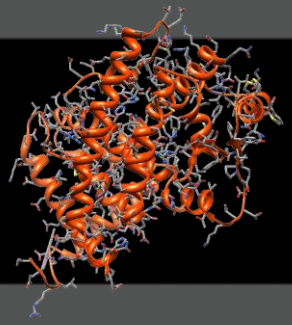
www.3D-QSAR.com
Three-Dimensional Quantitative Structure-Activity Relationships Server



Sapienza
Università di Roma

by www.RCMD.it

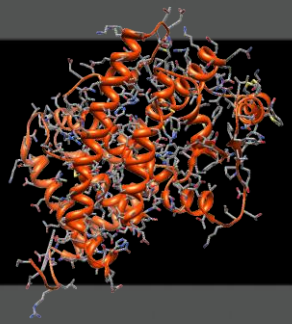
Studi 3-D QSAR su ligandi del Recettore gamma del Proliferatore Attivato dei Perossisomi (PPAR gamma).

Relatore:

Chiar.mo Prof. Rino Ragno

Laureando:

Raffaele Maio



Scopo del lavoro

Costruzione di un modello 3-D QSAR per Ligandi del PPAR-γ

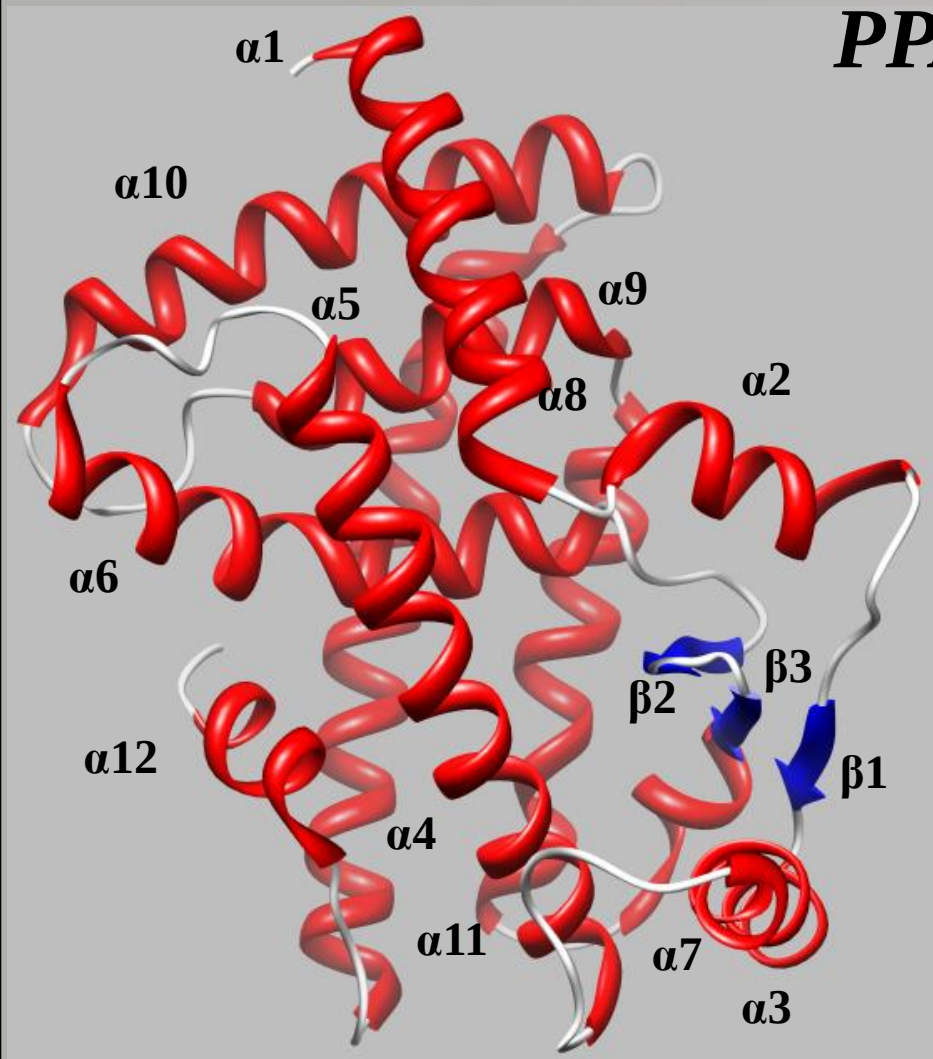
↓

Studio delle interazioni fondamentali

PPAR-γ ↔ **Ligandi sintetici**

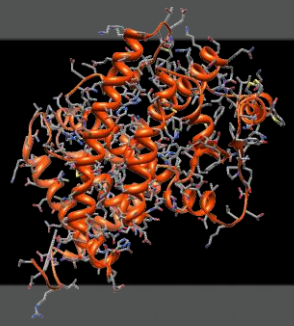
↓

Predizione attività di nuovi composti



PPAR-γ

- ***Recettore nucleare orfano***
  - **Mancanza di un ligando eletto**
- ***Struttura***
  - **12 α eliche e 3 foglietti β**
  - **Sito di legame → idrofobico, a forma di T**
- ***Classificazione***
  - **3 isoforme → α, γ, δ**
- ***Tiazolidinedioni (TZD) – Meccanismo di azione***
  - **Formazione eterodimero→ RXR**
  - **Induzione trascrizione genica**



