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Unusual Acid- and Base-Catalyzed C–N Bond Formation Approach through Reaction of Chromonyl Meldrum's Acid and Nitrogen Bi-nucleophiles

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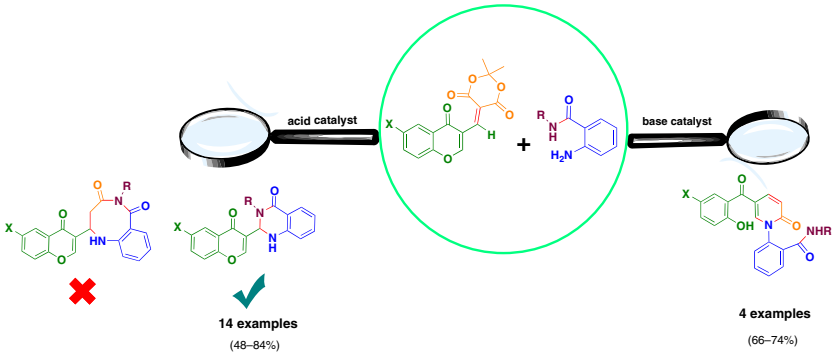

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Abstract Reaction of chromonyl Meldrum's acid and N-substituted 2-aminobenzamides was studied in the presence of acidic and basic catalysts. The use of methanesulfonic acid as a catalyst in this reaction led to the synthesis of chromonyl quinazolinones through employing Meldrum's acid as a carbon leaving group. However, in the presence of basic catalyst, this reaction gave functionalized 2-pyridones.

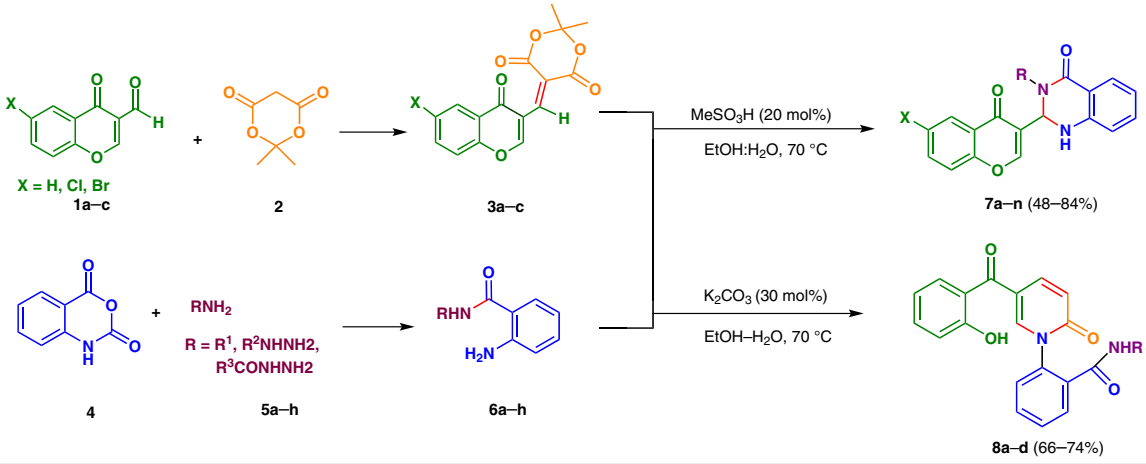
Keywords chromonyl Meldrum's acid, binucleophile, acid catalysis, base catalysis, chromonyl quinazolinines, domino Michael–elimination–cyclization reaction, functionalized 2-pyridones

Function-oriented synthesis (FOS) has an increasing and important role in producing therapeutic compounds in a step-economical fashion.[1] In this way, domino reactions are well-known to access compound collections with high structural diversity and molecular complexity.[2] Designed novel reaction sequences to obtain functionalized small-to-medium-sized molecules and active biologically molecules through domino reactions lead to reliable and efficient methodologies.[3]

