Collateral Sensitivity of Resistant MRP1-Overexpressing Cells to Flavonoids and Ferrocene Derivatives through GSH efflux.

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There have been many important developments in medicine over the years, but cancer remains a growing problem around the world. This can, to a great extent, be attributed to the growing problem of multi-drug resistance (MDR) of cancer. One strategy for addressing the MDR phenotype is to modulate the activity of the MRP1, an ABC transporter. Therefore, this work seeks to investigate the effects of ferrocene-based compounds on MRP1 mediated cancers that are MDR. Structurally, the molecules consist of a flavonoid core with a ferrocene group at position 2. The molecules were synthesized to obtain the Chalcone derivative, Aurone derivative and then Flavonoid derivative. A solution of 2-Methoxy-6-Hydroxycacetophenone in THF was added to NaH and stirred. After, a solution of carboxaldehyde was stirred and the solution was extracted. The molecules were characterized by NMR studies. The spectras were recorded on a Bruker AC-400 instrument operating at 400 MHz for 1H NMR. Chemical shifts (δ) are reported in ppm relative to Me4Si (internal standard) and the J-Coupling values in Hz. All reactions were followed using thin-layer chromatography (TLC) which used Macerevy-Nagel silica gel F-254 plates (thickness 0.25 mm). Unless otherwise stated, reagents were obtained from commercial sources and were used without further purification.

For NMR studies, spectra were recorded on a Bruker AC-400 instrument operating at 400 MHz for 1H NMR. Chemical shifts (δ) are reported in ppm relative to Me4Si (internal standard) and the J-Coupling values in Hz. All reactions were followed using thin-layer chromatography (TLC) which used Macerevy-Nagel silica gel F-254 plates (thickness 0.25 mm). Unless otherwise stated, reagents were obtained from commercial sources and were used without further purification.

In order to further improve this biological activity of the ferrocene and aurone a methoxy group was added, given their known benefits. The structure of these compounds is seen in the figure below and the synthesis technique was designed as followed:

However, the procedure to obtain the aurone derivative did not work as the literature suggested. It was decided that there would be a direct attempt to synthesize the chalcone derivative to the flavone derivative, skipping the aurone step. The chalcone derivative was dissolved in EIOH and treated with potassium tert-butoxide and AgO3SCF3 as seen below.

This work investigated the uses of ferrocene as an agent to reverse the MDR mediated by MRP1. Consolidating the novel approach called collateral sensitivity as an emerging strategy in cancer treatment, a new design of an anticancer agent targeting selective MDR tumors expressing MRP1 through the induction of a strong GSH efflux was synthesized. Different synthetic derivatives of Apigenin were studied and particularly derivatives with ferrocene group at position 2 of the flavonoid core which are going to be biologically tested in the near future.

In the future, other pharmacomodulations from the flavone core will be done in order to better understand the structure-activity relationship of this compound and to obtain active and selective MRP1-dependent apoptogenic compounds.

References


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