METODICHE DI MACHINE LEARNING E STRUCTURE BASED DRUG DESIGN PER L'INDIVIDUAZIONE DI NUOVI LIGANDI DI K-RAS

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Biotecnologie Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2016/2017

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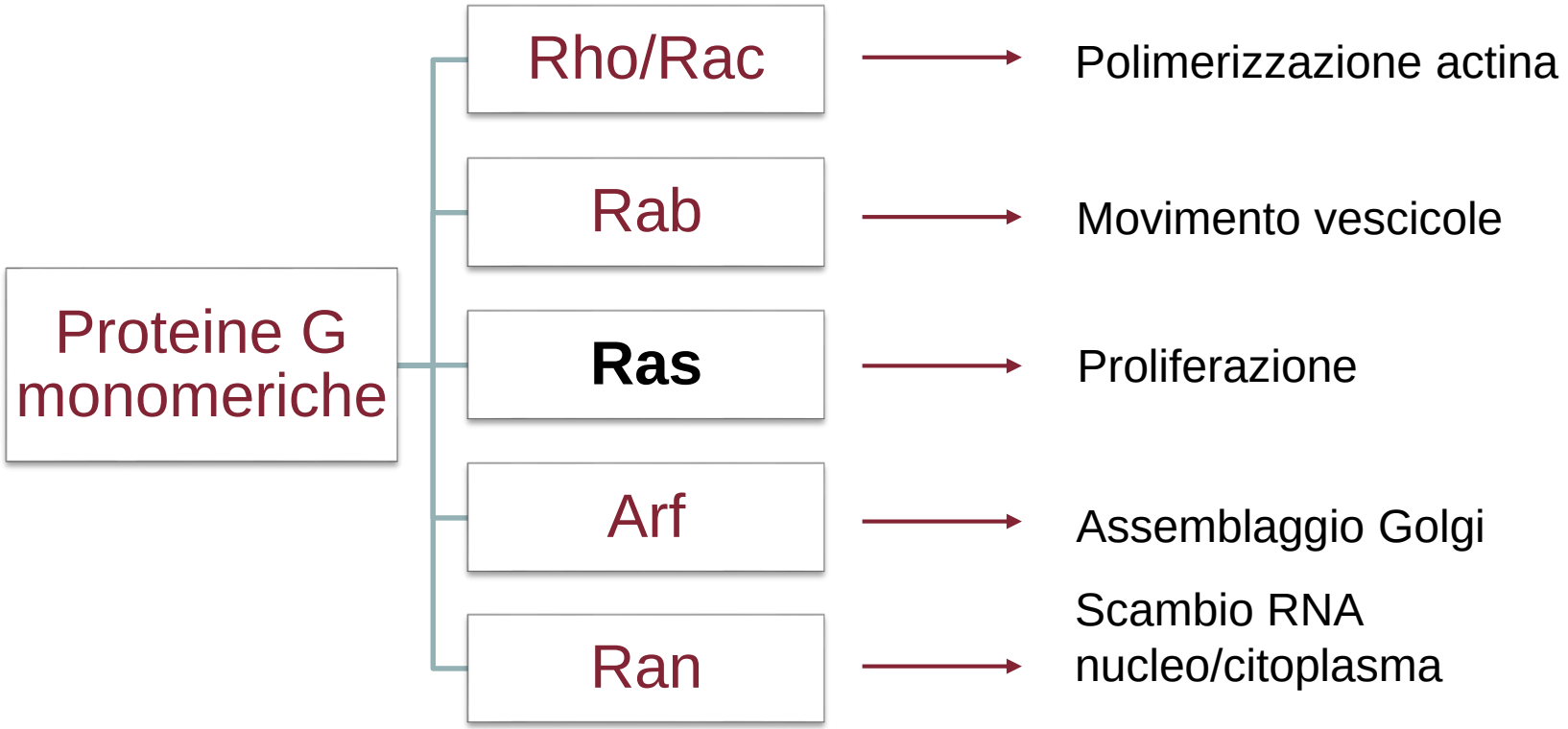
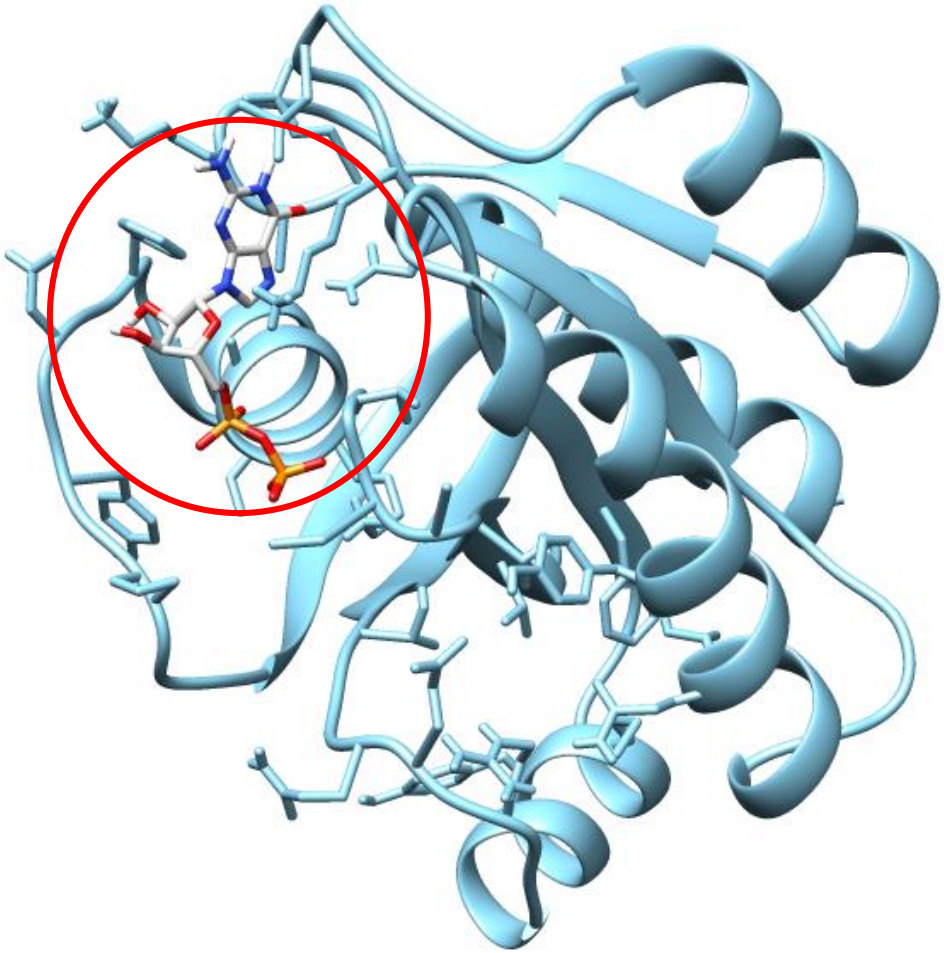
Matricola: 1556506

