Approcci Structure-Based per lo studio di potenziali ligandi quali interferenti della formazione del complesso 'EZH2-EED'

SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina
Corso di Laurea in Farmacia
Tesi Sperimentale in Chimica Farmaceutica
a.a. 2015/2016

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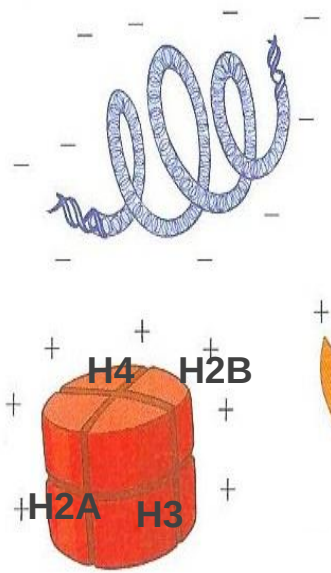
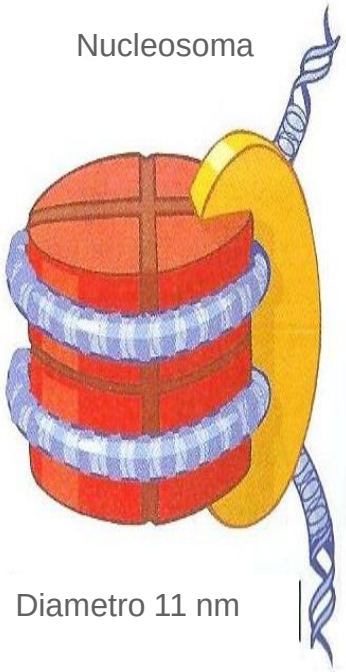
Matricola: 1320916

Relatore: prof. Rino Ragno

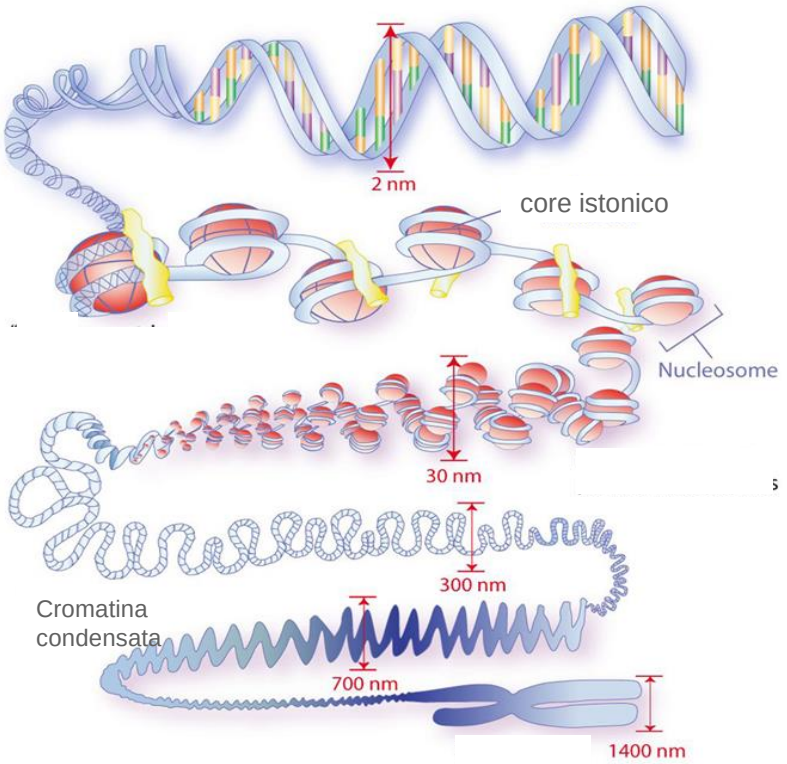
Epigenetica



8 molecole di istoni con carica positiva



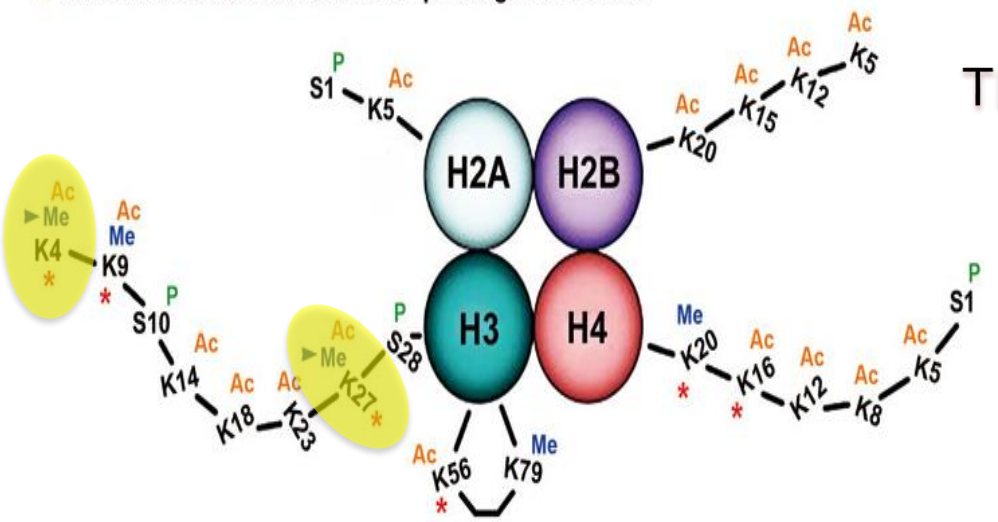
Diametro 11 nm



Metilazione

MODIFICAZIONI POST TRASCRIZIONALI

* implicated in cell fate determination in pluripotent or adult stem cells
► bivalent chromatin marks at development genes in PSCs



