Synthesis and Biological Evaluation of Some Novel 1,3,4-Oxadiazoles Bearing Coumarine Moiety

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ABSTRACT

A series of 1,3,4-Oxadiazoles bearing Coumarine moiety (5a-c) were synthesized by refluxing Schiff's bases (4a-c) with acetic anhydride. 4a-c needed for the synthesis was obtained by refluxing ethyl-2-oxo-2H-chromone-3-carbohydrazides (3a-c) with benzyl oxy benzaldehyde. Similarly, 3a-c were prepared by reacting hydrazine hydrate and ethyl-2-oxo-2H-chromene-3-carboxylates (2a-c), which in turn were synthesized by treatment of substituted 2-hydroxy benzaldehydes (1a-c) with diethyl malonoate. The structures of the newly synthesized 1,3,4-Oxadiazoles have been established on the basis of chemical transformations, elemental analysis, IR, ¹H NMR, and Mass spectral studies. The title compounds were screened in-vitro for antibacterial activity against two Gram positive and two Gram negative bacterial strains such as E. coli, S. aureus, B. thurengienesis and E. aerogenes. The zone of inhibition measured in mm revealed that the title compounds exhibited moderate to good antibacterial activity against Chloramphenicol as standard.

Keywords, 1,3,4-Oxadiazole, Coumarine, Schiff’s base, Carbohydrazides.

INTRODUCTION

1,3,4-Oxadiazole is an important isomer among the class of oxadiazoles and has become an important structural theme for the development of new drugs because of its various biological activities. Review available in the literature (Patel et al., 2014) have suggested different methods for the synthesis of 1,3,4-Oxadiazoles. The most commonly used pathway for synthesis 1,3,4-Oxadiazole backbone includes reactions of properly substituted acid hydrazides with either acid chlorides/carboxylic acids or by direct cyclization of diacylhydrazines using a variety of dehydrating agents (Bentiss and Lagrenee, 1999; Liras et al., 2000; Gomes et al., 2001; Kadi et al., 2007; Mickevicius et al., 2009; Souldozi and Ramazani, 2007). Similarly, 1,3,4-Oxadiazole is a highly privileged structure, the derivatives of which have been found to possess broad spectrum antimicrobial activity and exhibit a wide range of biological activities (Sahu et al., 2011) including antibacterial (Barbucenu et al., 2011), antitubercular (Kumar et
al. 2010), vasodialatory (Shirote and Bhatia, 2010), antifungal (Parkash et al., 2010) cytotoxic (Padmavathi et al., 2009), anti-inflammatory and analgesic (Idrees et al., 2009) hypolipidemic (Jayashankar et al., 2009) anticancer (Kumar et al., 2009) and ulcerogenic (Shashikan et al., 2008) activities. Hence, in view of the importance and inspections of the research work on these heterocycles and continuation of our previous work (Siddiqui and Mohammad, 2008) on hydrazides, it was found to be fascinating to synthesize and subsequently treat carbohydrazide derivatives bearing coumarine moiety with benzyl alcohol followed by acetic anhydride for the synthesis of few novel 1,3,4-Oxadiazoles and view for spectral characterization and study their biological importance.

**MATERIALS AND METHODS**

The melting points were recorded in open capillary in paraffin bath and are uncorrected. IR spectra were recorded on a Shimadzu IR Spectrophotometer (KBr, v max in cm-1). 1H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d6 as solvent. Chemical Shifts are given in parts per million (ppm). Positive-ion electrospray ionisation (ESI) mass spectra were obtained with a Waters Micromass Q-TOF Micro, Mass Spectrophotometer. Elemental analysis (CHN) was done using Elemental analyzer, Vario EL III. All the chemicals used for the synthesis were of AR grade of Merck, S.D. Fine and Aldrich. The compounds were analyzed for carbon, hydrogen, nitrogen and sulphur and the results were in good conformity with the calculated values.

**Experimental**

Synthesis of starting materials substituted ethyl-2-oxo-2H-chromene-3-carboxylates (2a-c) and substituted 2-Oxo-2H-chromene-3-carbohydrazides (3a-c) was done according to the reported procedure (Siddiqui and Mohammad, 2017) (Scheme 1).

- **2-Oxo-2H-chromene-3-carbohydrazide (3a),** Colourless needle like crystal; mp, 136-138 °C yield, 90.0%; M. F. C10H8O3N2; Recrystallizing solvent, Ethanol.
- **6-Chloro-2-oxo-2H-chromene-3-carbohydrazide(3b)** Colourless needle like crystal; mp, 158-160°C yield, 80.0%; M. F. C16H12O3N2Cl; Recrystallizing solvent, Ethanol.
- **6-Bromo-2-oxo-2H-chromene-3-carbohydrazide(3c)** Colourless needle like crystal; mp, 174-175°C yield, 85.0%; M. F. C16H12O3N2Br; Recrystallizing solvent, Ethanol.

