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Synthesis and Structural Confirmation of the Thiazole Alkaloids Derived from *Peganum harmala* L.

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Abstract: Peganumal A and B are thiazole alkaloids isolated from the seeds of *Peganum harmala* L. Thiazole moieties are rarely found in natural products, but diverse compounds possessing thiazole moieties have attracted attention owing to their broad range of biological activities. Peganumals are the first natural thiazole compounds isolated from the genus *Peganum.* It was difficult to define the exact structure of peganumal A via spectroscopic analysis. In this paper, we report the first total synthesis of peganumal A and B. The 5-benzylthiazole skeleton possessing methyl or hydrogen at the 2-position of the peganumals was efficiently constructed via the Hantzsch thiazole synthesis of the α-bromoaldehyde intermediate. Moreover, the spectral data of the synthetic 2*H*–thiazole compound were identical to those previously reported for peganumal A. The synthesis allowed the confirmation of the structure of peganumal A.

Keywords: peganumal; Hantzsch thiazole synthesis; total synthesis; structural confirmation

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1. Introduction

Peganum harmala L. (*Zygophyllaceae*), known as the Syrian rue, is an abundant wild-growing flowering plant. The seeds, roots, and aerial parts of the plant have been used as popular folk medicine in China and Middle-east Asia to treat several diseases. Many studies have been conducted using extracts from each part of the plant to evaluate the pharmacological properties and identify the bioactive compounds thereof. For instance, many alkaloids isolated from this plant, including β-carboline derivatives, exhibit diverse therapeutic effects, including anti-inflammatory, anticancer, and antibacterial activities [1–3].

Recently, a Chinese research group isolated the natural thiazole alkaloids peganumal A (**1**) and B (**2**) from the seeds of *Peganum harmala* L. They also evaluated their antiproliferative activities against HL-60, PC-3, and SGC-7901 cancer cell lines, but **1** and **2** did not show significant activities. It was claimed that thiazole was a rarely observed moiety in natural products and was reported for the first time in the genus Peganum [4]. They proposed that 1 and 2 have 2*H*–thiazole or 2-methylthiazole moieties connected with 4-hydroxy-3,5-dimethoxybenzene by a methylene bridge, respectively (Figure 1). Unlike 2, it was difficult to distinguish **1** by two-dimensional NMR studies from its possible regioisomer **1′**. Therefore, in the previous paper [4], the structure of peganumal A was not clearly defined and was proposed as **1** via ^{13}C NMR chemical shift calculations by quantum chemical methods.

Natural and unnatural thiazole compounds have been widely explored by synthetic organic and medicinal chemists because of their broad range of biological activities, including antioxidant, analgesic, antimicrobial, anticancer, antiallergic, antihypertensive, anti-inflammatory, and antipsychotic activities [5–7]. As part of our research interest in biologically active natural products, and because of their interesting structural features, we considered peganumals as attractive synthetic targets. To establish a synthetic procedure for **1** and **2**, which could be used for the structural confirmation of peganumal A, we planned a Hantzsch thiazole synthesis, one of the most reliable routes to

2,5-disubstituted thiazoles [8,9], between α-bromoaldehyde **3** and the corresponding thioamides. α-Bromoaldehyde **3** was expected to be obtained from commercially available syringaldehyde 4 by aldol reaction, hydrogenation, and α-bromination. In this paper, we describe the first total synthesis of peganumals and the structural confirmation of peganumal A.

