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Short communication

Synthesis and antimicrobial evaluation of new benzofuran derivatives

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ABSTRACT

Thirteen compounds, based on benzofuran skeleton bearing aryl substituents at its C-3 position through methanone linker, were synthesized and screened for their antibacterial and antifungal activities against four bacteria *Escherichia coli*, *Staphylococcus aureus*, Methicillin-resistant *S. aureus*, *Bacillus subtilis*, and a fungus *Candida albicans*. Four hydrophobic benzofuran analogs were found to exhibit favorable antibacterial activities (MIC_{80} = 0.39–3.12 μg/mL), which were better than the control drugs.

1. Introduction

Benzofuran derivatives are of special interest to natural product researchers for their biological activities and potential applications as pharmacological agents, *e.g.* corsifuran C (Fig. 1) [1–4]. Specifically, several benzofuran ring systems bearing various substituents at C-2 and C-3 positions are widely distributed in nature, the stilbenoids structural compounds, *e.g.* an oligostilbene derivative viniferin (Fig. 1), are known to possess antimicrobial, antiviral, antioxidant, antifungal, and antitumor activities [5–10].

Moreover, compounds containing methanone linker between the aromatic rings and benzofuran at the C-3 position had been investigated and reported as a uricosuricagent, a vasodilator, and a selective estrogen receptor modulator, such as benzbromarone and raloxifene (Fig. 2) [11–14]. In addition, phenyl(2-phenylbenzofuran-3-yl)methanone derivatives, *e.g.* SKF-64346, had been demonstrated to possess neuroprotective and antitumor activities [15]. As for antimicrobial activities of benzofuran families, researches have so far demonstrated that the antimicrobial activities of benzofuran families are a combination of substitutions at C-2 and C-3 positions of the benzofuran ring [16–23].

In our effort to search for better antimicrobial agents resulting from C-2 and C-3 substitutions, individually and collectively, we have initiated a study focusing on substitutions at the C-3 position of the benzofuran ring. In this report, we have purposely left 4′-methoxyphenyl unit at the C-2 position to eliminate contributions from C-2 substitutions. In natural products, corsifuran C analogs bearing the 4-methoxyphenyl substituent at the C-2 position were reported to have no antimicrobial activity. We introduced the carbonyl group between the aryl ring and benzofuran at the C-3 position, which is different from oligostilbenes, to evaluate the effects of substituents at the C-3 position on antimicrobial activities (Fig. 3).

2. Synthetic chemistry and biological evaluation

2.1. Synthetic chemistry

The benzofuran biphenyls described in this paper were prepared according to the synthetic Scheme 1 [24,25]. In Scheme 1, iodination of phenol **1** with NaI in the presence of NaOH and NaClO at low temperature (0 °C) gave the monoiodine-phenol **2**, which upon treatment with acetyl chloride produced intermediate **3**. Coupling of **3** with 1-ethynyl-4-methoxybenzene, using the Sonogashira protocol $Pd(PPh_3)_2Cl_2/CuI/Et_3N$, afforded diphenylethyne **4**. Compound **4** underwent an intra-molecular cyclization in potassium carbonate to furnish benzofuran **5**. Treatment of commercially available benzoic acids with $SOCl_2$ followed by the addition of **5** and tin (IV) chloride, using the Friedel–Crafts procedure furnished compounds **7** (**7a-h**). Acetylated compounds **7** were upon hydrolysis with KOH, resulting in their respective phenolic compounds **7i**–**7m** (Table 1).

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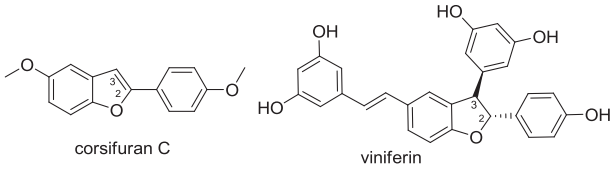


Fig. 1. Aryl benzofuran derivatives and oligostilbene derivatives.