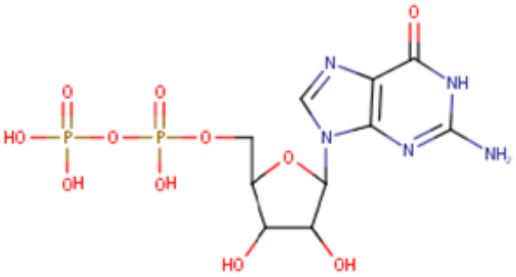
Relatore: prof. Rino Ragno

La superfamiglia



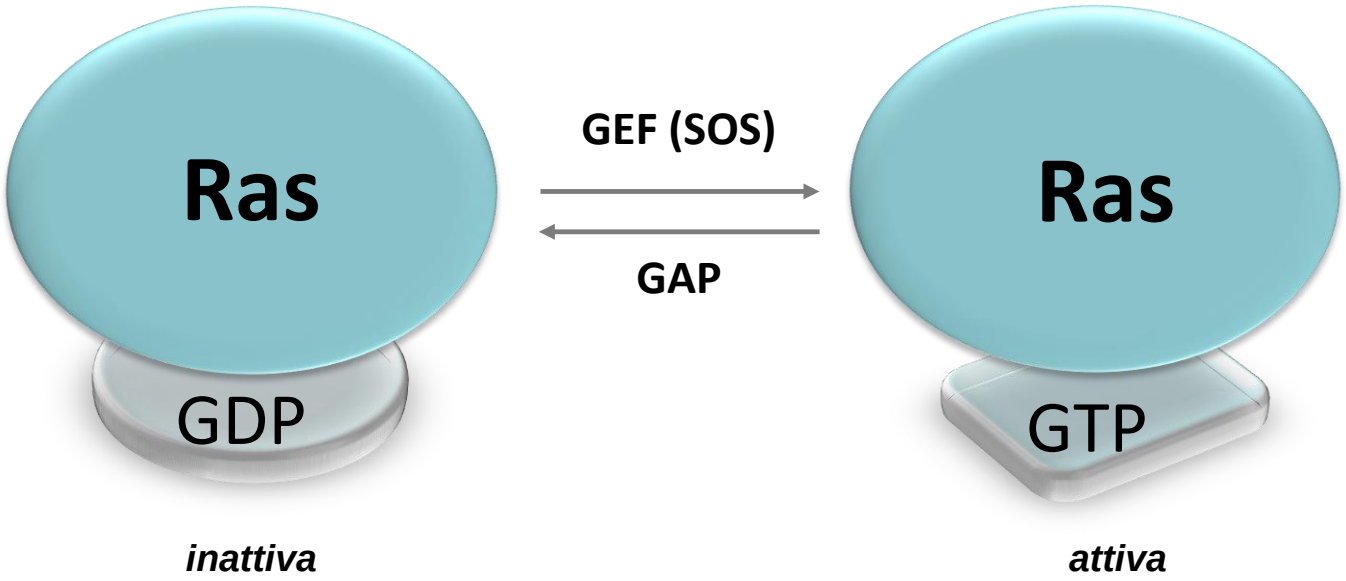
La proteina – KRAS4B





Le proteine Ras

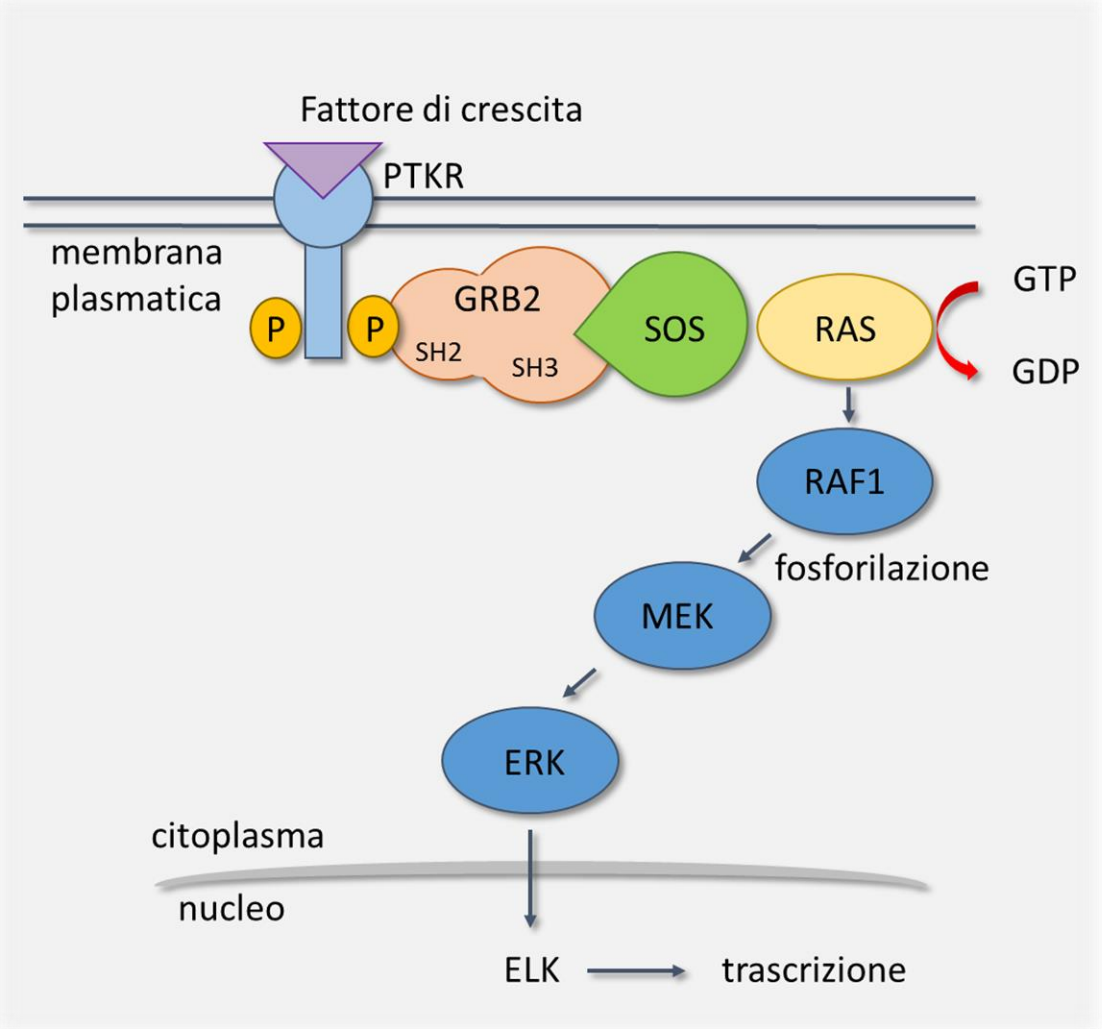
Interruttori molecolari
"on/off"

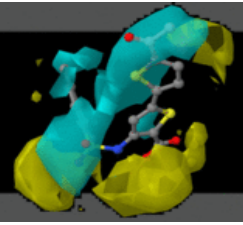


Lo stato funzionale delle proteine Ras è regolato da:

- **GEFs** → guanine nucleotide exchange factors
- **GAPs** → GTPases-activating proteins

Il pathway


Fattore di crescita
PTKR
membrana
plasmatica
P
P
GRB2
SH2
SH3
SOS
RAS
GTP
GDP
RAF1
fosforilazione
MEK
ERK
citoplasma
nucleo
ELK
trascrizione



Come agire?

- Proteina considerata «undruggable»
- Strategie:

✓ *Blocco delle modifiche post-traduzionali*

✓ *Inibire il legame KRAS/GDP*

Covalenti

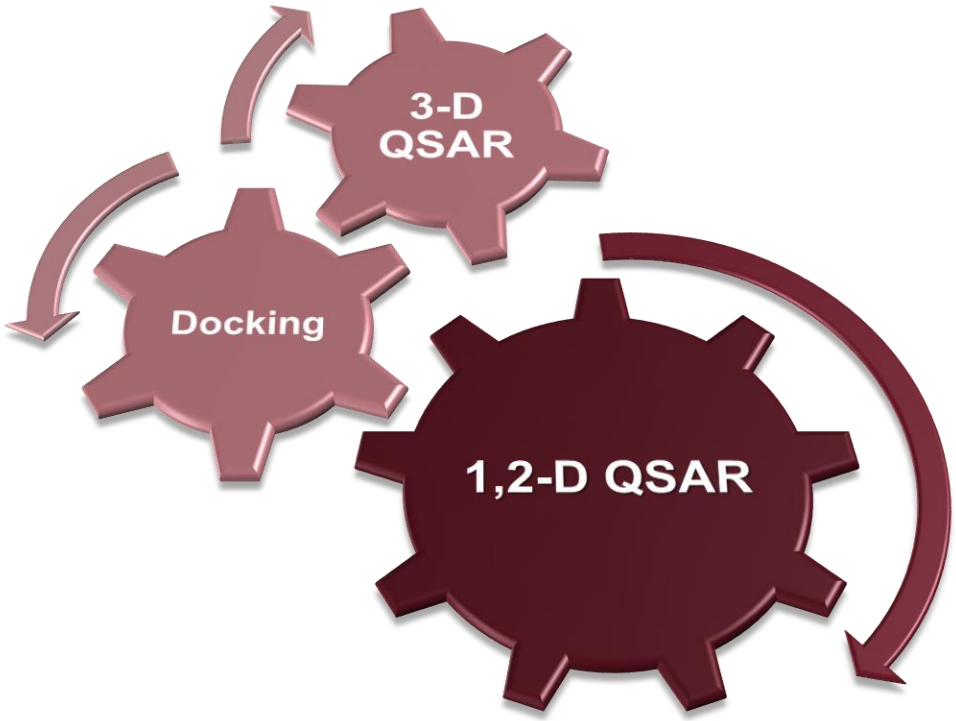
~~✓ Competitivi~~

✓ Allosterici

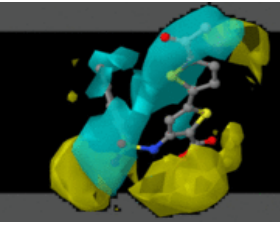
Reversibili

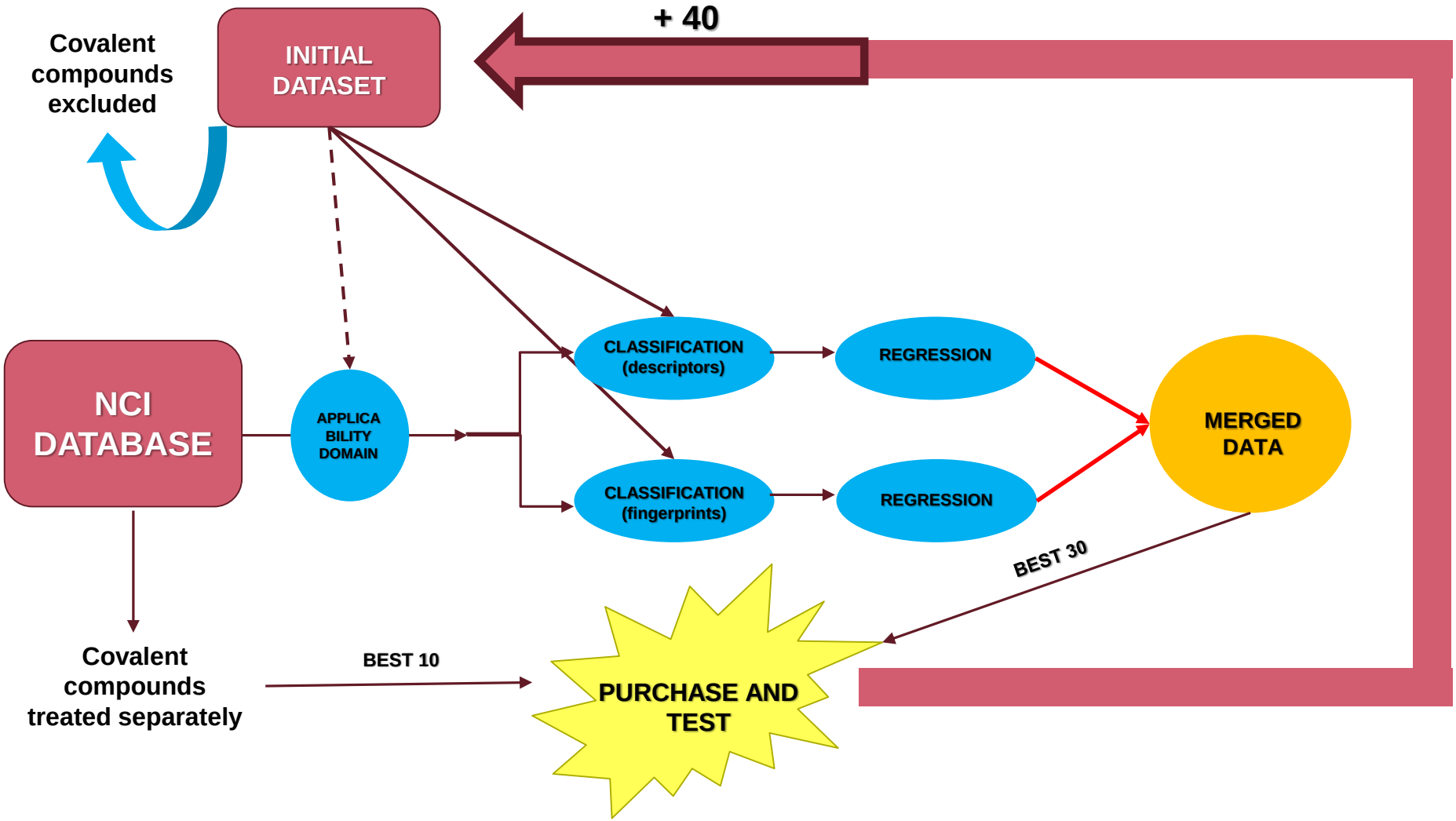
✓ Allosterici

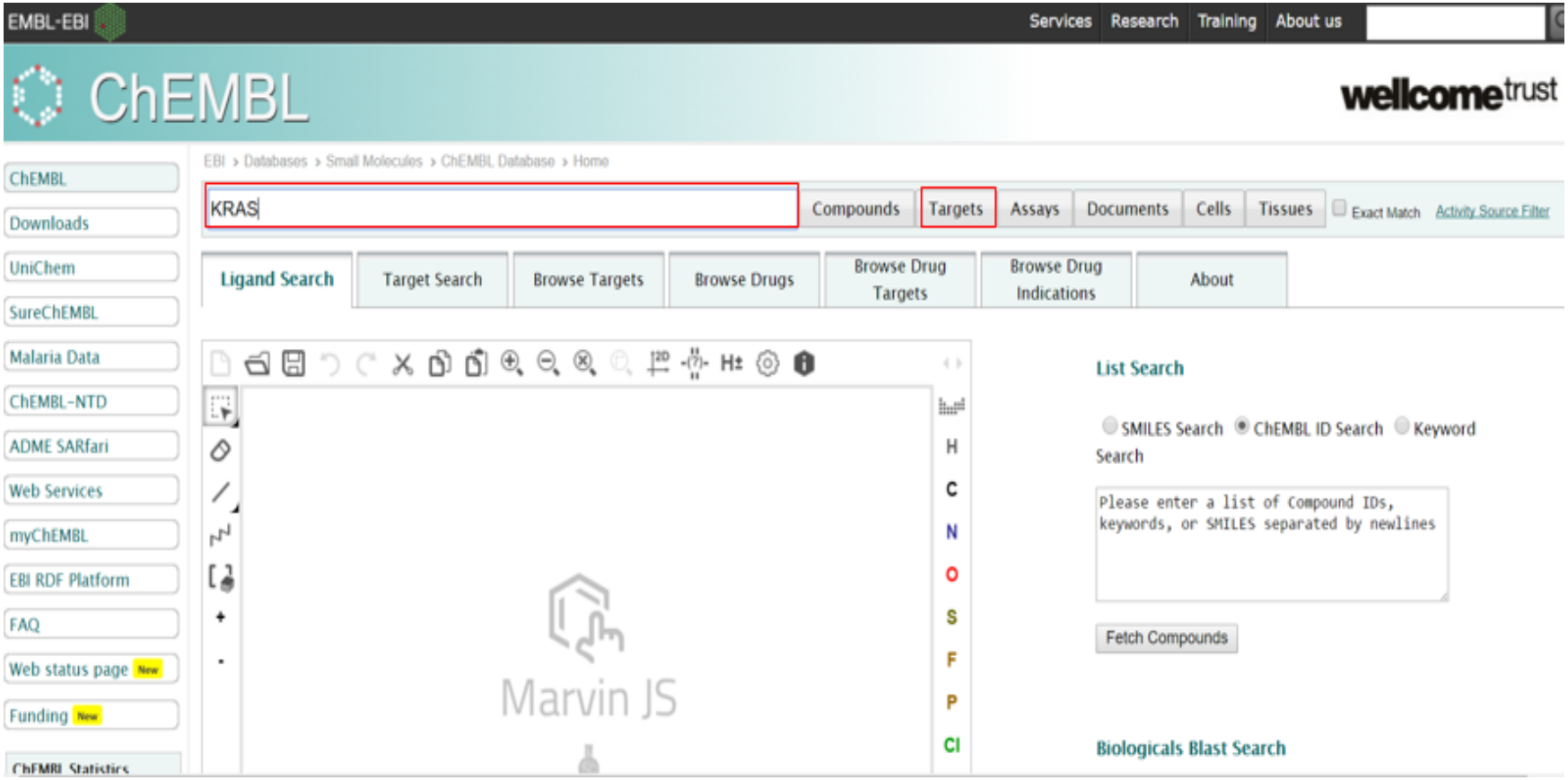
QSAR e Docking



Strategia 1,2-D QSAR by www.RCMD.it



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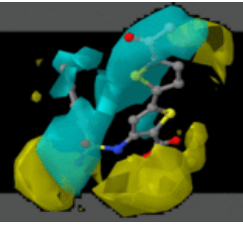
Please enter a list of Compound IDs, keywords, or SMILES separated by newlines
Fetch Compounds
Biologicals Blast Search

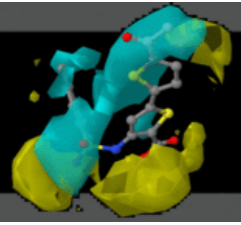


Database iniziale

by www.RCMD.it

59 molecole (38 reversibili)

	CANONICAL_SMILES	STANDARD_TYPE	STANDARD_UNITS	pVALUE
33	OCC1OC(C(O)C(O)C1O)N(CCOc1ccc2ccccc2c1)S(=O)(=...	IC50	microM	6.15
22	O=C1CN2CCN1Cc3cc(Oc4cc(Cn5cncc5C2)ccc4C#N)ccc3...	EC50	microM	5.97
1	Nc1ccc(cc1)S(=O)(=O)N1C(=O)CCCC1	Kd	microM	5.52
0	Nc1ccc(cc1)S(=O)(=O)NC(=C)C1CC1	Kd	microM	5.22
21	O=C1CN2CCN1c3cccc4ccc(Oc5cc(Cn6cncc6C2)ccc5C#N...	EC50	microM	5.00
30	Cc1ccc(NC(=S)NNc2c(cc(cc2[N+]([O-])=O)C(F)(F)F...	IC50	microM	5.00
29	OC(=O)CC1=C(/C(=C/c2cocc2)/c2c1cc(F)cc2)C	IC50	microM	4.52
20	ONC1=CC=C(C=C1)C(=O)NC[C@@H]1CC2O[C@H](COCC3=C...	IC50	microM	4.45
32	ONc1ccc(cc1)S(=O)(=O)NCCOc1ccc2ccccc2c1	IC50	microM	4.25
18	ONC1=CC=C(C=C1)S(=O)(=O)NC[C@H]1CC2O[C@H](COCC...	IC50	microM	4.24
23	ONC1=CC=C(C=C1)C(=O)NC[C@H]1CC2O[C@H](COCC3=CC...	IC50	microM	4.21
17	ONC1=CC=C(C=C1)S(=O)(=O)NC[C@@H]1CC2O[C@H](COC...	IC50	microM	4.12
25	OC(=O)CC1=C(/C(=C/c2cscc2)/c2c1cc(Cl)cc2)C	IC50	microM	4.00
31	[O-][N+](=O)c1cc(cc(c1NNC(=S)Nc1ccc(F)cc1)[N+]...	IC50	microM	4.00
26	OC(=O)CC1=C(/C(=C/c2cocc2)/c2c1cc(cc2)C)C	IC50	microM	3.80
24	OC(=O)CC1=C(/C(=C/c2cocc2)/c2c1cc(Cl)cc2)C	IC50	microM	3.74
15	CCC(C)C(N)C(=O)NC1=CC2N=C(CC3=CNC4=CC=CC=C34)N...	Kd	microM	3.72
19	OC(=O)CC1=C(/C(=C/c2ccc(SC)cc2)/c2c1cc(F)cc2)C	IC50	microM	3.68
27	CC1=C(CC(O)=O)c2ccc(Br)cc2\C1=C/C1=CSC=C1	IC50	microM	3.66
14	CC(C)C(N)C(=O)NC1=CC2N=C(CC3=CNC4=CC=CC=C34)NC...	Kd	microM	3.57



