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Synthesis of Multi-Functionalized Chromeno[2,3-*c*]pyrrol-9(2*H*)-ones: Investigation and Application of Baker–Venkataraman Rearrangement Involved Reactions Catalyzed by 4-(Dimethylamino)pyridine

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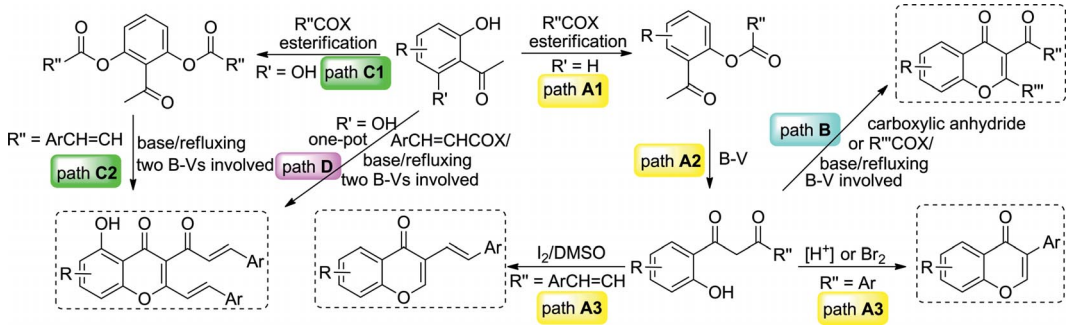
An efficient one-pot synthesis of multi-functionalized chromeno[2,3-*c*]pyrrol-9(2*H*)-ones from 1,3-diaryl-1,3-diketones and amino acids is described. The synthesis is based on the 4-(dimethylamino)pyridine-catalyzed Baker–Venkataraman rearrangement and subsequent reactions.

Introduction

Chromone (4*H*-1-benzopyran-4-one) containing compounds constitute a wide variety of naturally occurring and synthetic products. Representative analogues – flavones, xanthones, and their various derivatives – have shown broad pharmacological activities, such as anticancer,[1] anticardiovascular,[2] and anti-inflammatory,[3] and therefore, have useful medicinal applications. Syntheses of these chromone analogues have been approached in various ways, although in most of them the formation of the chromone moiety as intermediates or reactants was involved. Typical syntheses of chromone analogues include catalytic Sonogashira[4] and carbonylative annulation;[5] intramolecular Friedel–Crafts acetylation of 2-phenyloxybenzoate ester, and so forth;[6] or etherification of benzophenone intermediates[7] under various conditions. In addition, the Baker–Venkataraman (B–V) rearrangement,[8] accomplished with oxidative or acidic catalytic cyclization,[9] has also been revealed to be an efficient method for chromone formation (Scheme 1, paths A1–A3).

Classic B–V rearrangement is a base-induced (typically NaH, K_2CO_3 KOH, and NaOH) acyl transfer reaction of 2-acetylphenyl carboxylate, resulting in a 1,3-diketone with a free *o*-hydroxy group. In some cases,[10] acylation of the free *o*-hydroxy group by carboxylic anhydride in the presence of alkali compounds under reflux could give 2-alkyl-3-aroylchromones by another B–V reaction (Scheme 1, path B). Extensive results have been obtained by acylation



Scheme 1. Chromone formation reactions involving B–V rearrangement.

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of 2,6-dihydroxyacetophenone with cinnamoyl chloride at high temperature in K_2CO_3/acetone media, affording 3-cinnamoyl-2-styrylchromone analogues. In this multistep procedure, two B–V rearrangements are involved (Scheme 1, path C1–C2).[11] Recently, Waldvogel and co-

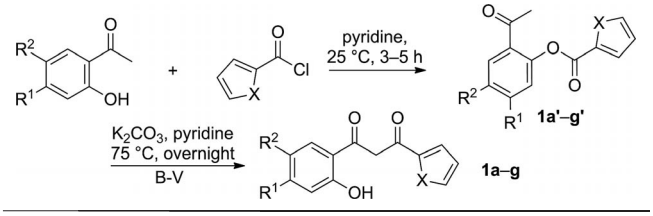
workers reported an optimized one-pot protocol for the synthesis of 3-cinnamoyl-2-styrylchromone analogues via α,α-dicinnamoylated acetophenone intermediates (Scheme 1, path D).[12] These works inspired the possibility to develop a new synthetic strategy to produce highly functionalized chromone analogues, which would facilitate the discovery of new bioactive molecules by organic and medicinal chemists. Herein, we describe the synthesis of 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones from diaryl-1,3-diketones and amino acids, based on 4-(dimethylamino)-pyridine (DMAP) catalyzed B–V rearrangement and subsequent reactions under mild conditions.

Results and Discussion

In our search for potent anticancer molecules, we proposed a chromone-based compound library with new structures and high diversity. As mentioned above, acylation of *o*-hydroxylated diaryl 1,3-diketones followed by a B–V rearrangement would be a promising way to achieve diversity expansion. However, the previously reported conditions usually required strong bases and high temperatures, and therefore, would hinder the introduction of a susceptive moiety. Direct acylation of 2,6-dihydroxyacetophenone with cinnamoyl chloride or other acylation reagents under basic catalysis at reflux is also deficient owing to the limitation of the 2,6-dihydroxy requirement,[11–12] which would restrict diversity expansion during library construction. Considering this information, we sought to find mild conditions for the formation of the chromone moiety in our current work.

