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Four Dammarane Triterpenes and Their Inhibitory Properties Against Eight Receptor Tyrosine Kinases

Leny Heliawati[1], Husnul Khatimah[2], Elvira Hermawati[2], and Yana Maolana Syah[2,*]

[1]*Department of Chemistry, Pakuan University, Jalan Pakuan PO Box 452, Bogor 16143, Indonesia*
[2]*Organic Chemistry Division, Institut Teknologi Bandung, Jalan Ganesha 10, Bandung 40132, Indonesia*

Abstract – In recent years, tyrosine kinases (TKs) have been the target to combat cancers, and most of the developed inhibitors are of synthetic origin. Natural compounds that have the properties as the TK's inhibitors are very limited. This paper described the isolation of a new dammarane triterpene from the tree bark of *Sandoricum koetjape*, along with three known related dammaranes from the damar resin of *Shorea javanica*, as well as their inhibitory properties against eight receptor TKs (RTKs: EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFRα, and PDGFRβ). Based on the NMR and mass spectral data the new compound was identified as (12β,20*S*)-12,20-dihydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (12β-hydroxydammarenolic acid) (**1**), while the three known compounds were identified as (20*S*)-20-hydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (dammarenolic acid) (**2**), (3β,20*S*)-3,20-dihydroxydammaran-24-ene (**3**), and (20*S*)-3-oxo-20-hydroxydammaran-24-ene (**4**). The tyrosine kinase assay of the four compounds resulted only **1** and **2** at concentration of 10 μM that had weak activity against EGFR and InsR, with their % inhibitory were 30%, 27% (**1**), 45%, and 32% (**2**), respectively. The results suggested that the presence of a linear carboxylic acid group in both compounds could be of significance to the inhibitory properties against the two RTKs.
Keywords – *Sandoricum koetjape*, *Shorea javanica*, 12β-Hydroxydammarenolic acid, *seco*-Dammarane triterpene, Receptor tyrosine kinase

Introduction

In recent years, the receptor tyrosine kinases (RTKs) have been the target in the development of cancer drugs. These enzymes activate other proteins through phosphorylation of tyrosine residues by ATP, and are involved in regulating cellular processes, including the development of tumor cells.[1] There are 58 RTKs in the human genome,[2] including the family of epidermal growth factor receptor (e.g. EGFR, HER2, HER4), insulin receptor (e.g. IGF1R, InsR), kinase insert domain receptor (e.g. KDR), and platelet-derived growth factor (e.g. PDGFRα and -β). Malfunction of these enzymes has been shown to have consequences to the formation of various diseases, such as cancers and degenerative diseases.[3] An effort to find the inhibitors of RTKs has succeeded in developing new anticancer drugs, such as erlotinib (EGFR), ponatinib (PDFGFR), and ceritinib (IGF1R and InsR).[4] These inhibitors are of synthetic origin, while natural compounds that have been tested for the RTK's inhibitor were very limited.[5]

Tetracyclic triterpenes are natural compounds that are widely distributed in the plant kingdom. The tetracyclic triterpenes include protostane, lanostane, cycloartane, curcubitane, dammarane, euphane, tirucallane, and apotirucallane classes.[6,7] The dammarane, in particular, is one of the interesting class of the tetracyclic triterpenes. They are not only the precursor of the plant's limonoid group,[8] but also they have various biological activities, including as anti-tumors.[9] *Sandoricum koetjape* Merr. (Meliaceae) is one of the famous tree in the southeast Asia countries. The rinds of the fruit are edible and have a uniques taste, while the aqueous extract of the bark has been used in Malaysia as a tonic for the women after childbirth. The same decoction has also been consumed in Indonesia and Malaysia for the treatment of colic and leukorrhea.[10] Phytochemically, the plant is known to produce sesquiterpenes, pentacyclic triterpenes, and limonoids.[11] However, the dammarane triterpene has not been reported from this plant. On the other hand, the plant resin of *Shorea javanica* (Dipterocarpaceae) locally known as 'Damar Mata

*Author for correspondence
Yana Maolana Syah, Organic Chemistry Division, Institut Teknologi Bandung, Jalan Ganesha 10, Bandung 40132, Indonesia.
Tel: +62-22-2502103; E-mail: yana@chem.itb.ac.id

