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.

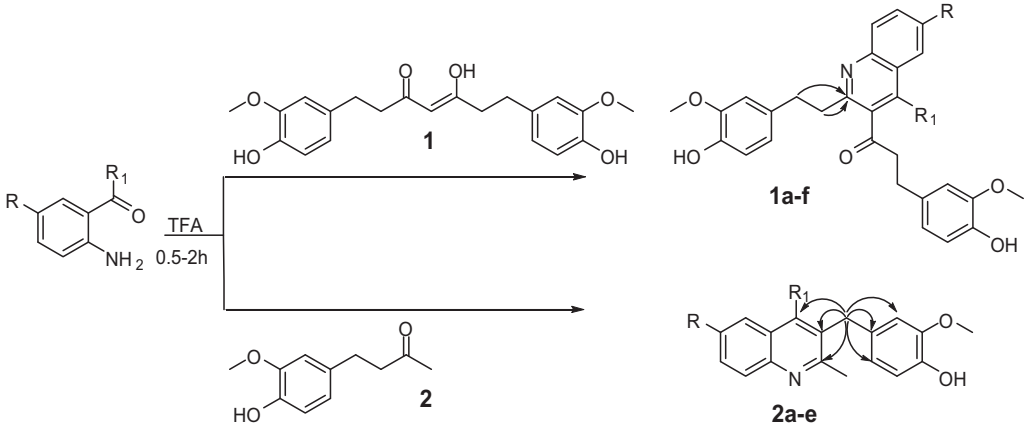
2. Materials and methods

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.

(m, 4H, H-13 & H-22), 2.48 (s, 3H, H-11); ^{13}C NMR: δ 207.27(C-12), 155.40 (C-2), 146.29 (C-27), 146.20 (C-18), 146.09 (C-10), 143.92 (C-28), 143.69 (C-17), 139.87 (C-4), 135.05 (C-3), 133.02 (C-24), 131.89 (C-15), 129.89 (C-7), 128.53 (C-8), 126.45 (C-6), 125.82 (C-9), 123.36 (C-5), 120.68 (C-25), 120.66 (C-20), 114.25 (C-26), 114.04 (C-19), 111.06 (C-16 & C-29), 55.56 (C-30), 55.50 (C-21), 47.16 (C-13), 38.61 (C-14), 35.10 (C-23), 28.69 (C-22), 15.04 (C-11); mass: calculated 471.2046; found; [M$^+$ + 1] = 472.8925.

2.3. General synthetic method for quinoline derivatives of tetrahydrocurcumin (**1b-1f**) and zingerone (**2a–2e**)

In a typical reaction, 2-aminoacetophenone, 2-aminobenzophenone or a substituted *2*-aminobenzophenone (5 mmol) was added with THC or zingerone (6 mmol) into a round-bottomed flask. To this mixture, TFA (2–3 mL) was added and stirred at 100 °C for the period mentioned in Tables 1 and 2. After completion of the reaction, as indicated by TLC analysis, the reaction mixture was neutralised with 100 mL of saturated sodium bicarbonate solution. The solid that separated was filtered and washed with distilled water and dried. The resultant crude material was further purified by triturating with ethyl acetate and petroleum ether (60–80 °C). It was then dried in a desiccator over fused calcium chloride for 12 h. The physical and spectroscopic data of individual pure compounds is presented below.

1-(2-(4-Hydroxy-3-methoxyphenethyl)-4-phenylquinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one **(1b)**; off-white solid; m. p. 165–166 °C; ^{1}H NMR: δ 8.17 (d, J = 8.3 Hz, 1H), 7.76 (ddd, J_1 = 8.4 Hz, J_2 = 6.8 Hz, J_3 = 1.3 Hz, 1H), 7.67 (dd, J = 8.6 Hz, J_2 = 1.5 Hz, 1H), 7.50–7.54 (m, 3H), 7.49 (ddd, J_1 = 8.5 Hz, J_2 = 6.8 Hz, J_3 = 1.1 Hz, 1H), 7.35–7.37 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 6.79 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8 Hz, 1H), 6.70 (d, J = 1.9 Hz, 1H), 6.38 (d, J = 2 Hz, 1H), 6.34 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.07–3.16 (m, 4H), 2.51 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H); ^{13}C NMR: δ 206.85, 156.32, 147.34, 146.02, 145.91, 144.01, 143.46, 134.97, 134.28, 133.41, 131.99, 129.93, 129.82, 128.69, 128.55, 128.36, 126.36, 125.80, 124.72, 120.78, 120.42, 113.86, 111.02, 110.65, 55.54, 55.46, 46.68, 38.87, 35.11, 28.92; Mass: Calculated 533.2202; Found; [M$^+$ + Na] = 556.5859.

1-(2-(4-Hydroxy-3-methoxyphenethyl)-6-nitro-4-phenylquinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one **(1c)**; light yellow solid; m. p. 172–175 °C; ^{1}H NMR: δ 8.61 (d, J = 2.3 Hz, 1H), 8.51 (dd, J_1 = 9.2 Hz, J_2 = 2.5 Hz, 1H), 8.27 (d, J = 9.1 Hz, 1H), 7.54–7.61 (m, 3H), 7.36 (d, J = 6.4 Hz, 2H), 6.83 (dd, J_1 = 7.9 Hz, J_2 = 0.6 Hz, 1H), 6.77 (d, J = 1.2 Hz, 1H), 6.72 (dd, J_1 = 8 Hz, J_2 = 0.6 Hz, 1H), 6.68 (dd, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H), 6.38 (d, J = 1.4 Hz, 1H), 6.34 (dd, J_1 = 8 Hz, J_2 = 1.4 Hz, 1H), 5.64 (b, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.09–3.19 (m, 4H), 2.54 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H); ^{13}C NMR: δ 205.79, 160.56, 149.37, 146.16, 146.02, 145.64, 145.45, 143.72, 143.67, 135.74, 133.41, 132.93, 131.68, 130.64, 129.80, 129.45, 128.88, 124.02, 123.24, 122.83, 120.75, 120.43, 114.06, 114.01, 110.94, 110.65, 55.57, 55.48, 46.47, 38.99, 34.51, 28.78; mass: calculated 578.2053; found; [M$^+$ + 1] = 579.6473.

