

**S-IN Soluzioni
Informatiche**

for Chemistry and Pharmaceutical Chemistry



ANGELINI

***In Silico* Lead Discovery and Lead Optimization Strategies Applied to PARP-1 and PPAR- γ Receptors**

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for Medical Chemistry

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Outline

- Materials and methods
- Physiological role
- **LEAD DISCOVERY PHASE**
 - *In silico* screening
 - Model preparation
 - Results
- **LEAD OPTIMIZATION PHASE**
 - Ligand-protein binding affinities prediction
 - Methods
 - Results

Materials and Methods

- Modeling tools

- **SCHRÖDINGER**

- GLIDE
 - LIGPREP
 - MACROMODEL
 - PRIME
 - XP VISUALIZER
 - LIAISON
 - MCPPro+

- Statistical tools

- **UMETRICS**

- SIMCA-P+
 - MODDE

- Other

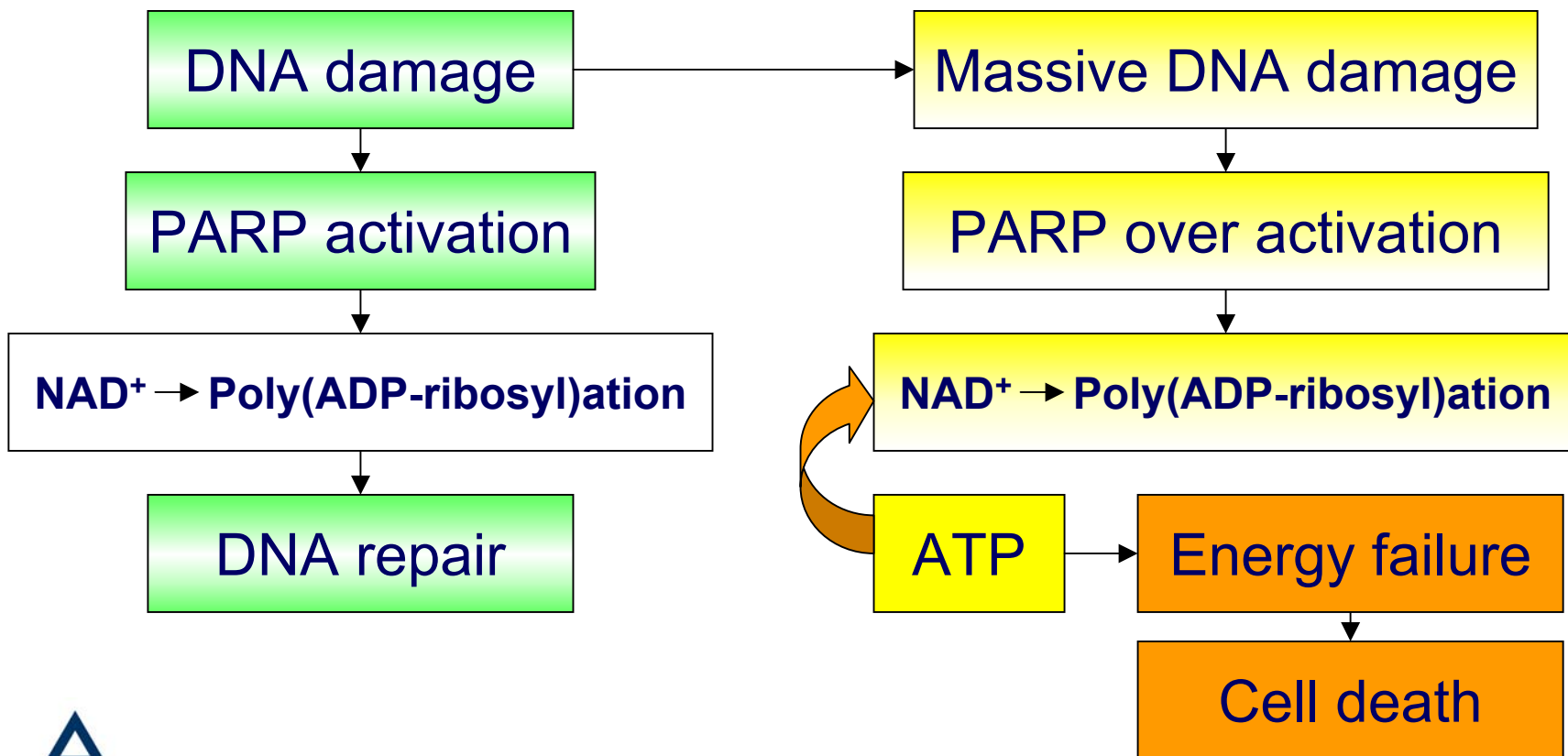
- **TALETE**

- DRAGON



Physiological role: PARP

- Poly(ADP-ribose) polymerase - involved in genomic repairs
- The Suicide Hypothesis



Physiological role: PPARs

Nuclear receptor superfamily of ligand-activated transcription factors

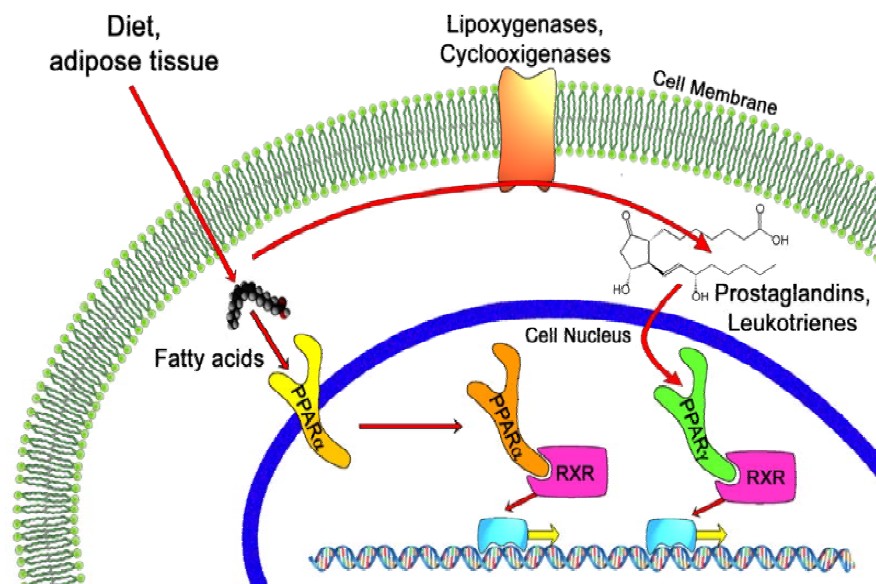
PPARs: family of 3 nuclear receptors (α , γ and δ)

