Flavanoids and Pterocarpans from the Bark of *Erythrina fusca*

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Three new isomeric flavanones, fuscaflavanones A_1 (1), A_2 (2) and B (3), together with six known flavanones, lupinifolin (4), lonchocarpol A (5), a mixture of lonchocarpols C_1 and C_2 (6a, b), and a mixture of lonchocarpols D_1 and D_2 (7a, b), five pterocarpans, sandwicensin (8), phaseollidin (9), erythrabissin I (10), and a mixture of dolichins A and B (11a, b), one chalcone, isobavachalcone (12), and one isoflavone, wighteone (13), were isolated from the bark of *Erythrina fusca* Lour. Their structures were elucidated on the basis of spectroscopic data. Some isolates were tested for antiplasmodial and cytotoxic activities and it was found that 5 and 9 exhibited moderate antiplasmodial activity against *Plasmodium falciparum*. For cytotoxicity, compounds 1, 4, 5, 9 and 12 showed moderate to weak activity against KB, BC and NCI-H187 cells, whereas 2 exhibited only weak activity against KB cells.

Key words *Erythrina fusca*; Leguminosae; flavanoid; pterocarpan; antiplasmodial activity; cytotoxicity

Erythrina fusca Lour. (Leguminosae), known in Thai as "Thong Long," is a medium to large, spreading tree, which grows up to 26 m tall. In Thailand, its root, bark and leaves are used as an antipyretic.[1] Previous studies on the seeds and leaves of this plant have yielded erythrina alkaloids,[2—4] while the stem bark yielded flavanones, pterocarpans and an isoflavone,[5—7] some of which have antibacterial and antimalarial activities.[8] As part of our continuing investigation of the secondary metabolites of the genus *Erythrina*, we now describe the isolation, structural elucidation, and evaluation of antiplasmodial and cytotoxic activities of isolates from the bark of *E. fusca*.

Results and Discussion

The EtOAc extract of *E. fusca* bark was separated by extensive column chromatography to give three new isomeric flavanones, named fuscaflavanones A_1 (**1**), A_2 (**2**) and B (**3**), along with six known flavanones, lupinifolin (**4**),[9] lonchocarpol A (**5**),[10,11] a mixture of lonchocarpols C_1 and C_2 (**6a**, **b**),[11,12] a mixture of lonchocarpols D_1 and D_2 (**7a**, **b**),[12] five pterocarpans, sandwicensin (**8**),[6,13] phaseollidin (**9**),[14] erythrabissin I (**10**),[14] and a mixture of dolichins A and B (**11a**, **b**),[15] one chalcone, isobavachalcone (**12**),[16] and one isoflavone, wighteone (**13**)[17,18] (Fig. 1). The structures of the known compounds were determined by comparing the spectroscopic data ($[\alpha]_D$, NMR, and MS) with reported values.

Compounds **1** and **2** were obtained as pale yellow gum with $[\alpha]_D^{27}$ −51.9 (c=0.31, $CHCl_3$) and +36.4 (c=0.30, $CHCl_3$), respectively. The UV spectra of **1** and **2** exhibited absorption maxima at 362, 301, 275, 223, and 205 nm. Their IR spectra revealed absorbance bands at 3421—3346 (O–H), 1638 (conj. C=O), 1628 (C=C), 1618 (C=C), and 1519 (C=C). Moreover, both compounds gave the same molecular formula, $C_{25}H_{26}O_6$, established by HR-electrospray ionization (ESI)-MS ($[M-H]^-$ at m/z 421.1652 and 421.1651, respectively), and displayed highly similar 1D and 2D NMR data, suggesting they were epimeric. The ^{1}H-NMR spectrum of **1** (Table 1) showed the characteristic signals for a 5-hydroxypyranoflavanone at δ_H 12.23 (1H, s, OH-5), 6.77 (1H, d, J=10.0 Hz, H-4″), 5.42 (1H, d, J=10.0 Hz, H-3″), 5.33 (1H, dd, J=12.7, 2.6 Hz, H-2), 3.02 (1H, dd, J=17.1, 12.7 Hz, H-3_{ax}) and 2.79 (1H, dd, J=17.1, 2.6 Hz, H-3_{eq}), one prenyl group at δ_H 5.10 (1H, t, J=7.1 Hz, H-2‴), 3.20 (2H, d, J=7.1 Hz, H-1‴), 1.67 (3H, s, C$\underline{H}_3$-4‴) and 1.65 (3H, s, C$\underline{H}_3$-5‴), and a p-substituted ring B at δ_H 7.28 (2H, d, J=8.2 Hz, H-2′, 6′) and 6.85 (2H, d, J=8.2 Hz, H-3′, 5′). In addition, the ^{1}H- and ^{13}C-NMR spectra of **1** closely resembled those of lupinifolin (**4**)[9] except for the presence of a hydroxymethyl group [δ_H 3.65 and 3.46 (each 1H, d, J=11.8 Hz); δ_C 68.2], instead of one of the two methyl groups of 2,2-dimethylpyran moiety in **4**. The heteronuclear multiple bond correlations (HMBC) from the oxymethylene protons (δ_H 3.65, 3.46) to C-2″ (δ_C 81.0), C-3″ (δ_C 121.8), and C-6″ (δ_C 23.0), and from H-6″ (δ_H 1.42) to C-2″, C-3″ and the oxymethylene

