Medicinal Chemistry-I

Bratislava, 2025 **Andrej Boháč**

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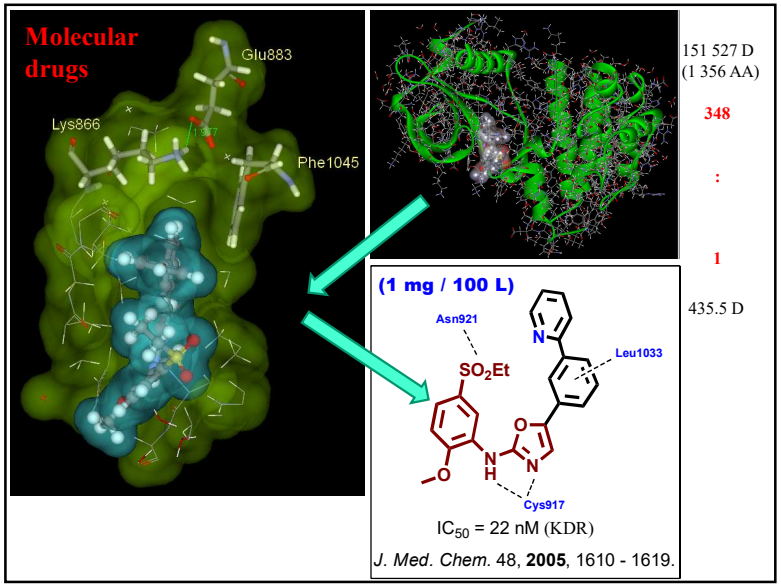

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What is Medicinal Chemistry?

- **not a basic chemistry course for medical students**
- **highly interdisciplinary research** dedicated to development of new drugs (not only)

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

http://www.fda.gov/

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

www.ema.europa.eu/

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What is a drug?

- In **medicinal chemistry**, the chemists **design and synthesize a pharmaceutical agent that has desired biological** effect on the human body or on other living species.

- **Drugs** are **compounds** that interact with a biological system to **produce a biological response**. No one is totally safe, they vary in **side effects**. Dose level of a compound determines whether it will act as a **medicine or as a poison**.

It is a dose that make from the compound a poison like: 100 aspirin tablets or 1 L of whisky or 9 kg of spinach...

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Drug development

- ❑ **selection of disease** (cardiovascular, autoimmune, infectious, hereditary, mental, cancer …)
- ❑ **molecular mechanism** of the pathology (medicine, molecular biology...)
- ❑ selection of a **key biomolecule to influence**
- ❑ **new active structure/compound identification: in Silico design, HTS** (High Throughput Screening) of organic molecules possessing appropriate drug-like properties (biologists, computer chemists)
- ❑ organic **synthesis** (chemists)
- ❑ biological or biophysical **assays** (biologists, physical chemists)
- ❑ **optimization** of activity and other molecular properties (solubility, toxicity ...)
- ❑ **IP** protection + **clinical trials** + up-scale synthesis + authority approval

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How many new drugs reach the World market yearly?

- **DD is highly interdisciplinary science that is time and resources consuming process:**

  10 years / from 870 000 000 to 2 000 000 000 USD / 1 new drug

  Adams C, Brantner V . *Health Aff airs (Millwood)* 2006 **25** 420–8.

- **global production ca 24 innovative drugs (new chemical entity) / year**

  (**2009**: 26, **2008**: 25, **2007**: 18, **2006**: 22, **2005**: 26, **2004**: 24, **2003**: 26, **2002**: 28, **2001**: 23, **2000**: 26)

- Many failures have been recorded in high stages of drug development, even in clinical trials) **Where is a problem?**

Drug-likeness was often missing.
Computer aided drug design (CADD) is preferred.

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- The FDA's 5-**year** annual average is now 43 **drugs per year**, nearly twice its nadir in 2009. Fig. 1 | Novel FDA approvals since 1993. Annual numbers of **new molecular entities (NMEs) and biologics license applications (BLAs) approved** by the Center for **Drug** Evaluation and Research (CDER).15. 1. 2019
- **2018 FDA drug approvals** (molekulárne entity (NME) a biologických liekov (BLA))

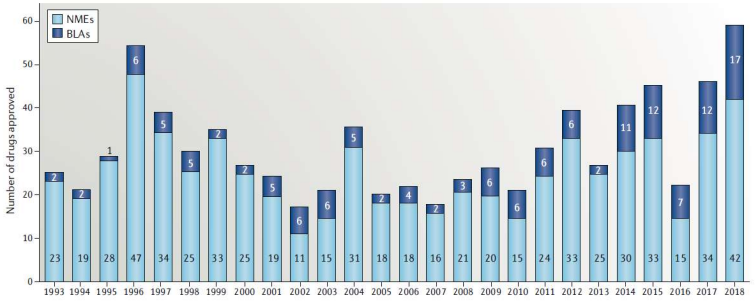

Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2018. Approvals of products such as vaccines by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see Table 2). Source: Drugs@FDA.

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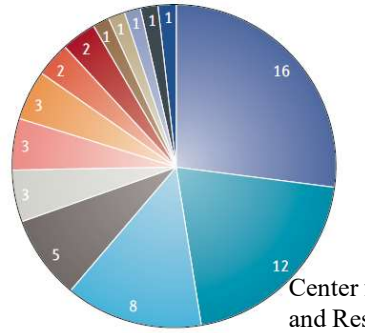

Center for **Drug** Evaluation and Research (CDER

Fig. 3 | **CDER approvals by therapeutic area in 2018.** Source: *Nature Reviews Drug Discovery*.

