

Full Research Paper

Synthesis and Antimicrobial Activity of Some Derivatives of (7-Hydroxy-2-oxo-2H-chromen-4-yl)-acetic Acid Hydrazide

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Abstract: (7-Hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide (**2**) was prepared from (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid ethyl ester (**1**) and 100% hydrazine hydrate. Compound **2**, is the key intermediate for the synthesis of several series of new compounds such as Schiff's bases **3a-1**, formic acid N'-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetyl] hydrazide (**4**), acetic acid N'-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl] hydrazide (**5**), (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxoethyl] hydrazide (**6**), 4-phenyl-1-(7-hydroxy-2-oxo-2H-chromen-4-yl)-thiosemicarbazide (**7**), ethyl 3-{2-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl]hydrazono}butanoate (**8**), (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[(4-trifluoromethylphenylimino)methyl] hydrazide (**9**) and (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[(2,3,4-trifluorophenylimino)-methyl] hydrazide (**10**). Cyclo-condensation of compound **2** with pentane-2,4-dione gave 4-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-7-hydroxy-2H-chromen-2-one (**11**), while with carbon disulfide it afforded 7-hydroxy-4-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-2H-chromen-2-one (**12**) and with potassium isothiocyanate it gave 7-hydroxy-4-[(5-mercapto-4H-1,2,4-triazol-3-yl)methyl]-2H-chromen-2-one (**14**). Compound **7** was cyclized to afford 2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-N'-(4-oxo-2-phenylimino-thiazolidin-3-yl) acetamide (**15**).

Keywords: Coumarin hydrazide, Schiff's bases, thiosemicarbazide, oxadiazole, triazole, thiazolidine, antimicrobial activity.

Introduction

A number of natural and synthetic coumarin (2-oxo-2*H*-chromene) derivatives have been reported to exert notably antimicrobial [1,2] as well as antifungal [3,4] and tuberculostatic [5] activity. Moreover, the antibiotic novobiocin belongs to the hydroxy coumarin series. On the other hand, a large number of hydrazides have been reported to be of biological interest [6,7], while oxadiazole derivatives and thiosemicarbazides have been reported to possess antibacterial [8,9], antifungal [10,11] and other biological activities. Furthermore, a number of substituted thiazolines and thiazolidinones were found to exhibit appreciable antimicrobial and antifungal activities [12-16]. It was therefore thought worthwhile to incorporate the hydrazide, thiosemicarbazide and oxadiazole moieties into the coumarin nucleus.

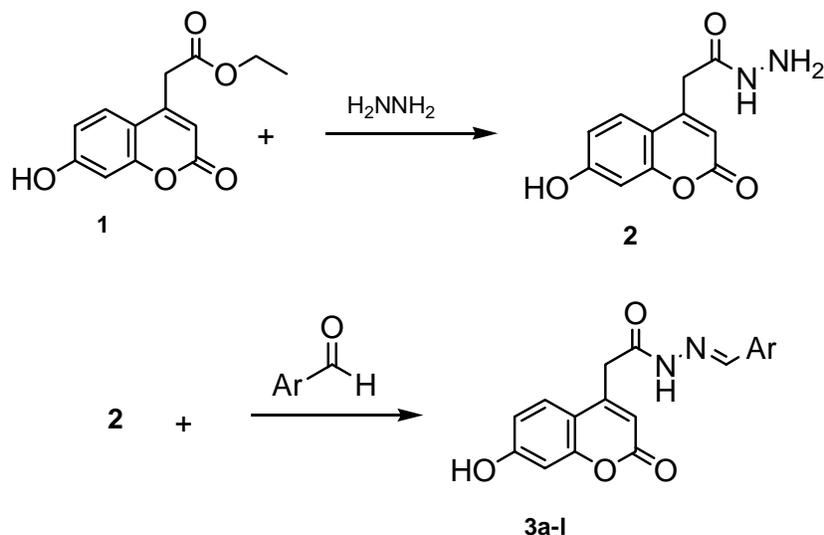
Hydrazinolysis of esters is the conventional method for preparing acyl hydrazides [17,18]. However, when this method was applied to an α , β -unsaturated ester, the predominant product was the corresponding pyrazolidinone, the result of hydrazinolysis and an undesired subsequent intramolecular Michael-type addition [19]. Alternatively, acyl hydrazides may be prepared by condensing carboxylic acids with hydrazine in the presence of coupling agents. Unfortunately, most of these methods afford low yields and involve complicated product isolations [20-22], although Zhang *et al.* have reported good yields using carbodiimide-based coupling reagents such as 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) [23]. In connection with our previous work [24-26] on the synthesis of coumarins, in the present paper we describe the preparation of the new hydrazide derivatives, heterocycles and Schiff's bases from (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid methyl ester.

Results and Discussion

The (7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid starting material was originally prepared by condensing resorcinol with acetonedicarboxylic acid in the presence of concentrated sulfuric acid, a procedure later simplified by Dey and Row [27]. Applying the hydrazinolysis of (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid ethyl ester (**1**), with 100% hydrazine hydrate in methanol at room temperature, (7-hydroxy-2-oxo-2*H*-chromen-4-yl)-acetic acid hydrazide (**2**) was prepared in good yields. The carbohydrazide **2** was then condensed with different aromatic aldehydes in ethanol/acetic acid (24:1) to give the corresponding Schiff's bases, i.e. (7-hydroxy-2-oxo-2*H*-chromen-4-yl) acetic acid arylidenehydrazides **3a-l**, in very good yields (Scheme 1). The IR spectra of carbohydrazide **2** showed absorption bands in the 3317 cm^{-1} (OH, hydrazide NH_2), 3269 cm^{-1} (aromatic C-H), 1711 cm^{-1} (>C=O carbonyl stretching) and 1621-1640 cm^{-1} ($-\text{CO-NH-NH}_2$ groups) regions, respectively. The $^1\text{H-NMR}$ spectra exhibited a singlet due to the $-\text{CO-NH-NH}_2$ NH proton at δ 9.32 ppm. Methylene protons resonated as a singlet at δ 4.23 ppm. The structures of the products **3a-l** were inferred from their analytical and spectral data. Thus, their IR spectra showed characteristic absorption bands at 3400-3240 cm^{-1} (NH; OH), 1710-1700 cm^{-1} (lactone C=O) and NHCO at 1650-1600 cm^{-1} . The $^1\text{H-}$

