Novel furoquinolinones from an Indonesian Plant, Lunasia amara

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Novel furoquinolinones from an Indonesian Plant, *Lunasia amara*

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ABSTRACT

Two new furanoquinolones, 3-oxolunacrine (**1**) and 2,3-dehydrolunacrine (**2**), and 22 known quinolones (**3–24**) were isolated from the methanol extract of the bark of *Lunasia amara*. The chemical structures of the newly isolated compounds were elucidated from HRMS and various NMR spectroscopic data. Pure (*S*)- and (*R*)-isomers of **1**, which was obtained as a racemate, were separated by chiral column chromatography. The possibility that racemic **1** occurs naturally was discussed based on a proposed biosynthetic pathway. Selected isolated quinoline alkaloids were evaluated for antiproliferative activities against five human tumor cell lines, including a multidrug-resistant cell line overexpressing p-glycoprotein.

Introduction

Indonesia is a megadiversity country [1] located in one of the world's rainforest areas. Its 17,000 islands have various types of habitats and an extremely complicated geological history [2]. The additional factors of biogeography, ecology, and climate have evolved megadiverse flora leading to a large total number of plant species, including a significant percentage of endemic ones. Accordingly, Indonesia has the second largest number of traditional medicinal plants after the Amazon area [3]. Unfortunately, these diverse species, which present significant pharmaceutical research opportunities, may be lost before they are even discovered or explored scientifically. Thus, the study of the constituents found in Indonesian plants is phytochemically important.

Lunasia amara (Rutaceae) has been used as an Indonesian medicinal plant to treat skin diseases, eye irritation, and bacterial infections, as well as an aphrodiasiac. Previous research revealed that *L. amara* contains several quinoline alkaloids, such as lunacrine, lunasine [4], lunacridine, lunamarine [5], lunidine, lunidonine [6], and related derivatives [7–12], which are characteristically found in the family Rutaceae. Surprisingly, after a report in 1960 [10,11], no phytochemical research on this species was reported until 2011 [12], although several biological studies using extracts of this species were published [13–20]. Our in-house evaluation indicated that a MeOH extract of *L. amara* showed 30–80% growth inhibitory effects against several chemosensitive human tumor cell lines at a concentration of 20 μg/mL. As part of our continuing phytochemical study of Indonesian plants [21], herein we describe the isolation of new furoquinolones and other known secondary metabolites from *L. amara*. Their antiproliferative effects against several human tumor cell lines are also reported.

The bark of *L. amara*, which was collected from the South Sulawesi Province in Indonesia in May 2015, was extracted with MeOH. The MeOH extract was partitioned between *n*-hexane and H_2O, which was further partitioned between ethyl acetate and H_2O. The organic phase was subjected to various types of column chromatography to yield novel furoquinoline alkaloids **1** and **2** (Fig. 1) along with known quinoline alkaloids **3–24** (Fig. 2), of which all spectrometric and spectroscopic data were identical to those reported [22–38].

Compound **1** was obtained as a colorless oil. Its molecular formula, $C_{16}H_{17}NO_4$, was suggested from the $[M + H]^+$ peak at *m/z* 288.1231 (calcd. for 288.1236) found in the HRFABMS spectrometric data. The ^{13}C NMR spectroscopic data also indicated the presence of 16 carbons, including two ketone carbonyl carbons at δ_c 192.5 and 172.0, a strongly deshielded quaternary carbon at δ_c 174.5, six aromatic carbons at δ_c 150.5 (deshielded by OMe), 129.6 (two overlapped carbons confirmed by HMBC correlations

