عنوان مقاله:

Experimental And Molecular Docking Study Of Novel Heterocyclic Compounds Against FLT3 Receptor TyrosineKinase

محل انتشار:

دومین سمپوزیوم بین المللی سرطان نسترن (سال: 1395)

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خلاصه مقاله:

Cancers, including Leukemia, are major causes of human mortality. Leukemia is the most commoncancer diagnosis in children who are younger than 15 years. Acute Myeloid Leukemia (AML) havebeen recognized as a prevalent type of leukemia by 25-30% of all. Internal tandem duplications (ITD)and point mutations in the tyrosine kinase domain (TKD) of the FLT3 receptor (FMS-Like Tyrosinekinase) are the most common genetic alterations in AML. Small Molecules Inhibitors (SIMs) of themutated kinases are considered as one of the most promising molecular strategies to combat withsuch genetic defects. A set of 8 novel heterocyclic compounds composed of a common core (7,7-dimethyl-7,8-dihydro-6H-tetrazolo[1,5-b][4,1,2]benzothiadiazin-6-one) structure and differentsubstituents used in this study. Two murine cell lines of FD-FLT3-WT and FD-FLT3-ITD dependent tohuman FLT3 receptor were used for doing cellular examinations. Cytotoxicity evaluation wasperformed using Resauzurin reagent for both cell lines in the presence of various growth factors(FLT3 ligand and GM-CSF) for the FD-FLT3-WT line to achieve IC50. The interactions of the inhibitorcompounds and the homology models FLT3 were evaluated by molecular docking method usingGOLD and Accelrys Discovery Studio software.The D8 compound with the amino substituent couldresult in the IC50 values of 14.28 and 0.93μM, respectively, in two cell lines of FD-FLT3-ITD and FDFLT3-WT. However, two D1 and D2 compounds were effective against the FD-FLT3-ITD line, but noton the FD-FLT3-WT cell line. Also, the docking results indicate these compounds were docked withmore favorable energy at the active forms of the receptor (homology models built based on 1PKGand 2GQG). In both experimental and in silico studies, compounds D1, D2 and D8 were considered asthe best compounds of this category due to their specific activity and potent receptor-ligandinteractions.

کلمات کلیدی: