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

Virayu Suthiphasilp
Mae Fah Luang University

Wisanu Maneerat
Mae Fah Luang University

Raymond J. Andersen
University of British Columbia

Piyaporn Phukhatmuen
Mae Fah Luang University

Stephen G. Pyne
University of Wollongong, spyne@uow.edu.au

See next page for additional authors

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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 μM, respectively.

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Authors

Virayu Suthiphasilp, Wisanu Maneerat, Raymond J. Andersen, Piyaporn Phukhatmuen, Stephen G. Pyne, and Surat Laphookhieo

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Virayu Suthiphasilp, [†, ‡] Wisanu Maneerat, [†, ‡] Raymond J. Andersen, [§] Piyaporn Phukhatmuen, [†, ‡] Stephen G. Pyne[#] and Surat Laphookhieo[*, †, ‡]

[†]Center of Chemical Innovation for Sustainability (CIS) and [‡]School of Science, Mae Fah Luang University, Chiang Rai 57100, Thailand

[§]Department of Chemistry and Department of Earth, Ocean & Atmospheric Sciences, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T 1Z1

[#]School of Chemistry and Molecular Biosciences, University of Wollongong, Wollongong, New South Wales 2522, Australia

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 IC_{50} values of 4.5 and 24.7 μM, 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 consumption[4] 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-inflammatory[14] 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 μg/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, $C_{19}H_{17}NO_5$, was deduced from the NMR and the HRESITOFMS data, which displayed an ion at *m/z* $[M + Na]^+$ 362.1001 (calcd for $C_{19}H_{17}NO_5Na$, 362.1004). The ^1H and ^{13}C 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, CH_3O-2), 4.19 (s, CH_3O-3), 4.00 (s, CH_3O-4), and 4.07 (s, CH_3O-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 ^{13}C NMR spectrum of **1** displayed 19 resonances including those for 14 sp^2 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 pattern[35] 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, $C_{19}H_{17}NO_5$ [HRESITOFMS *m/z* 340.1186 (calcd for $C_{19}H_{18}NO_5$, 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**) [$C_{18}H_{15}NO_5$, HRESITOFMS *m/z* 348.0849 $[M + Na]^+$ (calcd for $C_{18}H_{15}NO_5Na$, 348.0848)] indicated **3** to have one CH_3 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 $C_{18}H_{16}NO_5$, as indicated from its NMR and HRESITOFMS data ($[M + H]^+$ *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 $C_{17}H_{14}NO_4$, which was deduced from its NMR and HRESITOFMS data ($[M + H]^+$ *m/z* 296.0927, calcd 296.0923). Compound **5** was also demonstrated to be an aristolactam derivative, from its ^{1}H 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 $[M + H]^+$ (calcd for 165.0552) in the HRESITOFMS, corresponding to the molecular formula $C_9H_9O_3$. Compound **17** was a simple isobenzofuran-1(3*H*)-one derivative that displayed ^{1}H 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, CH_3O-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 IC_{50} values at 4.5 and 24.7 µM, which were more active than the positive control, acarbose, (IC_{50} value = 73.7 µM) while flavanone **16** showed a weaker α-glucosidase inhibitory activity (IC_{50} 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 ($Fr.D_1$–$Fr.D_8$). $Fr.D_2$ and $Fr.D_3$ 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 C_{18} HPLC (1.2:0.8 CH_3CN in H_2O, 2.0 mL/min). Fr.D_4 and Fr.D_5 were combined (3.3 g) and further separated by CC (1:4 MeOH in CH_2Cl_2) 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 CH_2Cl_2) 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. D_6 (2.34 g) by Sephadex LH-20 (100% MeOH) gave five fractions (Fr.D_6A–Fr.D_6E). Compound **4** (2.4 mg) was obtained from Fr.D_6C (70.3 mg) by CC (1:4 MeOH in CH_2Cl_2). Fr.D_6E (257.4 mg) was subjected to RP C_{18} HPLC (1.2:0.8 CH_3CN in H_2O, 2.0 mL/min) to give compound **7** (1.3 mg, t_R 20.5 min). Separation of Fr.D_6D (102.7 mg) over Sephadex LH-20 (100% MeOH) yielded six subfractions (Fr.D_6DA–Fr.D_6DF). Compounds **20** (10.5 mg) and **21** (13.5 mg) were isolated from Fr.D_6DD (51.6 mg) by CC (1:4 MeOH in CH_2Cl_2). Fr.D_6DE (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. D_6DF (58.6 mg) by CC (1:3 EtOAc in CH_2Cl_2) while **17** (1.5 mg), **24** (2.5 mg), and **25** (2.1 mg) were obtained from Fr. D_6DB (24.5 mg) by CC (1:4 MeOH in CH_2Cl_2).

