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Synthesis, structure, optical properties, antifungal and antibacterial activities of 2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)-3-imidazolyl-L-lactamic acid

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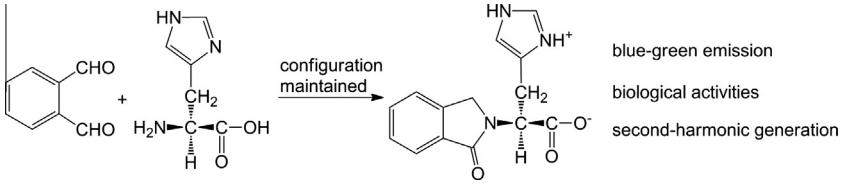
HIGHLIGHTS

- This paper described the preparation and full characterization of a new phthalimidin derivative.
- The compound exhibits blue–green emission with peaks at 354.5 and 486.5 nm.
- Second harmonic generation (SHG) property was investigated at the first time for this kind of compound.
- The compound has moderate antibacterial and antifungi activities.

GRAPHICAL ABSTRACT

This paper describes the preparation and full characterization of versatile Phthalimidin derivative 2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)-3-imidazolyl-L-lactamic acid with antibacterial and antifungi activity, blue-green fluorescent emission and second-harmonic generation (SHG) properties.



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ABSTRACT

2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)-3-imidazolyl-L-lactamic acid has been prepared conveniently by the condensation reaction of o-phthalaldehyde (OPA) with L-Histidine, and its single crystal structure has been characterized by X-ray crystallography method. The *in vitro* antifungal and antibacterial activities of the compound were investigated with the representative strains of *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Its luminescent and nonlinear optical properties have also been investigated. Second-harmonic-generation (SHG) measurements indicate that compound **1** displays a weak SHG response of about 0.75 times that of KH_2PO_4.

1. Introduction

In recent years, there is much current interest in Phthalimidino derivatives due to their unique chemical and biological properties [1]. Phthalimidine-containing drugs, such as indoprofen and γ-Diimine, are valuable for the treatment of a wide variety of diseases with respect to the potential antipsychotics, hypolipidemic and antimicrobial, etc. [2]. So far, studies have been focused on structural diversity and pharmacological activity, and a number of new Phthalimidines have been synthesized. Besides developing new member of Phthalimidine derivative with increased recognition ability and water-solubility, we also emphasize the further exploitation of the application scope of the phthalimidines [3]. In this case, we are allowed to design and recreate the drug from the reported or commercially available molecules easily without investing much time and effort in complicated synthesis. Viewing that asymmetric molecule or ligand possessing specific advantages for asymmetric synthesis, asymmetric catalysis and nonlinear materials [4], it will be interesting to prepare chiral phthalimidins by using the facile material such as amino acid as chiral source [5]. In this paper, we report a novel example in such

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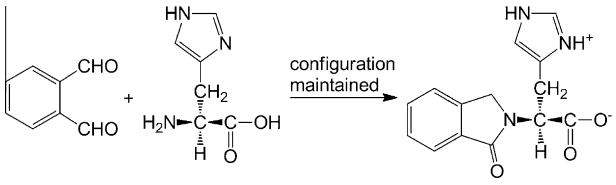

Scheme 1. Synthesis of PLH.

chiral phthalimidine family, i.e. 2-(1-oxo-1H-2,3-dihydroisoindol-2-yl)-3-imidazolyl-L-lactamic acid (**1**) (abbreviated PLH) by the convenient condensation reaction of o-phthalaldehyde (OPA) with L-Histidine(His) (Scheme 1). Histidine was used here in view of the following three factors [6,7]: (1) It can be available in high enantiomeric purity in R or S form; (2) imidazole and carboxyl functional groups could increase both the solubility and coordination ability; (3) as an essential amino acid in human and other mammal, it may reduce the toxicity of the drug and enhance the molecular recognition ability. The compound was fully characterized by elemental analysis, IR, ^{1}H NMR spectroscopies, and X-ray crystallography method. Its luminescence, nonlinear optical property, as well as *in vitro* antibacterial and antifungal activities of the compound have also been investigated.

2. Experimental

2.1. Materials and measurements

Chemicals and solvents were purchased commercially and used as received without further purification. Elemental analyses (C, H, N) were carried out with a Vario EL III elemental analyzer. Infrared spectrum was recorded in the range of 4000–400 cm^{-1} on a Nicolet Magna 750 FT-IR spectrometer. ^{1}H NMR spectrum was obtained at room temperature on Varian INOVA-400 spectrometer, and the chemical shift scale (ppm) is based on internal standard tetramethylsilane. Powder X-ray diffraction (PXRD) intensities for compounds were measured at 293 K on a D/max 2550 X-ray diffractometer (Rigaku, Japan) using Cu Kα radiation (λ = 0.1541 nm) in steps of 0.02° from 5° to 80° (diffraction angle 2θ) at a rate of 1 s per step, and the crushed single-crystalline powder samples were prepared by crushing the crystals. Photoluminescent spectrum was recorded with an F-7000 fluorescence spectrophotometer with the excitation and emission slit widths at 2.5 nm. ESI-MS measurements were performed on a Bruker Daltonics Esquire 3000Plus (Bremen, Germany) ion trap mass spectrometer. Mass spectra were recorded both in positive and negative ionization mode in the *m*/*z* 200–1200 range. Second harmonic generation test was performed by the powder technique of Kurtz and Perry using a pulsed Nd:YAG laser (λ = 1064 nm). Specific rotation was measured on an Anton Paar MCP200 (Anton Paar Co., Ltd., Beijing, China) Modular Circular digital polarimeter with a 1 cm optical length cell at 20 °C.

