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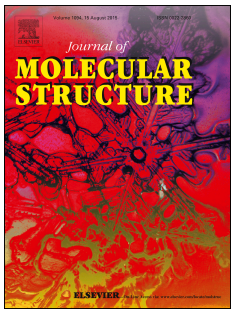

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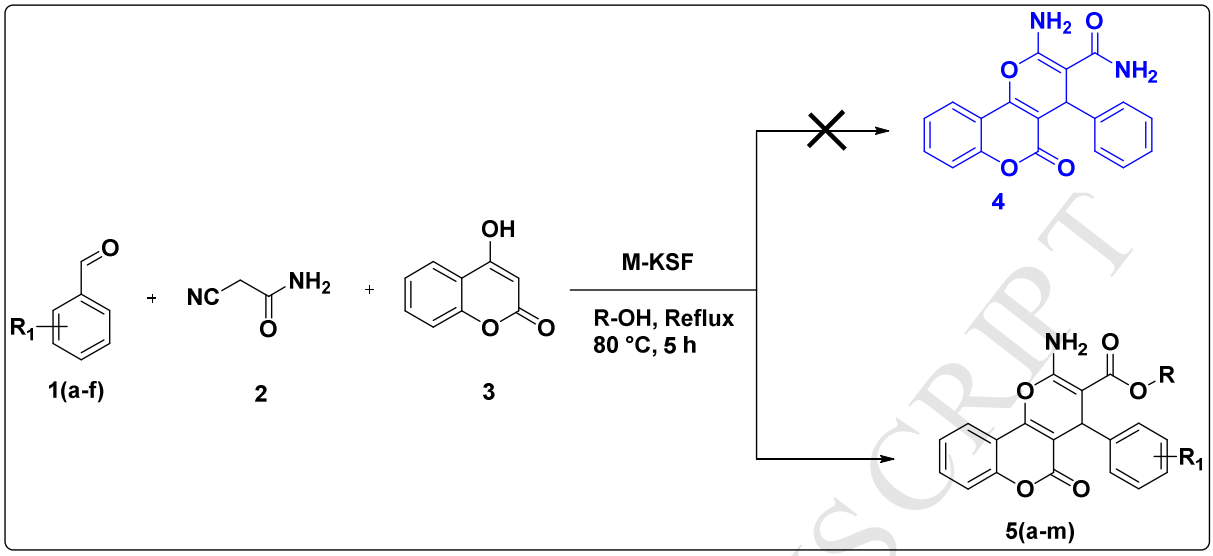

Montmorillonite-KSF Mediated One Step Synthesis of Pyranochromene Derivatives

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Abstract: One-pot three-component reaction of substituted aromatic aldehydes, 2-cyanoacetamide and 4-hydroxycoumarin in the presence of Montmorillonite-KSF (MKSF) in ethanol results in the formation of pyrano[3,2-c]chromene-3-carboxylates (5a-m) has been described. The reaction was tested in different alcohols, afforded pyrano [3,2-*c*] chromene-3-carboxylates (5a-m) of the corresponding alcohols in good yield. The mechanism reveals that the alcohol (as solvent) plays a major role in the inter conversion of amide to the corresponding esters with Montmorillonite KSF (M-KSF) as a catalyst. Excellent yields, inexpensive and readily available substrates, environmentally benign reaction condition, shorter reaction time, and easy workup are the major advantageous features of this protocol.

Keywords: Multicomponent reaction, Aromatic aldehydes, 4-Hydroxycoumarin, Montmorillonite KSF (MKSF), Pyrano[3,2-c]chromene, Heterogeneous catalyst.

1. Introduction

Nowadays multi component reactions (MCRs) have been designed to produce biologically active compounds and has become an important class of research in organic, medicinal and combinatorial chemistry [1]. The selection of the catalyst and the solvent also has a vital role in the formation of the product and selectivity [2-4]. Generally, researchers are interested and focused on the use of MCRs to synthesize a broad range of products [5]. Recently researcher's focused on the synthesis of pyrano[3,2-*c*]chromene derivatives, which can participate a significant role in pharmaceutical and biologically active compounds [6]. The compounds of pyrano system were found to have various biological activities such as anti-oxidant [7], antibacterial [8], antifungal [9], anti-inflammatory [10], anti-coagulant [11], anticancer [12, 13] and anti-HIV [14]. Generally, the biological and pharmaceutical activities of

chromenes depends on the nature of substituents (like Cl, F, OH, Br) being either on the pyrano system or on the adjacent rings.

The heterocyclic pyranochromenes are attractive targets in organic synthesis due to their biological activities as good as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals [15]. Therefore, searching efficient methods for the synthesis of these chromene compounds is interesting in organic synthesis and a few synthetic approaches have been reported to exploit three-component reaction of 1,3-diketones, aldehydes, malononitriles using DBU [16], DMAP [17], TBAB [18],ionic liquids [19], K_2CO_3 [20], Et_3N [21], piperidine [22], nano particles [23] and heteropoly acids [24]. Although, multicomponent reactions of aldehydes, malononitrile or cyanoacetic esters and 4-hydroxycoumarin is the one of the powerful methods for the synthesis of pyranochromenes as we discussed in the aforementioned section, usage of 2-cyanoacetamide has not been reported yet. The literature reports have their assets, but are often useful for the synthesis of only a narrow range of pyranochromenes and may necessitate using an expensive catalyst, longer reaction time, low yield and poor selectivity. Heterogeneous catalysts play a major role in numerous organic transformations.

