

Brønsted acidic ionic liquid catalyzed highly efficient synthesis of chromeno pyrimidinone derivatives and their antimicrobial activity

Janardhan Banothu, Rajitha Bavanthula*

Department of Chemistry, National Institute of Technology, Warangal 506004, AP, India

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Abstract

A series of 8,9-dihydro-2-(2-oxo-2*H*-chromen-3-yl)-5-aryl-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-diones (5a-j) have been synthesized by the reaction of 2-amino-5,6,7,8-tetrahydro-5-oxo-4-aryl-4*H*-chromene-3-carbonitrile (**4a-j**) with coumarin-3-carboxylic acid under neat conditions employing Brønsted acidic ionic liquid (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate as catalyst. Structures of all the compounds were established on the basis of analytical and spectroscopic data. All the compounds were evaluated for their *in vitro* antimicrobial activity against different bacterial and fungal strains.

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In recent years ionic liquids (ILs) playing an important role in synthetic chemistry due to their interesting properties like high thermal stability, non volatility, eco friendly and reusability [1]. Reactions under solvent-free conditions [2] are also continuously attracted to the researchers both from academia and industry, due to the fact that without solvent, reactions usually need shorter reaction time, simpler reactors and require simple and efficient workup procedures.

Chromene derivatives represent an important class of compounds. They are often used as structural unit in many natural products [3] and have been reported to possess various pharmacological activities such as antimicrobial [4], antitumor [5], antiaggregating [6], antidepressant [7] and antiproliferative activities [8]. It is well known that pyrimidine and coumarin derivatives were also found to possess antiallergic [9], antimicrobial [10], antioxidant [11], anti-inflammatory [12] and anticancer activities [13].

In view of the pharmaceutical importance of these compounds, many improved methods have been developed such as $\text{H}_3\text{PW}_{12}\text{O}_{40}$ [14], $\text{Yb}(\text{OTf})_3$ [15], carbon materials [16] and ionic liquid [17] catalyzed reactions, but these ionic liquid are expensive. To avoid this limitation and for the continuation of our studies on the synthesis of biologically important heterocyclic compounds [18], in the present work we have designed and synthesized a novel chromeno pyrimidinone derivatives incorporated coumarin moiety at second position utilizing an eco-friendly, reusable and inexpensive ionic liquid as a catalyst under neat conditions and evaluated their *in vitro* antimicrobial activity against different bacterial and fungal strains.

* Corresponding author.

E-mail address: rajitabhargavi@yahoo.com (R. Bavanthula).

1. Results and discussion

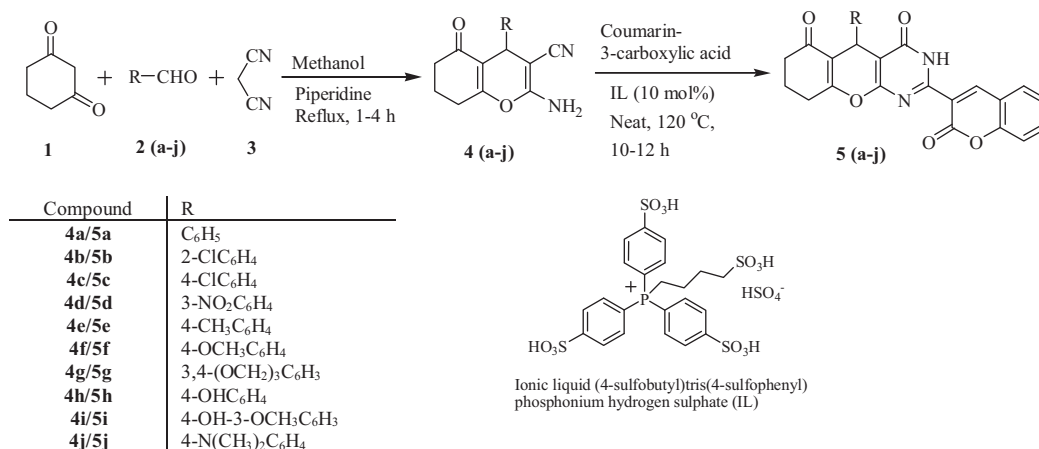
Ionic liquid (IL) has prepared according to the literature procedure [19]. The synthetic pathway of the title compounds was shown in Scheme 1. The intermediate **4a–j** were obtained by the three component condensation of cyclohexane-1,3-dione, aryl aldehyde **2a–j** with malononitrile under basic conditions in alcohol at refluxing temperature. Desire products **5a–j** were obtained by the reaction of **4a–j** with coumarin-3-carboxylic acid under neat conditions at 120 °C utilizing ionic liquid (IL) as catalyst.

