

Original Article

## Synthesis and antimicrobial activity of some novel derivatives of 7-hydroxy-4-methyl coumarin

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### ABSTRACT

Some novel derivatives of 7-hydroxy-4-methyl coumarin were synthesized. The title compounds were obtained by the reaction of 7-hydroxy-4-methyl coumarin with ethylchloroacetate in the presence of potassium carbonate in acetone afforded ethyl-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetate, which react with hydrazine hydrate in ethanol afforded 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide. Hydrazide was considered as the key intermediate for some novel compounds (MK1-MK6). The reaction of hydrazide with acetyl acetone and ethyl acetoacetate gave 7-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one (MK-1) and 1-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-3-methyl-1H-pyrazol-5(4H)-one (MK-2). Also reaction of hydrazide with isatin lead to the formation of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (MK-3). The other derivatives MK-4, MK-5 and MK-6 were obtained by treating the hydrazide with phthalic, maleic and succinic anhydrides respectively. The structures of these compounds were established on the basis of IR and <sup>1</sup>H-NMR spectral analysis. Compounds (MK1-MK6) were screened for their antimicrobial activity. All compounds exhibit significant antimicrobial activity as compared to standard drug.

### 1. INTRODUCTION

The major classes of almost all antibiotics are encountering resistance in clinical applications[1,2]. In order to overcome this rapid development of drug resistance, new scaffolds need to be developed, preferably consisting of chemical characteristics that clearly differ from those of existing agents [3,4]. 7-Hydroxy-4-Methyl Coumarin derivatives have been of great interest in medicinal chemistry for their role as potent antibacterial and antifungal agents. Also, the hydrazides form an important structural class possessing wide spectrum of biological activities that include antibacterial and antifungal activity [5-8]. In view of these observations, we herein report the synthesis of some novel coumarin derivatives and evaluate their antibacterial and antifungal activity.

### 2. CHEMICAL STUDIES

The synthesis of various novel derivatives of 7-Hydroxy-4-Methyl Coumarin

1. Synthesis of 7-hydroxy-4-methyl-2H- chromen-2-one.

2. Synthesis of ethyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate.
3. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide.
4. Synthesis of various novel Coumarin derivatives.
  - a. 7-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one (MK-1)
  - b. 1-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-3-methyl-1H-pyrazol-5(4H)-one (MK-2)
  - c. (13Z)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (MK-3)
  - d. 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(1,3-dioxoisindolin-2-yl)acetamide (MK-4)
  - e. 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)acetamide (MK-5)
  - f. 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxopyrrolidin-1-yl)acetamide (MK-6)

### 3. EXPERIMENTAL

The synthetic scheme is presented in Fig. 1. 7-hydroxy-4-methyl-2H-chromen-2-one, ethyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate and 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide were synthesized by the reported procedures. Synthesis of various novel Coumarin derivatives are discussed below [9-11]. The compounds were characterized by physical evaluation (Table 1), IR (Table 2) and <sup>1</sup>H-NMR (Table 3) spectrum analysis.

#### a. Synthesis of 7-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one (MK-1)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.0028 mole) and acetyl acetone (0.0028 mol) in ethanol (1000 ml), was refluxed on water bath for 8 hr. After cooling, the solvent was removed under reduced pressure and the separated solid was recrystallized from ethanol to yield 7-(2-(3, 5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one. Yield 75%, m.p. 139-140°C.

#### b. Synthesis of 1-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-3-methyl-1H-pyrazol-5(4H)-one (MK-2)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.0028 mole) and ethylacetoacetate (0.0028 mol) in ethanol (50 ml), was refluxed on water bath for 12 hr. After cooling, the solvent was removed under reduced pressure and the separated solid was recrystallized from ethanol to yield 7-(2-(3, 5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one. Yield 72%, m.p. 122-123°C.

#### c. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (MK-3)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.004 mole) and Isatin (0.004 mole) in glacial acetic acid (20 ml) was heated under reflux temperature for 12 hr. The reaction mixture was cooled, poured into crushed ice and the separated solid was filtered off and recrystallized from DMF to yield 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide. Yield 80%, m.p. 255-256 °C.

