Lagerindicine, a New Pyrrole Alkaloid Isolated from the Flowers of Lagerstroemia indica Linnaeus

Yi Chen1,3 · Song-Wei Li1 · Fang-Zhou Yin1 · Min Yang1 · Xia-Juan Huan1 · Ze-Hong Miao1 · Xiao-Ming Wang2,3 · Yue-Wei Guo1,4

Received: 13 August 2020 / Accepted: 12 October 2020 / Published online: 20 October 2020
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Abstract
A phytochemical investigation of the EtOH extract of the flowers of Lagerstroemia indica L. led to the isolation and characterization of a new pyrrole alkaloid, named lagerindicine (1), along with four known compounds (2–5). Their structures were elucidated by the detailed spectroscopic analysis and comparison with literature data, whereas the structure, particularly, the absolute configuration (AC) of 1, was firmly determined by total synthesis. All the isolates were evaluated for their cytotoxic effects against human colon cancer cell (HCT-116), and compound 3 exhibited weak cytotoxicity with IC50 value of 28.4 µM.

Graphic Abstract

Keywords Lagerstroemia indica Linnaeus · Pyrrole alkaloid · Total synthesis · Stereochemistry · Cytotoxicity

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13659-020-00273-x) contains supplementary material, which is available to authorized users.

Xiao-Ming Wang wxm1964@163.com
Yue-Wei Guo ywguo@simm.ac.cn

1 State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China
2 Hunan Academy of Forestry, 658 South Shao shan Road, Changsha 410004, Hunan, China
3 Changsha Engineering Technology Research Center of Woody Flower, 658 South shao shan Road, Changsha 410004, Hunan, China
4 College of Materials Science and Engineering, Central South University of Forestry and Technology, 498 South Shao shan Road, Changsha 410004, Hunan, China
1 Introduction

Terrestrial plants of Lythracea is a large family, widely used in architecture, landscaping, food and drug applications. The plants of genus *Lagerstroemia* comprise more than 15 species, which are either small trees or shrubs with colourful flowers distributed in warm temperate regions of China [1]. Earlier chemical investigation of the different species of Lythracea can trace back to decades, and a lot of structurally diverse and complex compounds, such as alkaloids, sesqui-, triterpenoids, steroids and flavonoids [2] were reported. Especially, alkaloids have attracted much attention of natural product chemists and pharmacologists due to their extensive biological activities, ranging from antifungal activities to cytotoxicity. The earlier phytochemical studies on the plants of the *Lagerstroemia indica* initiated in 1962. Ferris et al. had reported a series of phenylquinolizidine alkaloids from the aerial of title species [3−8]. Recently, several new biphenylquinolizidine alkaloids were also isolated from the aerial parts of *L. indica* by Bae et al. [9, 10]. It is interesting to note that the chemical constituents of the flowers of *L. indica* are not reported till now.

In our continuous efforts towards the searching for novel bioactive secondary metabolites from marine and terrestrial sources [11−14], we have recently collected the fresh flowers of *L. indica* L. from Hunan Province, China, and carried out a chemical investigation on the EtOH extract of the flowers. As a result, a new pyrrole alkaloid, namely lagerindicine (1), and four known compounds (2−5) were isolated and characterized. Herein, we reported the isolation, structural elucidation, especially total synthesis of 1, and in vitro biological evaluation of these isolates (Fig. 1).

2 Results and Discussion

The *n*-BuOH and EtOAc soluble portion of the EtOH extract was repeatedly column chromatographed over silica gel, Sephadex LH-20, and RP-HPLC to yield pure compounds 1, 2, and 3−5, respectively. The structures of the known compounds 2−5 were rapidly identified as pterolactam [15], betulinic acid [16], oleanolic acid [17] and 24-methylene-cycloartanol [18], respectively, by the comparison of their spectral data and optical rotations with those reported in the literature.

