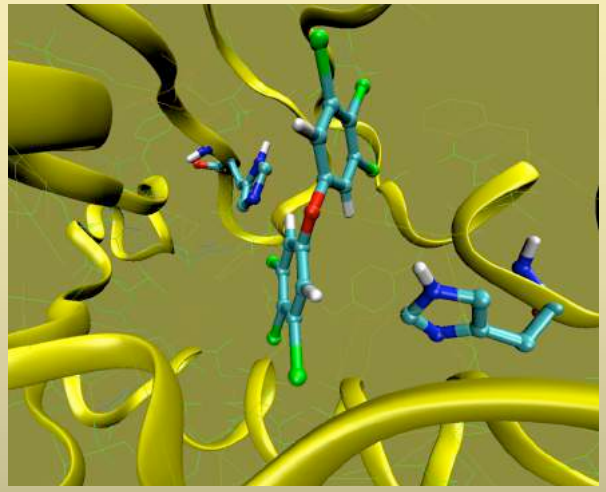
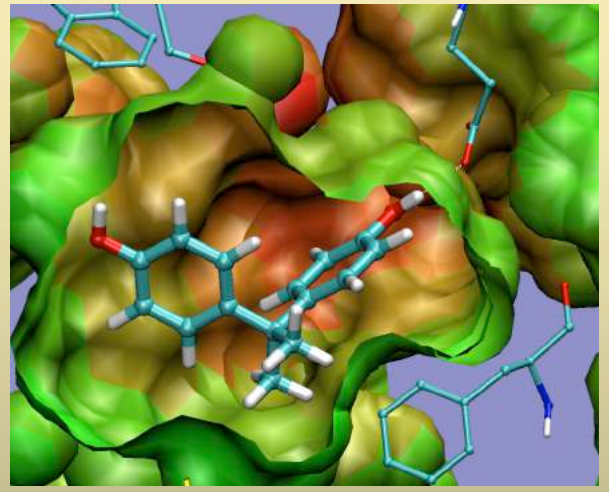
zh aw — 3. Wädenswiler Chemie-Tag 16. Juni 2011

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals



www.nrp50.ch



www.sfu.ca

- Modeling toxic phenomena
- Mixed-model QSAR
- The 16 virtual test kits
- The *VirtualToxLab* concept
- Examples: Toxic potentials and their mechanistic interpretation
- Applications of the *VirtualToxLab*

www.treehugger.com

Angelo Vedani, Department of Pharmaceutical Sciences, University of Basel

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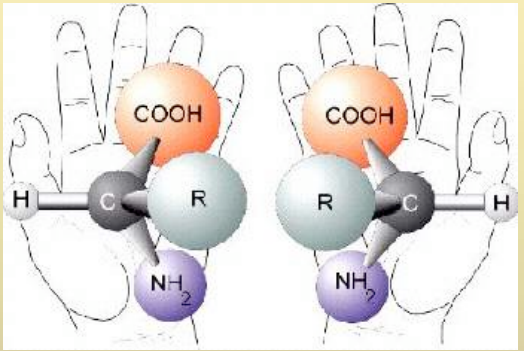
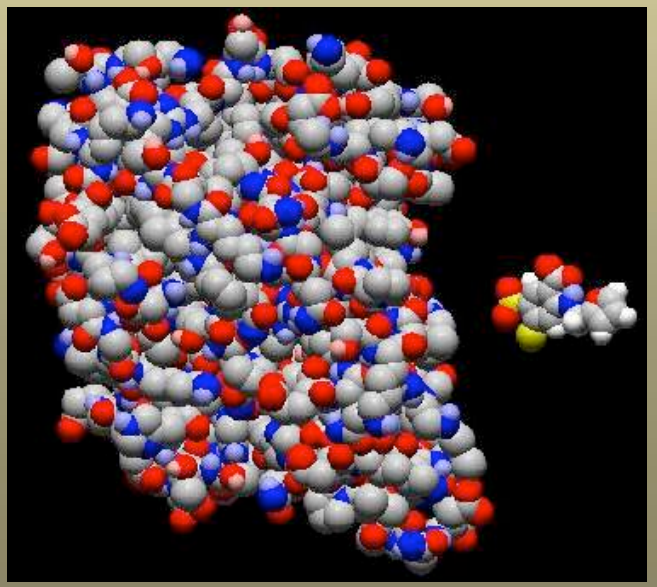
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Emil Fischer (1838–1914)

Emil Fischer (1894): Lock-and-Key Analogon



3D complimentarity leads to molecular recognition

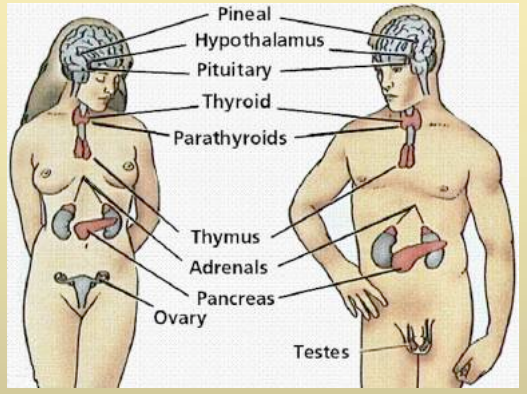


„Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glykosid zu einander passen müssen, wie Schloss und Schlüssel, um eine chemische Wirkung aufeinander ausüben zu können."

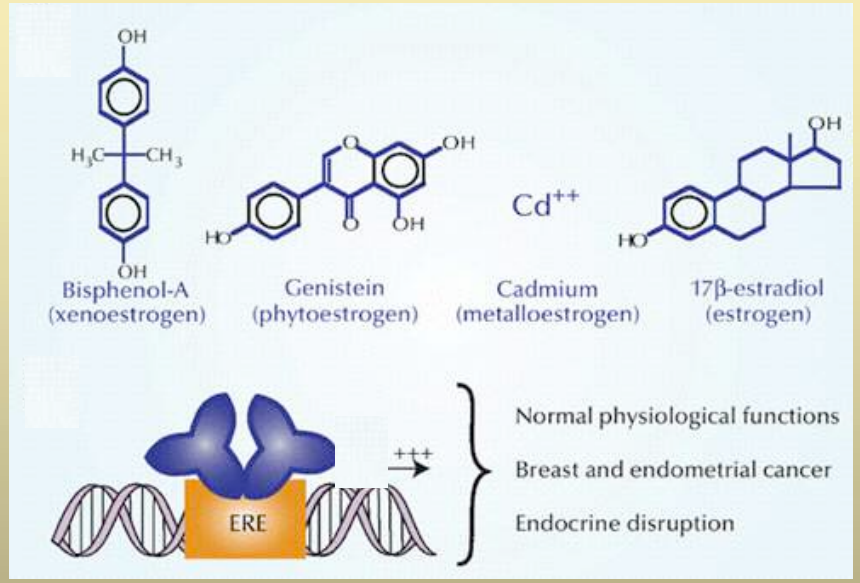
Emil Fischer (Nobel Laureate, 1902)

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

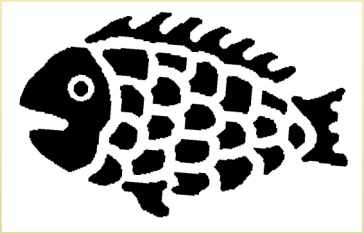
Endocrine disruptors



www.eco-thinker.com



www.medscape.com



www.nutri-notes.com

Endocrine disruptors — sometimes also referred to as hormonally active agents — are exogenous substances that act like hormones in the endocrine system and disrupt the physiological function of endogenous hormones. Studies have linked endocrine disruptors to adverse biological effects in animals, giving rise to concerns that low-level exposure might cause similar effects in humans.

www.treehugger.com

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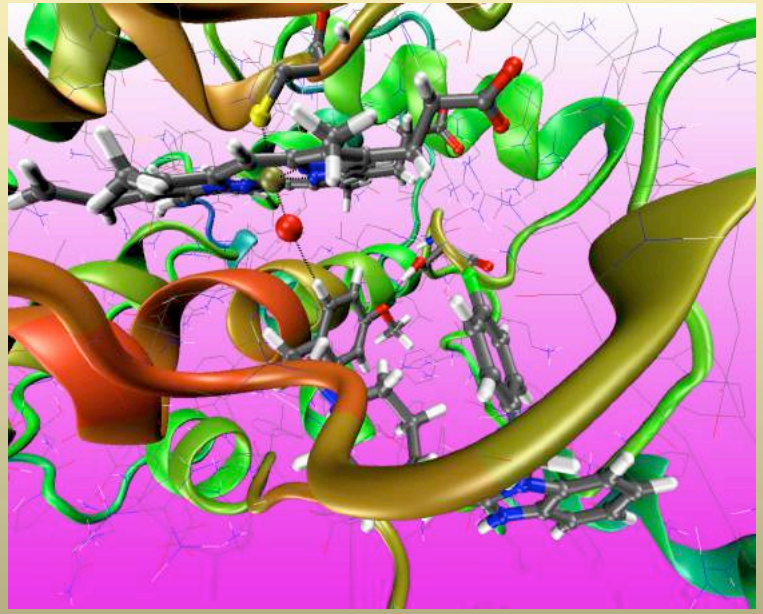
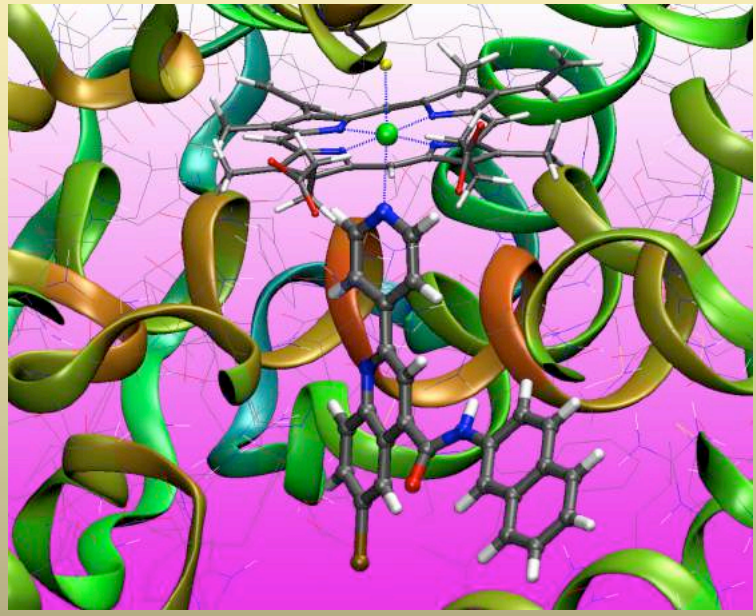
Metabolic disruptors

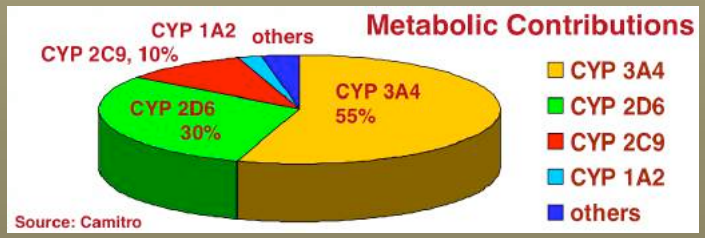


Compound acts as a substrate to CYP 3A4



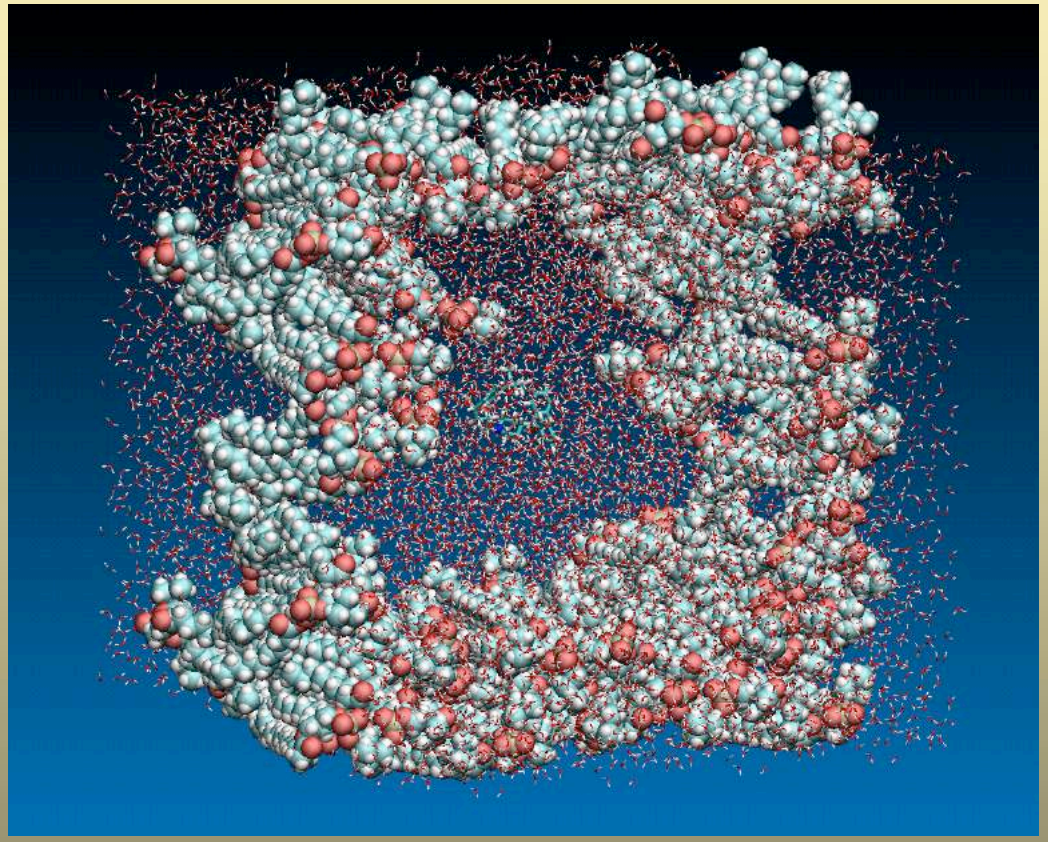
Compound acts as an inhibitor to CYP 2C9

Metabolic disruption refers to the interaction with metabolizing macromolecules — most prominently, enzymes from the cytochrome P450 family, for example CYP 1A2, CYP 2C9, CYP 2D6 and CYP 3A4.



VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Interference with the hERG K^+ channel



- **hERG** (human Ether-à-go-go Related Gene)
- Involved in cardiac action potential repolarization
- Drugs/chemicals blocking the channel can trigger a fatal disorder called **long QT syndrome**
- A number of clinically successful drugs inhibit hERG and trigger unwanted side effects
- Nowadays hERG is an **antitarget** which must be avoided during drug development

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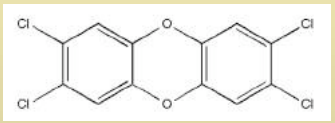
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

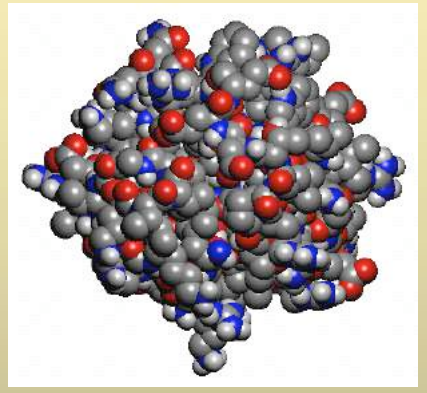
Computer simulations of receptor-mediated toxic phenomena



Contamination/intoxication

Cascade of events I

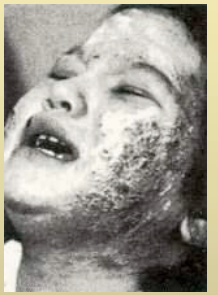
Biotransformation



Cascade of events II

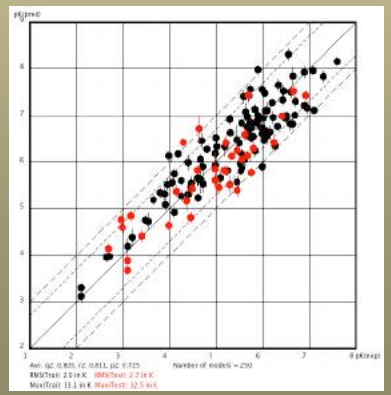
Signal transduction

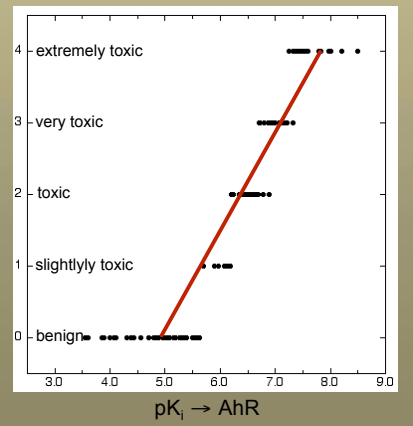
www.brooklyn.cuny.edu



Observed effect

Simulated binding to the target protein





Consequence: quantifying the binding affinity to a protein triggering adverse effects may predict the toxic potential but not toxicity.

