Rational Drug Design lecture 3

Łukasz Berlicki

Medical plants have been known in each civilisation

- First description of medical plants on clay plate from Mesopotamia (2 600 b.c.)
- licorice
- myrrh
- Poppy seed

Strong plant drugs known before 1800

- Ancient Greece
  - Opium (*Papaver somniferum*)
  - Belladonna (*Atropa belladona*)
- Americas
  - bark of the quince tree (*Cinchona* spp.)
  - Coca leaves (*Erythroxylon coca*)
- China
  - Ma Huang (*Ephedra* spp.)
- Europe
  - Ergot (*Claviceps purpurea*)

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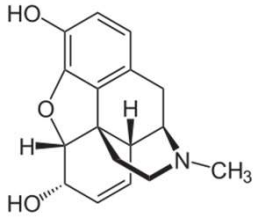
Poppy seed

Morphine
analgesic



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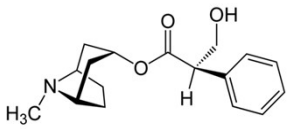
belladonna or **deadly nightshade**



Atropine
diastolic
Expanding pupils

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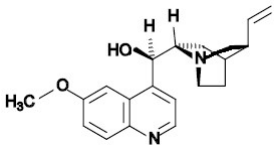
Cinchona tree



Quinine
antimalaria

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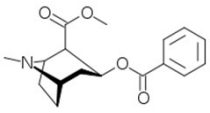
Coca tree



Cocaine
local anesthetic

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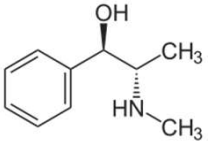
Ephedra



Ephedrine
anti-asthma
Upper respiratory tract infections

Strong plant drugs known before 1800

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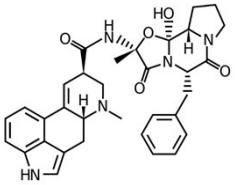
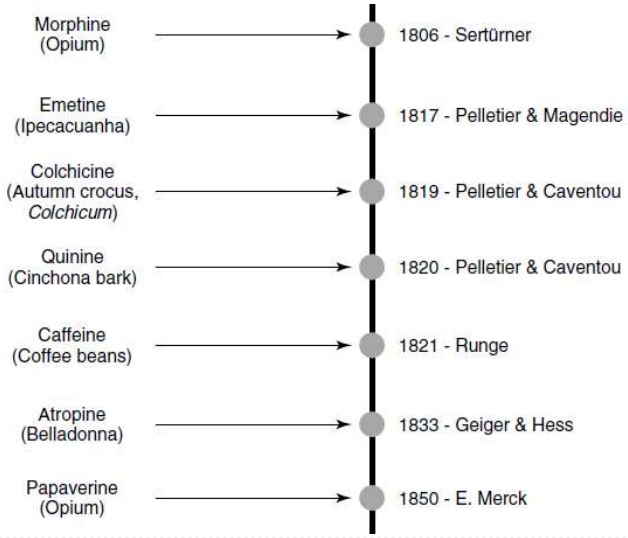
Ergot (parasite of cereals)

Ergotamine
migraine



Large number of alkaloids was isolated in XIX.



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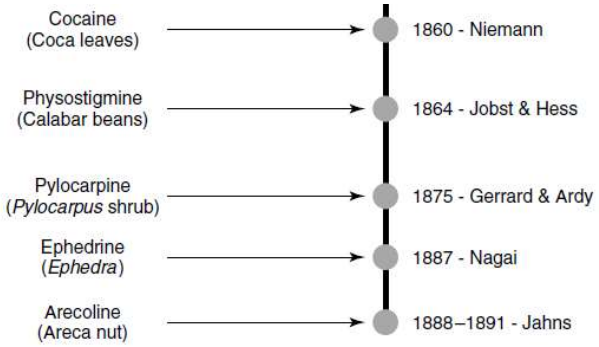


Quinine

- XVII c., Spanish missionaries in South America have learned about the healing properties of the bark of the cinchona tree.
- Most probably on the basis of observations of Indians who drank water from streams under these trees and did not suffer from malaria.
- The name comes from the Princess Cinchon (Peru), which was cured with the help of the bark of the cinchona tree.

