Arabian Journal of Chemistry (2013) **xxx**, xxx–xxx

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants

Javarappa Rangaswamy [a], Honnaiah Vijay Kumar [b,*], Salakatte Thammaiah Harini [a], Nagaraja Naik [a,*]

[a] *Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore 570006, Karnataka, India*
[b] *Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, Karnataka, India*

Received 15 January 2013; accepted 21 October 2013

KEYWORDS

Benzofuran;
Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds;
Benzoyl chlorides;
Free radicals;
Antioxidant activity;
Antimicrobial activity

Abstract A new class of functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a–q**) was synthesized by a four step reaction in good yields. Initially, *o*-alkyl derivative of salicyaldehyde (**1**) readily furnished corresponding 2-acetyl benzofuran (**2**) on treatment with potassium *tert*-butoxide (*t*-BuOK) in the presence of molecular sieves. Further, Claisen–Schmidt condensation reaction with 4-methoxy benzaldehyde and hydrazine hydrate followed by coupling of benzoyl chlorides afforded target compounds (**4a–q**). Representative of the synthesized compounds was characterized by IR, ^{1}H NMR, ^{13}C NMR, mass, elemental analysis and evaluated for antimicrobial and antioxidant activities. The results gathered are allowed to conclude that, all newly synthesized analogues exhibit a certain degree of antimicrobial and antioxidant activities. Among the analogues, compounds (**4h**) and (**4j**) showed an excellent antimicrobial activity in the well plate method. Meanwhile, compounds (**4e–f**), (**4l**) and (**4p**) showed good antioxidant activity, whereas compound (**4g**) and (**4q**) displayed dominant antioxidant efficacy compared to standard butylated hydroxy anisole (BHA).

1. Introduction

Benzofuran derivatives are an important class of heterocyclic compounds that are known to possess important biological properties. The chemistry of benzofurans in a large number of natural products has attracted a widespread interest due to their biological activities and their potential applications as pharmacological agents. Benzofurans have played an important role in medicinal chemistry and have drawn considerable attention due to their profound physiological and chemotherapeutic proper-

* Corresponding authors. Tel.: +91 9845348582 (H.V. Kumar), +91 9482959088 (N. Naik).
E-mail addresses: rangaswamyteertha@gmail.com (J. Rangaswamy), vijaycftri@gmail.com (H.V. Kumar), st.harini988@gmail.com (S.T. Harini), drnaikchem@gmail.com (N. Naik).

Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

1878-5352 © 2013 King Saud University. Production and hosting by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.arabjc.2013.10.012

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

ties (Vinod et al., 2012) Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature, *e.g.*, ailanthoidol (Fig. 1), an neolignan derivative, has been reported to have antiviral, antioxidant and antifungal activities (Kao and Chern, 2001).

Furthermore, most of the compounds prepared from 2-acetylbenzofuran have antimicrobial, anticancer, antitumor, anti-inflammatory activity, antitubulin and also used for treatment of cardiac arrhythmias (Basawaraj et al., 2001; Rida et al., 2006; Ujjinamatada et al., 2006; Romagnoli et al., 2008). Benzofuran nucleus may be combined with nitrogen heterocycles in different ways and the compounds including pyrazole nucleus (Fig. 2) are known to possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitor, antidiabetic and antibacterial activities (Parekh et al., 2011; Abdel-Wahab et al., 2008, 2009; Kamal et al., 2006). In recent years, 1,3,5 trisubstituted pyrazole bearing benzofuran derivatives exhibited a broad-spectrum of antimicrobial activities (Zdemir et al., 2007). Some benzofuran derivatives such as 2-acetylbenzofuran and 2-nitrobenzofuran are well-known biodynamic agents possessing various pharmacological properties (Kadin, 1972). On the other side pyrazoline derivatives are the electron rich nitrogen heterocycles which play an important role in the diverse biological activities. These heterocyclic compounds widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell. Considerable attention has been focused on the pyrazolines and substituted pyrazolines due to their interesting biological activities (Mohamad and Payal, 2011).

The literature survey approaching to the synthesis of pyrazole gathered with benzofuran moiety indicates the few references available. In the interest of the above suggestion and in continuation of our research work on the synthesis of novel classes of biologically active heterocyclic derivatives (Kumar and Naik, 2010; Kumar et al., 2011; Naik et al., 2011a,b) and encouraged by the successful results obtained from these works, we inspired to design and synthesize the functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds and examined their biological activities.

2. Experimental

2.1. General

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and used as provided.

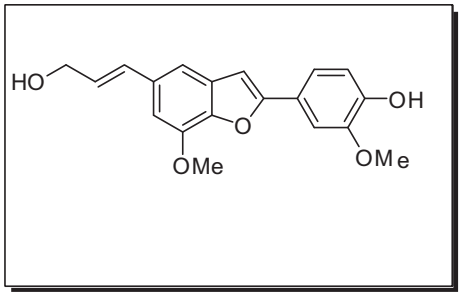


Figure 1 Structure of ailanthoidol.

DPPH, BHA and ABTS tablet were purchased from Sigma to Aldrich chemical Co. (St. Louis, MO, USA). Thin layer chromatography (TLC) analysis was performed on alumina sheets precoated with silica gel 60F-254 and SiO_2, 200–400 mesh (Merck) was used for column chromatography. ^1H NMR (AC 400) and ^{13}C NMR (AC 100) spectra were obtained by Bruker spectrometer in the appropriate (DMSO-d_6) solvent with TMS as internal reference. Melting points were obtained on a reichert thermopan melting point apparatus, equipped with a microscope and are uncorrected. Elemental analysis was performed on a Thermo Finnigan Flash EA 1112 elemental analyzer. Mass spectra were obtained by Water-Q-TOF ultima spectrometer.

2.2. Chemistry

Very recently, an efficient, 1,8-diaza biaza bicycle[5,4,0]undec-7-ene (DBU) assisted one pot synthesis of 2-acetyl benzofuran *via* intramolecular cyclo condensation of *o*-alkylation of salicylaldehyde with chloroacetone was reported (Rangaswamy et al., 2012). In the present investigation, we described a mild variant potassium *tert*-butoxide (*t*-BuOK) assisted one pot synthesis of 2-acetyl benzofuran (**2**) in the presence of molecular sieves Scheme 1. The mechanism involves, *o*-alkylation of salicylaldehyde (**IV**) with chloroacetone (**I**) in the presence of *t*-BuOK (**II**) as base furnished *o*-alkylated salicyaldehyde (**V**) which subsequently generates enolate anion (**VI**) undergo intramolecular cyclocondensation reaction afforded 2-acetyl benzofuran (**VIII**) in excellent yield (Scheme 2). In the next step, aldol condensation reaction of compound (**2**) with 4-methoxy benzaldehyde in the presence of $LiOH{\cdot}H_2O$ accomplished benzofuran chalcone i.e., (*E*)-1-(benzofuran-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (**3**) (Srikant et al., 2006). Generally, chalcones are considered to be useful intermediates in several cyclization reactions to produce different types of heterocyclic compounds of diverse biological importance, according to the reactants used and the reaction conditions (Yadav et al., 2005; Kim et al., 2005). Benzofuran chalcone (**3**) further treated with hydrazine hydrate in ethanol furnished 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (**4**). Finally, conjugation of benzofuran scaffold (**4**) with benzoyl chlorides in the presence of triethylamine as base afforded functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) (Scheme 1).

