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Dasymaschalolactams A-E, Aristolactams from a Twig Extract of Dasymaschalon dasymaschalum

Abstract

Five new aristolactam alkaloids (1-5), dasymaschalolactams A-E, and the first isolation of dasymaschalolactone (17) as a natural product, together with 19 known compounds (6-16 and 18-25) were isolated from the twig extract of *Dasymaschalon dasymaschalum*. Their structures were elucidated by spectroscopic methods as well as comparisons made from the literature. Compounds 20 and 21 showed α -glucosidase inhibitory activities with IC₅₀ values of 4.5 and 24.7 μ M, respectively.

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Dasymaschalolactams A-E, Aristolactams from **a** Twig Extract of *Dasymaschalon dasymaschalum*

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ABSTRACT: Five new aristolactam alkaloids (**1-5**), dasymaschalolactams A-E, and the first isolation of **dasymaschalolactone (17)** as a natural product, together with 19 known compounds (**6-16**, and **18-25**) were isolated from the twig extract of *Dasymaschalon dasymaschalum*. Their structures were elucidated by spectroscopic methods as well as comparisons made from the literature. Compounds **20** and **21** **showed** α -glucosidase inhibitory activities with IC₅₀ values of 4.5 and 24.7 μ M, respectively.

Diabetes mellitus (DM) is a non-communicable disease that has become a major public health problem, affecting 1.6 million people worldwide in 2016.^{1,2} This disease is characterized by hyperglycemia resulting from the inability to produce (type 1) or use insulin (type 2).³ The main risk factor leading to DM, especially type 2, is food consumption⁴ leading to high glucose levels in the blood. α -Glucosidases carry out the digestive breakdown of dietary polysaccharides, oligosaccharides, and disaccharides to glucose,⁵ a key step in the control of the amount of glucose in the blood. Drugs such as acarbose and miglitol used to decrease and control blood glucose levels are available on the market, but these can have undesired side effects and hence lead to poor compliance.⁶ Hence, the discovery of α -glucosidase inhibitors from natural sources that can postpone the release of glucose from dietary carbohydrates and delay glucose absorption without or with less side effects is desirable.

Plants of the genus *Dasymaschalon* are small- to medium sized-trees belonging to the family Annonaceae. This genus consists of about 40 species worldwide that are distributed throughout tropical countries in Asia (particularly in Thailand and the Malaysian peninsular) and Africa. In Thailand, only 12 species are recognized.⁷ Previous phytochemical investigations on this genus have resulted in the isolation of various classes of compounds including flavonoids,⁸ triterpenoids,⁸ alkaloids,^{9,10} neolignans,¹¹ benzyl benzoate derivatives,^{8,11} phenylpropanoids,¹² acetogenins,¹³ and oxygenated cyclohexene derivatives.^{10,14} Some of these compounds have shown interesting biological properties including cytotoxicity,^{8-11,14} antimalarial,¹⁰ anti-inflammatory¹⁴ and anti-HIV effects.^{12,14} *Dasymaschalon dasymaschalum* (Blume) I.M. Turner has many synonym names, including *D. blumei* Finet & Gagnep., *D. coelophloeum* (Scheff.) Merr., and *Desmos dasymaschalus* (Blume) Saff.¹⁵ The powdered stems of this plant have been used as an antipyretic drug.⁹ The isolation of aristolactams, aporphine alkaloids, flavonoids,

benzyl benzoate derivatives, and terpenoids have been reported from this plant.^{8,9} In a preliminary screening of the biological activities of Annonaceae plants, we found that the EtOAc extract of the twigs of *D. dasymaschalum* exhibited good α -glucosidase inhibitory activity with 89% inhibition at 200 μ g/mL, which prompted an investigation of the chemical constituents from this extract. Herein, the isolation, structural elucidation, and α -glucosidase inhibitory activities of the phytochemicals from this plant are described.

