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$Yb(OTf)_3$ Catalyzed Synthesis, Antimicrobial and Insecticidal activity of some Biscoumarins

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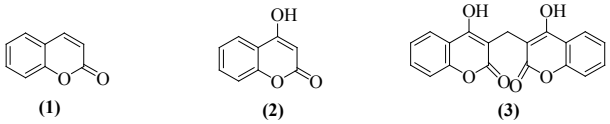
Abstract: In the present study, we report $Yb(OTf)_3$ catalyzed synthesis of biscoumarins by pseudo three-component reaction of aldehyde and 4-hydroxycoumarin. The synthesized biscoumarins were evaluated for antimicrobial and insecticidal activity. Results of antimicrobial activity were found to be moderate to good in terms of zones of inhibition and MIC values against *E. coli, P. vulgaris* and *S. aureus.* The compounds were inactive against the used fungal strains except **B4** in case of *Penicillium.* Insecticidal activity of the biscoumarins **B-1**, **B-3**, **B-5** and **B-11** was found to be good exhibiting 70-75% mortality effect on *Callosobruchus maculatus.*

Keywords: $Yb(OTf)_3$, Biscoumarins, Antimicrobial, Insecticidal

Introduction:

2*H*-Chromen-2-one or benzopyran-2-one **(1)**; commonly known as coumarin belongs to benzopyrone class of heterocyclic compounds. Coumarins constitute a biodynamic and significant class of naturally occurring compounds in the realm of natural products and synthetic organic chemistry [1].

4-Hydroxycoumarin **(2)** is a vitamin K antagonist [2]. Dicoumarol **(3)** is a naturally occurring anticoagulant, inhibitor of reductases and vitamin K deplete [3]. It is a natural compound of plant and fungal origin.

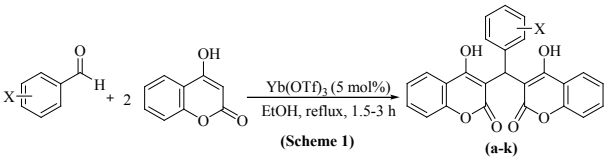


(1) (2) (3)

Coumarin based heterocyclic compounds are well renowned for therapeutic potential as well as many biological activities including

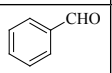
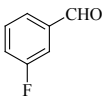
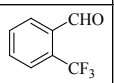
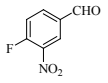
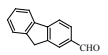
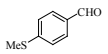
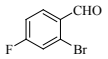
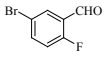
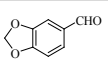
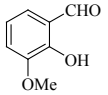
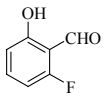
vitamin K antagonists [4], pesticides [5], anti-inflammatory agents [6], anti-coagulants [7] etc. A wide range of biological applications of coumarin based derivatives have intrigued organic and medicinal chemists to explore as drugs. This fact renders them attractive for derivatization and evaluation as novel therapeutic agents. Thus, coumarin related compounds constitute the significant targets in medicinal and pharmaceutical chemistry.

Rare earth metal triflates act as water tolerant, mild and efficient catalysts which are well established as environmentally benign Lewis acids particularly useful for green chemistry applications; offering functional group tolerance during reactions. Furthermore, the triflates do not lose their acidity even in the presence of Lewis bases containing oxygen, nitrogen, sulfur and phosphorus atoms. Among commonly used lanthanide metal triflates; ytterbium (III) trifluoromethanesulfonate or ytterbium (III) triflate; abbreviated as $Yb(OTf)_3$ is a water tolerant Lewis acid catalyst useful in many synthetic organic reactions. Recently it has been used in Meerwein-Ponndorf-Verley (MPV) reduction [8], Hantzsch reaction [9], thia-Michael addition to α, β-unsaturated ketones [10], Friedel-Crafts acylation [11], synthesis of α-amino phosphonates [12], substituted lactams [13], β-enaminones [14], benzoxanthenes [15] etc. Considering a wide range of biological activities and therapeutic potential of coumarin derivatives; in the present work we have synthesized some biscoumarins by ytterbium triflate catalyzed reaction of various aldehydes with 4-hydroxy coumarin (**Scheme 1**). Furthermore, the synthesized compounds were screened for antibacterial, antifungal and insecticidal activities.