1-(6-Chloro-2-(4-hydroxy-3-methoxyphenethyl)-4-phenylquinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one **(1d)**; light yellow solid; m. p. 125–128 °C; ^{1}H NMR: δ 8.44 (d, J = 9 Hz, 1H), 7.89 (dd, J_1 = 8.9 Hz, J_2 = 1.9 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.53–7.66 (m, 3H), 7.34 (d, J = 6.9 Hz, 2H), 6.81 (d, J = 1.6 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 6.67 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz,, 1H), 6.59 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 6.37 (d, J = 1.9 Hz, 1H), 6.31 (dd, J_1 = 8 Hz, J_2 = 1.9 Hz, 1H), 5.01 (b, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 3.14–3.24 (m, 2H), 2.98–3.12 (m, 2H), 2.53 (t, J = 7.1 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H); ^{13}C NMR: δ 204.03, 156.98, 149.39, 146.93, 146.64, 144.43, 144.16, 140.61, 135.88, 135.36, 134.14, 133.02, 131.86, 131.60, 130.51, 129.87, 129.43, 126.78, 126.04, 125.60, 121.04, 120.81, 114.57, 111.39, 111.20, 55.90, 55.86, 46.67, 37.03, 36.39, 29.06; mass: calculated 567.1813; found [M$^+$ + 1] = 568.6889.

1-(6-Amino-2-(4-hydroxy-3-methoxyphenethyl)-4-phenylquinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one **(1e)**; light yellow solid; m. p. 177–179 °C; ^{1}H NMR: δ 8.17 (d, J = 9.7 Hz, 1H), 7.95 (dd, J_1 = 7.4 Hz, J_2 = 2.1 Hz, 1H), 7.94 (s, 1H), 7.48–7.54 (m, 3H), 7.32–7.37 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.76 (d, J = 1.6 Hz, 1H), 6.71 (d, J = 8 Hz, 1H), 6.68 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 6.37 (d, J = 1.6 Hz, 1H), 6.33 (dd, J_1 = 8 Hz, J_2 = 1.6 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.04–3.15 (m, 4H), 2.51 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H); ^{13}C NMR: δ 206.58, 156.62, 146.05, 145.93, 145.37, 143.69, 143.50, 135.05, 134.36, 133.24, 133.09, 131.87, 130.17, 129.79, 128.90, 128.58, 125.03, 123.26, 120.76, 120.42, 115.99, 113.90, 110.98, 110.65, 55.55, 55.47, 46.58, 38.74, 34.91, 28.85; mass: calculated 548.2311; found [M$^+$ + Na] = 571.7599.

1-(6-Chloro-4-(2-chlorophenyl)-2-(4-hydroxy-3-methoxyphenethyl) quinolin-3-yl)-3-(4-hydroxy-3-methoxyphenyl)propan-1-one **(1f)**; light yellow solid; m. p. 70–75 °C; ^{1}H NMR: δ 8.12 (d, J = 9 Hz, 1H), 7.68 (dd, J_1 = 9 Hz, J_2 = 2.3 Hz, 1H), 7.55 (dd, J_1 = 8.1 Hz, J_2 = 1 Hz, 1H), 7.46 (dt, J_1 = 8.1, J_2 = 1.7 Hz, 1H), 7.37 (dt, J_1 = 7.5 Hz, J_2 = 1.3 Hz, 1H), 7.30 (dd, J_1 = 2.3 Hz, J_2 = 0.4 Hz, 1H), 7.21 (dd, J_1 = 7.5 Hz, J_2 = 1.7 Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.64 (dd, J_1 = 8 Hz, J_2 = 1.8 Hz, 1H), 6.48 (d, J = 1.9 Hz, 1H), 6.42 (dd, J_1 = 8 Hz, J_2 = 1.9 Hz, 1H), 5.89 (b, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.12–3.17(m, 2H), 3.06–3.11(m, 2H), 2.62–2.69 (m, 1H), 2.50–2.58 (m, 2H), 2.38–2.46 (m, 1H); ^{13}C NMR: δ 205.68, 156.87, 146.20, 146.09, 145.39, 143.70, 143.67, 140.49, 135.39, 133.05, 132.97, 132.66, 131.99, 131.82, 130.90, 130.57, 130.42, 129.63, 127.06, 125.12, 124.21, 120.76, 120.45, 114.11, 111.02, 110.72, 55.46, 45.79, 38.66, 34.90, 28.49; mass: calculated 601.1423; found [M$^+$ + 1] = 602.6826.

4-((2,4-Dimethylquinolin-3-yl)methyl)-2-methoxyphenol **(2a)**; off-white solid; m. p. 208–210 °C; ^{1}H NMR: δ 8.03 (dt J_1 = 8.6 J_2 = 1.1 Hz, 2H, H-5 & H-8), 7.68 (ddd, J_1 = 8.4 Hz, J_2 = 6.8 Hz, J_3 = 1.4 Hz, 1H, H-7), 7.54 (ddd, J_1 = 8.5 Hz, J_2 = 6.7 Hz, J_3 = 1.3 Hz, 1H, H-6), 6.80 (d, J = 8.1 Hz, 1H, H-18), 6.58 (d, J = 1.7 Hz, 1H, H-15), 6.47 (dd, J_1 = 8 Hz, J_2 = 1.7 Hz, 1H, H-19), 5.74 (br, 1H, Hydroxyl at C-17), 4.23 (s, 2H, H-13), 3.79 (s, 3H, H-20), 2.68 (s, 3H, H-12), 2.64 (s, 3H, H-11); ^{13}C NMR: δ 158.62 (C-2), 146.45 (C-16), 146.02 (C-10), 143.79 (C-17), 141.78 (C-4), 130.31 (C-14), 129.73 (C-3), 128.87 (C-8), 128.15 (C-7), 126.90 (C-9), 125.30 (C-6), 123.44 (C-5), 120.10 (C-19), 114.16 (C-18), 110.11 (C-15), 55.58 (C-20), 34.42 (C-13), 24.07 (C-12), 14.24 (C-11); mass: calculated 293.1416; found [M$^+$ + 2] = 295.5308.

