An Easy Access to Benzofurans via DBU Induced Condensation Reaction of Active 2-Hydroxy Acetophenones with Phenacyl Chlorides: A Novel Class of Antioxidant Agents

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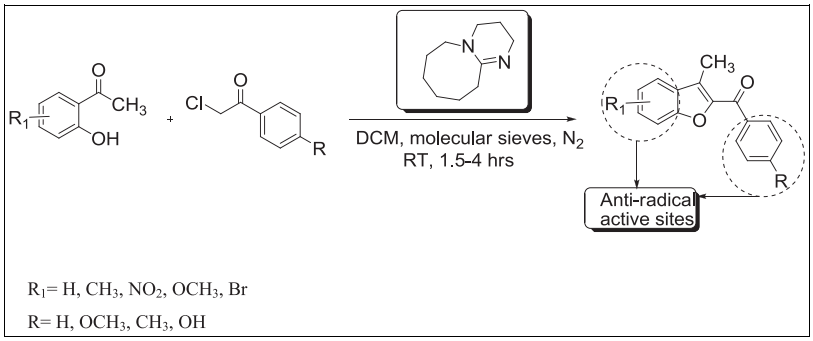

A convenient and efficient one-pot synthesis of benzofurans **3**(**a–t**) has been described from 2-hydroxy acetophenones and phenacyl chlorides in the presence of DBU. The procedure was applicable for a variety of phenacyl chlorides and provides a variety of benzofurans with higher yields. DBU acts as a base and as well as nucleophiles. All the derivatives were subjected to *in vitro* antioxidant screenings against representative 2,2′-diphenyl-1-picryl-hydrazyl and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) radicals and results worth for further investigations.

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INTRODUCTION

The benzofuran nucleus is a well-known pharmacophore. Multiply substituted benzofurans represent an interesting class of heterocycles, which are intensively studied in connection with a variety of applications [1]. A wide variety of pharmacological properties has been shown to be associated with benzofuran [2]. The benzofuran ring system itself is a common structural element that appears in a large number of medicinally important compounds [3]. Benzofuran and its heterocyclic systems are known to exhibit a wide range of biological properties such as antihyperglycemic, analgesic, antiinflammatory, antioxidants, antimicrobial, and antitumor activities [4–7]. Realizing the biological importance of benzofurans, there is continuous interest in the development of convenient and efficient synthesis of benzofurans. Most commonly, the Rap–Stoermer reaction [8] has been employed for the synthesis of benzofuran, which involves the cyclization of phenacyl bromide with *o*-hydroxy benzaldehyde in the presence of a base. However, the reported methods have some disadvantages such as use of corrosive strong bases [9]. In addition to this, some of the methods require expensive palladium catalyst, high boiling solvents (DMF) [10], and longer reaction time (24–72 h) [11].

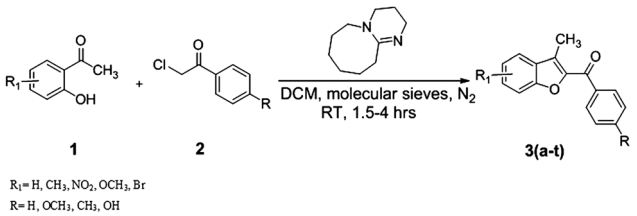
In the literature survey, approaching to synthesis of benzofurans from 2-hydroxy acetophenone moieties indicates lack of reference available. In the interest of earlier findings, we inspired to develop a simple and efficient synthesis of substituted benzofurans from efficient easy access method.

DBU has been employed as an organic base for various organic reaction such as deprotonation agent [12], excellent catalytic activity in Baylis–Hillman reaction, acts as nucleophile [13] and carbonylation of di-*n*-propylamine [14]. Our trial employing DBU as a base, which is cheap and commercially available, leads to a successful furnished *o*-alkylated acetophenone derivative. To the best of our knowledge, there is no report on the synthesis of benzofurans from 2-hydroxy acetophenone moieties by using organic base DBU. In continuation of our research work on the synthesis and antioxidant activity of novel classes heterocyclic derivatives [15–17] and encouraged by the successful results obtained from these work, the present investigation we wish to propose a general method for the synthesis of novel benzofurans (Scheme 1 and Table 1). This synthetic strategy affords some advantages such as operational simplicity, lower cost, reaction carried out at RT, and simple workup procedure.

