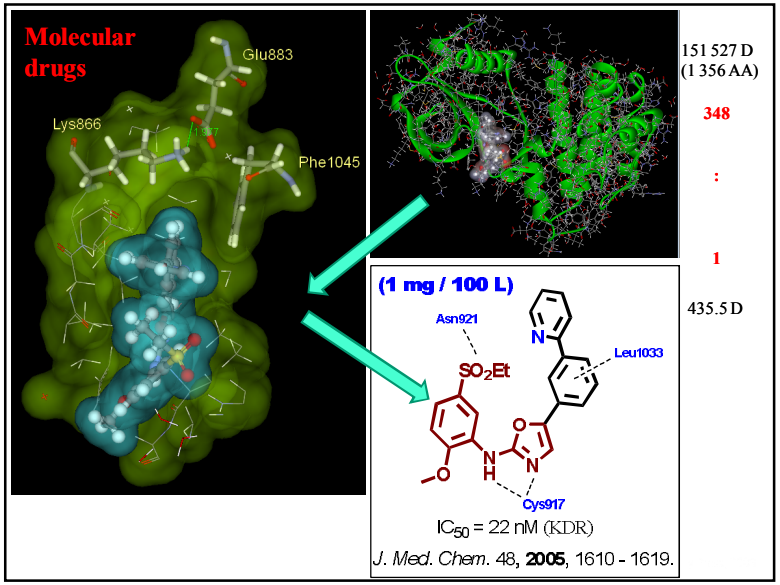
Medicinal Chemistry-I

DRUGS & DRUG TARGETS

Bratislava, 2014 **A. Boháč**



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

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

What is drug?

- In **medicinal chemistry**, the chemists **design and synthesize a pharmaceutical agent that has a desired biological effect** on the human body or some other living systems.
- **Drugs** in general are **compounds** which 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 bottle of whisky or 9 kg of spinach)

Chronology of 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,** of organic molecules possessing appropriate drug-like properties (biologists, computer chemists)
- ❑ organic **synthesis** (chemists)
- ❑ biological or biophysical **assays** (biologists)
- ❑ **optimization** of activity and other molecular properties (solubility, toxicity etc.)
- ❑ **IP** protection + **clinical trials** + up-scale synthesis + authority approval

How many new drugs reach the market yearly?

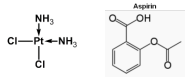
- **DD is highly interdisciplinary science that is time and resources consuming process:**
- **10 years / from 870 000 000 to 2 000 000 000 USD /1 new drug**
  Adams C, Brantner V . *Health Aff airs (Millwood)* 2006 **25** 420–8.
- **global production ca 24 innovative drugs (new chemical entity) / year**

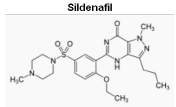
  (**2009**: 26, **2008**: 25, **2007**: 18, **2006**: 22, **2005**: 26, **2004**: 24, **2003**: 26, **2002**: 28, **2001**: 23, **2000**: 26)
- Many failures have been recorded in high stages of drug development, even in clinical trials) **Where is a problem?**

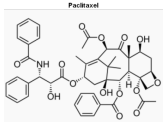
Drug-likeness was often missing.
Computer aided drug design is preferred.

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



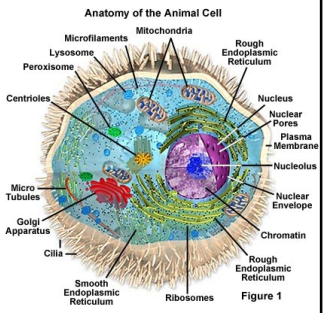




- ❑ **active**
  (stereoelectronicaly compatibile with target binding place)
- ❑ possesing **low toxicity** (selectivity, antitargets: e.g. cytochrome P450 enzymes, heart potassium ion channel hERG, P-glycoprotein...etc.)
- ❑ good **bioavailablity** (complex of physico-chemical and pharmacological properties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

