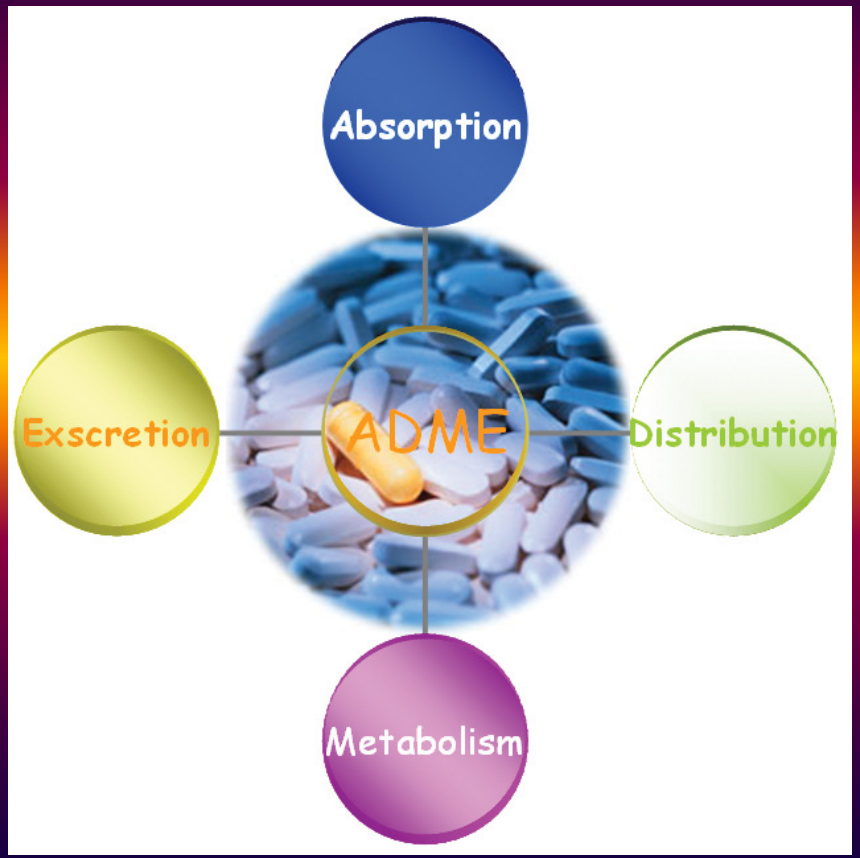
Εργαστήριο Σχεδιασμού Φαρμάκων

ΕΘΝΙΚΟ ΙΔΡΥΜΑ ΕΡΕΥΝΩΝ
ΙΝΣΤΙΤΟΥΤΟ ΟΡΓΑΝΙΚΗΣ & ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΧΗΜΕΙΑΣ
ΕΡΓΑΣΤΗΡΙΟ ΜΟΡΙΑΚΗΣ ΑΝΑΛΥΣΗΣ

LMA
Laboratory of Molecular Analysis

WORKSHOP
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ



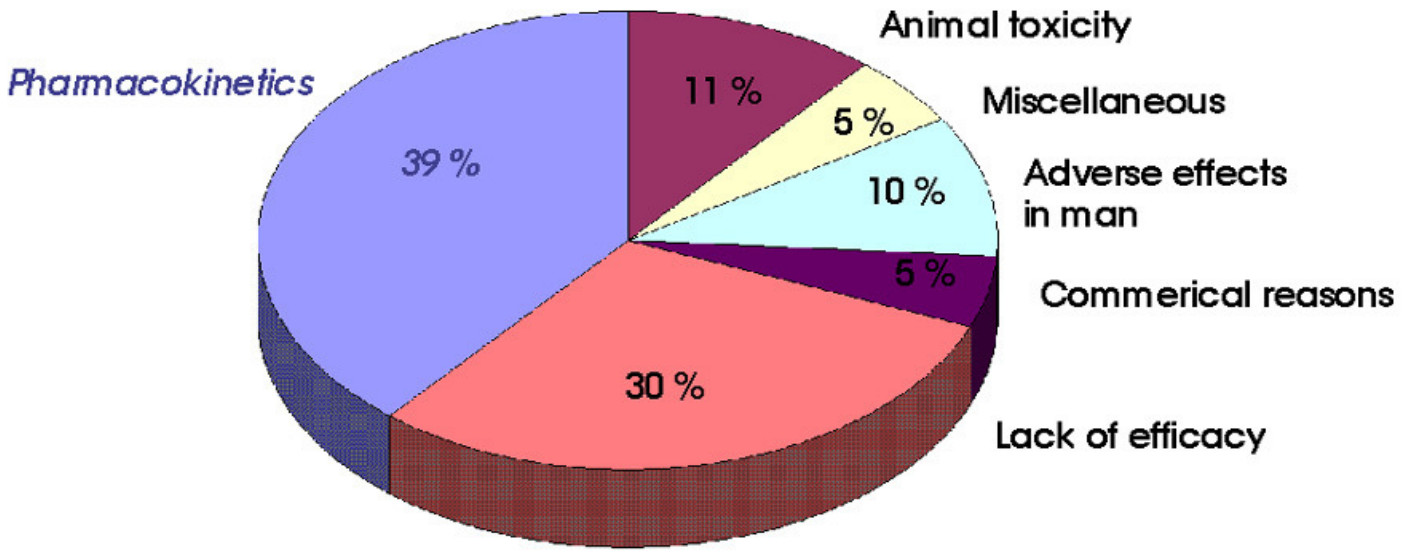
Πρόβλεψη ADME Ιδιοτήτων

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

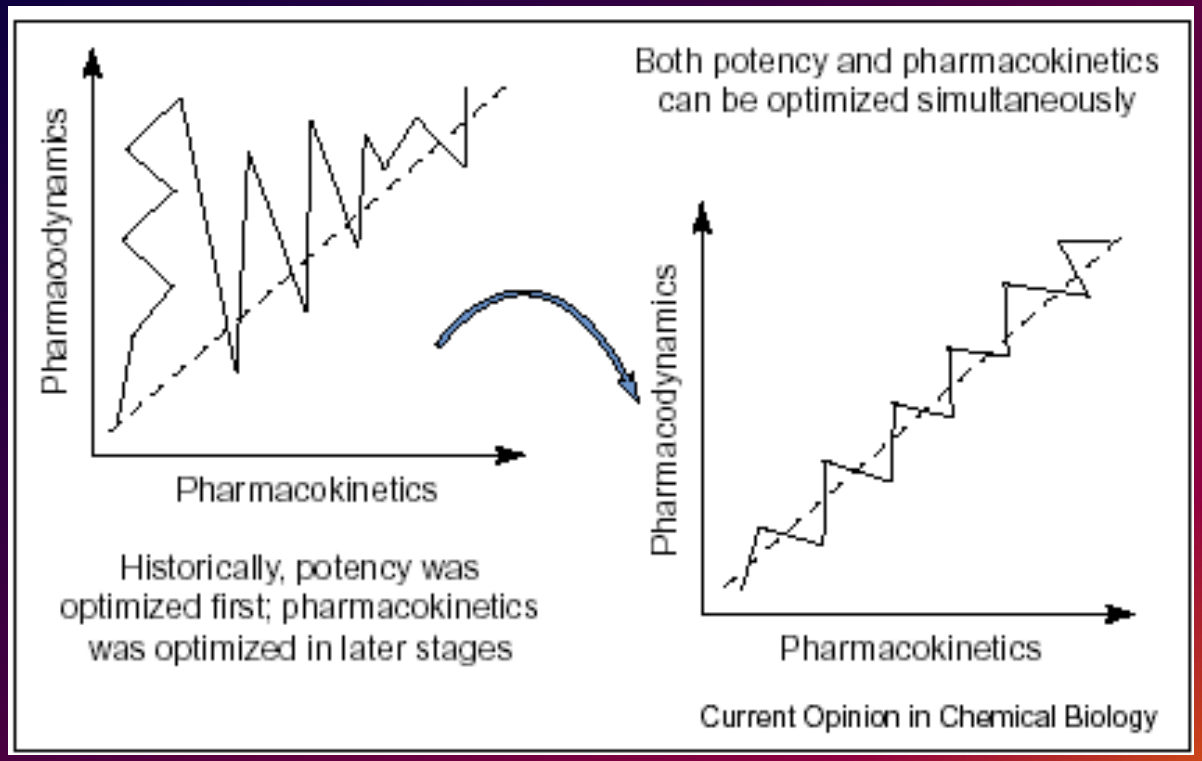
ADME(T)

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

Διάθεση (Disposition)

Κατανομή (Distribution)

+

Απομάκρυνση

Απορρόφηση (Absorpition)

Ρυθμός
Ποσό

Απέκκριση (Excretion)

+

Μεταβολισμός (Metabolism)

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**

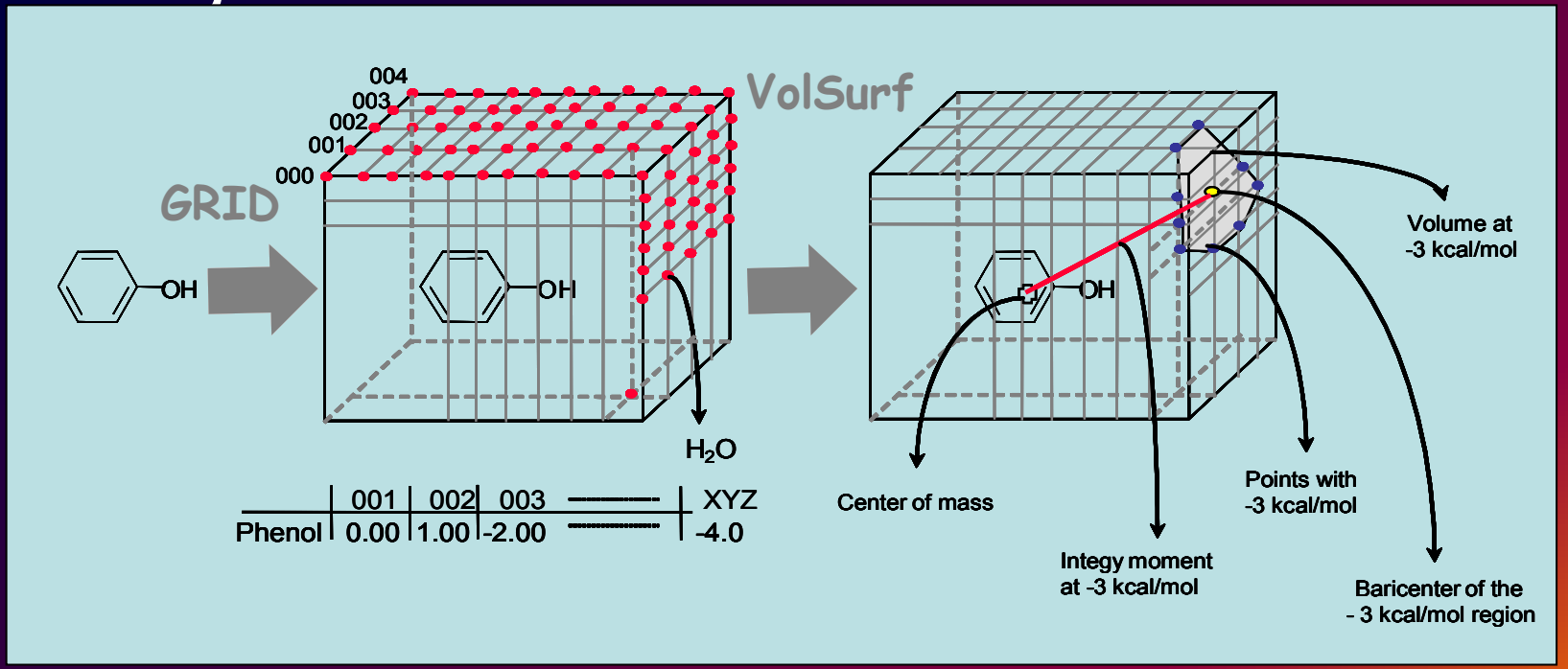
LIST OF *IN SILICO* ADMET PRODUCTS

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	acslXtreme
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, CSGenotox, 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, Kinetica

