Applicazione della tecnica 3-D QSAR a serie di molecole ad attività anti-PKC Theta

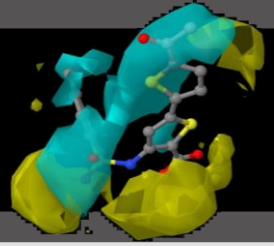
Facoltà di Farmacia e Medicina
Corso di Laurea in Biotecnologie

SAPIENZA
UNIVERSITÀ DI ROMA

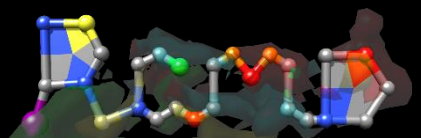
Candidato: Daniele Cavariani
Matricola: 1689398

Relatore: Prof. Rino Ragno

Anno Accademico 2018/2019



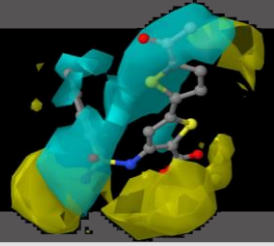
QSAR



(Quantitative Structure-Activity Relationships)

- **Mette in relazione l'attività biologica delle molecole con le caratteristiche geometriche e chimico–fisiche.**

- **Permette di stabilire le regole per valutare e predire l'attività di nuovi composti.**



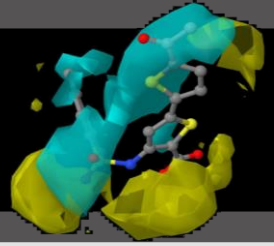
3D-QSAR

Di cosa abbiamo bisogno:

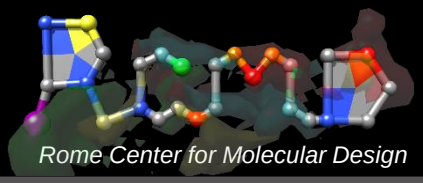
- Struttura molecolare
- Attività delle molecole

Procedura standard:

- Analisi Conformazionale
- Allineamento
- Creazione e ottimizzazione dei modelli
- Analisi dei risultati e delle mappe di contorno

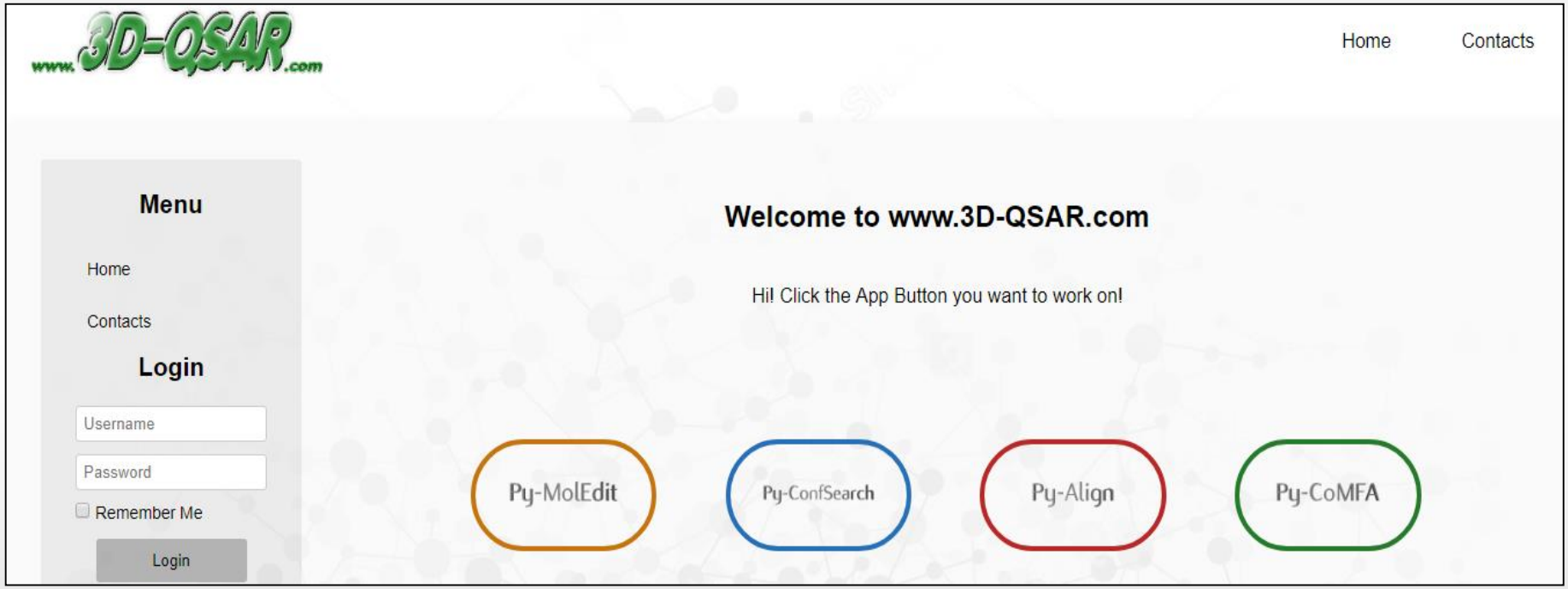


Obiettivo della tesi



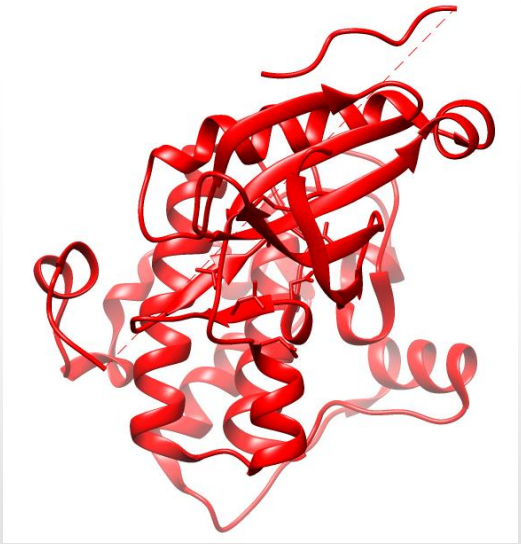
- 3D-QSAR attraverso il metodo CoMFA (Comparative Molecular Fields analysis).
- Modelli ligand-based.
- Utilizzo del portale www.3d-qsar.com

Sito web contenitore di una serie di applicazioni:



Protein-Chinasi C Theta

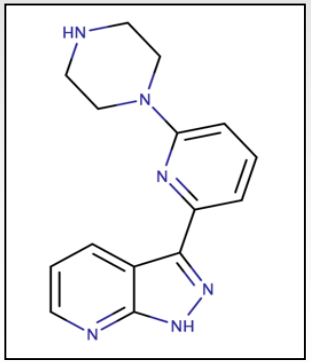
- **Tre studi 3D-QSAR.**
- **Famiglia delle chinasi.**
- **Ruolo nel differenziamento e nell'attivazione dei linfociti T.**
- **Coinvolte nelle malattie autoimmuni (Artrite Reumatoide, Psoriasi).**



