Bioactive Dammarane Triterpenes from the Mangrove Plant *Bruguiera gymnorrhiza*[⊥]

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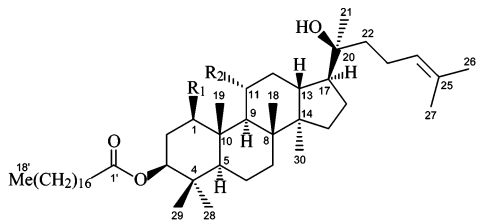
Three new dammarane triterpenes, bruguierins A−C (**1**−**3**), were isolated from a petroleum ether extract of the flowers of *Bruguiera gymnorrhiza*. Their structures were determined on the basis of physical and spectroscopic data interpretation. With stably transfected HepG2 cells, the three isolates activated antioxidant response element (ARE luciferase activation) with EC_{50} values of 7.8, 9.4, and 15.7 μM, respectively. Bruguierin A (**1**) also inhibited phorbol ester-induced NFκB (nuclear factor-κB) luciferase activation with an IC_{50} value of 1.4 μM and selectively inhibited cyclooxygenase-2 (COX-2) activity with an IC_{50} value of 0.37 μM. Compounds **2** and **3** were not active in these bioassays.

Bruguiera gymnorrhiza (L.) Savigny, a mangrove plant of the family Rhizophoraceae, is native to many countries of southern and eastern Africa, Asia, and northern Australia.[1] In Thailand, *B. gymnorrhiza* flowers are used as a vegetable.[2] The fruit and bark of this plant have been used traditionally for diarrhea in mainland China,[3] and its roots and leaves are used for treating burns.[4] Previous studies have reported the presence of a wide range of phytochemicals, including phenol, flavonoid, steroid, sulfur-containing, and terpenoid compounds.[5−9]

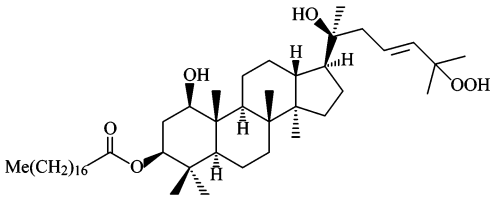
As part of a cancer chemoprevention study, we investigated previously a $CHCl_3$-soluble extract of the flowers of *B. gymnorrhiza*, collected in Thailand, and found stimulation of ARE-linked luciferase activity by cyclic dithiols, bruguiesulfurol, brugierol, and isobrugierol.[10] In the present study, we have evaluated a petroleum ether-soluble extract of the same plant material and found activation of ARE-linked luciferase activity (EC_{50} 0.7 μg/mL) and inhibition of NFκB-linked luciferase activation (IC_{50} 19.7 μg/mL). Further investigation of this extract has led to the isolation of three new dammarane triterpene fatty acid esters with biological activity, bruguierins A−C (**1**−**3**), as reported herein.

A crude petroleum ether extract of the dried and milled flowers of *B. gymnorrhiza* was fractionated by repeated flash column chromatography on silica gel to afford triterpenoids **1**−**3**.

