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The correlation between electronic structure and antitumor activity of a selective focal adhesion kinase inhibitors

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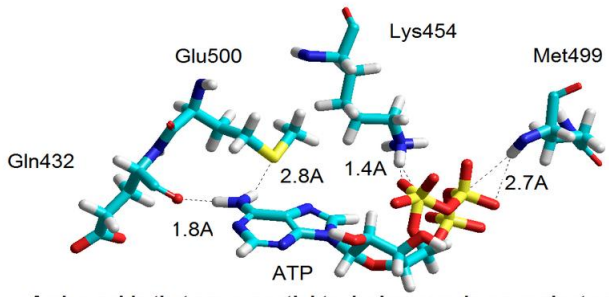
ABSTRACT: Focal Adhesion Kinase (FAK) is a non-tyrosine kinase responsible to phosphorylate other enzymes associated with signal transduction. This biochemical process plays an important role to control cancer. FAK is found overexpressed in the organism during metastasis. Since FAK may be involved in the invasion and metastasis of cancer, novel molecules based on drug design have been synthesized over the past few years. The inhibitors are designed to mimic the natural substrate which is the ATP molecule. This work studied the hydrogen bonds performed between inhibitors and FAK and other electronic properties involved in this interaction. The molecular structure of FAK docked with the inhibitors was simulated using classical molecular dynamics. FAK/ inhibitor complex obtained by dynamic was optimized using quantum mechanical *ab-initio* calculation. Our results show that all inhibitors interact with Cys502 located in the FAK-binding site. *Ab-initio* calculations show that HOMO orbital is situated under Met499 and Glu500 amino acids indicating chemical reactivity in this region. The results of molecular dynamics combined with quantum chemical calculations show that the sulfonamide has a strong hydrogen bond with close distances, while the thiazole has a weak hydrogen bond with long distances. Sulfonamide has known good activity against FAK while the thiazole molecule has an unknown activity. These results allow predicting that the molecule of thiazole is a not good inhibitor to FAK inhibition.



Amino acids that are essential to design new drugs against cancer.

1. Introduction

Cancer is a disease whose feature is the uncontrolled proliferation of cells, able to spread to other tissues. Cell proliferation is related with the biochemical process known as signal transduction. FAK and other kinases are enzymes which catalyze these reactions. During the signal transduction mechanism, chemical signals provided from cell exteriors are converted into physical responses within the cells[1-7].

Focal adhesion kinase (FAK) is a non-tyrosine kinase involved in signal transduction, which is the chemical process associated with the development of several kinds of cancers[8-14]. Consequently, the study of this enzyme is essential to design and synthesize new drugs against cancer. FAK acts in signal transduction mechanism promoting the phosphorylation of serine and tyrosine amino acids. Therefore, new drugs have been designed and synthesized to inhibit the phosphorylation of FAK. The basic chemical structure of these inhibitors is the adenine ring that mimics the ATP molecule.

The interactions among the amino acids in the FAK-binding site with different inhibitors have the

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same pattern of hydrogen bonds, even in the case of quite different chemical structure of inhibitors[15,16]. These chemical changes in the structure allow the drugs have different biological responses against the cancer. Pyrrolopyrimidine inhibitor has been synthesized in order to interact with Arg426, Cys502 and Lys545 in FAK binding site[17].

The PDB ID 3BZ3 ligand (C_{21} H_{20} F_3 N_7 O_3 S)[16] and ID PDB 3PXK ligand (C_{12} H_{14} N_2 S)[15] are examples of molecules that have different molecular structures and different ways to inhibit FAK phosphorylation. PDB ID 3BZ3 ligand is a potent ATP inhibitor that shows inhibition against FAK in the cellular environment. This molecule is an ATP-competitive, reversible inhibitor of FAK and Pyk2 catalytic activity with an IC_{50} of 1.5 and 14 nmol L^{-1}, respectively. Antitumor efficacy and regressions were observed in multiple human xenograft models for PDB ID 3BZ3 ligand. This drug has applications on the colon and lung cancer while the ID PDB 3PXK ligand (C_{12} H_{14} N_2 S) can induce apoptosis in different tumor lines. The differences of biological activity are linked to the molecular structure of inhibitors docked in the binding site.

