Aromatase Inhibitory Activity of Geranylated Coumarins, Mammeasins C and D, Isolated from the Flowers of *Mammea siamensis*

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A methanol extract of the flowers of *Mammea siamensis* (Calophyllaceae) was found to inhibit enzymatic activity against aromatase (IC \(_{50}\)=16.5\(\mu\)g/mL). From the extract, two new geranylated coumarins, mammeasins C (1) and D (2), were isolated together with seven coumarins: 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(2-methyl-1-oxobutyl)-4,5-dihydropyran[4,3,2-de]chromen-2-one (9), 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(3-methyl-1-oxobutyl)-4,5-dihydropyran[4,3,2-de]chromen-2-one (10), mammeas A/AA (14), A/AB (15), A/AA cyclo D (18), E/BA (23), and E/BC cyclo D (25). The structures of 1 and 2 were elucidated on the basis of spectroscopic evidence. Among the isolates including 17 previously reported coumarins, 1 (IC \(_{50}\)=2.7\(\mu\)M), 2 (3.6\(\mu\)M), and mammea B/AB cyclo D (21, 3.1\(\mu\)M) showed relatively strong inhibitory activities comparable to the activity of the synthetic nonsteroidal aromatase inhibitor anastrozole (2.0\(\mu\)M).

Key words Mammea siamensis; mammeasin; aromatase inhibitor; geranylated coumarin; Calophyllaceae

**Results and Discussion**

Effects of the Methanol Extract from the Flowers of *M. siamensis* against Human Recombinant Aromatase

Breast cancer is one of the most common reasons for mortality in women.26–30 Estrogens and estrogen receptors are widely studied molecular targets.28–30 The presence of high concentrations of estrogen in breast tissue increases the risk of developing breast cancer and the ability of immature breast tissue cells to strongly bind to carcinogens, decreasing their DNA repair capacity.31–32 Aromatase, a CYP19 enzyme, is the rate-limiting enzyme in the conversion of testosterone and androstenedione to the estrogens estrone and estradiol.26–30,32–34 It is involved in the final step of the estrogen biosynthetic pathway and its selective inhibition will not affect the production of other steroids in the pathway.32,35–37 The source of estrogen production in breast cancer tissues is intratumoral aromatase, and thus, inhibition of aromatase may inhibit the growth stimulation effect of estrogens in breast cancer tissues. Therefore, aromatase is considered a useful therapeutic target in the treatment and prevention of estrogen-dependent breast cancer.25

The dried flowers of *M. siamensis* (collected from Nakhon Si Thammarat Province, Thailand) were extracted with methanol under reflux (25.66% from the dried flowers). The methanol extract was partitioned into an EtOAc–H\(_2\)O (1 : 1, v/v) mixture to furnish an EtOAc-soluble fraction (6.84%).

The aqueous phase was subjected to Diaion HP-20 column chromatography (H\(_2\)O→MeOH) to give H\(_2\)O- and MeOH-eluted fractions (13.50, 4.22%, respectively), as described previously.1 As shown in Table 1, the methanol extract had an inhibitory effect on aromatase (IC \(_{50}\)=16.5\(\mu\)g/mL). A bioassay-guided fractionation revealed that the EtOAc-soluble and MeOH-eluted fractions also showed aromatase in-

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hibitory activities (IC$_{50}$ = 2.9, 8.5 µg/mL, respectively), whereas the H$_2$O-eluted fraction showed no noticeable activity.

**Isolation of Coumarin Constituents from the Methanol Extract**

In our previous report we described the isolation of 17 coumarins: mammeasins A (3, 0.0293%), and B (4, 0.0115%), surangins B (5, 0.0271%), C (6, 0.0571%), and D (7, 0.0632%), kayeassamins A (8, 0.0578%), E (11, 0.0113%), F (12, 0.0390%), and G (13, 0.0171%), mammeasins A/AC (16, 0.1056%), A/AD (17, 0.0022%), A/AB cyclo D (19, 0.0097%), A/AC cyclo D (20, 0.0109%), A/BB cyclo D (21, 0.0016%), B/AC cyclo D (22, 0.0062%), and E/BB (24, 0.0194%), and deacetylmammea E/BC cyclo D (26, 0.0073%), β-amyrin (0.0072%), and benzoic acid (0.0043%).

