

Structure based drug design di inibitori selettivi della demetilasi istonica specifica della lisina LSD1

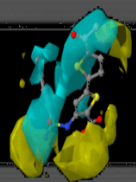


SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Chimica e Tecnologia Farmaceutiche
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2010/2011

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Matricola: 1038047

Relatore: Chiar.mo Prof. Rino Ragno



Scopo della Tesi

**Progettazione SBDD
(Molecular Docking)**

**Progettazione LBDD
(3-D QSAR)**

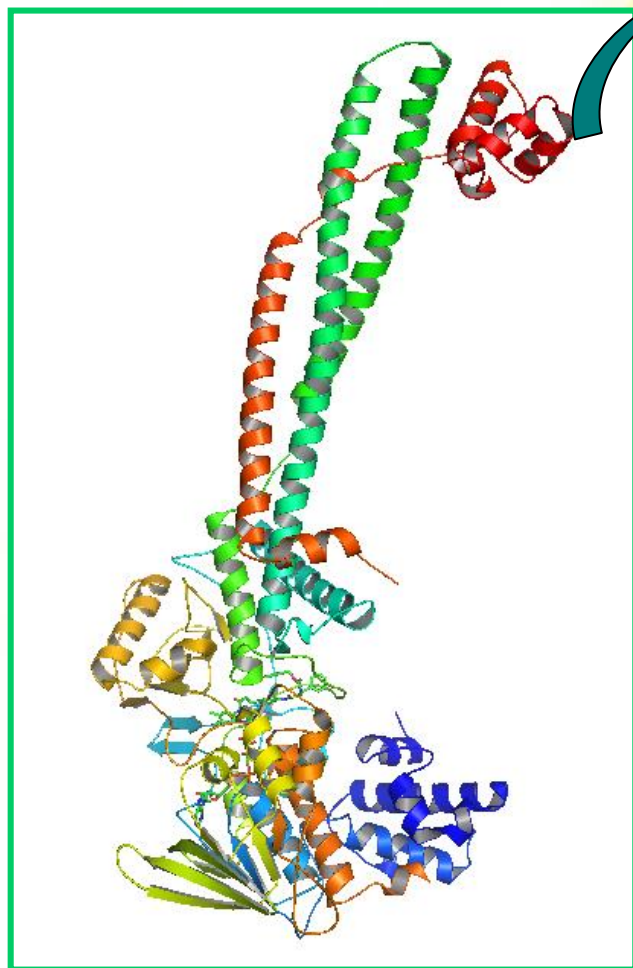
De Novo Drug Design

Inibitori per LSD1:

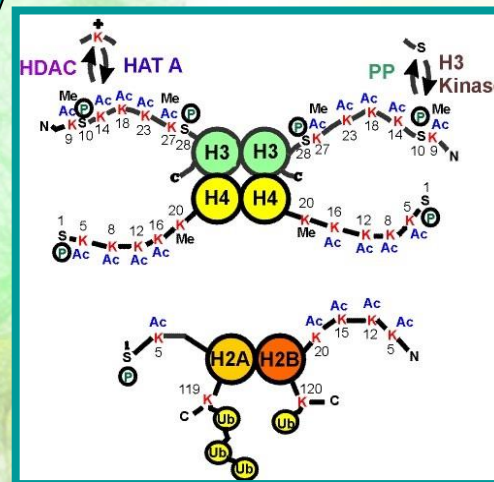
**irreversibili
reversibili
peptidici**



LSD1



2XAS



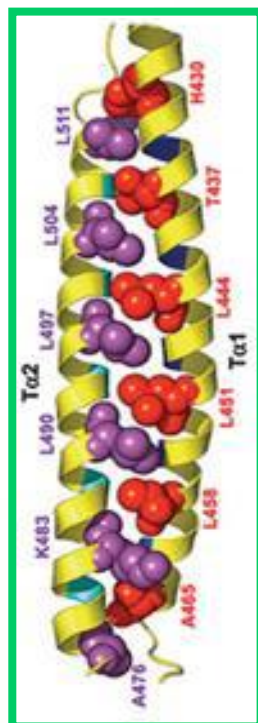
**Perdita di
metilazione di H3K4**

**Arricchimento di
metilazione di H3K9**

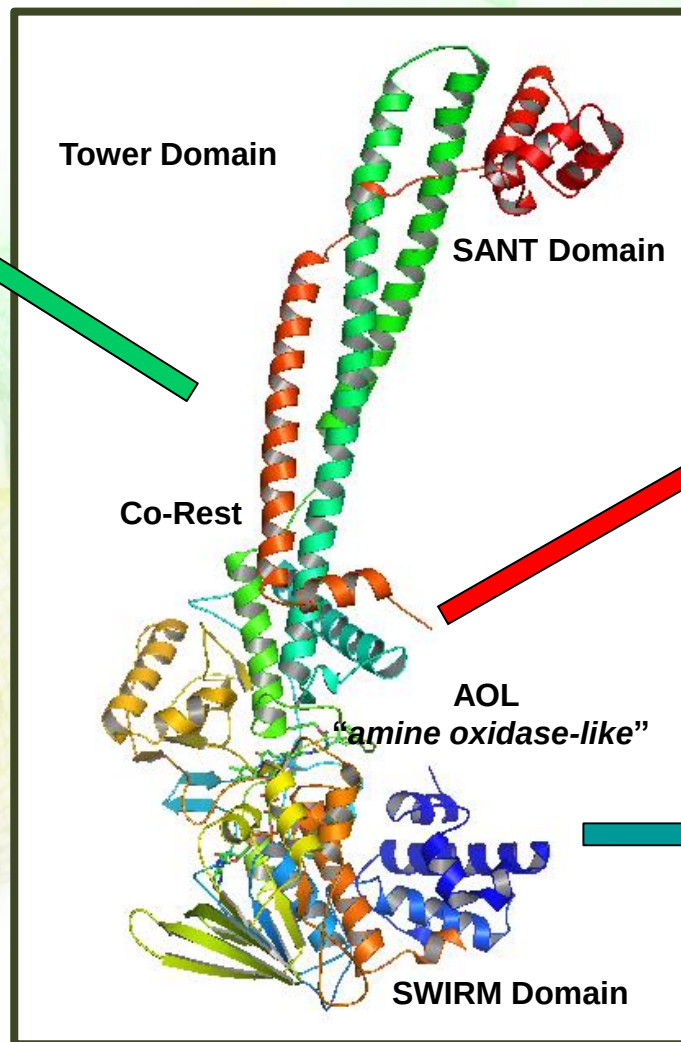
**Sviluppo di
patologie tumorali**



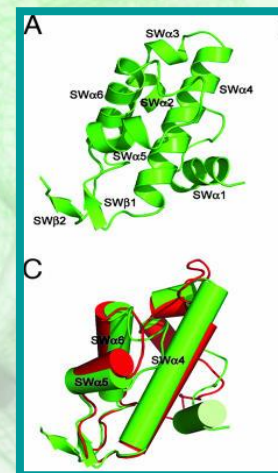
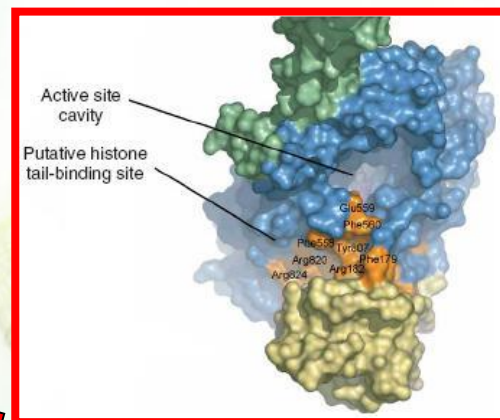
LSD1

