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Pseudo-Five-Component Reaction between 3-Formylchromones, Meldrum's Acid, Isocyanides and Primary Arylamines: Diversity-Oriented Synthesis of Novel Chromone-Containing Peptidomimetics

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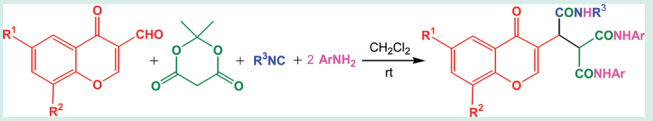
Supporting Information

ABSTRACT: An efficient and practical method has been developed for the diversity-oriented synthesis of chromone-containing tripeptides via pseudo-five-component reaction between 3-formylchromones, Meldrum's acid, isocyanides and primary aromatic amines for the generation of a wide range of structurally interesting and pharmacologically significant compounds at ambient temperature. It is worth mentioning that in the course of this reaction, five new bonds (two C−C bonds, two C−N bonds and one C═O bond) are formed. In the present reaction three amide bonds are newly formed.



KEYWORDS: 3-formylchromone, isocyanide, Meldrum's acid, multicomponent reaction, triamide

INTRODUCTION

The peptide bond is an important functional group in organic chemistry, biochemistry, and medicine.[1] Peptides play crucial roles in the human body and other organisms.[2] Among them, di- and tripeptides and their analogues have exhibited a wide spectrum of important bioactivities such as antibacterial,[3] antitumor,[4] anticarcinogenic,[5] neuroprotective,[6] and antidiabetic[7] activities. Because of the good affinity of the peptides toward cells and nucleic acids, the introduction of a peptide segment onto drugs can facilitate their interactions with cells and tissues and thereby provide a robust strategy to design new drugs or lead compounds. Heterocyclic compounds have distinguished themselves from other small molecules because of their profound bioactivities. The practice of attaching heterocyclic skeletons and peptides onto one molecule has received much attention from synthetic and medicinal chemists for the discovery of novel compounds with unknown or improved pharmacological properties.[8,5b] However, the scopes of bioactive small molecules, especially heterocyclic molecules used for incorporation with tripeptide segments are rather limited. As a result, it is a formidable and urgent task to synthesize a new class of tripeptide compounds containing bioactive skeletons.

The chromone moiety forms the nucleus of a class of heterocyclic natural products called flavanoids that occur naturally in fruits, vegetables, nuts, seeds, flowers, and barks.[9−11] They are an integral part of the human diet and have been reported to exhibit a wide range of biological effects.[12−19] Chromone is also part of pharmacophores of a large number of molecules of medicinal significance[20,21] including anticancer agents such as psorospermin and pluramycin A.[22,23] Some other recent examples include hetero- and carbo-annulated chromone derivatives which are useful antiplatelet,[24] antifungal[25] and anticancer agents.[26] They display not only spasmolytic, diuretic, clotting, antiviral, antitumoral, and antianaphylactic activity, but can also be used as pigments, photoactive materials, and biodegradable agrochemicals.[27]

Considering the versatile bioactivities of the above-mentioned structures, we hypothesize that the integration of chromone scaffold with a triamide segment may result in the discovery of new drug candidates with unknown bioactivities. However, the design of triamide compounds implanted with chromone frameworks for medicinal purpose has been less recognized. Therefore, the development of a facile approach to access these novel targets with structural diversity is highly desirable and valuable for medicinal chemistry and drug discovery.

Peptides are traditionally synthesized by the reaction of amines with activated carboxylic acid derivatives.[28] Among the protocols for the synthesis of peptides, one of the important methods is the Ugi four-component reaction (U-4CR).[29] The most commonly used U-4CR, in which a carboxylic acid, an amine, a carbonyl compound and an isocyanide are reacted to result in peptide-like products, has come into widespread use for generating large collections of molecules in combinatorial synthesis. Of notable outcome, although the Ugi four-component condensation was successfully performed by employing carboxylic acids as starting materials, in the course of our investigations[30] into the reactions between isocyanides and carbonyl compounds in

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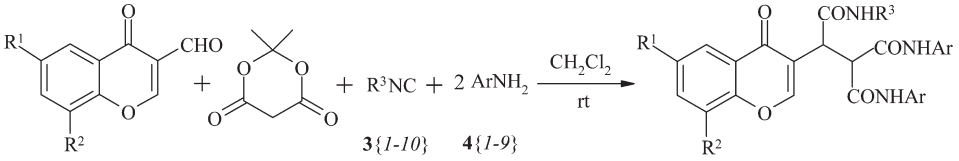
Scheme 1. Synthesis of Tripeptide-Bound Chromones 5



R^1 = H, Me, Cl
R^2 = H, Cl

1: 3-Formylchromones (Fig.1)
3: Isocyanids (Fig. 2)
4: Arylamines (Fig 3)

R^3 = cyclohexyl, *tert*-butyl, *n*-butyl, benzyl, *tert*-octyl, tosylmethyl, 2,6-dimethylphenyl, 2-naphthyl, -$CH_2CH_2CH_2Ph$, -CH_2COOMe
$ArNH_2$ = aniline, *p*-toluidine, *o*-toluidine, *p*-ethylaniline, *m*-nitroaniline, *o*-nitroaniline, 2,4-dimethoxyaniline, *p*-flouroaniline, 1-naphthylamine

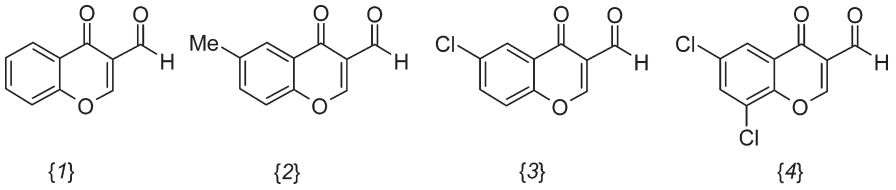


Figure 1. 3-Formylchromones **1**{*1*−*4*}.