In the present study we additionally isolated two new glycosylated coumarins, mammeasins C (1, 0.0008%) and D (2, 0.0047%), from the active EtOAc-soluble fraction together with seven coumarins: 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(2-methyl-1-oxobuty)-4,5-dihydropyran[4,3,2-de]chromen-2-one (9, 0.0015%), 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(3-methyl-1-oxobuty)-4,5-dihydropyran[4,3,2-de]chromen-2-one (10, 0.0012%), mammeasins A/AA (14, 0.0494%), A/AB (15, 0.0048%), A/AA cyclo D (18, 0.0035%), E/BA (23, 0.0045%), and E/BC cyclo D (25, 0.0058%), using normal-phase silica gel and reversed-phase octadecylsilane (ODS) column chromatography, and finally, HPLC (Fig. 1).

**Table 1. Inhibitory Effects of the Methanol Extract from the Flowers of M. siamensis and Its Fractions against Human Recombinant Aromatase**

|                     | Inhibition (%) | IC$_{50}$ (µg/mL) |
|---------------------|----------------|-------------------|
|                     | 3 µg/mL       | 10 µg/mL          | 30 µg/mL          | 100 µg/mL       |
| MeOH Extract        | 13.2±3.2      | 41.8±1.6**        | 80.0±3.1**        | 97.5±0.6**      | 16.5          |
| EtOAc-Soluble fraction | 46.3±4.4**    | 89.0±1.2**        | 100.1±0.6**       | 99.9±0.5**      | 2.9           |
| MeOH-Eluted fraction | 2.0±3.9       | 70.7±1.2**        | 93.0±1.0**        | 96.9±0.9**      | 8.5           |
| H$_2$O-Eluted fraction | −4.7±4.8     | 1.2±2.2           | −1.7±2.1          | −0.1±4.0        | >100          |

Each value represents the mean±S.E.M. (N=3). Significantly different from the control, **p<0.01.

**Fig. 1. Coumarin Constituents (1–26) from Flowers of M. siamensis**
lar formula was determined as C26H32O5 by high-resolution (HR)-EI-MS measurement. The 1H- and 13C-NMR spectra of I (Tables 2, 3, CDCl3) were assigned with the aid of distortion-enhancement by polarization transfer (DEPT), 1H–1H correlation spectroscopy (COSY), 1H-detected heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond connectivity (HMBC) experiments (Fig. 2). The spectra showed signals assignable to three secondary and three vinyl methyls (δ 1.26, 1.27 (3H each, both d, J = 6.6 Hz, 3°-H3), 1.54 (3H, d, J = 6.2 Hz, 1°-H2), 1.57 (3H, s, 10°-H2), 1.63 (3H, d, J = 0.7 Hz, 9°-H3), 1.78 (3H, s, 5°-H2)); four methylenes (δ 1.96 (2H, m, 4°-H2), 2.05 (2H, m, 6°-H2), [2.78 (1H, ddd, J = 1.4, 11.0, 17.2 Hz), 2.91 (1H, dd, J = 2.6, 17.2 Hz), 4-H2], 3.35 (2H, d, J = 7.2 Hz, 1°-H3)); two methines (δ 4.01 (1H, qq, J = 6.6, 6.6 Hz, 2°-H) 4.36 (1H, m, 5-H]); and two olefinic protons (δ 5.06 (1H, qt, J = 0.7, 6.9 Hz, 7°-H)), 5.20 (1H, brt, J = ca. 7 Hz, 2°-H)]. The 1H- and 13C-NMR spectroscopic properties of I were quite similar to those of 9 and 10, except for the signals due to the 1-oxo-alkyl moiety.12) The 1H–1H COSY experiment on I indicated the presence of partial structures, as indicated by the bold lines in Fig. 2. In the HMBC experiment, long-range correlations were observed between the following proton and carbon pairs: 3-H and 2,6,4-H; 4-H and 3,6b-C; 1°-H2 and 6a,7,8-C; 2°-H and 7°-H; 2°-H and 3°-C; 5°-H3 and 2°–4°-C; 7°-H3 and 9°-10°-C; 9°-H3 and 7°,8,9°-10°-C; 10°-H3 and 7°–9°-C; 2°-H and 1°-C. On the basis of comprehensive two dimensional (2D)-NMR experiments, we assigned the structure of I as 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(2-methyl-1-oxopropyl)-4,5-dihydropyrano[4,3,2-de]-chromen-2-one.

