Med Chem Res
DOI 10.1007/s00044-012-0117-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, antioxidant, and antibacterial studies of phenolic esters and amides of 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid

Sheelavanth Shankerrao · Yadav D. Bodke · Sundar S. Mety

Received: 4 January 2012 / Accepted: 22 May 2012

Abstract A new series of phenolic esters **2**(**a**–**j**) and amides **3**(**a**–**c**) of 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid were synthesized by the reaction of 2-(1-benzofuran-2-yl)-quinoline-4-carboxylic acid (**1**) with various substituted phenols and secondary amines using ethyl-(*N*′,*N*′-dimethylamino)propyl carbodiimide hydrochloride (EDC.HCl) as a coupling agent. The newly synthesized compounds were evaluated for in vitro antioxidant and antibacterial activity. Among all tested compounds **2a**, **2c**, **2e**, and **2h** showed good chelating ability with Fe^{+2} ions, whereas compounds **2g** and **2j** exhibited good scavenging activity with DPPH free radicals. Concerning antibacterial activities compounds **2a**, **2b**, **2c**, and **2h** were found to be equipotent to ampicillin against *Enterococcus* sp and *Staphylococcus aureus*, while compound **2e** is found to be as potent as ampicillin against *Pantoea Dispersa* and *Ochrobactrum* sp. amide derivatives **3**(**a**–**c**) were found to be less potent when compared to standard.

Keywords Phenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate · Antioxidant activity · Antibacterial activity

S. Shankerrao · Y. D. Bodke (✉)
Department of P.G. Studies and Research in Industrial Chemistry, School of Chemical Sciences, Kuvempu University, Jnana Sahyadri, Shankarghatta 577 451, Shivamogga Dist, Karnataka, India
e-mail: ydbodke@gmail.com

S. S. Mety
Department of Botany, Gulbarga University, Jnana Ganga, Gulbarga 585 106, Karnataka, India

Introduction

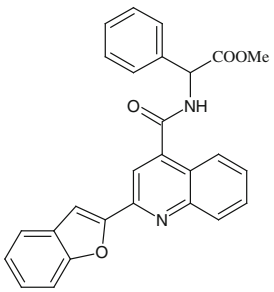
Antioxidants are gaining a lot of importance as universal remedy for a wide range of lifestyle-related diseases like early aging, cancer, diabetes, cardiovascular, and other degenerative diseases etc. owing to our deskbound way of life and stressful existence. Added to these are the harmful effects of pollution and exposure to carcinogenic chemicals. All these can cause accumulation of harmful free radicals. The main characteristic of an antioxidant is its ability to entrap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate degenerative disease (Jung *et al.*, 1999; Pietta *et al.*, 1998). Antioxidant compounds like phenolic acids, polyphenols, and flavonoids scavenge free radicals such as peroxide, hydroperoxide or lipid peroxyl and thus inhibit the oxidative mechanisms that lead to degenerative diseases (Van Acker *et al.*, 1996).

2-Heteroarylbenzofuran ring systems are widely distributed in nature and have been reported to possess antioxidant, antiviral, and antifungal activities (Fuganti and Serra, 1998; Abdel-Wahab *et al.*, 2009; Akgul and Anil, 2003; Venkatesh and Bodke, 2010; Ahmad *et al.*, 2006; Kirilmis *et al.*, 2008; Manna and Agrawal, 2009). Kapche *et al.* (2009) isolated prenylated 2-aryl benzofuran derivatives from *Morus mesozygia* plant and these compounds found to possess potent antioxidant property. Many researchers have demonstrated the efficient scavenging ability of 3-arylbenzofuranone derivatives on both carbon and oxygen centered radicals and are widely used as excellent antioxidants for polymers (Xin *et al.*, 2006; Solera, 1998; Pospisil and Nespurek, 1995; Michele and Paul, 2002; Peter *et al.*, 1995; Michael *et al.*, 2002). Benzofuran derivative extracted from yeast was

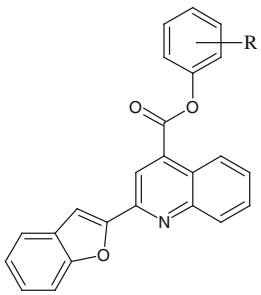
Published online: 07 June 2012

shown to protect in vitro the erythrocytes of vitamin E deficient rats from hemolysis (Jinno and Otsuka, 1999).

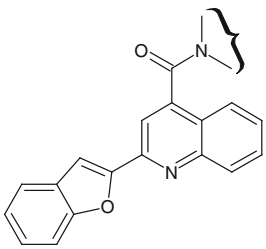
Cinchophen (2-phenyl quinoline-4-carboxylic acid) was first synthesized by Doebner and Giesecke in 1887 and was introduced into the therapeutic application by Weintraub in 1911 as a uricosuric agent in the treatment of gout. Later, cincophen and its numerous derivatives have been found to possess wide range of physiological functions such as uricosuric, analgesic, antiinflammatory etc. (Mishra *et al.*, 1988; Short and Bauer, 1957). Merely few reports were found about synthesis of 2-(benzofuran-2-yl) quinoline-4-carboxylic acid (Chatterjea, 1955; Bisagni *et al.*, 1955; Ardashev and Gaidzhurova, 1968); further this moiety was not exploited till now to get new compounds except one molecule methyl 2-(2-(benzofuran-2-yl) quinoline-4-carboxamido)-2-phenyl acetate [**I**] which was reported as a potent Selective Non-Peptide antagonists of Human neurokinin-3 receptor (Giardina *et al.*, 1997). Therefore, to exploit further in the present investigation



[I]



[II]



