

Synthesis and antimicrobial activity of new Schiff bases containing coumarin moiety and their spectral characterization

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Abstract

New Schiff base 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(substitutedmethylene)aceto hydrazides (**4a-p**) were synthesized by the condensation of aryl/hetero aromatic aldehydes with 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide under conventional and microwave conditions and characterized through IR, ¹H NMR and Mass spectral data. The synthesized compounds have been screened for antimicrobial activity.

Keywords: 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(substitutedmethylene)acetohydrazides, conventional method, microwave-irradiation, schiff base, spectral data, antimicrobial analysis

Introduction

Azomethine group (–C=N–) containing compounds typically known as Schiff bases have been synthesized by the condensation of primary amines with active carbonyls. Schiff bases form a significant class of compounds in medicinal and pharmaceutical chemistry with several biological applications that include antibacterial,¹⁻⁶ antifungal³⁻⁶ and antitumor activity.⁷⁻⁸ They have been studied extensively as a class of ligands⁹⁻¹¹ and are known to coordinate with metal ions through the azomethine nitrogen atom.

Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers.¹² Metal complexes make these compounds effective as stereospecific catalysts towards oxidation, reduction, hydrolysis, biological activity and other transformations of organic and inorganic chemistry.¹³ In organic compounds the presence of –C=N– along with other functional groups form more stable complexes compared to compounds with only –C=N– coordinating moiety.

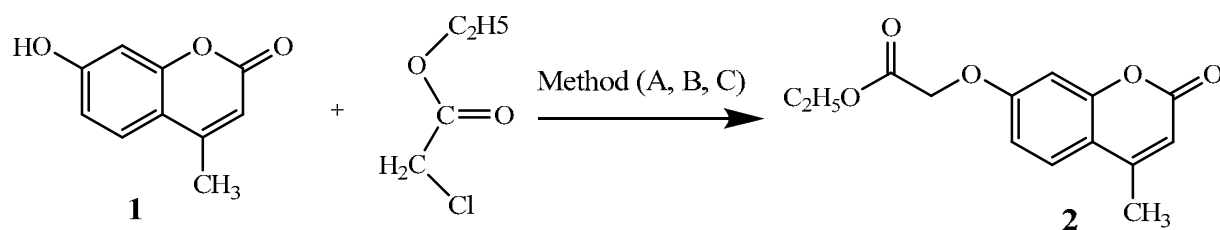
Similarly coumarin derivatives have been of great interest because of their role in natural and synthetic organic chemistry. Many products which contain a coumarin subunit exhibit biological activity such as molluscicides,¹⁴ anthelmintic, hypnotic, insecticidal¹⁵ activity and some are serving as anticoagulant agents¹⁶ and fluorescent brighteners. So coumarins containing a Schiff base are expected to have enhanced antitumor and other biological activities. It is well

established that the biological activity associated with the hydrazone compounds attributed to the presence of the active pharmacophore (-CONH-N=C-). Hence many hydrazone compounds containing this active moiety showed good anticancer bioactivities according to the literature.¹⁷

Microwave irradiation of organic reactions has rapidly gained popularity as it accelerates the reaction towards a variety of synthetic transformations, solventless procedures without the use of supporting reagents and hence eco-friendly. Chemical transformations that took hours or even days to complete can now be accomplished in minutes. Microwave energy offers numerous benefits for performing synthesis such as increased reaction rates, enhanced yields and cleaner chemistries. Hence, in this paper, we are reporting the synthesis of coumarin analogues with Schiff bases of 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide with different aryl and hetero aromatic aldehydes by conventional and microwave assisted methods, and their characterization through spectral data such as IR, ¹H NMR and Mass spectra. Their antimicrobial activity was also evaluated.

Results and Discussion

Resorcinol treated with ethylacetoacetate in the presence of sulphuric acid at 10 °C yielded 7-Hydroxy-4-methyl-2*H*-chromen-2-one (**1**).¹⁸ Treating compound **1** in dry DMF with ethyl chloroacetate in the presence of K₂CO₃ at 80 °C for 10 hours yielded Ethyl 2-[(4-methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetate (**2**) in 82 % yield, whereas in literature the conversion of **1** into **2** was reported under the refluxing conditions for 10 hrs in dry acetone¹⁹⁻²⁴ with 40 % yield. Much variation in yield percentage was not observed though the conversion of **1** into **2** is also effected by using anhydrous sodium bismuthate as catalyst instead of K₂CO₃ (Scheme 1).



