

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

Nasser Saad, khairia M. Youssef, Amna Gheith, Khaled A.M. Abouzid

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 15g are among the most active inhibitors with IC₅₀ values of 2.5, 5.48 and 2.27 μ M 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-G₁ phase 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.

Bioorganic Chemistry 2019, March