Montmorillonite KSFis a well-known and widely used solid acid catalyst in synthetic organic chemistry because of much importance in later years [25-27]. It has received considerable attention because of its ease of handling, good reactivity, recyclability, experimental simplicity, commercial availability, non-toxicity and cost effectiveness and air and water compatibility. Owing to strong catalytic activity as Bronsted acid, Montmorillonite clay has been used extensively as a catalyst in Diels Alder reaction [28], Friedlander synthesis [29] and Knoevenagel condensation [30]. In this report, we have demonstrated a new, handy, environmental protocol for the synthesis 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxylates **5**(**a-m**) from aromatic aldehydes **1**(**a-e**), 2-cyanoacetamide **2** and 4-hydroxycoumarin **3** in the presence of M-KSF catalyst in the different alcoholic media. Meanwhile the three reactants were subjected to condensation with M-KSF in water medium affording 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxamide, **4**. To the best of our knowledge this is the first time, one-pot multicomponent reaction of pyrano [3,2-*c*]chromene derivatives with MKSF attempted and to be reported.

2. Experimental Section

2.1. Materials and Methods

All the commercially available materials were purchased from suppliers and were used without further purification and the reactions were monitored by TLC. All the reactions were performed using oven dried glassware. Elchem digital melting point apparatus was used for recording melting points in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR values were obtained using a Bruker Avance-400 MHz spectrometer in $CDCl_3$ and DMSO-*d6* solvent with TMS as the internal standard. Chemical shift values (ϱ) were expressed in parts per million (ppm). Couplingconstants (*J*) are reported in Hertz (Hz). Abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and dd = doublet of doublets.

2.1.1. General procedure for the synthesis of 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate derivatives (5a-m)

An equimolar mixture of substituted benzaldehydes (1 mmol) and 2-cyanoacetamide (1 mmol) in alcohols with a catalytic amount of M-KSF (100 mg) was refluxed at 80 ºC for 30 min. After consumption of aldehydes, 4-hydroxycoumarin (1 mmol) was added and kept for stirring under reflux conditions. After the addition of 4-hydroxy coumarin, the completion of the reaction was monitored by TLC and the reaction mixture was cooled to room temperature, solid obtained was filtered off and washed with ethanol to obtain the desired product in good yield and characterized by spectral analysis.

2.1.2. General procedure for the synthesis of 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3- carboxamide (4)

Benzaldehyde (1 mmol) 2-cyanoacetamide (1 mmol) Montmorillonite KSF (100 mg) and 5 mL of water were placed in a 50 mL round bottomed flask and stirred. The reaction was continued to 1 h at reflux temperature. After the completion of aldehyde consumption, 4-hydroxycoumarin was added. The reaction was refluxed for 2 h, the progress of the reaction was monitored by TLC, for the disappearance of intermediate (*E*)-2-cyano-3-phenylacrylamide. After the completion of reaction mixture was allowed to cool at room temperature and water was

discarded. The solid was collected by simple filtration and washed with cold ethanol and recrystallized from hot ethanol to obtain pure products for spectral analysis.

2.2. Biological Evaluation

2.2.1. General procedure for the radical scavenging activity by DPPH method

The DPPH radical scavenging activity was carried out by the reported method [29]. In the DPPH assay, the antioxidants are able to donate a hydrogen to reduce the stable radical DPPH to the yellow-coloured non-radical diphenyl-picrylhydrazine (DPPH-H).The changes in the colour (from deep violet to light yellow) of the standard and compounds **5**(**a-m**)were measured at 517 nm on a UV-Vis light spectrophotometer.

Stock solutions were prepared by dissolving 1 mg of the compounds **5**(**a-m**) in 1 mL of methanol. Then, different concentrations of the sample, 50, 75, 100, and 125 µg, were prepared by dissolving in 3 mL methanol. The DPPH solution was prepared just before the UV measurements. Then, 3 mL of the test sample and 1 mL of the DPPH solution were mixed and placed for incubation for 30 min at room temperature. The absorbance of incubated test solutions and control (without sample) were measured at 517 nm. Ascorbic acid was used as the standard. The experiment was carried out in triplicate. The IC_{50} values were calculated for each sample as well as standard is represented in Table 5.

The radical scavenging activity was calculated by following formula

$$\% \text{ Inhibition} = [AB - AA/AB] \times 100$$

Where AB is the absorption of blank solution and AA is the absorption of the test sample

2.2.2. General procedure for the in-vitro antibacterial studies

All the newly synthesized compounds were executed for their *in vitro* antibacterial studies against Gram-positive organisms such as *Staphylococcus aureus* ATCC 700699, *B. subtilis* MTCC 430 *Micrococcus luteus* MTCC 2470 and Gram negative organisms such as *Klebsiella* ATCC 10273, *Escherichia coli* ATCC 11105 and *Pseudomonas aeruginosa* MTCC 2453 by the agar well technique [31]. All the compounds were dissolved in DMSO and different concentrations were made. After inoculation, wells were scooped out with 3 mm, sterile cork borer and the caps of the dishes were replaced. To every well different concentrations of test solutions were added. All the plates and controls were kept at 37 ºC for 24 h incubation. Standard

antibacterial ampicillin was used as reference antibacterial substances, respectively for comparison.

For MIC determination, all the compounds were dissolved in DMSO to get the concentrations of 4.6, 9.3, 18.75, 37.50, 75.0, 150, 300, 600 and 1200 µg/mL. Standard antibacterial ampicillin (standard) was also tested for the comparison. Serial dilutions of all the synthesized compounds were performed by the modified agar well diffusion method. Test organisms were lawn cultured on the MHA plates. The agar surface was bored by using a sterilize cork borer. The concentrations of the test cultures were seeded with a 100 µL microbial suspension of 0.5 MacFarland density. The test plates were incubated at 37 ºC for 24 h. The lowest concentration which showed a clear zone of inhibition considered as the MIC value of each compound. The experiments were repeated thrice and the minimum inhibitory values are represented in Table 6.