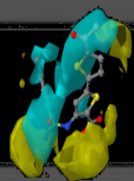


LSD1 in
associazione con
CoRest

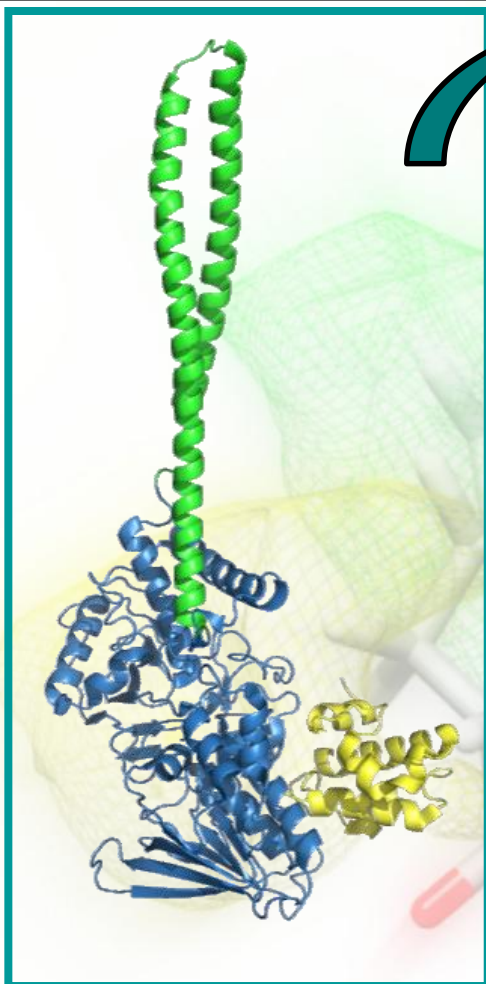


100 KDa

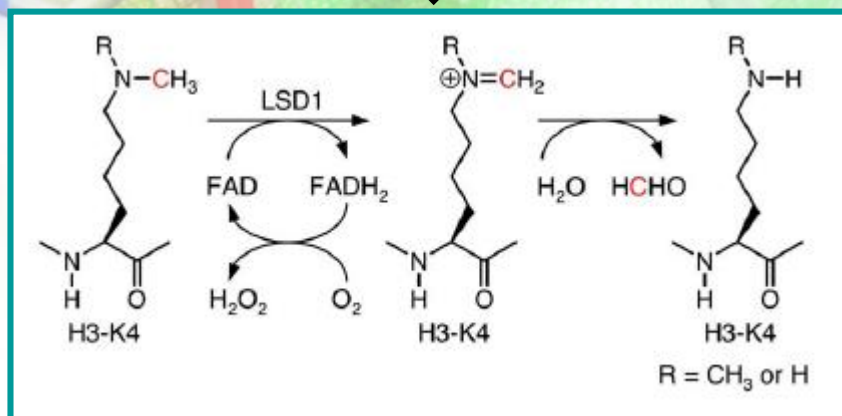
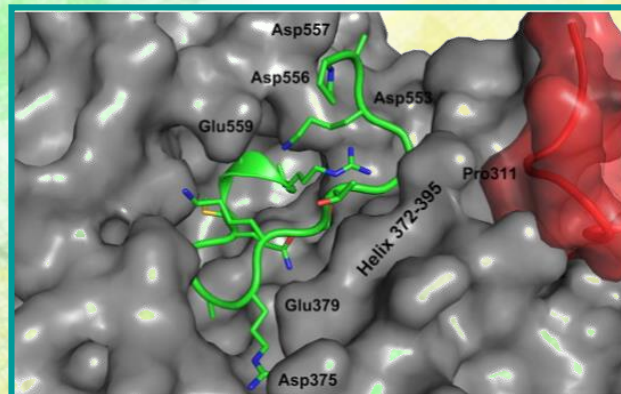


