Studi computazionali su inibitori irreversibili della demetilasi istonica specifica della lisina (KDM1A)

SAPIENZA
UNIVERSITÀ DI ROMA

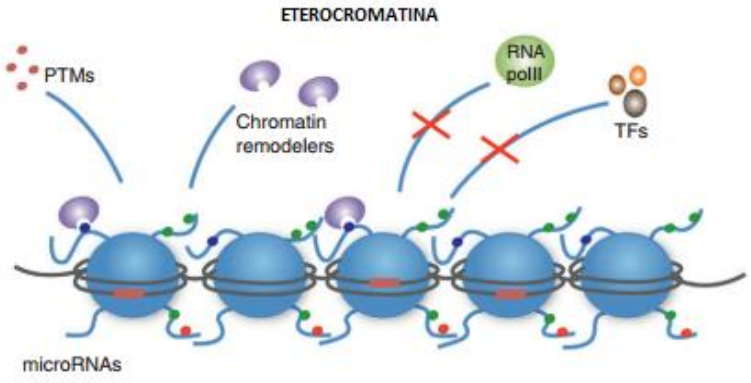
Facoltà di Farmacia e Medicina
Corso di Laurea in Biotecnologie Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2014/2015

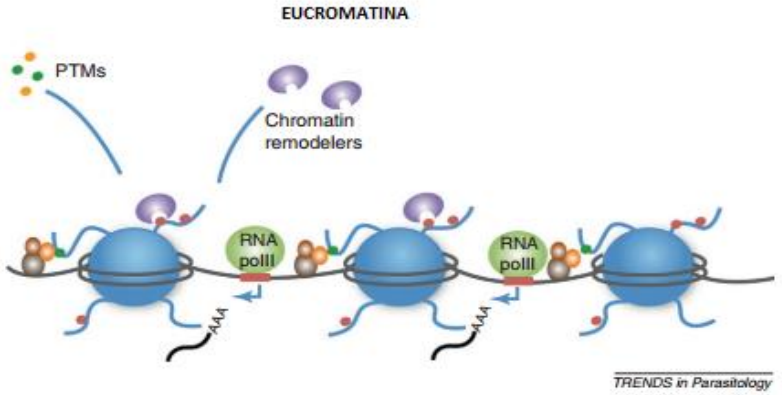
Laureanda: Martina Agostini

Relatore: prof. Rino Ragno

MODIFICHE CHIMICHE DELLA CROMATINA

- METILAZIONE DNA
- MODIFICHE COVALENTI CODE ISTONICHE





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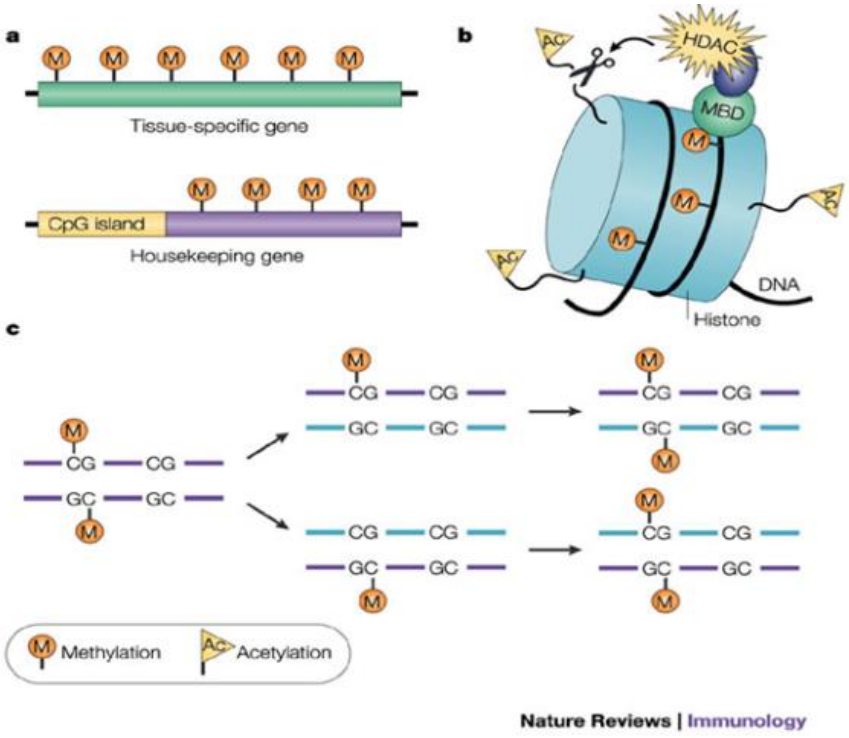
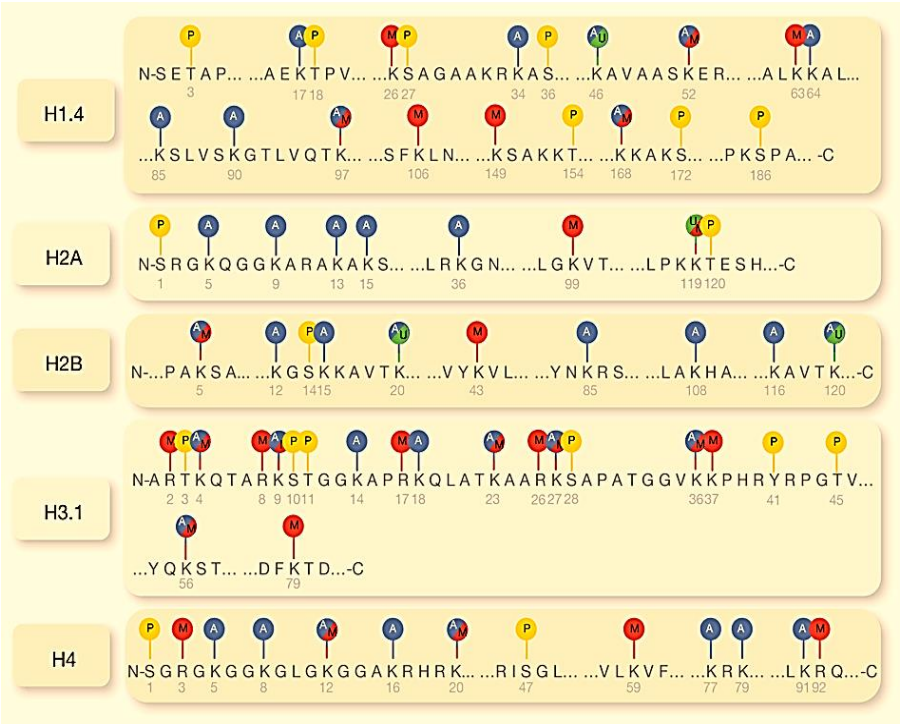
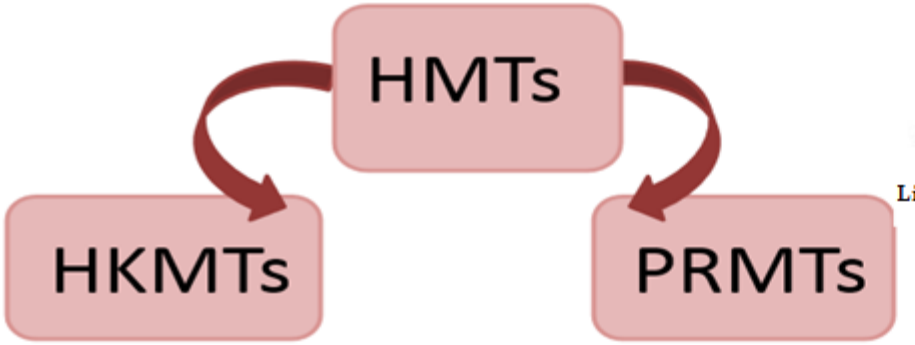
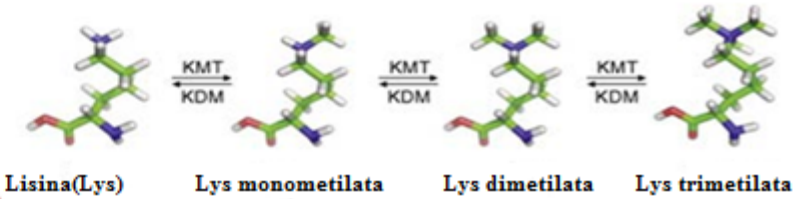