Quinine

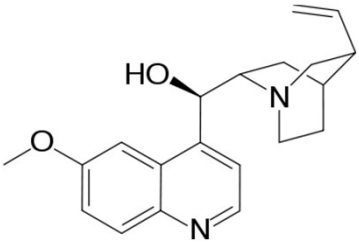
- 1648, the bark was brought to Europe
- It was named as "papal powder" or "Jesuit powder".
- Initially banned in the countries of the Reformation (England).
- Used to heal the King of England, Charles II (1670).

Quinine

- 1820, Joseph Peltier and Joseph Caventou isolated quinine from bark of cinchona tree.
- 1826, Peltier and Caventou produced 1800 kg of quinine from 150 tons of bark.
- Quinine was the first natural substance produced on an industrial scale.
- First factory isolating natural products was established by Emmanuelle Merck in Darmstadt.

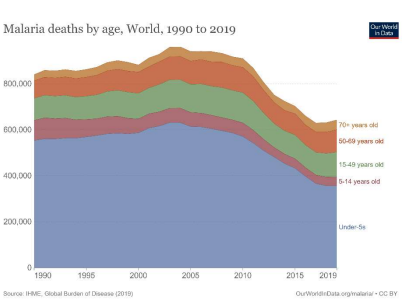
Quinine

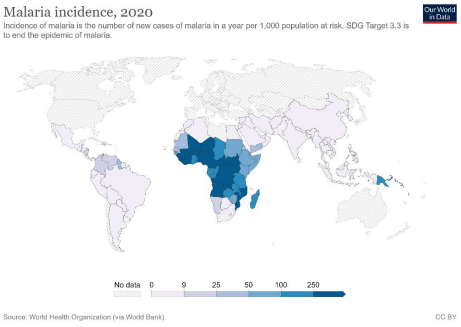
- 1854, Adolph Strecker established the structure of quinine.
- 1945, Robert Woodward – total synthesis.
- Quinine is still isolated from cinchona bark
- Quinine is still registered drug against malaria with unknown mode of action.



Quinine and malaria

- Malaria is caused by protozoa (*Plasmodium* spp.) delivered by mosquitos.
- Malaria still faces about 1 billion people.
- Malaria is still deadly disease.





Willow bark

- The history of application of extracts of willow bark is very long
- Ancient Egypt (2000 B.C.)
- Sumerians (2000 B.C.)
- Hippocrates (400 B.C.)
- Eastern Medicine
- Middle Ages

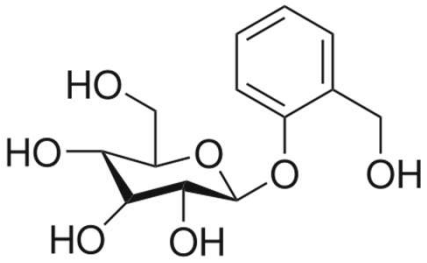
Hippocrates

Willow bark

- 1763, Edward Stone wrote the letter to Royal Society of London about curing of elevated body temperature using powdered willow bark.
- 1827, Johan Buchner (Monachium) isolated yellow crystalline compound named salicin
- 1829, Henri Leroux optimized procedure of extraction and isolated ca. 30g salicin from 1.5kg of bark

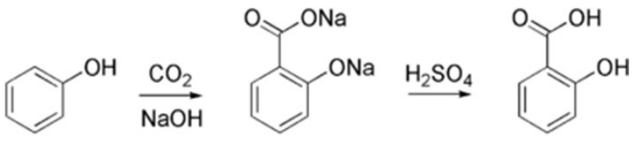
Salicin

- 1838, Rafaele Piria (Sorbona) hydrolyzed salicin to sugar and aromatic compound (salicylic aldehyde), which was converted to salicylic acid.



Salicylic acid

- 1860, Herman Kolbe elaborated the synthesis of salicylic acid from phenol (from coal tar)
- Salicylic acid was the first synthetic drug.
- Industrial scale synthesis was elaborated in 1874 by Friedrich von Heyden (Heyden Chemical Company).

