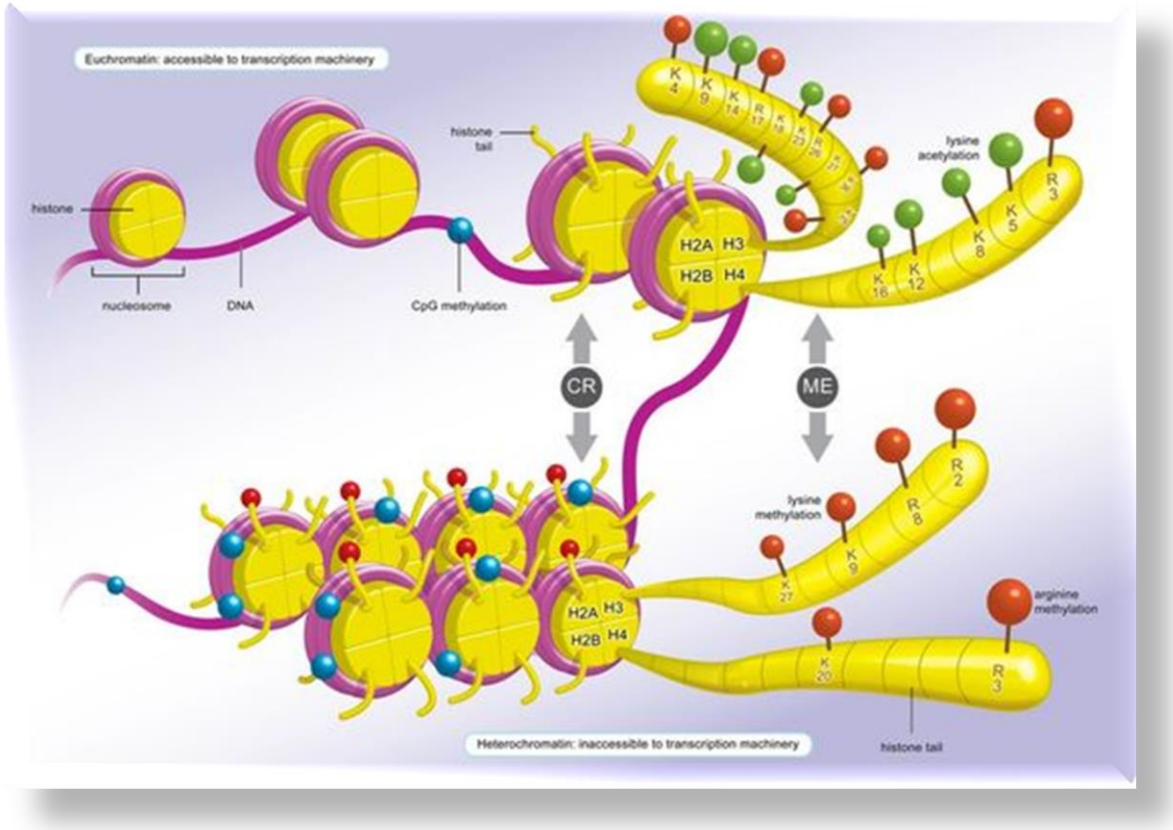
Studi computazionali su inibitori reversibili della demetilasi istonica 1 specifica per la lisina (KDM1A)

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi sperimentale in Chimica Farmaceutica
A.A. 2015/2016

Laureanda Gioia Tesone

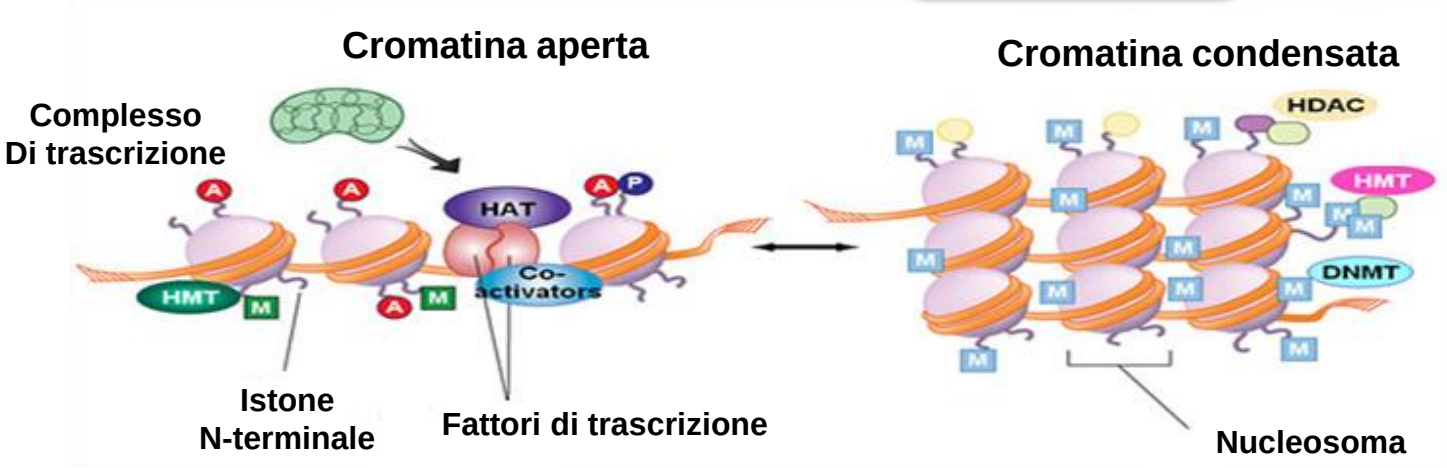
Relatore: prof. Rino Ragno



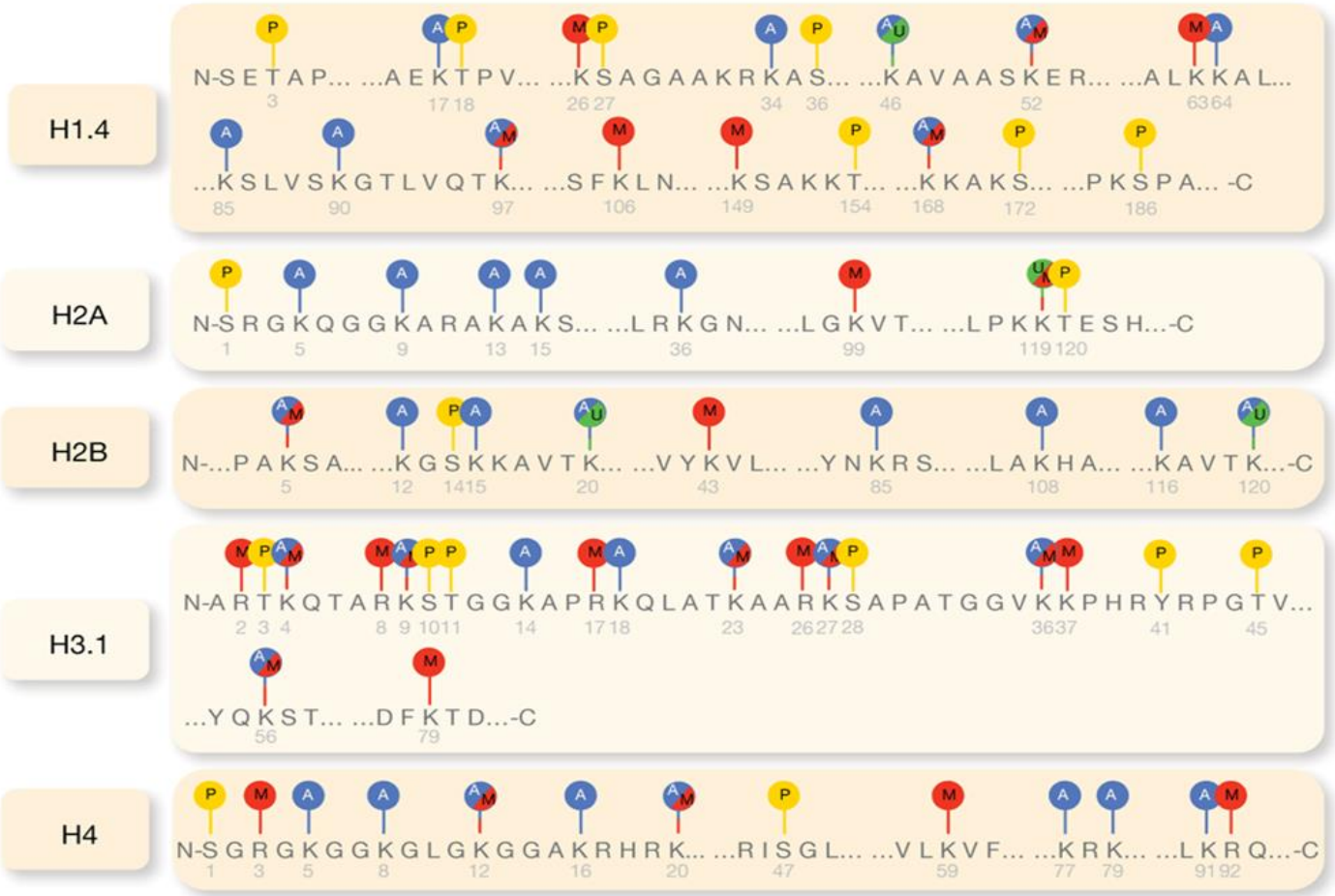
L'epigenetica comporta modifiche nella regolazione e nell'attività dei geni

