

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



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Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
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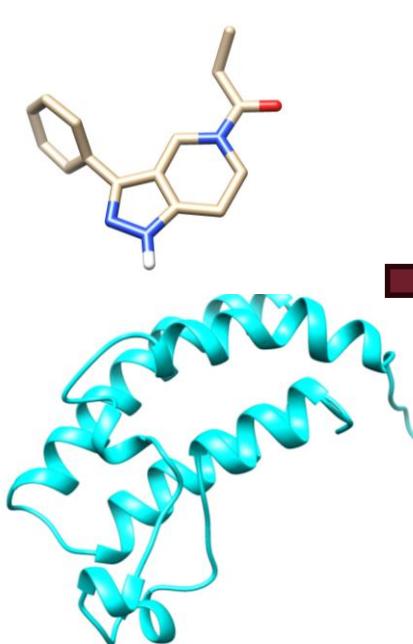
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Matricola: 1810291**

Relatore: prof. Rino Ragno

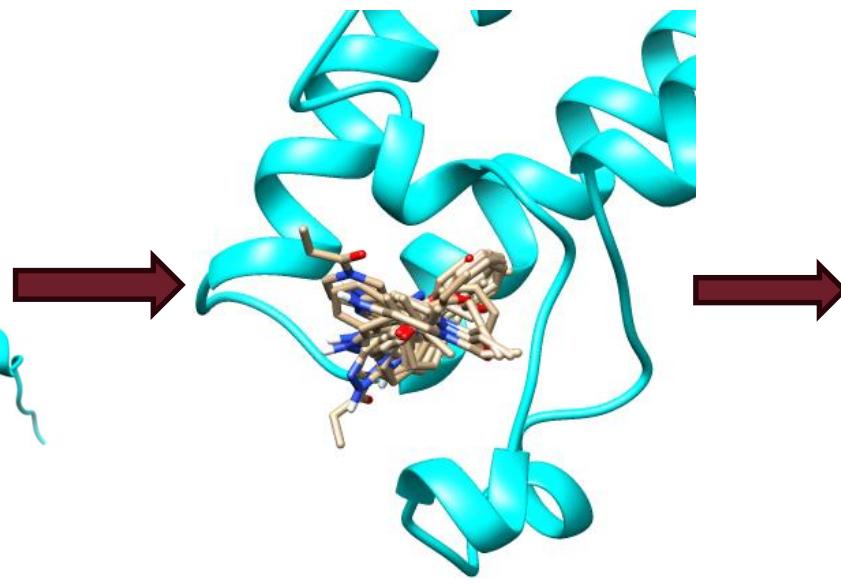


Il docking molecolare

Ligando



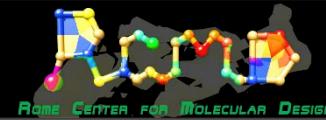
Proteina



Generazione delle pose

Selezione della posa

Validazione del docking molecolare

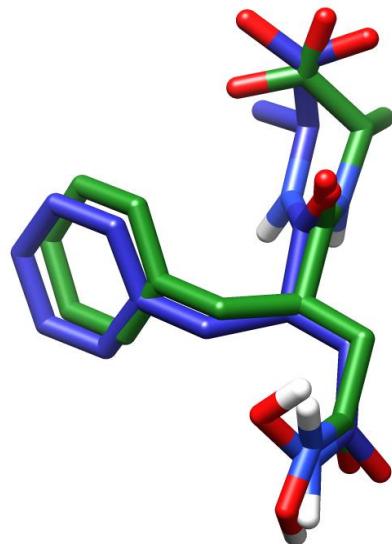


$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_{ci} - x_{di})^2 + (y_{ci} - y_{di})^2 + (z_{ci} - z_{di})^2}$$

