
Natural
Medicines

Volume 67, issue 2, April 2013

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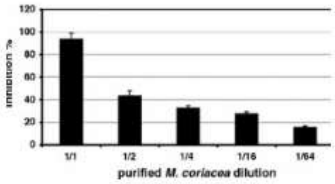
Andrea Medeiros, Nora Berois ... Eduardo Osinaga

Original Paper | Published: 30 May 2012 | Pages: 247 - 254



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Nuttavut Kosem, Kazuhiro Ichikawa ... Primchanien Moongkarndi

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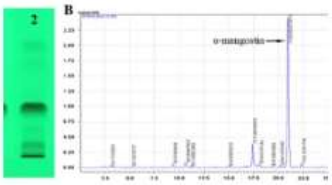

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Azis Saifudin, Shigetoshi Kadota & Yasuhiro Tezuka

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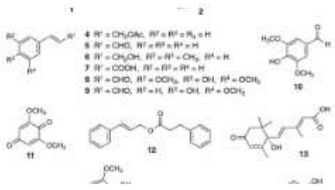

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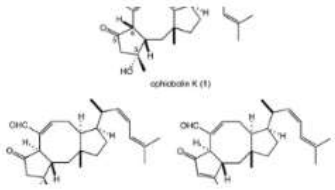

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Eiji Sakai, Tsuyoshi Katayama ... Mizuo Mizuno

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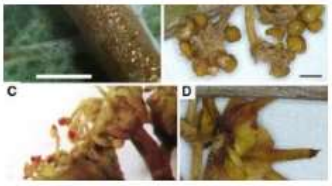

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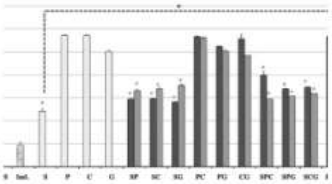

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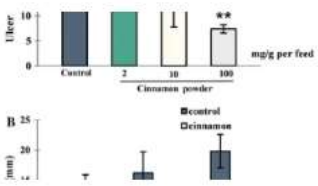

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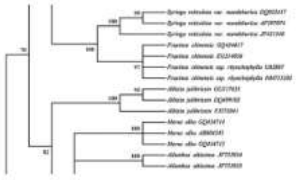

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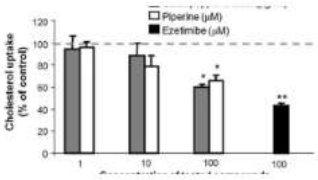

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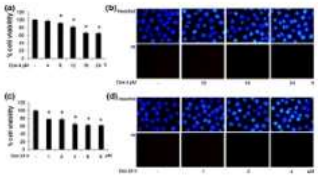

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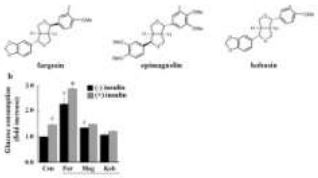

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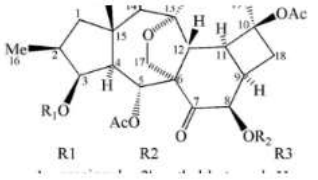

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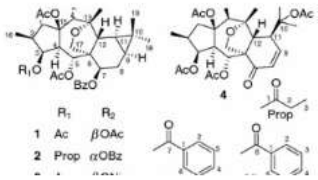

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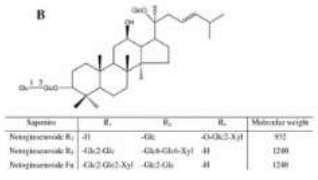

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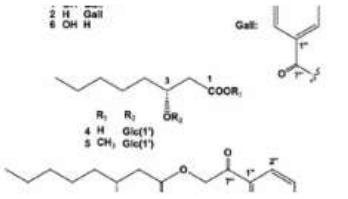

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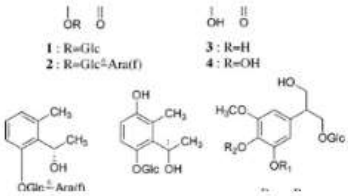

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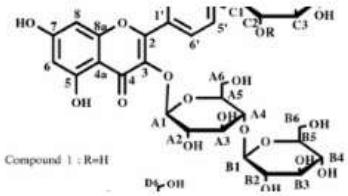

