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Synthesis and Structure Activity Relationships of Eusiderin A Derivatives as Antifeedant

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Abstract
Eusiderin A(**1**) which isolated from *Eusideroxylon zwagery* was converted into some derivatives**(2- 10)**in order to disclose the structure activity relationship as antifeedant. The structures of these compounds were determined based on their spectroscopic data including ^{1}H NMR, COSY, and NOESY spectra and mass spectra. The antifeedant activity and Brine Shrimp Lethality test have been evaluated to demonstrate that **2, 3, 6** and **7** increased significantly the antifeedant activity rather than eusiderin A, while all of the analogs were classified as non toxic.
Keywords: eusiderin A, *E. sparsa*, antifeedant, brine shrimp lethality test**.**

1. Introduction

Pesticides have played a significant role in increasing agricultural productivity. However continuous use of insecticidal resulted in insects gradually become resistant to these insecticides and sometimes these insecticidal destroy useful symbionts. Therefore these circumstance led usfor controlling insects by an alternative method becomes crucial. One of the best approaches for alternative insect control is by using secondary metabolite which influence insect chemosensory behavior such as antifeedants in order to control theinsect population.

The role of secondary metabolite in the defense of plant against insects and fungi has been increasingly recognized in recent years. *Eusideroxylon zwagery* is an endemic plant in which widely distributed throughout Jambi Province and Kalimantan Forest, commonly called as Kayu Ulin. It is a dense red-brown durable wood, proof to termite and other ubiquitous tropical wood-decayed insects and fungi. As a consequence, the wood is widely used for construction materials such as bridge, boat, window frame, etc. It is particularly prominent resistance towards wood decayed fungi that put the wood as first class timber, meanwhile the resistance to termite attack is categorized as second class (Hobbs *et al*. 1960*)*

In the course of our investigation on chemical potency of *E. zwagery*, we isolated eusiderin A as a major component from the heartwood of MeOH extract based on antifeedant activity guided isolation (Syamsurizal *et al*. 2001 or Syamsurizal *et al.* 2007) Eusiderin A**(1)** a neolignan type was the first time isolated by Hobbs and King in 1960 which is biogenetically derived from phenylpropanoid (Merlini *et al.* 1975). Compound **1** was reported at a concentration of 100 ppm to show significant inhibition, 66% on the mycelial growth of *Tyromeces polutris*(ouzuratake) and 52% against *Coriolus versicolor* (kawaratake) (Wasrin *et al*. 1987). In addition, **1** showed potent antifeedant activity at a concentration of 0.01% against *Epilachna sparsa* and without displayed toxic on the Brine Shrimp Lethality Test (LC_{50}> 500 ppm). It also could prevent *Etiella zinckenella* from destroying soybean, *Glicine max* at a conc. of 0.5%. On the other side of experiment,**1** gave the most effective inhibition ratio against *Fusarium oxysporum f.sp. lycopersici* (49.8%), *Sclerotium rolfsii* (49.6%), and *Rhizoctonia solani*(22.0%) at 5 ppm concentration (Muhaimin *et al.* 2007). This finding leads to the reason why this plant has durable wood. It suggested that eusiderin A play a role in the protection of the plant against insects and fungi.

These results have inspired us to transform the eusiderin A into several analogs **(2-10)** and designed by considering the clogP values then evaluated the antifeedant activity against *Epilachna sparsa*(Leo, 1993). ClogP is a parameter correlated to the permeability of drugs and is thus believed to be an important index in predicting the biological activity (Murakami *et al*. 2003). The results exhibited that three of the analogs**, 2, 3** and **6** which demethylated on the aromatic ring led to increase significantly the antifeedant activity and not toxic against *Artemia salina* (Syamsurizal *et al*. 2009). Meanwhile the other set of the experiment show that saturation on the allylic moiety **(7)** could afford enhancing the antifeedant actifity two times than **1**. However elongation on the site allylic**(8-10)** brought about declined the antifeedant activity.

