A Facile One Pot Synthesis of New Tricyclic Coumarins from Single Synthon [1]

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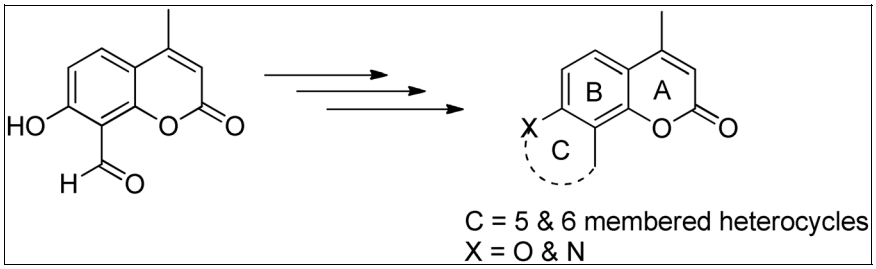

A high yielding method for the synthesis of new tricyclic coumarins is reported herein using 8-formyl-7-hydroxy-4-methyl coumarin as a single synthon. Different strategies were employed to synthesize tricyclic coumarins fused with isoxazole and pyran at C7-C8 position in the coumarin skeleton. Functional group modifications during the construction of pyrazolyl coumarin has resulted in novel oxidative ipso nitration. The *O*-tosylate was subjected to conditions of pressure in a sealed tube experiment, since it was not possible to replace the 7-hydroxy group of coumarin by regular methods. All the compounds synthesized during the present investigation were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, ESI-MS, and elemental analysis. The X-ray diffraction data of some of the intermediate hydrazones are also reported herein.

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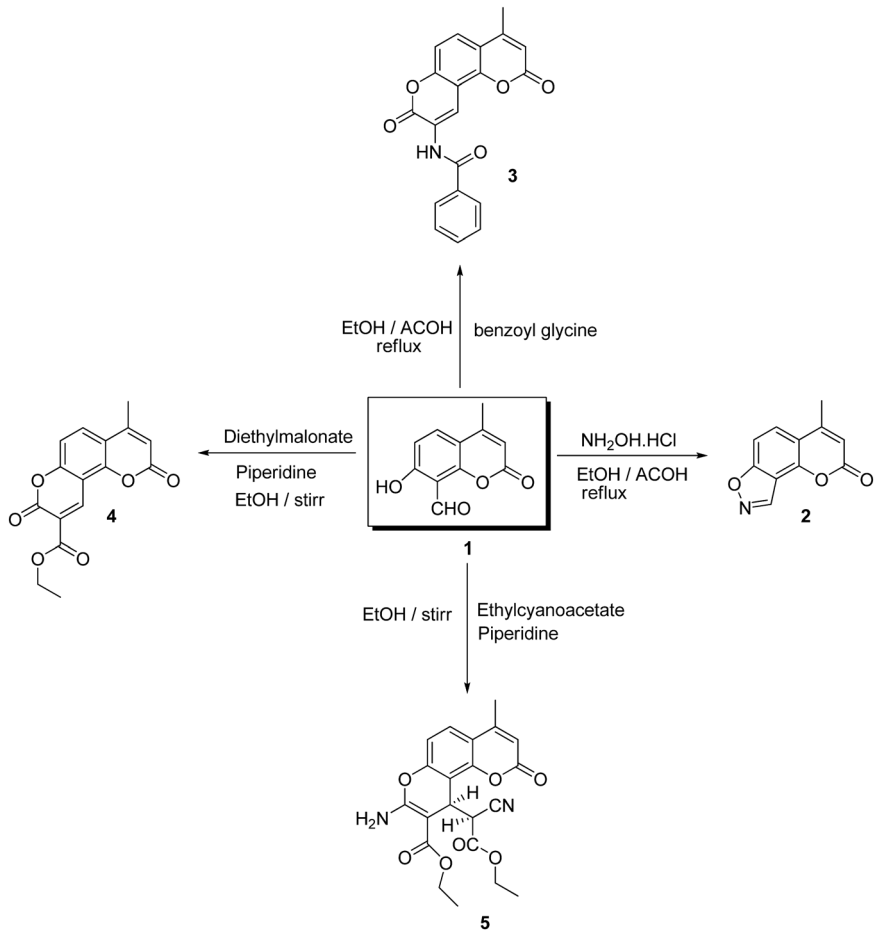
INTRODUCTION

Coumarins are the class of lactones with extensive occurrence in plants possessing wide range of biological activities such as antimicrobial, anticancer, anti-inflammatory and anti-HIV activities reviewed recently [2]. Synthetic coumarins have been reported as anti-inflammatory, antibacterial [3–7], antitumor [8], and antiviral agents [9]. Importance of 7,8 fused tricyclic coumarins came to light with the discovery of naturally occurring angelicins [10], [11], and the corresponding pyranyl coumarins [12], some of which exhibit anti-HIV activity [13]. Photophysical properties associated with 7-hydroxy and 7-amino coumarin derivatives have been used to study biological [14] and energy transfer processes [15].

