

Il docking molecolare come metodo structure-based per la progettazione di molecole bioattive: confronto dell'efficacia di diversi programmi applicati ad una serie di 60 famiglie di proteine

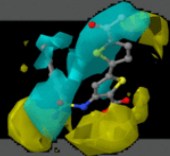


SAPIENZA
UNIVERSITÀ DI ROMA

**Facoltà di Farmacia e Medicina
Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2022/2023**

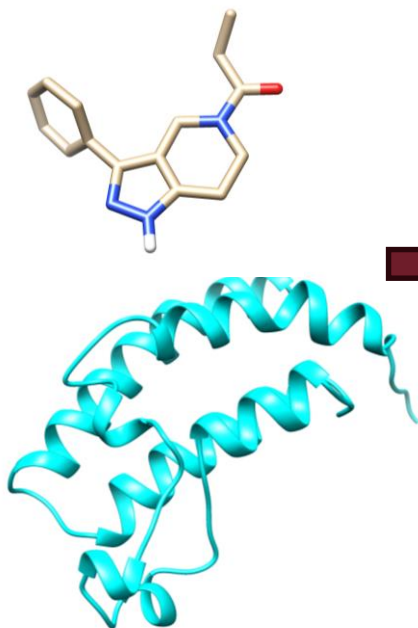
**Laureando: Lidia Giuliani
Matricola: 1810291**

Relatore: prof. Rino Ragno

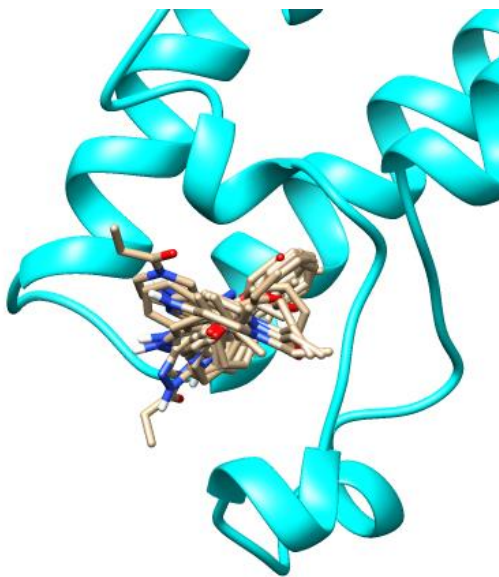


Il docking molecolare

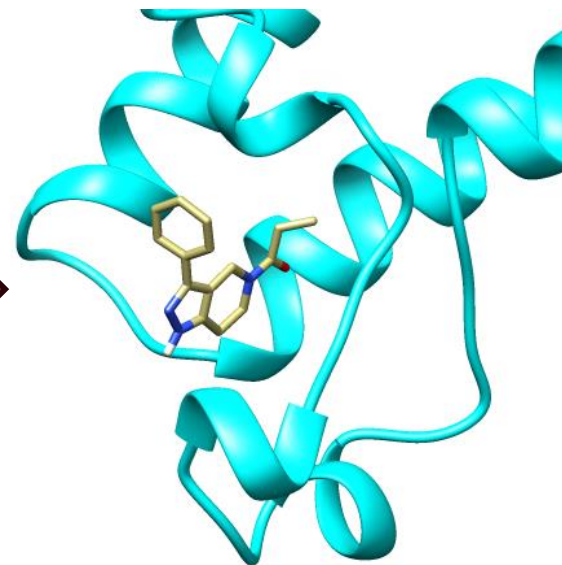
Ligando



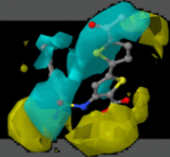
Proteina



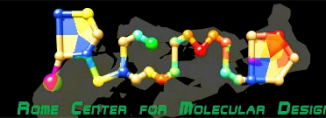
Generazione delle pose



Selezione della posa



Validazione del docking molecolare

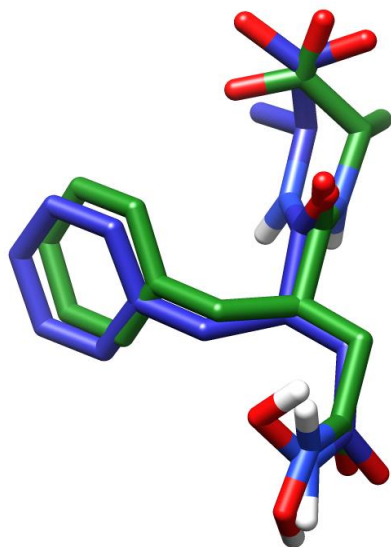


$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_{ci} - x_{di})^2 + (y_{ci} - y_{di})^2 + (z_{ci} - z_{di})^2}$$

