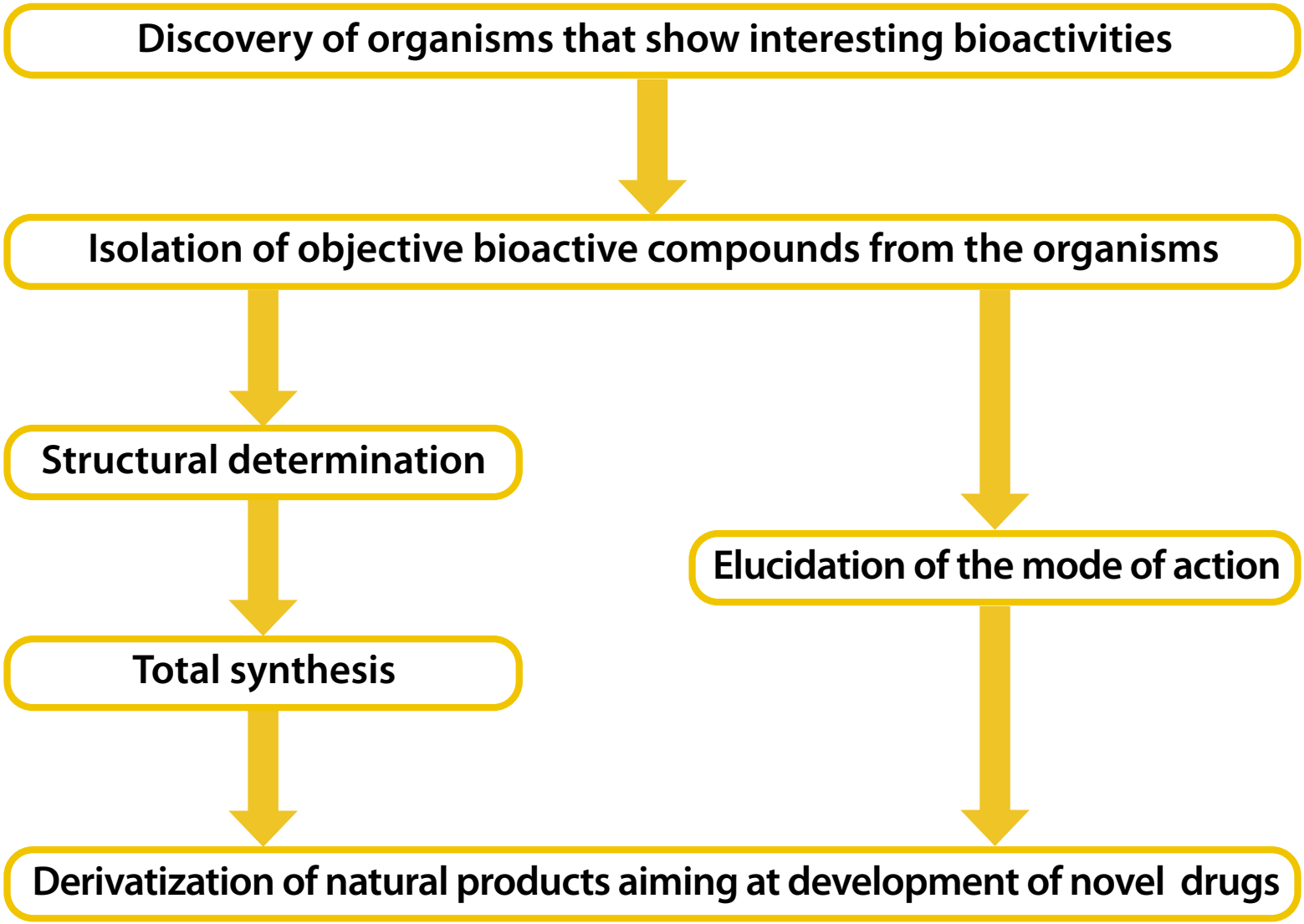
methicillin



salicylic acid

acetylsalicylic acid
(aspirin)

Typical flow in natural products chemistry



An example of drug development based on natural products

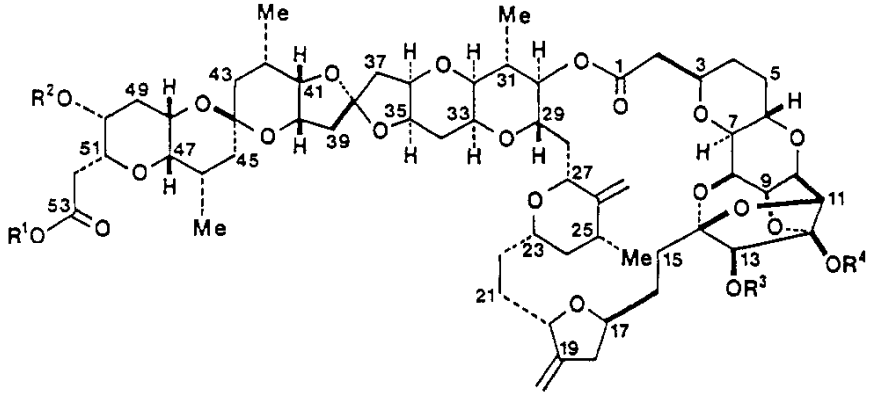
1985: Uemura *et al.*

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

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

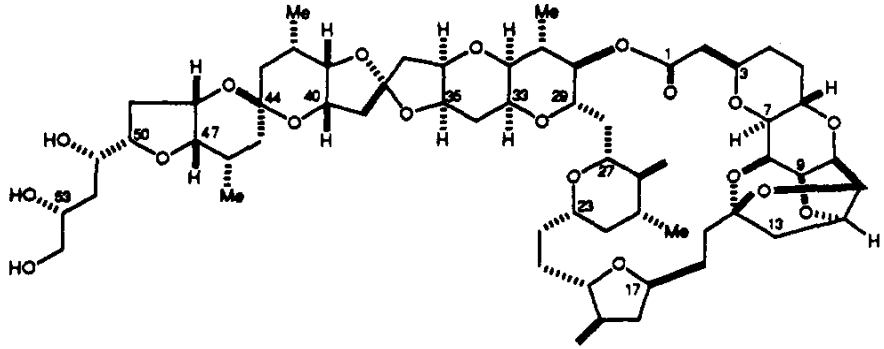
Discovery and identification of novel compounds with potent cytotoxicity
(named halichondrins)

