

One-pot synthesis of coumarin derivatives via microwave assisted Pechmann reaction and biological activity of substituted coumarin derivatives

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Pechmann reaction is mainly used for the synthesis of substituted coumarins as it can be executed with straight forward primary resources and gives coumarin derivatives with excellent yields. In the present work coumarin derivatives have been synthesized by condensation of β -ketoesters and substituted phenols under microwave irradiation in solvent free condition in which oxalic acid is used as catalyst. Oxalic acid is found to be a potential environment friendly catalyst for synthesis of coumarins. The new method of synthesis described here offers a number of advantages of being convenient, safe, gentle, shorter reaction time, high yield, and cleanness as compared to the conventional methods. The synthesized compounds have been systematically characterized by IR and MS analyses. All products are examined for antimicrobial activity against the Gram positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram negative (*Escherichia coli* and *Salmonella typhi*) bacteria and antifungal activity against two fungal species (*Aspergillus sp.* and *Fusarium graminearum*). All the compounds inhibited the growth of bacteria as well as fungi.

Keywords: Antimicrobial, Antifungal, Coumarins, One-pot Microwave irradiation, Oxalic acid, Pechmann condensation.

Coumarins are found under class benzopyrones of heterocyclic compounds and most of natural products contain this heterocyclic nucleus. Coumarin is a compound with comprehensive range of biological, pharmacological and various physiological activities. Coumarins are used as anticoagulant¹⁻³, antibacterial^{4,5}, antioxidative⁶, antiviral^{7,8}, antitumor⁹⁻¹², bacteriocidal¹³, fungicidal¹⁴, anti-inflammatory and anti-HIV agents^{15(a,b),16}. For the preparation of coumarins various methods for example von Pechmann condensation¹⁷, Knoevenagel condensation¹⁸, Wittig reaction¹⁹, Perkin reaction²⁰, Reformatsky reaction^{21(a-d)}, and Flash vacuum pyrolysis^{22(a,b)} are used. Among all these methods Pechmann reaction seems to be quite facile and efficient method which requires acidic catalysts. In various reported methods the catalysts used have many disadvantage such as moisture sensitive, too toxic to the atmosphere, rigorous experimental process and expensive. In order to synthesize coumarins through Pechmann reaction a relevant and moderate catalyst is desirable. Moreover the catalyst should be recyclable which can be consequently used in the further reactions to make the process environment friendly. Using simple filtration method

water soluble catalyst is separated from insoluble products. In our work we used oxalic acid (as catalyst) for the synthesis of coumarins through Pechmann reaction. Biological evaluation of substituted coumarin derivatives was also done by performing microbiological bioassay. The biological activity was determined against bacteria and fungi. In this work, our purpose of research is to propose innovative and suitable ways of synthesizing coumarin derivatives and evaluation of their biological activities.

Experimental Section

Materials

All chemicals used were of analytical grade. For biological activity cultures were used from MTCC (Microbial Type Culture Collection, Chandigarh) and media used are of Hi-media and Merck and instruments are of Remi. *Streptomycin* and *Amphotericin B* were used as standard drugs. The chromatoplates were prepared by using silica gel G. IR spectroscopic analysis was done by using Shimadzu Fourier Transform Infra Red Spectrophotometer (KBr in cm^{-1}) (UGC-DAE

Consortium for Scientific Research Indore, M.P.) and Mass spectra were recorded through a Shimadzu GCMS-QP1000 EX spectrometer (IISER, Bhopal, M.P.). Microwave irradiation was carried out in domestic microwave oven (Bajaj 700 W, 2450 MHz).