Company	Products
[illegible]	[illegible] 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

ADME Prediction

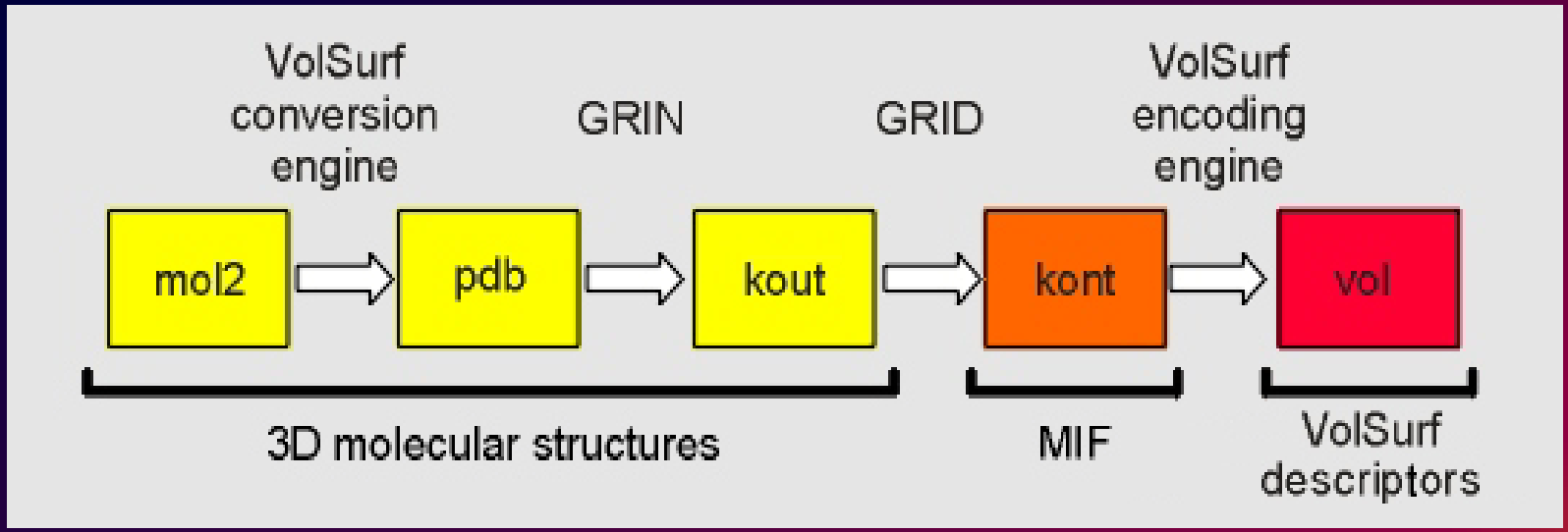
using GRID-Molecular Interaction Fields



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*

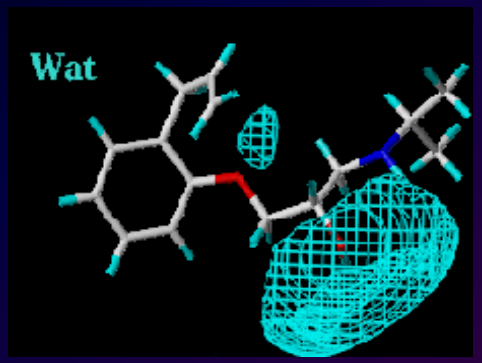
I. Zamora, T. Oprea,G. Cruciani, M. Pastor, A-L Ungell, Surface Descriptors for Protein-Ligand Affinity, J. Med. Chem., *2003, Vol. 46, No. 1*, 25-33

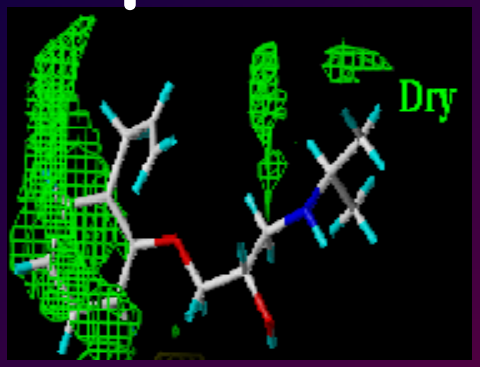
VolSurf

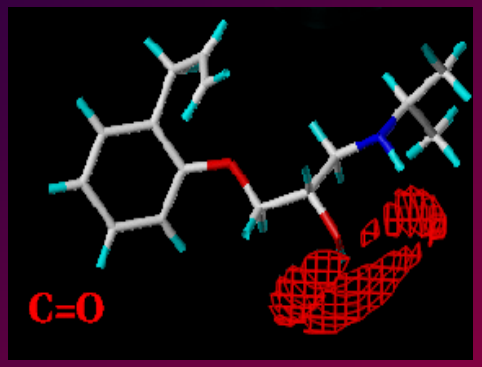


http://www.moldiscovery.com

VolSurf Descriptors





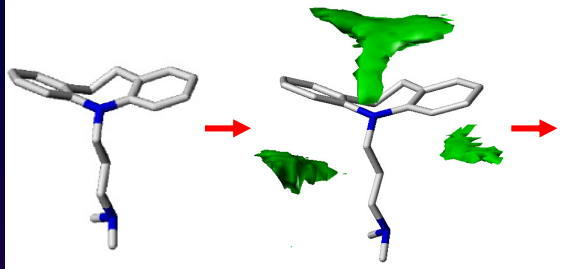


V
S
R
G
W1-W8
IW1-IW8
CW1-CW8
Emin1, Emin2,Emin3
D12, D13, D23

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

Wp1-Wp8
HB1-HB8

Multivariate Modeling with *VolSurf* Descriptors



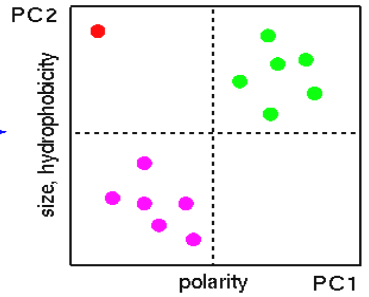
	molecular properties
molecule 1	lipophilic, steric, electronic, H-bonding
molecule n	

summarize properties in latent variables (principal properties)

multivariate statistics (PCA, PLS, PLS-DA) for pattern recognition and correlation with biologically relevant properties