Arylidene Meldrum's acid is known as an electrophilic Michael acceptor and has been used to generate extended heterocyclic skeletons and biologically active compounds. These compounds are termed 'neutral organic acids' and they have been extensively used in studies on conjugate addition.[4] In this regard, chromonyl Meldrum's acid is a suitable substrate for the synthesis of various heterocyclic skeletons and a source of the chromone scaffold for its insertion into the structure of biologically active compounds.[5]

Fillion found that Meldrum's acid could be used as a highly effective and convenient leaving group in nucleophilic substitution.[6] In the reported reaction, C–C σ bond cleavage and C–C bond formation were achieved using Lewis acids such as $AlCl_3$, $Sc(OTf)_3$, and TMSOTf. The reactions were carried out through direct modification of sp^3-hybridized tertiary and quaternary carbon centers via cleavage of a C–C σ bond.

Considering the versatile chemistry of the chromones,[7] designing an efficient synthetic approach to compounds that contain the chromone scaffold can profit from the application of domino reactions. In this way, the Knoevenagel reaction of 3-formylchromone and Meldrum's acid can lead to chromonyl Meldrum's acid derivatives that are Michael acceptors and could be used for nucleophilic addition.[8] Recently, we reported the three-component domino reaction of 3-formylchromones, Meldrum's acid, and primary amines in the presence of a catalytic amount of diammonium hydrogen phosphate in water which led to 2-pyridone 3-carboxylic acids.[9] The products were formed through nucleophilic addition of primary amines to chromonyl Meldrum's acid and led to the opening of the chromone skeleton. The reaction of chromonyl Meldrum's acid and 4-hydroxycoumarin in the presence of a base and alcohol led to C–C bond formation. In this case, the Meldrum's acid was opened and acetone and carbon dioxide were eliminated as is often observed.[10] However, based on the reagents added and also the reaction conditions, the chromonyl moiety could be opened and other heterocyclic skeletons could be formed.

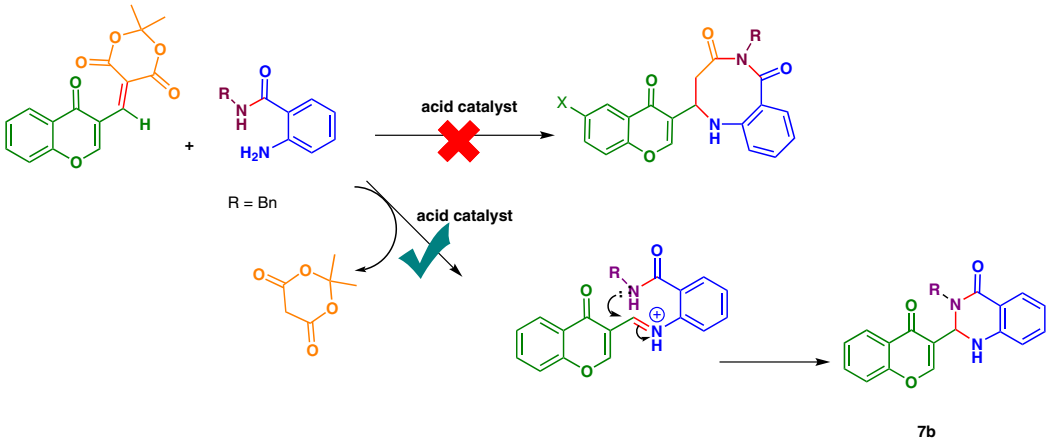


Scheme 1 Synthesis of chromonyl dihydroquinazolinones **7a–n** and functionalized 2-pyridones **8a–d**