Method A. Conventional using K₂CO₃

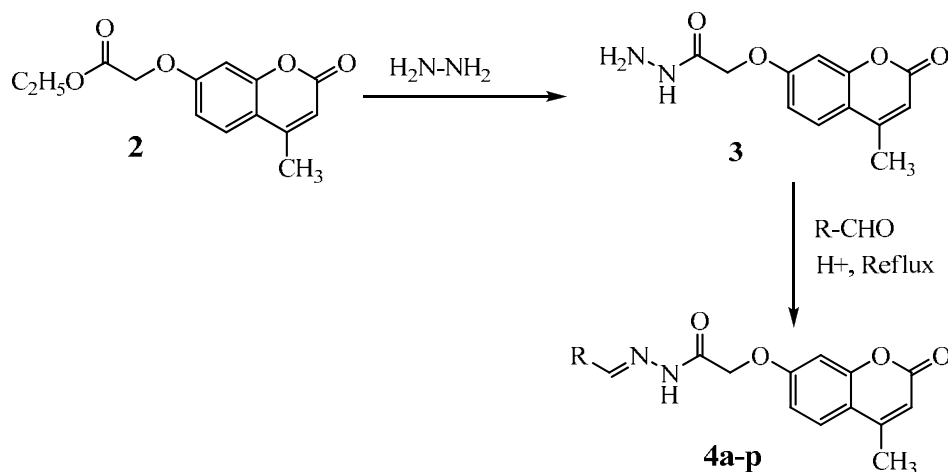
Method B. Conventional using NaBiO₃

Method C. Solvent-free synthesis under microwave irradiation

Scheme 1

Compound **2** was heated with hydrazine hydrate in ethanol on a water bath for 1 hour to obtain 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**3**). The 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]-N'-(substitutedmethylene)acetohydrazides (**4a-p**) synthesized by the

condensation of 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**3**) with different aryl/hetero aromatic aldehydes and characterized through the spectral data (Scheme 2).



Scheme 2

The synthesis of **4a** was optimized by varying the solvents, reaction time, temperature and the results are given in Table 1. It was found that the yield was up to 83.4 % when the reaction mixture was refluxed for 30 min. in a chloroform/methanol mixture.

Table 1. Yield of **4a** at different reaction conditions

Entry	Solvent	Time (min)	Temp. (°C)	Yield (%)
1	Ethanol	30	Reflux	65.6
2	Ethanol	60	Reflux	77.5
3	CHCl ₃ + Methanol	20	Reflux	82.6
4	CHCl ₃ + Methanol	30	Reflux	83.4
5	CHCl ₃ + Methanol	60	Reflux	86.2
6	CHCl ₃ + Methanol	30	75-80	81.1

In microwave assisted synthesis, the mixture of **3** with various aryl/hetero aromatic aldehydes is irradiated in an unmodified domestic microwave oven (800W) at 10 % intensity for 2-3 min. to yield the range of desired products **4a-p** depicted in Table 2. Optimal reaction time for the synthesis was 2-3 min. at 80W of microwave irradiation power. Similarly the synthesis of compounds **2** and **3** was also attempted under the microwave conditions and detailed procedures are included in the experimental part. The study clearly showed that all the steps involved in this synthesis resulted in higher yields under micro wave conditions than the conventional method.

Table 2. Comparison between microwave-assisted and conventional method of synthesis of **4a-p** in terms of yield and time

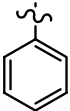
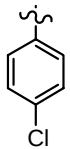
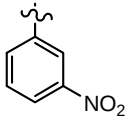
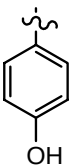
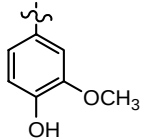
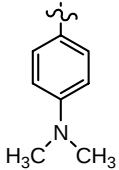
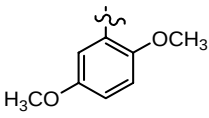
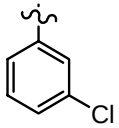
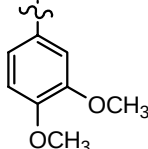
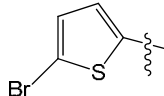
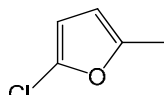
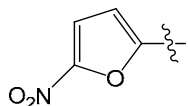
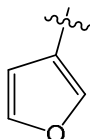
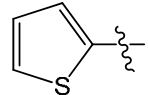
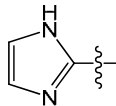
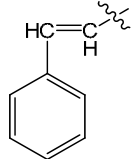
Entry	R	Microwave		Conventional		M.p. (°C)
		Time (min)	Yield (%)	Time (min)	Yield (%)	
4a		2	92.3	60	86.2	276-278
4b		2	91.7	60	83.5	296-298
4c		2.5	86.4	90	81.6	266-268
4d		2.5	87.6	60	84.3	280-282
4e		3	80.5	120	76.8	258-260
4f		3	80.1	120	69.7	260-262
4g		3	88.2	120	77.5	252-254
4h		2.5	93.5	60	83.2	266-268

Table 2. Continued

Entry	R	Microwave		Conventional		M.p. (°C)
		Time (min)	Yield (%)	Time (min)	Yield (%)	
4i		3	87.8	120	79.3	220-222
4j		2	93.6	60	89.4	288-290
4k		2.5	86.2	120	69.6	260-262
4l		2.5	83.5	120	64.8	284-286
4m		2.5	84.7	120	66.1	272-274
4n		2	92.7	60	86.1	274-276
4o		3	74.2	150	61.2	256-258
4p		2.5	81.3	120	72.6	270-272

Antimicrobial activity

Compounds **4c-l** were screened for their antibacterial activity against gram-positive *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* by the disc diffusion method in Mueller-Hinton agar medium at three concentrations (150, 200, 1000 ppm) in DMSO. These solutions were added to each filter disc, and the plates were incubated at 37 °C and examined for zone of inhibition around each disc after 48 hours. Results were compared with the activity of the standard antibiotic Ciproflaxacin. The results are summarized in Table 3.

According to preliminary antibacterial screening by the paper disc method, compounds **4c**, **4e**, **4g**, **4h**, **4j** and **4l** were found to be active against all the bacterial strains. The antibacterial activity of the synthesized compounds against standard and pathological strains was found to be similar (statistically insignificant difference). Most of the compounds exhibited mild to moderate antibacterial activity. All the compounds **4c-l** were effective against *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm), *Staphylococcus aureus* ATCC 25923 (1000 ppm), *Escherichia coli* ATCC 25922 (1000 ppm) and *Klebsiella pneumonia* ATCC 13883 (1000 ppm). Compounds **4k-l**, **4j**, **4c**, **4h** and **4e** exhibited highest activity against *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm), *Staphylococcus aureus* ATCC 25923 (150 ppm), *Bacillus subtilis* ATCC 29212 (150 ppm), *Klebsiella pneumoniae* ATCC 13883 (150 ppm) and *Bacillus subtilis* ATCC 29212 (150 ppm) respectively. Compounds **4d**, **4g**, **4i** and **4f** exhibited highest activity against *Escherichia coli* ATCC 25922 (1000 ppm) and *Pseudomonas aeruginosa* ATCC 2853 (1000 ppm) respectively.

Compounds **4k**, **4l** and **4e** were found to be the most active compounds against the screened gram positive and gram negative standard and pathological bacterial strains. Based on the above results, we can conclude that compounds **4g**, **4l** and **4k** are most effective as it inhibits 18mm, 15mm and 16mm diameter growth of *Staphylococcus aureus*, *Pseudomonas auregenosa*.

Table 3. Antibacterial activity of compounds **4c-l**

Compound	Antibacterial activity*									
	<i>S.aureus</i>			<i>Klebsiella Pneumonia</i>			<i>Bacillus subtilis</i>		<i>E.coli</i>	<i>P.aeruginosa</i>
	1000 ^a	200 ^a	150 ^a	1000 ^a	200 ^a	150 ^a	200 ^a	150 ^a	1000 ^a	1000 ^a
4c	11	-	7	9	10	8	10	11	10	8
4d	10	-	-	9	-	6	7	9	11	9
4e	9	9	-	11	10	9	9	11	7	10
4f	9	-	6	8	10	-	7	8	9	11

Table 3. Continued

Compound	Antibacterial activity*									
	<i>S.aureus</i>			<i>Klebsiella Pneumonia</i>			<i>Bacillus subtilis</i>		<i>E.coli</i>	<i>P.aeruginosa</i>
	1000 ^a	200 ^a	150 ^a	1000 ^a	200 ^a	150 ^a	200 ^a	150 ^a	1000 ^a	1000 ^a
4g	18	5	6	10	10	9	6	6	12	7
4h	9	-	-	7	8	10	8	9	10	11
4i	10	-	-	10	11	7	8	7	9	8
4j	13	7	9	10	9	10	-	10	6	11
4k	11	-	8	8	11	-	-	10	10	16
4l	10	8	-	11	5	10	7	5	8	15
Ciprofloxacin^b	26	15	13	20	25	15	16	16	16	18

*Zone of inhibition in mm.