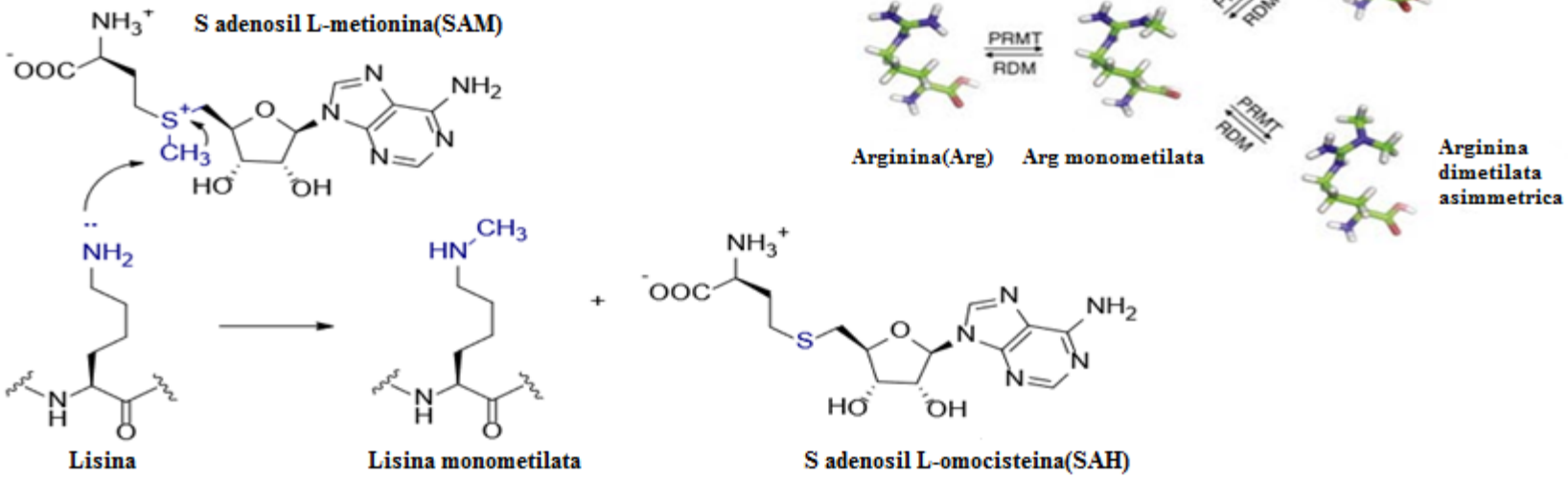
MODIFICHE CODE ISTONICHE



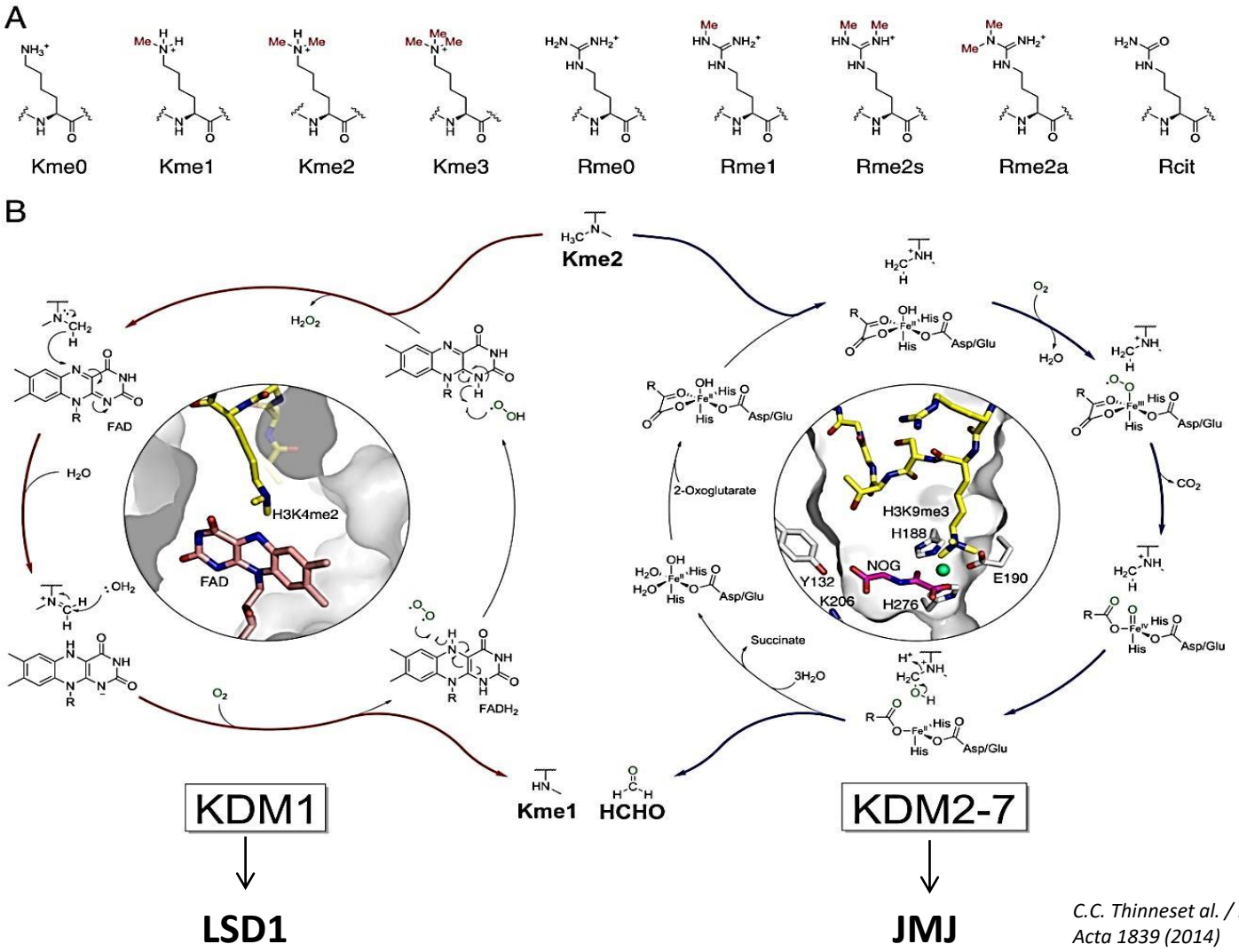
METILAZIONE ISTONICA





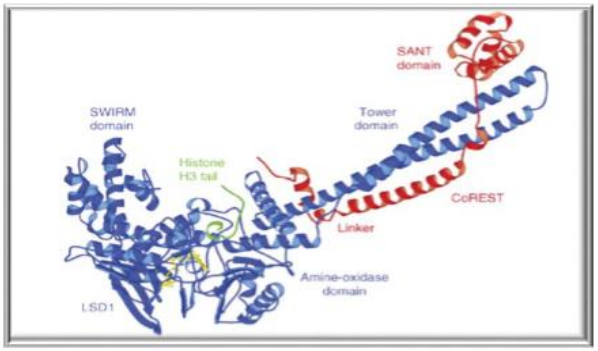


DEMETILASI ISTONICHE



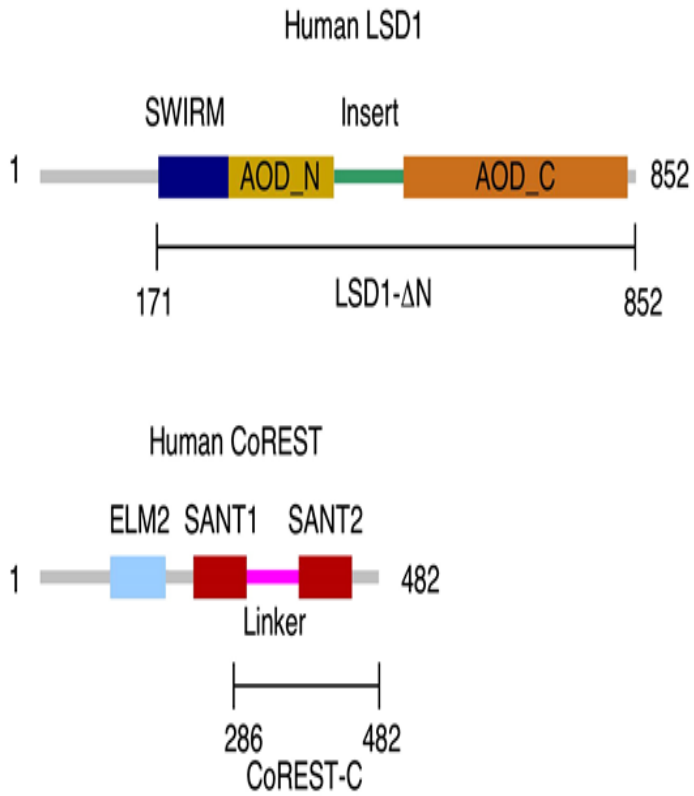
C.C. Thinneset al. / Biochimica et Biophysica Acta 1839 (2014)

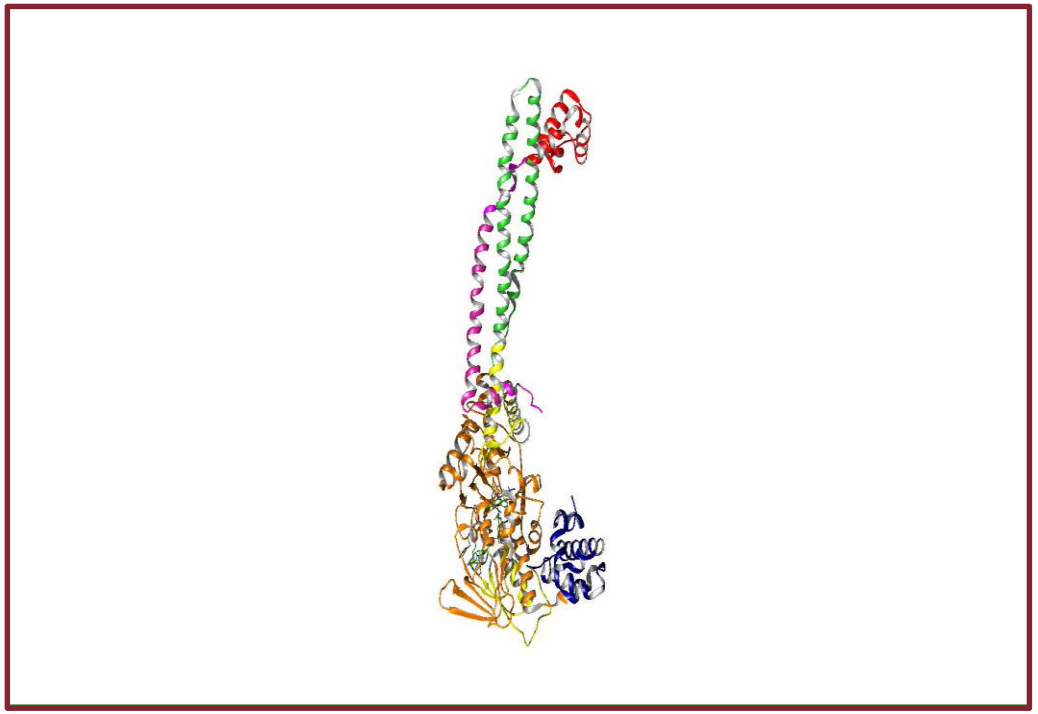
LSD1:MECCANISMO D'AZIONE



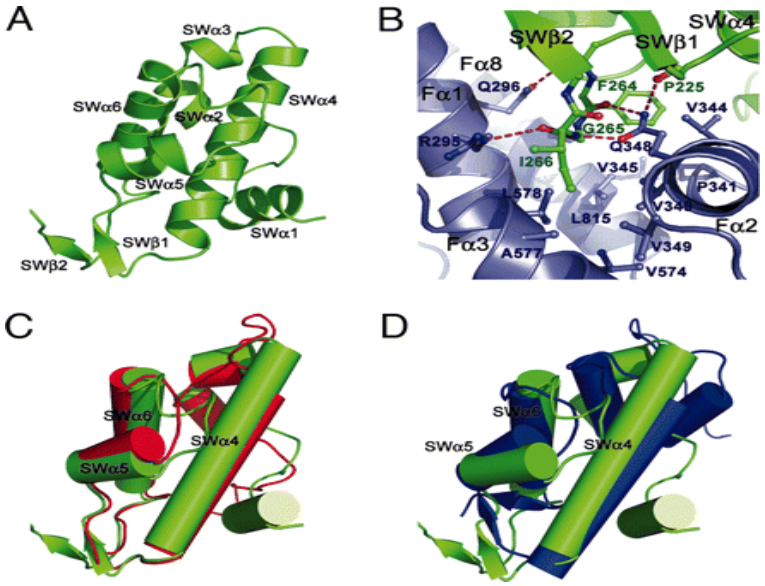
Shi Y et al. Cell 2004, *119*, 941-53. Karytinos A et al. J Biol Chem. 2009, *284*, 17775-82.