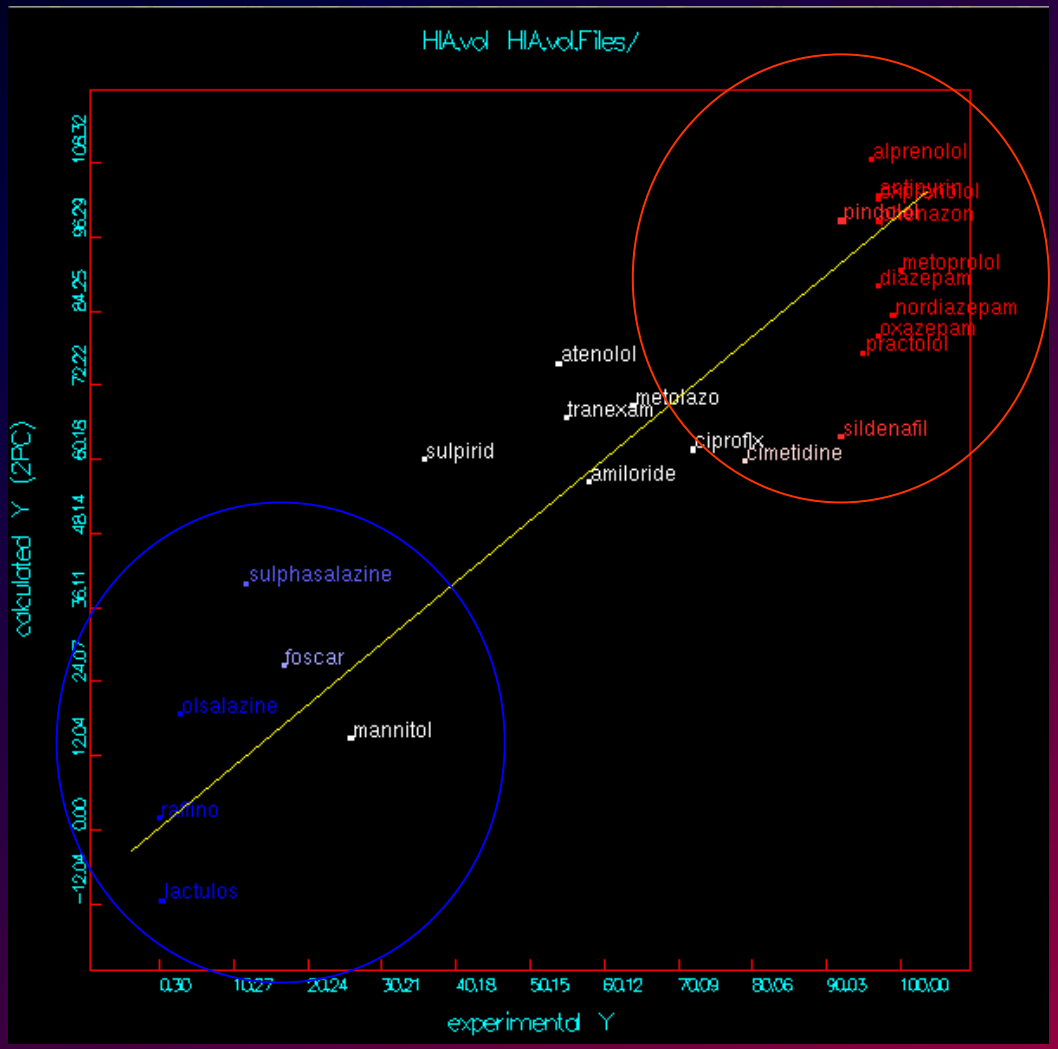
	PC1	PC2	PCn
molecule 1			
molecule n			

score plot describes systematic variation between molecules



http://www.moldiscovery.com

VolSurf in a set of passively absorbed drugs



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

Data set: 24 compounds

Probes: DRY, H_2O, O

Y: %HIA value for the 24 compounds

PLS model

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

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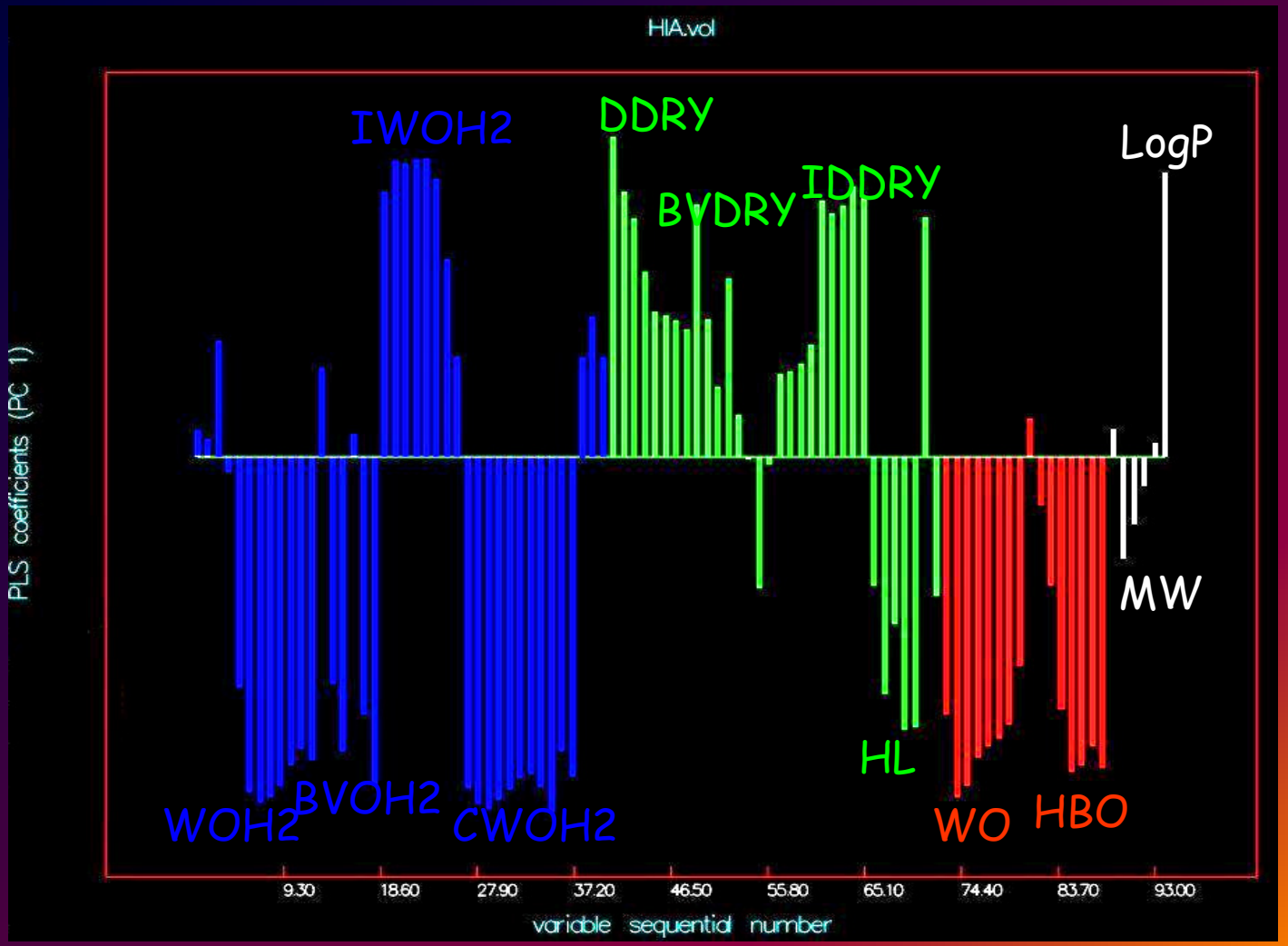
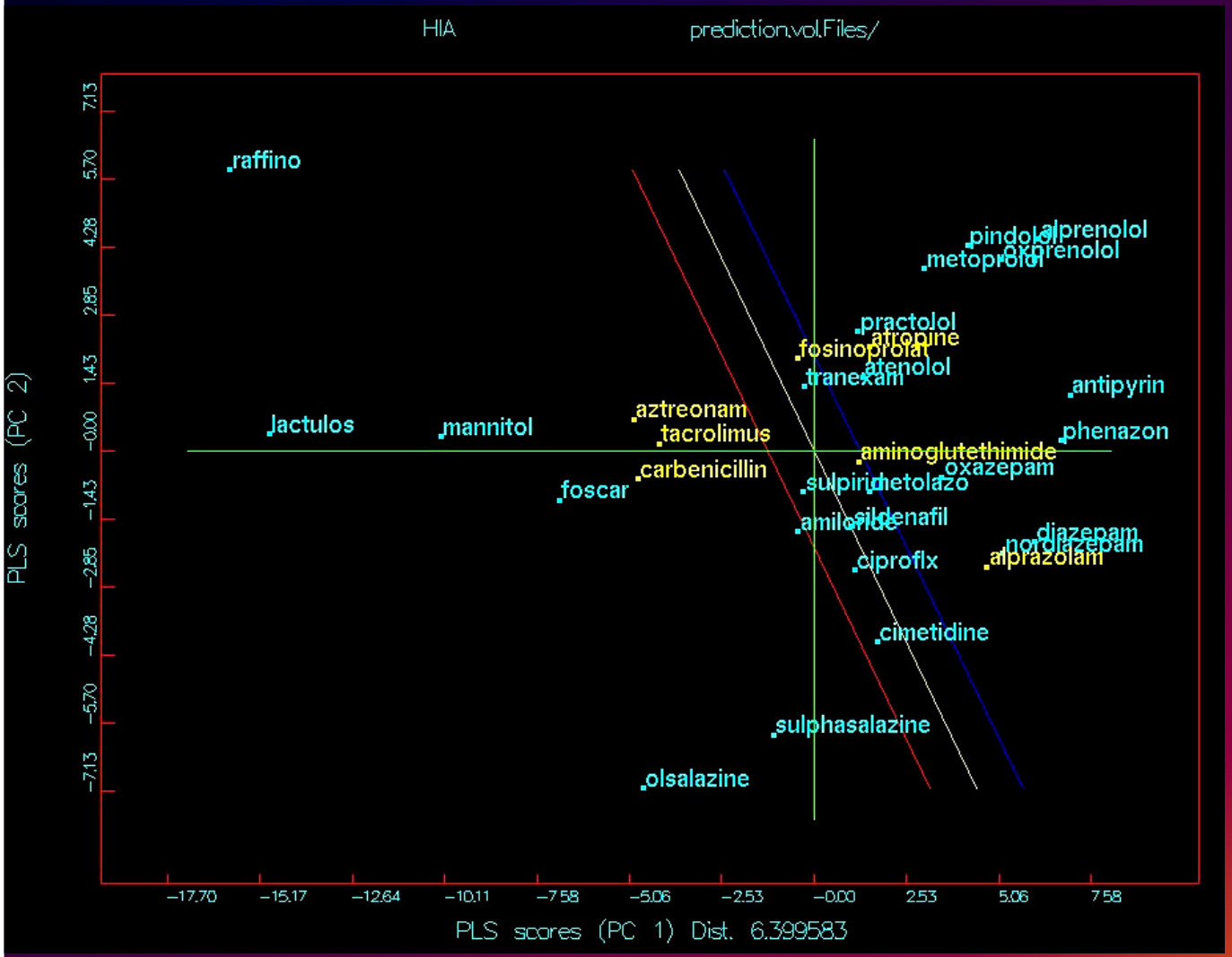
Use PLS to correlate %HIA with the VolSurf descriptors



External Prediction for % HIA



Data set: 7 compounds

Y: %HIA value ?