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Fact Sheet: FDA at a Glance October 2019

FDA-Registered Facilities

Program	Domestic	Foreign	Total
Animal Drugs	1,608	1,156	2,764
Animal Food	17,259	6,859	24,154
Biologics	4,832	439	5,271
Human Drugs	3,647	4,159	7,806
Human Food	80,525	108,998	189,523
Medical Devices	13,790	12,891	26,681
Tobacco	3,371	0	3,371
Total	**125,032**	**134,538**	**259,570**

v USA je registrovanych 3 647 lieciv pre ludi a 1 608 veterinarnych lieciv. V tabulke najdete **aj zahranicie**. Teda **spolu 7 806 lieciv pre ludi** a 2 764 pre zvierata. **Biologika** su uvedene v tabulke tiez. Existuje vraj viac ako **20 000 liekov** na predpis schválených na uvedenie na trh.

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Vyhladavanie approved lieciv na biologicke ciele

- http://db.idrblab.net/ttd/search/approved-drugs

Daj vegfr2 napr.

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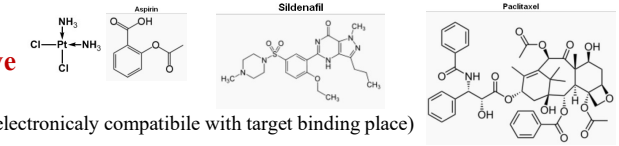
What kind of compounds are drugs?

- **Different** inorganic, more likely organic **compounds** and biomolecules (proteins, antibodies, siRNA…) that activates or inhibits the function of a target with benefit to the patient



- ❑ **active** (stereoelectronicaly compatibile with target binding place)
- ❑ possesing **low toxicity** (selectivity, antitargets: e.g. cytochrome P450 enzymes, heart potassium ion channel hERG, P-glycoprotein transporter…)
- ❑ good **bioavailablity** (complex of physico-chemical and pharmacological properties ensuring drug-likeness: MW, logP, pKA, PSA...)

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The names of the drugs

Názov aktívnej zložky lieku „API“: je triviálny názov charakterizujúci len aktívnu zložku lieku (**liečivo**), Pod týmto názvom jednoznačne nájdete liek, ktorý ju obsahuje.

1/ kyselina acetylsalicylová (antipyretikum...)
2/ metformín (antidiabetikum)

Komerčný názov lieku („Trade name“): zahŕňa aktívnu zložku - samotného liečiva (**API**) + **ostatné prímesi** ako aj formu lieku (tabletka, kvapky, čapíky, spray...). Takýchto názvov je viacero a závisí to od toho, kto daný liek vyrába a ako mu bol schválený. **Generické liečivá** sú lieky, ktoré už nemajú patentovú ochranu a vyrábajú ich viacerí výrobcovia, ktorí im dávajú rôzne mená:

1/ pre kyselina acetylsalicylová: **Aspirin® (Bayer), Acylpyrín® (Zentiva)...**
2/ pre metformín: **Glucophage XR, Carbophage SR, Riomet, Fortamet, Glumetza, Obimet, Gluformin, Dianben, Diabex, Diaformin, Siofor, Metfogamma…**

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A structure of eukaryotic cells

Human, animal and plant cells are eukaryotic cells

- **The nucleus contains the genetic blueprint for life (DNA)**
- **The fluid contents of the cell are known as the cytoplasm**
- **Structures within the cell are known as organelles**
- **Mitochondria are the source of energy production (DNA)**
- **Ribosomes are the cell’s protein ‘factories’**
- **Rough endoplasmic reticulum is the location for protein synthesis**

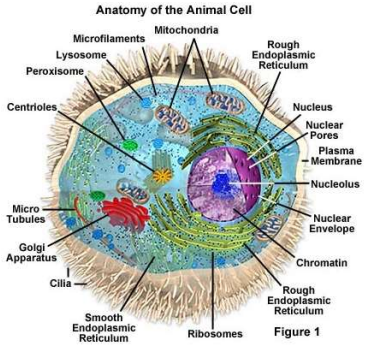

Figure 1

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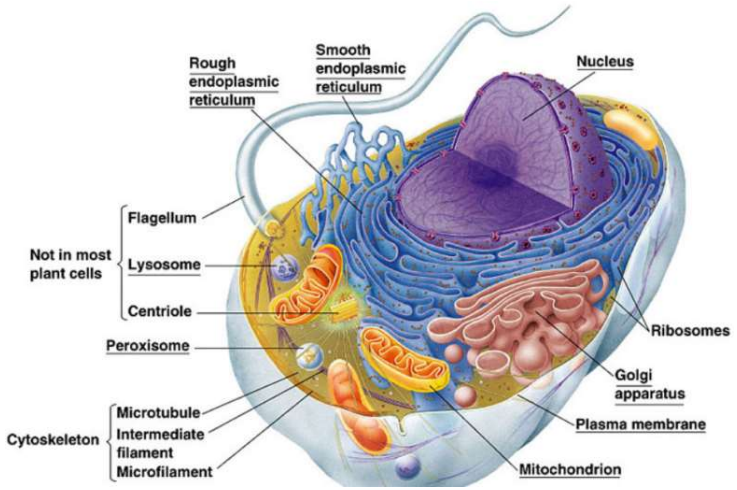

