

## **Nonclassical Antifolates: Synthesis, Biological Evaluation and Molecular Modeling Study of Some New Quinazolin-4-One Analogues as Dihydrofolate Reductase Inhibitors**

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**Abstract :** Dihydrofolate reductase (DHFR) is an enzyme that has pivotal importance in biochemistry and medicinal chemistry. It catalyzes the reduction of dihydrofolate to tetrahydrofolate and intimately couples with thymidylate synthase. Thymidylate synthase is a crucial enzyme that catalyzes the reductive methylation of (dUMP) to (dTMP) utilizing N5, N10-methylenetetrahydrofolate as a cofactor. A new series of 2-substituted thio-quinazolin-4-one analogs was designed that possessed electron withdrawing or donating functional groups (Cl or OCH<sub>3</sub>) at position 6- or 7-, 4-methoxyphenyl function at position 3-.The thiol function is used to connect to either 1,2,4-triazole, or 1,3,4-thiadiazole via a methylene bridge. Most of the functional groups designed to be accommodated on the quinazoline ring such as thioether, alkyl to increase lipid solubility of polar compounds, a character very much needed in the nonclassical DHFR inhibitors. The target compounds were verified with spectral data and elemental analysis. DHFR inhibitions, as well as antitumor activity, were applied on three cell lines (MCF-7, CACO-2, HEPG-2).

**Keywords :** nonclassical antifolates, DHFR Inhibitors, antitumor activity, quinazoline ring

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