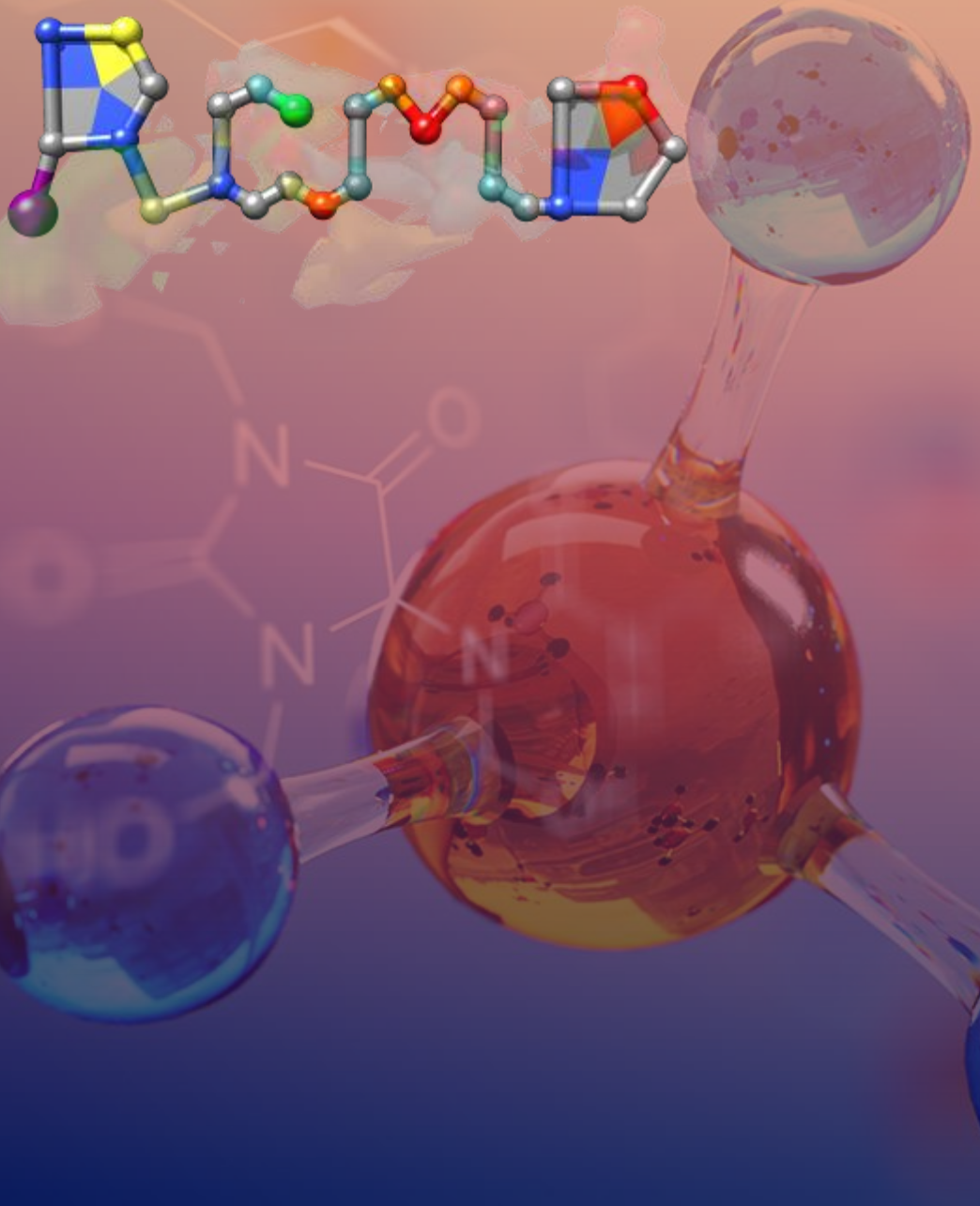


SAPIENZA
UNIVERSITÀ DI ROMA

LIGAND BASED INVESTIGATIONS BY 3-D QSAR ON SERIES OF SHMT INHIBITORS

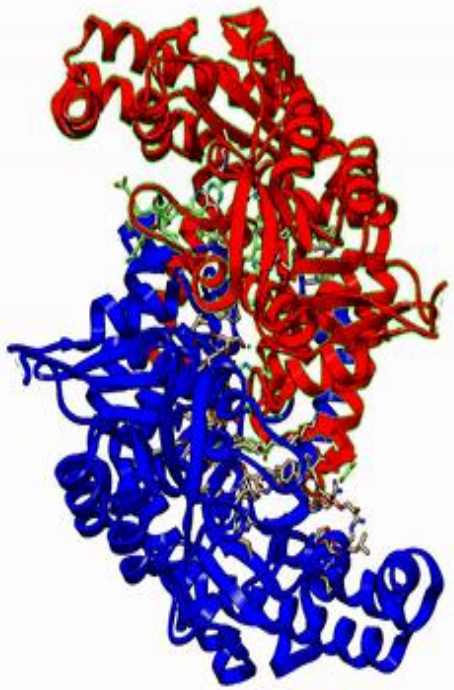
Relatore: Professor Rino Ragno

Student: Hadi Eidgah.T1734802

Academic Year 2019/2020

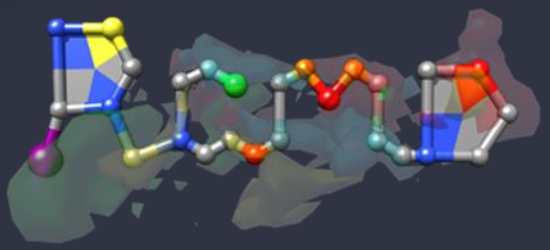
SERINE HYDROXYMETHYLTRANSFERASE
SHMT

SHMT&PLP



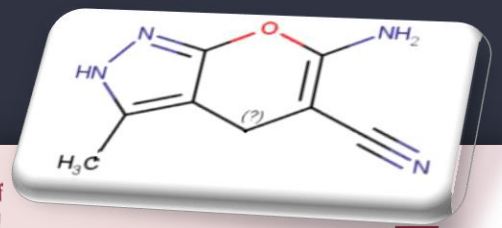
INTRODUCTION

- Dependent: Pyridoxal Phosphate (PLP) (Vitamin B6)
- Role: Cellular One-Carbon Pathway
- Provides Units for Amino acid and Nucleotide Metabolism
- Cancer cells require SHMT to generate tumors
- Ligand Based Investigations By 3D-QSAR on SHMT Inhibitors.



ANTIMALARIAL DRUGS

PYRAZOLPYRANS



ChemPubSoc Europe
DOI: 10.1002/cmdc.201800053
CHEMMEDCHEM Full Papers
Check for updates

Potent Inhibitors of *Plasmodial* Serine Hydroxymethyltransferase (SHMT) Featuring a Spirocyclic Scaffold

Geoffrey Schwertz,[a] Matthias C. Witschel,[b] Matthias Rottmann,[c, d] Ubolsree Leartsakulpanich,[e] Penchit Chitnumsub,[e] Aritsara Jaruwat,[e] Watcharee Amornwatcharapong,[f] Wanwipa Ittarat,[e] Anja Schäfer,[c, d] Raphael A. Aponte,[b] Nils Trapp,[a] Pimchai Chaiyen,[f, g] and François Diederich*[a]

