

# Applicazione e validazione di un metodo structure-based drug design per lo studio in silico di complessi di inclusione.

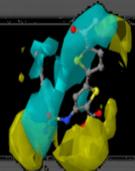


SAPIENZA  
UNIVERSITÀ DI ROMA

Facoltà di Farmacia e Medicina  
Corso di Laurea in Chimica e Tecnologia Farmaceutiche  
Tesi Sperimentale in Chimica Farmaceutica  
a.a. 2011/2012

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# Introduzione

- Le ciclodestrine (CDs) sono oligomeri ciclici costituiti da monomeri di D-(+)-glucopiranosio presentanti legami  $\alpha(1,4)$  glicosidici.
  
- Classificazione ciclodestrine:
  - Naturali
  - Derivatizzate: ➔ alchilate
  - ➔ dimeriche
  - ➔ polimeriche
  
- Applicazioni alimentari
- Applicazioni cosmetiche
- Applicazioni farmaceutiche
- Applicazioni computazionali

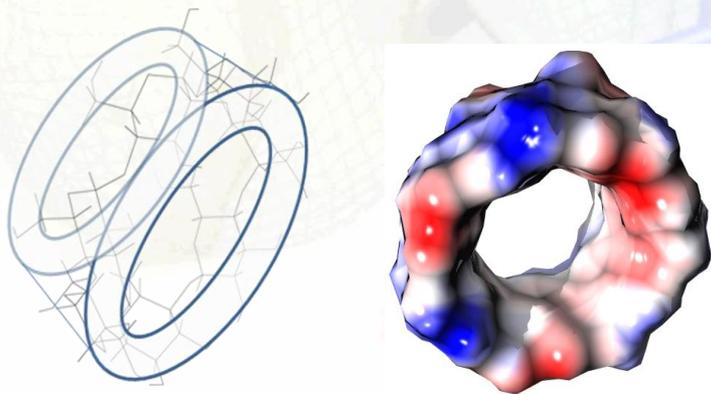


Figura 1. Struttura ciclodestrine

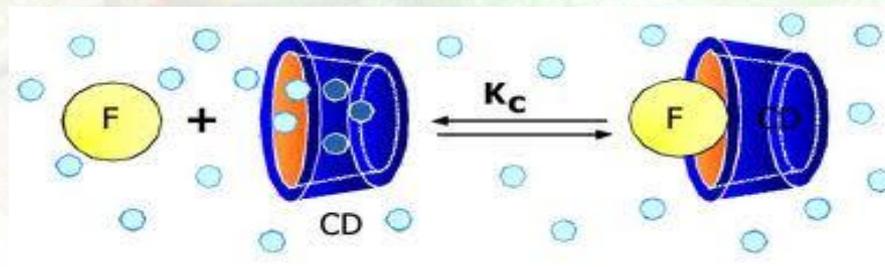
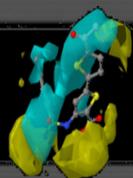
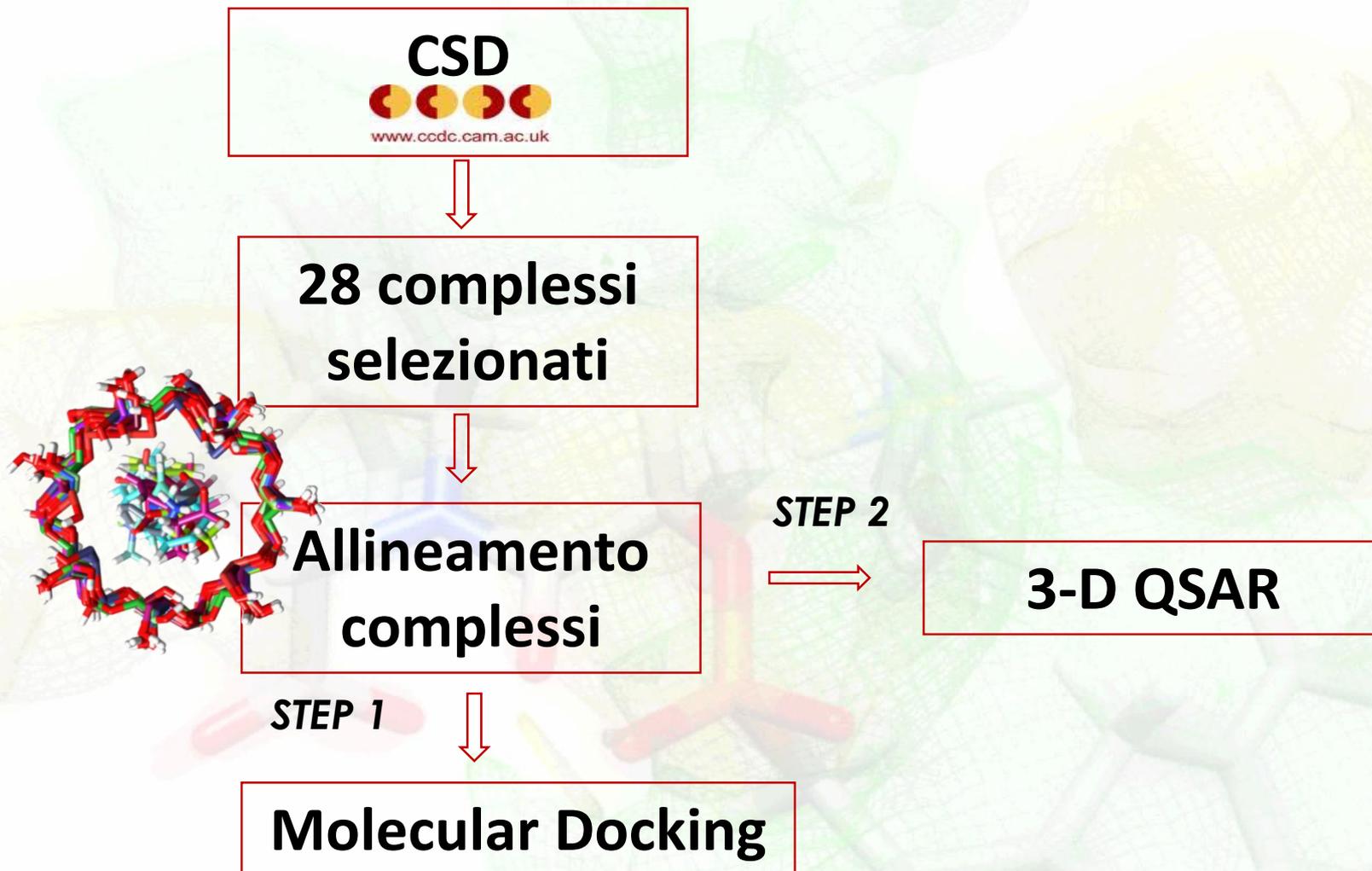
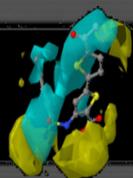