Dataset

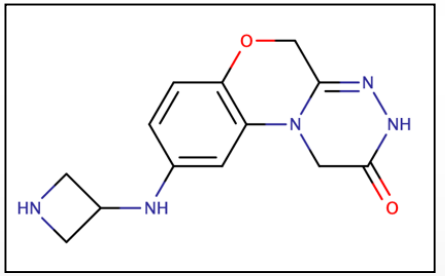
- **Dataset PKC THETA 1**
  (24 pridilpirazolpiridine)

1



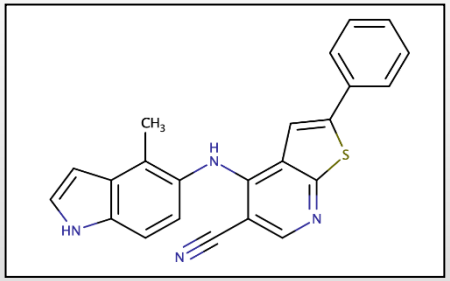
- **Dataset PKC THETA 2**
  (54 triazinoni triciclici)

2

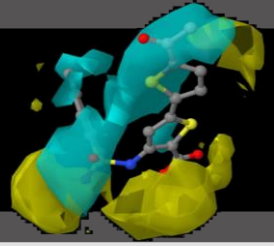


- **Dataset PKC THETA 3**
  (55 tienopiridincarbonitrili)

3



- **Dataset PKC THETA (All)**
  (133 molecole)

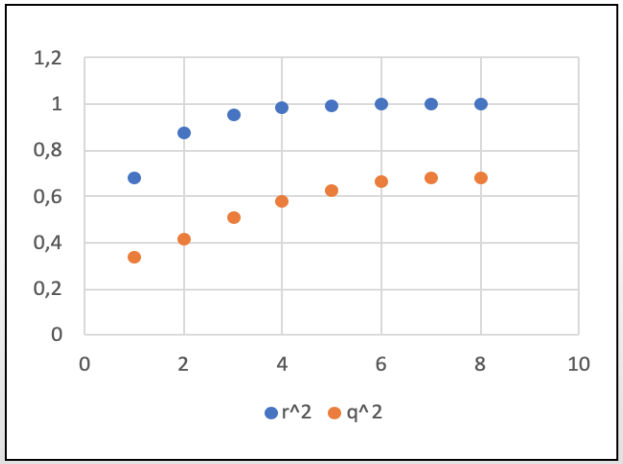


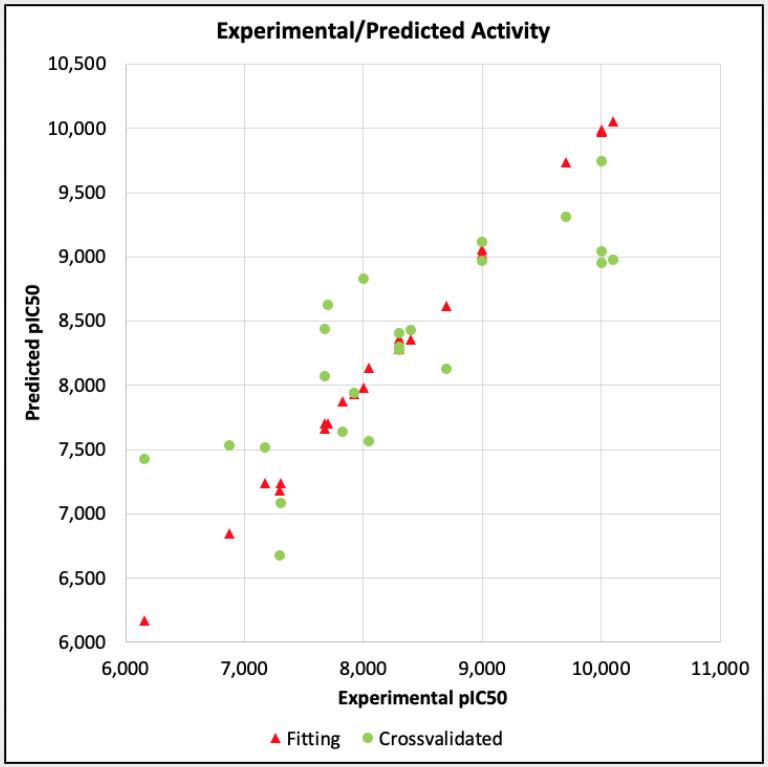
Modelli CoMFA

- **Modelli di default per ogni allineamento.**
- **Modifica di determinati parametri (Atomo Sonda, Spaziatura/Estensione della griglia, CutOff, Min. Sigma) → più di 300 modelli.**
- **Incremento del valore di q^2 dal 11% al 18%.**

Modello PKC THETA 1

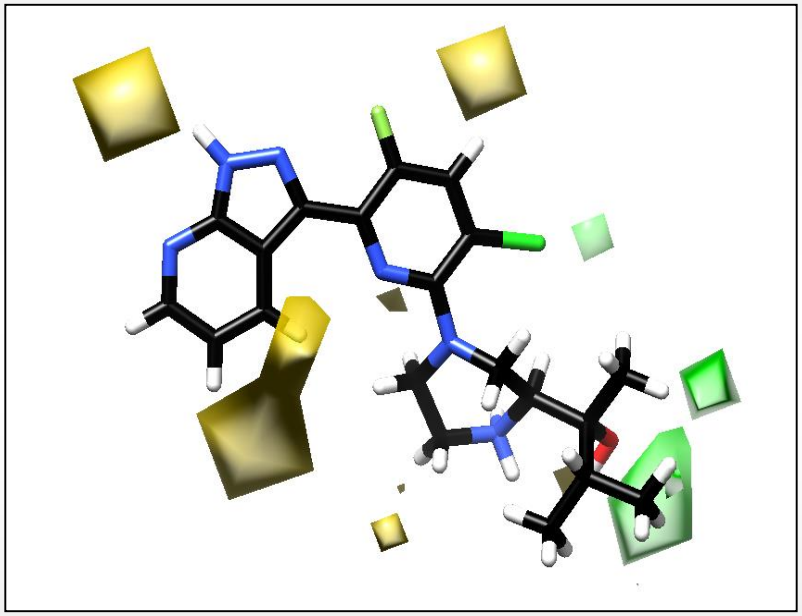
- $q^2 = 0{,}633$
- $r^2 = 0{,}998$
- ONPC = 6

