

UNIVERSITA' DEGLI STUDI DI ROMA "LA SAPIENZA"

Facoltà di Farmacia

Corso di Laurea in Chimica e Tecnologia Farmaceutiche

Tesi sperimentale di laurea in Chimica Farmaceutica e Tossicologica

**Relazioni quantitative struttura attività di tipo
tridimensionale (3D QSAR):
applicazione a diverse classi di inibitori non nucleosidici
(NNRTIs) della Trascrittasi inversa del virus
dell'immunodeficienza umano di tipo 1 (HIV-1)**

3D QSAR

Definizione

Con 3D QSAR si intendono tutti i modelli statistico-matematici che definiscono una relazione di tipo quantitativo tra la variazione dell'attività biologica di una serie di composti chimici in funzione delle diverse strutture chimiche considerate nella loro tridimensionalità.

Obiettivi

- 1) Ricerca di una correlazione struttura-attività
- 2) Progettazione di nuove molecole
- 3) Stima del valore di attività di composti non ancora sintetizzati per definire la priorità di sintesi

Procedura generale

Analisi strutturale

Allineamento

Calcolo dei descrittori molecolari (MIFs)

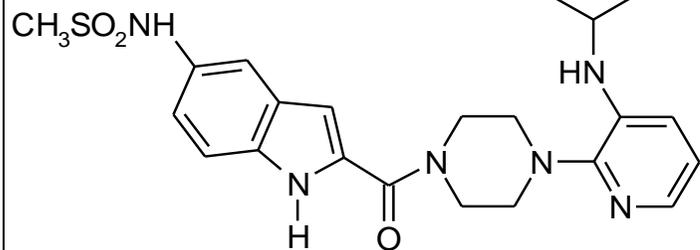
PLS e Crossvalidazione

Selezione delle variabili

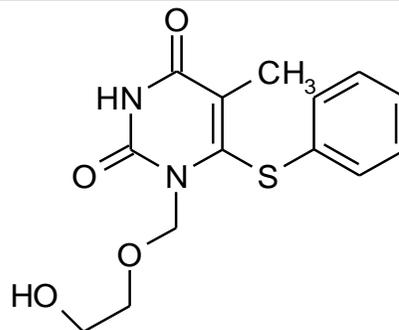
**QSAR: MODELLO PLS FINALE della
CORRELAZIONE
STRUTTURA ATTIVITA'**



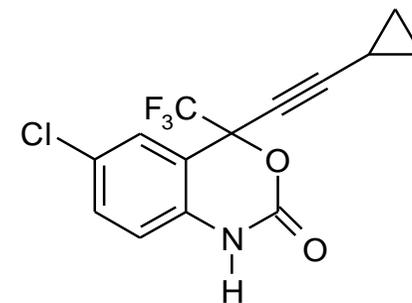
Inibitori non nucleosidici della Trascrittasi inversa (NNRTIs) considerati nel lavoro



