

# Medicinal Chemistry & Computer Aided Drug Designing

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## Computer-aided drug design (CADD): Synthesis and biological evaluation of potential caspase-3 inhibitors as novel Alzheimer's disease therapy

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Alzheimer Disease (AD) represents the most prevalent neurodegenerative disorder in the world. Until now the causes of the disease have not been elucidated. The pharmacological treatment currently used for AD is based on old hypotheses that have been questioned in the last years. Unfortunately, this treatment only improves patient's life quality but it is not efficient to cure the disease. For this reason, it is crucial to discover new targets involved in the onset of this disease. In this context, caspase-3 arises as a promising target since it has been found overexpressed in brains from AD patients during the early stages of the disease. In the present work, we propose the CADD of new caspase-3 selective inhibitors, aryl-triazole derivatives, based on reported mild but selective inhibitors of this enzyme. These derivatives bind at the substrate binding pocket and interact weakly with sub-sites S4-S5. It is worth noticing that although caspase-3 and caspase-7 are very similar, they contain relevant differences at sub-sites S4 and S5 that can be exploited in the search of selective inhibitors. Therefore, our compounds were designed to improve those interactions. Using docking and molecular dynamics simulations the inhibitors binding mode in caspase-3 and caspase-7 was determined. Results show that our novel molecules effectively interact at S4-S5 sub-sites in caspase-3 and at the hetero-tetramer interface in caspase-7. The designed compounds were synthesized and evaluated against both caspases. Those compounds with a better profile against caspase-3 were selected for studying their mechanism of action using theoretical and experimental approaches.

### Biography

Lucía Minini has completed her Biochemistry degree from Facultad de Ciencias, Udelar, Uruguay. She achieved a Scholarship for her Master's degree at Facultad de Química. She is involved in different research projects working on the development novel molecules as anti-cancer, anti-neurodegenerative and anti-trypansomal agents. Besides, she is studying beta-amyloid peptide's behavior related with AD. Recently, she published two articles in scientific journals.

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