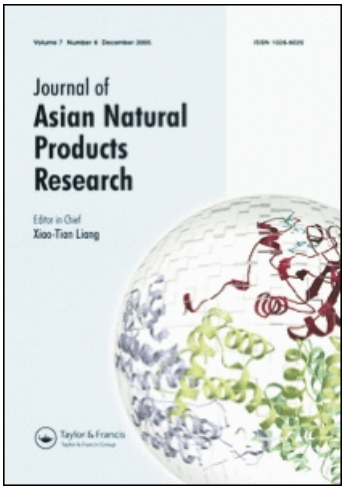

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Four new alkaloid derivatives from *Ligularia duciformis*

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Four new alkaloid derivatives from *Ligularia duciformis*

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Four new alkaloids, named 1-(4′-methylpyridazin-5′-yl)butane-1,2,3,4-tetraol (**1**), 3,9-dimethyl-5-nitropyrido[3,2,1-*ij*]quinazoline-1,7-dione (**2**), *N*,*N*-di(1-imine-propanyl)propionamidine (**3**), and 2,7-bis(isopropylimino)-2H,7H-dicyclopentacyclooctene-4,9-diol (**4**), were isolated from the rhizomes of *Ligularia duciformis*. Their structures were elucidated by spectral analysis.

Keywords: Compositae; *Ligularia duciformis*; alkaloids

1. Introduction

The roots and rhizomes of *Ligularia duciformis* (C. windl.) Hand-Mazz. ('Shan-zi-Wan' in Chinese) have been used as anti-tussive and expectorant herb in folk remedy [1]. Its chemical components have been reported and some pyrrolizidine alkaloids [2,3], especially large amount of isoline, were also obtained in our laboratory. Isoline, a retronecine-type PAs found in various *Ligularia* species including *L. duciformis*, is known to cause hepatoxic injury in rats [4–6]. In order to extensively investigate the alkaloid constituents of *L. duciformis*, some phytochemical studies were continued. In the present communication, the isolation and structure determination of four new alkaloids, 1-(4′-methylpyridazin-5′-yl)-butane-1,2,3,4-tetraol (**1**), 3,9-dimethyl-5-nitropyrido[3,2,1-*ij*]quinazoline-1,7-dione (**2**), *N*,*N*-di(1-imine-propanyl)propionamidine (**3**), and 2,7-bis(isopropylimino)-2H,7H-dicyclopentacyclooctene-4,9-diol (**4**), are described (Figure 1).

2. Results and discussion

Compound **1** was obtained as white amorphous powders. Its molecular formula was assigned by the quasi-molecular ion peak at *m/z* 213.0872 $[M-H]^-$ in the negative HR-ESI-MS. The IR spectrum displayed peaks at 3353 (hydroxy group), 1630, 1610, and 1032 cm^{-1} (aromatic residue). UV spectrum showed two absorption maxima at 217 and 273 nm. ^1H NMR spectrum of compound **1** displayed two olefinic proton signals at δ_H 8.60 (1H, s, H-6′) and 8.42 (1H, d, $J = 0.9$ Hz, H-3′), nine oxygen-conjoined proton signals at δ_H 5.24 (1H, d, $J = 6.4$ Hz), 4.93 (1H, brd, $J = 6.3$ Hz), 4.60 (1H, d, $J = 5.1$ Hz), 4.37 (1H, d, $J = 7.2$ Hz), 4.33 (1H, dd, $J = 5.4$, 5.4 Hz), 3.64 (1H, m), 3.60 (1H, m), 3.56 (1H, m), and 3.43 (1H, m), and one methyl proton signal at δ_H 2.46 (3H, brd, $J = 0.9$ Hz). The ^{13}C NMR and DEPT spectra showed nine carbon signals, including four olefinic carbons at δ_C 155.7 (—C═), 151.0 (—C═), 142.9 (═CH), and 140.7 (═CH), four oxygenated carbons at δ_C 74.0 (CH), 71.6