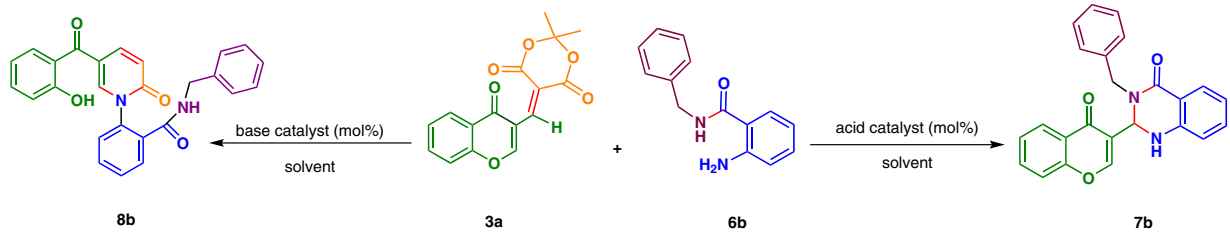
In continuation of our research work to design multicomponent reactions based on 3-formylchromone, we report herein the synthesis of chromonyl Meldrum's acid **3a–c** and also N-substituted 2-aminobenzamides **6a–h** and their reaction in the presence of methanesulfonic acid in ethanol to construct quinazolines **7a–n** that contain the chromone skeleton (Scheme 1). In contrast, carrying out the reaction between chromonyl Meldrum's acid and 2-aminobenzamides in the presence of potassium carbonate (30 mol%) as basic catalyst gave functionalized 2-pyridones **8a–d**.

The synthesized compounds contain the chromone skeleton in addition to quinazolinone scaffolds which are known as privileged heterocycles and are found in many biologically active compounds and also in naturally occurring alkaloids.[11]

Initially, the N-substituted 2-aminobenzamides **6a–h** were formed through the reaction of isatoic anhydride with primary amines, hydrazines, and hydrazides **5a–h**. The reaction of chromonyl Meldrum's acid **3a** and *N*-benzyl 2-aminobenzamide **6b** was selected as a model study. Stirring the reaction mixture at room temperature and elevated temperatures was investigated, but the reaction did not proceed in the absence of an acid. Therefore, the model reaction was carried out in the presence of a range of Brønsted acids including methanesulfonic acid, trifluoroacetic acid, phosphoric acid, *p*-toluenesulfonic acid, and fluoroboric acid, as well as Lewis acids such as zinc chloride and boron trifluoride. The product in all cases was 2-chromonyl dihydroquinazolinone **7b**, and the best yield was obtained using methanesulfonic acid in ethanol (84%)[12] (Scheme 2). The type and amount of acid and nature of the solvent have significant impact on reaction times and yields. After finding the most suitable acid catalyst, the model reaction was investigated in different solvents such as dichloromethane, 1,2-dichloroethane, *N*,*N*-dimethylformamide, and tetrahydrofuran but, in all cases, the yield of the desired product was lower compared to ethanol as solvent. After choosing



Scheme 2 Unexpected synthesis of **7b** through elimination of Meldrum's acid



Scheme 3 Model reaction for the synthesis of **7b** and **8b**

ethanol as the optimal solvent, the model reaction was investigated using 10, 20, and 30 mol% methanesulfonic acid and the obtained yield of product was 78, 84, and 84% respectively. Subsequently, the influence of reaction temperature at 50, 60, 70, and 80 °C in the formation of **7b** was investigated in ethanol using 20 mol% methanesulfonic acid and the isolated yields were 73, 76, 78, and 78%, respectively. Thus, the optimal reaction conditions for the synthesis of **7b** involved conducting the reaction in ethanol with 20 mol% methanesulfonic acid at 70 °C. At the outset of this study, the synthesis of the benzodiazapineone skeleton had been our goal, and the formation of chromonyl quinazolinone **7b** was an unexpected result which would appear to proceed through elimination of Meldrum's acid (Scheme 2).

A second study was carried out, this time using base as a catalyst. The same model reaction was investigated using different basic catalysts such as potassium carbonate, piperidine, *N*,*N*-diisopropylethylamine, trimethylamine, L-proline, and diammonium hydrogen phosphate. The model reaction was also investigated in a range of solvents including ethanol, tetrahydrofuran, acetonitrile, dichloromethane, 1,2-dichloroethane, and *N*,*N*-dimethylformamide. The product obtained was **8b**, and the best result was formed using potassium carbonate (30 mol%) in ethanol at 70 °C (Scheme 3).

After finding suitable reaction conditions for the synthesis of **7b**, the scope of the reaction was explored using different 3-formylchromones, primary amines, and phenyl hydrazine derivatives, as well as phenyl hydrazide to access 2-chromonyl dihydroquinazolinones **7a**–**n** in moderate to good yields and with no side reactions. The results are summarized in Table 1.

