DOCKING STUDIES ON THE INFLUENCE OF TAUTOMERS OF IDELALISIB ON THE PI3Kδ ENZYME

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Introduction

Isoform-selective phosphoinositide-3-kinase inhibitors (PI3Ki) are important therapeutical targets for cancer therapy, including some kinds of advanced malignancies[1]. The first isoform-selective PI3Ki approved by the FDA, Idelalisib, represents a milestone for myeloid cell cancer treatment and a lead compound for the development of new isoform-selective PI3Ki. This selectivity is related to the propeller-shaped conformation on the active site adopted by Idelelisib, which has a minimal effect on the ubiquitously expressed PI3Kα isoform[2]. To determine if the ligand's tautomerism may influence docking studies on the PI3Kδ isoform, we used all Idelalisib tautomeric forms in this study.

Method

A homology model was built using the SwissModel server[3] from the X-ray crystal structure of PI3Kδ (PDB ID:6G6W; R = 2.72 Å). Molecular docking simulation was performed using the Autodock 4.0 program[4]. The protein and ligand structures were performed using the Python Molecular Viewer extension of the ADT program (Autodock tools). Polar hydrogens were added and the charges of the atoms were indicated on the protein by the Kollman method. The grid map was built using the Autogrid 4.0 extension, with coordinates centered on x: 37.137; y: 12.601; z: 32.100, and dimensions with 60x60x60 Å. A Lamarckian algorithm was used to conduct docking calculation with the following parameters: population size of 150, maximum energy evaluations (2,500,000) and generations (27,000), a mutation rate of 0.02, a crossover rate of 0.8, and a number of runs of 10. This protocol was validated through redocking using the co-crystalized inhibitor LASW1976 as a ligand (RMSD = 0.2031Å). The 3D structures of Idelalisib tautomers were obtained using MarvinSketch 21.9.0[5]. Subsequently, the structures were processed on Chem3D Pro 12.0[6] to standard systematic conformational analysis using the MM2 semi-empirical method. The hydrogen bonding interaction evaluation and generation of figures were performed using the BIOVIA Discovery Studio Visualizer 2020[7] program. Each tautomer had its heat of formation calculated from the semi-empirical Parametrical Model 3 (PM3) using PC SpartanPro 1.0.5[8]. The population ratio was obtained by the Boltzmann equation.

Results and Discussion

Twenty-three Idelalisib tautomers were found (36 considering their constitutional isomers) on MarvinSketch 21.9.0. The tautomers and their isomers were docked to PI3Kδ forming a complex (PDB ID:6G6W) following the validated protocol. Lowest Binding Energy (LBE) values ranging from -9.72 to -6.61 Kcal/mol were obtained. Analysis of H-bonds interactions, as well as the Boltzmann population distribution to determine the most abundant tautomer (Table 1), were performed for the best performing tautomers (LBE < 9 Kcal/mol) (Figure 1). Although **T12S** presented the lowest LBE, only **T2** reproduced the same H-bonds as Idelalisib co-crystallized with PI3Kδ (PDB ID: 4XE0). Furthermore, **T2** has the greater Boltzmann ratio, indicating that it is the most abundant tautomeric form of Idelalisib (99.996%) in comparison with the others.

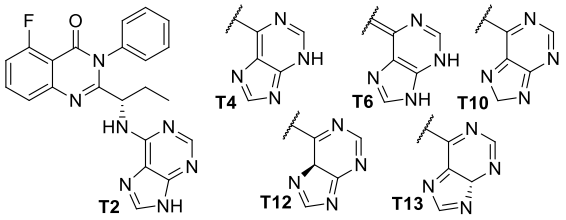

Figure 1: Idelalisib tautomers with LBE < 9 Kcal/mol.

Table 2: LBE, H-bond interactions and Boltzmann population distribution for the best performing Idelalisib tautomers.

Tautomer	LBE (kcal/mol)	Number of H-Bonds	Residues of Interaction	Boltzmann Molar Ratio	Boltzman population (%)
T2	-9,54	2	Glu826, Val828	1,00E+00	99,996%
T4	-9,65	1	Glu826	1,44E-09	0,000%
T6	-9,19	1	Pro758	4,00E-14	0,000%
T10	-9,25	1	Val828	2,45E-21	0,000%
T12S	-9,72	1	Val828	2,80E-24	0,000%
T13S	-9,65	1	Val828	1,99E-26	0,000%
Idelalisib*	-	2	Glu826, Val828	-	-

*Data from the PDB ID: 4XE0.

Conclusion

Our results show that considering the different ligand tautomers is relevant for the conducted docking studies. The Idelalisib tautomeric forms presented remarkable different results forLBE and H-bond interactions profile. Among the analyzed species, the **T2** tautomer showed the best results for LBE and H-bonds, in addition to being the most abundant form in the Boltzmann population ratio.

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