Bruguierin A (**1**) was obtained as a white wax from ethyl acetate, and its molecular formula was established as $C_{48}H_{86}O_4$ by HR-FABMS ($[M + Na]^+$ *m/z* 749.6438, calcd 749.6424). Its structure was determined to be a dammarane triterpene by analysis of its NMR data as well as by comparison with the spectroscopic data of known dammarane triterpenes.[11,12] The complete assignments of the ^1H and ^{13}C NMR spectra were achieved as shown in Table 1. The ^{13}C NMR (DEPT-90 and -135) and HSQC spectra were used to characterize eight tertiary methyls and one methyl, four methines, two oxygenated methines (δ 78.5 and 77.1), one olefinic methine (δ 124.9), four quaternary carbons, an olefinic quaternary carbon (δ 131.8), an oxygenated quaternary carbon (δ 75.6), and a carbonyl carbon (δ 173.7). The side chain in this dammarane triterpene (**1**) was confirmed by a 1D TOCSY NMR experiment. On selective excitation of the olefinic proton signal at δ 5.12 (H-24), the proton signals of the side chain spin system [δ 1.47 (H-22), 2.06 (H-23), 1.69 (H-26), and 1.62 (H-27)] were clearly observed. A double bond was assigned to $\Delta^{24,25}$ in the side chain due to the presence of HMBC correlations of C-24 and C-25 resonances with the 26,27-geminal methyl protons (Figure 1). The ^1H NMR spectrum of **1** displayed a downfield singlet at δ 1.14 for a methyl group at the C-21 position. Moreover, the resonances of these methyl protons with C-17 and C-20 were observed. The appearance of the downfield quarternary ^{13}C at δ 75.6 was attributed to C-20. Furthermore, the C-20 configuration of **1** was established to be *S* on the basis of a comparison of the ^{13}C NMR chemical shifts of C-20 through C-22 with those published for dammarenediol II (20*S*) [δ 75.4 (C-20), 24.9 (C-21), and 40.5 (C-22)] and dammarenediol I (20*R*) [δ 75.8 (C-20), 23.5 (C-21), and 41.8 (C-22)].[12] The two oxygenated methine carbons in **1** were assigned as C-1 and C-3, respectively, on the basis of the observation that in the $^1H-^1H$ COSY spectrum of **1** both the proton signals of H-1 and H-3 coupled with the signal of H-2 at δ 1.72. The ^3J long-range correlations of Me-19 to C-1 and Me-28, Me-29 to C-3 were also observed in the HMBC spectrum. The correlations of H-1 to H-2 and H-3 were confirmed by a 1D TOCSY experiment. Irradiation at H-1 caused the splitting of signals of the two protons



1 R_1 = OH, R_2 = H
2 R_1 = H, R_2 = OH



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[⊥] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

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Table 1. NMR Spectroscopic Data of Compounds **1**−**3**

	1[a]		**2**[b]		**3**[b]	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	3.53 dd (10.9, 4.4)	78.5 d		40.5 t	3.54 dd (11.3, 4.5)	78.7 d
2	1.72 m	34.5 t	1.63 m	24.1 t	1.70 m	34.7 t
3	4.50 dd (13.0, 4.4)	77.1 d	4.51 dd (10.0, 6.3)	80.4 d	4.51 dd (13.5, 4.5)	77.3 d
4		38.1 s		39.1 s		38.3 s
5	0.74 m	53.8 d		56.4 d	0.75 m	54.0 d
6	1.55 m	18.1 t	1.51 m	18.2 t	1.60 m	18.3 t
7	1.28 m	35.1 t	1.22 m	36.1 t	1.58 m	35.3 t
8		41.2 s		41.0 s		41.4 s
9	1.53 m	51.7 d	1.53 m	55.9 d	1.55 m	51.8 d
10		43.7 s		38.6 s		43.8 s
11	1.60 m	22.8 t	3.98 m	71.4 d	1.30 m	25.1 t
12	1.57 m	25.3 t	1.42 m	40.3 t	1.85 m	28.0 t
13	1.61 m	41.9 d	1.80 m	40.9 d	1.65 m	42.3 d
14		50.5 s		50.3 s		50.7 s
15	1.10 m	31.6 t	1.38 m	31.0 t	1.05 m	32.3 t
16		27.8 t	1.55 m	25.2 t	1.68 m	25.5 t
17	1.73 m	50.1 d		49.9 d	1.75 m	50.7 d
18	0.97 s	15.9 q	0.98 s	17.0 q	0.98 s	16.1 q
19	0.93 s	12.3 q	1.07 s	16.9 q	0.94 s	12.5 q
20		75.6 s		75.3 s		75.5 s
21	1.14 s	25.5 q	1.16 s	26.0 q	1.14 s	26.0 q
22	1.47 t (8.0)	41.0 t	1.44 m	40.8 t	2.25 m	44.0 t
23	2.06 m	22.9 t	2.05 m	22.8 t	5.78 m	127.6 d
24	5.12 t (6.5)	124.9 d	5.12 t (6.3)	124.8 d	5.62 d (15.8)	137.7 d
25		131.8 s		132.0 s		82.4 s
26	1.69 s	25.9 q	1.77 s	25.8 q	1.36 s	24.5 q
27	1.62 s	17.9 q	1.69 s	17.9 q	1.35 s	24.9 q
28	0.84 s	28.0 q	0.86 s	28.5 q	0.85 s	28.2 q
29	0.84 s	16.3 q	0.88 s	16.5 q	0.85 s	16.5 q
30	0.88 s	16.6 q	0.92 s	16.8 q	0.88 s	16.8 q
1′		173.7 s		173.9 s		173.9 s
2′	2.29 t (8.0)	34.9 t	2.29 t (7.1)	35.1 t	2.32 t (7.3)	35.1 t
3′−17′	1.25 brs	29.8−29.9 t	1.26 brs	29.8−29.9 t	1.26 brs	30.0−30.1 t
18′	0.88 t (6.0)	14.3 q	0.88 t (6.5)	14.3 q	0.88 t (5.8)	14.5 q

