

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

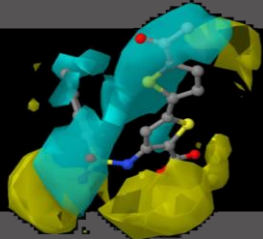


SAPIENZA
UNIVERSITÀ DI ROMA

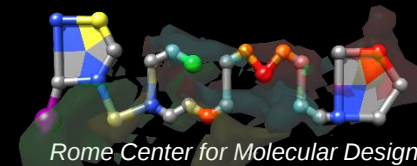
Candidato: Daniele Cavariani
Matricola: 1689398

Relatore: Prof. Rino Ragno

Anno Accademico 2018/2019

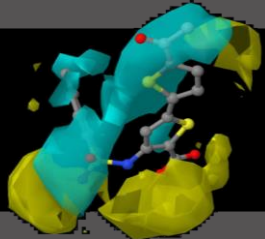


QSAR

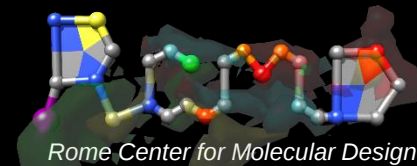


(Quantitative Structure-Activity Relationships)

- **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



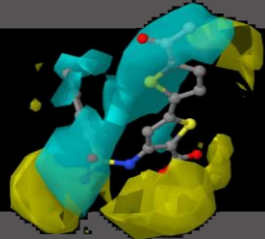
Rome Center for Molecular Design

Di cosa abbiamo bisogno:

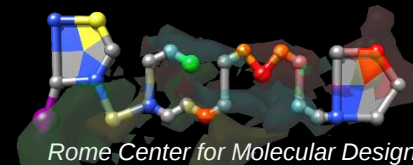
- **Struttura molecolare**
- **Attività delle molecole**

Procedura standard:

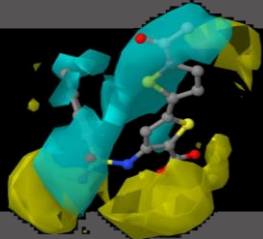
- **Analisi Conformazionale**
- **Allineamento**
- **Creazione e ottimizzazione dei modelli**
- **Analisi dei risultati e delle mappe di contorno**



Obiettivo della tesi

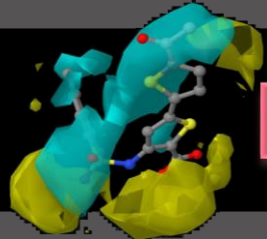


- 3D-QSAR attraverso il metodo CoMFA (Comparative Molecular Fields analysis).
- Modelli ligand-based.
- Utilizzo del portale www.3d-qsar.com

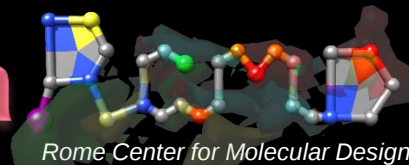


Sito web contenitore di una serie di applicazioni:

The screenshot shows the homepage of the 3D-QSAR website. At the top left is the logo 'www.3D-QSAR.com'. At the top right are links for 'Home' and 'Contacts'. On the left side, there is a 'Menu' section with links to 'Home' and 'Contacts', and a 'Login' section with input fields for 'Username' and 'Password', a 'Remember Me' checkbox, and a 'Login' button. The main content area features a welcome message 'Welcome to www.3D-QSAR.com' and a prompt 'Hi! Click the App Button you want to work on!'. Below this are four large, colored buttons: 'Py-MolEdit' (orange), 'Py-ConfSearch' (blue), 'Py-Align' (red), and 'Py-CoMFA' (green).



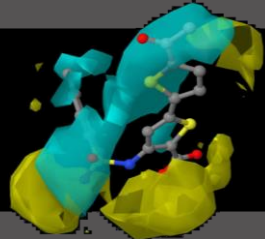
Protein-Chinasi C Theta



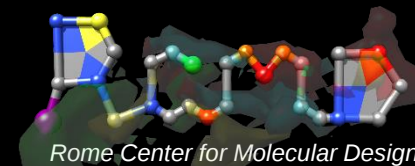
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- **Tre studi 3D-QSAR.**
- **Famiglia delle chinasi.**
- **Ruolo nel differenziamento e nell'attivazione dei linfociti T.**
- **Coinvolte nelle malattie autoimmuni (Artrite Reumatoide, Psoriasi).**



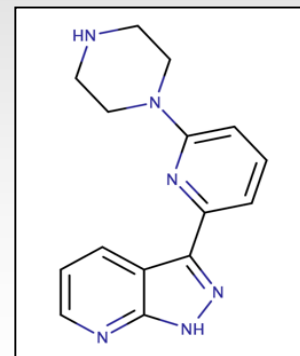


Dataset

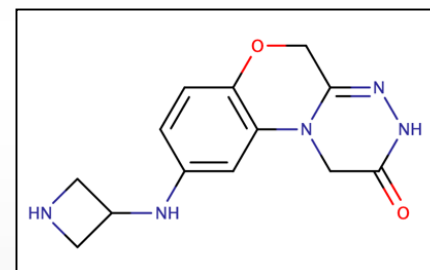


- **Dataset PKC THETA 1**
(24 pridilpirazolpiridine)
- **Dataset PKC THETA 2**
(54 triazinoni triciclici)
- **Dataset PKC THETA 3**
(55 tienopiridincarbonitrili)
- **Dataset PKC THETA (All)**
(133 molecole)

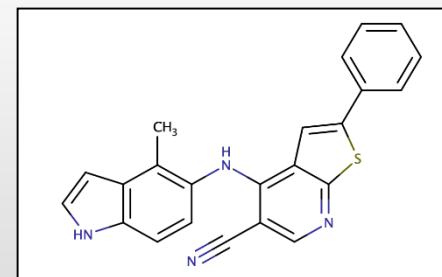
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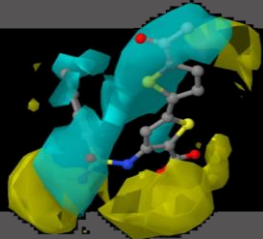


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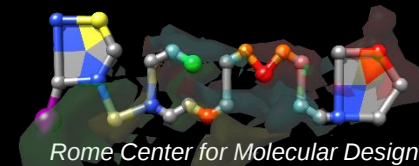


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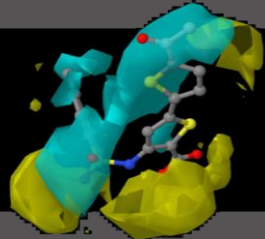




