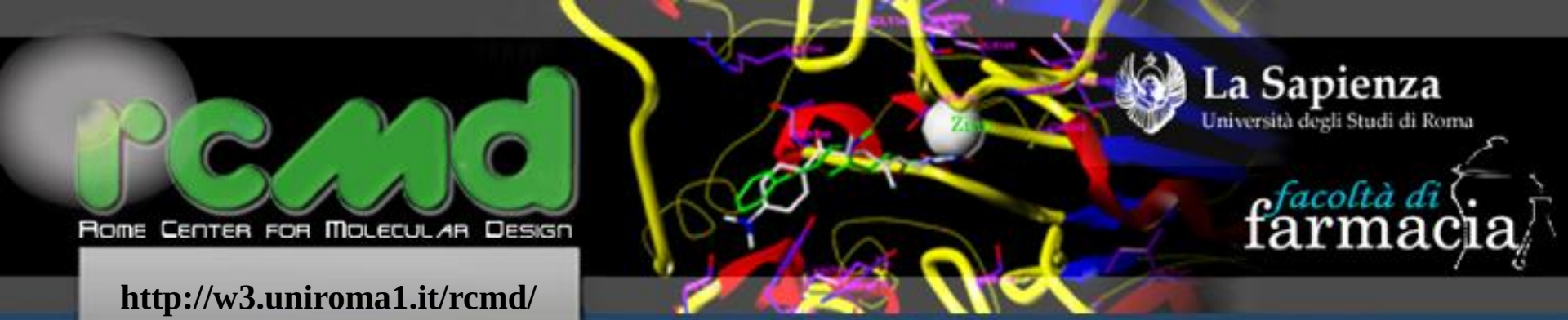


Tesi sperimentale di Laurea in Chimica Farmaceutica e Tossicologica

Interazioni Ligando-Recettore: analisi del "*binding mode*" di nuovi derivati indolici ad attività anti-HIV mediante simulazioni di docking molecolare al calcolatore.

Relatore:

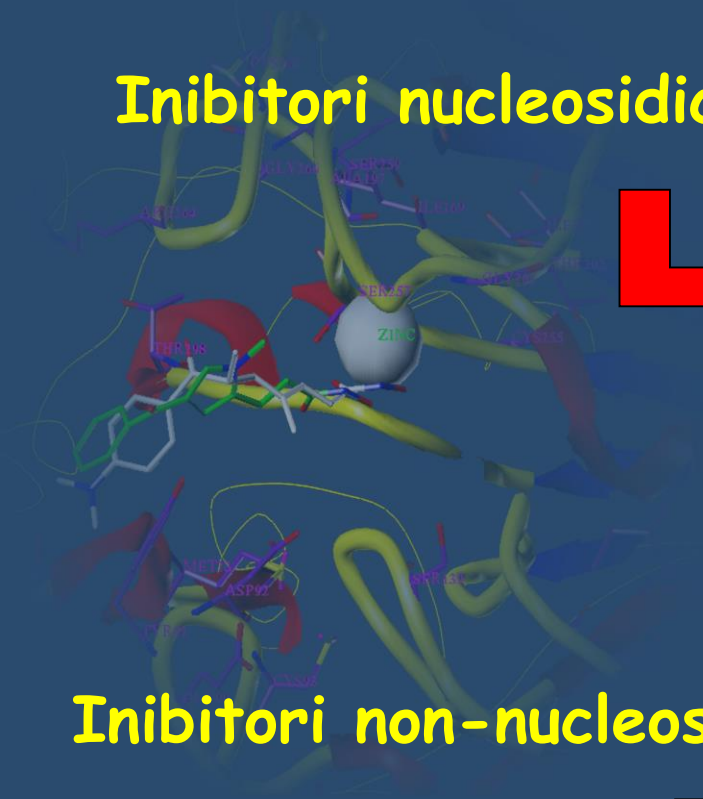
Chiar.mo Dott. Rino Ragno

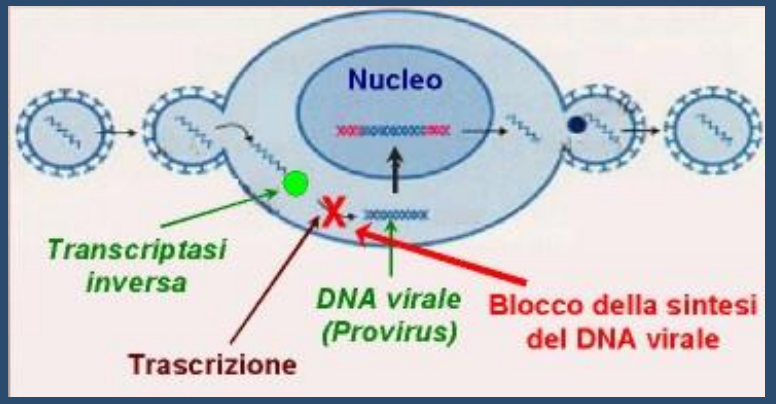
Laureanda:

Simona Frasca

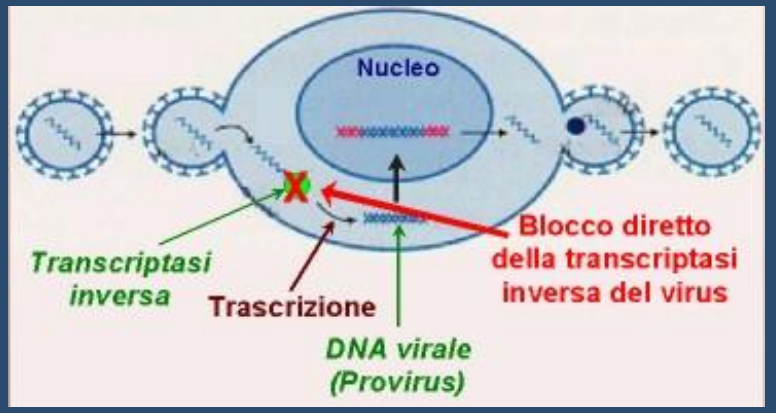
Terapia anti-HIV-RT

Inibitori nucleosidici

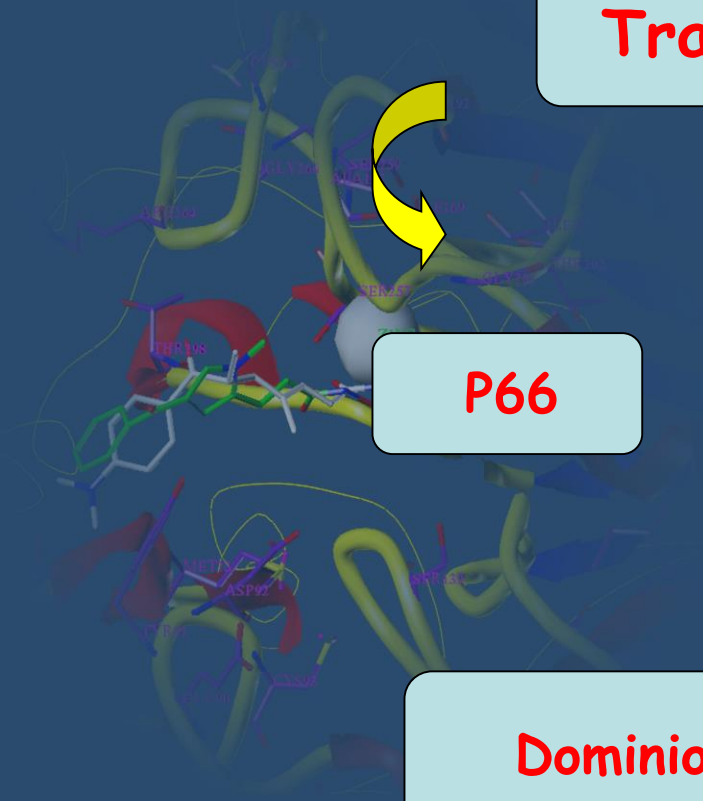




Inibitori non-nucleosidici



L'enzima Trascrittasi Inversa

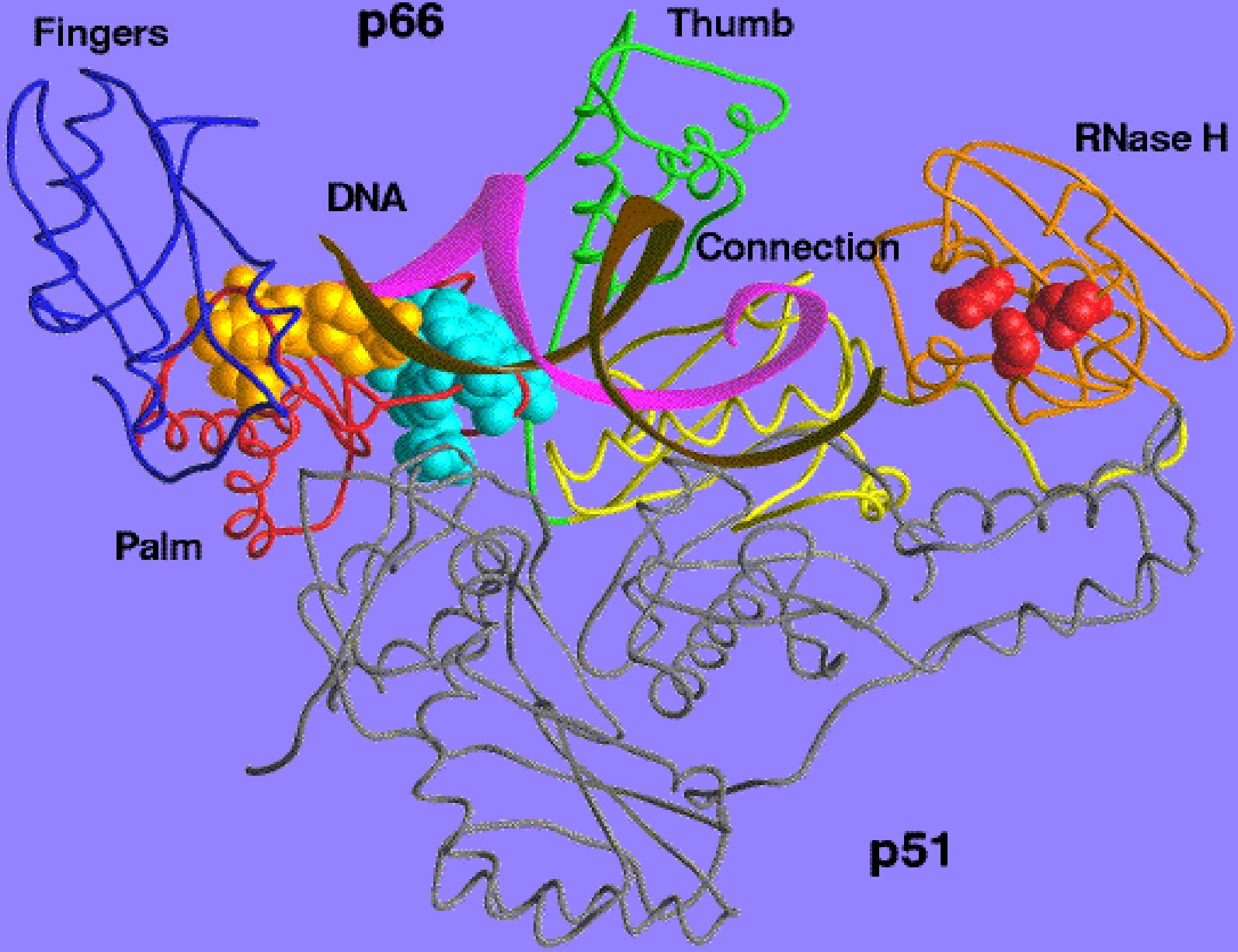


Trascrittasi Inversa

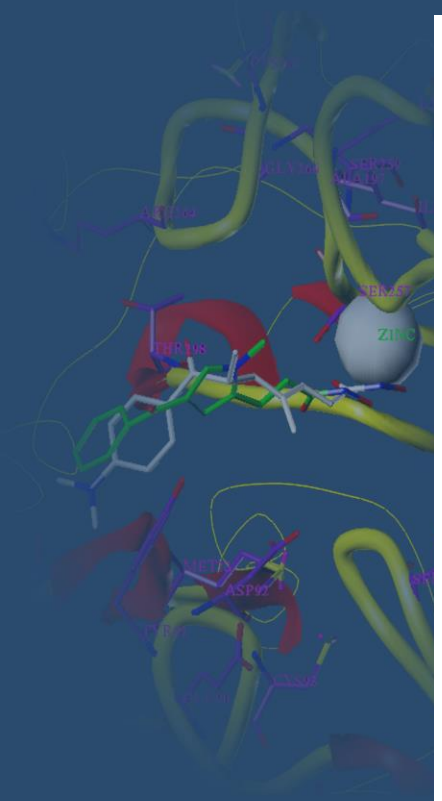
P66

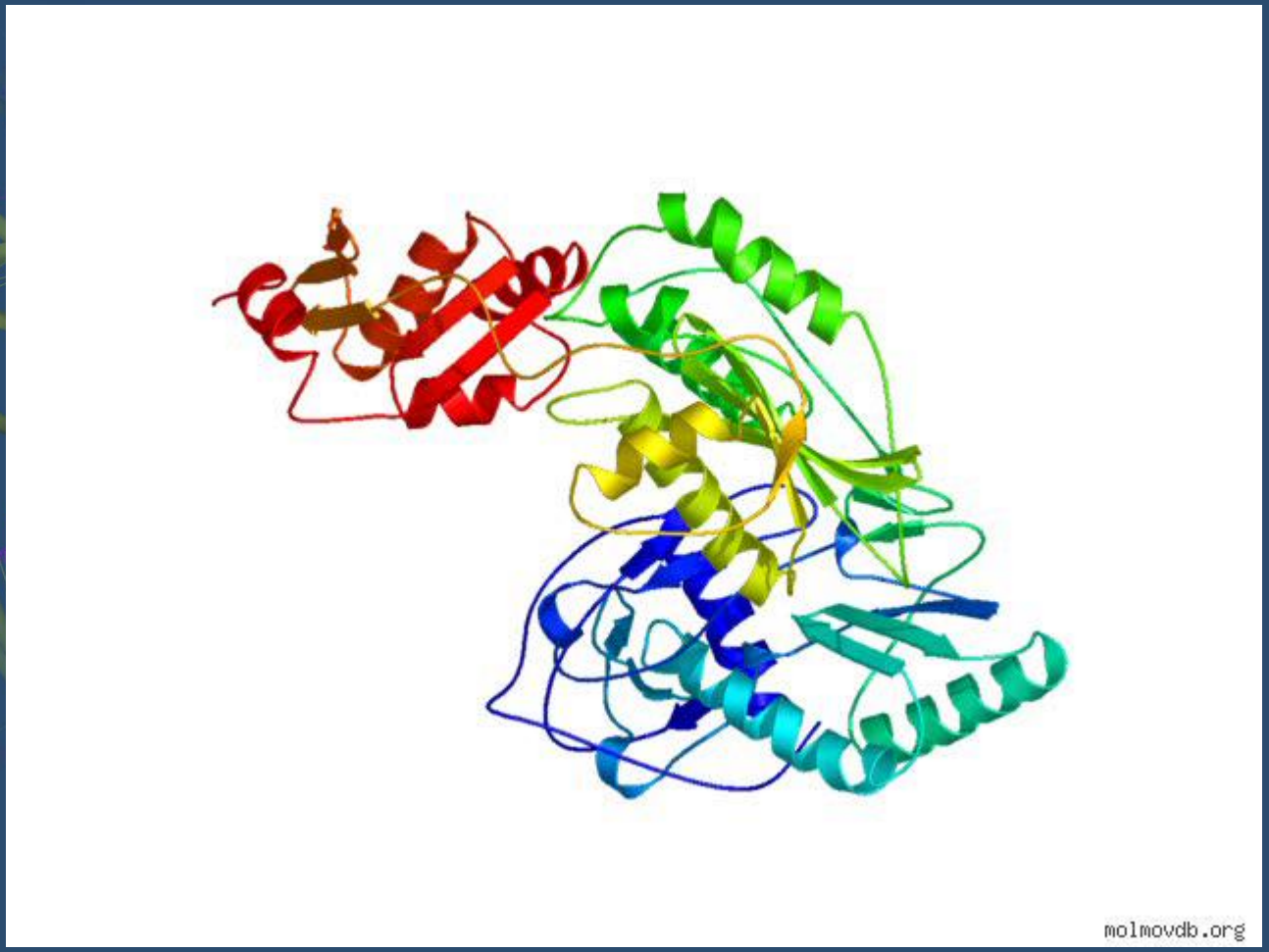
P51

Dominio RNAasico e polimerasico


Fingers
p66
Thumb
RNase H
DNA