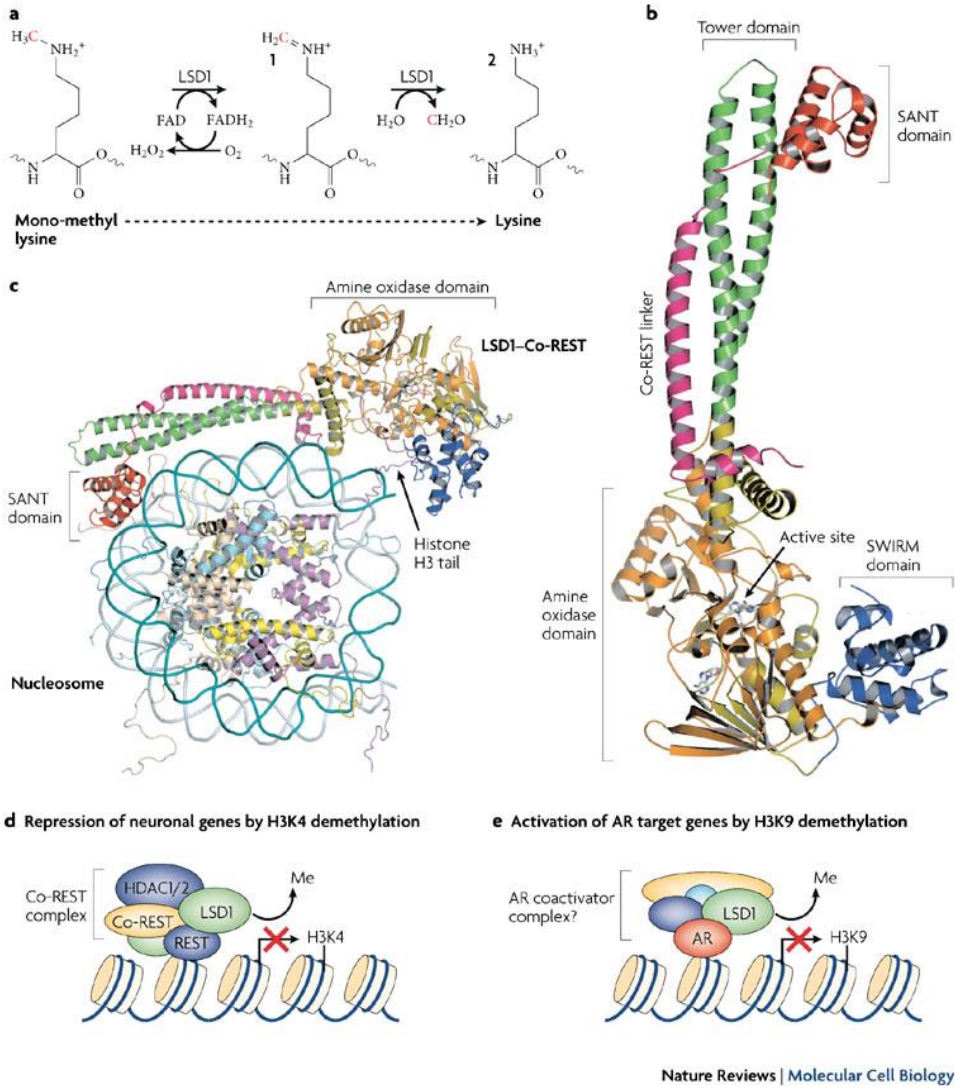
Rimodellamento della Cromatina

- **Metilazione DNA**
- **Modifiche post-traduzionali code istoniche**

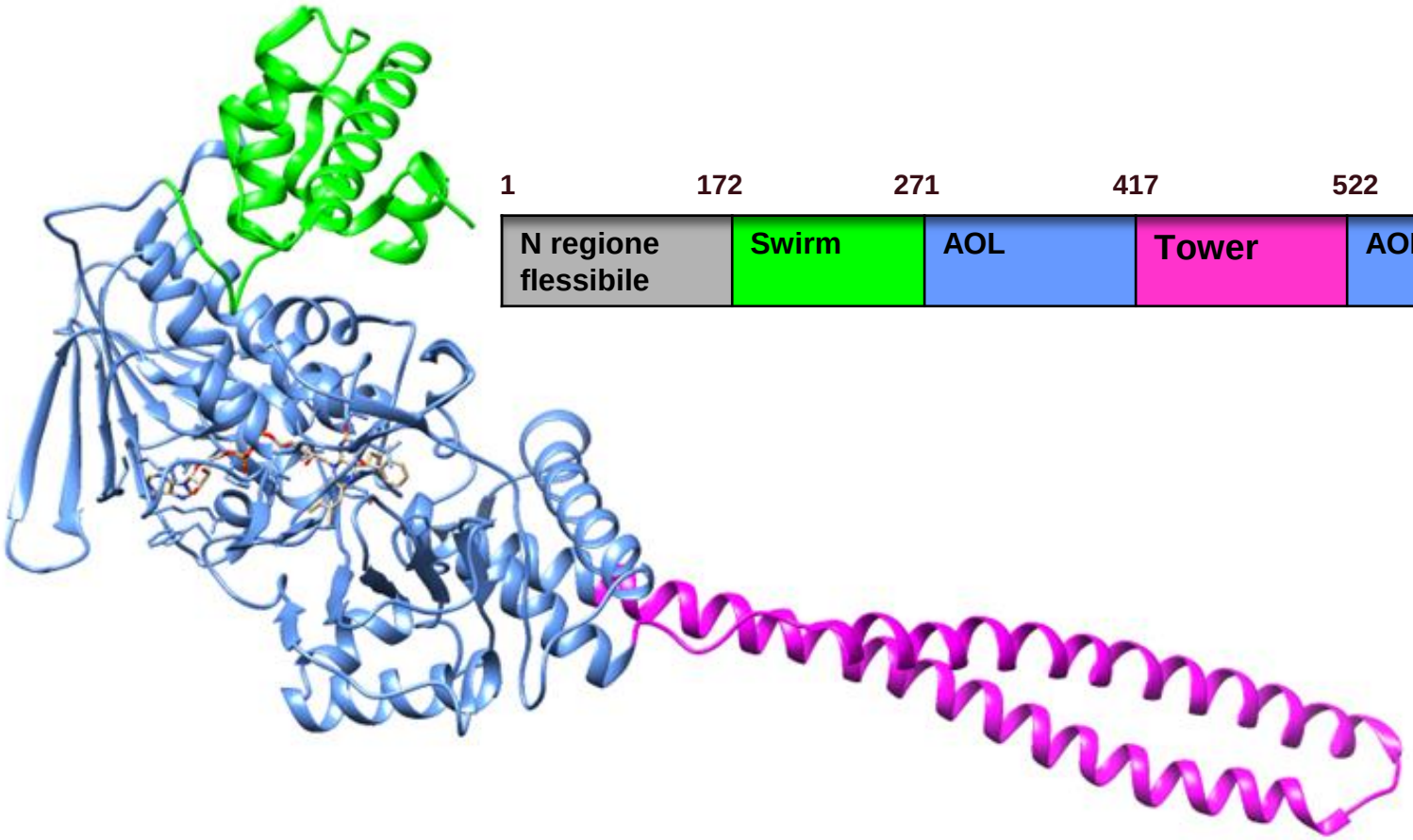


MODIFICHE CODE ISTONICHE



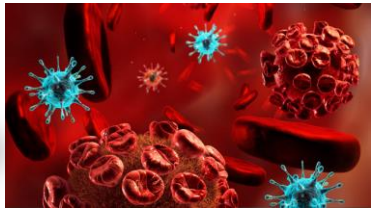

a
LSD1
FAD FADH2
H2O2 O2
1
LSD1
H2O CH2O
2
Mono-methyl lysine
Lysine
b
Tower domain
SANT domain
Co-REST linker
Active site
SWIRM domain
Amine oxidase domain
c
Amine oxidase domain
LSD1–Co-REST
SANT domain
Histone H3 tail
Nucleosome
d Repression of neuronal genes by H3K4 demethylation
Co-REST complex
HDAC1/2
Co-REST
LSD1
REST
Me
H3K4
e Activation of AR target genes by H3K9 demethylation
AR coactivator complex?
LSD1
AR
Me
H3K9
Nature Reviews | Molecular Cell Biology

LSD1

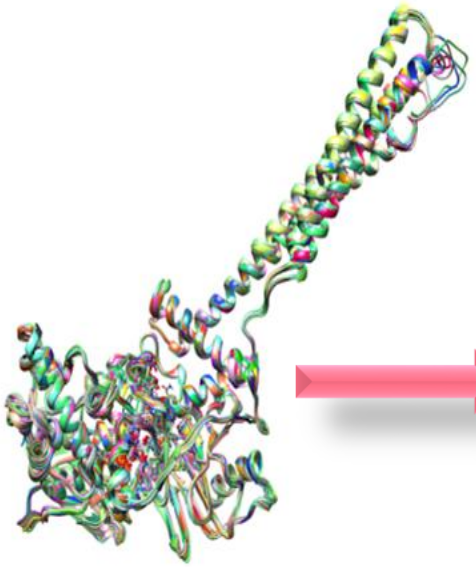


1
172
271
417
522
833
852
N regione flessibile
Swirm
AOL
Tower
AOL
Coda C

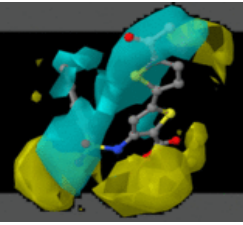
OBIETTIVO TESI

LSD1 → **Carcinogenesi** → 

Leucemia Mieloide Acuta

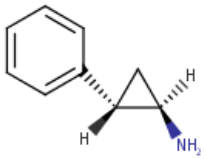


→ **Creazione di nuovi modelli matematico statistici** → **Progettazione Nuovi Inibitori Reversibili**

