Potential anti-allergic acridone alkaloids from the roots of *Atalantia monophylla*

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ABSTRACT

Acridone alkaloids, cycloatalaphylline-A (**1**), *N*-methylcyclo-atalaphylline-A (**2**) and *N*-methylbuxifolia-dine-E (**3**), were isolated from the dichloromethane and acetone extracts of the root of *Atalantia monophylla* along with eight known acridone alkaloids: buxifoliadine-A (**4**), buxifoliadine-E (**5**), *N*-meth-ylatalaphylline (**6**), atalaphylline (**7**), citrusinine-I (**8**), *N*-methylataphyllinine (**9**), yukocitrine (**10**) and junosine (**11**) and two known coumarins: auraptene (**12**) and 7-*O*-geranylscopoletin (**13**). Their struc-tures were elucidated on the basis of spectroscopic analyses. Compounds **2**, **5** and **8** possessed apprecia-ble anti-allergic activity in RBL-2H3 cells model with IC_{50} values of 40.1, 6.1 and 18.7 μM, respectively.

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1. Introduction

Atalantia monophylla (DC.) Corrêa is a plant in the Rutaceae family locally known as "Manao Pee". It is a shrub with a brown bark and thorny branches and is distributed in Southeast Asia, East Bengal, South India and Ceylon (Panda, 2004). Various parts of this plant have been used for folk medicine for several purposes such as the treatment of chronic rheumatism, paralysis (Basa, 1975), anti-spasmodic, stimulant and hemiplegia (Panda, 2004). The essential oil from the leaves showed antimicrobial and strong inhibitory activities against some pathogenic fungi (Prasad, 1988), whereas a decoction of the leaves is often applied for itching and other skin complaints (Panda 2004). In the previous report, limonoids and acridone alkaloids have been isolated from the petroleum ether extract of the root bark (Govindachari et al., 1970; Basu and Basa 1972; Kulkarni and Sabata, 1981). Acridone alkaloids have several biological activities such as inhibition of Epstein-Barr virus (EBV)-EA induction (Itoigawa et al., 2003), induction of human promyelo-cytic leukemia cell (HL-60) differentiation (Kawaii et al., 1999a), and antiproliferative (Kawaii et al., 1999b). We report herein the isolation of three new acridone alkaloids: cycloatalaphylline-A (**1**), *N*-methylcycloatalaphylline-A (**2**), and *N*-methylbuxifolia-dine-E (**3**) from dichloromethane and acetone extracts of *A. mono-phylla* together with eight known acridones: buxifoliadine-A (**4**) buxifoliadine-E (**5**) (Wu and Chen 2000), *N*-methylatalaphylline (**6**) (Basu and Basa 1972; Auzi et al., 1996), atalaphylline (**7**) (Basu and Basa 1972), citrusinine-I (**8**) (Kawaii et al., 1999a; Wu et al., 2001), *N*-methylataphyllinine (**9**) yukocitrine (**10**) and junosine

(**11**) (Auzi et al., 1996) and two known coumarins: auraptene (**12**) (Jiménez et al., 2000; Iranshahi et al., 2007) and 7-*O*-gera-nylscopoletin (**13**) (Rubal et al., 2007). In addition, their anti-aller-gic activity is also discussed (see Figs. 1–3).

2. Results and discussion

The CH_2Cl_2 and acetone extracts from the root of *A. monophylla* were subjected to repeated quick column and column chromatog-raphy over silica gel to furnish three new acridone alkaloids (**1–3**). The basic skeleton of all new compounds was characterized to have a 9-acridone chromophore by two main regions of UV absorption at λ_{max} 250–270 and 390–410 nm (Sangster and Stuart, 1965) and IR absorption at υ_{max} 1639 cm^{-1} (carbonyl of the acridone) (Kulkarni and Sabata, 1981; Bahar et al., 1982). The presence of hy-droxyl functionality (3300–3400 cm^{-1}) was also evident. A $FeCl_3$ test gave a deep green color indicating the presence of the phenolic hydroxyl group. The ^1H NMR singlet signal of a chelated hydroxyl proton was displayed between δ 14.45–14.74 ppm.

