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Synthesis, spectroscopy and electrochemistry of new 4-(4-acetyl-5-substituted-4, 5-dihydro-1, 3,4-oxodiazol-2-yl)methoxy)-2H-chromen-2-ones as a novel class of potential antibacterial and antioxidant derivatives

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ABSTRACT

The synthesis of the new 4-(4-acetyl-5- substituted -4, 5-dihydro-1,3,4-oxodiazol-2-yl)methoxy)-2H-chromen-2-ones derivatives **5** was accomplished by the use of 4-hydroxycoumarine as a starting material. The structures of the compounds were confirmed by analytical UV, IR, ^{1}H, ^{13}C-NMR, NOESY and HMBC NMR spectra to elucidate the different positions of protons and carbons. All the compounds exhibited one quasireversible redox process. The UV absorption spectra of the obtained compounds showed strong absorption bands between 264 and 291 nm assigned to π-π^* transitions of the oxadiazole group. All the newly synthesized compounds were screened for their antibacterial and antioxidant activities. Antimicrobial studies revealed that compounds **5a** and **5b** showed significant antibacterial activity against *Escherichia coli* and *Pseudomonas Aeruginosa* 27853. Furthermore these compounds showed antioxidant activities of different extents with respect to individual compounds as well as to the antioxidant methods. The compounds **5a-d** was found to be the most active antioxidant in the series then Trolox, which makes the investigated complexes promising a new class of antibacterial compounds.

1. Introduction

1,3,4-Oxodiazole derivatives are highly attractive compounds for the development of materials for organic electroluminescent (EL) devices since they possess high electron-accepting properties and display strong fluorescence with high quantum yield [1]. This behavior is exemplified by 2,5-diphenyl-1,3,4-oxodiazole and 2,5-di-2-naphthyl-1,3,4-oxodiazole, for which quantum yields of 0.80 and 0.85 in cyclohexane solution, respectively, were reported [2]. Thus, compounds involving 1, 3,4-oxadiazole rings have been used as electron transporting materials and emitters in organic EL devices [3–5]. Recently 1,3,4-oxodiazole derivatives have aroused considerable interest in the area of organic light-emitting diodes (OLEDs) [6–9]. Oxadiazole fragments have also been connected to classical chelating ligands (such as bipyridines) in luminescent complexes, to obtain multifunctional (emitting and charge transporting) molecular species [10–17]. Furthermore, it has been reported that substituted 1, 3,4-oxadiazole derivatives show a broad spectrum of biological activity including anticancer effects [18,19]. In recent years, the application of 1,3,4-oxodiazole consisting of five membered heterocyclic ring have been described [20–24].

On the other hand, coumarins and structurally related compounds have been shown to inhibit replication of HIV

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and thus exhibit a therapeutic potential [25]. A large number of structurally novel coumarin derivatives have been reported to show substantial cytotoxic and anti-HIV activity in vitro and in vivo [26,27]. A variety of synthetic coumarins have unique mechanisms of action referring to the different stages of HIV replication [28]. Thus, coumarins are important lead compounds for the development of antiviral and/or virucidal drugs against HIV [29–31].

Keeping in view of the properties of 1,3,4 oxodiazole derivatives and in prolongation of our research on biologically active molecules [32,33], we have carried out the present study to describe new convenient and general procedures to afford novel 2-[(coumarin-4-oxy)-methyl]-4-acetyl-5-substitued–1,3,4-oxodiazole **5** containing 4-hydroxycoumarine moieties and investigate both their electrochemistry and antimicrobial properties against *Staphylococcus aureus* (CIP 7625), *S. aureus*, *Escherichia coli ATCC 25922*, *Klebsiella pneumonia CIP 104727* and *Pseudomonas aeruginosa* 27853 (CIP 76110) using the agar disk diffusion assay. The antioxidant properties of these compounds have been studied using two different test methods, namely 2,2-diphenyl-1-picryl-hydrazyl and ABTS radicals, respectively. The differences of radical scavenging and antioxidant properties of 2-[(coumarin-4-oxy) methyl]-4-acetyl-5-substitued–1,3,4-oxodiazole were compared with similar doses of Trolox, a standard antioxidant commonly used in food and pharmaceutical industries.