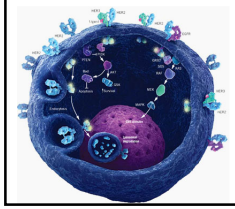
A structure of a cell

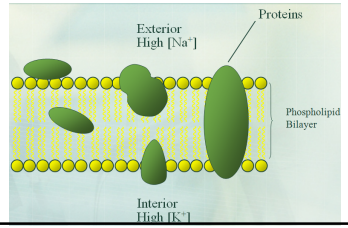
- **Human, animal and plant cells are eukaryotic cells**
- **The nucleus contains the genetic blueprint for life (DNA)**
- **The fluid contents of the cell are known as the cytoplasm**
- **Structures within the cell are known as organelles**
- **Mitochondria are the source of energy production**
- **Ribosomes are the cell's protein 'factories'**
- **Rough endoplasmic reticulum is the location for protein synthesis**

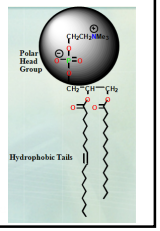


Cell membrane – protects its compartment

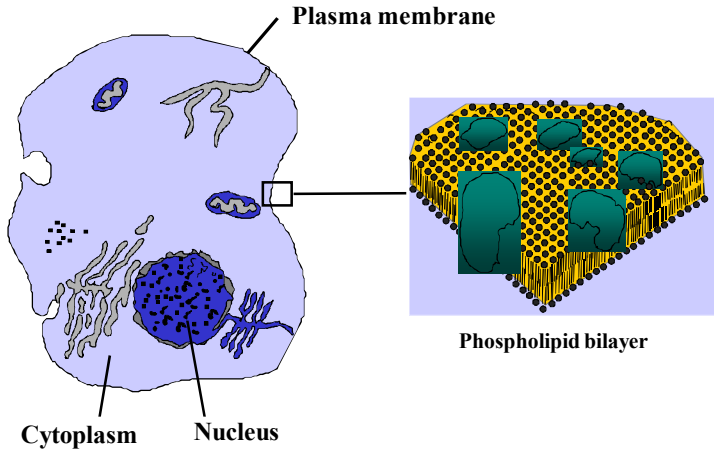
- CM composes from **phospholipid bilayer**, the **hydrophobic tails** interact with each other by van der Waals interactions and are hidden from the aqueous media
- The **polar head groups** (phosphatidylcholine) **interact with water** at the inner and outer surfaces of the membrane
- The cell membrane 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.





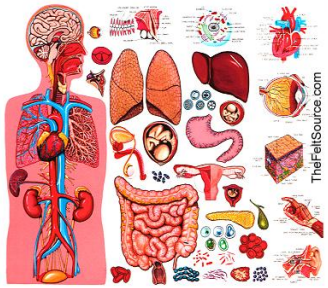


1. Cell Structure



Cells in a human body

- **Human body consists from up to 100 trillion (10E14) cells** organized in different organs and tissues (ca 200) 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** themselves.



Did you know? The length of all joined DNA from one adult body (111 mld km) is more as the distance between Earth and Pluto (7.5 mld km)!

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

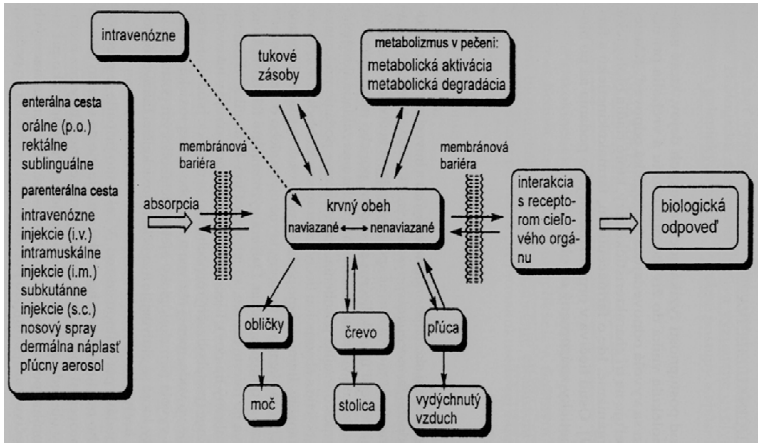
Length of all joined human DNA from one adult body is:
3.72 x 3 x 10E13 m = 11.16 x 10E10 km = 111 mld km !!!

