evropský sociální fond v ČR
EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

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 Therapéutique (French)
- etc.

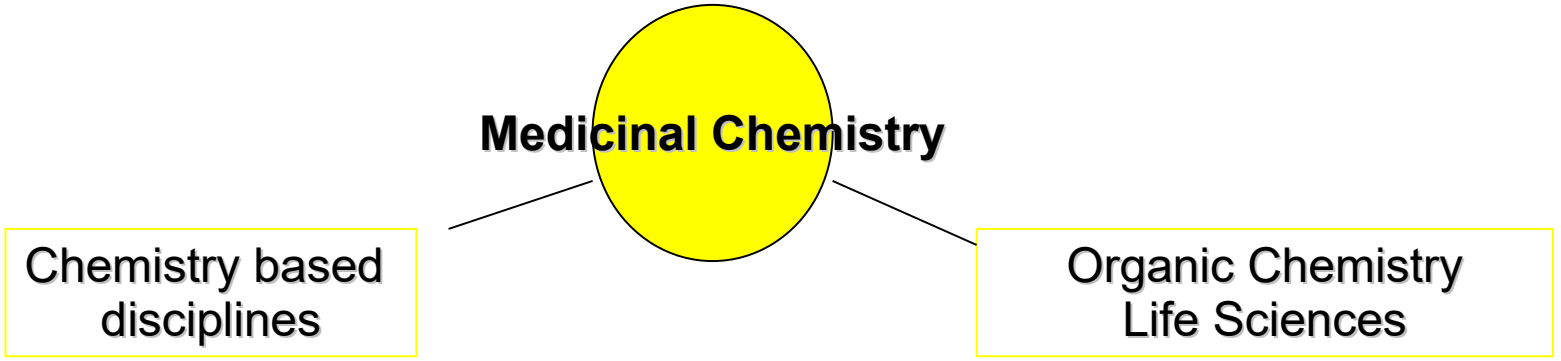
Medicinal Chemistry (MC) as an scientific field and one of the key disciplines of pharmaceutical study deals with a drug prepared in most by means of chemical procedures with preciously defined structure and properties.

•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
- Medicine (wo)men / witch doctors

Roots, plants, trees, berries, herbs

Often placebos

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 *(=Ephedra)* - 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, thyme, linseed, aloe and garlic.

India

•3500 - 3000 b.C.: origin of Ayurvedic medicin

•practiced by the Brahmin priests

•treatments were set out in sacred writings called Vedas

•*materia medica* extensive, in most based on herbs including cardamom and cinnamom

Greece

- castor oil and liseed as laxatives
- fennel plant for relief of intestinal colic and gas
- asafetida gum resin as an antispasmodic
- Hippocrates (400 b.C.)
  - *Hippocratic Corpus*
  - chew bark of willow tree for pain relief (childbirth and eye infections) – active component = salicin
- Dioscorides
  - *De Materia Medica:* contained descriptions of treatments based on 80% plant, 10% animal, and 10% mineral products
- Galenos (AD 129 – 179)
  - *Opera Omnia:* 20 volumes
  - *contraria contrariis curantur* (opposites cure opposites)

Rome

- Pliny the Elder (AD 23–79) (*Plinius*)
  - The Natural History: 900 herbs

Middle Ages

Arab peninsula - 9th 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 knowledge into Europe
  - *Albertus Magnus*

Renaissance (15th - 17th century)

