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DOCKING STUDY AND BINARY CLASSIFICATION MODEL OF ISOTHIAZOLONES AS IRREVERSIBLE INHIBITORS OF THE HISTONE ACETYLTRANSFERASE PCAF

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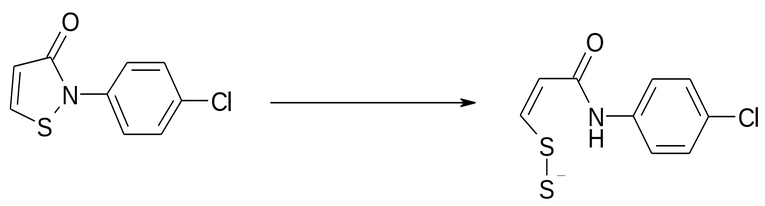
INTRODUCTION

Aryl and alkyl N-substituted isothiazolone compounds have been shown to inhibit the histone acetyltransferase (HAT) PCAF and p300 irreversibly. In this series of aryl and alkyl N-substituted isothiazolones, the inhibition is due to the irreversible interaction with thiol groups of the enzyme. PCAF inhibition of isothiazolones is abolished in the presence of thiol-reducing agents like dithiothreitol (DTT). Furthermore, the activity was not restored in experiments involving the incubation of PCAF with two isothiazolones followed by dialysis for 24 hours [1].

RESULTS and DISCUSSION

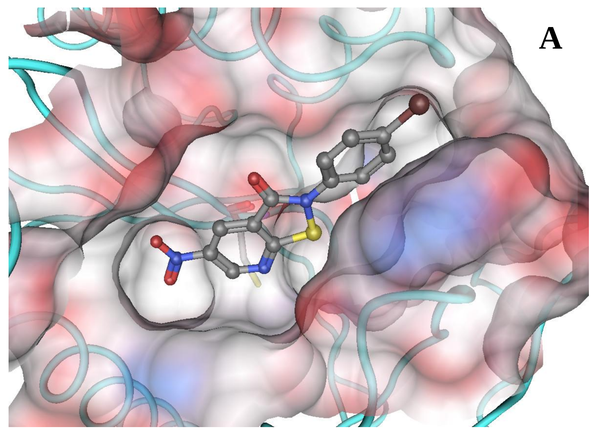
1. Isothiazolones - Covalent Docking

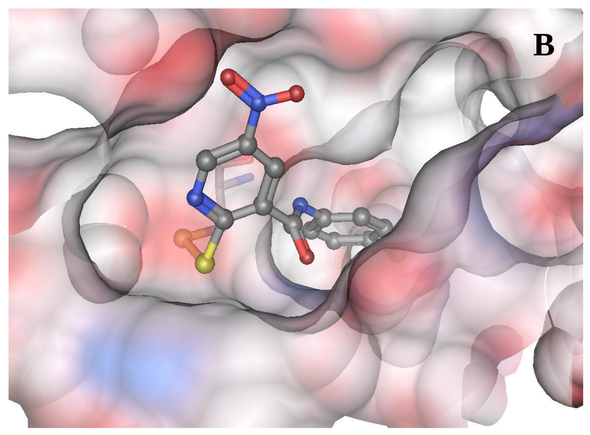
To perform a docking with the isothiazolone compounds a conversion to the open form of isothiazolone structure was necessary in order to simulate the covalent interaction with the enzyme. Using SVL (Scientific Vector Language), an integrated programming language of MOE, the opening of the isothiazolone ring and an appending of another sulfur atom to the original ring sulfur can be easily performed.



The selection of the correct configuration for the CYS side-chain is a critical step to establish the covalent docking. Using the MOE rotamer explorer, five different conformations of the SH-side chain of CYS574 in PCAF X-ray structure were calculated and used for docking.

2. Novel Isothiazolone Scaffold and Docking



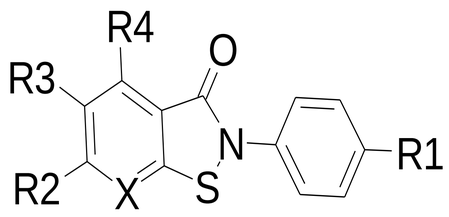


As a result of a virtual screening, compound NCI 694616 has been identified by our group as new isothiazolone as HAT inhibitor.
A series of related compounds (37 compounds) has been purchased or synthesized and tested for their inhibition of HAT PCAF activity by DELFIA method [2].

