Synthesis of Some Novel 3-Substituted Indole Derivatives Using Polyamine Functionalized Heterogeneous Catalyst

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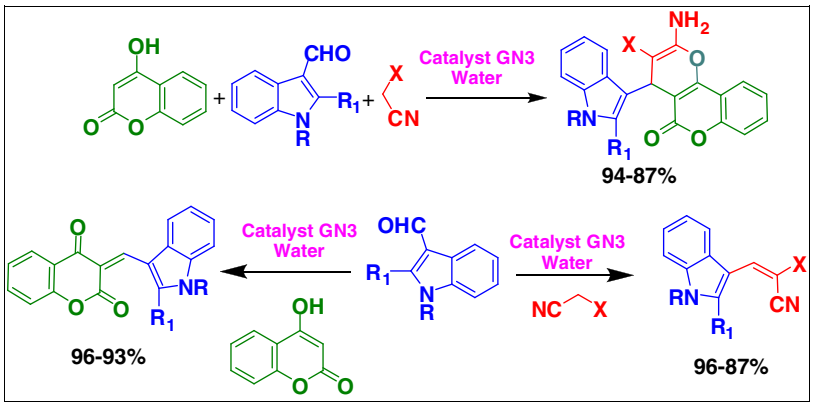

In present work, we have described the use of polyamine solid supported GN3 as catalyst in organic transformations using 1*H*-indole-3-carbaldehyde. To the best of our knowledge, reports for the synthesis of chromen substituted at 3C position of indole are extremely rare in the literature. The polyamine functionalized immobilized silica (GN3) was found to be an excellent catalyst for synthesis of novel 2-amino-4-(1*H*-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile derivatives and Knoevenagel condensation. Catalyst GN3 was able to furnish excellent yield for a wide range of products. Moreover, the catalyst was reusable and reused for several times without loss of its catalytic activity.

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INTRODUCTION

For the last few years, ordered mesoporous silicas have been studied to a great extent as catalysts, catalyst supports, adsorbents, and containers for cluster/nanowire growth [1]. Owing to their well-ordered structure, silica materials have attracted great attention of synthetic chemists to form heterogeneous catalyst by tethering active organic or inorganic homogeneous material [2]. Recently, some of the fundamental organic transformations such as Knoevenagel condensations [3] and the aldol condensations [4–6] were reported to be catalyzed by mono aminopropyl functionalized mesoporous silica materials as base material. Moreover, reports of the catalysts also exist in which organic material is grafted on ordered silica surface and metal is trapped in these organic compounds by chelation, which makes an effective catalyst system for organic transformation [7]. Recently, we have reported silica supported organo-amine catalysts, which was designated as GN3, and applied it in the synthesis of oxygen heterocycles (Fig. 1) [8].

The use of such heterogeneous catalysts offers several advantages in prospect of green chemistry as these catalysts effectively work in aqueous medium, has simple catalyst recovery that avoids tedious processes of catalyst separation, and most importantly can be reused in reaction cycle. The application of solid acidic and basic catalysts in clean technologies and sustainable chemistry is a "green" alternative for chemical processes.

Indole nucleus is the basic skeleton, frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals [9]. Owing to the diverse biological properties of indole derivatives, the synthesis of these molecules has accomplished great consideration [10]. Particularly, 3-substituted indole derivatives, which are important building blocks used for the synthesis of biologically important compounds. Some of the 3-substituted indole derivatives have displayed significant cytotoxicity against various human cancer cell lines [11].

Chromene derivatives constitute a class of heterocycles known for their applications as bioactive compounds [12]. The subclass of chromeno indoles, which are formed by merging indole and chromen, has been also identified as biologically active compounds [13]. Some of the chromeno indole derivatives exhibit the antiproliferative activity [14].

Owing to the useful biological properties of both 3-substituted indoles and chromene derivatives and in

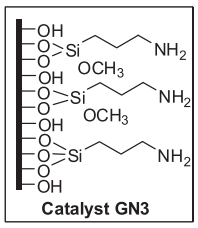


Figure 1. Structure of solid supported basic catalyst GN3.

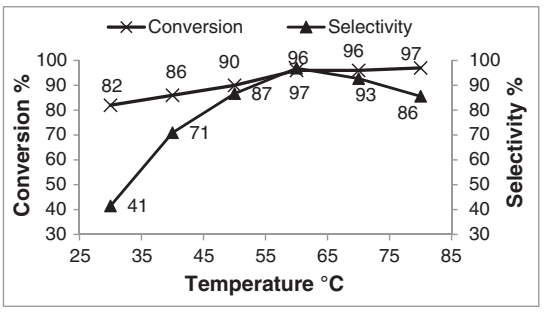


Figure 2. Influence of temperature on synthesis of **4a**. Reaction conditions: 1*H*-indole-3-carbaldehyde : 4-hydroxy coumarine : malanonitrile (1:1:1); catalyst GN3 0.03 g; 3 h.

continuation of our work on the synthesis of heterocyclic compound using heterogeneous catalysts [15] in the present study, we have coupled chromen molecule at 3C position of indole to enhance biological properties of the combined resultant structure. Herein, we report the use of heterogeneous polyamine-based solid catalyst in the preparation of rarely synthesized 2-amino-4-(1*H*-indol-3-yl)-5-oxo-4,5-dihydropyrano [3,2-*c*]chromene-3-carbonitrile derivatives.