^aIn DMSO, Concentration in ppm. ^bStandard reference.

Conclusions

To conclude, the modified procedure for the conversion of **1** into **2** with dry DMF at 80 °C instead of dry acetone resulted with improved yield of 82 %. The same conversion also effected by sodium bismuthate as a catalyst instead of K₂CO₃ resulted only 40% yield. The new Schiff base 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]-N'-(substitutedmethylene)acetohydrazides (**4a-p**) have been synthesised by reaction of 2-[(4-Methyl-2-oxo-2*H*-chromen-7-yl)oxy]acetohydrazide (**3**) with aryl/hetero aromatic aldehydes under conventional and microwave irradiation methods. The compounds **4c-l** were tested for antibacterial activity by disc diffusion method, showing moderate to potent inhibition.

Experimental Section

General Procedures. Infrared (IR) spectra were recorded at room temperature from 4000 cm⁻¹ to 400 cm⁻¹ with KBr pellets at a resolution of 4cm⁻¹, using Avatar 330 equipped with DTGS detector. Most of the obtained vibrational bands of the IR spectrum were identified and

compared with those available in literature. The ^1H NMR was measured on a Bruker AMX-400 instrument at room temperature using the X-WIN NMR version X-WIN NMR 1.3 cn drx software. The ^1H NMR was measured for ~ 0.03 M solutions in DMSO-d_6 using TMS as internal reference. The accuracy of the ^1H shifts is considered to be 0.02 ppm. The coupling constants J are in Hz. Mass spectra were obtained using LC-MS-MS (3200 Q-trap). Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Aldrich and Qualigens and used without further purification.

Procedure for the preparation of Ethyl 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]acetate (2)

(a) Conventional method using K_2CO_3 . Method A. To a solution of 7-Hydroxy-4-methyl-2H-chromen-2-one **1** in dry DMF, anhydrous potassium carbonate (1.0 molar equiv) and ethyl chloroacetate (1.0 molar equiv) were added. The resultant mixture was stirred at 80°C for 10h, cooled and then the reaction mixture was added to a large amount of water. The solid separated was filtered, washed with excess of water. The crude product was purified by crystallization from ethanol. The yield of product was 81-82 % [lit. yield 40 %]²⁴.

(b) Conventional method using NaBiO_3 . Method B. To a solution of 7-Hydroxy-4-methyl-2H-chromen-2-one **1** in dry DMF, anhydrous sodium bismuthate (1.0 molar equiv) and ethyl chloroacetate (1.0 molar equiv) were added. The resultant mixture was stirred at 80°C for 14h, cooled, filtered the reaction mixture and then the filtrate was added to a large amount of water. The solid separated was filtered and then the filtrate was extracted with ethyl acetate. The organic layer was separated and evaporated the solvent. The crude product was purified by crystallization from ethanol. The yield of product was 41-42.5 % [lit. yield 40 %]²⁴.

(c) Solvent free microwave irradiation method. Method C. This involves the irradiation of a mixture of 7-Hydroxy-4-methyl-2H-chromen-2-one **1** (0.01 mole), chloroethyl acetate (0.01 mole) and potassium carbonate (0.01 mole) in a microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 12 min. (six pulses each of 2 min.). After completion of reaction (by TLC), the mixture was poured into ice-cold water. The separated solid was filtered, washed with excess of cold water and dried at room temperature. The yield of product was 44-45.2 %. M.p. $94-96^\circ\text{C}$ [lit. $88-90^\circ\text{C}$]²⁴; IR (KBr) ν : 2999, 2917, 1765, 1724, 1615, 1391, 1196, 1508, 1476, 1196, 1080 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 7.69 (1H, d, J = 9.5Hz, 6-H), 6.99 (2H, m, 5, 8-H), 6.23 (1H, s, 3-H), 4.93 (2H, s, OCH_2), 4.18 (2H, q, J = 7.0Hz, CH_2), 2.39 (3H, s, CH_3), 1.22 (3H, t, J = 7.0Hz, CH_3); LC-MS: m/z 263.0 ($\text{M}+1$).

