Food Chemistry 136 (2013) 650–658

Contents lists available at SciVerse ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Synthesis of quinoline derivatives of tetrahydrocurcumin and zingerone and evaluation of their antioxidant and antibacterial attributes

J.R. Manjunatha [a,c], B.K. Bettadaiah [a,c], P.S. Negi [b,c], P. Srinivas [a,c,*]

[a] Department of Plantation Products, Spices and Flavour Technology, Central Food Technological Research Institute, Mysore 570 020, India
[b] Department of Human Resource Development, Central Food Technological Research Institute, Mysore 570 020, India
[c] Council of Scientific and Industrial Research, New Delhi, India

ARTICLE INFO

Article history:
Received 8 June 2012
Received in revised form 14 August 2012
Accepted 19 August 2012
Available online 13 September 2012

Keywords:
Quinolines
Tetrahydrocurcumin
Zingerone
Friedlander reaction
Radical scavenging activity
Antibacterial action

ABSTRACT

Tetrahydrocurcumin (THC, **1**) and zingerone (**2**) are biologically active molecules originating from the important spices turmeric and ginger, respectively. Novel quinoline derivatives of THC and zingerone have been synthesised by an efficient protocol involving their reaction with substituted 2-aminobenzophenones and 2-aminoacetophenone. Radical-scavenging activities (RSA) of THC, zingerone and their quinoline derivatives were evaluated. The amino-substituted quinoline derivative of THC, **1e**, showed antioxidant activity superior to those of **1** and **1a**. Derivatives **1b, 1c, 1d** and **1f** exhibited relatively lower RSA at equimolar concentrations (~50–55 μmol). A similar trend was also seen in zingerone (**2**) and its derivatives (**2a**–**2e**), with **2e** displaying the best RSA. Derivatives of THC (**1a**–**1f**) showed stronger antimicrobial activity than THC (**1**) against *Staphylococcus aureus, Bacillus cereus, Escherichia coli, and Yersinia enterocolitica.* Also, derivatives of zingerone (**2b**–**2e**) exhibited lower minimum inhibitory concentrations (MIC) values than zingerone (**2**) and its derivative, **2a** for both Gram-positive and Gram-negative bacteria. The molecules may have potential pharmacological applications.

1. Introduction

Turmeric (*Curcuma longa*) and ginger (*Zingiber officinale*) are spices that belong to the *Zingiberaceae* family. Ginger, a common ingredient for various foods and beverages, is also employed in medicine for the treatment of various ailments like headaches, nausea, rheumatism and colds. Turmeric is primarily used in Indian cuisine for its colouring characteristics. Curcuminoids, *viz*., curcumin, demethoxycurcumin and bis-demethoxycurcumin, are the yellow pigments of turmeric. Curcumin, the major constituent and a nutraceutical used worldwide, exhibits potent anti-inflammatory, antitumour and anti-cancer properties (Aggarwal, Kumar, Aggarwal, & Shishodia, 2005; Gupta et al., 2011; Joe, Vijaykumar, & Lokesh, 2004; Sharma, Gescher, & Steward, 2005). Biotransformation of curcumin to its reduced forms – di-, tri-, tetra-, hexa- and octahydrocurcumins – has been demonstrated in mice models (Pan, Huang, & Lin, 1999). Tetrahydrocurcumin (THC, **1**), a stable metabolite of curcumin, is indicated to play an important role in the biological effects of curcumin (Anand et al., 2008). Tetrahydrocurcumin is obtained by selective reduction of the olefinic bonds in curcumin. Zingerone [4-(4-hydroxy-3-methoxyphenyl)-2-butanone, **2**], an important bioactive constituent of ginger (Pulbutr, Thunchomnang, Lawa, Mangkhalathon, & Saenbol, 2011), is structurally similar to THC. Both THC and zingerone contain a 4-hydroxy-3-methoxyphenyl moiety and a carbonyl group in the side chain. These molecules, being lipophilic have little solubility in aqueous systems. Our recent attempts to render curcumin water-soluble by preparing its sugar and amino acid derivatives led to the preparation of a large number of curcumin derivatives, which exhibited potent antioxidant, antimicrobial and antimutagenic properties comparable to, and in several cases superior than, curcumin (Parvathy, Negi, & Srinivas, 2009, 2010). We also demonstrated that curcumin-β-diglucoside prevented oligomer formation and inhibited fibril formation of α-Synuclein, whose aggregation is centrally implicated in Parkinson's disease (PD) (Bharathi, Parvathy, Srinivas, Indi, & Rao, 2012). Clioquinol (5-chloro-7-iodoquinolin-8-ol), a quinoline compound, its analogues and their possible beneficial effects via the Zn^{2+} and Cu^{2+} chelating properties on neurodegenerative diseases and cancer have been explored in a variety of systems (Wang et al., 2009). However, this compound has been shown to have SMON toxicity. Also, the broad range of bio-activities associated with quinolines has fascinated researchers leading to their chemical - synthesis and the identification of newer applications. Compounds with a quinoline ring are known to possess anti-asthmatic, antibacterial, anti-inflammatory and anti-hypertension attributes (Chen, Fang, Sheu, Hsu, & Tzeng, 2001; Maguire, Sheets, Vety, Spada, & Zilberstein, 1994). Quinolines with various substitutions at 2, 4

