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Aristolactams and Flavanones from *Dasymaschalon wallichii* (Hook.f. & Thomson) Jing Wang & R.M.K.Saunders and Their α-Glucosidase Inhibitory Activity

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Abstract

The first phytochemical investigation of the twig and leaf extracts of *Dasymaschalon wallichii* led to the isolation and identification of 10 compounds, including 6 airstolactam alkaloids (**1**-**6**), 3 flavonoids (**7**-**9**) and one chalcone (**10**). The structures were elucidated through the analysis of NMR spectroscopic data and comparisons with those reported in the literature. Compounds **1**-**4** and **7**-**10** were evaluated for their α-glucosidase inhibitory activity. Among them, aristolactam AII (**1**) and 8-formyl-5,7dihydroxyflavanone (**8**) showed α-glucosidase inhibitory activity with IC_{50} values of 62.9 and 83.9 μM, respectively, which are better than the positive control (acarbose, IC_{50} = 178.2 μM). The potential binding modes of active compounds with α-glucosidase were also analyzed by molecular docking.

Keywords: *Dasymaschalon wallichii*, Anonaceae, α-glucosidase inhibitory activity, Aristolactam alkaloids, Flavonoids, Chalcone

Introduction

Diabetes mellitus (DM) is a chronic and non-communicable disease. It arises due to metabolic disorder, resulting in elevated levels of glucose in the bloodstream. Non-insulin-dependent or type 2 diabetes mellitus contributes approximately 90 - 95 % of all cases. In 2019, the number of people suffering from diabetes was estimated at 463 million, showcasing a significant rise in the number of patients diagnosed with this condition. It is expected that the trend of diabetes patients in the year 2045 will reach up to 700 million cases [1,2]. Chronic hyperglycemia has been regarded as one of the major causes of various fatal complications, including diabetic retinopathy, kidney failure, and nerve damage, and raises the risk of foot ulcers [3]. The inhibition of main carbohydrates digesting enzymes such as α-glucosidase is a significant way to control hyperglycemia. The inhibitors of these enzymes can decrease carbohydrate digestion, which delays the rate of glucose absorption [4]. However, some undesirable side effects from hypoglycemic agents or diabetes medications are inevitable. Thus, the finding of alternative inhibitors from bioactive compounds is urgently required.

The genus *Dasymaschalon* belongs to the family Annonaceae, which comprises about 40 species distributed in Africa and Southeast Asia, particularly in Thailand and the Malaysian Peninsula [5,6]. Previous phytochemical investigations on plants of this genus resulted in the isolation of a number of flavonoids [7,8], terpenoids [8], acetogenins [9], cyclohexene oxides [10], and alkaloids [11-13]. Some of these compounds exhibited several interesting biological activities, including cytotoxicity [10-12], anti-HIV [10,12], anti-inflammatory [10], antibacterial [12], antimalarial [11], and α-glucosidase inhibitory activities [14]. Suthiphasilp *et al*. [14] reported α-glucosidase inhibitory activity of 3 compounds isolated from the EtOAc extract of *D. dasymaschalum* twigs collected from Hat Yai District, Songkhla Province, Thailand. Two amide derivatives: paprazine displayed potent α-glucosidase inhibitory activity with an IC_{50} value of 4.5 μM; and *N-trans*-feruloyl tyramine exhibited good inhibitory with an IC_{50} value of 24.7 μM. In addition, 8-hydroxynaringenin-4′-methyl ether, a flavanone derivative, showed a weak α-glucosidase inhibitory activity with an IC_{50} value of 256.5 μM. To date, the phytochemical investigation, as well as the α-glucosidase inhibitory activity of *D. wallichii*, have not been reported. Our preliminary experiments demonstrated that the EtOAc extract of *D. wallichii* twigs possesses good α-glucosidase inhibitory activity. In order to explore the diversity of the structures, studies on the chemical constituents of *D. wallichii* have been carried out. Herein, we report the isolation and structural elucidation of ten known compounds (**1-10**) from the leaf and twig extracts of *D. wallichii* and evaluate their α-glucosidase inhibitory activity.

Materials and methods

General experimental procedures

The ^{1}H NMR spectra were measured using a 500 MHz Bruker AV-500 spectrometer with TMS as the internal standard. Chemical shifts are reported in parts per million (δ), and coupling constants (J) are expressed in Hertz (Hz). Quick column chromatography (QCC) and column chromatography (CC) were performed on silica gel C60 (0 - 20 μm, SiliCycle® Inc., Québec, QC G1P 4S6, Canada) and silica gel G60 (60 - 200 μm, SiliCycle® Inc., Québec, QC G1P 4S6, Canada), respectively. Reversed-phase silica gel C18 (40 - 63 μm, Merck) was used in reverse-phase column chromatography. Sephadex LH-20 (25 - 100 μm, Merck, Kenilworth, New Jersey, United States) was also used for column chromatography. Precoated TLC plates of silica gel 60 F254 were used for analytical purposes. HPLC was performed using an Agilent Technology HPLC 1260 Infinity II system, coupled to a 1260 Infinity II Diode Array Detector HS and equipped with a C-18 column.