2.3. *Spectral data of the synthesized compounds* ***5(a-m) & 4***

*2.3.1. Ethyl-2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5a**)*

White solid: Mp: 187-189 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ1.18 (t, J = 7.2 Hz, 3H), 4.09-4.12 (m, 2H), 4.96 (s, 1H), 6.44 (s, 2H), 7.16-7.28 (m, 4H), 7.33-7.39 (m, 4H), 7.56 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3): δ 14.1, 35.5, 60.0, 80.0, 100.0, 116.9, 122.1, 124.2, 126.7, 128.0,128.4, 132.1, 144.2, 152.6, 153.1, 157.9, 160.7, 168.7; Anal. Calcd for $C_{21}H_{17}NO_5$ 363.3690 found 363.3688.

*2.3.2. Ethyl-2-amino-4-(4-chlorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5b**)*

White solid: Mp: 190-191 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.08 (t, J = 6.8 Hz, 3H), 3.96-4.01 (m, 2H), 4.67 (s, 1H), 7.23 (s, 2H), 7.24-7.30 (m, 2H), 7.43-7.50 (m, 2H), 7.67-7.71 (m, 1H), 7.95 (d, J = 1,2 Hz, 1H), 7.97 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl3): δ 14.1, 34.8, 59.0, 76.5, 106.2, 113.0, 116.5, 122.5, 124.6, 127.8, 129.9, 130.9, 132.7, 143.9, 152.1, 153.2, 158.4, 159.8, 167.4; Anal. Calcd for $C_{21}H_{16}ClNO_5$ 397.8110 found 397.8109.

*2.3.3. Ethyl-2-amino-4-(4-fluorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5c**)*

White solid: Mp: 221-223 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 4.08-4.13 (m, 2H), 4.93 (s, 1H), 6.47 (s, 2H), 6.92 (t, J = 8.8 Hz, 2H), 7.28-7.38 (m, 4H), 7.56 (t, 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 34.9,60.0, 80.1, 107.7, 113.4, 114.7, 114.9, 116.9, 122.2, 124.3, 129.9, 130.0, 132.2, 140.0, 140.1, 152.6, 153.1, 157.8, 160.4, 160.7, 162.8, 168.6; Anal. Calcd for $C_{21}H_{16}FNO_5$ 381.3594 found 381.3592.

*2.3.4. Ethyl-2-amino4-(4-methoxyphenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5d**)*

White solid: Mp: 160-162 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ 1.19 (t, J = 6.8 Hz, 3H), 3.76 (s, 3H), 4.04-4.15 (m, 2H), 4.90 (s, 1H), 6.44 (s, 2H), 6.79 (d, J = 8.4 Hz, 2H), 7.28-7.34 (m, 4H), 7.36 (m, 1H), 7.83 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 34.6, 55.2, 60.0, 80.4, 108.1, 113.4, 113.5, 116.8, 122.1, 124.2, 129.4, 132.0, 136.6, 152.5, 152.9, 157.8, 158.3, 160.8, 168.8; Anal. Calcd for $C_{22}H_{16}NO_6$ 393.3950 found 393.3948.

*2.3.5. Ethyl-2-amino-4-(2,6-dichlorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5e**)*

White solid: Mp: 197-199 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3H), 3.90-3.94 (m, 2H), 5.59 (s, 1H), 7.18-7.26 (m, 2H), 7.41-7.49 (m, 3H), 7.67-7.72 (m, 1H), 7.94 (t, J = 1.2 Hz, 1H), 7.96 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 32.2, 58.8, 73.2, 102.5, 112.5, 116.4, 122.5, 124.6, 128.3, 129.8, 132.9, 134.0, 136.9, 137.9, 152.1, 154.0, 159.2, 167.7; Anal. Calcd for $C_{21}H_{15}C_{l2}NO_5$ 432.2530 found 432.2529.

*2.3.6. Methyl-2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5f**)*

White solid: Mp: 164-166 ºC; ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.67 (s, 3H), 4.96 (s, 1H), 6.47 (s, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 5.6 Hz, 2H), 7.32-7.35 (m, 2H), 7.38 (d, J = 8 Hz, 2H), 7.55-7,59 (m, 1H), 7.84 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 51.2, 80.1, 108.1, 113.5, 116.9, 122.1, 124.2, 126.8, 128.1, 128.2, 132.1, 144.1, 152.6, 153.1, 158.1, 160.6, 169.1; Anal. Calcd for $C_{20}H_{15}NO_5$ 349.3420 found 349.3418.

*2.3.7. Methyl-2-amino-4-(4-chlorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5g**)*

White solid: Mp: 226-227 ºC; ^{1}H NMR (400 MHz,$CDCl_3$): δ 3.66 (s, 3H), 4.92 (s, 1H), 6.49 (s, 2H), 7.22-7.25 (m, 2H), 7.28-7.35 (m, 4H), 7.56-7.60 (m, 1H), 7.83-7.85 (m, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 34.9, 51.3, 79.6, 107.5, 113.3, 116.9, 122.2, 124.3, 128.3, 129.7, 132.3, 132.5, 142.7, 152.6, 153.2, 158.1, 160.6, 168.9; Anal. Calcd for $C_{20}H_{14}ClNO_5$ 383.7840 found 383.7838.

*2.3.8. Methyl-2-amino-4-(4-fluorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5h**)*

White solid: Mp: 220-221 ºC; ^1H NMR (400 MHz,$CDCl_3$): δ 3.66 (s, 3H), 4.93 (s, 1H), 6.49 (s, 2H), 6.92 (t, J = 8.4 Hz, 2H), 7.33-7.37 (m, 4H), 7.56-7.60 (m, 1H), 7.84-7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.7, 51.3, 79.9, 107.8, 113.4, 114.8, 115.0, 116.9, 122.1, 124.3, 129.7, 129.8, 132.3, 139.9, 139.9, 152.6, 153.1, 158.0, 160.6, 169.0; Anal. Calcd for $C_{20}H_{14}FNO_5$ 367.3324 found 367.3322.