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

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

A fate of drug in a human body

(lipofilno-hydrofilné vlastnosti ovplyvňujú transfer cez membrány)



Drug targets

Lipids

Cell membrane lipids

Proteins

Receptors
Enzymes
Transport proteins
Structural proteins (tubulin)

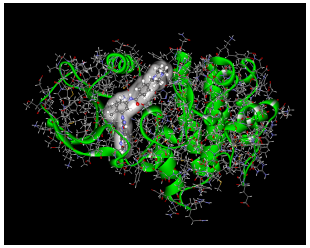
Nucleic acids

DNA
RNA

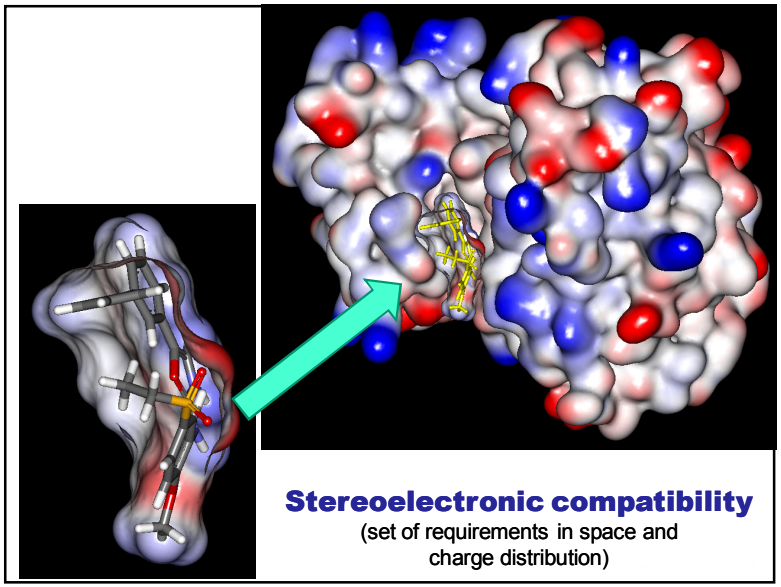
Carbohydrates

Cell surface carbohydrates
Antigens and recognition molecules

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



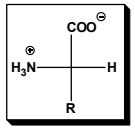
- **Most drug bind** to their targets by means of **intermolecular bonds** (electrostatics or ionic interactions, hydrogen bonds, van der Waals interactions).



Stereoelectronic compatibility

(set of requirements in space and charge distribution)

Biogenic aminoacids

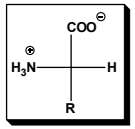


- **Unpolar (8)** – (lipophilic)

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 (Try; W) (indol-3-yl)CH_2-	**Proline** (Pro; P) -$(CH_2)_3$-	

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

Biogenic aminoacids

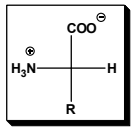


- **Polar (7)** – (hydrophilic)

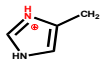
Glycine (Gly; G) H-	**Serine** (Ser; S) $HOCH_2$-	**Threonine (syn; 2S,3R)** (Thr; T) $HOCHCH_3$ |
Cysteine (Cys; C) $HSCH_2$-	**Tyrosine** (Tyr; Y) para-HOPh-CH_2-	**Asparagine** (Asn; N) NH_2COCH_2-
Glutamine (Gln; Q) $NH_2CO(CH_2)_2$-		

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

Biogenic aminoacids

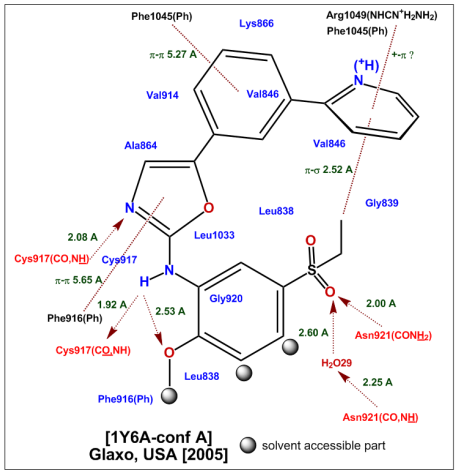


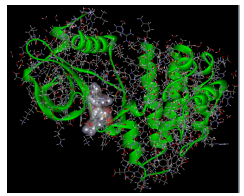
- **Ionized (5)**– (hydrophilic)

