Synthesis A. G. Neo et al. Special Topic

Enol-Ugi Reaction of Hydroxycoumarins: Straightforward Synthesis of Amino Acid Derived Coumarin Enamines

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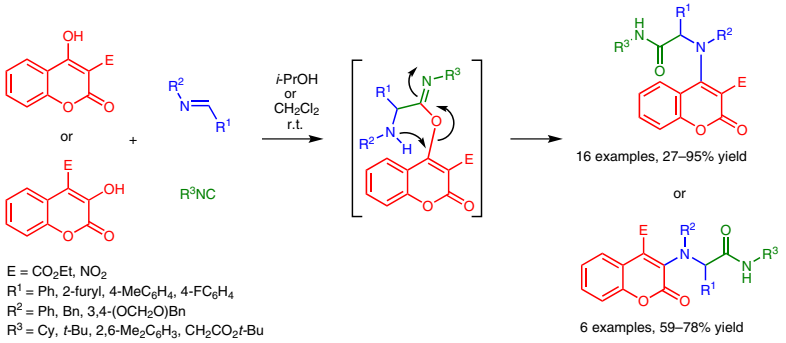

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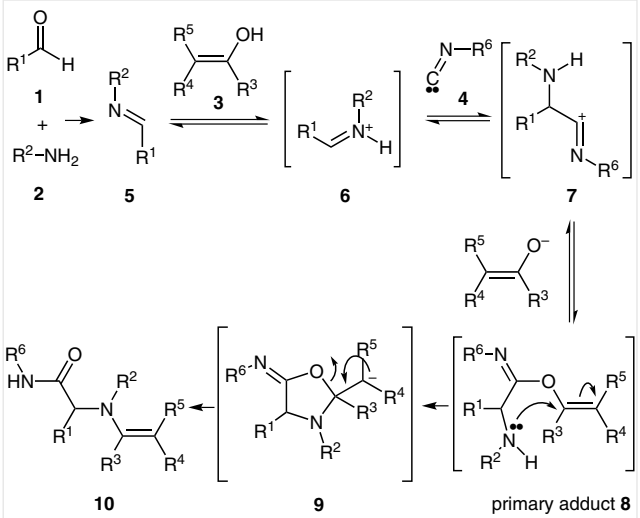
Abstract Hydroxycoumarins containing electron-withdrawing groups have been successfully used as acidic components in Ugi-type multicomponent condensations with imines and isocyanides. The reaction takes place smoothly at room temperature, with no need of catalysis, affording 3- and 4-coumarin enamines in a highly convergent manner. Key to this transformation is the conjugate addition-β-elimination rearrangement on the primary adduct, irreversibly leading to the final product.

Key words multicomponent reaction, heterocycles, Michael addition, natural products, combinatorial chemistry

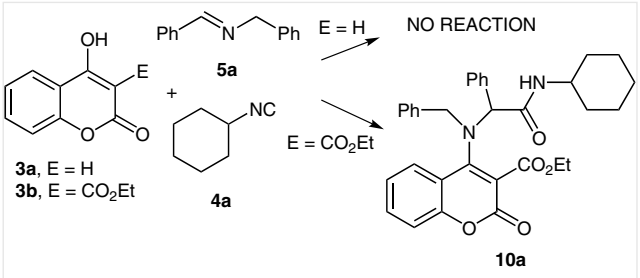
Coumarins constitute a large family of plant metabolites possessing important biological activities. Remarkably, 3- and 4-aminocoumarins are in the structural core of many pharmaceuticals. For example, 4-aminocoumarins have shown potent antimicrobial,[1] antiproliferative,[2] cytotoxic,[3] antiplatelet,[4] and anthrax inhibitory[5] activities. They have also been used as synthetic precursors of polycyclic 3,4-fused coumarins.[6] Natural 3-aminocoumarin antibiotics, such as novobiocin and coumermycin, are known DNA gyrase inhibitors[7] that have raised new attention due to their antitumor activity related to selective inhibition of heat shock protein 90.[8] Also, the 3-aminocoumarin alkaloids lamellarins have shown to selectively inhibit HIV-1 integrase. In spite of the interest of aminocoumarins, synthetic approaches to these compounds are scarce, and most of them are multi-step processes having limited applications in library synthesis.

Multicomponent reactions of isocyanides (IMCR) provide a highly convergent strategy for the synthesis of diverse molecular libraries through one-step processes with extraordinary atom and bond economy.[9] Prototypically, the Ugi four-component condensation of carboxylic acids, carbonyl compounds, amines, and isocyanides[10] has been extensively used for the synthesis of complex biologically active compounds.[11] We have recently demonstrated that enols **3** can react in one-pot with carbonyl compounds **1**, amines **2**, and isocyanides **4**, considerably widening the diversity attainable by IMCR.[12] Mechanistically, the reaction is similar to the Ugi condensation with carboxylic acids, but in this case the driving force is a Michael–retro-Michael rearrangement of the primary adduct, leading to a stable enamine **10** (Scheme 1). Accordingly, a structural determinant of the reaction is the presence of at least one α,β-unsaturated electron-withdrawing group in the enol, which facilitates this rearrangement. Enols derived from 3- and 4-hydroxycoumarins meeting this constraint are readily available starting materials for enol-Ugi reactions. Here we report the use of this new strategy for the straightforward synthesis of amino acid derived coumarin enamines.



Scheme 1 Mechanism of the enol-Ugi reaction

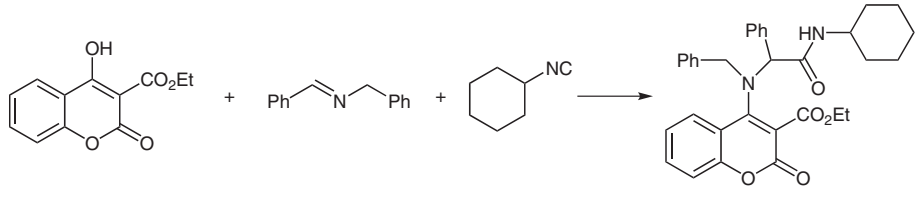
To begin our study, 4-hydroxycoumarin was used, which is a stable enol containing a conjugated lactone prone to enable the required Michael–retro-Michael final step of the enol-Ugi reaction. Thus, equimolar amounts of 4-hydroxycoumarin (**3a**), cyclohexyl isocyanide (**4a**), and (*E*)-*N*-1-diphenylmethanimine (**5a**) were mixed in methanol under different reaction conditions, but unfortunately no product was formed in any of the cases. We hypothesized that an extra withdrawing group would provide a more reactive Michael acceptor that could react in the expected manner. Accordingly, ethyl 4-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (**3b**), readily available from acetylsalicylic acid,[13] was used in the reaction. Thus, an equimolar mixture of this enol **3b** with imine **5a**, and cyclohexyl isocyanide (**4a**) was stirred in methanol at 25–30 °C for three days, giving a precipitate that was characterized as the enamine **10a** (Scheme 2). The structure of **10a** was further confirmed by monocrystal X-ray diffraction (Figure 1).