*2.3.9. Methyl-2-amino-4-(4-methoxyphenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5i**)*

White solid: Mp: 202-204 ºC; ^1H NMR (400 MHz,$CDCl_3$): δ 3.67 (s, 3H), 3.76 (s, 3H), 4.91 (s, 1H), 6.47 (s, 2H), 6.79 (d, J = 8.8 Hz, 2H), 7.89-7.35 (m, 4H), 7.54-7,58 (m, 1H), 7.82 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.4, 51.2, 55.2, 80.2, 108.2, 113.5, 116.8, 122.1, 124.2, 127.9, 129.2, 132.1, 136.4, 152.5, 152.9, 15.81, 158.3, 160.7, 169.1; Anal. Calcd for $C_{21}H_{17}NO_6$ 379.3680 found 379.3679.

*2.3.10. Methyl-2-amino-4-(4-bromophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5j**)*

White solid: Mp: 194-195 ºC; ^1H NMR (400 MHz,$CDCl_3$): δ 3.66 (s, 3H), 4.91 (s, 1H), 6.50 (s, 2H), 7.25 (t, J = 8.4 Hz, 2H), 7.33-7.39 (m, 4H), 7.57 (t, J = 6.8 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.0, 51.3, 79.5, 107.4, 113.3, 116.9, 120.6, 122.2, 124.3, 130.1, 131.2, 132.3, 143.2, 152.6, 153.2, 158.1, 160.6, 168.9; ; Anal. Calcd for $C_{20}H_{14}BrNO_5$ 428.2380 found 428.2378.

*2.3.11. Butyl-2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5k**)*

Yellow solid: Mp: 178-180 ºC; ^1H NMR (400 MHz,$CDCl_3$): δ 0.75 (t, J = 7.6 Hz, 3H), 1.08-1.16 (m, 2H), 1.39-1.46 (m, 2H), 3.91-3.98 (m, 2H), 4.84 (s, 1H), 7.05 (s, 2H), 7.05-7.14 (m, 2H), 7.14-7.18 (m, 2H), 7.21-7.24 (m, 2H), 7.28-7.46 (m, 1H), 7.73 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 19.0, 30.7, 35.5, 63.9, 76.7, 77.0, 77.3, 80.2, 80.2, 108.0, 113.5,

116.8, 122.1, 124.2, 126.7, 128.0, 128.4, 132.1, 144.2, 152.6, 153.0, 158.0, 160.7, 168.8; Anal. Calcd for $C_{23}H_{21}NO_5$ 391.4230 found 391.4228.

*2.3.12. Butyl-2-amino-4(4-fluorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5l**)*

Yellow solid: Mp: 197-198 ºC; ^{1}H NMR (400 MHz,DMSO-*d6*): δ 0.76 (t, J = 7.2 Hz, 3H), 1.08-1.18 (m, 2H), 1.39-1.45 (m, 2H), 3.92-3.99 (m, 2H), 4.82 (s, 1H), 6.38 (s, 2H), 6.82 (t, J = 8 Hz, 2H), 7.23 (m, 3H), 7.46 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H);^{13}C NMR (100 MHz, DMSO-*d6*): δ 13.7, 19.1, 30.6, 34.6, 64.0, 105.7, 113.2, 116.8, 122.3, 124.2, 126.2, 128.0, 130.0, 132.2, 133.9, 140.2, 152.7, 153.6, 158.1, 160.4, 168.9; Anal. Calcd for $C_{23}H_{20}NO_5$ 409.4134 found 409.4130.

*2.3.13. Butyl-2-amino-4(2,6-dichlorophenyl)-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**5m**)*

Yellow solid: Mp: 218-219 ºC; ^{1}H NMR (400 MHz,DMSO-*d6*): δ 0.73 (t, J = 7.2 Hz, 3H), 0.86-0.98 (m, 2H), 1.36-1.41 (m, 2H), 3.80-3.86 (m, 1H), 3.99-4.05 (m, 1H), 5.60 (s, 1H), 7.19-7.27 (m, 2H), 7.42-7.50 (m, 3H), 7.68-7.73 (m, 1H), 7.95 (d, J = 1.2 Hz, 1H), 7.97 (t, J = 1.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 13.5, 18.3, 30.2, 32.1, 62.6, 73.1, 102.5, 112.5, 116.4, 122.5, 124.6, 128.4, 128.5, 129.8, 132.9, 134.0, 136.8, 137.9, 152.1, 154.0, 159.2, 159.2, 167.8; Anal. Calcd for $C_{23}H_{20}C_{l2}NO_5$ 460.3070 found 460.3066.

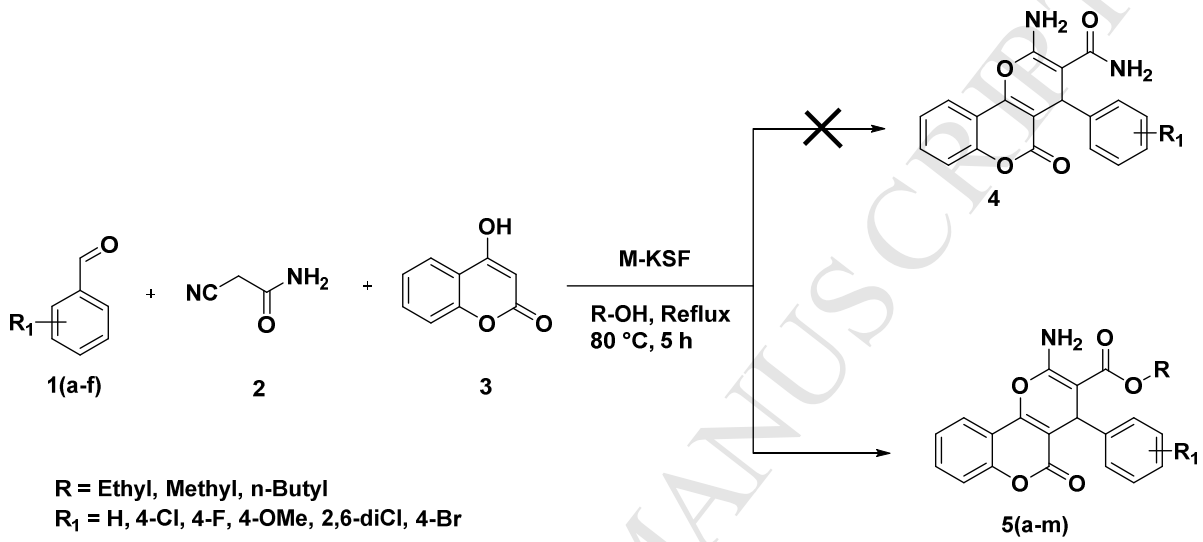
*2.3.14. 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxamide (**4**)*