Mammeasin D (2) was also isolated as pale yellow oil. Its molecular formula, C26H32O5, was found to be the same as that of I by HR-EI-MS measurement. The 1H- and 13C-NMR spectroscopic properties (Tables 2, 3, CDCl3) of 2 were simi-

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### Table 2. 1H-NMR (500 MHz, CDCl3) Data for Mammeasins C (1) and D (2)

| Position | δH (J Hz) | Position | δH (J Hz) |
|----------|-----------|----------|-----------|
| 3        | 5.94 (1H, brs) | 3        | 5.93 (1H, brs) |
| 4        | 2.78 (1H, ddd, 1.4, 11.0, 17.2) | 4       | 2.78 (1H, ddd, 1.5, 10.9, 16.9) |
| 5        | 4.36 (1H, m) | 5       | 4.36 (1H, m) |
| 1°       | 1.54 (3H, d, 6.2) | 1°       | 1.54 (3H, d, 6.3) |
| 1°       | 3.35 (2H, m, 7.2) | 1°       | 3.34 (2H, m, 6.9) |
| 2°       | 5.20 (1H, brt, ca. 7) | 2°       | 5.19 (2H, brt, ca. 7) |
| 3°       | 1.96 (2H, m) | 3°       | 1.96 (2H, m) |
| 3°       | 1.78 (3H, s) | 3°       | 1.78 (3H, s) |
| 4°       | 2.05 (2H, m) | 4°       | 2.05 (2H, m) |
| 7°       | 5.06 (1H, qt, 0.7, 6.9) | 7°       | 5.05 (1H, qt, 0.9, 6.9) |
| 9°       | 1.63 (3H, d, 0.7) | 9°       | 1.63 (3H, d, 0.9) |
| 10°      | 1.57 (3H, s) | 10°      | 1.57 (3H, s) |
| 2°       | 4.01 (1H, qq, 6.6, 6.6) | 2°       | 3.26 (2H, brt, ca. 7) |
| 3°       | 1.26 (3H, d, 6.6) | 3°       | 1.79 (2H, m) |
| 4°       | 1.27 (3H, d, 6.6) | 4°       | 1.05 (3H, t, 7.5) |
| 8-OH     | 14.55 (1H, s) | 8-OH     | 14.51 (1H, s) |

* a) Assignments may be interchangeable within the same column.

### Table 3. 13C-NMR (125 MHz, CDCl3) Data for Mammeasins C (1) and D (2)

| Position | δC | Position | δC |
|----------|----|----------|----|
| 2        | 159.8 | 1°      | 21.4 |
| 3        | 105.7 | 2°      | 121.2 |
| 3a       | 149.2 | 3°      | 135.8 |
| 4        | 35.1  | 4°      | 39.8  |
| 5        | 72.6  | 5°      | 16.1  |
| 6a       | 156.6 | 6°      | 26.7  |
| 6b       | 99.6  | 7°      | 124.3 |
| 7        | 113.1 | 8°      | 131.3 |
| 8        | 167.6 | 9°      | 25.6  |
| 9        | 103.2 | 10°     | 17.7  |
| 9a       | 154.3 | 1°      | 210.3 |
| 1°       | 20.7  | 2°      | 40.1  |
| 1°       | 19.15 | 3°      | 18.0  |
| 4°       | 19.21 | 4°      | 13.8  |

* a) Assignments may be interchangeable within the same column.
lar to those of 1, except for the signals due to an 1-oxobutyl moiety in the 9-position [δ 1.05 (3H, t, J=7.5 Hz, 4″-H2), 1.79 (2H, m, 3″-H3), 3.26 (2H, brt, J=ca. 7 Hz, 2″-H2)] instead of the 2-methyl-1-oxopropyl moiety of 1. As shown in Fig. 2, the connectivities of the quaternary carbons in 2 were elucidated on the basis of 1H–1H COSY and HMBC experiments. Thus, the structure of 2 was elucidated to be 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(1-oxobutyl)-4,5-dihydropyrano[4,3,2-de]chromen-2-one. Possible biogenetic pathway for the formation of the pyran ring in 9 and 10, having the same moiety with those of 1 and 2, from 6 and 7 have been reported previously.\(^5\) These new compounds (1, 2) might be derived through the same pathway. Further studies, e.g. total syntheses of 1 and 2, would be needed to elucidate the absolute stereochemistry and to verify whether these were the artifacts.

