Studio della tecnica 3-D QSAR. Un'applicazione ad una serie di potenziali agenti antitubercolari

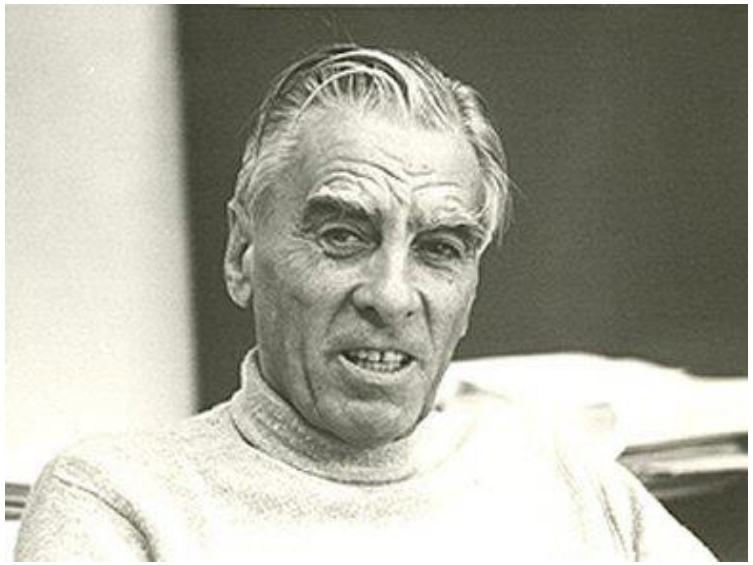
SAPIENZA
UNIVERSITÀ DI ROMA

Interfacoltà Scienze MM.FF.NN, Farmacia e Medicina, Medicina e Psicologia
Corso di Laurea in Biotecnologie
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2016/2017

Laureando: Francesco Noce
Matricola: 1556888

Relatore: prof. Rino Ragno

QUANTITATIVE **S**TRUCTURE **A**CTIVITY **R**ELATIONSHIP



Corwin Hansch

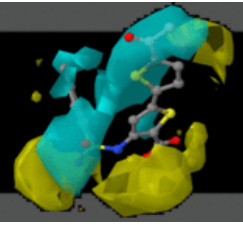
Equazione di Hansch

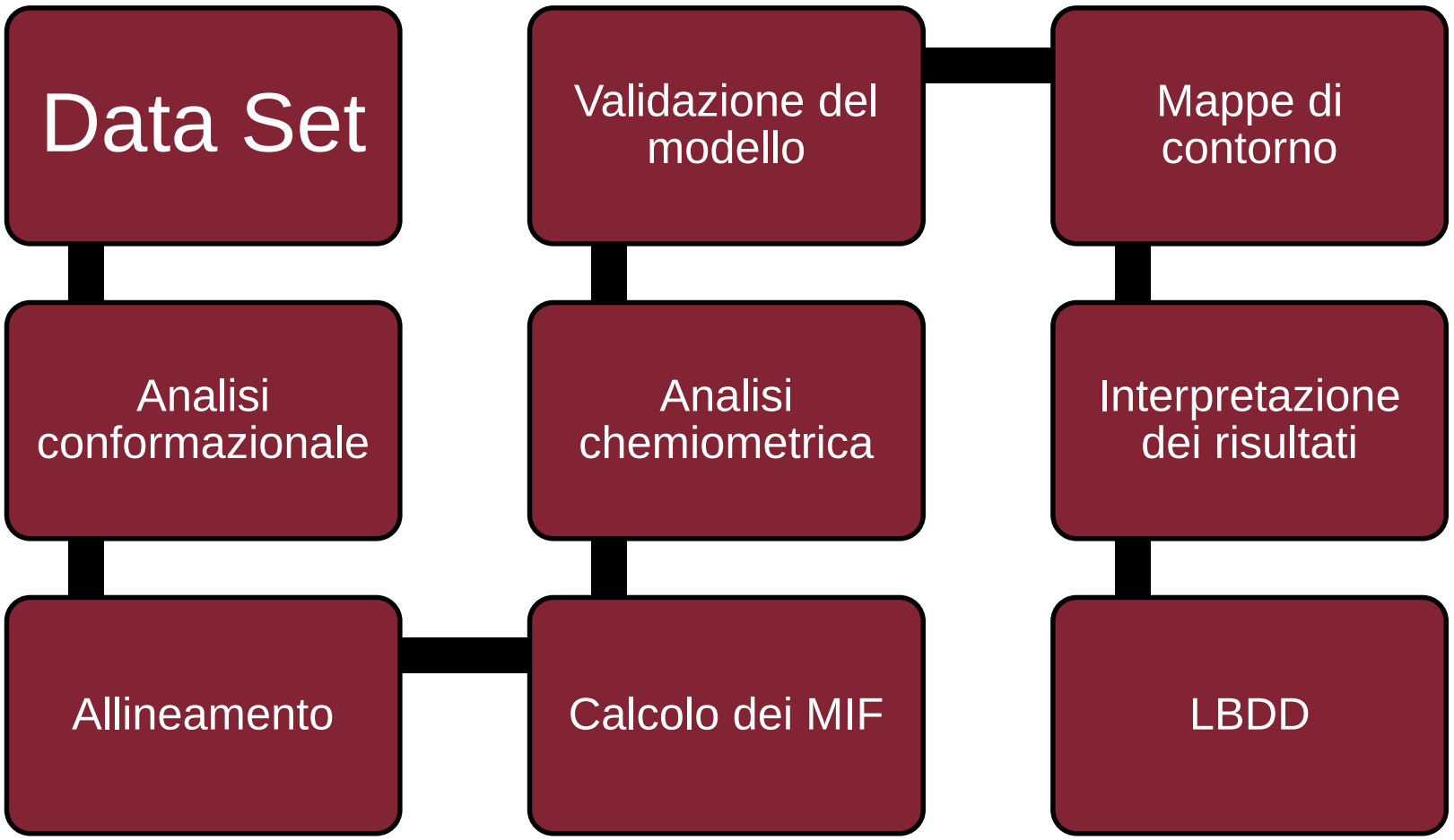
$$\log(1/C) = k_1 \log P - k_2 (\log P)^2 + k_3 \sigma + k_4$$