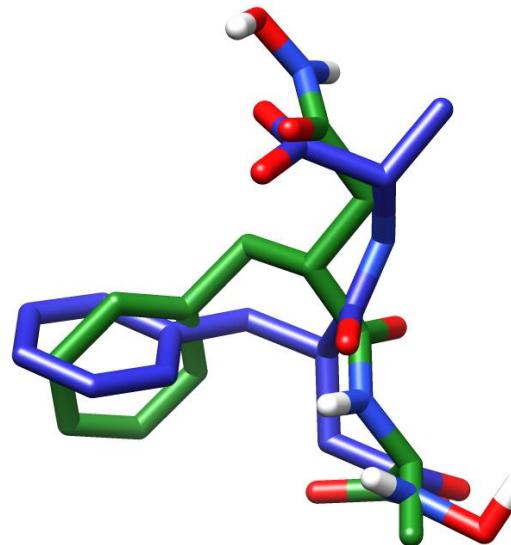
$$DA\% = \frac{f_{RMSD \leq 2} + 0,5f_{2 < RMSD \leq 3}}{f_{TOT}}$$

Atomic Docking Accuracy (ADA)

RMSD = 0.86



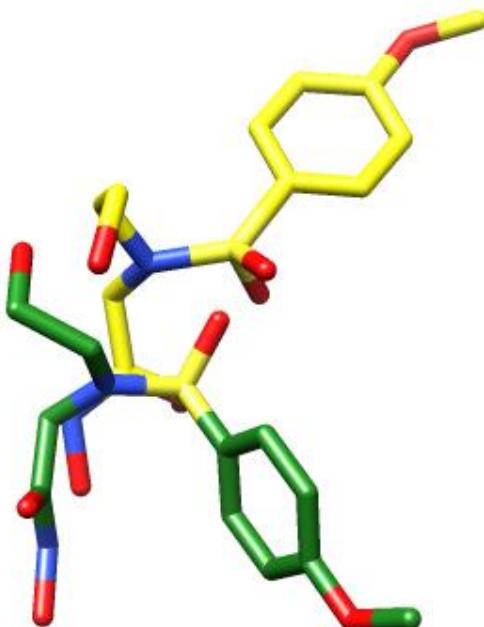
RMSD = 5.02



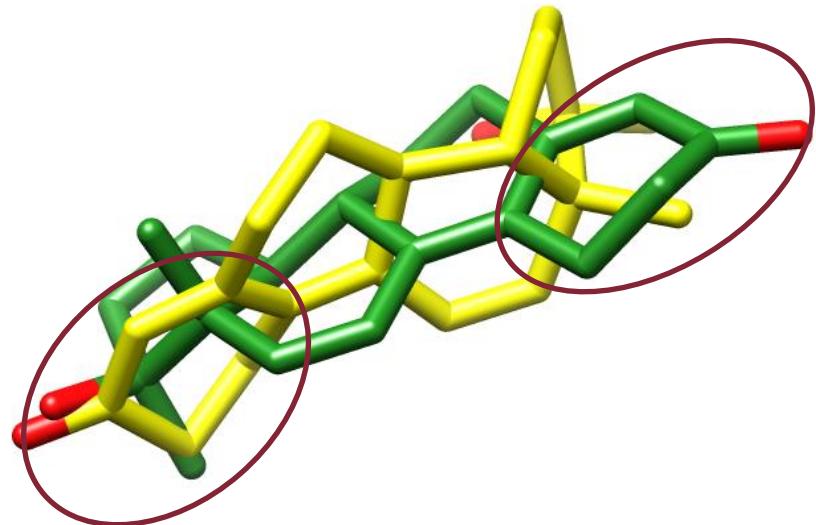
APPROCCIO ATOMICO

Limiti dell'approccio atomico

 conformazione sperimentale
 posa selezionata dal programma



RMSD = 6.15



RMSD = 6.25



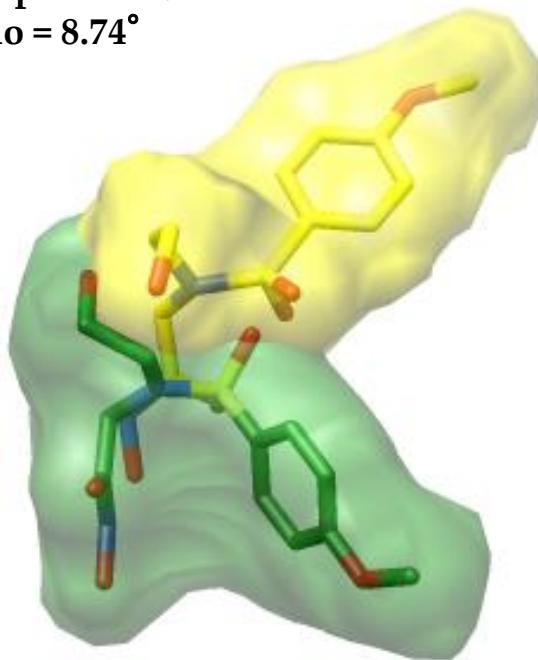
Volume di sovrapposizione

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

RMSD = 6.15

Overlap = 30.29%

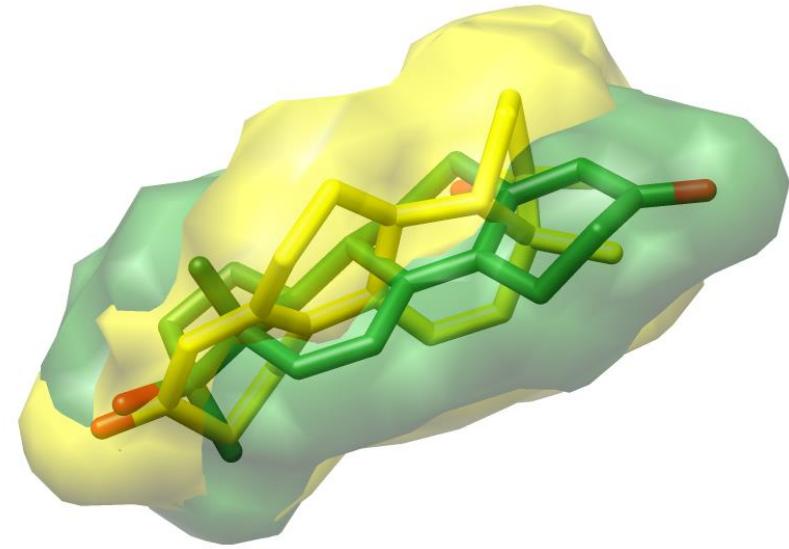
Angolo = 8.74°



RMSD = 6.25

Overlap = 71.27%

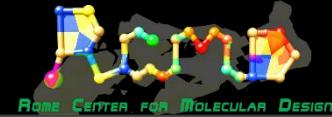
Angolo = 178.38°



APPROCCIO VOLUMETRICO



Finalità della tesi

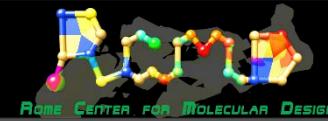


Derivare una docking accuracy dalle percentuali di sovrapposizione volumetrica da utilizzare per confrontare le prestazioni di diversi programmi di docking su 60 tipi di target .





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**

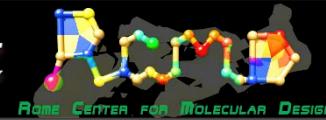


Validazione con **approccio atomico** e **volumetrico**





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)

Pulizia e allineamento
sulla piattaforma
3d-qsar.com



Target
monomerici
(60 targets)



*Selezione per struttura
quaternaria monomerica*

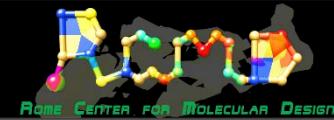
*Divisione dei ligandi
in quattro cluster*