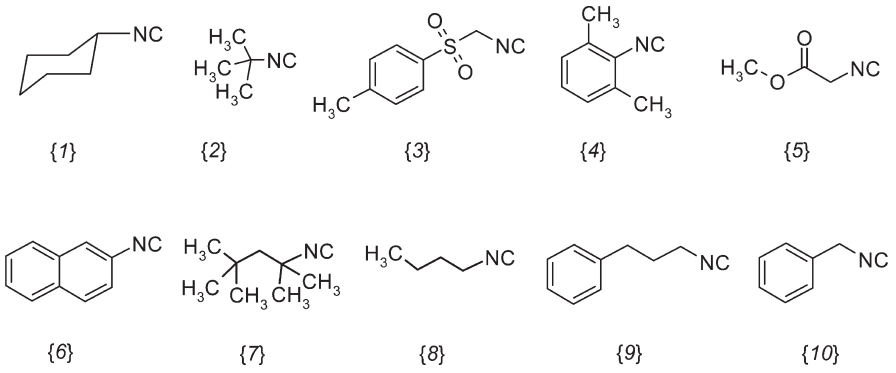


Figure 2. Isocyanides **3**{*1*−*10*}.

presence of CH-acids it is found that one of the useful modifications of this synthetic methodology can be the use of Meldrum's acid as the acid component. We envisaged that the combination of a chromone system with the peptide bonds would allow the development of a new class of biologically active molecules and useful synthetic building blocks in organic and medicinal chemistry.

RESULTS AND DISCUSSION

When a mixture of 3-formylchromones **1** and Meldrum's acid **2** as acid component in dry CH_2Cl_2 is treated with primary arylamines **4** in the presence of alkyl or aryl isocyanides **3** the reaction leads to N^2-alkyl or aryl-2-(4-oxo-4*H*-chromen-3-yl)-N^1,N^1-diarylethane-1,1,2-tricarboxamide derivatives **5**. The reaction allows the creation of three peptide bonds in a single operation.

The elucidation of the structure of **5** using ^{1}H and ^{13}C NMR spectroscopic data is discussed with **5**{*1,1,1*} as an example. The ^{1}H NMR spectrum of **5**{*1,1,1*} consisted of multiplet signals for the cyclohexyl rings (δ_H 0.91−1.58 ppm) and the NH−C*H* resonance (δ_H 3.30−3.42 ppm) and an AB system (J_{AB} = 11.6 Hz) for the two methine (δ_H 4.41 and 4.52 ppm) protons. A fairly broad doublet resonance (δ_H 7.99 ppm) was observed for the cyclohexyl-*NH* group and the aromatic protons gave rise to

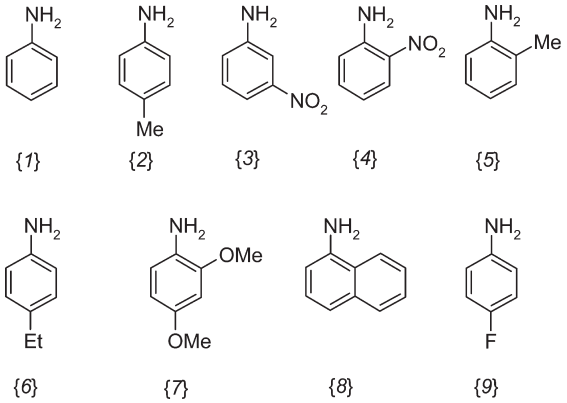


Figure 3. Arylamines **4**{*1*−*9*}.

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multiplets in the aromatic region of the spectrum (δ_H 6.94−7.74 ppm). The vinylic methine gives rise to a sharp singlet signal (δ_H 8.37 ppm). Two broad singlets (δ_H 9.76 and 9.97 ppm) were observed for the two Ph-*NH* protons. The ^{1}H decoupled ^{13}C NMR spectrum of **5**{*1,1,1*} showed 26 distinct resonances in agreement with the suggested structure. The ^{1}H and ^{13}C NMR spectra of **5**{*1,2,1*}-**5**{*4,1,1*} are similar to those of **5**{*1,1,1*} except for the R^1, R^2, R^3 or Ar groups, which exhibit characteristic signals with appropriate chemical shifts.

The formation of tripeptide-bound chromone **5** could be accounted for by a plausible reaction pathway outlined in Scheme 2. The reaction may be rationalized as by initial formation of conjugated electron-deficient heterodiene by *Knoevenogel* condensation of the 3-formylchromone **1** and Meldrum's acid **2**, followed by a [1 + 4] cycloaddition reaction[32] with isocyanide **3** to afford an iminolactone intermediate **7**. It is well-known that acylated Meldrum's acids[33] and also arylidene Meldrum's acids[34] can readily lose acetone in the presence of nucleophiles, so it is reasonable to assume that the reaction of fused iminolactone **7** with arylamine and subsequently loss of acetone from **8** leads to formation of iminolactone **8**. Finally, nucleophilic attack of the second molecule of arylamine to the activated carbonyl moiety of **8**, yields product **5**.

To gain an insight into a possible reaction mechanism, the 5-[(4-oxo-4*H*-chromen-3-yl)methylene]-Meldrum's acid as a representative Knoevenagel condensation adduct was synthesized separately by the condensation of 3-formylchromone and Meldrum's acid.[31] Then we examined the reaction of the isolated 5-[(4-oxo-4*H*-chromen-3-yl)methylene]-Meldrum's acid with one equivalent of cyclohexyl isocyanide in the presence of two equivalents of aniline in anhydrous CH_2Cl_2 at room temperature, and we obtained the product **5**{*1,1,1*} in excellent yield.

