Leuconoxine, Kopsinitarine, Kopsijasmine, and Kopsinone Derivatives from *Kopsia*

Siew-Huah Lim,[†] Kooi-Mow Sim,[†,§] Zanariah Abdullah,[†] Osamu Hiraku,[‡] Masahiko Hayashi,[‡] Kanki Komiyama,[‡] and Toh-Seok Kam*[,†]

Department of Chemistry, University of Malaya, 50603 Kuala Lumpur, Malaysia, and The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

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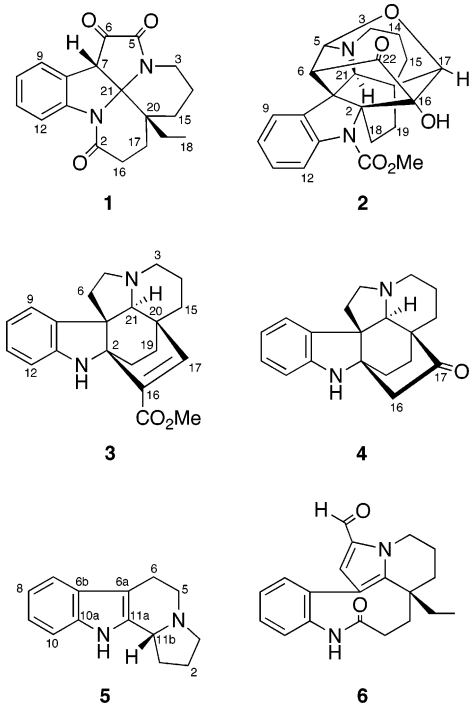
Four new indole alkaloids were obtained from two *Kopsia* species, 6-oxoleuconoxine (**1**) from the leaf extract of *K. griffithii* and kopsinitarine E (**2**), kopsijasminine (**3**), and kopsonoline (**4**) from the stem-bark extract of *K. teoi*. The structures of these alkaloids were determined using NMR and MS analysis. Kopsijasminine (**3**) showed moderate activity in reversing multidrug resistance in vincristine-resistant KB cells.

The genus *Kopsia*, widely distributed in Southeast Asia,[1−3] is rich in indole alkaloids, and the Malaysian representatives in particular are fertile sources of novel alkaloids with unusual or intriguing carbon skeletons and interesting biological activity.[4] In continuation of our studies on the Malaysian members of this genus,[5−24] we report the structures of four new indole alkaloids, viz., 6-oxoleuconoxine (**1**) from *K. griffithii* King & Gamble var. *griffithii*[3] and kopsinitarine E (**2**), kopsijasminine (**3**), and kopsonoline (**4**) from *K. teoi* L. Allorge.[3] We previously reported the structure of the tetrahydro-β-carboline derivative, (+)-harmicine,[24] as well as the antileishmanial activity of several other alkaloids, including the quasidimeric buchtienine, from *K. griffithii*.[25] Recent enantioselective syntheses of both (*S*)-(−)- and (*R*)-(+)-harmicine has resulted in the correct assignment of the absolute configuration of naturally occurring (+)-harmicine as *R*, as shown in **5**.[26,27] In this report we also include (see Experimental Section) the ^{1}H NMR data of (+)-harmicine, in view of some minor errors in our earlier report.[24] We have also previously reported the structure of the rhazinilam derivative rhazinal (**6**), which was then attributed to *K. teoi*.[28] Since our initial report, a synthesis of rhazinal has also been published.[29] In the light of Middleton's latest revision of the genus *Kopsia*[3] however, the source of this alkaloid requires amendment to *K. singapurensis*.

