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Chromanone-type compounds from marine sponge-derived *Daldinia eschscholtzii* KJMT FP 4.1

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ABSTRACT

In our investigation on chemical diversity of secondary metabolites from marine microorganisms, a sponge-derived fungus was found to produce a glycosylated aromatic compound, karimanone (**1**). The fungal strain was isolated from an Indonesian sponge *Xestospongia* sp. collected in Karimunjawa National Park, Central Java, Indonesia, and was identified as *Daldinia eschscholtzii* based on the internal transcribed spacer rRNA gene sequence. Herein, we describe the isolation and characterization of karimanone (**1**), a new chromanone-type compound, along with three biosynthetically related metabolites (**2**–**4**. All compounds were active against a multidrug-resistant strain of *Salmonella enterica* ser. Typhi with an MIC of 62.5 µg/ml for compound **2** and 125 µg/ml for compounds **1**, **3**, and **4**.

INTRODUCTION

Sponges are the most well-studied animals among the marine invertebrates, from which a vast array of bioactive compounds have been isolated (Hu *et al*., 2015). According to the review by Mehbub *et al*. (2014), Indonesia is the highest contributor of new compounds from marine sponges in tropical countries, and new compounds are continuously being found from the Indonesian marine sponges, as exemplified by tetradehydrohalicyclamine B from *Acanthostrongylophora ingens* (Kato *et al*., 2019), (+)-jasplakinolide Z6 from *Jaspis splendens* (Ebada *et al*., 2019), and nakijiquinone V from *Dactylospongia elegans* (Balansa *et al*., 2019). Intensive natural product screening from marine sponges in these several decades, however, makes it difficult to discover new structures. On the other hand, marine microorganisms are considered to have a potent capability of producing novel bioactive compounds that were acquired through the evolutionary pressure they suffer under unique physical, chemical, and biological conditions of the marine environment (Romano *et al*., 2017). Therefore, our interest in the screening source is shifting from marine sponges to the symbiotic microorganisms residing in sponges (Indraningrat *et al*., 2016).

In recent years, sponge-associated fungi are attracting attention as a productive source of new chemical entities (Liu *et al*., 2018; Pang *et al*., 2018; Wang *et al*., 2012). Furthermore, sponges are suggested to give influences to the diversity of compounds produced by associated fungi (Imhoff, 2016; Proksch *et al*., 2008). In Indonesia, the giant-barrel *Xestospongia* spp. is one of the most well-known genera for unique secondary metabolites such as aaptamine, isoaaptamine, demethyl(oxy)aaptamine, 2-(3*H*-diazirine-3-yl)benzaldehyde, manzamine C, xestosaprols, and *N*-methylniphatyne A (Agustina *et al*., 2018; Arai *et al*., 2016; Calcul *et al*., 2003; Dai *et al*., 2010; Millán-Aguiñaga *et al*., 2010; Murtihapsari *et al*., 2018). It is thus assumed that sponge-associated fungi from *Xestospongia* might have the potential to produce structurally diverse compounds. Unfortunately, only a few studies reported secondary metabolites from Indonesian *Xestospongia*-derived fungi to date. The first example is the antimicrobial xestodecalactones from *Xestospongia*-derived *Penicillium* cf. *montanense* reported by Edrada *et al*. (2002). Another case is a series of antibacterial chromones reported by Lin *et al*. (2003) from *Aspergillus versicolor* isolated from *Xestospongia exigua*.

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Since then, no additional studies on bioactive compounds have been reported from fungi associating with *Xestospongia* sponges.

Exploration of antibacterial compounds is becoming a core of natural product screening in this past few years, along with the increasing emergence of multidrug-resistant (MDR) bacteria (Asagabaldan *et al.*, 2017; Ayuningrum *et al.*, 2019; Goncalves *et al.*, 2016; Kristiana *et al.*, 2017; Magairakos *et al.*, 2011; Malhotra *et al.*, 2016; Sibero *et al.*, 2018a; 2018b). *Salmonella enterica* ser. Typhi is one of such MDR bacteria causing serious problematic infections (Crump *et al.*, 2015; Stephens *et al.*, 2019). This pathogen caused serious typhoid fever outbreak in several cities in China, Pakistan, Thailand, and Zimbabwe (Limpitikul *et al.* 2014; Muti *et al.*, 2014; Yan *et al.*, 2016; Wong *et al.*, 2018). In this paper, we report the isolation and structure determination of secondary metabolites possessing antibacterial activity against MDR *S. enterica* ser. Typhi from a *Xestospongia*-derived fungus.

