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Two new compounds from *Melodinus suaveolens*

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ABSTRACT

Two new compounds, 19-hydroxy-melodinine K (1) and melodiside (2), and 25 known compounds were isolated from leaves and twigs of *Melodinus suaveolens*. Their structures were elucidated based on 1- and 2-D NMR, FTIR, UV and MS spectroscopic data. 19-hydroxy-melodinine K showed cytotoxic activity against MDA-MB-231 breast, BCG-823 gastric, SW480 colon and Hela cancer cells.

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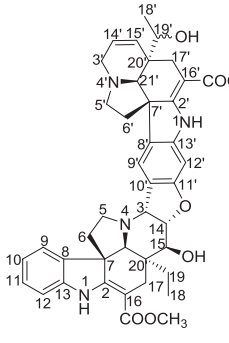
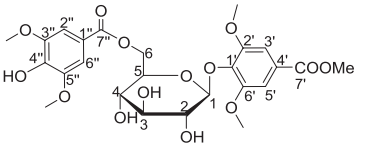


1

(1) 19-hydroxy-melodinine K;



2

(2) melodiside

1. Introduction

Plants of the genus *Melodinus suaveolens* Champ. ex Benth, family Apocynaceae, are woody lianas or sometimes low shrubs naturally distributed in tropical or subtropical Asia and Australia (Li et al. 1995). This genus has been shown to be a good source of monoterpenoid indole alkaloids (Bernauer et al. 1969; Mehri et al. 1978, 1991; Rabaron et al. 1978; Baassou et al. 1983, 1987; Mehri & Plat 1992; He et al. 1994; Zhang et al. 2003). Searches here for novel and/or bioactive alkaloids have identified some representative skeletons and cytotoxic

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compounds from local Yunnan *Melodinus* spp. (Feng et al. 2009; Feng, Cai et al. 2010; Feng, Li, Liu et al. 2010; Feng, Li, Wang et al. 2010; Cai et al. 2011, 2012; Zhang et al. 2016). Many novel alkaloids were obtained from *M. suaveolens* distributed in the Yunnan Province, China (Liu et al. 2012, 2013). In our continual study of alkaloids with cytotoxicity, we paid attention to titled plant from Guangdong Province, China. The present study describes the isolation, structural determination and cytotoxic activities of two new compounds (**1–2**) together with the 25 known ones, scandine (**3**), 10-hydroxy-scandine (**4**), scandine N^b-oxide (**5**), melodinine T (**6**), meloscandonine (**7**), 19-epimeloscandonine (**8**), meloscine (**9**), 11-hydroxytabersonine (**10**), 19-hydroxytabersonine (**11**), 11,19-dihydroxytabersonine (**12**), melodinine M (**13**), venalstonine (**14**), 17α-hydroxyvenalstonine (**15**), melodinine L (**16**), 14α,15α-epoxykopsinine (**17**), 19*R*-vindolinine (**18**), 19*R*-vindolinine N^b-oxide (**19**), 19S-vindolinine N^b-oxide (**20**), stricticine (**21**), compactinervine (**22**), 11-methoxy-14,15-dehydro-16-epivincamine (**23**), scandomelonine (**24**), scandomeline (**25**), 4′-hydroxy-2′,6′-dimethoxyphenol 1-*O*-*β*-D-(6-*O*-syringoyl) glucopyranoside (**26**) and bergenin (**27**).

2. Results and discussion

The MeOH extract of *M. suaveolens* was partitioned between H_2O and EtOAc combination with alkali treatment, and column chromatography on silica gel and C18 silica gel was used to separate the alkaloidal fraction into 27 compounds.