2. Experimental

2.1 General

The ^{1}H-NMR spectra was measured with a JEOL GX-500 (^{1}H: 500 MHz, using Me_4Si (0 ppm) as internal reference. Chemical Shifts were reported in parts per million (ppm). FAB mass spectra was recorded on a JEOL SX-102. All reactions were carried out under an argon atmosphere unless otherwise indicated. Column chromatography was conducted using silica gel (Fuji Sylisia BW-200). Thin-layer chromatography (TLC) analysis was performed on precoated Kieselgel 60F_{254} plates (0.25 mm, Merck). The spots were monitored under UV light (254 or 365 nm) and visualized by spraying agents phosphomolibdic acid in ethanolic solution

*2.2 Isolation and Purification of **1**.*

Sample of the heartwood of E. zwagery was collected from Senami Forest, Batanghari District, Jambi Province, Indonesia. The dried heartwood (8 Kg) was ground and extracted three times with MeOH at rt for 6 h and subsequently three times under reflux for 4 h. The MeOH extract (1.2 Kg) was fractionated by vacuum liquid chromatography on silica gel using combination of n-hexane and ethyl acetate with increasing polarity as eluent to give 6 fractions. Eusiderin A was identified on the second and third fraction then crystallized with benzene to afford **1** (1.6 gram).

*2.3 Synthesis of **2** and **3***

To a solution of 1 (50 mg) in dehydrated CH_2Cl_2 (1ml) cooled to 0^{o}C and added 62.5 µl of boron tribromides in CH_2Cl_2 (1 M) then stirred overnight at 0^{o}C. The reaction mixture was quenched with water at 0^{o}C and extracted with diethyl ether then dried over then the filtrate was concentrated under reduced pressure to give a crude 49.7 mg then subjected toSiO_2column chromatography (n-hexane: EtOAc =5:1) to afford **2** (15 mg) then the other fractions purified by normal phase HPLC [column: cosmosil 5SL-II (10 i.d. x 250 mm, Nacalai), mobile phase: n-hexane: EtOAc =2:1, detection: UV (250 nm), flow rate: 3 ml/min] to furnish3 (20.1 mg). ^{1}H-NMR of **2** and **3** as given Table 1. The MS data of 2 and 3 gave a molecular ion peak $(M+H)^+$ at m/z 373 and 359 respectively.

*2.4 Conversion of **1** into **(4 -6)***

To a solution of 1(100 mg) in dehydrated CH_2Cl_2 (1ml) cooled to 0^{o}C and added 500 µl of boron tribromides in CH_2Cl_2 (1 M) then stirred overnight at room temperature. The reaction mixture was quenched with water at 0^{o}C and extracted with diethyl ether then dried over then the filtrate was concentrated under reduced pressure to give a crude 120 mg then subjected toSiO_2column chromatography (n-hexane: EtOAc =5:1 and 3:1) to afford 4 (26 mg) then the other fractions were further subjected to reversephase HPLC [column: cosmosil ODS-5C_{18}AR-II (10 i.d. x 250 mm, Nacalai), mobile phase: MeOH:H_2O=35:65→ detection: UV (250 nm), flow rate: 3 ml/min], to furnish(5,15 mg) and (6, 23 mg).). ^{1}H-NMR of **4-6** as given Table 1. The MS data of 4-6 gave a molecular ion peak $(M+H)^+$ at m/z 181, 391 and 377 respectively.

*2.5 Synthesis of **1a** and **1b***

A solution of $NaBH_4$(20 mg) in dehydrated THF(0.4 mL) was treated with $BF_3.Et_2O$ then stirred at rt for 30 min. To the mixture was added dropwise solution of 1(13.5 mg) in dehydrated THF(0.4 mL) and stirred at rt for 30 min. The reaction mixture was cooled to 0^{o}C followed by adding 2M aq.NaOH(0.13 ml) and 30% H_2O_2(0.6 ml) then stirred at rt for 10 min. The reaction mixture was poured into water(50 mL) and extracted with EtOAc. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, followed by drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by chromatography on a silica gel column (1:1 n-hexane-EtOAc) to yield the desired product **1**a(10.3 mg).

To a solution of 1a (22.1 mg) in dehydrated CH_2Cl_2(1.1 mL) was added Dess Martin reagent (50.9 mg) and stirred at rt for 30 min. After completion the reaction, the mixture was poured into saturated aqueous $NaHCO_3$ and neutralized with saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. After being washed with saturated aqueous $NaHCO_3$ and brine. The EtOAc layer was dried over anhydrous $NaSO_4$ and concentrated to dryness. The crude product was purified by chromatography on a silica gel column (2:1 and 1:1 n-hexane-EtOAc) to give the desired product 1b(10.3 mg).

*2.6 Synthesis of **7-10***

A solution of 1 (20 mg) in dehydrated methanol1(ml) was treated with 10% Pd-C catalyst (5 mg). The reaction mixture was stirred at room temperature for 12 h under a H_2 atmosphere. After filtering,the filtrate was concentrated under reduced pressure to give a crude 22.6 mg then subjected toSiO_2column chromatography (5:1 n-hexane: EtOAc) to afford **7** (16.7 mg).