EXPERIMENTAL PROCEDURE

General experiment procedures

NMR spectra were recorded on a Bruker AVANCE II 500 spectrometer (Bruker Biospin K. K., Yokohama, Japan) and mass spectra were measured on a Bruker microTOF (Bruker Daltonics K. K., Yokohama, Japan). IR spectra were recorded on a Shimadzu FT-IR-300 spectrophotometer (Shimadzu Corp., Kyoto, Japan) and UV spectra on a Shimadzu UV-1800 (Shimadzu Corp., Kyoto, Japan). All compounds were analyzed by using reversed phase column Microsorb C_{18} (particle size 3 µm, pore size 50×4.6 mm). Compound **1** was eluted at t_R 5.31 minute compound **2** at 8.87 minutes, compound **3** at 13.41 minutes, and compound **4** at 11.23 minutes. Purification was carried out by using COSMOSIL Cholester Packed Column (Nacalai Tesque, 10.0 mm i.d. x 250 mm).

Sponge

A giant barrel sponge was purposively collected from Karimunjawa National Park, Central Java Indonesia with permission number 1096/T.34/TU/SIMAKSI/7/2017 by scuba diving. The sponge was identified as *Xestospongia* sp. KJMT. SP.04 by the specific giant-barrel shape. Approximately 3 × 3 cm tissues were taken using a blade and put into a zip-lock plastic bag then kept in a chilling temperature for fungal isolation.

Microorganism

The fungal strain KJMT FP 4.1 was isolated and identified as *Daldinia* with 99.9% similarity in the internal transcribed spacer (ITS) rRNA gene sequence (548 nucleotides; accession number MG972929.1 in GeneBank) to *Daldinia eschscholtzii* (GeneBank accession number KU304335).

Fermentation

This step was carried out according to the reported procedure (Shimoyama *et al.*, 2018). Strain KJMT FP 4.1 growing on malt extract agar medium was inoculated into 500 mL K-1 flasks, each containing 100 mL of V-22 medium [1% soluble starch, 0.5% glucose, 0.3% NZ-case, 0.2% yeast extract (Kyokuto Pharmaceutical Industrial, Co. Ltd, Tokyo Japan), 0.2% Tryptone (Difco Laboratories, Sparks, USA), 0.1% K_2HPO_4, 0.05% $MgSO_4 \cdot 7H_2O$, and 0.3% $CaCO_3$ in distilled water] at pH 7.0 for seed culture. The inoculated flasks were placed on a rotary shaker (200 rpm) at 30°C for 3 days. Then, 5 ml of the seed culture was transferred into 500 mL K-1 flasks each containing 100 mL of production medium (A-11M) consisting of 2% glucose, 2.5% soluble starch, 0.5% yeast extract, 0.5% polypeptone, 0.5% NZ-amine, 0.5% $CaCO_3$, and 1% Diaion HP-20 (Mitsubishi Chemical Co., Yokohama, Japan) at pH 7.0. The inoculated flasks were placed on a rotary shaker (200 rpm) at 30°C for 7 days.

Extraction and isolation

After fermentation, 100 ml 1-butanol was added to each flask and shaken on a rotary shaker (200 rpm) for 1 hour. The mixture was centrifuged at 6,000 rpm for 15 minutes, and the organic layer was separated from the aqueous layer containing the mycelium (Shimoyama *et al.*, 2018). The organic solvent was removed by evaporation with a rotary vacuum evaporator, providing 4.44 g of crude extract. It was then subjected to silica gel column chromatography with a step gradient of $CHCl_3$-MeOH (1:0, 20:1, 10:1, 4:1, 2:1, 1:1, and 1:1 v/v). The selected fractions were further purified using an ODS column chromatography with a step gradient of MeCN-0.1% HCO_2H (20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20 v/v). All compounds were purified by reversed-phase preparative high performance liquid chromatography (HPLC) using a Cosmosil Cholester Packed Column (Nacalai Tesque Inc., 20 × 250 mm). Compound **1** (88.8 mg) was obtained from an ODS 60:40 fraction of silica gel 20:1 fraction after HPLC purification using an isocratic condition (40% MeCN) at t_R 19.4 minutes. Compounds **2** (10.5 mg, t_R 18.6 minutes) and **3** (5.6 mg, t_R 23.2 minutes) were obtained from an ODS 40:60 fraction of silica gel 10:1 fraction, after HPLC purification with a gradient condition (0–25 minutes: 25%–40% MeCN). Compound **4** (17.1 mg, t_R 19.8 minutes) was isolated from an ODS 30:70 fraction of silica gel 4:1 fraction after HPLC purification with a gradient condition (0–25 minutes: 15%–30% MeCN in 0.1% HCO_2H).