NMR spectra did not only show the absence of the NH₂ protons at δ 3.34, but also the presence of the N=CH proton at δ 8.16 ppm.

Scheme 1.

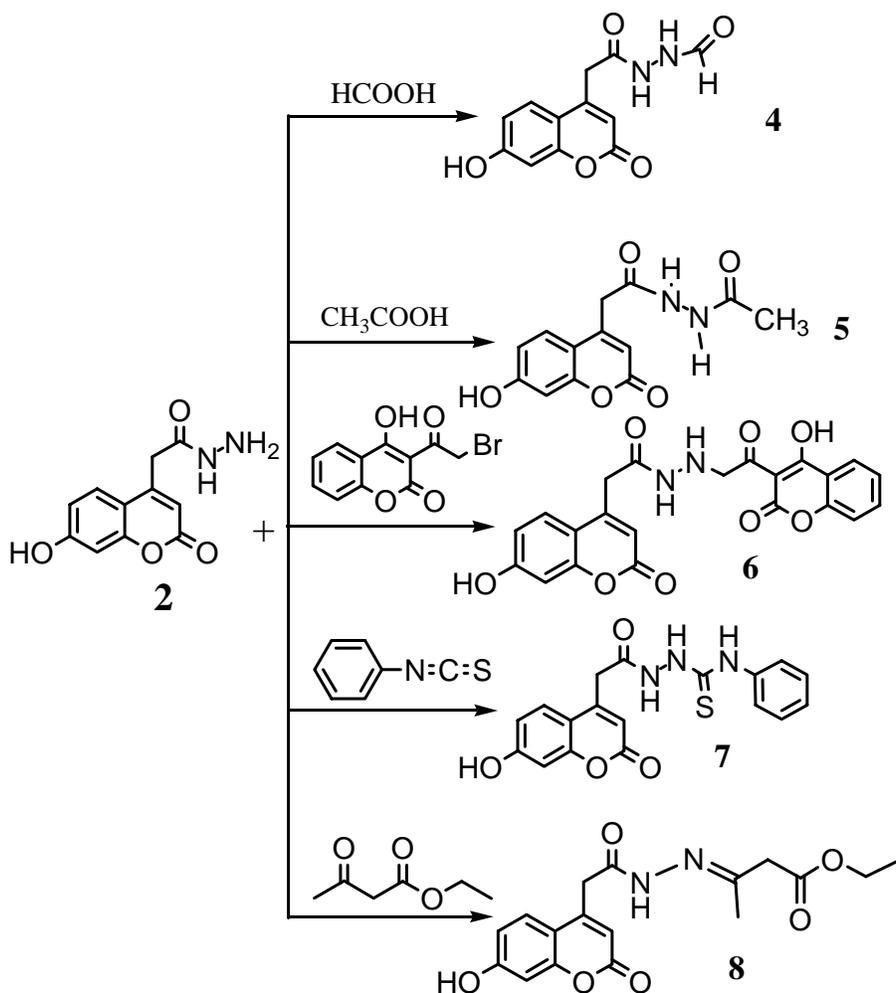


Entry	Ar	Entry	Ar
a	phenyl	g	2,5-dihydroxyphenyl
b	2-hydroxyphenyl	h	3-phenoxyphenyl
c	2-chlorophenyl	i	3-methoxy-4-hydroxyphenyl
d	3-chlorophenyl	j	styryl
e	2,3-dihydroxyphenyl	k	4-N,N-dimethylaminophenyl
f	2,4-dihydroxyphenyl	l	2-hydroxy-5-nitrophenyl

On the other hand, refluxing **2** in formic acid for 5 hours afforded the N-formyl derivative **4** in high yield. Acetylation of **2** by refluxing in acetic acid, afforded acetic acid N'-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl]-hydrazide (**5**) in good yield. Compound **6** was also obtained by refluxing **2** with 3-(2-bromoacetyl)-4-hydroxy-2H-chromen-2-one in ethanol. Reaction of compound **2** with phenyl isothiocyanate in ethanol at room temperature gave 4-phenyl-1-(7-hydroxy-2-oxo-2H-chromen-4-acetyl)-thiosemicarbazide (**7**).

Condensation of **2** with ethyl acetoacetate without a solvent gave ethyl 3-{2-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl]hydrazono}butanoate (**8**) in 48% yield (Scheme 2). The structures of compounds **4-8** were established by their analytical data and their IR and ¹H-NMR spectra. The IR absorptions due to the NH, OH and C=O functions appeared at 3450-3000 and 1728-1610 cm⁻¹, respectively. The absorption bands associated with other functional groups present all appeared in the expected regions. The ¹H-NMR spectra of compounds **4-8** exhibited singlets in the 8.03-10.58 ppm region corresponding to the NH and the OH protons.

Scheme 2.