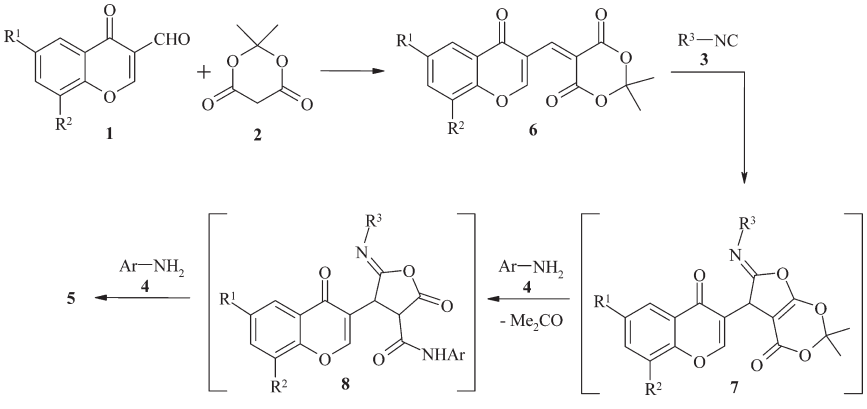
To survey the generality and scope of this one-pot pseudo five-component protocol, the methodology was applied to the synthesis of a variety of N^2-alkyl or aryl-2-(4-oxo-4*H*-chromen-3-yl)-N^1,N^1-diarylethane-1,1,2-tricarboxamide derivatives **5**{*1,1,1*}−**5**{*4,1,1*}. With the optimal condition in hand, we extended the reaction to other 3-formylchromone compounds, and results are indicated in Table 1. Four derivatives of 3-formylchromones afforded tripeptide-bound chromones from good to excellent isolated yields. The yield of the product seems to be affected by the nature of substituents at C-6 and C-8, and increases when electron- withdrawing substituents are present. To explore the scope of this reaction with respect to reactive isocyanides, we have examined ten alkyl or aryl isocyanides. We have found that the reaction proceeds very efficiently with both sterically hindered and less hindered alkyl or aryl isocyanides. A variety of aryl amines carrying different functional groups were subjected to the coupling reactions and in all cases the desired product was obtained in reasonable yields. It was observed that under similar conditions, a wide range of anilines containing electron-donating as well as electron-withdrawing groups, such as methoxy, methyl, ethyl, phenyl, fluoro, and nitro underwent condensation with good isolated yields. It seems that the groups attached on the aromatic ring of aryl amine do not affect the reaction significantly. Encouraged by the above results, we continued our task to explore the reactivity of different aliphatic primary and secondary amines with 3-formylchromone, Meldrum's acid and cyclohexyl isocyanide under similar reaction conditions. The reaction

Table 1. Pseudo-Five-Component Condensation Reactions of 3-Formylchromones, Meldrum's Acid and Alkyl or Aryl Isocyanides in the Presence of Primary Arylamines in Anhydrous Dichloromethane

entry	formylchromone	isocyanide	arylamine	product	yield [a] (%)
1	1{*1*}	3{*1*}	4{*1*}	5{*1,1,1*}	95
2	1{*1*}	3{*2*}	4{*1*}	5{*1,2,1*}	86
3	1{*1*}	3{*3*}	4{*1*}	5{*1,3,1*}	78
4	1{*1*}	3{*4*}	4{*1*}	5{*1,4,1*}	78
5	1{*1*}	3{*5*}	4{*2*}	5{*1,5,2*}	83
6	1{*1*}	3{*1*}	4{*3*}	5{*1,1,3*}	80
7	1{*1*}	3{*3*}	4{*4*}	5{*1,3,4*}	75
8	1{*2*}	3{*1*}	4{*2*}	5{*2,1,2*}	88
9	1{*2*}	3{*3*}	4{*2*}	5{*2,3,2*}	85
10	1{*2*}	3{*6*}	4{*5*}	5{*2,6,5*}	90
11	1{*2*}	3{*3*}	4{*6*}	5{*2,3,6*}	78
12	1{*2*}	3{*1*}	4{*6*}	5{*2,1,6*}	87
13	1{*2*}	3{*7*}	4{*7*}	5{*2,7,7*}	75
14	1{*2*}	3{*8*}	4{*8*}	5{*2,8,8*}	90
15	1{*2*}	3{*7*}	4{*3*}	5{*2,7,3*}	92
16	1{*3*}	3{*9*}	4{*5*}	5{*3,9,5*}	87
17	1{*3*}	3{*10*}	4{*5*}	5{*3,10,5*}	86
18	1{*3*}	3{*7*}	4{*9*}	5{*3,7,9*}	84
19	1{*4*}	3{*5*}	4{*8*}	5{*4,5,8*}	77
20	1{*4*}	3{*1*}	4{*1*}	5{*4,1,1*}	80

[a] Refers to purified yield, which is >95% as determined by ^{1}H NMR spectroscopy.

Scheme 2. Possible Mechanism for the Formation of Products 5



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system did not work well with aliphatic amines, such as *iso*-butylamine, benzylamine, 1-adamantylamine, morpholine, and diethyl amine, to generate the corresponding desired products, but only an intractable mixture was obtained in each case. This would be probably attributed to the higher nucleophilicity of the aliphatic primary and secondary amines toward the formylchromones-Meldrum's acid *Knoevenogel* adducts than aryl amines which can compete with isocyanides in attacking the above-mentioned adducts to produce complex reaction mixtures.

CONCLUSION

In summary, we have developed a pseudo-five-component condensation reaction for the formation of biologically interesting tripeptide-bound chromones, which is one-pot and atom and step economic. The reaction proceeds along a rather complex pathway but it is very simple from the experimental point of view and allows the creation of three peptide groups with concomitant formation of five new C−C and C-heteroatom bonds in a single operation.

EXPERIMENTAL PROCEDURES

General Procedure for Preparation of the Tripeptide-Bound Chromone Derivatives 5. The appropriate 3-formylchromone (0.5 mmol) and Meldrum's acid (0.5 mmol) were dissolved in 5 mL of anhydrous dichloromethane, and the mixture was stirred at room temperature for 3 h. To this solution arylamine (1.0 mmol) and the isocyanide (0.5 mmol) were added successively. The reaction mixture was stirred at ambient temperature for 12 h, and the completion of reaction was confirmed by TLC (EtOAc/*n*-hexane 1:1). Subsequently, the precipitated product was filtered off and the solid washed with diethyl ether several times to give **5**. The crude product was purified by crystallization from hot ethanol to yield pure **5**{*1,1,1*}−**5**{*4,1,1*}. The air-dried product thus obtained showed a single spot on TLC and was pure enough for all analytical purposes.

