Novel compounds as selective inhibitors of caspase-3: organic synthesis, *in silico* and *in vitro* evaluation

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INTRODUCTION: Alzheimer disease (AD) is the most prevalent neurodegenerative disorder worldwide. Up to now, different hypothesis about its appearance have been proposed but treatments based on them have not been able to stop or reverse this disease. In recent years, the enzyme caspase-3 has been identified as a new promising target because it is related with the first signs of AD.
OBJETIVE: The aim of this work was the synthesis of novel aminothiazole derivatives and their evaluation as potential selective inhibitors of caspase-3 through *in silico* and *in vitro* methods.
METHOD AND MATERIALS: Using conventional synthesis the desired aminothiazole derivatives were obtained. *In silico* evaluation was performed by molecular docking/molecular dynamics simulations. *In vitro*, we determined the ability of these compounds to inhibit the enzyme using a fluorogenic assay. Also, we determined compounds' citotoxicity in the mouse hippocampal cell line HT22.
RESULTS AND DISCUSSION: A group of aminothiazole derivatives with moderate to good yields (50-70%) were obtained. First, the citotoxicity of these compounds in HT22 cells was determined resulting not cytotoxic up to a 100 µM concentration. *In vitro* evaluation of these compounds in caspase-3 demonstrated that some of them are good inhibitors of the enzyme. *In silico* evaluation allowed us to find certain features that could explain the inhibition mechanism of these compounds providing a comprehensive insight into the binding sites together with changes in key residues and catalytic loops positions that are crucial for a proper caspase-3 activity. Due to the similarity between caspase-3/caspase-7 we evaluated *in silico* the ability of these compounds to interact with caspase-7 and our results showed that these aminothiazoles would be selective inhibitors of caspase-3.
CONCLUTIONS: We have synthesized novel aminothiazole derivatives that are able to inhibit caspase-3 and through *in silico* studies we were able to find out key structural features that are needed for a selective inhibition of this enzyme.

Key words: caspase-3, aminothiazole derivatives, Alzheimer disease
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