DIMERIC STILBENES FROM STEM BARK OF *SHOREA ROXBURGHII* AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

Shorea roxburghii (Family Dipterocarpaceae) was found to be rich in oligostilbenes with various biological activities. However, scientific investigation into its bioactivity remains limited. In the current study, phytochemical investigation of *S. roxburghii* stem bark was performed to obtain three dimeric stilbenes, which were identified as (−)-ε-viniferin (1), (−)-balanocarpol (2), and (−)-ampelopsin A (3) by comparison of their spectroscopic data with those previously reported. The compounds were assayed for their effect on antioxidant, anti-inflammatory, cytotoxicity against breast cancer, anti-melanogenesis, anti-tyrosinase, and α-glucosidase inhibitory activities. Results showed that compound 2 and its C-7b epimer 3 scavenged ABTS radicals with IC_{50} values of 12.5 and 40.1 μM, respectively, while compound 1 was inactive (IC_{50} > 50 μM). Unfortunately, it was found that all three compounds are not active in other assays conducted.

Keywords: *Shorea roxburghii*, Dimeric Stilbenes, Antioxidant

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INTRODUCTION

Natural products have significantly contributed to the field of drug development (Atanasov et al., 2021). *Shorea roxburghii* has been traditionally used for treating diarrhea, dysentery, and cholera due to its astringent properties (Morikawa et al., 2011). A number of medicinal advantages are provided by the plant extract or its bioactive components, including antioxidant (Subramanian et al., 2013), hepatoprotective (Ninomiya et al., 2017), cytotoxic (Patcharamun et al., 2011), antihyperlipidemic (Morikawa et al., 2012), and antidiabetic effects (Ninomiya et al., 2017) derived from the bark, wood, and root of *S. roxburghii*. The phenolic crude extract of this plant showed protective effects against CTX-mediated renal toxicity via its antioxidant and anti-inflammatory effects (Hu et al., 2022). In contrast, the ethyl acetate extracts improved diabetes-induced testicular damage by inhibiting oxidative stress and inflammation (Zhao et al., 2020). Most of the bioactive compounds isolated from this plant are a mix of shikimate and polyketide derivatives, including stilbenes, coumarins, and flavonoids. Although *S. roxburghii* has been traditionally used, scientific investigation into its bioactive properties remains limited. Thus, this present study aims to isolate the compounds from the stem bark of *S. roxburghii* and evaluate them with a series of biological activities.

LITERATURE REVIEWS

Biosynthesis of Dimeric Stilbenoid

Stilbenes such as resveratrol were biosynthesized via mixed polyketide-shikimate pathways together with flavonoids. In this pathway, pathogenic invasion, physical damage, or UV radiation was needed to trigger stilbene synthase enzyme gene transcription. The resveratrol and its derivatives were produced as a response to invasive microorganisms and may contribute to disease treatment in humans. The resveratrol monomer can be oligomerized to create complex polyphenolic secondary metabolites and is mostly expressed as a biological defense, which consists of resveratrol oligomers made up of 2-8 resveratrol units (Keylor et al., 2015).

