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Synthesis and *in-vitro* antimicrobial screening of 3-cinnamoyl coumarin and 3-[3-(*1H*-indol-2-yl)-3-aryl-propanoyl]-*2H*-chromen-2-ones

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ABSTRACT

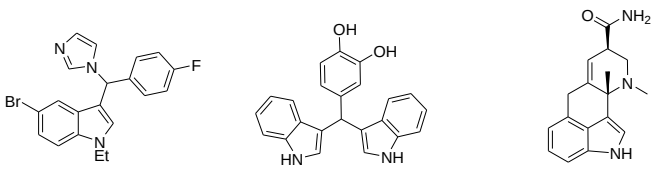
An efficient synthesis of some novel coumarin derivatives *via* 1, 4- Michael addition of indole to coumarin chalcones catalyzed by cellulose sulphonic acid (CSA) under solvent free conditions is described. The corresponding Michael addition products were obtained in good to excellent yield. The synthesized compounds were screened for their antibacterial activity against *E. coli*, *S. aureus* and anti-fungal activity against *C. albicans*. All the synthesized compounds show moderate to good antimicrobial activity.

Keywords*: Cellulose sulphonic acid(CSA), 3-acetyl coumarinn, chalcones, indole, 1,4-Michael addition, antibacterial activity.*

1. Introduction

Coumarin and its derivatives are naturally occurring poly-phenolic compounds distributed in plants, fungi and bacteria [1]. They possess a broad spectrum of biological activities including antibacterial [2], antifungal [3], anticoagulant [4], anti- inflammatory [5], antitumor [6], and anti-HIV [7]. Coumarin compounds are also used as additives in food, cosmetic and dyes [8,9]. Pyrazole-based coumarin derivatives have been regarded as anxiolytics [10], insecticides [11], LB_1 receptors [12] and growth inhibition agents [13a].

Indole derivatives with substituent at 3-position are considered as a precious pharmacophore in drug discovery They can also be found in various ranges of natural products such as $5HT_1B/1D$; which is used as a receptor agonist in the treatment of breast cancer (A), HIV-1 integrase inhibitor (B) and Ergine (C) (Fig. 1) [13(b-d)].



(A) (B) (C)

Fig. 1. Potentially active indole derivatives.

A list of structurally novel coumarin derivatives have been developed increasingly. Their pharmacological and biochemical properties depend upon the substitution pattern [14]. Therefore, a large number of attempts have been made for the synthesis of coumarin derivatives including condensation of 4-chloro-3-nitrocoumarin and corresponding hetroaylamines [15]. Prasad Y. R. *et al* have reported the synthesis of coumarin chalcones by Claisen- Schmidt reaction of 3-acetyl coumarin and aromatic aldehydes [16]. Stankovikova H. et al have reported the synthesis of 2-oxo-2*H*-chromenecarboxaldehyde and investigated their photochromic and thermochromic properties [17]. Govari S. *et al* [18], Langi B. P. *et al* [19] and Stanislav G *et al* [20] reported the synthesis of novel coumarin-based hetrocyclic compounds and studied their pharmacological potential.

Cellulose is one of the best renewable biopolymer which is extensively studied in organic transformation [21] Cellulose is found to be the most powerful biodegradable support for the preparation of valuable heterogeneous catalyst [22]. One of the best examples is thermally stable solid acid catalyst such as cellulose sulphonic acid (CSA) which can be prepared by the reaction of cellulose and chlorosulphonic acid. The formation of CSA has been confirmed by removal of HCl gas. The number of acidic (H^+) sites in the cellulose sulfuric acid is 0.50 meq/g in the basis of acid-base titration [23]. Due to remarkable acidic

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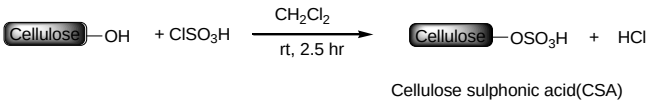
properties, it has been extensively used for synthesis of 1,8-Dioxo-octahydroxanthenes [24], imidazoazines [25], tetrahydropyranols [26], coumarins [27], 3,3'-indolyloxindole derivatives [28], 2,4,5-triarylimidazoles [29], *β*-acetamido carbonyl derivatives [30], Knoevenagel condensation [31], oxazolines, imidazolines and thiazolines [32].

