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ORIGINAL PAPER

Synthesis of bis-coumarins over acetic acid functionalized poly(4-vinylpyridinum) bromide (APVPB) as a green efficient catalyst under solvent-free conditions their biological activity

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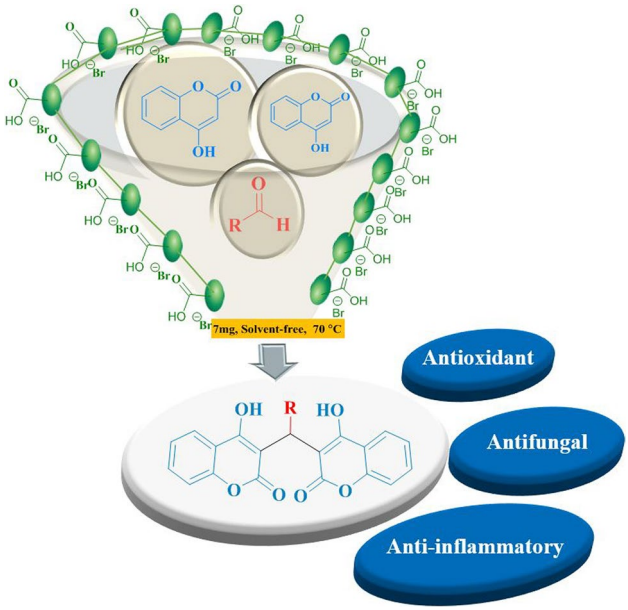
Abstract

In this work, acetic acid functionalized poly(4-vinylpyridinum) bromide as a green and reusable catalyst was successfully tested on the synthesis of various bis-coumarins under solvent-free conditions. In addition, antioxidant and anti-inflammatory activities of the synthesized bis-coumarins were in vitro screened by 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging and formalin-induced edema model system, respectively. Antifungal activity was also evaluated against Fusarium oxysporum. Results showed that the synthesized bis-coumarins studied possess strong antioxidant (IC_{50}; 0.149 ± 0.005 to 1.348 ± 0.006 mg/ml) and anti-inflammatory activities in comparison with ascorbic acid and diclofenac as positive controls, respectively. Also, the compounds showed good inhibition activity against Fusarium oxysporum (58 ± 1.4 to 100 ± 0.0%). For their biological activities, the synthesized bis-coumarins may be suggested to apply as biological agents for special use in future.

Graphical Abstract



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Extended author information available on the last page of the article

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Keywords Functionalized poly(4-vinylpyridinum) bromide · Bis-coumarin · Solvent-free · Anti-inflammatory · Antioxidant

Introduction

Solvent-free reactions have been demonstrated to be as an efficient technique for various organic transformations instead of using harmful organic solvents. Solvent-free conditions often lead to a remarkable decrease in reaction times, increased yields, easier workup, matches with green chemistry protocols and may enhance the regioselectivity and stereoselectivity of reactions [1–5].

Reactive oxygen or nitrogen species (ROS or RNS) are formed naturally in living cells have important roles in cell signaling. However, high amount of these compounds are hazardous to the cells and damage all major components, including nucleic acids, polypeptides chains, and lipids in cell membranes that play an important role in the development of diseases such as inflammation and other disorders [6, 7]. Inflammation is a complex phenomenon involving interrelationships between different factors including physical and chemical stimulants. ROS play a significant role in the inflammatory process. Antioxidants may act as scavenger, reducing, quencher agents and/or activators of cellular antioxidant enzymes to prevent the free radical damages in biological systems [8, 9]. In this regard, several natural or synthetic coumarins with various hydroxyl and other substituents were found to inhibit lipid peroxidation and to scavenge hydroxyl radicals and superoxide anions. Hence, they can influence processes involving free radical-mediated injury as some plant phenolics and flavonoids [10, 11]. Today, most of the bacteria and fungi showed resistance to classical antibiotics, [12–14] and the discovery of active compounds with novel mechanisms is a matter of urgency [15, 16].

The preparation of heterocyclic compounds with biological properties is very important. Nowadays coumarins, as a classification of the hetrocyclic compounds containing oxygen hetro-atom, are completely introduced due to their naturality [17–19], application as food additives, cosmetics [20], and optical brightening agents [21]. Moreover, their biological activities such as anticoagulant [22] antibacterial [23], antifungal [23], antibiotic [24], antitumor [24, 25], anti-HIV10 [26] as well as agrochemicals [27] and analytical reagents [28] have been represented. They have potential applications in various biomedical including anticoagulants [22, 29, 30], antioxidants [27], and also as non-ATP competitive inhibitor of c-Me [31].