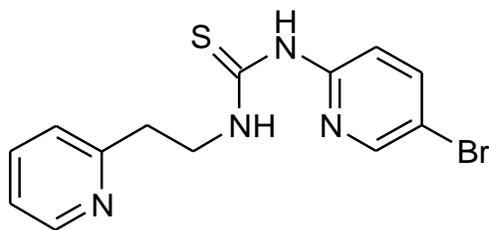
Delarvidina



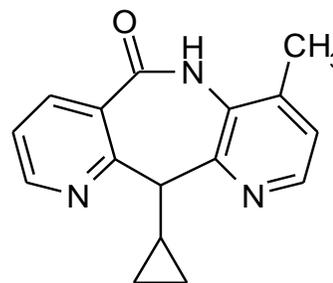
HEPT



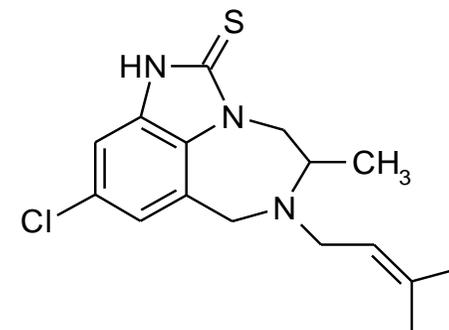
Efavirenz



Troviridina

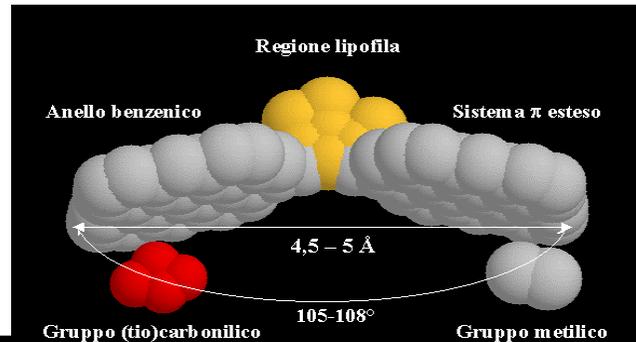


Nevirapina

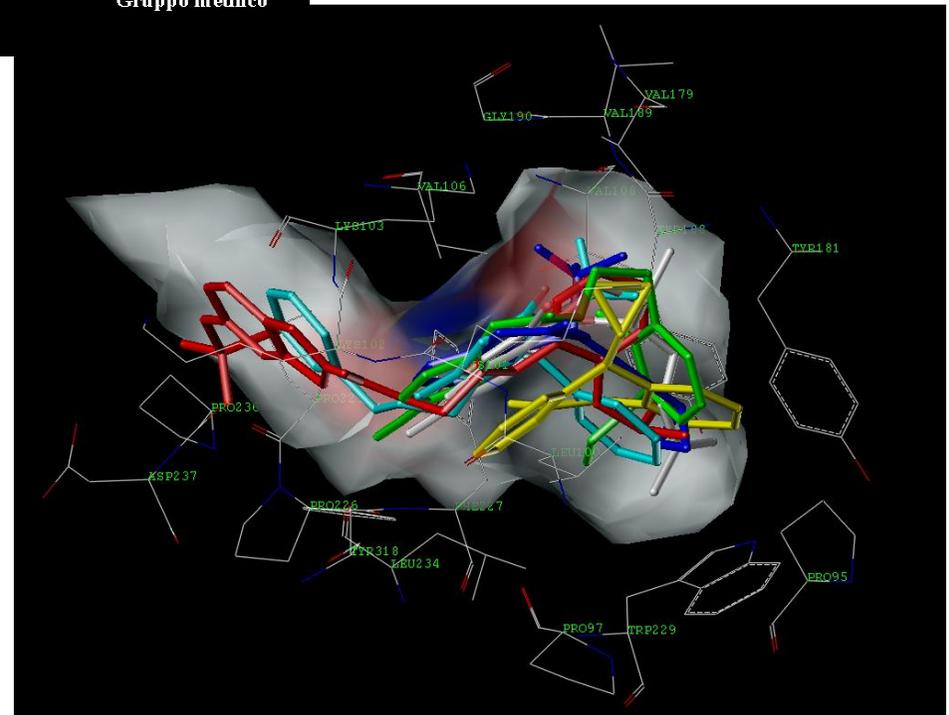
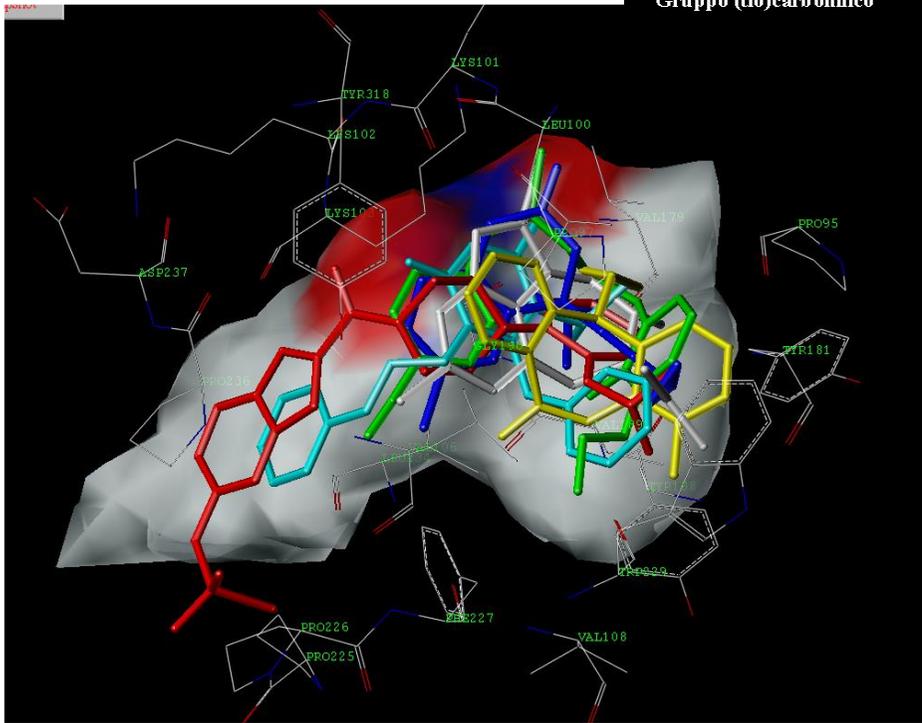