#### d. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(1,3-dioxoisindolin-2-yl) acetamide (MK-4)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.005mole) and phthalic anhydride (0.005mole) in 40 ml glacial acetic acid was refluxed for 12 hr. The reaction mixture was cooled then poured in to crushed ice. The separated solid product was filtered off, washed with water and recrystallized from ethanol to yield 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(1, 3-dioxoisindolin-2-yl) acetamide. Yield 79%, m.p. 240-241°C.

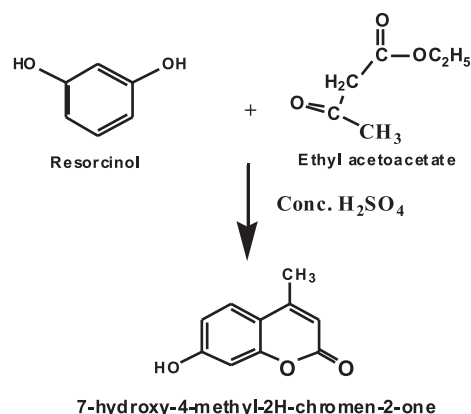
#### e. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)acetamide (MK-5)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.005 mole) and Maleic anhydride (0.005 mole) in 40 ml glacial acetic acid was refluxed for 12 hr. The reaction mixture was cooled then poured in to crushed ice. The separated solid product was filtered off, washed with water and recrystallized from ethanol to yield 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)acetamide. Yield 62%, m.p. 221-222°C.

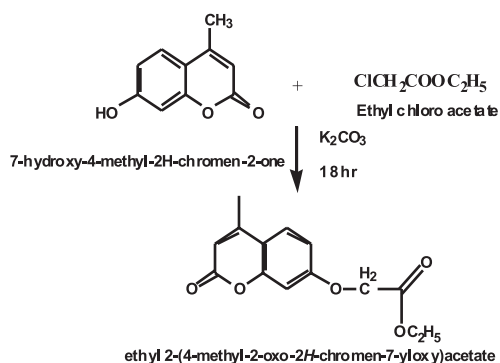
#### f. Synthesis of 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxopyrrolidin-1-yl)acetamide (MK-6)

A mixture of compound 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide (0.005 mole) and Succinic anhydride (0.005 mole) in 40 ml glacial acetic acid was refluxed for 12 hr. The reaction mixture was cooled then poured in to crushed ice. The separated solid product was filtered off, washed with water and recrystallized from ethanol to yield 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2, 5-dioxopyrrolidin-1-yl) acetamide. Yield 73%, m.p. 230-231°C.