Coumarins are well known for their applications in organic synthesis, particularly in the synthesis of heterocyclic molecules such as oxazoles [16], pyridazofurans [17], pyrazole, isoxazole, pyrimidines, pyran [18] bezofurans [19,20], pyridine [21], and quinolines [22]. Fused tricyclic coumarins are found to possess various biological properties and are used in the treatment of vitilago, psoriasis, and other diseases [23]. The physiological properties of natural and synthetic fused tricyclic coumarins have been reviewed by many workers [24]. In recent years, the tricyclic coumarins have been extensively used as laser materials, photosensitizers, optical brighters, intermediates for dyes, pesticides, in pharmaceutical preparations and in enzymology as biological probes [25]. The reactivity of coumarins to construct biologically active oxygenated bi-heterocycles, unsymmetrical triheterocycles, and pentacyclic heterocycles [26] is well documented from our laboratory. Many methods of synthesis of fused pyrazoles, isoxazoles, and pyrans have been reported in the literature as useful heterocyclic moieties as they possess a broad spectrum of biological activities such as antiviral, CNS depressant, and antimicrobial properties [27].

The synthesis of oxygen and nitrogen containing tricyclic systems across C7 and C8 positions would require the corresponding hydroxyl and amino coumarins. In view of the biological and structural relevance associated with such systems, we thought to evolve a common synthetic protocol for O, N 7,8 fused coumarins. The choice of 7-hydoxy-4-methyl-8-coumarin [28,29] for this purpose was based on the idea that, the nucleophilicity of 7-hydroxy group would be utilized to construct the oxygen fused systems where as addition across formyl group with nucleophiles would generate the nitrogen necessary for an intramolecular S_N-Ar displacement of the phenolic oxygen or its *O*-acetyl or *O*-tosyl derivative with aromatic

Scheme 1. Synthesis of 7,8-fused tricyclic coumarins.

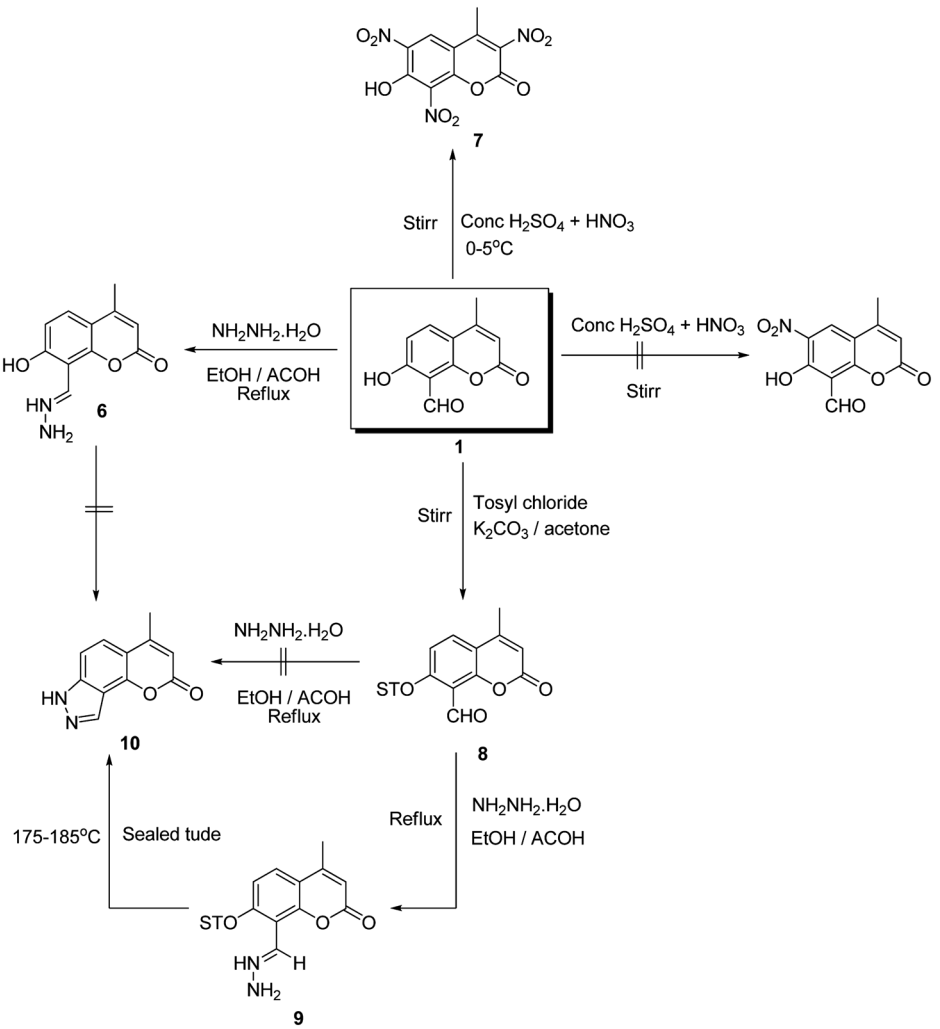


stability of the resulting tricyclic systems as the driving force. This article describes the results of our efforts during this investigation.

