



An effective strategy to develop active cinnamic acid-directed antioxidants based on elongating the conjugated chains



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ABSTRACT

To optimize antioxidant activity and lipophilicity of cinnamic acid derivatives (CAs) including ferulic acid, sinapic acid, 3,4-dimethoxycinnamic acid, and *p*-hydroxycinnamic acid, four analogs bearing an additional double bond between their aromatic ring and propenoic acid moiety were designed and synthesized based on the conjugated chain elongation strategy. The antioxidant performance of the CAs were investigated by 2,2'-diphenyl-1-picrylhydrazyl (DPPH[•])-scavenging, ferric reducing/antioxidant power, cyclic voltammetry, DNA strand breakage-inhibiting and anti-haemolysis activity assays. It was found that CAs with elongation of conjugated chains display increased DPPH[•]-scavenging, DNA strand breakage-inhibiting and anti-haemolysis activities as compared to their parent molecules, due to their improved hydrogen atom-donating ability and lipophilicity. Overall, this work highlights an effective strategy to develop potential CA-directed antioxidants by elongating their conjugated chain.

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1. Introduction

Polyphenols are a large family of bioactive compounds widely distributed in plant kingdom, among which cinnamic acid (CA) and its derivatives occupy an important position as known antioxidants found in plant foodstuffs (Block, Patterson, & Subar, 1992; Clifford, 1999; Herrmann & Nagel, 1989; Shahidi & Chandrasekara, 2010). A sufficient source of phenolic acids in the daily diet of plant origin not only plays an essential role in the organism protection against deleterious oxidative damage for the human health, but also prevents certain chemotherapy-caused side effects and slows down the cancer progression, such as angiogenesis, invasion and metastasis for cancer patients (Conklin, 2000; Weng & Yen, 2012). Oxidative stress induced by excessive production of reactive oxygen species (ROS) or free radicals is related to the development of a wide range of diseases, mainly atherosclerosis, inflammatory injury, neurodegenerative diseases, cancer, and the accelerated ageing of organisms (Darvesh, Carroll, Bishayee, Geldenhuys, & Van der Schyf, 2010; Fresco, Borges, Diniz, & Marques, 2006; Thomasset et al., 2006). On another hand, although ROS play important roles in prooxidant cancer therapy (Trachootham, Lu, Ogasawara, Rivera-Del Valle, & Huang, 2008), they are also responsible for some adverse effects of many clinically used anticancer drugs, such as gastrointestinal toxicity and mutagenesis (Conklin,

2000; Deavall, Martin, Horner, & Roberts, 2012). The CA derivatives (CAs) have become attractive in medicinal research mainly due to their natural origin and their preventive and defensive effects against the above diseases based on the antioxidant capacity against the damaging free radicals and ROS (Darvesh et al., 2010), lacking adverse health effects in humans.

Therefore, the past two decades have witnessed much interest in investigating antioxidant mechanisms (Cheng, Dai, Zhou, Yang, & Liu, 2007; Foti, Daquino, & Geraci, 2004) of CAs and modifying their molecule structure to improve antioxidant activity. Structural modifications of CAs focus mainly on optimizing the aromatic ring substitution (Bakalbassis et al., 2001; Gaspar et al., 2009; Rice-Evans, Miller, & Paganga, 1996) and grafting alkyl ester side chains (Figueroa-Espinoza & Villeneuve, 2005; Gaspar et al., 2010; Laguerre et al., 2009; López-Giraldo et al., 2009; Nenadis, Zhang, & Tsimidou, 2003; Reis et al., 2010). The second strategy is to improve their lipophilicity since the hydrophilic nature of CAs results in some drawbacks: a limited application in oil-based industrial processes and the poor membrane permeability which greatly influences the antioxidant behaviour in biological systems. Additionally, this structure modification strategy has also been applied in other hydrophilic phenols including an important tea polyphenols, epigallocatechin gallate (Zhong & Shahidi, 2011).

Currently, there are few researches focusing on the structure modification of the middle part (double bond moiety) of CAs in improving antioxidant activity. We have previously found that a middle part modification in the stilbene scaffold of resveratrol by

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inserting additional double bonds between two aromatic rings, could significantly improve its antioxidant performance including the hydrogen atom- or electron-donating ability and its lipophilicity (Tang et al., 2011). Thus, we tried to mimic this strategy of the conjugated chain elongation to modifying the molecule structure of CAs including ferulic acid (FA, **A1**), sinapic acid (**A2**), 3,4-dimethoxycinnamic acid (DMA, **A3**), and *p*-hydroxycinnamic acid (*p*-HCA, **A4**), where an additional double bond was inserted between the aromatic ring and the propenoic acid moiety to obtain more lipophilic derivatives (**B1–4**, Scheme 1). Furthermore, whether and how the conjugated chain elongation affects the antioxidant properties of CAs were also examined. The antioxidant activity of the eight CAs (**A1–4** and **B1–4**) was determined by employing five different and commonly used methods: the 2,2'-diphenyl-1-picrylhydrazyl (DPPH)-scavenging, ferric reducing/antioxidant power (FRAP), cyclic voltammetry, DNA strand breakage-inhibiting and anti-haemolysis activity assays. The assays are indicative of their formal hydrogen-transfer and electron-donating abilities, inhibitory ability against DNA damage induced by free

radicals and protective activity against lipid peroxidation in a heterogeneous environment, respectively.

