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A simple, one pot synthesis of furo[3,2-*c*]chromenes and evaluation of antimicrobial activity

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ABSTRACT

Synthesis of a number of 2-cyano-4-oxo-3-phenyl-3,4-dihydro-2*H*-furo[3,2-*c*]chromene-2-carboxylate compounds (**5**) have been accomplished by a simple, multicomponent one pot reaction and evaluated for in vitro antimicrobial activity against different Gram-positive and Gram-negative bacterial strains. The outcome of the screening study showed that compound **5c** exhibited promising activity against *Micrococcus luteus* MTCC 2470 and *Klebsiella planticola* MTCC 530. Whereas, compound **5g** exhibited excellent activity against *Bacillus subtilis* MTCC 121, *Micrococcus luteus* MTCC 2470, *Klebsiella planticola* MTCC 530, *Escherichia coli* MTCC 739 and displayed a moderate activity against *Staphylococcus aureus* MTCC 96 and *Candida albicans* MTCC 3017 when compared with Ciprofloxacin (standard control).

Polycyclic oxygen heterocycles are one of the important fused heterocycles found in numerous natural products and are known to possess interesting biological activities.[1] Among these scaffolds, fused coumarin system especially furocoumarines are the secondary metabolites found in some higher plants such as celery (*Apium graveolens*), parsnip (*Pastinaca sativa*) and carrot (*Daucus carota*).[2] Naturally occurring furocoumarines prevail in linear as well as in angular form. For example, Psoralen, Xanthotoxin and Bergapten are the most abundant linear furocoumarines, whereas the angular form is represented by angelicin, sphondin, and pimqinellin.[3] These compounds exhibit diverse biological activities such as fungicidal,[4] insecticidal,[5] insect antifeedant,[6] anti-HIV,[7] and anticancer.[8] Recently furocoumarines allured the attention owing to their abilities to arouse drug interactions through inhibition of cytochrome P450. Grapefruit juice is a well known example for food drug interaction.[9] Further, these compounds have gained a renewed interest with respect to human health because of their natural presence in common vegetables.[10] Therefore, development of methodical synthetic routes to prepare these compounds is an important task in modern organic synthesis.[11]

Accordingly, a great deal of efforts have been made and a number of reports have appeared on the synthesis of furocoumarines which includes manganese(III) acetate promoted reaction of 4-hydroxycoumarine with electron rich alkenes[12] and alpha bromonitroalkenes[13] independently. Via in situ generation of *N*-ylides,[3] one pot reaction of 4-hydroxycoumarine and aromatic aldehyde employing ionic liquid,[14] oxidative cyclization of the Michael adduct of cyclohexane 1,3 dione and chalcones involving combination of $PhI(OAc)_2/Bu_4NBr/t$-BuOK.[15] Michael addition/alkylation of the resultant product of 1,3-dicarbonylcompounds and 2-nitroacrylates[16] in presence of base, and $Yb(OTf)_3$ promoted propargylation and allylation of 4-hydroxycoumarines.[17] However, all these reports required the use of metal catalysts, ionic liquids, combination of bases, organic solvents involving multiple synthetic steps and the reported yields were poor in some cases. Therefore, there is still a need to emerge with simple methodologies to prepare these type of compounds.

On the other hand, multicomponent reactions (MCRs) have become a powerful tool in organic synthesis because of their atom economy, multiple bond forming efficiency and convergence. Additionally, MCRs based on 'bio-solvents' such as ethanol which is produced from renewable resources[18] is an important parameter as it is one of the best alternative to hazardous solvents due to the EHS (Environment, Health and Safety) properties such as increased biodegradability or reduced ozone depletion potential.[19] Considering these facts and in continuation to our ongoing research work on the synthesis of furan fused heterocyclic compounds of biological interest[20] herein, report the synthesis of furo[3,2-*c*]-chromenes in a one pot, multicomponent reaction in high yields.