2.2. Biological evaluation

As one of the largest groups of secondary plant metabolites, stilbenoids compounds were reported to be the defense response to microbial infections. Therefore, it was meaningful to investigate the antimicrobial activity for the synthesized compounds in vitro against the Gram-positive bacteria *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 33712), Methicillin-resistant *S. aureus* (ATCC 700699), the Gram-negative bacteria *Escherichia coli* (ATCC 11303), and fungi *Candida albicans* (ATCC 6258), following the procedure for the microtiter broth dilution method of the National Committee for Clinical Laboratory Standards (NCCLS) for susceptibility testing [26,27]. The minimal inhibitory concentration (MIC) is defined as the amount of compound required for >80% inhibition of bacterial growth, which made the visible clarity [8,28–30]. Resveratrol, Ceftazidime, Cefotaxime, Sodium penicillin, Miconazole nitrate, and Ketoconazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 2.

3. Results and discussion

In this present work, a series of thirteen new benzofuran derivatives were synthesized starting from 2-(4-methoxyphenyl)-5-methylbenzofuran (**5**) and benzoyl chloride (**6**) through the Friedel–Crafts reaction. Their ^{1}H NMR spectra suggested the presence of one characteristic ABX system [δ 7.26–7.51 (s, 1H, Hb), 7.12–7.19 (d, 1H, Hc), and 7.39–7.45 (d, 1H, Hd)], one methyl singlet [δ 2.40–2.46 (s, 3H)], and two doublet signals of 1,4-substituted benzene ring [δ 6.75–6.86 (d, 2H) and 7.46–7.63 (d, 2H)] in each case, which were consistent with those of **5**. Furthermore, the absence of the signal of Ha [δ 6.84 (s, 1H)] revealed the substituent at the C-3 position, respectively.

Preliminary anti-microorganism tests with thirteen compounds (Table 2) have established some interesting structure-activity relationships. Compound **7i**, with a hydroxyl group at C-4′, displayed the excellent antibacterial activities against *S. aureus* and MRSA with MIC_{80} values of 0.39 and 0.78 μg/mL, respectively, as compared to the positive control drugs. Its activities against *E. coli* and *B. subtilis* (Table 2) are comparable to that of Sodium penicillin against *E. coli* and that of Cefotaxime against *B.subtilis*, respectively. Compounds **7j** and **7m**, with additional substituents at C-3′ position, had shown medium antimicrobial activities with MIC_{80} values from 0.78 to 3.12 μg/mL against *E. coli* and *B. subtilis*. The presence of hydroxyl group at C-3′ position, compound **7k**, also had similar activities against all four bacteria as compound **7i** (MIC_{80} = 0.39–0.78 μg/mL). Unexpectedly, compound **7l**, when the hydroxyl group appeared at C-2′ position, has no activity against the bacteria (MIC_{80} > 200 μg/mL). On the other hand, compounds with the methylation of the hydroxyl group would reduce the solubility and decrease their antimicrobial abilities, such as compounds **7a** versus **7k** and **7b** versus **7i**. Much different from the natural products, compounds **7e**–**7h** with the halogen atoms substituents showed no antibacterial activity, whereas **7h** had favorable activity against *B. subtilis* with MIC_{80} of 0.78 μg/mL. All of the tested compounds showed no activity against *C. albicans*.

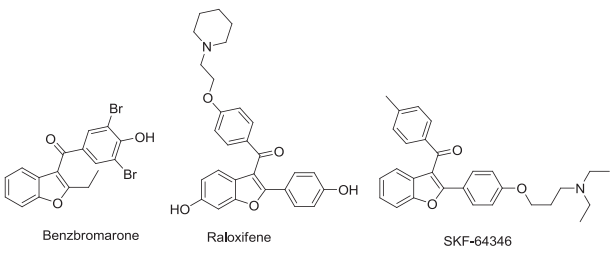
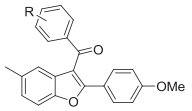


Fig. 2. Structure of benzbromarone, raloxifene and SKF-64346.



R = 3,5-dimethoxy(7a), 4-methoxy(7b), 2,3-dimethoxy(7c), 3,4,5-trimethoxy(7d), 4-chloro(7e), 3,5-dichloro(7f), 2-bomo,4,5-difluoro(7g), 2-bromo(7h), 4-hydroxy(7i), 4-hydroxy-3-methyl(7j), 3-hydroxyl-5-methoxyl(7k), 2-hydroxyl-3-methoxyl(7l), 4-hydroxyl-3-iodo(7m)

Fig. 3. Structure of synthesized compounds (**7a**–**7m**).

