Synthesis, biological evaluation and molecular modeling study of new (1, 2, 4-triazole or 1, 3, 4-thiadiazole)-methylthio-derivatives of quinazolin-4 (3H)-one as DHFR inhibitors

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Abstract

A new series of 2-mercapto-quinazolin-4-one analogues was designed, synthesized and evaluated for their in vitro DHFR inhibition, antitumor and antimicrobial activity. Compound 17 proved to be the most active DHFR inhibitor with IC50 value of 0.01 εM, eight fold more active than methotrexate (MTX). Compounds 16 and 24 showed antitumor activity against human Caco2 colon and MCF-7 breast tumor cell lines with IC50 values of 25.4 and 9.5 εg/ml, respectively. Compounds 15, 20, 21 and 30 showed considerable activity against the Gram-positive bacteria Staphylococcus aureus while 24 and 30 proved active against Bacillus subtilis with a magnitude of potency comparable to the broad spectrum antibiotic Ciprofloxacin. Strong activity was observed for 13, 14, 19, 20 and 24 against Candida albicans and Aspergillus flavus. Compound 17 shared a similar molecular docking mode with MTX and made a critical hydrogen bond and arene-arene interactions via Ala9 and Phe34 amino acid residues, respectively.

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