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Synthesis and Antibacterial Activity Study of C-3 α, β-Unsaturated Ketone Linked Benzofuran Derivatives

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Abstract

Based on a benzofuran skeleton bearing aryl substituent at its C-3 position through an α, β-unsaturated ketone linker, twenty-one new compounds were chemically synthesized and biologically evaluated for their antibacterial activities against four bacteria, *Escherichia coli*, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis.* Nine of the synthesized benzofuran derivatives exhibited antibacterial activities. Among them, compound 7e showed excellent MIC_{80} values from 0.78 to 1.56 μg/mL and was comparable to the positive control drugs.

Keywords: Antibacterial activity; Benzofuran; α, β-unsaturated ketone linker; Synthesis

Introduction

Oligostilbenes have been widely investigated as bioactive functional molecules in recent years. Substitution of the double bond linker with furan moiety is an effective method of structural modification in designing new derivatives from natural oligostilbene [1-4]. For example, natural product corsifuran C, a furan-substituted oligostilbene analogue bearing 4-methoxyphenyl group at the C-2′ position (Figure 1) was reported as a neuron-protective and anti-tumor agent. Another natural product viniferin, which bearing a substituted phenyl at the C-3′ position of its benzofuran skeleton, presented antimicrobial, antiviral, antifungal, and antitumor activities (Figure 1). The existing of methanone linker between benzofuran and aromatic group at C-3′ position was also confirmed to contribute towards the improvement of biofunctional performance of benzofuran derivatives [5-8]. To investigate the relationship between the antibacterial activities of benzofuran derivatives and their molecular structures, a structural modification focusing on the C-3 position of benzofuran skeleton was carried out in our previous research work [9]. Specifically, a series of corsifuran C derivatives containing a 2, 3-disubstituted benzofuran moiety as its central skeleton, was designed and synthesized. Several potential leading compounds (A, B, C and D) have been identified (Figure 1) through an antibacterial screening test, which exhibited a better and an even wider-range of inhibitory activity against *Escherichia coli*, *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, and *Bacillus subtilis,* but were inactive against *C. albicans* (Table 1). The structure and activity relationship (SAR) analysis of those derivatives prompted further structural modification described in this study. According to our previous SAR analysis [9], a key improvement of antibacterial activities was produced by introducing hydroxyl substituted phenyl and methanone linker into the C-3 position of the benzofuran skeleton. It is presumed that the C-3 position of benzofuran ring was a potential functional site, and the single or double hydroxyl substituted phenyl and mathanone linker on C-3 position were essential for antibacterial activity of benzofuran families. Meanwhile, it was noticed that introducing electron-rich groups into the leading compound is a conventional way of molecular structural modification, and may result better biological performance, for example, the ethylene group in Combrestastatin A-4 derivatives [1,3,4] and Chalcone family analogues [10-17]. To examine the effect of antibacterial activities induced by C-3′ linkers, we achieved a further structural modification on C-2 methoxyphenyl substituted benzofuran skeleton by introducing substituted phenyl groups through α, β-unsaturated ketone linker at the C-3′ position in this paper. Two series of new benzofuran derivatives (Figure 2), 1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-3-phenylprop-2-en-1-one compounds and 3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-1-phenylprop-2-en-1-one compounds were synthesized and the antibacterial activities of these compounds was investigated. Specifically, the carbonyl linker was constructed by benzoyl chloride reacted with 2-substituted benzofuran, following the Friedel-Crafts procedure. The benzoyl chloride could be replaced by acetyl chloride and reacted with

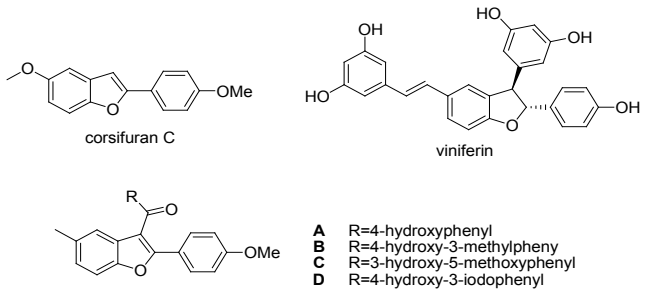

Figure 1: Structures of corsifuran C, viniferin and active benzofuran derivatives previously synthesized.

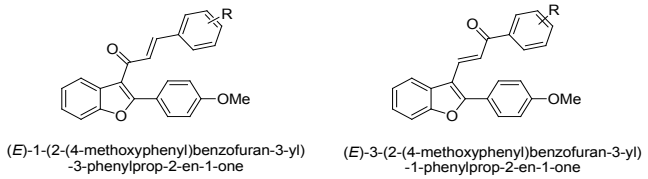

Figure 2: Structures of C-3 α, β-unsaturated ketone linker benzofuran derivatives.

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Compounds	Minimum inhibitory concentration (μg/ml)[a]				
	E. coil	*S. aureus*	MRSA	*B. subtilis*	*C. albicans*
A	0.78	<0.39	0.78	0.78	>200
B	0.78	0.78	0.78	1.56	>200
C	0.78	<0.39	0.78	0.78	>200
D	3.12	0.78	0.78	1.56	>200
Ceftazidime[b]	>200	0.78	12.5	6.25	-[c]
Cefotaxime[b]	>200	3.12	3.12	0.78	-
Sodium penicillin[b]	0.78	3.12	3.12	<0.39	-

[a]Minimum inhibitory concentration values are means of three experiments.
[b]Positive control.
[c]Not used in experiment

Table 1: *In vitro* antibacterial activity of benzofuran derivatives A-D.

benzofuran to afford the methanone substitute at C-3 position of the benzofuran skeleton. Treatment of methanone with sodium hydride, followed by the addition of benzaldehydes, using the Claisen-Schmidt procedure, α, β-unsaturated carbonyl bond was furnished. Meanwhile, the aldehyde group could be introduced to C-3′ position using $POCl_3$/DMF, which reacted with acetophenone to give another series of derivatives with α, β-unsaturated carbonyl linker (Figure 2).

Synthetic Procedures and Biological Evaluation

Synthetic procedures

Benzofuran derivatives described in this paper were prepared according to the follow synthetic route (Scheme 1). In general, salicylaldehyde 1 was reduced to alcohol 2 by Lithium aluminum hydride. Treating alcohol 2 with triphenylphosphine hydrobromide gave phosphonium salt 3. Coupling of the phosphonium salt with 4-methoxylbenzoic acid and cyclization under an adaptation of McKittrick and Stevenson's procedure gave benzofuran 4 [18]. Benzofuran 4 was treated with tin (IV) chloride and acetyl chloride at room temperature to give compound 5. Aldol condensation of 5 with substituted benzaldehydes gave compounds of series **7**. On the other hand, benzofuran 4 can be formylated with DMF/$POCl_3$ to produce 6, which coupled successively with substituted acetophenones to give compounds of series 8. Some methylmethoxylation compounds of series 7 and series 8 were undergone a deprotection process with HCl/MeOH, resulting in their respective phenolic compounds 7c-g and 8j-n (Scheme 2).

Biological evaluation

In vitro antibacterial activities of the synthesized new benzofuran derivatives against the Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 33712), Methicillin-resistant *Staphylococcus aureus* (ATCC 700699), and the Gram-negative bacteria *Escherichia coli* (ATCC 11303) were evaluated by the microtiter broth dilution method and susceptibility testing according to the National Committee for Clinical Laboratory Standards (NCCLS) [19,20]. The minimal inhibitory concentration (MIC_{80}) defined as the amount of compound required for the 80% inhibition of bacterial growth was recorded [8,21-25]. Resveratrol, Cephradine, Ceftazidime, Sodium cefotaxime and Sodium penicillin were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs were given in Table 2.

Materials and Methods

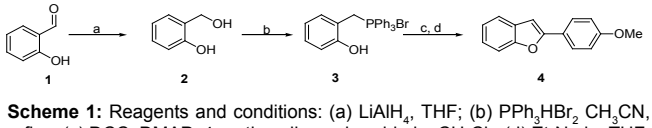
Chemistry

The ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Varian EM-360 spectrometer using TMS as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values are given in parts per million (ppm) and coupling constants (*J*) in Hertz. The mass spectra were recorded on an Esquire-LC-00075 mass spectrometer (Bruker). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}).

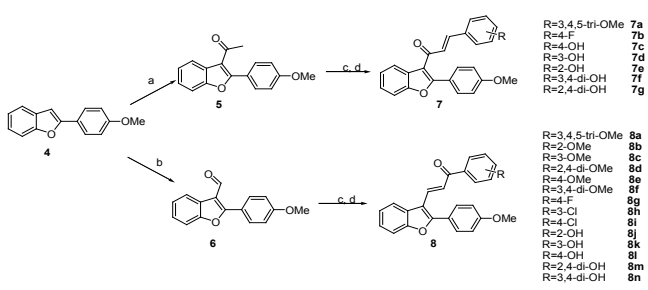
Compounds	R	Minimum inhibitory concentration (μg/mL)[a]			
		E. coli	*S. aureus*	MRSA	*B. subtilis*
7a	3,4,5-tri-OMe	>200	>200	>200	>200
7b	4-F	>200	>200	>200	>200
7c	4-OH	1.56	1.56	3.12	1.56
7d	3-OH	1.56	1.56	1.56	1.56
7e	2-OH	0.78	0.78	1.56	0.78
7f	3,4-di-OH	6.25	12.5	12.5	6.25
7g	2,4-di-OH	1.56	1.56	1.56	1.56
8a	3,4,5-tri-OMe	>200	>200	>200	>200
8b	2-OMe	>200	>200	>200	>200
8c	3-OMe	>200	>200	>200	>200
8d	2,4-di-OMe	>200	>200	>200	>200
8e	4-OMe	>200	>200	>200	>200
8f	3,4-di-OMe	>200	>200	>200	>200
8g	4-F	>200	>200	>200	>200
8h	3-Cl	>200	>200	>200	>200
8i	4-Cl	>200	>200	>200	>200
8j	2-OH	>200	>200	>200	>200
8k	3-OH	6.25	12.5	>200	6.25
8l	4-OH	12.5	25	25	6.25
8m	2,4-di-OH	6.25	12.5	12.5	6.25
8n	3,4-di-OH	6.25	12.5	6.25	6.25
Cephradine[b]		25	>200	>200	50
Ceftazidime[b]		>200	0.78	12.5	6.25
Sodium cefotaxime[b]		>200	3.12	3.12	0.78
Sodium penicillin[b]		0.78	3.12	3.12	<0.39
Resveratrol[b]		25	25	25	25

[a]Minimum inhibitory concentration values are means of three experiments.
[b]Positive control.

Table 2: *In vitro* antibacterial activity of twenty one synthesized benzofuran derivatives.



Scheme 1: Reagents and conditions: (a) $LiAlH_4$, THF; (b) PPh_3HBr_2 CH_3CN, reflux; (c) DCC, DMAP, 4-methoxylbenzoic acid, dry CH_2Cl_2; (d) Et_3N, dry THF, reflux.



Scheme 2: Reagents and conditions: (a) AcCl, $SnCl_4$, CH_2Cl_2; (b)$POCl_3$, DMF, reflux; (c) NaH, THF, PhCHO for **5**, $PhCOCH_3$ for **6**; d) HCl, MeOH, 55°C for 7c-g and 8j-n.

Synthesis of 2-(hydroxymethyl)- phenol (2): To a solution of $LiAlH_4$ (1.55 g, 40.9 mmol) in dry THF (50 mL) was added drop-wise salicylaldehyde (5 g, 40.9 mmol) in dry THF (50 mL) at 0°C. The suspension was stirred for 2 h, and quenched by water. The mixture was stirred at room temperature for 1 h, quenched with water. The suspension was filtered and the remained solvent was removed *in vacuo* to give phenol **2** as a white solid. Yield 100%; m.p. 84-88°C; EI-MS *m/z* 125.3; ^{1}H NMR (300 MHz, $CDCl_3$): 2.53 (brs, 1H, OH), 4.83 (s, 2H, $PhCH_2$), 6.83-6.88 (m, 2H, ArH), 7.03 (d, 1H, ArH, *J*=7.2 Hz), 7.20 (t, 1H, ArOH, *J*=8.1 Hz), 7.35 (s, 1H, ArH).

Synthesis of 2-(hydroxybenzyl)triphenylphosphonium bromide (3): Triphenylphosphine hydrobromide (11.1 g, 32 mmol) was added to a solution of phenol **2** (4 g, 32 mmol) in dry acetonitrile (100 mL) under nitrogen and the mixture heated under reflux for 2 h, then cooling to room temperature. The precipitate was filtered off and the solvent was removed *in vacuo* and the residue taken up in CH_2Cl_2 (20 mL). Diethyl ether was added and the resulting precipitate was filtered off and washed by diethyl ether to give the phosphonium salt **3** as a white powder. Yield 86%; m.p. 248-252°C; ^{1}H NMR (300 MHz, CD_3OD): 5.00 (s, 2H, CH_2Ph), 7.29 (m, 2H, ArH), 7.48-7.57 (m, 2H, ArH), 7.75-8.06 (m, 15H, PPh_3).

Synthesis of 2-(4-methoxyphenyl)-benzofuran (4): Dicyclohexylcarbodiimide (2.86 g, 13.9 mmol) in dry CH_2Cl_2 (10 mL) was added to a solution of phosphonium salt **3** (5 g, 11.12 mmol), 4-dimethylaminopyridine (271 mg, 2.22 mmol), and 4-methoxybenzoic acid (1.73 g, 11.4 mmol) in dry CH_2Cl_2 (100 mL) under nitrogen, and the mixture was stirred overnight. The solution was concentrated *in vacuo* and the residue dissolved in dry THF (100 mL). Triethylamine (9 mL, 64 mmol) was added and the mixture heated under reflux under nitrogen overnight. After cooling, the solution was filtered and the solvent removed *in vacuo*. Purification was performed by flash chromatography, and a gray solid **4** was obtained. Yield 83%; m.p.140-144°C; EI-MS *m/z* 225.3; ^{1}H NMR (300 MHz, $CDCl_3$): 3.86 (s, 3H, OMe), 6.89 (s, 1H, ArH), 6.98 (d, 2H, ArH, *J*=9.0 Hz), 7.28 (m, 2H, ArH), 7.48-7.57 (m, 2H, ArH), 7.80 (d, 2H, ArH, *J*=9.0 Hz).

Synthesis of 1-(2-(methoxylphenyl)benzofuran-3-yl)enthrone (5): $SnCl_4$ (0.697 g, 2.67 mmol) was added drop-wise to a mixture of **4** (0.5 g, 2.57 mmol) and the acetyl chloride (0.26 g, 3.34 mmol) in dry dichloromethane (50 mL) and the resulting solution was stirred at room temperature overnight. The reaction was quenched with ice and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over sodium sulfate. Purification was performed by flash chromatography, and the gray solid **5** was obtained. Yield 100%; m.p. 68-70°C; EI-MS *m/z* 267.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.53 (s, 3H, COMe), 4.02 (s, 3H, OMe), 7.16 (dd, 2H, ArH, *J*=6.6, 1.8 Hz), 7.47 (dd, 2H, ArH, *J*=6.3, 3.0 Hz), 7.63 (dd, 1H, ArH, *J*=6.3, 2.7 Hz), 7.85 (dd, 2H, ArH, *J*=7.2, 2.1 Hz), 8.19-8.22 (m, 1H, ArH).

2-(4-methoxyphenyl)benzofuran-3-carbaldehyde (6): $POCl_3$ (6.83 g, 44.6 mmol) was added to the mixture of **4** (2 g, 8.9 mmol) and DMF (3.26 g, 44.6 mmol) in 1,2-di-chloroethane under nitrogen and the resulting solution was heated to reflux for 2 h. Pour the mixture into ice-water, extracted with dichloromethane. The organic layers were washed with $NaHCO_3$ (aq.) and brine, dried over sodium sulfate. Purification was performed by flash chromatography, and the yellow solid **6** was obtained. Yield 100%; m.p. 158-162°C; EI-MS *m/z* 253.4; ^{1}H NMR (300 MHz, $CDCl_3$) δ:4.03 (s, 3H, OMe), 7.19 (d, 2H, ArH, J=9.0 Hz), 7.48-7.50 (m, 2H, ArH), 7.64-7.67 (m, 1H, ArH), 7.94 (d, 2H, ArH, J=9.0 Hz), 8.36-8.39 (m, 1H, ArH), 10.44 (s, 1H, CHO).

Genera l procedure for 7 and 8 using Claisen-Schmidt reaction: To a suspension of benzophenone (1 equiv.) and sodium hydroxide (6 equiv.) in dry THF (20 mL), benzaldehyde (1 equiv.) in THF was added under nitrogen at 0°C. The mixture was warm to room temperature, then stirred overnight. The resulting suspension was quenched with NH_4Cl (aq.). The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over sodium sulfate. Purification was performed by flash chromatography to provide compounds 7a-g and 8a-n.

(E)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-3-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one (7a): The title compound was obtained by the treatment of **5** and 3,4,5-trimethoxybenzaldehyde. Yield 76%; m.p. 134-138°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 6H, OMe), 3.98 (s, 6H, OMe), 6.65 (s, 2H, ArH), 6.98 (d, 1H, CH=CH, J=15.6 Hz), 7.15 (d, 2H, ArH, J=8.7 Hz), 7.47-7.50 (m, 2H, ArH), 7.64-7.67 (t, 1H, ArH), 7.75 (d, 1H, ArH, J=15.9 Hz), 7.90 (d, 2H, ArH, J=8.7 Hz), 8.26-8.29 (m, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): 189.1, 163.6, 157.5, 155.3, 143.4, 140.9, 135.3, 124.1, 123.8, 121.5, 119.3, 116.6, 114.5, 111.1, 110.2, 109.3, 107.2, 103.4, 55.3, 54.6, 53.9. HRMS [ESI(+)-MS]: $C_{27}H_{24}O_6$ $[M+H]^+$*m/z*, calc. 445.1651, found 445.1655.

