

Inibitori selettivi delle HDAC. Studio dei determinanti strutturali responsabili della selettività nelle varie isoforme mediante un approccio combinato tra *homology modeling*, *molecular docking* e *comparative binding energy analysis*.

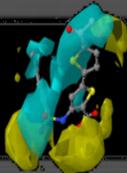


SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di farmacia e medicina
Corso di laurea in chimica e tecnologia farmaceutiche
Tesi sperimentale in chimica farmaceutica
a.a. 2010/2011

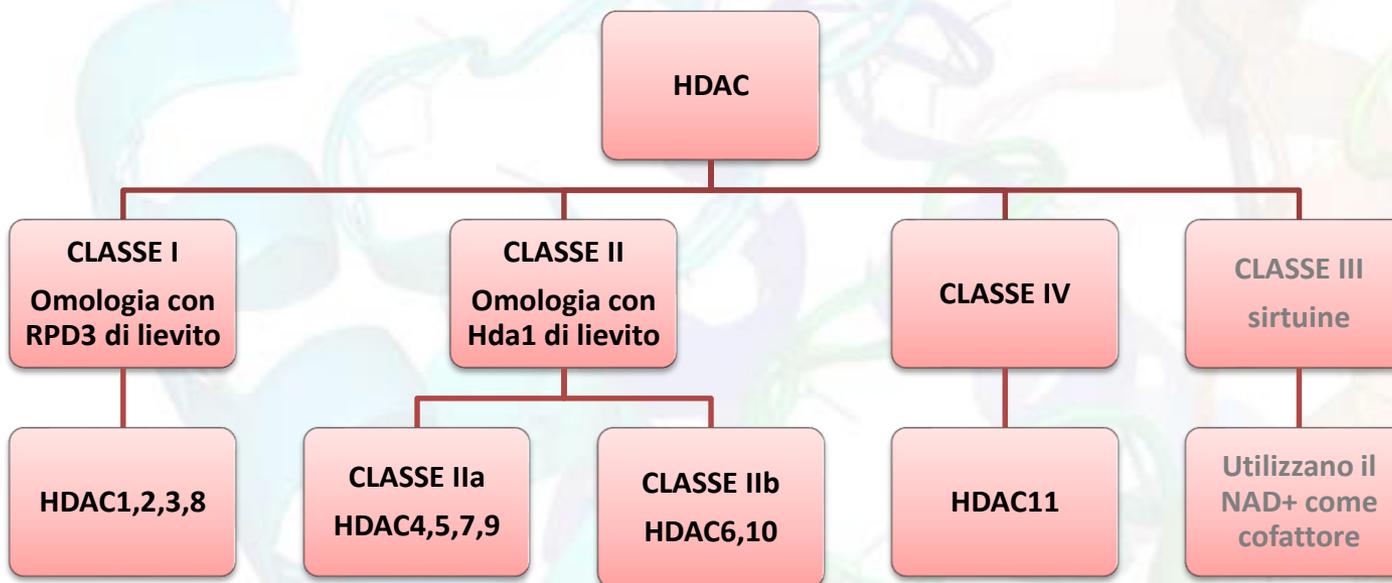
Laureanda: Laura Silvestri
Matricola: 314464

Relatore: prof. Rino Ragno

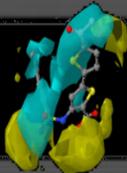


INTRODUZIONE: LA FAMIGLIA DELLE ISTONE DEACETILASI

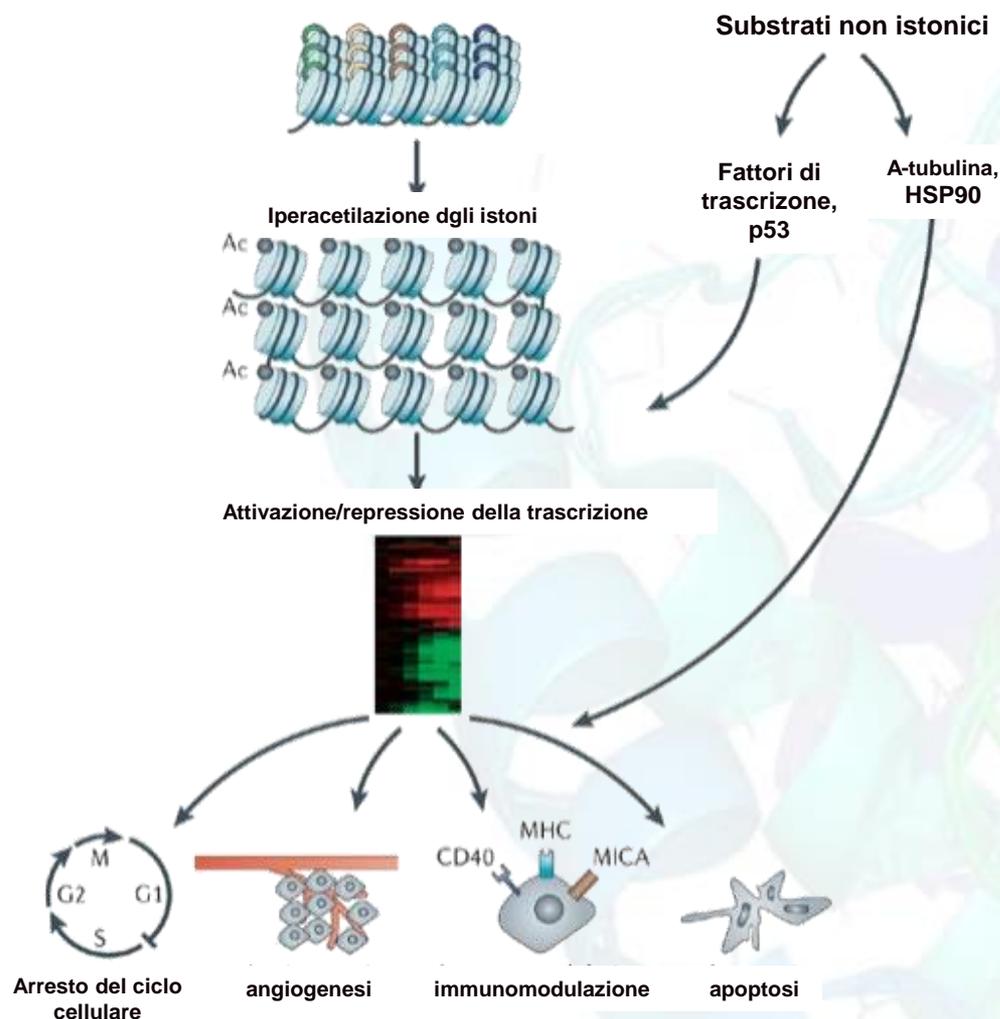
Le istone deacetilasi (HDAC) sono una famiglia di enzimi trovati nei batteri, funghi, piante e animali. Possono essere suddivise, strutturalmente e funzionalmente, in 4 classi:



Le HDAC di classI/III/IV sono proteasi Zn-dipendenti



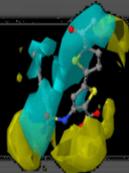
INTRODUZIONE: EFFETTI BIOLOGICI DELLE HDAC



HDAC come target di agenti terapeutici per il trattamento dei tumori, malattie neuro-degenerative e vari disordini

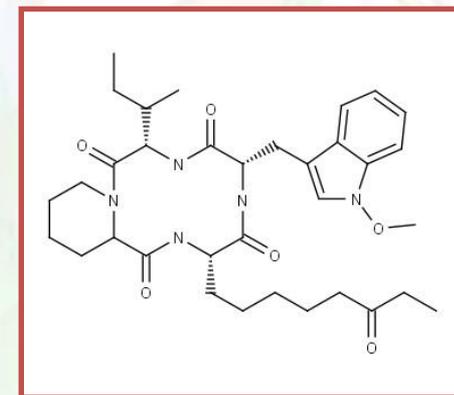
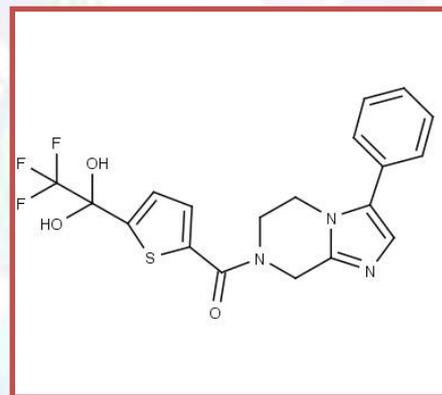
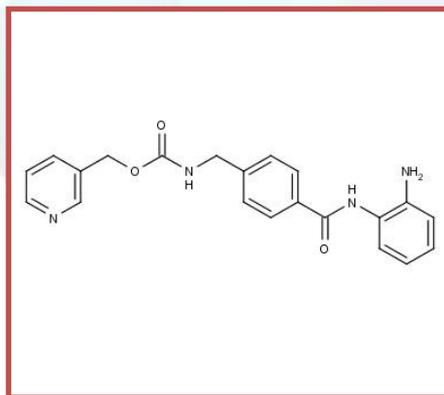
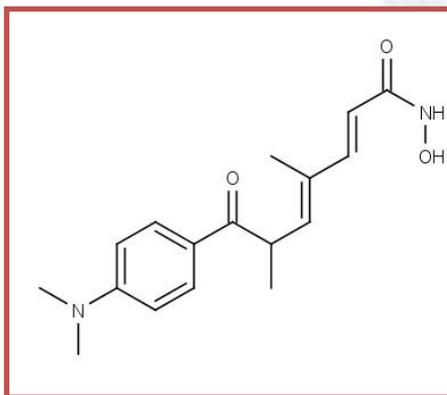
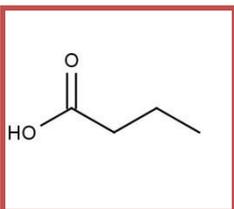


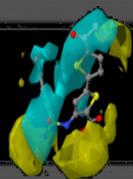
Diversi inibitori delle HDAC sono in trial clinico per la capacità di bloccare la crescita cellulare, promuovere la differenziazione e indurre l'apoptosi



Gli inibitori HDAC sono classificati in base alla loro struttura chimica e ogni agente presenta delle variabilità nella capacità di inibire particolari isoforme.

1. Acidi grassi a catena corta,
2. Acidi idrossammici,
3. Benzammidi,
4. Trifluorometilchetoni,
5. Peptidi ciclici.

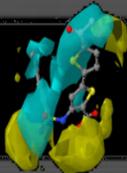




Obiettivo del presente lavoro è stato quello di ricercare un metodo in grado di delineare un profilo di selettività e di predire l'attività di composti verso le HDAC umane.



COSTRUZIONE DI UN MODELLO 3-D QSAR PER UNA SERIE D'INIBITORI TESTATI SULLE 11 ISOFORME DELLE HDAC, CON L'UTILIZZO DEL METODO COMBINE.



COMparative BINding Energy Analysis: TEORIA

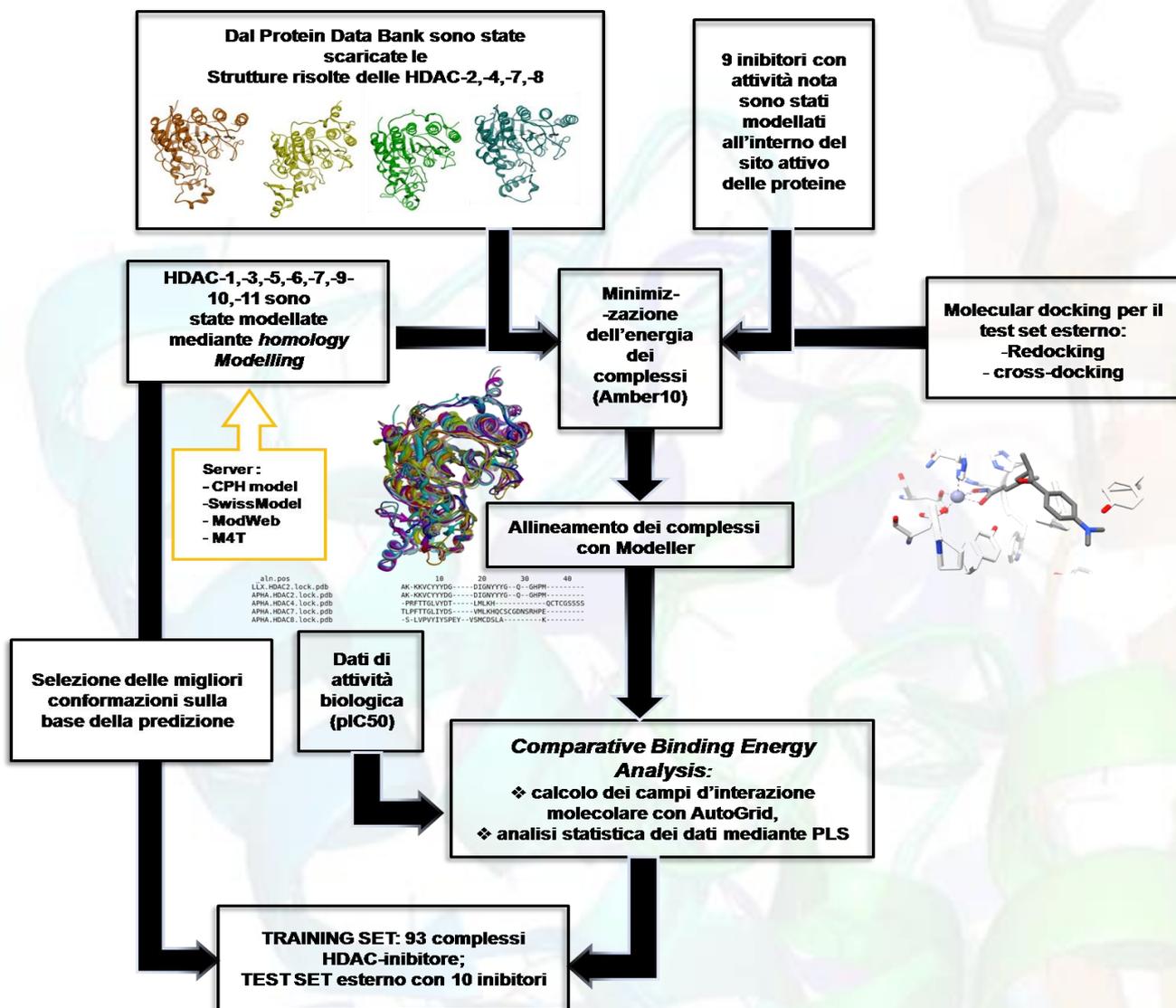
L'obiettivo di un'analisi COMBINE è quella di derivare un'espressione per l'energia libera di legame di un ligando, ΔG , della forma seguente:

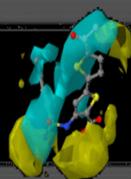
$$\Delta G = \sum_{i=1}^n w_i \Delta u_i + C$$

ΔU viene calcolato per le conformazioni dei complessi ligando-recettore e per i ligandi e i recettori non legati:

$$\begin{aligned} \Delta U = & \sum_{i=1}^{n_l} \sum_{j=1}^{n_r} u_{ij}^{VDW} + \sum_{i=1}^{n_l} \sum_{j=1}^{n_r} u_{ij}^{ELE} + \\ & \sum_{i=1}^{n_l} \Delta u_i^{B,L} + \sum_{i=1}^{n_l} \Delta u_i^{A,L} + \sum_{i=1}^{n_l} \Delta u_i^{T,L} + \sum_{i < j} \Delta u_{ij}^{NB,L} + \\ & \sum_{j=1}^{n_r} \Delta u_j^{B,R} + \sum_{j=1}^{n_r} \Delta u_j^{A,R} + \sum_{j=1}^{n_r} \Delta u_j^{T,R} + \sum_{j < j'} \Delta u_{jj'}^{NB,R} \end{aligned}$$

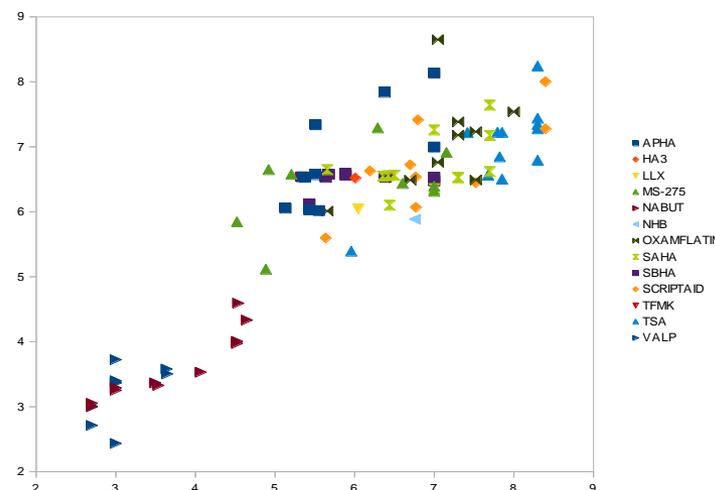
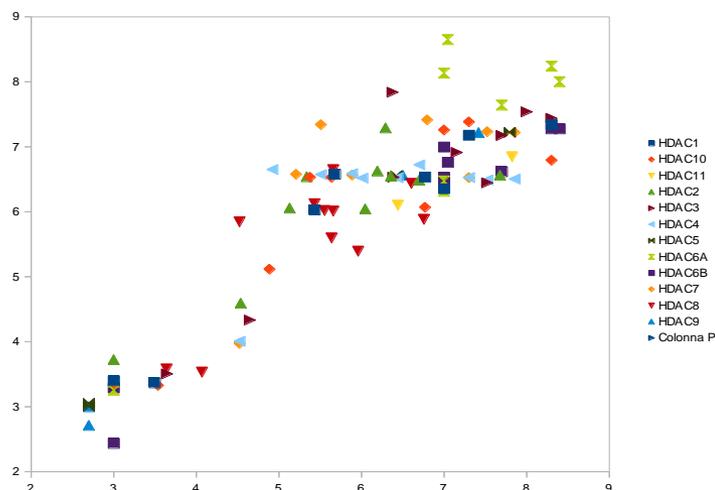
OVERVIEW DELLE PROCEDURE UTILIZZATE



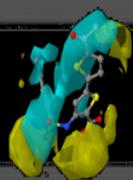


RISULTATI

PROBE	PC	r^2	SDEC	q^2 K5fold	q^2 LOO	SDEP
ELE	3	0.71	0.87	0.7	0.71	0.89
ELE+STE	3	0.77	0.79	0.73	0.73	0.85
ELE+DRY	3	0.83	0.66	0.8	0.8	0.73
ELE+STE+DRY	3	0.84	0.65	0.78	0.8	0.75



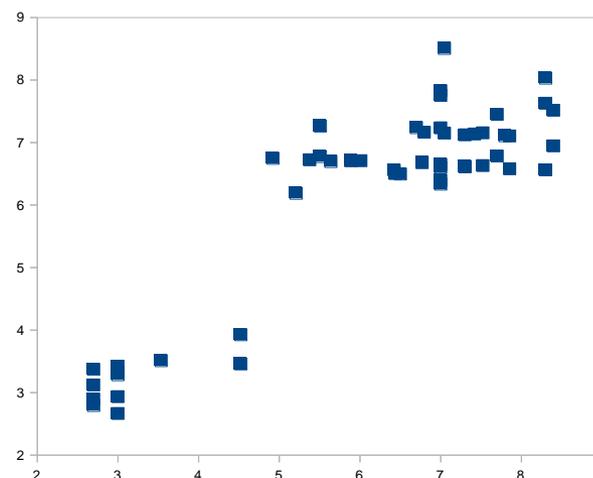
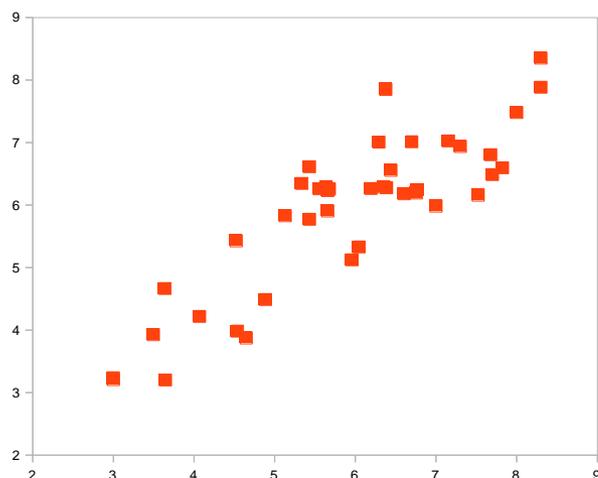
pIC₅₀ sperimentale vs pIC₅₀ predetto. Modello globale, probe ELE+STE+DRY cross-validazione K5-fold, PC=3.