**Procedure for the synthesis of N’-(4-(benzyloxy) benzylidene)-substituted 2-oxo-2H-chromene-3-carbohydrazide (4a-c):**

Ethyl-2-oxo-2H-chromene-3-carbohydrazide 3a (10 mmol) and 4-benzoyl alcohol benzaldehyde (10 mmol) in ethanol (90 mL) containing 2-3 drops of concentrated acetic acid was refluxed for 2h to get 4a. The reaction mixture was cooled, filtered, washed, dried and recrystallized from 1,4-dioxane (Scheme 2). Similarly, 4b-c were synthesized from 3b-c by extending the same procedure followed for 4a.
N’-(4-benzyloxy)benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (4a): Yellow amorphous solid; mp, 192-194 °C; yield, 90.0%; M. F. C₂₈H₁₈O₂N₂Cl

N’-(4-benzyloxy)benzylidene)-6-chloro-2-oxo-2H-chromene-3-carbohydrazide (4b): Yellow amorphous solid; mp, 258-260 °C; yield, 89.0%; M. F. C₂₈H₁₉O₂N₂Cl

N’-(4-benzyloxy)benzylidene)-6-bromo-2-oxo-2H-chromene-3-carbohydrazide (4c): Yellow amorphous solid; mp, 278-280 °C; yield, 91.0%; M. F. C₂₈H₁₉O₂N₂Br

3-(4-acetyl-5-(4-benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-bromo-2H-chromen-2-one (5c), Yellow amorphous solid; mp, 225-227 °C; yield, 88.0%; M. F. C₃₀H₂₁O₂NaBr; IR, 1772 (C=O, ester), 3019 (ArH), 2917, 2864 (CH₂), 1561 (C=O, ester); Calculated, C, 60.09%; H, 4.00%; N, 5.87%

Antimicrobial activity
The novel synthesized heterocyclic compounds such as were screened for their in vitro antimicrobial activity using cup plate method against two gram positive bacterial strains, B. thuringiensis and S. aureus and two gram negative strains, E. coli and E. aerogenes using Chloramphenicol as the standard drug.

General Procedure for the Determination of Zone of Inhibition by Cup Plate method: Test solutions were prepared with known weight of compound in DMSO and half diluted to give the resultant concentration of 31-500μg/mL. Whatmann no. 1 sterile filter paper discs (6 mm) were impregnated with solution and allowed to dry at room temperature. In vitro antibacterial activity was determined by using Mueller Hinton Agar obtained from Himedia Ltd., Mumbai. Petri plates were prepared by pouring 10mL of agar for bacteria containing microbial culture and were allowed to solidify. The discs

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Reaction Scheme : 2

3-(4-acetyl-5-(4-benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (5a), Yellow amorphous solid; mp, 208-210 °C; yield, 89.0%; M. F. C₂₉H₂₀O₂N₂ IR, 1767 (C=O, ester), 3015 (ArH), 2927, 2861 (CH₃, CH₂), 1508 (C=C), 1604,1619 (C=N), 1244 (C=O, ester); ¹H NMR, 7.25-8.67 (m, 15H, ArH), 5.20 (s, 2H, -CH₂), 2.37(s, 3H, -CH₃), MS , 440 [M⁺]; 473[M+Na]⁺; Calculated, C, 70.91%; H, 4.55%; N, 6.36%; Found, C, 69.99%; H, 4.64%; N, 6.01%

3-(4-acetyl-5-(4-benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-chloro-2H-chromen-2-one (5b), Yellow amorphous solid; mp, 219-221 °C; yield, 86.0%; M. F. C₂₉H₁₉O₂N₂Cl; IR, 1775 (C=O, ester), 3028 (ArH), 2918, 2845 (CH₆, CH₂), 1525 (C=C),1624,1621 (C=N), 1241 (C=O, ester); ¹H NMR, 7.37-8.91 (m, 14H, ArH), 5.24 (s, 2H, -CH₂), 2.41 (s, 3H, -CH₃), MS, 476 [M+1]⁺, 498 [M+Na]⁺; Calculated, C, 65.71%; H, 4.03%; N, 5.90; Found, C, 65.71%; H, 4.00%; N, 5.87%
were then applied and the plates were incubated at 37°C for 24h (bacteria), then inhibition zone were measured in mm. The results were compared using Chloramphenicol as standard. The zone of inhibition of the compounds is given in the Table 1.

RESULT AND DISCUSSIONS

The synthesis of the novel compounds (5a-c) is described in reaction scheme 2. The identities of the newly synthesized compounds have been established on the basis of their elemental analysis and spectral data such as IR, 1H NMR and Mass spectral studies. Substituted 2-hydroxy benzaldehydes (1a-c) and diethyl malonate were reacted in the presence of piperidine in ethanol to form ethyl-2-oxo-2H-chromene-3-carboxylate (2a-c); which on treatment with hydrazine hydrate resulted in 2-oxo-2H-chromone-3-carboxydrazide (3a-c), which was further reacted with different aldehydes to form Schiff bases (4a-c). Schiff bases on refluxing with acetic anhydride was found to cyclize to 1,3,4-Oxadiazoles (5a-c) which was confirmed from their elemental and spectral analysis.

### Table 1: Antibacterial Activity

<table>
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<th>Sr. No.</th>
<th>Compd. Code</th>
<th>Concentration (µg/mL)</th>
<th>Zone of Inhibition (mm)</th>
<th>Antibacterial Activity</th>
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unsubstituted derivative 5a that showed moderate activity against all the four bacterial strain chosen.

**CONCLUSION**

We have reported here synthesis of some new 1,3,4-Oxadiazole derivatives bearing Coumarine moiety (5a-c) in good yields via cyclization of substituted Schiff’s bases (4a-c) in presence of acetic anhydride. Their structures were also confirmed from spectral studies such as IR, 1H NMR, Mass and CHN analysis. Biological screening revealed that the synthesized chloro and bromo substituted oxadiazoles derivatives 5b and 5c exhibited good antibacterial activity as compared to 5a.

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