2-Methoxy-4-((2-methyl-4-phenylquinolin-3-yl)methyl)phenol **(2b)**; light yellow solid; m. p. 186–188 °C; ^{1}H NMR: δ 8.19 (d, J = 8.2 Hz, 1H), 7.69 (ddd, J_1 = 8.3 Hz, J_2 = 6.8 Hz, J_3 = 1.5 Hz, 1H), 7.44–7.48 (m, 3H), 7.35–7.43 (m, 2H), 7.22–7.25 (m, 2H), 6.75 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 1.5 Hz, 1H), 6.36 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 1H), 6.16 (B, 1H), 3.97 (s, 2H), 3.75 (s, 3H), 2.70 (s, 3H); ^{13}C NMR: δ 159.00, 148.17, 146.41, 145.39, 143.75, 136.53, 131.01, 129.52, 128.89, 128.77, 128.11, 127.70, 127.57, 126.68, 126.21, 125.70, 120.18, 114.11, 110.40, 55.537, 35.22, 23.50; mass: calculated 355.1572; found [M$^+$ + 2] = 357.6760.

2-Methoxy-4-((2-methyl-6-nitro-4-phenylquinolin-3-yl)methyl)phenol **(2c)**; yellow solid; m. p. 172–175 °C; ^{1}H NMR: δ 8.43 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.50–7.53 (m, 3H), 7.23–7.26 (m, 2H), 6.77 (d, J = 8.1 Hz, 1H), 6.45 (d, J_1 = 1.8 Hz, 1H), 6.36 (dd, J_1 = 8.1 Hz, J_2 = 1.8 Hz, 1H), 5.58 (b, 1H), 4.00 (s, 2H), 3.77 (s, 3H), 2.71 (s, 2H); ^{13}C NMR: δ 163.53, 148.99, 148.35, 146.35, 144.86, 143.83, 135.12, 131.57, 130.44, 130.02, 128.82, 128.53, 128.47, 125.82, 123.16, 121.96, 120.13, 114.12, 110.27, 55.55, 35.33, 24.42; mass: calculated 400.1423; found [M$^+$ + 1] = 401.4695.

Table 1
Quinoline derivatives of THC.

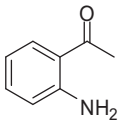
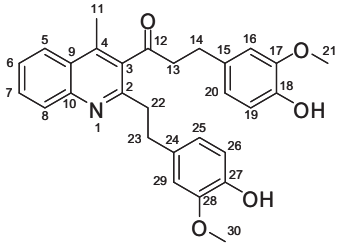
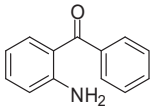
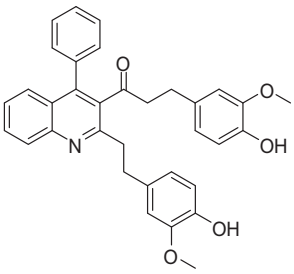
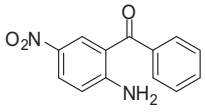
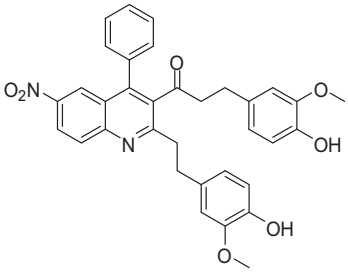
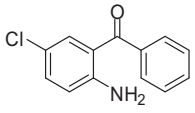
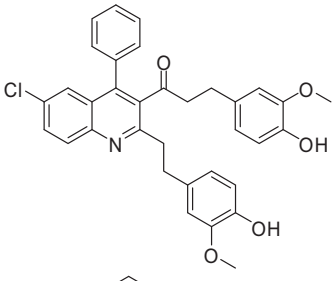
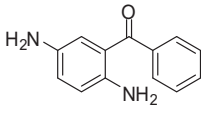
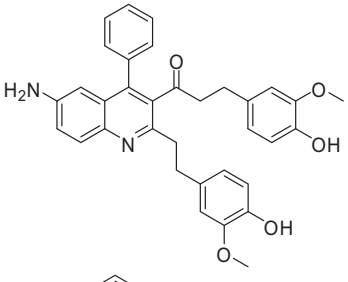
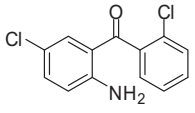
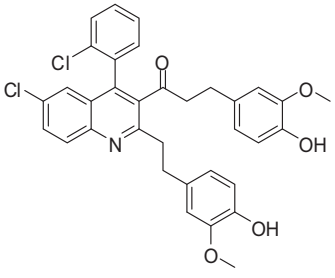
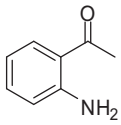
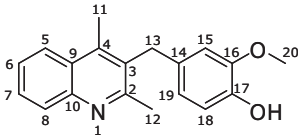
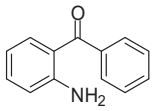
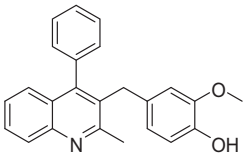
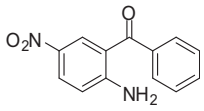
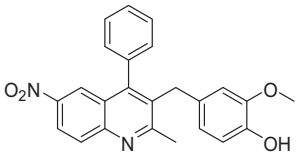
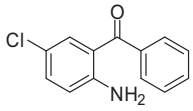
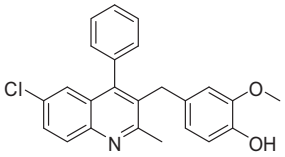
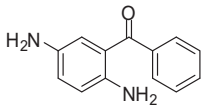
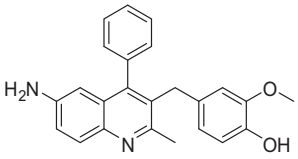
Reactant	Product	Structure	Time (min)	Yield (%)[a]
	1a		40	84
	1b		30	93
	1c		120	65
	1d		40	95
	1e		90	70
	1f		60	95

Table 2
Quinoline derivatives of zingerone.