Antimicrobial assay

Compounds **1**, **2**, **3**, and **4** were tested for antibacterial activity with microdilution method (Igarashi *et al.*, 2011). *Salmonella enterica* ser. Typhi were obtained from Dr. Kariadi General Hospital in Semarang and confirmed as a multi-drug resistant organism. The pathogen was refreshed from stock 24 hours before diluted into physiological saline solution with a density value of 0.5 McFarland. All compounds were diluted into mixture of Mueller Hinton Broth (MHB) and dimethyl sulfoxide (DMSO) (1:2) and delivered into a microplate with 250, 125, 62.5, 31.3, 15.6, 7.8, 3.9, and 2.0 µg to a volume of 50 µl in each well. Amoxicillin (PT. Graha Farma) was used as a positive control and DMSO as a negative control. Each well was then loaded with 145 µL MHB and 5 µL pathogen containing liquid, and incubated at 32°C for 24 hours. At the end of incubation, 10 µL of WST-1 indicator was added into each well and incubated for 1 hour at 32°C. Living bacteria were detected by the changing of color to yellow. The lowest concentration that inhibits pathogen growing was determined as minimum inhibitory concentration (MIC) value. Then 10 µl of the solution in each well was taken and spread onto Mueller-Hinton Agar and incubated at 32°C for 24 hours.

RESULTS AND DISCUSSION

Fungal strain KJMT FP 4.3 was isolated from a sponge *Xestospongia* sp. collected in Karimunjawa National Park, Central Java. This fungus was identified as a member of *Daldinia* on the basis of 99.9% similarity of ITS gene sequence to *D. eschscholtzii*. In the HPLC/UV analysis of the crude extract, four major peaks were detected and thus purified for structural analysis. One unknown major peak was characterized as a new compound designated karimanone (**1**), which is a diastereomeric mixture of α-D-ribofuranoside of (2*R*)- and (2*S*)-5,7-dihydroxy-2-methyl-4-chromanone. The other three compounds (**2**, **3**, and **4**) were identified as known compounds (Fig. 1).

Compound **1** was isolated as a yellow powder that showed a deprotonated molecule $[M-H]^-$ ion peak at *m/z* 325.0911 in the high resolution electrospray ionization mass spectrometry (HRESIMS) analysis, corresponding to a molecular formula of $C_{15}H_{18}O_8$ (calcd for $C_{15}H_{17}O_8$, 325.0923) with seven degrees of unsaturation. This compound showed IR absorption bands at 3,415 and 1,642 cm^{-1}, suggesting the presence of hydroxy and carbonyl groups. Investigation of the ^1H and ^{13}C NMR and heteronuclear single-quantum correlation (HSQC) spectra revealed 15 carbon resonances (Table 1), consisting of seven sp^2 carbons (δ_C 198.8, 166.9, 165.0, 164.6, 104.7, 98.1, and 97.2; including one carbonyl and three oxygenated), five oxygenated methine carbons (δ_C 101.7, 88.2, 75.7, 73.6, and 71.2), two methylene carbons (δ_C 68.2 and 44.3, one oxygenated), and one methyl carbon (δ_C 21.1).

The planar structure of **1** was assigned by the analysis of 1D and 2D NMR spectral data recorded in CD_3OD (Fig. 2). From the correlation spectroscopy (COSY) analysis, two ^1H-^1H spin systems, 2-Me/H2/H3 and H11/H12/H13/H14/H15 were identified. The oxygenated methine H2 showed heteronuclear multiple bond coherence (HMBC) correlations to C4 and C9 and methylene protons H3 were correlated to C4 and C10. These correlation data established the ether bridge between C2 and C9 and the presence of a ketone group being located between C3 and C10. Meanwhile, aromatic methine protons H6 and H8 were mutually HMBC-correlated and both protons were correlated to C10. Additionally, HMBC correlations were shown from H6 to C5 and C7 and from H8 to C7 and C9. Together with these HMBC correlations, high-field shifted chemical shifts for the carbons C6, C8, and C10 suggested that these carbons were positioned *ortho* to the oxygenated carbons C5, C7, and C9, thereby establishing the tetrasubstituted benzene ring comprising six carbons from C5 to C10. Therefore, along with the aforementioned correlations from H2 to C9 and H3 to C10, the 2-methyl-4-chromanone substructure was confirmed. Another COSY-defined fragment from H11 to H15 was deduced to form a pentofuranosyl moiety by the mutual HMBC correlations between H11 and H14. Finally, this sugar part was connected at C7 through the ether bond by an HMBC correlation from H11 to C7, completing the planar structure of **1** (Fig. 2).

