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ORIGINAL PAPER

Structural revision of sesbagrandiflorains A and B, and synthesis and biological evaluation of 6-methoxy-2-arylbenzofuran derivatives

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Abstract

Sesbagrandiflorains A (1) and B (2), isolated from the stem bark of the Indonesian fabaceous plant *Sesbania grandiflora*, were reported to be 6-methoxy-2-(2´,3´-dihydroxy-5´-methoxyphenyl)-1-benzofuran-3-carbaldehyde and 6-hydroxy-2-(2´,3´-dihydroxy-5´-methoxyphenyl)-1-benzofuran-3-carbaldehyde, respectively. However, based on reevaluation of their 1D and 2D NMR data, the chemical structures of 1 and 2 have been revised to 4-hydroxy-2-(4´-hydroxy-2´-methoxyphenyl)-6-methoxybenzofuran-3-carbaldehyde and 4-hydroxy-2-(4´-hydroxy-2´-hydroxyphenyl)-6-methoxybenzofuran-3-carbaldehyde, respectively. In addition, seven new derivatives of **1** have been synthesized from the natural product in good yields (65 – 93%). The chemical structures of the synthetic compounds—one diester (6), four ethers (7–10), one secondary amine (11), and one oxime (12)—were confirmed by MS and NMR analysis. Compound 6 exhibited moderate antibacterial activity against the plant pathogen *Rhodococcus fascians* with a MIC of 0.1 mg/mL. Compounds 8 and 12 demonstrated respectable cytotoxicity against A375 melanoma cancer cells line with the relative IC$_{50}$ values of 22.8 and 32.7 µM, respectively.

Keywords Antibacterial activity · Cytotoxicity · sesbagrandiflorain · *Sesbania grandiflora* · *Rhodococcus fascians*

Introduction

2-Arylbenzofurans are a group of natural products that exhibit various biological activities, e.g., α-glucosidase inhibitory activity [1], antioxidant [2–4], anti-inflammatory [5], tyrosinase inhibitory activity [6], antitumor [7–11], and anti-Alzheimer's [12]. Members of this class of compounds have been identified in a wide variety of plants from the family of Moraceae (e.g., *Chlorophora regia* [3], *Artocarpus gomezianus* [1], *Morus alba* [4, 11, 13], *Morus cathayana* [10, 14], *Morus insignis* [15], *Morus notabilis* [6], *Morus wittiorum* [5], *Morus yunannensis* [16]); Dipterocarpaceae (e.g., *Hopea megarawan* [8]); Lauraceae (e.g., *Nectandra purpurascens* [17]); Poaceae (e.g., *Oryza sativa* [2]); Melanthiaceae (e.g., *Schoenocaulon officinale* [18]); Fabaceae (e.g., *Erythrina burttii* [19], *Sophora tonkinensis* [20]); and Rutaceae (e.g., *Zanthoxylum capense* [9]). A subset of 2-arylbenzofuran natural products, the 2-arylbenzofuran-3-carbaldehydes (a.k.a. 3-formyl-2-arylbenzofurans), appear to be unique to certain plants from the family of Fabaceae (e.g., *Andira inermis* [21], *Erythrina variegata* [22], *Hedysarum multijugum* [23], *Medicago sativa* [24], and *Onobrychis ebenoides* [25, 26]), Iteaceae (*Itea ilicifolia* [27]), and Lamiaceae (e.g., *Salvia miltiorrhizae* [28]). Recently, a number of 2-arylbenzofuran-3-carbaldehydes (1–5) were isolated from the stem bark of an Indonesian fabaceous plant, *Sesbania grandiflora* (Fig. 1) [29, 30].

Noviany Noviany and Arash Samadi contributed equally.

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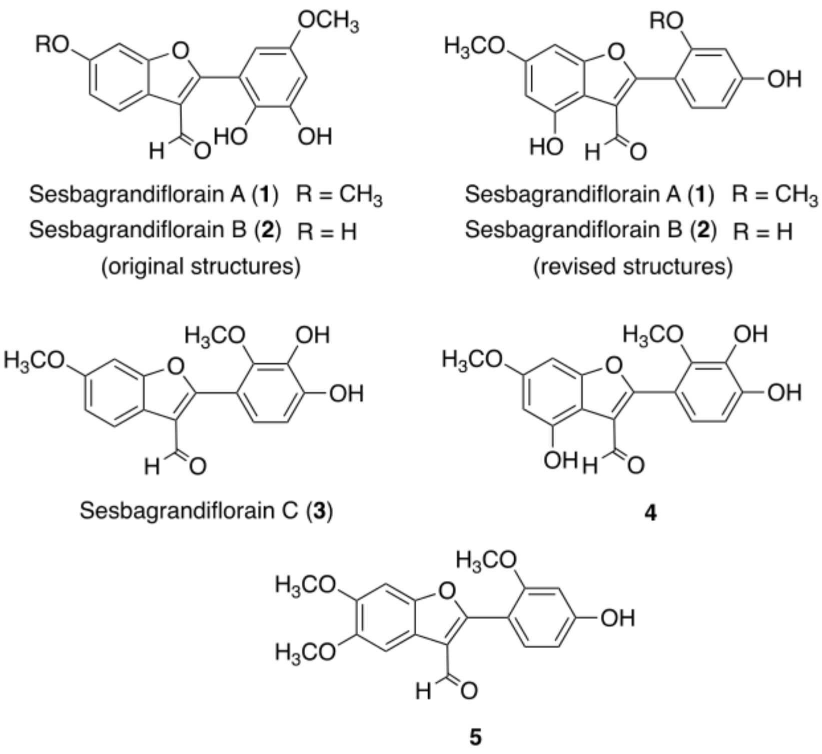
Fig. 1 Chemical structures of natural 2-arylbenzofurans from *S. grandiflora* stem bark



Sesbagrandiflorain A (1) was the major constituent among the 2-arylbenzofuran-3-carbaldehydes isolated from *S. grandiflora* stem bark [29, 30]. Limited biological studies revealed that it has a moderate activity against certain cancer cell lines but did not show growth inhibitory activity against most bacteria [30]. Furthermore, compounds 1–5 have somewhat different cytotoxicity profiles [30], indicating that minor modifications of their chemical structures may directly affect their biological activities. Therefore, structural modifications of the natural products may lead to improved biological properties.