Scheme 2 Enol-Ugi reaction of 4-hydroxycoumarins

Encouraged by this result, different conditions and catalysts were examined in order to optimize the reaction. As some enol remained unreacted at the end of the reaction, we decided to increase the molar ratio of imine and isocyanide. However, this did not seem to improve the reaction (Table 1, entry 2). Also, increasing the temperature did not reduce the reaction time and complex reaction mixtures or decomposed starting materials were obtained (entries 3 and 4). The use of different Lewis acid catalyst also did not improve the reaction. The use of different solvents were then explored. Best results were obtained both in isopropyl alcohol (entry 11) and water (entry 13), but in this latter

Table 1 Optimization of Enol-Ugi Reaction of Ethyl 4-Hydroxy-2-oxo-2*H*-chromene-3-carboxylate (**3b**)



3b **5a** **4a** **10a**

Entry	**3b**/**4a**/**5a** Ratio	Solvent	Temp (°C)	Time (h)	Catalyst	Yield (%) of **10a**
1	1:1:1	MeOH	25–30	72	–	52
2	1:2:2	MeOH	25–30	72	–	49
3	1:1:1	MeOH	70 (MW) + 25	5 min + 72 h	–	29
4	1:1:1	MeOH	75	72	–	NR[a]
5	1:1:1	MeOH	25–30	72	$Sc(OTf)_3$	40
6	1:1:1	MeOH	25–30	120	$Y(OTf)_3$	51
7	1:1:1	MeOH	25–30	96	$Mg(ClO_4)_2$	30
8	1:1:1	MeOH	25–30	96	$ZnCl_2$	34
9	1:1:1	MeOH	25–30	148	$Cu(OTf)_2$	32
10	1:1:1	CF_3CH_2OH	25–30	96	–	30
11	1:1:1	*i*-PrOH	25–30	96	–	63
12	1:1:1	toluene	25–30	72	–	CM[b]
13	1:1:1	H_2O	25–30	72	–	60
14	1:1:1	H_2O + SDS[c]	25–30	72	–	40
15	1:1:1	CH_2Cl_2	25–30	48	–	30

[a] NR: No reaction.
[b] CM: Complex mixture.
[c] SDS: Sodium dodecyl sulfate.

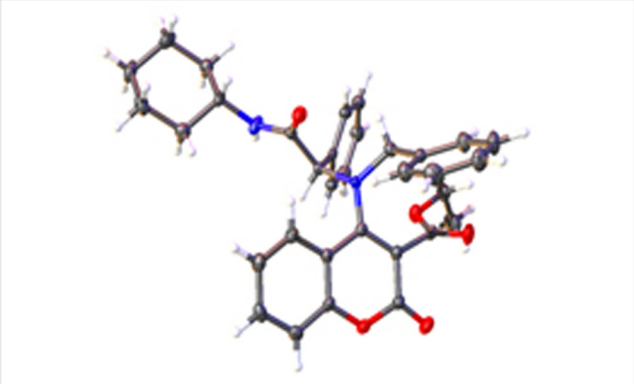
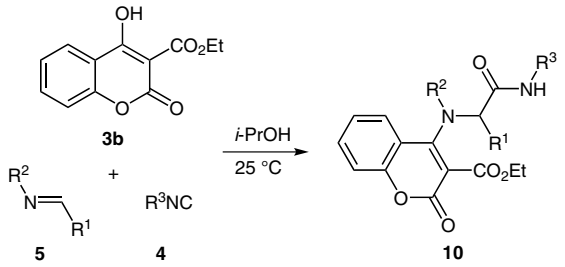


Figure 1 X-ray crystal structure of **10a**[14]

solvent, the formation of insoluble aggregates reduces the reproducibility of the reaction and the purity of the product. Conversely, when the reaction is performed in isopropyl alcohol the product precipitates from the reaction medium allowing to readily isolate it in high purity. Thus, optimal reaction conditions are the use of equimolar amounts of the three starting reagents in isopropyl alcohol at room temperature (entry 11).

To explore the scope of this reaction, different imines **5** and isocyanides **4** were treated with ethyl 4-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (**3b**) under the optimized conditions (Table 2). In all the cases, the expected enamine **10** precipitates from the reaction medium, and is obtained in moderate yields.

Table 2 3-Component Synthesis of 4-Aminoacylcoumarins **10**

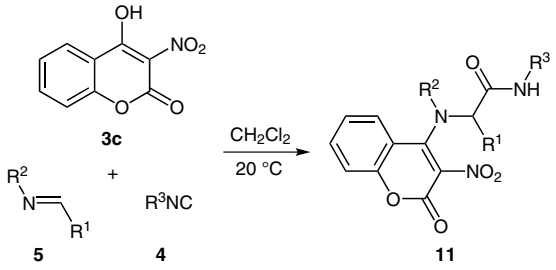


Entry	R^1	R^2	R^3	Product (yield, %)
1	Ph	Bn	*c*-C_6H_{11}	**10a** (63)
2	Ph	Bn	*t*-Bu	**10b** (60)
3	Ph	Bn	2,6-$Me_2C_6H_3$	**10c** (43)
4	Ph	Bn	CH_2CO_2*t*-Bu	**10d** (42)
5	Ph	3,4-(OCH_2O)Bn	*c*-C_6H_{11}	**10e** (65)
6	2-furyl	Bn	*c*-C_6H_{11}	**10f** (27)
7	Ph	Ph	*c*-C_6H_{11}	**10g** (62)
8	Ph	Ph	2,6-$Me_2C_6H_3$	**10h** (47)

In order to study the effect of the electron-withdrawing group on the enol, 4-hydroxy-3-nitrocoumarin (**3c**) was prepared by nitration of 4-hydroxycoumarin.[15] An additional interest of this enol is the possibility of reducing the nitro group after the condensation to obtain amino-derived adducts. Thus, the reaction of enol **3c** with equimolar amounts of imine **5a** and cyclohexyl isocyanide (**4a**) in isopropyl alcohol at room temperature for 24 hours gave the desired enamine adduct **11a** in a 56% yield; however, the reaction was much less clean than the corresponding reaction with enol **3b**. After some optimization, the reaction was successfully performed in dichloromethane at room temperature to cleanly afford **11a** in a 95% yield, in less than two hours.

Thus, the reaction of 4-hydroxy-3-nitrocoumarin (**3c**) with different combinations of isocyanides **4** and imines **5** under similar conditions readily afforded the expected coumarin enamines **11** in moderate to good yields (Table 3).

Table 3 Enol-Ugi Reactions of 4-Hydroxy-3-nitrocoumarin

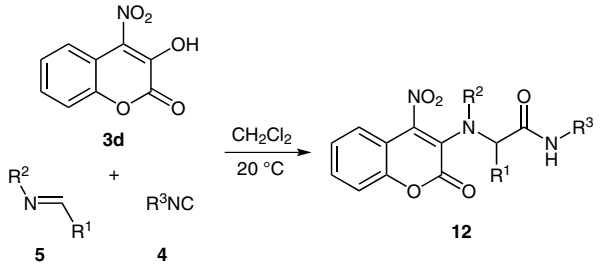


Entry	R^1	R^2	R^3	Product (Yield, %)
1	Ph	Bn	*c*-C_6H_{11}	**11a** (95)
2	Ph	Bn	*t*-Bu	**11b** (63)
3	Ph	Ph	*c*-C_6H_{11}	**11c** (63)
4	Ph	Ph	*t*-Bu	**11d** (42)
5	Ph	Ph	2,6-$Me_2C_6H_3$	**11e** (66)
6	4-FC_6H_4	Ph	*c*-C_6H_{11}	**11f** (48)
7	4-MeC_6H_4	Ph	*c*-C_6H_{11}	**11g** (65)
8	4-MeC_6H_4	Ph	*t*-Bu	**11h** (44)

Analogously, the isomeric enol **3d**, obtained by nitration of 3-hydroxycoumarin, reacted with a variety of isocyanides **4** and imines **5**, affording the corresponding enamine adducts **12** in good yields (Table 4).

