Phytochemistry Letters 46 (2021) 110–113

Contents lists available at ScienceDirect

Phytochemistry Letters

journal homepage: www.elsevier.com/locate/phytol

New triterpene and *nor*-diterpene derivatives from the leaves of *Adinandra poilanei*

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ARTICLE INFO

Keywords:
Adinandra poilanei
18α-oleanane
ent-atisane
nor-diterpene
α-Glucosidase
Cytotoxicity

ABSTRACT

Two new compounds, adinandrolide (**1**) and adipoiloside (**2**), together with twelve known compounds **3**–**14**, were isolated and identified from *Adinandra poilanei* leaves. In the α-glucosidase activity evaluation, compounds **5–7** and **10** strongly inhibited enzyme activity with IC_{50} values ranging from 1.29 ± 0.03 μg/mL to 3.13 ± 0.07 μg/mL. Compounds **9**, **11**, and **13–14** showed significant inhibition with IC_{50} values of 13.01 ± 0.32 μg/mL to 16.00 ± 0.35 μg/mL, while adipoiloside **(2)** displayed moderate inhibitory activity. In addition, pomolic acid (**10**) showed strong cytotoxicity against four tested cancer cell lines.

1. Introduction

The genus *Adinandra,* which are shrubs or evergreen trees in Pentaphylacaceae family, consist of over 100 species distributed in South Asia, China, Japan, and Africa. Thirteen *Adinandra* species in Vietnam have been documented (Ho, 2000; Son et al., 2014). Several *Adinandra* plants have been traditionally used for the treatment of throat cancer, stomach aches, and snake bites (Chi, 2012). However, scientific data on phytochemicals and biological activities of *Adinandra* species are quite limited. Most of the studies focus on *Adinandra nitida* species in China, which has been consumed as a health tea (Shiyacha) and herbal medicine due to its many curative effects, such as reducing blood pressure and blood lipids, antioxidant, and antitumor activity (Chen et al., 2015; Gao et al., 2010; Liu et al., 2010). Previous investigations of *A. nitida* revealed that this species contained flavonoids, flavonoid glycosides, and triterpenoid saponins (Gao et al., 2010; Zhang et al., 2006; Wang et al., 2008; Yuan et al., 2019).

The *Adinandra poilanei* species was found in central provinces of Vietnam, but no chemical or biological studies have been reported. Our preliminary study revealed the methanolic extract of *A. poilanei* leaves exhibited good cytotoxicity against the KB cancer cell line (IC_{50} of 9.41 ± 0.73 μg/mL) and strong α-glucosidase enzyme inhibition (IC_{50} of 0.28 ± 0.03 μg/mL). Herein, we describe the isolation and structural elucidation of phytochemicals from the leaves of *A. poilanei.* The inhibitory effect on the enzyme α-glucosidase and the cytotoxic activity of isolated compounds were also evaluated.

2. Results and discussion

Phytochemical study of the *n*-hexane and EtOAc extracts of the leaves of *A. poilanei* led to the isolation of a new 18α-oleanane triterpene (**1**) and an atisane-type *nor*-diterpene glucoside (**2**) (Fig. 1), together with twelve known compounds **3**–**14**. The known metabolites, including betulinal (**3**), betulin (**4**) (Sholichin et al., 1980), massagenic acid (**5**) (Macías et al., 1998), oleanderolide (**6**) (Fu et al., 2005), plantanic acid (**7**) (Fujoka et al., 1994), ursolic acid (**8**) (Woo et al., 2014), diospyrolide (**9**) (Kuo et al., 2000), pomolic acid (**10**) (Lee et al., 2005), 4,5-dihydroblumenol (**11**) (De Marino et al., 2004), sitoindoside I (**12**) (Zhang et al., 2013), syringaresinol (**13**) (Panyo et al., 2016), and kajiichigoside F1 (**14**) (Yuan et al., 2019), were identified by comparing their NMR data to the previously published literature (Fig. S1).