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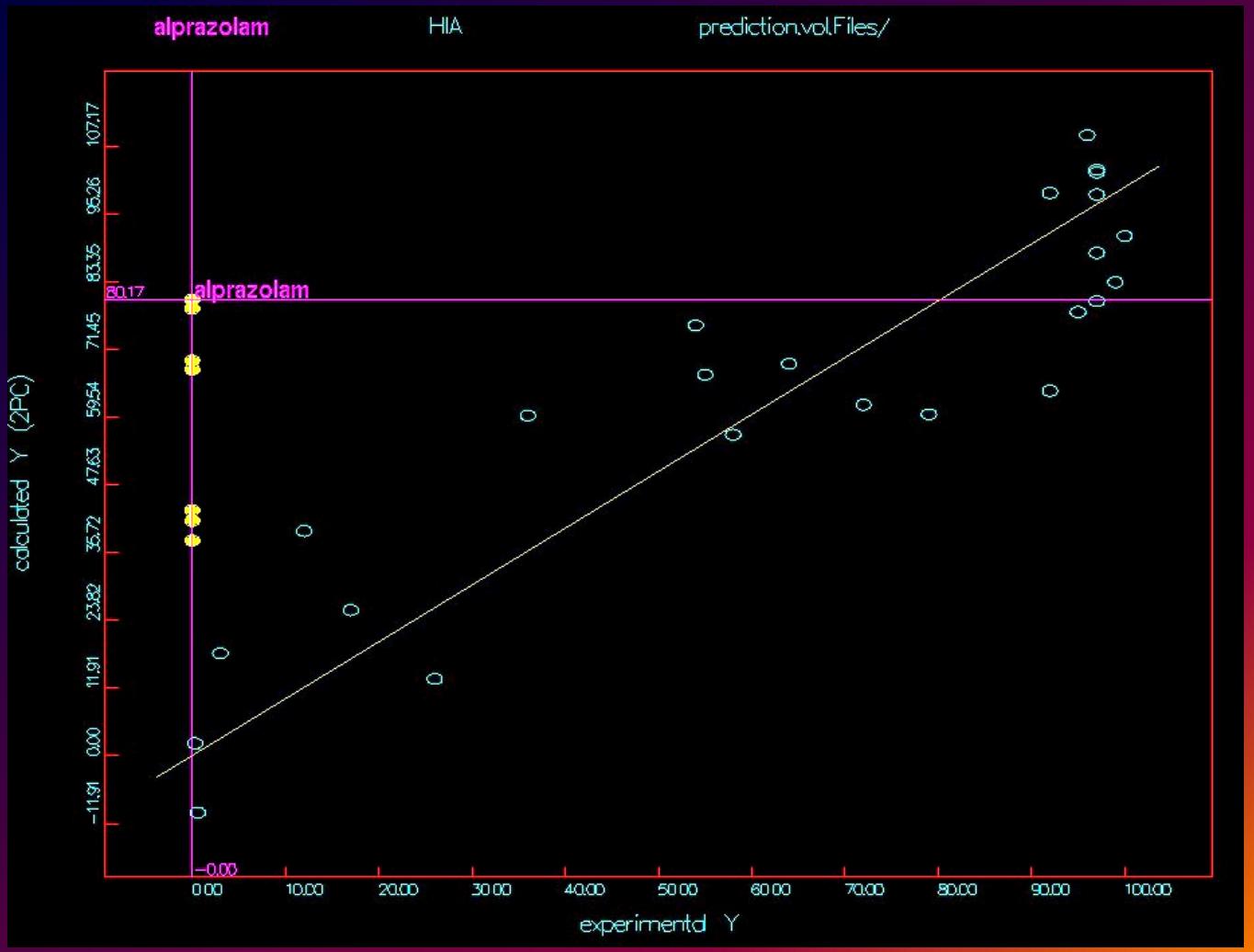
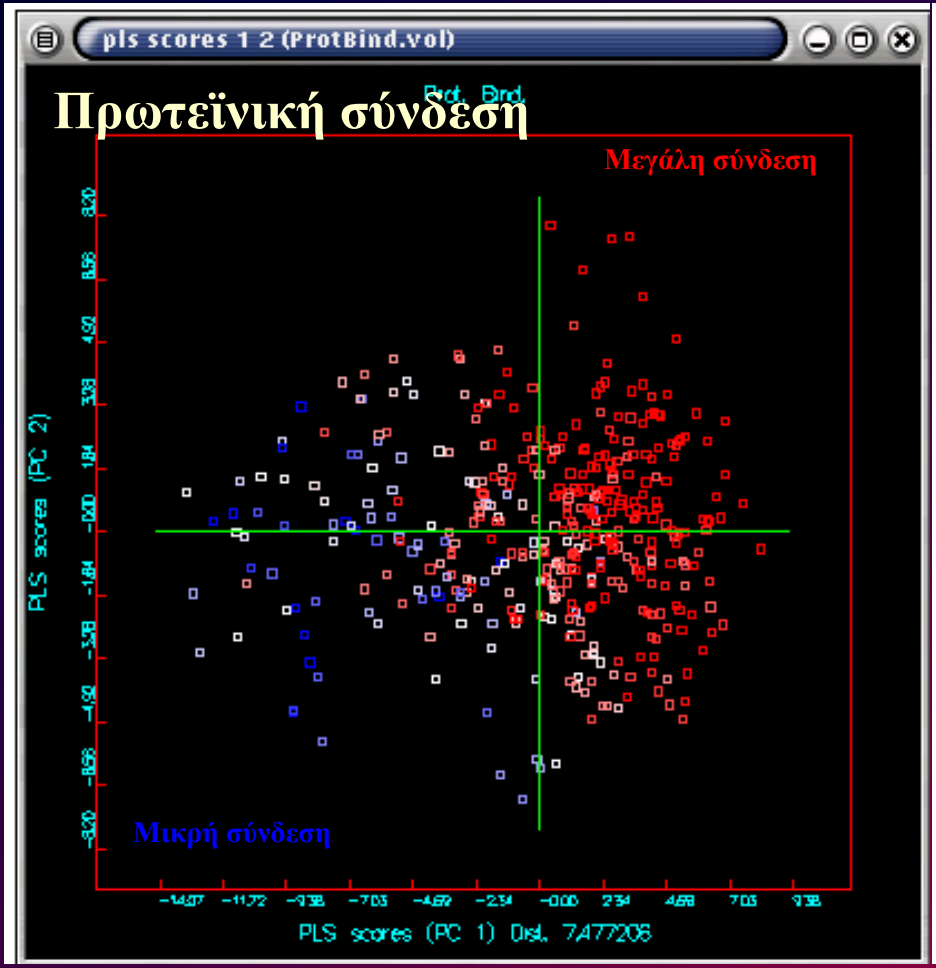
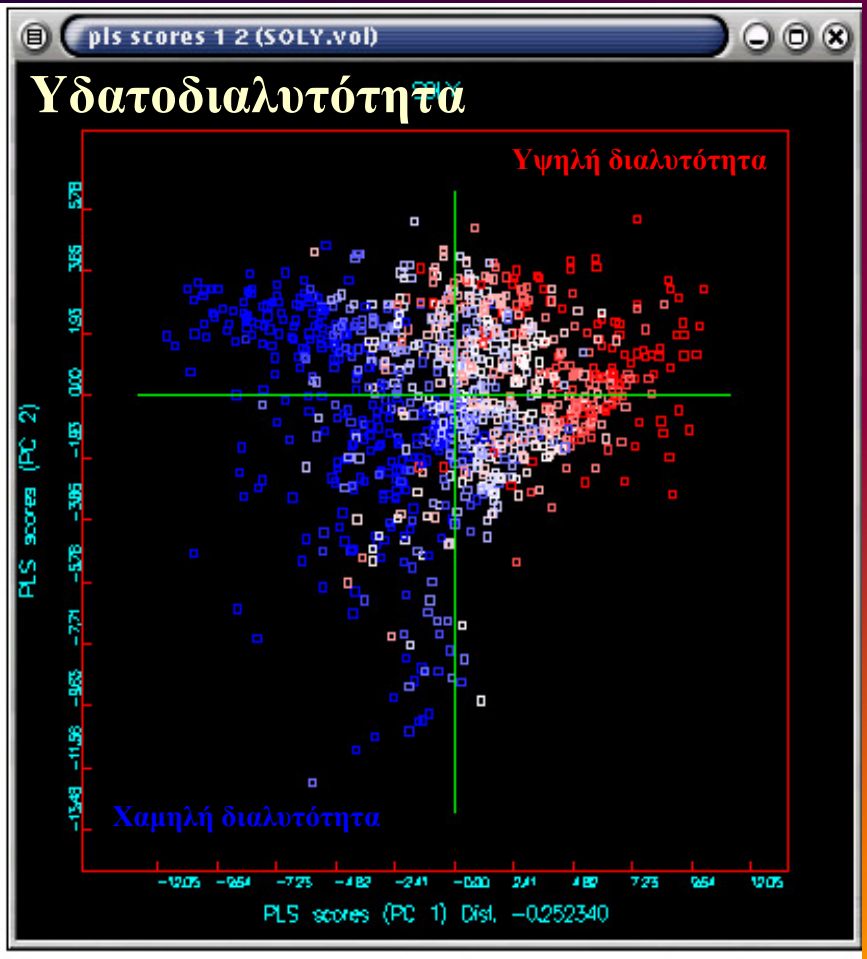
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