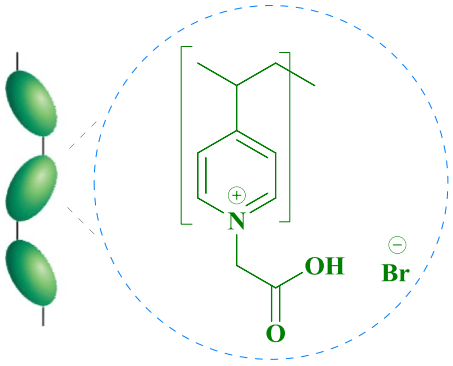
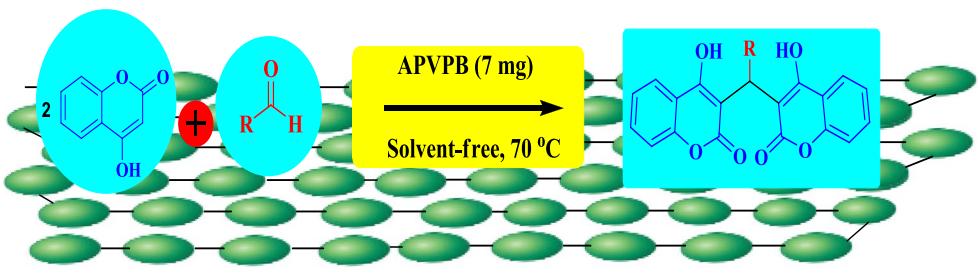


Fig. 1 Structure of acetic acid functionalized poly(4-vinylpyridinum) bromide (APVPB)

Several methods for the preparation of bis-coumarins were reported. The majority of them have been carried out by the knoevenagel reaction in the presence of various acidic catalysts, such as sulfuric acid, phosphoruspentoxide, aluminum chloride, iodine, and trifluoroacetic acid [32–34]. However, some of them suffer from drawbacks, such as the use of volatile organic solvents, high cost, and low yields. Therefore, it is highly desirable to develop efficient and cost-effective catalysts and procedures with high novelty for the preparation of these valuable compounds.

Ionic liquids have received considerable interest as eco-friendly solvents, catalysts, and reagents in organic transformations due to their unique properties, such as low volatility, non-flammability, high thermal stability, negligible vapor pressure, and the ability to dissolve a wide range of various materials [35]. Among them, Brønsted acidic ionic liquids, with useful characteristics of both solid acids and mineral liquid acids, have been introduced to replace traditional mineral liquid acids, like sulfuric acid and hydrochloric acid, in chemical procedures [36–51].



Scheme 1 Synthesis of bis-coumarins catalyzed by APVPB

Recently, we have introduced acid functionalized ionic liquid, and applied them as organocatalysts for the preparation of 14-aryl-14H-dibenzo [a,j]xanthenes [52], tetrahydrobenzo [b]pyrans [53], 2-aminobenzo[h] chromene [54], 4,4′-(arylmethylene)- bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)s [55].

Herein, in continuous of previous work on the preparation of Brønsted acidic ionic liquids and solid salts, we would like to introduce acetic acid functionalized poly(4-vinylpyridinum) bromide (APVPB) (Fig. 1) as an efficient and reusable catalysts for the synthesis of bis-coumarins by the condensation reaction of various aldehydes with 4-hydroxycoumarin at 70 °C under solvent-free conditions (Scheme 1).

Experimental

Chemistry

All chemicals were purchased from Merck or Fluka Chemical Companies. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^{1}H NMR (400–300 MHz) and ^{13}C NMR (100–75 MHz) were recorded on a BrukerAvance DPX FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the preparation of bis-coumarins

APVPB (7 mg) was added to a mixture of 4-hydroxycoumarin (0.324 g, 2 mmol) and aryl aldehyde (1 mmol) in a 25-mL round-bottomed flask connected to a reflux condenser, and the resulting mixture was stirred magnetically at 70 °C, and after that the reaction mixture was solidified, it was stirred with a small rod at same temperature. After the reaction was completed, as monitored by TLC, the reaction mixture was cooled to room temperature, ethyl acetate (95%) (20 mL) was added to it, stirred and refluxed for 3 min. Then, the mixture was centrifuged for separation of the catalyst from the product and the remaining starting materials. The solvent of the reaction mixture was evaporated, and the precipitate (the crude product) was purified by recrystallization from ethanol (95%). In this work, the catalyst was recovered and reused for 5 times without any significant changes in the yield and the reaction time.