RESULTS AND DISCUSSION

Benzofurans were obtained in modified Rap–Stoermer reaction condition using an inorganic base that is, K_2CO_3 [18]. However, using of K_2CO_3 (6 mmol) failed to deliver

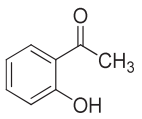
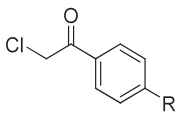
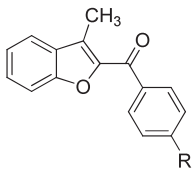
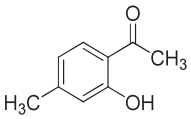
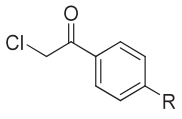
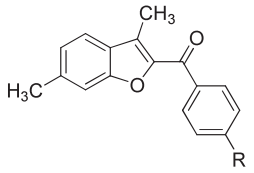
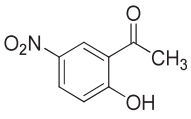
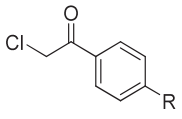
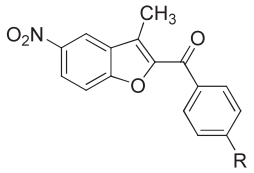
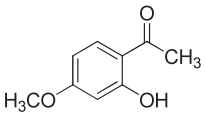
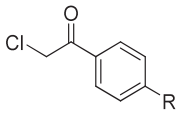
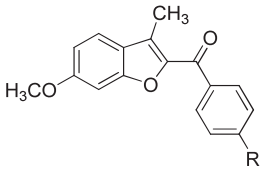
Scheme 1. DBU induced synthesis of benzofurans **3(a–t)**.



the total conversion of acetophenones to benzofurans even under reflux condition and longer reaction time (4 h) with lesser yields (62–70%). In this study, scrutiny with catalytic amount of DBU (4 mmol) as an organic base was found that the conversion was achieved under mild condition (RT) with lesser reaction time (except compounds **3d**, **3j**, and **3l**) with good yields (Table 1). In addition, the reactivity of various mono substituted 2-hydroxy

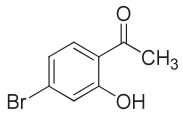
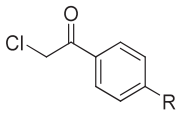
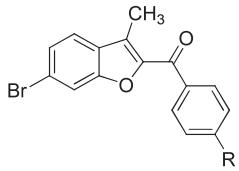
Table 1

An overview of synthesized benzofurans with yield **3(a–t)**.

Entry	2-Hydroxy acetophenones	Phenacyl chlorides	Time (h)	Product	Yield (%)	Melting point (°C)
						
3a		R=H	3.0	R=H	91.00	202–204
3b		R=OCH_3	2.5	R=OCH_3	90.20	231–233
3c		R=CH_3	2.0	R=CH_3	88.32	224–226[a]
3d		R=OH	4.0	R=OH	72.00	170–172
						
3e		R=H	2.0	R=H	83.00	218–220
3f		R=OCH_3	1.5	R=OCH_3	77.20	195–197
3g		R=CH_3	2.0	R=CH_3	80.35	191–193
3h		R=OH	3.0	R=OH	88.54	222–224
						
3i		R=H	3.5	R=H	85.10	234–236
3j		R=OCH_3	4.0	R=OCH_3	92.15	188–200
3k		R=CH_3	3.0	R=CH_3	89.16	212–214
3l		R=OH	4.0	R=OH	91.10	221–223
						
3m		R=H	1.5	R=H	80.00	85–87
3n		R=OCH_3	2.0	R=OCH_3	75.00	234–236
3o		R=CH_3	3.0	R=CH_3	76.20	191–193
3p		R=OH	3.0	R=OH	81.00	205–207

(*Continues*)

Table 1
(Continued)

Entry	2-Hydroxy acetophenones	Phenacyl chlorides	Time (h)	Product	Yield (%)	Melting point (°C)
						
3q		R=H	2.0	R=H	75.00	256–258
3r		R=OCH_3	1.5	R=OCH_3	63.55	231–233
3s		R=CH_3	2.5	R=CH_3	59.85	249–251
3t		R=OH	3.0	R=OH	73.20	271–273