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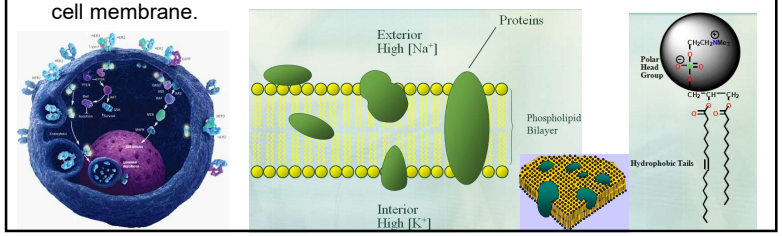
Cell membrane (CM) – protects its compartment

- CM composes from **phospholipid bilayer**, the **hydrophobic tails** interact with each other by van der Waals interactions and are hidden from the aqueous media
- The **polar head groups** (phosphatidylcholine) **interact with water** at the inner and outer surfaces of the membrane
- The **cell membrane** provides a **hydrophobic barrier** around the cell, **preventing the passage of water and polar molecules.** Proteins (receptors, ion channels and carrier proteins) are present, floating in the cell membrane.



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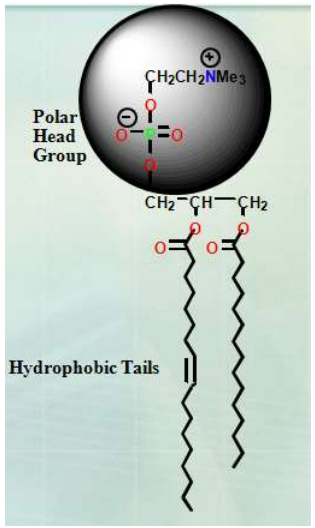
phosphatidylcholine



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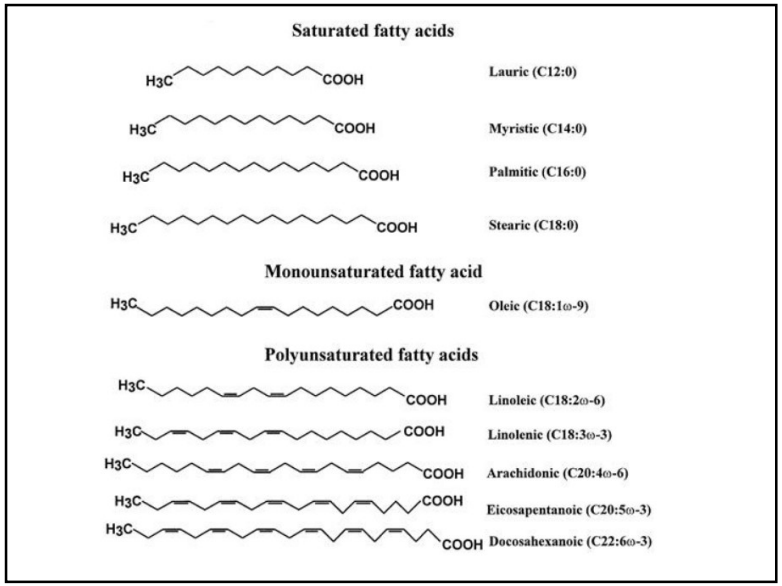

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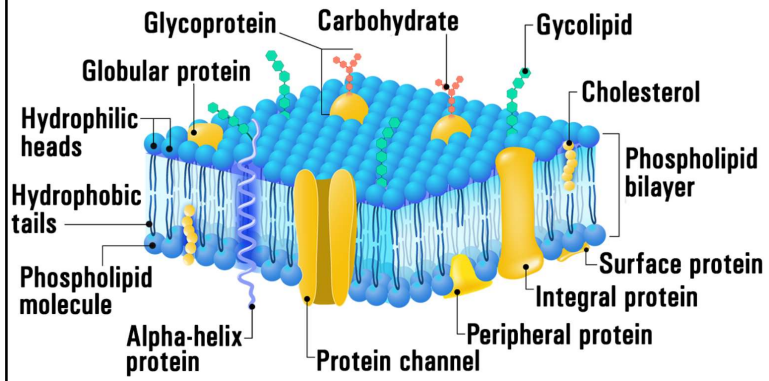

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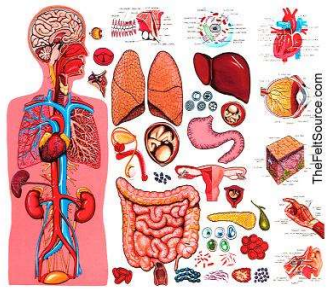
Cells in a human body

(100 000 000 000 000 100 biliónov buniek)

- **Human body consists from up to 100 trillion (100 x 10E12 => 10E14) cells** organized in different organs and (ca 200) tissues that operate on the molecular level (chemical reactions keeping body healthy and functional **homeostasis**).
- **Drug act on molecular targets** in cell membrane or within the **cells**.



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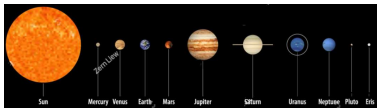
Did you know? The length of all joined DNA from one adult body is more as the distance between Earth and Pluto!