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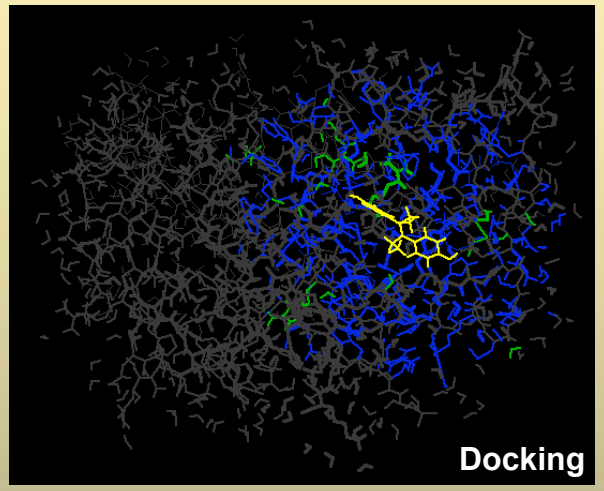
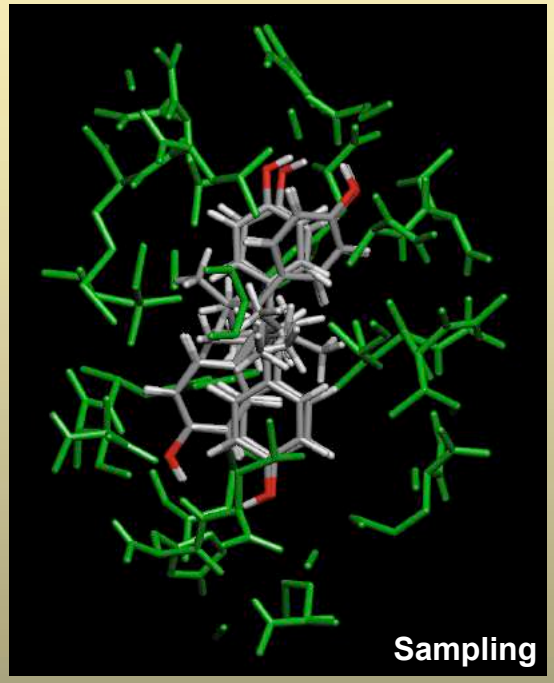
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

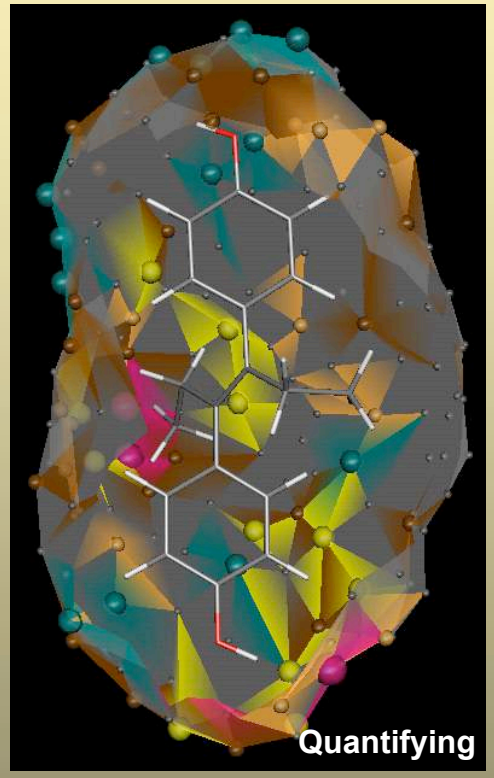
Mixed-model approach: automated, flexible docking + mQSAR



Automated, flexible docking (software Yeti)



Sampling low-energy poses → 4D data set



Quantifying the binding affinity using mQSAR (software Quasar, Raptor)

J. Med. Chem. **2005**, *48*, 3700–3703
ChemMedChem **2006**, *1*, 73–81
ChemMedChem **2007**, *2*, 78–87
Toxicol. Lett. **2007**, *173*, 17–23
ChemMedChem **2009**, *4*, 100–109
Toxicol. Lett. **2009**, *189*, 219–224
ATLA **2009**, *37*, 477–496
Mol. Inf. **2010**, 1, 27–36

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Automated, flexible docking using a directional force field

$$E_{total} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 +$$

$$\sum_{dihedrals} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{nb\ pairs} \frac{q_i \cdot q_j}{4\pi\varepsilon_o D(r) r_{ij}} + \sum_{nb\ pairs} \frac{A}{r_{ij}^{12}} - \frac{B}{r_{ij}^{6}}$$

$$+ \sum_{H-bonds} \left(\frac{C}{r_{H-Acc}^{12}} - \frac{D}{r_{H-Acc}^{10}} \right) \cdot \cos^2(\theta_{Don-H-Acc}) \cdot \cos^n(\omega_{H-Lig-LP})$$

$$+ \sum_{\substack{metal-ligand \\ pairs}} \frac{q_i^{CT} \cdot q_j^{CT}}{4\pi\varepsilon_o D(r) r_{ij}} + \sum_{\substack{metal-ligand \\ pairs}} \left(\frac{E}{r_{M-Lig}^{12}} - \frac{F}{r_{M-Lig}^{10}} \right)$$

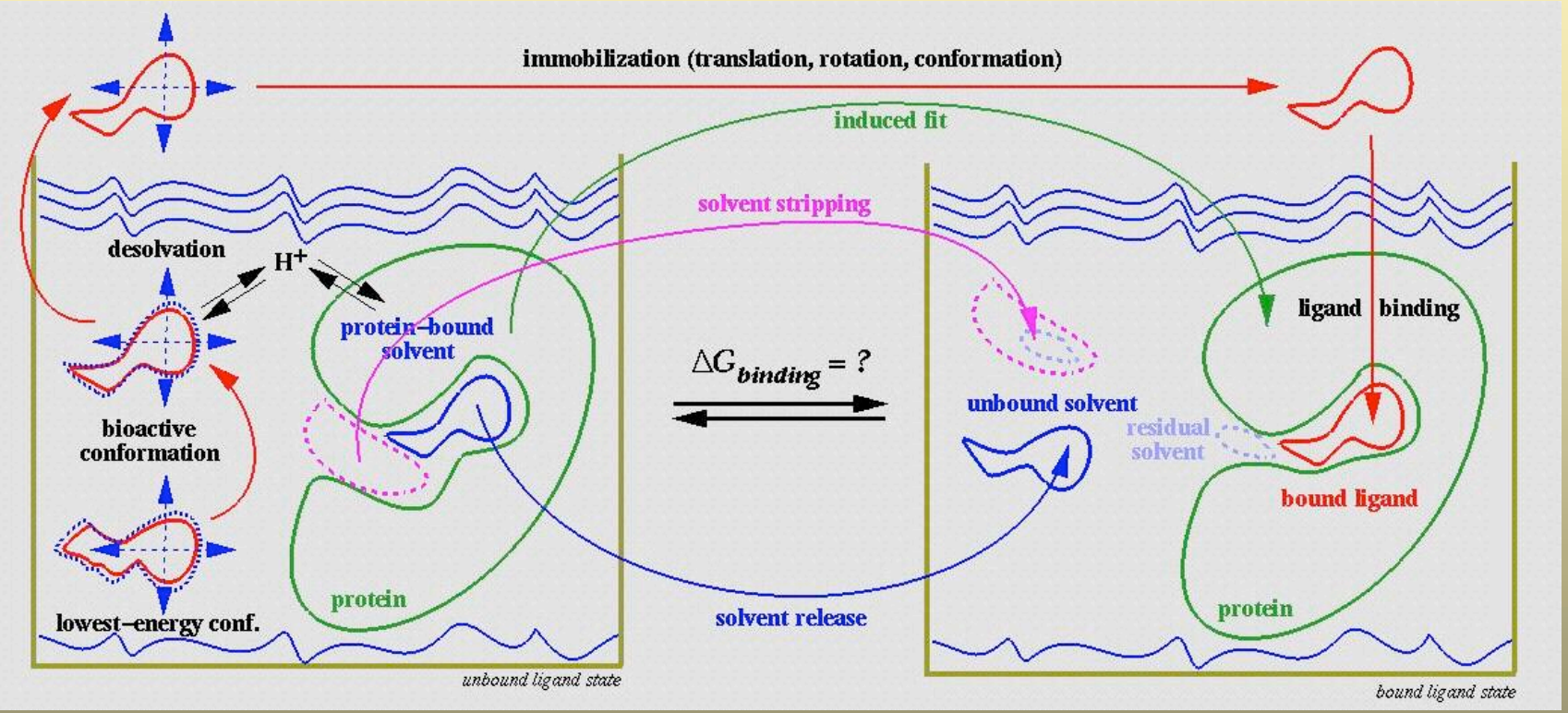
$$+ (E_{MC} + E_{LFS}) \cdot \prod_{\substack{indep. \\ angles}} \cos^2(\psi_{Lig-M-Lig'} - \psi_{eq}) \cdot \frac{1}{n} \sum_{1^{st}\ shell\ ligands} \cos^n(\omega_{M-Lig-LP})$$

J. Am. Chem. Soc. **1990**, *112*, 4759–4767

Angelo Vedani, Department of Pharmaceutical Sciences, University of Basel

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Quantifying ligand–protein interactions



$$\Delta G_{binding} \propto E_{ligand–protein} - E_{ligand\ desolvation} - E_{ligand\ internal\ strain} - T\Delta S - E_{induced\ fit}$$

J. Med. Chem. **2000**, *46*, 4416–4427
J. Med. Chem. **2002**, *45*, 2139–2149
J. Med. Chem. **2005**, *48*, 3700–3703

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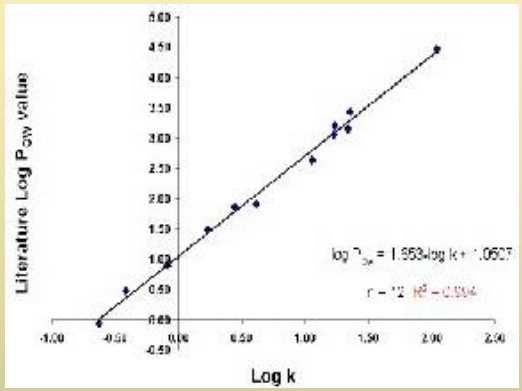
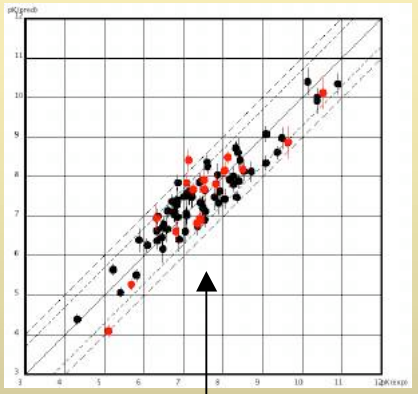
1D-QSAR



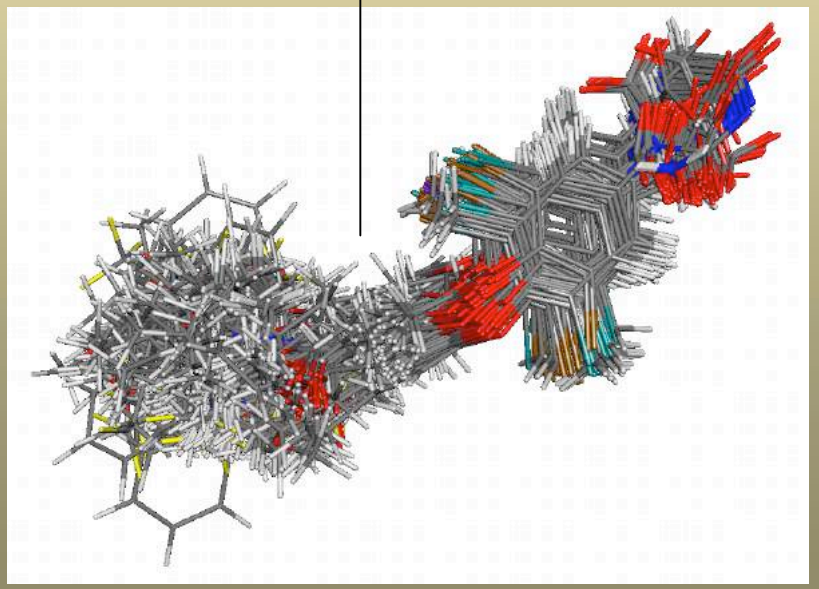
Hans-Horst Meyer, 1899

Activity of narcotica correlates with log P

3D-QSAR

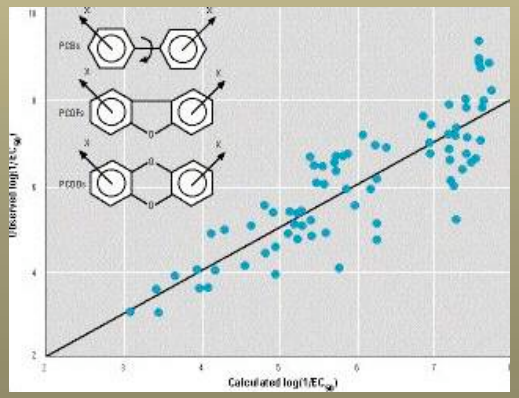


3D-QSAR



Activity of thyroid antagonists correlates with 3D structure
ChemMedChem **2007**, *2*, 78–87

2D-QSAR



Toxicity of chemicals correlates with structural motives

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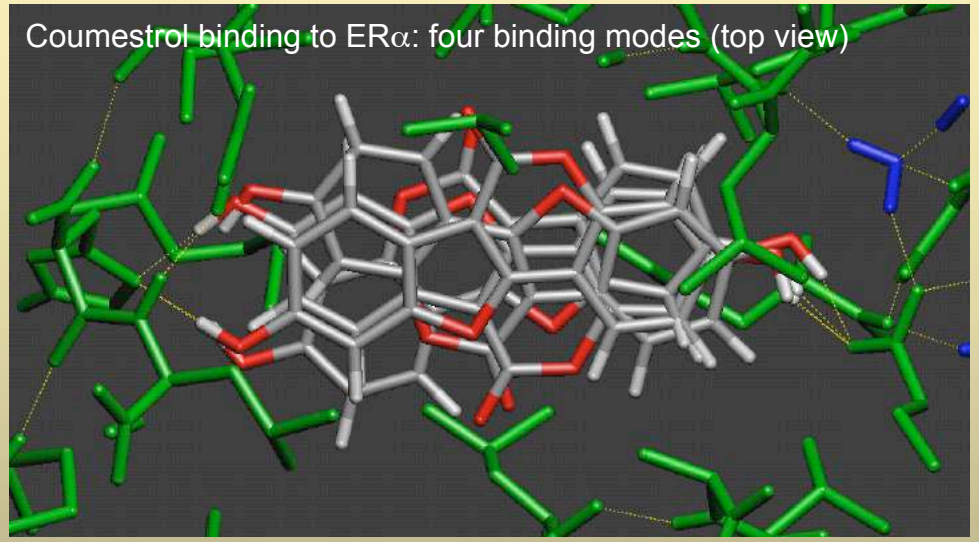
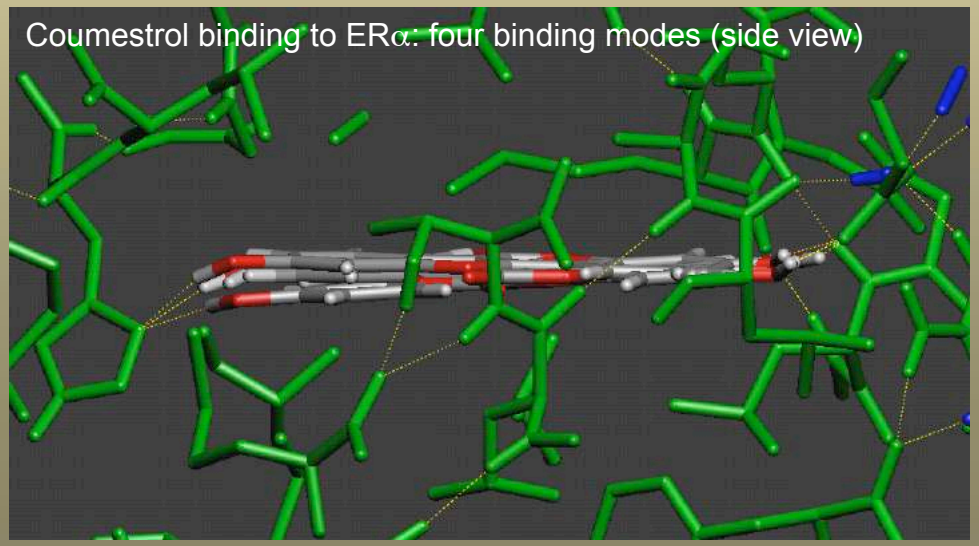
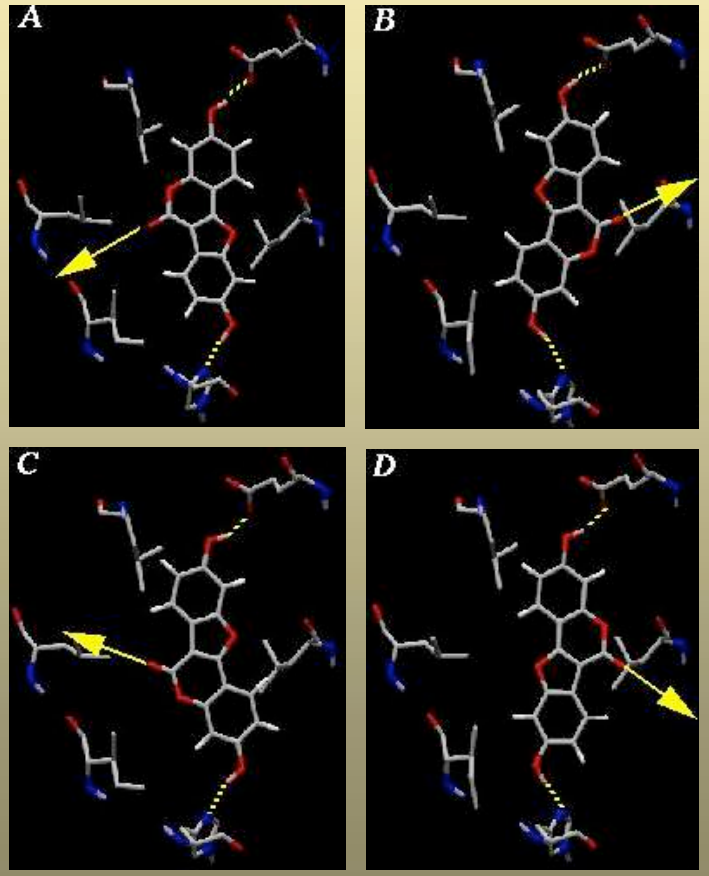