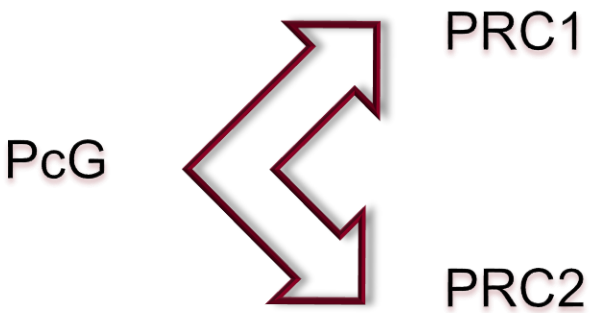
THRITORAX → H3K4me
-stato ATTIVO

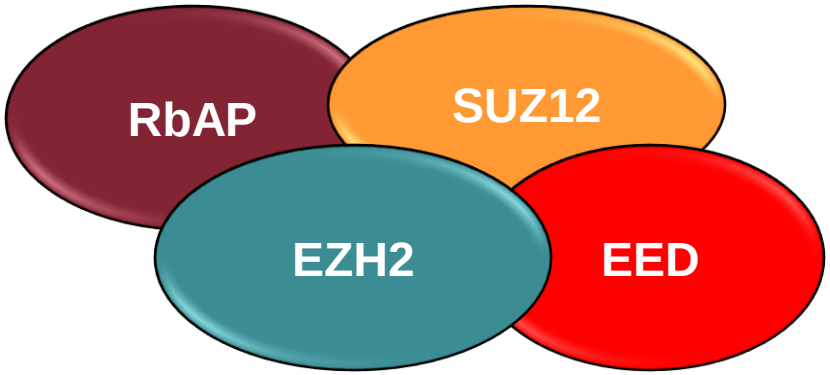
PcG → H3K27me
-stato INATTIVO

Situazioni di ipo/iper metilazione correlate con:

- ACCENSIONE di geni potenzialmente dannosi
- SPEGNIMENTO di geni che agiscono nei meccanismi di riparazione del DNA

Nei mammiferi





SUZ12 enzima Soppressore in equilibrio con
EZH2 enzima Attivatore
(regolano omeostasi e differenziamento cellulare)

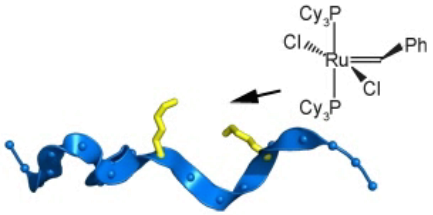
La deregolazione di PRC2 è coinvolta in genesi e progressione neoplastica

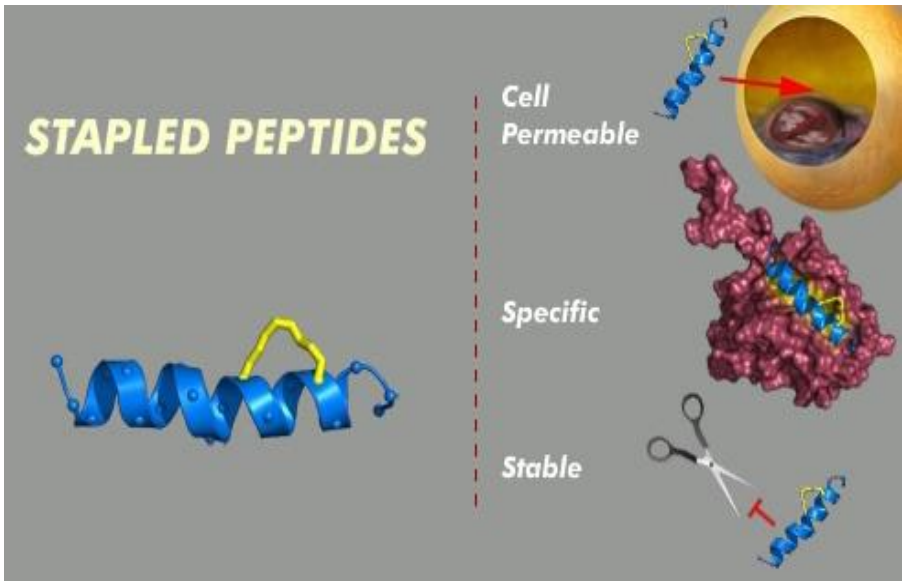
Stabilizzazione con tecnica del “Peptide Stapling”.

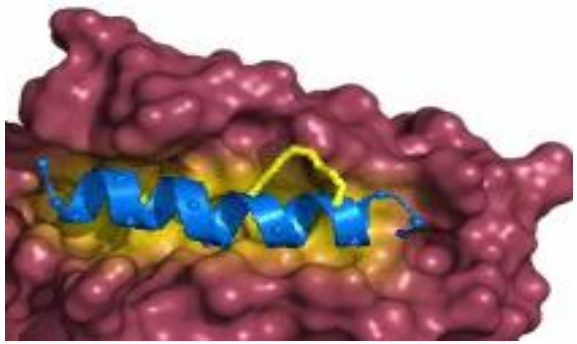
Cell PRESS
Structure
Article

Structural Basis of EZH2 Recognition by EED

Zhifu Han,[1] Xinmiao Xing,[1] Min Hu,[2] Yin Zhang,[1] Peiyuan Liu,[1] and Jijie Chai[1,*]
[1]National Institute of Biological Sciences, Beijing 102206, China
[2]Department of Molecular Biology, Princeton University, Princeton, NJ 08544, USA
*Correspondence: chaijijie@nibs.ac.cn







Cell PRESS

Structure
Article

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Zhifu Han,[1] Xinmiao Xing,[1] Min Hu,[2] Yin Zhang,[1] Peiyuan Liu,[1] and Jijie Chai[1,*]
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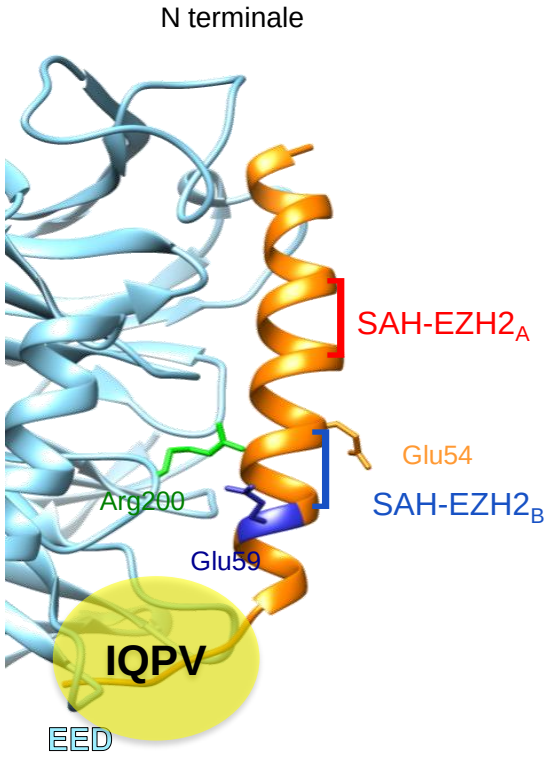
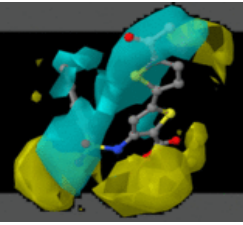