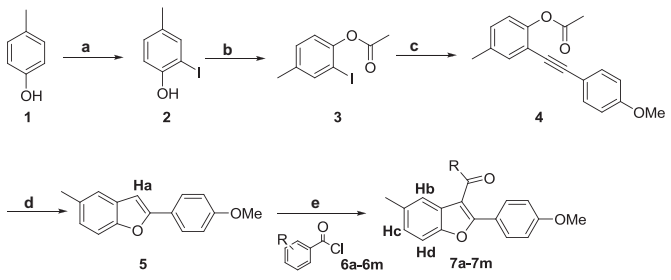
4. Conclusions

Thirteen new compounds with different substitutes at the C-3 position were prepared using reported methodologies. Surveying the data presented in Table 2, we have demonstrated that compounds with hydroxyl groups at C-3′ or C-4′ position had displayed antimicrobial activities similar to the findings with oligostilbene derivatives. Our results also indicated that the methanone linker makes no significant improvement from that of oligostilbenes in terms of antibacterial activities studied [5]. In addition, the hydroxyl groups on the aromatic ring enhanced the antimicrobial activity, whereas the methoxyl groups and halogen atoms reduced the activities.

5. Materials and methods

5.1. Chemistry

The ^{1}H NMR spectra were recorded at 300 MHz 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 and coupling constants (*J*) in Hertz. The mass spectra were recorded



Scheme 1. Reagents and conditions (a) NaI, NaOH, NaClO, H_2O, 0 °C; (b) Ac_2O, pyridine; (c) $Pd(PPh_3)_2Cl_2$ (2%), CuI (4%) and 1.2 equiv. 1-ethynyl-4-methoxybenzene, Et_3N, DMF, 60 °C; (d) K_2CO_3, methanol; (e) i) RCOCl, $SnCl_4$, CH_2Cl_2, ii) KOH, EtOH, H_2O (for **7i**–**7m**).

Table 1
Structures of targeted compounds, and their respective MS, m.p. and yield values.

	R	Modular	M.S	m.p.(°C)	Yield (%)
7a	3,5-dimethoxyphenyl	$C_{25}H_{22}O_5$	403.1	oil	49%
7b	4-methoxyphenyl	$C_{24}H_{20}O_4$	373.2	oil	64%
7c	2,3-dimethoxyphenyl	$C_{25}H_{22}O_5$	403.1	84–88	63%
7d	3,4,5-trimethoxyphenyl	$C_{26}H_{24}O_6$	433.1	56–60	63%
7e	4-chlorophenyl	$C_{23}H_{17}ClO_3$	342.2	58–62	37%
7f	3,5-dichlorophenyl	$C_{23}H_{16}Cl_2O_3$	411.0	102–106	70%
7g	2-bromo-4,5-difluorophenyl	$C_{23}H_{15}BrF_2O_3$	457.0/459.0	92–94	71%
7h	2-bromophenyl	$C_{23}H_{17}BrO_3$	421.0/422.1	98–100	71%
7i	4-hydroxyphenyl	$C_{23}H_{18}O_4$	359.1	166–170	48%
7j	4-hydroxy-3-methylphenyl	$C_{24}H_{20}O_4$	373.1	oil	65%
7k	3-hydroxy-5-methoxyphenyl	$C_{24}H_{20}O_5$	389.1	140–144	52%
7l	2-hydroxy-3-methoxyphenyl	$C_{24}H_{20}O_5$	389.3	oil	57%
7m	4-hydroxy-3-iodophenyl	$C_{23}H_{17}IO_4$	485.0	170–172	35%

on an Esquire-LC-00075 mass spectrometer (Bruker). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}).

*5.1.1. Synthesis of 2-iodo-4-methylphenol (**2**)*

To a solution of 4-methyphenol (2 g, 18.5 mmol), NaOH (0.74 g, 18.5 mmol), and NaI (2.77 g, 18.5 mmol) in methanol 50 mL, was added dropwise 5% NaClO 30 mL over 30 min, taking care to keep the mixture below 0 °C. After being stirred overnight at room temperature, the mixture was quenched by $Na_2S_2O_3$, extracted with Et_2O (50 mL × 3). The organic layer was washed by brine and dried over Na_2SO_4. The purification was carried out by flash chromatography, yielding pale yellow oil. Yield 17%; EI-MS *m*/*z* 234.6; ^{1}H NMR (300 MHz, $CDCl_3$): 2.42 (s, 3H, Me), 5.09 (brs, 1H, OH), 6.87 (d, 1H, ArH, *J* = 8.1 Hz), 7.03 (d, 1H, ArH, *J* = 8.1 Hz), 7.46 (s, 1H, ArH).