Compound **1** was isolated as yellow needles. It showed [M^+] at m/z 377.1626 ($C_{23}H_{23}NO_4$) in the HREIMS spectrum. The ^{13}C NMR and DEPT spectroscopic data (Table 1) exhibited 23 carbons, attrib-utable to four methyl, one methylene, six methine and twelve qua-ternary carbons. In the aromatic region of the ^1H NMR spectrum, three mutually coupling ABX signals at δ 7.76 (1H, *d*, *J* = 7.8 Hz), 7.25 (1H, *br d*, *J* = 7.8 Hz), and 7.12 (1H, *t*, *J* = 7.8 Hz), were attrib-uted to H-8, H-6 and H-7, respectively. A prenyl group in the mol-ecule was inferred by the resonances at δ 5.17 (1H, *br t*, *J* = 7.2 Hz, H-2″), 3.61 (2H, *d*, *J* = 7.2 Hz, 2H-1″), 1.99 and 1.76 (each 3H, *s*, Me-5″, Me-4″ respectively). The remaining signals at δ 6.77, 5.71 (each 1H, *d*, *J* = 9.9 Hz, H-1′, H-2′, respectively), and 1.49 (6H, *s*, Me-4′,

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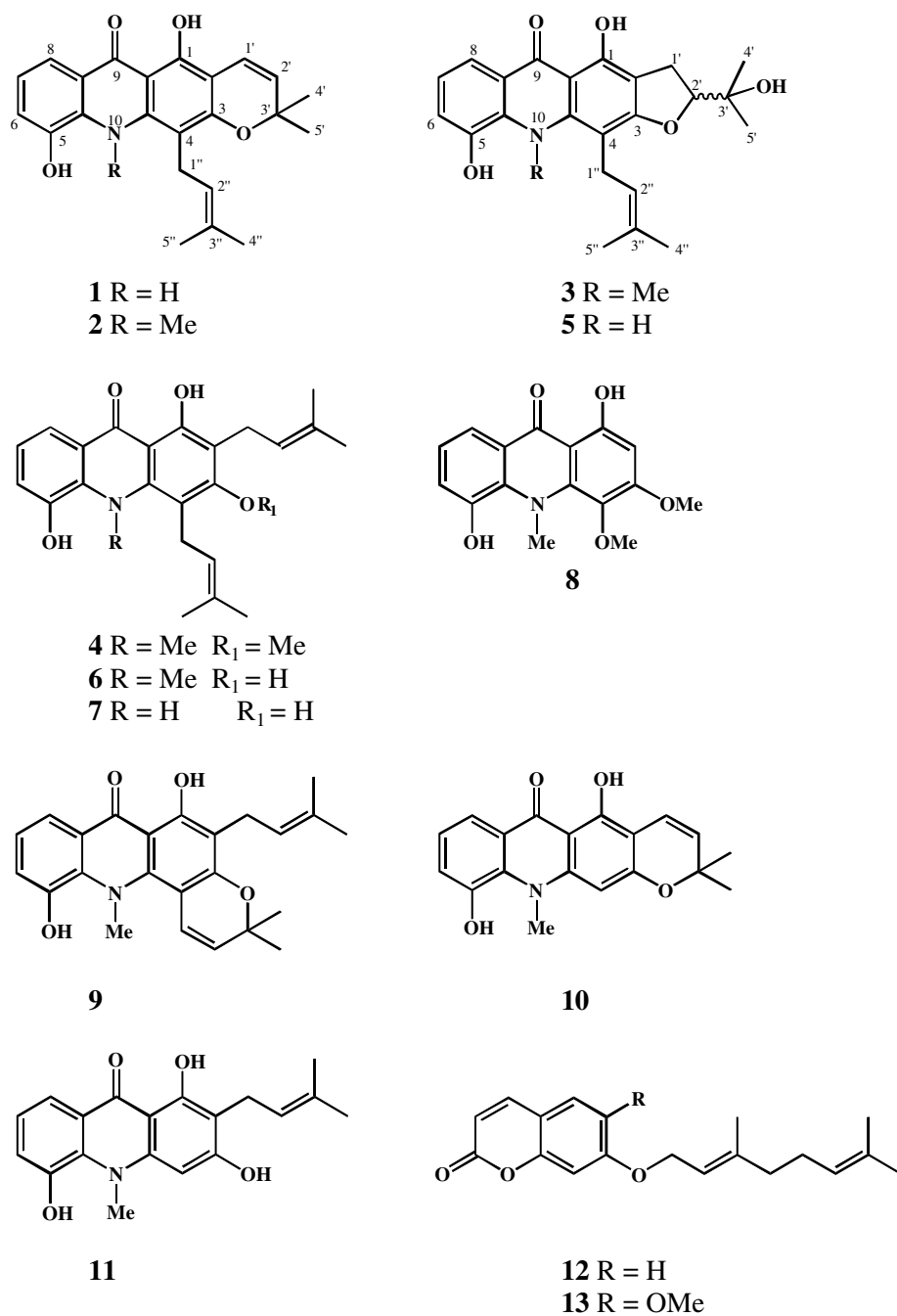*E-mail address:* chanita.p@psu.ac.th (C. Ponglimanont).
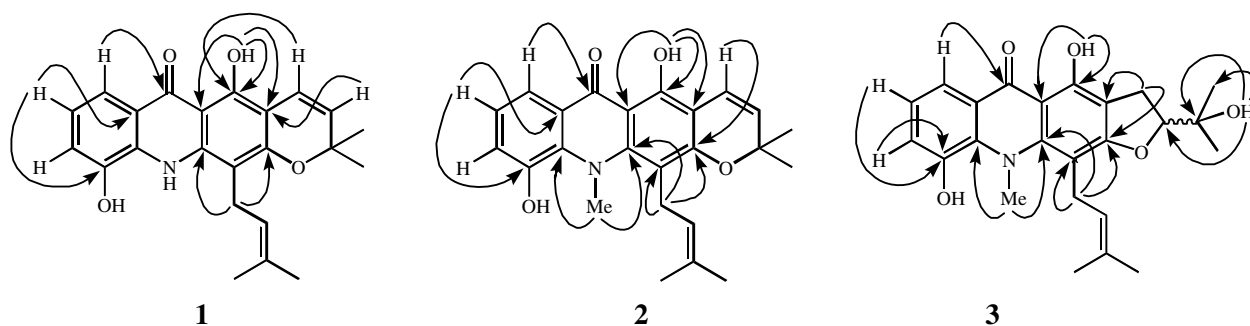
Fig. 1. Structures of compounds 1–13.

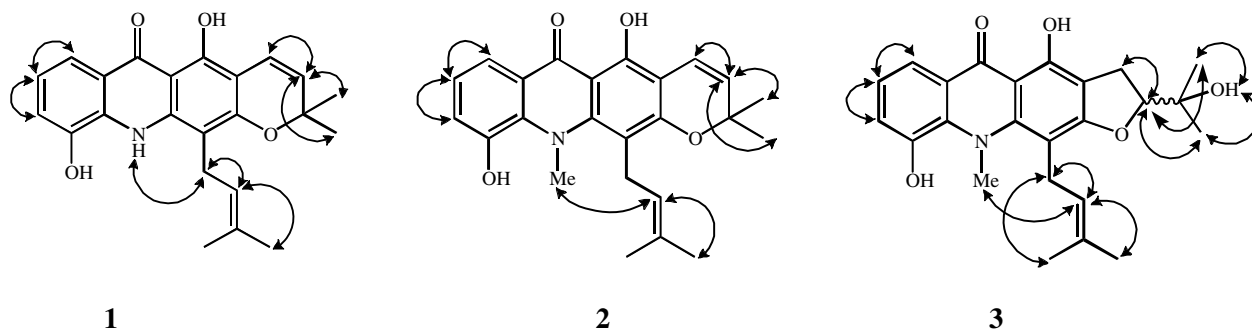Fig. 2. Selected HMBC correlations of compounds 1–3.