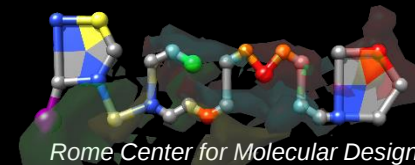
Modelli CoMFA



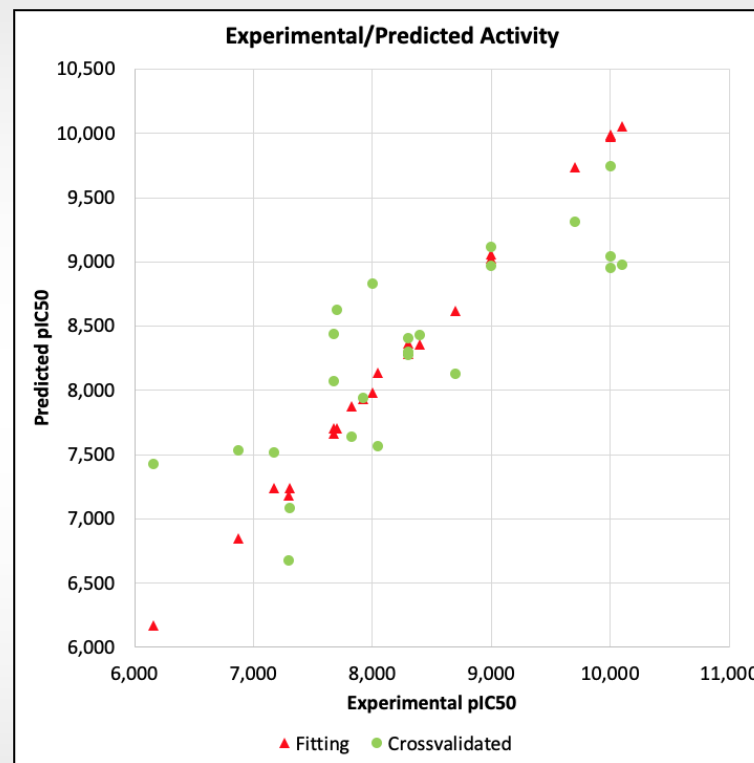
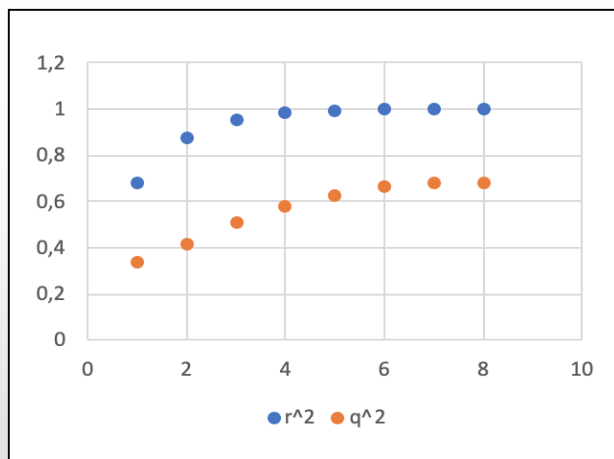
- **Modelli di default per ogni allineamento.**
- **Modifica di determinati parametri (Atomo Sonda, Spaziatura/Estensione della griglia, CutOff, Min. Sigma) → più di 300 modelli.**
- **Incremento del valore di q^2 dal 11% al 18%.**

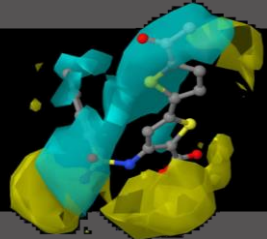


Modello PKC THETA 1

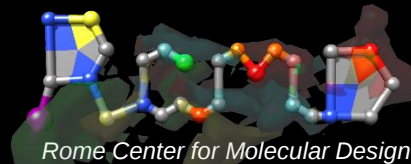


- $q^2 = 0,633$
- $r^2 = 0,998$
- ONPC = 6

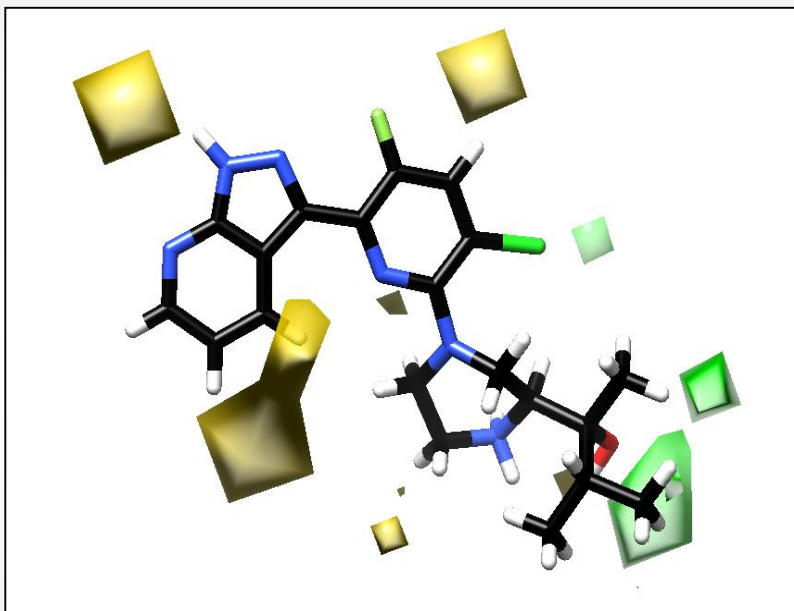




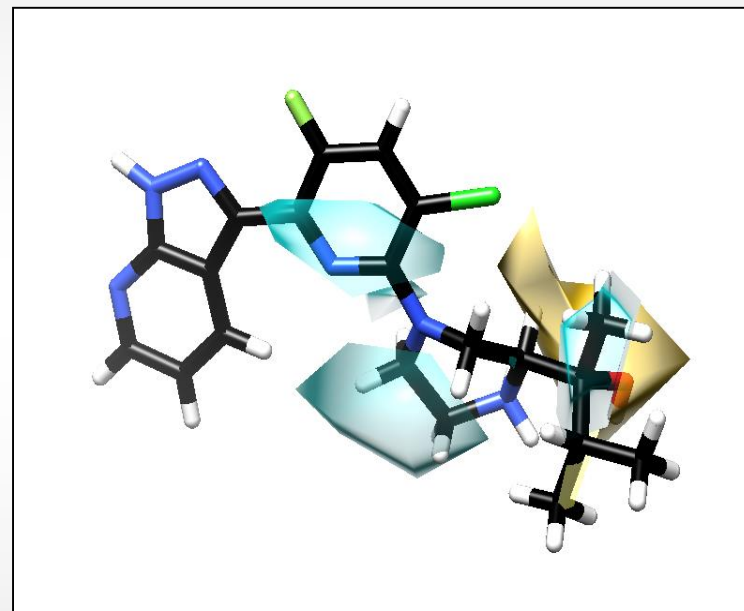
Modello PKC THETA 1



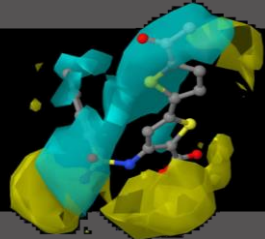
Molecola A24 (mappe CoMFA2)