Inadequate activation or inactivation is linked to

type 2 diabetes
cardiovascular diseases
obesity
dyslipidemia

PPAR- γ :

- key regulator of adipocyte differentiation and glucose homeostasis
- agonists improve insulin resistance



Model Preparation

PARP-1

3 structures

PPAR- γ

12 structures
8 open and 4 close form

Analysis of exp. structures

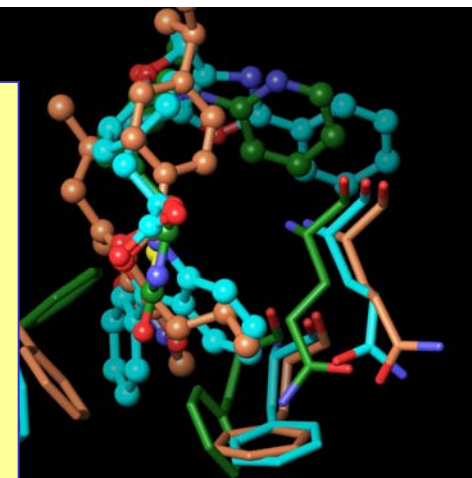
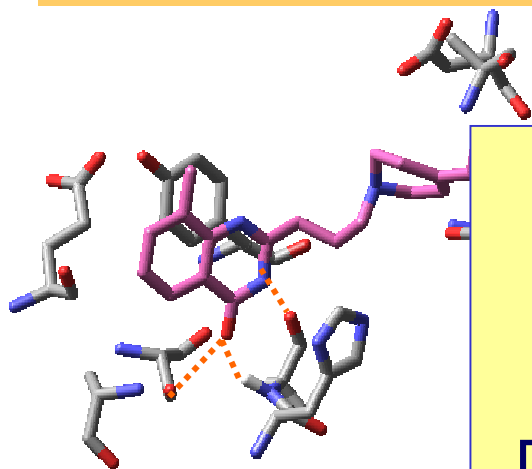
1 active site geometry

