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Nitrones as potential therapeutic agents against Alzheimer's disease

Alicia Merlino[1], **Saira Cancela**[1,2], **Paola Hernández**[2], **Gustavo Mourglia-Ettlin**[1] and **Williams Porcal**[1]
[1]University of the Republic, Uruguay
[2]Instituto de Investigaciones Biológicas Clemente Estable, Uruguay

Alzheimer's Disease (AD) is the most prevalent neurodegenerative disorder worldwide for which there is currently no cure. One of the main reasons that have prevented the development of an effective treatment for AD is that molecular factors that cause the disease have remained elusive. Recently, caspase-3 has been proposed as a potential therapeutic target for treating AD. Caspases inhibition is not an easy task because they are involved in a variety of cellular processes. However, since caspase-3 is overexpressed in brains from AD patients its selective modulation by non-covalent and selective inhibitors becomes an interesting strategy in the search of potential drugs against this neuropathology. With this in mind, our research group has been working in the capacity of a series of nitrones to inhibit caspase-3 mediated apoptosis in mouse hippocampal (HT22) cells. Moreover, the mechanism of inhibition of caspase-3 by nitrones was evaluated by means of molecular docking and Molecular Dynamics (MD) simulations. Most of the evaluated nitrones are able to inhibit apoptosis in neuronal HT22 cells. According to docking and MD results, these molecules would be able to act as caspase-3 inhibitors by binding into a region close to the substrate binding site and causing important allosteric changes at the catalytic site. Interestingly, nitrones interact with residues that are not conserved in other caspases and therefore they could be promising selective inhibitors of caspase-3. Enzymatic assays in order to test the capacity of these nitrones to selectively inhibit caspase-3 are currently underway.

Biography

Alicia Merlino completed his PhD in Medicinal Chemistry in 2010 at Facultad de Química, Universidad de la República, Uruguay. Since 2011, she works as Adjoint Professor at the Theoretical and Computational Chemistry Group in Facultad de Ciencias and has worked in CADD against different therapeutic targets in collaboration with several research groups. She has published numerous papers on this area in recognized journals. Since 2012, she has been responsible for the project "R&D of caspase-3 inhibitors as potential drugs against Alzheimer's Disease" for which has received a grant last year. She is mentoring a Pre-Grade student and two Master's students.

amerlino@adinet.com.uy

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