Thiazolo [4, 5-d] pyridazine analogues as a new class of dihydrofolate reductase (DHFR) inhibitors: Synthesis, biological evaluation and molecular modeling study.

Hussein El Subbagh,Hebatollah Atef Saad,Youmna Ibrahim,Mennatollah Atef ,Dalal A.Abou El Ellab,Deena S.Lasheen

Abstract

A new series of 1,3-thiazoles and thiazolo[4,5-d]pyridazine both bearing the 2-thioureido function were designed, synthesized and evaluated for their in vitro DHFR inhibition and antitumor activities. Compound 26 proved to be the most active DHFR inhibitor (IC50 of 0.06 εM). Compound 4, 20 and 21 showed in vitro antitumor activity against a collection of cancer cell lines. Compound 26 proved lethal to HS 578T breast cancer cell line with IC50 value of 0.8 εM, inducing cell cycle arrest and apoptosis. Molecular modeling studies concluded that recognition with key amino acids Phe 31 and Arg 22 is essential for DHFR binding. The obtained model could be useful for the development of new class of DHFR inhibitors.

Bioorganic Chemistry 2017, October