To a solution of methyl triphenylphosphonium bromide(78.6 mg) in dehydrated THF(2.43 mL) was added dropwise sodium bis(trimethylsilyl) amide(1M in THF) then stirred at rt for 15 min. After which time the reaction mixture was cooled down to 0^oC and solution of 1b in dehydrated THF(0.59 mL) was added dropwise 1b then the mixture was stirred for 15 min. After completion of the reaction, the mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine, and then dried over anhydrous MgSO4. The solvent was evaporated under reduce pressure. The residue was chromatographed on silica gel column (3:1 n-hexane: EtOAc) to afford compound **8**. In the same manner, the desired product **9**(9.3 mg) and **10**(13 mg) were synthesized by utilizing ethyl triphenylphosphonium bromide and butyl triphenylphosphonium bromide as reagent respectively,The 1H-NMR Data of**7-10** gave in Table 2

2.7 Antifeeding Assay

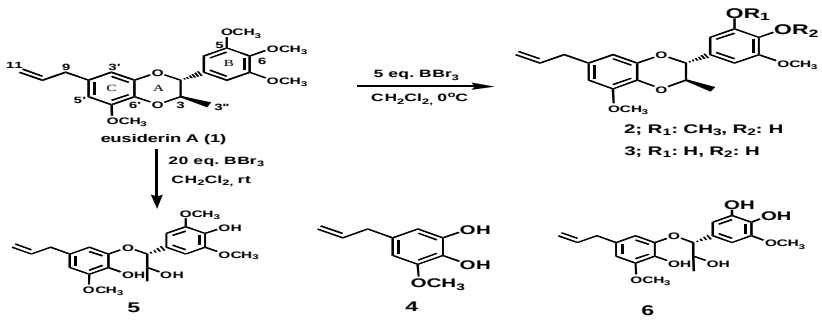
The test insects, Epilachna sparsa collected from vegetables field in Mendalo Darat Village, Jambi Province, Indonesia, where pesticides had not been applied. These insects were maintained in our laboratory under room temperature and fed daily with the leaf of Solanum nigrum until they lay eggs. When the eggs hatched to form the first-instar and reared until the third instar were used for testing. The antifeedant effect of the synthesized compounds against third-instar larvae of *E. sparsa* was determined using a conventional leaf disc method which modified from the assay described by Abdelgaleil and Aswad (Abdelgaleil *et al*. 2005) The leaf disc (60 mm diam) of *S. Nigrum* was divided into two sectors; the left side immersed in methanol for two seconds as control area and the right side by the same manner with methanol solution of tested compounds as treatment area. The discs were left to dry. Then two of the tested larvae, which starved for 12 h were placed in the center of each Petri dish. The bioassay terminated after 24 h. This choice test was conducted at a range concentrations of 100 to 1000 ppm. Three replicates of each concentration were carried out. The antifeedant percentage was calculated from the following equation: % antifeedant = 100 (C – T/C), where C is the wide area of leaf discs consumed in the control and T is the wide area of leaf discs consumed in the treatment.

2.8 Brine Shrimp Lethality Test

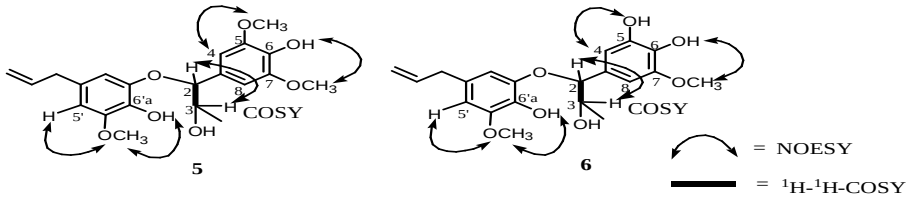
The brine shrimp lethality test (BST) was used to predict the presence of cytotoxic activity in the tested compounds [Meyer,1982]. Assay procedures and analysis of results was done as reported earlier (Syamsurizal *et al.* 2009).