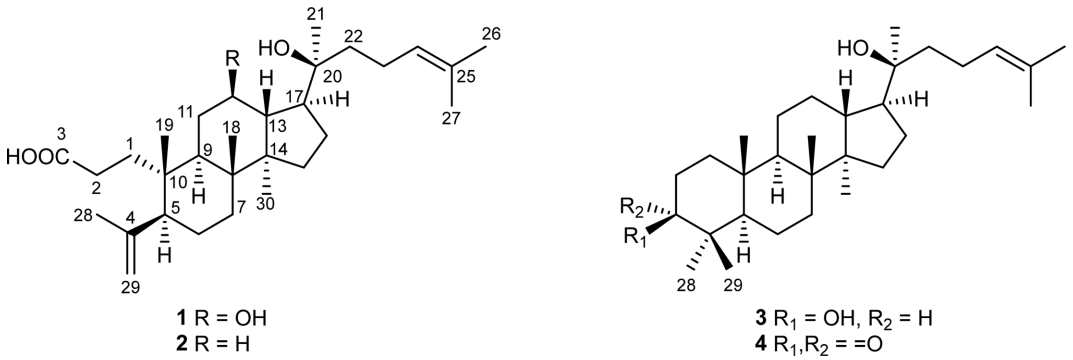

Fig. 1. Structures of tetracyclic triterpenes **1** - **4**.

Kucing', has been known to contain a number of dammarane triterpenes. Although there is no report on its medicinal uses, the isolated dammaranes from this resin have been tested for cytotoxic effects against human leukemia (HL60) and human melanoma (RL1579).[12]

In search of RTK's inhibitors from natural sources,[13] we have succeeded in isolating four dammarane derivatives **1** - **4** (Fig. 1) from the woods of *S. koetjape* and the resin of *S. javanica*, in which one of them, namely **1**, is a new compound. In this paper, we will describe the structure elucidation of **1**, and the assay results of these four compounds against eight RTKs (EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFRα, and PDGFRβ).

Experimental

General experimental procedures – Optical rotation were determined with an Autopol IV Rudolph Research Analytical. ^{1}H and ^{13}C NMR spectra were measured with a spectrometer of Agilent DD2 system operating at 500 and 125 MHz, respectively. High-resolution mass spectra were obtained with an ESI-TOF Waters LCT Premier XE mass spectrometer. Vacuum liquid chromatograhy (VLC) and centrifugal planar chromatography (CPC) were caaried on Merck silika gel 60 GF254 art. 7731 and 7749, respectively. Thin layer chromatography (TLC) analysis was done using precoated silica gel plates (Merck Kielselgel 60 GF254, 0.25 mm thickness). Spots on TLC were detected by UV irradiation and sprayed by $CeSO_4$ solution, which was followed by heating. Solvents (MeOH, acetone, EtOAc and *n*-hexane) for extraction, fractionation and purification were of technical grades, which were distilled before used. $CHCl_3$ used in the purification was a pro analysis grade.

Kinase Selectivity Profiling System (KSPS) Receptor Tyrosine Kinases TK1 (EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFR α and PDGFR β) was purchased from Promega and stored at -80 °C as one-time use aliquots. Kinase enzyme reaction setup, including compound dilution and preparation of kinase working stock, ATP/substrate working stock, addition of ADP-Glo and kinase detection reagent, were carried out using a Pipetmax-268 automatic liquid handler from Gilson. Automated KSPS protocols for Pipetmax were imported into Trilution micro 2.0 software (Gilson). Luminescent in the enzyme assay was measured with a GloMax Explorer, while data processing was done using SMART protocol present in the GloMax Explorer software.

Plant materials – The woods of *S. koetjape* were collected from Pandeglang, Banten Province, Indonesia, in August 2013. The plant identity was determined by the staf of Herbarium Bandungense, Institut Teknologi Bandung, and the voucher speciemen was deposited at the Herbarium (voucher number 11254). The damar resin of *S, javanica* was purchased in 2018 from on line shop, GBN-Lampung, Tokopedia, Indonesia.

Extraction and isolation – The dried powders of woods of *S. koetjape* (1.5 kg) were macerated with MeOH at room temperature (2 × 10 L, overnight) to obtain 60 g MeOH extract after solvent evaporation. Half of the extract (30 g) was fractionated into 16 fractions by VLC (silica gel 150 g, gradient eluents: *n*-hexane-EtOAc = 85:15 to 3:7 and then EtOAc). A solid (390 mg) appeared from the polar fraction P (1.8 g), which on TLC analysis showed the presence of a minor spot. The solid then purified by VLC (silica gel 10 g, eluent *n*-hexane-EtOAc = 4:1) to afford compound **1** (60 mg).