2.2.1. Synthesis of 2-acetyl benzofuran (2)

A mixture of salicyaldehyde (**1**) (2 mmol), chloroacetone (2 mmol) and potassium *tert*-butoxide (2 mmol) in 10 mL of dichloromethane (DCM) containing molecular sieves was refluxed at 30 °C for 3 h. Progress of the reaction was monitored by TLC using hexane:ethyl acetate (8:2) mixture as mobile phase. After the completion of the reaction, the reaction mixture was washed with 10% HCl solution followed by water. The organics were dried over anhydrous sodium sulfate. The yellow solid was obtained by desolventizing in a rotary evaporator at room temperature affords 2-acetyl benzofuran (**2**). m.p.: 73–75 °C, Yield-92%, IR (KBr) ν_{max} (cm^{-1}): 3087 (CH furan), 2900 (CH_3), 1675 (C═O), 1558 (C═C); ^1H NMR (DMSO-d_6 400 MHz) δppm: 7.46–7.73 (m, 5H, Ar-H), 2.25 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 186.0, 160.4, 147.8, 127.6, 124.8, 123.3, 120.9, 111.4, 103.9, 25.5;

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

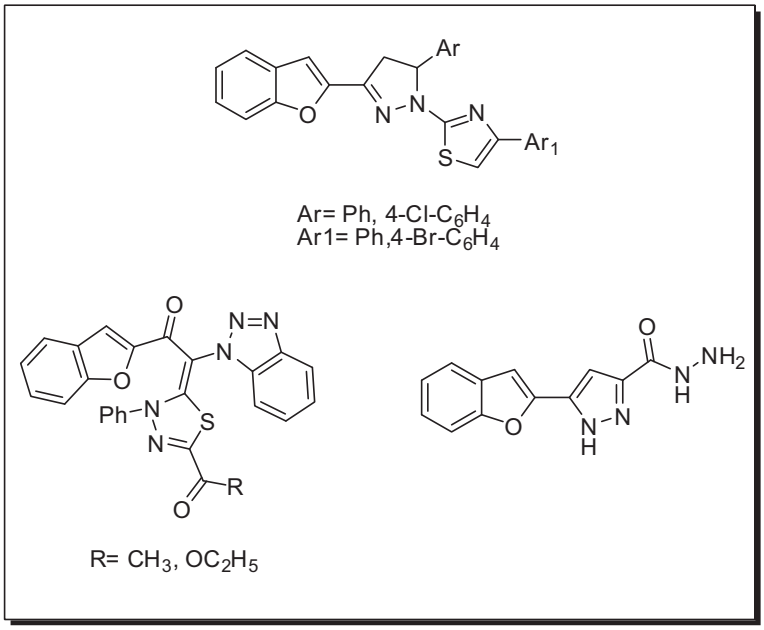


Figure 2 General structures of some bi-active entities of benzofuran combined with pyrazole nucleus.

MS (ESI) *m/z*: 160.05 (M^+). Anal. calcd. for $C_{10}H_8O_2$: C, 74.99; H, 5.03; O, 19.98%; found: C, 74.95; H, 5.07; O, 19.96%.

2.2.2. Synthesis of (E)-1-(benzofuran-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (3)

Compound (**2**) (1 mmol) in ethanol (0.5 mL) was treated with $LiOH{\cdot}H_2O$ (4 mg 0.1 mmol, 10 mol%) under magnetically stirred condition for 10 min at room temperature (~25–30 °C) followed by 4-methoxy benzaldehyde (1 mmol). The mixture was stirred magnetically until complete consumption of the compound (**2**) for 35 min. After the completion of the reaction a dark yellow precipitate was formed and this served as an indicator for monitoring the reaction. Ethanol was removed under reduced pressure. The residue was diluted with water (5 mL) neutralized with 2% aqueous HCl and extracted with ethylacetate (3 × 5 mL). The combined ethylacetate extracts were washed with brine solution (5 mL) dried over anhydrous Na_2SO_4 and concentrated under vacuum at room temperature to afford compound (**3**). Light yellow solid, m.p. : 118–120 °C, Yield-87%, IR (KBr) ν_{max} (cm^{-1}): 1624 (C═O), 1455 (CH═CH); ^1H NMR (DMSO-d_6 400 MHz) δppm: 7.10–7.60 (m, 9H, Ar-H), 6.75 (s, 2H, CH) 3.81 (m, 3H of OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 177.8, 160.4, 155.2, 149.1, 147.8, 145.0, 127.8, 127.5, 124.7, 123.3, 122.9, 121.2, 120.9, 116.7, 111.9, 111.4, 56.1; MS (ESI) *m/z*: 278.09 (M^+). Anal. calcd. for $C_{18}H_{14}O_3$: C, 73.46; H, 4.79; O, 21.75%; found: C, 73.44; H, 4.78; O, 21.73%.

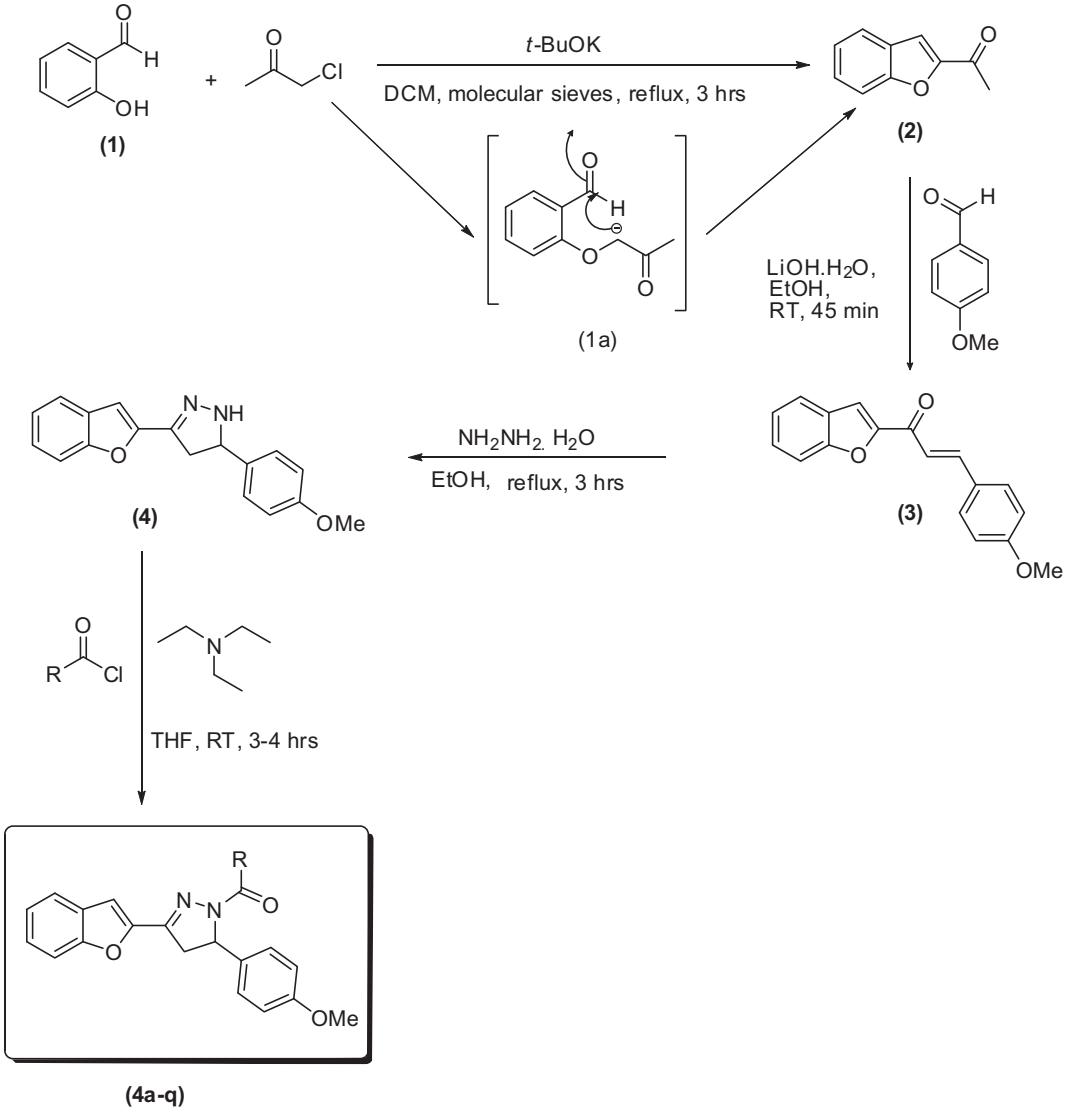
2.2.3. Synthesis of 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)4,5-dihydro-1H-pyrazole (4)

To a solution of (*E*)-1-(benzofuran-2-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**3**) (1 mmol) in ethanol as solvent, hydrazine hydrate (2 mmol) was added and the reaction mixture was refluxed for 3 h. After cooling the mixture was poured into crushed ice, the precipitate was obtained, filtered and washed with ethanol (2–5 mL) followed by water, dried in air and residue was collected (**4**). Light brown solid, m.p.: 195–197 °C, Yield-87%, IR (KBr) ν_{max} (cm^{-1}): 3311 (N–H) and 1595 (C═N); ^1H NMR (DMSO-d_6 400 MHz) δppm: 7.10 (s, 1H, N–H), 6.65–7.85 (m, 9H, Ar-H), 3.90–3.98 (dd, 2H, CH_2, pyrazoline, J = 4.1 Hz, 5.8 Hz), 3.88 (t, 1H, CH of pyrazoline, J = 7.5 Hz), 3.71 (s, 3H of OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 155.6, 155.0, 147.2, 146.7, 137.0, 134.5, 125.1, 124.7, 123.3, 120.9, 119.4, 115.5, 111.5, 110.2, 104.9, 56.1, 49.0, 40.9; MS (ESI) *m/z*: 292.12 (M^+). Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 70.12; H, 5.23; N, 9.09; O, 15.57%; found: C, 70.10; H, 5.25; N, 9.11; O, 15.55%. The spectral and analytical data for compounds (**2**), (**3**) and (**4**) are in agreement with that reported in the literature (Rangaswamy et al., 2012; Bakr et al., 2009; Basawaraj et al., 2009).