During the course of our semi-synthetic effort to produce derivatives of compound 1, we discovered that the reported chemical structure of 1 was incorrect. Here, we report structural revision of sesbagrandiflorain A (1) and its analog, sesbagrandiflorain B (2), as well as chemical derivatization of 1 and biological evaluation of the products against a number of bacterial strains, including the plant pathogen *Rhodococcus fascians*, and the melanoma cancer cells line A375.

Results and discussion

The chemical structure of sesbagrandiflorain A (**1**) was first reported to be 6-methoxy-2-(2´,3´-dihydroxy-5´-methoxyphenyl)-1-benzofuran-3-carbaldehyde (Fig. 1) [29]. However, upon careful reevaluation of the 1D and 2D NMR data for 1 (measured in both acetone-d_6 and $CDCl_3$), we concluded that the chemical structure of 1 is 4-hydroxy-2-(4´-hydroxy-2´-methoxyphenyl)-6-methoxybenzofuran-3-carbaldehyde (Fig. 1). In the revised structure, the positions of the hydroxy and methoxy groups in have been reassigned; the A ring contains a hydroxy group at C-4 and a methoxy group at C-6; whereas, the C ring contains a hydroxy group at C-4´ and a methoxy group at C-2´. HMBC correlations between the C-4 hydroxyl proton (δ_H 10.1 ppm) and C-4, C-5 and C-9 and between the C-6 methoxyl protons (δ_H 3.85 ppm) and C-6 (Fig. 3) support the reassignments of ring A; whereas, HMBC correlations between the C-2´ methoxyl protons (δ_H 3.87 ppm) and C-2´, and between the C-4´ hydroxyl proton (δ_H 5.21 ppm) and C-4´, C-5´, and C-6´ support the reassignments of ring C. In addition, NOESY correlations between the C-4 hydroxyl proton and H-5 (δ_H 6.47 ppm); the C-6 methoxyl protons and H-5; the C-2´ methoxyl protons and the aldehyde proton (δ_H 9.82 ppm); as well as H-6´ (δ_H 7.49 ppm) and the aldehyde proton further confirmed the chemical structure of 1. The revised chemical structure of sesbagrandiflorain A (1) is identical to a 2-arylbenzofuran-3-carbaldehyde found in the alfalfa plant *Medicago sativa* [24]. Comparisons of the ^1H NMR spectrum of 1 (taken in DMSO-d_6) with that reported in the literature (Table S1) unambiguously confirmed the identity of 1.

Similarly, sesbagrandiflorain B (2) was first reported as 6-hydroxy-2-(2´,3´-dihydroxy-5´-methoxyphenyl)-1-benzofuran-3-carbaldehyde [29]. Compound 2 differs from 1 only in the absence of a methyl group; and based on the reevaluation of the original 1D and 2D NMR data for 2, the chemical structure of 2 has been revised to 4-hydroxy-2-(4´-hydroxy-2´-hydroxyphenyl)-6-methoxybenzofuran-3-carbaldehyde. Sesbagrandiflorain B is identical to ebenfuran II from *Onobrychis ebenoides* [7]. The ^{1}H NMR spectrum of 2 (taken in CD_3OD) is in a complete agreement with that reported in the literature (Table S1). From this point on, to maintain the priority of the previous discoveries, we will avoid using the name 'sesbagrandiflorain' for compound 1 and its derivatives.

Compound 1 was isolated from *S. grandiflora* stem bark in a good yield [29, 30]. This natural product contains a formyl and two free aromatic hydroxy groups, which were expected to be accessible to chemical derivatizations. Using this relatively abundant natural product as the starting material, we synthesized seven new 2-arylbenzofuran derivatives, ranging from a diester (6) to ethers (7–10), secondary amine (11), and oxime (12) in high yields (65–93%) (Fig. 2).

Compound 6 was synthesized by treating 1 with acetic anhydride in pyridine at room temperature for 24 h. The acetylation of OH-4 and OH-4´ was confirmed by HR-ESI-TOF-MS (399.10897 $[M+H]^+$) and ^{1}H NMR spectrum, in which two resonances at δ_H 2.41 and 2.33 ppm (3H each, *s*) for acetyl groups were present (Table 1). The ^{13}C NMR spectrum of **6** also showed resonances for two acetyl groups, δ_C 20.5 and 168.9 ppm for CH_3COO- at C-4 and δ_C 20.1 and 168.4 ppm for CH_3COO- at C-4´ (Table 2). These assignments were confirmed by relatively weak but apparent 4JCH HMBC correlations between the acetyl protons at 2.41 ppm and C-4 (145.0 ppm) and between the acetyl protons at 2.33 ppm and C-4´ (154.6) (Fig. 3).

