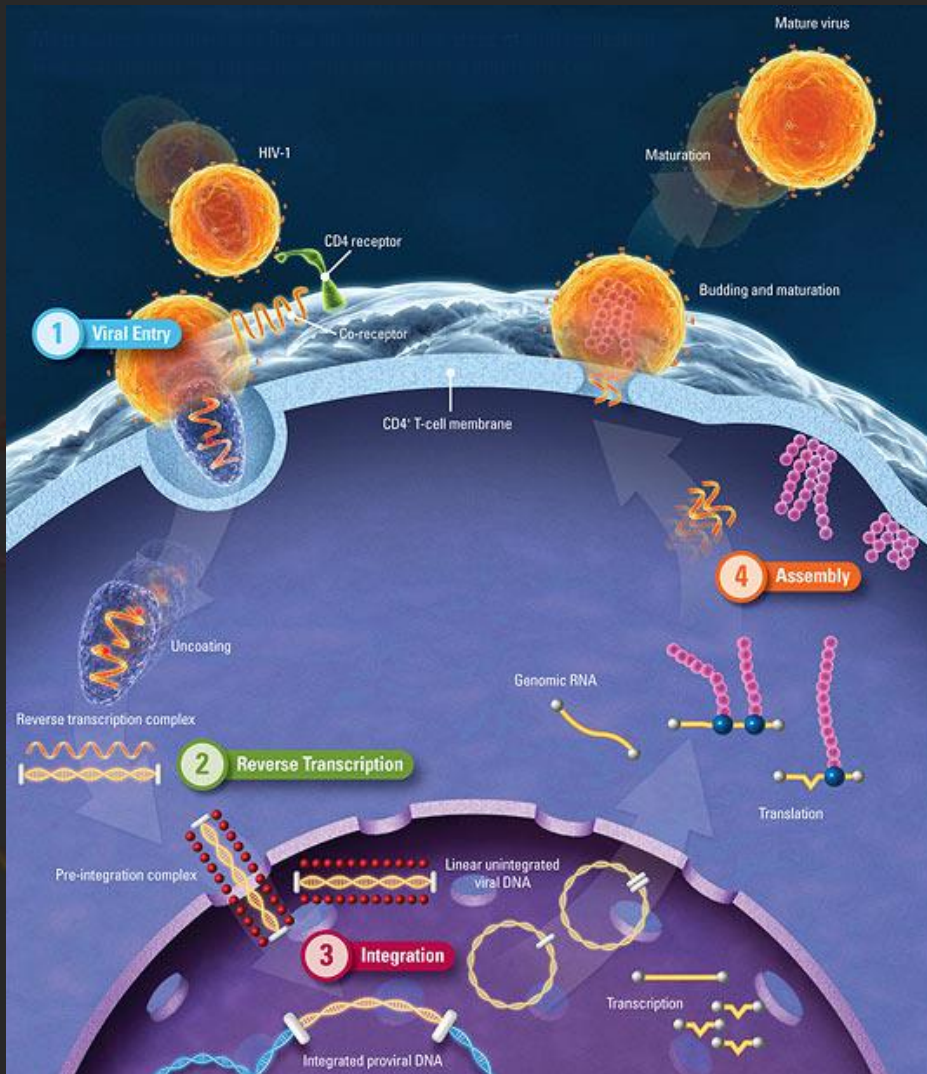


Trascrittasi Inversa dell'HIV:
Costruzione di un Modello 3D-QSAR
Predittivo Mediante la Tecnica
“Comparative Binding Energy Analysis”
(COMBINE)