The study was initiated by reacting 4-hydroxy coumarine (**1**), benzaldehyde (**2**) and malanonitrile (**3**) in ethanol at room temperature followed by reflux and obtained the compound **4** in high yields (Scheme 1).

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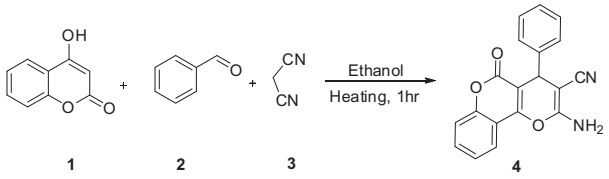
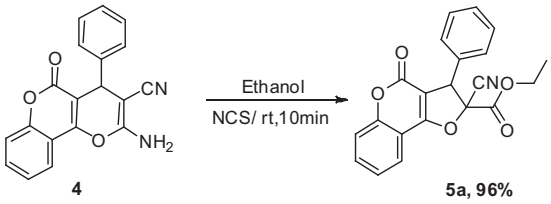


Scheme 1.



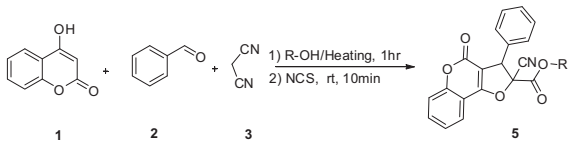
Scheme 2.

In order to synthesize the furochromenes, compound **4** was treated with *N*-chlorosuccinimide (NCS) in ethanol at room temperature. Interestingly, formation of ethyl 2-cyano-4-oxo-3-phenyl-3,4-dihydro-2*H*-furo[3,2-*c*]chromene-2-carboxylate (**5**) was obtained in high yields (Scheme 2).

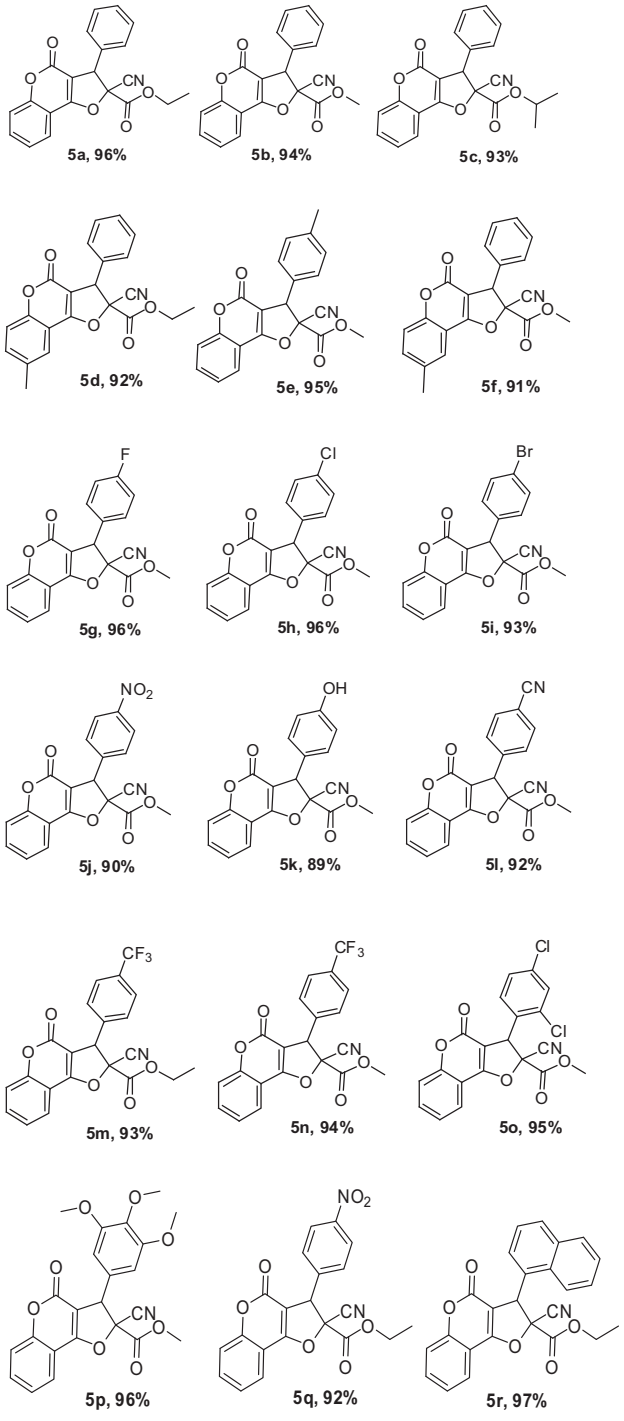
With the formation of a ring contraction product **5**, we planned to prepare the same in a single step. Consequently, 4-hydroxy coumarine (**1**), benzaldehyde (**2**) and malanonitrile (**3**) was reacted in ethanol at reflux temperature followed by sequential addition of NCS in the same pot (Scheme 3). To our satisfaction, this reaction gave **5** in high yields. Intrigued by the formation of **5** in a one pot multicomponent reaction, the same reaction was repeated in methanol and isopropanol independently and gratifyingly obtained the corresponding ester compounds **5** in almost equivalent yields.