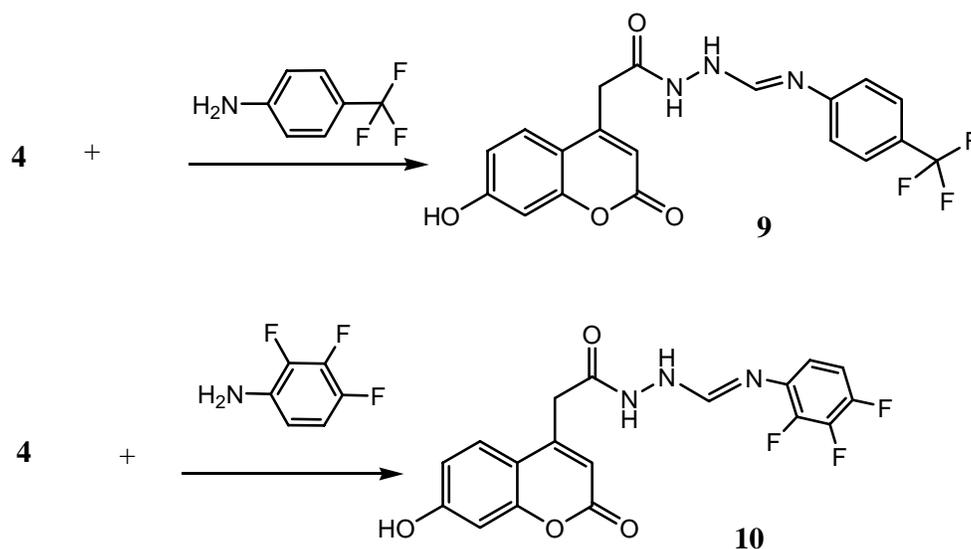


When **4** was refluxed with equimolar amounts of 4-trifluoromethylaniline or 2,3,4-trifluoroaniline in acetonitrile with a few drops of acetic acid, the compounds (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[(4-trifluoromethylphenylimino)-methyl] hydrazide (**9**) and (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[(2,3,4-trifluorophenylimino)-methyl] hydrazide (**10**) were obtained in good yields (Scheme 3).

The high frequency region of the IR spectra of these compounds contains (N-H, O-H) stretching vibration bands at 3398 and 3245 cm^{-1} . The absorption in the 1623-1598 cm^{-1} region corresponds to that of the amide group (-NHCO-). The presence of lactone carbonyl group (>C=O) is indicated by absorption bands at 1702 and 1700 cm^{-1} . The $^1\text{H-NMR}$ spectra of compounds **4-8** exhibited singlets in the 8.03-10.58 ppm region corresponding to the NH, -HC=N- and OH protons.

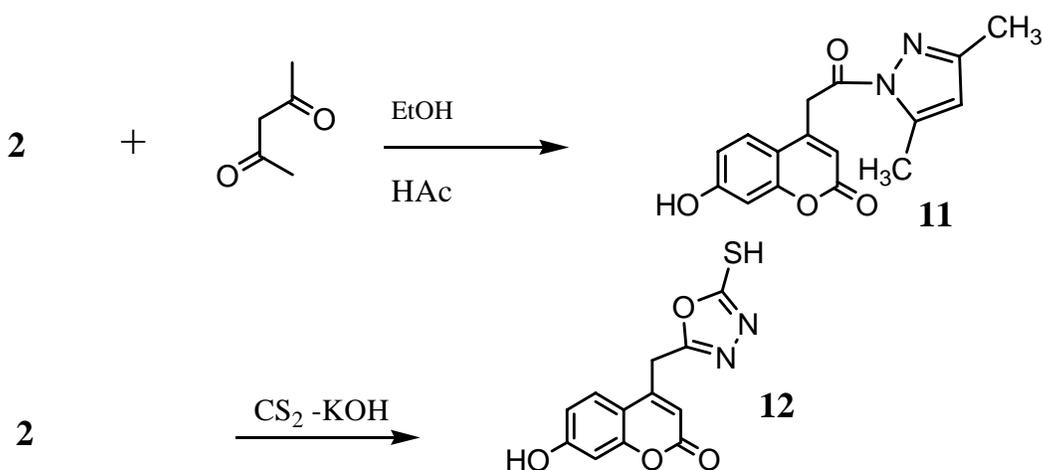
Upon condensation of **2** with acetylacetone in ethanol containing a catalytic amount of acetic acid, the corresponding derivative **11** was obtained in 54% yield. Compound **12** was prepared accordingly, by heating the carbohydrazide **2** with CS_2 in the presence of ethanolic potassium hydroxide. On the other hand, reaction of **2** with KSCN in refluxing ethanol containing catalytic amounts of HCl gave, after treating the salt **13**, which was converted directly to **14** by heating it in aqueous KOH followed by acidification with HCl in good yield.

Scheme 3.