Figura 2. Schema processo di inclusione



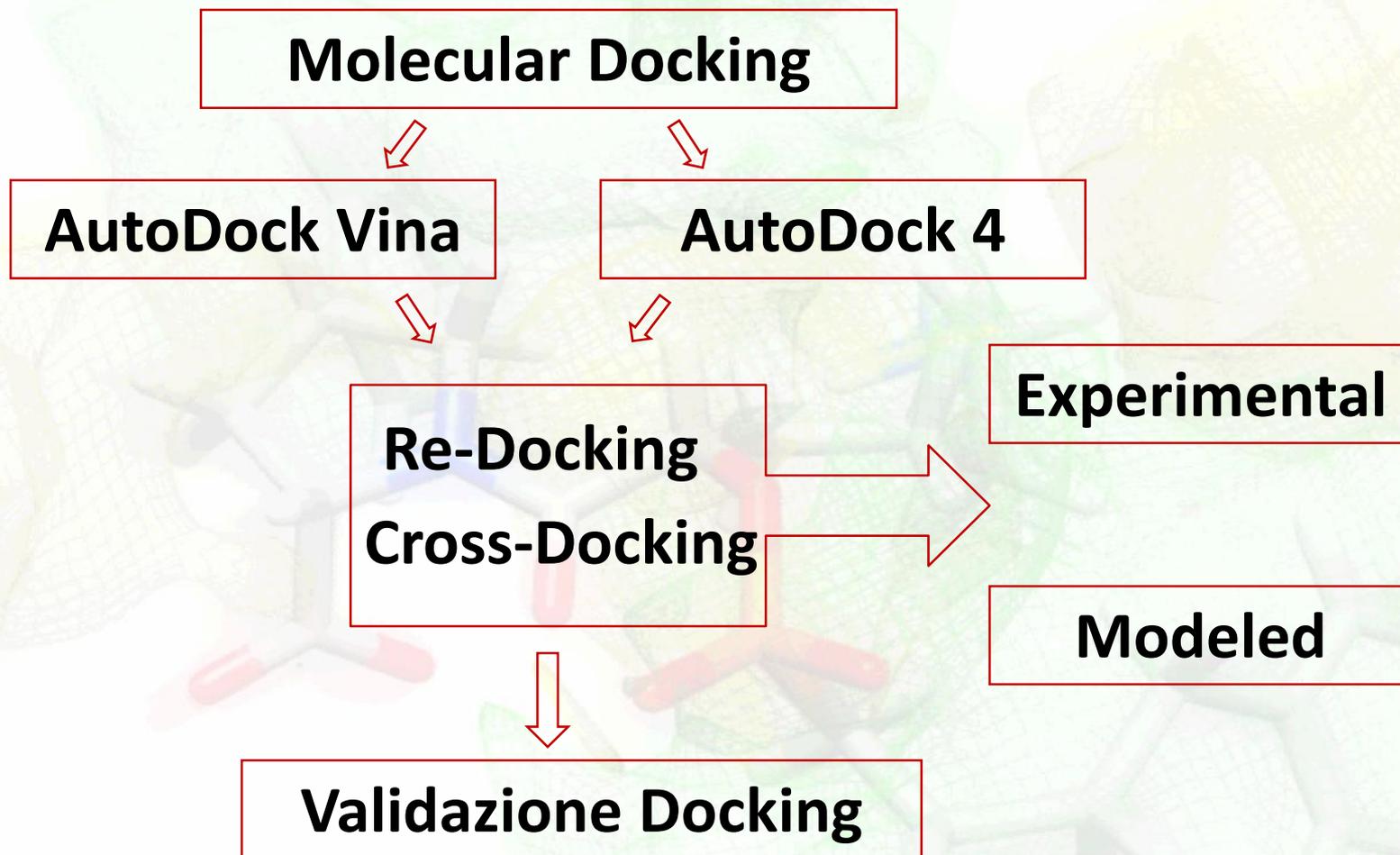
# Work Flow

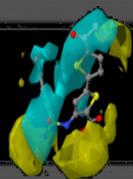




# Work Flow

## STEP 1





# Work Flow

*STEP 2*

**Selezione Training Set**



**Trasposizione centroidi**



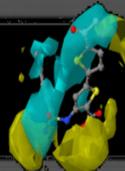
**Structure Based  
Alignment**



**3-D QSAR**



**COMBINE**



# Selezione complessi

CSD

Il presente lavoro è focalizzato sulle  $\beta$ -CDs.  
Sono state selezionati e scaricati 28 complessi 1:1  
(ligando: CD) dal *Cambridge Structural Database*  
(CSD).

