Synthesis and Biological Evaluation of Some Coumarin Derivatives

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Abstract**: Coumarin belongs to the family of benzopyrone found to have lot of biologically important. The present investigation focused on the synthesis of four derivatives from 4-Hydroxy-chromen-2-one and characterized using spectral (FTIR, ^{1}H and ^{13}C-NMR), Thermal (TGA) and morphological studies (SEM).**

Keywords: Ethyl Bromopropionate, Biological activity, SEM and TGA.

I. INTRODUCTION

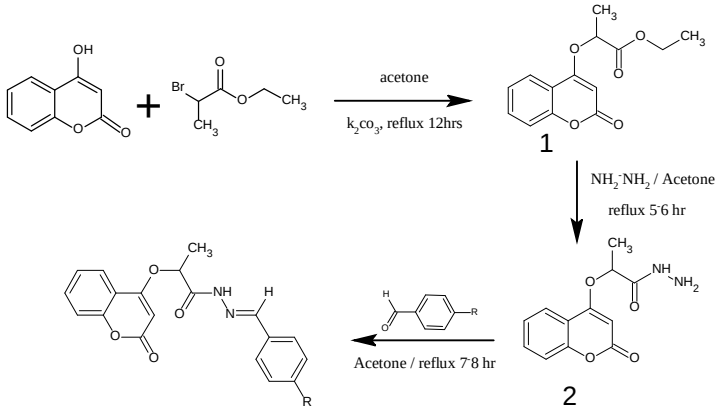
Coumarins belong to a group compounds known as the benzopyrones, all of which consist of a benzene ring joined to a pyrone. Coumarin and the other members of the coumarin family are benzo-α-pyrones, while the other main members of the benzopyrone group contain the pyrone group (Keating and O'Kennedy, 1997). Coumarins may also be found in nature in combination with sugars, as glycosides.

Coumarins shows a number of diverse biological and pharmaceutical activities, including plant growth regulation,[1] insecticidal action,[2] antioxidaton,[3] anticoagulant,[4] anti-tumar activity,[5] estrogenic, dermal photosensitizing, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity.[6-15]

Hence, the scope of the present investigation aimed in developing new coumarin derivatives, thus by, modifying the methyl substitution using ethyl bromopropionate and investigating their antibacterial activity against the micro organisms like staphylococcus aureus, E.coli and Klebsiella.

Many coumarin compounds after some suitable structure modification can be used as drugs.[16] The structures of all compounds were established on the bases of IR and ^{1}H NMR.

II. MATERIALS AND METHODS



	A	B	C	D	E
R	H	Cl	OCH_3	$N(CH_3)_2$	OH

a. Ethyl 2-[(2-oxo-2H-chromen-4-yl)oxy]propanoate (1)

A suspension of 4-hydroxy coumarin (6.10mmol) in acetone (30ml) was refluxed with ethylbromo propionate (9.15mmol) in presence of K_2CO_3 (4.69g, 33.91mmol) for 12hrs. After cooling the mixture was evaporated to dryness and the residue was portioned between $CHCl_3$ (50ml) and water (50). The organic phase was dried Na_2So_4, filtered and evaporated to dryness, recrystallized from acetone. MP: 120^0C. FT-IR 1743 (-C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching). ^{1}H NMR spectrum shows ester methyl and methylene of ethyl group respectively ppm 1.282 (d, 3H, CH_3), 4.268 (t, 2H, CH_2). 5.744ppm shows the proton in coumarin ring. The aromatic regions are 7.260 to 7.928 ppm. (d, 4H). ^{13}C NMR spectrum shows ppm 170 Coumarin carbonyl carbon, 164.53 Ester carbonyl, ppm162.58 Coumarin CH. Ppm 153.69, 124.09, 116.78, 115.48, 123.40, 132.40, & (aromatic region), 62.11(ester -CH_2), 18.03 (CH_3), 14.17 (ester –CH_3).

b. 2-[(2-oxo-2H-chromen-4-yl)oxy]propanehydrazide (2)