9-Cl-TIBO

Binding Mode degli NNRTIs

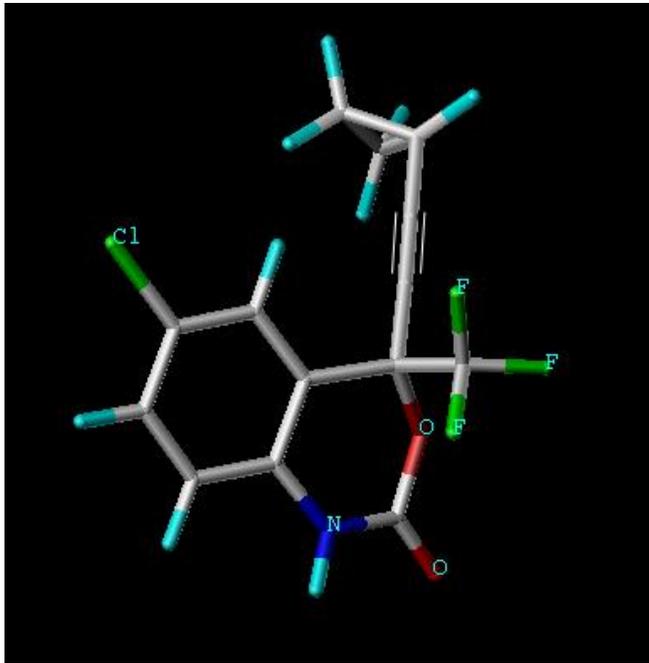


Schematizzazione del modello “a farfalla” di Schäffer

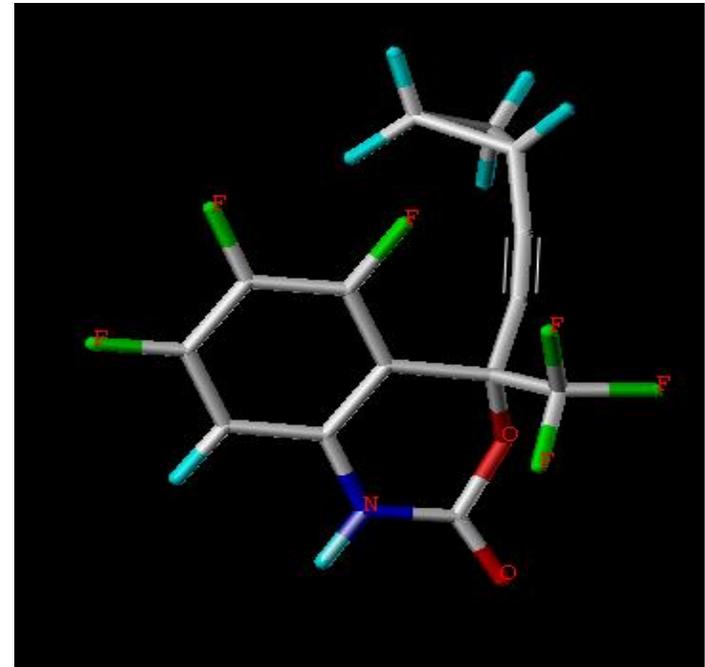
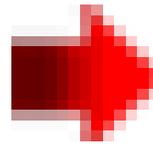


Vista ortogonale della tasca non nucleosidica (NNBS) della trascrittasi inversa nella quale sono inseriti gli NNRTIs: 9 Cl TIBO (bianco), Nevirapina (giallo), Efavirenz (blu), Delarvidina (rosso), Troviridina (verde) ed HEPT (celeste) in cui è possibile osservare la caratteristica conformazione di legame “a farfalla”.

Analisi strutturale

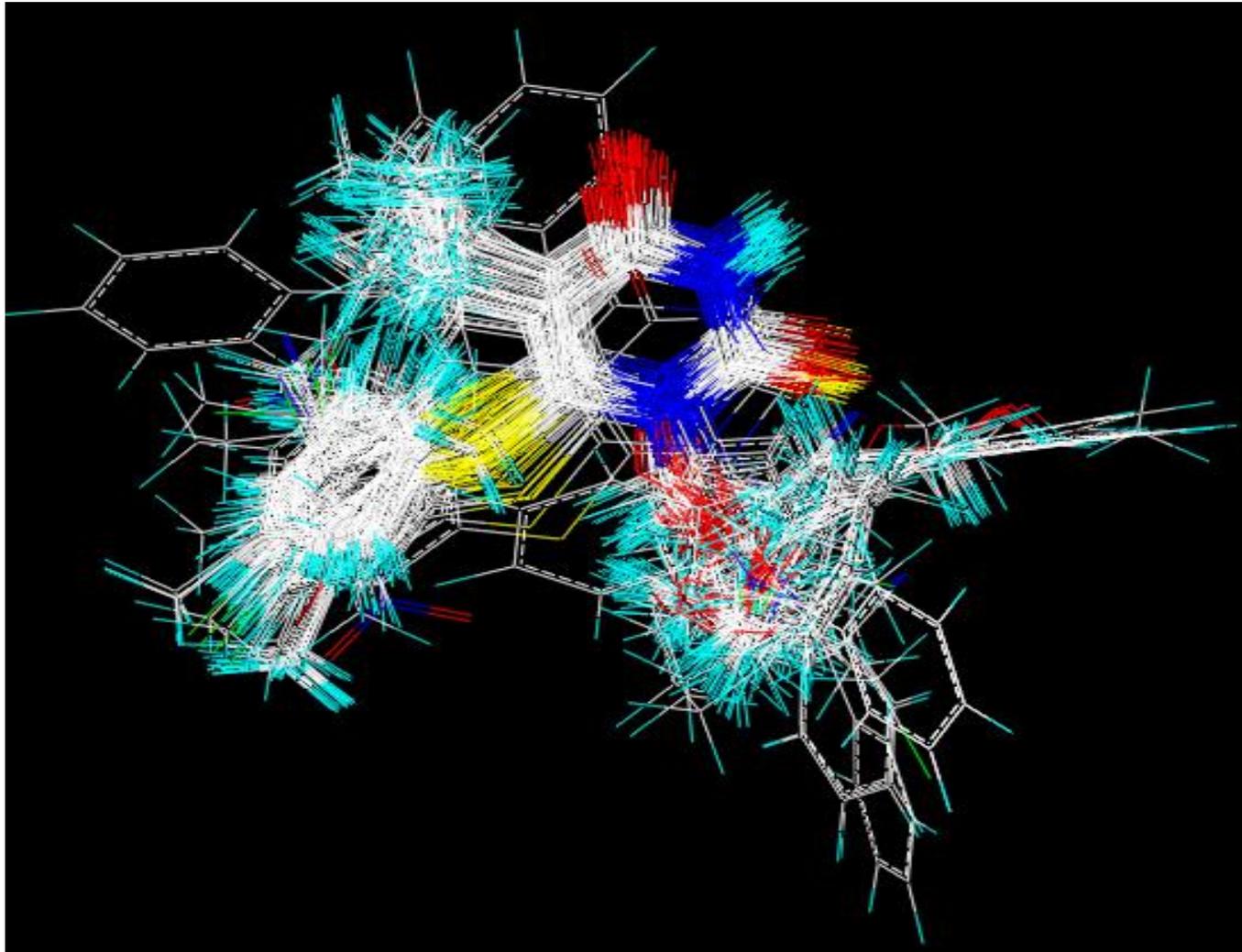


Struttura leader
“EFAVIRENZ”