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 ng/mL (= 80 pM)

Mode of action: Inhibition of cell division via targeting tubulin

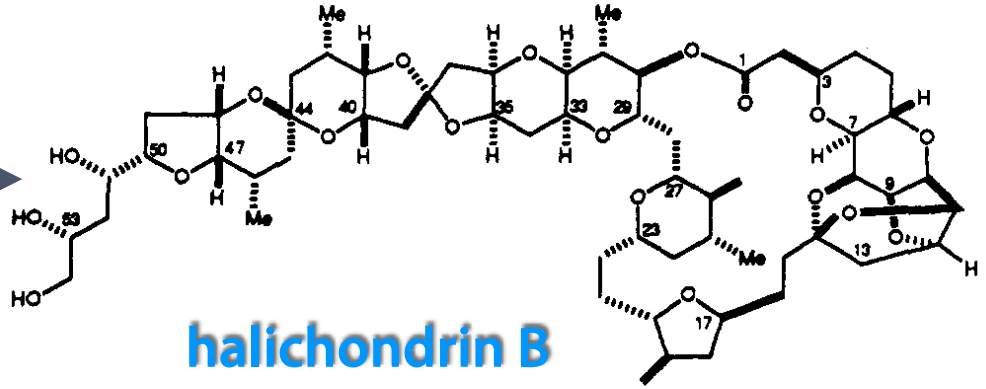
J. Biol. Chem. **266** (24): 15882–9

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

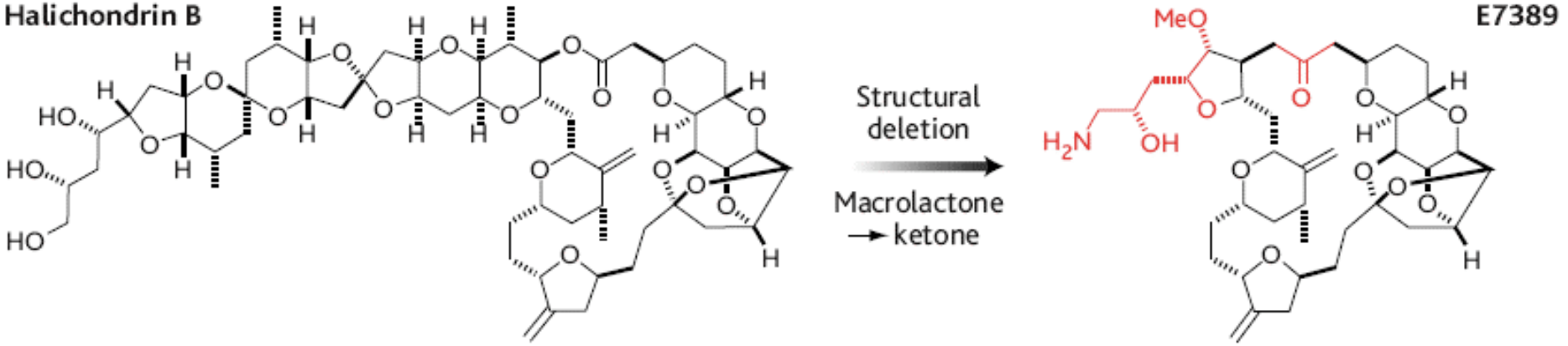


halichondrin B

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

2004: Eisai Co., Ltd.

Simplification of halichondorins - development of E7389



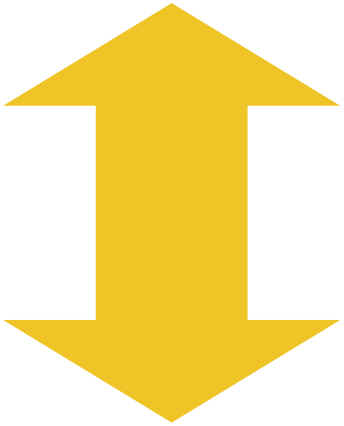
2/3 molecular weight and chiral centers

improved in vivo stability

FDA approval in 2010!