A solution of compound 1 (0.1mol) and hydrazine hydrate in acetone 0.02ml, 2ml in acetone was refluxed for 5-6 hr. Completion of reaction was judged by TLC. After cooling, the reaction mixture was poured into ice cold water. The solid was collected by filtration, dried and recrystallized from acetone. mp: 192-195^{0}C. FT-IR 3398 (-NH-NH_2), 1769 (-C=O Carbonyl stretching , 1707 (Lactonic-C=O Carbonyl stretching). ^{1}H NMR spectrum shows ppm 1.763 (d, 3H, CH-CH_3), 4.909 (m, 1H, CH-CH_3), 5.537 (S, 1H, CH), 8.493 (1H, NH), 7.926 (d, 2H, NH_2). ^{13}C NMR spectrum shows 169.25, 163.65 & 161.27 (Carbonyl region) 132.9, 124.24 & 122.92 (Aromatic region), 17.38 (CH_3).

c. 2-[(2-oxo-2H-chromen-4-yl)oxy]-N'-[(E)-phenylmethylidene] propanehydrazide (2a)

An equimolar mixture of 2 and an aromatic aldehyde was refluxed for 5-6 hr. Completion of reaction was judged by TLC. After cooling, the reaction mixture was poured into ice cold water. The solid was collected by filtration, dried and recrystallized from acetone. FT-IR 3396 (-NH-NH_2), 1753 (-C=O Carbonyl stretching), 1680 (Lactonic-C=O Carbonyl stretching), 1250 (C-O). The ^{1}H NMR spectrum shows ppm 1.760 (d, 2H, CH-CH_3), 4.907 (m, 1H, CH), 5.535 (s, 1H, CH), 10.013 (s, 1H, NH) (s, 1H, N=CH), around 7 is aromatic proton. ^{13}C NMR spectrum shows ppm 169.51, 163.64 & 161.27 (Carbonyl region), 132.89, 124.22, 122.91, 116.39 & 114.89 (Aromatic region), 91.40 (N=C-H), 17.37 (CH-CH_3).

d. N'-[(E)-(4-chlorophenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy] propanehydrazide (2b)

Pale yellow solid, recrystallized from acetone, mp: 206-208^{0}C, FT-IR 3394 (NH-NH_2), 1739 (C=O, Carbonyl stretching), 1705(Lactonic-C=O Carbonyl stretching), 1616, (-C=N-NH), 761(-C-Cl). The 1H NMR spectrum shows ppm 1.644 (d, 3H, CH_3), 5.383 (m, 1H, CH), 5.811 (s, 1H, CH), 9.860 (s, 1H, -N=CH), 10.013 (s, 1H, NH). ^{13}C NMR spectrum shows ppm 169.52, 163.65 & 161.27 (Carbonyl region), 152 (-N=C-H), 17.38 (CH-CH_3). ^{13}C NMR spectrum shows ppm 169.52, 163.65 & 161.27 (Carbonyl region), 152.73 (CH-CH_3), 132.90, 124.22, 122.91, 116.40 & 114.89 (aromatic region), 17.37 (CH-CH_3).

e. N'-[(E)-(4-methoxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy] propanehydrazide (2c)

Yellow solid, recrystallized from acetone, mp: 190-193^{0}C. FT-IR 1735 (-C=O Carbonyl stretching), 1703 (Lactonic-C=O Carbonyl stretching), 1614 (-C=N-NH). The ^{1}H NMR spectrum shows ppm 1.643 (d, 3H, CH_3), 3.023 (s, 3H, OCH_3), 5.575 (m, 1H, CH), 5.807 (s, 1H, CH), 9.685 (s, 1H, N=CH), 9.987 (s, 1H, NH). ^{13}C NMR spectrum shows ppm 169.51, 163.64 & 161.27 (carbonyl region), 132.87, 131.70, 131.25, 124.20, 122.90, 116.38 & 114.89 (aromatic region), 152.73 (N=C-H), 61.31 (O-CH_3), 17.37 (CH-CH_3).

f. **N'-{(E)-[4-(dimethylamino)phenyl]methylidene}-2-[(2-oxo-2H-chromen-4-yl)oxy]propanehydrazide (2d)**

Pale orange solid, recrystallised from acetone, mp: 197-199^0, FT-IR 1741 (-C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching), 1614 (-C=N-NH), 1327 (-C-N-$(CH_3)_2$). ^{1}H NMR spectrum shows ppm 1.644 (d, 3H, CH_3), 3.030 (s, 3H, $N(CH_3)_2$, 5.380 (m, 1H, CH), 5.812 (s, 1H, CH), 9.664 (s, 1H, N=CH), 9.899 (s, 1H, NH). ^{13}C NMR spectrum shows ppm 169.52, 163.65 & 161.28 (carbonyl region), 152.73 (N=C-H), 132.90, 131.72, 131.45, 124.46, 124.23, 116.41 & 114.91 (aromatic region), 17.38 (CH-CH_3).