MLR

$$y = b_0 + b_{i1} x_1 + b_{i2} x_2 + b_{in} x_n + E$$

Protocollo 3-D QSAR by www.RCMD.it





Portale PY-COMFA

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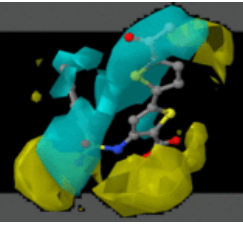
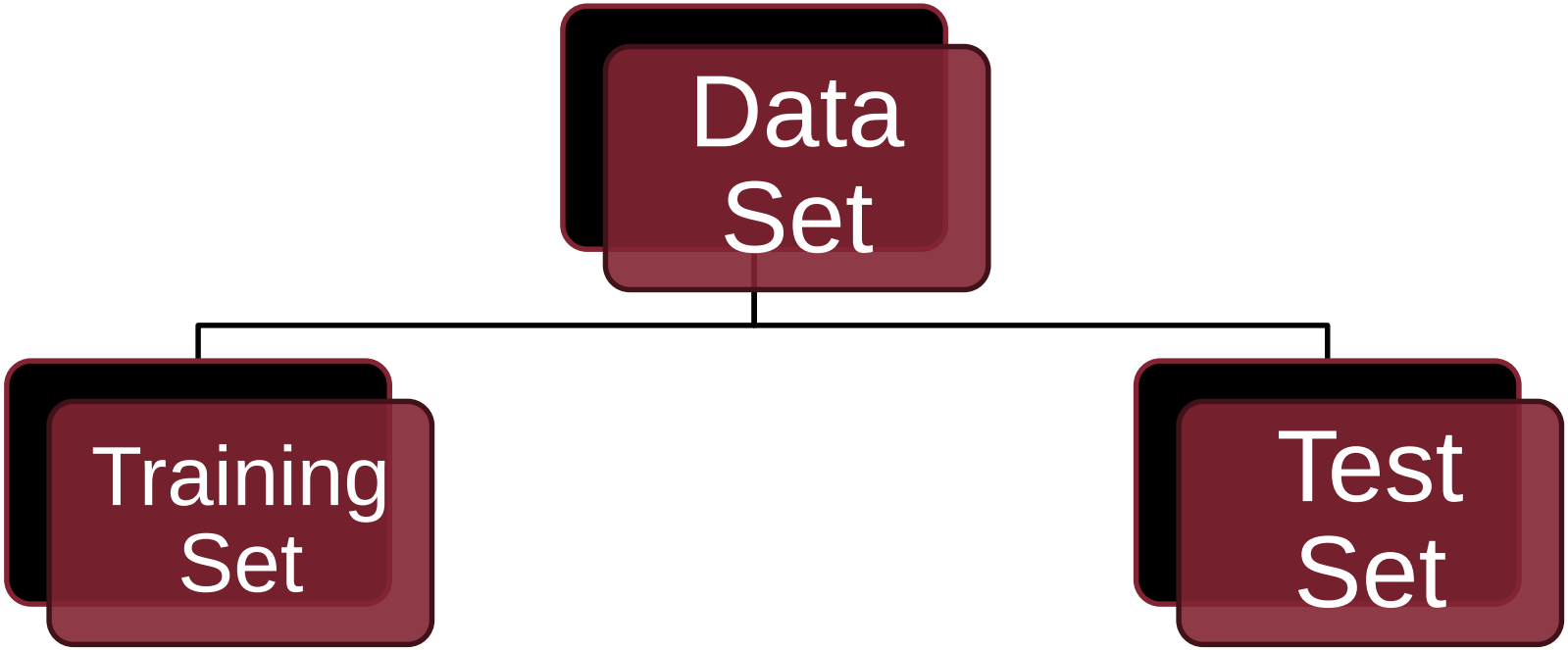
SAPIENZA UNIVERSITÀ DI ROMA