Fig. 3. Selected NOESY correlations of compounds **1**–**3**.

Table 1
^{1}H and ^{13}C NMR spectroscopic data of compounds **1**–**3** in acetone-d_6 (300 and 75 MHz)

Position	1		2		3	
	δ_C	δ_H (mult., J, Hz)	δ_C	δ_H (mult., J, Hz)	δ_C	δ_H (mult., J, Hz)
1-OH		14.74 (1H, s)		14.63 (1H, s)		14.45 (1H, s)
1	157.1		157.5		157.2	
2	102.1[b]		103.4		106.7[a]	
3	156.2		158.8		167.0	
4	102.2[b]		108.5		103.0	
5	144.7		148.6		148.4	
5-OH		9.82 (1H, br s)		9.41 (1H, br s)		9.32 (1H, br s)
6	116.0[a]	7.25 (1H, br d, 7.8)	119.7	7.29 (1H, br d, 7.5)	119.4	7.27 (1H, dd, 7.8, 1.5)
7	121.3	7.12 (1H, t, 7.8)	123.1	7.18 (1H, t, 7.5)	122.8	7.17 (1H, t, 7.8)
8	115.7	7.76 (1H, d, 7.8)	116.1	7.76 (1H, d, 7.5)	116.2	7.77 (1H, dd, 7.8, 1.5)
9	181.4		182.7		182.3	
4a	139.9		150.0		150.0	
5a	130.8		138.0		138.0	
8a	120.3		124.9		125.0	
9a	104.2		106.9		107.0[a]	
1′	115.9[a]	6.77 (1H, d, 9.9)	115.6	6.73 (1H, d, 9.9)	26.7	3.22 (1H, dd, 15.6, 7.5)
						3.15 (1H, dd, 15.6, 9.3)
2′	126.6	5.71 (1H, d, 9.9)	126.9	5.70 (1H, d, 9.9)	91.0	4.82 (1H, dd, 9.3, 7.5)
3′/3′-OH	77.5		77.7		70.8	3.76 (1H, s)
4′/5′	27.5	1.49 (6H, s)	27.6	1.48 (6H, s)	24.9	1.28 (6H, s)
1″	21.5	3.61 (2H, d, 7.2)	25.7	3.51 (2H, br d, 6.3)	25.9	3.53 (2H, br d, 6.3)
2″	121.8	5.17 (1H, br t, 7.2)	123.9	5.36 (1H, m)	123.1	5.39 (1H, m)
3″	133.8		130.7		131.2	
4″	25.0	1.76 (3H, s)	24.9	1.70 (3H, s)	25.3	1.69 (3H, s)
5″	17.2	1.99 (3H, s)	17.3	1.80 (3H, s)	17.2	1.78 (3H, s)
10-NH		9.05 (1H, br s)				
10-N-Me			47.7	3.71 (3H, s)	47.2	3.73 (3H, s)

[a] Values interchangeable within column.
[b] Values interchangeable within column.

Me-5′) represented the presence of a 2,2-dimethylpyrano moiety. The HMBC correlation of H-1″ at δ 3.61 with the carbons at δ 156.2 (C-3) and 139.9 (C-4a), and its NOESY cross peak with the N–H proton at δ 9.05 supported the attachment of a prenyl group at C-4. Additional HMBC correlation of H-1′ (δ 6.77) with the carbon at δ 157.1 (C-1), of H-2′ (δ 5.71) with δ 102.1 (C-2) suggested that the dimethyl pyran ring was fused to the acridone nucleus with linear orientation. On the basis of the above analysis, the structure of **1** was identified and named as cycloatalaphylline-A.

