Synthesis, Antioxidant and Insecticidal Activities of Some Coumarin Derivatives

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Dedicated to Prof. Dr. Atta-ur-Rahman on the occasion of his 60th birthday

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Summary: 7-Hydroxy-4-methyl-2*H*-chromen-2-one (**2**) and their some derivatives were synthesized for exploring selected biological screening. The compounds **12** and **13** had shown high degree of antioxidant activity. Two compounds **3** and **8** showed high degree of insecticidal activity amongst the present series.

Introduction

A number of coumarins and their derivatives are reported to exhibit wide spectrum of biological and pharmacological activities [1]. Osthal, alloimpersatorin, isopimpinellin possess antimicrobial properties. Among a number of furocoumarins, *viz.* xanthotoxin, imperatorin, psoralene, angelicin, the most potent therapeutic agent is psoralene in the restoration of melanin depleted skin, *i.e.* in the treatment [2] of vitiligo and psoriasis. The oestrogenic activities of caumentans [3] and the insecticidal properties of rotenoids [4] are well established. The family of coumarins have been implicated in the pathogenicity of a number of infectious microorganisms [5-7].

Coumarins are members of the class of compounds called benzopyrones and display a variety of pharmacological properties [5] depending on their substitution pattern. Natural [8] and synthetic coumarins [9] are also known to possess antifungal and antibacterial properties [6, 7]. The diverse biological activity of coumarin derivatives [10] as anticoagulants and antithrombotics is well known. Some 3-substituted-4-hydroxycoumarines [11] and tricoumarol [12] possess HIV inhibitory potency. Some 1-benzopyranol{3,4-f}quinolines are nonsteroidal human progesterone receptor (HPR) agonists [13, 14]. Heterocycles fused at 3,4-position of coumarine also draw special attention [15-17]. Several reports [18-23] on new synthetic routes of this class of compounds appeared during last two decades. A variety of interesting biological as well as pharmacological activities with some of our own results [24] initiated us to synthesize and explore their selected biological activities. In course of our study to extend the scope of the coumarins, we have synthesized various derivatives of 7-hydroxy-4-methyl coumarin in search of their selected antioxidant and insecticidal activities.

Results and Discussions

Resorcinol (**1**) was treated with methyl acetoacetate in the presence of sulphuric acid at 10 °C to give 7-hydroxy-4-methyl-2*H*-chromen-2-one (**2**). Reaction of **2** with ethyl bromoacetate in the presence of K_2CO_3 in THF afforded ethyl 2' [(4-methyl-2-oxo-2*H*-chromene-7-yl)-oxy]acetate (**3**) and in the similar way *p*-toulenesulfonyl chloride in THF in the presence of potassium carbonate gave 4-methyl-2-oxo-2*H*-chromene-7-yl 4'-methylbenzenesulfonate (**4**). Similarly, the compounds 4-methyl-2-oxo-2*H*-chromene-7-yl methanesulfonate (**5**), 4-methyl-2-oxo-2*H*-chromene-7-yl acetate (**6**), 4-methyl-2-oxo-2*H*-chromene-7-yl 2',3',4'-trimethoxybenzoate (**7**) and 4-methyl-2-oxo-2*H*-chromene-7-yl benzoate (**8**) were synthesised by treatment of compound **2** in THF with methanesulfonyl chloride, acetic anhydride, trimethoxybenzoyl chloride and benzoyl chloride, in the presence of potassium carbonate at room temperature for 24 h, respectively [25].

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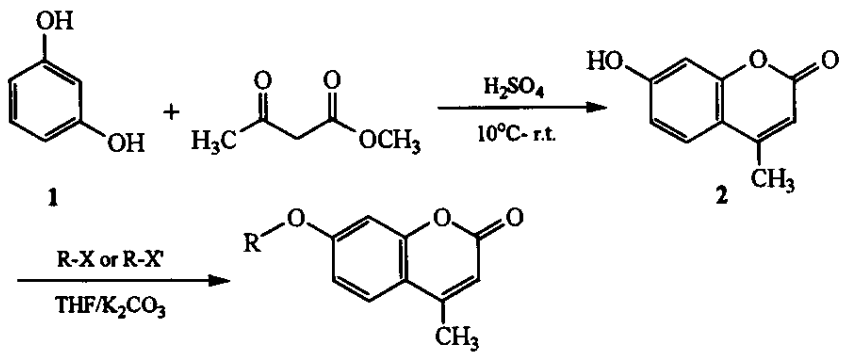


