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An efficient three-component synthesis of coumarin-3-carbamides by use of Ni-NiO nanoparticles as magnetically separable catalyst

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An efficient and ecofriendly synthesis of coumarin-3-carbamides, a class of compounds known for their remarkable biological activities and fluorescent properties, has been developed by a three-component reaction of 2-hydroxybenzaldehydes, aliphatic primary/secondary amines and diethyl malonate using Ni-NiO nanoparticless as catalyst in the green solvent ethanol. The method is compatible with various functional groups and moieties.

Introduction

Coumarin-3-carbamides or 2-oxo-2*H*-chromene-3-carboxamides form an important class of compounds in pharmaceutical and chemical industries as their structural unit is frequently found in the core of a diverse range of biologically and pharmaceutically active molecules.[1] A good number of coumarin-3-(*N*-aryl)carbamides are known to arrest breast cancer cell growth by inhibiting ErbB-2 and ERK1.[2] They are also known to act as monoamine oxidase inhibitors,[3] β-secretase (BACE1) inhibitors[4] and anti-*Helicobactor pylori* agents.[5] In addition, the structural framework of these molecules has attracted current attention for their remarkable applications in different FRET dyes,[6] microRNA inhibition study *in vivo*,[7] fluorescent probe for Fe(II)[8] and molecular sensor for monitoring O_2 levels in living cells.[9] Several interesting molecules of this category which find recent applications[7-9] are shown in Fig. 1. Literature survey reveals the existence of a number of protocols for the synthesis of coumarin-3-carbamides involving time consuming multi-step reactions,[10] and this encouraged us to develop a straight-forward, efficient, time-economic and environmentally benign methodology for the purpose. It may be pointed out here that the said molecules contain an amide bond and development of methodologies for construction of this bond is also an important topic in synthetic organic chemistry even in current years.[11]

Multi-component assembly processes are expedient synthetic routes as there three or more reactants are joined together to constitute a complex target molecule through a set of reactions in one pot.[12] Interestingly, the products of such reactions are very sensitive to the reaction components.[13] This is why in some of the apt approaches multi-component reactions offer broad implications in synthetic methodology, green chemistry, biological screening and library production of medicinal scaffolds.[14]

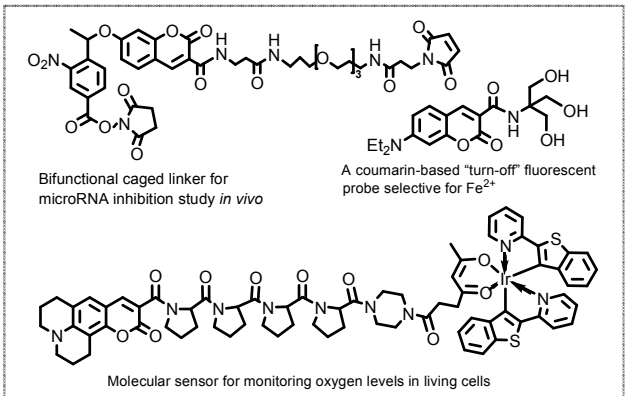

Fig. 1 Some coumarin-3-carbamides having important applications.

Recently, attention in catalysis by nanoparticles has increased considerably because of their recyclability, sustainability, selective reactivity, high catalytic activity and ecological safety.[15,16] In particular, catalysis by nanoparticles of compounds of metals of the first transition series such as those of Cu, Fe, Ni etc. has received much interest due to their large surface area and distinctive thermal, chemical, electronic, magnetic and optical properties.[16] The use of inexpensive Ni-NiO nanoparticles as catalyst has been receiving recent attention due to their benign nature[17] and interesting catalytic activities.[18] However, only a few examples of such applications are known so far.[18] This prompted us to undertake the present work, and herein we report the applicability of Ni-NiO nanoparticles as a catalyst in a multi-component assembly process leading to synthesis of a variety of coumarin-3-carbamides (Scheme 1).

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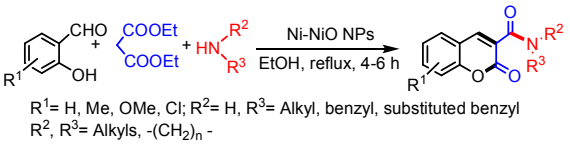


R^1= H, Me, OMe, Cl; R^2= H, R^3= Alkyl, benzyl, substituted benzyl
R^2, R^3= Alkyls, $-(CH_2)_n-$

Scheme 1 Multi-component reaction of 2-hydroxybenzaldehyde, amine and diethyl malonate.

Results and discussion

The results obtained from a long screening test with a series of solvents, temperatures and reaction times are summarized in Table 1, which standardized the reaction conditions for the representative multi-component reaction involving 2-hydroxybenzaldehyde (**1**), benzylamine (**2**) and diethyl malonate (DEM). Various solvents like water, ethanol, toluene, PEG-400, THF and DMF were used and the green solvent ethanol[19] was found to be the best, affording the product **3d** in 93% yield at 78 ^{O}C within 4 h (Table 1, entry 6).

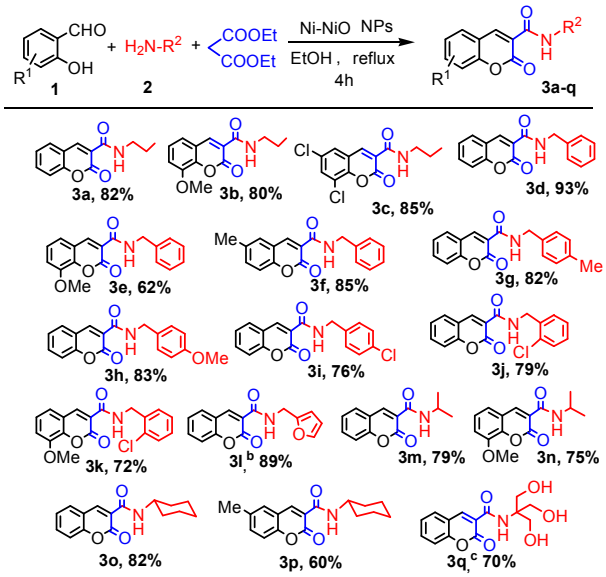
To judge the opportunity, generalize the protocol and bring out a library of functionalized coumarin-3-carbamides, a variety of substituted 2-hydroxybenzaldehydes were made to participate in this multi-component assembly process with DEM and diversely substituted aliphatic primary amines under the optimized reaction conditions. The results are shown in Table 2. Substituents like Me, OMe and Cl in 2-hydroxybenzaldehyde did not show considerable role to influence the reaction. Primary amines containing primary alkyl groups (*e.g.*, n-propylamine, benzylamines etc.) were converted to corresponding products (compounds **3a-l** in Table 2) very efficiently. It is noticeable that even the heat sensitive compound furfurylamine gave very good yield of **3l**. Isopropylamine and cyclohexylamine, primary amines containing a secondary alkyl group, also underwent reaction. Although the reaction was not successful with t-butylamine, a primary amine containing a tertiary alkyl group, the sterically hindered highly polar amine, 2-amino-2-(hydroxymethyl)propane-1,3-diol successfully produced the corresponding carbamide **3q**[8] (Table 2).