Connection
Palm
p51

Adattamento indotto di HIV-RT

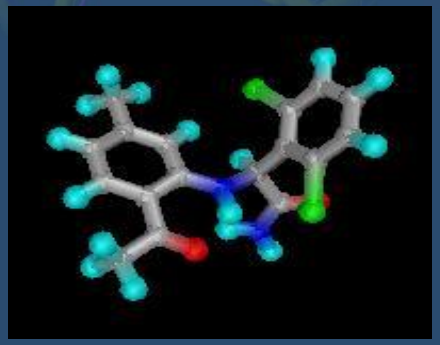




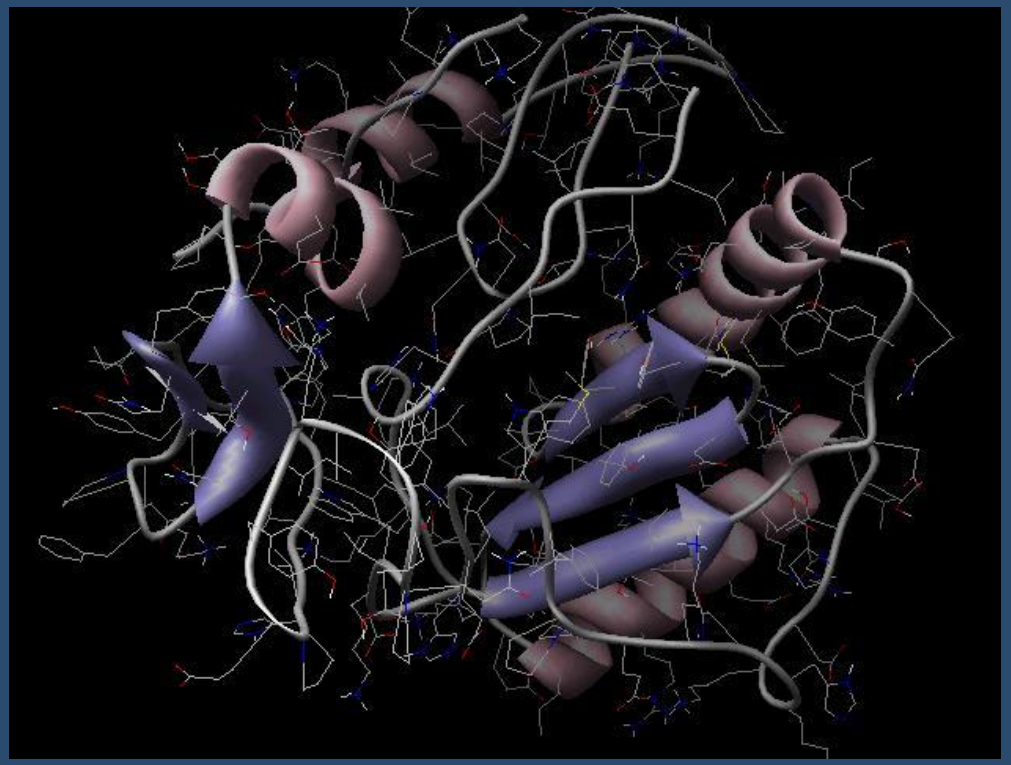
Farmaci della prima generazione

1TVR-Loviride

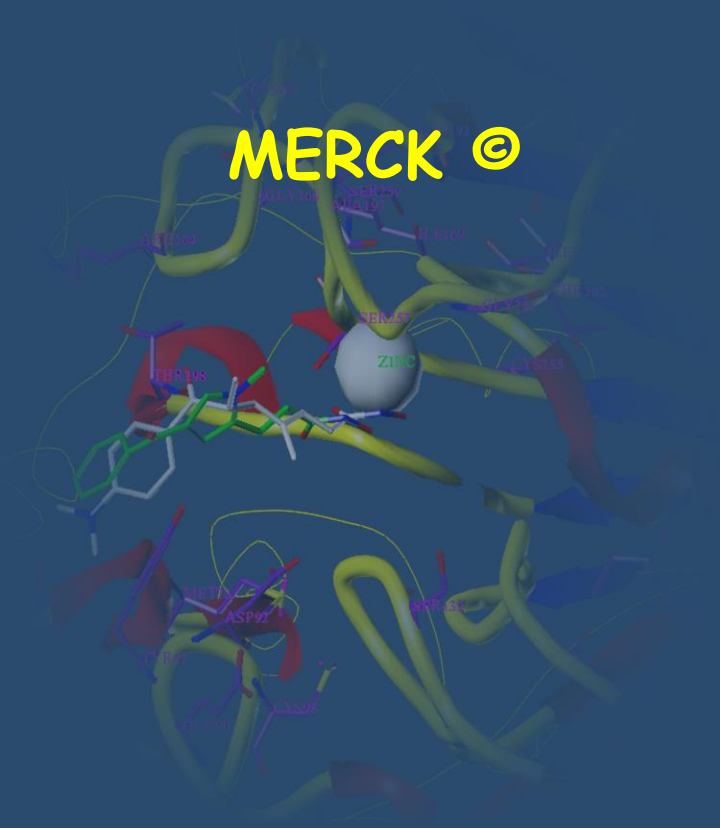
1HNI- Tivirapina

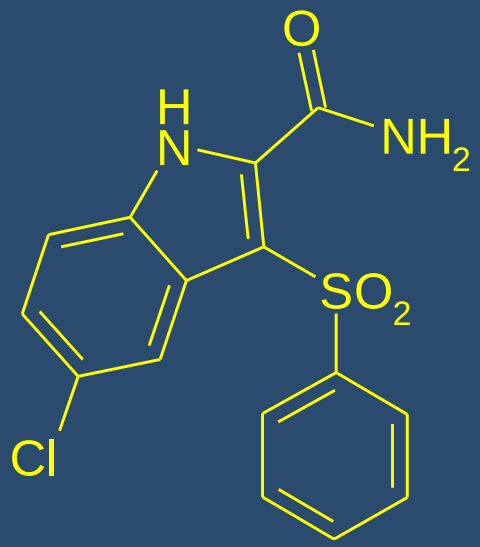


RT-HIV



MERCK ©

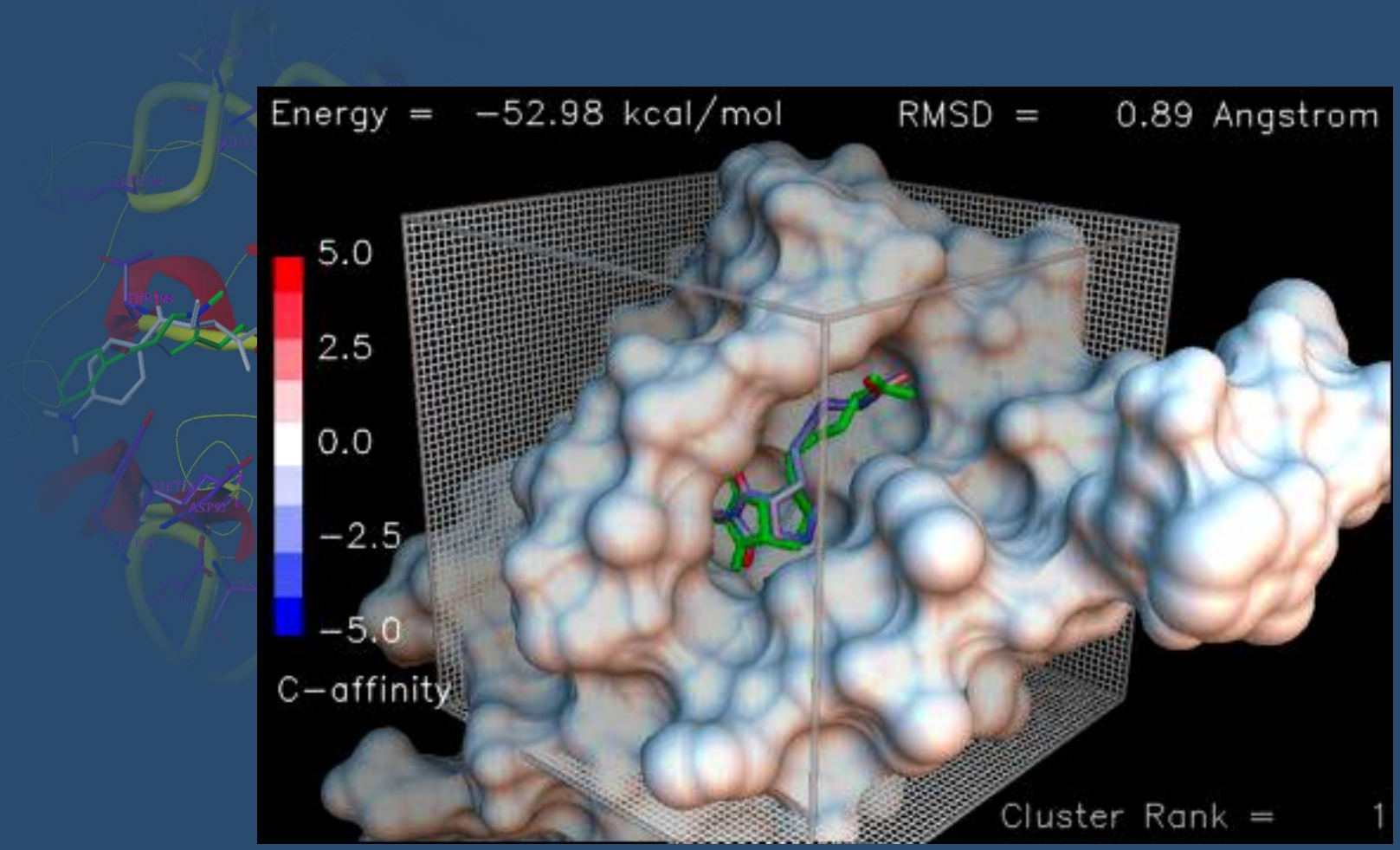




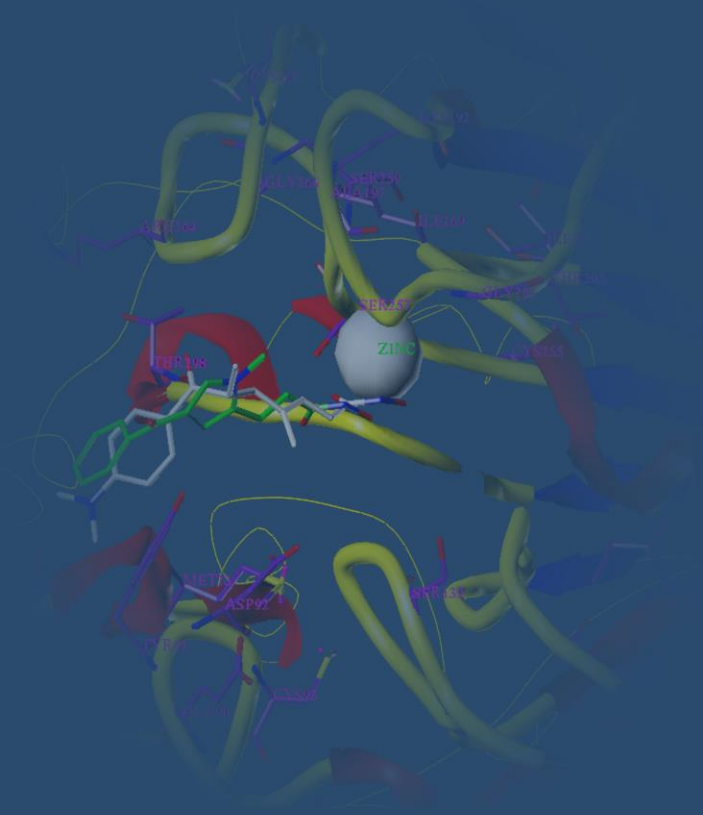
RS1202

Bassa Biodisponibilità NO!