Having obtained the compound **5** in high yields, experiments were carried out with varying NCS quantity. However, best yields were obtained with 1 equiv. Similar results were also obtained with NBS and NIS. Whereas, I_2, KI, CuBr, CuI and $NaClO_2$ failed to give the product **5** (see Table 1). Structure of **5** was characterized based on the spectral data and was also comparable with the previous report.[21] With the set of reaction conditions in hand, this protocol was generalized by reacting compound **1** with various aromatic aldehydes, malanonitrile and obtained the corresponding products **5a**–**5r**. A wide range of functional groups such as electron donating and electron withdrawing groups on **2** were well tolerated. However, yields are varied. Electron releasing groups gave better yields than electron withdrawing groups. Fused aromatic aldehydes such as naphthaldehyde produced the corresponding furo chromene product (**5r**) However, 2-methoxy naphthaldehyde could not produce the pyran compound and olefin (Knoevenagel product) is recovered. Further, hetero aromatic aldehydes are ended up with only pyran compounds and not leading to the desired products even in ethanol, methanol, isopropyl alcohol and water. Furthermore, aliphatic aldehydes also failed to produce the pyran compound (**4**) and only the Knoevenagel product recovered.

Based on the previous reports, a plausible mechanism is proposed. It is very well known that compound **4** can be obtained by the reaction of 4-hydroxy coumarine, benzaldehyde and malanonitrile by Knoevenagel condensation followed by Michael addition. Thus obtained compound **4** upon treatment with NCS gives imine '**A**'. Then the alkoxy group from the solvent interacts with the imine resulting in C—O bond dissociation followed by elimination of HCl leading to five membered ring. Further, hydrolysis of imine leads to the desired product **5**.



R = Ethyl, Methyl, Isopropyl



Scheme 3. Reaction conditions: 4-hydroxy coumarine (**1**, 2.8 mmol), benzaldehyde (**2**, 2.8 mmol) and malononitrile (**3**, 2.8 mmol) in 5 mL ethanol at 80 °C temperature about 1 h and then added NCS (**4**, 2.8 mmol) rt 15 min. Yields refers to pure products.