The relative configuration of the pentose moiety was established by NOESY analysis. NOE correlations were observed for H11/H12, H12/H13, and H13/H15, confirming that H11, H12, and H13 were on the same side, and H14 was on the opposite side (Fig. 3). The coupling constant $^3J_{HH}$ of the anomeric proton H11 showed 4.8 Hz, a typical value for the α-ribofuranoside. β-Ribofuranosides usually give a singlet proton signal for the anomeric proton with *J* values near 0 Hz (Du *et al*., 2008; Sharma *et al*., 2012). Therefore, the α-ribofuranosyl configuration was established.

The absolute configuration of **1** was estimated by comparing its specific rotation with the reported values of 2-ribofuranosides (Fig. 6) (Walker and Hogenkamp, 1974; Du *et al*., 2008; Sharma *et al*., 2012). Since α-D-ribofuranosides always provide positive $[\alpha]_D$ values, the positive specific rotation value shown by **1** ($[\alpha]^{22}_D$ +181 (*c* 1.0, MeOH)) suggested the

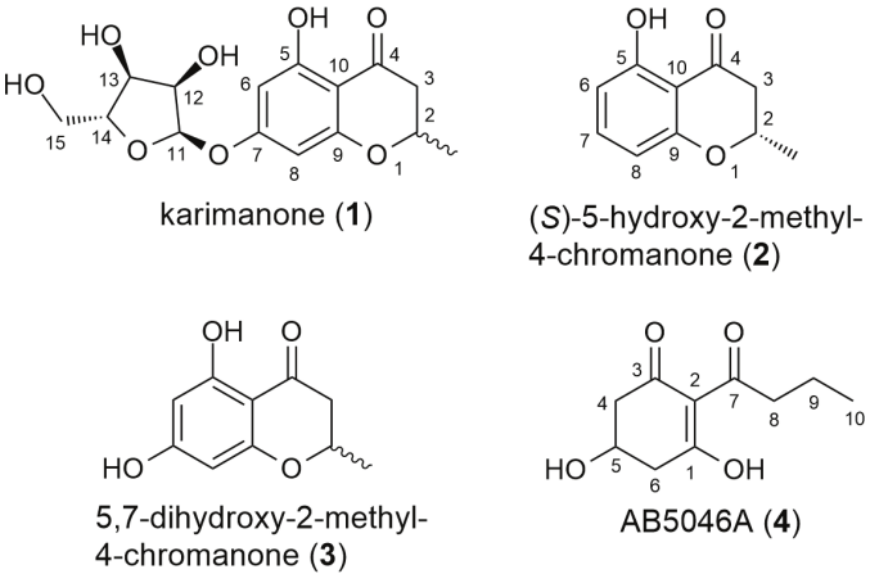

Figure 1. Structures of compounds **1**,**2**,**3**, and **4**

α-D-ribofuranoside with 11*R*, 12*R*, 13*S*, and 14*R*-configurations. L-Ribofuranosides have not been reported from natural products to date.

The remaining chiral center C2 was deduced to be racemic based on the following observations. Several unexpected splitting patterns were found in ^{1}H and ^{13}C NMR spectra. The anomeric proton H11 appeared as two doublet signals and the carbon signals for 2-Me, C2, C3, C4, C5, and C7 displayed weak splitting (Table 1, Figs. 4–5). These carbons were located in the chromanone moiety, indicating that compound **1** was obtained as a diastereomeric mixture regarding the C2 chiral center. This conclusion was further supported by the isolation of compound **3** as a racemic mixture from this strain, an aglycon part of which might be a biosynthetic precursor of **1**. Therefore, **1** was determined to be a mixture of (2*R*)- and (2*S*)-isomers of 7-α-D-ribofuranosyl-5-hydroxy-2-methyl-4-chromanone.