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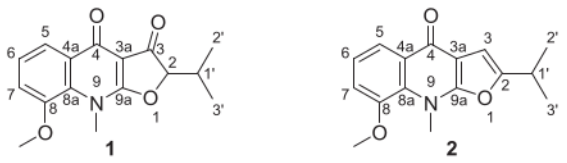
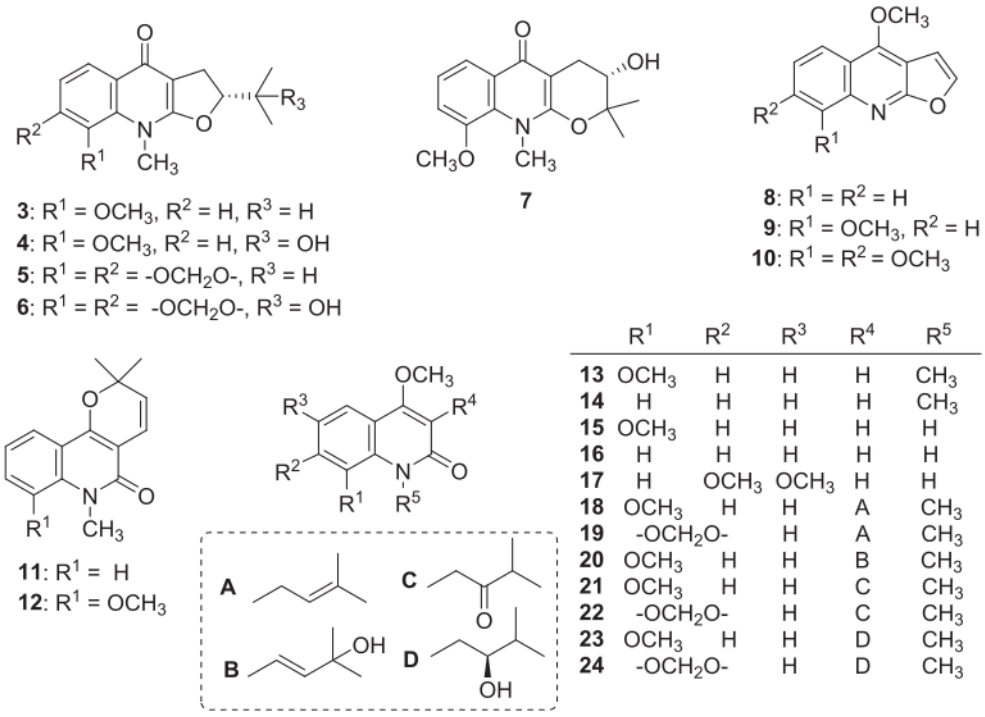


Fig. 1. New furoquinolines **1** and **2** isolated from the bark of *L. amara*.

of H-6/H-7 with δ_c 129.6), 125.5, 120.1, and 116.1, a *O*-methyl carbon at δ_c 56.6, a *N*-methyl carbon at δ_c 36.2, two methine carbons at δ_c 91.4 (oxymethine deshielded by a neighboring ketone) and 30.3, and two sp^3 methyl carbons at δ_c 18.9 and 15.3 (Table 1). The ^{1}H NMR spectrum showed three aromatic protons at δ_H 8.11 (dd, J = 7.9, 1.5 Hz), 7.35 (t, J = 7.9 Hz), and 7.21 (dd, J = 7.9, 1.5 Hz), four methyl protons at δ_H 4.04, 3.97 (s, *N*-CH_3 and *O*-CH_3, respectively), 1.21, and 0.93 (both d, J = 6.9 Hz), as well as two methine protons at δ_H 4.62 (d, J = 3.6 Hz) and 2.46 (dsep, J = 6.9 and 3.6 Hz). A quinoline skeleton was constructed based on HMBC correlations between H-6 and C-4a/C-8, H-5 and C-4/C7, H-7 and C-8a, as well as *N*-CH_3 and C-8a/9a. Subsequently, the position of the methoxy group was determined by a HMBC correlation between *O*-CH_3 and C-8 (Fig. 3). Further HMBC and ^{1}H-^{1}H COSY analyses revealed the presence and location of an isopropyl group at C-2. The NMR data of **1** were similar to those of (−)-lunacrine (**3**),[22] except for the differences consistent with the presence of a ketone at C-3 in **1**. In the ^{1}H NMR spectra, different coupling constants were found between H-2 and H-1′, J = 3.6 Hz for **1** and J = 6.5 Hz for **3**. This dissimilarity was explained by a difference in the dihedral angle, which was affected by the substituent at C-3. The coupling constants obtained by density functional theory (DFT) calculations, J = 3.2 Hz for **1** and J = 6.4 Hz for **3**, were consistent with the experimental findings (Fig. S15, ESI). Based on all of the data, compound **1** was characterized as 3-oxolunacrine. The optical rotation and CD data implied that **1** was a racemate. Chiral column chromatography was used to separate the enantiomers, (−)-**1a** and (+)-**1b**. The value of both specific rotations was identical. The absolute configurations of (−)-**1a** and (+)-**1b** were tentatively determined by comparison with the specific rotation of the related levorotatory compound **3** (Fig. 4), since comparison of the measured ECD and the calculated one did not provide meaningful results.