Drug development using artificial compounds

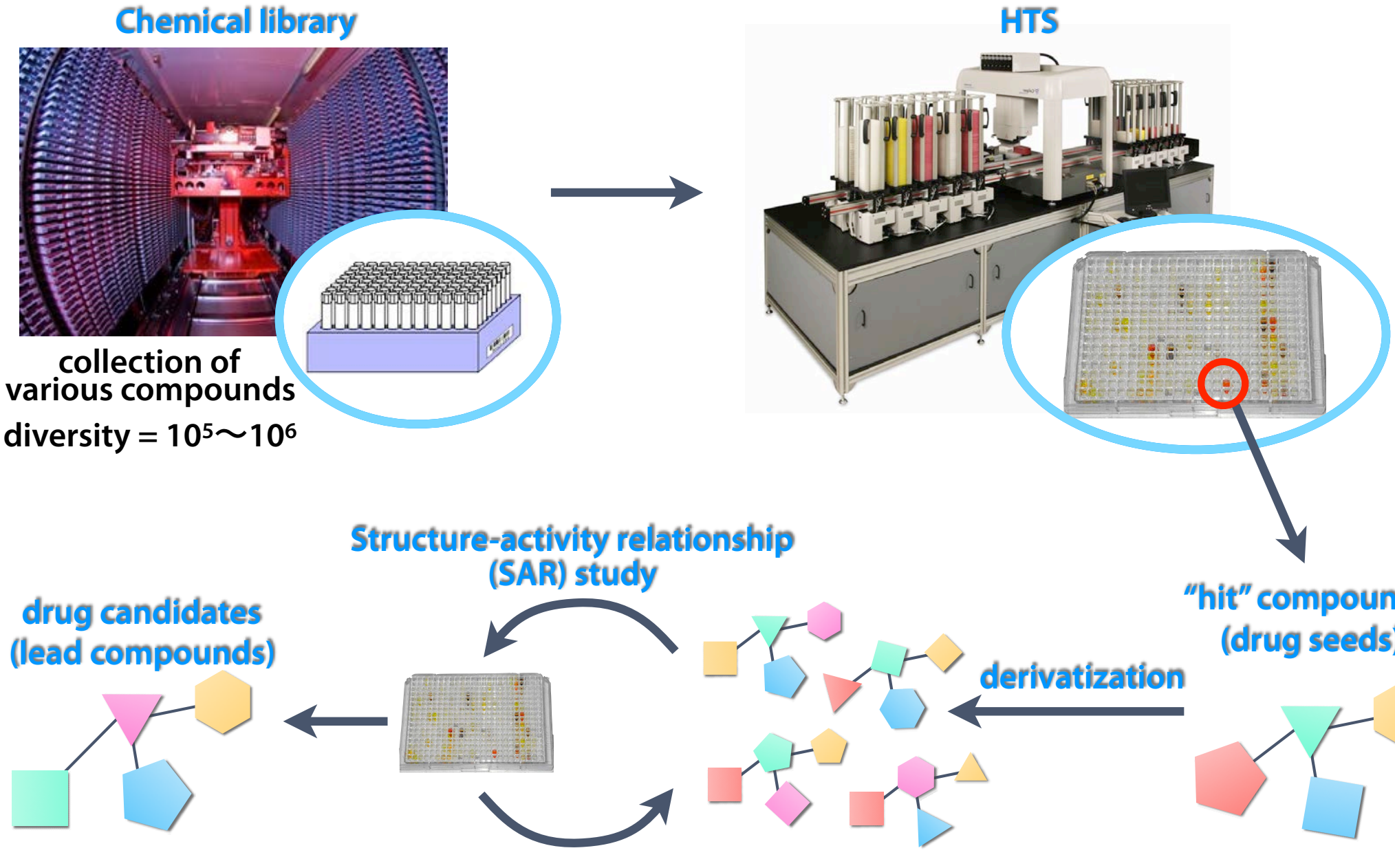
- **Drug development based on natural products chemistry**
  - Discover the "seeds" of objective drugs from nature, and brush them up to develop desirable drugs



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

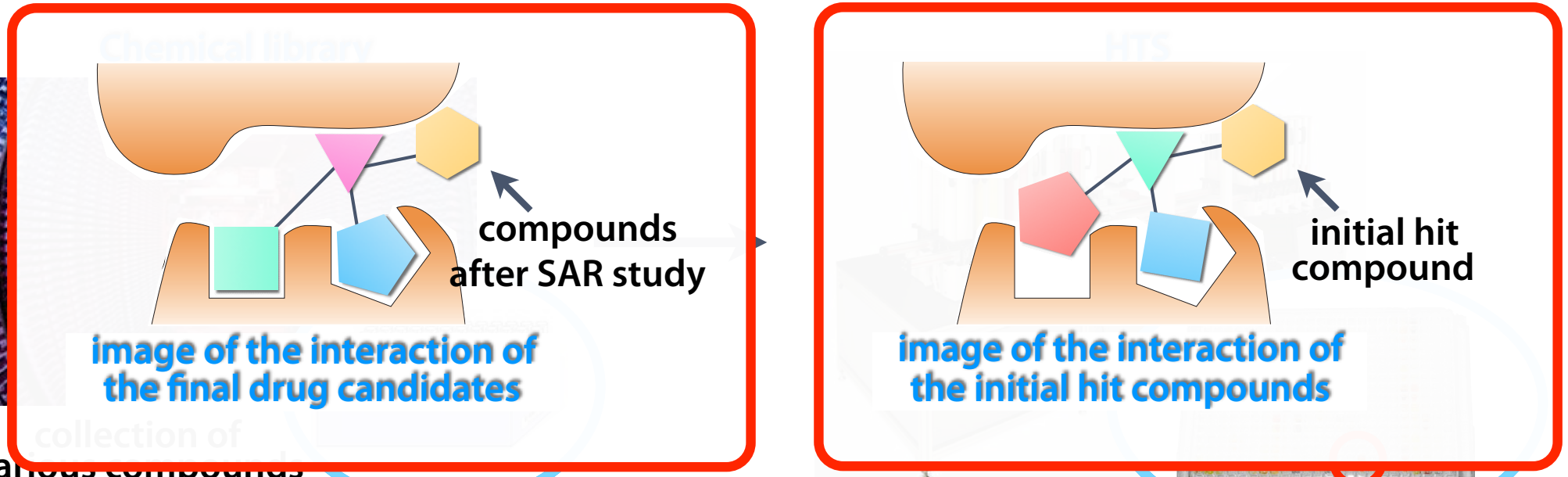
Drug development using artificial compounds