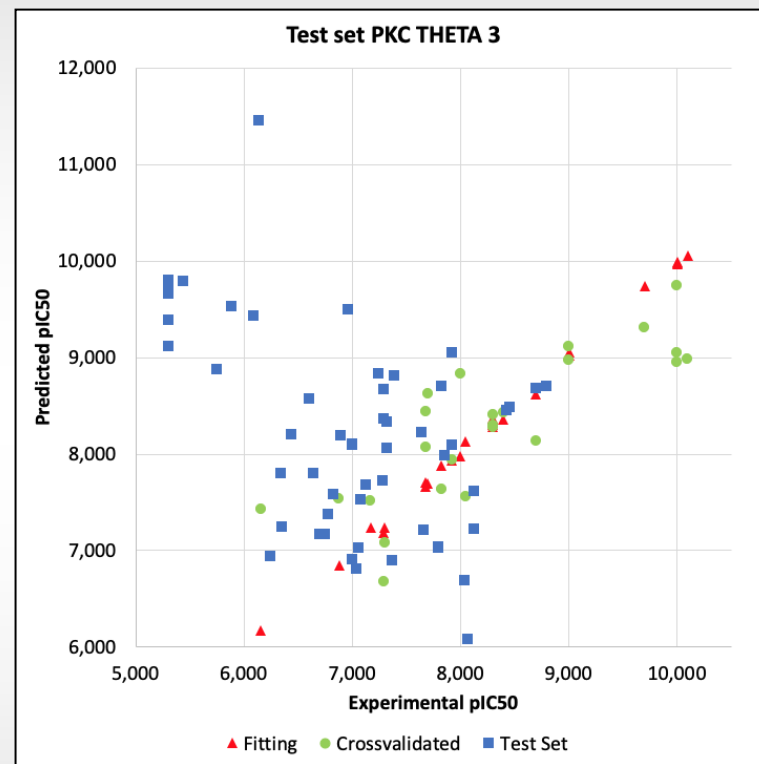
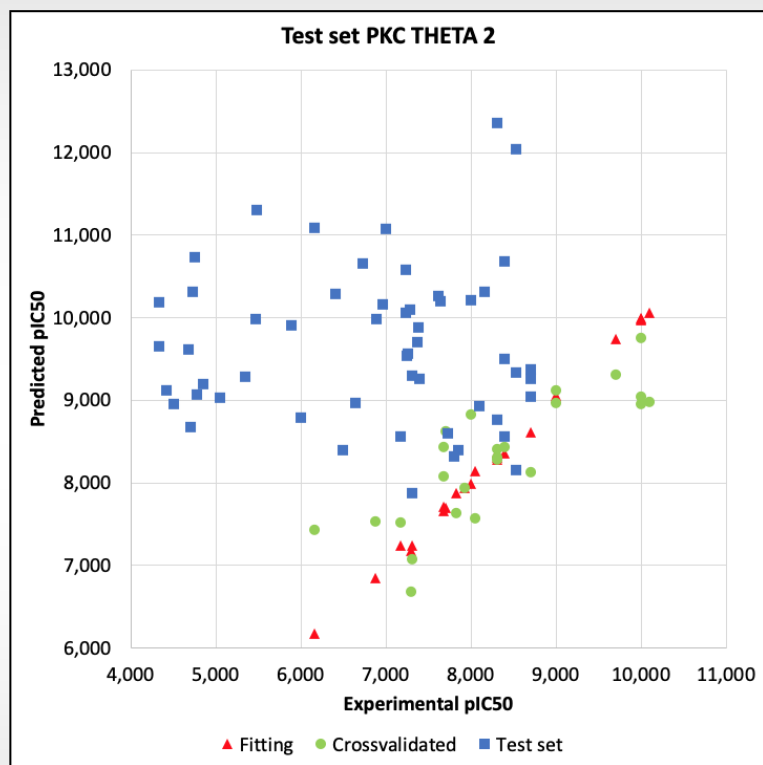
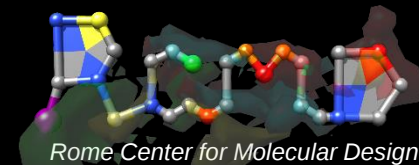
Campo sterico

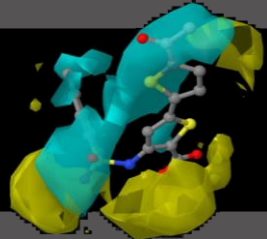


Campo elettrostatico

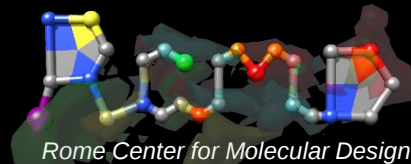


Modello PKC THETA 1

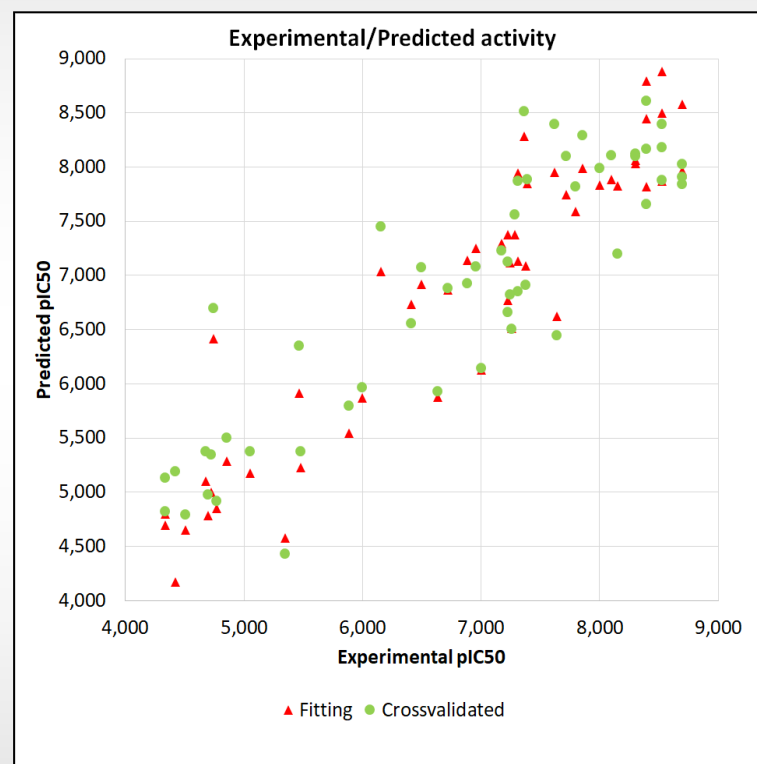
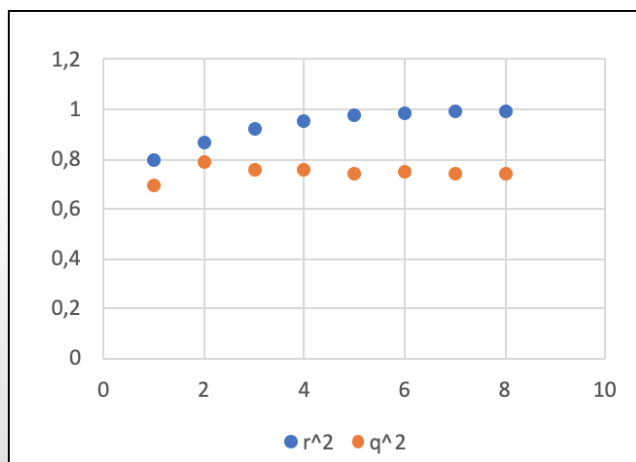


