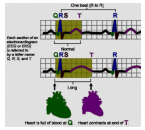
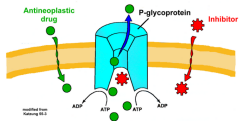
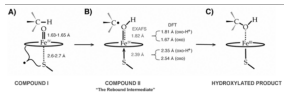
Antitargets

hERG - **potassium ion channel** that **coordinates the heart's beating**. When **this channel is inhibited** by application of drugs **it can result in a potentially fatal disorder called long QT syndrome**; a number of clinically successful drugs in the market have had the tendency to inhibit hERG, and create a concomitant risk of **sudden death, as an unwanted side effect**, **hERG inhibition must be avoided during drug development**





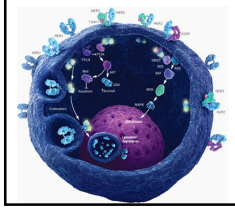


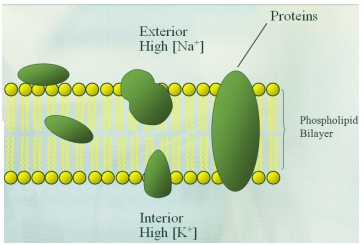
P-glycoprotein **transports substrates across the cell membrane, efflux pump for xenobiotics (e.g. drugs)** with broad substrate specificity. It is responsible for **multidrug-resistantance** and often mediates the development of resistance to anticancer drugs.

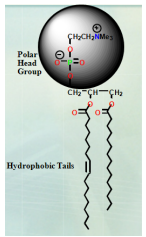
Cytochrome P450 are the major enzymes involved in **metabolism** (~75%), they catalyze the oxidation of organic substrates, drugs included.

Cell Membrane – protects cell compartment

- The cell membrane provides a **hydrophobic barrier** around the cell, **preventing a passage of water and polar molecules.** Proteins (receptors, ion channels and carrier proteins) are present, floating in the cell membrane.







Bioavailability
(PK - pharmacokinetic)

- *(in vitro)* **active compound, to perform as a drug, has to reach its target** in the human body (*in vivo*)
- **Drug-likeness** **is** qualitative **concept to estimate bioavailability from** the molecular **structure** **before the substance is synthesized**.

The **drug-like molecule** should have:

- **an optimal MW** and appropriate **number of HBD**, **HBA** (affecting solubility and absorption)
- **optimal water and fat solubility,** **partition coeficient logP** (octanol / water) to penetrate cellular membrane to rich target inside cells. The **distribution coefficient (Log D)** is the correct descriptor for ionisable systems. **logD is pH dependent** (e.g. pH = 7.4 is the physiological value of blood serum)

Lipinski's Rule of Five (Ro5)

Lipinski Ro5
(an empiric rule, all numbers are multiples of five)

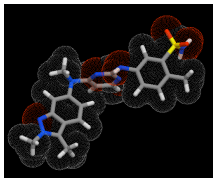
for prediction of bioavailability (**not activity**!) to quickly eliminate compounds that have poor physicochemical properties for an oral bioavailability

- an **orally active drug** has no more than one violation of the **following criteria**:
  - **MW** ≤ 500
  - **Lipophilicity** (logP ≤ 5) octanol-water partition coefficient (**better log D ≤ 5** respecting the ionic states present at physiological pH values)
  - Sum of **hydrogen bond donors** ≤ 5 (NH,OH)
  - Sum of **hydrogen bond acceptors** ≤ 10 (N,O)

C.A. Lipinski et al. Adv. Drug Del. Rev. **1997**, 23, 3. (Ro5)
G.M. Pearl et al., Mol. Pharmaceutics, **2007,** 4, 556–560. (log D introduced)

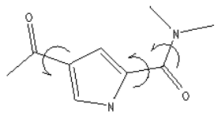
Additional drug-like parameters

- **MW** ≤ 500
- **Lipophilicity** (logP ≤ 5) octanol-water partition coefficient
- Sum of **hydrogen bond donors** ≤ 5 (NH,OH)
- Sum of **hydrogen bond acceptors** ≤ 10 (N,O)



- **PSA < 140 Å²** (Molecular Polar Surface Area – sum of surfaces of polar atoms (N,O...with H) that correlates with human intestinal and BBB absorption), or (**PSA < 60 Å²**) for good BBB penetration

- **Number of rotatable bonds < 10**
(high NRB → many conformers)



*Ertl, P. in Molecular Drug Properties, R. Mannhold (ed), Wiley-VCH , **2007**, 111 – 126.*

Differences in drug-like selection criteria

- **Optimization often gives** drugs with **higher molecular weight**, **more rings**, **more rotatable bonds**, and a **higher lipophilicity.**

T. I. Oprea et all. J. Chem. Inf. Comput. Sci. 2001, ***41***, 1308–1315.

	Ro3		Ro5
Fragment[3]		**Lead-Like**[2]	**Drug-Like**[1]
MW < 300		MW < 450	MW < 500
LogP < 3		LogP < 4.5	LogP < 5
Proton Donors < 3		Proton Donors < 5	Proton Donors < 5
Proton Acceptors < 6		Proton Acceptors < 10	Proton Acceptors < 10
Rotatable Bonds < 6		Rotatable Bonds < 10	Rotatable Bonds < 10
tPSA < 60		tPSA < 150	tPSA < 150