Procedure for the preparation of 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]acetohydrazide (3).

Ethyl 2-[(4-methyl-2-oxo-2H-chromen-7-yl)oxy]acetate (**3**, 0.01 mole) in ethanol (20 mL) was stirred at room temperature for 20 min. To this mixture hydrazine hydrate (0.014 mole) was added. The resultant mixture was stirred at room temperature for 15 min, and the solid filtered with a sintered glass funnel. The residue was dried and then desiccated to afford a crystalline powder. The powder was recrystallised from chloroform/methanol and gave colorless needles. The yield of product was 88-90 %. M.p. $202-204^\circ\text{C}$ [lit. $198-200^\circ\text{C}$]²⁴; IR (KBr) ν : 3331, 3268,

3082, 2958, 1731, 1676, 1609, 1508, 1439, 1153, 1074 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 9.41 (1H, s, NH), 7.69 (1H, d, J = 8.8Hz, 6-H), 7.00 (1H, dd, J = 8.8Hz, J = 2.4Hz, 5-H), 6.9 (1H, d, J = 10.3Hz, 8-H), 6.21 (1H, s, 3-H), 4.61 (2H, s, NH_2), 4.35 (2H, s, OCH_2), 2.39 (3H, s, CH_3); LC-MS: m/z 249.0 ($M+1$).

Procedure for the synthesis of 2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(substituted methylene)acetohydrazides (4a-p)

Conventional. A mixture of compound **3** (0.01 mole) in chloroform/methanol (1:1) mixture (30 mL), aryl / hetero aromatic aldehyde (0.01 mole) and 1mL of glacial acetic acid was refluxed on a water bath for 60-150 minutes. The mixture was allowed to cool, and then the separated solid was filtered, washed with excess of methanol.

Microwave. This involves the irradiation of a mixture of compound **3** (0.01 mole) and aryl / heterocyclic aldehyde (0.01 mole) in a microwave oven (MW domestic type oven 800W SANYO) at 10 % intensity for 2-3 min. (four to six pulses each of 30 sec.) and the product was set aside to cool. The separated solid was filtered, washed with excess of methanol and dried. When solid aldehyde was used, the mixture of compound **3** (0.01 mole), aryl / hetero aromatic aldehyde (0.01 mole) and alumina (1.0g, mesh: 70-290 ASTM, pH = 4.5) were finely ground in mortar and pestle then, the mixture was irradiated in microwave oven (MW domestic type oven 800W, SANYO) at 10 % intensity for 2-3 min. (four to six pulses each of 30 sec.) and set aside to cool. The resultant solid mixture was poured into 30 mL of methanol, and then solid separated was filtered, washed with methanol.

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(benzylidene)acetohydrazide (4a). M.p. 276-278 $^{\circ}\text{C}$; IR (KBr) ν : 3072, 2969, 1712, 1686, 1615, 1511, 1435, 1393, 1271, 1160, 1084 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.66 (1H, d, J = 7.5Hz, $\text{HC}=\text{N}$), 8.32 & 8.02 (1H, 2s, NH), 7.72 (1H, s, 6-H), 7.43 (5H, s, Ph-H), 7.04 (2H, d, J = 18.7Hz, 5, 8-H), 6.23 (1H, d, J = 8.2Hz, 3-H), 5.30 (1H, s, OCH_2), 4.81 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 335 ($M-1$).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-chlorobenzylidene)acetohydrazide (4b). M.p. 296-298 $^{\circ}\text{C}$; IR (KBr) ν : 3188, 3065, 2966, 1711, 1687, 1617, 1511, 1435, 1390, 1270, 1139, 1084 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.70 (1H, s, $\text{HC}=\text{N}$), 8.32 & 8.01 (1H, 2s, NH), 7.76 (2H, d, J = 8.3Hz, 3', 5'-H), 7.71 (1H, dd, J = 8.6Hz, 6-H), 7.51 (2H, d, J = 8.3Hz, 2', 6'-H), 7.00 (2H, d, J = 11.9Hz, 5, 8-H), 6.23 (1H, d, J = 8.2Hz, 3-H), 5.30 (1H, s, OCH_2), 4.81 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 371 ($M+1$).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(3-nitrobenzylidene)acetohydrazide (4c). M.p. 266-268 $^{\circ}\text{C}$; IR (KBr) ν : 3073, 2958, 1720, 1687, 1617, 1529, 1433, 1387, 1347, 1275, 1138, 1085 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.88 (1H, s, $\text{HC}=\text{N}$), 8.52 & 8.45 (1H, 2s, NH), 8.25 (1H, d, J = 5.8Hz, 6'-H), 8.21 (1H, d, J = 7.7Hz, 4'-H), 8.15 (1H, s, 2'-H), 7.8 (1H, t, J = 5.5Hz, 5'-H), 7.71 (1H, d, J = 9.0Hz, 6-H), 7.01 (2H, d, J = 10.3Hz, 5, 8-H), 5.36 (1H, s, OCH_2), 4.85 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 382 ($M+1$).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-hydroxybenzylidene)acetohydrazide (4d). M.p. 280-282 $^{\circ}\text{C}$; IR (KBr) ν : 3280, 3079, 2908, 1717, 1670, 1610, 1512, 1423, 1390, 1356,