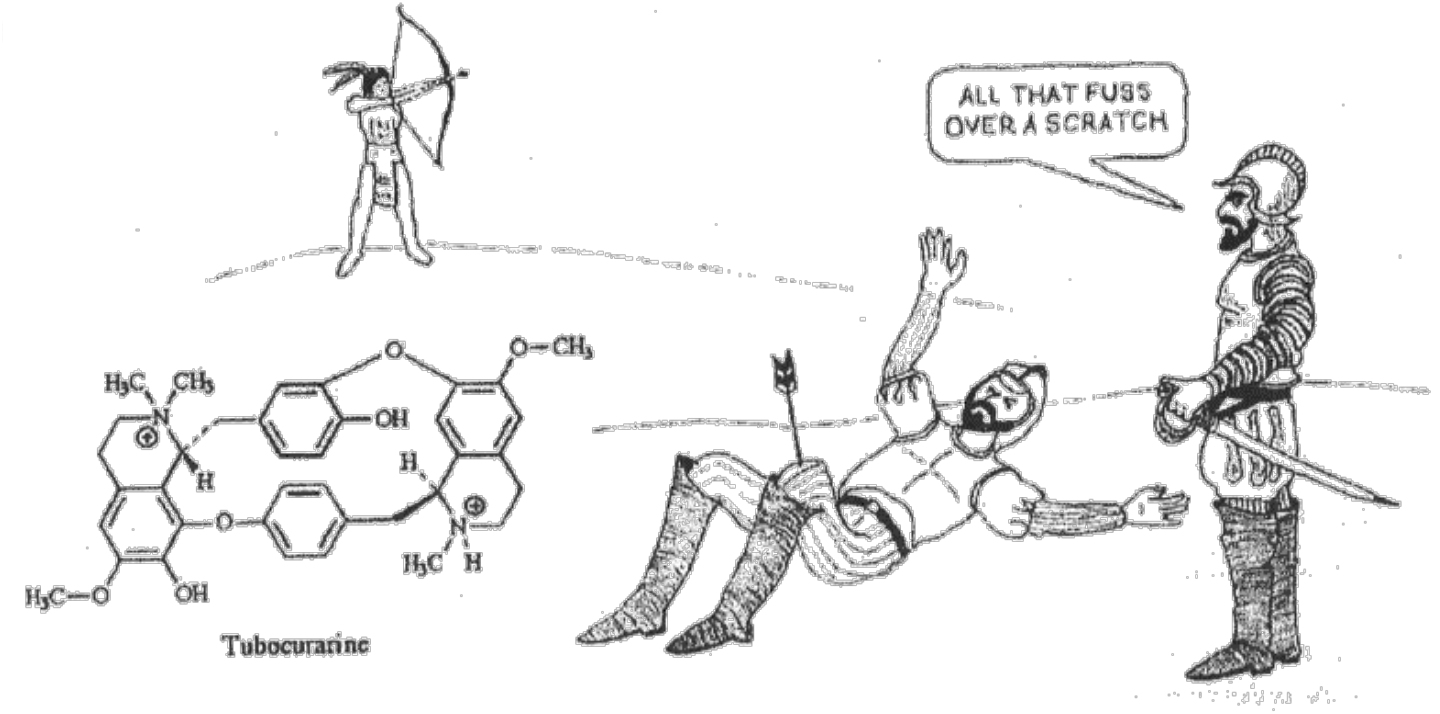
Western and Central Europe

- further development of alchemy
  - knowledge of:
    - sulfuric acid
    - diethylether („*aether sulphuricus*“) - Valerius Cordus 1544
    - Hg_2S
    - $AgNO_3$ („*lapis infernalis*“) etc.

- Paracelsus (own name *Theophrastus Bombastus von Hohenheim; 1493 - 1541*) –
  - 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 …)
  - Hg^{2+} (or Hg^{+} ?) salts in ointments or vapors of metallic Hg against syphilis – the first known truly effective therapy of this disease (but over-dosage $\Rightarrow$ intoxication); $HgCl_2$ as diuretics
  - his followers called „Paracelsians“ were in opposition to „orthodox medicine“

- 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* = quinnip bark – transported into Spain 1633: antimalaric, antipyretic; later source of alkaloida (quinine, quinidine, cinchonin, cinchoninidine)
    - curare – arrow poison of Indians of South America – mixture of extracts of various plants



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

Inventions of 18th 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 desinficient (Berthelot 1786)