1° Data Set

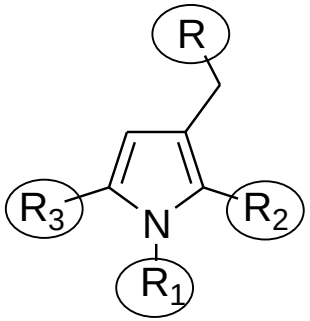


- Molecole con attività
- Cross validazione interna
- Robustezza del modello

- Validazione esterna
- Predittività del modello

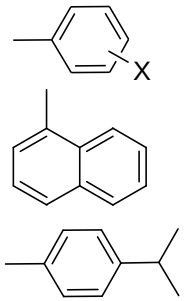
Training Set

71 DERIVATI
DEL **PIRROLO**

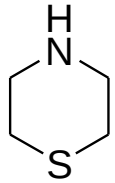


Pirrolo

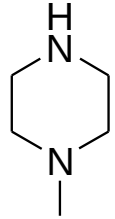
R_1, R_2, R_3 : Me



R = Tiomorfolina (Fig.**1**) e
Metilpiperazina (Fig.**2**)



(Fig.**1**)

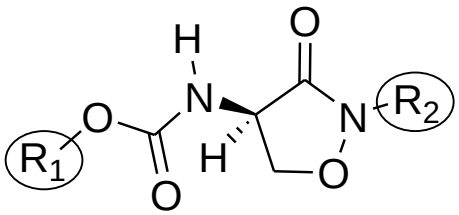


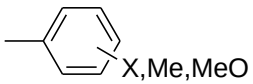
(Fig.**2**)

13 DERIVATI DEGLI
***R*-4-AMMINO-3-ISOSSAZOLIDINONI**

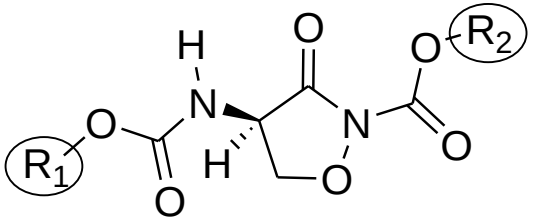
3 Classi:

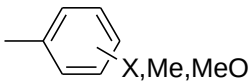
Monocarbammati (5)



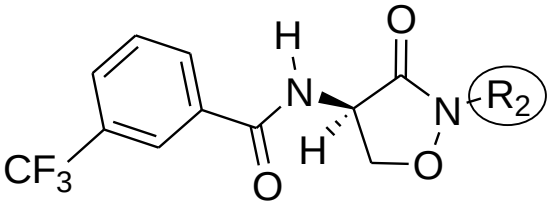
R_1, R_2 : H, 

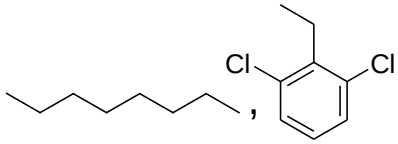
Dicarbammati (6)



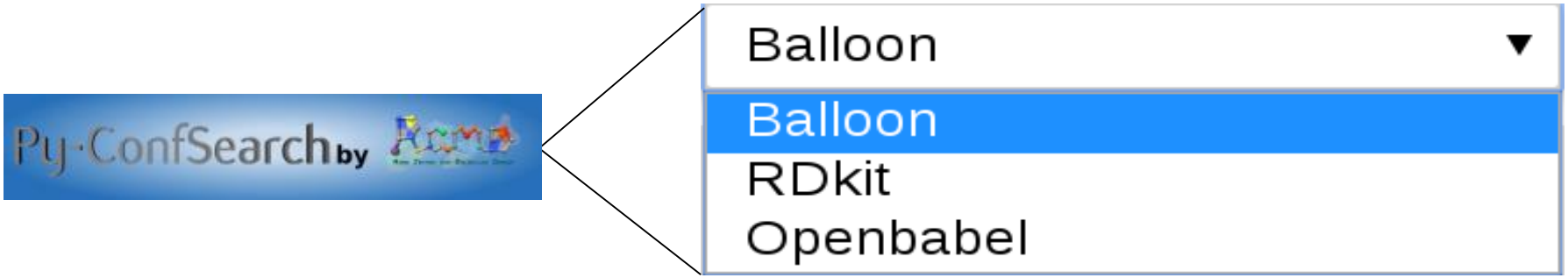
R_1, R_2 : 

Ammidi (2)



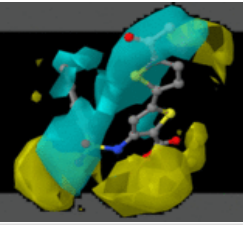
R_2 : 