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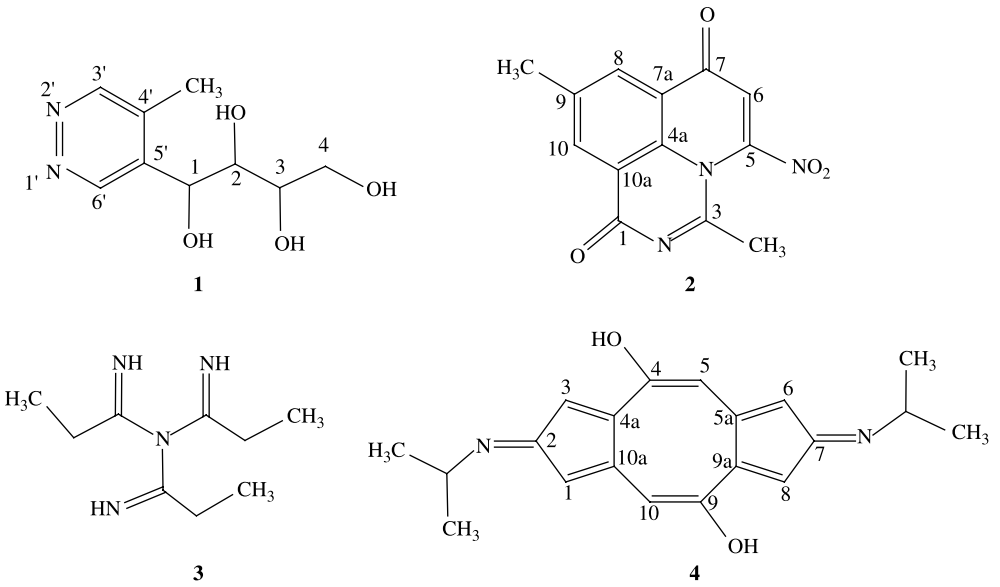

Figure 1. Structures of compounds **1**–**4**.

(CH), 71.5 (CH), and 63.8 (CH_2), and one methyl carbon at δ_C 20.8 (CH_3). By extensive analysis of $^1H-^1H$ COSY and HSQC spectra, four sharp oxygen-conjoined proton signals at δ_H 5.24 (1H, d, $J = 6.4$ Hz, 1-OH), 4.60 (1H, d, $J = 5.1$ Hz, 2-OH), 4.37 (1H, d, $J = 7.2$ Hz, 3-OH), and 4.33 (1H, dd, $J = 5.4$, 5.4 Hz, 4-OH) may be assigned to be hydroxyl groups, another five oxygenated aliphatic protons [δ_H 4.93 (1H, d, $J = 6.3$ Hz), 3.64 (1H, m), 3.60 (1H, m), 3.43 (1H, m), and 3.56 (1H, m)] corresponded to four aliphatic oxygenated carbon signals at δ_C 74.0, 71.6, 71.5, and 63.8 in HSQC spectrum. The correlations between olefinic protons at δ_H 8.41 (1H, d, $J = 0.9$ Hz, H-3′) and methyl signal at δ_H 2.46 (3H, d, $J = 0.9$ Hz) can be obtained in the $^1H-^1H$ COSY spectrum. In NOESY spectrum of **1**, olefinic proton at δ_H 8.60 (1H, s, H-6′) showed long-range correlation with aliphatic proton at δ_H 4.93 (1H, brd, $J = 6.3$ Hz, H-1), methyl proton at δ_H 2.46 (3H, d, $J = 0.9$ Hz) showed correlations with olefinic protons at δ_H 8.42 (1H, d, $J = 0.9$ Hz, H-3′) and aliphatic proton at δ_H 4.93 (1H, brd, $J = 6.3$ Hz, H-1). Then, according to the unsaturated degree of $C_9H_{14}N_2O_4$, the moieties of pyridazine and polyol are assumed in the structure of **1** (Figure 2).