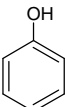
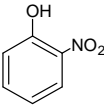
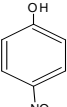
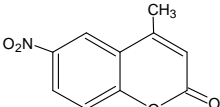
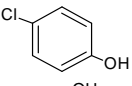
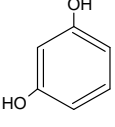
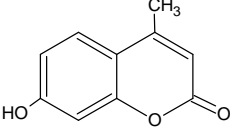
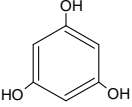
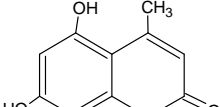
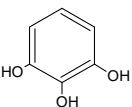
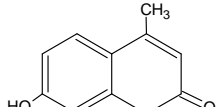
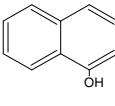
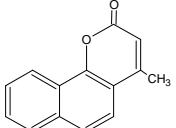
Method

General method used for the synthesis of coumarin derivatives:

Mixture of substituted phenols (10 mmol) and methyl acetoacetate (β - ketoester) (10 mmol) with oxalic acid (catalyst) (1 gram) were stirred at room temperature in the absence of solvent and performed inside a domestic microwave oven for an appropriate time (5-10 min) (Scheme 1). The development of the reaction was checked by TLC. After finishing point of the synthetic reaction, the resultant crude output was

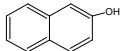
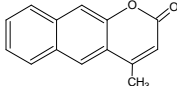
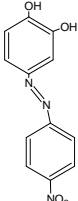
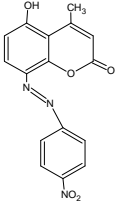
filtered. The filtrate was dissolved in hot ethanol-water. The product dissolved in ethanol leaving the impurities floating in the liquid. Ethanol was evaporated to obtain purified product in the form of crystals. Synthesized coumarin derivatives were evaluated for physical properties such as melting point and TLC. The melting points of the synthesized derivatives were determined through open capillary tube method using paraffin bath and are uncorrected. All the synthesized derivatives were subjected to TLC analysis on silica gel G plates using benzene-acetone (5:5) as developer detected by iodine vapors (Table 1). The MP, IR and MASS spectroscopic techniques of the obtained products were found to be the identical with those reported in the literatures^{23(a,b), 24(a,b)}.

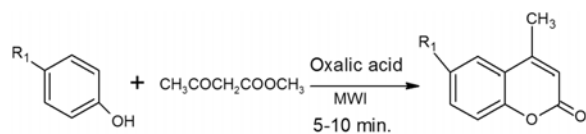
Table 1 — Synthesis of coumarins from substituted phenols and methyl acetoacetate in catalytic amount of oxalic acid via Pechmann reaction.

Entry	Phenol	Product	Reaction temp. (°C)	Reaction time (Min.)	Yield (%)	m.p. (°C)	Rf value
1		Not obtained	140-170	10-15	—	—	—
2		Not obtained	140-170	10-12	—	—	—
3			140-170	10	85	135-140	0.86
4		Not obtained	140-170	10-12	—	—	—
5			140-170	7	90	180-182	0.62
6			140-170	6	92	295-300	0.55
7			140-170	5	84	236-240	0.60
8			140-170	12	80	150-155	0.87

(Contd.)

Table 1 — Synthesis of coumarins from substituted phenols and methyl acetoacetate in catalytic amount of oxalic acid via Pechmann reaction.

Entry	Phenol	Product	Reaction Temp. (°C)	Reaction Time (Min.)	Yield (%)	MP (°C)	Rf value
9			140-170	10	85	179-182	0.86
10			140-170	5	95	185-190	0.44



Scheme 1 — Pechmann condensation

To compare the efficiency of the catalyst the reaction was examined with several catalysts in solvent free condition under microwave irradiation. Thus a mixture of various phenols and ethyl acetoacetate was heated under microwave irradiation with different catalysts. The results are listed under Table 2, as it is clear from the results that lower yields and longer reaction time were observed with different catalysts (Montmorillonite K 10²⁵, Amberlyst 15 dry²⁶ and Silica ball). The oxalic acid catalyst was easily recovered by simple filtration and was reused without significant loss of activity as compare to other catalyst.

To compare the efficiency of the catalyst with temperature, the reaction was executed at different temperatures under microwave irradiation. Thus the mixture of resorsinol, ethyl acetoacetate and oxalic acid was heated under microwave irradiation at four different temperatures. The results are shown in Table 3. As it is clear from the result that as the power increases there is increases in yields but no significant change at high power and similar tendency was shown in the synthesis of other coumarins.

