SYNTHESIS OF 2,6-DIAMINO-5-HETARYLPYRIMIDINES AS POTENTIAL ANTIFOLATES

Dihydrofolate reductase (DHFR) is an essential enzyme and plays a key role in the folate biosynthetic pathway. Inhibition of the folate cycle prevents biosynthesis of thymidine leading to inhibition of DNA biosynthesis and thus to inhibition of cell growth and proliferation. DHFR is an important target for drug development against cancer and a variety of infectious diseases caused by bacteria, protozoa, and fungi. Inhibitors of dihydrofolate reductase (DHFR) have been in clinical use as well-known anticancer, antibacterial, and antimalarial drugs, for example, methotrexate, trimethoprim, and pyrimethamine. All DHFR inhibitors exhibiting IC_{50}'s in the micromolar range or less contain the 2,6-diaminopyrimidine pharmacophore. The pharmaceutical with aromatic, aliphatic and saturated heterocyclic moieties in the fifth position of the 2,6-diaminopyrimidines are well-known. Therefore, the 2,6-diamino-5-hetarylpyrimidine derivatives have been prepared as bioisosteric replacements.

A general synthetic pathway for the preparation of 2,6-diaminopyrimidine scaffold consists of condensing enol ethers of β-ketonitriles with guanidine. 2-Hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles 1 represent versatile building blocks in the synthetic chemistry on account of their 3-functionalized acrylonitriles fragment incorporated into unsaturated heterocyclic ring which can react with N-nucleophiles by a ring transformation. In this process the nucleophilic substitution of the bridged heteroatom causes a disconnectionof the starting ring giving a ω-hydroxyalkyl side chain. In the present work the 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles 1 were employed as 1,3-bielectrophilic synthon containing the heterocyclic moiety in the synthesis of 2,6-diamino-5-hetarylpyrimidines 3. The reaction of nitriles 1 with guanidine carbonate 2 in the presence of sodium ethoxide gave rise to desired 3-[2,6-diamino-5-hetaryl-4-pyrimidinyl]-1-propanols 3. The reaction has been suggested to proceed through the intermediate formation of Michael's adduct 4 with the subsequent disclosing tetrahydrofuranyliden ring and the intramolecular interaction of the spatially close amino and cyano groups that leads to pyrimidine derivatives 3. Thus, present investigation has resulted in the efficient synthesis of biologically relevant compounds – 2,6-diamino-5-hetarylpyrimidines. Biological evaluation of compounds obtained as inhibitors of DHFR is currently in progress.

Key words: antifolate agents, diaminopyrimidines, 2-hetaryl-2-(tetrahydro-2-furanyliden)acetonitriles.