Reactant	Product	Structure	Time (min)	Yield (%)[a]
	2a		30	90
	2b		30	96
	2c		90	70
	2d		30	86
	2e		60	56

[a] Isolated yields.

4-((6-Chloro-2-methyl-4-phenylquinolin-3-yl)methyl)-2-methoxyphenol **(2d)**; light yellow solid; m. p. 168–170 °C; ^{1}H NMR: δ 8.02 (d, J = 8.9 Hz, 1H), 7.59 (dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz, 1H), 7.45–7.48 (m, 3H), 7.31 (d, J = 2.3 Hz, 1H), 7.20–7.23 (m, 2H), 6.75 (d, J = 8.1 Hz, 1H), 6.44 (d, J = 1.7 Hz, 1H), 6.36 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H), 5.91 (b, 1H), 3.95 (s, 2H), 3.75 (s, 3H), 2.64 (s, 3H); ^{13}C NMR: δ 159.57, 146.58, 146.34, 144.61, 143.71, 136.05, 131.22, 130.93, 130.33, 129.87, 129.25, 128.88, 128.28, 127.89, 127.43, 124.94, 120.18, 114.08, 110.33, 55.52, 35.31, 23.95; mass: calculated 389.1183; found [M^+ + 1] = 390.4632.

4-((6-Amino-2-methyl-4-phenylquinolin-3-yl)methyl)-2-methoxyphenol **(2e)**: light yellow solid; m.p. 176–178 °C; ^{1}H NMR: δ 9.25 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.94 (dd, J_1 = 9 Hz, J_2 = 2.1 Hz, 1H), 7.63 (d, J = 2.1 Hz, 1H), 7.33–7.37 (m, 3H), 7.16–7.20 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 6.48 (br, 1H), 6.44 (s, 1H), 6.33 (d, J = 8 Hz, 1H), 3.95 (s, 2H), 3.73 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.44, 147.33, 146.49, 144.01, 143.77, 136.08, 132.71, 130.87, 130.48, 129.17, 128.73, 128.19, 127.83, 126.94, 122.18, 120.07, 116.72, 114.16, 110.47, 55.47, 35.29, 23.60; mass: calculated 370.1681; found [$M^+ - 1$] = 369.6773.

2.4. Radical-scavenging activity of quinolines by DPPH method

Radical-scavenging activity of several quinoline derivatives was analysed by DPPH method (Moon & Terao, 1998). Individual samples were prepared by dissolving each compound in methanol (1 mg/ml). The samples were assayed at different concentrations with suitable dilutions, making them up to 1 mL with 100 mM Tris–HCl buffer (pH 7.4), followed by addition of 4 mL of 2,2-diphenyl-1-picrylhydrazyl (0.1 mM solution in methanol) and mixing the contents by vigorous shaking. Controlswere prepared by the same protocol wherein the compound was not included. The tubes were incubated in the dark at room temperature for 20 min. The absorbance was then recorded at 517 nm using methanol as a blank for baseline correction. The % radical-scavenging activity was calculated using the following formula:

$$\text{Radical-scavenging activity}(\%) = [(\text{Control OD}-\text{Sample OD})/\text{Control OD}] \times 100$$

All the experiments were carried out in triplicate. EC_{50} values reported correspond to the concentration of the derivatives where 50% RSA was observed.

2.5. Antibacterial studies of quinolines

The antibacterial assay of quinolines was tested by the pour plate method against *Bacillus cereus* (F 4810, Public Health Laboratory, London, UK), *Staphylococcus aureus* (FRI 722, Public Health Laboratory, The Netherlands), *Escherichia coli* (MTCC 108, Microbial Type Culture Collection, Institute of Microbial Technology, Chandigarh, India) and *Yersinia enterocolitica* (MTCC 851, Microbial Type Culture Collection, Institute of Microbial Technology, Chandigarh, India) by the method of Negi, Jayaprakasha, Rao, and Sakariah (1999). Samples were prepared by dissolving the compounds in DMSO. To flasks containing 20 mL of melted warm agar, different concentrations of test material in DMSO were added. An equivalent amount of DMSO was used as controls. One hundred μL (about 10^3 cfu/mL) of test bacterium was inoculated into the flasks under aseptic conditions. The media were then mixed and poured onto sterilized Petri plates and incubated at 37 °C for 24 h for growth. The minimum inhibitory concentration (MIC) value, i.e., the lowest concentration of the compound capable of inhibiting the complete growth of the bacterium being tested, was determined for each

compound by carrying out the experiments in duplicate and was repeated three times.

2.6. Statistical analysis

All the experiments were repeated three times and the data were calculated as mean ± SD. The data of all the assays were analysed by one-way ANOVA. The Duncan's multiple range test (DMRT) was used to make the comparisons (Gomez & Gomez, 1984).

3. Results and discussion

3.1. Synthesis of quinoline derivatives of tetrahydrocurcmin and zingerone

The method is very useful as no solvent is used for the reaction and TFA is easily available and inexpensive. In a typical experiment, reaction of 2-aminoacetophenone with THC was carried out using TFA at 100 °C. Completion of the reaction was indicated by solidification of the reaction mass and further