- High-throughput screening (HTS) of chemical libraries

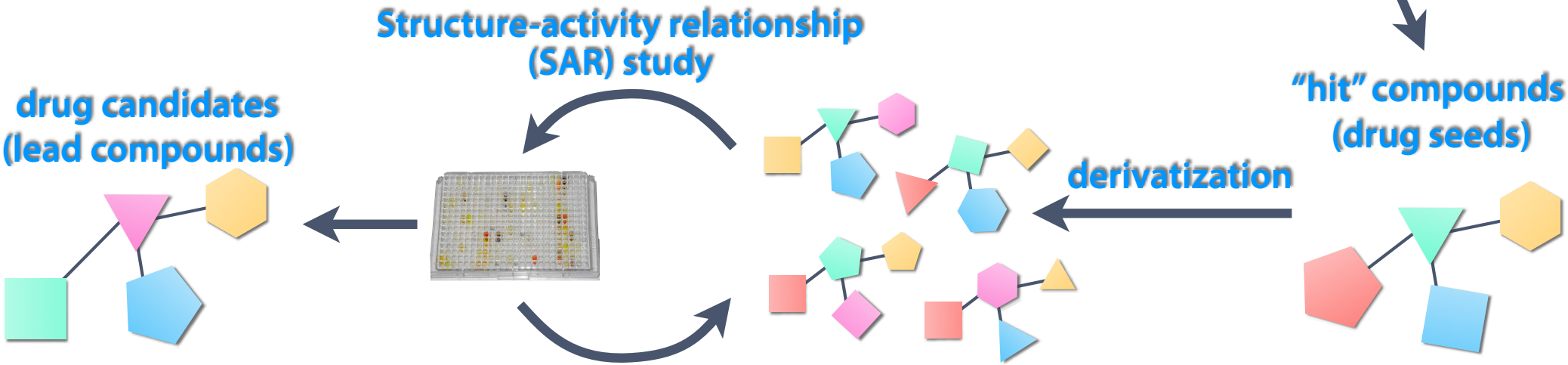


Drug development using artificial compounds

High-throughput screening (HTS) of chemical libraries

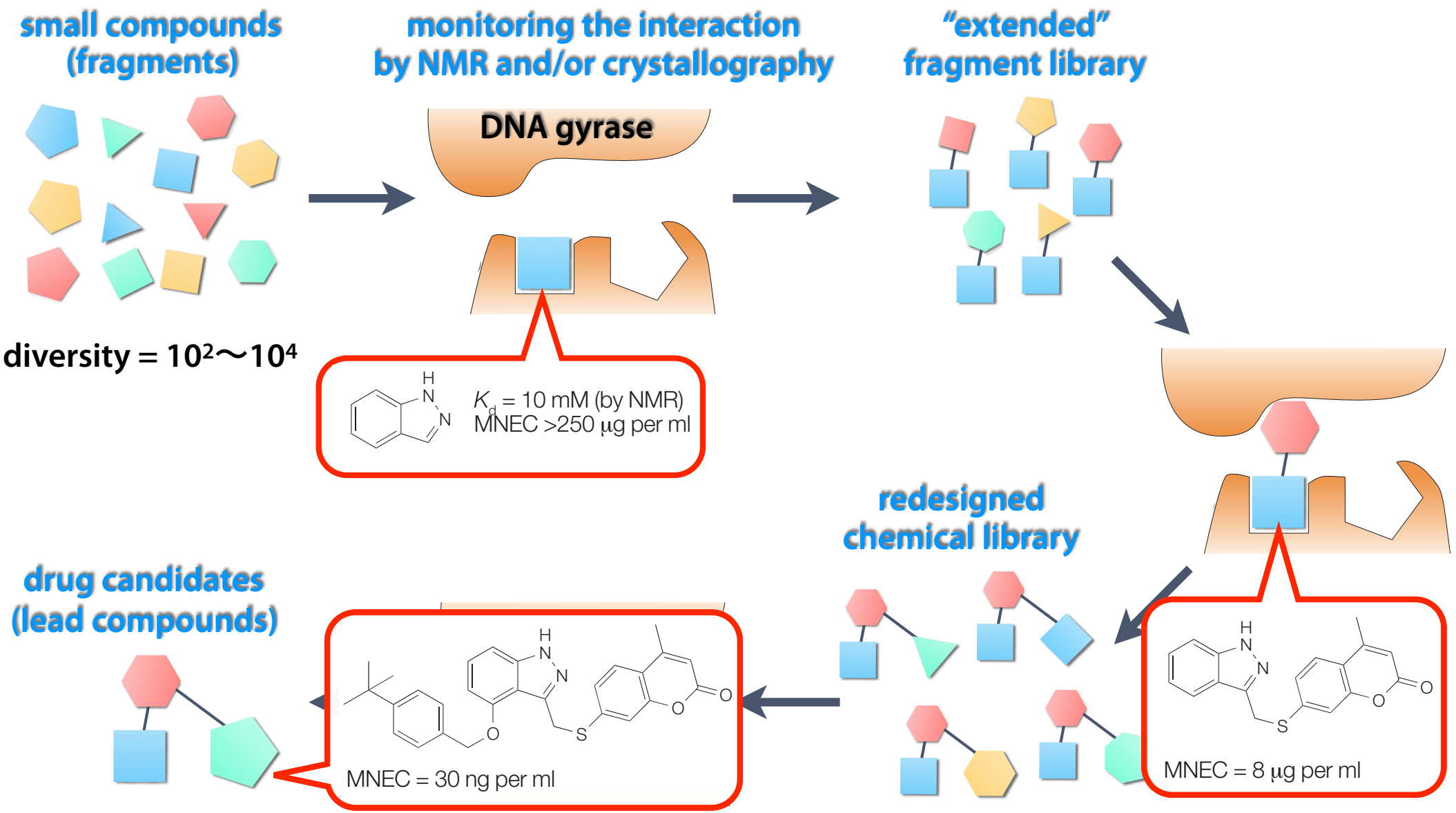


diversity = 10^5〜10^6



Drug development using artificial compounds

Fragment-based drug discovery (FBDD)