Plant materials

D. wallichii twigs and leaves were collected in May 2023 from Narathiwat Province, Thailand. The plant was identified by Mr. Abdulromae Baka (Independent Research Group on Plant Diversity in Thailand, Sichon, Nakhon Si Thammarat, 80120, Thailand). The voucher specimen (MFU-NPR0218) was deposited at the Natural Products Research Laboratory, School of Science, Mae Fah Luang University.

Extraction and isolation

The air-dried twigs (0.6 kg) and leaves (0.8 kg) of *D. wallichii* were individually macerated in EtOAc (10 L) over 3 days. Each extracted solution was evaporated under reduced pressure to provide 11.3 and 30.6 g of twig and leaf extracts, respectively.

The twig extract (11.3 g) was subjected to Sephadex-LH20 (100 % MeOH) to give 4 fractions (DTA−DTD). Fraction DTB (3.1 g) was further separated by Sephadex-LH20 (1:4 v/v, CH_2Cl_2−MeOH) to obtain 3 fractions (DTB1−DTB3). Fraction DTB1 (346.2 g) was purified by column chromatography (CC) over silica gel (3:2 v/v, EtOAc−hexanes) to give 5 subfractions (DTB1a−DTB1e). Compound **6** (1.1 mg)

was obtained from the fraction DTB1d (13.7 mg) via repeated silica gel CC (2:3 v/v, EtOAc−hexanes). Fraction DTB1e (47.3 mg) was purified by CC over silica gel (1:1 v/v, EtOAc−hexanes) to obtain compounds **1** (1.6 mg), **2** (1.5 mg), and **3** (5.5 mg). Fraction DTB2 (52.9 mg) was fractionated by Sephadex-LH20 (100 % MeOH) to give 3 fractions (DTB2a−DTBb2c). Fraction DTB2a (15.1 mg) was further separated by semipreparative C_{18} RP-HPLC (2:3 v/v, MeCN–H_2O, 2 mL/min) to yield compounds **4** (1.5 mg, t_R 20.2 min) and **5** (1.1 mg, t_R 22.7 min) (**Figure 1**).

The leaf extract (30.6 g) was subjected to QCC over silica gel (100 % hexanes to 100 % EtOAc), yielding 7 fractions (DLA−DLG). Fraction DLB (7.8 g) was subjected to a C_{18} reverse-phase silica gel CC (1:4 v/v, MeOH–H_2O) to afford 3 fractions (DLB1–DLB3). Fraction DLB2 (130.1 mg) was further purified by CC over silica gel (1:4 v/v, EtOAc−hexanes) to obtain compounds **8** (2.5 mg) and **10** (3.2 mg). Fraction DLB3 (98.1 mg) was separated by Sephadex LH-20 (1:4 v/v, CH_2Cl_2−MeOH), yielding compound **9** (3.3 mg). Fraction DLD (104.0 mg) was chromatographed by CC using C_{18} reversed-phase silica gel (1:4 v/v, MeOH–H_2O) to yield 3 fractions (DLD1−DLD3). Compound **7** (12.6 mg) from the fraction DLD1 (52.8 mg) via repeated silica gel CC (100 % CH_2Cl_2) (**Figure 2**).