* Corresponding author. Address: Department of Plantation Products, Spices and Flavour Technology, Central Food Technological Research Institute, Cheluvamba Mansion, Mysore 570 020, India. Tel.: +91 821 2512352; fax: +91 821 2517233.
E-mail address: psrinivas@cftri.res.in (P. Srinivas).

0308-8146/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.foodchem.2012.08.052

and 6 positions have important bioactive attributes such as antimicrobial and antioxidant activities (Kouznetsov, Mendez, & Gomez, 2005). In the present study, we envisaged the preparation of the quinoline derivatives of the important bioactive ingredients of curcumin and ginger *viz*., THC and zingerone, which have the appropriate functional moiety of keto groups with a methylene moiety at the alpha position for reaction with aromatic amines *via* a Friedlander type reaction.

Quinoline derivatives are prepared by various methods like Skraup, Doebner-Von Miller, Combes and Friedlander (Denmark & Venkatraman, 2006). Poly-substituted quinolines are synthesised by the Friedlander method, using various BrØnsted acids such as sulphamic acid, hydrochloric acid, *p*-toluenesulphonic acid, perchloric acid, phosphoric acid and trifluoroacetic acid (Shaabani, Soleimani, & Badri, 2007; Wang, Jia, & Dong, 2006). Lewis acids such as $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $AuCl_3$, $CeCl_3{\cdot}7H_2O$ and ionic liquids have also been employed in the Friedlander annulations (Bose & Kumar, 2006; De & Gibbs, 2005). These conditions have either the limitations of low yields, severe experimental conditions or prolonged reaction times. In our efforts to prepare new quinoline derivatives of biologically important molecules *viz*., tetrahydrocurcumin (THC) and zingerone, initially we investigated the reaction of these substrates with 2-aminobenzophenone and 2-aminoacetophenone using $Y(OTf)_3$ as catalyst. While the corresponding quinolines were obtained in good yields, this catalyst failed to achieve the reaction with mono-chloro, dichloro, nitro and amino substituted 2-aminobenzophenone substrates. On the other hand, trifluoroacetic acid (TFA) promoted annulations even with substituted benzophenones. We report here the synthesis of novel quinoline derivatives of THC and zingerone with TFA as the catalyst (Fig. 1) and evaluation of their anti-oxidant and antibacterial activities.

