

Imidazo [2', 1': 2, 3] thiazolo [4, 5-d] pyridazinone as a new scaffold of DHFR inhibitors: Synthesis, biological evaluation and molecular modeling study

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Abstract

New series of thiazolo[4,5-d]pyridazin and imidazo[2,3-b]thiazolo[4,5-d]pyridazin analogues were designed, synthesized and evaluated for their in vitro DHFR inhibition and antitumor activity. Compounds 13 and 43 proved to be DHFR inhibitors with IC_{50} values of 2028 nM, respectively. 43 proved lethal to OVCAR-3 cells with IC_{50} of 2068 nM, respectively. The active compounds formed hydrogen bond at DHFR binding site between N1-nitrogen of the pyridazine ring with Glu30; the carbonyl group with Trp24, Arg70 or Lys64; π -cation interaction with Arg22 and π - π interaction with Phe31 residues. Ring annexation of the active 1,3-thiazole ring analogue 13 into the bicyclic thiazolo[4,5-d]pyridazine (18,19) or imidazo[2,1-b]thiazoles 45-47 decreased the DHFR inhibition activity; while the formation of the tricyclic imidazo[2,3-b]thiazolo[4,5-d]pyridazine 48 increased potency. The obtained model could be useful for the development of new class of DHFR inhibitors

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