In addition to the alkaloids previously reported,[24,25] we wish to report the structure of a new leuconoxine derivative from the leaf extract of *K. griffithii*. Compound **1** was obtained as a colorless oil, $[\alpha]_D$ +75 (*c* 0.03, $CHCl_3$). The IR spectrum showed bands due to ketone (1715 cm^{-1}) and lactam carbonyl (1689 cm^{-1}) functions, while the UV spectrum showed absorption maxima at 202, 234, 251, and 349 nm, which is somewhat similar to those of leuconoxine.[30] The EIMS of **1** showed a molecular ion at *m*/*z* 324, which analyzed for $C_{19}H_{20}N_2O_3$. The ^{13}C NMR spectrum (Table 1) showed a total of 19 resonances, comprising one methyl, six methylenes, five methines, and seven quaternary carbon atoms, in agreement with the molecular formula. The observed quaternary carbon resonances at δ 192.5, 157.5, and 172.2 are consistent with the presence of ketone and lactam functionalities. The ^{1}H NMR spectrum (Table 2) showed the presence of four aromatic hydrogens and an ethyl side chain. The spectrum bears some similarities to that of leuconoxine, with the characteristically deshielded H-12 due to anisotropy by the proximate lactam carbonyl.[30] Similarity with leuconoxine was further reinforced by the presence of the characteristic quaternary carbon resonance at δ 88.0, corresponding to the doubly spirocyclic C-21, as well as the characteristic resonance due to the benzylic H-7 in the ^{1}H NMR spectrum of **1**.[30] In leuconoxine, H-7 is a doublet at δ 3.81, while in compound **1**, the H-7 resonates as a singlet at δ 4.23. Analysis of the COSY and HMQC spectral data of **1** revealed the presence of some fragments also present in leuconoxine, such as $NCH_2CH_2CH_2$ and CH_2CH_2, corresponding to the C(3)−C(14)−C(15) and C(16)−C(17) units, respectively. Conspicuously absent was the $CHCH_2$ fragment corresponding to the C(7)−C(6) unit of leuconoxine. This, coupled with the observation of H-7 as a singlet, suggested C-6 as the site of oxygenation and accounts for the ketone resonance observed at δ 192.5. Further verification was provided by the HMBC data, which showed the key two-bond correlation from H-7 to C-6. The HMBC data also permitted differentiation of the two lactam carbonyl resonances; the resonance at δ 157.5 is assigned to C-5 from the observed three-bond correlations from H-3 and H-7 to C-5, while that at δ 172.2 is due to C-2 from the observed three-bond correlation from H-17 to C-2. Compound **1** is therefore 6-oxoleuconoxine.



* To whom correspondence should be addressed. Phone: 603-79674266. Fax: 603-79674193. E-mail: tskam@um.edu.my.
† University of Malaya.
‡ The Kitasato Institute.
§ Present address: Faculty of Engineering & Science, Universiti Tunku Abdul Rahman, Jalan Genting Kelang, 53300 Kuala Lumpur, Malaysia

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Table 1. ^{13}C NMR Data for **1**−**4** (100 MHz, $CDCl_3$)[a]

C	1	2	3	4
2	172.2	70.6	70.4	64.5
3	37.8	46.7	47.3	47.4
5	157.5	94.5	49.9	48.7
6	192.5	58.9	37.1	35.4
7	53.4	57.7	62.5	56.8
8	126.2	132.9	136.5	138.1
9	125.1	122.8	122.4	122.2
10	125.9	124.6	119.8	120.3
11	129.9	128.8	127.2	127.2
12	121.0	116.6	110.8	110.9
13	142.6	141.3	149.9	149.1
14	20.1	22.5	16.5	16.4
15	26.3	34.2	28.5	29.9
16	29.5	87.6	134.9	44.7
17	26.6	91.5	146.0	213.6
18	7.3	17.5	33.9	29.7
19	27.7	27.6	33.4	29.3
20	37.6	30.1	39.0	44.2
21	88.0	65.7	69.7	69.8
22		206.5		
NCO_2Me		53.9		
NCO_2Me		156.2		
CO_2Me			51.7	
CO_2Me			164.9	

[a] Assignments based on COSY and HETCOR.