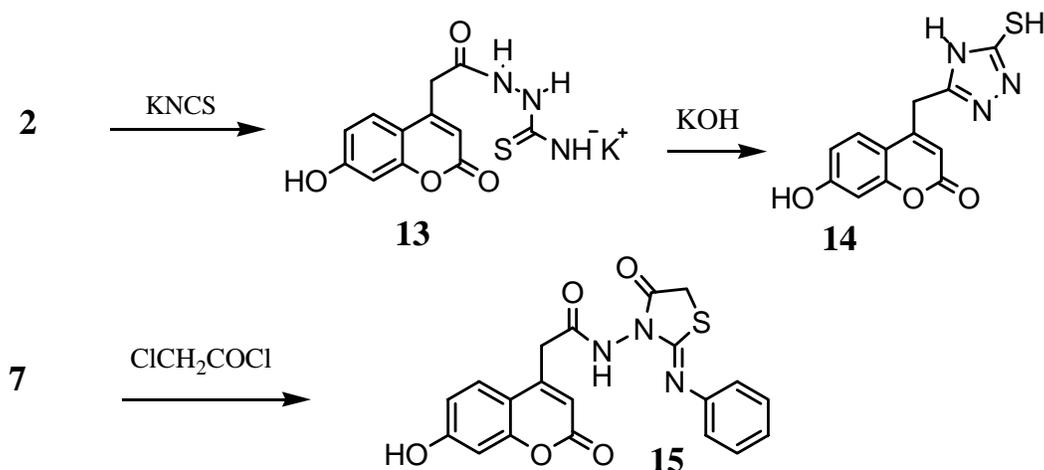


Cyclization of thiosemicarbazide **7** with chloroacetylchloride in chloroform afforded thiazolidinone derivative **15** (Scheme 4). The structures of compounds **11-15** were confirmed by their analytical data and their IR and $^1\text{H-NMR}$ spectra. The IR absorptions due to the (OH) and C=O functions appeared at 3224 and 1712 cm^{-1} . The absorption bands associated with other functional groups present all appeared in the expected regions. The $^1\text{H-NMR}$ spectra of compounds **11-15** exhibited singlets at δ 4.06 ppm for the methylenic group (CH_2) and at δ 10.65 ppm corresponding to the OH protons.

Scheme 4.



Scheme 4. (Cont).



Antibacterial activity

Compounds **3a-1** and **4-15** described here were examined for their antimicrobial activity. Good results were obtained in the cases of (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid N'-[2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxo-ethyl]-hydrazide (**6**), 4-phenyl-1-(7-hydroxy-2-oxo-2H-chromen-4-acetyl) thiosemicarbazide (**7**), 4-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-7-hydroxy-2H-chromen-2-one (**11**), 7-hydroxy-4-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-2H-chromen-2-one (**12**) and 7-hydroxy-4-[(5-mercapto-4H-1,2,4-triazol-3-yl)methyl]-2H-chromen-2-one (**14**). All these compounds were found to possess high antimicrobial activity against *Staphylococcus pneumoniae* and were slightly less active against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Bacillus cereus*, and *Salmonella panama*. The other compounds showed either moderate or no activity against these organisms. Further investigation is in progress.

Experimental Section

General

The melting points were taken on an Electrothermal capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed with fluorescent silica gel plates HF₂₅₄ (Merck), and plates were viewed under UV 254 and 265 light. Silica gel (230-400 mesh) was used for flash chromatography separations. The elemental analyses for C, H and N were done on a Perkin-Elmer Analyzer 2440. Infrared spectra ($\nu\text{-cm}^{-1}$) were recorded on a Beckmann FT-IR 3303, using KBr disks. ¹H-NMR spectra were recorded on JEOL EX-270 MHz NMR Spectrometer at 293 °K in DMSO-d₆. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS.

(7-Hydroxy-2-oxo-2H-chromen-4-yl) acetic acid hydrazide (2).

Compound **1** (12.40 g, 50 mmol) was dissolved in a solution containing methanol (120 mL) and 100 % hydrazine hydrate (12 mL) and the mixture was left standing overnight at 25°C. The product was separated, collected by suction filtration, washed with methanol and light petroleum, and recrystallized from diluted acetic acid or water to give compound (**2**) in 70% yield; mp: 246 °C, IR: 3317, 3269, 3063, 2594, 1711, 1640, 1621, 1565, 1377, 1326 and 1141 cm⁻¹; ¹H-NMR δ: 3.34 (s, 2H, NH₂), 4.23 (s, 2H, CH₂), 6.24 (s, 1H, H-3), 6.79 (s, 1H, H-8), 6.80 (d, 1H, H-6), 7.63 (d, 1H, H-5), 9.32 (s, 1H, NH), 10.52 (s, 1H, OH); Anal. calcd. for C₁₁H₁₀N₂O₄: C 56.41, H 4.30, N 11.96. Found: C 56.40, H 4.32, N 11.91.

General procedure for the preparation of (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid arylidenehydrazides 3a-l.

A mixture of compound **2** (1.17 g, 5.0 mmol) and the appropriate aromatic aldehyde **a-l** (5.0 mmol) was refluxed in ethanol/acetic acid (24:1, 25 mL) for 3 hours. The excess of solvent was then removed under reduced pressure, the precipitate formed after cooling was collected by filtration and recrystallized from ethanol to give compounds **3a-l**.

N'-benzylidene -2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (3a)

Yield: 80% yield; mp: 265 °C; IR: 3179, 3087, 2963, 1706, 1670, 1621, 1564, 1393, 1265 and 1139 cm⁻¹; ¹H-NMR δ: 4.23 (s, 2H, CH₂); 6.24 (s, 1H, H-3), 6.74 (s, 1H, H-8), 6.82 (d, 1H, H-6), 7.2 (d, 1H, H-5), 7.14-7.42 (m, 5H, arom.), 8.16 (s, 1H, NH), 8.34 (s, 1H, HC=N), 10.70 (s, 1H, OH); Anal. calcd. for C₁₈H₁₄N₂O₄: C 67.07, H 4.38, N 8.69. Found: C 67.02, H 4.40, N 8.63.

N'-(2-hydroxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (3b)

Yield: 54%; mp: 268 °C; IR: 3284, 3182, 3052, 1702, 1656, 1600, 1489, 1395, 1258 and 1139 cm⁻¹; ¹H-NMR δ: 4.20 (s, 2H, CH₂), 6.04 (s, 1H, H-3), 6.40 (s, 1H, H-8), 6.49 (d, 1H, H-6), 7.10 (d, 1H, H-5), 7.12-140 (m, 4H, arom.), 8.0(s, 1H, NH), 8.11 (s, 1H, HC=N), 10.20 (s, 1H, OH), 10.82 (s, 1H, OH); Anal. calcd. for C₁₈H₁₄N₂O₅: C 63.90, H 4.17, N 8.28. Found: C 63.88, H 4.19, N 8.24.