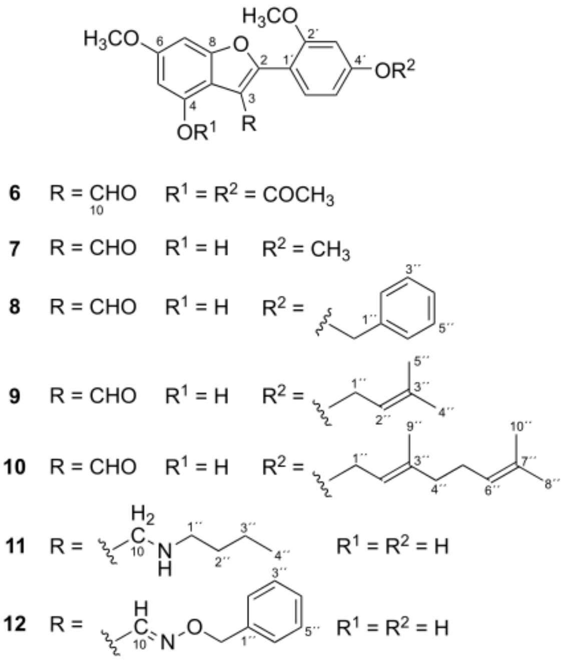


Fig. 2 Chemical structures of compound 1 derivatives

Compound 7 was prepared by treating 1 with K_2CO_3 and CH_3I (2 mol. eq.) at 40 ℃ for 24 h. Direct comparisons of the ^{1}H and ^{13}C NMR spectra of 7 with those of 1 suggested that the methylation reaction took place regioselectively at the C-4´ hydroxy group. This was further confirmed by the HMBC correlation between the CH_3O protons (3.93 ppm) with C-4´ (163.5 ppm). Interestingly, addition of CH_3I up to 10 mol. eq. to the reaction mixture did not yield any permethylated product. It is postulated that the C-4 hydroxy group is less accessible than the C-4´ hydroxy group, as the formyl moiety may form steric hindrance and/or hydrogen bonding with the C-4 hydroxy group.

Compound 8 was synthesized by treating 1 with K_2CO_3 and benzyl bromide at room temperature for 2 h. On the other hand, compounds 9 and 10 were synthesized by activating 1 with K_2CO_3 in DMF at room temperature for 30 min and then reacting it with prenyl bromide and geranyl bromide, respectively, for 3 h. Similar to compound 7, benzylation or prenylation of 1 only occurred at the C-4´ hydroxy group as deduced by comparing their ^{1}H and ^{13}C NMR spectra with those of 1. Analysis of the 2D NMR data (HSQC, HMBC, and NOESY) for 9 also confirmed the regioselectively of the ether formation (Fig. 3).

Compound 11 was synthesized by treating 1 with *n*-butylamine followed by reduction with $NaBH_4$. The ^{1}H NMR of 11 exhibited resonances at δ_H 1.60 (2H, *q*, $J=7.5$ Hz), 1.41 (2H, *m*), and 0.95 (3H, *t*, $J=7.3$ Hz) ppm, attributed to alkyl protons, along with two sets of methylene protons attached to a nitrogen atom at δ_H 2.78 (2H, *t*, $J=7.3$ Hz) and 3.84 (s) ppm. The ^{13}C NMR spectrum of 11 showed all of the carbon resonances expected for 11 (Table 2).

The synthesis of 12 was carried out by treating 1 with $BnONH_3Cl$ in pyridine at room temperature for 24 h. The product was confirmed by NMR and HRESIMS. The positive-ion mode HRESIMS of 12 displayed a characteristic molecular ion peak $[M+H]^+$ at *m/z* 420.14569 (calcd for $C_{24}H_{21}NO_6^+$, 420.14416), establishing the molecular formula of 12 as $C_{24}H_{20}NO_6$ with 15 degrees of unsaturation. This is consistent with the expected additional one degree of unsaturation from the C=N moiety in 12. The ^{1}H NMR spectrum of 12 revealed the presence of an imine proton at δ_H 8.16 (1H, *s*), methylene protons at δ_H 5.23 (2H, *s*), and monosubstituted benzene protons at δ_H 7.47 (2H, *t*,

