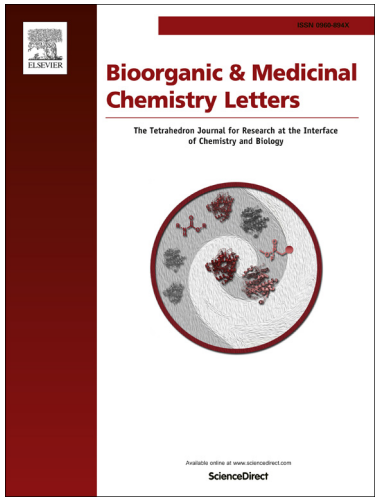

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Synthesis and biological evaluation of novel pyrimidine-benzimidazol hybrids as potential anticancer agents

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Abstract: A series of pyrimidine-benzimidazol hybrids was synthesized and evaluated for anticancer activity on four human cancer cell lines including MCF-7, MGC-803, EC-9706 and SMMC-7721. Some of the synthesized compounds exhibited moderate to potent activity against MGC-803 and MCF-7. Among them, compounds **5a-b** and **6a-b** showed most effective activity. Compounds **5b** and **6b** were more cytotoxic than 5-fluorouracil against all tested four human cancer cell lines, with IC_{50} values ranging from 2.03 to 10.55 μM and 1.06 to 12.89 μM, respectively. Flow cytometry analysis demonstrated that treatment of MGC-803 with **6b** led to cell cycle arrest at G2/M phase accompanied by an increase in apoptotic cell death.

Key words: pyrimidine; benzimidazole; anticancer; cell cycle arrest ; apoptosis.

Cancer is a leading cause of death worldwide, accounting for 8.7 million deaths (around 14% of all deaths) in 2012. The pharmacological fight against cancer has made significant progress in the last twenty years. In 2012 (October 1, 2011–September 30, 2012) 35 novel drugs were approved by the FDA, among which, 10 (28.57%) were used for the treatment of cancer.[1] Although many chemotherapeutic agents have been developed to treat different kinds of cancer effectively, some side effects could happen simultaneously. Therefore novel molecules to fight this disease are still urgently needed.[2,3]

Pyrimidine is found as a core structure in a large variety of compounds that exhibit important biological activity, and several member of this class has earned valued places in chemotherapy as effective agents, like 5-fluorouracil, erlotinib, gefitinib and caneratinib.[4] Many papers have reported that pyrimidine derivatives showed impressive anticancer activity.[5-13] On the other hand, benzimidazole being an isostere of purine nucleosides and an important scaffold in various biologically active molecules is widely explored for development of anticancer agents. Several promising antitumor active agents were found to contain the benzimidazole ring system. They were found to exert their antitumor activity by acting mainly as antiangiogenic agents,[14–15] alkylating agents[16–18] and topoisomerases inhibitors.[19–21]

In 2010, Heba T. Abdel-Mohsenreported that benzimidazole-pyrimidine conjugates exhibited high antitumor activity.[22] Inspired by the literature and in continuation of our previous work,[23] we herein reported the synthesis of novel pyrimidine-benzimidazole hybrids and their anticancer activity. The anticancer activity evaluation results revealed that the pyrimidine-benzimidazole hybrids exhibited potent anticancer activity.

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