Our route started with the synthesis of 1,3-diaryl-1,3-diketones **1** through esterifications and classical B–V rearrangements from 2-hydroxyacetophenones and aromatic acyl chlorides. In this way, *o*-acylated phenol esters **1a′**–**g′** were obtained in 86–94% isolated yields through treatment of 2-hydroxyacetophenones with different aromatic acyl chlorides in pyridine (Py) at 25 °C. Subsequently, B–V rearrangements were induced by treating **1a′**–**g′** with K_2CO_3 (1 equiv.) in Py at 75 °C to give **1a**–**g** in 70–83% yields (Table 1).

Table 1. Synthesis and structural information of **1a′**–**g′** and **1a**–**g**.



Entry	R^1	R^2	X	Ester (yield [%])	Diketone (yield [%])
1	H	H	CH=CH	**1a′** (90)	**1a** (72)
2	H	H	O	**1b′** (89)	**1b** (83)
3	H	OCH_3	O	**1c′** (87)	**1c** (70)
4	H	CH_3	O	**1d′** (94)	**1d** (77)
5	H	H	S	**1e′** (86)	**1e** (79)
6	OCH_3	H	S	**1f′** (89)	**1f** (71)
7	H	CH_3	S	**1g′** (90)	**1g** (76)

After **1a**–**g** were obtained, model reactions were conducted with **1a** and acetic anhydride in Py with or without non-nucleophilic base to find an efficient catalyst for chromone formation. Briefly, **1a** (120 mg) and Ac_2O (75 mg) were dissolved in Py (1.5 mL); four parallel reactions were conducted at 25 °C with or without the addition of DMAP, diisopropylethylamine (DIEA), or triethylamine (0.2 equiv.). After stirring for 1 h, the reaction mixture was acidified with 10% HCl and extracted with EtOAc. The EtOAc layer was analyzed with DIONEX Ultimate 3000 HPLC by using purified **1a**, **2a**, and **3a** as references (Figure 1). The results in Figure 1 suggested that the esterifications proceeded quickly in Py, affording the ester intermediate **2a** in high yield (Table 2); the addition of DMAP (0.2 equiv.) resulted in complete consumption of **1a**, and the chromone **3a** appeared as the main product in the reaction mixture. Replacement of DMAP by DIEA or NEt_3 led to little chromone **3a** formation, with ester **2a** as the main product. Similarly, the Py-only system resulted in **2a** as the

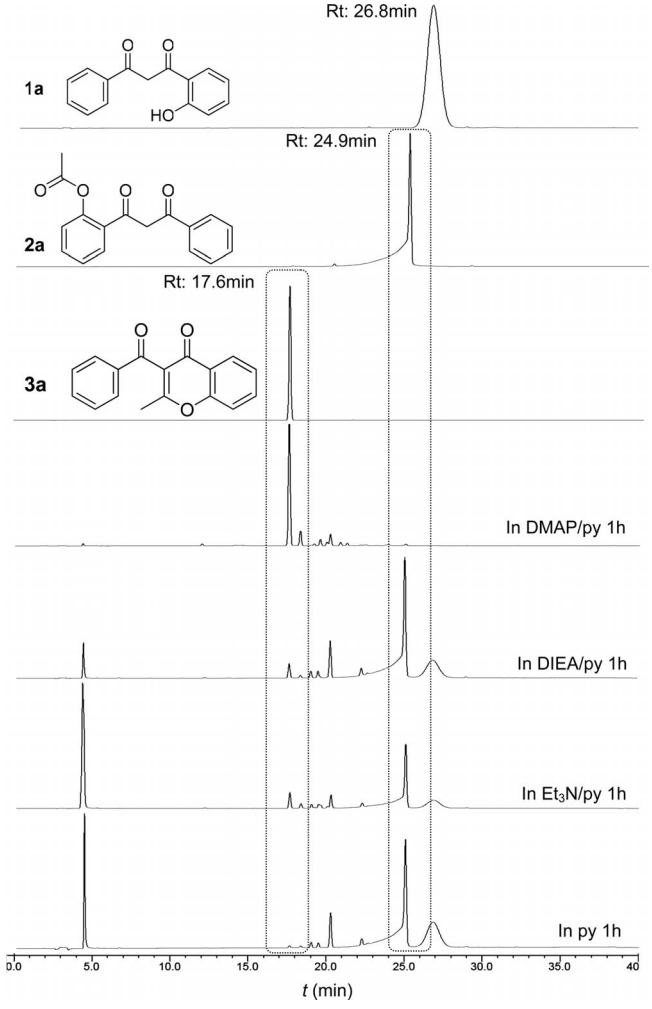
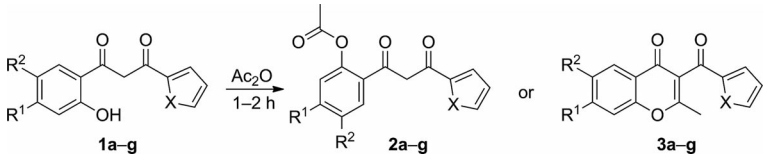


Figure 1. HPLC analysis of the reaction of **1a** and Ac_2O in Py with or without DMAP, DIEA, or Et_3N. Samples were diluted with CH_3CN. Column: DIONEX C18, 5 μm, 120 Å, 4.6 × 250 mm; flow rate: 1 mL min^{-1}. 5 μL of sample was eluted with a gradient of 30–95% CH_3CN in double-deionized H_2O over 35 min by using UV detection at 254 nm.

Table 2. Synthesis and structural information of **2a**–**g** and **3a**–**g**.