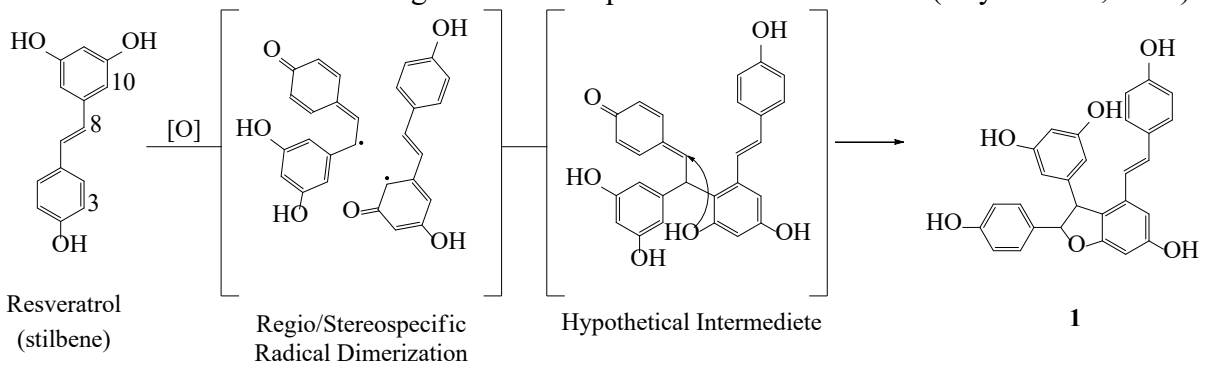

Figure 1 Biosynthesis of stilbene 8a-10b dimerization

Resveratrol oligomerization involves oxidatively generated phenoxyl radicals. Most oligostilbenes exhibit dimerization through three regioisomeric modes: 8a-10b coupling, 8a-8b coupling, and 3a-8b coupling. Plants belonging to the Dipterocarpaceae family produce a highly oxidized and structurally altered 8a-10b dibenzocycloheptane dimer that is unique to this family such as ε-viniferin (1) (Keylor et al., 2015).

Ethnobotanical Uses of *Shorea roxburghii*

Shorea roxburghii is a large-sized rainforest tree of the Dipterocarpaceae family that can grow to 40 meters. This species is geographically distributed throughout northern Peninsular Malaysia, Vietnam, Cambodia, Laos, Myanmar, India, and Thailand (Ly et al., 2017). *S. roxburghii* was called White Meranti in English, whereas those who live in Thailand call it Phayom. The locals have employed various traditional uses to utilize *S. roxburghii* from the roots, bark, and leaf. People from Khok Phayuung Village, Kaapchoeng District, Thailand, use

the root of *S. roxburghii* as a tonic (Chuakul & Saralamp, 2002). The ethnoperfumery industry has also been helped by the flowers, which emit a characteristic floral fragrance that is more sustainable than other fragrances obtained from the wood part (Yingngam et al., 2021). In South India, it is used as thatching in medical fields (Kumar et al., 2019).

Chemical Composition and Bioactivities

The bark of *S. roxburghii* that was taken from Phatthalung province, Thailand, reported that 26 compounds had been isolated, and among the isolates, (−)-hopeaphenol and (+)-α-viniferin exhibited moderate α-glucosidase inhibitory activity with maltase and sucrase IC_{50} 338, 195 and >400 (32.2), >400 (37.8) μM, respectively, compared to positive control 2.0, 1.7 μM. It aligns with its aldose reductase inhibitory with IC_{50} 69.0 μM, which moderately inhibits compared to positive control 0.072 μM (Morikawa et al., 2011). In addition, these compounds exhibited protective effects against liver injury induced by d-GalN/LPS in mice at a dose of 100 mg/kg, p.o., which was more potent than resveratrol. These compounds, like curcumin, are not toxic to the mouse hepatocytes, a naturally occurring hepatoprotective compound. Significantly inhibited LPS-activated NO production with IC_{50} 4.6 and 9.7 μM compared to resveratrol (IC_{50} 17.8 μM). (+)-α-viniferin reduces the TNF-α-sensitive cell line with a more excellent value than the positive control. These showed the mechanism of action of (-)-hopeaphenol and (+)-α-viniferin as hepatoprotective agents (Ninomiya et al., 2017). In 2011, (−)-hopeaphenol isolated from the roots actively acted as an anti-cancer with IC_{50} cytotoxicity values against KB and HeLa cells 8.5 and 10.1 μg/mL compared to its monomer, resveratrol with IC_{50} > 50 μg/mL (Patcharamun et al., 2011). The anti-melanoma effect was also studied for oligostilbenoid isolated from the bark of *S. roxburghii*. (−)-hopeaphenol and (+)-α-viniferin reducing the SK-MEL-28 cell viability with cytotoxic IC_{50} value 3.6 and 7.1 μM greater than resveratrol (IC_{50} 21.0 μM) which in line with its anti-proliferative activity. The cell cycle assay demonstrated that (+)-α-viniferin induces DNA damage, thereby initiating apoptosis, and inhibits cell cycle progression in SK-MEL-28 cells, which suggests that (+)-α-viniferin may serve as a chemotherapeutic agent against skin cancer (Moriyama et al., 2016).