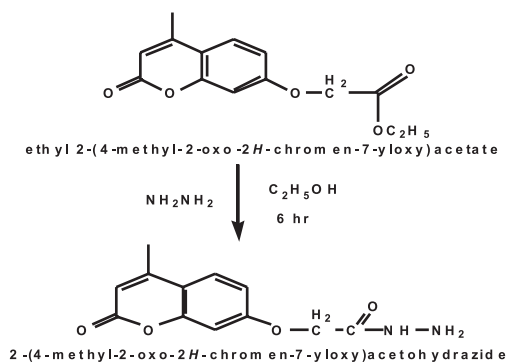
#### STEP 1



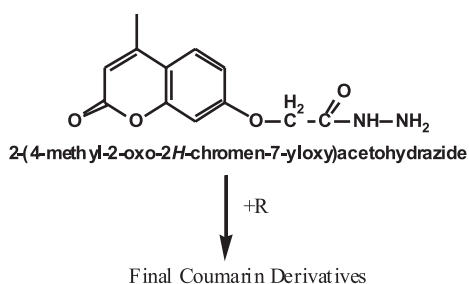
#### STEP 2



STEP 3



STEP 4

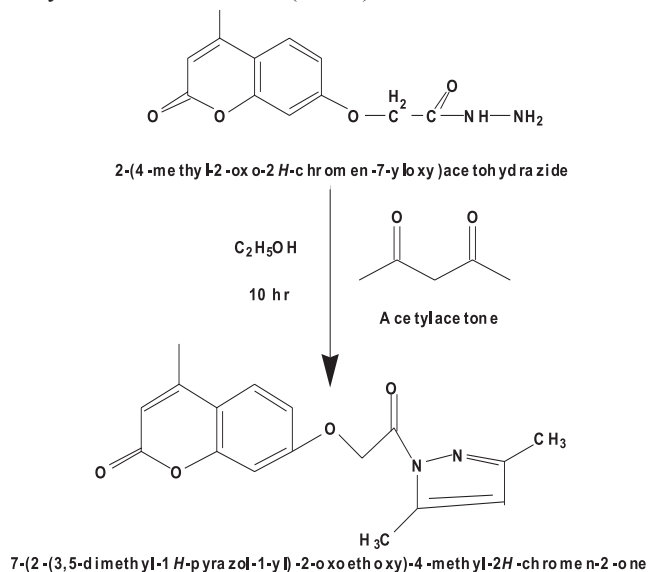


Where R is-

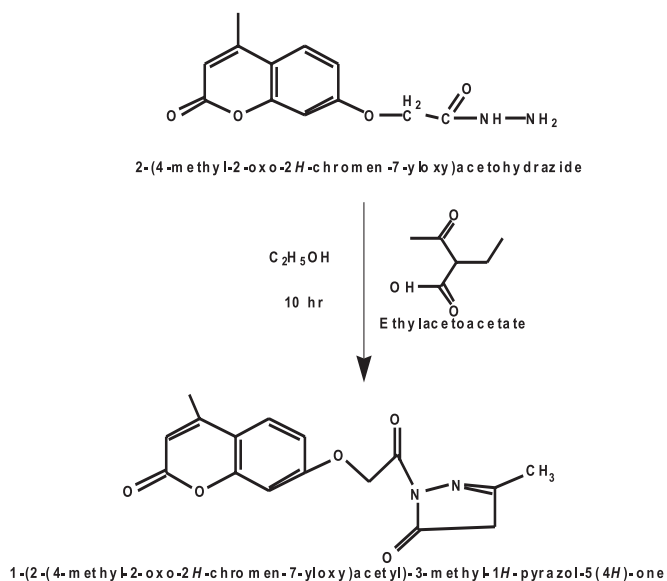
1. Acetyl acetone
2. Ethyl acetoacetate
3. Isatin
4. Phthalic anhydride
5. Maleic anhydride
6. Succinic anhydride

Synthesis of various novel coumarin derivatives

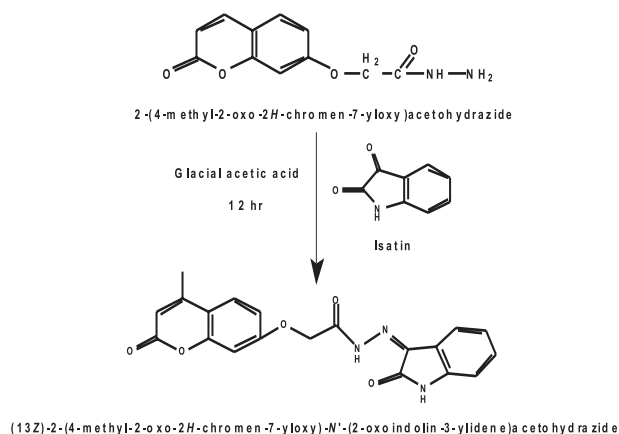
(a) 7-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy)-4-methyl-2H-chromen-2-one (MK-1)