In conclusion, coumarin enamines **10**, **11**, or **12** containing α-amino amide substituents at position 3 or 4 can be readily obtained by the new enol-Ugi condensation of imines, isocyanides, and hydroxycoumarins containing electron-withdrawing groups at positions 4 and 3, respectively. The reaction mechanism is similar to that of the classical Ugi condensation, except that in this case the final step leads to the product through a conjugate addition-β-elimi-

Table 4 Enol-Ugi Reactions of 3-Hydroxy-4-nitrocoumarin



Entry	R^1	R^2	R^3	**12** (% Yield)
1	Ph	Bn	*c*-C_6H_{11}	**12a** (78)
2	Ph	3,4-(OCH_2O)Bn	*c*-C_6H_{11}	**12b** (59)
3	Ph	Ph	*c*-C_6H_{11}	**12c** (78)
4	Ph	Ph	*t*-Bu	**12d** (64)
5	Ph	Ph	2,6-$Me_2C_6H_3$	**12e** (73)
6	4-MeC_6H_4	Ph	*c*-C_6H_{11}	**12f** (67)

nation rearrangement on the primary adduct. These transformations of coumarin derivatives demonstrate the utility of enol-Ugi reactions to efficient introduce complex functionality on electron-deficient heterocyclic enols.

Melting points are uncorrected. IR spectra were recorded as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a 400 or 500 MHz spectrometer. The assignments of signals in ^{13}C NMR were made using DEPT. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using chemical ionization (CI) with CH_4, or ESI-TOF. Liquid reagents were measured using positive-displacement micropipettes with disposable tips and pistons.

Enol-Ugi Adducts 10; General Procedure

To a solution of imine **5** (0.5 mmol) in *i*-PrOH (1 mL) were added successively isocyanide **4** (0.5 mmol) and enol **3b** (0.5 mmol). The reaction mixture was stirred at 25–30 °C for 48–96 h, and then cooled to 0 °C. The resulting precipitate was filtered and washed with hexanes (4 mL), yielding analytically pure product **10**. Then, 10% aq HCl (4 mL) and H_2O (20 mL) were added to the filtrate, and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, gradient from 100% hexanes to hexanes–EtOAc, 7:3), giving a solid that was combined with the previously isolated precipitate (Table 2).

Ethyl 4-{Benzyl[2-(cyclohexylamino)-2-oxo-1-phenylethyl]amino}-2-oxo-2*H*-chromene-3-carboxylate (10a)

Yield: 170 mg (63%); white solid; mp 127–130 °C.

IR (KBr): 3304, 3061, 2926, 2853, 1717, 1667, 1595, 1541, 1449, 1346, 1237, 1049, 752, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.36 (m, 3 H), 7.35–7.30 (m, 1 H), 7.25–7.11 (m, 8 H), 7.06–6.99 (m, 3 H), 5.17 (s, 1 H), 4.54–4.41 (m, 2 H), 4.44 (d, *J* = 14.9 Hz, 1 H), 4.29 (d, *J* = 14.5 Hz, 1 H), 3.65–3.59 (m, 1 H), 1.75–1.05 (m, 10 H), 1.43 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.89 (C), 166.38 (C), 159.58 (C), 159.30 (C), 152.91 (C), 135.90 (C), 135.27 (C), 132.72 (CH), 129.40 (CH), 128.69 (CH), 128.60 (CH), 128.51 (CH), 128.20 (CH), 127.70 (CH), 123.60 (CH), 119.33 (C), 116.84 (CH), 71.76 (CH), 62.64 (CH_2), 57.77 (CH_2), 48.36 (CH), 32.75 (CH_2), 32.38 (CH_2), 25.40 (CH_2), 24.85 (CH_2), 24.79 (CH_2), 14.11 (CH_3).

MS (CI): *m*/*z* (%) = 539 ($M^{+\bullet}$, <5), 234 (27), 218 (90), 188 (62), 93 (56).

HRMS (CI): *m*/*z* calcd for $C_{33}H_{36}N_2O_5$: 539.2546; found: 539.2544.

Ethyl 4-{Benzyl[2-(*tert*-butylamino)-2-oxo-1-phenylethyl]amino}-2-oxo-2*H*-chromene-3-carboxylate (10b)

Yield: 154 mg (60%); yellow solid; mp 195–197 °C.

IR (KBr): 3325, 3057, 2971, 1723, 1670, 1597, 1537, 1452, 1406, 1346, 1233, 1049, 762, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.37 (m, 4 H), 7.26–7.14 (m, 7 H), 7.08–7.01 (m, 3 H), 6.89 (br s, 1 H), 5.05 (s, 1 H), 4.52–4.35 (m, 2 H), 4.46 (d, *J* = 14.2 Hz, 1 H), 4.28 (d, *J* = 14.4 Hz, 1 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.23 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.94 (C), 166.05 (C), 159.48 (C), 159.31 (C), 152.86 (C), 135.88 (C), 135.38 (C), 132.63 (CH), 129.35 (CH), 128.73 (CH), 128.52 (CH), 128.48 (CH), 128.14 (CH), 127.72 (CH), 123.59 (CH), 119.41 (C), 116.78 (CH), 72.64 (CH), 62.50 (CH_2), 57.69 (CH_2), 51.47 (C), 28.41 (CH_3), 14.07 (CH_3).

MS (CI): *m*/*z* (%) = 513 ($M^{+\bullet}$ + 1, <5), 278 (14), 192 (58), 188 (41), 136 (100).

HRMS (CI): *m*/*z* calcd for $C_{31}H_{33}N_2O_5$: 513.2389; found: 513.2389.

Ethyl 4-(Benzyl{2-[(2,6-dimethylphenyl)amino]-2-oxo-1-phenylethyl}amino)-2-oxo-2*H*-chromene-3-carboxylate (10c)

Yield: 121 mg (43%); yellow solid; mp 118–120 °C.

