



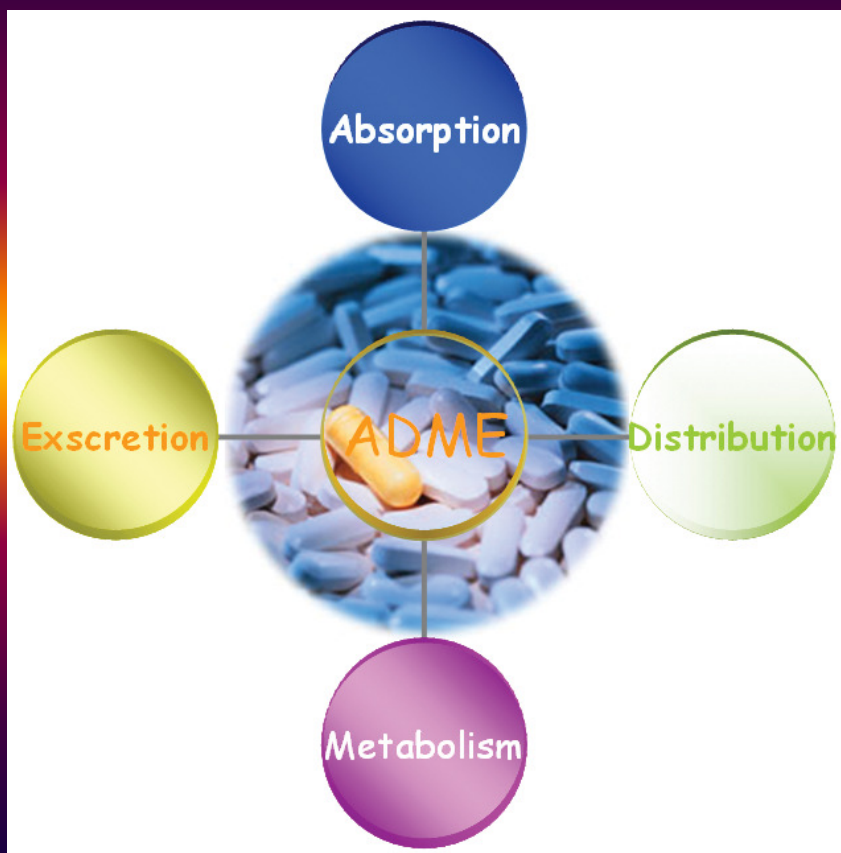
Εργαστήριο Σχεδιασμού Φαρμάκων



ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
ΙΝΣΤΙΤΟΥΤΟ ΟΡΓΑΝΙΚΗΣ & ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΧΗΜΕΙΑΣ
ΕΡΓΑΣΤΗΡΙΟ ΜΟΡΙΑΚΗΣ ΑΝΑΛΥΣΗΣ



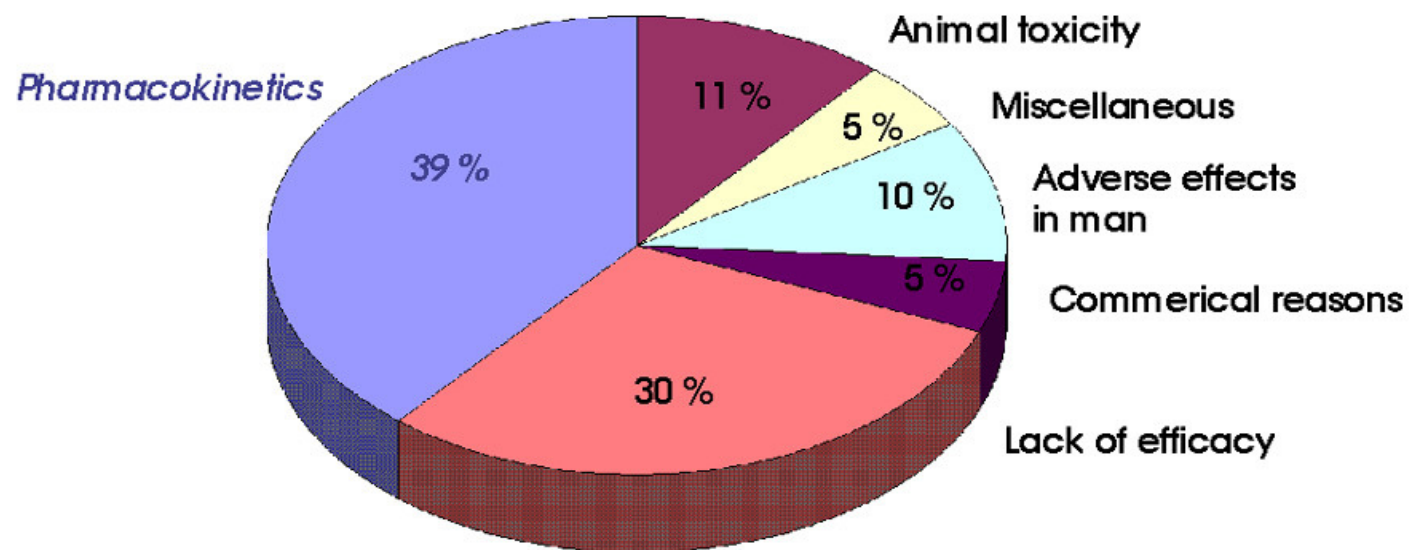
WORKSHOP
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ



Πρόβλεψη ADME Ιδιοτήτων

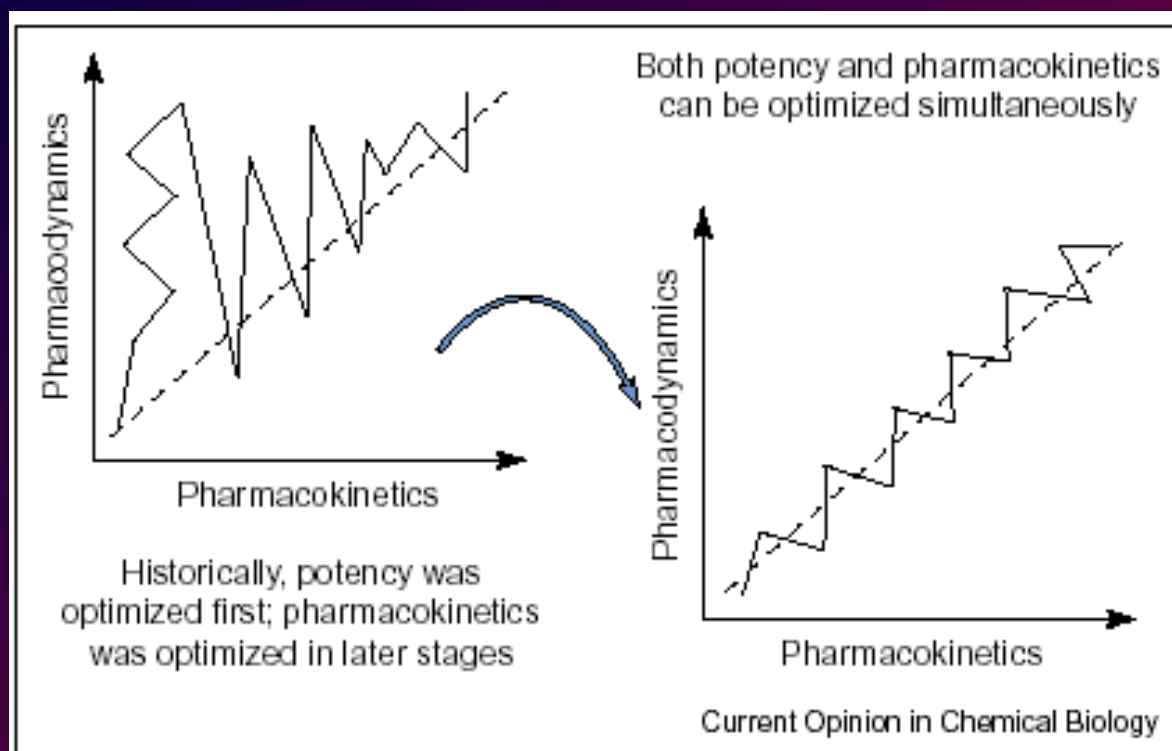
ADME(T)

T. Kennedy, *Drug Disc. Today* 1997, 2, 436–444 from survey by Center for Medicines Research
R.A Prentis, Y. Lis, S.R. Walker, *Br. J. Clin. Pharmacol.* 1988, 387–396
monitoring pharma companies from 1964–1985.



Causes of Candidate Failures in Man

Προτεινόμενη πορεία: ταυτόχρονη βελτιστοποίηση των φαρμακοδυναμικών και φαρμακοκινητικών ιδιοτήτων

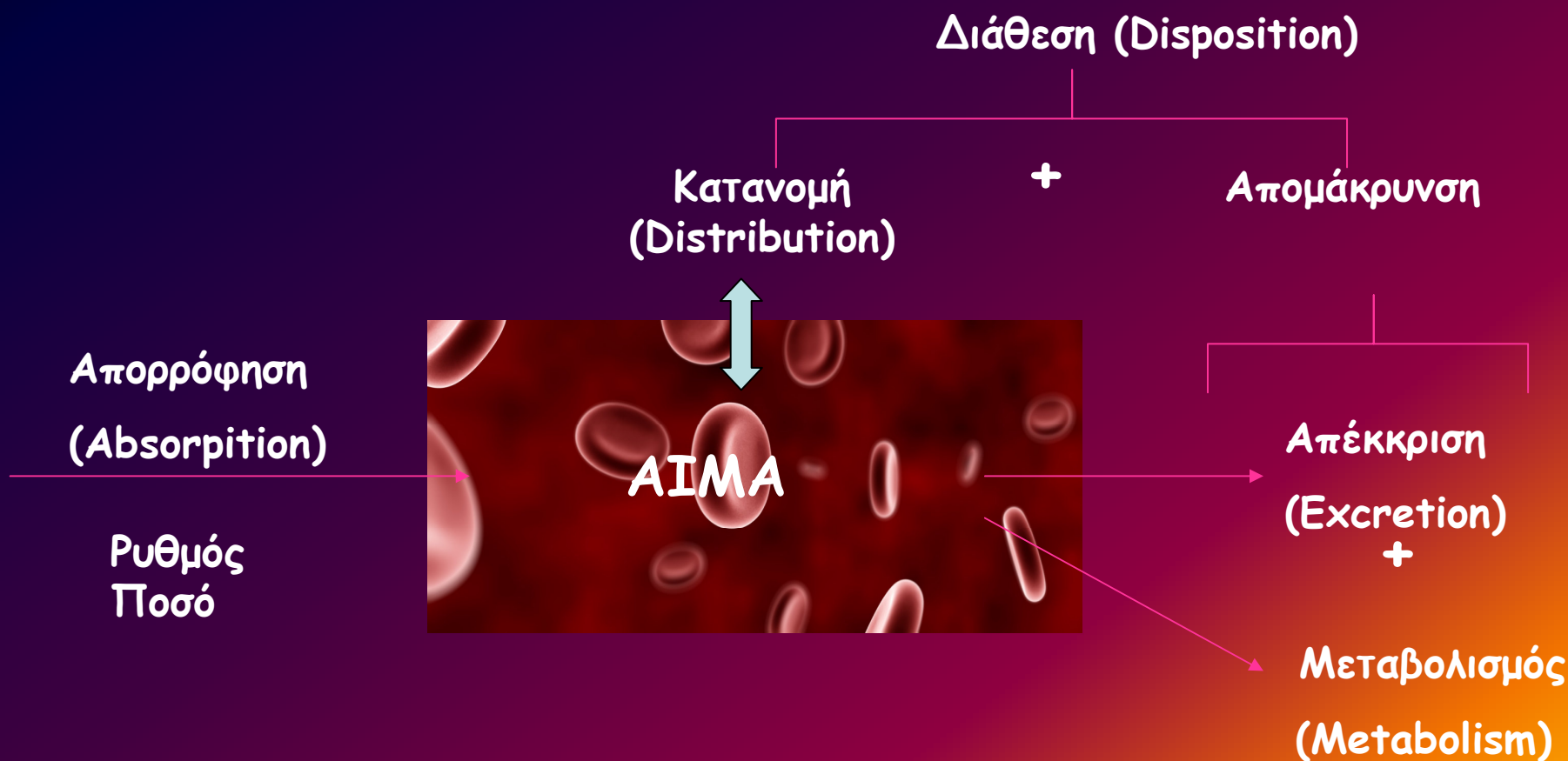


Tudor I Opreaa, and Hans Matterb, Integrating virtual screening in lead discovery, *Current Opinion in Chemical Biology* 2004, 8:349–358