N'-(2-chlorobenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (3c)

Yield: 88% yield; mp: 239 °C; IR: 3208, 3180, 3050, 1701, 1600, 1565, 1403, 1323 and 1139 cm⁻¹; ¹H-NMR δ: 4.25 (s, 2H, CH₂), 6.26 (s, 1H, H-3), 6.81 (s, 1H, H-8), 6.84 (d, 1H, H-6), 7.41-7.94 (m, 5H, arom), 7.95 (d, 1H, H-5), 8.00 (s, 1H, NH), 8.12 (s, 1H, HC=N), 10.58 (s, 1H, OH); Anal. calcd. for C₁₈H₁₃ClN₂O₄: C 60.60, H 3.67, N 7.85. Found: C 60.57, H 3.70, N 7.84.

N'-(3-chlorobenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3d**)

Yield: 82%; mp: 278 °C; IR: 3207, 3182, 3049, 1700, 1598, 1560, 1397, 1320 and 1139 cm⁻¹; ¹H-NMR δ: 4.25 (s, 2H, CH₂), 6.26 (s, 1H, H-3), 6.81 (s, 1H, H-8), 6.84 (d, 1H, H-6), 7.41-7.94 (m, 5H, arom.), 7.95 (d, 1H, H-5), 8.00 (s, 1H, NH), 8.12 (s, 1H, HC=N), 10.58 (s, 1H, OH); Anal. calcd. for C₁₈H₁₃ClN₂O₄: C 60.60, H 3.67, N 7.85. Found: C 60.57, H 3.70, N 7.84.

N'-(2,3-dihydroxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3e**)

Yield: 40%; mp: 267 °C; IR: 3400, 3276, 3180, 3040, 1710, 1592, 1564, 1400, 1310 and 1137 cm⁻¹; ¹H-NMR δ: 3.79 (s, 2H, CH₂), 6.29 (s, 1H, H-3), 6.82 (s, 1H, H-8), 6.84 (d, 1H, H-6), 7.30 – 7.84 (m, 3H, arom.), 7.95 (d, 1H, H-5), 8.21 (s, 1H, NH), 8.30 (s, 1H, HC=N), 10.58 (s, 1H, OH), 11.21 (s, 1H, OH), 11.90 (s, 1H, OH); Anal. calcd. for C₁₈H₁₄N₂O₆: C 61.02, H 3.98, N 7.91. Found: C 60.99, H 3.40, N 7.88.

N'-(2,4-dihydroxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3f**)

Yield: 52% ; mp: 261 °C; IR: 3390, 3284, 3170, 3080, 1712, 1590, 1565, 1406, 1311 and 1137 cm⁻¹; ¹H-NMR δ: 3.79 (s, 2H, CH₂), 6.29 (s, 1H, H-3), 6.82 (s, 1H, H-8), 6.84 (d, 1H, H-6), 7.30 (d, 1H, arom.), 7.65 (d, 1H, arom.), 7.84 (s, 1H, arom.), 7.95 (d, 1H, H-5), 8.21 (s, 1H, NH), 8.30(s, 1H, HC=N), 10.58 (s, 1H, OH), 11.21 (s, 1H, OH), 11.90 (s, 1H, OH); Anal. calcd. for C₁₈H₁₄N₂O₆: C 61.02, H 3.98, N 7.91. Found: C 60.98, H 3.41, N 7.87.

N'-(2,5-dihydroxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3g**)

Yield: 40%; mp: 264 °C; IR: 3398, 3270, 3186, 3040, 1710; 1590; 1564; 1400; 1310 and 1136 cm⁻¹; ¹H-NMR δ: 3.79 (s, 2H, CH₂); 6.29 (s, 1H, H-3); 6.82 (s, 1H, H-8); 6.84 (d, 1H, H-6); 7.20-7.81 (m, 3H, arom.); 7.95 (d, 1H, H-5); 8.22 (s, 1H, NH); 8.36 (s, 1H, HC=N); 10.58 (s, 1H, OH); 11.21 (s, 1H, OH); 11.90 (s, 1H, OH); Anal. calcd. for C₁₈H₁₄N₂O₆: C 61.02, H 3.98, N 7.91. Found: C 60.99, H 3.96, N 7.92.

N'-(3-phenoxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3h**)

Yield: 70%; mp: 209 °C; IR: 3369, 3183, 3095, 1706, 1668, 1614, 1580, 1393, 1260 and 1137 cm⁻¹; ¹H NMR δ: 4.06 (s, 1H, CH₂), 6.19 (s, 1H, H-3), 6.73 (s, 1H, H-8), 6.79 (d, 1H, H-6), 7.02-7.20 (m, 4H, arom.), 7.36-7.48 (m, 5H, arom.), 7.52 (d, 1H, H-5), 8.03 (s, 1H, NH), 8.20 (s, 1H, HC=N), 10.57 (s, 1H, OH); Anal. calcd. for C₂₄H₁₈N₂O₅: C 69.56, H 4.38, N 6.76. Found: C 69.58, H 4.35, N 6.74.