(Scheme 1)

Table 1: Ytterbium triflate catalyzed synthesis of biscoumarins

Sr. No.	Aldehyde	Product	Code	Time (h)	Yield (%)[@]	M. P. (°C)
1		(a)	B1	1.5	83	227-229 [22]
2		(b)	B2	1.5	78	243-245
3		(c)	B3	1.5	74	182-184
4		(d)	B4	2.0	80	173-175
5		(e)	B5	1.5	87	255-257
6		(f)	B6	1.5	90	225-227
7		(g)	B7	3.0	79	178-180
8		(h)	B8	3.0	74	280-282
9		(i)	B9	1.5	85	230-232
10		(j)	B10	3.0	78	272-274
11		(k)	B11	3.0	75	248-250

[@]Reactions were carried on aldehyde (2 mmol) and 4-hydroxycoumarin (4 mmol) in ethanol (5 mL) using $Yb(OTf)_3$ (5 mol%).

Materials and Methods:

Chemicals used were SD fine or Aldrich made. Melting points of the products were recorded in capillaries open at one end on a digital melting point apparatus (Optics Technology). Progress of the reaction was monitored by TLC (70% ethyl acetate: n-hexane). Antimicrobial activity of the synthesized compounds was carried out by using reported methods.

General procedure for the synthesis of biscoumarins:

$Yb(OTf)_3$ (5 mol%) was added to a solution of aldehyde (2 mmol) and 4-hydroxycoumarin (4 mmol) in ethanol (5 mL) and contents were refluxed for the specified time (**Table 1)**. Progress of the reaction was monitored by TLC (70% ethyl acetate: n-hexane). After completion of reaction as indicated by TLC; contents were concentrated under reduced pressure, diluted with water (10 mL) and the precipitated solid was further purified by crystallization with ethanol to afford pure product. The aqueous layer was concentrated in vacuum to give a white crystalline solid as the recovered catalyst which can be recycled.

Spectral data of representative compounds is mentioned below:

3-[(4-Fluoro-3-nitrophenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-4-hydroxy-2H-chromen-2-one] (Entry 4, Table 1): M. P. 173-175 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ ppm 6.19 (s, 1H), 7.15 (d, 1H), 7.36 (d, 5H), 7.6 (t, 2H), 7.8 (d, 1H), 8.0-8.2 (dd, 2H), 11.32 (1H, brs, -OH), 11.70 (1H, brs, -OH), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 35.46, 59.57, 103.48, 115.93, 117.73, 123.89, 132.02, 134.67, 136.69, 137.26, 151.68, 152.21, 154.27, 164.74, 165.09; EI-MS: 474.2 (M-1) (Negative mode), 476.2 (M+1) (Positive mode); IR (neat) cm^{-1} 2970.8, 1739.48, 1649.84, 1615.12, 1598.21,1346.45, 762.36.

3-[(9H-fluoren-2-yl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl]-4-hydroxy-2H-chromen-2-one: (Entry 5, Table 1): M. P. 255-257, ^1H NMR (400 MHz, $CDCl_3$) δ ppm 3.98 (s, 2H), 6.21 (s, 1H), 7.37 (d, 2H), 7.4-7.54 (m, 7H), 7.6-7.9 (m, 4H), 8.1 (dd, 2H), 11.35 (brs, 1H, -OH), 11.59 (brs, 1H, -OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 35.97, 36.37, 104.60, 116.04, 117.07, 119.55, 123.27, 123.94, 124.88, 125.43, 126.52, 132.10, 137.53, 139.18, 140.90, 143.04, 152.09, 164.34, 165.14; EI-MS: 499.3 (M-1) (Negative mode), 501.3 (M+1) (Positive mode); IR (neat) cm^{-1} 2981, 1739.44, 1661.93, 1610.22, 1563.54, 1346.65, 755.38.