The dried powdered (5 g) of damar resins (*S. javanica*) were extracted with MeOH to afford a white MeOH extract (3.5 g). The MeOH extract was fractionated using VLC (silica gel 90 g, gradient eluents: *n*-hexane-EtOAc = 19:1 to 1:1 and then EtOAc) to give 17 fractions 1-16. The fraction 10 (140 mg) was found to be a white solid and was crystallized in MeOH to give **4** (60 mg). Fraction

Table 1. ^{1}H NMR data of compounds **1** - **4** in $CDCl_3$

C No.	**1**	**2**	**3**	**4**
1	1.70 (*m*) 1.62 (*m*)	1.62 (2H, *m*)	1.68 (*m*) 0.96 (*m*)	1.90 (*m*) 1.42 (*m*)
2	2.27 (2H, *m*)	2.18 (*m*) 2.19 (*m*)	1.58 (2H, *m*)	2.46 (*m*) 2.41 (*m*)
3	-	-	3.19 (*dd*, 11.3, 4.7)	-
4	-	-	-	-
5	2.00 (*dd*, 12.8, 2.7)	1.97 (*dd*, 12.7,2.8)	0.72 (*br d*, 11.7)	1.35 (*m*)
6	1.81 (*m*) 1.38 (*m*)	1.83 (*m*) 1.36 (*m*)	1.51 (*m*) 1.43 (*m*)	1.53 (*m*) 1.43 (*m*)
7	1.52 (*m*) 1.24 (*m*)	1.53 (*m*) 1.22 (*m*)	1.52 (*m*) 1.26 (*m*)	1.53 (*m*) 1.28 (*m*)
8	-	-	-	-
9	1.59 (*br d*, 13.0)	1.51 (*m*)	1.30 (*m*)	1.39 (*m*)
10	-	-	-	-
11	1.76 (*m*) 1.26 (*m*)	1.42 (*m*) 1.28 (*m*)	1.48 (*m*) 1.22 (*m*)	1.46 (*m*) 1.28 (*m*)
12	3.59 (*td*, 10.7, 4.8)	1.83 (*m*) 1.28 (*m*)	1.84 (*m*) 1.24 (*m*)	1.89 (*m*) 1.25 (*m*)
13	1.75 (*t*, 10.7)	1.65 (*m*)	1.60 (*m*)	1.71 (*m*)
14	-	-	-	-
15	1,48 (*m*) 1.05 (*m*)	1.45 (*m*) 1.08 (*m*)	1.45 (*m*) 1.06 (*m*)	1.44 (*m*) 1.05 (*m*)
16	1.85 (*m*) 1.27 (*m*)	1.76 (*m*) 1.50 (*m*)	1.72 (*m*) 1.47 (*m*)	1.72 (*m*) 1.30 (*m*)
17	2.05 (*m*)	1.75 (*m*)	1.72 (2H, *m*)	1.71 (*m*)
18	1.02 (*s*)	1.01 (*s*)	0.95 (*s*)	0.97 (*s*)
19	0.86 (*s*)	0.85 (*s*)	0.84 (*s*)	0.91 (*s*)
20	-	-	-	-
21	1.67 (*s*)	1.15 (*s*)	1.13 (*s*)	1.10 (*s*)
22	1.60 (*m*) 1.36 (*m*)	1.48 (2H, *m*)	1.46 (2H, *m*)	1.44 (2H, *m*)
23	2.15 (*m*) 2.01 (*m*)	2.04 (2H, *m*)	2.04 (2H, *m*)	2.02 (2H, *m*)
24	5.14 (*br t*, 7.2)	5.12 (*br t*, 7.0)	5.11 (*t*, 6.8)	5.08 (*t*, 7.1)
25	-	-	-	-
26	1.69 (*s*)	1.69 (*s*)	1.68 (*s*)	1.65 (*s*)
27	1.62 (*s*)	1.63 (*s*)	1.62 (*s*)	1.59 (*s*)
28	1.73 (*s*)	1.73 (*s*)	0.76 (*s*)	1.05 (*s*)
29	4.85 (*br s*) 4.65 (*br s*)	4.87 (*br s*) 4.67 (*br s*)	0.96 (*s*)	1.00 (*s*)
30	0.91 (*s*)	0.89 (*s*)	0.87 (*s*)	0.86 (*s*)

11 (200 mg) was purified using CPC (silica gel, eluent: *n*-hexane-EtOAc = 9:1) afforded **3** (30 mg), while from fraction 14 using the same method (CPC, silica gel, eluent: *n*-hexane-acetone = 9:1 - 4:1) gave **1** (30 mg).