[III]

we are reporting the synthesis and characterization hitherto unknown 2-(1-benzofuran-2-yl) quinoline-4-substituted derivatives containing 2-(benzofuran-2yl) quinoline as a pharmacophore; phenyl carboxylates [**II**] **2**(**a**–**j**) and tertiary amides [**III**] **3**(**a**–**c**). Further it comprises the evaluation of antioxidant activity using two models namely DPPH free radical scavenging assay, which is more efficient and reliable; another model is iron chelating assay, it is important because in earlier reports it is mentioned that common antioxidants inactivate ROS (reactive oxygen species) only after they have been formed, but iron chelators are able to prevent their formation. Iron can redox-cycle between its two states—Fe^{2+} and Fe^{3+}—and acts as a catalyst for hydroxyl radical formation (Fenton and Haber–Weiss reactions). Iron chelation is considered to be an important tool to decrease anthracycline cardiotoxicity as documented by the beneficial effect of dexrazoxane (Schroeder and Hasinoff, 2002) as well as other chelators of iron (Šimůnek *et al.*, 2005; Štěrba *et al.*, 2006). Further the new compounds were investigated for antibacterial potency against four selected causative organisms agar-well diffusion method and minimum inhibitory concentration (MIC) was determined by serial broth-dilution method.

Results and discussion

Chemistry

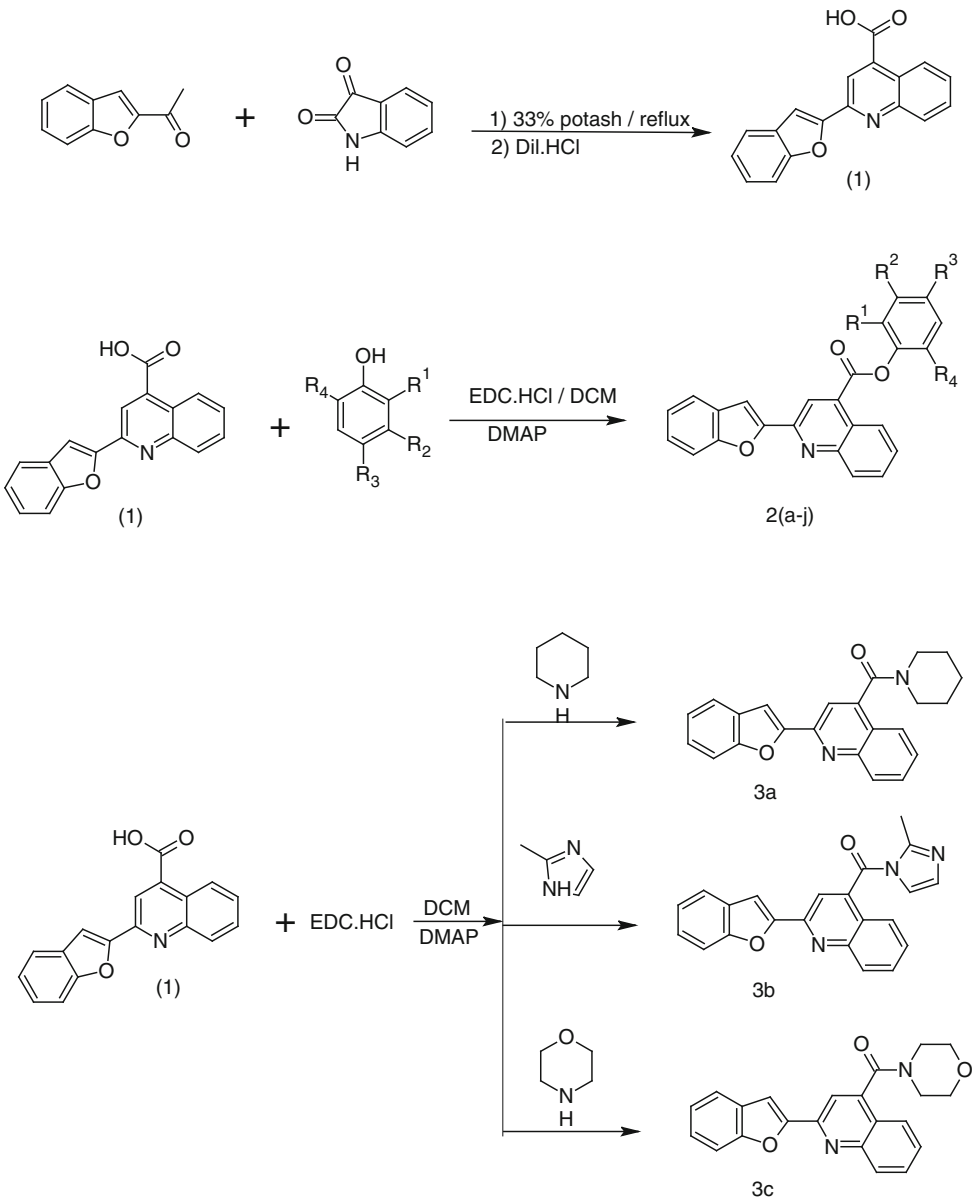
The key intermediate 2-(1-Benzofuran-2-yl) quinoline-4-carboxylic acid (**1**) was synthesized by Pfitzinger method (Ardashev and Gaidzhurova, 1968) which involves the reaction of 2-acetyl benzofuran with isatin under basic condition. Compound (**1**) upon reaction with different substituted phenols using EDC.HCl as a coupling reagent in the presence of catalytic amount of dimethyl ammonium pyridine furnished corresponding phenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate derivatives **2**(**a**–**j**). In the same way when piperidine, morpholine, and 2-methyl imidazole were made to react with compound **1** under same reaction condition, it furnished the corresponding tertiary amides **3a**–**c** (Scheme 1). The structures of newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and Mass Spectral data. The characterization data of the newly synthesized compounds are given in Table 1.