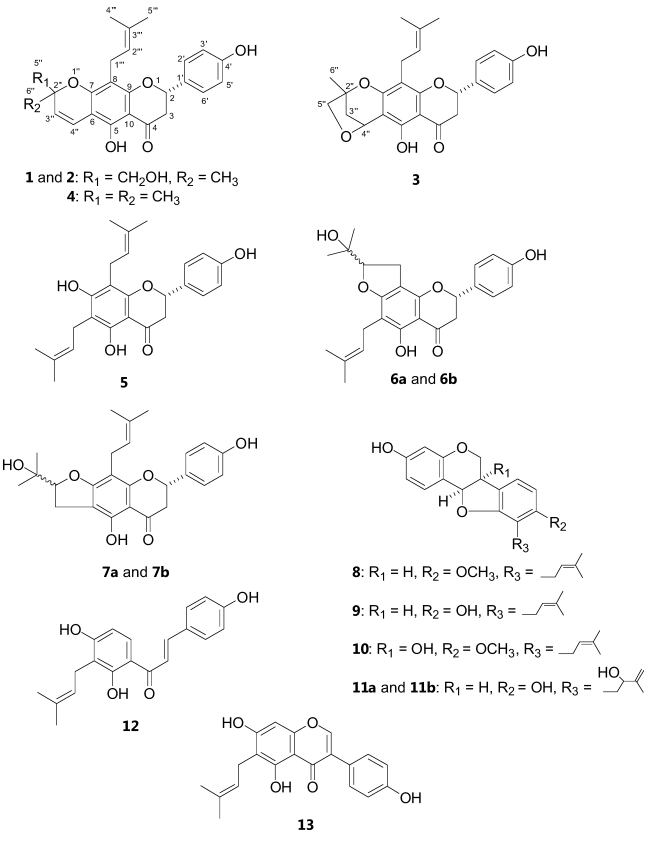

Fig. 1. Chemical Structures of Isolated Compounds

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Table 1. ^{1}H- (400 MHz) and ^{13}C- (100 MHz) NMR Data for Compounds **1**—**3** in $CDCl_3$

