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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-2*H*-chromone-3-carbohydrazides (3a-c) with benzyloxy benzaldehyde. Similarly, 3a-c were prepared by reacting hydrazine hydrate and ethyl-2-oxo-2*H*-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, ^{1}H 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 benzyloxy benzaldehyde 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). ^{1}H NMR spectra are recorded on a Bruker AM 400 instrument (400 MHz) using tetramethylsilane (TMS) as an internal reference and DMSO-d_6 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-2*H*-chromene-3-carboxylates **(2a-c)** and substituted 2-Oxo-2*H*-chromene-3-carbohydrazides **(3a-c)** was done according to the reported procedure (Siddiqui and Mohammad, 2017) (Scheme **1**).

2-Oxo-2*H*-chromene-3-carbohydrazide (3a),

Colourless needle like crystal; mp, 136-138 °C yield, 90.0%; M. F. $C_{10}H_8O_3N_2$; Recrystallizing solvent, Ethanol.

6-Chloro-2-oxo-2*H*-chromene-3-carbohydrazide(3b)

Colourless needle like crystal; mp, 158-160˚C yield, 80.0%; M. F. $C_{10}H_7O_3N_2Cl$; Recrystallizing solvent, Ethanol.

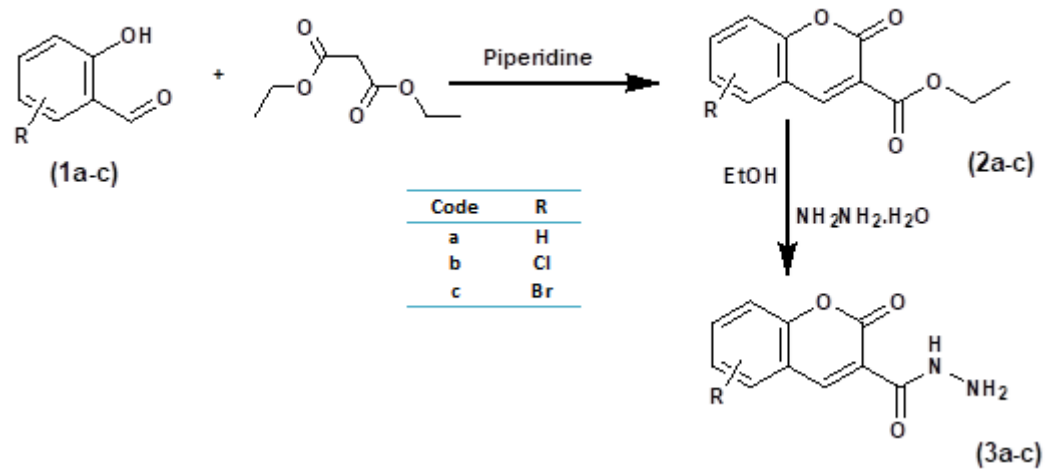
6-Bromo-2-oxo-2*H*-chromene-3-carbohydrazide(3c)

Colourless needle like crystal; mp, 174-175˚C yield, 85.0%; M. F. $C_{10}H_7O_3N_2Br$; Recrystallizing solvent, Ethanol.

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

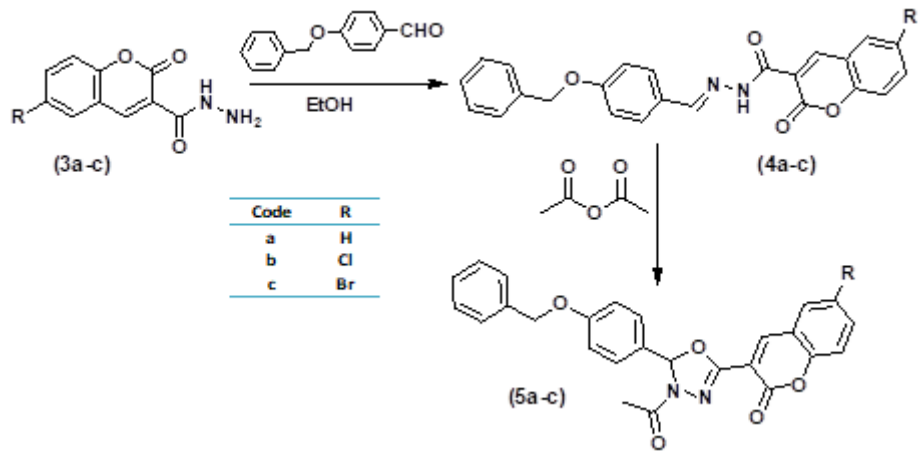
Ethyl-2-oxo-2*H*-chromene-3-carbohydrazide **3a** (10 mmol) and 4-benzyloxy benzaldehyde (10 mmol) in ethanol (90 mL) containing 2-3 drops of concentrated acetic acid was refluxed for 2h to get **4a**. The reaction mixture was cooled, filtered, washed, dried and recrystallized from 1,4-dioxane (Scheme **2**). Similarly, **4b-c** were synthesised from **3b-c** by extending the same procedure followed for **4a.**

Reaction Scheme : 1



Code	R
a	H
b	Cl
c	Br

Reaction Scheme : 2



Code	R
a	H
b	Cl
c	Br

N'-(4-(benzyloxy)benzylidene)-2-oxo-2*H*-chromene-3-carbohydrazide(4a): Yellow amorphous; mp, 192-194 °C yield, 90.0%; M. F. $C_{24}H_{18}O_4N_2$

N'-(4-(benzyloxy)benzylidene)-6-chloro-2-oxo-2*H*-chromene-3-carbohydrazide (4b): Yellow amorphous solid; mp, 258-260˚C, yield, 89.0%; M. F. $C_{24}H_{17}O_4N_2Cl$

N'-(4-(benzyloxy)benzylidene)-6-bromo-2-oxo-2*H*-chromene-3-carbohydrazide (4c): Yellow amorphous solid; mp, 278-280˚C, yield, 91.0%; M. F. $C_{24}H_{17}O_4N_2Br$

Procedure for the synthesis of 3-(4-acetyl-5-(4-(benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-substituted-2*H*-chromen-2-one (5a-c), A mixture of N'-{[4-(benzyloxy) phenyl]methylidene}-2-oxo-2*H*-chromene-3-carbohydrazide **5a** (2 mmol) and acetic anhydride (10 mL) was refluxed for 1h. The excess acetic anhydride was distilled off at reduced pressure and residue was poured into ice cold water. The solid produced was filtered, dried and recrystallized from 1,4-dioxane (Scheme **2**).