1260, 1145, 1086 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.43 (1H, d, J = 15.9Hz, HC=N), 9.90 (1H, s, OH), 8.21 & 7.91 (1H, 2s, NH), 7.71 (1H, d, J = 8.7Hz, 6-H), 7.63 (2H, d, J = 8.4Hz, 3', 5'-H), 7.00 (2H, m, 5, 8-H), 6.81 (2H, d, J = 8.4Hz, 2', 6'-H), 6.22 (1H, d, J = 7.7Hz, 3-H), 5.25 (1H, s, OCH_2), 4.77 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 353 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-hydroxy-3-methoxybenzylidene)acetohydrazide (4e). M.p. 258-260 $^{\circ}\text{C}$; IR (KBr) ν : 3482, 3135, 3086, 2975, 1710, 1697, 1612, 1518, 1428, 1390, 1267, 1161, 1077 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.46 (1H, d, J = 23.8Hz, HC=N), 9.50 (1H, s, OH), 8.19 & 7.90 (1H, 2s, NH), 7.71 (1H, d, J = 7.8Hz, 6-H), 7.27 (1H, d, J = 9.9Hz, 8-H), 6.98 (3H, m, 2', 5', 6'-H), 6.82 (1H, dd, J = 2.8Hz, J = 8.1Hz, 5-H), 6.22 (1H, d, J = 8.8Hz, 3-H), 5.28 (1H, s, OCH_2), 4.78 (1H, s, OCH_2), 3.80 (3H, s, OCH_3), 2.40 (3H, s, CH_3); LC-MS: m/z 383 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(4-dimethylaminobenzylidene)acetohydrazide (4f). M.p. 260-262 $^{\circ}\text{C}$; IR (KBr) ν : 3316, 2913, 1706, 1683, 1615, 1525, 1444, 1366, 1270, 1152, 1081 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.36 (1H, d, J = 20.9Hz, HC=N), 8.16 & 8.31 (1H, 2s, NH), 7.71 (1H, d, J = 4.8Hz, 6-H), 7.51 (2H, d, J = 5.3Hz, 3', 5'-H), 7.0 (2H, m, 5, 8-H), 6.73 (2H, d, J = 5.3Hz, 2', 6'-H), 6.22 (1H, d, J = 8.2Hz, 3-H), 5.24 (1H, s, OCH_2), 4.76 (1H, s, OCH_2), 2.96 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.40 (3H, s, CH_3); LC-MS: m/z 378 (M-1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(2,5-dimethoxybenzylidene)acetohydrazide (4g). M.p. 252-254 $^{\circ}\text{C}$; IR (KBr) ν : 3271, 3094, 2979, 1715, 1695, 1621, 1535, 1494, 1361, 1297, 1150, 1080 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.65 (1H, d, J = 16.2Hz, HC=N), 8.31 & 8.64 (1H, 2s, NH), 7.71 (1H, d, J = 6.2Hz, 6-H), 7.35 (1H, 2d, J = 3.8Hz, 6'-H), 7.01 (4H, m, 5, 8, 3', 4'-H), 6.22 (1H, d, J = 8.5Hz, 3-H), 5.30 (1H, s, OCH_2), 4.78 (1H, s, OCH_2), 3.80 (3H, s, 2'-H), 3.73 (3H, s, 5'-H), 2.40 (3H, s, CH_3); LC-MS: m/z 395 (M-1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(3-chlorobenzylidene)acetohydrazide (4h). M.p. 266-268 $^{\circ}\text{C}$; IR (KBr) ν : 3101, 2976, 1713, 1682, 1617, 1510, 1433, 1390, 1273, 1157, 1083 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.76 (1H, s, HC=N), 8.30 & 8.0 (1H, 2s, NH), 7.75 (1H, t, 5'-H), 7.71 (1H, d, J = 8.7Hz, 6-H), 7.5 (2H, t, J = 4.9Hz, 4', 6'-H), 7.02 (2H, m, 5, 8-H), 6.23 (1H, d, J = 8.9Hz, 3-H), 5.32 (1H, s, OCH_2), 4.82 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 371 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[3,4-dimethoxybenzylidene]acetohydrazide (4i). M.p. 220-222 $^{\circ}\text{C}$; IR (KBr) ν : 3189, 3086, 2927, 2834, 1731, 1682, 1615, 1509, 1421, 1391, 1267, 1155, 1080 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.52 (1H, d, J = 23.5Hz, HC=N), 8.24 & 7.94 (1H, 2s, NH), 7.70 (1H, d, J = 8.7Hz, 6-H), 7.31 (1H, d, J = 17.0Hz, 5'-H), 7.20 (1H, t, J = 8.2Hz, 6'-H), 7.01 (2H, d, J = 7.9Hz, 5, 8-H), 6.96 (1H, dd, J = 2.4Hz, 2'-H), 6.22 (1H, d, J = 9.2Hz, 3-H), 5.30 (1H, s, OCH_2), 4.79 (1H, s, OCH_2), 3.81 (6H, s, $(\text{OCH}_3)_2$), 2.40 (3H, s, CH_3); LC-MS: m/z 397 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-bromothiophen-2-yl)methylene]acetohydrazide (4j). M.p. 288-290 $^{\circ}\text{C}$; IR (KBr) ν : 3053, 2917, 1713, 1681, 1616, 1510, 1429, 1389, 1274, 1139, 1083 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), δ = 11.68 (1H, d, J = 21.8Hz, HC=N), 8.47 & 8.10 (1H, 2s, NH), 7.71 (1H, d, J = 8.7Hz, 6-H), 7.28 (2H, m, 3', 4'-H), 6.99