N'-(4-hydroxy-3-methoxybenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3i**)

Yield: 68%; mp: 252 °C; IR: 3345, 3167, 3077, 2962, 1705, 1627, 1589, 1518, 1394 and 1266 cm^{-1} ; $^1\text{H-NMR}$ δ : 3.77 (s, 3H, OCH_3), 4.19 (s, 1H, CH_2), 6.24 (s, H, H-3), 6.72 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.04 (d, 1H, arom.), 7.08 (d, 1H, arom.), 7.25 (s, 1H, H arom.), 7.59 (d, 1H, H-5), 7.91 (s, 1H, NH), 8.12 (s, 1H, $\text{HC}=\text{N}$), 9.50 (s, 1H, OH), 10.58 (s, 1H, OH); Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_6$: C 61.95, H 4.38, N 7.61. Found: C 61.93, H 4.40, N 7.59.

2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-*N*-(3-phenylallidene) acetohydrazide (**3j**)

Yield: 48% yield; mp: 260 °C; IR: 3433, 3174, 3091, 2971, 1708, 1666, 1605, 1562, 1395, 1268 and 1143 cm^{-1} ; $^1\text{H-NMR}$ δ : 4.12 (s, 2H, CH_2), 6.23 (s, 1H, H-3), 6.74 (s, 1H, H-8), 6.82 (d, 1H, H-6), 7.11 (d, 1H, H-5), 7.30-7.41 (m, 5H, arom.), 7.5 (d, 1H, $\text{HC}=\text{CH}$), 7.62 (d, 1H), 7.89 (d, 1H,), 7.90 (d, 1H), 10.56 (s, 1H, OH); Anal. calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4$: C 68.96, H 4.63, N 8.04. Found: C 68.95, H 4.60, N 8.01.

N'-[4-(*N,N*-dimethylamino)benzylidene]-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3k**)

Yield: 80%; mp: 234 °C; IR: 3268, 3180, 3051, 2922, 1702, 1600, 1565, 1403, 1323 and 1139 cm^{-1} ; $^1\text{H-NMR}$ δ : 2.78 (s, 6H, $(\text{CH}_3)_2\text{N}$), 3.78 (s, 2H, CH_2), 6.26 (s, 1H, H-3), 6.72 (s, 1H, H-8), 6.77 (d, 1H, H-6), 6.89 (d, 1H, H-5), 7.6 (d, 2H, arom.), 7.70 (d, 2H, arom.), 7.92 (s, 1H, NH), 8.14 (s, 1H, $\text{HC}=\text{N}$), 10.56 (s, 1H, OH); Anal. calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_4$: C 65.74, H 5.24, N 11.50. Found: C 65.71, H 5.25, N 11.47.

N'-(2-hydroxy-5-nitrobenzylidene)-2-(7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**3l**)

Yield: 60%; mp: 267 °C; IR: 3294, 3182, 3072, 1702, 1669, 1601, 1566, 1489, 1395, 1258 and 1139 cm^{-1} ; $^1\text{H-NMR}$ δ : 4.26 (s, 2H, CH_2), 6.23 (s, 1H, H-3), 6.73 (s, 1H, H-8), 6.80 (d, 1H, H-6), 6.85 (d, 1H, H-5), 7.55-7.65 (m, 3H, arom.), 8.12 (s, 1H, NH), 8.35 (s, 1H, $\text{HC}=\text{N}$), 10.55 (s, 1H, OH), 11.77 (s, 1H, OH); Anal. calcd. for $\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_7$: C 56.40, H 3.42, N 10.96. Found: C 56.38, H 3.43, N 10.93.

N'-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl]-formic acid hydrazide (**4**)

A solution of compound **2** (1.17 g, 5.0 mmole) in formic acid (20 mL) was refluxed for 1 hour. The solvent was evaporated and the residue was crystallized from ethanol to give compound **4** in 82% yield; mp: 248 °C; IR: 3342, 3256, 3003, 1702, 1621, 1557, 1515, 1396, 1314 and 1139 cm^{-1} ; $^1\text{H-NMR}$ δ : 3.73 (s, 2H, CH_2), 6.25 (s, 1H, H-3), 6.73 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.62 (d, 1H, H-5), 8.03 (s, 1H, NH), 10.07 (s, 1H, NH), 10.32 (s, 1H, $\text{HC}=\text{O}$), 10.58 (s, 1H, OH); Anal. calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_5$: C 54.97, H 3.84, N 10.68. Found: C 54.95, H 3.82, N 10.64.

N'-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-acetyl] acetic acid hydrazide (**5**)

Compound **2** (1.17 g, 5.0 mmole) was refluxed in acetic acid (20 mL) for 5 hours. The reaction mixture was cooled, and the crystalline product was collected by filtration to give compound in 38% yield; mp: 235-237 °C; IR: 3410, 3294, 3240, 3117, 2829, 1682, 1658, 1618, 1567, 1501, 1384, 1333 and 1147 cm⁻¹; ¹H-NMR δ: 1.87 (s, 3H, CH₃), 3.72 (s, 2H, CH₂), 6.27 (s, 1H, H-3), 6.76 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.65 (d, 1H, H-5), 9.88 (s, 1H, NH), 10.15 (s, 1H, NH), 10.58 (br. s, 1H, OH); Anal. calcd. for C₁₃H₁₂N₂O₅: C 56.52, H 4.38, N 10.14. Found: C 56.50, H 4.39, N 10.11.

N'-[2-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-oxoethyl]-2-(-7-hydroxy-2-oxo-2H-chromen-4-yl) acetohydrazide (**6**)

To a solution of compound **2** (2.34 g, 10.0 mmole) in ethanol (100 mL), 3-(2-bromoacetyl)-4-hydroxy-2H-chromen-2-one (2.87 g, 10.0 mmole) was added. The mixture was refluxed for 3 hours. The precipitate was filtered and crystallized from ethanol to give compound **6** in 80% yield; mp: 196 °C; IR: 3385, 3288, 3197, 3073, 1695, 1649, 1620, 1601, 1560, 1509, 1454, 1396, 1271, 1213 and 1134 cm⁻¹; ¹H-NMR δ: 3.72 (s, 2H, CH₂), 6.27 (s, 1H, H-3), 6.76 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.10-7.40 (m, 5H, arom.), 7.65 (d, 1H, H-5), 9.96 (s, 1H, NH), 10.25 (s, 1H, NH), 10.40 (s, 1H, OH), 10.58 (br. s, 1H, OH); Anal. calcd. for C₂₂H₁₆N₂O₈: C 60.55, H 3.70, N 6.42. Found: C 60.53, H 3.69, N 6.39.