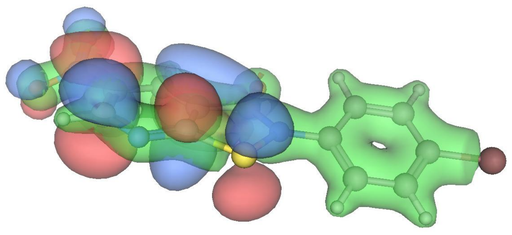
Normal (A) and Covalent (B) docking has been performed using GOLD 4.1, which proves that in all cases the sulphur atom of the isothiazolone ring could be accessed by the thiol group of Cys574 in the active site of PCAF.

Docking scores like Goldscore or GBSA score in both cases of covalent and non-covalent docking showed no correlation with the biological activities measured with PCAF.

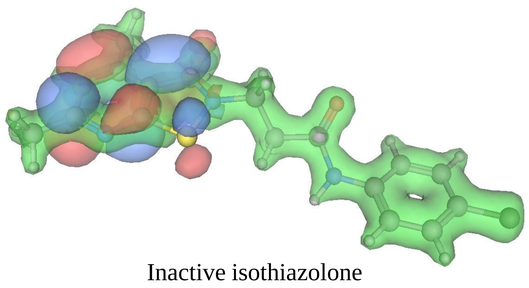
3. Activity and Reactivity



General structure of novel Isothiazolone compounds



Active isothiazolone



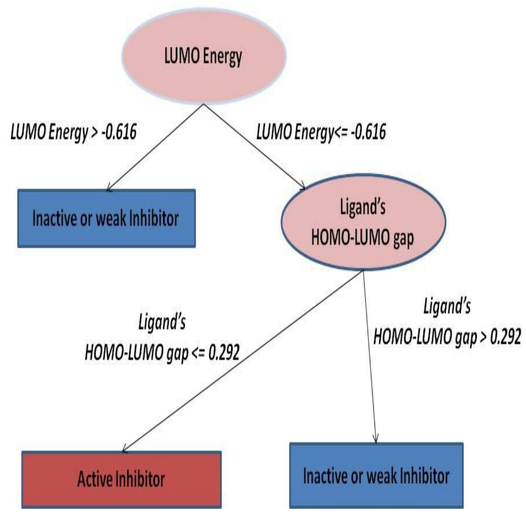
Inactive isothiazolone

The distribution of LUMO energy and LUMO orbitals (in red and blue) on the Isothiazolones, shows the influence of the substituents on LUMO energy and the electron density (in green) especially nearby the SN-bond.

The inhibition activity of isothiazolones is actually related to the reactivity of the N-S bond, which is also related to the electron-pushing and withdrawing properties of the substituents on both sides of the isothiazolone core (R1, R2, R3, and R4). As predictor for the reactivity, the HOMO and LUMO energy (depending on the frontier molecular orbitals theory) could be used. The reactivity of the system is determined by the difference between HOMO of the nucleophile (CYS574) and the LUMO of the electrophile (isothiazolone). The smaller the HOMO-LUMO gap, the more reactive the system is expected. As the nucleophile is constant, then in our case the reactivity of our compounds increase when the LUMO energy is lower. We calculated HOMO and LUMO energies for the docking conformations using AM1 semi-empirical method (MOPAC package applied in MOE.2008.10). Other QM descriptors as dipole, electrophilic softness (σ), chemical potential (μ), and electrophilicity Index (ω), have been also calculated.

- The electrophilic softness is the ease with which electron distribution takes place during covalent bonding. (Softness = $2/(E_{LUMO}-E_{HOMO})$).
- Chemical potential = $(E_{LUMO}+E_{HOMO})/2$ is considered as descriptor for compound's reactivity. The electrophilicity index is a higher order QM parameter that combines the softness and the chemical potential.

4.Binary Classification Model



To test the ability of QM descriptors to classify the isothiazolones, we used a data set of 9 active (IC_{50} range 3.40 μM – 25 μM) and 9 inactive isothiazolones .
The docking scores (Goldscore and GBSA score) for the top selected non-covalent docking solutions, in addition to the QM descriptors, have been used to construct binary classification models (Classification Trees) using the QuaSar Module in MOE.2008.10. Four collections of equal numbers of active and inactive compounds have been selected as training set. The compounds which are not included in the training set has been used for validation. The best model (left) has misclassification rate $R(T)_{training}$= 0 while $R(T)_{validation}$ is 0.0315, and for the whole set R(t)=0.05.

Results and Conclusions

- Series of isothiazolones have been identified as irreversible PCAF inhibitors.
- Non-covalent and covalent docking of these compounds proved the accessibility of the SN-bond in isothiazolones to the thiol group of Cys574.
- The activity of irreversible inhibitors is related not only to the molecular recognition between the inhibitor and the protein, but also to the reactivity of the ligands and the nucleophilic softness of the thiol group in the protein.
- We found that QM descriptors related to frontier MO theory can describe the reactivity and give good classification models for the studied isothiazolones.

References

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