IR (KBr): 3433, 3030, 1691, 1604, 1555, 1494, 1454, 1242, 1031, 760, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, 320 K): δ = 8.49 (br s, 1 H), 7.61 (d, *J* = 7.2 Hz, 2 H), 7.44–7.32 (m, 2 H), 7.30–7.14 (m, 7 H), 7.12–7.06 (m, 2 H), 7.04–6.88 (m, 4 H) 5.45 (s, 1 H), 4.60 (d, *J* = 14.2 Hz, 1 H), 4.45 (m, 3 H), 1.89 (br s, 6 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$, 278 K): δ = 166.34 (C), 159.61 (C), 159.26 (C), 152.98 (C), 135.43 (C), 134.89 (C), 133.41 (C), 132.83 (CH), 129.57 (CH), 128.87 (CH), 128.72 (CH), 128.54 (CH), 128.33 (CH), 128.31 (CH), 127.69 (CH), 127.24 (CH), 123.70 (CH), 119.57 (C), 117.84 (C), 116.81 (CH), 72.20 (CH), 62.75 (CH_2), 58.21 (CH_2), 18.30 (CH_3),14.12 (CH_3).

MS (CI): *m*/*z* (%) = 561 ($M^{+\bullet}$ + 1, 62), 560 (58), 188 (43), 278 (31), 240 (100).

HRMS (CI): *m*/*z* calcd for $C_{35}H_{33}N_2O_5$: 561.2389; found: 561.2394.

Ethyl 4-[Benzyl(2-{[2-(*tert*-butoxy)-2-oxoethyl]amino}-2-oxo-1-phenylethyl)amino]-2-oxo-2*H*-chromene-3-carboxylate (10d)

Yield: 120 mg (42%); white solid; mp 137–139 °C.

IR (KBr): 3445, 1725, 1678, 1599, 1557, 1450, 1391, 1368, 1342, 1292, 1246, 1158, 1053, 757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.11 (m, 14 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 5.23 (s, 1 H), 4.69 (d, *J* = 14.6 Hz, 1 H), 4.42 (q, *J* = 7.3 Hz, 2 H), 4.37 (d, *J* = 14.7 Hz, 1 H), 4.10 (dd, *J* = 17.8, 6.3 Hz, 1 H), 3.76 (dd, *J* = 17.9, 3.9 Hz, 1 H), 1.45 (s, 9 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.77 (C), 168.89 (C), 166.39 (C), 159.66 (C), 158.97 (C), 153.15 (C), 135.59 (C), 135.39 (C), 132.68 (CH), 129.63 (CH), 129.08 (CH), 128.91 (CH), 128.81 (CH), 128.64 (CH), 128.27 (CH), 127.73 (CH), 123.70 (CH), 119.53 (C), 117.41 (C), 116.96 (CH), 82.27 (C), 71.56 (CH), 62.82 (CH_2), 57.60 (CH_2), 42.16 (CH_2), 28.22 (CH_3), 14.20 (CH_3).

MS (CI): *m*/*z* (%) = 571 ($M^{+\bullet}$ + 1, 6), 515 (24), 324 (26), 86 (100).

HRMS (CI): *m*/*z* calcd for $C_{33}H_{35}N_2O_7$: 571.2443; found: 571.2444.

Ethyl 4-{(Benzo[*d*][1,3]dioxol-5-ylmethyl)[2-(cyclohexylamino)-2-oxo-1-phenylethyl]amino}-2-oxo-2*H*-chromene-3-carboxylate (10e)

Yield: 189 mg (65%); white solid; mp 128–130 °C.

IR (KBr): 3435, 2932, 1664, 1607, 1530, 1490, 1448, 1397, 1249, 1037, 812, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 4 H), 7.37–7.16 (m, 4 H), 7.15–7.03 (t, *J* = 7.6 Hz, 2 H), 6.64 (d, *J* = 7.9 Hz, 1 H), 6.57 (s, 1 H), 6.50 (d, *J* = 7.2 Hz, 1 H), 5.92 (s, 2 H), 5.20 (s, 1 H), 4.56–4.41 (m, 2 H), 4.37 (d, *J* = 14.4 Hz, 1 H), 4.21 (d, *J* = 14.4 Hz, 1 H), 3.70–3.58 (m, 1 H), 1.77–1.08 (m, 13 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.15 (C), 166.50 (C), 159.64 (C), 159.47 (C), 153.11 (C), 147.88 (C), 147.67 (C), 136.06 (C), 132.97 (CH), 129.33 (C), 128.88 (CH), 128.81 (CH), 127.82 (CH), 123.89 (CH), 123.21 (CH), 119.51 (C), 117.11 (CH), 109.83 (CH), 108.33 (CH), 101.30 (CH_2), 71.96 (CH), 62.84 (CH_2), 57.67 (CH_2), 48.58 (CH), 32.97 (CH_2), 32.58 (CH_2), 25.56 (CH_2), 25.05 (CH_2), 24.99 (CH_2), 14.28 (CH_3).

MS (CI): *m*/*z* (%) = 583 ($M^{+\bullet}$ + 1, <5), 189 (13), 134 (100).

HRMS (CI): *m*/*z* calcd for $C_{34}H_{35}N_2O_7$: 583.2443; found: 583.2444.

Ethyl 4-{Benzyl[2-(cyclohexylamino)-1-(furan-2-yl)-2-oxoethyl]amino}-2-oxo-2*H*-chromene-3-carboxylate (10f)

Yield: 71 mg (27%); white solid; mp 183 °C (dec.).

IR (KBr): 3333, 2933, 1730, 1677, 1602, 1560, 1451, 1397, 1341, 1241, 1112, 1052, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.31–7.05 (m, 9 H), 6.42 (s, 1 H), 6.28 (s, 1 H), 5.45 (s, 1 H), 4.51–4.33 (m, 4 H), 3.73 (br s, 1 H), 1.86–1.59 (m, 5 H), 1.38 (t, *J* = 7.0 Hz, 3 H), 1.33–1.16 (m, 5 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.67 (C), 166.12 (C), 159.60 (C), 157.92 (C), 153.44 (C), 148.84 (C), 143.20 (CH), 136.42 (C), 132.89 (CH), 128.66 (CH), 128.60 (CH), 128.04 (CH), 127.29 (CH), 124.21 (CH), 118.62 (C), 117.40 (CH), 111.87 (CH), 111.00 (CH), 65.31 (CH), 62.75 (CH_2), 55.29 (CH_2), 49.10 (CH), 32.90 (CH_2), 32.83 (CH_2), 25.62 (CH_2), 25.10 (CH_2), 14.17 (CH_3).

MS (CI): *m*/*z* (%) = 529 ($M^{+\bullet}$ + 1, <5), 402 (14), 358 (6), 266 (12), 234 (8), 206 (100).

HRMS (CI): *m*/*z* calcd for $C_{31}H_{33}N_2O_6$: 529.2339; found: 529.2338.

Ethyl 4-{[2-(Cyclohexylamino)-2-oxo-1-phenylethyl](phenyl)amino}-2-oxo-2*H*-chromene-3-carboxylate (10g)

Yield: 163 mg (62%); white solid; mp 101–103 °C.