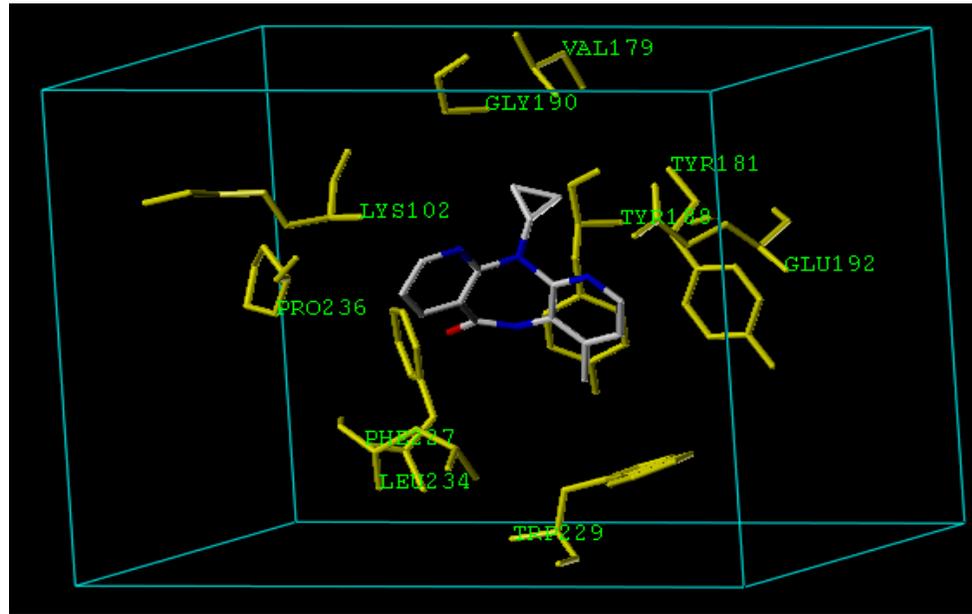


Derivato “EFAV_54”
Molecola più attiva

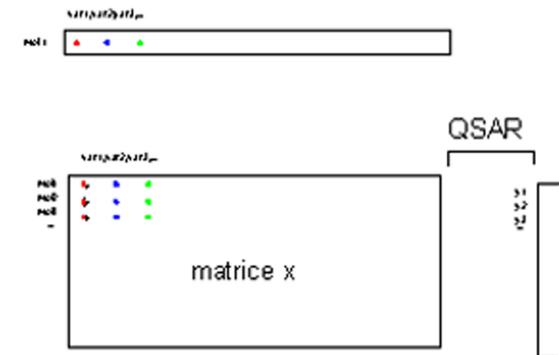
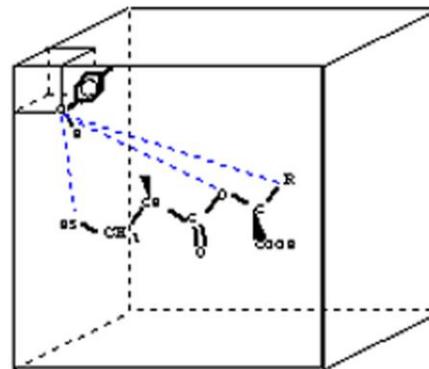
Allineamento del database dei derivati dell'HEPT



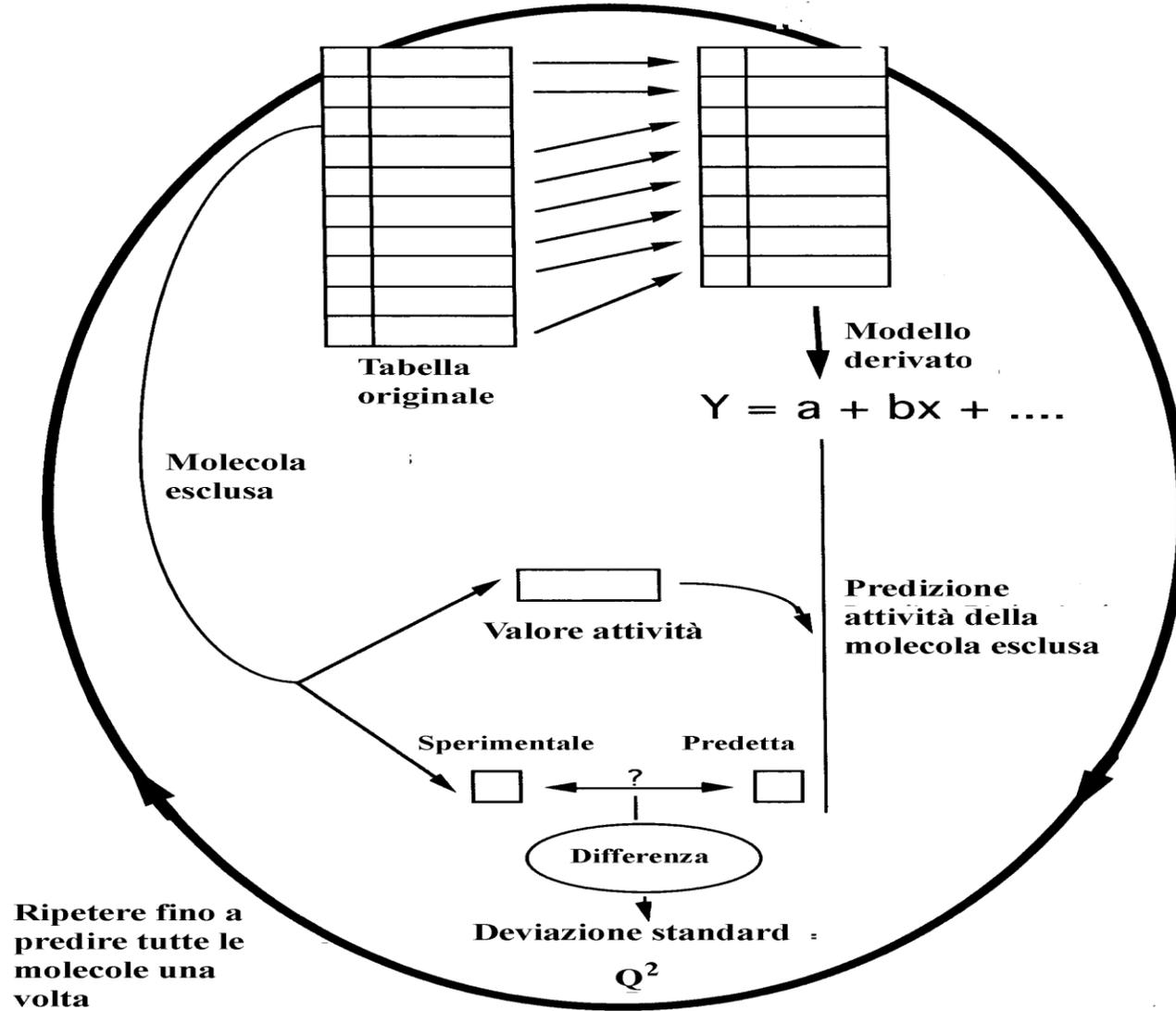
Calcolo dei descrittori molecolari (MIFs)