4D-QSAR



J. Med. Chem. **2005**, *48*, 3700–3703

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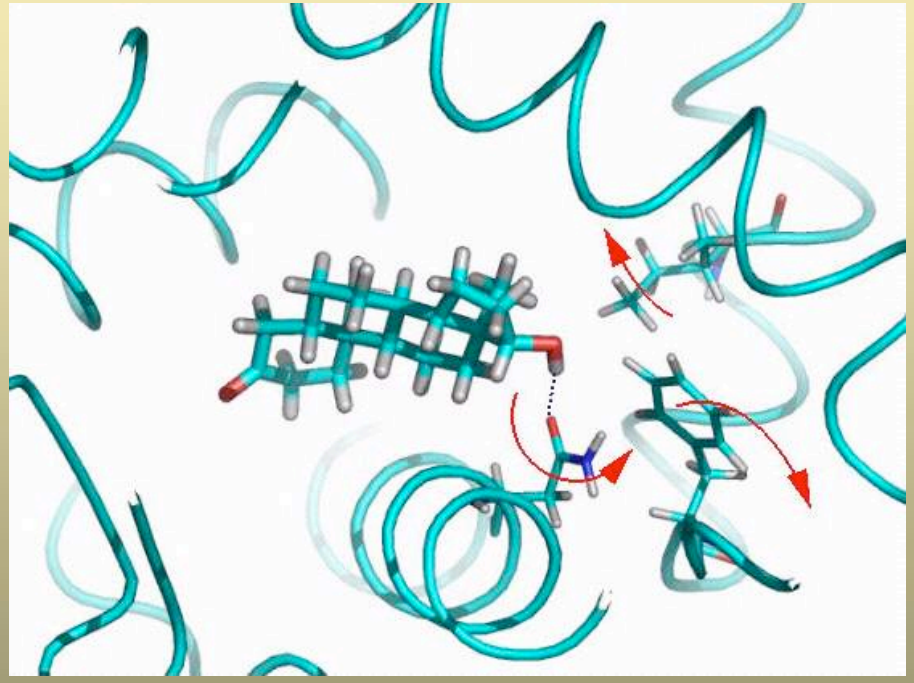
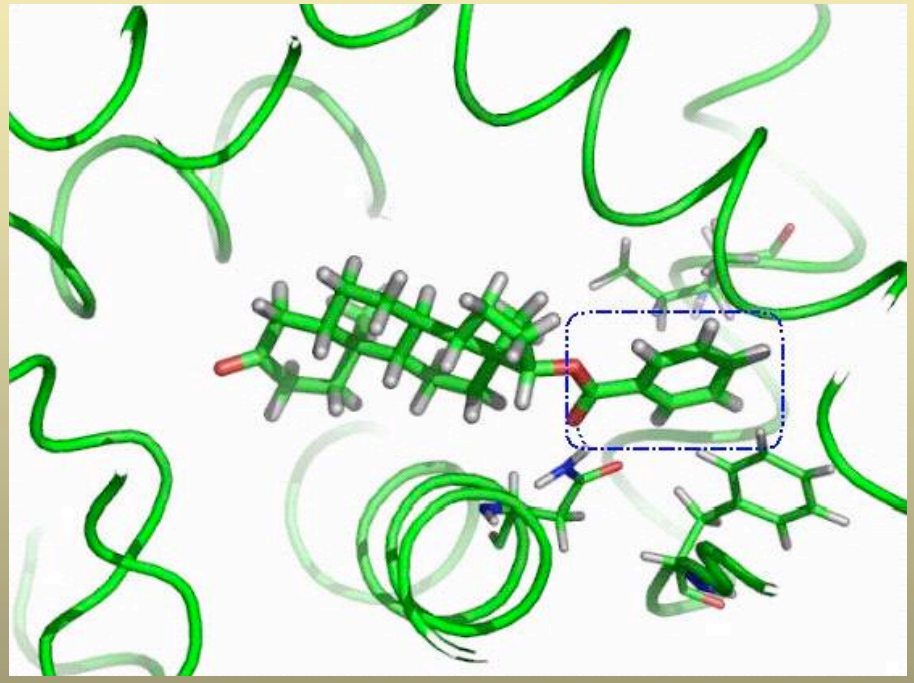
Induced Fit — Adaptation of the protein to the small-molecule ligand



Androgen receptor wirh bound dihydrotestosterone



Androgen receptor with bound dihydrotestosterone benzoate

J. Med. Chem. **2000**, *46*, 4416–4427
J. Med. Chem. **2002**, *45*, 2139–2149
J. Med. Chem. **2005**, *48*, 3700–3703

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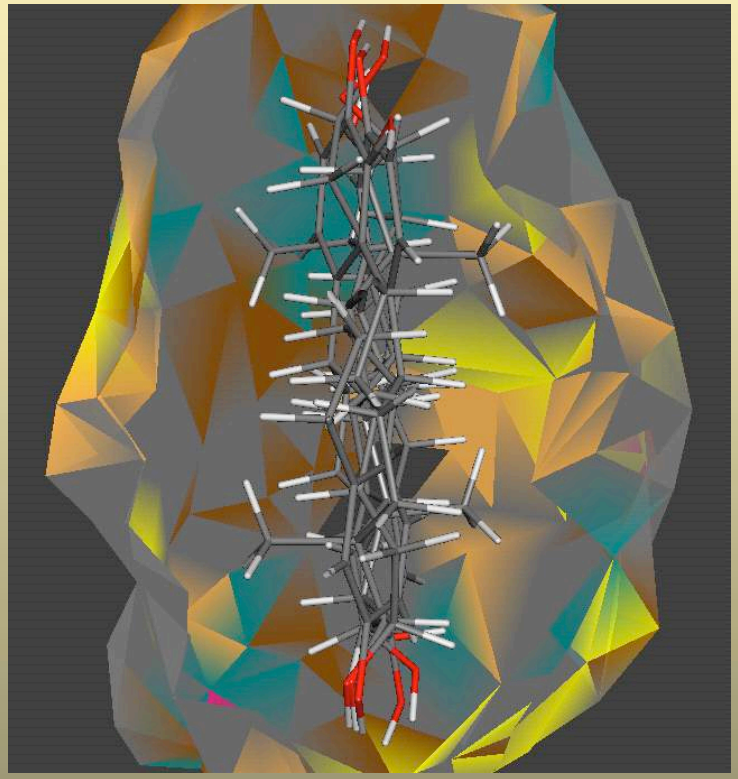
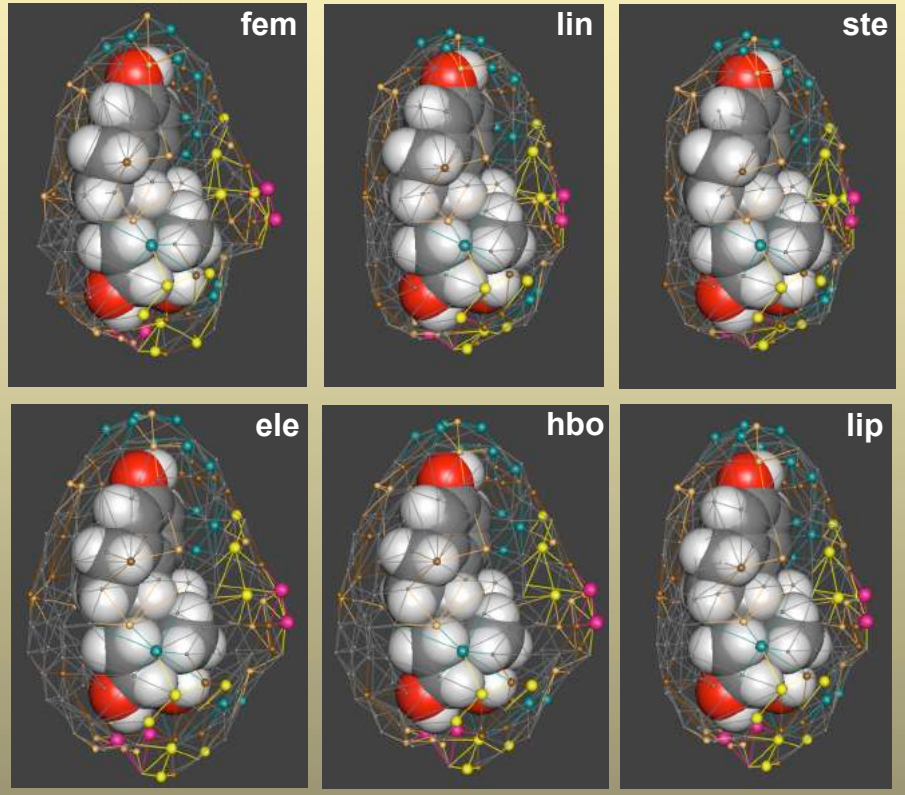
Multi-dimensional QSAR (mQSAR: software Quasar and Raptor)



4D-QSAR: ligands are represented as an ensemble of positions,orientations, conformations and protonation states



5D-QSAR: protein is represented by several induced-fit scenarios

4D-QSAR: *J. Med. Chem.* **2000**, *46*, 4416–4427
5D-QSAR: *J. Med. Chem.* **2002**, *45*, 2139–2149
6D-QSAR: *J. Med. Chem.* **2005**, *48*, 3700–3703

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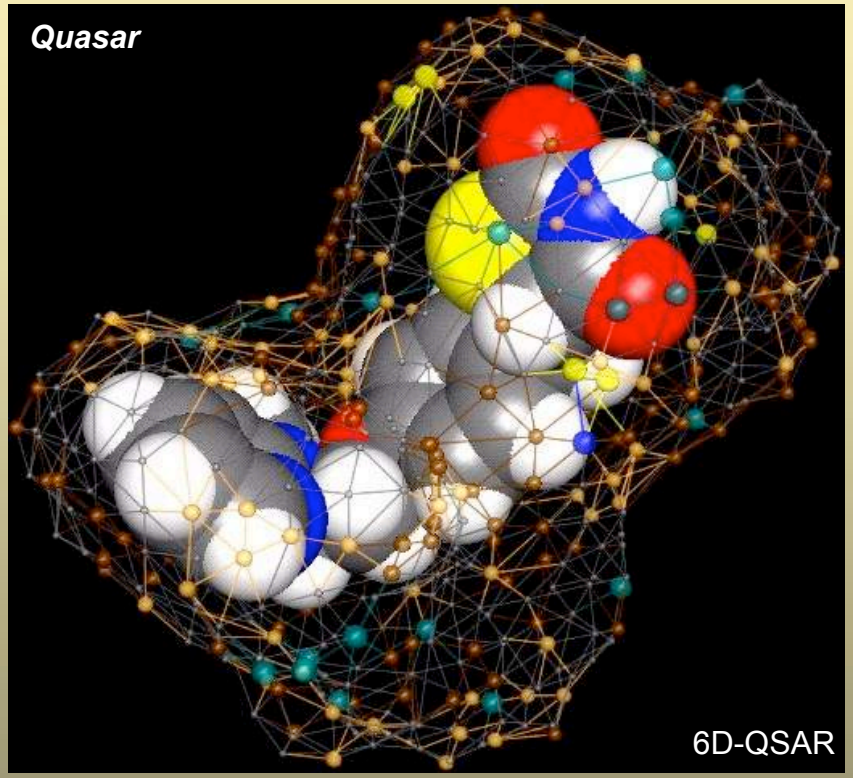
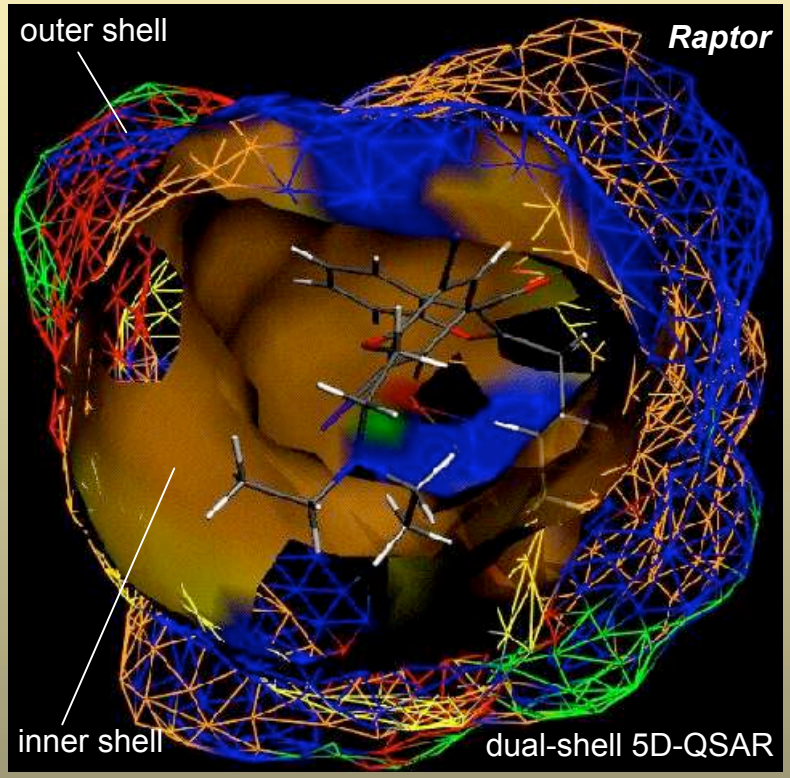
Consensus scoring: software *Quasar* and *Raptor*





$$\Delta G_{binding} \propto E_{prot-lig} - E_{solv,lig} - E_{int,lig} - T\Delta S - E_{IndFit}$$
$$E_{prot-lig} = E_{elec} + E_{vdW} + E_{HBond} + E_{polarization}$$

J. Med. Chem. **2002**, *45*, 2139–2149
J. Med. Chem. **2005**, *48*, 3700–3703

$$\Delta G_{binding} \propto E_{prot-lig} - T\Delta S - E_{IndFit}$$
$$E_{prot-lig} = E_{HBond} + E_{hydrophobic}\ (shell_1 + shell_2)$$

