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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

3D-QSAR studies on lipid peroxidation inhibitory activity of chromone derivatives

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Abstract Lipid peroxidation has been implicated in disease states such as atherosclerosis, asthma, neurodegenerative disorders, Parkinson's disease, cancer, etc. In this study, the anti-lipid peroxidation activity for a series of chromone compounds, evaluated in vitro by ferric thiocyanate and thiobarbituric acid assays, were subjected to three-dimensional quantitative structure-activity relationship studies using comparative molecular field analysis and comparative molecular similarity indices analysis. From ferric thiocyanate assay, the best comparative molecular field analysis and comparative molecular similarity indices analysis models gave cross-validated r^2 (q^2) = 0.563 and 0.593 and non cross-validated r^2 = 0.974 and 0.929, respectively. The best comparative molecular field analysis and comparative molecular similarity indices analysis models derived from thiobarbituric acid assay gave q^2 = 0.558 and 0.612, and non cross-validated r^2 = 0.959 and 0.919, respectively. The generated hydrogen donor contour maps support the previously reported structure-activity relationship that the presence of a catechol moiety in ring A is essential for high potency.

Keywords Chromone derivatives · Anti-lipid peroxidation activity · 3D-QSAR · CoMFA · CoMSIA

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Introduction

Lipid peroxidation is an important mediator of pathophysiological events in central nervous system disorders such as cerebral ischemia, trauma (Hall, 1993; 1995), and Alzheimer disease (Aluise et al., 2011; Butterfield et al., 2010). It is also implicated in many disease states including atherosclerosis, asthma, kidney damage, and cancer (Abrescia and Golino, 2005; Valko et al., 2007). Lipid peroxidation is induced by free radicals with the major species of reactive oxygen species (ROS). ROS are very unstable and react readily with a wide range of biological substrates such as lipids, DNA, and protein, leading to cell damage (Farber, 1994; Radak et al., 2011; Young and Woodside, 2001). The destruction of membrane lipids and the end-products of lipid peroxidation reactions are especially dangerous for the viability of cells and tissues. Many natural and synthetic compounds with anti-lipid peroxidation activity have been reported to retard oxidative damage and disease progression (Geronikaki and Gavalas, 2006; Kontogiorgis et al., 2005; Maxwell, 1995; Szajdek and Borowska, 2008). Polyphenols, the most abundant plant secondary metabolites, exhibit the strongest protective effect regarding cellular oxidative damage (Cyboran et al., 2012; Raudoniūtė et al., 2011). Flavonoids, the natural phenyl substituted chromones (Fig. 1), show potent peroxyl radical scavenging abilities, which contribute to inhibiting lipid peroxidation and oxidation of low density lipoprotein (Castelluccio et al., 1995; Kardum et al., 2014; Salah et al., 1995).

In our previous study, a series of chromone derivatives with different hydroxy substitution patterns at chromone nucleus and various substitutions at C-2 and C-3 (Table 1) were evaluated for their in vitro lipid peroxidation inhibitory activity using ferric thiocyanate (FTC) and