Relatore: Dr. Rino Ragno

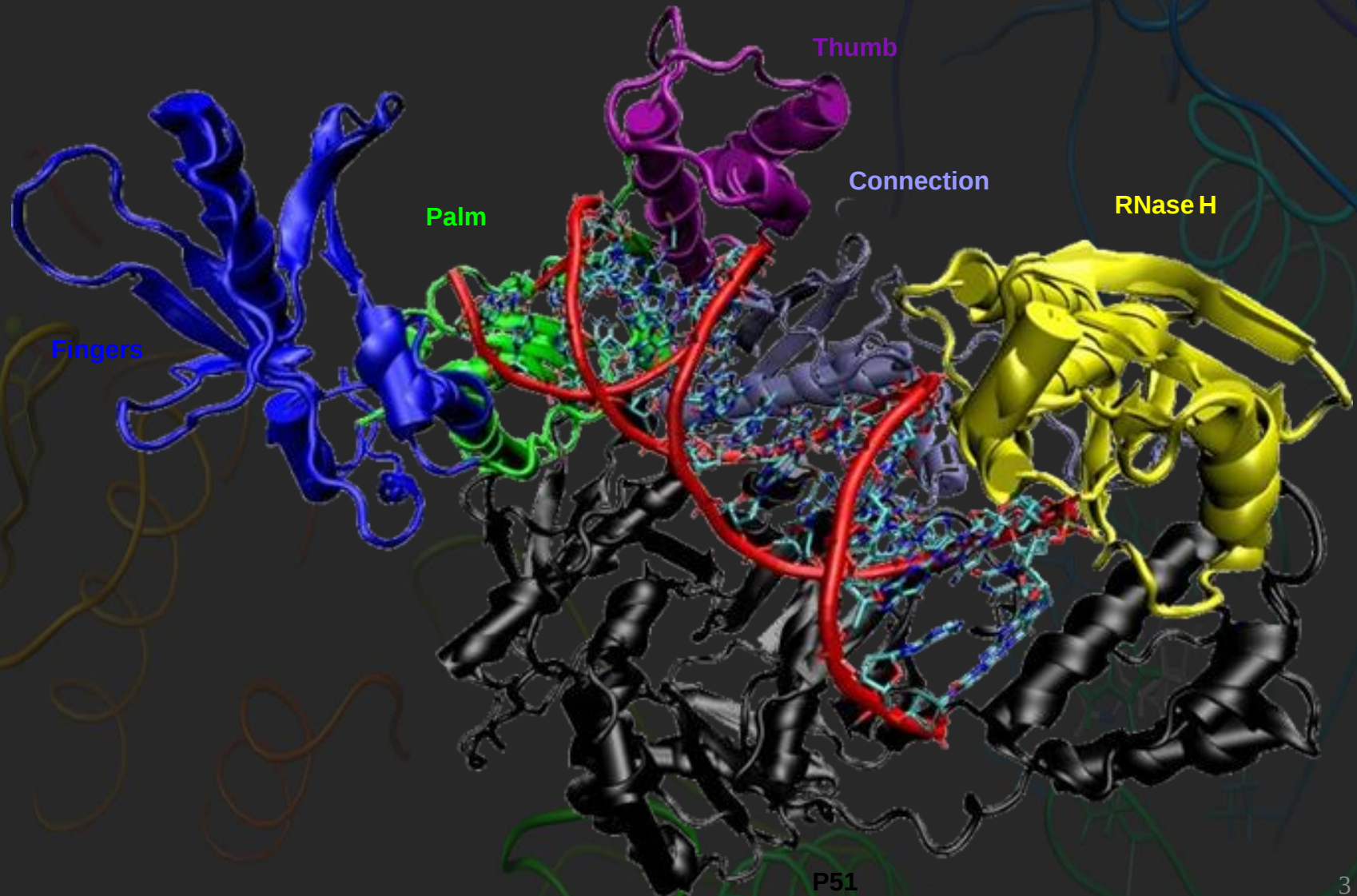
Laureando: Riccardo De Santis

HIV

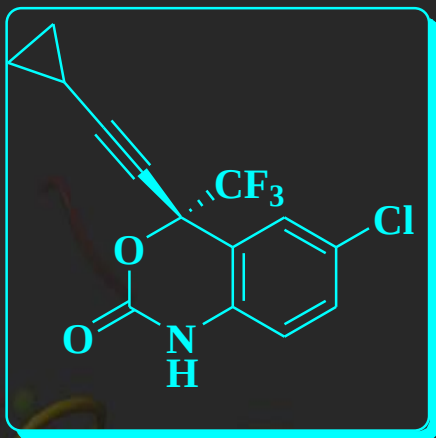


- 1) Modulatori dell'espressione del recettore cellulare CD4;
- 2) Inibitori della fase di attacco del virus all'ospite;
- 3) Antagonisti dei recettori delle chemochine;
- 4) Inibitori della fusione cellulare;
- 5) Inibitori della trascrittasi inversa:
 - 5.1) Inibitori nucleosidici della trascrittasi inversa (NRTIs);
 - 5.2) Inibitori nucleotidici della trascrittasi inversa (NtRTIs);
 - 5.3) Inibitori non nucleosidici della trascrittasi inversa (NNRTIs);
- 6) Inibitori dell'integrasi;
- 7) Inibitori della trascrizione;
- 8) Inibitori della proteasi (PIs) ;
- 9) Inibitori della ribonucleasi H.

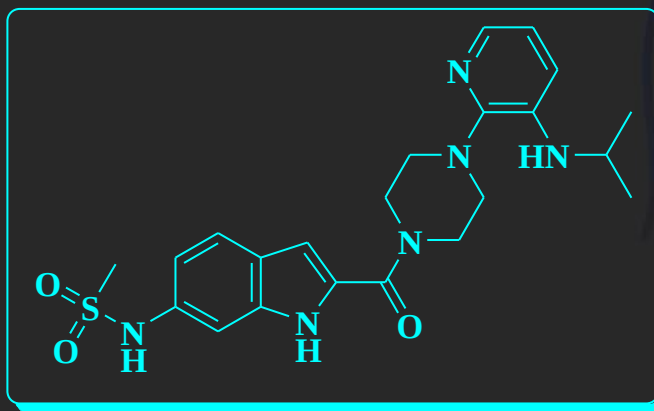
TRASCRITTASI INVERSA (RT)



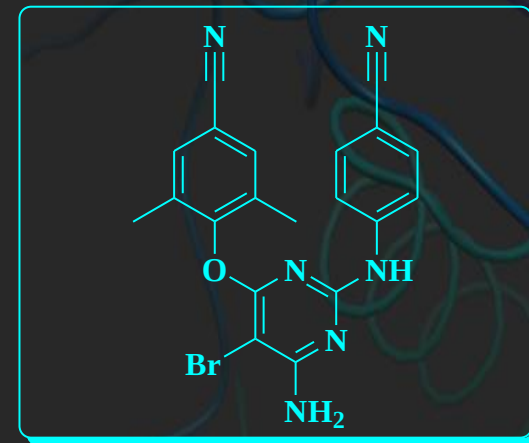
INIBITORI NON-NUCLEOSIDICI



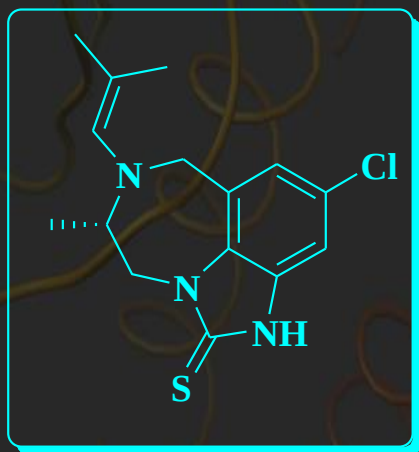
Efavirenz



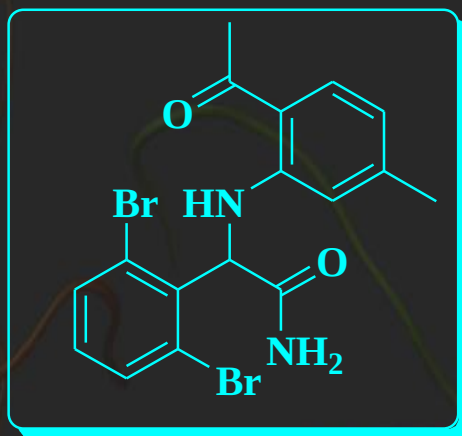
Delavirdina



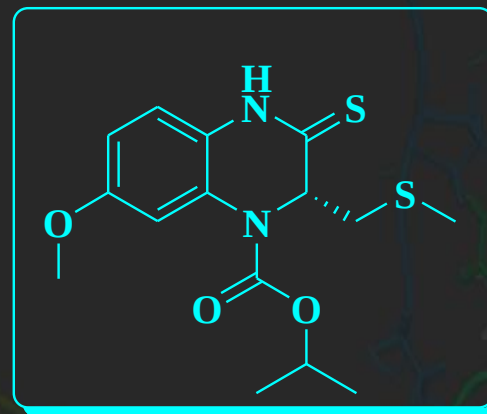
Etravirina



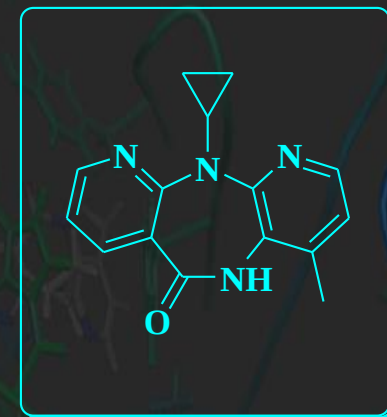
9-Cl-TIBO



Br-APA



HBY-097



Nevirapina

COMBINE

- Generazione di modelli di meccanica molecolare di una serie di ligandi complessati con il loro recettore e di ligandi e recettori separati
- Analisi di regressione lineare delle energie di interazione calcolate per ottenere costanti di legame dell'inibitore o attività, per soppesare le componenti energetiche dell'interazione ligando recettore e derivare una funzione matematica del tipo:

$$\Delta U = \sum_{(i=1)}^{(n_l)} \sum_{(j=1)}^{(n_r)} u_{ij}^{vdw} + \sum_{(i=1)}^{(n_r)} \sum_{(j=1)}^{(n_r)} u_{ij}^{ele} + \sum_{(i=1)}^{(n_l)} \Delta u_i^{(B,L)} + \sum_{(i=1)}^{(n_l)} \Delta u_i^{(A,L)} + \sum_{(i=1)}^{(n_l)} \Delta u_i^{(T,L)} + \sum_{(i < i')}^{(n_l)} \Delta u_{(ii')}^{(N)} + \sum_{(j=1)}^{(n_r)} \Delta u_j^{(B,R)} + \sum_{(j=1)}^{(n_r)} \Delta u_j^{(A,R)} + \sum_{(j=1)}^{(n_r)} \Delta u_j^{(T,R)} + \sum_{(j < j')}^{(n_r)} \Delta u_{(jj')}^{(N)}$$