Φαρμακοκινητική φάση

- Δοσολογία φαρμάκου
- Συχνότητα χορήγησης φαρμάκου
- Οδό χορήγησης φαρμάκου
- Σχέσεις μεταξύ της ποσότητας ή της συγκέντρωσης του φαρμάκου στο σώμα και του χρόνου

Φαρμακοκινητικές διαδικασίες φαρμάκων



Στόχος των *in silico* μεθόδων

Η έγκαιρη εντόπιση των προβληματικών μορίων είναι δυνατό να μειώσει το κόστος και τον χρόνο ανάπτυξης νέων φαρμακευτικών μορίων



Έγκαιρη διάγνωση των υποψήφιων προβληματικών φαρμακευτικών μορίων



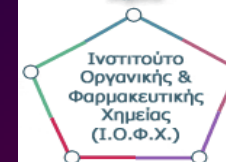
Μείωση του αριθμού των πειραμάτων



Σύνδεση των φαρμακοκινητικών ιδιοτήτων με μοριακές δομές



Μετατροπή των δεδομένων σε πληροφορία και επομένως σε γνώση



LIST OF *IN SILICO* ADMET PRODUCTS

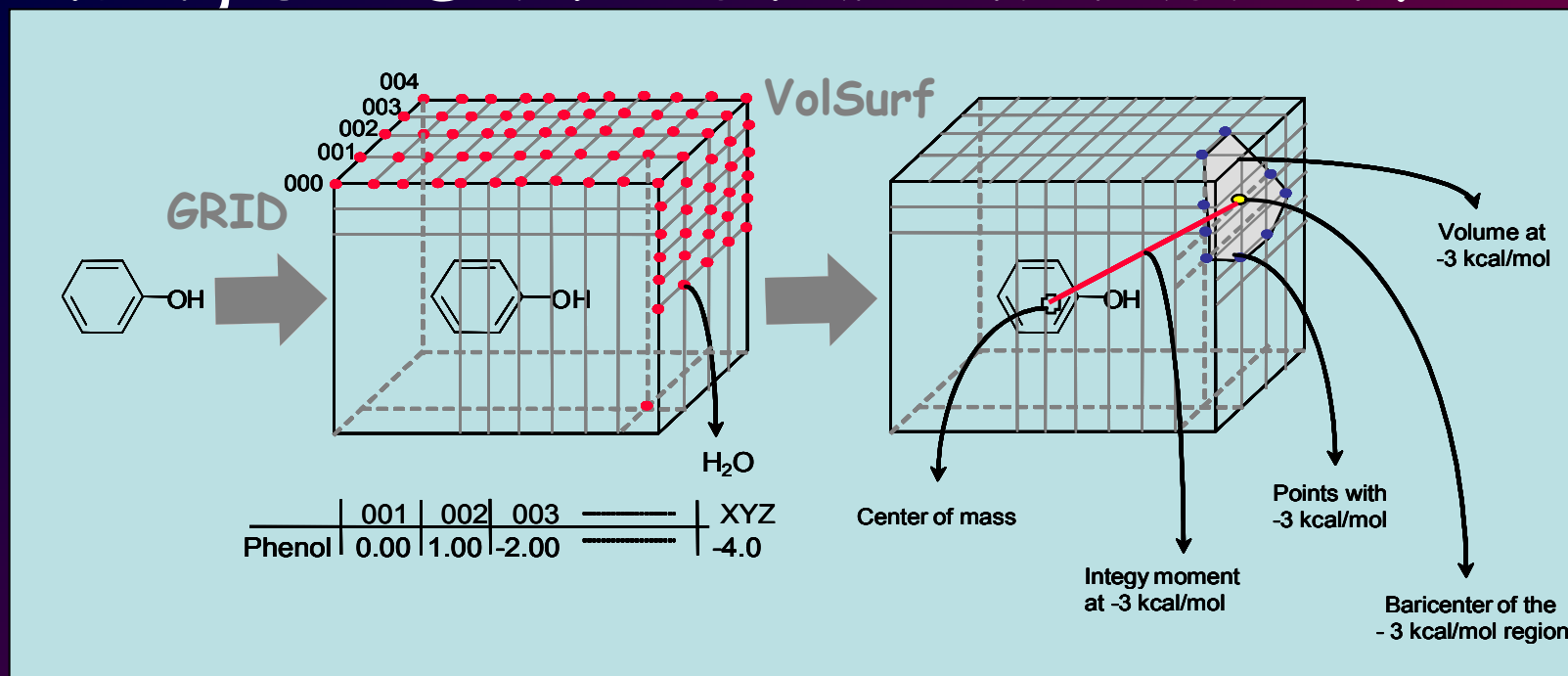
Company	Products
ACD/Labs	ACD/LogD Suite and ACD/Log Sol Suite, ACD/LogD Batch and ACD/Log Sol Batch, ACD/Structure Design Suite, ACD/PhysChem Batch
Aegis Technologies Group	acsIXtreme
Applied Biosystems	Metabolite ID Software
Aureus Pharma	AurScope, AurQuest
BioByte	Bio-Loom, CQSAR, ClogP
BioKin Limited	BatchKi, Dynafit, PlateKi, SteadyFit
Bio-Rad	KnowItAll
BioReason	Class Pharmer Suite
Cerep	BioPrint
Chemical Computing Group	MOE
ChemSilico	CSLogWS, CSLogD, CSLogP, CSpKa, CSBBB, CSPB, CSGlobal, CSHIA
Chenomx	Chenomx NMS Suite 4.0
ComGenex	Pallas Software Family
CompuDrug	Hazard Expert, Hazard Expert Pro, MetabolExpert, MEXAlert, pKalc, TPSA, Rule of 5, PrologP, ToxAlert
Cyprotex	Cloe PK
Daylight Chemical Information Systems	PC Models
EduSoft	Hint, Molconn-Z, Zap, HASL
Elsevier – MDL	MDL QSAR, MDL Toxicity Database, MDL Metabolite, MDL Sculpt, MDL ISIS for Excel, MDL Carcinogenicity Module, RTECS
Entelos	PhysioLab Technology
Equbits	Equbits Foresights
Evotec OAI	Evotec Profile
Exonhit Therapeutics	Safe-Hit
Gene Logic	ToxExpress System, BioExpress System
GeneGo	MetaCore, MetaDrug
Genomatica	SimPheny
Globomax Icon	NONMEM, PDx-Pop, PDx-IVIVC
Golden Helix	ChemTree, HelixTree
Iconix Pharmaceuticals	DrugMatrix
IDBS	ActivityBase, BioBook, ChemXtra, PredictionBase
InnaPhase	Galileo, Watson, Newton, Kinetic

Company	Products
LeadScope	LeadScope Toxicity Database, LeadScope Known Drugs Databases, LeadScope Enterprise, LeadScope Personal
LHASA	DEREK for Windows, METEOR, Vitic
Biowisdom/LION	iDEA, LeadNavigator
MDS Pharma Services	Pharmotif Solutions
Molecular Discovery Limited	GRID, VolSurf, MetaSite, Almond, ADRIANA
MulticASE	MCASE/MC4PC, CASETOX, ToxLite, METAPC, MCWEB
Nimbus Biotechnology	PK-Map
NorayBio	CacoReady Software, NorayNet ADME
Novatia	Metlab Profiler
Partek	Partek Screener's Solution, Partek QSAR Solution, Partek Discovery Suite
Pharma Algorithms	Algorithm Builder, QSAR Builder, ADME Boxes v. 3.0, Tox Boxes v. 1.0, ADME/Tox WEB, DMSO Solubility, ADME Batches, Absolv
Bayer Technology Services	PK-SIM
pION	ELM-Evolution Library Manager
Schrodinger	QikProp
Supernus Pharmaceuticals	ProPhile, RADAR, ProScreen, OptiScreen
Simcyp	Simcyp
Simulations Plus, Inc.	ADMET Modeler, ADMET Predictor, Class Pharmer 4.0, GastroPlus, DDDPlus
Sirius	RefinementPro2
Spotfire	DecisionSite for Lead Discovery
Strand Life Sciences	ADMETIS
Summit PK	PK Solutions, Metabase
Syracuse Research Corporation	PHYSPROP
TerraBase	TerraQSAR Programmes, TerraTox Database Products
Thermo Electron Corporation	Metabolite ID 2.0
TimTec	SLIPPER, DISCON, HYBOT-PLUS
Tripos	VolSurf
Umetrics	SIMCA-P, SIMCA-P +
Waters	MetaboLynx Application Manager
White Carbon	Pathways for Adaptive ADME/Tox

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ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

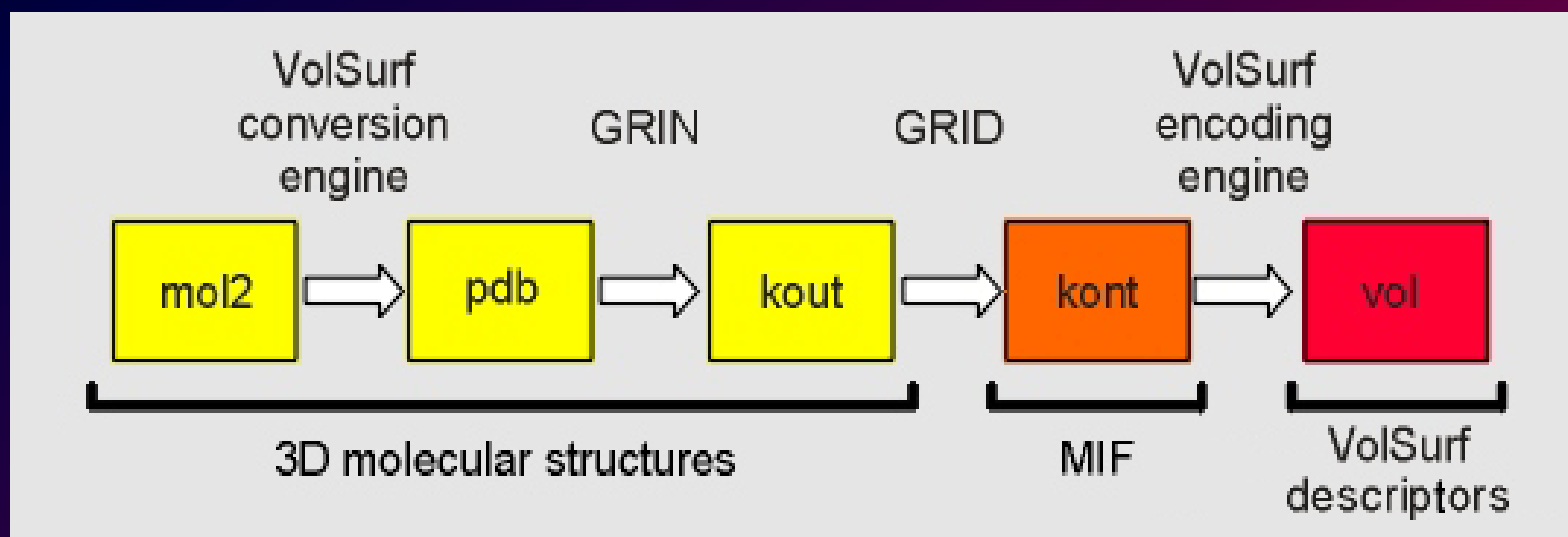
ADME Prediction using GRID-Molecular Interaction Fields



G. Cruciani, M. Pastor, W. Guba, VolSurf: a new tool for the pharmacokinetic optimization of lead compounds, *Eur. J. Pharm. Sci.*, Vol.11, Suppl 2, Pages S29-S39