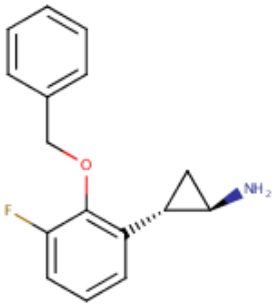


COMPLESSI PDB DERIVATI DELLA TRANILCIPROMINA

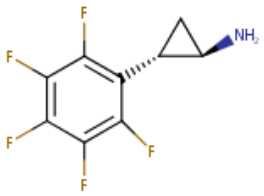
by www.RCMD.it



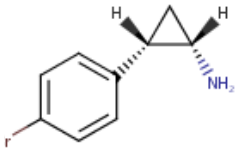
2EJR
2Z3Y
2Z5U



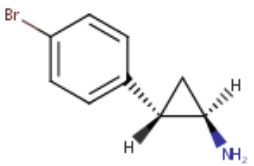
3ABU



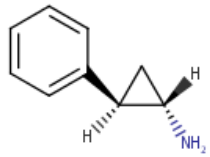
3ABT



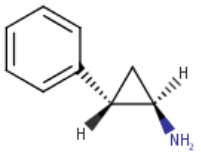
2XAF



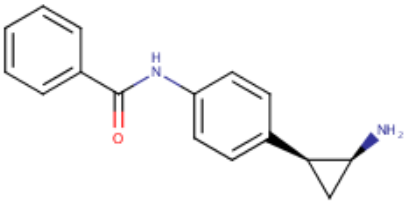
2XAG



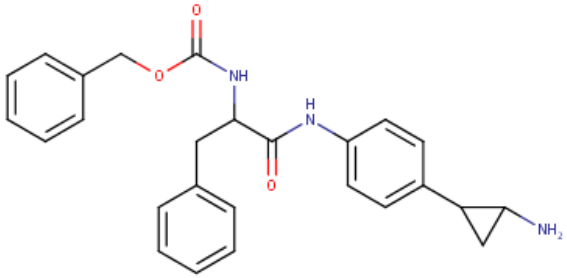
2XAH



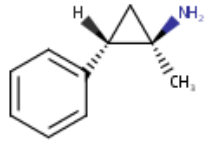
2XAJ



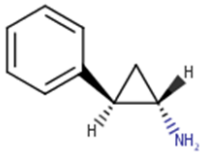
2XAQ



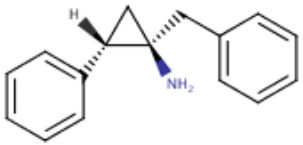
2XAS



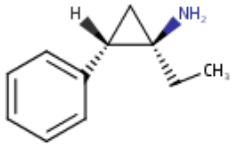
4UVA



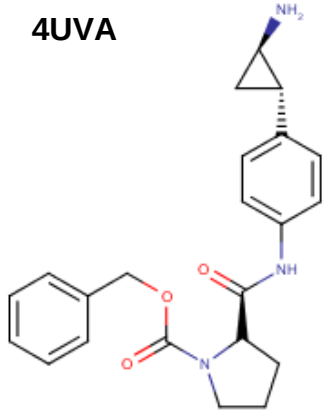
4UVB



4UV8



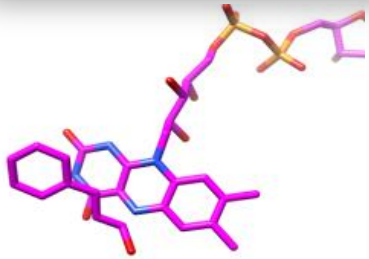
4UV9



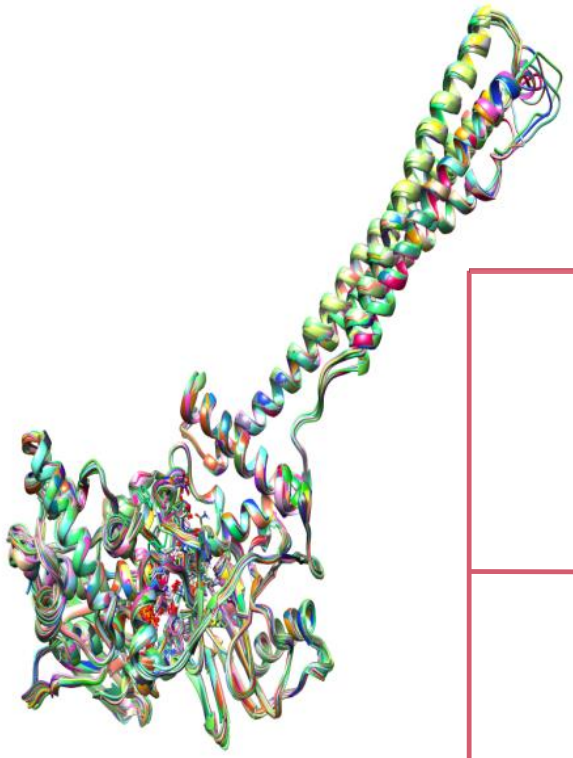