3:	R =	$-C_4H_7O_2$,	X = Br
4:	R =	$-C_7H_7SO_2$,	X = Cl
5:	R =	$-CH_3SO_2$,	X = Cl
6:	R =	$-C_2H_3O$,	X' = $-C_2H_3O$
7:	R =	$-C_{10}H_{11}O_4$,	X = Cl
8:	R =	$-C_7H_5O$,	X = Cl
9:	R =	$-C_2H_5$,	X = I
10:	R =	$-C_5H_{11}$,	X = I

Scheme-1

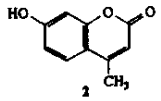
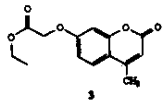
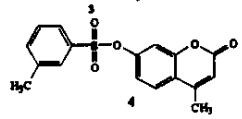
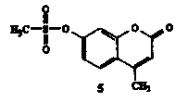
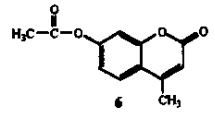
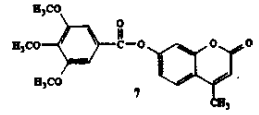
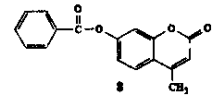
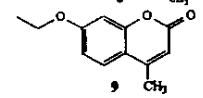
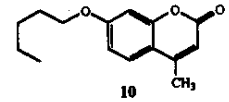
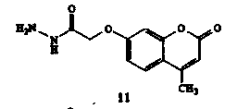
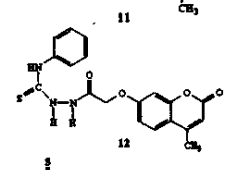
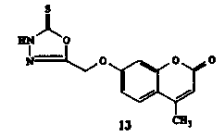
The syntheses of 7-ethoxy-4-methyl-2*H*-chromen-2-one (**9**) and 4-methyl-7-(pentyloxy)-2*H*-chromen-2-one (**10**) were also accomplished by treatment of compound **2** with ethyl iodide and iodopentane in THF in the presence of potassium carbonate for 10 days, respectively (Scheme-1) [25].

Furthermore, ethyl 2' [(4-methyl-2-oxo-2*H*-chromene-7-yl)-oxy] acetate (**3**) was treated with hydrazine hydrate in EtOH at room temperature for 15 min to provide 2'-[4-methyl-2-oxo-2*H*-chromene-7-yl)oxy] acetohydrazide (**11**), which was then reacted with phenyl isothiocyanate in EtOH and refluxed for 72 h gave 2'-[2'-{(4-methyl-2-oxo-2*H*-chromene-7-yl)oxy}acetyl]-*N*-phenyl-1-hydrazine-carbo-thioamide (**12**). Also when compound **11** was treated with 2.5 molar equivalent of carbon disulfide at room temperature in EtOH and then with 2 N potassium hydroxide on refluxing for 24 h gave 4-methyl-7-[(5'-thioxo-4',5'-dihydro-1',3',4'-oxadiazole-2'-yl)methoxy]-2*H*-chromen-2-one (**13**) (Scheme-2) [25].

Antioxidant Bioassay

The entire synthesized compounds were screened for their free radical scavenging activities according to literature protocol [26]. The results of free radical scavenging activity are depicted in Table-1. The thiooxadiazole **13** demonstrated highest degree (94.01%) of free radical scavenging activity, whereas standard propyl gallate has 91%. The compound **12** also displayed 93.29% of activity, which is higher than the standard. The hydrazide **11** also exhibited significant scavenging activity but lesser than propyl gallate. The benzoate ester showed an indicative amount of activity. The structure activity relationship (SAR) demonstrated that thiocarbonyl group could be responsible for this activity in addition to other electronic factors. In case of compound **13** the thiocarbonyl group appeared in its thiooxadiazole form and in compound **12** it was as a hydrazinecarbothioamide residue. It is obvious that the thiocarbonyl will be more radical scavenger than hydrazinecarbothioamide. These results need more work on this type of compounds in order to get a more potent compound.