Table 1 ^{1}H NMR data for compounds 1 and 6–12

Position	1^a	6	7^c	8^d	9^b	10^b	11^a	12^d
	δ_H; J^e	δ_H; J	δ_H; J	δ_H; J	δ_H; J	δ_H; J	δ_H; J	δ_H; J
HO-(4)	10.1 (*s*)	–	10.18 (*s*)	10.21 (*s*)	10.20 (*s*)	10.20 (*s*)	–	10.37 (*s*)
5	6.47 (*d*, 2.0)	6.74 (*d*, 2.0)	6.47 (*d*, 2.0)	6.37 (*s*)	6.37 (*d*, 2.0)	6.36 (*d*, 2.0)	6.39 (*d*, 2.0)	6.27 (*d*, 2.1)
7	6.60 (*m*)	7.16 (*d*, 2.0)	6.61 (*s*)	6.71 (*s*)	6.70 (*d*, 2.0)	6.70 (*d*, 2.0)	6.55 (*d*, 2.0)	6.60 (*d*, 2.1)
MeO-(6)	3.85 (*s*)	3.93 (*s*)	3.85 (*s*)	3.86 (*s*)	3.86 (*s*)	3.86 (*s*)	3.83 (*s*)	3.83 (*s*)
10	9.82 (*s*)	9.82 (*s*)	9.82 (*s*)	9.86 (*s*)	9.85 (*s*)	9.85 (*s*)	3.84 (*s*)	8.16 (*s*)
MeO-(2´)	3.87 (s)	3.91 (s)	3.88 (*s*)	3.95 (*s*)	3.94 (*s*)	3.94 (*s*)	3.85 (*s*)	3.82 (*s*)
3´	6.59 (*m*)	7.10 (*d*, 2.0)	6.62 (*s*)	6.94 (*s*)	6.82 (*d*, 2.0)	6.82 (*d*, 2.2)	6.57 (*d*, 2.0)	6.67 (*d*, 2.1)
HO-(4´)	5.21 (*s*)	–	–	–	–	–	n.o	9.0
5´	6.60 (*m*)	7.00 (*dd*, 8.5, 2.0)	6.67 (*d*, 8.4)	6.89 (*d*, 8.4)	6.79 (*dd*, 8.5, 2.0)	6.79 (*dd*, 8.5, 2.2)	6.54 (*dd*, 9.0, 2.0)	6.62 (*dd*, 8.4, 2.1)
6´	7.49 (*d*, 8.9)	7.71 (*d*, 8.5)	7.55 (*d*, 8.4)	7.68 (*d*, 8.4)	7.65 (*d*, 8.5)	7.65 (*d*, 8.5)	7.32 (*d*, 9.0)	7.36 (*d*, 8.4)
CH_2O	–	–	–	5.30 (s)	–	–	–	5.23 (*s*)
MeO-(4´)	–	–	3.93 (*s*)	–	–	–	–	–
MeCOO-(4)	–	2.41 (*s*)	–	–	–	–	–	–
MeCOO-(4´)	–	2.33 (*s*)	–	–	–	–	–	–
1´´	–	–	–	–	4.73 (*m*)	4.76 (*d*, 6.3)	2.78 (*t*, 7.3)	–
2´´	–	–	–	7.46 (*t*, 7.7)	5.54 (*t*, 6.5)	5.54 (*m*)	1.60 (*q*, 7.5)	7.47 (*t*, 7.7)
3´´	–	–	–	7.56 (*t*, 7.7)	–	–	1.41 (*m*)	7.41 (*t*, 7.7)
4´´	–	–	–	7.39 (*t*, 7.7)	1.81 (*s*)	2.18 (*m*)	0.95 (*t*, 7.3)	7.35 (*t*, 7.7)
5´´	–	–	–	7.56 (*t*, 7.7)	1.82 (*s*)	2.13 (*m*)	–	7.41 (*t*, 7.7)
6´´	–	–	–	7.46 (*t*, 7.7)	-	5.14 (*m*)	–	7.47 (*t*, 7.7)
8´´	–	–	–	–	–	1.67 (*s*)	–	–
9´´	–	–	–	–	–	1.63 (*s*)	–	–
10´´	–	–	–	–	–	1.82 (*s*)	–	–

s singlet, *d* doublet, *dd* doublet of doublets, *dt* doublet of triplets, *t* triplet, *q* quartet, *m* multiplet, coupling constants (apparent splittings) are reported as numerical values in Hz, *n.o.* not observed

[a] ^{1}H NMR (500 MHz) measured in $CDCl_3$

[b] ^{1}H NMR (500 MHz) measured in acetone-d_6

[c] ^{1}H NMR (700 MHz) measured in $CDCl_3$

[d] ^{1}H NMR (700 MHz) measured in acetone-d_6

[e] Multiplicity of signals is given in parentheses

$J = 7.7$ Hz), 7.41 (2H, *t*, $J = 7.7$ Hz), and 7.35 ppm (1H, *t*, $J = 7.7$ Hz), confirming the presence of an *O*-benzyl oxime moiety in 12. This was also supported by its ^{13}C NMR data (Table 2).

Compounds 6–12 were evaluated for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Rhodococcus fascians* using an agar diffusion assay. The results showed that only compound 6 had moderate antibacterial activity against the plant pathogen *R. fascians*, with a MIC of 0.1 mg/mL (Fig. 4a, b). None of the other compounds including 1 were active against the tested bacteria. The presence of acetyl groups at C-2´ and C-3´ in the B-ring of 6 may play a role in the growth inhibitory activity and/or in the uptake of the compound into *R. fascians*.

In addition, the compounds were also tested for their cytotoxicity against A375 melanoma cancer cells line (Fig. 4c). The results showed that compounds 8 and 12 showed better cytotoxicity than 1 and the other derivatives against the cancer cell line with the relative IC_{50} values of 22.80 and 32.73 μM, respectively (Figs. 4c and 3d). Compounds 8 and 12 contain an additional benzene ring in their structures, which may contribute to the growth inhibitory activity against A375 melanoma cancer cells. Further investigations on the anti-Rhodococcal activity of compound 6 and the cancer cell growth inhibitory activity of compounds 8 and 12 are warranted to understand the mechanisms underlying their antibacterial activity or cytotoxicity and to develop more active antibacterial or anticancer agents.

