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Sesbagrandiflorain F, a New 2-Arylbenzofuran from the Stem Bark of *Sesbania grandiflora* L.

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Abstract – Sesbagrandiflorain F (**1**), a novel 2-arylbenzofuran, and two more 2-arylbenzofurans (**2-3**), were isolated from the stem bark of *Sesbania grandiflora* L. Based on information HRESIMS data, 1D, and 2D NMR spectra, the structure of **1** was fully assigned. Compounds **1-3** were tested for cytotoxicity in MCF-7 and HeLa cells. Compounds **1** and **3** showed moderate activity against MCF-7 cells with an IC_{50} value of 2.68 and 4.08 μg/mL, respectively. Conversely, all of the isolates were inactive towards HeLa cells.
Keywords – Sesbagrandiflorain F, 2-Arylbenzofuran, *Sesbania grandiflora*, Cytotoxic

Introduction

The plant *Sesbania grandiflora* L. (Fabaceae), sometimes known as 'Turi,' is endemic to Indonesia. The leaves and roots of this plant are used to treat fevers, colds, and diarrhea. In addition, the blossoms are also used as a vegetable. Secondary metabolites discovered in the *Sesbania* genus include flavonoids, isoflavonoids, and 2-arylbenzofurans. Studies have demonstrared that *Sesbania grandiflora* has anticancer and antimicrobe activities.[1-4] However, data of the anticancer effectiveness of 2-arylbenzofurans from *Sesbania* is limited.[1-3] Sesbagrandiflorain D, a 2-arylbenzofuran derivative found in *Sesbania grandiflora* L., was firmly against MCF-7 and WiDr cells.[3] The purpose of this study was to discover the cytotoxicity of 2-arylbenzofurans from *S. grandiflora* L. In addition, we reported the isolation of sesbagrandiflorain F (**1**), a new 2-arylbenzofuran derivative, as well as two known 2-arylbenzofurans, spinosans A (**2**) and B (**3**), from *S. grandiflora* L. stem barks (Fig. 1). Compounds **1-3** were cytotoxic to breast cancer cells (MCF-7) and human cervical cells (HeLa).

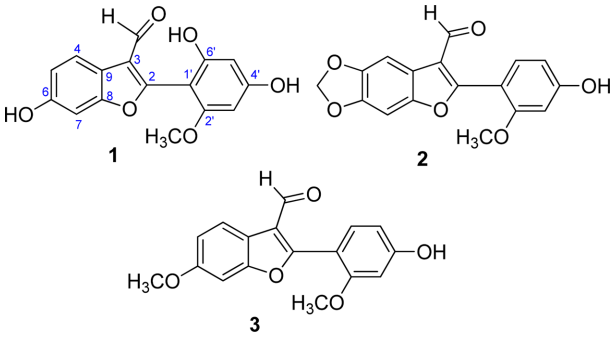

Fig. 1. 2-Arylbenzofurans (**1-3**) from *S. grandiflora* stem barks.

Experimental

Modify the formation procedures as the folowing – The UV-VIS spectrophotometer (UV-1800-Shimadzu) was used to determine each component's maximum absorption (λ_{max}). The functional groups of compounds **1-3** were recorded using an FTIR spectrophotometer recorded the (IR Tracer-100- Shimadzu). The NMR spectra of compounds in acetone-d_6 were examined using a JEOL FTNMR ECA 400 spectrometer. A Waters LCT PremierTM XE mass spectrometer was used to examine the chemical formula of isolates. Column chromatography was performed using Si gel G_{60} and Sephadex LH-20. The use of a UV lamp and cerium sulfate reagent to

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visualize chemicals on TLC.

Plant materials – Dr. M. Affandi, a botanist from the Biology Department, Universitas Airlangga, identified fresh stem barks of *Sesbania grandiflora* L. collected in Kemiri Village, Districts Sidoarjo, East Java, Indonesia, in December 2018, and a specimen (SG 20181203) was deposited.