Compound **1** exhibited a positive reaction with Dragendorff's reagent. Its UV spectrum showed absorption maxima characteristic of a *β*-anilinoacrylate chromophore (330 and 242 nm) (Moza et al. 1964), while the IR spectrum showed absorption bands due to OH and NH (3398 and 3290 cm^{-1}) and conjugated ester (1653 cm^{-1}) functions. The molecular formula $C_{42}H_{46}N_4O_7$ was established by HRESIMS *m/z* = 719.3443 $[M + H]^+$, consistent with those of bisindole. In the ^{1}H NMR spectrum (Table S1) of **1**, two singlets at δ_H 9.24 (1H) and 9.33 (1H) suggested two NH groups of indole alkaloids. Two signals at δ_H 0.65 (3H, t, *J* = 7.2 Hz) and 1.00 (3H, d, *J* = 6.5 Hz) were assigned to two methyl groups CH_{3-18}/18′, and singlets at δ_H 3.67 and 3.69 (each 3H, s) were perhaps assigned to two ester methoxyls. In the ^{13}C NMR spectrum of **1** (Table S1), 42 carbon resonances were observed. Of them, six quaternary carbon resonances (δ_C 91.7, 92.8, 165.5, 166.8, 168.7 and 169.0) and two methoxy signals (δ_C 50.9) were readily assigned to two *β*-anilinoacrylate moieties conjugated with a methyl ester unit, respectively. According to the ^{13}C NMR data, compound **1** could be divided into two tabersonine units (Table S1) (Ziegler & Bennett 1973). The coupled protons at δ_H 4.84 (1H, d, *J* = 7.2 Hz, H-X) and 4.94 (1H, dd, *J* = 7.2, 3.5 Hz, H-Y), together with HMBC correlations of δ_H 4.10 (1H, H-15)/δ_C 27.8 (C-19), 86.7 (C-Y) and 60.0 (C-X), revealed the connection of C-X/Y/15, namely: C-3/14/15. In other unit, two singlets at δ_H 7.43 and 6.56 suggested the presence of 10,11-bissubstituted indole ring A. The forth singlet showed HMBC correlation to C-7′ (δ_C 55.8), suggesting it is assigned to H-9′. Likewise, δ_H 6.56 correlating with δ_C 131.1 (s, C-8′) could be assigned to H-12′. Further, up-fielded H-12 and its corresponding carbon signal (δ_C 93.8) suggested oxy-substitute at its adjacent carbon C-11′. The coupling constant (*J* = 6.3 Hz) of H-18′ indicated its neighbour carbon was substituted by hydroxyl, in combination with the HMBC correlations of δ_H 3.57 (19-OH′) and 1.00 (H-18′) with δ_C 66.3 (C-19′). The HMBC correlations of H-3 with δ_C 115.2 (s, C-10′) and δ_C 161.6 (s, C-11′) and 120.1 (d, C-9′) suggested linkage of two units by bonds of C-3/C-10′. Unfortunately, there were no additional HMBC correlations between both the units. However, 22 unsaturation degrees of

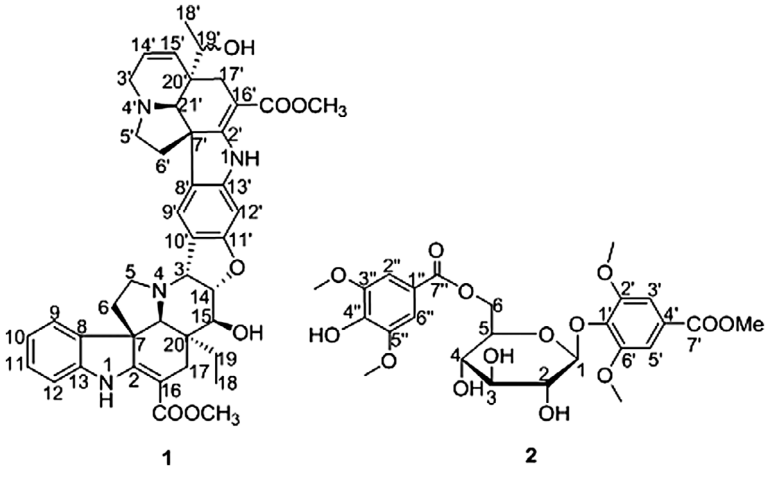

Figure 1. Structures of new compounds **1–2**.

1 implied presence of another ring. Analysis of chemical shifts of C-3/14/10′/11′ further disclosed presence of a furan ring (Kam et al. 1993) inconsistent with molecular model. The ^{13}C NMR data suggested that **1** was similar to melodinine K (Feng, Li, Wang et al. 2010) except for a methylene (δ_C 35.0) in melodinine K was replaced by a methine (δ_C 66.3) in **1**. The ROESY correlations of H-19/H-15 suggested that the both of them were at *α*-orientation. The coupling constants of H-3, H-14 and H-15 suggested that the relative configuration of **1** was the same as that of conophyllidine and melodinine K. The structure of compound **1** was established, therefore, as shown in Figure 1.