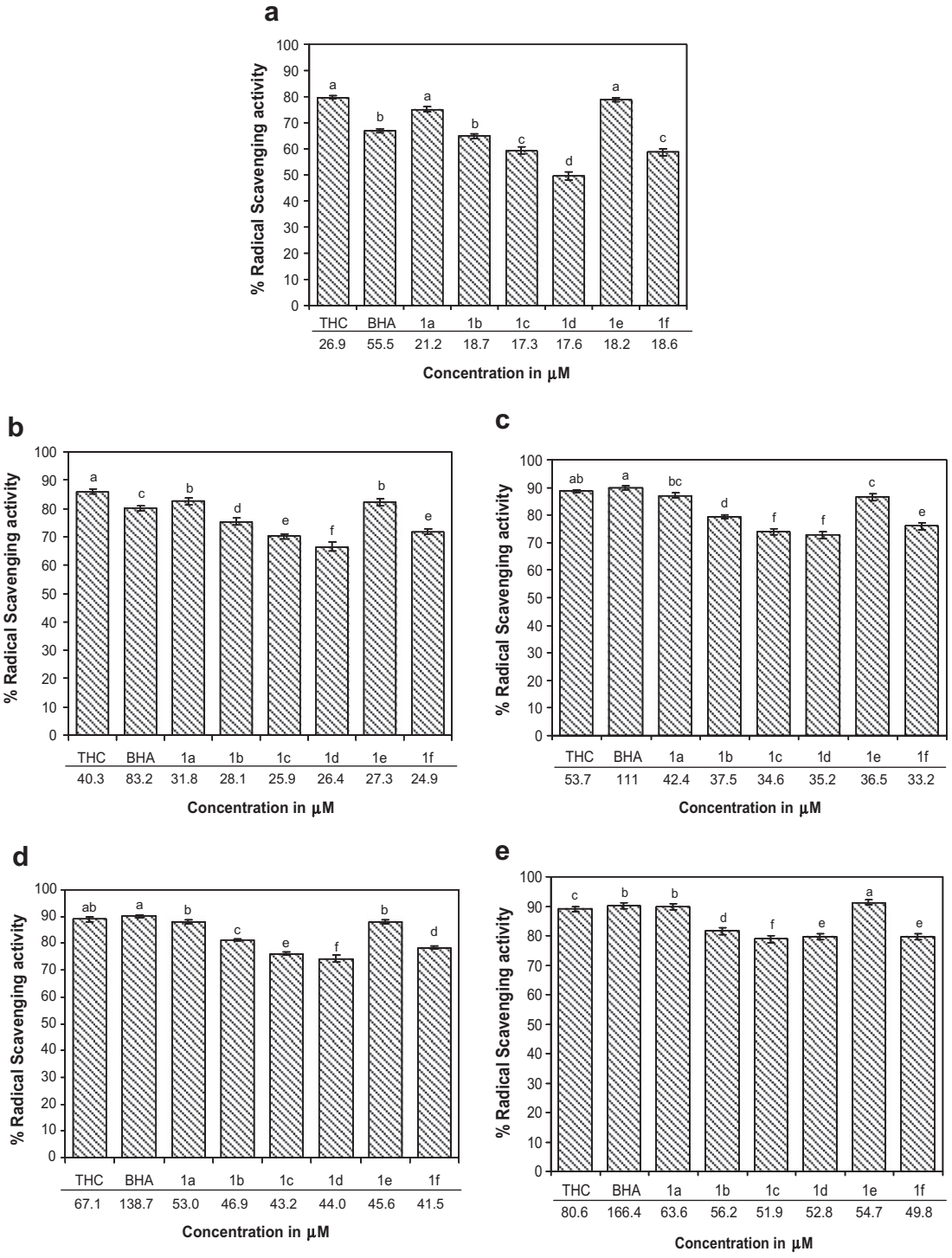


Fig. 2. RSA of quinoline derivatives **1a–1f** compared with THC and BHA; bar graphs **a–e** represents concentration 10, 15, 20, 25 and 30 ppm, respectively. Bars followed by same letter are not significantly ($p \leqslant 0.05$) different.