Position	**1**		**2**		**3**	
	δ_H (m, *J* in Hz)	δ_C	δ_H (m, *J* in Hz)	δ_C	δ_H (m, *J* in Hz)	δ_C
2	5.33 (dd, 12.7, 2.6)	78.6	5.31 (dd, 12.8, 2.9)	78.6	5.29 (br d, 12.3)	78.4, 78.5
3_{ax}	3.02 (dd, 17.1, 12.7)	43.1	3.03 (dd, 17.1, 12.8)	43.1	2.99 (dd, 17.1, 12.3)	43.1
3_{eq}	2.79 (dd, 17.1, 2.6)		2.79 (dd, 17.1, 2.9)		2.77 (br d, 17.1)	
4		196.5		196.6		196.36, 196.40
5		156.8		156.8		157.4
6		102.9		102.7		106.5
7		159.3		159.3		160.7
8		108.3		108.3		108.00, 108.08
9		159.5		159.6		159.5
10		102.7		102.9		102.50, 102.59
1′		130.7		130.6		131.0
2′, 6′	7.28 (d, 8.2)	127.7	7.28 (d, 8.4)	127.7	7.28 (d, 8.2)	127.6
3′, 5′	6.85 (d, 8.2)	115.5	6.84 (d, 8.4)	115.5	6.84 (d, 8.2)	115.5
4′		156.0		156.1		155.9
2″		81.0		80.9		85.0, 85.1
3″	5.42 (d, 10.0)	121.8	5.42 (d, 10.0)	121.8	2.15 (dd, 12.2, 5.3) 2.05 (br d, 12.2)	38.2
4″	6.77 (d, 10.0)	118.6	6.77 (d, 10.0)	118.6	5.45 (t, 5.3)	68.66, 68.68
5″	3.65 (d, 11.8) 3.46 (d, 11.8)	68.2	3.66 (d, 11.8) 3.48 (d, 11.8)	68.3	4.06, 4.07 (d, 10.2) 3.79 (d, 10.2)	78.9, 79.0
6″	1.42 (s)	23.0	1.41 (s)	22.9	1.62 (s)	20.6
1‴	3.20 (d, 7.1)	21.4	3.20 (d, 7.2)	21.5	3.14 (d, 7.0)	21.40, 21.43
2‴	5.10 (t, 7.1)	122.8	5.10 (t, 7.2)	122.8	5.11 (t, 7.0)	122.2
3‴		132.1		132.0		131.2
4‴	1.67 (s)	17.7	1.65 (s)	17.7	1.60 (s)	17.7
5‴	1.65 (s)	25.6	1.66 (s)	25.6	1.62 (s)	25.7
5-OH	12.23 (s)		12.22 (s)		12.18, 12.19 (s)	

carbon (δ_C 68.2) confirmed that the hydroxymethyl group is located at C-2″. The circular dichroism (CD) spectra of **1** and **2** displayed positive and negative Cotton effects near 340—380 and 310 nm, respectively, suggesting the absolute stereochemistry at C-2 was *S*,[19,20] whereas an attempt to determine configuration at C-2″ failed. However, comparison of the sign of $[\alpha]_D$ values and CD curves of **1** and **2** with those of lonchocarpols D_1 and D_2 (**7a**, **b**), separated by HPLC in this study, further supported that **1** differed from **2** only in the stereochemistry at C-2″. Thus, compounds **1** and **2** were 2″-epimers, identified as (2*S*)-5,4′-dihydroxy-8-(3,3-dimethylallyl)-2″-hydroxymethyl-2″-methylpyrano[5,6:6,7]flavanone, and named fuscaflavanones A_1 and A_2, respectively.

Compound **3** was obtained as a pale yellow gum with $[\alpha]_D^{27}$ −4.7 (*c*=0.41, $CHCl_3$). The HR-ESI-MS gave an $[M-H]^-$ peak at *m/z* 421.1650 corresponding to the same molecular formula $C_{25}H_{26}O_6$ as **1**. Compound **3** exhibited IR absorptions at 3329 (O–H), 1643 (conj. C=O), 1594 (C=C), and 1519 (C=C) cm^{-1} as well as UV absorptions at 342, 298, 223, and 205 nm. Its ^{1}H- and ^{13}C-NMR spectra (Table 1) closely resembled those of **1**. The marked difference between the ^{1}H-NMR spectra of **3** and **1** was in the resonance position and the splitting patterns of signals from the protons at C-3″ and C-4″. Hence, protons at C-3″ in **3** showed a doublet of doublets and a broad doublet each integrating for one proton at δ_H 2.15 (*J*=12.2, 5.3 Hz) and 2.05 (*J*=12.2 Hz), respectively, whereas the protons at C-4″ appeared as a triplet integrating for one proton at δ_H 5.45 (*J*=5.3 Hz). In compound **1**, the signals for the protons on the corresponding carbons were integrated for one proton each and appeared as two sets of doublets at δ_H 5.42 and 6.77 (each *J*=10.0 Hz), respectively. The chemical shift positions and the splitting patterns for H-3″ and H-4″ in the two compounds indicated that the –CH=CH– moiety in **1** was replaced by the $-CH_2-\overset{1}{C}H-O-$ moiety in **3**. Further support was obtained from ^{13}C-NMR spectra which revealed that the C-3″ and C-4″ signals in **1** at δ_C 121.8 and 118.6, respectively, disappeared in the spectrum of **3**, and instead the signals at δ_C 38.2 and 68.6 were observed. In addition, the downfield shifts of C-6″ methyl protons (δ_H 1.62) and C-5″ oxymethylene protons (δ_H 4.06, 3.79), compared with those of **1**, were observed in the ^{1}H-NMR spectrum of **3**. These results indicated the presence of a 1-methyl-2,6-dioxabicyclo[3,2,1]oct-3-ene moiety in **3**, presumably derived from ring closure between the C-5″ hydroxy group and the adjacent double bond at C-4″ of 2″-hydroxymethyl-2″-methylpyran moiety in **1**. The location of the 1-methyl-2,6-dioxabicyclo[3,2,1]oct-3-ene moiety was determined to be at the C-6 and C-7 positions of the A-ring on the basis of HMBC correlations from H-4″ (δ_H 5.45) to C-5 (δ_C 157.4), C-6 (δ_C 106.5) and C-7 (δ_C 160.7). Furthermore, HMBC correlations, particularly from H-4″ to C-2″ (δ_C 85.0) and C-5″ (δ_C 78.9) as well as correlations from H-5″ (δ_H 4.06, 3.79) to C-2″, C-3″ (δ_C 38.2), C-4″ (δ_C 68.6) and C-6″ (δ_C 20.6), supported that the C-5″ methylene was linked *via* an oxygen atom to C-4″ to form a fused tetrahydrofuran ring. Careful examination of both ^{1}H- and ^{13}C-NMR spectra of **3** suggested that compound **3** was a diastereoisomeric mixture, as evident from the split of some ^{1}H- and ^{13}C-NMR signals into a doublet in nearly 1 : 1 ratio (Table 1). The CD spectrum of **3** showed similar characteristics as those of **1** and **2**, suggesting this compound also has the *S*-configuration at C-2, whereas the stereochemistry of the junction chiral cen-