Effects of Coumarin Constituents of the Flowers of *M. siamensis* and Related Compounds on Human Recombinant Aromatase

Table 4. Inhibitory Effects of Constituents from the Flowers of *M. siamensis* and Related Compounds against Human Recombinant Aromatase

| Constituent                      | \(IC_{50}\) (µM) | \(IC_{90}\) (µM) |
|---------------------------------|------------------|------------------|
| Mammeeasin C (1)               | 2.7              | 7.2              |
| Mammeeasin D (2)               | 3.6              | 24.1             |
| Mammeeasin A (3)               | 8.7              | 35.0             |
| Mammeeasin B (4)               | 4.1              | 3.1              |
| Surangin B (5)                 | 9.8              | 24.6             |
| Surangin C (6)                 | 8.8              | 16.6             |
| Surangin D (7)                 | 18.1             | 18.6             |
| Kayeassamin A (8)              | 10.0             | 11.5             |
|                                  | 7.5              | 16.6             |
| 1                              | 10.8             | >100 (24.4)\(^a\) |
| Kayeassamin E (11)             | 14.9             | >100 (–3.4)\(^a\) |
| Kayeassamin F (12)             | 19.7             |                  |
| Kayeassamin G (13)             | 27.8             |                  |
| Mammee A/AA (14)               | 6.9              |                  |
| Mammee A/AB (15)               | 8.6              |                  |
| Mammee A/AC (16)               | 13.7             |                  |
| Mammee A/AD (17)               | 11.3             |                  |
| Mammee A/AA cyclo D (18)       |                  |                  |
| Mammea A/AB cyclo D (19)       |                  |                  |
| Mammea A/AC cyclo D (20)       |                  |                  |
| Mammea B/AB cyclo D (21)       |                  |                  |
| Mammea B/AC cyclo D (22)       |                  |                  |
| Mammea E/BA (23)               |                  |                  |
| Mammea E/BC cyclo D (25)       |                  |                  |
| Deacetyl-mammea E/BC cyclo D (26) |                  |                  |
| β-Amyrin                       | >100 (24.4)\(^a\) |                  |
| Benzoic acid                   | >100 (–3.4)\(^a\) |                  |
| Umbelliferone                  | >100 (2.6)\(^a\)  |                  |
| Scopeolitin                    | >100 (–15.9)\(^a\) |                  |
| 4-Hydroxycoumarin              | >100 (10.9)\(^a\) |                  |
| Aminoglutethimide              |                  | 2.0              |

Each value represents the mean±S.E.M. (\(N=3\)). \(^a\) Values in parentheses present inhibition % at 100µM.

... of the coumarin skeleton is essential for the inhibitory activity. In particular, mammeeasins C (1, 2.7 µM) and D (2, 3.6 µM), and mammee B/AB cyclo D (21, 3.1 µM) show relatively potent activity, comparable to that of aminoglutethimide (2.0 µM).\(^40,41\) Therefore, these coumarins may be useful in the treatment of hormone-dependent breast cancer. Detailed structural requirements of coumarins for aromatase inhibitory activity and the mechanism of action, however, need further exploration.

### Experimental

The following instruments were used to obtain physical data: UV spectra, UV-1600 spectrometer (Shimadzu Co., Kyoto, Japan); IR spectra, FTIR-8100 spectrometer (Shimadzu Co.); EI-MS and HR-ESI-MS, JMS-GCMATE mass spectrometer (JEOL Ltd.); 1H-NMR spectra, JNM-ECA500 (500MHz), and JNM-ECS400 (400MHz) spectrometers (JEOL); 13C-NMR spectra, JNM-ECA500 (125MHz), and JNM-ECS400 (100MHz) spectrometers (JEOL Ltd.) with tetramethylsilane as an internal standard; HPLC detector, SPD-10Avp UV-VIS detector (Shimadzu Co.); HPLC column, Cosmosil 5C\(_{18}\)-MS-II (Nacalai Tesque, Inc., Kyoto, Japan), 4.6×250mm i.d. and 20×250mm i.d. for analytical and preparative studies, respectively.

The following experimental conditions were used for chromatography (CC): ordinary-phase silica gel column chromatography, silica gel 60N (Kanto Chemical Co., Tokyo,
Japan; 63–210 mesh, spherical, neutral); reverse-phase silica gel CC, Diaion HP-20 (Nippon Rensui, Tokyo, Japan) and Chromatorex ODS DM1020T (Fuji Silysia Chemical, Aichi, Japan; 100–200 mesh); normal-phase TLC, pre-coated TLC plates with silica gel 60F254 (Merck, Darmstadt, Germany; 0.25 mm); reverse-phase TLC, pre-coated TLC plates with silica gel RP-18 F254S (Merck, 0.25 mm), detection was carried out by spraying 1% Ce(SO4)2·10H2O on the plates, followed by heating.