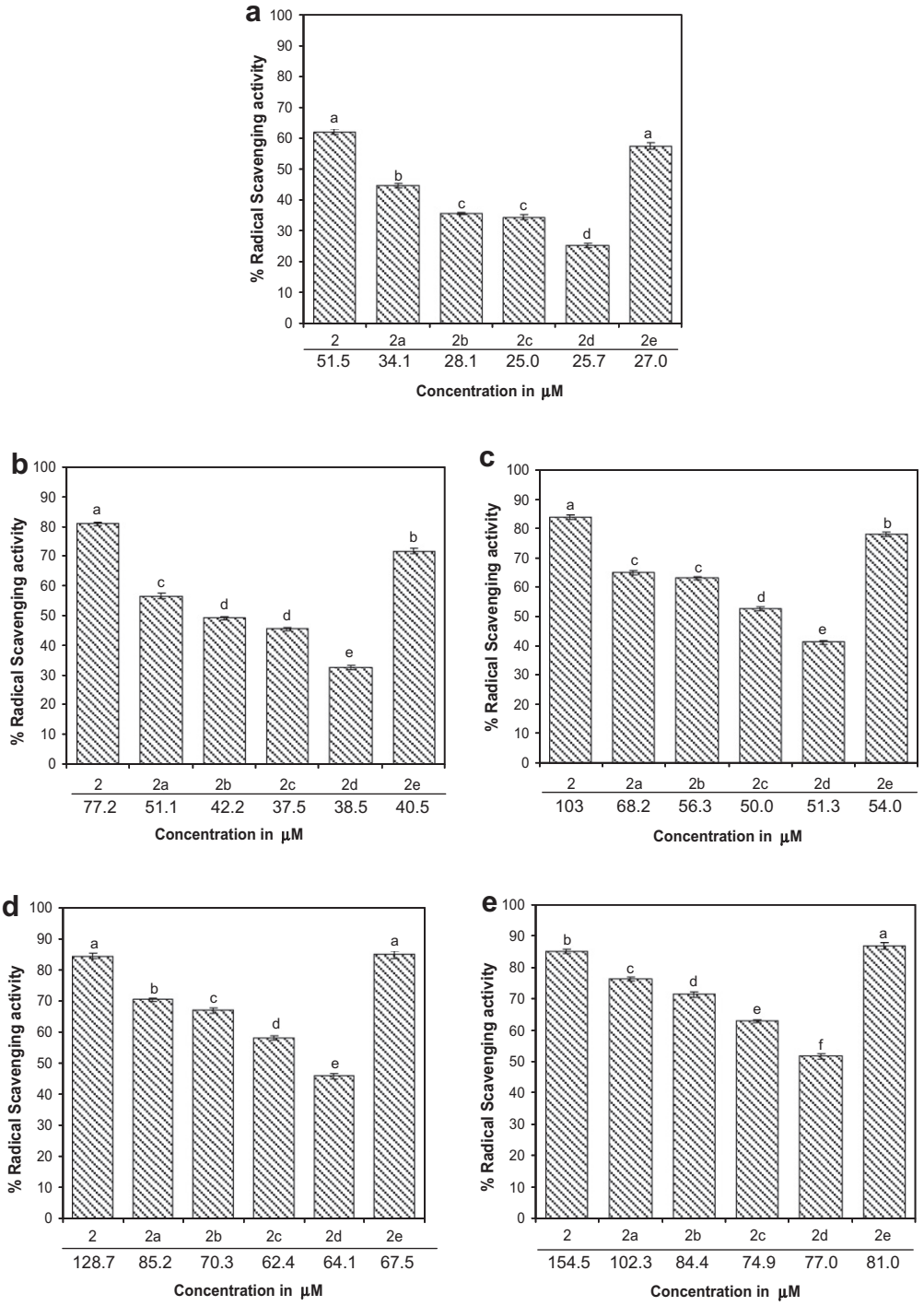


Fig. 3. RSA of quinoline derivatives **2a**–**2e** compared with zingerone; bar graphs **a**–**e** represent concentrations of 10, 15, 20, 25 and 30 ppm, respectively. Bars followed by same letter are not significantly ($p \leqslant 0.05$) different.

confirmed by TLC analyses. Neutralisation with saturated $NaHCO_3$ resulted in product separation, which was filtered, washed and dried. Further, trituration of the crude product with ethyl acetate and petroleum ether afforded the pure compound (**1a**, Fig.1). Similarly, substituted quinoline derivatives (**1b**–**1f**) were synthesised from the reaction of various substituted 2-aminobenzophenones with THC. Further, the scope of the reaction was extended to zingerone, a bio-active ingredient of ginger containing a methylene group alpha to a carbonyl moiety. The substituted quinoline derivatives of zingerone (**2a**–**2e**) were conveniently prepared as above, except in the case of the dichloro substituted benzophenone. The prolonged heating (>3 h) of the reaction mixture containing dichloro aminobenzophenone resulted in its dimerisation.

All the syntheses were carried out on 5 mmol scale of 2-aminoacetophenone and substituted 2-aminobenzophenones with 1.2 equivalents of THC and zingerone in the presence of 2–3 mL TFA under solvent free conditions at 100 °C for 0.5–3 h. The reaction times in the case of the preparation of un-substituted quinolines (entries 1 & 2, Tables 1 and 2) were usually shorter than those for reactions with substituted quinolines. The product yield was good to excellent in all cases (56–96%).

To our knowledge, all synthesised compounds (Fig. 1) are new and are reported here for the first time. They have been characterised by ^{1}H NMR, ^{13}C-NMR spectral data and HRMS. The ^{1}H NMR of **1a**–**1f** and **2a**–**2e** for the proton at the 8th position was observed down field (8.0–8.7 ppm) compared to the same in the reactant which usually manifests at 6.5–7 ppm. This is the common feature observed in quinoline derivatives. The signals at 153–163 ppm in ^{13}C-NMR are assigned to a quaternary carbon at the second position of compounds **1a**–**1f** and **2a**–**2e** which is typical of quinoline compounds. Further, from 2D-NMR spectral analyses, the nature and correlation of protons and carbons were confirmed. In the HMBC spectra of compounds **1a**–**1f,** the correlation of methylene protons with the quaternary carbon of the quinoline nucleus indicated the attachment of THC with quinoline (Fig. 1). In the case of compounds **2a**–**2e**, the HMBC correlations of the benzylic proton of zingerone with four quaternary and two carbons in the aromatic nucleus, ascertain connectivity between two moieties involved in the annulations.

3.2. Radical-scavenging activities of quinoline derivatives of tetrahydrocurcumin and zingerone

Radical-scavenging assays were carried out for THC and zingerone, using standard BHA as reference. Compounds were dissolved in methanol at 10–30 ppm concentrations, which corresponded to different micro molar concentrations as indicated in Figs. 2 and 3. Similarly, quinoline derivatives of THC (**1a**–**1f**) and zingerone (**2a**–**2e**) were dissolved in methanol at 10–30 ppm concentrations and the radical-scavenging activity (RSA) for all the compounds was determined by the DPPH$^{\bullet}$ method. In all cases, the RSA was proportional to the concentration. The EC_{50} values determined for THC, zingerone and BHA were 16.8, 41.6 and 41.5 μmol, respectively. Radical-scavenging activities of THC, zingerone and BHA were 79.8%, 61.8% and 66.8% at 10 ppm, respectively, and at 15 ppm the values were 86%, 81% and 80%, respectively, showing THC to be a more powerful antioxidant at lower concentrations (10–15 ppm). At higher concentrations (20 to 30 ppm), THC and BHA showed comparable antioxidant activity, but was superior to zingerone. The RSA of 90% was achieved with **1e** at a much lower concentration (~55 μmol) compared with **1**, which showed a similar effect only at a higher concentration (~80 μmol). However, derivatives **1a, 1b, 1c** and **1f** exhibited lower activities compared to those of **1e**. This is also reflected by the EC_{50} value of **1e** (11.5 μmol) compared to those of **1a**, **1b**, **1c** and **1f** (14.1–14.5 μmol). The THC quinoline derivative **1d** displayed the lowest RSA at all concentrations and also had the EC_{50} value of 17.8 μmol. Earlier workers have suggested that THC exhibits the same physiological and pharmacological properties as the active form of curcumin *in vivo* by means of its β-diketone moiety as well as the phenolic hydroxy groups (Sugiyama, Kawakishi, & Osawa, 1996). In the quinoline derivatives of THC one of the keto groups is involved in the quinolone ring formation, but the phenolic groups are intact. This explains the marginal reduction in the radical scavenging activity of the compounds **1b-1d** and **1f**. In the case of zingerone derivatives, the amino-substituted quinoline **2e** had the lowest EC_{50} value of 22.7 μmol. The corresponding EC_{50} values for **2b, 2c, 2d** and **2f** were 38.3, 39.5, 36.3 and 73.3 μmol, respectively. The derivative **2e** showed better RSA (78%) compared to zingerone (**2**) and its derivatives (**2a-2d**) at ~50–55 μmol concentrations. Here again, the carbonyl group in zingerone is involved in the quinoline ring formation, but the phenolic group is unaffected which could explain the slight reduction in their radical scavenging activity. The quinoline derivatives of both THC and zingerone (**1e and 2e**) with aminobenzophenone substitution exhibited the most potent radical scavenging activity due to the presence of an electron donating amino ($-NH_2$) group. In contrast, derivatives of THC and zingerone with aminobenzophenone having the electron withdrawing groups, NO_2 (**1c** and **2c**) and Cl (**2c and 2d**) had the lowest antioxidant activity. This Structure–Activity Relationship (SAR) exhibited by the RSA of these derivatives underscores the influence of the nature of the substituents on the antioxidant action of the compounds.