(E)-3-(4-fluorophenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (7b): The title compound was obtained by the treatment of **5** and 4-fluorobenzaldehyde. Yield 48%; m.p. 98-102°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.88 (s, 3H, OMe), 6.92 (d, 1H, CH=CH, *J*=15.6 Hz), 7.01 (d, 2H, ArH, *J*=8.7 Hz), 7.02 (t, 2H, ArH, *J*=8.4 Hz), 7.36 (t, 2H, ArH, *J*=3.3 Hz), 7.32-7.37 (m, 2H, ArH), 7.70 (d, 1H, CH=CH, *J*=15.6 Hz), 7.52-7.55 (m, 1H, ArH), 7.80 (d, 2H, ArH, *J*=9.0 Hz), 8.06-8.09 (m, 1H, ArH). HRMS [ESI (+) -MS]: $C_{24}H_{17}FO_3$ $[M+H]^+$*m/z*, calc. 373.1239, found 373.1242.

(E)-3-(4-hydroxyphenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (7c): The title compound was obtained by the treatment of **5** and 4-(methoxymethoxy) benzaldehyde, then deprotection by HCl/MeOH. Yield 65%; m.p. 156-160°C ;^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, OMe), 5.25 (brs, 1H, OH), 6.79 (d, 2H, ArH, *J*=8.4 Hz), 6.90 (d, 1H, CH=CH, *J*=15.9 Hz), 7.01 (d, 2H, ArH, *J*=8.7 Hz), 7.29 (d, 2H, ArH, *J*=8.7 Hz), 7.52-7.55 (m, 1H, ArH), 7.33-7.36 (m, 2H, ArH), 7.69 (d, 1H, CH=CH, *J*=15.9 Hz), 7.81 (d, 2H, ArH, *J*=9.0 Hz), 8.03-8.06 (m, 1H, ArH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_4$ $[M+H]^+$ *m/z*, calc. 371.1283, found 371.1288.

(E)-3-(3-hydroxyphenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)prop-2-en-1-one (7d): The title compound was obtained by the treatment of **5** and 3-(methoxymethoxy) benzaldehyde, then deprotection by HCl/MeOH. Yield 63%; m.p. 160-164°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.95 (s, 3H, ArH), 6.94 (dd, 1H, ArH, *J*=7.8, 1.8 Hz), 7.00 (d, 2H, ArH, *J*=9.0 Hz), 7.05 (d, 1H, CH=CH, *J*=15.9 Hz), 7.19 (d, 2H, ArH, *J*=8.7 Hz), 7.25 (t, 1H, ArH, *J*=8.4 Hz), 7.40-7.50 (m, 3H, ArH), 7.67 (d, 1H, CH=CH, *J*=15.9 Hz), 7.68 (dd, 1H, ArH, *J*=7.2, 1.2 Hz), 7.90 (dd, 2H, ArH, *J*=6.9, 2.7 Hz), 8.10 (dd, 1H, ArH, *J*=7.5, 1.2 Hz), 8.65 (s, 1H, OH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_4$ $[M+H]^+$*m/z*, calc. 371.1283, found 371.1287.

(E)-3-(2-hydroxyphenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (7e): The title compound was obtained by the treatment of **5** and 2-(methoxymethoxy) benzaldehyde, then deprotection by HCl/MeOH. Yield 59%; m.p. 150-154°C;^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.95 (s, 3H, OMe), 6.87 (t, 1H, ArH, *J*=7.5 Hz), 6.98 (d, 1H, ArH, *J*=8.1 Hz), 7.17 (dd, 2H, ArH, *J*=6.9, 2.4 Hz), 7.23-7.30 (m, 2H, ArH), 7.26 (d, 1H, CH=CH, *J*=16.2 Hz), 7.37-7.49 (m, 3H, ArH), 7.67 (dd, 1H, ArH, *J*=6.9, 1.2 Hz), 7.91 (dd, 2H, ArH, *J*=6.6, 1.8

Hz), 8.09-8.11 (m, 1H, ArH), 8.12 (d, 1H, CH=CH, *J*=15.9 Hz), 9.23 (brs, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): 189.8, 168.5, 157.1, 155.3, 151.9, 141.4, 128.6, 127.3, 125.1, 124.1, 122.2, 120.6, 119.3, 118.2, 116.5, 115.7, 112.1, 110.2, 109.3, 107.2, 54.8. HRMS [ESI(+)-MS]: $C_{24}H_{18}O_4$ $[M+H]^+$*m/z*, calc. 371.1283, found 371.1285.

(E)-3-(3,4-dihydroxyphenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (7f): The title compound was obtained by the treatment of **5** and 3, 4-bis-(methoxymethoxy) benzaldehyde and then deprotection by HCl/MeOH. Yield 37%; m.p. 216-220°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.94 (s, 3H, OMe), 6.86-6.97 (m, 1H, ArH), 6.92 (d, 1H, CH=CH, *J*=15.6 Hz), 7.04 (brs, 1H, ArH), 7.17 (d, 2H, ArH, *J*=9.3 Hz), 7.38-7.46 (m, 3H, ArH), 7.64 (d, 1H, CH=CH, *J*=15.9 Hz), 7.61-7.67 (m, 1H, ArH), 7.89 (d, 2H, ArH, *J*=8.7 Hz), 8.04-8.07 (m, 1H, ArH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_5$ $[M+H]^+$*m/z*, calc. 387.1232, found 387.1236.