Table 1 Standardization of Reaction Conditions[a]

Entry	Catalyst [Amt. in mg]	Solvent	T [^{o}C]	Time [h]	Yield [%][b]
1	0	-	25	24	-
2	0	H_2O	80	24	-
3	6.5	H_2O	60	24	-
4	0	EtOH	78	24	25
5	2.5	EtOH	78	4	65
6	**6.5**	**EtOH**	**78**	**4**	**93**
7	10	EtOH	78	4	91
8	13	EtOH	78	4	90
9	6.5	CH_3CN	82	4	77
10	6.5	Toluene	80	4	65
11	6.5	PEG-400	80	4	81
12	6.5	$CHCl_3$	60	4	31
13	6.5	THF	66	4	29

[a] Reaction conditions: 2-hydroxybenzaldehyde (1.0 mmol), benzylamine (1.2 mmol), DEM (1.0 mmol), solvent, Ni-NiO nps (in mg/mmol of **1** or DEM), heat; [b]Yields of isolated pure product.

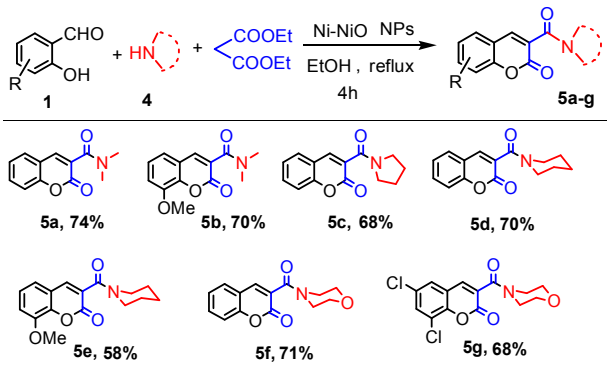
Table 2 Scope of substrate for multi-component reaction of aldehyde, primary amine and DEM[a]



[a]Reaction conditions: 2-hydroxybenzaldehyde (1.0 mmol), primary amine (1.2 mmol), DEM (1.0 mmol), Ni-NiO NPs (6.5 mg/mmol of **1**) in ethanol, 4h, under reflux. [b]6h, [c]10h.

The multicomponent assembly process so developed gave interesting results with secondary amines. Among the acyclic secondary amines dimethylamine, diethylamine, diisopropylamine and di-n-butylamine, only the first compound underwent reaction. Again, all the cyclic secondary amines pyrrolidine, piperidine and morpholine afforded the corresponding products in good yield

Table 3 Scope of substrate for multi-component reaction of aldehyde, secondary amine and DEM[a]



[a]Reaction conditions: 2-hydroxybenzaldehyde (1.0 mmol), secondary amine (1.2 mmol), DEM (1.0 mmol), Ni-NiO NPs (6.5 mg/mmol of **1**), ethanol, 4h, reflux.

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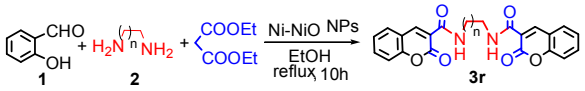
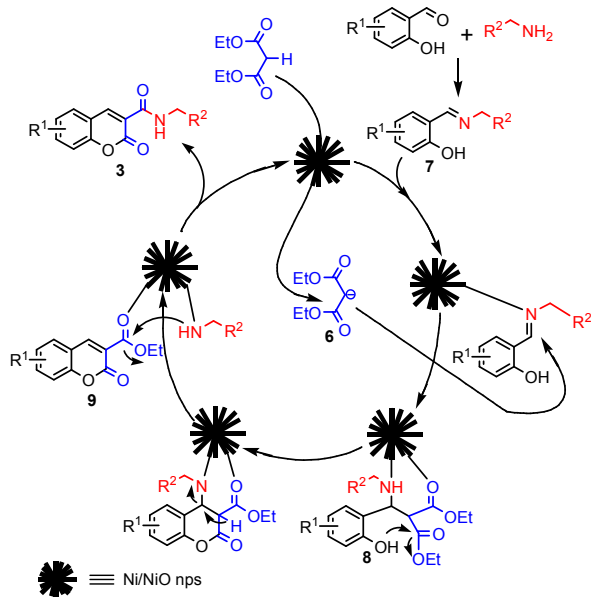
Table 4 Multi-component reaction of aldehyde, amine having two NH_2 groups and DEM



(Table 3).

A very satisfactory result was obtained when several primary diamines were used for the reaction. Thus, reaction with the compounds ethane-1,2-diamine, propane-1,3-diamine and butane-1,4-diamine with 2-hydroxybenzaldehyde (**1**) and DEM produced the corresponding coumarin-bis-3-carbamide (**3r**, Table 4) in good yield. However, the reaction was not successful to yield the amides (**3** or **5**) with aromatic primary amines and esters of the α-amino acids alanine and proline.

While carrying out the reactions, it was a general observation that on mixing the reactants and catalyst the mixture immediately turned yellow to red, which was indicative of formation of an imine or iminium ion from the 2-hydroxybenzaldehyde and an amine (p- or s-) in the first step. This matter was settled from the success of the reaction done by using a preformed imine and DEM under the same catalytic condition to give the final product. It may therefore be suggested that the reaction proceeds through the pathway outlined in Scheme 2. Possibly, NiO nanoparticles facilitate the enolization of DEM to produce the corresponding enolate **6**. On the other hand, Ni nannoparticles activate the imine **7** formed by the reaction of 2-hydroxybenzaldehyde and an amine. These two intermediate species then combine to give **8** which subsequently produces ethyl 2-oxo-2*H*-chromene-3-carboxylate (**9**) through transesterification followed by amine elimination. Finally, the ester **9** (isolated in trace amount in combinations which resulted **3q**, **5c**



Scheme 2 Probable mechanistic pathway for multicomponent reaction of aldehyde, amine and DEM.