Theoretical calculations permit to explore the interactions among the amino acids in the FAK-binding site with different inhibitors. Dynamical calculation can show the possible hydrogen bonds performed by the inhibitors while quantum mechanical calculation can describe important electronic properties. In this work, we described the pattern of hydrogen bonds at the catalytic site using molecular dynamics and quantum mechanical calculations in order to understand how these hydrogen bonds are linked to the FAK inhibition.

2. Materials and methods

2.1 Quantum Chemical and Molecular Dynamic Calculations

X-Ray molecular structure based on PDB ID 3BZ3[16], 3PXK[15], and 2IJM[18] were used as initial geometry to describe the interaction of the methane sulfonamide diaminopyrimidine, pyrrolo[2,3-d]thiazole and ATP respectively. One nanosecond of molecular dynamics was performed to search possible hydrogen bonds. This simulation was calculated using the program Hyperchem[19]. An implicit solvent with dielectric constant equal to 80 was used in order to simulate the water solvent. The constant temperature of 300 K was used during the simulation and NVE ensemble was used. Molecular optimization with the force field Charm[20] was performed in order to avoid atom superimposition before the molecular dynamics using a *steepest decent* algorithm. SwissParam[21] was used to provide parameters and topologies for the ligands. Pair correlation function was calculated to hydrogen bonds inside the catalytic site. CHELPG charge derivative of HF/6-31G was used to describe atomic charge for the inhibitor inside the catalytic site for dynamic calculation. Molecular dynamic was used to search different hydrogen bonds. Quantum chemical calculations were used to describe the hydrogen bonds present in the FAK inhibitors interaction. The ONIOM[22-25] method, present in a Gaussian program, was used to describe the molecular structures cited above. In order to depict the higher layer, the amino acids Cys502, Lys454, Met499, Arg426, Ala452, Glu506, Glu471, Arg508, Arg550, Asp564, Leu501, Glu430 and Thr605[17] were selected from molecular dynamic results. The quantum mechanical calculations based on PM6, B3LYP/6-31g, HF/6-31g, RMNDO were employed in the higher layer that was optimized using the keyword quadmac[25]. This keyword does a quadratic step in the coordinates of all the atoms. UFF (Universal Force Field) was used in order to describe the Van-der Walls and electrostatic potential for the atoms in the lower layer. Qeq[26] method was used to get the charges for UFF[27] force field. Molecular frontier orbitals were calculated using HF *ab-initio* method. The hydrogen bond energies were investigated with electronic calculation MP2 and the base function 6-31G ++ (d, p) coupled to the CPCM method for water solvent. The strength of the hydrogen bonds was investigated using the interaction energy between the inhibitors and the amino acid.

3. Results and discussion

3.1 Quantum optimizations

HF 6-31G was the method used to describe the hydrogen bonds and other interactions for all inhibitors, because other methods did not perform a full convergence of biological systems studied. Successive errors associated with internal coordinates and the dihedral angles were observed for the methods PM6 and B3LYP/6-31g. MNDO semi-empirical method performed a full optimization for the entire biological system, but it

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is a less robust approach when compared with HF approach. Therefore, the combination HF 6-31G and UFF were used to obtain the equilibrium geometry of the system FAK docked with all the inhibitors. The hydrogen bonds in the binding site obtained from ONIOM calculations are shown in Figure 1.