- SAH-EZH2 è il dominio essenziale strutturato ad α-elica che ingaggia EED.
- SAH agisce dissociando il complessoEZH2-EED che porta a soppressione della metilazione H3K27.
- La struttura determinante è il COOH terminale IQPV (65-68)



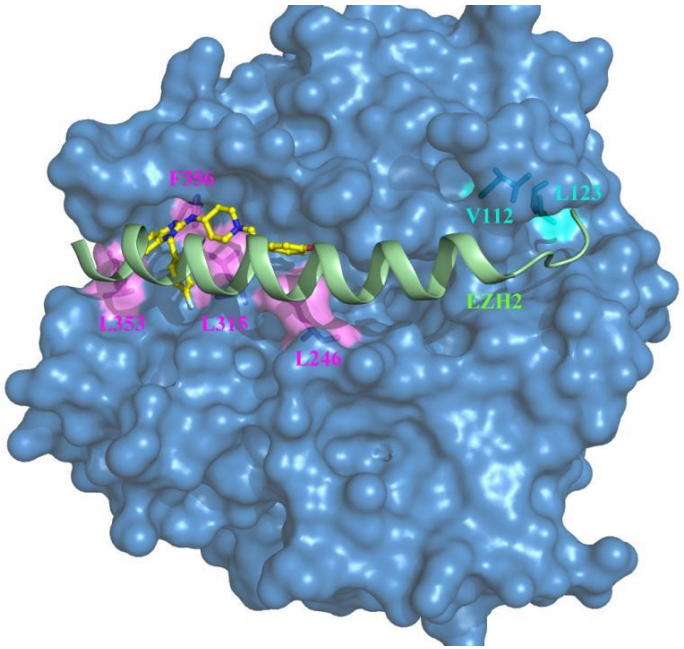
Disruptor EZH2-EED

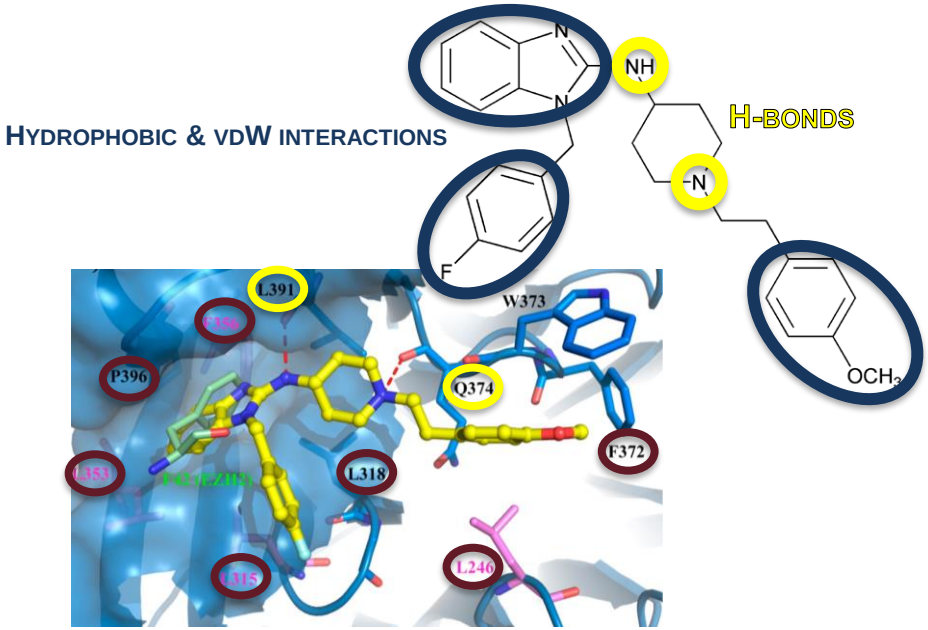
by www.RCMD.it

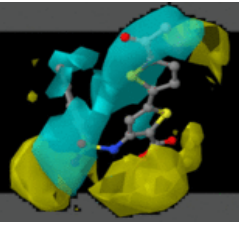
Nat Chem Biol. 2013 October ; 9(10): 643–650. doi:10.1038/nchembio.1331.

Targeted Disruption of the EZH2/EED Complex Inhibits EZH2-dependent Cancer

Woojin Kim[1,2,3], **Gregory H. Bird**[2,3,4], **Tobias Neff**[5], **Guoji Guo**[1,2,3], **Marc A. Kerenyi**[1,2,3], **Loren D. Walensky**[1,2,3,4,*], and **Stuart H. Orkin**[1,2,3,6,*]

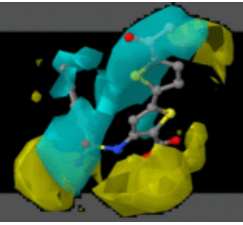






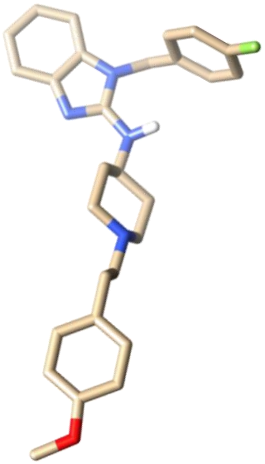
Scopo della Tesi

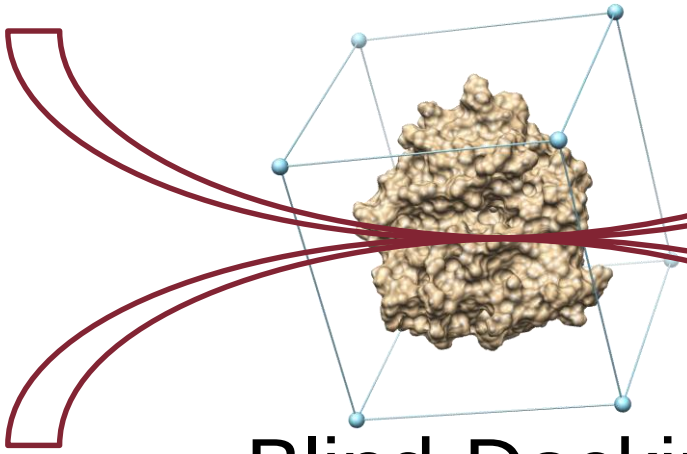
- Conferma del Binding Mode dell'Astemizolo
- Studio del Binding Mode di EZH2-EED disruptors (SB e LB)