Table 2. Antiplasmodial and Cytotoxic Activities of Some Isolated Compounds

Compound	Antiplasmodial (IC_{50}, μg/ml)	Cytotoxicity (IC_{50}, μg/ml)		
		KB	BC	NCI-H187
1	Inactive[a)]	13.4	14.62	6.26
2	Inactive[a)]	15.07	Inactive[b)]	Inactive[b)]
4	Inactive[a)]	6.44	15.6	12.79
5	9.18	8.49	5.14	13.19
9	9.09	7.7	14.32	5.05
12	Inactive[a)]	18.08	14.87	6.25
13	Inactive[a)]	Inactive[b)]	Inactive[b)]	Inactive[b)]

a) Inactive at $\geq$10 μg/ml; *b*) Inactive at >20 μg/ml.

ters C-2″ and C-4″ was not defined. Therefore, compound **3** was identified as (2*S*)-5,4′-dihydroxy-8-(3,3-dimethylallyl)-1-methyl-2,6-dioxabicyclo[3,2,1]octano[3,4:6,7]flavanone, and named fuscaflavanone B.

To our knowledge, compound **3** is the first example of flavanone having a fused 1-methyl-2,6-dioxabicyclo[3.2.1]oct-3-ene ring. The known compounds, a mixture of lonchocarpols C_1 and C_2 (**6a**, **b**), a mixture of lonchocarpols D_1 and D_2 (**7a**, **b**), and a mixture of dolichins A and B (**11a**, **b**), were identified for the first time from the genus *Erythrina*. Compounds **1**, **2**, **4**, **5**, **9**, **12** and **13** were evaluated for antiplasmodial and cytotoxic activities. The results are presented in Table 2. Compounds **5** and **9** exhibited moderate antiplasmodial activity against *Plasmodium falciparum* with IC_{50} values of 9.18 and 9.09 μg/ml, respectively, whereas the rest of the compounds tested were inactive. For cytotoxicity, compounds **1**, **4**, **5**, **9** and **12** showed moderate to weak activity against KB, BC and NCI-H187 cells (IC_{50} 5.05—18.08 μg/ml), whereas **2** exhibited only weak activity against KB cells (IC_{50} 15.07 μg/ml). Only compound **13** was inactive in all cytotoxicity tests.