Antioxidant activity

Chelating ability of metal ion

Initially ferrozine quantitatively forms complex with Fe^{+2} ions present in the solution. In the presence of chelating agent, the initial complex was competitively destroyed and hence resulting in the reduction in red color. The reduction in color allows for estimation of the ability of test compounds to form stable complex by chelating with metal ions. The results of chelating ability of different esters with Fe^{+2} were shown in Fig. 1. The range and mean of Fe^{+2} chelating capacities varied significantly among different

Scheme 1 Synthesis of esters **2a–j** and amides **3a–c** of 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid



compounds on the basis of substitution on the molecules (Fig. 1). Phenyl ester **2a** and para substituted phenyl esters, **2c**, **2e**, and **2h** have showed good chelating ability. When phenyl ring replace with bulkier rings like 1-nephthol, **2i** and 2-nephthol, **2j**, respectively exhibited decreasing trend in chelating ability.

Scavenging effect on DPPH

The radical scavenging activities of synthesized compounds were carried out using methanolic solution of the stable free radical, DPPH. The freshly prepared DPPH solution exhibits a deep purple color with the absorption maximum at 517 nm. This purple color generally fades when antioxidant is present in the medium. The results of DPPH scavenging activities of different esters were shown in Fig. 2. The lone pair electrons present on the ring heteroatom may be responsible for blocking the DPPH free radical by donating electron pair and hence fading the color. From the Fig. 2, it is clear that **2j** and **2g** have showed excellent scavenging activity, whereas compound **2i**, **2d**, and **2c** showed moderate activity. Further the IC_{50} values of compounds showing good scavenging activity were determined and the results are shown in Table 2. The results reveal that compound **2j** and **2g**, respectively showed lower concentration of 15.6 and 24.3 μg/mL.

Antibacterial activity

The experiment designed to investigate the antibacterial potency of the phenolic esters and tertiary amides of

Table 1 Characterization data of compounds **2**(**a**–**j**) and **3**(**a**–**c**)

Comp. code	R1	R2	R3	R4	Molecular formula	Melting point (°C)	% yield
2a	H	H	H	H	$C_{24}H_{15}NO_3$	137	72
2b	CH_3	H	H	H	$C_{25}H_{17}NO_3$	142	85
2c	H	H	CH_3	H	$C_{25}H_{17}NO_3$	173	89
2d	Cl	H	H	H	$C_{24}H_{14}NO_3Cl$	181	70
2e	H	H	Cl	H	$C_{24}H_{14}NO_3Cl$	202	68
2f	Cl	H	Cl	H	$C_{24}H_{13}NO_3Cl_2$	168	68
2g	Cl	H	Cl	Cl	$C_{24}H_{12}NO_3Cl_3$	190	65
2h	H	H	Br	H	$C_{24}H_{14}NO_2Br$	163	80
2i	1-Naphathol				$C_{28}H_{17}NO_3$	218	84
2j	2-Naphathol				$C_{28}H_{17}NO_3$	182	86
3a	Piperdine				$C_{23}H_{20}N_2O_2$	124	73
3b	Morpholine				$C_{22}H_{18}N_2O_3$	165	78
3c	2-Methyl imidazole				$C_{22}H_{15}N_3O_2$	104	75

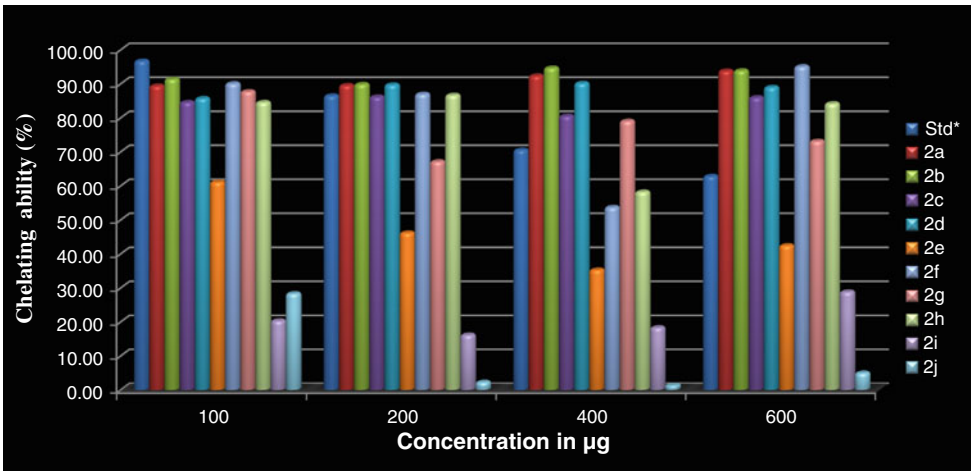


Fig. 1 Ferrous ion chelating activity of test compounds

2-(benzofuran-2-yl) quinoline-4-carboxylic acid against selected species *Pantoea dispersa*, *Ochrobacterium* species, *Entercoccus* species, and *staphylococcus aureus.* The preliminary test was done using agar-well diffusion method; further the antibacterial potency of the compounds was quantified by determining MIC using serial broth-dilution method. The results are presented in Table 3. The obtained data revealed that all tested compounds were inhibited the growth of the tested micro-organisms in vitro showing MIC values ranging from 0.5 and 0.06 mg mL^{-1}. Among phenolic esters **2**(**a**–**j**), the compounds **2a**, **2b**, **2c**, and **2h** against *S. aureus*; compound **2c** and **2h** against *Entercoccus* sp.; compound **2a** and **2d** against *Ochrobacterium* species and compound **2d** against *Pantoea dispersa* have showed MIC's at lowest concentration of 0.06 mg/mL, respectively and these results are comparable with the standard ampicillin MIC's values. All other compounds showed varying degrees of MIC values from 0.12 to above 0.5 mg/mL. Among tertiary amides **3**(**a**–**c**), compound **3c** showed the MIC of 0.12 mg/mL against *Entercoccus* species and compounds **3a** showed MIC of 0.25 mg/mL against *Pantoea dispersa*, *Ochrobacterium* species. From the results it is evident that on varying the functionalities on the phenyl ring of ester group **2**(**a**–**j**) has shown modest effect on the antibacterial potency. On substituting methyl group on ortho and para position in **2b**, **2c**, respectively retained the activity without much variation. Among chloro substituted derivatives, *o*-chloro substituted derivative **2d** found to be less active than para chloro derivative **2e**, further declining trend in activity was found in 2,4-dichloro, 2,4,6-trichloro substituted derivatives **2g**, **2h**, respectively. When phenyl ring was replaced with bulkier 1-naphthol and 2-naphthol ring system in compound **2i**, **2j**, respectively showed decrease in activity. From the results it clearly indicates that by increasing the bulkiness of the phenyl ring either by increasing the number of substitution **2**(**f**–**g**) or by replacing phenyl ring with other bulkier rings **2**(**i**–**j**) leads to the decrease in activity. All tertiary amide derivatives piperdanyl, morpholinyl, and 2-methyl imidazolyl **3**(**a**–**c**) showed low activity against all tested organisms.