Target con complessi
dei quattro centroidi



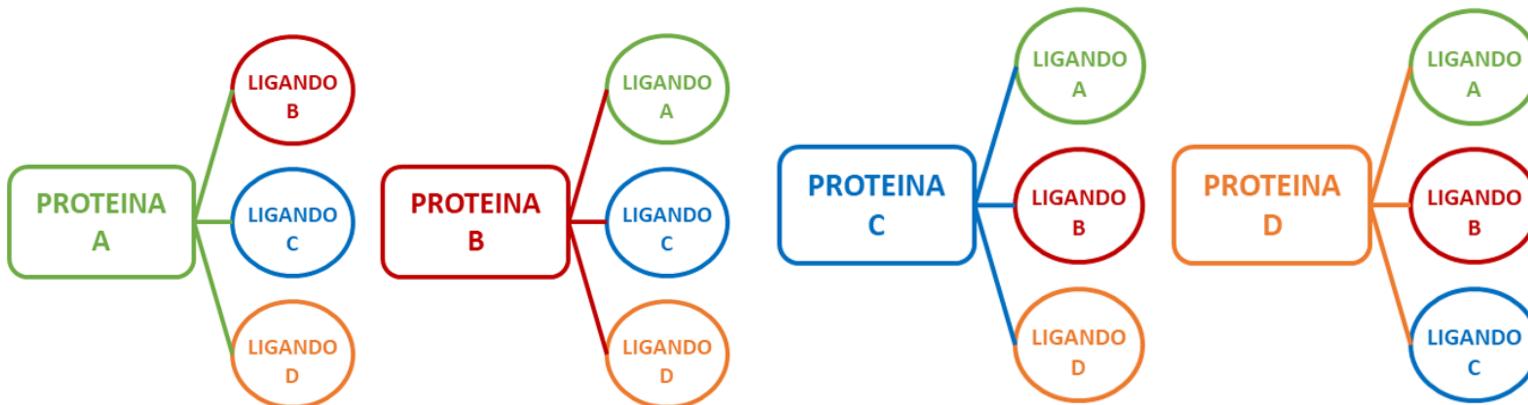
Esecuzione del docking molecolare



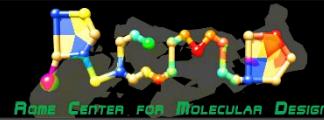
Re-docking → ligando nella proteina originale