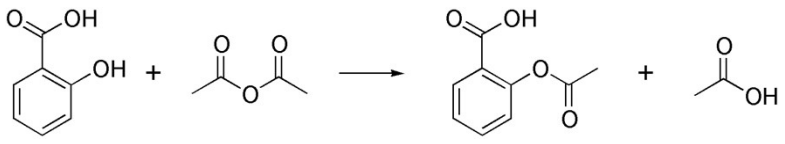


Salicylic acid

- 1876, Salomon Stricker used salicylic acid against fever.
- In second half of XIX c. the use of salicylic acid, sodium salicylate and salicin spreaded (pain, fever, inflammation).
- Salicylic acid 5p/28g (ounce),
- Sodium salicylate 7.5p/28g,
- Salicin 50p/28g.
- Unfortunately, side effects - irritation of the digestive tract restricted the use.

Aspirin

- 1890, Bayer has started the research programme for developing new drugs.
- 1897, Felix Hoffman has got the task of finding a less irritating salicylic acid derivative.
- He developed the synthesis from salicylic acid and acetic anhydride.



Aspirin

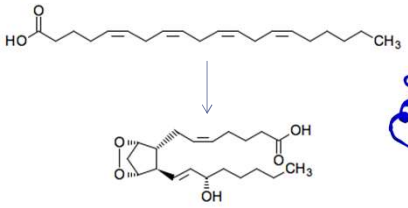
- Eichengrün, Hoffman (chemists) and Dreser (pharmacologist) are considered to be discoverers of aspirin.
- The name of Aspirin is from German name *Acetylspirsäure* (a - acetyl, spir – spirsäure, in – ending for drugs)
- 1899, introdution to the market.

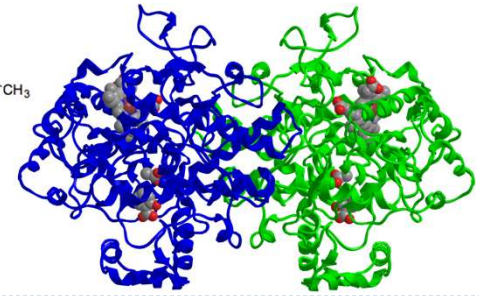
Aspirin

- Annual production of aspirin is 35 000 tons, what gives 100 billions of pills.
- Indications:
  - pain, fever, inflammation
  - Antithrombotic in the prevention of stroke and heart attacks

Aspirin – mode of action

- 1971, John Vane discovered mode of action of aspirin (Nobel prize 1982).
- Aspirin is inhibiting prostaglandin synthesis.
- It is irreversible inhibitor of cyclooxigenase 1 (COX-1)





Yew

Death tree

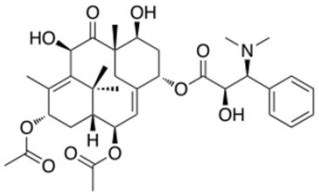
- Yew was named as Death Tree by Celts and Greeks
- Julius Caesar describes the king of the Celts, Cativulco, who committed suicide with the use of yew extracts.
- The yew trees are long-lived - they can live 2000-3000 years

Henry Yew

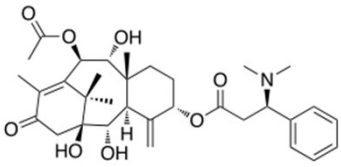
- The oldest tree in Poland
- ca. 1250 years
- Henryków Lubański near Lubań

Yew

- Yew toxicity is associated with alkaloid taxin. LD_{50} = 20 mg/kg (mouse and rats)
- Consumption causes cardiovascular disorders (drop in blood pressure, cardiac arrhythmias, ventricular fibrillation). It can be fatal.



Taxin A



Taxin B

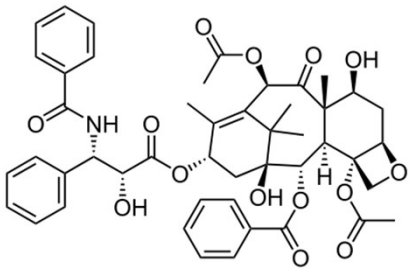
Taxol

- The compounds isolated from western yew were shown to be anti-cancer.
- National Cancer Institute and US Department of Agriculture progremme, since1960 – high throughput screening (100 000 compounds).
- First isolation of paclitaxel by Wall and Wani in1964 (0.5g from 12kg bark).