Three additional minor alkaloids were obtained from the stem-bark extract of *K. teoi*. Compound **2** was obtained as a light yellowish oil, $[\alpha]_D$ −21 (*c* 0.04, $CHCl_3$). The IR spectrum showed bands due to OH (3351 cm^{-1}), ketone (1772 cm^{-1}), and carbamate (1677 cm^{-1}) functions, while the UV spectrum showed dihydroindole absorptions at 207, 238, 279, and 287 nm. The FABMS of **2** showed an $[M + H]^+$ ion at *m*/*z* 395, and high resolution measurements gave the formula $C_{22}H_{22}N_2O_5$. The ^1H NMR spectrum (Table 2) showed the presence of an unsubstituted aromatic moiety, an OH resonance at δ 6.90, a methoxy resonance at δ 3.92 associated with a carbamate function (δ_C 156.2), two vicinally coupled AX doublets at δ 5.24 and 2.63 with $J = 5$ Hz, and another pair of coupled doublets with a smaller coupling of 2 Hz at δ 4.10 and 3.57. The ^{13}C NMR spectrum (Table 1) showed, in addition to the presence of a carbamate carbonyl, two oxymethines at δ 94.5 and 91.5 and a low-field quaternary resonance at δ 87.6. All these features are strongly reminiscent of the cage kopsinitarines, previously obtained from the leaf extract of the same plant.[20,22] Thus, the AX doublets at δ 5.24 and 2.63 are due to H-5 and H-6, respectively, while the other pair of doublets at δ 4.10 and 3.57 are due to H-17 and H-21, respectively, with *W*-coupling of 2 Hz. The characteristic quaternary resonance at δ 87.6 is due to C-16. The main differences in compound **2** compared to the other kopsinitarines are the lack of aromatic methoxy substitution and 14,15-unsaturation and the absence of OH substitution at C-15. The NMR data are in complete accord with this conclusion, as are the 2-D NMR data, where the COSY spectrum showed fragments due to *N*$CH_2CH_2CH_2$, CH_2CH_2, and CHCH, in addition to the long-range *W*-coupling between H-21 and H-17. Compound **2** is therefore a new kopsinitarine congener, which we designate as kopsinitarine E.

Compound **3**, kopsijasminine, was isolated as a light yellowish oil, $[\alpha]_D$ −60 (*c* 0.05, $CHCl_3$). The IR spectrum showed bands due to NH (3367 cm^{-1}) and ester carbonyl (1709 cm^{-1}) functions, while the UV spectrum showed dihydroindole absorptions at 206, 243, and 292 nm. The FABMS of **3** showed an $[M + H]^+$ ion at *m*/*z* 337, and high resolution measurements gave the formula $C_{21}H_{24}N_2O_2$. The observation of the ester carbonyl stretching at lower frequency suggested conjugation, and this is supported by the observed shift of the carbonyl function at δ 164.9 in the ^{13}C NMR spectrum. The ^1H and ^{13}C NMR data (Tables 1 and 2) are typical of an aspidofractinine compound. Notable features include an unsubstituted indole ring, absence of a carbamate substituent on the indolic nitrogen from the observed NH resonance at δ 4.32, a vinylic singlet at δ 7.03, the downfield shift being characteristic of a β-hydrogen of an α,β-unsaturated carbonyl moiety, and a trisubstituted double bond (δ_C 134.9, 146.0). The latter two features are reminiscent of dehydropleiocarpine-type alkaloids[31−33] and correspond to the presence of unsaturation across the 16,17-bridge in aspidofractinine compounds. Comparison with the *Kopsia* alkaloid kopsijasmine[33] from *K. jasminiflora* showed similar NMR data except for the absence of the carbamate function. Kopsijasminine (**3**) is therefore the *N*(1)-decarbomethoxy derivative of kopsijasmine.

Table 2. ^1H NMR Data for **1**−**4** (400 MHz, $CDCl_3$)[a]

H	1	2	3	4
3	3.10 ddd (13,11,4)	3.23 td (14, 6)	3.10 m	3.08 m
	4.11 ddd (13, 5, 2.3)	3.45 dd (14, 6)	3.10 m	3.08 m
5		5.24 d (5)	2.66 td (9, 7)	2.67 td (10.5, 6.5)
			2.79 t (9)	2.75 ddd (10.5, 8.5, 1)
6		2.63 d (5)	1.67 dt (14, 9)	1.69 ddd (14, 10.5, 8.5)
			2.29 dd (14, 7)	2.58 ddd (14, 6.5, 1)
7	4.23 s			
9	7.22 dd (7.6, 1)	7.33 br d (7.5)	7.26 br d (7.5)	7.30 dd (7.5, 1)
10	7.16 td (7.6, 1)	7.09 td (7.5, 1)	6.78 td (7.5, 1)	6.84 td (7.5, 1)
11	7.37 td (7.6, 1)	7.24 td (7.5, 1)	7.04 td (7.5, 1)	7.06 td (7.5, 1)
12	7.82 dd (7.6, 1)	7.52 br d (7.5)	6.73 br d (7.5)	6.70 br d (7.5)
14	1.7 m	1.52 m	1.35 m	1.27 m
	1.7 m	2.47 qt (14, 6)	1.96 m	2.02 m
15	1.7 m	1.61 m	1.18 dd (12, 2)	1.08 td (13, 4)
	2.05 m	1.97 dd (14,6)	1.88 ddd (12, 9, 5)	2.18 m
16	2.59 ddd (19, 6, 1.4)			2.52 d (19)
	2.86 ddd (19, 14, 6.5)			3.03 dd (19, 3)
17	1.66 td (14, 6)	4.10 d (2)	7.03 s	
	1.98 ddd (14, 6.5, 1.4)			
18	0.92 t (7.4)	1.57 m	1.46 td (12,3.5)	1.41 m
		2.19 ddd (13, 11, 2)	2.01 m	1.41 m
19	1.23 dq (13, 7.4)	1.35 ddd (13, 11, 2)	1.12 dd (12, 5)	1.41 m
	1.49 dq (13, 7.4)	1.47 m	1.38 m	2.07 m
21		3.57 d (2)	3.37 s	3.50 s
NCO_2Me		3.92 s		
CO_2Me			3.82 s	
NH			4.32 br s	3.56 br s
16-OH		6.90 br s		