Table 1 Effect of the catalyst amount and temperature on the reaction between 4-hydroxycoumarin and 4-chlorobenzaldehyde

Entry	Amount of catalyst (mg)	Temp. (°C)	Time (min)	Yield[a] (%)
1	3	70	40	55
2	5	70	25	70
3	7	70	15	92
4	10	70	15	92
5	7	50	30	45
6	7	90	15	92
7	7	110	15	92

[a]Isolated yield

Biological activity

Antioxidant capacity

Free radical scavenging activity of the compounds was measured according to Mensor et al. [71]. In order to obtain dilutions, different samples concentrations were prepared in methanol (0.2–1 mg/ml), and 2.5 ml of each concentration were added to 1 ml of alcohol solution of DPPH (0.3 mM). The samples were first kept in darkness at room temperature for 30 min, and then bleaching of DPPH was read at 517 nm against a blank (methanol). The inhibition in percent for each concentration was calculated according to the following formula:

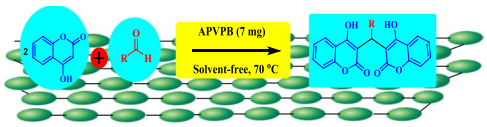
$$\text{DPPH free radical scavenging (\%)} = \left[1-(\text{As}-\text{Ab})/\text{Ac}\right] \times 100$$

where As is absorbance of the reaction mixture containing 2.5 ml of samples + 1 ml of DPPH, Ab is absorbance of the reaction mixture containing 2.5 ml of samples + 1 ml methanol, and Ac is absorbance of control sample containing 1 ml of DPPH + 2.5 ml methanol. Also IC_{50} value, which represented the concentration of the sample that caused 50% inhibition, was determined. Tests were carried out in triplicate and ascorbic acid was used as a positive control.

Animals

Mature Sprague Dawley rats (180–200 g) were obtained from animal house of Bu-Ali Sina University, Hamedan, Iran and were allowed to adapt themselves with their location for 1 week. The rats were divided into three groups as follows: group 1 as negative control (DMSO), group 2 as positive control (diclofenac treated) and group 3 as bis-coumarin treated (C_6). The animals, which have been bred in our laboratory, were housed under standard conditions and received a diet of commercial food pellets and water ad libitum during the maintenance, but they were entirely fasted

Table 2 Solvent-free synthesis of bis-coumarin from aryl aldehydes, 4-hydroxycoumarin, and catalyzed by APVPB at 70 °C



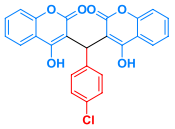
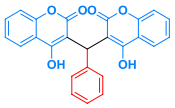
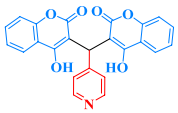
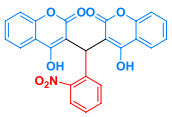
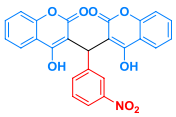
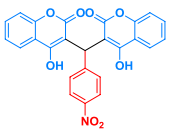
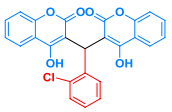
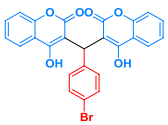
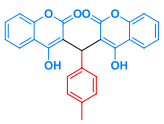
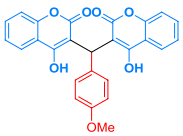
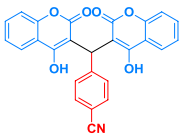
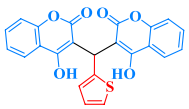
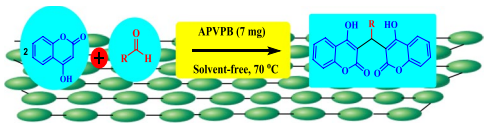
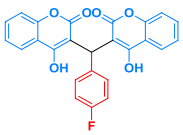
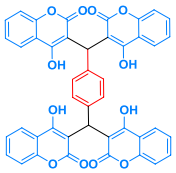
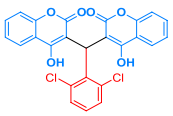
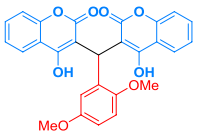
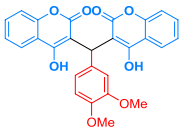
Entry	Product	Time (min)	Yield[a] (%)	*Mp*. °C (Lit.) [References]
C_1		15	92	257–260 (259–261) [57]
C_2		17	88	232–234 (230–232) [57]
C_3		17	87	275–277 (270–274) [57]
C_4		12	92	205–207 (204) [59]
C_5		13	89	236–238 (234–236) [58]
C_6		12	94	238–240 (232–234) [58]
C_7		15	91	218–220 (224–226) [58]
C_8		10	91	268–270 (266–268) [58]
C_9		15	86	262–264 (266–268) [58]
C_{10}		18	87	247–249 (246–248) [58]
C_{11}		10	90	262–264 (260–262) [57]
C_{12}		17	89	203–206 (197–201) [57]