*N^2-Cyclohexyl-2-(4-oxo-4H-chromen-3-yl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5**{1,1,1}):* White powder (0.255 g, 95%); mp 278−280 °C; R_f (50% *n*-hexane/EtOAc) 0.52; IR (KBr) (ν_{max}, cm^{-1}) 3294 (N−H), 1680 and 1647 (C═O), 1600 (C═C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 0.91−1.58 (10 H, m, 5 CH_2), 3.30−3.42 (1 H, m, NCH), 4.41 and 4.52 (2 H, AB-system, $^3J_{HH}$ = 11.6 Hz, CH−CH), 6.94−7.74 (14 H, m, arom.), 7.99 (1 H, d, $^3J_{HH}$ = 7.6 Hz, NH), 8.37 (1 H, s, ═CH−O), 9.76 and 9.97 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.9, 170.0, 167.4, 166.9, 157.6, 156.7, 140.2, 139.6, 135.5, 130.0, 126.8, 126.3, 125.0, 124.7, 124.5, 121.3, 120.4, 120.3, 119.6, 56.6, 49.1, 43.9, 33.3, 26.4, 25.8, 25.7; Anal. Calcd for $C_{32}H_{31}N_3O_5$ (537.60) C 71.49, H 5.81, N 7.82%; Found C 71.32, H 5.79, N 7.85%.

*N^2-(tert-Butyl)-2-(4-oxo-4H-chromen-3-yl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5**{1,2,1}):* White powder (0.220 g, 86%); mp 286−288 °C; R_f (50% *n*-hexane/EtOAc) 0.54; IR (KBr) (ν_{max}, cm^{-1}) 3302 and 3291 (N−H), 1679, 1649, and 1635 (C═O), 1600 (C═C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 1.09 (9H, s, 3 Me), 4.43 and 4.53 (2 H, AB-system, $^3J_{HH}$ = 11.7 Hz, CH−CH), 6.95−8.01 (15 H, m, arom. +NH), 8.38 (1 H, s, ═CH−O), 9.86 and 9.90 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.9, 170.3, 167.2, 166.9, 157.0, 156.6, 140.1, 139.6, 135.6, 130.1, 130.0, 126.9, 126.4, 125.0, 124.8, 124.4, 121.6, 120.5, 120.4, 119.6, 57.1, 51.5, 43.9, 29.6; Anal. Calcd. for $C_{30}H_{29}N_3O_5$ (511.56) C 70.43, H 5.71, N 8.21%; Found C 70.61, H 5.69, N 8,18%.

*N^2-{[(4-Methylphenyl)sulfonyl]methyl}-2-(4-oxo-4H-chromen-3-yl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5**{1,3,1}):* Cream powder (0.243 g, 78%); mp 276−278 °C; R_f (30% *n*-hexane/EtOAc) 0.65; IR (KBr) (ν_{max}, cm^{-1}) 3340 and 3312 (N−H), 1692, 1656, and 1630 (C═O), 1599 (C═C), 1324 and 1143 (SO_2); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 2.18 (3 H, s, Me), 4.42−4.53 (4 H, m, CH_2 + CH−CH), 6.92−8.65 (20 H, arom. +NH + ═CH−O), 9.73 and 9.96 (2 H, 2 br s, 2 NH), ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.7, 171.3, 166.9, 166.4, 157.9, 156.7, 145.4, 140.1, 139.5, 136.0, 135.6, 130.5, 130.1, 130.0, 129.5, 127.0, 126.4, 125.0, 124.8, 124.5, 120.4, 120.3, 119.6, 61.7, 55.7, 43.5, 22.3; Anal. Calcd for $C_{34}H_{29}N_3O_7S$ (623.67) C 65.48, H, 4.69; N, 6.74%; Found C 65.62, H 4.70, N 6.76%.

*N^2-(2,6-Dimethylphenyl)-2-(4-oxo-4H-chromen-3-yl)-N^1,N^1-diphenylethane-1,1,2-tricarboxamide (**5**{1,4,1}):* White powder (0.218 g, 78%); mp 280−282 °C; R_f (30% *n*-hexane/EtOAc) 0.80; IR (KBr) (ν_{max}, cm^{-1}) 3271 and 3295 (N−H), 1676 and 1647 (C═O), 1600 (C═C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 1.94 (6 H, s, 2 Me), 4.69 and 4.72 (2 H, AB-system, $^3J_{HH}$ = 6.0 Hz, CH−CH), 6.93−7.58 (17 H, m, arom.), 8.52 (1 H, s, ═CH−O), 9.14 (1 H, br s, NH), 9.80 and 10.05 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 177.1, 169.7, 167.3, 166.7, 158.1, 156.8, 140.2, 139.6, 136.8, 136.2, 135.6, 130.0, 128.8, 127.7, 126.9, 126.3, 125.0, 124.7, 124.6, 121.1, 120.4, 120.2, 119.7, 56.3, 44.2, 19.0; Anal. Calcd for $C_{34}H_{29}N_3O_5$ (559.61) C 72.97, H 5.22, N 7.51%; Found C 73.16, H 5.20, N 7.48%.

*Methyl N-[4-[(4-methylphenyl)amino]-3-{[(4-methylphenyl)-amino]carbonyl}-4-oxo-2-(4-oxo-4H-chromen-3-yl)butanoyl]-glycinate (**5**{1,5,2}):* White powder (0.230 g, 83%); mp 278−280 °C; R_f (50% *n*-hexane/EtOH) 0.81; IR (KBr) (ν_{max}, cm^{-1}) 3330 and 3295 (N−H), 1758, 1699, 1656, and 1633 (C═O), 1607 (C═C); ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 2.13 and 2.21 (6 H, 2 s, 2 Me), 3.47 (3 H, s, OMe), 3.71 and 3.76 (2 H, m, CH_2), 4.51 (2 H, s, CH−CH), 6.95−8.01 (13 H, m, arom. + NH), 8.42 (1 H, s, ═CH−O), 9.59 and 9.92 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.9, 171.7, 171.3, 167.1, 166.5, 157.8, 156.8, 137.8, 137.1, 135.5, 133.9, 133.5, 130.4, 130.3, 126.8, 126.4, 124.5, 121.0, 120.4, 120.3, 119.6, 56.0, 52.8, 43.5, 42.1, 21.7, 21.6; Anal. Calcd. for $C_{31}H_{29}N_3O_7$ (555.57) C 67.02, H 5.26,; N 7.56%; Found C 66.78, H 5.28, N 7.59%.