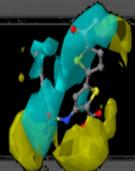
RISULTATI

Risultati statistici dei modelli costruiti per il triplo probe ELE+STE+DRY.

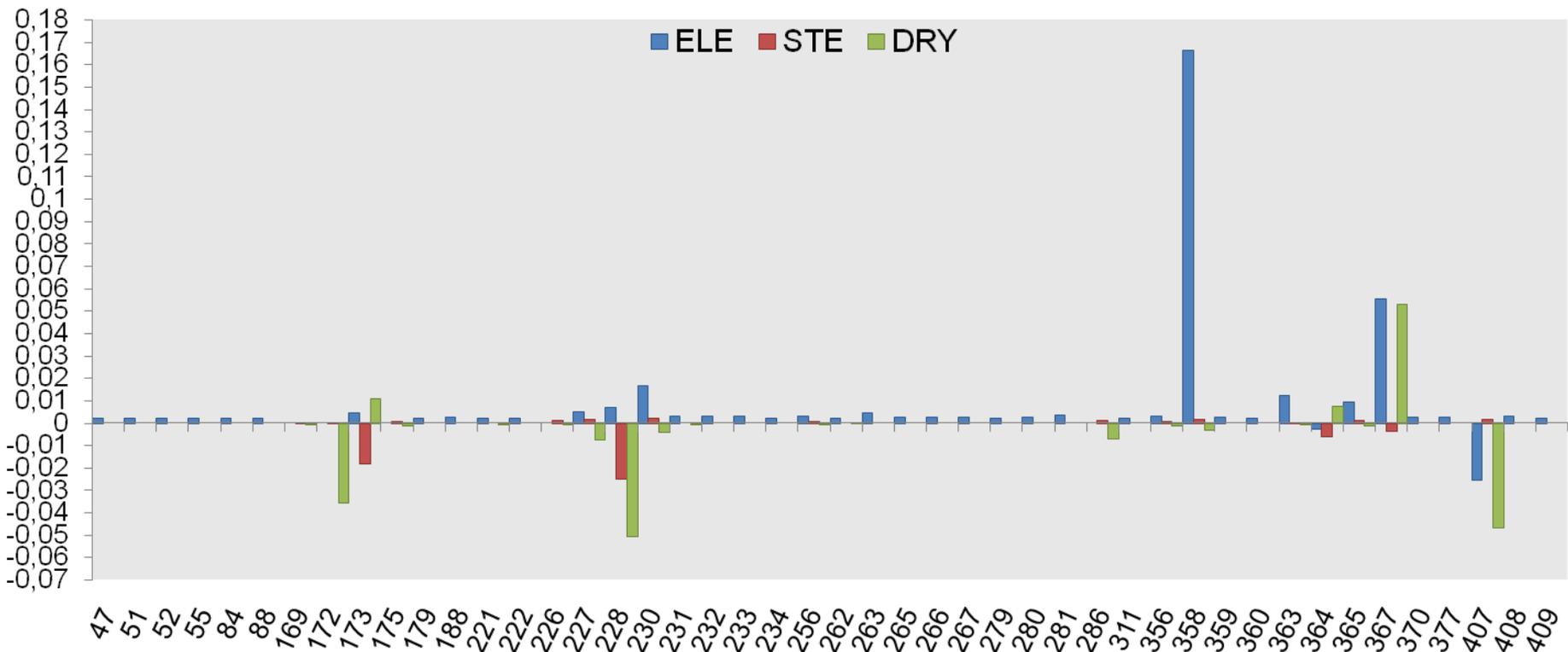
PROBE	PC	r^2	SDEC	q^2 K5fold	q^2 LOO	SDEP
Mod.cristallizzate	2	0.62	0.73	0.47	0.47	0.98
Mod.classe I	3	0.84	0.55	0.74	0.75	0.72
Modello classe II	3	0.85	0.70	0.79	0.81	0.81
Modello globale	3	0.84	0.65	0.78	0.8	0.75

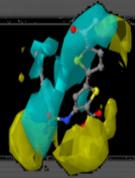


pIC50 sperimentale vs pIC50 predetto. Modello classe I (a sinistra) e modello classe II (a destra), probe ELE+STE+DRY cross-validazione K5-fold, PC=3.



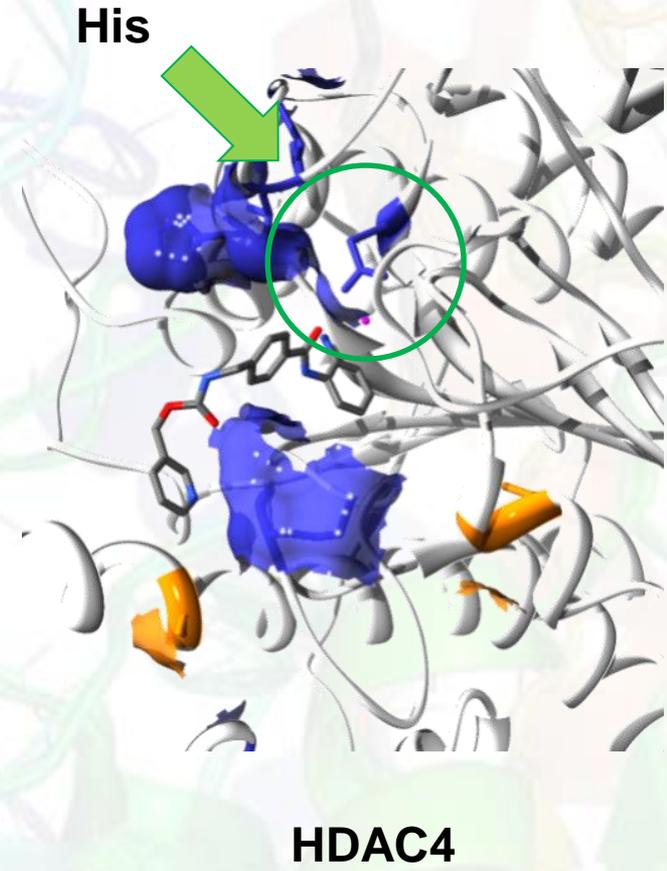
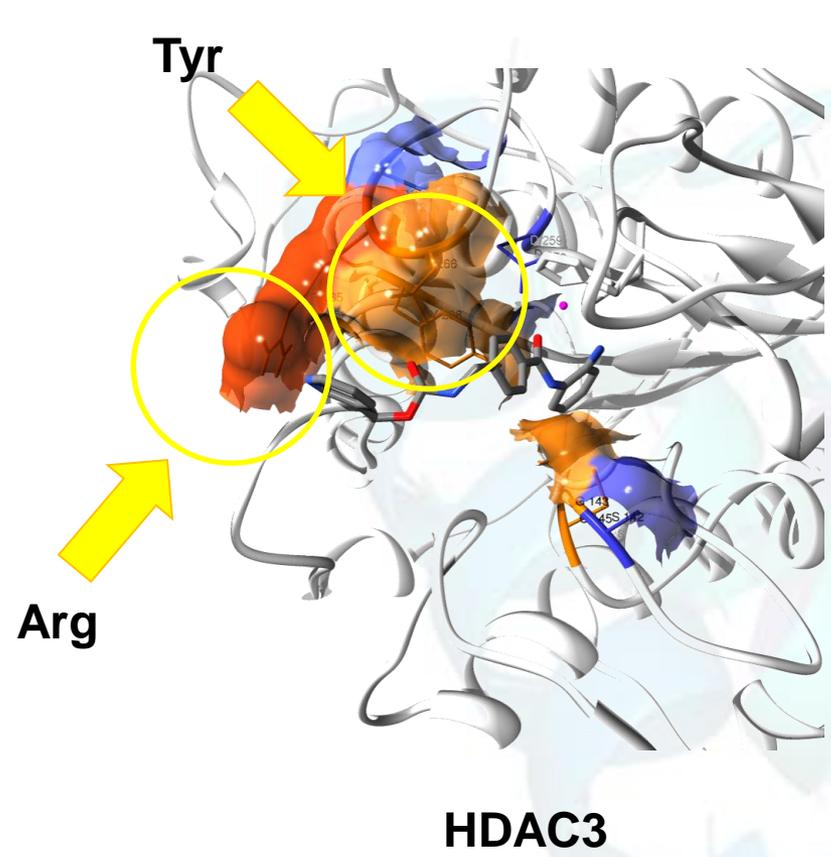
Il grafico dei coefficienti di PLS