Table 2 (continued)



Entry	Product	Time (min)	Yield[a] (%)	*Mp*. °C (Lit.) [References]
C_{13}		10	94	210–212 (212–214) [58]
C_{14}		20	82	230–232 (224) [61]
C_{15}		16	88	180–182 (178–180) [58]
C_{16}		20	85	188–190 (181.6) [60]
C_{17}		20	85	265–268 (263–265) [58]

[a]Isolated yield

during the experiment period. Our studies were in accordance with recognized guidelines on animal experimentation.

Anti-inflammatory activity

Anti-inflammatory activity was assessed as inhibition of the formalin-induced edema by the synthesized coumarins. Edema was induced in the feet rats by the intradermal injection of 0.1 ml 2% formalin. The tested compound (C_6), 0.01 mM/kg body weight, was suspended in DMSO. The rats were euthanized 15 min after formalin injection. The difference between the weight of the injected and uninjected paws of rats was measured for each animal, and changes of paw weight were compared with that in control animals (treated only with DMSO and diclofenac).

Antifungal activity

Antifungal activity of bis-coumarin derivatives was assessed against Fusarium oxysporum cultivated in Potatoes Dextrose Agar (PDA) medium. The samples bis-coumarin derivatives (C_1, C_3, C_7, and C_{17}) in two concentrations (500–1000 ppm) were added to cultivation medium. In order to make the control group, double-distilled water and DMSO were added to the plates. After a 7-day incubation of fungus on culture medium containing samples, radial growth of fungal mycelium was recorded. The following formula was used for calculation of the inhibition rate (%):

$$\text{Inhibition rate } (\%) = (R - r/R) \times 100$$

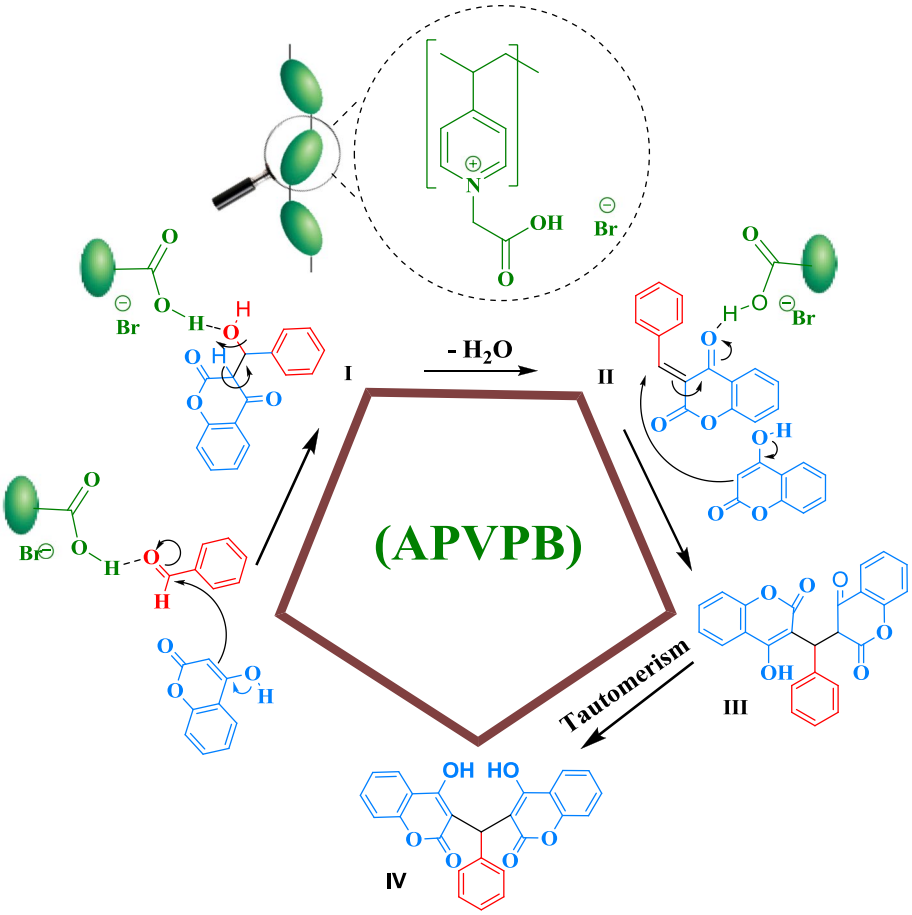
where R is the radial growth of fungal mycelia on the control plate and r is the radial growth of fungal mycelia on the plate treated with bis-coumarin derivatives.