3. Results and Discussion

Demethylation of methoxyl groups of **1** could only be achieved by employing of 5eq BBr_3 in CH_2Cl_2 at 0^oC to proceed compound **2** and **3**, meanwhile compounds(**4-6**) were obtained after adding 20eq of BBr_3 at room temperature. The synthetic route of comp. **2-6** as shown in (Scheme 1). Demethylation which occurred at comp. **2** and **3** were proved by NOESY spectra where to show cross peak correlation between hydroxyl group at C-6 and both of methoxyl groups at C-5 and C-7 of **2**. Structure of **3** was indicated by significance changed proton signal at H-4 and H-8 to the lower frequency. In addition to proton signal at H-**4** was correlated with hydroxyl signal at C-5. The presence of methoxyl group at C-6'for all derivatives were displayed by cross peak correlation between H-5'and 6'-OCH_3 group. The excess adding of BBr_3 let to bring about dioxane ring was opened to give comp. **4** which characterized by the aromatic proton signal at C-4 and C-8 disappeared. Meanwhile comp. **5** and **6** exhibited significance changed proton signal at H-2 and H-3 then correlated each other as shown in COSY spectra. Besides that appearance of hydroxyl signal at 6'a and NOESY spectra showed cross peak correlation with methoxyl group at C-6(Scheme 2) (Wasril *et al*. 1987)

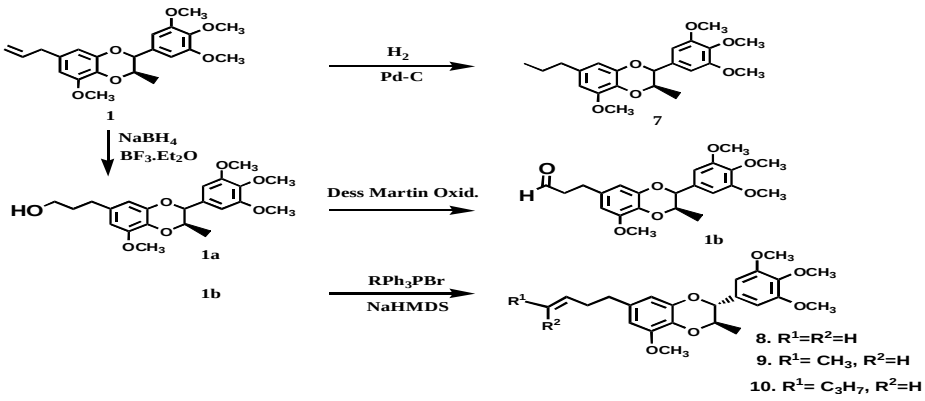


Scheme 1. Synthetic route of compound **2-6**



Scheme 2. Correlation of ^{1}H-^{1}H-COSY and NOESY of compound**5 and 6**

Allylic moiety was hydrogenated stoichiometrically by adding Pd-C catalyst at room temperature to furnish **7** with yield 83%. The result was indicated by disappeared olefin signal at δ 5.94 ppm (1H, ddt like, *J* = 17.7, 3.6, 7.0 Hz H-10) and 5.07 ppm (2H, dd like, *J* = 18.0 10.0 Hz, H-11), then appeared aliphatic signal at δ 1.62 ppm (2H, m, H-10) and 0.94 ppm(3H, t, *J* = 7.3 Hz, H-11). In addition, hydrogenation on allylic moiety let to bring about significant chemical shift to lower frequency at position H-9(Δ0.8 ppm). Whereas proton signals at other position no much changed the chemical shift. The structure of **7** as shown in Scheme 3



Scheme 3. Synthetic route of comp. **8-10**.

Structure of **8** was indicated by characteristic methylen signal at δ 5.06(dd, *J* =17.2, 1.8 Hz, H-12) besides that significant changed chemical shift to the lower frequency at position of H-9(Δ: 0.68 ppm) and H-10(Δ 3.59 ppm) but signal proton at H-11 changed to higher frequency(Δ: 0.73-0.86 ppm). ^{1}H-NMR data of 9 showed olefin signat at δ 5.38-5.53(m, H-12) and specific methyl signal 1,59(d, J =5.3Hz, H-13). As found in comp. **8** that changed chemical shift to lower frequency was occured at position H-9(Δ:0.72 ppm), H-10(Δ: 3.60 ppm) then shifted to higher frequency of H-11(Δ: 0,31-0,46 ppm). Structure of **10** is also to exhibite the chemical environtment changed especially at position H-9(Δ: 0.73 ppm) and H-10(Δ: 3.60 ppm) which shifted to the lower frequency whereas H-11(Δ; 0,34 ppm) shifted to the higher frequency. Meanwhile new methine signal at δ(5.41(m, H-12) and aliphatic signals at position H-13, H-14 and characteristic methyl group (H-15) appeared. Nevertheless chemical environtment of other proton signals (**8-10**) were relative unchanged.