Western yew
Taxus brevifolia

Taxol

- The structure of taxol was published in 1971.
- 9 stereogenic centers in four-ring system and two stereogenic centers in substituent.

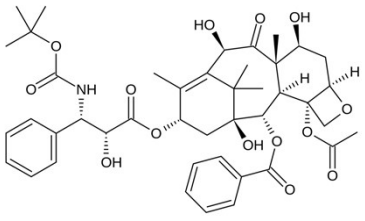


Taxol

- It was a big problem to get the right amount of compound.
- Barking damages the tree irretrievably.
- 1 kg of compound from 2000-2500 trees;
- Taxol is present only in T*axus brevifolia* (Western yew), not present in more common *Taxus baccata*.
- In years1967-1993 Western yew was the only source of taxol.

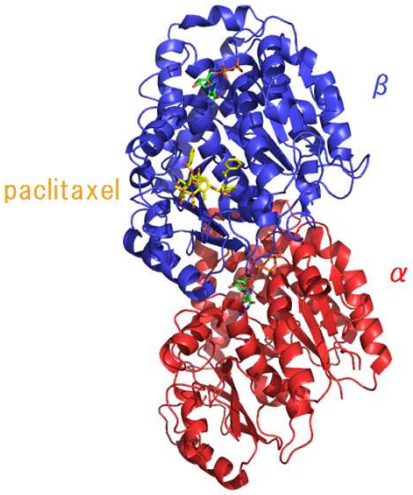
Taxol and Taxotere

- Taxol was introduced to the market in1990, by Bristol-Myers Squibb
- Application against cancer of: ovary, lung, breast, testis.
- Sanofi-Aventis introduced the taxol derivative – docetaxel (Taxotere);

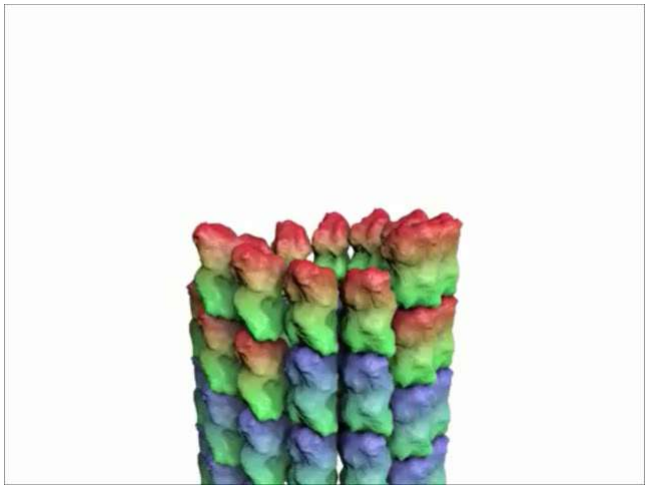


Taxol – mode of action

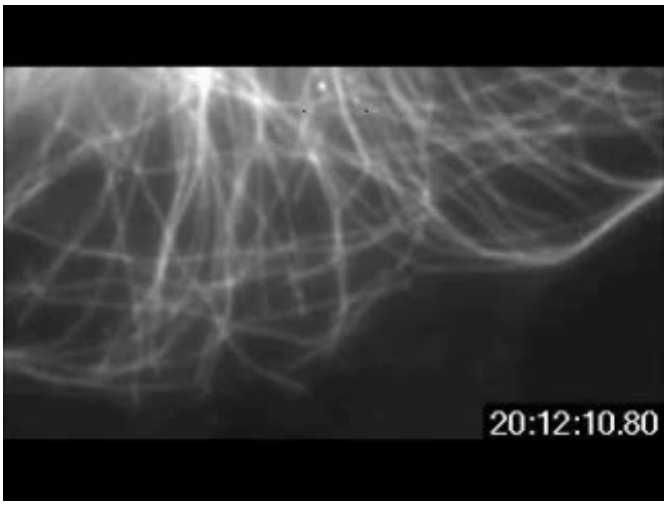
- Taxol is binding to tubulin, which is forming mirotubules – cell cytoskeleton.
- Taxol inhibits decomposition of microtubules, and changes cytoskeleton dynamics, thus inhibiting mitosis.