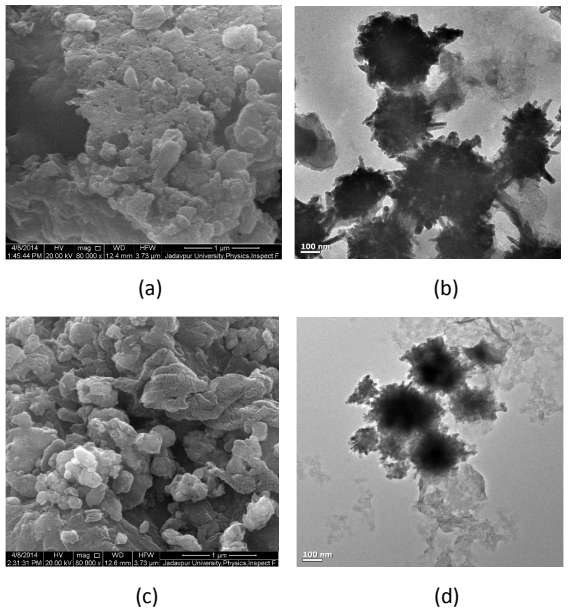


Fig. 2 (a) FESEM and (b) TEM of the fresh catalyst and (c) FESEM and (d) TEM of catalyst after use for the seventh time

and **5g**) undergoes a nucleophilic attack of amine under the catalytic condition employed to give the amide **3**. It may be mentioned here that reaction of **9** with an amine under our reaction condition was found to be successful to generate the final products.

Synthesis of esters of 2-oxo-2*H*-chromene-3-carboxylic acid (*e.g.*, **9**) by secondary amine catalyzed reaction of 2-hydroxybenzaldehyde and malonate esters is well-known in the literature.[20] The commonly proposed mechanism for the process involves an interaction of the conjugate base of malonate ester with 2-hydroxybenzaldehyde or its condensation product with an amine in the first step which is followed by a cyclization.[20,21] Apart from the secondary amine catalyzed method, there are a number of other catalytic processes known for the said transformation.[20b,c , 21] Ni-NiO nps used by us was also found to act as an effective catalyst. Thus, not only majority of the combinations which failed to produce amide but also separate reactions of **1** and DEM in ethanol using Ni-NiO nps as catalyst afforded the ester **9** in good yield**.** Regarding the direct reaction of **9** with amines, the reports known so far are somewhat controversial – some reports inaccessible to us state that the reaction is facile[22] while others state that it is not efficient mainly due to a competitive reaction involving attack at the 4-position of coumarin.[23] Development of good synthetic route to coumarin-3-carbamides therefore required a diversion through the use of reactive intermediates like acid chlorides[10a-d], 2-oxazolone 3-amides[10e], *N*-hydroxysuccinimide esters[10f] etc. The importance of our methodology is that it produces the target amides in good to excellent yield directly from 2-hydroxybenzaldehydes. One point having relevance to the present work is that in case of use of aniline, the reaction did not proceed beyond the imine 2-((*E*)-(phenylimino)methyl)phenol, possibly due to significant stability of such product. Again, some unfavourable steric factor may be responsible for not formation of coumarin-3-carbamide from long chain secondary amines.

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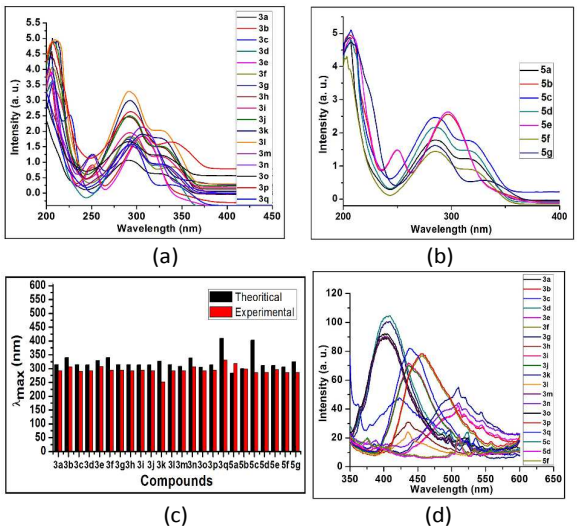

Fig. 3 UV-visible spectra of (a) primary amides and (b) secondary amides; (c) a comparison of UV-visible spectra obtained from theory and experiment; (d) fluorescence spectra of some of the primary and secondary amides.

Ni-NiO nanoparticles were prepared through the hydrazine reduction method done in EtOH-water.[24] Using powder X-ray diffraction, formation of two types of Ni species were confirmed and the size of Ni-NiO nanoparticles were determined to be ~25 nm applying Scherrer's equation. The surface morphology of the particles was examined using the field emission scanning electron microscope (FESEM) and high resolution transmission electron microscope (HRTEM) (Figs. 2a & b). The micrographs showed that nanoparticles were present in the catalyst unit and their average particle size was estimated to be around 100 nm; however, as mentioned above it was found to be 20-30 nm from Scherrer's equation. Again, energy-dispersive X-ray (EDX) analysis showed the weight % of Ni and O to be 67.64 and 32.35, and their atomic % 36.30 and 63.69, respectively (EDX, powder X-ray and mapping data have been provided in Supporting Information).

From the points of view of catalysis and green chemistry, the recyclability of a heterogeneous catalyst is a very important aspect. The catalyst used here easily separated magnetically and it could be made free from organic materials by washing with dichloromethane and reused for seven times (recovery *ca.* 91% after one cycle of reaction) with negligible change in catalytic activity.[24] The FESEM and HRTEM images of the catalyst after seventh cycles showed that its morphology was almost similar to that of the fresh catalyst (Figs. 2c & d).

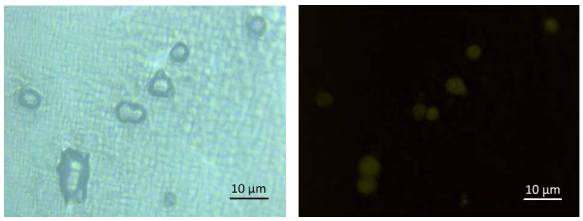

Fig. 4 Scanning microscopic images of (a) CHO cells incubated with **3d** (5μM) and (b) its fluorescence intensities.