In the HMBC spectrum, methyl proton at δ_H 2.46 (3H, d, $J = 0.9$ Hz) showed correlation with olefinic carbons at δ_C 155.7 (C-5′), 151.0 (C-4′), and 142.4 (C-3′), one olefinic proton at δ_H 8.60 (1H, s, H-6′) showed correlations with carbons at δ_C 151.0 (C-4′) and 71.6 (C-1), another olefinic proton at δ_H 8.42 (1H, d, $J = 0.9$ Hz, H-3′) showed correlations with carbons at δ_C 155.7 (C-5′) and 20.8 (methyl group), and the oxygenated proton at δ_H 4.93 (1H, brd, $J = 6.3$ Hz, H-1) showed correlations with carbon signals at δ_C 155.7 (C-5′), 151.0 (C-4′), 142.5 (C-6′), 74.0 (C-2), and 71.5 (C-3); one hydroxyl proton at δ_H 5.24 (1H, d, $J = 6.3$ Hz) also showed correlations with carbons at δ_C 155.7 (C-5′), 74.0 (C-2), and 71.6 (C-1). Finally, compound **1** was deduced as a pyridazine derivative with polyol moiety and possess the same [α] value with its isomer of 6-(D-arabino-tetritol-1-yl)-3-methylpyridazine [7], which can be obtained from 2-methyl-(1,2,3,4-tetra-*O*-acetyl-D-tetriol-1-yl)-3-furoic acid after photo-oxygenation with hydrazine.

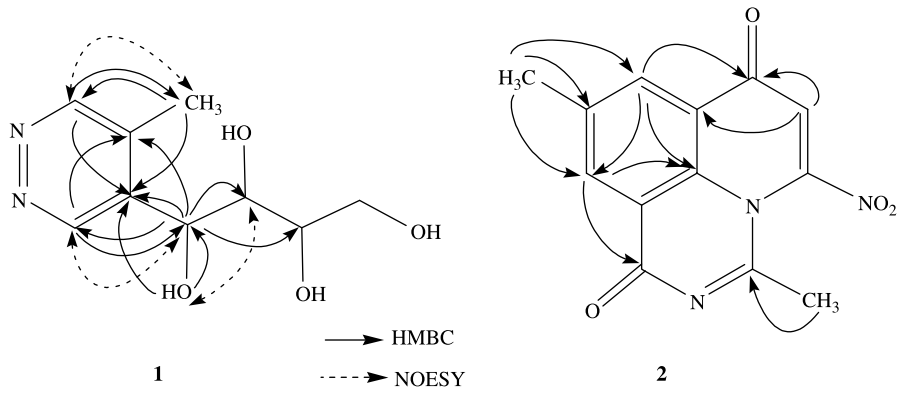

Figure 2. Key HMBC and NOESY correlations of compounds **1** and **2**.

The location of polyol moiety and methyl can also be confirmed by analysis of NOESY spectrum (Figure 2).

Based on the above analyses, the structure of **1** was concluded to be 1-(4′-methylpyridazin-5′-yl)butane-1,2,3,4-tetraol and named liguducimine A.

Compound **2** was obtained as red amorphous powders with a quasi-molecular ion peak at *m/z* 270.0 $[M-H]^-$ in the negative ESI-MS and at *m/z* 270.0527 $[M-H]^-$ in the negative HR-ESI-MS spectrum. The IR spectrum displayed peaks at 1625, 1610, 1097, 772 (aromatic residue) cm^{-1}, its sharp and mediate bands at 1514, 1384 cm^{-1} were due to asymmetric and symmetric vibrations of NO_2 group [8]. ^1H NMR spectrum of **2** showed three aromatic proton signals at δ_H 7.49 (1H, brs, H-8), 7.02 (1H, brs, H-10), and 7.06 (1H, s, H-6), two methyl protons at δ_H 2.39 (3H, s, 9-CH_3) and 1.89 (3H, s, 3-CH_3). ^{13}C NMR spectrum showed 11 olefinic carbons and two methyl carbon signals. There were three aromatic proton signals at δ_H 7.49 (1H, brs, H-8), 7.02 (1H, brs, H-10), and 7.06 (1H, s, H-6), corresponding to carbon signals at δ_C 121.2 (C-8), 125.5 (C-10), and 114.5 (C-6) in HSQC spectrum of **2**.