In our initial experiments toward the development of novel methodologies under green chemical approaches, we selected synthesis of 2-amino-4-(1*H*-indol-3-yl)-5-oxo-4, 5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile **4a** (Scheme 1). The condensation reaction of 1*H*-indole-3-carbaldehyde, 4-hydroxy coumarine, and malanonitrile using catalyst GN3 in water was studied to obtain **4a** as a model compound. The application of base material GN3 as catalyst to this condensation reaction in a pure water was studied under various parameters.

Effect of temperature on the reaction. Temperature effect of reaction was studied to establish the optimum temperature for this reaction. Condensation was performed in temperature range of room temperature to 80°C using solid GN3 catalyst in water solvent for 3 h. Figure 2 shows that the temperature did not show strong effect on conversion of aldehyde; however, selectivity for compound **4a** radically varies with the temperature. At near to room temperature conditions, although conversion of indole aldehyde was high, the selectivity for product **4a** was very low owing to the formation of Knoevenagel adducts. The highest selectivity 97% for the **4a** was observed at 60°C where 96% of aldehyde was converted principally to the product yield (93%). Further elevation in temperature considerably decreased selectivity of product **4a**, which indicates that more side reaction occurs at high temperatures.

Effect of reaction time. Variation in product and conversion of aldehyde with time were studied using catalyst GN3, and the obtained results are plotted in Figure 3. The reaction products were collected from time to time and analyzed by gas chromatography (GC). As it can be seen from Figure 3, the percentage of conversion of aldehyde and the selectivity of product **4a** showed appreciable variation with reaction time. Almost all aldehyde was converted to the product after 30 min of reaction time. But the desired product selectivity plot was gradually increasing. When reaction time was reached to 1 h, product **4a** formation was high with excellent 98% selectivity. When reaction was carried out for longer time, decrease in the selectivity was observed, signifying that an extended reaction time leads to more byproducts.

Effect of 1*H*-indole-3-carbaldehyde to 4-hydroxy coumarine and malanonitrile. The molar ratio of indole aldehyde proved to be a vital parameter in the reaction. In order to

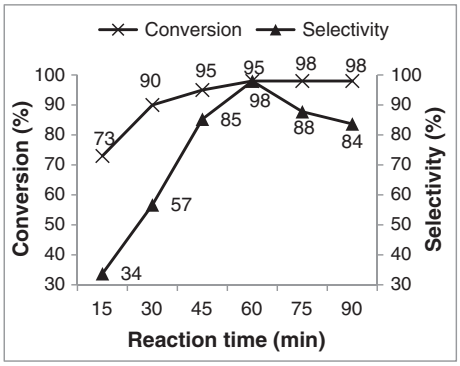
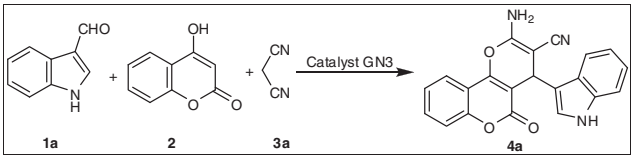


Figure 3. Influence of reaction time on synthesis of **4a**; reaction conditions: 1*H*-indole-3-carbaldehyde : 4-hydroxy coumarine : malanonitrile (1:1:1); catalyst GN3, 60°C; catalytic loading 0.03 g.

Scheme 1. Synthesis of 2-amino-4-(1*H*-indol-3-yl)-5-oxo-4, 5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (**4a**).



obtain high selectivity for product **4a**, it was very necessary to pick suitable molar ratio of aldehyde (Fig. 4). A decreasing trend was observed in plot of effect of indole aldehyde concentration. At lower concentration, high conversion of indole aldehyde was seen with high selectivity. The reaction also yielded unreacted 4-hydroxy coumarine and malanonitrile as byproducts. At equimolar concentration of indole aldehyde, conversion and selectivity were highest at 98%. When concentration was increased further, selectivity dropped drastically and reached 26% at highest molar ratio.

The results obtained from aforementioned studies demonstrated that catalyst GN3 was the most efficient basic catalyst for the Knoevenagel condensation and the synthesis of chromeno indoles under different temperature conditions in aqueous medium. The best optimum conditions for both reactions were obtained at 0.03 g catalyst loading in water solvent. The Knoevenagel condensation worked well at room temperature to provide excellent yields of corresponding products, whereas for the synthesis of chromeno indoles, the temperature was raised to 60°C for 60 min, which offered superior 93% yield of desired product **4a** with greatest selectivity 98% with respect to indole aldehyde.