RESULTS AND DISCUSSION

The key starting compound required for the present investigation was synthesized from resorcinol and ethylacetoacetate and the spectra (IR and NMR) of product obtained (Scheme 1) upon formylation using hexamine agreed with the literature reports [30,31]. Reaction with hydroxyl amine hydrochloride in refluxing ethanol resulted in the formation of oxazole **2**. Similarly reaction with benzoyl glycine also resulted in formation of dipyran amide **3.** Attempted Knoevenagel condensation with diethyl malonate also resulted in the formation of carbethoxy dipyran **4**. Reaction with ethyl cyanacetate did not give the expected cyano compound, instead a compound **5** corresponding to the reaction of two equivalents of ethylcyanoacetate was observed. Literature survey on the reaction of salal with ethylcyanoacetate revealed formation of chromene bis esters, which has been confirmed by diffraction studies [32]. To construct the pyrazole ring across 7, 8-positions (Scheme 2), compound **1** was converted to the hydrazone **6** by the reaction with hydrazine hydrate in ethanol, which did not afford the desired compound **10**. With a view to increase the nucleophilicity at C-7, nitration of compound was attempted, which resulted in the tri-nitro compound **7**. Formation of **3**, **6** dinitro compound was expected based on the reactivity pattern of coumarin. However, the disappearance of the formyl proton in the ^{1}H-NMR prompted us to think in terms of an oxidative decarboxylation followed by an electrophilic substitution at C-8 due to the activating **7**-hydroxy group. In the next strategy, we tosylated the 7-OH group and the intermediate **8** (Fig. 1) was refluxed with hydrazine hydrate in ethanol, and acetic acid which also did not yield the cyclized compound **10**, instead only the hydrazone **9** was obtained which is confirmed by X-ray diffraction study (Fig. 2) [33]. Hydrazone **9** when refluxed in solvents like xylene, benzene, bromobenzene for long hours (24 h), also did not yield any cyclized compound **10**. The hydrazone **9** was heated in a sealed tube (175–185°C) for 5 h, and the work up revealed

Scheme 2. Synthesis of pyrazolo [8,7-*d*] coumarin.



the loss of the tosyl group leading to the formation of pyrazolo [7,8-*e*]coumarin **10**. It was planned to extend this method to various hydrazones to obtain N-substituted pyrazoles. However, the compounds **11–13** (Scheme 3) did not exhibit any ring closure even under long hours of refluxing under pressure. Stability by intramolecular hydrogen bonding and the poor nucleophilicity of the

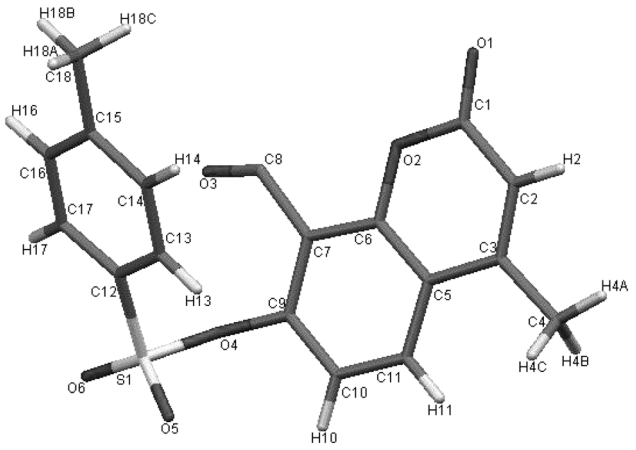


Figure 1. ORTEP diagram of toluene-4-sulfonic acid-8-formyl-4-methyl-2-oxo-2*H*-chromen-7-ylester **8** (CCDC No. 668470).