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

Interaction analysis map





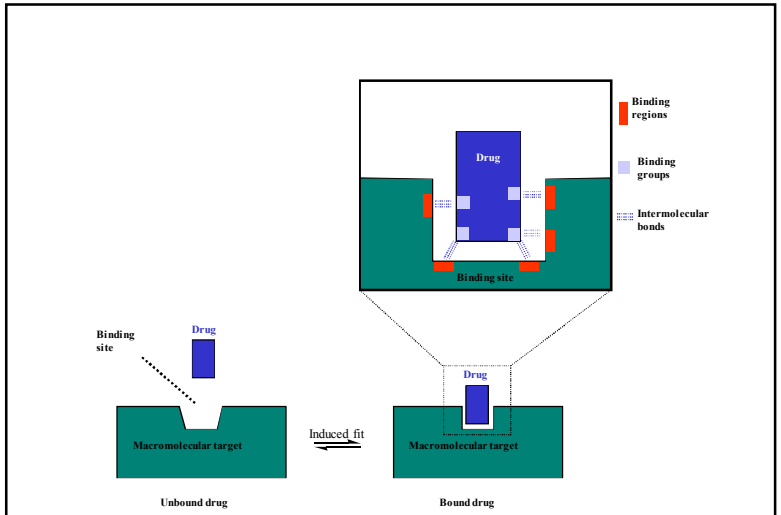
Electrostatic interactions:
(5-10 kcal mol^{-1})
(C-C: 80 kcal /mol)

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

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

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 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



Induced fit

- Binding interactions usually result in an induced fit where the binding site changes shape to accommodate the drug

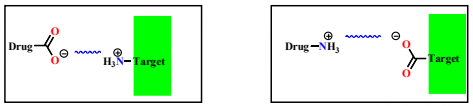
- The induced fit may also alter the overall shape of the drug target important to the pharmacological effect of the drug

Intermolecular bonding forces

Electrostatic or ionic bond

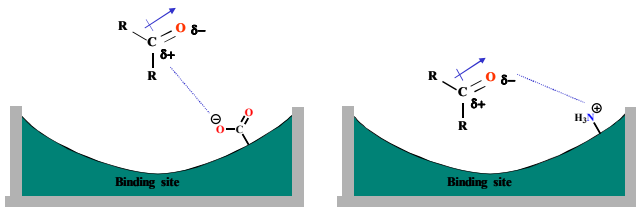
Average bond energies, kcal/mole	
C-H	98
O-H	110
C-C	80
C-O	78
H-H	103
C-N	65
O=O	116 (2 x 58)
C=O	187* (2 x 93.5)
C=C	145 (2 x 72.5)
(* as found in CO_2)	

- 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



Ion-dipole interactions

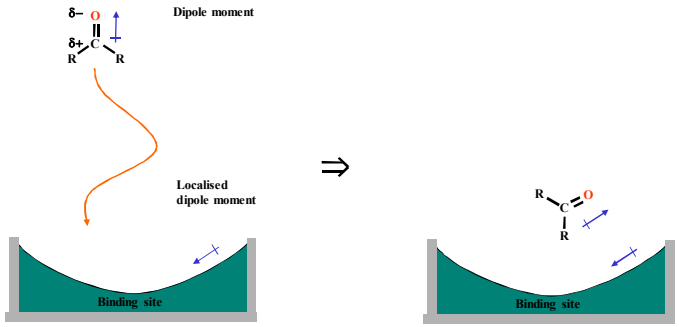
- Occur where the charge on one molecule interacts with the dipole moment of another
- Stronger than a dipole-dipole interaction
- Strength of interaction falls off less rapidly with distance than for a dipole-dipole interaction