External Prediction for % HIA



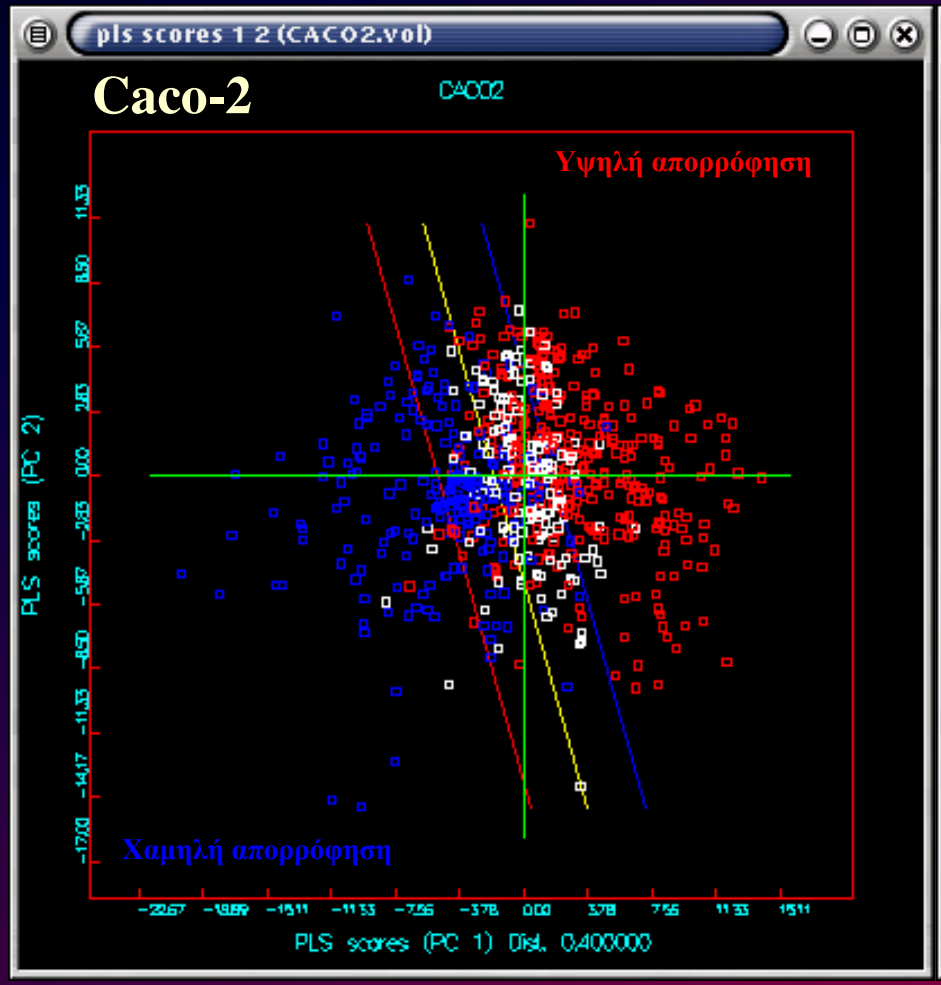
ADME Models

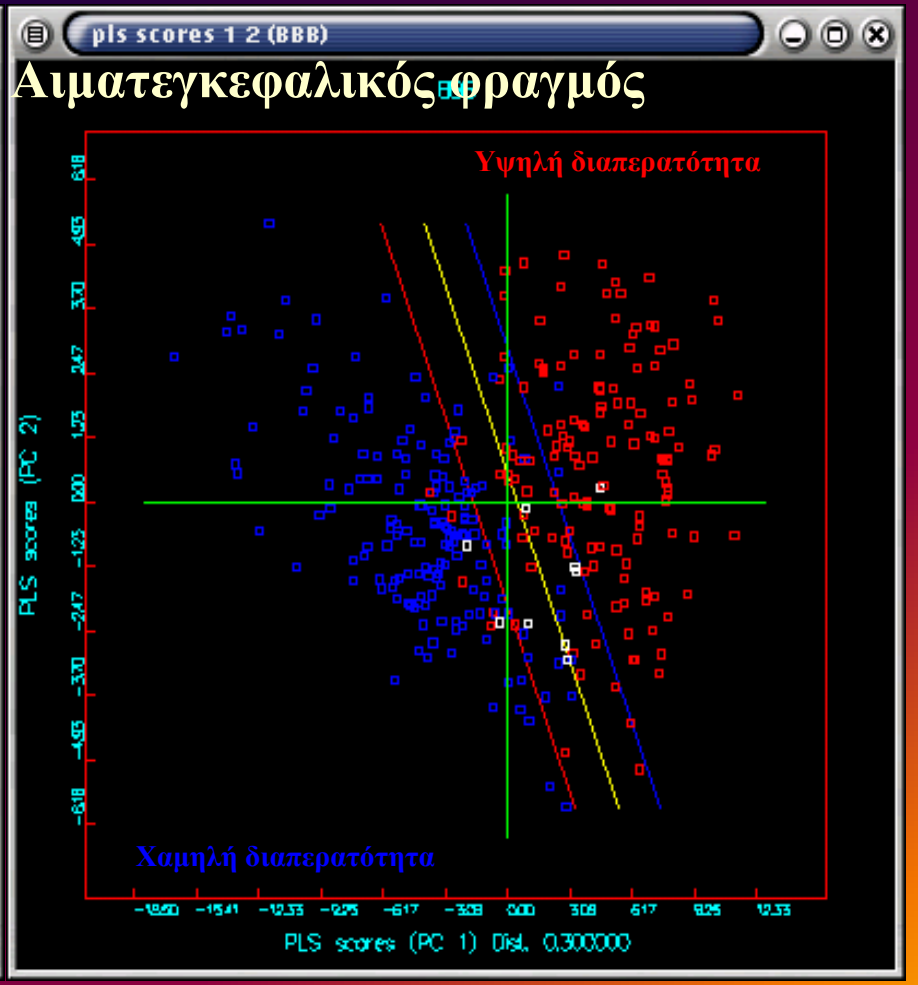




http://www.moldiscovery.com

ADME Models



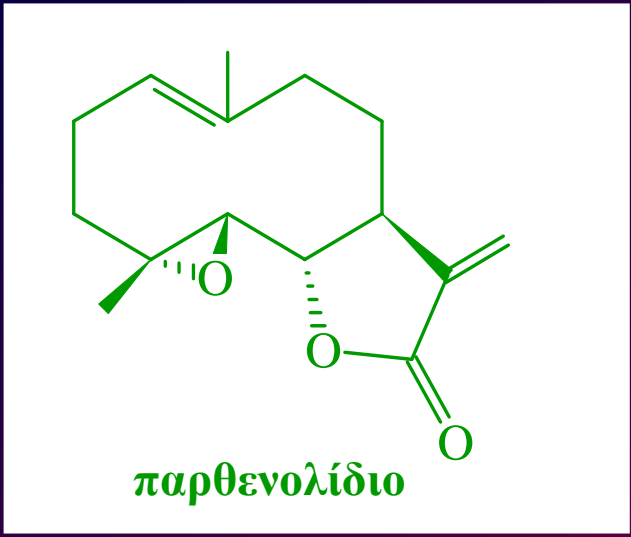


http://www.moldiscovery.com

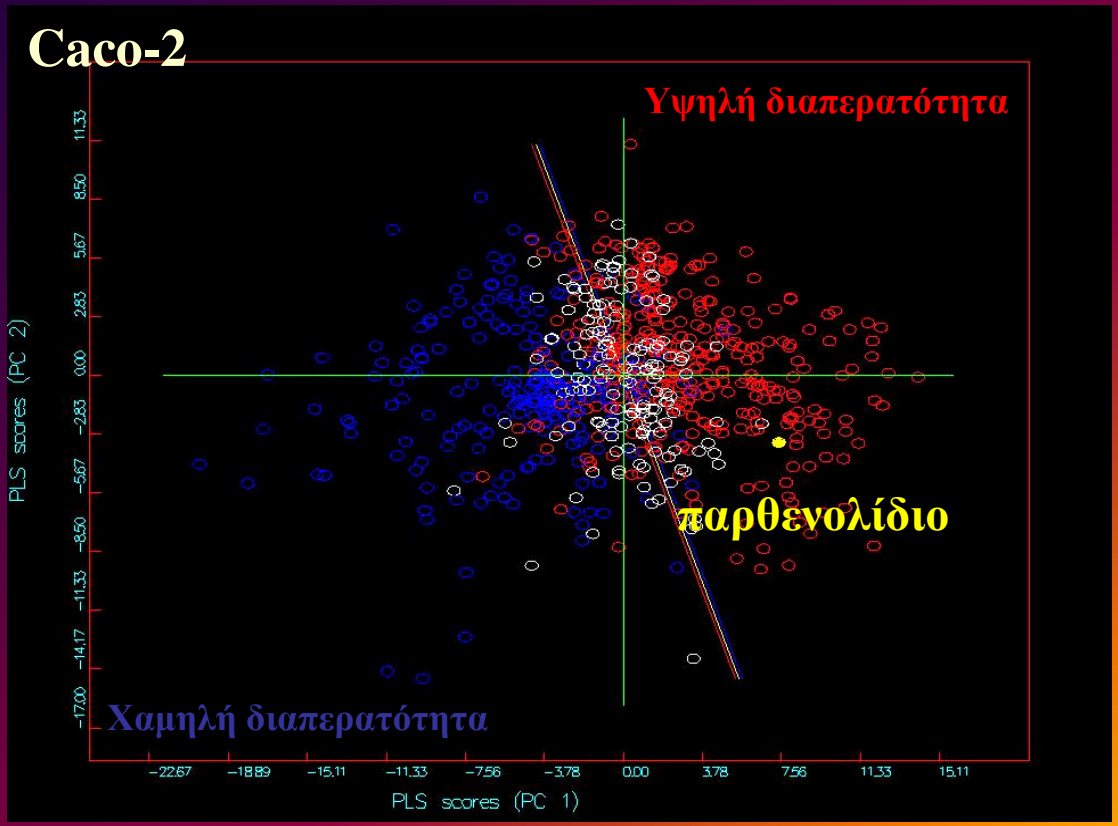
ΑΝΑΛΥΣΗ *IN SILICO* ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΩΝ ΙΔΙΟΤΗΤΩΝ ΣΕΣΚΙΤΕΡΠΕΝΙΚΩΝ ΛΑΚΤΟΝΩΝ ΜΕ ΑΝΤΙΜΥΚΗΤΙΑΣΙΚΗ ΔΡΑΣΗ

Πειραματικά δεδομένα:

•διαπερνά τα κύτταρα Caco-2



παρθενολίδιο



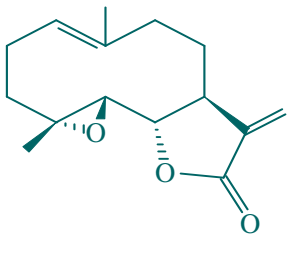
Βιβλιογραφία:

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

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

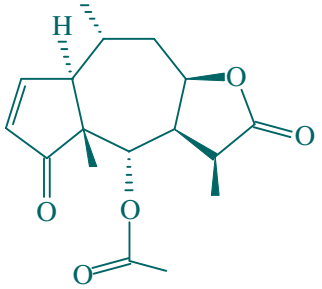
Πειραματικά δεδομένα:

- δεν εμφανίζουν πρωτεϊνική σύνδεση



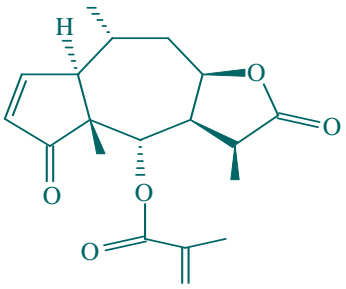
παρθενολίδιο

1



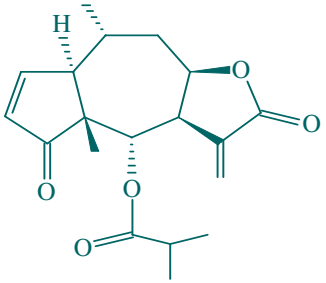
οξικός εστέρας της διυδροελεναλίνης

2



μεθακρυλικός εστέρας της διυδροελεναλίνης

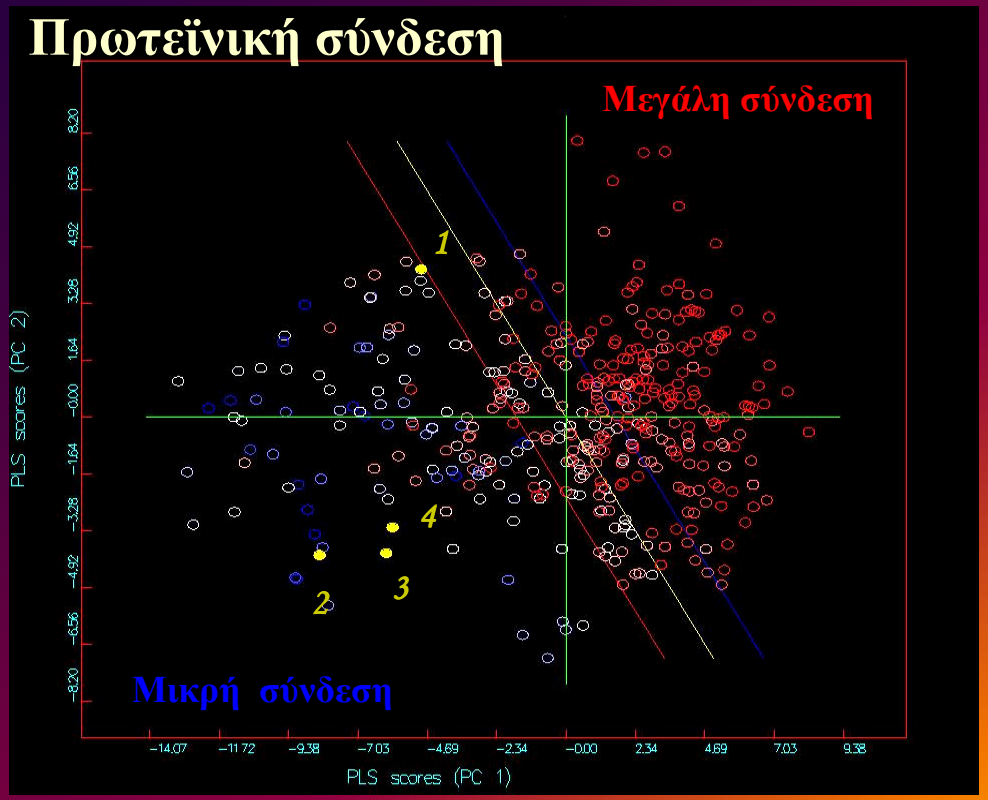
3



ισοβουτυρικός εστέρας της διυδροελεναλίνης

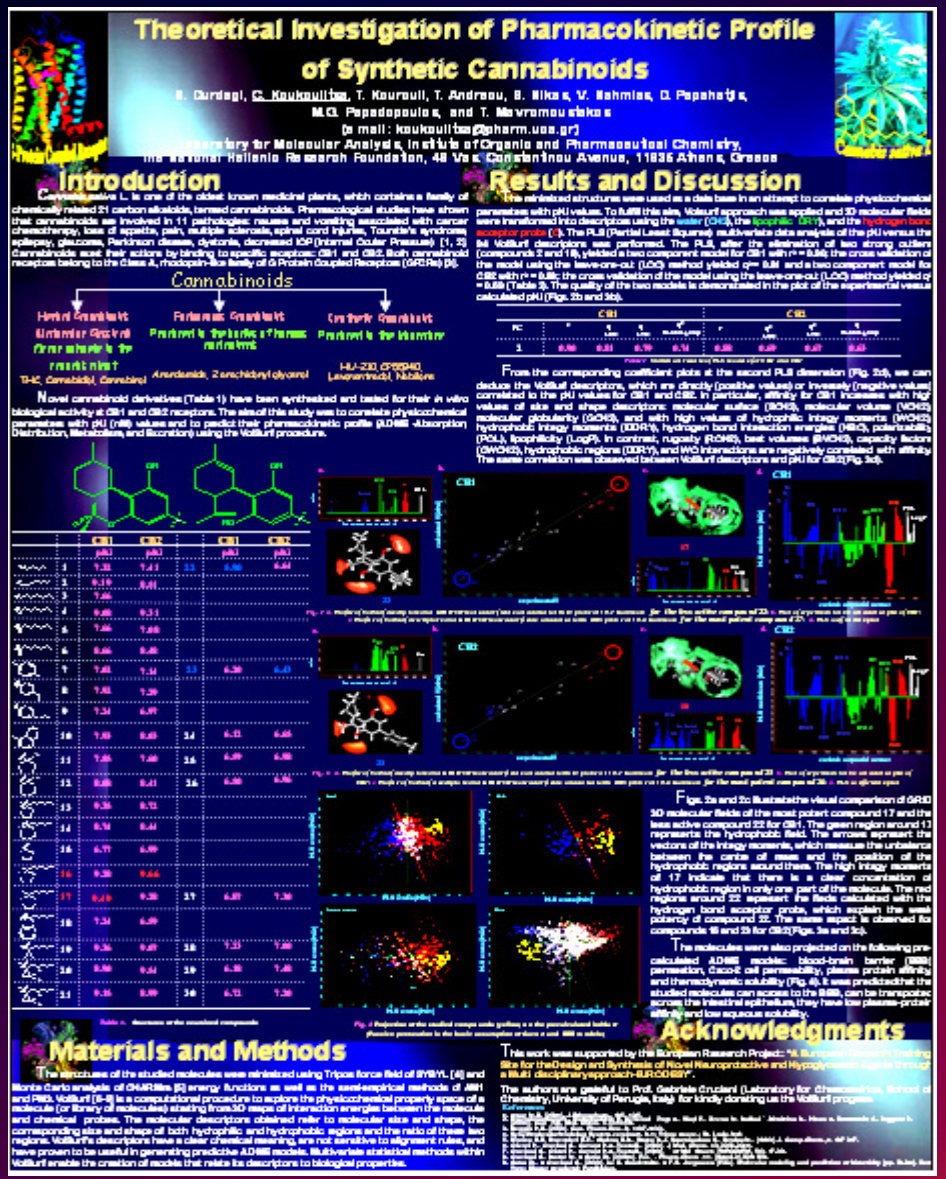
4

Πρωτεϊνική σύνδεση



Βιβλιογραφία:

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



The 16th European Symposium on Quantitative Structure-Activity Relationships & Molecular Modelling

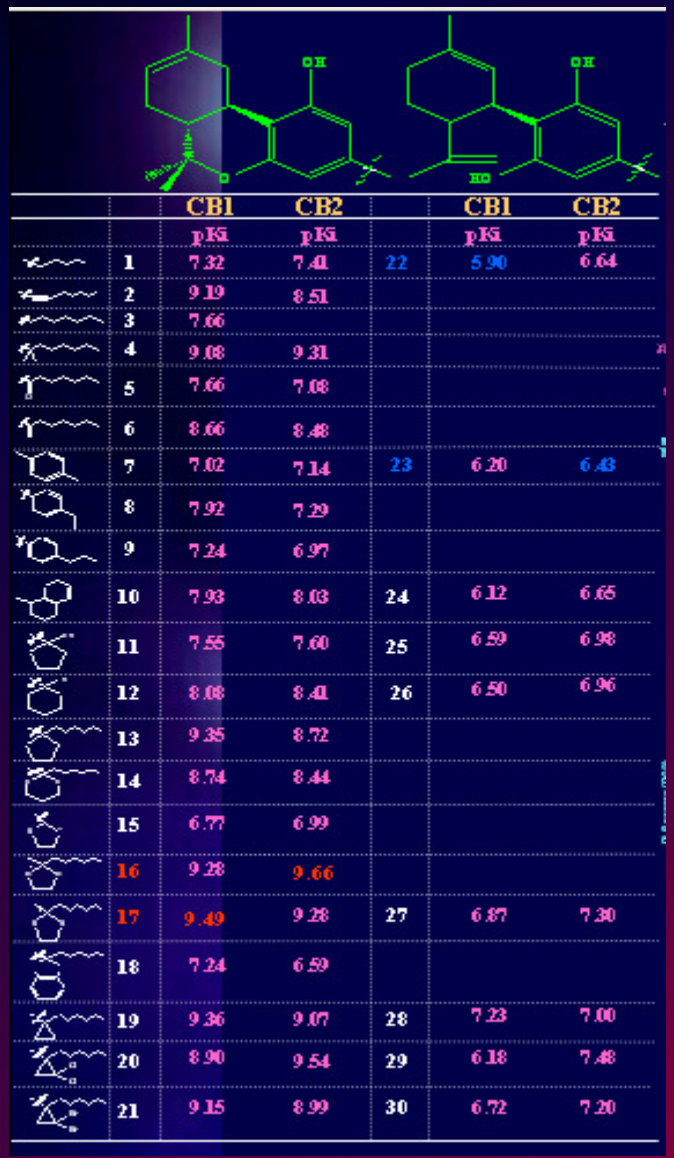
Italy, 10 - 17 September 2006

WORKSHOP

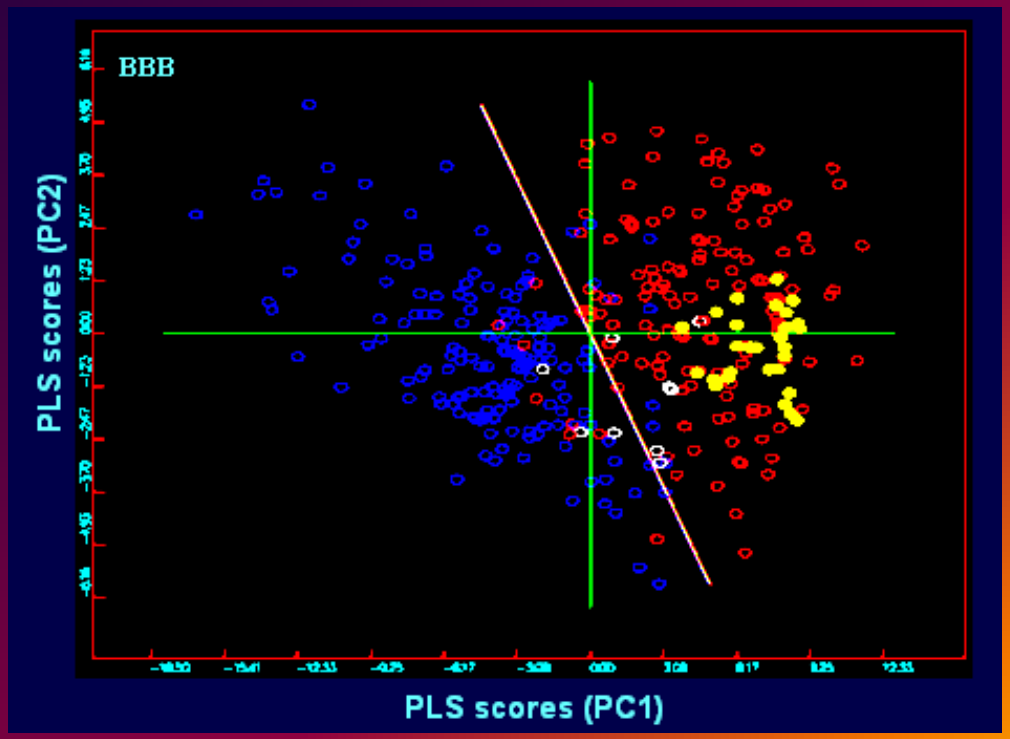
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

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 pKi	CB2 pKi		CB1 pKi	CB2 pKi
	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	7.48
	21	9.15	8.99	30	6.72	7.20

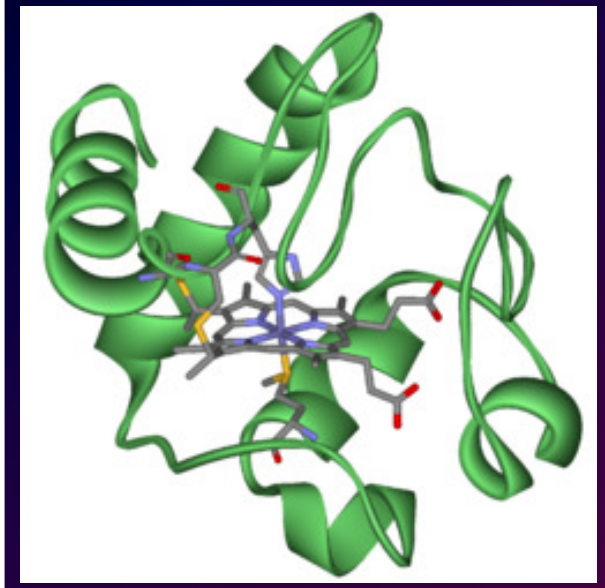


WORKSHOP

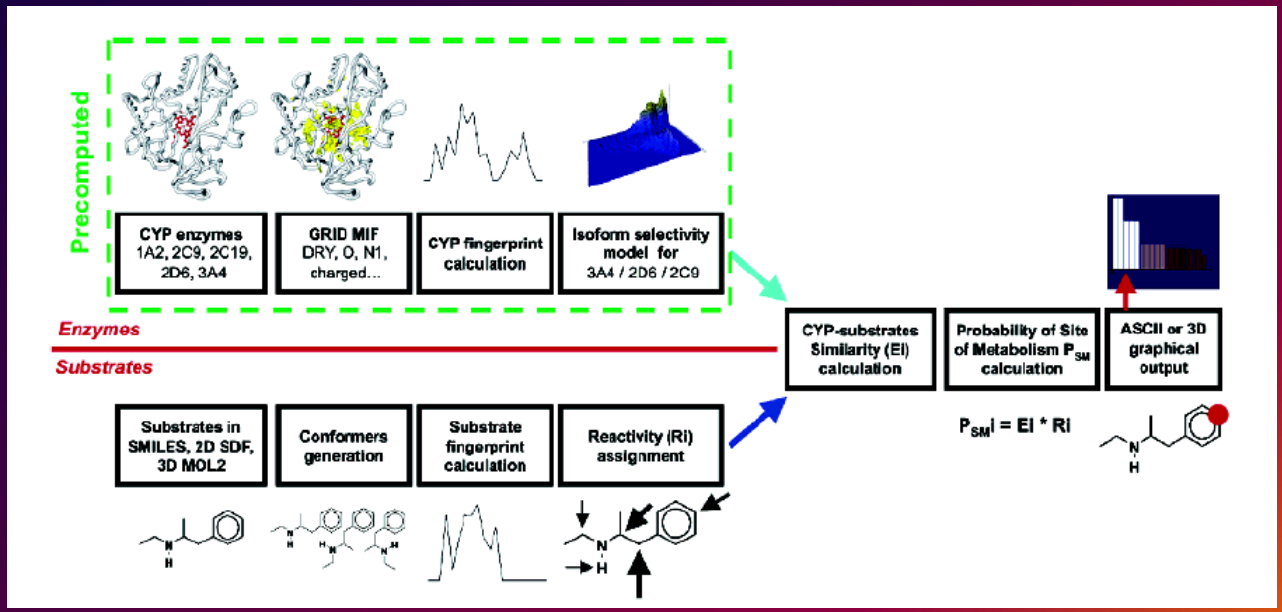
ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

