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Synthesis and characterization of novel *N*-(4-methyl-2-oxo-2H-chrome-7-yl)-2-(5-phenylsubstituted-1,3,4-oxadiazol-2-ylthio)acetamide derivatives

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ABSTRACT

*In the present study, we have synthesized a series of N-(4-methyl-2-Oxo-2H-chrome-7-yl) -2-(5-phenylsubstituted-1,3,4-oxadiazol-2-ylthio) acetamide derivatives (**1a-h**) by the nucleophilic substitution of 2-chloro-N-(4-methyl-2-Oxo-2H-chrome-7-yl) acetamide (**7**) with suitable 1,3,4-oxadiazole- 2-thiols (**5a-h**). The chemical structures of the compounds were characterized confirmed by the IR, ^{1}H-NMR, ^{13}C-NMR and LC-MS spectral data.*

Key Words: 7-Amino-4-methyl coumarin, Acetamide, 1,3,4-oxadiazole-2-thiol.

INTRODUCTION

Among the heterocyclic compounds coumarin is one of the simple and important molecular scaffolds in medicinal chemistry [1]. Coumarins revealing a variety of pharmacological activities such as antibacterial, anti-inflammatory [2], Alzheimer's [3], antimicrobial, cytotoxicity [4], anti-HIV [5], antituberculosis [6], anti-fungal, antioxidant [7], antiviral [8], anti-influenza [9]. Some naturally occurring coumarin based anti–biotic *viz* novobiocin and clorobiocin effect the functioning of DNA gyrase [10] and anticonvulsant activities [11].

A privileged structure 1,3,4-oxadiazoles are well known for their variety of biological activities including anti-inflammatory [12], anticonvulsant [13], hypoglycemic [14], anti-anxiety and antidepressant [15] activities. Insight by the above findings in the perpetuation of our laboratory for the synthesis of heterocyclic compounds [16, 17], our research was concentrated on the construction of novel *N*-(4-methyl-2-oxo-2H-chrome-7-yl) -2-(5-phenylsubstituted-1,3,4-oxadiazol-2-ylthio)acetamidederivatives (**1a-h**) and characterized by ^{1}H & ^{13}C NMR and LCMS spectral data.

MATERIALS AND METHODS

Chemistry:
Melting points were determined by Open Capillary Method using VEEGO, Programmable Digital Melting Point Apparatus and are uncorrected. Unless stated otherwise, all materials obtained from commercial suppliers were used without further purification. TLC controls were carried out on precoated silica gel plates (F254 Merck) using Chloroform-Ethyl acetate (7:3) as solvents. IR spectra were recorded on FT-IR 470 plus spectrophotometer (JASCO) using KBr as the internal standard (ν_{max} in cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in DMSO on a Bruker 400 MHz spectrometer using tetramethylsilane (TMS) as the internal reference (chemical shift was measured in δ ppm). Mass spectra (ESI-MS) were measured on Applied Bio systems 3200 Q-TRAP LC-MS/MS. The progress

of the reaction and the purity of the synthesized compounds were verified on ascending thin layer chromatography (TLC) plates coated with silica gel G (Merck). An iodine chamber and UV lamp were used for the visualization of the TLC spots.

*Synthesis of 7–amino–4–methyl coumarin (**6**)*
7-Amino-4-methyl coumarin was synthesized by the von Pechmann condensation of 3- amino phenol with methyl chloroformate by earlier reported method [18].

*Synthesis of 2-chloro-N-(4-methyl-2-oxo-2H-chrome-7-yl) acetamide (**7**)*
To a stirring solution of 7-amino-4-methyl coumarin(**6**) (1 g, 5.71 mmol) and TEA (1.3 g, 8.56 mmol) in DMF (10 mL), chloroacetyl chloride (0.77 g, 6.85 mmol) was added very slowly at 0 ^{0}C under inert atmosphere. The reaction mixture was transferred into crushed ice with continuous stirring, the solid was filtered out and washed with water to give a compound **7**.