Molecole covalenti

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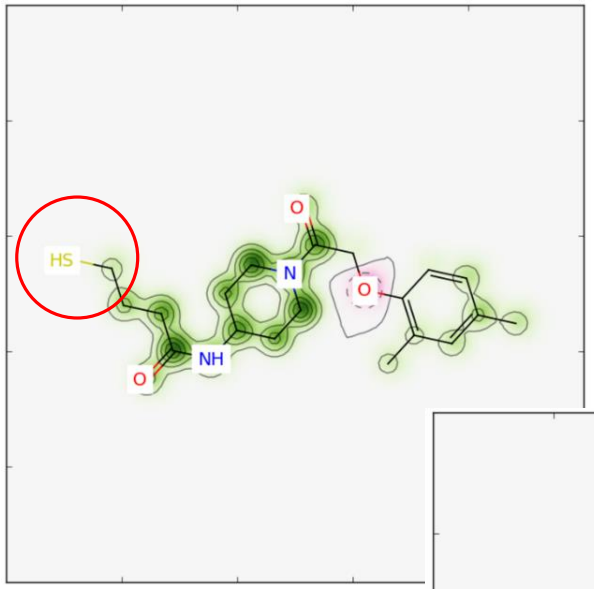

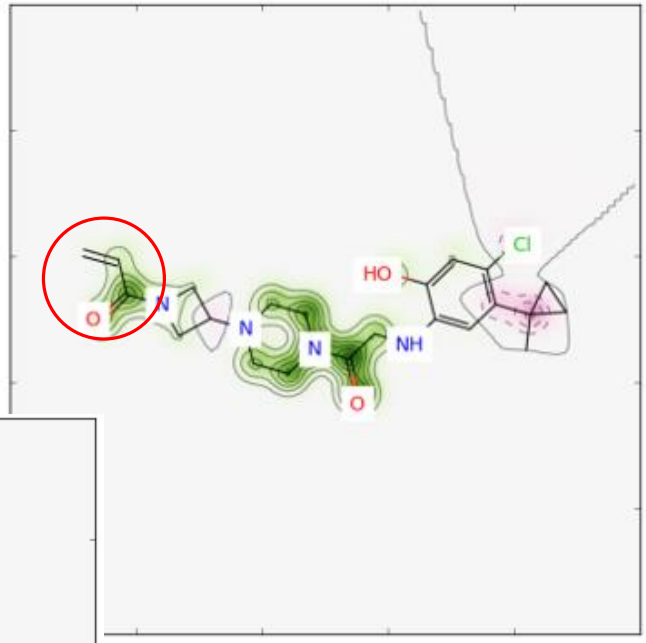

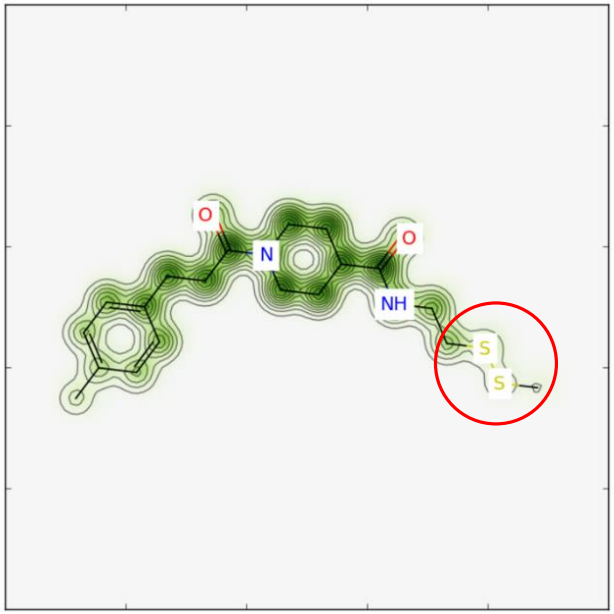

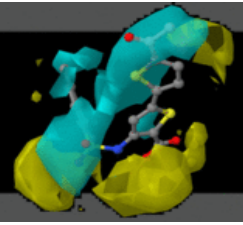

Molecole covalenti

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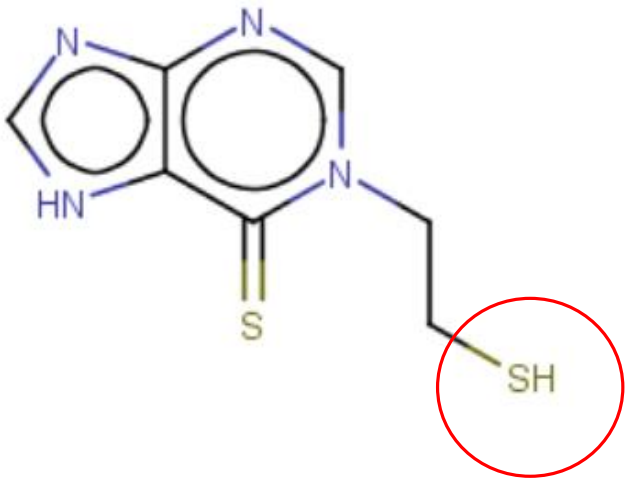
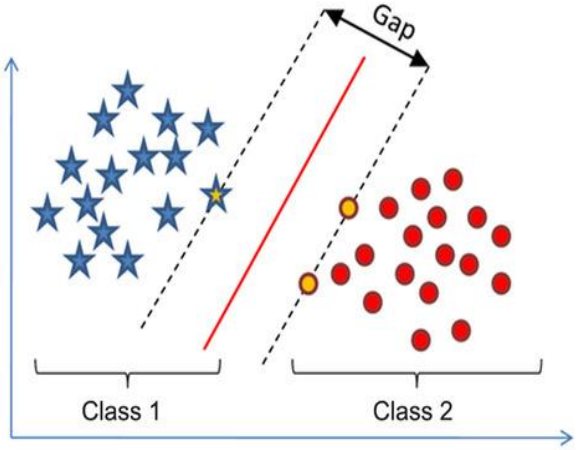
	CANONICAL_SMILES_NO_SALT	NSC	[fp]median_activity	[fp]Rank	[desc]median_activity	[desc]Rank	mean_rank
0	S=c1c2[nH]cnc2ncn1CCS	404823.0	5.346527	33	6.047139	2	35.0
1	O=C(NCCS)C(=O)NCCS	120714.0	5.418880	13	5.880083	26	39.0
2	C=CC(=O)NC(=N)NC(N)=O	372157.0	5.369232	29	5.899250	14	43.0
3	C=CC(=O)NC(O)C(Cl)(Cl)Cl	22403.0	5.369427	28	5.889128	18	46.0
4	C=CC(=O)OCC(C)(C)COC(=O)C=C	97407.0	5.482500	8	5.865417	42	50.0

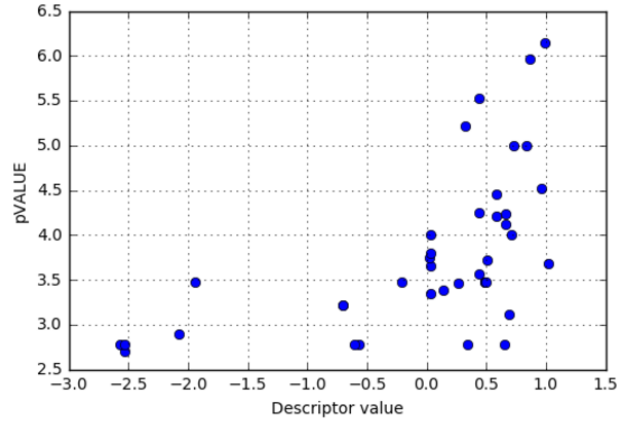


Molecole reversibili



	Algorithm	q^2 K-Fold	q^2 Shufflesplit
Descriptors	Logistic Regression	0.673	0.592
Fingerprints	PassiveAggressive	0.577	0.562

Importanza descrittori



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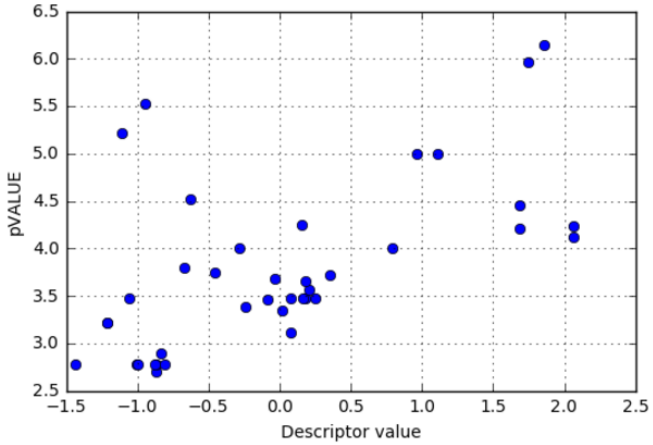