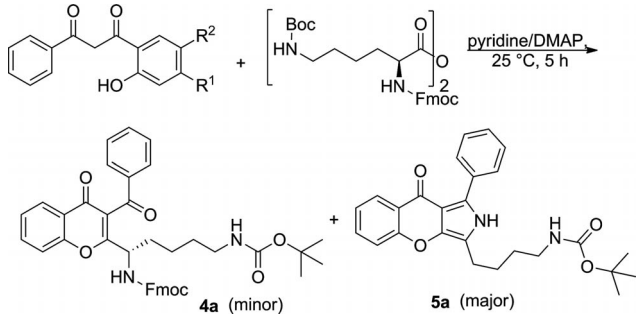
Entry	R^1	R^2	X	In Py Ester (yield [%])	In DMAP (0.2 equiv.)/Py Chromone (yield [%])
1	H	H	CH=CH	**2a** (93)	**3a** (89)
2	H	H	O	**2b** (90)	**3b** (85)
3	H	OCH_3	O	**2c** (95)	**3c** (91)
4	H	CH_3	O	**2d** (74)	**3d** (69)
5	H	H	S	**2e** (84)	**3e** (81)
6	OCH_3	H	S	**2f** (79)	**3f** (73)
7	H	CH_3	S	**2g** (75)	**3g** (67)

main product with only a trace amount of **3a**. In Table 2, the production data from reactions of more diketones **1b**–**g** with Ac_2O in Py or Py/DMAP is also summarized. These results revealed that DMAP was good at promoting the formation of chromones under mild conditions.

Then, we examined the possibility of extending the above finding to the synthesis of new chromone analogues. Acetic anhydride was replaced by natural amino acid anhydrides. We chose amino acids because they are biological molecules with various side chains, which would be beneficial in tuning the structures of the final products during bioactivity evaluation. To avoid unexpected side reactions, the α-amino groups of the amino acids were protected with 9-fluorenylmethyloxycarbonyl (Fmoc); this group is commonly adopted in peptide synthesis. In addition, the active side chains of the amino acids were also protected with different protective reagents, depending on the nature of the active group. The α-amino group and side-chain-protected amino acids are commercially available.

In our first attempt, protected lysine, Fmoc-Lys(Boc)-OH (Boc = *tert*-butoxycarbonyl), was treated with dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 to form the symmetric amino acid anhydrides as the main substrates for activation.[13] After filtering off the insoluble byproduct dicyclohexylurea (DCU), CH_2Cl_2 was evaporated to give a residue that was mixed with **1a** in DMAP (0.2 equiv)/Py to initiate the reaction. Compound **1a** disappeared quickly as expected, and a major yellow spot could be observed by TLC after 5 h. This product was therefore isolated and purified by column chromatography to give a yellow powder. Unexpectedly, instead of the target amino acid residue, functionalized 3-benzoyl-4*H*-chromen-4-one (**4a**, Scheme 2), this product was identified as 3-(*N*-Boc-4-aminobutyl)-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (**5a**, Scheme 2) based on the analysis of HRMS, ^1H and ^{13}C NMR spectroscopy, HMBC, and HSQC data. Furthermore, we obtained single crystals of **5a**, and its structure was confirmed by X-ray analysis (Figure 2).[14]

This interesting result suggested that 1,3-disubstituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones could be synthesized in the presence of DMAP. Several conditions for the reaction



Scheme 2. Synthesis of **5a**.

of **1a** with Fmoc-Leu-OH were therefore investigated to optimize the reaction. Compound **1a** (0.5 mmol) was acylated in Py (exactly 10 mL)/DMAP (0.6 equiv.) either by using excess pre-prepared symmetric Fmoc-Leu anhydride or by excess Fmoc-Leu-OH/DCC directly, while different reaction times and temperatures were applied. In brief, compound **1a** was acylated at 15 °C by using different reagents first, and after **1a** disappeared (about 30 min), as determined by TLC, the reaction mixture was stirred under various time and temperature conditions (Table 3). Next, the reaction mixture was centrifuged, and 80 μL of the supernatant was removed and diluted to 1.0 mL with acetonitrile for HPLC analysis. Signals of 5 μL of sample were recorded with a UV detector at 390 nm to avoid noise from byproducts, and the product peak areas were calculated by integration. Meanwhile, the final product **5b** (see Table 4 below for structure information) was purified by column chromatography and characterized. A standard curve was obtained by plotting the peak area versus the mass of 5 μL of purified **5b** with various concentrations in acetonitrile, and was analyzed with linear regression to give a standard equation $A = 98.34M$, in which A is the obtained peak area in mAu min, mAu is the Absorbance unit × 1/1000), M is the determined mass of 5 μL of sample in mg, and the constant 98.34 is the slope, k, for **5b** from the general standard curve equation $A = kM$. The HPLC yield was calculated according to $Y_{HPLC} = 100\% \times [M \times (1.0\ mL/0.08\ mL) \times 10\ mL]/N = 100\% \times 125A/kN$, in which N is the theoretical yield in

