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Hexahydropyrimidine-2,4-Diones: Synthesis and Cytotoxic Activity

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Abstract : The discovery of new drugs in cancer chemotherapy is still a major topic because of severe side effects, selectivity problems and resistance development potential of existing drugs. In recent years, combined anticancer therapies or multi-acting drugs are clinically preferred over traditional cytotoxic treatment, with the aim of avoiding resistance and toxic side effects. Arrangement of multi-acting targets can be carried out either by combination of several drugs with different mechanisms or by usage of a single chemical compound capable of regulating several targets of a disease with multiple factors. In literature, several pyrimidine and piperazine derivatives have been involved in the structure of many compounds which have been used as chemotherapeutic agents along with wide clinical applications. The aim of this study is to combine pyrimidine and piperazine core structures to research and develop novel piperazinylpyrimidine derivatives with selective cytotoxicity over cancer cells. In this study, a group of novel 6-fluorophenyl-3-[2-(substitutedpiperazinyl)ethyl] hexahydropyrimidine-2,4-dione derivatives designed to observe the desired anticancer activity due to pyrimidine and piperazine based scaffolds. Target compounds were obtained by the reaction of appropriate piperazine derivatives and 6-(2/4-fluorophenyl)-3-(2-chloroethyl)hexahydropyrimidine-2,4-dione. The synthetic pathway of 6-(2/4-fluorophenyl)-3-(2-chloroethyl)hexahydropyrimidine-2,4-dione was started with Rodionov reaction using aldehyde, malonic acid and ammonium acetate in ethanol. Isolated β-fluorophenyl-β-amino acids were treated with 2-chloroethylisocyanate in the presence of an aqueous sodium hydroxide solution at room temperature to yield the sodium salts of the corresponding ureido acids. By addition of a mineral acid, ureido acids were precipitated. Later, these ureido acids were refluxed in thionyl chloride to give the 6-(2/4-fluorophenyl)-3-(2-chloroethyl)hexahydropyrimidine-2,4-di-one which were furthermore treated with secondary amines. Structures of purified compounds were characterized with IR, 1H-NMR, 13C-NMR, mass spectroscopies and elemental analysis. All of the compounds gave satisfactory analytical and spectroscopic data, which were in full accordance with their depicted structures. In IR spectra of the compounds, N-H group was seen at 3230-3213 cm^{-1}. C-H was seen at 3100-2820 cm^{-1} and C=O vibrational peaks were observed approximately at 1725 and 1665 cm^{-1} in accordance with literature. In the NMR spectra of target compounds, the methylene protons of piperazine give two separate multiplet peaks around 3.5 and 4.5 ppm representing the successful N-alkylation of the structure. The cytotoxic activity of the synthesized compounds was investigated on human bronchial epithelial (BEAS 2B), lung (A549), colon adenocarcinoma (COLO205) and breast (MCF7) cell lines, by means of sulphorhodamine B (SRB) assays in triplicate. IC_{50} values of the screened derivatives were found in range of 11.8-78 µM. This project was supported by The Scientific and Technological Research Council of Turkey (TUBITAK, Project no: 215S157).

Keywords : cytotoxicity, hexahydropyrimidine, piperazine, sulphorhodamine B assay
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