3-D QSAR

J. Am. Chem. Soc. **1988**, *110*, 5959–5967

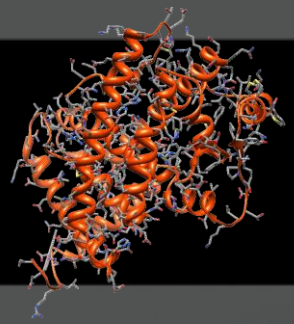
Comparative Molecular Field Analysis (CoMFA). 1. Effect of Shape on Binding of Steroids to Carrier Proteins

Richard D. Cramer, III,* David E. Patterson, and Jeffrey D. Bunce

Contribution from Tripos Associates, 1699 South Hanley Road, St. Louis, Missouri 63144. *Received January 5, 1988*

Abstract: Comparative molecular field analysis (CoMFA) is a promising new approach to structure/activity correlation. Its characteristic features are (1) representation of ligand molecules by their steric and electrostatic fields, sampled at the intersections of a three-dimensional lattice, (2) a new "field fit" technique, allowing optimal mutual alignment within a series, by minimizing the RMS field differences between molecules, (3) data analysis by partial least squares (PLS), using cross-validation to maximize the likelihood that the results have predictive validity, and (4) graphic representation of results, as contoured three-dimensional coefficient plots. CoMFA is exemplified by analyses of the affinities of 21 varied steroids to corticosteroid- and testosterone-binding globulins. Also described are the sensitivities of results to the nature of the field and the definition of the lattice and, for comparison, analyses of the same data using various combinations of other parameters. From these results, a set of ten steroid-binding affinity values unknown to us during the CoMFA analysis were well predicted.

www.3D-QSAR.com
THREE-DIMENSIONAL QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS SERVER



SAPIENZA UNIVERSITÀ DI ROMA

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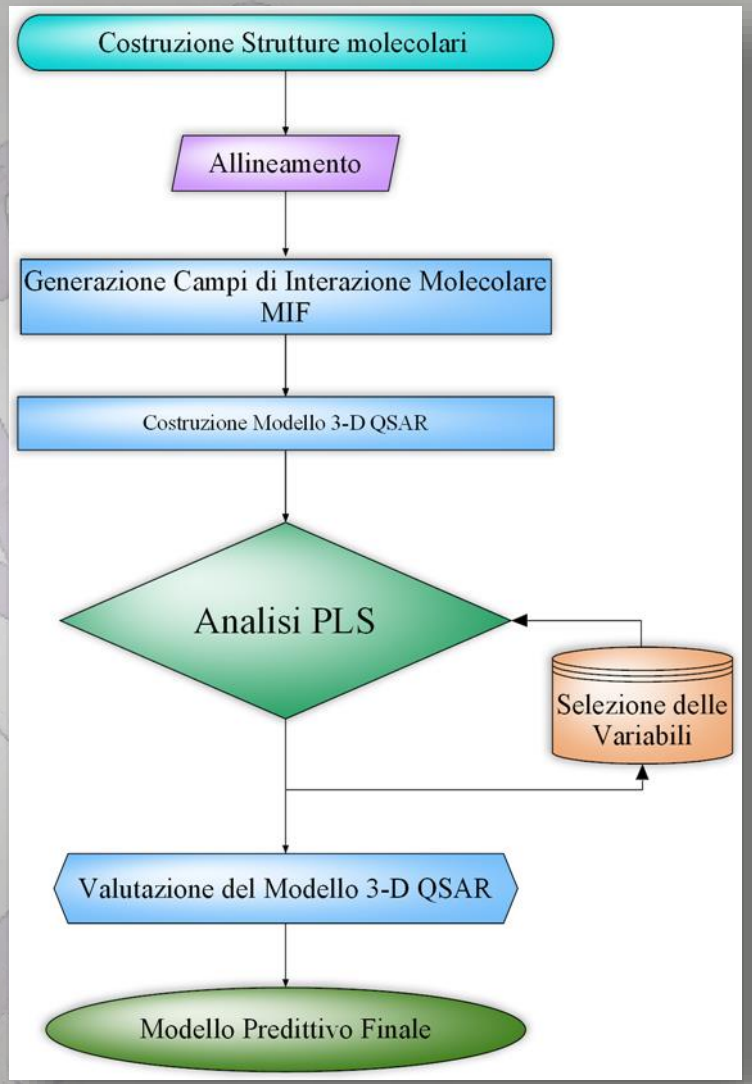
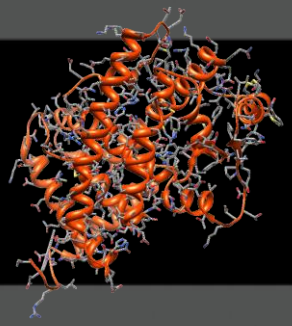
3-D QSAR

$$r^2 = 1 - \frac{\sum_{i=1}^{N}(Y_{\exp,i} - Y_{calc,i})^2}{\sum_{i=1}^{N}(Y_{\exp,i} - \bar{Y})^2} \qquad q^2 = 1 - \frac{\sum_{i=1}^{N}(Y_{\exp,i} - Y_{pred,i})^2}{\sum_{i=1}^{N}(Y_{\exp,i} - \bar{Y})^2}$$

$$SDEP = \sqrt{\frac{\sum_{i=1}^{N}(Y_{\exp,i} - Y_{pred,i})^2}{N}} \qquad S_{PRESS} = \sqrt{\frac{SDEP}{N - C - 1}}$$