In this study, **1** was obtained as an inseparable mixture of two diastereomers containing (2*R*)- and (2*S*)-isomers of **1**. (2*R*)-Isomer is known as a metabolite of an endophytic *Daldinia* but (2*S*)-isomer has not been reported to date (Hu *et al*., 2017). (*S*)-**3** was isolated from a botanical source *Diospyros maritima* (Chang *et al*., 2009), while (*R*)-**3** is not found from nature to date. This is the first finding of **3** from microorganisms. (*S*)-**2** was isolated from *Daldinia* (Nadeau and Sorensen, 2011), and (*R*)-**2** from *Nodulisporium*, *Cryptosporiopsis*, and *Daldinia* (Dai *et al*., 2006; Hu *et al*., 2017; Pathania *et al*., 2015; Zilla *et al*., 2013). (*R*)-**2** has potent anti-leukemic activity, while no obvious biological activity was found from (*S*)-**2**. Compound **4** was previously isolated from *Nodulisporium* and *Daldinia* with herbicidal activity (Hu *et al*., 2017; Igarashi *et al*., 1993; Wang and Liu, 2004). Antibacterial activity of the single compounds is shown in Table 2.

It is noted that compound **2** had MIC (minimum inhibitory concentration) value of 62.5 µg/mL and compounds **1**, **3** and **4** had MIC value of 125 µg/mL, while the MIC for amoxicillin as the positive control was 250 µg/mL (Table 2). Enantiomerically pure compound (2*R*)-**1** was reported has antibacterial activity against non-MDR *Staphylococcus aureus* with MIC value of 64 µg/mL (Hu *et al*., 2017). CLSI (2016) stated that *Salmonella* spp. could be stated as resistant to amoxicillin if the MIC value is > 36 µg/ml. Table 2 shows that the *S. enterica* ser. Typhi that used in this study was resistant to amoxicillin. Moreover, the result of antibacterial activity indicated that these compounds had stronger antibacterial activity against MDR *S. enterica* ser. Typhi than the positive control.

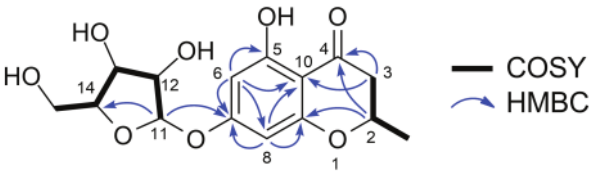

Figure 2. COSY and key HMBC correlations of compound **1**.

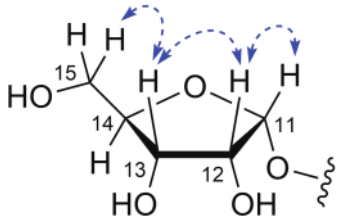

Figure 3. NOESY correlations of the ribose part of compound **1**.

Karimanone (1): yellow powder; $[\alpha]^{22}_{D}$ + 181 (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ε) 284 (5.48), 325 (4.71) nm; IR ν_{max} 3,415, 1,642 cm^{-1}; see Table 1 for ^{1}H NMR and ^{13}C NMR data; HR-ESITOFMS $[M - H]^{-}$ *m/z* 325.0911 (calcd for $C_{15}H_{17}O_8$, 325.0923).

(*S*)-5-Hydroxy-2-methyl-4-chromanone (2): pale pink powder; $[\alpha]^{22}_{D}$ -1.9 (*c* 1.0, MeOH lit. (*R*)-**2**: $[\alpha]^{25}_{D}$ +6 (*c* 0.19, CH_2Cl_2),[11] (*S*)-**2**: $[\alpha]^{22}_{D}$ -1.19[15]}; UV (MeOH) λ_{max} (log ε) 204 (5.41), 220 (5.26), 271 (5.15), 348 (4.67) nm; IR ν_{max} 1,622, 1214, 1,056 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.70 (1H, s, O*H*), 7.32 (1H, t, *J* = 8.2 Hz, H7), 6.47 (1H, = 8.3 Hz, H6), 6.40 (1H, *J* = 8.3 Hz, H8), 4.54 (1H, m, H2), 2.67 (2H, m, H3),1.49 (3H, d, *J* = 6.4 Hz, H11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6 (C4), 162.2 (C5), 161.8 (C9), 138.3 (C7), 109.2 (C6), 108.1 (C10), 107.4 (C8), 73.9 (C2), 43.9 (C3), 20.9 (C11); HR-ESITOFMS $[M - H]^{-}$ *m/z* 177.0521 (calcd 177.0552 for $C_{10}H_9O_3$).