Dipole-dipole interactions

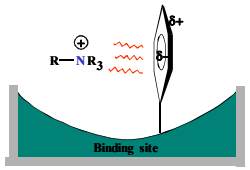
- Can occur if the drug and the binding site have dipole moments
- Dipoles align with each other as the drug enters the binding site
- Dipole alignment orientates the molecule in the binding site
- Orientation is beneficial if other binding groups are positioned correctly with respect to the corresponding 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 electrostatic interactions, but less quickly than with van der Waals interactions

Dipole-dipole interactions



Induced dipole interactions

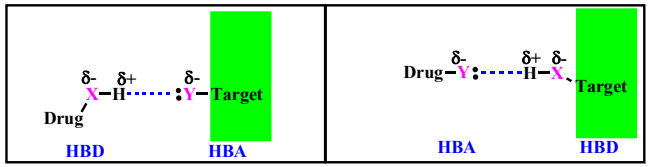
- occur where the charge on one molecule induces a dipole on another
- between a quaternary ammonium ion and an aromatic ring (e.g. Lys, Arg)



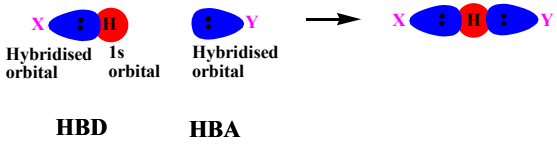
Hydrogen bonds

- Vary in strength
- Weaker than electrostatic interactions but stronger than van der Waals 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)

- 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)



- **Optimum 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°**

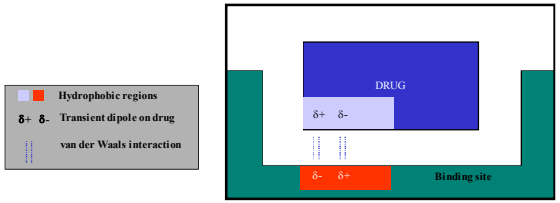


Hydrogen bonds

- **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^+

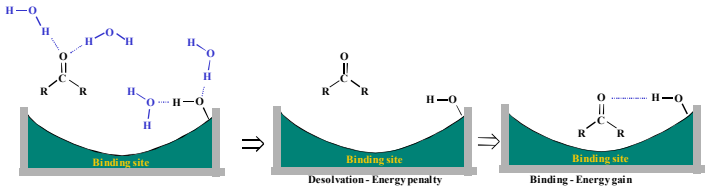
Van der Waals interactions

- 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
- The overall contribution of van der Waals interactions can be crucial to binding



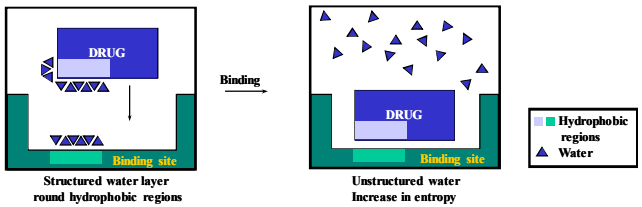
5. Desolvation penalties

- 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

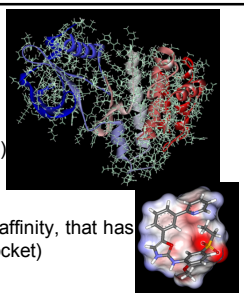


6. Hydrophobic interactions

- 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
- Results in an increase in entropy that is beneficial to binding energy



Basic terms in medicinal chemistry

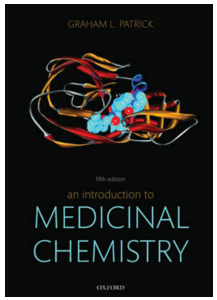


- **TARGET** (biomacromolecule to interfere with a drug)
- **BINDING POCKET – ACTIVE SITE**
  (part of the target appropriate to bind a small ligand)
- **LIGAND** (small organic molecule possessing target affinity, that has to be stereoelectronically compatible with binding pocket)
  - ❑ **HIT** – an compound identified in a screen with **confirmed structure** and **activity** (need to be developed into a lead compound)
  - ❑ **LEAD** active compound with convenient properties: **drug-likeness, solubility, synthetic feasibility, novel structure** (patentable)
  - ❑ **DRUG CANDIDATE high activity, good selectivity, low toxicity, good preclinical efficiency**
  - ❑ **DRUG** successfull 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)