[a] Assignments based on COSY and HETCOR.

Compound **4**, kopsonoline, was isolated as a light yellowish oil, $[\alpha]_D$ +27 (*c* 0.41, $CHCl_3$). The IR spectrum showed bands at 3340 and 1708 cm^{-1} due to NH and ketone functions, respectively, while the UV spectrum showed dihydroindole absorptions at 209, 241, and 291 nm. The FABMS of **4** showed an $[M + H]^+$ ion at *m*/*z* 295, and high resolution measurements gave the formula $C_{19}H_{22}N_2O$. The presence of a ketone function was confirmed by the observed ketone carbonyl at δ 213.6 in the ^{13}C NMR spectrum, while the indolic NH resonated as a broad singlet at δ 3.56 in the ^1H NMR spectrum. The NMR data (Tables 1 and 2) were also characteristic of aspidofractinine compounds, which was supported by the COSY spectrum, which indicated the presence of one $CH_2CH_2CH_2$ and two ethylene fragments. In addition, an isolated methine characteristic of H-21 resonated as a singlet at δ 3.50, while an isolated methylene was evident from the resonances at δ 3.03 (dd, $J = 19$, 3 Hz) and 2.52 (d, $J = 19$ Hz). The chemical shift of the methylene hydrogens suggested that it was adjacent to a carbonyl function and together with the COSY data indicated either position 19 or 17 as the site of oxygenation. The absence of *W*-coupling to H-21 indicated that oxygenation was likely at C-17. This was further confirmed by comparison of the ^{13}C NMR data with synthetic racemic 17-oxoaspidofractinine (after correcting for the assignments of the carbon shifts)[34] and 19-oxoaspidofractinine,[35,36] which revealed a close correspondence with the former. Kopsonoline (**4**) is therefore 17-oxoaspidofractinine, and while the racemic form constitutes one of the intermediate compounds in the synthesis of various aspidofractinine alkaloids,[34−36] it is here encountered as an optically active natural product for the first time.

Comparison of the results of the present study (see Experimental Section) with those of the previous one carried out on a sample collected from the same locality but at an earlier date[37,38] revealed some differences that clearly demonstrate a seasonal dependence of the alkaloidal composition. Compounds **2**−**4** showed no appreciable cytotoxicity against drug-sensitive and vincristine-resistant KB cells. Kopsijasminine (**3**), however, showed moderate activity in reversing multidrug resistance in vincristine-resistant KB (VJ300) cells (IC_{50} 38.7 μM in the presence of 0.12 μM vincristine; the IC_{50} values of vincristine against KB and KB/VJ300 strains are 0.0167 and 1.335 μM, respectively).

Experimental Section

General Experimental Procedures. Optical rotations were determined on a JASCO P-1020 digital polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400 spectrometer at 400 and 100 MHz, respectively. Mass spectral measurements were obtained courtesy of Dr. Komiyama of the Kitasato Institute, Tokyo, Japan, and at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia.

Plant Material. Details of collection, identification, and deposition of plant materials have been reported previously.[24,37] *K. griffithii* was collected in August 1993, while *K. teoi* was collected in February 1994.