Table 2 ^{13}C NMR data for compounds 1 and 6–12

Position	1^a δ_C	6^b δ_C	7^c δ_C	8^d δ_C	9^b δ_C	10^b δ_C	11^c δ_C	12^d δ_C
2	162.6	162.7	162.8	163.0	163.2	163.2	152.3	154.6
3	119.0	118.2	119.0	118.7	118.6	118.6	114.2	109.4
4	151.9	145.0	152.0	152.0	151.9	152.0	145.7	151.7
5	98.3	107.2	98.2	98.1	98.1	98.1	97.3	97.6
6	160.9	159.4	160.9	161.2	161.2	161.2	157.7	160.6
7	88.2	93.7	88.2	87.7	87.6	87.7	87.5	87.4
8	156.6	156.7	156.6	156.6	156.6	156.6	156.7	156.9
9	107.2	111.9	107.3	107.8	106.9	106.9	107.0	107.4
MeO-(6)	55.8	55.6	55.8	55.5	55.4	55.5	55.7	55.1
10	191.1	184.8	191.1	190.1	190.2	190.1	44.5	145.5
1´	110.3	114.5	110.3	109.9	109.5	109.6	111.9	109.8
2´	158.9	158.7	158.7	159.0	158.9	158.9	158.4	158.7
3´	99.7	106.4	99.2	99.9	99.5	99.6	99.5	99.8
4´	159.5	154.6	163.5	163.1	163.2	163.2	159.7	160.9
5´	108.1	114.2	105.6	106.9	106.8	106.9	107.5	107.8
6´	132.9	132.5	132.8	132.8	132.7	132.7	132.1	132.3
MeO-(2´)	55.9	55.7	55.8	55.2	55.2	55.2	55.7	55.0
CH_2O	–	–	–	70.1	–	–	-	76.1
MeO-(4´)	–	–	55.6	–	–	–	–	–
<u>Me</u>COO-(4)	–	20.5	–	–	–	–	–	–
<u>Me</u>COO-(4´)	–	20.1	–	–	–	–	–	–
Me<u>C</u>OO-(4)	–	168.9	–	–	–	–	–	–
Me<u>C</u>OO-(4´)	–	168.4	–	–	–	–	–	–
1´´	–	–	–	136.8	65.0	65.1	48.5	137.1
2´´	–	–	–	127.7	119.6	119.6	31.4	128.3
3´´	–	–	–	128.5	137.8	141.1	20.3	128.4
4´´	–	–	–	128.0	17.3	39.3	13.8	128.1
5´´	–	–	–	128.5	24.9	26.2	–	128.4
6´´	–	–	–	127.7	–	123.8	–	128.3
7´´	–	–	–	–	–	131.3	–	–
8´´	–	–	–	–	–	24.9	–	–
9´´	–	–	–	–	–	16.8	–	–
10´´	–	–	–	–	–	15.8	–	–

[a] ^{13}C NMR (125 MHz) measured in $CDCl_3$

[b] ^{13}C NMR (125 MHz) measured in acetone-d_6

[c] ^{13}C NMR (176 MHz) measured in $CDCl_3$

[d] ^{13}C NMR (176 MHz) measured in acetone-d_6

Experimental section

General experimental procedures

All of the solvents, reagents, and chemicals used in this study were purchased from Aldrich Chemical (Saint Louis, MO, USA) and Merck AG (Saint Louis, MO, USA). Thin-layer chromatography (TLC) was conducted on pre-coated silica gel 60 GF_{254} plates (Merck, Darmstadt, Germany) with an absorbent thickness of 0.25 mm sprayed with $Ce(SO_4)_2$ solution for spot visualization. Preparative TLC was performed on square glass plates with a side length of 0.2 m coated with 0.5-mm Kieselgel F_{254} (Merck), which were air dried and used without prior activation. Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh ASTM; Merck). HPLC was performed using a Shimadzu dual LC-20AD solvent delivery system with a Shimadzu SPD-M20A UV/vis photodiode array detector. Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded in acetone-d_6 or $CDCl_3$ with tetramethylsilane as an internal standard on a Bruker Avance III 700-MHz spectrometer equipped with a 5-mm ^{13}C cryogenic probe or a