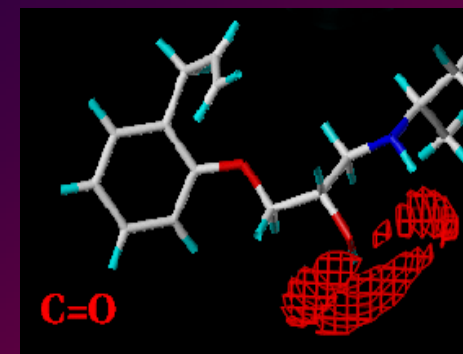
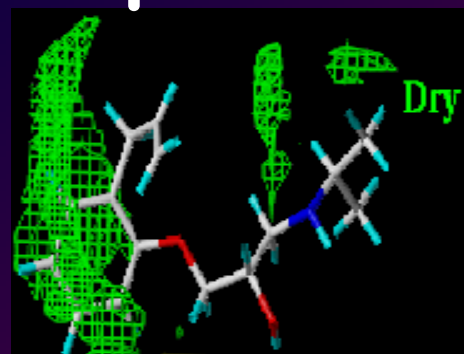
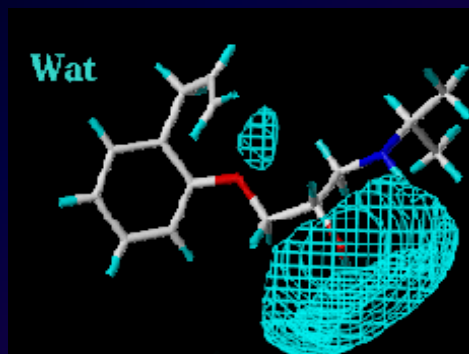
I. Zamora, T. Oprea, G. Cruciani, M. Pastor, A-L Ungell, Surface Descriptors for Protein-Ligand Affinity, *J. Med. Chem.*, 2003, Vol. 46, No. 1, 25-33

VolSurf



<http://www.moldiscovery.com>

VolSurf Descriptors

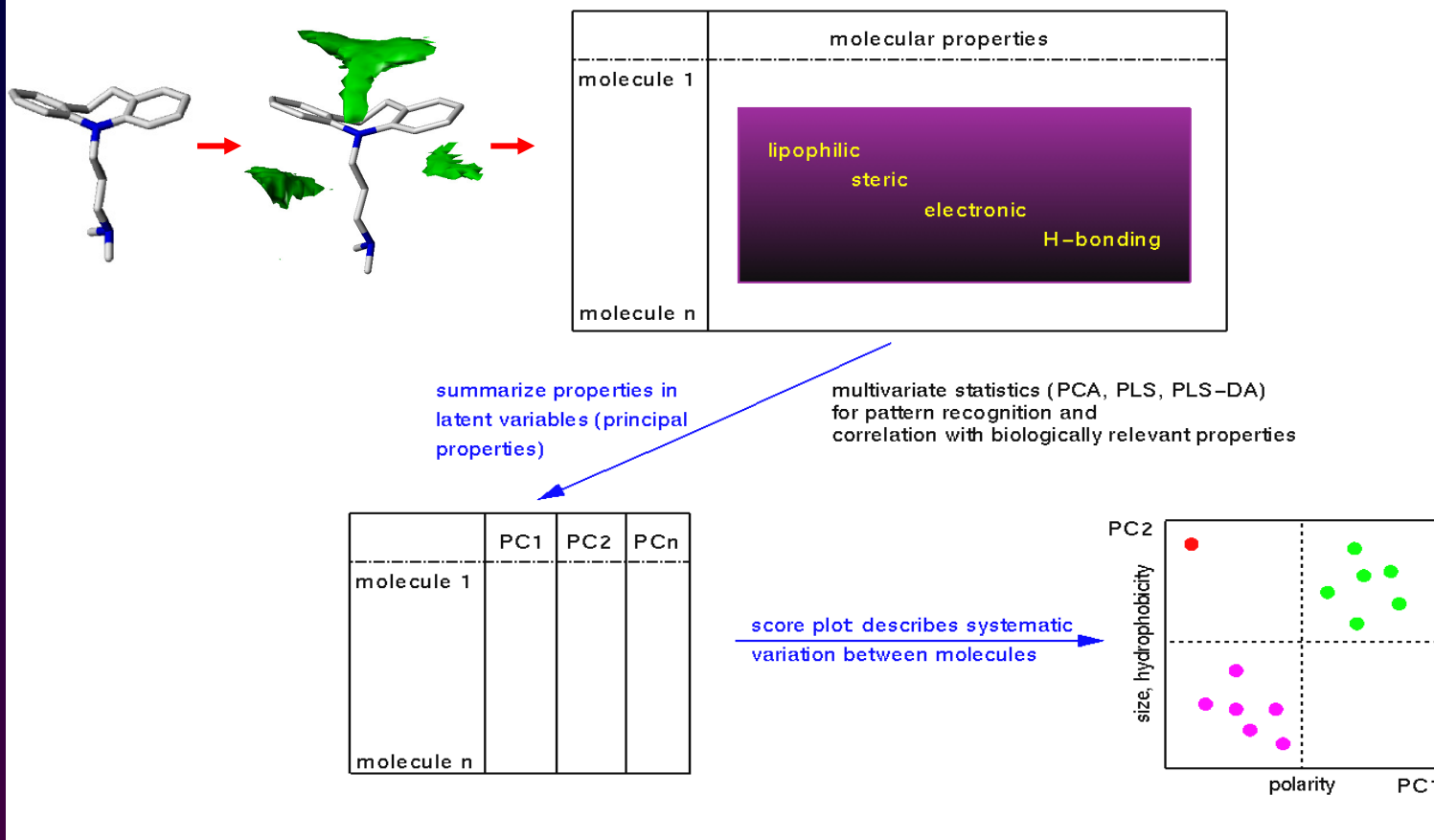


V
S
R
G
W1-W8
IW1-IW8
CW1-CW8
Emin1, Emin2, Emin3
D12, D13, D23

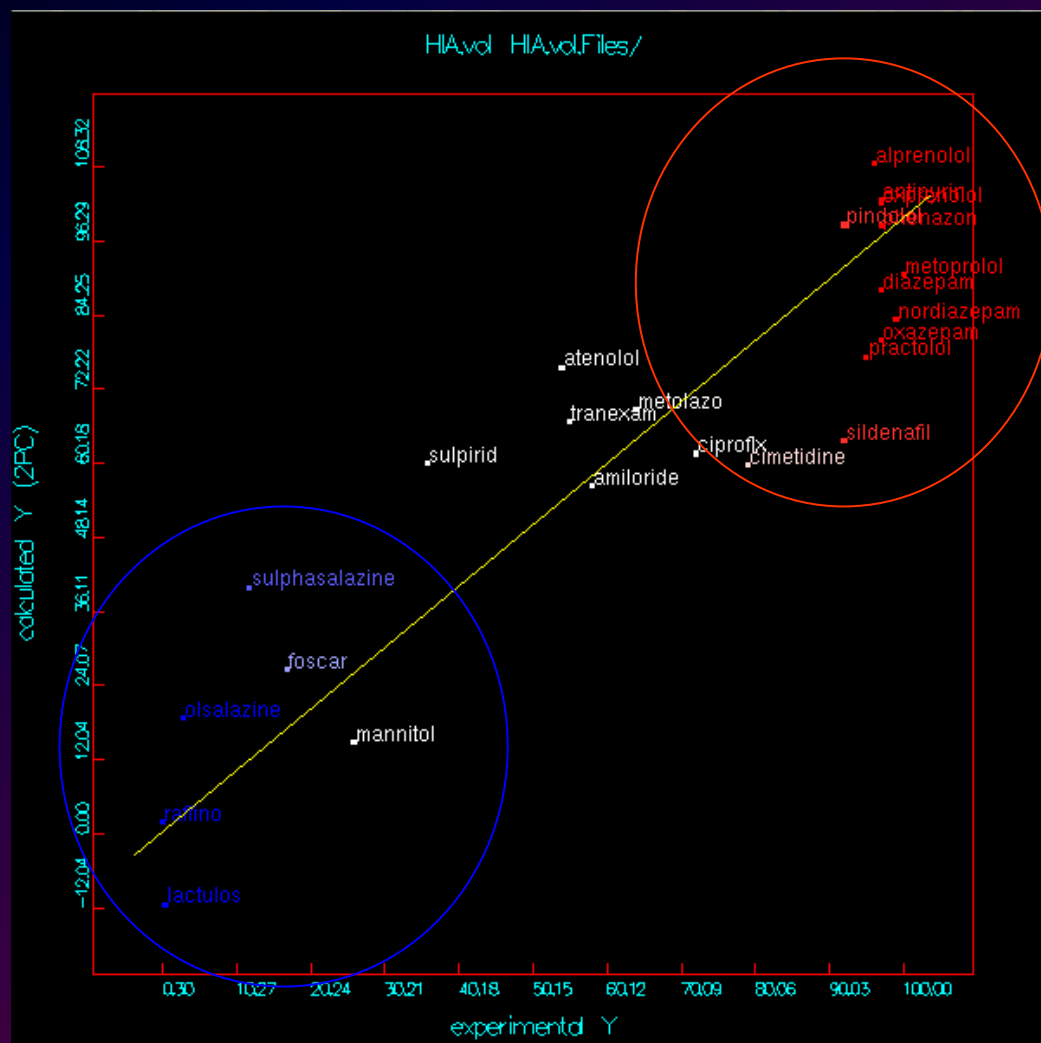
D1-D8
ID1-ID8
HL1-HL2
A
CP
POL

Wp1-Wp8
HB1-HB8

Multivariate Modeling with VolSurf Descriptors



VolSurf in a set of passively absorbed drugs



Derivation of a Quantitative Structure Property model for the Human Intestistinal Absorption (HIA)

