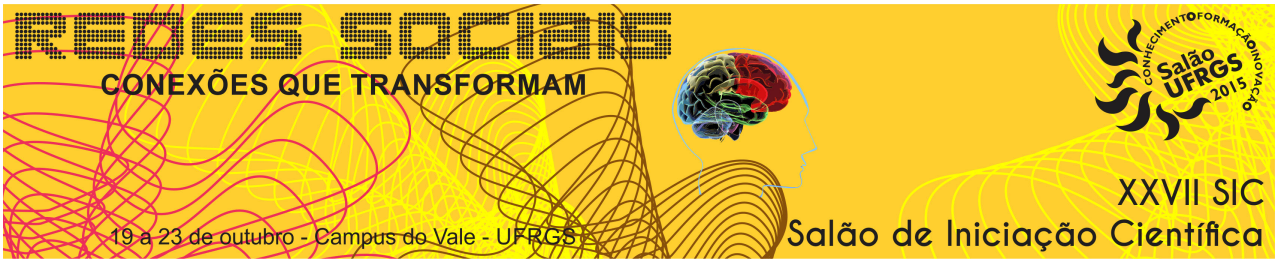

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Título	CYTOTOXIC ACTIVITY AND CELL CYCLE DISTURBANCES INDUCED BY PYRIMIDOBENZIMIDAZOLES DERIVATIVES IN MCF-7 BREAST CANCER CELLS
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CYTOTOXIC ACTIVITY AND CELL CYCLE DISTURBANCES INDUCED BY PYRIMIDOBENZIMIDAZOLES DERIVATIVES IN MCF-7 BREAST CANCER CELLS

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INTRODUCTION: Conventional chemotherapy is the main treatment for cancer and benefits patients in the form of decreased relapse and metastasis and longer overall survival. However, as the target therapy drugs is not wholly precise, it also results in quite a few side effects. In the present study, we report the biologic evaluation and molecular mechanism of a series of substituted 3-trifluoro(oxo)pyrimido[1,2-*a*]benzimidazoles derivatives (PBZ 1-10) against the growth of several human cancer cell lines.

METHODS: The potential antitumoral activity of the compounds was evaluated in vitro by examining the cytotoxic effects against human cancer cell lines (MCF-7, HepG-2, T-24, HCT-116, HT-29 and CACO-2) and a nontumoral cell HEK-293T. After the treatment the cytotoxicity was expressed as IC_{50} values, i.e. the concentrations of the test agent inducing 50% reduction in cell numbers compared with control cultures. Selective index (SI) was calculated by IC50 in HEK-293T cells/IC50 in tumoral cells. The well-known drug mitoxantrone (MXT) was used as reference compound. Compounds showing cytotoxic activities were subjected to other tests. Genotoxicity induction was analyzed by single-cell gel electrophoresis (comet assay). The production of reactive oxygen species (ROS) and changes in mitochondrial membrane potential ($\Delta\Psi m$) were studied using specific fluorescence probes, DCFH(2)-DA (2',7'-dichlorodihydrofluorescein diacetate) and rhodamine-123 by flow cytometry. The cell cycle was determined by flow cytometry and changes in protein expression (γ-H2AX) were examined by western blotting. Topo I activity was evaluated in a cell-free system.

RESULTS: Our results suggest that PBZ 04, 05 and 09 exerted the highest cytotoxicity against MCF-7 cells, with IC50 values of 15.41, 19.52 and 8.11 μM, respectively. The most promising compound was the PBZ 09 in MCF-7 cells. Flow cytometric analysis indicates that PBZ 09 alters cell cycle progression, induces G1 arrest and causes DNA polyploidy (>4N). PBZ 09 generates ROS and γ-H2AX phosphorylation. The pretreatment with N-acetyl cysteine (NAC) abrogates PBZ 09-induced ROS production. Topo I inhibition was observed only for PBZ 09.

CONCLUSION: Among the 3 compounds studied, PBZ 09 seems to present the most promising antitumoral activity, especially against MCF-7 cells. Our results demonstrate that PBZ 09 interacts with Topo I enzyme, generates ROS leading to DNA damage, γH2AX induction, cell cycle arrest and cell death. Therefore, further studies with this small molecule are essential for its safety management in breast cancer therapy.

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