J. Med. Chem. **2004**, *47*, 6174–6186

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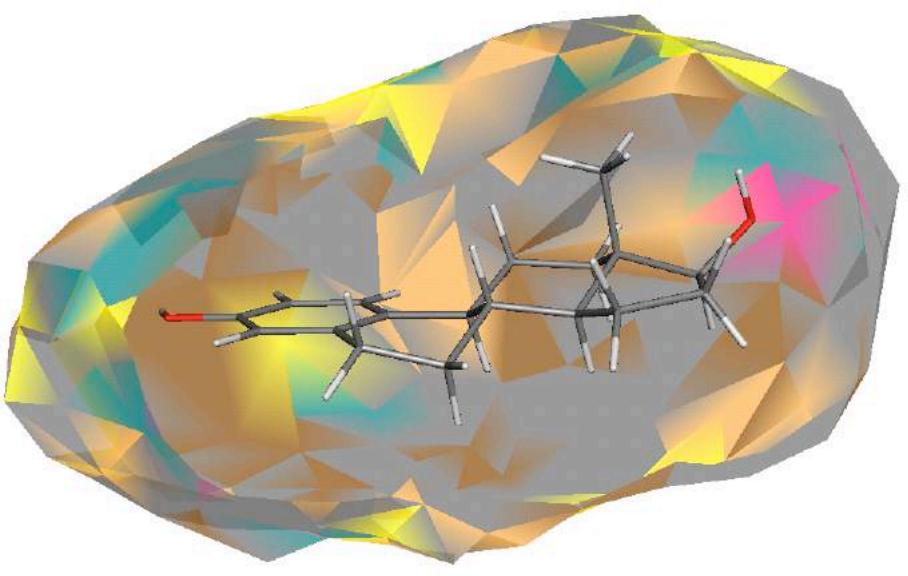
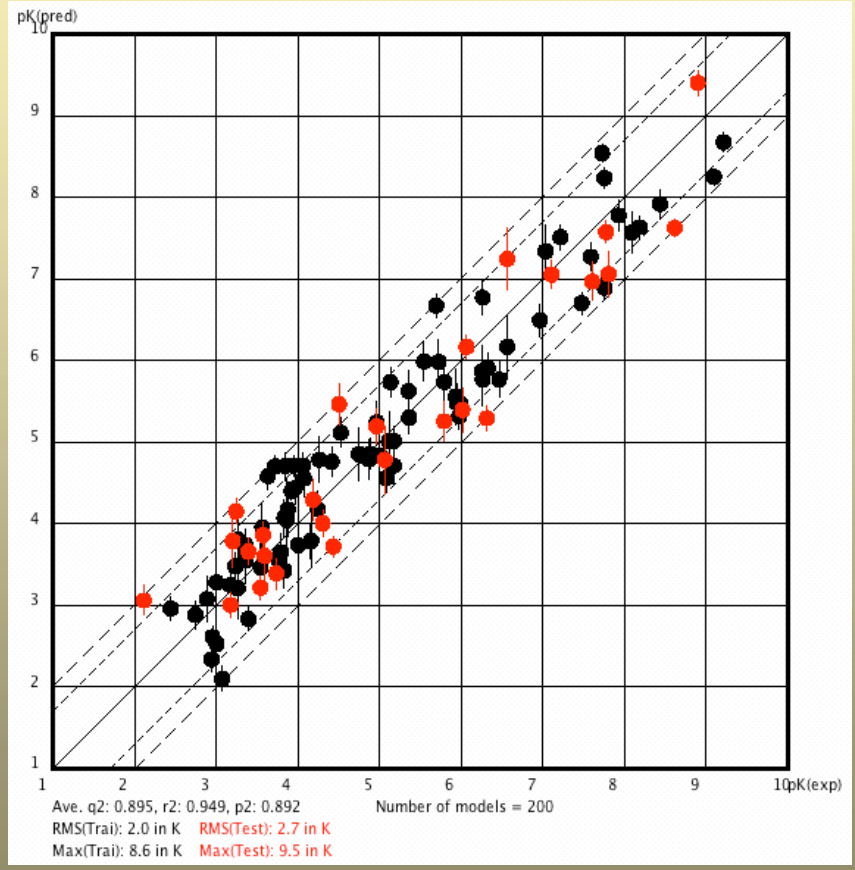
mQSAR models for nuclear receptors: AR, ERαβ, GR, LXR, MR, PPARγ, TRαβ



mQSAR model for the estrogen receptor α

J. Med. Chem. **2005**, *48*, 3700–3703



6D-QSAR (software *Quasar*): 106 compounds

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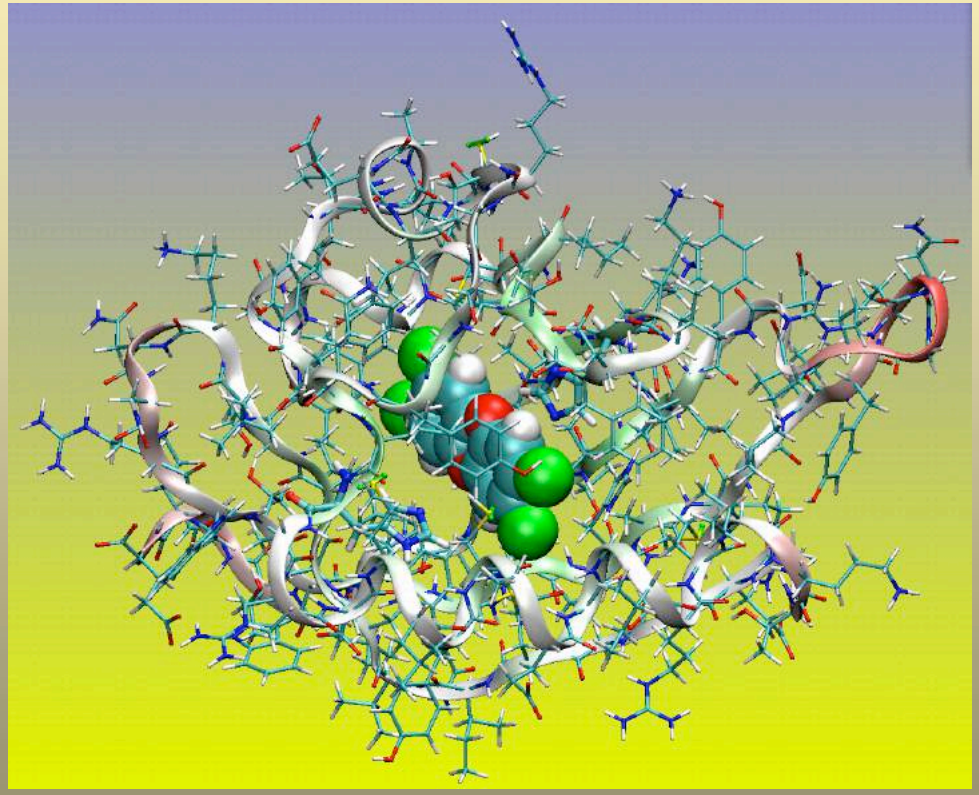
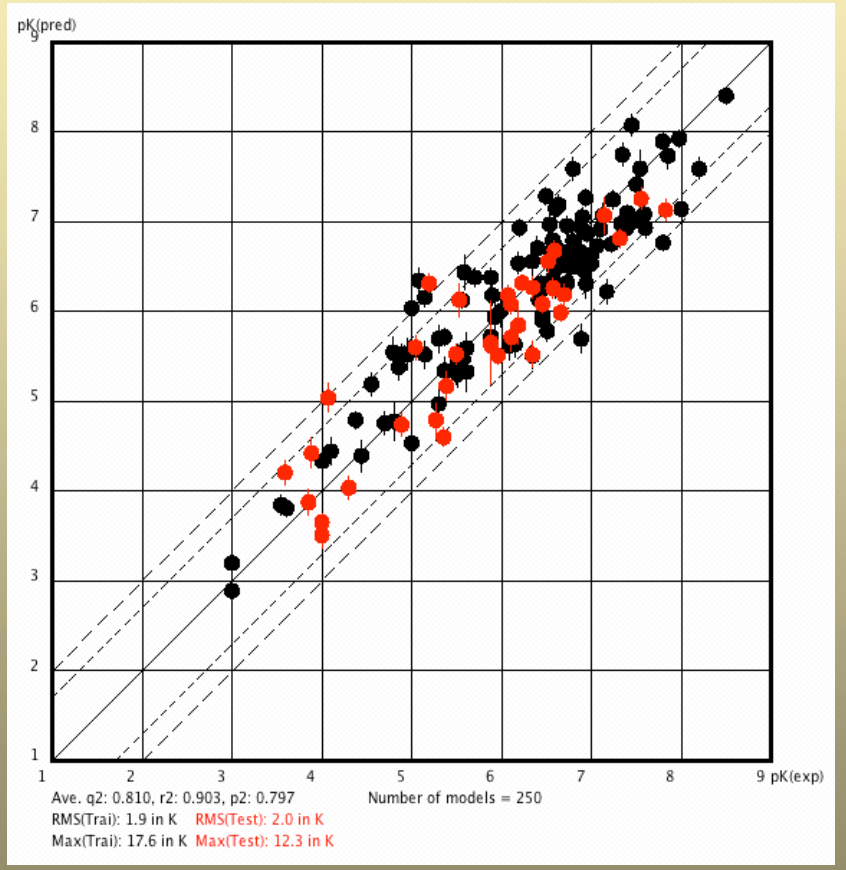
mQSAR model for the Aryl hydrocarbon receptor



MM/MD optimized homology model of the AhR with bound TCDD

Pharmacol. Toxicol. **2006**, *99*, 195–208



6D-QSAR (software *Quasar*): 140 compounds

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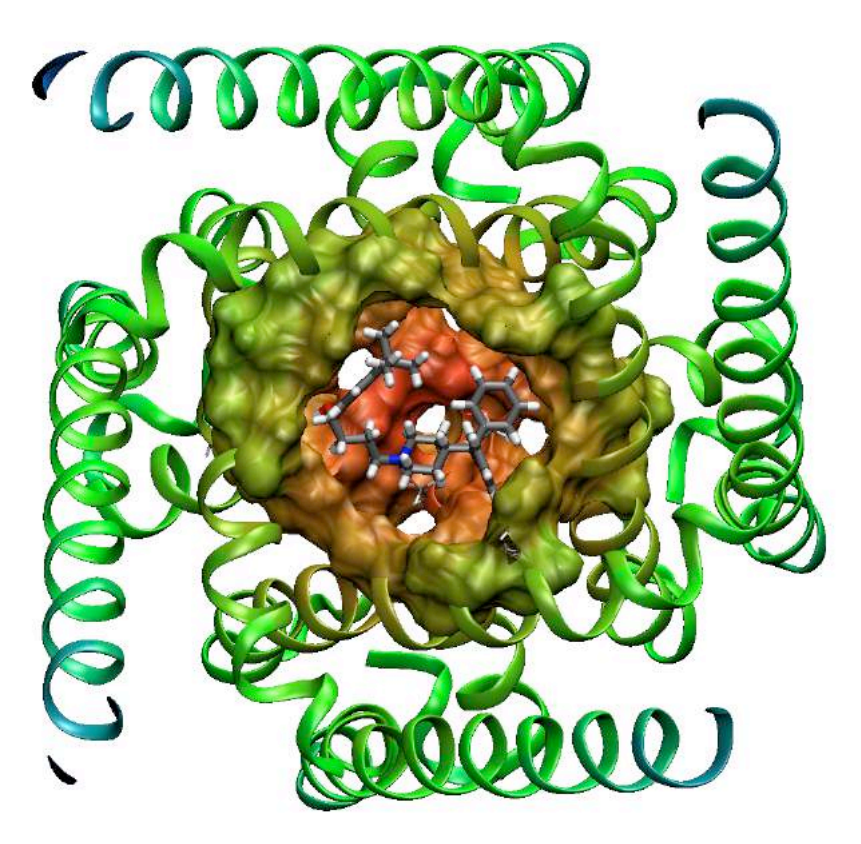
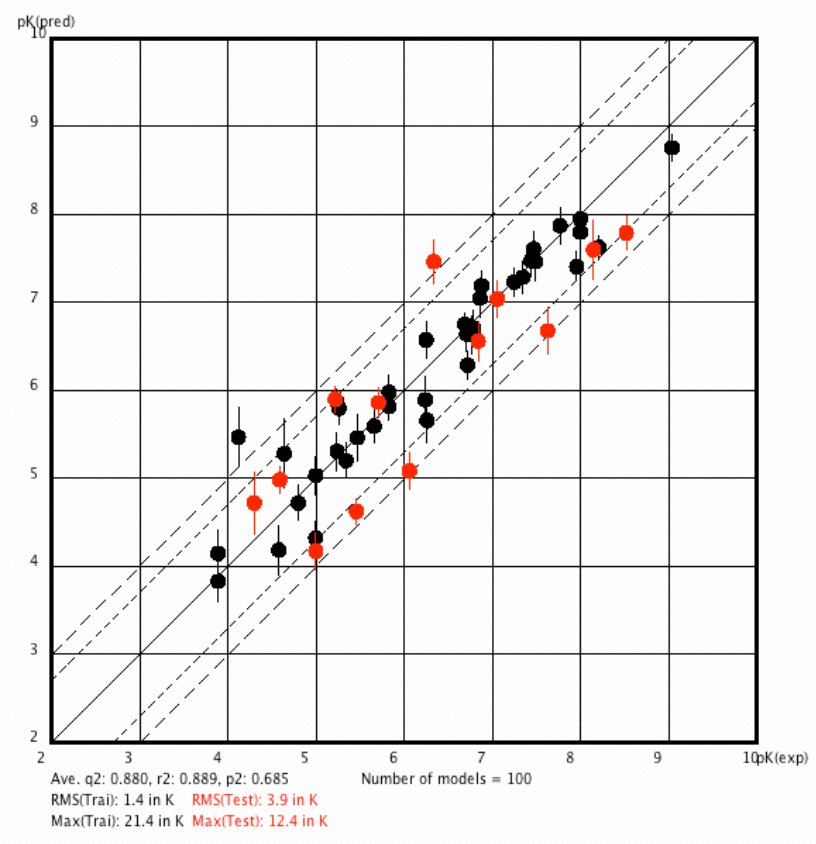
mQSAR model for the hERG K^+ channel



hERG: homology model with docked (*S*)-terfenadine



6D-QSAR (software *Quasar*): 50 compounds

ATLA ***2009****, 37*, 477–496

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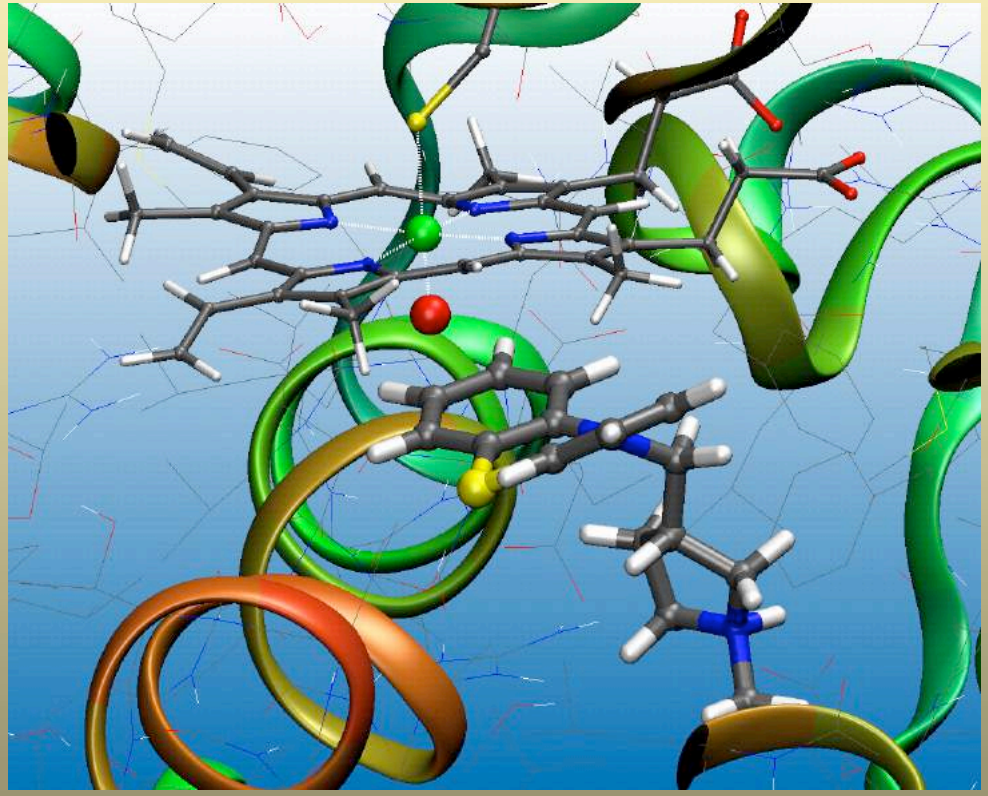
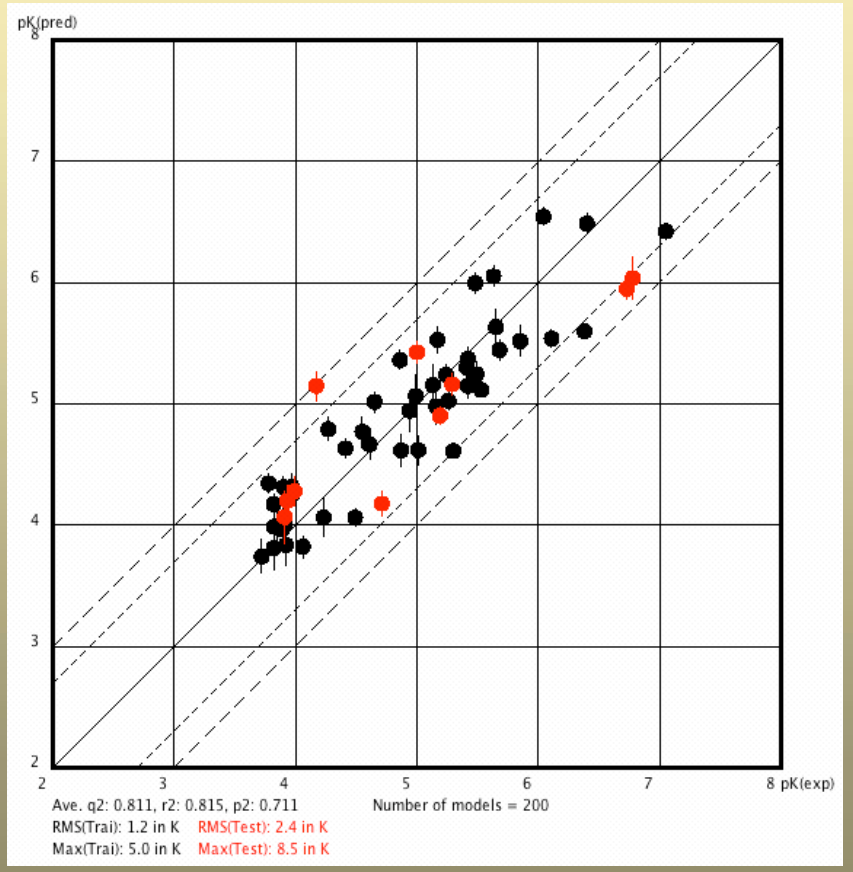
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