Results and discussion

Chemistry

At first, acetic acid functionalized poly(4-vinylpyridinum) bromide (APVPB) was prepared in three steps. Initially, bromo ethyl acetate prepared according to previous literature [56]. Then, to optimize the reaction conditions, a mixture of 4-chlorobenzaldehyde (1 mmol) and 4-hydroxycoumarin

Scheme 2 Proposed mechanism for the synthesis of bis-coumarins



(2 mmol), as a model reaction, was stirred in the presence of different amounts of APVPB at range of 50–110 °C under solvent-free conditions. The respective results are displayed in Table 1. As it can be seen in Table 1, 7 mg of APVPB was sufficient to catalyze the reaction at 70 °C. In these reaction conditions, the expected bis-coumarin was prepared in 92% yield within 15 min (Table 1, entry 3).

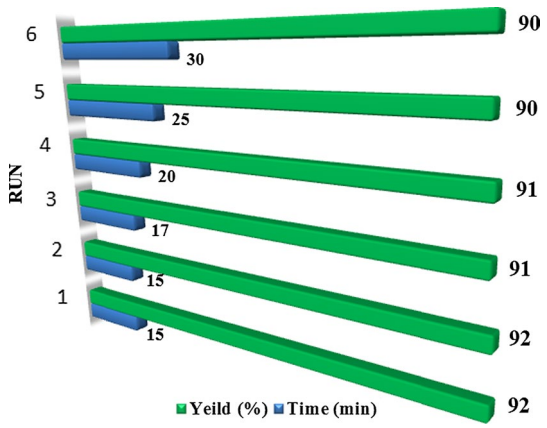


Fig. 2 Condensation of 4-chlorobenzaldehyde with 4-hydroxycoumarin in the presence of recycled catalyst

To investigate the efficacy and the generality of the catalyst, 4-hydroxycoumarin was reacted with various aromatic aldehydes (benzaldehyde as well as aryl aldehyde containing electron-withdrawing groups, electron-donating groups, and halogens), under the optimized reaction conditions (Table 2). As it is shown in Table 2, all reactions proceeded efficiently to obtain the expected bis-coumarin derivatives in high yields and in short reaction times. Therefore, APVPB was a highly efficient and general catalyst for the synthesis of bis-coumarins.

In a purposed mechanism which is shown in Scheme 2, initially, the carbonyl group of aldehyde is activated by the acidic moiety of APVPB and reacted with 4-hydroxycoumarin to give **I**. Intermediate **I** is converted to **II** by the elimination of one molecule of H_2O. In the next step, **II**, as a Michael acceptor, is activated by the catalyst, and reacted with another molecule of 4-hydroxycoumarin to afford **III**. At the end, **III** is converted to **IV** (the product) after tautomerization.

To investigate the recyclability of APVPB, the reaction of 4-chlorobenzaldehyde (2 mmol) with 4-hydroxycoumarin (1 mmol) was performed using APVPB (7 mg) at 70 °C. After the reaction was completed, the reaction mixture was cooled to room temperature, ethyl acetate (95%) (20 mL)

Table 3 DPPH radical scavenging activity (%) of coumarins ($C_{1–17}$) at different concentrations and ascorbic acid as standard