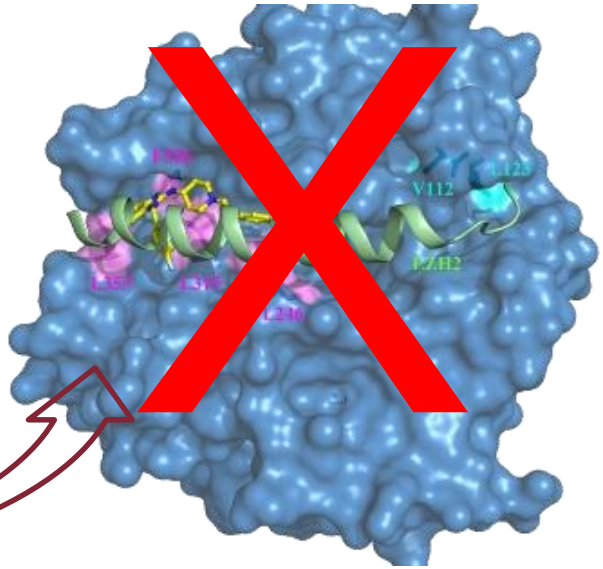


Binding Mode dell'Astemizolo

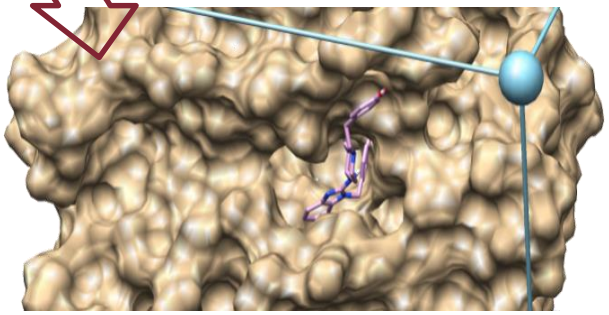
by www.RCMD.it

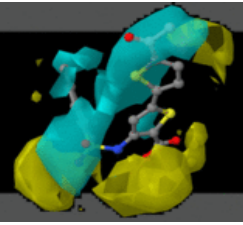






Blind-Docking
(Vina)