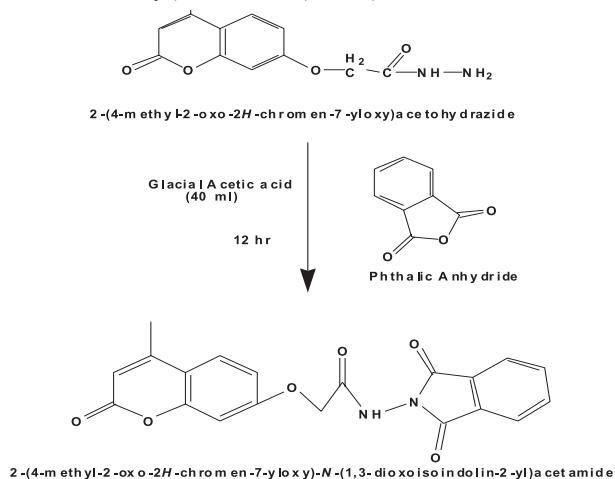
(b) 1-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-3-methyl-1H-pyrazol-5(4H)-one (MK-2)



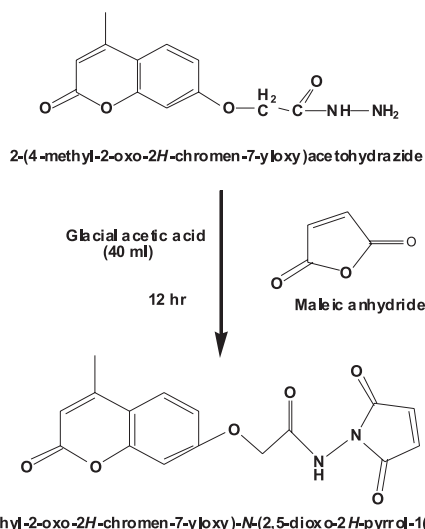
(c) (13Z)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (MK-3)



(d) 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(1,3-dioxisoindolin-2-yl)acetamide (MK-4)



(e) 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)acetamide (MK-5)



(f) 2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-N-(2,5-dioxopyrrolidin-1-yl)acetamide (MK-6)

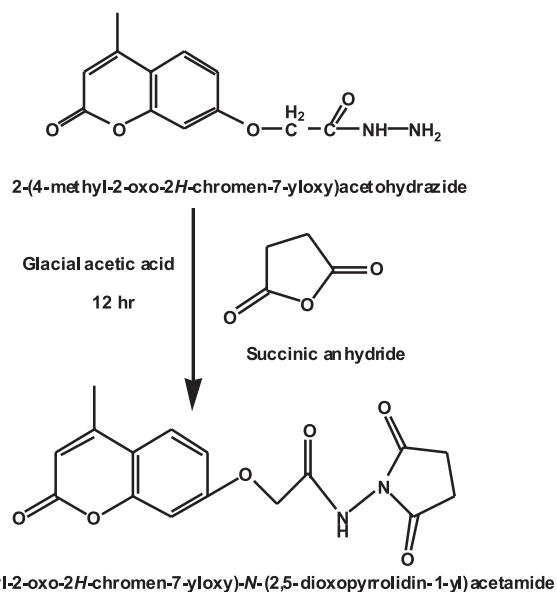


Fig. 1. Synthetic scheme of various novel derivatives of 7-Hydroxy-4-Methyl Coumarin

Table 1. Physical constants of some novel derivatives of 7-hydroxy-4-methyl coumarin

S.No	Compound	Molecular formula (M.wt.)	Yield (%) Color	M.P. °C (Solvent of recrystallization)	R <sub>f</sub> value
(a) 1	MK-1	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> (312.32)	75% Brownish	139-140°C (Ethanol)	0.50
(b) 2	MK-2	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub> (314.29)	72% White	122-123°C (Ethanol)	0.78
(c) 3	MK-3	C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>5</sub> (377.35)	80% Yellowish	255-256°C (DMF)	0.81
(d) 4	MK-4	C <sub>20</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> (378.33)	79% White	240-241°C (Ethanol)	0.79
(e) 5	MK-5	C <sub>16</sub> H <sub>12</sub> N <sub>2</sub> O <sub>6</sub> (328.28)	62% White	221-222°C (Ethanol)	0.43
(f) 6	MK-6	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> (330.29)	73% White	230-231°C (Ethanol)	0.80