Compound 1, named lagerindicine, was isolated as a colorless oil. Its molecular formula was determined to be C_{7}H_{13}O_{3}N by the 13C NMR data and HR-ESIMS positive ion at *m/z* 182.0782 [M + Na]^{+} (calcd. for C_{7}H_{13}NO_{3}Na, 182.0788), indicating two degrees of unsaturation. Consistent with this data, analysis of the 13C NMR and the HSQC
spectra revealed the presence of 7 carbon signals, comprising one sp³ methyl carbon (oxygenated at δC 53.7), four sp³ methylene carbons (one oxygenated at δC 60.5), one sp³ methine carbon (oxygenated at δC 92.8), and one carbonyl carbon resonating at δC 178.2 (Table 1). The 1H NMR data showed resonance of one methoxyl singlet at δH 3.31 (3H, s, −OMe). The four protons resonating at δH 2.02 (1H, dddd, J = 13.8, 9.9, 8.6, 6.1 Hz, H-4a), 2.21 (1H, dddd, J = 13.8, 9.9, 8.6, 6.1 Hz, H-4b), 5.08 (1H, dd, J = 1.2, 6.1 Hz, H-5), suggested the direct connection from C-3 to C-5 through C-4. The above observations were further confirmed by the observed key HMBC correlations depicted in Fig. 2. Lagerindicine is N-hydroxyethyl derivative of 2.

Since there is only one chiral center (C-5) in compound 1, the final step to complete the full structure of 1 is to determine its absolute configuration. Since the AC of co-occurring related compound 2 is 5S [15], it is obvious that 1 should share the same S absolute configuration at C-5 based on the biogenetic consideration.

This assignment was supported by observing the same optical rotation signs of both compounds 1 and 2 {1: [α]D20 = 13 (c 0.05 MeOH); 2: [α]D20 = 12 (c 0.2 MeOH)}. However, considering the different substitution pattern at N-1, which may cause unexpected influence on the optical properties of 1 and 2, we decided to synthesize 1 so as to confirm the deduced absolute stereochemistry of 1. As shown in Scheme 1, a total synthesis of both (+)- and (−)-enantiomers of 1 was carried out. Thus, the key intermediate 2-pyrrol-1-ylethan-1-ol (7) was prepared starting from the commercially available 2,5-dimethoxylactam (8) [20], which, in turn,

![Fig. 2 1H-1H COSY and the key HMBC correlations of compound 1](image)

**Table 1** 1H and 13C NMR data of compound 1a and 2b

| No. | 1          | 2          |
|-----|------------|------------|
|     | δH (mult, J in Hz) | δC, type | δH (mult, J in Hz) | δC, type |
| 2   | 178.2, C   | 181.4, C   |
| 3a  | 3.55 (dt, 14.0, 5.8) | 53.7, CH3 | 3.26 (s) | 54.8, CH3 |
| 3b  | 3.67 (t, 5.8) | 60.5, CH2 |          |          |
| 4a  | 2.02 (dddd, 13.8, 8.6, 2.8, 1.2) | 44.3, CH2 | 2.02 (dd, 1.2, 6.4) | 88.7, CH |
| 4b  | 2.21 (ddddd, 13.8, 9.9, 8.6, 6.1) | 48.5, CH2 | 2.02 (dd, 1.2, 6.4) | 88.7, CH |
| 5   | 5.08 (dd, 1.2, 6.1) | 92.8, CH3 | 5.08 (dd, 1.2, 6.4) | 88.7, CH |
| 1a  | 3.55 (dt, 14.0, 5.8) | 53.7, CH3 |          |          |
| 1b  | 3.27 (dt, 14.0, 5.8) |          |          |          |
| 2   | 4.85 (dd, 1.2, 6.4) | 88.7, CH | 4.85 (dd, 1.2, 6.4) | 88.7, CH |
| 3   | 1.00 (dt, 17.3, 8.6) | 29.8, CH2 | 1.00 (dt, 16.0, 8.4) | 29.4, CH2 |
| 4a  | 2.21 (ddddd, 13.8, 9.9, 8.6, 6.1) | 24.8, CH2 | 2.21 (ddddd, 13.8, 9.9, 8.6, 6.1) | 24.8, CH2 |
| 4b  | 2.02 (dd, 1.2, 6.4) | 28.8, CH2 | 2.02 (dd, 1.2, 6.4) | 28.8, CH2 |
| 5   | 5.08 (dd, 1.2, 6.1) | 92.8, CH3 | 5.08 (dd, 1.2, 6.4) | 92.8, CH3 |

*a At 400 MHz for 1H and 100 MHz for 13C NMR experiments in CD3OD. δ (ppm) were referenced to MeOH (δH 3.31, δC 49.0), assignments made by DEPT, 1H-1H COSY, HSQC, and HMBC experiments