*N^2-Cyclohexyl-N^1,N^1-bis(3-nitrophenyl)-2-(4-oxo-4H-chromen-3-yl)ethane-1,1,2-tricarboxamide (**5**{1,1,3}):* Light orange powder (0.251 g, 80%); mp 264−266 °C; R_f (30% *n*-hexane/EtOAc) 0.74; IR (KBr) (ν_{max}, cm^{-1}) 3294 (N−H), 1698 and 1625 (C═O), 1599 (C═C), 1530 and 1349 (NO_2); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 0.09−1.59 (10 H, m, 5 CH_2), 3.38−3.43 (1H, m, NCH), 4.48 and 4.53 (2 H, AB-system, $^3J_{HH}$ = 11.2 Hz, CH−CH), 7.35−8.37 (13 H, m, arom. +NH), 8.60 (1 H, s, ═CH−O), 10.20 and 10.61 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.8, 170.0, 167.9, 167.5, 157.7, 156.7, 149.1, 149.0, 141.2, 140.5, 135.5, 131.5, 131.4, 126.8, 126.6, 126.5, 126.2, 124.4, 120.9, 119.6, 119.2, 114.8, 114.6, 57.3, 49.3, 43.8, 33.3, 26.4, 25.9, 25.7; Anal. Calcd. for $C_{32}H_{29}N_5O_9$ (627.60) C 61.24, H 4.66, N 11.16%; Found C 61.48, H 4.64, N 11.11%.

*N^2-{[(4-Methylphenyl)sulfonyl]methyl}-N^1,N^1-bis(2-nitrophenyl)-2-(4-oxo-4H-chromen-3-yl)ethane-1,1,2-tricarboxamide (**5**{1,3,4}):* White powder (0.268 g, 75%); mp 274−276 °C; R_f (50% *n*-hexane/EtOH) 0.36; IR (KBr) (ν_{max}, cm^{-1}) 3337 and 3312 (N−H), 1692, 1656, and 1630 (C═O), 1599 (C═C), 1526

and 1355 (NO_2), 1324 and 1143 (SO_2); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 2.17 (3 H, s, CH_3), 4.28−4.71 (4 H, m, CH−CH + SO_2CH_2), 6.95−8.07 (16 H, m, arom.), 8.19 (1 H, s, =CH−O), 8.87 (1 H, t, $^3J_{HH}$ = 6.7 Hz, CH_2NH), 10.25 and 10.41 (2 H, 2 s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.7, 172.4, 170.4, 167.1, 166.3, 156.9, 156.8, 156.0, 145.6, 135.9, 135.7, 135.6, 135.2, 132.3, 130.7, 130.5, 129.7, 129.5, 126.8, 126.4, 126.3, 126.2, 126.1, 126.0, 124.5, 122.4, 119.7, 61.7, 55.2, 39.3, 37.7, 22.3; Anal. Calcd for $C_{34}H_{27}N_5O_{11}S$ (713.67) C 57.22, H 3.81, N 9.81%; Found C 57.37, H 3.80; N 9.77%.

*N^2-Cyclohexyl-2-(6-methyl-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(4-methylphenyl)ethane-1,1,2-tricarboxamide (**5**{2,1,2}):* White powder (0.255 g, 88%); mp 294−296 °C; R_f (70% *n*-hexane/EtOAc) 0.74; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3291 (N−H), 1677 and 1646 (C=O), 1600 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 0.87−1.58 (10 H, m, 5 CH_2), 2.12, 2.20, and 2.38 (9 H, 3 s, 3 Me), 3.34−3.42 (1 H, m, NCH), 4.39 and 4.46 (2 H, AB-system, $^3J_{HH}$ = 11.4 Hz, CH−CH), 6.95−7.55 (11 H, m, arom.), 7.75 (1 H, br s, NH), 8.33 (1 H, s, =CH−O), 9.66 and 9.86 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 176.9, 170.1, 167.2, 166.7, 157.4, 154.1, 137.8, 137.1, 136.5, 136.4, 133.9, 133.6, 130.3, 125.5, 124.2, 121.1, 120.4, 119.4, 56.5, 49.0, 43.8, 33.3, 26.4, 25.8, 25.7, 21.8, 21.7, 21.6; Anal. Calcd for $C_{35}H_{37}N_3O_5$ (579.68) C 72.52, H 6.43, N 7.25%; Found C 72.23, H 6.40, N 7.29%.

*2-(6-Methyl-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(4-methylphenyl)-N^2-{[(4-methylphenyl)sulfonyl]methyl}ethane-1,1,2-tricarboxamide (**5**{2,3,2}):* White powder (0.283 g, 85%); mp 252−254 °C; R_f (25% *n*-hexane/EtOAc) 0.70; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3319 (N−H), 1688, 1647, and 1630 (C=O), 1600 (C=C), 1321 and 1143 (SO_2); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 1.94 (12 H, 4 s, 4 Me), 4.40−4.50 and 4.67−4.70 (4 H, 2 m, CH−CH + CH_2), 6.94−7.79 (15 H, m, arom.), 8.23 (1 H, s, =CH−O), 8.60 (1 H, t, $^3J_{HH}$ = 6.0 Hz, NH), 9.59 and 9.82 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.6, 171.4, 166.7, 157.7, 155.0, 145.3, 137.7, 137.0, 136.7, 136.5, 136.0, 134.0, 133.7, 130.5, 130.4, 130.3, 129.4, 125.6, 124.3, 120.3, 120.2, 119.4, 61.6, 55.6, 43.4, 22.3, 21.8, 21.7, 21.6; Anal. Calcd for $C_{37}H_{35}N_3O_7S$ (665.75) C 66.75, H 5.30, N 6.31%; Found C 66.94, H 5.33, N 6.26%.