In the previous result disclosed that three congeners i.e.**2, 3** and **6** enhanced significantly the antifeedant activities where Comp. **2** showed two times and **6** five times increased the antifeedant acitivity whereas comp. **3** which demonstrated 10 times increased rather than **1**. These results showed that demethylation especially vicinal diol at position of C-5 and C-6 on the aromatic ring could afford increasing the antifeedant activity. It is having play an important role to enhance the antifeedant activity. Meanwhile when the dioxane ring is opened let to undergo decomposed and tend to decrease the antifeedant activity rather than (**1**) as seen at comp. **5** dan **6** (Syamsurizal *et al*. 2009)

On the other hand, elongation aliphatic at allylic moiety which possesses the clogP value larger than (**1**) could not bring about increased the antifeedant activity however when the allylic moiety was saturated by hydrogenation to show enhanced the antifeedant activity two times than (**1**) Besides that based on Brine Shrimp Lethality test to the synthesized compounds**(2-10)** to show the LC_{50}> 500 ppm, so that in such case comp.**(1-10)** were considered no toxic (Meyer *et al.* 1982). The antifeedant effects of 24 h exposure of the derivatives at the concentration of 250 ppm against the 3rd instar larvae of *E. sparsa* are shown in Table 3.

4. Conclusion

Compound **(1)** could be transformed into several derivatives **(2-10)**. Based on the antifeedant evaluation against *E. sparsa* could be summarized the structure activity relationship of eusiderin A derivatives *i.e.* demethylated methoxyl group at C-5 and C-6 could afford bring about significant increasing the antifeedant activity **(3).** These results indicated that vicinal diol at C-5 and C-6 play an important role to enhance the antifeedant activity. Meanwhile dioxane ring is necessary to maintain the conformation and stability. However aliphatic elongation on allylic moiety tends to reduce the antifeedant activity.

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Supporting Information:

Table 1 : 1H-NMR Data of **(1)** and the derivatives **(2-6)** in $CDCl_3$ (500 MHz)

Proton	**1**	**2**	**3**	**4**	**5**	**6**
H-8	6.57 (s)	6.58 (s)	6.47(s)	-	6.36(brs)	6.43(d, *J* = 1.5 Hz)
H-4	6.57 (s)	6.58 (s)	6.48(s)	-	6.36(brs)	6.43(d, *J* = 1.5 Hz)
H-5’	6.49 (s)	6.48(d, *J* = 1.6 Hz)	6.62(d, *J* = 1.2 Hz)	6.44(brs)	6.23(brs)	6.24(d, *J* = 1.6 Hz)
H-3’	6.38 (s)	6.38(d, *J* = 1,6 Hz)	6.36(d, *J* = 1,4 Hz)	6.30(brs)	6.23(brs)	6.23(d, *J* = 1.8 Hz)
3’-OH	-	-	-	5,40(s)	-	-
H-9	3.30(d, *J* = 6.7 Hz)	3.30(d, *J* = 6.8 Hz)	3.29(d, *J* = 7.0 Hz)	3.27(d, *J* = 6.7 Hz)	2.87(d, *J* = 7.3 Hz)	2.90(d, *J* = 7.0 Hz)
H-10	5,94 (ddt, *J* =17, 7,3, 6,7 Hz)	5,94 (m)	5.94 (m)	5.92 (m)	5.66 (m)	5.68 (m)
H-11	5,07(dd, *J* =18,0, 10,9 Hz)	5,07(dd, *J* =16,1, 9,1 Hz)	5,08(dd, *J* =15,7, 8,4 Hz)	5,08(dd, *J* =15,9, 9,1 Hz)	4,93(dd, *J* =16,7, 7,4 Hz)	4,94(dd, *J* =15,0, 10,4 Hz)
H-2	4,55(d, *J* = 7,9 Hz)	4,54(d, *J* = 8,1 Hz)	4,51(d, *J* =8,8 Hz)	-	4,02(d, *J* = 6,1 Hz)	3,99(d, *J* =7,1 Hz)
H-3	4,10(dq, *J* = 7,9, 6,1 Hz)	4,10(dq *J* = 7,0, 5,9 Hz)	4,08(m)	-	4,71(dq, *J* = 6,8, 6,1 Hz)	4,69(dq, *J* =7,0, 6,7 Hz)
H-3”	1,26 (d, *J* = 6,1 Hz)	1,24 (d, *J* = 6,4 Hz)	1,25 (d, *J* = 7,0 Hz)	-	1,51 (d, *J* = 6,9 Hz)	1,50 (d, *J* =6,6 Hz)
3-OH					Obscured	Obscured
5-OH	-	-	5,38(s)	-	-	5,28(s)
6-OH	-	5,58 (s)	5,47(s)	-	5,18(s)	5,24(s)
5-OCH_3	3,88(s)	3,91(s)	-	-	3,83(s)	-