White solid: Mp: 283-285 ºC; ^{1}H NMR (400 MHz,DMSO-*d6*); δ 6.28 (s, 1H), 7.08 (t, J = 7.2 Hz, 3H), 7.15 (t, J = 7.2 Hz, 2H), 7.22-7.28 (m, 4H), 7.49-7.81 (m, 2H), 7.81 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 36.0, 63.9, 103.4, 115.4, 119.8, 122.9, 124.0, 124.8, 126.6, 127.6, 130.9, 142.2, 152.4, 164.6, 167.6; Anal. Calcd for $C_{19}H_{14}N_2O_4$ 334.3310 found 334.3308.

3. Results and Discussion

For the synthesis of highly functionalized pyrano[3,2-*c*]chromene derivatives such as ethyl 2-amino-4,5-dihydropyrano[3,2-*c*]chromenes, **5**(**a-e**) methyl 2-amino-4,5-dihydropyrano[3,2-*c*]chromenes, **5**(**f-j**) butyl 2-amino-4,5-dihydropyrano[3,2-*c*]chromenes **5**(**k-m**) and M-KSF was used as the catalyst in different alcoholic medium (Scheme 1). To optimize the conditions, systematic study of different solvents that influencing the reaction yields was

performed with an equimolar mixture of 4-chlorobenzaldehyde **1b**, 2-cyanoacetamide **2**, 4-hydroxy coumarin **3** (Scheme 1) and the results has been summarized in Table 1. Only a trace amount of the desired product **5b** was obtained under reflux conditions with different base catalysts except piperidine.



Scheme 1. Synthesis of pyrano[3,2-*c*]chromene-carboxylate derivatives

Then the 30 mol % of piperidine was found to afford 65% yield of the desired product **5b**. The same reaction when tried with M-KSF the desired product**5b** are precipitated out from the reaction mixture, which was essentially pure and was used without any further purification.Compared to the all employed catalysts, M-KSF afforded the compound **5b** in good yield, among them M-KSF gave a very high yield with lesser time. The products **5**(**a-m**) were fully characterized by ^{1}H NMR and ^{13}C NMR and Mass analysis. In ^{1}H NMR spectrum the aromatic signals appear in the range of 7.97-6.47 ppm. The NH_2 proton signals in the ranges of 7.23-6.39 ppm. The methane proton (CH) appear as a singlet in the range of 5.60-4.67 ppm, the methoxy (OCH_3) proton peaks appear in the range of 3.76 ppm, the methylene (CH_2) protons appear as multiplet in the range of 4.12-3.90 ppm, and methyl (CH_3) protons appear as a triplet in the range of 1.22-0.73 ppm. The ^{13}C NMR supports the formation of pyranochromenes. Initially aldehydes **1**(**a-f**) and cyanoacetamide, **2** reacts in the presence of M-KSF readily form an intermediate (*E*)-2-cyano-3-phenylacrylamide, **6**(**a-m**) and the addition of 4-hydroxy coumarin yields the compound **4**.

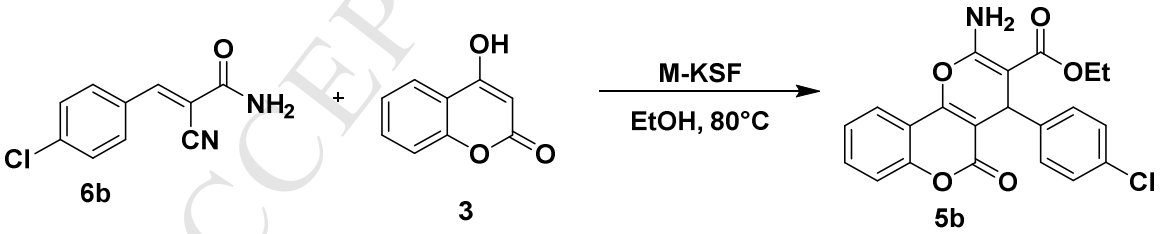
Entry	Catalyst	Catalyst loading (mol%)	Time(h)	Yield[b](%)
1	-	-	24	-
2	-	-	24	-
3	DMAP	30	10	20
4	piperidine	10	10	50
5	piperidine	20	10	58
6	piperidine	30	8	65
7	Morpholine	30	8	40
8	Pyrrolidine	30	8	35
9	NaOH	30	10	50
10	KOH	30	10	30
11	DBU	30	10	23

Table 1. Optimization of the three-component reaction under various conditions[a]

12	imidazole	20	10	20
13	MKSF	(100 mg)	5	85

[a]Reaction Conditions: 4-Chlorobenzaldehyde (1 mmol), 2-Cyanoacetamide (1 mmol), 4-Hydroxycoumarin (1 mmol), Ethanol (5 mL) in the presence of different catalysts at 80 °C.
[b]Isolated Yields.