The structures of products **7a**–**n** were confirmed using NMR spectroscopy, and high-resolution mass spectrometry (ESI). A characteristic resonance for all of these compounds in the ^{1}H NMR spectra appeared as a singlet at δ = 5.80–6.30 ppm for the aliphatic methine proton and also a distinctive peak in the ^{13}C NMR spectra for sp^{3} carbon at δ = 63.0–68.0 ppm. The ^{13}C NMR spectra of **7a**–**n** exhibited characteristic signals in the δ = 160.0–192.0 ppm region associated with the carbonyls of the amide and ketone moieties.[12] The structures of compounds **7c** and **7k** were further confirmed by X-ray crystallographic analysis (Figure 1). The X-ray crystallographic data showed clearly the orientation of the chromonyl substituent and also the primary amine group. There is a suitable disposition for hydrogen bonding between the carbonyl group and NH when benzhydrazide was used. In support of this, a deshielded NH group was observed at δ = 10.56–10.62 ppm in compounds **7l**–**n**.

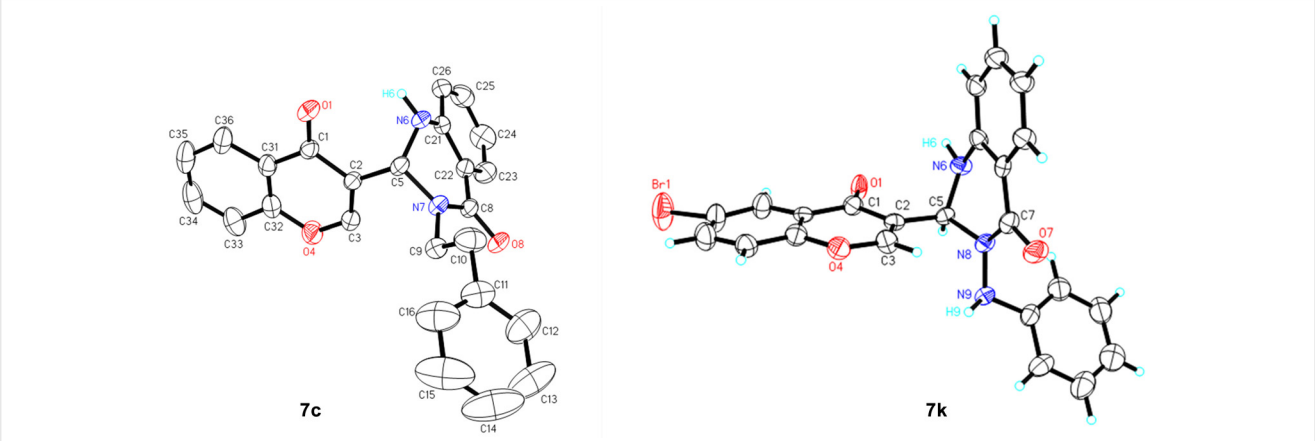
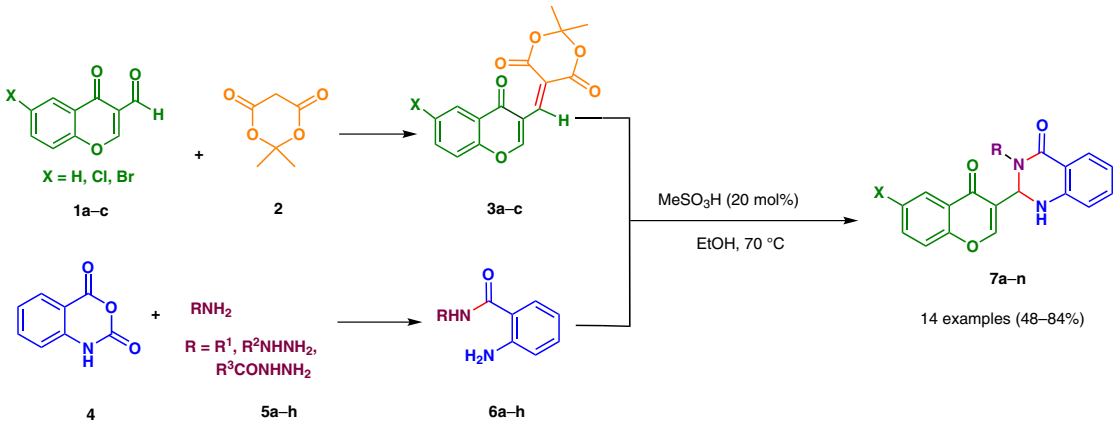
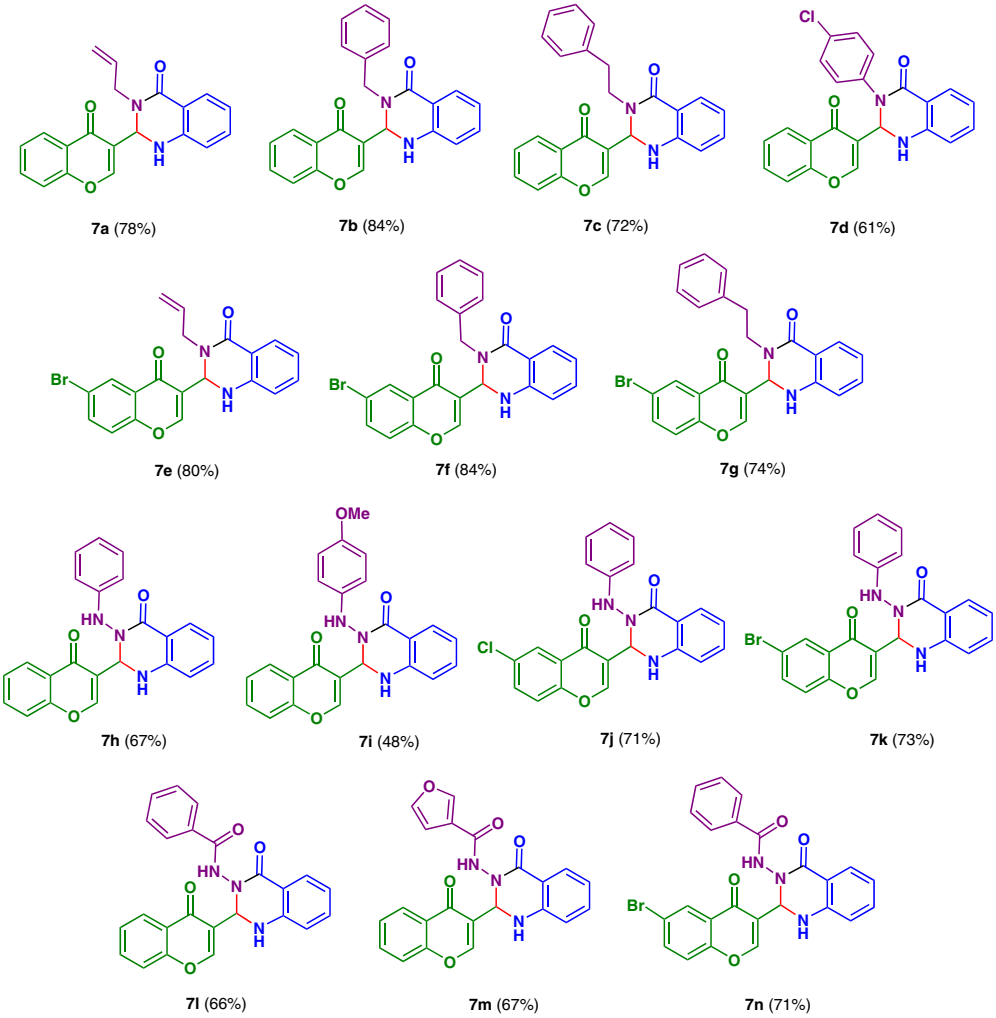