Yield: 88%; m.p: 168-170 ^{0}C; IR (KBr) (ν_{max}/cm^{-1}): 3435, 2985, 1718, 1563; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.24 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.28 (s, 1H, Coumarin-CH), 7.55 (dd, 1H, J_{HH}= 8.0, 2.0 Hz, CH), 7.76 (m, 2H, Coumarin Ar-H) 10.37 (s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 19.03, 38.98, 113.36, 115.27, 118.73, 125.12, 139.49, 152.61, 155.30, 160.75; LC-MS (70 eV): *m/z*= 252.03 $(M+H)^+$.

*General procedure for the preparation of titled compounds **1a-h***
To a solution of compound **5a-h** (0.510 mmol) and 1N NaOH (1.2 mmol) in DMF was added to the compound **7** (0.765 mmol) at room temperature and the reaction mixture was refluxed for 6-8 h. There after the reaction mixture was transferred into crushed ice the precipitate was filtered and recrystallized with EtOH to give **1a**–**h** with good yields. The progress of the reaction was monitored by thin layer chromatography chloroform/ethyl acetate (7:3) as solvent system [21].

*N-(4-Methyl-2-oxo-2H-chromen-7-yl)-2-(5-p-tolyl-1,3,4-oxadiazol-2-ylthio)acetamide (**1a**)*
Yield: 88 % (colorless solid); IR (KBr) (ν_{max}/cm^{-1}): 3430, 2985, 1698, 1563; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.94 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 5.94 (s, 1H, Coumarin-CH), 7.40 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.53 (dd, 1H, J_{HH}= 2.0, 1.6 Hz, CH), 7.72 (d, 2H, J_{HH}= 4.0 Hz, Ar-CH), 7.74 (d, 2H, J_{HH}= 4.0 Hz, Ar-CH), 7.85 (d, 1H, J_{HH}= 4.0 Hz, CH), 10.29 (s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 20.03, 34.98, 59.11, 114.36, 119.73, 120.68, 126.26, 129.70, 130.62, 135.23, 137.49, 141.61, 144.02, 149.75, 152.01, 158.30, 163.58, 166.94, 168.41; LC-MS (70 eV): *m/z*= 406 $(M-H)^-$.

*2-(5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (**1b**)*
Yield: 69 % (white solid); IR (KBr) (ν_{max}/cm^{-1}): 3395, 2995, 1700, 1539; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.41 (s, 3H, CH_3), 3.43 (s, 3H, OCH_3), 3.68 (s, 2H, CH_2), 6.18 (s, 1H, coumarin-CH), 7.08 (d, 2H, J_{HH}= 8.0 Hz, Ar-CH), 7.26 (d, 2H, J_{HH}= 4.0 Hz, Ar-CH), 7.38 (d, 1H, J_{HH}= 12.0 Hz, CH), 7.69 (dd, 1H, J_{HH}= 6.2, 2.4 Hz, CH), 7.82 (d, 1H, J_{HH}= 4.0 Hz, CH), 10.36 (s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 23.71, 37.16, 54.73, 119.43, 120.62, 121.04, 124.17, 127.34, 128.09, 131.47, 138.82, 139.05, 141.83, 147.42, 150.75, 154.22, 160.08, 163.47, 165.27; LC-MS (70 eV): m/z = 424 $(M+H)^+$.

*N-(4-Methyl-2-oxo-2H-chromen-7-yl)-2-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-ylthio) acetamide (**1c**)*
Yield: 78% (light yellow solid); IR (KBr) (ν_{max}/cm^{-1}): 3435,2087, 1705, 1556; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.91 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 5.98 (s, 1H, Coumarin-CH), 7.42 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.56 (dd, 1H, J_{HH}= 8.0, 4.0 Hz, CH), 7.69 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.92 (d, 2H, J_{HH}= 8.0 Hz, Ar-CH), 8.02 (d, 2H, J_{HH}= 12.0 Hz, Ar-CH), 9.94(s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 19.20, 36.71, 117.27, 119.10, 122.37, 124.72, 127.06, 129.47, 132.39, 139.52, 140.44, 142.71, 146.48, 150.26, 153.46, 159.32, 161.68, 166.09; LC-MS (70 eV): m/z = 439 $(M+H)^+$.

*2-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (**1d**)*
Yield: 83% (light yellow solid); IR (KBr) (ν_{max}/cm^{-1}): 3340, 2090, 1695, 1576; ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 2.13 (s, 3H, CH_3), 4.06 (s, 2H, CH_2), 6.15 (s, 1H, Coumarin-CH), 7.22 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.31 (d, 2H, J_{HH}= 12.0 Hz, Ar-CH), 7.71 (dd, 1H, J_{HH}= 4.0, 2.4 Hz, CH), 7.73 (d, 1H, J_{HH}= 1.2 Hz, CH), 7.86 (d, 2H, J_{HH}= 4.0 Hz, Ar-CH), 9.96(s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 20.71, 42.33, 117.23, 118.09, 121.28, 124.32,

126.40, 127.19, 132.14, 133.20, 139.92, 146.09, 148.11, 153.57, 158.32, 161.03, 164.71, 168.36; LC-MS (70 eV): m/z = 428 $(M+H)^+$.

*2-(5-(4-Bromophenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (**1e**)*
Yield: 90% (light yellow solid); IR (KBr) (ν_{max}/cm^{-1}): 3325, 2965, 1700, 1563; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.83 (s, 1H, CH_3), 3.74 (s, 2H, CH_2), 6.26 (s, 1H, coumarin-CH), 7.08 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.39 (dd, 1H, J_{HH}= 8.0, 4.0 Hz, CH), 7.61 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.75 (d, 1H, J_{HH}= 12.0 Hz, Ar-CH), 7.79 (t, 1H, J= 5.6 Hz, Ar-CH), 7.86 (d, 1H, J_{HH}= 4.0 Hz, Ar-CH), 7.97 (t, 1H, J = 5.8 Hz, Ar-CH), 9.86 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 21.68, 39.41, 114.28, 117.91, 119.39, 121.72, 126.88, 129.04, 132.90, 135.24, 137.19, 140.26, 146.93, 149.33, 153.27, 156.46, 159.72, 163.50, 166.22, 167.74; LC-MS (70 eV): m/z = 471 $(M+H)^+$.

*2-(5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl)acetamide (**1f**)*
Yield: 72% (light yellow solid); IR (KBr) (ν_{max}/cm^{-1}): 3343, 2942, 1692, 1568; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.86 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 5.98 (s, 1H, coumarin-CH), 7.28 (d, 1H, J_{HH}= 4.0 Hz, CH), 7.34 (d, 2H, J_{HH}= 4.0 Hz, Ar-CH), 7.64 (dd, 1H, J_{HH}= 8.0, 2.4 Hz, CH), 7.88 (d, 1H, J_{HH}= 8.0 Hz, CH), 7.92 (dd, 2H, J_{HH}= 4.0, 1.2 Hz, Ar-CH), 10.21(s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 17.49, 39.42, 116.09, 118.25, 120.39, 123.03, 125.11, 129.78, 130.01, 136.82, 138.48, 142.90, 149.30, 152.40, 156.63, 163.22, 165.40, 167.30; LC-MS (70 eV): m/z = 410 $(M-H)^-$.