The carboxamide moieties in the 3-positions of the pyran ring were highly active and these functional groups react with alcohols for further synthetic transformations. In this study, we expected 2-amino-4,5-dihydropyrano[3,2-c]chromene-3-carboxamide, **4** from the aromatic aldehydes **1**(**a**-**f**), 2-cyanoaceamide **2**, and 4-hydroxycoumarin **3**, but the product we obtained was pyrano[3,2-c]chromene carboxylates, **5**. In the present work alcoholic functional groups are regarded as one of the stimulant and the corresponding functional group inter conversion from carboxamide to carboxylate was either occurring in the intermediate itself or during the final conversion (Scheme 2). To confirm that the intermediate, **6b**has been isolated and characterization was carried out and found thatconversion was happening towards the end. A possible mechanism of these reactions is given in Scheme 4.



Scheme 2. Synthesis of pyrano[3,2-*c*]chromene derivatives

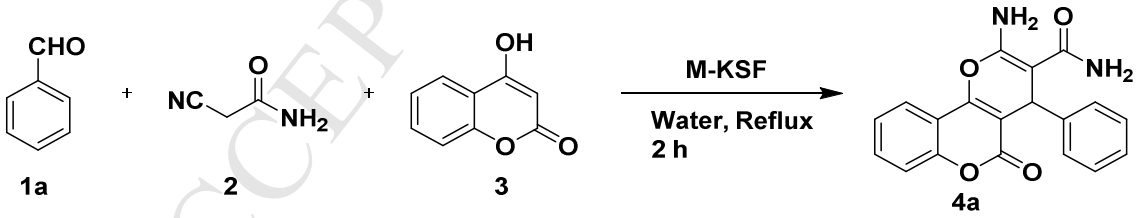
Table 2. Optimization of the three-component reaction under various loading of catalyst[a]

Entry	Catalyst (mg) MKSF	Time(h)	Yield[b] (%)
1	10	10	20
2	20	10	35

3	40	10	43
4	60	8	50
5	80	8	72
6	**100**	**5**	**85**
7	110	5	84
8	120	5	85

[a]Reaction Conditions: 4-Chlorobenzaldehyde (1 mmol), 2-Cyanoacetamide (1 mmol), 4-Hydroxycoumarin (1 mmol), Ethanol (10 mL) and M-KSF at 80 °C. [b]Isolated Yields.

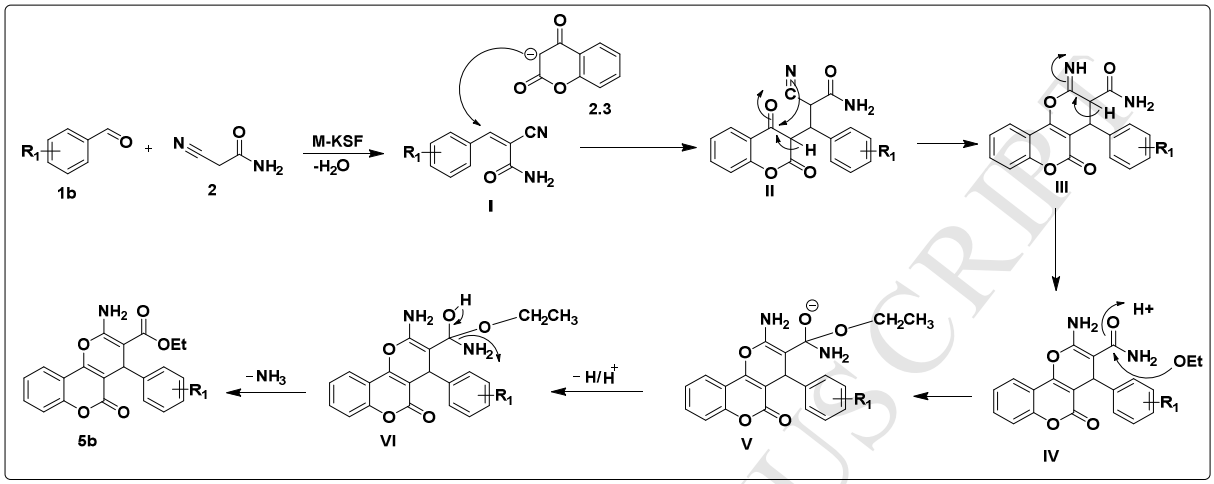
In order to generalize the optimized conditions, different derivatives of 2-amino-4,5-dihydropyrano[3,2-c]chromene-carboxylates **5**(**a-m**) were synthesized from the one-pot reaction of substituted aldehydes **1**(**a-f**), 2-cyanoacetamide **2**, 4-hydroxycoumarin **3** in the presence of M-KSF (100 mg) in different alcohols (Ethanol, Methanol, *n*-Butanol) under reflux conditions (Scheme 1). Optimization of the catalyst M-KSF was carried out from 10 mg to 120 mg (Table 2). With 100 mg the yield was high and it has been arbitrarily fixed. The results of the synthesized compounds has been tabulated in Table 3.As we know that in multicomponent reactions solvent and catalyst plays a major role which may be attributed to the capability of the alcoholic functional groups.



Scheme 3. One-pot Three-component reaction of pyrano[3,2-*c*]chromene derivatives

The synthesis of pyrano chromenes was performed in different protic and aprotic solvents with M-KSF to check the formation of the compound 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxylate, **5b**. Interestingly, with water as solvent the compound 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxamide, **4** was formed with good yield.The same reaction when tried under solvent less condition, pyrano

chromene-3-carboxamide, **4** was found with a lesser yield. This created an interest to check for various solvents and with water the expected compound, **4** was formed in high yield (Scheme 3).