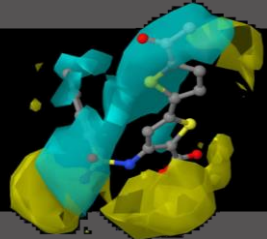


Modello PKC THETA 2

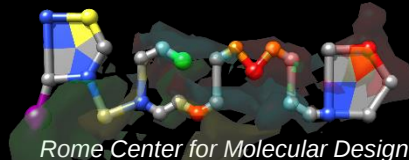


- $q^2 = 0,790$
- $r^2 = 0,871$
- ONPC = 2

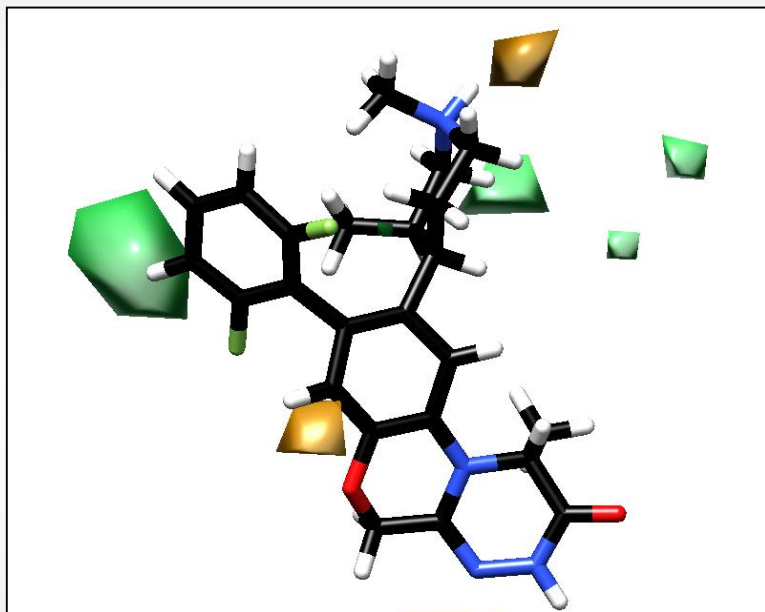




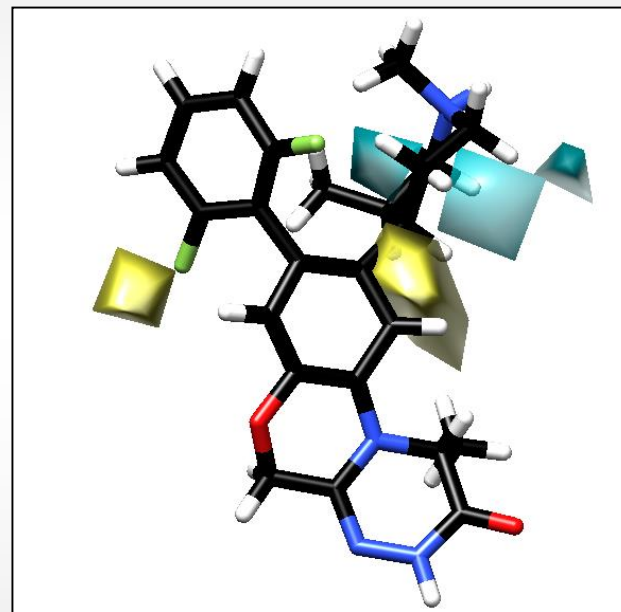
Modello PKC THETA 2



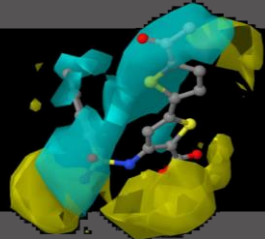
Molecola B51 (mappe CoMFA2)



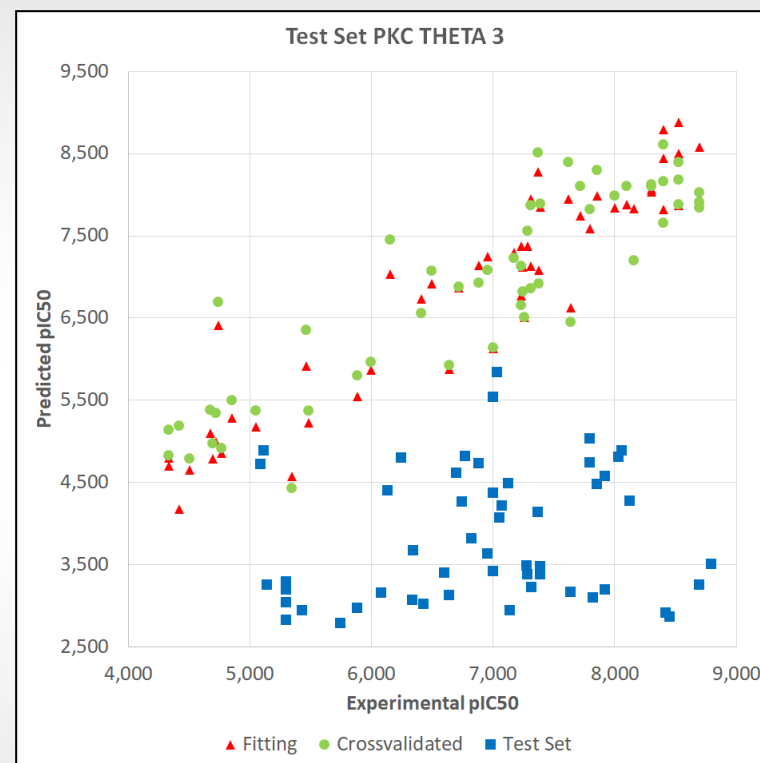
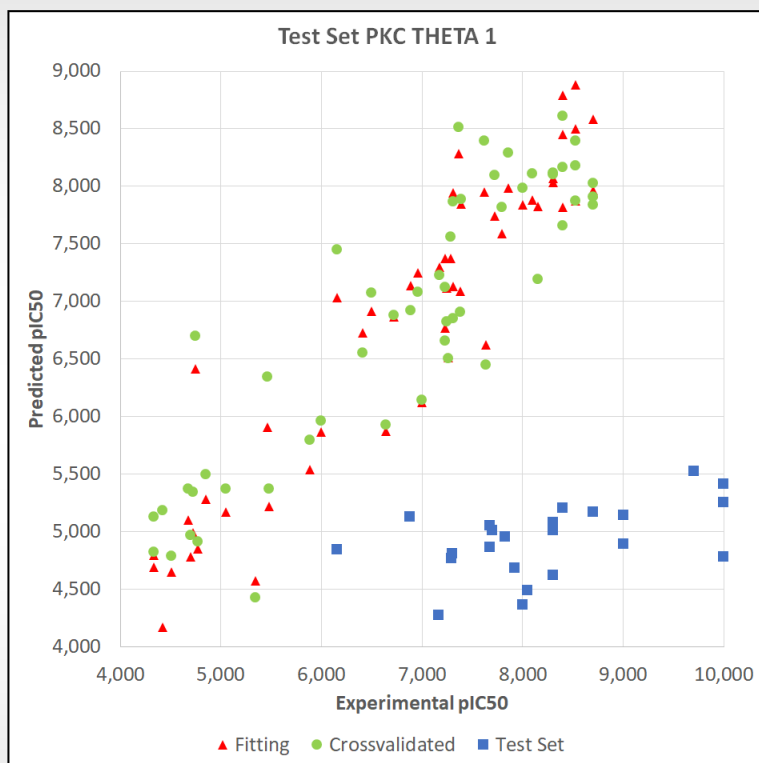
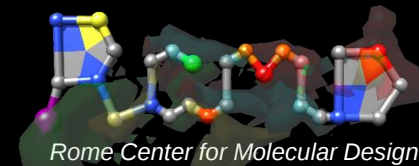
Campo sterico