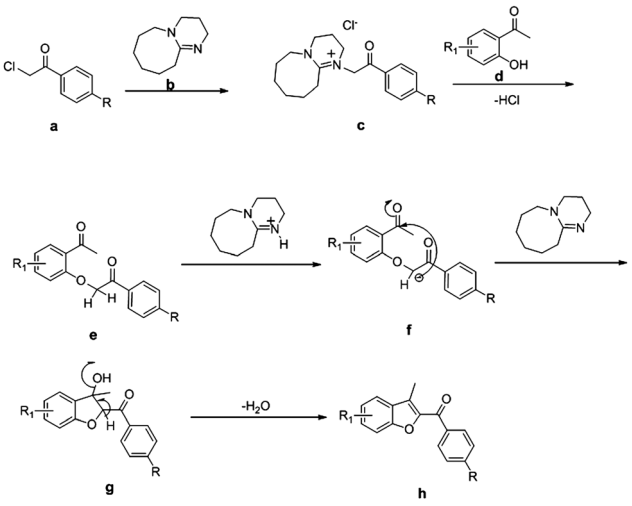
[a]Indicates the boiling point.

acetophenones was found to be efficient under the present conditions. Herein, we described a DBU assisted one-pot synthesis of benzofurans (Scheme 1). Initially, we have carried out the reaction of 2-hydroxy acetophenone (2 mmol), phenacyl chloride (2 mmol), and DBU (2 mmol) in dichloromethane (DCM) containing molecular sieves under N_2 atm (1.5–4 h), afforded expected product (3-methylbenzofuran-2-yl)(phenyl)methanone (**3a**), which was isolated in 65% yield. To improve the yield, we performed the reaction with increased DBU (3, 4 mmol). It was noted that, DBU (4 mmol) was optimal and isolated in 91% yield. But, increased (5–6 mmol) and decreased (1 mmol) in the DBU concentration did not favor improved yield.

Optimization of reaction conditions was carried out at different solvents such as acetone, THF, DCM, acetonitrile, MeOH, and EtOH, respectively. However, DCM was the better solvent in regard to best yield and reaction time. To extend the scope of one-pot procedure, next, we discovered various substituted 2-hydroxy acetophenones and phenacyl chlorides in the optimized condition. It was observed that, 2-hydroxy acetophenones emphasizes with either electron-withdrawing or electron-donating substituents reacted effectively with phenacyl chlorides and led to good yields of benzofurans **3**(**a–t**). It was noticed that, present synthetic strategy was very efficient and applicable for a variety of phenacyl chlorides results in corresponding benzofurans (Scheme 1). This method may be applicable for the preparation of large number of benzofurans under mild condition because of the easy availability of phenacyl chlorides and 2-hydroxy acetophenones (Table 1). The mechanism involves, *o*-alkylation of substituted 2-hydroxy acetophenones (**d**) with phenacyl chlorides (**a**) in presence of DBU (**b**) as organic base furnished *o*-alkylated derivative (**e**), which subsequently generates enolate anion (**f**) undergo intramolecular cyclocondensation reaction afforded benzofurans (**h**) in excellent yields (Scheme 2).

The synthesized compounds were also evaluated for their antioxidant activity by using two *in vitro* assays,

Scheme 2. General synthetic mechanism of the title compounds **3**(**a–t**).



such as 2,2′-diphenyl-1-picryl-hydrazyl (DPPH) [19] and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) [20] free radical scavenging activity (RSA).

Free radical scavenging is one of the best known mechanism by which antioxidants inhibit the oxidation and offers a rapid technique for screening the RSA of specific compounds. Majority of the tested compounds in these series showed low to moderate interaction with DPPH and ABTS radical (Table 2). Ascorbic acid was used as standard antioxidant. In the both assays, among the tested compounds, **3a**, **3e**, **3i**, **3m**, and **3q**, which does not have any substituents on the phenacyl ring and as well as benzofuran ring, does not boost up the activity. Compounds **3b**, **3f**, and **3n**, which contains electron-donating methoxy group on the phenacyl ring showed moderate inhibitory effect. The reaction of 4-hydroxy substituted phenacyl chloride with substituted 2-hydroxy acetophenones led to the compounds **3d**, **3h**, **3l**, and **3t** exhibited good antioxidant activity but less than the standard. The maximum

Table 2

The 50% inhibition of DPPH and ABTS radical by compounds **3(a–t)**. Each value represents mean ± SD ($n = 3$).