2° Analisi conformazionale



2 Balloon + 1 RDKit + 1 OpenBabel =

4 Analisi totali



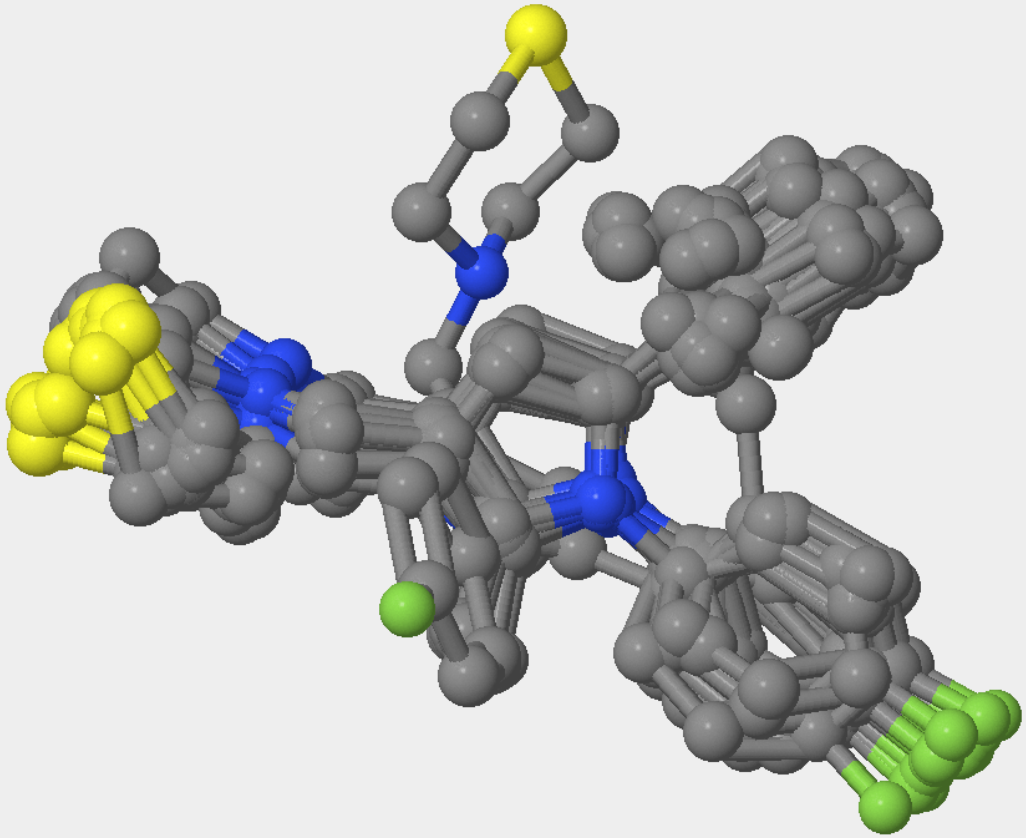
Parametri

by www.RCMD.it

Method:	Balloon
No Bad Models:	☑
# Conformations:	30
No GA:	☑
Add Conformer Number To Name:	☑
Full Force:	☑
Rebuild Geometry:	☑
Max Post Process Iter:	100
Max Shape Iter:	300
Max Time:	120
Gradient Tolerance:	0.05
Niche Radius:	1.5
RMSDtol:	0.5
Energy Constant:	10

Stereo (Inversion of Configuration can Occur!):	☐
Max Iter:	50
Use Simplex:	☑
Max Simplex Iterations:	50
Simplex Step Length:	1
Simplex Function Tolerance:	0.1
# Initial Dimensions:	4
No VdW Cutoff:	☑
No E Cutoff:	☑
Charge Model:	EEM
Distance Dependent:	☑
Dielectric:	8
Max Ring Size:	-1
Max Flip Distance:	20

Mol ID: 78 **Software**: Balloon **Algoritmo**: GA **Conformeri**: 50



3° Allineamento

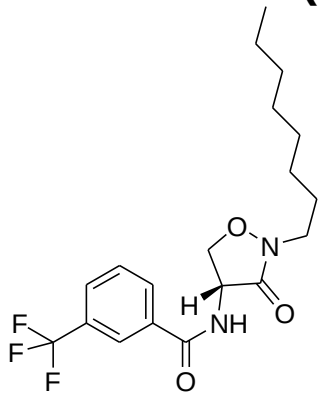
by www.RCMD.it

Method:	Shaep
Scoring Function:	Similarity
Min Hit Similarity:	0
Spot Offset:	0.2
Flatness Limit:	0.97
Curvature Radius:	10
Curvature Bin Size:	1
Dielectric:	1
Distance Tolerance:	1
Transform Distance:	2
Esp Tolerance:	0.5
Curvature Tolerance:	0.86599999999999999
Charge Weighted:	☑
Esp Radius:	2
Esp Weight:	0.5
Align On:	Least Active
Molecule (Only for 'Align On User Selected Molecule'):	24667 - 1