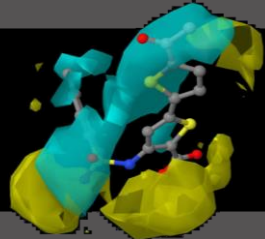


Campo elettrostatico

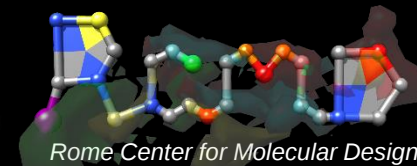


Modello PKC THETA 2

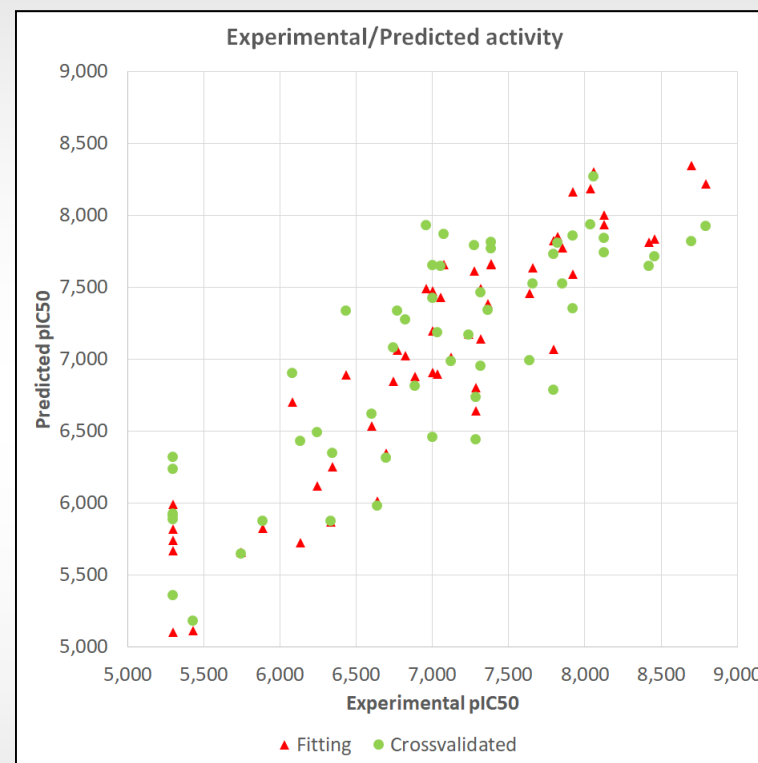
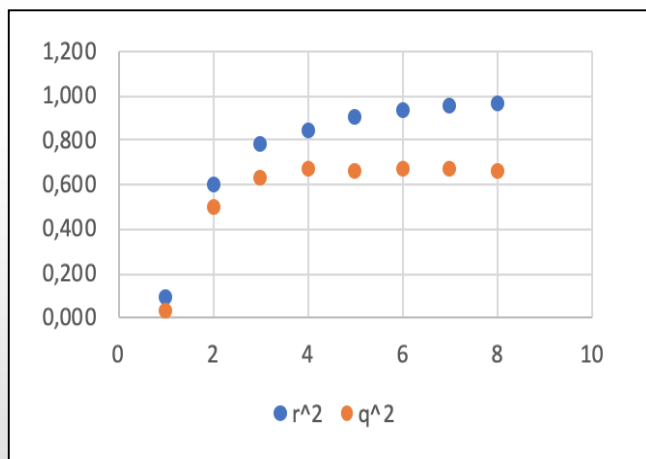


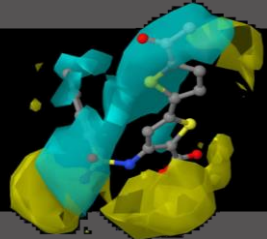


Modello PKC THETA 3

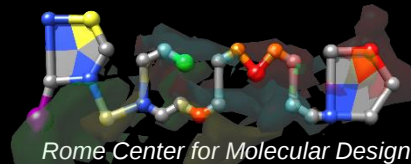


- $q^2 = 0,671$
- $r^2 = 0,844$
- ONPC = 4

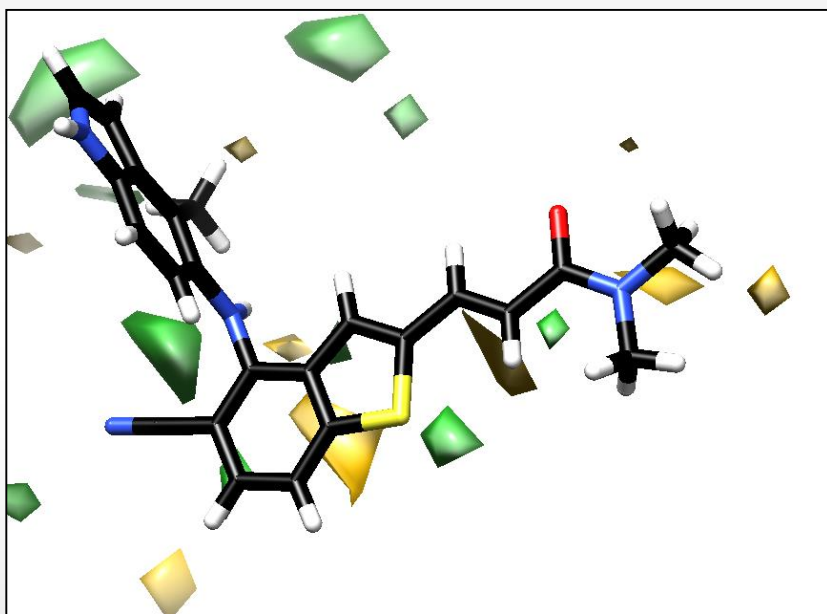




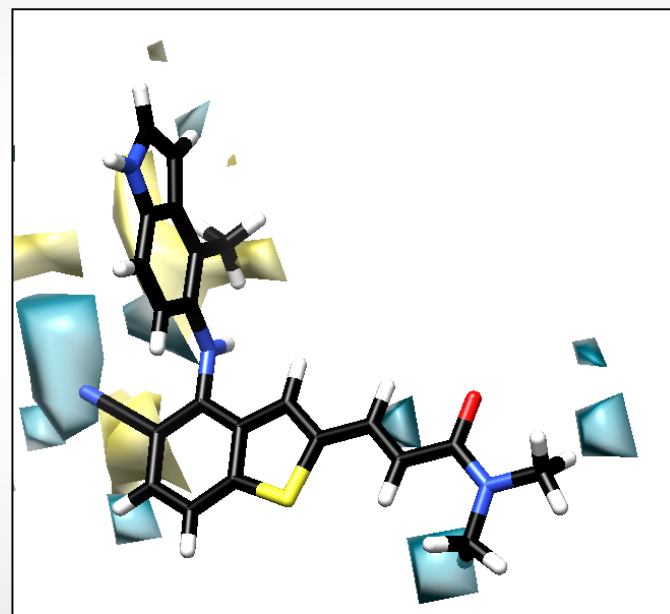
Modello PKC THETA 3



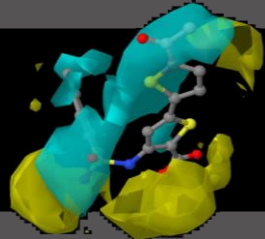
Molecola C43 (mappe CoMFA2)