UV-visible spectra of primary and secondary amides presented in Tables 2 and 3 were taken in acetonitrile and they are shown in Figs. 3a & b. A double hump spectrum was obtained for all the compounds. The λ_{max}values were found to be consistent with those calculated by Time Dependent Density Functional Theory (TD-DFT) at the B3LYP/6-31G level of theory using Gaussian 09W[25] (Fig. 2c).

The synthesized compounds have interesting fluorescent property (Fig. 3d) and they were found to behave as fluorescent probes for *in vivo* cellular imaging. Thus, treatment of Chinese hamster ovarian cells (CHO cells) with the compounds **3d** and **5f**, each at 5 μM dose, for 2 h gave an intracellular green fluorescence in the vicinity of 530 nm (Fig. 4). Low quantum yield[24] of tertiary amides as compared to secondary ones made them less effective as a fluorescent probe. In addition, an insignificant effect on mortality of CHO cells even at higher dosage (60 μM) of the said two compounds[24] increased their importance as bio-active device to monitor subtle biology.

Conclusions

In conclusion, the methodology using Ni-NiO nanoparticles provides a simple, clean, efficient and green one-pot three-component synthesis of a wide range of coumarin-3-carbamides. It has been found to be effective with various amines having sensitive moieties like furan, high substitution etc. Again, the use of inexpensive, recyclable and ecofriendly catalyst, a green solvent and low cost commercially available starting material in the method endows it with several important advantages. The facile amide bond formation taking place here is also an interesting aspect. Moreover, the compounds can find application as fluorescence probes in living cells.

Experimental

Materials and methods

Melting points were recorded on a Köfler block. Analytical samples were dried *in vacuo* at room temperature. IR spectra were recorded on a Perkin Elmer FT-IR Spectrophotometer (Spectrum BX II) as KBr pellets. NMR spectra were recorded at 300, 400 or 500 MHz for ^{1}H and 75, 100 or 125 MHz for ^{13}C, respectively, using a Bruker 300, 400 or 500 MHz spectrometer. Chloroform or DMSO was used as an internal reference for ^{1}H NMR spectra and Chloroform-d or DMSO-d_6 for ^{13}C NMR spectra. HRMS was performed on Waters Xevo G2QT. For powder X-Ray diffraction and EDX analysis Bruker AXS Inc., Model-D8, Madison, WI and FEI (Technai S-twin), respectively, were used. Field emission scanning electron microscopic (FESEM) study was done (detector distance from sample: 15 mm; detector voltage: 20 kV; magnification: 80,000x; emission current: 180 μA) by use of an INSPECT F50, Netherlands and high resolution transmission electron microscopic (HRTEM) study (detector distance: 11.8 mm; accelerator voltage: 200 keV; beam current: 1 nA) by an FEI (Technai S-twin). UV-Vis spectra were recorded on a SIMADZU UV3101PC and fluorescence spectra were recorded on Cary Eclipse Fluorescence Spectrophotometer, Agilent Technologies. For scanning microscopic images of CHO cell Axio Lab

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A1 was used. Column chromatography was performed on neutral alumina using petroleum ether (60–80 °C) and petroleum ether-ethyl acetate mixtures as eluents. TLC was done with silica gel G. Starting materials used in the reaction were commercially available (Sigma-Aldrich). Different substituted benzylamines were prepared by reduction of oxime of corresponding aldehydes.[26]

General procedures for synthesis of coumarin-3-carbamides (3 or 5)

In a 10 mL round bottomed flask equipped with a condenser and stirring bar, ethanol (3 ml) was taken and to it 2-hydroxybenzaldehyde (**1**) (1.0 mmol), diethylmalonate (1.0 mmol), amine (1.2 mmol) and Ni-NiO nanoparticles (6.5 mg/mmol of **1**) were added. The color of the reaction mixture turned yellow or red depending upon the amine. It was refluxed for 4 h with stirring and then allowed to cool to room temperature. The catalyst was separate by use of a magnet. Water (10 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The amide thus obtained was purified by crystallization or by column chromatography followed by crystallization (when required). [It may be mentioned here that for synthesis of **3r1**, **3r2** and **3r3**, 2-hydroxybenzaldehyde (**1**) (2.0 mmol), diethylmalonate (2.0 mmol), amine (1.2 mmol) and Ni-NiO nanoparticles (6.5 mg/mmol of **1**) were taken.]. The yields, melting points and spectral data of the products are given below.

2-Oxo-*N*-propyl-2*H*-chromene-3-carboxamide (3a). Yield - 82%, colorless crystalline solid, M.P. 128-130 °C; IR (KBr pellet): 3333, 3055, 2921, 1712, 1669, 1527, 1458, 1037,970, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, *J*= 7.2 Hz, 3H, CH_3), 1.59-1.71 (m, 2H, -CH_2-C$\underline{H}_2$-CH_3), 3.40-3.46 (m, 2H, -NH-C$\underline{H}_2$-), 7.35-7.42 (m, 2H, H-6, H-8), 7.63-7.71 (m, 2H, H-5, H-7), 8.83 (br.s, 1H, NH), 8.91 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 22.7, 41.6, 116.6, 118.6, 118.7, 125.2, 129.8, 133.9, 148.2, 154.4, 161.4, 161.5; HRMS: *m/z* calculated for $C_{13}H_{13}NO_3$ $[M+Na]^+$: 254.0793, Found 254.1056.

8-Methoxy-2-oxo-*N*-propyl-2*H*-chromene-3-carboxamide (3b). Yield- 80%, colorless crystalline solid, M.P. 158-160 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J*= 7.5 Hz, 3H, CH_3), 1.64-1.72 (m, 2H, -CH_2-C$\underline{H}_2$-CH_3), 3.43-3.47 (m, 2H, -NH-C$\underline{H}_2$-), 4.1 (s, 3H, OCH_3), 7.21 (d, *J*=7.5 Hz, 1H, H-7), 7.26 -7.33 (m, 2H, H-5, H-6), 8.86 (br.s, 1H, -NH-), 8.91(s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 22.8, 41.7, 56.5, 115.6, 119.0, 119.5, 121.1, 125.2, 144.3, 147.2, 148.5, 161.2; HRMS: *m/z* calculated for $C_{14}H_{15}NO_4$ $[M+K]^+$: 284.0899, Found 284.0901.