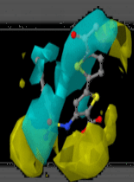


LSD1

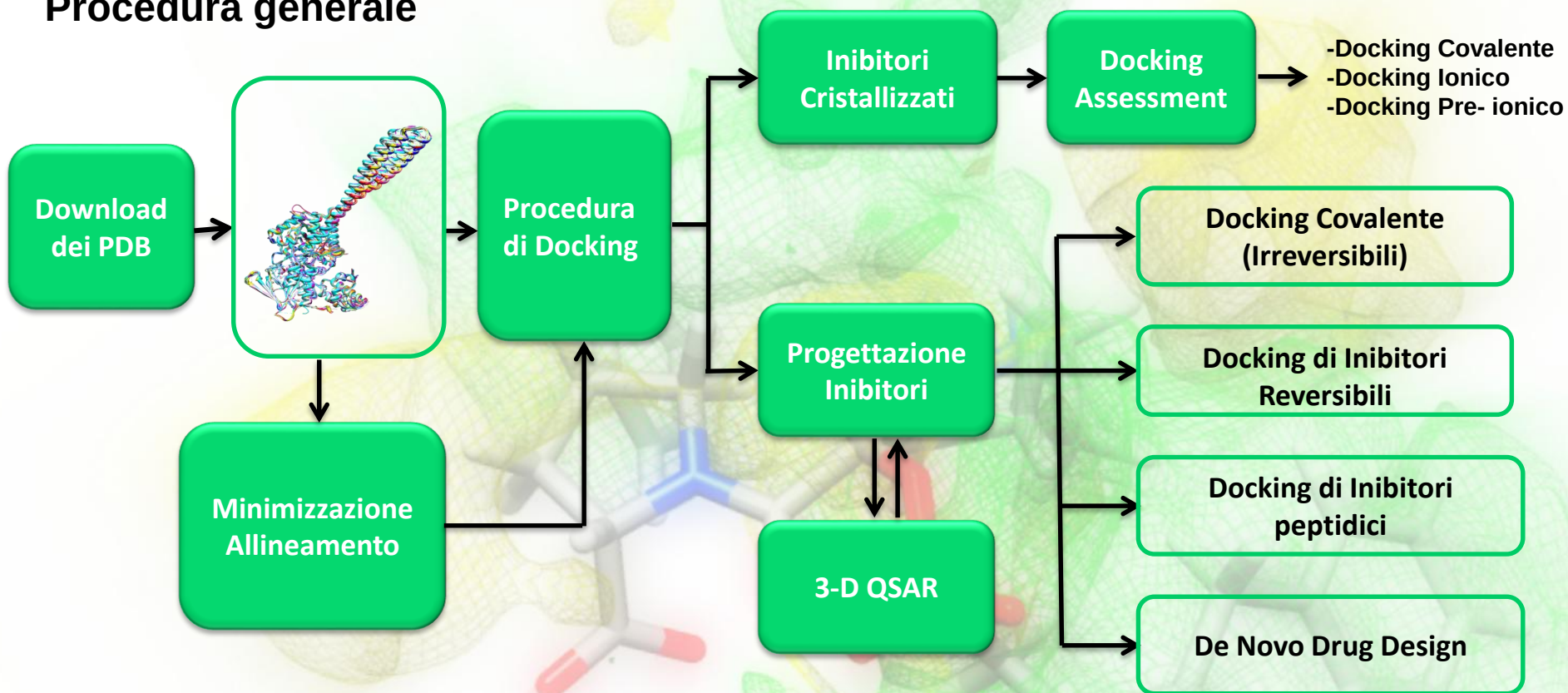


Complesso 2V1D/H3

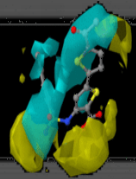




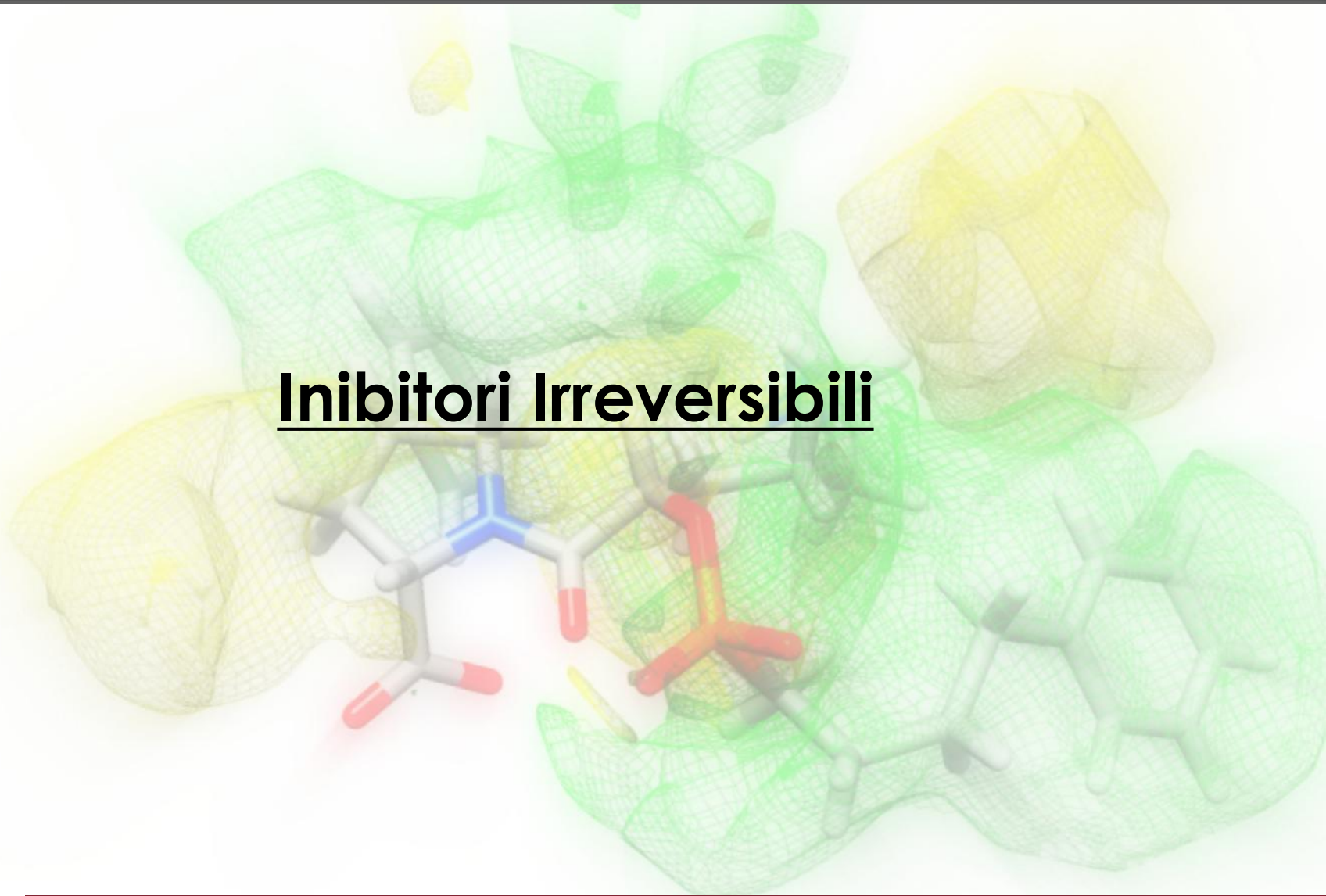
Procedura generale

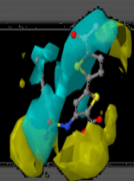


Giorgio Ortar, Enrico Morera, Luciano De Petrocellis, Alessia Ligresti, Aniello Schiano Moriello, Ludovica Morera, Marianna Nalli, **Rino Ragno, Adele Pirolli**, Vincenzo Di Marzo. Biaryl tetrazolyl ureas inhibitors of endocannabinoid metabolism: modulation at the N-portion and distal phenyl ring. Eur. J. Med. Chem. (2012). [Accettato per la pubblicazione].

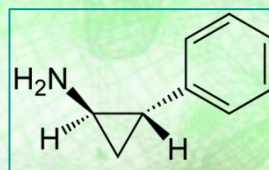
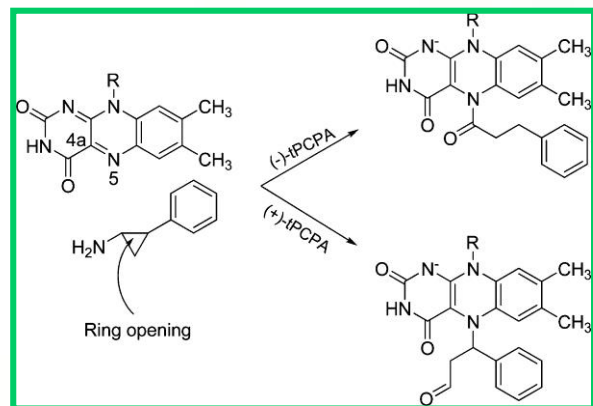


Inibitori Irreversibili

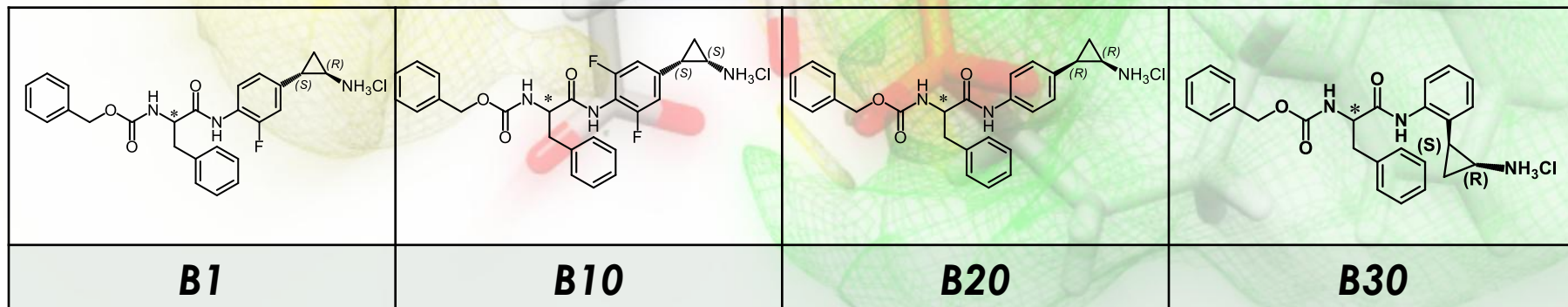
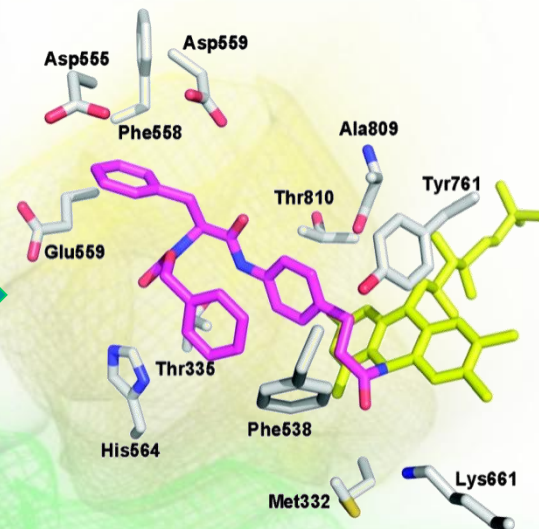


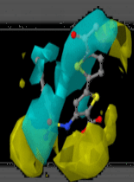


Inibitori Irreversibili



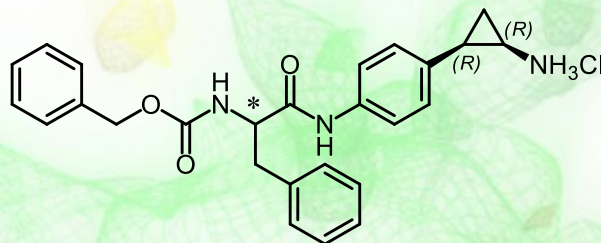
Tranilcipromina



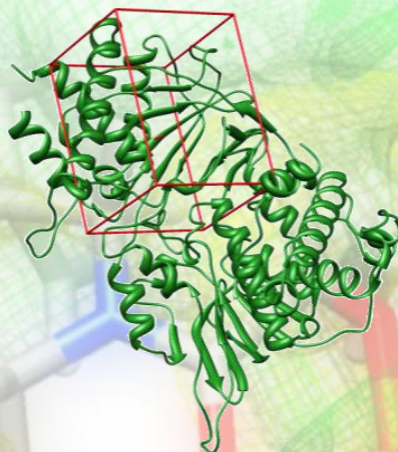


Docking Covalente

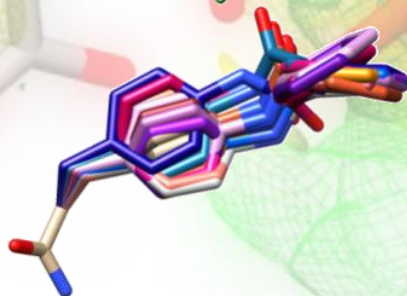
Preparazione file di
input



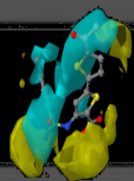
Determinazione
dimensioni del sito
attivo