Journal of Medicinal Chemistry
Article
pubs.acs.org/jmc

Antimalarial Inhibitors Targeting Serine Hydroxymethyltransferase (SHMT) with in Vivo Efficacy and Analysis of their Binding Mode Based on X-ray Cocrystal Structures

Geoffrey Schwertz,[†] Matthias C. Witschel,[‡] Matthias Rottmann,[§,∥] Roger Bonnert,[⊥] Ubolsree Leartsakulpanich,[#] Penchit Chitnumsub,[#] Aritsara Jaruwat,[#] Wanwipa Ittarat,[#] Anja Schäfer,[§,∥] Raphael A. Aponte,[‡] Susan A. Charman,[▽] Karen L. White,[▽] Abhijit Kundu,[○] Surajit Sadhukhan,[○]

ChemPubSoc Europe
DOI: 10.1002/chem.201703244
CHEMISTRY A European Journal Full Paper

Drug Design

Conformational Aspects in the Design of Inhibitors for Serine Hydroxymethyltransferase (SHMT): Biphenyl, Aryl Sulfonamide, and Aryl Sulfone Motifs

Geoffrey Schwertz,[a] Michelle S. Frei,[a] Matthias C. Witschel,[b] Matthias Rottmann,[c, d] Ubolsree Leartsakulpanich,[e] Penchit Chitnumsub,[e] Aritsara Jaruwat,[e] Wanwipa Ittarat,[e] Anja Schäfer,[c, d] Raphael A. Aponte,[b] Nils Trapp,[a] Kerstin Mark,[a] Pimchai Chaiyen,[f, g] and François Diederich*[a]