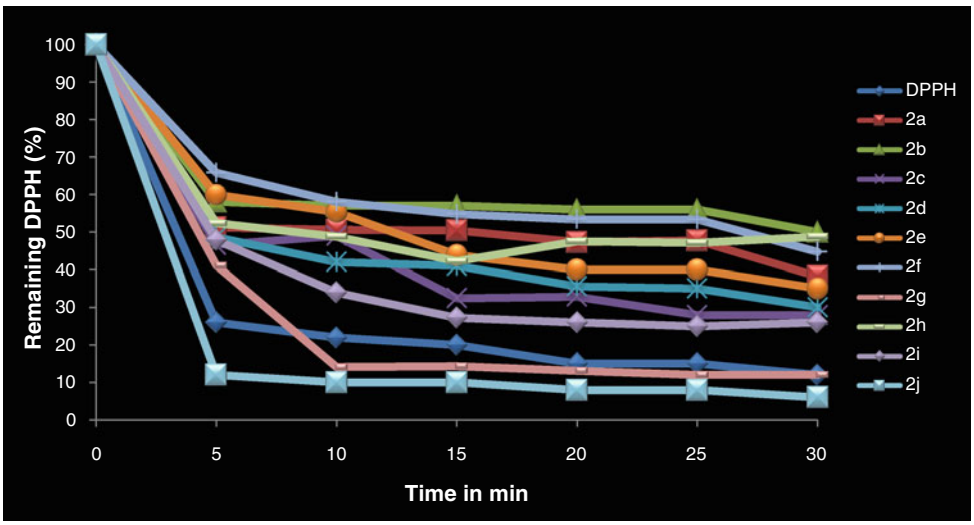


Fig. 2 DPPH free radical scavenging activity of test compounds

Table 2 IC_{50} values of DPPH scavenging activity

Compound	DPPH (IC_{50}) (μg/mL)
2c	49.5 ± 0.4*
2d	≫100
2g	24.34 ± 0.1*
2i	45.6 ± 0.5*
2j	15.6 ± 0.18*

* Each value represents the mean value of three determinations ± standard deviation. * $P \leq 0.05$

Experimental

All the chemicals used were of analytical grade. Melting points were determined in open capillary and are uncorrected. Purity of the compounds was checked by TLC on silica gel. ^{1}H NMR spectra were recorded on a Bruker supercon FT NMR (400 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 and TMS as an internal standard. The chemical shifts are expressed in δ units. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

Table 3 Zone of inhibition and MIC values of compounds **2**(**a**–**j**) and **3**(**a**–**c**)

Zone of inhibition in mm (1 mg/mL)					Minimum inhibitory concentration (MIC mg/mL)			
Compound	*Pantoea dispersa* 100 μL	*Ochrobactrum* sp 100 μL	*Enterococcus* sp 100 μL	*S. aureus* 100 μL	*Pantoea dispersa*	*Ochrobactrum* sp	*Enterococcus* sp	*S. aureus*
2a	18	16	12	16	0.12	0.06	0.12	0.06
2b	19	18	16	17	0.12	0.025	0.06	0.06
2c	13	20	19	19	0.25	0.06	0.06	0.06
2d	16	14	10	12	0.12	0.25	0.5	0.5
2e	18	17	14	17	0.06	0.06	0.12	0.12
2f	16	14	11	14	0.12	0.12	0.25	0.25
2g	14	12	10	12	0.25	0.5	0.5	0.5
2h	14	15	16	18	0.5	0.25	0.06	0.06
2i	15	11	13	14	0.12	0.5	0.5	0.25
2j	12	12	10	12	0.25	>0.5	>0.5	0.5
3a	10	09	07	11	>0.5	>0.5	>0.5	>0.5
3b	15	12	09	08	0.25	0.25	>0.5	>0.5
3c	13	11	13	10	0.25	0.5	0.12	>0.5
Std *Ampicillin*	20	21	24	20	0.06	0.06	0.06	0.06

General method of synthesis of 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid (1)

The compound (1) was synthesized by literature method (Chatterjea, 1955; Bisagni *et al.*, 1955; Ardashev and Gaidzhurova, 1968); with slight modification. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate to suspend impurities in organic layer. Then aqueous layer was acidified with dilute hydrochloric acid. The resulting yellow solid mass was filtered and dried to get pure compound. The melting point was 243–246 °C (literature 248–50 °C).

*2-(Benzofuran-2-yl) quinoline-4-carboxylic acid (**1**)*

IR (KBr) (v, cm^{-1}), IR 3426.9 (OH), 1702.1 (C=O), 1599, 1510, 1246. ^{1}H NMR (DMSO-d_6, 400 MHz): 14.15 (s, 1H, COOH), 8.70–8.72 (d, $J = 8.4$, 1H Ar–H), 8.48 (s, 1H quinoline 3C–H), 8.18–8.20 (d, $J = 8.4$, 1H Ar–H), 8.014–8.018(d, $J = 16$, 1H, Ar–H),7.78–7.82 (q, 2H, Ar–H), 7.72–7.77 (t, 1H, Ar–H), 7.45–7.49 (t, 1H,Ar–H), 7.34–7.38 (t, 1H, Ar–H). MS: $m/z = 290.1$ (M+1), 291.1 (M+2).