6,8-Dichloro-2-oxo-*N*-propyl-2*H*-chromene-3-carboxamide (3c). Yield- 85%, colorless crystalline solid, M.P. 228-230 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 1.00 (t, *J*= 7.5 Hz, 3H, CH_3), 1.62-1.70 (m, 2H, -CH_2-C$\underline{H}_2$-CH_3), 3.41-3.45 (m, 2H, -NH-C$\underline{H}_2$-), 7.58 (d, *J*=2.0 Hz,1H, H-7), 7.69 (d, *J*= 2.0 Hz, 1H, H-5), 8.68 (br.s, 1H, -N$\underline{H}$-), 8.81(s, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 22.7, 41.9, 120.6, 122.8, 127.4, 130.6, 133.8, 146.8, 147.8, 148.8, 160.0, 160.6; HRMS: *m/z* calculated for $C_{13}H_{11}Cl_2NO_3$ $[M+K]^+$: 337.9753, Found 338.3463.

***N*-Benzyl-2-oxo-2*H*-chromene-3-carboxamide (3d).** Yield- 93%, colorless crystalline solid, M.P. 160-162 °C; IR (KBr pellet): 3318, 3045, 2927, 2428, 1710, 1528, 1446, 1247, 799, 765, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.67 (d, *J*= 5.7 Hz, 2H, -NH-C$\underline{H}_2$-), 7.28-7.42 (m, 7H, ArH), 7.64-7.71 (m, 2H, ArH), 8.95 (s, 1H, H-4), 9.18 (br.s, 1H, -N$\underline{H}$-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.9, 116.6, 118.5, 118.7, 125.3, 127.5, 127.7, 128.7, 129.8, 134.1, 137.9, 148.6, 154.5, 161.4, 162.0; HRMS: *m/z* calculated for $C_{17}H_{13}NO_3$ $[M+Na]^+$: 302.0793, Found 302.0785.

***N*-Benzyl-8-methoxy-2-oxo-2*H*-chromene-3-carboxamide (3e).** Yield- 62%, colorless crystalline solid M.P. 208-210 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H, OCH_3,), 4.67 (d, *J*= 6.0 Hz, 2H, -NH-C$\underline{H}_2$-), 7.19 (d, *J*= 8.8 Hz, 1H, H-7), 7.27-7.36 (m, 7H, ArH), 8.93 (s, 1H, H-4), 9.20 (br. s, 1H, -NH-); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.8, 56.4, 115.6, 119.3, 120.9, 125.1, 127.4, 127.7, 128.7, 137.9, 147.1, 148.7, 161.4; HRMS: *m/z* calculated for $C_{18}H_{15}NO_4$ $[M+Na]^+$: 332.0899, Found 332.0926.

Benzyl-6-methyl-2-oxo-2*H*-chromene-3-carboxamide (3f). Yield-85%, colorless crystalline solid, M.P. 284-286 °C; IR (KBr pellet): 3050, 2921, 1704, 1527, 1229, 1059, 786, 713cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ2.45 (s, 3H, CH_3), 4.67 (d, *J*= 5.8 Hz, 2H, -NH-C$\underline{H}_2$-), 7.28-7.47 (m, 8H, ArH), 8.90 (s, 1H, H-4), 9.21 (br.s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 20.7, 43.8, 116.3, 118.4, 127.4, 127.7, 127.8, 128.7, 129.4, 135.2, 135.3, 138.0, 148.5, 152.7, 161.7; HRMS: *m/z* calculated for $C_{18}H_{15}NO_3$ $[M+Na]^+$: 316.0950, Found 316.0971.

***N*-(4-Methylbenzyl)-2-oxo-2*H*-chromene-3-carboxamide (3g).** Yield- 82%, colorless crystalline solid, M.P. 134-140 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.62 (d, *J*= 5.8 Hz, 2H, -NH-C$\underline{H}_2$-), 7.15 (d, *J*= 8.1 Hz, 2H, H-3', H-5'), 7.25 (d, *J*= 5.6 Hz, 2H, H-2', H-4'), 7.36-7.41 (m, 2H, H-6, H-8), 7.64-7.71 (m, 2H, H-5, H-7), 8.95 (s, 1H, H-4), 9.13 (s, 1H, NH); ^{13}C NMR (75 MHz, CDCl3) : δ 21.1, 43.7, 116.6, 118.5, 118.7, 125.3, 127.7, 129.4, 129.8, 134.0, 134.9, 137.1, 148.5, 154.5, 161.4, 161.5; HRMS: *m/z* calculated for $C_{18}H_{15}NO_3$ $[M+Na]^+$: 316.0950, Found 316.0909.

***N*-(4-Methoxybenzyl)-2-oxo-2*H*-chromene-3-carboxamide (3h).** Yield- 83%, colorless crystalline solid, M.P. 146-148 °C; IR (KBr pellet) : 2937, 2357, 1712, 1535, 1514, 1237cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$):δ 3.80 (s, 3H, OCH_3), 4.59 (d, *J*= 5.8 Hz, 2H, -NH-C$\underline{H}_2$-), 6.87 (d, *J*= 8.5 Hz, 2H, H-3', H-5'), 7.29 (d, *J*= 8.5 Hz, 2H, H-2', H-4'), 7.36-7.41 (m, 2H, H-6, H-8), 7.65-7.70 (m, 2H, H-5, H-7), 8.94 (s, 1H, H-4), 9.09 (br. s, 1H, NH); ^{13}C NMR (75 MHz, CDCl3): δ 43.4, 55.3, 114.1, 116.6, 118.5, 118.7, 125.3, 129.1, 129.8, 130.0, 134.0, 148.5, 154.4, 159.0, 161.4; HRMS: *m/z* calculated for $C_{18}H_{15}NO_4$ $[M+Na]^+$: 332.0899, Found 332.0581.

***N*-(4-Chlorobenzyl)-2-oxo-2*H*-chromene-3-carboxamide (3i).** Yield-76%, colorless crystalline solid, M.P. 176-178 °C; IR (KBr pellet): 3340, 3058, 2945, 1717, 1527, 1478, 1245, 1164, 1059, 963, 798, 761, 673, 530, 399 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.63 (d, *J*= 5.8, 2H, -NH-C$\underline{H}_2$-), 7.26-7.42 (m,6H, ArH), 7.65-7.71 (m, 2H, ArH), 8.94 (s, 1H, H-4), 9.20 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.1, 116.6, 118.2, 118.6, 125.3, 128.8, 129.1, 129.8, 133.2, 134.2, 136.5,

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148.7, 154.4, 161.4, 161.6; HRMS: *m/z* calculated for $C_{17}H_{12}ClNO_3$ $[M+H]^+$: 314.0584, Found 314.0915.

