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A.C.Camargo Cancer Center
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Guttiferone-A derivative bearing triazole ring induces cell cycle arrest at G1/S transition by inducing cyclins D and E downregulation in HepG2 cells

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Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. In general, the intrinsic or acquired resistance of the tumor cells to available drugs is associated with treatment failure. Therefore, it is important to increase the therapeutic arsenal for HCC. In this way, natural products have been useful as chemical scaffolds to obtain new anticancer drugs. **Aims:** In the present study a natural polyisoprenylated benzophenone guttiferone-A (GA) was used as a chemical scaffold to obtain a series of GA-derivatives bearing 1,2,3-triazole ring, which was tested regarding antitumor potential.

Methods

The active substances were screened by sulforhodamine B cell viability assay using A549, MCF-7, and HepG2 cell lines. Cell cycle analysis, clonogenic capacity assay, and BrdU incorporation were performed to evaluate the effects of the most active compound on proliferative behavior of HepG2 cells. Gene expression profiles of critical regulators of cell cycle were assessed through RT-qPCR and Western blotting to understand the molecular mechanism underlying the antiproliferative activity of the lead compound on HepG2 cells.

Results

The compounds (6), (10), and (12), that present bromobenzyl, benzo-dioxolmethyl, and fluorobenzyl, respectively, linked to the triazole ring, displayed significant cytotoxic activity on A549 and HepG2 cells, but compound (10) was highly selective toward HepG2 cells. This compound effectively inhibited the clonogenic capacity of HepG2 cells and induced cycle arrest at G1/S transition. Antiproliferative activity of the compound (10) was associated with its ability to promote Cyclins D and E downregulation and p21 upregulation.

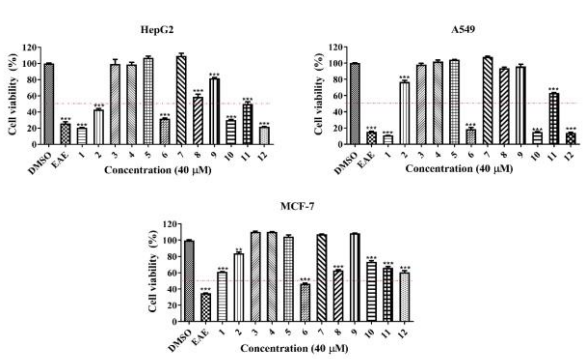

Figure 1: Cell viability was determined by sulforhodamine B after 48 h of treatment.

Conclusion

The natural polyisoprenylated benzophenone (guttiferone-A), isolated from *G. gardneriana,* was used as a scaffold to obtain a series of triazole derivatives. The compound (10) was selected as a lead compound based on cytotoxic and selectivity profiles on HepG2 cell line. This substance effectively inhibits proliferative behavior of HepG2 cells by inducing cell cycle arrest at G1/S transition. The effects of the compound (10) on HepG2 cells were associated with its ability to inhibit ERK signaling leading to cyclins D and E downregulation. Compound (10) also stimulated the p21 expression, a universal inhibitor of the cyclin-CDK complexes. Taken together, the data showed that compound (10) is a promising antitumor agent and should be considered for further *in vivo* investigation.

Results

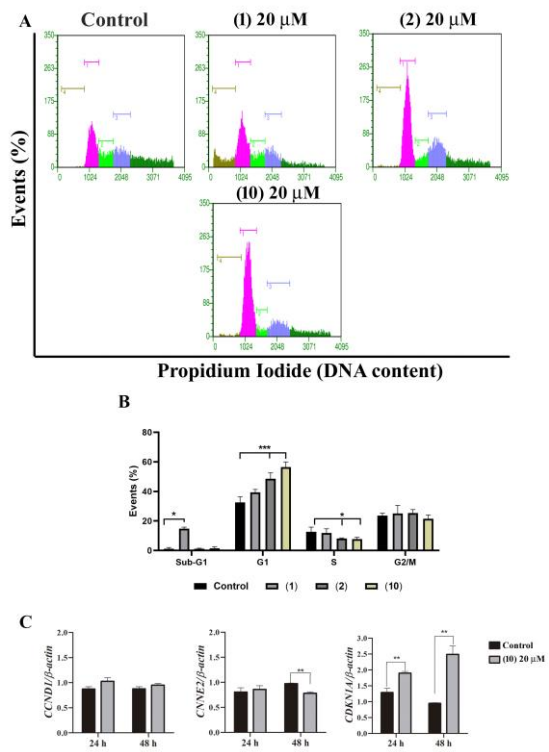

Figure 2: (A, B) Cell cycle analysis showing that compounds (2) and (10) induced cell cycle arrest at G1/S; and cytotoxic activity of the compound (1). (C) Relative expression of *CCND1* (cyclin D), *CNNE2* (cyclin E), and *CDKN1A* (p21) determined by qPCR.

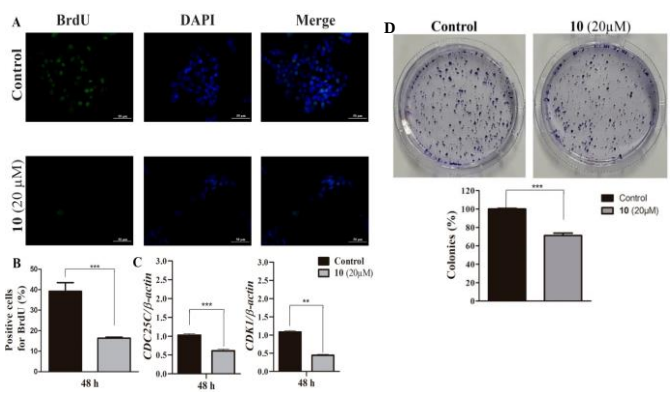

Figure 3: (A, B) Frequency of cell in S-phase determined by BrdU incorporation. (C) Relative expression of *CDC25C* and *CDK1* determined by q-PCR. (D) clonogenic assay.

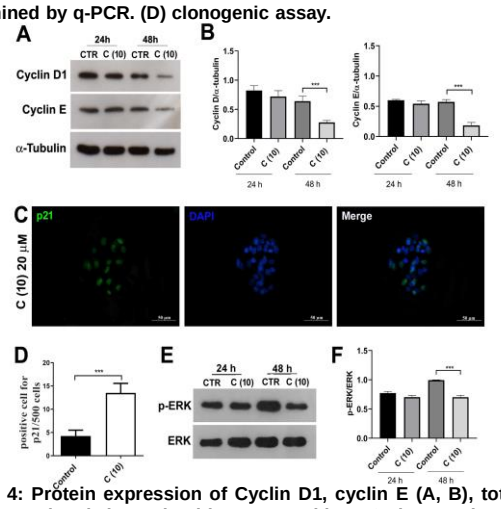

Figure 4: Protein expression of Cyclin D1, cyclin E (A, B), total ERK, and p-ERK (E, F) determined by western blot. p21 immunolocalization (C), and frequency of positive cells for p21 (D).

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