*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 $[M + Na]^+$ (calcd for $C_{19}H_{17}NO_5Na$, 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}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS *m/z* 340.1186 $[M + H]^+$ (calcd for $C_{19}H_{18}NO_5$, 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}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS *m/z* 348.0849 $[M + Na]^+$ (calcd for $C_{18}H_{15}NO_5Na$, 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}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS *m/z* 326.1031 $[M + H]^+$ (calcd for $C_{18}H_{16}NO_5$, 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}; ^{1}H and ^{13}C NMR, see Tables 1 and 2; HRESITOFMS *m/z* 296.0927 $[M + H]^+$ (calcd for $C_{17}H_{14}NO_4$, 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}; ^{1}H 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 μM.

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).

AUTHOR INFORMATION

Corresponding Author

*Tel: +66-5391-6238. Fax: +66-5391-6776. E-mail: surat.lap@mfu.ac.th (S. Laphookhieo).

ORCID

Raymond J. Andersen: 0000-0002-7607-8213

Stephen G. Pyne: 0000-0003-0462-0277

Surat Laphookhieo: 0000-0002-4757-2781

Notes

The authors declare no competing financial interest.

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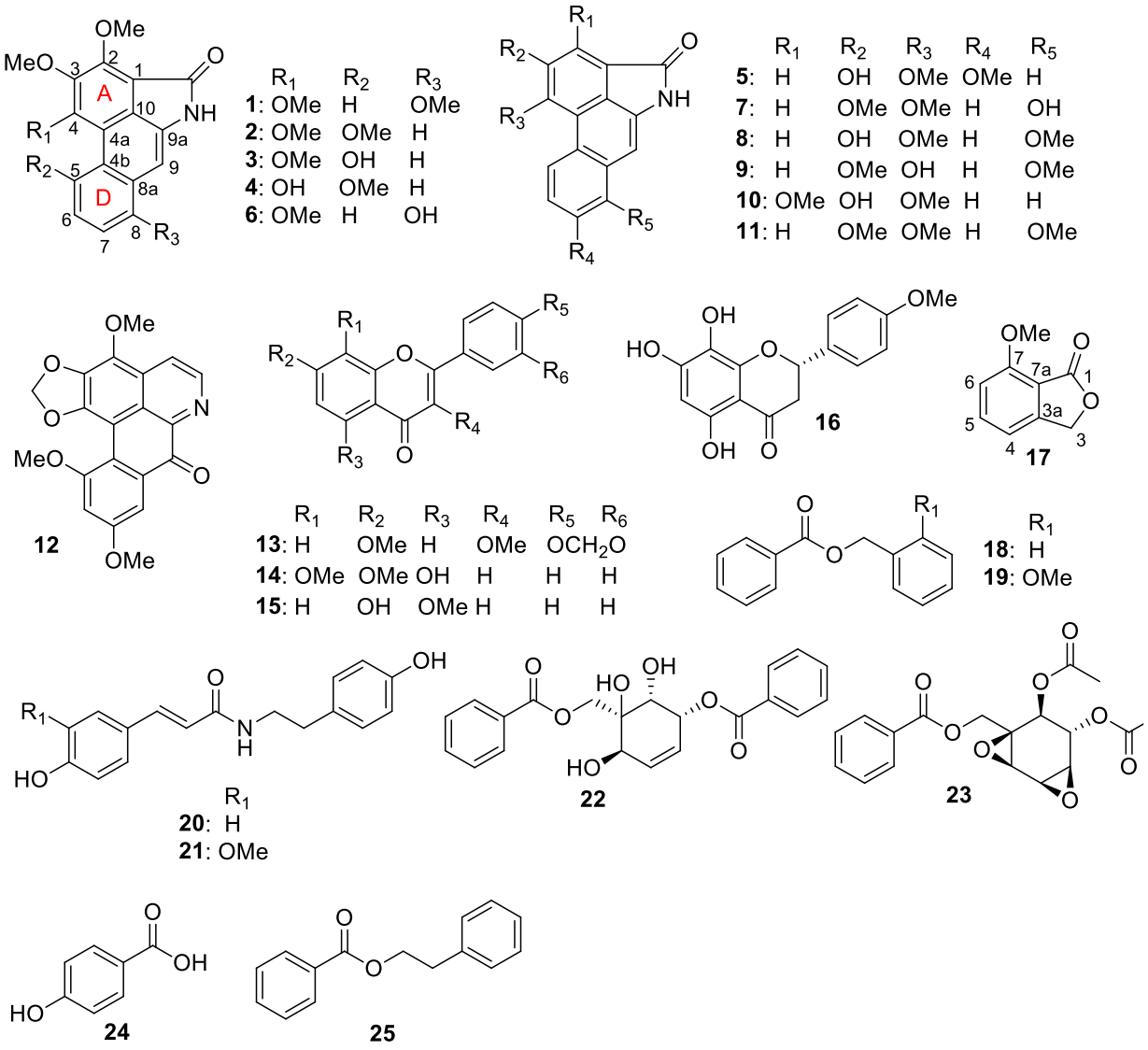