Preparazione del Training-set

I. Download PDB

II. "Pulitura" complessi proteina - ligando

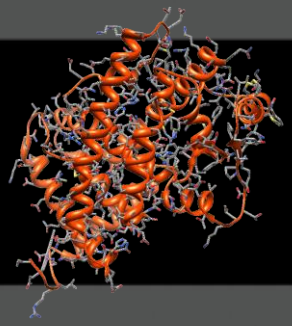
III. Allineamento complessi

IV. Separazione in ligando (key) e proteina (lock)

V. Completamento delle lock

VI. Controllo delle key

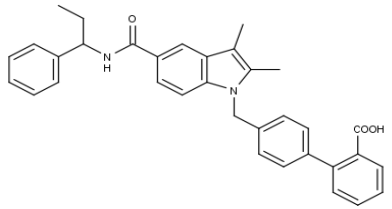
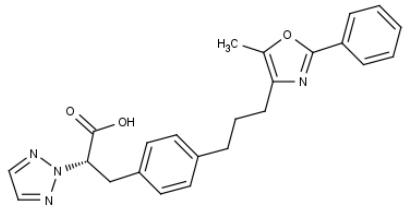
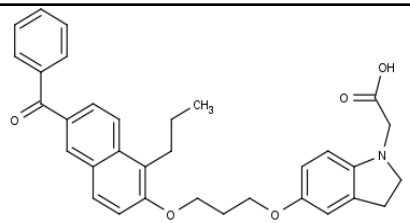
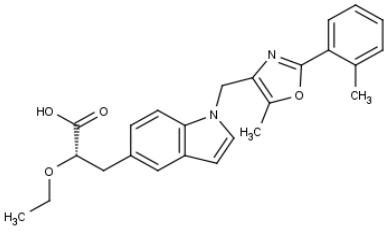
VII. Minimizzazione delle key mediante AMBER10



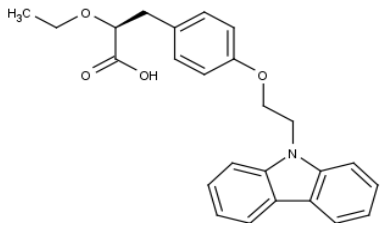
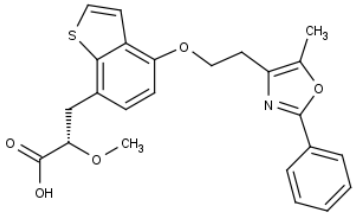
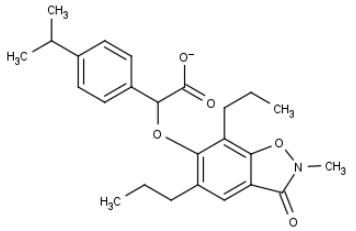
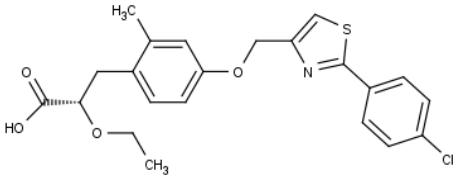
Valori di attività training set

PDB	pIC_{50}	PDB	pIC_{50}	PDB	pIC_{50}
2P4Y_B	9.00	3NOA_B	7.57	2Q8S_A	6.73
1FM9_D	8.94	2Q59_B	7.40	1I7I_B	6.70
2I4P_A	8.70	2PRG_B	7.40	1ZEO_A	6.68
2I4Z_A	8.70	1ZGY_A	7.33	2GTK_A	6.60
3IA6_A	8.52	1FM6_X	7.33	2G0G_A	6.30
3BC5_A	8.30	2F4B_A	7.30	3LMP_A	6.21
3KMG_D	8.10	4PRG_A	7.15	2I4J_A	6.16
2Q5S_A	8.01	2Q6S_B	7.00	3OSW_A	6.15
3G9E_A	7.72	1WM0_X	7.00	3FEJ_A	6.13
2G0H_A	7.64	3DZU_D	7.00	3CS8_A	5.77
2Q5P_B	7.64	2ATH_B	6.82	3OSI_A	5.22

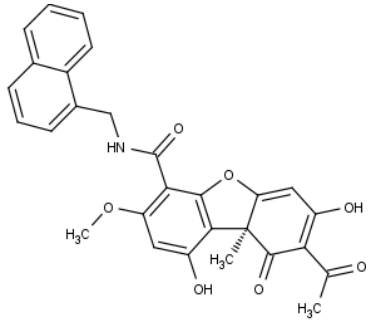
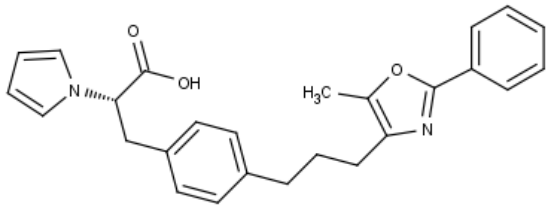
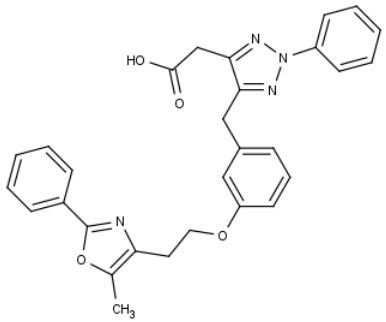
Scaffold

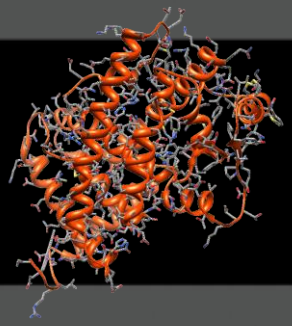
Serie degli acidi fenilbenzoici	3KMG	
Serie degli acidi fenilpropanoici	3IA6	
Serie degli acidi indol-1-il acetici	2F4B	
Serie degli acidi propionici α-alcossi sostituiti	2GTK	