COMBINE

Recettore non legato

Ligando non legato

Complesso ligando + recettore

Minimizzazione energetica per tutti i modelli

Calcolo $\Delta U = E_{lr} - E_r - E_l$
per ciascun ligando

Partizionamento di ΔU nelle sue componenti

Pretrattamento della matrice (selezione delle variabili)

Correlazione delle componenti di ΔU con le energie libere
di legame calcolate (ΔG) (o attività) tramite PLS
per derivare un modello $\Delta G \approx \sum w_i \Delta u_i^{sel} + C$

Effettuare predizioni per nuovi ligandi

PARTE SPERIMENTALE

1. Preparazione dei complessi

Scelta e selezione del Training-Set

Allineamento del Training-Set

Parametrizzazione dei complessi

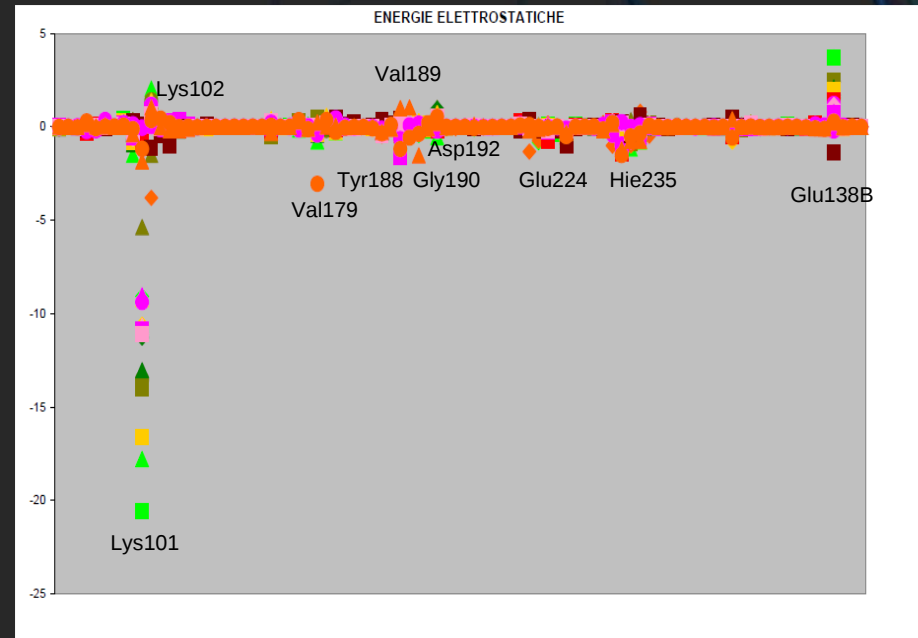
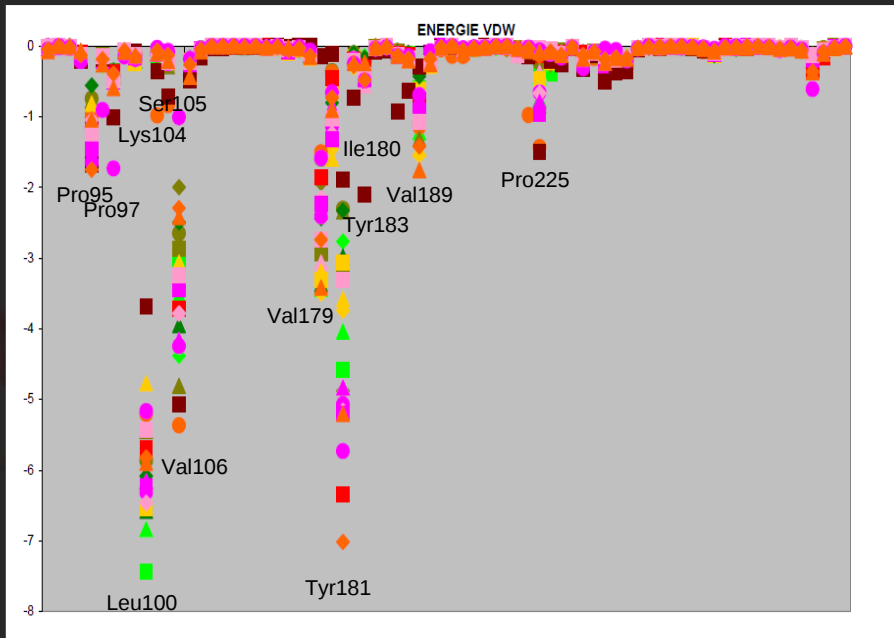
Minimizzazione dei complessi