Compound **2**, $C_{24}H_{25}NO_4$ [M]$^+$ m/z 391.1748 was obtained as yellow-orange crystals. Its MW was 14 mass units more than that of **1**. The ^{1}H and ^{13}C NMR spectra were closely related to those of **1**, except that the N–H proton signal at δ 9.05 in **1** was replaced by a N-methyl resonance in **2** at δ_H 3.71: δ_C 47.7. A prenyl group was placed at C-4 due to HMBC correlation of H-1″ (δ 3.51) with the carbons at δ 108.5 (C-4), 150.0 (C-4a) and 158.8 (C-3), and a NOESY cross peak between N–Me (δ 3.71) and H-2″ (δ 5.36). Hence, **2** was an N-methyl derivative of **1** and named as N-methylcycloatala-phylline-A.

Compound **3** was yellow needles. The molecular formula $C_{24}H_{27}NO_5$ was suggested on the basis of HREIMS (m/z 409.1888). The N-methyl singlet signal was displayed at δ_H 3.73: δ_C 47.2. The ^{1}H and ^{13}C NMR spectroscopic data of **3** were partly comparable with those of **1** and **2**, suggesting an acridone chromophore with a prenyl side-chain attached at C-4 from HMBC correlation of H-1″ (δ 3.53) with the carbons at δ 103.0 (C-4), 150.0 (C-4a) and C-3 (167.0). The ^{1}H NMR spectroscopic data, different from those of **1** and **2**, were shown as signals at δ 4.82 (1H, dd, J = 9.3, 7.5 Hz, H-2′), 3.76 (1H, s, 3′-OH), 3.22 and 3.15 (each 1H, dd, J = 15.6, 7.5 Hz and 15.6, 9.3 Hz, respectively, 2H-1′), and 1.28 (6H, s, Me-4′,5′). These data were consistent with a hydroxyisopropyldihydrofurano moiety whose location was placed between C-2 and C-3 due to HMBC correlation of H-1′ (δ 3.22) with the carbon at δ 106.7 (C-2), of H-1′ (δ 3.15) with δ 167.0 (C-3). Based on these data, **3** was identified as N-methyl derivative of buxifoliadine-E previously isolated from Severinia buxifolia (Wu and Chen, 2000) and named as N-methylbuxifolia-dine-E.

The anti-allergic activity of isolated compounds (with enough material) was determined. Three acridone alkaloids: buxifoliadine-E (**5**), citrusinine-I (**8**), and N-methylcycloatalaphylline-A (**2**) exhibited appreciable anti-allergic activity against antigen-induced β-hexosaminidase release with IC_{50} values of 6.1, 18.7 and 40.1 μM, respectively. All these compounds possessed stronger anti-allergic activity than ketotifen fumarate, a clinically used drug (IC_{50} = 47.5 μM). It was shown that the anti-allergic effect of buxifoliadine-E (**5**, IC_{50} = 6.1 μM) was comparable to that of quercetin (IC_{50} = 4.5 μM), a positive reference compound and N-methylcyclo-atalaphylline-A (**2**, IC_{50} = 40.1 μM), a new compound, also possessed marked anti-allergic effect. The active compounds were also tested on the enzyme activity of β-hexosaminidase and showed weak inhibition at 100 μM, whose results indicated the inhibition of the antigen-induced degranulation, but not the activity of β-hexosaminidase. Hence, buxifoliadine-E (**5**) could provide a platform for structure-based design of acridone class anti-allergic agents. Compounds **6**, **7**, **9**, **12** and **13** exhibited no activity.

3. Experimental

3.1. General experimental procedures

Melting points were determined on a Fisher-John melting point apparatus. The specific rotation $[\alpha]_D$ value was determined with a JASCO P-1020 polarimeter. UV spectra were measured with a SPE-CORD S 100 (Analytikjena). The IR spectra were measured with a Perkin–Elmer FTS FT-IR spectrophotometer. The ¹H and ¹³C NMR spectra were recorded using a 300 MHz Bruker FTNMR Ultra Shield™ spectrometer. Chemical shifts are recorded in part per million (ppm) in acetone-d_6 with tetramethylsilane (TMS) as an internal reference. The EIMS was obtained from a MAT 95 XL mass spectrometer. Quick column chromatography (QCC) and column chromatography (CC) were carried out on silica gel 60 F_{254} (Merck) and silica gel 100 (Merck), respectively. Precoated plates of silica gel 60 F_{254} were used for analytical purposes.