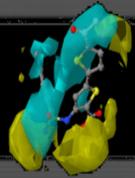




INTERPRETAZIONE DEI RISULTATI

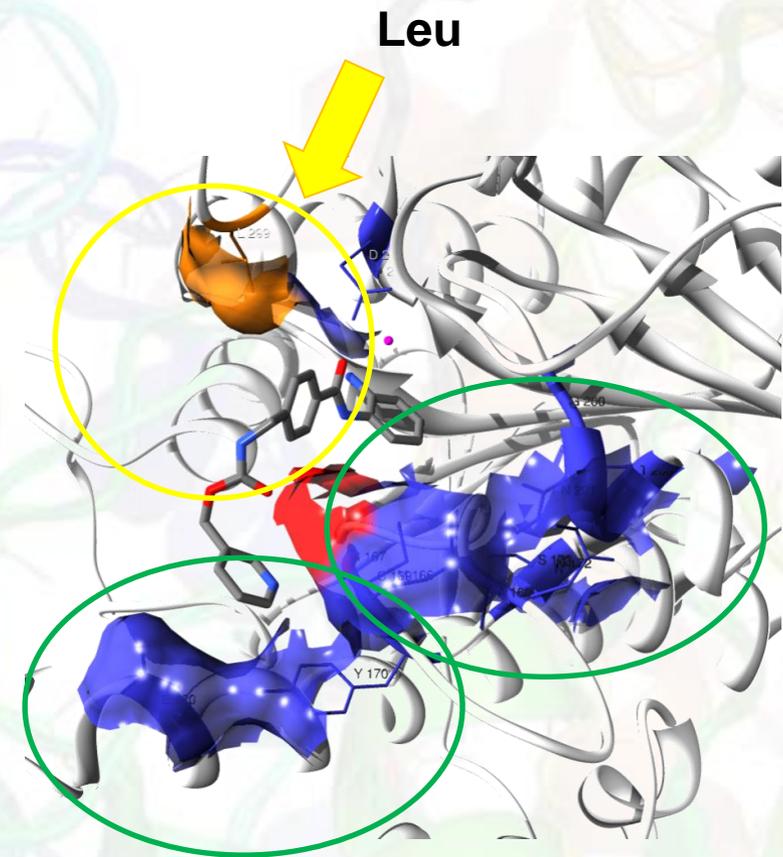
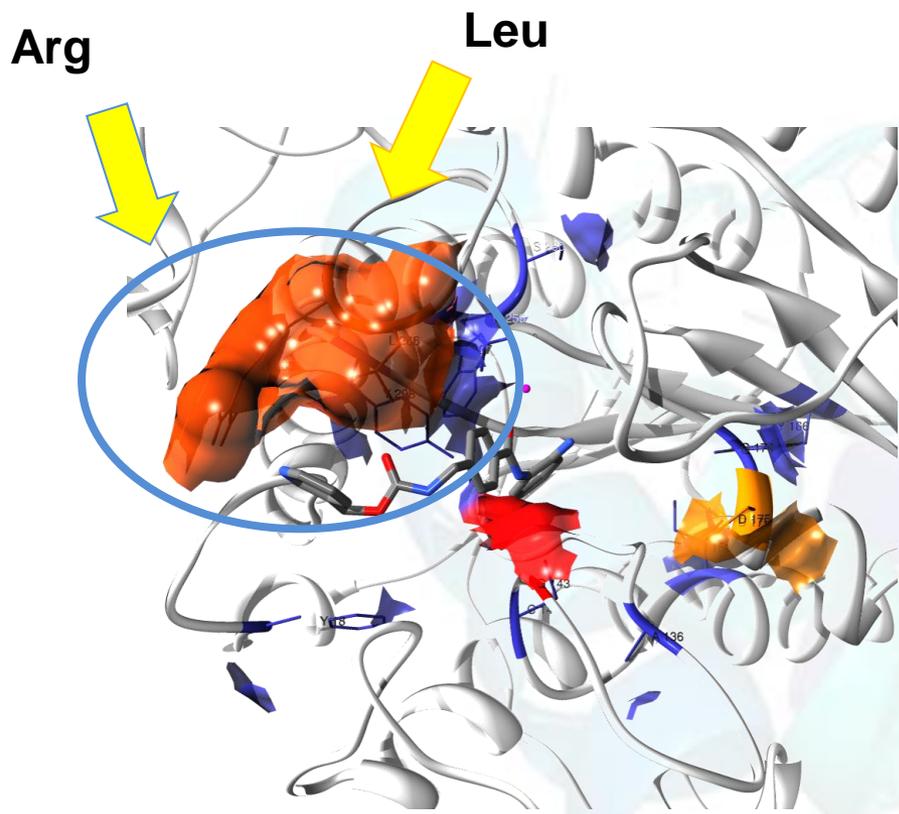
Activity contribution plot. MS-275 interazioni elettrostatiche