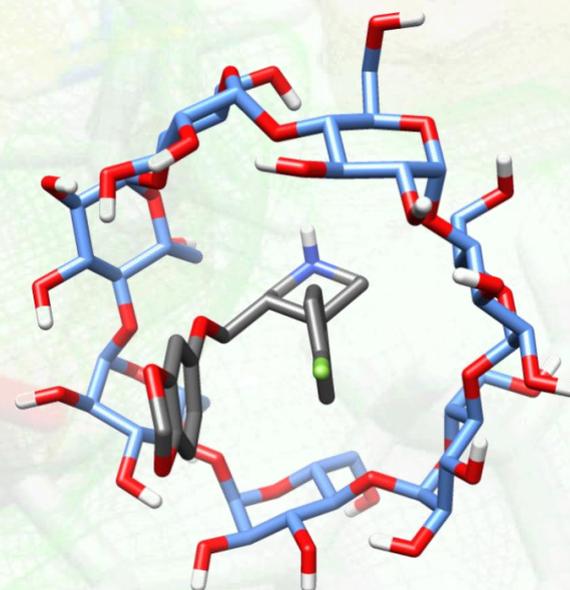
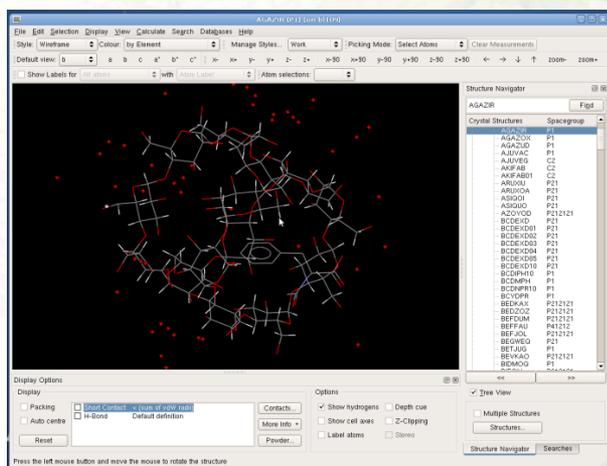
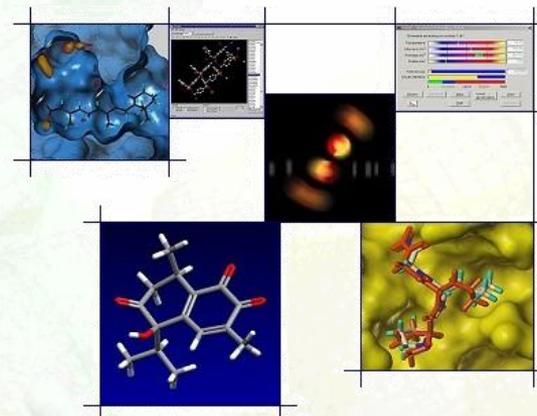
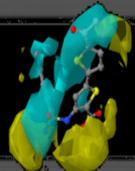
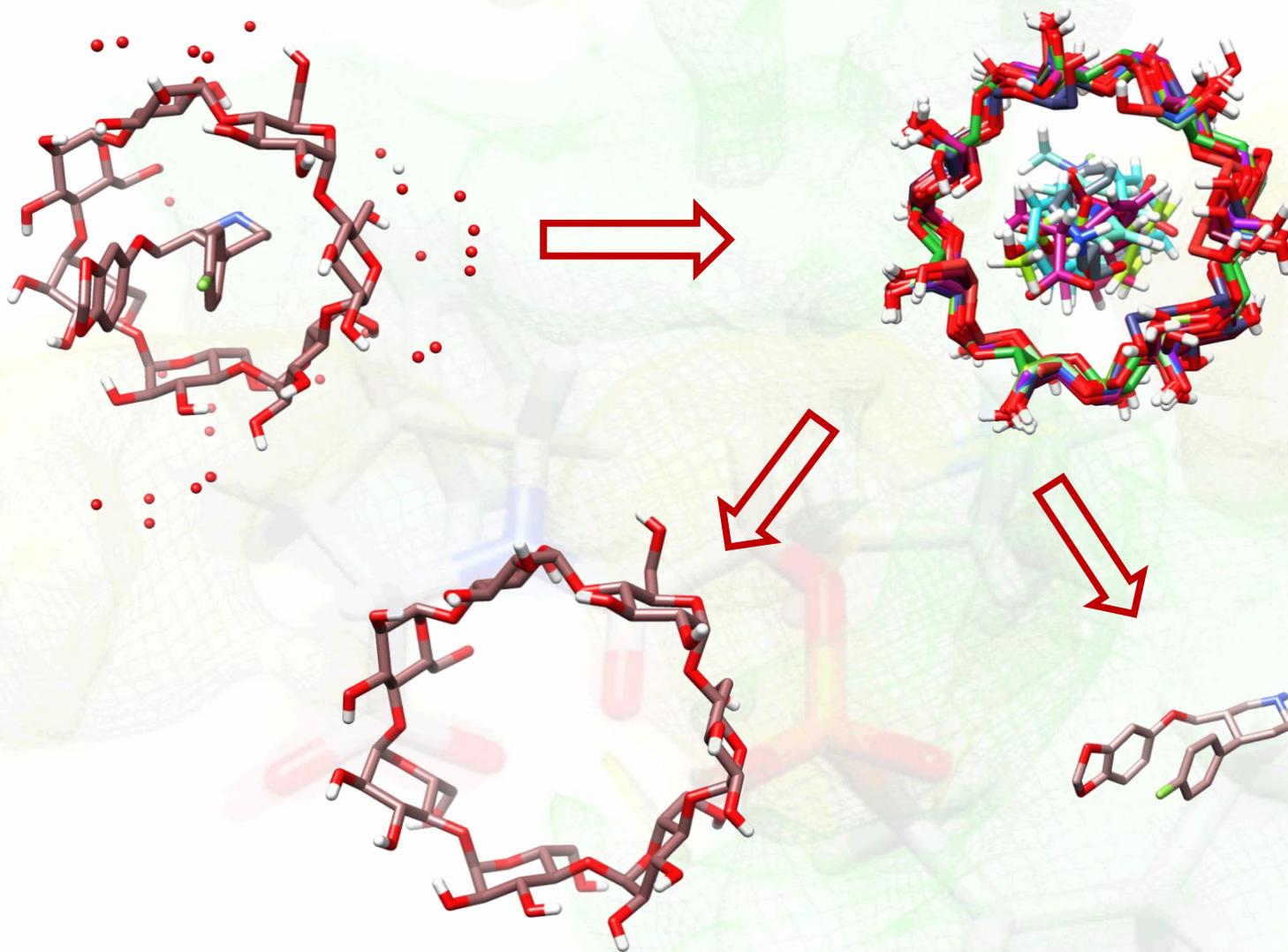
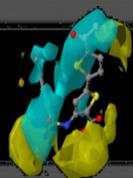