6-OCH_3	3,88(s)	-	-	-	-	-
6'a-OH	-	-	-	5,36(s)	5.43(s)	5,34(s)
7-OCH_3	3,86(s)	3,91(s)	3,90(s)	-	3,83(s)	3,87(s)
6'-OCH_3	3,89(s)	3,89(s)	3,89(s)	3,86(s)	3,88(s)	3,81(s)

Tabel.2 ^{1}H-NMR Data of **1** and congeners (**7-10**) ($CDCl_3$, 500 MHz)

Proton	**1**	**7**	**8**	**9**	**10**
H-2	4.55 (d,*J* = 7.9 Hz)	4.56 (d, *J* = 7.9 Hz)	4.56 (d, *J* = 7.9 Hz)	4.56 (d, *J* = 7.9 Hz)	4.56 (d, *J* = 7.7Hz)
H-3	4.10 (dq, *J* =7.9, 6.1 Hz)	4.11(m)	4.10 (dq, *J* = 7.9, 6.4 Hz)	4.10 (dq, *J* =7.9, 6.4 Hz)	4.10 (dq, *J* = 7.0, 6.6 Hz)
H-4	6.57 (s)	6.58 (s)	6.58 (s)	6.58 (s)	6.58 (brs)
H-8	6.57 (s)	6.58 (s)	6.58 (s)	6.58 (s)	6.58 (brs)
H-9	3.30 (d,*J* = 6.7 Hz)	2.50(t, *J* = 7.5 Hz)	2.62 (t, *J* = 7.2 Hz)	2.58 (t, *J* =7.0 Hz)	2.57(t, *J* = 7.2 Hz)
H-10	5.94 (ddt, *J* = 17, 7.3, 6.7 Hz)	1,62 (m)	2.35 (dt, *J* = 7.7, 6.8 Hz)	2.34 (dt, *J* = 8.6, 6.4 Hz)	2.34 (dt, *J* = 8.4, 6.2 v)
H-11	5.07 (dd, *J* = 18, 10 Hz)	0.94(t, *J* = 7.3 Hz)	5.80-5.93(m)	5.38-5.53(m)	5.41 (m)
H-12	-	-	5.06(dd, *J* = 17.2, 1.8 Hz)	5.38-5.53 (m)	5.41 (m)
H-13	-	-	-	1.59 (d, 5.3 Hz)	2.0(dt,*J* = 13.2, 6.6 Hz)
H-14	-	-	-	-	1.35(m)
H-15	-	-	-	-	0.88(3H, t,*J* = 7.0 Hz)
H-3'	6.38 (brs)	6.37(brs)	6.38(d, *J* = 1.8 Hz)	6.39 (d, *J* =1,8Hz)	6.39 (brs)
H-5'	6.49 (brs)	6.47(brs)	6.48(d, *J* = 2.0 Hz)	6.49 (d, *J* =1.8)	6.49 (brs)
H-3"	1.26 (d, *J* = 6.1 Hz)	1.26 (d, *J* =6.2 Hz)	1,26 (d, *J* = 6.2 Hz)	1.26 (d, *J* =6.4 Hz)	1.26 (d, *J* = 6,1 Hz)
5-OCH_3	3.88 (s)	3.88 (s)	3.88 (s)	3.88 (s)	3.89 (s)
6-OCH_3	3.89 (s)	3.90 (s)	3.90 (s)	3.90 (s)	3.90 (s)
7- CH_3	3.88 (s)	3.88 (s)	3.88 (s)	3.88 (s)	3.87 (s)
6'-OCH_3	3.75 (s)	3.86 (s)	3.86 (s)	3.86(s)	3.81 (s)

Table 3. Antifeedant Activities of (**1**-**10**)

Compound	Antifeedant(AC90, w/v)[*]
1	1.02
2	0.50
3	0.10
4	1.12
5	2.01
6	0.21
7	1.30
8	1.51
9	1.82
10	2.23
Azadirachtin[**]	1.15

[*]AC_{90}: antifeedant concentration where 90% of tested leave did not consumed.
[**]: as Positive Control