Two new benzofuran derivatives from the roots of *Zanthoxylum flavum*

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Two new benzofuran derivatives (**1** and **2**) have been isolated from the roots of *Zanthoxylum flavum* Vahi. The structures of the new compounds **1** and **2** were characterised as 6-methoxybenzofuran-5-propionylmethylester (**1**) and 6,7-dimethoxybenzofuran-5-propionyl-methylester (**2**) based on one- and two-dimensional NMR spectroscopy and high-resolution mass spectrometry.

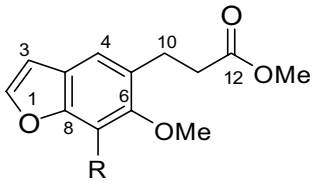
Keywords: benzofurans, *Zanthoxylum flavum*, Rutaceae

Zanthoxylum flavum Vahi. (Rutaceae), known as Espinillo (Dominican Republic), Yellow sanders (Jamaica), and Noyer Bois noyer (Guadeloupe), is an evergreen tree found in Lower Florida Keys, Bermuda, Bahamas, Cuba, Jamaica, Hispaniola, Puerto Rico, and Lesser Antilles from Anguilla to St. Luciain. *Zanthoxylum* species are reported to have many medicinal properties,[1] and phytochemical studies on the genus have shown it to be a rich source of coumarins, lignans, and alkaloids, with febrifuge, sudorific, and diuretic properties.[2-16] Previous studies[16] on the root and stem bark of *Z. flavum* reported the isolation of three alkaloids and four coumarins and our recent study[9] on the roots of *Z. flavum* led to the isolation of seven coumarins, one lignan, seven alkaloids, β-sitosterol glucoside, stigmasterol and lupeol. Further investigations on *Zanthoxylum* species[9-11] led to the isolation of several compounds and in the present communication, we describe the isolation and characterisation of the two new benzofuran derivatives from the roots of *Z. flavum*.

The roots of *Z. flavum* were air-dried, ground, and exhaustively extracted with methanol at room temperature. The methanol extract was subjected to silica gel vacuum-liquid chromatography followed by column chromatography and reverse-phase HPLC to yield compounds **1** and **2**.

Compound **1** was obtained as a light-yellow gum, and showed a molecular ion peak at *m/z* 235.0983 $[M + H]^+$, corresponding to the molecular formula, $C_{13}H_{14}O_4$. The ^{13}C NMR spectrum exhibited 13 carbons including two methoxyls, two methylenes, four methines and five quaternary carbons. This accounted for 7 double bond equivalents and hence compound **1** is bicyclic. An ester group was revealed by IR absorption at 1713 cm^{-1} and a ^{13}C NMR signal at δ 173.4. The ^1H NMR spectrum exhibited two-proton signals at δ 7.82 (δ_c 145.0, C-2) and δ 6.86 (δ_c 107.2, C-3), each integrating for one proton with a *J* value of 2.4 Hz, indicating a typical disubstituted furan ring in **1**. These assignments were confirmed using the ^1H–^1H COSY spectrum. Two multiplets, each integrating for two protons at δ 2.88 (δ 28.9) and 2.59 (δ 34.8) accounted for the presence of two adjacent methylene groups (H-10 and 11). Two singlets, each integrating for three protons at δ 4.06 and 3.58, suggested the presence of two methoxy groups (δ 60.8 and 51.7), which were placed at C-6 and C-12, based on HMBC correlations. These spectroscopic features suggested that compound **1** has benzofuran skeleton substituted at C-6 with a methoxy group and at C-5 with propionyl methylester. Data from the ^1H–^1H–COSY, HMQC, and HMBC spectra provided additional support to justify the gross structure shown for **1**, 6-methoxybenzofuran-5-propionylmethylester.

Compound **2** was obtained as pale brown gum. The HREIMS data of compound **2** suggested the molecular formula $C_{14}H_{16}O_5$ with a molecular ion at *m/z* 265.1062 $[M + H]^+$. IR absorption at 1728 cm^{-1} and ^{13}C NMR peak at *δ* 173.2 implied the presence of an ester carbonyl. The ^{13}C NMR data of **2** showed the presence of 14 carbon signals, which were identified by the assistance of a DEPT spectrum as three methoxyls, two methylenes, three methines, and six quaternary carbons including those of one ester carbonyl and led to the formulation of this compound as $C_{14}H_{16}O_5$. Two olefinic proton doublets (*J* = 2.0 Hz), each integrating for one proton at δ 7.93 (1H, d, *J* = 2.0, H-2) and δ 6.81 (1H, d, *J* = 2.0 Hz, H-3), were attributable to the presence of a furan system in **2**. The ^1H NMR spectrum also showed the presence of pentasubstituted benzene ring and three methoxy functionalities in **2**. Comparison of the ^1H and ^{13}C NMR data of **2** with those of compound **1** indicated that **2** is methoxy analog of **1** and the molecular formula of **2** supported the presence of this additional group. This group was located at the C-7 position based on the HMBC correlations. From these findings, compound **2** was characterised as 6, 7-dimethoxybenzofuran-5-propionylmethylester.