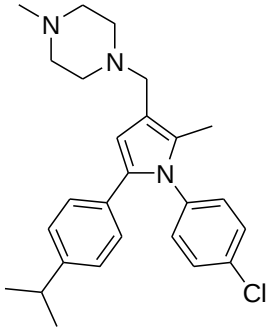
Allineamenti totali

4 Analisi conformazionali → **24 Allineamenti totali** ← 6 Allineamenti possibili

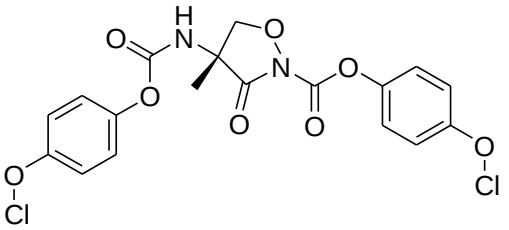
1) **Meno Attiva (3h)**



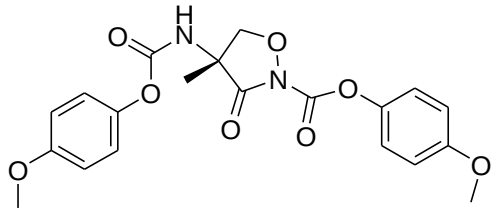
2) **Più Attiva (60)**



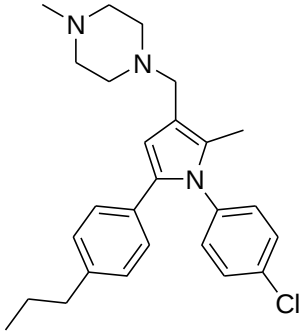
3) **Più Pesante (2e)**



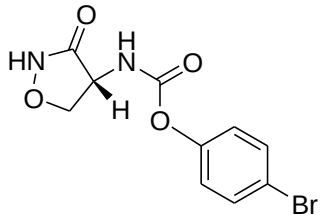
4) **Più Lunga (2c)**



5) **Più Rigida (59)**



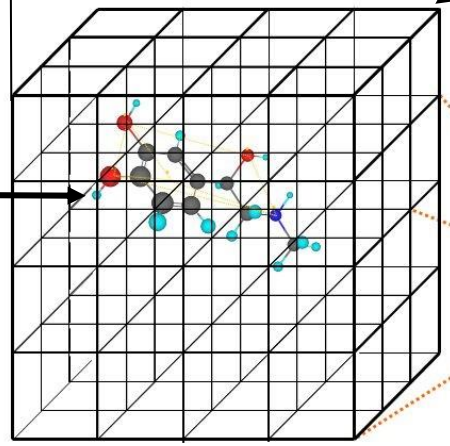
6) **Più Flessibile (1e)**



MIF = Molecular Interaction Field

GRIGLIA (GRID)

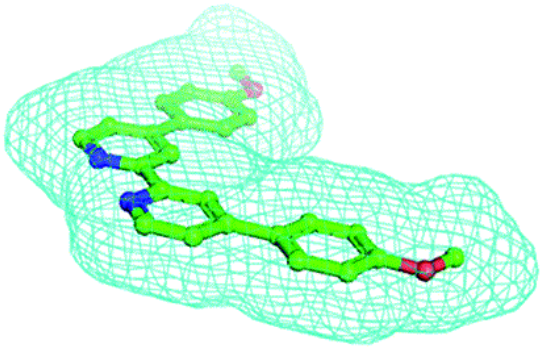
MOLECOLE ALLINEATE



NODI CON SONDE (PROBES)

=

STE

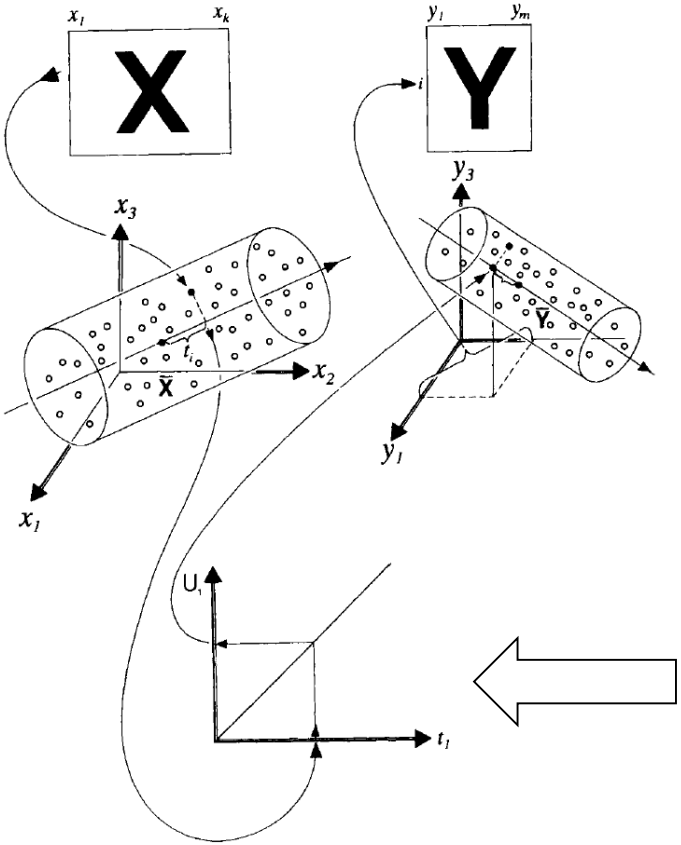


ELE

PLS = Partial Least Square regression

- Variante PCA
- \+
- MLR

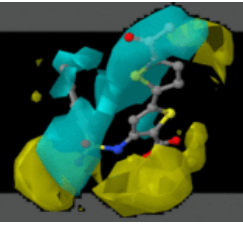
DESCRITTORI



ATTIVITA'