Recommended literature and other sources

MCH book

An Introduction to Medicinal Chemistry 5e



Graham L. Patrick

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

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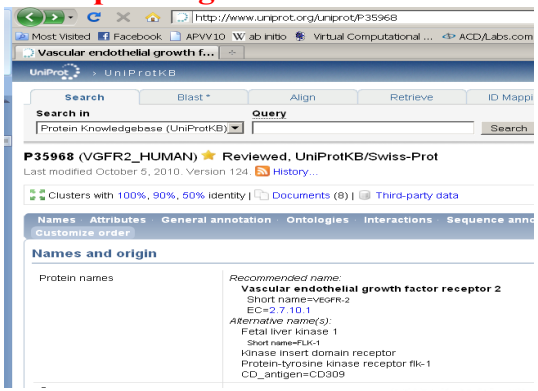
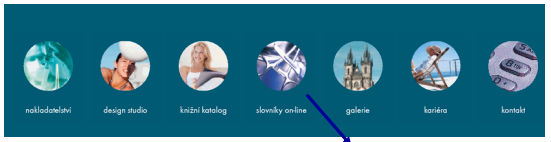
Free Biological DB - UNIPROT (gene, AA sequences, biomolecular properties)

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

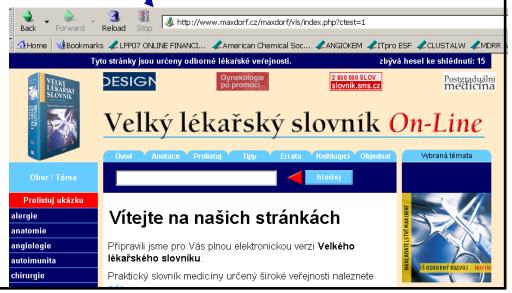


Medicinal terms database

http://www.maxdorf.cz



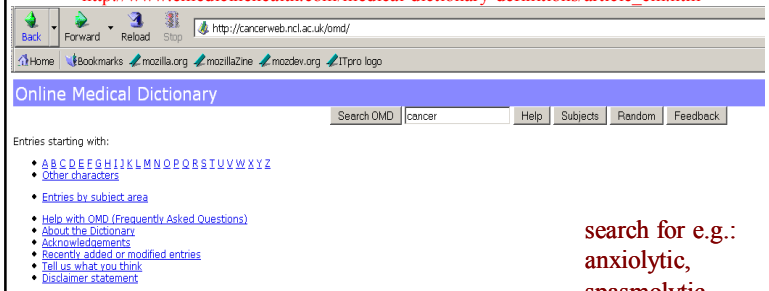
search for e.g.:
anxiolytika,
spasmolytika,
apoptóza, PSA ...



Medical terms dictionary

http://dictionary.reference.com/medical/

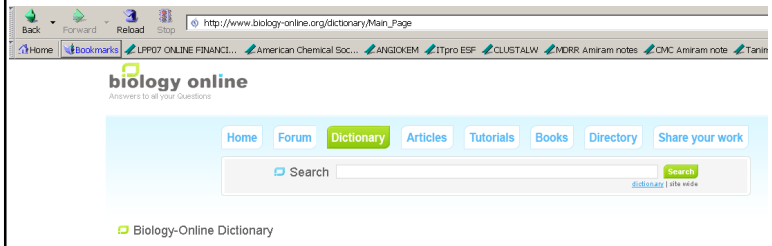
http://www.emedicinehealth.com/medical-dictionary-definitions/article_em.htm