mQSAR models for metabolizing enzymes: CYP1A2, CYP2A13, CYP2C9, CYP2D6, CYP3A4



Binding pocket of CYP450 2D6 with bound methdilazine

ChemMedChem. **2010**, *5*, 2088–2101



6D-QSAR (software *Quasar*): 56 compounds

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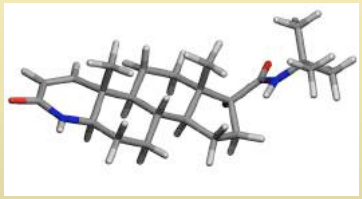
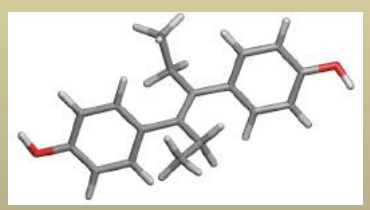
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

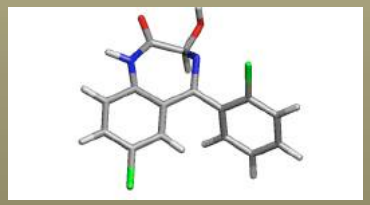
Using a mQSAR model for predictive purposes (example: ERα)



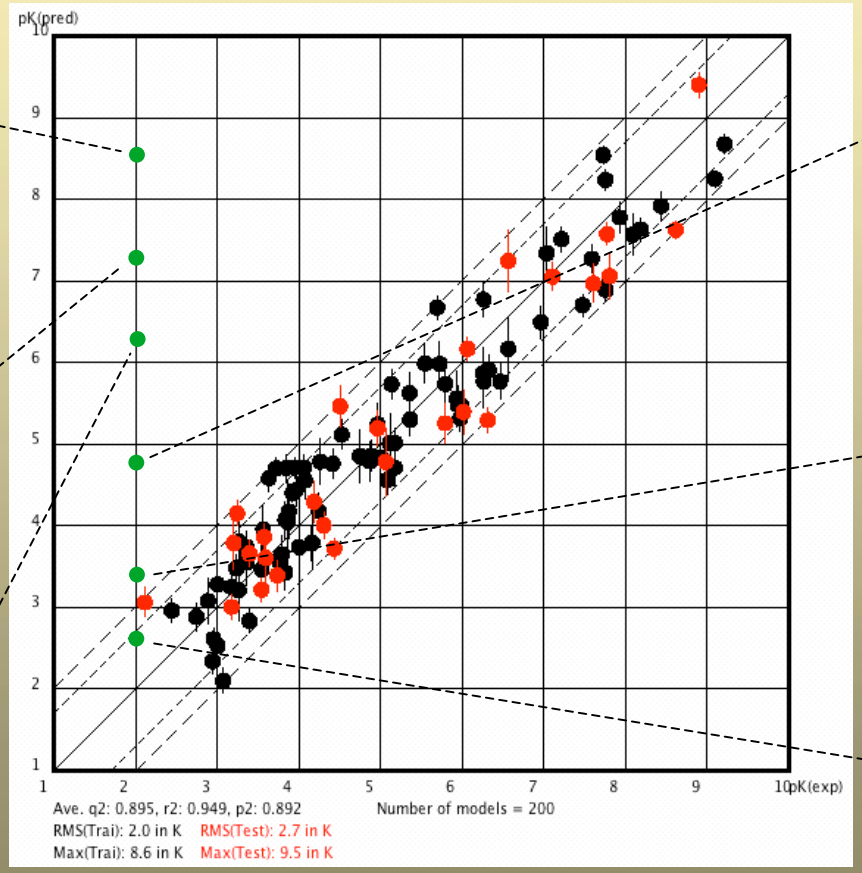
Finasteride



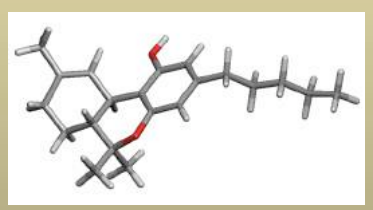
Diethylstilbestrol



(*R*)-Lorazepam



1,2,3,4,7,8-Hexachlorodibenzofuran



Tetrahydrocannabinol

2,2‘,6,6‘-Tetrabromobisphenol A

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VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Summary: Virtual Test Kits

Protein	training + test = total compounds	q^2	p^2	max. test	Reference
Receptors					
Androgen	88 + 26 = 114	0.858	0.792	13.9	*J. Med. Chem.* 2005b
Aryl hydrocarbon	105 + 35 = 140	0.824	0.769	13.5	*Pharmacol. Toxicol.* 2006
Estrogen α	80 + 26 = 106	0.895	0.892	9.5	*J. Med. Chem.* 2005a
Estrogen β	72 + 24 = 96	0.802	0.699	13.4	*ALTEX* 2009
Glucocorticoid	88 + 22 = 110	0.702	0.719	4.9	*ChemMedChem* 2009
hERG	38 + 12 = 50	0.935	0.754	4.9	*ATLA* 2009
Liver X	40 + 12 = 52	0.763	0.697	3.3	*Mol. Inf.* 2010
Mineralocorticoid	40 + 8 = 48	0.810	0.661	4.2	*Toxicol. Lett.* 2009
PPARγ	75 + 20 = 95	0.832	0.723	3.9	*Toxicol. Lett.* 2007
Thyroid α	64 + 18 = 82	0.919	0.814	10.0	*ChemMedChem* 2007
Thyroid β	64 + 18 = 82	0.909	0.796	8.8	*ChemMedChem* 2007
Enzymes					
CYP 1A2	40 + 12 = 52	0.881	0.651	3.4	*ATLA* 2009
CYP 2A13	18 + 6 = 24	0.854	0.661	1.7	*Chimia* 2008
CYP 2C9	68 + 17 = 85	0.687	0.423	4.8	*ChemMedChem* 2010
CYP 2D6	40 + 10 = 56	0.811	0.711	8.5	*ChemMedChem* 2010
CYP 3A4	38 + 10 = 48	0.825	0.659	7.1	*ChemMedChem* 2006

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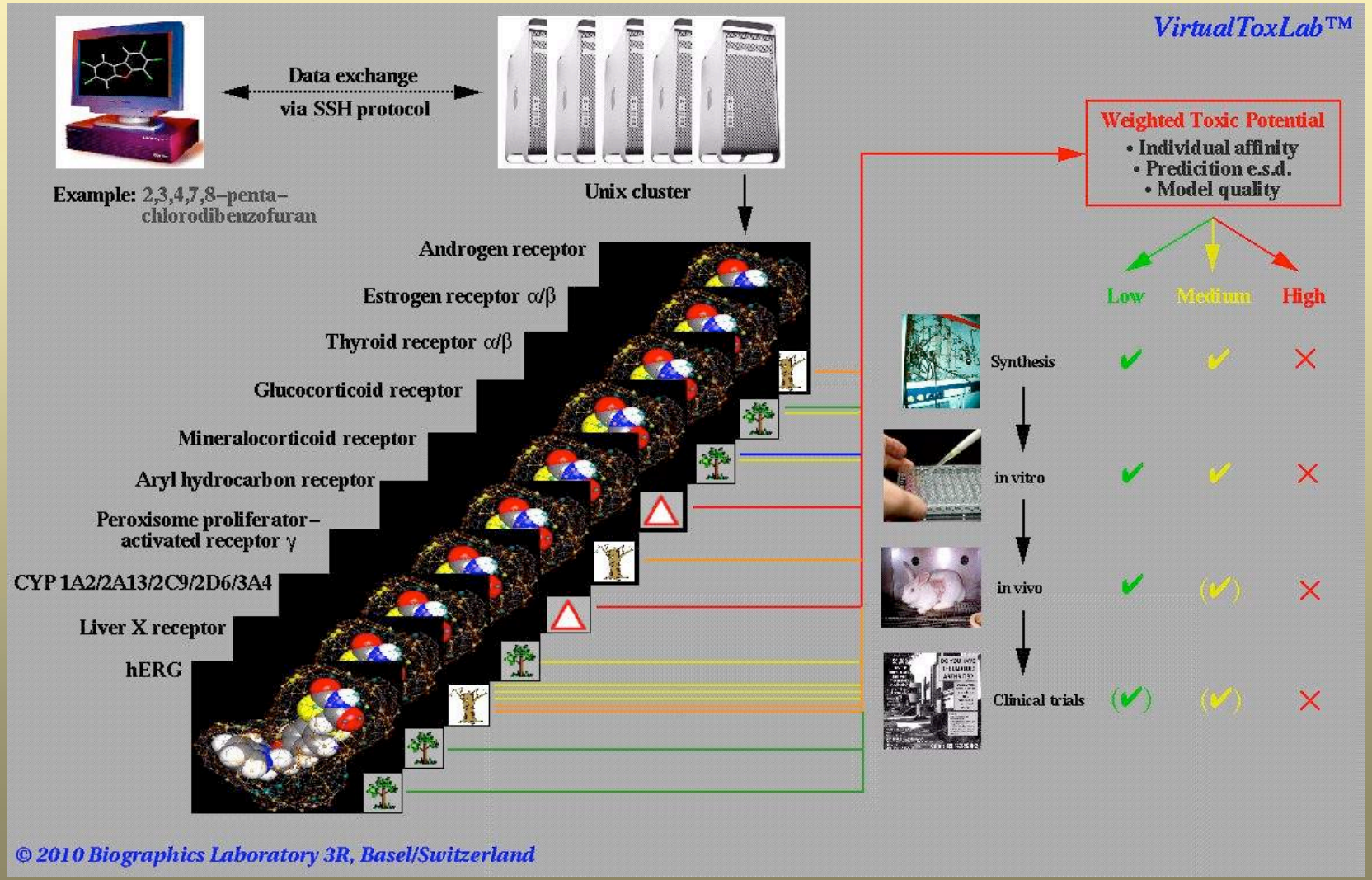

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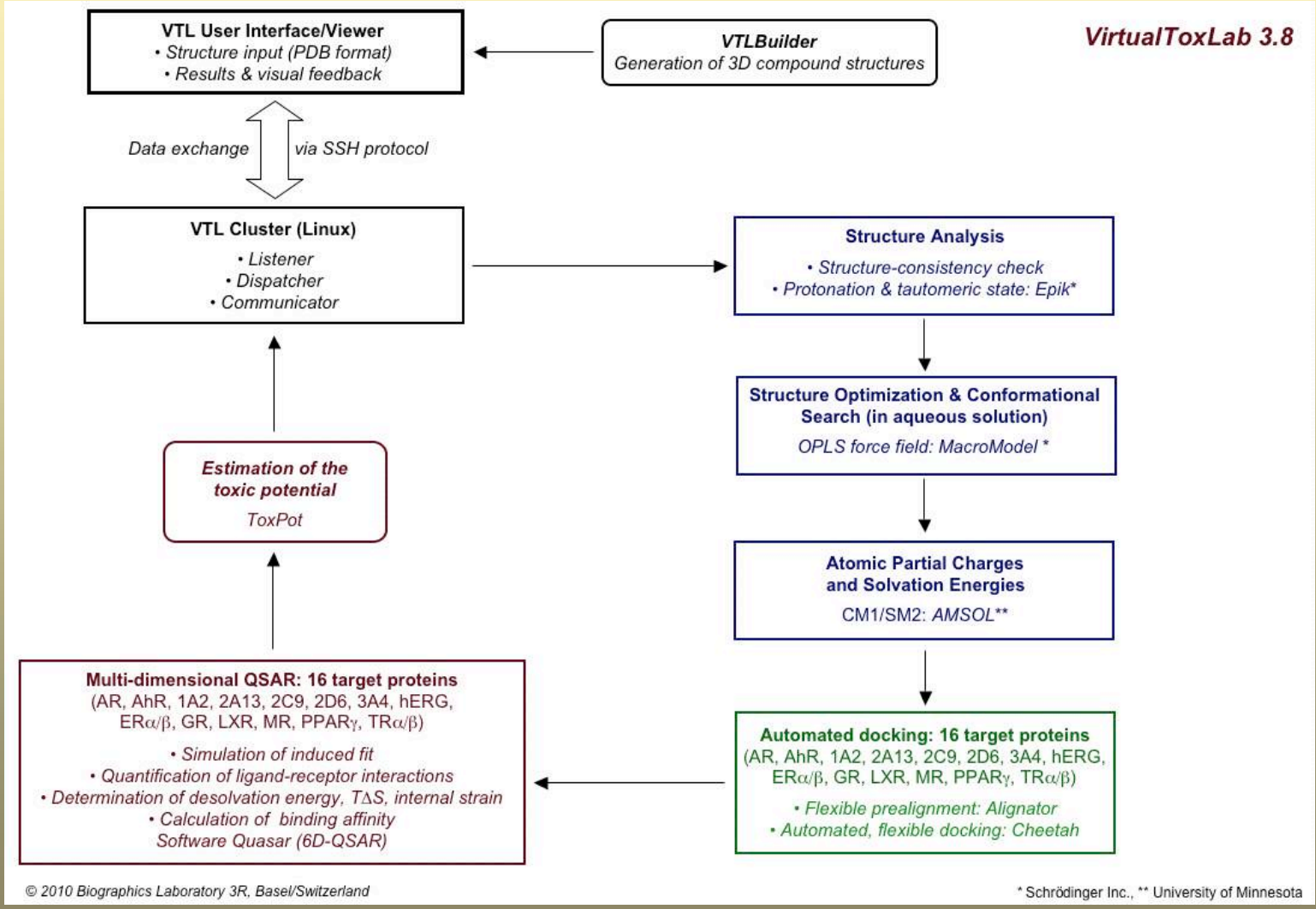
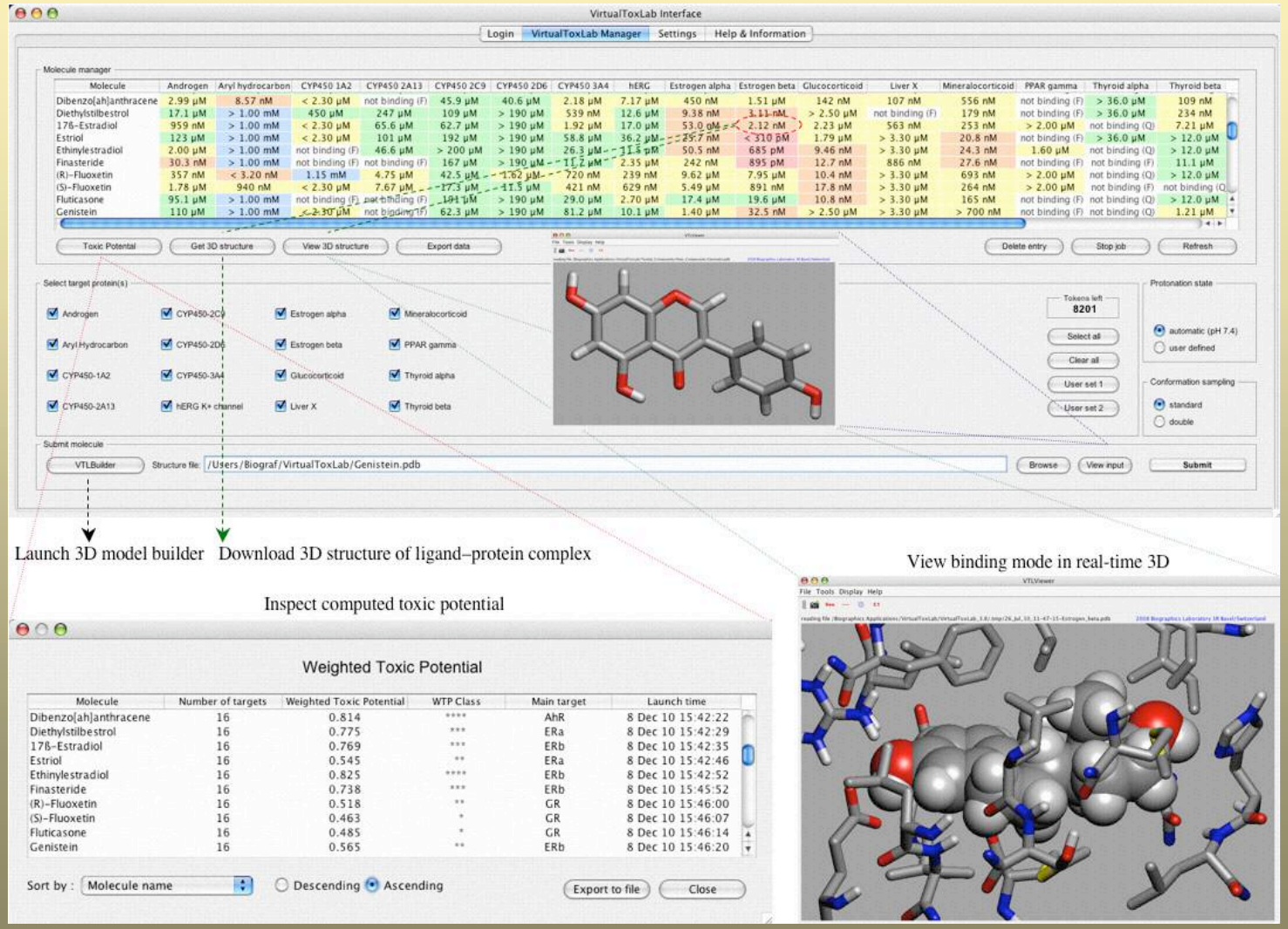