IR (KBr): 3431, 2931, 1702, 1649, 1602, 1521, 1497, 1461, 1414, 1384, 1229, 1041, 755, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 7.9 Hz, 1 H), 7.67 (dd, *J* = 11.4, 4.2 Hz, 1 H), 7.34–7.22 (m, 8 H), 6.85 (s, 2 H), 6.69 (d, *J* = 7.8 Hz, 2 H), 6.03 (br s, 1 H), 4.98 (s, 1 H), 4.04–3.98 (m, 2 H), 3.74 (br s, 1 H), 2.22–1.00 (m, 10 H), 1.46 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.78 (C), 172.08 (C), 157.86 (C), 154.70 (C), 147.21 (C), 135.62 (CH), 128.69 (CH), 128.59 (CH), 128.20 (CH), 125.34 (CH), 124.39 (CH), 123.14 (CH), 119.68 (CH), 117.10 (CH), 115.00 (C), 114.02 (CH), 93.39 (C), 64.63 (CH), 62.93 (CH_2), 60.09 (CH), 33.31 (CH_2), 32.67 (CH_2), 26.00 (CH_2), 25.14 (CH_2), 24.97 (CH_2), 14.41 (CH_3).

MS (ESI-FIA-TOF): *m*/*z* (%) = 547 ($M^{+\bullet}$ + Na, 40), 435 (24), 384 (28) 182 (100).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{32}H_{32}N_2O_5Na$: 547.2203; found: 547.2201.

Ethyl 4-({2-[(2,6-Dimethylphenyl)amino]-2-oxo-1-phenylethyl}(phenyl)amino)-2-oxo-2*H*-chromene-3-carboxylate (10h)

Yield: 128 mg (47%); white solid; mp 127–129 °C.

IR (KBr): 3433, 1720, 1605, 1566, 1499, 1382, 1240, 1046, 761, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.97 (br s, 1 H), 7.60 (d, *J* = 7.5 Hz, 2 H), 7.47 (dt, *J* = 8.7, 1.5 Hz, 1 H), 7.34–7.27 (m, 2 H), 7.21–7.05 (m, 9 H), 7.01 (d, *J* = 7.4 Hz, 3 H), 5.79 (s, 1 H), 4.36–4.19 (m, 2 H), 1.93 (s, 6 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.66 (C), 164.80 (C), 158.22 (C), 153.51 (C), 145.72 (C), 135.31 (C), 133.24 (CH), 133.20 (C), 132.64 (C), 130.53 (CH), 129.66 (CH), 129.25 (CH), 128.30 (CH), 128.11 (CH), 127.25 (CH), 127.13 (CH), 124.47 (CH), 121.76 (CH), 119.09 (C), 116.84 (CH), 116.00 (CH), 62.79 (CH_2), 18.22 (CH_3), 13.88 (CH_3).

MS (CI): *m*/*z* (%) = 547 ($M^{+\bullet}$ + 1, <5), 500 (12), 398 (21), 309 (64), 238 (100).

HRMS (CI): *m*/*z* calcd for $C_{34}H_{31}N_2O_5$: 547.2233; found: 547.2236.

Enol-Ugi Adducts 11 and 12; General Procedure

To a solution of imine **5** (0.5 mmol) in CH_2Cl_2 (1 mL) were added isocyanide **4** (0.5 mmol) and enol **3c**/**d** (0.5 mmol) successively. The reaction mixture was stirred at 20 °C for 2–3 h, and then concentrated. The residue was purified by column chromatography (SiO_2, gradient from 100% hexanes to hexanes–EtOAc, 7:3) to give the enamine **11** or **12** as an analytically pure solid (Tables 3 and 4).

2-[Benzyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino]-*N*-cyclohexyl-2-phenylacetamide (11a)

Yield: 243 mg (95%); yellow solid; mp 110–112 °C.

IR (KBr): 3385, 2930, 2854, 1728, 1680, 1601, 1550, 1453, 1404, 1350, 1117, 1056, 761, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.57 (dt, *J* = 6.7, 1.6 Hz, 1 H), 7.39–7.31 (m, 6H), 7.27 (dd, *J* = 8.3, 1.0 Hz, 1 H), 7.23–7.15 (m, 5 H), 6.00 (d, *J* = 8.1 Hz, 1 H), 5.24 (s, 1 H), 4.69 (d, *J* = 14.9 Hz, 1 H), 4.20 (d, *J* = 15.0 Hz, 1 H), 3.78–3.67 (m, 1 H), 1.89–1.54 (m, 5 H), 1.36–0.97 (m, 5 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.00 (C), 154.98 (C), 153.17 (C), 152.28 (C), 135.18 (C), 134.75 (C), 133.79 (CH), 129.28 (CH), 129.02 (CH), 129.00 (CH), 128.98 (CH), 128.42 (CH), 128.27 (CH), 128.25 (C), 124.84 (CH), 118.20 (C), 117.48 (CH), 71.12 (CH), 55.85 (CH_2), 48.86 (CH), 32.55 (CH_2), 32.48 (CH_2), 26.92 (CH_2), 25.32 (CH_2), 24.74 (CH_2), 24.66 (CH_2).

MS (ESI-FIA-TOF): *m*/*z* (%) = 534 ($M^{+\bullet}$ + Na, 100), 512 ($M^{+\bullet}$ + 1, 50), 340 (67).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{30}H_{30}N_3O_5$: 512.2180; found: 512.2178.

2-[Benzyl(3-nitro-2-oxo-2*H*-chromen-4-yl)amino]-*N*-(*tert*-butyl)-2-phenylacetamide (11b)[12]

Yield: 153 mg (63%); yellow solid; mp 84–89 °C.

IR (KBr): 3379, 2968, 1685, 1601, 1548, 1455, 1364, 1364, 1222, 760, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.58 (dt, *J* = 8.5, 1.5 Hz, 1 H), 7.39–7.27 (m, 7 H), 7.24–7.19 (m, 3 H), 7.18–7.14 (m, 2 H), 5.84 (s, 1 H), 5.12 (s, 1 H), 4.68 (d, *J* = 14.9 Hz, 1 H), 4.21 (d, *J* = 14.9 Hz, 1 H), 1.26 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.02 (C), 154.96 (C), 153.36 (C), 152.25 (C), 135.12 (C), 134.86 (C), 133.77 (CH), 131.86 (C), 129.22 (CH), 129.03 (CH), 128.97 (CH), 128.47 (CH), 128.35 (CH), 128.28 (CH), 124.76 (CH), 118.29 (C), 117.47 (CH), 71.56 (CH), 56.16 (CH_2), 51.93 (C), 28.36 (CH_3).

MS (CI): *m*/*z* (%) = 486 ($M^{+\bullet}$ + 1, 40), 385 (56), 328 (57), 297 (58), 263 (63), 105 (100).

HRMS (CI): *m*/*z* calcd for $C_{28}H_{28}N_3O_5$: 486.2029; found: 486.2015.

***N*-Cyclohexyl-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]-2-phenylacetamide (11c)**

Yield: 157 mg (63%); red solid; mp 174–176 °C.

IR (KBr): 3445, 2929, 2856, 1746, 1655, 1607, 1557, 1496, 1453, 1384, 760, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.34–7.17 (m, 7 H), 7.16–7.11 (m, 2 H), 7.07–6.99 (m, 3 H), 6.46 (d, *J* = 7.6 Hz, 1 H), 5.61 (s, 1 H), 3.86–3.75 (m, 1 H), 1.93–0.92 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.77 (C), 153.95 (C), 152.69 (C), 150.30 (C), 144.59 (C), 137.77 (C), 134.15 (CH), 132.57 (C), 129.82 (CH), 129.54 (CH), 129.41 (CH), 128.76 (CH), 128.54 (CH), 125.19 (CH), 123.22 (CH), 118.45 (CH), 117.98 (C), 117.24 (CH), 70.02 (CH), 48.63 (CH), 32.55 (CH_2), 32.27 (CH_2), 25.32 (CH_2), 24.57 (CH_2), 24.47 (CH_2).

