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 (7ï25) 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 7ï25 were tested for their in vitro DHFR inhibition. As an application 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 (IC50 0.6, 0.2, and 0.1 εM, respectively). Compounds 12, 17,
18, 20, and 24 proved to be broad spectrum antitumor with median IC50 values of 0.6,
0.6, 0.5, 0.6, and 0.7 εM, 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 counterparts 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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