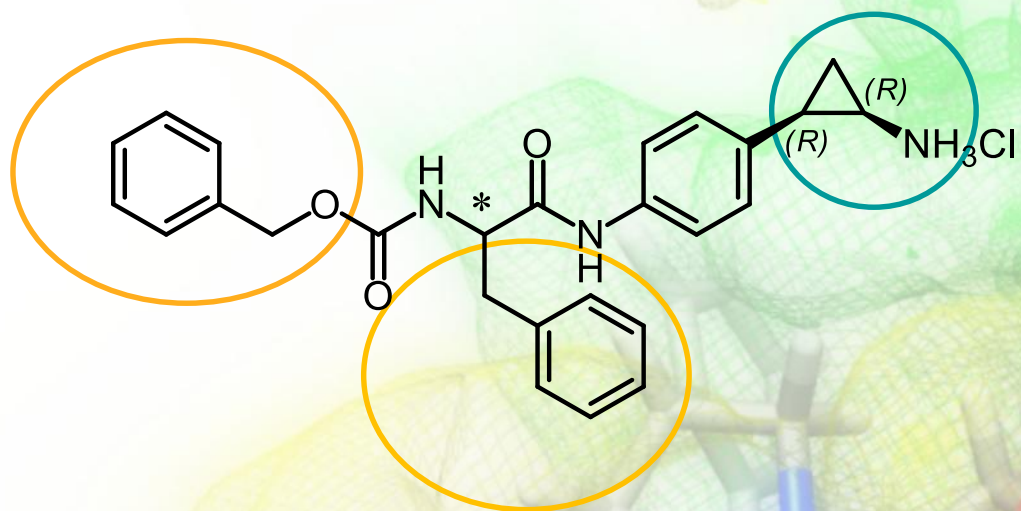
Procedura di docking
covalente



Ranking



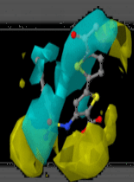
Inibitori Irreversibili



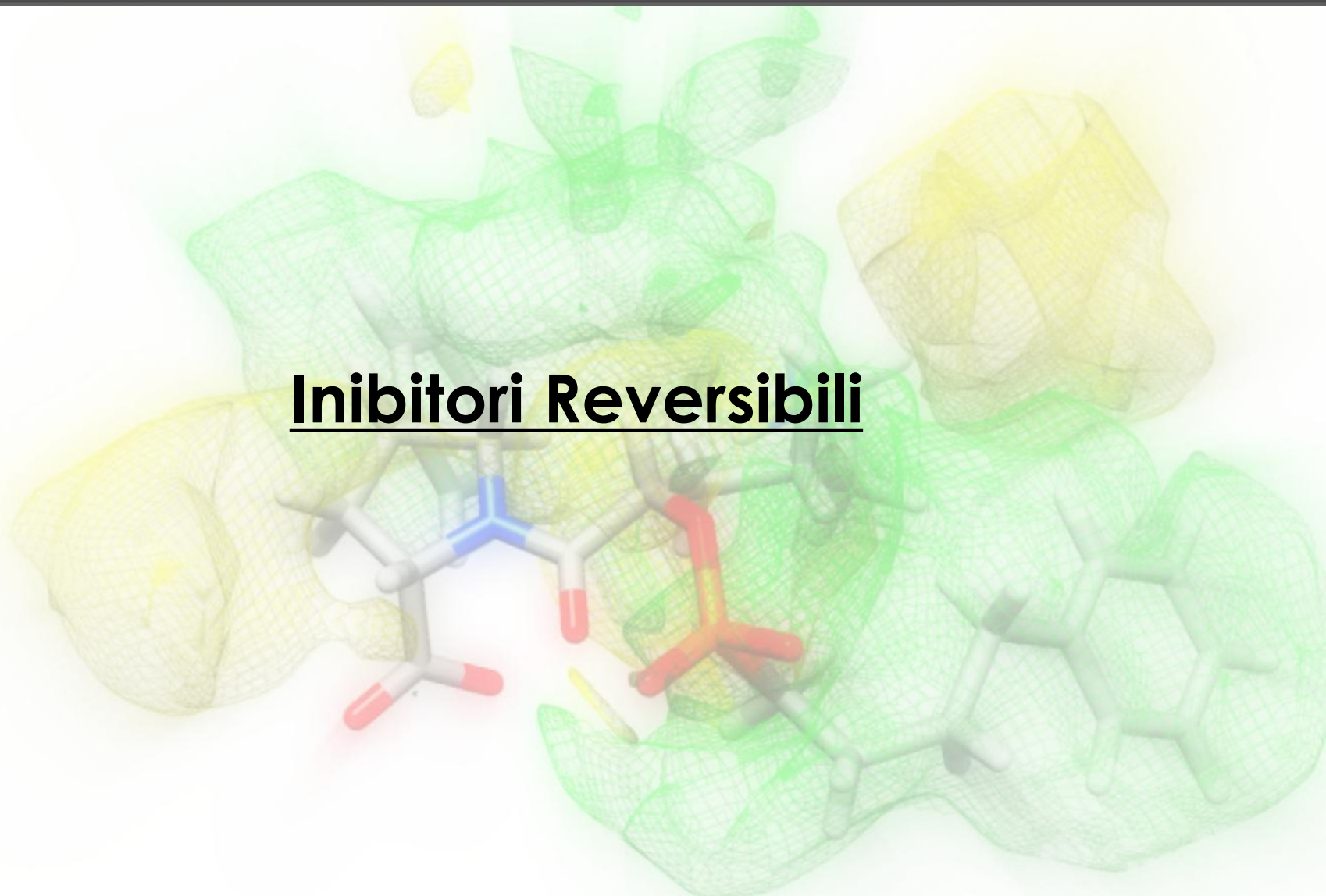
Ligand Name	R/S	Binding Energy	Binding Energy
B10	R	-7,33	-0,06
B10	S	-7,604	-0,06
B11	R	-8,25	-0,08
B12	S	-7,8	-0,06
B13	R	-8,02	-0,07

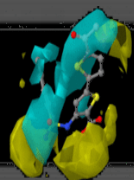
ENTRY	BINDING ENERGY
B29SS	-9,65
B22S	-9,44
B18R	-9,31
B15S	-9,25
B17R	-9,18
B24S	-9,17
B8S	-9,13
B5S	-8,99
B3R	-8,99
B14R	-8,96
B23R	-8,91
B32SR	-8,88
B31RS	-8,81
B18S	-8,75
B23S	-8,74
B5R	-8,67
B22R	-8,67

Risultati Autodock-Inibitori Irreversibili

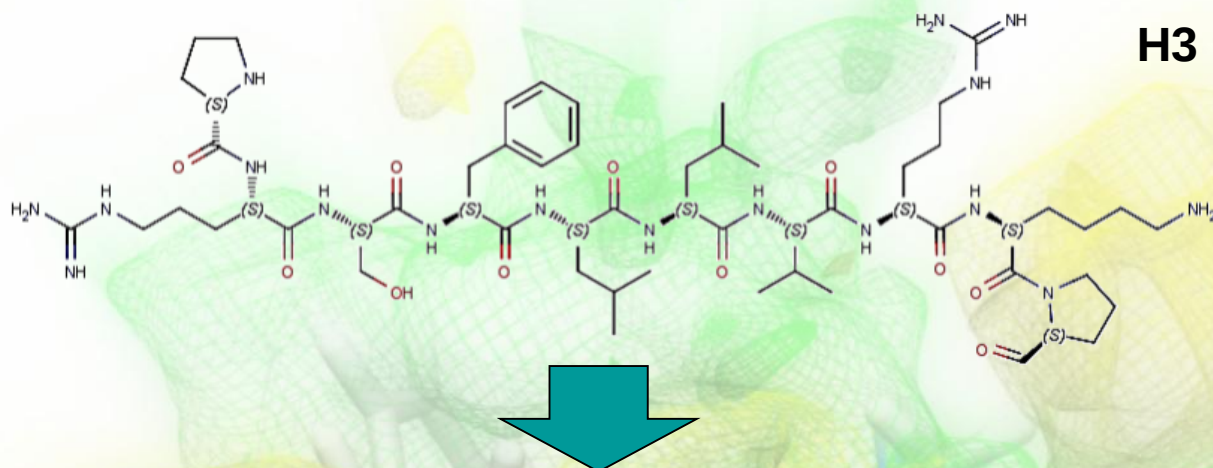


Inibitori Reversibili

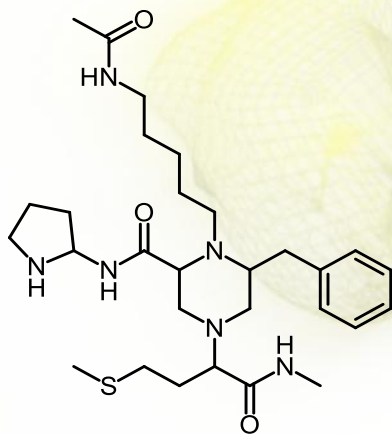




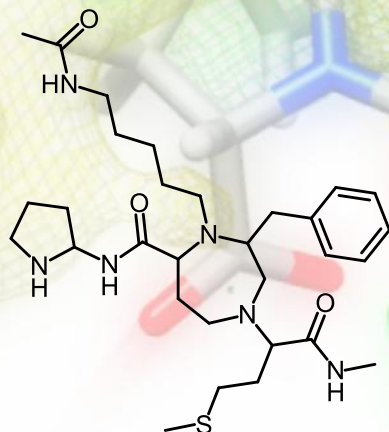
Inibitori reversibili



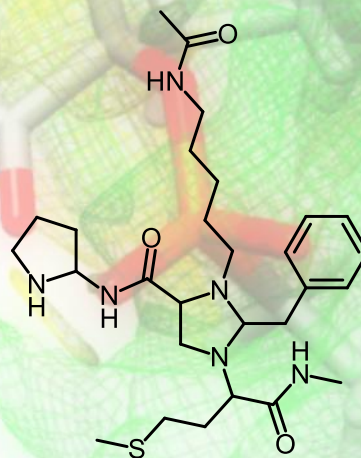
A1 (A1-A4)