	X	Y	Z
Angolo basso (A)	6.0	-46.0	-12.0
Angolo alto (B)	28.0	-14.0	10.0
Distanza di step	1.0	1.0	1.0
Numero di steps	23	33	23
Atomo sonda C.ar			



PLS e Crossvalidazione

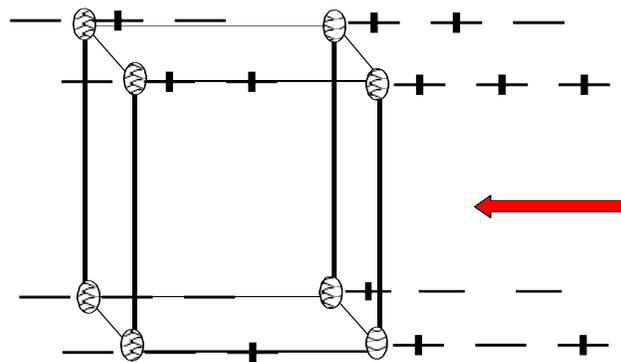


Risultati delle analisi PLS e CV

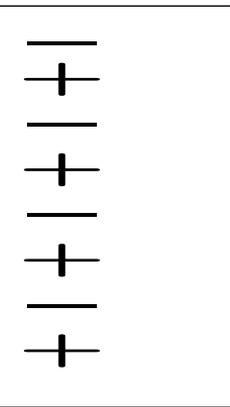
	Iniziale					Advanced Pretreatment			
	<i>N</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>
EFAVIRENZ	55	0.28	0.87	5	7833	0.28	0.86	5	1530
BHAP	64	0.45	0.86	5	11924	0.56	0.73	2	2716
NEVIRAPINA	92	0.33	0.60	3	7316	0.32	0.60	3	1209
PETT	106	0.62	0.88	5	8673	0.62	0.88	5	1745
TIBO	112	0.66	0.83	4	8549	0.67	0.83	4	1532
HEPT	148	0.60	0.82	5	12179	0.60	0.82	5	2690
	Prima FFD					Seconda FFD			
	<i>N</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>
EFAVIRENZ	55	0.50	0.85	5	1122	0.61	0.86	5	750
BHAP	64	0.62	0.78	3	2207	0.67	0.80	3	1937
NEVIRAPINA	92	0.39	0.62	3	1073	0.42	0.64	3	973
PETT	106	0.71	0.86	4	1156	0.77	0.86	3	821
TIBO	112	0.72	0.86	4	1199	0.75	0.86	4	1079
HEPT	148	0.69	0.78	3	1564	0.72	0.80	3	1073
	Terza FFD					Quarta FFD			
	<i>N</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>	Q^2	R^2	<i>N.com</i>	<i>N.variabili</i>
EFAVIRENZ	55	0.68	0.86	4	456	0.72	0.84	3	332
BHAP	64	0.70	0.82	3	1660	0.72	0.84	3	1462
NEVIRAPINA	92	0.47	0.66	3	856	0.53	0.70	3	661
PETT	106	0.81	0.88	3	618	0.82	0.89	3	557
TIBO	112	0.76	0.86	3	950	0.78	0.87	3	864
HEPT	148	0.76	0.82	3	877	0.76	0.83	3	718