Distance Earth-Neptun is 4.4 mld km.
http://www.universetoday.com/21628/how-far-is-neptune-from-earth/

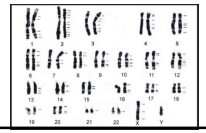


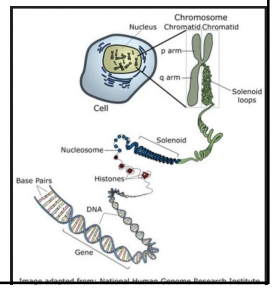
Distance Earth-Pluto is 7.5 mld km.
http://www.universetoday.com/14313/how-far-is-pluto-from-earth/

Adult human body consists from ca 3.72 x 10E13 cells.
Ann Hum Biol 2013 40 471. http://www.ncbi.nlm.nih.gov/pubmed/23829164

Current lenght of human DNA is ca 3 m.
http://hypertextbook.com/facts/1998/StevenChen.shtml

Length of all joined human DNA from one adult body is:
3 m x 3.72 E13 = 11.1 E10 km = **111 mld km !!!**





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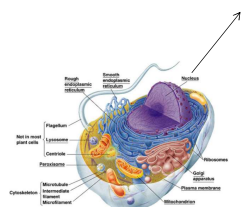
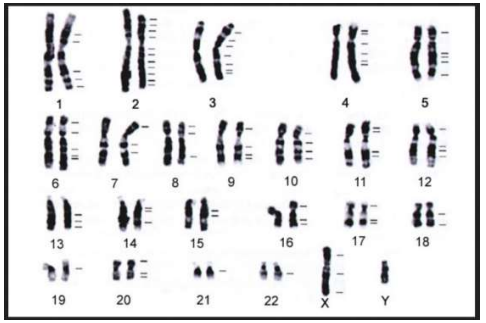
Jadrová DNA eukaryotov je **chránená od metabolických procesov** prebiehajúcich v cytoplazme **dvojitou jadrovou membránou. DNA je rozdelená do viacerých oddelených molekúl**. V interfáze, **vo fáze medzi deleniami bunky, je komplex DNA a bielkovín označovaný ako chromatín. Chromatín sa skladá z nukleozómov**, čo sú **asociácie 8 molekúl špeciálnych bielkovín – histónov, ktoré sú 2,5-krát obtočené molekulou DNA. V čase bunkového delenia sa chromatín preorganizuje na chromozómy, ktoré sa počas delenia správajú ako samostatné elementy** a sú viditeľné aj svetelným mikroskopom. **Proteíny, s ktorými je DNA asociovaná, napomáhajú jej špiralizácii a majú aj regulačnú úlohu** pri realizácii genetickej informácie.
V telových bunkách *človeka* je prítomných **46 *chromozómov* v 23 pároch**
Žena má chromozómy 46 XX, muž 46 XY





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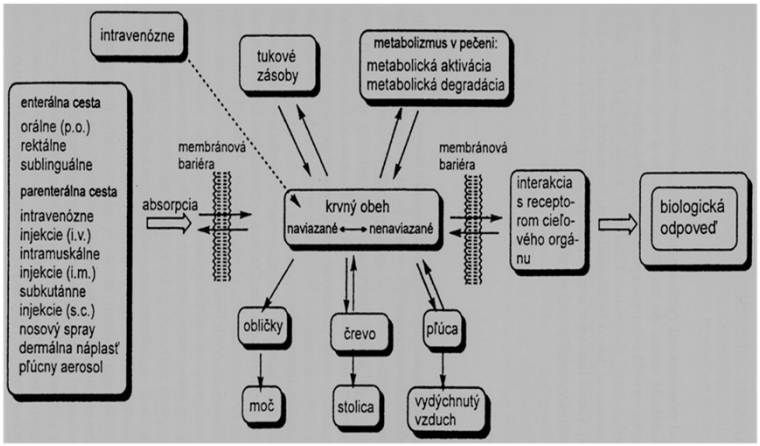
A fate of drug in a human body

(lipofilno-hydrofilné vlastnosti ovplyvňujú transfer lieku cez membrány)



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Drug targets

Lipids

Cell membrane lipids

Proteins

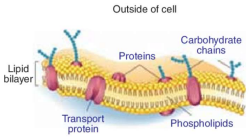
Receptors
Enzymes
Transport proteins
Structural proteins (tubulin)

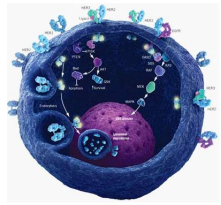
Nucleic acids

DNA
RNA

Carbohydrates

Cell surface carbohydrates
Antigens and recognition molecules





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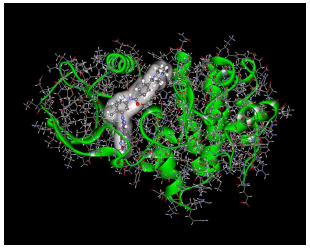
- **Drug targets are macromolecules** that have a binding site into which the drug fits and binds.



- **Most drug bind** to their targets by means of **intermolecular bonds** (ionic or electrostatics interactions , hydrogen bonds, van der Waals interactions).

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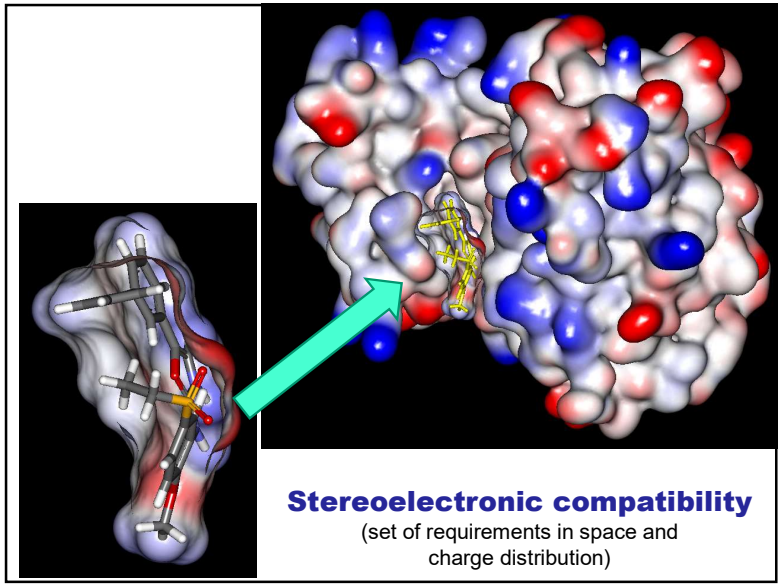