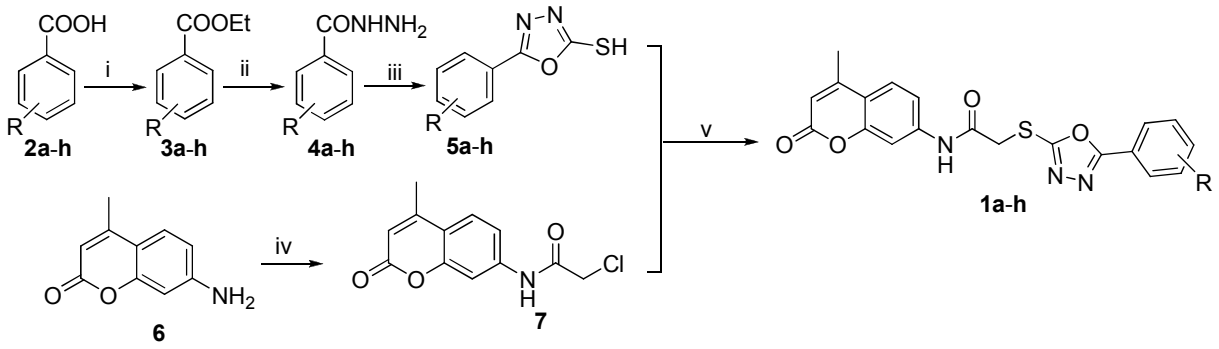
*2-(5-(4-Tert-butylphenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (**1g**)*
Yield: 82% (light yellow solid); IR (KBr) (ν_{max}/cm^{-1}): 3330,2985, 1658, 1576; ^{1}H NMR (400 MHz; DMSO-d_6): δ_H 1.72 (s, 9H, CH_3), 2.48 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 6.12 (s, 1H, coumarin-CH), 7.34 (d, 1H, J_{HH}= 4.0 Hz, CH), 7.62 (dd, 1H, J_{HH}= 4.0, 2.6 Hz, CH), 7.81 (d, 2H, J_{HH}= 8.0 Hz, Ar-CH), 7.88 (d, 2H, J_{HH}= 8.0 Hz, Ar-CH), 7.93 (d, 1H, J_{HH}= 12.0 Hz, CH), 10.12 (s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): δ_C 17.82, 24.41, 37.04, 54.63, 118.37, 119.20, 122.72, 124.78, 128.42, 133.83, 136.27, 139.08, 142.85, 147.43, 150.67, 154.82, 159.09, 161.36, 164.77, 165.20; LC-MS (70 eV): m/z = 450 $(M+H)^+$.

*2-(5-(4-Ethylphenyl)-1,3,4-oxadiazol-2-ylthio)-N-(4-methyl-2-oxo-2H-chromen-7-yl)acetamide (**1h**)*
Yield 87%; white solid; IR (KBr) (ν_{max}/cm^{-1}): 3355, 3112, 2926, 1702, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.32 (t, 3H, J_{HH} = 6.4 Hz, $CH_2C\underline{H}_3$), 2.71 (quartet, 2H, J_{HH} = 6.5 Hz, $C\underline{H}_2CH_3$), 2.32 (s, 3H, CH_3), 3.98 (d, 2H, J_{HH} = 6.0 Hz, CH_2), 5.92 (s, 1H, coumarin -CH), 6.55 (d, 1H, J_{HH}= 2.0 Hz), 6.7 (dd, 1H, J_{HH} = 8.6, 2.0 Hz, Ar-CH), 7.33-7.21 (m, 3H, Ar-CH), 7.44 (d,1H, J_{HH}= 8.6 Hz, Ar-CH),7.7 (d, 2H , J_{HH}= 8.3 Hz, Ar-CH), 10.23 (s, 1H, NH); ^{13}C NMR (100 MHz; DMSO-d_6): 15.21, 17.90, 27.91, 54.63, 118.47, 119.22, 122.52, 124.58, 128.22, 133.83, 136.47, 139.18, 142.75, 147.43, 151.47, 154.86, 159.12, 161.36, 164.67, 165.12; LC-MS (70 eV): m/z = 422 $(M+H)^+$.

RESULTS AND DISCUSSION

Initially the synthesis of 7-amino-4-methyl coumarin (**6**) was carried out by the condensation of 3-amino-phenol with methylchloroformate and followed by von Pechmann procedure earlier reported methods [18]. The coupling of **6** with chloroacetyl chloride [19] in the presence of TEA leads to the formation of 2-chloro-*N*-(4-methyl-2-oxo-2H-chrome-7-yl) acetamide (**7**). Various phenyl substituted 1,3,4- oxadiazole-2-thiol (**5a–h**) were synthesized from the corresponding benzoic acids using a well-known method [20]. Finally the targeted compounds **1a-h** were synthesized via nucleophilic substitution reaction on **7** with corresponding 1,3,4-oxadiazole-2-thioles **5a-h** in the presence of sodium hydroxide in DMF to afford 65–90 % yields. The chemical structures of the synthesized compounds were elucidated on the basis of their IR, ^{1}H & ^{13}C NMR and mass spectral data.