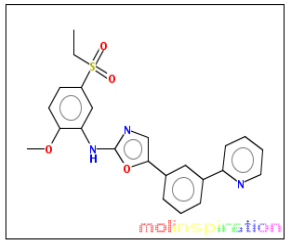
Others Properties, Solubility – calculated and measured, LogD, pKa

1/ Lipinski, C.A et al. Adv. Drug Del. Rev. 1997, 23, 3. (Rule of 5)
2/ Verheij, H.J. Molecular Diversity 2006, 10, 377. (Lead-Likeness)
3/ Congreve, M. et al. Drug Discov. Today 2003, 8, 876. (Fragments)

Ro5 determined from 2D tructure
http://www.molinspiration.com

molinspiration

SMILES CCS(=O)(=O)c4ccc(OC)c(Nc3ncc(c2cccc(c1ccccn1)c2)o3)c4



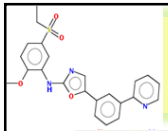
Molinspiration property engine v2009.01

miLogP	4.117
TPSA	94.327
natoms	31
MW	435.505
nON	7
nOHNH	1
nviolations	0
nrotb	7
volume	374.267

Get data as text (for copy / paste).

Get 3D geometry BETA

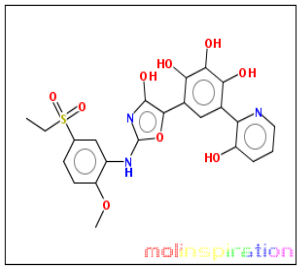
Ertl, P. et al., *J. Med. Chem.* 2000, 43: 3714-3717. (molecular property prediction toolkit)



Ro5 violations

molinspiration

SMILES CCS(=O)(=O)c4ccc(OC)c(Nc3nc(O)c(c2cc(c1ncccc1O)c(O)c(O)c2O)o3)c4



Molinspiration property engine v2009.01

miLogP	2.904
TPSA	195.467
natoms	36
MW	515.5
nON	12
nOHNH	6
nviolations	3
nrotb	7
volume	414.356

Get data as text (for copy / paste).

Get 3D geometry BETA

Absorption as f(PSA, LogP)

- **pKa** (influences binding Ki and logP)
  https://epoch.uky.edu/ace/public/pKa.jsp (free of charge)
  commercial software SPARC http://www.archemcalc.com/ (5USD/monthly)
- **AlogP** (lipophilicity, water solubility)
  http://www.vcclab.org/ **(Virtual Computational Chemistry Laboratory)**

Intestinal and other **absorption**

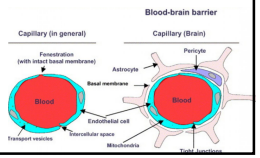
- **% ABS = 109 – 0.345 PSA**
  (good when % ABS > 30 %; **lower PSA, higher absorption**)

Zao YH et al. Pharm Res 2002, 19, 1446-1457.

BBB absorption

- **LogBB = -0.0148 PSA + 0.152 CLogP + 0.139**

CNS drug: logBB > -0.5 (otherwise side effects can be expected)
non CNS drugs: logBB < -1



Other considerations

- **despite good druglikeness** some compounds should be avoided as drug candidates:
  - ❑ **substructures with known reactive, toxic, mutagenic or teratogenic properties** affect the usefulness (RCOX, $(RCO)_2O$, Michael acceptors, epoxides, $-NO_2$, -NO, $-N_3$, NH-NH, N=N…)
  - ❑ and with **bad metabolic parameters**, e.g. fast metabolism **can quickly destroy the pharmacological activity** of the compound
    (metabolic half life, metabolic clearance should be determined)

From were to get the active compounds?

A) The Natural World	**Micro-organisms** (bacteria, fungi) **Marine chemistry** (corals, bacteria, fish etc) **Plant life** (flowers, trees, bushes) **Animal life** (frogs, snakes, scorpions) **Biochemicals** (neurotransmitters, hormones)
B) The Synthetic World	**Chemical synthesis** (traditional, combinatorial synthesis, chemical collections, commercial sources)
C) The Virtual World	**Computer** aided drug design (CADD)

to call them „active compounds" evaluation through biological screening is essential

ACTIVE compounds can be obtained as hits in screening focused on selected biological target

- **Screenings** (in vitro: enzymatic, cellular or biophysical assays):
  - ❑ **High-throughput screening (HTS)** rapid screening of large numbers of compounds (up to 100 000/day)
  - ❑ **Biopysical screening** (NMR, PSR, X-ray screening)
- **Sources**
  - ❑ **LMW synthetic compounds** (collections from combinatorial chemistry / parallel synthesis, historical corporate collections…)
  - ❑ **Fragment-based** screening (not direct hit generation)
  - ❑ **Pure natural products, bioextracts** (e. g. plant or microbial) **ethnopharmacology** (Chinese traditional medicine…)
  - ❑ **SOSA approach** based on known Drugs/Clinical development compounds where side effects observed from *in vivo* screenings or human clinical trials