(E)-3-(2,4-dihydroxyphenyl)-1-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (7g): The title compound was obtained by the treatment of **5** and 2, 4-bis-(methoxymethoxy) benzaldehyde, and then deprotection by HCl/MeOH. Yield 41%; m.p. 214-216°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.95 (s, 3H, OMe), 6.87-6.93 (m, 1H, ArH), 6.91 (d, 1H, CH=CH, *J*=15.9 Hz), 7.03 (brs, 1Hm ArH), 7.18 (dd, 2H, ArH, *J*=6.9, 2.1 Hz), 7.38-7.48 (m, 3H, ArH), 7.38-7.48 (m, 3H, ArH), 7.63 (d, 1H, CH=CH, *J*=15.9 Hz), 7.66 (d, 1H, ArH, *J*=7.5 Hz), 7.90 (dd, 2H, ArH, *J*=6.9, 2.1 Hz), 8.04-8.07 (m, 1H, ArH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_5$ $[M+H]^+$*m/z*, calc. 387.1232, found 387.1238.

(E)-1-(3,4,5-trimethoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8a): The title compound was obtained by the treatment of **6** and 1-(3,4,5-trimethoxyphenyl)-ethanone. Yield 70%; m.p. 136-140°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 3.96 (s, 3H, OMe), 3.97 (s, 6H, OMe), 7.07 (d, 2H, ArH, *J*=9.0 Hz), 7.26 (s, 2H, ArH), 7.38-7.41 (m, 1H, ArH), 7.56-7.60 (m, 1H, ArH), 7.72 (d, 1H, CH=CH, *J*=15.6 Hz), 7.77 (d, 2H, ArH, *J*=9.3 Hz), 7.91-7.94 (m, 1H, ArH), 8.18 (d, 1H, CH=CH, *J*=15.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 190.5, 156.4, 160.3, 157.3, 151.5, 144.8, 136.2, 125.7, 123.8, 122.5, 119.6, 116.7, 116.4, 113.9, 110.4, 108.8, 105.2, 101.6, 56.7, 55.1, 54.3. HRMS [ESI(+)-MS]: $C_{27}H_{24}O_6$ $[M+H]^+$*m/z*, calc. 445.1651, found 445.1656.

(E)-1-(2-methoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8b): The title compound was obtained by the treatment of **6** and 1-(2-methoxyphenyl)-ethanone. Yield 59%; m.p. 122-126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 3.96 (s, 3H, OMe), 7.04 (d, 2H, ArH, *J*=8.7 Hz), 7.70 (d, 1H, CH=CH, *J*=15.3 Hz), 7.34-7.37 (m, 2H, ArH), 7.46-7.56 (m, 2H, ArH), 7.70-7.75 (m, 1H, ArH), 7.74 (d, 2H, ArH, *J*=8.7 Hz), 7.93-7.96 (m, 1H, ArH), 8.02 (d, 1H, CH=CH, *J*=15.9 Hz). HRMS [ESI (+) -MS]: $C_{25}H_{20}O_4$ $[M+H]^+$*m/z*, calc. 385.1439, found 385.1443.

(E)-1-(3-methoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8c): The title compound was obtained by the treatment of **6** and 1-(3-methoxyphenyl)-ethanone. Yield 74%; m.p. 116-120°C; ^{1}H NMR (300Hz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 3.91 (s, 3H, OMe), 7.06 (d, 2H, ArH, *J*=8.7 Hz), 7.15 (dd, 1H, ArH, *J*=8.1, 2.1 Hz), 7.38-7.41 (m, 2H, ArH), 7.45 (t, 1H, ArH, *J*=7.8 Hz), 7.56-7.59 (m, 1H, ArH), 7.63 (d, 1H, ArH, *J*=13.8 Hz), 7.70 (d, 1H, CH=CH, *J*=16.8 Hz), 7.76 (d, 2H, ArH, *J*=8.7 Hz), 7.94-7.97 (m, 1H, ArH), 8.19 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{25}H_{20}O_4$ $[M+H]^+$*m/z*, calc. 385.1439, found 385.1445.

(E)-1-(2, 4-di-methoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8d): The title compound was obtained by the treatment of **6** and 1-(2, 4-di-methoxyphenyl)-ethanone. Yield 73%; m.p. 118-122°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.88 (s, 6H, OMe), 3.97 (s, 3H, OMe), 6.53 (d, 1H, ArH, *J*=1.8 Hz), 6.58-6.61 (m, 1H, ArH), 7.04 (d, 2H, ArH, *J*=8.4 Hz), 7.33-7.36 (m, 2H, ArH), 7.53-7.56 (m, 1H, ArH), 7.76 (d, 2H, ArH, *J*=8.7 Hz), 7.86 (d, 1H, ArH, *J*=9.0 Hz), 7.86 (d, 1H, CH=CH, *J*=15.6 Hz), 7.94-7.97 (m, 1H, ArH), 8.07 (d, 1H ArH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{26}H_{22}O_5$ $[M+H]^+$*m/z*, calc. 415.1545, found 415.1548.

(E)-1-(4-methoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8e): The title compound was obtained by the treatment of **6** and 1-(4-methoxyphenyl)-ethanone. Yield 85%; m.p. 136-140°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 3.91 (s, 3H, OMe), 7.02 (d, 2H, ArH, *J*=8.7 Hz), 7.06 (d, 2H, ArH, *J*=8.7 Hz), 8.10 (d, 2H, ArH, *J*=8.7 Hz), 7.37-7.41 (m, 2H, ArH), 7.56-7.59 (m, 1H, ArH), 7.77 (d, 2H, ArH, *J*=8.1 Hz), 7.78 (d, 1H, CH=CH, *J*=15.6 Hz), 8.18 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{25}H_{20}O_4$ $[M+H]^+$*m/z*, calc. 385.1439, found 385.1442.

(E)-1-(3, 4-di-methoxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8f): The title compound was obtained by the treatment of **6** and 1-(3, 4-di-methoxyphenyl)-ethanone. Yield 85%; m.p. 138-142°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OMe), 3.99 (s, 6H, OMe), 6.97 (d, 1H, ArH, *J*=8.7 Hz), 7.06 (d, 2H, ArH, *J*=9.0 Hz), 7.36-7.40 (m, 2H, ArH), 7.56-7.59 (m, 1H, ArH), 7.68 (d, 1H, ArH, *J*=1.8 Hz), 7.73 (d, 1H, ArH, *J*=2.1 Hz), 7.77 (d, 2H, ArH, *J*=8.4 Hz), 7.80 (d, 1H, CH=CH, *J*=15.6 Hz), 7.94-7.97 (m, 1H, ArH), 8.18 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{26}H_{22}O_5$ $[M+H]^+$*m/z*, calc. 415.1545, found 415.1547.

