Synthesis, antitumor testing and molecular modeling study of some new 6-substituted amido, azo or thioureido-quinazolin-4(3H)-ones

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Abstract

A new series of 6-substituted amido, azo or thioureido-quinazolin-4(3H)-one was synthesized and tested for their in-vitro antitumor activity. Compounds 21, 53 and 60 showed broad spectrum antitumor activity with average IC50 values of 6.7, 7.6 and 9.1jεM, respectively compared with methotrexate (1, IC50 19.26jεM). As an attempt to reveal the mechanism of the antitumor potency, cell cycle analysis and DHFR inhibition were performed. Compounds 59 and 61 induced their cytotoxicity in Hela (IC50 10.6jεM) and HCT-116 (IC50 15.5jεM) cell lines, respectively through Pre-G1 apoptosis, inhibiting cell growth at G2-M phase. Compounds 29, 33, 59 and 61 showed DHFR inhibitory potency at IC50 0.2, 0.2, 0.3 and 0.3jεM, respectively. The active DHFR inhibitors showed high affinity binding toward the amino acid residues Thr56, Ser59 and Ser118. The active compounds obeyed Lipinskiôs rule of five and could be used as template model for further optimization

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