4UXN

Rottura del legame covalente : Formazione complessi reversibili

Complessi covalenti scaricati dal PDB



Minimizzazione Gromacs 1000 steps convergenza

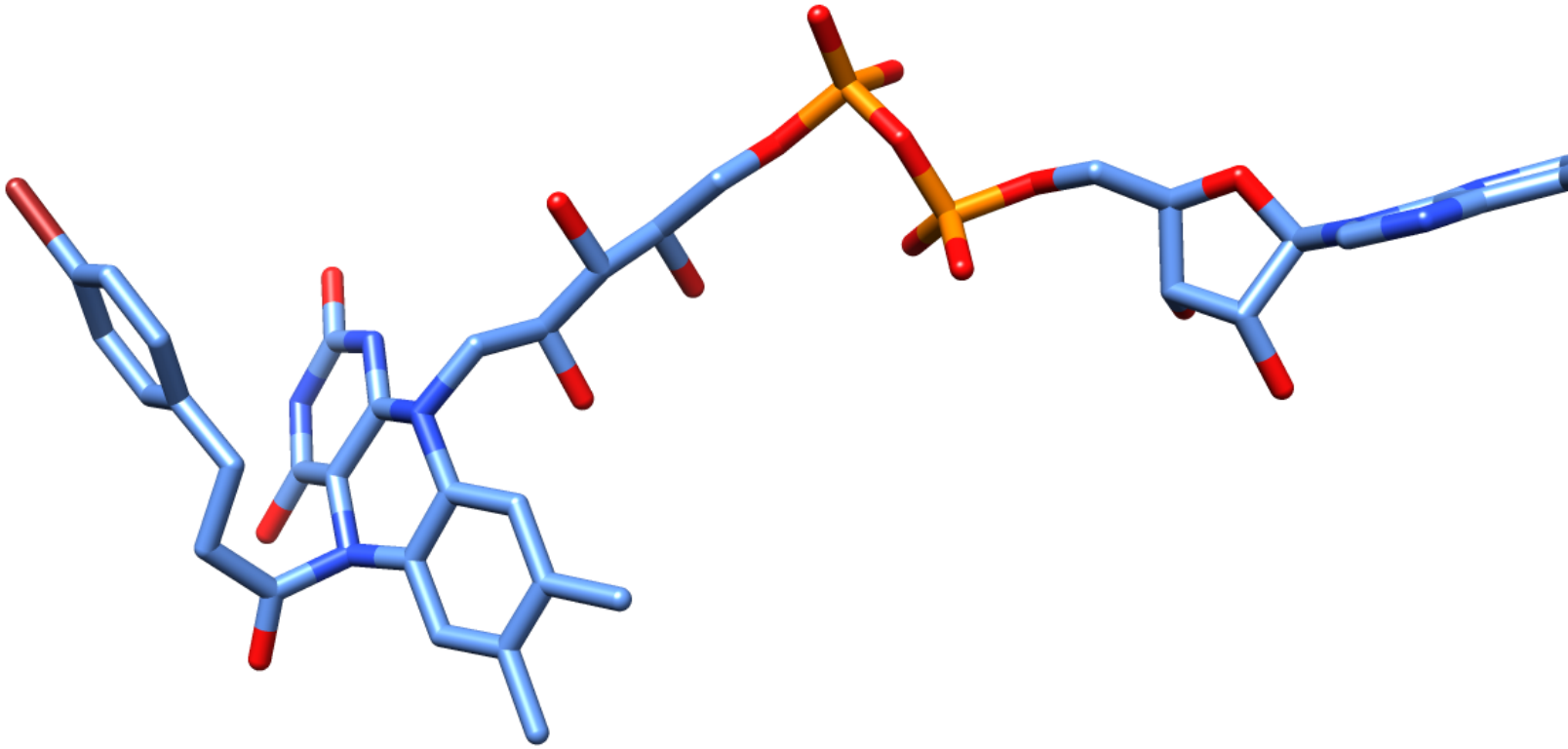


Allineamento Match Maker structure -based

Modelli 3-D QSAR

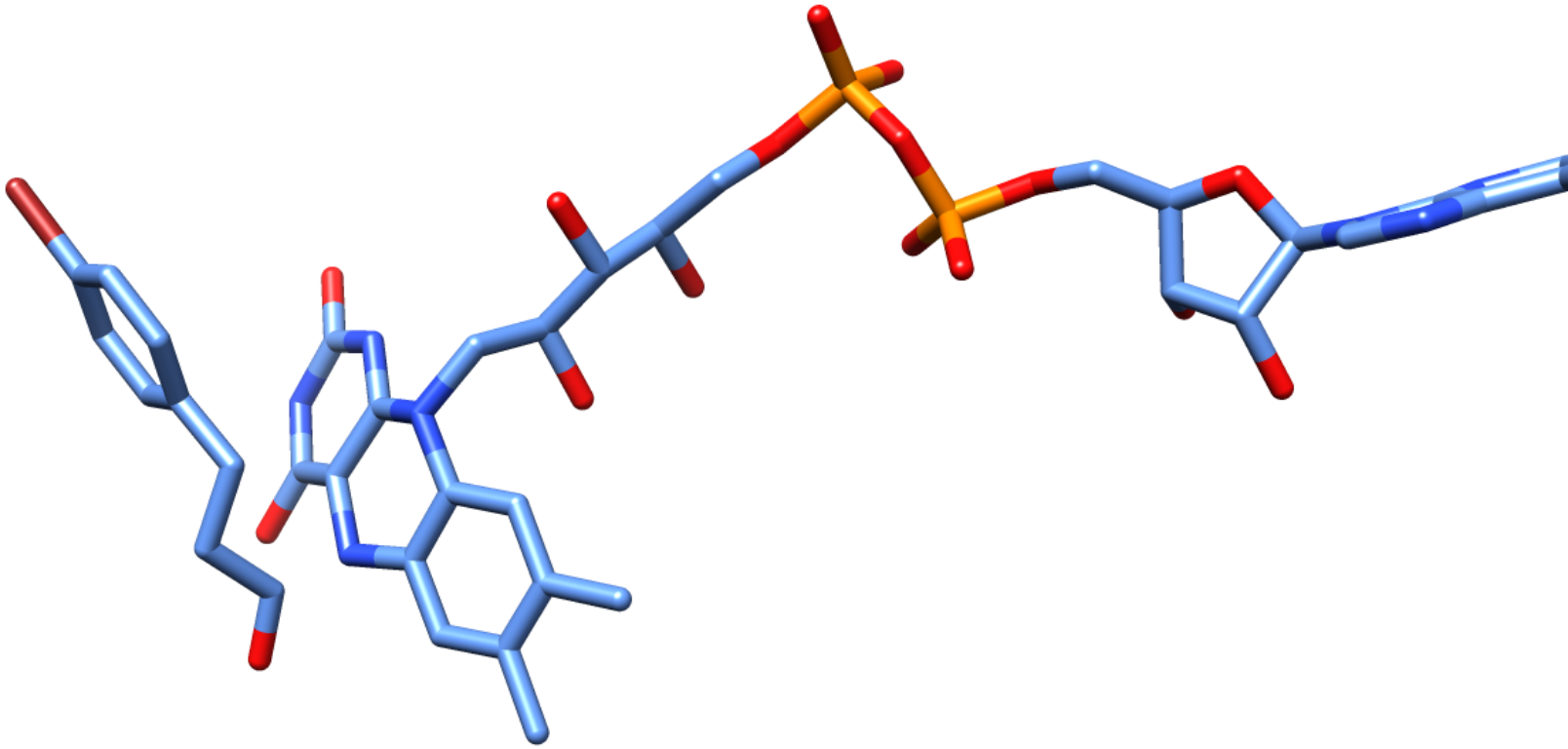
Modelli COMBINE

Metodologie sperimentali : Costruzione inibitori reversibili

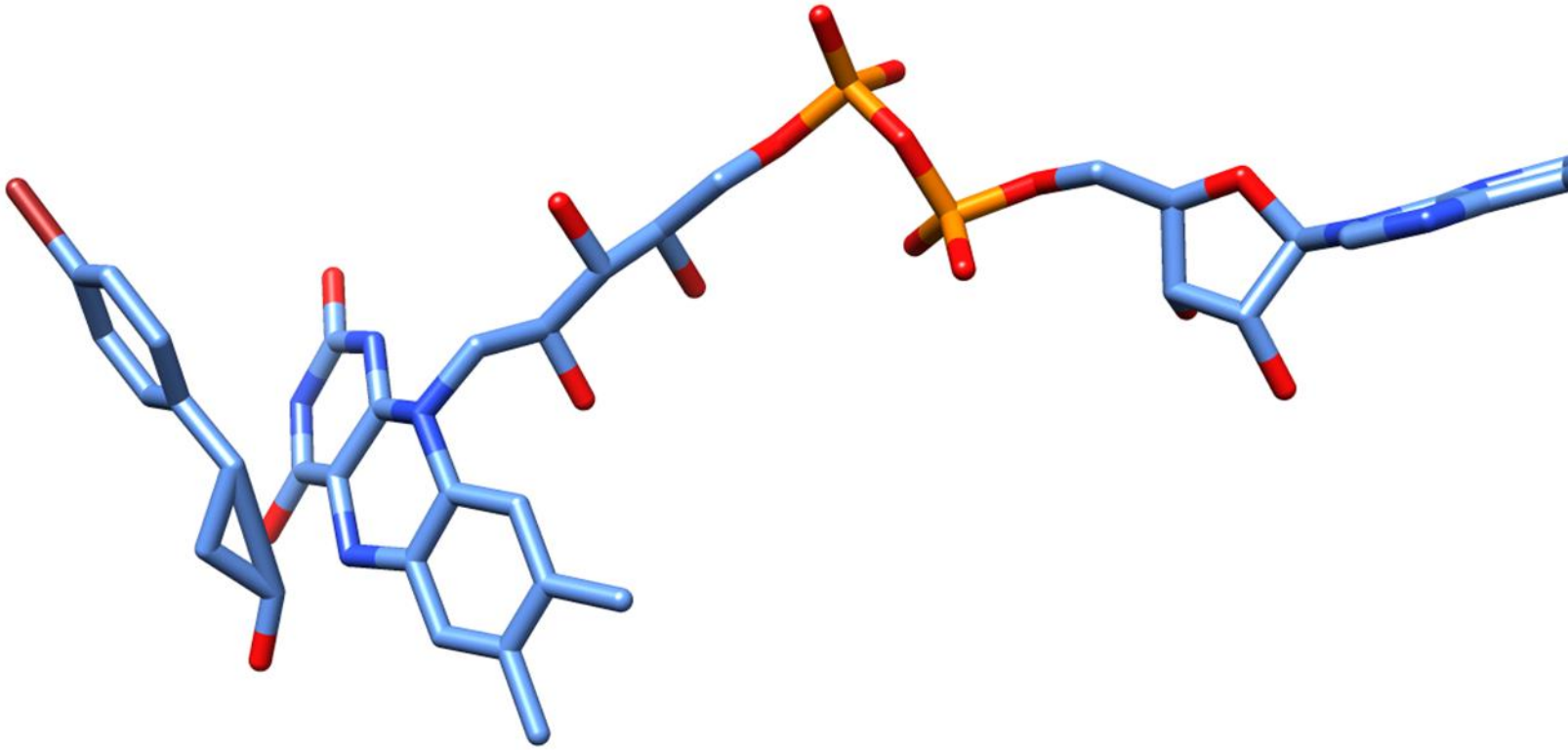


Complesso covalente 2XAG: FAD +Tranilcipromina

Metodologie sperimentali : Costruzione inibitori reversibili

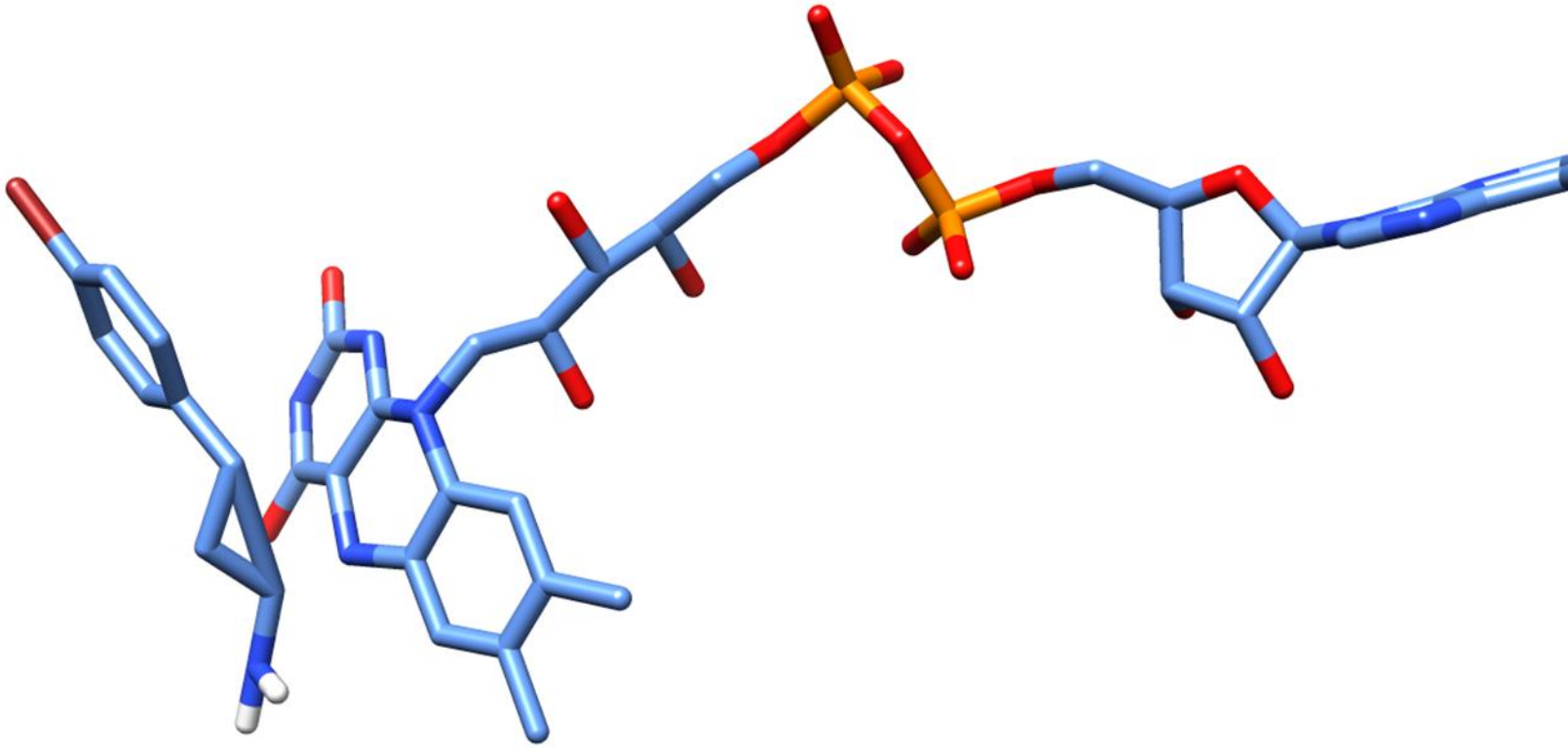


Rottura legame covalente N5 FAD e C1 ciclopropano



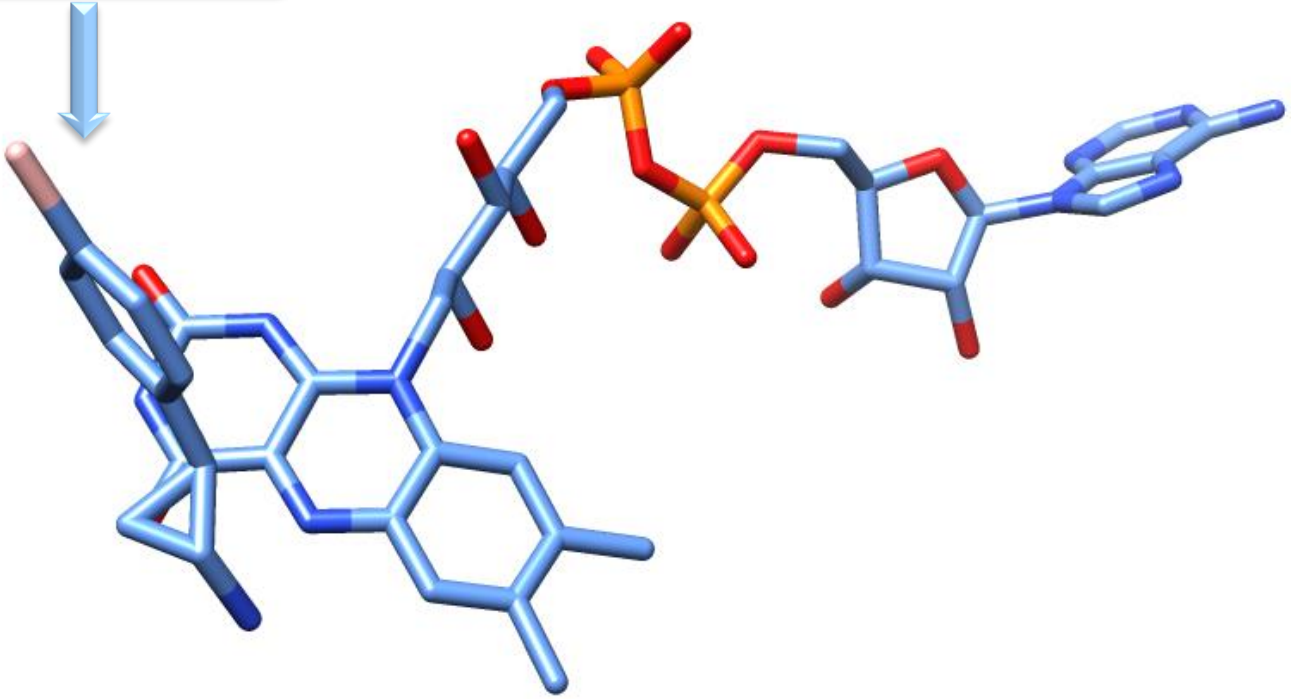
Formazione Complesso reversibile
Aggiunta del legame C-C per la formazione del ciclopropano