(E)-1-(4-fluorophenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8g): The title compound was obtained by the treatment of **6** and 1-(4-fluorophenyl)-ethanone. Yield 77%; m.p. 124-126°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 7.06 (d, 2H, ArH, *J*=8.7 Hz), 7.21 (t, 2H, ArH, *J*=8.7 Hz), 7.39 (dd, 2H, ArH, *J*=6.0, 3.0 Hz), 7.53 (m, 1H, ArH), 7.75 (d, 1H, CH=CH, *J*=15.6 Hz), 7.76 (d, 2H, ArH, *J*=9.3 Hz), 7.94 (dd, 1H, ArH, *J*=5.7, 3.0 Hz), 8.11 (dd, 2H, ArH, *J*=9.0, 5.7 Hz), 8.19 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{24}H_{17}FO_3$ $[M+H]^+$*m/z*, calc. 373.1239, found 373.1246.

(E)-1-(3-chlorophenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8h): The title compound was obtained by the treatment of **6** and 1-(3-chlorophenyl)-ethanone. Yield 39%; m.p. 116-120°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 7.07 (d, 2H, ArH, *J*=8.7 Hz), 7.40 (dd, 2H, ArH, *J*=5.7, 3.3 Hz), 7.49 (d, 1H, ArH, *J*=8.1 Hz), 7.56 (s, 1H, ArH), 7.56-7.59 (m, 1H, ArH), 7.68 (d, 1H, CH=CH, *J*=15.6 Hz), 7.75 (d, 2H, ArH, *J*=9.0 Hz), 7.92-7.96 (m, 2H, ArH), 8.03 (brs, 1H, ArH), 8.18 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{24}H_{17}FO_3$ $[M+H]^+$*m/z*, calc. 373.1239, found 373.1243.

(E)-1-(4-chlorophenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8i): The title compound was obtained by the treatment of **6** and 1-(4-chlorophenyl)-ethanone. Yield 47%; m.p. 142-146°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 7.06 (d, 2H, ArH, *J*=9.0 Hz), 7.39 (dd, 2H, ArH, *J*=5.7, 3.0 Hz), 7.51 (d, 2H, ArH, *J*=8.4), 7.57 (dd, 1H, ArH, *J*=6.0, 3.0 Hz), 7.72 (d, 1H, CH=CH, *J*=15.3Hz), 7.75 (d, 2H, ArH, *J*=8.7 Hz), 7.94 (dd, 1H, ArH, *J*=5.7, 3.0 Hz), 8.02 (d, 2H, ArH, *J*=8.4 Hz), 8.19 (d, 1H, CH=CH, *J*=15.6 Hz). HRMS [ESI(+)-MS]: $C_{24}H_{17}ClO_3$ $[M+H]^+$*m/z*, calc. 389.0944, found 389.0948.

(E)-1-(2-hydroxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8j): The title compound was obtained by the treatment of **6** and 1-(2-(methoxymethoxy)-phenyl)-ethanone, then deprotection by HCl/MeOH. Yield 52%; m.p. 150-154°C; ^{1}H NMR (300

MHz, CD_3COCD_3) δ: 3.99 (s, 3H, OMe), 7.05-7.11 (m, 2H, ArH), 7.27 (dd, 2H, ArH, *J*=6.6, 2.4 Hz), 7.49-7.53 (m, 2H, ArH), 7.82-7.73 (m, 2H, ArH), 7.88 (dd, 2H, ArH, *J*=6.9, 2.4 Hz), 8.15 (d, 1H, CH=CH, *J*=15.3 Hz), 8.27-8.29 (dd, 1H, ArH, *J*=5.4, 2.7 Hz), 8.32 (d, 1H, CH=CH, *J*=15.3 Hz), 8.35-8.38 (m, 1H, ArH), 13.6 (brs, 1H, OH). HRMS [ESI (+) -MS]: $C_{24}H_{18}O_4$ $[M+H]^+$*m/z*, calc. 371.1283, found 371.1284.

(E)-1-(3-hydroxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8k): The title compound was obtained by the treatment of **6** and 1-(3-(methoxymethoxy)-phenyl)-ethanone, then deprotection by HCl/MeOH. Yield 63%; m.p. 188-192°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.98 (s, 3H, OMe), 7.18 (ddd, 1H, ArH, *J*=0.9, 2.4, 6.8), 7.26 (dd, 2H, ArH, *J*=1.5, 7.2), 7.44-7.52 (m, 3H, ArH), 7.64-7.65 (m, 1H, ArH), 7.69-7.75 (m, 2H, ArH), 7.86 (dd, 2H, ArH, *J*=1.8, 6.3), 7.95 (d, 1H, CH=CH, *J*=15.9), 8.16 (d, 1H, CH=CH, *J*=15.9), 8.22-8.25 (m, 1H, ArH), 8.90 (brs, 1H, OH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_4$ $[M+H]^+$*m/z*, calc. 371.1283, found 271.1287.

(E)-1-(4-hydroxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8l): The title compound was obtained by the treatment of **6** and 1-(4-(methoxymethoxy)-phenyl)-ethanone, then deprotection by HCl/MeOH. Yield 58%; m.p. 210-214°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.98 (s, 3H, OMe), 7.06 (dd, 2H, ArH, *J*=6.6, 1.8 Hz), 7.25 (dd, 2H, ArH, *J*=6.6, 1.8 Hz), 7.45-7.53 (m, 2H, ArH), 7.68-7.71 (m, 1H, ArH), 7.86 (dd, 2H, ArH, *J*=6.9, 2.4 Hz), 8.02 (d, 1H, CH=CH, *J*=15.3 Hz), 8.16 (d, 1H, CH=CH, *J*=15.3 Hz), 8.19 (dd, 2H, ArH, *J*=6.6, 1.8 Hz), 8.23-8.26 (m, 1H, ArH), 9.38 (brs, 1H, OH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_4$ $[M+H]^+$*m/z*, calc. 371.1283, found 371.1287.