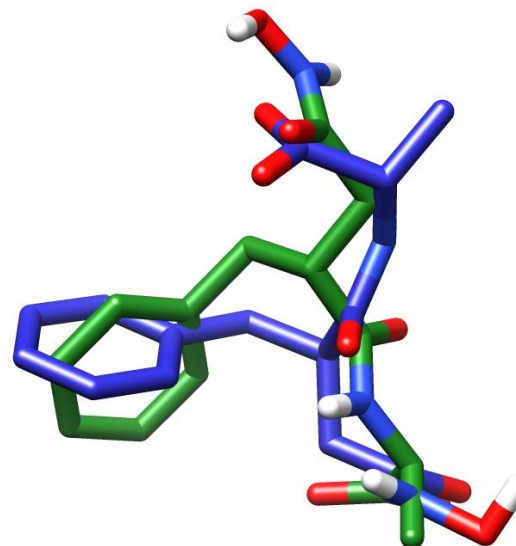
$$DA\% = \frac{f_{RMSD \leq 2} + 0,5f_{2 < RMSD \leq 3}}{f_{TOT}}$$

Atomic Docking Accuracy (ADA)

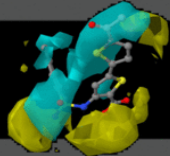
RMSD = 0.86



RMSD = 5.02

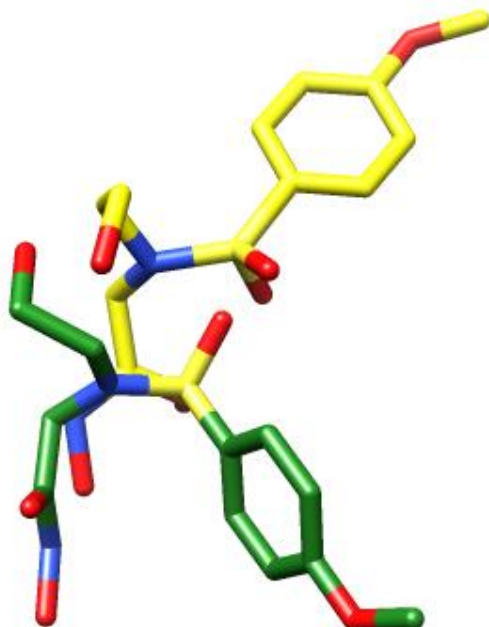


APPROCCIO ATOMICO

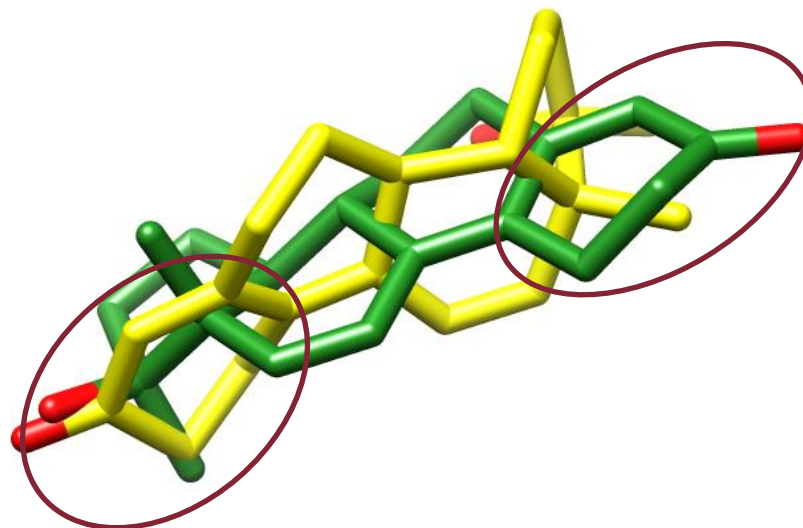


Limiti dell'approccio atomico

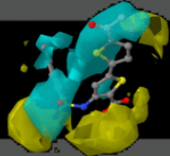
conformazione sperimentale
 posa selezionata dal programma