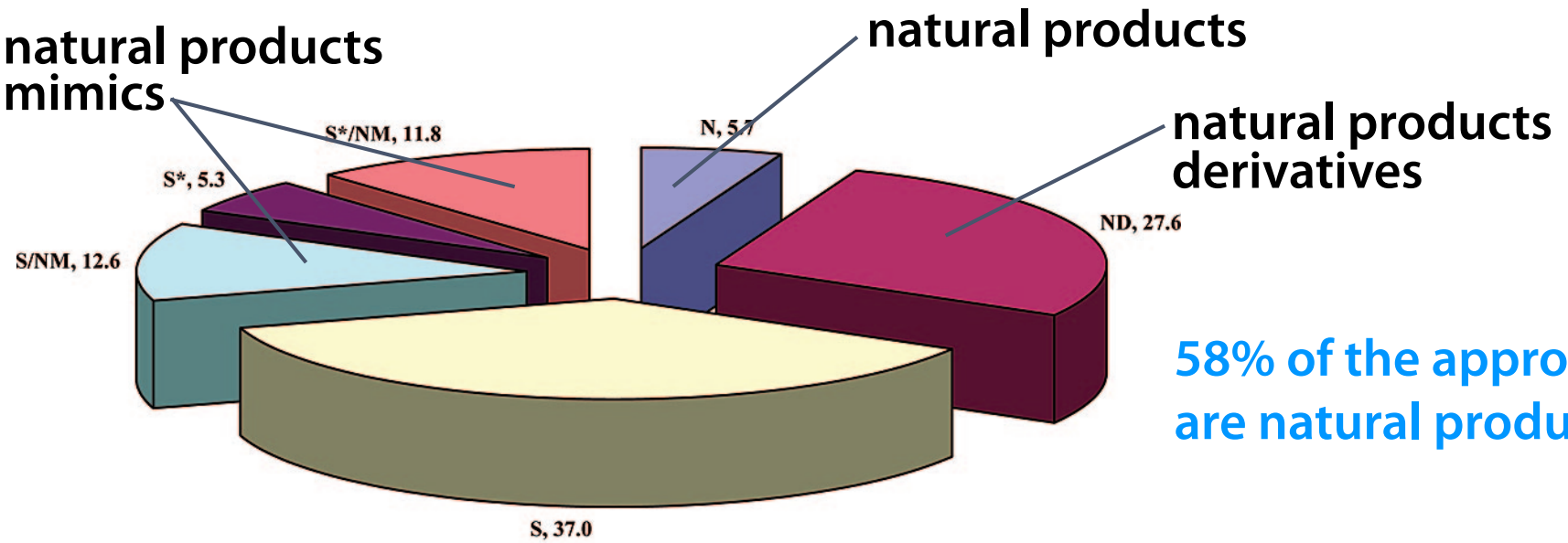


Natural products vs artificial compounds

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.

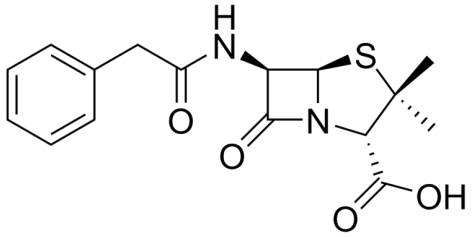
sources of small molecule drugs, 1981–2006 (N = 983)

J. Med. Chem., *51*, 2589–2599 (2008)

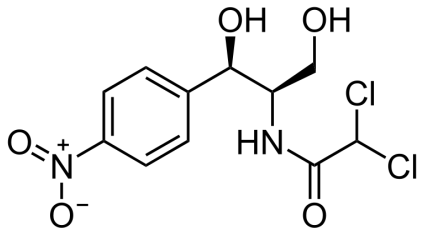
Power of natural products –1

Antibiotics

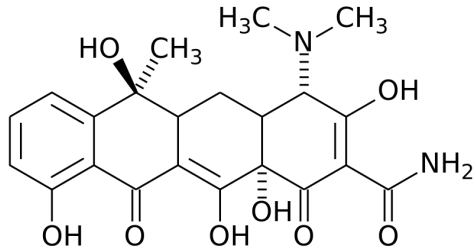
- Antibiotics are compounds that kill bacteria or suppress bacteria growth
- Many natural products exhibit antibiotic activities.