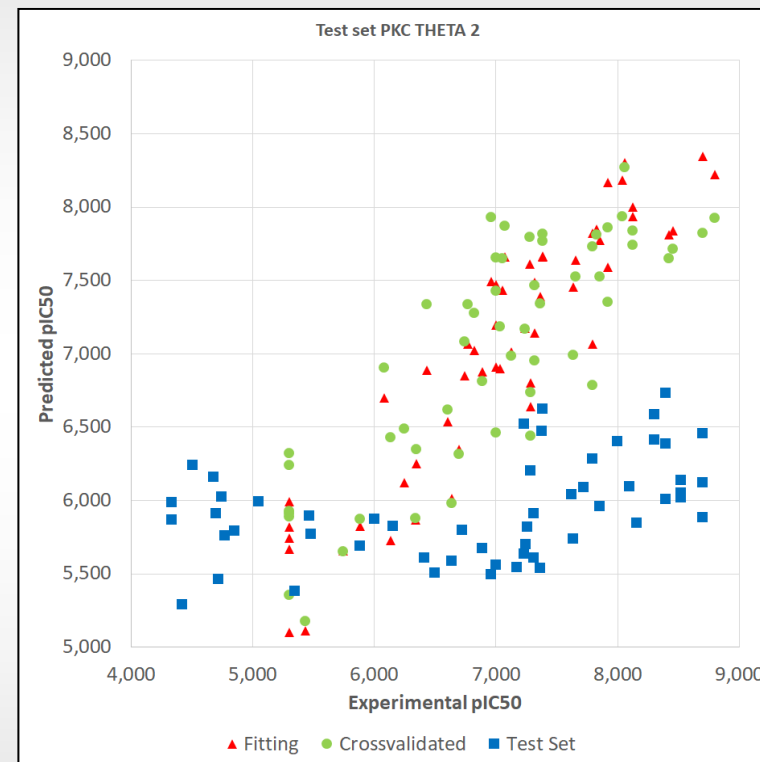
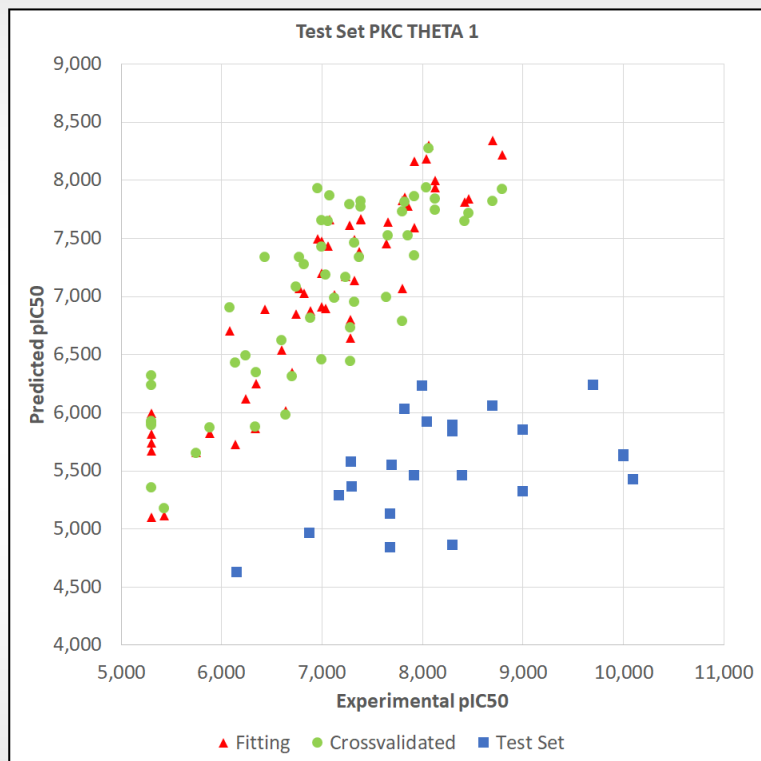
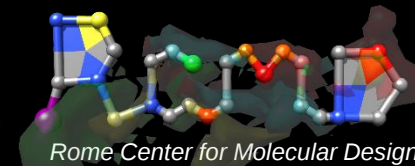
Campo sterico