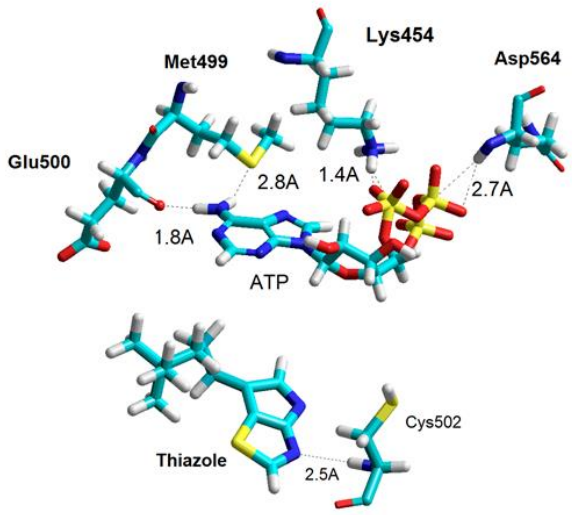

Figure 1. Hydrogen bonds performed by the inhibitors and the ATP molecule after ONIOM optimization.

The hydrogen bonds formed are similar to all inhibitors. Sulfonamide and the thiazole molecule perform hydrogen bonds with the amino acid Cys502. The thiazole molecule has a single interaction with the Cys502 amine group with 2.5 Å of distance. Sulfonamide performs two hydrogen bonds with Cys502 amino group with 2.3 Å and other bond with hydroxyl group at 1.9 Å of distance. The Cys502 hydrogen bond has been seen on others FAK inhibitors in accord to literature[17]. Amber force field optimization for 7-h-pirrolopirimidine shows a hydrogen bond with a Cys502 amino group with 2.15 Å of distance. Quantum mechanical calculation did not show this hydrogen bond to the ATP molecule. Sulfonamide drug can interact yet with the Arg426 amino group with a distance of 1.9 Å. This hydrogen bond is found in 7-h-pyrrolopyrimidine inhibitors. The hydrogen bond with Asp424 is found in the 7-h-pyrrolopyrimidine inhibitor 32, which has the best IC_{50} between pyrrolopyrimidine drugs[17].

ATP is a special case. There are hydrogen bonds with Gln432 and Glu500 that happen with the adenine ring. On the other hand, phosphate groups interact with the amino acids Lys454 and Met499. In recent literature[17], the interaction with Lys454 has been associated with the increase of FAK inhibition. The most powerful pirropyrimidine inhibitor, named 32, also interacts with the amino acid Met499[17].

3.2 Molecular dynamics

The results of molecular dynamics and the pair correlation function are shown in the Figure 2. The pair correlation function is related to the probability of finding the center of a particle a given distance from the center of another particle. Figure 2 shows the probability of finding two atoms with a given separation.