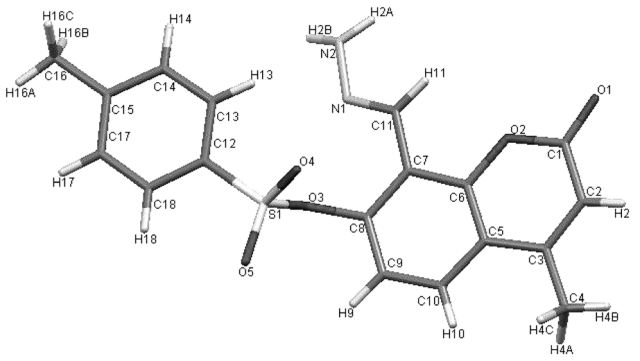
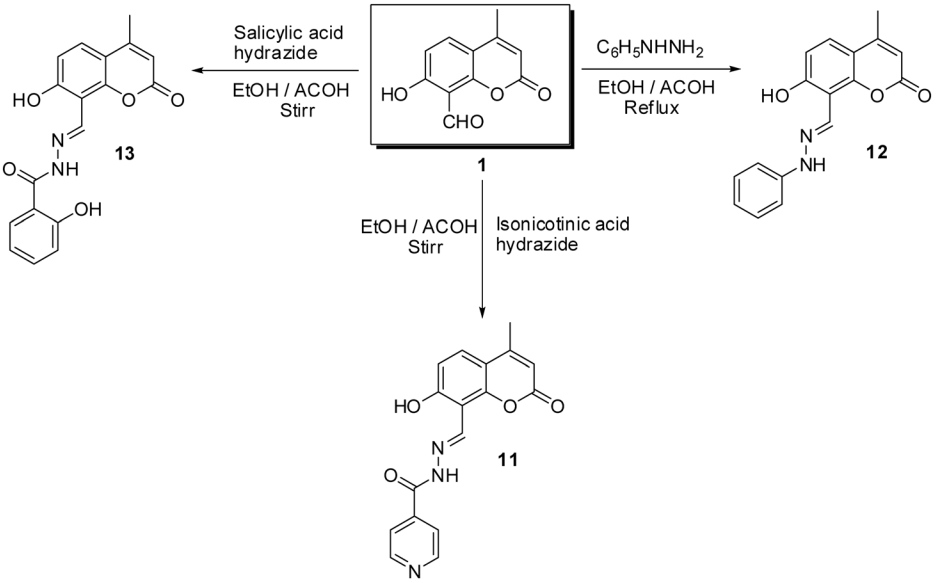


Figure 2. ORTEP diagram of toluene-4-sulfonic acid-8-hydrazonomethyl-4-methyl-2-oxo-2*H*-chromen-7-yl-ester **9** (CCDC No. 668471).

Scheme 3. Synthesis of 7-hydroxy-8-arylidine-4-methyl coumarins.



aromatic nitrogens seem to be the cause of lack of reactivity of these compounds.

SPECTRAL CHARACTERIZATION

To construct the 7,8-fused tricyclic coumarins, the synthetic potential of 8-formyl-7-hydroxy-4-methyl-coumarin, as a single synthon, has been explored. The basic synthetic methodologies used for the construction of various new tricyclic coumarins are outlined in Schemes 1–3. The tricyclic coumarin **2** and **3** were prepared in moderate yield by the reaction of **1** with hydroxylamine hydrochloride and benzoyl glycine respectively in ethanol and acetic acid mixture at water bath temperature. The formation of compounds **2** and **3** was confirmed by the absence of a sharp band around 1644 cm^{-1}, which was due to aldehyde carbonyl function in IR spectrum. The ^{1}H-NMR showed the absence of CHO and OH protons at δ 10.63 and δ 12.20, respectively, and displayed a singlet at δ 8.97 for N=C-H in compound **2** and a broad singlet for NH at δ 11.40 in compound **3**. Similarly, the tricyclic coumarins **4** and **5** were synthesized by the reaction of **1** with diethylmalonate and ethylcyanoacetate respectively in presence of catalytic amount of piperidine at room temperature. Similarly, the formation of compound **4** was confirmed by the presence of a sharp band at 1782 cm^{-1} due to ester carbonyl and absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR displayed characteristic triplet and quartet for ethyl group of ester at around δ 1.40 and δ 4.40, respectively. The formation of compound **5** was also confirmed by the presence of two sharp bands at 1748 cm^{-1} and 2221 cm^{-1} due to ester carbonyl and $\nu_{C\equiv N}$ respectively, and absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR displayed characteristic two multiplets for two ethyl group of ester around δ 1.14 and δ 4.10, respectively (Scheme 1).

Similarly, with an interest to construct the pyrazolyl coumarins, **1** was condensed with hydrazine hydrate, isonicotinic acid hydrazide, phenyl hydrazine hydrate, and salicylic acid hydrazide respectively in ethanol and acetic acid mixture at water bath temperature. The 7-hydroxy group of coumarin, being a phenolic OH group, was not possible to be replaced easily. Thus, hydrazides **6, 11, 12,** and **13** were obtained instead of the cyclized pyrazolyl coumarins (Schemes 2 and 3). Hydrazides **6** and **11** were confirmed by the presence of sharp bands at 3363 cm^{-1} and 3461 cm^{-1} respectively for $\nu_{\text{-NH}}$ and absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR spectra of compounds **6** and **7** respectively displayed characteristic two singlets for NH_2 and NH at around δ 7.35 and δ 10.98, respectively. The formation of compound **12** and **13** were also confirmed by the presence of sharp bands at 3416 cm^{-1} and 3454 cm^{-1} respectively for $\nu_{\text{-NH}}$, presence of sharp bands at 1654 cm^{-1} and 1674 cm^{-1} respectively for amide carbonyl function and the absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR spectra of compounds **12** and **13** respectively displayed characteristic two singlets for NH at around δ 11.45 and δ 11.35, respectively.

