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Biological evaluation of new diarylpentanoid analogues for antitumor activity

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Abstract

Background: Cancer is associated with high mortality rates and its incidence worldwide is increasing significantly [1]. Several therapeutic strategies have been used in cancer therapy such as microtubule-targeting agents [2]. However, these drugs are highly toxic and are associated with high tumor resistance, making their long-term use unfeasible [3,4]. Therefore, new small molecules that can overcome the disadvantages associated with the drugs currently in use in the clinic are needed. We previously reported the *in vitro* growth inhibitory effect of the diarylpentanoid BP-M345 on human cancer cells, as well as its cellular mechanism of action [5]. Here, BP-M345 analogues have been synthetized in a goal to improve the antimitotic/antitumor efficacy of the original BP-M345. **Objective:** The present study aimed to characterize BP-M345 analogues regarding their cytotoxic activity and mechanism of action, focusing on their potential as antimitotic agent. **Methods:** A sulforhodamine B assay was used to determine the GI_{50} of BP-M345 analogues in different cancer cell lines. To evaluate the antimitotic activity, the mitotic index was determined. In addition, lung cancer cells were exposed to compounds, for 24- or 48 hours, and the consequence on spindle morphology, cellular proliferation and cell death were evaluated using the following assays: immunofluorescence, colony-formation assay, and flow cytometry, respectively. Time-lapse microscopy imaging was also performed to follow in real time the cell fate of the compound-treated cells. **Results:** BP-M345 analogues showed potent growth inhibition activity on cancer cells and exhibited a potent antimitotic activity. Mechanistically, BP-M345 analogues induced perturbation of the mitotic spindles through microtubule instability. Consequently, treated cells exhibit defects in chromosome congression during mitosis, which induced a prolonged spindle assembly checkpoint-dependent mitotic arrest, followed by apoptosis. **Conclusions:** BP-M345 analogues have been shown to be highly potent antimitotic agents, more effective than the original BP-M345 leading to massive cancer cell death.

Keywords: diarylpentanoid; anticancer; antimitotics; apoptosis; cancer

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