Extraction and isolation – The dry stem bark powder from *S. grandiflora* (3.0 kg) was extracted in 90% methanol (2 × 30 L) for three days at room temperature, giving methanol extract (350 g) following vaporization under low pressure. The methanol extract was 9:1 watered down before being partitioned with n-hexane (80 g) and EtOAc (20 g) in that order. By separating EtOAc extract (19 g) on a silica gel column chromatography and eluting it with a mobile phase of increasing polarity (hexane, hexane-EtOAc, EtOAc), five fractions (A-E) were produced. Fraction D (3.0 g) was chromatographed on a Sephadex LH-20 column and eluted with methanol, yielding three subfractions D_1-D_3. Compounds **2** (25 mg) and **3** (25 mg) were purified on silica gel radial chromatography using n-hexane-EtOAc (from 9:1 to 4:1 v/v). Purification of subfraction D_3 using the same techniques and n-hexane-diisopropyl ether (from 1:1 to 1:4), and 100% diisopropyl ether to obtain compound **1** (13 mg).

Sesbagrandiflorain F (**1**) – Yellow solid, UV (MeOH) λ_{max} nm (log ε): 268 (4.11), 296 (3.70), and 346 nm (3.91). IR (KBr) ν_{max} cm^{-1}: 3373, 1663, 1602, and 1516. Table 1 shows the NMR spectral data of **1**. HRESIMS: *m/z* $[M+H]^+$ calculated for $C_{16}H_{12}O_6$ 300.0643, found 300.0641.

Spinosan A (**2**) – Yellow solid, UV (MeOH) λ_{max} nm (log ε): 250 (4.07), 295 (3.71), and 345 nm (3.85). The NMR spectra of **2** have similarities to data from the literature.[5]

Spinosan B (**3**) – Yellow solid, UV (MeOH) λ_{max} nm (log ε): 246 (4.27), 280 (3.79), and 342 nm (3.95). The NMR spectra of **3** were compared and found to be almost equivalent to the data in the literature.[5]

Cytotoxic activity – The MTT assay was used to assess the cytotoxic activity of **1-3** against human cervical cells (HeLa) and human breast cells (MCF-7) following the previous experiment.[6-8] For 48 hours, HeLa and MCF-7 cells were grown in RPMI-1640 media containing 10% FBS at 37 ºC with 5% CO_2 flow. Compounds **1-3** were introduced to Hela and MCF-7 cells in 96-well plates and incubated for 24 hours at 37 ºC with 5% CO_2. The microplate reader spectrometer measured the active compound's capacity to kill cancer cells at λ 590 nm. As a positive control for the cytotoxic assay, doxorubicin was used.[9-10]

Result and Discussion

Compound **1** (sesbagrandiflorain F) was produced as a yellow solid and exhibited the chemical formula $C_{16}H_{12}O_6$ by high-resolution ESIMS at $[M+H]^+$ ion *m/z* 300.0641 (calcd 300.0643). The UV spectra of **1** revealed the maximum absorption at λ_{max} (log ε): 268 (4.11), 296

Table 1. ^1H (400 MHz),^{13}C NMR data (100 MHz) of **1** in acetone-d_6

No.C	δ_H (mult, *J* in Hz)	δ_C	HMBC
2	-	164.6	-
3	-	118.7	-
4	7.52 (*d*, 8.6)	133.5	C-6; C-8
5	6.65 (*dd*, 8.4; 2.2)	109.1	C-7; C-9
6	-	157.8	-
7	6.66 (*d*, 2.2)	104.1	C-8; C-9
8	-	162.4	-
9	-	108.2	-
1'	-	107.8	-
2'	-	161.8	-
3'	6.33 (*d*, 2.0)	98.8	C-1', C-2'; C-4'; C-5'
4'	-	152.7	-
5'	6.71 (*d*, 2.0)	88.4	C-1', C-3'; C-6'
6'	-	157.3	-
4'-OH	10.26 (*s*)	-	C-3'; C-4'
2'-OCH_3	3.82 (*s*)	56.0	C-2'
CHO	9.96 (*s*)	191.3	C-3; C-9

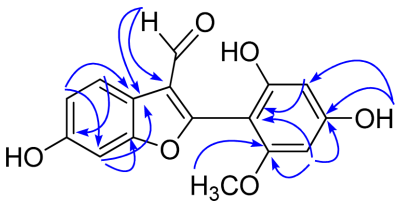

Fig. 2. HMBC of sesbagrandiflorain F (**1**).

