Discovery of new modulators of caspase family proteins using the yeast approach

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Accumulating evidence has shown the crucial role of the caspase family in both initiation and regulation of apoptosis [1]. Caspases-3 and -7 are at the core of the execution phase of apoptosis. Like most proteases, these “executioner” caspases are stored as proenzymes that once activated by proteolysis cleave a large set of substrates, ultimately resulting in the characteristic morphological and biochemical hallmarks of apoptosis. Therefore, the search for activators of these proenzymes has deserved particular attention in the field of anticancer drug discovery [2,3]. Nevertheless, to date, only few small-molecule caspase activators have been reported [2,4]. A previous study from our group have reported the identification of two potential activators of caspase-7, 5,6-dihydroxy-7-prenoxylloxalane (1a) and 3-hydroxy-7-geranyloxylloxalane (2a) by using a yeast target-based screening assay, based on the heterologous expression of these human proteins in Saccharomyces cerevisiae [5]. These results led us to the present project under the thesis for Masters in Pharmaceutical Chemistry aiming to discover new caspases-3 and -7 activators. In the present work, several derivatives of compounds 1a and 2a will be synthesised and the activity as activators of caspases-3 and -7 will be evaluated using the yeast approach followed by validation of the molecular mechanism of action in human tumor cells. With this work it is intended to identify new activators of caspases-3 and -7 with improved pharmacological activities.

Acknowledgments: This work is funded through national funds from FCT—Fundação para a Ciência e a Tecnologia under the projects REQUIMTE-Pest-C/EBB/ LA0006/2013 and CEQUIMED—PEst-OE/SAU/UI406/2014.

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