Initially the reaction between compound **4a** and coumarin-3-carboxylic acid was carried out under neat conditions at 120 °C without and with different acid catalyst (sulfuric acid, silica sulfuric acid, cellulose sulfuric acid, ionic liquid each 10 mol%) and observed maximum yield with ionic liquid. Also observed, the change in the amount of the catalyst (ionic liquid) has no effect on the product yield and reaction time.

At these optimistic conditions (solvent-free, 120 °C, 10 mol% of IL) we synthesized various chromeno pyrimidinones **5a–j** (Table 1). After completion of the reaction the catalyst was recovered by evaporating the aqueous layer, washed with acetone, dried and reused for subsequent reactions without significant loss in its activity. All the synthesized compounds were confirmed by their analytical and spectroscopic data (see the supporting information).

1.1. Antimicrobial activity

All the newly synthesized compounds **5a–j** were screened for their *in vitro* antibacterial and antifungal activities against *Bacillus subtilis* (Bs), *Staphylococcus aureus* (Sa), *Staphylococcus epidermidis* (Se) (Gram-positive),



Scheme 1. Synthetic pathway of the chromeno pyrimidinones.

Table 1
Synthesis of chromeno pyrimidinones **5(a–j)** using ionic liquid (IL).^a

Analog	R	Time (h)	Yield ^b (%)	M.p. (°C)
5a	C ₆ H ₅	12	68, (68, 67, 65, 64) ^c	276–278
5b	2-ClC ₆ H ₄	12	65	235–236
5c	4-ClC ₆ H ₄	10	74	248–250
5d	3-NO ₂ C ₆ H ₄	12	69	269–270
5e	4-CH ₃ C ₆ H ₄	10	71	234–236
5f	4-OCH ₃ C ₆ H ₄	10	68	220–222
5g	3,4-(OCH ₂) ₃ C ₆ H ₃	10	65	242–244
5h	4-OHC ₆ H ₄	12	70	230–232
5i	4-OH-3-OCH ₃ C ₆ H ₃	12	75	267–269
5j	4-N(CH ₃) ₂ C ₆ H ₄	12	67	273

^a Reaction conditions: Compounds **4a–j** (1 mmol), coumarin-3-carboxylic acid (1 mmol), ionic liquid (10 mol%), neat, 120 °C.

^b Yields refer to the pure isolated products.

^c Yields refer to the reusability of catalyst over additional four times.

Table 2

In vitro antimicrobial activity of compounds **5a–j**.

Analog	Minimum inhibitory concentration (MIC) in $\mu\text{g/mL}$									
	Bacterial strains						Fungal strains			
	Bs	Sa	Se	Ec	Pa	Kp	Af	Rsp	An	Ca
5a	150	150	150	75	150	150	150	150	150	50
5b	150	150	150	50	150	150	150	150	150	50
5c	25	100	50	50	100	100	150	150	150	50
5d	150	150	150	75	150	150	100	100	100	25
5e	150	150	150	75	150	150	100	150	150	50
5f	100	100	100	50	100	50	100	100	100	50
5g	50	50	100	12.5	50	50	100	100	100	50
5h	150	150	150	50	150	150	150	100	100	50
5i	150	150	150	75	150	150	100	100	100	50
5j	150	150	150	75	150	150	100	50	100	25
CPF	24	25	22	25	12.5	25	–	–	–	–
AMP-B	–	–	–	–	–	–	50	25	50	25

–, not performed.

Standard drugs: Ciprofloxacin (CPF), Amphotericin-B (AMP-B).

Escherichia coli (Ec), *Pseudomonas aeruginosa* (Pa), *Klebsiella pneumonia* (Kp) (Gram-negative) bacterial strains and *Aspergillus flavus* (Af), *Rhizopus schipperae* (Asp), *Aspergillus niger* (An), *Candida albicans* (Ca) fungal strains by the liquid dilution method [20] using Ciprofloxacin (for bacterial) and Amphotericin-B (for fungal) as standard drugs.