Formazione del complesso reversibile

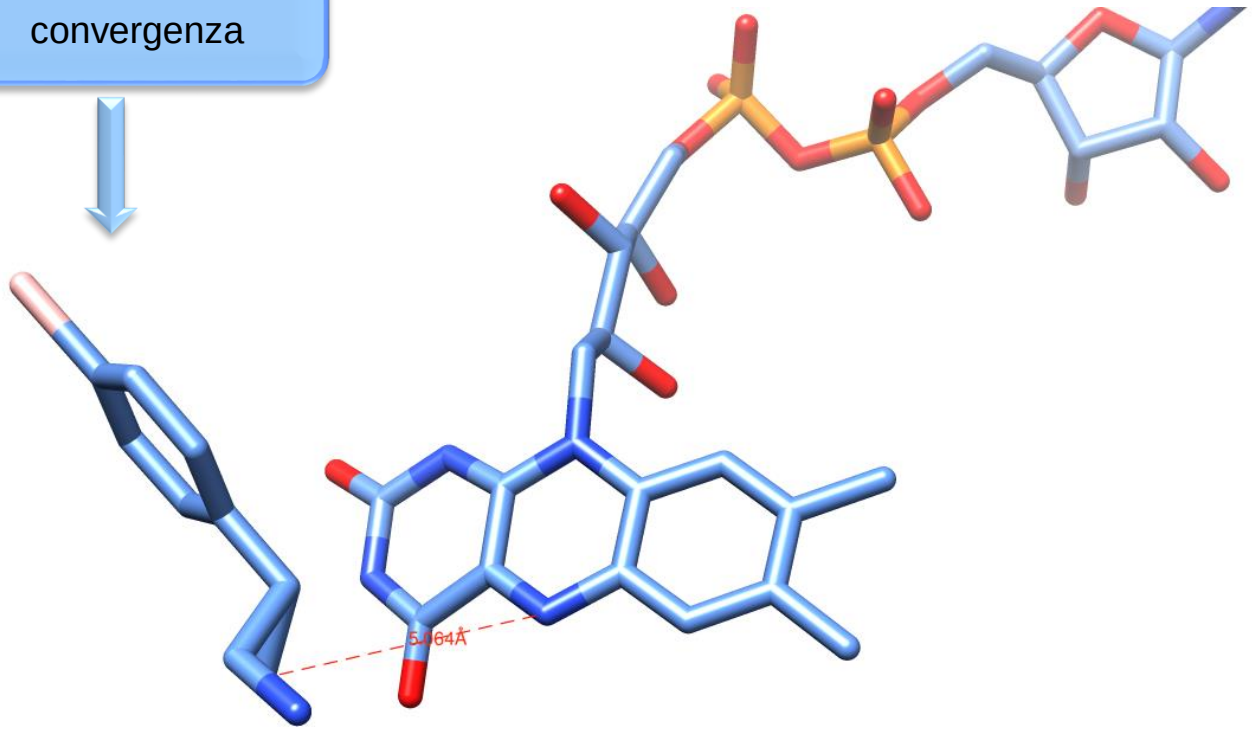


Sostituzione del gruppo chetonico sul C1 del ciclopropano con il gruppo amminico: formazione Tranilcipromina

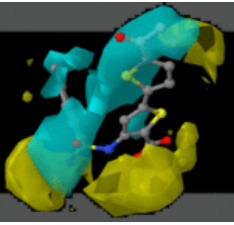
Complesso 2XAG
1000 steps

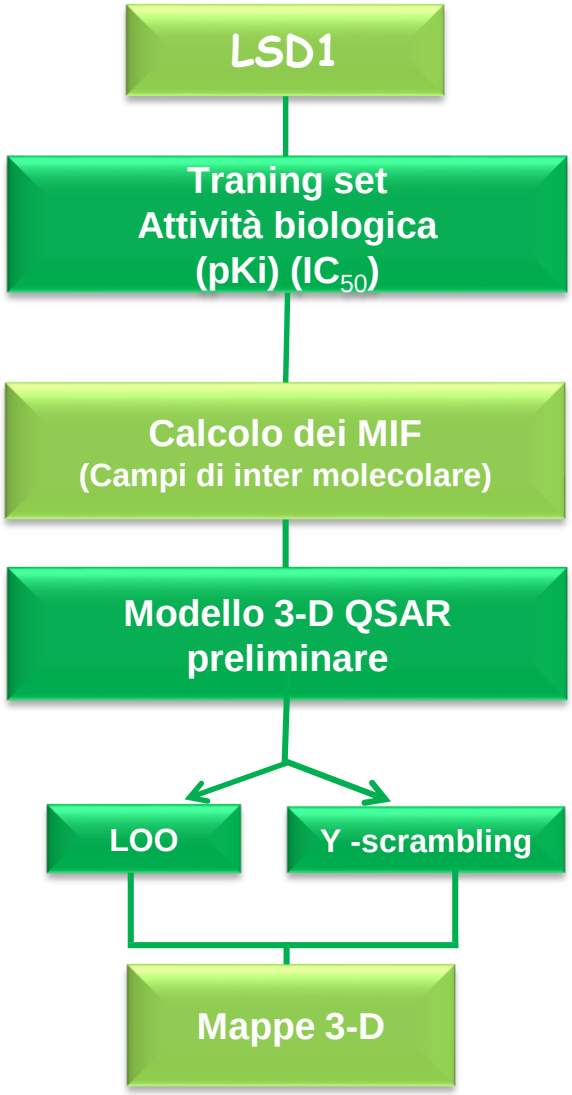


2XAG
convergenza



3-D QSAR

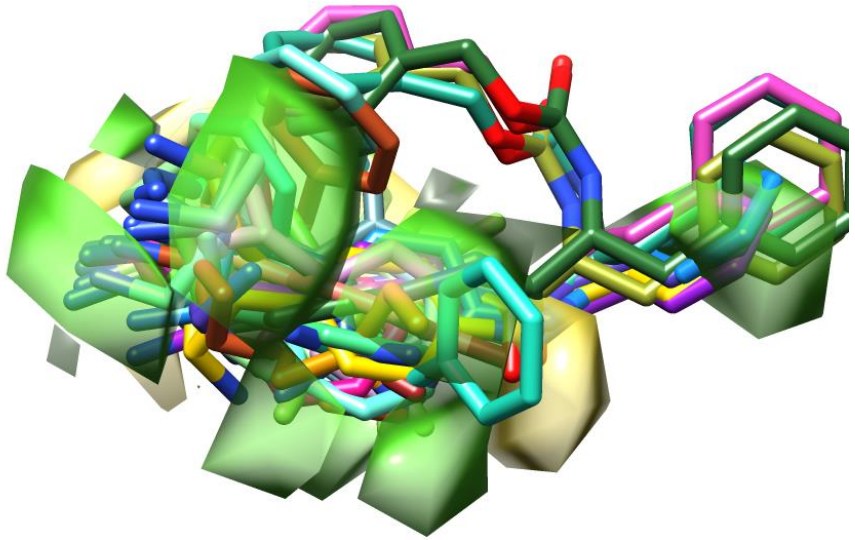


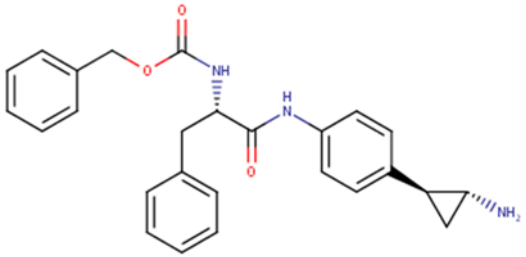


CODICE ID	ATTIVITÀ	CODICE ID	ATTIVITÀ
2EJR(1S)(2R)	5.7	2XAS(1R)(1S)(2R)	7.30
2EJR(1R)(2S)	5.7	2XAS(1S)(1R)(2S)	6.44
2XAF(1S)(2S)	4.64	2XAS(1S)(1S)(2R)	7.52
2XAG(1R)(2S)	4.55	3ABT(1R)(2S)	5.05
2XAH(1S)(2R)	3.55	3ABT(1S)(2R)	5.05
2XAJ(1R)(2S)	3.77	3ABU(1R)(2S)	5.09
2XAQ(1R)(2R)	5.96	3ABU(1S)(2R)	5.09
2XAQ(1R)(2S)	5.96	4UV8(1S)(2S)	6.48
2XAQ(1S)(2R)	5.96	4UV9(1R)(2S)	6.01
2XAQ(1S)(2S)	5.96	4UVA(1R)(2S)	5.75
2XAS(1R)(1R)(2S)	6.41	4UVB(1S)(2R)	5.49

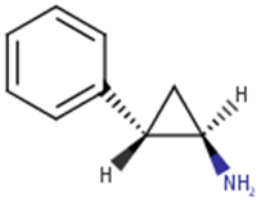
Risultati 3-D QSAR

PROBE	PC	r^2	q^2_{LOO}	q^2_{YS}
A	4	0.977	0.734	-0.856
C	4	0.978	0.734	-0.647
OA	4	0.984	0.670	-0.725
N	4	0.980	0.701	-0.560
d	5	0.882	0.701	-1.216
NA	4	0.983	0.673	-0.581
HD	4	0.990	0.669	-0.537