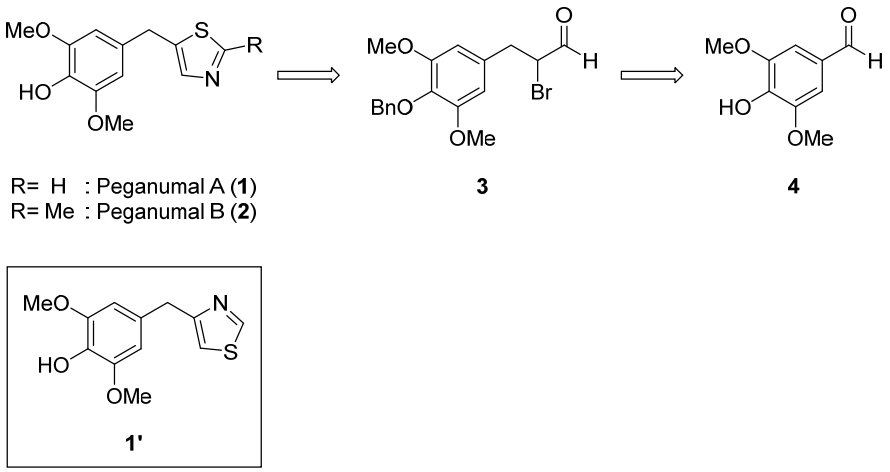


Figure 1. Structure and retrosynthetic analysis of peganumal A (**1**) and B (**2**), and the possible regioisomer of peganumal A (**1′**).

2. Materials and Methods

2.1. General Experimental

Unless otherwise noted, all reactions were performed under an argon atmosphere in oven-dried glassware. The starting materials and solvents were used as received from commercial suppliers without further purification. Thin layer chromatography was carried out using Merck silica gel 60 F254 plates, and visualized with a combination of UV, *p*-anisaldehyde, and potassium permanganate staining. Flash chromatography was performed using Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh). ^{1}H and ^{13}C spectra were recorded on a Bruker 500′54 Ascend (500 MHz) spectrometer at the Center for Bio-medical Engineering Core Facility (Dankook University, Cheonan, Korea), Jeol RESONANCE ECZ 400S (400 MHz), or Bruker Ascend III (700 MHz) in deuterated solvents. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), bd (broad doublet), dd (doublet of doublets), dt (doublet of triplets), or dq (doublet of quartets); the coupling constants are reported in hertz (Hz).

2.2. Ethyl (E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)acrylate (**5**)

Monoethyl malonate (1.2 mL, 11 mmol) was added to the solution of syringaldehyde **4** (1.0 g, 5.5 mmol) and piperidine (0.25 mL) in pyridine (15 mL). After being refluxed for 6 h at 120 °C, the reaction mixture was cooled to ambient temperature and diluted with EtOAc and water. The organic layer was washed with 2N HCl aqueous solution, dried over $MgSO_4$, and concentrated in vacuo. The purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded cinnamate **5** (1.2 g, 89%) as a white solid. LRMS (FAB) *m/z* 253 (M + H$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.9 Hz, 1H), 6.77 (s, 2H), 6.30 (d, *J* = 15.9 Hz, 1H), 5.76 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.91 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 147.4, 147.4, 145.0, 137.2, 126.1, 116.2, 105.2, 105.2, 60.5, 56.5, 56.5, 14.5.

2.3. Ethyl 3-(4-Hydroxy-3,5-dimethoxyphenyl)propanoate (**6**)

To a solution of cinnamate **5** (495 mg, 2.0 mmol) in EtOAc (20 mL) was added a catalytic amount of 5% palladium on activated carbon. The reaction mixture was stirred under a hydrogen atmosphere until TLC analysis showed the complete disappearance of **5**, and was filtered using a Celite pad. The filtrate was concentrated in vacuo. The purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:4) afforded propanate **6** (505 mg, 100%) as a white solid. LRMS (FAB) *m/z* 255 (M + H^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.85, (s, 3H), 3.85 (s, 3H), 2.73 (t, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 147.1, 147.1, 133.3, 131.9, 105.1, 105.1, 60.6, 56.4, 56.4, 36.5, 31.3, 14.3.

2.4. Ethyl 3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)propanoate (**7**)

To a solution of hydroxyphenylpropanate **6** (505 mg, 2.0 mmol) and K_2CO_3 (495 mg, 3.6 mmol) in acetone (20 mL) was added benzyl bromide (0.56 mL, 4.8 mmol) at ambient temperature. The reaction mixture was refluxed for 15 h and cooled to ambient temperature. The reaction mixture was concentrated in vacuo. The residue was dissolved in water and then extracted with ethyl acetate. The combined organic layer was washed with brine and dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded benzyloxyphenylpropanate **7** (665 mg, 97%) as a colorless oil. LRMS (FAB) *m/z* 345 (M + H^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.46 (m, 2H), 7.35–7.26 (m, 3H), 6.40 (s, 2H), 4.96 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 2.89 (t, *J* = 7.8 Hz, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 153.5, 153.5, 138.1, 136.5, 135.6, 128.5, 128.5, 128.2, 128.2, 127.8, 105.5, 105.5, 75.1, 60.5, 56.2, 56.2, 36.2, 31.5, 14.3.

