Dihydrofolate reductase (DHFR) inhibition and molecular modeling study of some 6-bromo- or 6,8-dibromo-quinazolin-4(3H)-ones

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Abstract

Objectives: The dihydrofolate reductase (DHFR) inhibitory activity of 6-bromo- and 6,8-dibromo-quinazolin-4(3H)-ones (7–25) were studied to define the structural features and requirements that enhance selectivity and specificity for the proper binding to the enzyme active site. Methods: Compounds 7–25 were tested for their in vitro DHFR inhibition. As an appli - cation of the use of DHFR inhibitors, in vitro antitumor activity using disease-oriented human cell lines assay was performed. Key findings: Compounds 19, 20, and 22 showed remarkable DHFR inhibitory activity, inhibitory concentration (IC 50 0.6, 0.2, and 0.1 Î¼M, respectively). Compounds 12, 17, 18, 20, and 24 proved to be broad spectrum antitumor with median IC 50 values of 0.6, 0.6, 0.5, 0.6, and 0.7 Î¼M, respectively. Molecular docking study results revealed that the active DHFR inhibitors 22 and 20 bind to DHFR with similar amino acid residues as methotrexate, especially Arg 28. Conclusions: The mono-bromo series proved to be more active than the di-bromo coun - terparts and the 3-(2 -hydrazinyl-acetyl)- is more active than its 3-(acetohydrazide) isoster. The investigated compounds could be used as template model for further optimization.

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