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Synthesis, bioassay, crystal structure and ab initio studies of Erlenmeyer azlactones

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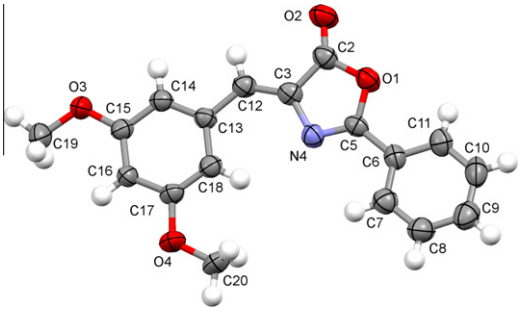
HIGHLIGHTS

- 4-Arylidene-2-phenyl-5(4H)-azlactones were synthesized and fully characterized.
- Antimicrobial and antioxidant activity.
- The structure of **5** & **6** were studied by X-ray study and compared to DFT calculations.
- DFT calculations of two compounds were suggested the stability of the Z-conformer.
- Crystal packing was stabilized by H-bond, weak C—H···π and π···π interactions were observed.

GRAPHICAL ABSTRACT

A series of 4-arylidene-2-phenyl-5(4H)-azlactones have been synthesized, characterized on the basis of systematic spectral studies and screened for their biological activity. Moreover, the *Z*-configuration and stability of compounds was ascertained on the basis of spectroscopy techniques, X-ray studies as well as DFT calculations.



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ABSTRACT

Several 4-arylidene-2-phenyl-5(4H)-azlactones have been synthesized *via* Erlenmeyer method. The synthesized compounds have been characterized on the basis of systematic spectral studies (IR, ^{1}H NMR, ^{13}C NMR, and MS). The compound (4*Z*)-4-(3,5-dimethoxybenzylidene)-2-phenyl-1,3-oxazol-5(4H)-one, $C_{18}H_{15}NO_4$, (**5**), crystallizes in the orthorhombic system, space group $P2_12_12_1$, with $a = 5.6793(3)$ Å, $b = 15.2038(7)$ Å, $c = 17.6919(10)$ Å, $Mr = 309.31$, $V = 1527.64(14)$ Å^3, $Z = 4$ and $R = 0.0547$. The compound (4*Z*)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1,3-oxazol-5(4H)-one, $C_{19}H_{17}NO_5$, (**6**) crystallizes in triclinic geometry with space group *P-1*, having unit cell parameters $a = 7.3814(3)$ Å, $b = 8.1446(3)$ Å, $c = 13.9845(5)$ Å, $\alpha = 86.918(3)$, $\beta = 83.314(2)$, $\gamma = 82.462(3)$, $Mr = 339.34$, $V = 827.16(5)$ Å^3, $Z = 2$ and $R = 0.0433$. The DFT calculations of compounds (**5**) and (**6**) have been carried out to ascertain the stability of *Z*-conformer. The *in vitro* antimicrobial activity of all the compounds (**1–6**) was evaluated by the disk diffusion method against gram +ve and gram −ve microorganism and fungal strains. The MIC of the synthesized compounds was determined by agar well diffusion method in 96-well microtiter plate. All the synthesized compounds were also screened for their free radical scavenging activity by DPPH method.

Introduction

During the past few decades many research papers have been published in the area of Erlenmeyer synthesis by using different methods [1–5]. The synthesis of azlactones involves the condensation of aromatic or aliphatic aldehydes and hippuric acid with a

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stoichiometric amount of fused sodium acetate in presence of acetic anhydride as the dehydrating agent, the reaction is called Erlenmeyer Plöchl reaction [6]. The Erlenmeyer reaction was first described in 1893 by Friedrich Gustav Carl Emil Erlenmeyer [7] who reported the condensation of benzaldehyde with N-acetylglycine in the presence of acetic anhydride and sodium acetate. The Erlenmeyer azlactones are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The C–2 and C–4 positions of the azlactones are significant for their various biological activities [8].