2.2.4. General procedure for the synthesis of functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole scaffolds (**4a-q**)

3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-*1H*-pyrazole (1.2 mmol) was suspended in dry THF (5 mL) in an inert atmosphere (N_2). To this suspension, at room temperature triethylamine (1.5 mmol) and different benzoyl chlorides (RCOCl) (1 mmol in 3 mL of THF) were added and reaction mixture was stirred for 3–4 h. The progress of reaction mixture was monitored by TLC using hexane:ethylacetate (6:4). The reaction mixture was then desolventized in a rotary evaporator and the compound was extracted in ethylacetate. The ethylacetate layer was washed with water and dried over anhydrous sodium sulfate. The products were obtained by further desolventation in a rotary evaporator at 50 °C. The respective products were purified through column chromatography using hexane:ethylacetate (6:4).

*2.2.4.1. (3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1yl) (phenyl) methanone (**4a**).* Light brown solid, m.p.: 180–183 °C. Spectroscopic analysis: IR (KBr) ν_{max}



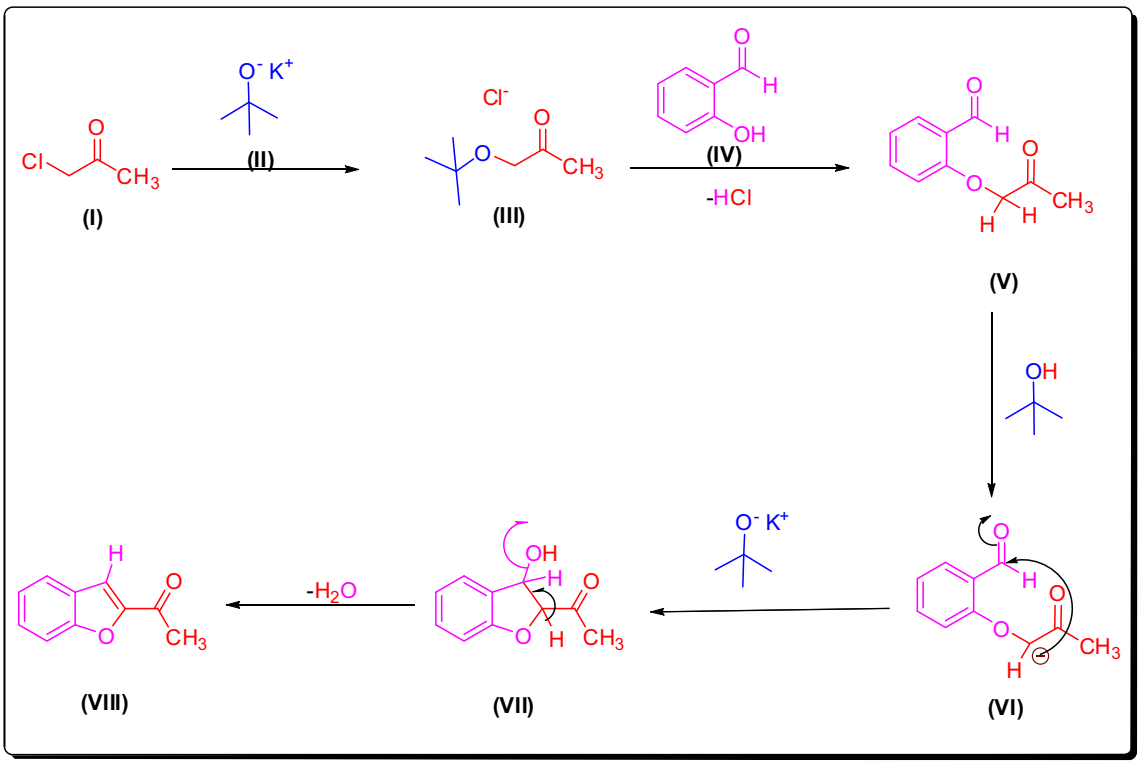
Scheme 1 Reaction pathway for the synthesis of functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**).

(cm^{-1}): 3131–2973 (Ar-CH), 1680 (C═O), 1624 (C═N Pyrazole), 1365 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.72–7.42 (m, 14H, Ar-H), 4.70 (t, 1H, CH of pyrazoline, J = 7.3 Hz), 3.71–3.95 (dd, 2H, CH_2 of pyrazoline, J = 4.2 Hz, 7.8 Hz), 3.81 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.0, 160.6, 155.5, 149.3, 143.5, 134.2, 131.1, 130.4, 129.9, 129.4, 128.5, 128.4, 125.3, 124.7, 123.1, 120.8, 114.8, 110.3, 104.5, 104.3, 58.7; MS (ESI) m/z: 396.15 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_3$: C, 76.13; H, 4.60; N, 7.10; O, 12.17%; found: C, 76.10; H, 4.63; N, 7.12; O, 12.15%.

*2.2.4.2. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1yl) (nitrophenyl) methanone (**4b**).* Reddish brown solid, m.p.: 298–301 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3129–2975 (Ar-CH), 1672 (C═O), 1641 (C═N Pyrazole), 1515–1560 (N–O), 1368 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.68–7.45 (m, 13H, Ar-H), 4.82 (t, 1H, CH of pyrazoline, J = 7.5 Hz), 3.75–3.97 (dd, 2H, CH_2 of pyrazoline, J = 4.8 Hz, 8.3 Hz), 3.65 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.5, 159.6, 155.5, 150.3, 143.5, 134.2, 131.1, 130.4, 129.7, 129.3, 128.5, 128.4, 125.3, 124.7, 123.1, 120.8, 114.7, 110.3, 104.5, 104.3, 58.7; MS (ESI) m/z: 441.13 (M^+). Anal. calcd. for $C_{25}H_{19}N_3O_5$: C, 68.02; H, 4.34; N, 9.52; O, 18.12%; found: C, 68.05; H, 4.53; N, 9.44; O, 18.25%.

*2.2.4.3. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (3,5 dinitrophenyl) methanone (**4c**).* Brown solid, m.p.: 213–215 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3129–2975 (Ar-CH), 1675 (C═O), 1658 (C═N Pyrazole), 1525–1570 (N–O), 1365 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.69–7.53 (m, 12H, Ar-H), 4.62 (t, 1H, CH of pyrazoline, J = 5.5 Hz), 3.72–4.01 (dd, 2H, CH_2 of pyrazoline, J = 4.8 Hz, 6.2 Hz), 3.85 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.9, 161.6, 154.3, 149.1, 143.2, 134.0, 131.5, 130.5, 130.7, 129.7, 129.5, 129.8, 128.4, 128.6, 125.2, 124.8, 123.1, 120.9, 115.0, 110.3, 104.7, 104.7, 58.8; MS (ESI) m/z: 486.12 (M^+). Anal. calcd. for

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012



Scheme 2 Mechanism toward the synthesis of 2-acetyl benzofuran by using *t*-BuOK.

$C_{25}H_{18}N_4O_7$: C, 61.73; H, 3.73; N, 11.52; O, 23.02%; found: C, 62.00; H, 3.53; N, 11.43; O, 23.25%.

*2.2.4.4. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (4-hydroxyphenyl) methanone (**4d**).* Brown semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3465 (−OH), 3122–2985 (Ar-CH), 1664 (C═O), 1655 (C═N Pyrazole), 1365–1317 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.60–7.41 (m, 13H, Ar-H), 5.30 (s, 1H, OH), 4.70 (t, 1H, CH of pyrazoline, J = 5.0 Hz), 3.71–3.96 (dd, 2H, CH_2 of pyrazoline, J = 5.8 Hz, 7.8 Hz), 3.79 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.3, 160.5, 155.8, 149.5, 143.6, 134.1, 131.9, 130.7, 129.5, 129.3, 129.3, 129.1, 128.3, 128.4, 125.2, 124.8, 123.1, 120.6, 116.8, 116.1, 115.0, 110.5, 104.7, 104.5, 58.6; MS (ESI) m/z: 412.14 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79; O, 15.52% found: C, 72.75; H, 4.69; N, 6.82; O, 15.51%.