Compound **2** was isolated as a white powder. The FTIR spectra of **2** exhibited absorption bands for OH (3342 cm^{-1}), and ester carboxylic group (1712 cm^{-1}) and benzene ring (1616 and 1520 cm^{-1}). Its UV spectrum showed the characteristic absorption bands at 246 and 323 nm. The positive HRESI spectrum showed a sodiated molecular ion peak at *m/z* = 577.1530 [M + Na]$^+$, with a molecular formula of $C_{25}H_{30}O_{14}Na$. The ^{1}H NMR spectrum of **2** displayed two pair of aromatic signals at δ_H 7.06 (s, 2H) and 6.99 (s, 2H), which demonstrated two 1, 3, 4, 5-tetrasubstituted aromatic rings (Shao et al. 2004). Its ^{1}H NMR spectrum (Figure S6) also exhibited two singlets due to five methoxyl groups at δ_H 3.80 (s, 3H) and δ_H 3.70 (s, 12H), respectively. The above information, together with the observation of a methyl ester signal (δ_C 165.6 (s), 52.2 (q)), indicated the presence of two 4-hydroxy-3,5-dimethoxy benzoic units in the molecule. Furthermore, a glucosyl unit (δ_C 101.7, 76.4, 74.2, 74.0, 70.5 and 63.8) was observed in the ^{13}C NMR spectrum of **2**. In addition, HMBC correlations were observed between the anomeric proton signal at δ_H 5.09 (1H, d, *J* = 7.2 Hz) with δ_C 137.9 (C-4′), and between δ_H 4.43 and 4.19 (H-6) with δ_C 165.4 (C-7″). So **2** was determined as shown in Figure 1 and named as melodiside. The *J* value (7.2 Hz) of the anomeric proton of the sugar moieties revealed the *β*-configuration of the glucosyl residue. The identification of the sugar residue was continued by hydrolysis with 10% HCl to afford D-glucose which was confirmed by comparison with authentic samples and determination of their optical rotation values ($[\alpha]_D^{20} = +19.5°$) (Eskander et al. 2005)

Other compounds **3–27** were identified by comparison of their NMR spectroscopic data with the literature. Compounds **1–27** were evaluated for their cytotoxicity against four

human cancer cell lines. Only **1** showed moderate cytotoxicity against MDA-MB-231, BCG-823, SW480 and Hela cell lines, with IC_{50} values of 1.43, 1.84, 4.96 and 2.15 μM, respectively, while by comparison, cisplatin gave IC_{50} values of 4.43, 11.84, 15.33 and 16.56 μM. The other compounds were found to be inactive under these conditions.

3. Experimental

3.1. General experimental procedures

UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer (Shimadzu Corp., Kyoto, Japan). Scanning IR spectroscopy was performed on a Tenor 27 spectrophotometer using KBr pellets. ESI and HRESI mass spectroscopy were performed on Bruker HCT/Esquire and API QSTAR Pulsar 1 spectrometer (Applied Biosystems, Ltd., Warrington, UK). 1D- and 2D- NMR spectra were obtained on Bruker DRX-500 and AM-400 MHz spectrometers (Bruker BioSpin GmBH, Rheinstetten, Germany) with TMS as an internal standard. Column chromatography (CC) was performed on silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd, Qingdao, China) and C_{18}-silica gel (20–45 μm, Fuji Silysia Chemical Ltd.). Fractions were monitored by TLC on silica gel plates (GF254, Qingdao Haiyang Chemical Co., Ltd.) and spots were visualised with Dragendorff's reagent spray. Medium pressure liquid chromatography (MPLC) was employed using a Buchi pump system coupled with C_{18}-silica gel-packed glass columns (15 × 230 and 26 × 460 mm). High-performance liquid chromatography (HPLC) was performed using a Waters 1525EF pump (Waters Corp., Milford, MA, USA) coupled with a HPLC Sunfire and Xbridge C18 columns (250 × 19 mm) and Cosmosil C18 columns (250 × 20 mm). The HPLC system employed a Waters 2998 photodiode array detector and a Waters fraction collector III (Waters Corp.).

3.2. Plant material

Leaves and twigs of *M. suaveolens* Champ. ex Benth were collected in July 2012 in *Zhongshan*, Guangdong Province, P.R. China, and identified by Dr. Xi-Feng Teng. A voucher specimen (Cai120706) was deposited in the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences.