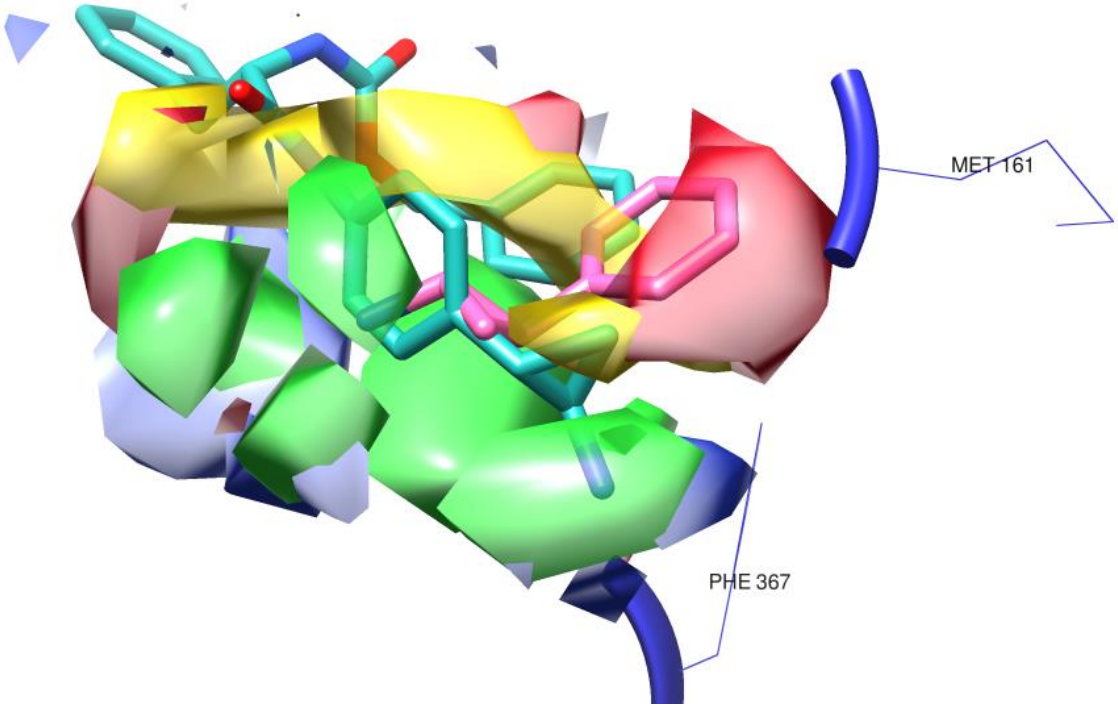




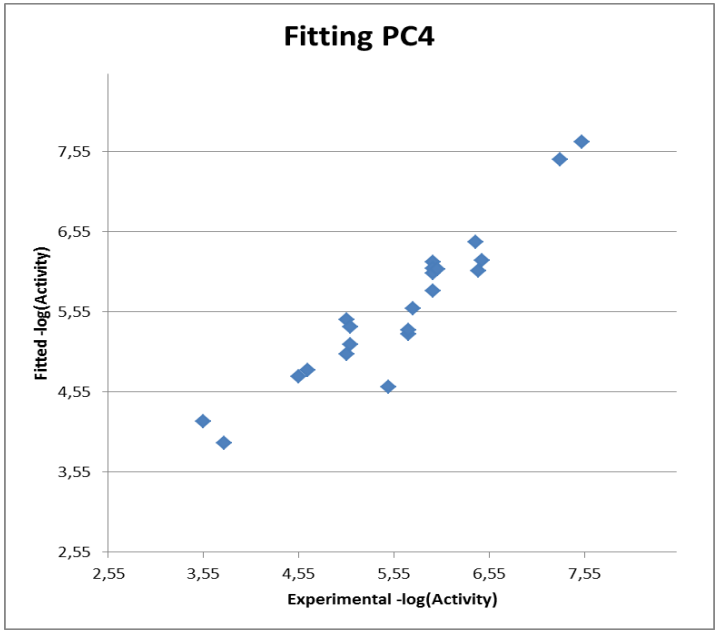
2XAS (1S) (1S)(2R) IC_{50} = 0,03 µM

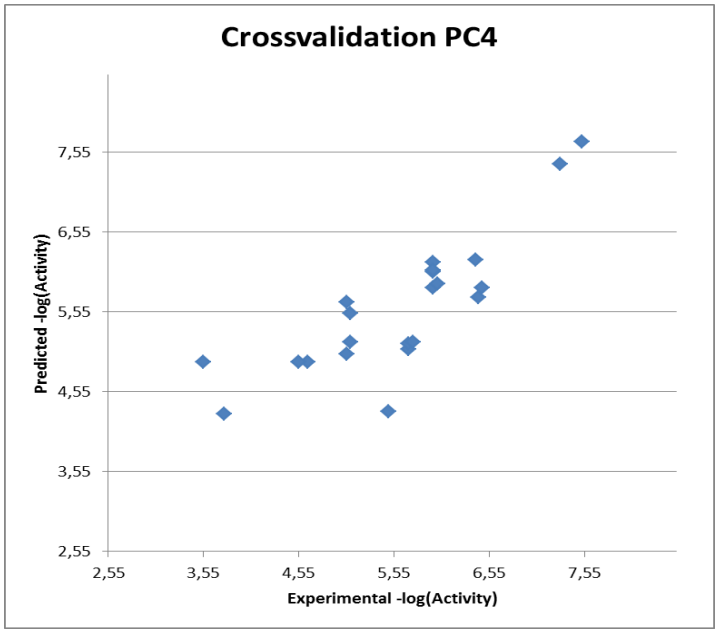


2XAH Ki=168 µM



COMBINE RISULTATI STATISTICI





PROBE	PC	r^2	q^2_{LOO}	q^2_{YS}
STE-DRY-ELE-HB	4	0,89	0,679	-0,972


ASP 384
ALA 368
PHE 367

0,45
0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
-0,05
PHE367
VAL163
ASP384
SER589
LEU158
GLY159
ALA160
MET161
VAL162
VAL163
THR164
LYS184
LYS186
ALA363
ASN364
LEU365
GLU366
PHE367
ALA368
ASN369
ALA370
HIE380
TRP381
GLN383
ASP384
ASP385
ASP386
PHE387
GLU388
PHE389
SER392
HIE393
ASN487
LEU488
ASN489
PHE523
TRP524
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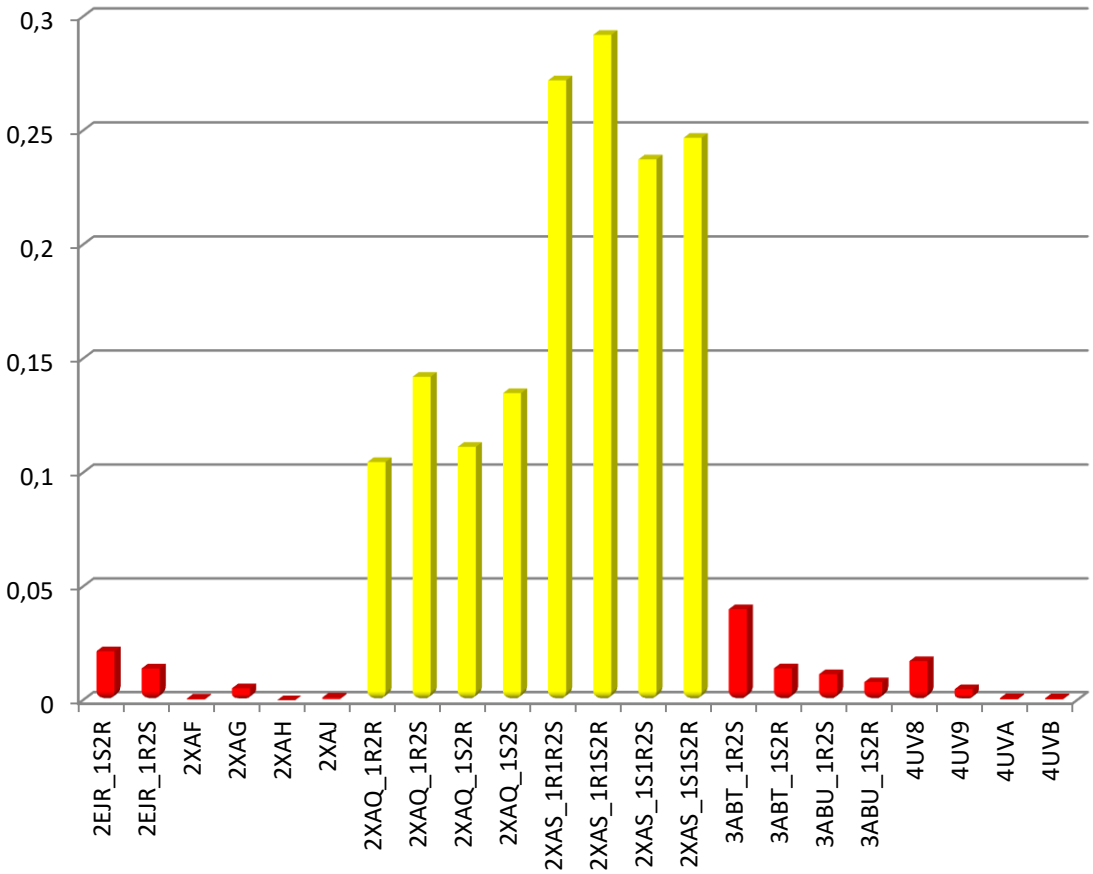
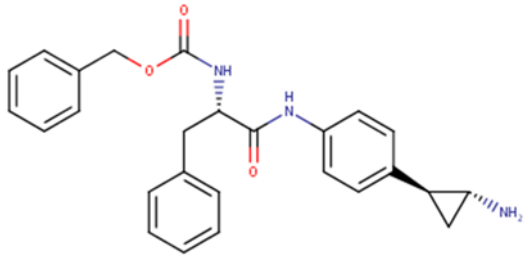
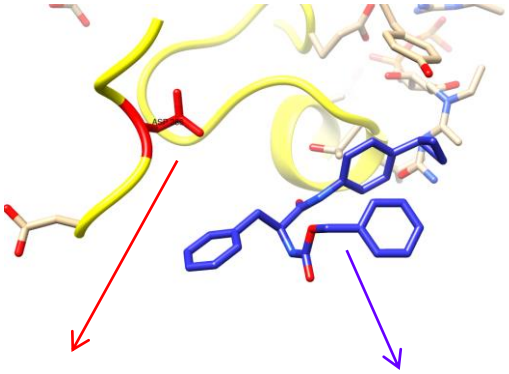
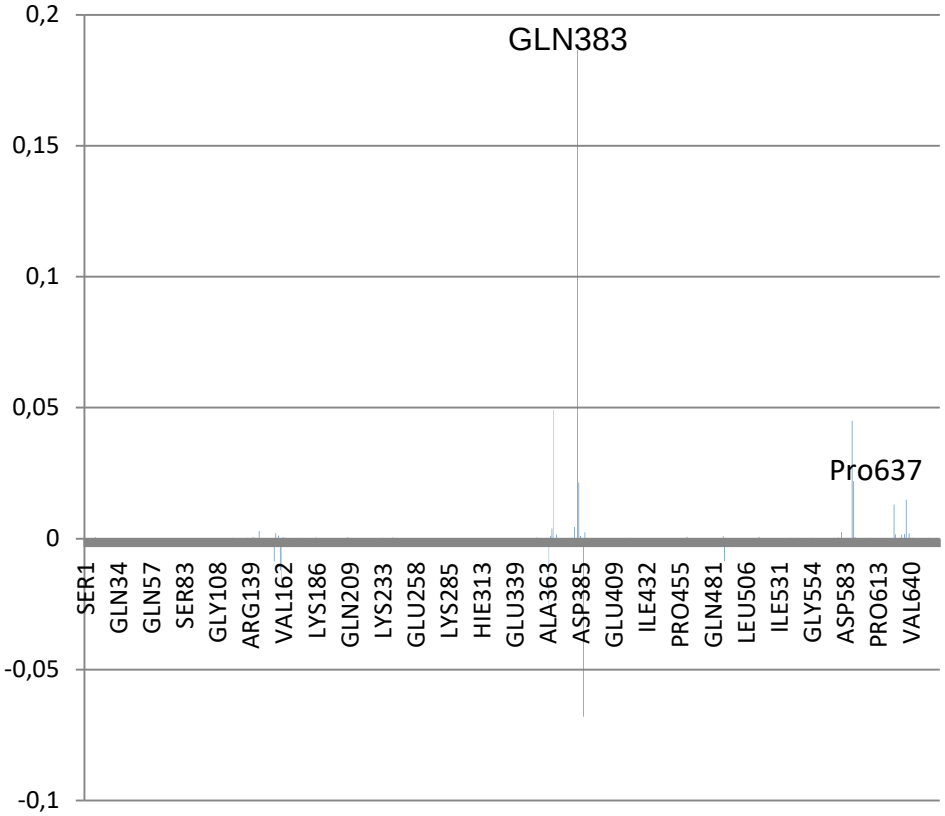