*2.2.4.5. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (3 hydroxyphenyl) methanone (**4e**).* Light yellow semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3545 (−OH), 3135–2943 (Ar-CH), 1691 (C═O), 1619 (C═N Pyrazole), 1365–1324 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.72–7.42 (m, 13H, Ar-H), 5.25 (s, 1H, OH), 4.65 (t, 1H, CH of pyrazoline, J = 4.9 Hz), 3.69–3.94 (dd, 2H, CH_2 of pyrazoline, J = 4.8 Hz, 7.6 Hz), 3.73 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 166.0, 161.0, 155.8, 149.2, 143.1, 134.1, 131.3, 130.7, 129.5, 129.2, 128.9, 128.4, 125.2, 124.5, 123.2, 120.4, 116.7, 115.3, 114.7, 110.2, 104.4, 104.5, 58.4; MS (ESI) m/z: 412.14 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79; O, 15.52% found: C, 72.78; H, 4.91; N, 6.85; O, 15.61%.

*2.2.4.6. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (2-hydroxyphenyl) methanone (**4f**).* Brown solid. m.p.: 195–198 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3465 (−OH), 3135–2963 (Ar-CH), 1675 (C═O), 1643 (C═N Pyrazole), 1378–1325 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.60–7.41 (m, 13H, Ar-H), 5.36 (s, 1H, OH), 4.58 (t, 1H, CH of pyrazoline, J = 7.8 Hz), 3.68–3.89 (dd, 2H, CH_2 of pyrazoline, J = 4.2 Hz, 7.5 Hz), 3.72 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 166.1, 161.3, 155.8, 149.2, 143.1, 134.1, 131.3, 130.7, 129.5, 129.3, 129.3, 129.0, 128.4, 128.3, 125.6, 124.5, 123.2, 120.4, 116.7, 115.3, 114.5, 110.2, 104.5, 104.3, 58.3; MS (ESI) m/z: 412.14 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79; O, 15.52% found: C, 72.73; H, 4.93; N, 6.83; O, 15.45%.

*2.2.4.7. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (3,4,5 trihydroxyphenyl) methanone (**4g**).* Yellow semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3265–3592 (−OH), 3261–2933 (Ar-CH), 1678 (C═O), 1637 (C═N Pyrazole), 1348 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.80–7.42 (m, 11H, Ar-H), 5.30–7.03 (s, 3H, OH), 4.93 (t, 1H, CH of pyrazoline, J = 8.3 Hz), 3.71–3.98 (dd, 2H, CH_2 of pyrazoline, J = 3.8 Hz, 6.8 Hz), 3.92 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.9, 160.8, 155.3, 149.4, 143.95, 134.5, 131.2, 130.5, 130.0, 129.8, 129.5, 129.2, 128.8, 128.1, 125.8, 125.0, 123.6, 120.9, 116.5, 115.8, 114.5, 110.2, 104.7, 59.0, 37.9; MS (ESI) m/z: 444.13 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_6$: C, 67.56; H,

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

4.54; N, 6.30; O, 21.60% found: C, 67.50; H, 4.33; N, 6.42; O, 21.45%.

*2.2.4.8. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-fluorophenyl) methanone (**4h**).* Dark yellow solid, m.p.: 237–240 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3128–2984 (Ar-CH), 1682 (C═O), 1626 (C═N Pyrazole), 1354 (C–N), 1255 (C–F); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.69–7.44 (m, 13H, Ar-H), 4.73 (t, 1H, CH of pyrazoline, J = 7.3 Hz), 3.75–4.05 (dd, 2H, CH_2 of pyrazoline, J = 4.0 Hz, 6.5 Hz), 3.83 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.9, 161.2, 156.4, 149.4, 144.0, 134.75, 131.1, 130.4, 129.7, 129.4, 129.3, 129.2, 128.5, 128.4, 125.3, 124.7, 123.1, 120.8, 116.5, 115.8, 114.8, 110.3, 104.5, 58.7, 38.1; MS (ESI) m/z: 414.14 (M^+), Anal. calcd. for $C_{25}H_{19}FN_2O_3$: C, 72.45; H, 4.62; N, 6.76; O, 11.58% found: C, 72.41; H, 4.59; N, 6.75; O, 11.57%.

*2.2.4.9. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (4-bromophenyl) methanone (**4i**).* Brown semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3135–2976 (Ar-CH), 1683 (C═O), 1628 (C═N Pyrazole), 1357 (C–N), 524–595 (C–Br); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.58–7.43 (m, 13H, Ar-H), 4.90 (t, 1H, CH of pyrazoline, J = 8.8 Hz), 3.74–4.01 (dd, 2H, CH_2 of pyrazoline, J = 5.5 Hz, 8.0 Hz), 3.84 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.1, 160.9, 155.2, 149.3, 143.5, 134.2, 130.6, 130.2, 129.8, 129.5, 129.5, 129.1, 128.4, 125.2, 124.1, 123.3, 120.6, 117.5, 116.0, 114.6, 110.4, 104.7, 104.2, 58.5; MS (ESI) m/z: 474.06 (M^+). Anal. calcd. for $C_{25}H_{19}BrN_2O_3$: C, 63.17; H, 4.03; N, 5.89; O, 10.10% found: C, 63.20; H, 4.01; N, 5.87; O, 10.13%.

*2.2.4.10. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (4-chlorophenyl) methanone (**4j**).* Reddish brown semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3133–2971 (Ar-CH), 1682 (C═O), 1626 (C═N Pyrazole), 1363 (C–N), 695–783 (C–Cl); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.68–7.39 (m, 13H, Ar-H), 4.68 (t, 1H, CH of pyrazoline, J = 7.5 Hz), 3.69–3.99 (dd, 2H, CH_2 of pyrazoline, J = 4.5 Hz, 6.9 Hz), 3.88 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.0, 160.2, 155.5, 149.3, 143.5, 134.2, 131.0, 130.4, 129.8, 129.5, 129.3, 129.2, 128.4, 128.4, 125.3, 124.6, 123.1, 120.7, 116.5, 115.7, 114.8, 104.5, 104.3, 58.6, 38.1; MS (ESI) m/z: 430.11 (M^+). Anal. calcd. for $C_{25}H_{19}ClN_2O_3$: C, 69.69; H, 4.44; N, 6.50; O, 11.14%; found: C, 69.72; H, 4.41; N, 6.53; O, 11.12%.

*2.2.4.11. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (3-chlorophenyl) methanone (**4k**).* Light yellow solid, m.p.: 265–268 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3125–2968 (Ar-CH), 1678 (C═O), 1622 (C═N Pyrazole), 1363 (C–N), 695–784 (C–Cl); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.71–7.45 (m, 13H, Ar-H), 4.88 (t, 1H, CH of pyrazoline, J = 5.8 Hz), 3.73–3.98 (dd, 2H, CH_2 of pyrazoline, J = 5.8, 6.2 Hz), 3.73 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.11, 160.5, 155.8, 150.05, 144.3, 134.2, 131.6, 130.0, 129.3, 129.0, 128.5, 128.4, 125.3, 124.6, 123.2, 120.8, 116.5, 115.7, 114.8, 104.54, 104.3, 58.6, 37.6; MS (ESI) m/z: 430.11 (M^+). Anal. calcd. for $C_{25}H_{19}ClN_2O_3$: C, 69.69; H, 4.44; Cl, 8.23; N, 6.50; O, 11.14%; found: C, 69.73; H, 4.57; Cl, 8.24; N, 6.52; O, 11.15%.

*2.2.4.12. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (4-methoxyphenyl) methanone (**4l**).* Black semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3133–2971 (Ar-CH), 1679 (C═O), 1628 (C═N Pyrazole), 1368 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.69–7.46 (m, 13H, Ar-H), 4.68 (t, 1H, CH of pyrazoline, J = 4.6 Hz), 3.70–3.97 (dd, 2H, CH_2 of pyrazoline, J = 4.6, 5.8 Hz), 3.84 (s, 6H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.1, 160.6, 155.9, 150.1, 143.1, 134.2, 131.6, 130.5, 129.4, 129.5, 128.5, 125.3, 124.6, 123.1, 120.6, 114.7, 110.3, 104.3, 59.7, 57.9, 38.0; MS (ESI) m/z: 426.16 (M^+). Anal. calcd. for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20; N, 6.57; O, 15.01%; found: C,73.50; H, 5.23; N, 6.62; O, 15.09%.

*2.2.4.13. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (2,4-dimethoxyphenyl) methanone (**4m**).* Yellow solid, m.p.: 232–235 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3128–2976 (Ar-CH), 1685 (C═O), 1629 (C═N Pyrazole), 1359 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.64–7.51 (m, 12H, Ar-H), 4.63 (t, 1H, CH of pyrazoline, J = 6.0 Hz), 3.74–4.01 (dd, 2H, CH_2 of pyrazoline, J = 5.6, 8.0 Hz), 3.79 (s, 9H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.1, 160.2, 155.4, 149.2, 143.6, 134.1, 131.1, 130.4, 129.8, 129.5, 128.4, 125.3, 124.6, 123.2, 120.7, 114.8, 110.3, 104.3, 55.7, 55.7 55.4, 37.9; MS (ESI) m/z: 456.17 (M^+). Anal. calcd. for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14; O, 17.52%; found: C, 71.10; H, 5.35; N, 6.12; O, 17.75%.