Figura 3. Software Mercury a sinistra, a destra complesso BEGWEQ

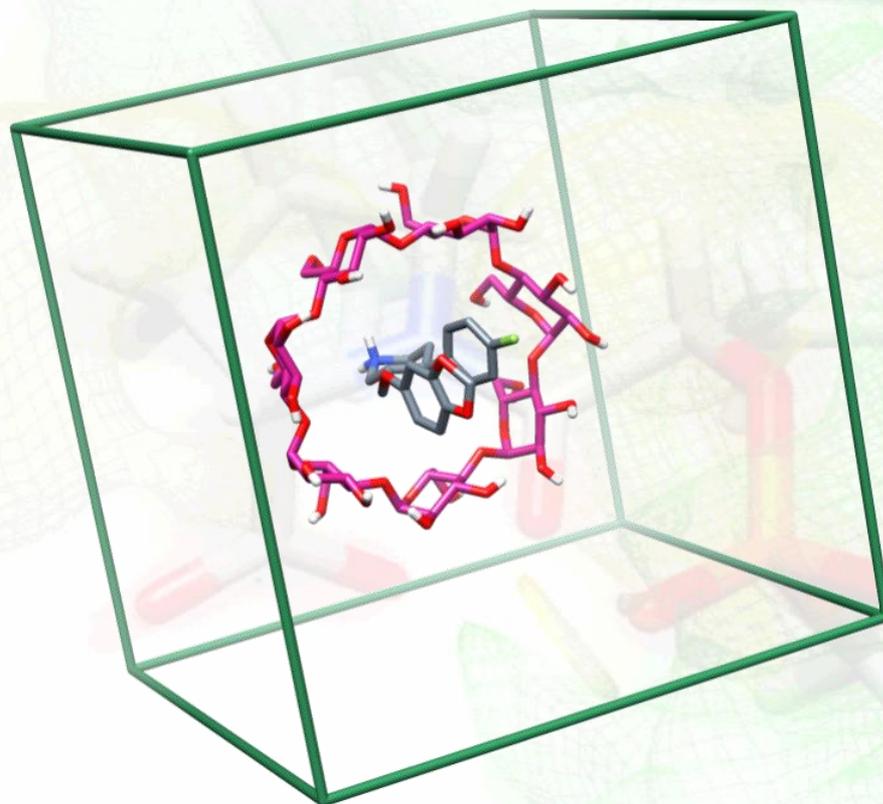


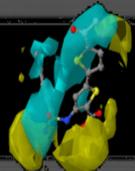
# Allineamento complessi



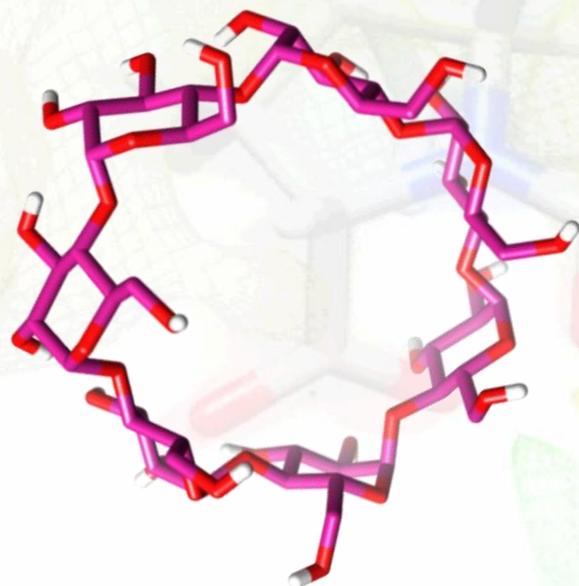


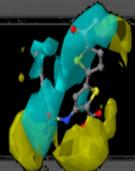
# Molecular Docking



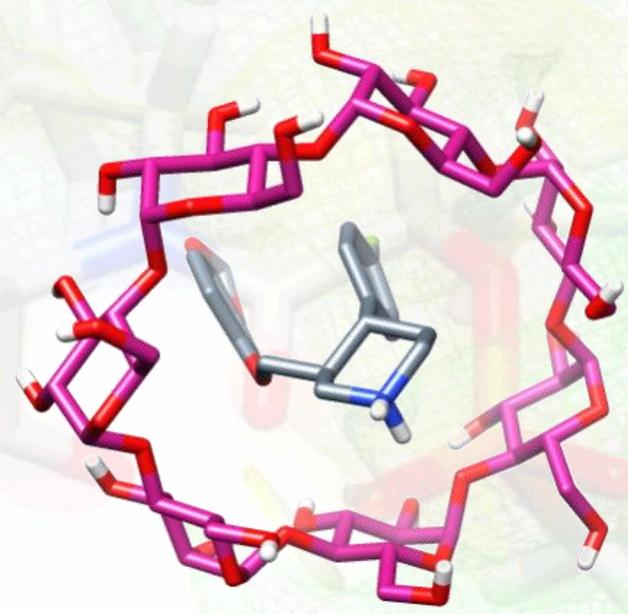


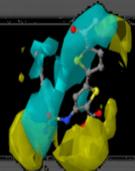
# Molecular Docking



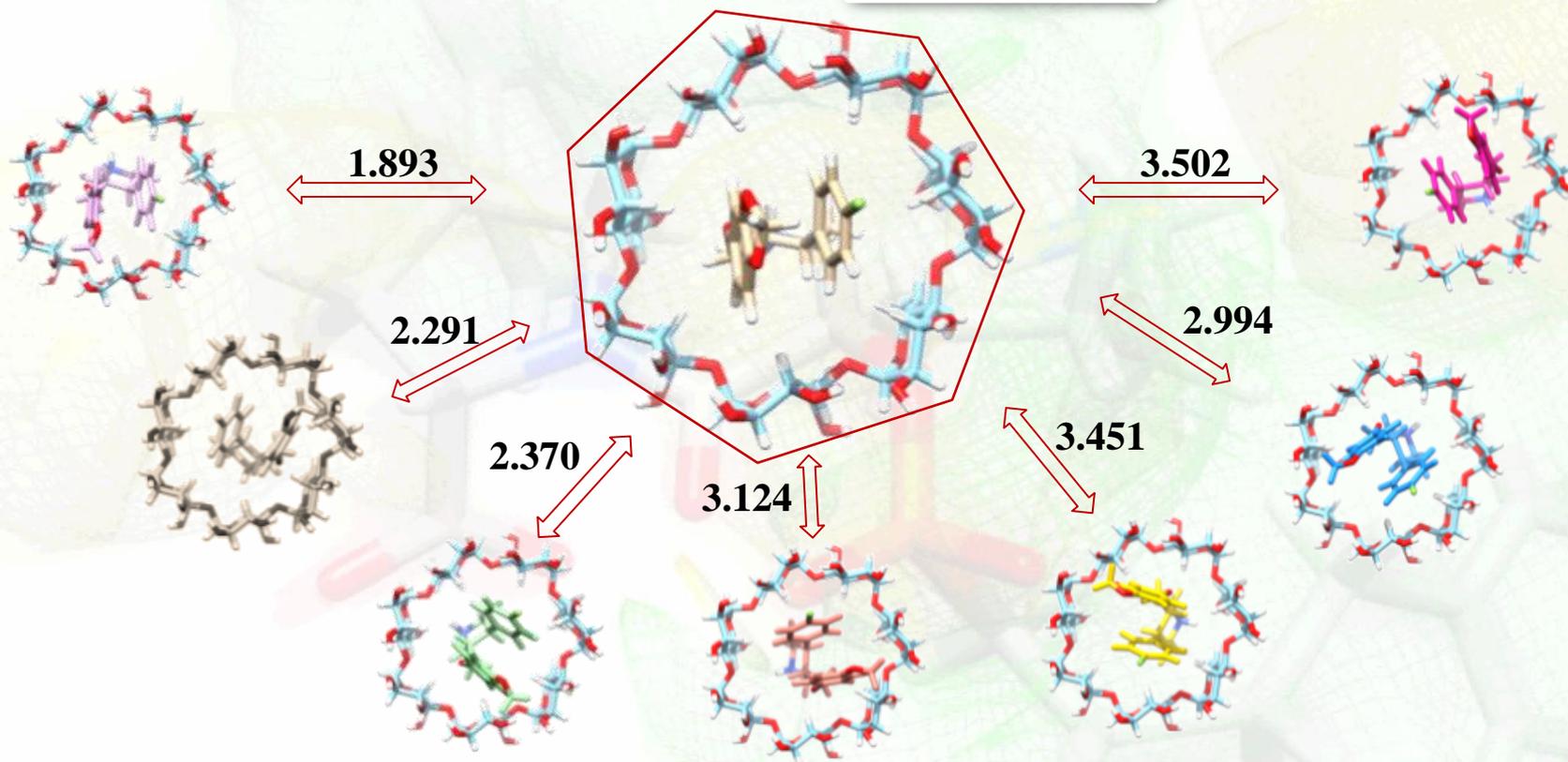


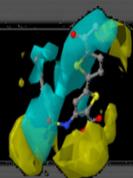
# Molecular Docking





# Molecular Docking





# Molecular Docking



➤ **BD (Best Docked)**

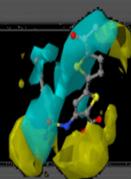


➤ **BC (Best Cluster)**

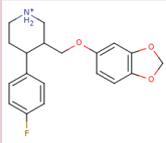
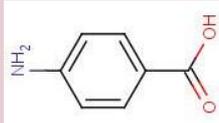
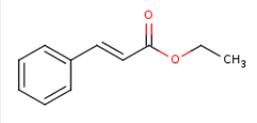
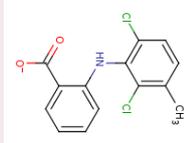
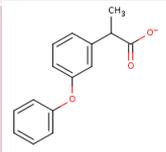
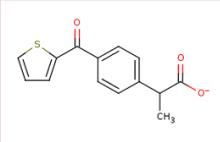
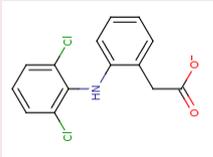
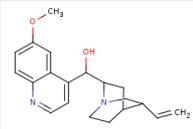
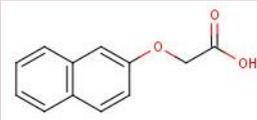
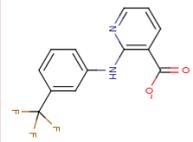
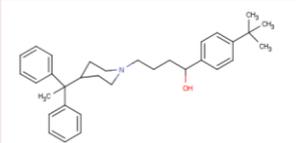
**PDB  
Binding Energy  
RMSD**

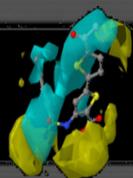


$$\text{RMSD}(\theta_1, \theta_2) = \sqrt{\text{MSE}(\theta_1, \theta_2)} = \sqrt{E((\theta_1 - \theta_2)^2)} = \sqrt{\frac{\sum_{i=1}^n (x_{1,i} - x_{2,i})^2}{n}}$$



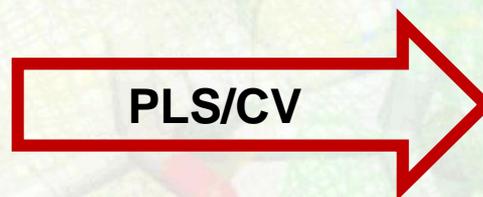
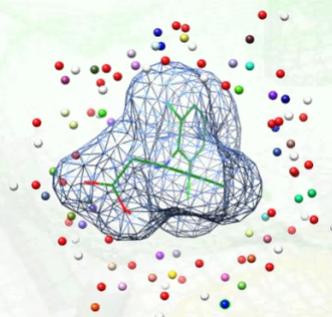