Scaffold

Serie degli acidi triciclici-α-alchilossifenil propionici	1KNU	
Serie degli acidi α-alcossi-β-arilpropionici	3G9E	
Serie degli acidi α-ariloxifenilacetico	1ZEO	
Serie degli acidi α-etossi-fenilpropanoici	3FEJ	

Scaffold

Serie della N-benzilcarbossamide	3LMP	
Serie dell'acido fenilpropanoico	2Q8S	
Serie delle ossibenzilglicine	3BC5	



Costruzione modelli 3-D QSAR

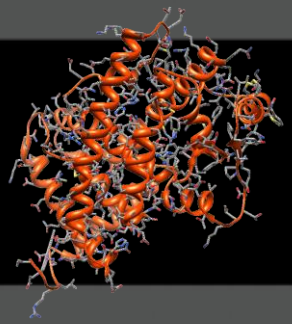
Dataset: 56 molecole → ***Test Set: 23 molecole***

↓

Training Set: 33 molecole

↓

Autogrid/R —*8 probe*→ ***8 modelli*** → ***modello HD***, ***modello OA***



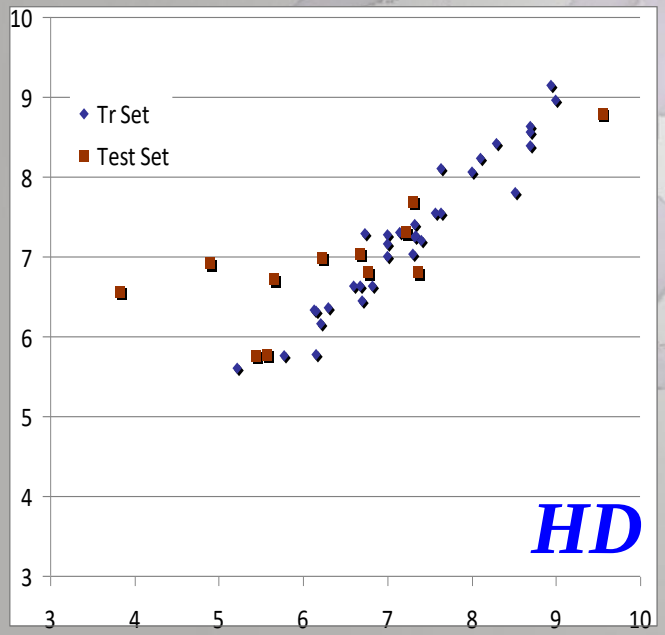
Risultati statistici

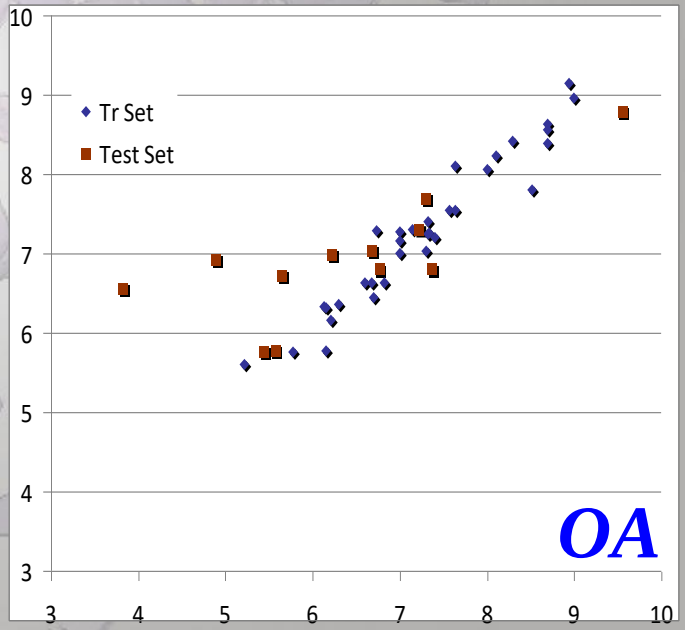
PROBE	PC	R^2	Q^2 K-Fold CV
A	2	0,88	0,42
C	3	0,91	0.46
OA	3	0,94	0.51
HD	3	0,95	0.63
NA	3	0,92	0.50
N	3	0,87	0.49
e	4	0,92	0.38
d	3	0,60	0.31