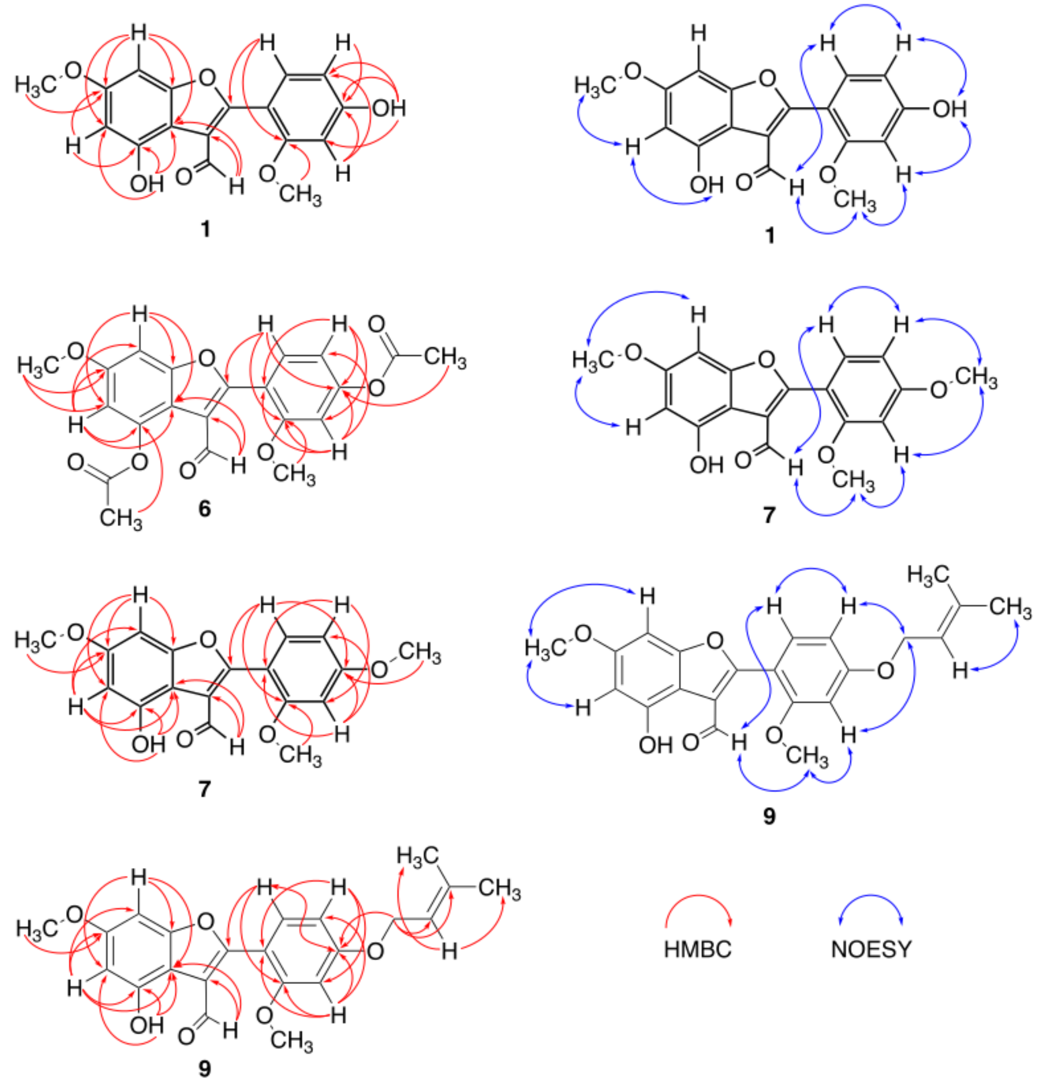


Fig. 3 HMBC and NOESY correlations of compound 1 and some of its derivatives

Bruker 500-MHz spectrometer. High-resolution ESI mass spectrometry was performed in positive-ion mode on a 6230 TOF mass spectrometer (Agilent Technologies, Santa Clara, CA).

Isolation of compound 1 from the stem bark of *S. grandiflora*

Compound **1** was isolated from the stem bark of *S. grandiflora* using the method described in our previous report [29]. The identity of the compound was confirmed by NMR and MS.

Synthesis of compound 1 derivatives

Synthesis of 2-(4-acetoxy-2-methoxyphenyl)-3-formyl-6-methoxybenzofuran-4-yl acetate (6). Compound 1 (5 mg, 0.0159 mmol) was dissolved in acetic anhydride (0.44 mL) and pyridine (0.44 mL). The solution was stirred at room temperature for 24 h. The reaction completion was confirmed by TLC (CH_2Cl_2–MeOH = 9:1). The reaction mixture was then poured into ice water and the precipitate was collected by filtration. The precipitate was subjected to SiO_2 flash column chromatography eluted with CH_2Cl_2–MeOH (40:1) to give compound 6 as a colorless oil (5.9 mg, 93%).

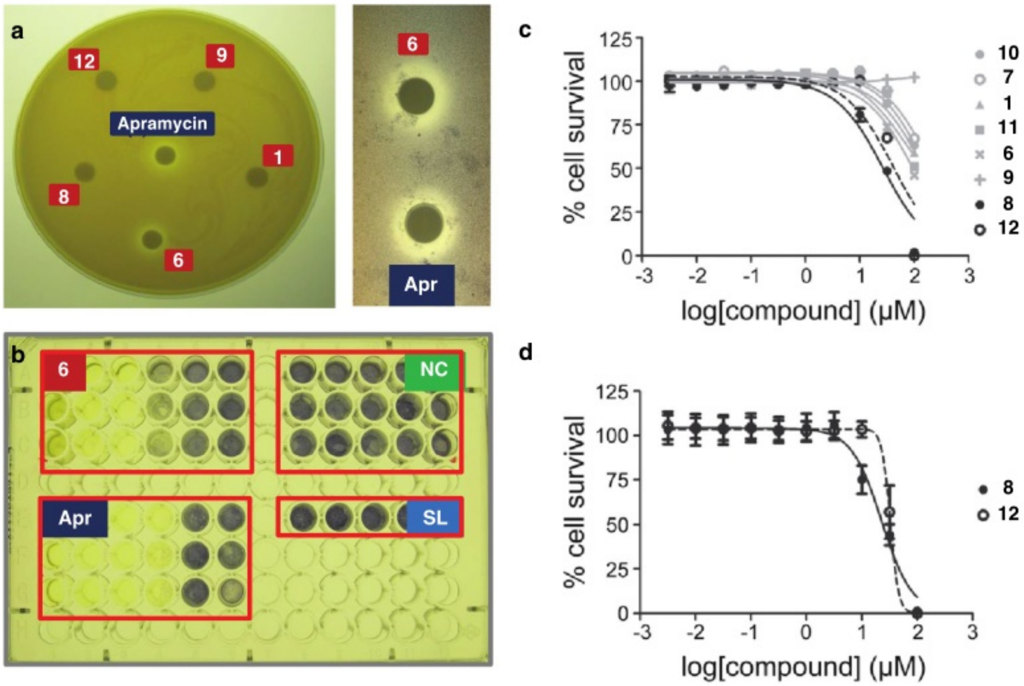


Fig. 4 Antibacterial activity and cytotoxicity of compound 1 derivatives. **a** Agar-based disc diffusion assay of 1, 6, 8, 9, 12 against *R. fascians*; **b** Micro-dilution assay of 6 against *R. fascians*; Compound 6: 10–0.0001 mg/mL; Apramycin (Apr): 0.0001 mg/mL; NC (no compound or negative control); SL (solvent only); **c**, **d** Dose–response curves for the effect of compounds **6 – 12** on survival of A375 human metastatic melanoma cells following 48 h of treatment. **c** Results from the primary screen and **d** validation of hit compounds. Data represent the mean ± standard deviation for triplicate values from one experiment **c** or two independent experiments performed in triplicate **d**

ESI-TOF-MS *m/z* 399.10897 $[M+H]^+$, calculated for $C_{21}H_{18}O_8$ for 399.10744; ^1H and ^{13}C NMR spectral data (acetone-d_6): see Tables 1 and 2, respectively.