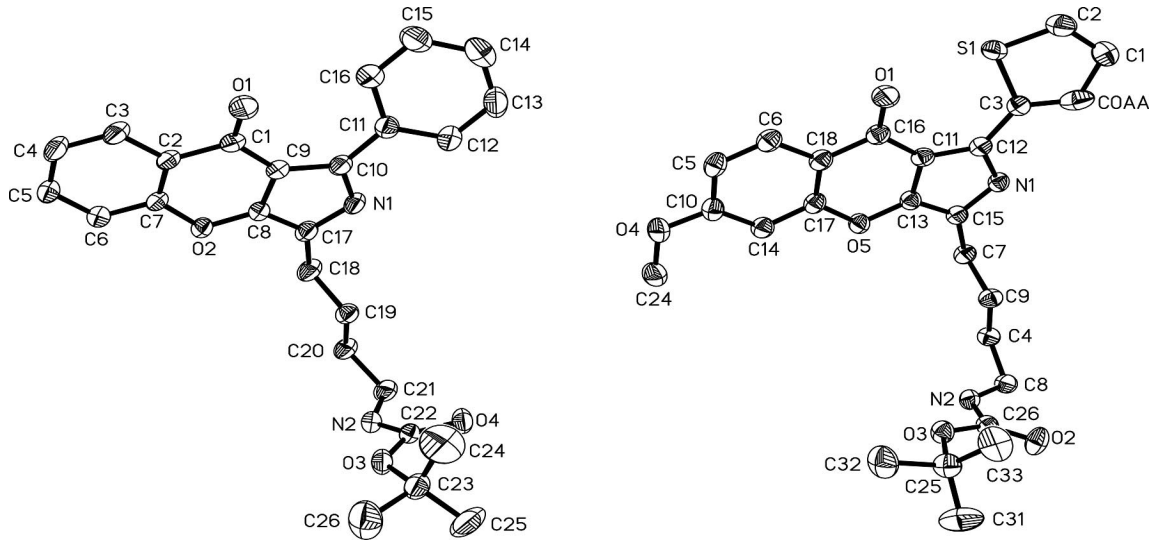


Figure 2. X-ray structures of **5a** (left) and **5o** (right).

Table 3. Synthesis of **5b** under various conditions.

Entry	Reaction conditions			Y_{HPLC}[a] [%]
	Base	Acylation	Conditions	
1	DMAP/Py	Leu anhydride	15 °C 30 min, then 15 °C for further 5 h	7.6
2	DMAP/Py	Leu anhydride	15 °C 30 min, then 15 °C for further 5 h, then 40 °C 2 h	64.0
3	DMAP/Py	DCC + Leu	15 °C 30 min, then 15 °C for further 5 h	23.3
4	DMAP/Py	DCC + Leu	15 °C 30 min, then 15 °C for further 5 h, then 40 °C for 2 h	97.1
5	DMAP/Py	DCC + Leu	15 °C 30 min, then 40 °C for 2 h	95.9
6	DIEA/Py	DCC + Leu	15 °C 30 min, then 40 °C for 2 h	1.3
7	NEt_3/Py	DCC + Leu	15 °C 30 min, then 40 °C for 2 h	7.4
8	Py	DCC + Leu	15 °C 30 min, then 40 °C for 2 h	0.77

[a] Determined by HPLC. Column: DIONEX C18, 5 μm, 120 Å, 4.6 × 250 mm; flow rate: 1 mL min^{-1}. A 5 μL sample was eluted with a gradient of 55–99% CH_3CN in double-deionized H_2O over 30 min by using UV detection at 390 nm.

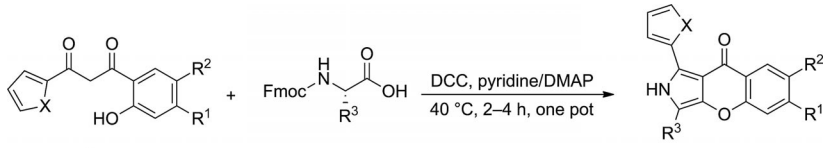
mg, (here 158.5 mg, calculated based on 0.5 mmol of starting material **1a**). The results are summarized in Table 3 (Entries 1–5).

The data in Table 3 indicated that the direct acylation of **1a** with leucine/DCC followed by 2 h of stirring at 40 °C would be the most efficient conditions (Table 3, Entry 5) for the synthesis of **5b**. More reactions were therefore carried out under these conditions by replacing DMAP with NEt_3 or DIEA, or simply by removing DMAP for comparison purposes. As expected, these conditions only led to the formation of **5b** in very low yields (Table 3, Entries 6–8), revealing the important contribution of DMAP in 1,3-disubstituted chromeno[2,3-*c*]pyrrol-9(2*H*)-one formation.

Encouraged by these results, we adopted the optimized conditions (Table 3, Entry 5) for the diversity expansion of chromeno[2,3-*c*]pyrrol-9(2*H*)-ones. To investigate the scope and generality of this one-pot procedure, different β-diketone intermediates **1a**–**g** with various amino acids, including lysine, aspartic acid, alanine, leucine, phenylalanine, tyrosine, and methionine, with different side chains were used. Briefly, different amino group and side-chain-protected amino acids (0.75 mmol), DMAP (0.3 mmol), and DCC (0.9 mmol) were dissolved in Py (exactly 10 mL) and mixed with different *o*-hydroxylated 1,3-diaryl-1,3-diketones (**1a**–**g**; 0.5 mmol), and the reaction mixtures were stirred at 15 °C until the 1,3-diketones **1** had disappeared, as monitored by TLC. Each reaction mixture was then warmed to 40 °C for 2–4 h, then 80 μL of the supernatant was removed for HPLC analysis, according to the procedure described above. After that, the Py was evaporated from the rest of the mixture to give a residue, which was purified by column chromatography to give the final product. Eighteen new 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones (**5a**–**r**, Table 4) were successfully obtained in 44–89% yields, which were characterized by using IR spectroscopy, HRMS and NMR spectroscopy. Furthermore, single crystals of **5o** were also isolated and analyzed by using X-ray diffraction[14] (Figure 2). Each standard curve of the obtained pure products **5a**–**r** was determined and used to calculate overall yields, Y_{HPLC}, according to the above-described procedure. Moderate to high production rates of **5a**–**r** were obtained, and both the isolated yields and HPLC yields are listed in Table 4.