(2H, m, 5, 8-H), 6.23 (1H, d, $J = 8.1\text{Hz}$, 3-H), 5.18 (1H, s, OCH_2), 4.78 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 320 (M-1), 322(M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-chlorofuran-2-yl)methylene]acetohydrazide (4k). M.p. 260-262 °C; IR (KBr) ν : 3052, 2928, 1715, 1686, 1616, 1512, 1434, 1393, 1272, 1159, 1084 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 11.68$ (1H, d, $J = 3.2\text{Hz}$, $\text{HC}=\text{N}$), 8.14 & 8.31 (1H, 2s, NH), 7.71 (1H, d, $J = 7.8\text{Hz}$, 6-H), 6.99 (1H, d, $J = 3.3\text{Hz}$, 4'-H), 6.96 (1H, d, $J = 3.3\text{Hz}$, 3'-H), 6.93 (1H, d, $J = 3.2\text{Hz}$, 8-H), 6.67 (1H, d, $J = 4.6\text{Hz}$, 5-H), 6.23 (1H, d, $J = 8.9\text{Hz}$, 3-H), 5.22 (1H, s, OCH_2), 4.80 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 358.9 (M-1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(5-nitrofuran-2-yl)methylene]acetohydrazide (4l). M.p. 284-286 °C; IR (KBr) ν : 3112, 1715, 1701, 1679, 1614, 1500, 1456, 1390, 1351, 1260, 1137, 1081 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 12.03$ (1H, d, $J = 10.0\text{Hz}$, $\text{HC}=\text{N}$), 8.30 & 7.97 (1H, 2s, NH), 7.79 (1H, dd, $J = 3.8\text{Hz}$, $J = 10.1\text{Hz}$, 4'-H), 7.71 (1H, d, $J = 8.6\text{Hz}$, 6-H), 7.28 (1H, dd, $J = 3.8\text{Hz}$, $J = 18.9\text{Hz}$, 3'-H), 7.00 (2H, m, 5, 8-H), 6.23 (1H, d, $J = 8.8\text{Hz}$, 3-H), 5.28 (1H, s, OCH_2), 4.86 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 372 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(furan-3-yl)methylene]acetohydrazide (4m). M.p. 272-274 °C; IR (KBr) ν : 3110, 2958, 1710, 1688, 1617, 1511, 1433, 1390, 1272, 1158, 1086 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 11.52$ (1H, d, $J = 21.7\text{Hz}$, $\text{HC}=\text{N}$), 8.28 & 8.13 (1H, 2s, NH), 7.97 (1H, s, 2'-H), 7.74 (1H, s, 5'-H), 7.71 (1H, d, $J = 8.7\text{Hz}$, 6-H), 7.00 (1H, d, $J = 2.4\text{Hz}$, 8-H), 6.99 (1H, d, $J = 2.4\text{Hz}$, 5-H), 6.96 (1H, dd, $J = 2.3\text{Hz}$, $J = 9.1\text{Hz}$, 