Compound **1** was isolated as a white amorphous powder. The IR spectrum showed absorption bands at 3375 cm^{-1} (OH group) and 1706 cm^{-1} (C═O). The negative HR-ESI-MS spectrum showed the ion peak *m/z* 507.3235 [M + Cl]- corresponding to the molecular formula of $C_{30}H_{48}O_4$ (calcd. for $C_{30}H_{48}O_4Cl^-$ 507.3247). The NMR spectrum

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https://doi.org/10.1016/j.phytol.2021.10.003
Received 27 July 2021; Received in revised form 5 October 2021; Accepted 6 October 2021
Available online 12 October 2021

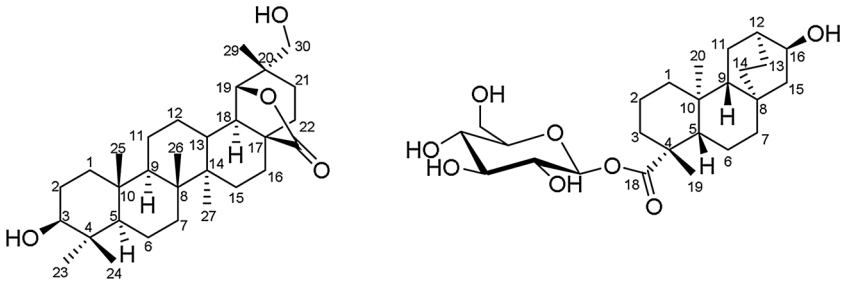

Fig. 1. The chemical structure of compounds **1**–**2**.

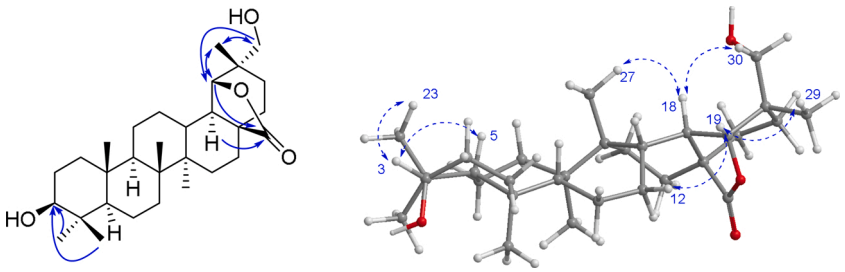

Fig. 2. Key HMBC and NOESY correlations of compound **1**.

revealed characteristic signals of a pentacyclic triterpene with six angular methyl groups at δ_H 1.06, 0.96, 0.94, 0.91, 0.87, and 0.76 (each 3H, s) and two modified methyls as a hydroxymethylene group (δ_H 3.65 [d, $J = 11.0$ Hz] and 3.40 [d, $J = 11.0$ Hz]; δ_C 67.2) and a carbonyl group (δ_C 182.2). The HMBC correlations from oxygenated methine proton H-19 (δ_H 4.28) to C-17 (δ_C 46.7)/C-18 (δ_C 46.8)/C-28 (δ_C 182.2) suggested the presence of a 28,19-γ-lactone ring in **1**. Furthermore, the singlet lactonic proton H-19 at δ_H 4.28 is associated with a 28β,19β-configuration in an 18α-oleanane structure due to the a *quasi* 90 ° angle between H-18α and H-19α (Macías et al., 1996). The hydroxy group was found at the C-30 position based on the HMBC cross-peaks of these hydroxymethylene protons (H-30: δ_H 3.65 and 3.40) to carbon signals C-19 (δ_C 85.5)/C-20 (δ_C 39.0)/C-21 (δ_C 29.2)/C-29 (δ_C 24.0) and NOESY correlations of H-19 (δ_H 4.28) to H-29 (δ_H 1.06) and of H-18 (δ_H 1.97) to H-30 (δ_H 3.65) (Fig. 2). The coupling constants (J = 5.5 Hz and 11.0 Hz) of oxymethine signal at δ_H 3.16 (1H, dd) suggested the remaining hydroxy group was at the 3β position (Macías et al., 1996). Therefore, compound **1** is assigned as 3β,30-dihydroxy-18Hα-oleane-28β,19β-olide, named adinandrolide.