Data set: 24 compounds

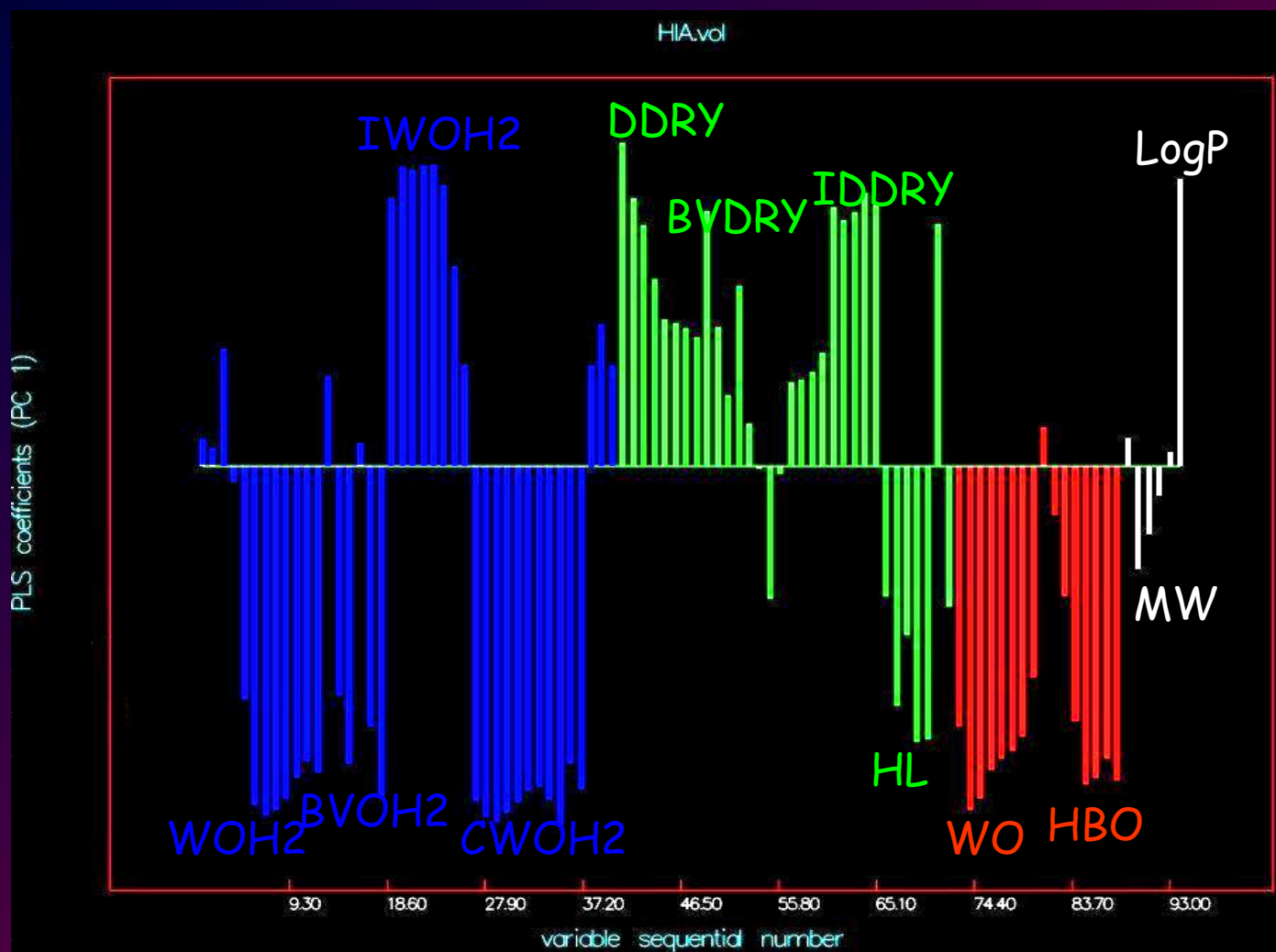
Probes: DRY, H₂O, O

Y: %HIA value for the 24 compounds

PLS model

$A = 2$ $r^2 = 0.83$ $q^2 = 0.70$

Use PLS to correlate %HIA with the VolSurf descriptors

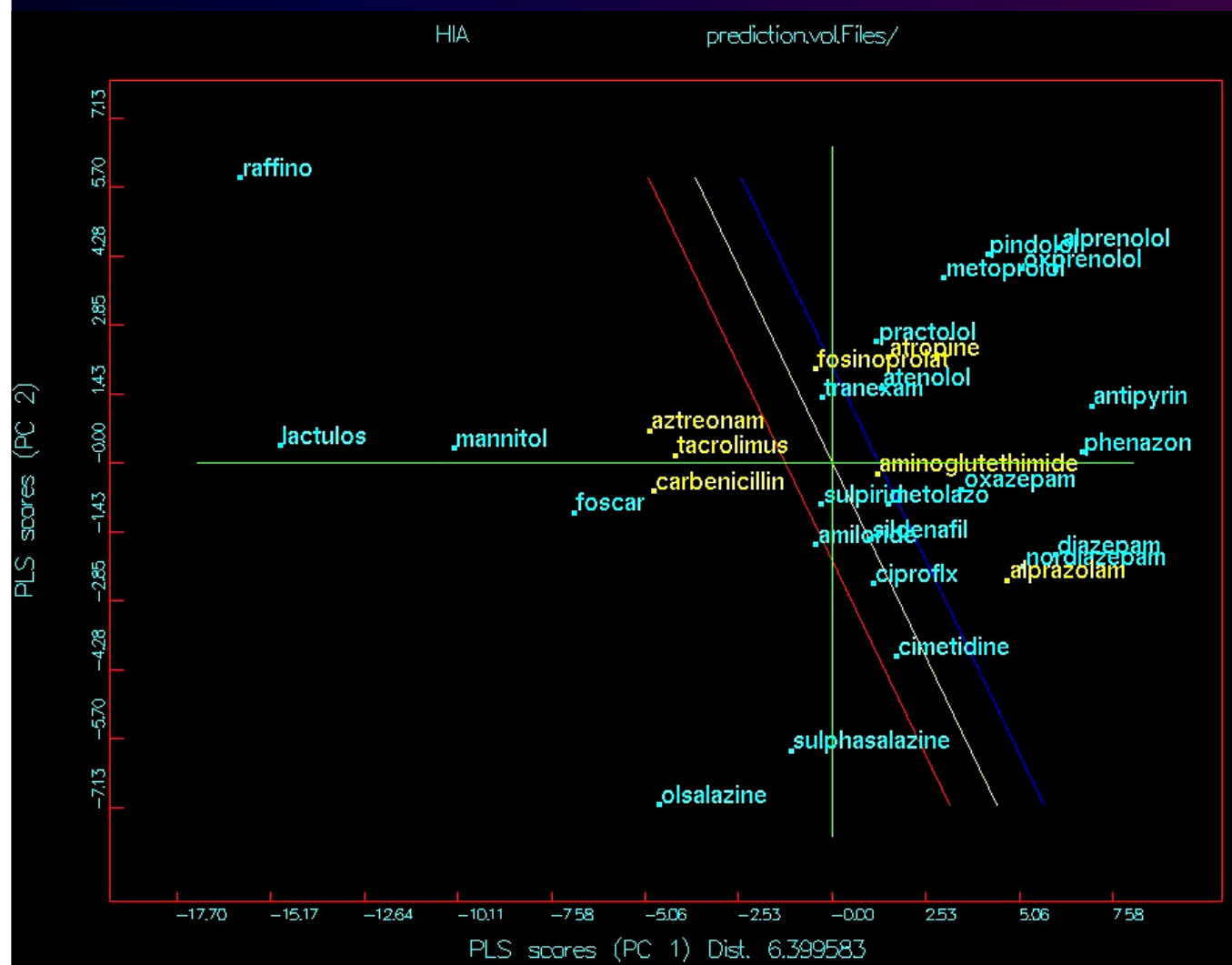


WORKSHOP

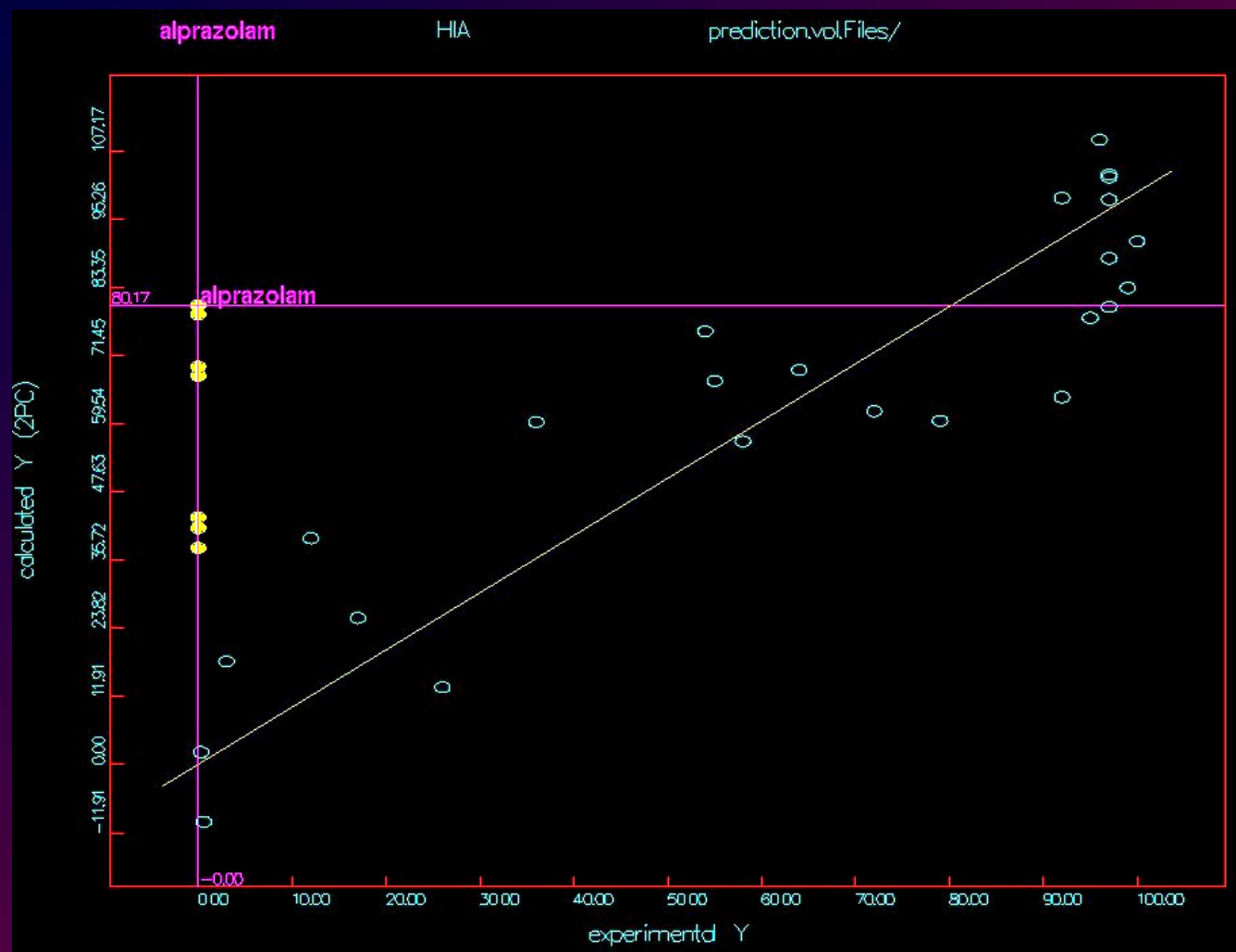
External Prediction for % HIA

Data set: 7 compounds

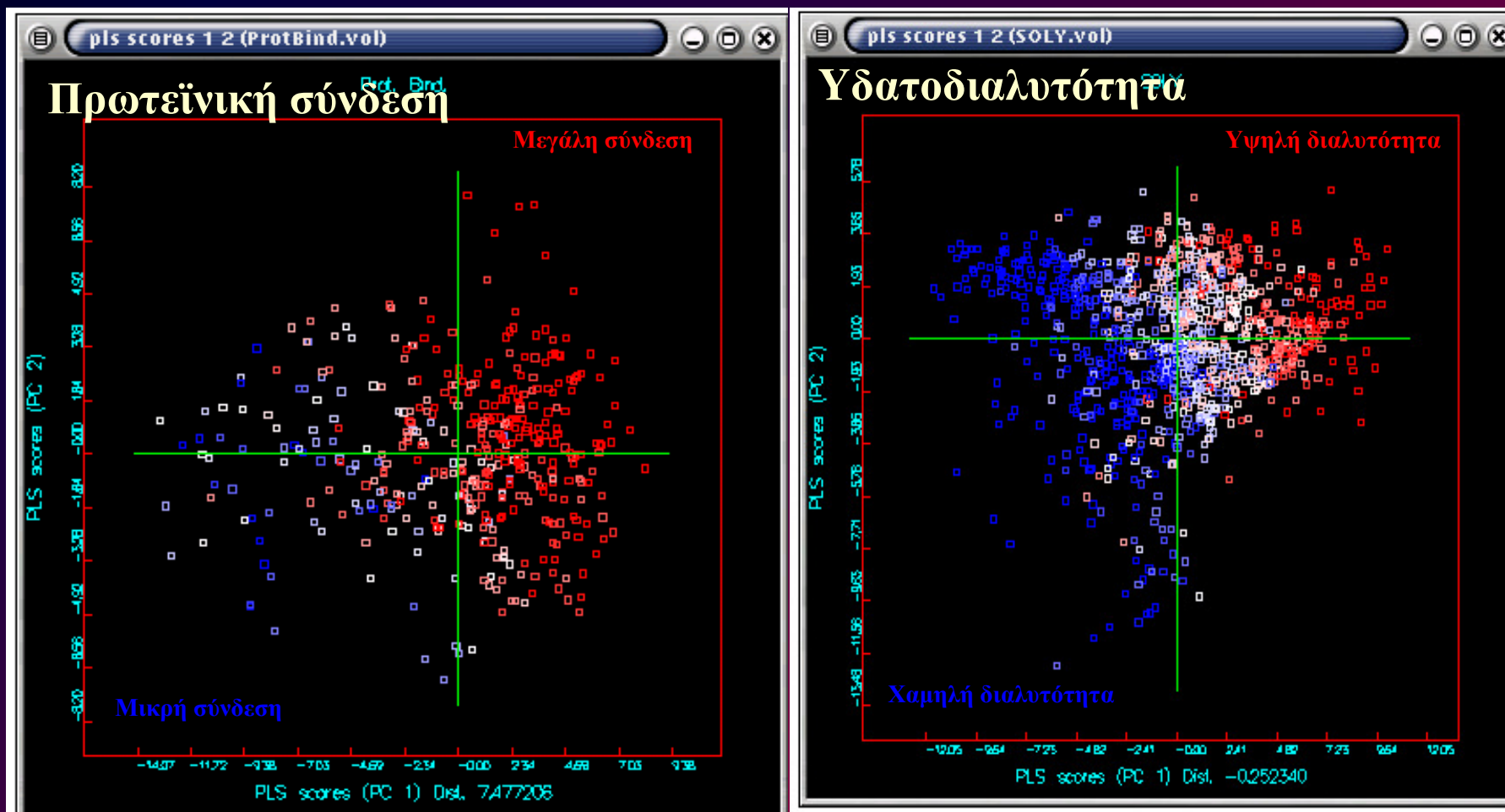
Y: %HIA value ?