3.3. Extraction and isolation

After being dried and powdered, 11 kg of *M. suaveolens* leaves and twigs were extracted with MeOH (3 × 50 L) at room temperature, and the solvent were removed *in vacuo*. The residue was dissolved in 0.3% aqueous hydrochloric acid (v/v), basified with 5% aqueous ammonia to pH 8–9 and partitioned with EtOAc (3 × 3 L). The EtOAc phase (21 g) was subjected to CC over silica gel (300 g) and eluted with a $CHCl_3$–acetone gradient (from 1:0 to 2:1, v/v) to produce seven fractions (I–VII). Fraction I (1.5 g) was purified by C_{18} MPLC with a MeOH–H_2O gradient (from 1:1 to 4:1, v/v) to yield subfractions I-1~6. Compound **3** (121 mg) was crystallised from subfractions I-5 and fraction II (1.2 g) from methanol. Subfraction I-2 (193 mg) was purified on a Cosmosil preparative C_{18} HPLC column with a gradient of MeOH–H_2O (50:50–70:30, v/v) to yield **17** (7 mg). Subfraction I-4 (55 mg) was further subjected to same HPLC column using a MeOH–H_2O (70:30–80:20, v/v) gradient eluent to yield **14** (6 mg).

Subfraction I-6 (42 mg) was further subjected to sunfire C18 HPLC column using a MeCN–H_2O (40:60–55:45, v/v) gradient eluent to yield **11** (6 mg). Fraction III (5.2 g) was separated on a C_{18} MPLC column with a gradient of MeOH–H_2O (40:60–75:25, v/v) to yield subfraction III-1~6. Subfraction III-1 (77 mg) was further purified on a sunfire C_{18} HPLC column with a gradient of MeCN–H_2O (35:65–55:45, v/v) to afford **7** (21 mg), **8** (6 mg) and **6** (17 mg). Subfraction III-3 (320 mg) was further preparatively purified on a sunfire C_{18} HPLC column with a gradient MeCN–H_2O (35:45–50:37, v/v) to afford subfraction III-3–1~6. Subfraction III-3–1 (34 mg) was purified on a sunfire C_{18} HPLC column with a gradient MeOH–H_2O (50:50–55:45, v/v) to yield **12** (7 mg) and **1** (6 mg). Compounds **21** (17 mg) and **15** (4 mg) were obtained from subfraction III-3–2 (39 mg) on a Xbridge preparative C_{18} column with a gradient MeOH–H_2O (50:50–60:40, v/v). Subfraction III-3–3 (52 mg) was purified on a sunfire C_{18} MPLC column with a MeOH–H_2O gradient eluent (from 50 to 65%, v/v) to yield **13** (11 mg). Alkaloids **3** (6 mg) and **23** (4 mg) were purified on a sunfire C_{18} MPLC column from subfraction III-3–4. Subfraction III-3–6 was further separated on the Xbridge C18 column with a gradient MeOH–H_2O (50:50–65:35, v/v) to yield **17** (7 mg) and **18** (3 mg). Subfraction III-5 (58 mg) was purified by sunfire C_{18} HPLC with a MeOH–H_2O gradient (from 60:40 to 80:20, v/v) to yield **25** (4 mg), **10** (4 mg) and **1** (3 mg). Subfraction III-6 (34 mg) was further separated on a semi-preparative sunfire C_{18} HPLC column with a gradient MeOH–H_2O (70:30–75:25, v/v) to yield **24** (7 mg) and **25** (11 mg). Fraction IV (2.9 g) was purified on a C_{18} MPLC column with a MeOH–H_2O gradient (from 1/1 to 4/1, v/v) to yield subfracti'on IV-1~4. Subfraction IV-2 (74 mg) further was applied to a silica gel column using a petroleum ether–acetone gradient eluent (from 3:1–2:1, v/v) to yield subfraction IV-2–1~2. Subfraction IV-2–1 (51 mg) was further separated on a preparative C_{18} HPLC column with a gradient MeOH–H_2O (30:70–60:40, v/v) to afford **16** (6 mg) and **22** (11 mg). Same column [MeOH–H_2O (25:75–40:60, v/v)] was used to purify subfraction IV-2–2 to obtain **5** (4 mg), **20** (5 mg) and **19** (7 mg). Subfraction IV-2 (46 mg) was further separated on a sunfire C_{18} preparative column with a gradient MeOH–H_2O (30:70–60:40, v/v) to produce **4** (6 mg). Fraction V (2.5 g) was purified on C_{18} column with a MeCN–H_2O gradient eluent (from 13:87 to 25:75, v/v) to yield **9** (3 mg) and **2** (11 mg). Compounds **26** (11 mg) and **27** (14 mg) were crystallised from fractions VI and VII from methanol, respectively.

