DESIGN, SYNTHESIS AND CYTOTOXIC ACTIVITY EVALUATION OF NEW 3,7-DIARYLSUBSTITUTED-6-AZAINDOLES

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The majority of protein kinase inhibitors used in cancer treatment consists of compounds that compete ATP in its binding pocket within the active site of enzymes that are usually upregulated in several types of cancer. This inhibition results in the blockage of signaling pathways that are related with the growth and the proliferation of the cancer cells. Purine analogues often possess kinase inhibitory activity, due to their structural similarity with the adenine moiety of the ATP, and a great number of these derivatives have been already been approved as anticancer agents.

With the aim to discover novel derivatives with potential cytotoxic activity, our research group has previously synthesized a great number of purine analogues that exhibited promising cytotoxic activity, with IC_{50} values in the low μM or even at nM concentration, against a variety of cancer cell lines of human origin. In this work, we have designed and synthesized a number of new 6-azaindole derivatives, possessing two aryl groups attached to positions -3 and -7 of the 6-azaindole scaffold. Commercially available 2-amino-3-nitro-4-methylpyridine was used as the starting material for the preparation of the target compounds. In total, 20 novel derivatives were synthesized and were subsequently evaluated for their potential to inhibit the proliferation of cancer cell lines, with the MTT assay. Additionally, their effect on the proliferation of normal, non cancer, cells was evaluated as well.

The evaluation of the cytotoxicity results revealed interesting SARs concerning the effect of the substitution pattern of the novel compounds on the antiproliferative activity. The analogues bearing the 2,4-dimethoxyphenyl group at position -7 of the 6-azaindole core proved to be the most potent, with IC_{50} values between 12-18 nM against the HT-1080 and MDA-MB-231 cancer cell lines. Notably, all analogues showed insignificant effect on the normal cell line AG01523, thus possessing great selectivity indices. In order to investigate the possible mechanism of action of the novel derivatives, a cell cycle analysis was performed for the most active compounds. The novel derivatives proved to cause a significant cycle arrest at phase G2/M when tested at the breast cancer cell line MDA-MB-231.