RESEARCH METHODOLOGY

Isolation of Pure Compounds from *S. roxbrughii* Stem Bark

The stem bark of *S. roxburghii* was collected in August 2023 from Ubon Ratchathani Province, Thailand. The dried stem bark powder (1 kg) was extracted twice with 3 L ethyl acetate (EtOAc) for 3 days each, yielding 32 g of crude extract after rotary evaporation. Then, the residue powder was extracted by the same method with 3 liters of MeOH (2 × 3 days) to get 53.7 grams of dark green crude MeOH extract. The EtOAc crude extract was chromatographed using a SiO_2 column in a normal phase with gradient condition from lowest polarity to high polarity solvent, started with n-hexane: DCM (1:1) to 100% DCM and gradually increasing percent of acetone to 100% acetone to get twelve fractions (A-L). Fraction G was separated using the SiO_2 column in n-hexane: DCM: acetone (1:2:2) to get six subfractions (6A- 6F). The 6B subfraction was purified with reverse phase ODS (C-18) CC with H_2O: MeOH (1:1) to get compound 1 (9.5 mg). On the other hand, subfraction 6F was purified using the SiO_2 column in DCM: EtOAc: MeOH (6:3:1) to get five fractions (7A-7E). The subfraction 7D was then purified with reverse phase ODS (C-18) CC with H_2O: MeOH (1:1) to get four pure compounds, including compounds 2 (2.7 mg) and 3 (4.3 mg). This step is presented in Figure 2.

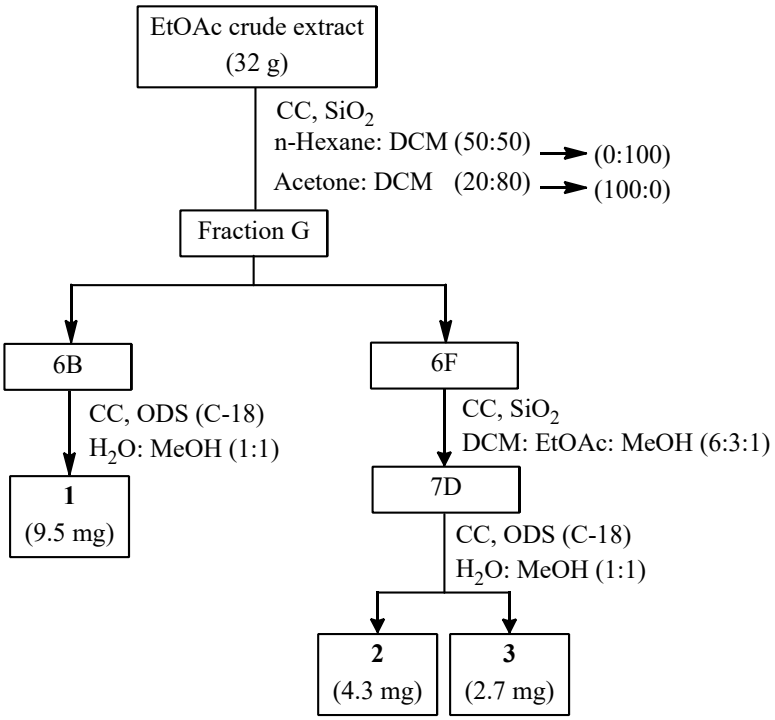

Figure 2 Isolation Scheme of Dimeric Stilbenes from *Shorea roxburghii*

Biological Activity Assay

The compound isolated from *S. roxburghii* was assayed on anti-oxidant, anti-inflammatory, cytotoxicity against breast cancer, anti-melanogenesis, anti-tyrosinase, and α-glucosidase inhibitory activity. Each experiment was performed in triplicate.

Antioxidant Activity

Antioxidant assay was done by two methods, DPPH assay and ABTS assay. DPPH radical scavenging activity was done by adopting a colorimetric approach that quantifies the reduction of DPPH (2,2-Diphenyl-1-picrylhydrazyl) to DPPH radical (diphenyl-(2,4,6-trinitrophenyl) iminoazanium) as described in the literature Brand-Williams et al. (1995) with slight modification. ABTS radical scavenging activity was done by adopting a colorimetric approach that quantifies the reduction of ABTS+ generated by sodium persulfate ($K_2S_2O_8$) to ABTS (2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid)) as described in the literature by Re et al. (1999) with slight modification. Trolox was used as the positive control in both assays.

α-Glucosidase Assay

α-glucosidase inhibitory assay of isolated compounds was done with maltase as the substrate and α-glucosidase as the enzyme. This assay was done by adopting a colorimetric approach that quantifies the total glucose produced from the substrate after enzymatic reaction, detected by glucose oxidase as described in the literature by Ramadhan and Phuwapraisirisan (2015), with slight modification. Acarbose was used as the positive control.