General method for synthesis of compounds **2**(**a**–**j**)

An equimolar mixture of 2-(1-benzofuran-2-yl)quinoline-4-carboxylic acid 0.578 g (2 mmol) and various phenols were taken in 10 ml of dichloromethane. To that 0.768 g (4 mmol) of EDC.HCl and catalytic amount of dimethylaminopyridine is added and the reaction mixture was stirred at room temperature for about 10 h. After completion of the reaction, the solvent was evaporated to dryness and the resulting product quenched with water, filtered, dried, and recrystallized from diethyl ether to furnish compounds **2**(**a**–**j**).

*Phenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2a**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.81 (s, 1H) 8.71–8.73 (d, $J = 8$, 1H), 8.25–8.27 (d, $J = 8$, 1H), 8.03 (s, 1H), 7.93–7.97 (t, 1H), 7.79–7.84 (t, 3H), 7.46–7.50 (m, 5H), 7.35–7.41 (t, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.75(1C), 156.77 (1C), 156.2(1C), 150.57(1C), 149.39(1C), 138.67(1C), 134.64(1C), 130.45(1C), 130.06(1C), 129.82(2C), 129.69(1C), 128.97(1C), 128.12(1C), 127.48(1C), 126.38(1C), 125.28 (1C), 124.09(1C), 123.3(1C), 123.56(1C), 122.34(1C), 121.63(2C) and 120.84(1C) MS: $m/z = 366.12$ (M+1).

*2-Methylphenyl 2-(1-benzofuran-2-yl)quinoline-4-carboxylate (**2b**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.79 (s, 1H) 8.70–8.72 (d, $J = 8$, 1H), 8.25–8.27 (d, $J = 8$, 1H), 8.05 (s, 1H), 7.93–7.96 (t, 1H), 7.78–7.83 (t, 3H), 7.46–7.50 (m, 1H), 7.35–7.40 (m, 5H), 2.51 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.47(1C), 156.82(1C), 155.2(1C), 149.45(1C), 149.24(1C), 147.8(1C), 138.72(1C), 135.6(1C), 134.54(1C), 131.44(1C), 130.48(1C), 130.10(1C), 129.85(1C), 129.01(1C), 128.17(1C), 127.50(1C), 127.22(1C), 126.58(1C), 125.33(1C), 123.8 (1C), 123.3(1C), 121.90(1C), 120.82(1C), 102.7(1C) and 18.52(1C). MS: $m/z = 379(M^+)$, 380 (M+1).

4-Methylphenyl 2-(1-benzofuran-2-yl)quinoline-4-carboxylate (2c)

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.79 (s, 1H) 8.70–8.72 (d, $J = 8$, 1H), 8.24–8.27 (d, $J = 12$, 1H), 8.05 (s, 1H), 7.93–7.97 (t, 1H), 7.79–7.84 (t, 3H), 7.46–7.50 (m, 1H), 7.35–7.40 (m, 5H) 2.51 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.47(1C), 156.82(1C), 155.2(1C), 149.24(1C), 148.4(1C), 147.8(1C), 138.72(1C), 135.6(1C), 135.2(1C), 134.54(1C), 130.48(1C), 130.10(1C), 129.01(2C), 128.17(1C), 127.50 (1C), 127.22(1C), 123.8(1C), 123.3(1C), 121.60(2C), 120.82(1C), 111.5(1C), 102.7(1C) and 24.52(1C). MS: $m/z = 379(M^+)$, 380 (M+1).

*2-Chlorophenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2d**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.85–8.87 (t, $J = 8$, 2H), 8.29–8.31 (d, $J = 8$, 1H), 7.82–7.86 (t, 1H), 7.67–7.73 (q, 1H), 7.79–7.84 (t, 4H), 7.39–7.45 (m, 3H), 7.30–7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.17(1C), 155.82(1C), 155.2 (1C), 149.35(1C), 149.24(1C), 147.8(1C), 138.72(1C), 135.6 (1C), 134.54(1C), 131.44(1C), 130.48(1C), 130.10(1C), 129.85(1C), 129.01(1C), 128.17(1C), 127.50(1C), 127.22(1C), 126.58(1C), 125.33(1C), 123.80(1C), 123.3(1C), 121.90(1C), 120.82(1C) and 102.7(1C) MS: $m/z = 400.62$ (M+1).

*4-Chlorophenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2e**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.87–8.90 (t, $J = 12$, 2H), 8.29–8.31 (d, $J = 8$, 1H), 7.82–7.86 (t, 1H), 7.67–7.73 (q, 1H), 7.79–7.84 (t, 4H), 7.39–7.45 (m, 3H), 7.30–7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.80(1C), 156.82(1C), 155.2 (1C), 149.24(1C), 148.4(1C), 147.8(1C), 138.72(1C), 135.6 (1C), 135.2(1C), 134.54(1C), 131.48(1C), 130.10(1C), 129.02(2C), 128.17(1C), 127.50(1C), 127.22(1C), 123.8(1C), 123.2(1C), 123. 01(2C), 120.82(1C), 111.5(1C) and 102.7(1C) MS: $m/z = 399.04$ (M^+), 400.65 (M+1).

*2,4-Dichlorophenyl 2-(1-benzofuran-2-yl)quinoline-4-carboxylate (**2f**)*

^{1}H-NMR ($CDCl_3$, 400 MHz: 8.84–8.87 (t, $J = 12$, 2H), 8.29–8.31 (d, $J = 8$, 1H), 7.82–7.87 (t, 1H), 7.67–7.74

(q, 4H), 7.60 (s, 1H), 7.40–7.43 (m, 2H) 7.27–7.34 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.32, 157.45, 149.59, 149.22, 138.12, 134.79, 131.48, 131.33, 130.29, 129.12, 129.61, 128.82, 126.54, 126.34, 125.78, 124.58, 122.43 and 121.19. MS: $m/z = 434.17$ (M^+), 435.12 (M+1).