STRUTTURA LSD1



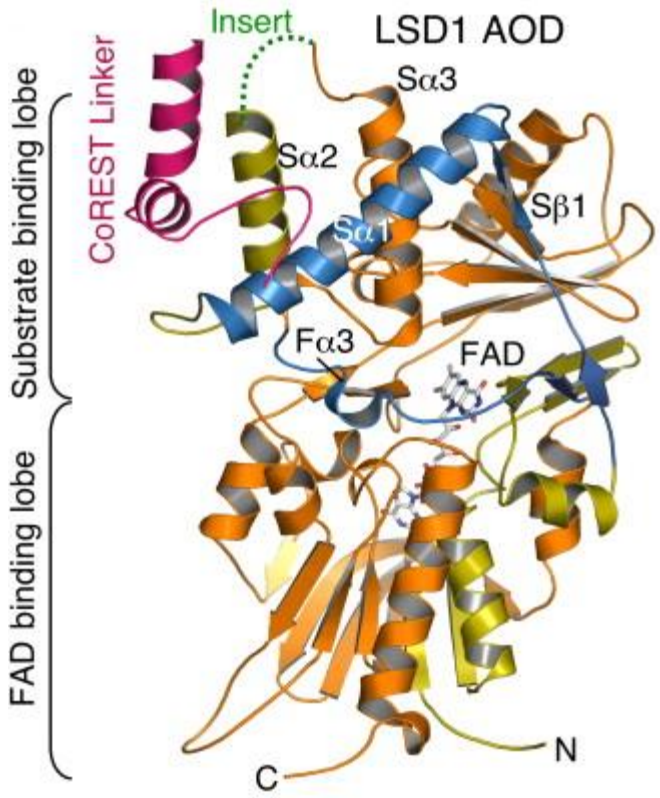


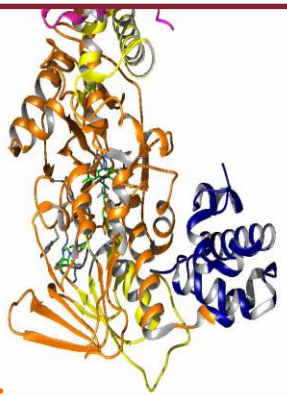
DOMINIO SWIRM



DOMINIO SWIRM

DOMINIO AOD

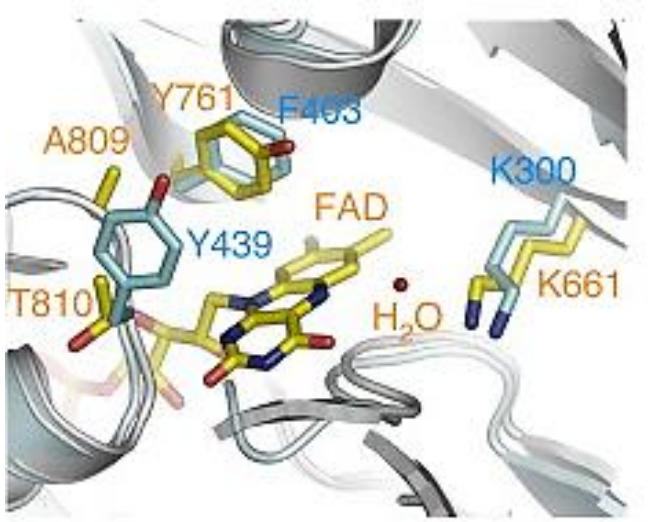


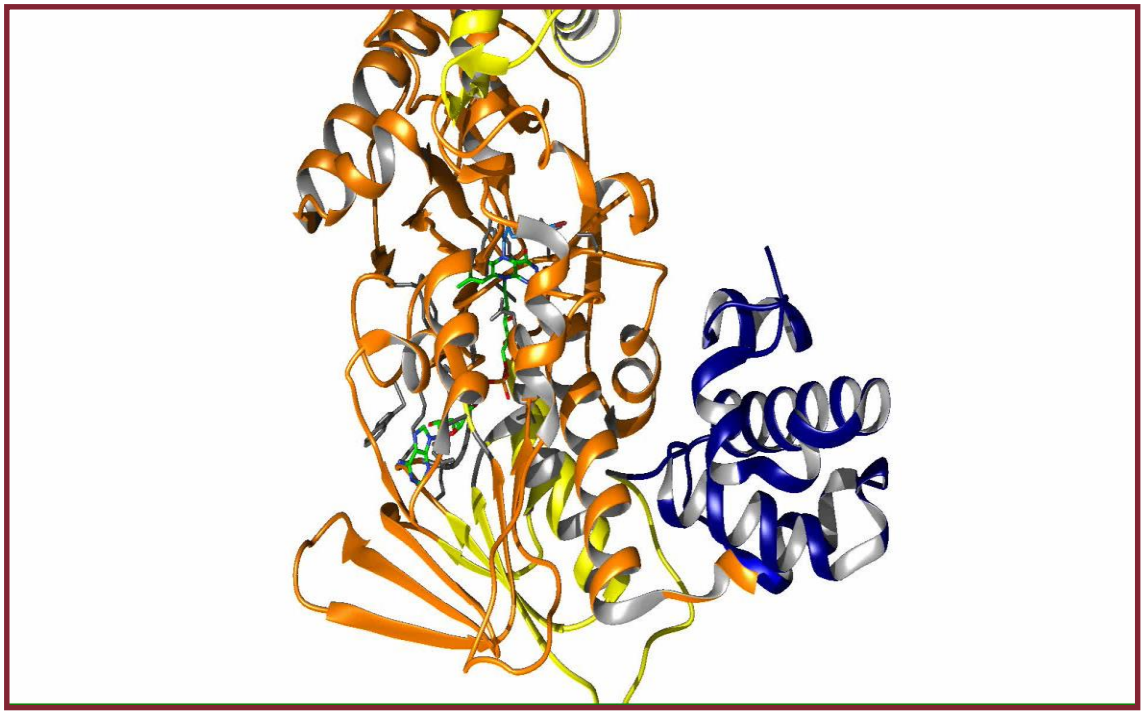


DOMINIO AOD :