Stereoelectronic compatibility
(set of requirements in space and charge distribution)

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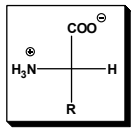
Biogenic aminoacids



- **Unpolar (8)** – (lipophilic)

Alanine (Ala; A) Me-	**Valine** (Val; V) ^{i}Pr-	**Leucine** (Leu; L) ^{i}Bu-
Isoleucine (ILE; I) ^{s}Bu-	**Methionine** (Met; M) $CH_3S(CH_2)_2$-	**Phenylalanine** (Phe; F) $PhCH_2$-
Tryptophan (Trp; W) (indol-3-yl)CH_2-	**Proline** (Pro; P) -$(CH_2)_3$-	

covalent bonds > ionic bonds > hydrogen bonds > van der Waals interactions

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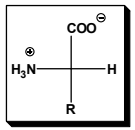
Biogenic aminoacids



- **Polar (7)** – (hydrophilic)

Glycine (Gly; G) H-	**Serine** (Ser; S) $HOCH_2$-	**Threonine (syn; 2S,3R)** (Thr; T) $HOCHCH_3$ |
Cysteine (Cys; C) $HSCH_2$-	**Tyrosine** (Tyr; Y) para-$HOPh-CH_2$-	**Asparagine** (Asn; N) NH_2COCH_2-
Glutamine (Gln; Q) $NH_2CO(CH_2)_2$-		

covalent bonds > ionic bonds > hydrogen bonds > van der Waals interactions

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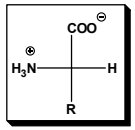
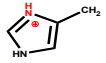
Biogenic aminoacids



- **Ionized (5)**– (hydrophilic)

Lysine (Lys; K) $H_3N^+(CH_2)_4$-	**Arginine** (Arg; R) $H_2N(NH_2^+)CNH(CH_2)_3$-	**Histidine** (His; H) 
Aspartic acid (Asp; D) $^-OOCCH_2$-	**Glutamic acid** (Glu; E) $^-OOC(CH_2)_2$-	

covalent bonds > ionic bonds > hydrogen bonds > van der Waals interactions

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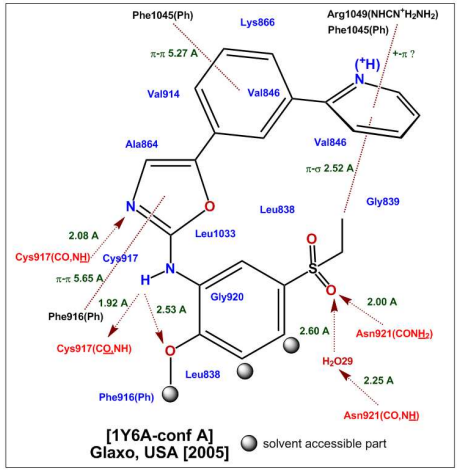
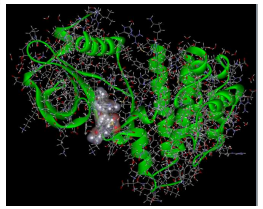
Interaction analysis map





Electrostatic interactions:
(5-10 kcal mol^{-1})
(C-C: 80 kcal /mol)

Hydrogen bonds:
vary in strength (1-6 kcal mol^{-1})

Van der Waals interactions:
are very weak (0.5 -1 kcal mol^{-1})

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Drug / target binding terms

- **Drug targets are large molecules - macromolecules**
- **Drugs are generally much smaller than their targets**
- **Drugs interact with their targets by binding to target binding sites**
- **Binding sites are typically hydrophobic hollows or clefts on the surface of macromolecules**
- **Binding interactions typically involve intermolecular bonds**
- **Most drugs are in equilibrium between being bound and unbound to their target**
- **Functional groups on the drug are involved in binding interactions and are called binding groups**
- **Specific regions within the binding site that are involved in binding interactions are called binding regions**

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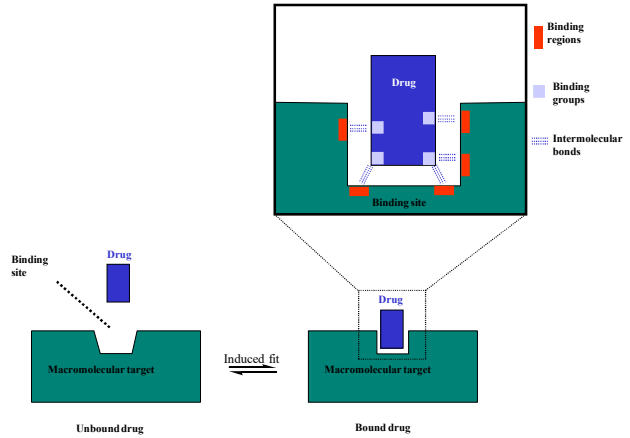

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Induced fit

• Binding interactions usually result in an **induced fit** where the **binding site changes its shape** to accommodate the drug.

• The induced fit **may also alter the overall shape** of the **drug-target complex.** This influence can be important to the pharmacological effect of the drug.