**Plant Material** The flowers of *Mammea siamensis* were collected from Nakonnithammarat Province, Thailand, in September 2006, as described previously.1) The plant material was identified by one of the authors (Y.P.). A voucher specimen (2006.09. Raj-04) for this plant has been deposited in our laboratory.

**Extraction and Isolation** Dried flowers of *M. siamensis* (1.8 kg) were extracted three times with MeOH under reflux for 3 h. Evaporation of the combined extracts under reduced pressure afforded the MeOH extract (463.7 g, 25.66%). An aliquot (89.45 g) was subjected to Diaion HP-20 CC (2.4 kg, H2O (110.34 g, 6.84%) and an aqueous phase. The aqueous phase was purified by HPLC [Cosmosil 5C18-MS-II, MeOH–1% aqueous AcOH (90:10, v/v)] to give mammeas C (1, 0.0008%) and D (2, 60.9 mg, 0.0047%), 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(2-methyl-1-oxobutyl)-4,5-dihydropyran[4,3,2-de]chromen-2-one (9, 19.8 mg, 0.0015%), and 8-hydroxy-5-methyl-7-(3,7-dimethyl-octa-2,6-dienyl)-9-(3-methyl-1-oxobutyl)-4,5-dihydropyran[4,3,2-de]chromen-2-one (10, 16.3 mg, 0.0012%) together with 16 (6.0 mg, 0.0005%) as reported previously.1)

**Mammeasin C (1)** Pale yellow oil. HR-ESI-MS: Calcd for C26H32O5 (M+) 424.2250. Found: 424.2243. UV [MeOH, nm (log ε):] 221 (4.32), 292 (4.22), 328 (4.05). IR (film): 1748, 1717, 1634, 1601, 1450, 1404, 1385, 1327, 1194, 1171, 1132, 1109 cm−1. 1H-NMR (500 MHz, CDCl3): δ: see Table 2. 13C-NMR data (125 MHz, CDCl3) δ:c: see Table 3. EI-MS m/z: 424 (M+, 37), 301 (100).

**Mammeasin D (2)** Pale yellow oil. HR-ESI-MS: Calcd for C26H32O5 (M+): 424.2250. Found: 424.2243. UV [MeOH, nm (log ε):] 221 (4.39), 292 (4.29), 324 (4.09). IR (film): 1734, 1717, 1636, 1617, 1456, 1387, 1235, 1192, 1115, 1049 cm−1. 1H-NMR (500 MHz, CDCl3) δ:c: see Table 3. 13C-NMR data (125 MHz, CDCl3) δ:c: see Table 3. EI-MS m/z: 424 (M+, 30), 301 (100).

**Bioassay**

**Reagents** Dibenzylfluorescein (DBF) and Human CYP19 + P450 Reductase SUPERSOMES (human recombinant aromatase) were purchased from BD Biosciences (Heidelberg, Germany). The other chemicals used in this study were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

**Inhibitory Effects against Human Recombinant Aromatase** The experiments were performed according to the method described previously but with a slight modification.42) A test sample was dissolved in dimethyl sulfoxide (DMSO) and the solution was diluted with potassium phosphate buffer (50 mM, pH 7.4) containing MgCl2 (0.5 mM) to afford the test sample solution (concentration of DMSO: 2%). An enzyme/substrate solution in the buffer (20 µL, 1.6 µM DBF, 8 nM human recombinant aromatase) and the test sample solution (20 µL) were mixed into a 96-well half area black microplate (Greiner Bio-One, Frickenhausen, Germany) at 37°C for 10 min. The enzymatic reaction was initiated by the addition of reduced nicotinamide adenine dinucleotide phosphate (NADPH) solution (40 µL, 500 µM) at 37°C for 30 min. After 30 min incubation, NaOH (30 µL, 2 mM) was added, and the reaction mixture was incubated at 37°C for 2 h to induce the fluorescent signals. Fluorescence was measured using a fluorescence microplate reader (SH-9000, CORONA) at excitation wavelength of 485 nm and emission wavelength of 535 nm. Experiments were performed in triplicate, and IC50 values were determined graphically. The aromatase inhibitor amino-glutethimide was used as a reference compound.
Statistics Values are expressed as the mean±standard error of the mean (S.E.M.). One-way ANOVA, followed by Dunnett’s test, was used for statistical analysis. Probability (p) values less than 0.05 were considered significant.