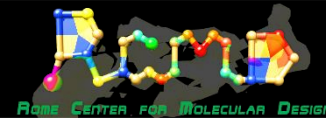
RMSD = 6.15



RMSD = 6.25

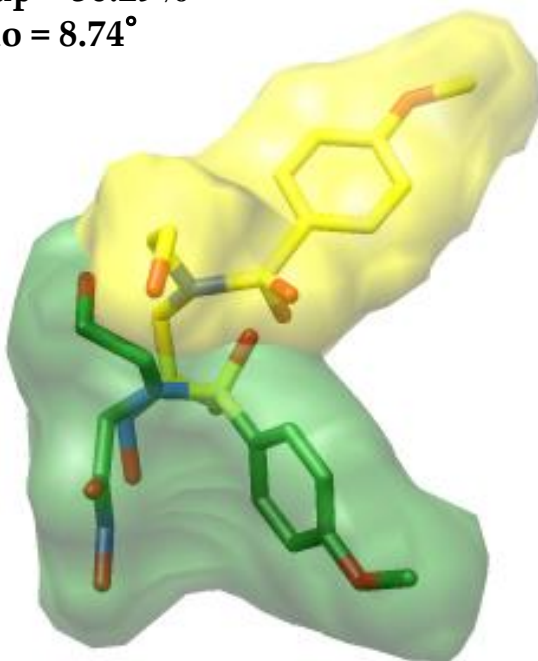


Volume di sovrapposizione

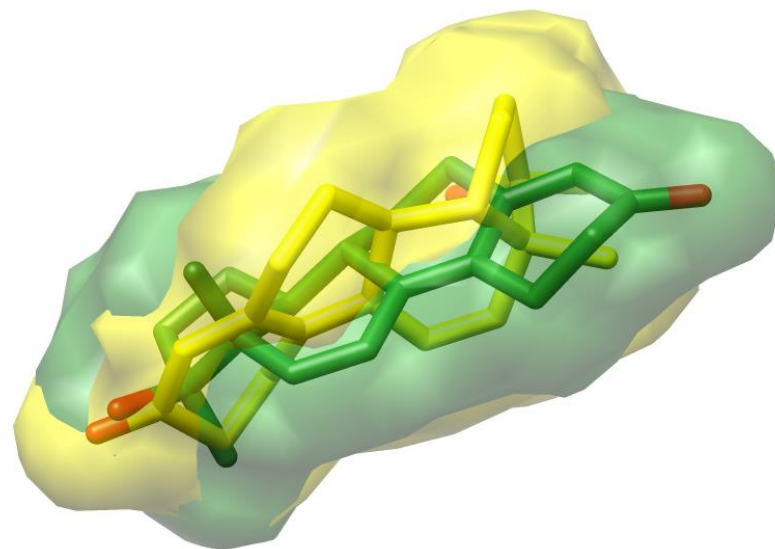


$$\%VolOverlap = \frac{V_{sovrapposto}}{V_{conf.sperim}} \cdot 100$$

RMSD = 6.15
Overlap = 30.29%
Angolo = 8.74°



RMSD = 6.25
Overlap = 71.27%
Angolo = 178.38°

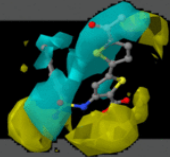


APPROCCIO VOLUMETRICO

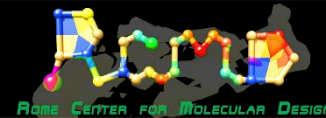


Derivare una docking accuracy dalle percentuali di sovrapposizione volumetrica da utilizzare per confrontare le prestazioni di diversi programmi di docking su 60 tipi di target .





Struttura del progetto



Selezione e preparazione
del **dataset di complessi**



Esecuzione dei **re-docking** e **cross-docking**
partendo dalla conformazione sperimentale e
randomica



Definizione della **DA volumetrica**

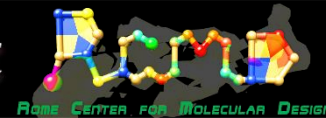


Validazione con **approccio atomico** e **volumetrico**





Selezione e preparazione del dataset



Refined-set dal
PDBBind database
(1412 targets)



*Selezione per numero di
complessi ≥ 4*

Target con almeno 4
complessi
(309 targets)

Targets con
numero di
complessi da 5 a 4
(102 targets)

*Divisione dei ligandi
in quattro cluster*



Pulizia e allineamento
sulla piattaforma
3d-qsar.com



Target
monomerici
(60 targets)



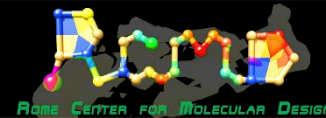
*Selezione per struttura
quaternaria monomerica*