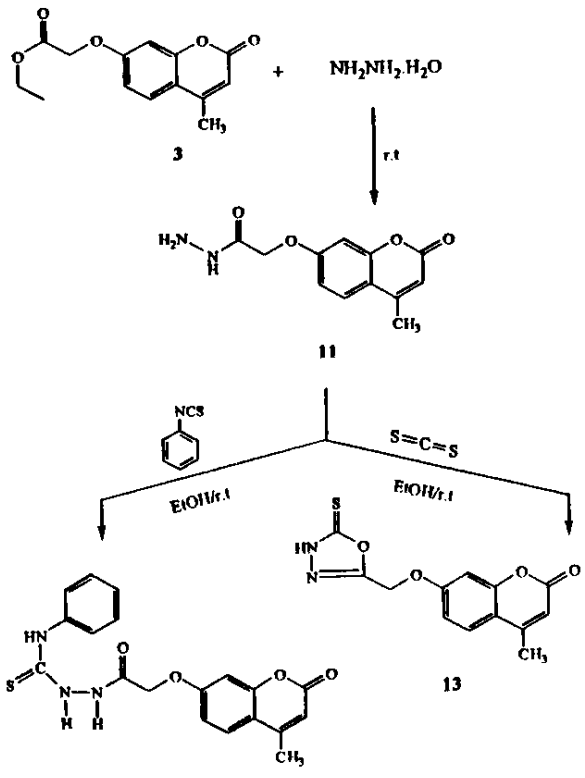
Table-1: Results of Antioxidant Bioassay.

S. No.	Compound	Free radical scavenging (%)
1		-
2		-
3		-
4		-
5		-
6		-
7		36.83
8		-
9		-
10		72.70
11		93.29
12		94.01
Standard propyl gallate		91.00

These all compound scavenging at 1m molar concentration against 1,1-diphenyl-2-picrylhydrazy radical (DPPH).

Insecticidal Bioassay

Five out of twelve synthesized compounds were tested for their insecticidal activity against



Scheme-2

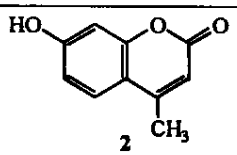
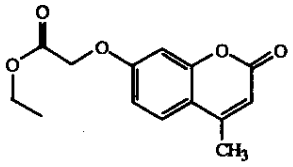
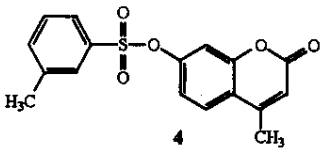
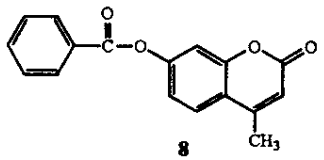
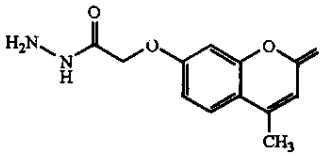
Trogoderma granarium, Rhyzopertha dominica, Setaphilus oryzae and *Callosobrachus analis*. The results of insecticidal activity are displayed in Table-2. The compound **3** and **8** showed moderate activity against all tested insects, however, all other compounds were tested against *Trogoderma granarium, Rhyzopertha dominica, Setaphilus oryzae* and *Callosobrachus analis* and were found to be almost inactive.

Experimental

General

The ultraviolet spectra were measured in methanol with a Pye-Unicam sp-800G instrument. Infrared spectra (KBr discs) were recorded with a JASCO IRA-1 spectrometer. Electron impact (EIMS) mass spectra were determined with a Finnigan MAT-312, Varian MAT-112 double focussing mass spectrometer connected to a PDP 11/34 (DEC) computer system. The ^{1}H-NMR spectra were recorded in CD_3OD, $CDCl_3$ or in DMSO-d_6 with Bruker AM 300 and AM 400 spectrometers operating at 300 and 400 MHz, respectively. ^{1}H-NMR chemical shifts are reported in δ (ppm) and coupling constants in Hz. The purity of the products were checked on

Table-2: Results of Insecticidal Bioassay.

S. No.	Compound	Insect	Concentration (μg/cm²)	Test
1	 2	*Trogoderma granarium*	393.17	10
		Rhyzopertha dominica and *Callosobrachus analis*	"	10
		Setaphilus oryzae	"	00
2	 3	*Trogoderma granarium*	393.17	30
		Rhyzopertha dominica and *Callosobrachus analis*	"	10
		Setaphilus oryzae	"	10
3	 4	*Trogoderma granarium*	393.17	10
		Rhyzopertha dominica and *Callosobrachus analis*	"	00
		Setaphilus oryzae	"	0
4	 8	*Trogoderma granarium*	393.17	30
		Rhyzopertha dominica and *Callosobrachus analis*	"	10
		Setaphilus oryzae	"	00
5	 11	*Trogoderma granarium*	393.17	10
		Rhyzopertha dominica and *Callosobrachus analis*	"	00
		Setaphilus oryzae	"	00

TLC plates (Merck, Darmstadt, Germany), coated with silica gel PF_{254}, and the spots were visualized under ultra violet light at 254 and 366 nm and by spraying with iodine vapours. Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected.