*2.2.4.14. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (3,4,5 trimethoxyphenyl) methanone (**4n**).* Brown solid, m.p.: 338–341 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3129–2975 (Ar-CH), 1682 (C═O), 1625 (C═N Pyrazole) 1371 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.71–7.44 (m, 11H, Ar-H), 4.72 (t, 1H, CH of pyrazoline, J = 7.2 Hz), 3.71–3.98 (dd, 2H, CH_2 of pyrazoline, J = 5.0, 9.6 Hz), 3.84 (s, 12H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 165.11, 160.1, 155.5, 149.3, 143.5, 134.2, 131.0, 130.4, 129.8, 129.5, 129.2, 129.1, 128.8, 128.4, 125.3, 124.7, 123.2, 120.9, 114.7, 110.3, 104.3, 55.6, 55.8 55.4, 54.1, 38.5; MS (ESI) m/z: 486.18 (M^+). Anal. calcd. for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76; O, 19.73%; found: C, 69.52; H, 4.98; N, 5.78; O, 19.75%.

*2.2.4.15. 2-(3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbonyl) phenylacetate (**4o**).* Dark brown semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm^{-1}): 3130–2973 (Ar-CH), 1684 (C═O), 1620 (C═N Pyrazole), 1365 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.70–7.44 (m, 13H, Ar-H), 4.67 (t, 1H, CH of pyrazoline, J = 5.8 Hz), 3.70–4.00 (dd, 2H, CH_2 of pyrazoline, J = 5.3, 8.1 Hz), 3.79 (s, 3H, OCH_3), 2.31 (s, 3H, $COCH_3$); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 169.0, 165.9, 160.6, 155.5, 153.5, 149.3, 143.5, 134.2, 131.1, 130.4, 129.7, 129.4, 128.4, 125.3, 124.7, 123.1, 120.8, 114.8, 110.3, 104.3, 55.8, 37.9, 20.2; MS (ESI) m/z: 454.47 (M^+). Anal. calcd. for $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16; O, 17.60%; found: C, 71.41; H, 4.83; N, 6.12; O, 17.55%.

*2.2.4.16. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (p-tolyl) methanone (**4p**).* Brown solid, m.p.: 358–361 °C. Spectroscopic analysis: IR (KBr) ν_{max} (cm

$^{-1}$): 3133–2971 (Ar-CH), 1679 (C=O), 1628 (C=N Pyrazole), 1368 (C–N); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 7.69–7.46 (m, 13H, Ar-H), 4.71 (t, 1H, CH of pyrazoline, J = 9.0 Hz), 3.78–4.02 (dd, 2H, CH_2 of pyrazoline, J = 6.2, 6.8 Hz), 3.41–3.84 (s, 6H, OCH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 162.1, 160.8, 155.4, 150.1, 147.5, 143.4, 135.6, 129.8, 129.5, 128.9, 128.6, 128.5, 128.5. 128.5, 127.9, 125.5, 124.7, 123.8, 121.0, 114.9, 114.8, 104.9, 64.2, 58.0, 38.0, 28.1; MS (ESI) m/z: 410.16 (M^+). Anal. calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82; O, 11.69%; found: C, 75.50; H, 5.43; N, 6.72; O, 11.15%.

*2.2.4.17. (3-(Benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl) (2,4-dihydroxyphenyl) methanone (**4q**).* Brown semisolid. Spectroscopic analysis: IR (KBr) ν_{max} (cm $^{-1}$): 1363–1317 (C–N), 3129–2976 (Ar-CH), 1668 (C=O), 1632 (C=N Pyrazole), 3465 (–OH); ^{1}H NMR (DMSO-d_6 400 MHz) δppm: 6.65–7.43 (m, 12H, Ar-H), 5.30 (s, 2H, OH), 4.62 (t, 1H, CH of pyrazoline, J = 8.0 Hz), 3.68–3.93 (dd, 2H, CH_2 of pyrazoline, J = 5.5, 6.9 Hz), 3.38–3.77 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6 100 MHz) δppm: 167.3, 163.5, 160.7, 155.8, 149.5, 143.6, 134.2, 131.8, 130.7, 129.5, 128.3, 128.4, 125.3, 124.8, 123.1, 120.6, 115.7, 112.1, 111.0, 104.7, 58.6, 38.6; MS (ESI) m/z : 428.14 (M^+). Anal. calcd. for $C_{25}H_{20}N_2O_5$: C, 70.08; H, 4.71; N, 6.54; O, 18.67%; found C, 70.12; H, 4.53; N, 6.62; O, 18.25%.

2.3. Antimicrobial activity

2.3.1. Antibacterial studies

The antibacterial activities of newly synthesized compounds (**4a-q**) were determined by the well plate method in Mueller–Hinton Agar (Arthington-Skaggs et al., 2000). The antibacterial activity was carried out against 24 h old cultures of bacterial strains. In this work, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were used to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentration of 1 and 0.5 mg/mL. 20 mL of sterilized agar media was poured into each pre-sterilized petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. About 60 mL of 24 h old culture suspension was poured and neatly swabbed with the pre-sterilized cotton swabs. Six millimeter diameter well was then punched carefully using a sterile cork borer and 30 mL of test solutions of different concentrations was added into each labeled well. The plates were incubated for 24 h at 37 °C. The inhibition zone that appeared after 24 h, around the well in each plate was measured as zone of inhibition in mm. Experiments were triplicates and standard deviation was calculated.

2.3.2. Antifungal studies

Antifungal studies of newly synthesized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) were carried out against *Aspergillus flavus, Chrysosporium keratinophilum, Candida albicans*. Sabourands agar media were prepared by dissolving peptone (10 g), D-glucose (40 g) and agar (20 g) in distilled water (1000 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species (Mac Lowry et al., 1970). 20 mL of agar media was poured into each petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for 1 h. Using sterile cork borer punched carefully, wells were made on these seeded agar plates and different concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The petri dishes were prepared in triplicate and maintained at 25 °C for 72 h. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with fluconazole as standard and zones of inhibition were determined for all the synthesized compounds (**4a-q**).

2.4. Antioxidant evaluation

2.4.1. DPPH radical scavenging assay

The evaluation of antioxidant activity of newly synthesized compounds was done by DPPH radical scavenging activity (Blois, 1958). Internal standard BHA and the synthesized compounds of different concentrations were prepared in distilled ethanol, 1 mL of each compound solution having different concentrations (10, 25, 50, 100, 200 and 500 μM) was taken in different test tubes, 4 mL of 0.1 mM ethanol solution of DPPH was added and shaken vigorously. The tubes were then incubated in the dark room at RT for 20 min. A DPPH blank was prepared without compound and ethanol was used for the baseline correction. Changes (decrease) in the absorbance at 517 nm were measured using a UV–visible spectrophotometer and the remaining DPPH was calculated. The percent decrease in the absorbance was recorded for each concentration and percent quenching of DPPH was calculated on the basis of the observed decrease in absorbance of the radical. The radical scavenging activity was expressed as the inhibition percentage and was calculated using the formula:

$$\text{Radical scavenging activity } (\%) = [(A_0 - A_1)/A_0 \times 100]$$

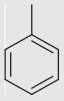
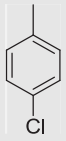
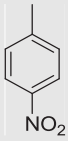
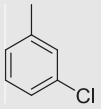
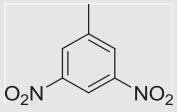
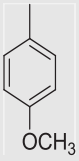
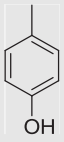
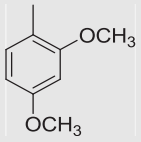
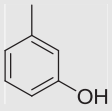
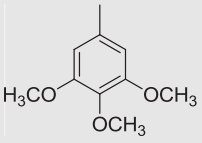
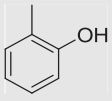
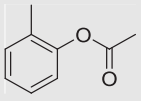
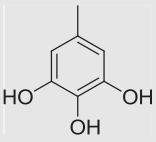
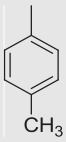
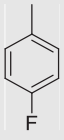
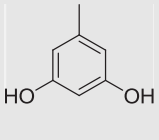
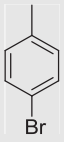
where A_0 is the absorbance of the control (blank, without compound) and A_1 is the absorbance of the compound.