In order to evaluate the generality of the process, several indole aldehydes were employed. The results are summarized in Table 1. The reactions of several substituted indole aldehydes proceeded smoothly with 4-hydroxyl coumarine and C–H acid in the presence of solid acid catalyst GN3 offering the corresponding products in excellent yields

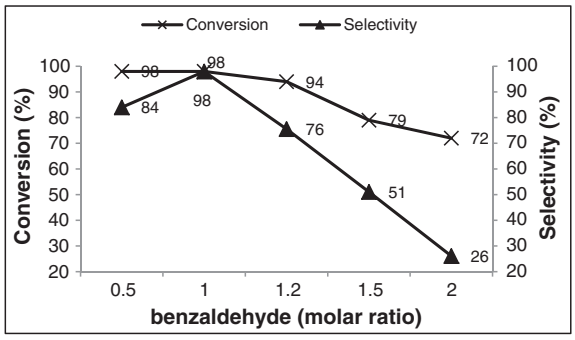
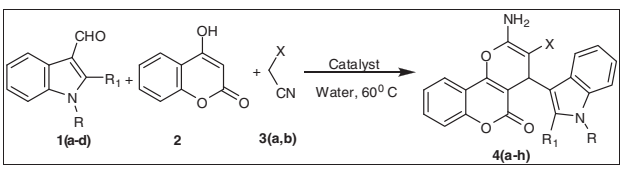


Figure 4. The effect of 1*H*-indole-3-carbaldehyde concentration on the synthesis of **4a**. Reaction conditions: 1*H*-indole-3-carbaldehyde : 4-hydroxy coumarine : malanonitrile (*x*:1:1); catalyst GN3, 60°C; catalytic loading 0.03 g; 60 min.

Scheme 2. Synthesis of 3-substituted chromeno indole derivatives **4(a–h)**.



(Scheme 2). The catalyst was able to draw excellent yields for all desired products with maximum selectivity.

The catalytic scope of the catalyst GN3 was also extended to the Knoevenagel condensation between 1*H*-indole-3-carbaldehyde and 4-hydroxy coumarine or active methylene compound at room temperature (Table 2). The base promoted reaction of 1*H*-indole-3-carbaldehyde with malonic esters offered 3-substituted indoles as products in excellent yields (Scheme 3).

Based on obtained results and literature support [8,16], the mechanism of reaction is drawn in Scheme 4. The mechanism for one pot reaction is supposed to start with the Knoevenagel condensation *in situ*. Step I shows the Knoevenagel condensation, and the reaction starts with the removal of hydrogen atom from C–H active compounds with the help of catalysts GN3 to generate nucleophile **X** or **Y**. Owing to the bendable [17] aminopropyl chain in the catalyst GN3, removed proton was assembled between nitrogen atoms, which reinforce the basicity of the catalyst GN3. Subsequently, these nucleophiles on reaction with 1*H*-indole carboxaldehyde form Knoevenagel product **5** or **6**. In the second step, reaction takes place by two pathways, A and B. In the reaction pathway A, compound **5** reacts with anion **Y** to give intermediate **III.** Similarly, in pathway B, compound **6** after reaction with anion **X** transforms into cyclic structure. Desired product **4a** was obtained after the rearrangement and tautomeric proton shift of cyclic structure.

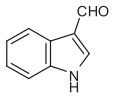
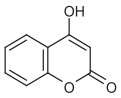
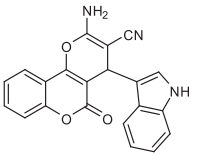
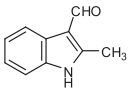
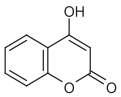
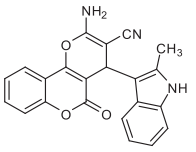
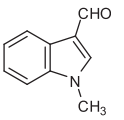
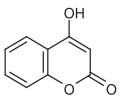
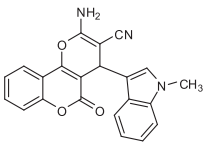
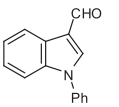
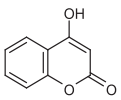
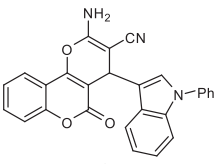
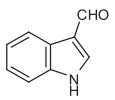
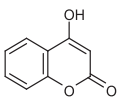
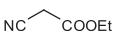
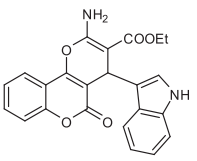
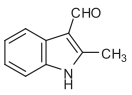
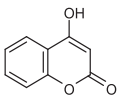
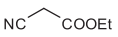
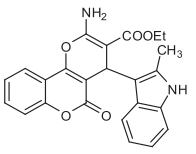
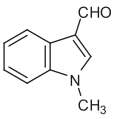
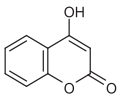
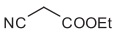
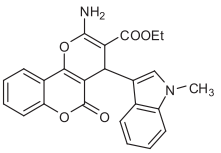
Reusability of catalyst. Reusability is another important parameter of efficient catalysts. After the completion of reaction, chloroform was added to the reaction mixture, and the catalyst was separated by a simple filtration from the resulting heterogeneous mixture, washed with water, and dried at 150°C for 2 h. The catalyst was reused for a consecutive run under similar reaction conditions. The average isolated yields of **4a** for five consecutive runs were 91%, which clearly demonstrates the practical reusability of GN3 catalyst.