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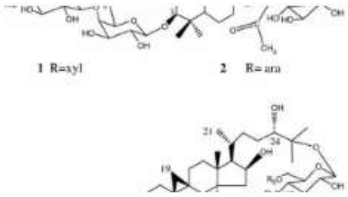

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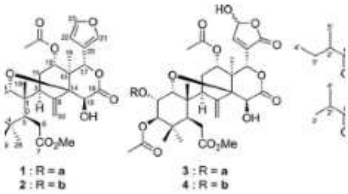

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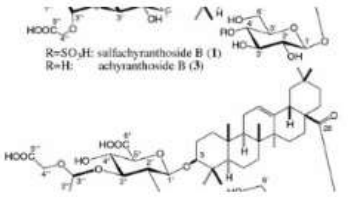

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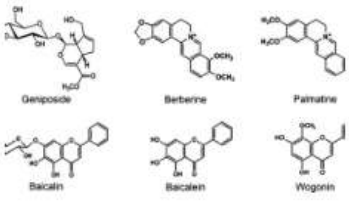

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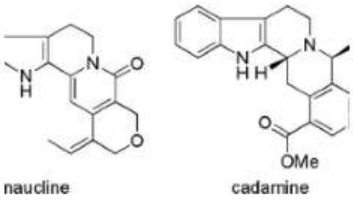

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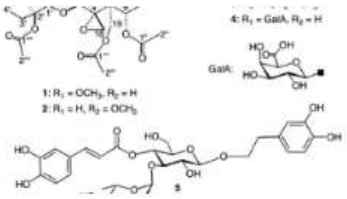

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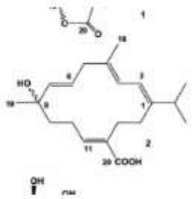

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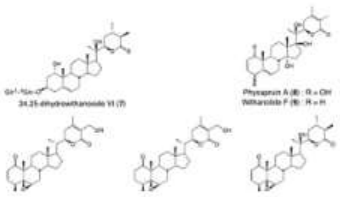

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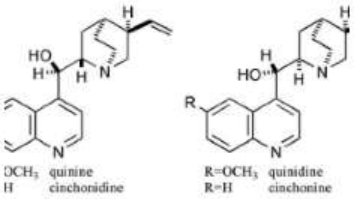

Erratum to: *Withania somnifera* extract attenuates stem cell factor-stimulated pigmentation in human epidermal equivalents through interruption of ERK phosphorylation within melanocytes

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Journal of Natural Medicines

Editors

Source details

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Journal of Natural Medicines

Formerly known as: Natural Medicines

Scopus coverage years: from 2006 to Present

Publisher: Springer Nature

ISSN: 1340-3443 E-ISSN: 1861-0293

Subject area: Medicine: Complementary and Alternative Medicine | Pharmacology, Toxicology and Pharmaceutics: Pharmaceutical Science | Chemistry: Organic Chemistry | Pharmacology, Toxicology and Pharmaceutics: Drug Discovery

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SUBJECT AREA AND CATEGORY

Chemistry
- Organic Chemistry

Medicine
- Complementary and Alternative Medicine
- Medicine (miscellaneous)

Pharmacology, Toxicology and Pharmaceutics
- Drug Discovery
- Pharmaceutical Science

