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[Bmim]Cl Mediated Synthesis of Novel 3-(pyridine-2-yl)/Phenyl-2H-Chromene-2-one Derivatives Under Solvent-Free Conditions and their Antibacterial, Antifungal, Antioxidant Study

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ABSTRACT: In this study we are willing to report a simple and efficient method for the synthesis of 3-(pyridine-2-yl)/phenyl-2H-chromene-2-one derivatives under solvent free conditions catalyzed by 1-butyl, 3-methyl imidazolium chloride ([Bmim]Cl) ionic liquid. The newly synthesized compounds were tested for their antimicrobial & antioxidant activities. The structures of all novel compounds reported herein are established using FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy techniques.

KEYWORDS: Ionic liquid, Salicylaldehyde, Aryl acetonitrile, Chromene-2-one, Antibacterial and antifungal activity.

■ Introduction

Over the past few decades, fight against antimicrobial agents among bacterial and fungal pathogens stand for major global health problem in terms of deformity and mortality. [1] Infections caused by resistant microorganism repeatedly fail to respond to the usual treatment, resulting in unceasing illness, higher health care cost and a high risk of death. Thus, overcoming such multidrug resistant pathogens is challenging task. Looking at the backdrop of the current corona eruption, diseases rising from any sort of microorganisms cannot be taken lightly; whenever possible, they can go through an alteration in their structure and create severe health problems [2].

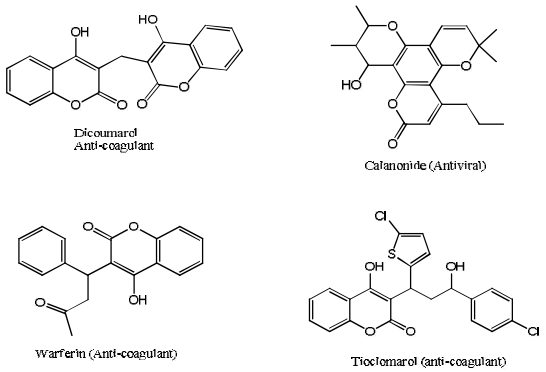

Figure 1: Few drugs containing coumarin moiety.

In spite of extensive progress in antimicrobial therapy, infectious diseases caused by microorganisms are still a major health alarm due to the increase in resistance to existing antibacterial medicines [3-7]. Therefore, it is essential need to discover and develop new antimicrobial agents with more effective promising antimicrobial action and superior activity. At present, coumarins are one of the classes of

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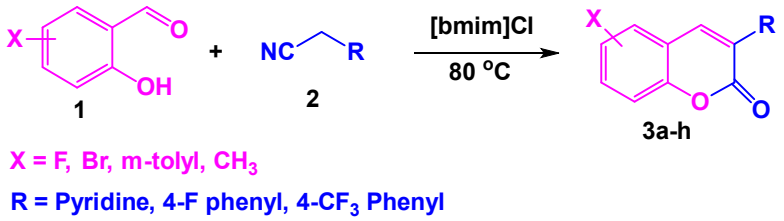
versatile biodynamic agents. Coumarins or benzopyran-2-ones these are a group of nature occurring lactones, first derived from Tonka beans in 1820. Coumarins are one of the attractive oxygen containing heterocyclic moiety, with many derivatives being known for more than a century. The potential biological profile offered by coumarin and its derivatives attributed to vast diversity in substitution patterns on core scaffold. Coumarin represents an effective group of natural products; the majority of them acquire helpful medicinal & pharmaceutical activity with a variety of applications as an anti-HIV agent [8], anticancer agent [9], anti-fungal [10], anti TB [11], anti-microbial [12], anti-viral [13], anti-inflammatory [14], neuro protective [15] and anti-oxidant activity [16]. These fascinating biological profiles of the coumarins put together as adaptable target in organic synthesis. Few remarkable examples of coumarin are depicted in **Figure 1.** In last two decade, ionic liquids have become an important choice to conventional organic solvents and catalysts because of their distinguishing physical and chemical properties, such as zero vapor pressure, chemical stability, excellent solubility with organic and inorganic compounds, with the ease of recovery and reuse [17]. Ionic liquids, especially imidazolium-based ionic liquids has been noticed as self-assembled solvents that can accommodate incoming organic molecules by creating cavities and hence present an exceptional platform for catalysis. [18, 19] in recent times, these media are used in a wide range of organic reactions [20, 21] greater than ever importance in the context of green synthesis.

So, based on the above literature survey, in this article we thirst to report an efficient and simple method for the synthesis of novel 3-(pyridin-2-yl)-2H-chromen-2-one and 3-(phenyl) -2H-chromen-2-one derivatives by using [Bmim]Cl ionic liquid.