2. Results and discussion

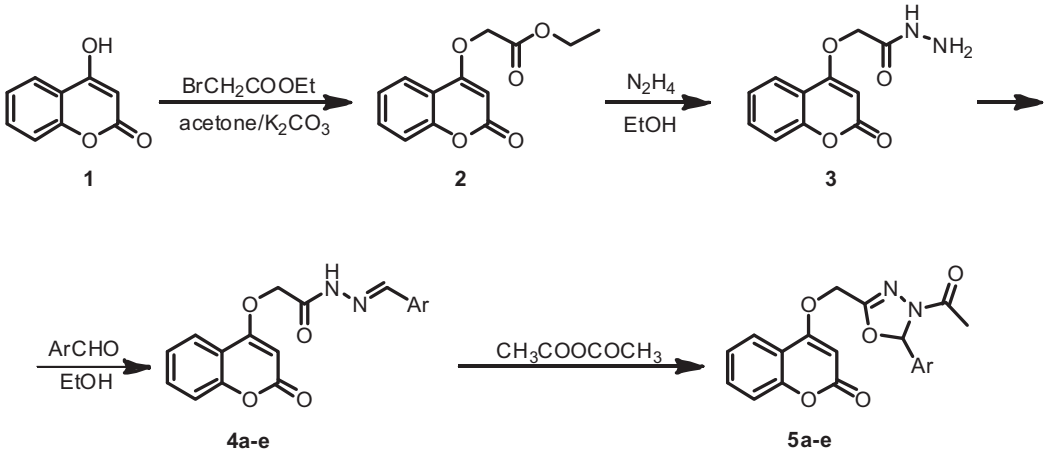
Compound **2** was prepared by reaction of 4-hydroxycoumarine with ethylbromoacetate in the presence of anhydrous potassium carbonate in dry acetone, followed by refluxing with hydrazine hydrate in absolute ethanol, generating a colorless crystalline product for which structure **3** was assigned.

The resulting of carbohydrazide **3** was reacted with arylaldehydes to give rise the (E)2-(coumarin-4-oxyacetic)-N-benzylideneacetohydrazide **4**, which precipitated by mixing the carbohydrazide **3** and the corresponding ArCHO in hot ethanol.

The obtained compounds **4** were then refluxed with acetic anhydride to give the corresponding 4-(4-acetyl-5-substituted -4, 5-dihydro-1,3,4-oxodiazol-2-yl)methoxy)-2H-chromen-2-ones **5** in good yields according to Scheme 1.

All the new 4-(4-acetyl-5- substituted -4, 5-dihydro-1,3,4-oxodiazol-2-yl)methoxy)-2H-chromen-2-ones **5**, have been characterized by UV, IR, 1H, ^{13}C-NMR spectra as well as by NOESY and HMBC NMR experiments to elucidate their structures and assign completely the structural network of both protons and carbons. The obtained spectral data were in accordance with the proposed structures.

As example, the IR spectra of compound **5c** showed the characteristic absorption bands for 1612(C=C), 1472(N=N) and 1289(C–O–C). In addition, the detection of a strong C=N stretching band at 1555 cm^{-1} evidenced the formation of the 1,3,4-oxodiazol ring. The ^{1}H NMR spectra of **5c** displays a signal at δ 6.07 ppm that ascribable to the proton H-3 from the coumarine moiety. A characteristic singlet proton signal at δ 8.53 ppm was assigned to H-5' proton from the oxodiazole fragment. In addition, the aromatic protons (both coumarinic and oxodiazolinic) are observed between δ 7.08 and δ 7.91 ppm (see experimental), and the expected singlet for methylenic moiety is observed at δ 5.47 ppm. The methyl protons of the acyl group arose at δ



Compound		Ar
4a	5a	phenyl
4b	5b	4-fluorophenyl
4c	5c	4-methoxy-phenyl
4d	5d	4-nitro-phenyl
4e	5e	3,4,5-trimethoxy-phenyl

Scheme 1. Synthesis of 4-(4-acetyl-5- substituted -4, 5-dihydro-1, 3,4-oxodiazol-2-yl)methoxy)-2H-chromen-2-ones5.