The presence of a natural racemate in *L. amara* seems unusual, because all related quinoline alkaloids isolated from this genus are optically active with the same absolute configuration at C-2. This phenomenon can also be found elsewhere in the family Rutaceae, although myrtopsine[39] isolated from *Myrtopsis sellingii* (Rutaceae) has the inverted absolute configuration at C-2. The stereochemistry could be explained by the postulated biosynthetic pathway (Fig. 5). An asymmetric epoxidation occurs after the attachment of a prenyl group to a quinolinone skeleton produced from anthranilic acid. The resulting optically active epoxide **A** can serve as a common biosynthetic intermediate for all quinoline alkaloids found in *L. amara*. Compounds **4** and **6** could be biosynthesized enantioselectively *via* the cyclization indicated by the red arrows to form a dihydrofuran ring. Subsequent dehydration and reduction would give the optically active compounds **3** and **5**. If compound **1** is formed through this pathway, the isolated **1** should be chiral and, thus, the racemization might occur during the purification process. In fact, the pure (+)-**1b** was racemized in the presence of SiO_2/MeOH at room temperature. However, we cannot eliminate the possibility of racemic **1** being naturally produced through other biosynthetic pathways, such as routes I or II.



	R^1	R^2	R^3	R^4	R^5
13	OCH_3	H	H	H	CH_3
14	H	H	H	H	CH_3
15	OCH_3	H	H	H	H
16	H	H	H	H	H
17	H	OCH_3	OCH_3	H	H
18	OCH_3	H	H	A	CH_3
19	-OCH_2O-		H	A	CH_3
20	OCH_3	H	H	B	CH_3
21	OCH_3	H	H	C	CH_3
22	-OCH_2O-		H	C	CH_3
23	OCH_3	H	H	D	CH_3
24	-OCH_2O-		H	D	CH_3

Fig. 2. Known quinolone alkaloids isolated from *L. amara*.

Table 1
^{1}H and ^{13}C NMR spectroscopic data of **1** and **2**.

Position	**1** ($CDCl_3$) δ_H (J in Hz) [a]	δ_C	**2** ($CDCl_3$) δ_H (J in Hz) [a]	δ_C
2	4.62, d (3.6)	91.4		157.7
3		192.5	6.64, d (1.0)	100.2
3a		101.1		107.4
4		172.0		172.5
4a		129.6		127.9
5	8.11, dd (7.9, 1.5)	120.1	8.21, dd (7.9, 1.4)	119.5
6	7.35, t (7.9)	125.5	7.28, t (7.9)	122.7
7	7.21, dd (7.9, 1.5)	116.1	7.16, dd (7.9, 1.4)	113.7
8		150.5		150.4
8a		129.6		129.6
9a		174.5		156.7
1′	2.46, dd (6.9, 3.6)	30.3	3.03, dd (6.9, 1.0)	27.8
2′	1.21, d (6.9)	18.9	1.34, d (6.9)	20.7
3′	0.93, d (6.9)	15.3	1.34, d (6.9)	20.7
OCH_3-8	3.97, s	56.6	3.96, s	56.5
NCH_3-9	4.04, s	36.2	4.21, s	37.1

[a] ^{1}H NMR: 600 MHz, ^{13}C NMR: 150 MHz in $CDCl_3$.

