



## INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Farmaceutická chemie I.

2. rok studia

**Farmaceutická chemie: definice, vymezení, historie oboru. Názvosloví léčiv.**

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**Medicinal Chemistry** = chemistry of medicines (= drugs = therapeutic agents)

≠ Medical Chemistry (= chemistry for physicians)

- some librarians cannot recognize this difference
- Farmaceutická chemie (Czech)
- Pharmazeutische Chemie (German)
- Chimie Thérapeutique (French)
- etc.

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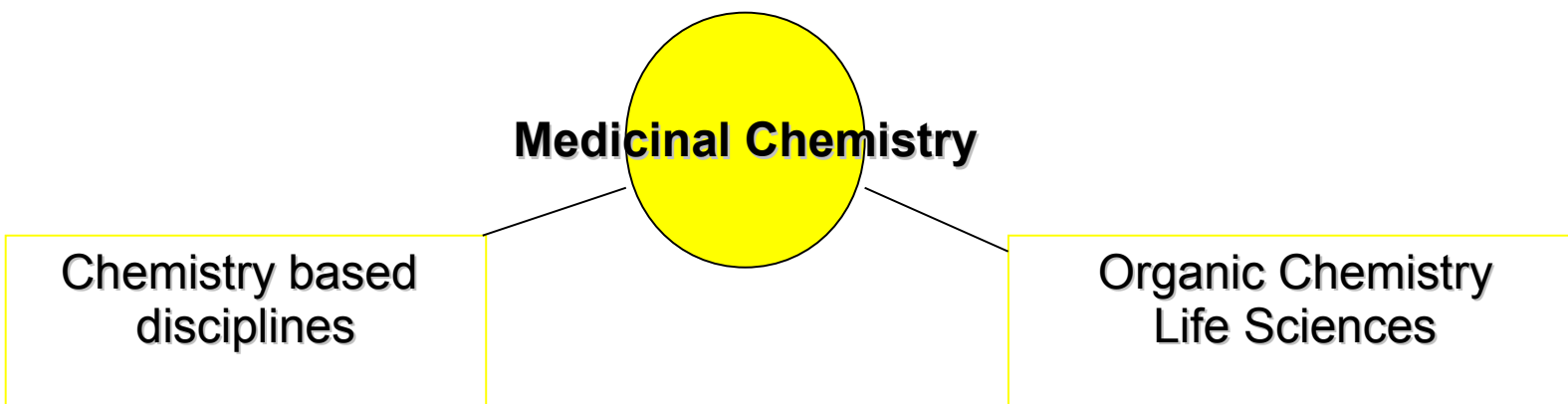
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- etc.

**Medicinal Chemistry (MC)** as an scientific field and one of the key disciplines of pharmaceutical study deals with a drug prepared in most by means of chemical procedures with precisely defined structure and properties.

- MC is **not only** organic or inorganic chemistry **simply applied** to synthesis of drugs
- MC studies relationships between chemical structure and biological activity of drugs (structure-activity relationships, SAR) by means of chemical, physical, biophysical, biochemical, pharmacological and other methods
- MC is devoted to design and discovery of novel therapeutic agents and for such purpose it uses also knowledges of bioinformatics, genetics, genomics, proteomics and other modern biological disciplines

- **OR: Medicinal Chemistry** could be defined as an interdisciplinary science situated at the interface of organic and inorganic chemistry and life sciences (such as biochemistry, pharmacology, molecular biology, immunology, pharmacokinetics and toxicology) on one side and chemistry-based disciplines (such as physical chemistry, crystallography, spectroscopy and computer-based information technologies) on the other.



Terms more or less synonymous with medicinal chemistry

Pharmacochemistry

Molecular pharmacochemistry

Drug design

Bioorganic or bioinorganic chemistry

# History of Medicinal Chemistry

- Studied/practiced for thousands of years
- Sages, medicine (wo)men / witch doctors

Roots, plants, trees, berries, herbs

Often placebos

Leeches and maggots

## Antiquity

China – about 3100 b. C. - legendary emperor Sheng Nong: Sheng Nong Ben Cao Jing (The Pharmacopoeia of Sheng Nong) - book of herbs:

**Ma Huang** - contains ephedrine; used as a heart stimulant and for asthma. Now used by body builders and endurance athletes because it quickly converts fat into energy and increases strength of muscle fibers.