PUBLISHER

Springer Verlag

H-INDEX

41

PUBLICATION TYPE

Journals

ISSN

13403443, 18610293

COVERAGE

2006-2020

INFORMATION

Homepage

How to publish in this journal

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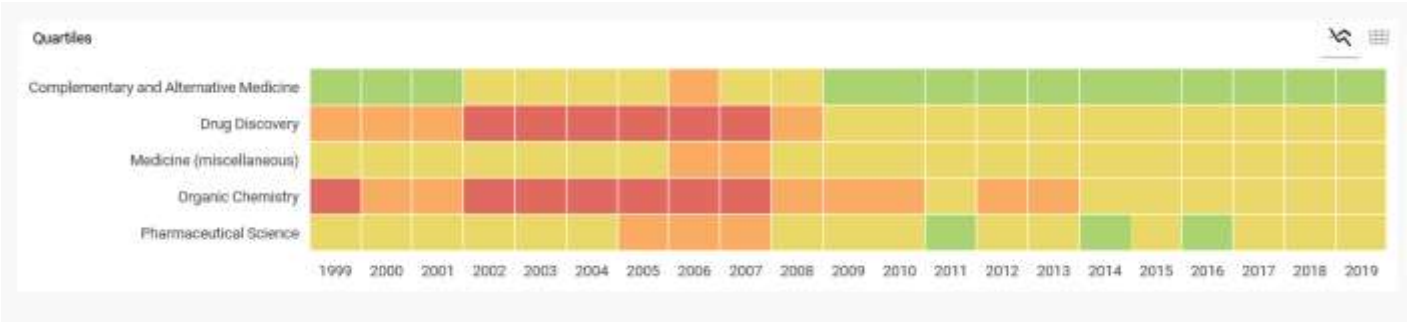
SCOPE

The Journal of Natural Medicines is an international journal publishing original research in naturally occurring medicines and their related foods and cosmetics. It covers: -chemistry of natural products -biochemistry of medicinal plants -pharmacology of natural products and herbs, including Kampo formulas and traditional herbs -botanical anatomy -cultivation of medicinal plants. The journal accepts Original Papers, Notes, Rapid Communications and Natural Resource Letters. Reviews and Mini-Reviews are generally invited.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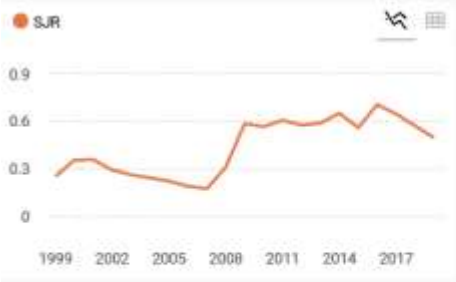
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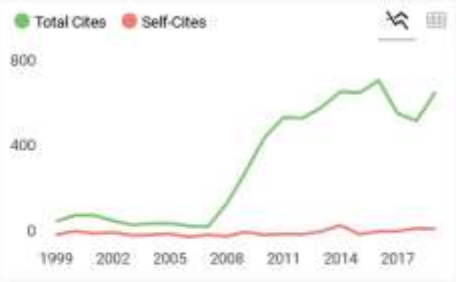
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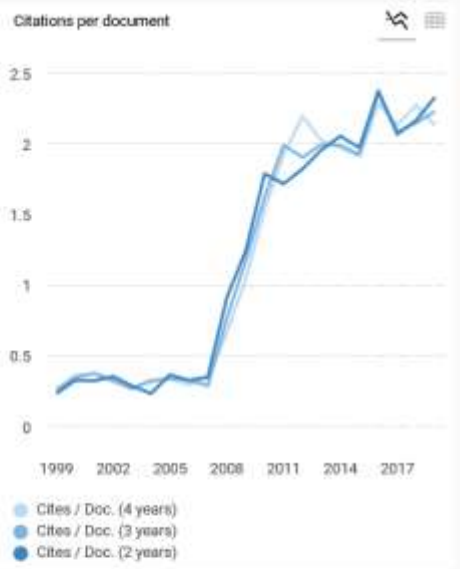
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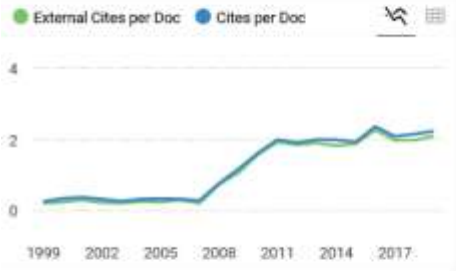
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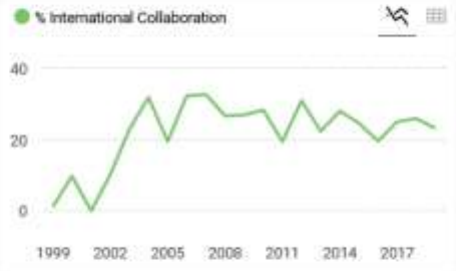
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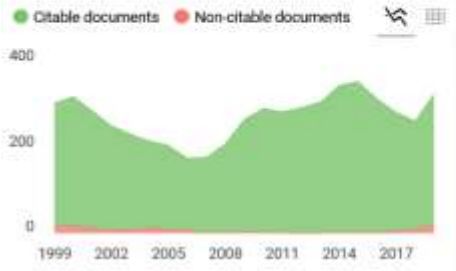
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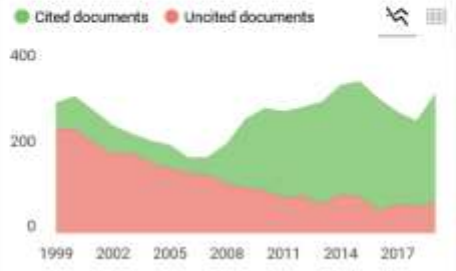
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J Nat Med (2013) 67:381–385
DOI 10.1007/s11418-012-0677-4