Taxol – mode of action



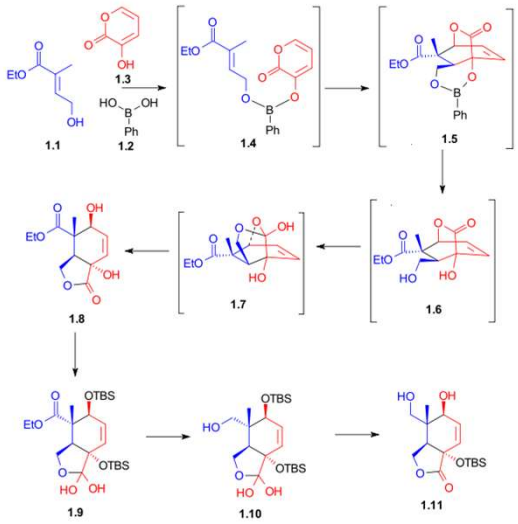
Taxol – mode of action



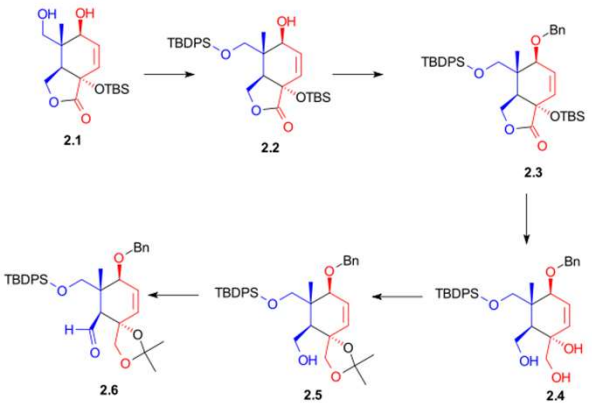
Taxol – total synthesis

- In 90-ties, over 30 research groups in the world have been working on taxol total synthesis.
- In February 1994, two groups simultaneously published a total synthesis(C. Nikolau, R. Holton).
- „photo finish"
- Total synthesis has so much complexity that it has no practical significance.

Taxol – total synthesis



Taxol – total synthesis



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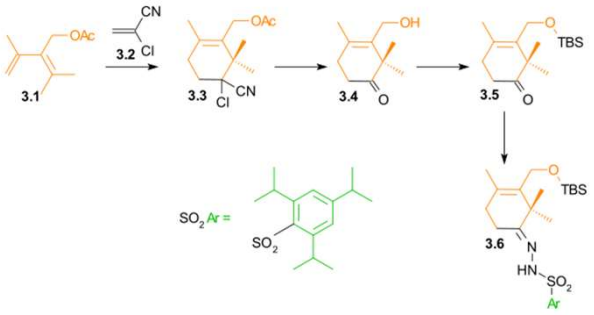
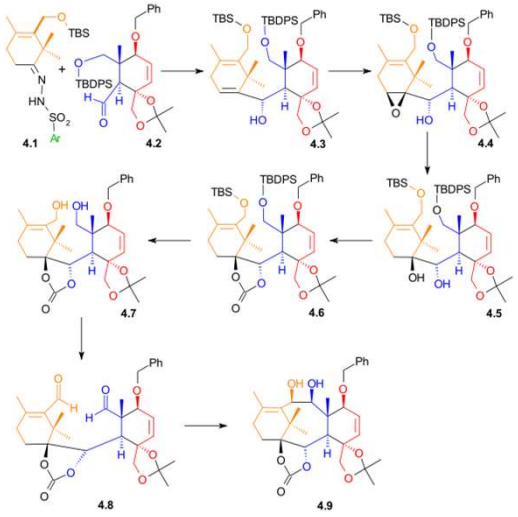