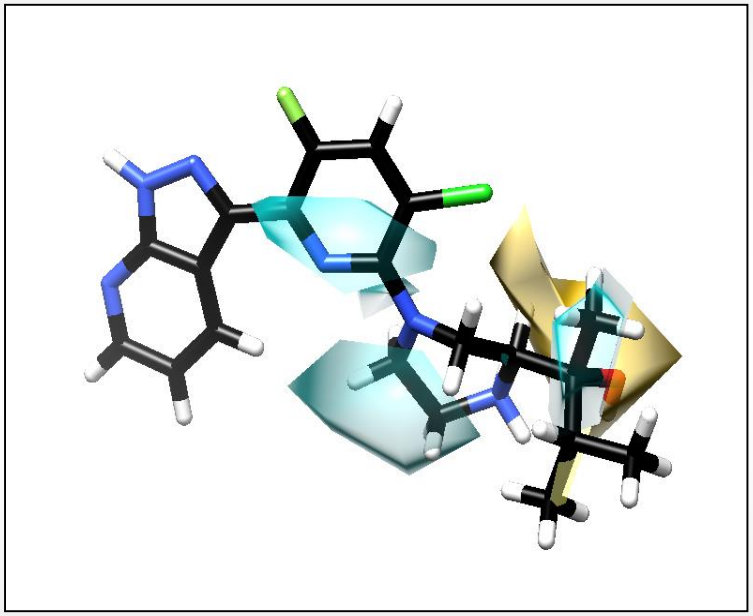




Modello PKC THETA 1

Molecola A24 (mappe CoMFA2)