■ Results and Discussion

A series of novel 3-(pyridine-2-yl) chromene-2-one & phenyl-2H-chromene-2-one derivatives were synthesized in good to excellent yield *via* one-pot synthesis of salicylaldehyde & substituted acetonitrile in the presence of [Bmim] Cl ionic liquid under stirring conditions. Primarily the ionic liquid was prepared by the reaction of 1-butyl chloride and 1-methyl imidazole as per previously reported method. [22] At the beginning of our research we tried the reaction between salicylaldehyde and pyridyl-2-acetonitrile in [Bmim]Cl was studied as model reaction. Initially the model reaction was stirred at room temperature; unluckily the reaction did not proceed even after 12 hrs.

To optimize the reaction condition of reaction temperature we have tried the study of the model reaction from 30-100°C in the gap of 10°C. The best result in terms of time and yield for the model reaction has been observed at 80 °C (**Table 1**). There was no product formation at 30 & 40°C even after 12 hrs. At 50°C there is trace amount of desired product was observed (by tlc) & from 60 to 90°C not only the appearance of product yield increased but the time it took to complete the reaction also decreased. However a further rise in the temperature resulted in the reduction of the yield. This suggested the optimum temperature condition to be 80 °C (**Scheme 1**).



Scheme 1. [Bmim]Cl Ionic liquid mediated synthesis of 3-(pyridine-2-yl)/ phenyl-2H-chromene-2-one derivatives.

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Table 1. Optimization of reaction temperature for the synthesis of 3-(pyridine-2-yl)-2H-chromen-2-one. (3a) [a].

Entry	Temperature (°C)	Time (h)	Yield (%) [b]
1	30	12	No reaction
2	40	12	No reaction
3	50	10	Trace
4	60	8.5	60
5	70	6.0	75
6	**80**	**4.5**	**88**
7	90	4.5	88
8	100	4.5	82

[a] Reaction conditions: salicylaldehyde (1mmol), pyridyl-2-acetonitrile (1mmol), [Bmim] (0.5mmol) at 80 °C. [b] Yield of isolated product.

Table 2. Optimization of solvent for the synthesis of 3-(pyridine-2-yl)-2H-chromen-2-one. (3a) [a]

Entry	Solvent	Temperature(°C)	Time (h)	Yield (%)[b]
1	Water	Reflux	7	No reaction
2	Ethanol	78	7	45
3	Methanol	64	7	40
4	Acetone	60	7	20
5	Dichloromethane	40	7	No reaction
6	Acetonitrile	80	7	45
7	DMF	80	7	40
8	DMSO	80	7	45
9	Solvent free	80	7	No reaction
10	[Bmim]Cl	80	4.5	88

[a] Reaction conditions: salicylaldehyde (1mmol), pyridyl-2-acetonitrile (1mmol) [b] Yield of isolated product.

After a preliminary study of temperature optimization, the influence of several solvents has also been examined to find out any other solvents could afford the formation of **3a** with a higher yield than [Bmim]Cl. Nevertheless, unluckily, none of the other solvents gave a higher yield than [Bmim]Cl (**Table 2**). To mark the importance of [Bmim]Cl, we also performed the solvent-free synthesis of **3a** (**Table 2**) and as expected, it does not produce the desired product. In order to extend the strength and scope of this protocol, we investigated a reaction with variety of substituted salicylaldehyde and various substituted acetonitrile. The results are summarized in **Table 3**.

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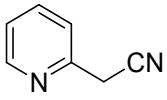
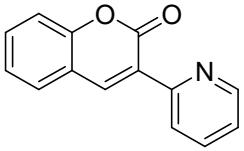
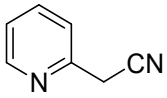
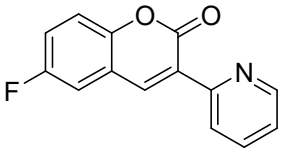
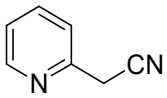
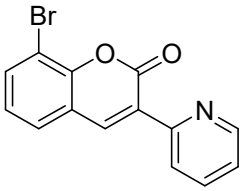
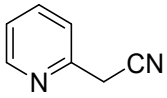
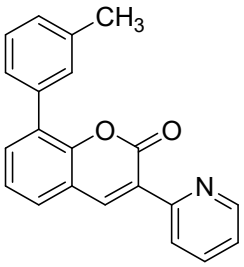
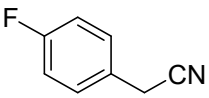
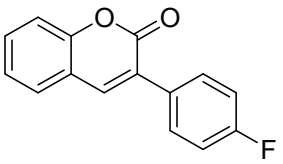
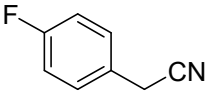
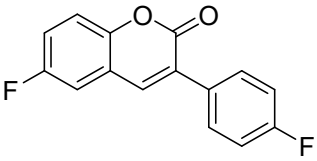
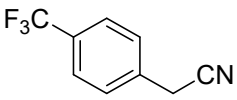
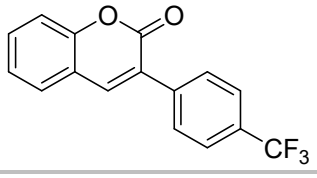
Table 3 Ionic liquid, [Bmim]Cl catalyzed synthesis of chromene-2-one derivatives [a]