Based on the above results, we propose a mechanism for the formation of 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones, in which a DMAP-catalyzed B–V rearrangement and subsequent reactions are involved. In the first step, a DMAP-catalyzed B–V rearrangement occurs soon

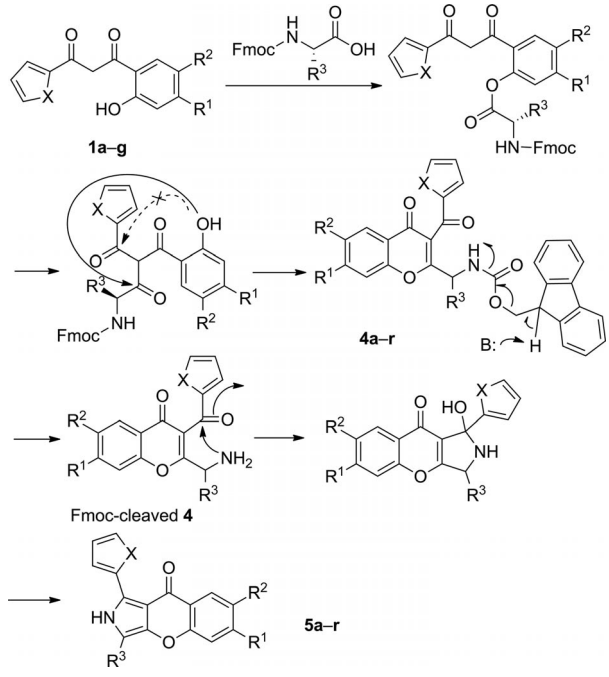
Table 4. Synthesis and structural information of **5a**–**r**.



Entry	Product	R^1	R^2	R^3	X	Retention time [min]	k[a]	Yield [%] Y_{HPLC}[b]	$Y_{isolated}$
1	**5a**	H	H	$CH_2(CH_2)_3NHCOOtBu$	CH=CH	12.63	62.62	90.4	76
2	**5b**	H	H	$CH_2CH(CH_3)_2$	CH=CH	14.92	98.34	95.9	81
3	**5c**	H	H	$CH_2CH_2SCH_3$	CH=CH	10.69	40.44	91.4	80
4	**5d**	H	H	$CH_2COOtBu$	CH=CH	12.17	26.71	82.9	75
5	**5e**	H	H	CH_3	CH=CH	8.49	90.51	88.1	77
6	**5f**	H	H	$CH_2C_6H_5$	CH=CH	13.47	80.99	63.1	51
7	**5g**	H	H	$CH_2C_6H_4$(*p*-O*t*Bu)	CH=CH	18.02	55.61	92.3	78
8	**5h**	H	H	$CH_2CH(CH_3)_2$	O	13.91	23.95	82.4	71
9	**5i**	H	CH_3	$CH_2CH(CH_3)_2$	O	14.14	46.91	77.3	63
10	**5j**	H	OCH_3	$CH_2CH(CH_3)_2$	O	16.87	73.57	98.7	86
11	**5k**	H	H	$CH_2CH(CH_3)_2$	S	14.21	73.82	60.7	47
12	**5l**	OCH_3	H	$CH_2CH(CH_3)_2$	S	13.21	114.9	95.8	79
13	**5m**	H	H	$CH_2(CH_2)_3NHCOOtBu$	O	11.63	37.25	92.3	77
14	**5n**	H	H	$CH_2(CH_2)_3NHCOOtBu$	S	13.99	38.20	73.7	61
15	**5o**	OCH_3	H	$CH_2(CH_2)_3NHCOOtBu$	S	11.26	85.92	57.1	44
16	**5p**	H	CH_3	$CH_2(CH_2)_3NHCOOtBu$	S	14.06	51.39	80.2	69
17	**5q**	OCH_3	H	$CH_2C_6H_4$(*p*-O*t*Bu)	S	16.29	93.61	67.9	54
18	**5r**	H	H	$CH_2CH_2SCH_3$	S	10.07	54.14	102	89

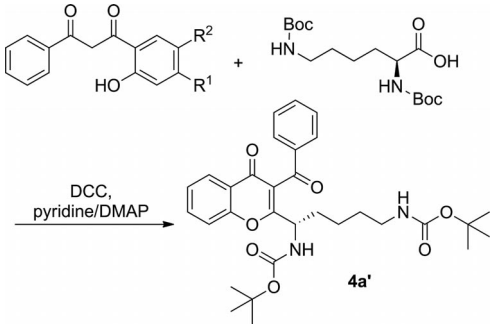
[a] Slope of the standard curve equation $A = kM$ of each compound. [b] Determined by HPLC. Column: DIONEX C18, 5 μm, 120 Å, 4.6 × 250 mm; flow rate: 1 mL min^{-1}. Gradient: 55–99 % CH_3CN in double-deionized H_2O over 30 min by using UV detection at 390 nm.

after the esterification of **1**, leading to the chromone intermediate **4** (Scheme 3). The achieved regioselectivity should result from the conjugation effect of the aromatic ring, which decreases the electropositivity of the adjacent carbonyl carbon atom. On the other hand, although the protective Fmoc group is generally cleaved at room temperature by piperidine (20 % or higher) in peptide chemistry, our results strongly suggest that Fmoc can be removed by DMAP under the current conditions, which are consistent with those previously reported.[15] Once the amino group of **4** is liberated, a subsequent intramolecular carbonyl addition by the adjacent free amino group occurs and is followed by elimination to afford the final products **5a**–**r** (Scheme 3).



Scheme 3. Proposed mechanism for 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-one formation.