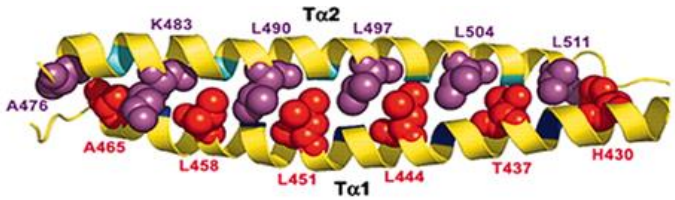
- **N-Terminale**
- **C-terminale**

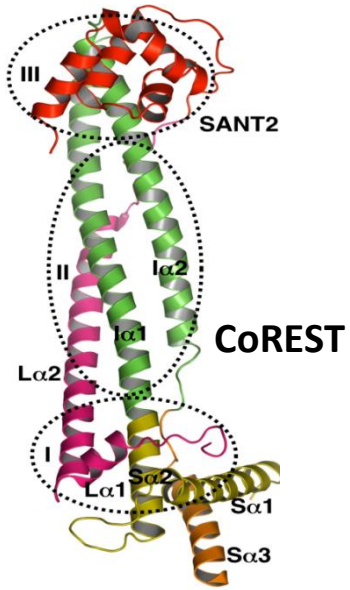
TASCA CATALITICA

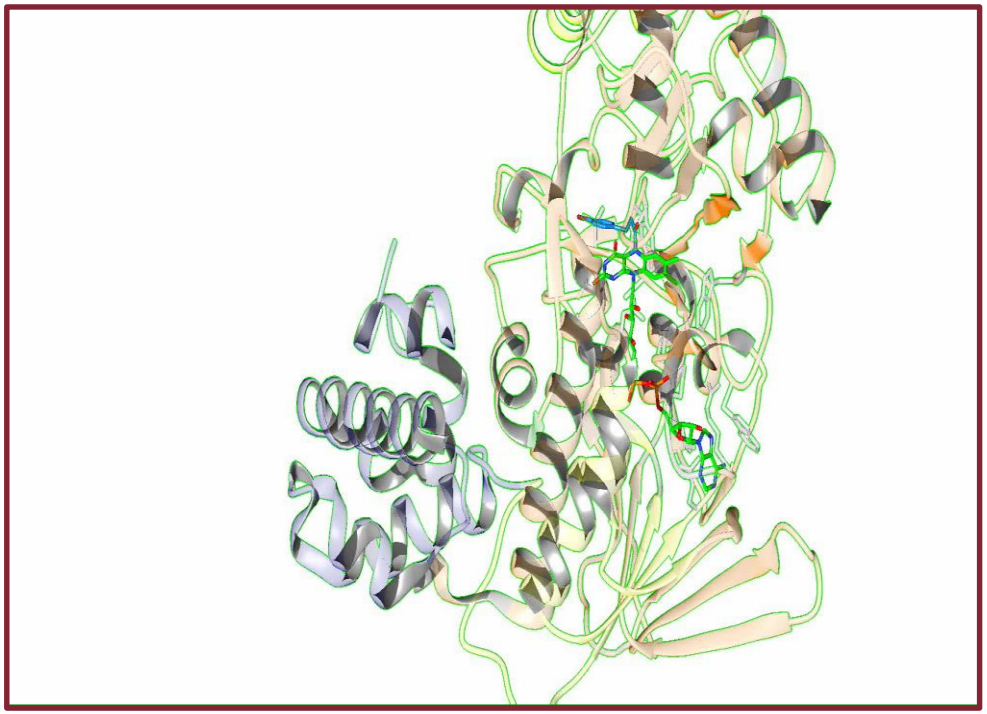




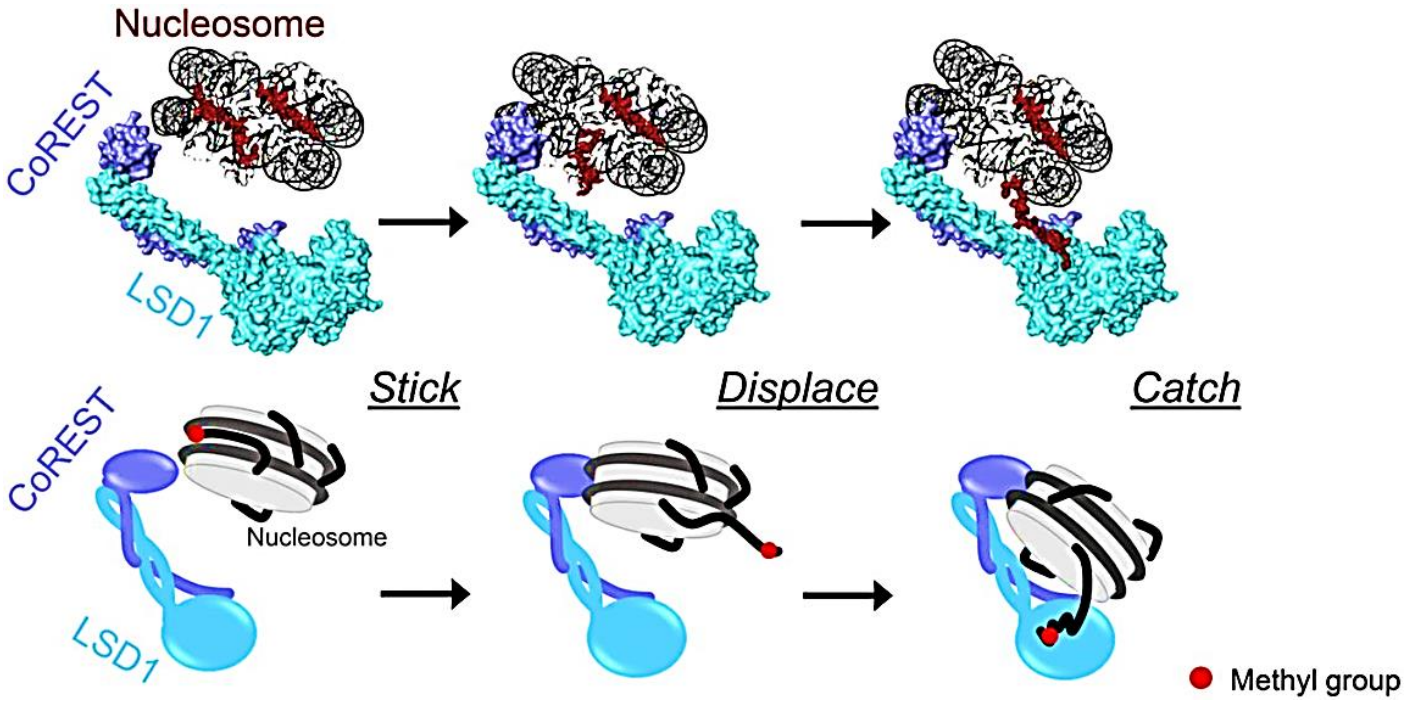
DOMINIO TOWER





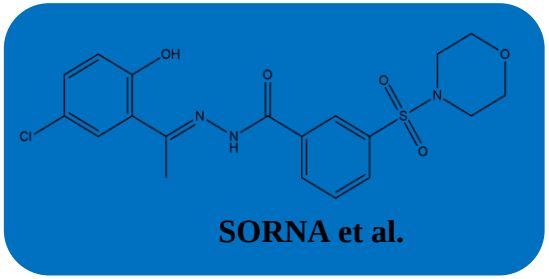


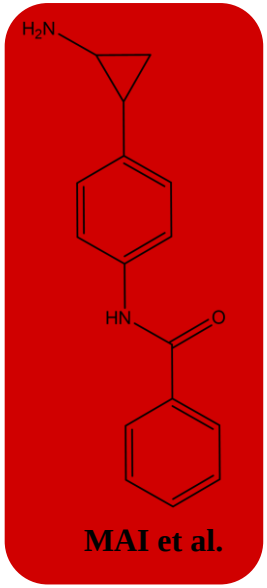
MODELLO *STICK&CATCH*

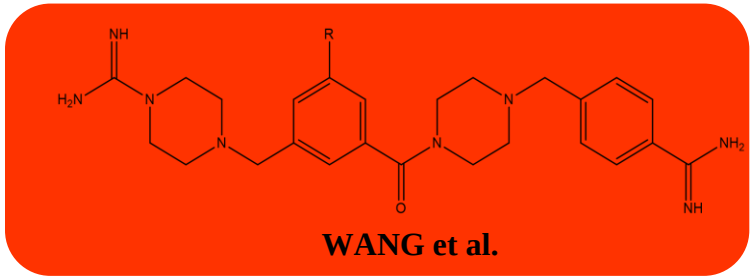


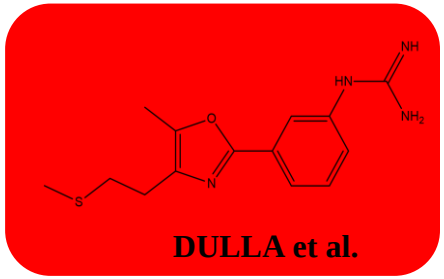
Pilotto, S., et al. Proc Natl Acad Sci U S A, 2015.

INIBITORI LSD1



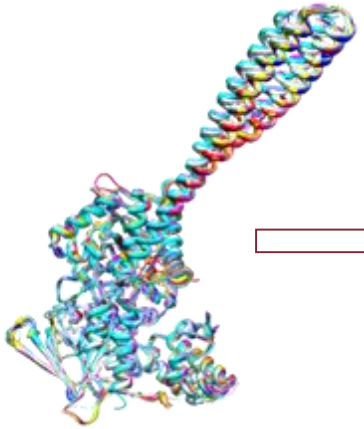






COINVOLTO IN DIVERSE PATOLOGIE:

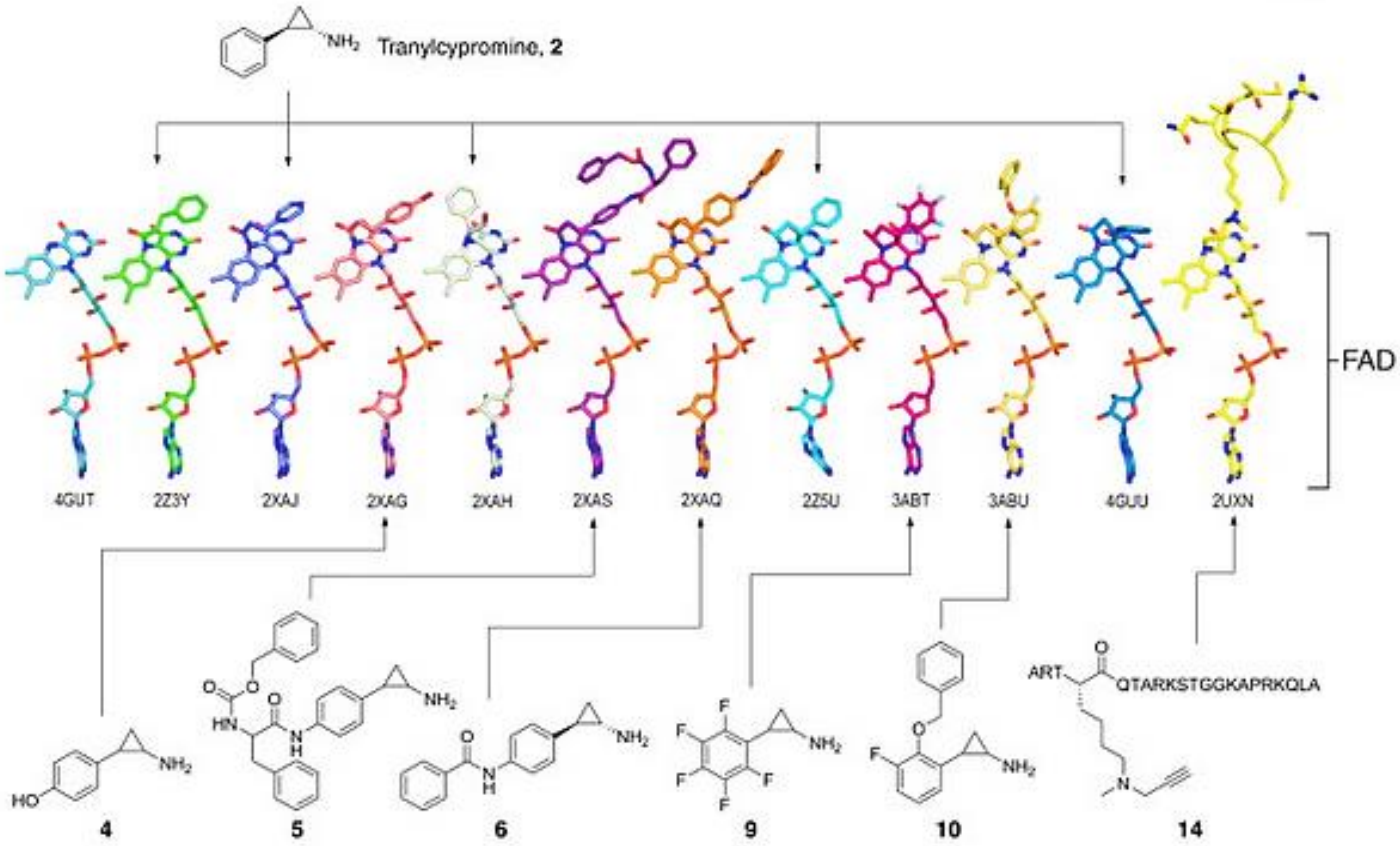
- TUMORE AL POLMONE
- TUMORE AL COLON
- LEUCEMIE



CREAZIONE DI NUOVI MODELLI MATEMATICI-STATISTICI

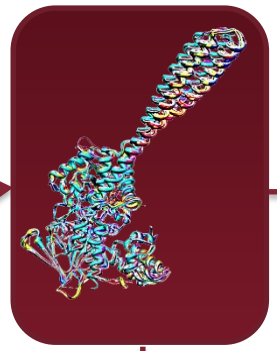
PREDIZIONE ATTIVITA' DI NUOVI COMPOSTI

DERIVATI TRANILCIPROMINA



C.C. Thinneset al. / Biochimica et Biophysica Acta 1839 (2014)

METODOLOGIA SPERIMENTALE



Download dei PDB

Minimizzazione allineamento

Procedura di modellazione tramite Modeller

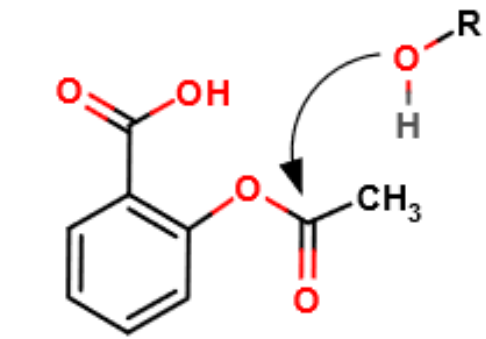
Docking Assessment

Docking covalente (Irreversibili)

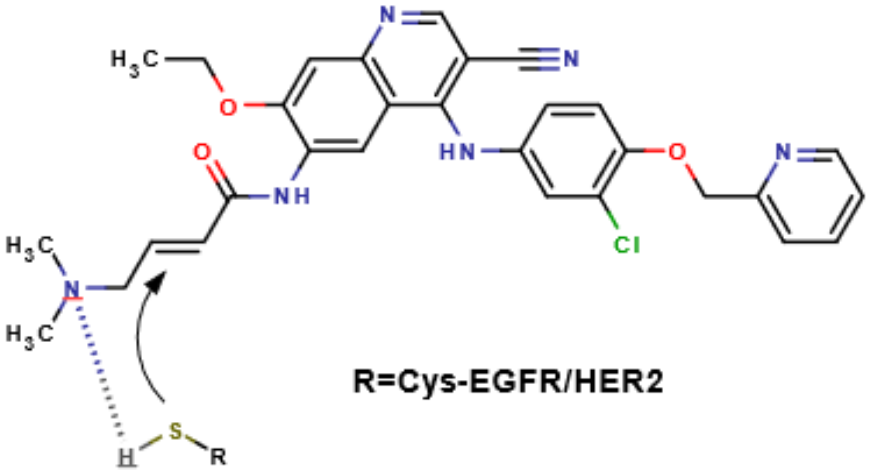
Modello preliminare 3-D QSAR

Studio COMBINE

DOCKING COVALENTE

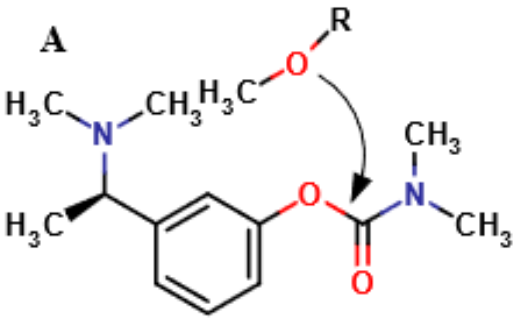


R=Ser-CoX

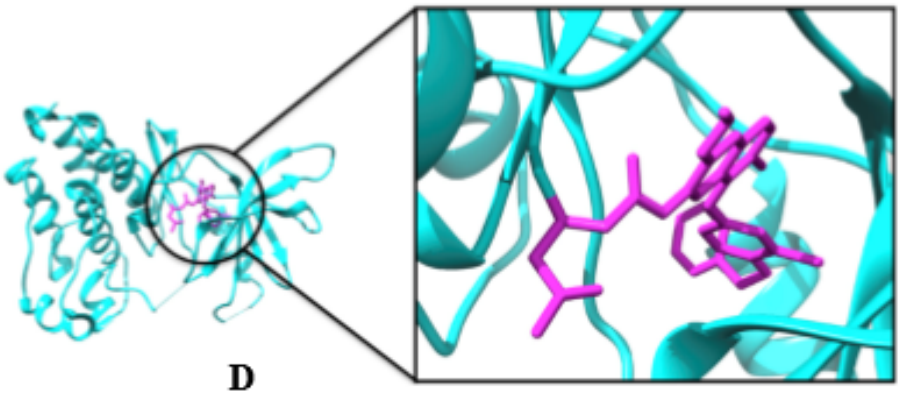


R=Cys-EGFR/HER2

B



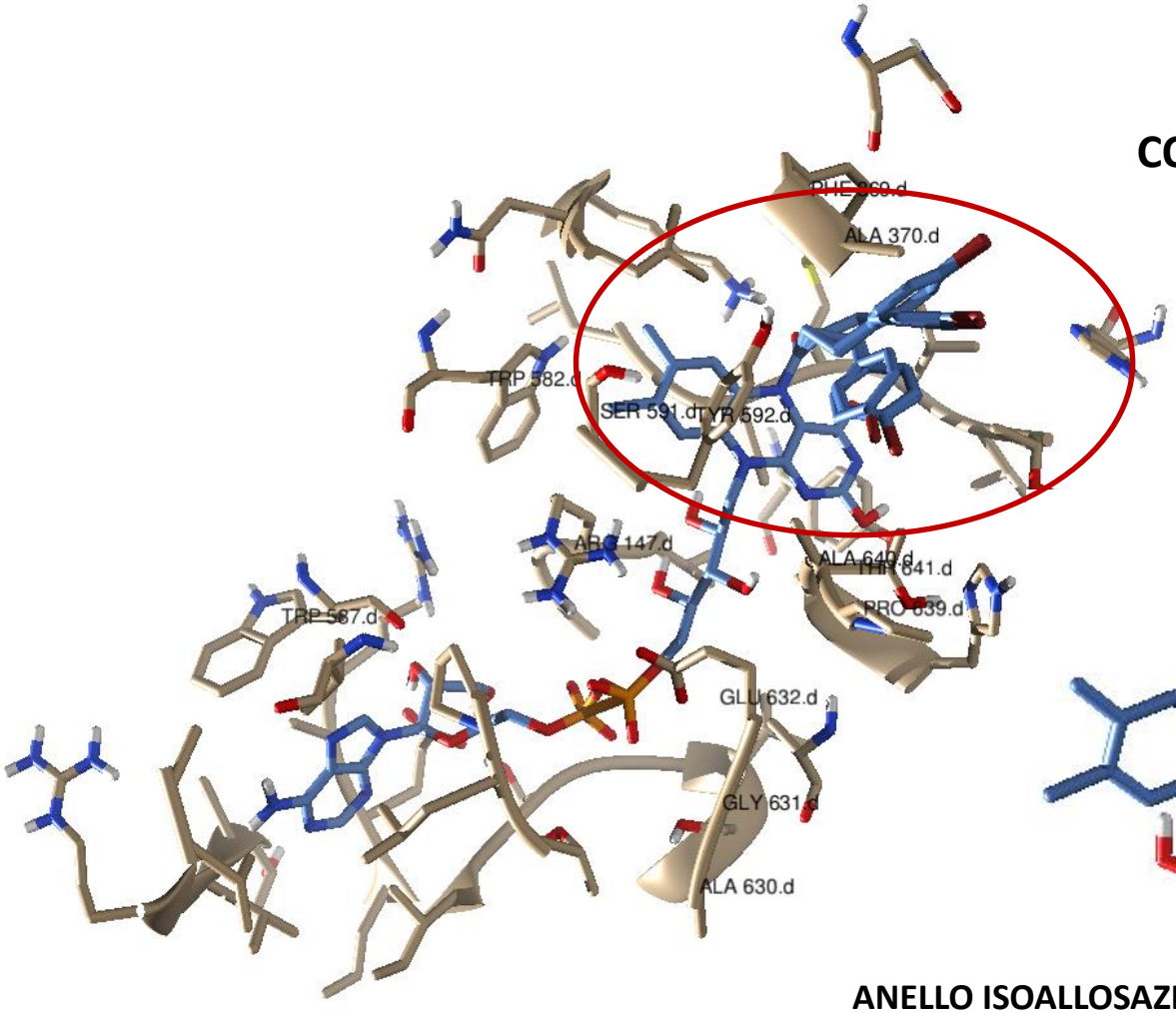
C R=Ser-AChE



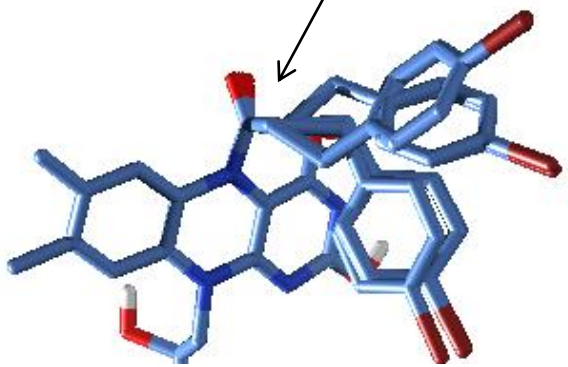
D

Singh, J., et al., The resurgence of covalent drugs. Nat Rev Drug Discov, 2011.