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO-1020 polarimeter. CD spectra were recorded on a JASCO J-810 spectropolarimeter, and UV spectra were measured on a Analytik Jena SPECORD S100 spectrophotometer. IR spectra were obtained using a Perkin Elmer FT-IR Spectrum BX spectrophotometer. 1D and 2D NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer. Chemical shifts (δ) are expressed in ppm with reference to the solvent signals. ES-MS and HR-ESI-MS were recorded on a Finnigan LC-Q mass spectrometer and a Micromass Instrument type QTOF2 spectrometer, respectively. Column chromatography (CC) was carried out using Merck silica gel 60 (<0.063 mm) and Amersham Biosciences Sephadex LH-20. For TLC, Merck precoated silica gel 60 F_{254} plates were used. Spots on TLC were visualized under UV light and by spraying with anisaldehyde–H_2SO_4 reagent followed by heating. HPLC purification was carried out on a Agilent 1200 Series apparatus, equipped with quarternary pump, photodiode array detector, and ChemStation software using a Phenomenex SphereClone ODS(2) column (4.60×250 mm, 5 μm).

Plant Material The bark of *E. fusca* was collected from Panomsarakam District, Chachoengsao Province, Thailand, in February 2007. A voucher specimen (No. BKF 112379) has been deposited at the herbarium of the Royal Forest Department, Ministry of Agriculture and Cooperatives, Bangkok.

Extraction and Isolation The air-dried, powdered bark of *E. fusca* (2.92 kg) was extracted successively with *n*-hexane, EtOAc and MeOH at room temperature. The hexane, EtOAc and MeOH extracts were filtered and concentrated to dryness under reduced pressure.

The EtOAc extract (280.1 g) was subjected to CC, using a gradient solvent system of hexane, hexane–EtOAc and EtOAc in increasing polarity to give 13 fractions (E1—E13). Fraction E4 (749 mg) was subjected to repeated CC, using EtOAc–hexane (90 : 10) to afford **8** (590 mg), whereas E6 (3.4 g) was fractionated by CC, using hexane–EtOAc (80 : 20) to give seven fractions (E14—E20). Fraction E16 (370 mg) was separated by CC, using hexane–EtOAc (80 : 20) and further purified over Sephadex LH-20 eluted with MeOH to yield **4** (265 mg). Fraction E18 (506 mg) was rechromatographed, using hexane–EtOAc (85 : 15) to furnish **5** (475 mg). Fraction E7 (3.3 g) was separated by CC twice in succession, using hexane–EtOAc (80 : 20) and CH_2Cl_2 to give **9** (18 mg) and a mixture of **11a** and **11b** (9 mg). Fraction E9 (18.1 g) was subjected to CC twice in succession, using hexane–EtOAc (80 : 20) and CH_2Cl_2–MeOH (99 : 1) to afford five fractions (E21—25). Fraction E23 (2.6 g) was fractionated by CC, using CH_2Cl_2–MeOH (99 : 1) to furnish four fractions (E26—29). Fraction E27 (31 mg) was separated on Sephadex LH-20 eluted with MeOH and further purified by repeated CC, using CH_2Cl_2–MeOH (99 : 1) to yield **12** (9 mg). Fraction E28 (150 mg) was subjected to repeated CC, using CH_2Cl_2–MeOH (99.5 : 0.5) to give **1** (12 mg). Fraction E24 (4.1 g) was rechromatographed, using CH_2Cl_2–MeOH (99.5 : 0.5) to give six fractions (E30—35). Fraction E33 afforded **13** (19 mg), whereas E34 (2.8 g) was chromatographed in the same manner as E9 to furnish five fractions (E36—40). Fraction E36 (25 mg) was purified by CC, using hexane–EtOAc (80 : 20) to afford **3** (10 mg). Fraction E37 (90 mg) was separated by CC twice in succession, using CH_2Cl_2–MeOH (99.5 : 0.5) and hexane–EtOAc (80 : 20) to give three fractions (E41—43). Fraction E42 yielded **2** (7 mg), whereas E43 (44 mg) was purified by CC, using hexane–EtOAc (85 : 15) to afford a mixture of **6a** and **6b** (9 mg). Fraction E38 furnished **10** (72 mg), whereas E39 (315 mg) was purified in the same manner as E37 to give a mixture of **7a** and **7b** (120 mg). The mixture of **7a** and **7b** was further purified by HPLC using a gradient of 40 : 27 to 60 : 73 H_2O–MeOH at 1.0 ml/min to give **7a** (t_R=17.63 min) and **7b** (t_R=18.73 min).