3-(4-acetyl-5-(4-(benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2*H*-chromen-2-one (5a), Yellow amorphous solid; mp, 208-210˚C, yield, 89.0%; M. F. $C_{26}H_{20}O_5N_2$, IR, 1767 (C=O, ester), 3015 (ArH), 2927, 2861 (CH_3, CH_2), 1508 (C=C),1604,1619 (C=N), 1244 (C-O, ester); ^{1}H NMR, 7.25-8.67 (m, 15H, ArH), 5.20 (s, 2H, -CH_2), 2.37(s, 3H, -CH_3), 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-2*H*-chromen-2-one (5b), Yellow amorphous solid; mp, 219-221˚C, yield, 86.0%; M. F. $C_{26}H_{19}O_5N_2Cl$; IR, 1775 (C=O, ester), 3028 (ArH), 2918, 2845 (CH_3, CH_2), 1525 (C=C),1624,1621 (C=N), 1241 (C-O, ester); ^{1}H NMR, 7.37-8.91 (m, 14H, ArH), 5.24 (s, 2H, -CH_2), 2.41 (s, 3H, -CH_3), MS, 476 $[M+1]^+$, 498 $[M+Na]^+$; Calculated , C, 65.76; H, 4.03; N, 5.90; Found, C, 65.71%; H, 4.00%; N, 5.87%.

3-(4-acetyl-5-(4-(benzyloxy)phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-bromo-2*H*-chromen-2-one (5c), Yellow amorphous solid; mp, 225-227 ˚C, yield, 88.0%; M. F. $C_{26}H_{19}O_5N_2Br$; IR, 1772 (C=O, ester), 3019 (ArH), 2917, 2864 (CH_3, CH_2), 1561 (C=C),1622 (C=N), 1240 (C-O, ester); ^{1}H NMR, 7.33-8.88 (m, 14H, ArH), 5.23 (s, 2H, -CH_2), 2.39 (s, 3H, -CH_3), MS, 519 $[M]^+$; Calculated , C, 60.13; H, 3.69; N, 5.39; Found, C, 60.09%; H, 4.00%; N, 5.27%.

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. thurengienesis* and *S. aureus* and two gram negative strains, *E. coli* and *E. aerugenes* 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

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[19] such as IR, ^{1}H 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-2*H*-chromene-3-carboxylate (2a-c); which on treatment with hydrazine hydrate resulted in 2-oxo-2*H*-chromonene-3-carbohydrazide (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.

IR spectra of 5a-c showed absorption bands in the range of 1767-1775 cm^{-1} for C=O, 1240-1244 cm^{-1} for C-O-C stretching and bands at 2927-2861 cm^{-1} for -CH_3, -CH_2 aliphatic stretch. The ^{1}H NMR spectra showed a multiplet of fifteen, fourteen and fourteen aromatic protons in the range of δ 7.25-8.67, 7.37-8.91 and 7.33-8.88 ppm for 5a, 5b and 5c respectively. Similarly, singlet in the range of δ 5.20-5.24 in 5a-c also confirms the presence of two methylene protons -CH_2. Mass spectra also confirms the formation of 5a-c, as molecular ion peaks are obtained at 440 $[M]^+$, 476$[M+1]^+$ and 519$[M]^+$, having the molecular formula $C_{26}H_{20}N_2O_5$, $C_{26}H_{19}O_5N_2Cl$ and $C_{26}H_{19}O_5N_2Br$ respectively (Scheme 2).

Antimicrobial activity, Synthesized title compounds (5a-c) were screened for antimicrobial activity. Table no. 1, shows the inhibition zone calculated in mm at different concentrations from 31-500 µg/mL using Chloramphenicol as the standard drug. The zone of inhibition revealed that the title compounds exhibited moderate to good antibacterial activity against the standard. 1,3,4-Oxadiazoles bearing chloro and bromo substitution i.e. 5b and 5c were found to have good antibacterial activity when compared with the

Table 1: Antibacterial Activity

Sr. No.	Compd. Code	Concentration (µg/mL)	Zone of Inhibition (mm)			
			Antibacterial Activity			
			S. aureus	*E. coli*	*B. thurengienesis*	*E. areogenes*
1.	Chloramphenicol	500	28	19	19	15
		250	28	18	20	17
		125	20	16	16	15
		62.5	18	15	14	14
		31	20	20	15	15
2.	**5a**	500	20	13	12	10
		250	19	12	14	11
		125	14	10	11	9
		62.5	12	10	8	9
		31	13	10	10	7
3.	**5b**	500	24	15	14	12
		250	21	14	14	13
		125	17	12	13	12
		62.5	15	15	11	10
		31	17	16	14	11
4.	**5c**	500	23	14	15	11
		250	21	13	15	12
		125	15	12	14	10
		62.5	16	14	11	10
		31	15	16	12	9

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, ^{1}H 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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