2.4.2. Inhibition of microsomal lipid peroxidation assay

Liver excised from adult male Wister rats, were homogenized with a polytron (speed setting 7–8) in 10 mL of ice cold Tris–HCl buffer (20 mM, pH 7.4) by the method of Liu and Ng, 2000. The homogenate was centrifuged at 14,000 rpm for 15 min. The supernatants (1 mL) were incubated with different concentrations of compounds (10, 25, 50, 100, 200 and 500 μM) in the presence of 10 μM $FeSO_4$ and 0.1 mM ascorbic acid at 37 °C for 1 h. The reaction was terminated by the addition of 1.0 mL of trichloroacetic acid (TCA; 28%) and 1.5 mL of thiobarbituric acid (TBA 1%). The solution was heated at 100 °C for 15 min, cooled to room temperature, and centrifuged at 2500 rpm for 15 min, and the color of the MDA–TBA complex in the supernatant was read at 532 nm using a spectrophotometer. BHA was used as a positive control. The inhibition ratio (%) was calculated using the following formula: inhibition ratio $(\%) = (A - A_1)/A \times 100$, where A is the absorbance of the control and A_1 is the absorbance of the test sample.

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

Table 1 Chemical structures and yields of synthesized compounds (**4a-q**).

Compound number	R	Yield %	Compound number	R	Yield %
4a		87.53	**4j**		71.86
4b		75.26	**4k**		71.60
4c		68.30	**4l**		80.28
4d		77.00	**4m**		74.35
4e		65.50	**4n**		67.77
4f		75.06	**4o**		79.80
4g		82.00	**4p**		76.82
4h		72.80	**4q**		78.35
4i		69.11			

2.4.3. $ABTS^+$ free radical scavenging assay

The ability of the test sample to scavenge $ABTS^+$ radical cation was determined according to the literature method (Re et al., 1999). The $ABTS^+$ radical cation was pregenerated by mixing 7 mM $ABTS^+$ stock solution with 2.45 mM potassium persulfate (final concentration) and incubating for 12–16 h in the dark at room temperature until the reaction was complete and the absorbance was stable. The absorbance of the $ABTS^+$ solution was equilibrated to 0.70 (±0.02) by diluting with water at room temperature, then 1 mL was mixed with different concentrations of the test sample (10, 25, 50, 100, 200 and 500 μM) and the absorbance was measured at 734 nm after 6 min. The scavenging capability of $ABTS^+$ radical was calculated using the following equation:

$$ABTS^+ \text{scavenging effect} \quad (\%) = [(A_c - A_s)/A_c] \times 100$$

where, A_c is the initial concentration of the $ABTS^+$ and A_s is the absorbance of the remaining concentration of $ABTS^+$ in the presence of compounds.

3. Results and discussion

3.1. Chemistry

In the present work, 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) were obtained from salicylaldehyde (**1**) as starting material (Scheme 1). Very firstly, *t*-BuOK promoted synthesis of 2-acetyl benzofuran (**2**) was done and it was confirmed by IR, ^{1}H NMR and mass spectral studies. In the IR spectrum study, the appearance of acetyl carbonyl (C═O) band at the region 1675 cm^{-1} and the absence of salicylaldehyde −OH stretching at 3262–3602 cm^{-1} and aldehydic (C═O) stretching at 1720 cm^{-1} confirmed the synthesis of 2-acetyl benzofuran (**2**) (Scheme 2). Whereas, in ^{1}H NMR spectrum, the signals resonated at δ 2.25 (s, 3H, $COCH_3$), 7.38 (s, 1H, furan C–H), absence of hydroxy signal at δ 5.34 (s, 1H, −OH) and aldehydic signal at 10.40 (s, 1H, CHO). In the mass spectrum, the molecular ion peak at m/z 160.05 was noticed which confirmed the formation of (**2**). Aldol condensation reaction between compound (**2**) and 4-methoxy benzaldehyde in the presence of LiOH H_2O furnished compound (**3**). The IR frequency exhibited at 1624 and 1455 cm^{-1} due to C═O and C═C functions respectively and in the ^{1}H NMR spectrum, signals at δ 6.75 (s, 2H, CH), 3.81 (s, 3H, OCH_3) and 7.10–7.60 (m, 9H, Ar-H) confirmed the condensed product (*E*)-1-(benzofuran-2-yl)-3-(4-methoxyphenyl) prop-2-en-1-one (**3**). The benzofuran chalcone (**3**) was further treated with hydrazine hydrate to accomplish 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-*1H*-pyrazole (**4**), its IR spectrum exhibited band at 3311 cm^{-1} due to N–H function and ^{1}H NMR spectrum signal for N–H proton resonated at δ 7.10 (s, 1H, N–H) and the absence of C–H proton at 7.66 (s, 1H, C–H). In the final step, 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (**4**) was further conjugated with different benzoyl chlorides in the presence of triethylamine to afford functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) (Scheme 1). The IR spectrum of all the scaffolds showed the absence of N–H band at 3311 cm^{-1} and presence of C═O stretching at the region 1664–1691 cm^{-1}. Whereas, ^{1}H NMR revealed the absence of N–H proton at δ 7.10 (s, 1H, N–H) which confirmed the products.

3.2. Antimicrobial activity

3.2.1. Antibacterial activity

The antibacterial activity of newly synthesized functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) was determined by the well plate method. In this study, *E. coli* ATCC 25922 (Gram-negative), *S. aureus*

Table 2 Inhibitory zone (diameter) mm of the synthesized compounds (**4a-q**) against tested bacterial strains by the well plate method. Each value represents mean ± SD (n = 3).

Tested compounds concentration (mg/mL)	*Escherichia coli*		*Staphylococcus aureus*		*Pseudomonas aeroginosa*	
	1.0	0.5	1.0	0.5	1.0	0.5
4	2 ± 0.02	1 ± 0.01	3 ± 0.01	2 ± 0.01	1 ± 0.01	1 ± 0.02
4a	3 ± 0.02	2 ± 0.01	4 ± 0.02	3 ± 0.01	2 ± 0.01	1 ± 0.01
4b	7 ± 0.02	5 ± 0.01	6 ± 0.02	4 ± 0.02	4 ± 0.02	3 ± 0.01
4c	9 ± 0.01	8 ± 0.01	5 ± 0.02	5 ± 0.02	4 ± 0.02	3 ± 0.02
4d	2 ± 0.02	1 ± 0.01	3 ± 0.01	1 ± 0.01	1 ± 0.01	1 ± 0.02
4e	3 ± 0.01	1 ± 0.02	2 ± 0.02	1 ± 0.02	4 ± 0.02	3 ± 0.01
4f	4 ± 0.02	3 ± 0.01	5 ± 0.01	3 ± 0.01	2 ± 0.01	1 ± 0.02
4g	2 ± 0.01	1 ± 0.01	3 ± 0.02	2 ± 0.02	3 ± 0.01	2 ± 0.01
4h	19 ± 0.03	13 ± 0.02	15 ± 0.01	10 ± 0.02	16 ± 0.02	13 ± 0.02
4i	13 ± 0.01	8 ± 0.02	10 ± 0.02	8 ± 0.02	11 ± 0.02	8 ± 0.01
4j	17 ± 0.02	11 ± 0.01	13 ± 0.01	9 ± 0.01	15 ± 0.01	12 ± 0.02
4k	10 ± 0.01	5 ± 0.01	7 ± 0.02	4 ± 0.02	9 ± 0.01	6 ± 0.01
4l	4 ± 0.01	3 ± 0.01	5 ± 0.01	3 ± 0.01	5 ± 0.01	4 ± 0.01
4m	3 ± 0.02	2 ± 0.01	2 ± 0.02	1 ± 0.02	4 ± 0.02	3 ± 0.01
4n	3 ± 0.01	2 ± 0.02	4 ± 0.01	2 ± 0.01	4 ± 0.01	3 ± 0.02
4o	4 ± 0.02	3 ± 0.02	2 ± 0.01	1 ± 0.01	4 ± 0.01	3 ± 0.02
4p	5 ± 0.02	4 ± 0.01	6 ± 0.02	4 ± 0.02	5 ± 0.02	3 ± 0.01
4q	4 ± 0.01	2 ± 0.01	4 ± 0.02	2 ± 0.01	2 ± 0.02	2 ± 0.01
Streptomycin	18 ± 0.01	12 ± 0.01	15 ± 0.02	12 ± 0.01	17 ± 0.01	13 ± 0.01

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

Table 3 Inhibitory zone (diameter) mm of the synthesized compounds (**4a-q**) against tested fungal strains by the well plate method. Each value represents mean ± SD (n = 3).