3 active site geometry
2 open and 1 close form

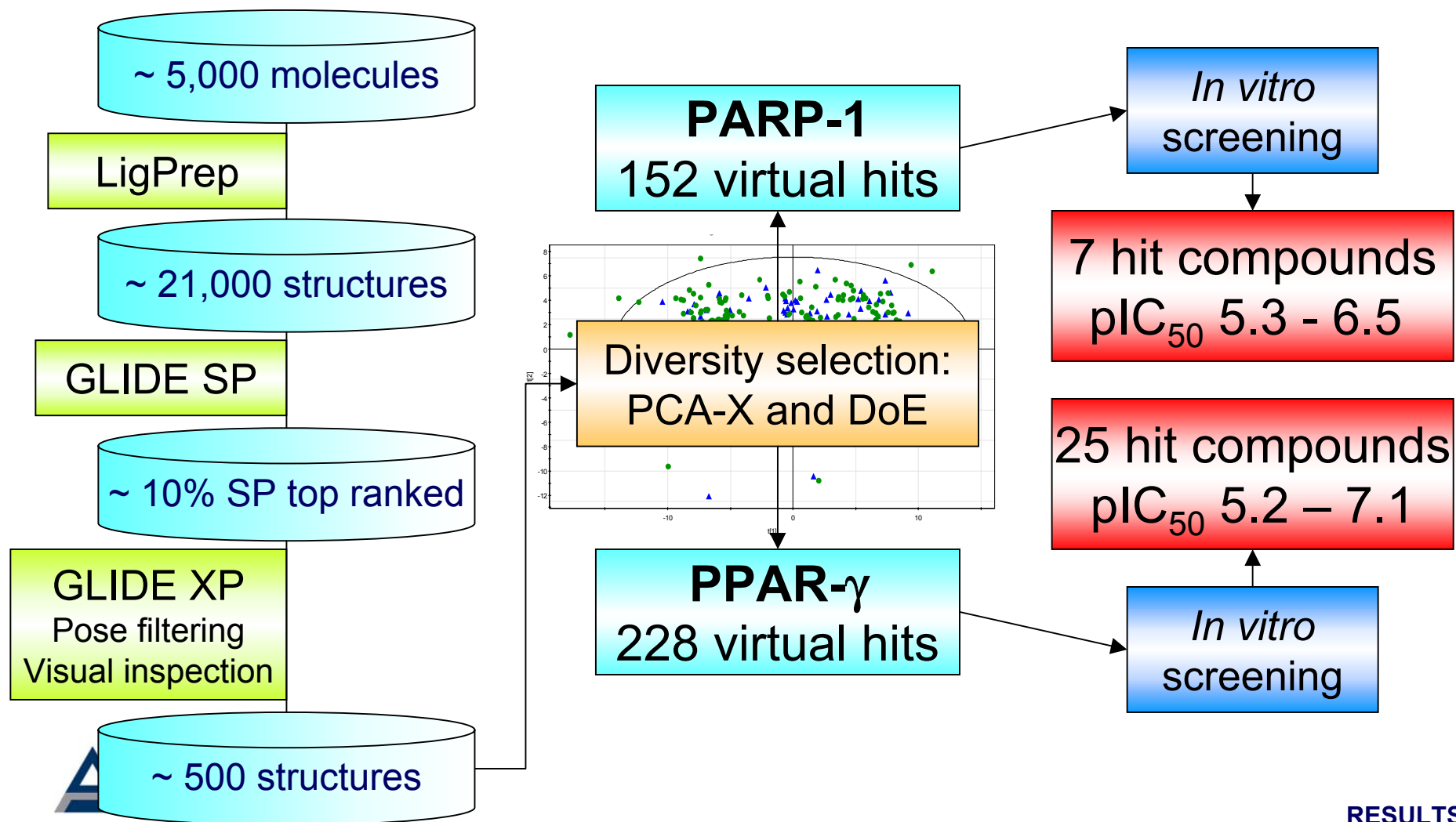
Cross-docking

Ensemble-docking

Different receptor structures
Different docking parameters



Virtual screening Results



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Ligand-protein binding affinities prediction methods

- **Docking scores**

- **GLIDE** SP and XP scores
- **XP Visualizer** descriptors

- **Free Energy Calculations**

- **LIAISON**: LIA (Linear Interaction Approximation)

$$\Delta G = \alpha(U_{\text{VDW bound}} - U_{\text{VDW free}}) + \beta(U_{\text{el bound}} - U_{\text{el free}}) + \gamma(U_{\text{cavity bound}} - U_{\text{cavity free}})$$