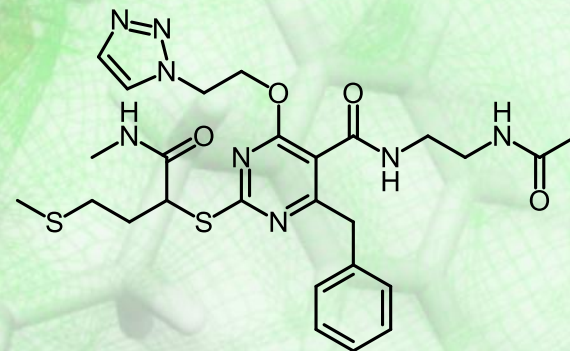
A5 (A5-A12)



A13 (A13-A20)



A23(A23-A24)

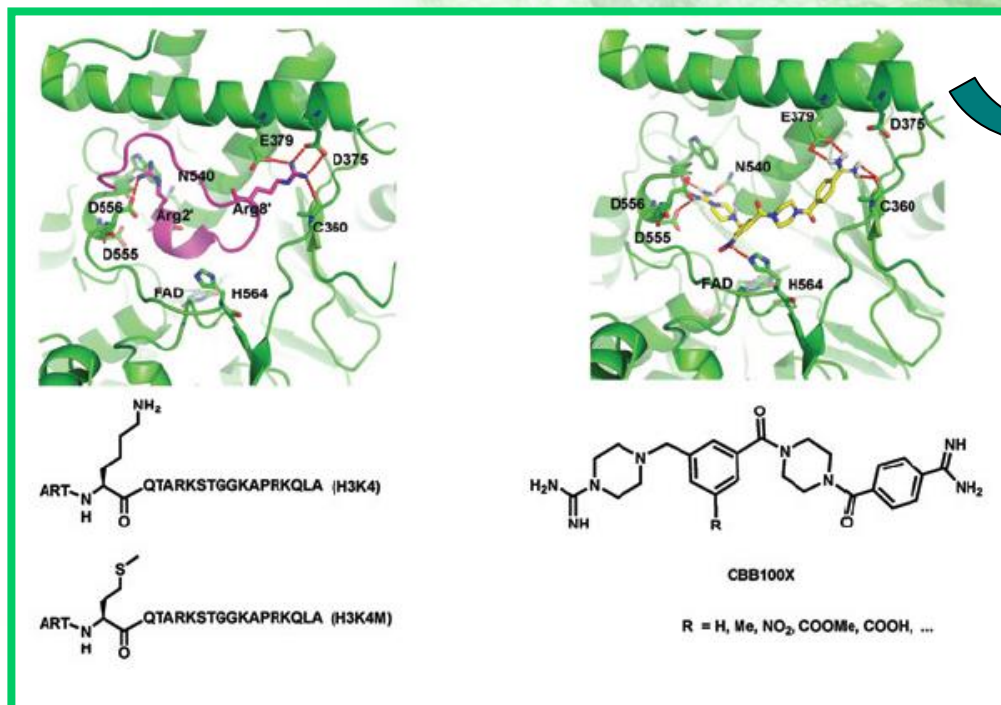


Inibitori Reversibili



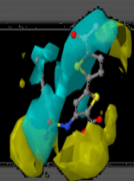
Inibitori reversibili

Entry	BD		BC	
	Rank	Value	Rank	Value
A11_rev	3	-9,73	1	-9,73
A18_rev	4	-9,51	2	-9,51
A20_rev	4	-9,51	2	-9,51
A19_rev	5	-9,37	3	-9,37
A17_rev	11	-8,91	3	-9,37



PLANTS

- Plp
- Chemplp

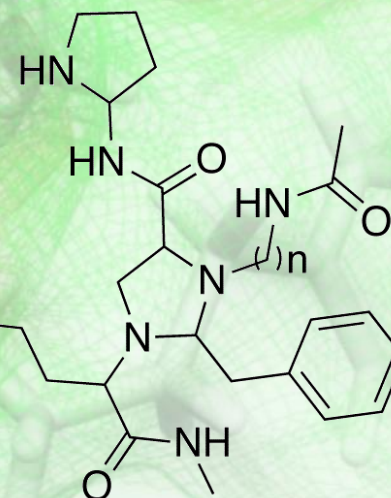


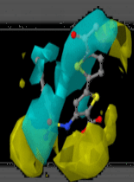
Inibitori reversibili

Entry	BD		BC	
	Rank	Value	Rank	Value
A11_rev	3	-9,73	1	-9,73
A18_rev	4	-9,51	2	-9,51
A20_rev	4	-9,51	2	-9,51
A19_rev	5	-9,37	3	-9,37
A17_rev	11	-8,91	3	-9,37

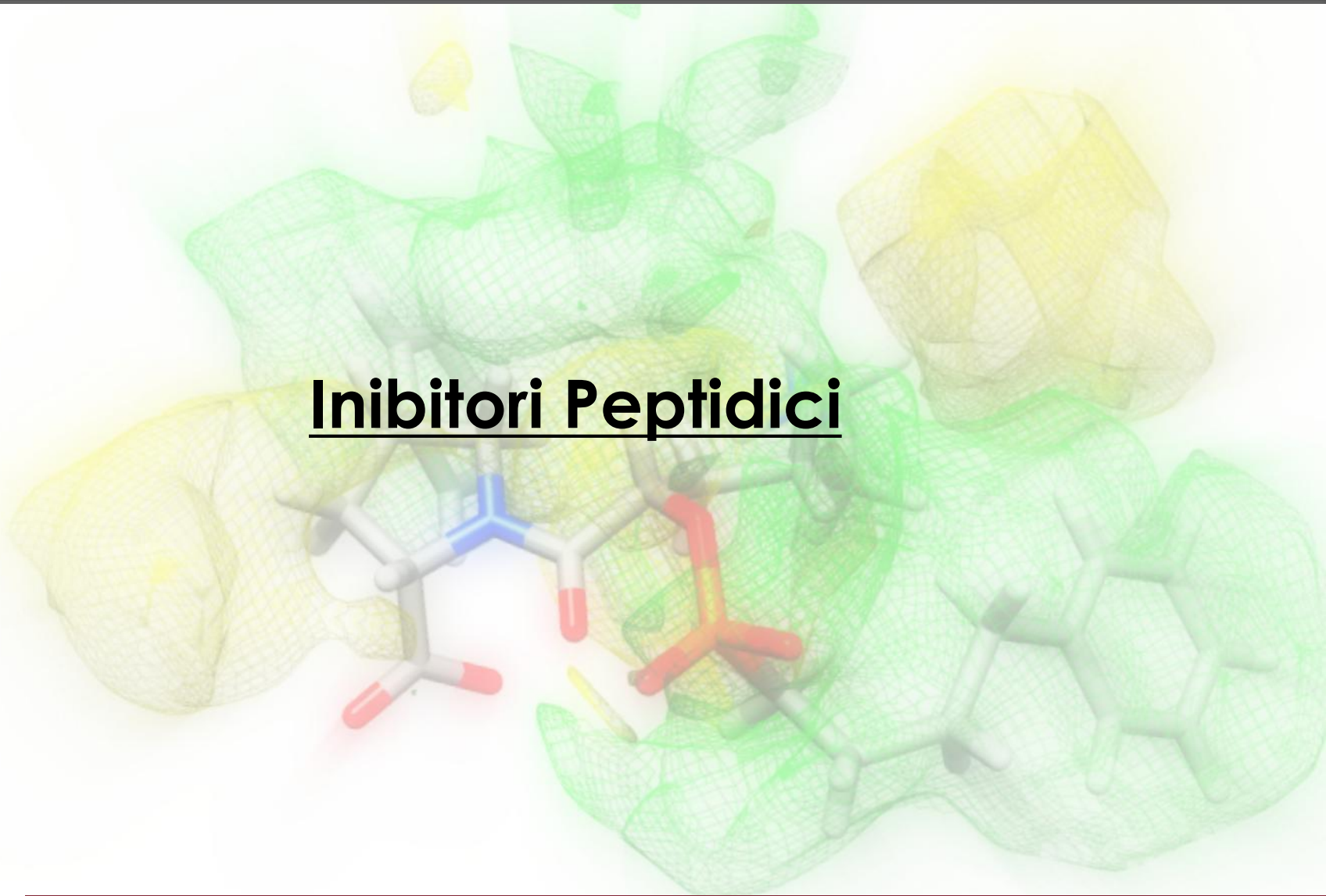


	TOTAL_SCORE
A19_rev	-110,717
A1_rev	-109,999
A17_rev	-109,106
A24_rev	-107,906
A18_rev	-104,972
A23_rev	-104,865
A14_rev	-103,529
CBB1005	-103,255
A5_rev	-102,833
A10_rev	-102,64
A4_rev	-101,965