**San Qi = Ginseng (*Panax notoginseng*):**

Indications: an anti-stress and mediator of well-being

## Egypt

- crude oil used for various therapeutical purposes
- antibacterial effect of plant resins used for conservation of mummies
- origin of alchemy
- Ebers papyrus (about 3000 b.C.) provided 877 prescriptions and recipes for internal medicine, eye and skin problems, and gynecology
- Kahun papyrus of around 1800 b.C.: detailed treatments for gynecological problems. Medications were based mainly on herbal products such as myrrh, frankincense, castor oil, fennel, **sienna**, thyme, linseed, aloe and garlic.

## India

- 3500 - 3000 b.C.: origin of Ayurvedic medicine
- practiced by the Brahmin sages
- treatments were set out in sacred writings called Vedas
- *materia medica* extensive, in most based on herbs including cardamom and cinnamon



## Greece

- Hippocrates (400 b.C.)
  - chew bark of willow tree for pain (childbirth and eye infections) – active component = salicin

## Rome

- Pliny (*Plinius*)
- Celsus

## Middle Ages

Arab peninsula - 9<sup>th</sup> century

- Avicenna – works translated into Latin
- development of alchemy: not theory but practice gave chemistry including MC useful procedures and compounds

invention of distillation  $\Rightarrow$  concentrated ethanol from fermentation products ( $\Rightarrow$  herbal tinctures)