To verify the formation of intermediate **4**, Fmoc-Lys-(Boc)-OH was replaced by Boc-Lys(Boc)-OH, and the reaction was conducted under the same conditions. As expected, chromone product **4a**′ was obtained in high yield (Scheme 4). Furthermore, to identify possible intermediates and byproducts, the reaction mixture from the synthesis of **5a** obtained by the unoptimized anhydride method was analyzed by using HPLC and LC–MS, and reaction intermediates such as ester intermediates **4a** and Fmoc-cleaved **4a** were detected in addition to target **5a** and cleaved Fmoc species[15] (Figures S4 and S5 in the Supporting Information), without the observation of other side products. Noticeably, although they could be detected, chromone intermediate **4a** and Fmoc-cleaved **4a** were difficult to separate for further analysis owing to their low content and instability in the reaction mixture. These results support the assumption that final products **5a**–**r** are formed via chromone intermediate **4**, as shown in Scheme 3.



Scheme 4. Synthesis of **4a′**.

Conclusions

A new mild synthetic method for the synthesis of 1,3-substituted chromeno[2,3-*c*]pyrrol-9(2*H*)-ones was discovered from an unexpected one-pot reaction of 2′-hydroxy-1,3-diaryl-1,3-diketones with various amino acids. This procedure is based on DMAP-catalyzed B–V rearrangements and subsequent Fmoc cleavage, cyclization, and elimination. As isosteres of xanthones, nitrogen-containing heterocyclochromones, such as pyrrolidine,[16] Py,[17] and lactam-fused chromones,[18] have attracted much attention in the design of drugs[17a,19] and fluorescent labels for biological substrates.[17b–17f] However, compared with the extensive studies of these azacyclochromones, there have been few reports of pyrroles fused to chromones. Although Kelly and Moiseyeva have reported the total synthesis of two benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones, which are aglycones of the natural antibiotics pyralomicins,[20] and a few syntheses of *N*-alkylated benzopyranopyrrolone analogues have been reported,[21] these procedures usually require harsh conditions and/or long reaction sequences. Based on the finding that chromone moieties could be formed by DMAP-catalyzed B–V rearrangements, our work has established a facile way to synthesize new chromeno[2,3-*c*]pyrrol-9(2*H*)-ones under mild conditions. A variety of rings and substitution patterns (amino acids with various active side chains) were examined and proven to be well tolerated under our reaction conditions. Among the obtained compounds, **3c**–**d**, **3f**, and **5a**–**r** were identified as new chromone derivatives. Noticeably, the resulting new compounds have multiple substituents and could be easily modified by using various starting materials. We believe that our findings will benefit organic and medicinal chemists to expand the diversity of chromeno[2,3-*c*]pyrrol-9(2*H*)-one derivatives for further biological activity screening, and such work is being actively undertaken in our group.

Experimental Section

General: All reagents were commercially available. Solvents were treated by using standard techniques. All amino acids were used as the following protected forms: α-amino groups of all amino acids were protected with Fmoc, the side chains of lysine were protected with Boc, and the side chains of aspartic acid and tyrosine were protected as *t*Bu. Reactions were monitored by TLC on glass plates coated with silica gel with fluorescent indicator (GF_{254}). Flash chromatography was performed on silica gel H. Melting points were determined by using an XT-4 apparatus. NMR spectra were recorded with a Bruker Avance III (400 MHz for ^1H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported as parts per million (ppm) relative to the signal for internal tetramethylsilane (δ = 0 ppm for ^1H) for solutions in $CDCl_3$. ^1H NMR spectroscopic data are reported in chloroform (δ = 7.26 ppm), methanol (δ = 3.30 ppm), and DMSO (δ = 2.50 ppm). ^{13}C NMR spectroscopic data are reported in chloroform (δ = 77.0 ppm) and DMSO (δ = 39.5 ppm). Multiplicities are reported by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constants in Hz. HRMS spectra were recorded with an LCMS-IT-TOF (SHIMADZU) instrument. IR data were recorded with a Bruker FTIR spectrometer. HPLC analyses were performed with a DIONEX Ultimate 3000 chromatograph; HPLC conditions were as follows: DIONEX C18, 5 μm, 120 Å, 4.6 × 250 mm column; flow rate: 1 mL min^{-1}. For each test, 5 μL of sample was used and eluted in different gradients, using a UV monitor at 254 or 390 nm detection wavelengths, depending on the analytical requirements.

Synthesis of 2-Acetylphenyl Benzoate (1a′): 2-Hydroxyacetophenone (10.0 mmol, 1.36 g) and benzoyl chloride (12.0 mmol, 1.68 g) were dissolved in Py (25 mL) and stirred at 25 °C. When 2-hydroxyacetophenone was consumed, in about 3 h as determined by using TLC, a large excess of water was added, and then the pH of the solution was adjusted to 5.0 with 10% HCl. The product precipitated and was collected by filtration, giving **1a′** as a white powder (2.16 g, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, *J* = 8.3, 1.2 Hz, 2 H, Ar-H), 7.87 (dd, *J* = 7.8, 1.6 Hz, 1 H, Ar-H), 7.66 (t, *J* = 7.5 Hz, 1 H, Ar-H), 7.61–7.56 (m, 1 H, Ar-H), 7.53 (t, *J* = 7.7 Hz, 2 H, Ar-H), 7.37 (td, *J* = 7.7, 1.1 Hz, 1 H, Ar-H), 7.24 (dd, *J* = 8.1, 0.9 Hz, 1 H, Ar-H), 2.55 (s, 3 H, CH_3) ppm.