Target con complessi
dei quattro centroidi





Esecuzione del docking molecolare

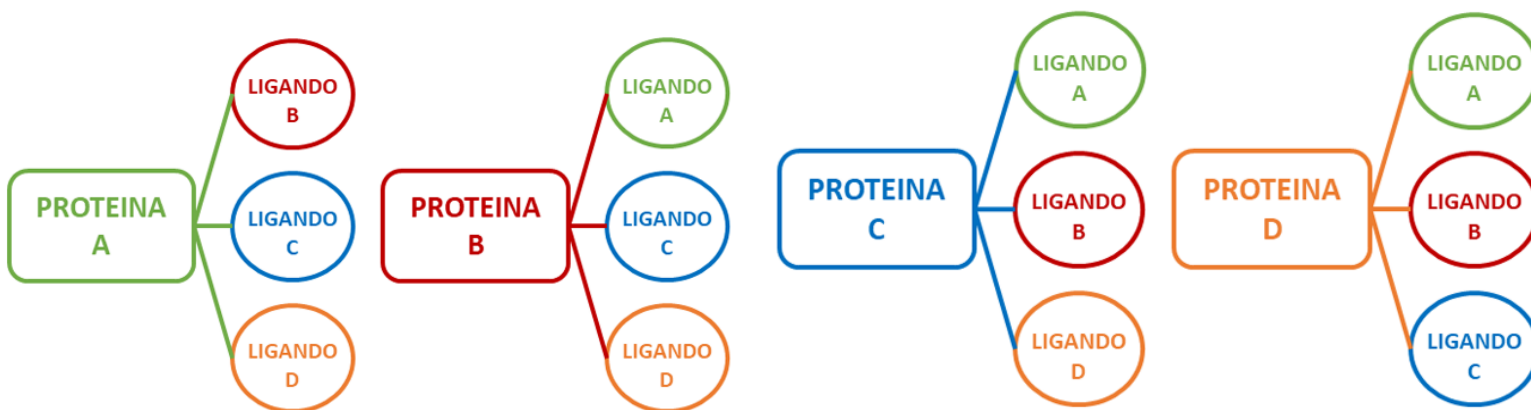


ROME CENTER FOR MOLECULAR DESIGN

Re-docking → ligando nella proteina originale

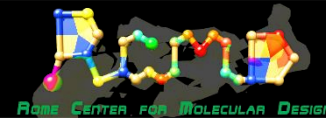


Cross-docking → ligando nelle tre proteine non native





Programmi di docking utilizzati



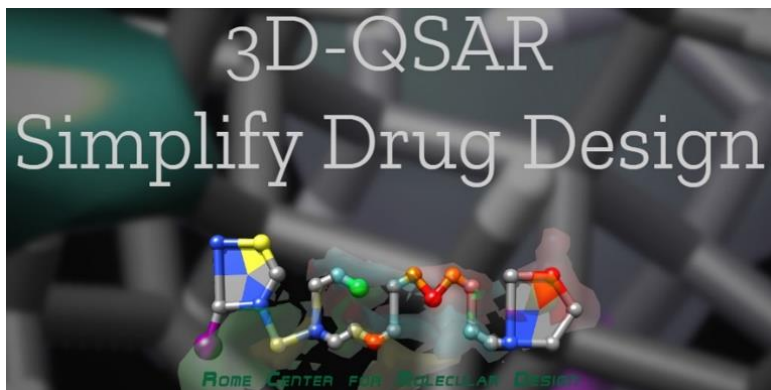
Sono stati utilizzati 4 differenti programmi, con ogni *scoring function* disponibile, per un totale di 8 combinazioni.