5,7-Dihydroxy-2-methyl-4-chromanone (3): pale yellow powder; $[\alpha]^{22}_{D}$ -6.6 (*c* 1.0, MeOH) {lit. (*S*)-**3**: $[\alpha]_{D}$ -58.6 (*c* 1, MeOH) (Rao *et al*., 2017)}; UV (MeOH) λ_{max} (log ε) 211 (5.40), 228 (sh, 5.20), 288 (5.35), 330 (sh, 4.56) nm; IR ν_{max} 3,163, 1,601, 1,301, 1,164 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.84 (1H, s,

Table 1. NMR spectroscopic data (500 MHz, CD_3OD) for Karimanone (**1**).

Position	δ_C	Type	δ_H (*J* in Hz)	HMBC[a]
2-Me	21.11 21.13	CH_3	1.46, d (6.3)	2, 3, 9
2	75.64 75.68	CH	4.53, m	1, 4, 9
3	44.26 44.34	CH_2	2.62, dt (17.4, 3.7) 2.70, dd (17.4, 12.6)	1, 2, 4, 10 1, 2, 4
4	198.75 198.77	C		
5	164.96 165.01	C		
6	98.1	CH	6.21, s	5, 7, 8, 10
7	166.92 166.96	C		
8	97.2	CH	6.21, s	6, 7, 9, 10
9	164.6	C		
10	104.7	C		
11	101.7	CH	5.67, d (4.8) 5.68, d (4.8)	7, 12, 13, 14
12	73.6	CH	4.20, t (5.4)	11, 13, 14
13	71.2	CH	4.09[b]	11, 12, 14, 15
14	88.2	CH	4.11[b]	11, 12, 13, 15
15	63.2	CH_2	3.64, dd (12.2, 3.5) 3.70, dd (12.2, 3.0)	13, 14

[a]HMBC correlations are from proton(s) stated to the indicated carbon.
[b]Overlapped signals.

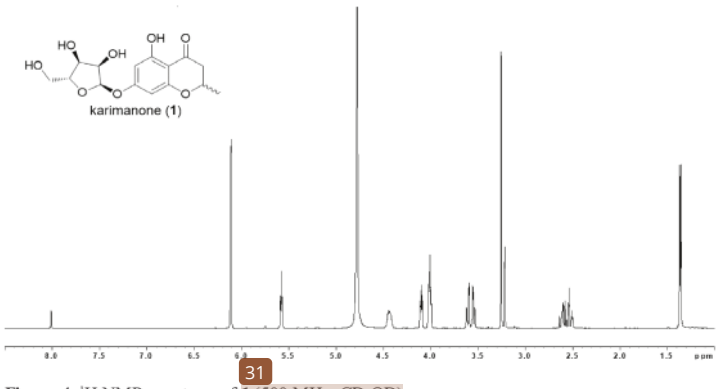

Figure 4. ^{1}H NMR spectrum of **1** (500 MHz, CD_3OD)

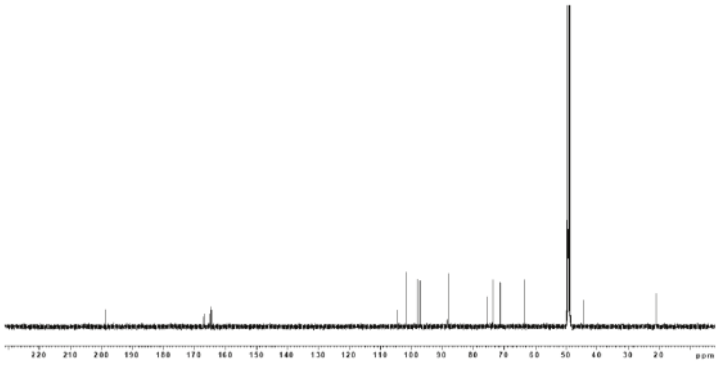

Figure 5. ^{13}C NMR spectrum of **1** (125 MHz, CD_3OD)