External Prediction for % HIA



ADME Models

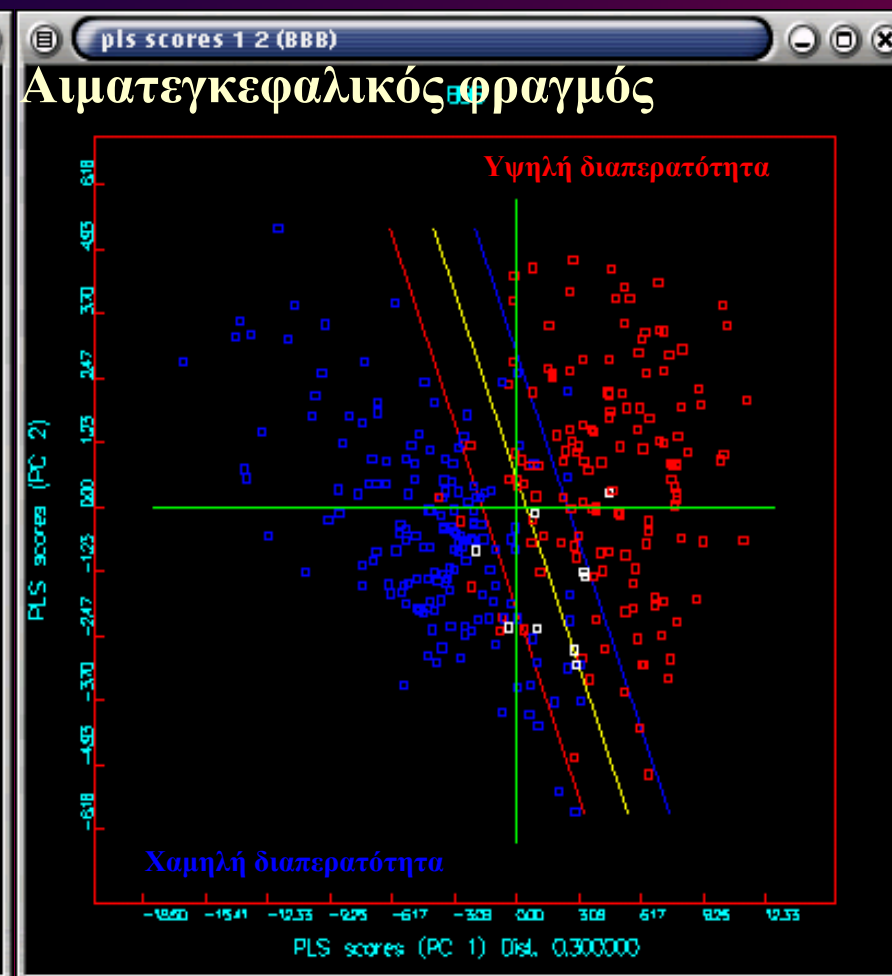
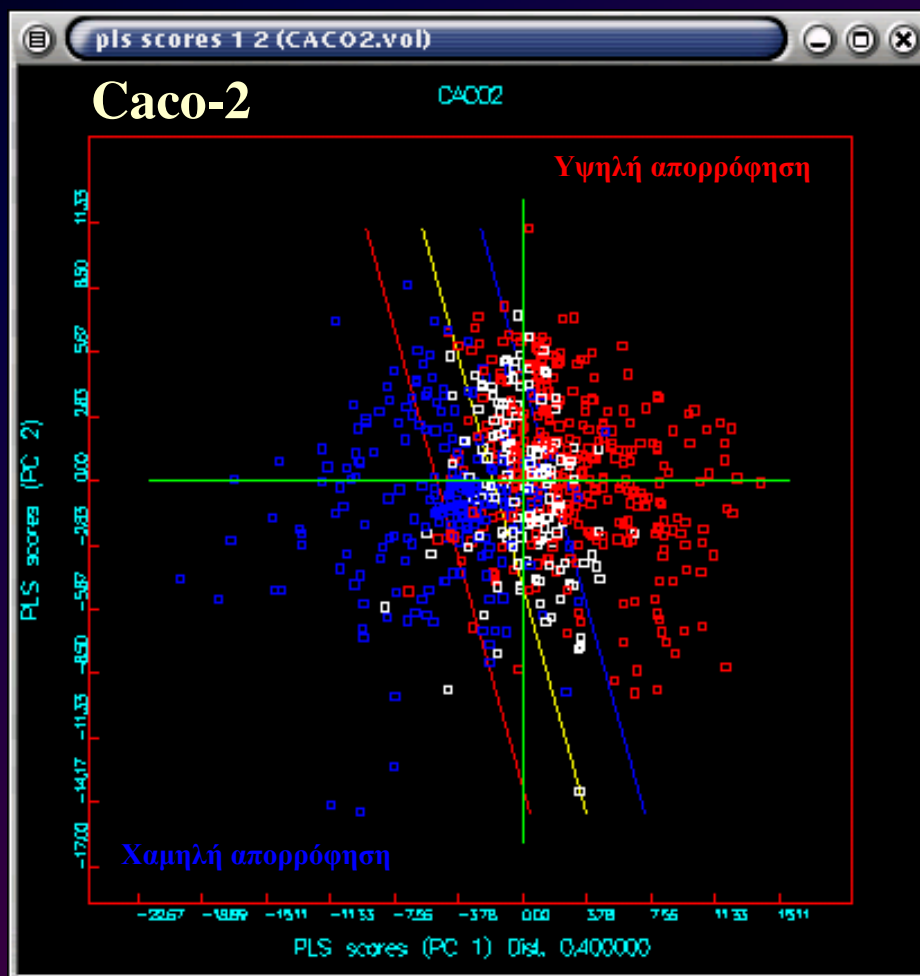


<http://www.moldiscovery.com>

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ADME Models



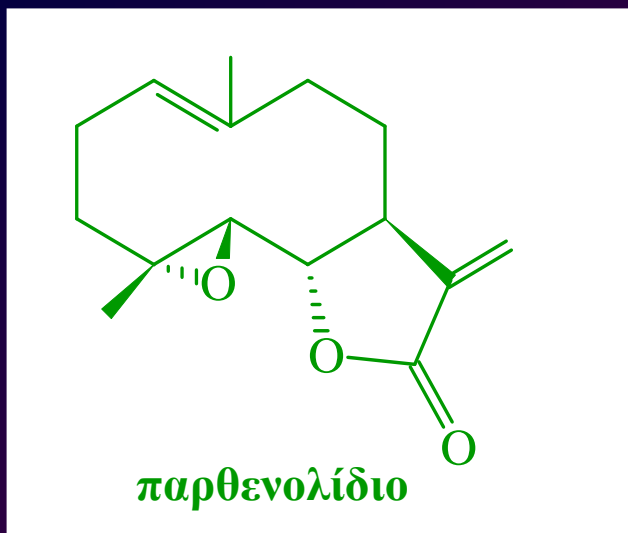
<http://www.moldiscovery.com>

WORKSHOP

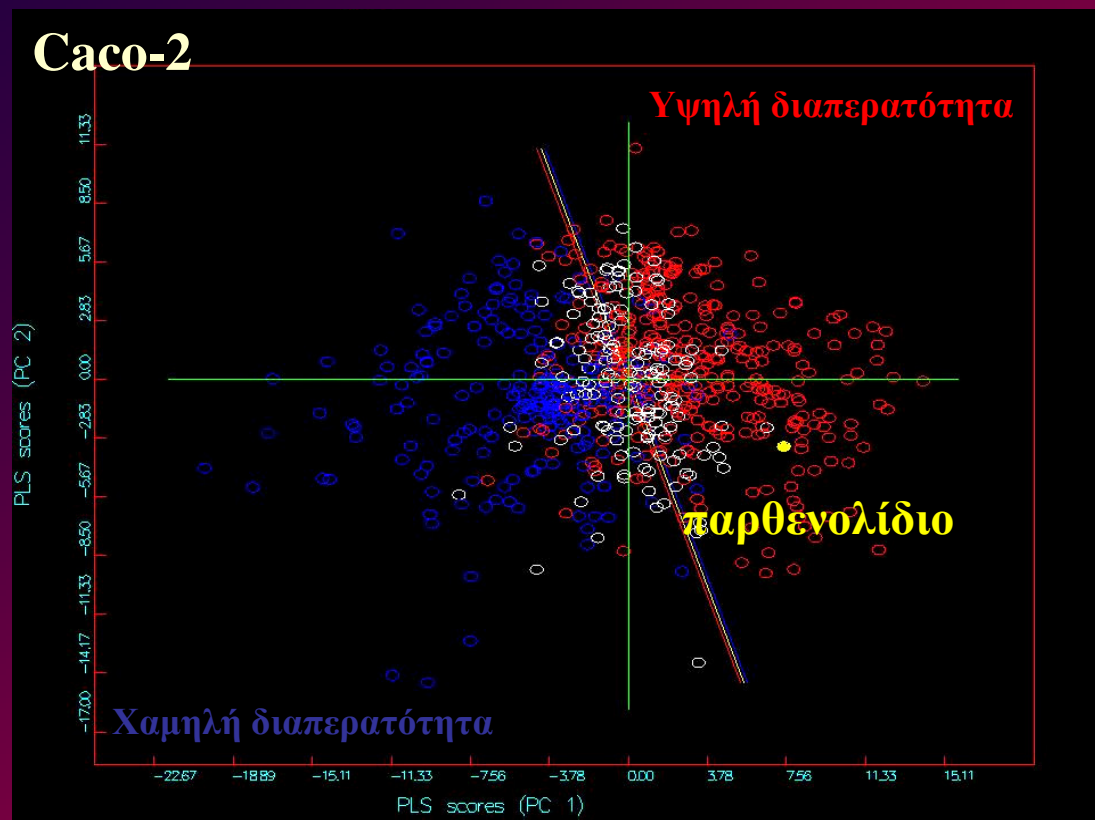
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

ΑΝΑΛΥΣΗ *IN SILICO* ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΩΝ ΙΔΙΟΤΗΤΩΝ ΣΕΣΚΙΤΕΡΠΕΝΙΚΩΝ ΛΑΚΤΟΝΩΝ ΜΕ ΑΝΤΙΜΥΚΗΤΙΑΣΙΚΗ ΔΡΑΣΗ

Πειραματικά δεδομένα:
• διαπερνά τα κύτταρα Caco-2



Βιβλιογραφία:
Khan S. I *et al.*, Transport of parthenolide across human intestinal cells (Caco-2), 2003, *Planta Med.*, 69, 1009-1012