In the present paper, we have described the synthesis of novel coumarin-based compounds by 1,4-Michael addition using cellulose sulphonic acid as an efficient biodegradable catalyst (Scheme 1). The synthesis of the CSA is performed by the reaction of commercial grade cellulose and chlorosulphonic acid in dichloromethane at room temperature.



Scheme 1.

2. Experimental

2.1 Material, methods and instruments

All chemicals used, are of Analytical Grade. Melting points were recorded on an open capillary and were uncorrected. Reactions were carried out in an open round bottom flask with 50 ml capacity. Completion of the reaction was judged by Thin Layer Chromatography (TLC) technique using petroleum ether: ethyl acetate (4:1) as solvent system. ^{1}H NMR spectra were recorded on 300 MHz spectrometer in DMSO-d_6 as a solvent. Purity of the compounds was checked by TLC, ^{1}H NMR, Mass spectra.

*2.2 Typical procedure for the preparation of 3-acetyl coumarin using CSA (**3**)*

A mixture of salicylaldehyde (5mmol) and ethyl acetoacetate (5 mmol) and CSA (200 mg) was stirred at 80^{0}C temperature under solvent free conditions for 3.5 hrs. After completion of reaction, the reaction mixture was mixed with hot ethanol (5 ml) and filtered. Filtrate was cooled in ice to obtain pale yellow coloured 3-acetyl coumarin with 88% yield; m.p.= 120-122 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.64 (s, 1H, =C-H), 7.44-7.6 (m, 4H, Ar-H), 2.58 (s, 3H, -CO-CH_3). Mass= (M.F. = $C_{11}H_8O_3$, M. W. = 188) = 189.24 (M+1).

2.3 General procedure for the synthesis of 3-cinnamoyl coumarins 5(a-e).

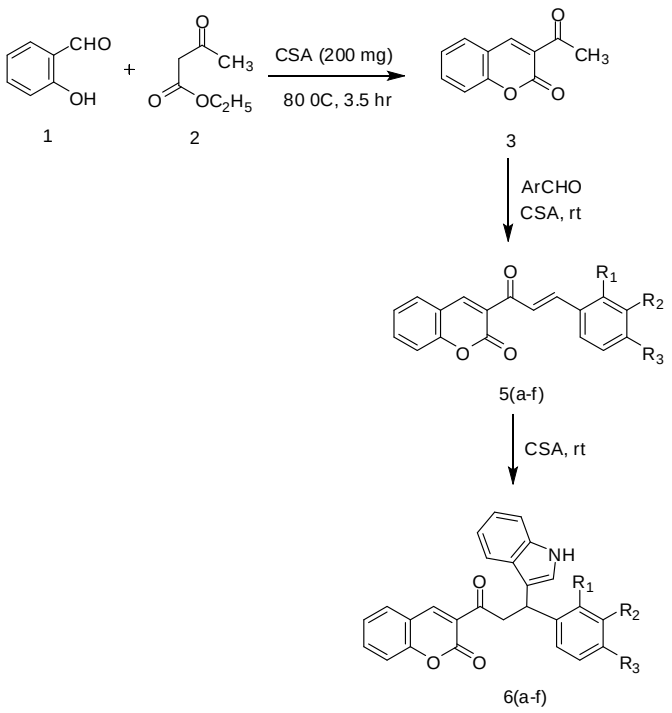
A mixture of 3-acetyl coumarin (5 mmol), benzaldehyde derivatives (5 mmol), and CSA (200 mg) were grinded for 1.5 hr at room temperature. Reaction mixture was mixed with hot ethanol (5 ml) and reaction mixture was filtered in ice to afford 3-cinnamoyl coumarin (Table 1); Spectral data of representative compound 5a represented as M. P. = 200- 202 ^{0}C. ^{1}H-NMR (300 MH$_Z$, DMSO-d_6, ppm) δ: 8.77 (s, 1H, =C-H), 7.82-7.82 (m, 11H, 9 aromatic proton and two –CH=CH- protons are merged); Mass: (M.F. = $C_{18}H_{12}O_3$: M.W. = 276) = 277.48(M+1).