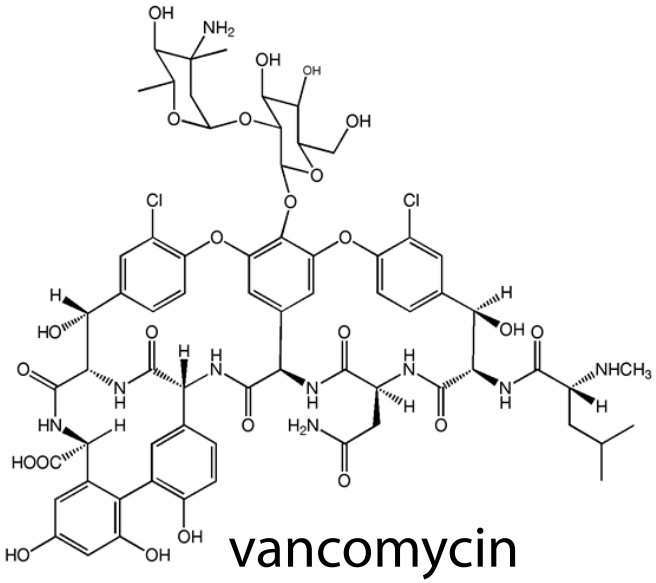
penicillin



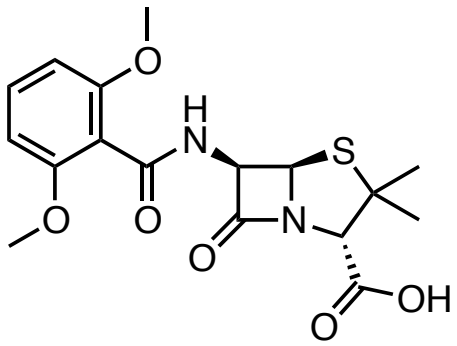
chloramphenicol



tetracycline



vancomycin



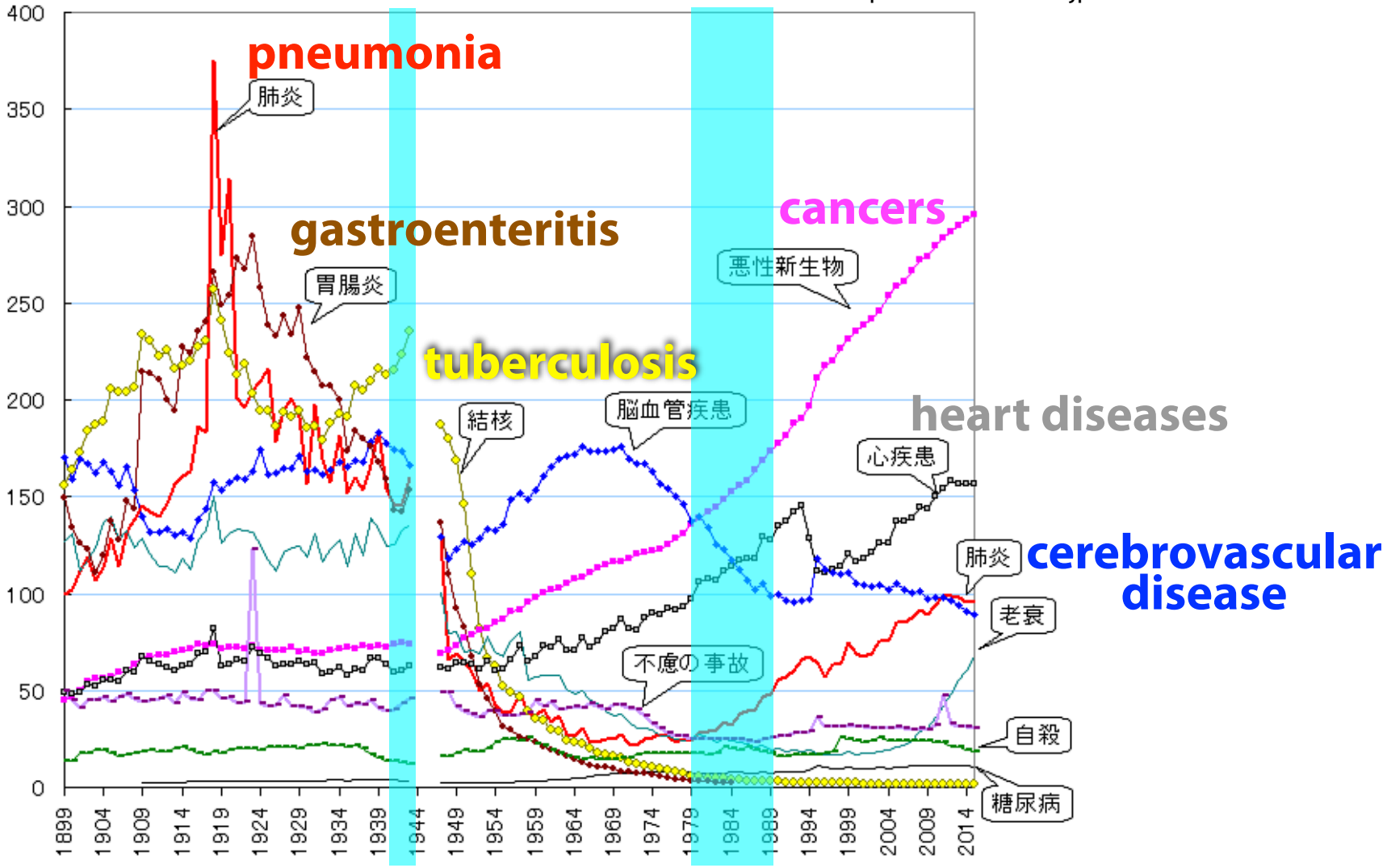
methicillin

Power of natural products –1

Development of antibiotics changed the world.