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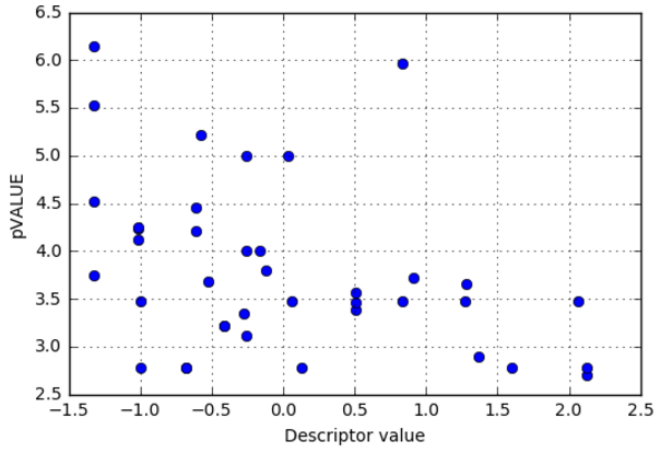

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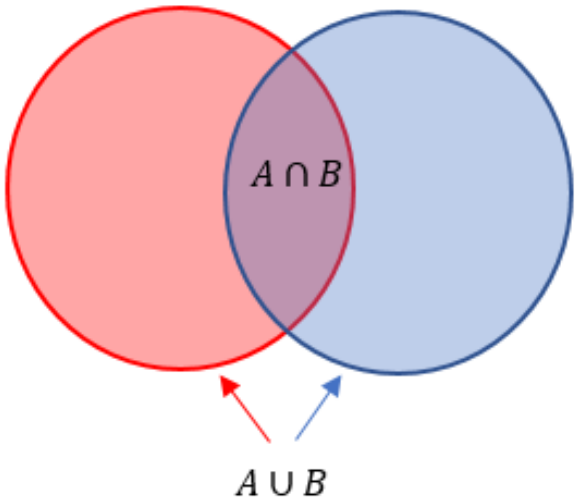
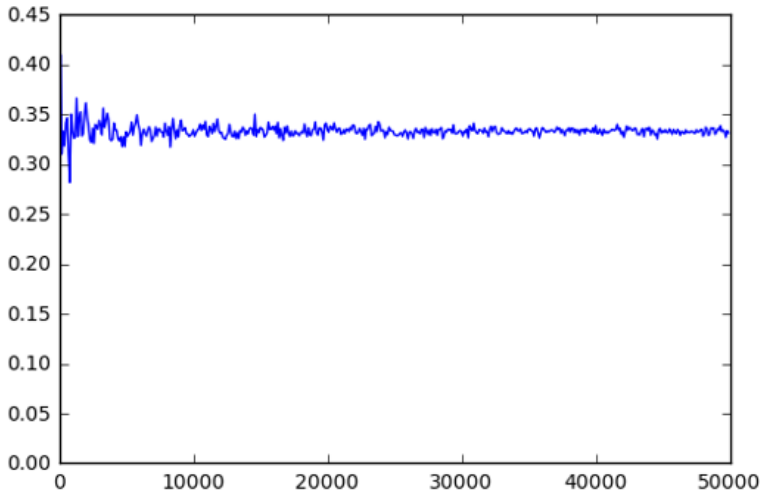
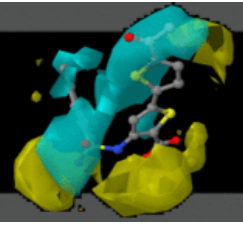
$$\frac{A \cap B}{A \cup B}$$



$$\frac{A \cdot B}{|A^2| + |B^2| - A \cdot B}$$





Risultati dello screening

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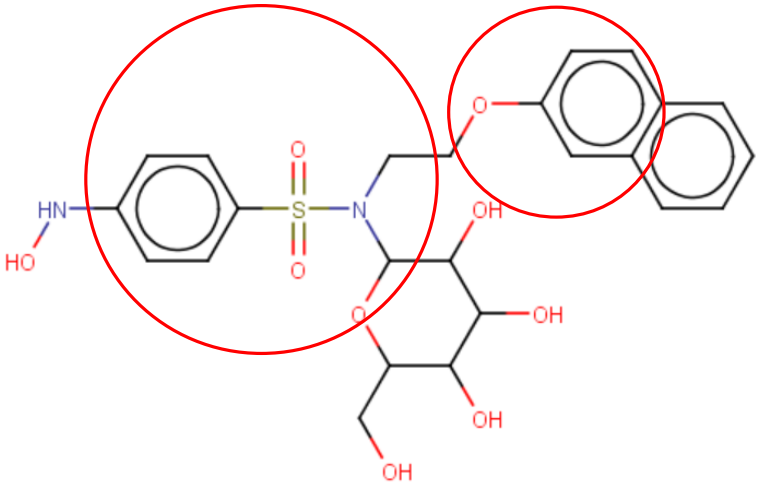
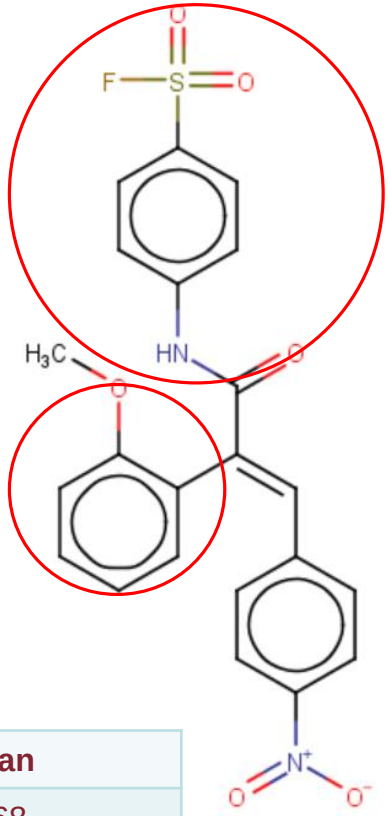
CANONICAL_SMILES_NO_SALT	Morgan	Atom_pair	Topological_torsion	RDKF
Nc1ccc(S(=O)(=O)N2CCCCC2)cc1	0.571429	0.750000	0.526316	0.727955
Nc1ccc(S(=O)(=O)N2CCCc3ccccc32)cc1	0.560976	0.668831	0.510638	0.362538
CCC(=N)NS(=O)(=O)c1ccc(N)cc1	0.552632	0.442029	0.566667	0.633987
N=C(NS(=O)(=O)c1ccc(N)cc1)NS(=O)(=O)c1ccc(N)cc1	0.542857	0.268085	0.447368	0.464078
NC(=O)NS(=O)(=O)c1ccc(N)cc1	0.542857	0.467742	0.607143	0.494692
Cc1ccc([N+](=O)[O-])cc1NC(=O)NNc1c([N+](=O)[O-...	0.540984	0.580000	0.750000	0.673469
Cc1ccc([N+](=O)[O-])cc1NC(=O)NNc1c([N+](=O)[O-...	0.540984	0.580000	0.750000	0.673469
Cc1ccc(S(=O)(=O)N2CCCCC2=O)cc1[N+](=O)[O-]	0.533333	0.521739	0.555556	0.666239
N=C(N)NS(=O)(=O)c1ccc(N)cc1	0.527778	0.453125	0.607143	0.500000
NC(=S)NS(=O)(=O)c1ccc(N)cc1	0.527778	0.476190	0.607143	0.493644
Nc1ccc(S(=O)(=O)NC2CCC(NS(=O)(=O)c3ccc(N)cc3)C...	0.527778	0.277372	0.319149	0.641350
Nc1ccc(S(=O)(=O)NC2CCC(NS(=O)(=O)c3ccc(N)cc3)C...	0.527778	0.277372	0.319149	0.641350
CC(=O)NS(=O)(=O)c1ccc(N)cc1	0.527778	0.456693	0.607143	0.590604
CC(=N)NS(=O)(=O)c1ccc(N)cc1	0.513514	0.449612	0.607143	0.605856
CSC(=N)NS(=O)(=O)c1ccc(N)cc1	0.512821	0.437956	0.566667	0.474206
Nc1ccc(S(=O)(=O)NC2CCC(O)CC2)cc1	0.500000	0.432927	0.384615	0.618661
Nc1ccc(S(=O)(=O)NO)cc1	0.500000	0.417391	0.482759	0.444700
Cc1cc([N+](=O)[O-])c(Nc2ccc(C)c(Cl)c2)c([N+](=...	0.490909	0.378453	0.693878	0.523636
Cc1cc([N+](=O)[O-])c(Nc2ccc(C)c(Cl)c2)c([N+](=...	0.490909	0.378453	0.693878	0.523636
COc1ccc2c(c1)CCCN2S(=O)(=O)c1ccc(N)cc1	0.489362	0.520408	0.480000	0.349908