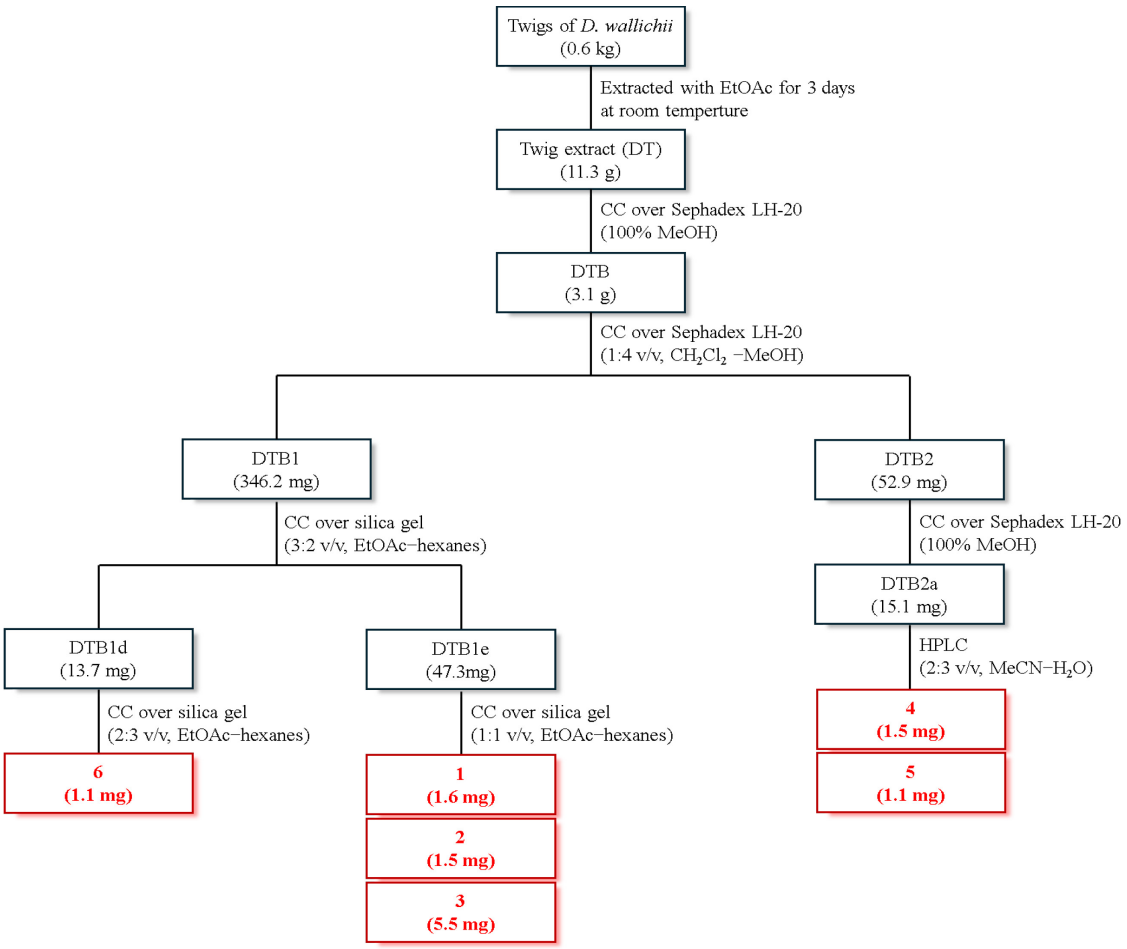

Figure 1 Flowchart of the extraction and isolation of compounds **1-6** from the twig extract.

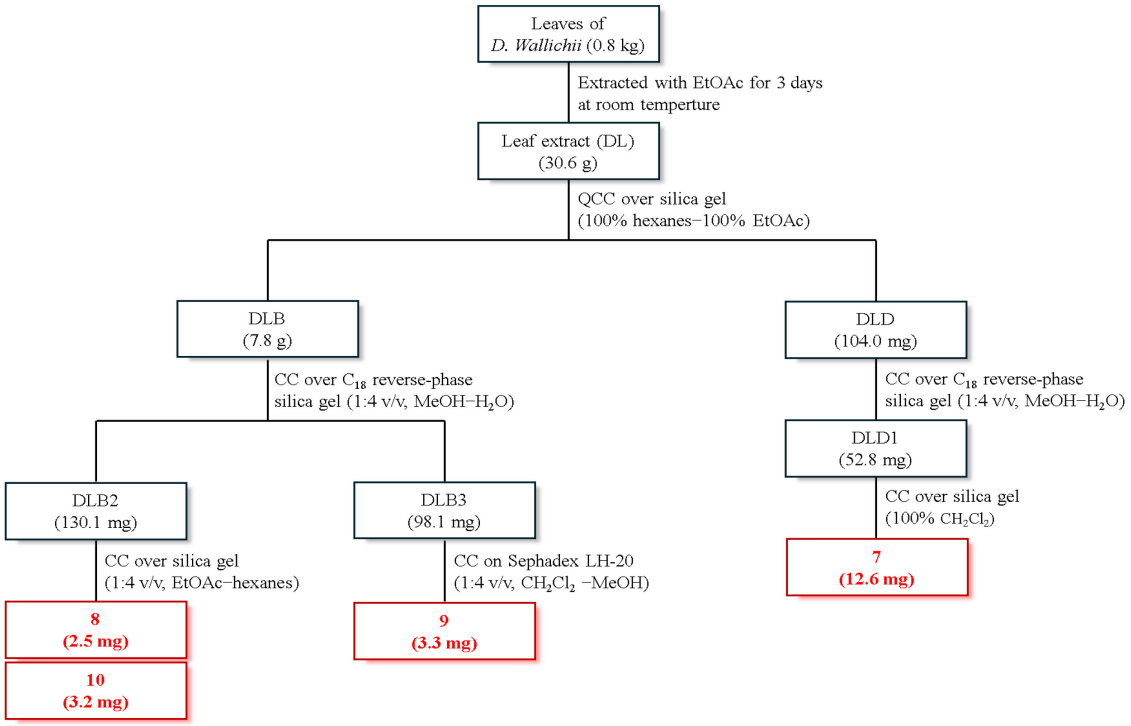

Figure 2 Flowchart of the extraction and isolation of compounds **7-10** from the leaf extract.