1 R = H

2 R = OMe

Experimental

General experimental procedures

UV and IR spectra were obtained using a Perkin-Elmer Lambda 3B UV/vis spectrophotometer and an AATI Mattson Genesis Series FT-IR spectrometer, respectively. The ^1H and ^{13}C NMR spectra as well as 2D NMR spectra (COSY, HMQC, HMBC) were recorded in $CDCl_3$ using Bruker, DRX NMR spectrometers operating at 400 or 500 MHz for ^1H and 100 or 125 MHz for ^{13}C using the solvent peak as internal standard. The HRMS were measured using a Bioapex FTESI-MS, with electrospray ionisation. A Chromatotron 8924 (Harrison Research, Palo Alto, CA) with a silica gel 60 PF 254 (1 mm) plates was used. TLC analysis was carried out on precoated silica gel G_{254} or aluminum oxide ALOX-100 UV_{254} 500 μm plates with visualisation by 5% H_2SO_4 in EtOH and heating and with Dragendorff's reagent.

Plant material: Roots of *Z. flavum* were identified and collected in August 2003 from the Montgomery Botanical Centre, Old Culture Road region in Florida by Dr Charles L. Burnadt and a voucher specimen is deposited at his private herbarium (518 Audubon, Oxford, MS-38655).

Extraction and isolation: The air-dried and powdered roots of *Z. flavum* (660 g) were extracted with MeOH and the concentrated extract (40 g) was chromatographed on Si gel column (600 g Silica, 5.25 μm) and eluted with *n*-hexane, *n*-hexane–chloroform (1: 1), chloroform, chloroform–methanol (1%–20%) and finally with methanol. Twelve fractions (ZC1-F1 to ZC1-F12, 3L each) were

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collected. Further work-up (purification on silica gel, alumina and RP-HPLC) on a fraction (ZC7-2-6) resulted in the isolation of two compounds that were characterised as 6-methoxybenzofuran-5-propionylmethylester (**1**) (12 mg) and 6,7-dimethoxy-benzofuran-5-propionylmethylester (**2**) (9.5 mg).

6-Methoxybenzofuran-5-propionylmethylester (**1**): Light-yellow gum, IR (KBr) ν_{max} KBr cm^{-1} 1713, 1660, 1640, 1612, 1498; ^1H NMR (400 MHz) δ 7.82 (1H, d, *J* = 2.0 Hz, H-2), 7.37 (1H, s, H-4), 7.22 (1H, s, H-7), 6.86 (1H, d, *J* = 2.0 Hz, H-3), 4.06 (3H, s, 6-OMe), 3.58 (3H, s, 12-OMe), 2.59 (2H, m, H-10) and 2.59 (2H, m, H-11); ^{13}C NMR (100 MHz) δ 173.4 (C-12), 155.9 (C-8), 154.7 (C-6), 145.0 (C-2), 125.1 (C-9), 121.4 (C-4), 119.9 (C-5), 107.2 (C-3), 94.9 (C-7), 60.8 (C-6-OMe), 51.7 (C-12-OMe), 34.8 (C-11) and 28.9 (C-8); HREIMS (*m/z*) 235.0983 (calcd for $C_{13}H_{14}O_4$, $[M + H]^+$, 235.0970).

6,7-Dimethoxybenzofuran-5-propionylmethylester (**2**): Pale brown gum, IR (KBr) ν_{max} KBr cm^{-1} 1728, 1652, 1631, 1614, 1486; ^1H NMR (400 MHz) δ 7.93 (1H, d, *J* = 2.4 Hz, H-2), 7.09 (1H, s, H-4), 6.81 (1H, d, *J* = 2.4 Hz, H-3), 3.83 (3H, s, 6-OMe), 3.81 (3H, s,7-OMe),3.59 (3H, s, 12-OMe), 2.88 (2H, m, H-10) and 2.59 (2H, m, H-11); ^{13}C NMR (100 MHz) δ 173.2 (C-12), 145.6 (C-8), 146.9 (C-6), 146.4 (C-2), 130.1 (C-7), 124.8 (C-9), 114.7 (C-4), 119.9 (C-5), 106.8 (C-3), 61.4 (C-6-OMe), 56.2 (C-7-OMe), 51.8 (C-12-OMe), 34.2 (C-11) and 26.2 (C-10); HREIMS (*m/z*) 265.1062 (calcd for $C_{14}H_{17}O_5$, $[M + H]^+$, 265.1076).

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