Synthesis of 2-(2,4-dimethoxyphenyl)-4-hydroxy-6-methoxybenzofuran-3-carbaldehyde (7). Compound 1 (5 mg, 0.0159 mmol) was dissolved in DMF (0.03 mL) and stirred with K_2CO_3 (10 eq, 0.159 mmol, 22 mg) and CH_3I (10 eq, 0.159 mmol, 0.01 mL) at 40 ℃ for 24 h. The reaction completion was confirmed by TLC (CH_2Cl_2–MeOH = 9:1). The mixture was diluted with EtOAc, and washed with water and brine. The EtOAc fraction was dried with Na_2SO_4 and the volatiles were removed *in vacuo*. The resulting pale yellow oil was purified by flash chromatography (CH_2Cl_2–MeOH = 95:5) to yield 7 as white crystals (4.1 mg, 78%).

ESI-TOF-MS *m/z* 329.10340 $[M+H]^+$, calculated for $C_{18}H_{16}O_6$ for 329.10196. ^1H and ^{13}C NMR spectral data ($CDCl_3$): see Tables 1 and 2, respectively.

Synthesis of 2-(4-(benzyloxy)-2-methoxyphenyl)-4-hydroxy-6-methoxybenzofuran-3-carbaldehyde (8). Compound 1 (1.0 eq, 5.00 mg, 0.0159 mmol) was dissolved in DMF (0.03 mL). Benzyl bromide (2.0 eq, 0.01 mL, 0.0318 mmol) and K_2CO_3 (7 mg, 0.047 mmol) were added to the solution. The yellow mixture was stirred at room temperature for 2 h, poured into a solution of Et_2O–H_2O (1:1), and stirred for 10 min. The ethereal layer was separated. The aqueous layer was extracted with Et_2O. The combined extract was washed with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The resulting pale yellow oil was purified by flash column chromatography (hexane–acetone = 9:1) to yield product 8 as a pale yellow solid (5.2 mg, 80%).

ESI-TOF-MS *m/z* 405.13463 $[M+H]^+$, calculated for $C_{24}H_{20}O_6$ for 405.13463. ^1H and ^{13}C NMR spectral data (acetone-d_6): see Tables 1 and 2, respectively.

Synthesis of 4-hydroxy-6-methoxy-2-(2-methoxy-4-((3-methylbut-2-en-1-yl)oxy)phenyl)benzofuran-3-carbaldehyde (9). To a solution of compound 1 (5 mg, 1.0 eq, 0.0159 mmol) in DMF (0.2 mL) was added K_2CO_3 (9 mg, 0.063 mmol), and the reaction mixture was stirred for 30 min at rt. Subsequently, prenyl bromide (4 μL, 0.0318 mmol) was added to the reaction mixture and stirred for another 3 h until complete consumption of the starting material as judged by TLC. The reaction was then quenched with potassium phosphate buffer pH 7.0 and extracted with EtOAc twice. The EtOAc layer was dried over anhydrous Na_2SO_4, then the organic solvent was dried *in vacuo*. The extract was subjected to SiO_2 column chromatography using hexane–acetone (9:1) as mobile phase. Fractions containing the product were pooled and dried under vacuum to give the title compound 9 as a pale yellow solid (4.0 mg, [illegible]%).

ESI-TOF-MS *m/z* 383.15035 $[M+H]^+$, calculated for $C_{22}H_{22}O_6$ for 383.15035. ^1H NMR (acetone-d_6) and ^{13}C NMR spectral data (acetone-d_6): see Tables 1 and 2, respectively.

Synthesis of (Z)-2-(4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-2-methoxyphenyl)-4-hydroxy-6-methoxybenzofuran-3-carbaldehyde (10). To a solution of compound 1 (5 mg, 1.0 eq, 0.0159 mmol) in DMF (0.2 mL) was added K_2CO_3 (9 mg, 0.066 mmol), and the reaction mixture was stirred for 30 min at rt. Subsequently, geranyl bromide (6 µL, 0.0318 mmol) was added to the reaction mixture and stirred for another 3 h until complete consumption of the starting material as judged by TLC. The reaction was then quenched with potassium phosphate buffer pH 7.0 and extracted with EtOAc twice. The EtOAc layer was dried over anhydrous Na_2SO_4; then the organic solvent was dried in vacuo. The extract was subjected to silica gel column chromatography using hexane–acetone (9:1) as mobile phase. Fractions containing the product were pooled and dried under vacuum to give the title compound 10 as a pale yellow solid (4.8 mg, 66%).

ESI-TOF-MS *m/z* 451.21298 $[M+H]^+$, calculated for $C_{27}H_{30}O_6$ for 451.21152. ^1H NMR (acetone-d_6) and ^{13}C NMR spectral data (acetone-d_6): see Tables 1 and 2, respectively.

Synthesis of 2-(4-hydroxy-2-methoxyphenyl)-6-methoxy-3-((propylamino)methyl)benzofuran-4-ol (11). A suspension of *n*-butyl amine (0.02 mL, 1.1 eq, 0.0175 mmol) in pyridine (0.2 mL) was added to compound 1 (5 mg, 0.0159 mmol), then stirred at room temperature for 24 h. TLC (CH_2Cl_2–MeOH = 10:1) indicated reaction complete. The solvent was evaporated *in vacuo*. The reaction was diluted with EtOAc, washed with 0.1-M HCl, water, saturated $NaHCO_3$, water, brine and dried over Na_2SO_4, filtered and volatiles removed in vacuo. The resulting product (5.6 mg, 0.0151 mmol) was added to MeOH (0.03 mL) and the resulting mixture was stirred at rt, then $NaBH_4$ (2.0 eq, 0.04 mmol, 1 mg) was added at 0 ℃, and stirring was continued overnight at rt. The resulting mixture was acidified with 2 N HCl and then neutralized with saturated aqueous $NaHCO_3$ solution to yield a white solution. The solution was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield product 11 as brown oil (4.5 mg, 80%, 2 step).