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

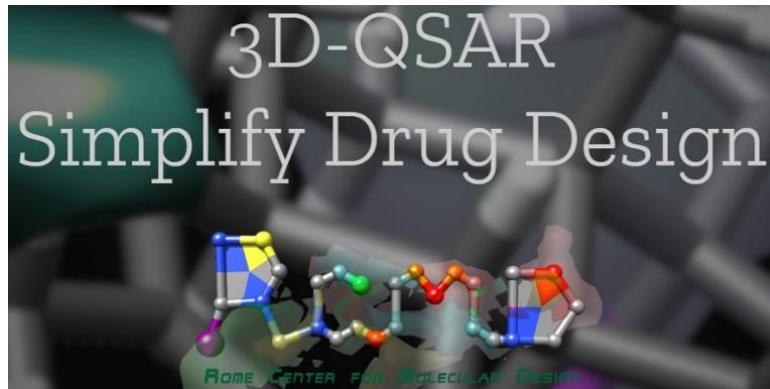
- plp
- plp95
- chemplp

Smina

- vinardo
- vina
- ad4

SLIDE

GlamDock

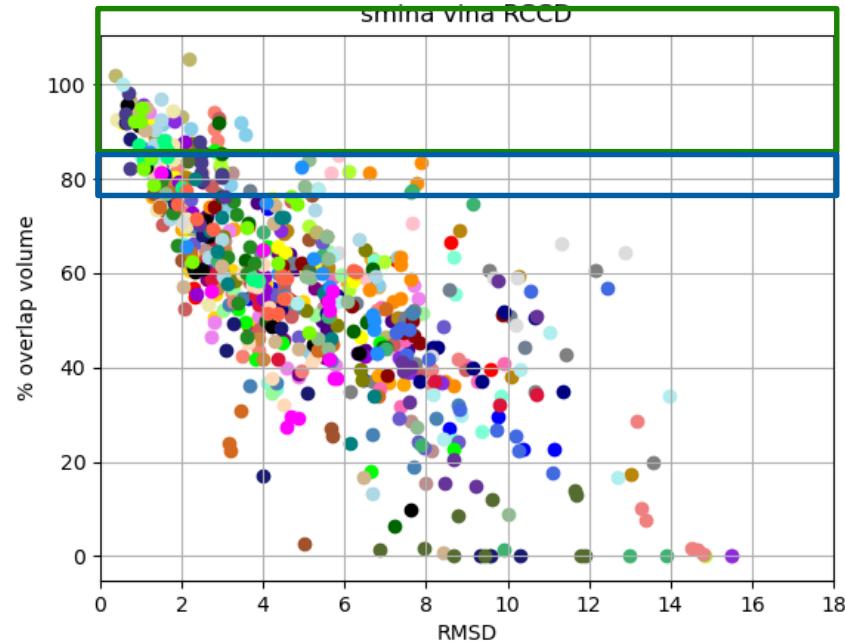
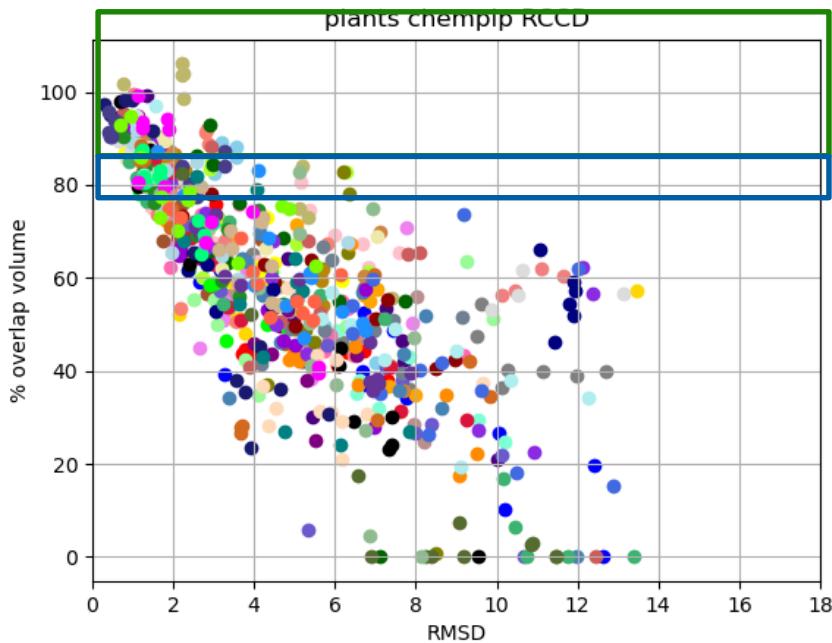




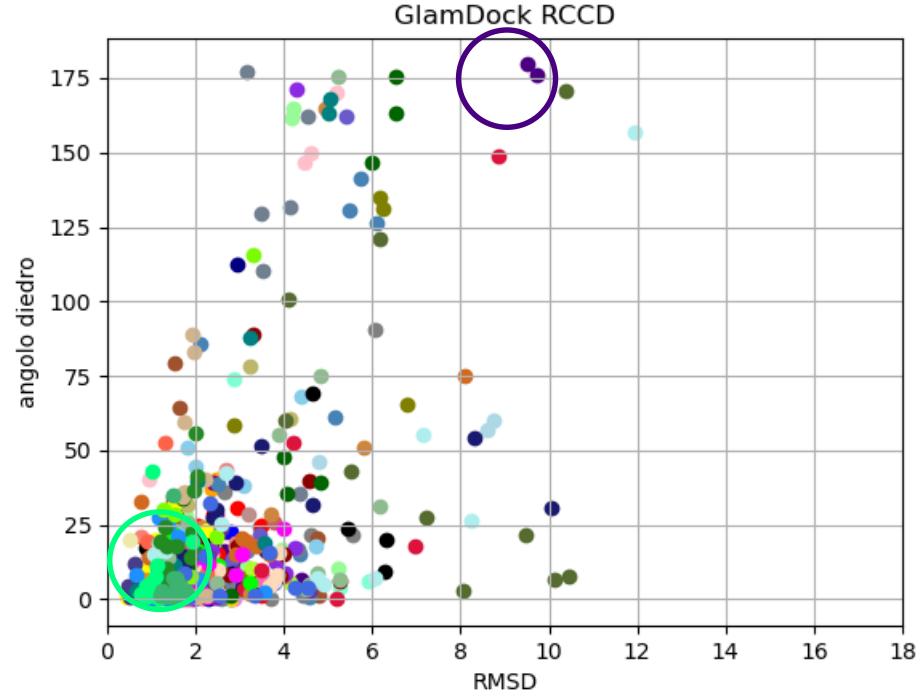
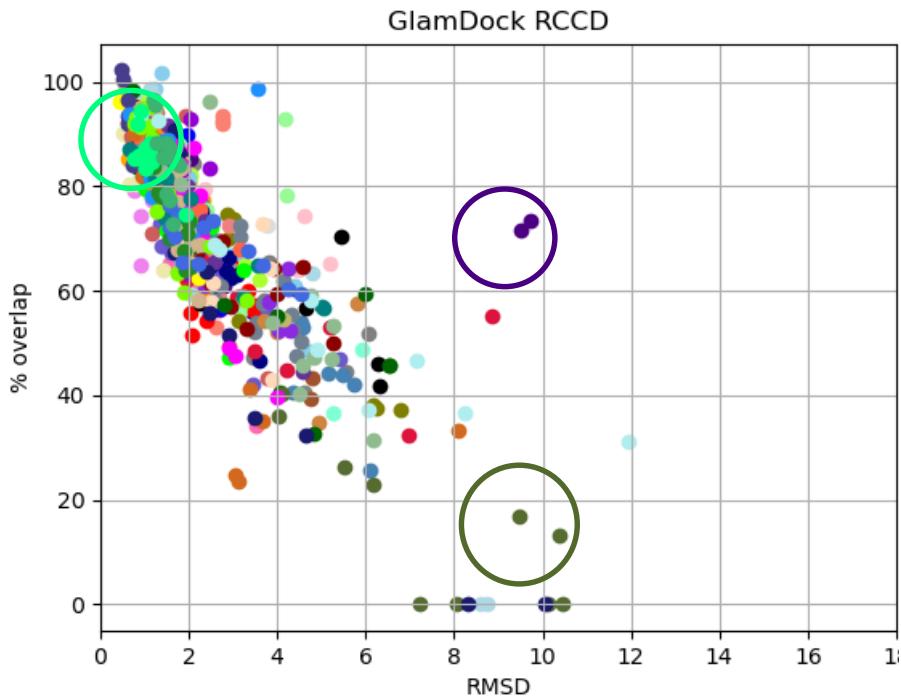
Definizione della VDA