[a] Recorded at 400 MHz. [b] Recorded at 300 MHz; coupling constants (Hz) are shown in parentheses.

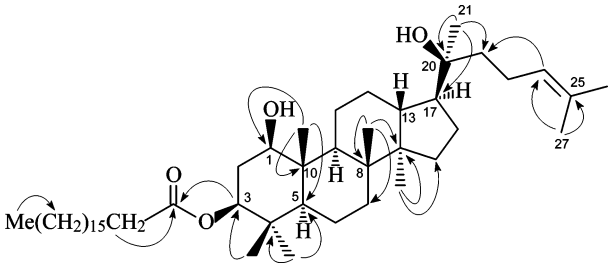

Figure 1. Selected HMBC correlations for compound **1**.

of H-2 at δ 1.67 (m) and 1.87 (m), while the proton of H-3 was observed as a doublet of doublets (J = 13.0, 4.4 Hz) at δ 4.5. The multiplicity of the H-2 protons was observed as a doublet of doublets (J = 11.1 Hz) at δ 1.67 and multiplet at δ 1.87 when H-3 was irradiated. The ^{1}H NMR spectrum of **1** showed a broad, intensive singlet signal at δ 1.25 due to methylene protons, indicating the presence of a long fatty acid ester chain moiety. By subtraction of the dammarane triterpene unit from the molecular formula of **1**, the fatty acid ester moiety was calculated as stearic acid. On basic hydrolysis and GC-MS analysis, the fatty acid side chain of **1** was confirmed to be octadecanoic acid. The stearic acid ester moiety was attached to C-3 due to the presence of the HMBC correlations between H-3 and the carbonyl carbon signal of the fatty acid ester chain. Finally, both oxygen-containing groups at C-1 and C-3 were determined to be β-oriented due to the large coupling constants of H-1 (J = 10.9 Hz, 4.4 Hz) and H-3 (J = 13.0 Hz, 4.4 Hz).[11] Thus, compound **1** was determined to be 1β,20-(*S*)-dihydroxydammar-24(25)-ene-3β-*O*-stearate and has been given the trivial name bruguierin A.

Bruguierin B (**2**) was isolated as white needles from ethyl acetate, and its molecular formula was shown to be the same as **1** by HRFABMS ([M + Na]$^+$ *m*/*z* 749.6396, calcd 749.6424 for $C_{48}H_{86}O_4$). The similarity of the NMR spectroscopic data (Table 1) of these two compounds suggested that **2** is a positional isomer of **1**. The only difference between the two structures was that the second hydroxy group in **2** was located at C-11 instead of C-1 as in **1**. The chemical shift of H-11 was shifted downfield from δ 1.6 in **1** to δ 3.98 in **2**. The COSY experiment revealed correlations of resonances of the methine proton (δ 3.98) at the C-11 position with the methine proton of H-9 and the methylene protons of H-12. In addition to the ^{13}C NMR chemical shift of the oxymethine, C-11 was observed to be at much higher field for **2** (δ 71.4) than for **1** (δ 78.5), which is in accordance with literature.[13] On basic hydrolysis and GC-MS analysis, the fatty acid side chain of **2** was again confirmed to be octadecanoic acid. The hydroxy group of C-11 in **2** was determined to be α-oriented by comparison of the NMR data with those of the known compound dammar-24-en-3β,11α,20(*S*)-triol, which possesses the same dammarane triterpene nucleus.[13] Thus, **2** was determined to be 11α,20(*S*)-dihydroxydammar-24(25)-ene-3-*O*-stearate and has been given the trivial name bruguierin B.