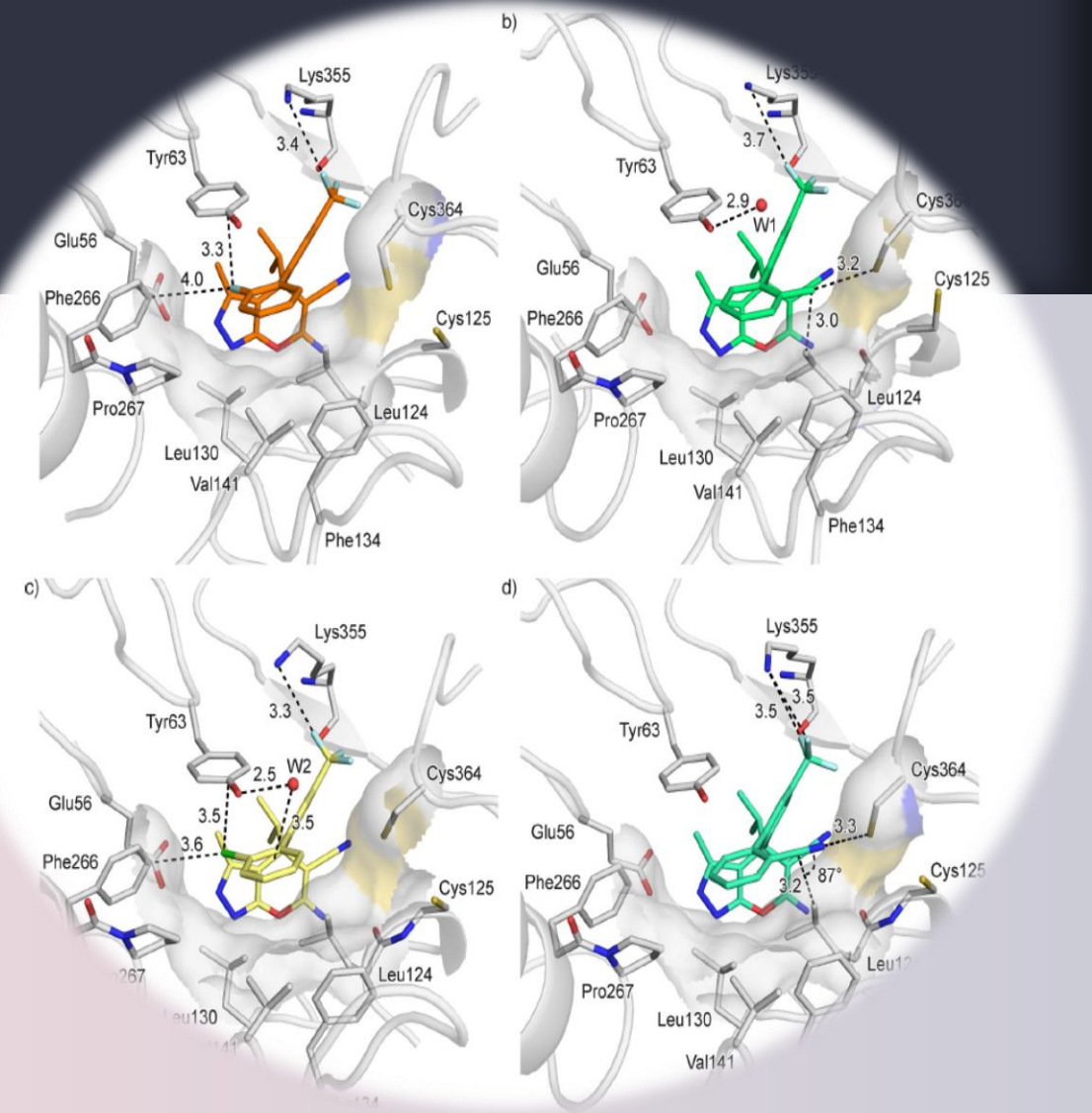
Abstract: Malaria remains a major threat to mankind due to the perpetual emergence of resistance against marketed drugs. Twenty-one pyrazolopyran-based inhibitors bearing terminal biphenyl, aryl sulfonamide, or aryl sulfone motifs were synthesized and tested towards serine hydroxymethyltransferase (SHMT), a key enzyme of the folate cycle. The best ligands inhibited *Plasmodium falciparum* (*Pf*) and *Arabidopsis thaliana* (*At*) SHMT in target, as well as *Pf*NF54 strains in cell-based assays in the low nanomolar range (18–56 nM). Seven co-crystal structures with *P. vivax* (*Pv*) SHMT were solved at 2.2–2.6 Å resolution. We observed an unprecedented influence of the torsion angle of *ortho*-substituted biphenyl moieties on cell-based efficacy. The peculiar lipophilic character of the sulfonyl moiety was highlighted in the complexes with aryl sulfonamide analogues, which bind in their preferred staggered orientation. The results are discussed within the context of conformational preferences in the ligands.

Journal of Medicinal Chemistry
Article
pubs.acs.org/jmc

Inhibitors of Plasmodial Serine Hydroxymethyltransferase (SHMT): Cocrystal Structures of Pyrazolopyrans with Potent Blood- and Liver-Stage Activities

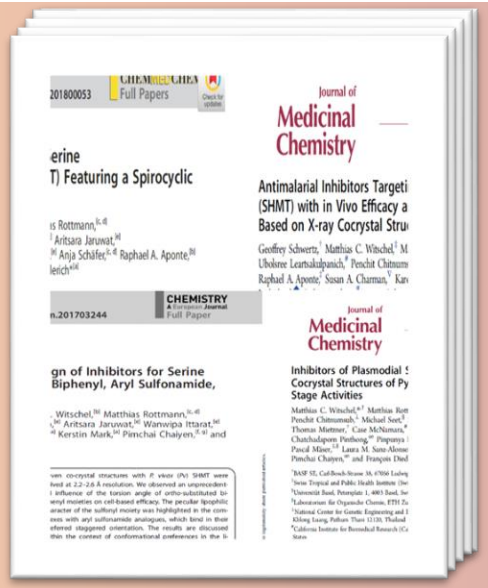
Matthias C. Witschel,*[,†] Matthias Rottmann,[‡,§] Anatol Schwab,[∥] Ubolsree Leartsakulpanich,[⊥] Penchit Chitnumsub,[⊥] Michael Seet,[∥] Sandro Tonazzi,[∥] Geoffrey Schwertz,[∥] Frank Stelzer,[†] Thomas Mietzner,[†] Case McNamara,[#] Frank Thater,[†] Céline Freymond,[‡,§] Aritsara Jaruwat,[⊥] Chatchadaporn Pinthong,[∞] Pinpunya Riangrungroj,[⊥] Mouhssin Oufir,[×] Matthias Hamburger,[×] Pascal Mäser,[‡,§] Laura M. Sanz-Alonso,[¶] Susan Charman,[○] Sergio Wittlin,[‡,§] Yongyuth Yuthavong,[⊥] Pimchai Chaiyen,[∞] and François Diederich*[,∥]