α-Glucosidase inhibitory assay

The α-glucosidase inhibitory activity of tested compounds was measured using a spectrophotometric method according to literature reports with slight modifications [15,16]. The yeast α-glucosidase enzyme (0.05 U/mL) and 1mM *p*-nitrophenyl-*α*-*D*-glucopyronoside (*p*-NPG) were dissolved in 0.1 M phosphate buffer (pH 6.9). The experiment was determined on 96-well plates. A 50 µL of tested compounds and a 50 µL of enzyme were incubated at 37 °C for 10 min. After incubation, 50 µL of substrate was added and incubated for a further at 37 °C for 20 min. Finally, 100 µL of 0.3 M Na_2CO_3 was added to terminate the reaction. The activity was quantified by measuring the absorbance at 405 nm. Acarbose was used as a standard drug, and all samples were evaluated in triplicate at different concentrations to obtain the IC_{50} value.

Molecular docking

Molecular docking studies were conducted based on Auto Dock Tools 1.5.4 (ADT), Auto Dock 4.2 programs, and the Lamarckian genetic algorithm (LGA). The structures of compounds were sketched by Gaussview and Gaussian 03 W. The structure of α-glucosidase enzyme [PDB entry code: 2QMJ] was obtained from the Protein Data Bank (http://www.rcsb.org/pdb). A grid box size of 60×60×60 points with a spacing of 0.375 Å between the grid points was implemented and covered almost the entire *α*-glucosidase protein surface [17].

Results and discussion

Compounds isolated from leaves and twigs of D. wallichii

The EtOAc extracts of the leaf and twig of *D. wallichii* were separated and purified by various chromatographic techniques to afford 10 known compounds (**Figure 3**). The compounds were identified as aristolactam AII (**1**) [13,18], taliscanine (**2**) [14], velutinam (**3**) [14,18], piperlactam C (**4**) [13],

dasymachalolactam A (**5**) [14], oldhamactam (**6**) [13], cryptostrobin (**7**) [19], 8-formyl-5,7-dihydroxyflavanone (**8**), 8-formyl-7-hydroxy-5-methoxyflavanone (**9**), and 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone (**10**) [20] by NMR spectroscopic data and comparisons made with NMR spectroscopic data reported in the literature.

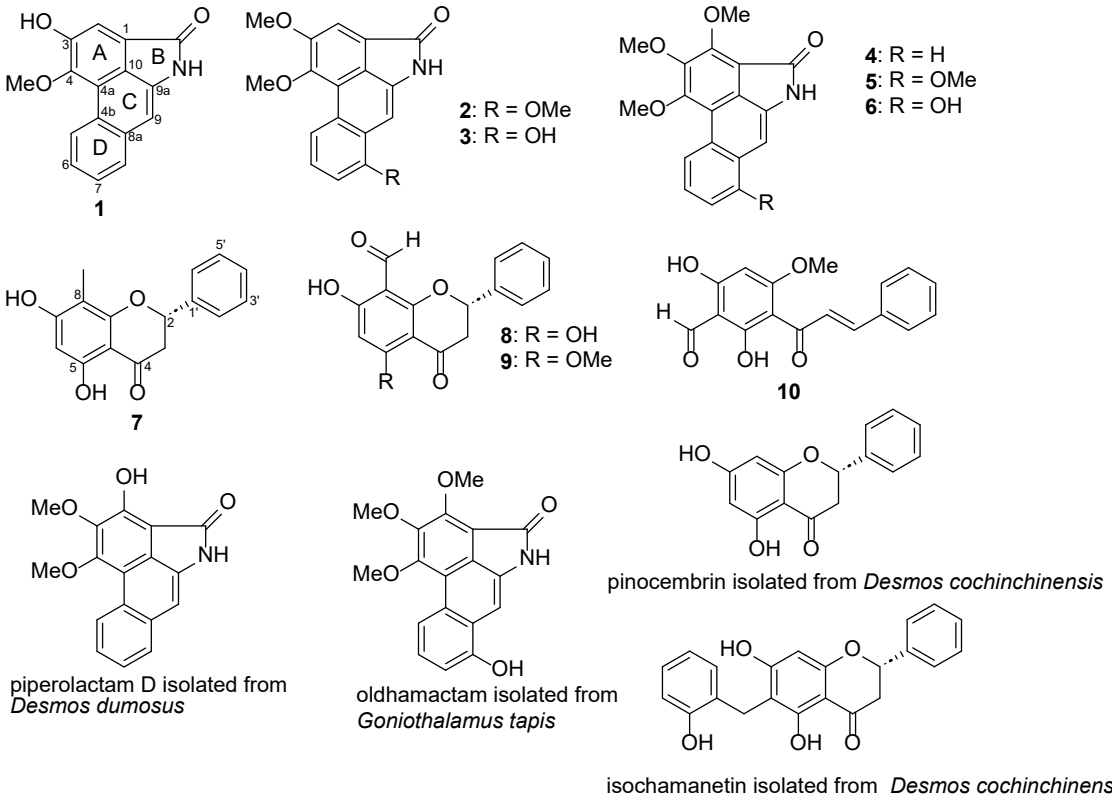

Figure 3 Compounds isolated from *D. wallichii* and related compounds previously reported from other genera of the Annonaceae family.