Tested compounds concentration (mg/mL)	*Aspergillus flavus*		*Chrysosporium keratinophilum*		*Candida albicans*	
	1.0	0.5	1.0	0.5	1.0	0.5
4	2 ± 0.01	1 ± 0.01	4 ± 0.01	3 ± 0.01	4 ± 0.02	5 ± 0.01
4a	2 ± 0.02	1 ± 0.01	3 ± 0.02	2 ± 0.01	3 ± 0.01	2 ± 0.01
4b	6 ± 0.03	5 ± 0.02	4 ± 0.01	3 ± 0.02	7 ± 0.02	5 ± 0.02
4c	5 ± 0.01	4 ± 0.01	7 ± 0.02	5 ± 0.01	6 ± 0.01	4 ± 0.01
4d	2 ± 0.02	1 ± 0.01	3 ± 0.01	1 ± 0.01	4 ± 0.01	2 ± 0.02
4e	3 ± 0.01	2 ± 0.02	2 ± 0.02	1 ± 0.02	2 ± 0.02	1 ± 0.01
4f	3 ± 0.02	1 ± 0.01	4 ± 0.01	3 ± 0.01	3 ± 0.01	2 ± 0.02
4g	2 ± 0.01	1 ± 0.02	2 ± 0.02	2 ± 0.02	3 ± 0.01	3 ± 0.01
4h	9 ± 0.02	6 ± 0.01	9 ± 0.01	8 ± 0.01	11 ± 0.01	10 ± 0.02
4i	8 ± 0.01	7 ± 0.02	6 ± 0.02	6 ± 0.02	10 ± 0.02	7 ± 0.01
4j	12 ± 0.03	10 ± 0.02	17 ± 0.01	15 ± 0.02	21 ± 0.02	19 ± 0.02
4k	6 ± 0.01	5 ± 0.01	7 ± 0.02	5 ± 0.01	9 ± 0.01	8 ± 0.01
4l	5 ± 0.01	3 ± 0.01	1 ± 0.02	2 ± 0.01	4 ± 0.02	3 ± 0.01
4m	4 ± 0.02	2 ± 0.01	4 ± 0.02	3 ± 0.02	4 ± 0.02	3 ± 0.01
4n	3 ± 0.01	2 ± 0.02	4 ± 0.01	3 ± 0.01	2 ± 0.01	1 ± 0.02
4o	5 ± 0.02	4 ± 0.02	5 ± 0.01	4 ± 0.01	6 ± 0.01	4 ± 0.02
4p	4 ± 0.02	2 ± 0.01	3 ± 0.02	2 ± 0.02	3 ± 0.01	2 ± 0.02
4q	3 ± 0.01	2 ± 0.01	2 ± 0.02	3 ± 0.01	2 ± 0.02	1 ± 0.01
Fluconazole	14 ± 0.01	12 ± 0.02	17 ± 0.02	16 ± 0.01	20 ± 0.02	18 ± 0.02

Table 4 Concentration required for 50% scavenging (IC_{50}) of DPPH·, LPO and $ABTS^{\cdot+}$ radicals by the compounds (**4a–q**) and the standard antioxidant BHA. Each value represents mean ± SD (n = 3).

Tested compounds	Scavenging activity (IC_{50})[a]		
	DPPH·	LPO	$ABTS^{\cdot+}$
4	312 ± 0.10	142.6 ± 0.60	185.0 ± 0.12
4a	> 500	161.6 ± 0.21	350.85 ± 0.53
4b	> 500	121.6 ± 0.10	296.86 ± 0.47
4c	450 ± 0.02	97.3 ± 0.61	287.34 ± 0.12
4d	15 ± 0.63	7.12 ± 0.37	29.3 ± 0.45
4e	18 ± 0.12	12.1 ± 0.24	36.6 ± 0.61
4f	16 ± 0.65	9.7 ± 0.34	32.3 ± 0.23
4g	9 ± 0.58	4.3 ± 0.21	18.9 ± 0.11
4h	250 ± 0.52	63.3 ± 0.65	150.45 ± 0.12
4i	189 ± 0.11	28.3 ± 0.31	126.21 ± 0.54
4j	201 ± 0.23	31.2 ± 0.72	134.0 ± 0.22
4k	234 ± 0.25	38.7 ± 0.36	143.21 ± 0.24
4l	27 ± 0.66	14.6 ± 0.74	69.16 ± 0.14
4m	53 ± 0.78	18.2 ± 0.91	81.32 ± 0.27
4n	70 ± 0.23	22.3 ± 0.58	95.30 ± 0.16
4o	> 500	133.8 ± 0.12	309.64 ± 0.32
4p	135 ± 0.45	87.3 ± 0.71	112.16 ± 0.10
4q	10 ± 0.62	5.2 ± 0.21	19.7 ± 0.14
BHA	12.5 ± 0.12	6.4 ± 0.12	20.9 ± 0.12

[a] The values are expressed as μM concentration. Lower IC_{50} values indicate higher radical scavenging activity.

ATCC 25923 (Gram-positive) and *P. aeruginosa* ATCC 27853 (Gram-negative) were selected due to their infectious nature. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at concentrations of 1 and 0.5 mg/mL. (Table 1)

The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains (Table 2). The results indicated that among the tested compounds **4h** (*p*-fluro substituted) and **4j** (*p*-chloro substituted) on the 1-substituted phenyl ring showed excellent activity against *P. aeruginosa* and *E. coli* at the concentrations of 1 and 0.5 mg/mL compared to standard drug streptomycin. Compounds **4i** (*p*-bromo substituted) and **4k** (*m*-chloro substituted) showed similar activity as that of standard, against *E. coli*. Whereas, compounds **4b** (*p*-nitro substituted) and **4c** (3,5-dinitro substituted) revealed moderately good activity against *E. coli* at 1 mg/mL concentrations. The remaining compounds showed very least activity against all of the three tested bacterial strains. From these results it could be concluded that, the chloro, fluoro, bromo, and nitro functionalized derivatives showed better activity and the others showed less activity against all bacterial strains.

3.2.2. Antifungal activity

Newly synthesized compounds (**4a-q**) were also screened for their antifungal activity against *A. flavus* MTCC 3306, *C. keratinophilum* MTCC 2827 and *C. albicans* MTCC 3017, because of their infectious nature. The compounds were dissolved in DMSO and antifungal activity was determined by the well plate method at concentrations of 1 and 0.5 mg/mL.

The antifungal result data (Table 3) indicated that, the synthesized compounds showed a variable degree of inhibition against the tested fungi. As a result, the presence of chloro substituent on the 1-substuted phenyl ring in compound (**4j**) has exhibited a highly potent activity against *C. albicans* compared with standard, fluconazole. Compounds (**4h**), (**4i**) and (**4k**) incorporating with fluoro, bromo, chloro moieties on the 1-substituted phenyl ring at different positions displayed considerable activity against *C. keratinophilum*. The other analogues of 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole showed less activity against all the tested microorganisms compared to standard. It can be concluded that some of the prepared compounds were superior to standard against *C.*

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

albicans tested microbial strains. From these results it could be generalized that, the presence of halogen substituents on the phenyl ring showed better activity compared to other analogues.

3.3. Antioxidant evaluation

The antioxidant potential of functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) was determined as an index of pharmacological usefulness. Three *in vitro* model systems were used for the evaluation of antioxidant properties namely, 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (RSA), inhibition of microsomal lipid peroxidation (LPO) assay and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) ($ABTS^+$) free-radical scavenging assay. The antioxidant properties were expressed in terms of 50% inhibitory concentration (IC_{50}) values (Table 4).

3.3.1. DPPH radical scavenging assay

Free radical scavenging is one of the best known mechanisms by which antioxidants inhibit the oxidation and offer a rapid technique for screening the radical scavenging activity of specific compounds. All tested 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) exhibited as certain degree of radical scavenging activity. Initially, benzofuran scaffold (**4**) showed considerable activity, this could be due to the presence of the electron donating methoxy group on the phenyl ring and also the presence of the N–H functional group in the pyrazole ring (Mei and Fang, 2004). Further, introducing benzoyl chlorides having different functional sites gave the significant enhancement in activity. The inhibition results of the derivatives appeared to be related to the nature of the substituent groups on the 1-susbtituted phenyl ring. Compounds (**4g**) and (**4q**) exhibited better radical scavenging potential (Table 4), this may be due to the presence of more than one hydroxyl group on the 1-substituted phenyl ring at different positions. The conjugation of these two benzoyl chlorides (3,4,5-tri-hydroxybenzoyl chloride and 3,5-di-hydroxybenzoyl chloride) to compound (**4**) have exhibited thirty folds more activity compared to 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (**4**) and even more higher activity than that of standard, butylated hydroxyanisole. The presence of electron donating substituents, such as hydroxy, methoxy and methyl on the phenyl ring in compounds (**4d-f**, **4l-n** and **4p**) showed good radical scavenging activity but slightly less than the standard, whereas, compounds (**4b-c** and **4h-k**) possessing electron withdrawing (nitro, halogens) substituents exhibited less activity and compound (**4a**) and (**4o**) without any substituents and acetyl substituents showed least DPPH radical scavenging potential.