To make the phenolic OH group more active, it was thought to prepare 6-nitro derivative of **1** with the view to make the carbon bearing OH group more electron deficient and hence the attack of lone pair of electron of nitrogen bearing NH_2 group for the displacement, which has resulted in novel oxidative ipso nitration, and a poly nitro derivative of the type **7** was obtained. The poly nitro

derivative of the type **7** was confirmed by the absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR showed the absence of CHO proton at δ 10.63 and absence of C3-H at δ 6.22. The same was also confirmed by the presence of m/z at 311. With the view to make OH group as an easily leaving species, the corresponding *O*-Tosylated product **8** was prepared by the base catalyzed reaction of **1** with tosyl chloride in room temperature, since the tosyl group being a better leaving group. Further intermediate **8** upon treatment with Hydrazine hydrate and refluxing for more than 10 h, instead of cyclized product, a simple Hydrazide **9** was obtained. Further, *O*-Tosylated product **8** was confirmed by the absence of the absence of OH function at 3446 cm^{-1} in IR spectrum. The ^{1}H-NMR showed the presence of one more singlet at δ 2.51 for tolyl CH_3 and extra signals in the aromatic region. The corresponding Hydrazide **9** was also confirmed by the absence of aldehyde carbonyl function at 1644 cm^{-1} in IR spectrum. The ^{1}H-NMR also showed the absence of CHO proton at δ 10.63 indeed the presence of two NH2 protons at δ 7.34 was observed. Further efforts to cyclize in different solvents like benzene, toluene, and dry bromobenzene were unsuccessful, since it was not possible to obtain the desired pyrazolyl coumarin. Finally, the construction of novel pyrazolyl coumarin **10** was achieved by the thermal decomposition of **9** under the pressure in sealed tube of 6 cm in length and 4 mm in diameter at 175–185°C in an oil bath (Scheme 2). The formation of compound **10** was confirmed by the presence of two sharp bands at 3429 cm^{-1} and 1618 cm^{-1} due to $\nu_{\text{-NH}}$ and $\nu_{C=N}$, respectively, in the IR spectra. The ^{1}H-NMR spectra of compound **10** displayed the characteristic singlet at δ 9.50 due to N=CH, the one more characteristic singlet for NH was absent due to protonation by addition of TFA in $CDCl_3$. The formation of compound **10** was also confirmed by mass, the ESI-MS displayed the molecular ion peak at m/z 201 (M+H) (27%) and the base peak at m/z 173 (M+H) (100%).

CONCLUSION

In conclusion, we have developed a simple and high-yielding protocol for synthesizing a library of various tricyclic coumarins from 8-formyl-7-hydroxy-4-methyl coumarin as a single synthon. The different reactions were carried out to synthesize tricyclic coumarins fused with pyrazoles, isoxazoles, and pyrans at C7-C8 position in the coumarin skeleton. The construction of pyrazole demanded modifications of the groups and the strategies designed for this have resulted in oxidative ipso nitration. The tosylate when reacted under pressure resulted in the required intramolecular displacement. However, the substituted hydrazones did not undergo any cyclization.

EXPERIMENTAL

The melting points of the products were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact-410 FTIR Spectrophotometer, using KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-300F 300 MHz spectrometer in $CDCl_3$ and in DMSO-d_6 using TMS as an internal standard with ^{1}H resonant frequency of 300 MHz and ^{13}C resonant frequency of 75 MHz. D_2O exchange was applied to confirm the assignment of the signals of NH protons. The mass spectra were recorded on an Autospec ESI-MS. The elemental analysis was carried out by using Heraus CHN rapid analyzer. All the compounds gave C, H, and N analysis within ±0.4% of the theoretical values. The homogeneity of the compounds was described by TLC on aluminum silica gel 60 F_{254} (Merck) detected by UV light (254 nm) and iodine vapors. The reagents were all analytical reagent-grade or chemically pure. All solvents were dried, deoxygenated, and redistilled before use. Data are reported as follows: chemical shift [multiplicity {singlet (s), doublet (d), triplet (t), quartet (q), broad (br), and multiplet (m)}].

8-Formyl-7-hydroxy-4-methyl-coumarin (1). A mixture of 7-hydroxy-4-methyl-coumarin (5 g, 3 mmol) and Hexamethylenetetramine (10 g, 6 mmol) in glacial acetic acid (40 mL) was heated on a water bath for 6 h. The hexamine adduct so formed was hydrolyzed with 20% HCl (75 mL) and the mixture was heated for another 30 min. After cooling, the reaction mixture was extracted with diethyl ether, the solvent was removed under reduced pressure, and the pale yellow colored solution was poured to crushed ice to get the pale yellow solid of 8-formyl-7-hydrtoxy-4-methyl coumarin which was crystallized from ethanol and dioxan mixture. Yield 22%; yellow crystalline solid (ethanol + dioxan); mp 176−178°C; R_f 0.53 (benzene); IR (KBr) cm^{-1} 3446, 1742, 1644, 1594; ^{1}H-NMR ($CDCl_3$) δ 2.44 (3H, s), 6.22 (1H, s), 6.90 (1H, d, J = 9.0 Hz), 7.73 (1H, d, J = 9.0 Hz), 10.63 (1H, s), 12.22 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 187.45, 164.82, 160.24, 152.16, 151.23, 131.80, 120.10, 116.14, 112.50, 112.12, 19.10; Anal. Calcd. for $C_{11}H_8O_4$: C, 64.71; H, 3.95%; Found: C, 64.41; H, 3.70%.

