Design, synthesis and molecular modeling study of certain VEGFR-2 inhibitors based on thienopyrimidine scaffold as cancer targeting agents

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Abstract

Different series of novel thieno [2,3-d]pyrimidine derivative (9a-d,10a-f,l,m and 15a-m) were designed, synthesized and evaluated for their ability to in vitro inhibit VEGFR-2 enzyme. Also, the cytotoxicity of the final compounds was tested against a panel of 60 different human cancer cell lines by NCI. The VEGFR-2 enzyme inhibitory results revealed that compounds 10d, 15d and 15¡g are among the most active inhibitors with IC50 values of 2.5, 5.48 and 2.27¡ÕM respectively, while compound 10a remarkably showed the highest cell growth inhibition with mean growth inhibition (GI) percent of 31.57%. It exhibited broad spectrum anti-proliferative activity against several NCI cell lines specifically on human breast cancer (T7-47D) and renal cancer (A498) cell lines of 85.5% and 77.65% inhibition respectively. To investigate the mechanistic aspects underlying the activity, further biological studies like flow cytometry cell cycle together with caspase-3 colorimetric assays were carried on compound 10a. Flow cytometric analysis on both MCV-7 and PC-3 cancer cells revealed that it induced cell-cycle arrest in the G0-G1phase and reinforced apoptosis via activation of caspase-3. Furthermore, molecular modeling studies have been carried out to gain further understanding of the binding mode in the active site of VEGFR-2 enzyme and predict pharmacokinetic properties of all the synthesized inhibitors.

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