NOTE

Sanjecumins A and B: new limonoids from *Sandoricum koetjape*

Yuta Nagakura · Alfarius Eko Nugroho · Yusuke Hirasawa · Takahiro Hosoya · Abdul Rahman · Idha Kusumawati · Noor Cholies Zaini · Hiroshi Morita

Received: 23 April 2012 / Accepted: 23 May 2012 / Published online: 22 June 2012

Abstract Two new limonoids, sanjecumins A (**1**) and B (**2**), have been isolated from the leaves of *Sandoricum koetjape*, together with sandoripins A (**3**) and B (**4**). Their structures and absolute configurations were elucidated on the basis of NMR and CD data. Sandoripins A (**3**) and B (**4**) moderately inhibited nitric oxide production in mouse macrophage-like cell line J774.1 stimulated by lipopolysaccharide.

Keywords *Sandoricum koetjape* · Sanjecumins A and B · iNOS inhibition activity

Introduction

Sandoricum koetjape (Burm.f.) Merr. (Meliaceae) is a medicinal plant distributed in tropical Asia. Investigations on the constituents of this species have revealed several bioactive terpenoids [1–7]. In our continuing search for bioactive compounds from tropical plants [8–21], two new limonoids, sanjecumins A (**1**) and B (**2**), were isolated from the leaves of *S. koetjape*, together with two related compounds, sandoripins A (**3**) and B (**4**) (Fig. 1) [7]. Structure elucidation and nitric oxide (NO) production inhibition activity of the isolated compounds are reported herein.

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Results and discussion

Sanjecumin A {**1**, $[\alpha]_D^{25}$ −90 (*c* 0.14, $CHCl_3$)} was isolated as a colorless solid, with molecular formula $C_{36}H_{48}O_{13}$, as determined by HRESITOFMS [*m*/*z* 711.2994 $(M+Na)^+$, Δ 0.1 mmu]. IR absorptions suggested the presence of carbonyl (1735 cm^{-1}) and hydroxy (3450 cm^{-1}) groups. The ^1H NMR data (Table 1) suggested the presence of a furan ring (δ_H 7.49, 7.38, and 6.48), and the ^{13}C NMR data (Table 1) revealed 36 carbon resonances due to 5 carbonyls, 2 sp^2 quaternary carbons, 4 sp^3 quaternary carbons, 3 sp^2 methines, 9 sp^3 methines, an sp^2 methylene, 3 sp^3 methylenes, and 9 methyls. Further analysis of the ^1H and ^{13}C NMR data suggested the structural similarity of **1** and **3** [7], and **1** and a sandoricin derivative reported by Pancharoen et al. [22], which was further confirmed by 2D NMR analysis.

Analysis of the ^1H–^1H COSY of **1** (Fig. 2) revealed 5 partial structures: **a** (C-2′–C-5′), **b** (C-1–C-3), **c** (C-5 and C-6), **d** (C-9, C-11, and C-12), and **e** (C-22 and C-23). HMBC correlations of H_3-19 to C-1, C-5, C-9, and C-10 revealed the connectivity of partial structures **b**, **c**, **d**, and C-19 through C-10. The connectivity of partial structures **b**, **c**, C-28, and C-29 through C-4 was suggested by the HMBC correlations of H_3-29 to C-3, C-4, C-5, and C-28. The presence of a 2-methylbutanoate group at C-2, acetoxy groups at C-3 and C-12, and a methoxycarbonyl group at C-6 were deduced from the HMBC correlations of H-2 and H_3-5′ to C-1′, H-3 and a methyl (δ_H 2.04) to an ester carbonyl (δ_C 169.8), H-12 and a methyl (δ_H 1.53) to an ester carbonyl (δ_C 169.0), and H_2-6 and a methyl (δ_H 3.62) to an ester carbonyl (δ_C 173.6). The HMBC correlations of H_2-30 to C-8, C-9, and C-14 revealed the presence of an exomethylene group connecting C-9 and C-14. The presence of a furan group at C-17 and a δ-lactone moiety were deduced from the HMBC correlations