Compound **2** was isolated as a white solid. The molecular formula of **2** was identified as $C_{25}H_{40}O_8$ based on the negative ion peak at m/z 503.2421 $[M + Cl]^-$ in the HR-ESI-MS spectrum (calcd. for $C_{25}H_{40}O_8Cl^-$ 503.2417). The ^{1}H NMR spectrum showed signals of a β-configuration glycoside compound with the anomeric proton at δ_H 5.43 (d, $J = 8.0$ Hz, H-1'), four oxymethine groups at δ_H 3.44–3.33 (4H, H-2', 3', 4', 5'), and a hydroxymethylene group at δ_H 3.84 (1H, dd, $J = 2.0$, 12.0 Hz, H-6'a) and 3.70 (1H, dd, $J = 4.5$, 12.0 Hz, H-6'b). The aglycone moiety had two tertiary methyl groups at δ_H 1.23 and 0.93 (each 3H, s) and an oxymethine proton at δ_H 3.90 (dd, $J = 9.5$, 3.5, 3.0 Hz). The ^{13}C NMR and DEPT spectra showed 25 carbon signals, including six signals of a hexose at δ_C 95.6 (C-1'), 74.1 (C-2'), 78.7 (C-3'), 71.2 (C-4'), 78.7 (C-5'), and 62.5 (C-6'), which suggested a glucopyranosyl moiety (Galala et al., 2016). The aglycone skeleton presented two methyls, nine methylenes, four methines, and four quaternary carbons. The HMBC showed the correlations of H-1' (δ_H 5.43) and methyl group (δ_H 1.23) to the carboxyl group (δ_C 178.2). From the spectral evidence, compound **2** was deduced as glucoside of a tetracylic *nor*-diterpene with an *ent*-atisane or *ent*-kaurane skeleton with a hydroxy group at the C-16 position and a carboxylate ester group at the C-18 or C-19 position, respectively. The chemical shift of C-16 of compound **2** was 70.4 ppm, suggesting the structure of **2** was *ent*-atisane skeleton (Ding et al., 1991). The *ent*-atisane structure was further confirmed by ^{1}H-^{1}H COSY correlations of H-11/H-12/H-16/H-15 and H-12/H-13/H-14 systems. The hydroxy group of C-16 was assigned at β-orientation due to the NOESY correlation of H-16 (δ_H 3.90) to H-13 (δ_H 1.52). On the other hand, the NOESY spectrum showed the cross-peaks of H-5 (δ_H 1.10) and H-6β (δ_H 1.75) to H-19, which suggested the carboxyl group was located at the C-18 position. Other important NOESY cross-peaks between H-20 (δ_H 0.93) and H-2α (δ_H 1.40)/H-6α (δ_H 2.00)/H-14 (δ_H 1.95) and between H-5 and H-9 (δ_H 1.22), together with the lack of correlations between H-16 (δ_H 3.90) and H-20 (δ_H 0.93)/H-11 (δ_H 1.93, 1.20), led to assign the complete stereostructure of **2** (Fig. 3). Thus, **2** was identified as *ent*-17-nor--atisane-16β-hydroxy-18-oic acid β-glucopyranosyl ester, which was named adipoiloside.

Since the MeOH extract of the leaves of *A. poilanei* exhibited strong α-glucosidase enzyme inhibition (IC_{50} value of 0.28 ± 0.03 μg/mL), several isolated compounds showed good α-glucosidase inhibitory activity in the assay (Table S1). Compounds **5–7** and **10** strongly inhibited