changes in causes of death

http://www2.ttcn.ne.jp/honkawa/2080.html



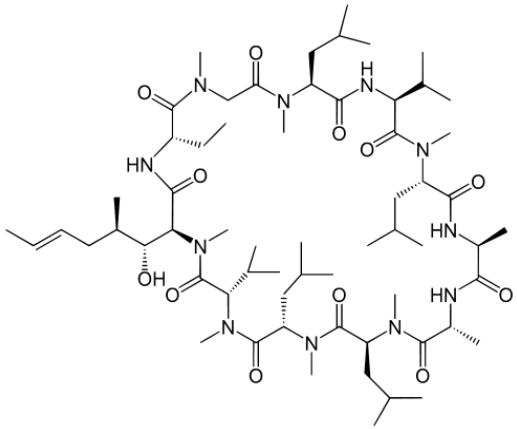
benzylpenicillin release in 1942

emergence of MRSA in 1980s

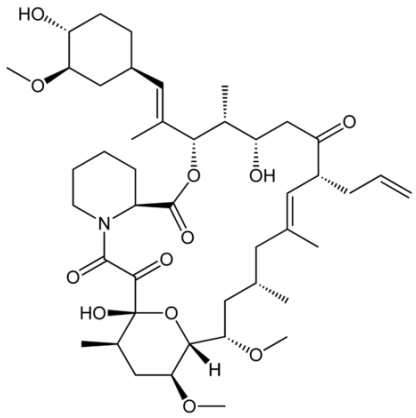
Power of natural products –2

Immunosuppressive drugs

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

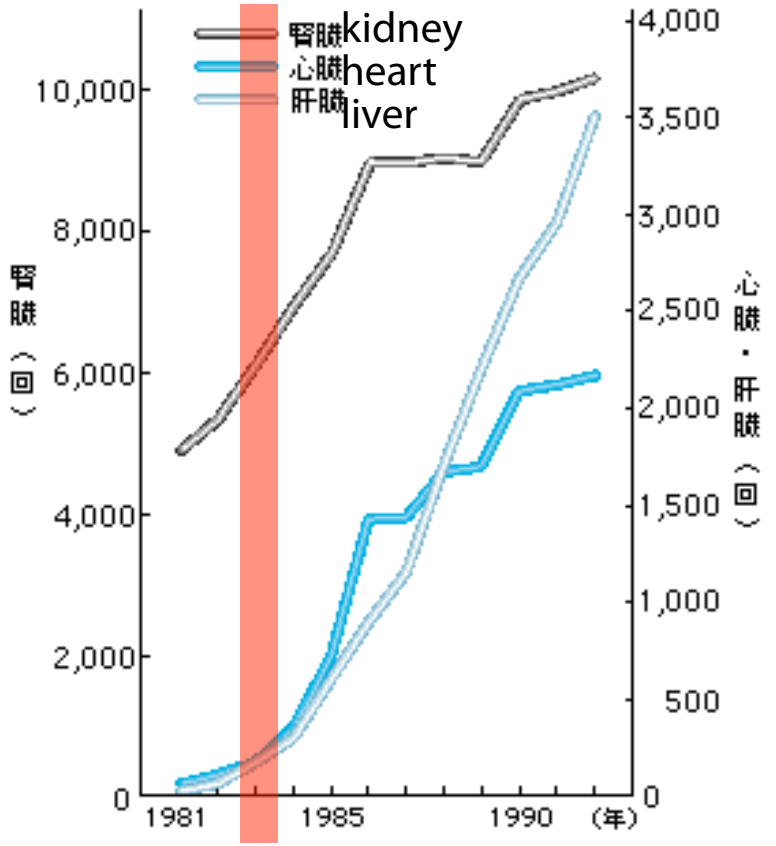


cyclosporin
discovered by Sandoz (now Novartis)
approved in 1983



tacrolimus
discovered by Fujisawa (now Astellas)
approved in 1994

Number of transplantation in US

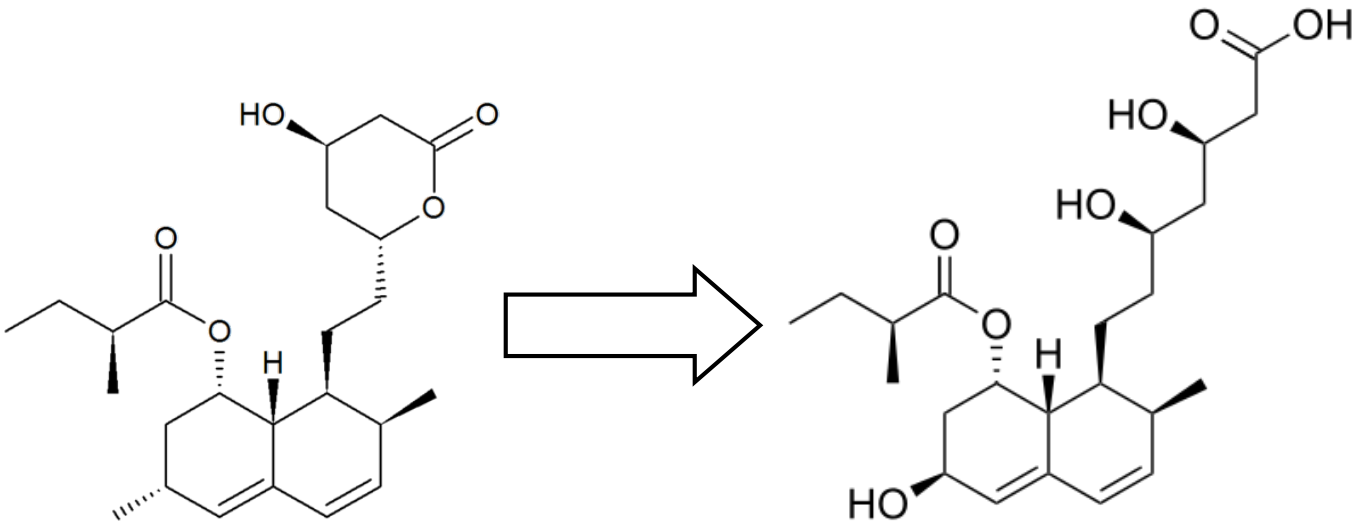


http://www.medi-net.or.jp/tcnet/tc_1/1_2.html

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.



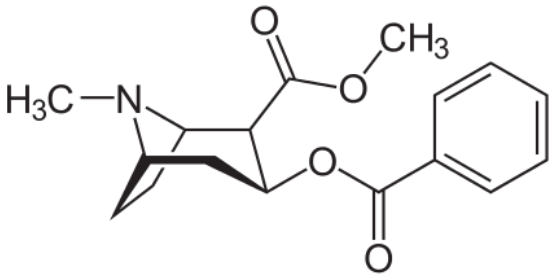
Mevastatin
natural product

Mevalotin
natural product derivative

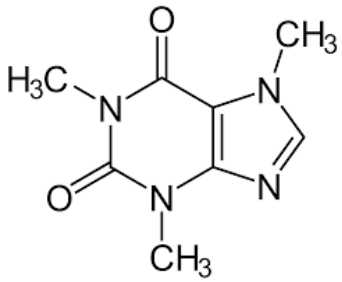
Daiichi-Sankyo/BMS
4,746 million $ sales in 2003
(約5000億円)

Major categories of natural products

alkaloids (highly modified amino acids)

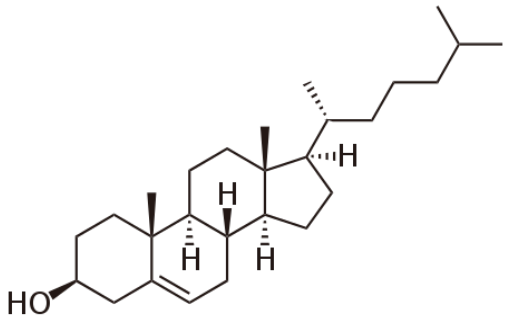


cocaine

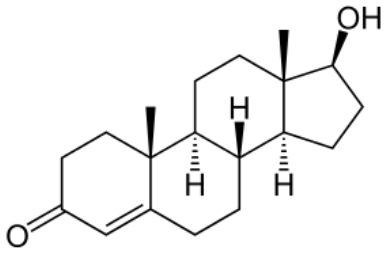


caffeine

steroids (terpenes with a specific ring system)

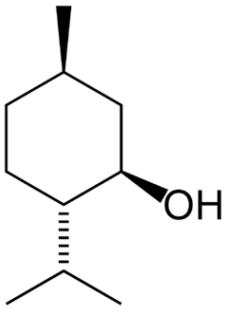


cholesterol

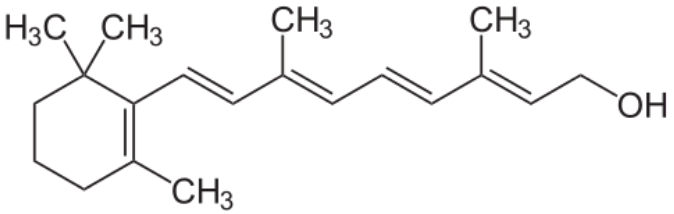


testosterone

terpenoids (oligomerized isoprenes)