[†]BASF SE, Carl-Bosch-Strasse 38, 67056 Ludwigshafen, Germany
[‡]Swiss Tropical and Public Health Institute (Swiss TPH), Socinstrasse 57, 4051 Basel, Switzerland
[§]Universität Basel, Petersplatz 1, 4003 Basel, Switzerland
[∥]Laboratorium für Organische Chemie, ETH Zurich, Vladimir-Prelog-Weg 3, 8093 Zurich, Switzerland
[⊥]National Center for Genetic Engineering and Biotechnology, 113 Thailand Science Park, Phahonyothin Road, Khlong Nueng, Khlong Luang, Pathum Thani 12120, Thailand
[#]California Institute for Biomedical Research (Calibr), 11119 North Torrey Pines Road, Suite 100, La Jolla, California 92037, United States
[∞]Department of Biochemistry and Center of Excellence in Protein Structure and Function, Faculty of Science, Mahidol University, 272 Rama VI Road, Bangkok 10400, Thailand



CHEMO-INFORMATICS AND MODELING

- Statistical Tools to Discover molecular entities
- 3D Quantitative Structure-Activity Relationship(3D-QSAR)
- Algorithms (PLS)
- Prediction of activity based on modifying structures

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miles
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OC(=O)C1=CC=C(S1)C1=CC(=CC(=C1)C#N)[C@@]1(C(C)C)C2=C(C)NN=C2OC(N)=C1C#N
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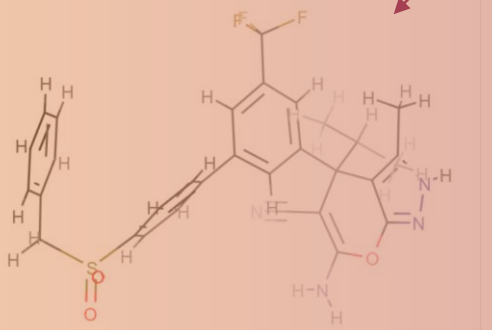
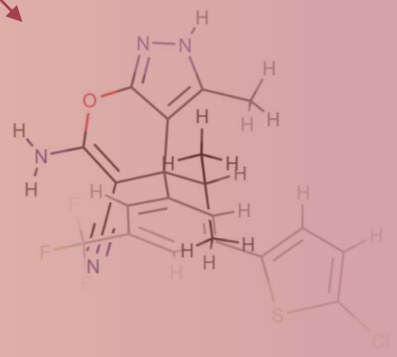




STRATEGY OF THE WORKFLOW!

DATA COLLECTION

- Investigations on target's inhibitors
- Collecting the structures and biological activities
- Conversion to "SMILES" structure (2D)
- Creating a database
- 3D representation of compounds

STRATEGY OF THE WORKFLOW!

Introducing to WWW.3D-QSAR.com

Welcome to www.3D-QSAR.com

The underlying idea of any field-based 3-D QSAR is that differences in a target propriety, e.g., biological activity, are often closely related to equivalent changes in shapes and intensities of noncovalent calculated interaction surrounding the molecules (also called molecular interaction fields, MIFs). This concept was introduced in 1988 by Cramer et al. with the well-known Comparative Molecular Field Analysis (CoMFA). The procedure to build a MIF-based 3-D QSAR model involves the following steps: Training-set selection, alignment of molecules' conformations, MIFs calculation, statistical model definition, model validation, and graphical interpretation. To perform all the steps, any user is asked to install specialized software, either costly or even open source, which require the user to have informatics skills. Here, the very first 3-D QSAR series of web applications is presented by which 3-D QSAR models can be easily built and graphically analyzed. The following web applications are included: (1) Py-MolEdit enables the compilation of the data set through either uploading a list of molecules in any openbabel recognized format or by direct drawing through a java script molecular editor; (2) Py-ConfSerch contains different conformational analysis engines to generate conformational ensembles for each dataset molecules; (3) Py-Align, through automatic molecular alignment software, leads to molecular alignment on up to 16 pre-defined different templates conformations or user selected ones; (4) the Py-CoMFA web application allows the building and validation of the 3-D QSAR model in the same fashion of the original CoMFA software. Different tools are available to inspect the models' results either