In HMBC spectrum, one olefinic proton at δ_H 7.49 showed correlations with carbon signals at δ_C 184.9 (C-7), 115.5 (C-4a), 125.5 (C-10), and 22.4 (9-CH_3), another olefinic proton at δ_H 7.02 showed correlations with carbon signals at δ_C 115.5 (C-4a), 121.2 (C-8), 22.4 (9-CH_3), and 163.7 (C-1), and correlations were also obtained between one methyl proton at δ_H 2.39 (3H, s, 9-CH_3) and carbon signals at δ_C 149.1 (C-9), 121.2 (C-8), and 125.5 (C-10). On the basis of NOESY spectrum, the location of the two olefinic protons at δ_H 7.49 (H-8) and 7.02 (H-10) and the methyl proton at δ_H 2.39 (3H, s) were finally confirmed, and a 1,2,3,5-tetra-substituted benzene moiety in the structure of **2** was obtained. By extensive analysis of HMBC spectrum (Figure 2), correlations were obtained between the proton at δ_H 7.06 (1H, s, H-6) and carbon at δ_C 184.9 (C-7) and 109.0 (C-7a), but the methyl proton at δ_H 1.89 (3H, s) showed only correlation with carbon signal at δ_C 180.1 (C-1). The unsaturated degree of molecular formula of **2** was 11. Except for the unsaturated degrees from 1,2,3,5-tetra-substituted benzene moiety, two ketone groups, one nitro group, and two double bonds, there are still two degrees of unsaturation. So, the structure of **2** was deduced as a three cyclic derivative compound (Figure 2). On the basis of the above analysis, compound **2** was assigned to be 3,9-dimethyl-5-nitropyrido[3,2,1-*ij*]quinazoline-1,7-dione and named liguducimine B.

Compound **3** was obtained as colorless slide crystals with a quasi-molecular ion peak at *m/z* 183.0 $[M+H]^+$ in the positive ESI-MS and 183.1603 $[M+H]^+$ on the positive

HR-ESI-MS, and its unsaturated degree of molecular formula was 3. Absorption bands at 3441 (NH stretching vibrations) and 1638 (weak, C=N), 2998, 2819, and 2775 (aliphatic residue) cm^{-1} in the IR spectrum showed that compound **3** possibly has C=N and NH moieties in its structures. The ^{1}H NMR spectrum of **3** only showed one characteristic ethyl group at δ_H 3.04 (2H, q, $J = 1.0$ Hz), 1.48 (3H, t, $J = 1.0$ Hz), and one proton signal at δ_H 9.53 (1H, brs). In the ^{13}C NMR spectrum of **3**, only three carbon signals at δ_C 11.1, 42.2, and 163.5 were obtained. So, compound **3** can be deduced as an alkaloid derivative with symmetric structure. In its HMBC spectrum, ethyl proton signals at δ_H 3.04 (2H, q, $J = 1.0$ Hz) and 1.48 (3H, t, $J = 1.0$ Hz) showed long-range correlations with olefinic carbon at δ_C 163.5. So, with the help of HR-ESI-MS spectrum, the structure of **3** was determined as *N*,*N*-di(1-imine-propanyl) propionamidine and named liguducimine C.