Azlactones, or 2,4-substituted oxazolin-5-ones, are important intermediates in the preparation of several fine chemicals, including amino acids, [9] peptides, [10] some heterocyclic precursors [11] as well as biosensors or coupling and photosensitive devices for proteins [12]. Erlenmeyer azlactone derivatives possess important biological activities such as an antimicrobial [13], antitumor [14], anti-inflammatory [15], anti-HIV [16,17], anticonvulsant [18] and antihypertensive [19]. They have been used in active site titrations of enzymes [20]. Recently, some new reagents have been explored for the synthesis of azlactones, such as Al_2O_3—H_3BPO_3 [21], $Bi(OAc)_3$ [22], $Bi(OTF)_3$ [23], and $Yb(OTF)_3$ [24]. Although these method are suitable, but some of them need elevated temperatures and hence possess difficult in handling.

In this work, we report the synthesis and the crystal structures of compounds (4Z)-4-(3,5-dimethoxybenzylidene)-2-phenyl-1,3-oxazol-5(4H)-one, $C_{18}H_{15}NO_4$, (**5**), and (4Z)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1,3-oxazol-5(4H)-one, $C_{19}H_{17}NO_5$ (**6**), as determined by single-crystal X-ray analysis. To investigate the effect of the intermolecular interactions in the conformation of the molecules we have also performed the optimization of the geometries of the compounds using density functional theory (DFT) calculations. Moreover, the compounds (**1–6**) have also been screened for the antimicrobial and antioxidant properties.

Experimental

Physical measurements

All the solvents and chemical were purchased from commercial sources (Sigma–Aldrich, Merck) and others and used as received or dried using standard procedures. Melting points were determined on a Kofler apparatus and uncorrected. Elemental analysis (C, H, N) were conducted using Carlo Erba analyzer model 1108. The IR spectra were recorded on KBr pellets with Interspec 2020 (FT-IR) spectrometer, Spactro Lab UK and its values are given in cm^{-1}. The UV spectra were recorded with UV VIS-1800 spectrophotometer (Shimadzu). ^1H and ^{13}C NMR spectra were run in $CDCl_3$ on a Bruker Avance-II 400 MHz and 100 MHz instrument respectively. TMS was used as an internal standard; *J* values are given in Hertz. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Thin layer chromatography (TLC) glass plates (20 × 5) were coated with silica gel (E-Merck G_{254}, 0.5 mm thickness) and exposed to iodine vapors to check the purity as well as the progress of the reaction.

*General method for the preparation of (4Z)-2-phenyloxazol-5(4H)-ones (**1–6**)*

An equimolar mixture of hippuric acid and suitable aldehyde (15 mmol) in freshly distilled acetic anhydride (10 mL) containing fused anhydrous sodium acetate (1.2 g) was heated on an oil bath at 140–150 °C for 2 h and then cooled. Progress of the reaction was monitored by TLC. After completion, the compounds were filtered, washed with light petroleum ether (60–80 °C) and air-dried. They were triturated with cold saturated solution of sodium carbonate and filtered, washed with water, air dried and recrystallized from suitable solvent to yield the representative compounds.

*(4Z)-4-(2-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**1**)*

It was recrystallized from $CHCl_3$—EtOH as bright yellow solid; Yield: 80%, m.p. 154–55 °C (lit. m.p. 154 °C) [2]; Anal. Calc. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.98; H, 4.64; N, 4.98. IR ν_{max}^{KBr} cm^{-1}: 1788 (C=O), 1669 (C=N), 1653 (C=C), 1248 (C—O Lactone); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.78 (s, 3H, CH_3), 6.98 (d, 1H, *J* = 8.2, H-6″), 7.18–7.28 (m, 2H, H-4″,5″), 7.35 (s, 1H, =CH=), 7.40–7.46 (d, 1H, *J* = 8.4, H-3″), 7.48–7.52 (m, 2H, H-3′,5′), 8.12–8.14 (m, 2H, H-2′,6′), 8.70 (dd, 1H, *J* = 7.4 H-4′); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): 55.8 (CH_3), 113.6 (C3″), 121.3 (C5″), 127.9 (C3′&5′), 128.7 (C2′&6′), 129.0 (C6″), 131.1 (C1″), 132.2 (C4′), 133.8 (C1′), 135.8 (CH=C), 144.0 (C4), 161.1 (C2″), 164.4 (C2), 181.6 (C5); MS (ES+) m/z: 280 $(M+H)^+$.