*2-(6-Methyl-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(2-methylphenyl)-N^2-2-naphthylethane-1,1,2-tricarboxamide (**5**{2,6,5}):* White powder (0.280 g, 90%); mp 274−276 °C; R_f (25% *n*-hexane/EtOAc) 0.79; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3281 (N−H), 1672 and 1641 (C=O), 1600 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 1.88, 2.20, and 2.36 (9 H, 3 s, 3 Me), 4.61 and 4.90 (2 H, AB-system, $^3J_{HH}$ = 11.2 Hz, CH−CH), 7.04−8.14 (18 H, m, arom.), 8.48 (1 H, s, =CH−O), 9.40, 9.43, and 9.92 (3 H, 3 s, 3 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 177.1, 170.3, 167.7, 167.2, 158.5, 155.1, 137.9, 137.3, 136.9, 136.7, 136.5, 134.5, 132.7, 132.5, 131.7, 131.6, 131.0, 129.4, 128.7, 128.5, 127.6, 127.3, 126.8, 126.5, 125.8, 125.7, 125.6, 125.5, 124.4, 121.6, 120.4, 119.4, 116.9, 54.9, 45.7, 21.7, 19.0, 18.6; Anal. Calcd for $C_{39}H_{33}N_3O_5$ (623.69) C 75.10, H 5.33 N 6.74%; Found C 74.87, H 5.35, N 6.71%.

*N^1,N^1-Bis(4-ethylphenyl)-2-(6-methyl-4-oxo-4H-chromen-3-yl)-N^2-{[(4-methylphenyl)sulfonyl]methyl}ethane-1,1,2-tricarboxamide (**5**{2,3,6}):* White powder (0.270 g, 78%); mp 254−256 °C; R_f (30% *n*-hexane/EtOAc) 0.65; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3308 (N−H), 1677, 1655, and 1640 (C=O), 1603 (C=C), 1328 and 1144 (SO_2); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 0.97−1.08 (6 H, m, 2 CH_2CH_3), 2.14 (3 H, s, CH_3), 2.36−2.48 (7 H, m, 2 CH_2CH_3 + CH_3), 4.38−4.48 (4 H, 2 m, CH−CH + SO_2CH_2), 6.91−7.76 (18 H, m, arom.), 8.21 (1 H, s, =CH−O), 8.58 (1 H, t, $^3J_{HH}$ = 5.4 Hz, NH), 9.58 and 9.81 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.6, 171.3, 166.7, 166.2, 157.7, 154.9, 145.3, 140.4, 140.2, 137.8, 137.2, 136.6, 136.5, 136.0, 130.5, 129.4, 129.2, 129.1, 125.6, 124.3, 120.4, 120.3, 120.2, 119.4, 61.6, 55.5, 43.4, 28.8, 28.7, 22.2, 21.7, 17.0, 16.9; Anal. Calcd for $C_{39}H_{39}N_3O_7S$ (693.80) C 67.51, H, 5.67, N 6.06%; Found C 67.70, H 5.65; N 6.02%.

*N^2-Cyclohexyl-N^1,N^1-bis(4-ethylphenyl)-2-(6-methyl-4-oxo-4H-chromen-3-yl)ethane-1,1,2-tricarboxamide (**5**{2,1,6}):* White powder (0.264 g, 87%); mp 270−272 °C; R_f (30% *n*-hexane/EtOAc) 0.83; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3314 (N−H), 1675 and 1652 (C=O), 1609 (C=C); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H 1.02−2.16 (10, m, 5 CH_2), 1.11 (6 H, t, 2 CH_2CH_3), 2.43−2.52 (4 H, m, 2 CH_2CH_3), 3.57 (1 H, s, NCH), 5.19 and 5.29 (2 H, AB-system, $^3J_{HH}$ = 11.3 Hz, CH−CH), 6.79−7.57 (12 H, m, =CH−O + arom.), 9.03, 10.07, and 10.51 (3 H, 3 br s, 3 NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 178.2, 171.9, 167.6, 167.1, 158.2, 155.5, 140.7, 140.1, 137.2, 137.0, 135.7, 135.6, 128.6, 128.3, 125.9, 124.2, 121.3, 121.2, 121.0, 118.7, 56.0, 49.7, 45.3, 33.3, 33.2, 29.1, 26.2, 25.5, 25.4, 21.5, 16.59; Anal. Calcd for $C_{37}H_{41}N_3O_5$ (607.73) C 73.12, H 6.80, N 6.91%; Found C 72.88, H 6.83, N 6.95%.

*N^1,N^1-Bis(2,4-dimethoxyphenyl)-2-(6-methyl-4-oxo-4H-chromen-3-yl)-N^2-(1,1,3,3-tetramethylbutyl)ethane-1,1,2-tricarboxamide (**5**{2,7,7}):* Dark violet powder (0.263 g, 75%); mp 238−240 °C; R_f (50% *n*-hexane/EtOAc) 0.46; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3218 (N−H), 1658 and 1614 (C=O), 1574 (C=C); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H 0.78 (9 H, s, $C(Me)_3$), 1.24 and 1.25 (6 H, 2 s, $C(Me)_2$), 1.50 and 1.72 (2 H, AB-system, $^3J_{HH}$ = 14.8 Hz, CH_2), 2.40 (3 H, s, Me), 3.68, 3.70, 3.76, and 3.78 (12 H, 4 s, 4 OMe), 4.26 and 4.71 (2 H, AB-system, $^3J_{HH}$ = 12.0 Hz, CH−CH), 6.26−8.21 (9 H, m, arom.), 6.51 (1 H, br s, NH), 8.25 (1 H, s, =CH−O), 8.44 and 8.81 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 178.1, 169.7, 167.6, 165.8, 157.7, 155.9, 155.2, 151.3, 150.7, 136.0, 135.9, 126.0, 124.0, 122.4, 121.9, 121.7, 121.3, 119.8, 118.9, 104.5, 104.3, 99.4, 99.3, 57.8, 56.6, 56.5, 56.3, 56.2, 52.1, 45.3, 32.2, 32.0, 29.8, 29.6, 21.7; Anal. Calcd for $C_{39}H_{47}N_3O_9$ (701.80) C 66.74, H 6.75, N 5.99%; Found C 66.50, H 6.79, N 6.01%.