4'-H), 6.23 (1H, d, $J = 8.5\text{Hz}$, 3-H), 5.22 (1H, s, OCH_2), 4.77 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 327 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(thiophen-2-yl)methylene]acetohydrazide (4n). M.p. 274-276 °C; IR (KBr) ν : 3055, 2917, 1732, 1685, 1618, 1513, 1432, 1390, 1272, 1143, 1085 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 11.62$ (1H, d, $J = 21.8\text{Hz}$, $\text{HC}=\text{N}$), 8.31 & 8.20 (1H, 2s, NH), 7.71 (1H, d, $J = 5.8\text{Hz}$, 6-H), 7.65 (1H, d, $J = 8.0\text{Hz}$, 5'-H), 7.47 (1H, s, 3'-H), 7.13 (1H, m, 4'-H), 7.00 (2H, m, 5, 8-H), 6.23 (1H, d, $J = 7.7\text{Hz}$, 3-H), 5.20 (1H, s, OCH_2), 4.79 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 341 (M-1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-[(1H-imidazol-2-yl)methylene]acetohydrazide (4o). M.p. 256-258 °C; IR (KBr) ν : 3316, 3126, 3030, 2915, 1715, 1683, 1626, 1536, 1446, 1386, 1257, 1150, 1087 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 12.60$ (1H, s, NH), 11.65 (1H, d, $J = 10.2\text{Hz}$, $\text{HC}=\text{N}$), 8.23 & 7.89 (1H, 2s, NH), 7.71 (1H, d, $J = 3.4\text{Hz}$, 6-H), 7.34 (1H, s, 4'-H), 7.07 (1H, s, 5'-H), 7.03 (1H, d, $J = 2.3\text{Hz}$, 8-H), 7.00 (1H, d, $J = 2.2\text{Hz}$, 5-H), 6.23 (1H, d, $J = 5.8\text{Hz}$, 3-H), 5.26 (1H, s, OCH_2), 4.82 (1H, s, OCH_2), 2.40 (3H, s, CH_3); LC-MS: m/z 327 (M+1).

2-[(4-Methyl-2-oxo-2H-chromen-7-yl)oxy]-N'-(3-phenylallylidene)acetohydrazide (4p). M.p. 270-272 °C; IR (KBr) ν : 3313, 3043, 2914, 1704, 1685, 1625, 1533, 1421, 1390, 1251, 1151, 1084 cm^{-1} ; ^1H NMR (400 MHz, DMSO, ppm), $\delta = 11.54$ (1H, d, $J = 15.3\text{Hz}$, $\text{HC}=\text{N}$), 8.09 & 7.84 (1H, 2d, $J = 8.8\text{Hz}$, NH), 7.70 (1H, d, $J = 8.8\text{Hz}$, 6-H), 7.61 (2H, d, 2', 6'-H), 7.38 (2H, t, $J =$

7.2Hz, 4'-H), 7.09 (4H, m, 5, 8-H, HC=CH), 6.22 (1H, d, J = 7.8Hz, 3-H), 5.18 (1H, s, OCH₂), 4.78 (1H, s, OCH₂), 2.40 (3H, s, CH₃); LC-MS: m/z 363 (M+1).

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