Biological evaluation of biscoumarins:

Determination of antibacterial activity:

Antibacterial activity was studied by using reported disc diffusion method [16, 17]. Nutrient agar medium was prepared and plated with the microbial cultures - *Escherichia coli* (gram -ve), *Proteus vulgaris* (gram -ve) and *Staphylococcus aureus* (gram +ve), *A. Niger, A. Fumigatus* and *Penicillium.* 10^{-6} CFU/mL (Colony Forming Unit per mL) was inoculated separately on the solidified agar on each petri dish by streaking with the help of a wire loop. Discs (5 mm diameter) were prepared in each of these plates. Solutions of the test compounds were prepared at a concentration of 500 µg/mL and 30 µL of each sample was added onto the disc. Thus prepared plates were kept in refrigerator (4 ^oC) for 30 minutes for uniform diffusion of sample into media. The plates were incubated at 37 °C for 24 hr in incubator and the diameter of zone of inhibition was expressed in millimeter (mm) (**Table 2**).

Each sample was assayed in triplicate and the mean values were determined. The efficiency of samples against bacteria was compared with the broad spectrum antibiotic rifampicin and ampicillin (each at 500 µg/mL concentration) by measuring the zone of inhibition. The minimum inhibitory concentration (MIC) is defined as the lowest drug concentration inhibiting bacterial growth which makes the zone of inhibition just visible. The MIC values for selected compounds were determined on solid medium (Nutrient agar) and expressed by average of three assays using Collin's method [18]. The range of concentration used was 350 ppm-450

ppm (**Table 3**).

Table 2: Antimicrobial evaluation of biscoumarins

Sr. No.	Comp.	Zone of inhibition (mm)					
		E. Coli	*P. Vulgaris*	*S. Aureus*	*A. Niger*	*A. Fumigatus*	*Penicillium*
1	B1	*	*	*	*	*	*
2	B2	*	*	*	*	*	*
3	B3	*	*	*	*	*	*
4	B4	*	*	*	*	*	19 mm
5	B5	9 mm	*	6 mm	*	*	*
6	B6	*	*	*	*	*	*
7	B7	*	*	*	*	*	*
8	B8	11 mm	10 mm	10 mm	*	*	*
9	B9	*	*	*	*	*	*
10	B10	*	*	*	*	*	*
11	B11	3 mm	2 mm	7 mm	*	*	*
12	Rif	12 mm	11 mm	16 mm			
13	Amp	28 mm	*	*	18	20	30

* = No zone of inhibition below 500 µg/mL

Table 3: Determination of MIC

Sr. No.	Comp	*E. Coli (mm)*				*P. Vulgaris (mm)*				*S. Aureus (mm)*			
		450 ppm	400 ppm	350 ppm	300 ppm	450 ppm	400 ppm	350 ppm	300 ppm	450 ppm	400 ppm	350 ppm	300 ppm
1	B5	6	4	1	NR	NR	NR	NR	NR	2	NR	NR	NR
2	B8	8	2	NR	NR	6	1	NR	NR	4	NR	NR	NR
3	B11	NR	NR	NR	NR	NR	NR	NR	NR	2	NR	NR	NR
4	Rif	10	7	3	NR	9	5	2	NR	11	8	5	2

Determination of insecticidal activity:

A study was performed to evaluate insecticidal activity of biscoumarin derivatives against bean weevil *Callosobruchus maculatus* (F); the most dangerous pest of stored grains. Infected grains of *phaseolus* were purchased from market and *C. maculatus* (F) were separated from other species on the basis of morphological difference. These were separately reared in a glass jar containing *phaseolus* which was covered by muslin cloth and tied with rubber band to provide proper aeration to the culture and used as the stock. After 28-30 days newly hatched adult *C. maculatus* were observed inside the jar which was used to study the mortality effect of biscoumarins.

The grains were initially washed with water and dried in oven at 40-45 ^{o}C so as to destroy the infected stages of any pest if exists in grains. Each pre-sterilized glass jar was filled with 10 gm of the grains. Then each compound with 500 µg/mL concentration was applied on grains and left for 48 h to evaporate the solvent. 10 Beetles were allowed to enter inside each jar which was covered with muslin cloth and observed after an interval of 24 h each for 96 h. The rate of mortality was recorded for each compound against *C. maculatus* (**Table 4**). The experiment was carried in triplicate and percentage adult mortality was determined by counting the number of dead insects divided by the total number of insects introduced multiplied by 100 [19].