zh aw — 3. Wädenswiler Chemie-Tag 16. Juni 2011

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals



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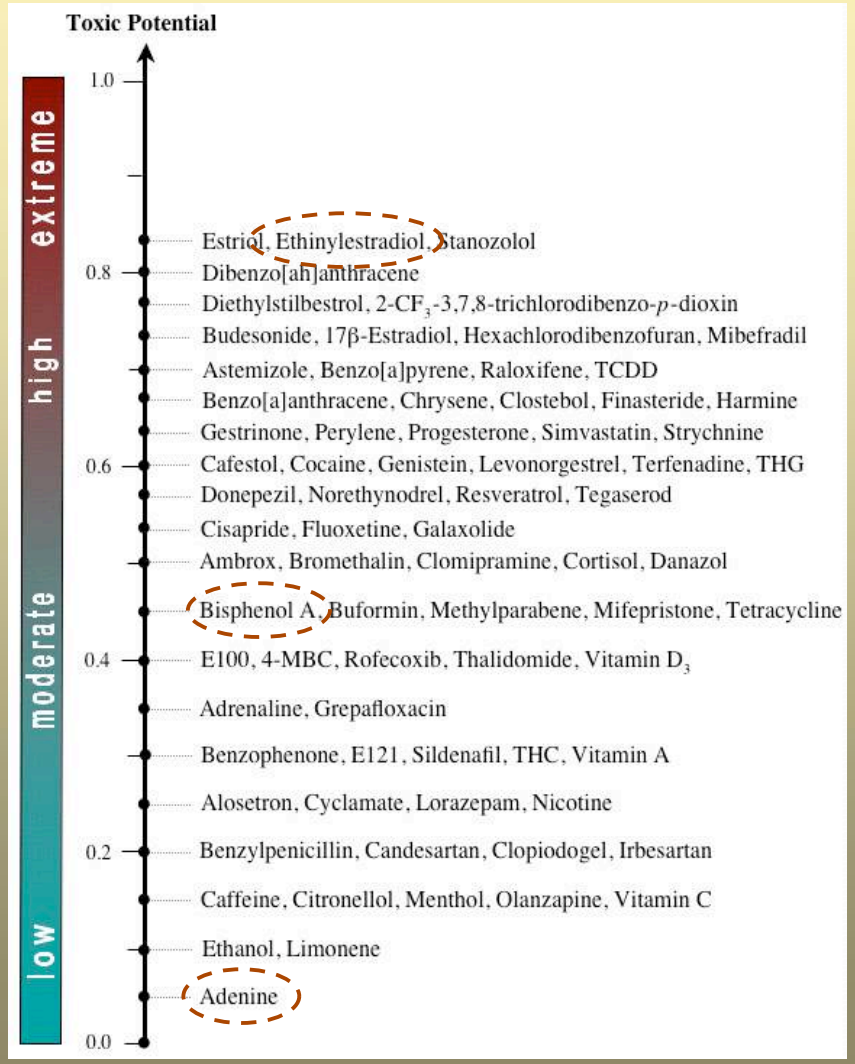
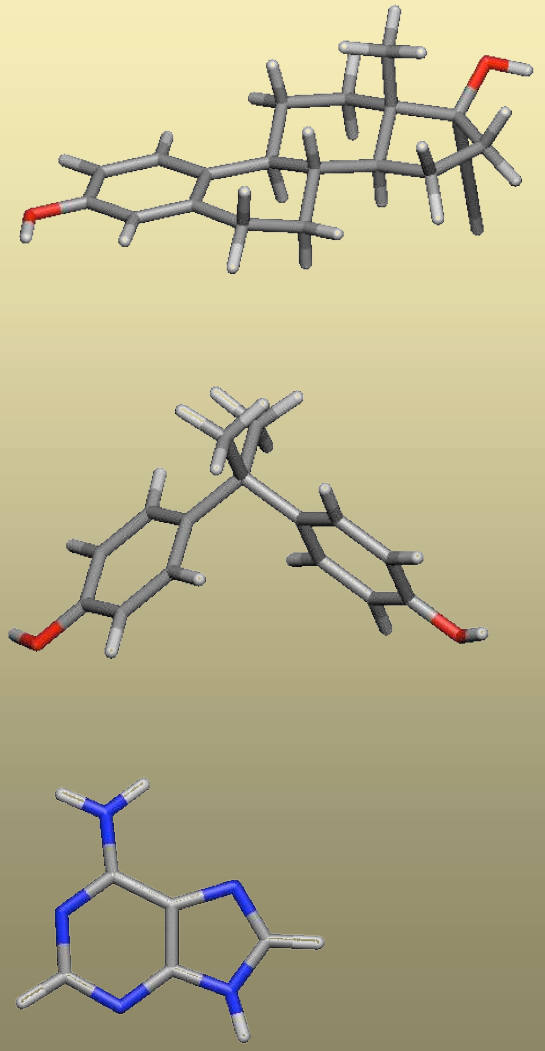
zh aw — 3. Wädenswiler Chemie-Tag 16. Juni 2011

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals





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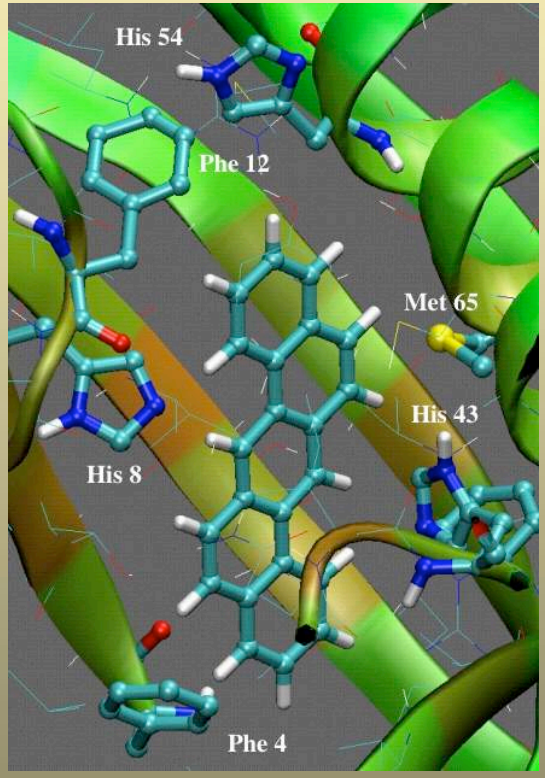
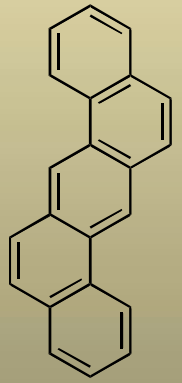
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Atomistic interpretation of the results I

Dibenzo[ah]anthracene → Aryl hydrocarbon receptor

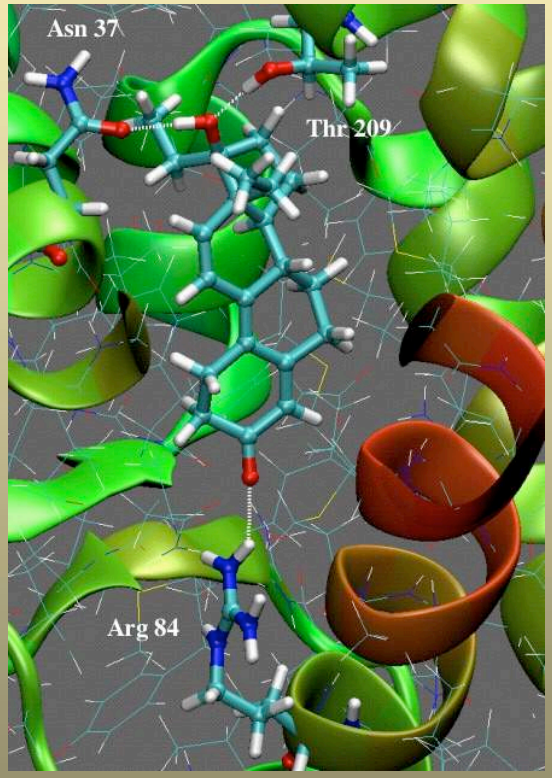


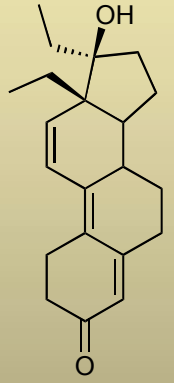


Toxic potential = 0.831

Binding affinities: AhR = 6.8 nM, GR = 110 nM, LXR = 310 nM

Tetrahydrogestrinone → Androgen receptor





Toxic potential = 0.621

Binding affinities: AR = 9.5 nM , MR = 150 nM, GR = 160 nM

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VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Tetrahydrogestrinone — „The Clear“

Tetrahydrogestrinone

From Wikipedia, the free encyclopedia

Tetrahydrogestrinone (often referred to as **THG** or **The Clear**) is an anabolic steroid developed by Patrick Arnold.[1] It has affinity to the androgen receptor and the progesterone receptor, but not to the estrogen receptor.[2] The drug has been considered a designer drug, closely related to the banned anabolic steroids gestrinone and trenbolone,[3] and was banned by the Food and Drug Administration (FDA) at the end of 2003.[citation needed]

Contents [hide]
1 Pharmacology
2 Method of action
3 Side effects
4 History
5 See also
6 References
7 External links

Tetrahydrogestrinone

Systematic (IUPAC) name
(13S,17S)-13,17-diethyl-17-hydroxy-1,2,6,7,8,13,14,15,16,17-decahydrocyclopenta[a]phenanthren-3-one

Identifiers
CAS number 618903-56-3
ATC code ?
ChemSpider 2058259

Chemical data
Formula $C_{21}H_{28}O_2$
Mol. mass 312.46 g/mol
Synonyms Tetrahydrogestrinone, THG, The Clear

Therapeutic considerations
Pregnancy cat. ?
Legal status Schedule I (US)
Routes Oral, Intramuscular

Pharmacology [edit]

Structure-activity relationship studies report that the potency of the drug is outstanding, surpassing, on a milligram per milligram basis, every known synthesized or commercial available anabolic steroid at the time of its development. It is a highly potent agonist for the androgen and progesterone receptors,[4] around 10 times more potent than the comparison drugs nandrolone or trenbolone, but with no estrogenic activity. It has been found to bind to the androgen receptor with similar affinity to dihydrotestosterone and produces growth of muscle tissue.[5] According to Patrick Arnold, due the drug's potency, he never had to supply significant quantities to BALCO, because "just a couple of drops under the tongue" were a sufficient dose.[1]

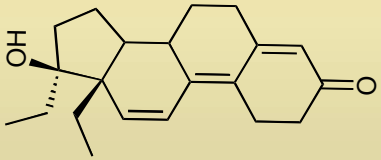
Method of action [edit]

When THG reaches the nucleus of a cell, it binds to the androgen receptor at the ligand-binding pocket. Here it changes the expression of a variety of genes, turning on several anabolic and androgenic functions.[6]

It is the ligand's structure which determines the number of interactions that can take place with the human androgen receptor ligand-binding domain. Even minor modifications in the ligand's structure have a great impact on the strength of the interactions this ligand has with the androgen receptor. THG, possessing a high affinity, establishes more van der Waals contacts with the receptor than with many other steroids. It is this higher affinity and specific geometry of THG which makes these interactions with the Androgen Receptor so strong, resulting in THG's potency.[7]

Side effects [edit]

Side effects from prolonged use are likely to include infertility in both men and women, as well as other steroid side effects such as acne and hirsutism.[8] Unlike most other anabolic steroids, THG also binds with high affinity to the glucocorticoid receptor, and while this effect may cause additional weight loss, it is also likely to cause extra side effects such as immunosuppression that are not seen with most other steroids.[2]



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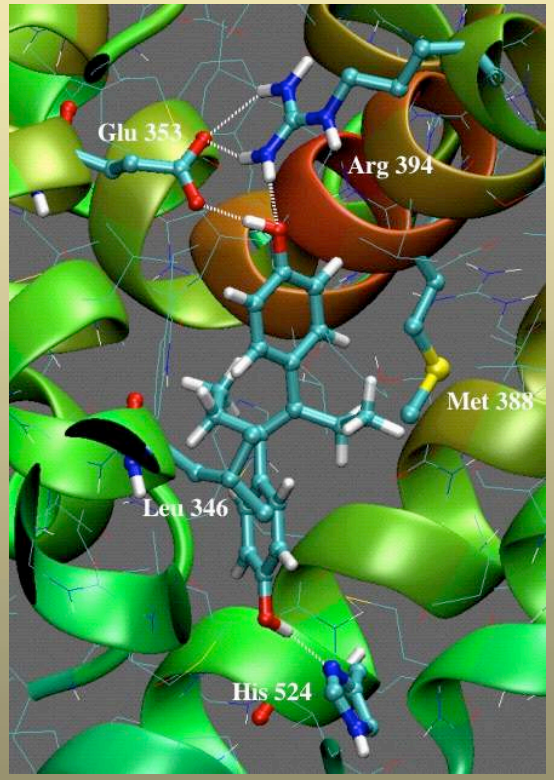
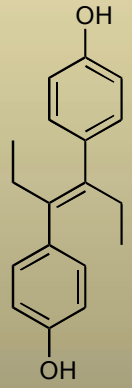
Atomistic interpretation of the results II