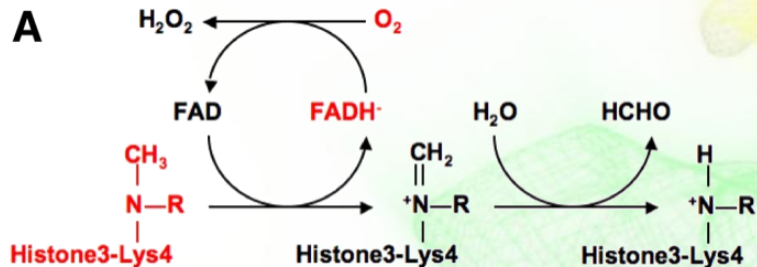


Inibitori Peptidici





Inibitori peptidici

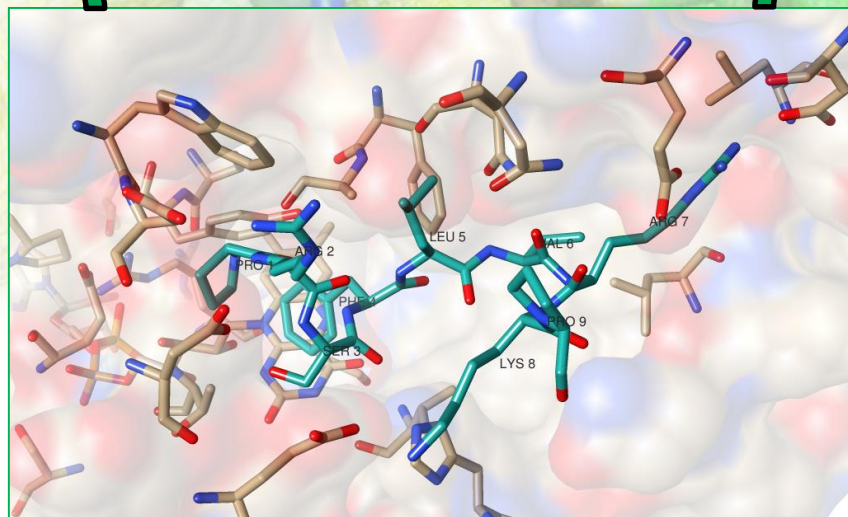


1	ARTQTARKSTGGKAPRKQLA	21	histone H3
1	PRSF-LVRKPSDPNRKPNYS	20	SNAIL1
1	PRAFL-VKKPCVSTCKRNWSE	20	OVO-like1
1	PRSF-LVKKVKLDAFSSADLE	20	SCRATCH1
1	PRSF-LVSKKKAHSYHQPRSP	20	gfi1
1	PRGFL-VKRSKKSTPVSRYVR	20	insm1

P-R-S-F-L-V-R-K-P-Prot

Autodock

Docking di SNAIL
-5,6,7,8 Residui



PLANTS

- A) Docking di H3 - 4,5,6,7,8,9 Residui
- B) Docking di SNAIL - 4,5,6,7,8,9 Residui



Inibitori peptidici

Conf	SCORE
2v1d_tagliato4.01	-49,8624
2v1d_tagliato4.02	-46,6844
2v1d_tagliato4.03	-45,0863
2v1d_tagliato4.04	-43,6297
2v1d_tagliato4.05	-42,7257
2v1d_tagliato4.06	-39,651

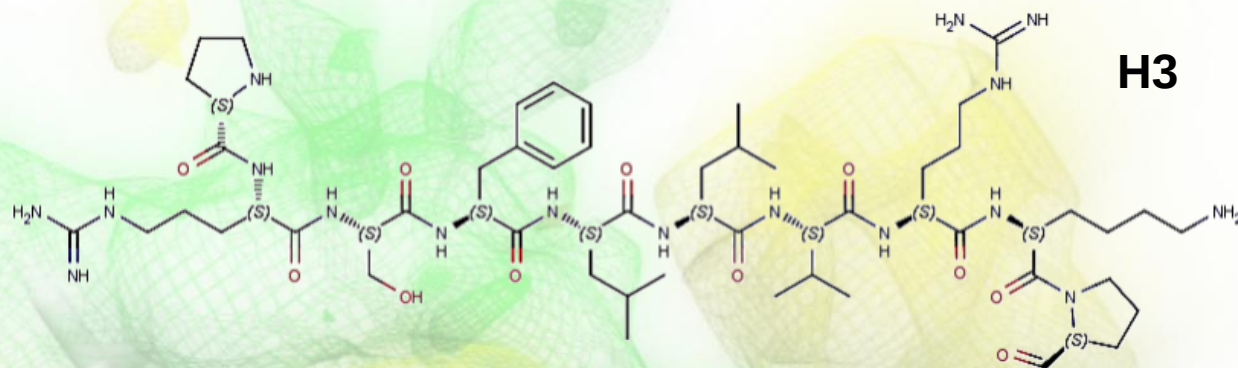
4 residui

Conf	SCORE
2v1d_tagliato5.01	-102,092
2v1d_tagliato5.02	-101,501
2v1d_tagliato5.03	-100,247
2v1d_tagliato5.04	-98,5579
2v1d_tagliato5.05	-96,4671
2v1d_tagliato5.06	-91,8541

5 residui

Conf	SCORE
2v1d_tagliato6.01	-102,408
2v1d_tagliato6.02	-101,046
2v1d_tagliato6.03	-99,0723
2v1d_tagliato6.04	-97,5728
2v1d_tagliato6.05	-96,1609
2v1d_tagliato6.06	-94,4952