g. N'-[(E)-(4-hydroxyphenyl)methylidene]-2-[(2-oxo-2H-chromen-4-yl)oxy] propanehydrazide (2e)

Yellow solid, recrystallised from acetone, mp: 216-218^{0}C, FT-IR 3464 (-OH), 1745 (-C=O Carbonyl stretching), 1695 (Lactonic-C=O Carbonyl stretching), 1614 (-C=N-NH) 1319 (-C-N-$(CH_3)_2$). ^{1}H NMR spectrum shows ppm 1.644 (d, 3H, CH_3), 5.381 (m, 1H, CH), 5.810 (s, 1H, CH), 9.653 (s, 1H, N=CH), 9.901 (s, 1H, NH), 10.594 (s, 1H, OH). ^{13}C NMR spectrum shows ppm 169.52, 163.65 & 161.28 (carbonyl region), 152.73 (N=C-H), 132.89, 124.22, 122.91, 116.40 & 114.90 (aromatic region), 17.38 (CH-CH_3).

III. Thermal studies

According to the TGA and DTG data, the thermal degradation occurs in two stage decomposition. The relative thermal stability of different organic compounds and composites was assessed by comparing the weight loss in temperature range ambient to 750^{0}C. TGA of all prepared organic compounds 1, 2, 2a, 2b, 2c, 2d & 2e showed weight loss in two stages.

Table.1 Thermal studies on synthesized courmarin derivatives

Compd. Code.	Temperature in percentage									
	10%	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**	**100%**
1	212	230	241	255	260	266	270	276	285	355
2	218	226	240	255	263	270	276	280	282	410
2A	205	223	238	245	252	261	270	275	280	360
2B	218	228	240	252	260	265	270	276	280	340
2C	219	236	246	255	260	270	174	280	283	375
2D	176	202	218	230	240	248	260	270	275	290
2E	219	232	244	250	268	275	281	290	293	400

Thermogravimetric analysis was employed to get information on thermal stability of the prepared organic compounds. It can be observed that all samples have undergone two stage decomposition with the major weight loss occurring between 280 to 430 ^{0}C. The peak temperature and the percentage of residue of all the samples for the both decomposition are listed Table. 1 The 10% weight loss of all compounds was observed at 212, 218, 205, 218, 219, 176 and 219 ^{0}C respectively. The 20% weight loss found to have around 230 ^{0}C for all compounds. Similarly 50%weight loss was observing around 260 ^{0}C. The maximum 70% weight loss have been observe at around 270 ^{0}C. Whereas 2D was found to have only at 260 ^{0}C. This might be due to the lesser hardness imparted by the compound 2D.

IV. Antimicrobial activity

The newly synthesized compounds were screened for their antimicrobial activities in vitro against two species of Gram-positive bacteria Bacillus subtilis (NCTC- 10400) (BS), Staphylococcus aureus (NCTC 7447) (SA), and three Gram-negative bacteria, Escherichia coli (NCTC 10410) (EC), Candida albicans (IMRU 3669) (CA), and one fungus, Aspergillus niger (ATCC 6275) (AN). The activities of these compounds were tested using the disc diffusion method. [17-18] The area of zone of inhibition was measured using neomycin (30 μg mL^{-1}) as standard antibiotic

Bacterial activity

MICROORGANISM	Control	1	2	2A	2B	2C	2D	2E	CIPROFLOXACIN
Bacillus cereus (mm)	-	12	15	8	10	11	9	7	10
Staphylococcus aureus (mm)	-	13	14	12	8	10	13	10	12
Escherichia coli (mm)	-	9	12	14	9	10	12	9	12

FUNGEL ACTIVITY

MICROORGANISM	Control	1	2	2A	2B	2C	2D	2E	Amphotericin-B
Candida albicans (mm)	-	-	-	-	-	-	8	11	9
Penicillium sps (mm)	-	9	-	9	-	8	10	8	8
Aspergillus niger (mm)	-	9	10	8	5	11	10	-	9

V. CONCLUSIONS

A synthesis of coumarin derivatives was prepared. The chemical structures of synthesize compounds were determined according to extensive NMR data. The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria and fungi. The compound **2** showed moderate bacterial activity.

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