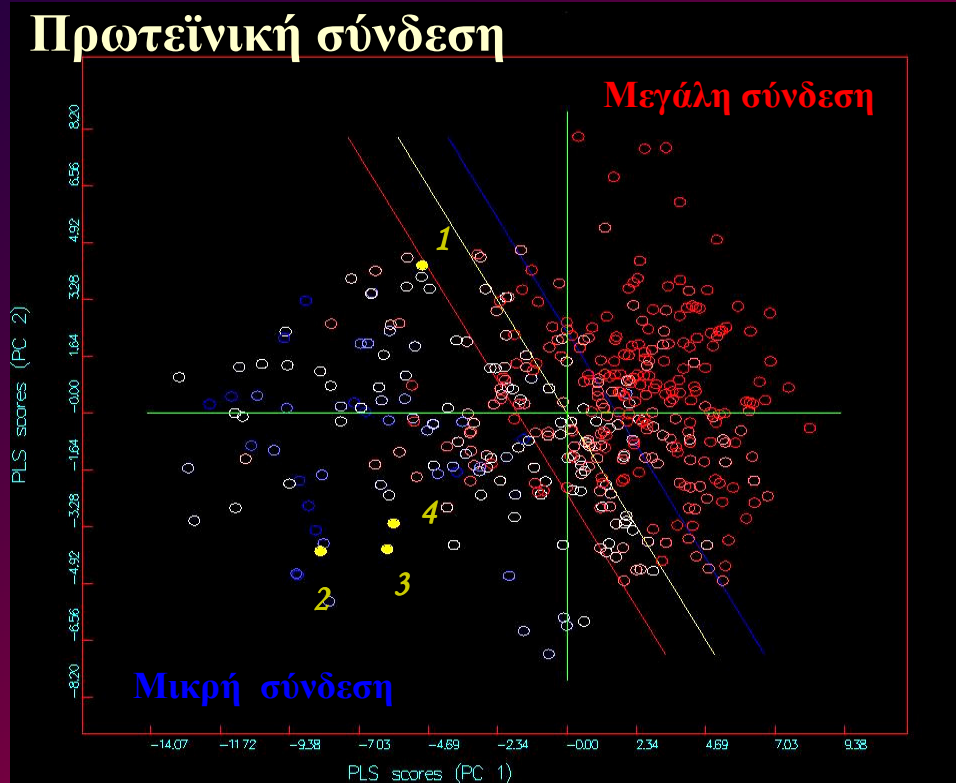
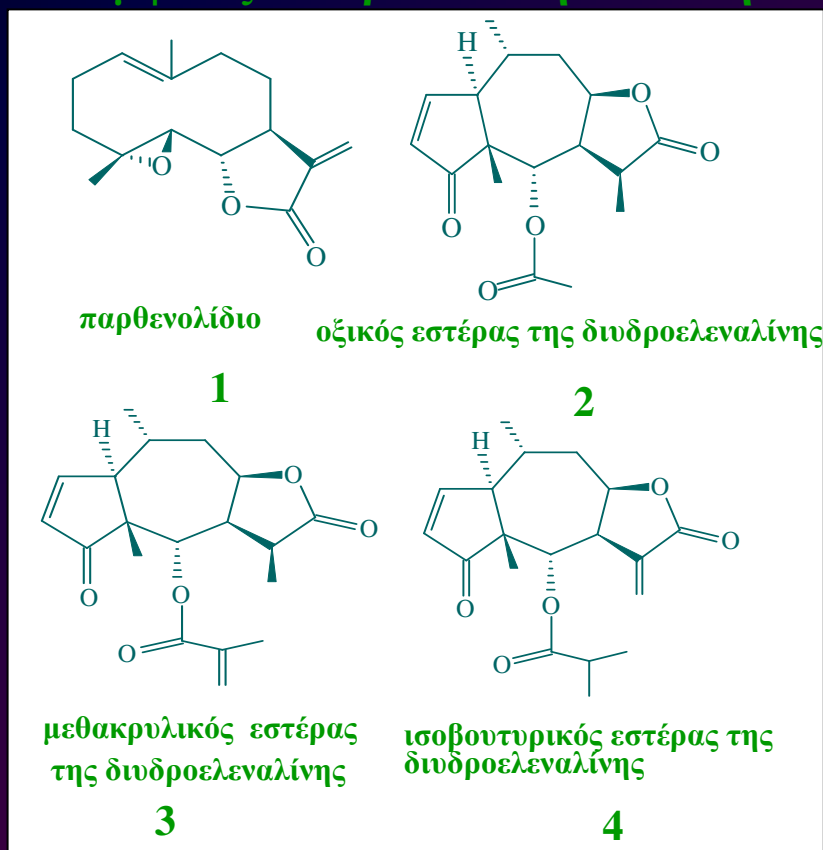
WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

ΑΝΑΛΥΣΗ *IN SILICO* ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΩΝ ΙΔΙΟΤΗΤΩΝ ΣΕΣΚΙΤΕΡΠΕΝΙΚΩΝ ΛΑΚΤΟΝΩΝ ΜΕ ΑΝΤΙΜΥΚΗΤΙΑΣΙΚΗ ΔΡΑΣΗ

Πειραματικά δεδομένα:

► δεν εμφανίζουν πρωτεϊνική σύνδεση



Βιβλιογραφία:

Wagner S. *et al.*, *In vitro* behaviour of sesquiterpene lactones and sesquiterpene lactone-containing plant preparations in human blood, plasma and human serum albumin solutions, *Planta Med.*, 2003, 70, 227-233.

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

Theoretical Investigation of Pharmacokinetic Profile of Synthetic Cannabinoids

B. Durdegi, C. Koukoulitsa, T. Kourouli, T. Andreou, B. Nikas, V. Sahnias, O. Papahadjis, M.C. Papadopoulos, and T. Mavroumatakis
(e-mail: koukoulitsa@pharm.uoi.gr)

Laboratory for Molecular Analysis, Institute of Organic and Pharmaceutical Chemistry, National Hellenic Research Foundation, 49 'Acad. Constantinou Avenue, 11526 Athens, Greece

Introduction

Cannabis sativa L. is one of the oldest known medicinal plants, which contains a family of chemically related 21 carbon alkaloids, termed cannabinoids. Pharmacological studies have shown that cannabinoids are involved in 11 pathologies: nausea and vomiting associated with cancer chemotherapy, loss of appetite, pain, multiple sclerosis, spinal cord trauma, Tourette's syndrome, epilepsy, glaucoma, Parkinson disease, dystonia, decreased IOP (Intraocular Pressure) [1, 2]. Cannabinoids exert their actions by binding to specific receptors: CB1 and CB2. Both cannabinoid receptors belong to the Class A, rhodopsin-like family of G-Protein Coupled Receptors (GPCRs) [3].

Results and Discussion

The selected structures were used as a data base in an attempt to correlate physicochemical parameters with pK_i values. To fulfill this aim, VolSurf approach was applied and 3D molecular fields were transformed into descriptors using the vector (Vols), the topographic (TOPO), and the hydrophobic moment (HMO) descriptors [4]. The PLS (Partial Least Squares) multivariate data analysis of the pK_i versus the 3d VolSurf descriptors was performed. The PLS, after the elimination of two strong outliers (compounds 2 and 16), yielded a two component model for CB1 with $r^2 = 0.81$; the cross validation of the model using the leave-one-out (LCO) method yielded q² = 0.81 and a two component model for CB2 with $r^2 = 0.81$; the cross validation of the model using the leave-one-out (LCO) method yielded q² = 0.81 (Table 3). The quality of the two models is demonstrated in the plot of the experimental versus calculated pK_i (Figs. 2b and 2c).

Materials and Methods

The structures of the studied molecules were retrieved using Tripos force field of SYBYL [5] and Monte Carlo analysis of QM3(BB) energy functions as well as the semiempirical methods of AM1 and PM3. VolSurf [6-8] is a computational procedure to explore the physicochemical property space of a molecule (or family of molecules) in terms of interaction regions between the molecule and chemical probes. The molecular descriptors obtained refer to molecular size and shape, the corresponding sites and shape of both hydrophilic and hydrophobic regions and the ratio of these two components. Both the descriptors and the corresponding energy, are not alternative to molecular models, and have proven to be useful in generating predictive ADMET models. In addition, statistical methods with VolSurf enable the creation of models that relate its descriptors to biological properties.

Acknowledgments

The work was supported by the European Research Project: "A. S. Papadopoulos' Training Site for the Design and Synthesis of Novel Neuroprotective and Neurodegenerative Agents in the AD/Alzheimer's Disease Research Program".
The authors are grateful to Prof. Gabriele Crivello (Laboratory for Chemoinformatics, School of Chemistry, University of Perugia, Italy) for kindly donating us the VolSurf program.

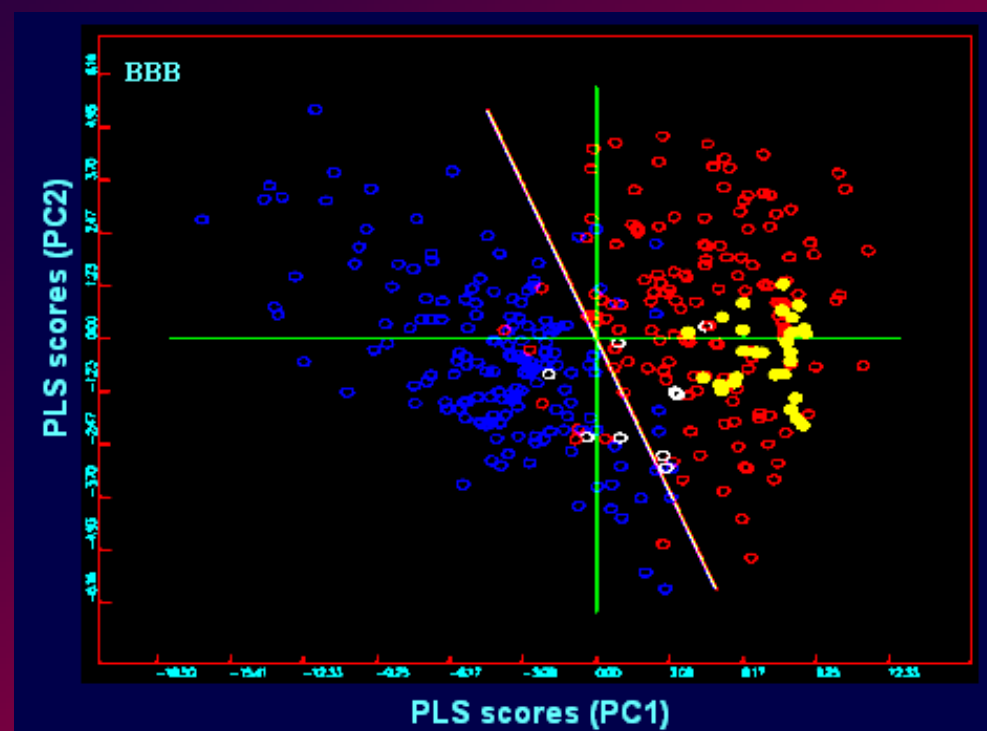


The 16th European Symposium on
Quantitative Structure-Activity
Relationships
& Molecular Modelling
Italy, 10 - 17 September 2006

Theoretical Investigation of Pharmacokinetic Profile of Synthetic Cannabinoids

S. Durdagi, C. Koukoulitsa, T. Kourouli, T. Andreou, S. Nikas, V. Nahmias, D. Papahatjis, M.G. Papadopoulos, and T. Mavromoustakos

		CB1	CB2		CB1	CB2
		pK _i	pK _i		pK _i	pK _i
	1	7.32	7.41	22	5.90	6.64
	2	9.19	8.51			
	3	7.66				
	4	9.08	9.31			
	5	7.66	7.08			
	6	8.66	8.48			
	7	7.02	7.14	23	6.20	6.43
	8	7.92	7.29			
	9	7.24	6.97			
	10	7.93	8.03	24	6.12	6.65
	11	7.55	7.60	25	6.59	6.98
	12	8.08	8.41	26	6.50	6.96
	13	9.35	8.72			
	14	8.74	8.44			
	15	6.77	6.99			
	16	9.28	9.66			
	17	9.49	9.28	27	6.87	7.30
	18	7.24	6.59			
	19	9.36	9.07	28	7.23	7.00
	20	8.90	9.54	29	6.18	7.46
	21	9.15	8.99	30	6.72	7.20