- **MCPRO+**: LRM (Linear Response)
- **PRIME**: MM-GBSA prediction

$$\Delta G = G_{\text{complex}} - (G_{\text{protein}} + G_{\text{ligand}})$$

$$G = E_{\text{MM}} + G_{\text{SGB}} + G_{\text{Non polar}}$$

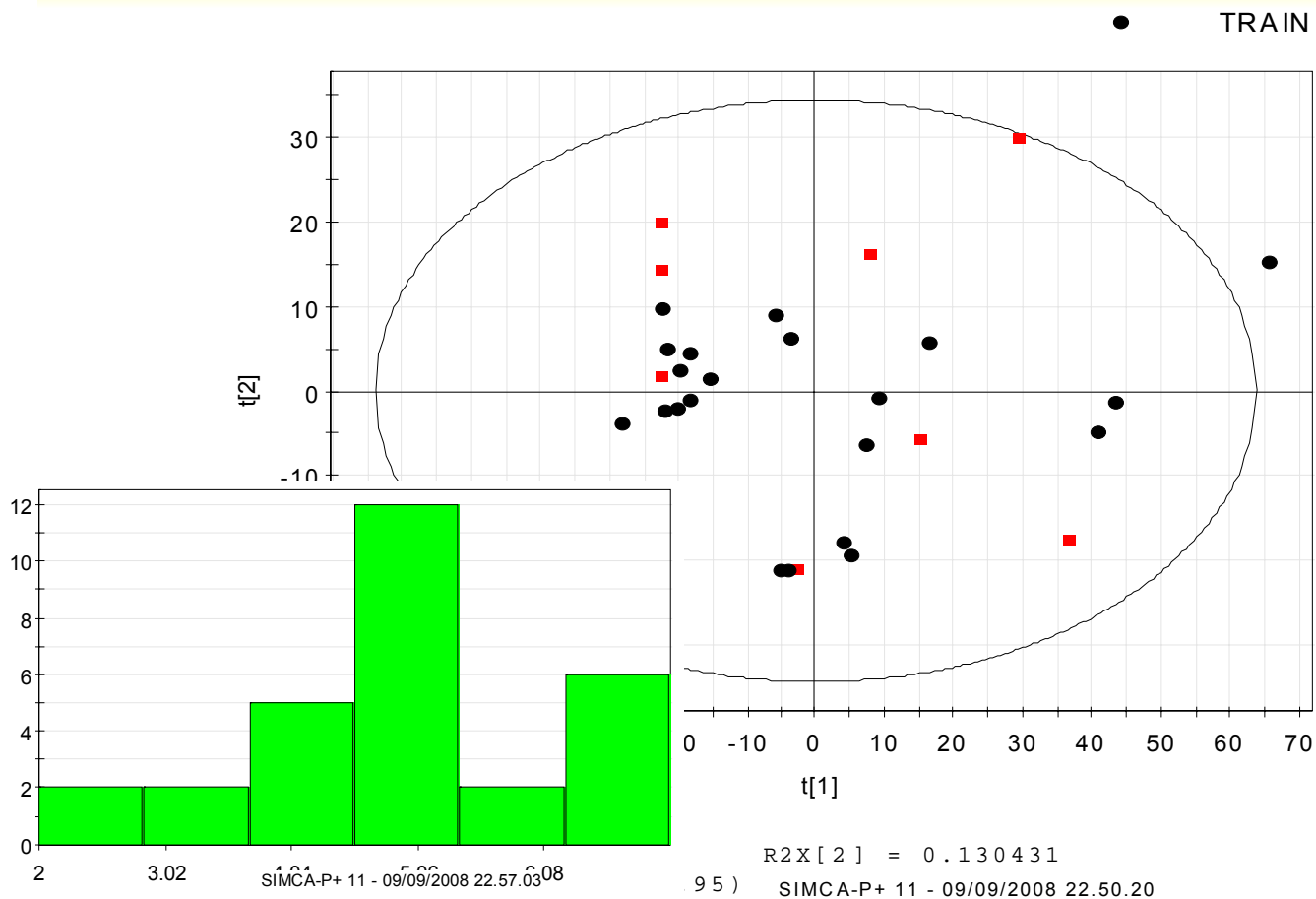
- **Classical QSAR approach**

- **DRAGON** molecular descriptors and PLS analysis



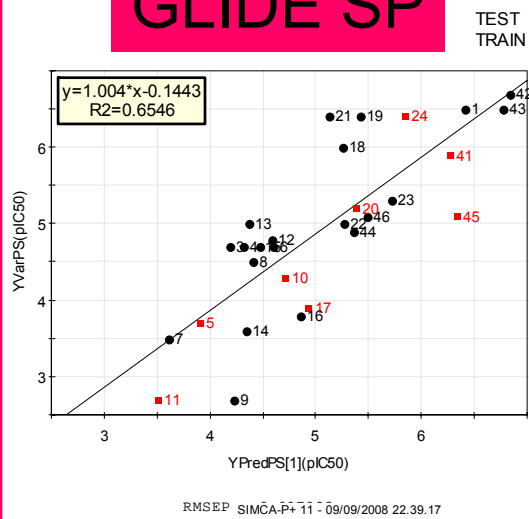
PARP-1

29 PARP-1 inhibitors Training (21) and test (8) set



PARP-1

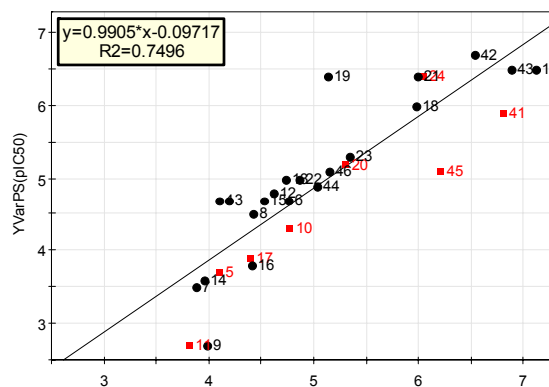
GLIDE SP



$R^2= 0.63$
 $Q^2= 0.60$
SDEP = 0.70

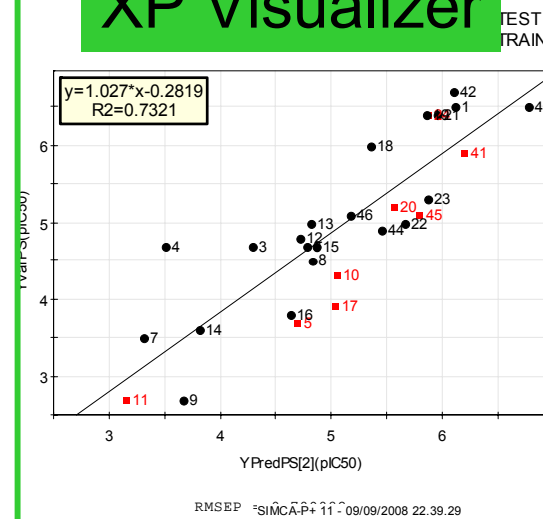
$R^2= 0.75$
 $Q^2= 0.63$
SDEP = 0.71

LIAISON TEST TRAIN



LIAISON

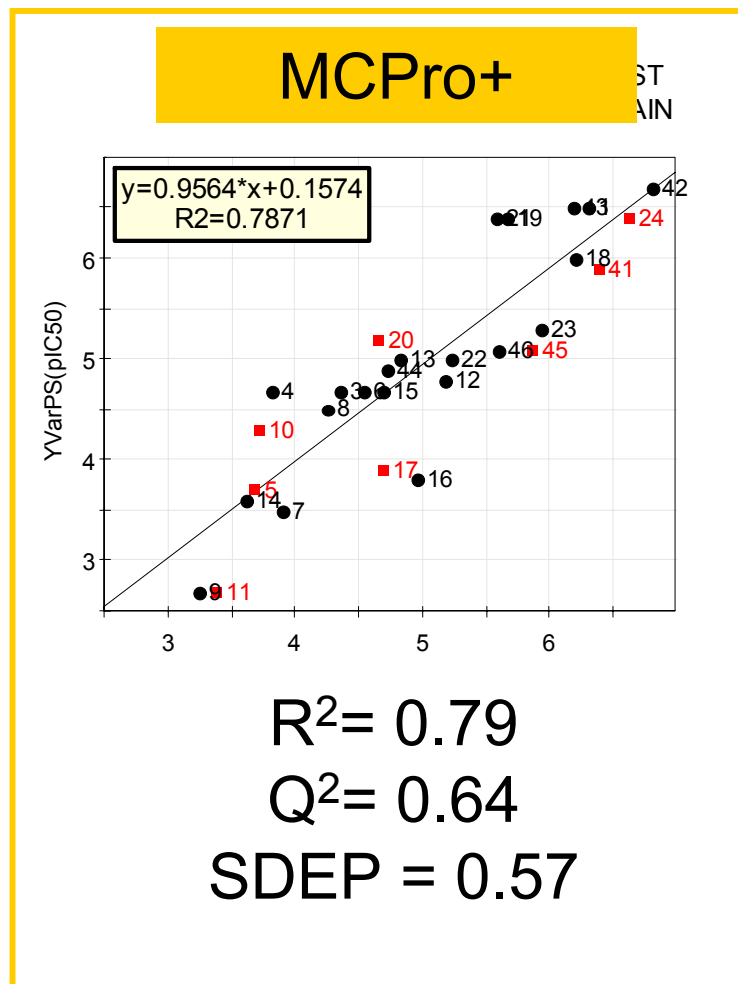
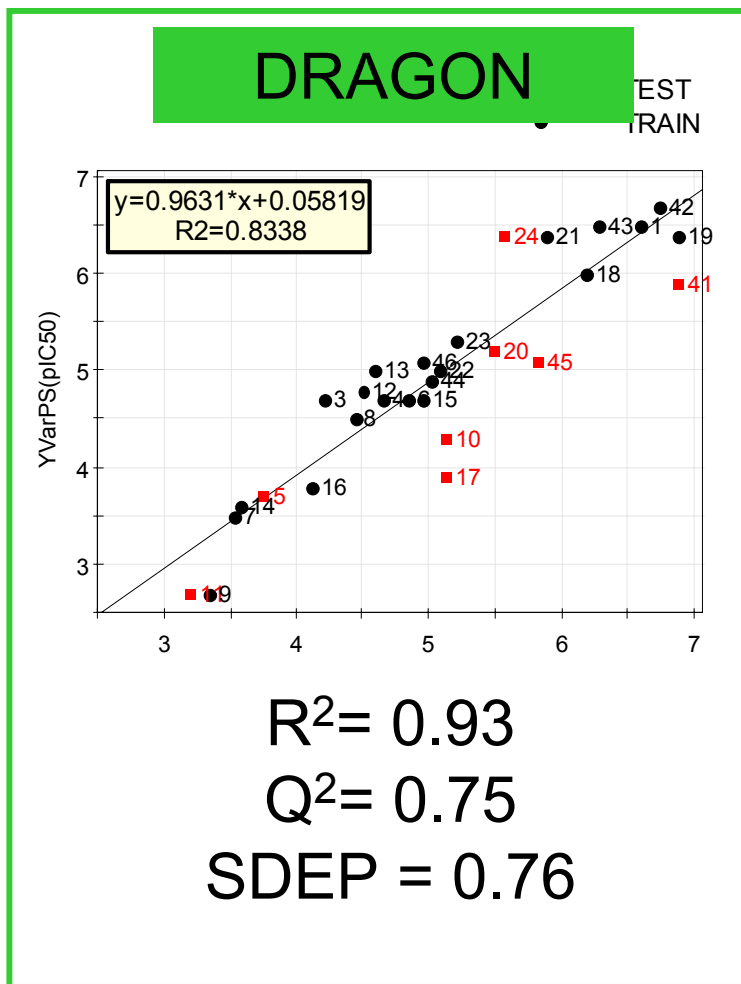
XP Visualizer