MetaSite

Μεταβολισμός



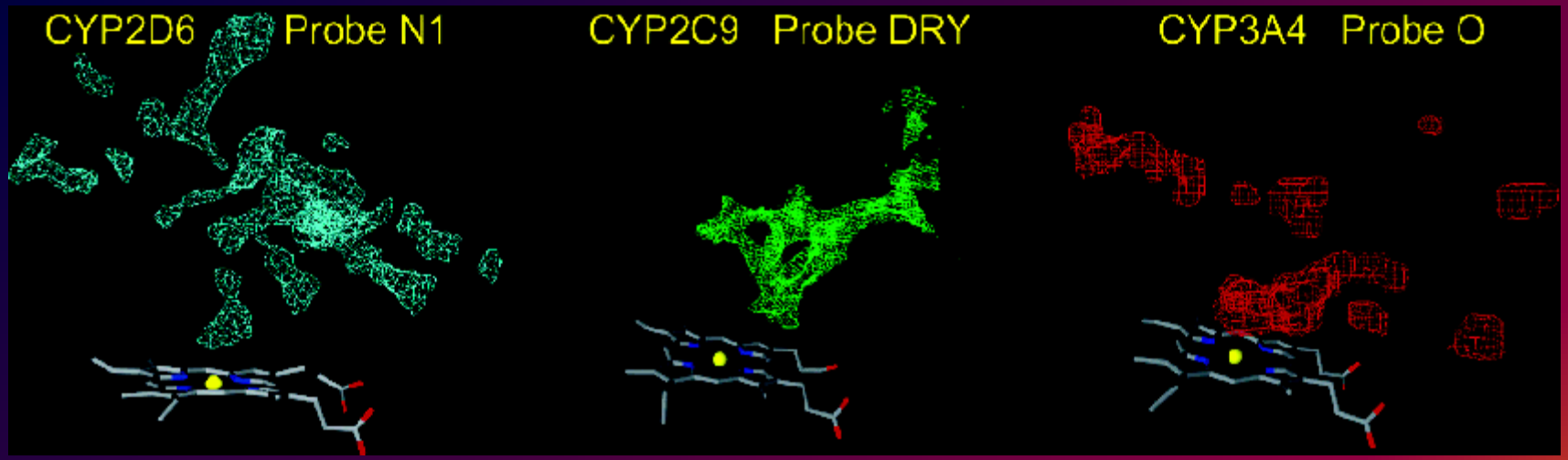
Κυττόχρωμα P450



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

http://www.moldiscovery.com

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

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

MetaSite

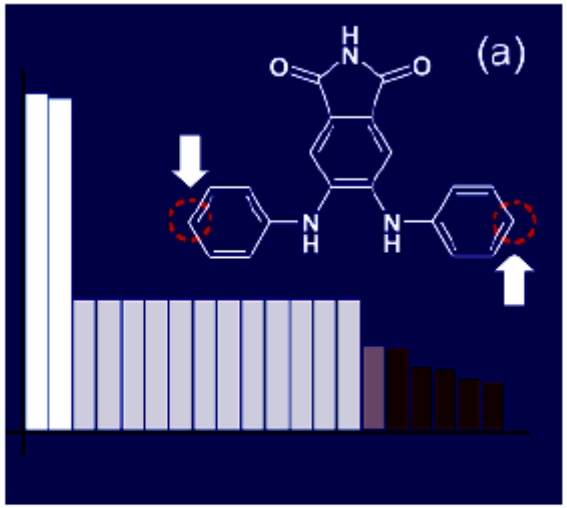


Figure 8. (a) The predicted sites of oxidation are ranked according to probability values and reported in the histogram. White bars highlight the higher probability values that correspond to the para position of the molecule (indicated by white arrows in the 2D structure). (b) Compound CGP53353, a metabolically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

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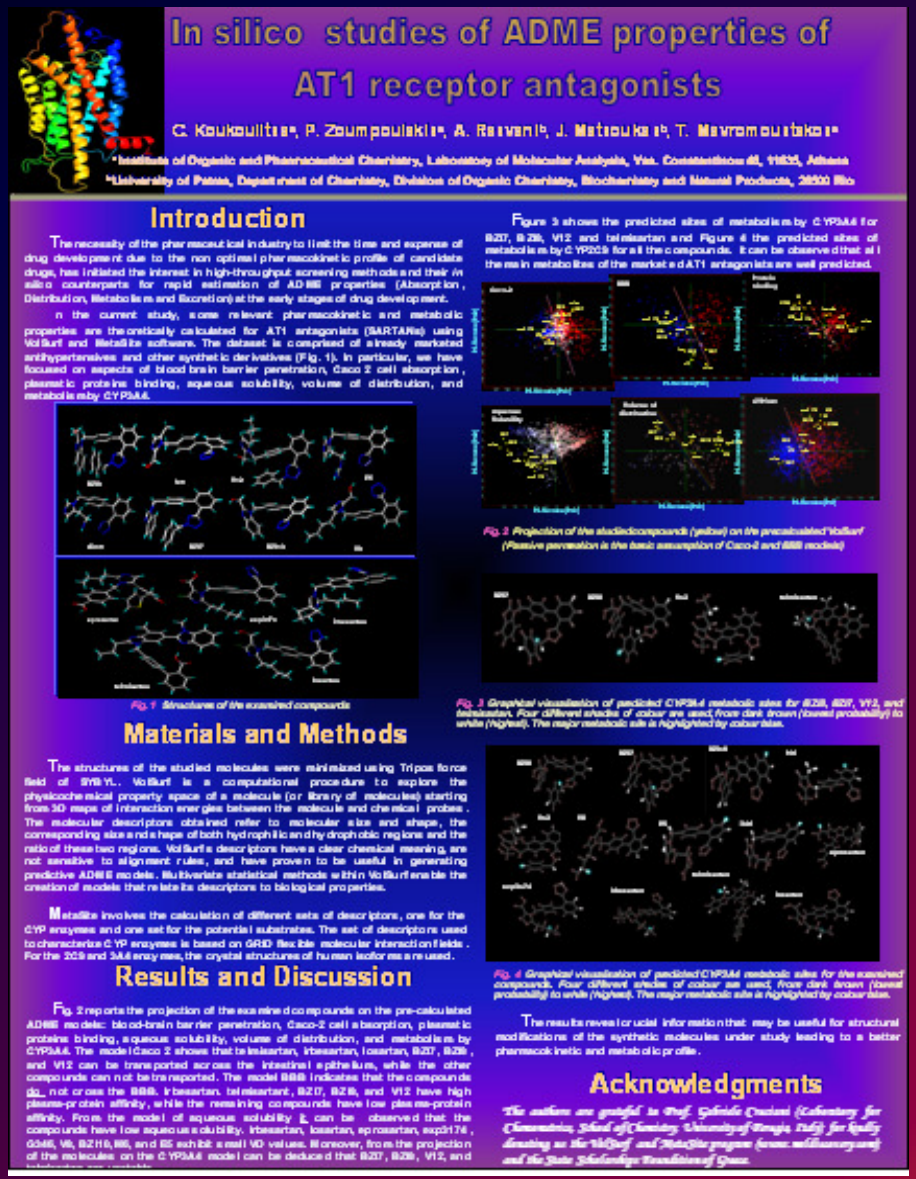

In silico studies of ADME properties of AT1 receptor antagonists

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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 (SARTANs) using VolSurf and MetaSite softwares. 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, plasmatic protein binding, aqueous solubility, volume of distribution, and metabolism by CYP3A4.

Fig. 1 Structures of the examined compounds

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 the descriptors to biological properties.

MetaSite 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 2C9 and 3A4 enzymes, the crystal structures of human isoforms are used.

Results and Discussion

Fig. 2 reports the projection of the examined compounds on the pre-calculated ADME models: blood-brain barrier penetration, Caco-2 cell absorption, plasmatic proteins binding, aqueous solubility, volume of distribution, and metabolism by CYP3A4. The model Caco 2 shows that telmisartan, irbesartan, losartan, BZ37, BZ38, 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. Irbesartan, telmisartan, BZ37, BZ38, 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. Irbesartan, losartan, eprosartan, exp3174, GR48, V8, BZH8, R6, and E5 exhibit small VD values. Moreover, from the projection of the molecules on the CYP3A4 model can be deduced that BZ37, BZ38, V12, and

Figure 3 shows the predicted sites of metabolism by CYP3A4 for BZ37, BZ38, V12 and telmisartan and Figure 4 the predicted sites of metabolism by CYP2C9 for all the compounds. It can be observed that all the main metabolites of the marketed AT1 antagonists are well predicted.

Fig. 2 Projection of the studied compounds (yellow) on the pre-calculated VolSurf (Passive permeation is the basic assumption of Caco-2 and BBB models)

Fig. 3 Graphical visualization of predicted CYP3A4 metabolic sites for BZ38, BZ37, V12, and telmisartan. Four different shades of colour are used, from dark brown (lowest probability) to white (highest). The major metabolic site is highlighted by colour blue.

Fig. 4 Graphical visualization 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.

The results reveal crucial information that may be useful for structural modifications of the synthetic molecules under study leading to a better pharmacokinetic and metabolic profile.

Acknowledgments

The authors are grateful to Prof. Gabriele Cruciani (Laboratory for Chemometrics, School of Chemistry, University of Perugia, Italy) for kindly donating us the VolSurf and MetaSite program (www.moldiscovery.com) and the State Scholarships Foundation of Greece.

ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ

8ο Διεθνές Συνέδριο

Ιατρική Χημεία:

Σχεδιασμός και Ανάπτυξη Φαρμακευτικών Προϊόντων

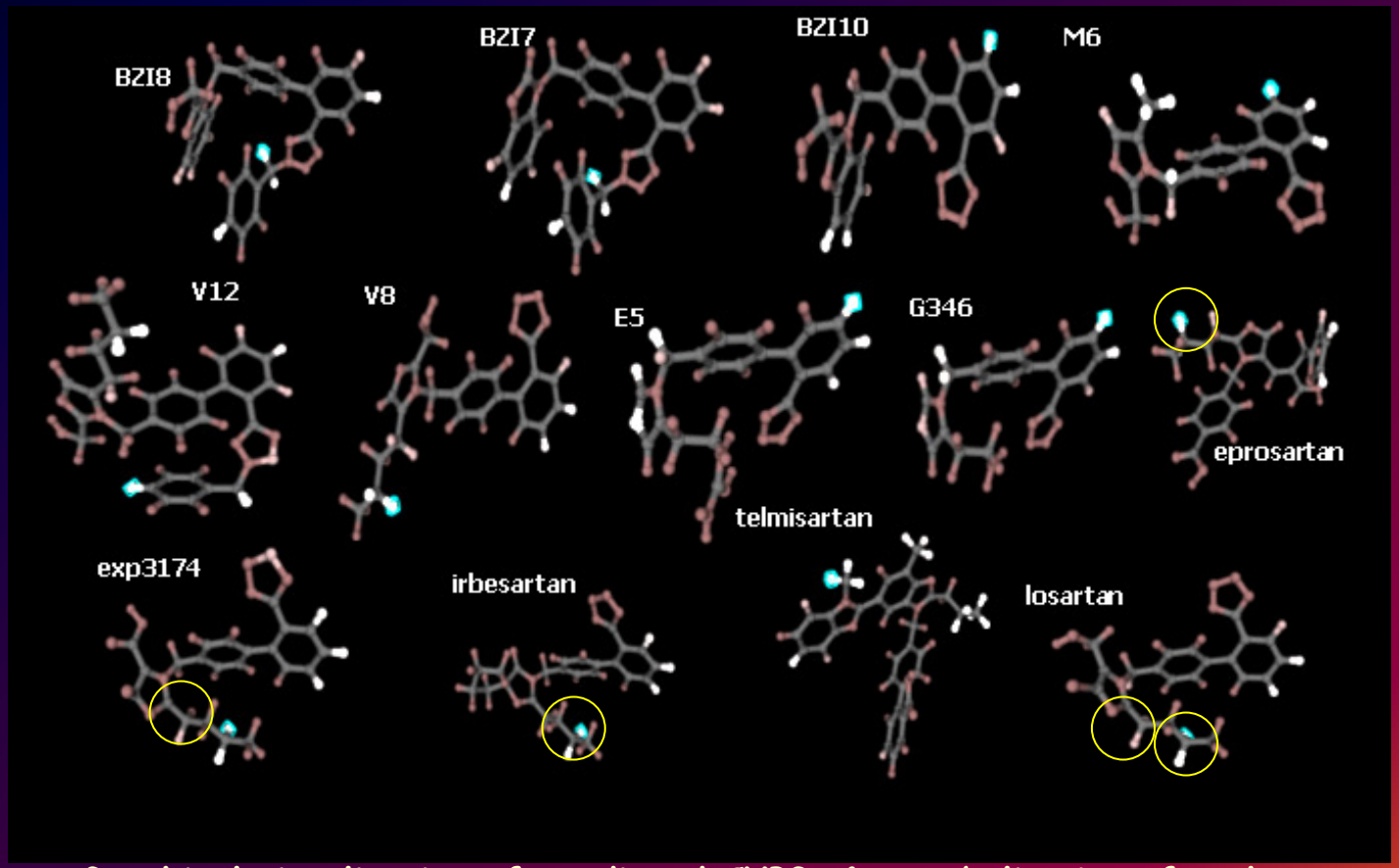
Πάτρα, 15-17 Μαρτίου 2007

WORKSHOP

ΣΧΕΔΙΑΣΜΟΥ ΦΑΡΜΑΚΟΥ

In Silico Studies of ADME Properties of AT1 antagonists

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

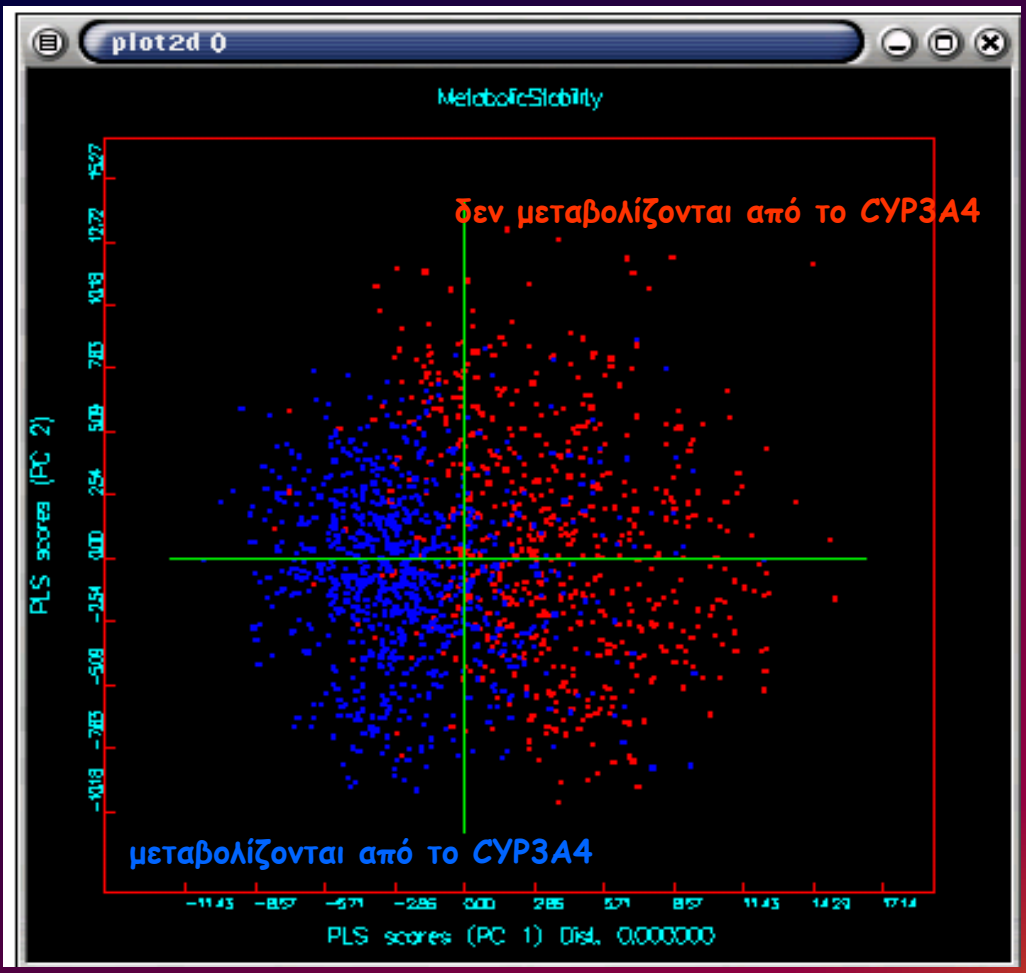


- CYP2C9
- CYP3A4

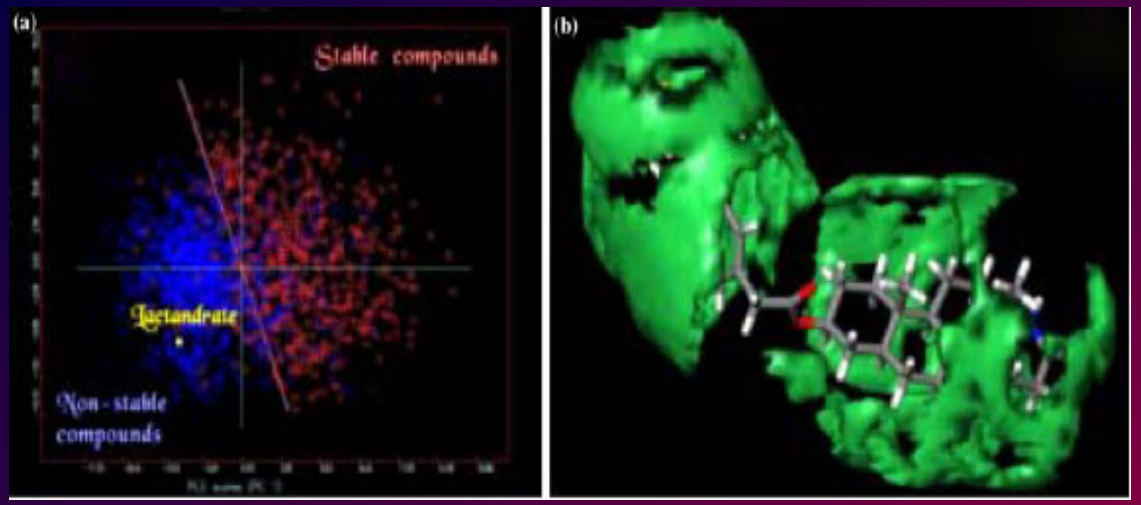
All the main AT1 metabolites of the market are well predicted

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



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Lactandrate: a D-homo-aza-androsterone alkylator in the treatment of breast cancer

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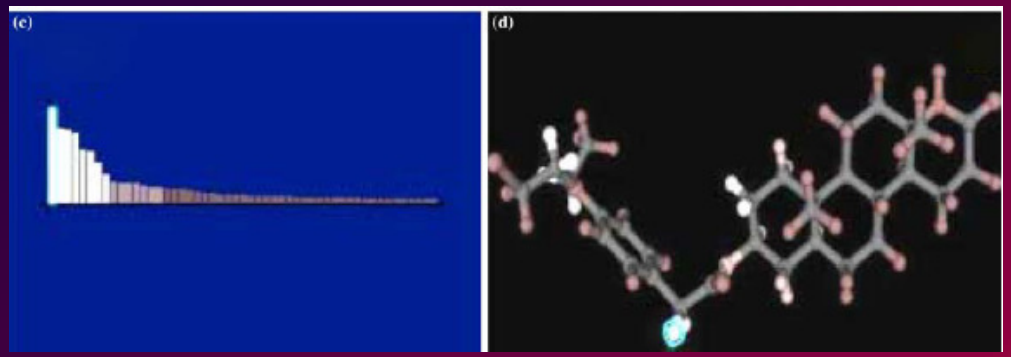

The 18th European Symposium on Quantitative Structure-Activity Relationships & Molecular Modelling

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