***N*-(2-Chlorobenzyl)-2-oxo-2*H*-chromene-3-carboxamide (3j).** Yield- 79%, colorless crystalline solid, M.P. 196-198 °C; IR (KBr pellet): 3055, 1712, 1664, 1525, 1454, 1255, 1035, 917, 802, 761, 632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.75 (d, *J*= 5.8 Hz, 2H, -NH-C$\underline{H}_2$-), 7.22-7.26 (m, 2H, ArH), 7.36-7.46 (m, 4H, ArH), 7.65-7.70 (2H, m, ArH), 8.93 (s, 1H, H-4), 9.29 (br. s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.8, 116.7, 118.4, 118.6, 125.3, 127.0, 128.9, 129.6, 129.8, 133.7, 134.1, 135.3, 148.6, 154.5, 161.4, 161.7; HRMS: *m/z* calculated for $C_{17}H_{12}ClNO_3$ $[M+H]^+$: 314.0584, Found 314.0536.

***N*-(2-Chlorobenzyl)-8-methoxy-2-oxo-2*H*-chromene-3-carboxamide (3k).** Yield- 72%, colorless crystalline solid, M.P. 218-220 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 4.00 (s, 3H, OCH_3), 4.77 (d, *J*=6.0 Hz, 2H, -NH-C$\underline{H}_2$-), 7.20-7.39 (m, 5H, ArH), 7.40 (d, *J*= 6.5 Hz, 1H, ArH), 7.45 (d, *J*= 6.5 Hz, 1H, ArH), 8.91(s, 1H, H-4), 9.31 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ41.9, 56.5, 115.8, 118.7, 119.4, 121.1, 125.3, 127.1, 129.0, 129.7, 129.9, 133.8, 135.5, 144.3, 147.2, 148.9, 161.0, 161.8; HRMS: *m/z* calculated for $C_{18}H_{14}ClNO_4$ $[M+H]^+$: 344.0690, Found 344.0656.

***N*-((Furan-2-yl)methyl)-2-oxo-2*H*-chromene-3-carboxamide (3l).** Yield- 89%, colorless crystalline solid, M.P. 180-182 °C; ^1H NMR (300 MHz, $CDCl_3$): δ4.66 (d, *J*= 6.0 Hz, 2H, -NH-C$\underline{H}_2$-), 6.32 (d, *J*= 6.0 Hz, 2H, furyl H-3,H-4), 7.28-7.42 (m, 3H, ArH), 7.61-7.71 (m, 2H, ArH), 8.93 (s, 1H, H-4), 9.12 (br. s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 107.5, 110.4, 116.6, 118.3, 118.6, 125.3, 129.8, 134.1, 142.3, 148.6, 151.0, 154.5, 161.3, 161.4; HRMS: *m/z* calculated for $C_{15}H_{11}NO_4$ $[M+Na]^+$: 292.0586, Found 292.0483.

***N*-Isopropyl-2-oxo-2*H*-chromene-3-carboxamide (3m).** Yield- 79%, colorless crystalline solid, M.P. 113-117 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, *J*=6.6 Hz, 6H, 2 × CH_3), 4.23-4.30 (m, 1H, CH), 7.35-7.42 (m, 2H, ArH), 7.63-7.70 (m, 2H, ArH), 8.68 (br. s, 1H, NH), 8.91 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 41.9, 116.6, 118.7, 125.2, 129.7, 133.9, 148.1, 154.4, 160.5, 161.4; HRMS: *m/z* calculated for $C_{13}H_{13}NO_3$ $[M+Na]^+$: 254.0793, Found 254.1358.

***N*-Isopropyl-8-methoxy-2-oxo-2*H*-chromene-3-carboxamide (3n).** Yield- 75%, colorless crystalline solid, M.P. 125-127 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, *J*= 6.6 Hz, 6H, 2×CH_3), 3.99 (s, 3H, OCH_3), 4.23-4.30 (m, 1H, CH), 7.17-7.32 (m, 3H, ArH), 8.69 (br. s, 1H, NH), 8.88 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 41.7, 56.1, 115.2, 118.6, 119.1, 120.4, 124.5, 144.6, 146.8, 148.1, 160.3, 160.7; HRMS: *m/z* calculated for $C_{14}H_{15}NO_4$ $[M+H]^+$: 262.1079, Found 262.1628.

***N*-Cyclohexyl-2-oxo-2*H*-chromene-3-carboxamide (3o).** Yield- 82 %, colorless crystalline solid, M.P. 176-178 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24-1.45 (m, 6H,-C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-), 1.73-1.77 (m, 2H,-NH-CH-C$\underline{H}_2$-), 1.78-2.00 (m, 2H,-NH-CH-C$\underline{H}_2$-), 3.94-4.03 (m, 2H, -NH-C$\underline{H}$-CH_2-), 7.34-7.42 (m, 2H, H-6, H-8), 7.62-7.70 (m, 2H, H-5, H-7), 8.76 (br. s, 1H, N$\underline{H}$), 8.90 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 25.6, 32.7, 48.5, 116.6, 118.7, 118.8, 125.2, 129.7, 133.8, 148.1, 154.4, 160.3, 161.4; HRMS: *m/z* calculated for $C_{16}H_{17}NO_3$ $[M+Na]^+$: 294.1106, Found 294.2049.

***N*-Cyclohexyl-6-methyl-2-oxo-2*H*-chromene-3-carboxamide (3p).** Yield- 60 %, colorless crystalline solid, M.P. 182-184 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23-1.48 (m, 6H, -C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-), 1.73-1.77 (m, 6H, -C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$-), 1.96-1.99 (m, 2H, -NH-CH-C$\underline{H}_2$-), 2.43 (s, 3H, CH_3), 3.96-3.99 (m, 2H,-NH-C$\underline{H}$-CH_2-), 7.26 (d, *J*= 4.5 Hz, 1H, H-8), 7.44 (d, *J*= 6.3 Hz, 2H, H-5, H-7), 8.40 (br. s, 1H, N$\underline{H}$), 8.84 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 24.7, 25.6, 32.8, 48.5, 116.3, 118.5, 118.6, 129.3, 135.0, 135.1, 148.1, 152.6, 160.5, 161.7; HRMS: *m/z* calculated for $C_{17}H_{19}NO_3$ $[M+Na]^+$: 308.1263, Found 308.2237.