Risultati dello screening



Attività (pVALUE)	6.15



	desc	fp	Mean
Attività (pVALUE)	4.26	5.11	4.68

Strategia Docking e 3-D QSAR

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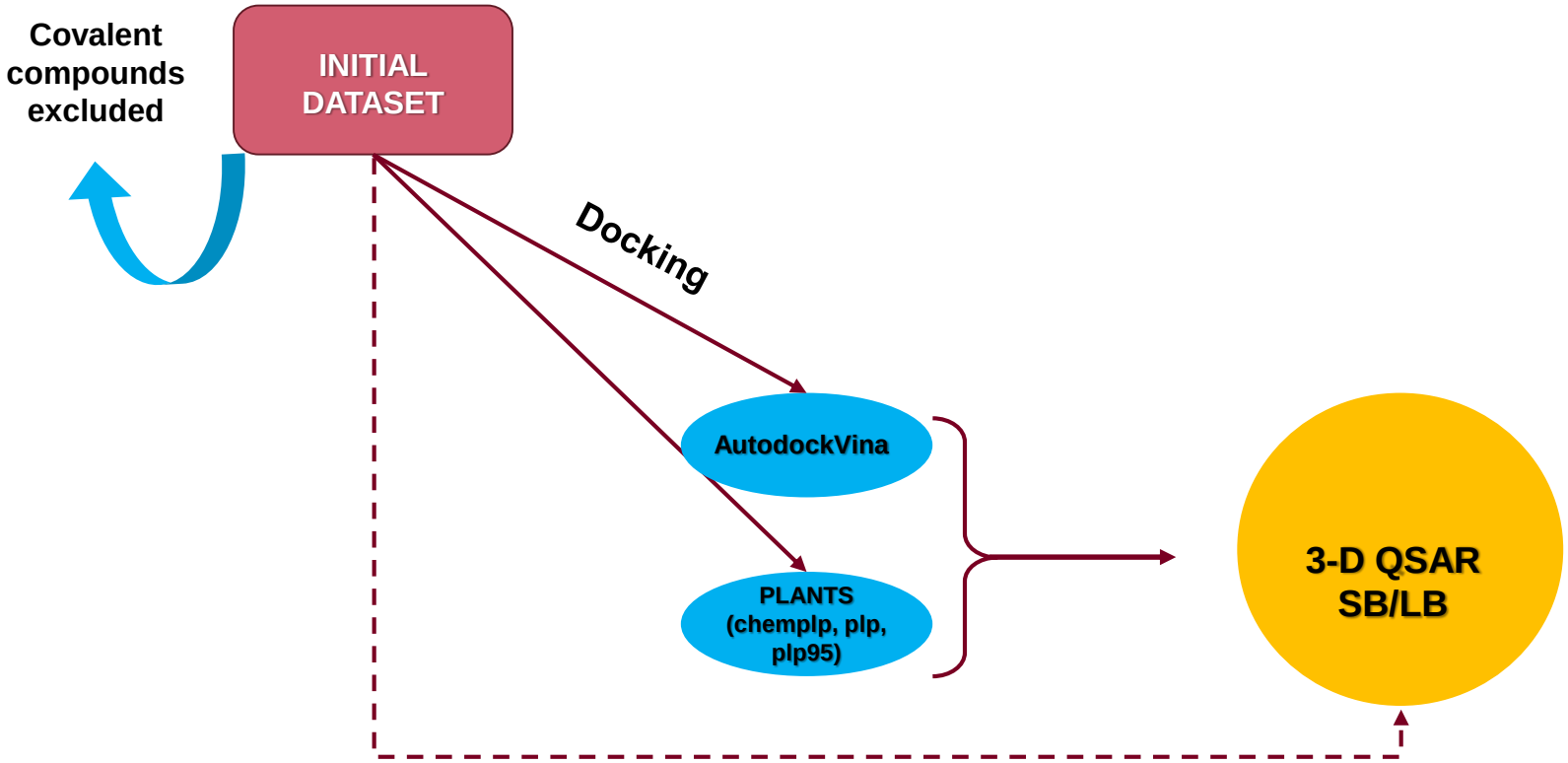
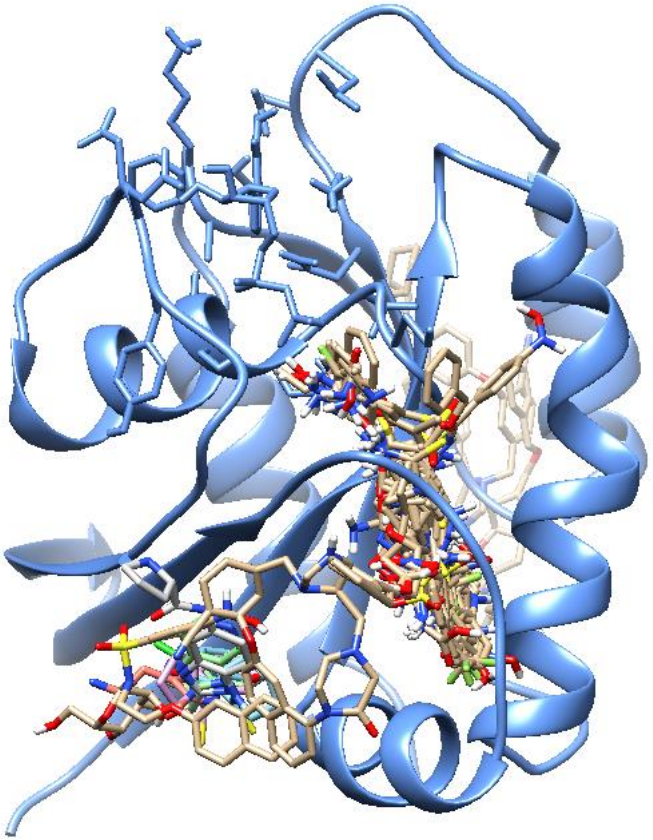
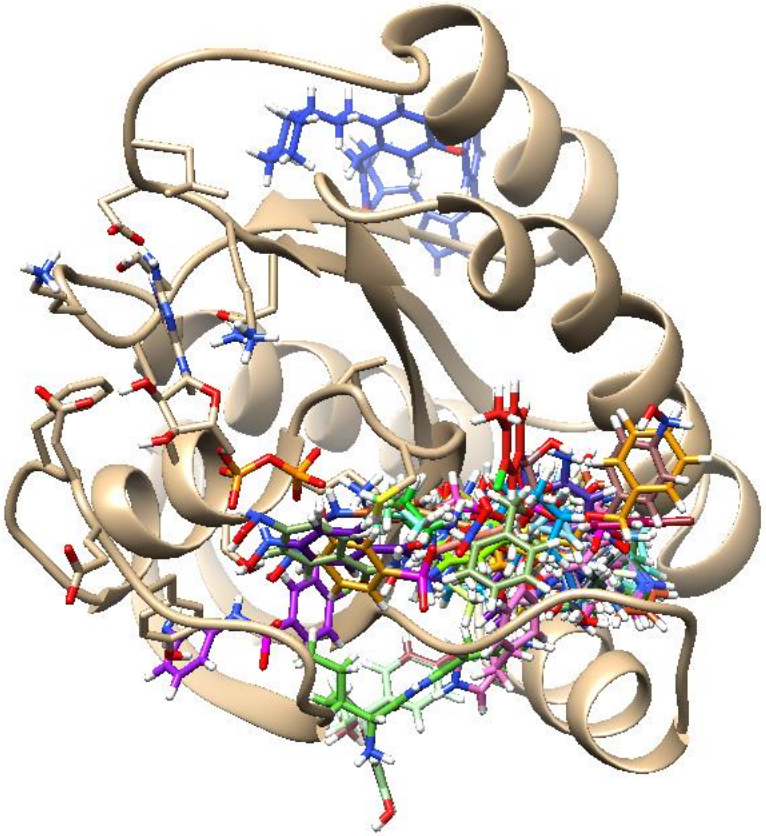
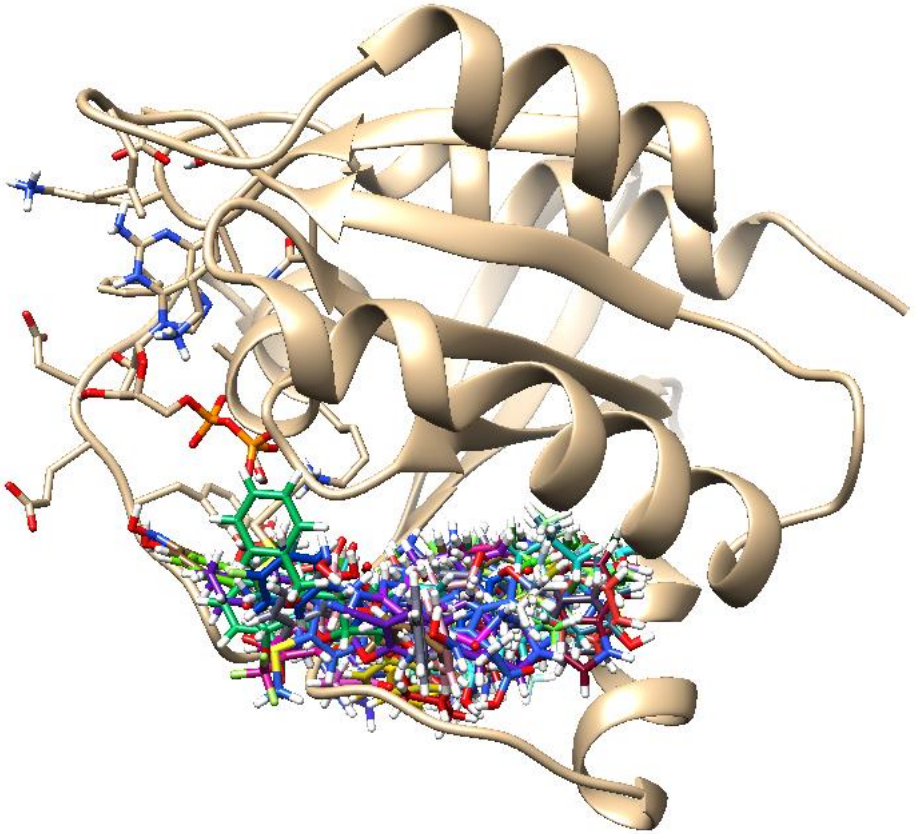