4-Methyl-chromeno [8, 7-*d*] isoxazol-2-one (2). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (1) (1.2 g, 6 mmol) and hydroxylamine hydrochloride (0.41 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure, the separated solid was filtered, washed with excess of cold water, dried and crystallized from acetic acid. Yield 78%; colorless crystalline solid (acetic acid); mp 260−262°C; R_f 0.66 (hexane); IR (KBr) cm^{-1} 1722, 1628, 1580; ^{1}H-NMR ($CDCl_3$+TFA) δ 2.54 (3H, s), 6.40 (1H, s), 7.09 (1H, d, J = 9.4 Hz), 7.76 (1H, d, J = 9.4 Hz), 8.97 (1H, s); ^{13}C-NMR ($CDCl_3$+TFA) δ 159.73, 153.64, 151.78, 144.04, 127.22, 124.06, 112.82, 112.06, 110.71, 104.96, 18.24; Anal. Calcd. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96%; Found: C, 65.31; H, 3.20; N, 6.77%.

***N*-(4-Methyl-2, 8-dioxo-2*H*, 8*H*-pyrano [2, 3-*f*] chromen-9-yl)-benzamide (3).** A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (1) (1.2 g, 6 mmol) and benzoylglycine (1.07 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with

excess of cold water, dried and crystallized from ethanol and dioxan mixture. Yield: 73%; pale yellow solid (ethanol + dioxan); mp 180−182°C; R_f 0.58 (benzene + ethyl acetete); IR (KBr) cm^{-1} 3434, 1727, 1677, 1547; ^{1}H NMR ($CDCl_3$ + TFA) δ 2.44 (3H, s), 6.38 (1H, s), 7.10 (8H, m), 11.40 (1H, s); ^{13}C NMR ($CDCl_3$ + TFA) δ 163.65, 159.11, 155.13, 154.86, 153.59, 152.90, 144.04,133.30, 127.09, 126.80, 125.76, 122.73, 116.55, 113.86, 113.53, 111.84, 111.07, 109.01, 104.00, 18.30; Anal. Calcd. for $C_{20}H_{13}NO_5$: C, 69.16; H, 3.77; N, 4.03%; Found: C, 69.00; H, 3.50; N, 4.00%.

4-Methyl-2, 8-dioxo-2*H*, 8*H*-Pyrano [2, 3-f] chromen-9-carboxylic acid ethyl ester (4). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (1) (1.2 g, 6 mmol) and diethyl malonate (0.6 g, 6 mmol) in 10 mL absolute alcohol and in presence of catalytic amount of piperidine was stirred in room temperature for 4 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold ethanol, dried and crystallized from ethanol dioxan mixture. Yield: 83%; Colorless crystalline solid (ethanol + dioxan); mp: 220−222°C; R_f 0.70 (benzene); IR (KBr) cm^{-1}: 1782, 1737, 1573; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, J = 9.2 Hz), 2.50 (3H, s), 4.40 (2H, q, J = 9.2 Hz), 6.35 (1H, s), 7.26 (1H, d, J = 9.2 Hz), 7.84 (1H, d, J = 9.2 Hz), 9.06 (1H, s); ^{13}C NMR ($CDCl_3$) δ 164.05, 160.01, 158.33, 154.60, 153.59, 152.88, 142.44, 130.34, 120.19, 118.80, 116.76, 114.73, 109.90, 62.78, 19.68, 16.30; ESI-MS; m/z 301 (M+H) (100%); Anal. Calc. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%; Found: C, 63.91; H, 3.88%.

8-Amino-10-(cyano-ethoxy carbonyl methyl)-4-methyl-2-oxo-2*H*, 10*H*-pyrano [2, 3-f] chromen-9-carboxylic acid ethyl ester (5). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (1) (1.2 g, 6 mmol) and ethylcyanoacetate (1.7 g, 12 mmol) in 10 mL absolute alcohol and in presence of catalytic amount of piperidine was stirred in room temperature for 4 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold ethanol, dried, and crystallized from ethanol. Yield: 86%; colorless crystalline solid (ethanol); mp 162−164°C; R_f 0.58 (benzene); IR (KBr) cm^{-1}: 3416, 2221, 1738, 1685, 1531; ^{1}H NMR (DMSO-d_6) δ 1.14 (3H, t, J = 9.6 Hz), 1.22 (3H, t, J = 9.6 Hz), 2.48 (3H, s), 4.10 (4H, m, J = 9.6 Hz), 4.82 (1H, d, J = 9.6 Hz), 4.88 (1H, d, J = 9.6 Hz), 6.38 (1H, s), 7.16 (1H, d, J = 9.6 Hz), 7.74 (1H, d, J = 9.6 Hz), 7.88 (2H, s); ^{13}C NMR (DMSO-d_6): δ 168.20, 165.54, 160.18, 159.30, 152.16, 151.20, 148.42, 123.20, 122.36, 115.80, 113.12, 112.56, 110.18, 87.56, 62.54, 61.30, 37.50, 18.54, 14.20, 14.00, 13.44; Anal.Calc.for $C_{21}H_{20}N_2O_7$: C, 61.16; H, 4.89; N, 6.79%; Found; C, 61.01; H, 4.60; N, 6.47%.