Compound no	DPPH activity IC_{50} (μM/mL)[a]	ABTS activity IC_{50} (μM/mL)[a]
3a	> 500	485 ± 0.09
3b	110 ± 0.12	126 ± 0.15
3c	163 ± 0.13	174 ± 0.36
3d	68 ± 0.25	56 ± 0.19
3e	495 ± 0.13	> 500
3f	103 ± 0.32	116 ± 0.54
3g	142 ± 0.14	159 ± 0.23
3h	49 ± 0.35	58 ± 0.20
3i	472 ± 0.56	> 500
3j	152 ± 0.56	146 ± 0.51
3k	315 ± 0.12	342 ± 0.23
3l	71 ± 0.68	86 ± 0.12
3m	> 500	> 500
3n	89 ± 0.59	96 ± 0.35
3o	130 ± 0.14	126 ± 0.66
3p	39 ± 0.52	45 ± 0.41
3q	> 500	> 500
3r	254 ± 0.23	289 ± 0.16
3s	395 ± 0.52	412 ± 0.55
3t	101 ± 0.14	152 ± 0.21
Ascorbic acid	17 ± 0.32	26 ± 0.71

DPPH, 2,2′-diphenyl-1-picryl-hydrazyl; ABTS, 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) .

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

RSA was observed in compound **3p**, containing methoxy and hydroxy substituents on the benzofuran and as well as phenacyl ring. Whereas, compounds **3c**, **3g**, and **3o** possessing methyl group on phenacyl ring at *para* position exposed the considerable activity. The remaining benzofurans **3j**, **3k**, **3r**, and **3s** contains electron-withdrawing (nitro) and halogens (bromo) groups on benzofuran ring might be the reason, which does not favor the noteworthy activity compared with standard. Interestingly, from both the antioxidant assays, we noted that presence of hydroxy and electron-donating group substituents at different C-terminals of phenacyl ring and as well as benzofuran ring may be favorable for significant increase in the activity.

In summary, we have developed a simple and efficient one-pot synthetic procedure for preparation of benzofurans. The advantage of this methodology lies in higher yields, operational simplicity, use of simple and inexpensive catalyst, and less pollution to environment. Moreover, this procedure will provide a good to excellent method for synthesis of substituted benzofurans. Among the tested benzofurans, compounds **3p** exhibited better *in vitro* antioxidant activity, suggesting that the benzofurans moiety may be a beneficial scaffold for therapeutic purpose. The preliminary antioxidant activity results are very interesting, the further investigation with increased antioxidant potency is currently underway.

EXPERIMENTAL

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and were used as provided. DPPH, ABTS, and ascorbic acid were purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA). TLC analysis was performed on alumina sheets precoated with silica gel 60 F-254 and SiO_2, 200–400 mesh (Merck) was used for column chromatography. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained AC Bruker spectrometer (Madison, Wisconsin, USA) in the appropriate (DMSO-d_6) solvent. Melting points were obtained on a Reichert Thermopan mp apparatus (Mumbai, India), equipped with a microscope and are uncorrected. Mass spectra were obtained by Water-Q-TOF ultima spectrometer (Kratos, Manchester, UK). Micro analytical data were obtained by elemental-Vario EL-III (Frankfurt, Germany).

General procedure for synthesis of benzofurans 3(a–t). A mixture of 2-hydroxy acetophenones (**1**) (2 mmol), phenacyl chlorides (**2**) (2 mmol), and 1,8-diaza bicyclo [5.4.0] undec-7-ene (4 mmol) in 10 mL of DCM containing molecular sieves was stirred under N_2 atm for the stipulated period (Table 1). 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 solids were obtained by desolventized in a rotary evaporator at RT affords respective benzofurans **3(a–t)**. All the structures of products were characterized by IR, ^{1}H and ^{13}C-NMR, ESI-MS, and elemental analysis. The spectral and analytical data for compounds (**3a–d**) [21(a-d)], **(3j)** and **(3l)** [22(a)], **(3 m)** [18] and **(3n-o)** [22(b-c)] are in agreement with that reported in the literature.