3.2. Plant material

Root of *A. monophylla* was collected from Trang province, Thailand in June 2006. Identification was made by Assoc. Prof. Dr. Kitichate Sridith and a specimen (No. 0012995) deposited at PSU herbarium, Department of Biology, Faculty of Science, Prince of Songkla University.

3.3. Extraction and isolation

The air-dried and pulverized root (6.0 kg) was successively extracted with CH_2Cl_2 and acetone (2 × 20 L for one week for each solvent) at room temperature to furnish a yellow viscous residue of the CH_2Cl_2 extract (52.5 g) and brownish acetone extract (15.0 g). The crude CH_2Cl_2 extract was subjected to QCC over silica gel using solvents of increasing polarity from n-hexane through EtOAc. The eluents were combined into 18 fractions on the basis of TLC analysis. Fraction 2 (1.5 g) was subjected to QCC with a gradient of EtOAc–hexane, followed by CC with acetone–hexane (1:5, v/v) to give **12** (53.3 mg). Fraction 6 (150.0 mg) was separated by CC with acetone–hexane (1:5, v/v) to give **2** (7.0 mg) and **6** (20.0 mg). Fraction 9 (1.2 g) was purified by QCC with a gradient of EtOAc–CH_2Cl_2 to give **9** (25.0 mg). Fraction 11 (2.5 g) was purified by QCC with a gradient of acetone–hexane to afford 8 fractions (11A–11H). Subfraction 11C (154.0 mg) was separated by CC with acetone–hexane (1:6, v/v) to give **1** (2.3 mg). Subfraction 11D (147.0 mg) was purified by CC with acetone–hexane (1:5, v/v) to give **13** (3.7 mg). Fraction 12 (4.3 g) was purified by QCC with a gradient

of acetone–hexane to afford 6 fractions (12A–12F). Subfraction 12C (385.0 mg) was purified by QCC with a gradient of acetone–hexane to give **7** (22.0 mg). Subfraction 12D (115.0 mg) was purified by CC with acetone–hexane (1:5, v/v) to give **4** (2.8 mg). Subfraction 12E (250.0 mg) was purified by QCC with a gradient of acetone–CH_2Cl_2 and followed by CC with EtOAc–CH_2Cl_2 (1:25, v/v) to give **8** (6.5 mg). Fraction 15 (3.1 g) was purified by QCC with a gradient of acetone–hexane to afford 8 fractions (15A–15H). Subfraction 15A (120.0 mg) was purified by CC with EtOAc–hexane (1.5:5, v/v) to give **10** (2.5 mg). Subfraction 15F (112.0 mg) was purified by CC with acetone–hexane (1:5, v/v) to give **5** (6.7 mg).

The crude acetone extract of *A. monophylla* was further purified by QCC using hexane as eluent and increasing polarity with acetone and MeOH to give eight fractions. Fraction 4 (1.2 g) was purified by QCC with a gradient of acetone–hexane to afford 8 fractions (4A–4H). Subfraction 4C (112.0 mg) was purified by CC with acetone–hexane (1:5, v/v) to give **11** (2.3 mg). Fraction 5 (615.0 mg) was purified by QCC with a gradient of acetone–hexane to afford 8 fractions (5A–5H). Subfraction 5B (50.0 mg) was purified by CC with EtOAc–CH_2Cl_2 (1:10, v/v) to give **3** (2.1 mg).