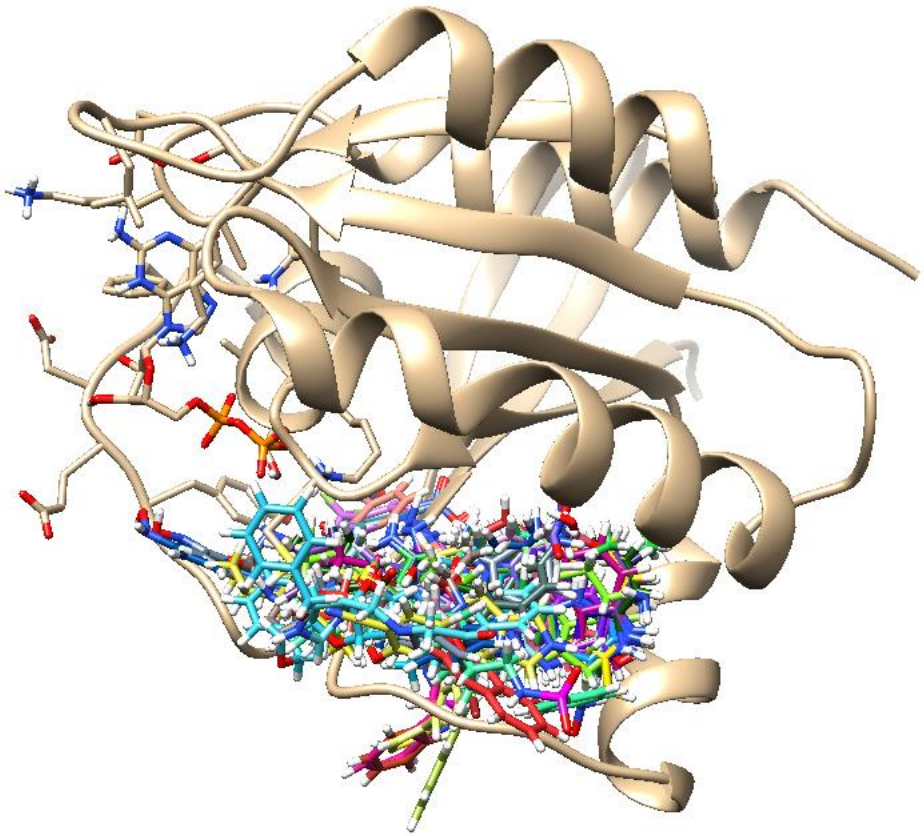
PLANTS - chemplp



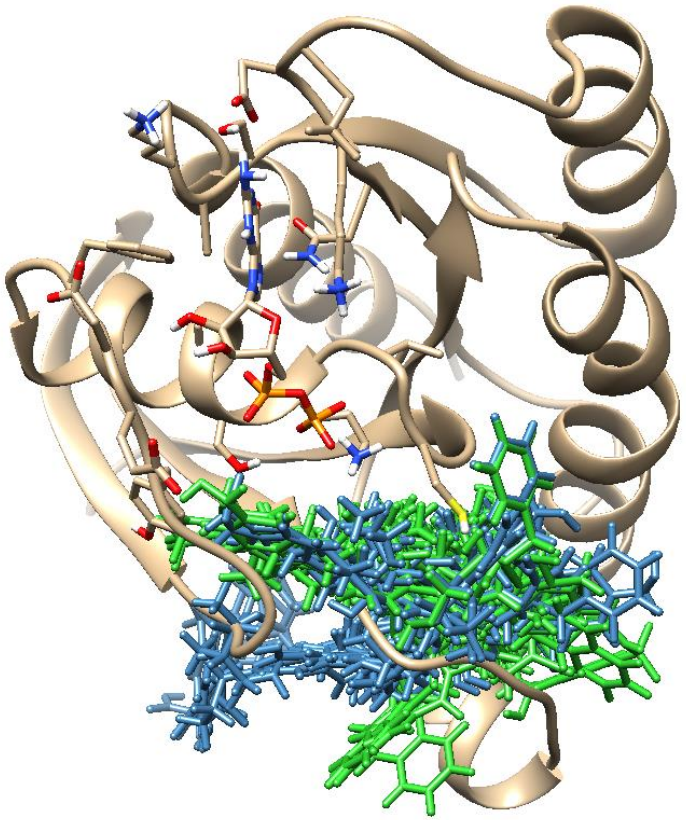
PLANTS - plp



PLANTS – plp95

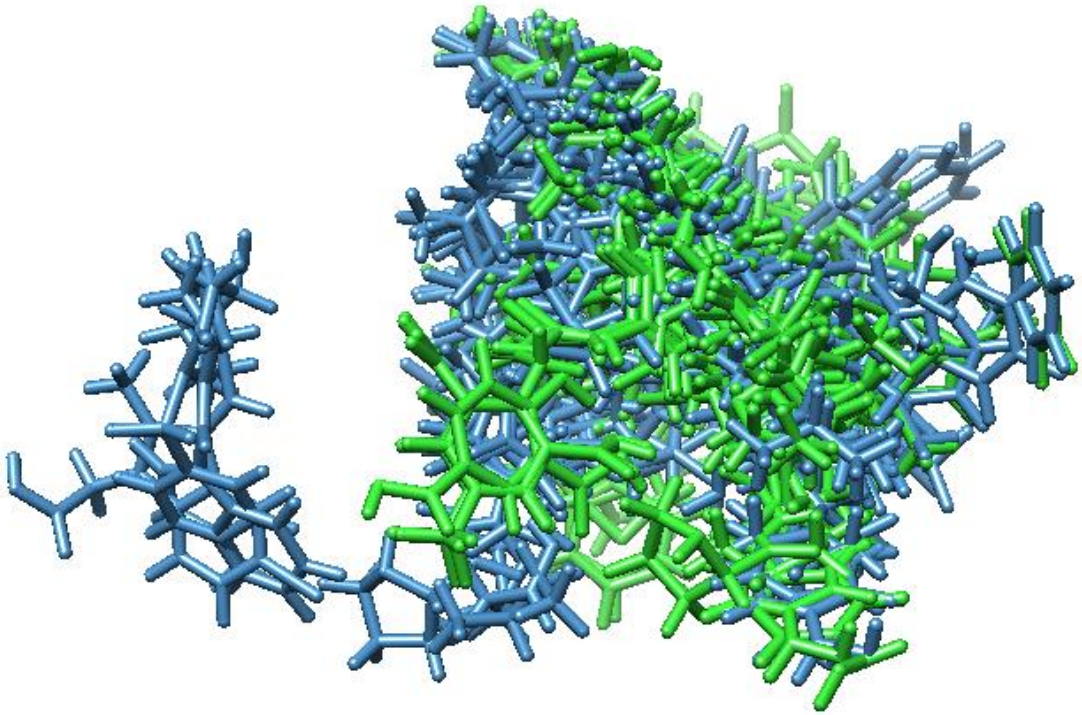


Scelta allineamento migliore



- plp95
- plp

Scelta allineamento migliore



- plp95
- plp

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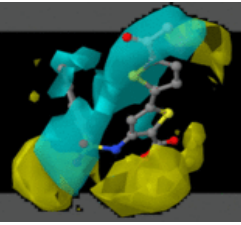

3DQSAR – StructureBased

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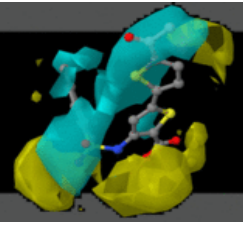
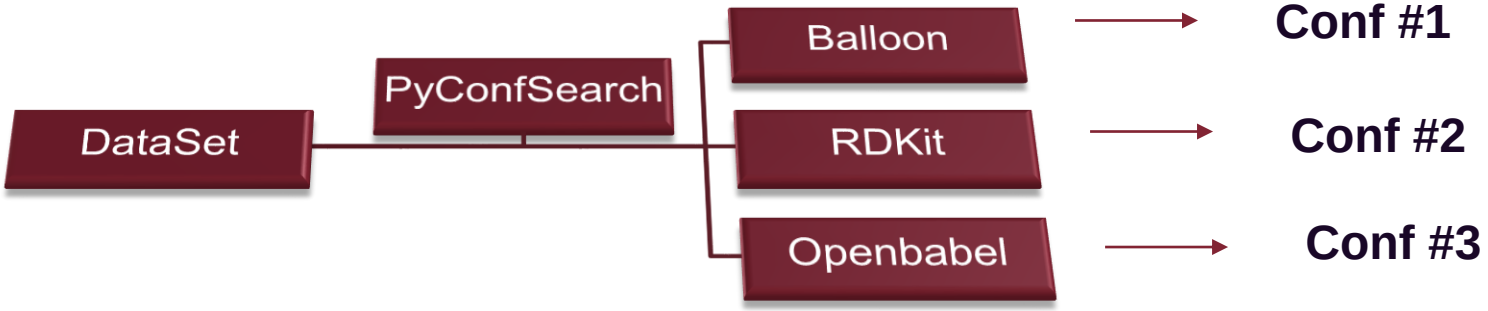
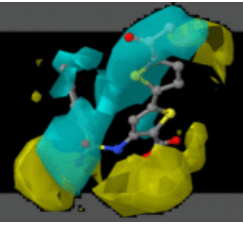
Probe	Q^2 ELE (PC)	Q^2 STE (PC)	Q^2 BOTH (PC)	CV
C.2	**0.037(1)**	**0.131(8)**	**0.06(2)**	**LOO**
C.2	**0.084(8)**	**0.231(8)**	**0.106(4)**	**LSO**
C.3	0.037(1)	0.08(8)	0.06(2)	LOO
C.3	0.082(7)	0.149(5)	0.071(2)	LSO
C.cat	0.037(1)	0.12(8)	0.06(2)	LOO
C.cat	0.034(1)	0.136(7)	0.062(5)	LSO
H	0.033(1)	0.12(8)	0.056(2)	LOO
H	0.042(4)	0.256(8)	0.054(2)	LSO
N3	0.036(1)	0.117(8)	0.059(2)	LOO
N3	0.053(1)	0.154(8)	0.1(4)	LSO
O.3	0.036(1)	0.093(8)	0.06(2)	LOO
O.3	0.088(1)	0.138(8)	0.091(4)	LSO