PLANTS

- plp
- plp95
- chemplp

Smina

- vinardo
- vina
- ad4



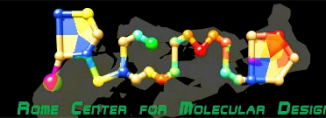
SLIDE

GlamDock



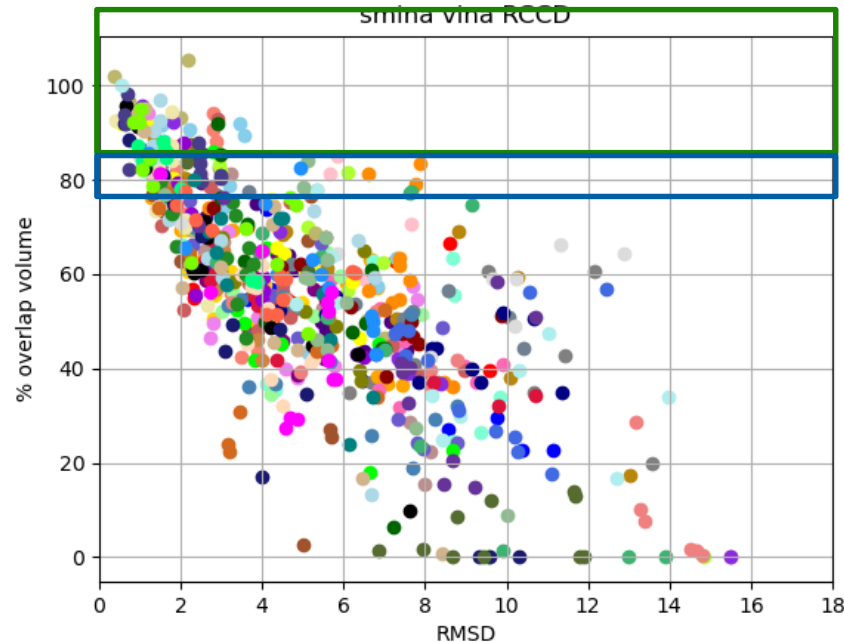
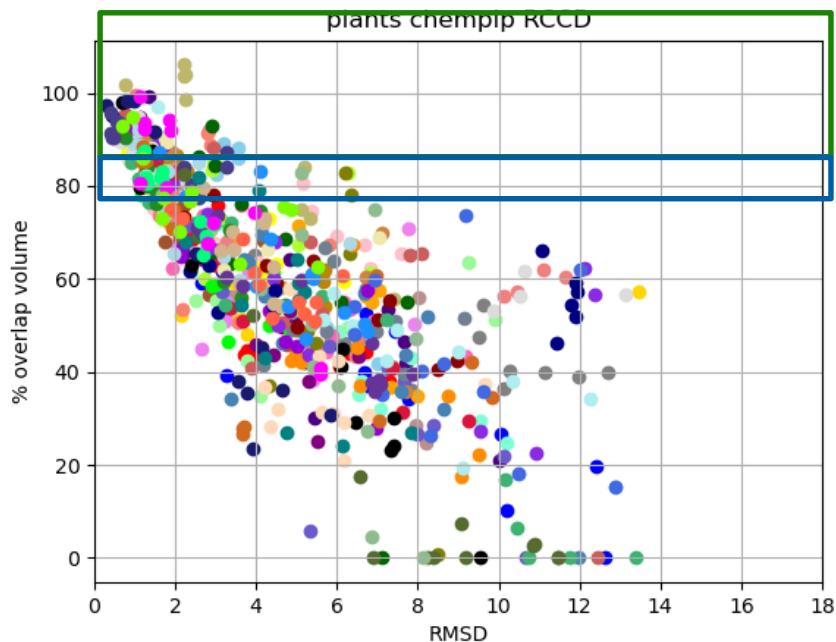