Entry	X	R	Product	Time (h)	Yield (%) [b]
3a	H			4.5	88
3b	5-F			4.0	85
3c	3-Br			6.0	86
3d	3-(m-tolyl)			7.0	88
3e	H			5.5	90
3f	5-F			6.2	88
3g	H			5.0	84

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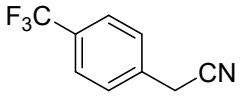
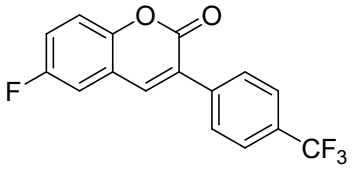
3h	5-F			5.5	85

[a] Reaction conditions: 1 (1mmol), 2 (1mmol), [Bmim]Cl (0.5mmol) at 80 ºC ; [b] Yield of isolated product.

Structural determination of isolated compound

Primary elucidation of the structure for the optimized reaction isolated product starts with FT-IR spectra. A medium band obtained at 3052cm^{-1} represents the =CH stretch in aromatic, a strong band at 1722 cm^{-1} represents the presence of α, β- unsaturated carbonyl group (C=O stretch) in &-lactones, a medium band at 1243 & 1108 cm-1 represent the C-O stretch in ester, and absent of band between the region 2000-2300cm^{-1} confirms the starting material is completely reacted i.e. absent of –CN (acetonitrile). The determination of structure for the product was further confirmed by 1H NMR spectra. A singlet obtained at 8.82 (s, 1H, -CH) and the entire protons in aromatic region confirms the formation of product. In addition the absent of any peak (broad) above 9.0 confirms that the aldehydic proton and –OH are completely reacted. Also the mass of the product is confirmed by the LC-MS spectra indicating the line at 224.1 giving (M+1) peak authenticates the formation product.

Biological Study

Antimicrobial activities

Antimicrobial activity of newly synthesized compounds 3-(pyridine-2-yl)/phenyl-2H-chromene-2-one derivatives (**3a-3h**) against human pathogens were analyzed by using disk diffusion method and the MIC was calculated using Resazurin microtitre plate method. The results of the assays are depicted in **table 4 & 5** which conceded the antimicrobial potential of synthesized compounds against selected human pathogens. Compounds **3b, 3c & 3f** were found to be competent growth **(MIC = 7.81** µg/mL**)** of the selected microbial human pathogens as compared to the standard drugs Streptomycin **(MIC= 1.95** µg/mL**) and Fluconazole (MIC=1.95** µg/mL**)** for bacteria and fungi respectively. Compounds **3d, 3e, 3g** also showed good to moderate antimicrobial activity **(MIC= 62.5** µg/mL **to 15.62** µg/mL**).** Remaining compounds showed moderate to minimum antimicrobial activity towards selected pathogens.

Antioxidant activity

Antioxidants play a key role in many diseases including pathogenic diseases. Antioxidants reduce the tissue inflammation and oxidative stress formed during active infection by resisting the effect of reactive oxygen species (ROS). The newly synthesized compounds showed good antimicrobial activity, it is essential to evaluate its antioxidant property. Antioxidant activity was carried out by using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and Hydroxyl radical (OH) scavenging method taking ascorbic acid and α-Tocopherol as standard. Results of DPPH and OH radical scavenging assay for compounds (**3a-3h**) were expressed as % antioxidant activity **(Figure 2**).

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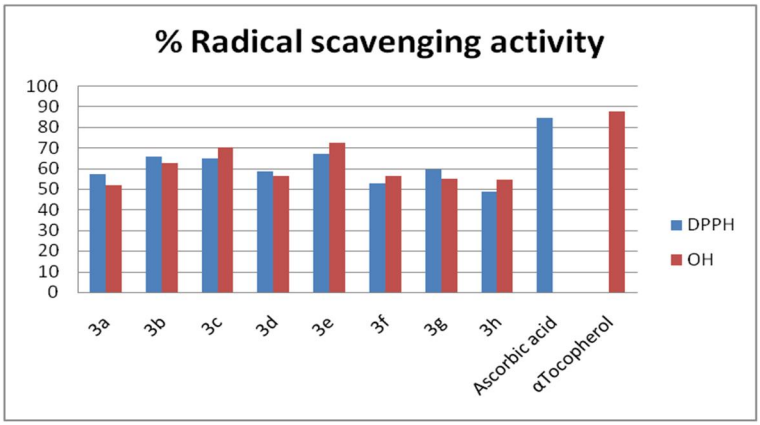

Figure 2. % radical scavenging activity of synthesized compounds.