EZH2-EED disruptors

by www.RCMD.it

Structure-Based

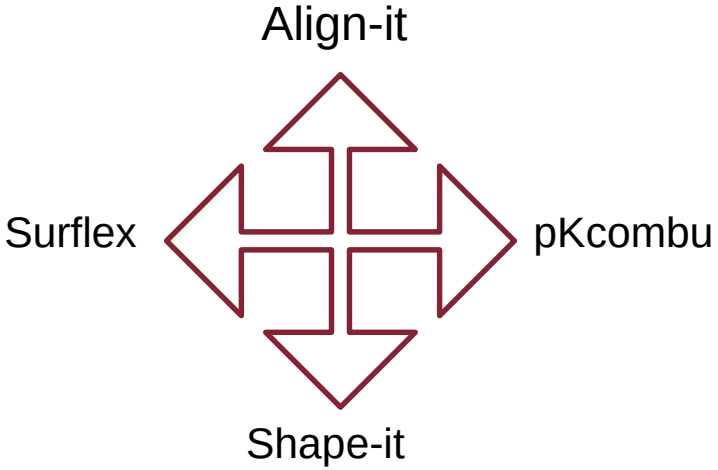
Programmi di Docking

- Vina
- Autodock
- Plants → CHEMPLP
  PLP
  PLP95
- Surflex

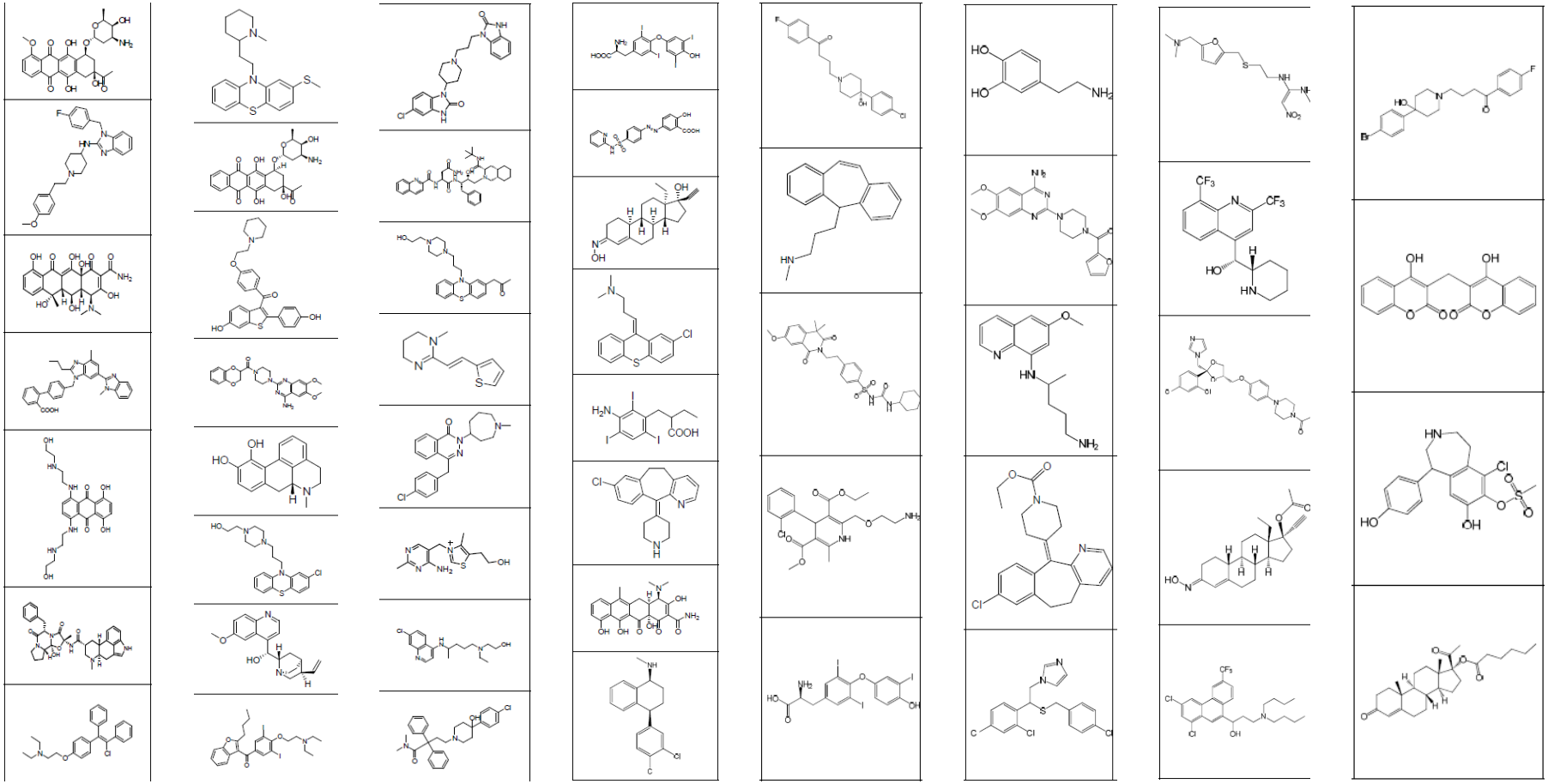
-Paradock → PMF04
PSCORE

Ligand-Based

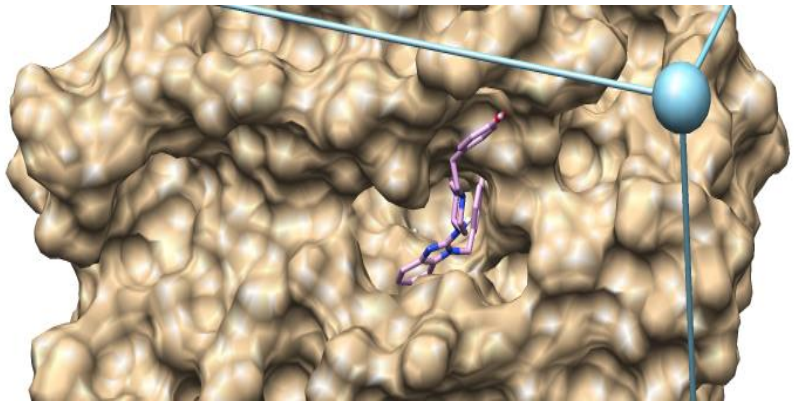
Programmi di Allineamento

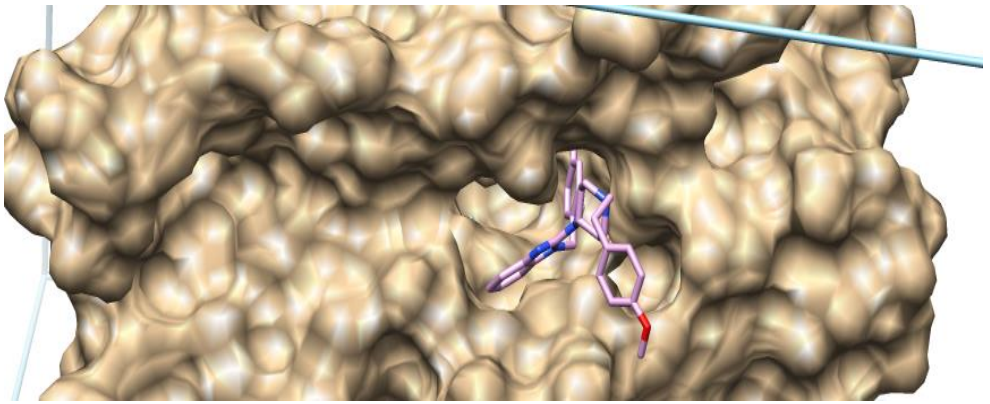


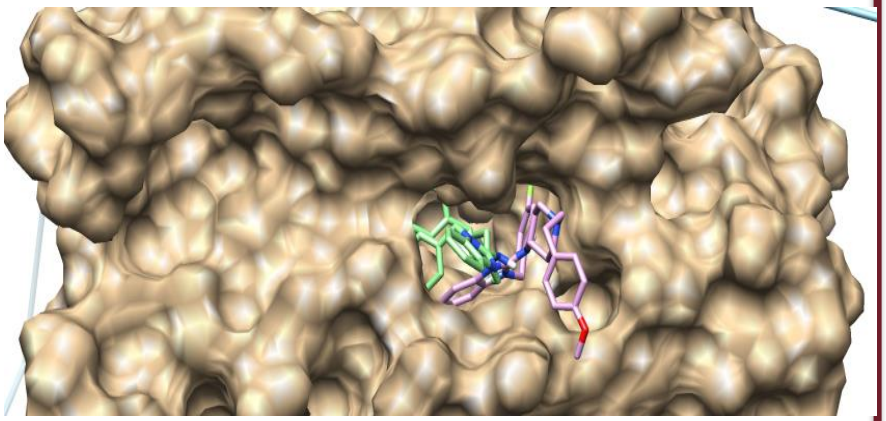
49 Farmaci dockati

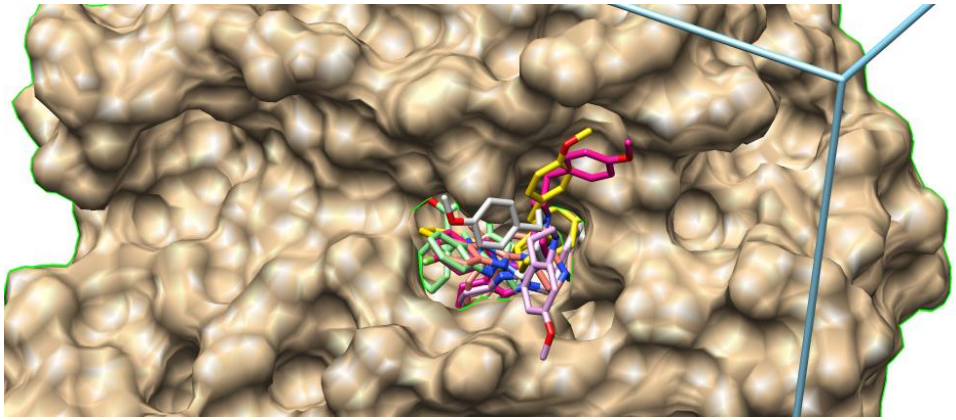


EZH2-EED disruptors - SB