MS (ESI-FIA-TOF): *m*/*z* (%) = 520 ($M^{+\bullet}$ + Na, 100), 498 ($M^{+\bullet}$ + 1, 20), 188 (46).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{29}H_{28}N_3O_5$: 498.2023; found: 498.2019.

***N*-(*tert*-Butyl)-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]-2-phenylacetamide (11d)**

Yield: 99 mg (42%); red solid; mp 151–153 °C.

IR (KBr): 3391, 2966, 2925, 1746, 1671, 1603, 1493, 1461, 1370, 1057, 758, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.59–7.54 (m, 1 H), 7.31–7.18 (m, 7 H), 7.14 (t, *J* = 7.3 Hz, 2 H), 7.07 (d, *J* = 7.4 Hz, 1 H), 7.03 (d, *J* = 7.9 Hz, 2 H), 6.37 (s, 1 H), 5.49 (s, 1 H), 1.32 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.84 (C), 153.89 (C), 152.66 (C), 150.22 (C), 144.71 (C), 137.95 (C), 134.18 (CH), 132.69 (C), 129.78 (CH), 129.55 (CH), 129.42 (CH), 128.71 (CH), 128.55 (CH), 125.20 (CH), 123.14 (CH), 118.13 (CH), 117.92 (C), 117.23 (CH), 70.61 (CH), 51.90 (C), 28.25 (CH_3).

MS (ESI-FIA-TOF): *m*/*z* (%) = 494 ($M^{+\bullet}$ + Na, 100), 472 ($M^{+\bullet}$ + 1, 20), 162 (24).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{27}H_{26}N_3O_5$: 472.1867; found: 472.1863.

***N*-(2,6-Dimethylphenyl)-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]-2-phenylacetamide (11e)**

Yield: 171 mg (66%); red solid; mp 156–158 °C.

IR (KBr): 3383, 1742, 1715, 1604, 1536, 1499, 1381, 1278, 1043, 769 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 7.5 Hz, 1 H), 7.80 (s, 1 H), 7.58 (dt, *J* = 8.7, 1.6 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 2 H), 7.33–7.23 (m, 5 H), 7.20–7.17 (m, 4 H), 7.11–7.05 (m, 2 H), 7.01 (d, *J* = 7.5 Hz, 2 H), 5.87 (s, 1 H), 1.95 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.53 (C), 153.96 (C), 152.59 (C), 150.56 (C), 144.73 (C), 135.07 (C), 134.37 (CH), 132.80 (C), 131.96 (C), 130.18 (CH), 129.78 (CH), 129.74 (CH), 129.01 (CH), 128.61 (CH), 128.42 (CH), 127.48 (CH), 125.33 (CH), 123.44 (CH), 118.46 (CH), 118.36 (C), 117.11 (CH), 70.26 (CH), 18.31 (CH_3).

MS (ESI-FIA-TOF): *m*/*z* (%) = 542 ($M^{+\bullet}$ + Na, 60), 520 ($M^{+\bullet}$ + 1, 65), 238 (100).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{31}H_{25}N_3O_5$: 520.1867; found: 529.1877.

***N*-Cyclohexyl-2-(4-fluorophenyl)-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]acetamide (11f)**

Yield: 124 mg (48%); red solid; mp 166–167 °C.

IR (KBr): 3427, 3300, 2933, 2856, 1744, 1655, 1607, 1530, 1509, 1385, 1231, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.59 (dt, *J* = 8.7, 1.5 Hz, 1 H), 7.33–7.20 (m, 6 H), 7.08–7.05 (m, 1 H), 7.03–7.01 (m, 2 H), 6.85 (t, *J* = 8.6 Hz, 2 H), 6.34 (d, *J* = 8.1 Hz, 1 H), 5.55 (s, 1 H), 3.86–3.76 (m, 1 H), 1.92–0.96 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.57 (C), 163.99 (C), 162.00 (C), 153.78 (C), 152.72 (C), 149.97 (C), 144.39 (C), 137.87 (C), 134.29 (CH), 131.81 (CH), 131.74 (CH), 129.63 (CH), 128.48 (CH), 128.43 (C), 128.41 (C), 125.29 (CH), 123.44 (CH), 118.45 (CH), 117.81 (C), 117.46 (CH), 115.75 (CH), 115.58 (CH), 69.23 (CH), 48.69 (CH), 32.57 (CH_2), 32.28 (CH_2), 25.28 (CH_2), 24.55 (CH_2), 24.44 (CH_2).

MS (ESI-FIA-TOF): *m*/*z* (%) = 538 ($M^{+\bullet}$ + Na, 100), 516 ($M^{+\bullet}$ + 1, 25), 206 (54).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{29}H_{27}FN_3O_5$: 516.1929; found: 516.1926.

***N*-Cyclohexyl-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]-2-(*p*-tolyl)acetamide (11g)**

Yield: 166 mg (65%); red solid; mp 157–160 °C.

IR (KBr): 3450, 3307, 2933, 2856, 1476, 1656, 1607, 1629, 1384, 1277, 1120, 1051, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 1 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.30–7.21 (m, 5 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 7.03 (t, *J* = 7.4 Hz, 2 H), 6.94 (d, *J* = 7.9 Hz, 2 H), 6.40 (d, *J* = 8.2 Hz, 1 H), 5.56 (s, 1 H), 3.87–3.74 (m, 1 H), 2.23 (s, 3 H), 1.95–0.92 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.96 (C), 153.98 (C), 152.69 (C), 150.38 (C), 144.70 (C), 139.41 (C), 137.85 (C), 134.11 (CH), 129.70 (CH), 129.53 (CH), 129.41 (C), 129.25 (CH), 128.75 (CH), 125.18 (CH), 123.10 (CH), 118.29 (CH), 118.04 (C), 117.25 (CH), 69.83 (CH), 48.57 (CH), 32.57 (CH_2), 32.28 (CH_2), 25.33 (CH_2), 24.58 (CH_2), 24.47 (CH_2), 21.09 (CH_3).

MS (ESI-FIA-TOF): *m*/*z* (%) = 534 ($M^{+\bullet}$ + Na, 100), 488 (20), 304 (40), 202 (30).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{30}H_{29}N_3O_5Na$: 534.1999; found: 534.2000.

N-(*tert*-Butyl)-2-[(3-nitro-2-oxo-2*H*-chromen-4-yl)(phenyl)amino]-2-(*p*-tolyl)acetamide (11h)

Yield: 107 mg (44%); red solid; mp 181–183 °C.