2.5. 3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)propan-1-ol (**8**)

Lithium aluminum hydride (24 mg, 0.8 mmol) at 0 °C was slowly added to a solution of **7** (143 mg, 0.42 mmol) in diethyl ether (4.5 mL). After being stirred at ambient temperature for 5 h, the reaction mixture was cooled to 0 °C, diluted with diethyl ether, and quenched with water followed by saturated Rochelle salt solution. The resulting mixture was then stirred vigorously overnight. The organic layer was washed with brine and dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:1) afforded propanol **8** (119 mg, 94%) as colorless oil. LRMS (FAB) *m/z* 303 (M + H^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.28–7.36 (m, 3H), 6.41 (s, 2H), 4.97 (s, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.92–1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 153.5, 138.1, 137.8, 135.3, 128.5, 128.5, 128.2, 128.2, 127.8, 105.6, 105.6, 75.1, 62.4, 56.2, 56.2, 34.3, 32.6.

2.6. 3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)propanal (**9**)

Dess–Martin periodinane (466 mg, 1.2 mmol) at ambient temperature was slowly added to a solution of propanol **8** (335 mg, 1.1 mmol) in anhydrous CH_2Cl_2. After being stirred for 3 h at the same temperature, the reaction mixture was filtered using a Celite pad. The filtrate was concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:3) afforded propanal **9** (300 mg, 92%) as yellow oil. LRMS (FAB) *m/z* 301 (M + H^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.41 (d, *J* = 7 Hz, 2H), 7.28–7.19 (m, 3H), 6.32 (s, 2H), 4.90 (s, 2H), 3.74 (s, 3H), 3.74 (s, 3H), 2.83 (t, *J* = 7.4 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 153.7, 153.7, 138.1, 136.3, 135.6, 128.6, 128.6, 128.2, 128.2, 127.9, 105.5, 105.5, 75.2, 56.3, 56.3, 45.5, 28.6.

2.7. 3-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-2-bromopropanal (**3**)

To a solution of propanal **9** (233 mg, 0.78 mmol) in anhydrous THF (8 mL) were added 5,5-dibromomeldrum's acid (118 mg, 0.39 mmol) and 6 μL of 35% HCl at ambient temperature. After being stirred for 3 h at the same temperature, the reaction mixture was diluted with EtOAc and quenched with saturated aqueous $NaHCO_3$ solution. The organic

layer was washed with brine and dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded bromopropanal **3** (178 mg, 60%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (d, *J* = 2.6 Hz, 1H), 7.40 (d, *J* = 7.2 Hz 2H), 7.29–7.20 (m, 3H), 6.34 (s, 2H), 4.91 (s, 2H), 4.35–4.38 (m, 1H), 3.74 (s, 3H), 3.74 (s, 3H), 3.35 (dd, *J* = 14.5, 7.1 Hz, 1H), 3.04 (dd, *J* = 14.6, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 153.8, 137.9, 136.4, 132.1, 132.1, 128.6, 128.6, 128.3, 128.3, 127.9, 106.5, 106.5, 75.1, 56.3, 56.3, 54.6, 38.5.

2.8. 5-(4-(Benzyloxy)-3,5-dimethoxybenzyl)thiazole (**10**)

To a solution of bromopropanal **3** (30 mg, 0.079 mmol) in dimethylformamide (1 mL) was added thioformamide [10] (5.3 mg, 0.087 mmol) at ambient temperature. After being stirred at 60°C for 3 h, the reaction mixture was diluted with EtOAc, and quenched with a saturated $NaHCO_3$ solution. The organic layer was washed with brine and dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:2) afforded thiazole **10** (16 mg, 60%) as yellow oil. LRMS (FAB) *m/z* 342 (M + H$^+$); ^{1}H NMR (500 MHz, MeOD) δ 8.75 (s, 1H), 7.57 (s, 1H), 7.35–7.33 (m, 2H), 7.23–7.18 (m, 3H), 6.46 (s, 2H), 4.82 (s, 2H), 4.06 (s, 2H), 3.68 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.9, 152.7, 140.9, 138.7, 138.0, 136.1, 135.1, 128.6, 128.6, 128.3, 128.3, 127.9, 105.8, 105.8, 75.2, 56.3, 56.3, 33.4.