$VDA = f\% \text{Vol.Overlap} \geq 80 + 0,75f \quad 70 \leq \% \text{Vol.Overlap} < 80$

Volumetric Docking Accuracy (VDA)



Risultati



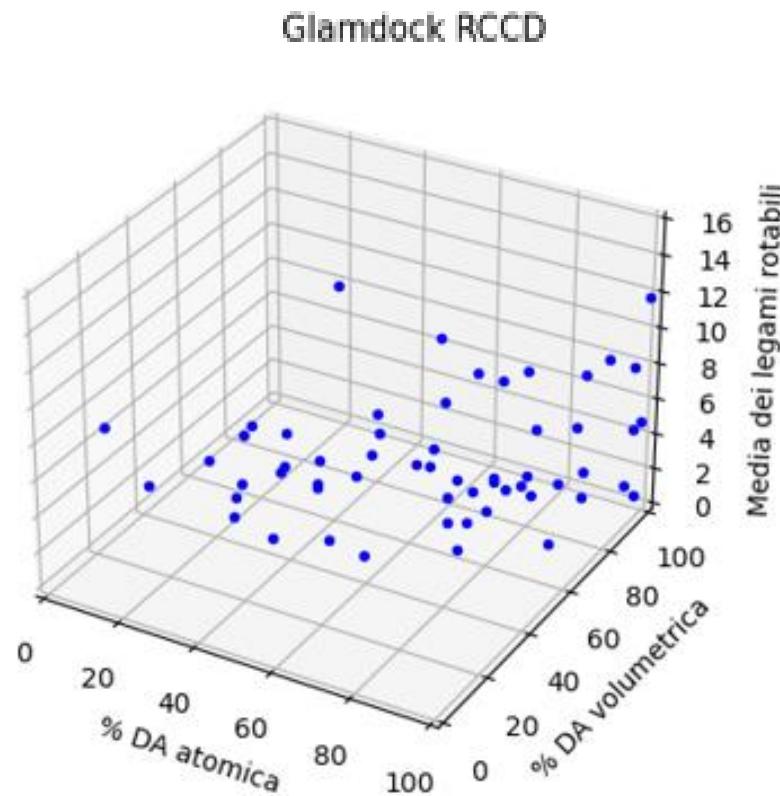
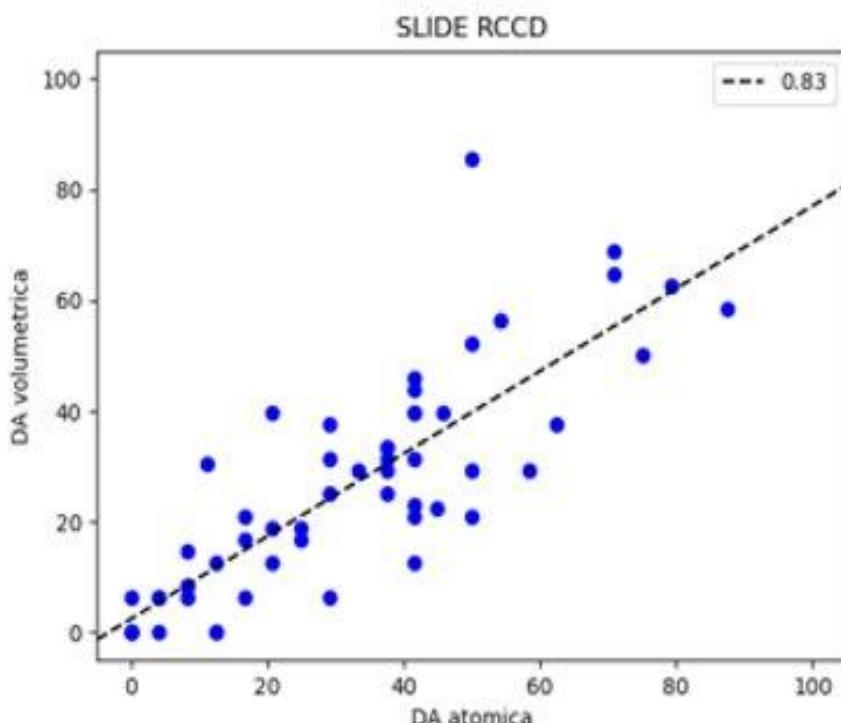
RMSD \leq 2, %overlap \geq 80 e corretto orientamento
RMSD elevato per orientamento della posa inverso
RMSD elevato per mal posizionamento