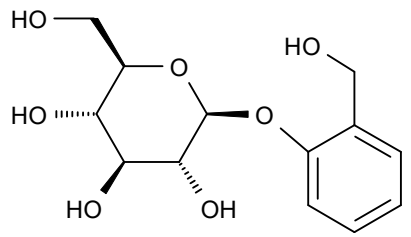
19th century

- Isolation of pure alkaloida
  - 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
- Peyron's chloride *cis*-$[Pt^{II}(NH_3)_2Cl_2]$ prepared (1845); much later recognized as an potent antineoplastic (cisplatin)
- Synthetic organic medicines introduced:
  - diethylether (1846) and chloroforme (1847) general anesthetics
  - cocaine as a local anesthetic (Wöhler 1860)
  - phenol as a desinficient in surgery (Lister 1865)
  - chloral hydrate as the first synthetic hypnotic (Liebreich 1869)

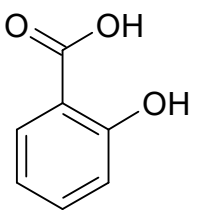
19th century – continued

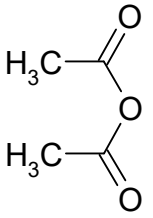
- origin, development and influence of chemical and pharmaceutical industry
  - mainly Germany, later UK, USA and other countries
  - originaly pharmacies (Merck) or chemical dyes factories
- more organic synthetic drugs introduced:
  - antipyrine (Knorr 1883) and acetanilid (1886 - Antifebrin®) as antipyretics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

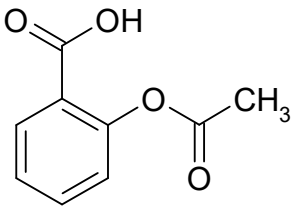
History of acetylsalicylic acid (ASA)



hydrolysis
oxidation







salicin
(2-hydroxymethylphenyl)-β-D-glucopyranoside

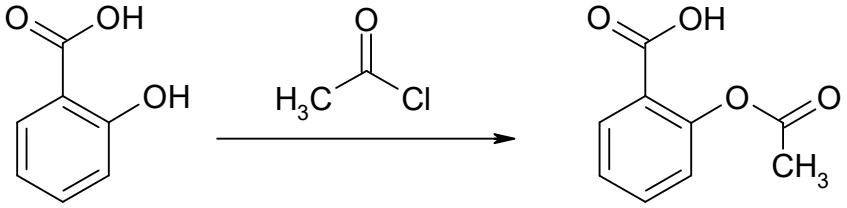
600 b.C. Hippocrates: chewig of willow bark
(*Cortex salicis - Salix sp.)*
1827 Leroux: isolation from willow bark

salicylic acid
2-hydroxybenzooic acid

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

acetylsalicylic acid
2-acetoxybenzooic acid

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



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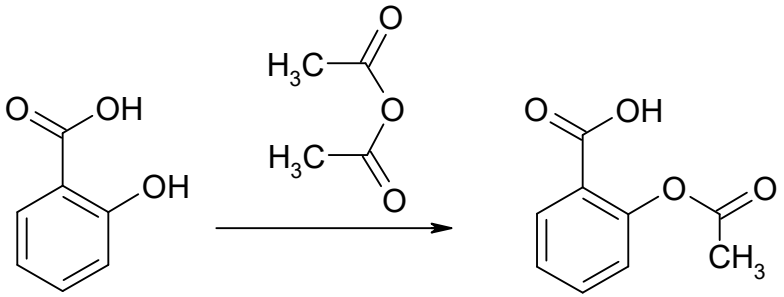
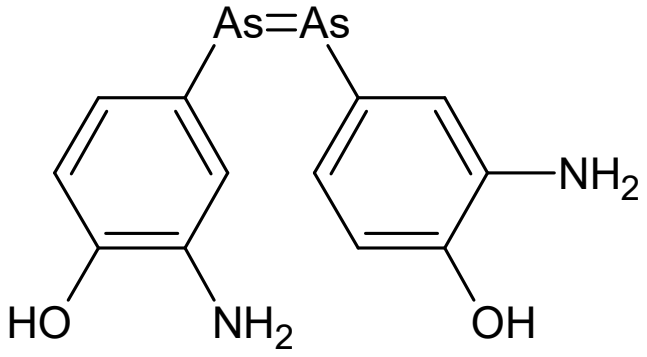
Gilm, Justus Liebigs Ann. Chem. **112,** 181 (1859)
Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)