2.9. 5-(4-(Benzyloxy)-3,5-dimethoxybenzyl)-2-methylthiazole (**11**)

According to the synthetic procedure of thiazole **10**, methylthiazole **11** (176 mg, 83%) was obtained as a yellow solid from bromopropanal **3** (226 mg, 0.60 mmol) by using thioacetamide (49 mg, 0.66 mmol) instead of thioformamide. LRMS (FAB) *m/z* 356 (M + H$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.1 Hz, 2H), 7.22–7.16 (m, 3H), 7.15 (s, 1H), 6.30 (s, 2H), 4.87 (s, 2H), 3.91 (s, 2H), 3.68 (s, 3H), 3.68 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 153.9, 153.9, 138.6, 138.5, 138.0, 136.1, 135.0, 128.6, 128.6, 128.3, 128.3, 128.0, 105.8, 105.8, 75.2, 56.3, 56.3, 33.7, 19.1.

2.10. Peganumal A (**1**)

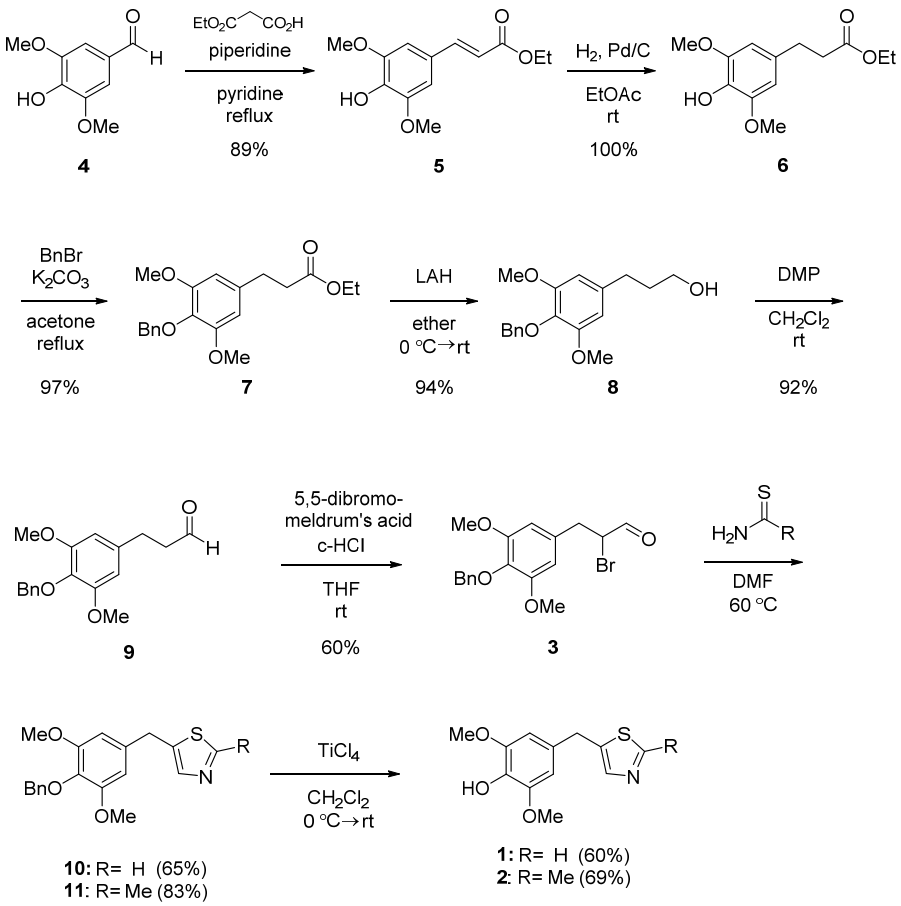
A total of 1 M solution of titanium tetrachloride in methylene chloride (0.04 mL, 0.040 mmol) at 0 °C was slowly added to a solution of **10** (9 mg, 0.024 mmol) in anhydrous methylene chloride. After being stirred at ambient temperature for 4 h, the reaction mixture was diluted with EtOAc, and quenched with a saturated $NaHCO_3$ solution. The organic layer was washed with brine and dried with $MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography (EtOAc:*n*-hexane = 1:1) afforded peganumal A (**1**; 5.4 mg, 89%) as a white solid. The NMR spectra data were consistent with the previously reported [4]. HRMS (FAB) calcd for $C_{12}H_{14}NO_3S^+$ (M + H$^+$): 252.0689; found 252.0695; ^{1}H NMR (500 MHz, DMSO) δ 8.91 (1H, d, *J* = 0.6 Hz), 8.21 (1H, s), 7.70 (1H, d, *J* = 0.6 Hz), 6.52 (1H, s), 6.52 (1H, s), 4.08 (2H, s), 3.71 (3H, s), 3.71 (3H, s); ^{13}C NMR (125 MHz, DMSO) δ 153.1, 148.0, 148.0, 140.5, 139.4, 134.2, 130, 105.9, 105.9, 56.0, 56.0, 31.9.