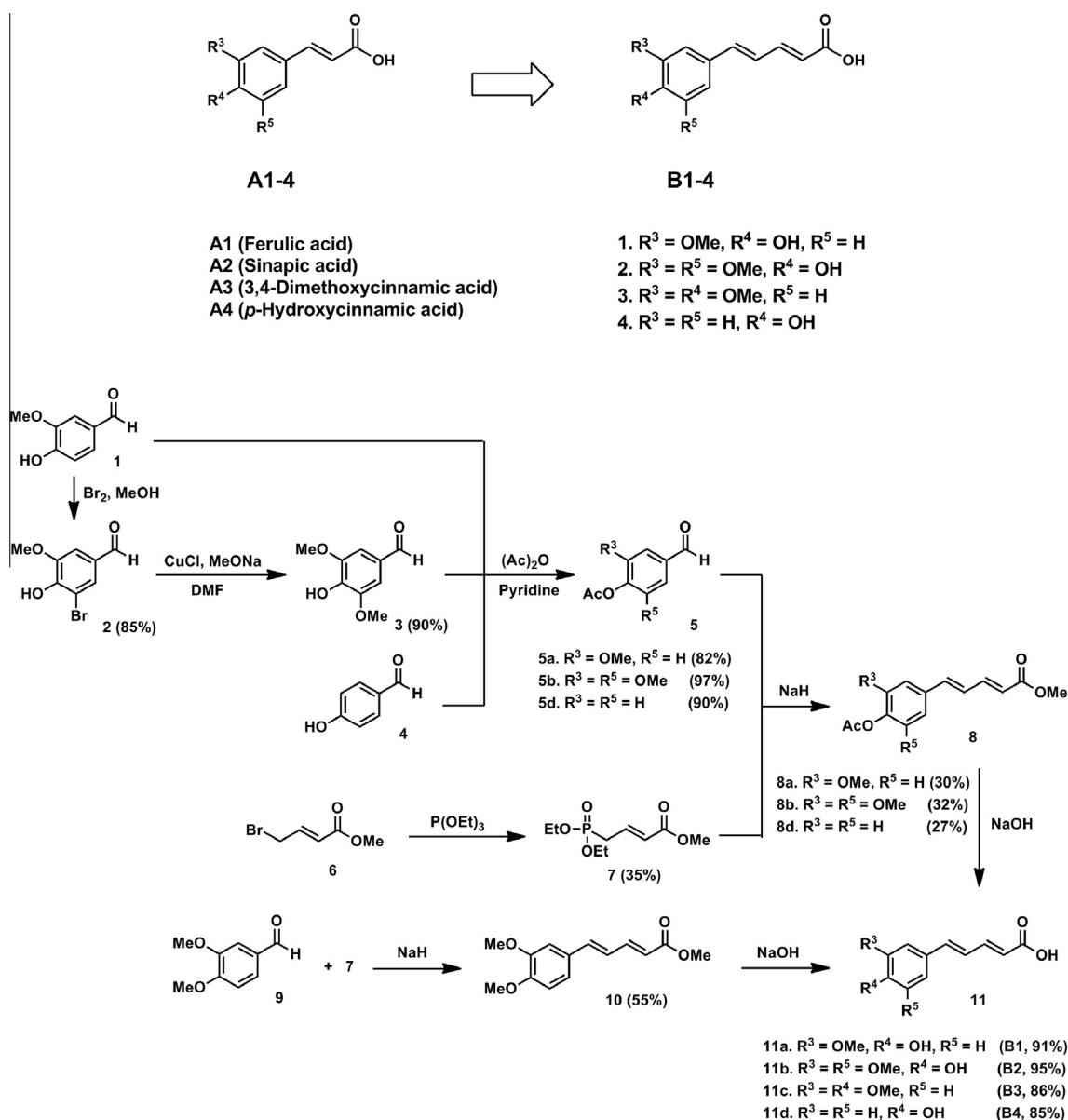
2. Materials and methods

2.1. Materials

2,2'-Diphenyl-1-picrylhydrazyl radical (DPPH), pBR322 DNA and 2,2'-azobis (2-amidinopropane hydrochloride) (AAPH), were obtained from Sigma-Aldrich Inc., (St. Louis, MO, USA). 2,4,6-Tri(2-pyridyl)-S-triazine (TPTZ) was from Alfa Aesar Co., Ltd. (MA, USA). The compounds (**A1–4**) were purchased from Adamas Reagent Co. Ltd., (Shanghai, China). Other chemicals used were of analytical grade.

2.2. Synthesis

The synthetic details and spectra (^1H , ^{13}C NMR and MS) of the target compounds (**B1–4**) were described in the [Supplementary](#)



Scheme 1. Molecular structures and synthesis of cinnamic acid derivatives with the conjugated chain elongation.

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