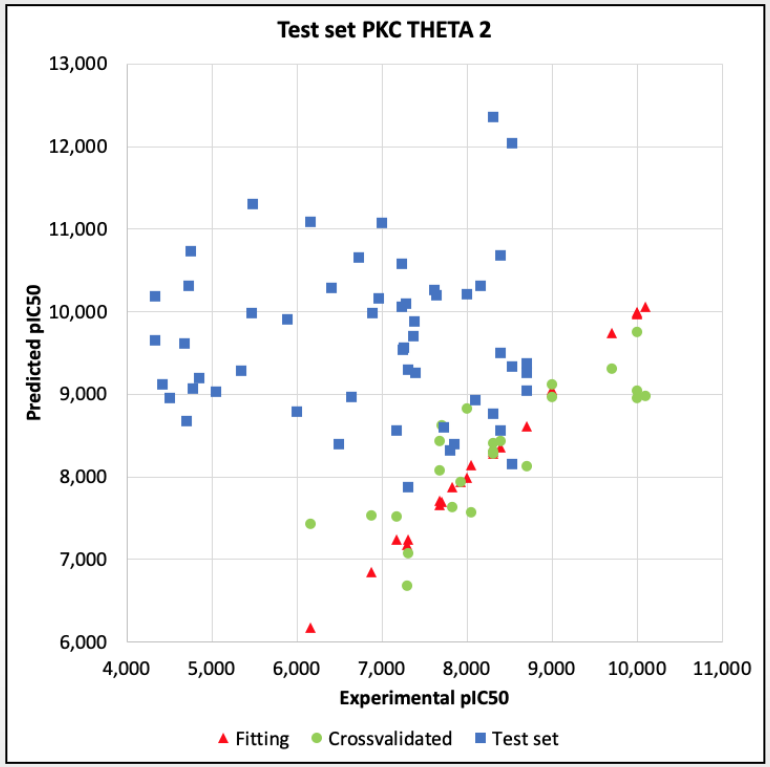


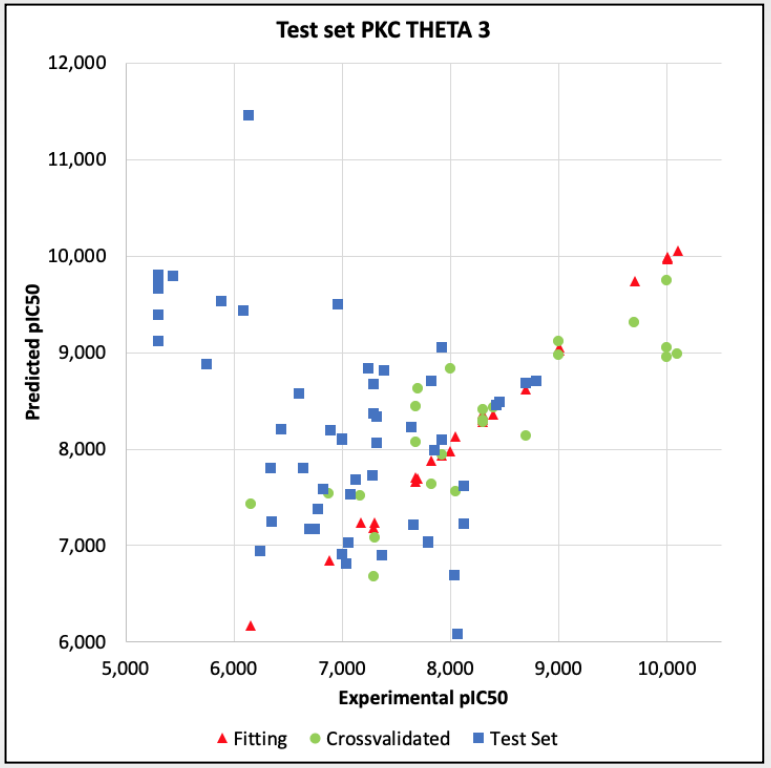


Campo sterico

Campo elettrostatico

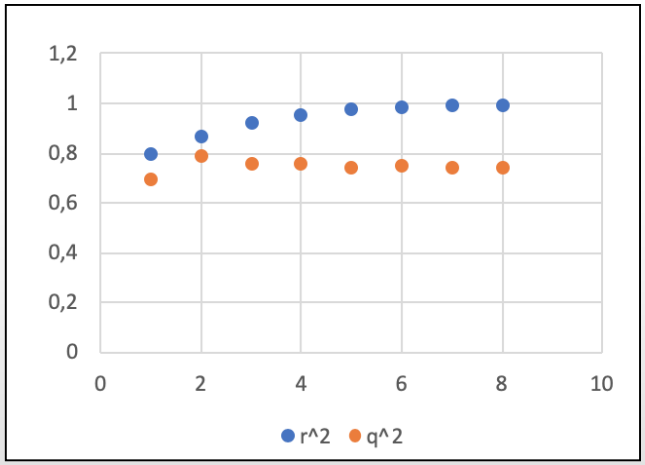
Modello PKC THETA 1

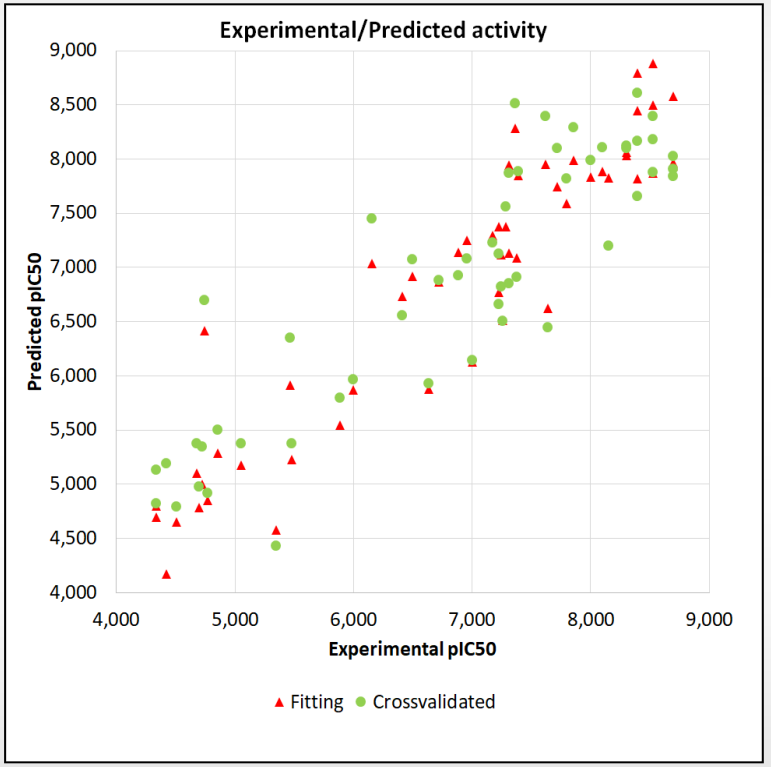




Modello PKC THETA 2

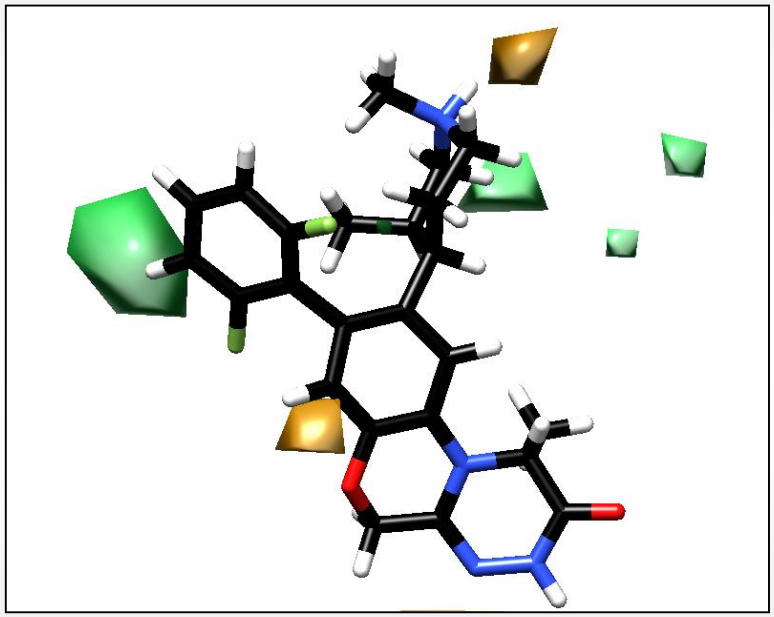
- $q^2 = 0{,}790$
- $r^2 = 0{,}871$
- ONPC = 2



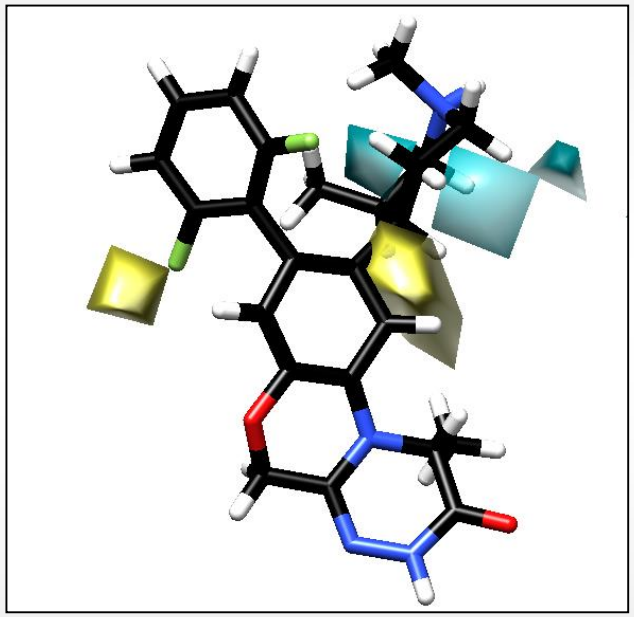


Modello PKC THETA 2

Molecola B51 (mappe CoMFA2)

