

# Thiazolo [4, 5-d] pyridazine analogues as a new class of dihydrofolate reductase (DHFR) inhibitors: Synthesis, biological evaluation and molecular modeling study.

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## Abstract

A new series of 1,3-thiazoles and thiazolo[4,5-d]pyridazine both bearing the 2-thioureido function were designed, synthesized and evaluated for their in vitro DHFR inhibition and antitumor activities. Compound 26 proved to be the most active DHFR inhibitor (IC<sub>50</sub> of 0.06 M). Compound 4, 20 and 21 showed in vitro antitumor activity against a collection of cancer cell lines. Compound 26 proved lethal to HS 578T breast cancer cell line with IC<sub>50</sub> value of 0.8 M, inducing cell cycle arrest and apoptosis. Molecular modeling studies concluded that recognition with key amino acids Phe 31 and Arg 22 is essential for DHFR binding. The obtained model could be useful for the development of new class of DHFR inhibitors.

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