Chart 1. Compounds isolated from the twig extracts of *D. dasymaschalum*.

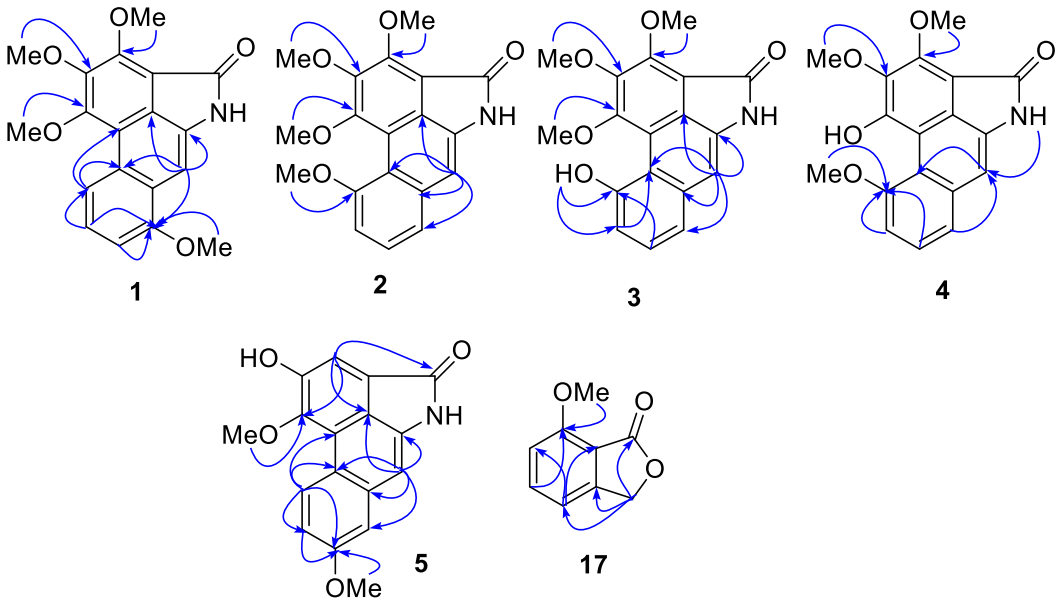

Figure 1. Key HMBC correlations for compounds **1-5** and **17**

Table 1. ^{1}H 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				

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