Compounds **1**-**6** are aristolactam alkaloids, which displayed ^{1}H NMR resonance for an *N*H at ca. δ_H 9.85 - 9.91 (**Figure 4**). Aristolactam **1** (aristolactam AII) displayed 2 substituted groups, hydroxy (C-3) and methoxy (C-4) groups, on the A ring; however, aristolactams **2** (taliscanine) and **3** (velutinam) displayed dimethoxy (C-3 and C-4) groups. In addition, aristolactams **2** and **3** also contained methoxy and hydroxy groups, respectively, on the D ring. In contrast, aristolactams **4** (piperlactam C), **5** (dasymachalolactam A), and **6** (oldhamactam) were fully substituted by 3 methoxy groups on the A ring. For D ring substitution (C-8), aristolactam **4** was an aromatic proton, whereas **5** and **6** revealed methoxy and hydroxy groups, respectively. Compounds **7** (cryptostrobin), **8** (8-formyl-5,7-dihydroxyflavanone), and **9** (8-formyl-7-hydroxy-5-methoxyflavanone) were identified as simple flavanone derivatives. Flavanone **7** contained a methyl group at C-8, whereas flavanones **8** and **9** were a formyl group (**Figure 5**). The structure of flavanone **9** also contained an additional methoxy group at C-5. Compound **10** (3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone) was identified as a simple chalcone derivative containing hydroxy, formyl, hydroxy, and methoxy groups at C-2′, C-3′, C-4′, and C-6′, respectively.

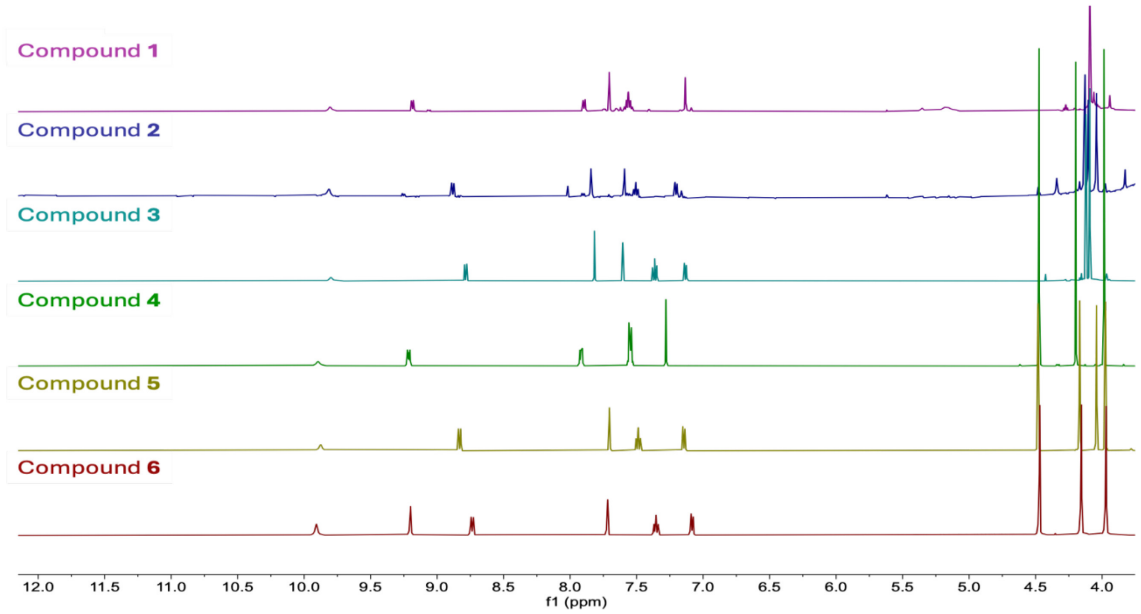

Figure 4 ^{1}H NMR spectra of compounds **1-6**.