Twenty-five compounds, including 11 aristolactam alkaloids (**1-11**), one isoquinoline alkaloid (**12**), four flavonoids (**13-16**), a lactone (**17**), three benzyl benzoate derivatives (**18, 19** and **25**), two amides (**20** and **21**), two polyoxygenated cyclohexenes (**22** and **23**), and one benzene derivative (**24**) were isolated and characterized from the EtOAc extract of the twigs of *D. dasymaschalum*. All of the new compounds (**1-5**) were found to be aristolactam derivatives. Compound **17**, an isobenzofuran-1(3*H*)-one derivative, was isolated for the first time from Nature. The known compounds were characterized as oldhamactam (**6**),^{16,17} velutinam (**7**),¹⁸ enterocarpam-III (**8**),¹⁹ griffithinam (**9**),²⁰ goniopedalin (**10**),²¹ taliscanine (**11**),²¹ duguevalline (**12**),²² desmethoxykanugin (**13**),²³ 7,8-dimethoxy-5-hydroxyflavone (**14**),²⁴ alpinetin (**15**),²⁵ 8-hydroxynaringenin-4'-methyl ether (**16**),²⁶ 7-methoxyisobenzofuran-1(3*H*)-one (**17**),²⁷ benzyl benzoate (**18**),²⁸ 2-methoxybenzyl benzoate (**19**),²⁸ paprazine (**20**),²⁹ *N-trans*-feruloyltyramine (**21**),³⁰ (–)-zeylenol (**22**),³¹ (+)-crotepoxide (**23**),³² 4-hydroxybenzaldehyde (**24**),³³ and 2-phenylethyl benzoate (**25**),³⁴ by comparison of their spectroscopic and physical data with published values.

Dasymaschalolactam A (**1**) was isolated as a yellow viscous oil, and its molecular formula, C₁₉H₁₇NO₅, was deduced from the NMR and the HRESITOFMS data, which displayed an ion at m/z [M + Na]⁺ 362.1001 (calcd for C₁₉H₁₇NO₅Na, 362.1004). The ¹H and ¹³C NMR

data of **1** (Tables 1 and 2) showed resonances for an ABC pattern of aromatic protons [δ_{H} 8.86 (d, $J = 8.5$ Hz, H-5), 7.51 (t, $J = 8.5$ Hz, H-6), and 7.17 (d, $J = 8.5$ Hz, H-7)], one aromatic proton [δ_{H} 7.73 (s, H-9)], four methoxy groups [δ_{H} 4.51 (s, CH₃O-2), 4.19 (s, CH₃O-3), 4.00 (s, CH₃O-4), and 4.07 (s, CH₃O-8)], and one NH proton [δ_{H} 9.86 (brs, NH)]. The latter assignment was consistent with the IR spectrum, which displayed an absorption band at 3224 cm⁻¹.³⁵ The ¹³C NMR spectrum of **1** displayed 19 resonances including those for 14 sp² carbons, one lactam carbonyl carbon, and four methoxy carbons. These NMR spectroscopic data were closely related to that of stigmalactam isolated from *Fissistigma oldhamii*.³⁵ The major difference was the splitting pattern of the aromatic protons on the D ring. Stigmalactam showed an ABX pattern³⁵ for H-5, H-7, and H-8 while compound **1** showed resonances for an ABC pattern for H-5, H-6, and H-7. In addition, an additional methoxy proton resonance was also observed at δ_{H} 4.07 which was assigned to OMe-8 on the basis of the HMBC correlations shown in Figure 1. The structure of compound **1** was determined as shown.

Dasymaschalolactam B (**2**) gave the same molecular formula, C₁₉H₁₇NO₅ [HRESITOFMS m/z 340.1186 (calcd for C₁₉H₁₈NO₅, 340.1185)] as dasymaschalolactam A (**1**). The NMR data (Tables 1 and 2) as well as the HMBC correlations (Figure 1) were almost identical to those of **1**, except that the ¹H NMR spectrum of **2** displayed an ABC pattern for H-6 (δ_{H} 7.16, dd, $J = 7.7$, 1.1 Hz), H-7 (δ_{H} 7.52, t, $J = 7.7$ Hz), and H-8 (δ_{H} 7.49, dd, $J = 7.7$, 1.1 Hz). The HMBC correlations shown in Figure 1 confirmed the structure of dasymaschalolactam B as shown.

The molecular formula of dasymaschalolactam C (**3**) [C₁₈H₁₅NO₅, HRESITOFMS m/z 348.0849 [M + Na]⁺ (calcd for C₁₈H₁₅NO₅Na, 348.0848)] indicated **3** to have one CH₃ group less than **2**. The NMR spectroscopic data of **3** (Tables 1 and 2) were almost identical to those of **2**.

except the methoxy group resonance (δ_{H} 4.09) at C-5 of **2** was replaced by that for a hydroxy group (δ_{H} 10.88) in **3**. This was further confirmed by the HMBC correlations between the OH-5 (δ_{H} 10.88) with C-4b (δ_{C} 113.6), C-5 (δ_{C} 154.7), and C-6 (δ_{C} 113.8). The structure of **3** was established as depicted.