8-Hydrazonomethyl-7-hydroxy-4-methyl-chromen-2-one (6). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol) and hydrazine hydrate (0.3 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold water, dried and crystallized from DMF. Yield 66%; Green crystalline solid (DMF); mp 298−300°C; R_f 0.52 (benzene); IR (KBr) cm^{-1}: 3462, 3363, 1728, 1608; ^{1}H-NMR (DMSO-d_6) δ 2.50 (3H, s), 6.20 (1H, s), 6.84 (1H, d, J = 9.0 Hz), 7.35 (2H, s), 7.53 (1H, d, J = 9.0 Hz), 8.40 (1H, s), 12.78 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 161.12, 159.36, 152.78, 149.20, 144.50, 129.30, 120.10, 114.76, 113.12, 112.65, 19.50; ESI-MS; m/z 219 (M+H)(100%); Anal.Calc.for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84%; Found: C, 60.31; H, 4.50; N, 12.77%.

7-Hydroxy-4-methyl-3, 6, 8-trinitro-chromen-2-one (7). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol) in 10 mL concentrated H_2SO_4 was cooled to 0−5°C. To the cooled suspension a nitrating mixture (10 mL) was added drop wise with a dropping funnel. The mixture was stirred for 2 h at room temperature and then decomposed with crushed ice. A yellow colored solid obtained was filtered, washed with excess of cold water, dried, and crystallized from benzene and ethyl acetate mixture. Yield: 62%; yellow crystalline solid (benzene + ethyl acetate); mp 230−232°C; R_f 0.73 (benzene); IR (KBr) cm^{-1} 3456, 1744, 1594; ^{1}H-NMR (DMSO-d_6) δ 2.48 (3H, s), 8.63 (1H, s), 12.20 (1H, br s); ^{13}C-NMR (DMSO-d_6) δ 155.98, 154.37, 153.30, 148.12, 135.36, 130.10, 129.14, 127.90, 115.28, 18.70; Anal. Calcd. for $C_{10}H_5N_3O_9$: C, 38.60; H, 1.62; N, 13.50%; Found: C, 38.44; H, 1.42; N, 13.30%.

Toluene-4-sulfonic acid-8-formyl-4-methyl-2-oxo-2*H*-chromen-7-ylester (8). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol), *p*-toluenesulfonylchloride (1.14 g, 6 mmol) and powdered anhydrous K_2CO_3 (0.828 g, 6 mmol) in 20 mL super dry acetone was stirred in room temperature for 12 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure, the separated solid was filtered, washed with 50 mL of dilute hydrochloric acid and than with excess of cold water, dried, and crystallized from ethanol and dioxin mixture. Yield 80%; light green crystalline solid (ethanol + dioxan); mp 180−182°C; R_f 0.43 (benzene); IR (KBr) cm^{-1}: 1734, 1708, 1303; ^{1}H-NMR ($CDCl_3$) δ 2.47 (3H, s), 2.51 (3H, s), 6.35 (1H, s), 7.32 (6H, m), 10.34 (1H, s); ^{13}C-NMR ($CDCl_3$): δ 190.20, 160.12, 156.80, 153.19, 150.30, 140.23, 132.56, 132.40, 132.20, 130.28, 126.70, 114.20, 112.60, 112.24, 21.32, 18.80; Anal. Calcd. for $C_{18}H_{14}O_6S$: C, 60.33; H, 3.94%; Found: C, 60.13; H, 3.70%.

Toluene-4-sulfonic acid-8-hydrazonomethyl-4-methyl-2-oxo-2*H*-chromen-7-ylester (9). A mixture of toluene-4-sulfonic acid-8-formyl-4-methyl-2-oxo-2*H*-chromen-7-ylester (8) (2.1 g, 6 mmol), and hydrazine hydrate (0.3 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold water, dried, and crystallized from ethanol and dioxin mixture. Yield: 78%; colorless crystalline solid (ethanol); mp: 160−162°C; R_f 0.66 (benzene); IR (KBr) cm^{-1}: 3405, 1724, 1627, 1341; ^{1}H-NMR ($CDCl_3$ + TFA) δ 2.37 (3H, s), 2.54 (3H, s), 6.47 (1H, s), 7.34 (2H, s), 7.47 (6H, m), 8.68 (1H, s); ^{13}C-NMR ($CDCl_3$ + TFA) δ 159.67, 156.20, 152.70, 149.67, 143.34, 139.30, 132.43, 130.40, 128.78, 127.76, 120.15, 112.70, 112.13, 111.14, 21.56, 19.10; Anal. Calc. for $C_{18}H_{16}N_2O_5S$: C, 58.05; H, 4.33; N, 7.52%; Found: C, 57.91; H, 4.20; N, 7.27%.