Risultati statistici

PROBE	PC	R^2	Q^2 K-Fold CV
OA	3	0,94	0.51
HD	3	0,95	0.63

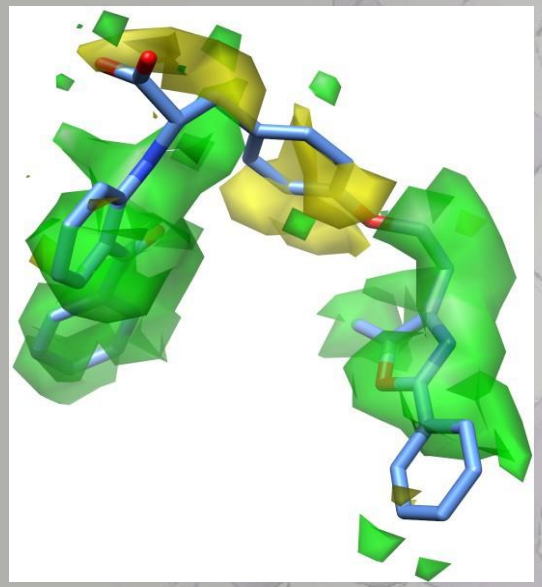
Predizione





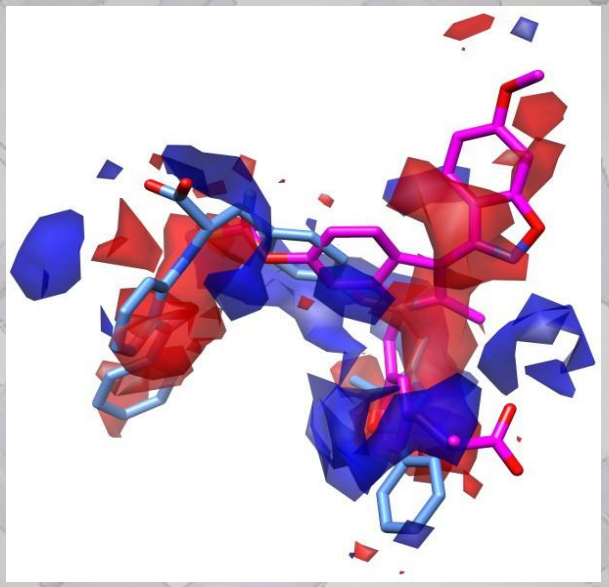
Probe HD

Ligandi più attivi



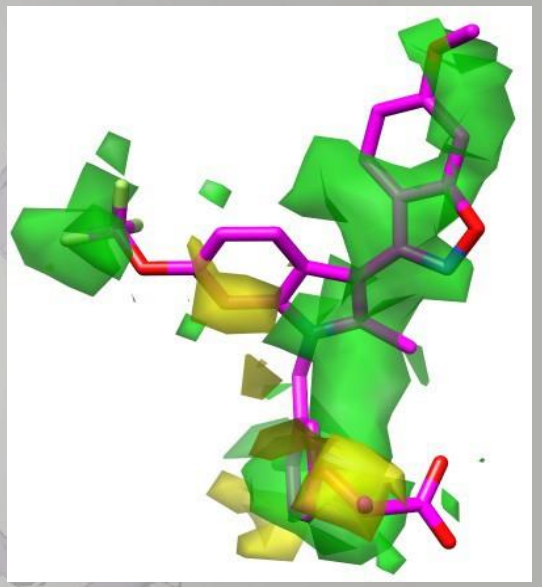
Activity Contribution Plot
1FM9_D (pIC_{50} = 8.94)

Positivo Verde: 25%
Negativo Giallo: 25%



Coefficienti PLS

Positivo Rosso: 30%;
Negativo Blu: 30%

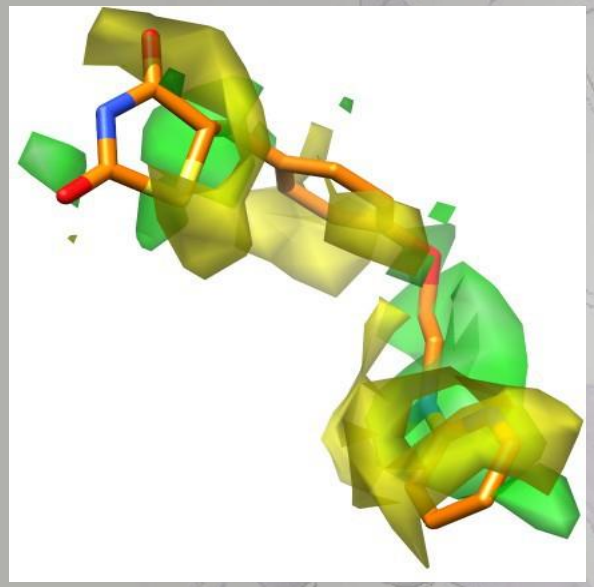


Activity Contribution Plot
2P4Y_B (pIC_{50} = 9.00)

Positivo Verde: 25%
Negativo Giallo: 25%

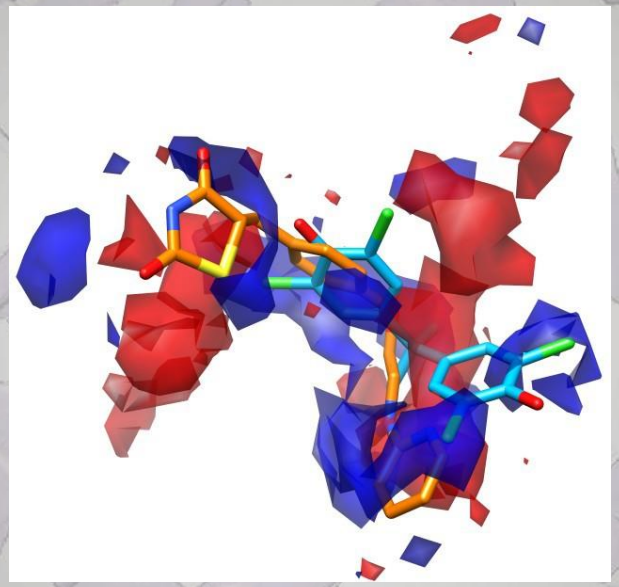
Probe HD

Ligandi meno attivi



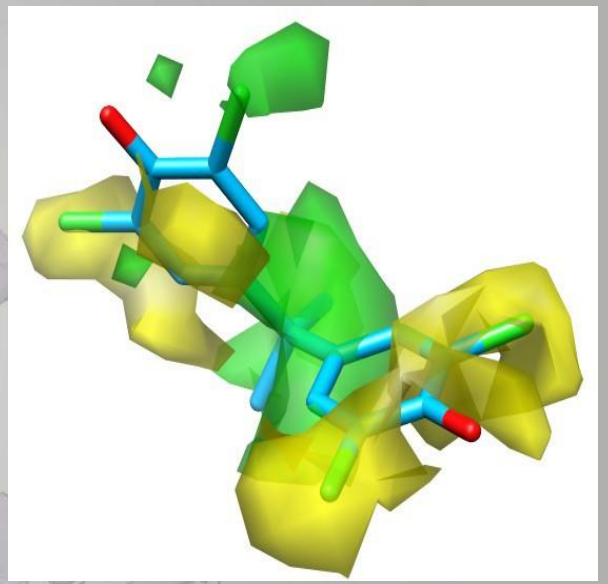
Activity Contribution Plot
3CS8_A (pIC_{50} = 5.77)