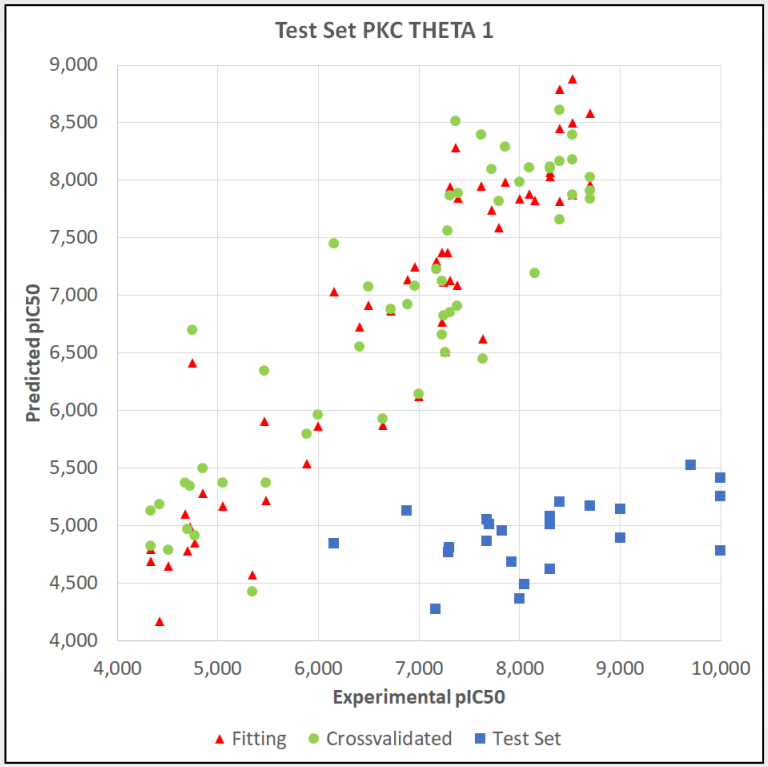


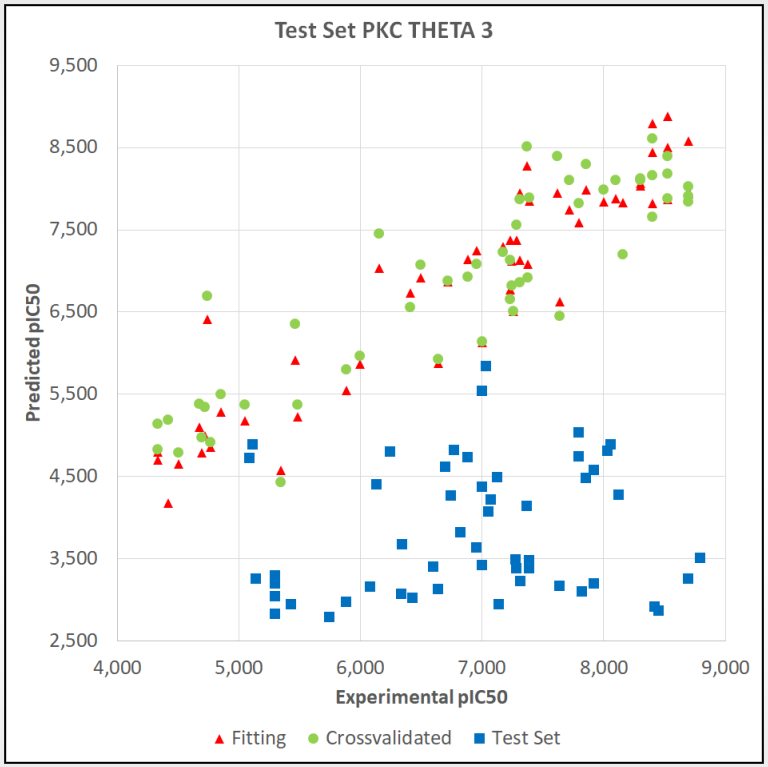
Campo sterico



Campo elettrostatico

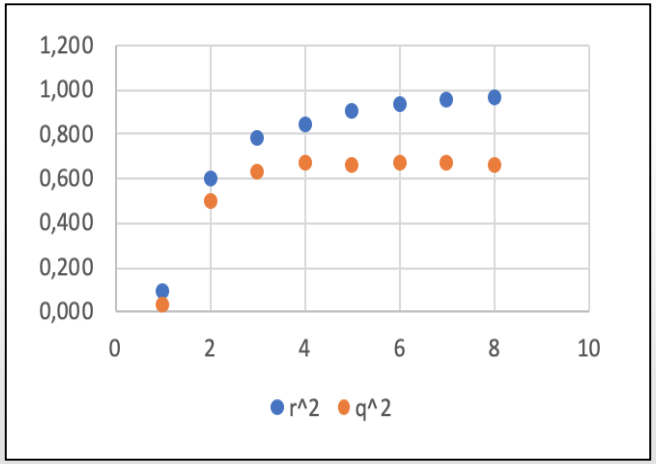
Modello PKC THETA 2

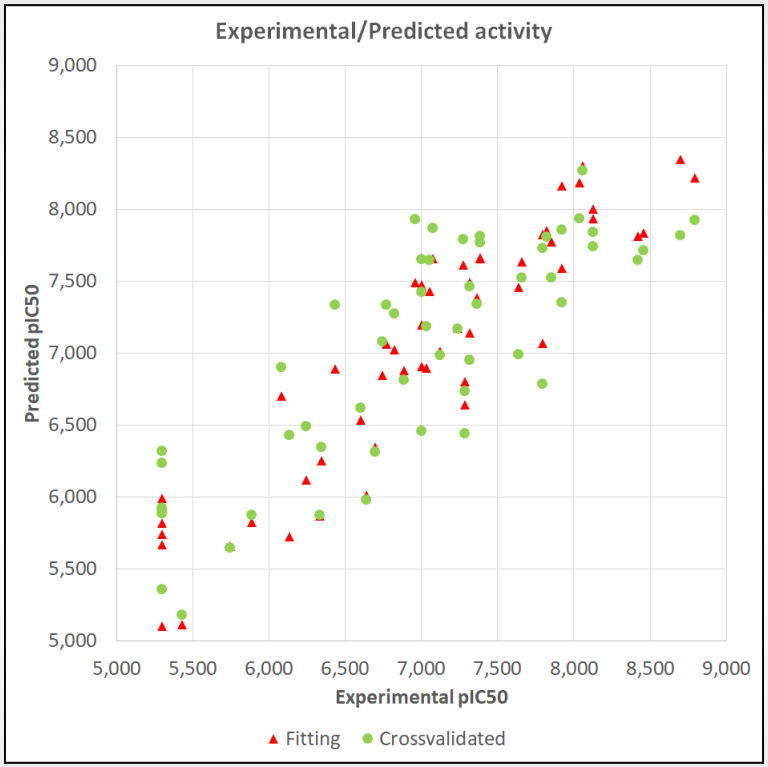




Modello PKC THETA 3

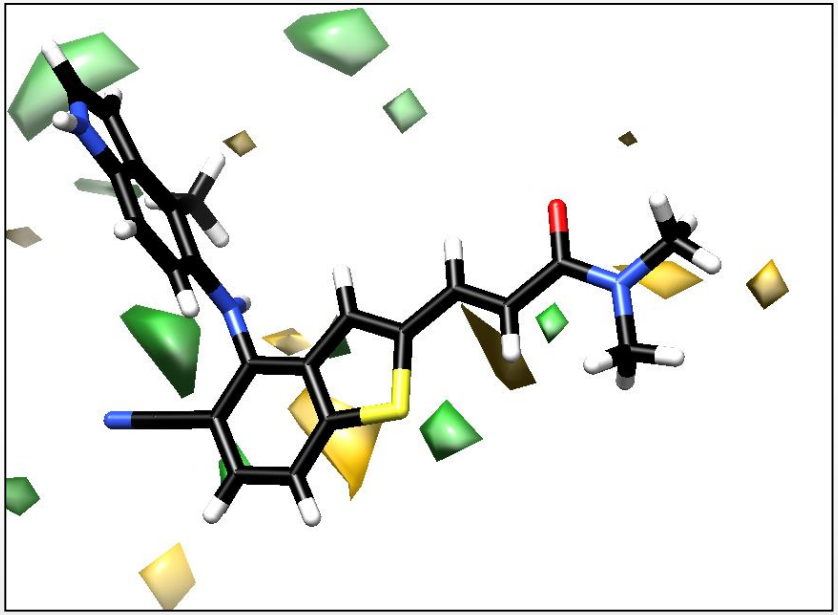
- $q^2 = 0{,}671$
- $r^2 = 0{,}844$
- ONPC = 4



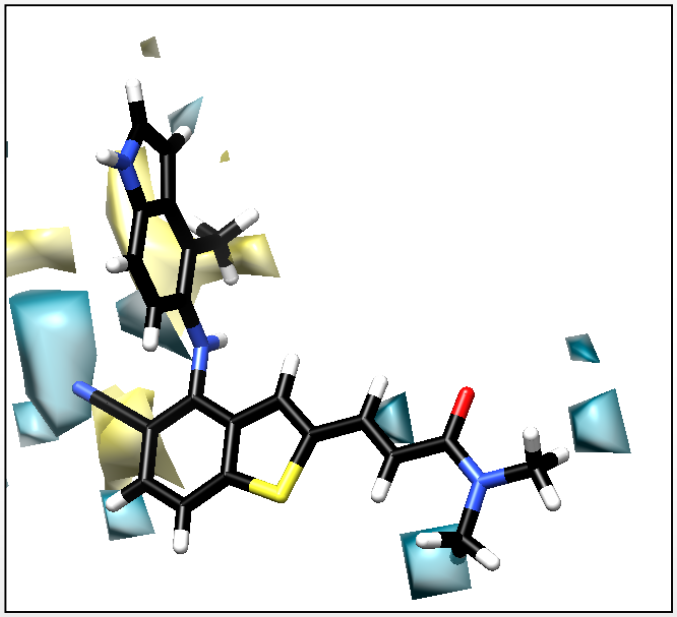


Modello PKC THETA 3

Molecola C43 (mappe CoMFA2)

