

Synthesis, Anticancer Activity and Molecular Docking Studies of Novel N-Mannich Bases of 1,3,4-Oxadiazole Based on 4,6-Dimethylpyridine Scaffold

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Streszczenie

Cancer is one of the greatest challenges in modern medicine today. Difficult and long-term treatment, the many side effects of the drugs used and the growing resistance to treatment of neoplastic cells necessitate new approaches to therapy. A very promising targeted therapy is based on direct impact only on cancer cells. As a continuation of our research on new biologically active molecules, we report herein the design, synthesis and anticancer evaluation of a new series of N-Mannich-base-type hybrid compounds containing morfoline or different substituted piperazines moieties, a 1,3,4-oxadiazole ring and a 4,6-dimethylpyridine core. All compounds were tested for their potential cytotoxicity against five human cancer cell lines, A375, C32, SNB-19, MCF-7/WT and MCF-7/DX. Two of the active N-Mannich bases (compounds 5 and 6) were further evaluated for growth inhibition effects in melanoma (A375 and C32), and normal (HaCaT) cell lines using clonogenic assay and a population doubling time test. The apoptosis was determined with the neutral version of comet assay. The confocal microscopy method enabled the visualization of F-actin reorganization. The obtained results demonstrated that compounds 5 and 6 have cytotoxic and proapoptotic effects on melanoma cells and are capable of inducing F-actin depolarization in a dose-dependent manner. Moreover, computational chemistry approaches, molecular docking and electrostatic potential were employed to study non-covalent interactions of the investigated compounds with four receptors. It was found that all the examined molecules exhibit a similar binding affinity with respect to the chosen reference drugs.

Słowa kluczowe

dimethylpyridine, N-Mannich base, anticancer activity, cytotoxicity, molecular docking, non-covalent interactions, 1,3,4-oxadiazole

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