(3,6-Dimethylbenzofuran-2-yl)(phenyl)methanone (3e). Off white solid. IR (KBr)ν_{max}(cm^{-1}): 1683 (C═O), 1560 (C═C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 7.89 (d, 2H, $J = 8.9$ Hz, C_6H_5CO), 7.77 (d, 1H, $J = 8.3$ Hz, $CH_3C_6H_3$), 7.70–762 (m, 1H, C_6H_5CO), 7.64–7.53 (m, 2H, C_6H_5CO), 7.15 (m, 1H, $CH_3C_6H_3$), 6.90 (d, 1H, $J = 8.0$ Hz, C_6H_5CO), 2.55 (s, 3H, CH_3C_4O), 2.34 (s, 3H, $C_6H_3CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.1, 158.8, 150.4, 138.0, 132.9, 132.4, 129.7, 128.8, 129.5, 123.6, 118.1, 111.6, 21.3, 9.8; MS (ESI) *m/z*: 250.10 (M^+). *Anal*. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.78; found: C, 81.60; H, 5.60; O, 12.81%.

(3,6-Dimethylbenzofuran-2-yl)(4-methoxyphenyl)methanone (3f). Off white solid. IR (KBr)ν_{max}(cm^{-1}): 1678 (C═O), 1562 (C═C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 7.75 (d, 2H, $J = 8.5$ Hz, $OCH_3C_6H_4CO$), 7.68 (d, 1H, $J = 8.0$ Hz, $CH_3C_6H_3$), 7.52–7.29 (m, 1H, $CH_3C_6H_3$), 7.18 (d, 2H, $J = 8.1$ Hz, $OCH_3C_6H_4CO$), 6.92 (d, 1H, $J = 8.5$ Hz, $CH_3C_6H_3$), 3.82 (s, 3H, OCH_3), 2.52 (s, 3H, CH_3C_4O), 2.35 (s, 3H, $C_6H_3CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.1, 164.3, 158.9, 150.4, 133.0, 130.8, 129.6, 123.6, 114.5, 118.1, 111.6, 55.8, 21.6, 9.6; MS (ESI) *m/z*: 280.12 (M^+). *Anal*. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; O, 17.12; found: C, 77.08; H, 5.72; O, 17.16%.

(3,6-Dimethylbenzofuran-2-yl)(p-tolyl)methanone (3g). Light gray solid. IR (KBr)ν_{max}(cm^{-1}): 1680 (C═O), 1563 (C═C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 7.77 (d, 2H, $J = 8.3$ Hz, $CH_3C_6H_4CO$), 7.64–7.57 (m, 1H, $CH_3C_6H_3$), 7.45 (d, 2H, $J = 9.0$ Hz, $CH_3C_6H_4CO$), 7.34–7.29 (m, 1H, $CH_3C_6H_3$), 6.93 (d, 1H, $J = 8.3$ Hz, $CH_3C_6H_3$), 2.52 (s, 3H, CH_3C_4O), 2.35 (s, 6H, $C_6H_3CH_3$ and $C_6H_4CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.3, 158.6, 150.4, 142.4, 135.3, 132.9, 129.7, 129.0, 123.6, 118.0, 111.5, 21.6, 21.3, 9.3; MS (ESI)

m/z: 250.10 (M^+). *Anal*. Calcd. for $C_{18}H_{16}O_2$: C, 81.58; H, 5.64; O, 12.78; found: C, 81.60; H, 5.60; O, 12.81%.

(3,6-Dimethylbenzofuran-2-yl)(4-hydroxyphenyl)methanone (3h). Off white solid. IR (KBr)ν_{max}(cm^{-1}): 1675 (C=O), 1559 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 7.78 (d, 1H, J = 8.3 Hz, $CH_3C_6H_3$), 7.70 (d, 2H, J = 8.3 Hz, OHC_6H_4CO), 7.21 (m, 1H, $CH_3C_6H_3$), 6.97 (d, 1H, J = 8.0 Hz, $CH_3C_6H_3$), 6.89 (d, 2H, J = 9.0 Hz, OHC_6H_4CO), 5.30 (s, 1H, OH), 2.53 (s, 3H, CH_3C_4O), 2.34 (s, 3H, $C_6H_3CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.5, 162.4, 158.7, 150.4, 132.8, 131.1, 130.7, 129.7, 129.4, 123.6, 118.0, 116.0, 111.4, 21.5, 9.4; MS (ESI) *m/z*: 266.09 (M^+). *Anal*. Calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30; O, 18.02; found: C, 76.71; H, 5.28; O, 18.04%.