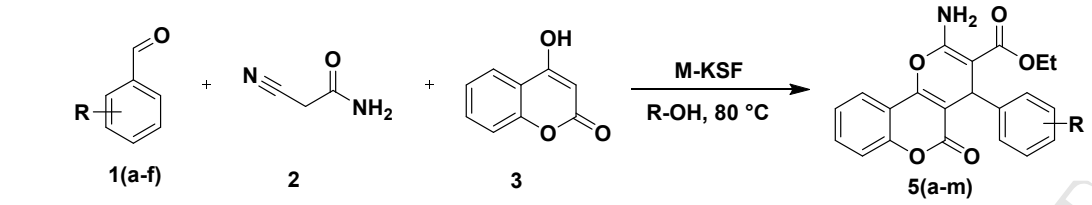


Scheme 4. Plausible Mechanism for the Synthesis of 2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxylates

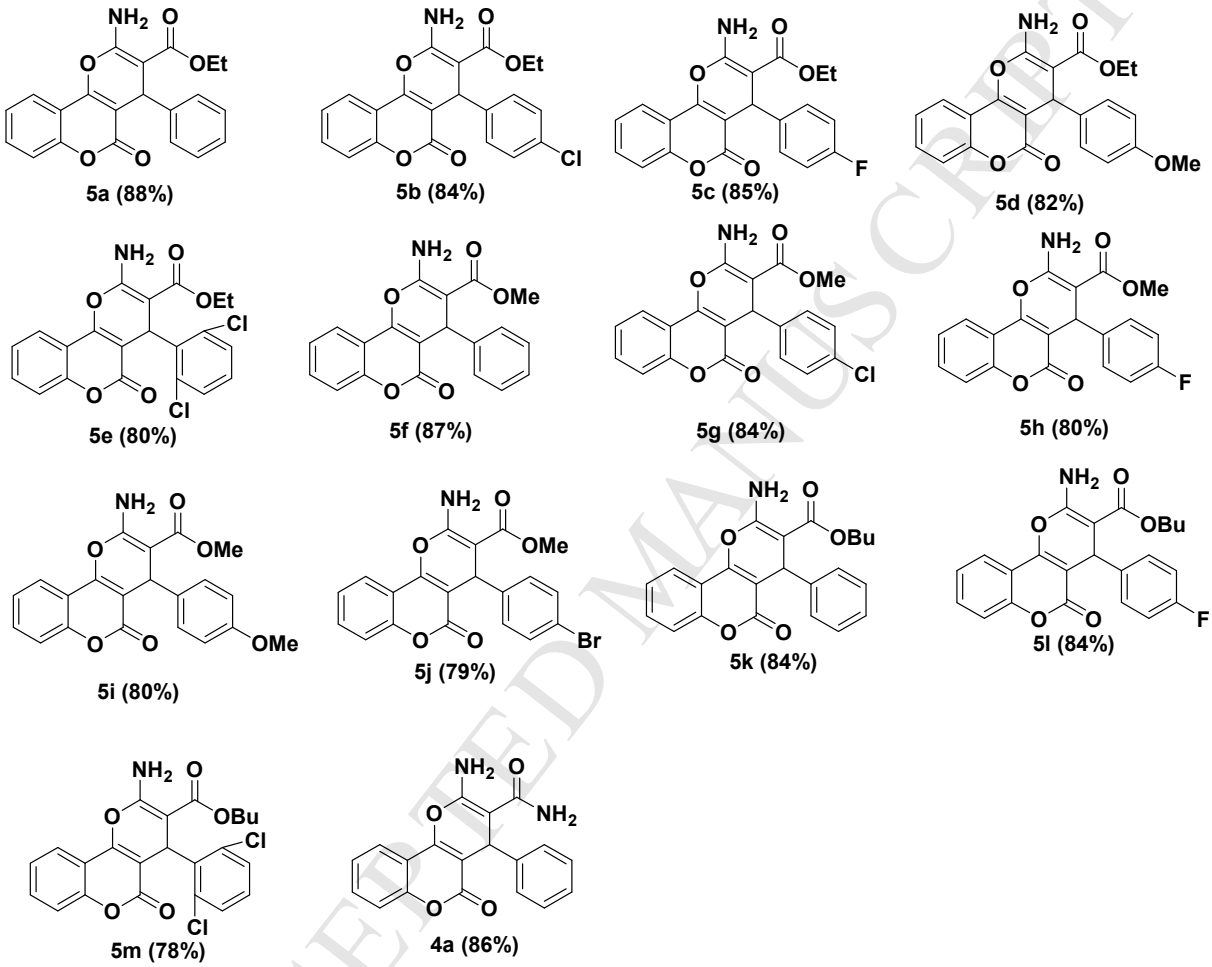
3.1. Reusability of Catalyst

The recyclability of the M-KSF is one of the most important advantages of this protocol that makes it useful for commercial applications. The reaction mixture was allowed to cool and catalyst was filtered off from the reaction mixture at the end of the reaction. It was washed with ethanol and water, dried and activated at hot air oven for 5h. The catalyst was reused for further cycles. The reaction proceeded efficiently even after five cycles. The use of a catalyst for the first time offered a yield of 85%, and although the same catalyst repeatedly reused up to four times under similar conditions, the yields obtained were 85%, 82% and 78% and 75% respectively (Table 4). The experimental results reveal that the catalyst showed good recyclability in all these reactions.

Table 3. Synthesis of Pyrano[3,2-*c*]chromene Derivatives **5**(**a-m**)[a,b]



1(a-f) 2 3 5(a-m)



[a]Reaction Conditions: Substituted Benzaldehydes (1 mmol), 2-Cyanoacetamide (1 mmol), 4-Hydroxycoumarin (1 mmol), Alcohol (10 mL), (R = Ethyl, Methyl, *n*-Butyl) and 100 mg of M-KSF. [b]Isolated Yields.