Compound	Concentration (mg/ml)					Average
	0.2	0.4	0.6	0.8	1	
C_1	28.05 ± 2.9^a	34.16 ± 1.6^b	33.71 ± 4.4^b	41.15 ± 2.4^c	46.45 ± 3.5^c	36.70
C_2	32.22 ± 2.3^a	28.10 ± 1.3^a	28.43 ± 3.8^a	34.18 ± 3.2^a	37.09 ± 1.2^a	32.00
C_3	30.00 ± 1.7^a	34.14 ± 2.2^a	52.23 ± 2.4^b	61.47 ± 1.3^c	72.51 ± 2.1^d	50.07
C_4	28.16 ± 1.2^a	38.15 ± 3.3^b	49.56 ± 1.8^b	58.25 ± 1.4^c	66.21 ± 2.7^d	48.07
C_5	61.16 ± 3.1^a	62.02 ± 1.6^a	65.31 ± 2.2^a	65.17 ± 3.7^a	65.87 ± 1.5^a	63.89
C_6	66.91 ± 4.1^a	64.27 ± 2.9^a	73.82 ± 1.9^b	70.68 ± 0.9^b	71.31 ± 1.1^b	69.40
C_7	67.12 ± 1.2^a	65.22 ± 3.1^a	70.35 ± 2.6^b	72.51 ± 2.2^b	71.11 ± 1.8^b	69.26
C_8	64.80 ± 3.2^a	63.19 ± 2.1^a	62.97 ± 1.6^a	67.73 ± 3.4^a	67.41 ± 1.1^a	65.22
C_9	24.33 ± 1.3^a	26.41 ± 0.8^a	23.16 ± 2.9^a	36.52 ± 1.7^b	41.11 ± 3.6^b	30.31
C_{10}	32.43 ± 3.3^a	33.16 ± 1.5^a	43.52 ± 1.3^a	47.18 ± 3.2^a	52.23 ± 3.1^a	41.70
C_{11}	34.14 ± 2.2^a	38.25 ± 1.2^a	48.33 ± 3.3^b	55.21 ± 2.8^c	60.16 ± 2.2^d	47.22
C_{12}	16.11 ± 0.8^a	24.54 ± 3.4^b	21.27 ± 0.9^b	28.22 ± 1.2^c	40.43 ± 1.8^d	26.11
C_{13}	18.33 ± 2.6^a	23.13 ± 2.4^a	21.27 ± 2.2^a	21.17 ± 3.1^a	47.23 ± 2.8^b	26.23
C_{14}	24.53 ± 1.2^a	21.65 ± 1.1^a	27.32 ± 0.6^b	38.77 ± 1.7^c	46.43 ± 1.2^d	29.74
C_{15}	24.33 ± 1.5^a	33.41 ± 0.8^a	40.16 ± 2.2^a	49.52 ± 3.6^a	62.11 ± 4.2^a	41.91
C_{16}	27.33 ± 1.7^a	26.41 ± 2.2^a	25.16 ± 1.7^a	37.32 ± 1.9^b	41.24 ± 1.6^b	30.51
C_{17}	26.61 ± 3.3^a	29.31 ± 3.4^a	58.26 ± 3.7^b	57.22 ± 3.2^b	55.19 ± 2.2^b	45.32
Ascorbic acid	78.74 ± 2.7^a	80.26 ± 3.4^b	81.85 ± 2.4^b	80.31 ± 1.1^b	80.24 ± 2.6^b	80.28

Experiment was performed in triplicate and expressed as mean ± SD. Values within column with different superscripts are significantly different ($p < 0.05$)

was added, stirred and refluxed for 2 min. Then, the resulting mixture was centrifuged to separate of the nanocatalyst from the product and remaining starting materials. The remained catalyst was washed with hot ethyl acetate (10 mL) and dried to use for the next run. Catalytic activity of APVPB was restored within the limits of the experimental errors for 5 successive recycle runs (Fig. 2).

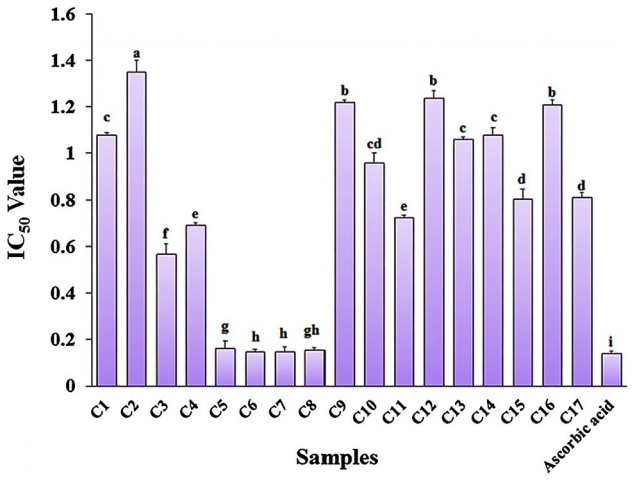


Fig. 3 Comparison of DPPH radical scavenging ability (IC50 Value) of the studied coumarins and ascorbic acid as a positive control