7-Hydroxy-4-methyl-2H-chromen-2-one (2)

To a solution of resorcinol (**1**, 10 g, 90.90 mmol) in THF, freshly distilled methyl acetoacetate (9.8 ml, 90.90 mmol) was added drop wise. The mixture was stirred, and the temperature was kept below 10°C by means of ice. After all the solution has been added (about 30 minutes) the reaction mixture was set aside for 4-5 h without further cooling. The reaction mixture was now poured with vigorous stirring into a mixture of ice (200 g) and water (300 ml) and kept in refrigerator for over night. The solid was filtered and thoroughly washed with cold water till the pH of filtrate become neutral. The residue was dried over a sintered glass funnel by vacuum and then in desiccators afforded yellow crystalline powder [25].

General Procedure for the Preparation of Compounds 3-10

7-Hydroxy-4-methyl-2*H*-chromen-2-one (**2**) (1.0 mmol) in 10 ml THF was stirred at room temperature for 15 min. To this mixture solid potassium carbonate (2.0 mmol) was added. The resultant mixture was stirred at room temperature for 15 min and then appropriate halides (1.1 mmol) were added (see scheme 1). The mixture was refluxed for 24 h and after completion of reaction (TLC analysis), the solid was filtered off. The filtrate was evaporated on a rotary evaporator and solid residue was

crystallized from appropriate solvent to afford compounds **3-10** [25].

2'-[(4-Methyl-2-oxo-2H-chromene-7-yl)oxy] acetohydrazide (11)

Ethyl 2'-[(4-methyl-2-oxo-2*H*-chromene-7-yl)oxy] acetate (**3**, 5g, 19.08 mmol) in 10 ml ethanol was stirred at room temperature for 20 min. To this mixture hydrazine hydrate (3.6 ml, 116.11 mmol) was added. The resultant mixture was stirred at room temperature for 15 min. The solid was filtered with a sintered glass funnel. The residue was dried on a two stage pump (high vacuum) and then in desiccator to afford white crystalline powder [25].

2'-[2'-{(4-Methyl-2-oxo-2H-chromene-7-yl)oxy}acetyl]-N-phenyl-1-hydrazine-carbothioamide (12)

2'-[(4-Methyl-2-oxo-2*H*-chromene-7-yl)oxy] acetohydrazide (**11**, 1 g, 4.0322 mmol) in 7 ml ethanol was stirred at room temperature for 20 min. To this mixture phenylisothiocyanate (0.6 ml, 5.02 mmol) was added and the mixture was refluxed for 72 h. After completion of reaction the mixture was filtered with filter paper. The solid material was dried on a two stage pump (high vacuum) and then in desiccator to afford white crystalline powder [25].

4-Methyl-7-[(5'-thioxo-4',5'-dihydro-1',3',4'-oxadiazol-2'-yl)methoxy]-2H-chromen-2-one (13)

2'-[(4-Methyl-2-oxo-2*H*-chromene-7-yl)oxy] acetohydrazide (**11**, 5 g, 20.16 mmol) in 70 ml ethanol was stirred at room temperature for 20 min. To this mixture carbondisulfide (3 ml, 49.97 mmol) was added and the resultant mixture was stirred at room temperature for 15 min. 2N potassium hydroxide (5 ml) was added very carefully and dropwise. After refluxing the reaction for 24 h, the reaction mixture was filtered and filtrate was dried under vacuum. The crude product was acidified with 10% hydrochloric acid and extracted thrice with chloroform. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure [25].

Biological testing

Antioxidant Bioassay

An antioxidant may be defined as a substance which can prevent or inhibit the oxidation of autooxidizable materials in living cells [26, 27]. In the results of oxidation free radicals are formed [28] which play an important role in carcinogenesis through their involvement in breaking of DAN strands [29]. They also cause many other diseases like heart diseases, diabetes, arthritis, artheriosclerosis and arthritis [30], since every part of the body are subjected to the adverse effect of free radicals. Free radicals are also involved in the deterioration of food and oil. Antioxidants are the compounds which can retard aging [31], cancer [32] and heart diseases [33] in humans by inhibiting or quenching free radicals and reactive oxygen species [28]. They can also increase the shelf life and quality of food and oils.

Insecticidal Bioassay

Almost any stored material, whether of plant or animal origin, is subjected to attack by insects, especially the species of Coleoptera (usually stored grain pests). Among the products that are frequently damaged are grains and their derivatives. Stored grain pests are the major problem for various countries. Grains and other seed pests damage substantial quantities economically valuable food. Development of resistance against conventional pesticides is another problem associated with the use of insecticides in grain protection. Consequently, there is an urgent need to develop economically safer and sounder pest control techniques [34-39].

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