Tyrosinase Inhibitory Assay

Tyrosinase inhibition of isolated compounds was done with L-DOPA as the substrate and mushroom tyrosinase as the enzyme. This assay adopted a colorimetric approach that quantifies the reduction of L-DOPA to dopachrome, as described in the literature by Likhitwitayawuid and Sritularak (2001), with slight modification. Kojic acid was used as the positive control.

Cell culture

Human breast cancer cell lines (MDA-MB-231), murine melanoma cell lines (B16F10), and female mice with reticulum cell sarcoma (J774A.1) were cultured at 37°C in a humidified 95% air and 5% CO_2

Anti-inflammatory Assay

The isolated compounds' anti-inflammatory activity was done by observing the inhibition of nitric oxide (NO) production in LPS-activated murine macrophage J774.A1 cells, as described in the literature by Suthiphasilp et al. (2021) with slight modification. Indomethacin was used as a positive control.

Cytotoxicity Assay

The isolated compound's cytotoxicity against breast cancer cell lines (MDA-MD-231) was assessed. This was done by adopting a colorimetric approach that quantifies the reduction of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) as described in the literature by Suthiphasilp et al. (2021) with slight modification. Doxorubicin was used as a positive control.

Anti-Melanogenesis Assay

The isolated compound's melanin inhibitory assay was done by observing the inhibition of total melanin and the viability of melanocytes B16F10 cells as described in the literature by Jiménez-Pérez et al. (2017) with slight modification. α-arbutin was used as a positive control.

Statistical analysis

Data presented as mean ± S.D. values. GraphPad prism^{TM} ver. 10 programs with one-way analysis of variation were used for testing the significance; P-value (p) < 0.05 was considered as statistical significance.

RESEARCH RESULTS

Isolation of Dimeric Stilbenes from *Shorea roxburghii* stem bark

The compounds isolated from the stem bark *S. roxburghii* in ethyl acetate extract were confirmed to be three known dimeric stilbenes as (−)-ε-viniferin (1), (−)-balanocarpol (2), and (−)-ampelopsin A (3). The structure of each compound is shown in Figure 3.

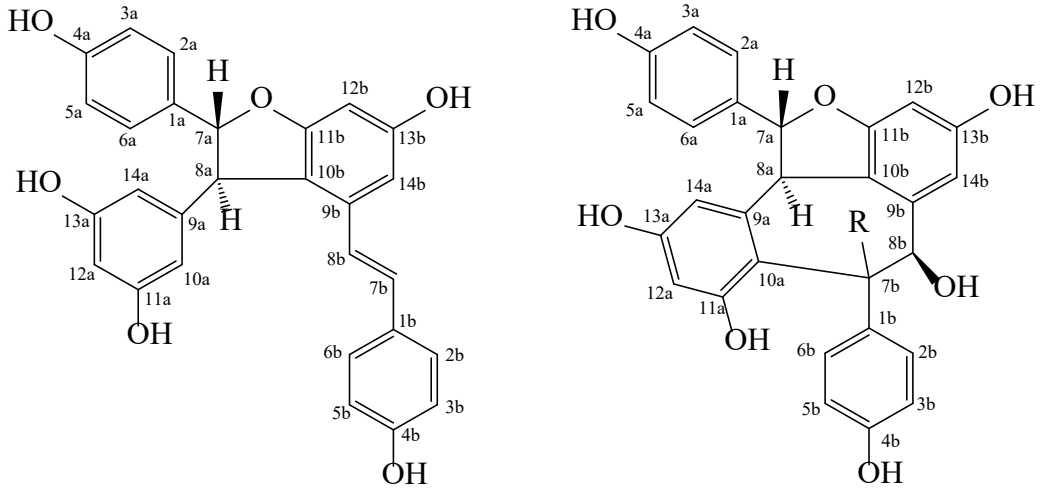

Figure 3 Chemical Structures of Dimeric Stilbenes **1**-**3** Isolated from *Shorea roxburghii*