*N^2-Butyl-2-(6-methyl-4-oxo-4H-chromen-3-yl)-N^1,N^1-di-1-naphthylethane-1,1,2-tricarboxamide (**5**{2,8,8}):* Light pink powder (0.281 g, 90%); mp 240−242 °C; R_f (30% *n*-hexane/EtOAc) 0.72; IR (KBr) ($\nu_{max,}$ cm^{-1}) 3280 (N−H), 1675, 1649, and 1623 (C=O), 1600 (C=C); ^{1}H NMR (400.1 MHz, DMSO-d_6) δ_H 0.73 (3 H, t, $^3J_{HH}$ = 7.2 Hz, Me), 1.14 (2 H, sex., $^3J_{HH}$ = 7.1 Hz, CH_2CH_3), 1.28 (2 H, quin., $^3J_{HH}$ = 7.1 Hz, $CH_2CH_2CH_3$), 2.39 (3 H, s, Me), 3.00 (2 H, q, $^3J_{HH}$ = 6.4 Hz, NCH_2), 4.48 and 5.05 (2 H, 2 d, $^3J_{HH}$ = 11.2 Hz, CH−CH) 7.14−8.18 (18 H, m, arom. +NH), 8.46 (1 H, s, =CH−O), 9.93 and 10.07 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 177.1, 171.1, 168.4, 168.1, 157.8, 155.2, 136.6, 136.4, 135.0, 134.9, 134.7, 134.1, 129.5, 129.4, 129.0, 127.4, 127.3, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 125.6, 124.5, 123.9, 123.3, 122.8, 122.6, 121.3, 119.4, 55.7, 44.4, 39.9, 32.4, 21.7, 20.6, 14.9; Anal. Calcd for $C_{39}H_{35}N_3O_5$ (625.71) C 74.86, H 5.64, N 6.72%; Found C 74.63, H 5.62, N 6.75%.

*2-(6-Methyl-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(3-nitrophenyl)-N^2-(1,1,3,3-tetramethylbutyl)ethane-1,1,2-tricarboxamide (**5**{2,7,3}):* White powder (0.309 g, 92%); mp 276−278 °C; R_f

(50% *n*-hexane/EtOAc) 0.58; IR (KBr) (ν_{max}, cm^{-1}) 3286 (N−H), 1708, 1655, and 1619 (C═O), 1604 (C═C), 1530 and 1351 (NO_2); ^1H NMR (400.1 MHz, DMSO-d_6) δ_H 0.71 (9 H, s, $C(Me)_3$), 1.13 (6 H, s, $C(Me)_2$), 1.48−1.60 (2 H, AB-system, $^3J_{HH}$ = 24.0 Hz, CH_2), 2.32 (3 H, s, Me), 4.45−4.62 (2 H, AB-system, $^3J_{HH}$ = 9.2 Hz, CH−CH), 7.15 (1 H, br s, NH), 7.45−8.62 (11 H, m, arom.), 8.35 (1 H, s, ═CH−O), 10.31 and 10.46 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 169.7, 167.6, 167.4, 156.7, 155.0, 149.1, 141.2, 140.5, 136.7, 136.5, 131.5, 126.7, 125.5, 119.6, 119.3, 114.8, 57.5, 55.6, 51.7, 43.8, 32.3, 32.2, 30.3, 29.7, 21.6; Anal. Calcd for $C_{35}H_{37}N_5O_9$ (671.69) C 62.58, H 5.55, N 10.43%; Found C 62.74, H 5.58, N 10.39%.

*2-(6-Chloro-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(2-methylphenyl)-N^2-(3-phenylpropyl)ethane-1,1,2-tricarboxamide (**5**{3,9,9}):* White powder (0.277 g, 87%); mp 240−242 °C; R_f (50% *n*-hexane/EtOAc) 0.63; IR (KBr) (ν_{max}, cm^{-1}) 3283 (N−H), 1673 and 1651 (C═O), 1600 (C═C); ^1H NMR (400.1 MHz, DMSO-d_6) δ_H 1.55−1.56 (2 H, m, CH_2CH_2Ph), 1.89 and 2.20 (6 H, 2 s, 2 Me), 2.40 (2 H, t, $^3J_{HH}$ = 7.7 Hz, CH_2CH_2Ph), 2.92−3.07 (2 H, m, NCH_2), 4.39 and 4.75 (2 H, AB-system, $^3J_{HH}$ = 11.2 Hz, CH−CH), 6.97−7.97 (17 H, m, arom. + NH), 8.47 (1 H, s, ═CH−O), 9.30 and 9.36 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.0, 170.8, 167.7, 167.3, 158.4, 155.4, 143.2, 137.5, 136.9, 135.5, 132.6, 132.5, 131.6, 131.3, 129.5, 129.4, 127.3, 127.2, 126.9, 126.7, 126.4, 125.8, 125.7, 125.4, 125.2, 122.2, 121.6, 55.1, 44.4, 39.7, 33.6, 32.3, 19.0, 18.5; Anal. Calcd for $C_{37}H_{34}ClN_3O_5$ (636.13) C 69.86, H 5.39, N 6.61%; Found C 70.06, H 5.36, N 6.59%.