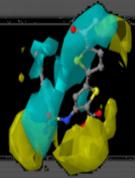




INTERPRETAZIONE DEI RISULTATI

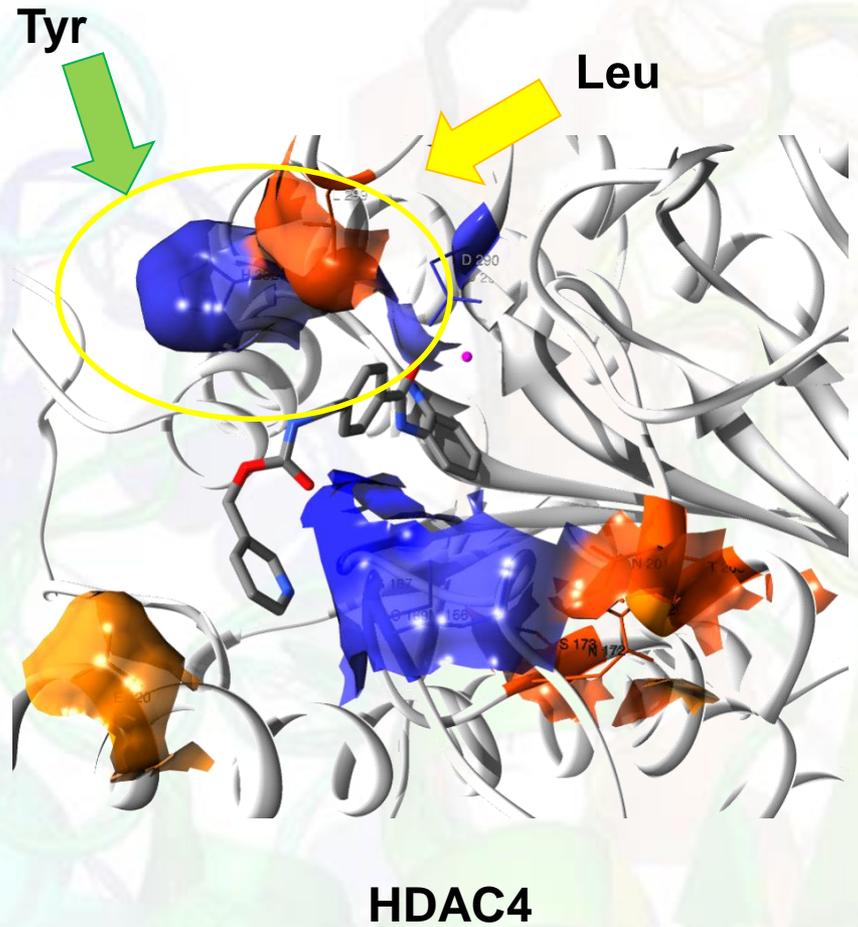
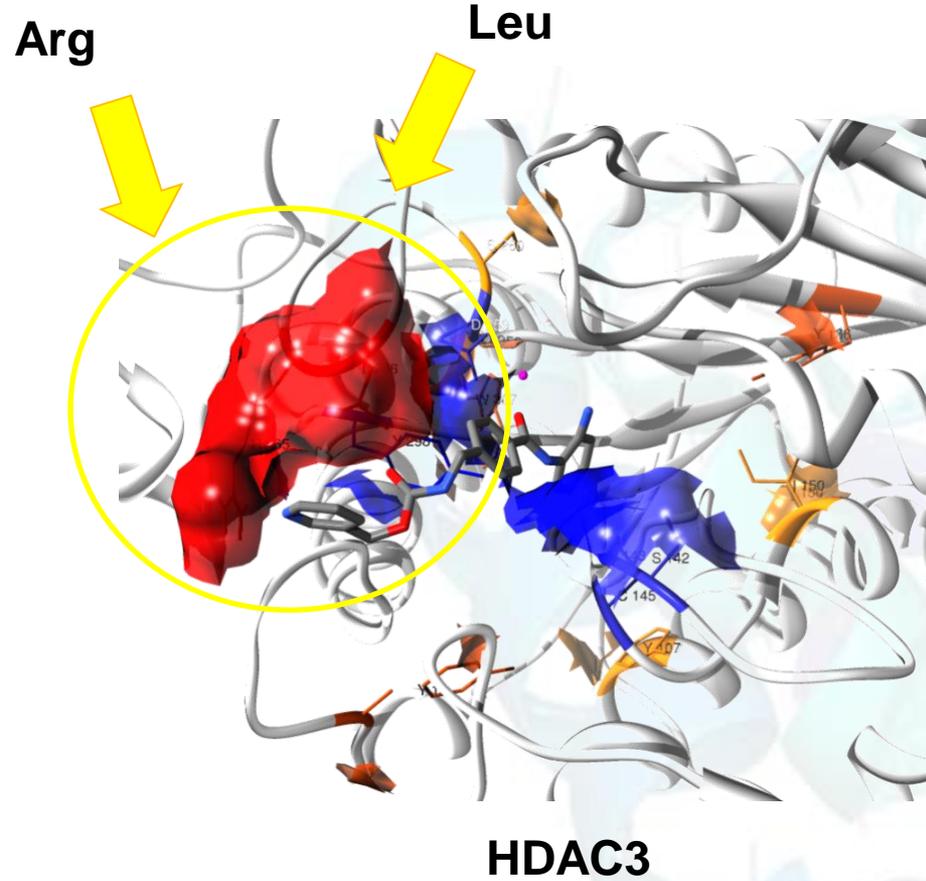
Activity contribution plot. MS-275 interazioni steriche