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

Biological terms databse

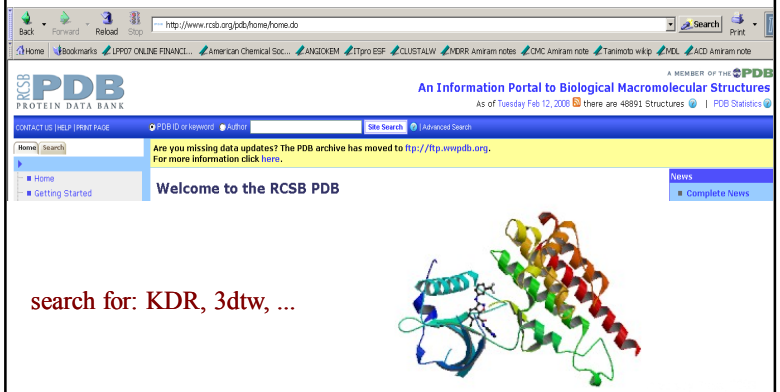
http://www.biology-online.org/dictionary/



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

Protein Data Bank – 3D-structure of macromolecules

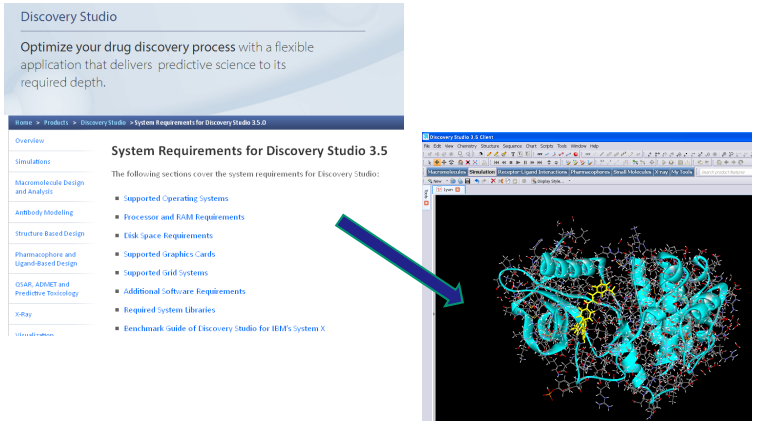
http://www.rcsb.org



search for: KDR, 3dtw, ...

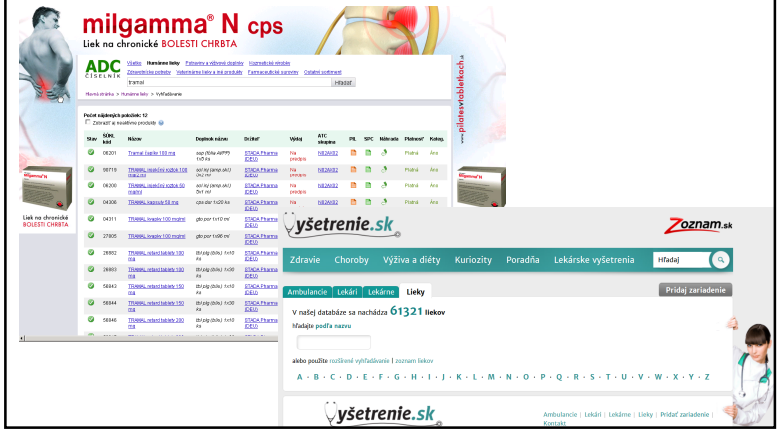
DISCOVERY STUDIO VISUALIZER 4.0 – free to download

http://accelrys.com/products/discovery-studio/requirements/technical-requirements-350.html



Vyhľadanie liekov a ich príbalových informácií

http://www.adcc.sk/ alebo na **http://vysetrenie.zoznam.sk/lieky/abecedny-zoznam**