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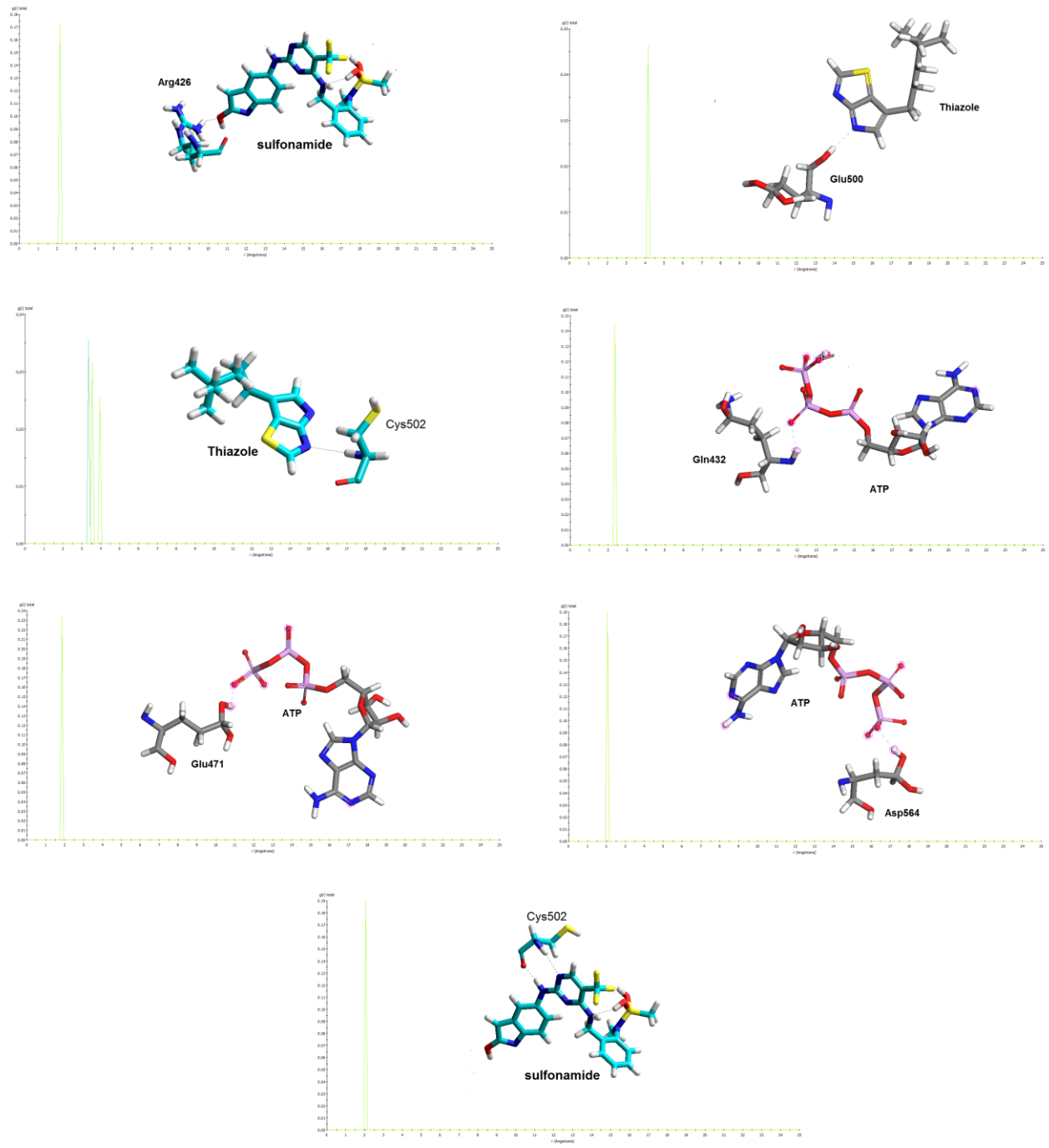

Figure 2. Hydrogen bonds performed by the inhibitors and ATP using molecular dynamics and the graphic of pair function correlation.

Molecular dynamic shows that the sulfonamide molecule can bind with Cys502 and Arg426. The average of binding distances is equal to 2 Å for both amino acids. Thiazole molecule performs a hydrogen bond with the amino acid Cys502 and the amino acid Glu500. An average of 4.0 Å of distance for these interactions was described by molecular dynamic calculation. ATP molecule performs hydrogen bonds with Asp564, Gln432 and Glu471. The interaction with Gln432 and Asp564 is close to 2.5 Å while the interaction with Glu471 is close to 2.0 Å. These results show a distribution of hydrogen bond distances during the molecular dynamics. The differences between ONIOM (HF/6-31G/UFF) results compared with molecular dynamics are described in Table 1.

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Table 1. Hydrogen Bonds distances performed between the amino acids localized in the binding site and the inhibitors using different methodologies (MD- Molecular Dynamics and ONIOM, HF/6-31G/UFF).

Amino acid	*Sulfonamide* ONIOM Hydrogen Bond *Distances* (Å)	*Sulfonamide* MD Hydrogen Bond *Distances* (Å)	Thiazole ONIOM Hydrogen Bond *Distances* (Å)	*Thiazole* MD Hydrogen Bond Distances (Å)	*ATP* ONIOM Hydrogen Bond Distances (Å)	*ATP* MD Hydrogen Bond *Distances* (Å)
Lys454					1.4	1.6
Cys502	1.9, 2.3	****	2.5	4.0		2.5
Arg426	1.9	****				
Glu500				3.5-4.0	2.8	2.06
Met499					2.7	1.6
Gln432					1.8	2.5
Asp564	2.4	****				2.0