Selezione delle variabili con il metodo FFD

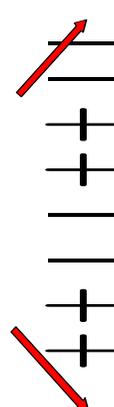
FD



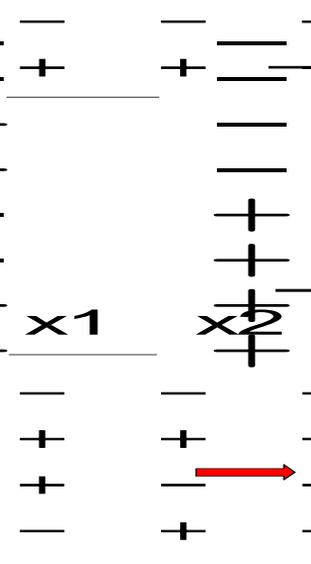
x_1



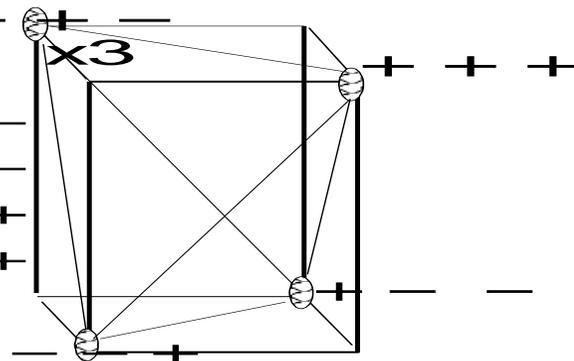
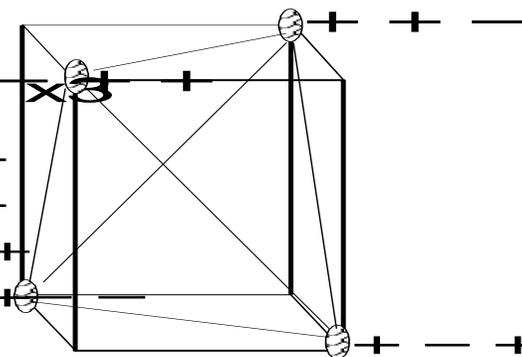
x_2