Determination of Antimicrobial Activity of Substituted Coumarins:

Evaluation of antimicrobial activity of substituted coumarins was done by performing Cup diffusion method²⁷. The biological activity was determined against bacteria and fungi.

Determination of Antibacterial Activity:

Test organism

For antimicrobial activity two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*)

Table 2 — Comparison of different catalysts used for the synthesis of various substituted coumarin.

Catalyst	Reaction time (min.)	Yield (%)	Recovery of catalyst
Oxalic acid	5-10	90	Simple filtration
Montmorillonite K 10	10-20	67	Separation by organic solvent
Amberlyst 15 dry	10-15	70	Separation by organic solvent
Silica ball	10-20	60	Separation by organic solvent

Table 3 — Comparison of different reaction temperature for the synthesis of various substituted coumarin.

Reaction temp. (°C)	Yield (%)
80-110	55
110-140	68
140-170	90
170-200	60

and two Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi*) were used. The cultures used for the experiment were 24 h old.

Samples and reference standard

The synthesized and reference compounds (*Streptomycin*) were dissolved in absolute alcohol having concentration of 0.1 mg/mL.

Bioassay

The bioassay was performed by Cup diffusion method. The test organism was inoculated in nutrient agar and poured in respectively labeled and sterilized petri plates. The medium was allowed to solidify. Wells were punched in solid nutrient agar medium with 8 mm sterilized metallic borer. The samples and reference compound (80 µL) were loaded in respectively labeled wells. The plates were kept in refrigerator for 20 min at 4°C to allow diffusion of the samples. The plates were transferred to incubator and incubated overnight at 37°C. After 24 h of incubation the zone of inhibition was measured to the nearest millimeter.

Determination of antifungal activity:**Test organism**

Two fungal species (*Aspergillus sp.* and *Fusarium graminearum*) were used for determination of antifungal activity. Spore suspension was used as inoculum for the bioassay. Spore suspension was prepared from the test fungal strains grown on Rose Bengal Agar medium.

Samples and reference standard

The synthesized and reference compounds (*Amphotericin B*) were dissolved in absolute alcohol and the concentration of each compound was 0.1mg/1 mL.

Bioassay

For the bioassay of antifungal activity Potato Dextrose Agar medium was used. Potato Dextrose Agar plates (PDA) were prepared by adding 0.1 mL of spore suspension in 20 mL of molten PDA and the medium was poured in petri plates in aseptic conditions. The medium was allowed to solidify. After solidification wells were punched on these plates with 8 mm sterilized metallic borers. The wells were properly labeled on the undersides of the plates. Respectively labeled wells were loaded with 80 μ L (0.08 mL) of the samples and reference compound. The plates were placed in refrigerator for 20 min to allow diffusion of samples into the medium. The plates were incubated at 28°C for 48-72 h and observed in every 24 h. Zone of inhibition developed due to the effect of samples and reference solution were measured and expressed to the nearest millimetre.

Results and Discussion

The oxalic acid implemented the Pechmann reaction within gentle synthetic environment. In view of current push in catalytic process oxalic acid for Pechmann condensation of substituted phenols with methyl acetoacetate by microwave irradiation, this modification has resulted in excellent yield and high

purity. Oxalic acid is easily recovered by simple filtration as compared to other catalysts that we used in our experiments. The recovery of other catalysts is done by using of organic solvents which is hazardous to the environment. Our method of one-pot synthesis not only sustains the ingenuity of the Pechmann reaction but also generates excess yields of the coumarin derivatives and to a great extent reduces environmental pollution. We have also performed the experiment at different temperatures which shows that as the temperature increases the yield increase and at high temperature no significant change was observed. Spectral analysis of products supported the success of the MW-mediated condensation reaction.

Spectral data of coumarin derivatives: 4-Methyl-6-nitro coumarin (Entry 3): IR (ν in cm^{-1}): 3243.35 (-OHstr.)1515, 1475, 1456 (aromatic ring), 1685 (C=O), 1596, 1386 (-NO₂), 1274, 1240, 1149 (C-O), M⁺(205.1) (Fig. 1).