*b At 400 MHz for 1H and 100 MHz for 13C NMR experiments in CD3OD, [15]
was further separated by the chiral-phase HPLC to generate the expected (+)-5-methoxylactam \{8a, \([\alpha]_{D}^{20} + 131 \text{ (c 0.1 MeOH)}\}\) and (−)-5-methoxylactam \{8b, \([\alpha]_{D}^{20} - 121 \text{ (c 0.1 MeOH)}\}\), respectively. Furthermore, as the presence of a \(\alpha,\beta\)-unsaturated lactone chromophore in structures 8a and 8b, the absolute configuration of this pair of optically pure enantiomers could be further determined to be 5S and 5R, respectively, by the observed opposite Cotton effects due to the \(n-\pi^*\) and \(\pi-\pi^*\) transitions (Fig. 3) [21], in combination with the results of TDDFT-ECD calculation (Fig. 4), respectively. Having confirmed the AC at C-5, the subsequent reduction of the olefin of 8a and 8b with PtO\(_2\) in EtOH yielded the target molecule (+)-1 and its enantiomer (−)-1, respectively. Finally, overall comparison of the physical and

Scheme 1  Total synthetic route of (+)-1 and (−)-1

Fig. 3  Correlation of the Cotton effects with absolute configuration

Fig. 4  The TDDFT-ECD calculation results of 8a and 8b

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3 Experimental

3.1 General Experimental Procedures

Optical rotations were measured on a Perkin-Elmer 241MC polarimeter (PerkinElmer, Fremont, CA, USA). ECD spectra were recorded on a Jasco J-810 spectropolarimeter (JASCO, Japan) at ambient temperature using chromatographic grade CH$_3$OH and acetonitrile as solvent. IR spectra were recorded on a Nicolet Magna FT-IR 750 spectrometer (Thermo Scientific, Waltham, MA, USA); peaks are reported in cm$^{-1}$. The NMR spectra were measured at 300 K on a Bruker DRX-400 (400 MHz for $^{1}$H and 100 MHz for $^{13}$C) spectrometer (Bruker Biospin AG, Fällanden, Germany). Chemical shifts ($\delta$) are reported in parts per million (ppm) in CD$_3$OD and coupling constants ($J$) in Hz, with the residual CH$_3$OH ($\delta_H = 3.31$ and $\delta_C = 49.0$) as internal standard. LR-ESIMS and HR-ESIMS were carried out on a Bruker Daltonics Esquire 3000 plus instrument (Bruker Daltonics K. K., Kanagawa, Japan) and a Waters Q-TOF Ultima mass spectrometer (Waters, MA, USA), respectively. The semi-preparative HPLC was performed on an Agilent 1260 series liquid chromatography equipped with a DAD G1315D detector at 210 and 254 nm, and a semi-preparative ODS-HG-5 column [5 μm, 250 × 9.4 mm] was also employed. Commercial silica gel plates (Yan Tai Zi Fu Chemical Group Co., Yantai, China, G60 F-254) were used for analytical TLC. All solvents used for extraction and isolation were of analytical grade.

### Table 2 The inhibitory effect of the isolated compounds on the proliferation of HCT-116

| Compounds  | IC$_{50}$ (μM)$^a$ | HCT-116 |
|------------|-------------------|---------|
| 1          | > 50              |         |
| 2          | > 50              |         |
| 3          | 28.4              |         |
| 4          | > 50              |         |
| 5          | > 50              |         |
| TAK-243$^b$| 0.002             |         |