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Intermolecular binding forces

Electrostatic or ionic bond

- **Strongest of the intermolecular bonds (20-40 kJ mol^{-1})** (5 – 10 kcal/mol, C-C: 80 kcal /mol, C-H 110 kcal/mol)
- **Takes place between groups of opposite charge**
- **The strength of the ionic interaction is inversely proportional to the distance between the two charged groups**
- **Stronger interactions occur in hydrophobic environments**
- **The strength of interaction drops off less rapidly with distance than with other forms of intermolecular interactions**
- **Ionic bonds are the most important initial interactions as a drug enters the binding site**

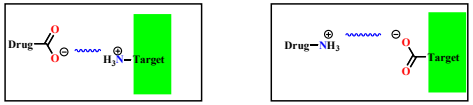
Electrostatic interactions: (5-10 kcal mol^{-1}) (C-C: 80 kcal /mol)

Hydrogen bonds: vary in strength (1-6 kcal mol^{-1})

Van der Waals interactions: are very weak (0.5 -1 kcal mol^{-1})

Average bond energies, kcal/mole	
C-H	98
O-H	110
C-C	80
C-O	78
H-H	103
C-N	65
O=O	116 (2 x 58)
C=O	187* (2 x 93.5)
C=C	145 (2 x 72.5)
(* as found in CO_2)	

1 kcal = 4.1868 kJ



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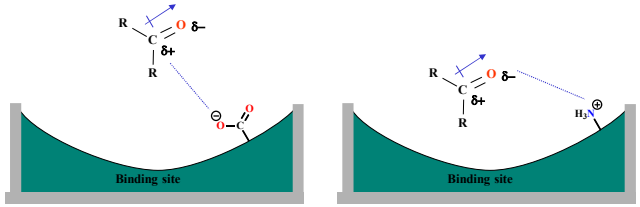
Ion-dipole interactions

- **occur where the charge on one molecule interacts with the dipole moment of another one**
- **stronger than a dipole-dipole interaction**
- **strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction**



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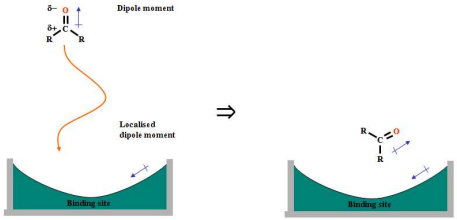
Dipole-dipole interactions

- **can occur if the drug and the binding site have dipole moments**
- **dipoles align with each other as the drug enters the binding site**
- **dipole alignment orientates the molecule in the binding site**
- **orientation is beneficial if other binding groups are positioned correctly with respect to the corresponding binding regions**
- **orientation is detrimental if the binding groups are not positioned correctly**
- **the strength of the interaction decreases with distance more quickly than with other electrostatic interactions, but less quickly than with van der Waals interactions**



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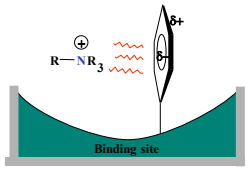
Induced dipole interactions

- occur where the charge on one molecule induces a dipole on another
- between a quaternary ammonium ion and an aromatic ring (e.g. Lys, Arg)



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Hydrogen bonds

Electrostatic interactions: (5-10 kcal mol-1) (C-C: 80 kcal /mol)
Hydrogen bonds: vary in strength (1-6 kcal mol-1)
Van der Waals interactions: are very weak (0.5 -1 kcal mol-1)

- vary in strength
- weaker than electrostatic interactions but stronger than van der Waals (VdW) interactions
- a hydrogen bond takes place between an electron deficient hydrogen and an electron rich heteroatom (N or O)
- the electron deficient hydrogen is usually attached to a heteroatom (O or N)

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- the **electron deficient hydrogen** is called a **hydrogen bond donor** (HBD)
- the **electron rich heteroatom** is called a **hydrogen bond acceptor (HBA)**
- **HB distance ≤ 2.5 Å** (e.g. C-C bond is 1.54 Å, 0.154 nm)

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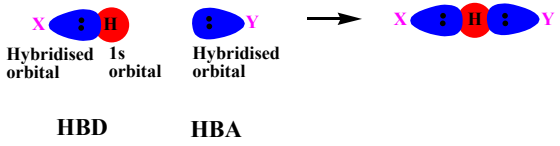
- **an optimal HB orientation is where the X-H bond points directly to the lone pair on Y such that the angle between X, H and Y is 180°**



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Hydrogen bonds

- strong hydrogen bond acceptors (HBA)
  - carboxylate ion, phosphate ion, tertiary amine
    $RCOO^-$, $RP(=O)(O^-)_2$, R_3N
- moderate hydrogen bond acceptors (HBA)
  - carboxylic acid, amide oxygen, ketone, ester, ether, alcohol
    RCOOH, RC(=O)NHR´, RC(=O)R´,RCOOR´, ROR´, ROH
- poor hydrogen bond acceptors (HBA)
  - sulphur, fluorine, chlorine, aromatic ring, amide nitrogen, aromatic amine
    S, F, Cl, Ph, RC(=O)NHR´, ArNH-
- good hydrogen bond donors (HBD)
  - quaternary ammonium ion R_3HN^+

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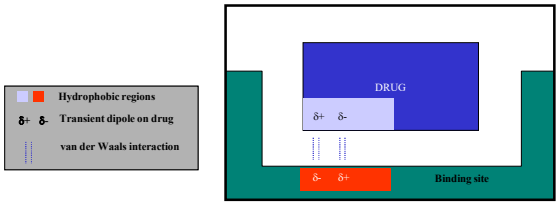
Van der Waals interactions