7-Hydroxy-4-methyl coumarin (Entry 5): IR (ν in cm^{-1}): 3313 (-OH str.), 1513, 1479 (aromatic ring), 1673 (C=O), 1228, 1186, 1062 (C-O), M⁺(177.1) (Fig. 2).

5,7-Dihydroxy-4-methyl coumarin (Entry 6): IR (ν in cm^{-1}): 3066 (-OHstr.), 1560, 1486 (aromatic ring), 1718 (C=O), 1216, 1099, 1031 (C-O), M⁺(193.1) (Fig. 3).

7,8-Dihydroxy-4-methylcoumarin (Entry 7): IR(ν in cm^{-1}): 686, 754, 1029, 1174, 1228 (C-O), 1398, 1452, 1486, 1562, (aromatic ring), 1710, (C=O) (Fig. 4), M⁺(191.3).

4-Methyl-2-H benzo coumarin (Entry 8): IR (ν in cm^{-1}): 3155, 1697, (C=O), 1521, 1448 (aromatic ring), 1340, 1159, 1072 (C-O), M⁺(211.1) (Fig. 5).

4-Methyl-2-H benzo coumarin (Entry 9): IR (ν in cm^{-1}): 1685 (C=O), 1589, 1550, 1473 (aromatic ring), 1159, 1097 (C-O), M⁺(211.1) (Fig. 6).