*5.1.2. Synthesis of 2-iodo-4-methylphenyl acetate (**3**)*

An excess of acetic anhydride (0.5 mL) was added to a solution of **2** (0.74 g, 3.16 mmol) in pyridine. After being stirred for 2 h, the reaction was poured onto EtOAc, washed with 2 N HCl, 5% $NaHCO_3$ and brine. The organic layers was dried over anhydrous sodium sulfate, filtered, and evaporated under pressure. The residue was directly used for the next reaction without further purification.

*5.1.3. Synthesis of 2-((4-methoxyphenyl)ethynyl)-4-methylphenyl acetate (**4**)*

Into a round-bottomed flask, stirred magnetically, were placed **3** (0.78 g, 3.16 mmol), dichloro-bis-(triphenylphosphine)-palladium (II) (44 mg, 0.06 mmol), and copper iodide (24 mg, 0.13 mmol) in DMF. After the reaction vessel was sealed, triethylamine (0.88 mL, 6.32 mmol) and 1-ethynyl-4-methoxybenzene (0.84 g, 6.32 mmol) in DMF were injected through the septum. The reaction mixture was heated for 6 h at 60 °C. Purification was performed by flash chromatography, and an amorphous solid was obtained. Yield 80%; m.p. 58–60 °C; EI-MS *m*/*z* 281.3; ^{1}H NMR (300 MHz, $CDCl_3$): 2.33 (s, 3H, COMe), 2.35 (s, 3H, Me), 3.83 (s, 3H, OMe), 6.87 (d, 2H, ArH, *J* = 8.7 Hz), 6.99 (d, 1H, ArH, *J* = 8.4 Hz), 7.13 (dd, 1H, ArH, *J* = 9.0, 1.5 Hz), 7.36 (d, 1H, ArH, *J* = 0.6 Hz), 7.42 (d, 2H, ArH, *J* = 9.0 Hz).

*5.1.4. Synthesis of 2-(4-methoxyphenyl)-5-methylbenzofuran (**5**)*

To a solution of compound **4** (0.6 g, 2.3 mmol) in methanol was added potassium carbonate (0.79 g, 5.75 mmol). The reaction mixture was heated to 60 °C overnight, then being left to cool. The reaction was poured onto EtOAc, washed with brine, and dried over anhydrous sodium sulfate. Purification was performed by flash chromatography, and an amorphous solid was obtained. Yield 90%; m.p. 170–172 °C; EI-MS *m*/*z* 239.2; ^{1}H NMR (300 MHz, $CDCl_3$): 2.47 (s, 3H, Me), 3.80 (s, 3H, OMe), 6.84 (s, 1H, ArH), 6.99 (d, 2H, ArH, *J* = 8.7 Hz), 7.08 (d, 1H, ArH, *J* = 7.5 Hz), 7.36 (s, 1H, ArH), 7.40 (d, 1H, ArH, *J* = 8.4 Hz), 7.81 (d, 2H, ArH, *J* = 8.7 Hz).

*5.1.5. General procedures for benzoyl chloride (**6a**–**6m**)*

The selected acid was refluxed in thionyl chloride for 2–3 h, and then the solution was cooled to room temperature, and the remaining thionyl chloride was evaporated to afford the acyl chloride, which was used without further purification.

*5.1.6. General procedure for (3,5-dimethoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7a**)*

$SnCl_4$ (1.2 eq.) was added dropwise to a mixture of **5** (50 mg, 0.21 mmol) and the 3,5-dimethoxybenzoyl chloride (1.2 eq.) in dry dichloromethane 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 yellow oil was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.69 (s, 6H, OMe), 3.80 (s, 3H, OMe), 6.57 (s, 1H, ArH), 6.81 (d, 2H, ArH, *J* = 9.0 Hz), 6.99 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.16 (d, 1H, ArH, *J* = 8.1 Hz), 7.43 (d, 1H, ArH, *J* = 7.2 Hz), 7.42 (brs, 1H, ArH), 7.58 (d, 2H, ArH, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 191.5, 160.3, 160.2, 157.6, 151.7, 139.2, 132.9, 129.5, 128.2, 125.8, 121.9, 120.6, 114.2, 113.4, 110.0, 106.9, 105.7, 55.1, 54.9, 20.9. HRMS [ESI (+) -MS]: $C_{25}H_{22}O_5$ $[M + H]^+$ *m*/*z*, calc. 403.1545, found 403.1542.