$R^2= 0.77$
 $Q^2= 0.67$
SDEP = 0.71

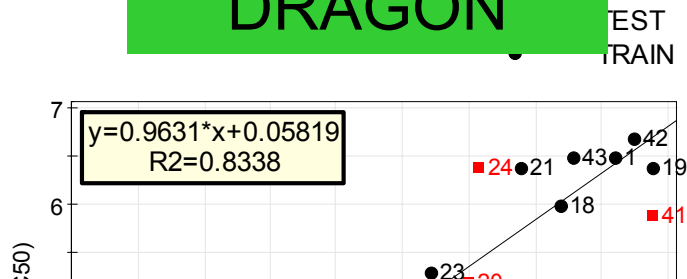


PARP-1

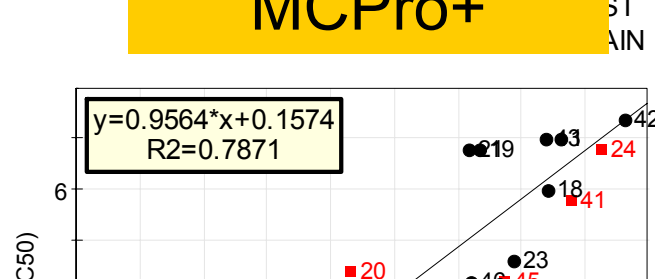


PARP-1

DRAGON



MCPPro+



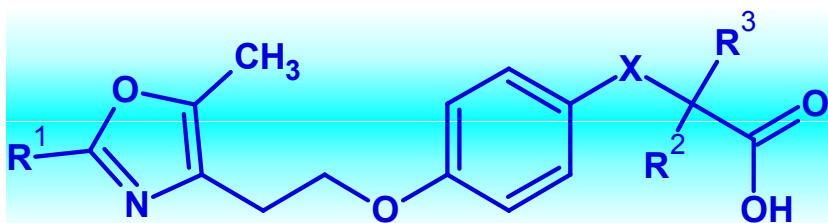
Dataset 21 molecules - test set 8 molecules

	PCs	R2	Q2	SDEP
MCPRO+	2	0.79	0.64	0.57
Liaison	2	0.75	0.63	0.71
XP visualizer	2	0.7	0.67	0.71
SP gscore	1	0.63	0.6	0.7
DR	3	0.93	0.75	0.76