***N*-(1,3-Dihydroxy-2-(hydroxymethyl)propan-2-yl)-2-oxo-2*H*-chromene-3-carboxamide (3q).** Yield- 70%, colorless crystalline solid, M.P. 194-196 °C; IR (KBr pellet): 2969, 1720, 1525, 1444, 1239, 1046, 956, 803, 745 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ3.66 (d, *J*=5.0 Hz, 6H, 3 × CH_2), 4.81 (t, *J*=5.0 Hz, 3H, 3 × OH), 7.43(t, *J*= 7.5 Hz, 1H, H-6), 7.50 (d, *J*= 8.5 Hz, 1H, H-8), 7.73 (t, *J*=8.0 Hz, 1H, H-7), 7.97 (d, *J*= 7.5 Hz, 1H, H-5), 8.89 and 8.96 (each s, 1H, NH and H-4); ^{13}C NMR (75 MHz, DMSO-d_6): δ 60.6, 62.9, 116.6, 118.9, 119.4, 125.6, 130.8, 134.6, 148.1, 154.4, 161.2, 161.4; HRMS: *m/z* calculated for $C_{14}H_{15}NO_6$ $[M+H]^+$: 294.0978, Found 294.0884.

***N*,*N*-Dimethyl-2-oxo-2*H*-chromene-3-carboxamide (5a).** Yield- 74%,colorless crystalline solid, M.P. 150-152 °C; IR (KBr pellet): 3064, 2978, 2928, 2914, 1766, 1607, 1563, 1450, 1206, 1032, 1023, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.29-7.37 (m, 2H, H-6, H-8), 7.52-7.61 (m, 2H, H-5, H-7), 7.91 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.3, 38.4, 116.8, 118.3, 124.9, 125.8, 128.5, 132.7, 142.9, 154.1, 157.8, 165.0; HRMS: *m/z* calculated for $C_{12}H_{11}NO_3$ $[M+H]^+$: 218.0817, Found 218.1080.

8-Methoxy-*N*,*N*-dimethyl-2-oxo-2*H*-chromene-3-carboxamide (5b). Yield- 70%, colorless crystalline solid, M.P. 162-164 °C; IR (KBr pellet): 3410, 2942, 1710, 1638, 1612, 1579, 1478, 1282, 1260, 1198, 1109, 771, 734, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (s, 3H, CH_3), 3.13 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.11-7.16 (m, 2H, H-5, H-7), 7.27 (t, *J*= 8.0 Hz, 1H, H-6), 7.92(s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ35.3, 38.3, 56.3, 114.5, 119.0, 119.8, 124.7, 126.0, 143.2, 143.8, 147.2, 157.3, 165.0; HRMS: *m/z* calculated for $C_{13}H_{13}NO_4$ $[M+Na]^+$: 270.0742, Found 270.0839.

***N*,*N*-Tetramethylene-2-oxo-2*H*-chromene-3-carboxamide (5c).** Yield- 68%, colorless crystalline solid, M.P. 140-142 °C; IR (KBr pellet): 3423, 3053, 2971, 2875, 1723,620, 1627, 1570, 1425, 1337, 1192, 1049, 763, 971, 925, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91-2.00 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-), 3.46 (t, *J* = 6.0 Hz, 2H, >N-CH_2-), 3.64 (t, *J* = 6.0 Hz, 2H, >N-CH_2-), 7.29-7.37 (m, 2H, H-6, H-8), 7.53-7.62 (m, 2H, H-5, H-7), 7.97 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2, 26.0, 46.2, 47.5, 116.7, 118.3, 124.9, 126.2, 128.6, 132.8, 143.1, 154.1, 157.7, 163.2; HRMS: *m/z* calculated for $C_{14}H_{13}NO_3$ $[M+Na]^+$: 266.0793, Found 266.1015.

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***N,N*-Pentamethylene-2-oxo-2*H*-chromene-3-carboxamide (5d).** Yield- 70 %, colorless crystalline solid, M.P. 156-158 °C; IR (KBr pellet): 3043, 3002, 2921, 2855, 1713, 1627, 1612, 1570, 1470, 1442, 1366, 1252, 1179, 1122, 1042, 990, 972, 805, 673, 611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 1.62-1.69 (m, 6H, -C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.33 (br. s, 2H, >N-C<u>H</u>$_2$-), 3.71 (br. s, 2H, >N-C<u>H</u>$_2$-), 7.28-7.36 (m, 2H, H-6, H-8), 7.51-7.59 (m, 2H, H-5, H-7), 7.86 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 24.4, 25.4, 26.2, 43.0, 48.4, 116.8, 118.4, 124.8, 125.9, 128.4, 132.5, 142.2, 154.0, 158.0, 163.3; HRMS: *m/z* calculated for $C_{15}H_{15}NO_3$ $[M+H]^+$: 258.1130, Found 258.1359.

8-Methoxy-*N,N*-pentamethylene-2-oxo-2*H*-chromene-3-carboxamide (5e). Yield- 58%, colorless crystalline solid, M.P. 188-190 °C; IR (KBr pellet): 3035, 2939, 2848, 1720, 1617, 1485, 1439, 1364, 1276, 1250, 1108, 969, 791, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):δ 1.59-1.67 (m, 6H, -C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.31 (t, *J* = 4.8 Hz, 2H, >N-C<u>H</u>$_2$-), 3.69 (br. s, 2H, >N-C<u>H</u>$_2$-), 3.96 (s, 3H, OCH_3), 7.08-7.12 (m, 2H, H-5, H-7), 7.23 (t, *J* = 7.8 Hz, 1H, H-6), 7.84 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ24.4, 25.4, 26.2, 43.1, 48.4, 56.3, 114.4, 119.1, 119.8, 124.7, 126.2, 142.6, 143.7, 147.2, 157.4, 163.3; HRMS: *m/z* calculated for $C_{16}H_{17}NO_4$ $[M+Na]^+$: 310.1055, Found 310.1180.