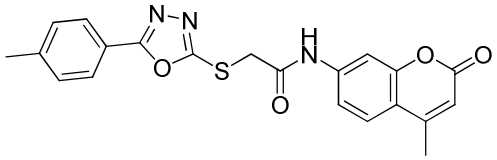
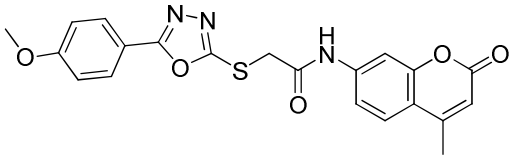
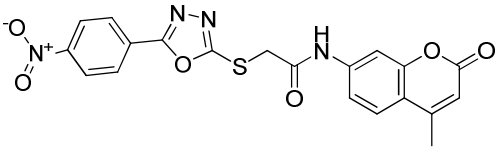
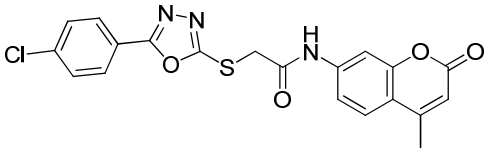
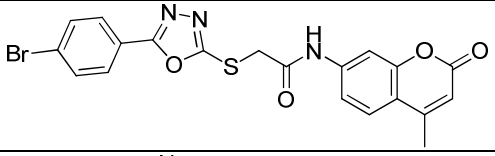
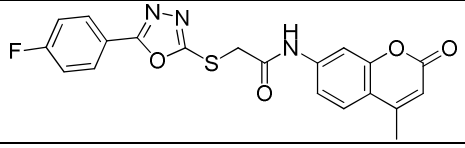
In the ^{1}H-NMR spectra of the targeted compounds, the signal due to the amide proton appears at 9.94–10.36 ppm as a broad peak. The signal due to –S–CH_2– group protons rise to a singlet at 3.37-4.06 ppm and the coumarin protons of all the derivatives are observed in the region 5.9-8.0 ppm. Other aromatic protons were observed in expected regions. Where as in their ^{13}C-NMR spectra the signal due to the amide carbon is observed at 165-168 ppm as a evident for formation of amide moiety. The signal due to the –S–CH_2– carbon appears at 27-42 ppm. The mass spectra of all the compounds are obtained at expected mass value of each compound.

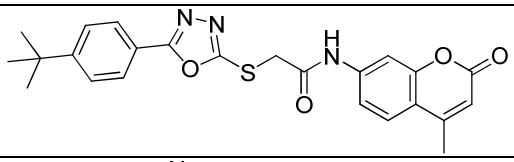
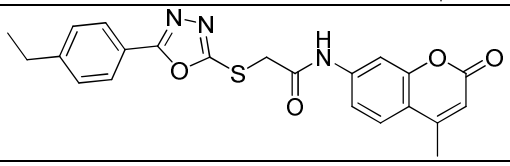


Scheme 1

Reagents and conditions: (i) Ethanol, reflux, 8 h; (ii) $NH_2NH_2.H_2O$, 6 h; (iii) CS_2,ethnol, reflux, 5 h; (iv) Chloroacetyl chloride, T.E.A, D.M.F, 0-r.t, 2 h; (v) NaOH, Ethanol, reflux, 6-8 h.

Physical data of the final molecules 1a-h

Compound	m.p. ^{0}C	Yield (%)	Structure of the compound
1a	189-191	88	
1b	195-197	69	
1c	198-200	73	
1d	189-191	88	
1e	201-213	90	
1f	199-201	**72**	

1g	205-207	82	
1h	202-204	87	

CONCLUSION

In conclusion, a series of novel coumarin based acetamide derivatives are synthesized in good yields and characterized by spectral data.

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