4-Methyl-7*H*-Pyrano [2, 3-e] indazol-2-one (10). Toluene-4-sulfonicacid-8-formyl-4-methyl-2-oxo-2*H*-chromen-7-ylester (**9**) (1.11 g, 3 mmol) was sealed in a glass tube (6 cm in length and 4 mm in diameter) and heated on oil bath (178−184°C) for 4 h. After cooling, the product was isolated by breaking the glass tube from one end, it was then washed with excess of cold ethanol, dried, and crystallized from ethanol and dioxan mixture. Yield: 66%; brown yellow solid (ethanol + dioxan); mp: 288−290°C; IR

(KBr) cm^{-1}: 3429, 1733, 1618, 1596; ^{1}H-NMR ($CDCl_3$ + TFA) δ 2.54 (3H, s), 6.36 (1H, s), 7.11 (1H, d, J = 9.0 Hz), 7.73 (1H, d, J = 9.0 Hz), 9.50 (1H, s); ^{13}C NMR ($CDCl_3$ + TFA) δ 161.12, 152.56, 143.17, 142.12, 128.19, 123.23, 119.24, 115.29, 112.50, 110.34, 18.56; ESI-MS m/z 201 (M+H) (27%), m/z 173 (M+H) (100%). Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99%; Found: C, 65.79; H, 3.88; N, 12.87%.

Isonicotic acid-[7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-ylmethylene]-hydrazide (11). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol) and isonicotinic acidhydrazide (0.822 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold water, dried, and crystallized from acetic. Yield: 78%; green crystalline solid (acetic acid); mp: 290−292°C; R_f 0.60 (benzene); IR (KBr) cm^{-1}: 3454, 3261, 1715, 1674, 1612; ^{1}H NMR (DMSO-d_6) δ 2.48 (3H, s), 6.32 (1H, s), 6.95 (6H, m), 9.10 (1H, s), 11.35 (1H, s), 12.48 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 160.93, 160.79, 158.84, 153.35, 152.39, 150.26, 144.40, 138.96, 127.94, 121.19, 113.21, 111.60, 110.56, 113.45, 112.68, 105.18, 18.03; ESI-MS *m/z* 324 (M+H) (100%); Anal. calc. for $C_{17}H_{13}N_3O_4$: C, 63.15; H, 4.05; N, 13.00%; Found: C, 63.10; H, 3.90; N, 12.87%.

7-Hydroxy-4-methyl-8-[phenyl-hydrazonomethyl]-chromen-2-one (12). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol) and phenyl hydrazine (0.64 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure, the separated solid was filtered, washed with excess of cold water, dried and crystallized from acetic acid. Yield: 77%; pale green crystalline solid (ethanol + dioxan); mp: 268−270°C; R_f 0.78 (benzene); IR (KBr) cm^{-1}: 3461, 3269, 1714, 1597; ^{1}H NMR (DMSO-d_6) δ 2.44 (3H, s), 6.28 (1H, s), 6.84 (7H, m), 8.66 (1H, s), 10.98 (1H, s), 12.08 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 159.33, 153.75, 152.77, 151.12, 143.54, 133.53, 129.43, 125.78, 124.90, 119.82, 113.80, 112.82, 111.99, 111.68, 110.62, 106.63, 18.24; Anal. calc. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52%; Found: C, 69.41; H, 4.50; N, 9.27%.

2-Hydroxy-benzoicacid-[7-hydroxy-4-methyl-2-oxo-2*H*-chromen-8-yl-methylene]-hydrazide (13). A mixture of 8-formyl-7-hydroxy-4-methyl coumarin (**1**) (1.2 g, 6 mmol) and salicylic acid hydrazide (0.91 g, 6 mmol) in 20 mL ethanol-acetic acid mixture (2:1) was refluxed on water bath for 6 h. The reaction was monitored by TLC, after completion of the reaction the solvent was removed under reduced pressure; the separated solid was filtered, washed with excess of cold water, dried and crystallized from acetic acid. Yield: 74%; Pale green crystalline solid (DMF); mp: 294−296°C; R_f 0.58 (benzene); IR (KBr) cm^{-1}: 3416, 3273, 1713, 1654, 1611; ^{1}H NMR (DMSO-d_6) δ 2.47 (3H, s), 6.30 (1H, s), 6.92 (6H, m), 9.16 (1H, s), 11.45 (1H, s), 12.38 (1H, br s), 12.76 (1H, br s); ^{13}C-NMR (DMSO-d_6) δ 160.08, 159.19, 153.85, 152.67, 151.12, 144.40, 133.32, 128.39, 125.78, 119.04, 117.33, 116.82, 113.45, 112.68, 111.22, 105.48, 18.26; ESI-MS *m/z* 339 (M+H) (100%); Anal. Calc. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28%; Found: C, 63.61; H, 4.10; N, 8.17%.

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