3-Methyl-imidazo[2,1-b]thiazole derivatives as a new class of antifolates: Synthesis, in vitro/in vivo bio-evaluation and molecular modeling simulations

Mennatollah Atef ,Heba A. Ewida, Ramzia I. ElBagary

Abstract

Inhibiting the Dihydrofolate reductase (DHFR) enzyme has been validated in multiple clinical manifestations related to bacterial infection, malaria, and multiple types of cancer. Herein, novel series of 3-methyl-imidazo [2,1-b] thiazole-based analogs were synthesized and biologically evaluated for their in vitro inhibitory profile towards DHFR. Compounds 22 and 23 exhibited potent inhibitory profile targeting DHFR (IC50 0.079 and 0.085 εM, respectively comparable to MTX IC50 0.087 εM). Compounds 22 and 23 showed promising cytotoxicity against MCF7 breast cancer cell lines inducing cell cycle arrest and apoptosis. Furthermore, Compound 23 showed its potential to reduce body weight and tumor volume significantly, using Ehrlich ascites carcinoma (EAC) solid tumor animal model of breast cancer, compared to control-treated groups. Further, molecular modeling simulations validated the potential of 22 and 23 to have high affinity binding towards Arg22 and Phe31 residues via ´-´ interaction and hydrogen bonding within DHFR binding pocket. Computer-assisted ADMET study suggested that the newly synthesized analogs could have high penetration to the blood brain barrier (BBB), better intestinal absorption, non-inhibitors of CYP2D6, adequate plasma protein binding and good passive oral absorption. The obtained model and pattern of substitution could be used for further development of DHFR inhibitors.

bioorganic chemistry 2021, July