Non Classical Antifolates, Part 5. Benzodiazepine Analogs as a New Class of DHFR Inhibitors: Synthesis, Antitumor Testing and Molecular Modeling Study

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Abstract

A new series of tetrahydro quinazoline and tetrahydro 1H dibenzo diazepine analogs were synthesized and tested for their DHFR inhibition and in vitro antitumor activity. Compound 35 showed a remarkable DHFR inhibitory potency which is twenty fold more active than methotrexate (MTX). Compounds 17 and 23 proved to be fifteen fold more active than the known antitumor 5 FU, with MG MID GI50, TGI and LC50 values of 1.5, 46.8, 93.3 and 1.4, 17.4, 93.3 respectively. Computer modeling studies allowed the identification that methoxy and methyl substituents, the system of the chalcone core, the nitrogen atoms, on the dibenzodiazepine ring as pharmacophoric features essential for activity. These mark points could be used as template model for further future optimization.

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