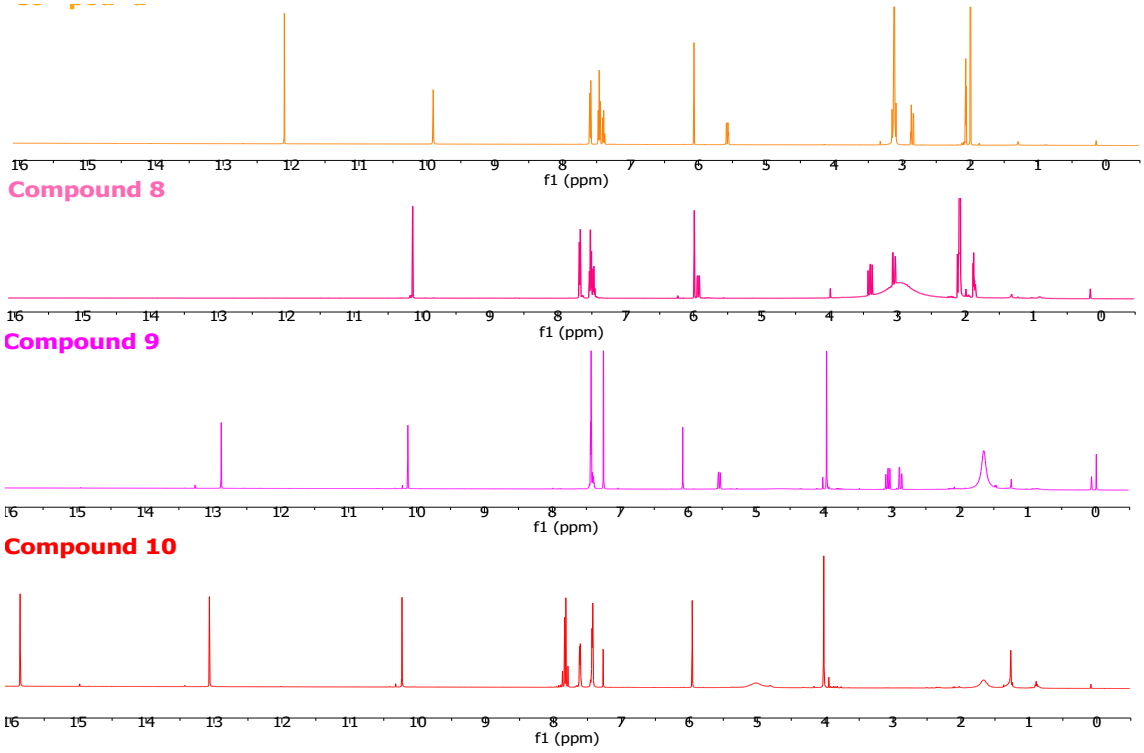

Figure 5 ^{1}H NMR spectra of compounds **7-10**.

Aristolactam alkaloids have been reported in several genera of the Annonaceae; however, they are one of the major compounds found in the *Dasymachalon* genus [13,14]. Previous phytochemical investigations reported that aristolactam AII (**1**), piperlactam C (**4**), and oldhamactam (**6**) have been isolated from *Dasymaschalon rostratum* [13]. In the case of taliscanine (**2**), velutinam (**3**), and dasymachalolactam A (**5**), they were previously isolated from *Dasymaschalon dasymaschalum* [14]. These aristolactams were also reported from another genus, *Goniothalamus*, of the Annonaceae, including *Goniothalamus sesquipedalis* [21], *Goniothalamus marcanii* [22], *Goniothalamus velutinus* [23], and *Goniothalamus amuyon* [24]. In the case of the flavanone and chalcone derivatives, cryptostrobin (**7**) was previously isolated from *Pinus krempfii* (Pinaceae) [19], *Pinus dalatensis* (Pinaceae) [25], and *Myrica serrata* (Myricaceae) [26]. 8-Formyl-5,7-dihydroxyflavanone (**8**), 8-formyl-7-hydroxy-5-methoxyflavanone (**9**), and 3′-formyl-2′,4′-dihydroxy-6′-methoxychalcone (**10**) were previously isolated from *Friesodielsia discolor* [20]. All compounds were isolated for the first time from *D. wallichii*.

α-Glucosidase inhibitory assay

Most of the isolated compounds (**1**-**4** and **7**-**10**) were evaluated for their α-glucosidase activity. Of these, compounds **1** and **8** exhibited good α-glucosidase inhibitory activity with IC_{50} values of 62.9 and 83.9 μM, respectively, which were more active than the positive control (acarbose, IC_{50} = 178.2 μM). All remaining were found to be inactive (**Table 1**). The significantly higher inhibitory activity of compound **1** suggested specific structural features that may enhance α-glucosidase inhibition. In particular, the presence of hydroxy and methoxy groups at the C-3 and C-4 positions, respectively, on ring A appeared to contribute to this increased inhibitory effect. Previously, Suthiphasilp *et al*. [27] reported that piperolactam D, isolated from *Desmos dumosus* (Annonaceae), exhibited potent α-glucosidase inhibitory activity with an IC_{50} value of 10.5 μM. A structural comparison of compound **1** with piperolactam D (**Figure 3**) revealed that while compound **1** possesses a hydrogen atom at C-2, piperolactam D contains a hydroxy group at this position, which may be crucial for enhancing α-glucosidase inhibitory activity. A similar structure-activity relationship was observed in oldhamactam, isolated from *Goniothalamus tapis* [28]. Oldhamactam differs from piperolactam D at the C-8 position. Specifically, piperolactam D features a hydroxy group at C-2 and a hydrogen atom at C-8, whereas oldhamactam (IC_{50} value = 57.9 μM) contains a methoxy group at C-2 and a hydroxy group at C-8. This structural difference may account for the reduced α-glucosidase inhibitory activity of oldhamactam. Compound **1** and oldhamactam, however, displayed the same range of α-glucosidase inhibitory activity.