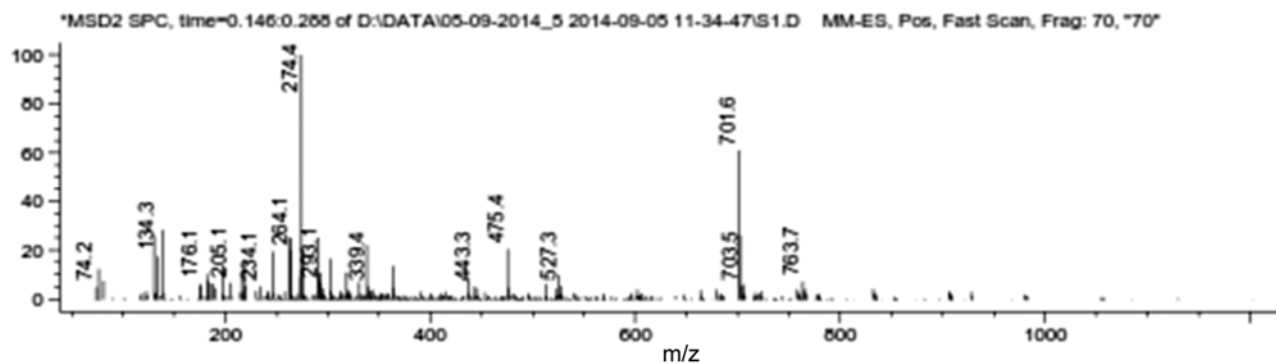


Fig. 1— Mass Spectra of 4-methyl-6-nitro coumarin

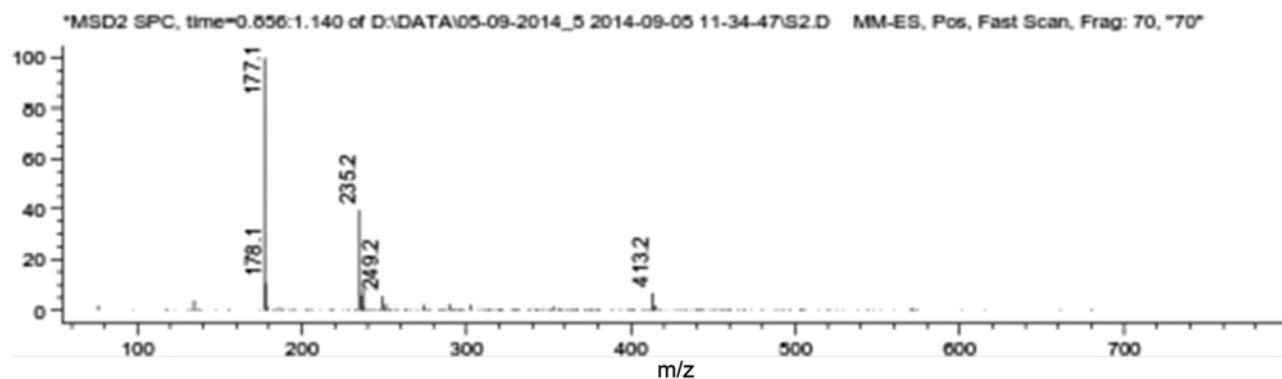


Fig. 2 — Mass Spectra of 7-hydroxy-4-methyl coumarin

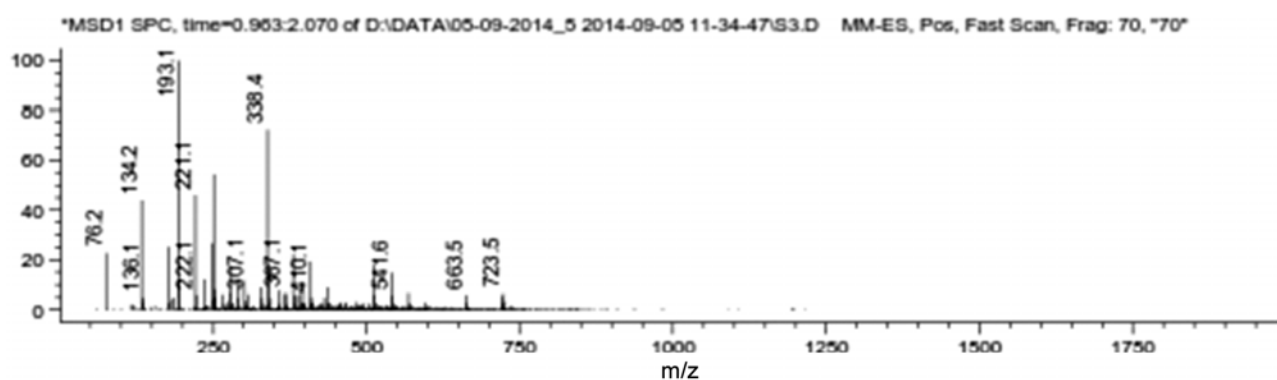


Fig. 3 — Mass Spectra of 5,7-dihydroxy-4-methyl coumarin

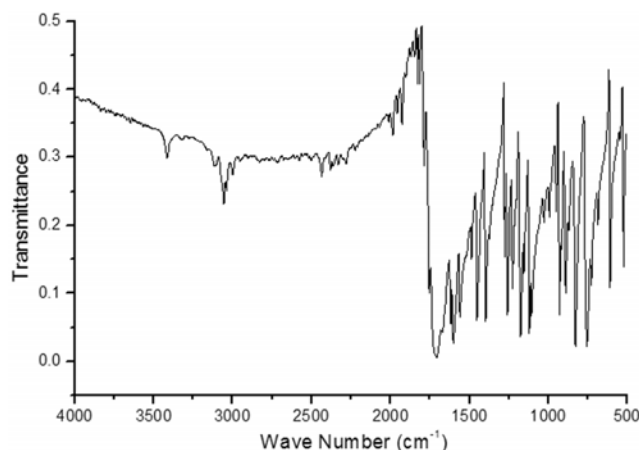


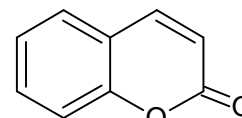
Fig. 4 — IR Spectra of 7,8-dihydroxy-4-methyl coumarin

4-(p-Nitro phenyl azo)-5-hydroxy-4-methyl coumarin (Entry 10): IR (ν in cm^{-1}): 3482 (NH), 3102 (-OH str.), 1679 (C=O), 1585, 1511 (aromatic ring), 1456 (N=N), 1213, 1186, 1159 (C-N) (Fig. 7), $M^+(325.5)$ (Fig. 8).

Biological activity

Coumarins are well known for biological activity but substitution by the various groups enhances the activity of parent coumarin. In our work all synthesized coumarin compounds were screened for

their *in-vitro* antibacterial and antifungal activity for four strains of bacteria and two strains of fungi respectively.