6 residui



P-R-S-F-L-V-R-K-P-Prot



P-R-S-F-L-V-R-K-P-Prot



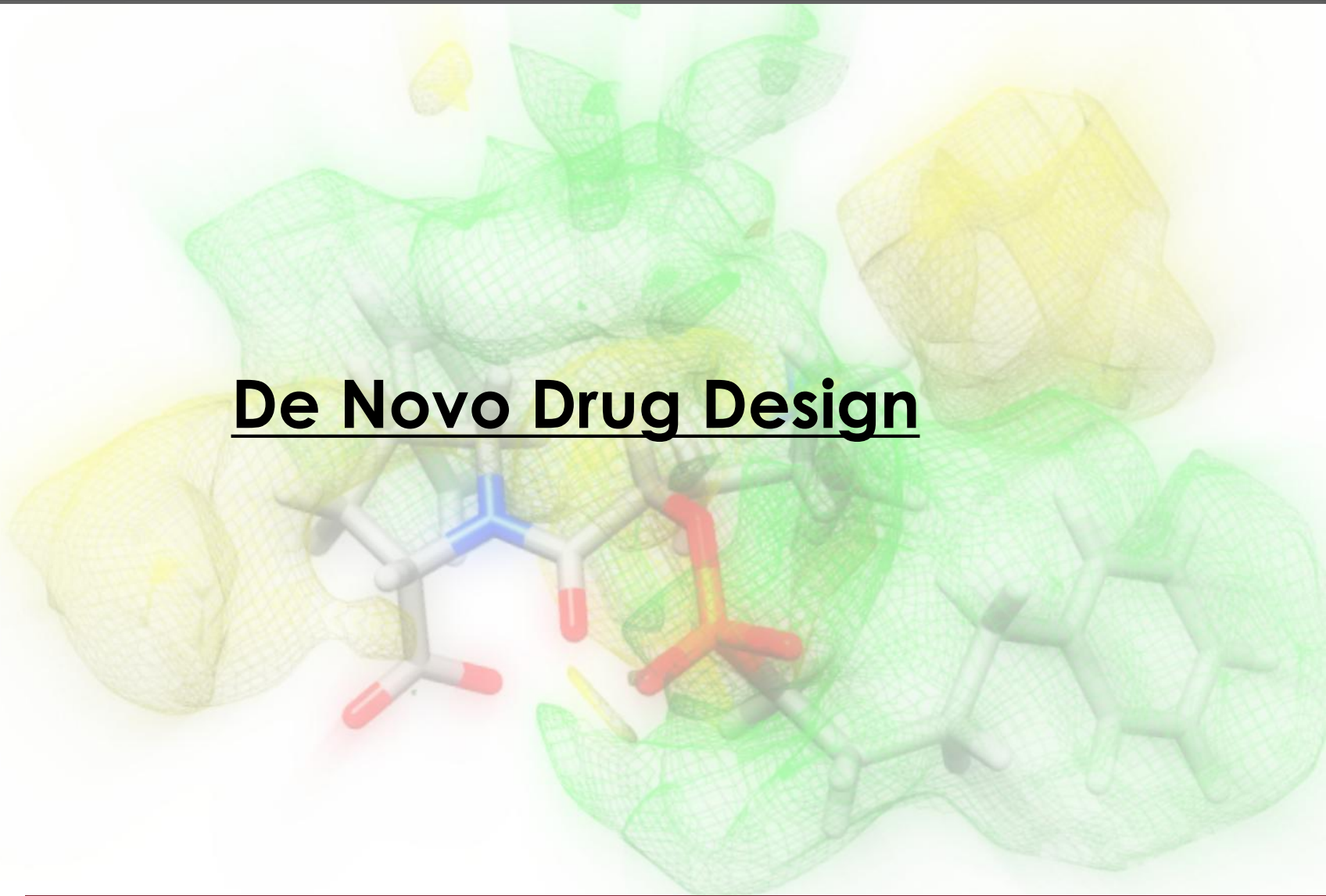
P-R-S-F-L-V-R-K-P-Prot

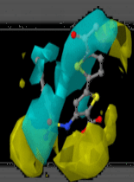


P-R-S-F-L-V-R-K-P-Prot



De Novo Drug Design





De Novo Drug Design

AUTOGROW

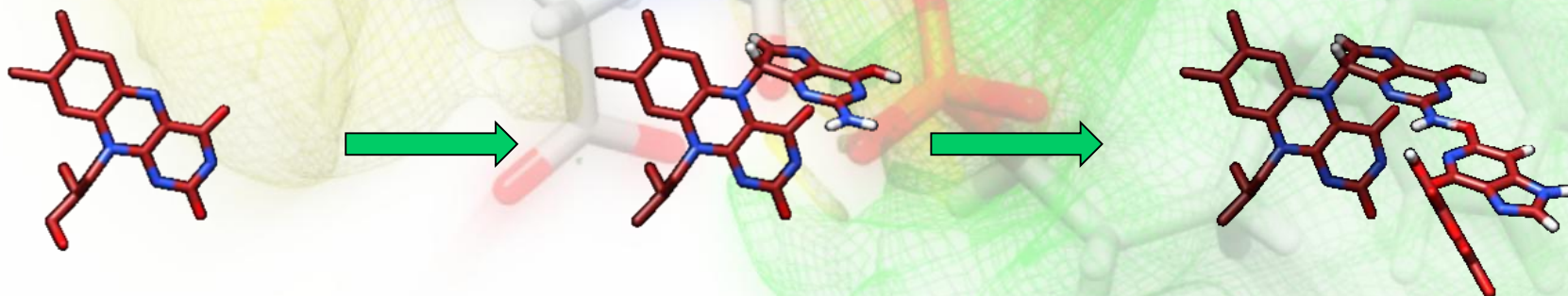
Rational Drug Design

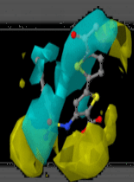
L'algoritmo di de novo drug design utilizzato da Autogrow, prevede l'utilizzo di tecniche di crescita *fragment based* del ligando all'interno del sito attivo. Questi algoritmi includono tipicamente tre operatori:

➤ **Selezione**

➤ **Mutazione**

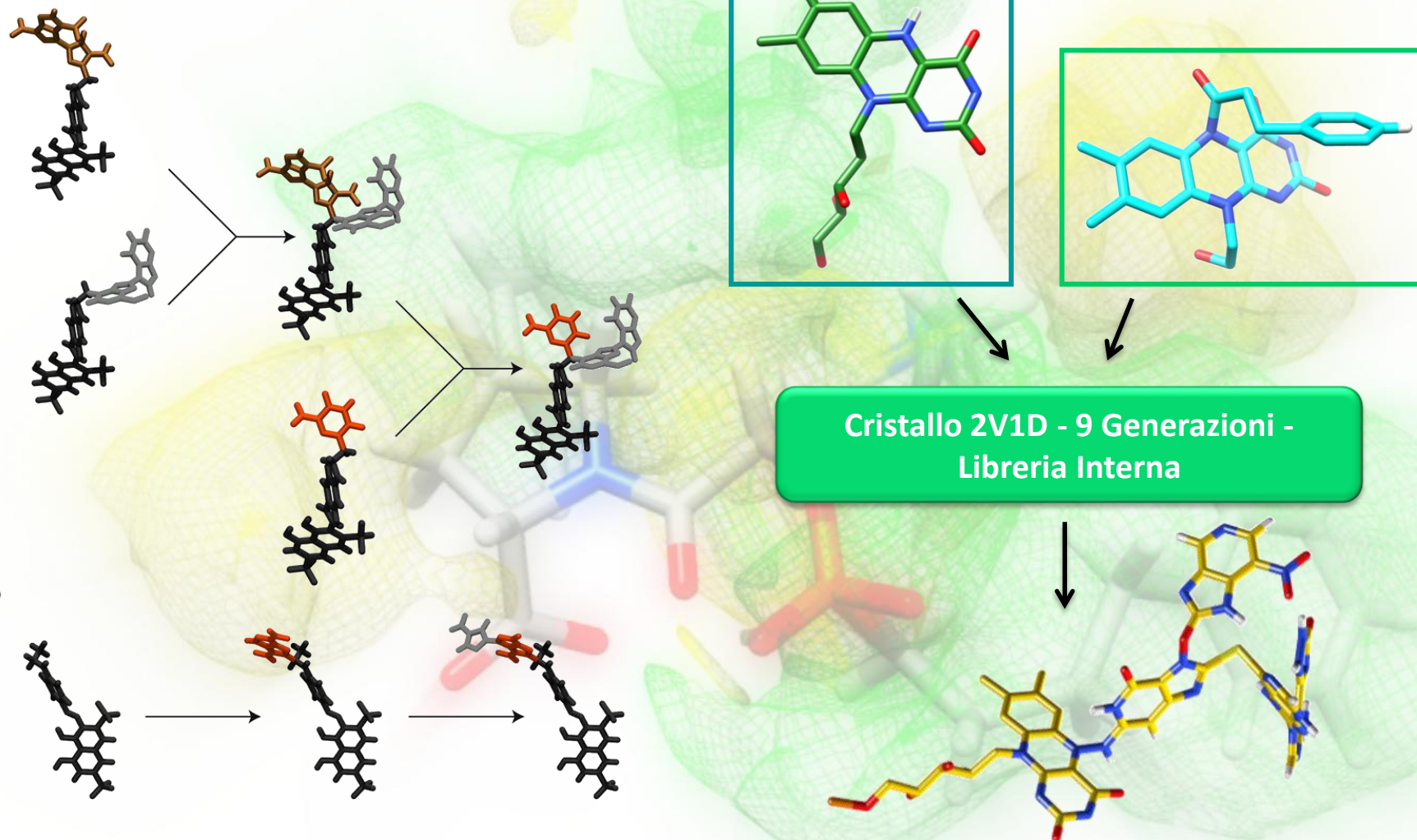
➤ **Crossover**



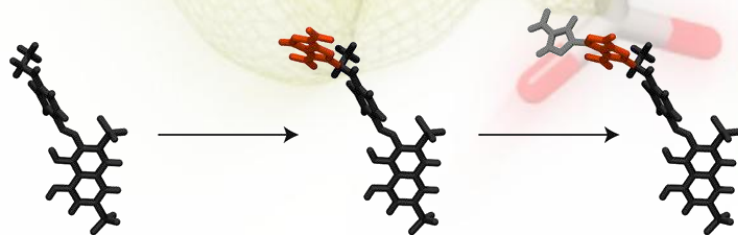


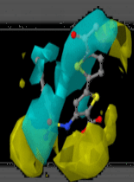
De Novo Drug Design

A

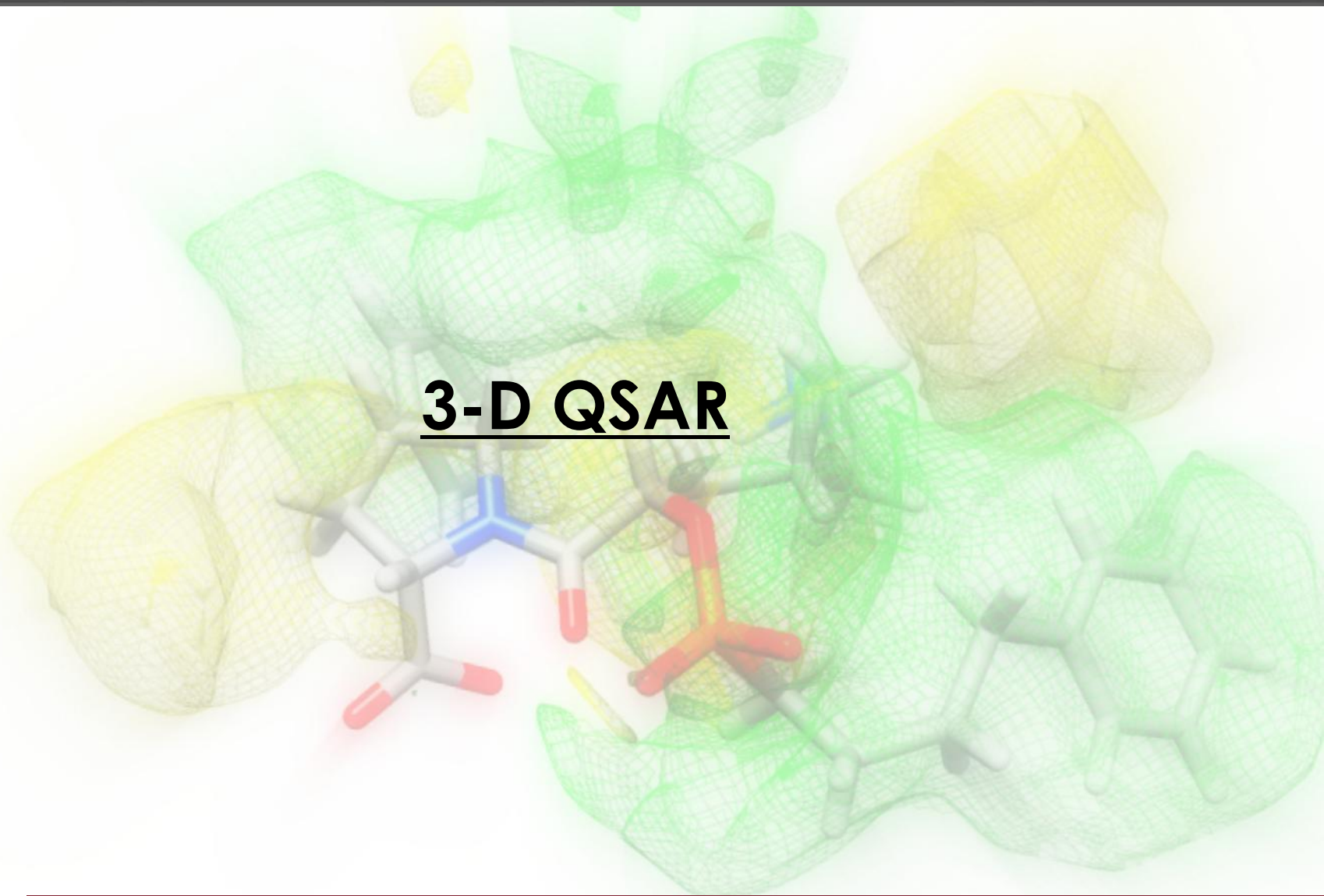


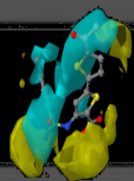
B



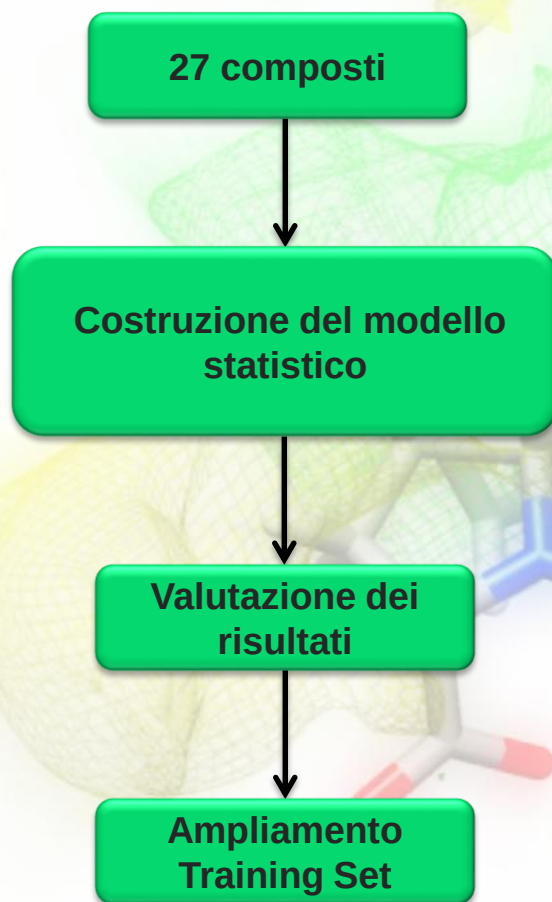


3-D QSAR

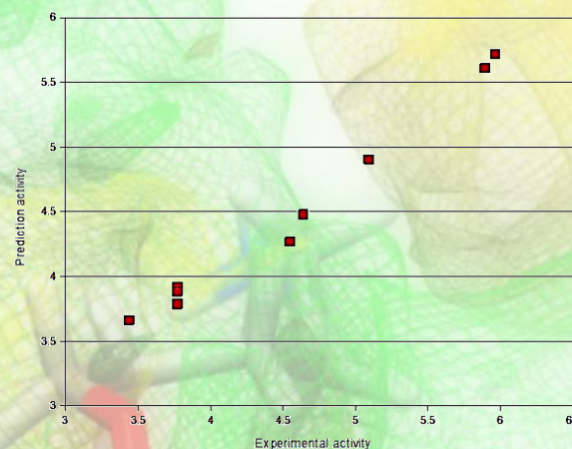




3-D QSAR



Statistical results. Probe A

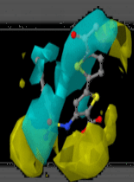


Cross Validation results ,
probe Aromatic
cross-validation K5-fold, PC=2.



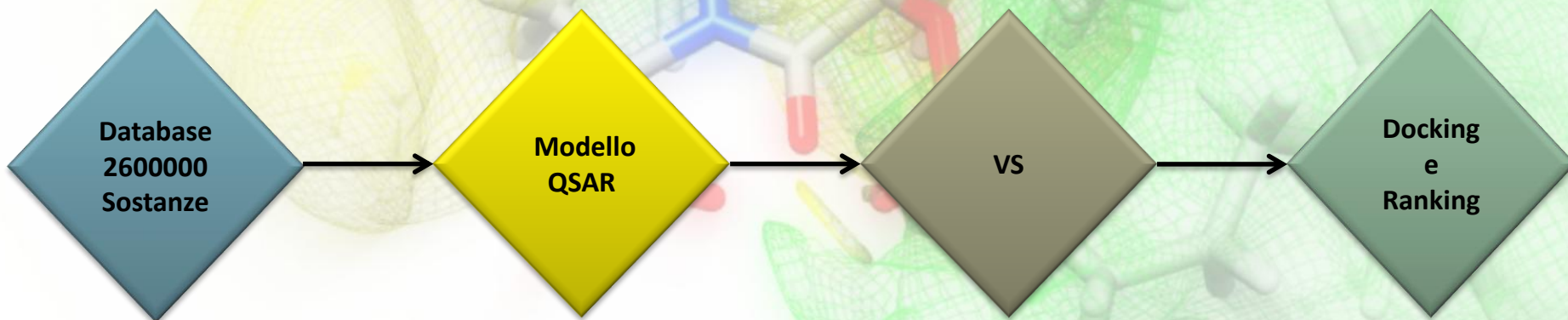
Discussione e Conclusioni

- **Esiste notevole accordo tra i risultati ottenuti dai diversi programmi di docking**
 1. Conferma della presenza dell'anello eterociclico
 2. Conferma della migliore predizione di molecole con gruppi che presentano un elevato ingombro sterico
- **Sono stati individuati nuovi possibili inibitori reversibili**
- **Possibilità di sviluppare nuovi possibili inibitori utilizzando come scaffold la tranilcipromina**



Sviluppi futuri:

- Progettazione di nuovi inibitori di natura peptidomimetica
- Costruzione di una libreria interna di frammenti per Autogrow e progettazione di nuovi composti utilizzando come *scaffold* la tranilcipromina
- Docking di inibitori peptidici attraverso la sostituzione di residui sia sul fattore di trascrizione SNAIL1 che su H3
- Studio COMBINE
- Virtual Screening





Grazie per l'attenzione