2.11. Peganumal B (**2**)

According to the synthetic procedure of peganumal A (**1**), peganumal B (**2**; 88 mg, 69%) was obtained as a white solid from **11** (176 mg, 0.50 mmol) by using 1 M solution of titanium tetrachloride in methylene chloride (0.75 mL, 0.75 mmol). The NMR spectra data were consistent with the previously reported [4]. HRMS (FAB) calcd for $C_{13}H_{16}NO_3S^+$ (M + H$^+$): 266.0845; found 266.0855; ^{1}H NMR (500 MHz, DMSO) δ 8.21 (brs, 1H), 7.38 (s, 1H), 6.50 (s, 1H), 6.50 (s, 1H), 3.98 (s, 2H), 3.71 (s, 3H), 3.71 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 164.1, 148.0, 148.0, 139.1, 138.8, 134.2, 130.1, 105.9, 105.9, 56.0, 56.0, 32.3, 18.8.

3. Results and Discussion

As shown in Scheme 1, the syntheses of **1** and **2** commenced with decarboxylative aldol condensation between syringaldehyde **4** and diethyl malonate to yield ethyl cinnamate **5**. Hydrogenation of **5**, using palladium on activated carbon as a catalyst, quantitatively afforded ethyl propanate **6**, which was subjected to benzyl protection to provide benzyloxyphenylpropanate **7**. With **7** in hand, several sets of synthetic routes were investigated for the synthesis of α-bromoaldehyde **3**, a key intermediate in Hantzsch thiazole synthesis. When propanate **7** was fully reduced to propanol **8** using lithium aluminum hydride (LAH), followed by oxidation using Dess–Martin periodinane (DMP), propanal **9** was readily obtained in high yield. The α-Bromination of slightly unstable propanal **9** using 5,5-dibromomeldrum's acid and concentrated HCl, afforded α-bromoaldehyde **3** in the best yield (60%). The Hantzsch thiazole synthesis of α-bromoaldehyde **3** using thioformamide or thioacetamide, provided 2*H*–thiazole **10** and 2-methylthiazole **11**, respectively, in moderate yields. The debenzylation of benzyloxybenzenes (**10** and **11**) using titanium tetrachloride readily afforded the desired 2,6-dimethoxyphenols (**1** and **2**) in moderate yields (60% and 69%, respectively). The spectral data of synthesized **1** and **2** (see Tables S1 and S2 in the Supporting Information) were identical to those previously reported for peganumal A and B, respectively.



Scheme 1. Synthesis of peganumal A (**1**) and B (**2**).

4. Conclusions

The concise total synthesis of peganumal A and B, rare natural thiazoles derived from *Peganum harmala* L., has been accomplished for the first time, in eight steps with overall yields of 17.5% and 25.7%, respectively. The 5-benzylthiazole skeleton possessing methyl or hydrogen at the 2-position was efficiently constructed via the Hantzsch thiazole synthesis of the α-bromoaldehyde intermediate. Moreover, as expected, the spectral data of synthetic

2*H*–thiazole **1** were identical to those previously reported for peganumal A. The synthesis allowed the confirmation of the structure of peganumal A. Further studies on the biological properties of peganumals are underway and will be reported in due course.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/app12010078/s1, Table S1: ^{1}H- and ^{13}C-NMR assignment of peganumal B, and Table S2: ^{1}H- and ^{13}C-NMR assignment of peganumal A.

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Conflicts of Interest: The authors declare no conflict of interest.

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