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Polybrominated diphenyl ethers with broad spectrum antibacterial activity from the Indonesian marine sponge *Lamellodysidea herbacea*

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ABSTRACT

The marine sponge *Lamellodysidea herbacea* is one of the marine organisms containing unique organobromine molecules polybrominated diphenyl ethers (PBDEs) which have diverse biological activities. Compounds **1**−**4** have been successfully isolated and their structures were elucidated using nuclear magnetic resonance (NMR) spectroscopy, single-crystal x-ray diffraction, and comparison with data in literature. Compound **1**, $C_{12}H_6O_4Br_6$, was isolated in gram quantity (1.35 g) and elucidated as 2,3,4,5-tetrabromo-6-(3′,5′-dibromo-2′-hydroxyphenoxy)phenol after NMR and X-ray analysis. Compound **1** takes a twist-like conformation with torsion angle ϕ_1 = 27.7 (6)°; ϕ_2 = 86.5 (5)°, while the angle of the ether bond is 117.5°. Compounds **2**−**4** were elucidated as 2,3,5-tribromo-6-(3′,5′-dibromo-2′-hydroxyphenoxy)anisole, 2,3,5-tribromo-6-(3′,5′-dibromomethoxyphenoxy) phenol, 2,3,5-tribromo-6-(3′,5′-hydroxyphenoxy)phenol, respectively. Antibacterial evaluation of **1**−**4** on Gram-positive and Gram-negative pathogens showed that the potent activity was at 0.08 µg/disk, 12 ± 0 mm (*Staphylococcus aureus* ATCC 6538); 6.25 µg/disk, 10 ± 0 mm (*Klebsiella pneumoniae*); and 50 µg/disk, 12 ± 0 mm (ampicillin-resistant *Escherichia coli*). Compounds **1**, **2**, and **4** showed ichthyotoxicity (zebrafish embryos, *Danio rerio*) at a level of LC_{50} >10 µg/ml [dead, 48 hours postfertilization (hpf)]. This is the first report that compound **4** inhibits the growth of antibiotic-resistant bacteria.

INTRODUCTION

Infectious disease is defined as any cause by pathogenic microorganisms, such as bacteria, viruses, parasites, or fungi, which can be directly or indirectly spread from one person to another. This problem becomes even more difficult if antimicrobial resistance is faced. Of the 194 countries, only 129 countries provided any national data on drug resistance (Reardon 2014). Most countries had found to have five antibiotic-resistant bacteria-drug pairs (Reardon 2014). The challenge is even greater in developing countries where the burden of infectious disease is high. This is because of the increasing use of antibiotics, poor sanitation and hygiene in communities and hospitals, and the increasing frequency of global travel, trade, and disease transmission (Laxminarayan *et al*. 2013). Indonesia has started to face this problem since 1990 (Parathon *et al*. 2017). Survey of Indonesian public hospitals reported that patients in the national hospital were increased for antibiotic-resistant *Escherichia coli* (52%), Enterobacteriaceae producing extended-spectrum β-lactamase, *Klebsiella pneumoniae* (58%), and methicillin-resistant *Staphylococcus aureus* (MRSA) (Hadi *et al*. 2013). This was due to the high inappropriate use of antibiotics. In the global issue, infectious diseases caused by pathogenic Gram-positive vancomycin-resistant enterococci (VRE) and MRSA have paid attention over the past two decades.

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However, the global current focus is emphasized to discover new antibiotics that can cure infectious diseases from Gram-negative *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and Enterobacter species pathogens and their resistant forms. This pressing treatment challenge is that because the discovery for Gram-negative antibiotics is more difficult than those of Gram-positive bacteria (Walsh and Wencewicz, 2014). Only two approvals of antibiotic drugs, synercid and daptomycin, are largely used in response to VRE and MRSA, and there had not been a new antibiotic scaffold for Gram-negative pathogens (Walsh and Wencewicz, 2014). In 2015, a polybrominated diphenyl ether (PBDE) discovered from the marine sponge *Dysidea* (*Lamellodysidea*) was able to inhibit various pathogenic Gram-negative bacteria including resistant strains (Sun *et al*., 2015).

The marine sponge *Lamellodysidea herbacea* is known to have a unique group of marine natural products named with PBDEs. Interestingly, the true producer of PBDE was revealed as a marine cyanobacterium *Oscillatoria spongelliae* (Faulkner *et al*., 1994). This class of compounds has been found to exhibit a variety of bioactivities such as antibacterial (Handayani *et al*. 1997; Hanif *et al*., 2007; Liu *et al*., 2016; Sun *et al*., 2015), antifungal (Sionov *et al*., 2005), anti-cancer (Arai *et al*., 2017; Fu *et al*., 1995; Liu *et al*., 2004; Xu *et al*. 2005), and antiviral (Salam *et al*., 2014; Yamashita *et al*., 2015). PBDE is a unique molecule containing phenyl rings, -OH, ether, and -Br functional groups. The latter group is very useful in aromatic chemistry as a protecting group (Choi and Chi, 2001; Effenberger, 2002) and is rarely explored. All isolated PBDEs were evaluated for their activities using Gram-positive *S. aureus* and Gram-negative bacteria, including *K. pneumoniae* and *E. coli* ampicillin resistance. To become ready as antibacterial drug leads, we combine our assays using zebrafish embryos toxicity assay (Hanif *et al*., 2018). Antibacterial drugs should have the lowest possible toxic effect. It is quite challenging to discover antibacterial drugs with the lowest toxicity effect (Walsh and Wencewicz, 2014).

In our continuing interest on bioactive marine organisms (Hanif *et al*., 2018), four compounds (**1**−**4)** have been successfully isolated from the marine sponge *L. herbacea* collected in Ujung Kulon, and their structures were elucidated using NMR and IR spectroscopy, X-ray crystallography, and electrospray ionization mass spectrometry (ESIMS) spectrometry as well as comparison with the data in literature. We also evaluated the isolated compounds against Gram-positive *S. aureus*, Gram-negative *K. pneumoniae*, and *E. coli* ampicillin-resistant pathogens. Embryos zebrafish *Danio rerio* were used to evaluate the isolated compounds for their toxicity. We report here the isolation and structure elucidation of the compounds and the results of bioactivities.

MATERIAL AND METHODS

General

Ultraviolet (UV) and IR spectra were obtained on a Perkin Elmer Spectrum One Fourier-transformed infrared and on a Shimadzu pharmaspec 1700 spectrophotometer, respectively. ESIMS data were obtained from Waters Acquity Xevo G2-S quadrupole time-of-flight mass spectrometry with positive mode, and nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 500 spectrometer (500 MHz for ^{1}H). Chemical shifts (δ) were referenced to trimethylsilane, deuterated chloroform ($CDCl_3$), or deuterated acetone (Me_2CO-d_6) signals and are expressed in parts per million (ppm), and coupling constants (*J*) are in Hz. X-ray analysis was performed on a Rigaku AFC10 goniometer equipped with a Saturn 724+ detector. High-performance liquid chromatography (HPLC) separations were carried out on a Hitachi L-6000 pump fitted with a Shodex RI-101 refractive index and SPD-20A Shimadzu UV detectors. The column used for HPLC was Cosmosil 5SL-II-MS (10 × 250 mm), and analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and visualized with sulfuric acid with cerium sulfate. All solvents used were reagent grade.

Animal material

The marine sponge was collected by hand using scuba off Ujung Kulon, Indonesia, in March 2018. A voucher specimen has been deposited in the Department of Chemistry, IPB University, Indonesia (Code NH-G1-0067-17c).

Extraction and isolation

The marine sponge specimen (wet, 300 g) stored in ethanol (EtOH, C_2H_6O) was extracted three times using methanol (MeOH, CH_4O) (3 × 200 ml). The combined extracts were concentrated under reduced pressure, and the residue was partitioned between *n*-hexane (C_6H_{14}) and aqueous methanol (MeOH, CH_4O) (90%). The latter layer was partitioned further between dichloromethane (CH_2Cl_2) and aqueous methanol (MeOH, CH_4O) (50%). After the removal of methanol (MeOH, CH_4O) from the latter layer and the addition of water (H_2O), the residue was extracted with *n*-butanol (*n*-BuOH, $C_4H_{10}O$). All layers (n-hexane, C6H14; dichloromethane, CH2Cl2; n-butanol, n-BuOH, C4H10O) were checked for their activity against Gram-positive and Gram-negative bacteria. Crystallization of the most active layer (CH_2Cl_2) from $CHCl_3$−Me_2CO−MeCN (1:1:2) gives **1** (1.36 g in total). A noncrystalline fraction was successively separated using either a silica gel column eluted with hexane−EtOAc, EtOAc−MeOH, and MeOH followed by recrystallization, or by silica HPLC eluted with hexane−EtOAc to give compound **2** (5.4 mg), a mixture of compounds **2** and **3** (5.6 mg), and compound **4** (136.5 mg).

Evaluation of antibacterial activity and toxicity against fish embryos

Antibacterial activity (Hanif *et al*., 2007) was evaluated using agar-plate diffusion assay. Paper disks were impregnated with isolated compounds ranging from 0.08 to 50 µg/disks and placed on agar plates inoculated with *S. aureus* ATCC 6538, *K. pneumoniae*, *E. coli*, or ampicillin-resistant *P. aeruginosa* was used qualitatively to check whether the layer was active or not. Prior to and after the testing, all the materials were sterilized at 121°C for 20 mintues. DMSO was used as a negative control, while ampicillin and chlorampenicol were used as a positive control.

For toxicity (Hanif *et al*., 2018), fertilized and normally developed embryos of *D. rerio* were used. A series of sample concentrations was prepared from 1.25 to 10 µg/mL. After the 4-hour fertilization, the eggs were collected and rinsed with an

embryo rearing solution medium. The fertilized and normally divided eggs were selected under the microscope. The embryos were exposed to the compounds for 24, 48, and 72 hours in 24-well microplates. Observation of the embryos was based on whether it is dead or alive. The number of embryos used for each assay was 10. A positive control was 3,4-dichloroaniline, while the negative control was DMSO. The LC_{50} was calculated by using the statistical software SPSS IBM 23.0. The experiment was repeated three times.

NMR analysis

A sample dissolved in $CDCl_3$ or Me_2CO-d_6 or a mixture of the two NMR solvents was measured with a Bruker Avance III 500 spectrometer (500 MHz for ^{1}H). The samples were measured for their ^{1}H NMR after scanning for 16–32 times. Tetramethylsilane was used as an internal standard.

X-ray analysis

All measurements were made on a Rigaku AFC10 goniometer equipped with Saturn724+ detector mounted graphite monochromated Mo-Kα radiation (λ = 0.71075 Å). A suitable crystal was selected and mounted in inert oil and transferred to the cold N_2 gas stream of the diffractometer. The crystal was kept at 123 K during data collection. The data were collected using CrystalClear-SM 1.4.0 SP1 (Rigaku, 2008) and processed with CrysAlisPro 1.171.39.46 (Rigaku, 2018).

Using Olex2 (Dolomanov *et al*., 2009), the structure was solved by the SHELXT (Sheldrick, 2015) structure solution program using Direct Methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The structure was refined with the SHELXL (Sheldrick, 2008) refinement package using least-squares minimization. All hydrogen atoms were placed in idealized positions and refined as riding atoms isotropically. The crystal data, data collection, and structure refinement can be seen in Table 1.

RESULT AND DISCUSSION

Four PBDEs **1**−**4** have been isolated and their structures were identified by analyzing NMR, IR, UV spectral data, and X-ray diffraction study as well as comparison with published data in literatures. The major compound **1**, $C_{12}H_4O_3Br_6$, was obtained as crystals. The molecular formula of **1** was also confirmed by ESIMS $[M + Na]^+$ to have $C_{12}H_4O_3Br_6Na$.

The ^{1}H NMR spectrum taken in $CDCl_3$ exhibited only a pair of *meta*-coupled signals at δ 6.36 (1H, *d*, *J* = 2.2 Hz) and 7.41 (1H, *d*, *J* = 2.2 Hz). The presence of phenolic hydroxyls was inferred by the IR spectrum (3490 cm^{-1}). The presence of a substituted phenol group with auxochromes was also confirmed by UV absorption at λ_{max} (log ε) 293.4 nm (2.98). Comparison of the NMR data with those in literature (Calcul *et al*., 2009; Hanif *et al*., 2007; Norton *et al*., 1981) concluded that compound **1** is a hexabrominated diphenyl ether. Since the ratio of H/C is less than 1, confirmation of the chemical structure of **1** is very suitable for X-ray crystallography. X-ray analysis disclosed the conformation of **1** in addition to the structure as in Figure 1. Compound **1** takes a twist-like conformation with $\phi_1 = 27.7(6)°$; $\phi_2 = 86.5(5)°$ and the angle of ether bond is 117.5°. This conformation may be explained by the presence of an *ortho*-bromo substituent (Klösener *et al*., 2008; Luthe *et al*., 2008) and by the rotation barrier of the *meta*- and the *para*-substitutions as well as a buttressing effect (Luthe *et al*., 2008).

The ^{1}H NMR data of **2** taken in $CDCl_3$/Me_2CO-d_6 (2/1) showed the presence of *meta*-coupled protons at δ 6.53 (1H, d, *J* = 1.5 Hz) and 7.36 (1H, d, *J* = 1.5 Hz) as in **1** with a methoxy group (δ 3H, s, 3.84) in one of the rings. An additional aromatic singlet at δ 7.78 (1H, s) suggested that **2** is a debromo analog of **1**. Comparison with literature values (Norton *et al*., 1981) confirmed that **2** is 3,5-tribromo-6-(3',5'-dibromo-2'-hydroxyphenoxy)anisole. Crystals of compound **2** were formed using the $CHCl_3$−Me_2CO solution at room temperature. The purity of compound **2** was confirmed using TLC analysis to give R_f 0.62 [Hex/EtOAc, 4/1].

Compound **3** was elucidated as 2,3,5-tribromo-6-(3',5'-dibromomethoxyphenoxy)phenol after analyzing NMR spectra taken in $CDCl_3$/Me_2CO-d_6 (1/1) and comparing the data with literature (Hanif *et al*., 2007; Norton *et al*., 1981). Two methoxy groups were observed at δ 3.84 (3H, *s*) and 3.85 (3H, *s*). The remaining signals agreed for two sets of *meta*-coupled protons at δ 6.62 (1H, *d*, *J* = 2.1 Hz) and 7.37 (1H, *d*, *J* = 2.1 Hz). Two

Table 1. Crystal data, data collection, and structure refinement.

Crystal data	
Chemical formula	$C_{12}H_4Br_6O_3 \cdot H_2O$
M_r	693.63
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	123
a, *b*, *c* (Å)	4.74979 (10), 18.7360 (3), 18.3463 (4)
β (°)	91.6135 (19)
V (Å^3)	1632.02 (6)
Z	4
Radiation type	Mo *Kα*
μ (mm^{-1})	14.77
Crystal size (mm)	0.28 × 0.28 × 0.22
Data collection	
Diffractometer	Rigaku AFC10 goniometer with Saturn 724+ detector
Absorption correction	Numerical *CrysAlis PRO* 1.171.39.46 (Rigaku Oxford Diffraction, 2018) Spherical absorption correction using equivalent radius and absorption coefficient. Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.006, 0.024
No. of measured, independent and observed [$I > 2\sigma>I$)] reflections	20,780, 4,898, 4,152
R_{int}	0.037
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.728
Refinement	
$R[F^2 > 2\sigma>F^2)]$, $wR(F^2)$, *S*	0.044, 0.127, 1.09
No. of reflections	4898
No. of parameters	207
No. of restraints	3
H-atom treatment	H-atom parameters constrained
$\Delta\rangle_{max}$, $\Delta\rangle_{min}$ (e Å^{-3})	1.42, −0.77

singlet aromatic signals appeared in 7.83 (1H, *s*) and 7.80 (1H, *s*). The former downfield signal was dealt with the presence of the methoxy group in A ring (Hanif *et al*., 2007; Norton *et al*., 1981). In addition, the TLC analysis of the NMR sample indicated two spots with R_f 0.62 [Hex/EtOAc 4/1, $Ce(SO_4)_2$] and R_f 0.52 [Hex/EtOAc 4/1]. This result clearly indicates that compounds **2** and **3** were in a mixture with ratio 1:1 (1: 0.94 in NMR integration).

Compound **4** was shown to have molecular formula $C_{12}H_5Br_5O_3$ after NMR analysis (Me_2CO-d_6) and comparing the data with literature values (Norton *et al*., 1981). A pair of *meta*-coupled protons at δ 6.83 (1H, *d*, *J* = 2.2 Hz) and 7.39 (1H, *d*, *J* = 2.2 Hz) and an aromatic singlet at δ 7.56 (1H, *s*) were observed. The absence of a methoxy group in **4** suggested that **4** is a demethoxy analog of **2**. The purity of **4** was confirmed by using HPLC and NMR analysis. Compound **4** is 2,3,5-tribromo-6-(3′,5′-dibromophenoxy)phenol. Chemical structures of compounds **2**−**4** are shown in Figure 2.

The results of the antibacterial assays are shown in Table 2. In the standard disk diffusion assay, compounds **1** and **4** showed activity against *S. aureus* ATCC 6538 in the range of 0.08−1.25 µg/disk with zone of inhibition 16 ± 0 – 14 ± 0 mm, while compounds **1** and **4** exhibited activity against *K. pneumoniae* in the range of 6.25−50 µg/disk with inhibition zone as 13 ± 0 – 10 ± 0 mm. Only compound **4** inhibited the

Figure 1. Chemical structure of **1** and crystal structure of **1** with displacement ellipsoids drawn at the 50% probability level.

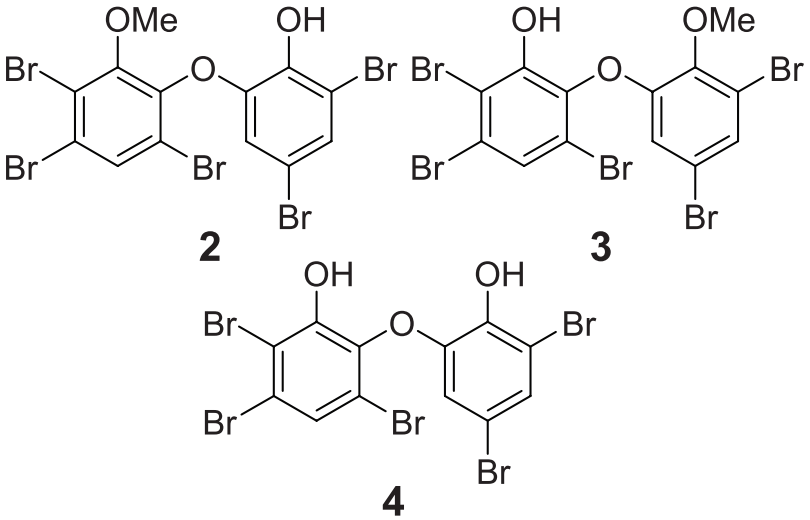

Figure 2. Chemical structure of **2**−**4**.

Table 2. Antibacterial activity against *S. aureus* ATCC 6538 and *K. pneumonia*.

Com.	Concentration (µg/disk)/Zone inhibition ± Standard deviation (mm)										
	S. aureus ATCC 6538					*K. pneumonia*					
	0.08	0.16	0.31	0.63	1.25	1.56	3.13	6.25	12.5	25	50
1	12 ± 0	12.5 ± 0.71	12.5 ± 0.71	13 ± 0	14 ± 0	0 ± 0	0 ± 0	0 ± 0	9 ± 0	10 ± 0	12.5 ± 0.71
2	0 ± 0	0 ± 0	0 ± 0	9 ± 0	9 ± 0	0 ± 0	0 ± 0	9 ± 0	0 ± 0	NT	NT
4	12 ± 0	13 ± 0	14 ± 0	15 ± 0	16 ± 0	0 ± 0	0 ± 0	10 ± 0	10 ± 0	11 ± 0.71	13 ± 0

NT = not tested.

growth of ampicillin-resistant *E. coli* at 12 ± 0 mm at 50 µg/disk. These results point out that the presence of two phenolic hydroxyl groups as well as the less number of bromine atoms is important for the antibacterial activity. The finding also showed the antibacterial drug leads not only active against Gram-positive bacteria, but also especially against Gram-negative ampicillin-resistant *E. coli*. In the toxicity assay against embryos of the zebrafish *D. rerio*, compounds **1**, **2**, and **4** did not kill the embryos at 10 µg/ml.

CONCLUSION

Compounds **1**−**4** belonging to PBDEs were isolated and their structures were identified by using NMR spectroscopy, single-crystal X-ray diffraction, and comparison with the data in literature. Compound **1** has a twist-like conformation with torsion angle ϕ_1 = 27.7 (6)°; ϕ_2 = 86.5 (5)°, while the angle of the ether bond is 117.5°. The isolated PBDEs showed broad-spectrum antibacterial, activity, especially Gram-negative bacteria *K. pneumoniae* and ampicillin-resistant *E. coli*. This is the first report in which compound **4** showed antibacterial activity.

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AUTHORS' CONTRIBUTION

Conceived and designed the experiments: N.H. and J.T. Performed the experiments: N.H., M.S.A., D.T., A.M., and J.T. Analyzed the data: M.S.A., D.T., M.F.D., NJdV, A.M., J.T.. Contributed reagents/materials/analysis tools: N.H. and J.T. Wrote the paper: N.H. and J.T.

CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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