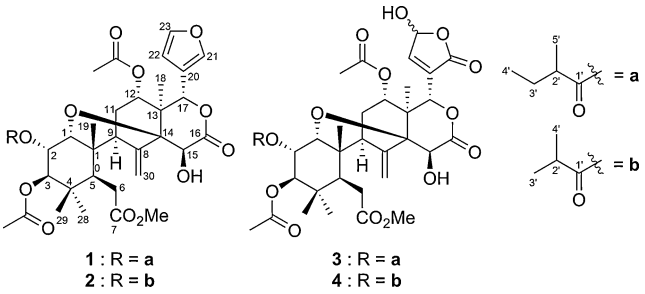

Fig. 1 Structures of sanjecumins A (**1**) and B (**2**) and sandoripins A (**3**) and B (**4**)

of H_3-18 to C-12, C-13, C-14, and C-17, H-17 to C-16, C-20, C-21, and C-22, H-23 to C-21, 15-OH proton to C-14 and C-15, and H-15 to C-16. Finally, the presence of an ether bond connecting C-1 and C-14 was suggested by the HMBC correlation of H-1 to C-14. Thus, **1** was determined as a new methyl angolensate-type of limonoid with a 2-methylbutanoate group at C-2, acetoxy groups at C-3 and C-12, and a hydroxyl group at C-15.

The relative configuration of **1** was determined by analyses of the ^{1}H–^{1}H coupling constant data and NOESY correlations. Coupling constants of $^3J_{\text{H-1/H-2}}$ (4.6 Hz) and $^3J_{\text{H-2/H-3}}$ (11.2 Hz) suggested the orientation of H-1, H-2, and H-3 to be β, β, and α, respectively. The β-orientation of C-19 and C-29 was deduced from the NOESY correlations of H-2/H_3-19 and H_3-29, and the NOESY correlation of H-3/H-5 suggested the α-orientation of H-5. The relative configurations of C-9, C-12, C-13, C-14, and C-17 were deduced to be as shown in Fig. 3 from the NOESY correlation of H-3/H-5 and H-17, H-5/H-12, H_2-6/H-9, and H-12/H-17, and the orientation of H-15 was suggested by the NOESY correlation of H-15/H_3-18. Thus, the relative configuration of **1** was elucidated to be as shown in Fig. 1.

Sanjecumin B {**2**, $[\alpha]_D^{27}$ −96 (*c* 0.10, $CHCl_3$)} was isolated as a colorless solid and had the molecular formula $C_{35}H_{46}O_{13}$, as determined by HRESITOFMS [*m/z* 697.2834 $(M+Na)^+$, Δ −0.2 mmu]. IR absorptions suggested the presence of carbonyl (1735 cm^{-1}) and hydroxy (3450 cm^{-1}) groups. The ^{1}H and ^{13}C NMR data (Table 1) of **2** are highly similar to those of **1**, suggesting the presence of the same core structure in both compounds. Further analysis of the NMR data suggested the existence of 2-methylpropanoyl group (2 doublet methyl at δ_H 1.11 and 1.12, and a septet methyne at δ_H 2.51) in **2** instead of 2-methylbutanoyl in **1**. Analysis of the 2D-NMR data (HSQC, ^{1}H–^{1}H COSY and HMBC, Fig. 2) confirmed the structure of **2** to be a new methyl angolensate-type of limonoid with a 2-methylpropanoate group at C-2, acetoxy groups at C-3 and C-12, and a hydroxy group at C-15. The ^{1}H–^{1}H coupling constant data (Table 1) and NOESY correlations of **2** (Fig. 3) are almost identical to **1**. Thus, the relative configuration of **2** was assigned to be the same as **1**.