3.3.1. 19-Hydroxy-melodinine K (1)

White powder: $[\alpha]_D^{20} = -146$ (*c*, 0.30, CH_3OH); UV (CH_3OH) λ_{max}^{MeOH} nm (log ε): 330 (4.34), 242 (3.97); IR (KBr) ν_{max} 3398, 3290, 1653, 1648, and 1435 cm^{-1}; The ^1H NMR (500 MHz) (acetone-d_6) δ_H 9.24 (1H, s, H-1), 9.33 (1H, s, H-1′), 7.43 (1H, s, H-9′), 6.96 (1H, t, *J* = 7.4 Hz, H-11), 6.91 (1H, d, *J* = 7.3 Hz, H-12), 6.56 (1H, s, H-12′), 6.54 (1H, t, *J* = 7.4 Hz, H-10), 6.05 (1H, d, *J* = 7.4 Hz, H-9), 5.86 (1H, overlap, H-14′), 5.84 (1H, overlap, H-15′), 4.94 (1H, dd, *J* = 7.2, 3.5 Hz, H-14), 4.84 (1H, d, *J* = 7.2 Hz, H-3), 4.10 (1H, dd, *J* = 3.5, 7.0 Hz, H-15), 3.69 (3H, s, C′OOMe′), 3.67 (3H, s, COOMe), 3.57 (1H, d, *J* = 6.0 Hz, 19′-OH), 3.55 (1H, dq, *J* = 6.0, 6.3, H-19′), 3.46 and 3.10 (each 1H, m, H-5), 3.01 and 2.42 (each 1H, d, *J* = 14.5 Hz, H-17′), 2.97 (1H, s, H-21′), 2.93 and 2.74 (eac 1H, m, H-3′), 2.89 and 2.92 (each 1H, m, H-5′), 2.65 (1H, s, H-21), 2.68 and 2.57 (each 1H, d, *J* = 15.5 Hz, H-17), 2.08 and 1.74 (each 1H, m, H-6), 1.95 and 1.54 (each 1H, m, H-6′), 1.07 and 0.76 (each 1H, qd, *J* = 14.6, 7.2 Hz, H-19), 1.00 (3H, d, *J* = 6.3 Hz, H-18′), 0.65 (3H, t, *J* = 7.2 Hz, H-18); ^{13}C NMR (125 MHz) spectroscopic data (acetone-d_6) δ_C 169.0 (s, CO_2Me), 168.7 (s, C′O_2Me), 166.8 (s, C-2′), 165.5 (s, C-2), 161.6 (s, C-11′), 146.5 (s, C-13′), 144.6 (s, C-13), 139.0 (s, C-8), 131.1 (d, C-15′), 131.1 (s, C-8′), 128.4 (d, C-11), 126.7 (d, C-14′), 122.1 (d, C-9), 121.2 (d, C-12), 120.1 (d, C-9′), 115.2 (s, C-10′), 110.3 (d, C-10), 93.8 (d, C-12′), 92.8 (s, C-16′), 91.7 (s,

C-16), 86.7 (d, C-14), 70.0 (d, C-15), 67.2 (d, C-21′), 66.3 (d, C-21/19′), 60.0 (d, C-3), 55.8 (s, C-7′), 55.2 (s, C-7), 51.4 (t, C-5), 51.1 (t, C-3′), 50.9 (q, $CO_2\underline{Me}$, C′$O_2\underline{Me}$), 47.5 (s, C-20′), 46.5 (t, C-5′), 46.2 (t, C-6′), 45.6 (s, C-20), 43.1 (t, C-6), 28.5 (t, C-17′), 27.8 (t, C-19), 23.4 (t, C-17), 19.5 (q, C-18′), 7.5 (q, C-18); Positive ESIMS *m/z* 719 $[M + H]^+$; and HRESIMS *m/z* 719.3443 $[M + H]^+$ (calcd. for $C_{42}H_{47}N_2O_7$, 719.3445).

