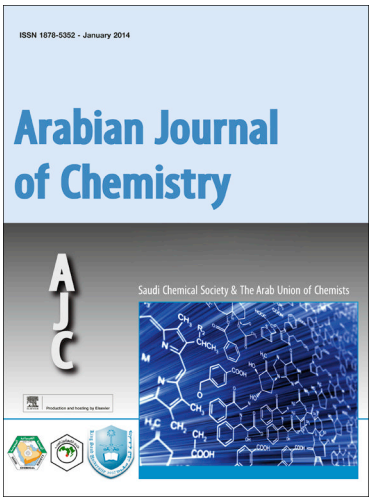

Original article

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Synthesis and antioxidant study of new polyphenolic hybrid-coumarins.

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ABSTRACT

The antioxidant capacity of hydroxylated coumarins and hydroxybenzoic acids has been widely described. However, there is little information on the antioxidant activity when both systems are functionalized. In this work, new hybrid compounds synthesis with a common coumarin scaffold and hydroxybenzoic acids is described. Their antioxidant capacity was evaluated against reactive oxygen species (ROS) using oxygen radical absorbance capacity-fluorescein (ORAC-FL), electron spin resonance (ESR) spin trapping, quenching of superoxide anion, cellular antioxidant activity (CAA) and a ferric reducing ability of plasma (FRAP assay). Additionally, the local reactivity indicator (Fukui index) was calculated to discriminate different reactive sites in the new molecules in which the oxidative process occurs. Likewise, the BDE values were calculated in order to obtain information about the antioxidant capacity for HAT mechanisms. The insertion of organic phenols in a simple coumarin structure produced new derivatives with an improved antioxidant capacity in relation to coumarin 1a. For compound 3c, a synergy phenomenon in ORAC-FL and the FRAP test was observed. For compound 3b, this phenomenon was observed in the superoxide scavenging test. According to the CAA assay results, the activity of the new compounds is limited to those oxidative processes in lipophilic media (e.g., bio membranes).

1. Introduction

Polyphenols are a widely distributed family of compounds in the vegetable kingdom and perform plant secondary metabolites functions, e.g., UV sunscreens, pigments, signal compounds, growth regulators, and defence mechanisms (phytoalexins, **Lattanzio et al., 2009**). Their biological activity includes anti-inflammatory, cardio protective, vasodilatory, anti-aging, anti-carcinogenic and anti-microbial properties (**Xia et al., 2010; Dua et al., 2013; Cimino et al., 2012; Keerthi et al., 2014**). Several studies report the antioxidant polyphenolic properties (**Pulido et al., 2000; Nouger et al 2014; Gülçin, 2006; Li et al., 2011)** and their human health effect (**Pereira et al., 2014**). **Jeong *et al 2011*** studied an *Erigeron annuus* buthanolic extract with an caffeic acid content, which showed neuroprotective and antioxidant effects on neuronal cells.

Coumarins (2H-1-benzopyran-2-one) are substances in seeds, roots and leaves of plants. Natural and synthetic coumarins have been applied in cosmetics (**Abernethy et al., 1969; Ma et al., 2015**), food additives (**Wang et al., 2013**), and agriculture (**Lopes et al., 1995**). These compounds have well-known biological activities such as anticoagulant, anti-inflammatory, antifungal, antitumor, hepato-protective, ulcerogenic, anti-HIV and an interesting antioxidant activity (**Asif et al., 2014; Kale etal., 2014; Jayashree et al., 2014; Kostova et al., 2006; Kim et al., 2008; Payá et al., 1992; Payá et al., 1996**). Regarding the latter property, **Payá *et al*., 1994,** studied a mono and dihydroxylated coumarin series towards reactive oxygen species (ROS). They found that simple *ortho* hydroxyl derivatives are radical inhibitors in the lipid peroxidation process. The authors also observed that dihydroxy coumarins could scavenge superoxide in human leucocytes. This topic is interesting because several pathologies such as hypertension, atherosclerosis, diabetes mellitus, cardiovascular pathologies and others are closely linked to the cell redox imbalance (**Valko et al., 2007**).

Most human diseases (e.g., cancer, diabetes, and neurodegenerative diseases) are complex and multifactorial. Several investigations in the literature focused on new multi-target drug development, which implies active pharmacophores incorporation in one scaffold (**Meunier et al., 2008; Lazar et al., 2004; Teiten et al., 2014**). New hybrids have been successfully tested and proposed, such as potential drug candidates, e.g.,