In summary, we have reported the use of solid base material GN3 as catalyst synthesis of 2-amino-4-(1*H*-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile and Knoevenagel condensation under mild reaction conditions. To the best of our knowledge, reports for the synthesis of chromen substituted at 3C position of indole are extremely rare in the literature. The catalysts showed excellent stability and activity for both reactions. The scope of catalyst GN3 was further explored using other indole aldehydes. The reactions proceeded well for various indole aldehydes, giving excellent yield of the respective products. Finally, silica supported polyamine catalyst GN3 can be recovered by simple filtration process and can be used again without any loss in its activity.

All the solvents were used as commercial anhydrous grade without further purification. The column chromatography

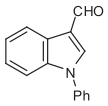
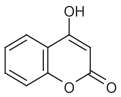
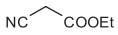
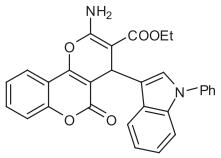
Table 1

Synthesis of 3-substituted chromeno indole derivative.[a]

Sr. no.	Substrate 1	Substrate 2	Substrate 3	Product	Time (min)	Yield[b] (%)
1				 **4a**	60	93
2				 **4b**	60	91
3				 **4c**	60	94
4				 **4d**	60	90
5				 **4e**	60	90
6				 **4f**	60	92
7				 **4g**	60	87

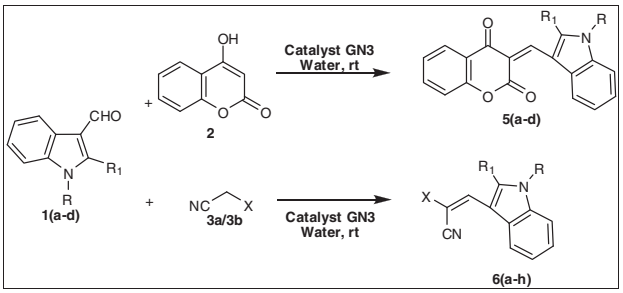
(*Continues*)

Table I.
(*Continued*)

Sr. no.	Substrate 1	Substrate 2	Substrate 3	Product	Time (min)	Yield[b] (%)
8				 **4h**	60	89

[a]Reaction conditions: catalyst GN3 (0.025 g), indole aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and malononitrile/ethylcyanoacetate (1 mmol) in water solvent at 60°C. Progress of reaction was monitored by gas chromatography.
[b]Isolated yields.

Scheme 3. Synthesis of 3-substituted indole derivatives.



was carried out over silica gel (80–120 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz spectrometer (Brucker Avance 300 MHz, Hydrabad, India) in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscientific GC–MS (Pune, India).

General procedure for the synthesis of catalysts GN3. The synthesis and characterization of the catalyst are reported in our earlier communication [8] and also in literature [18].

General procedure for the synthesis of 2-amino-4*H*-chromene derivative. The mixture of 3-indole aldehydes (1 mmol), 4-hydroxy coumarine (1 mmol), and active methylene compound was taken in water solvent. To this mixture, 0.03 g of silica gel polyamine catalyst GN3 was added. The reaction mixture was stirred at 60°C for appropriate time (as shown in Table 1), and the progress of reaction was monitored by GC. After completion of reaction, reaction mixture was cooled at room temperature, and to the cooled reaction mixture solvent, chloroform was added. The solid heterogeneous catalyst GN3 was removed by a simple filtration process. The organic layer was collected, and solvent was removed under vacuum to obtain crude product. The obtained product was purified by column chromatography using Pet ether : ethyl acetate (7:3) as elluent to obtain the desired compound **4(a–h)**.

Characterization data for representative compound. ***2-Amino-4-(1H-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4a).*** White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.09 (br s, 1H, NH), 7.86–7.92 (m, 1H), 7.54–7.72 (m, 3H), 7.32–7.43 (m, 2H), 7.11–7.22 (m, 3H), 6.93 (br s, 2H, NH), 4.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 164.2, 163.1, 153.7, 136.8, 133.3, 127.6, 127.2, 123.1, 122.7, 120.0, 115.8, 115.4, 113.1, 112.8, 111.6, 103.1, 103.8, 56.2, 42.3; GC–MS *m/z* 355 (M^+). Elemental analysis: Calcd. $C_{21}H_{1H3}N_3O_3$: C, 70.98; H, 3.69; N, 11.83. Found: C, 71.01; H, 3.72; N, 11.85.