(3.70), and 346 nm (3.91) characteristics for a 2-arylbenzofuran skeleton.[5] According to the IR spectra, the functional group of sesbagrandiflorain F comprises hydroxyl groups (3373 cm^{-1}), aldehyde (1663 cm^{-1}), and aromatic C=C (1516 and 1602 cm^{-1}).[1] The protons of two aromatic units, hydroxy, methoxy, and aldehyde, are found in the ^1H NMR data (Table 1). In-ring A, there is an ABX system at δ_H 7.52 (1H, *d*, *J* = 8.4 Hz, H-4), δ_H 6.66 (1H, *d*, *J* = 2.2 Hz, H-7), δ_H 6.65 (1H, *dd*, *J* = 8.4; 2.2 Hz, H-5), and two *meta*-coupled (*J* = 2.0 Hz) protons in the ring C at δ_H 6.71 (H-5'), and δ_H 6.33 (H-3'). In addition, the protons of a hydroxy at δ_H 10.26 (1H, s, 4'-OH), a methoxy at δ_H 3.82 (3H, s, 2'-OCH_3), and an aldehyde at δ_H 9.96 (1H, s, 3-CHO) were exposed by sesbagrandiflorain F. The ^{13}C NMR of sesbagrandiflorain F exhibits signals for sixteen carbons, including a methoxy carbon, five methine carbons, and ten quaternary carbons (see Table 1). The HMBC and HMQC spectra confirmed the positioning of hydroxy, methoxy, and aldehyde groups in the structure of 2-arylbenzofuran. An ABX system proton at δ_H 7.52 (H-4) was found to be connected to two oxyaryl carbons at δ_C 162.4 (C-8) and δ_C 157.8 (C-6) in the HMBC spectrum (Fig. 2). A signal at δ_H 6.65 (H-5) revealed long-range correlations with a methine carbon [δ_C 104.1 (C-7)], and a quaternary carbon [δ_C 108.2 (C-9)], as well as a proton at δ_H 6.66 (H-7) correlated to C-8, and C-9 in the ring A. In the ring C, a meta coupled proton at δ_H 6.63 (H-3') showed HMBC correlation to a methine carbon at δ_C 88.4 (C-5'), a quaternary carbon at δ_C 107.7 (C-1'), and two oxyaryl carbons at δ_C 161.8 (C-2') and δ_C 152.7 (C-4'). In contrast, the other *meta*-coupled proton at δ_H 6.71 (H-5') showed a correlation with C-1', a methine at δ_C 98.8 (C-3'), and an oxyaryl at δ_C 157.3 (C-6'). The designated position for the hydroxy group at C-4' was clear by a hydroxy proton at δ_H 10.26 (4'-OH) connected to C-3' and C-4'. A methoxy signal at δ_H 3.82 (2'-OCH_3) was also found to be connected to C-2'. In addition, an aldehyde group at δ_H 9.96 (3-CHO) was discovered to be linked to two quaternary carbons in the 2-arylbenzofuran skeleton, δ_C 119.1 (C-3), and 114.1 (C-9). Based on NMR data, the structure of compound **1** was determined to be 2-(2,4-dihydroxy-6-methoxyphenyl)-6-hydroxy-benzofuran-3-carbaldehyde, which was given the name sesbagrandiflorain F.

Table 2. Cytotoxicity data of compounds **1-3**

Compounds	IC_{50} (µg/mL)	
	MCF-7	HeLa
Sesbagrandiflorain F (**1**)	2.68 ± 0.83	> 100
Spinosan A (**2**)	> 100	90.05 ± 1.20
Spinosan B (**3**)	4.08 ± 1.03	44.98 ± 0.85
Doxorubicin	5.67 ± 0.74	4.60 ± 0.23

Compounds **1-3** were tested for cytotoxicity towards MCF-7 and HeLa cells (Table 2) using the MTT assay.[6-10] Compounds **1** and **3** had moderate activity against MCF-7 cells, with IC_{50} values of 2.68 and 4.08 µg/mL, respectively. In addition, none of the isolates had any effect on HeLa cells. The only variations between compounds **1-3** are the hydroxy, methoxy, and methylenedioxy groups in the 2-arylbenzofuran structure. Compound **1** is distinguished from compound **2-3** by an -OH group at C-6' in the ring B, which increases cytotoxic action.

In conclusion, a new 2-arylbenzofuran, sesbagrandiflorain F (**1**), and spinosans A (**2**) and B (**3**) were isolated from the stem bark of *S. grandiflora*. Compounds **1** and **3** exhibited moderate activity against MCF-7 cells with an IC_{50} value of 2.68 and 4.08 µg/mL. However, all of the 2-arylbenzofurans were inactive against HeLa cells lines.

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