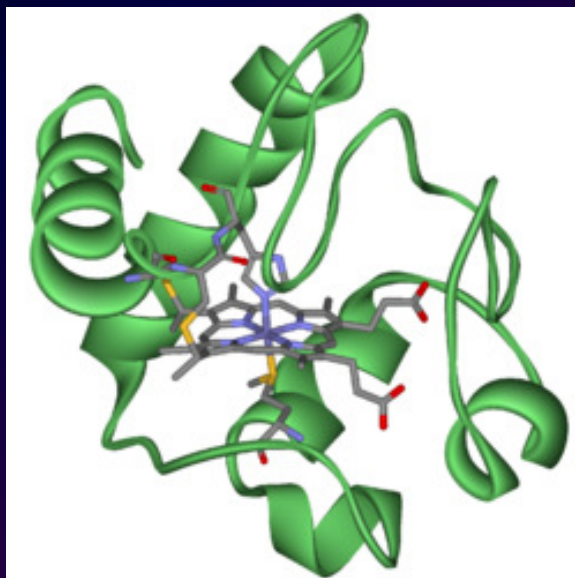
WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

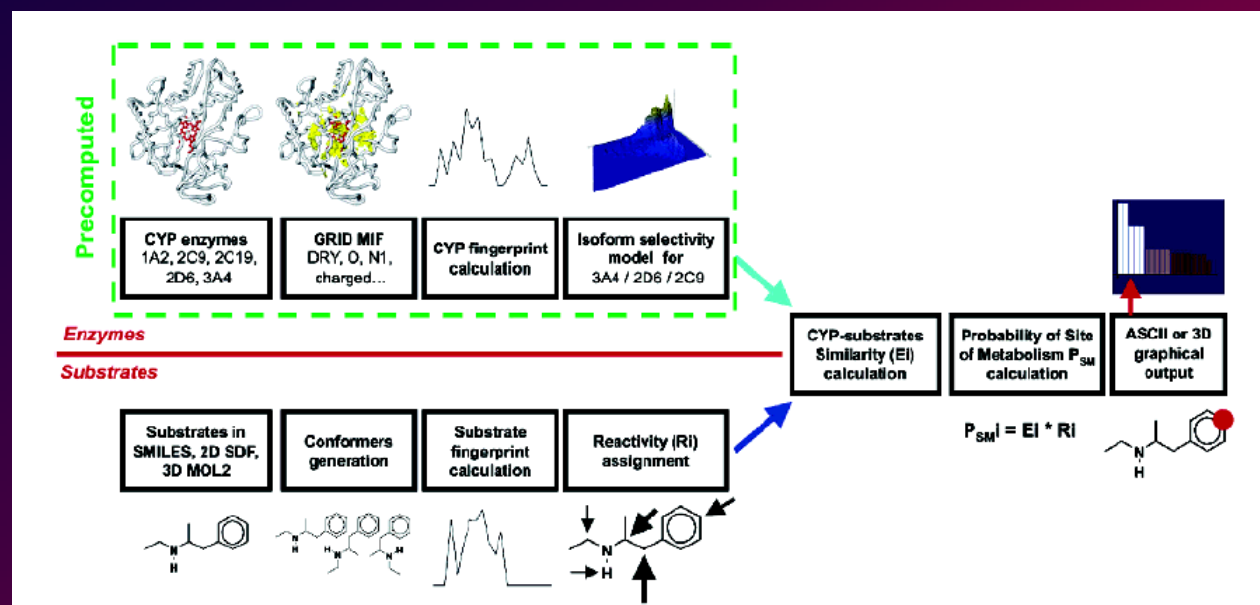


MetaSite

Μεταβολισμός

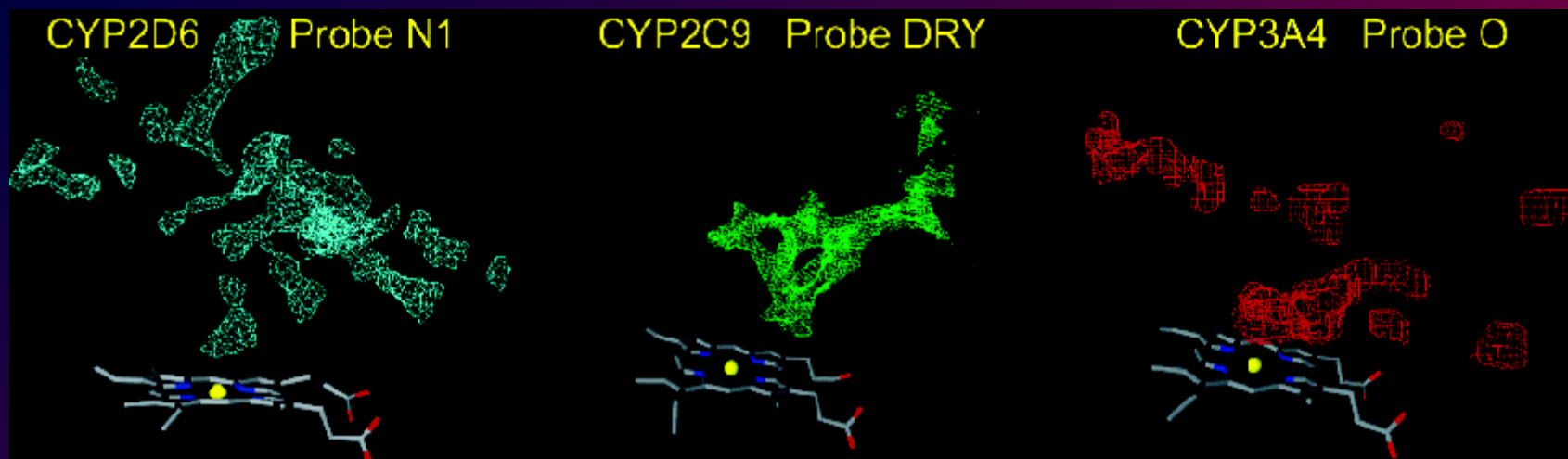


Κυτόχρωμα P450



G. Cruciani, E. Carosati, B. Boeck, K. Ethirajulu, C. Mackie, T. Howe, R. Vianello, MetaSite: Understanding Metabolism in Human Cytochromes from the Perspective of the Chemist, *J. Med. Chem.* 2005, 48, 6970-6979

MetaSite



G. Cruciani, E. Carosati, B. Boeck, K. Ethirajulu, C. Mackie, T. Howe, R. Vianello, MetaSite: Understanding Metabolism in Human Cytochromes from the Perspective of the Chemist, *J. Med. Chem.* 2005, 48, 6970-6979

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ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

MetaSite

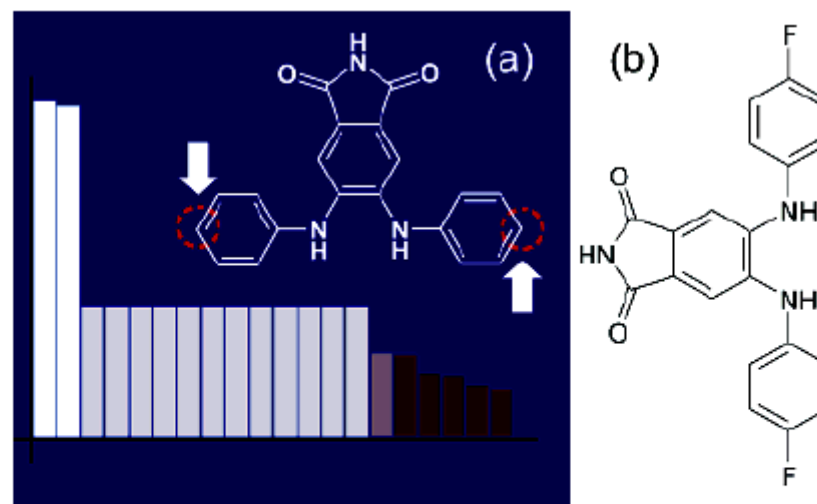


Figure 8. (a) The predicted sites of oxidation are ranked according to probability values and reported in the histogram. White bars highlight the higher probability values that correspond to the para position of the molecule (indicated by white arrows in the 2D structure). (b) Compound CGP53353, a metabolically stable EGF-receptor kinase inhibitor.

G. Cruciani, E. Carosati, B. Boeck, K. Ethirajulu, C. Mackie, T. Howe, R. Vianello, MetaSite: Understanding Metabolism in Human Cytochromes from the Perspective of the Chemist, *J. Med. Chem.* 2005, 48, 6970-6979

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

In silico studies of ADME properties of AT1 receptor antagonists

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*Institute of Organic and Pharmaceutical Chemistry, Laboratory of Molecular Analysis, Vex. Constantinou 46, 11525, Athens
*University of Patras, Department of Chemistry, Division of Organic Chemistry, Biochemistry and Natural Products, 26500 Bilo

Introduction

The necessity of the pharmaceutical industry to limit the time and expense of drug development due to the non optimal pharmacokinetic profile of candidate drugs, has initiated the interest in high-throughput screening methods and their in silico counterparts for rapid estimation of ADME properties (Absorption, Distribution, Metabolism and Excretion) at the early stages of drug development.

In the current study, some relevant pharmacokinetic and metabolic properties are theoretically calculated for AT1 antagonists (BARTANs) using VolSurf and Metable software. The dataset is comprised of already marketed antihypertensives and other synthetic derivatives (Fig. 1). In particular, we have focused on aspects of blood brain barrier penetration, Caco-2 cell absorption, plasma protein binding, aqueous solubility, volume of distribution, and metabolism by CYP3A4.

Materials and Methods

The structures of the studied molecules were minimized using Tripos force field of SYBYL. VolSurf is a computational procedure to explore the physicochemical property space of a molecule (or library of molecules) starting from 3D maps of interaction energies between the molecule and chemical probes. The molecular descriptors obtained refer to molecular size and shape, the corresponding size and shape of both hydrophilic and hydrophobic regions and the ratio of these two regions. VolSurf's descriptors have a clear chemical meaning, are not sensitive to alignment rules, and have proven to be useful in generating predictive ADME models. Multivariate statistical methods within VolSurf enable the creation of models that relate its descriptors to biological properties.

Metable involves the calculation of different sets of descriptors, one for the CYP enzymes and one set for the potential substrates. The set of descriptors used to characterize CYP enzymes is based on GRID flexible molecular interaction fields. For the CYP2D6 and CYP3A4 enzymes, the crystal structures of human isozymes are used.

Results and Discussion

Fig. 2 reports the projection of the examined compounds on the pre-calculated ADMET models: blood-brain barrier penetration, Caco-2 cell absorption, plasma protein binding, aqueous solubility, volume of distribution, and metabolism by CYP3A4. The model Caco-2 shows that telisartan, losartan, lisartan, B27, B28, and V12 can be transported across the intestinal epithelium, while the other compounds can not be transported. The model BBB indicates that the compounds do not cross the BBB. Lisartan, telisartan, B27, B28, and V12 have high plasma-protein affinity, while the remaining compounds have low plasma-protein affinity. From the model of aqueous solubility it can be observed that the compounds have low aqueous solubility. Lisartan, losartan, eprosartan, espirtan, G246, V6, B27H, H6, and B5 each has a small VD value. Moreover, from the projection of the molecules on the CYP3A4 model can be deduced that B27, B28, V12, and

Figure 3 shows the predicted sites of metabolism by CYP3A4 for B27, B28, V12 and telisartan and Figure 4 the predicted sites of metabolism by CYP2D6 for all the compounds. It can be observed that all the main metabolites of the marketed AT1 antagonists are well predicted.

Fig. 1 Structures of the examined compounds

Fig. 2 Projection of the examined compounds (yellow) on the pre-calculated VolSurf (Passive penetration in the basic assumption of Caco-2 and BBB models)

Fig. 3 Graphical visualization of predicted CYP3A4 metabolic sites for B27, B28, V12, and telisartan. Four different shades of colour are used, from dark brown (lowest probability) to white (highest). The major metabolic site is highlighted by colour size.