(12β,20*S*)-12,20-dihydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (12β-hydroxydammarenolic acid) (1) – White powders. $[\alpha]^{20}_D = +46.0^o$ (c 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$) see Table 2; HRESITOF-MS: $[M-H]^-$ ion *m/z* 473.3630 (calcd. $[M-H]^-$ ion for $C_{30}H_{50}O_4$: *m/z* 473.3636, Δ 1.3 ppm).

(20*S*)-20-Hydroxy-3,4-seco-dammaran-4,24-dien-3-oic acid (dammarenolic acid) (2) – White powders. $[\alpha]^{20}_D = +43.5^o$ (c 0.285, $CHCl_3$) ($[\alpha]^{20}_D = +43^o$)[14]; ^{1}H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$) see Table 2; HRESITOF-MS: $[M-H]^-$ ion *m/z* 457.3683 (calcd. $[M-H]^-$ ion for $C_{30}H_{50}O_3$: *m/z* 457.3687, Δ 0.9 ppm).

Table 2. ^{13}C NMR data of compounds **1** - **4** in $CDCl_3$

C No.	1	2	3	4
1	34.5	34.3	39.0	39.9
2	28.9	28.4	27.5	34.1
3	178.3	179.8	78.9	218.2
4	147.3	147.5	39.1	47.4
5	50.4	50.8	55.9	55.3
6	24.6	24.6	18.3	19.6
7	33.6	33.8	35.3	34.6
8	39.5	40.0	40.5	40.3
9	40.4	41.0	50.6	50.0
10	39.4	39.0	37.3	36.8
11	31.8	22.1	21.6	22.0
12	70.5	27.4	27.4	27.5
13	47.4	42.3	42.5	42.3
14	52.1	50.6	50.5	50.0
15	31.1	31.2	31.2	31.0
16	26.4	24.8	24.8	25.3
17	53.4	49.7	49.9	49.5
18	15.6	15.3	15.5	15.2
19	20.1	20.2	16.2	16.0
20	74.3	75.6	75.4	75.7
21	26.3	25.3	25.4	23.6
22	34.7	40.6	40.5	41.8
23	22.3	22.5	22.6	22.3
24	125.1	124.6	124.7	124.8
25	131.4	131.6	131.6	131.6
26	25.8	25.7	25.7	25.7
27	17.7	17.7	17.7	17.7
28	23.3	23.2	28.0	26.7
29	113.6	113.4	15.4	21.0
30	16.8	16.4	16.5	16.3

(3β,20*S*)-3,20-Dihydroxydammaran-24-ene (3) – White powders. $[\alpha]^{20}_D = +30.2^o$ (c 0.285, $CHCl_3$) (lit. $[\alpha]^{20}_D = +30.2^o$)[14]; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$) see Table 2; HRESITOF-MS: failed to find $[M+H]^+$ or $[M+Na]^+$ ion.

(20*S*)-3-oxo-20-hydroxydammaran-24-ene (4) – White powders. $[\alpha]^{20}_D = +65.4^o$ (c 0.26, $CHCl_3$) ($[\alpha]^{20}_D = +66^o$)[14]; ^1H NMR ($CDCl_3$) see Table 1; ^{13}C NMR ($CDCl_3$) see Table 2; HRESITOF-MS: $[M+H]^+$ ion *m/z* 443.3885 (calcd. $[M+H]^+$ ion for $C_{30}H_{50}O_2$: *m/z* 443.3884, Δ 0.2 ppm).

Kinase enzyme assay – The assay was done according to previously described,[13] Briefly, the tested compound was made 5% in DMSO and was diluted to a final concentration 10 μM by 4X kinase buffer (64.5 μL) and nuclease-free water (175 μL). Each kinase stock was also diluted with 2.5X reaction buffer (95 μL), while the substrate/cofactor stock was diluted with 80 μM ATP solution (20 μL). The assay was done as follows: the kinase (2 μL), the ATP/substrate (1 μL), and tested compound (1 μL) were dispensed to each well of the 384-well plate, and then was allowed to react for 1 hour (22 - 25 °C). After this, the ADP-Glo reagent was added (5 μL), and the was incubated for 40 minutes (22 - 25 °C), which was followed by the addiition of kinase detection reagent (10 μL) to be incubated again for 30 minutes. After the reaction was completed, the luminescent was measured, which corresponds to the kinase activity. The negative control (100% activity) was the well without the tested compound solution, while the background luminescent (0% activity) was obtained from the well without enzyme solution. The % kinase activity was calculated by subtracting the background luminescent from all kinase reactions (Table 3). This assay used erlotinib as the control positive (1 μM), while the purity of **1** - **4** (>95%) were determined by NMR.