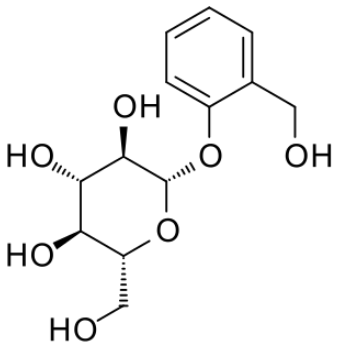


menthol

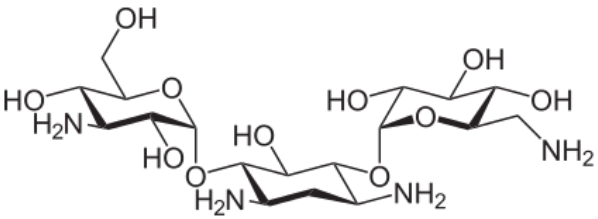


retinol

glycoside (highly modified sugars)



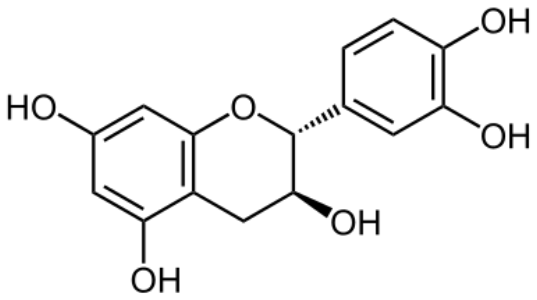
salicin



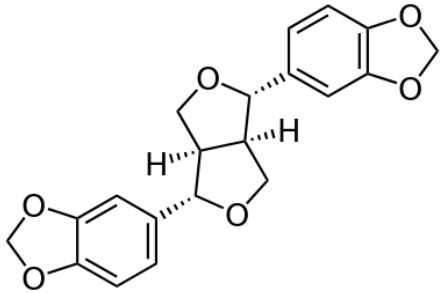
kanamycin

Major categories of natural products

polyphenol

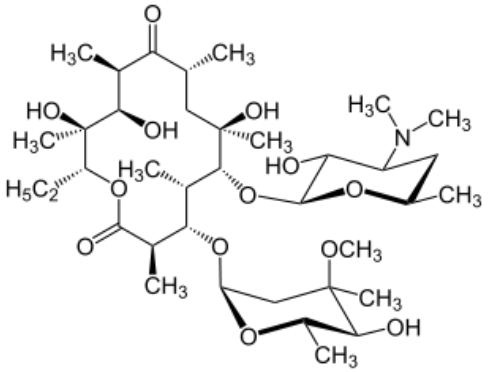


catechin

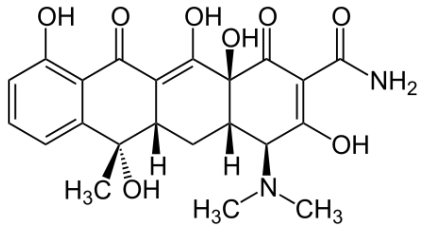


sesamin

polyketide (oligomerized malonic acid)

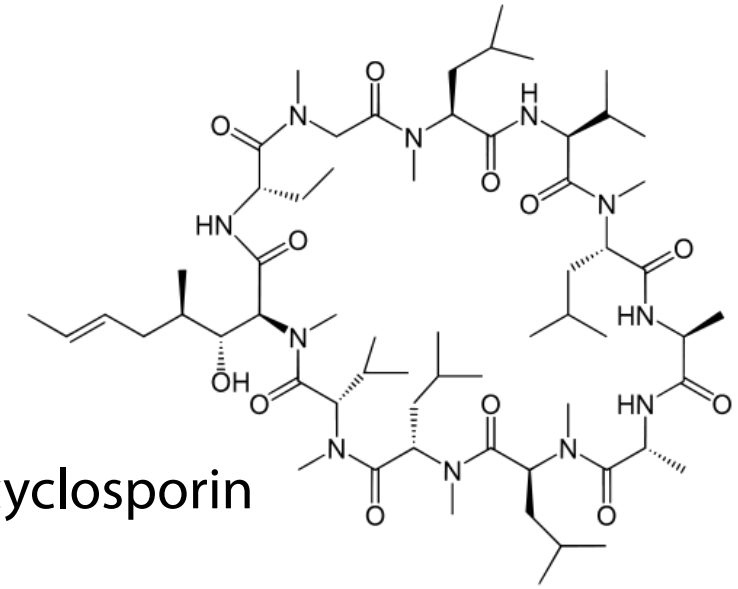


erythromycin

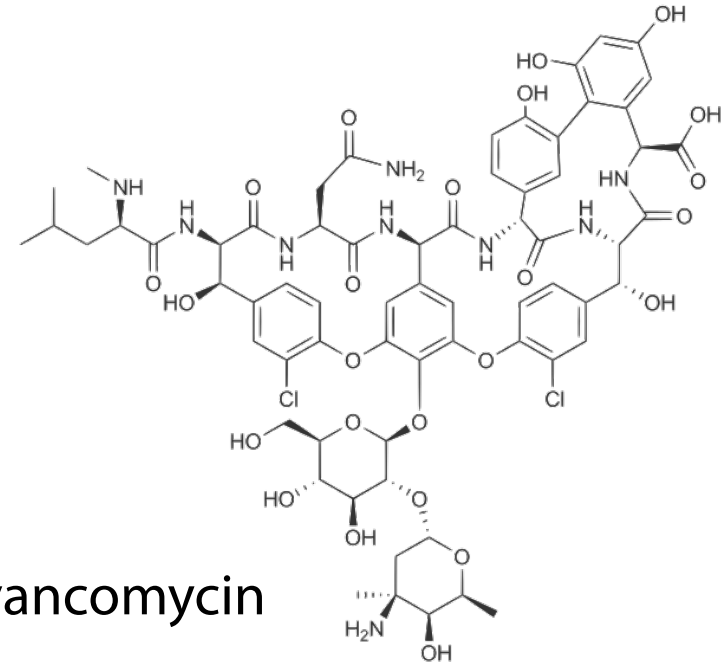


tetracycline

peptides (amino acid oligomers)



cyclosporin



vancomycin