2XAS(1S)(1S)(2R) IC50 = 0,03 µM




GLN383
Pro637
0,2
0,15
0,1
0,05
0
-0,05
-0,1
SER1
GLN34
GLN57
SER83
GLY108
ARG139
VAL162
LYS186
GLN209
LYS233
GLU258
LYS285
HIE313
GLU339
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GLU409
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ILE531
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PRO613
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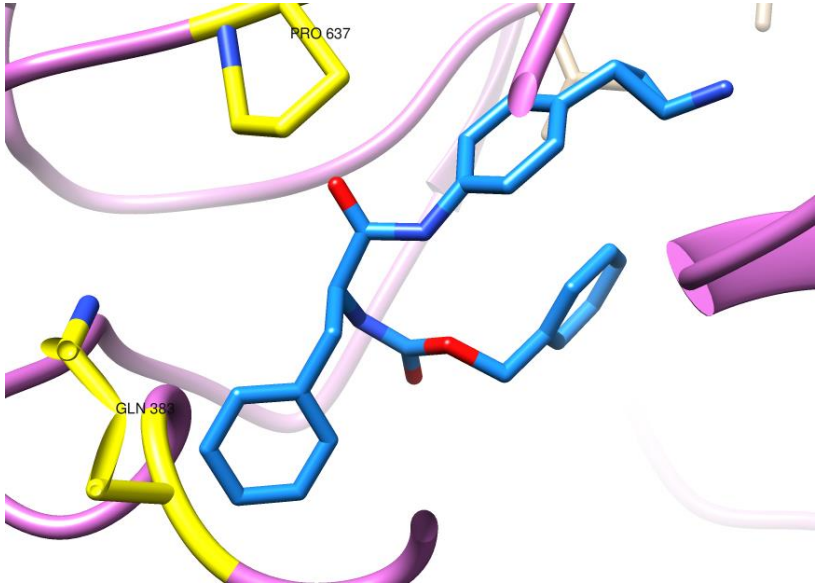
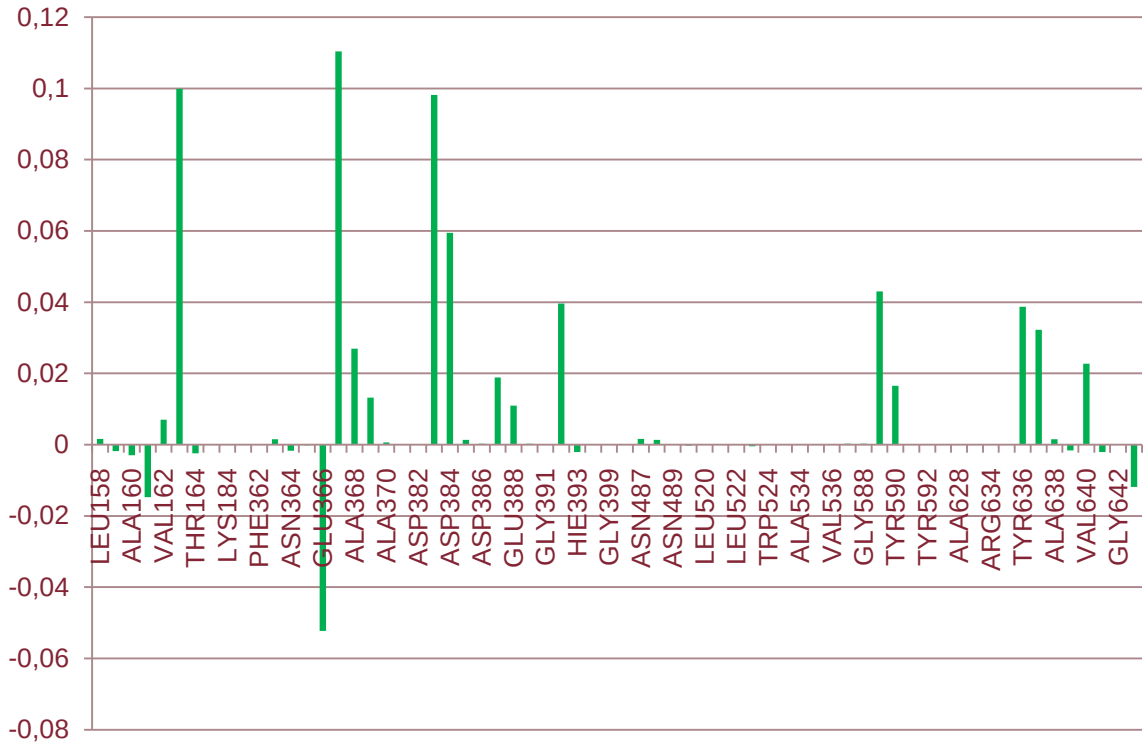

PRO 637
GLN 383


0,12
0,1
0,08
0,06
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0,02
0
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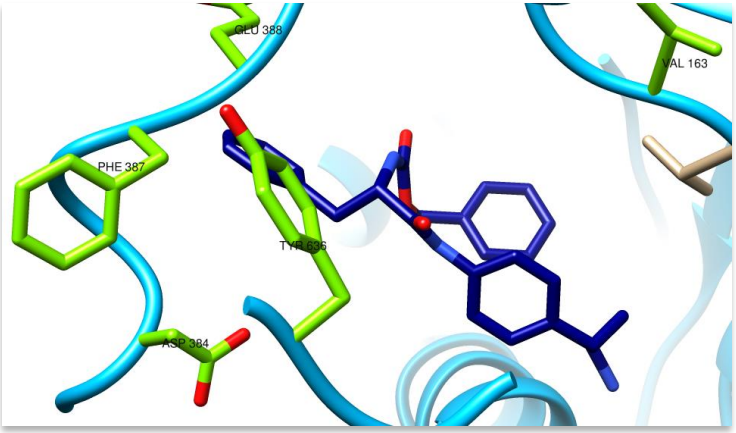
-0,04
-0,06
-0,08
LEU158
ALA160
VAL162
THR164
LYS184
PHE362
ASN364
GLU366
ALA368
ALA370
ASP382
ASP384
ASP386
GLU388
GLY391
HIE393
GLY399
ASN487
ASN489
LEU520
LEU522
TRP524
ALA534
VAL536
GLY588
TYR590
TYR592
ALA628
ARG634
TYR636
ALA638
VAL640
GLY642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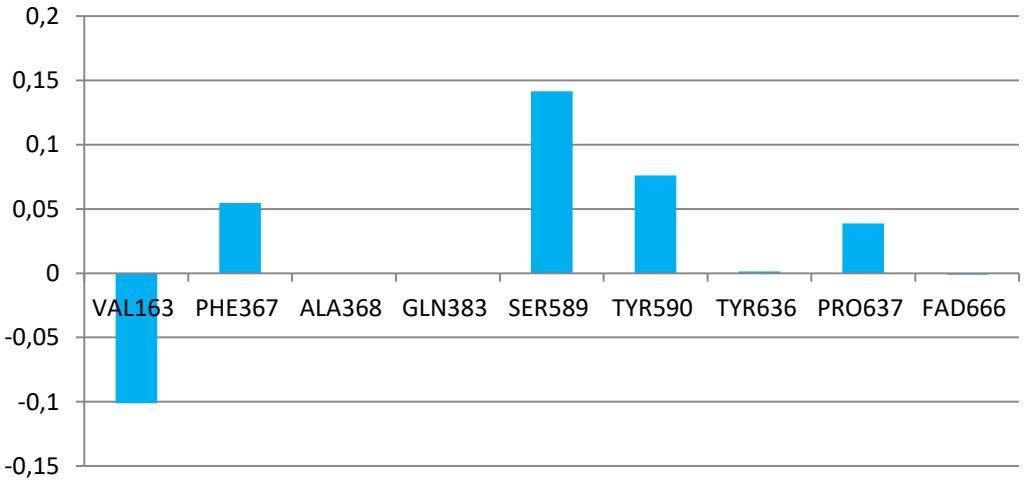
VAL 163
PHE 387
TYR 636
ASP 384


