

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 M, 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 g/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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