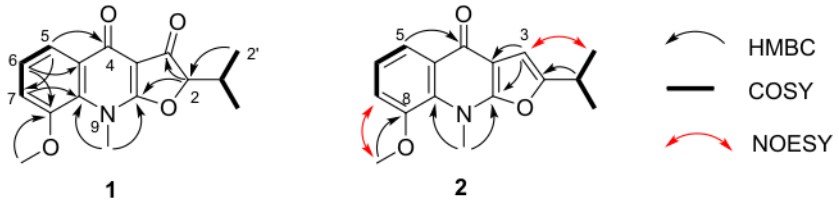


Fig. 3. Selected HMBC, ^{1}H–^{1}H COSY, and NOESY correlations of **1** and **2**.

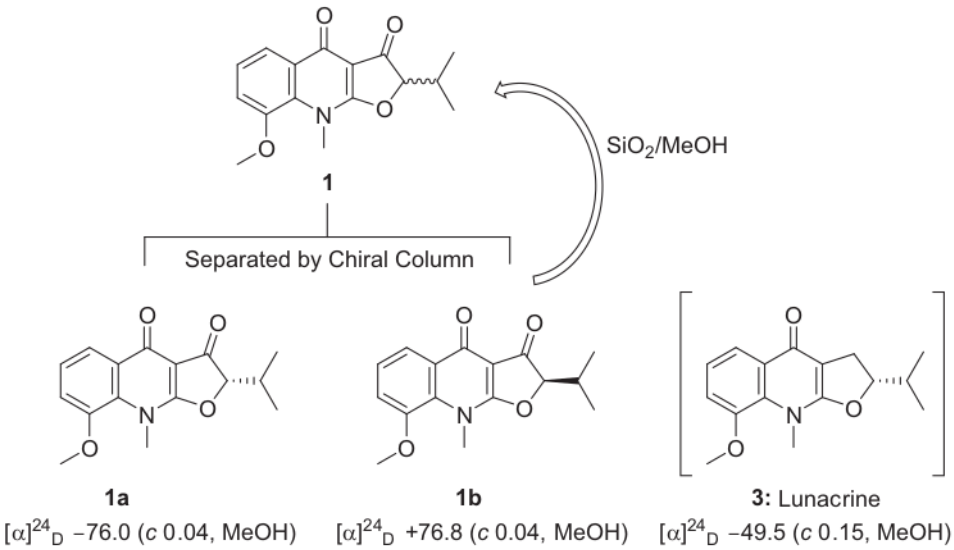


Fig. 4. The stereochemical study of compound **1**.

In a previously proposed biosynthetic pathway to **8**, compounds **9** and **10** are produced through the oxidation of **8** [40–42]. However, the oxygenation of ring-A may occur after the construction of the quinolinone skeleton, since compounds **13**–**17** were isolated from this plant.

Compound **2** was obtained as a colorless amorphous solid. Its molecular formula, $C_{16}H_{17}NO_3$, was deduced from the $[M + H]^+$ peak at m/z 272.1284 (calcd. for 272.1287) found in HRFABMS spectrometric data, consistent with the loss of an oxygen and a hydrogen from that of **1**. The ^{1}H- and ^{13}C NMR spectra of **2** were