2.2. Synthesis of $C_{14}H_{13}N_3O_3$ (**1**)

Compound **1** was prepared according to the literature method [8]. Ortho-phthalaldehyde (OPA) (0.2683 g, 2 mmol) in EtOH (20 mL) was added dropwise to a stirred mixture of L-Histidine (0.3103 g, 2 mmol) in a 10:1 EtOH/H_2O solution (30 mL). The reaction mixture was then heated to reflux for about 3 h at about 90 °C. The yellow precipitate was produced. After the completion of reaction (TLC), the resulting solution was cooled to room temperature followed by filtering. The precipitate was washed with ethanol and recrystallized from water to give compound **1**. Yields (based on OPA): 0.3147 g of 1 (1.16 mmol, yield: 58%). Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of water at room temperature. Anal. Calcd. for $C_{14}H_{13}N_3O_3$ (%): C, 61.97; N, 15.50; H, 4.83. Found: C, 63.02; N, 15.27; H, 4.54. IR (KBr, cm^{-1}): 3442 (m), 3114 (m), 3019 (m), 2850 (m), 2667 (m), 1678 (vs), 1637 (vs), 1596 (s), 1471 (m), 1423 (m), 1367 (s), 1336 (m), 1308 (m), 1259 (m), 1228 (s), 1187 (m), 1101 (w), 943 (m), 889 (m), 798 (m), 740 (m), 682 (m), 636 (m), 572 (w), 576 (w), 509 (w), 453 (w) cm^{-1}. NMR for **1** (D_2O, 400 MHz): δ 3.353 (dd, *J* = 16, 11.2 Hz, H, imidazol–C*H*$_2$CH), δ 3.525 (dd, *J* = 15.6, 4.8 Hz, H, imidazol–C*H*$_2$CH), δ 4.578 (s, 2H, ArC*H*$_2$N), 5.076 (q, *J* = 11.2, 4.8 Hz, 1H, imidazol–CH$_2$C*H*CO), 7.137 (s, 1H, imidazol–C*H*), 7.537 (t, *J* = 7.2 Hz, 1H, Ar–*H*), 7.619 (d, *J* = 7.6 Hz, 1H, Ar–*H*), 7.673 (t, *J* = 7.2 Hz, 1H, Ar–*H*), 7.725 (d, *J* = 7.6 Hz, 1H, Ar–*H*), 8.529 (s, 1H, imidazol–N*H*). –c ESI MS (*m*/*z*) for **1**: 540.7, 464.7, 424.8, 381.8, 332.9, 305.9, 269.9, 226.1. The observed rotation was $[\alpha]_D$ -109.67 (*l* = 1, *d* = 0.0040 g/cm^3, H_2O).

2.3. X-ray data collection and structure determination

Single crystal X-ray intensity data of **1** was collected on a Rigaku Mercury 70 CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at 273 (2) K by using an ω-2θ scan mode. Intensity data were corrected for Lorentz and polarization effects as well as for an empirical absorption. The structures were solved by the direct methods [9]. All non-hydrogen atoms were generated from successive difference Fourier syntheses. The positions of the H atoms on N and O atoms were generated from difference Fourier maps with restrained (DFIX) treatment, the positions of other H atoms were added theoretically and riding on their parent carbon atoms before the final cycle of refinement. The final refinement was performed by full-matrix least-squares method on F^2, with anisotropic displacement parameters for all non-hydrogen atoms. All calculations were performed using the SHELXTL program [10]. The crystallographic data and experiment details for structural analysis are summarized in Table 1.

Table 1
Crystallographic data and refinement parameters for compound **1**.

Empirical formula	$C_{14}H_{13}N_3O_3$
Formula weight	271.27
Temperature (K)	273(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Crystal size (mm)	0.50 × 0.50 × 0.47
Unit cell dimensions (Å or °)	*a* = 8.9719(3)
	b = 10.6840(4)
	c = 13.3227(5)
Cell volume (Å^3)	1277.06(8)
Z	4
D_{calc} (g/cm^3)	1.411
μ (mm^{-1})	0.102
F(000)	568
2θ range	2.44 – 28.00
Limiting indices	$-5 \leqslant h \leqslant 11$
	$-14 \leqslant k \leqslant 8$
	$-17 \leqslant l \leqslant 10$
Rint	0.0197
Reflections collected	4607
Independent reflections	1758
Data/restraints/parameters	1758/2/191
GOF on F^2	1.064
R_1, wR_2 ($I > 2\sigma(I)$)	0.0415, 0.1131
R_1, wR_2 (all data)	0.0462, 0.1221
Largest diffractionpeak/hole (e Å^{-3})	0.353/−0.203