$^a$The results are averages of two independent experiments

$^b$TAK-243 (MLN7243) was used as a positive control

The fresh flowers (10 kg) were picked off on the morning, and then dried at room temperature. The dried flowers were crushed and extracted exhaustively three times with 95% EtOH (3 × 5 L), each time for 24 h. After evaporation of the solvent under vacuum, the concentrate was suspended in H$_2$O (2 L), acidified to pH 4–5 with H$_2$SO$_4$, extracted three times with EtOAc (3 × 2 L). The EtOAc extract (59.9 g) was obtained after removing the solvents under vacuum. The aqueous layer was then basified with Na$_2$CO$_3$ to pH 9–10 and extracted three times with CHCl$_3$ (3 × 2 L), after filtration, the organic solvents were removed under vacuum to give the CHCl$_3$ extract (0.5 g). The aqueous layer was further extracted three times with $n$-BuOH (3 × 2 L), each time for 24 h. After evaporation of the solvent under vacuum, the concentrate was suspended in H$_2$O (2 L), acidified to pH 4–5 with H$_2$SO$_4$, extracted three times with EtOAc (3 × 2 L). The EtOAc extract (59.9 g) was obtained after removing the solvents under vacuum. The aqueous layer was then basified with Na$_2$CO$_3$ to pH 9–10 and extracted three times with CHCl$_3$ (3 × 2 L), after filtration, the organic solvents were removed under vacuum to give the CHCl$_3$ extract (0.5 g). The aqueous layer was further extracted three times with $n$-BuOH (3 × 2 L), each time for 24 h. After evaporation of the solvent under vacuum, the concentrate was suspended in H$_2$O (2 L), acidified to pH 4–5 with H$_2$SO$_4$, extracted three times with EtOAc (3 × 2 L). The EtOAc extract (59.9 g) was obtained after removing the solvents under vacuum.

In conclusion, this is the first phytochemical investigation on the flowers of L. indica. Interestingly, the previously reported metabolites from the different parts of the title plant, such as phenyl quinolizidine alkaloids, flavonoids, and flavone glycosides, etc. were not found in the present work. Moreover, it is noteworthy that pyrrole alkaloids and flavone glycosides, etc. were not found in the present work. Furthermore, other pharmaceutical screens, such as anti-inflammatory, and insecticidal assays are undergoing.

### 3.2 Plant Material

The flowers of L. indica L. were collected from the experimental forest farm of Hunan Academy of Forestry, Hunan province, China, in July 2019. The plant was identified by Dr Xiao-Ming Wang (Hunan Academy of Forestry, Hunan, China). A voucher specimen (No. 19-HN-1) was deposited at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

### 3.3 Extraction and Isolation

The fresh flowers (10 kg) were picked off on the morning, and then dried at room temperature. The dried flowers were crushed and extracted exhaustively three times with 95% EtOH (3 × 5 L), each time for 24 h. After evaporation of the solvent under vacuum, the concentrate was suspended in H$_2$O (2 L), acidified to pH 4–5 with H$_2$SO$_4$, extracted three times with EtOAc (3 × 2 L). The EtOAc extract (59.9 g) was obtained after removing the solvents under vacuum. The aqueous layer was then basified with Na$_2$CO$_3$ to pH 9–10 and extracted three times with CHCl$_3$ (3 × 2 L), after filtration, the organic solvents were removed under vacuum to give the CHCl$_3$ extract (0.5 g). The aqueous layer was further extracted three times with $n$-BuOH (3 × 2 L), each time for 24 h. After evaporation of the solvent under vacuum, the concentrate was suspended in H$_2$O (2 L), acidified to pH 4–5 with H$_2$SO$_4$, extracted three times with EtOAc (3 × 2 L). The EtOAc extract (59.9 g) was obtained after removing the solvents under vacuum.
L). After filtration, the organic solvents were removed under vacuum to give the n-BuOH extract (5.0 g). The n-BuOH extract was successively separated by silica column chromatography (CC) (column: 30 × 6 cm, eluting with petroleum ether: Acetone = 100:0 → 0:100), Sephadex LH-20 CC (column: 150 × 4 cm, eluting with dichloromethane: methanol = 1:1), and reversed-phase HPLC (CH3CN:H2O = 5:95) to afford compound 1 (3.6 mg, tR = 16.0 min) and compound 2 (4.1 mg, tR = 14.6 min). The EtOAc extract was repeatedly separated via silica CC (column: 30 × 6 cm, eluting with petroleum ether: diethyl ether = 100:0 → 0:100), Sephadex LH-20 CC (column: 150 × 4 cm, eluting with petroleum ether: dichloromethane: methanol = 2:1:1) to obtain compound 3 (4.8 mg), compound 4 (38.0 mg) and compound 5 (10.3 mg).