(3-Methyl-5-nitrobenzofuran-2-yl)(phenyl)methanone (3i). Light yellow solid. IR (KBr)ν_{max}(cm^{-1}): 1673 (C=O), 1558 (C=C), 1543 (N-O); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.42 (m, 1H, $NO_2C_6H_3$), 8.10 (d, 1H, J = 7.9 Hz, $NO_2C_6H_3$), 7.92 (d, 1H, J = 8.0 Hz, $NO_2C_6H_3$), 7.85 (d, 2H, J = 7. 9 Hz, C_6H_5CO), 7.73–7.68 (m, 1H, C_6H_5CO), 7.69–7.64 (m, 2H, C_6H_5CO), 2.52 (s, 3H, CH_3C_4O); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.3, 162.2, 150.4, 145.8, 138.2, 133.4, 132.6, 129.7, 128.5, 120.2, 116.8, 112.4, 9.5; MS (ESI) *m/z*: 281.07 (M^+). *Anal*. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98; O, 22.75; found: C, 68.35; H, 3.90; N, 5.01; O, 22.73%.

(3-Methyl-5-nitrobenzofuran-2-yl)(p-tolyl)methanone (3k). Off white solid. IR (KBr)ν_{max}(cm^{-1}): 1681 (C=O), 1555 (C=C), 1545 (N-O); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.51–8.41 (m, 1H, $NO_2C_6H_3$), 8.12 (d, 1H, J = 8.1 Hz, $NO_2C_6H_3$), 7.92 (d, 1H, J = 7.0 Hz, $NO_2C_6H_3$), 7.77 (d, 2H, J = 8.0 Hz, $CH_3C_6H_4CO$), 7.40 (d, 2H, J = 8.9 Hz, $CH_3C_6H_4CO$), 2.54 (s, 3H, CH_3C_4O), 2.32 (s, 3H, $C_6H_4CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.3, 1614, 150.4, 145.3, 142.3, 138.7, 133.3, 129.6, 129.1, 120.8, 116.8, 112.2, 21.2, 9.6; MS (ESI) *m/z*: 295.07 (M^+). *Anal*. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74; O, 21.67; found: C, 69.19; H, 4.46; N, 4.70; O, 21.63%.

(4-Hydroxyphenyl)(6-methoxy-3-methylbenzofuran-2-yl)methanone (3p). Brown solid. IR (KBr)ν_{max}(cm^{-1}): 1681 (C=O), 1555 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 7.72 (d, 2H, J = 8.5 Hz, OHC_6H_4CO), 7.64 (d, 1H, J = 8.5 Hz, $OCH_3C_6H_3$), 7.22 (m, 1H, $OCH_3C_6H_3$), 6.98 (d, 1H, J = 8.0 Hz, $OCH_3C_6H_3$), 6.88 (d, 2H, J = 9.0 Hz, OHC_6H_4CO), 5.32 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3C_4O); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.4, 162.4, 161.3, 157.6, 150.4, 131.1, 130.7, 129.7, 124.8, 118.8, 116.0, 111.3, 96.3, 55.8, 9.7; MS (ESI) *m/z*: 282.09 (M^+). *Anal*. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00; O, 22.67; found: C, 72.35; H, 5.10; O, 22.60%.

(6-Bromo-3-methylbenzofuran-2-yl)(phenyl)methanone (3q). Dark brown solid. IR (KBr)ν_{max}(cm^{-1}): 1670 (C=O), 1561 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.26 (m, 1H, BrC_6H_3), 7.89 (d, 2H, J = 8.7 Hz, C_6H_5CO), 7.79 (d, 1H, J = 8.5 Hz, BrC_6H_3), 7.75–7.69 (m, 1H, C_6H_5CO), 7.62–7.53 (m, 2H, C_6H_5CO), 7.30 (d, 1H, J = 8.0 Hz, BrC_6H_3), 2.53 (s, 3H, CH_3C_4O); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.0, 162.5, 150.3, 138.7, 132.5, 131.5, 129.8, 128.9, 127.8, 123.0, 117.5, 115.0, 9.6; MS (ESI) *m/z*: 313.95 (M^+). *Anal*. Calcd. for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52; Br, 25.35; O, 10.15; found: C, 61.03; H, 3.58; Br, 25.31; O, 10.25%.