*****No changes verified in the hydrogen bond distances compared with ONIOM optimization

The results of molecular dynamics are close to ONIOM approach. Sulfonamide molecule performs hydrogen bonds close to 2.0 Å for both methods. ATP molecule shows similar distances of hydrogen bond for the two methods. The exception is the molecule of Thiazole. During the molecular dynamic the hydrogen bond with Cys502 keep a distance close to 4.0 Å, while the ONIOM optimization shows a distance of 2.5 Å. The MP2 method shows that this bond has energy close to 1 kcal, while the same bond to sulfonamide has an energy interaction close to 40 kcal. The same result is seen to the interaction with Glu500. The energy to the interaction between the thiazole inhibitor and the amino acid Glu500 is close to 2 kcal. These results justify the discrepancy between the quantum mechanical optimization and the molecular dynamics. There is no experimental quantity activity to thiazole molecule. However, we believe that this inhibitor does not have a good activity to FAK inhibition due to weak interaction energy with the FAK binding site associate with long hydrogen bond distances. On the other hand, the sulfonamide molecule has a good activity to inhibit FAK and very strong hydrogen bonds.

3.3 Orbitals analysis

The molecular orbitals obtained from *ab-initio* calculation are shown below in Figure 3.

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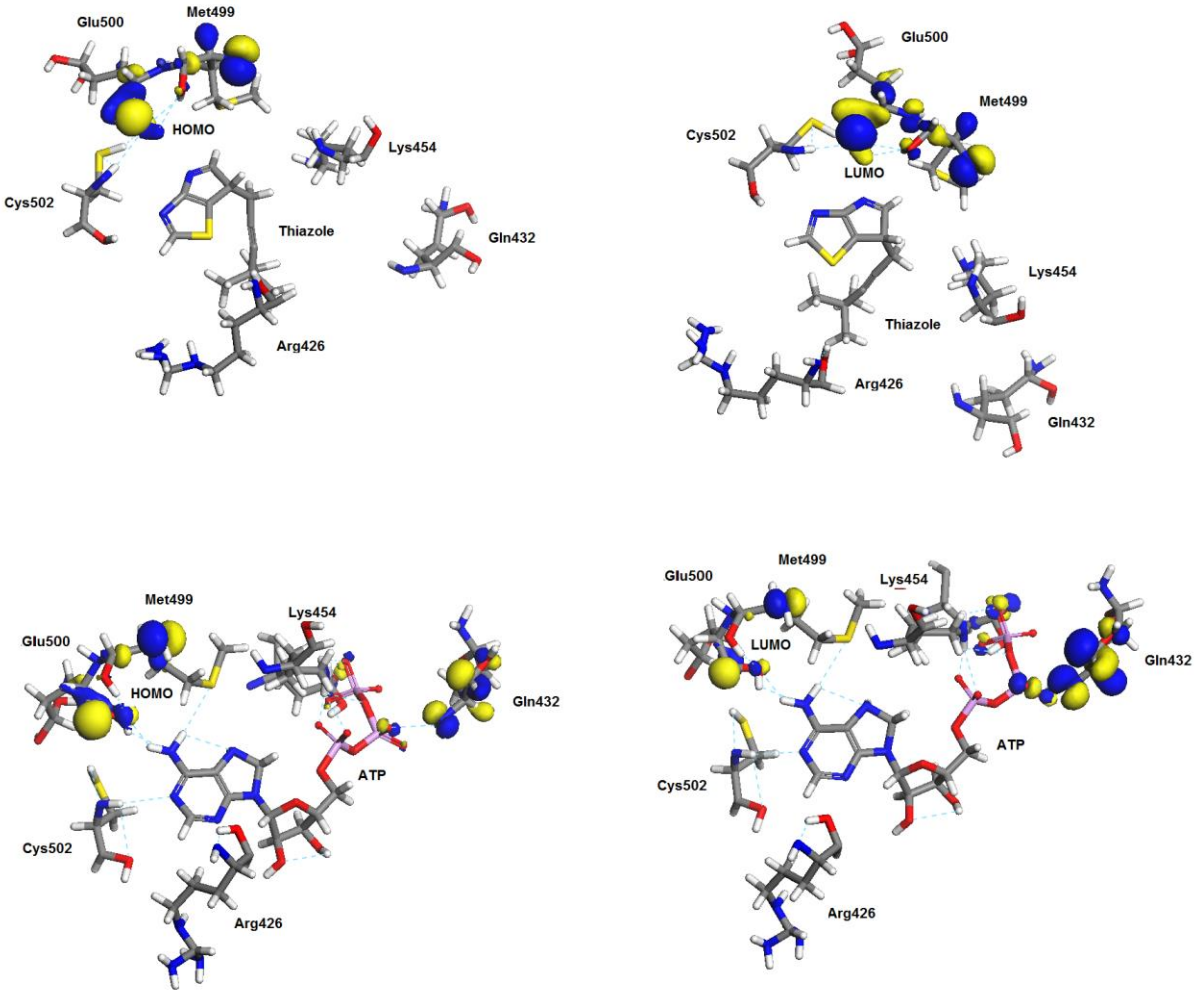