3.3.1 Lagerindicine (1)

Colorless oil; [α]D20 + 13 (c 0.05 MeOH); UV (MeOH) λmax (log ε) 210 (3.10) nm, λmax (log ε) 270 (2.20) nm; IR: ν = 3418, 2932, 1682, 1456, 1373, 1259, 1175, 1076, 800 cm−1; 1H and 13C NMR data see Table 1; HR-ESIMS m/z 182.0788 [M+ Na]+ (calcd. for C7H13NO3Na, 182.0782 [M+ Na]+).

3.3.2 Pterolactam (2)

White amorphous powder (MeOH); [α]D20 + 12 (c 0.2 MeOH); Lit [15]: [α]D20 + 10 (c 0.1, MeOH). 1H NMR and 13C NMR data see Table 1.

3.4 Synthesis Procedures

3.4.1 2-Pyrrol-1-ylethan-1-ol (7)

Ethanolamine (6.6 mL, 0.1 mmol) was added to glacial acetic acid (12 mL) at 0 °C, and kept the temperature at 15–25 °C. Then, 2.5- dimethoxytetrahydrofuran (6) (3.4 mL, 0.02 mmol) was added and the reaction was stirred at 110 – 120 °C. After 2 h at that temperature, the residual liquid in the reaction vessel was cooled to rt and water was added. The usual work-up (DCM, brine, saturated aqueous Na2CO3) afforded a residue that was dissolved in MeOH (6.7 mL). NaOH (20 wt %, 3.3 mL) was added, and the solution was stirred at rt for 1 h, then poured into brine, and extracted with DCM. The solvent was removed under reduced pressure to afford 7 (1.2 g, 44%) as a yellow oil. The spectroscopic data of 7 are as follows: 1H NMR (400 MHz, CDCl3) δH 6.70 (t, 2H), 6.18 (t, 2H), 4.00 (t, 2H), 3.81 (t, 2H) ppm.

3.4.2 1-(2-Hydroxyethyl)-5-methoxy-1H-pyrrol-2(5H)-one (8)

A solution of the compound 7 (1.8 mmol) in methanol (50 mL) containing a catalytic amount of sensitizer Rose Bengal (RB) was placed in a flask, and oxygen was gently bubbled through it. The solution was cooled to 0 °C and irradiated with a 250 W long arc mercury lamp for 2 h. The photooxidations gave complex mixtures of oxygenated products, and compound 8 (49.9 mg, 18%) were purified by flash column chromatography using silica gel (petroleum ether: Acetone = 5:1 → 1:1 v/v). The EtOAc extract was repeatedly separated via silica CC (column: 30 × 6 cm, eluting with petroleum ether: diethyl ether = 100:0 → 0:100), Sephadex LH-20 CC (column: 150 × 4 cm, eluting with petroleum ether: dichloromethane: methanol = 2:1:1) to obtain compound 3 (4.8 mg), compound 4 (38.0 mg) and compound 5 (10.3 mg).

3.4.3 (±)-Lagerindicine (1)

Compound 8a (9.6 mg, 0.067 mmol) and 8b (11.5 mg, 0.071 mmol) in 5 mL of EtOH were reduced with H2 at room temperature, using the catalytic amount of PtO2 (2.0 mg) as catalyst, respectively. At the end of 2.5 h, the mixtures were filtered. Upon removed of the EtOH, compounds (+)-1 (8.9 mg, [α]D20 + 6.8 (c 0.1 MeOH), 92%) and (−)-1 (10.9 mg, [α]D20 −12.7 (c 0.1 MeOH), 93%) were obtained, respectively. The NMR spectra of (+)-1 and (−)-1 see Figure S19–22.

3.5 Cytotoxicity Assays

The cytotoxicity of the isolated compounds was evaluated against the HCT-116 by using the sulforhodamine B (SRB) method, according to the protocols described in previous literature [23]. The cytotoxicity of the compounds was expressed as the half-maximal inhibition (IC50, μM). TAK-243 (MLN7243) was used as a positive control.

Acknowledgements This research work was financially supported by the National Natural Science Foundation of China (NSFC) (Nos. 81991521, 41676073), the National Key Research and Development Program of China (No. 2018YFC0310903), the Drug Innovation Major Project (No. 2018ZX09971-001-001-009), and the SKLDR/ SIMM Project (No. SIMM1903ZZ-04). Changsha Engineering Technology Research Center of Woody flower (kq1907081).
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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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