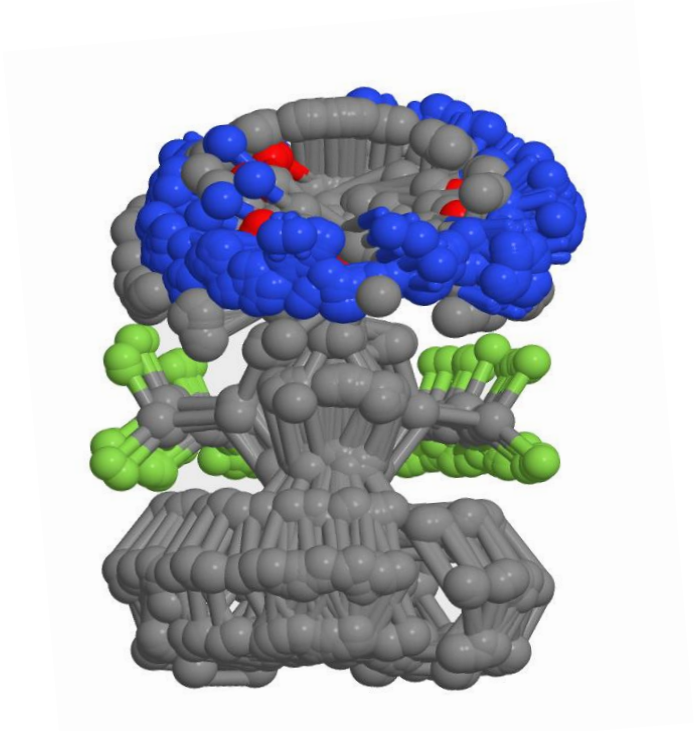
Py-MolEdit

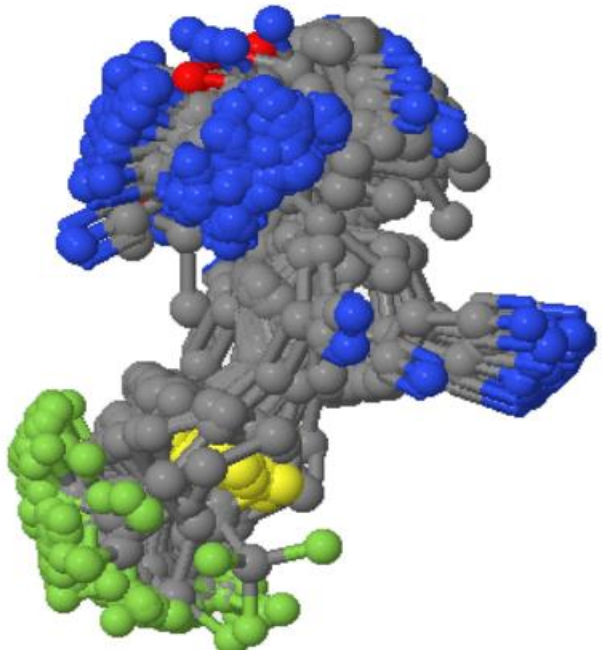
Py-ConfSearch

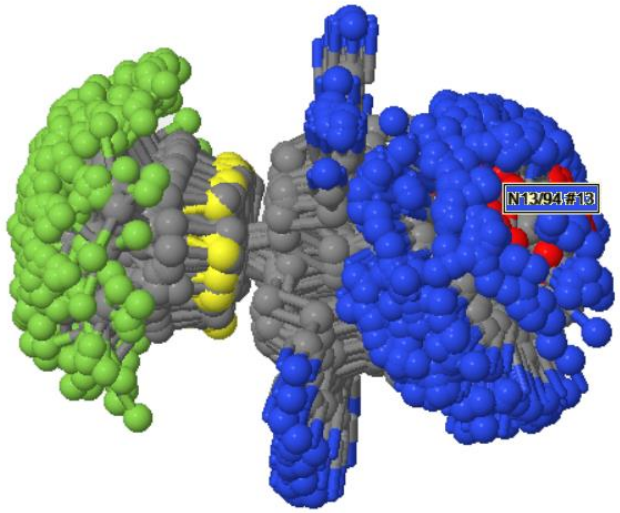
Py-Align

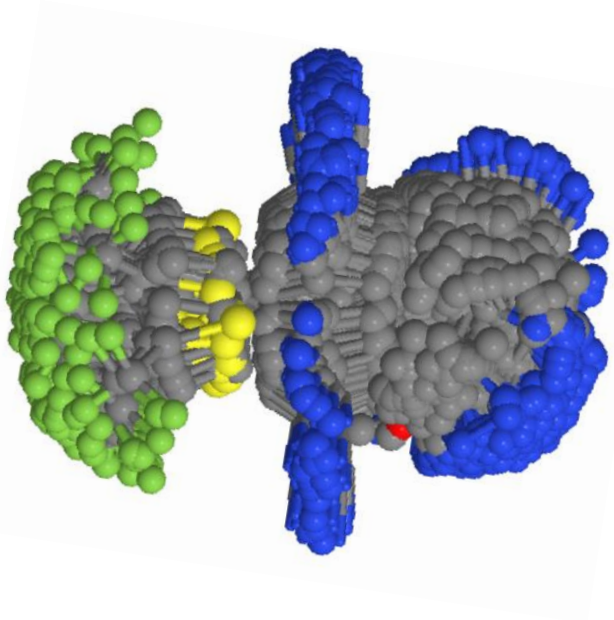
Py-CoMFA

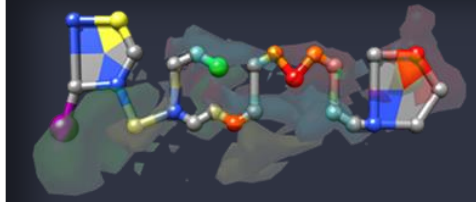
- Rome Center for Molecular Design
- Python Implementation
- Statistical Modeling
- Algorithms and Machine Learning
- 3D Quantitative Structure-Activity Relationship