Table 2. IR\* Spectrum analysis of synthesized compounds

MK-1		MK-2		MK-3	
v (cm <sup>-1</sup> )	Functional Group Assignment	v (cm <sup>-1</sup> )	Functional Group Assignment	v (cm <sup>-1</sup> )	Functional Group Assignment
3412.2	N-H str. In 2 <sup>o</sup> amides	3411.1	N-H str. In 2 <sup>o</sup> amides	3349.5	N-H str. In 2 <sup>o</sup> amides
2972.3	Aromatic C-H str.	3034.1	Aromatic C-H str.	3065.4	Aromatic C-H str.
2856.7	C-H str. in methylene group	2849.9	C-H str. in methylene group	2918.4	C-H str. in methylene group
1683.8	C=O str. in ketone	1719.6	C=O str. in ketone	1653.5	C=O str. in ketone
1615.7	C=O str. in amide	1624.1	C=O str. in amide	1623.1	C=O str. in amide
1509.3	C=C str. in aromatic	1591.3	C=C str. in aromatic	1591.3	C=C str. in aromatic
1397.2	C-H def. in methylene group	1397.2	C-H def. in methylene group	1387.8	C-H def. in methylene group
1132.0	C-O str. in C-O-C	1080.1	C-O str. in C-O-C	1078.2	C-O str. in C-O-C
3188.1	N-N str.	3227.9	N-N str.	3254.0	N-N str.
944.5	Aromatic C-H def.	890.1	Aromatic C-H def.	832.3	Aromatic C-H def.

1415.4	C-N str.in amide	1430.2	C-N str.in amide	1387.8	C-N str.in amide
2395.9	C=N str.	743.5	C-H def. in aromatic mono substituted in benzene.	2210.5	C=N str.
751.4	C-H def. in aromatic				

\* IR (KBr)  $\text{cm}^{-1}$

MK-4		MK-5		MK-6	
$\nu(\text{cm}^{-1})$	Functional Group Assignment	$\nu(\text{cm}^{-1})$	Functional Group Assignment	$\nu(\text{cm}^{-1})$	Functional Group Assignment
3402.5	N-H str. In 2 <sup>o</sup> amides	3377.5	N-H str. In 2 <sup>o</sup> amides	3362.0	N-H str. In 2 <sup>o</sup> amides
3098.7	Aromatic C-H str.	3071.4	Aromatic C-H str.	3036.9	Aromatic C-H str.
2914.5	C-H str. in methylene group	2913.3	C-H str. in methylene group	2915.0	C-H str. in methylene group
1654.0	C=O str. in ketone	1706.3	C=O str. in ketone	2846.0	C-O str. in O-CH <sub>3</sub>
1613.5	C=O str. in amide	1621.6	C=O str. in amide	1622.6	C=O str. in amide
1558.5	C=C str. in aromatic	1525.4	C=C str. in aromatic	1558.5	C=C str. in aromatic
1388.7	C-H def. in methylene group	1364.9	C-H def. in methylene group	1388.7	C-H def. in methylene group
1071.4	C-O str. in C-O-C	1076.5	C-O str. in C-O-C	1078.5	C-O str. in C-O-C
3297.4	N-N str.	3314.4	N-N str.	3312.6	N-N str.
838.1	Aromatic C-H def.	806.2	Aromatic C-H def.	3535.9	O-H str.
1423.5	C-N str.in amide	1148.8	C-N str. aliphatic amines	1388.3	C-N str.in amide
2354.2	C=N str.	1364.9	C-N str. in aromatic amines	2354.2	C=N str.
701.1	C-H def. in aromatic mono substituted in benzene.	742.6	C-H def. in aromatic mono substituted in benzene.	701.6	C-H (meta) def. in aromatic disubstituted in benzene.
1533.4	N=O str.			803.7	C-H (para) def. in aromatic disubstituted in benzene.