2. Analisi dei dati

Deconvoluzione residuale delle energie

Elaborazione statistica dei modelli 3-D QSAR

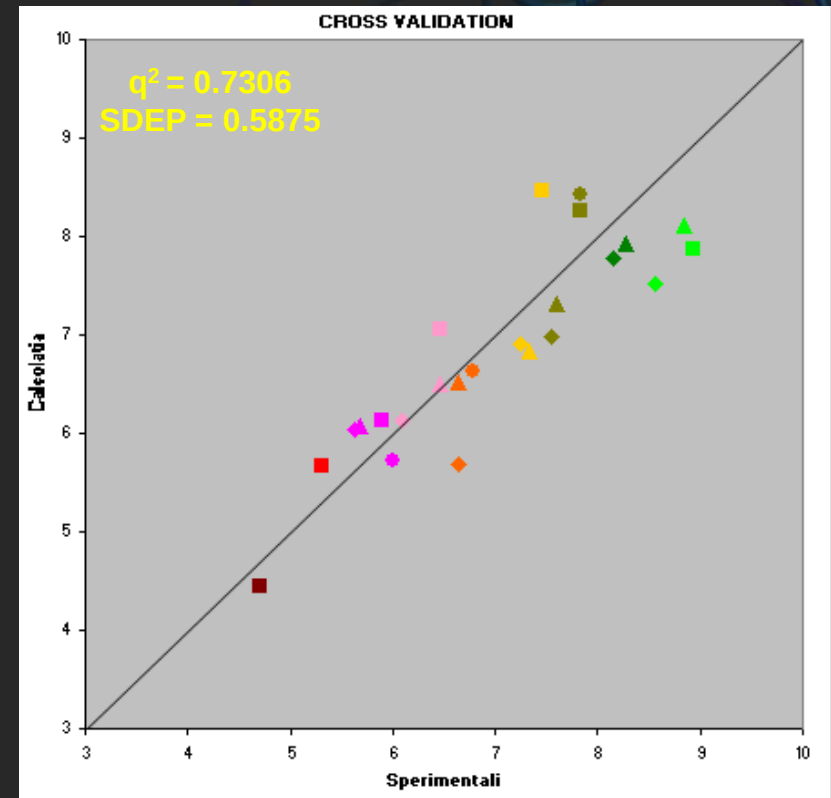
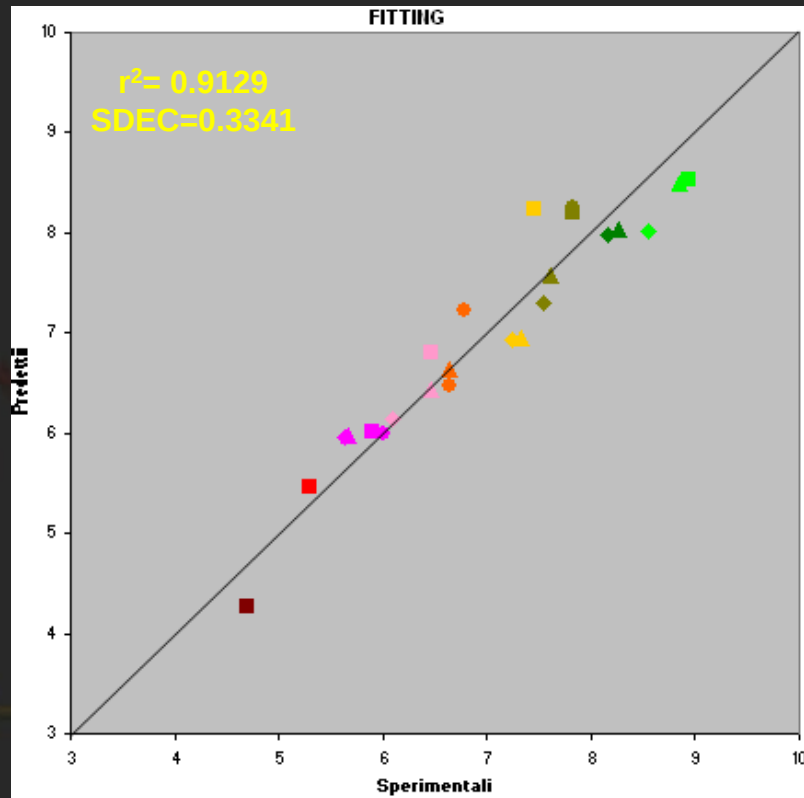
ANALISI DEI RISULTATI



◆ 1BQM ▲ 1DTQ ■ 1DTT ◆ 1EET ■ 1FK9 ◆ 1HNV ● 1IKW ● 1KLM ▲ 1REV ▲ 1RT1 ▲ 1RT4 ■ 1RT5
 ◆ 1RT6 ▲ 1RT7 ■ 1RTH ● 1TKT ◆ 1TKZ ■ 1TL1 ▲ 1TL3 ■ 1TV6 ■ 1TVR ● 1VRT ◆ 1VRU ▲ 1HNI

att. μM	4.5-5	5-5.5	5.5-6	6-6.5	6.5-7	7-7.5	7.5-8	8-8.5	8.5-9

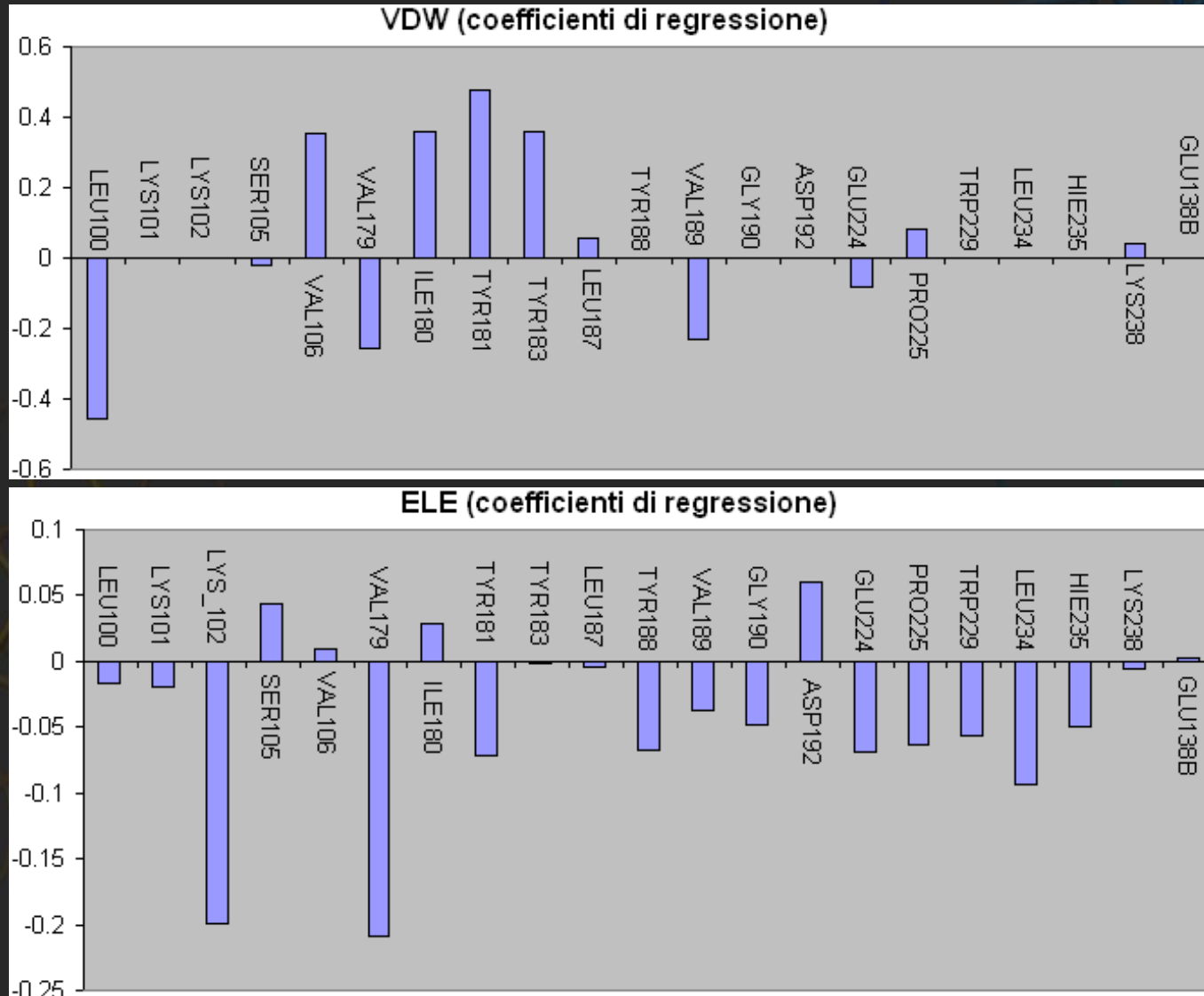
ANALISI DEI RISULTATI



◆ 1BQM ▲ 1DTQ ■ 1DTT ◆ 1EET ■ 1FK9 ◆ 1HNV ● 1IKW ● 1KLM ▲ 1REV ▲ 1RT1 ▲ 1RT4 ■ 1RT5
◆ 1RT6 ▲ 1RT7 ■ 1RTH ● 1TKT ◆ 1TKZ ■ 1TL1 ▲ 1TL3 ■ 1TV6 ■ 1TVR ● 1VRT ◆ 1VRU ▲ 1HNI