*2,4,6-Trichlorophenyl 2-(1-benzofuran-2-yl)quinoline-4-carboxylate (**2g**)*

^{1}H-NMR ($CDCl_3$, 400 MHz: 8.85–8.87 (t, $J = 8$, 2H), 8.30–8.32 (d, $J = 8$, 1H), 7.82–7.87 (t, 1H),7.67–7.74 (q, 4H), 7.60 (s, 1H), 7.40–7.44 (m, 1H) 7.27–7.34 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.80(1C), 156.82(1C), 155.2(1C), 150.24(1C), 148.4(1C), 147.8(1C), 138.72(1C), 135.6(1C), 135.2(1C), 134.54(1C), 133.48(1C), 132.7(2) 130.10(1C), 128.8(2C) 128.17(1C), 127.50(1C), 127.22(1C), 123.8(1C), 123.2(1C), 123. 01(1C), 111.5(1C) and 102.7(1C) MS: $m/z = 471.34$ (M^{+2}).

*4-Bromophenyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2h**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.85–8.89 (t, 2H), 8.28–8.31 (d, $J = 12$, 1H), 7.82–7.86 (t, 1H), 7.67–7.73 (q, 1H), 7.79–7.84 (t, 4H), 7.39–7.45 (m, 3H), 7.30–7.35 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 164.80(1C), 156.82(1C), 155.2(1C), 150.24(1C), 148.4(1C), 147.8(1C), 138.72(1C), 135.6(1C), 135.2(1C), 134.54(1C), 131.48(2C), 130.10 (1C), 129.02(1C), 128.17(1C), 127.50(1C), 127.22(1C), 123.8(1C), 123.2(1C), 123.01(2C), 119.82(1C), 111.5(1C) and 102.7(1C) MS: $m/z = 445.01$ (M+1).

*Naphthalen-1-yl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2i**)*

^{1}H-NMR ($CDCl_3$, 400 MHz: 8.90–8.92 (d, $J = 8$, 1H), 8.84 (s, 1H), 8.30–8.32 (d, $J = 8$, 1H), 7.99–8.01 (d, $J = 8$, 1H),7.84–7.92 (q, 4H), 7.67–7.75 (q, 4H), 7.49–7.56 (t, 3H) 7.40–7.43 (t, 1H) 7.27–7.34 (q, 1H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 165.10(1C), 156.82(1C), 155.2(1C), 150. 24(1C), 148.4(1C), 147.8(1C), 138.72(1C), 135.6(1C), 135.2(1C), 134.7(1C), 133.48(1C), 132.7(1C) 130.10(1C), 128.8(2C) 128.17(1C), 127.50(1C), 127.22(1C), 126.32(2C), 125.1(1C), 123.8(1C), 123.2(1C), 123.01(1C), 121.7(1C), 121.1(1C), 111.5(1C), 109.5(1C) and 102.7 (1C) MS: $m/z = 416.10$ (M+1).

*Naphthalen-2-yl 2-(1-benzofuran-2-yl) quinoline-4-carboxylate (**2j**)*

^{1}H-NMR ($CDCl_3$, 400 MHz: 8.89–8.92 (d, $J = 12$, 1H), 8.86 (s, 1H), 8.30–8.32 (d, $J = 8$, 1H), 7.99–8.01 (d, $J = 8$, 1H), 7.86–7.92 (q, 4H), 7.67–7.75 (q, 4H), 7.49–7.56 (t, 3H) 7.40–7.43 (t, 1H) 7.27–7.34 (q, 1H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 165.10(1C), 156.82(1C), 155.2(1C), 150.24(1C), 148.4 (1C), 147.8(1C), 138.72(1C), 135.6(1C), 135.2(1C), 134.7(1C), 133.48(1C), 132.7(1C) 130.10(1C), 129.8(1C), 129.1 (1C), 127.50(1C), 127.22(1C), 126.7(1C), 126.32(2C), 125.1(1C), 123.8(1C), 123.2(1C), 121.7(1C), 121.1(1C), 117.5(1C),111.5(1C), 109.5(1C) and 102.7(1C) MS: $m/z = 416.10$ (M+1).

*[2-(1-Benzofuran-2-yl) quinolin-4-yl](piperidin-1-yl) methanone (**3a**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.16–8.18 (d, $J = 8$, 1H), 8.10 (s, 1H), 7.94 (s, 1H), 7.86–7.90 (q, 1H), 7.78–7.82 (q, 3H), 7.68–7.72 (t, 1H), 7.44–7.50 (q, 1H), 7.33–7.37 (t, 1H), 3.84–3.88 (m, 1H), 3.71–3.76 (m, 1H), 3.13–3.16 (t, 2H), 1.65–1.71 (m, 4H), 1.44–1.48 (q, 1H), 1.32–1.37 (q, $J = 20$, 1H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 172.31(1C), 156.86(1C), 155.23(1C), 149.92(1C), 146.8(1C), 146.4(1C), 130.42(1C), 129.21(1C), 128.4(1C), 128.0(1C) 124.7(1C), 123.84(1C), 123.32(1C), 121.72(1C), 120.76(1C), 117.4(1C), 111.58(1C), 102.711(1C), 35.1(2C), 25.73 (2C), and 24.5(1C) MS: $m/z = 357.41$ (M+1).