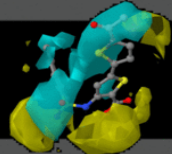
Definizione della VDA



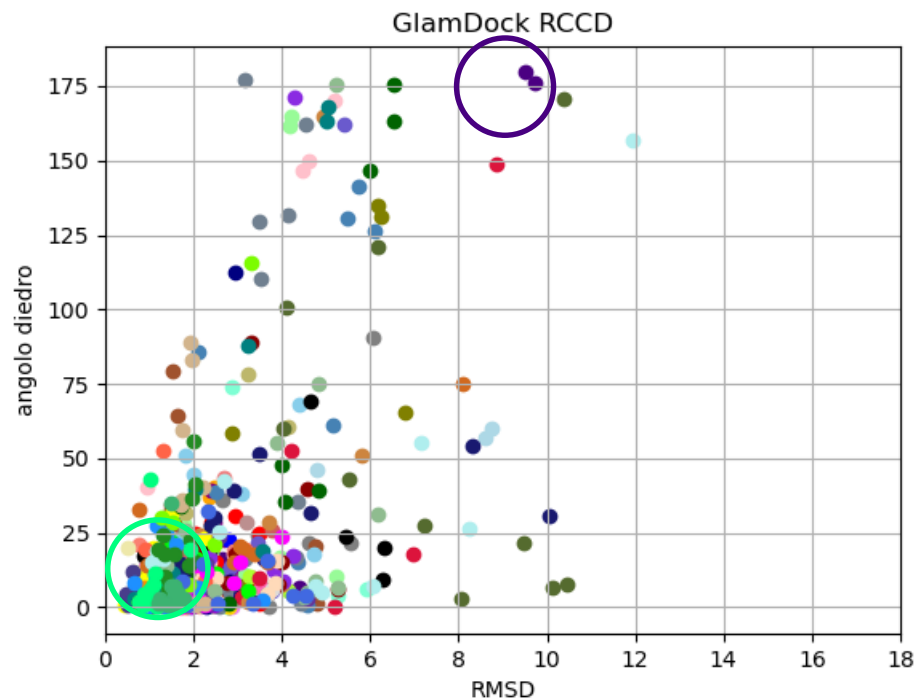
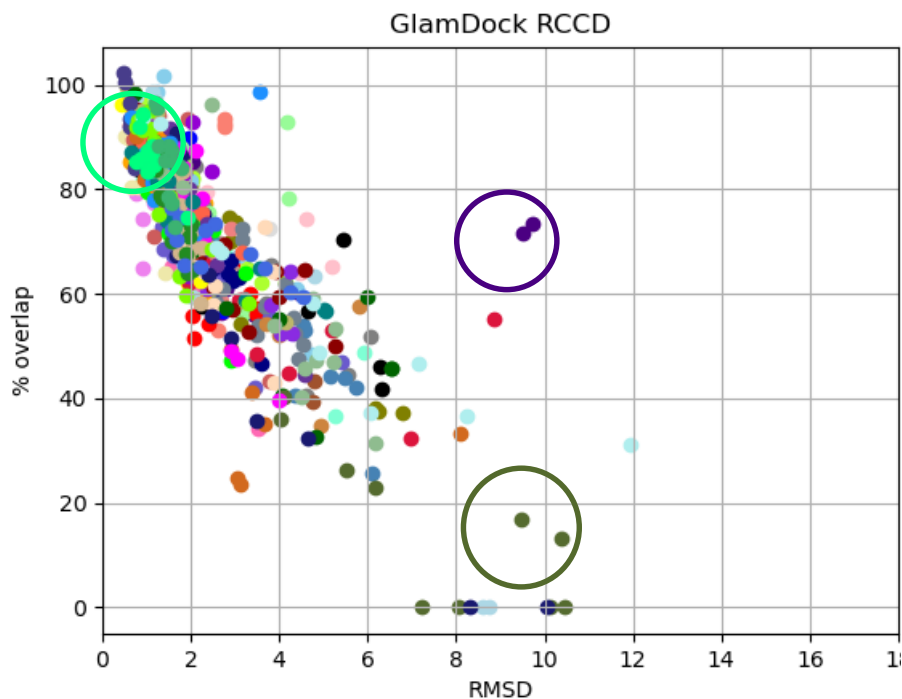
$$VDA = f\%Vol.Overlap \geq 80 + 0,75f70 \leq \%Vol.Overlap < 80$$

Volumetric Docking Accuracy (VDA)