IR (KBr): 3385, 2967, 2926, 1747, 1674, 1606, 1534, 1497, 1367, 1278, 1228, 1054, 761, 600 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.66 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.57 (dt, *J* = 8.7, 1.5 Hz, 1 H), 7.31–7.22 (m, 4 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 7.06 (d, *J* = 7.4 Hz, 1 H), 7.04–7.00 (m, 2 H), 6.94 (d, *J* = 7.8 Hz, 2 H), 6.34 (s, 1 H), 5.44 (s, 1 H), 2.23 (s, 3 H), 1.31 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.99 (C), 153.93 (C), 152.67 (C), 150.31 (C), 144.83 (C), 139.39 (C), 138.02 (C), 134.12 (CH), 129.66 (CH), 129.58 (C), 129.52 (CH), 129.26 (CH), 128.71 (CH), 125.18 (CH), 123.01 (CH), 118.00 (CH), 117.23 (CH), 70.43 (CH), 51.81 (C), 28.26 (CH_3), 21.09 (CH_3).

MS (ESI-FIA-TOF): *m*/*z* (%) = 508 ($M^{+\bullet}$ + Na, 100), 462 (20), 304 (80), 284 (70), 220 (50), 192 (45), 176 (55).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{28}H_{27}N_3O_5Na$: 508.1843, found: 508.1850.

2-[Benzyl(4-nitro-2-oxo-2*H*-chromen-3-yl)amino]-*N*-cyclohexyl-2-phenylacetamide (12a)

Yield: 200 mg (78%); orange solid; mp 87–89 °C.

IR (KBr): 3383, 2930, 2853, 1740, 1660, 1607, 1544, 1453, 1107, 750, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.45 (m, 3 H), 7.46–7.18 (m, 8 H), 7.14 (dd, *J* = 6.4, 2.8 Hz, 2 H), 7.06 (d, *J* = 7.8 Hz, 1 H), 6.88 (br s, 1 H), 5.13 (s, 1 H), 4.17 (d, *J* = 12.8 Hz, 1 H), 4.14 (d, *J* = 12.8 Hz, 1 H), 3.87–3.74 (m, 1 H), 2.11–1.17 (m, 10 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.44 (C), 159.25 (C), 152.00 (C), 135.39 (C), 132.88 (CH), 129.98 (CH), 129.84 (CH), 129.04 (CH), 128.89 (CH), 128.70 (CH), 128.54 (CH), 125.55 (CH), 123.31 (CH), 117.26 (CH), 111.76 (C), 72.55 (CH), 57.92 (CH_2), 48.26 (CH), 33.13 (CH_2), 33.03 (CH_2), 25.68 (CH_2), 24.91 (CH_2), 24.85 (CH_2), 21.26 (CH_2).

MS (CI): *m*/*z* (%) = 512 ($M^{+\bullet}$ + 1, <5), 340 (21), 174 (61), 104 (100).

HRMS (CI): *m*/*z* calcd for $C_{30}H_{30}N_3O_5$: 512.2183; found: 512.2185.

2-[(Benzo[*d*][1,3]dioxol-5-ylmethyl)(4-nitro-2-oxo-2*H*-chromen-3-yl)amino]-*N*-cyclohexyl-2-phenylacetamide (12b)

Yield: 164 mg (59%); orange solid; mp 88–90 °C.

IR (KBr): 3385, 2928, 2852, 1739, 1661, 1608, 1544, 1503, 1490, 1447, 1250, 1101, 1038, 929, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.52 (m, 1 H), 7.50–7.48 (m, 2 H), 7.30–7.19 (m, 4 H), 7.10 (dd, *J* = 8.3, 1.4 Hz, 1 H), 6.82 (br s, 1 H), 6.67 (d, *J* = 7.9 Hz, 1 H), 6.64 (d, *J* = 1.6 Hz, 1 H), 6.57 (dd, *J* = 7.9, 1.6 Hz, 1 H), 5.94 (dd, *J* = 7.4, 1.4 Hz, 2 H), 5.09 (s, 1 H), 4.26 (d, *J* = 12.9 Hz, 1 H), 4.09 (d, *J* = 12.9 Hz, 1 H), 3.84–3.75 (m, 1 H), 1.98–1.20 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.20 (C), 159.04 (C), 151.87 (C), 147.86 (C), 147.64 (C), 139.0 (C), 135.17 (C), 132.69 (CH), 129.60 (CH), 129.01 (C), 128.83 (CH), 128.52 (CH), 125.66 (C), 125.36 (CH), 123.44 (CH), 123.13 (CH), 117.10 (CH), 111.65 (C), 109.93 (CH), 108.28 (CH), 101.11 (CH_2), 72.22 (CH), 57.51 (CH_2), 48.06 (CH), 32.95 (CH_2), 32.83 (CH_2), 25.48 (CH_2), 24.72 (CH_2), 24.65 (CH_2).

MS (ESI-FIA-TOF): *m*/*z* (%) = 578 ($M^{+\bullet}$ + Na, 100), 384 (80), 262 (70), 135 (70).

HRMS (ESI-FIA-TOF): *m*/*z* calcd for $C_{31}H_{29}N_3O_7Na$: 578.1898; found: 578.1904.

N-Cyclohexyl-2-[(4-nitro-2-oxo-2*H*-chromen-3-yl)(phenyl)amino]-2-phenylacetamide (12c)

Yield: 194 mg (78%); red solid; mp 104–106 °C.

IR (KBr): 3410, 2930, 2853, 1740, 1661, 1605, 1545, 1497, 1453, 1383, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (ddd, *J* = 8.7, 7.5, 1.4 Hz, 1 H), 7.47 (d, *J* = 6.8 Hz, 2 H), 7.43–7.39 (d, *J* = 7.7 Hz, 1 H), 7.38–7.34 (m, 2 H), 7.31–7.19 (m, 6 H), 7.02 (t, *J* = 7.4 Hz, 1 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 5.57 (s, 1 H), 3.90–3.80 (m, 1 H), 2.10–0.89 (m, 10 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.55 (C), 160.36 (C), 156.09 (C), 152.26 (C), 145.06 (C), 133.68 (CH), 133.04 (C), 130.33 (CH), 129.41 (CH), 129.34 (CH), 128.60 (CH), 125.76 (CH), 123.51 (CH), 123.06 (C), 122.34 (CH), 117.36 (CH), 116.54 (CH), 111.38 (C), 69.49 (CH), 47.87 (CH), 32.58 (CH_2), 32.19 (CH_2), 25.42 (CH_2), 24.40 (CH_2), 24.17 (CH_2).

MS (CI): *m*/*z* (%) = 498 ($M^{+\bullet}$ + 1, 20), 342 (60), 254 (100).

HRMS (CI): *m*/*z* calcd for $C_{29}H_8N_3O_5$: 498.2029; found: 498.2029.

N-(*tert*-Butyl)-2-[(4-nitro-2-oxo-2*H*-chromen-3-yl)(phenyl)amino]-2-phenylacetamide (12d)

Yield: 151 mg (64%); red solid; mp 167–169 °C.

IR (KBr): 3328, 2976, 1728, 1673, 1604, 1544, 1503, 1454, 1277, 1166, 1056, 759, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–6.69 (m, 15 H), 5.41 (s, 1 H), 1.29 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.84 (C), 160.37 (C), 156.36 (C), 152.49 (C), 145.40 (C), 133.88 (CH), 133.46 (C), 130.50 (CH), 129.60 (CH), 129.50 (CH), 128.80 (CH), 125.95 (CH), 123.71 (CH), 123.20 (C), 122.50 (CH), 117.56 (CH), 116.67 (CH), 111.53 (C), 70.41 (CH), 51.51 (C), 28.49 (CH_3).