3DQSAR – LigandBased





1603_kras_least_active

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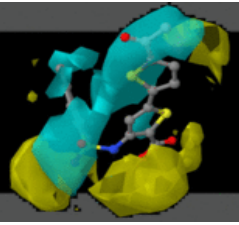
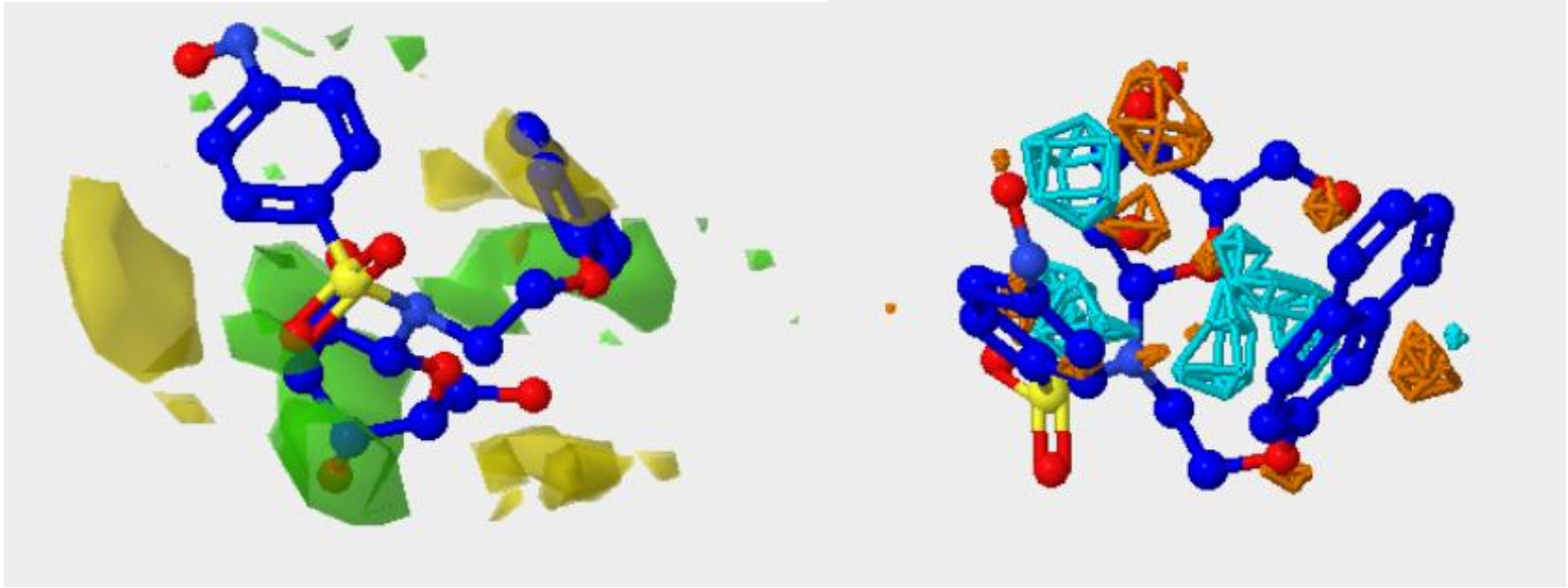
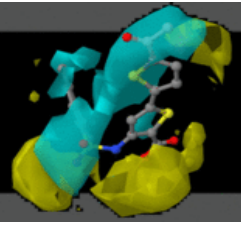
Probe	Q2 ELE (PC)	Q2 STE (PC)	Q2 BOTH (PC)	CV
C.3	**0.548(8)**	**0.032(2)**	**0.524(7)**	**LOO**
C.cat	0.548(8)	0.032(2)	0.524(7)	LOO
N.3	0.551(8)	0.032(2)	0.521(7)	LOO
O.3	0.550(8)	0.032(2)	0.521(7)	LOO
H	0.538(6)	0.032(2)	0.513(7)	LOO
C.2	0.548(8)	0.032(2)	0.524(7)	LOO
C.3	**0.553(8)**	**0.018(2)**	**0.507(6)**	**LSO**
C.cat	0.535(6)	0.034(2)	0.474(6)	LSO
N.3	0.518(7)	0.027(2)	0.5(7)	LSO
O.3	0.512(6)	0.03(2)	0.496(6)	LSO
H	0.509(7)	0.027(2)	0.491(7)	LSO
C.2	0.512(8)	0.047(2)	0.479(8)	LSO

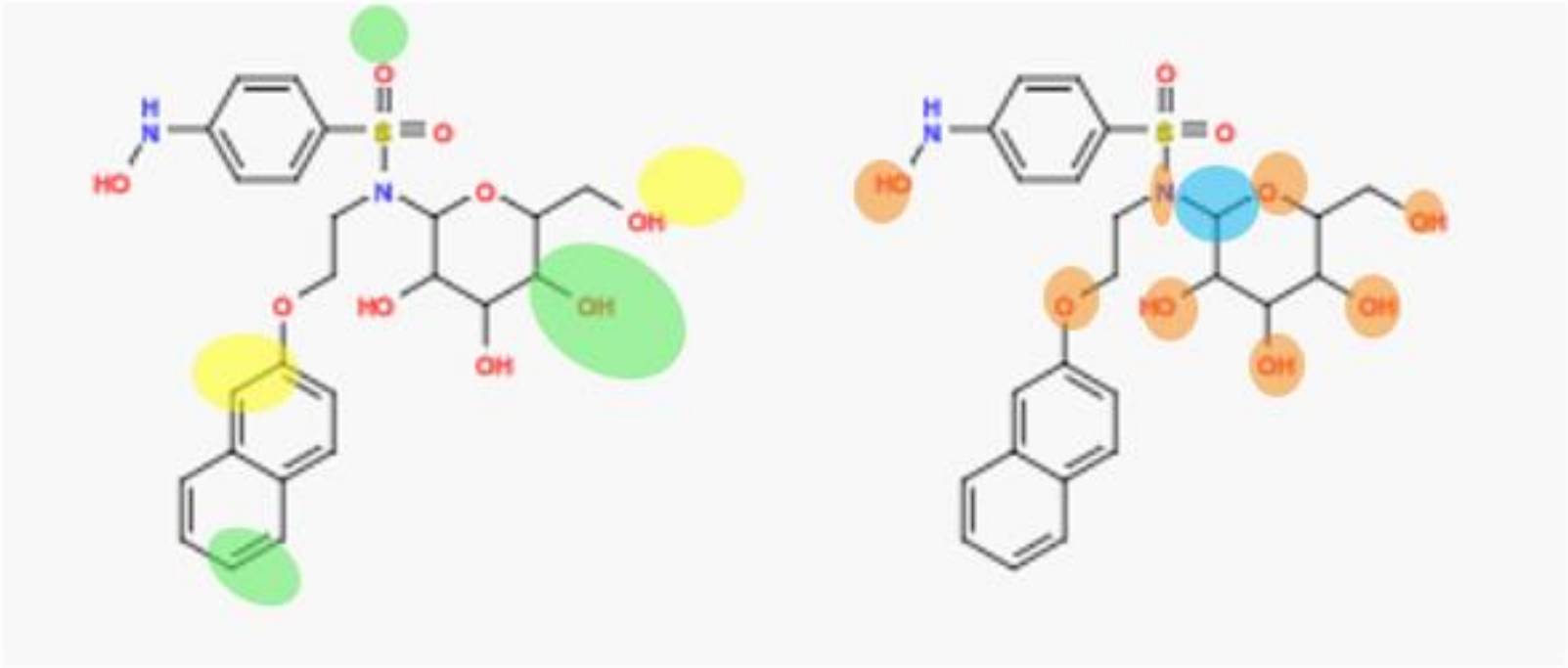


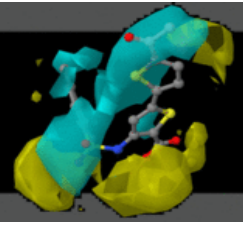
Mappe CoMFA





Mappe CoMFA





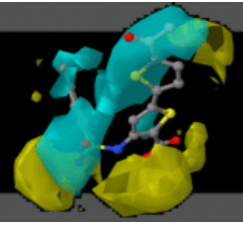
CONCLUSIONI

- Modello 3DQSAR SB: non sufficientemente robusto (q^2 <0.3)
- Modello 3DQSAR LB: molto buono (q^2 >0.5)
- Docking non abbastanza accurato

- 1,2-D QSAR:

✓ Evidenziata correlazione dei singoli descrittori

✓ **Arricchimento del training set con i risultati dello screening**



Grazie per l'attenzione.