■ Summary and Outlook

In conclusion we have developed an efficient and simple synthetic protocol for the synthesis of novel coumarin derivatives (3a-h) using [bmim]Cl ionic liquid as green solvent. The synthesized novel compounds were characterised by spectrochemical methods i.e. IR, ^{1}HNMR, ^{13}CNMR & Mass spectroscopy techniques. The novel compounds have been carried out for their in vitro antimicrobial, antifugal, antioxidant activity against bacterial and fungal strain. The antibacterial activity of compound 3b **MH-02** and 3e **MH-05** showed excellent activity with MIC of **7.56 µg/ml** against selected human pathogens. 3b, 3c & 3e **MH-02, 03** and **05** showed best DPPH and OH radical scavenging potential as compared with the standard ascorbic acid.

■ Experimental

General procedure

In 50 mL RB flask, containing [Bmim]Cl (0.5 mmol) was added to a mixture of pyridyl-2-acetonitrile (1.0 mmol) and 2-hydroxybenzalaldehyde (1.0 mmol.) and heated to 80°C for 4 to 8 h. Progress of the reaction was monitored by TLC. Upon completion of reaction, reaction mass was quenched in 5 % aqueous H_2SO_4 and stirred for 0.5 h. The precipitated solid was collected by filtration and purified by silica gel flash column chromatography using 0-20 % ethyl acetate in *n*-hexane to get pure chromene derivative.

Disk diffusion assay.

The antibacterial and antifungal potential of synthesized compounds was evaluated as per the previous reported method [23,24]. Briefly, each dried paper disk (whatmann filter paper No.1) contained synthesized compounds 50 µL (1 mg/ mL). Each disk was then placed on the surface of the sterile solidified Muller Hilton agar which were previously spreaded with inoculums of selected human pathogens *E. coli, B. subtilis, S. typhi, S. aureus, R. oryzae, P. chrysogenum, A. niger and C. albicans.* Streptomycin and fluconazole was used as standard (1 mg/mL). The plates were kept in refrigerator for diffusion for 1 hr and then transferred to the incubator at 37ºC for 24 hrs. After incubation, the zones around the discs were measured by the zone scale (Himedia Pvt. Ltd. Mumbai).

Resazurin microtiter plate assay (REMA)

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The REMA plate assay was carried out as described [24,25]. Briefly, 100 µL of respective broth medium was dispensed in each well of a sterile flat-bottom 96-well plate, and serial twofold dilutions of each synthesized compound were prepared directly in the plate. One hundred micro litres of inoculums was added to each well. Sterile cold water was added to all perimeter wells to avoid evaporation during the incubation. The plate was covered, sealed in a plastic bag, and incubated at 37°C. After 24 hrs of incubation, 30 µL of resazurin solution (0.01% in sterile deionized water) was added to each well, and the plate was re-incubated overnight. A change in color from blue to pink indicated the growth of bacteria, and the MIC was defined as the lowest concentration of drug that prevented this change in color. The drug concentration ranges used were as follows: for synthesized nanoparticles and standards 0.97- 500 µg/mL.

Antioxidant assay:

2, 2-diphenyl-1-picrylhydrazyl radical scavenging assay (DPPH)

The electron donation ability of the any compound was measured from the bleaching of the purple colored solution of DPPH [24,25]. DPPH is stable reagent used in this spectrophotometric assay. Briefly, the assay was performed by mixing of equal quantity of DPPH solution and the test compound, so that the final volume is made up to 3 mL incubate the samples for 20 min, read the absorbance at 517 nm using UV Spectrophometer (Shimadzu Corp. Japan). Ascorbic acid (1 mM) was used as a standard. Percent inhibition was calculated using following formula:

% radical scavenging activity = 1 – T/C x 100

Hydroxyl radical assay (OH).

The OH radical scavenging activity was demonstrated with Fenton reaction [20, 21]. Briefly, the typical reaction mixture contained 60 µL of $FeCl_2$ (1 mM), 90 µL of 1-10 phenanthroline (1 mM), and 2.4 mL of phosphate buffer (0.2 M, pH 7.8), 150 µL of H_2O_2 (0.17 M) and 1.5 mL Of individual synthesized compound (1 mg/mL). The reaction was started by adding H_2O_2. After 5 min incubation at room temperature, the absorbance was read at 560 nm using UV Spectrophometer (Shimadzu Corp. Japan). Ascorbic acid (1 mM) was used as reference.

% radical scavenging activity = 1 – T/C x 100

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