Mutational Analysis of Human K-ras G12C and Design and Molecular Docking of ARS-853 derivatives

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K-Ras is a Ras family protein primarily involved in the regulation of celular proliferation, cell differentiation and apoptosis, alternating between an inactive form bound to GDP and an active GTP-bound form. K-ras mutations occur in approximately 30% of all cases of human cancer. However,despite of intensive research, relevant therapies for cancers with mutations in this protein have not been developed yet. K-ras G12C is the most common variant in lung cancer and specific therapies for this oncoprotein are in initial stages of development. ARS-853 is a potent inhibitor that binds to the inactive form of K-ras G12C, preventing its activation. This work purposes to design molecules with optimized affinity and complementarity in relation to receptor and relate the inhibitor interactions to structural stability of K-ras G12C. The native and mutant K-ras structures were analyzed by alanine scanning, stability calculations and interaction energy estimation between GDP and proteins in the Fold-X program. Based on redocking, physical-chemical profile analysis and prediction of pharmacokinetic and toxicological properties, ARS-853 derivatives were designed and docked to Switch II cavity. Our results provided evidences that G12C mutation has a neutral effect on the stability of K-ras. Likewise, the alanine scanning showed that the residues G12 and C12 have neutral contribuition in protein stability, but the presence of C12 induces a charge inversion in the electrostatic potential map of the Switch II cavity that can be critical to selective inhibition of mutant K-ras. The presence of ARS-853 generated a high increase on the total energy of K-ras G12C and the interaction between GDP and the oncoprotein with inhibitor was destabilized. Two molecules derived from ARS-853 (Moldock score -202.09) were obtained (Moldock scores -227.66 and -215.77, respectively) with high complementarity to receptor and both are chemically simplified compared to the reference inhibitor. ARS-853 and its derivatives conserved some non-covalent interactions: hydrogen bonds with E63, R68 and D69 and hydrophobic pi-alkyl interactions with C12 and V103. Overall, these results reinforce experimental evidences that ARS-853 inhibits K-ras G12C with high selectivity, altering the stability of the mutant form. We conclude that it is prototype with great potential for development of new anticancer drug against this protein.