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Table 1
Optimization of reaction conditions for the synthesis of furochromene compounds (**5**)

S. no	Solvent	Reagent	Temperature	Yields of **5** (%)
1	**Ethanol**	**NCS (1 equiv)**	**Reflux**	**96**
2	Methanol	NCS (1 equiv)	Reflux	94
3	Isopropanol	NCS (1 equiv)	Reflux	95
4	Ethanol	NCS (0.1 equiv)	Reflux	32
5	Ethanol	NCS (0.2 equiv)	Reflux	47
6	Ethanol	NCS (0.5 equiv)	Reflux	68
7	Ethanol	NIS (1 equiv)	Reflux	95
8	Ethanol	NBS (1 equiv)	Reflux	95
9	Ethanol	I_2	Reflux	NR
10	Ethanol	KI	Reflux	NR
11	Ethanol	CuBr	Reflux	NR
12	Ethanol	CuI	Reflux	NR
13	Ethanol	$NaClO_2$	Reflux	NR

Reflux = Reflux to room temperature, NR = No Reaction.
Bold indication for high yields that are obtained with these parameters.

Table 2
Antimicrobial activity of furochromene compounds (**5a**–**5r**)

Entry	Test compounds	Minimum inhibitory concentration (μg/mL)							
		Staphylococcus aureus MTCC 96	*Bacillus subtilis* MTCC 121	*S. aureus* MLS16 MTCC 2940	*Micrococcus luteus* MTCC 2470	*Klebsiella planticola* MTCC 530	*Escherichia coli* MTCC 739	*Pseudomonas aeruginosa* MTCC 2453	*Candida albicans* MTCC 3017
1	**5a**	>250	>250	>250	>250	>250	>250	>250	>250
2	**5b**	>250	>250	>250	>250	>250	>250	>250	>250
3	**5c**	**125**	**62.5**	**125**	**15.6**	**15.6**	>250	>250	>250
4	**5d**	>250	**250**	>250	>250	**250**	>250	>250	>250
5	**5e**	>250	>250	>250	**125**	>250	>250	>250	>250
6	**5f**	>250	>250	>250	>250	>250	>250	>250	>250
7	**5g**	**62.5**	**7.8**	**62.5**	**7.8**	**7.8**	**15.6**	>250	**62.5**
8	**5h**	>250	>250	>250	>250	>250	**62.5**	>250	>250
9	**5i**	>250	>250	>250	>250	>250	**125**	>250	>250
10	**5j**	>250	>250	>250	>250	>250	>250	>250	>250
11	**5k**	>250	>250	>250	>250	>250	>250	>250	>250
12	**5l**	>250	>250	>250	>250	>250	>250	>250	>250
13	**5m**	>250	**250**	>250	>250	**250**	>250	>250	>250
14	**5n**	>250	>250	>250	>250	>250	>250	>250	>250
15	**5o**	>250	>250	>250	>250	>250	>250	>250	>250
16	**5p**	**62.5**	>250	>250	>250	>250	>250	>250	>250
17	**5q**	>250	>250	>250	>250	>250	>250	>250	>250
18	**5r**	>250	>250	>250	>250	>250	>250	>250	250
Miconazole (Standard control)		[a]–	–	–	–	–	–	–	7.8
Ciprofloxacin (Standard control)		0.9	0.9	0.9	0.9	0.9	0.9	0.9	[a]–

The highlighted values are the indication for best results.
[a] No activity.

Plausible mechanism

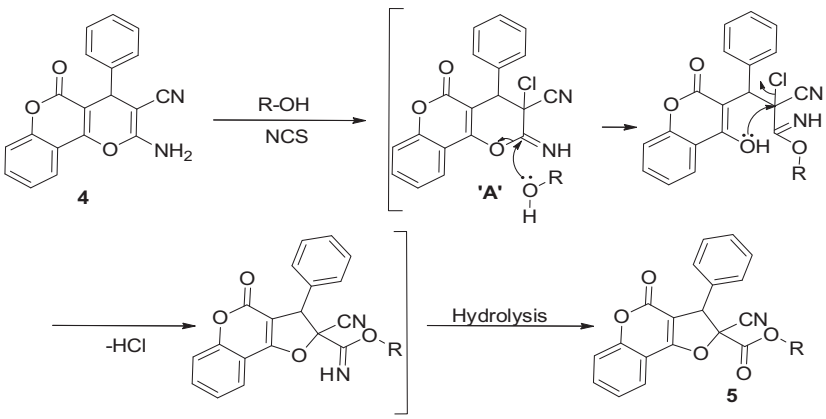

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Table 3
Minimum bactericidal concentration (MBC) of furochromene compounds (**5c** and **5g**)