Dasymaschalolactam D (**4**) gave a molecular formula of $\text{C}_{18}\text{H}_{16}\text{NO}_5$, as indicated from its NMR and HRESITOFMS data ($[\text{M} + \text{H}]^+ m/z$ 326.1031, calcd 326.1028). Analysis of the NMR spectroscopic data of **4** (Tables 1 and 2) showed that its structure is closely related to that of **3**. The main difference found was that the methoxy group at C-4 of **3** was replaced by a hydroxy group in **4**. This was further supported by the HMBC correlations shown in Figure 1. Hence, the structure of **4** was proposed as shown.

Dasymaschalolactam E (**5**) showed a molecular formula of $\text{C}_{17}\text{H}_{14}\text{NO}_4$, which was deduced from its NMR and HRESITOFMS data ($[\text{M} + \text{H}]^+ m/z$ 296.0927, calcd 296.0923). Compound **5** was also demonstrated to be an aristolactam derivative, from its ^1H NMR spectroscopic data (Tables 1 and 2), which showed two singlet aromatic proton resonances at δ_{H} 7.71 (s, H-2) and 7.14 (s, H-9), a set of ABX aromatic proton resonances at δ_{H} 9.24 (d, $J = 9.0$ Hz, H-5), 7.19 (dd, $J = 9.0, 2.8$ Hz, H-6), and 7.44 (d, $J = 2.8$ Hz, H-8), and two methoxy group resonances at δ_{H} 3.96 (s, CH_3O -7), 4.13 (s, CH_3O -3). The observed HMBC correlations (Figure 1) confirmed the structure of **5** as shown.

Dasymaschalolactone, [7-methoxyisobenzofuran-1(3*H*)-one] (**17**), showed a protonated molecular ion at m/z 165.0553 $[\text{M} + \text{H}]^+$ (calcd for 165.0552) in the HRESITOFMS, corresponding to the molecular formula $\text{C}_9\text{H}_9\text{O}_3$. Compound **17** was a simple isobenzofuran-1(3*H*)-one derivative that displayed ^1H NMR resonances for an ABC pattern of aromatic protons [δ_{H} 7.16 (dd, $J = 7.5, 0.8$ Hz, H-4), 7.72 (dd, $J = 8.2, 7.5$ Hz, H-5), and 7.11 (d, $J = 8.2$ Hz, H-6)],

one oxymethylene group of **a** lactone ring [δ_{H} 5.28 (s, H-3)], and one methoxy group [3.96 (s, CH₃O-5)]. Compound **17** was one of the key products from the regiocontrolled rearrangement of isobenzofuran.²⁷ **This** is the first report of the isolation of **17** from Nature.

Most of the isolated compounds (**1-4**, **7-8**, **10-11**, **13**, **15-16**, **18-21**, and **24**) were evaluated for their α -glucosidase **activity**. **Of the compounds listed**, amides **20** and **21** exhibited good α -glucosidase inhibitory activities with IC₅₀ values at 4.5 and 24.7 μM , which were more active than the positive control, acarbose, (IC₅₀ value = 73.7 μM) while flavanone **16** showed **a** weaker α -glucosidase inhibitory **activity** (IC₅₀ value = 256.5 μM) than that of acarbose.

EXPERIMENTAL SECTION

General Experimental Procedures. The general information on instruments and chromatographic materials **was** the same as in previous reports.³⁶⁻⁴⁰

Plant Material. The twigs of *D. dasymaschalum* were collected in May 2018 from Kuan Khao Wang Literary Botanic Garden, Chalung, Hat Yai **District**, Songkhla Province, Thailand. **The plant was identified by one of the authors (S.L.) from a comparison with the authentic plant growing in Mae Fah Luang University. A** voucher specimen (MFU-NPR0191) was deposited at the Natural Products Research Laboratory of Mae Fah Luang University.

Extraction and Isolation. The chopped and air-dried twigs of *D. dasymaschalum* (5.6 kg) were extracted with EtOAc (10 L) at room temperature and concentrated under reduced pressure to provide an EtOAc extract (120.7 g). This crude extract was subjected to quick column chromatography (QCC) over silica gel (100% hexanes to 100% EtOAc) to give eight fractions (Fr.D₁–Fr.D₈). Fr.D₂ and Fr.D₃ were combined (8.5 g) and fractionated over Sephadex LH-20 (100% MeOH) to give seven **further** fractions (Fr.D_{2,3}A–Fr.D_{2,3}G). Compounds **22** (3.2 mg) and **23** (6.7 mg) were obtained from Fr.D_{2,3}D (497.5 mg) by CC (3:2 acetone in hexanes).