Positivo Verde: 25%
Negativo Giallo: 25%



Coefficienti PLS

Positivo Rosso: 30%;
Negativo Blu: 30%

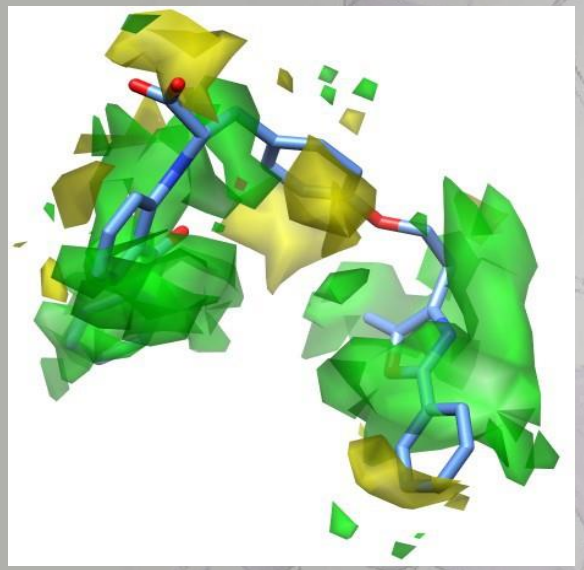


Activity Contribution Plot
3OSI_A (pIC_{50} = 5.22)

Positivo Verde: 25%
Negativo Giallo: 25%

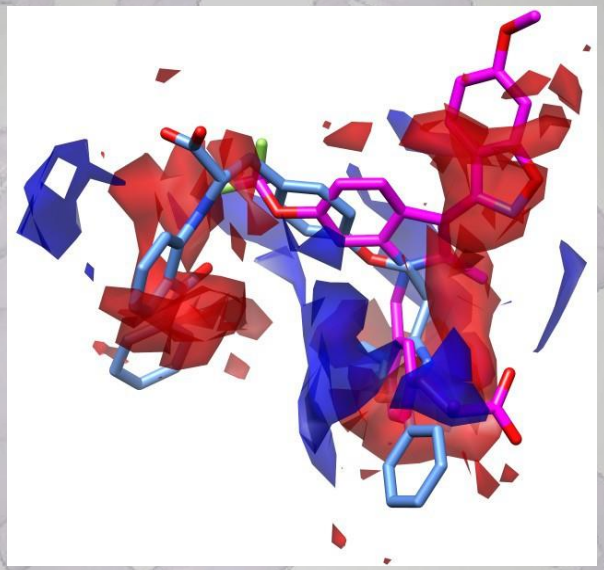
Probe OA

Ligandi più attivi



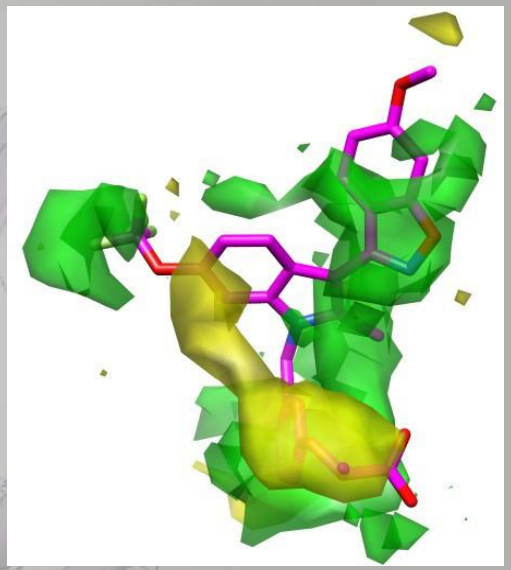
Activity Contribution Plot
1FM9_D (pIC_{50} = 8.94)

Positivo Verde: 25%
Negativo Giallo: 25%



Coefficienti PLS

Positivo Rosso: 30%;
Negativo Blu: 30%

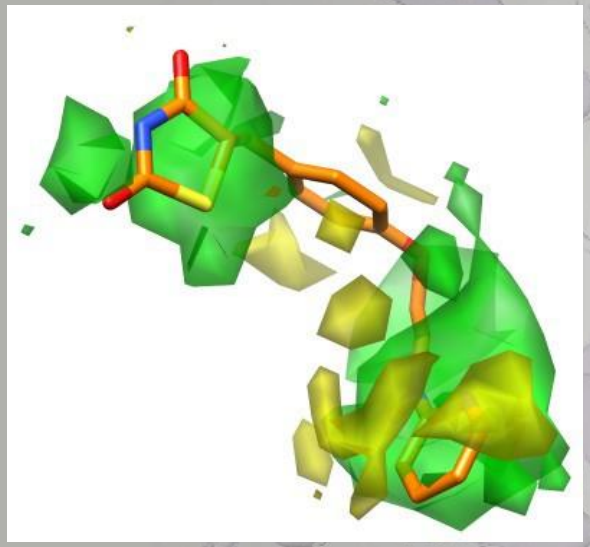


Activity Contribution Plot
3CS8_A (pIC_{50} = 5.77)