r^2 = Coefficiente di determinazione

Grafico PLS



Parametri

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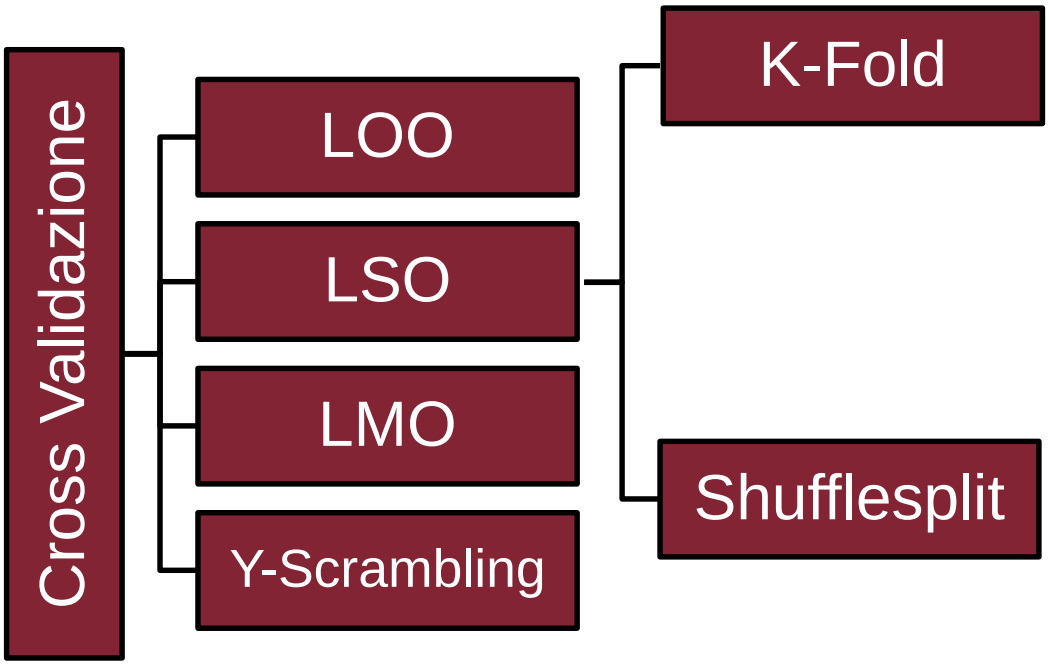
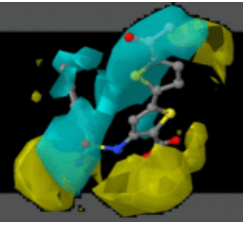
Py-CoMFA by RCMD

Probe Atom:	C.3
Probe Charge:	+1
Dielectric Constant:	8
Molecular Interaction Field (BOTH = STE + ELE):	BOTH
Maximum Number of Principal Components:	8
Grid Spacing:	1
Grid Extension:	5
Max/Min Energy of Cutoff Value:	30
Minimum Sigma:	0.05
CV Type:	LOO
CV Groups (Only for LSO):	5
CV Iterations (Only for LSO):	10
CV Random:	True
Minimum SDEP Increment:	0
Make Y-Scrambling:	False
Y-Scrambling Iterations:	10
Apply Model to Test Set Molecules:	False

q^2 = r^2 cross validato



Validazione Esterna



Scelta del modello

by www.RCMD.it

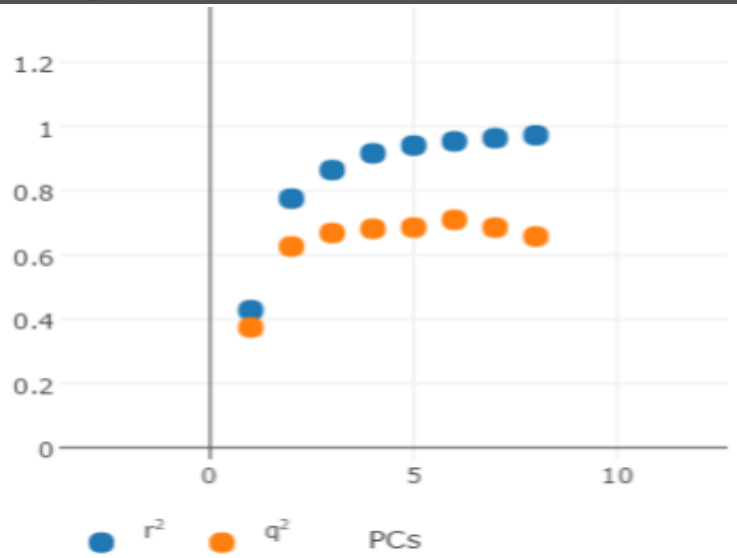
6 Probes ⟷ 24 Allineamenti

144 Modelli 3-D QSAR !

ID	Status	Maps	nTrMols	External Pred	q² ELE (PC)	q² STE (PC)	q² BOTH (PC)	Probe	Probe Charge	Min Sigma
1149	completed	Available	71	True	0.659 (5)	0.435 (4)	0.709 (6)	C.3	1	2.0
1150	completed	Missing	71	True	0.669 (5)	0.499 (5)	0.669 (5)	C.cat	1	2.0
1151	completed	Missing	71	True	0.602 (2)	0.377 (3)	0.633 (4)	N.3	1	2.0
1152	completed	Missing	71	True	0.572 (2)	0.480 (3)	0.641 (6)	O.3	1	2.0
1153	completed	Missing	71	True	0.547 (2)	0.435 (4)	0.627 (3)	H	1	2.0
1154	completed	Missing	71	True	0.669 (5)	0.499 (5)	0.669 (5)	C.2	1	2.0

q^2>, Modello migliore!