Taxol – total synthesis



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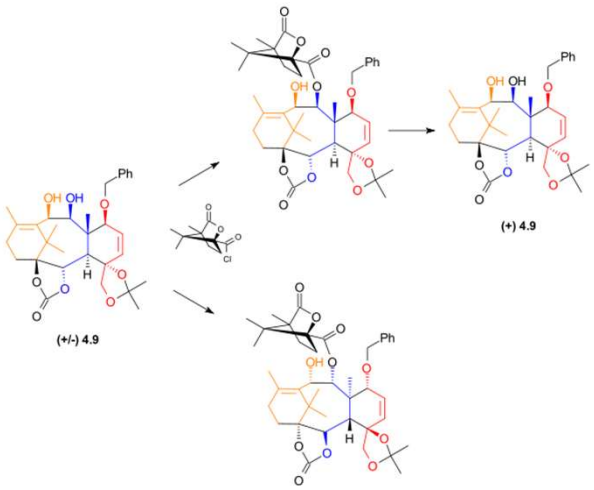

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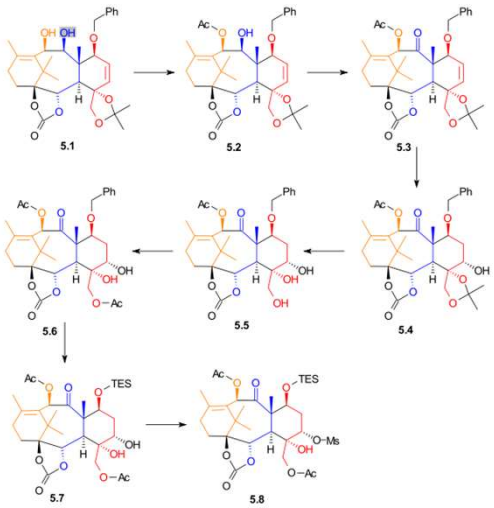
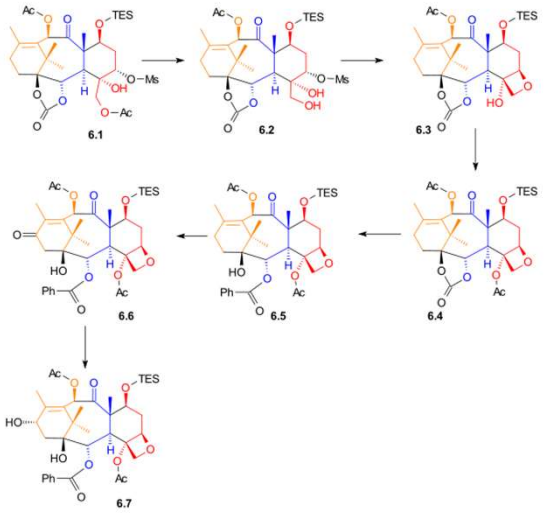
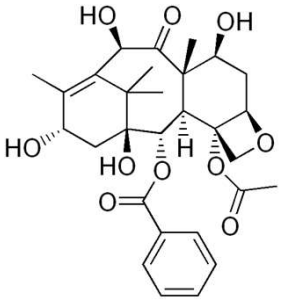


Taxol – total synthesis



Practical ways of obtaining taxol

- Pierre Potier developped method of isolation of 10-deacetylbacatin from needles of *Taxus baccata* (common yew) and conversion of this compound to taxol.



10-deacetylbacatin

Pierre Potier,

Taxol on the market

- Currently, BMS produces taxol using plant tissue culture technology.
- In 2000, taxol brought record revenues of $ 1.6 billion
- Taxol is currently a generic drug and brings about $ 200 million in revenue

Natural products as drugs

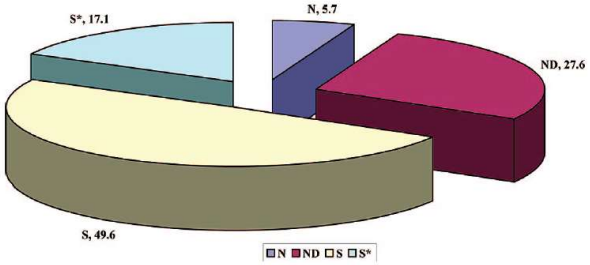
- Secondary metabolites - organic compounds, which are not directly necessary for growth and development of the organism.