3.3.2. Inhibition of microsomal lipid peroxidation assay

A well-recognized result of oxidant injury is peroxidation of membrane lipids to organic peroxyl radicals, which initiates a chain reaction that may explain many membrane-mediated effects of reactive oxygen species (ROS). The concentration-dependent inhibitory effects of 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) on lipid peroxidation (LP) in liposomes were estimated by the amount of thiobarbituric acid reactive substances (TBARS). BHA was used as a reference antioxidant (Table 4). All tested compounds exhibited some degree of inhibitory effect on the Fe^{3+}/ascorbic acid-induced LP whereas, two compounds showed higher than that of standard. Based on the IC_{50} values (effective concentration at which TBARS were reduced to 50% with respect to controls), the compounds (**4g**) and (**4q**) possessing 3,4,5-tri-hydroxy and 3,5-di-hydroxy substituents on the 1-substituted phenyl ring accounted for significant LPO inhibitors than the other 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds. The compounds (**4d-f**), (**4l**), (**4m**) and (**4n**), have good inhibitory effect, this may be due to the presence of hydroxyl and methoxy functions on the 1-substituted ring respectively. Whereas, compounds having halogens (**4h-k**), nitro (**4b-c**), acetyl (**4o**), methyl (**4p**) and non-substituted (**4a**) showed lowest inhibitory effect compared with the standard as well as other compounds.

3.3.3. ABTS radical scavenging assay

The ABTS method is based on the ability of hydrogen or electron-donating antioxidants to decolorize the performed radical monocation of 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) generated due to oxidation of ABTS with potassium persulfate. The radical scavenging abilities showed by 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds toward this assay typically revealed that, compounds (**4g**) and (**4q**) exhibit significantly better activity than standard BHA. Whereas *para, meta, ortho*-free hydroxy substituted (**4d-f**) and methoxy substituted (**4l-n**) derivatives permit the moderate radical scavenging ability, respectively. The presence of electron-withdrawing groups on the 1-substituted phenyl ring at 3–5 positions might not favor the activity. Thus, compounds (**4b-c**) and (**4h-k**) which contain NO_2 and halogen groups on the phenyl ring at different positions showed low ABTS radical activity than the other compounds (Table 4). The data presented in Table 2 reflect that compounds (**4g**) and (**4q**) exhibit effective antioxidant potential compared to the standard BHA.

4. Conclusion

In conclusion, a novel, simple and efficient methodology was described for the synthesis of 2-acetyl benzofuran (**2**). Later, we have proposed an effective strategy for the synthesis of functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds (**4a-q**) in good yields and evaluated their antimicrobial and antioxidant activities. Antimicrobial studies suggest that compounds (**4h**) and (**4j**) having halogen substituents on the pyrazole 1-substituted phenyl ring at *para* position showed an excellent antibacterial and antifungal activity in the well plate method. Interestingly, from all the antioxidant assays we noted that introduction of benzoyl chlorides possessing hydroxy and EDG (electron donating group) substituents at different C-terminals to the pyrazole ring resulted in a significant increase in the activity. Among all the synthesized analogues, compounds (**4g**) and (**4q**) exhibit a significant antioxidant potential. Whereas, compounds (**4e-f**) and (**4l**) exhibited moderate antioxidant activity. These results provide useful information for operating as a positive reinforcement of the tendency to use antimicrobial and antioxidant properties as a guideline of the rational design of this class of compounds.

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012

Acknowledgements

The authors are thankful to NMR Research Center, Indian Institute of Science, Bangalore for providing spectral data and also thank Mr. S.K. Peethambar, Department of Studies in Biochemistry, Kuvempu University for extending help to access antimicrobial activity studies.

References

Abdel-Wahab, B.F., Abdel-Aziz, H.A., Ahmed, E.M., 2009. Eur. J. Med. Chem. 44, 2632–2635.
Abdel-Wahab, B.F., Abdel-Aziz, H.A., Ahmed, E.M., 2008. Arch. Pharm. Chem. Life Sci. 341, 734–739.
Arthington-Skaggs, B.A., Motley, M., Warnock, D.W., Morrison, C.J., 2000. J. Clin. Microbiol. 38, 2254–2260.
Bakr, F.A., Hatem, A.A., Essam, M.A., 2009. Eur. J. Med. Chem. 44, 2632–2635.
Basawaraj, R., Goled, S., Sangapure, S.S., 2009. Indian J. Heterocycl. Chem. 19, 201–202.
Basawaraj, R., Yadav, B., Sangapure, S.S., 2001. Indian J. Heterocycl. Chem. 11, 31–34.
Blois, M.S., 1958. Nature 181, 1199.
Kadin, S.B., 1972. J. Med. Chem. 15, 551–552.
Kamal, M.D., Hassan, A.G., Eman, A.R., Mohey, E., Hanan, A.M., 2006. Bioorg. Med. Chem. 14, 3672–3680.
Kao, C.L., Chern, J.W., 2001. Tetrahedron Lett. 42, 1111–1113.
Kim, S., Ahn, C., Keum, S., Koh, K., 2005. Dyes Pigm. 65, 179–182.
Kumar, H.V., Naik, N., 2010. Eur. J. Med. Chem. 45, 2–10.
Kumar, H.V., Kumar, C.K., Naik, N., 2011. Med. Chem. Res. 20, 101–108.
Liu, F., Ng, T.B., 2000. Life Sci. 66, 725–735.
Mac Lowry, D.J., Jaqua, M.J., Selepak, S.T., 1970. Appl. Microbiol. 20, 46–53.
Mohamad, Y., Payal, J., 2011. Arabian J. Chem.. http://dx.doi.org/10.1016/j.arabjc.2011.09.013.
Mei, H.S., Fang, Y.K., 2004. Bioorg. Med. Chem. 12, 4633–4643.
Naik, N., Kumar, V.H., Harini, S.T., 2011a. Eur. J. Chem. 2, 337–341.
Naik, N., Kumar, V.H., Vidyashree, P.B., 2011b. J. Pharm. Res. 4, 2686–2689.
Parekh, S., Bhavsar, D., Savant, M., Thakrar, S., Bavishi, A., Parmar, M., Vala, H., Radadiya, A., Pandya, N., Serly, J., Molnar, J., Shah, A., 2011. Eur. J. Med. Chem. 46, 1942–1948.
Rangaswamy, J., Kumar, H.V., Harini, S.T., Naik, N., 2012. Bioorg. Med. Chem. Lett. 22, 4773.
Re, R., Pellergini, N., Proteggenete, A., Pannala, A., Yang, M., Rice Evans, C., 1999. Free Radical Biol. Med. 26, 1231–1237.
Rida, S.M., El-Hawash, S.A.M., Fahmy, H.T.Y., Hazzaa, A.A., El-Meligy, M.M.M., 2006. Arch. Pharm. Res. 29, 826–833.
Romagnoli, R., Baraldi, P.G., Sarkar, T., Caral, C.L., Lopez, O.C., Carrion1, M.D., Preti1, D., Tolomeo, M., Balzarini, J., Hamel, E., 2008. Med. Chem. 4, 558–564.
Srikant, B., Ratnesh, S., Devesh, M.S., Lalima, S., Asit, K.C., 2006. J. Mol. Catal. A: Chem. 244, 20–24.
Ujjinamatada, R.K., Appala, R.S., Agasimundin, Y.S., 2006. J. Heterocycl. Chem. 43, 437–441.
Vinod, U., Harun, P., Bijal, P., Sanjay, B., 2012. Arabian J. Chem.. http://dx.doi.org/10.1016/j.arabjc.2012.09.011.
Yadav, P.P., Gupta, P., Chaturvedi, A.K., Skukla, P.K., Maurya, R., 2005. Bioorg. Med. Chem. 13, 1497–1505.
Zdemir, A.O., Zitouni, G.T., Kaplancikli, Z.A., Revial, G., Guven, K., 2007. Eur. J. Med. Chem. 42, 403–409.

Please cite this article in press as: Rangaswamy, J. et al., Functionalized 3-(benzofuran-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole scaffolds: A new class of antimicrobials and antioxidants. Arabian Journal of Chemistry (2013), http://dx.doi.org/10.1016/j.arabjc.2013.10.012