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Study of Molecular Dynamics, NBO and QTAIM for inhibitors of ALK-5

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Introduction: TGF-β Receptor Type 1 (TGF-β1), also known as activin kinase type 5 (ALK-5), is a biological target related to some types of cancer, such as breast cancer. Inhibition of this target is a strategy that has been studied as a way to treat cancer. In this way, the objective of this work is to use computational chemistry to evaluate the main interactions that occur between the main residues in the active site of ALK-5 (Tyr249, His283 and one structural water) and two inhibitors of this receptor [1, 2].
Materials and methods: To evaluate the interactions between the two molecules and the ALK-5 target, the following methodologies were used: molecular docking (GOLD 5.2), molecular dynamics (70 ns, force field ff99SB, AMBER12), QM/MM (ONIOM, B3LYP/cc-PVDZ:UFF, Gaussian 09), analysis of natural bond orbitals (NBO, B3LYP/cc-PVDZ, Gaussian 09) and topological analysis of electronic density of interactions by quantum theory atom in molecules (QTAIM) [3].
Results and discussion: Figure 1 shows the results obtained from molecular docking and molecular dynamics simulations.

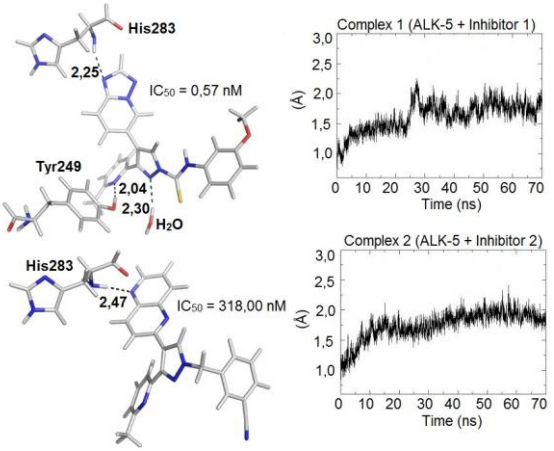

Figure 1. Hydrogen bonds between the inhibitors 1 and 2 and the main residues of ALK-5; RMSD values obtained from molecular dynamics to the two complexes.

Figure 1 shows that ALK-5 with the inhibitor 1 (the most active, IC_{50} = 0,57 nM) docked on its active site, as well as hydrogen bonds with the main residues and the structural water. The RMSD values obtained from molecular dynamics simulations

indicate that the complex 1 (ALK-5 + inhibitor 1) presents a greater flexibility. After these analyzes, the conformation of the complexes obtained from the molecular dynamics was used for the QM/MM ONIOM calculations with the objective of evaluating the electronic behavior of the interactions between ALK-5 and the two inhibitor molecules. From the ONIOM results, NBOs were analyzed in order to evaluate the electronic transfer between the ligands and the receptor. Thus, Table 1 shows the results obtained from ONIOM and NBO calculations.

Table 1. E_{ONIOM} values and interaction intensities obtained from NBO calculations

Interactions - Complex 1 (E_{ONIOM} = -2.732.543,53 kcal/mol)	NBO Donor	NBO Aceptor	ΔE^2(kcal/mol)
1 - Inhibitor 1 + H_2O	LP N	BD*(π) O-H	2,83
2 - Inhibitor 1 + Tyr249	LP N	BD*(π) O-H	11,89
3 - Inhibitor 1 + His283	LP N	BD*(π) N-H	3,82
Interactions - Complex 2 (E_{ONIOM} = -2.56.836,81 kcal/mol)	NBO Donor	NBO Aceptor	ΔE^2(kcal/mol)
4 - Inhibitor 2 + His283	LP N	BD*(π) N-H	0,81

Table 1 shows that the complex 1 (the most active) has a lower value of E_{ONIOM} and from the NBO analyses, it is possible to notice from the values of ΔE^2 that the hydrogen bonds that occur between the inhibitor 1 and ALK-5 residues are more intense. Finally, the electron density (ρ) and laplacian of electron density (∇2ρ) of the bond critical points (BCPs) were analyzed using the QTAIM methodology, and the results obtained can be seen in Table 2.

Table 2. Values of electron density and laplacian of electron density

(BCPs)	**ρ (u.a.)**	**$\nabla^2\rho$ (u.a.)**
N_{27}-H_{18} (Inhibitor 1 + Tyr249)	0,025	0,065
N_{31}-H_{10} (Inhibitor 1 + His283)	0,013	0,040
N_1-H_{54} (Inhibitor 1 + H_2O)	0,013	0,036
N_{15}-H_{68} (Inhibitor 2 + His283)	0,010	0,029

The results presented in Table 2 show that ρ and ∇2ρ for both interactions are positive, confirming the electronic character of a hydrogen bond from the QTAIM theory. Another important finding is that the QTAIM theory corroborates the NBO model, because for both techniques, the interactions with the inhibitor 1 are more intense, and the interaction between the inhibitor 1 and Tyr249 is the most intense.

Conclusions: From the obtained results it was possible to analyse the behavior of two inhibitors in the active site of ALK-5, and NBO and QTAIM analyses showed that the inhibitor 1 makes more intense interactions with the biological target, increasing the stability of the complex.

Key-words: ALK-5, cancer, inhibitors. ONIOM, NBO, QTAIM.
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