3.3.2 Melodiside (2)

White powder: $[\alpha]_D^{20} = -57$ (*c*, 0.22, CH_3OH); UV (CH_3OH) λ_{max}^{MeOH} nm (log ε): 212 (4.12), 246 (3.42), and 323 (3.34); IR (KBr) ν_{max} 3343, 1712, 1616 and 1520 cm^{-1}; The ^1H NMR (400 MHz) (DMSO-d_6) δ_H 7.06 (2H, s, H-2′, 6′), 6.99 (2H, s, H-2″, 6″), 5.08 (1H, d, *J* = 7.2 Hz, H-1′), 4.43 (1H, d, *J* = 15.0 Hz, H-6), 4.19 (1H, dd, *J* = 15.0, 7.6 Hz, H-6), 3.80 (3H, s, $COO\underline{CH_3}$), 3.70 (12H, s, 3′,5′,3″,5″-OCH_3), 3.44 (1H, m, H-5), 3.25 (2H, m, H-3, 2), 3.20 (1H, m, H-4); ^{13}C NMR spectroscopic data (DMSO-d_6) δ_C 165.6 (s, C-7′), 165.3 (s, C-7″), 152.4 (s, C-3′,5′), 147.4 (s, C-3″, 5″), 140.7 (s, C-4″), 137.9 (s, C-41′), 124.6 (s, C-4′), 119.1 (s, C-1″), 106.7 (d, C-2′, 6′, 2″, 6″), 101.7 (d, C-1), 76.4 (d, C-3), 74.2 (d, C-5), 74.0 (d, C-2), 70.5 (d, C-4), 63.8 (t, C-6); 56.2 (q, 3′/5′-OCH_3), 55.9 (q, 3″/5″-OCH_3), 52.2 (q, 7′-OCH_3); positive ESIMS *m/z* 577 $[M + Na]^+$; and HRESIMS *m/z* 577.1530 $[M + Na]^+$ (calcd. for $C_{25}H_{30}O_{14}Na$, 577.1533).

3.4. Cytotoxicity assay

Four human cancer cell lines, MDA-MB-231 breast, BCG-823 gastric, SW480 colon and Hela, were used for cytotoxic assays. Cells were cultured in RPMI-1640 (Sigma–Aldrich, St. Louis, MO, USA) or DMEM medium (Hyclone, Logan, UT, USA), supplemented with 10% foetal bovine serum (Hyclone) in 5% CO_2 at 37 °C. Cytotoxicity assays were performed according to the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) method in 96-well micro plates. Briefly, 100 µL of adherent cell types were seeded into each well of 96-well cell culture plates and allowed to adhere for 12 h before the addition of test compounds. Suspended cell types were seeded at an initial density of 1×10^5 cells/mL just before drug addition. Each tumor cell line was exposed to a test compound at concentrations of 0.04, 0.2, 1.0, 5.0 and 25.0 µM in DMSO in triplicate for 48 h, with cisplatin (Sigma–Aldrich) as the positive control. After treatment, cell viability was assessed, cell growth graphed and IC_{50} values calculated by Reed and Muench's method (Reed & Muench 1938).

4. Conclusions

Alkaloidal fraction of *M. suaveolens* afforded two new compounds, 19-hydroxy-melodinine K (**1**) and melodiside (**2**), and 25 known compounds. 19-hydroxy-melodinine K showed cytotoxic activity against cancer cells, which was consistent with this type skeleton as previously reported in the genus. This type of bisindole could stimulate future phytochemical studies.

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References

Baassou S, Mehri HM, Rabaron A, Plat M. 1983. (+)Melonine and N_B-oxy melonine, a new indoline skeleton. Tetrahedron Lett. 24:761–762.

Baassou S, Mehri H, Plat M. 1987. Alkaloids of *Melodinus celastroides*. Isolation of four new alkaloids. Ann Pharm Fr. 45:49–56.

Bernauer K, Englert G, Vetter W, Weiss EK. 1969. Constitution of *Melodinus* alkaloid (+)-meloscine, (+)-epimeloscine and (+)-scandine. 1. Alkaloid from *Melodinus scandens* Forst. Helv Chim Acta. 52:1886–1905.

Cai XH, Jiang H, Li Y, Cheng GG, Liu YP, Feng T, Luo XD. 2011. Cytotoxic indole alkaloids from *Melodinus fusiformis* and *M. morsei*. Chin J Nat Med. 9:259–263.