*(4Z)-4-(3-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**2**)*

Compound (**2**) was recrystallized from $CHCl_3$—MeOH as yellow solid; Yield: 80%, m.p. 102–03 °C (lit. m.p. 102–04 °C) [25]; Anal. Calc. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.10; H, 4.67; N, 5.04. IR ν_{max}^{KBr} cm^{-1}: 1795 (C=O), 1665 (C=N), 1652 (C=C), 1249 (C—O Lactone); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.80 (s, 3H, CH_3), 7.02 (d, 1H, *J* = 8.4, H-4″), 7.16 (s, 1H, —CH=), 7.30 (m, 2H, H-3′,5′), 7.42 (m, 1H, H-5″), 7.52 (d, 1H, *J* = 8.4, H-6″), 7.80 (s, 1H, H-2″), 8.10–8.06 (m, 2H, H-2′,6′), 8.40 (dd, 1H, *J* = 7.4 H-4′); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): 55.2 (CH_3), 115.5 (C2″), 117.1 (C4″), 122.5 (C6″), 127.6 (C3′&5′), 128.1 (C2′&6′), 132.2 (C4′), 133.1 (C5″), 133.4 (C1″), 134.2 (C1′), 135.8 (—CH=C), 145.3 (C4), 155.1 (C2), 159.3 (C3″), 184.5 (C=O); MS (ES+) m/z: 280 $(M+H)^+$.

*(4Z)-4-(4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one (**3**)*

It was recrystallized from $CHCl_3$—MeOH as orange colored solid; Yield: 90%, m.p. 155 °C (lit. m.p. 157 °C) [26]; Anal. Calc. for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 73.10; H, 4.68; N, 5.06. IR ν_{max}^{KBr} cm^{-1}: 1791 (C=O), 1668 (C=N), 1650 (C=C), 1245 (C—O Lactone); ^1H NMR (400 MHz, DMSO, δ, ppm): 3.87 (s, 3H, CH_3), 7.10–7.18 (d, 2H, *J* = 8.2, H-3″,5″), 7.32 (s, 1H, —CH=), 7.50, (d, 2H, *J* = 8.2, H-2″,6″), 7.70–7.75 (m, 2H, H-3′,5′), 8.10 (dd, 1H, *J* = 7.4, H-4′), 8.30 (d, 2H, *J* = 7.2, H-2′,6′); 13C NMR (100 MHz, DMSO, δ, ppm): 55.4 (CH_3), 114.5 (C3″&5″), 126.6 (C2″&6″), 127.6 (C3′&5′), 128.0 (C1″), 128.5 (C2′&6′), 132.3 (C4′), 133.4 (C1′), 135.5 (—CH = C), 142.3 (C4″), 144.4 (C4), 162.0 (C2), 182 (C=O); MS (ES+) m/z: 280 $(M+H)^+$.

*(4Z)-4-(2, 5-dimethoxybenzylidene)-2-phenyloxazol-5(4H)-one (**4**)*

Its recrystallized from $CHCl_3$—MeOH as bright yellow colored solid; Yield: 80%, m.p. 140–41 °C; Anal. Calc. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53, Found: C, 69.85; H, 4.86; N, 4.54. IR ν_{max}^{KBr} cm^{-1}: 1795 (C=O), 1651 (C=N), 1570 (C=C), 1274 (C—O Lactone); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.90–3.93 (s, 6H, 2 × CH_3), 7.02 (m, 2H, H-4″,6″), 7.51 (t, 2H, *J* = 7.4, H-3′,5′), 7.60 (t, 1H, *J* = 7.2, H-3″),7.71 (s, 1H, —CH=), 8.17 (d, 2H, *J* = 8.2, H-2′,6′), 8.46 (m, 1H,H-4′); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 56.4 (CH_3), 118.3 (C6″), 119.1 (C5″) 124.1 (C4″), 127.2 (C3′&5′), 128.5 (C2′&6′), 131.6 (C1″), 132.4 (C4′), 133.5 (C1′), 135.1 (—CH=C), 145.0 (C4), 151.8 (C3″), 154.7 (C2″), 160.8 (C2), 184.2 (C=O); MS (ES+) m/z: 310 $(M+H)^+$.