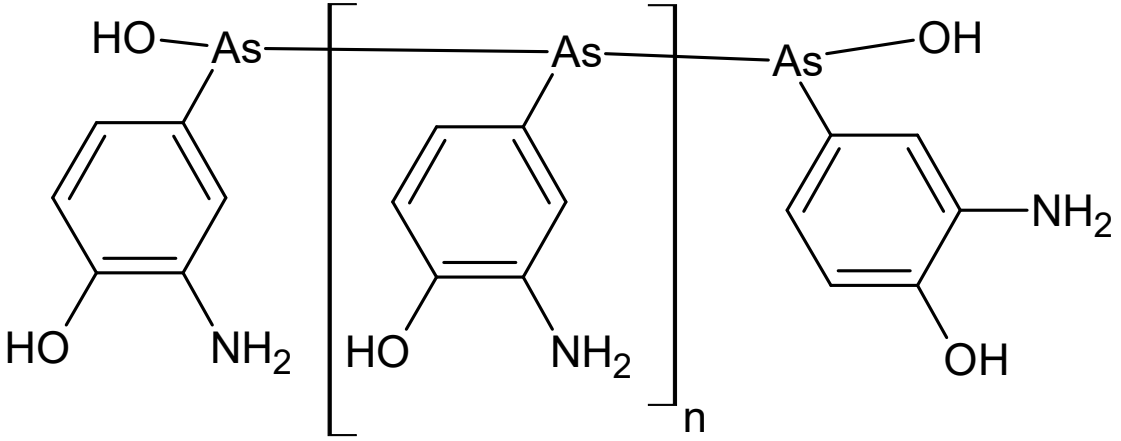
Hoffmann

20th century

- more synthetic drugs:
  - barbital as a hypnotic (Fischer, Mehring 1903)
  - procaine as local anethetic (Einhorn 1904)
  - arsphenamine (Ehrlich 1910) for treatment of syphilis
    - first antibacterial chemotherapeutic



Structure proposed by Ehrlich

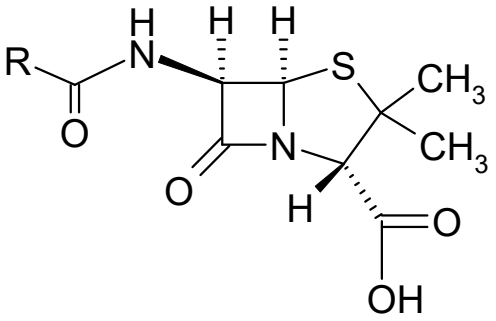


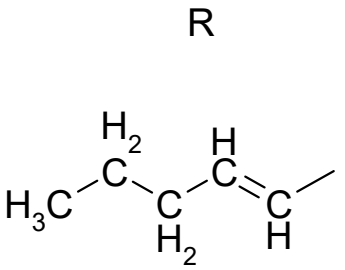
Structure as it is recognized today

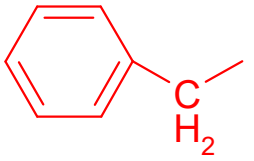
asphenamine (Salvarsan ®)

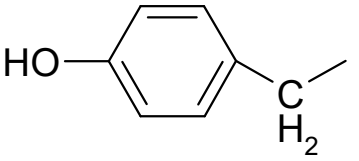
20th century

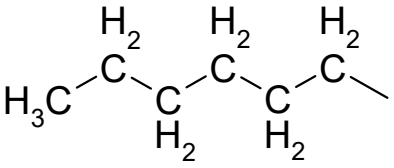
- penicillin: 1929 Alexander Fleming discovered antibacterial action of cultivation media of the mould *Penicillium notatum;* 1943 Howard Florey and Ernst Chain isolated therapeutically usefull mixture of crystalline penicillines, the pure benzylpenicillin was prepared by addition of phenylacetic acid into cultivation media