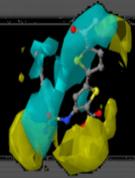




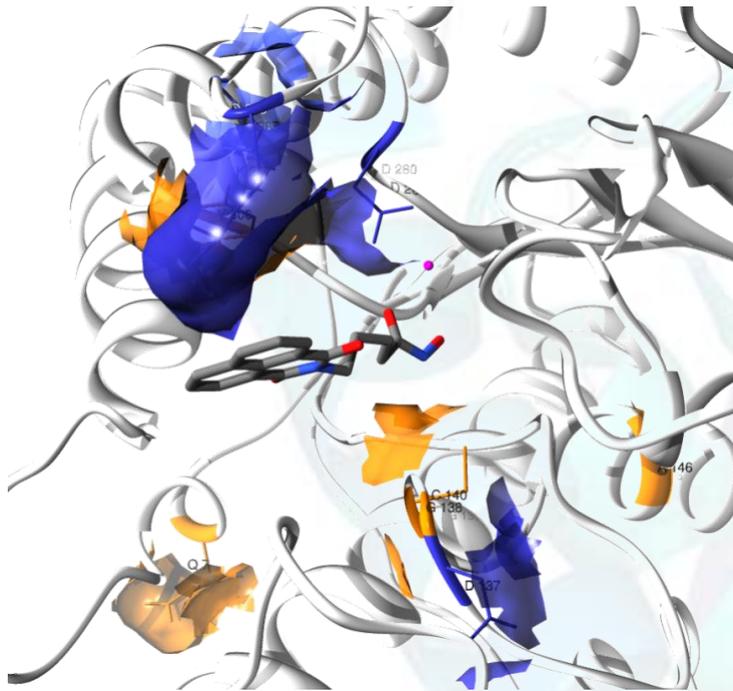
INTERPRETAZIONE DEI RISULTATI

Activity contribution plot. MS-275 interazioni di desolvatazione

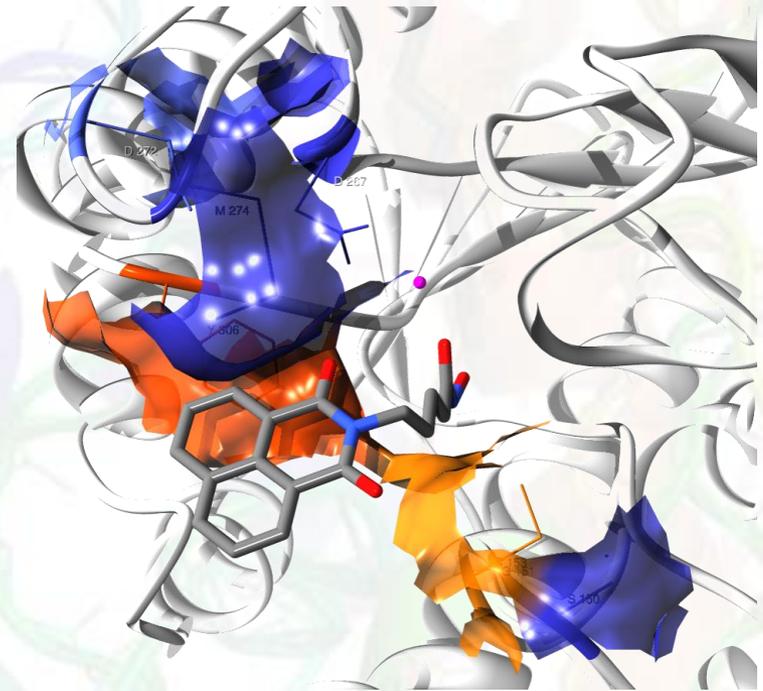




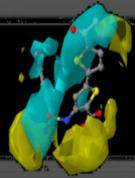
Activity contribution plot. SCRIPTAID interazioni elettrostatiche