Molecular Docking



PROGRAMMI DI DOCKING



SANDOCK

GRAMM

LIGIN

FLEXX

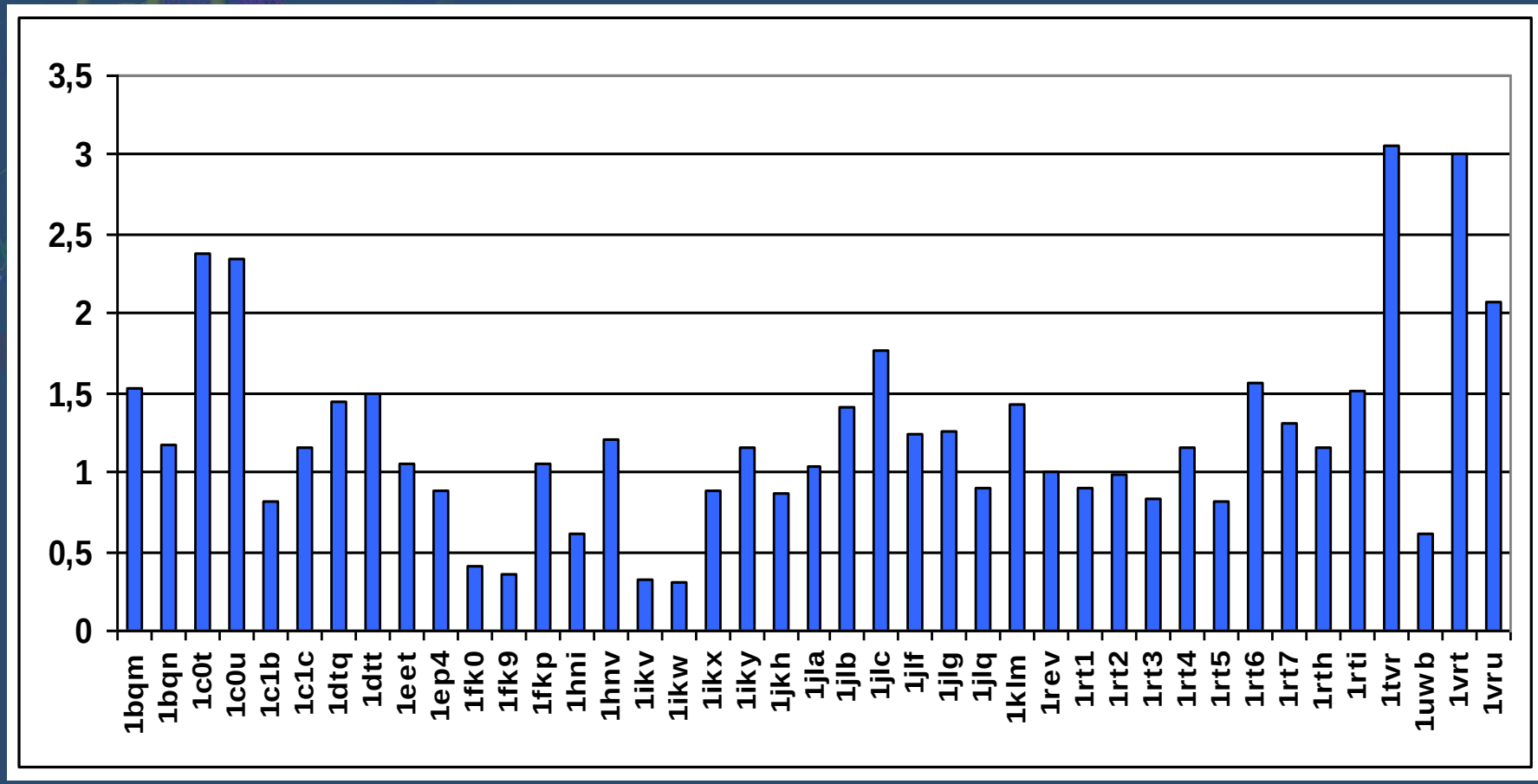
DREAM++

DOCK

AUTODOCK

AUTODOCK

RMSD di 41 complessi RT-inibitore



Crossdocking

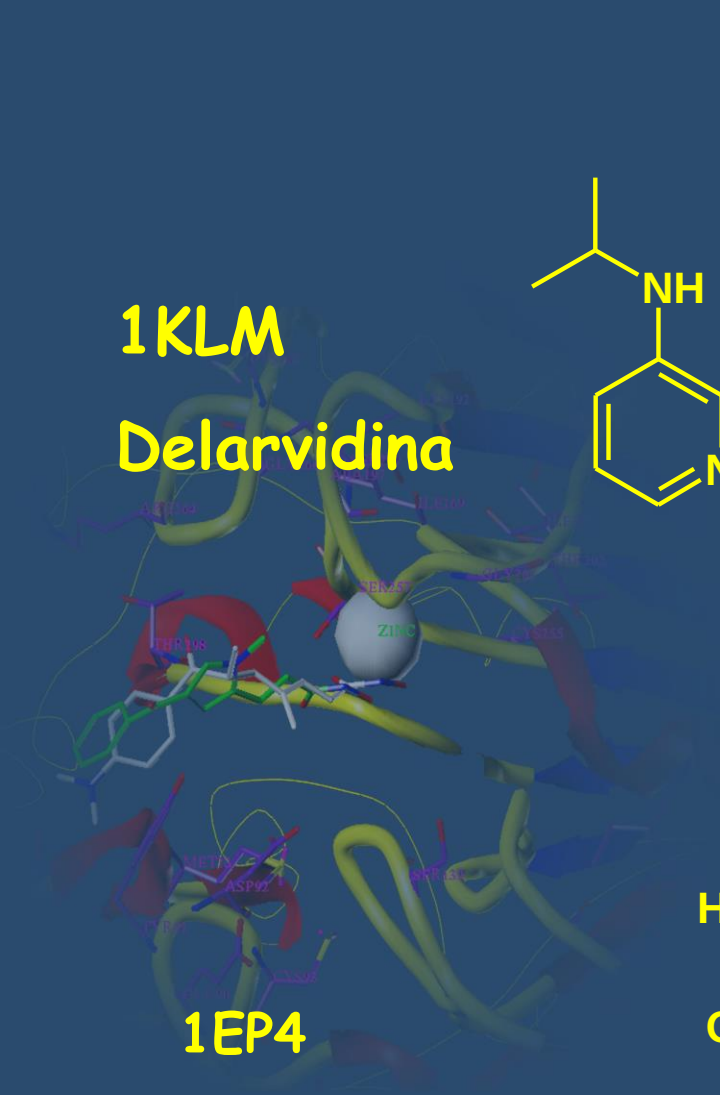
Ligands \ Proteins	1BQM	1C0T	1C0U	1C1B	1C1C	1DTQ	1DTT	1EET	1EP4	1FK9	1HNI	1HNV	1JLQ	1KLM	1REV	1RT1	1RT2	1RT3	1RT4	1RT5	1RT6	1RT7	1RTH	1RTI	1TVR	1VRT	1VRU	DA
1BQM	**1.53**	2.39	1.38	1.60	1.66	1.39	1.38	1.38	1.94	1.06	2.37	2.43	2.52	5.26	1.81	1.74	1.61	2.04	1.88	1.94	1.02	2.54	2.39	1.71	1.53	2.13	2.34	0.80
1C0T	2.24	**2.38**	0.89	1.03	1.79	2.34	2.23	2.28	3.02	0.89	2.15	2.27	2.26	0.82	2.77	0.83	2.46	1.93	2.48	2.49	2.13	2.84	2.19	2.79	2.59	3.12	2.75	0.59
1C0U	1.95	2.52	**2.35**	1.06	2.41	1.15	2.05	1.08	1.59	2.06	2.64	2.15	1.97	0.89	2.30	2.64	0.72	2.03	2.60	2.63	2.39	1.59	1.95	3.49	2.35	2.68	2.27	0.67
1C1B	2.60	0.86	0.99	**0.82**	0.99	1.00	0.93	2.27	1.02	2.35	1.52	0.95	0.92	1.21	1.12	1.11	0.96	1.85	1.42	1.43	0.76	1.54	0.88	1.34	1.40	1.40	1.08	0.94
1C1C	1.87	0.79	1.07	1.01	**1.16**	1.21	2.77	1.84	1.12	1.33	1.12	1.74	1.09	1.22	1.36	1.35	0.97	3.09	1.44	2.68	1.04	1.68	0.87	1.27	1.26	1.42	1.29	0.93
1DTQ	1.67	1.54	1.57	3.59	2.78	**1.44**	1.46	1.55	3.39	1.99	4.87	1.56	1.49	2.97	4.55	7.20	1.58	2.86	1.93	2.00	1.41	1.79	2.12	3.87	3.49	2.95	3.04	0.59
1DTT	4.06	2.35	1.68	1.30	2.89	1.55	**1.49**	1.44	3.33	1.27	3.01	1.82	1.62	4.13	2.26	1.41	1.68	3.85	1.93	1.69	1.35	1.93	2.74	2.93	5.29	1.92	2.02	0.67
1EET	3.26	1.00	1.78	1.19	1.90	1.64	0.98	**1.06**	3.32	2.09	2.16	2.11	0.71	4.80	2.07	2.22	3.54	3.68	1.91	2.06	1.74	2.78	1.26	4.12	2.11	2.41	2.69	0.59
1EP4	2.87	3.53	8.20	7.11	2.62	2.78	2.66	2.65	**0.89**	4.23	4.58	3.64	3.38	4.37	3.33	3.03	2.58	3.04	5.04	3.39	3.23	3.24	5.32	1.41	3.70	8.21	3.65	0.19
1FK9	1.28	0.93	0.82	1.03	2.52	3.79	1.18	1.17	1.38	**0.35**	0.92	3.75	1.12	0.87	3.80	0.75	1.13	1.79	1.24	1.19	0.85	2.09	3.71	1.50	3.02	2.03	1.16	0.76
1HNI	1.91	1.29	2.35	1.38	2.30	1.70	2.19	1.97	2.96	1.02	**0.61**	2.28	1.44	2.14	2.22	2.32	2.49	10.10	1.51	1.73	1.96	2.20	0.79	2.02	2.24	1.59	1.49	0.74
1HNV	0.97	1.28	1.10	1.43	2.79	1.26	1.20	1.30	2.98	1.08	0.73	**1.20**	1.14	2.91	1.66	2.63	2.59	1.97	1.47	1.63	1.09	2.71	2.48	3.43	2.51	2.12	1.39	0.80
1JLQ	2.68	1.84	2.73	2.09	3.06	2.64	2.45	2.51	3.20	1.83	2.14	2.63	**0.90**	1.14	2.87	2.91	2.95	3.01	2.69	2.92	2.35	2.43	1.91	3.08	2.78	1.56	1.86	0.56
1KLM	5.70	5.67	5.90	2.02	1.94	6.00	5.91	3.63	2.07	5.92	5.28	3.84	6.93	**1.42**	5.59	2.07	2.41	6.50	6.04	5.75	6.06	5.52	5.73	1.81	2.01	5.72	6.31	0.20
1REV	1.65	1.65	1.66	1.70	1.31	1.65	1.61	1.41	5.30	1.37	1.50	1.37	2.82	1.82	**1.00**	3.13	2.98	1.84	1.14	1.41	1.35	1.04	2.71	1.81	3.01	1.25	2.94	0.81
1RT1	1.76	1.00	1.14	1.50	1.11	1.05	2.43	2.31	1.04	1.03	1.36	1.89	2.07	1.15	2.29	**0.90**	1.13	3.12	1.40	1.61	0.94	1.60	1.90	2.39	1.73	1.24	1.17	0.87
1RT2	1.41	1.91	2.01	1.11	1.12	2.10	2.05	2.06	2.14	2.38	2.79	2.11	2.23	1.08	2.85	0.87	**0.99**	2.81	2.74	2.11	1.88	2.84	2.26	1.85	1.81	4.02	2.31	0.67
1RT3	3.42	2.60	3.16	3.33	3.04	2.72	2.50	2.98	3.16	2.51	2.77	3.59	2.99	2.99	2.65	3.25	3.34	**0.83**	2.12	2.97	2.90	1.82	2.64	3.35	3.41	2.02	2.48	0.35
1RT4	1.97	1.77	1.77	1.97	1.91	1.76	1.64	2.28	6.94	1.40	3.02	1.92	1.60	3.58	3.00	1.91	1.77	2.26	**1.16**	1.22	1.71	2.09	1.63	2.21	1.91	2.99	1.58	0.76
1RT5	1.76	1.66	1.54	1.92	2.15	1.61	1.60	1.83	1.94	1.35	1.60	1.67	2.00	3.91	2.21	2.10	2.06	1.99	0.91	**0.81**	1.44	1.97	1.47	2.42	1.82	1.62	1.45	0.87
1RT6	2.32	3.03	1.63	1.86	2.81	2.79	1.83	2.83	3.33	1.62	2.89	2.55	1.68	3.33	2.92	3.03	3.13	2.95	1.81	3.11	**1.57**	1.66	1.66	2.94	2.89	2.69	2.92	0.56
1RT7	2.42	2.78	2.01	2.39	3.60	3.07	3.00	2.80	3.26	1.96	3.33	2.90	2.88	3.73	3.02	4.69	4.06	2.35	1.66	3.33	1.84	**1.30**	1.91	3.68	4.03	1.42	2.61	0.39
1RTH	2.78	0.88	2.44	2.63	2.53	2.17	1.26	2.96	3.29	2.03	1.91	2.37	2.07	2.21	2.36	2.58	2.66	2.21	3.18	2.11	2.38	2.27	**1.16**	2.62	2.83	1.36	1.19	0.57
1RTI	2.46	1.12	1.27	1.61	2.95	2.17	2.49	2.00	2.83	2.89	1.28	2.19	0.96	1.38	2.82	1.60	2.94	2.16	2.42	2.61	2.52	1.86	2.21	**1.51**	2.17	2.27	2.79	0.69
1TVR	3.05	0.67	0.90	1.21	3.07	1.00	1.12	1.14	3.82	0.72	0.81	1.04	0.93	1.22	2.05	0.72	2.89	1.73	1.44	1.53	0.85	3.01	2.62	2.94	**3.05**	3.29	0.82	0.70
1VRT	3.02	1.98	2.50	2.75	2.71	1.44	2.56	2.66	3.43	2.29	2.69	2.66	2.51	2.62	2.35	2.73	3.08	2.12	2.35	2.56	2.46	1.48	2.40	2.96	2.89	**2.10**	2.32	0.50
1VRU	1.61	2.16	2.10	1.55	2.37	2.42	2.45	2.72	1.69	1.31	2.92	1.51	2.00	2.09	1.84	2.88	1.46	10.27	2.37	2.77	2.27	1.93	2.21	2.36	2.50	1.06	**2.07**	0.65
D.A.	0.63	0.78	0.76	0.81	0.63	0.74	0.72	0.74	0.43	0.80	0.61	0.65	0.76	0.59	0.52	0.59	0.63	0.50	0.76	0.65	0.80	0.72	0.69	0.56	0.48	0.63	0.67	