Table 1 α-Glucosidase inhibitory activities of compounds **1**-**4** and **7**-**10**.

Compounds	**α-Glucosidase inhibitory activity**	
	% Inhibition at 250 *μ*g/mL	**IC_{50}, μM**
1	99.9 ± 0.1	62.9 ± 0.5
2	85.2 ± 0.7	inactive
3	94.3 ± 1.1	inactive
4	98.7 ± 1.2	inactive
7	93.4 ± 0.7	inactive
8	99.8 ± 0.5	83.9 ± 0.7
9	90.1 ± 1.4	inactive
10	88.3 ± 0.8	inactive
Acarbose	68.3 ± 2.2	178.2 ± 1.3

Among the flavanone derivatives (**7-9**), compound **8** exhibited more potent α-glucosidase inhibitory effects compared to compounds **7** and **9**, suggesting that the formyl group at C-8 and the hydroxy group at C-5 may be crucial for α-glucosidase inhibition. Meesakul and co-workers previously reported 2 flavanone derivatives isolated from *Desmos cochinchinensis* with potent α-glucosidase inhibitory activity [29]: pinocembrin (IC_{50} = 4.3 μM) and isochamanetin (IC_{50} = 2.9 μM). A structural analysis reveals that pinocembrin contains 2 hydroxy groups at C-6 and C-8, which may contribute to its enhanced α-glucosidase inhibitory activity compared to compound **8**. Additionally, the 2-hydroxybenzyl moiety of isochamanetin appears to play a crucial role in augmenting its α-glucosidase inhibitory potency (**Figure 3**).

In silico molecular docking of compounds 1 and 8

Compounds **1** and **8** were subjected to molecular modeling to explore their binding modes with α-glucosidase. The results showed that compound **1** could enter the active site of α-glucosidase with a lower binding energy of −7.1 kcal/mol (**Table 2**). As shown in **Figure 6**, residue Asp203 was involved in the formation of hydrophilic interactions (hydrogen bonding) with the hydrogen atom of *NH* (B ring) to enhance the stability of the α-glucosidase-**1** complex. Meanwhile, compound **1** could bind with residues Tyr299, Trp406, Met444, and Phe575 of α-glucosidase *via* the formation of hydrophobic interactions. Compound **8** was able to occupy the active pocket of α-glucosidase with a lower binding energy of –6.7 kcal/mol (**Table 2**). The oxygen atom of the formyl group (8-CHO), and hydrogen atom of the hydroxy group (7-OH), and 2 π-alkyl interactions of the residues Phe575 with the benzene ring A were observed to have a stabilizing effect on the α-glucosidase-**8** complex (**Figure 7**). The docking results indicated that **1** and **8** could reduce the enzyme activity by binding to the active sites of α-glucosidase and thereby blocking substrate access.

Table 2 *In silico* α-Glucosidase inhibitory activities of compounds **1** and **8**.

Compounds	Binding affinity		Hydrophilic interactions (Hydrogen bonding)	Hydrophobic interactions
	Δ***G*** (kcal/mol)	K_i (μM)		
1	−7.1	6.26	Asp203	Tyr299, Trp406, Met444, Phe575
8	−6.7	12.18	Thr205	Phe575
Acarbose	−8.98	0.26	Asp 203, Asp542, Gln603	Phe 450