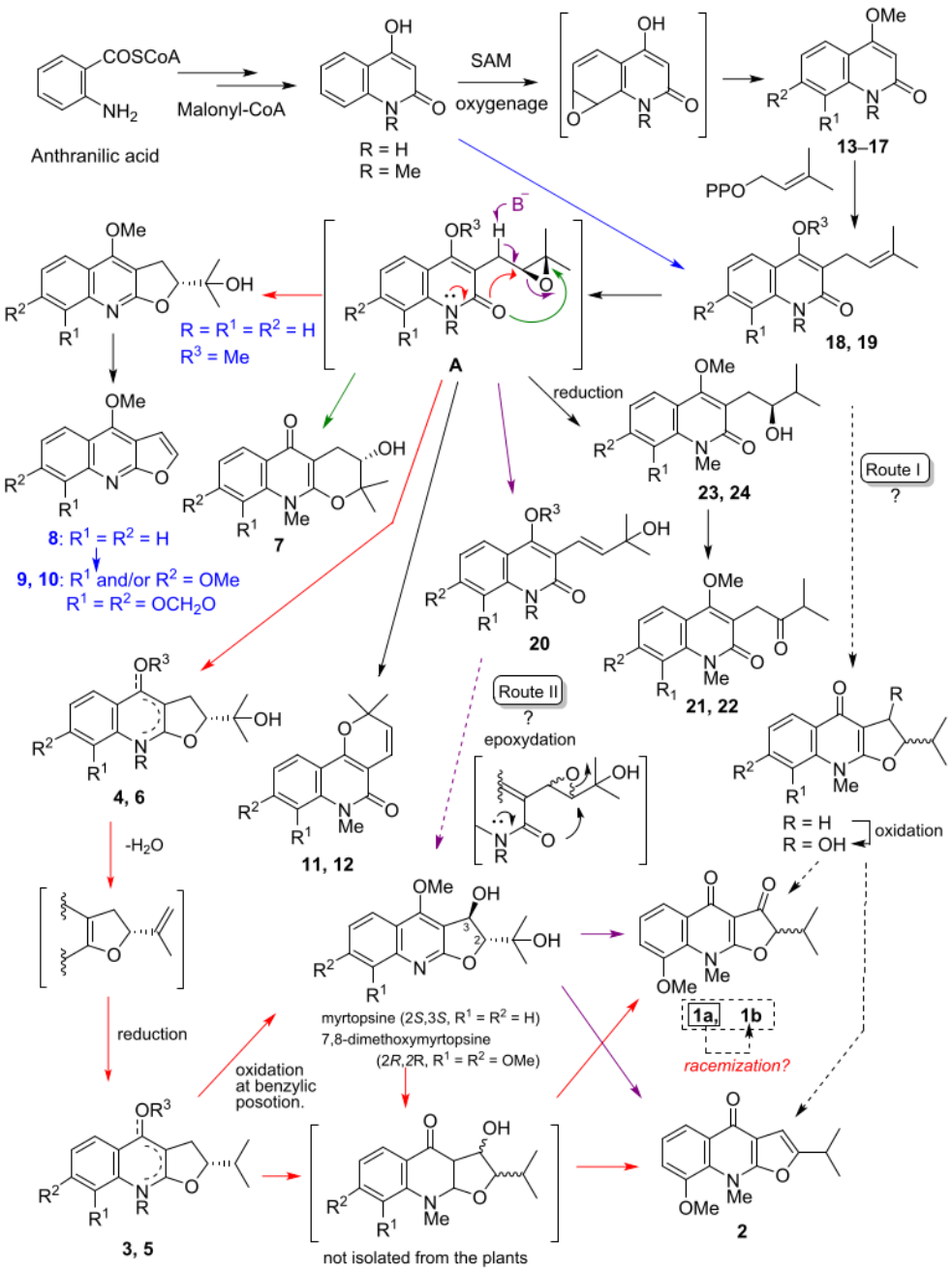


Fig. 5. Proposed systematic biosynthetic pathway to quinoline alkaloids from *L. amara*.

quite similar to those of **1**; however, the appearance of a proton signal at δ_H 6.64 for H-3 was accompanied by the loss of the proton signal for H-2 as well as corresponding changes in the chemical shifts of C-2 and C-3 (Table 1). These results suggested that a double bond is present between C-2 and C-3. The HMBC, ^{1}H–^{1}H COSY, and NOESY correlations (Fig. 3) supported the structural assignment of **2** as 2,3-dehydrolunacrine.

Compounds **3**, **4**, **6**, **8**, **9**, **12**–**14**, **16**, **17**, and **21**–**24**, which were isolated in sufficient quantity, were evaluated for antiproliferative activities against the following human tumor cell lines: lung carcinoma (A549), epidermoid carcinoma (KB, Hela derivative), vincristine-resistant KB subline with p-gp overexpressing (KB-VIN), triple-negative breast cancer (MDA-MB-231), and estrogen receptor-positive breast cancer (MCF-7) [43]. None of them showed

significant antiproliferative activity, suggesting that they would be nontoxic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151861.

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