RMSD < 1	1 < RMSD < 2	2 < RMSD < 3	3 < RMSD < 4	4 < RMSD < 5	RMSD > 5

Valori di RMSD dei complessi RT-ligando

1KLM

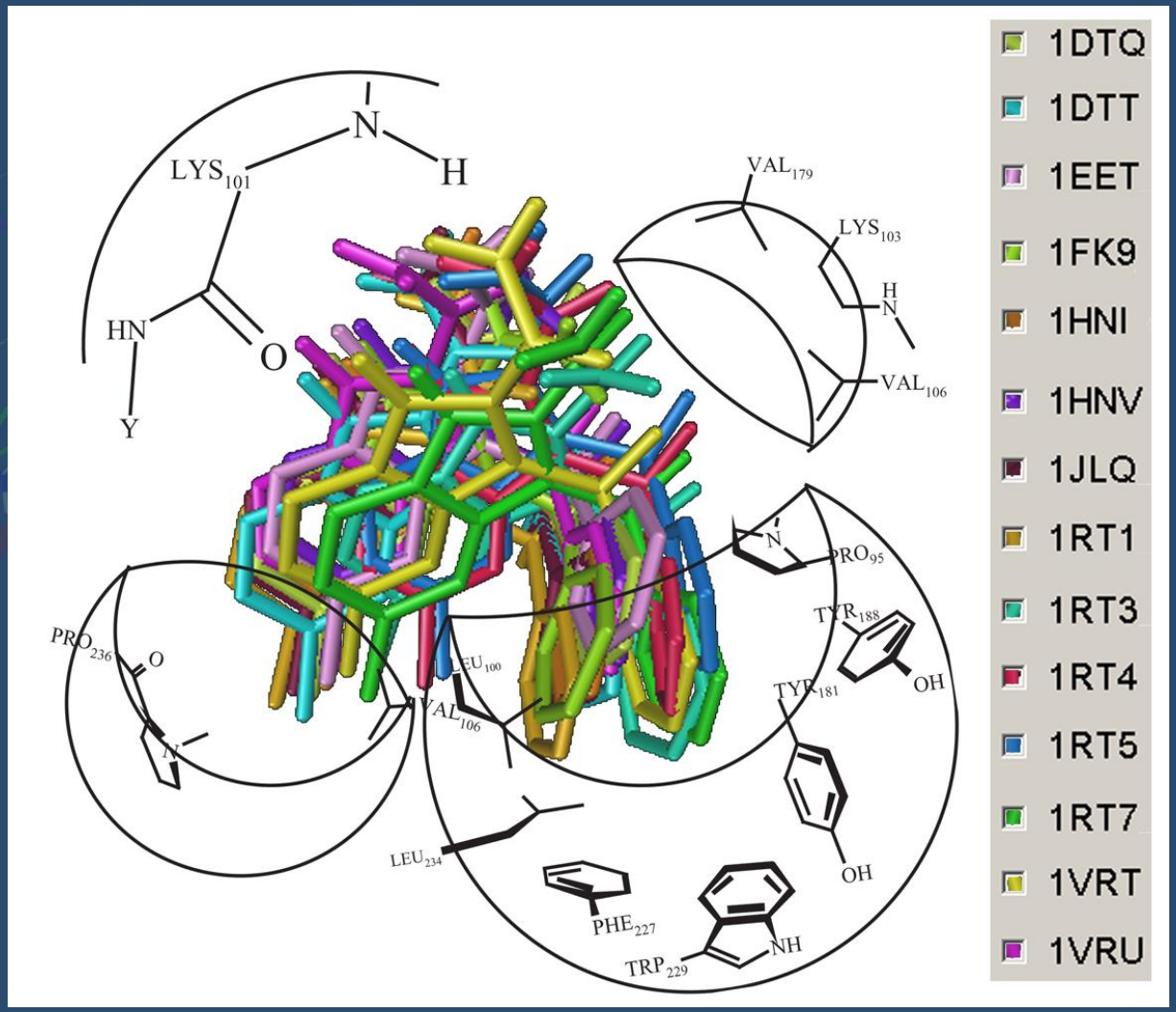
Delarvidina



1EP4

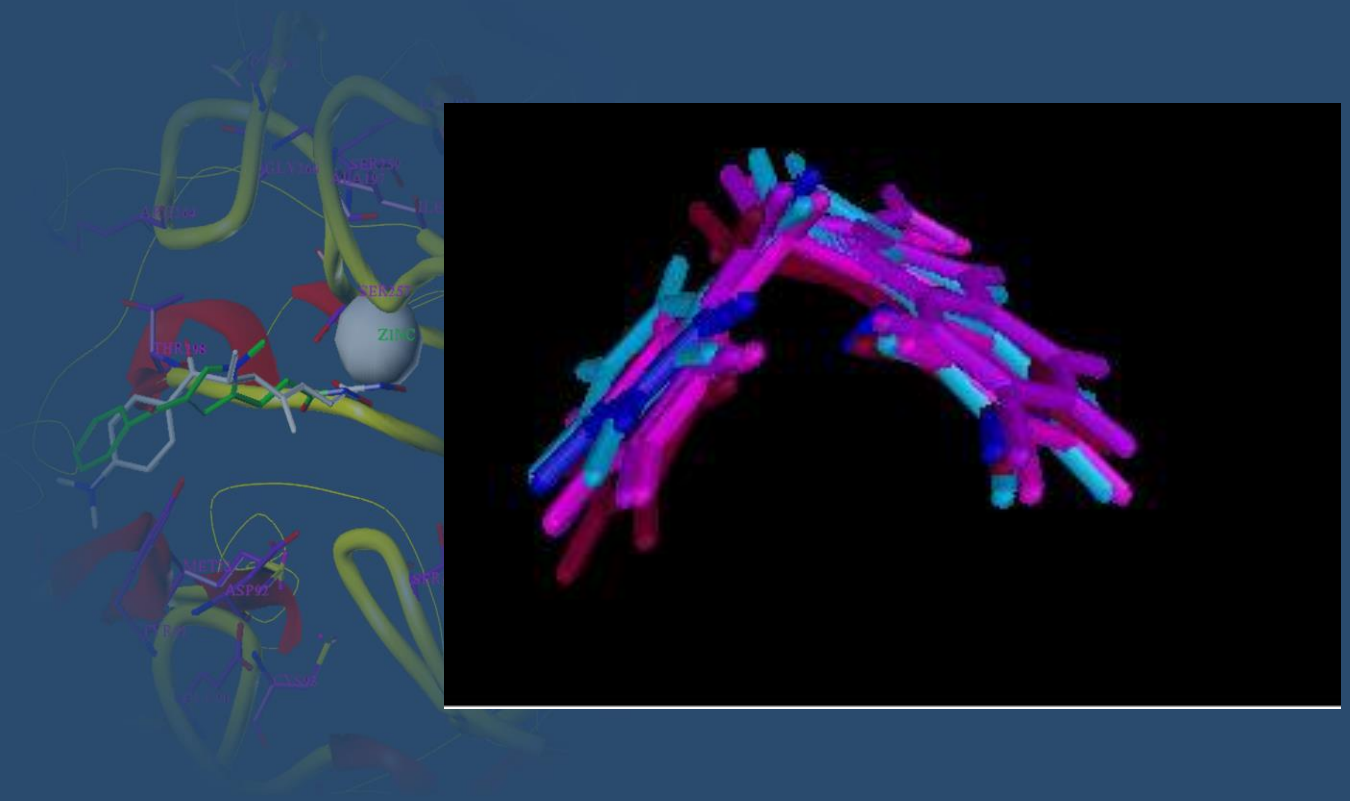
S1153

DOCKING DI RS1202



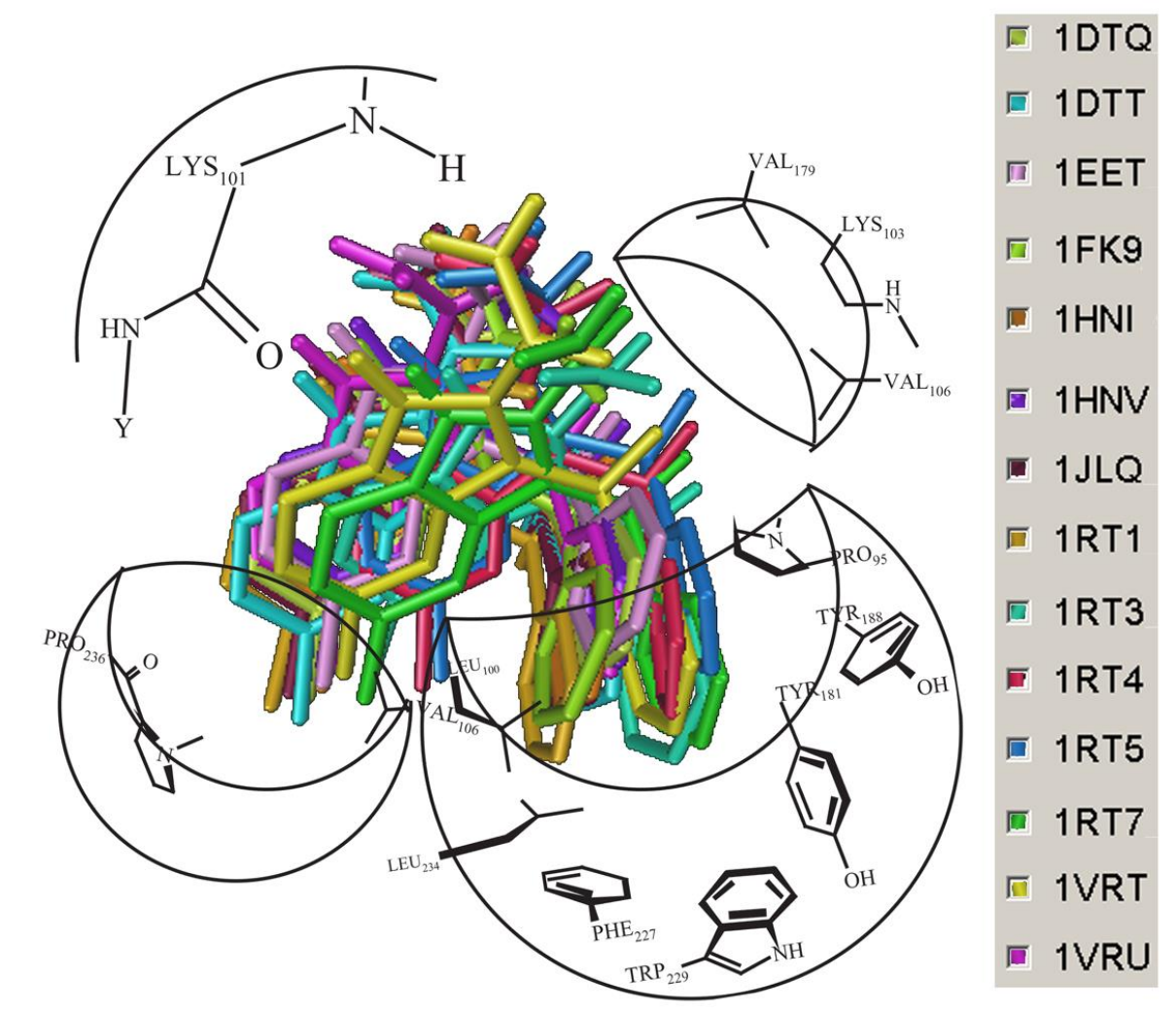
Conformazioni di docking del derivato RS1202 all'interno di 14 NNRTIs

Butterfly-like di RS1202



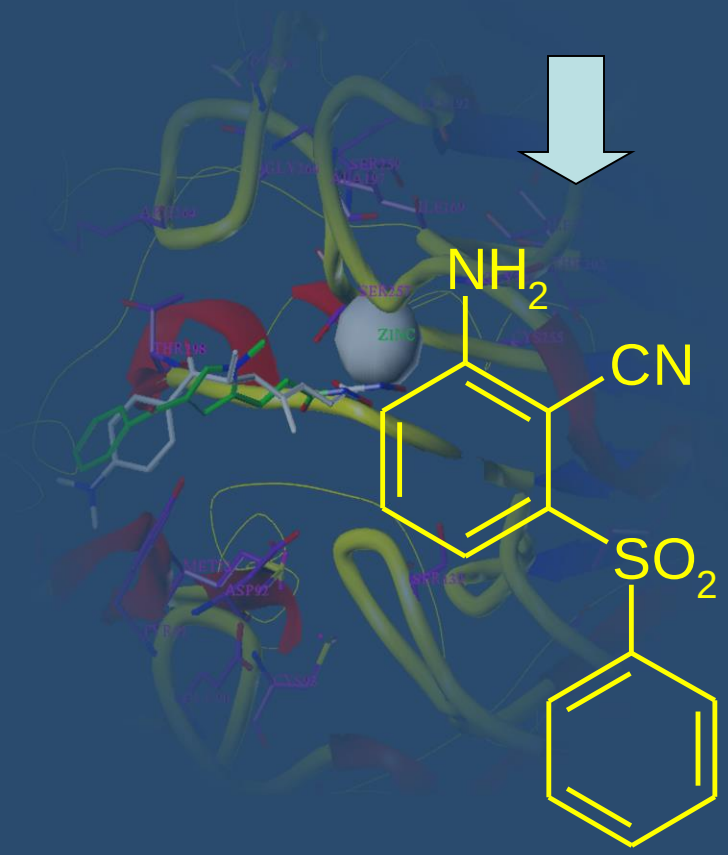
RS1202 dockata all'interno di 1dtq, 1fk9, 1hni, 1jlq