\*IR (KBr)  $\text{cm}^{-1}$

**Table 3.** NMR\* Spectrum analysis of synthesized compounds

MK-1			MK-2			MK-3		
Chemical shift ( $\delta$ ) (ppm)	No. of protons	Inferences	Chemical shift ( $\delta$ ) (ppm)	No. of Protons	Inferences	Chemical shift ( $\delta$ ) (ppm)	No. of protons	Inferences
4.72	2H	-CH <sub>2</sub> attached to carbonyl group	4.81	2H	-CH <sub>2</sub> attached to carbonyl group	4.74	2H	-CH <sub>2</sub> attached to carbonyl group
11.65	1H	-NH attached to CONH	11.82	1H	-NH attached to CONH	11.62	1H	-NH attached to CONH
8.32	1H	-CH attached to phenyl ring	8.39	1H	-CH attached to phenyl ring	8.18	1H	-CH attached to phenyl ring
6.5-7.6	8H	Ar-H	6.9-7.7	7H	Ar-H	6.8-6.98	4H	Ar-H
5.28	1H	-CH close to carbonyl gp.in coumarin ring,	5.37	1H	-CH close to carbonyl gp. in coumarin ring.	5.26	1H	-CH close to carbonyl gp. in coumarin ring.
1.78	3H	-CH in CH <sub>3</sub> attached to coumarin ring	2.38	3H	-CH in CH <sub>3</sub> attached to coumarin ring	2.32	3H	-CH in CH <sub>3</sub> attached to coumarin ring
						3.75	9H	-CH in CH <sub>3</sub> attached to phenyl ring

\*<sup>1</sup>H-NMR (300 MHz, DMSO) (ppm)

MK-4			MK-5			MK-6		
Chemical shift ( $\delta$ ) (ppm)	No. of protons	Inferences	Chemical shift ( $\delta$ ) (ppm)	No. of protons	Inferences	Chemical shift ( $\delta$ ) (ppm)	No. of protons	Inferences
4.63	2H	-CH <sub>2</sub> attached to carbonyl group	4.57	2H	-CH <sub>2</sub> attached to carbonyl group	4.71	2H	-CH <sub>2</sub> attached to carbonyl group
11.73	1H	-NH attached to CONH	11.18	1H	-NH attached to CONH	11.42	1H	-NH attached to CONH
8.18	1H	-CH attached to phenyl ring	7.9	1H	-CH attached to phenyl ring	8.10	1H	-CH attached to phenyl ring
6.7-7.5	7H	Ar-H	6.04-7.47	7H	Ar-H	5.19	1H	-OH group attached to phenyl ring
5.99	1H	-CH close to carbonyl gp. in coumarin ring.	5.05	1H	-CH close to carbonyl gp. in coumarin ring.	3.73	3H	-OCH <sub>3</sub> group attached to phenyl ring
2.18	3H	-CH in CH <sub>3</sub> attached to coumarin ring	2.31	3H	-CH in CH <sub>3</sub> attached to coumarin ring	6.8-7.15	6H	Ar-H
			2.77	6H	-N(CH <sub>3</sub> ) gp. attached to phenyl ring	6.13	1H	-CH close to carbonyl gp. in coumarin ring.
						2.32	3H	-CH in CH <sub>3</sub> attached to coumarin ring

\*1 H-NMR (300 MHz, DMSO) (ppm)

#### 4. ANTIMICROBIAL ACTIVITY

The antibacterial and antifungal testing was performed using the cup diffusion technique [12]. The synthesized compounds, as 1 mg/ml solutions in dimethyl formamide (DMF), were evaluated *in vitro* for activity against *B. subtilis* (NCIM 2439), *E. coli* (NCIM 2831), *A. niger* (NCIM 618) and *C. albican* (NCIM 3557) by the cup diffusion technique. Compounds showing inhibitory zones of at least 18 mm were considered active and were further evaluated for their minimal inhibitory concentration (MIC) using the two-fold serial dilution method [13]. Ampicillin was used as a standard antibacterial agent and fluconazole was used as a standard antifungal agent. Dimethyl formamide was used as a control. Sterile nutrient agar was inoculated with the test organisms (each 100 ml of the medium received 1 ml of 24 h broth culture), and then seeded agar was poured into sterile petridishes. Cups (8 mm in diameter) were cut in the agar, and each cup received 0.1 ml of the test compound solution. The plates were then incubated at 37°C for 24 h. The activities were estimated as zones of inhibition in mm diameter (Tables 4-7). An

Ampicillin solution (5µg/ml) was used as reference standards. DMF did not show any inhibition zones.