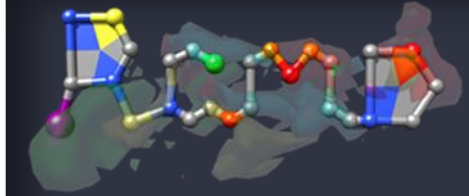


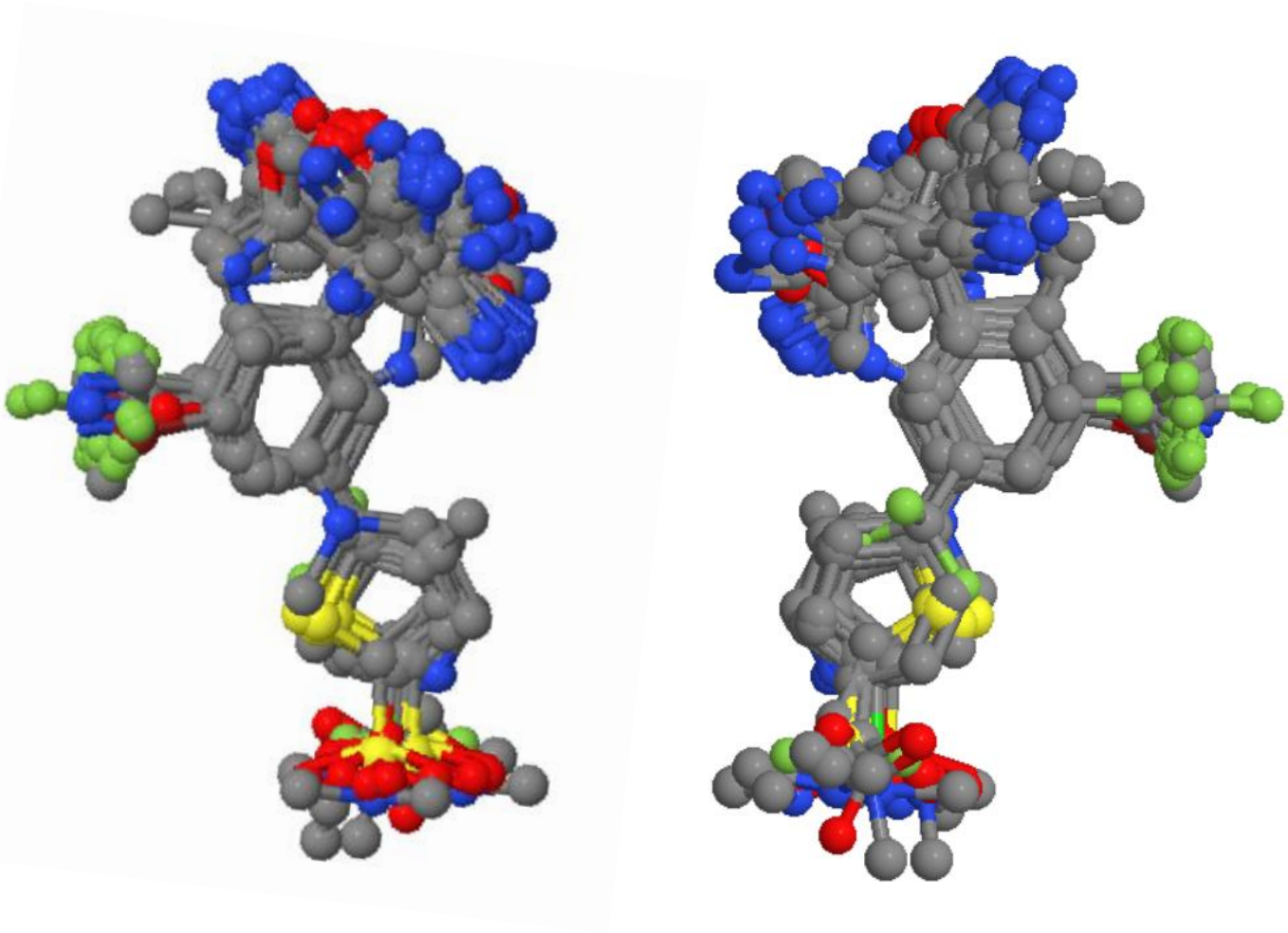




GENERATING 3D-CONFORMATIONS

- Explore the conformational space of each molecule
- Provide an idea of the flexibility
- 3 Methods:
- Rdkit * Openbabel *Balloon