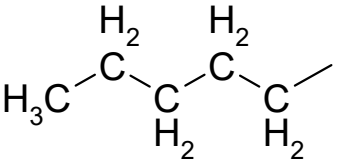




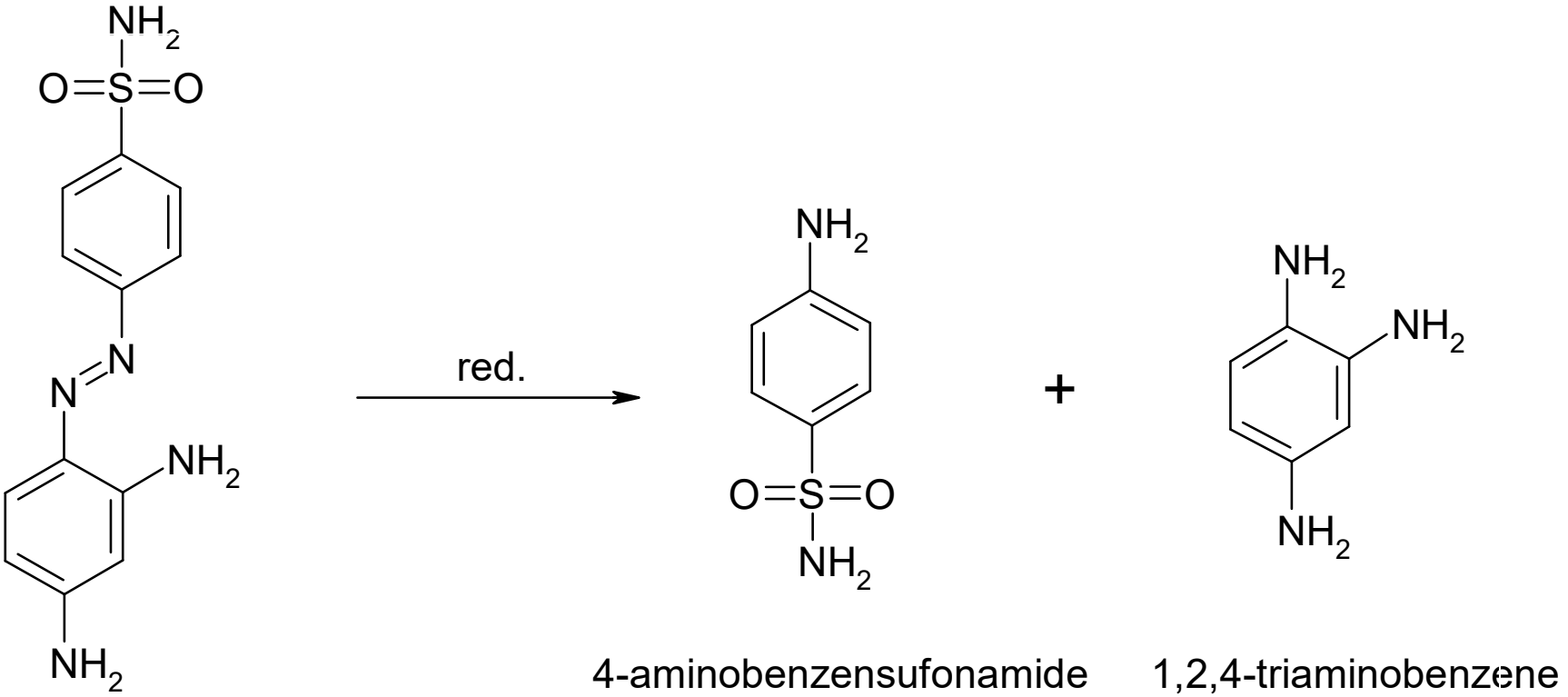








20th century Sulfonamides



4-aminobenzensufonamide
sulfanilamide

1,2,4-triaminobenzene

4-(2,4-diaminophenylazo)benzenesulfonamide

Prontosil rubrum
1932: synthesis by Mietsch and Klarer; successfully tested by Domagk against streptococci