Result and Discussion

Compound **1** was isolated from the woods of *S. koetjape* as white powders. The molecular formula $C_{30}H_{50}O_4$ was deduced to **1** based on its high-resolution mass spectrum (time of flight technique, negative mode, found $[M-H]^-$ ion at *m/z* 473.3630), suggesting that this compound is a triterpene. The NMR data (^1H, ^{13}C, APT-HSQC, and HMBC spectra) (Table 1, Table 2, and Fig. 1) showed the presence of a propen-2-yl (δ_H 1.73; δ_C 23.3 and δ_H 4.85, 4.65; δ_C 147.3, 113.6) and a carboxylic (δ_C 178.3) groups, which is a typical for a 3,4-*seco*-triterpene derivative. Further analysis of the NMR data revealed the presence of six additional methyl groups (δ_C 26.3, 25.8, 20.1, 17.7, 16.8, 15.6), three quarternary carbons (δ_C 52.1, 39.5, 39.4) atoms, and a tertiary alcohol (δ_C 74.3) group, indicating that **1** has a basic structure of a dammarane triterpene with a double bond (δ_H 5.14; δ_C 131.4, 125.1) at C-24. The remaining functional group present is a secondary alcohol (δ_H 3.59; δ_C 70.5), which is attached to C-12 from the HMBC correlations (Fig. 2). Other HMBC correlations, as shown in Fig. 2A, confirmed the basic structure for 12-hydroxy-3,4-*seco*-dammar-4,24-dien-3-oic acid. The axial orientation of H-3, H-9, H-13, and H-17, as deduced from their coupling constants (Table 1), corroborated the dammarane skeleton. Using the same method, the H-12 was also determined to be in an axial orientation (*td*, $J = 10.7$, 4.8 Hz). This stereochemical determination was further confirmed by the NOE correlations as found in the ROESY spectrum, as shown

Table 3. Tyrosine kinase activity of compounds **1** - **4** at concentration 10 μM

Compounds	% Activity[b]							
	EGFR	HER2	HER4	IGF1R	InsR	KDR	PDGFRa	PDGFRb
1	70	120	101	104	73	106	108	85
2	55	160	83	90	68	94	101	114
3	82	159	94	97	140	112	96	106
4	93	125	102	87	139	105	108	114
Erlotinib[a]	0	41	38	97	42	6	26	16

[a] positive control at concentration of 1 μM.
[b] strong: <20%, moderate: 20-60%, weak or not active: >60%.

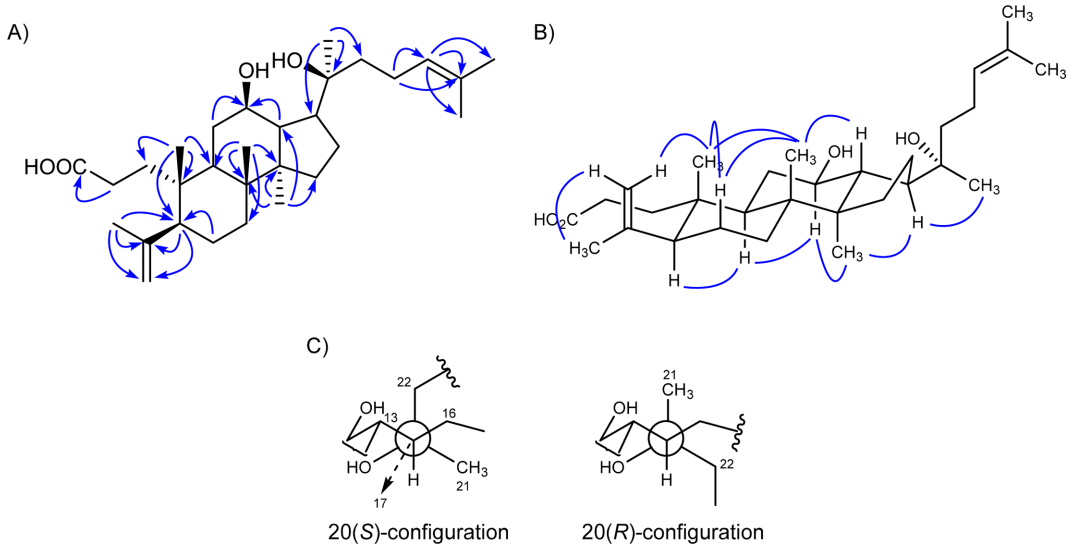

Fig. 2. Selective HMBC (A) and ROESY (B) correlations in **1**, and projections of the *S* and *R* configurations around C-17-C-20 (C).

in Fig. 2B.