2-Acetylphenyl Furan-2-carboxylate (1b′): 2-Hydroxyacetophenone (10 mmol, 1.36 g) and furoyl chloride (12.0 mmol, 1.56 g) were dissolved in Py (25 mL) and stirred at 25 °C. When 2-hydroxyacetophenone was consumed, in about 5 h as determined by using TLC, a large excess of water was added, and then the pH of the solution was adjusted to 5.0 with 10% HCl. The solution was extracted with EtOAc (50 mL) three times, and then the organic layers were combined and washed with water to pH = 7.0, dried with $MgSO_4$, and evaporation of EtOAc gave **1b′** as a white powder (2.05 g, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar-H), 7.70 (dd, *J* = 1.6, 0.8 Hz, 1 H, Ar-H), 7.62–7.55 (m, 1 H, Ar-H), 7.42 (dd, *J* = 3.5, 0.7 Hz, 1 H, Ar-H), 7.37 (td, *J* = 7.6, 1.1 Hz, 1 H, Ar-H), 7.26 (dd, *J* = 8.1, 1.0 Hz, 1 H, Ar-H), 6.62 (dd, *J* = 3.5, 1.7 Hz, 1 H, Ar-H), 2.57 (s, 3 H, CH_3) ppm.

2-Acetyl-4-methoxyphenyl Furan-2-carboxylate (1c′): 2-Hydroxy-5-methoxyacetophenone (10.0 mmol, 1.66 g) and furoyl chloride (12.0 mmol, 1.56 g) were treated by the same procedure as that used for the synthesis of **1a′**, except for the reaction time (4 h), giving **1c′** as a salmon-pink powder (2.26 g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.69 (dd, *J* = 1.7, 0.8 Hz, 1 H, Ar-H), 7.42 (dd, *J* = 3.5, 0.7 Hz, 1 H, Ar-H), 6.87 (dd, *J* = 8.8, 2.5 Hz, 1 H, Ar-H), 6.74 (d, *J* = 2.5 Hz, 1 H, Ar-H), 6.62 (dd, *J* = 3.5, 1.7 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 2.52 (s, 3 H, CH_3) ppm.

2-Acetyl-4-methylphenyl Furan-2-carboxylate (1d′): 2-Hydroxy-5-methylacetophenone (10.0 mmol, 1.50 g) and furoyl chloride

(12.0 mmol, 1.56 g) were treated by using the same procedure as that used for the synthesis of **1a′**, giving **1d′** as a salmon-pink powder (2.29 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, J = 1.7, 0.8 Hz, 1 H, Ar-H), 7.64 (d, J = 1.9 Hz, 1 H, Ar-H), 7.41 (dd, J = 3.5, 0.8 Hz, 1 H, Ar-H), 7.37 (dd, J = 8.0, 2.4 Hz, 1 H, Ar-H), 7.13 (d, J = 8.2 Hz, 1 H, Ar-H), 6.61 (dd, J = 3.5, 1.7 Hz, 1 H, Ar-H), 2.55 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3) ppm.

2-Acetylphenyl Thiophene-2-carboxylate (1e′): 2-Hydroxyacetophenone (10.0 mmol, 1.36 g) and thenoyl chloride (12.0 mmol, 1.75 g) were treated by using the same procedure as that used for the synthesis of **1b′**, giving **1e′** as a stramineous powder (2.12 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J = 3.8, 1.2 Hz, 1 H, Ar-H), 7.86 (dd, J = 7.8, 1.7 Hz, 1 H, Ar-H), 7.70 (dd, J = 5.0, 1.2 Hz, 1 H, Ar-H), 7.62–7.55 (m, 1 H, Ar-H), 7.37 (td, J = 7.7, 1.1 Hz, 1 H, Ar-H), 7.26 (dd, J = 8.1, 1.0 Hz, 1 H, Ar-H), 7.20 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 2.58 (s, 3 H, CH_3) ppm.

2-Acetyl-5-methoxyphenyl Thiophene-2-carboxylate (1f′): 2-Hydroxy-4-methoxyacetophenone (10.0 mmol, 1.66 g) and thenoyl chloride (12.0 mmol, 1.75 g) were treated by using the same procedure as that used for the synthesis of **1a′**, except for the reaction time (5 h), giving **1f′** as a stramineous powder (2.46 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J = 3.8, 1.3 Hz, 1 H, Ar-H), 7.89 (d, J = 8.8 Hz, 1 H, Ar-H), 7.69 (dd, J = 5.0, 1.3 Hz, 1 H, Ar-H), 7.20 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 6.87 (dd, J = 8.8, 2.5 Hz, 1 H, Ar-H), 6.74 (d, J = 2.5 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OCH_3), 2.52 (s, 3 H, CH_3) ppm.

2-Acetyl-4-methylphenyl Thiophene-2-carboxylate (1g′): 2-Hydroxy-5-methylacetophenone (10.0 mmol, 1.50 g) and thenoyl chloride (12.0 mmol, 1.75 g) were treated by using the same procedure as that used for the synthesis of **1a′**, except for the reaction time (5 h), giving **1g′** as a stramineous powder (2.34 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (dd, J = 3.8, 1.2 Hz, 1 H, Ar-H), 7.69 (dd, J = 5.0, 1.2 Hz, 1 H, Ar-H), 7.64 (d, J = 1.9 Hz, 1 H, Ar-H), 7.37 (dd, J = 8.3, 2.1 Hz, 1 H, Ar-H), 7.19 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 7.13 (d, J = 8.2 Hz, 1 H, Ar-H), 2.55 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3) ppm.

1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-dione (1a): K_2CO_3 (1.10 g, 8.0 mmol) was added to a solution of above-obtained **1a′** (8.0 mmol, 1.92 g) in Py (40 mL). The resulting mixture was heated to 75 °C overnight. When the reaction was finished, as monitored by using TLC, a large excess of water was added, and the pH of the solution was adjusted to 5.0 with 10% HCl. The mixture was extracted with EtOAc (50 mL) three times, then the organic layers were combined and washed with water to neutral pH, dried with $MgSO_4$, and then EtOAc was evaporated to give the crude product, which was purified by recrystallization from alcohol to give **1a** as a yellow powder (1.38 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.54 (s, 1 H, OH), 12.09 (s, 1 H, OH), 7.94 (dd, J = 7.1, 1.5 Hz, 2 H, Ar-H), 7.79 (dd, J = 8.1, 1.6 Hz, 1 H, Ar-H), 7.59–7.43 (m, 4 H, Ar-H), 7.01 (dd, J = 8.4, 0.9 Hz, 1 H, Ar-H), 6.95–6.90 (m, 1 H, Ar-H), 6.85 (s, 1 H, C=CH) ppm.