Table 4: Insecticidal activity of biscoumarins

Compound	Number of insects dead after				Total % mortality
	24 h	48 h	72 h	96 h	
B1	1	1-2	2	3	75
B2	0	1	1	3	50
B3	1	2	2	2	70
B4	1	1	1	2	50
B5	0	1	2	4	70
B6	0	0	0	1	10
B7	0	0	2	2	40
B8	1	1	2	3	70
B9	1	1	2	2	60
B10	0	1	1	1	30
B11	0	2	1	4	70

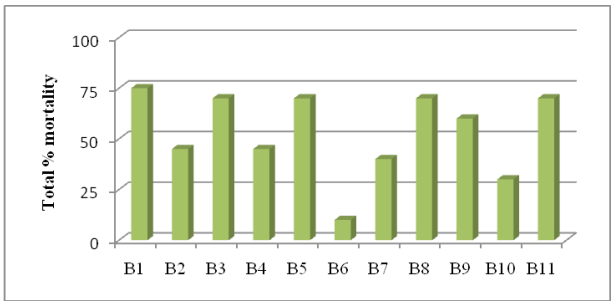


Figure 4: Plot of total % mortality after 96 h

Results and Discussion:

In the present work, $Yb(OTf)_3$ was successfully used as a catalyst for the pseudo three-component condensation of aldehyde and 4-hydroxy coumarin in ethanol under reflux condition. Optimization of catalyst concentration for a model reaction of benzaldehyde with 4-hydroxy coumarin showed that only 5 mol% of the catalyst was found to be enough sufficient to catalyze the transformation. Almost all the screened aldehydes including sterically hindered ones reacted under these conditions to afford the corresponding biscoumarin derivatives in good yields.

Antibacterial activity of the synthesized biscoumarins revealed that the compound **B-8** was active against all the three bacterial strains viz. *E. Coli, P. Vulgaris, S. Aureus* which showed significant zone of inhibition comparable with that of the standard Rifampicin in case of *E. Coli* as well as *P. Vulgaris* but less than in the case of *S. Aureus*. Biscoumarin **B-5** was effective against *E. Coli* and *S. Aureus* only and inactive against *P. Vulgaris*. Compound **B-11** was less effective against all the three bacterial strains employed. The remaining biscoumarins were observed to be inactive against the used bacterial strains. The results of minimum inhibitory concentration (MIC) determination for the selected compounds **B-5**, **B-8** and **B-11** are mentioned in **Table 3**. Antifungal activity of the biscoumarins revealed that only the compound **B-4** was active against *Penicillium fugus* and not active against *A. Niger* and *A. Fumigatus* at 500 µg/mL concentration. Antifungal activity of the compound **B-4** can be attributed to the presence of $-NO_2$ group at meta and F-atom at para position. The remaining compounds were not active against all the three fungi below 500 µg/mL concentration.

Compounds **B-1**, **B-3**, **B-5** and **B-11** showed about 70-75% mortality effect on *Callosobruchus maculatus* whereas **B-2**, **B-4** and **B-8** showed 50% of mortality i.e. moderate effect and B-6 showed the least mortality rate to control *C. maculatus*.

Conclusion:

In the present study $Yb(OTf)_3$ was used as a catalyst for the synthesis of biscoumarins by pseudo three-component reaction of aldehyde and 4-hydroxycoumarin. The reactions were successful even with sterically hindered aldehydes. Antibacterial activity study revealed that the compounds **B-5**, **B-8** and **B-11** possessed moderate to good zones of inhibition against the bacterial strains used. Compound **B-4** was found to be active against *Penicillium* fungus but inactive against *Aspergillus niger* and *Aspergillus fumigatus* fungal species. Compounds **B-1**, **B-3** and **B-5** showed good mortality rates against C. maculatus (70-75% mortality) after 96 h.

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