Antioxidant capacity

Coumarins and its derivatives are a very large class of compounds, which are naturally found in plants [62]. They have been attracted considerable attention due to their wide spectrum of pharmacological and biological activities such as antifungal, antiviral, antibacterial, anti-inflammatory, and antioxidant capacities [63]. Antioxidants are very important due to their role in the deleterious of free radicals [64, 65]. Our results showed that the synthesized coumarins showed excellent dose-dependent (0.2–1 mg/ml) antiradical properties (26.10–69.40%) (Table 3). It has been reported that in vitro antioxidant activity of phenolic compounds on a molar basis is higher than that of vitamins E and C65, and more antioxidant activity is reflected in a lower IC50 value. Vitamin C (ascorbic acid) as a synthetic antioxidant represented the IC50 value lowers than of the most of compounds studied here (Fig. 3). The effectiveness of the compounds as DPPH radical scavengers ranged in the following descending order: ascorbic acid > C6 = C7 = C8 ≥ C5 > C17 > C3 ≥ C4 > C11 > C15 > C10 ≥.

Anti-inflammatory activity

The in vivo anti-inflammatory activity of the compounds was assessed by using the functional model of formalin-induced rat paw edema (Table 4). Formalin-induced edema is a nonspecific inflammation resulting from a complex

Table 4 Anti-inflammatory activity of a coumarin sample, positive, and negative controls

Time (min)	Diameter (mm)			
	Coumarin sample C_6	Positive control Diclofenac	Negative control DMSO	Uninjected hind Control rats
0	27.0 ± 0.2	26.0 ± 0.3	26.0 ± 0.1	21.0 ± 0.3
15	26.5 ± 0.3	26.0 ± 0.2	26.0 ± 0.3	21.0 ± 0.3
30	24.5 ± 0.2	25.5 ± 0.4	26.0 ± 0.3	21.0 ± 0.3
45	23.5 ± 0.1	25.5 ± 0.3	25.4 ± 0.5	21.0 ± 0.3
60	22.5 ± 0.2	24.0 ± 0.1	25.2 ± 0.2	21.0 ± 0.3
75	22.0 ± 0.1	22.5 ± 0.1	25.0 ± 0.3	21.0 ± 0.3

Experiment was performed in triplicate and expressed as mean ± SD

of diverse mediators [66]. The increase in diameter of the paws reached about 6–7 mm of the diameter of the control paw 15 min (0 min in table) after the injection of formalin (Fig. 4). At higher dose, the diameter increased at the right hind paw (26.5 ± 0.3 mm) in comparison with the uninjected left hind paw (21.0 ± 0.3 mm). As shown in Table 4, compound C_6 induced protection against formalin-induced paw edema (5 mm). The reference drug, diclofenac, is a non-steroidal anti-inflammatory drug (NSAID) induced 3.75 mm protection at an equivalent concentration. The sample was the most potent (5 mm diameter), whereas DMSO as negative control had the lowest effect (1 mm). Our results indicated that the studied compounds can be used to treat inflammation diseases.

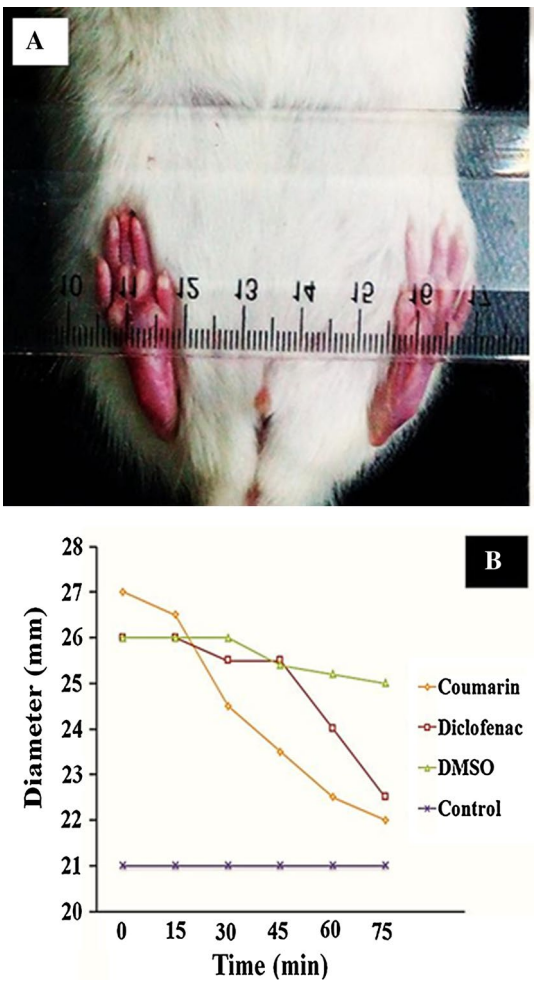


Fig. 4 **a** Increasing of diameter in formalin-injected right hind paw (26.5 ± 0.3 mm) in comparison with the uninjected left hind paw **b** anti-inflammatory activity of the coumarin, positive, and negative controls