*5.1.6.1. (4-Methoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7b**).* The title compound was obtained by the treatment of **5** and 4-methoxybenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.80 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.76 (d, 2H, ArH, *J* = 8.7 Hz), 6.81 (d, 2H, ArH, *J* = 8.7 Hz), 7.12 (d, 1H, ArH, *J* = 7.2 Hz), 7.29 (s, 1H, ArH), 7.42 (d, 1H, ArH, *J* = 8.1 Hz), 7.61 (d, 2H, ArH, *J* = 9.3 Hz), 7.79 (d, 2H, ArH, *J* = 8.7 Hz). HRMS [ESI (+) -MS]: $C_{24}H_{20}O_4$ $[M + H]^+$ *m*/*z*, calc. 373.1440, found 373.1438.

*5.1.6.2. (2,3-Dimethoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7c**).* The title compound was obtained by the treatment of **5** and 2,3-dimethoxybenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.77 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.76 (d, 2H, ArH, *J* = 8.7 Hz), 6.89 (m, 3H, ArH), 7.13 (d, 1H, ArH, *J* = 8.1 Hz), 7.39 (d, 1H,

Table 2
In vitro antimicrobial activity of compounds (**7a**–**7m**).

Compounds	Minimum inhibitory concentration (μg/mL)				
	E. coli	*S. aureus*	MRSA	*B. subtilis*	*C. albicans*
7a	>200	>200	>200	>200	>200
7b	>200	>200	>200	>200	>200
7c	>200	>200	>200	>200	>200
7d	>200	>200	>200	>200	>200
7e	>200	>200	>200	>200	>200
7f	>200	>200	>200	>200	>200
7g	>200	>200	>200	>200	>200
7h	>200	>200	>200	0.78	>200
7i	0.78	<0.39	0.78	0.78	>200
7j	0.78	0.78	0.78	1.56	>200
7k	0.78	<0.39	0.78	0.78	>200
7l	>200	>200	>200	>200	>200
7m	3.12	0.78	0.78	1.56	>200
Ceftazidime	>200	0.78	12.5	6.25	–
Cefotaxime	>200	3.12	3.12	0.78	–
Sodium penicillin	0.78	3.12	3.12	<0.39	–
Resveratrol	25	25	25	25	>200
Ketoconazole	–	–	–	–	<0.39
Miconazole nitrate	–	–	–	–	<0.39

(–) means not used in experiment.

ArH, $J = 8.1$ Hz), 7.51 (s, 1H, ArH), 7.58 (d, 2H, ArH, $J = 8.7$ Hz). HRMS [ESI (+) -MS]: $C_{25}H_{22}O_5$ $[M + H]^+$ m/z, calc. 403.1545, found 403.1544.

*5.1.6.3. (3,4,5-Trimethoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7d**).* The title compound was obtained by the treatment of **5** and 3,4,5-trimethoxybenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.43 (s, 3H, Me), 3.71 (s, 6H, OMe), 3.80 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.82 (d, 2H, ArH, $J = 9.0$ Hz), 7.14 (brs, 2H, ArH), 7.17 (d, 1H, ArH, $J = 9.0$ Hz), 7.45 (d, 1H, ArH, $J = 9.0$ Hz), 7.51 (brs, 1H, ArH), 7.56 (d, 2H, ArH, $J = 8.7$ Hz). HRMS [ESI (+) -MS]: $C_{26}H_{24}O_6$ $[M + H]^+$ m/z, calc. 433.1651, found 433.1649.