Diethylstilbestrol → Estrogen receptor α

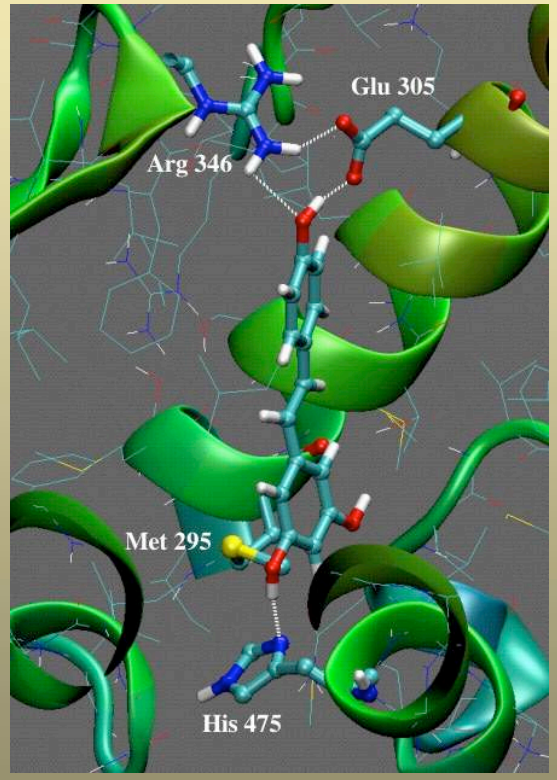


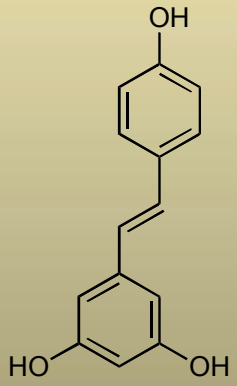


Toxic potential = 0.756

Binding affinities: ERβ = 2.4 nM, ERα = 9.4 nM, GR = 210 nM

Resveratrol → Estrogen receptor α





Toxic potential = 0.718 (MD: 0.574)

Binding affinities: ERβ = 0.62 nM, ERα = 1.5 μM, GR = 1.5 μM

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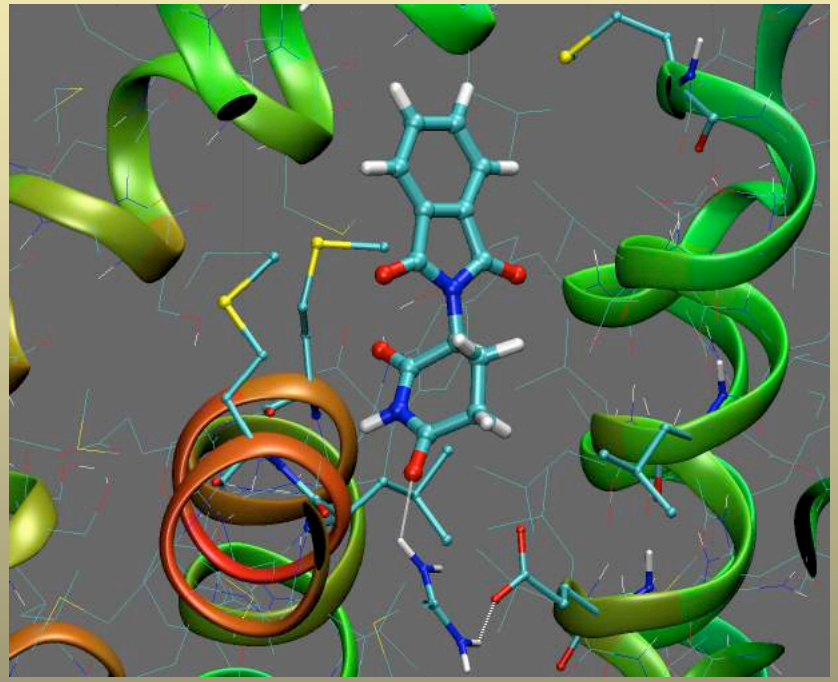
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Atomistic interpretation of the results III

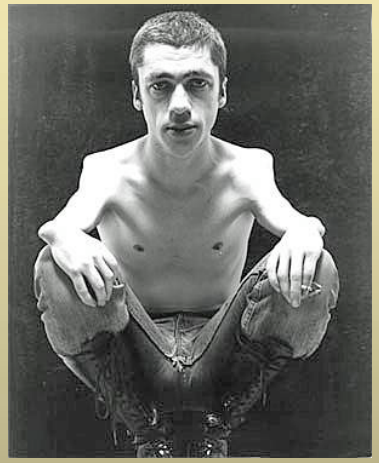
(*S*)-Thalidomid(sedative) → Estrogen receptor β

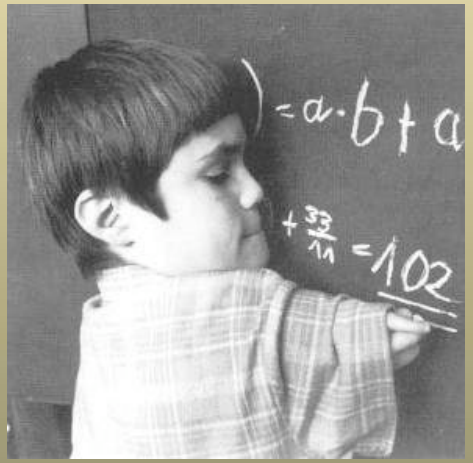


Toxic potential = 0.378
Highest binding affinity: ER β = 0.9 µM

The primary target of thalidomide is cereblon (CRBN). CRBN forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1)
→ Science **2010**, *327*, 1345–1350

Contergan tragedy: Federal Republic Germany (1961)





☞ **5,000–10,000 Contergan-geschädigte Kinder**

1957–1961 als Beruhigungs- und Schlafmittel vertrieben, u.a. gegen die morgendliche "Schwangerschaftsübelkeit". Thalidomid galt aufgrund von Tierversuchen als **besonders sicher** (…)

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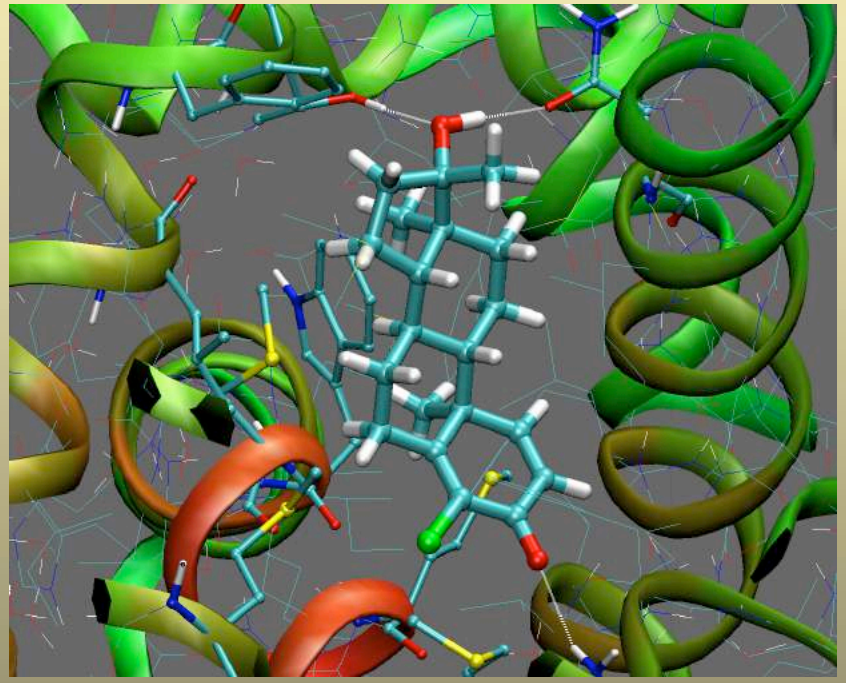
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Atomistic interpretation of the results IV

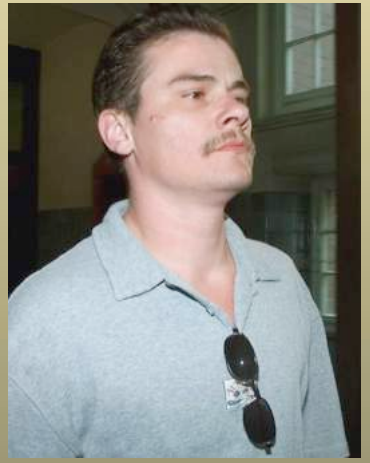
Dehydrochloromethyltestosterone → Androgen receptor



Toxic potential = 0.723
Highest binding affinity: AR = 6.2 nM

„Side effects“ of Oral-Turinabol (doping agent in the DDR):

Heidi Krieger (1986)



Andreas Krieger (2000)

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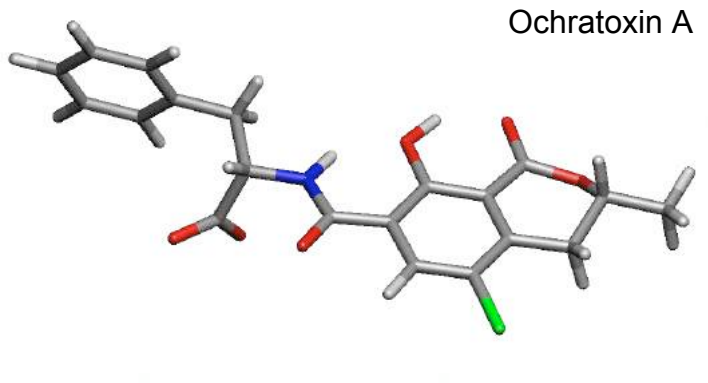
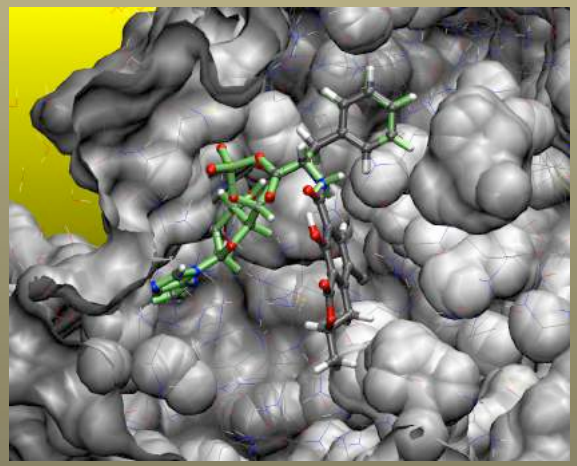
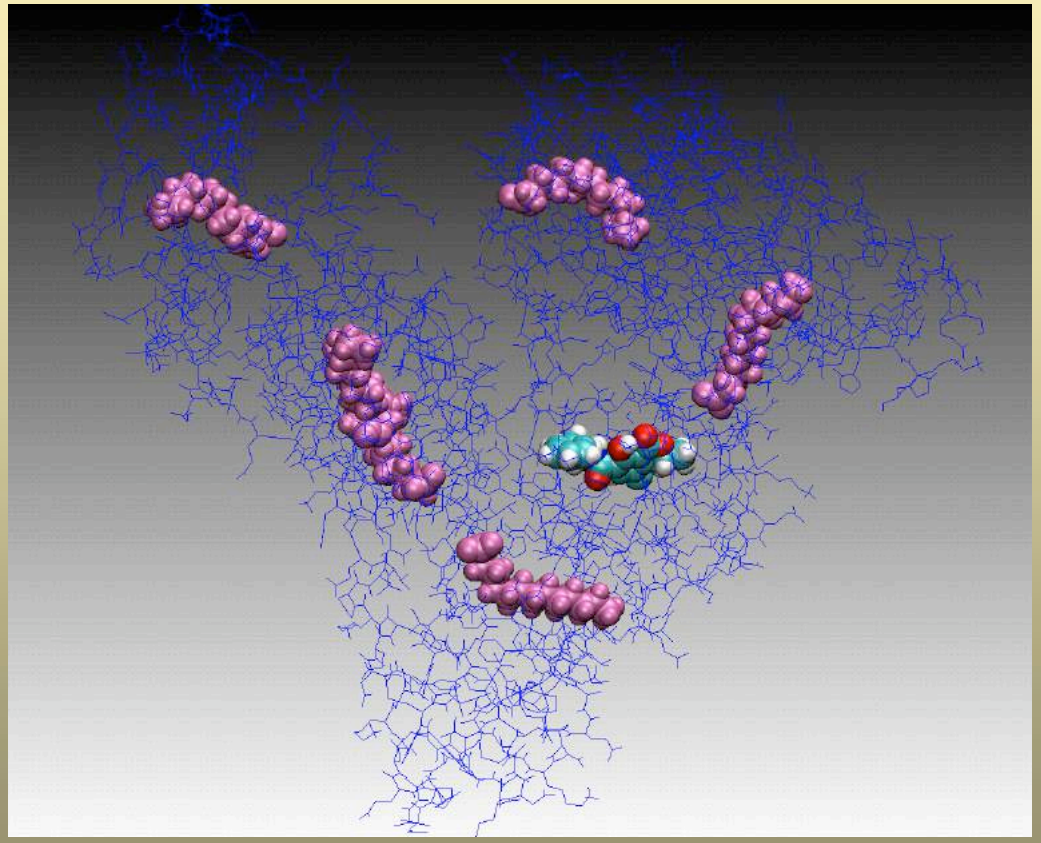
Limitation: false-negative predictions



Example: **Ochratoxin A** (mycotoxin, carcinogenic in mice), world-wide problem

ToxPot = 0.228 → does not bind to any of the 16 target proteins

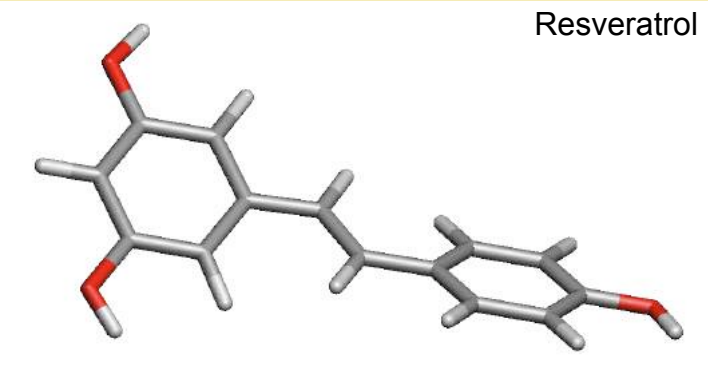


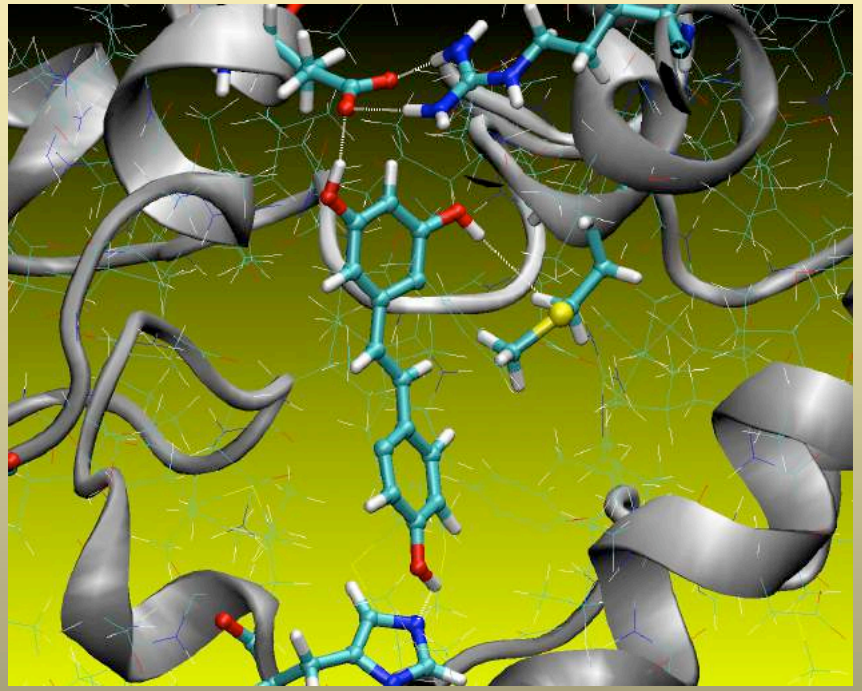


Ochratoxin A binds to human serum albumin and, therefore, is retained in the body for too long periods of time. The primary target for toxicity is unknown. Hypotheses that it binds to Phe-metabolizing enzymes could not be verified *in silico* and *in vitro*.