(6-Bromo-3-methylbenzofuran-2-yl)(4-methoxyphenyl)methanone (3r). Brown solid. IR (KBr)ν_{max}(cm^{-1}): 1673 (C=O), 1565 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.31 (m, 1H, BrC_6H_3), 7.78 (d, 2H, J = 8.0 Hz, $OCH_3C_6H_4CO$), 7.75 (d, 1H, J = 7.6 Hz, BrC_6H_3), 7.35 (d, 1H, J = 8.1 Hz, BrC_6H_3), 7.33 (d, 2H, J = 8.4 Hz, $OCH_3C_6H_4CO$), 3.82 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3C_4O); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.5, 164.5, 162.7, 150.3, 131.5, 130.5, 129.7, 123.1, 117.8, 115.1, 114.4, 55.8, 9.8; MS (ESI) *m/z*: 344.00 (M^+). *Anal*. Calcd. for $C_{17}H_{13}BrO_3$: C, 59.15; H, 3.80; Br, 23.15; O, 13.90; found: C, 59.21; H, 3.85; Br, 23.12; O, 13.85%.

(6-Bromo-3-methylbenzofuran-2-yl)(p-tolyl)methanone (3s). Brown solid. IR (KBr)ν_{max}(cm^{-1}): 1679 (C=O), 1558 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.24–8.19 (m, 1H, BrC_6H_3), 7.75 (d, 2H, J = 8.5 Hz, $CH_3C_6H_4CO$), 7.55 (d, 1H, J = 8.0 Hz, BrC_6H_3), 7.42 (d, 2H, J = 8.8 Hz, $CH_3C_6H_4CO$), 7.25 (d, 1H, J = 7.5 Hz, BrC_6H_3), 2.55 (s, 3H, CH_3C_4O), 2.34 (s, 3H, $C_6H_4CH_3$); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.3, 162.5, 150.5, 142.3, 135.3, 131.4, 129.5, 129.0, 127.9, 123.1, 117.8, 115.1, 21.2, 9.6; MS (ESI) *m/z*: 328.01 (M^+). *Anal*. Calcd. for $C_{17}H_{13}BrO_2$: C, 62.03; H, 3.98; Br, 24.27; O, 9.72; found: C, 62.00; H, 4.12; Br, 24.15; O, 9.79%.

(6-Bromo-3-methylbenzofuran-2-yl)(4-hydroxyphenyl)methanone (3t). Light brown solid. IR (KBr)ν_{max}(cm^{-1}): 1678 (C=O), 1563 (C=C); ^{1}H-NMR (DMSO-d_6 400 MHz) δ ppm: 8.26–8.20 (m, 1H, BrC_6H_3), 7.81 (d, 1H, J = 8.0 Hz, BrC_6H_3), 7.72 (d, 2H, J = 8.7 Hz, OHC_6H_4CO), 7.35 (d, 1H, J = 9.0 Hz, BrC_6H_3), 6.88 (d, 2H, J = 8.8 Hz, OHC_6H_4CO), 5.32 (s, 1H, OH), 2.57 (s, 3H, CH_3C_4O); ^{13}C-NMR (DMSO-d_6 100 MHz) δ ppm: 167.2, 162.6, 162.4, 150.2, 131.5, 131.0, 130.9, 127.8, 123.1, 117.8, 116.0, 115.1, 9.6; MS (ESI) *m/z*: 329.99 (M^+). *Anal*. Calcd. for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35; Br, 24.13; O, 14.49; found: C, 58.13; H, 3.28; Br, 24.18; O, 14.35%.

Antioxidant evaluation

Assay for DPPH scavenging potential. The evaluation of antioxidant activity of newly synthesized benzofurans **3(a–t)** was performed by DPPH RSA assay. Internal standard Ascorbic acid and the synthesized compounds of different concentrations were prepared in distilled EtOH, 1 mL of each compound solutions having different concentrations (10, 25, 50, 100, 200, and 500 μM) were taken in different test tubes, 4 mL of 0.1 m*M* EtOH 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 EtOH 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 decreased in absorbance of the radical. The RSA was expressed as the inhibition percentage and was calculated using the formula:

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

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

Assay for ABTS$^+$ scavenging potential. The ability of the test sample to scavenge $ABTS^+$ radical cation was determined according to the literature method. The $ABTS^+$ radical cation was pregenerated by mixing 7 m*M* $ABTS^+$ stock solution with 2.45 m*M* potassium persulfate (final concentration) and incubating for 12–16 h in the dark at RT 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 RT, then 1 mL was mixed with different concentration of the test sample (10–500 μM), and the absorbance was measured at 734 nm

after 6 min. The scavenging capability of $ABTS^+$ radical was calculated using the following equation:

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

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.

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