Cai XH, Li Y, Liu YP, Li XN, Bao MF, Luo XD. 2012. Alkaloids from *Melodinus yunnanensis*. Phytochemistry. 83:116–124.

Eskander J, Lavaud C, Abdel-khalik SM, Soliman HSM, Mahmoud II, Long C. 2005. Saponins from the leaves of *Mimusops laurifolia*. J Nat Prod. 68:832–841.

Feng T, Cai XH, Li Y, Wang YY, Liu YP, Xie MJ, Luo XD. 2009. Melohenines A and B, two unprecedented alkaloids from *Melodinus henryi*. Org Lett. 11:4834–4837.

Feng T, Cai XH, Liu YP, Li Y, Wang YY, Luo XD. 2010. Melodinines A–G, monoterpenoid indole alkaloids from *Melodinus henryi*. J Nat Prod. 73:22–26.

Feng T, Li Y, Liu YP, Cai XH, Wang YY, Luo XD. 2010. Melotenine A, a cytotoxic monoterpenoid indole alkaloid from *Melodinus tenuicaudatus*. Org Lett. 12:968–971.

Feng T, Li Y, Wang YY, Cai XH, Liu YP, Luo XD. 2010. Cytotoxic indole alkaloids from *Melodinus tenuicaudatus*. J Nat Prod. 73:1075–1079.

He YL, Chen WM, Feng XZ. 1994. Melomorsine, a new dimeric indoline alkaloid from *Melodinus morsei*. J Nat Prod. 57:411–414.

Kam TS, Loh KY, Wei C. 1993. Conophylline and conophyllidine: new dimeric alkaloids from *Tabernaemontana divaricata*. J Nat Prod. 56:1865–1871.

Li PT, Leeuwenberg AJM, Middleton DJ. 1995. Apocynaceae. Flora of China. 16:2.

Liu YP, Li Y, Cai XH, Li XY, Kong LM, Cheng GG, Luo XD. 2012. Melodinines M–U, cytotoxic alkaloids from *Melodinus suaveolens*. J Nat Prod. 75:220–224.

Liu YP, Zhao YL, Feng T, Cheng GG, Zhang BH, Li Y, Cai XH, Luo XD. 2013. Melosuavines A–H, cytotoxic bisindole alkaloid derivatives from *Melodinus suaveolens*. J Nat Prod. 76:2322–2329.

Mehri H, Plat M. 1992. The Structure of scandomelidine, bisindole alkaloid from *Melodinus scandens*. J Nat Prod. 55:241–244.

Mehri MH, Rabaron A, Sevenet T, Plat MM. 1978. Plants of new caledonia. 26. Alkaloids of *Melodinus balansae* var pacivenosus. Phytochemistry. 17:1451–1452.

Mehri H, Baassou S, Plat M. 1991. 10, 10′-Methylene-bis[(+)Na-norvallesamidine], Nb, Nb′-methylene-[bis(+)meloninium] dichloride, Nb′-chloromethylcelastrome-linium chloride and Nb′-chloromethylcelastromelidinium chloride-dimeric alkaloids, possible artifacts in extraction of *Melodinus celastroides* compounds. J Nat Prod. 54:372–379.

Moza BK, Trojánek J, Bose AK, Das KG, Funke P. 1964. The structure of lochnericine and lochnerinine. Tetrahedron Lett. 5:2561–2566.

Rabaron A, Mehri MH, Sevenet T, Plat MM. 1978. Plants of new caledonia. 50. alkaloids of *Melodnus celastroides*. Phytochemistry. 17:1452–1453.

Reed LJ, Muench H. 1938. A simple method of estimating fifty percent endpoints. Am J Hyg. 27:493–497.

Shao ZY, Zhu DY, Guo YW. 2004. Oldhamioside, a new phenolic glucoside from *Daphniphyllum oldhamii*. Chin Chem Lett. 15:52–54.

Zhang YW, Yang R, Cheng Q, Ofuji K. 2003. Henrycinols A and B, two novel indole alkaloids isolated from *Melodinus henryi* Craib. Helv Chim Acta. 86:415–419.

Zhang PZ, Zhang YM, Gu J, Zhang GL. 2016. Two new alkaloids from *Melodinus hemsleyanus Diels*. J Nat Prod. 30:162–167.

Ziegler FE, Bennett GB. 1973. Claisen rearrangement in indole alkaloid synthesis. Total synthesis of (+-)-tabersonine. J Am Chem Soc. 95:7458–7464.