(E)-1-(2, 4-di-hydroxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8m): The title compound was obtained by the treatment of **6** and 1-(2, 4-bis-(methoxymethoxy)-phenyl)-ethanone, then deprotection by HCl/MeOH. Yield 47%; m.p. 212-216°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.99 (s, 3H, OMe), 6.45 (d, 1H, ArH, *J*=2.1 Hz), 6.58 (dd, 1H, ArH, *J*=9.0, 2.7 Hz), 7.27 (dd, 2H, ArH, *J*=7.2, 2.4 Hz), 7.48-7.52 (m, 2H, ArH), 7.69-7.72 (m, 1H, ArH), 7.88 (dd, 2H, ArH, *J*=6.9, 2.1 Hz), 8.06 (d, 1H, CH=CH, *J*=15.3 Hz), 8.22 (brs, 1H, ArH), 8.27 (d, 1H, CH=CH, *J*=15.6 Hz), 8.26-8.28 (m, 1H, ArH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_5$ $[M+H]^+$*m/z*, calc. 387.1232, found 387.1236.

(E)-1-(3, 4-di-hydroxyphenyl)-3-(2-(4-methoxyphenyl)-benzofuran-3-yl)-prop-2-en-1-one (8n): The title compound was obtained by the treatment of **6** and 1-(3, 4-bis-(methoxymethoxy)-phenyl)-ethanone, then deprotection by HCl/MeOH. Yield 39%; m.p. 220-224°C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ: 3.98 (s, 3H, OMe), 7.04 (d, 1H, ArH, *J*=8.4 Hz), 7.25 (dd, ArH, 2H, *J*=6.9, 2.1 Hz), 7.48-7.51 (m, 2H, ArH), 7.68-7.78 (m, 3H, ArH), 7.86 (dd, 2H, ArH, *J*=6.6, 1.8 Hz), 7.98 (d, 1H, CH=CH, *J*=15.0 Hz), 8.15 (d, 1H, CH=CH, *J*=15.3 Hz), 8.22-8.25 (m, 1H, ArH). HRMS [ESI(+)-MS]: $C_{24}H_{18}O_5$ $[M+H]^+$*m/z*, calc. 387.1232, found 387.1237.

Antibacterial activities

The antimicrobial activities of the synthesized compounds were determined by the minimum inhibitory concentration (MIC) in accordance with NCCLS guideline M7-A6 and M38-P [19,20]. Pre-cultures of the tested bacteria were made by inoculating 10 mL of Luria-Bertani (LB) and incubating for 24 h at 37°C. The tested fungus, *Candida albicans*, was made by grown on Potato dextrose agar (PDA) for more than three days at 28°C. The colonies were harvested, suspended in sterile saline, and adjusted to a concentration that yielded an absorbance similar to that of a 0.5 McFarland standard in a spectrophotometer, bacteria at 625 nm or fungi at 530 nm, the equivalence of 1-2 × 10^8 cfu/mL. Then the samples were further diluted 1:10000 in LB or PDA to 1 × 10^4 cfu/mL. For the test, from a stock solution of the compounds of 4 mg/mL in DMSO, 10 μL tested solution was pipette into the wells in column 2 in 96-well plate. Using the multipipettes, 100 μL medium with microorganisms were dispensed into wells from column 3 to column 11. Another 200 μL broth bacteria dilution was dispensed into column 2, then being mixed up and down 6-8 times. Withdraw 100 μL mixtures from column 2 and add this to column 3. This made column 3 a twofold dilution of column 2. Repeat the procedure down to column 11. Discard 100 μL from column 11 rather than putting them in column 12. The compounds were diluted two fold concentration from 200 μg/mL to 0.39 μg/mL, from column 2 to column 11. Pipette 100 μL of sterile medium into column 1, and medium with microorganisms into column 12 as control groups. After incubating another 24 h for bacteria or 48 h for fungi, the lowest concentration of compounds that inhibited the visible growth of the organism was considered as MIC_{80}.

Results and Discussion

In this paper, the key intermediate 4 was synthesized starting from salicylaldehyde according to the literature method [18]. Seven derivatives of series **7** were prepared from 4 and respective substituted benzaldehyde compounds through Aldol condensation with a yield of 37-76%. Fourteen derivatives of series 8 were prepared from 4 and respective substituted acetophenone compounds in a similar procedure with a yield of 39-85%. The antibacterial screening results are shown in Table 2. In general, the hydroxyl-bearing compounds 7c-7g, 8k-8n showed the marked antibacterial activities against all four bacteria, whereas methoxyl group or halogen (F, Cl) atoms bearing ones showed no inhibitory effect against bacterial lines tested. Specifically, according of the preliminary anti-bacterial tests, the different substitute position of hydroxyl group on phenyl ring caused variational impact on the inhibitory activities. Compound 7e, with single hydroxyl group at C-2′, displayed the excellent antibacterial activities against *E. coli*, *S. aureus*, *B. subtilis* with MIC_{80} values of 0.78 μg/mL, and MRSA with that of 1.56 μg/mL, respectively, as compared to the positive control drugs. The presence of hydroxyl group at C-3′ position, compound 7d showed the favorable antibacterial activities against all the four bacteria with MIC_{80} value of 1.56 μg/mL. Compound 7c with the hydroxyl group at C-4′ position showed the similar activities against *E. coli*, *S. aureus*, *B. subtilis* as that of compound 7d, and two folds lower than that of 7d against *MRSA*. Compound 7g, with two hydroxyl groups at C-2′ and C-4′ positions, showed the similar activities against MRSA as that of compound 7e, and two folds lower than that of 7e against *E. coli*, *S. aureus*, and *B. subtilis*. When the hydroxyl groups appear at C-3′ and C-4′ positions, compound 7f showed weak activities against *E. coli* and *B. subtilis* with the MIC_{80} values of 6.25 μg/mL, and against *S. aureus* and MRSA with that of 12.5 μg/mL respectively. However, compound 8j**,** the isomer of 7e**,** bearing hydroxyl group at C-2′ position, was presented none antibacterial activities. Compound 8k, with a hydroxyl group at C-3′ position, compared with 7d, showed four folds weaker against *E. coli* and *B. subtilis* with MIC_{80} value of 6.25 μg/mL, and eight folds weaker against *S. aureus* with MIC_{80} value of 12.5 μg/mL, respectively. Meanwhile, similar declines of antibacterial activity were observed at other derivatives of 8 series. The MIC_{80} values of compounds 7c-g and 8k-n were illustrated in two curves respectively (Figure 3). For a further SAR discussion, we chose compounds 7d and 8k for an activity comparison, which bearing the same substituted phenyl ring in C-3 linker of benzofuran skeleton. Another two couples compound (7c versus 8l**,** and 7g versus 8m) were also chosen for this activity comparison. The MIC_{80} values of these six compounds against three bacteria *E. coli*, *S. aureus* and *B. subtilis* were exhibited in Figure 4