1935: Jacques and Therése Tréfoulé: holder of activity is sulfanilamide (*Prontosil album)*

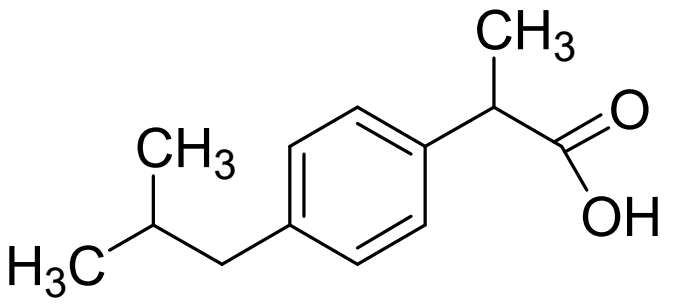
Examples of other important drug inventions of 20th century

- 1921 Banting and Best: insuline as the first peptidic hormone
- 1928 Szent-Györgyi: isolation of vitamine C
- 1935 Domagk: quarternary ammonium salts as disinfectants
- 1935 Prelog, Štěpán: prepared „nitrogenous ypperite“ which later became the lead compound for alkylating antineoplastics
- 1939 Müller: DDT as an insecticide
- 1944 Waksmann et al.: streptomycine as the first antituberculotic antibiotic
- 1946 Saret, Reichstein: partial sythesis of cortisone
- 1946 Lehman: *p*-aminosalicylic acid as an antituberculotic
- 1951 Woodward, Robinson: total synthesis of steroidal hormones
- 1952 Laborit, Huguenard, Delay, Deniker: chlorpromazine as the first antipsychotic
- 1953 Du Vigneaud: synthesis of peptide hormone oxytocine
- 1956 Frank, Fuchs: carbutamide as the first oral antidiabetic
- 1961 Kappeler et al.: synthesis of tetracosactide as a synthetic analogue of corticotropine
- 1963 Black et al.: propranolol as the first β-adrenolytic
- 1965 Rosenberg et al.: (re)discovery of cisplatin as the first platinum antineoplastic
- 1972 Woodward: total synthesis of vitamine B_{12}
- about 1980 Genetech corp.: production of interferone by a recombinat technology
- ...and many others

Drug nomenclature

A drug usually has (at least) 3 names:

1. (Systematic) Chemical
2. International Non-proprietary names and/or other Non-proprietary
3. Commercial or Trade (with ®)



Chemical: 2-[4-(2-methylpropyl)phenyl]propanoic acid
Non-proprietary： Ibuprofen
Commercial： Brufen, APO-Ibuprofen, Ibalgin …
Pharmacopoeial: Ibuprofenum PhEur

Systematic chemical names

- according to rules of
  - IUPAC (International Union of Pure and Applied Chemistry) and/or IUBMB (International Union of Biochemistry and Molecular Biology) if the drug is sugar, enzyme, peptide, steroid …
    - Joint Commission on Biochemical Nomenclature (of IUPAC and IUBMB)

2-[4-(2-methylpropyl)phenyl]propanoic acid or 2-(4-*iso*-butylphenyl)propanoic acid

  - Chemical Abstracts: basic chain or ring followed by substituents in alphabetic order

propanoic acid, 2-(4-*iso*-butylphenyl)

  - WHO systematic nomenclature: similar to older versions of IUPAC names; the longest chain with the most priorietary group need not be basic

α-methyl-4-(2-methylpropyl)acetic acid

Non-proprietary names

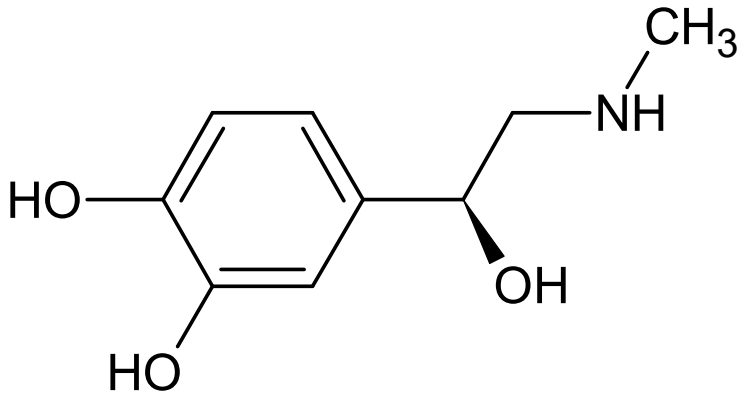
Convenient to remember, needed when apply for registration, cannot be trade marked or patented. One compound has only one name.

