PHARMACOCHEMICAL DEVELOPMENT OF NEW PYRROLE DERIVATIVES & THEIR CINNAMOYL HYBRIDS

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Inflammation is part of the body's natural defense mechanism against foreign and harmful stimuli. While acute inflammation is an essential and protective response to infections and injured tissues, dysregulation of its magnitude or duration has been associated with the pathophysiology of several multifactorial conditions.

Among the various enzymes implicated in the development and progression of chronic inflammatory conditions, lipoxygenases (LOXs) are of great importance. It has long been known that chronic inflammation and oxidative stress are inextricably interrelated. Thus, overactivation of the 5-LOX pathway during a chronic inflammatory response contributes to elevated levels of reactive oxygen species (ROS) resulting in oxidative damage of nucleic acids, lipids and proteins.

Molecular hybridization has emerged as a promising approach in the treatment of diseases exhibiting multifactorial aetiology leading to a new single chemical entity with synergistic effects and improved pharmacokinetic-pharmacodynamic properties relative to the parent compounds.

Cinnamic acid and its derivatives are considered an important class of aromatic carboxylic acids presenting a broad range of biological applications. Several studies have reported the synthesis of various cinnamic-hybrids with antioxidative and anti-inflammatory properties.

Among well-known non-steroidal anti-inflammatory drugs (NSAIDs), pyrrole derivatives are of remarkable interest. In the literature there have been reports of 3,4-disubstituted-pyrrole derivatives inhibiting the cyclooxygenase (COX) pathway, while presenting low or no action against LOX [1,2].

In light of the above, our research was focused on the molecular design, prediction of pharmacokinetic properties, synthesis, drug-likeness and biological evaluation of novel 3,4-disubstituted-pyrrole derivatives and pyrrole-cinnamate hybrids as potential lipoxygenase inhibitors and antioxidant agents.

All hybrids exhibited stronger antioxidant activity than their corresponding pyrroles and more potent anti-LOX activity compared to cinnamic acid. The majority of the hybrids presented improved activity against LOX relative to their pyrrole precursors. Docking studies revealed that allosteric interactions govern the LOX inhibitory binding activity.

References

1. Pontiki E, Hadjipavlou-Litina D. (2019) *Molecules*. *24*(1), 12.
2. Noti V, Hadjipavlou-Litina D. (2022) *Molbank*. *2022*(1), M1314.