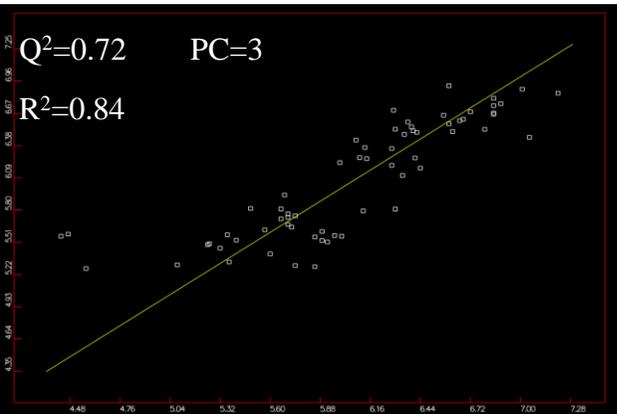
x_3



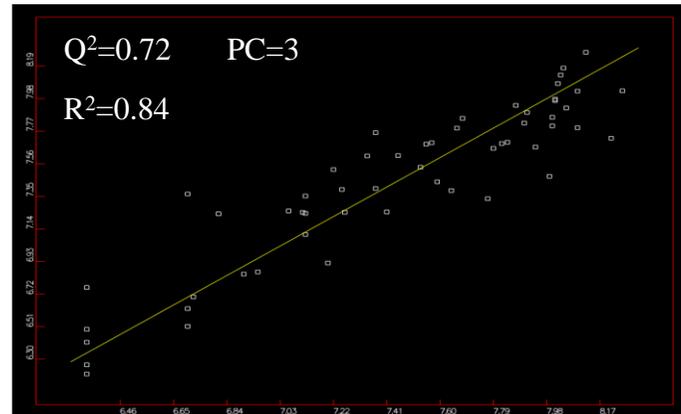
FFD



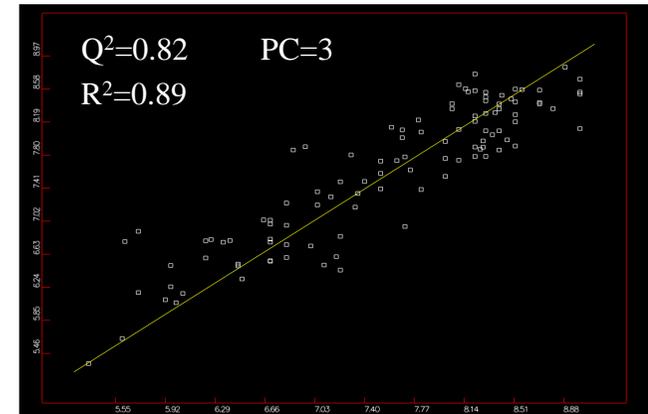
GRAFICI DEI MODELLI FINALI DI ATTIVITA' SPERIMENTALE-RICALCOLATA



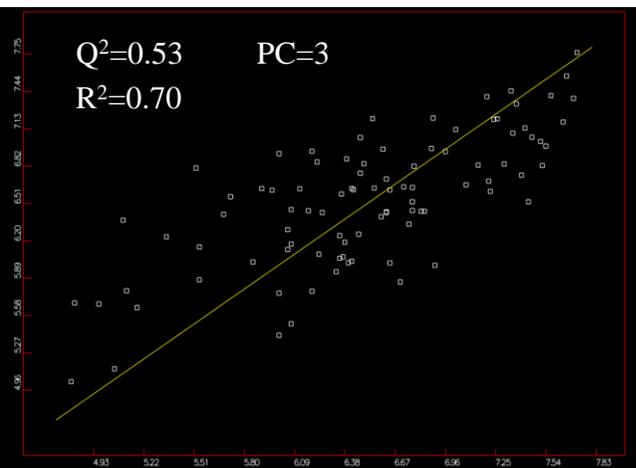
BHAP



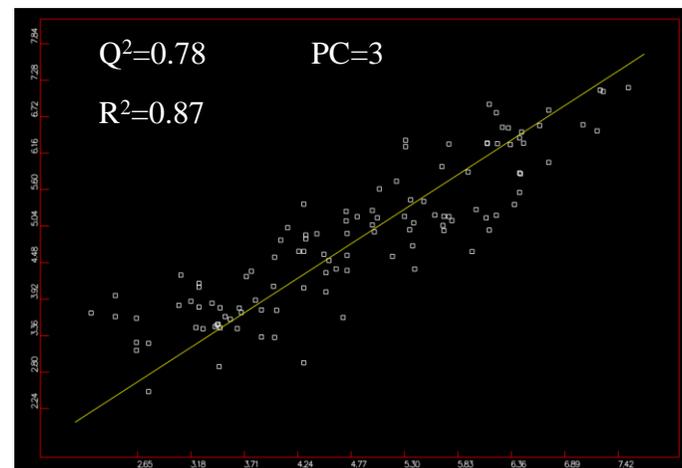
EFAVIRENZ



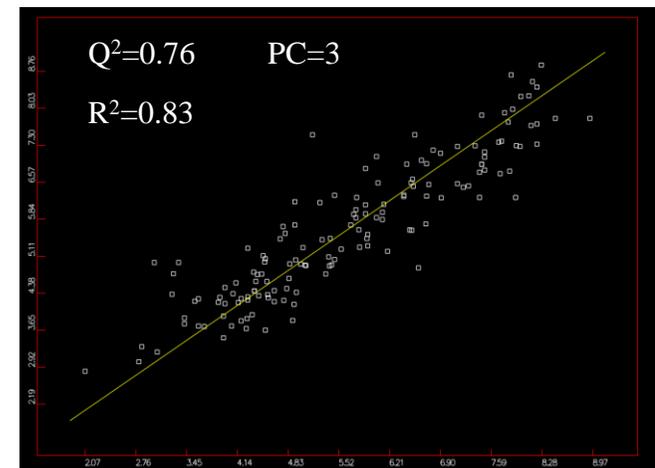
PETT