0,2
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0
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PHE367
ALA368
GLN383
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TYR590
TYR636
PRO637
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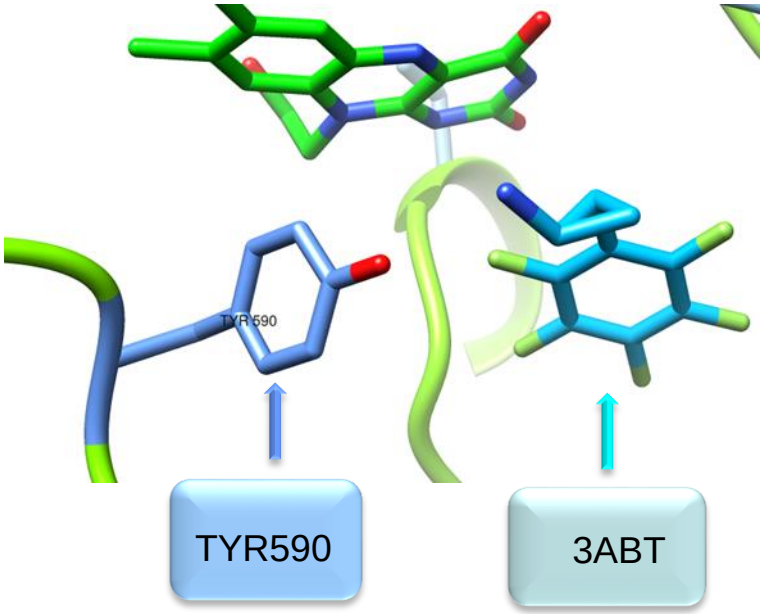
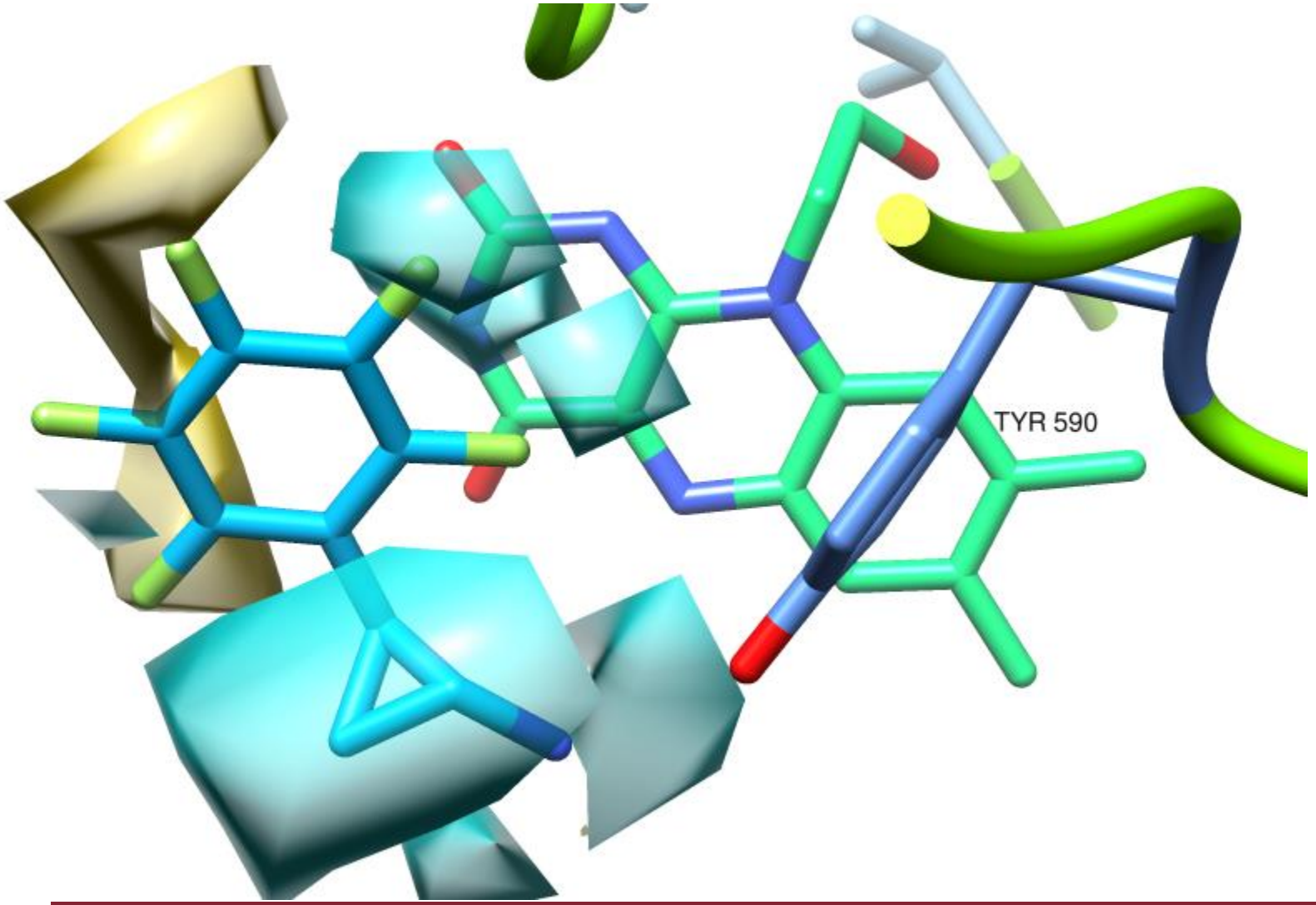
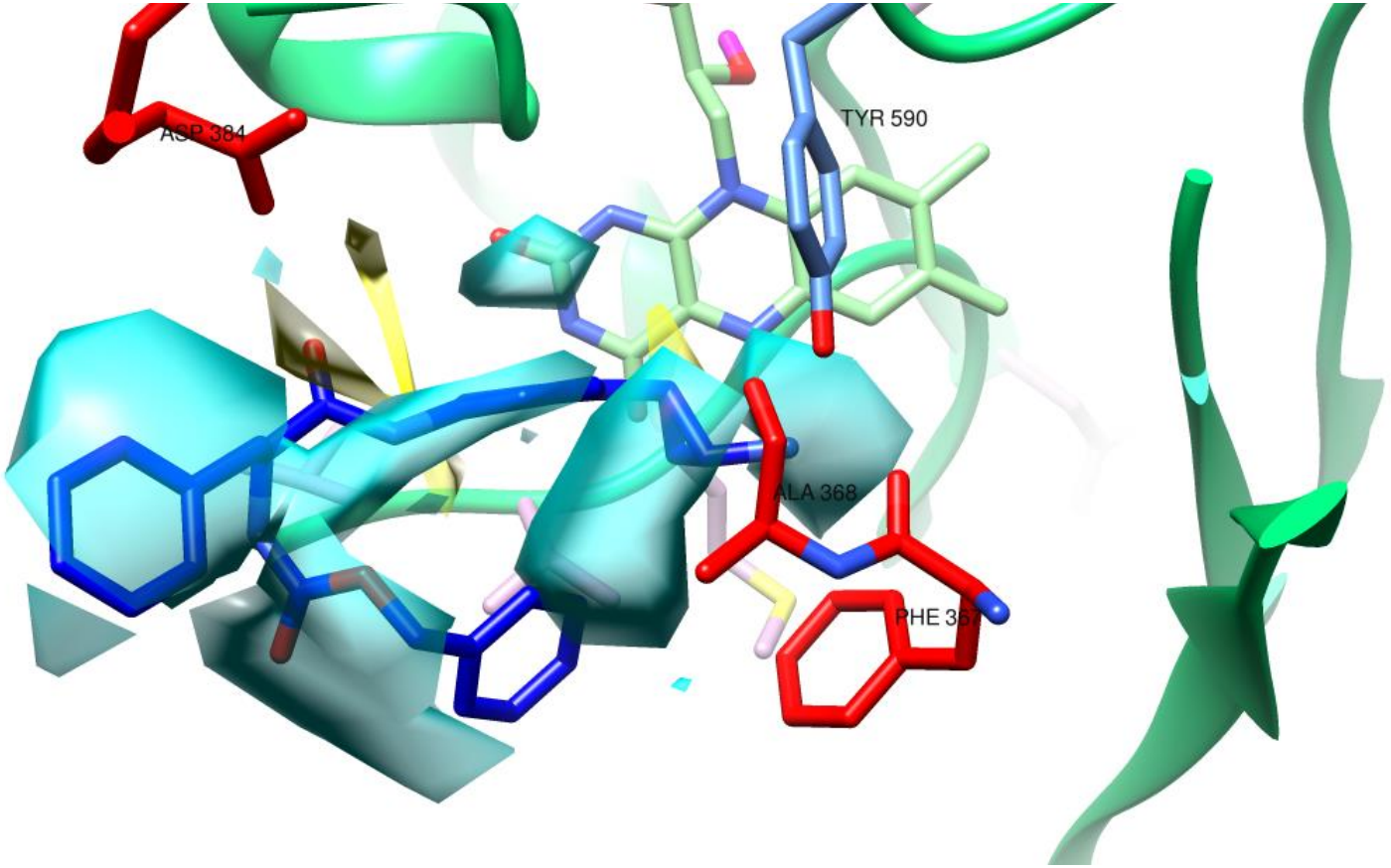

TYR590
TYR590
3ABT


TYR 590

CONCLUSIONI

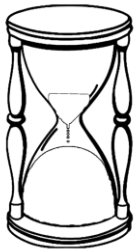
- MODELLI 3-D QSAR
- MODELLI COMBINE
- STUDIO INTERAZIONI NON COVALENTI LIGANDO - RECETTORE

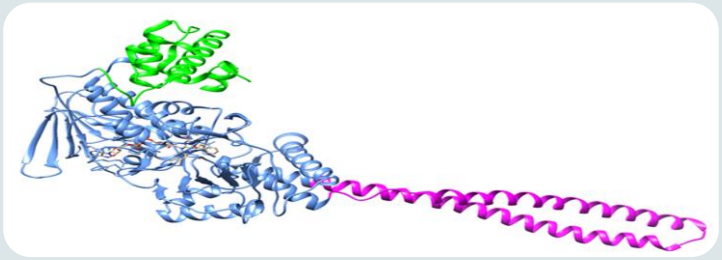


OBIETTIVI FUTURI

- **AMPLIARE IL NUMERO DELLE MOLECOLE NEL TRAINING SET PER CREARE MODELLI PIÙ GENERALIZZATI**

- **PROGETTARE NUOVI INIBITORI REVERSIBILI E SELETTIVI NEI CONFRONTI DI LSD1**





GRAZIE

PER L'ATTENZIONE