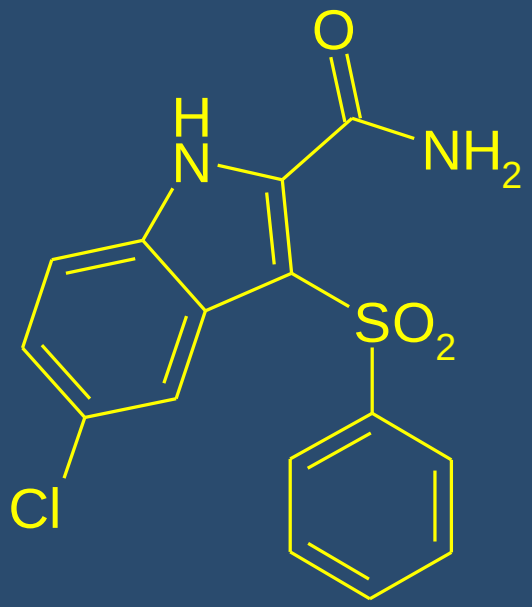
DOCKING DI RS1202



Conformazioni di docking del derivato RS1202 all'interno di 14 NNRTIs

SCELTA DELLA CONFORMAZIONE MACROMOLECOLARE





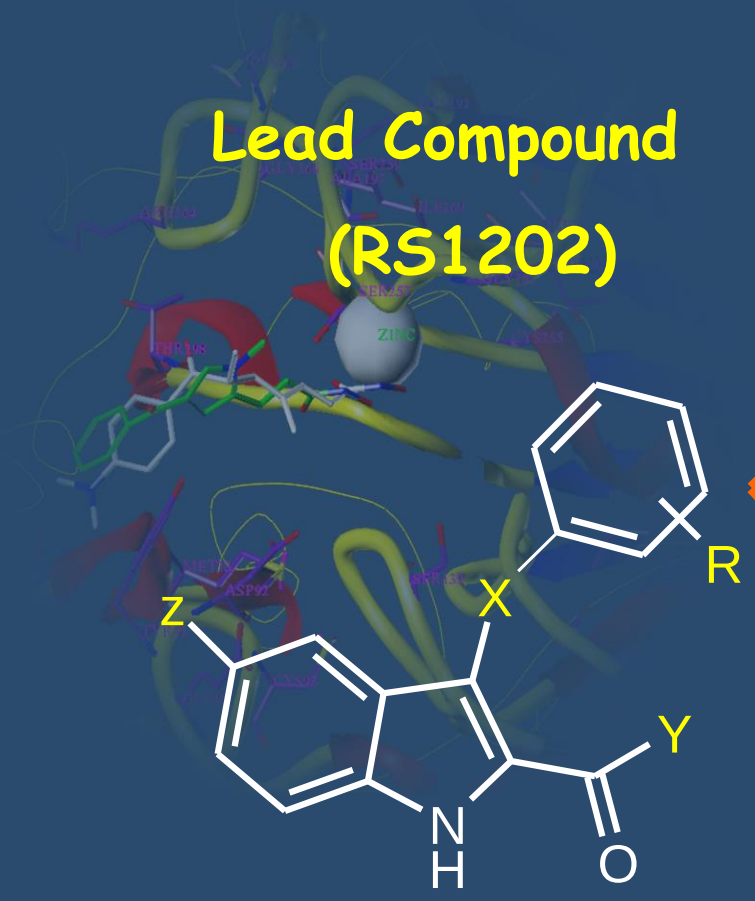
1JLQ-739W94

RS1202

NUOVI INIBITORI

Lead Compound

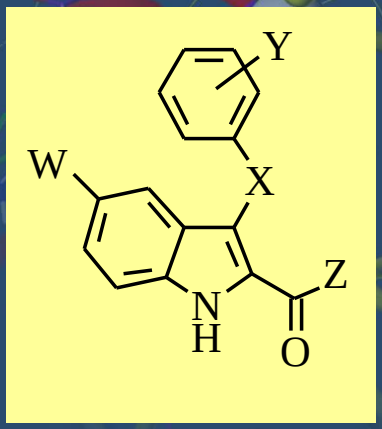
(RS1202)

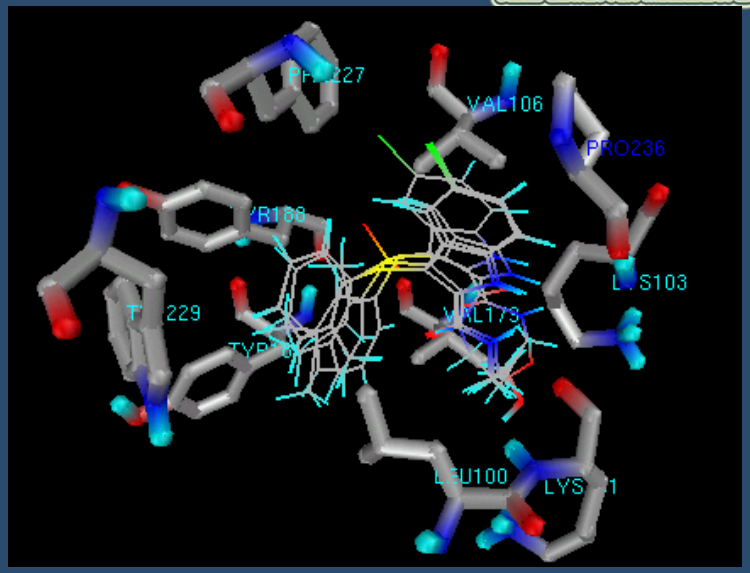


- Derivati Carbossiamidici
- Derivati Carbossiidrazidici
- Derivati Peptidici
- Derivati Eterociclici
- Derivati Sostituiti
- Analoghi di RS1202