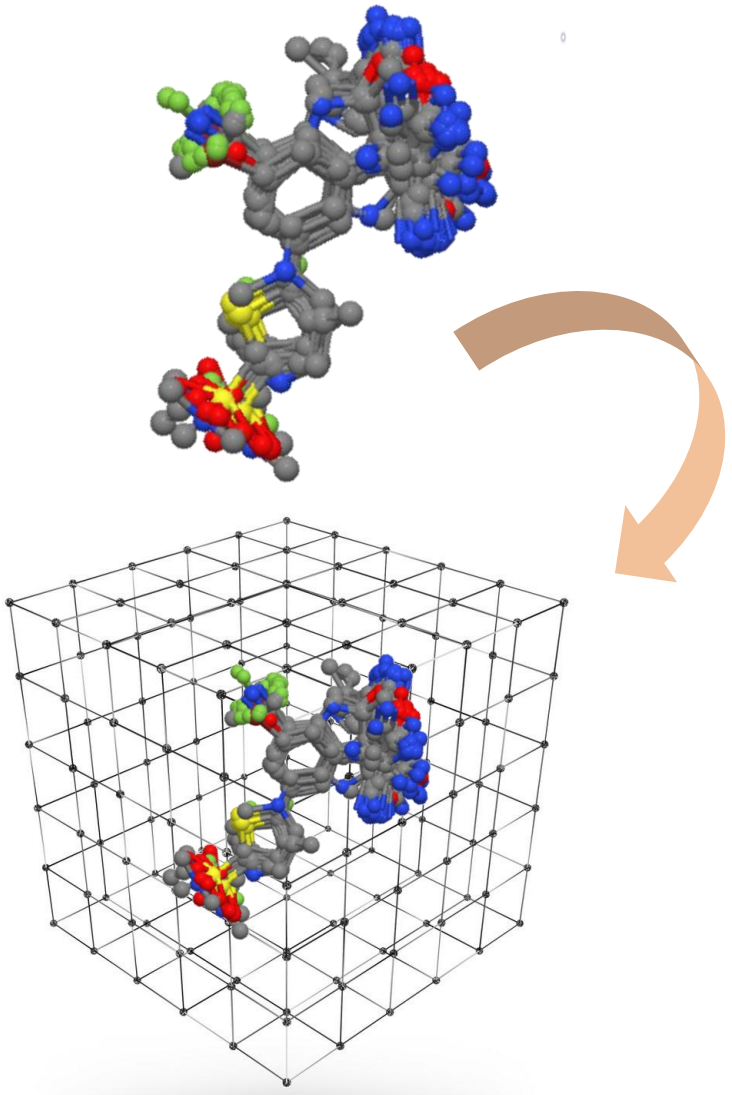




ALIGNMENT

- Superimposition of the molecules of a single conformation
- Final step of training set preparation
- Different approaches
- *Methods * Scoring functions *Reference based
- 96 Alignments on each Conformation analysis

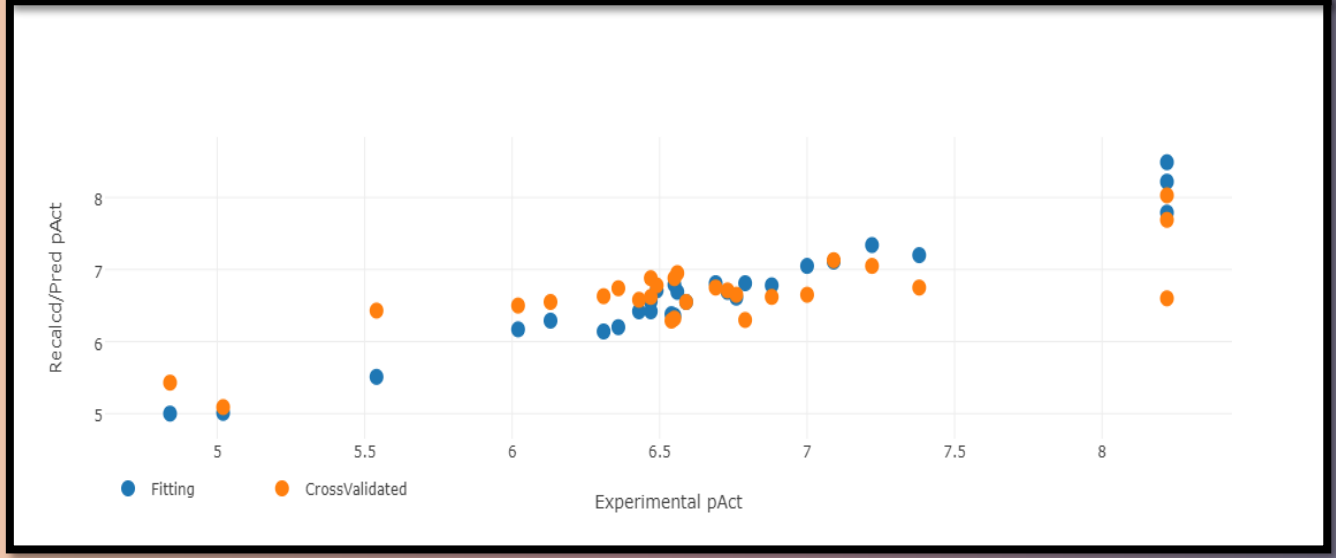
CALCULATION OF MIF FIELDS AND MODEL GENERATION



- Generation of a 3D-QSAR model on each aligned training set(Py-CoMFA)
- Molecular Interaction Fields between ligands and probe atoms, in the center of a grid box.
- Generation of variable models
- More than 1186 models for our dataset.