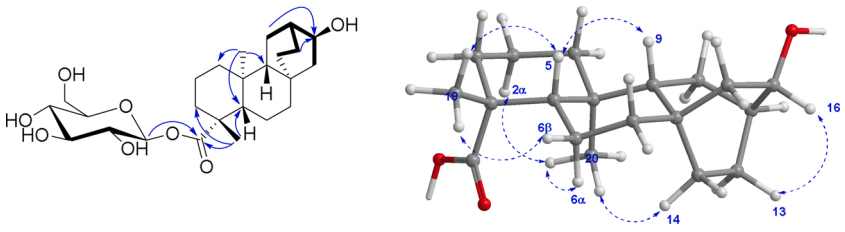

Fig. 3. Key ^{1}H-^{1}H COSY and HMBC correlations of compound **2** and NOESY correlations of the *ent*-atisane aglycone.

enzyme activity with IC_{50} values ranging from 1.29 ± 0.03 μg/mL to 3.13 ± 0.07 μg/mL. Compounds **9**, **11**, and **13–14** showed significant inhibition with IC_{50} values of 13.01 ± 0.32 μg/mL to 16.00 ± 0.35 μg/mL. Adipoiloside **(2)** also showed moderate enzyme α-glucosidase inhibitory activity with an IC_{50} value of 64.05 ± 1.59 μg/mL, while adinandrolide (**1**) was inactive.

The isolated compounds were also evaluated for their cytotoxicity against four cancer cell lines including KB, MCF-7, HepG-2, and Lu-1 using MTT method (Ha et al., 2020). However, only pomolic acid (**10**) showed strong cytotoxicity against all tested cancer cell lines with IC_{50} values ranging from 0.65 ± 0.05 μg/mL to 5.83 ± 0.49 μg/mL. Our results showed that pomolic acid (**10**) made the most significant contribution to the biological activity of the leaves of *A. poilanei*.

3. Materials and methods

3.1. Plant materials

The plant leaves were collected in Bidoup Nui Ba National Park, Lam Dong Province in May 2018 and taxonomically identified as *Adinandra poilanei* by Dr. Luong Van Dung (Department Biology, Dalat University) and Dr. Bui Thu Ha (Department of Botany, Hanoi National University of Education). A voucher specimen (AP-2) was deposited at the Herbarium of the Institute of Marine Biochemistry, Vietnam Academy of Science and Technology.

3.2. General experimental procedures

Optical rotations were determined on a JASCO P-2000 polarimeter. IR spectra were obtained on a Bruker TENSOR 37 FT-IR spectrometer. The 1D and 2D NMR spectra were recorded on an AVANCE III HD 500 spectrometer with tetramethylsilane (TMS) used as an internal standard. High-resolution mass spectra (HR-ESI-MS) were obtained on an Agilent 6530 Accurate-Mass Q-TOF LC/MS system. Column chromatography (CC) was conducted using 230–400 mesh silica gel, Sephadex LH-20, and RP-18 (YMC*GEL, ODS-A, 30–50 μm). Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} (Merck) and RP-18 F_{254S} plates (Merck), and the spots were visualized by spraying with 10 % H_2SO_4 in water, followed by heating. The compound models were generated using MM2 force field calculations in Chem3D Ultra Software Perkin Elmer ver. 18.2.0.48.

3.3. Extractions and isolation of compounds 1 and 2

The dried, powdered stems of *A. poilanei* (3.4 kg) were macerated with MeOH at room temperature (15 L × 4 times ×24 h). The combined filtrate was evaporated under reduced pressure to obtain 242 g crude extract. It was suspended in distilled water then partitioned with *n*-hexane and EtOAc, successively. The organic solvent layers were separated and evaporated *in vacuo* to obtain *n*-hexane (46 g) and EtOAc (104.2 g) residues.