4-Phenyl-1-(7-hydroxy-2-oxo-2H-chromen-4-acetyl-) thiosemicarbazide (**7**)

To a solution of compound **2** (0.234 g, 1 mmole) in ethanol (5-10 mL) phenyl isothiocyanate (0.135 g, 1 mmole) and sodium hydroxide (40 mg, 1 mmole, as a 2N solution) were added. The mixture was stirred for 24 hours and filtered. The filtrate was acidified with hydrochloric acid. The precipitate was filtered and crystallized from ethanol/water, to give compound **7** in 84% yield; mp: 199-200 °C; IR: 3400, 3197, 3053, 2934, 1728, 1686, 1609, 1572, 1519, 1433, 1391, 1300, 1256 and 1135 cm⁻¹; ¹H-NMR δ: 3.74 (s, 1H, NH), 4.02 (s, 2H, CH₂), 5.84 (s, 1H, H-3), 6.70 (s, 1H, H-8), 6.84 (d, 1H, H-6), 7.10-7.20 (m, 5H, arom.), 7.35 (d, 1H, H-5), 9.96 (s, 1H, NH), 10.25 (s, 1H, NH), 10.58 (br s, 1H, OH); Anal. calcd. for C₁₈H₁₅N₃O₄S: C 58.53, H 4.09, N 11.38, S 8.68. Found: C 56.50, H 4.09, N 11.40, S 8.65.

*Ethyl 3-{2-[2-(7-hydroxy-2-oxo-2H-chromen-4-yl)acetyl] hydrazono}butanoate (**8**)*

A mixture of compound **2** (0.375 g, 1.6 mmole) and ethyl acetoacetate (0.208 g, 1.6 mmole) was condensed without solvent at 145-155 °C for 10 min. The reaction mixture was cooled and refluxed in ethanol (25 mL) for 2 hours. The precipitate formed after cooling was collected by filtration and recrystallized from ethanol to give compound **8** in 48% yield; mp: 178 °C; IR: 3383, 3175, 3042, 2931, 2824, 2724, 1718, 1686, 1659, 1612, 1565, 1396, 1332 and 1142 cm⁻¹; ¹H-NMR δ: 1.17 (t, 3H, CH₃), 1.98 (s, H, CH₃), 4.08 (s, 2H, CH₂), 4.10 (s, 2H, CH₂), 4.12 (q, 2H, CH₂), 6.19 (s, 1H, H-3), 6.78 (s,

1H, H-8), 6.80 (d, 1H, H-6), 7.61 (d, 1H, H-5), 9.28 (s, 1H, NH), 9.45 (s, 1H, N=CH), 10.58 (br s, 1H, OH); Anal. calcd. for C₁₇H₁₈N₂O₆: C 58.96, H 5.24, N 8.09. Found: C 58.93, H 5.26, N 8.06.

2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N'-[4-(trifluoromethyl)phenylimino]methyl]acetohydrazide (9)

4-(Trifluoromethyl)benzenamine (0.161 g, 1 mmole) was added to a mixture of compound **4** (0.262 g, 1 mmole) in acetonitrile (15-20 mL) containing a few drops of acetic acid. The reaction mixture was vigorously stirred with the refluxing for 5 hours. Excess solvent was then removed under reduced pressure, the precipitate resulting after cooling was collected by filtration and recrystallized from ethanol to give compound **9** in 65% yield; mp: 249-250 °C; IR: 3382, 3255, 3014, 1716, 1700, 1623, 1598, 1560, 1471, 1396, 1314, 1273 and 1139 cm⁻¹; ¹H-NMR δ: 4.10 (s, 2H, CH₂), 6.26 (s, 1H, H-3), 6.73 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.56 (d, 1H, H-5), 7.90-7.97 (m, 4H, arom.), 10.27 (s, 1H, NH), 10.34 (s, 1H, HC=N), 10.38 (s, 1H, NH), 10.63 (br s, 1H, OH); Anal. calcd. for C₁₉H₁₄F₃N₃O₄: C 56.30, H 3.48, N 10.37. Found: C 56.29, H 3.46, N 10.35.

2-(7-Hydroxy-2-oxo-2H-chromen-4-yl)-N'-[(2,3,4-trifluorophenylimino)methyl] acetohydrazide (10)

Compound **10** was prepared in 62% yield in an analogous fashion as described above for **9**; mp: 269-270 °C; IR: 3392, 3245, 3010, 1718, 1702, 1621, 1600, 1559, 1473, 1395, 1314, 1273 and 1139 cm⁻¹; ¹H-NMR δ: 4.13 (s, 2H, CH₂), 6.25 (s, 1H, H-3), 6.74 (s, 1H, H-8), 6.80 (d, 1H, H-6), 7.65 (d, 1H, H-5), 7.90-7.98 (m, 2H, arom.), 10.05 (s, 1H, NH), 10.14 (s, 1H, HC=N), 10.32 (s, 1H, NH), 10.65 (br s, 1H, OH); Anal. calcd. for C₁₈H₁₂F₃N₃O₄: C 55.25, H 3.09, N 10.74. Found: C 55.23; H 3.06; N 10.71.