NEVIRAPINA

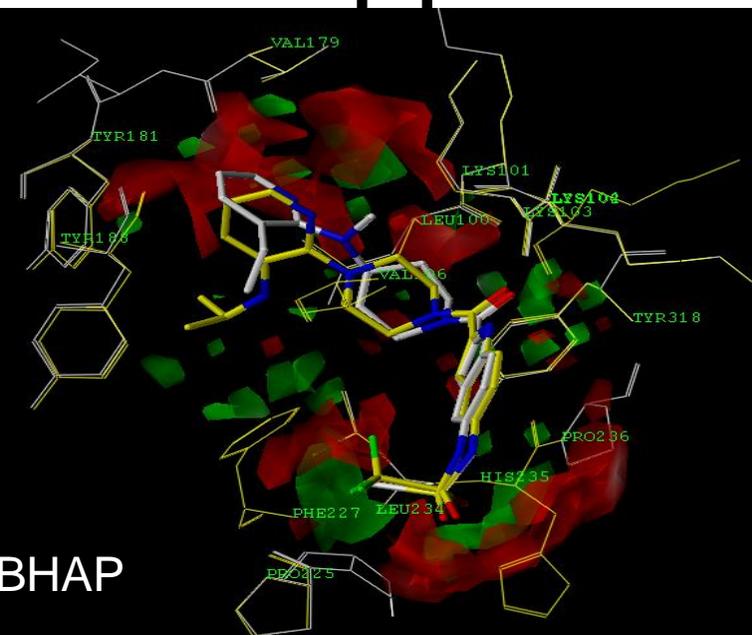


TIBO

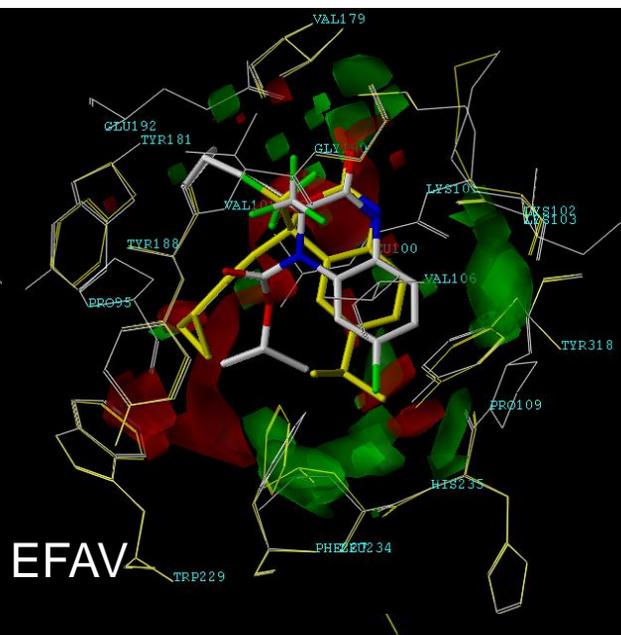


HEPT

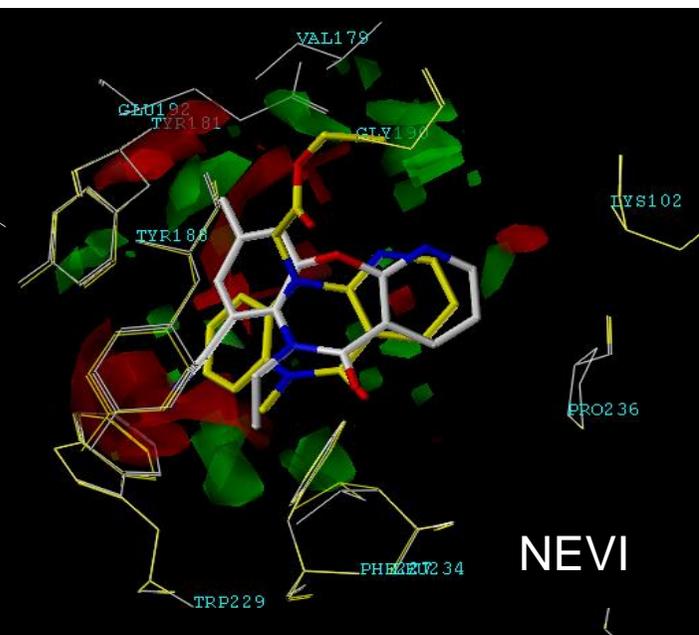
Mappe di correlazione 3D QSAR



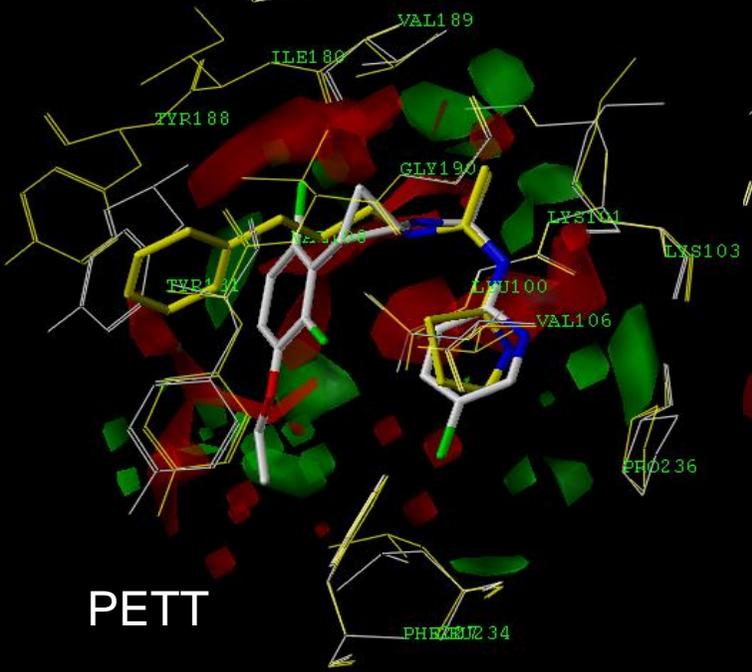
BHAP



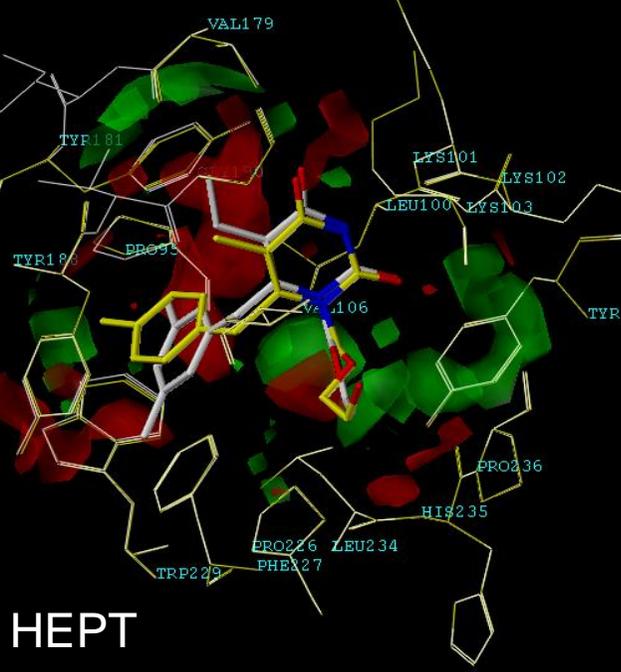
EFAV



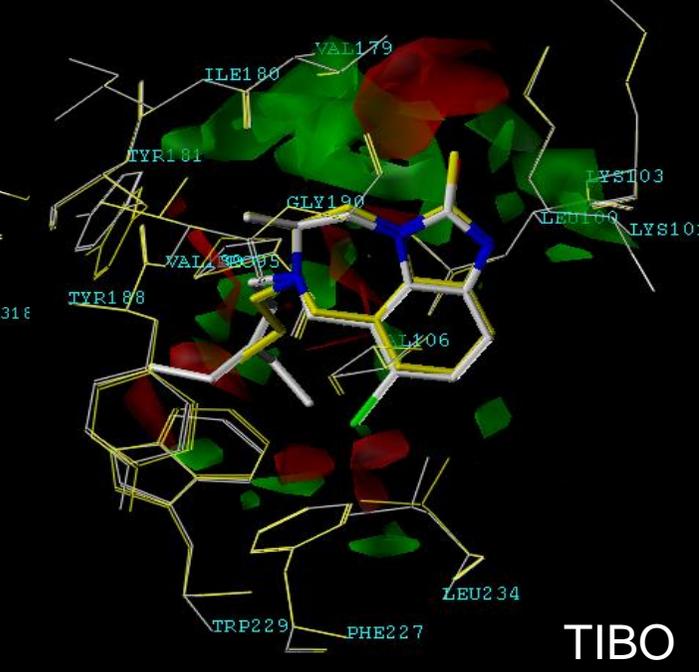
NEVI



PETT



HEPT



TIBO