- plants
- microorganisms
- Mushrooms
- Marine organisms
- invertebrates

Compound of natural origin in drugs

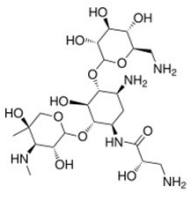
- Natural compounds and their derivatives are a significant group of active substances in medicines
- They are used in 87% of disease types,
- In particular: antibacterial, antineoplastic, anticoagulant, antiprotozoal and immunosuppressive

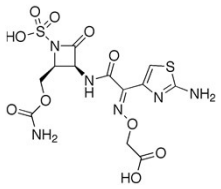
N – natural compounds
ND – derivatives of natural compounds
S* – synthetic inspired by natural compounds
S – synthetic



Antibacterial drugs

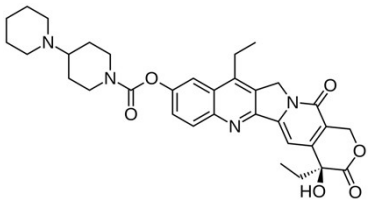
- Natural compounds are particularly important in the discovery of antimicrobial agents
- In the years 1982-2002 90 new active substances with antibacterial properties were introduced, of which about 80% were natural substances or their derivatives.



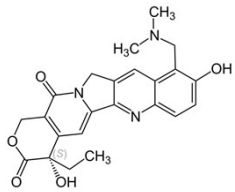


Anticancer drugs

- Natural substances and their derivatives have a significant market share in cancer drugs
- Paclitaxel and docetaxel (taxans)
- Irynotekan and topotekan (derivatives of kamptotecin, topoisomerase inhibitors)



irynotekan



topotekan

Camptotheca acuminata

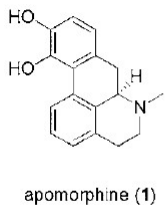
Methods of searching for natural therapeutic compounds

- High-troughput screening
  - National Cancer Institute (USA) in years1960-1981 – discivery of taxol and kamptotecin. 35 000 of plants tested.
  - Central Drug Research Institute (India) tested ca. 2000 plants.
- Ethnomedicine - search for active substances based on information from traditional medicine (Chinese, Indian, shamanism, etc.)

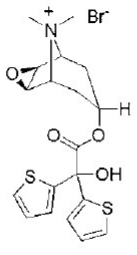
Natural compounds

- Why are natural-origin compounds good candidates for drugs?
  - Very structurally diverse,
  - biocompatible,
  - Often the function in the natural environment is similar to the action of the drug (eg. antibacterial).
- Major problems
  - Acquisition of biological samples
  - An extensive *in vitro* test panel and a large number of diverse samples
  - Obtaining the appropriate amount of compound (synthesis vs isolation)

Biodiversity

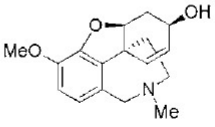


apomorphine (**1**)

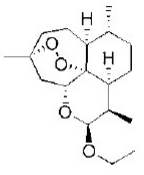


tiotropium (**2**)

nitisinone (**3**)



galanthamine (**4**)

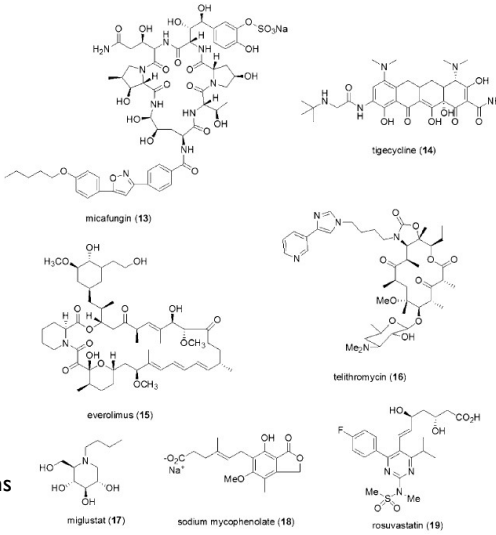


arteether (**5**)

New drugs from plants

Biodiversity

New drugs from microorganisms



Biodiversity

New drugs from marine organisms