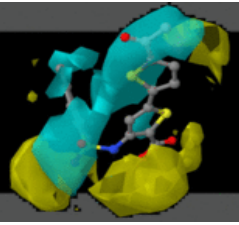
Modello migliore



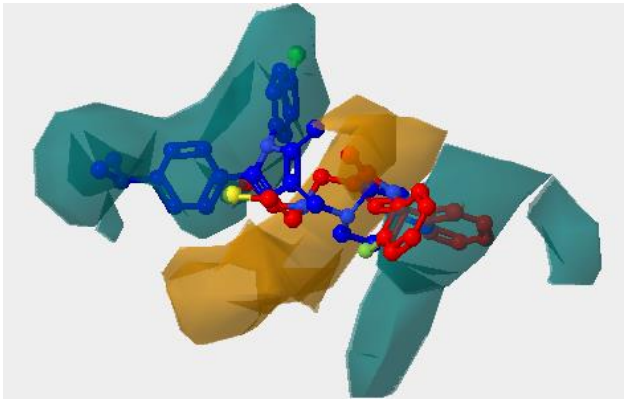
SDEC = Deviazione standard dell'errore sull'attività calcolata

SDEP = Deviazione standard dell'errore sull'attività predetta

PC	r²	SDEC	q²	SDEP	r² YS	q² YS	SDEP YS	CutOff	Minimum Sigma
1	0.428	0.537	0.374	0.561	0.119	-0.055	0.728	30.000	2.000
2	0.775	0.336	0.626	0.434	0.307	-0.226	0.785	30.000	2.000
3	0.864	0.262	0.668	0.409	0.513	-0.341	0.818	30.000	2.000
4	0.916	0.206	0.681	0.401	0.611	-0.501	0.868	30.000	2.000
5	0.940	0.174	0.685	0.398	0.723	-0.404	0.840	30.000	2.000
6	0.953	0.154	0.709	0.383	0.761	-0.513	0.869	30.000	2.000
7	0.963	0.137	0.685	0.399	0.826	-0.743	0.934	30.000	2.000
8	0.972	0.120	0.657	0.416	0.880	-0.474	0.858	30.000	2.000

