# DESIGN AND SYNTHESIS OF ORIGINAL PHENOLIC COMPOUNDS TARGETING HEMICHANNEL CONNEXINS

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Chronic non-communicable diseases characterized by inflammation account for 74% of deaths worldwide.[1] Reducing this mortality rate is crucial. A membrane protein known as connexin could potentially become a promising new therapeutic target to achieve this goal.
Connexins (Cx), found in most vertebrate tissues, have two main roles. Firstly, they can form hemichannels (HC) accross the membrane of individual cells, facilitating the exchange of metabolites between the cytoplasm and the extracellular environment. Secondly, two opposed HC can dock to create gap junctions channels (GJC) between two adjacent cells, allowing the diffusion of molecules up to 1.5 kDa.[2] While GJCs are essential for cell survival, HCs are at the root of many pathologies.

Under normal conditions, HC are either not expressed or are expressed minimally, with a low probability of opening. However, during inflammation, infectious agents release inflammatory stress signals of the pathogen-associated molecular pattern (PAMPs) class. This triggers HC hyperactivity in epithelial cells, prompting the release of inflammatory signals of the damage-associated molecular pattern (DAMPs) class.[3] The increased presence of HC in epithelial cells in response to PAMPs and DAMPs may contribute to the heightened release of injury signals during inflammatory events, potentially driving the progression of chronic inflammation.[4]

The development of analogues based on a promising first diarylheptanoid hit with selective HC inhibitory activity will be presented.[5] Through interdisciplinary work combining docking calculations, syntheses and cell bioassays, we aim to create a library of effective molecules that selectively target HC without affecting GJC, in order to restore the barrier function of epithelial cells under inflammatory conditions. This could represent a decisive step towards the treatment of diseases related to chronic inflammation.

References:

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