MS (CI): *m*/*z* (%) = 472 ($M^{+\bullet}$ + 1, 7), 371 (20), 162 (100).

HRMS (CI): *m*/*z* calcd for $C_{27}H_{26}N_3O_5$: 472.1877; found: 472.1872.

N-(2,6-Dimethylphenyl)-2-[(4-nitro-2-oxo-2*H*-chromen-3-yl)(phenyl)amino]-2-phenylacetamide (12e)

Yield: 190 mg (73%); red solid; mp 98–100 °C.

IR (KBr): 3287, 3062, 1720, 1674, 1598, 1548, 1499, 1455, 1282, 1239, 1164, 1125, 754 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 7.72–7.69 (m, 2 H), 7.68–7.66 (m, 1 H), 7.39–7.24 (m, 7 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.10–7.03 (m, 4 H), 6.01 (d, *J* = 7.5 Hz, 1 H), 5.85 (s, 1 H), 1.95 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.94 (C), 160.98 (C), 155.66 (C), 152.20 (C), 145.26 (C), 135.12 (C), 133.75 (CH), 133.32 (C), 132.82 (C), 130.62 (CH), 129.74 (CH), 129.59 (CH), 128.66 (CH), 128.36 (CH), 127.07 (CH), 125.86 (CH), 123.61 (CH), 123.07 (CH), 117.66 (CH), 117.40 (CH), 111.53 (C), 70.27 (CH), 18.41 (CH_3).

MS (CI): *m*/*z* (%) = 520 ($M^{+\bullet}$ + 1, 6), 473 (22), 339 (14), 238 (48), 105 (100).

HRMS (CI): *m*/*z* calcd for $C_{36}H_{27}N_3O_5$: 520.1868; found: 520.1872.

N-Cyclohexyl-2-[(4-nitro-2-oxo-2*H*-chromen-3-yl)(phenyl)amino]-2-(*p*-tolyl)acetamide (12f)

Yield: 171 mg (67%); red solid; mp 84–85 °C.

IR (KBr): 3336, 2929, 1730, 1672, 1606, 1546, 1501, 1454, 1283, 1246, 1163, 1144, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (dt, *J* = 8.6, 1.5 Hz, 1 H), 7.43–7.32 (m, 5 H), 7.30–7.24 (m, 2 H), 7.03 (dd, *J* = 6.3, 4.3 Hz, 2 H), 7.00 (d, *J* = 7.4 Hz, 1 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 5.52 (s, 1 H), 3.87–3.79 (m, 1 H), 2.21 (s, 3 H), 1.97–0.90 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.77 (C), 160.38 (C), 156.08 (C), 152.32 (C), 145.17 (C), 140.38 (C), 139.18 (C), 133.59 (CH), 130.22 (CH), 129.98 (C), 129.30 (CH), 125.72 (CH), 123.55 (CH), 123.21 (C), 122.26 (CH), 117.37 (CH), 116.55 (CH), 69.30 (CH), 47.83 (CH), 32.57 (CH_2), 32.20 (CH_2), 25.44 (CH_2), 24.39 (CH_2), 24.16 (CH_2), 21.10 (CH_3).

MS (CI): *m*/*z* (%) = 472 ($M^{+\bullet}$ + 1, 7), 371 (20), 162 (100).

HRMS (CI): *m*/*z* calcd for $C_{27}H_{26}N_3O_5$: 472.1877; found: 472.1872.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380436.

References

(1) Dekic, B. R.; Radulovic, N. S.; Dekic, V. S.; Vukicevic, R. D.; Palic, R. M. *Molecules* **2010**, *15*, 2246.
(2) Di Braccio, M.; Grossi, G.; Roma, G.; Marzano, C.; Baccichetti, F.; Simonato, M.; Bordin, F. *Farmaco* **2003**, *58*, 1083.
(3) Dong, Y.; Nakagawa-Goto, K.; Lai, C.-Y.; Morris-Natschke, S. L.; Bastow, K. F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4085.
(4) Roma, G.; Braccio, M. D.; Carrieri, A.; Grossi, G.; Leoncini, G.; Grazia Signorello, M.; Carotti, A. *Bioorg. Med. Chem.* **2003**, *11*, 123.
(5) Zhu, P. J.; Hobson, J. P.; Southall, N.; Qiu, C.; Thomas, C. J.; Lu, J.; Inglese, J.; Zheng, W.; Leppla, S. H.; Bugge, T. H.; Austin, C. P.; Liu, S. *Bioorg. Med. Chem.* **2009**, *17*, 5139.
(6) (a) Peng, S.; Wang, L.; Huang, J.; Sun, S.; Guo, H.; Wang, J. *Adv. Synth. Catal.* **2013**, *355*, 2550. (b) Lin, C.-H.; Yang, D.-Y. *Org. Lett.* **2013**, *15*, 2802. (c) Iaroshenko, V. O.; Erben, F.; Mkrtchyan, S.; Hakobyan, A.; Vilches-Herrera, M.; Dudkin, S.; Bunescu, A.; Villinger, A.; Sosnovskikh, V. Y.; Langer, P. *Tetrahedron* **2011**, *67*, 7946. (d) Liao, Y.-X.; Kuo, P.-Y.; Yang, D.-Y. *Tetrahedron Lett.* **2003**, *44*, 1599. (e) Trkovnik, M.; Kalaj, V.; Kitan, D. *Org. Prep. Proced. Int.* **1987**, *19*, 450.
(7) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, J. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474.
(8) (a) Radanyi, C.; Le, B. G.; Messaoudi, S.; Bouclier, C.; Peyrat, J.-F.; Brion, J.-D.; Marsaud, V.; Renoir, J.-M.; Alami, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2495. (b) Burlison, J. A.; Neckers, L.; Smith, A. B.; Maxwell, A.; Blagg, B. S. J. *J. Am. Chem. Soc.* **2006**, *128*, 15529. (c) Marcu, M. G.; Schulte, T. W.; Neckers, L. *J. Natl. Cancer Inst.* **2000**, *92*, 242.
(9) Cioc, R.; Ruijter, E.; Orru, R. *Green Chem.* **2014**.
(10) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
(11) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.
(12) Castellano, T. G.; Neo, A. G.; Marcaccini, S.; Marcos, C. F. *Org. Lett.* **2012**, *14*, 6218.
(13) Stefanou, V.; Matiadis, D.; Melagraki, G.; Afantitis, A.; Athanasellis, G.; Igglessi-Markopoulou, O.; McKee, V.; Markopoulos, J. *Molecules* **2011**, *16*, 384.
(14) For a detailed description of the crystal structure, see the Supporting Information.
(15) Savel'ev, V. L.; Artamonova, O. S.; Troitskaya, V. S.; Vinokurov, V. G.; Zagorevskii, V. A. *Chem. Heterocycl. Compd.* **1973**, *9*, 816.