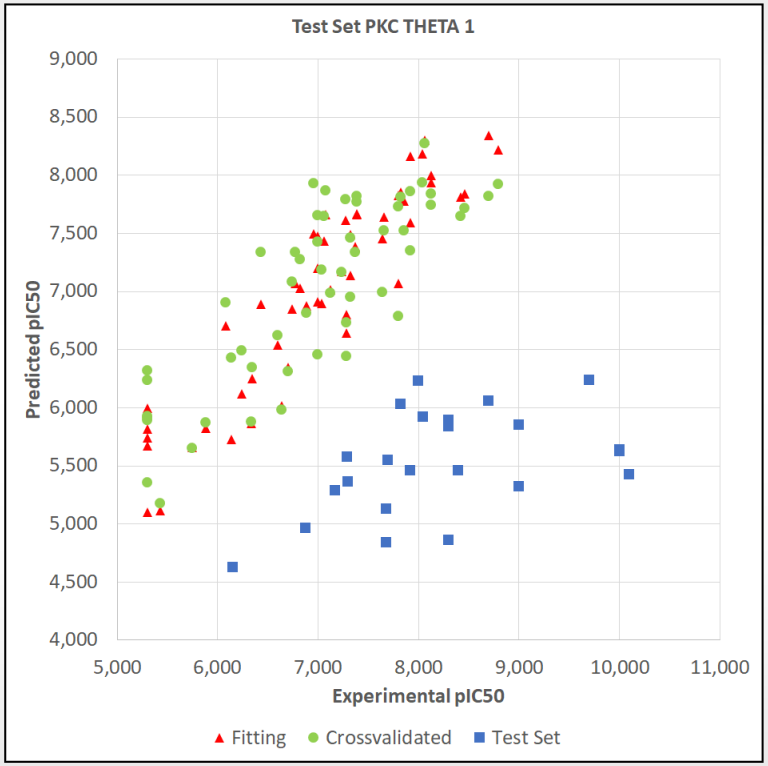


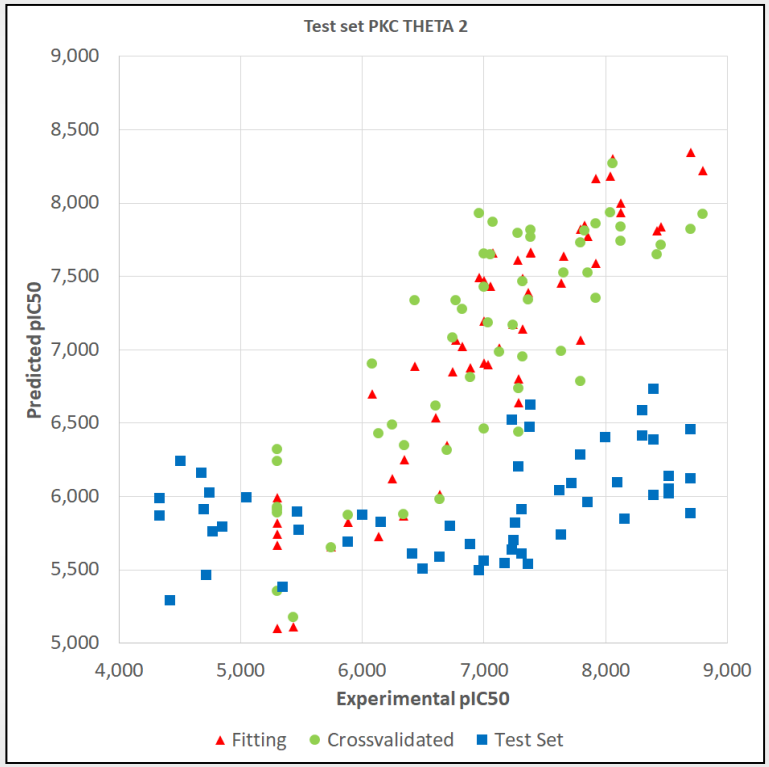
Campo sterico



Campo elettrostatico

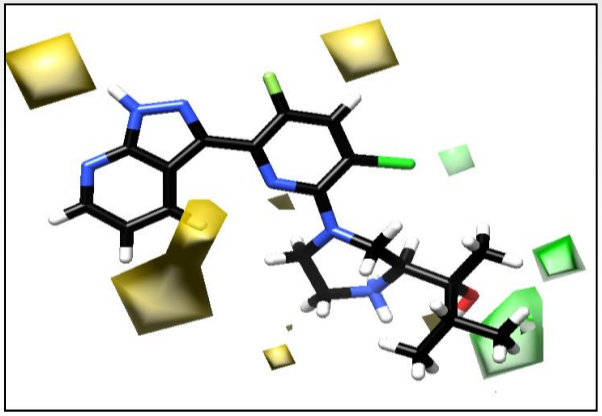
Modello PKC THETA 3

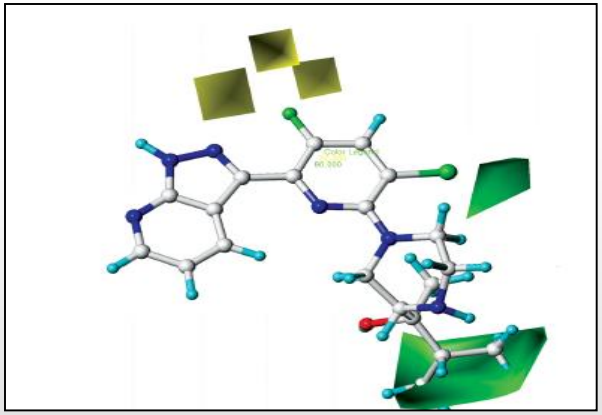




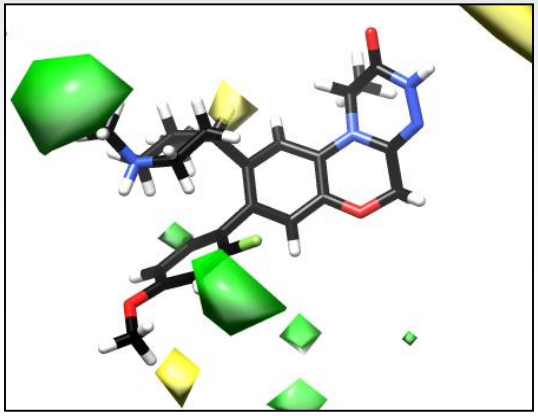
Confronto con modelli pubblicati

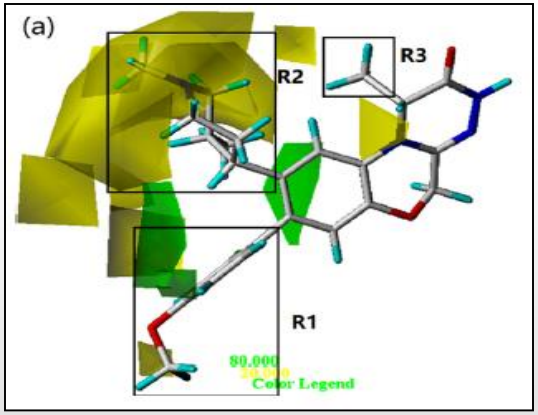
PKC THETA 1



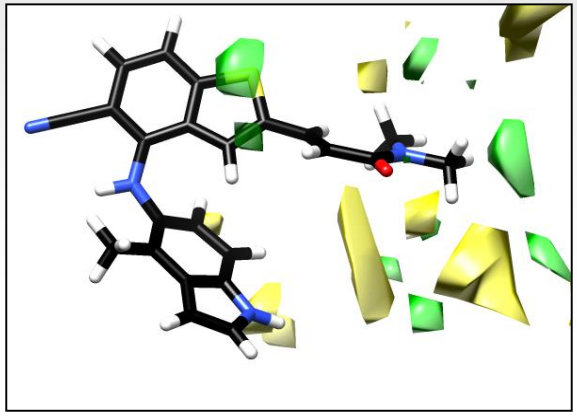


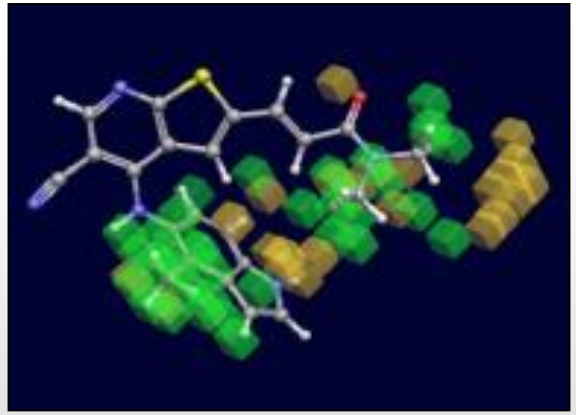
PKC THETA 2





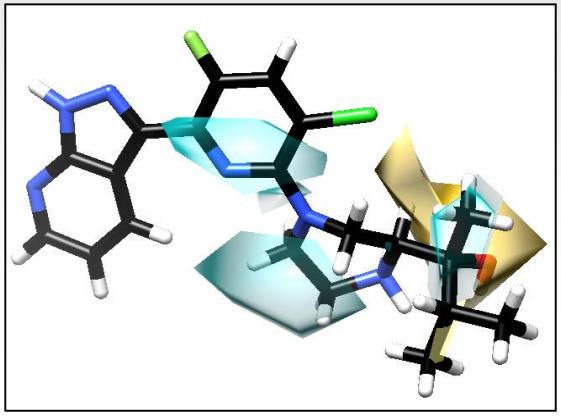
PKC THETA 3