Structure of parent coumarin

All substituted coumarins show better activity than parent coumarin. The antimicrobial and antifungal screening results of the synthesized compounds are shown in Table 4. The Table 4 depicts that all the tested compounds are active against *Salmonella typhi*, *Staphylococcus aureus*, *Bacillus subtilis* and *Fusarium graminearum* except compound 1 and 3 which exhibited moderate activities. Compound 2, 4, 5, 6, 7 and 8 are more active while all other compounds were moderately active. Interesting results were observed for compound 2, 4, 5, 6, 7 and 8 against *Escherichia Coli*, *Fusarium graminearum* and *Aspergillus sp.* which were more active than the standard drug *Streptomycin* and *Amphotericin B*. The Table-4 depicts that all the tested compounds showed more or less pronounced antibacterial activity affecting both Gram-negative and

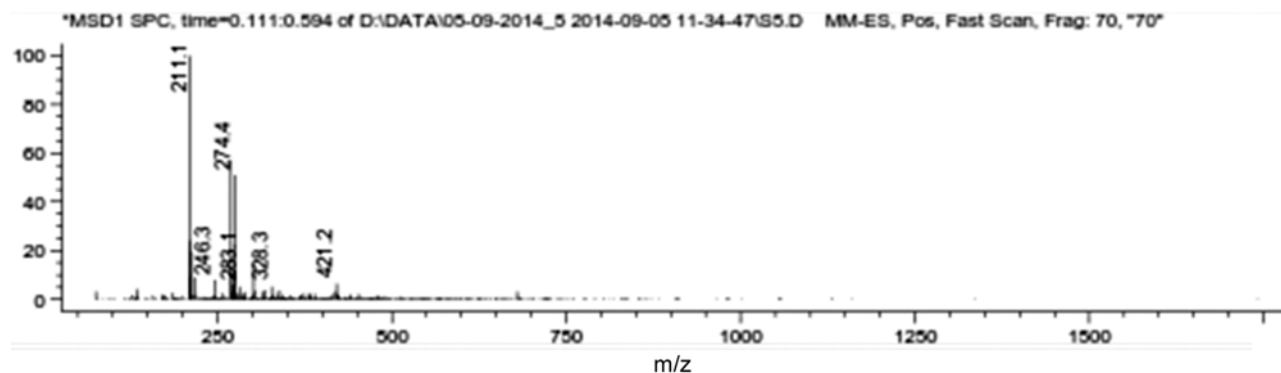


Fig. 5 — Mass Spectra of 4-methyl-2-benzo coumarin

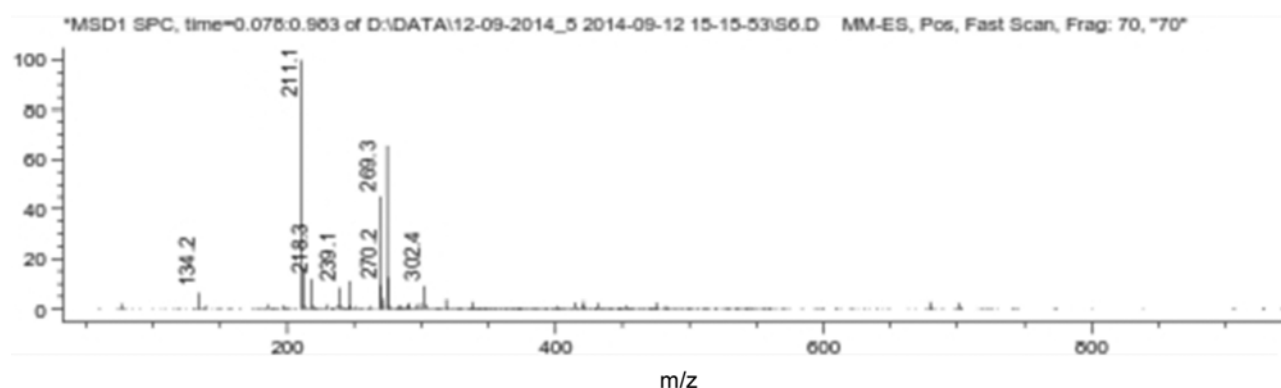


Fig. 6 — Mass Spectra of 4-methyl-2-benzo coumarin

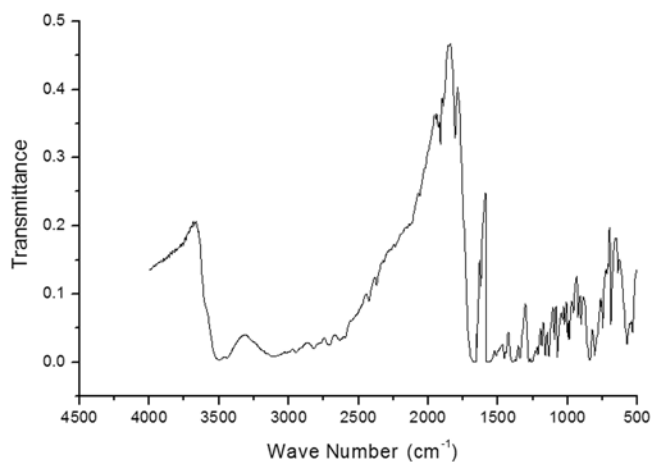


Fig. 7 — IR Spectra of 4-(p-nitro phenyl azo)-5-hydroxy-4-methyl coumarin

Gram-positive microorganism and antifungal activity. Some results show significant zone of inhibition as compared with standard drugs. Absolute alcohol which was used as control did not exhibit any activity as shown in Table 4.