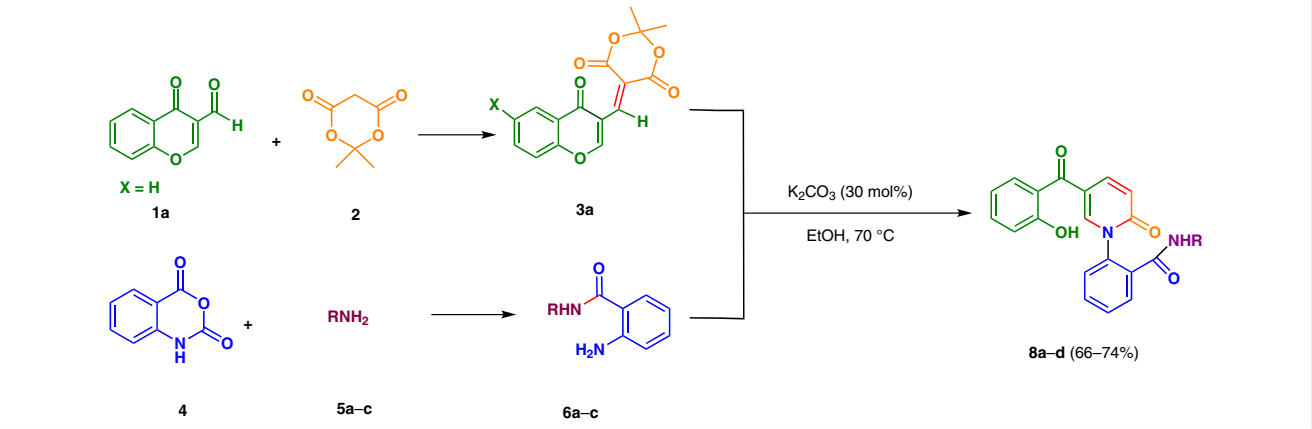
Figure 1 ORTEP structures of compound **7c** and **7k**

Table 1 Acid-Catalyzed Synthesis of Chromonyl Dihydroquinazolinones **7a–n** in Ethanol



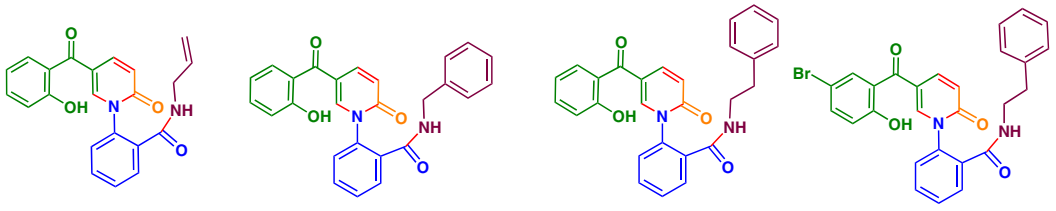


In a further study, reaction of chromonyl Meldrum's acids **3a**,**b** with N-substituted-2-aminobenzamides **6a–c** was investigated in ethanol in the presence of 30 mol% potassium carbonate and this led to 2-pyridones **8** (Scheme 4). To extend the range of 2-pyridone derivatives, allylamine and 2-phenylethylamine were used as well as benzylamine, and



Scheme 4 Synthesis of functionalized 2-pyridones **8a–d** using potassium carbonate (30 mol%)

Table 2 Base-Catalyzed Synthesis of Functionalized 2-Pyridones **8a–d**



the products **8a–d** were obtained (Table 2). A distinctive feature in the structure of these products compared to our last report[9] is the absence of the carboxylic acid moiety.