*N^2-Benzyl-2-(6-chloro-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(2-methylphenyl)ethane-1,1,2-tricarboxamide (**5**{3,10,9}):* White powder (0.261 g, 86%); mp 278−280 °C; R_f (50% *n*-hexane/EtOAc) 0.55; IR (KBr) (ν_{max}, cm^{-1}) 3281 (N−H), 1676 and 1653 (C═O), 1600 (C═C); ^1H NMR (400.1 MHz, DMSO-d_6) δ_H 1.89 and 2.19 (6 H, 2 s, 2 Me), 4.19- 4.22 (2 H, m, CH_2), 4.45 and 4.81 (2 H, AB-system, $^3J_{HH}$ = 11.2 Hz, CH−CH), 6.98−7.99 (16 H, m, arom.), 8.20 (1 H, $^3J_{HH}$ = 5.9 Hz, NH), 8.48 (1 H, s, ═CH−O), 9.30 and 9.37 (2 H, 2 br s, 2 NH)); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 176.1, 171.0, 167.8, 167.2, 158.6, 155.4, 140.7, 137.5, 136.9, 135.5, 132.6, 132.4, 131.6, 131.5, 131.4, 129.3, 128.1, 127.8, 127.4, 127.3, 126.7, 126.4, 125.8, 125.7, 125.4, 125.1, 122.3, 121.4, 55.0, 44.5, 43.6, 19.0, 18.6; Anal. Calcd for $C_{35}H_{30}ClN_3O_5$ (608.08) C 69.13, H 4.97, N 6.91%; Found C 68.91, H 4.96, N 6.94%.

*2-(6-Chloro-4-oxo-4H-chromen-3-yl)-N^1,N^1-bis(4-fluorophenyl)-N^2-(1,1,3,3-tetramethylbutyl)ethane-1,1,2-tricarboxamide (**5**{3,7,10}):* White powder (0.267 g, 84%); mp 270−272 °C; R_f (50% *n*-hexane/EtOAc) 0.37; IR (KBr) (ν_{max}, cm^{-1}) 3329 and 3305 (N−H), 1702, 1655, and 1622 (C═O), 1598 (C═C); ^1H NMR (400.1 MHz, $CDCl_3$) δ_H 0.73 (9 H, s, $C(Me)_3$), 1.17−1.23 (6 H, m, $C(Me)_2$), 1.45−1.73 (2 H, m, CH_2), 4.85−4.90 (2 H, m, CH−CH), 6.67−7.62 (12 H, m, arom. + ═CH−O), 8.75 (1 H, br s, NH), 9.90 and 10.29 (2 H, 2 br s, 2 NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 177.0, 170.4, 167.0, 159.1, 155.4, 135.6, 135.2, 134.5, 132.5, 124.9, 123.1, 123.0, 122.6, 122.5, 121.1, 116.3, 116.1, 115.8, 115.5, 56.7, 56.1, 53.2, 32.2, 32.1, 29.9; Anal. Calcd for $C_{34}H_{34}ClF_2N_3O_5$ (638.10) C 64.00, H 5.37, N 6.59%; Found C 63.87, H 5.39, N 6.60%.

*Methyl N-{2-(6,8-Dichloro-4-oxo-4H-chromen-3-yl)-4-(1-naphthylamino)-3-[(1-naphthylamino)carbonyl]-4-oxobutanoyl}glycinate (**5**{4,5,8}):* Brown powder (0.268 g, 77%); mp 240−242 °C; R_f (50% *n*-hexane/EtOAc) 0.32; IR (KBr) (ν_{max}, cm^{-1}) 3273 (N−H), 1747, 1667, and 1655 (C═O), 1596 (C═C); ^1H NMR (400.1 MHz, DMSO-d_6) δ_H 3.31 (3 H, s, Me), 3.71−3.85 (2 H, m, CH_2), 4.61 and 5.06 (2 H, AB-system, $^3J_{HH}$ = 11.2 Hz, CH−CH), 7.21 (1 H, t, $^3J_{HH}$ = 7.2 Hz, NH), 7.43−8.46 (16 H, m, arom.), 8.69 (1 H, s, ═CH−O), 9.93 and 10.12 (2 H, 2 br s, 2 NH)); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 175.5, 171.5, 171.3, 168.2, 167.8, 158.7, 151.3, 135.1, 135.0, 134.9, 134.7, 134.0, 131.3, 129.6, 129.5, 129.0, 128.9, 127.4, 127.3, 127.2, 127.1, 126.9, 126.8, 126.7, 126.6, 125.0, 124.7, 123.8, 123.1, 122.8, 122.7, 121.8, 112.5, 55.2, 52.9, 44.0, 42.3; Anal. Calcd for $C_{37}H_{27}Cl_2N_3O_7$ (696.53) C 63.80, H 3.91, N 6.03%; Found C 63.98, H 3.90, N 6.05%.

*N^2-Cyclohexyl-2-(6,8-dichloro-4-oxo-4H-chromen-3-yl)-N^1,>N^1-diphenylethane-1,1,2-tricarboxamide (**5**{4,1,1}):* White powder (0.243 g, 80%); mp 277−279 °C; R_f (50% *n*-hexane/EtOAc) 0.75; IR (KBr) (ν_{max}, cm^{-1}) 3287 (N−H), 1679 and 1649 (C═O), 1599 (C═C); ^1H NMR (400.1 MHz, DMSO-d_6) δ_H 0.88−1.58 (10 H, m, 5 CH_2), 3.30−3.42 (1 H, m, NCH), 4.40 and 4.56 (2 H, AB-system, $^3J_{HH}$ = 10.8 Hz, CH−CH), 6.95−8.12 (12 H, m, arom.), 7.47 (1 H, d, $^3J_{HH}$ = 6.8 Hz, NH), 8.49 (1 H, s, ═CH−O), 9.70 and 9.99 (2 H, 2 s, 2 NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ_C 175.3, 169.5, 167.3, 166.7, 158.1, 151.2, 140.2, 139.5, 135.0, 131.1, 130.1, 130.0, 126.4, 125.0, 124.7, 124.5, 121.7, 120.4, 120.3, 56.4, 49.2, 43.9, 33.3, 26.4, 25.9, 25.8; Anal. Calcd for $C_{32}H_{29}Cl_2N_3O_5$ (606.49) C 63.37, H 4.82, N 6.93%; Found C 63.17; H 4.80, N 6.89%.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and FT-IR, ^1H, and ^{13}C NMR spectra of compounds **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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