- International non-proprietary names (INN) – introduced by Nomenclature commision of WHO
  - names have their Latin form and are transformed into all national languages with necessary change of both spelling and pronunciation

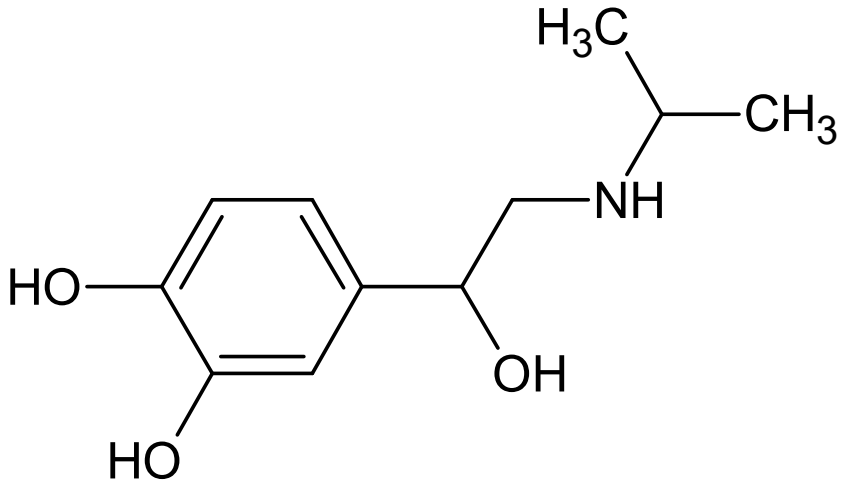
ibuprofenum (Latin), ibuprofene (English, French), ibuprofen (Czech), ibuprofeno (Spanish) ...

- other non-proprietary names – nations or states feeling themselves to be „drug powers“ have their own nomenclature systems
  - USAN: United States Approved Names
  - BAN: British Approved Names
  - JAN: Japanese Approved Names

Examples of different INN, BAN and USAN names



Systematic (IUPAC): (R)-4-[1-Hydroxy-2-(methylamino)ethyl]-1,2-benzenediol
INN = USAN = JAN: epinephrine
BAN: adrenaline



Systematic (IUPAC): (R)-4-[1-Hydroxy-2-(isopropylamino)ethyl]-1,2-benzenediol
INN: isoprenaline
JAN = USAN: isoproterenol

Basic principle of INN: common suffixes or prefixes for a particular therapeutical or chemical group

- -cillin: β-lactame antibiotics of peniciline group
- cef-: β-lactame antibiotics of cefalosporine group
- -caine: local anesthetics
- -vir: antivirotics
- -oxacin: anibacterial quinolones
- -nidazol: nitroimidazole antiprotozoal agents
- -tidin: H_2-recepeptor antagonists
- -profen: anti-infalamatory drugs – propionic acid derivatives
- … etc.

Trade or Commercial names

- names of a particular preparation of a particular manufacturer
- usualy with ® : they are **trademarks**
  - protected from (mis)use by another company by patent or copyright law
  - a trademark protects only trade name and/or its graphic form, not a structure of active ingredient or its manufacturing procedure or a composition of a drug form; these are protected by patents as an **intelectual property**

Generic names

- names given to a drug by its authors
- in older drugs often adopted by WHO as INN names
- actually only alphanumeric codes are given

Pharmacopoeial names

- used for drug substances, not for preparations
- often in Latin and identical with Latin form of INN
- followed by a shortening of a particular Pharmacopoeia (PhEur, USP, PhB, PhInt ...)