Antifungal activity

The inhibition zone values were determined for some randomly selected compounds synthesized here (C_1, C_3, C_6, and C_{17}) against *Fusarium oxysporum* (Table 5). *F. oxysporum* is a soil inhabitant that attacks its host by entering through the root and grows in the plant xylem, eventually blocking the vascular system. It prevents transport of water, and nutrients can cause severe losses of crop and ultimately death of the

Table 5 Antifungal activity of some synthesized coumarin

Compound	Inhibition of radial growth of fungal mycelium (%)	
	Concentration (ppm)	*F. oxysporum*
C_1	500	60 ± 3.2
	1000	100 ± 0.0
C_3	500	86 ± 2.8
	1000	100 ± 0.0
C_7	500	78 ± 2.3
	1000	100 ± 0.0
C_{17}	500	58 ± 1.4
	1000	91 ± 1.2
DMSO	–	NA

Experiment was performed in triplicate and expressed as mean ± SD
NA No active

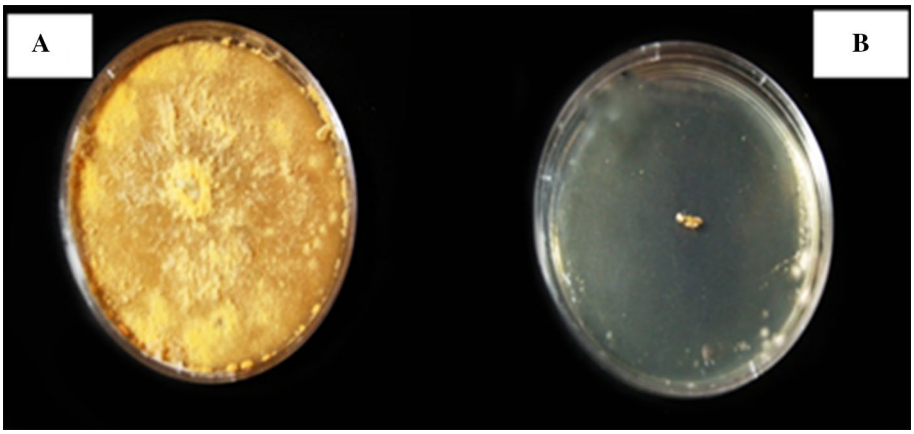


Fig. 5 Antifungal activity **a** control (water distillation) **b** coumarin treated

plants of great economic importance [67, 68]. It has been shown that biological activity such as antimicrobial activity of a compound is attributed mainly to its major components. However, today, it is known that the synergistic or antagonistic effect of any compounds in minor percentages has to be considered [69, 70]. Most of the old synthetic fungicides usually are difficult to degrade and are toxic to humans. Therefore, the searches for new compounds endophytic fungi which are safe and more environmental friendly were introduced to replace the synthetic fungicides. In this research, it was determined that solvent DMSO as negative control had no antifungal activity against F. oxysporum (Table 5). All samples showed excellent antifungal activity (Fig. 5). Hence, the examined samples may be used to treat plant diseases caused by *F. oxysporum* and also to increase resistance in a wide variety of crop plants.

Statistical analysis

All data are the average of triplicate analyses. Statistical analysis of variance was performed using Student's *t*-test by SPSS program, and p value < 0.05 was regarded as significant. Data are expressed as mean ± standard deviation.

Conclusion

In summary, we have reported acetic acid functionalized poly(4-vinylpyridinum) bromide (APVPB) as a reusable, stable, general and heterogeneous catalyst for the synthesis of bis-coumarins under solvent-free conditions. Low temperature, short reaction times, solvent-free and mild reaction conditions and reusability of catalyst are some advantages of this work. Also results from present study clearly displayed that all coumarin derivatives exhibit biological properties which might be helpful in preventing the progress of various diseases and development of new therapeutic agents.

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