2-Amino-4-(2-methyl-1H-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4b). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.11 (br s, 1H, NH), 8.17–8.25 (m, 1H), 7.71–7.81–7.88 (m, 1H), 7.49–7.70 (m, 2H), 7.19–7.32 (m, 3H), 6.99 (br s, 2H, NH), 4.29 (s, 1H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 166.3, 165.6, 154.7, 139.4, 132.8, 131.0, 129.3, 127.9, 126.8, 126.1, 125.3, 117.7, 116.5, 110.1, 107.7, 103.3, 61.2, 43.4, 16.8; GC–MS *m/z* 369 (M^+). Elemental analysis: Calcd. $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.57; H, 4.11; N, 11.41.

2-Amino-4-(1-methyl-1H-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4c). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–8.08 (m, 1H), 7.79–7.88 (m, 1H), 7.47 –7.69 (m, 4H), 7.10–7.19 (m, 3H), 6.99 (br s, 2H, NH), 6.69–6.77 (m, 1H), 4.22 (s, 1H), 3.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 164.2, 163.8, 158.4, 141.4, 127.7, 126.2, 125.0, 124.4, 120.0, 114.6, 113.8, 111.5, 107.0, 61.9, 31.6, 24.6; GC–MS *m/z* 369 (M^+). Elemental analysis: Calcd. $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.56; H, 4.06; N, 11.37.

2-Amino-5-oxo-4-(1-phenyl-1H-indol-3-yl)-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (4d). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–8.06 (m, 2H), 7.07–7.81 (m, 10H), 6.94 (br s, 2H, NH), 6.71–6.80 (m, 2H), 4.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9, 161.4, 161.0, 154.1, 148.0, 141.3, 131.8, 131.2, 131.0, 126.1, 125.3, 124.9, 122.6, 122.0, 119.8, 118.2, 113.0, 112.1, 107.8, 106.5, 106.0, 59.8, 42.0; GC–MS *m/z* 431 (M^+). Elemental analysis: Calcd. $C_{27}H_{17}N_3O_3$: C, 75.16; H, 3.97; N, 9.74. Found: C, 75.19; H, 3.94; N, 9.76.

Ethyl 2-amino-4-(1H-indol-3-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (4e). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.09 (br s, 1H, NH), 7.90–8.01 (m, 2H), 7.63–7.80 (m, 2H), 7.29–7.32 (m, 2H), 7.22

Table 2

Synthesis of 3-substituted indole derivative.[a]

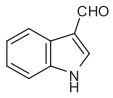
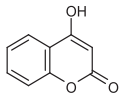
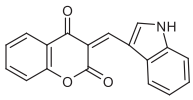
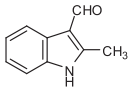
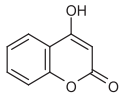
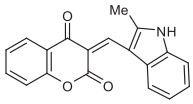
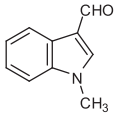
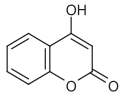
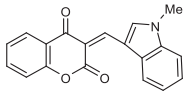
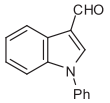
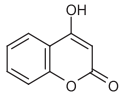
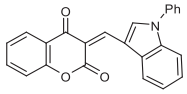
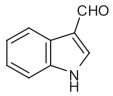
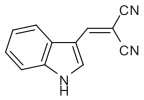
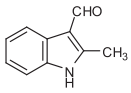
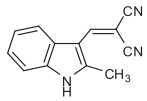
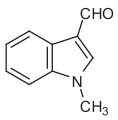
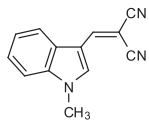
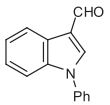
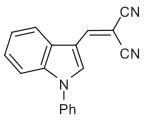
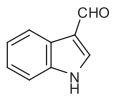
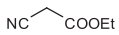
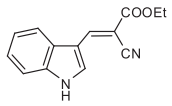
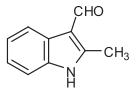
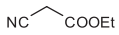
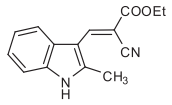
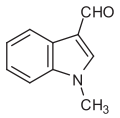
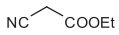
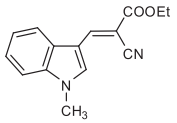
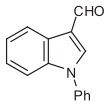
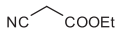
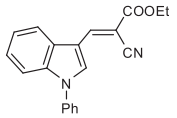
Sr. no.	Substrate 1	Substrate 2	Product	Time (min)	Yield[b] (%)
1			 **5a**	30	96
2			 **5b**	30	92
3			 **5c**	30	91
4			 **5d**	30	93
5			 **6a**	20	94
6			 **6b**	20	96
7			 **6c**	20	93
8			 **6d**	20	89

