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Cytotoxic arylbenzofuran and stilbene derivatives from the twigs of *Artocarpus heterophyllus*

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ABSTRACT

Four new natural products, including three arylbenzofurans named heterophyllenes A-C (**1**–**3**), and one stilbene named heterophyllene D (**4**), together with twenty-one known compounds were isolated from the twigs of *Artocarpus heterophyllus* and their structures elucidated by spectroscopic methods, mainly 1D and 2D NMR spectroscopy. The cytotoxic activity of selected compounds against KB, MCF-7 and NCI-H187 cell lines was evaluated. Heterophyllene C (**3**) exhibited cytotoxicity against the MCF-7 cell line with an IC_{50} value of 12.56 μM. Additionally, the known compounds norartocarpin and artocarpin showed cytotoxic activity against MCF-7 and KB cell lines with IC_{50} values of 10.04 and 13.57 μM, respectively. Both compounds also displayed cytotoxicity against the NCI-H187 cell line with values of 14.78 and 14.21 μM, respectively.

Artocarpus heterophyllus (jackfruit), belonging to the family Moraceae, is widely distributed in tropical regions of Asia including Thailand, Sri Lanka, China and Vietnam. Many parts of *A. heterophyllus* have been used as traditional medicines for alleviating asthma (roots), diarrhea (seeds), and relieving wounds (leaves).[1,2] *A. heterophyllus* is a rich source of phenolic compounds, flavonoids, stilbenoids and arylbenzofurans possessing antibacterial, antimalarial and *anti*-inflammatory activities.[1,3] Herein, we describe the isolation and structural determination of chemical constituents from the methanol extract of twigs from *A. heterophyllus* which exhibited cytotoxic activity against oral human carcinoma (KB), human breast cancer (MCF-7) and lung cancer (NCI-H187) cell lines with IC_{50} values of 20.3, 21.5 and 34.4 μg/mL, respectively. Purification of the methanol extract led to the isolation of four new natural products; three arylbenzofurans, heterophyllenes A (**1**), B (**2**) and C (**3**), and one stilbene, heterophyllene D (**4**), along with twenty-one known compounds, demethylmoracin I (**5**),[4] moracin C (**6**),[5] moracin M (**7**),[6] norartocarpetin (**8**),[7] albanin A (**9**),[8] licoflavone C (**10**),[9] 5,7,2′,4′-tetrahydroxy-6-[3″-methylbut-3″-enyl]-flavone (**11**),[10] norartocarpin (**12**),[11] cudraflavone C (**13**),[12] artocarpin (**14**),[13] steppogenin (**15**),[14] artocarpanone (**16**),[15] isogemichalcone C (**17**),[4] artocarmitin (**18**),[16] artocarmin B (**19**),[16] morachalcone A (**20**),[17] brosimone I (**21**),[18] cycloartocarpin (**22**),[14] cudraflavones A (**23**)[15] and B (**24**)[14] and artogomezianone (**25**).[13] The cytotoxic activity of selected compounds was evaluated against KB, MCF-7, NCI-H187 and non-tumorigenic Vero (African green monkey kidney fibroblast) cell lines.

The isolated compounds **1**–**25** (Fig. 1) were purified from the methanolic crude extract using various chromatographic techniques (ESI) and their structures determined by spectroscopic data (IR, UV, 1D and 2D NMR, and MS). For known compounds, the structures were confirmed by comparison of their ^{1}H and ^{13}C NMR data with those previously reported in the literature.

Heterophyllene A (**1**) was obtained as a pale yellow gum with the molecular formula $C_{21}H_{16}O_5$ assigned from HRESI-TOFMS. The UV spectrum displayed maximum absorption bands at λ_{max} 224, 245, 275 and 310 nm, suggesting the presence of a benzofuran chromophore,[19] while the IR spectrum showed absorption bands for hydroxy and double bond functional groups at 3420 and 1645 cm^{-1}, respectively. The ^{1}H NMR spectrum (Table 1) showed signals for the three aromatic protons of a 1,2,4-trisubstituted benzene ring [δ_H 7.38 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.4, 2.0 Hz, 1H)], three singlet aromatic protons [δ_H 6.97, 6.87, 6.85, each s, 1H)] and a dimethylchromene ring [δ_H 6.64 and 5.64, each d, J = 10.0 Hz, 1H), 1.40 (s, 6H)]. Compound **1** displayed carbon resonances for eleven quaternary (δ_C 155.6, 154.7, 154.1, 154.0, 153.6 (2C), 151.5, 122.8, 113.8, 101.2, 76.3), eight methine (δ_C 129.6, 121.2, 116.2, 112.1, 105.6, 103.9, 101.6, 98.2) and two methyl [δ_C 27.8 (2C)] carbons in the ^{13}C NMR and DEPT