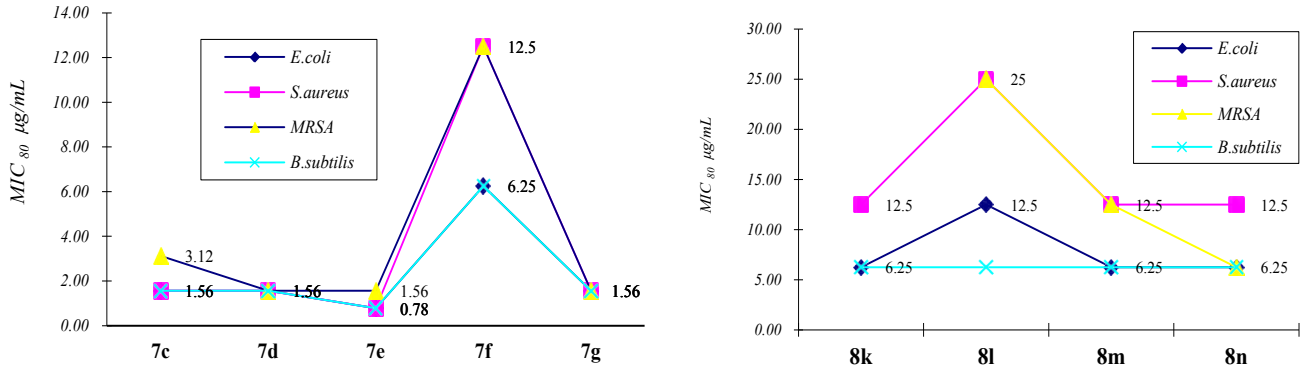


Figure 3: MIC_{80} values of compounds 7c-g and 8k-n against four bacteria.

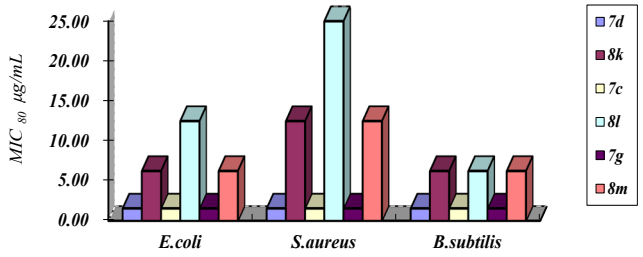


Figure 4: Activity comparison between active derivatives of 7 and 8 series with same side chains.

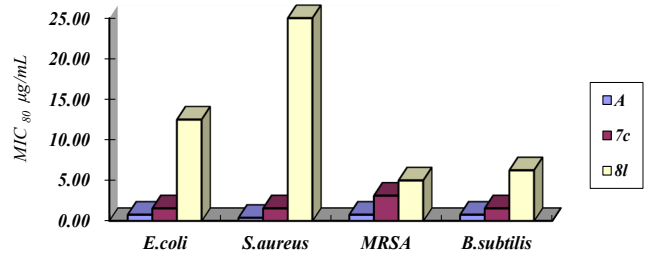


Figure 5: The comparison between the antibacterial activities of derivatives 7c, 8l and A.

to illustrate their antibacterial activity performance. An obvious trend can be observed that the antibacterial activities of the compound of 8 series were generally weaker than that of 7 series. To evaluate the antibacterial effect by introducing α, β-unsaturated ketone linker at C-3 position of the benzofuran skeleton, the antibacterial activities of compounds 7c and 8l were compared with that of the precious synthesized compound A. Compound A, bearing a methanone linker at C-3 position and 4'-OH substituted phenyl ring at the end of the linker, exhibited marked activity against tested bacteria. Compounds 7c and 8l were structural isomers, bearing 3-(4-hydroyl-phenylpro)-2-en-1-one and 1-(4-hydroyl-phenylpro)-2-en-1-one as side chains at C-3 position respectively. The MIC_{80} values of these three compounds against four screening bacteria were shown in Figure 5. Compound 7c was observed a two folds activity decline against *E. coli, S. aureus* and *B. subtilis* and a four folds decline against *MRSA* than that of compound A. Compound 8l was shown large gap decline than that of compound A, especially against *S. aureus*.

Conclusion

Twenty-one new benzofuran derivatives bearing α, β-unsaturated ketone linker and different substituted phenyl as side chains at C-3 position were prepared in 37-85% yield. The SAR analysis of the synthesized derivatives revealed that hydroxyl group on the phenyl ring enhanced antibacterial activity, whereas the methoxyl groups and halogen (F, Cl) atoms reduced and even dispelled it, which is consistent with our previous findings [9]. Among the screened compounds, derivatives of 7 series were generally better than that of 8 series, and 7e with hydroxyl substituted at C'-2 position displayed an outstanding activity as well as compound A. The present results also indicated that introducing α, β-unsaturated ketone linker, has not produced obviously advance on antibacterial activity compared with the precious designed carbonyl linker derivatives [9], which means more work and new method should be discussed in the future.

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