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

khairia M. Youssef , Amna Ghith, Khairia M. Youssef , Nasser S. M. Ismail, Khaled A. M. Abouzid

Abstract

Different seriesof novel thieno [2,3-d]pyrimidine derivative (9a-d,10a-f,l,m and15a-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 inhibitoryresultsrevealedthatcompounds10d,15dand15 gareamongthemostactiveinhibitorswithIC50 valuesof2.5,5.48and2.27µMrespectively,whilecompound10 aremarkablyshowedthehighestcellgrowth inhibitionwithmeangrowthinhibition (GI)percentof31.57%.Itexhibitedbroadspectrumanti-proliferative activityagainstseveralNCIcelllinesspecificallyonhumanbreastcancer(T7-47D)andrenalcancer(A498)cell lines of 85.5% and 77.65% inhibition respectively. To investigate the mechanistic aspects underlying the activity,furtherbiologicalstudieslikeflowcytometrycellcycletogetherwithcaspase-3 colorimetricassayswere carried on compound 10a. Flow cytometric analysis on both MCV-7 and PC-3 cancer cells revealed that it inducedcell-cyclearrestintheG0-G1phaseandreinforcedapoptosisviaactivationofcaspase-3.Furthermore, molecular modeling studies have been carried out to gain further understanding of the binding mode in the activesiteofVEGFR-2 enzymeandpredictpharmacokineticpropertiesofallthesynthesizedinhibitors.

Bioorganic Chemistry, 83, 2019, 111-128 2018, November