Positivo Verde: 25%
Negativo Giallo: 25%

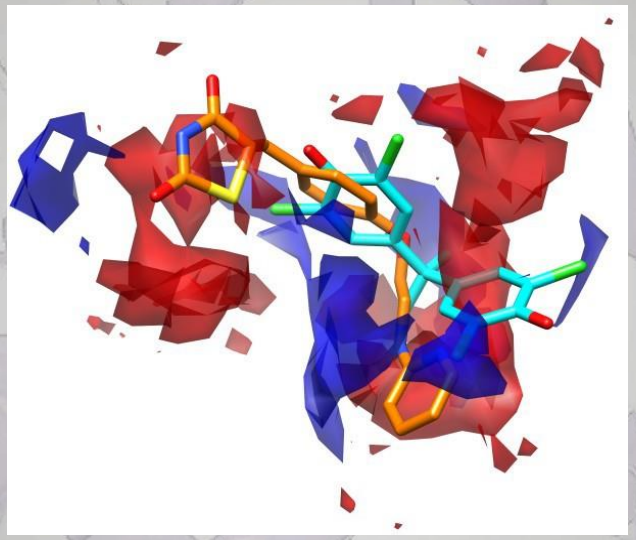
Probe OA

Ligandi meno attivi



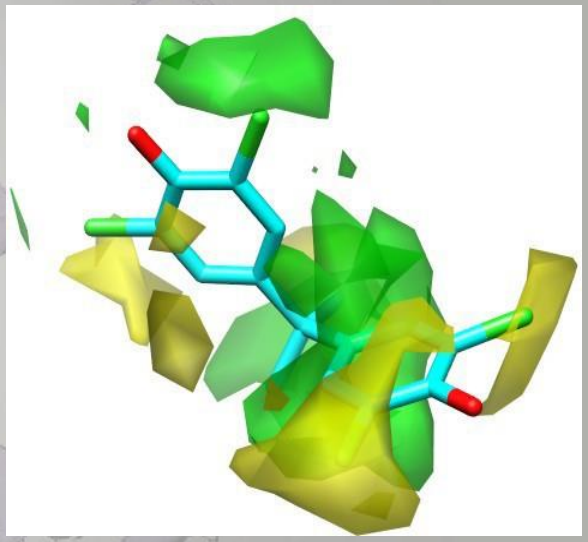
Activity Contribution Plot
3CS8_A (pIC_{50} = 5.77)

Positivo Verde: 25%
Negativo Giallo: 25%



Coefficienti PLS

Positivo Rosso: 30%;
Negativo Blu: 30%



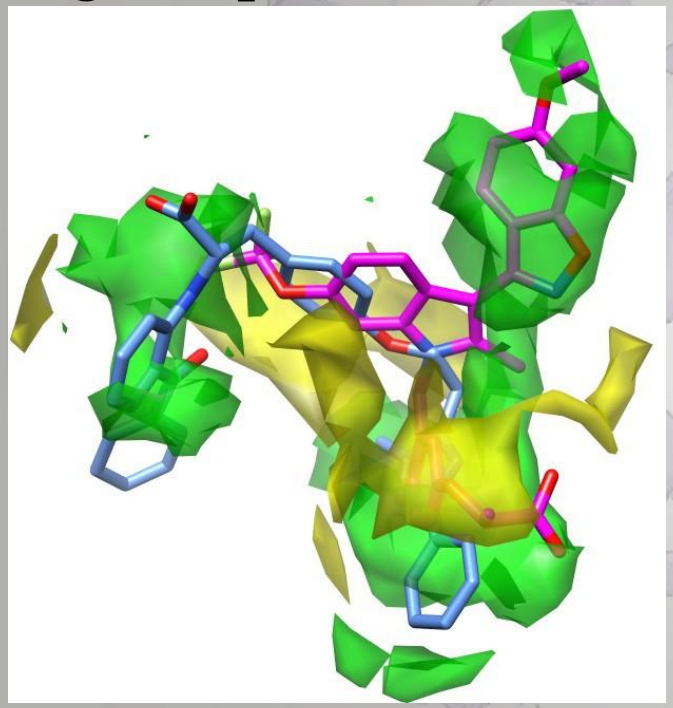
Activity Contribution Plot
3OSI_A (pIC_{50} = 5.22)