Compound **4** was obtained as blue amorphous powder with a quasi-molecular ion peak at *m/z* 643.2 $[2M-H]^-$ and 323.2 $[M+H]^+$ in the ESI-MS and at *m/z* 323.1760 $[M+H]^+$ in the positive HR-ESI-MS, which suggested the molecular formula of **4** as $C_{20}H_{22}N_2O_2$, and the unsaturated degree of its molecular formula was 11. The IR spectrum displayed strong peaks at 3443 (OH), 1637, 1594, and 1560 (aromatic residue) and 1072 (Ar-H) cm^{-1}. The ^{1}H NMR spectrum showed isopropanyl signals at δ_H 3.90 (1H, q, $J = 6.0$ Hz) and 1.38 (6H, d, $J = 1.0$ Hz), which may be conjoined with N or O atom according to the downfield chemical shift of 3.90 ppm, three aromatic protons at δ_H 8.35 (1H, dd, $J = 3.3$, 3.2 Hz, H-1 and 6), 7.70 (1H, d, $J = 3.3$ Hz, H-5 and 10), 7.28 (1H, d, $J = 3.2$ Hz, H-3 and 8), and one downfield shift proton signal at δ_H 10.91 (1H, brs, OH). The ^{13}C NMR spectrum of **4** showed only 10 carbon signals that were assigned to be $4 \times C$, $4 \times CH$, and $2 \times CH_3$ with the help of HSQC and DEPT experiments. In the HSQC spectrum, three aromatic protons at δ_H 8.35 (1H, d, $J = 3.3$ Hz, H-1 and 6), 7.70 (1H, d, $J = 3.3$ Hz, H-5 and 10), and 7.28 (1H, d, $J = 3.2$ Hz, H-3 and 8) corresponded to the carbon signals at δ_C 126.5, 132.0, and 124.8, respectively. On the basis of the above spectral analysis and its molecular formula of $C_{20}H_{23}N_2O_2$, compound **4** was designed to be a symmetric alkaloid derivative with isopropyl moiety.

In the HMBC spectrum of **4**, proton signal at δ_H 8.35 (1H, dd, $J = 3.3$, 3.2 Hz) showed long-range correlations with carbon signals at δ_C 182.5, 134.0, and 132.0, the singlet at δ_H 7.28 (1H, d, $J = 3.2$ Hz, H-3 and 8) showed correlations with the carbon at δ_C 182.5, 110.0, and 145.0. The HMBC correlations between protons at δ_H 7.70 (1H, d, $J = 3.3$ Hz) and the carbons at δ_C 126.5 and 134.0 can also be seen. But the proton at δ_H 3.90, which corresponds to the carbon at δ_C 44.1 in HSQC spectrum, showed only correlations with methyl carbons at δ_C 23.4 ($2 \times$ C). Consequently, the isopropyl group was linked with N atom, and there was one five-ring moiety in the semi-structures of **4** (Figure 3).

In the NOESY spectrum, the proton signal at δ_H 8.35 (1H, d, $J = 3.3$ Hz) showed correlation with the proton at δ_H 7.70 (1H, d, $J = 3.3$ Hz, H-5 and 10), the correlations between the proton at δ_H 10.91 (1H, s, OH), and olefinic protons at δ_H 7.70 (1H, d, $J = 3.3$ Hz, H-5 and 10) can also be seen. Thus, the structure of **4** was determined as 2,7-bis(isopropylimino)-2H,7H-dicyclopentacyclooctene-4,9-diol and named liguducimine D.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a JASCO P-1020 digital automatic polarimeter. The UV spectra were recorded on a Shimadzu UV-2501 spectrometer (Kyoto, Japan). IR spectra were taken on a Nicolet Impact 410 infrared spectrophotometer (Madison, WI, USA). HR-ESI-MS were obtained on an Aglient G3250AA LC/MSD TOF mass spectrometer (Santa Clara, CA, USA). NMR experiments were performed on a Brucker

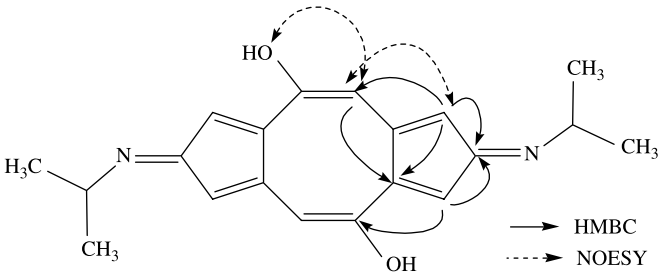

Figure 3. Key HMBC and NOESY correlations of compound **4**.