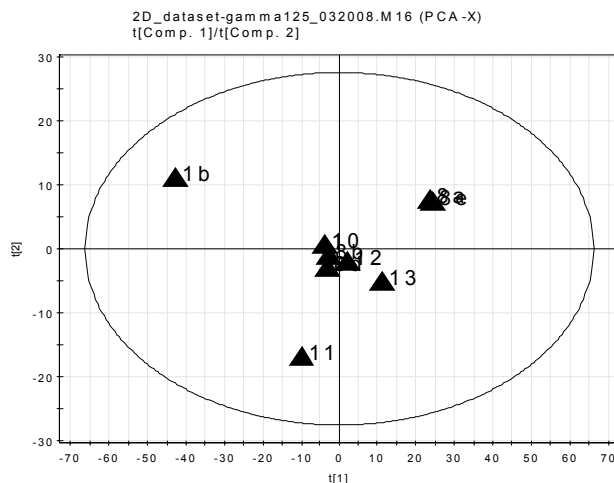


PPAR- γ

15 PPAR- γ agonists



J. Med.Chem. 2004, 47, 2422



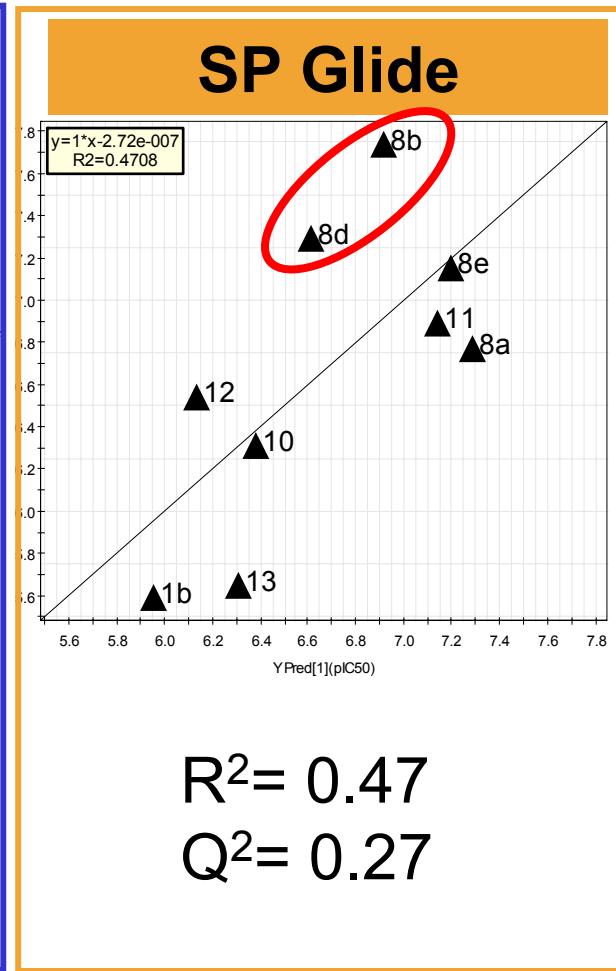
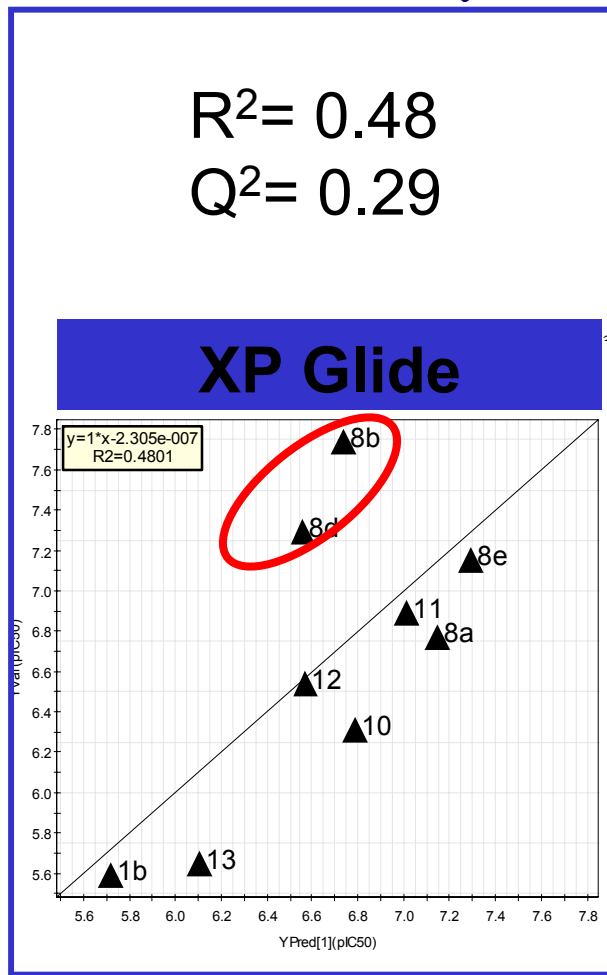
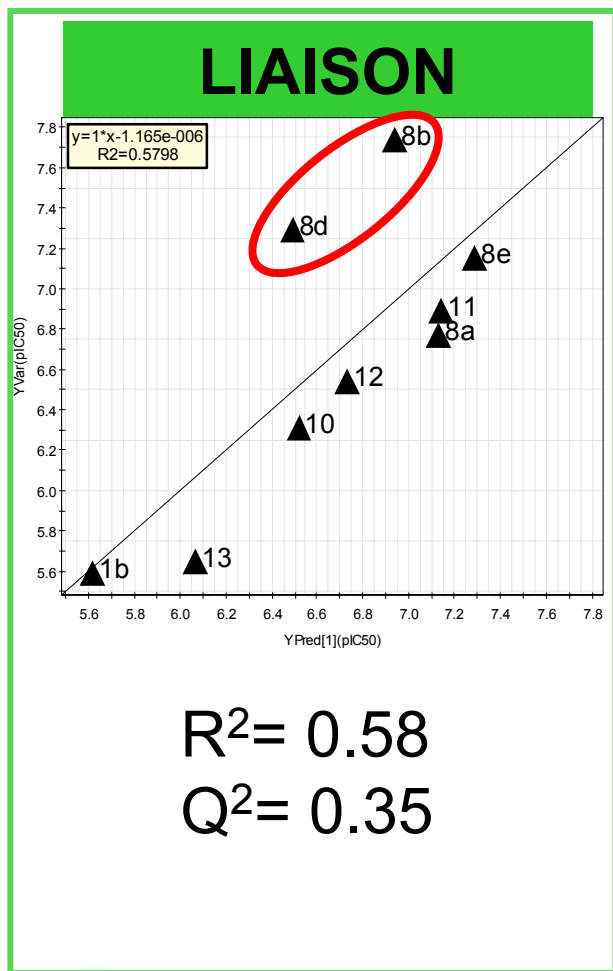
R2X[1] = 0.682262 R2X[2] = 0.11845
Ellipse: Hotelling T2 (0.95) SIMCA-P 11 - 10/04/2008 12.17.53

9 PPAR- γ agonists

name	R1	R3	R2	Chirality	plC50
2	-	-	-	-	-
15	-	-	-	-	-
17	cicloesile	OPh	S-Me	S	7.82
8b	Ph	OPh	Me	rac	7.74
8c	2-tioPh	OPh	Me	rac	7.62
8d	cicloesile	OPh	Me	rac	7.29
8e	3-biPh	OPh	Me	rac	7.15
11	Ph	OPh	H	rac	6.89
8a	4-biPh	OPh	Me	rac	6.77
12	Ph	OPh	Et	rac	6.54
16	2-tioPh	OPh	R-Me	R	6.53
14	Ph	OPh	R-Me	R	6.41
10	Ph	Bz	Me	rac	6.31
13	Ph	OPh	n-Bu	rac	5.65
1b	Ph	Me	Me	-	5.59