4-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-7-hydroxy-2H-chromen-2-one (11)

A mixture of compound **2** (0.234 g, 1 mmole), acetyl acetone (0.142 g, 1 mmole) and acetic acid (1.0 mL) was refluxed in ethanol (10 mL) for 5 hours. The precipitate which formed after cooling was collected by filtration and recrystallized from ethanol to give compound **11** in 54% yield; mp: 250-251 °C; IR: 3224, 3134, 2994, 2930, 1712, 1681, 1597, 1568, 1397, 1330, 1237, 1206 and 1138 cm⁻¹; ¹H-NMR δ: 1.18 (s, 3H, CH₃), 3.35 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 6.18 (s, 1H, H-3), 6.74 (s, 1H, H-8), 6.80 (d, 1H, H-6), 7.47 (d, 1H, H-5), 9.28 (s, 1H, HC=C), 10.50 (br s, 1H, OH); Anal. calcd. for C₁₆H₁₄N₂O₄: C 64.42, H 4.73, N 9.39. Found: C 64.40, H 4.74, N 9.40.

7-Hydroxy-4-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]-2H-chromen-2-one (12)

To a mixture of carbohydrazide **2** (2.34 g, 10 mmole) in ethanol (150 mL) a solution of potassium hydroxide (0.84 g, 15 mmole) in ethanol (10 mL) was added followed by carbon disulfide (20 mL). The reaction mixture was heated under reflux for 6 hours, then it was concentrated, acidified with diluted HCl and the resulting solid was collected, washed with water and recrystallized from a mixture of DMFA-H₂O. Compound (**2**) was obtained in 78% yield; mp: 234-235 °C; IR: 3379, 3090, 3052, 2961, 2929, 1686, 1621, 1605, 1561, 1477, 1401, 1321, 1206 and 1139 cm⁻¹; ¹H-NMR: δ 3.38 (br s,

1H, -SH), 4.06 (s, 2H, CH₂), 6.30 (s, 1H, H-3), 6.76 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.65 (d, 1H, H-5), 10.56 (br s, 1H, OH); Anal. calcd. for C₁₂H₈N₂O₄S: C 52.17, H 2.92, N 10.14, S 11.61. Found: C 52.14, H 2.91, N 10.11, S 11.59.

7-hydroxy-4-[(5-mercapto-4H-1,2,4-triazol-3-yl)methyl]-2H-chromen-2-one (14)

A mixture of **2** (0.656 g, 2.8 mmole) and KSCN (0.5 g, 5.1 mmole) was refluxed for 3 hours in ethanol (50 mL) containing a few drops of conc. HCl. The precipitate formed was collected by filtration and dried to give compound (**13**); IR: 3386, 3318, 3269, 3063, 2939, 1709, 1680, 1605, 1565, 1397, 1326, 1250 and 1139 cm⁻¹; ¹H-NMR δ: 4.06 (s, 2H, CH₂), 6.30 (s, 1H, H-3), 6.76 (s, 1H, H-8), 6.81 (d, 1H, H-6), 7.65 (d, 1H, H-5), 8.6 (s, 1H, NH), 9.82 (s, 1H, NH), 9.90 (s, 1H, NH); Anal. calcd. for C₁₂H₉K₂N₃O₄S: C 39.01, H 2.46, N 11.37, S 8.68. Found: C 39.03, H 2.43, N 11.31, S 8.62. A mixture of compound **13** (0.431 g, 1.3 mmole), which was used without further purification, and KOH (0.1 g, 1.6 mmole) was refluxed in H₂O (25 mL) for 3 hours. The reaction mixture was cooled and then acidified with HCl to give compound **14** in 75% yield; mp: 173 °C; IR: 3316, 3269, 3187, 3069, 1710, 1678, 1605, 1566, 1396, 1326, 1273, 1250 and 1139 cm⁻¹. ¹H NMR: δ 3.38 (br s, 1H, -SH), 4.06 (s, 2H, CH₂), 6.30 (s, 1H, H-3), 6.76 (s, H, H-8), 6.81 (d, H, H-6), 7.65 (d, 1H, H-5), 8.42 (s, 1H, NH), 10.56 (br s, 1H, OH); Anal. calcd. for C₁₂H₉N₃O₃S: C 52.36, H 3.30, N 15.26, S 11.65. Found: C 52.34, H 3.28, N 15.23, S 11.60.

2-(7-hydroxy-2-oxo-2H-chromen-4-yl)-N-[4-oxo-2-(phenylimino)thiazolidin-3-yl] acetamide (15)

A mixture of compound **7** (0.369 g, 1 mmole) and chloroacetylchloride (0.113 g, 1 mmole) in chloroform/ethanol (60 mL) was refluxed for 6 hours. The solvent was distilled off under reduced pressure and the residue was washed with ethanol, filtered, washed again with water and crystallized from DMFA-water, affording compound **15** in 45% yield; mp: 143 °C; IR: 3240, 3190, 2926, 2905, 1715, 1686, 1609, 1570, 1516, 1433, 1391, 1300, 1256 and 1135 cm⁻¹; ¹H-NMR: δ 3.76 (s, 1H, CH₂), 6.28 (s, 1H, H-3), 6.74 (s, 1H, H-8), 6.80 (d, 1H, H-6), 7.28-7.49 (m, 5H, arom.), 7.67 (s, 1H, H-5), 9.96 (s, 1H, NH), 10.61 (br s, 1H, OH); Anal. calcd. for C₂₀H₁₅N₃O₅S: C 58.67, H 3.69, N 10.26, S 7.83. Found: C 58.65, H 3.70, N 10.23, S 7.81.

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