***N,N*-(3-Oxapentamethylene)-2-oxo-2*H*-chromene-3-carboxamide (5f).** Yield-71%, colorless crystalline solid, M.P. 136-138 °C, IR (KBr pellet): 3036, 2925, 2860, 1722, 1627, 1468, 1447, 1367, 1273, 1243, 1171, 1110, 994, 929, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.40 (t, *J*= 4.4 Hz, 2H, >N-C<u>H</u>$_2$-), 3.72(t, *J*= 4.4 Hz, 2H, >N-C<u>H</u>$_2$-), 3.79 (s, 4H, 2 × -O-C<u>H</u>$_2$-), 7.31-7.37 (m, 2H, H-6, H-8), 7.54-7.62 (m, 2H, H-5, H-7), 7.96 (s, 1H, H-4);^{13}C NMR (100 MHz, $CDCl_3$): δ 42.8, 47.8, 66.7, 66.8, 117.0, 118.4, 125.0, 125.1, 128.8, 133.1, 143.8, 154.3, 158.1, 163.7; HRMS *m/z* calculated for $C_{14}H_{13}NO_4$ $[M+Na]^+$: 282.0742, Found 282.0971.

6,8-Dichloro-*N,N*-(3-oxapentamethylene)-2-oxo-2*H*-chromene-3-carboxamide (5g). Yield- 68%, colorless crystalline solid, M.P. 220-222 °C, IR (KBr pellet): 3449, 1730, 1635, 1610, 1560, 1430, 1241, 1110, 1005, 874, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.39 (t, *J*= 4.5 Hz, 2H, >N-C<u>H</u>$_2$-), 3.74 (t, *J*= 4.5 Hz,2H, >N-C<u>H</u>$_2$-), 3.81 (s, 4H, 2 × -O-C<u>H</u>$_2$-), 7.46 (d, *J*= 2.1 Hz, 1H, H-5), 7.67 (d, *J*= 2.1 Hz, 1H, H-7), 7.88 (s, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.7, 47.6, 66.5, 66.6, 120.1, 122.9, 126.2, 126.8, 130.2, 132.8, 142.0, 148.4, 156.3, 162.5;HRMS *m/z* calculated for $C_{14}H_{11}Cl_2NO_4$ $[M+Na]^+$: 349.9963, Found 350.0179.

1,2-(Bis-2-oxo-2*H*-chromene-3-carboxamido)ethane (3r1). Yield-80%, colorless crystalline solid, M.P. 118-120 °C [Lit. [3] 112-118 °C]; ^1H NMR (400 MHz, $CDCl_3$): δ3.74 (d, *J* = 5.6 Hz, 4H, -CH_2-CH_2-), 7.36-7.42 (m, 4H, H-6, H-8 & H-6', H-8'), 7.64-7.71 (m, 4H, H-5, H-7 & H-5', H-7'), 8.92 (s, 2H, H-4 & H-4'), 9.06 (br. s, 2H, 2 × NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.6, 116.8, 118.5, 118.8, 125.4,130.0, 134.2, 148.7, 155.0, 161.5, 162.3.

1,3-(Bis-2-oxo-2*H*-chromene-3-carboxamido)propane (3r2). Yield-72%,colorless crystalline solid, M.P. 74-76 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.97 (quintet, *J*= 6.6 Hz, 2H, -CH_2-C<u>H</u>$_2$-CH_2-), 3.59 (q, *J* = 6.6 Hz, 4H,-C<u>H</u>$_2$-CH_2-C<u>H</u>$_2$-), 7.36-7.42 (m, 4H, H-6, H-8 & H-6', H-8'), 7.64-7.71 (m, 4H, H-5, H-7 & H-5', H-7'), 8.93 (s, 2H, H-4 & H-4'), 9.02 (br. s, 2H, 2 × NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 37.4, 116.6, 118.5, 118.7, 125.2, 129.8, 134.0, 148.3, 154.4, 161.4, 161.8; HRMS: *m/z* calculated for $C_{23}H_{18}N_2O_6$ $[M+Na]^+$: 411.1063, Found 411.2314.

1,4-(Bis-2-oxo-2*H*-chromene-3-carboxamido)butane (3r3). Yield-78%, colorless crystalline solid, M.P. 83-85 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 3.51 (br. s, 4H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-), 4.36 (q, *J* = 7.5 Hz, 4H, -C<u>H</u>$_2$-CH_2-CH_2-C<u>H</u>$_2$-), 7.38-7.46 (m, 4H, H-6, H-8 & H-6', H-8'), 7.66-7.71 (m, 4H, H-5, H-7 & H-5', H-7'), 8.88 (s, 2H, H-4 & H-4'), 8.91 (br. s, 2H, 2 × NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 39.7, 116.8, 118.7, 118.9, 125.4, 130.0, 134.1, 148.5, 154.6, 161.6, 161.7; HRMS: *m/z* calculated for $C_{24}H_{20}N_2O_6$ $[M+H]^+$: 433.1400, Found 433.1425.

For getting an insight of the reaction mechanism, the imine **7d** (generated from 2-hydroxybenzaldehyde and benzylamine) and ethyl 2-oxo-2*H*-chromene-3-carboxylate (**9**) were subjected to the reaction condition as mentioned in the text. The ^1H NMR spectral data of these two compounds are given below:

Imine 7d. Yellow oil, ^1H NMR (300 MHz, $CDCl_3$): δ 4.82 (s, 2H, Ph-C<u>H</u>$_2$-), 6.89 (t, *J* = 7.5 Hz, 1H, H-5), 6.97 (d, *J* = 7.5 Hz, 1H, H-3), 7.29-7.39 (m, 7H, Ar-H), 8.45 (s, 1H, >CH=N-), 13.40 (br. s, 1H, OH).

Ethyl 2-oxo-2*H*-chromene-3-carboxylate (9). In a 10 mL round-bottomed flask equipped with a condenser and stirring bar, ethanol (3 ml) was taken and to it 2-hydroxybenzaldehyde (**1**) (1.0 mmol), DEM (1.0 mmol), and Ni-NiO nanoparticles (6.5 mg/mmol of **1**) were added. The mixture was refluxed for 4 h with stirring, allowed to cool to room temperature and then the catalyst was separated. Water (10 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The ester **9** thus obtained was purified by crystallization. It was a colourless crystalline solid, yield-70%, M.P. 85-87 °C, ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, *J*= 7.2 Hz, 3H, CH_3), 4.40 (q, *J*=7.2, 2H, -C<u>H</u>$_2$-CH_3), 7.26-7.39 (m, 2H, H-6 & H-8), 7.60-7.65 (m, 2H, H-5 & H-7), 8.51 (s, 1H, H-4).

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An efficient three-component synthesis of coumarin-3-carbamides by use of Ni-NiO nanoparticles as magnetically separable catalyst

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