AV-300 spectrometer (Fallanden, Switzerland) with TMS as the internal standard. Silica gel (200–300 mesh for column chromatography and GF_{254} for TLC) was obtained from Qingdao Marine Chemical Company (Qingdao, China). Sephadex LH-20 was from Amersham Biosciences (Uppsala, Sweden).

3.2 Plant material

The rhizomes of *L. duciformis* (C. windl.) Hand-Mazz. were collected from Kangding, Sichun Province, China, in 2005, and authenticated by Dr Mian Zhang. A voucher specimen (No. LD-04-12) has been deposited in Research Department of Pharmacognosy, China Pharmaceutical University.

3.3 Extraction and isolation

The rhizomes of *L. duciformis* (60 kg) were extracted with 70% ethanol under reflux and evaporated *in vacuo* to yield a syrupy residue (8000*g*). The residue was suspended in water (8000 ml), then acidified with HCl to pH 2–3, and extracted with $CHCl_3$ (8000 ml × 2), then $CHCl_3$ was discarded and ammonia was added to pH 10–11 in residue water, which was continually extracted $CHCl_3$ (8000 ml × 3). Finally, the $CHCl_3$ extract was evaporated in vacuum to give an alkaloid residue (330 g). The alkaloid residue (300 g) was subjected to column chromatography on silica gel and eluted gradiently with $CHCl_3$–MeOH solvent system to yield five fractions (Fractions 1–5). Fraction 4 was rechromatographed on silica gel column with $CHCl_3$–MeOH (20:1 to 5:1) as eluent and Sephadex LH-20 column with $CHCl_3$–MeOH (1:1) as eluent to yield compounds **1** (15.0 mg) and **2** (5.0 mg). Fraction 2 was chromatographed on silica gel column eluted with $CHCl_3$–MeOH (10:1) and on Sephadex LH-20 eluted with $CHCl_3$–MeOH (1:1) to yield compound **3** (7.8 mg). Fraction 1 (21.0 g) was chromatographed on silica gel eluted with a petroleum ether–acetone gradient system (30:1 to 1:1) to yield subfractions (1A–1E). Subfraction 1A (5.7 g) was subjected to repeated column chromatography on silica gel with petroleum ether–acetone (20:1) as eluent and then on Sephadex LH-20 (MeOH system) to afford compound **4** (11.5 mg).

3.3.1 *1-(4′-Methylpyridazin-5′-yl)butane-1,2,3,4-tetraol (**1**)*

Colorless amorphous powder; $[\alpha]_D^{20} + 13.3$ ($c = 0.6$, MeOH). IR (KBr) ν_{max} (cm^{-1}): 3353, 2965, 1630, 1610, 1442, 1372, 1105, 1032, 898. UV (MeOH) λ_{max} (nm) (log ε): 217 (3.87), 273 (3.81). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.60 (1H, s, H-6′), 8.42 (1H, d, $J = 0.9$ Hz, H-3′), 5.24 (1H, d, $J = 6.4$ Hz, 1-OH), 4.93 (1H, d, $J = 6.3$ Hz, H-1), 4.60 (1H, d, $J = 5.1$ Hz, 2-OH), 4.37 (1H, d, $J = 7.2$ Hz, 3-OH), 4.33 (1H, dd, $J = 5.4$, 5.4 Hz, 4-OH), 3.60 (1H, m, H-2), 3.56 (1H, m, H-3), 3.64 (1H, m, H-4a), 3.43 (1H, m, H-4b), 2.46 (3H, d, $J = 0.9$ Hz, Me-4′). ^{13}C NMR: δ 155.7 (C-5′), 151.0 (C-4′), 142.9 (C-3′), 140.7 (C-6′), 71.6 (C-1), 74.0 (C-2), 71.5 (C-3), 63.8 (C-4), 20.8 (Me-4′). Positive

ion ESI-MS: *m/z* 215 $[M+H]^+$, 237 $[M+Na]^+$. Negative ion ESI-MS: *m/z* 213 $[M-H]^-$. HR-ESI-MS: *m/z* 213.0872 $[M-H]^-$ (calcd for $C_9H_{13}N_2O_4$, 213.0880).