Table 2
(*Continued*)

Sr. no.	Substrate 1	Substrate 2	Product	Time (min)	Yield[b] (%)
9			 **6e**	20	90
10			 **6f**	20	91
11			 **6g**	20	89
12			 **6h**	20	87

[a]Reaction conditions: catalyst GN3 (0.025 g), indole aldehyde (1 mmol), 4-hydroxycoumarin/malononitrile/ethylcyanoacetate (1 mmol) in water solvent at room temperature. Progress of reaction was monitored by gas chromatography.
[b]Isolated yields.

(m, 1H), 7.08–7.21 (m, 2H), 6.97 (br s, 2H, NH), 4.49–4.69 (q, $J = 7.4$ Hz, 2H), 4.21 (s, 1H), 1.29 (t, $J = 8.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 163.7, 158.2, 157.7, 150.2, 135.9, 130.8, 129.9, 126.2, 124.1, 123.6, 121.2, 117.0, 114.4, 114.0, 113.1, 109.0, 101.9, 100.3, 71.8, 63.0, 40.5, 29.5, 18.1; GC–MS *m/z* 402 (M^+). Elemental analysis: Calcd. $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.67; H, 4.53; N, 6.99.

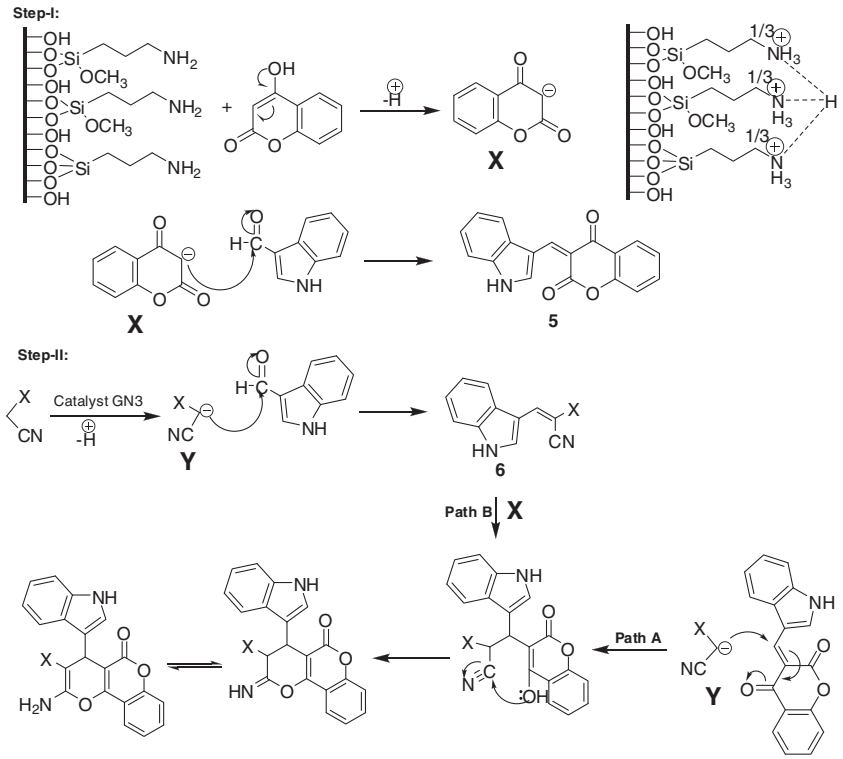
Ethyl 2-amino-4-(2-methyl-1H-indol-3-yl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4f). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.04 (br s, 1H, NH), 7.77–7.89 (m, 1H), 7.61–7.72 (m, 1H), 7.41–7.53 (m, 2H), 7.20–7.40 (m, 4H), 6.91 (br s, 2H, NH), 4.52–4.72 (q, $J = 7.1$ Hz, 2H), 4.25 (s, 1H), 2.69 (s, 3H), 1.27 (t, $J = 7.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 160.8, 159.4, 157.7, 152.0, 138.1, 131.2, 128.9, 128.3, 122.5, 121.8, 121.2, 119.9, 119.3, 119.1, 116.7, 115.7, 11.2, 110.8, 113.0, 78.1, 62.8, 38.9, 19.8, 16.1; GC–MS *m/z* 416 (M^+). Elemental analysis: Calcd. $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.19; H, 4.86; N, 6.71.