In basic medium, the nucleophilic addition of amine binucleophile to the unsaturated carbonyl system leads to the opening of the chromone skeleton. After nucleophilic addition of the amine to the carbonyl group, elimination of acetone and carbon dioxide leads to the formation of functionalized 2-pyridines **8a–d**. A characteristic signal for the functionalized 2-pyridones **8a–d** was a doublet at δ = 7.80–7.90 ppm for the olefinic (H-6) pyridone proton. Meanwhile the phenolic hydrogen resonated at δ = 10.30 ppm and, in all cases, the NH group was observed as a triplet at δ = 8.80–9.00 ppm. The ^{13}C NMR spectra of **8a–d** all exhibited characteristic signals in the δ = 160–192 ppm region associated with the carbonyl groups of the amide and ketone moieties.[12]

In conclusion, we have reported a novel approach to access 2-chromonyl quinazolinone derivatives **7a–n** in good yields through reaction of chromonyl Meldrum's acid **3a–c** and N-substituted 2-aminobenzamides **6a–h** in the presence of methanesulfonic acid in ethanol. Meanwhile, the reaction of N-substituted 2-aminobenzamides with chromonyl Meldrum's acid in the presence of potassium carbonate led to 2-pyridones **8a–d**. The ease of workup and compatibility with a range of active functional groups are features of this methodology.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560383. Copies of ^{1}H NMR, ^{13}C NMR for compound **3a** and ^{1}H NMR, ^{13}C NMR, IR, HRMS spectra for compounds **7a–n** and **8a–d**, and X-ray crystal data for compounds **7c** and **7k** are included.

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(12) **General Procedure for the Synthesis of 3, 7, and 8**

Typical Procedure for 3

To a solution of 3-formylchromone (**1**; 1 mmol, 174 mg) in EtOH–H_2O (4 mL; 1:1) was added Meldrum's acid (**2**; 1 mmol, 144 mg), and the mixture was stirred for 3 h at ambient temperature. The precipitate formed was isolated by filtration.

2,2-Dimethyl-5-[(4-oxo-4*H*-chromen-3-yl)methylene]-1,3-dioxane-4,6-dione (3a)

Yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.78 (s, 6 H, 2 CH_3), 7.56 (t, 1 H, *J* = 7.6 Hz, HAr), 7.73 (d, 1 H, *J* = 8.4 Hz, HAr), 7.87 (t, 1 H, *J* = 7.5 Hz, HAr), 8.10 (d, 1 H, *J* = 7.5 Hz, HAr), 8.26 (s, 1 H, =CH), 9.31 [s, 1 H, $(CO_2)_2$C=CH]. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.0, 104.9, 117.9, 118.0, 118.7, 123.1, 125.7, 126.7, 135.1, 145.5, 155.1, 159.8, 162.0, 162.2, 173.3.

General Procedure for 7

To a solution of isatoic anhydride (**4**; 1 mmol, 163 mg) in EtOH (4 mL) was added the primary amine, aryl hydrazine, or aryl hydrazide **5a**–**h** (1 mmol), and the mixture was heated for 1 h at 70 °C. This mixture was used for the synthesis of **7a**–**n** or **8a**–**d** without purification.

To a solution of product **6a**–**h** (1 mmol) in EtOH (10 mL) was added product **3** (1 mmol), and methanesulfonic acid (20 mol%, 20 mg), and the mixture was heated for 12 h at 70 °C. The reaction reached completion as indicated by TLC (EtOAc–*n*-hexane, 1:3), and the precipitate was filtered. The precipitate was washed with MeOH, and the resulting powder was pure product **7a**–**n** (yields 48–84%).

2-(4-Oxo-4*H*-chromen-3-yl)-3-phenethyl-2,3-dihydroquinazolin-4(1*H*)-one (7c)

Yellow powder, 285 mg (72%), mp 228–230 °C. IR (KBr): ν = 3327, 1724, 1632 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.88 (dt, 2 H, *J* = 15.0, 6.6 Hz, CH_2Ph), 3.10–3.14 (m, 1 H, CHPh), 4.05–4.09 (m, 1 H, CHN), 5.97 (s, 1 H, CH), 6.68 (t, 1 H, *J* = 7.1 Hz, HAr), 6.75 (d, 1 H, *J* = 7.9 Hz, HAr), 6.92 (s, 1 H, NH), 7.16 (d, 1 H, *J* = 6.6 Hz, HAr), 7.19–7.23 (m, 5 H, HAr), 7.45 (t, 1 H, *J* = 7.2 Hz, HAr), 7.53 (d, 1 H, *J* = 6.6 Hz, HAr), 7.68–7.77 (m, 2 H, HAr), 7.97 (s, 1 H, =CH), 8.04 (d, 1 H, *J* = 7.6 Hz, HAr). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.8, 46.2, 64.3, 114.8, 114.9, 117.5, 118.4, 121.4, 123.1, 124.9, 125.7, 126.1, 127.4, 128.3, 128.7, 133.1, 134.5, 138.9, 146.0, 153.2, 155.7, 162.1, 176.1. ESI-HRMS: *m/z* calcd for $C_{25}H_{21}N_2O_3$ [M + H]$^+$: 397.1545; found: 397.1545.