**Table 4.** Antibacterial activity data of synthesized compounds against *E. coli*

Standard and Test compound	Zone of inhibition in mm*	
	<b>E.coli (ESS 2231)</b>	
	100µg	50µg
Control	-	-
ampicillin	25	22
M-1	13	12
M-2	15	13
M-3	16	15
M-4	17	14
M-5	13	11
M-6	16	15

\*[Zone of inhibition (in mm) against the microbes by the compounds MK 1-MK 6]\*

**Table 5.** Antibacterial activity data of synthesized compounds against *B. Subtilis*

Standard and Test compound	Zone of inhibition in mm*	
	<i>B. Subtilis</i> (ACC-132)	
	100 µg	50 µg
Control	-	-
Ampicillin	26	25
M-1	15	14
M-2	17	16
M-3	16	14
M-4	18	16
M-5	13	11
M-6	15	13

\*[Zone of inhibition (in mm) against the microbes by the compounds MK 1-MK 6]\*

**Table 6.** Antifungal activity data of synthesized compounds against *A. Niger*

Standard and Test compound	Zone of inhibition in mm*	
	<i>Aspergillus niger</i>	
	100µg	50µg
Control	-	-
fluconazole	25	23
M-1	14	12
M-2	15	14
M-3	16	14
M-4	17	16
M-5	12	11
M-6	18	17

\*[Zone of inhibition (in mm) against the microbes by the compounds MK 1-MK 6]\*

**Table 7.** Antifungal activity data of synthesized compounds against *C. Albicans*

Standard and Test compound	Zone of inhibition in mm*	
	<i>C. albicans</i>	
	100 µg	50 µg
Control	-	-
fluconazole	22	20
M-1	14	12
M-2	16	14
M-3	17	14
M-4	17	15
M-5	12	10
M-6	17	18

\*[Zone of inhibition (in mm) against the microbes by the compounds MK 1-MK 6]\*

## 5. RESULTS AND DISCUSSION

Six different derivatives of 7-hydroxy-4-methyl coumarin were synthesized. The Synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one was done by reacting H<sub>2</sub>SO<sub>4</sub> with resorcinol and ethylacetoacetate. The synthesis of ethyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate was accomplished by reacting 7-hydroxy-4-methyl coumarin and ethylchloroacetate in the presence of potassium carbonate in acetone. The ethyl 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetate was reacted with hydrazine hydrate in ethanol to afford 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide. Then 2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetohydrazide was considered as the key intermediate for the synthesis of several series off new compounds viz, MK-1, MK-2, MK-3, MK-4, MK-5 & MK-6. Yields obtained from 62% to 80%. The structures of these compounds were established on the basis of IR spectral analysis and <sup>1</sup>H-NMR spectral studies. The purity and homogeneity of all compounds were confirmed by their melting point and TLC. All the above result positively confirmed the formation of the synthesized compounds and hence correctness of the anticipated structures drawn for synthesized compounds. All the synthesized compounds have been tested for antimicrobial by Paper-disk-plate technique. The compounds showed mild to good antimicrobial activity.

## 6. CONCLUSION

A series of 7-Hydroxy-4-Methyl Coumarin derivatives viz, MK-1, MK-2, MK-3, MK-4, MK-5 & MK-6 were synthesized according to scheme and the identity of the compounds were confirmed on the basis of their sharp melting point, TLC, IR and <sup>1</sup>H-NMR data. All the synthesized compounds MK-1, MK-2, MK-3, MK-4, MK-5 & MK-6 showed significant activity against both strain as compared to Ampicillin. The compound MK-1 showed maximum zone of inhibition 21mm against *B. subtilis* (MTCC-441) and 20 mm against *E.coli* (ESS 2231). All the synthesized compounds MK-1, MK-2, MK-3, MK-4, MK-5 & MK-6 showed significant activity against both strain as compared to fluconazole. MK-1 showed maximum zone of inhibition 21mm against *A.niger* and 19 mm against *C.albicans*.

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