ESI-TOF-MS *m/z* 372.1[illegible]2 $[M+H]^+$, calculated for $C_{21}H_{25}NO_5$ for 372.18222. ^1H and ^{13}C NMR spectral data ($CDCl_3$): see Tables 1 and 2, respectively.

Synthesis of (E)-4-hydroxy-2-(4-hydroxy-2-methoxyphenyl)-6-methoxybenzofuran-3-carbaldehyde O-benzyl oxime (12). A suspension of $BnONH_3Cl$ (3 mg, 1.1 eq, 0.0159 mmol) in pyridine (0.2 mL) was added to compound 1 (5 mg, 0.0159 mmol), then stirred at room temperature for 24 h. The solvent was evaporated *in vacuo* and the reaction mixture was diluted with EtOAc, consecutively washed with 0.1-M HCl, saturated $NaHCO_3$, water, and brine. The organic fraction was then dried over Na_2SO_4, filtered, and the solvent was evaporated *in vacuo* to afford product 12 as white solid (4.6 mg, 70%).

ESI-TOF-MS *m/z* 420.1[illegible]69 $[M+H]^+$, calculated for $C_{24}H_{21}NO_6$ for 420.14416. ^1H and ^{13}C NMR spectral data (acetone-d_6): see Tables 1 and 2, respectively.

Antibacterial activity assay

Agar-based disc diffusion assay was used to test the activity of all the tested derivative compounds. Five different bacteria, *S. aureus* ATCC 12,600, *B. subtilis* ATCC 6051, *P. aeruginosa* ATCC 9721, *M. smegmatis* ATCC 14,468, and *E. coli* ATCC 11,775 were used. The EtOAc extract was dissolved in MeOH to a concentration of 10 mg/mL. The positive control for this experiment was either ampicillin (for *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli*) or apramycin (for *M. smegmatis*). All the tested compounds and the positive control (10 µL each) were loaded onto sterile diffusion discs and left to dry for 20 min. For *S. aureus, B. subtilis, P. aeruginosa, and M. smegmatis*, the agar plates were prepared by adding a layer of bacterial infused YMG soft agar to an YMG plate and left to solidify. The bacterial infused YMG soft agar was prepared by growing each of the bacteria in separate 15-mL falcon tubes with liquid YMG medium for two days and mixed it with warm YMG agar. The paper discs, impregnated with the compound and the positive control, were placed onto each plates using antiseptic techniques. All plates were incubated for 24 h at 30 ℃. For *E. coli*, all procedures mentioned above were done using Luria–Bertani (LB) medium instead of YMG. In addition, the *E. coli* plates and liquid cultures were incubated at 37 ℃. After 24 h of incubation, the plates were stained with MTT (1 mg/mL in deionized water) to enhance the contrast of the inhibition zones to the bacterial growth.

Antibacterial activity of compound 6 against *Rhodococcus fascians* was determined by both agar-based disc diffusion and micro-dilution assays. *R. fascians* from a − 80 ℃ stock was streaked on MM nutrient agar medium [mannitol (10 g), casein (4 g), peptone (4 g), NH_4Cl (1 g), $MgSO_4$ (0.3 g), NaCl (0.2 g), yeast extract (3 g), and KH_2PO_4

(0.5 g)] and grown at 30 ℃ for 3 days. A colony was transferred to MM nutrient broth and incubated at 30 ℃ for 3 days. Turbidity of the inoculum was measured to a proper density at 600 nm–0.1. For plate preparation, inoculum (500 µL) was mixed thoroughly with warm nutrient agar (50 mL) and poured to 25-mL plates. The agar plate was let to solidify and dry for 30 min before assay. Sterile blank paper disks (Becton–Dickinson) were impregnated with the compound (10 mg/mL, 20 µL) and dried at rt. The disks were placed onto inoculated agar plates and incubated at 30 ℃ for 3 days. Micro-dilution assays were performed in a 96-well plate. Compound 6 was serially diluted and added to the bacterial suspension at final concentrations of 10, 1, 0.1, 0.01, 0.001 and 0.0001 mg/mL. After incubation at 30 ℃ for 3 days, 0.25% MTT developing dye (50 µL) was added. Control assays were done using the same protocol using apramycin or MeOH.

Cytotoxicity assay

Cell culture

A375 (ATCC: CRL-1619, Manassas, VA, USA) human metastatic melanoma cells were cultured in complete growth medium consisting of DMEM (Gibco, Waltham, MA, USA) supplemented with 10% FBS (Atlanta Biologicals, Flowery Brach, GA, USA) and 1% penicillin–streptomycin (Gibco). Cells were cultured in 75-cm^2 flasks (Greiner Bio-One, Kremsmünster, Austria), incubated in a humidified environment at 37 ℃ with 5% CO_2, and were kept below 20 passages.

Dose–response assays

Cells were seeded at 7000 cells/well into white, opaque 96-well plates (Greiner Bio-One) and incubated for 24 h prior to compound treatment. Wells on the outer edge of the plate were excluded for these assays and filled with PBS. Compounds dissolved in DMSO were then added to construct a 10-point dose–response curve in triplicate using a half-log serial dilution starting at 100 µM. For each serial dilution, a concurrent vehicle control serial dilution was performed in triplicate on the same plate. Treated cells were then allowed to incubate for 48 h. Afterwards, the percentage of viable cells was determined using the CellTiter-Glo Assay (Promega, Madison, WI, USA) with luminescence output measured using a Synergy4 (Biotek, Winooski, VT, USA) plate reader. Dose–response curves were fit to either a 3-parameter IC_{50} model (primary screen) or a 4-parameter IC_{50} model (hit validation) using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

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