

CINNAMIC AMIDES OF NATURAL AMINO ACIDS AS MULTI-TARGET HYBRID AGENTS FOR MULTIFACTORIAL DISEASES

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Multi-target drug design (MTD) aims to integrate multiple pharmacophores into a single drug molecule in order to make it active on several molecular biological targets simultaneously. Since most diseases are multifactorial in nature, MTD is seriously considered to result in improved structures-products in complex diseases as neurodegenerative, cardiovascular, diabetes, metabolic and inflammatory diseases, especially where multi-target strategies are a promising alternative to the classical "one target-one drug" design approach.

Inflammation is a part of the complex biological response of body tissues to harmful stimuli, and is a protective response involving immune cells, blood vessels, and molecular mediators. Neuroinflammation is a defense mechanism that initially protects the brain by removing or inhibiting diverse pathogens and is associated with neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Two of the most important targets regarding inflammation are cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), since they act as key enzymes in the production of inflammatory mediators such as leukotrienes and prostaglandins.

Cinnamic acids and coumarins comprise a fruitful pool of bioactive compounds since they entail activities such as neuroprotective, antioxidant and anticancer. Herein we will illustrate how various functionalities have been combined in a structure's library containing single amide structures to act as neuroprotective hybrid agents and how this combination has affected their biological outcome, starting from in silico modelling, ADMET and drug-likeness studies. The amino acids used were GABA, glycine and L-glutamate, whose role as neurotransmitters is well known.

The hybrids were studied for their antioxidant, anti-COX, anti-LOX and anti-inflammatory activities. Lead molecules were identified for the design of more selective bioactive agents.