- slow transfer of knowledges into Europe
  - *Albertus Magnus*

## Renaissance (15<sup>th</sup> - 17<sup>th</sup> century)

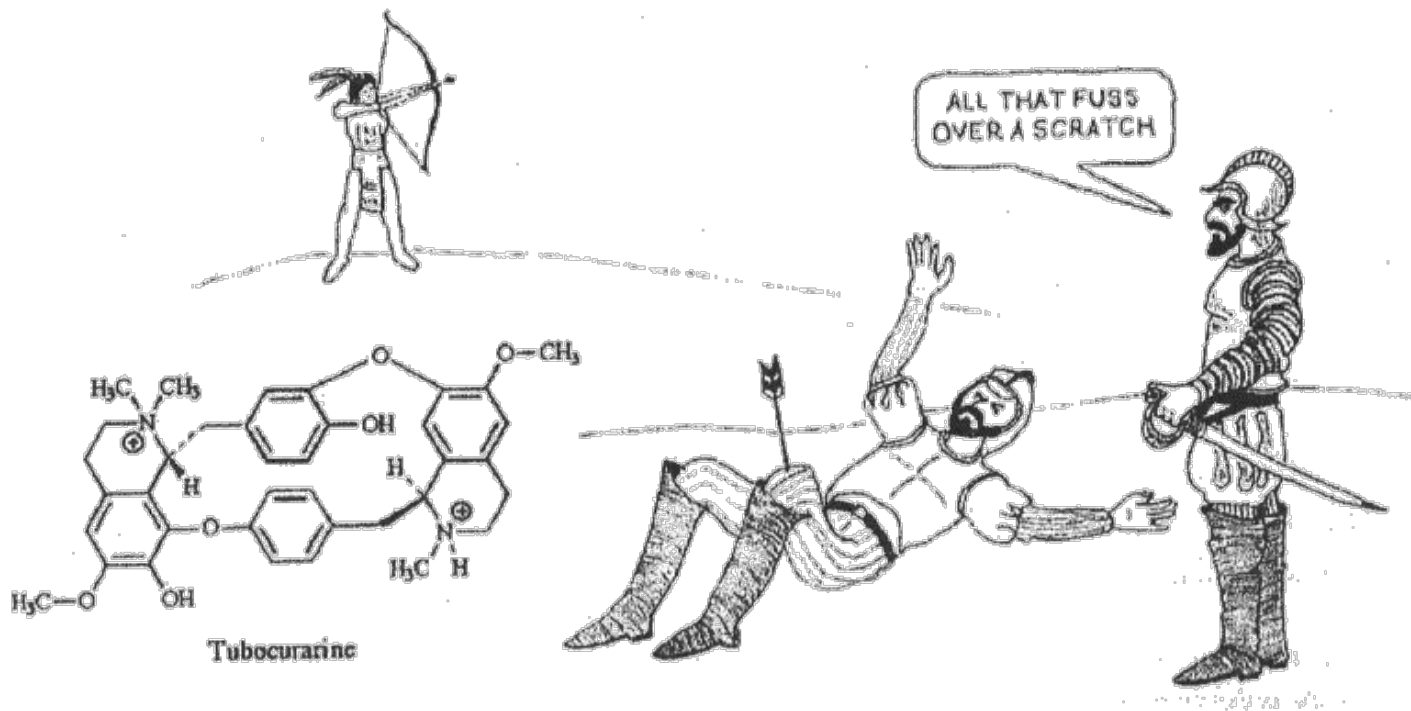
### Western and Central Europe

- further development of alchemy
  - knowledge of:
    - sulfuric acid
    - diethylether („*aether sulphuricus*“) - Valerius Cordus 1544
    - $\text{Hg}_2\text{S}$
    - $\text{AgNO}_3$  („*lapis infernalis*“) etc.

- Paracelsus („in opposite to Celsus“; own name *Theophrastus Bombastus von Hohenheim*) – his knowl-
  - therapy based on empirical experience, not on hypotheses taken from old books
  - an effect depends on a dose
  - founder of **iatrochemistry** – predecessor of MC
  - use of herbal tinctures, but also salts of heavy metals (Ag, Cu, Hg, Bi ...)
  - $\text{Hg}^{2+}$  (or  $\text{Hg}^+$  ?) salts in ointments or vapours of metallic Hg against syphilis – the first known truly effective therapy of this disease (but overdose  $\Rightarrow$  intoxication);  $\text{HgCl}_2$  as diuretics

- further development of European apothecary shops — ancient pharmacies
  - 1668, Darmstadt, Germany: a small apothecary shop had been founded which later originated Merck Company from
- sodium sulfate prepared as laxative (Glauber 1658)
- preparation of basic bismuth nitrate (Lefèvbre 1661)
- powdered iron used in anemia (Sydeham 1681)

- Columbus: „discovery“ of America
  - transfer of new medicaments and raw materials of plant origin:
    - *Cortex chinae* – transported into Spain 1633: antimalaric, antipyretic; later source of alkaloids (quinine, quinidine, cinchonin, cinchonidine)
    - curare – arrow poison of Indians of South America – mixture of extracts of various plants namely from families



- coca leaves (*Erythroxylon coca*) – stimulant and „anti-hunger agent“ of South American Indians; later cocaine isolated (better: partially synthesized) – lead compound for local anesthetics, drug of abuse

## Inventions of 18<sup>th</sup> century

- boric acid prepared from borax - „*sal sedativum*“ - Homberg and Lemery
- discovery of sugar in beet *Beta vulgaris* (Marggraf 1747)
- isolation of some organic acids and glycerol (Scheele 1769 - 1785)
- discovery of diuretic action of foxglove *Digitalis purpurea* (Withering 1785)
- sodium hypochlorite solution as a desinfectant (Berthelot 1786)