2.4 General procedure for preparation of 3-[3-(1H-indol -2-yl)-3-aryl propanoyl]-2-H- Chromen-2-ones catalyzed by cellulose sulphonic acid 6(a-f)

To a mixture of 3-cinnamoyl coumarin **5** (1 mmol) and indole (1 mmol), CSA (200 mg) was added. Reaction mixture was stirred for specified time at ambient temperature (Table 2). After completion of reaction (TLC), reaction mixture was mixed with DMF (5 ml). Reaction mixture was further filtered in ice cold water to afford crystalline products. The spectral data of representative compound '6d' is represented as, yield = 81 %; m.p. = 221- 223 °C. ^{1}HNMR (300 MH$_Z$, DMSO-d_6, ppm) δ: 10.70 (s, 1H, -NH), 6.81- 7.53 (m, 12H, Ar-H), 6.40 (s, 1H, =C-H), 4.87 (t, 1H, -CH), 3.57 (d, 2H, -CH_2), 3.52 (s, 1H, -NH); Mass: (M F = $C_{26}H_{18}O_5N_2$; MW = 438) = 437.61(M+1).

3. Results and Discussion

In continuation to our ongoing research on the development of novel methods for easy access bioactive compounds [33], we explored the use of green methods for the synthesis of coumarin derivatives *via* 1,4-Michael addition of indole to 3-cinnamoyl coumarin. In the present study 3-acetyl coumarin (3) was synthesized by the reaction of salicylaldehyde and ethyl acetoacetate using CSA (200 mg) as a catalyst at 80 °C under solvent-free condition (Scheme 2). The resultant 3-acetyl coumarin was obtained in 88% yield. Coumarin chalcones 5(a-f) were synthesized by Claisen-Schmidt reaction of 3-acetyl coumarin and aldehyde derivatives 4(a-f) using CSA under solvent free condition (Table 1). The corresponding 3-(4-aryl)acryloyl-2*H*-chromene-2-one is obtained in good to excellent yield (67- 81%). With seven chalcones in hand, we optimized the 1,4-Michael addition of indole (2 mmol) to chalcone 5a (2 mmol) in acetonitrile using CSA (200 mg) at ambient temperature. Initiation of reaction was observed on TLC and 47 % of product 6a was isolated. Being encouraged by these results, we have decided to investigate the effect of solvent using ethanol, dichloromethane, and THF. It was observed that reaction progress was not good for above solvents and negligible amount of product was formed after careful workup. We further conducted the same reaction under solvent-free conditions using 50, 100, 150 and 200 mg of catalyst.



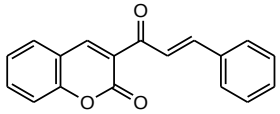
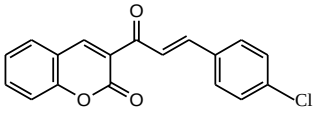
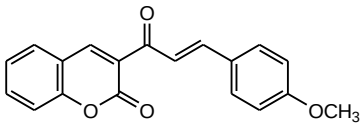
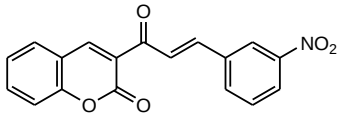
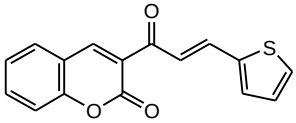
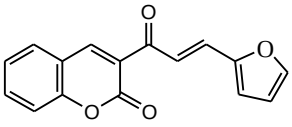
Scheme 2.

When reaction was carried out in presence of 200 mg of catalyst under solvent-free conditions at room temperature, product yield dramatically increased from 51 to 90% (51% for 50 mg of CSA, 67% for 100 mg, 82% for 150 mg, 90% for 200 mg). However, further increase in catalyst amount to 250 mg did not affect the yield of the final product. Hence, 200 mg of CSA under solvent-free was determined as optimized conditions for further study. The resultant 1,4-Michael addition products were further characterized by ^{1}HNMR and Mass spectral data. The data of antimicrobial screening of chalcone and 1,4-Michael addition products clearly indicated the enhancement in inhibitory activity due to presence of indole moiety.