Figure 3. Molecular Orbitals HOMO and LUMO obtained from *ab-initio* calculations of the ligands (ATP, Sulfonamide and Thiazole) in the binding site.

The HOMO and LUMO molecular orbitals obtained from *ab-initio* calculations show a pattern in the binding site for the ligands studied. HOMO orbitals are located mainly in the amino acids Glu500 and Met499. In the ATP molecule, the LUMO orbital is located at the amino acid Gln432 while in the thiazole molecule, LUMO orbital remains on the amino acids Glu500 and Met499. The orbital of the sulfonamide is located on the amino acid Cys502. Fluorine atoms of the sulfonamide inhibitor interact with amino acids Met499 and Glu500, while in the ATP molecule the interaction occurs with the chemical group Adenine. The bicyclic ring of the thiazole molecule has the same function as the adenine ring of the ATP molecule and the fluorine atoms of the sulfonamide molecule.

The construction of new inhibitors should be focused on towards the compliance of the hydrogen bonds obtained, as well as the arrangement of the HOMO / LUMO orbitals that emphasize the importance of the connections and interactions with the amino acids Met499 and Glu500. The inhibitor thiazole has a long hydrogen bond and a weak hydrogen bond with the amino acids where are localized the orbitals HOMO and LUMO. On the other hand, the inhibitor sulfonamide is close to HOMO and LUMO orbital at the same time and it has high bond energy. The sulfonamide has a low IC_{50} indicating that less quantity of molecule is necessary to inhibit FAK. The thiazole has

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unknown quantity experimental data (IC_{50}). These data can reveal that thiazole can be not a good inhibitor to FAK.

4. Conclusions

We studied two inhibitors using two kinds of calculations (Molecular Dynamic and ONIOM quantum mechanical approach). Both calculations show similar hydrogen bonds to the inhibitors compared with ATP molecule. However, the hydrogen bond distances and the bond energies are different to inhibitors. Sulfonamide has a strong hydrogen bond with the amino acids Glu500 and Cys502 while the thiazole inhibitor has a weak hydrogen bond with these amino acids. Molecular dynamics show close hydrogen bonds to sulfonamide and long hydrogen bond distances to thiazole. HOMO orbital is localized close to amino acid Glu500 in the binding site. ATP and Sulfonamide are close to this orbital while the thiazole is far from the HOMO orbital. There is no number of activity (IC50) to thiazole. However, these results show that thiazole molecule could have a low experimental activity against FAK, because the sulfonamide inhibitor has high activity with close hydrogen bonds to the amino acids (including the amino acids where are located HOMO and LUMO orbitals) of the catalytic site at the same time it has strong hydrogen bonds with these amino acids.

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