HDAC6A

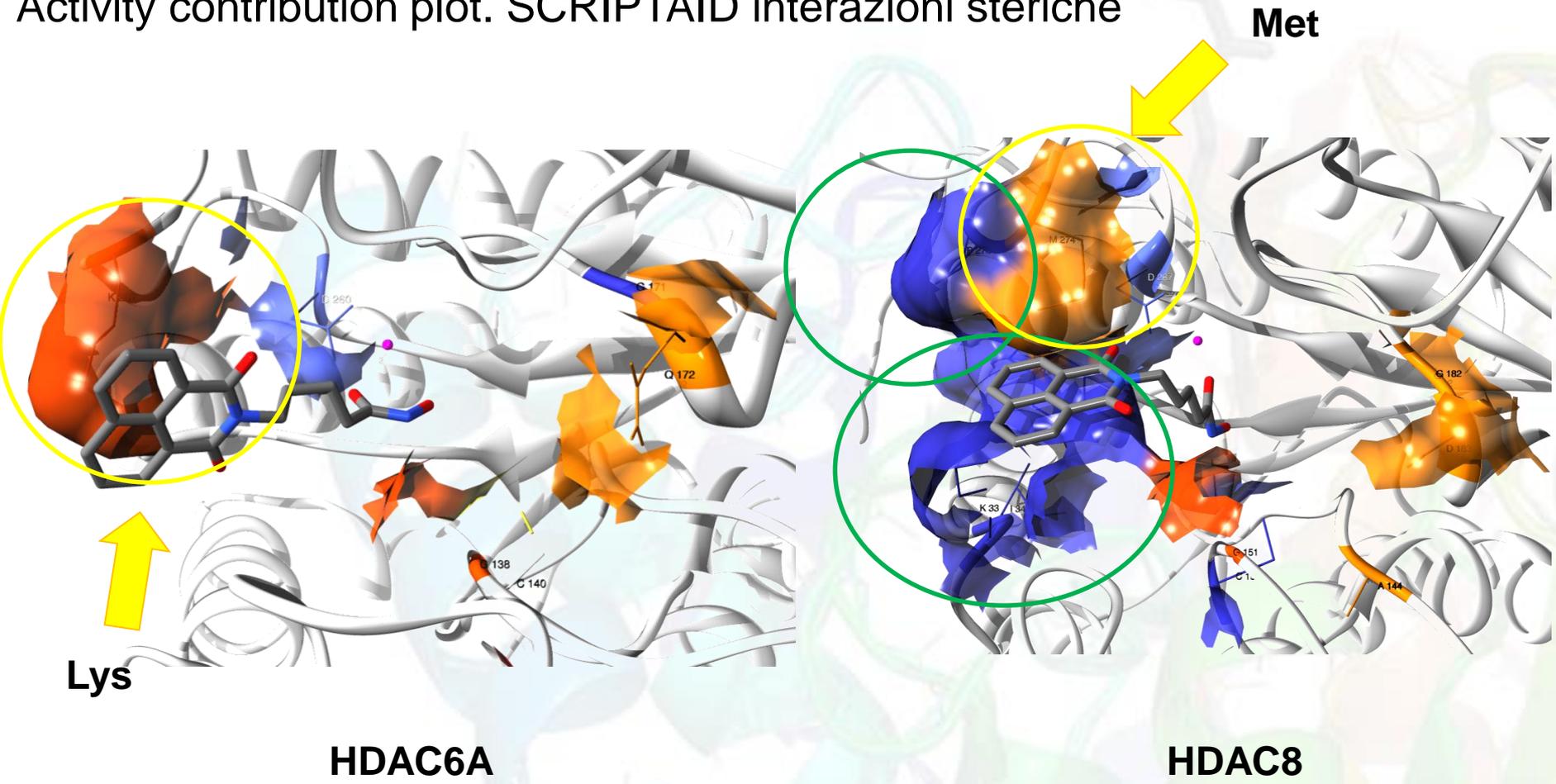


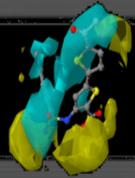
HDAC8



INTERPRETAZIONE DEI RISULTATI

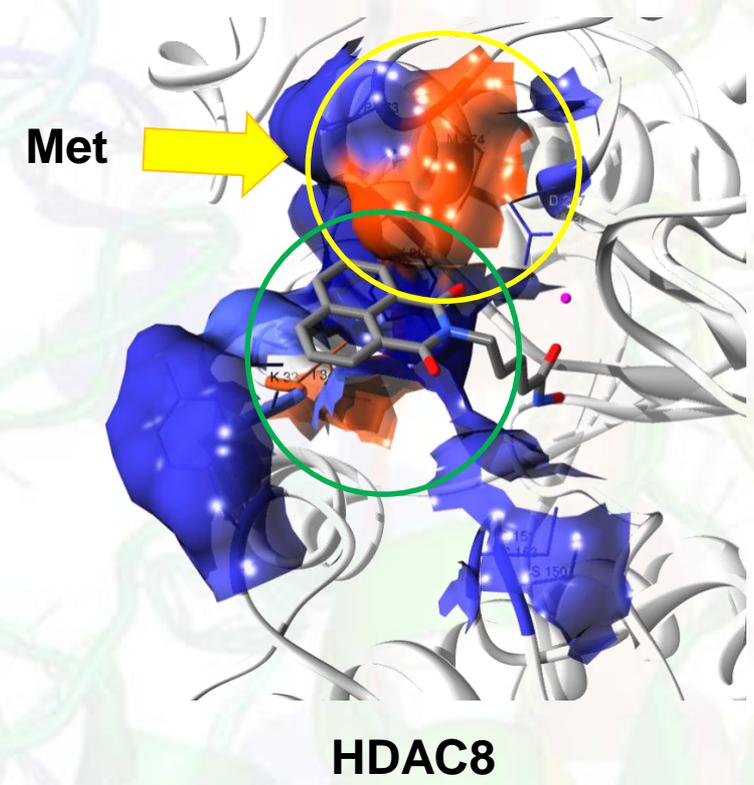
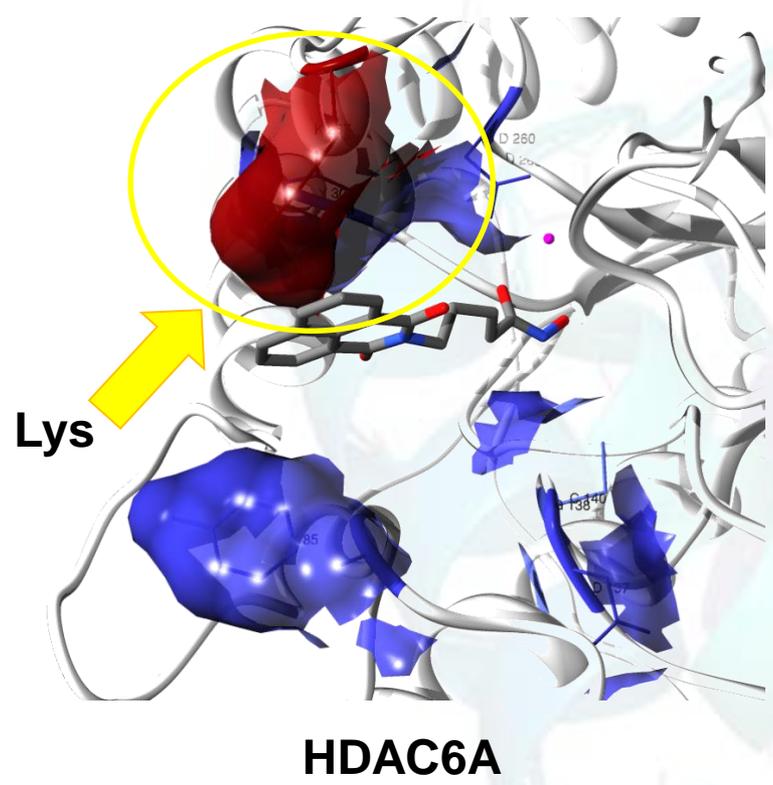
Activity contribution plot. SCRIPTAID interazioni steriche

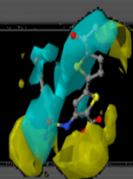




INTERPRETAZIONE DEI RISULTATI

Activity contribution plot. SCRIPTAID interazioni di desolvatazione

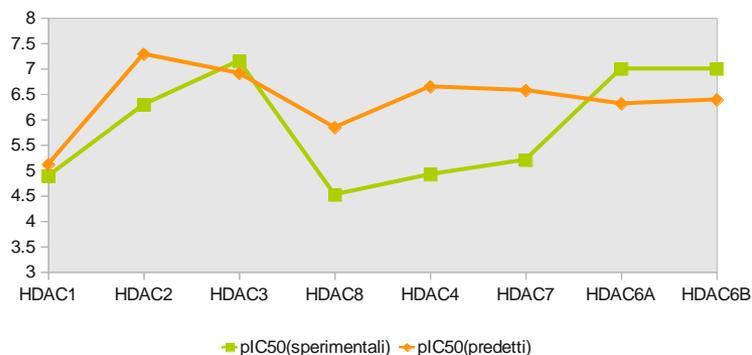




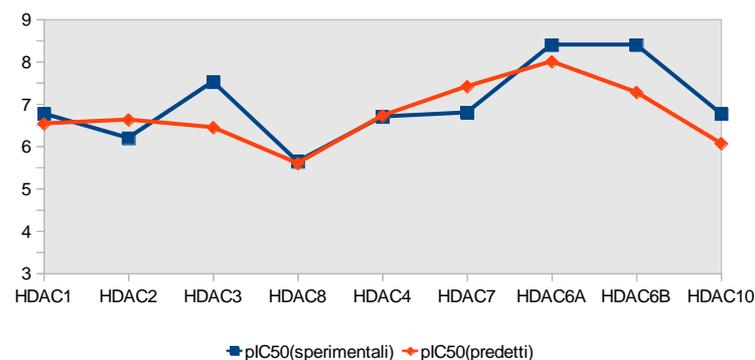
CONCLUSIONI

Il modello costruito è risultato predittivo, dotato di buoni coefficienti statistici e in grado di spiegare i diversi valori di attività mostrati dagli inibitori considerati.

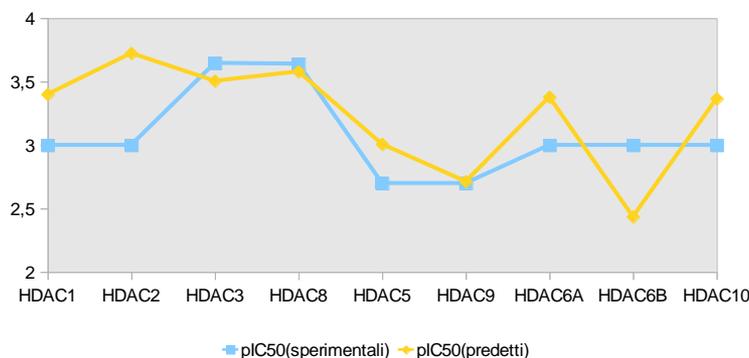
MS-275

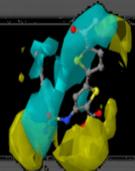


SCRIPTAID



ACIDO VALPROICO





CONCLUSIONI

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A 3-D QSAR MODELS DATABASE for Virtual Screening

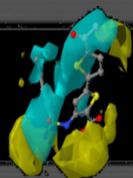
Substance libraries, composed of million of compounds, are tested in the pharmaceutical industry with robotic systems. Furthermore, the follow-up of the "hits" is often so expensive that essentially only large companies can use this method. Virtual screening helps to decide which compounds to screen, which libraries to synthesis and which compounds to purchase from an external supplier reducing the overall cost associated to the discovery and development of new drugs.

Main classes of virtual screening methods are:

- Similarity search (ligand-based virtual screening)
- Identify a common 3-D pharmacophore, then do a 3-D database search
- Train a machine learning technique
- Protein-ligand docking

Most of these methods are computationally intensive and complex. 3-D QSAR methods are nowadays used widely in drug design, since they are computationally not demanding and afford fast generation of QSARs from which the biological activity of molecules can be predicted.

Grazie per l'attenzione.



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