Purification of Fr.D_{2.3}E (389 mg) by CC (1:3 EtOAc in hexanes) gave **11** (2.6 mg), together with 11 fractions (Fr.D_{2.3}EA–Fr.D_{2.3}EU). Compound **2** (7.2 mg) was obtained from Fr.D_{2.3}EH (10.5 mg) by CC (1:3 EtOAc in hexanes), whereas **1** (3.1 mg, *t_R* 15.4 min), **3** (2.5 mg, *t_R* 17.5 min), and **6** (0.7 mg, *t_R* 20.1 min) were obtained from Fr.D_{2.3}D (120 mg) by RP C₁₈ HPLC (1.2:0.8 CH₃CN in H₂O, 2.0 mL/min). Fr.D₄ and Fr.D₅ were combined (3.3 g) and further separated by CC (1:4 MeOH in CH₂Cl₂) to give six fractions (Fr.D_{4.5}A–Fr.D_{4.5}F). Fr.D_{4.5}B (2.4 g) was subjected to CC (1:4 EtOAc in CH₂Cl₂) to yield six fractions (Fr.D_{4.5}BA–Fr.D_{4.5}BF). Compound **19** (3.7 mg) was isolated from Fr.D_{4.5}BB (35.7 mg) by CC (2:4 EtOAc in hexanes). Purification of Fr.D_{4.5}BD (98.7 mg) by CC (2:4 EtOAc in hexanes) yielded **18** (5.7 mg). Purification of Fr.D_{4.5}C (40.2 mg) over Sephadex LH-20 (100% MeOH) gave **14** (4.2 mg) and **15** (5.1 mg). Fractionation of Fr. D₆ (2.34 g) by Sephadex LH-20 (100% MeOH) gave five fractions (Fr.D₆A–Fr.D₆E). Compound **4** (2.4 mg) was obtained from Fr.D₆C (70.3 mg) by CC (1:4 MeOH in CH₂Cl₂). Fr.D₆E (257.4 mg) was subjected to RP C₁₈ HPLC (1.2:0.8 CH₃CN in H₂O, 2.0 mL/min) to give compound **7** (1.3 mg, *t_R* 20.5 min). Separation of Fr.D₆D (102.7 mg) over Sephadex LH-20 (100% MeOH) yielded six subfractions (Fr.D₆DA–Fr.D₆DF). Compounds **20** (10.5 mg) and **21** (13.5 mg) were isolated from Fr.D₆DD (51.6 mg) by CC (1:4 MeOH in CH₂Cl₂). Fr.D₆DE (30.5 mg) was subjected to Sephadex LH-20 CC (100% MeOH) to yield compounds **12** (0.5 mg) and **16** (3.5 mg). Compounds **5** (3.0 mg), **8** (2.5 mg), **9** (2.0 mg), and **10** (2.1 mg) were obtained from Fr. D₆DF (58.6 mg) by CC (1:3 EtOAc in CH₂Cl₂) while **17** (1.5 mg), **24** (2.5 mg), and **25** (2.1 mg) were obtained from Fr. D₆DB (24.5 mg) by CC (1:4 MeOH in CH₂Cl₂).

Dasymaschalolactam A (1): yellow viscous oil; UV (MeOH) λ_{max} (log ϵ) 358 (2.76), 279 (3.58), 235 (3.52), 214 (3.55) nm; IR (neat) ν_{max} 3224, 2998, 1670, 1448, 1350, 1287 cm⁻¹; ¹H

and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS m/z 362.1001 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_5\text{Na}$, 362.1004).

Dasymaschalolactam B (2): light yellow viscous oil; UV (MeOH) λ_{max} (log ϵ) 399 (2.66), 276 (3.39), 258 (3.44), 229 (3.29), 204 (3.38) nm; IR (neat) ν_{max} 3241, 2939, 1688, 1378, 1083 cm^{-1} ; ^1H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS m/z 340.1186 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_5$, 340.1185).

Dasymaschalolactam C (3): yellow viscous oil; UV (MeOH) λ_{max} (log ϵ) 400 (2.69), 257 (3.52), 233 (3.37) nm; IR (neat) ν_{max} 3203, 2925, 2858, 1694, 1468, 1382 cm^{-1} ; ^1H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS m/z 348.0849 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_5\text{Na}$, 348.0848).

Dasymaschalolactam D (4): brown viscous oil; UV (MeOH) λ_{max} (log ϵ) 396 (2.64), 276 (3.41), 258 (3.47), 233 (3.42), 204 (3.32) nm; IR (neat) ν_{max} 3241, 2935, 1682, 1383, 1260, 1076 cm^{-1} ; ^1H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS m/z 326.1031 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_5$, 326.1028).

