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‴,1‴:2,3]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 IC50 0.05 and 0.06 μM, respectively. 43 proved lethal to OVCAR-3 Ovarian cancer and MDA-MB-435 Melanoma at IC50 0.32 and 0.46 μM, 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; ´-cation interaction with Arg22 and ´-´ 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 (23ï25) decreased the DHFR inhibition activity; while the formation of the tricyclic imidazo [2‴,1‴:2,3]-thiazolo[4,5-d]pyridazine (43ï54) increased potency. The obtained model could be useful for the development of new class of DHFR inhibitors

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