Positivo Verde: 25%
Negativo Giallo: 25%

CoMFA- like

Contributi sterici

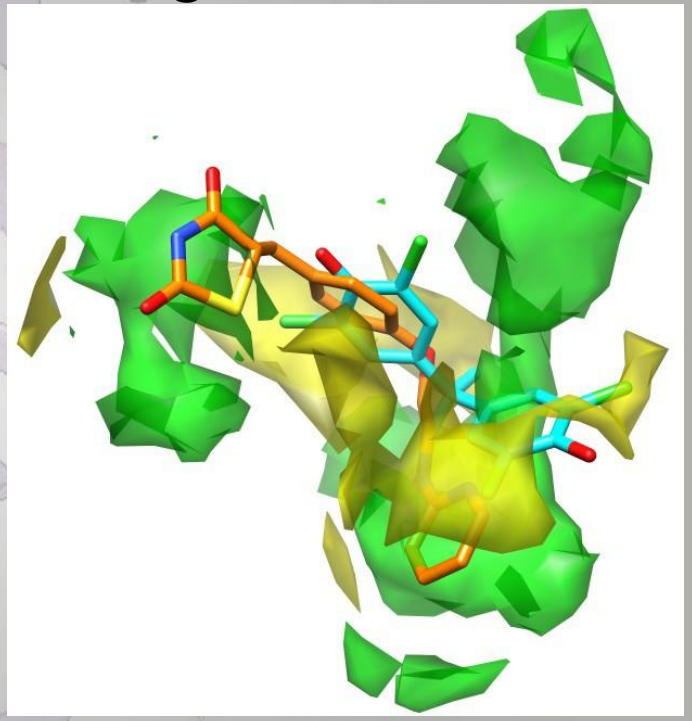
Ligandi più attivi



CoMFA map Plot
1FM9_D (blu) e
2P4Y_B (magenta)

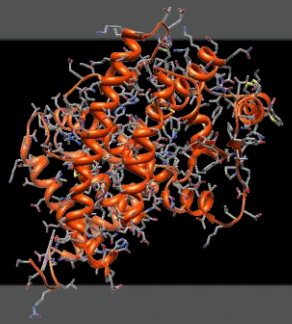
Positivo Verde: 30%
Negativo Giallo: 30%

Ligandi meno attivi



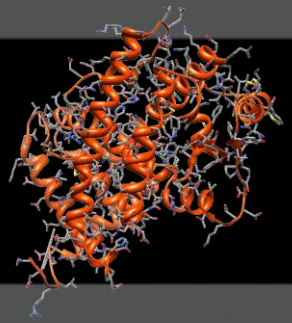
CoMFA map Plot
3CS8_A (arancione) e
3OSI_A (ciano)

Positivo Verde: 30%
Negativo Giallo: 30%



Cross-Docking

- ***Definizione***
  - **docking di ogni ligando in tutti i recettori disponibili, eccetto il proprio**
- ***Scopo***
  - **conoscere le migliori conformazioni che i ligandi possono assumere nell'interazione con il recettore**
  - **analizzare il docking di molecole non ancora sintetizzate**



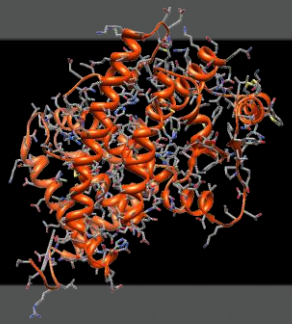
Risultati Cross-Docking

BD	28	6	11
BC	30	3	12

PDB	TORS	RMSDcrossdock exp		
		BD	BC	BF
1FM6_D	7	4,45	4,45	0,8
1FM6_X	7	3,97	4,36	1,11
1FM9_D	12	2,64	2,39	1,57
1I7I_A	11	4,72	4,08	1,21
1I7I_B	11	4	2,06	1,38
1K74_D	12	6,19	1,97	1,49
1KNU_A	9	1,42	1,42	1,42
1NYX_A	9	1,95	2,92	1,05
1WM0_X	5	0,81	0,81	0,81
1ZEO_A	10	6,04	6,04	2,57
2ATH_A	11	2,39	2,39	1,11
2ATH_B	11	2,93	1,72	1,72
2F4B_A	12	3,63	3,14	1,5
2G0G_A	5	1,46	6,47	1,11
2G0H_A	7	0,99	4,35	0,99

PDB	TORS	RMSDcrossdock exp		
		BD	BC	BF
2G0H_B	7	0,97	5	0,97
2GTK_A	8	1,04	1,04	1,04
2HWQ_A	12	1,43	1,78	1,43
2HWR_A	12	1,26	3,86	1,26
2I4J_A	14	4,62	6,48	1,34
2I4P_A	14	4,33	1,98	1,93
2I4Z_A	14	4,25	4,25	1,59
2OM9_A	8	3,05	0,93	0,93
2OM9_B	8	1,28	5,07	1,28
2OM9_C	8	0,92	0,92	0,92
2OM9_D	8	3,53	4,98	1,25
2P4Y_A	9	5,06	1,71	1,71
2P4Y_B	9	2,07	2,2	2,05
2PRG_A	7	3,78	3,78	1,21
2PRG_B	7	1,38	1,38	1,27

PDB	TORS	RMSDcrossdock exp		
		BD	BC	BF
2Q59_A	9	2,38	2,38	1,27
2Q59_B	9	0,74	4,67	0,74
2Q5P_A	9	4,02	2,35	1,67
2Q5P_B	9	2,35	2,35	1,09
2Q5S_A	5	0,81	0,81	0,81
2Q5S_B	5	1,4	1,4	1,4
2Q61_A	5	1,42	1,42	1,42
2Q61_B	5	1,87	1,87	1,42
2Q6R_A	6	1,97	1,97	1,86
2Q6R_B	6	5,35	1,22	1,22
2Q6S_B	5	0,85	0,85	0,85
4PRG_A	18	2,2	1,83	1,62
4PRG_B	18	2,72	2,92	1,61
4PRG_C	18	3,89	2,47	1,87
4PRG_D	18	2,9	2,9	1,73



Conclusioni e Prospettive

- *Modelli 3-D QSAR per ligandi di sintesi del PPAR-gamma*
- *Buona predittività interna ed esterna*
- *Vasto range di attività (~ 5 pIC_{50})*
- *Validi per un ampio range di scaffold molecolari*
- *Metodica di allineamento di molecole tramite cross-docking*

- *Progettazione di nuovi ligandi del PPAR-gamma*