*[2-(1-Benzofuran-2-yl) quinolin-4-yl](morpholin-4-yl) methanone (**3b**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.76 (s, 1H) 8.14–8.17 (q, 2H), 7.81–7.83 (d, $J = 8$, 1H), 7.75–7.79 (m, 1H), 7.78–7.81 (d, $J = 12$, 1H), 7.58–7.61 (q, 1H), 7.55–7.56 (d, $J = 4$, 1H), 7.50–7.54 (m, 1H), 6.46–6.49 (q, 1H), 3.85–3.91(m, 4H), 3.19–3.26 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 168.9(1C), 156.8 (1C), 155. 32 (1C), 149.92 (1C), 146.8(1C), 146.4(1C), 130.42(1C), 129.21(1C), 128.4(1C), 128.0(1C), 124.7(1C), 123.84(1C), 123.32(1C), 121.72(1C), 120.76(1C), 117.54(1C), 111.58(1C), 102.711 (1C), 65.8(2C), and 46.1(2C), MS: $m/z = 359$ (M+1).

*[2-(1-Benzofuran-2-yl) quinolin-4-yl](2-methyl-1H-imidazol-1-yl) methanone (**3c**)*

^{1}H-NMR ($CDCl_3$, 400 MHz): 8.74 (s, 1H), 8.27–8.29 (d, $J = 12$, 1H) 8.16–8.20 (q, 2H), 7.97 (s, 1H), 7.82–7.84 (m, 1H), 7.78–7.81 (d, $J = 12$, 1H), 7.59–7.62 (d, $J = 12$, 1H), 7.56–7.58 (q, 1H), 7.54–7.55 (m, 2H), 6.80–6.85 (q, 2H), 2.83 (s, 1H, $-CH_3$). ^{13}C-NMR ($CDCl_3$, 100.5 MHz): 167.82(1C), 158.6(1C), 155.3(1C), 149.92(1C), 146.8(1C), 146.4(1C), 135.2(1C), 132.4(1C), 130.42(1C), 129.21(1C), 128.4(1C), 128.0(1C), 124.7(1C), 123.84(1C), 123.32(1C), 121.72(1C), 120.76(1C), 117.4(1C), 115.6(1C), 111.5(1C), 108.3, 106.6, 102.7(1C), and 17.4(1C) MS: $m/z = 354.31$ (M+1).

Antioxidant activity

Chelating effects on ferrous ions

The chelating effect was determined according to the method of Decker and welch (1990), (Nevcihan *et al.,* 2010). In brief, 2 mL of different concentrations (0.5–2.0 mg/mL) of the compound in methanol was added to a solution of 2 mM $FeCl_2$ (0.05 mL). The reaction was initiated by the addition of 5 mM ferrozine (0.2 mL) and total volume was adjusted to 5 mL with methanol. Then, the mixture was shaken vigrously and left at room temperature for 10 min. Absorbance of the solution was measured spectrophotometrically at 562 nm. The inhibition percentage of ferrozine-Fe^{+2} complex formation was calculated using the formula given below.

$$\text{Metal chelating effect}\ (\%) = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/ A_{\text{control}}\right] \times 100$$

where $A_{control}$ is the absorbance of control (the control contains $FeCl_2$ ferrozine complex formation molecules) and A_{sample} is the absorbance of test compound. Ascorbic acid is used as control.

Scavenging effect on DPPH

The hydrogen atoms or electrons donation ability of the corresponding test compounds and standard compound were measured from the bleaching of purple colored methanol solution of DPPH. The effect of methanolic solution of the test compounds on DPPH radical was estimated according to Kerby and Schimdt (1997). In brief, 0.004 % DPPH radical solution in methanol was prapared and then 4 mL of this solution was mixed with 1 mL of various concentrations (1 mg/mL) of the test compounds in methanol. Finally, the samples were incubated for 30 min in dark at room temperature and scavenging capacity was read spectrophotometrically by monitoring the decrease in absorbance at 517 nm. Inhibition of free radical DPPH in percent (1 %) was calculated in following way.

$$1\,\% = 100 \times (A_1 - A_2)/A_o$$

where A_1 was the absorbance of DPPH solution in the presence of the test compound, A_2 was the absorbance without DPPH solution, and A_0 was the absorbance of control (DPPH solution without the test compound).

Further the compounds which exhibited good scavenging activity were assayed by performing the experiment at different concentrations by serial dilution method. The IC_{50} was calculated when allowed according to the scavenging efficiency.

Antibacterial activity

The bacterial strains were obtained from the laboratory stock culture from the Department of biochemistry Gulbarga University, Gulbarga. All synthesized compounds were dissolved in dimethyl formamide (DMF) to prepare chemicals stock solution at the concentration of 1 mg/mL. The antibacterial activity was carried out by agar-well diffusion method which is a simple susceptibility screening method. Each microorganism was suspended in nutrient broth and diluted approximately colony forming unit (cfu)/mL. They were "flood-inoculated" onto the surface of nutrient agar and then dried. Five millimeter diameter wells were cut from the agar using a sterile cork-borer; 100 µL of the test compound solution were delivered into the wells. The plates were incubated for 24 h at 35 °C. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin was used as standard drug and dimethyl formamide is used as solvent control.

Determination of the MICs

MIC was determined by micro-broth dilution technique using nutrient broth. Serial twofold dilutions ranging from 1,000 to 0.031 mg/mL were prepared in media. The inoculum was prepared using a 4–6 h old broth culture of each bacterium and diluted in broth media to give a final concentration of 5×10^5 cfu/mL of bacteria in the test tray. The trays were covered and placed in plastic bags to prevent evaporation and are incubated at 35 °C for 18–20 h. The MIC was defined as the lowest concentration of the compound giving complete inhibition of visible growth.

Acknowledgments The authors are thankful to IISc Bangalore for providing spectral data. One of the authors (Sheelavanth S) is thankful to DST-Govt. of India, for awarding Inspire fellowship.