Risultati

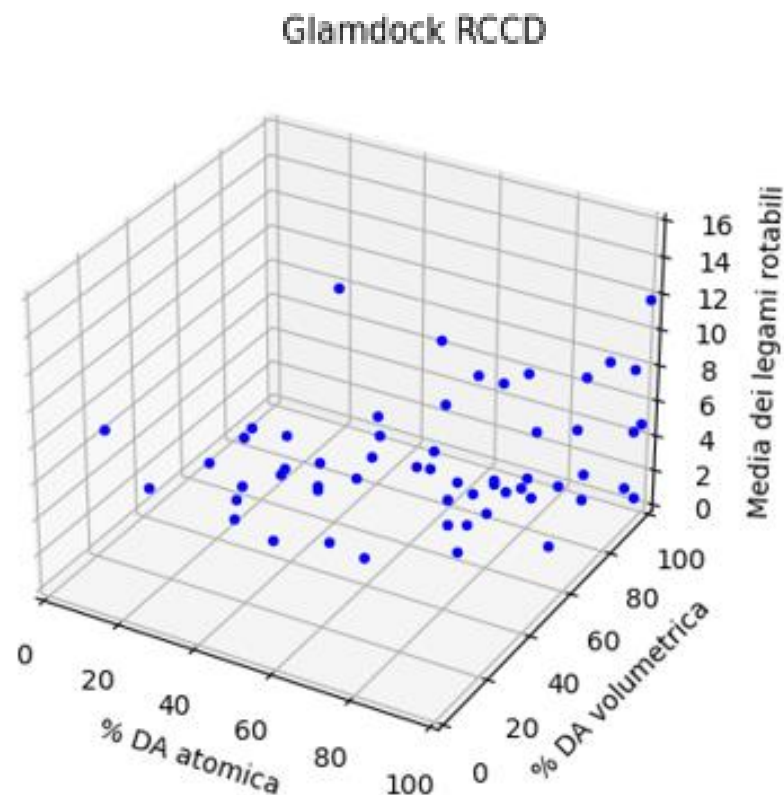
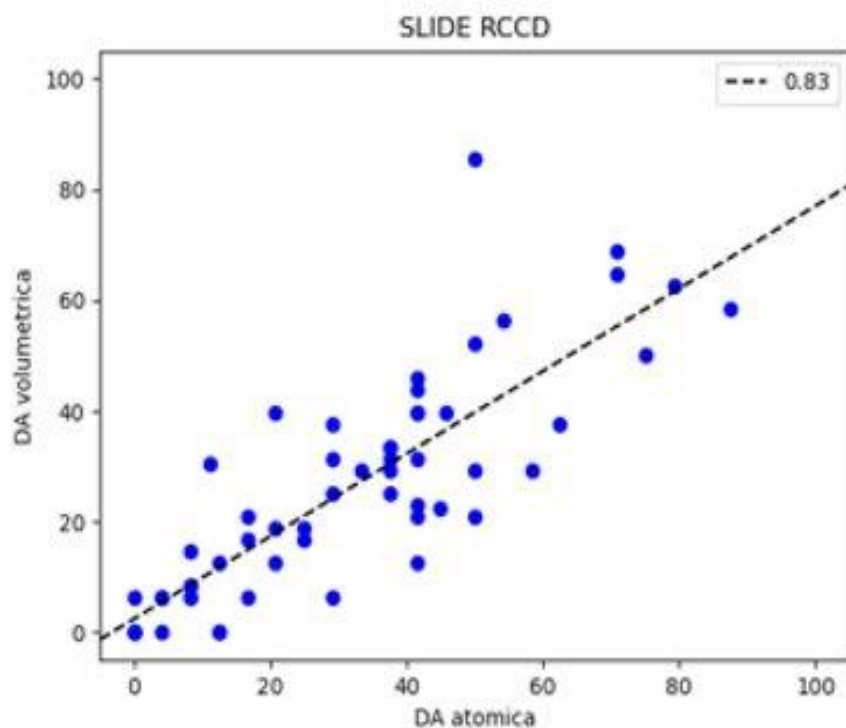


$\text{RMSD} \leq 2$, %overlap ≥ 80 e corretto orientamento
RMSD elevato per orientamento della posa inverso
RMSD elevato per mal posizionamento



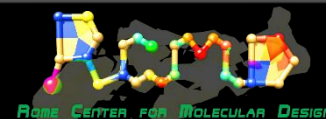
Correlazione tra ADA e VDA

I coefficienti di Pearson sono risultati compresi tra 0.75 e 0.93 indicano una correlazione lineare tra %ADA% e %VDA.



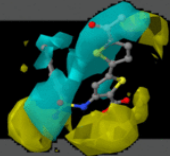


Risultati

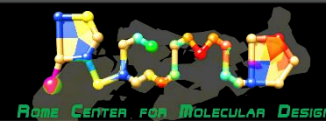


Targets	% ADA RCCD								% VDA RCCD							
	plp	plp95	chemplp	vina	vinardo	ad4	slide	glamdock	plp	plp95	chemplp	vina	vinardo	ad4	slide	glamdock
CASEIN KINASE II ALPHA SUBUNIT	12.50	8.33	12.50	12.50	0.00	0.00	11.11	87.50	14.58	14.58	22.92	22.92	29.17	12.50	30.56	93.75
GALACTOCEREBROSIDASE	33.33	37.50	66.67	66.67	29.17	25.00	50.00	100.00	100.00	100.00	95.83	97.92	91.67	87.50	85.42	95.83
BETA-MANNOSIDASE	66.67	70.83	54.17	33.33	45.83	8.33	87.50	95.83	64.58	77.08	56.25	31.25	50.00	50.00	58.33	60.42
PROTEIN POLYBROMO-1	70.83	54.17	75.00	87.50	79.17	58.33	79.17	100.00	72.92	35.42	70.83	85.42	77.08	64.58	62.50	89.58
HEAT SHOCK PROTEIN HSP90-ALPHA	8.33	12.50	8.33	8.33	8.33	16.67	20.83	29.17	8.33	22.92	20.83	20.83	16.67	12.50	39.58	33.33
HISTONE-LYSINE N-METHYLTRANSFERASE NSD3	33.33	20.83	33.33	37.50	29.17	25.00	41.67	83.33	54.17	60.42	70.83	45.83	58.33	64.58	39.58	75.00
ALPHA-MANNOSIDASE II	29.17	33.33	25.00	12.50	12.50	8.33	54.17	41.67	47.92	64.58	39.58	29.17	37.50	20.83	56.25	29.17
TRANSPORTER	41.67	45.83	45.83	29.17	29.17	4.17	45.83	54.17	41.67	41.67	41.67	22.92	31.25	22.92	39.58	33.33
ANDROGEN RECEPTOR	50.00	41.67	45.83	37.50	37.50	25.00	29.17	66.67	62.50	70.83	64.58	66.67	64.58	50.00	37.50	70.83
POLY ADP-RIBOSE POLYMERASE 1	25.00	37.50	33.33	20.83	22.22	16.67	20.83	79.17	25.00	29.17	29.17	22.92	33.33	33.33	18.75	70.83
CEREBLON ISOFORM 4	29.17	37.50	37.50	33.33	41.67	29.17	70.83	75.00	47.92	50.00	47.92	47.92	56.25	47.92	68.75	72.92