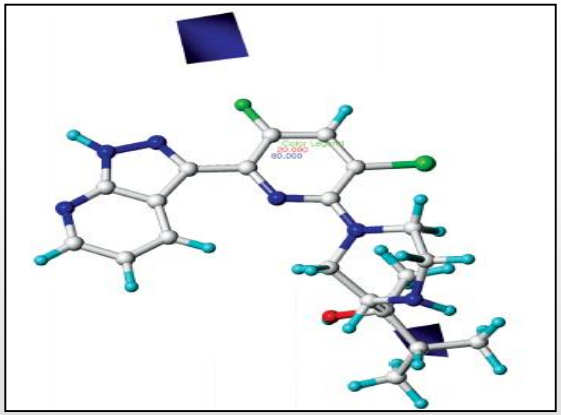




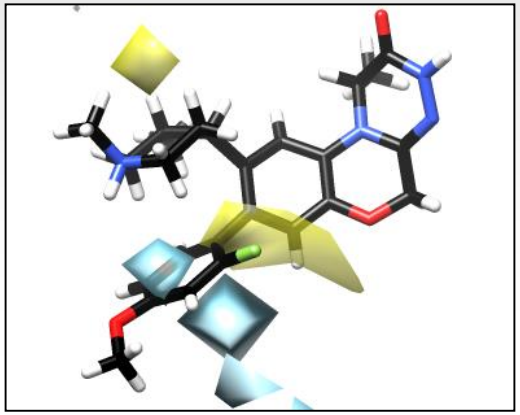
Confronto con modelli pubblicati

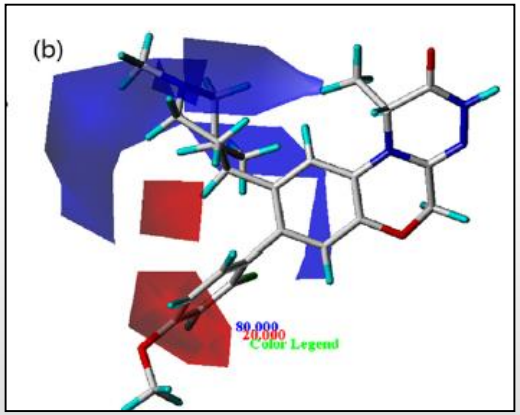
PKC THETA 1



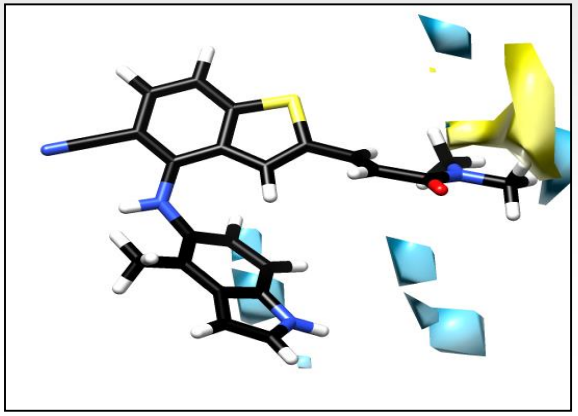


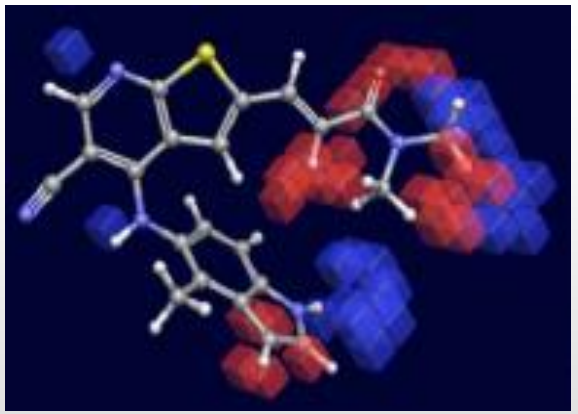
PKC THETA 2





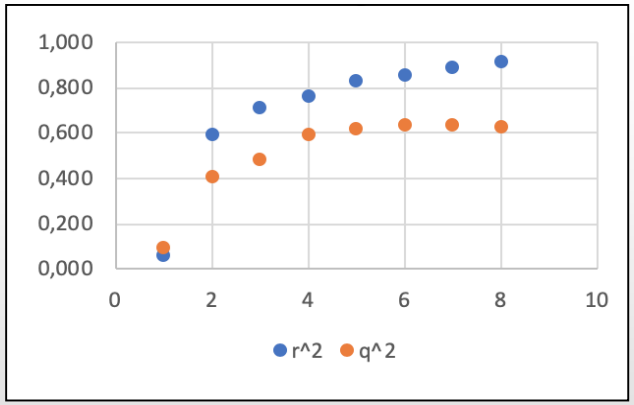
PKC THETA 3

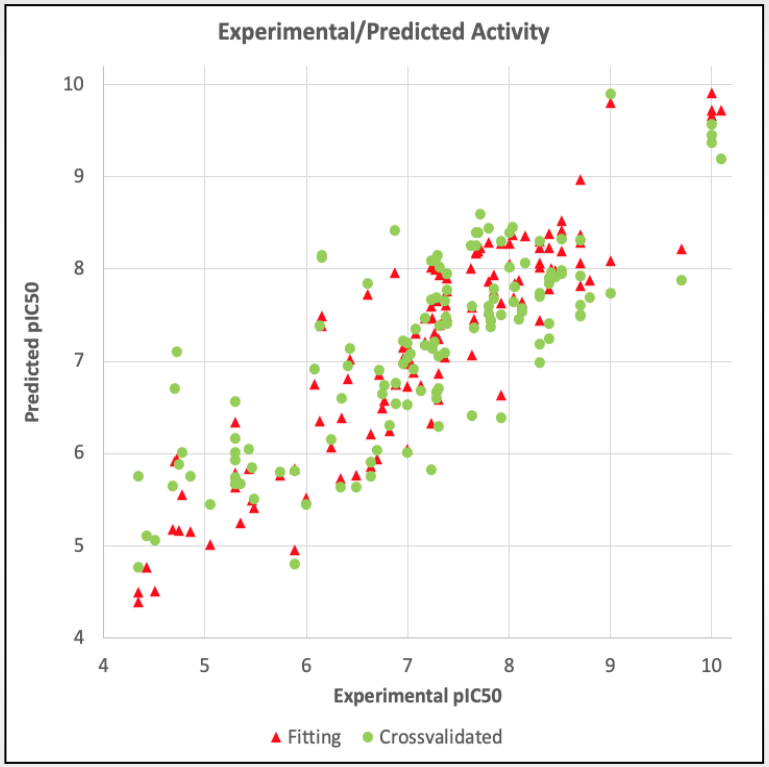




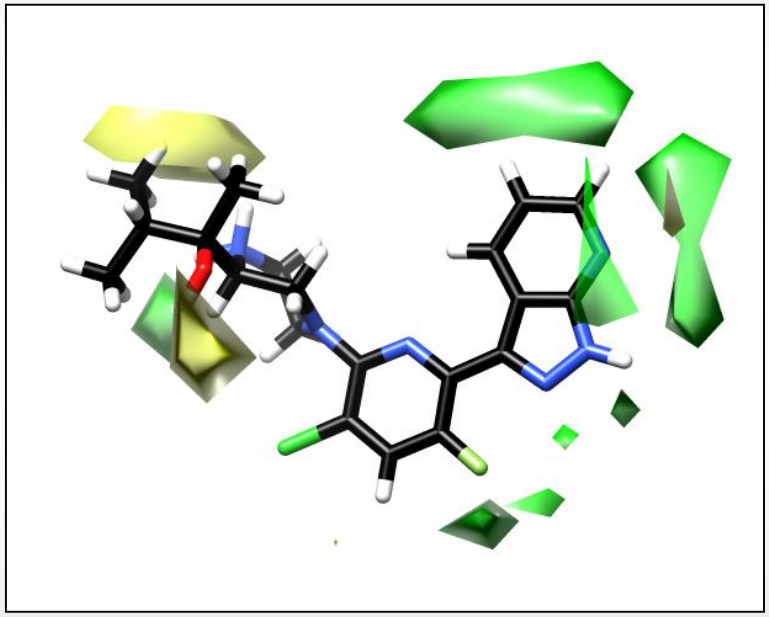
Modello PKC THETA (AII)

- $q^2 = 0{,}623$
- $r^2 = 0{,}828$
- ONPC = 5

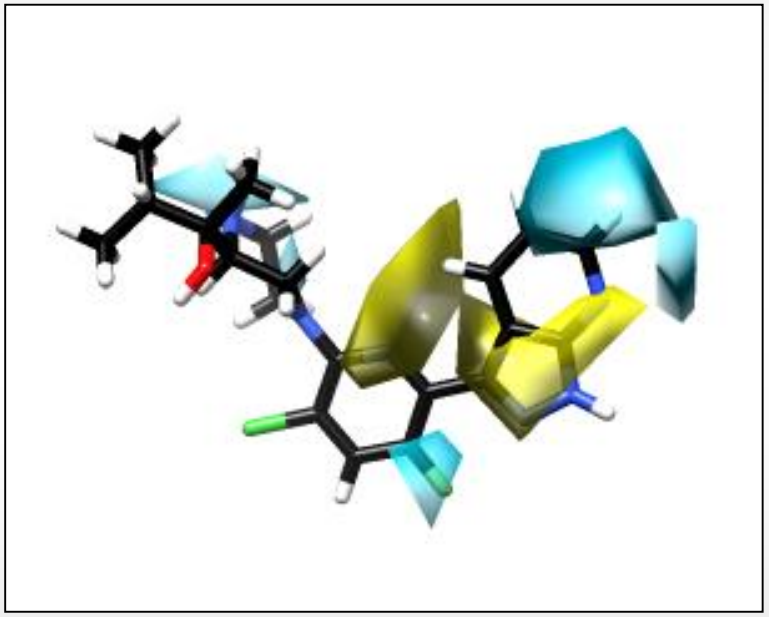




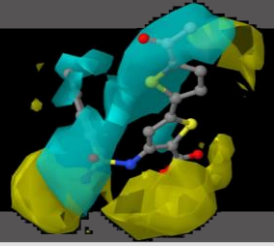
Molecola A24 (mappe CoMFA2)



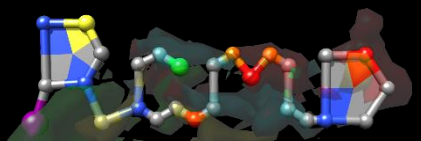
Campo sterico



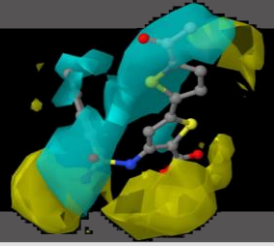
Campo elettrostatico



Conclusioni



- **La tecnica può essere considerata valida.**
- **I modelli PKC THETA 1/2/3 hanno buona validità locale e sono confrontabili con quelli pubblicati.**
- **Il modello PKC THETA (All) copre una più ampia gamma di strutture molecolari, rimanendo affidabile.**



Grazie dell'attenzione