References

Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM (2009) Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-aryl-butan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles. Eur J Med Chem 44: 2632–2635

Ahmad G, Mishra PK, Gupta P, Yadav PP, Tiwari P, Tamrakar AK, Srivastava AK, Maurya R (2006) Synthesis of novel benzofuran isoxazolines as protein tyrosine phosphatase 1B inhibitors. Bioorg Med Chem Lett 16:2139–2143

Akgul YY, Anil H (2003) A new benzofuran and a new cyclobutaoxirene from the seeds of Styrax officinalis (600 g). Phytochem 63:939–943

Ardashev BI, Gaidzhurova VP (1968) Analogs of atophan containing a furan nucleus. Khimiya Geterotsiklichskikhi Soedineii 4: 202–203

Bisagni M, Buu-Hol, Royer R (1955) Oxygen heterocycles part III; the reactivity of benzofurans and 2-alkylbenzofuran. J Chem Soc. doi:10.1039/JR9550003681

Chatterjea JN (1955) Experiments on the synthesis of furano compounds part V. J Indian Chem Soc 32:265–272

Decker EA, Welch B (1990) Role of ferritin as a lipid oxidation catalyst in muscle food. J Agric Food Chem 38:674–677

Fuganti C, Serra S (1998) A new approach to 2-aryl-7-alkoxy-benzofurans: synthesis of ailanthoidol, a natural neolignan. Tetrahedron Lett 39:5609–5610

Giardina GAM, Sarau HM, Farina C, Medhurst AD, Grugni M, Raveglia LF, Schmidt DB, Rigolio R, Luttmann M, Vecchietti V, Hay DWP (1997) Discovery of a novel class of selective non-peptide antagonists for the human neurokinin-3 receptor. 1. identification of the 4-quinolinecarboxamide frame work. J Med Chem 40:1794–1807

Jinno S, Otsuka N (1999) Total synthesis of a natural antioxidant and structure activity relationships of related compounds. Chem Pharm Bull 47:1276–1283

Jung HA, Park JC, Chung HY, Kim J, Choi JS (1999) Antioxidant flavonoids and chlorogenic acid from the leaves of *Eriobotrya japonica*. Arch Pharm Res 22:213–218

Kapche GDWF, Christian DF, Jean HD, Ghislain WF, Dawe A, Angèle NT, Merhatibeb B, Paul FM, Bonaventure TN, Berhanu MA (2009) Prenylated arylbenzofuran derivatives from *Morus mesozygia* with antioxidant activity. Phytochemistry 70:216–221

Kirby AJ, Schimdt RJ (1997) The antioxidant activity of Chinese herbs for eczema and placebo herbs. J Ethnopharmacol 56:103–108

Kirilmis C, Ahmedzade M, Servi S, Koca M, Kizirgil A, Kazaz C (2008) Synthesis and antimicrobial activity of some novel derivatives of benzofuran: Part 2 The synthesis and antimicrobial activity of some novel 1-(1-benzofuran-2-yl)-2-mesitylethanone derivatives. Eur J Med Chem 43:300–308

Manna K, Agrawal YK (2009) Microwave assisted synthesis of new indophenazine 1,3,5-trisubstruted pyrazoline derivatives of benzofuran and their antimicrobial activity. Bioorg Med Chem Lett 19:2688–2692

Michael T, Samuel A, Peter N (2002) Process for the preparation of 3-arylbenzofuranones. US 6417358

Michele G, Paul D (2002) Process for the preparation of 3-aryl-benzofuran-2-ones. EP 1170296

Mishra P, Agrawal RK, Maini UK (1988) Cinchophen analogs as analgesic and antiinflammatory agents. Indian J Pharm Sci 50: 269–271

Nevcihan G, Cengiz S, Bektas T, Halil SM (2010) Evaluation of antioxidant activities of 3 edible mushrooms; *Ramaria flava, Rhizopogan roseolusand Russula delica*. Food Sci Biotech 19(3): 691–696

Peter N, Samuel E, Ralf S (1995) Process for the production of 3-arylbenzofuranones. EP 0648765

Pietta P, Simonetti P, Mauri P (1998) Antioxidant activity of selected medicinal plants. J Agric Food Chem 46:4487–4490

Pospisil J, Nespurek S (1995) Chain-breaking stabilizers in polymers: the current status. Polym Degrad Stab 49:99–110

Schroeder PE, Hasinoff BB (2002) The doxorubicin-cardioprotective drug dexrazoxane undergoes metabolism in the rat to its metal ion-chelating form ADR-925. Cancer Chemother Pharmacol 50:509–513

Short CL, Bauer W (1957) Cinchophen hypersensitiveness a report of four cases and a review. Ann Intern Med 470:826–834

Šimůnek T, Klimtová I, Kaplanová J, Štěrba M, Mazurová Y, Adamcová M, Hrdina R, Geršl V, Poňka P (2005) Study of daunorubicin cardiotoxicity prevention with pyridoxal isonicotinoyl hydrazone in rabbits. Pharmacol Res 51:223–231

Solera P (1998) New trends in polymer stabilization. J Vinyl Add Tech 4(3):197–210

Štěrba M, Popelová O, Šimůnek T, Mazurová Y, Potáčová A, Adamcová M, Kaiserová H, Poňka P, Geršl V (2006) Cardioprotective effects of a novel iron chelator, pyridoxal 2-chlorobenzoyl hydrazone, in the rabbit model of daunorubicin-induced cardiotoxicity. J Pharmacol Exp Ther 319:1336–1347

Van Acker SABE, Van Den Berg DJ, Tromp MNJL, Desiree HG, Wout PVB, Wim JFVV, Bast A (1996) Structural aspects of antioxidant activity of flavonoids. Free Radical Bio Med 20: 331–342

Venkatesh KB, Bodke YD (2010) Synthesis of some mannich bases and novel benzofuran derivatives containing imidazo[2,1-b][1,3,4]thiadiazoles as biological agents. Curr Chem Biol 4:15–145

Xin M, Weiguang G, Zhong X, Zhi C (2006) Study on the antioxidant activities of benzofuranones in melt processing of polypropylene. Poly Degrad Stab 91:2888–2893