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Conflict of Interest The authors declare no conflict of interest.

References
1) Morikawa T., Sueyoshi M., Chaipetch S., Matsuda H., Nomura Y., Yabe M., Matsunoto T., Ninomiya K., Yoshikawa M., Pongpiriyadacha Y., Hayakawa T., Muraoka O., Bioorg. Med. Chem., 20, 4968–4977 (2012).
2) Mahidol C., Kaweetripob W., Prawat H., Ruchirawat S., J. Nat. Prod., 65, 757–760 (2002).
3) Laphookhieo S., Maneerat W., Kiattansakul R., J. Nat. Prod., 3) Laphookhieo S., Maneerat W., Kiattansakul R., J. Nat. Prod., 62–69 (2012).
4) Pham H. D., Nguyen L.-H. D., Vo H. V., Vang O., Muraoka O., Mini Rev. Org. Chem., 10, 141–159 (2013).
5) Ngo N. T. N., Nguyen V. T., Pongpiriyadacha Y., Yoshikawa M., Muraoka O., Mini Rev. Org. Chem., 25, 544–550 (2014).
6) Kaweetripob W., Mahidol C., Pongpiriyadacha Y., Yoshikawa M., Muraoka O., Phytomed. Anal., 3) Laphookhieo S., Maneerat W., Kiattansakul R., J. Nat. Prod., 2012.
7) Mahidol C., Kaweetripob W., Prawat H., Ruchirawat S., J. Nat. Prod., 65, 757–760 (2002).
8) Prachyawardakorn V., Mahidol C., Ruchirawat S., Phytochemistry, 67, 924–928 (2006).
9) Nguen T. N., Nguyen V. T., Ho V. H., Pongpiriyadacha Y., Yoshikawa M., Muraoka O., Mikrochim. Acta, 2006, 557–564 (2007).
10) Gray J., Evans N., Taylor B., Rizzo J., Walker M., Int. J. Occup. Environ. Health, 15, 43–58 (2009).
11) Muraoka O., Morikawa T., Miyake S., Akaki J., Ninomiya K., Yoshikawa M., Muraoka O., J. Med. Chem., 58, 1480–1493 (2015).
12) Morikawa T., Akaki J., Ninomiya K., Kinouchi E., Tanabe G., Pongpiriyadacha Y., Yoshikawa M., Muraoka O., Nat. Med., 71, 179–189 (2016).
13) Benson J. R., Raviskear O., Curr. Cancer Ther. Rev., 3, 67–79 (2007).
14) Monteiro R., Faria A., Azevedo I., Calhau C., J. Steroid Biochem. Mol. Biol., 105, 124–130 (2007).
15) Osborne C. K., Schirr R., Fuqua S. A., Shou J., Clin. Cancer Res., 7 (Suppl.), 4338–4342, discussion, 4411–4412s (2001).
16) Balunas M. J., Su B., Brueggemeier R. W., Kinghorn A. D., J. Nat. Prod., 71, 1161–1166 (2008).
17) Balunas M. J., Kinghorn A. D., Planta Med., 76, 1087–1093 (2010).
18) Gray J., Evans N., Taylor B., Rizzo J., Walker M., Int. J. Occup. Environ. Health, 15, 43–58 (2009).
19) Ahmad I., Shagufta, Eur. J. Med. Chem., 102, 375–386 (2015).
20) Muller L. H., Matthews K. A., Meilahn E. N., J. Steroid Biochem. Mol. Biol., 74, 297–309 (2000).
21) Simpson E. R., Clyne C., Rubin G., Boon W. C., Robertson K., Britt K., Speed C., Jones M., Annu. Rev. Physiol., 64, 93–127 (2002).
22) Mutafugia Y., Mustata G., Bioorg. Med. Chem. Lett., 20, 3050–3064 (2010).
23) Mokbel K., Int. J. Clin. Oncol., 7, 279–283 (2012).
24) Maiti A., Cuenedt M., Cray V. L., Endringer D. C., Pezzuto J. M., Cushman M., J. Med. Chem., 56, 2499–2506 (2013).
25) Verotta L., Lovaglio E., Vidari G., Finzi P. V., Neri M. G., Rai, 8646–8648 (2012).
26) Yang H., Prota P., Gil R. R., Jiang B., Baggett S., Basile M. J., Breast Cancer Res. Treat., 94, 249–254 (2005).
27) Jacobson N. W., Halling-Sorensen B., Birkved F. K., Toxicol. In Vitro, 22, 146–153 (2008).