The EtOAc extract was subjected to normal-phase silica gel CC, eluted with gradient solvent of *n*-hexane/EtOAc (from 100:1 to 0:1), which resulted in 6 fractions (E1–E6). Fraction E4 (20.8 g) was applied to normal-phase silica gel CC, eluted with a solvent mixture of CH_2Cl_2/EtOAc (9:1) to obtain 7 subfractions (E4.1–E4.7). Subfraction E4.4 (1.21 g) was purified by normal-phase silica gel CC, eluted with *n*-hexane/EtOAc (8/2, v/v) to give 8 smaller fractions (E4.4.1–E4.4.8). Subfraction E4.4.8 (84 mg) was purified on silica gel CC, eluted with *n*-hexane/EtOAc (7/3, v/v) to afford **1** (5.3 mg). Fraction E6 (13.5 g) was fractionated by Sephadex LH-20 CC using MeOH as eluent to give 6 subfractions (E6.1–E6.6). Subfraction E6.3 (2.3 g) was purified by normal-phase silica gel CC then eluted with *n*-hexane/EtOAc (8/2, v/v) to afford 5 smaller fractions (E6.3.1–E6.3.5). Fraction E6.3.3 (200 mg) was first fractionated by silica gel CC then purified by C18 reversed-phase silica gel CC using gradient elution (20 %–50 % MeOH/water) to obtain compound **2** (9.5 mg).

Table 1
^{1}H (500 MHz) and ^{13}C-NMR (125 MHz) data of compounds **1–2**.

	1 (in $CDCl_3$+CD_3OD)			**2** (in CD_3OD)	
C	δ_H	δ_C	**C**	δ_H	δ_C
1	1.72 (m, 1 H) 0.94 (m, 1 H)	39.7	1	1.63 (m, 1 H) 0.91 (m, 1 H)	40.7
2	1.63 (m, 2 H)	27.4	2	1.95 (m, 1 H) 1.40 (m, 1 H)	19.8
3	3.16 (1H, dd, *J* = 6.0 Hz; 11.0 Hz)	79.1	3	2.20 (brd, *J* = 13.0 Hz, 1 H) 1.10 (m, 1 H)	39.2
4	–	39.4	4	–	45.1
5	0.71 (br d, *J* = 11.0 Hz)	56.3	5	1.10 (m, 1 H)	58.9
6	1.54 (m, 1 H) 1.38 (m, 1 H)	18.8	6	2.00 (m, 1 H) 1.75 (m, 1 H)	21.4
7	1.47 (m, 1 H) 1.38 (m, 1 H)	34.4	7	1.40 (m, 1 H) 1.10 (m, 1 H)	41.1
8	–	40.5	8	–	33.3
9	1.34 (m, 1 H)	52.0	9	1.22 (m, 1 H)	53.0
10	–	37.8	10	–	39.6
11	1.53 (m, 1 H) 1.37 (m, 1 H)	21.5	11	1.93 (m, 1 H) 1.20 (m, 1 H)	22.1
12	1.70 (m, 1 H) 1.06 (m, 1 H)	26.9	12	1.66 (m, 1 H)	34.0
13	1.38 (m, 1 H)	37.1	13	1.52 (m, 2 H)	25.3
14	–	41.2	14	1.95 (m, 1 H) 0.86 (m, 1 H)	27.9
15	1.29 (m, 2 H) 1.25 (m, 2 H)	28.5	15	1.70 (dd, *J* = 13.5, 10.0 Hz) 0.97 (ddd, *J* = 13.5, 3.5, 3.0 Hz)	51.6
16	1.80 (m, 1 H) 1.41 (m, 1 H)	26.1	16	3.90 (ddd, *J* = 9.5, 3.5, 3.0 Hz)	70.4
17	–	46.7	17	–	–
18	1.97 (d, *J* = 11.0 Hz)	46.8	18	–	178.2
19	4.28 (s)	85.5	19	1.23 (s)	29.0
20	–	39.0	20	0.93 (s)	12.8
21	1.44 (m, 2 H) 1.32 (m, 2 H)	29.2	***Glc***		
22	1.70 (m, 1 H) 1.06 (m, 1 H)	32.5	1'	5.43 (d, *J* = 8.0 Hz)	95.6
23	0.96 (s)	28.3	2'	3.37 (m, 1 H)	74.1
24	0.76 (s)	15.8	3'	3.40 (m, 1 H)	78.7
25	0.87 (s)	16.9	4'	3.38 (m, 1 H)	71.2
26	0.94 (s)	15.9	5'	3.40 (m, 1 H)	78.7
27	0.91 (s)	14.0	6'	3.84 (dd, *J* = 2.0 Hz, 12.0 Hz) 3.70 (dd, *J* = 4.5 H, 12.0 Hz)	62.5
28	–	182.2			
29	1.06 (s)	24.0			
30	3.65 (d, *J* = 11.0 Hz) 3.40 (d, *J* = 11.0 Hz)	67.2			