att. μM	4.5-5	5-5.5	5.5-6	6-6.5	6.5-7	7-7.5	7.5-8	8-8.5	8.5-9

ANALISI DEI RISULTATI



ANALISI DEI RISULTATI

CONTRIBUTO TOTALE ELE +VAN DER WAALS		1DTT	1DTQ*	1BQM	1RT4*	1RT6	1FK9*	1IKW*	1RT1*	1EET	1RT5*	1RT7	1HNW	1KLM	1VRU	1HNI	1REV	1TVR*	1TKZ	1VRT	1TL1	1TL3	1TKT	1RTH	1TV6	MAX
LEU_100		3.41	3.15	2.96	3.02	2.78	2.87	2.69	2.48	2.87	3.00	2.18	2.49	2.37	2.66	2.70	2.59	2.48	2.96	2.36	2.86	2.82	2.89	2.60	1.68	3.41
VAL_179		0.61	1.04	0.76	0.94	0.63	0.65	0.36	0.73	0.49	0.91	0.79	0.92	0.43	1.34	0.82	0.79	0.72	0.55	0.49	0.57	0.58	0.61	0.50	0.04	1.34
GLU_138B		1.01	1.01	0.40	0.57	0.08	0.67	0.65	0.09	0.42	0.53	0.47	0.22	0.05	0.08	0.07	0.22	0.02	0.31	-0.06	0.20	0.22	0.33	0.38	-0.36	1.01
LYS_102		0.14	0.28	0.27	0.20	0.10	0.25	0.25	0.31	0.15	0.14	0.34	0.36	0.27	0.35	0.37	0.21	0.25	0.19	0.16	0.22	0.18	0.20	0.17	0.07	0.37
LYS_101		0.39	0.34	0.17	0.25	0.22	0.27	0.26	0.10	0.26	0.32	0.18	0.20	0.01	0.02	0.04	0.20	0.21	0.21	0.00	0.21	0.17	0.18	0.02	0.00	0.39
VAL_189		0.07	0.03	0.03	0.03	0.04	0.07	0.06	0.00	0.06	0.03	0.00	0.07	0.07	0.07	0.06	0.02	-0.01	0.05	-0.01	0.05	0.05	0.05	0.07	-0.01	0.07
GLU_224		0.03	0.04	0.01	0.01	0.02	0.01	0.02	0.03	0.05	0.02	0.02	0.01	0.02	0.03	0.02	0.01	0.01	0.01	0.00	0.02	0.01	0.01	0.04	0.06	0.06
TYR_188		0.01	0.05	0.02	-0.03	0.03	0.01	0.01	-0.01	0.06	0.00	0.07	-0.02	0.05	0.08	-0.07	0.00	-0.01	0.03	0.04	0.11	0.02	0.02	0.02	-0.03	0.11
LEU_234		0.01	-0.03	0.03	-0.01	0.06	-0.01	-0.01	0.06	0.01	-0.01	0.04	0.04	0.03	0.03	0.01	0.02	0.04	0.00	-0.01	0.00	0.01	0.00	-0.01	0.02	0.06
HIE_235		0.01	0.00	0.02	0.01	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.01	0.17	0.00	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.17
GLY_190		0.00	-0.01	0.02	0.00	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.03	0.02	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.01	0.00	0.00	0.03
ASP_192		0.00	-0.01	0.02	-0.01	0.00	0.01	0.01	0.01	0.00	-0.01	-0.01	0.00	0.01	0.02	0.07	0.00	0.00	0.00	-0.01	0.00	0.00	0.00	0.00	0.01	0.07
TRP_229		-0.01	-0.01	0.05	0.00	-0.02	-0.01	-0.01	0.02	-0.02	-0.01	0.00	-0.02	0.09	-0.02	-0.01	0.00	0.01	-0.03	0.04	-0.02	-0.01	-0.02	-0.03	0.00	0.09
SER_105		-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	-0.01	-0.01	-0.01	-0.01	-0.01	0.00
PRO_225		-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.04	-0.01
LYS_238		-0.03	-0.02	0.01	-0.06	-0.01	-0.01	-0.02	-0.05	-0.07	-0.04	-0.01	0.00	-0.07	-0.01	0.00	-0.03	0.00	-0.05	0.00	-0.07	-0.06	-0.05	-0.01	-0.11	0.01
LEU_187		-0.17	-0.41	-0.08	-0.16	-0.19	-0.18	-0.28	0.30	-0.20	-0.18	-0.28	-0.16	0.76	-0.07	-0.21	-0.15	-0.13	-0.16	-0.01	-0.18	-0.23	-0.23	-0.18	0.22	0.76
ILE_180		-0.07	-0.05	-0.05	-0.07	-0.06	-0.09	-0.07	-0.07	-0.08	-0.11	-0.09	-0.19	-0.08	-0.17	-0.09	-0.20	-0.14	-0.15	-0.17	-0.17	-0.12	-0.14	-0.10	-0.75	-0.05
TYR_183		-0.18	-0.21	-0.26	-0.33	-0.28	-0.21	-0.13	-0.21	-0.17	-0.22	-0.55	-0.51	-0.13	-0.25	-0.32	-0.33	-0.36	-0.44	-0.23	-0.47	-0.30	-0.40	-0.16	-0.04	-0.04
VAL_106		-1.07	-1.25	-1.55	-1.40	-0.88	-1.02	-0.94	-1.70	-0.71	-1.15	-1.08	-1.16	-1.90	-0.81	-0.85	-1.14	-1.15	-1.34	-0.36	-1.22	-1.47	-1.50	-1.31	-1.79	-0.36
TYR_181		-2.16	-1.90	-1.31	-1.42	-1.10	-1.55	-1.11	-1.11	-2.31	-1.47	-1.69	-1.78	-1.48	-3.32	-2.48	-2.28	-1.58	-2.46	-2.76	-2.48	-2.31	-2.42	-3.01	-0.93	-0.93
recalc		8.55	8.58	8.06	8.11	7.97	8.29	8.30	7.55	7.36	8.31	6.95	7.02	7.25	6.59	6.69	6.52	6.91	6.23	6.02	6.15	6.09	6.07	5.55	4.55	13.13
exp		8.55	8.85	8.94	7.55	7.83	7.24	7.83	6.79	6.46	7.61	8.27	7.46	8.16	7.33	5.30	5.63	6.10	5.90	5.68	4.70	6.46	6.00	6.63	6.63	