Table 1 ^{1}H- and ^{13}C-NMR data of compounds 1-3

Position	1		2		3	
	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)
1a	134.0	-	134.1	-	129.6	-
2a	127.7	7.14 d, 8.5	129.0	7.53 d, 8.5	128.8	6.99 d, 8.5
3a	118.0	6.76 d, 8.5	118.6	6.99 d, 8.5	114.8	6.67 d, 9.0
4a	159.0	-	158.7	-	157.5	
5a	118.0	6.76 d, 8.5	118.6	6.99 d, 8.5	114.8	6.67 d, 9.0
6a	127.7	7.14 d, 8.5	129.0	7.53 d, 8.5	128.8	6.99 d, 8.5
7a	94.7	5.36 d, 6.0	92.2	5.73 d, 9.5	87.8	5.67 d, 11.0
8a	58.4	4.35 d, 6.0	59.5	5.20 d, 9.5	48.4	3.99 d, 12.0
9a	145.6	-	144.7	-	142.0	-
10a	108.1	6.16 d, 2.0	119.4	-	104.0	-
11a	160.9	-	158.0	-	158.0	-
12a	102.6	6.18 t, 2.0	100.6	6.13 d, 2.5	100.2	6.29 d, 2.5
13a	160.9	-	155.7	-	156.1	-
14a	108.1	6.16 d, 2.0	105.3	6.00 d, 2.0	117.8	6.07 d, 2.5
1b	130.1	-	132.6	-	131.8	-
2b	128.1	7.03 d, 8.5	130.7	6.78 d, 9.0	127.7	6.80 d, 8.0
3b	118.8	6.65 d, 8.5	115.4	6.48 d, 8.5	114.3	6.56 d, 9.0
4b	159.0	-	154.5	-	154.8	-
5b	118.8	6.65 d, 8.5	115.4	6.48 d, 8.5	114.3	6.56 d, 9.0
6b	128.1	7.03 d, 8.5	130.7	6.78 d, 9.0	127.7	6.80 d, 8.0
7b	130.4	6.82 d, 16.0	49.1	4.94 d, 3.5	42.8	5.37 d, 4.5
8b	125.1	6.57 d, 16.0	72.5	5.43 s	70.3	5.39 d, 5.0
9b	136.8	-	143.9	-	138.5	-
10b	121.7	-	112.5	-	109.4	-
11b	164.4	-	161.0	-	158.8	-
12b	96.7	6.25 d, 2.0	93.8	6.23 d, 3.5	96.2	6.08 d, 2.0
13b	160.4	-	160.8	-	159.1	-
14b	106.5	6.63 d, 2.0	103.9	6.30 d, 3.0	118.6	6.50 d, 2.0

Note: Measure in methanol-d_4

(−)-ε-viniferin (1) was obtained as a brownish-red solid. $[\alpha]^{23}_D$ − 19.8 (*c* 0.1, MeOH). DART-MS: *m/z* 453.3763 $[M-H]^-$ (calcd for $C_{28}H_{22}O_6$, 454.1416). Spectrum ^{1}H-NMR & ^{13}C-NMR data, Table 1.

(−)-balanocarpol (2) was obtained as a brownish-yellow solid. $[\alpha]^{23}_D$ − 23.0 (*c* 0.1, MeOH). DART-MS: *m/z* 471.3415 $[M+H]^+$ (calcd for $C_{28}H_{22}O_7$, 470.1366). Spectrum ^{1}H-NMR & ^{13}C-NMR data, Table 1.

(−)-ampelopsin A (3) was obtained as a brownish-red solid; $[\alpha]^{23}_D$ − 23.1 (*c* 0.1, MeOH). DART-MS: *m/z* 471.3827 $[M+H]^+$ (calcd for $C_{28}H_{22}O_7$, 470.1366). Spectrum ^{1}H-NMR & ^{13}C-NMR data, Table 1.

Biological Activity

Three dimeric stilbenes isolated from *S. roxburghii* did not show significant effect (IC_{50} > 50 μM) in the DPPH assay, while in the ABTS assay, compounds 2 and 3 showed higher activity (shown in Table 2) than compound 1 (IC_{50} > 50 μM).

Table 2 Antioxidant Activity of Dimeric Stilbenes from *S. roxburghii* in DPPH and ABTS

Compound	IC_{50} (μM) ± SD	
	DPPH Assay	**ABTS Assay**
1	> 50	> 50
2	> 50	12.5 ± 21.7
3	> 50	40.1 ± 69.5
Trolox	18.5 ± 0.4	11.4 ± 0.2

Note: The IC_{50} value of the positive control (Trolox) was cited from Li et al. (2017)

Three dimeric stilbenes isolated from *S. roxburghii* showed low activity (IC_{50} > 50 μM) in the NO inhibitory assay, cytotoxicity against MDA-MB-231 cells, α-glucosidase inhibitory assay, anti-melanogenesis assay, and tyrosinase inhibitory assay (shown in Table 3).