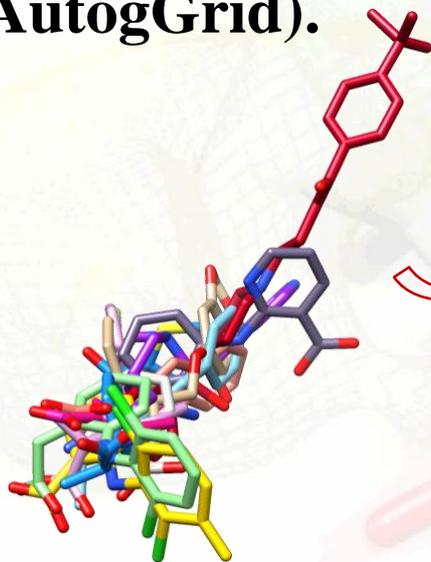
# Scelta Training Set

Nome	Struttura	Nome	Struttura
Begweq		Vojliq	
Bidmoq		Wergow	
Getpaw		Wezsie	
Hehjej		Xegtaf	
Odejow		Xopgis	
Vofjik		Xuhtid	

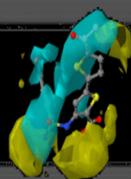


# COMBINE

**Calcolo delle energie di interazione tra ogni atomo facente parte la  $\beta$ -CD e il suo ligando (Autogrid).**

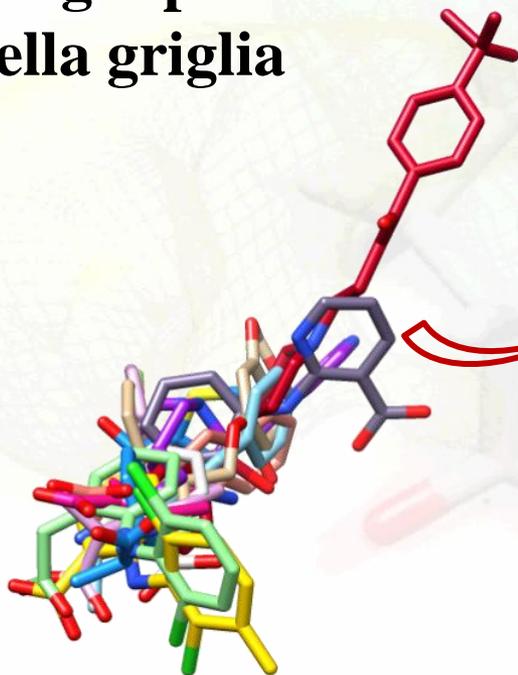


**Modello  
COMBINE**



# 3-D QSAR

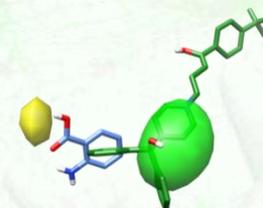
Interazioni energetiche tra *probe* e il ligando in ogni punto della griglia

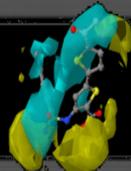


Calcolo dei campi di interazione molecolare (MIF)



Modello 3-D QSAR





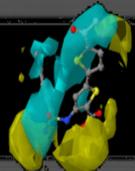
# RISULTATI

## DOCKING:

	Re-Docking		Cross-Docking		Re-Docking Modeled		Cross-Docking Modeled	
	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>
Media RMSD	2.89	2.96	2.97	3.14	2.98	2.91	2.91	2.98

	Re-Docking		Cross-Docking		Re-Docking Modeled		Cross-Docking Modeled	
	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>
Media RMSD	2.58	2.46	2.63	2.56	2.62	2.42	2.74	2.48

	Re-Docking		Cross-Docking		Re-Docking Modeled		Cross-Docking Modeled	
	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>	<b>BD</b>	<b>BC</b>
RMSD $\leq 2$	9	11	12	9	6	6	3	7
RMSD $\leq 3$	21	21	21	18	24	25	21	24
% DA	53.57%	57.14%	58.93%	48.21%	53.57%	55.36%	42.86%	55.36%
% RMSD $\leq 3$	75%	75%	75%	64,3%	85,71%	89,3%	75%	85,71%