Electrostatic interactions: (5-10 kcal mol^{-1}) (C-C: 80 kcal /mol)

Hydrogen bonds: vary in strength (1-6 kcal mol^{-1})

Van der Waals interactions: are very weak (0.5 -1 kcal mol^{-1})

- very weak interactions (2-4 kJ mol^{-1})
- occur between hydrophobic regions of the drug and the target
- transient areas of high and low electron densities cause temporary dipoles
- interactions drop off rapidly with distance
- drug must be close to the binding region for interactions to occur
- but the overall contribution of van der Waals interactions can be crucial to binding



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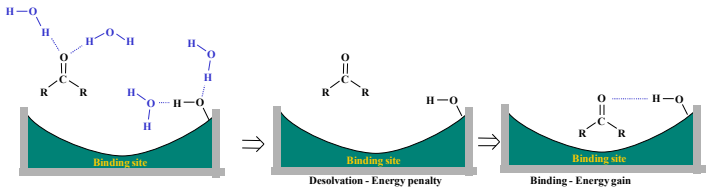
Desolvation penalties

- polar regions of a drug and its target are solvated prior to interaction
- desolvation is necessary and requires energy
- the energy gained by drug-target interactions must be greater than the energy required for desolvation



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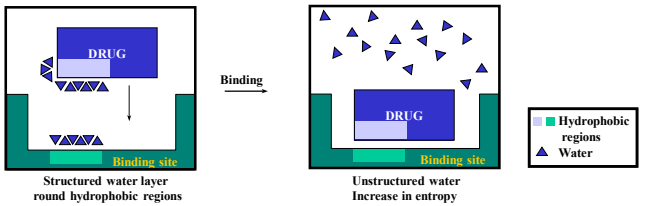
Hydrophobic interactions

- hydrophobic regions of a drug and its target are not solvated
- water molecules interact with each other and form an ordered layer next to hydrophobic regions (negative entropy)
- Interactions between the hydrophobic regions of a drug and its target 'free up' the ordered water molecules (positive entropy)
- results in an increase in entropy that is beneficial to binding energy



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Summary

Electrostatic or ionic bonds (strength, initial interactions, in hydrophobic environments, drops)
- **Dipole-dipole interactions** (contribution),
- **Ion-dipole interactions**,
- **Induced dipole interactions** (occurrence)

Hydrogen bonds (HBD, HBA, optimum, strong-poor)
Van der Waals interactions (nature, strength, contribution)

Desolvation penalties (influence on binding energy),
Hydrophobic interactions (influence on binding energy)

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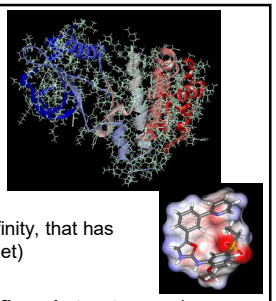
Basic terms in medicinal chemistry



- **TARGET** (biomacromolecule to interfere with a drug)
- **BINDING POCKET – ACTIVE SITE** (part of the target appropriate to bind a small ligand)
- **LIGAND** (small organic molecule possessing target affinity, that has to be stereoelectronically compatible with binding pocket)

  - **HIT** – an compound identified in a screen with **confirmed structure** and **activity** (need to be developed into a lead compound *H2L process*)
  - **LEAD** – an active compound with convenient properties: **drug-likeness, solubility, synthetic feasibility, structure novelty** (patentable)
  - **DRUG CANDIDATE possesses high activity, good selectivity, low toxicity, good preclinical efficiency**
  - **DRUG** successful in **clinical trials**, **approved** by FDA, EMEA for the market

- **BIOAVAILABILITY** – basic condition to reach the target in the body
- **DRUG-LIKENESS** – **complex properties including ADME/Tox** (**A**bsorption **D**istribution **M**etabolism **E**xcretion / **T**oxicity)

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Recommended literature and other sources

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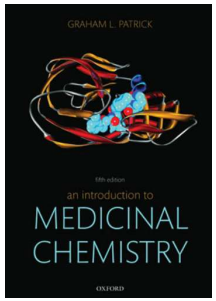
MCH book

An Introduction to Medicinal Chemistry 5e



Graham L. Patrick

ISBN 9780199697397 **2013** 5th Edition, Oxford University Press Inc., New York

http://global.oup.com/uk/orc/chemistry/patrick5e/
» Student **Tests** + Evaluation

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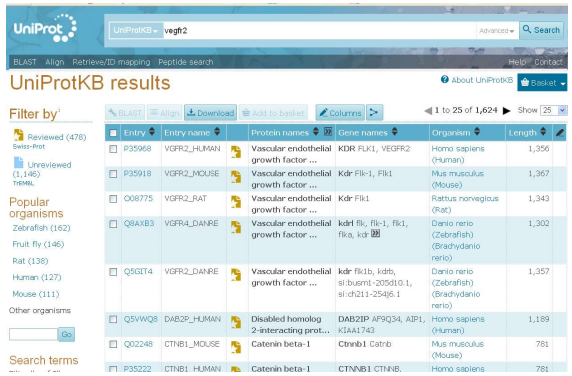
Free Biological DB - UNIPROT
(gene, AA sequences, biomolecular properties)

- **http://www.uniprot.org/**

VEGFR2



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Medicinal terms database

http://lekarske.slovniky.cz/
http://www.maxdorf.cz

search for e.g.:
anxiolytika,
spasmolytika,
apoptóza, PSA ...