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ANALISI DEI RISULTATI

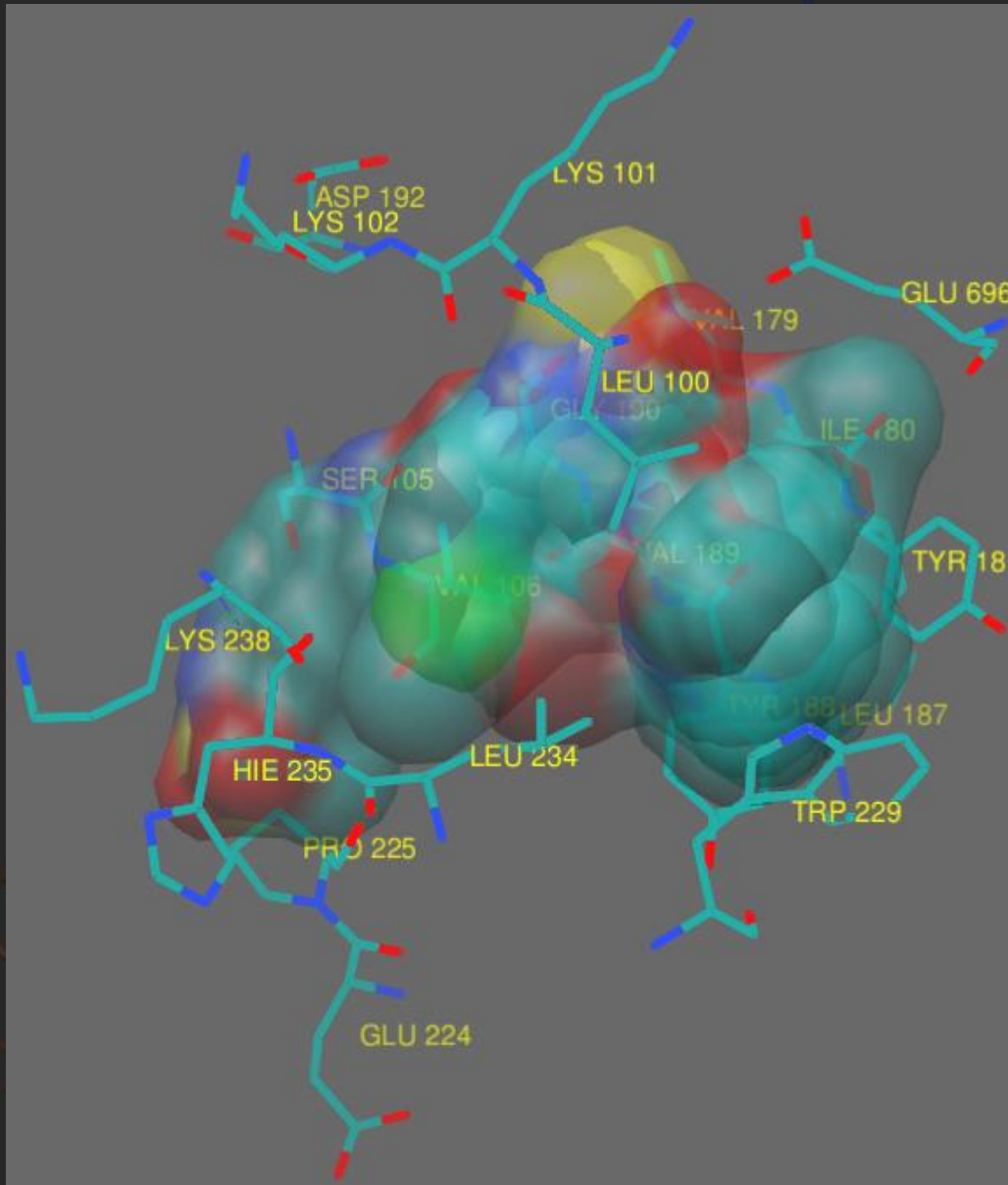
CONTRIBUTO TOTALE																									Ideale
	1DTT	1DTQ	1BQM	1RT4	1RT6	1FK9	1IKW	1RT1	1EET	1RT5	1RT7	1HNH	1KLM	1VRU	1HNI	1REV	1TVR	1TK2	1VRT	1TL1	1TL3	1TKT	1RTH	1TV6	MAX
LEU_100	3.41	3.15	2.96	3.02	2.78	2.87	2.69	2.48	2.87	3.00	2.18	2.49	2.37	2.66	2.70	2.59	2.48	2.96	2.36	2.86	2.82	2.89	2.60	1.68	3.41
LVS_101	0.39	0.34	0.17	0.25	0.22	0.27	0.26	0.10	0.26	0.32	0.18	0.20	0.01	0.02	0.04	0.20	0.21	0.21	0.00	0.21	0.17	0.18	0.02	0.00	0.39
LVS_102	-0.17	-0.41	-0.08	-0.16	-0.19	-0.18	-0.28	0.30	-0.20	-0.18	-0.28	-0.16	0.76	-0.07	-0.21	-0.15	-0.13	-0.16	-0.01	-0.18	-0.23	-0.23	-0.18	0.22	0.76
SEP_105	0.00	-0.01	0.02	0.00	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.03	0.02	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.01	0.00	0.00	0.03
VAL_106	-1.07	-1.25	-1.55	-1.40	-0.88	-1.02	-0.94	-1.70	-0.71	-1.15	-1.08	-1.16	-1.90	-0.81	-0.85	-1.14	-1.15	-1.34	-0.36	-1.22	-1.47	-1.50	-1.31	-1.79	-0.36
VAL_179	0.61	1.04	0.76	0.94	0.63	0.65	0.36	0.73	0.49	0.91	0.79	0.92	0.43	1.34	0.82	0.79	0.72	0.55	0.49	0.57	0.58	0.61	0.50	0.04	1.34
ILE_180	-0.18	-0.21	-0.26	-0.33	-0.28	-0.21	-0.13	-0.21	-0.17	-0.22	-0.55	-0.51	-0.13	-0.25	-0.32	-0.33	-0.36	-0.44	-0.23	-0.47	-0.30	-0.40	-0.16	-0.04	-0.04
TYR_181	-2.16	-1.90	-1.31	-1.42	-1.10	-1.55	-1.11	-1.11	-2.31	-1.47	-1.69	-1.78	-1.48	-3.32	-2.48	-2.28	-1.58	-2.46	-2.76	-2.48	-2.31	-2.42	-3.01	-0.93	-0.93
TYR_183	-0.07	-0.05	-0.05	-0.07	-0.06	-0.09	-0.07	-0.07	-0.08	-0.11	-0.09	-0.19	-0.08	-0.17	-0.09	-0.20	-0.14	-0.15	-0.17	-0.17	-0.12	-0.14	-0.10	-0.75	-0.05
LEU_187	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.04	-0.01
TYR_188	0.01	0.05	0.02	-0.03	0.03	0.01	0.01	-0.01	0.06	0.00	0.07	-0.02	0.05	0.08	-0.07	0.00	-0.01	0.03	0.04	0.11	0.02	0.02	0.02	-0.03	0.11
VAL_189	0.14	0.28	0.27	0.20	0.10	0.25	0.25	0.31	0.15	0.14	0.34	0.36	0.27	0.35	0.37	0.21	0.25	0.19	0.16	0.22	0.18	0.20	0.17	0.07	0.37
GLY_190	0.00	-0.01	0.02	-0.01	0.00	0.01	0.01	0.01	0.00	-0.01	-0.01	0.00	0.01	0.02	0.07	0.00	0.00	0.00	-0.01	0.00	0.00	0.00	0.00	0.01	0.07
ASP_192	0.01	-0.03	0.03	-0.01	0.06	-0.01	-0.01	0.06	0.01	-0.01	0.04	0.04	0.03	0.03	0.01	0.02	0.04	0.00	-0.01	0.00	0.01	0.00	-0.01	0.02	0.06
GLU_224	0.01	0.00	0.02	0.01	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.01	0.17	0.00	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.17
PRO_225	-0.03	-0.02	0.01	-0.06	-0.01	-0.01	-0.02	-0.05	-0.07	-0.04	-0.01	0.00	-0.07	-0.01	0.00	-0.03	0.00	-0.05	0.00	-0.07	-0.06	-0.05	-0.01	-0.11	0.01
TRP_229	0.03	0.04	0.01	0.01	0.02	0.01	0.02	0.03	0.05	0.02	0.02	0.01	0.02	0.03	0.02	0.01	0.01	0.01	0.00	0.02	0.01	0.01	0.04	0.06	0.06
LEU_234	-0.01	-0.01	0.05	0.00	-0.02	-0.01	-0.01	0.02	-0.02	-0.01	0.00	-0.02	0.09	-0.02	-0.01	0.00	0.01	-0.03	0.04	-0.02	-0.01	-0.02	-0.03	0.00	0.09
HIE_235	0.07	0.03	0.03	0.03	0.04	0.07	0.06	0.00	0.06	0.03	0.00	0.07	0.07	0.07	0.06	0.02	-0.01	0.05	-0.01	0.05	0.05	0.05	0.07	-0.01	0.07
LVS_238	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	-0.01	0.00	-0.01	-0.01	-0.01	-0.01	-0.01	0.00
GLU_138B	1.01	1.01	0.40	0.57	0.08	0.67	0.65	0.09	0.42	0.53	0.47	0.22	0.05	0.08	0.07	0.22	0.02	0.31	-0.06	0.20	0.22	0.33	0.38	-0.36	1.01
resale	8.55	8.58	8.06	8.11	7.97	8.29	8.30	7.55	7.36	8.31	6.95	7.02	7.25	6.59	6.69	6.52	6.91	6.23	6.02	6.15	6.09	6.07	5.55	4.55	13.13
exp	8.55	8.85	8.94	7.55	7.83	7.24	7.83	6.79	6.46	7.61	8.27	7.46	8.16	7.33	5.30	5.63	6.10	5.90	5.68	4.70	6.46	6.00	6.63	6.63	