Fuscaflavanone A_1 (**1**): Pale yellow gum; $[\alpha]_D^{27}$ −51.9 (*c*=0.31, $CHCl_3$); CD (*c*=0.15, MeOH) $[\theta]_{380}$ +10.90, $[\theta]_{347}$ +9.78, $[\theta]_{331}$ −0.03, $[\theta]_{310}$ −14.16; UV λ_{max} (MeOH) nm (log ε): 362 (3.36), 301 (3.89), 275 (4.41), 223 (4.16), 205 (4.25); IR (KBr) ν_{max}: 3346, 2966, 2924, 1638, 1628, 1618, 1519, 1455, 1375, 1336, 1297, 1205, 1171, 1126, 1104, 1056, 899, 833 cm^{-1}; for ^{1}H- and ^{13}C-NMR spectroscopic data, see Table 1; ES-MS *m/z*: 421 $[M-H]^-$; HR-ESI-MS *m/z*: 421.1652 (Calcd for $C_{25}H_{26}O_6$–H, 421.1651).

Fuscaflavanone A_2 (**2**): Pale yellow gum; $[\alpha]_D^{27}$ +36.4 (*c*=0.30, $CHCl_3$); CD (*c*=0.07, MeOH) $[\theta]_{383}$ +5.34, $[\theta]_{341}$ +3.67, $[\theta]_{332}$ −0.19, $[\theta]_{312}$ −7.79; UV λ_{max} (MeOH) nm (log ε): 362 (3.16), 301 (3.90), 275 (4.05), 223 (3.89), 203 (4.00); IR (KBr) ν_{max}: 3421, 2970, 2925, 2868, 1639, 1628, 1618, 1519, 1459, 1452, 1380, 1339, 1205, 1171, 1126, 1111, 1057, 901, 834 cm^{-1}; for ^{1}H- and ^{13}C-NMR spectroscopic data, see Table 1; ES-MS *m/z*: 421 $[M-H]^-$; HR-ESI-MS *m/z*: 421.1651 (Calcd for $C_{25}H_{26}O_6$–H, 421.1651).

Fuscaflavanone B (**3**): Pale yellow gum; $[\alpha]_D^{27}$ −4.7 (*c*=0.41, $CHCl_3$); CD (*c*=0.07, MeOH) $[\theta]_{369}$ +15.55, $[\theta]_{354}$ +0.25, $[\theta]_{317}$ −14.64; UV λ_{max} (MeOH) nm (log ε): 342 (3.45), 298 (3.98), 223 (4.22), 205 (4.20); IR (KBr) ν_{max}: 3329, 2925, 2878, 1643, 1594, 1519, 1444, 1382, 1311, 1263, 1217, 1174, 1147, 1122, 1100, 1079, 1026, 954, 884, 835 cm^{-1}; for ^{1}H- and ^{13}C-NMR spectroscopic data, see Table 1; ES-MS *m/z*: 421 $[M-H]^-$; HR-ESI-MS *m/z*: 421.1650 (Calcd for $C_{25}H_{26}O_6$–H, 421.1651).

Lonchocarpol D_1 (**7a**): Pale yellow gum; $[\alpha]_D^{31}$ +23.6 (*c*=0.15, $CHCl_3$); CD (*c*=0.04, MeOH) $[\theta]_{331}$ +30.14, $[\theta]_{319}$ −0.24, $[\theta]_{305}$ −12.28.

Lonchocarpol D_2 (**7b**): Pale yellow gum; $[\alpha]_D^{31}$ −18.0 (*c*=0.26, $CHCl_3$); CD (*c*=0.13, MeOH) $[\theta]_{365}$ +14.23, $[\theta]_{347}$ −0.43, $[\theta]_{298}$ −15.67.

Antiplasmodial Assay Antiplasmodial activity was evaluated against the parasite *Plasmodium falciparum* (K1, multidrug resistant strain) which was cultured continuously according to the method of Trager and Jensen.[21] Quantitative assessment of antiplasmodial activity *in vitro* was determined by means of the microculture radioisotope technique based upon the method described by Desjardins *et al.*[22] The inhibitory concentration (IC_{50}) represents the concentration which causes 50% reduction in parasite growth as indicated by the *in vitro* uptake of [^{3}H]-hypoxanthine by *P. falciparum*. An IC_{50} value of 1 ng/ml was observed for the standard compound, dihydroartemisinin, in the same test system.

Cytotoxicity Assay Cytotoxicity assays against oral human epidermal carcinoma (KB), human breast cancer (BC) and human small cell lung cancer (NCI-H187) cells were performed employing the colorimetric method.[23] The standard drug ellipticine exhibited IC_{50} values against these cell lines at 1.33, 1.46 and 0.39 μg/ml, respectively.

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