Solvent chemical shifts in CD_3OD + $CDCl_3$: δ_H 7.58 ($CHCl_3$), 4.52 (HDO), 3.36 (CH_3OD); δ_C 78.1 ($CDCl_3$), 49.0 (CD_3OD).
Solvent chemical shifts in CD_3OD: δ_H 4.83 (HDO), 3.36 (CH_3OD); δ_C 49.0 (CD_3OD).

3.3.1. Adinandrolide (1)

White amorphous powder, $[\alpha]_D^{25}$ + 27.7 (c 0.18, MeOH); IR ν_{max} (KBr) 3376, 2940, 1706, 1453, 1381, 1247 cm^{-1}; HR-ESI-MS: *m/z* 507.3235 $[M+^{35}Cl]^-$ and 509.3214 $[M+^{37}Cl]^-$. For ^{1}H-NMR (500 MHz, $CDCl_3$ + CD_3OD) and ^{13}C-NMR (125 MHz, $CDCl_3$ + CD_3OD), see Table 1.

3.3.2. Adipoiloside (2)

White amorphous powder, $[\alpha]_D^{25}$ - 34.3 (c 0.35, MeOH); IR ν_{max} (KBr) 3379, 2899, 1719, 1264, 1220 cm^{-1}; HR-ESI-MS: *m/z* 503.2421 $[M+^{35}Cl]^-$ and 505.2400 $[M+^{37}Cl]^-$. For ^{1}H-NMR (500 MHz, CD_3OD) and ^{13}C-NMR (125 MHz, CD_3OD), see Table 1.

3.4. α-Glucosidase inhibition assay

The *in vitro* α-glucosidase enzyme (G0660, Sigma-Aldrich) inhibition assay of compounds was performed in triplicate following the previously published method (Tran et al., 2014). The sample solution (2 μL dissolved in dimethyl sulfoxide) and 0.5 U/mL α-glucosidase (40 μL) were mixed in 120 mL of 0.1 M phosphate buffer (pH 6.8) were preincubated at 37 °C for 5 min. After incubation, 5 mM *p*-nitrophenyl-α-D-glucopyranoside solution (40 μL) was added, and the solution was incubated again at 37 °C for another 30 min. The absorbance of the resulting mixture was measured at 410 nm by using a microplate reader (Biotek, USA). Acarbose was used as positive control. IC_{50} values of potent inhibitors were determined using the program Table Curve.

3.5. Cytotoxicity assay

The evaluation of cytotoxic activity against the KB, MCF-7, HepG-2, and LU cancer cell lines (ATCC) was previously described in our article (Ha et al., 2020).

4. Conclusion

Two new compounds adinandrolide (**1**) and adipoiloside (**2**), along with thirteen known compounds, were isolated from the leaves of *A. poilanei*. Adipoiloside (**2**) showed moderate α-glucosidase inhibitory activity with IC_{50} value of 64.05 ± 1.59 μg/mL and compounds **5–7**, **9–11**, and **13–14** inhibited enzyme activity, with IC_{50} values ranging from 1.29 ± 0.03 μg/mL to 16.00 ± 0.35 μg/mL. In the cytotoxic assay, pomolic acid (**10**) displayed strong cytotoxicity against all tested cancer cell lines.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

This research is funded by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2018.16. Vu Thi Kim Oanh was funded by Vingroup Joint Stock Company and supported by the Domestic Master/PhD Scholarship Program of Vingroup Innovation Foundation (VINIF), Vingroup Big Data Institute (VINBIGDATA), code VINIF.2020.TS.65.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2021.10.003.

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