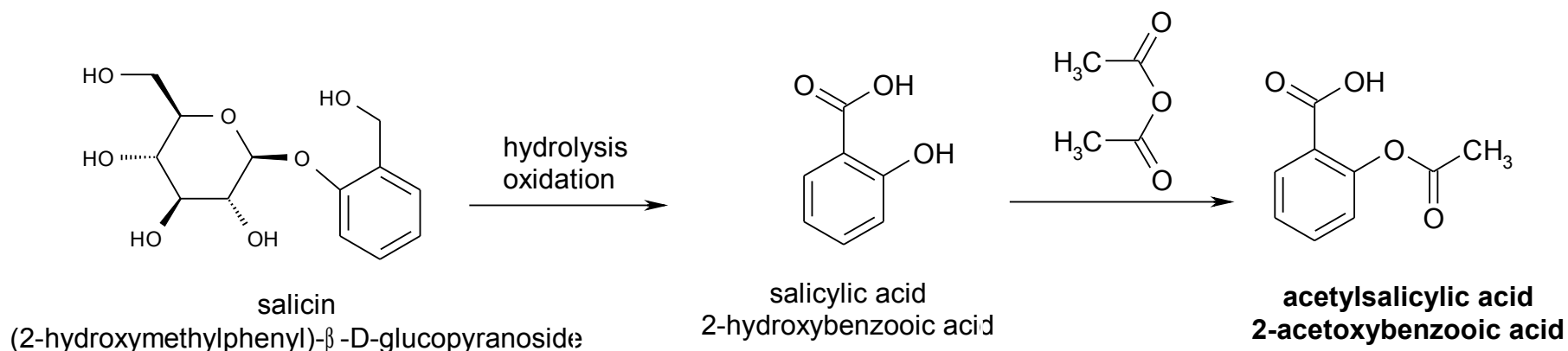
## 19<sup>th</sup> century

- Isolation of pure alkaloids
  - the word *alkaloid* = „alkali-like“ introduced by Meissner (German pharmacist) 1820
  - morphine – isolated from opium by Sertürner (German pharmacist) 1804
  - quinine, emetine and strychnine – Pelletier and Caventou 1818 – 1820
- Synthetic organic medicines introduced:
  - diethylether (1846) and chloroforme (1847) general anesthetics
  - cocaine as a local anesthetic (Wöhler 1860)
  - phenol as a disinfectant in surgery (Lister 1865)
  - chloral hydrate as the first synthetic hypnotic (Liebreich 1869)

## 19<sup>th</sup> century – continued

- origin, development and influence of chemical and pharmaceutical industry
  - namely Germany, later UK, USA and other countries
  - originally pharmacies (Merck) or chemical dyes factories
- more organic synthetic drugs introduced:
  - antipyrine (Knorr 1883) and acetanilid (1886 - Antifebrin<sup>®</sup>) as antipyretics
  - 1897 Bayer, Leverkusen, Germany: industrial synthesis of acetylsalicylic acid as an antipyretic drug by Felix Hoffmann – (Aspirin<sup>®</sup> introduced since 1899)
  - phenolphthalein as a laxative (Vamosy 1898)
  -

# History of acetylsalicylic acid (ASA)

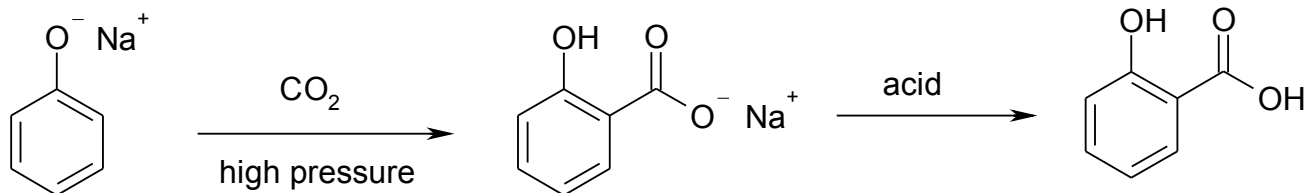


600 b.C. Hippocrates: chew of willow bark  
*(Cortex salicis - Salix sp.)*  
 1827 Leroux: isolation from willow bark

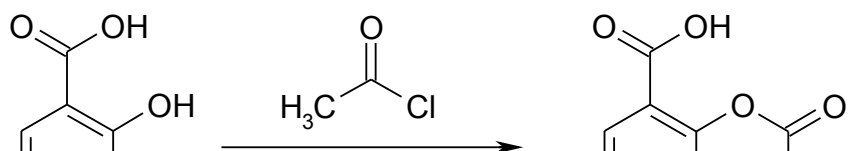
1838 Piria: the first synthesis  
 Kolbe: efficient industrial synthesis  
 since 1878 used as antipyretic  
 and antirheumatic

**1897 Felix Hoffmann - synthesis for industry**  
**1899 - Aspirin(R) - Bayer**

## Kolbe's synthesis of salicylic acid



## The first published syntheses of ASA



Gerhardt, Justus Liebigs Ann. Chem. **87**, 164 (1853)  
 Gilm, Justus Liebigs Ann. Chem. **112**, 181 (1859)  
 Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)

## 20<sup>th</sup> century

- more synthetic drugs:
  - barbital as a hypnotic (Fischer, Mehring 1903)
  - procaine as local anethetics (Einhorn 1904)
  - arsphenamine (Ehrlich)

Last 150 years: Mechanism of reaction/response

1909: first chemotherapy (Ehrlich)

Salvarsan (compound "606") for syphilis

Aside: naming drugs (drug name vs. trade name)

Later replaced with penicillin (1940s)

2005: Structure determination