*5.1.6.4. (4-Chlorophenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7e**).* The title compound was obtained by the treatment of **5** and 4-chlorobenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.80 (s, 3H, OMe), 6.81 (d, 2H, ArH, $J = 8.4$ Hz), 7.15 (d, 1H, ArH, $J = 8.4$ Hz), 7.29 (d, 2H, ArH, $J = 8.7$ Hz), 7.36 (s, 1H, ArH), 7.43 (d, 1H, ArH, $J = 7.8$ Hz), 7.56 (d, 2H, ArH, $J = 9.6$ Hz), 7.76 (d, 2H, ArH, $J = 8.7$ Hz). HRMS [ESI (+) -MS]: $C_{23}H_{17}ClO_3$ $[M + H]^+$ m/z, calc. 377.0944, found 377.0950.

*5.1.6.5. (3,5-Dichlorophenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7f**).* The title compound was obtained by the treatment of **5** and 3,5-dichlorobenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.45 (s, 3H, Me), 3.80 (s, 3H, OMe), 6.77 (d, 2H, ArH, $J = 9.0$ Hz), 7.05–7.09 (m, 1H, ArH), 7.18 (d, 1H, ArH, $J = 9.0$ Hz), 7.26 (s, 2H, ArH), 7.42 (d, 1H, ArH, $J = 8.7$ Hz), 7.46 (d, 2H, ArH, $J = 8.4$ Hz), 7.67 (s, 1H, ArH,). HRMS [ESI (+) -MS]: $C_{23}H_{16}Cl_2O_3$ $[M + H]^+$ m/z, calc. 411.0554, found 411.0559.

*5.1.6.6. (2-Bromo-4,5-difluorophenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7g**).* The title compound was obtained by the treatment of **5** and 2-bromo-4,5-difluorobenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.46 (s, 3H, Me), 3.81 (s, 3H, OMe), 6.79 (d, 2H, ArH, $J = 8.7$ Hz), 7.13 (dd, 1H, ArH, $J = 10.3$, 8.4 Hz), 7.19 (d, 1H, ArH, $J = 8.4$ Hz), 7.30 (dd, 1H, ArH, $J = 8.1$, 6.9 Hz), 7.43 (d, 1H, ArH, $J = 8.4$ Hz), 7.48 (d, 2H, ArH, $J = 9.0$ Hz), 7.68 (t, 1H, ArH, $J = 5.6$ Hz). HRMS [ESI (+) -MS]: $C_{23}H_{15}BrF_2O_3$ $[M + H]^+$ m/z, calc. 457.0251, found 457.0260.

*5.1.6.7. (2-Bromophenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7h**).* The title compound was obtained by the treatment of **5** and 2-bromobenzoyl chloride as described for **7a**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.42 (s, 3H, Me), 3.78 (s, 3H, OMe), 6.75 (d, 2H, ArH, $J = 9.0$ Hz), 7.13–7.18 (m, 3H, ArH), 7.27–7.30 (m, 1H, ArH), 7.41 (d, 1H, ArH, $J = 8.7$ Hz), 7.46–7.49 (m, 1H, ArH), 7.51 (d, 2H, ArH, $J = 9.0$ Hz), 7.53–7.56 (m, 1H, ArH). HRMS [ESI (+) -MS]: $C_{23}H_{17}BrO_3$ $[M + H]^+$ m/z, calc. 421.0439, found 421.0442.

*5.1.6.8. (4-Hydroxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7i**).* The title compound was obtained by the treatment of **5** and 4-(chlorocarbonyl)phenyl acetate as described for **7a**. The ester was dissolved in aqueous ethanol solution with KOH and stirred overnight. The solution was partially concentrated, dispersed in dichloromethane and the organic phase was washed with 1 N HCl, and brine; the organic phase was dried over sodium sulfate and concentrated to yield pure compound. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.80 (s, 3H, OMe), 6.76 (d, 2H, ArH, $J = 8.7$ Hz), 6.81 (d, 2H, ArH, $J = 8.7$ Hz), 7.12 (d, 1H, ArH, $J = 7.2$ Hz), 7.29 (s, 1H, ArH), 7.42 (d, 1H, ArH, $J = 8.1$ Hz), 7.61 (d, 2H, ArH, $J = 9.3$ Hz), 7.79 (d, 2H, ArH, $J = 8.7$ Hz), 8.10 (t, 1H, OH, $J = 8.4$ Hz). HRMS [ESI (+) -MS]: $C_{23}H_{18}O_4$ $[M + H]^+$ m/z, calc. 359.1283, found 359.1288.