Bruguierin C (**3**) was obtained as a colorless gum. The HR-FABMS data ([M + Na]$^+$ *m*/*z* 781.6322, calcd 781.6322) was used to establish its molecular formula as $C_{48}H_{86}O_6$. The ^{1}H and ^{13}C NMR spectra of **3** closely resembled those of **1**, especially the signals from the fatty acid moiety and rings A−D. Analysis of the MS data revealed that the fatty acid moiety is the same stearic acid moiety of **1** and also was assigned to C-3 according to the HMBC spectroscopic data (Figure 2). Compound **3** differed from **1** only by the C-17 side chain. In **3**, the double bond was positioned at $\Delta^{23,24}$, as evidenced by an analysis of the ^{1}H−^{1}H COSY and HMBC data. The ^{1}H NMR spectrum of **3** showed two olefinic proton signals at δ 5.62 (d, J = 15.8 Hz, H-24) and 5.78 (m, H-23), which was

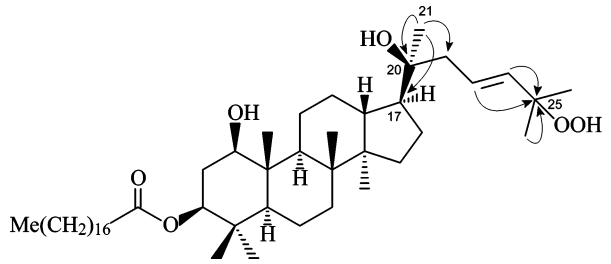

Figure 2. Selected HMBC correlations for compound **3**.

due to a double bond at C-23, C-24 from the presence of HMBC correlations between H-23/C-20, H_3-26/C-24, and H_3-27/C-24. The double bond (H-23, H-24) was assigned an *E* configuration due to the large coupling constant ($J = 15.8$ Hz) between its two protons. The effect of the hydroperoxyl group downfield of the quaternary carbon and the allylic carbon by 10 and 5 ppm, respectively, was reported.[14] This phenomenon was observed in compound **3**. The low-field signals at δ 82.4 and 127.6 were assigned as quarternary ^{13}C-25 and allylic ^{13}C-23, respectively. The correlations of C-25 to methyl protons at the 26 and 27 positions and olefinic proton at the 23 position were elucidated by a HMBC experiment. Furthermore, the comparison of the molecular formula of compound **1** to that of compound **3** showed two additional oxygen atoms, consistent with a hydroperoxyl group at the low-field quarternary C-25. On basic hydrolysis and GC-MS analysis, the fatty acid side chain of **3** was confirmed to be octadecanoic acid. Thus, the structure of **3** was assigned as 1β,20(*S*)-dihydroxy-25-hydroperoxydammar-23-(24)-ene-3-*O*-stearate and was given the trivial name bruguierin C.

The three dammarane triterpene stearic acid esters (**1**−**3**) were subjected to COX-1, COX-2, and luciferase assays. Compound **1** demonstrated significant inhibition against COX-2, with an IC_{50} value of 0.37 μM, whereas compounds **2** and **3** were inactive. However, none of these compounds exhibited activity toward COX-1. Bioassays for cancer chemopreventive activity, namely, the inhibition of TPA-activated NFκB luciferase and the induction of ARE luciferase, were also employed. The petroleum ether extract and bruguierin A (**1**) were found to inhibit activation, with IC_{50} values of 19.7 μg/mL and 1.4 μM, respectively. For induction of ARE luciferase, the petroleum ether extract of *B. gymnorrhiza* showed activity with an EC_{50} value of 0.7 μg/mL, whereas compounds **1**−**3** were active with EC_{50} values of 7.8, 9.4, and 15.7 μM, respectively.