COMPLESSO PDB : 2XAG

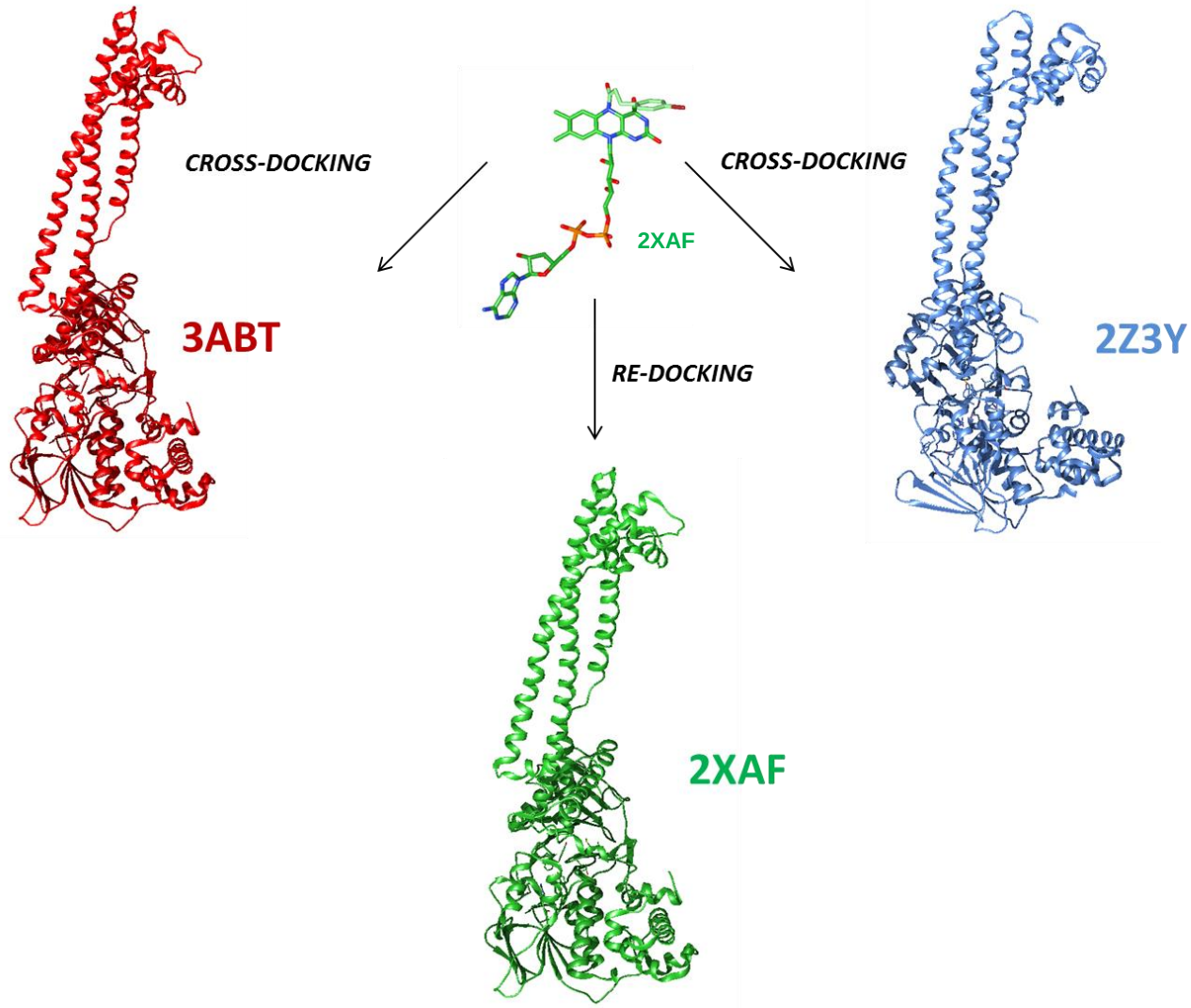


LIGANDO COVALENTE

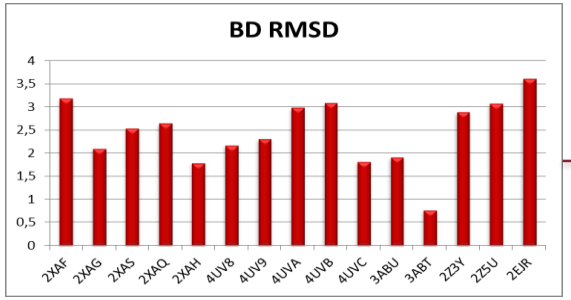


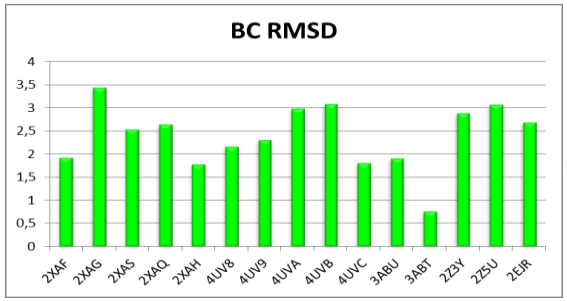
ANELLO ISOALLOSAZINICO FAD

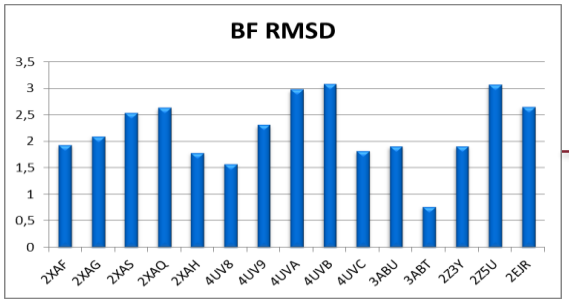
DOCKING COVALENTE

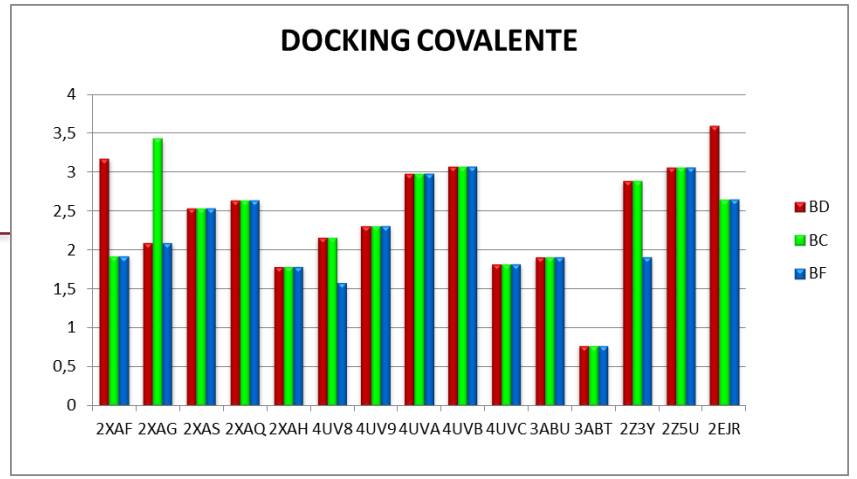


DOCKING COVALENTE: Re-Docking



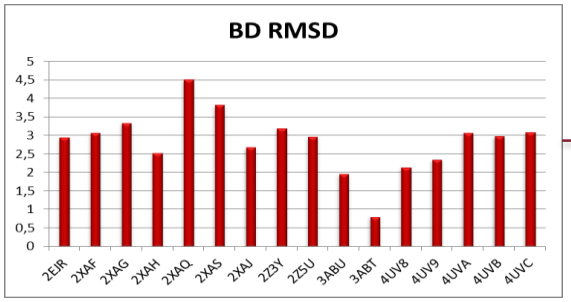


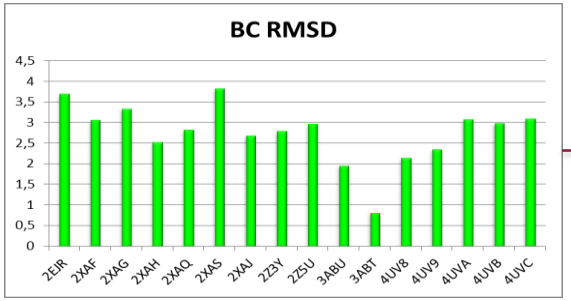


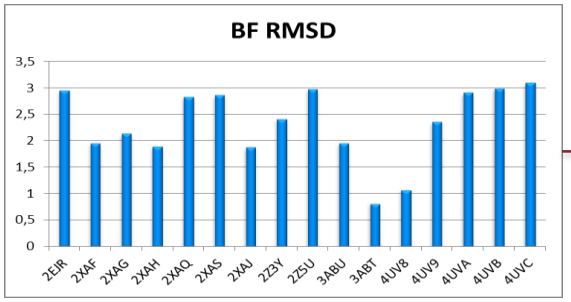


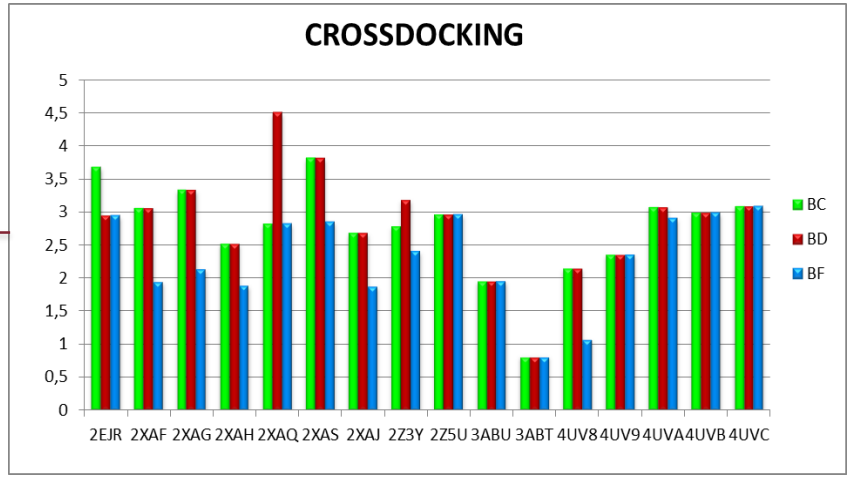
%DA: 68,75%

DOCKING COVALENTE: Cross-Docking









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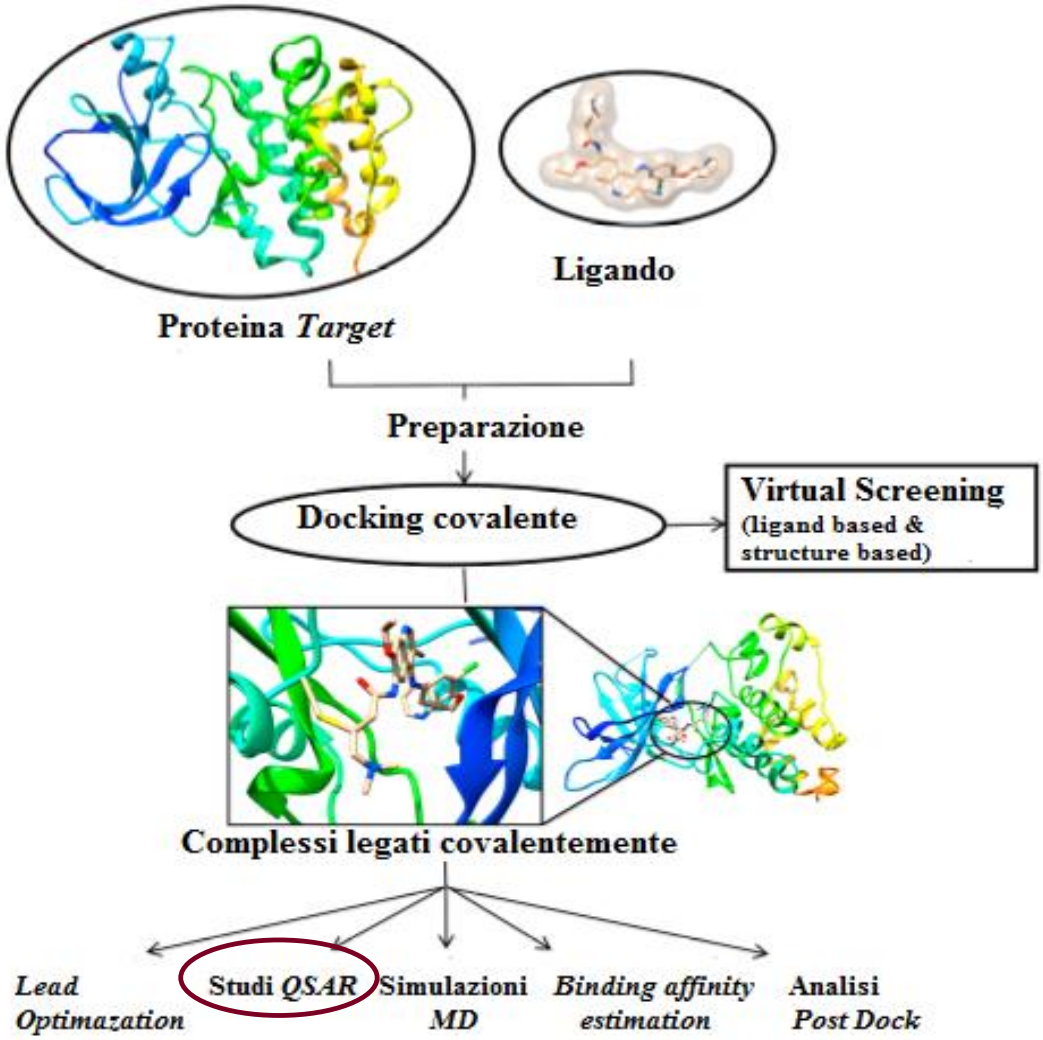
ALTRI STUDI COMPUTAZIONALI



3-D QSAR

KDM1A

Training Set
ATTIVITA' BIOLOGICA : pKi