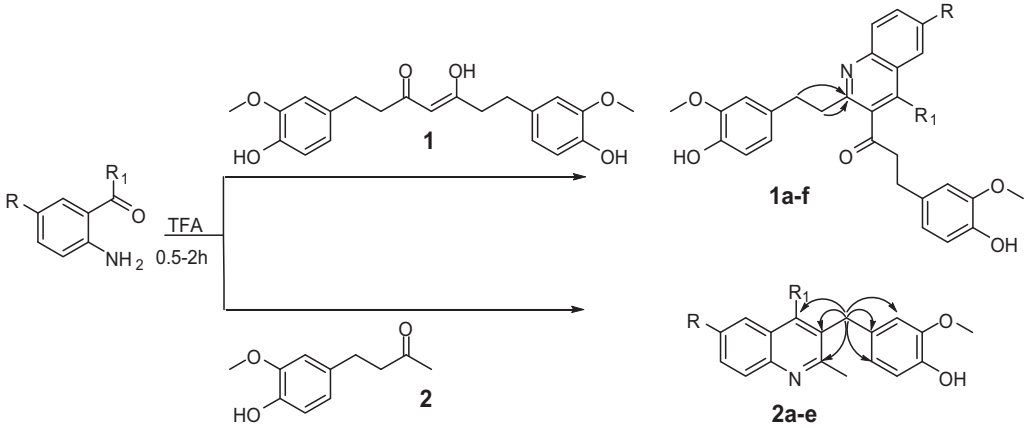
2. Materials and methods

2.1. Materials and equipment

All the solvents and reagents used for the syntheses were of analytical grade. THC was prepared in the laboratory by hydrogenation of curcumin over $Pd/BaSO_4$ in acetone at 30 psi hydrogen pressure (Sneharani, Sridevi, Annapurna Singh, Srinivas, & Appu Rao, 2011). Zingerone was prepared by hydrogenation of dehydrozingerone, which was obtained by aldol condensation of vanillin and acetone in the presence of KOH, at 30 psi hydrogen pressure in the presence of $Pd/BaSO_4$ in methanol (Kim & Kim, 2004). 2-Aminoacetophenone, *2*-aminobenzophenones, BHA and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) were procured from Sigma Chemical Co. (St. Louis, MO, USA). ^1H NMR and ^{13}C spectra for the compounds were recorded on a 500 MHz NMR spectrometer (Bruker Avance, Reinstetten, Germany) using $CDCl_3$ solvent. Chemical shift values and coupling constants are given in δ and Hz, respectively. Mass spectral analyses of compounds were carried out using MS (Waters Q-Tof Ultima, Manchester, UK) in the ESI positive mode. Spectrophotometric studies were carried out on an Ultraviolet–Visible Spectrometer (Cintra-10, GBC, Australia). Thin-layer chromatographic (TLC) analysis was performed on silica gel 60 F_{254} (Merck, Germany) coated on alumina sheet with 3% methanol in chloroform as the developing solvent. Isolation of the products was carried out by trituration of the crude product with ethyl acetate and petroleum ether. All the chemicals and petri-plates used for microbial studies were procured from Hi Media Ltd., Mumbai, India.

2.2. Synthesis of 1-(2-(4-hydroxy-3-methoxyphenethyl)-4-methylquinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one (**1a**, Fig. 1)

2-Aminoacetophenone (0.675 g, 5 mmol) was taken in a round-bottomed flask along with THC (2.23 g, 6 mmol). To this was added TFA (2–3 mL) and the mixture stirred at 100 °C for 40 min. The progress of the reaction was monitored by TLC. Also, the formation of a solid mass was noticed towards completion of the reaction. It was then neutralised with saturated $NaHCO_3$ solution (100 mL). The solid that separated was filtered, washed with water and dried. The resultant crude material was then triturated using ethyl acetate and petroleum ether. The material at this stage was dried in a desiccator over fused $CaCl_2$ for 12 h. Yield: 1.98 g, 84%. Light yellow solid; m. p. 112–115 °C; ^1H NMR: δ 8.17 (d, J = 8.3 Hz, 1H, H-8), 7.98 (d, J = 8.3 Hz, 1H, H-5), 7.7 (ddd, J_1 = 8.6 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz, 1H, H-7), 7.6 (ddd, J_1 = 8.3 Hz, J_2 = 6.9 Hz, J_3 = 1.1 Hz, 1H, H-6), 6.84 (d, J = 8 Hz, 1H, H-26), 6.81 (d, J = 8 Hz, 1H, H-19), 6.75 (d, J = 1.4 Hz, 1H, H-29), 6.73 (d, J = 1.9 Hz, 1H, H-16), 6.70 (dd, J_1 = 7.9 Hz, J_2 = 1.9 Hz, 1H, H-25), 6.63 (dd, J_1 = 8 Hz, J_2 = 1.8 Hz, 1H, H-20), 5.79 (br, 2H, Hydroxyls at C-27 & C-18), 3.82 (s, 3H, H-30), 3.78 (s, 3H, H-21), 3.04–3.08 (m, 4H, H-23 & H-14), 3.0–3.04



1a: R=H, R_1=CH_3; **1b**: R=H, R_1=Ph; **1c**: R=NO_2, R_1=Ph; **1d**: R=Cl, R_1=Ph; **1e**: R=NH_2, R_1=Ph; **1f**: R=*o*-Cl(Ph), R_1=Ph

2a: R=H, R_1=CH_3; **2b**: R=H, R_1=Ph; **2c**: R=NO_2, R_1=Ph; **2d**: R=Cl, R_1=Ph; **2e**: R=NH_2, R_1=Ph

Fig. 1. Synthesis of quinoline derivatives.