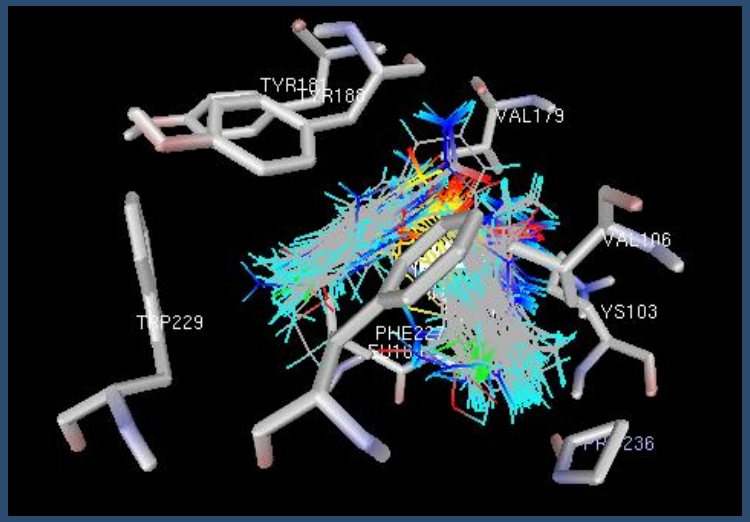
DERIVATI

Carbossiamidici

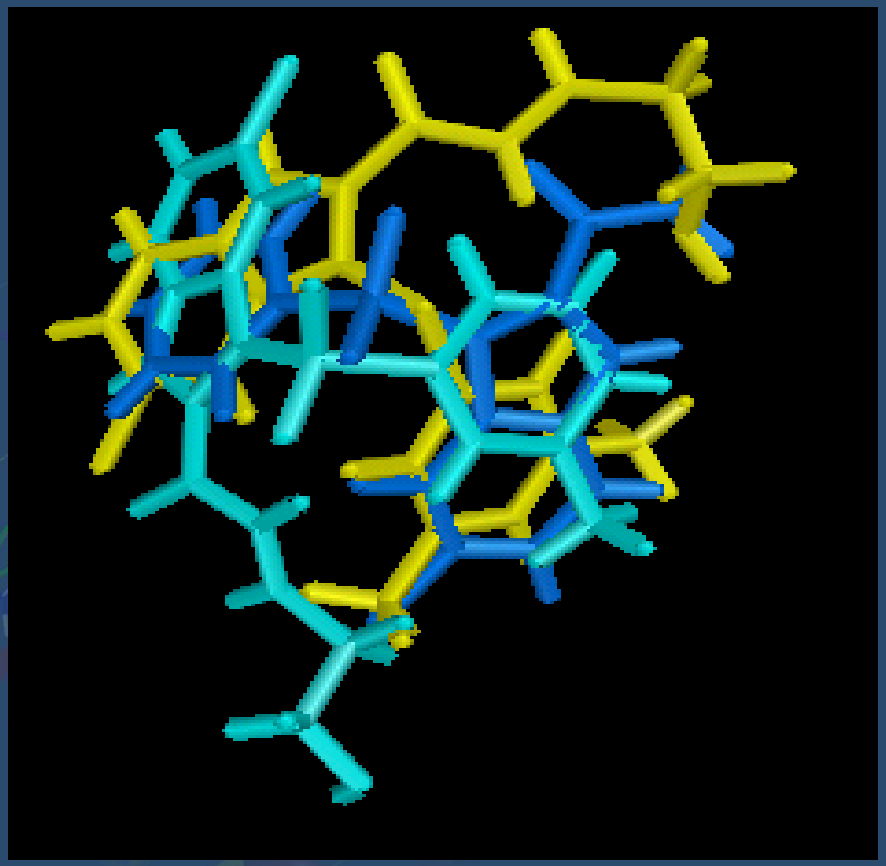




Analoghi

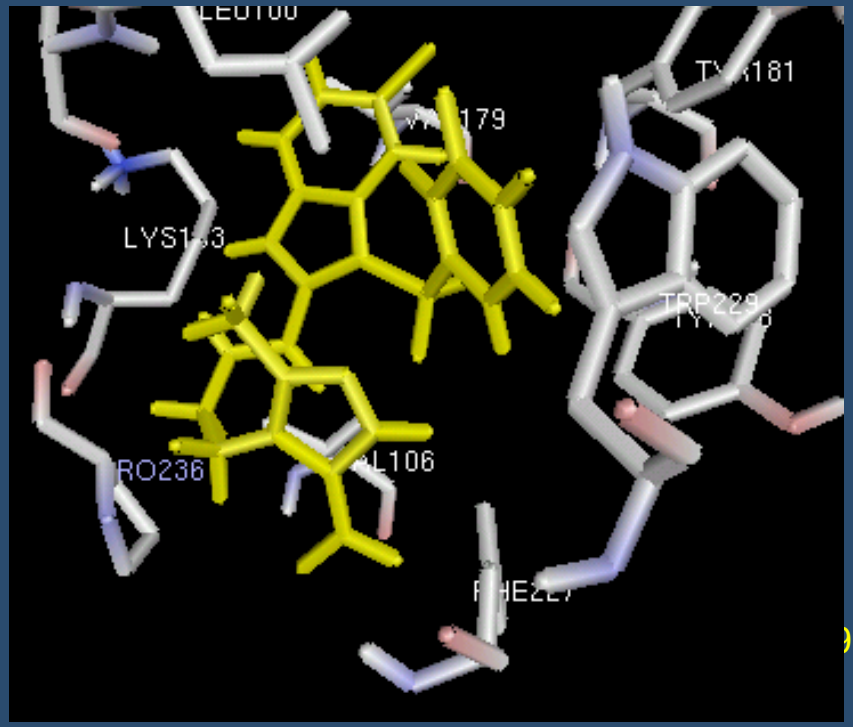


Binding mode di altri derivati



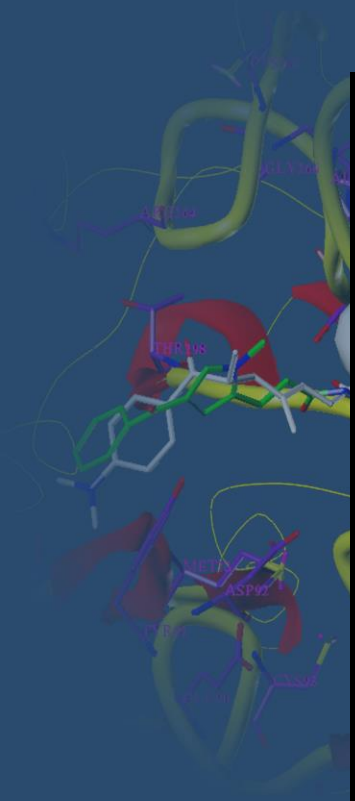
A - Carbossiidrazidici

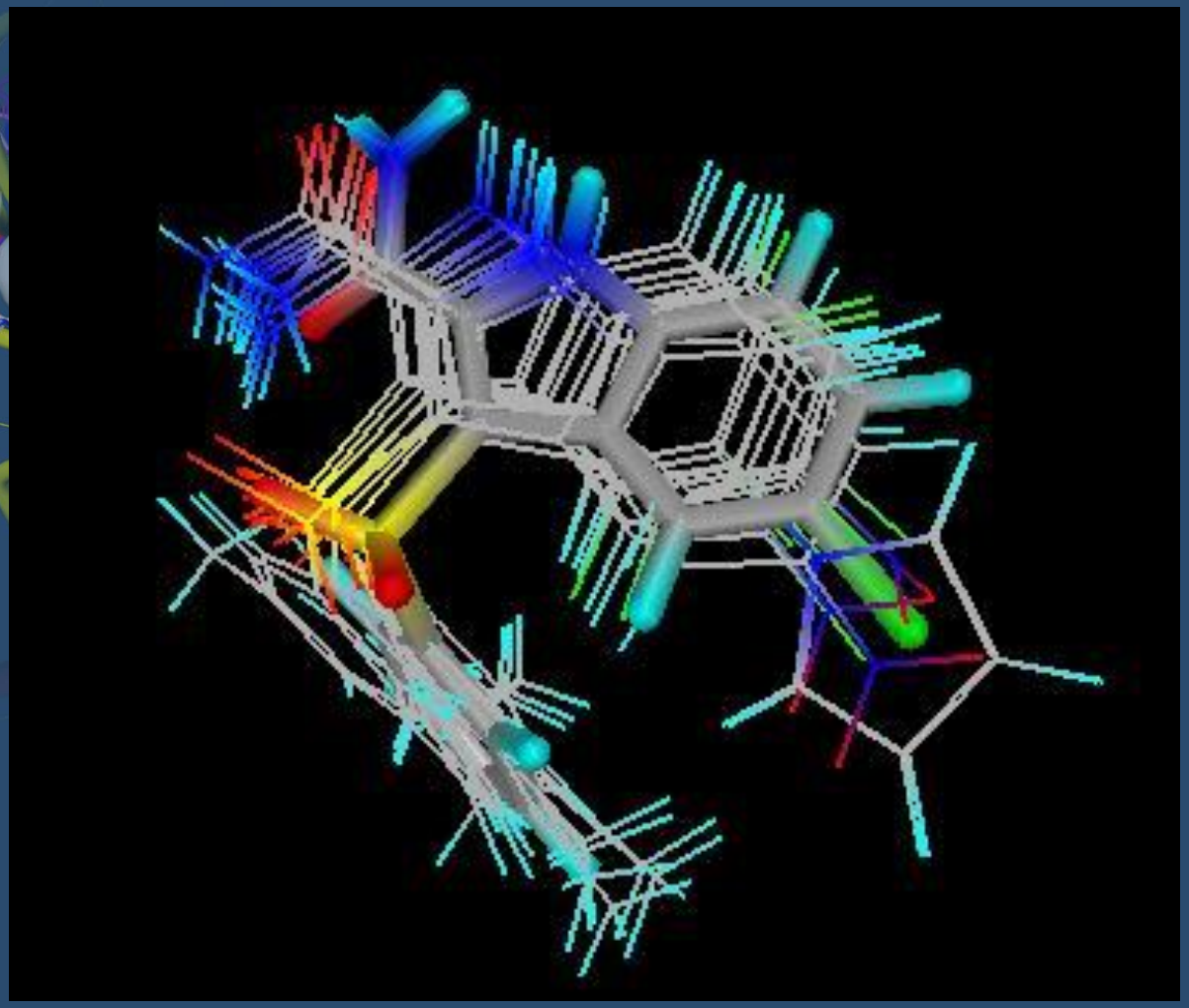
B - Peptidici, eterociclici



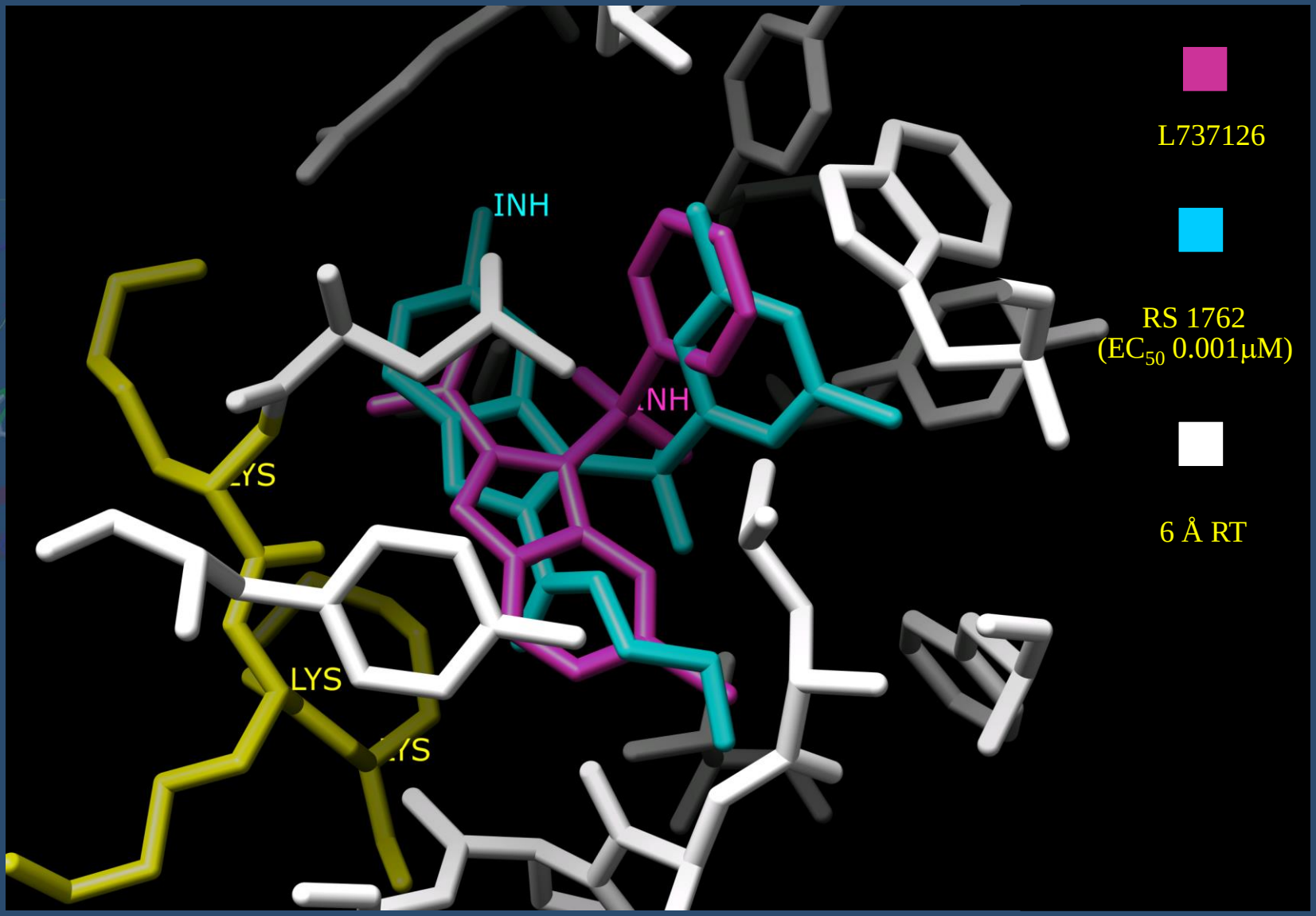
Ancora altri derivati

C - Sostituiti

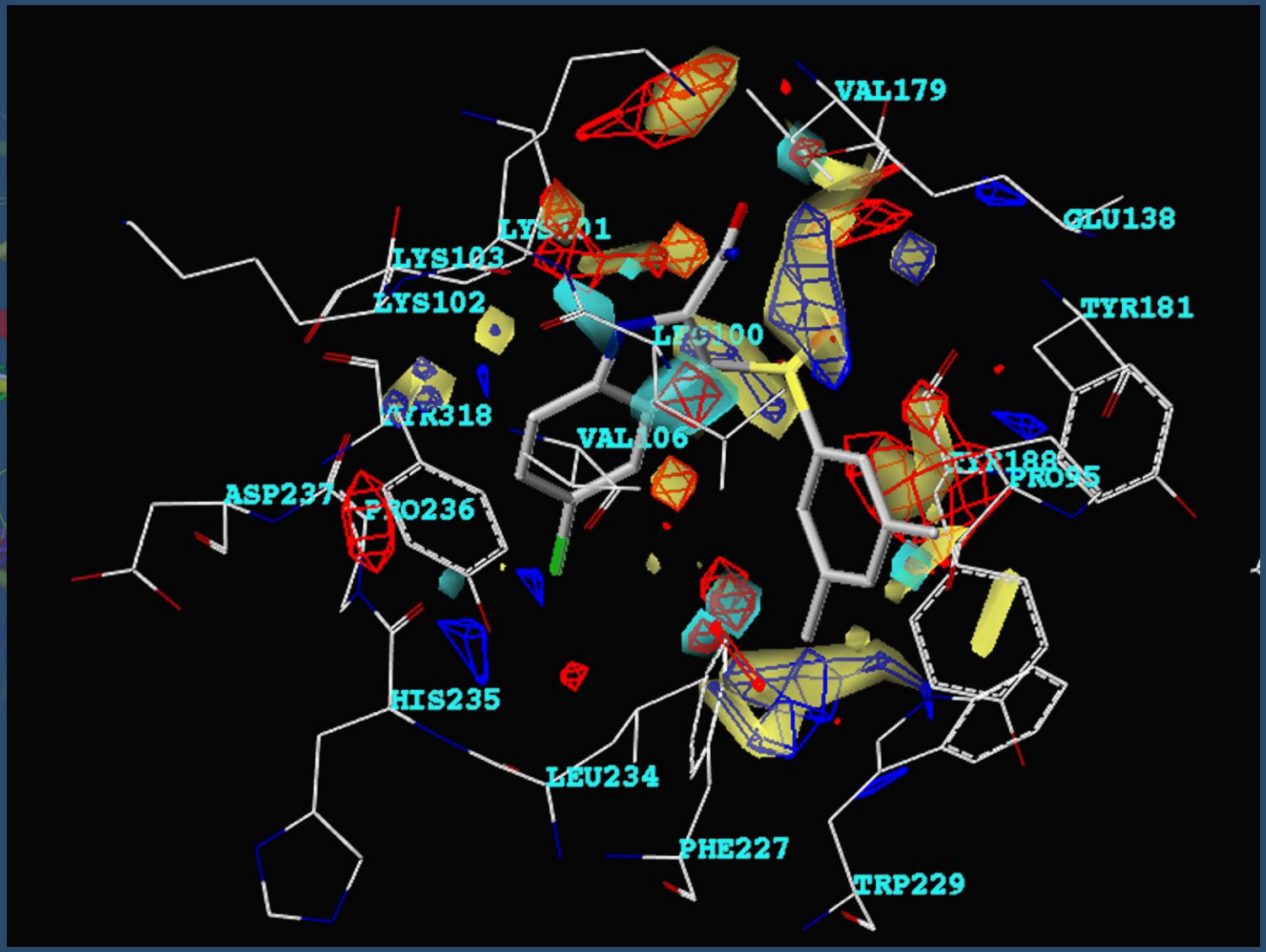




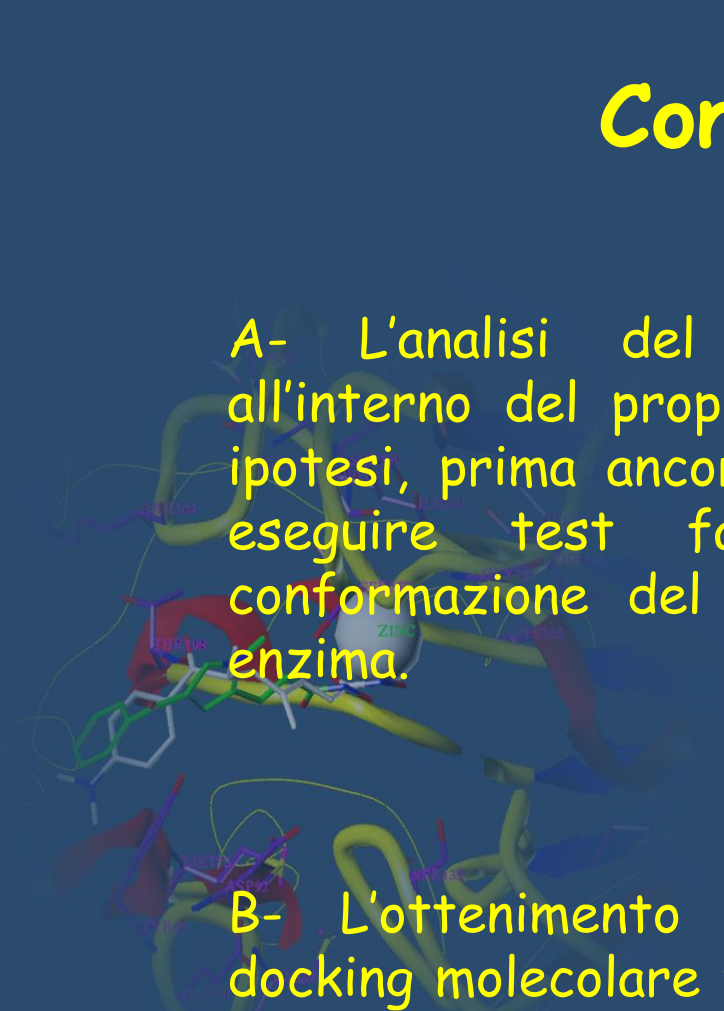
3D-QSAR: Binding Mode



Modello 3D-QSAR



Conclusioni



A- L'analisi del *binding* mode di un ligando all'interno del proprio enzima permette di fare delle ipotesi, prima ancora di provare sperimentalmente ad eseguire test farmacologici, circa la possibile conformazione del ligando nel sito di legame di un enzima.

B- L'ottenimento di strutture allineate mediante docking molecolare permette di correlare direttamente la conformazione del ligando con il proprio enzima in modo da poter effettuare modifiche strutturali allo scopo di aumentarne l'attività.