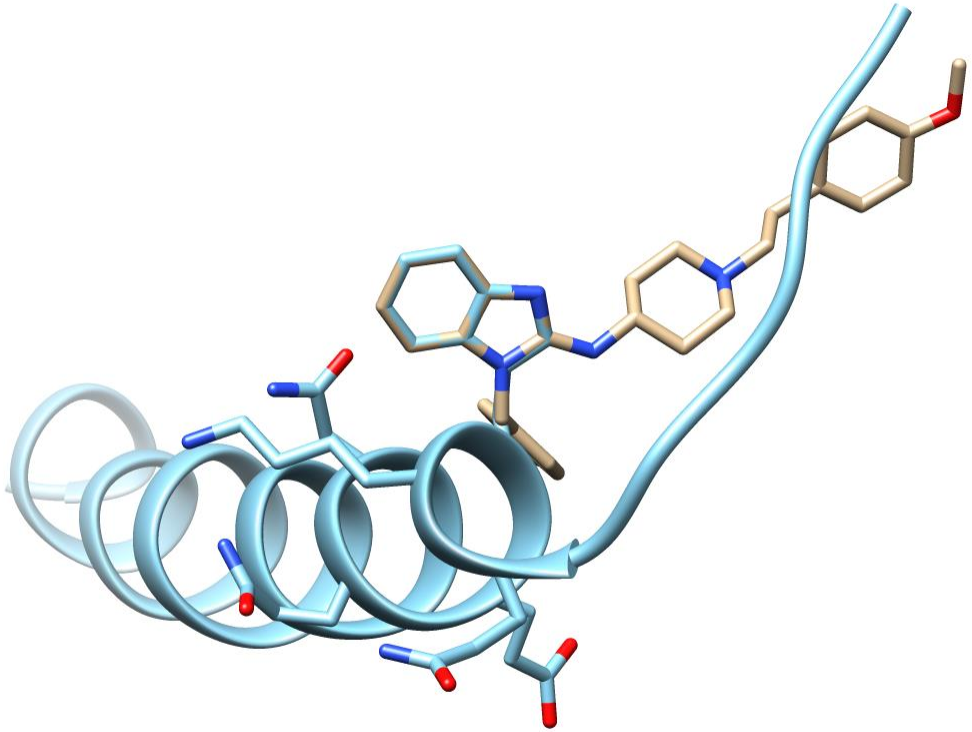






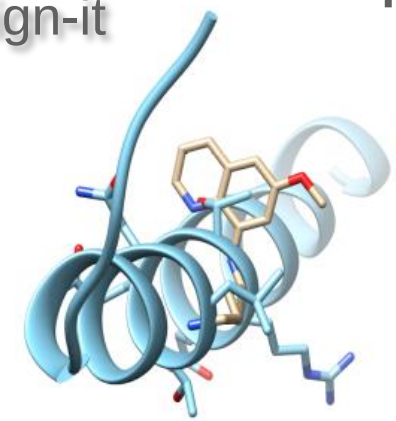


Allineamento LB per Astemizolo

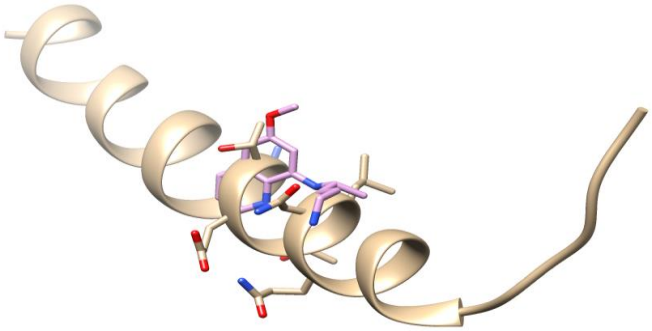


Primachina

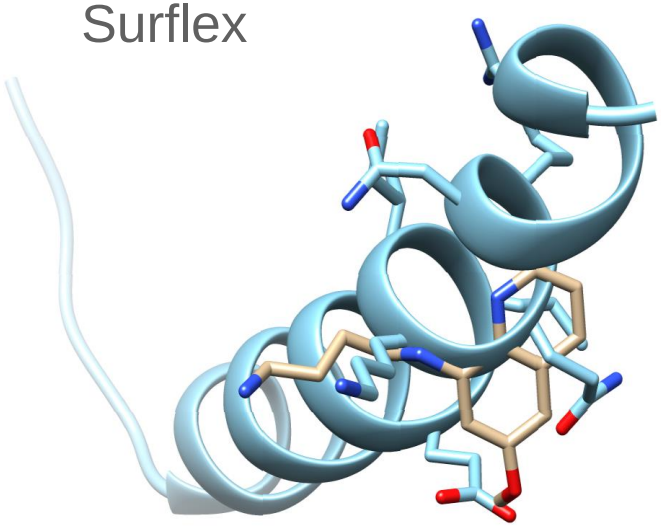
Align-it



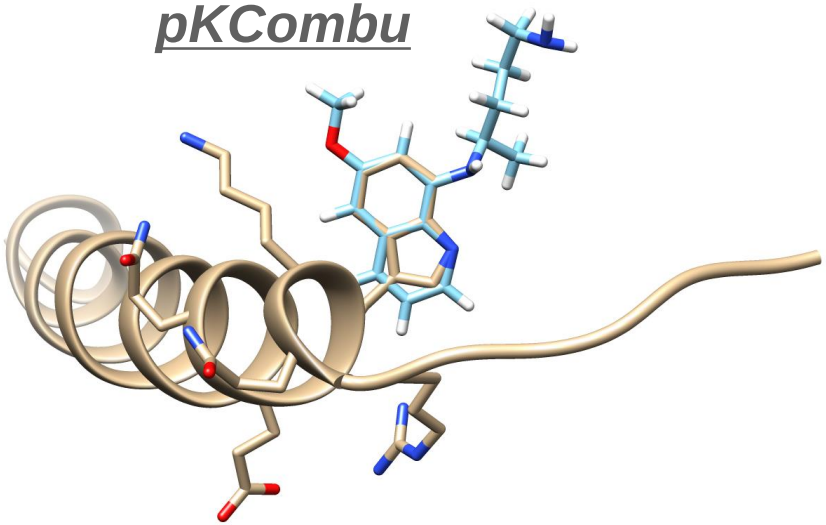
Shape-it



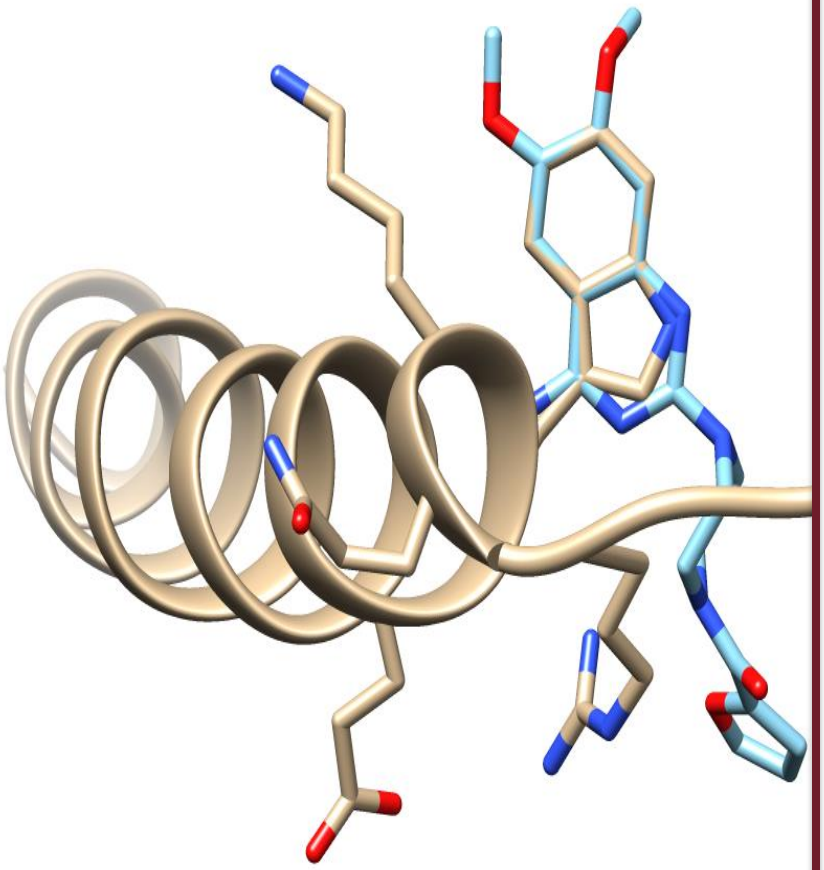
Surflex



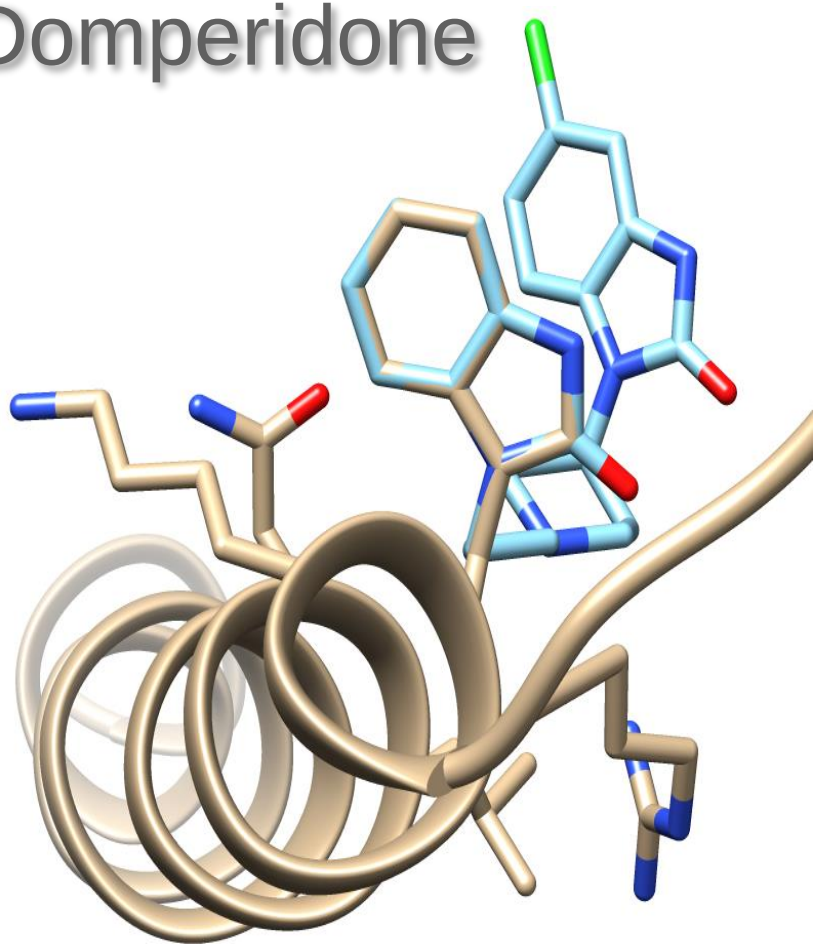
pKCombu



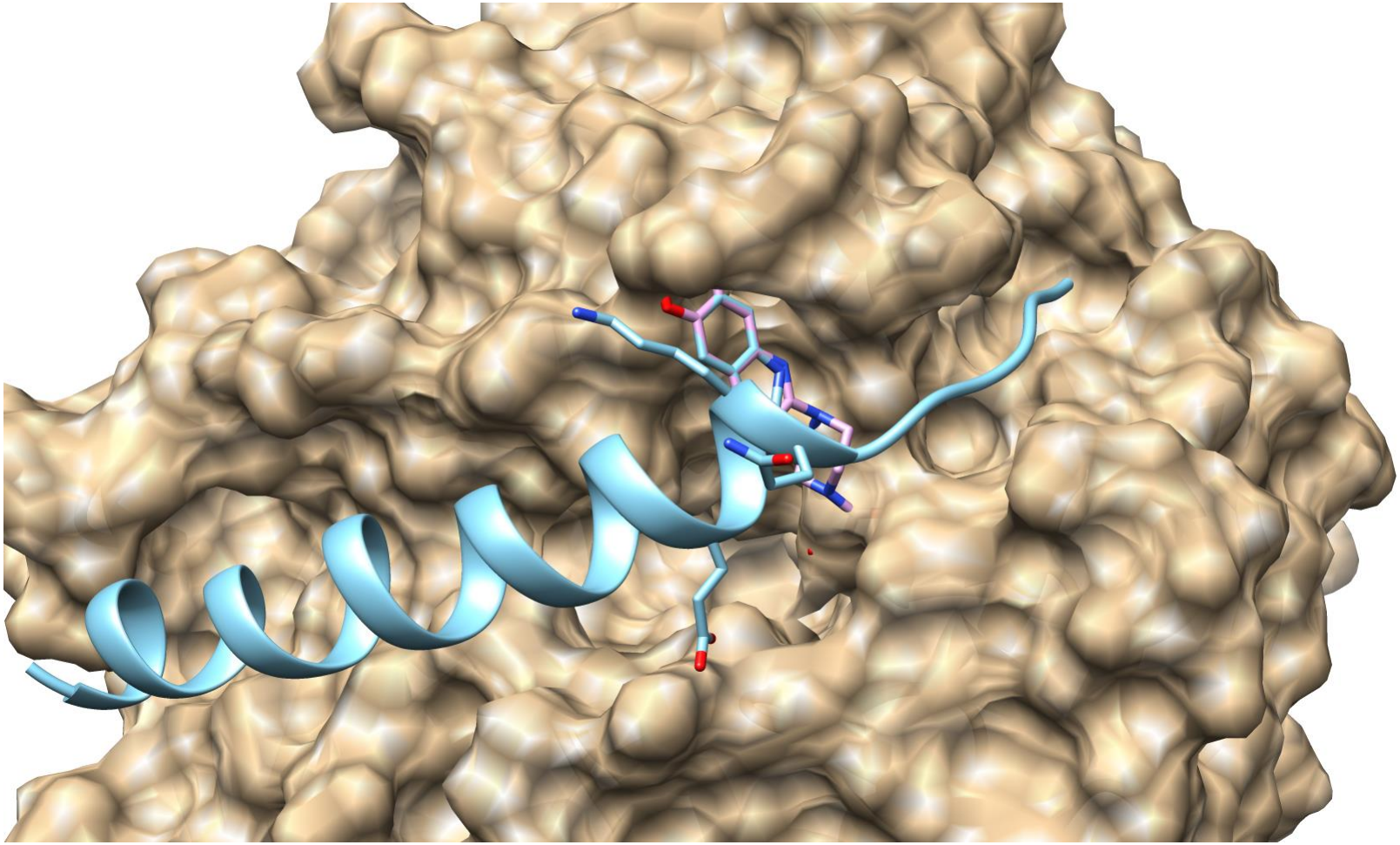
Prazosina



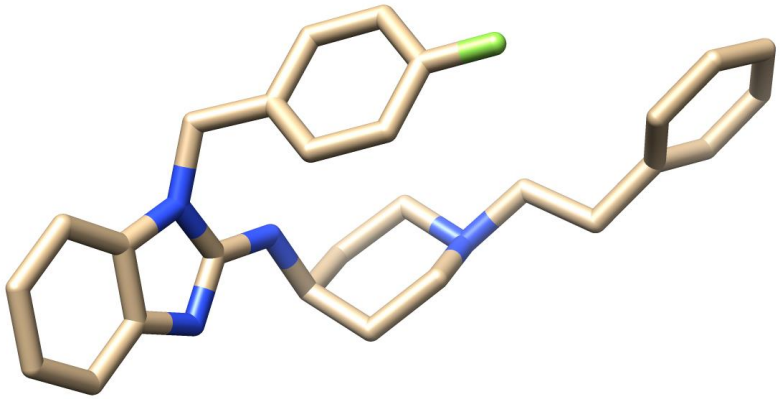
Domperidone