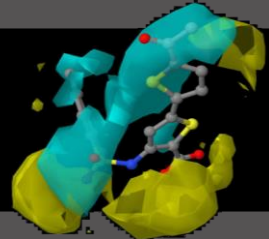


Campo elettrostatico

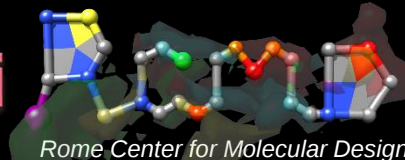


Modello PKC THETA 3

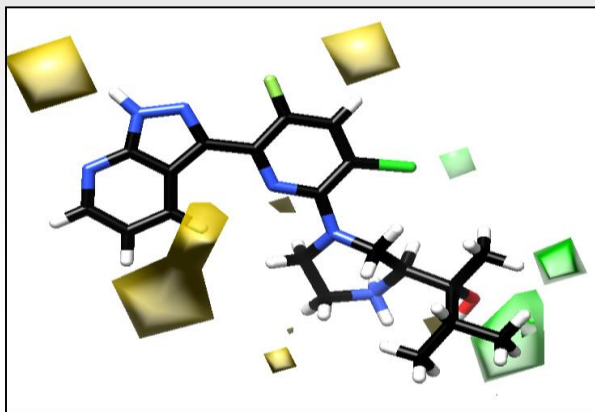




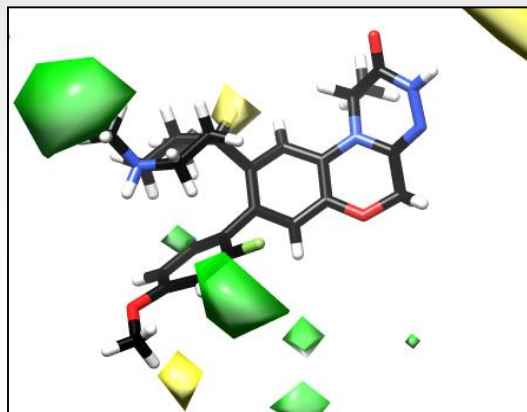
Confronto con modelli pubblicati



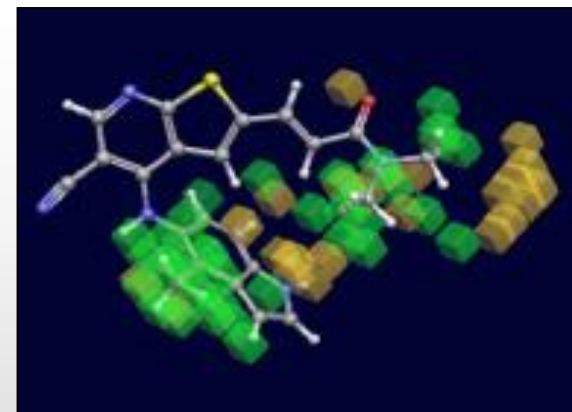
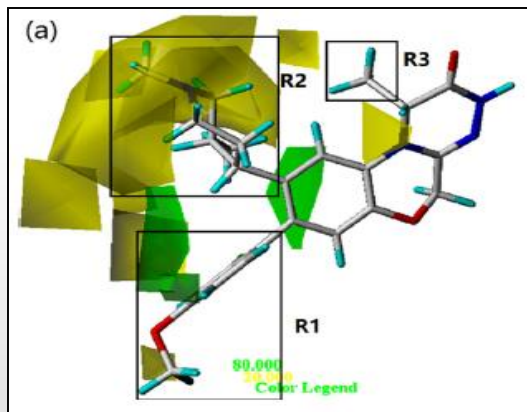
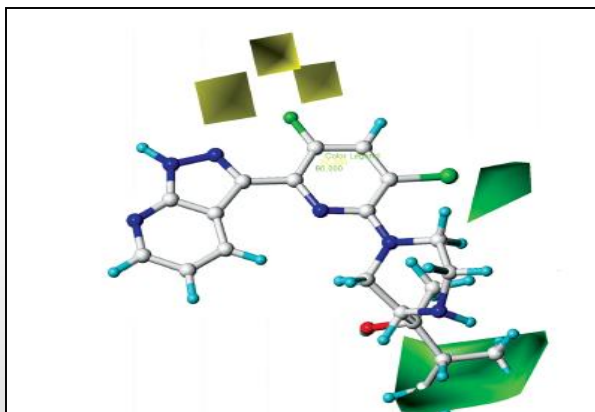
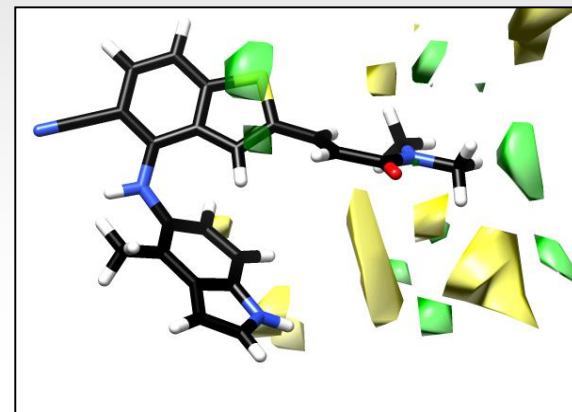
PKC THETA 1

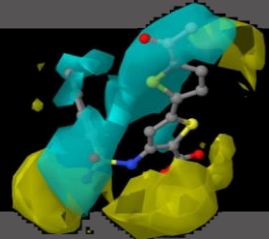


PKC THETA 2

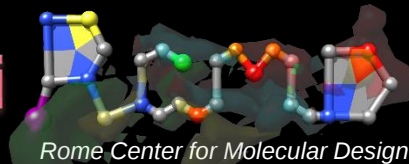


PKC THETA 3

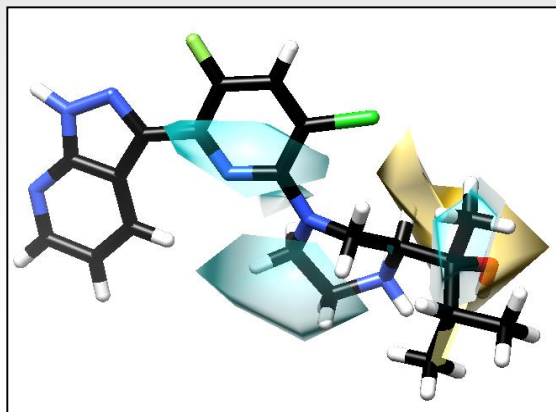




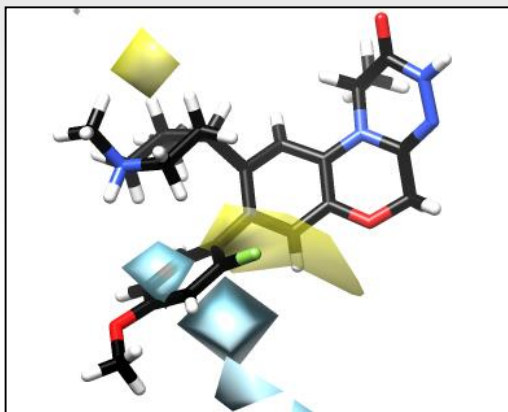
Confronto con modelli pubblicati



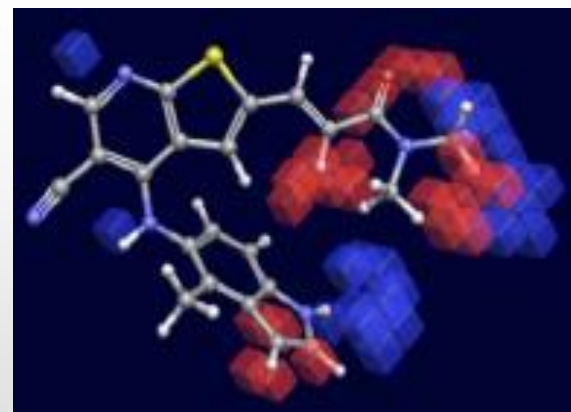
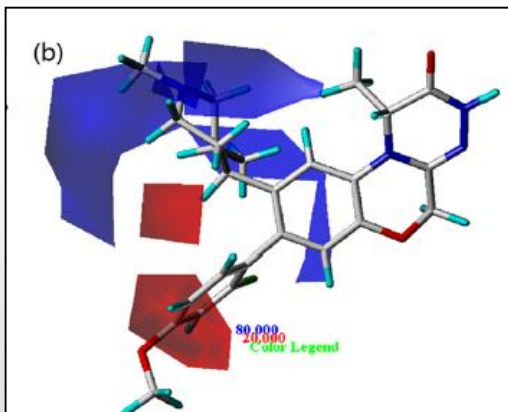
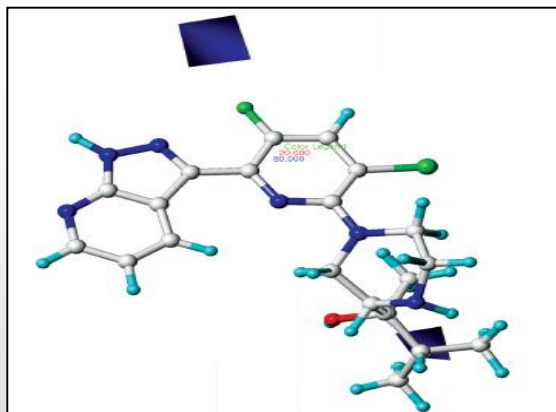
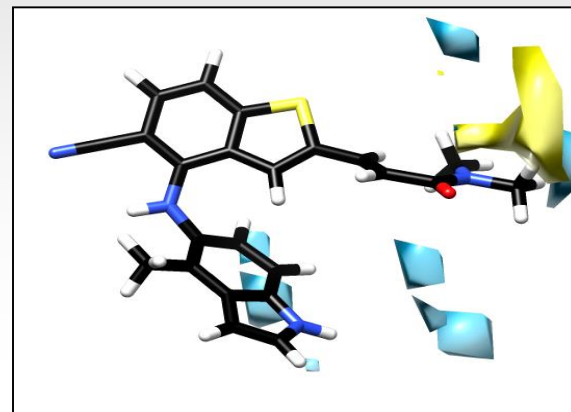
PKC THETA 1

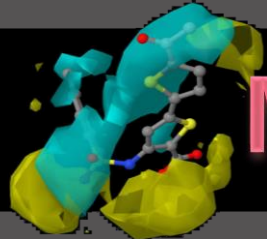


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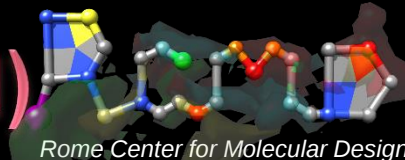