3.3.1. Cycloatalaphylline-A (*1*)

Yellow needles, m.p. 238–240 °C; UV λ_{max} (MeOH) (log ϵ): 275 (1.13), 305 (0.98), 334 (0.79), 376 (0.69), 401 (0.54) nm; IR (KBr) ν_{max}: 3363 (OH), 1639 (>C=O) cm⁻¹; For ¹H NMR (acetone-d_6, 300 MHz) and ¹³C NMR (acetone-d_6, 75 MHz) spectroscopic data, see Table 1; EIMS: m/z 377 (19) [M]⁺; 376 (84), 361 (100), 333 (28), 305 (36), 293 (10), 153 (11); HREIMS: m/z [M]⁺ 377.1626 (calcd for $C_{23}H_{23}NO_4$, 377.1627).

3.3.2. N-methylcycloatalaphylline-A (*2*)

Yellow-orange crystals, m.p. 240–241 °C; UV λ_{max} (MeOH) (log ϵ): 204 (1.24), 272 (1.15), 323 (0.86), 345 (0.73), 417 (0.37) nm; IR (KBr) ν_{max}: 3369 (OH), 1639 (>C=O) cm⁻¹; For ¹H NMR (acetone-d_6, 300 MHz) and ¹³C NMR (acetone-d_6, 75 MHz) spectroscopic data, see Table 1; EIMS: m/z 391 (23) [M]⁺; 390 (96), 375 (100), 347 (50), 335 (54), 321 (30), 317 (18), 279 (13), 119 (17); HREIMS: m/z [M]⁺ 391.1748 (calcd. for $C_{24}H_{25}NO_4$, 391.1784).

3.3.3. N-methylbuxifoliadine-E (*3*)

Yellow needles, m.p. 250–252 °C; $[\alpha]_D^{27}$ ±0° (c 0.12, MeOH). UV λ_{max} (MeOH) (log ϵ): 252 (1.19), 276 (1.03), 282 (1.29), 327 (0.98), 395 (0.65) nm; IR (KBr) ν_{max}: 3374 (OH), 1639 (>C=O) cm⁻¹; For ¹H NMR (acetone-d_6, 300 MHz) and ¹³C NMR (acetone-d_6, 75 MHz) spectroscopic data, see Table 1; EIMS: m/z 409 (23) [M]⁺; 408 (100), 393 (71), 335 (36), 321 (48), 104 (12); HREIMS: m/z [M]⁺ 409.1888 (calcd for $C_{24}H_{27}NO_5$, 409.1889).

3.4. Bioassays

3.4.1. Inhibitory effects on the release of β-hexosaminidase from RBL-2H3 cells

Inhibitory effects on the release of β-hexosaminidase from RBL-2H3 were evaluated by the following method (Matsuda et al., 2002). The β-hexosaminidase is the enzyme released along with histamine from mast cells or basophils when cells degranulate, this enzyme is therefore used as the marker for mast cell degranulation in RBL-2H3 cell line.

3.4.2. β-Hexosaminidase inhibitory activity

In order to clarify that the anti-allergic effects of samples were due to the inhibition on β-hexosaminidase release and not β-hexosaminidase activity, the following assay was carried out. The cell suspension (5 × 10⁶ cells) in 10 ml of PBS was sonicated. The solution was then centrifuged; and the supernatant diluted with

Siraganian buffer and adjusted to equalize the enzyme activity of the degranulation tested above. The enzyme solution (45 µl) and test sample solution (5 µl) were transferred into a 96-well microplate and incubated with 50 µl of the substrate solution at 37 °C for 1 h. The reaction was stopped by adding 200 µl of the stop solution (0.1 M Na_2CO_3/$NaHCO_3$, pH 10.0). The absorbance was measured using a microplate reader at 405 nm and the results were expressed as mean ± SEM of four determinations. The IC_{50} values were calculated using the Microsoft Excel program. The statistical significance was calculated by one-way analysis of variance (ANOVA), followed by Dunnett's test.

3.5. Statistics

The results of anti-allergic activity were expressed as mean ± S.E.M of four determinations. The IC_{50} values were calculated using the Microsoft Excel program. Statistical significance was calculated by one-way analysis of variance (ANOVA), followed by Dunnett's test.

Acknowledgments

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