Experimental Section

Gerneral Experimental Procedures. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. IR spectra were run on a JASCO FT/IR-410 spectrometer, equipped with a Specac Silver Gate ATR system by applying a film on a germanium plate. 1D and 2D NMR spectra were recorded on a Bruker DPX 300 or a 400 MHz spectrometer. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. FABMS were recorded on a JEOL GC Mate II spectrometer. GC-MS was carried out on an Agilent 6890N, with a fused silica capillary column (HP-INNOWAX, 0.32 mm (i.d.) × 30 m × 0.25 μm). The column temperature was first set at 140 °C and then programmed from 140 °C to 240 °C at a rate of 4 °C/min. The column was held at the final temperature for 15 min. The inlet temperature was kept at 250 °C. Split injections were performed with a 20:1 split ratio. Helium carrier gas was used at a constant flow rate of 1 mL/min with a constant pressure of 2.01 psi. The mass spectrometric detector was operated in the electron-impact ionization mode (EI, 70 eV). Column chromatography was carried out on silica gel G_{60} (0.063−0.2 mm, E. Merck). Thin-layer chromatography (TLC) was performed on TLC aluminum sheets coated with 0.25 mm layers of silica gel 60. Fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 30% H_2SO_4 in MeOH.

Plant Material. The flowers of *Bruguiera gymnorrhiza* were collected in Samutsongkram Province, Thailand, in September 2003. The plant material was identified by one of us (W.C.). Voucher specimens (nos. PBM 3757, 3758, and 3759) have been deposited in the Herbarium of the Department of Pharmaceutical Botany, Mahidol University, Bangkok, Thailand.

Extraction and Isolation. The air-dried and milled flowers of *B. gymnorrhiza* (1.2 kg) were extracted exhaustively in a Soxhlet apparatus with petroleum ether, cooled to room temperature, filtered, and evaporated to dryness under vacuum to yield 40 g of a crude extract. A portion of the extract (13 g) was fractionated by flash column chromatography over a silica gel G_{60} (0.063−0.2 mm, 150 g) column developed by solvent systems containing petroleum ether and increasing concentrations of chloroform and/or ethyl acetate to afford 21 fractions [petroleum ether−$CHCl_3$/10:0 (eluates F1, F2, each 0.5 L), 9.5:0.5 (eluates F3, F4, each 1.2 L), 8.5:1.5 (eluate F5, 0.8 L), 8:2 (eluate F6, 0.4 L), 6:4 (eluates F7−F9, each 0.8 L), 3:7 (eluates F10, F11, each 0.8 L), 1.5:8.5 (eluate F12, 1.4 L), respectively; $CHCl_3$−EtOAc/10:0 (eluates F13−F15, each 2 L), 8:2 (eluates F17, F18, each 0.8 L), 6:4 (eluate F19, 0.4 L), 0:10 (eluates F20, F21, each 1 L), respectively]. Fraction F15 (1.61 g) was rechromatographed on a silica gel G flash column (0.063−0.2 mm, 29 g), using a stepwise gradient system of $CHCl_3$−EtOAc, to give 12 fractions (F15.1−F15.12). Compound **3** (15 mg) was obtained from fraction F15.9 as a colorless gum. Fraction F16 (2.84 g) was subjected to repeated flash column chromatography on silica gel G (0.063−0.2 mm, 30 g), eluting with $CHCl_3$−EtOAc (9.5:0.5), to afford seven fractions (F16.1−F16.7). Fraction F16.3 was further fractionated on a prepacked Combi flash silica gel column (35−60 μm, 12 g) using $CHCl_3$−EtOAc (8:2) to afford compound **1** as a white wax (6.3 mg) by precipitation from EtOAc. Fraction F17 (0.47 g) was rechromatographed on a silica gel G (0.063−0.2 mm, 45 g) column, eluting sequentially with $CHCl_3$ and increasing volume of EtOAc to afford six fractions (F17.1−F17.6). Fraction F17.4 was further separated by a prepacked Combi flash silica gel column (35−60 μm, 3 g) using $CHCl_3$−EtOAc (7:3) to afford compound **2**. Compound **2** was obtained as white needles (15 mg) by crystallization from EtOAc.