To determine the absolute configuration of sanjecumins A (**1**) and B (**2**), CD calculations were performed for the stable conformations of **2**. As can be seen in Fig. 4, the calculated CD spectrum of (1*R*, 2*R*, 3*R*, 5*S*, 10*S*, 9*R*, 12*S*, 13*S*, 14*S*, 15*S*, 17*R*)-**2** agrees well with the experimental CD spectrum of **2**, suggesting the absolute configuration of **2** to be 1*R*, 2*R*, 3*R*, 5*S*, 10*S*, 9*R*, 12*S*, 13*S*, 14*S*, 15*S*, and 17*R*. Furthermore, the experimental CD spectrum of **1** is similar to **2**, suggesting the absolute configuration of **1** to be the same as **2**.

Compounds **1**–**4** were tested for the inhibition of NO production in LPS-stimulated J774.1 cell line. Sandoripins A (**3**) and B (**4**) were found to inhibit NO production with IC_{50} values of 16.4 and 30.4 μM, respectively.

Experimental section

General experimental procedures

Optical rotations were measured on a JASCO DIP-1000 polarimeter. UV spectra were recorded on a Shimadzu UVmini-1240 spectrophotometer and IR spectra on a JASCO FT/IR-4100 spectrophotometer. CD spectra were recorded on a JASCO J-820 polarimeter. High-resolution ESI MS were obtained on a LTQ Orbitrap XL (Thermo Scientific). ^{1}H and 2D NMR spectra were measured on a 700-MHz spectrometer at 300 K, while ^{13}C NMR spectra were measured on a 175-MHz spectrometer. The residual $CHCl_3$ chemical shift in $CDCl_3$ used as an internal standard was δ_H 7.26 and δ_C 77.1. Standard pulse sequences were used for the 2D NMR experiments.

Materials

The leaves of *S. koetjape* were collected at Pasuruan, East Java, Indonesia, in 2008. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.

Extraction and isolation

The leaves of *S. koetjape* (1.45 kg) were extracted with methanol to obtain 170 g of extract. A part of the methanol extract (14 g) was successively partitioned with *n*-hexane, chloroform, ethyl acetate, *n*-butanol, and water, and the hexane-soluble materials were further separated with a Diaon HP-20 column (H_2O/MeOH, 1:4 → 0:1, acetone). The 100 % methanol fraction was subjected to a silica gel column (*n*-hexane/EtOAc, 1:0 → 1:1, $CHCl_3$/MeOH 1:0 → 0:1) and the fraction eluted by *n*-hexane/EtOAc (6:4) was further separated by ODS HPLC (Cadenza 5CD-

Table 1 ^{1}H and ^{13}C NMR data of sanjecumins A (**1**) and B (**2**) in $CDCl_3$ at 300 K