4. Antimicrobial Screening

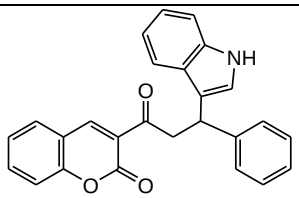
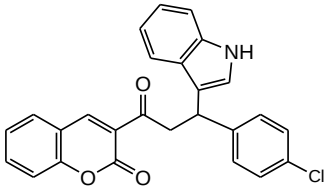
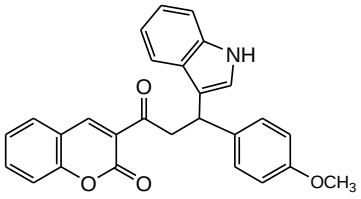
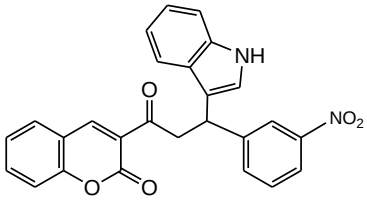
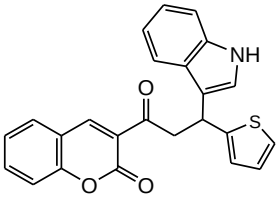
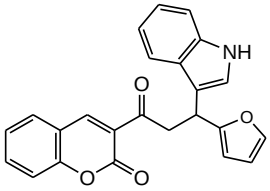
The antimicrobial activities of synthesized compounds were determined using cup plate method. *In vitro* antimicrobial activity was carried out against 24 hour old culture of *E. coli*, *S. aureus* and *C. albicans*. The compounds were tested at a concentration of 0.001 mol/ml in *N,N*-dimethyl formamide against all the organisms. Streptomycin and Nystatin (0.001 mole/ml) were used as the standard for antibacterial activity.

Table 1. Synthesis of 3- cinnamoyl coumarin under solvent free conditions.

Sr. No.	Entry	Product	Yield [%][a]	m.p. (°C)]
1	**5a**		81	200-202
2	**5b**		80	188-190
3	**5c**		68	205-206
4	**5d**		81	199-201
5	**5e**		57	197- 198
6	**5f**		76	180- 182

[a]Isolated yield of the products after purification.

Table 2. Synthesis of 3-[3-(1*H*-indol-2-yl)-3-aryl propanoyl]-2-*H*-Chromen-2-one derivatives catalyzed by CSA at ambient temperature.

Entry	Product	Time (min)	Yield (%)[a,b]	m.p.(°C)
1	 **6a**	30	90	206-208
2	 **6b**	30	60	190-192
3	 **6c**	45	77	210-213
4	 **6d**	30	80	221-223
5	 **6e**	40	75	193-195
6	 **6f**	60	72	Decomposed

[a]Isolated yield of the products after purification.
[b]Products were characterized by physical constants, [1]HNMR and Mass spectral data.

Table 3. Anti-microbial screening of the synthesized compounds.

Sr. No.	Compound		*Zone of inhibition (mm)[a]					
			E. coli		*S. aureus*		*C. albicans*	
			5	**6**	**5**	**6**	**5**	**6**
1	**5a**	**6a**	06	18	10	-	26	20
2	**5b**	**6b**	14	21	11	16	10	19
3	**5c**	**6c**	-	15	09	18	21	24
4	**5d**	**6d**	06	22	13	28	20	23
5	**5e**	**6e**	12	24	18	26	14	-
6	**5f**	**6f**	04	12	21	17	-	22
7	**Streptomycin**		26		30		-	
8	**Nystatin**		-		-		24	

* DMF is used as a solvent for dissolution of all compounds.

Out of the screened compounds, 5a, 5c, 5d, 5e, 6a and 6c shows moderate to good susceptibility. The obtained result clearly indicated that indole derivatives were more potent than 3-cinnamoyl coumarin (Table 3).

In conclusion, we have developed a simple and efficient method for synthesis of structurally diverse 1,4-Michael addition products by the reaction of 3-cinnamoyl coumarin and indole by using cellulose sulphonic acid as a biodegradable catalyst. The method presented here, contribute to chemistry of bioactive molecules using biodegradable catalyst.

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