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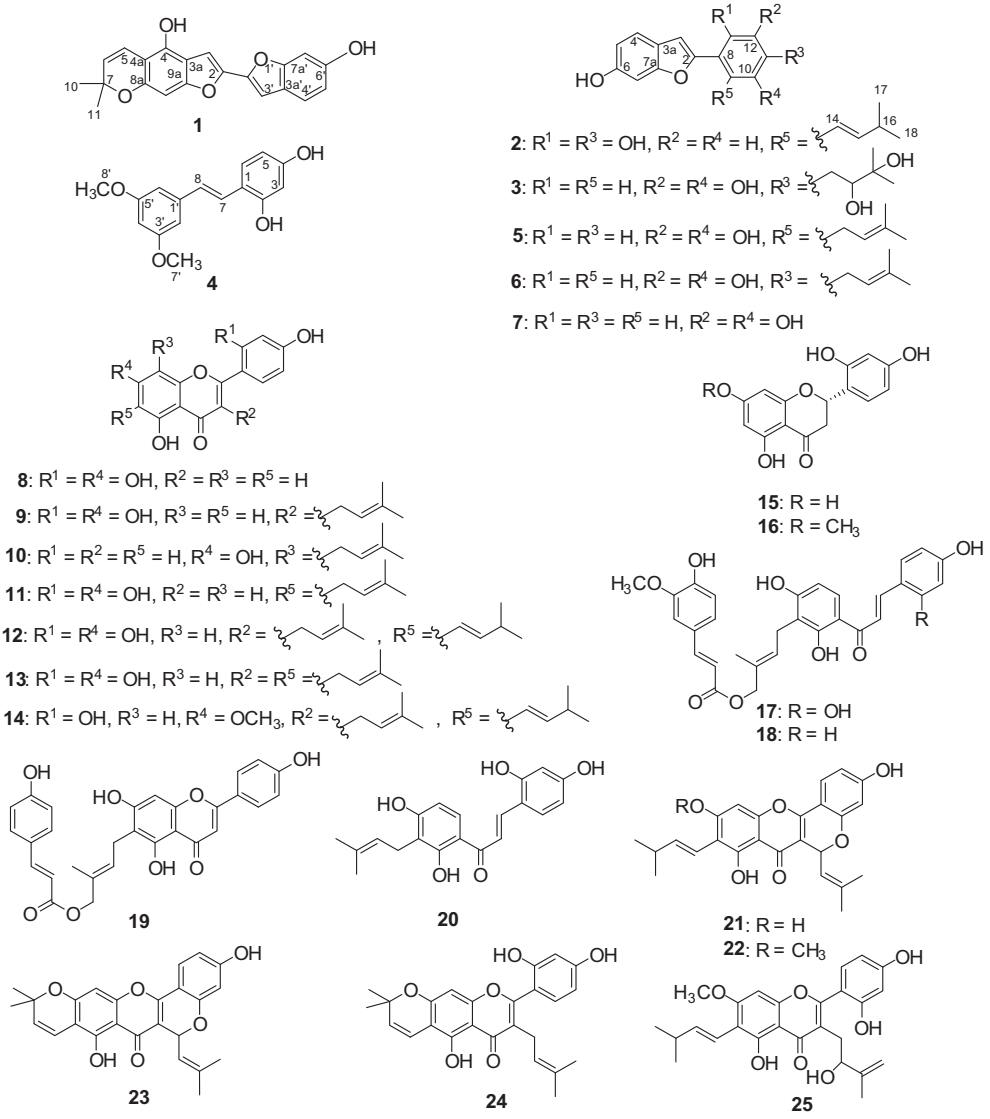

Fig. 1. Structures of compounds **1**–**25** isolated from the twigs of *Artocarpus heterophyllus*.

Table 1
^{1}H (400 MHz, $CDCl_3$) and ^{13}C NMR data (100 MHz, $CDCl_3$) of heterophyllene A (**1**).

Position	δ_H (J in Hz)	δ_C (type)	HMBC
2		154.1 (C)	
3	6.87, s	105.6 (CH)	2, 3a, 4, 9a, 2′
3a		113.8 (C)	
4		151.5 (C)	
4a		101.2 (C)	
5	6.64, d (10.0)	116.2 (CH)	4, 4a, 7, 8a
6	5.64, d (10.0)	129.6 (CH)	7, 10
7		76.3 (C)	
8a		154.0 (C)	
9	6.85, s	101.6 (CH)	3a, 4a, 9a
9a		154.7 (C)	
10	1.40, s	27.8 (CH_3)	6, 7, 11
11	1.40, s	27.8 (CH_3)	6, 7, 10
2′		153.6 (C)	
3′	6.97, s	98.2 (CH)	2′, 3a′, 7a′
3a′		122.8 (C)	
4′	7.38, d (8.4)	121.2 (CH)	3′, 3a′, 6′, 7a′
5′	6.76, dd (8.4, 2.0)	112.1 (CH)	3a′, 6′, 7a′
6′		155.6 (C)	
7′	6.81, d (2.0)	103.9 (CH)	3a′, 5′, 6′, 7a′
7a′		153.6 (C)	

135 spectra (Table 1). Three aromatic protons resonating at δ_H 7.38, 6.81 and 6.76 were assigned as H-4′, H-7′ and H-5′, respectively, on the basis of their multiplicities and coupling constants. H-4′ showed HMBC correlations (Fig. 2) with C-3′ (δ_C 98.2), C-3a′ (δ_C 122.8), C-6′ (δ_C 155.6) and C-7a′ (δ_C 153.6), H-7′ was correlated with C-3a′, C-6′ and C-7a′, and H-3′ showed HMBC correlations with C-2′ (δ_C 153.6), C-3a′ and C-7a′. These data together with the chemical shifts of C-2a′, C-6′ and C-7a′ helped construct a 2-substituted benzofuran moiety with a hydroxy group at C-6′, supporting the benzofuran chromophore observed in the UV spectrum. The aromatic proton resonating at δ_H 6.87 was assigned as H-3 and showed HMBC cross peaks with C-2 (δ_C 154.1), C-3a

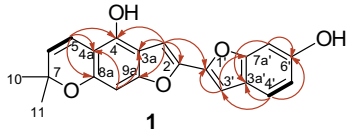

Fig. 2. Selected COSY (bold line) and HMBC ( ) correlations for **1**.