# RISULTATI

## 3-D QSAR:

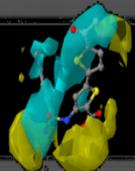
PROBE	PC	$r^2$	$q^2_{LOO}$	$q^2_{K5FCV}$
d	1	0.77	0.36	0.36

## COMBINE:

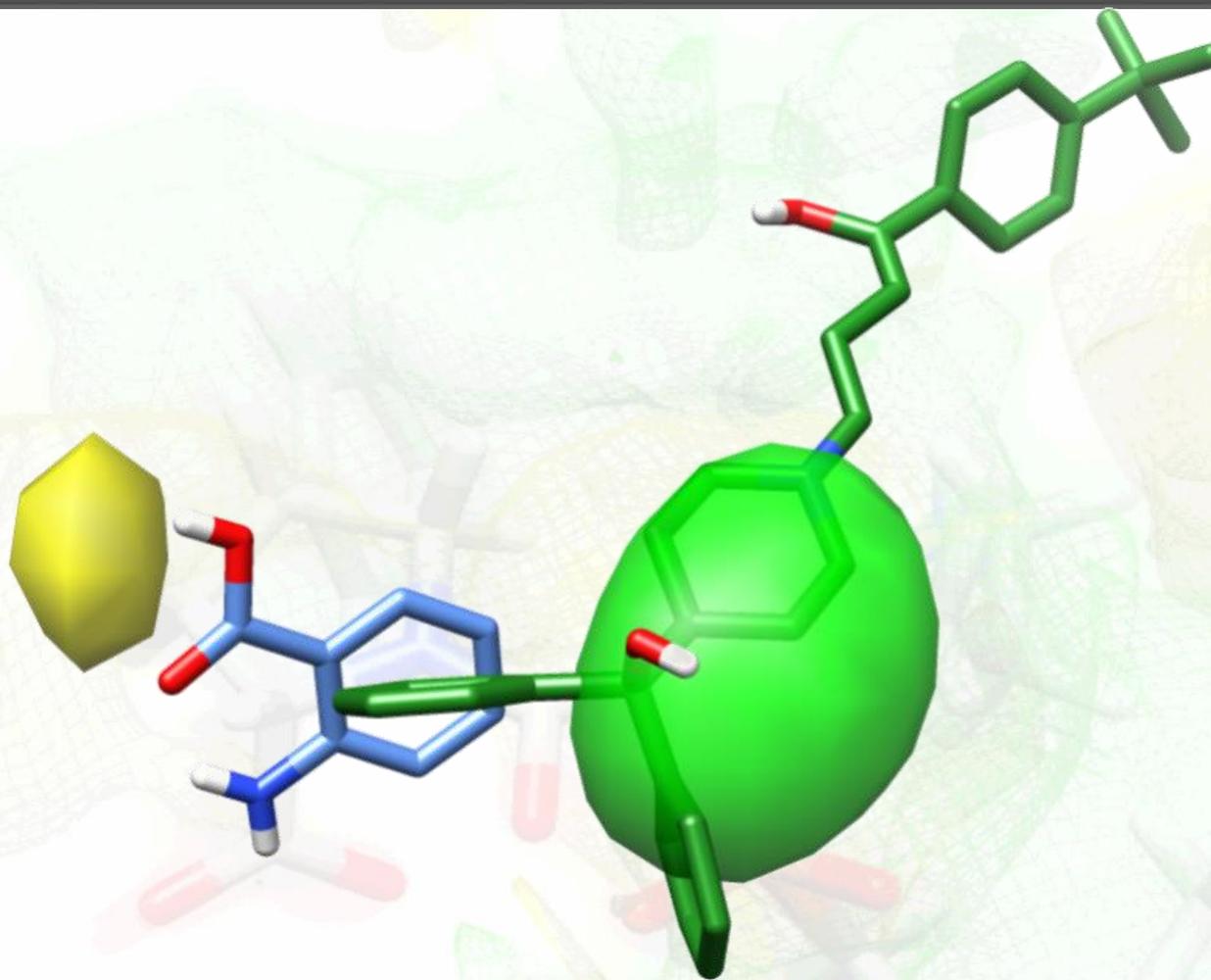
Fields	PC	$r^2$	$q^2_{LOO}$	$q^2_{K5FCV}$
dry_ele_ste	3	0.9	0.34	0.3

<u>Test Set</u>	<u>pKs Exp</u>	<u>pKs Pred</u>	
		3-D QSAR	COMBINE
hehjejP	3.18	2.74	2.59
vojliqP	2.9	2.45	2.26
xegtafP	4.92	3.04	3.21
xopgisP2	3.05	2.88	2.59
xopgisP	3.05	2.88	2.83
xuhtidP	3.95	3.59	3.59
SDEP		0.86	0.83