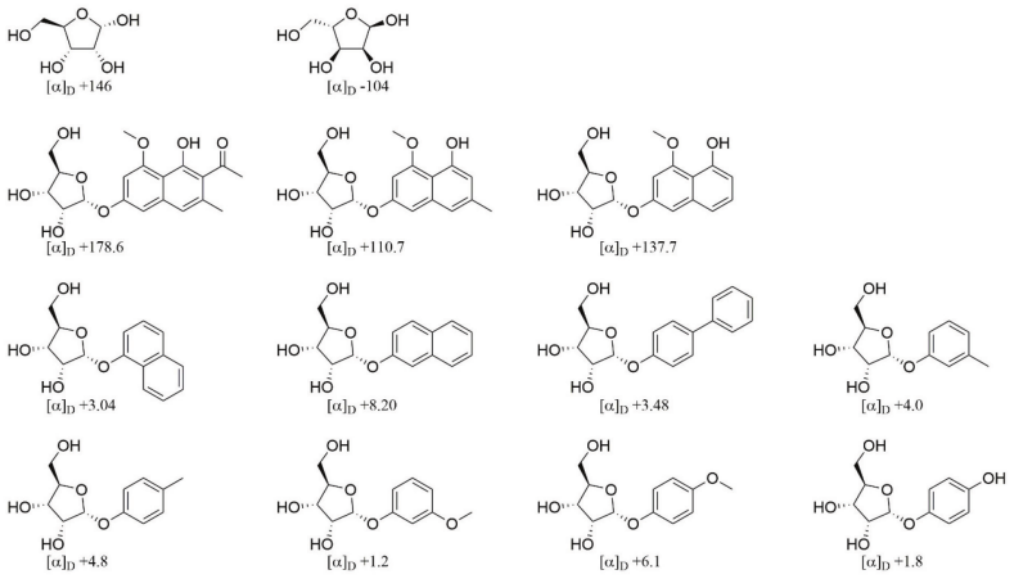

Figure 6. Specific rotation values of *α*-ribofuranosides

Table 2. Antibacterial activity of the pure compounds against *S. enterica* ser. Typhi.

Compounds	MIC (µg/ml)
1	125
2	62.5
3	125
4	125
Positive control (Amoxicillin)	250

H6), 5.84 (1H, s, H8), 4.50 (1H, m, H2), 2.66, 2.57 (each 1H, dd, J = 12.3, 17.1 Hz, dd, J = 3.1, 17.1 Hz, H3), 1.44 (3H, d, J = 6.3 Hz, H11); ^{13}C NMR (125 MHz, CD_3OD) δ 198.1 (C4), 168.4 (C7), 165.6 (C5), 165.1 (C9), 103.4 (C10), 97.0 (C8), 96.1 (C6), 75.5 (C2), 44.2 (C3), 21.1 (C11); HR-ESITOFMS $[M - H]^-$ m/z 193.0545 (calcd for $C_{10}H_9O_4$, 193.05

AB5046A (4): yellow oil; UV (MeOH) λ_{max} (log ε) 229 (4.39), 273 (4.86), 340 (3.72) nm; IR ν_{max} 3364, 2963, 1549, 1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (1H, br, H5), 2.77, 2.65 (each 1H, d, J = 5.8, 16.3 Hz, H4), 3.01 (2H, t, J = 7.3 Hz, H8), 2.80 (each 1H, dd, J = 2.0, 18.0 Hz, o, H6), 1.64 (2H, sextet, J = 7.3 Hz, H9), 0.99 (3H, t, J = 7.4 Hz, H10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7 (C7), 196.2 (C3), 193.2 (C1), 113.2 (C2), 63.7 (C5), 47.4 (C4), 42.4 (C8), 41.7 (C6), 18.2 (C9), 14.1 (C10); HR-ESITOFMS $[M + Na]^+$ m/z 221.0745 (calcd 221.0790 for $C_{10}H_{14}O_4Na$).

CONCLUSION

Four compounds (**1–4**) were successfully isolated from *D. eschscholtzii* KJMT FP 4.1, an Indonesian sponge-associated fungus. Karimanone (**1**) showed an interesting structure due to the glycosylated aromatic structure. Moreover, **1** was obtained as an inseparable mixture of two diastereomers containing (2*R*)- and (2*S*)-isomers for the chromanone part. (2*R*)-Isomer is known as a metabolite of an endophytic *Daldinia*, while (2*S*)-isomer has not been reported to date. All compounds were active against the multidrug-resistant strain of *S. enterica* ser. Typhi with an MIC of 62.5 µg/ml for **2** and 125 µg/ml for **1**, **3**, and **4**.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest regarding the publication of this work.

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