Correlazione tra ADA e VDA

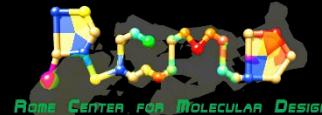


I coefficienti di Pearson sono risultati compresi tra 0.75 e 0.93 indicano una correlazione lineare tra %ADA% e %VDA.





Risultati



% ADA RCCD

% VDA RCCD

Targets	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

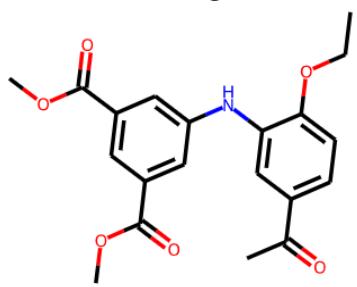


Test finale

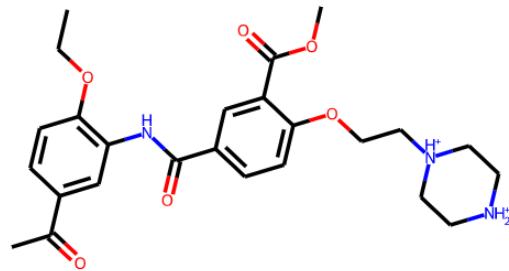


CREB-BINDING PROTEIN

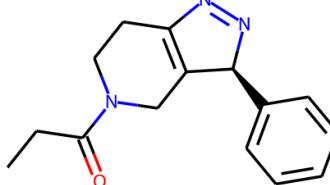
5MME



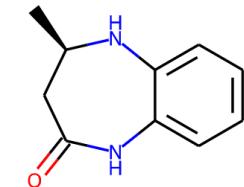
5ENG



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 NEW

Py-PDB NEW

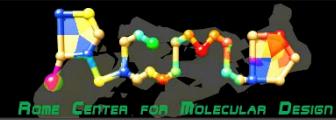
Py-Graph NEW



- ✓ 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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Dott. Lorenzo Antonini

Dott.ssa Eleonora Proia

Dott.ssa Roberta Astolfi

Dott. Filippo Sapienza

Pietro Sciò

Nicolò Maria Pasquini



GRAZIE PER L'ATTENZIONE