Extraction and Isolation. Extraction of the leaves of *K. griffithii* and stem bark of *K. teoi* was carried out in the usual manner by partitioning the concentrated EtOH extracts with dilute acid, as has been described in detail elsewhere.[24,37] The alkaloids were isolated by initial column chromatography on silica gel using $CHCl_3$ with increasing proportions of MeOH, followed by rechromatography of the appropriate partially resolved fractions using centrifugal TLC. For the leaf extract of *K. griffithii*, two successive centrifugal TLC (SiO_2, Et_2O/hexane) of the first fraction eluted from column chromatography provided compound **1** (yield, 0.001 g kg^{-1}). Solvent systems used for centrifugal TLC in the case of the stem-bark extract of *K. teoi* were Et_2O, Et_2O/hexane, EtOAc/hexane, EtOAc, EtOAc/NH_3-saturated, $CHCl_3$/NH_3-saturated, and EtOAc/MeOH. The yields (g kg^{-1}) of the alkaloids were as follows: **2** (0.001), **3** (0.001), **4** (0.009), kopsinine (0.018), 16-*epi*-kopsinine (0.005), 17α-hydroxykopsinine (0.004), N_1-methoxycarbonyl-12-methoxy-$\Delta^{16,17}$-kopsinine (0.002), kopsamine (0.007), kopsinganol (0.006), kopsingine (0.115), kopsidine A (0.003), akuammiline (0.003), 16-deacetylakuammiline (0.010), 16-*epi*-akuammiline (0.003), 16-*epi*-deacetylakuammiline (0.011), aspidodasycarpine (0.027), lonicerine (0.057), pleiocarpamine (0.008), 16-hydroxymethylpleiocarpamine (0.004), tetrahydroalstonine (0.001), and leuconoxine (0.002).

6-Oxoleuconoxine (1): colorless oil; $[\alpha]_D$ +75 (*c* 0.03, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 202 (4.42), 234 (4.12), 251 (4.02), 349 (3.10) nm; IR (dry film) ν_{max} 1715, 1689 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; EIMS *m*/*z* 324 $[M]^+$ (50), 308 (100), 280 (34), 279 (35), 267 (25), 256 (25), 251 (25), 237 (9), 212 (29), 181 (16), 167 (14), 149 (25); HREIMS *m*/*z* 324.1482 (calcd for $C_{19}H_{20}N_2O_3$, 324.1474).

(+)-Harmicine[24] (5): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1H, br s, *N*H), 7.48 (1H, dd, $J = 7.0$, 1.2 Hz, H-7), 7.31 (1H, dd, $J = 7.0$, 1.2 Hz, H-10), 7.14 (1H, td, $J = 7.0$, 1.2 Hz, H-9), 7.09 (1H, td, $J = 7$, 1.2, H-8), 4.26 (1H, m, H-11b), 3.31 (1H, ddd, $J = 13$, 5, 2, H-5), 3.09 (1H, ddd, $J = 13$, 10, 5, H-5), 2.99 (1H, m, H-6), 2.94 (1H, m, H-3), 2.92 (1H, m, H-3), 2.68 (1H, m, H-6), 2.29 (1H, m, H-1), 1.91 (1H, m, H-2), 1.89 (1H, m, H-2), 1.86 (1H, m, H-1).

Kopsinitarine E (2): light yellowish oil; $[\alpha]_D$ −21 (*c* 0.04, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 207 (4.13), 238 (3.82), 279 (3.14), 287 (3.06) nm; IR (dry film) ν_{max} 3351, 1772, 1677 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; FABMS *m*/*z* 395 $[M + H]^+$; HRFABMS *m*/*z* 395.1617 (calcd for $C_{22}H_{22}N_2O_5$ + H, 395.1607).

Kopsijasminine (3): light yellowish oil; $[\alpha]_D$ −60 (*c* 0.05, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 206 (4.36), 243 (3.77), 292 (3.30) nm; IR (dry film) ν_{max} 3367, 1709 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; FABMS *m*/*z* 337 $[M + H]^+$; HRFABMS *m*/*z* 337.1920 (calcd for $C_{21}H_{24}N_2O_2$ + H, 337.1916).

Kopsonoline (4): light yellowish oil; $[\alpha]_D$ +27 (*c* 0.41, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 209 (4.06), 241 (3.77), 291 (3.32) nm; IR (dry film) ν_{max} 3340, 1708 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Tables 2 and 1, respectively; FABMS *m*/*z* 295 $[M + H]^+$; HRFABMS *m*/*z* 295.1818 (calcd for $C_{19}H_{22}N_2O$ + H, 295.1810).

Cytotoxicity Assays. Cytotoxicity assays were carried out following the procedure that has been described in detail previously.[39]

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