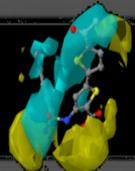
Predictions



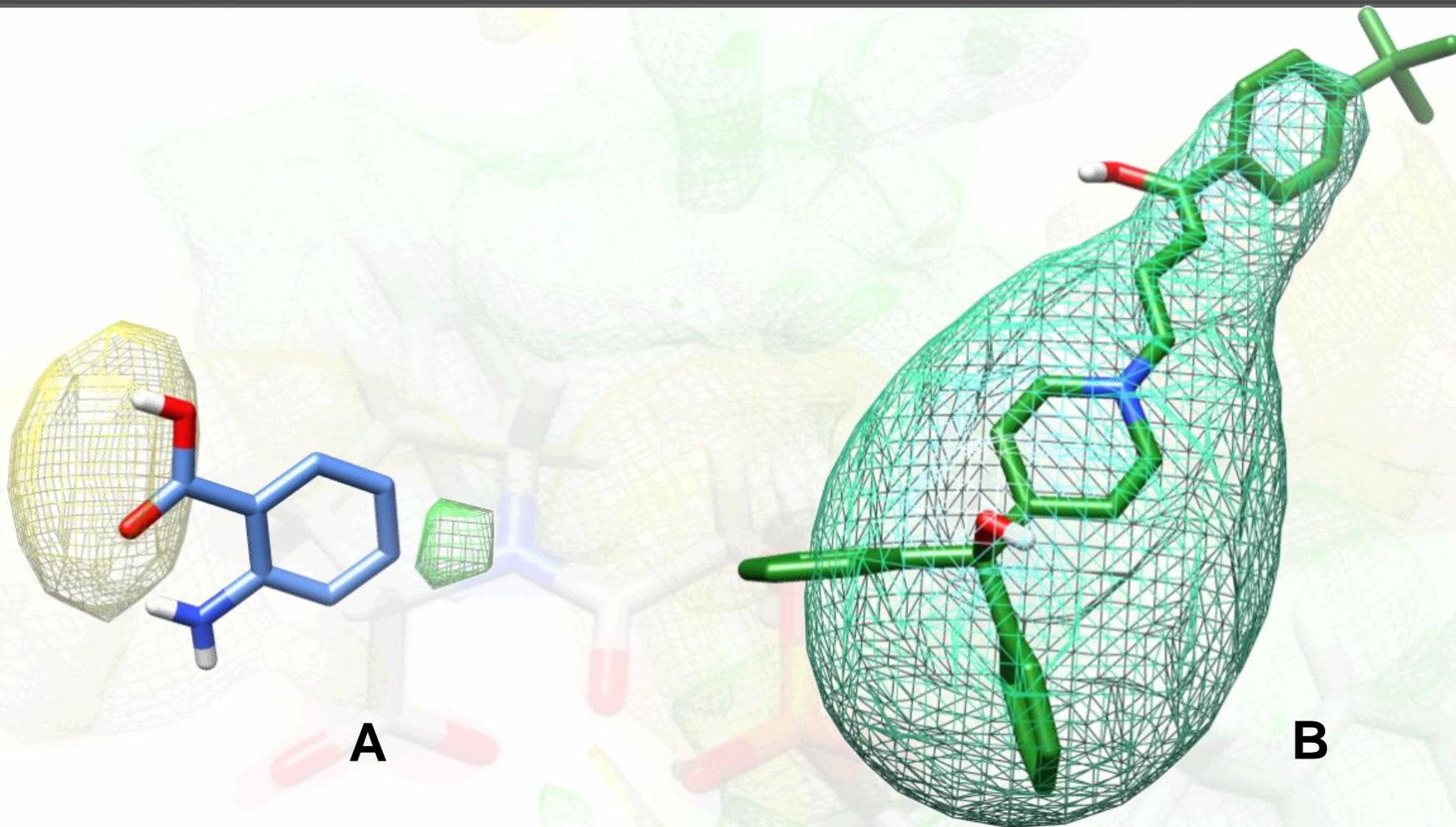
# RISULTATI



***“CoMFA-like” map modello 3-D QSAR.***



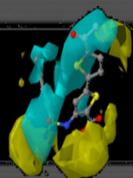
# RISULTATI



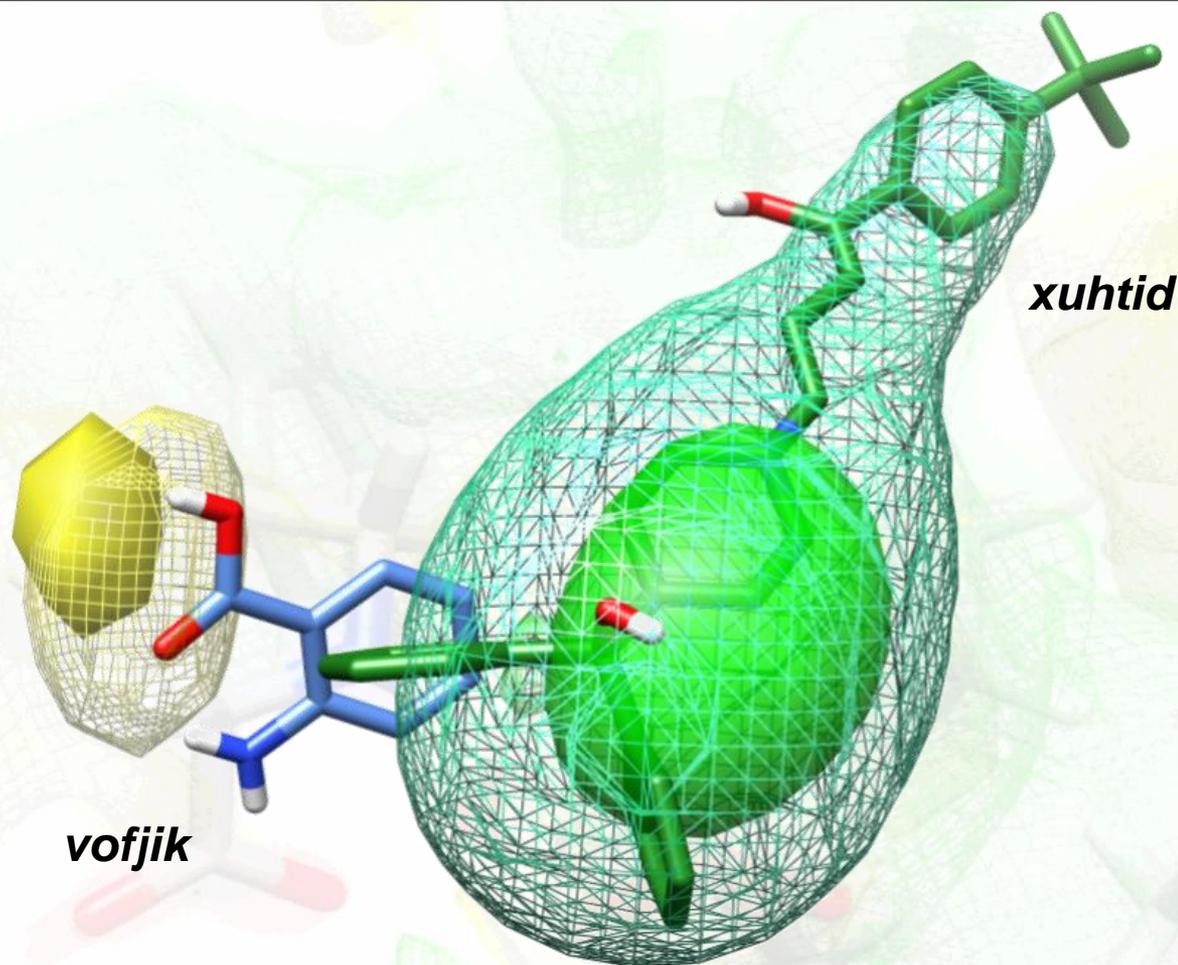
A

B

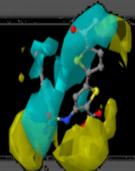
*“Activity Contribution Plot” probe d modello “raw” 3-D QSAR, A: vofjik (pKs=1.56) e B (pKs=3.95).*