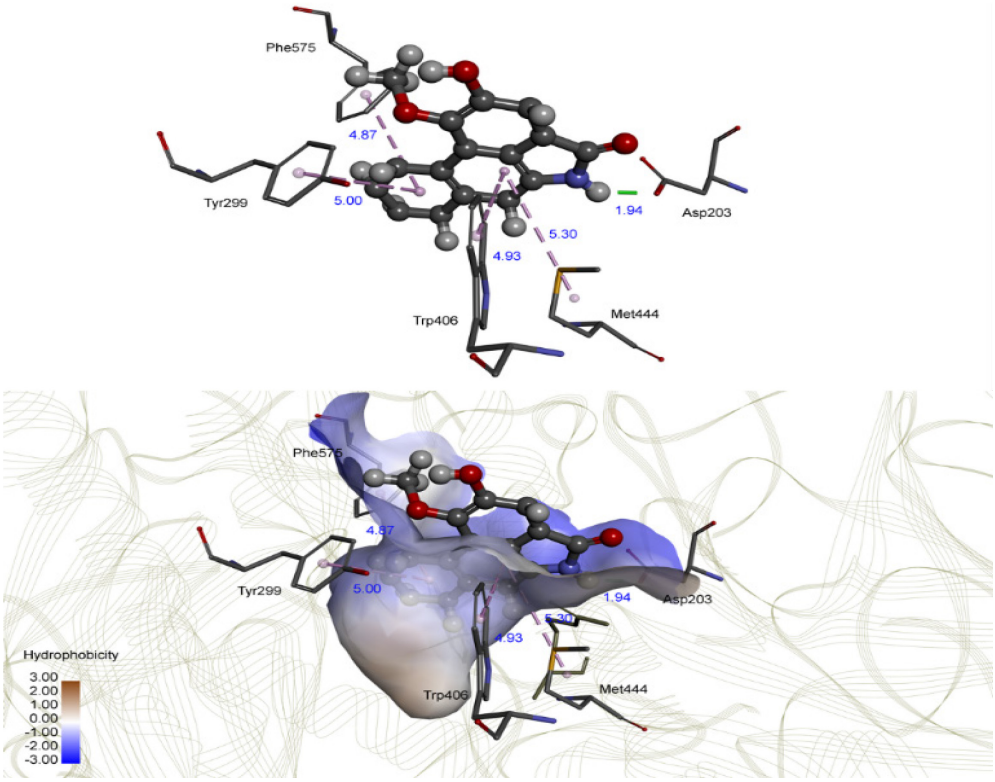

Figure 6 Molecular docking of compound 1 with α-glucosidase.

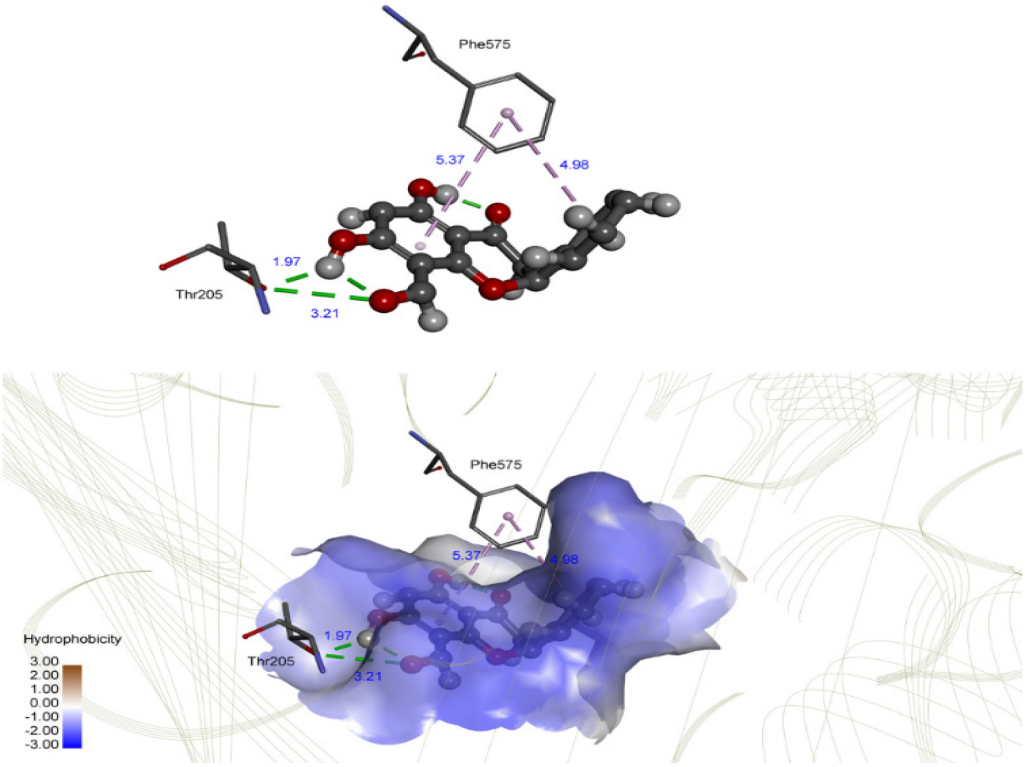

Figure 7 Molecular docking of compound 8 with α-glucosidas.

Conclusions

In summary, the first phytochemical investigation of the twigs and leaves of *Dasymaschalon wallichii* led to the isolation and identification of 10 known compounds, including 6 aristolactams (**1**-**6**), 3 flavanones (**7**-**9**), and 1 chalcone (**10**) were isolated from the twigs and leaves of *D. wallichii*. The analysis of the ^{1}H NMR spectroscopic data clearly elucidated the structures of all isolated compounds. Interestingly, compounds **1** and **8** showed the most potent inhibition against α-glucosidase with the IC_{50} values of 62.9 and 83.9 μM, respectively, stronger than those of the positive control acarbose. The molecular docking indicated that compounds **1** and **8** could exert inhibitory effects by binding to the active sites of α-glucosidase and thereby blocking substrate access. Therefore, the aristolactam and flavanone constituents from *D. wallichii* twigs and leaves could be a potential source of natural α-glucosidase inhibitors.

Acknowledgments

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