Table 4. Recyclability of Montmorillonite KSF[a]

Cycles	Catalyst recovered (%)	Product yield[b] (%)
Initial	94	85
1	92	85
2	89	82
3	86	78
4	85	75

[a]Reaction Conditions: 4-Chlorobenzaldehyde (1 mmol), 2-Cyanoacetamide (1 mmol), 4-Hydroxycoumarin (1 mmol), Ethanol (10 mL) and M-KSF. [b]Isolated Yields.

3.2. Antioxidant Activity

The DPPH values of methanolic solutions of pyrano[3,2-c]chromene derivatives **5**(**a-m**) were examined and compared (Table 5).Then the absorbance was measured at 517 nm using a UV-VIS spectrophotometer. From examination of Table 5, we can conclude that the pyrano[3,2-c]chromene derivatives **5**(**a-m**) scavenging effects of DPPH radicals increase in the concentration. We have measured the percentage inhibition at different concentrations of all the synthesized compounds, **5**(**a-m**)and calculated its corresponding IC_{50} values, which are given in Table 5. The results revealed that all the synthesized compounds, **5**(**a-m**) showed the moderate scavenging property when compared with Ascorbic acid, a standard antioxidant agent.The presence of substitutions on the benzaldehydes like Cl, dichloro, and Br (**5b**, **5e**, **5g**, **5j** and **5m**) groups shown significant antioxidant activity compared to other functional groups like unsubstituted, fluoro and methoxy.

3.3. *In Vitro* Antibacterial Activity

The compounds **5**(**a-m**) were screened for their *in vitro* antibacterial activity. The results of antibacterial activity indicated a variable degree of efficacy of the compounds against different strains of bacteria. Compound **5m** exhibited very strong activity (9.375 µg/mL), against *S. aureus*, *Bacillus subtilis* and *K. pneumoniae*. Whereas compounds **5b**, **5e**, **5g** and **5j** displayed significant activity against *S. aureus*, *Bacillus subtilis*, *Micrococcus luteus* and *P. aeruginosa* (18.75 µg/mL). The compounds **5c**, **5k** and **5l** presented significant activity against *S. aureus*, *Bacillus subtilis* and *K. pneumoniae* (37.50 µg/mL). The results of this study as indicated in Table 6. The substitutions present on the phenyl rings of pyranochromene moiety with Cl, Br and

dichloro have shown more activity, when compared to fluoro and methoxy substitutions.Pyranochromenes without any substitution did not show any activity and the pyranochromene system containing dichloro substitution on the phenyl ring with butyl ester have revealed more activity when compared to ethyl and methyl esters.

Table 5. Antioxidant activity of pyrano[3,2-*c*]chromene derivatives **5(a-m)**

Entry	Compound	% of inhibition at different concentrations (mM)				IC_{50}
		50	70	100	125	
1	5a	51.27	63.08	70.14	81.02	0.813
2	5b	53.79	61.22	69.35	80.47	0.678
3	5c	53.81	62.17	71.29	84.58	0.751
4	5d	51.20	61.50	71.15	80.60	0.854
5	5e	54.73	65.37	72.12	83.94	0.502
6	5f	50.41	63.36	69.54	81.29	0.891
7	5g	51.90	63.58	72.40	81.93	0.741
8	5h	50.73	62.89	71.46	82.71	0.884
9	5i	51.28	60.72	72.67	82.33	0.909
10	5j	53.62	62.46	72.04	83.67	0.707
11	5k	52.29	64.19	70.43	82.73	0.740
12	5l	51.45	64.90	71.65	80.54	0.714
13	5m	55.92	66.37	72.50	84.65	0.378
14	Ascorbic acid	56.81	67.91	72.29	85.58	0.265

Table 6. Antibacterial activity of pyrano[3,2-*c*]chromene derivatives **5(a-m)**

	Minimum inhibitory concentration (MIC) (in µg/mL)					
Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*M. luteus*	*E.coli*	*k. pneumoniae*	*P. aeruginosa*
5a	>150	>150	>150	>150	>150	>150
5b	18.75	18.75	18.75	>75.0	>150	18.75
5c	>75.0	37.50	>37.50	>150	>150	>150
5d	>18.75	>18.75	>75.0	>150	>75.0	>75.0
5e	18.75	18.75	18.75	>75.0	>300	18.75
5f	>75.0	>150	>150	>150	>150	>150
5g	18.75	18.75	>37.50	>150	>37.50	>37.50
5h	>150	>75.0	>75.0	>300	>300	>300
5i	>75.0	>150	>300	>150	>150	>300
5j	18.75	18.75	18.75	>75.0	>75.0	>150
5k	>75.0	37.50	>150	>300	>300	>75.0
5l	75.0	37.50	>75.0	>75.0	>75.0	>150
5m	9.3	9.3	>75	>150	9.3	>75
Ampicillin	4.6	4.6	4.6	9.3	4.6	9.3

4. Conclusions

In conclusion, the synthesis of 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carboxylate derivatives **5(a-m)** were reported by one-pot three component reaction between substituted aldehydes, 2-cyanoacetamide and 4-hydroxycoumarin in the presence of MKSF an efficient catalyst to predict the pyranochromene derivatives. Particularly, this method includes excellent yields, cost effective and readily available substrates, mild reaction conditions, reduced environmental impact and simple straightforwardness of procedure which make attractive process these useful important compounds. In addition to this we have studied the antioxidant and antibacterial properties of all the synthesized pyranochromene derivatives **5(a-m)**. Among all the compounds **5m** was showing excellent antibacterial as well as antioxidant activity.

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Highlights of work

- Montmorillonite-KSF is an effective heterogeneous catalyst.
- Easy to handle and simple reaction procedure.
- Cost effective and high yields were observed in shorter reaction time.
- Reusability of catalyst.