	1		**2**	
	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C
1	4.11 (1H, d, 4.2)	78.7	4.03 (1H, d, 4.2)	78.5
2	5.12 (1H, dd, 11.6, 4.2)	67.6	5.07 (1H, dd, 11.6, 4.2)	67.9
3	5.30 (1H, d, 11.6)	73.0	5.30 (1H, d, 11.6)	72.9
4		40.2		40.1
5	2.68 (1H, br.d, 10.8)	41.9	2.69 (1H, br.d, 10.0)	41.9
6a	2.49 (1H, dd, 15.2, 10.8)	33.4	2.49 (1H, m)	33.4
6b	2.04 (1H, d, 15.2)		2.05 (1H, m)	
7		173.6		173.6
8		140.3		140.2
9	2.25 (1H, br.d, 3.6)	50.4	2.25 (1H, dd, 1.6, 5.4)	50.3
10		44.4		44.3
11a	2.39 (1H, m)	30.1	2.39 (1H, ddd, 14.2, 5.6, 1.6)	30.0
11b	1.44 (1H, m)		1.45 (1H, ddd, 14.2, 12.0, 5.4)	
12	5.46 (1H, dd, 11.9, 5.7)	69.2	5.48 (1H, dd, 12.0, 5.6)	69.2
13		47.3		47.2
14		83.2		83.2
15	4.62 (1H, br.s)	68.7	4.62 (1H, d, 1.7)	68.6
15-OH	2.90 (1H, br.s)		2.88 (1H, d, 1.7)	16
		174.0		174.1
17	5.86 (1H, s)	79.3	5.85 (1H, s)	79.3
18	1.29 (3H, s)	10.0	1.29 (3H, s)	10.0
19	0.97 (3H, s)	21.4	0.97 (3H, s)	21.3
20		120.5		120.5
21	7.49 (1H, br.s)	142.5	7.50 (1H, br.s)	142.5
22	6.48 (1H, d, 1.2)	110.2	6.48 (1H, d, 1.2)	110.2
23	7.38 (1H, d, 1.2)	142.0	7.39 (1H, t, 1.2)	143.0
28	0.92 (3H, s)	27.3	0.93 (3H, s)	27.3
29	1.06 (3H, s)	16.7	1.06 (3H, s)	16.4
30a	5.39 (1H, s)	115.4	5.39 (1H, s)	115.4
30b	5.23 (1H, s)		5.24 (1H, s)	
OMe	3.62 (3H, s)	51.8	3.63 (3H, s)	51.8
3-*O*-COMe		169.8		169.8
3-*O*-COMe	2.04 (3H, s)	20.9	2.04 (3H, s)	20.9
12-*O*-COMe		169.0		169.0
12-*O*-COMe	1.53 (3H, s)	20.1	1.53 (3H, s)	20.1
1′		176.1		176.6
2′	2.33 (1H, sextet, 7.4)	40.6	2.51 (1H, septet, 7.0)	33.4
3′a	1.65 (1H, m)	26.0	1.11 (3H, d, 7.0)	19.2
3′b	1.40 (1H, m)			
4′	0.93 (3H, t, 7.4)	11.7	1.12 (3H, d, 7.0)	18.4
5′	1.08 (3H, d, 7.4)	16.4		

C18; 250 × 10 mm, gradient elution 70–100 % MeOH aq./30 min, flow rate 2.0 mL/min, UV detection at 210 nm) to yield **4** (7.2 mg, 0.006 %, t_R 13 min, purity >99 %), **3** (39.7 mg, 0.03 %, t_R 15 min, purity >99 %), and a mixture of **1** and **2** (t_R 18 min). The mixture of **1** and **2** was further separated by a silica gel column (*n*-hexane/EtOAc, 1:0 → 0:1) to give pure **1** (3.6 mg, 0.003 %) and **2** (2.4 mg, 0.002 %).

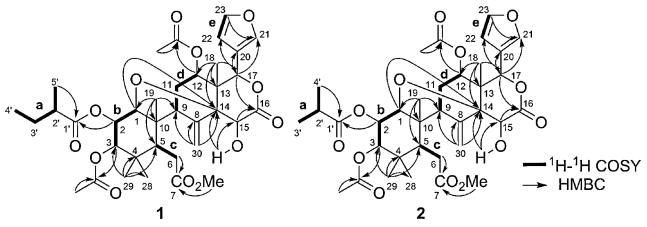

Fig. 2 Selected 2D NMR correlations for sanjecumins A (**1**) and B (**2**)

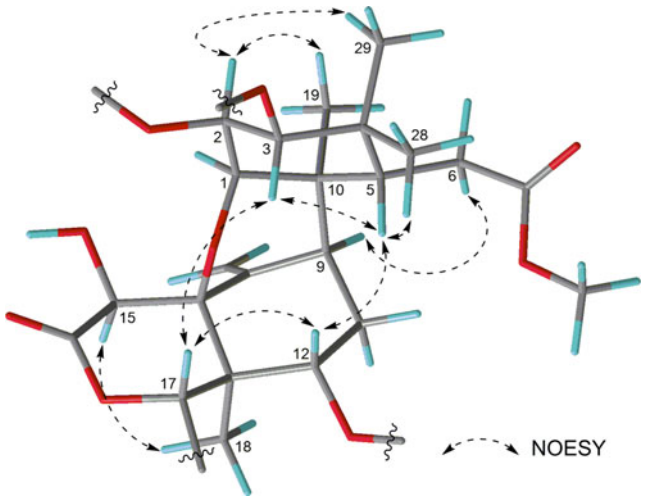

Fig. 3 Selected NOESY correlations for sanjecumins A (**1**) and B (**2**)