*5.1.6.9. (4-Hydroxy-3-methylphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7j**).* The title compound was obtained by the treatment of **5** and 4-(chlorocarbonyl)-2-methylphenyl acetate as described for **7i**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.28 (s, 3H, Me), 2.42 (s, 3H, Me), 3.80 (s, 3H, OMe), 5.38 (brs, 1H, OH), 6.83 (d, 2H, ArH, $J = 8.7$ Hz), 7.03 (d, 1H, ArH, $J = 7.5$ Hz), 7.15 (d, 1H, ArH, $J = 9.0$ Hz), 7.28 (s, 1H, ArH), 7.34 (s, 1H, ArH), 7.44 (d, 1H, ArH, $J = 8.7$ Hz), 7.55 (s, 1H, ArH), 7.63 (d, 2H, ArH, $J = 9.0$ Hz). HRMS [ESI (+) -MS]: $C_{24}H_{20}O_4$ $[M + H]^+$ m/z, calc. 373.1440, found 373.1437.

*5.1.6.10. (3-Hydroxy-5-methoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7k**).* The title compound was obtained by the treatment of **5** and 3-(chlorocarbonyl)-5-methoxyphenyl acetate as described for **7i**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.41 (s, 3H, Me), 3.66 (s, 3H, OMe), 3.80 (s, 3H, OMe), 5.34 (brs, 1H, OH), 6.53 (t, 1H, ArH, $J = 2.3$ Hz), 6.82 (d, 2H, ArH, $J = 9.0$ Hz), 6.93 (brs, 2H, ArH), 7.14 (d, 1H, ArH, $J = 7.4$ Hz), 7.39 (s, 1H, ArH), 7.42 (d, 1H, ArH, $J = 8.7$ Hz), 7.59 (d, 2H, ArH, $J = 9.0$ Hz). HRMS [ESI (+) -MS]: $C_{24}H_{20}O_5$ $[M + H]^+$ m/z, calc. 389.1389, found 389.1392.

*5.1.6.11. (2-Hydroxy-3-methoxyphenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7l**).* The title compound was obtained by the treatment of **5** and 2-(chlorocarbonyl)-6-methoxyphenyl acetate as described for **7i**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.40 (s, 3H, Me), 3.81 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.61 (t, 1H, ArH, $J = 8.1$ Hz), 6.86 (d, 2H, ArH, $J = 8.7$ Hz), 7.03 (d, 1H, ArH, $J = 8.1$ Hz), 7.13 (dd, 1H, ArH, $J = 7.8$, 1.2 Hz), 7.15 (d, 1H, ArH, $J = 6.9$ Hz), 7.27 (s, 1H, ArH,), 7.43 (d, 1H, ArH, $J = 8.7$ Hz), 7.63 (d, 2H, ArH, $J = 8.7$ Hz), 12.58 (s, 1H, OH). HRMS [ESI (+) -MS]: $C_{24}H_{20}O_5$ $[M + H]^+$ m/z, calc. 389.1389, found 389.1394.

*5.1.6.12. (4-Hydroxy-3-iodophenyl)(2-(4-methoxyphenyl)-5-methylbenzofuran-3-yl)methanone (**7m**).* The title compound was obtained by the treatment of **5** and 4-(chlorocarbonyl)-2-iodophenyl acetate as described for **7i**. ^{1}H NMR (300 MHz, $CDCl_3$): 2.42 (s, 3H, Me), 3.83 (s, 3H, OMe), 6.86 (d, 2H, ArH, $J = 8.7$ Hz), 6.88 (d, 1H, ArH, $J = 7.5$ Hz), 7.16 (d, 1H, ArH, $J = 9.0$ Hz), 7.36 (brs, 1H, ArH), 7.44 (s, 1H, ArH), 7.45 (d, 1H, ArH, $J = 6.6$ Hz), 7.62 (d, 2H, ArH, $J = 9.6$ Hz), 7.71 (dd, 1H, ArH, $J = 8.1$, 2.1 Hz), 8.28 (brs, 1H, OH). HRMS [ESI (+) -MS]: $C_{23}H_{17}IO_4$ $[M + H]^+$ m/z, calc. 485.0250, found 485.0261.

5.2. Antimicrobial 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 [26,27].

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, *C. 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 $\times$ 10^8 cfu/mL. Then the samples were further diluted 1:10,000 in LB or PDA to 1 $\times$ 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 two-fold 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}.

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