Dasymaschalolactam E (5): yellow viscous oil; UV (MeOH) λ_{max} (log ϵ) 335 (3.18), 284 (3.87), 234 (3.72), 215 (3.75) nm; IR (neat) ν_{max} 3224, 2942, 1678, 1605, 1376, 1109, 1035 cm^{-1} ; ^1H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS m/z 296.0927 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{17}\text{H}_{14}\text{NO}_4$, 296.0923).

Dasymaschalolactone (17): colorless viscous oil; UV (MeOH) λ_{max} (log ϵ) 295 (3.17), 237 (3.64), 208 (4.35) nm; IR (neat) ν_{max} 2950, 2901, 1750, 1604, 1180 cm^{-1} ; ^1H NMR (600 MHz, acetone- d_6) δ_{H} 7.72 (1H, dd, J = 8.2, 7.5 Hz, H-5), 7.16 (1H, dd, J = 7.5, 0.8 Hz, H-4), 7.11 (1H, d, J = 8.2, H-6), 5.28 (1H, s, H-3), 3.96 (3H, s, OMe-7); ^{13}C NMR (150 MHz, acetone- d_6) δ_{C} 169.5 (C-1), 158.6 (C-7), 150.1 (C-3a), 135.6 (C-5), 113.5, (C-4), 112.9 (C-7a), 110.2 (C-

6), 67.8 (C-3), 59.2 (OMe-7); HRESITOFMS m/z 165.0553 $[M + H]^+$ (calcd for $C_9H_9O_3$, 165.0552).

α -Glucosidase inhibitory Assay. A colorimetric α -glucosidase (Sigma, St. Louis, MO, USA, cat. No. G5003) assay was performed using the previously reported method.⁴⁰ Acarbose was used as a positive control with an IC_{50} value of 73.7 μ M.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

HRESITOFMS, 1D and 2D NMR spectra of new compounds **1-5** and **17** (PDF).

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Notes

The authors declare no competing financial interest.

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Figure 1. Key HMBC correlations for compounds **1-5** and **17**

Table 1. ^1H NMR (600 MHz) Spectroscopic Data of Compounds **1-5** in Acetone- d_6 (δ in ppm, J in Hz)

position	1	2	3	4	5
2					7.71, s
5	8.86, d (8.5)				9.24, d (9.0)
6	7.51, t (8.5)	7.16, dd (7.7, 1.1)	7.06, dd (7.7, 1.4)	7.13, dd (7.6, 1.1)	7.19, dd (9.0, 2.8)
7	7.17, d (8.5)	7.52, t (7.7)	7.49, t (7.7)	7.52, t (7.6)	
8		7.49, dd (7.7, 1.1)	7.45, dd (7.7, 1.4)	7.49, dd (7.6, 1.1)	7.44, d (2.8)
8a					
9	7.73, s	7.19, s	7.29, s	7.20, s	7.14, s
OMe-2	4.51, s	4.44, s	4.14, s	3.90, s	
OMe-3	4.19, s	3.95, s	4.47, s	3.98, s	4.13, s
OMe-4	4.00, s	3.93, s	4.08, s		
OH-5			10.88, s		
OMe-5		4.09, s		4.08, s	
OMe-7					3.96, s
OMe-8	4.07, s				
NH	9.86, br s	9.78, s	9.96, s	9.62, s	9.60, s

Table 2. ^{13}C NMR (150 MHz) Spectroscopic Data Compounds **1-5** in Acetone- d_6 (δ in ppm)

position	1	2	3	4	5
1	108.9	111.4	111.6	104.5	106.5
2	153.6	153.1	151.5	156.5	106.1
3	156.4	156.7	152.7	143.4	147.8
4	146.0	146.5	146.4	149.6	147.6
4a	115.5	114.0	115.1	112.8	120.3
4b	126.7	115.6	113.6	116.1	114.5
5	118.4	157.2	154.7	156.9	128.8
6	124.9	106.6	113.8	106.6	113.4
7	105.9	126.8	127.9	120.6	157.9
8	155.1	120.3	120.2	126.2	109.9
8a	123.8	135.4	135.9	135.3	136.9
9	98.2	104.5	106.3	104.9	103.6
9a	133.5	133.0	133.7	125.9	116.4
10	125.1	126.8	125.5	128.3	123.8
C=O	165.7			166.9	168.2
OMe-2	61.7	61.6	63.3	59.7	
OMe-3	59.8	59.9	61.9	60.1	56.3
OMe-4	60.5	60.3	60.9		
OMe-5		54.8		54.8	
OMe-6					54.3
OMe-7	54.8				

Table of Content

Dasymaschalon dasymaschalum

α -glucosidase inhibitory (IC₅₀)

20: H (4.5 μ M)
21: OMe (24.7 μ M)