> Media+Dev.St.
 tra Media-Dev.St. e 0
 < Media-Dev.St.

ANALISI DEI RISULTATI

Interazioni Steriche

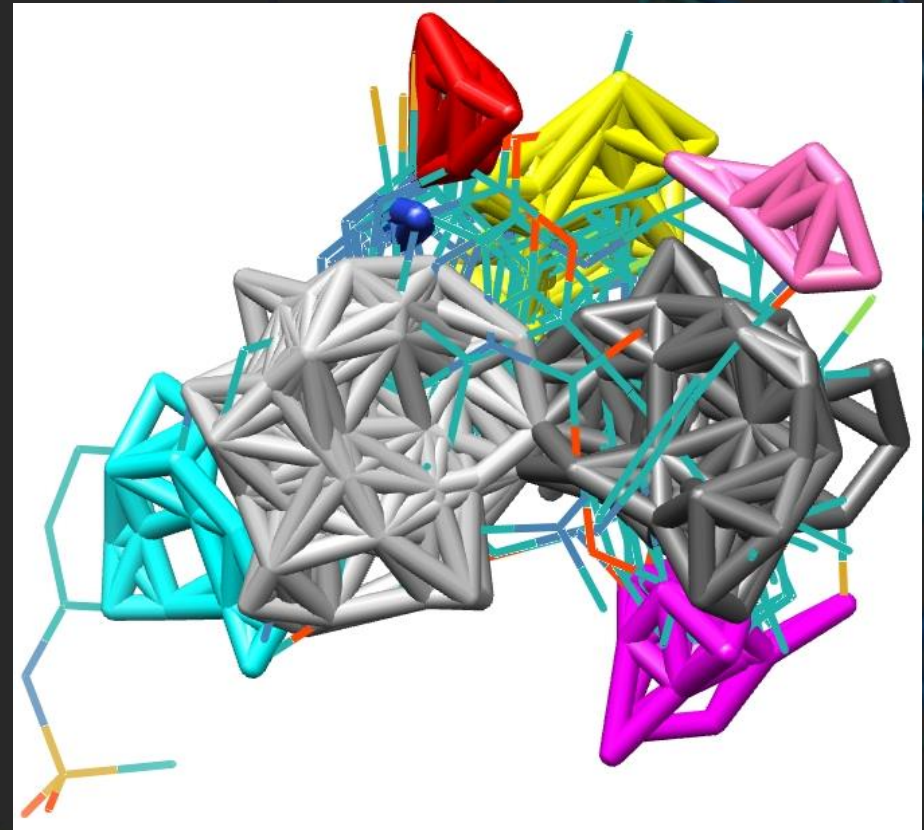
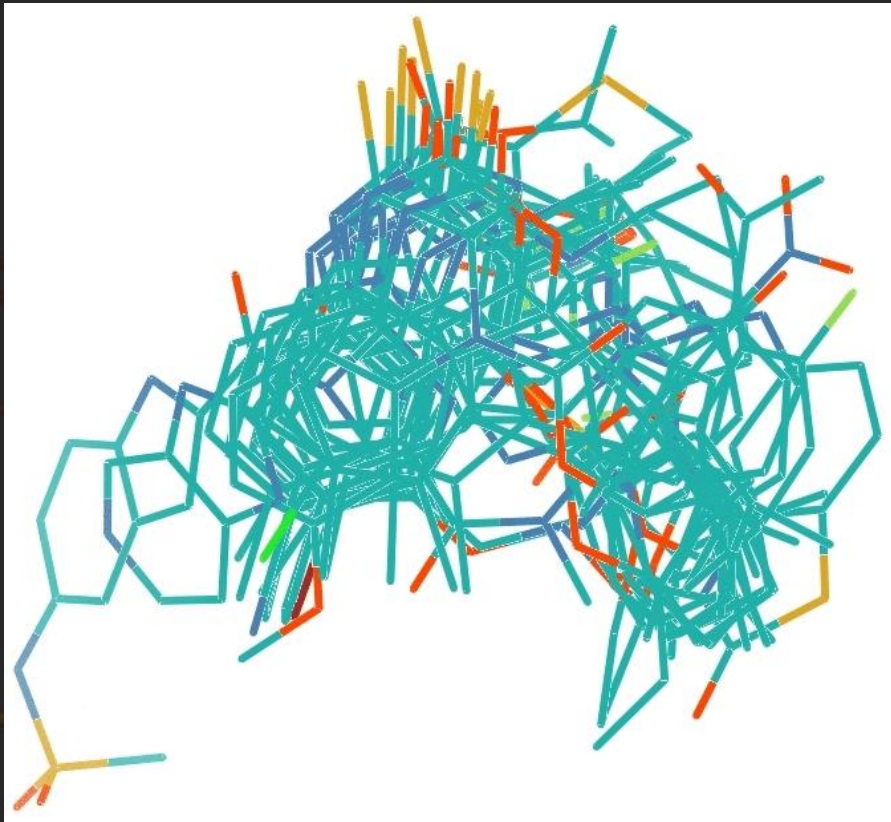
Lys101
Lys102
Val179
Tyr188
Gly190
Asp192
Glu224
Pro225
Trp229
LEu234
Hie235
Glu138B