Test compounds	Minimum bactericidal concentration (μg/mL)			
	Bacillus subtilis MTCC 121	*Micrococcus luteus* MTCC 2470	*Klebsiella planticola* MTCC 530	*Escherichia coli* MTCC 739
5c	–	62.5	62.5	–
5g	62.5	62.5	62.5	62.5
Ciprofloxacin	1.17	1.17	1.17	1.17

Next, compounds **5a**–**5r** were screened for in vitro antimicrobial activity against different Gram-positive strains such as *Staphylococcus aureus* MTCC 96, *Bacillus subtilis* MTCC 121 *Staphylococcus aureus* MLS16 MTCC 2940 and *Micrococcus luteus* MTCC 2470, and Gram-negative bacterial strains such as *Klebsiella planticola* MTCC 530, *Escherichia coli* MTCC 739, *Pseudomonas aeruginosa* MTCC 2453 and *Candida albicans* MTCC 3017. The outcome of the screening study showed that compound **5c** (Table 2, entry 3) exhibited promising activity against *Micrococcus luteus* MTCC 2470 and *Klebsiella planticola* MTCC 530. Whereas, moderate activity was observed against *Bacillus subtilis* MTCC 121. Further, compound **5g** (Table 2, entry 7) showed excellent antimicrobial activity (MIC values ranging between 7.8 and 15.6 μg/mL) against *B. subtilis* MTCC 121, *Micrococcus luteus* MTCC 2470, *K. planticola* MTCC 530 and *Escherichia coli* MTCC 739 and displayed a moderate activity against *Staphylococcus aureus* MTCC 96 and *Candida albicans* MTCC 3017. Compounds **5h** and **5p** also exhibited a good antimicrobial activity against *E. coli* MTCC 739 and *S. aureus* MTCC 96.

When the structure–activity relationship (SAR) studies were compared between compounds **5a**–**c**, it was observed that all the three compounds are basic scaffolds without any substitution except variation in ester functional group on the furan ring. In case of **5c** probably isopropyl group might have contributed to the activity. Whereas, in case of compound **5g** probably fluoro substitution on the phenyl ring could be a reason for high activity. Surprisingly, compound **5n** which has CF_3 functional, did not show any activity. Presence of other electron withdrawing and electron releasing groups on the phenyl ring did not impact the activity as the remaining compounds (**5**, **5a**, **5c**, **5d**, **5e**, **5i**, **5j**, **5k**, **5l**, **5m, 5p,5q** and**5r**) did not show antimicrobial activity up to the maximum tested concentration of 250 μg/mL. The results to this regard are tabulated in Table 2.

Based on the promising antimicrobial activity of compounds **5c** and **5g**, they were further screened for minimum bactericidal concentration (MBC) activity. Outcome of the study showed that, compound **5c** exhibited moderate MBC activity 62.5 μg/mL against *Micrococcus luteus* MTCC 2470 and *Klebsiella planticola* MTCC 530, while **5g** exhibited moderate MBC activity 62.5 μg/mL against *Bacillus subtilis* MTCC 121, *Micrococcus luteus* MTCC 2470, *Klebsiella planticola* MTCC 530 and *Escherichia coli* MTCC 739.

In conclusion, we have synthesized a number of new furo[3,2-*c*] chromene compounds in a multicomponent one pot reaction, evaluated for in vitro antimicrobial activity against different Gram-positive and Gram-negative bacterial strains and emerged with two prominent compounds (**5c**, **5g**) with excellent antimicrobial activity and a moderate MBC activity as presented in Tables 2 and 3.

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Supplementary data

Supplementary data (^{1}H, and ^{13}C spectra of representative compounds (**5a**–**5r**) and general information) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.09.022.

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