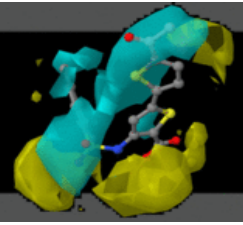


LB su EED



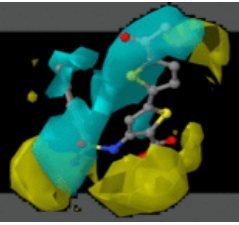
29 nuovi composti quali potenziali EZH2-EED disruptors con binding mode “Astemizolo-like” in collaborazione con il Laboratorio del prof. Antonello Mai





Conclusioni

- In seguito ad approfonditi studi di docking molecolare è stato possibile ipotizzare un binding mode per l'astemizolo differente da quello pubblicato
- Il binding mode è stato validato mediante l'uso di diversi programmi di docking molecolare
- L'applicazione di metodiche LB hanno ulteriormente confermato che il binding mode dell'astemizolo possa avvenire in maniera differente da quanto pubblicato
- Il binding mode di nuovi analoghi dell'astemizolo e' stato studiato e siamo in attesa dei dati biologici



Obiettivi Futuri

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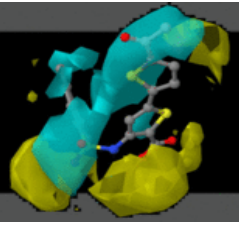
Molecole SB Allineate

3-D QSAR BINARIA

Predizione Attive/Inattive

Progettazione Nuovi Inibitori



Grazie per l'attenzione !