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MOLECULAR DOCKING STUDY ON BINDING MODES OF ISOXAZOLO- AND THIAZOLOHYDRAZILIDENE-CHROMANE-2,4-ONES WITH B-RAF KINASE

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Recently a series of novel isoxazolo- and thiazolohydrazilidene-chromane-2,4-ones was synthesized and shown to exhibit cytotoxicity on human breast cancer cell line MDA-MB-231 [1]. MDA-MB-231 cells are very sensitive to treatment with B-Raf kinase inhibitors blocking the RAF/MEK/ERK signaling pathway and affecting the tumor growth. Among the three RAF isoforms in humans (A-Raf, B-Raf, and C-Raf), B-Raf is the most critical to mediate Ras activity. A significant fraction of melanoma, colorectal, thyroid and breast cancers have activating B-Raf mutations, particularly at valine 599 [2].

The results of a molecular docking study conducted in effort to throw more light on the possible interaction of the synthesized isoxazolo- and thiazolohydrazilidene-chromane-2,4-ones with B-Raf are presented. The compounds were docked into the crystal structure of human oncogenic ^{V599E}B-Raf in complex with the inhibitor sorafenib. All of them occupied an internal pocket formed by the activation segment and the P-loop of ^{V599E}B-Raf. The ligand-pocket binding was driven by hydrogen bonding to amino acid residues Lys482, Glu500, Thr528 and Asp593 and hydrophobic interactions with Leu504, Leu513, Gly592 and Phe594. In this way, the ligands connected simultaneously to the activation segment and the catalytic loop of ^{V599E}B-Raf, were being able to promote an inactive conformation of the enzyme and hinder its phosphorylation.

Key words: hydrazinyldiene-chroman-2,4-diones, molecular docking, B-Raf kinase

References:

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