Table 3 Effects of Dimeric Stilbenes on NO inhibitory assay, cytotoxicity assay against MDA-MB-231 cells, α-glucosidase inhibitory assay, anti-melanogenesis assay, and tyrosinase inhibitory assay

Compound	IC_{50} (μM) ± SD				
	NO Inhibitory Assay	**Cytotoxicity Assay**	**α-glucosidase inhibitory assay**	**Anti-melanogenesis Assay**	**Tyrosinase Inhibitory Assay**
1	> 50	> 50	> 50	> 50	> 50
2	> 50	> 50	> 50	> 50	> 50
3	> 50	> 50	> 50	> 50	> 50

DISCUSSION & CONCLUSION

The structure of compounds **2** and **3** was determined by comparing the ^{1}H-NMR and ^{13}C-NMR from earlier research, and the stereochemistry was validated by NOESY spectra. The structure of (−)-ε-viniferin (1) was confirmed by comparison of its NMR data with previous literature (Kurihara et al., 1991). Key features include a dimeric stilbene skeleton, hydroxylation at C-4a and C-4b, and a furan ring, evidenced by C-7a (δ_C 94.7) and C-8a (δ_C 58.4) and a trans double bond at C-7b/C-8b, confirmed by J = 16.0 Hz. The stereochemistry of compound 1 was determined by the coupling constant between H-7a and H-8a, which has a J = 6.0 Hz dihedral angle of 120° in *trans* position and confirmed by optical rotation from previous literature. (−)-balanocarpol (2) and (−)-ampelopsin A (3) are dimeric stilbene with lacks a double bond and instead has a hydroxylated methine at C-8b, distinguishing it from compound 1 (Diyasena et al., 1985; Tanaka et al., 2000). Compound 3 has a similar structure to compound 2 but with epimerization at C-7b (δ_C 42.8), confirmed by NOESY cross-peaks (shown in Figure 4).

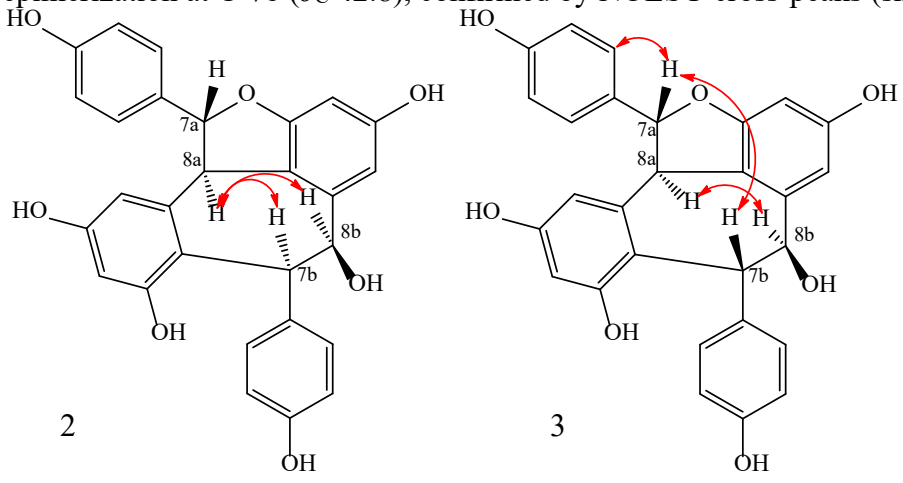

Figure 4 Selected NOESY correlations of compounds 2 and 3

The antioxidant activity in this report uses two *in vitro* methods, DPPH and ABTS assay. Compound 2 and its C-7b epimer 3 scavenged ABTS radicals with IC_{50} values of 12.5 ± 21.7 and 40.1 ± 69.5 μM, respectively, while compound 1 was inactive (IC_{50} > 50 μM) compared to the trolox with IC_{50} values of 11.4 ± 0.2 μM. In contrast, the DPPH assay showed no activity from any compounds, while trolox still scavenged DPPH radicals with IC_{50} values of 18.5 ± 0.4 μM. The observed differences between the DPPH and ABTS assays may be due to steric hindrance affecting radical scavenging activity, as previously reported (Prior et al., 2005). All the compounds showed no activity in the cytotoxicity against breast cancer (MDA-MB-231 cells), anti-melanogenesis, tyrosinase inhibitory assay, α-glucosidase inhibitory assay, or NO inhibitory assay. Differences in stilbene's stereochemistry, hydroxylation pattern, and dimerization may impact the assay's outcome.

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