PKC THETA 3

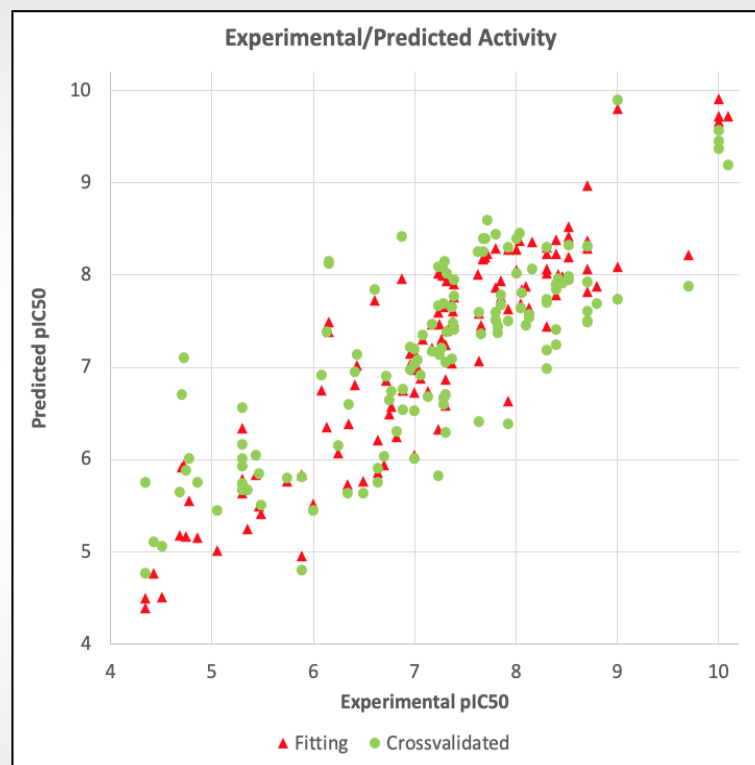
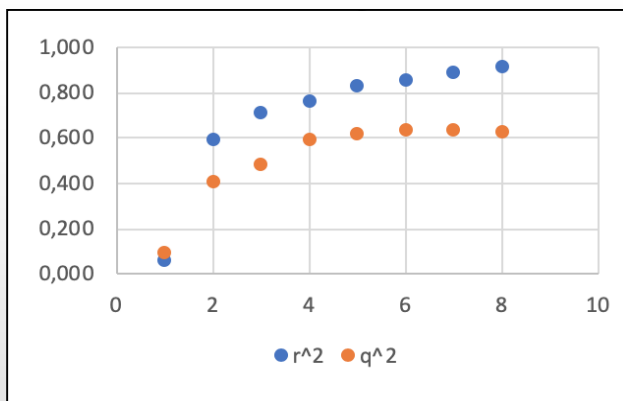


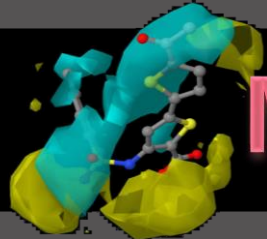


Modello PKC THETA (AII)

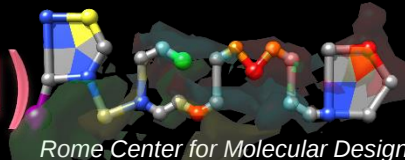


- $q^2 = 0,623$
- $r^2 = 0,828$
- ONPC = 5



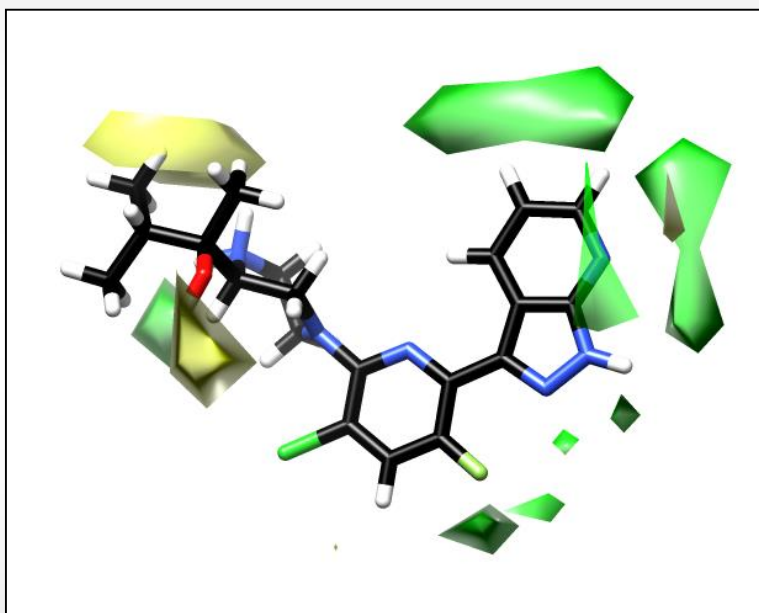


Modello PKC THETA (AII)

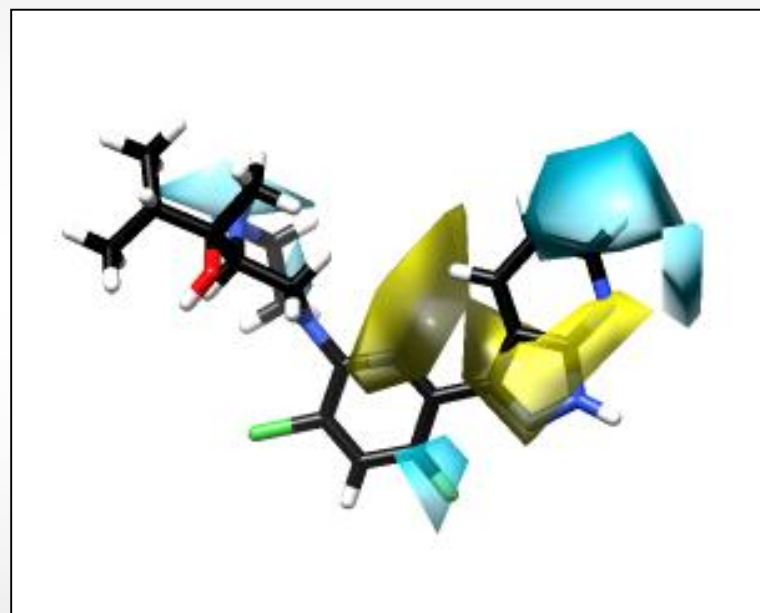


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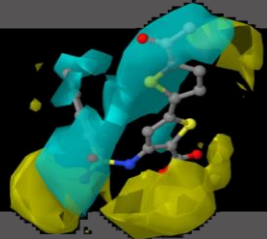
Molecola A24 (mappe CoMFA2)



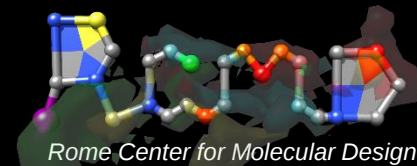
Campo sterico



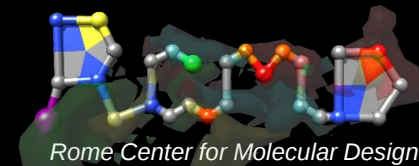
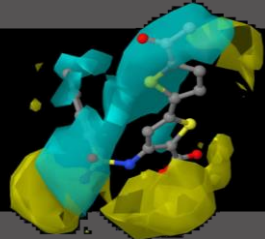
Campo elettrostatico



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