3.3. Antibacterial activities of quinoline derivatives of tetrahydrocurcumin and zingerone

Compounds **1a**–**1f** and **2a**–**2e** were tested for their antibacterial potential against two Gram-positive (*B. cereus* and *S. aureus*) and two Gram-negative bacteria (*E. coli* and *Y. enterocolitica*). The MIC values of these compounds are presented in Table 3. Among all the compounds tested, **2d** was the most effective against Gram-positive and **1c** was the most effective against Gram- negative bacteria as the MIC values were lowest for these compounds against tested bacteria. In general, **2d**, **1c** and **1b** were found to be very effective against all the bacteria tested in the present study. Compounds **1e**, **2c** and **2e** showed moderate activity, but **1**, **2** and **2a** were less effective against the tested bacteria. The antibacterial activity of **2b** was very high against *B. cereus,* but it was ineffective against *S. aureus, Y. enterocolitica* and *E. coli*. Similarly **1e** and **1f** showed better activity against *B. cereus* than against the other bacteria.

A comparable trend has been observed for various natural and synthetic compounds displaying variable activity depending on compound and bacterium (Negi, Jayaprakasha, & Jena, 2010; Parvathy et al., 2009). While comparing the activity of individual compounds against bacteria, it was observed that almost all the compounds showed higher MIC values against Gram-negative bacteria than against Gram-positive ones. A similar trend of higher resistance to Gram-negative bacteria than Gram-positive bacteria is reported in the literature and this effect has been attributed to their differences in cell structure (Negi, Jayaprakasha, & Jena, 2008; Nostro, Germano, D'Angelo, Marino, & Cannatelli, 2000). The Gram-positive bacteria contain an outer peptidoglycan layer, which is an ineffective permeability barrier (Scherrer & Gerhardt, 1971). In the case of Gram-negative bacteria, the outer phospholipidic membrane is impermeable to lipophilic solutes. In addition, porins present in the cell membrane act as a selective barrier to the hydrophilic solutes, thus making the cells resistant to antibacterial compounds (Nikaido & Vaara, 1985).

In conclusion, a facile and efficient synthetic protocol has been delineated for the synthesis of several novel quinoline derivatives of THC and zingerone. The results of their *in vitro* biological assays demonstrated that certain quinoline derivatives of THC and

Table 3
MIC of quinoline derivatives of THC and zingerone against gram-positive and gram-negative bacteria.

Entry	Compound	MIC (μM)			
		B. cereus	*S. aureus*	*Y. enterocolitica*	*E. coli*
1	**1**	1049	1311	2098	1704
2	**1a**	724	983	931	1242
3	**1b**	503	914	686	823
4	**1c**	422	674	506	843
5	**1d**	774	946	860	817
6	**1e**	534	800	711	978
7	**1f**	649	973	811	933
8	**2**	1256	>2000	>2000	>2000
9	**2a**	>2000	>2000	>2000	>2000
10	**2b**	412	1098	1030	1236
11	**2c**	609	792	853	975
12	**2d**	219	501	752	877
13	**2e**	593	790	856	1054

zingerone possess significant antioxidant and antibacterial properties. The effects revealed that the modification carried out with THC and zingerone at its carbonyl functionality in the side chain of these molecules improved the antibacterial and antioxidant attributes. An interesting structure–activity relationship was identified as the quinoline derivative with the electron-donating amino group exhibited the most potent radical-scavenging activity. These molecules may have important pharmacological applications.

Acknowledgments

J.R.M. thanks the Indian Council of Medical Research, New Delhi, India for the scholarship. The authors are grateful to Dr. G. Venkateswara Rao, Director, CFTRI and Dr. M.C. Varadaraj, Head, Human Resources Development, CFTRI for their support and constant encouragement for the work. The help of Mr. Padmere Mukund Lakshman in the MS studies of the compounds is gratefully acknowledged.

References

Aggarwal, B. B., Kumar, A., Aggarwal, M. S., & Shishodia, S. (2005). *Phytopharmaceuticals in cancer chemoprevention, curcumin derived from turmeric (Curcuma longa): A spice for all seasons*. CRC Press LLC, pp. 350–379.

Anand, P., Thomas, S. G., Kunnumakkara, A. B., Sundaram, C., Harikumar, K. B., Sung, B., et al. (2008). Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. *Biochemical Pharmacology, 76*, 1590–1611. and references cited therein.

Bharathi, S. G., Parvathy, K. S., Srinivas, P., Indi, S. S., & Rao, K. S. (2012). Curcumin-glucoside, a novel synthetic derivative of curcumin, inhibits α-synuclein oligomer formation: Relevance to Parkinson's disease. *Current Pharmaceutical Design, 18*(1), 76–84.

Bose, D. S., & Kumar, R. K. (2006). An efficient, high yielding protocol for the synthesis of functionalized quinolines via the tandem addition/annulation reaction of *o*-aminoaryl ketones with α-methylene ketones. *Tetrahedron Letters, 47*, 813–816.