Ethyl 2-amino-4-(1-methyl-1H-indol-3-yl)-5-oxo-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4g). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22–8.34 (m, 1H), 7.98–8.18 (m, 2H), 7.72–7.87 (m, 1H), 7.54–7.72 (m, 2H), 7.32–7.51 (m, 2H), 7.23 (s, 1H), 6.99 (br s, 2H, NH), 4.70–4.90 (q, $J = 6.8$ Hz, 2H), 4.30 (s, 1H), 3.68 (s, 3H), 1.20 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 159.1, 157.2, 156.9, 152.0, 140.0, 125.9, 125.3, 123.0, 129.8, 122.5, 120.7, 114.9, 114.0, 112.9, 109.2, 108.0, 101.8, 100.7, 78.9, 61.9, 40.6, 34.5, 19.0; GC–MS *m/z* 416 (M^+). Elemental analysis: Calcd. $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.24; H, 4.87; N, 6.76.

Ethyl 2-amino-5-oxo-4-(1-phenyl-1H-indol-3-yl)-4,5-dihydropyrano [3,2-c]chromene-3-carboxylate (4h). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–8.08 (m, 2H), 7.60–7.89 (m, 4H), 7.34–7.56 (m, 5H), 7.29 (s, 1H), 7.01 (br s, 2H, NH), 6.61–7.80 (m, 1H), 4.40–4.66 (q, $J = 7.9$ Hz, 2H), 4.21 (s, 1H), 1.22 (t, $J = 7.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 160.2, 159.9, 159.3, 155.7, 151.0, 141.7, 130.1, 129.1, 127.8, 127.2, 126.1, 124.9, 124.5, 121.1, 117.2, 116.0, 114.2, 113.7, 108.8, 106.5, 102.6, 76.5, 64.1, 43.7, 17.2; GC–MS *m/z* 478 (M^+). Elemental analysis: Calcd. $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.85. Found: C, 72.81; H, 4.66; N, 5.88.

General procedure for Knoevenagel condensation. The preceding procedure was carried out using 3-indole aldehydes

Scheme 4. Possible mechanism of chromene derivatives using GN3 catalyst.



(1 mmol) and 4-hydroxy coumarine/active methylene compound (1 mmol) at room temperature conditions.

3-[(1H-Indol-3-yl)methylene]chroman-2,4-dione (5a). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.48 (br s, 1H, NH), 8.89 (s, 1H), 7.82–7.89 (m, 1H), 7.58–7.70 (m, 2H), 7.31–7.42 (m, 2H), 7.05–7.17 (m, 2H), 6.81–6.92 (m, 1H) 6.51 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.0, 157.6,151.9, 154.1, 138.0, 132.3, 131.9, 130.3, 129.9, 129.1, 123.3, 124.4, 120.2, 118.8, 117.7, 113.1, 107.7, 107.3, GC–MS *m/z* 289 (M^+). Elemental analysis: Calcd. $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.76; H, 3.85; N, 4.82.

3-[(2-Methyl-1H-indol-3-yl)methylene]chroman-2,4-dione (5b). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.12 (br s, 2H, NH), 8.60 (s, 1H), 8.23–8.33 (m, 1H), 7.82–7.98 (m, 2H) 7.40–7.49 (m, 1H), 7.08–7.17 (m, 1H), 6.71–6.97 (m, 3H), 2.65 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.7, 158.8, 152.9, 152.3, 132.9, 132.5, 129.1, 128.9, 129.6, 126.8, 126.4, 124.1, 121.1, 119.9, 116.2, 111.9, 110.2, 102.3, 14.5; GC–MS *m/z* 303 (M^+). Elemental analysis: Calcd. $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.26; H, 4.35; N, 4.64.

3-[(1-Methyl-1H-indol-3-yl)methylene]chroman-2,4-dione (5c). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.46–8.55 (m, 1H), 8.20–8.30 (m, 2H) 7.81–7.93 (m, 2H), 7.56–7.69 (m, 2H), 7.19–7.40 (m, 2H), 4.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 161.2, 155.1, 154.3, 139.0, 138.1, 137.5, 136.8, 129.5, 129.128.5, 128.1, 127.2, 121.1, 199.9, 118., 111.2, 109.0, 108.0, 35.8; GC–MS *m/z* 303 (M^+). Elemental analysis: Calcd. $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.26; H, 4.30; N, 4.66.

3-[(1-Phenyl-1H-indol-3-yl)methylene]chroman-2,4-dione (5d). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 8.04–8.13 (m, 1H), 7.88–7.92 (m, 1H), 7.51–7.73 (m, 2H), 7.21–7.48 (m, 2H), 6.89–7.18 (m, 6H), 6.68–6.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 160.0, 153.5, 153.3, 147.1, 138.8, 134.1, 133.2, 130.0, 129.1, 128.3, 128.1, 127.3, 126.9, 126.0, 125.3, 124.8, 121.1, 120.5, 119.9, 116.1, 115.8, 109.6; GC–MS *m/z* 365 (M^+). Elemental analysis: Calcd. $C_{24}H_{15}NO_3$: C, 78.89; H, 4.14; N, 3.83. Found: C, 78.92; H, 4.17; N, 3.85.