VALIDATION AND ROBUSTNESS OF THE MODEL

	PC	r²	SDEC	q²	SDEP	r² YS	q² YS	SDEP YS	CutOff	Minimum Sigma
○	1.000	0.650	0.459	0.197	0.696	0.000	0.000	0.000	30.000	0.600
○	2.000	0.811	0.338	0.349	0.626	0.000	0.000	0.000	30.000	0.600
○	3.000	0.890	0.258	0.597	0.493	0.000	0.000	0.000	30.000	0.600
◉	4.000	0.960	0.155	0.629	0.473	0.000	0.000	0.000	30.000	0.600
○	5.000	0.979	0.114	0.605	0.488	0.000	0.000	0.000	30.000	0.600
○	6.000	0.993	0.064	0.606	0.487	0.000	0.000	0.000	30.000	0.600
○	7.000	0.996	0.048	0.600	0.491	0.000	0.000	0.000	30.000	0.600
○	8.000	0.998	0.034	0.597	0.493	0.000	0.000	0.000	30.000	0.600



Statistical Tools

- PLS and Generation of Principal Components
- The r squared correlation coefficient

$$r^2 = 1 - \frac{\sum_{i=1}^{n} (y_{\text{exp}\_i} - y_{\text{calc}\_i})^2}{\sum_{i=1}^{n} (y_{\text{exp}\_i} - \bar{y})^2}$$

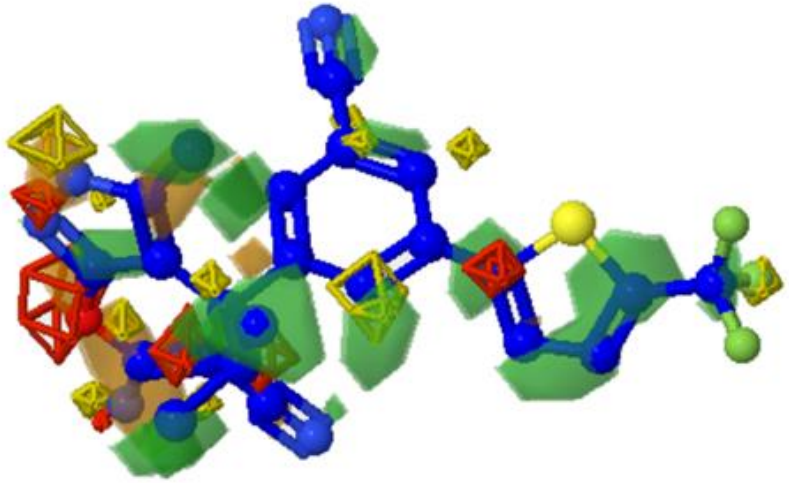
- Cross-Validation

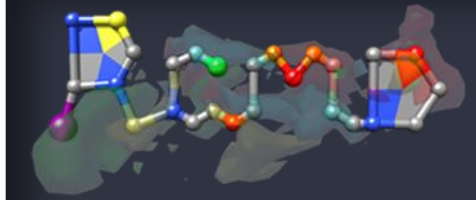
$$q^2 = 1 - \frac{\sum_{i=1}^{n} (y_{\text{exp}\_i} - y_{\text{pred}\_i})^2}{\sum_{i=1}^{n} (y_{\text{exp}\_i} - \bar{y})^2}$$

- Standard Deviation Error Prediction

$$\text{SDEP} = \frac{\sqrt{\sum_{i=1}^{n} (y_{\text{exp}\_i} - y_{\text{pred}\_i})^2}}{n - 1}$$

Overall Model Observation





RESULTS AND GRAPHICAL INTERPRETATION

- Visualizing through Polyhedrons by connecting similar grid points.
- Standard CoMFA Contour maps

at each grid point the product of PLS coefficient by the corresponding MIF standard deviation calculated on all training set molecules

CONCLUSION

- A python implementation of CoMFA in the www.3d-qsar.com models proved effective models built on Ligand Based investigations of pyrazolopyran scaffolds as SHMT inhibitors. The models were built and analyzed, studied and predicted the activity of the compounds obtained from the Medical journals. We have demonstrated the effectiveness of a tool with a quiet appropriate approach in drug design and discovery and in pharmaceutical concept and medicine; here most importantly, Pyrazolpyran core that inhibit the enzyme SHMT which can be profoundly affected by conformational change of the geometry and biological activity of this target. we understand that there is a considerable need to develop novel scaffolds that are different from the existing ligands to overcome cross-resistance, having in hand models, helping the professionals in this field to predict where and how to modify the core scaffolds.


THANK YOU