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

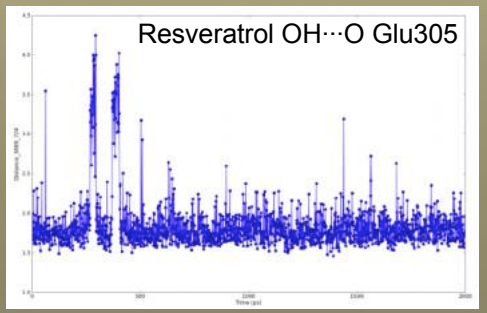
Limitation: false-positive predictions

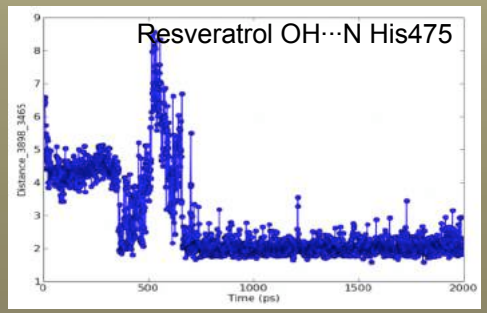


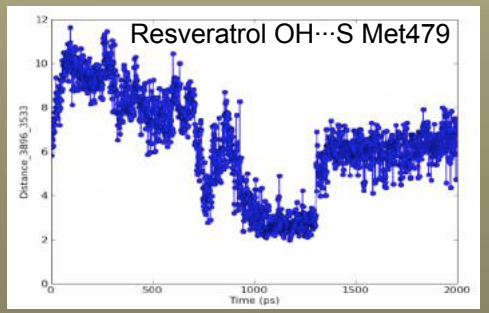


Reasons: compound is not bioavailable
complex is thermodynamically favorable but kinetically unstable

Example: Resveratrol (phytoalexin), ToxPot = 0.718
subsequent molecular-dynamics simulations suggest ToxPot < 0.6







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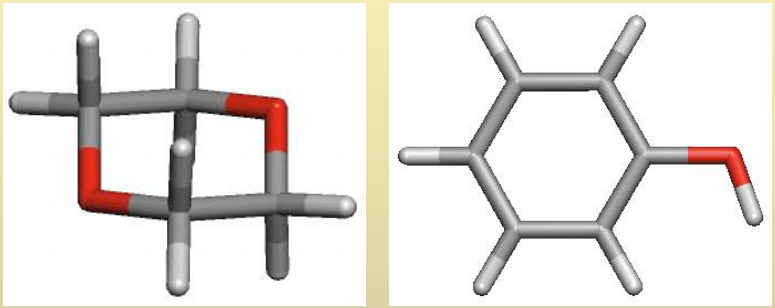
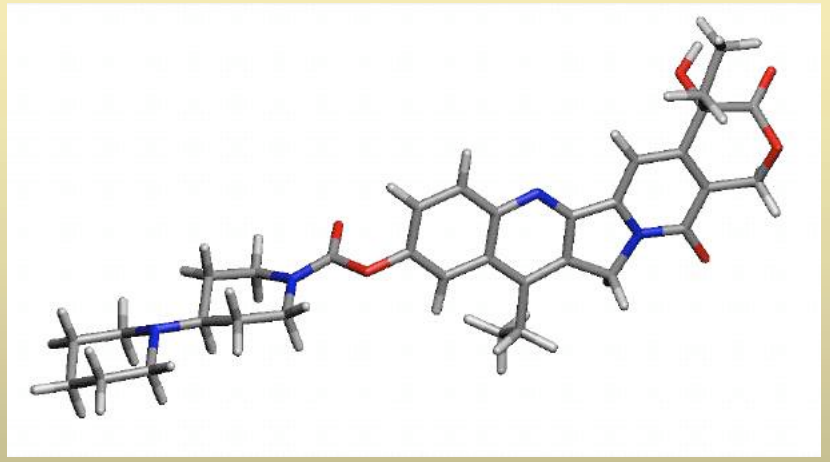
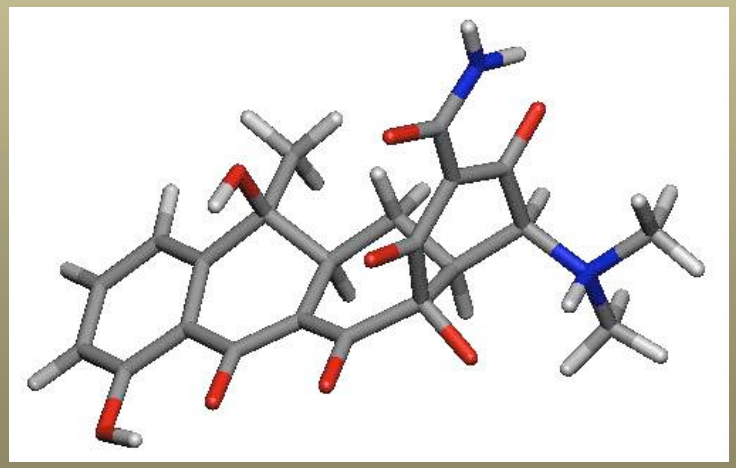
Limitation: size, protonation state, metabolites



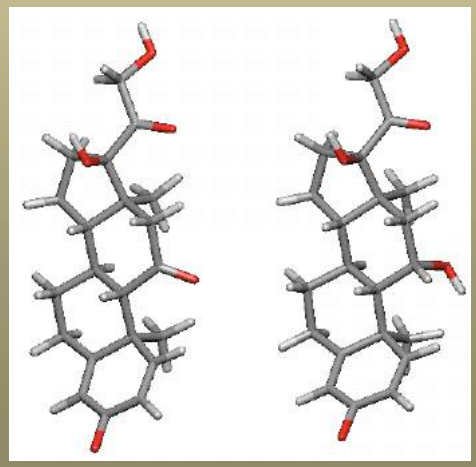
Too small: MW < 100: Sampling not exhaustive with the larger target proteins (e.g. hERG, 3A4)



Too large: MW > 500: Induced fit may be simulated but not quantified



Uncertain protonation state: Protonation state in binding pocket may be differrent from aqueous solution

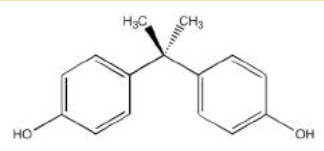


Metabolites: Parent compound (left) and active metabolite (right)

VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Affinity profiling

Bisphenol A (plasticizer)

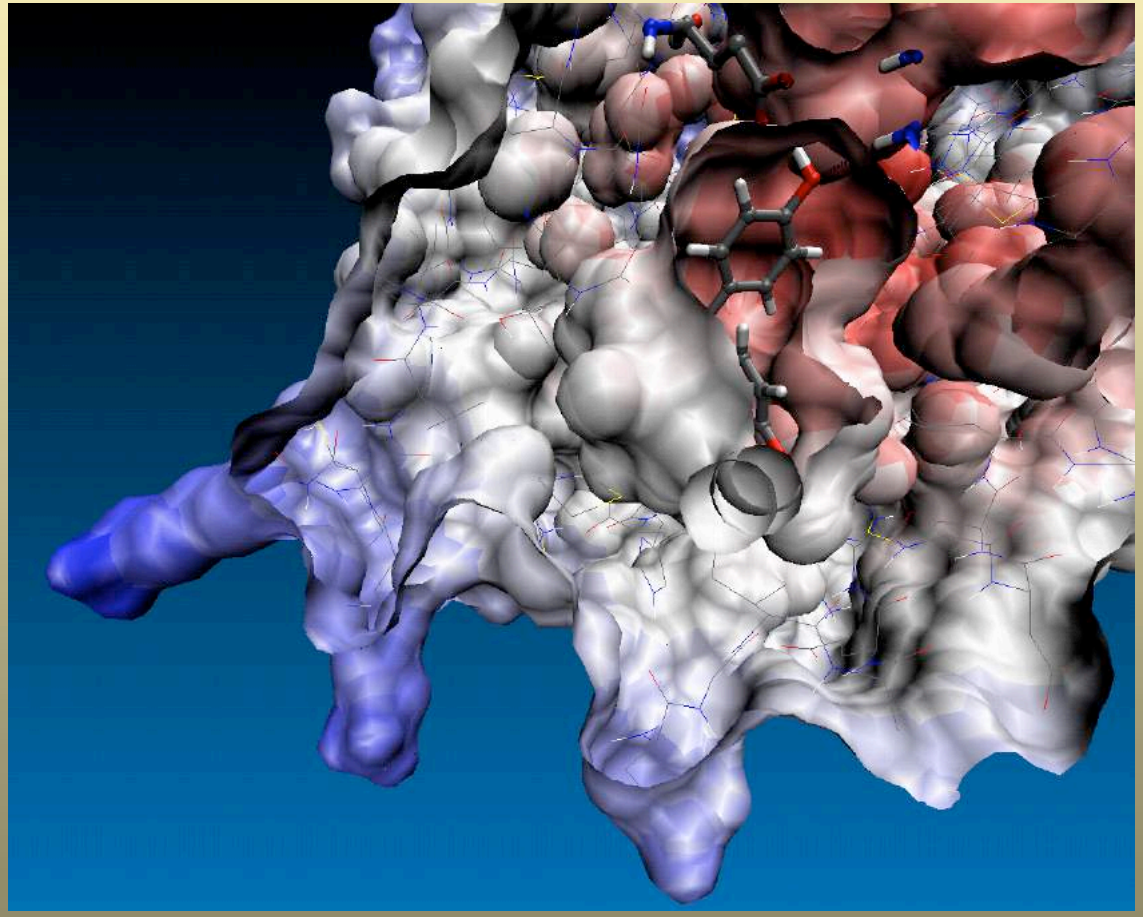


AR: 48.8 µM
AhR: not binding
ERα: 47.4 µM
ERβ: 177 nM
GR: >2.5 µM
LXR: >3.3 µM
MR: >700 nM
PPARγ: >2.0 µM
TRα: not binding
TRβ: > 12µM

hERG: 18.5 µM

CYP1A2: 1.14 mM
CYP2A13: 35.5 µM
CYP2C9: 177 µM
CYP2D6: > 190 µM
CYP3A4: 398 µM

Toxic potential = 0.459



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VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

Screening of environmental chemicals

Toxic potential:

Benzo[a]anthracene = 0.665

Benzo[a]pyrene = 0.690

Methylbenzylidene camphor = 0.393

Bisphenol A = 0.459

Bibenzo[ah]anthracene = 0.778

Dibenzoxazinylnaphtalene = 0.721

Dipiperazinylbenzamidol = 0.732

Galaxolide = 0.509

Hexachlorodibenzofuran = 0.734

TCDD = 0.740

17β-Estradiol = 0.691

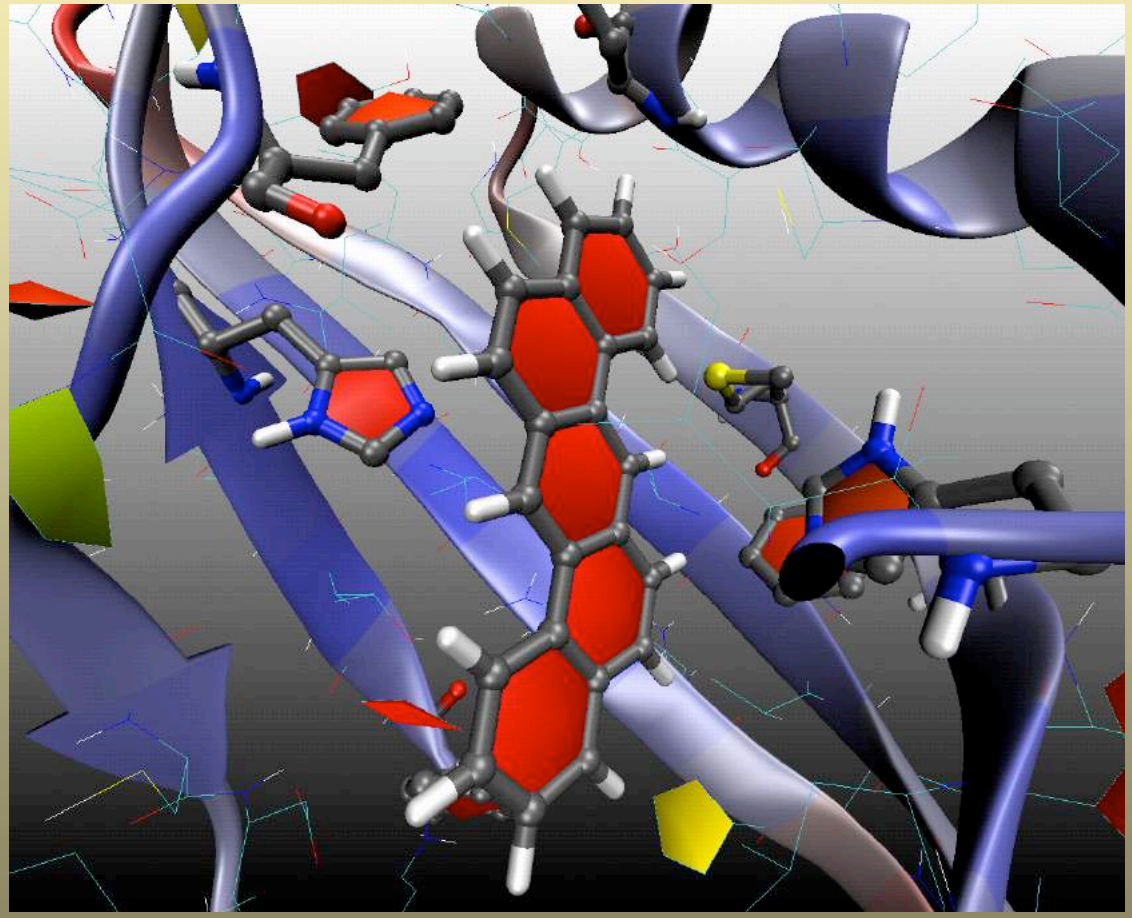
2-Trifluoro-TCDD = 0.735

Coronene = 0.720

OCDD = 0.783

Picene = 0.794

Tetracene = 0.724



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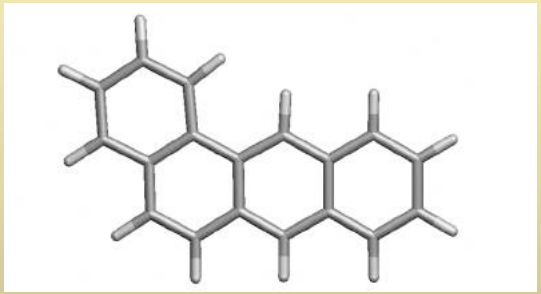
VirtualToxLab™ — In silico prediction of the toxic potential of drugs and chemicals

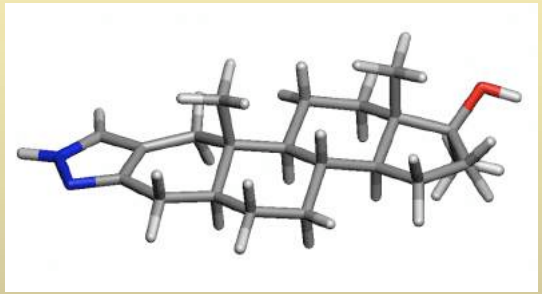
Performance and Availability

Small, rigid compound



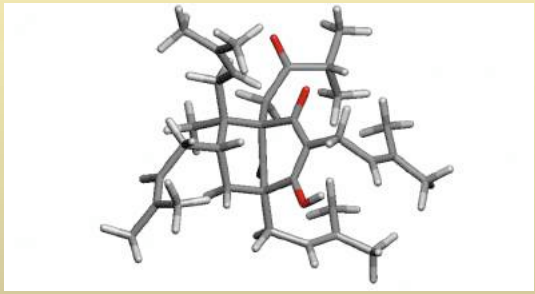
Example: Benzo[a]anthracene
ToxPot = 0.665, cpu time = 6 h

Medium size/flexible compound



Example: Stanozolol
ToxPot = 0.815, cpu time = 10 h

Large, flexible compound



Example: Hyperforin
ToxPot = 0.242, cpu time = 36 h

- Low throughput technology (15–20 compounds/day on a 3.0 GHz 8-processor CPU)
- Freely available for non-profit oriented organizations: OpenVirtualToxLab™
- Release includes graphical-user interface, 3D viewer and model builder
- Interface runs on all plattforms (Macintosh, Linux, Unix, Windows); secure SSH protocol
- Currently 128 dedicated processor cores (total peak performance = 2×10^{12} FLOPS = 2 TFLOPS)
- Documentation and application on-line: http://www.virtualtoxlab.org

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Summary

- **Simulation and quantification of small-molecule binding to 16 target proteins**: AR, AhR , CYP 1A2, CYP2A13, CYP2C9, CYP2D6 CYP3A4, ERα, ERβ, GR, hERG, LXR, MR, PPARγ, TRα, TRβ
- Mixed-model approach: automated, flexible docking + mQSAR (induced fit, solvation, entropy)
- **Toxic potential + individual binding affinites**
- **3D structure of ligand–protein complex**; real-time visualization
- 20+ publications (*J.Med.Chem, ChemMedChem, Mol.Inf.,Tox.Let., ALTEX, ATLA, Pharmacol.Toxicol.)*
- **2,500+ compounds tested** ☞ http://www.virtualtoxlab.org
- **Fully automated technology**, secure SSH protocol, all computer platforms (Mac, Linux, Windows)
- Free for non-profit organizations: OpenVirtualToxLab™

☞ http://www.virtualtoxlab.org

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