Colorless crystal (polyhedron), dimensions 0.270 × 0.150 × 0.130 mm^3, crystal system monoclinic, space group *C*2/*c*, *Z* = 8, *a* = 21.6199(9) Å, *b* = 15.8126(7) Å, *c* = 12.0816(5) Å, *α* = 90°, *β* = 95.9595(18)°, *γ* = 90°, *V* = 4108.0(3) Å^3, ρ = 1.282 g cm^{-3}, *T* = 200(2) K, θ_{max} = 25.661°, radiation Mo Kα, λ = 0.71073 Å, 0.5° ω scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.29 and a completeness of 98.6% to a resolution of 0.83 Å, 17018 reflections measured, 3847 unique [*R*(int) = 0.0280], 2992 observed [I > 2σ(I)], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 0.09 mm^{-1}, T_{min} = 0.89, T_{max} = 0.96, structure refined against F^2 with a full-matrix least-squares algorithm using the SHELXL (Version 2014-3) software, 275 parameters refined, hydrogen atoms were treated using appropriate riding models, except H6

at N6, which was refined isotropically, goodness of fit 1.03 for observed reflections, final residual values $R1(F) = 0.038$, $wR(F^2) = 0.090$ for observed reflections, residual electron density –0.17 to 0.18 eÅ^{-3}. CCDC 1057685 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for the Synthesis of 8

To a solution of chromonyl Meldrum's acid (**3**, 1 mmol) in EtOH (10 mL) was added product **6** (1 mmol) and K_2CO_3 (30 mol%, 50 mg), and the mixture was heated at 70 °C for 12 h, monitoring progress of reaction by TLC (eluent: EtOAc–*n*-hexane, 1:3). The EtOH was removed under vacuum, and further purification was carried out using preparative TLC (*n*-hexane–EtOAc, 2:1). The products were obtained as yellow oils.

***N*-Benzyl-2-[5-(2-hydroxybenzoyl)-2-oxopyridin-1(2*H*)-yl]benzamide (8b)**

Yellow oil; 314 mg (74%). IR (KBr): ν = 3263, 1677, 1658 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.31 (dd, 1 H, *J* = 15.0, 8.0 Hz, CH_2), 4.35 (dd, 1 H, *J* = 15.0, 6.0 Hz, CH_2), 6.53 (d, 1 H, *J* = 9.5 Hz, HAr), 6.88 (t, 1 H, *J* = 9.5 Hz, HAr), 6.94 (d, 1 H, *J* = 7.8 Hz, HAr), 7.18–7.30 (m, 5 H, HAr), 7.35 (t, 1 H, *J* = 7.4 Hz, HAr), 7.44 (d, 1 H, *J* = 7.4 Hz, HAr), 7.55–7.67 (m, 3 H, HAr), 7.85 (d, 1 H, *J* = 2.5 Hz, HAr), 7.89 (dd, 1 H, *J* = 8.7, 2.5 Hz, HAr), 9.00 (t, 1 H, *J* = 5.9 Hz, NH), 10.29 (s, 1 H, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.9, 116.3, 116.6, 116.7, 119.2, 119.4, 124.4, 124.5, 126.7, 127.0, 128.2, 128.4, 129.3, 129.9, 131.2, 132.8, 134.2, 138.1, 139.1, 139.2, 146.4, 155.8, 156.0, 161.3, 165.9, 191.6. ESI-MS: *m/z* = 425.0 [M + H]$^+$. Anal. Calcd. for $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.49; H, 4.79; N, 6.64.