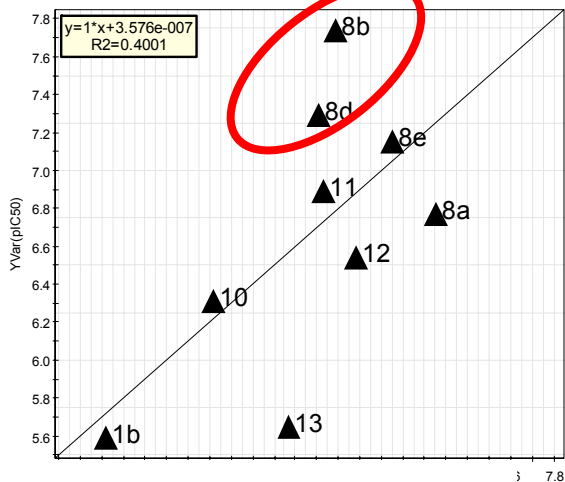
PPAR- γ



PPAR- γ

XP visualizer

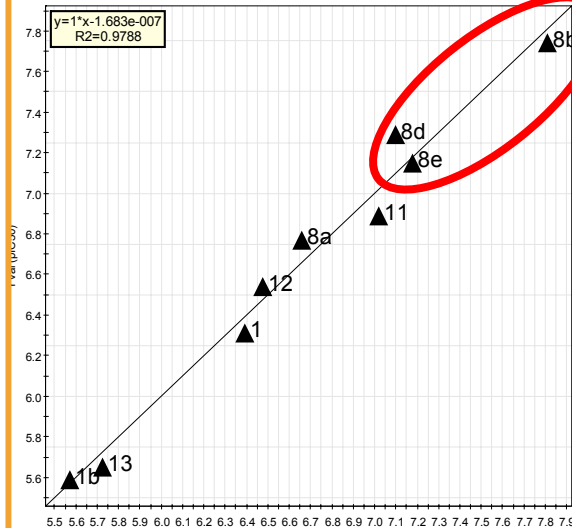
20080409_matrice_descrittori_testset.M31 (PLS), XPvisualizer train
YPred[Last comp.](pIC50)YVar(pIC50)



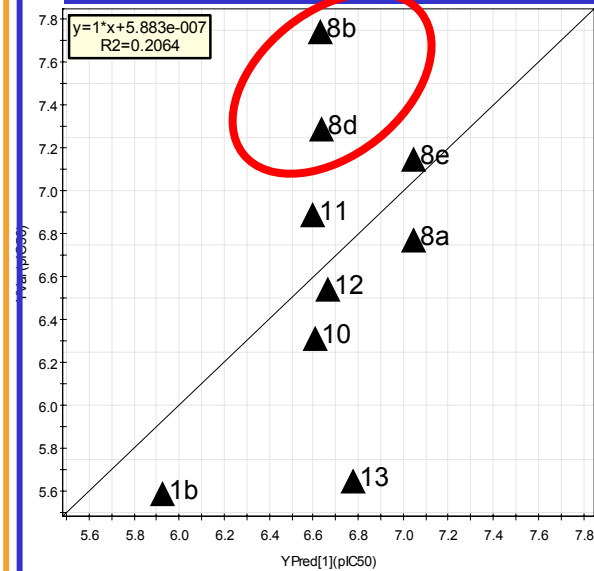
$R^2= 0.38$
 $Q^2= 0.09$

$R^2= 0.98$
 $Q^2= 0.90$

MCPPro+



DRAGON



$R^2= 0.21$
 $Q^2= 0.16$

RMSEE = 0.687SIMCA-P 11 - 10/04/2008 16.54.31

PPAR- γ

XP visualizer

DRAGON

$R^2 = 0.98$

$y = 1 + 5.883e-007$

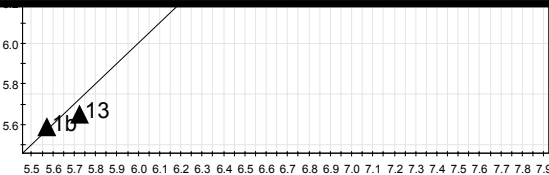
18b

Dataset 9 molecules

	PCs	R2	Q2	SDEC
MCPRO+	3	0.98	0.9	0.13
Liaison fix	1	0.58	0.35	0.5
XP visualizer	1	0.38	0.088	0.6
SP gscore	1	0.47	0.27	0.56
XP gscore	1	0.48	0.29	0.56
DR	1	0.21	0.16	0.69