The 20-OH configuration was assigned based on the carbon chemical shifts of C-21 and C-22 which will be affected by the non-bonded interactions due to the hydrogen bond between 12-OH and 20-OH.[15] By using the Newman projection at C-17 and C-20 (Fig. 2C), the C-21 in the 20*S*-configuration will experience less non-bonded interactions than the C-22, and therefore the chemical shift of C-21 will be more deshielded than C-22. The opposite situation will happen to the 20*R*-configuration. The carbon chemical shifts of C-21 and C-22 of **1** were found to be 26.9 and 34.7, respectively, which is consistent for the 20*S*-configuration (typical for the 20*R*-configuration is 21.8 and 42.3, respectively[9]). Thus, **1** was determined as (12β,20*S*)-12,20-dihydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid or 12β-hydroxy-dammarenolic acid. Compound **1** is the first tetracyclic triterpene found in *S. koetjape*. Most of the terpenoid compounds in this plant are pentacyclic triterpenes[10,16-17] and limonoids.[11,18-22]

From the resin of *S. javanica* three known dammarane triterpenes had been isolated, namely (20*S*)-20-hydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (**2**),[12] (3β,20*S*)-3,20-dihydroxydammaran-24-ene (dammarenediol II) (**3**),[12] and (20*S*)-3-oxo-20-hydroxydammaran-24-ene (**4**).[12] The confuguration at C-20 were also determined to be *S* by examining the carbon chemical shifts at C-21 and C-22. Compound **2** is related to **1** as the former is a deoxy derivative of the later. The NMR data of **2** - **4** are shown in the Tables 1 and 2.

The isolated damarane derivatives **1** - **4** were tested as the inhibitor of RTKs (EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFRα, and PDGFRβ) at concenttration 10 μM. Compounds **1** and **2** showed weak activity against EGFR and InsR with their % inhibition were 30%, 27% (**1**), 45%, and 32% (**2**), respectively, and were not active against the rest of RTKs (Table 3). These data also showed that **2** was more active than **1**. On the other hand, **3** and **4** were practically not active to the all tested RTKs. These results suggested that the *seco*-dammarane triter-

penes **1** and **2**, which has a polar carboxylic acid group, could be an important factor for the activity of both compounds against EGFR and InsR. However, by comparing the structure of **1** and **2**, it seems that the presence of the hydroxyl group at C-12 in **1** decreases its activity against the two RTKs.

In recent years TKs have been the target to search new chemicals as the inhibitor of the enzymes. Most developed inhibitors are synthetic compounds containing *N*-heterocyclic fragments, and currently about 80 candidates have been entered to the clinical evaluation.[23] Study of natural compounds as the inhibitor of TKs are very limited.[5] For example, only three natural compounds that have been claimed to be active against EGFR, namely artemisinin (sesquiterpene), butein (chalcone), and honokiol (lignan). A report of natural compounds to be tested against InsR has not been found.[5] Thus, this study is the first report of tetracyclic triterpenes of dammarane derivatives **1 - 4** as the inhibitor of some RTKs, in which **1** and **2** showed weak activity against EGFR and InsR. These the two compounds have no resemblance to artemisinin, butein, and honokiol. Although **1** and **2** are not potent inhibitors, the presence of the linear carboxylic acid group in **1 - 2** seems to contribute to the activity. which could be the model for further searching of natural compounds as TK's inhibitors.

In conclusion, a 3,4-*seco*-dammarane triterpene, 12β-hydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (**1**), has been isolated as a new natural compound from the wood of *S. koetjape*. Three known similar triterpenes, namely (20*S*)-20-hydroxy-3,4-*seco*-dammaran-4,24-dien-3-oic acid (**2**), (3β,20*S*)-3,20-dihydroxydammaran-24-ene (dammarenediol II) (**3**), and (20*S*)-3-oxo-20-hydroxydammaran-24-ene (**4**), have also been isolated from the resin of *S. javanica*. The four dammarane derivatives **1 - 4** were tested as the inhibitors of eight RTKs (EGFR, HER2, HER4, IGF1R, InsR, KDR, PDGFRα, and PDGFRβ), and found only **1** and **2** were active against EGFR and InsR.

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