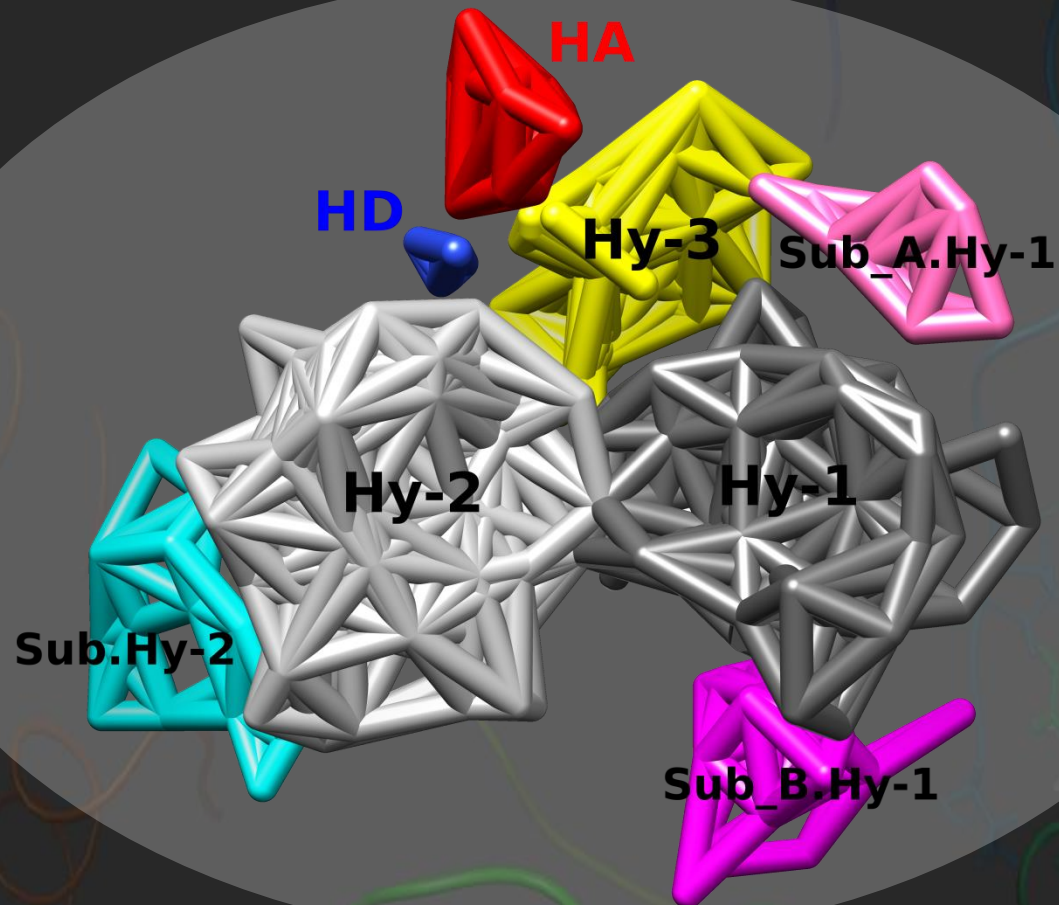
Interazioni Elettrostatiche

Leu100
Ser105
Val106
Val179
Ile180
Tyr181
Tyr183
Leu187
Val189
Glu224
Pro225
Lys238

ANALISI DEI RISULTATI

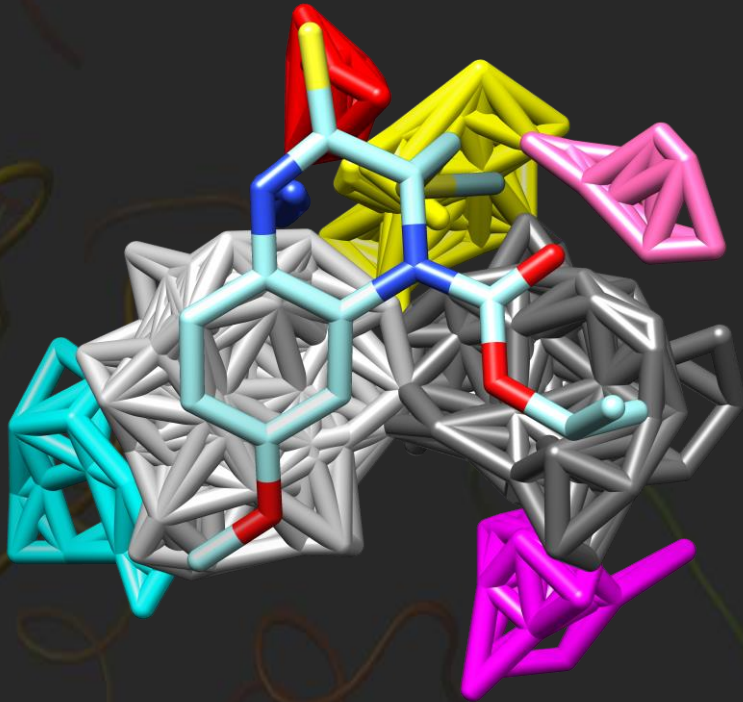


CONCLUSIONI



CONCLUSIONI

Complesso con il composto più attivo



Complesso con il composto meno attivo