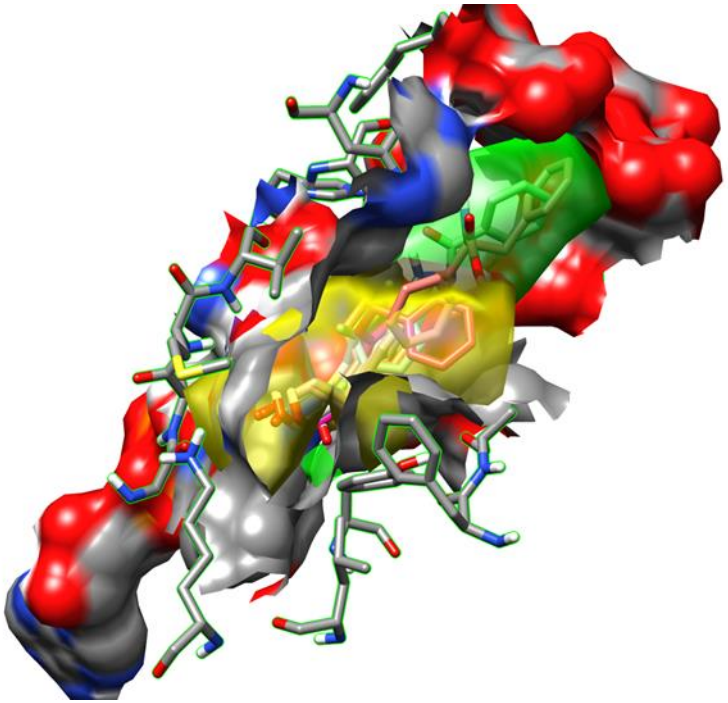
Calcolo dei MIF
(campi di interazione molecolare)

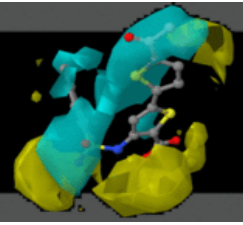
Modello 3-D QSAR preliminare

Validazione Interna

LOO | **Y-Scrambling**

Mappe Tridimensionali





MODELLO PRELIMINARE 3D-QSAR

by www.RCMD.it

TRAINING SET

CODICE ID	ATTIVITA' pKi (Molare)
2XAH	3.55
2XAJ	3.77
3ABU	4
2XAF	4.24
2XAG	4.55
3ABT	4.77
2XAS	5.89
2XAQ	5.96

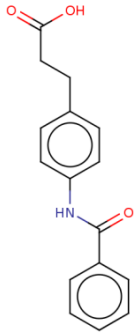
RISULTATI MODELLO PRELIMINARE 3D-QSAR

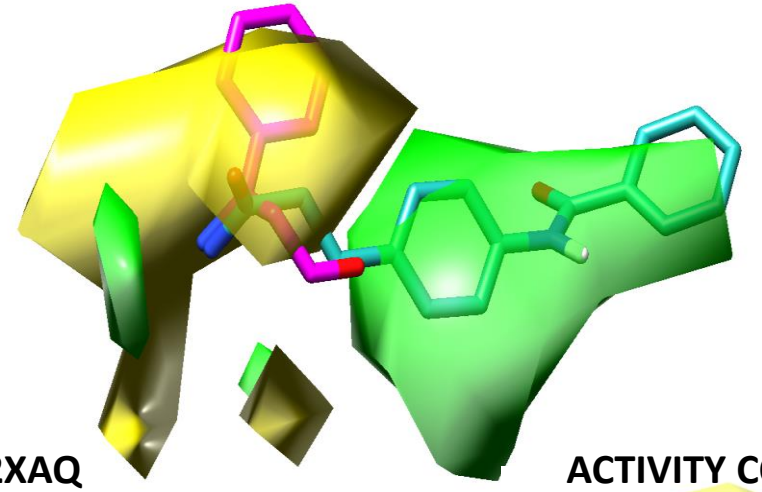
PROBE	PC	r^2	q^2 LOO	q^2 YS
A	2	0,997	0,591	-0,812
C	2	0,978	0,590	-0,624
HD	3	0,999	0,596	-1,276
NA	2	0,978	0,524	-0,553
N	3	0,992	0,596	-0,742
OA	3	0,997	0,590	-0,624
e	2	0,969	0,171	-0,814
d	2	0,916	0,768	-1,973