**SCELTA DEL PROGRAMMA CON MIGLIORI PRESTAZIONI PER
OGNIUNO DEI TARGET CONSIDERATI**

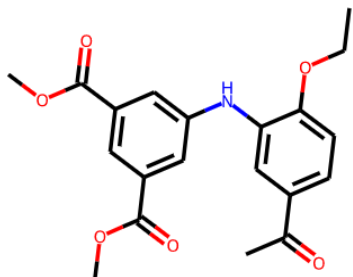


Test finale

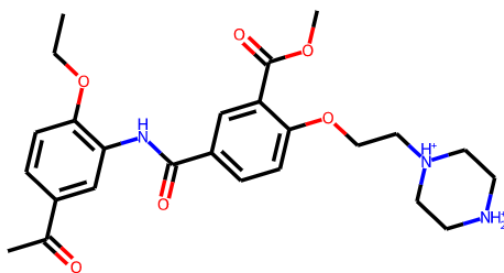


CREB-BINDING PROTEIN

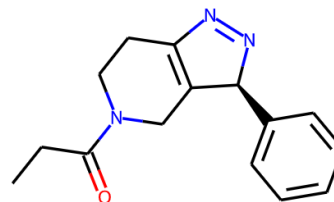
5MME



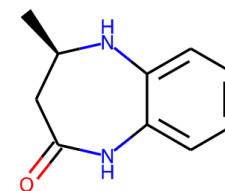
5ENG



5TB6



4YK0



Metodo	% ADA (test)	% VDA (test)	% ADA (modello)	% VDA (modello)
ECRD	100	87.5	100	87.50
ECCD	91.67	60.42	87.50	68.75
RCRD	87.50	68.75	87.50	93.75
RCCD	70.83	50	91.67	72.92

RCCD



DIFFERENZA %ADA = 20,84 %

DIFFERENZA %VDA = 22,92 %



Applications

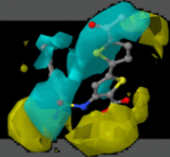
Click on any button to start using the platform. If you want to know a bit more about the application, visit the link below to see all you will be able to do.

[Explore Apps](#)

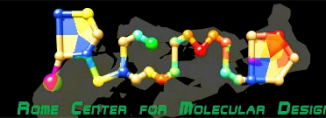
Py-MolEdit	Py-ConfSearch	Py-Align
Py-CoMFA	Py-ComBinE	Py-Docking
Py-Pharm <small>NEW</small>	Py-PDB <small>NEW</small>	Py-Graph <small>NEW</small>

Diagram illustrating the applications available on the 3d-qsar.com platform. A central grid of application buttons is shown, with arrows pointing to specific applications: an orange arrow points to Py-MolEdit, a blue arrow points to Py-Docking, and a pink arrow points to Py-PDB.

- ✓ Preparazione di ligandi e delle proteine
- ✓ Editor per la correzione delle strutture cristallografiche
- ✓ Esecuzione del docking e calcolo dei parametri di validazione



CONCLUSIONI



APPROCCIO
VOLUMETRICO

+

APPROCCIO
ATOMICO



VALIDAZIONE PIU' ACCURATA
DEI PROGRAMMI DI DOCKING

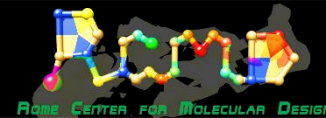


AIUTO NELLA SCELTA DEL PROGRAMMA

WORK IN PROGRESS
«SUPER PROGRAMMA» DI VALIDAZIONE



RINGRAZIAMENTI



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GRAZIE PER L'ATTENZIONE