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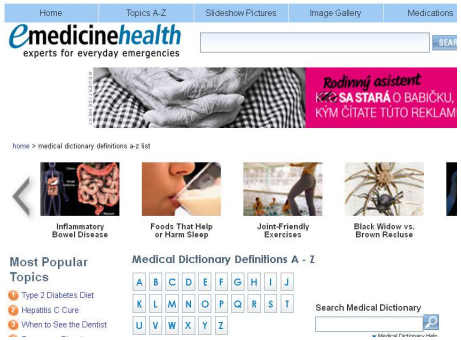
Medical terms dictionary

http://www.emedicinehealth.com/medical-dictionary-definitions/article_em.htm



search for e.g.:
anxiolytic,
spasmolytic,
apoptosis...

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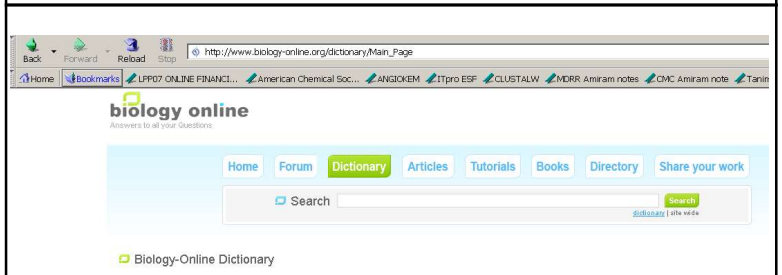
Biological terms databse

http://www.biology-online.org/dictionary/



search for:
apoptosis, VEGFR-2, Tie-2...

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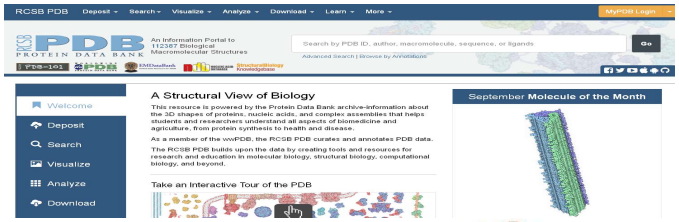
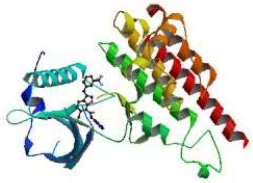
Protein Data Bank – 3D-structure of macromolecules

http://www.rcsb.org



search for: KDR, 3dtw, ...



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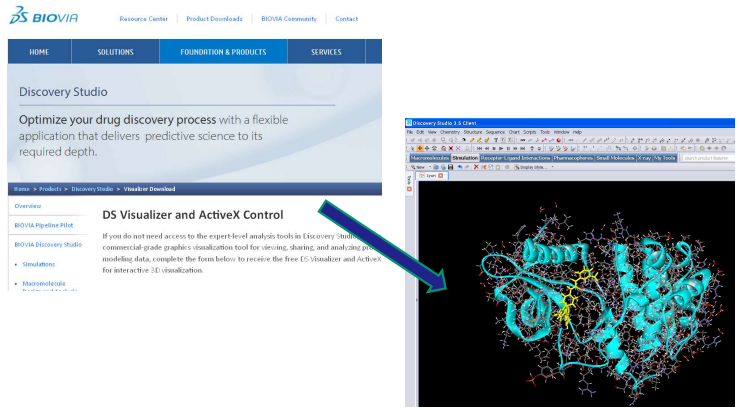
DISCOVERY STUDIO VISUALIZER 4.5 – free to download

http://accelrys.com/products/collaborative-science/biovia-discovery-studio/visualization-download.php



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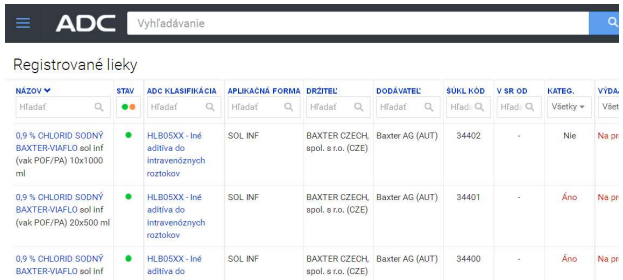
Vyhľadanie liekov a ich príbalových informácií

http://www.adcc.sk/



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Top 100 Most Prescribed Drugs

http://www.medscape.com/viewarticle/849457

Top 100 Brands by Sales

Product	Sales, $
Humira	$8,566,451,647
Abilify	$7,238,451,779
Enbrel	$6,139,812,530
Crestor	$6,090,223,570
Lantus Solostar	$5,023,092,599
Sovaldi	$4,925,098,469
Advair Diskus	$4,769,250,836
Nexium	$4,709,542,900
Januvia	$3,792,531,657

Medscape

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Prednášky a semináre z MCH

Nájdete aktualizované na:
http://www.mch.estranky.sk/clanky/mch-ss18.html

SEMINÁR MCH - VLASTNOSTI ZAUJÍMAVÝCH LIEKOV
spracovane vlastnosti 1 nizkomolekulového lieku / študenta podľa uvedeného vzoru a inf. zdrojov / nájdite (použitú lit. treba citovať v docx dokumente, príbalový leták a EN Wikipédia sú povinné zdroje, iné zdroje - napr. na vysvetlenie mechanizmu pôsobenia lieku, youtube, videa...sú vítané a mozete za ne dostat k hodnoteniu 40% navyše, Kritériom dobrého prednesu je jasnosť, informačná stručnosť a zaujmave podanie
(bližšie informácie k semináru najdete na horeuvedenej stránke)

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