*3.3.2 3,9-Dimethyl-5-nitropyrido [3,2,1-*ij*] quinazoline-1,7-dione (**2**)*

Red amorphous powder; mp 361–362°C. IR (KBr) ν_{max} (cm^{-1}): 2925, 2851, 1626, 1514, 1384, 1276, 1224, 772, 776. UV (MeOH) λ_{max} (nm) (log ε): 212 (3.94), 252 (3.32), 289 (3.27), 438 (2.73). ^{1}H NMR (acetone-d_6, 300 MHz): δ 7.06 (1H, s, H-6), 7.49 (1H, brs, H-8), 7.02 (1H, brs, H-10), 1.89 (3H, s, 3-CH_3), 2.39 (3H, brs, 9-CH_3). ^{13}C NMR (acetone-d_6, 75 MHz): δ 163.7 (C-1), 180.1 (C-3), 115.5 (C-4a), 136.9 (C-5 or C-10a), 114.5 (C-6), 184.9 (C-7), 109.0 (C-7a), 121.2 (C-8), 149.1 (C-9), 125.5 (C-10), 135.2 (C-10a or C-5), 24.4 (3-CH_3), 22.4 (9-CH_3). Negative ESI-MS: *m/z* 270.0 $[M-H]^-$, 224.3 $[M-NO_2]^-$; negative HR-ESI-MS: *m/z* 270.0527 $[M-H]^-$ (calcd for $C_{13}H_8N_3O_4$, 270.0520).

3.3.3 N,N-*di(1-imine-propanyl) propionamidine (**3**)*

Colorless slide crystals; mp 194–196°C. IR (KBr) ν_{max} (cm^{-1}): 3441, 2998, 2819, 2775, 2467, 1638, 1458, 1391, 1045, 798. ^{1}H NMR spectra ($CDCl_3$, 300 MHz): δ 9.53 (1H, brs), 3.04 (2H, q, $J = 1.0$ Hz), 1.48 (3H, t, $J = 1.0$ Hz). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 11.1, 42.2, and 163.5. Positive ESI-MS: *m/z* 183.0 $[M+H]^+$; positive HR-ESI-MS: *m/z* 183.1603 $[M+H]^+$ (calcd for $C_9H_{19}N_4$, 183.1604).

*3.3.4 2,7-Bis(isopropylimino)-2H,7H-dicyclopentacyclooctene-4,9-diol (**4**)*

Blue amorphous; mp 289–291°C. IR (KBr) ν_{max} (cm^{-1}): 3443, 1637, 1594, 1559, 1161, 1072, 670. UV (MeOH) λ_{max} (nm) (log ε): 203 (3.55), 231 (3.41), 259 (3.46), 277 (3.17). ^{1}H NMR spectra ($CDCl_3$, 300 MHz): δ 10.91 (1H, brs, OH), 8.35 (1H, dd, $J = 3.3$, 3.2 Hz, H-1 and 6), 7.70 (1H, d, $J = 3.3$ Hz, H-5 and 10), 7.28 (1H, d, $J = 3.2$ Hz, H-3 and 8), 3.90 (1H, d, $J = 6.0$ Hz, CH), 1.38 (6H, d, $J = 6.0$ Hz, 2× CH_3). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 126.5 (C-1 and 6), 182.5 (C-2 and 7), 124.8 (C-3 and 7), 145.0 (C-4 and 9), 132.0 (C-5 and 10), 134.0 (C-4a and 9a), 110.0 (C-5a and 10a), 44.1 (CH), 23.4 (2× CH_3). Positive ESI-MS: *m/z* 323.2 $[M+H]^+$; negative ESI-MS: *m/z* 462.3 $[2M-H]^-$; positive HR-ESI-MS: *m/z* 323.1760 $[M+H]^+$ (calcd for $C_{20}H_{23}N_2O_2$, 323.1754).

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