Parent coumarin exhibited less activity as compared to standard drug against *Bacillus subtilis* but compound 7 exhibited better activity against it.

Against *Salmonella typhi* parent coumarin and compound 3 exhibited lesser activity and other synthesized coumarins show moderate activity as compared to standard drug.

Parent coumarin is inactive against *Escherichia Coli* and other compounds show comparable activity as compared to streptomycin but compound 8 exhibited better activity in the series.

Parent coumarin and all the synthesized coumarins inhibit the growth of *Staphylococcus aureus* and compound 8 exhibited highest inhibition.

Parent coumarin and compound 3 are inactive against *Aspergillus sp.* but compound 2 (4-methyl-6-nitro coumarin), compound 6 (4-methyl-2-H benzo coumarin) and compound 7 (4-methyl-2-H benzo coumarin) exhibited greater activity (>40) than standard *Amphotericin B*.

Parent coumarin and all the substituted coumarins show activity against *Fusarium graminearum* but compound 2 (4-methyl-6-nitro coumarin) exhibited highest activity (>60) and compound 4 (7,8-dihydroxy-4-methyl coumarin), compound 6 and 7 (4-methyl-2-H benzo coumarin) exhibited more activity than standard drug.

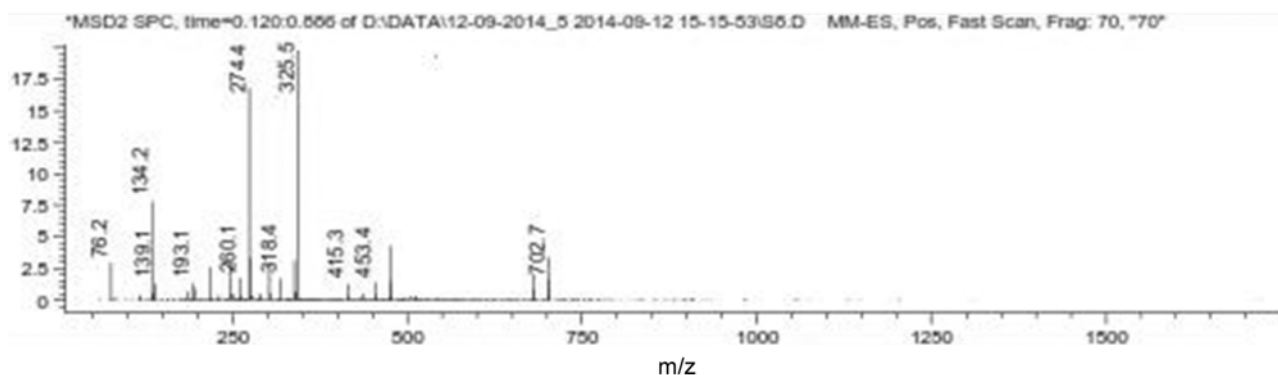


Fig. 8 — Mass Spectra of 4-(p-nitro phenyl azo)-5-hydroxy-4-methyl coumarin

Table 4 — Biological activity of the substituted coumarin derivatives.