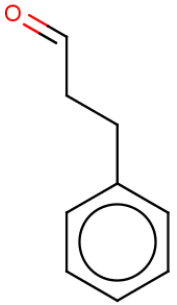
PROBE *C*

STUDIO MAPPE COMFA2

2XAQ

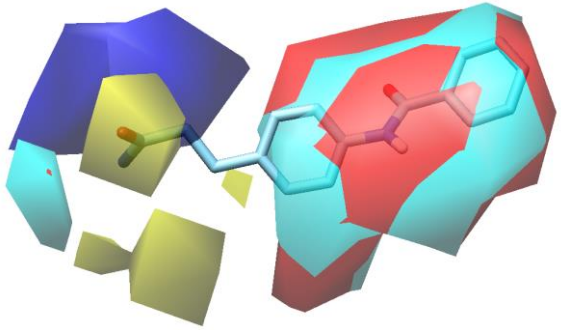




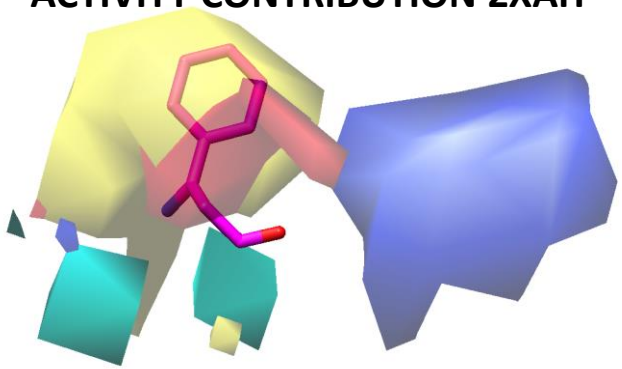


2XAH

ACTIVITY CONTRIBUTION 2XAQ



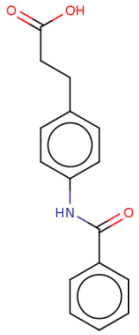
ACTIVITY CONTRIBUTION 2XAH

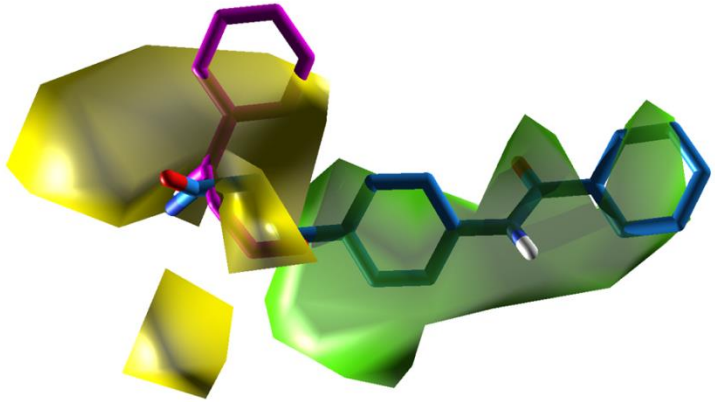


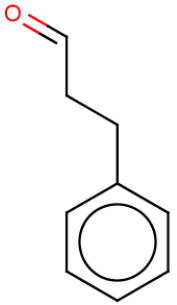
PROBE *HD*

STUDIO MAPPE COMFA2

2XAQ

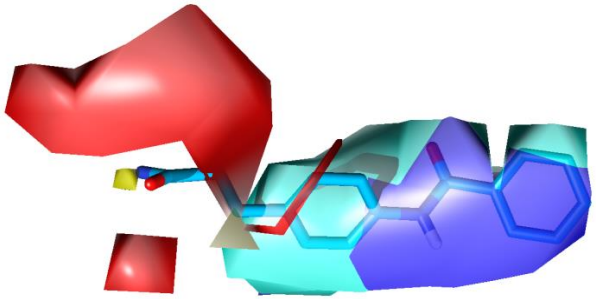


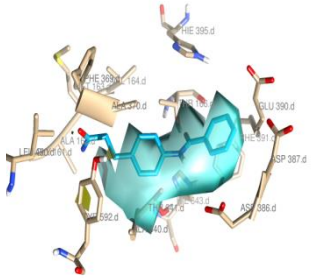




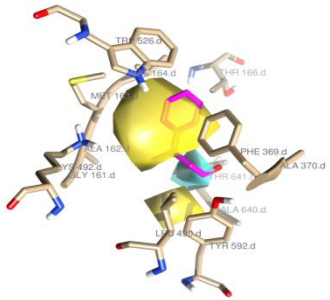
2XAH

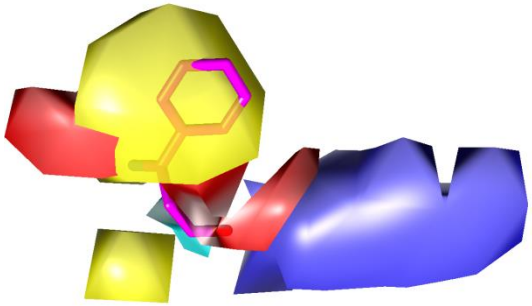
ACTIVITY CONTRIBUTION 2XAQ

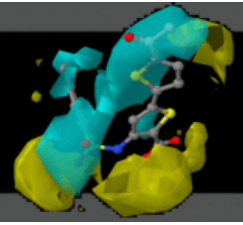




ACTIVITY CONTRIBUTION 2XAH







COMBINE

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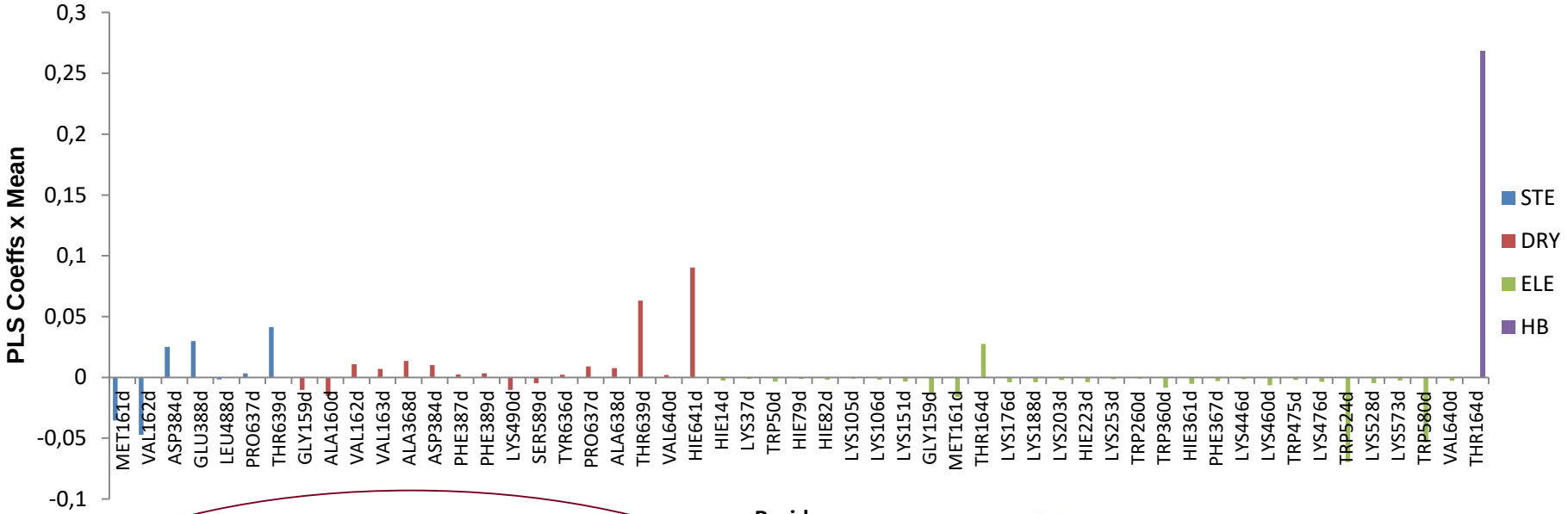
TRAINING SET

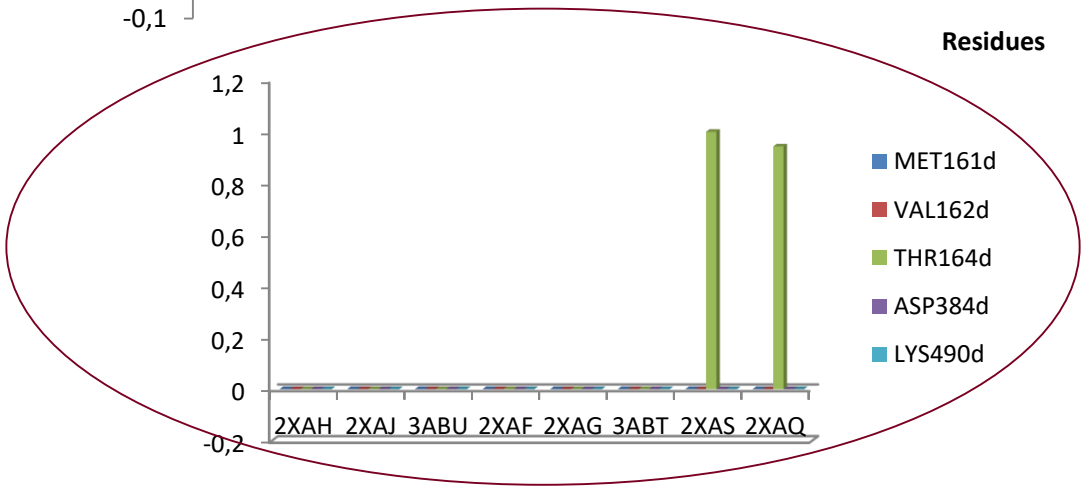
CODICE ID	ATTIVITA' pKi (Molare)
2XAH	3.55
2XAJ	3.77
3ABU	4
2XAF	4.24
2XAG	4.55
3ABT	4.77
2XAS	5.89
2XAQ	5.96

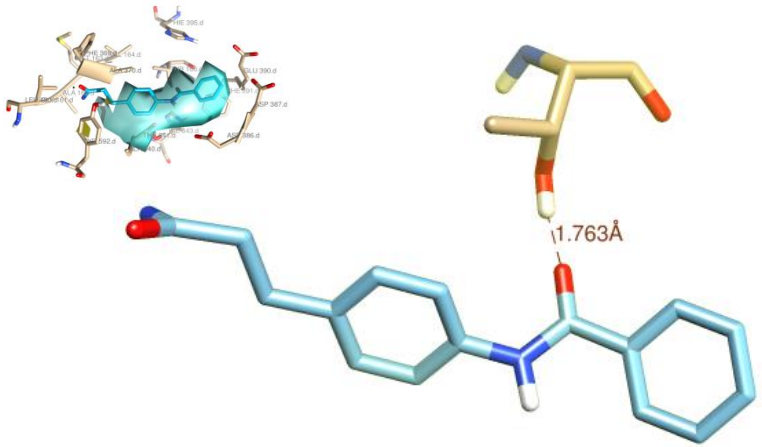
RISULTATI MODELLO PRELIMINARE COMBINE

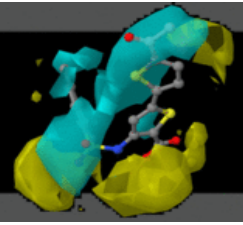
PROBE	PC	r^2	q^2LOO
STE	2	0,949	0,741
DRY	3	0,951	0,358
ELE	2	0,844	0,676
HB	2	0,853	0,596
STE-DRY	1	0,817	0,542
STE-ELE	2	0,951	0,668
STE-HB	1	0,832	0,504
DRY-ELE	2	0,929	0,722
DRY-HB	1	0,854	0,569
ELE-HB	2	0.946	0,866
STE-DRY-ELE	2	0,924	0,699
STE-DRY-HB	1	0,850	0,567
STE-ELE-HB	3	0,962	0,811
DRY-ELE-HB	2	0,943	0,790
STE-DRY-ELE-HB	2	0,940	0,743

COMBINE: RISULTATI







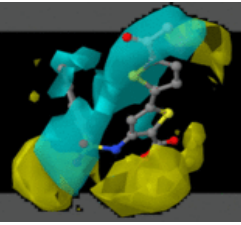


CONCLUSIONI

STUDIO *STRUCTURE-BASED* DI *DOCKING* MOLECOLARE

CREAZIONE MODELLO 3-D QSAR

STUDIO COMBINE



OBIETTIVI FUTURI

by www.RCMD.it

- AMPLIARE IL NUMERO DI MOLECOLE DA STUDIARE
- CREARE MODELLI PIU' GENERALIZZATI E GLOBALI
- PROGETTAZIONE DI NUOVI INIBITORI

GRAZIE PER L'ATTENZIONE

«C'è una forza motrice più forte del vapore, dell'elettricità e dell'energia atomica: la volontà.»
Albert Einstein