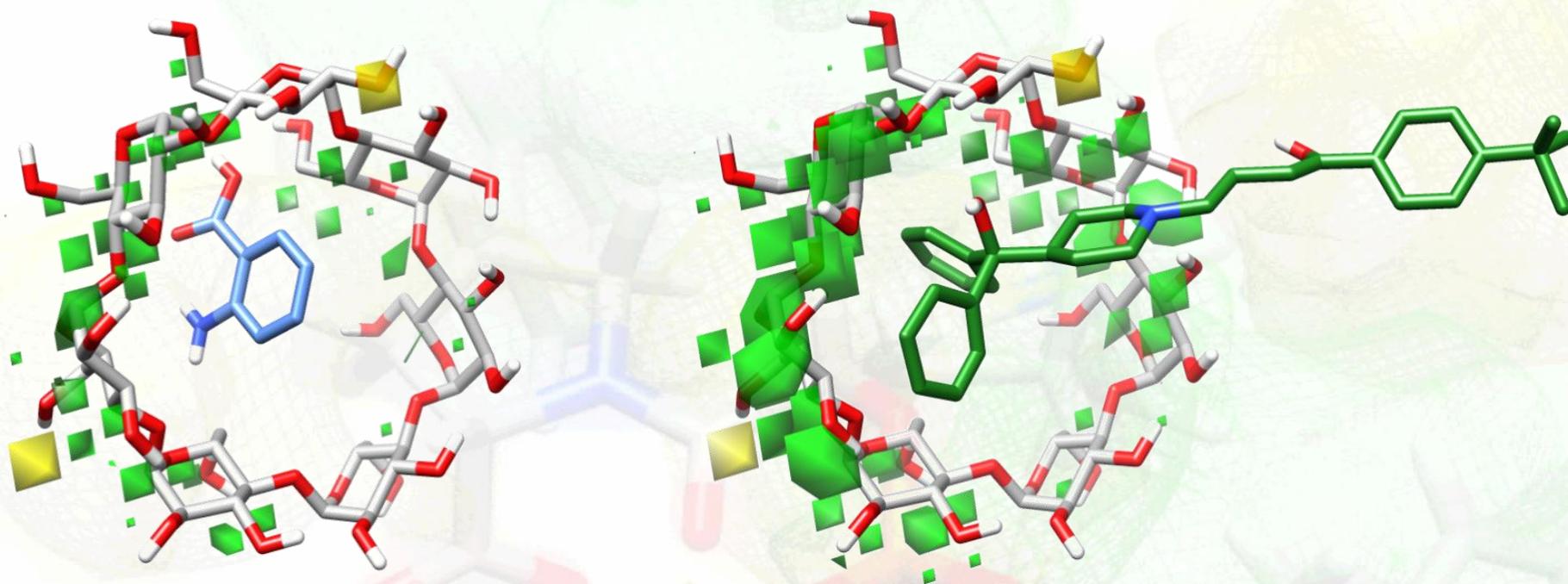
# RISULTATI



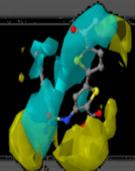
**“CoMFA-like” e “Activity Contribution Plot “  
vofjik (pKs=1.56) e xuhtid (pKs=3.95).**



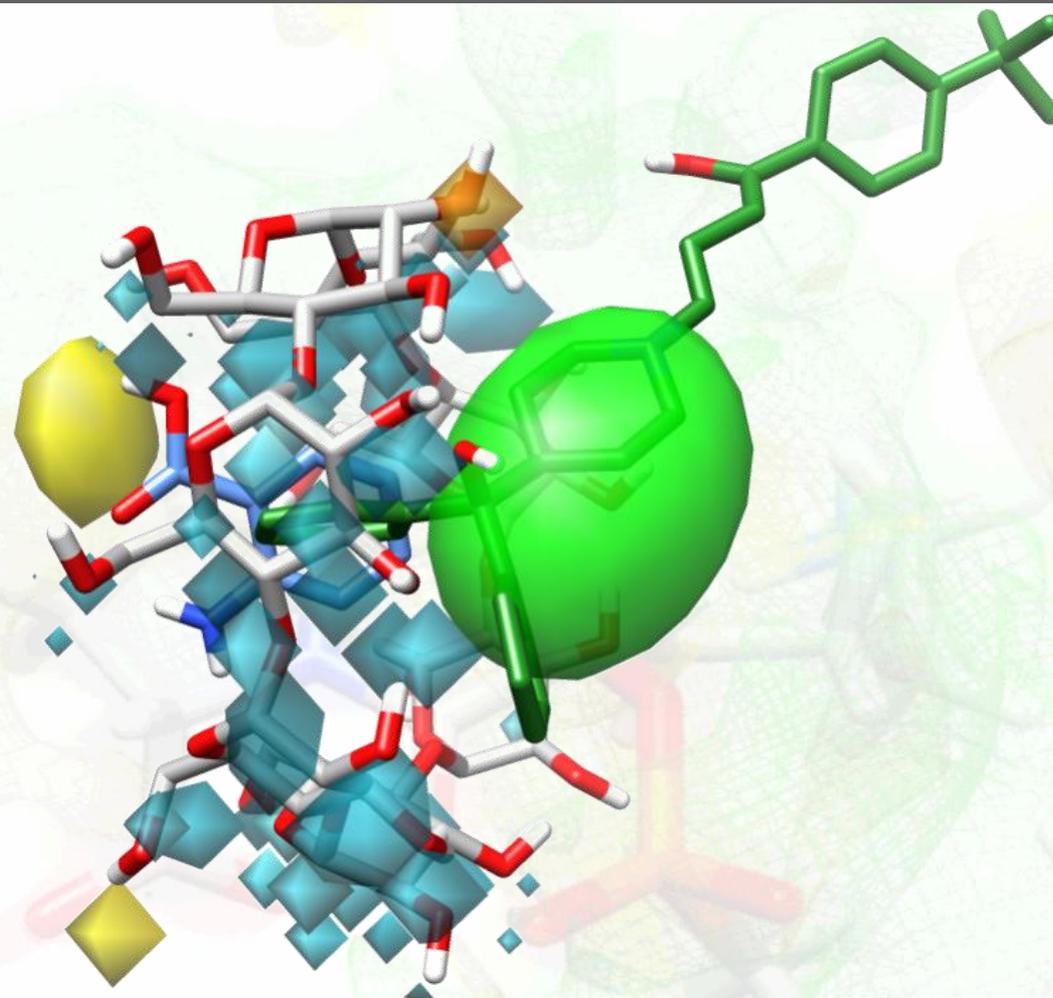
# RISULTATI



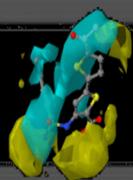
***Activity Contribution Plot multi-fields dry-ele-ste del modello COMBINE***



# RISULTATI

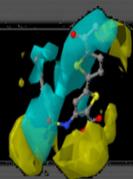


***“3-D QSAR e COMBINE.***



# CONCLUSIONI

- Un nuovo protocollo di docking per determinare la posa di molecole incluse è stato validato
- Utilizzando le tecniche 3-D QSAR e COMBINE sono stati sviluppati modelli che permettono la predizione di costanti di stabilità per molecole di cui non sono noti esperimenti di inclusione
- Questa è la prima applicazione di un uso combinato di docking e SB 3-D QSAR alle CDs



# SVILUPPI FUTURI

- Il metodo sarà applicato anche a diverse CDs e nuovi modelli saranno sviluppati
- I risultati ottenuti suggeriscono di sviluppare un modello combinato 3-D QSAR/COMBINE
- L'applicazione della metodica è in corso su diversi principi attivi per effettuare una ulteriore validazione.