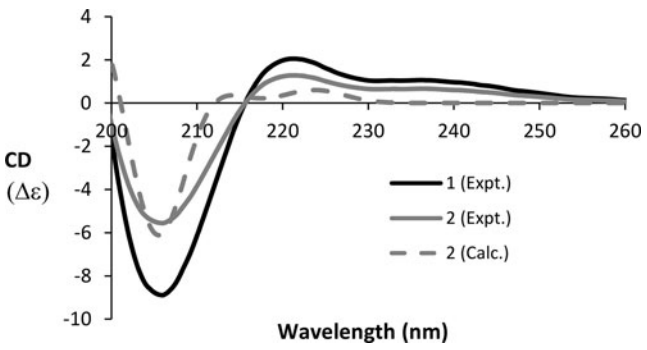

Fig. 4 Experimental CD spectra of **1** and **2**, and calculated CD spectrum of (1*R*, 2*R*, 3*R*, 5*S*, 10*S*, 9*R*, 12*S*, 13*S*, 14*S*, 15*S*, 17*R*)-**2**

*Sanjecumin A (**1**)*

Colorless solid; $[\alpha]_D^{25}$ −90 (*c* 0.14, $CHCl_3$); UV (MeOH) λ_{max} 203 (ε 10600) nm; CD (MeOH) λ_{max} 205 (θ −30000), 221 (+6800), and 239 (3300) nm; IR (KBr) ν_{max} 3450, 2980, 1735, and 1235 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); ESIMS *m/z* 711 $(M+Na)^+$; HRESITOFMS *m/z* 711.2994 ($[M+Na]^+$; calcd. for $C_{36}H_{48}O_{13}Na$, 711.2993).

*Sanjecumin B (**2**)*

Colorless solid; $[\alpha]_D^{27}$ −96 (*c* 0.10, $CHCl_3$); UV (MeOH) λ_{max} 202 (ε 4170) nm; CD (MeOH) λ_{max} 205 (θ −18700), 221 (+4100), and 239 (1900) nm; IR (KBr) ν_{max} 3450, 1735, and 1235 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); ESIMS *m/z* 697 $(M+Na)^+$; HRESITOFMS *m/z* 697.2834 ($[M+Na]^+$; calcd. for $C_{35}H_{46}O_{13}Na$, 697.2836).

Computational details

The CD calculations were performed by Turbomole 6.3 [23] using TD-DFT-B3LYP/SVP level of theory on RI-DFT-B3LYP/SVP optimized geometries [24–27]. The conformer used for the CD calculations was the model obtained by using MC calculations (MMFF94 force field [28–31], MacroModel 9.1 [32]). The CD spectra were simulated by overlapping Gaussian functions for each transition, where the width of the band at 1/*e* height is fixed at 0.1 eV, and the resulting spectra were scaled to the experimental values.

NO production by J774.1 cells

J774.1 cells were cultured in RPMI-1640 medium supplemented with 10 % fetal bovine serum and penicillin/streptomycin. J774.1 cells were seeded into a 96-well microtiter plate at 1×10^5 cells in 100 μL per well and pre-incubated for 12 h at 37 °C in a humidified atmosphere containing 5 % CO_2. The cells were cultured in the medium containing LPS (5 μg/mL) with or without the test sample at different concentrations for 24 h. NO production was then determined by the Griess assay. Supernatant of the cultured medium (100 μL) was transferred to a 96-well microtiter plate, and then 100 μL of Griess reagent (1 % sulfanilamide, 0.1 % *N*-1-naphthylethylenediamine dihydrochloride in 2.5 % H_3PO_4 was added). After incubation at room temperature for 15 min, the absorbance at 540 and 620 nm was measured with a microplate reader (Benchmark Plus microplate spectrometer, Bio-Rad). L-NMMA, an NO synthase inhibitor, was used as a positive control (IC_{50} 13.8 μg/mL).

Cell viability assay

The cell viability was determined by the MTT assay. MTT (15 μL of a 5 mg/mL solution) was added into each well of the cultured medium. After a 2-h incubation period, the medium was removed, and then 50 μL of DMSO was added to resolve the formazan crystals. Optical density measurements were made using a microplate reader equipped with a two-wavelength system at 550 and

700 nm. In each experiment, three replicates were prepared for each sample. The ratio of living cells was determined on the basis of the difference of the absorbance between those of samples and controls.

Acknowledgments This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and a grant from the Open Research Center Project of Hoshi University.

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