Different concentrations of analogs and the positive control drugs were prepared in DMSO. Inoculums of the bacterial and fungal cultures were also prepared. Inoculum (0.2 mL) and sterile water (3.8 mL) were added to a series of test tubes each containing 1 mL of test solution at different concentrations. The tubes were incubated for 24 h at 37 °C and carefully observed for the presence of turbidity. The minimum concentration at which no growth was observed was taken as the MIC value (Table 2).

From the activity report (Table 2) it was notified that, most of the compounds showed moderate activity against all the bacterial and fungal strains but compounds **5c** (MIC: 25 $\mu\text{g/mL}$) and **5g** (MIC: 12.5 $\mu\text{g/mL}$) has shown excellent antibacterial activity against *B. subtilis* and *E. coli* respectively on par with standard drug Ciprofloxacin. Similarly compounds **5d** (MIC: 25 $\mu\text{g/mL}$) and **5j** (MIC: 25 $\mu\text{g/mL}$) has shown good antifungal activity against *C. albicans* compared with standard drug Amphotericin-B.

2. Experimental

The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded on Thermo Nicolet Nexus 670 spectrophotometer using KBr pellet, values are expressed in cm^{-1} . NMR spectra were recorded on Bruker 300-MHz spectrometer using DMSO as solvent and TMS as internal standard, chemical shifts are expressed in ppm. The C, H and N analysis of the compounds were done on a Carlo Erba modal EA1108. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

2.1. General procedure for the synthesis of **5a–j**

Ionic liquid (10 mol%) was added to a mixture of **4a–j** (1 mmol) and coumarin-3-carboxylic acid (1 mmol), heated at 120 °C for about 10–12 h. After completion of the reaction 2 mL of water was added and stirred at RT for 5 min. The precipitated product was filtered, washed with water, dried and purified over column chromatography using silica gel (230–400 mesh) with *n*-hexane and ethyl acetate (8:2) as eluent. The aqueous layer containing catalyst was recovered, washed with acetone, dried and reused for subsequent reactions without loss in its activity and product yield.

8,9-Dihydro-2-(2-oxo-2H-chromen-3-yl)-5-p-tolyl-3H-chromeno[2,3-d]pyrimidine-4,6 (5H,7H)-dione (5e): Pale yellow solid; IR (KBr, cm^{-1}): 3298 (NH), 1724 (CO of lactone), 1685 (CO of ketone), 1641 (CO of lactum), 1604

(C=N), 1202 (C–O–C); ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 1.89–1.95 (m, 2H), 2.26 (s, 3H), 2.56 (t, 4H), 4.33 (s, 1H), 7.03–7.13 (m, 2H), 7.39–7.45 (m, 2H), 7.71–7.92 (m, 4H), 8.75 (s, 1H), 10.71 (s, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 193.9, 170.5, 163.9, 163.4, 156.6, 154.4, 153.6, 136.8, 134.9, 134.2, 130.1, 129.1, 127.4, 124.7, 118.3, 117.9, 116.0, 113.5, 100.6, 37.0, 36.2, 26.2, 20.7, 20.5; MS (ESI), 70 eV, m/z : 453 (M+1); Anal. Calcd. For $\text{C}_{27}\text{H}_{20}\text{N}_2\text{O}_5$: C, 71.67; H, 4.46; N, 6.19; Found: C, 71.56; H, 4.55; N, 6.42.

3. Conclusion

Various chromeno pyrimidinones (**5a–j**) were synthesized using an efficient, eco-friendly, reusable and inexpensive Brønsted acidic ionic liquid (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate as a catalyst. All the synthesized compounds were screened for their *in vitro* antimicrobial activity. Compound **5g** has shown excellent antibacterial activity against *E. coli* with MIC 12.5 $\mu\text{g/mL}$ compared to the standard drug ciprofloxacin (MIC 25 $\mu\text{g/mL}$). Similarly, compounds **5d** (MIC 25 $\mu\text{g/mL}$) and **5j** (MIC 25 $\mu\text{g/mL}$) have shown good antifungal activity against *C. albicans* with respect to positive control drug Amphotericin-B (MIC 25 $\mu\text{g/mL}$).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.cclet.2012.06.041>.

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