2-[(1H-Indol-3-yl)methylene]malononitrile (6a). Blackish solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.01 (bs, 1H, NH), 8.52–8.78 (m, 2H), 7.39–7.61 (m, 2H), 7.06–7.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 143.8, 130.1, 128.1, 123.9, 122.5, 121.3, 115.6, 112.1, 110.4, 85.6; GC–MS *m/z* 193 (M^+). Elemental analysis: Calcd. $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.57; H, 3.68; N, 21.73.

2-((2-Methyl-1H-indol-3-yl)methylene)malononitrile (5b). Gray solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.30 (bs, 1H, NH), 8.46 (s, 1H), 7.49–7.65 (m, 1H), 6.94–7.28 (m, 3H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1, 139.9, 133.1, 122.2, 120.0, 114.5, 112.6, 104.8, 91.3, 14.2; GC–MS *m/z* 207 (M^+). Elemental analysis: Calcd. $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.37; H, 4.41; N, 20.31.

2-[(1-Methyl-1H-indol-3-yl)methylene]malononitrile (6c). Gray solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.09–

8.18 (m, 1H), 7.59 (s. 1H), 7.20–7.40 (m, 2H), 6.99–7.08 (m, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 136.0, 132.7, 127.8, 122.9, 121.0, 119.9, 115.4, 114.0, 113.1, 91.8, 39.9; GC–MS *m/z* 207 (M^+). Elemental analysis: Calcd. $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.32; H, 4.35; N, 20.26.

2-[(1-Phenyl-1H-indol-3-yl)methylene]malononitrile (6c). Black solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.33 (s, 1H), 7.98–8.09 (m, 1H), 7.19–7.71 (m, 6H), 6.89–6.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 145.6, 137.7, 127.5, 124.9, 124.3, 123.9, 122.8, 121.0, 115.5, 114.8, 114.1, 107.8, 90.9; GC–MS *m/z* 269 (M^+). Elemental analysis: Calcd. $C_{18}H_{11}N_3$: C, 80.28; H, 4.12; N, 15.60. Found: C, 80.31; H, 4.15; N, 15.57.

Ethyl 2-cyano-3-(1H-indol-3-yl)acrylate (6e). Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.29 (br s, 1H, NH), 8.44 (s, 1H), 7.96 (s, 1H), 7.49–7.54 (m, 1H), 7.25–7.39 (m, 2H), 6.92–7.21 (m, 2H); 3.61–3,75 (q, J = 6.4 Hz, 2H), 1.20 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 145.6, 137.7, 127.5, 124.9, 124.3, 123.9, 122.8, 121.0, 115.5, 114.8, 114.1, 107.8, 90.9; GC–MS *m/z* 240 (M^+). Elemental analysis: Calcd. $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.02; H, 5.05; N, 11.64.

Ethyl 2-cyano-3-(2-methyl-1H-indol-3-yl)acrylate (6f). Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 13.20 (br s, 1H, NH), 8.79 (s, 1H), 7.56–7.71 (m, 2H), 6.95–7.21 (m, 2H), 4.28–4.49 (q, J = 6.9 Hz, 2H), 2.60 (s, 3H), 1.27 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 153.6, 138.7, 129.0, 128.9, 121.3, 122.8, 116.7, 116.3, 112.1, 107.4, 16.9, 61.8, 14.7, 15.3; GC–MS *m/z* 254 (M^+). Elemental analysis: Calcd. $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.82; H, 5.58; N, 11.04.

Ethyl 2-cyano-3-(1-methyl-1H-indol-3-yl)acrylate (6g). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41–8.50 (m, 1H), 7.80 (s, 1H), 7.52–7.60 (m, 1H), 7.19–7.39 (m, 2H), 6.91–7.00 (m, 1H), 4.06–4.17 (q, J = 6.7 Hz, 2H), 3.69 (s, 3H), 1.29 (t, J = 8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 156.8,134.1, 130.7, 129.6, 123.0, 121.4, 119.8, 117.2, 108.3, 108.1, 107.9, 57.5, 46.3, 18.1; GC–MS *m/z* 254 (M^+). Elemental analysis: Calcd. $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.87; H, 5.53; N, 10.99.

Ethyl 2-cyano-3-(1-phenyl-1H-indol-3-yl)acrylate (6h). White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19–8.30 (m, 2H), 8.02 (s, 1H), 7.79 (s, 1H), 7.29–7.60 (m, 6H), 6.89–7.05 (m, 2H), 4.04–4.18 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 1.10 (t, J = 7.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 154.8, 143.2, 137.4, 128.7, 128.3, 127.7, 124.6, 124.3, 121.1, 119.9, 118.7, 118.3, 114.7, 107.8, 107.2, 60.1, 16.2; GC–MS *m/z* 316 (M^+). Elemental analysis: Calcd. $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.95; H, 5.13; N, 8.89.

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