Bruguierin A (1): white wax; $[\alpha]_D^{20}$ +31.5 (*c* 0.37, $CHCl_3$); IR (film) ν_{max} 3498 (br), 2924, 2853, 1714, 1465, 1376, 1181, 1117, 1098 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; FABMS *m*/*z* 750 [M + Na]$^+$ (9), 734 (1), 710 (1), 622 (1), 465 (1), 439 (1), 425 (6), 341 (2), 329 (2), 315 (2), 299 (3), 289 (1), 269 (1), 257 (2), 245 (2), 229 (3), 217 (5), 203 (11), 176 (41), 161 (16), 149 (25), 135 (34), 121 (43), 109 (100); HRFABMS *m*/*z* 749.6438 (calcd for $C_{48}H_{86}NaO_4$, 749.6424).

Bruguierin B (2): white needles; $[\alpha]_D^{20}$ +23.6 (*c* 0.13, $CHCl_3$); IR (film) ν_{max} 3466 (br), 3341 (br), 2920, 2861, 1722, 1485, 1367, 1249, 1104, 1025 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; FABMS *m*/*z* 750 [M + Na]$^+$ (4), 722 (2), 694 (1), 666 (1), 622 (1), 553 (1), 502 (1), 479 (1), 465 (1), 459 (1), 441 (1), 425 (2), 407 (2), 330 (6), 329 (12), 199 (10), 176 (100), 154 (38), 136 (25), 115 (14), 109 (20), 81 (18), 69 (51), 55 (30); HRFABMS *m*/*z* 749.6396 (calcd for $C_{48}H_{86}NaO_4$, 749.6424).

Bruguierin C (3): colorless gum; $[\alpha]_D^{20}$ +26.9 (*c* 0.58, $CHCl_3$); IR (film) ν_{max} 3414 (br), 2924, 2853, 1709, 1466, 1377, 1264, 1181, 1117 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; FABMS *m*/*z* 782 [M + Na]$^+$ (100), 754 (43), 687 (22), 681 (9), 597 (7), 515 (15), 510 (7), 413 (14), 408 (11), 361 (8); HRFABMS *m*/*z* 781.6322 (calcd for $C_{48}H_{86}NaO_6$, 781.6322).

Basic Hydrolysis[15] of 1−3. Compounds **1** (4.0 mg), **2** (4.0 mg), and **3** (1.4 mg) were hydrolyzed by 5% KOH in MeOH (2 mL) and stirred at 80 °C for 3 h. Each reaction mixture was neutralized with 2% HCl in MeOH (pH 4−5) and filtered. The filtrate was poured into 10 mL of water and then extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. After evaporation, the residues **1a** (3.0 mg), **2a** (2.5 mg), and **3a** (1.0 mg) were identified by GC-MS analysis. Compounds **1a**−**3a**: colorless gum, t_R 14.06 min; EIMS *m*/*z* [M]$^+$ 298 (16), 267 (5), 255 (14), 213 (3), 199 (8), 185 (4), 157 (1), 143 (19), 129 (7), 111 (3), 97 (7), 87 (69), 74 (100), 55 (28), 43 (37), 28 (12). In comparison with standard compounds, the methylated products **1a**−**3a** were found to correspond to octadecanoic acid methyl ester ([M]$^+$ *m*/*z* 298).

COX Assays. The effect of test compounds on cyclooxygenase-1 and -2 (COX-1 and -2) was determined by measuring PGE_2 production as previously described.[10] Indomethacin was used as a positive control, yielding IC_{50} values between 0.05−0.1 and 1−5 μM observed with COX-1 and COX-2, respectively.

Luciferase Assays. Luciferase assays were conducted as previously described.[10] Data for ARE induction (EC_{50} values) were expressed as

the concentration of compound that provoked an activation halfway between baseline (DMSO control) and maximum response at a concentration of 20 μg/mL. Data for NFκB constructs were expressed as IC_{50} values (the concentration required to inhibit TPA-activated NFκB activity by 50%). For ARE induction, sulforaphane (EC_{50} 4−6 μM), 4′-bromoflavone (EC_{50} 30 μM), and β-naphthoflavone (EC_{50} 8 μM) were used as standard inducer. With the experimental conditions employed, no signs of overt cellular toxicity were observed with the test compounds or extracts.

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