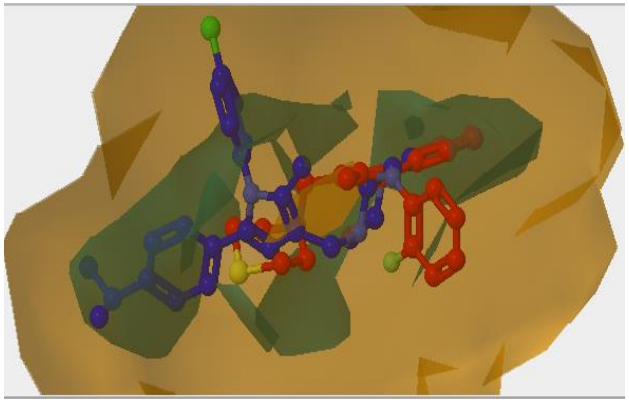


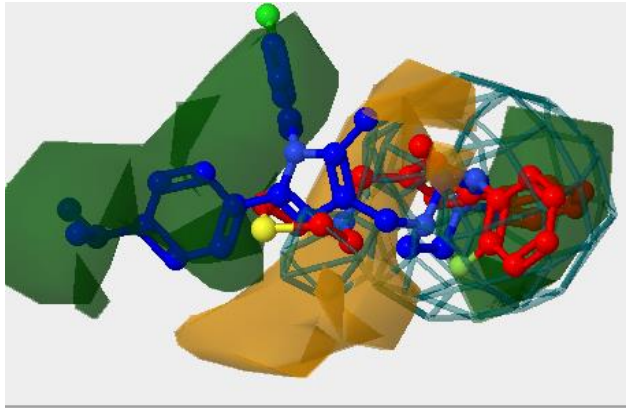
7° Mappe di contorno



COEFF

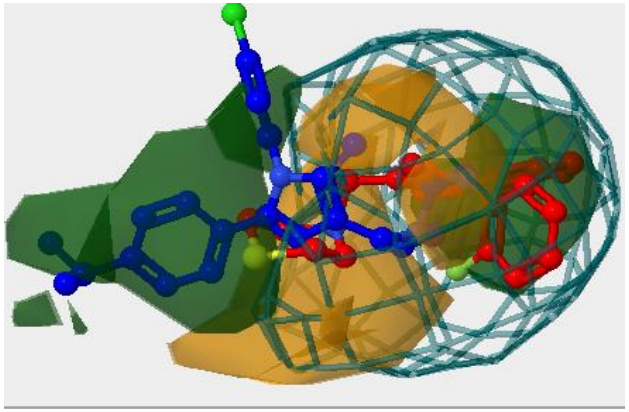
STDS



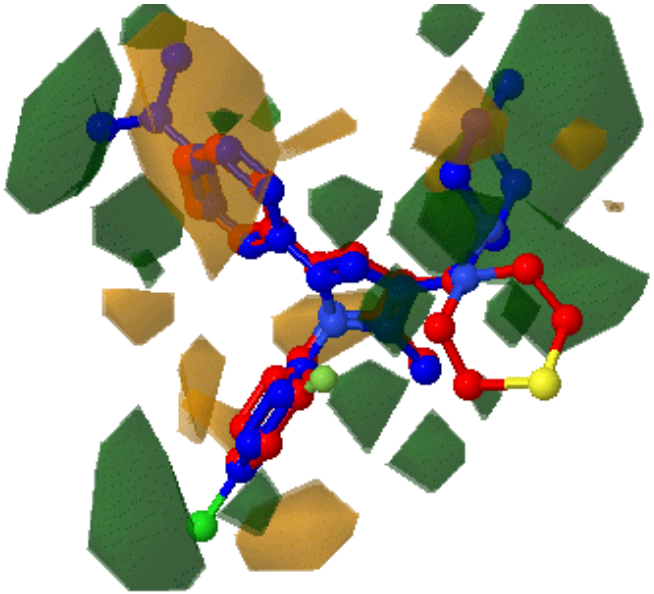


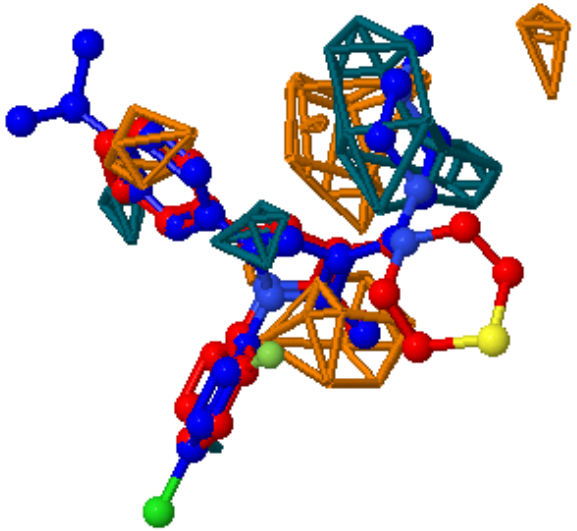
CoMFA

CoMFA2



8° Interpretazione





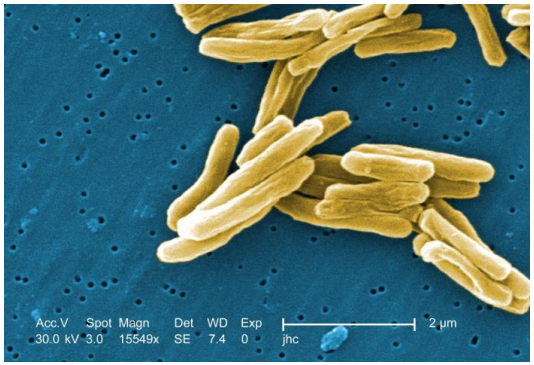
Stericità > attività

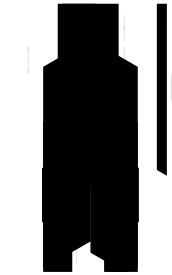
Attrazione elettrostatica > attività

Stericità < attività

Repulsione elettrostatica > attività

Applicazione





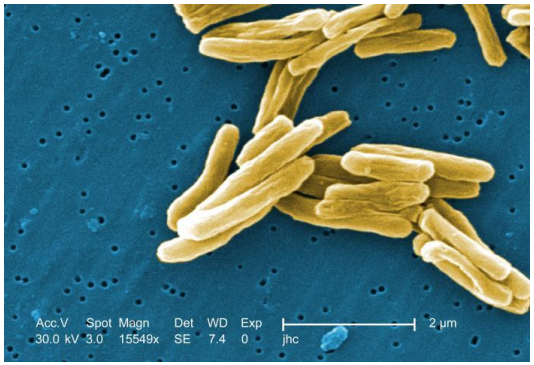
Isoniazide

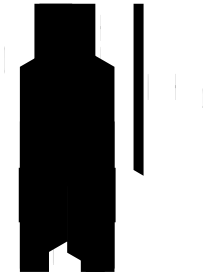
Resistenza

- Acquisita
- Primaria

- MDR — Multi Drug Resistant
- XDR — eXtensively Drug Resistant
- TDR — Totally Drug Resistant

Applicazione





Isoniazide

Resistenza

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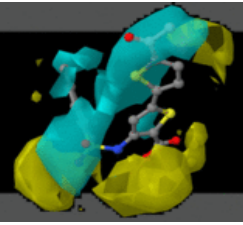
- XDR — eXtensively Drug Resistant
- TDR — Totally Drug Resistant



Conclusioni

by www.RCMD.it

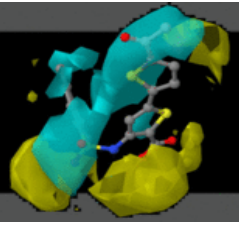
Obiettivo

RESISTENZE

✓ **Efficacia**

Strategia

3D-QSAR →



Grazie per l'attenzione