Top 100 Most Prescribed Drugs

http://www.medscape.com/viewarticle/825053#1

Table 1. Top 100 Drugs by Sales

Rank	Drug (Brand Name)	Sales Through March 2014
1	Abilify	$6,895,243,368
2	Nexium	$6,271,376,299
3	Humira	$5,936,289,498
4	Crestor	$5,502,148,010
5	Advair Diskus	$5,112,576,549
6	Enbrel	$4,696,267,318
7	Remicade	$4,235,535,358
8	Cymbalta	$4,095,537,942
9	Copaxone	$3,679,837,035
10	Neulasta	$3,634,919,067
11	Lantus Solostar	$3,375,632,862
12	Rituxan	$3,320,475,967
13	Spiriva Handihaler	$3,140,602,715
14	Januvia	$2,975,320,499
15	Abilify	$2,894,627,347
16	Lantus	$2,796,784,267
17	Avastin	$2,742,284,655
18	Lyrica	$2,611,451,728
19	Oxycontin	$2,528,601,587
20	Epogen	$2,346,224,521
21	Celebrex	$2,342,549,444
22	Truvada	$2,307,970,304
23	Diovan	$2,190,542,892
24	Gleevec	$1,995,042,989
25	Herceptin	$1,971,724,243
26	Lucentis	$1,917,919,037
27	Namenda	$1,871,956,353
28	Vyvanse	$1,848,814,801
29	Zetia	$1,826,260,072
30	Levemir	$1,775,037,064
31	Symbicort	$1,733,830,589
32	Sovaldi	$1,724,887,241
33	Novolog Flexpen	$1,482,659,229
34	Novolog	$1,409,680,368
35	Tecfidera	$1,394,704,148
36	Suboxone	$1,388,805,102
37	Humalog	$1,310,236,982
38	Xarelto	$1,263,697,546
39	Seroquel XR	$1,251,615,894
40	Viagra	$1,235,125,299
41	Alimta	$1,205,717,422
42	Victoza 3-Pak	$1,186,784,355
43	Avonex	$1,184,476,004
44	Nasonex	$1,180,165,756
45	Cialis	$1,170,843,904
46	Gilenya	$1,097,409,827
47	Strattera	$1,083,660,282
48	Flovent HFA	$1,078,422,967
49	Prezista	$1,046,464,870
50	Procrit	$1,037,298,436
51	Ibandronic	$1,037,220,122
52	Januvet	$1,026,179,032
53	Renvela	$1,023,751,529
54	Humalog Kwikpen	$1,003,100,788
55	Orencia	$990,449,529
56	Desirent	$967,408,551
57	Vesicare	$967,408,277
58	Neupogen	$944,389,150
59	Reyataz	$935,417,307
60	Lunesta	$927,689,337
61	Synthroid	$899,215,864
62	Pradaxa	$862,604,444
63	Zyliga	$861,683,197
64	Benicar	$860,761,655
65	Xolair	$859,052,353

Medscape

Prednášky a semináre z MCH

Nájdete aktualizované na:
http://www.mch.estranky.sk/clanky/mch---ss14.html

MCH-seminare14
S01_02.10.2014 - VLASTNOSTI ZAUJÍMAVÝCH LIEKOV-1 - spracovanie vlastnosti nizkomolekulového lieku, 1 liečivo / študenta podľa uvedeného vzoru a zdrojov + Wikipedia + iné inf. zdroje / nájdite (použitú lit. treba citovať v docx dokumente, príbalový leták a EN Wikipédia sú povinné zdroje, iné zdroje - napr. na vysvetlenie mechanizmu pôsobenia lieku, videa...sú vítané)
zdroj na výber liečiva: Top 100 Most Prescribed Drugs
vzorový dokument: docx
zoznam liekov / príbalový leták: link1, alebo link2
harmonogram: na S01 prvých 5 študentov podľa abecedy
organizácia: študenti prinesú na S01 spracovaný docx subor a prednesú ho, duplicita sa nepripúšťa (informujte sa medzi sebou)
odovzdáva sa: povinne Váš docx súbor (názov suboru bude mať formu, ako má vzor!)
k tomu môže byť aj pptx súbor, video atp. (ak viac suborov, tak kniznica s názvom formou, ako má vzor!)
hodnotenie: max 100% (hodnotí sa kvalita informácii, ich spracovanie a zaujmavosť prednesu, hladajte aj iné zdroje, doplnkové informácie, napr. nájdený a vysvetlený mechanismzus pôsobenia lieku, ci jasne vysvtelujuce video budu bónusom až do +50 % hodnotenia navyse)

S02_09.10.2014 - VLASTNOSTI ZAUJÍMAVÝCH LIEKOV-2
propozície ako S01, **harmonogram:** na S02 posledných 5 študentov podľa abecedy