Fig. 4 Graphical visualization of predicted CYP2D6 metabolic sites for the examined compounds. Four different shades of colour are used, from dark brown (lowest probability) to white (highest). The major metabolic site is highlighted by colour size.

Acknowledgments

The authors are grateful to Prof. Gheorghe Cristinel (Laboratory for Chromatography, School of Chemistry, University of Cluj-Napoca, Cluj, Romania) for kindly donating us the VolSurf and Metable programs (www.vol-surf.com) and the State Scholarship Foundation of Greece.



8^ο Διεθνές Συνέδριο Ιατρική Χημεία:

Σχεδιασμός και Ανάπτυξη Φαρμακευτικών Προϊόντων

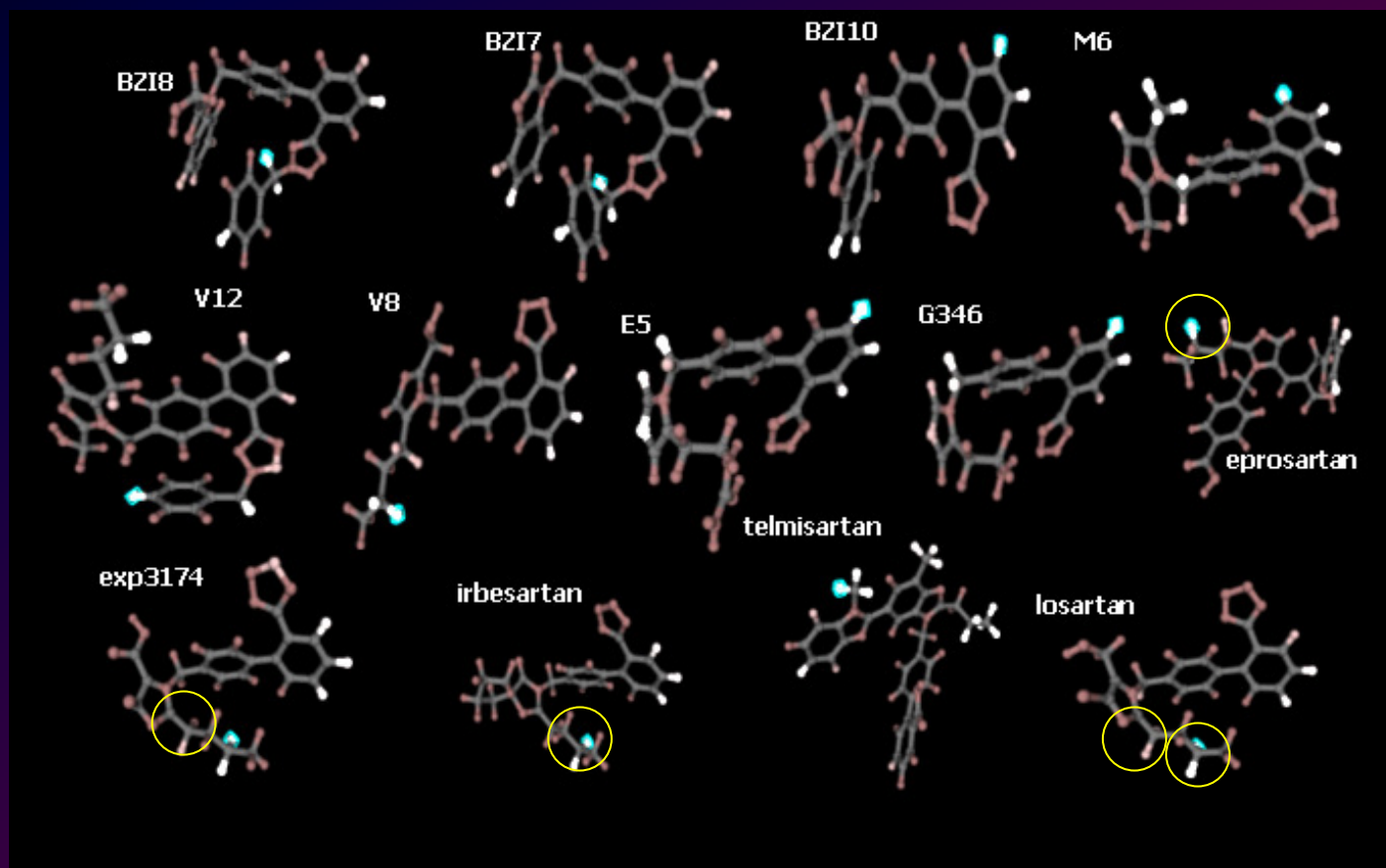
Πάτρα, 15-17 Μαρτίου
2007

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

In Silico Studies of ADME Properties of AT1 antagonists

C. Koukoulitsa, P. Zoumpoulakis, A. Resvani, J. Matsoukas, T. Mavromoustakos

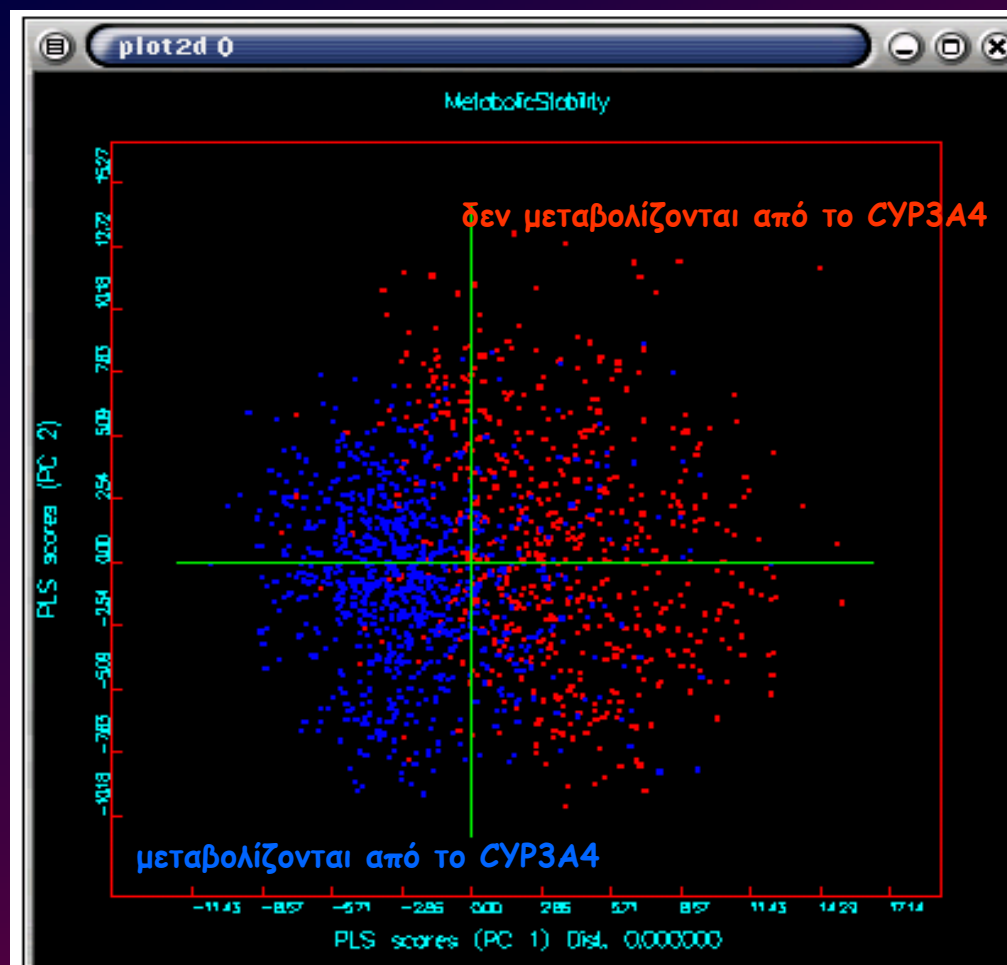


- CYP2C9
- CYP3A4

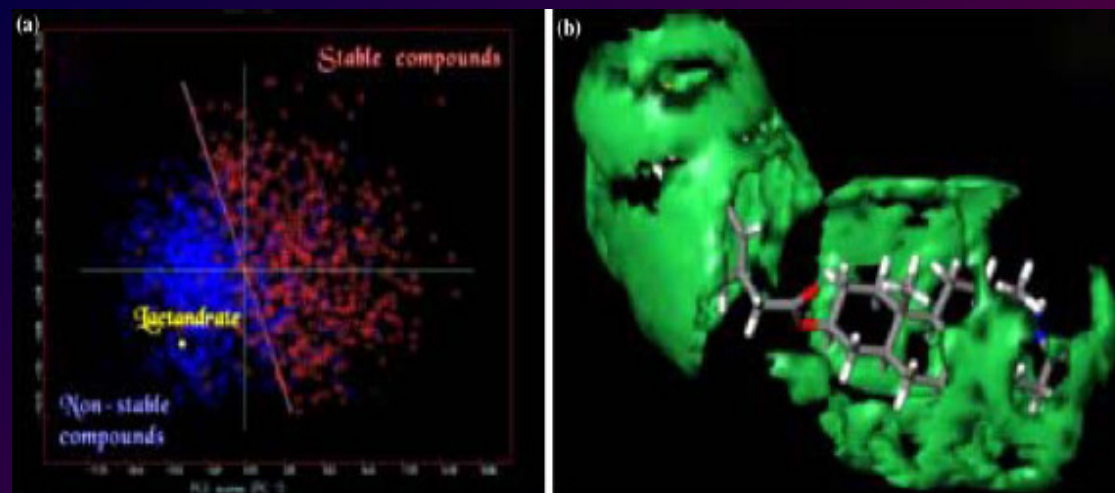
All the main AT1 metabolites of the market are well predicted

Graphical visualisation of predicted CYP3A4 metabolic sites for the examined compounds. Four different shades of colour are used, from dark brown (lowest probability) to white (highest). The major metabolic site is highlighted by colour blue.

ADME Models - CYP3A4



CYP3A4

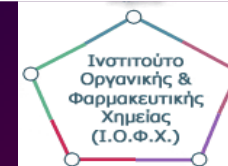


Breast Cancer Research and Treatment (2006) 97: 17–31
DOI 10.1007/s10549-005-9083-x

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Dimitrios T.P. Trafalis^{1,2}, George D. Geromichalos³, Catherine Koukoulitsa⁴, Athanasios Papageorgiou⁵, Panayiotis Karamanacos⁵, and Charalambos Camoutsis¹

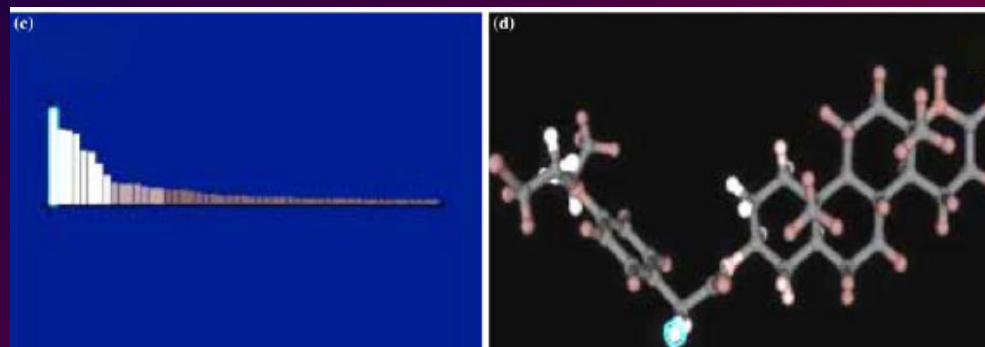


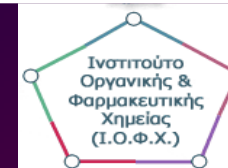
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The 18th European Symposium on Quantitative Structure-Activity Relationships & Molecular Modelling

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2010



WORKSHOP

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