

# Exploring Cinnamic Acid Multitarget Hybrids in Terms of 2D-QSAR

Dimitra Hadjipavlou-Litina, Aristotle University of Thessaloniki, Thessaloniki, Greece

Aikaterini Peperidou, Aristotle University of Thessaloniki, Thessaloniki, Greece

## ABSTRACT

Cinnamic acids hybrids present a variety of significant biological activities and are characterized as pleiotropic agents. The 2D- QSAR analysis presented here attempts to identify the structural features and physicochemical properties of cinnamic acids hybrids presenting: a) antitumor activity; b) immunosuppressive activity; c) inhibitory activity on various enzymes; d) antioxidant activity. A 2D-QSAR analysis was carried out for 26 data sets of compounds taken from the literature using the C-QSAR program of Biobyte. In 5 cases hydrophobicity appeared to be important. Steric factors in the form of overall molar refractivity (CMR), molar refractivity of the substituents (MR), molar volume (MgVol) and the Verloop Sterimol parameters have a significant impact on the biological activity whereas electronic parameters as Hammett  $\sigma_p$ ,  $\sigma_m$ ,  $\sigma_o$  or  $\Sigma\sigma$  appear in most of the cases. The anticancer as well as anti-inflammatory and antioxidant activities of caffeic acid hybrids are governed by lipophilicity, electron and stereochemical factors.

## KEYWORDS

Cinnamic Acid, Electronic Effects, Hybrids, Lipophilicity, Metalloproteinases, QSAR, Stereochemical Effects

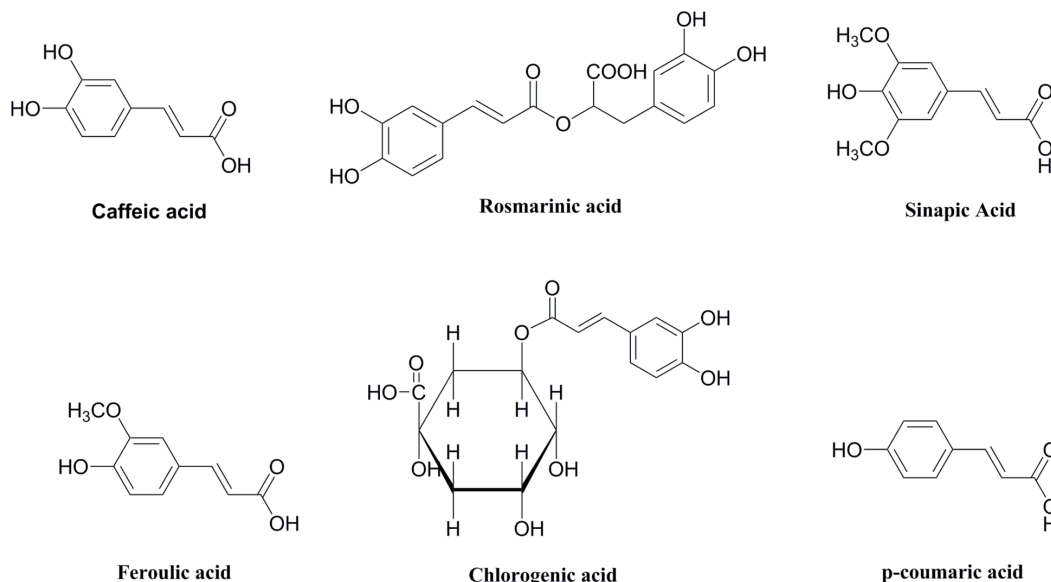
## INTRODUCTION

Cinnamic acid derivatives are widely studied natural phenolic compounds presenting a wide variety of biological activities. (Upadhyay et al., 2013; Zhang et al., 2014; Landete et al., 2012; Scalbert et al., 2005; Visioli et al., 2011) It is well known that “cinnamic” derives from the spice *Cinnamomum zeilanicum* commonly called cinnamon, which has been used mainly as a flavoring agent bearing antiseptic, stimulant, carminative and insecticide activities. Piplartine, includes in its structure a cinnamamide moiety and it was isolated from the roots of *Piper tuberculatum* and emerged to be a promising anti-cancer agent. (Sharma P. et al., 2011; Hermann et al., 1995; Kroon et al., 1999; Boerjan et al., 2003). Hydroxy-cinnamic acid is an important intermediate in biochemical pathways of phenylpropanoids and secimic esters, which are represented in natural products. (Macheix et al., 1990; Heleno et al., 2015) During the last decade scientists have focused on cinnamic acid moiety due to its significant biological spectrum e.g., Anti-Alzheimer, antioxidant (Rapta et al., 1995), antiinflammatory (Grabias et al., 1998; Melzig et al., 2001; Peperidou et al., 2014) and anticancer activity (Pontiki et al., 2014). (Figure 1)

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Figure 1. Hydroxy-cinnamic acid derivatives as intermediates in nature kingdom (Clifford et al., 2000)



Polypharmacology is linked to the administration of two or more drugs together. Three cases of multidrug therapy are described: 1) simultaneously administration of two or more drugs, 2) co-formulation of two or more active agents in a single tablet and 3) hybrid molecules synthesized by the combination of two or more chemical entities capable to modulate multiple targets. (Shaveta et al., 2016; Boran et al., 2010) The simultaneous use of more than one drug as it happens in chemotherapy demands a lot of patient compliance. Thus, the combination of appropriate pharmacophores groups has been developed to find out promising drug candidates as inhibitors of multiple biological targets. (Paolini et al., 2006; Yildirim et al., 2007) The hybrid approach is mainly offered in the treatment of diseases with complex combining two or more drugs in a single molecule with the goal of creating an agent more medically effective than its individual components. (Durrant et al., 2010; Oprea et al., 2012)

Antioxidant, anti-inflammatory and anti-cancer cinnamic acids hybrids are referred in the literature and this 2D-QSAR study attempts to explore and understand the role of the physicochemical properties that are important for these activities.

## BACKGROUND

It is well known that in the development of most drugs based on Rational Drug Design, Computational Chemistry plays a key role, utilizing modern chemistry and computer technology (Computer Aided Molecular Design, CAMD), followed by quantitative structure-activity relationships (QSAR), which is an indirect design process. QSAR leads to a mathematical correlation with the primary aim to search for new chemical entities with the required desired properties. Quantitative structure- activity relationships attempt to correlate biological activity with structural features by using physicochemical properties. These physicochemical properties are expressed by parameters that refer to hydrophobicity, electronic and steric effects. The QSAR procedures include calculational operations.

Hansch et al. developed quantitative structure-activity relationships (QSARs) for different series of hydroxy-cinnamic acid derivatives in order to understand the chemical-biological interactions governing antitumor activity against six different tumor cell lines, nitric oxide production, anti-HIV and inhibitory activities of enzymes LOX and COX and binding affinity to the Ick domain. Their reported

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