Compound No.	Name of Compound	Zone of inhibition (in mm)					
		Gram Negative bacteria		Gram Positive bacteria		Fungi	
		<i>Escherichia Coli</i>	<i>Salmonella typhi</i>	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Fusarium graminearum</i>	<i>Aspergillus Sp.</i>
1.	Coumarin	No Activity	12	10	17	20	No Activity
2.	4-methyl-6-nitro coumarin	18	22	18	20	>60	>40
3.	5,7-dihydroxy-4-methyl coumarin	No Activity	11	13	13	19	No Activity
4.	7,8-dihydroxy-4-methylcoumarin	23	17	18	15	>40	14
5.	7-hydroxy-4-methyl coumarin	22	26	21	23	31	30
6.	4-methyl-2-H benzo coumarin	22	23	22	16	>40	40
7.	4-methyl-2-H benzo coumarin	20	25	26	26	60	>40
8.	4-(p-nitro phenyl azo)-5-hydroxy-4-methyl coumarin	24	25	33	19	23	11
9.	Standard reference drugs (<i>Streptomycin</i> and <i>Amphotericin B</i>)	19	36	39	32	38	26
10.	Absolute alcohol (control)	No Activity	No Activity	No Activity	No Activity	No Activity	No Activity

Furthermore, it was also noted that coumarin is more active against Gram-positive micro organisms as an antibacterial agent than against Gram-negative as shown in Table-4. Our results are in accordance with the study reported by Simone²⁸, representing high activity against Gram positive bacteria (*Staphylococcus aureus*). The reason for difference in the sensitivity between Gram-positive and Gram-negative bacteria could be due to morphological differences between these micro-organisms as Gram-negative bacteria possess additional lipid layer²⁹. Antibacterial activity of Coumarin samples is also stronger than antibacterial activity of Chalcone prepared from 2-hydroxy-1- acetone and 3-acetylcoumarin³⁰. The remarkable biological activity showed that coumarin can be used as an antibacterial and antifungal agent in to treat bacterial and fungal infections. The antifungal activity of coumarins is higher than its antibacterial activity. This result opens up ways for further studies for application of these

compounds as antifungal agents in various preparations after going through the toxicity studies.

Because of its biochemical efficacy coumarins were introduced for use in clinical medicine. They can be evaluated for the remedies of diverse clinical conditions. The results here are encouraging for future work in the field of derivatisation and finding new therapeutic agents.

Conclusion

An effective, suitable, intense and environment friendly procedure for preparation of substituted coumarin derivatives has been used. The structures of the synthesized compounds are interpreted on the basis of IR and Mass spectral data. The current effort is to emphasize on the synthesis of coumarin derivatives by the eco-friendly method which are also examined for the biological activity. Benzopyran nucleus is present as an active component in several standard drugs to increase the

biological properties. All the synthesized compounds exhibited higher activity as compared to standard drugs against all the tested bacterial and fungal cultures which leads a strong motivation for further research in this area. The derivatives specially 4-methyl-6-nitro coumarin, 7,8-dihydroxy-4-methyl coumarin and 4-methyl-2-H benzo coumarin inhibit the fungal strains to a great extent and can be used for restricting the spread of fungal infections after checking it's toxicity. Our derivatives such as 7,8-dihydroxy-4-methyl coumarin, 4-methyl-2-H benzo coumarin and 4-(p-nitro phenyl azo)-5-hydroxy-4-methyl coumarin can also be put to use against drug resistant organisms because they are more active than the standard drug used for the assay.

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