Chen, Y. L., Fang, K. C., Sheu, J. Y., Hsu, S. L., & Tzeng, C. C. (2001). Synthesis and antibacterial evaluation of certain quinoline derivatives. *Journal of Medicinal Chemistry, 44*, 2374–2377.

De, S. K., & Gibbs, R. A. (2005). A mild and efficient one-step synthesis of quinolines. *Tetrahedron Letters, 46*, 1647–1649.

Denmark, S. E., & Venkatraman, S. (2006). On the mechanism of the Skraup–Doebner–Von Miller quinoline synthesis. *The Journal of Organic Chemistry, 71*, 1668–1676.

Gomez, K. A., & Gomez, A. A. (1984). Comparison between treatment means. In K. A. Gomez & A. A. Gomez (Eds.), *Statistical procedures for agricultural research* (pp. 207–240). New York: Wiley.

Gupta, S. C., Prasad, S., Kim, J. H., Patchva, S., Webb, L. J., Priyadarsini, I. K., et al. (2011). Multitargeting by curcumin as revealed by molecular interaction studies. *Natural Product Reports, 28*, 1937–1955.

Joe, B., Vijaykumar, M., & Lokesh, B. R. (2004). Biological properties of curcumin – Cellular and molecular mechanisms of action. *Critical Reviews in Food Science and Nutrition, 44*(2), 97–111.

Kim, D. S. H. L., & Kim, J. Y. (2004). Side-chain length is important for shogaols in protecting neuronal cells from β-amyloid insult. *Bioorganic and Medicinal Chemistry Letters, 14*, 1287–1289.

Kouznetsov, V. V., Mendez, L. Y. V., & Gomez, C. M. M. (2005). Recent progress in the synthesis of quinolines. *Current Organic Chemistry, 9*(2), 141–161.

Maguire, M. P., Sheets, K. R., Vety, K. M., Spada, A. P., & Zilberstein, A. (1994). A new series of PDGF receptor tyrosine kinase inhibitors: 3-Substituted quinoline derivatives. *Journal of Medicinal Chemistry, 37*, 2129–2137.

Moon, J., & Terao, J. (1998). Antioxidant activity of caffeic acid and dihydrocaffeic acid in lard and human low-density lipoprotein. *Journal of Agricultural Food Chemistry, 29*, 273–300.

Negi, P. S., Jayaprakasha, G. K., & Jena, B. S. (2008). Antibacterial activity of the extracts from the fruit rinds of *Garcinia cowa* and *Garcinia pedunculata* against food borne pathogens and spoilage bacteria. *LWT Food Science Technology, 41*, 1857–1861.

Negi, P. S., Jayaprakasha, G. K., & Jena, B. S. (2010). Evaluation of antioxidant and antimutagenic activities of the extracts from the fruit rinds of *Garcinia cowa*. *International Journal of Food Properties, 13*, 1256–1265.

Negi, P. S., Jayaprakasha, G. K., Rao, L. J. M., & Sakariah, K. K. (1999). Antibacterial activity of turmeric oil: A by-product from curcumin manufacture. *Journal of Agricultural and Food Chemistry, 47*, 4297–4300.

Nikaido, H., & Vaara, M. (1985). Molecular basis of bacterial outer membrane permeability. *Microbiological Reviews, 49*, 1–32.

Nostro, A., Germano, M. P., D'Angelo, V., Marino, A., & Cannatelli, M. A. (2000). Extraction methods and bio-autography for evaluation of medicinal plant antimicrobial activity. *Letters in Applied Microbiology, 30*, 379–384.

Pan, M.-H., Huang, T. M., & Lin, J. K. (1999). Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metabolism and Disposition, 27*(1), 486–494.

Parvathy, K. S., Negi, P. S., & Srinivas, P. (2009). Antioxidant, antimutagenic and antibacterial activities of curcumin-β-diglucoside. *Food Chemistry, 115*, 265–271.

Parvathy, K. S., Negi, P. S., & Srinivas, P. (2010). Curcumin–amino acid conjugates: Synthesis, antioxidant and antimutagenic attributes. *Food Chemistry, 120*, 523–530.

Pulbutr, P., Thunchomnang, K., Lawa, K., Mangkhalathon, A., & Saenbol, P. (2011). Lipolytic effects of zingerone in adipocytes isolated from normal diet-fed rats and high fat diet-fed rats. *International Journal of Pharmacology, 7*, 629–634.

Scherrer, R., & Gerhardt, P. (1971). Molecular sieving by the *Bacillus megaterium* cell wall and protoplast. *Journal of Bacteriology, 107*, 718–735.

Shaabani, A., Soleimani, E., & Badri, Z. (2007). Triflouroacetic acid as an efficient catalyst for the synthesis of quinoline. *Synthetic Communications, 37*, 629–635.

Sharma, R. A., Gescher, A. J., & Steward, W. P. (2005). Curcumin: The story so far. *European Journal of Cancer, 41*, 1955–1968.

Sneharani, A. H., Sridevi Annapurna Singh Srinivas, P., & Appu Rao, A. G. (2011). Inhibition of lipoxygenase-1 by tetrahydrocurcumin. *European Food Research Technology, 233*, 561–568.

Sugiyama, Y., Kawakishi, S., & Osawa, T. (1996). Involvement of the beta-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. *Biochemical Pharmacology, 52*(4), 519–525.

Wang, G. W., Jia, C. S., & Dong, Y. W. (2006). Benign and highly efficient synthesis of quinolines from 2-aminoarylketone or 2-aminoarylaldehyde and carbonyl compounds mediated by hydrochloric acid in water. *Tetrahedron Letters, 47*, 1059–1063.

Wang, Y., Branicky, R., Stepanyan, Z., Carroll, M., Guimond, M.-P., Abdelmadjid Hihi, A., et al. (2009). The anti-neurodegeneration drug clioquinol inhibits the aging-associated protein CLK-1. *Journal of Biological Chemistry, 284*(1), 314–323.