$R^2 = 0.38$

$Q^2 = 0.09$



$R^2 = 0.21$

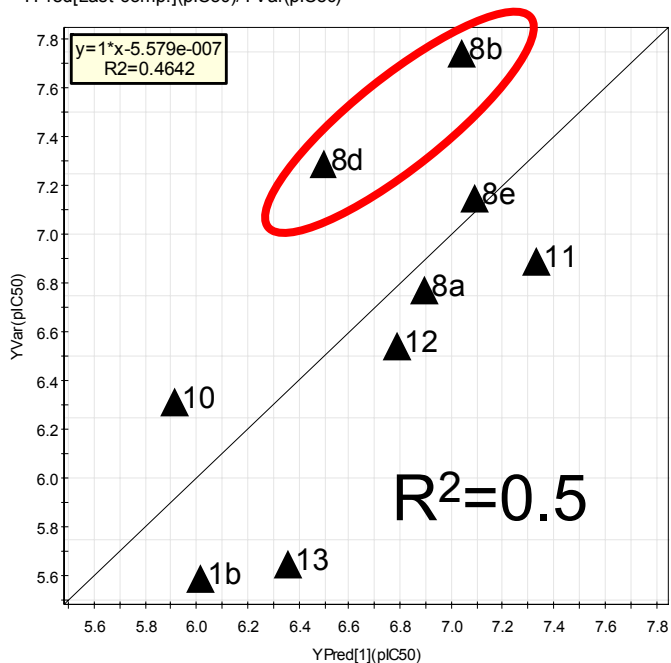
$Q^2 = 0.16$

PPAR- γ

MM-GBSA Results

pIC50 vs ΔG_{bind}
Shell frozen

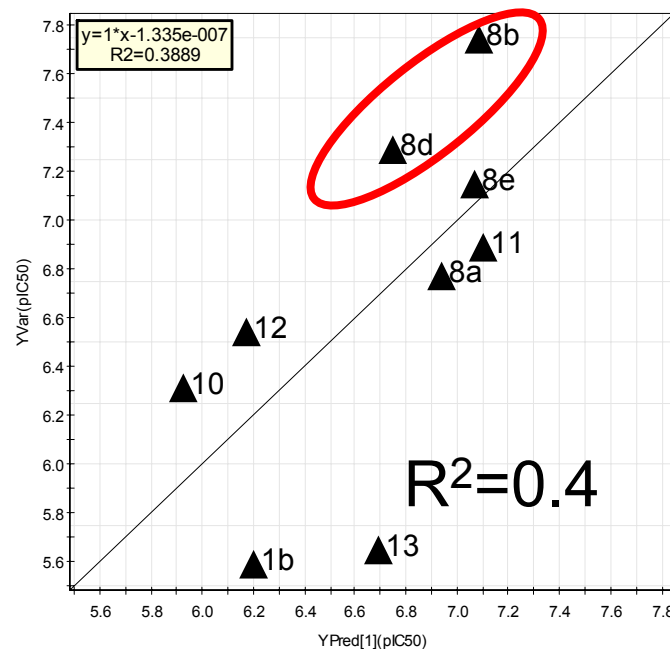
20080409_matrice_descrittori_testset.M43 (PLS), M22 meno stereoisomeri
YPred[Last comp.](pIC50)/YVar(pIC50)



RMSEE = 0.565 SIMCA-P 11 - 10/04/2008 18.24.38

pIC50 vs ΔG_{bind}
Shell 4 A°

20080409_matrice_descrittori_testset.M45 (PLS), M24 meno stereoisomeri
YPred[Last comp.](pIC50)/YVar(pIC50)



RMSEE = 0.60 SIMCA-P 11 - 10/04/2008 18.26.08

LEAD OPTIMIZATION RESULTS: PPAR- γ 4/4



Take home message

- **LEAD DISCOVERY**
 - Our virtual screening protocol is useful to retrieve new hits (pIC50 between 5 and 7)
 - Ensemble docking worked well even with a flexible receptor
- **LEAD OPTIMIZATION**
 - MCPRO+ (Linear Response Method) was the best approach to predict ligand-protein affinity binding data
- This approach appears a powerful *in silico* screening for drug discovery process

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www.angelini.it/

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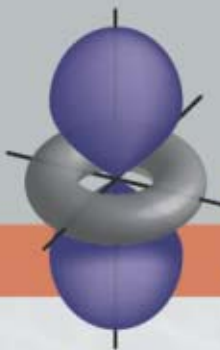
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- **Jörg Weiser**

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- **Massimo Mabilia**
- **Marco Parenti**





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MCPRO+

- Based on MCPRO backend from Jorgensen's group (Yale)
- Plus" refers to the many features that have been added by Schrödinger to improve setup, execution, and analysis
- Five solutions:
 - Free energy differences via FEP (DG)
 - Relative protein-ligand binding affinities via FEP (DDG)
 - Protein-ligand binding affinities via Linear Response
 - Perform general-purpose Monte Carlo sampling
 - Energy minimization
- Simple FEP interface likely to be shared by Chorus backends



MCPRO FEP References

- Relative binding affinity prediction via FEP theory:
 - **Trypsin/benzamidines**: J. Phys. Chem. B 101, 9663 (1997)
 - **Cyclophilin/cyclosporin**: Angew. Chem. Int. Ed. Engl. 36, 1466 (1997)
 - **FKBP/ligands**: J. Med. Chem. 41, 3928 (1998)
 - **COX-1/COX-2/ligands**: J. Am. Chem. Soc. 122, 9455 (2000)
 - **HIV-RT/sustiva**: J. Am. Chem. Soc. 122, 12898 (2000); Bioorg. Med. Chem. Lett. 11, 2799 (2001)
 - **HIV-RT/TMC125**: J. Am. Chem. Soc. 125, 6016 (2003)
 - **HIV-RT/Efavirenz**: J. Med. Chem. 47, 2389 (2004)
 - **FAAH/alpha-ketoheterocycles**: J. Am. Chem. Soc. 127 17377 (2005)
 - **HIV-RT/ligands**: J. Am. Chem. Soc. 128, 15372 (2006); Bioorg. Med. Chem. Lett. 16, 663 (2006); Bioorg. Med. Chem. Lett. 16, 668 (2006); Bioorg. Med. Chem. Lett. 16, 5664 (2006)



MCPRO FEP References

- Binding affinity prediction via Linear Response:
 - **Thrombin/MD-805** J. Med. Chem. 40 1539 (1997)
 - **FKBP/ligands**: J. Med. Chem. 41, 3928 (1998)
 - **FKBP/ligands**: Bioorg. Med. Chem. 7, 851 (1999)
 - **Thrombin/ligands**: J. Med. Chem. 44, 1043 (2001)
 - **COX-2/ligands**: Bioorg. Med. Chem. Lett. 12, 267 (2002)
 - **HIV-RT/ligands**: J. Med. Chem. 45, 2970 (2002)
 - **HIV-RT/sustiva**: Bioorg. Med. Chem. Lett. 13, 3337 (2003)
 - **Factor Xa/ligands**: J. Med. Chem. 46 5691 (2003)
 - **CDK2,p38,Lck kinases/ligands**: J. Med. Chem. 47, 2534 (2004)