1-(Furan-2-yl)-3-(2-hydroxyphenyl)propane-1,3-dione (1b): Above-obtained **1b′** (8.0 mmol, 1.84 g) was treated by the same procedure as that used for the synthesis of **1a**, giving **1b** as a yellow powder (1.53 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.08 (s, 1 H, OH), 12.07 (s, 1 H, OH), 7.78 (dd, J = 8.1, 1.5 Hz, 1 H, Ar-H), 7.61 (d, J = 1.0 Hz, 1 H, Ar-H), 7.49–7.43 (m, 1 H, Ar-H), 7.18 (d, J = 3.5 Hz, 1 H, Ar-H), 6.99 (dd, J = 8.4, 0.8 Hz, 1 H, Ar-H), 6.94–6.88 (m, 1 H, Ar-H), 6.78 (s, 1 H, C=CH), 6.60 (dd, J = 3.5, 1.7 Hz, 1 H, Ar-H) ppm.

1-(Furan-2-yl)-3-(2-hydroxy-5-methoxyphenyl)propane-1,3-dione (1c): Above-obtained **1c′** (8.0 mmol, 2.08 g) was treated by using the same procedure as that used for the synthesis of **1a**, giving **1c** as a yellow powder (1.46 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.19 (s, 1 H, OH), 11.64 (s, 1 H, OH), 7.62 (d, J = 0.9 Hz, 1 H, Ar-H), 7.20 (d, J = 3.0 Hz, 1 H, Ar-H), 7.19 (dd, J = 3.5, 0.5 Hz, 1 H, Ar-H), 7.10 (dd, J = 9.0, 3.0 Hz, 1 H, Ar-H), 6.94 (d, J = 9.0 Hz, 1 H, Ar-H), 6.72 (s, 1 H, C=CH), 6.61 (dd, J = 3.5, 1.7 Hz, 1 H, Ar-H), 3.84 (s, 3 H,OCH_3) ppm.

1-(Furan-2-yl)-3-(2-hydroxy-5-methylphenyl)propane-1,3-dione (1d): Above-obtained **1d′** (8.0 mmol, 1.95 g) was treated by using the same procedure as that used for the synthesis of **1a**, giving **1d** as a yellow powder (1.50 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.16 (s, 1 H, OH), 11.88 (s, 1 H, OH), 7.62 (dd, J = 1.6, 0.7 Hz, 1 H, Ar-H), 7.54 (s, 1 H, Ar-H), 7.30–7.27 (m, 1 H, Ar-H), 7.18 (dd, J = 3.5, 0.6 Hz, 1 H, Ar-H), 6.90 (d, J = 8.5 Hz, 1 H, Ar-H), 6.77 (s, 1 H, C=CH), 6.60 (dd, J = 3.5, 1.7 Hz, 1 H), 2.34 (s, 3 H, CH_3) ppm.

1-(2-Hydroxyphenyl)-3-(thiophen-2-yl)propane-1,3-dione (1e): Above-obtained **1e′** (8.0 mmol, 1.97 g) was treated by using the same procedure as that used for the synthesis of **1a**, giving **1e** as a yellow powder (1.55 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.66 (s, 1 H, OH), 11.96 (s, 1 H, OH), 7.79 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.73 (dd, J = 8.1, 1.5 Hz, 1 H, Ar-H), 7.61 (dd, J = 5.0, 1.0 Hz, 1 H, Ar-H), 7.49–7.43 (m, 1 H, Ar-H), 7.18 (dd, J = 4.9, 3.9 Hz, 1 H, Ar-H), 7.00 (dd, J = 8.4, 0.8 Hz, 1 H, Ar-H), 6.96–6.89 (m, 1 H, Ar-H), 6.70 (s, 1 H, C=CH) ppm.

1-(2-Hydroxy-4-methoxyphenyl)-3-(thiophen-2-yl)propane-1,3-dione (1f): Above-obtained **1f′** (8.0 mmol, 2.21 g) was treated by using the same procedure as that used for the synthesis of **1a**, giving **1f** as a yellow powder (1.57 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.45 (s, 1 H, OH), 12.47 (s, 1 H, OH), 7.75 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.64 (d, J = 8.9 Hz, 1 H, Ar-H), 7.57 (dd, J = 5.0, 1.1 Hz, 1 H, Ar-H), 7.16 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 6.57 (s, 1 H, C=CH), 6.48 (dd, J = 8.9, 2.5 Hz, 1 H, Ar-H), 6.45 (d, J = 2.5 Hz, 1 H, Ar-H), 3.85 (s, 3 H, OCH_3) ppm.

1-(2-Hydroxy-5-methylphenyl)-3-(thiophen-2-yl)propane-1,3-dione (1g): Above-obtained **1g′** (8.0 mmol, 2.08 g) was treated by using the same procedure as that used for the synthesis of **1a**, giving **1g** as a yellow powder (1.58 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.74 (s, 1 H, OH), 11.75 (s, 1 H, OH), 7.80 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.61 (dd, J = 5.0, 1.0 Hz, 1 H, Ar-H), 7.49 (d, J = 1.3 Hz, 1 H, Ar-H), 7.29–7.26 (m, 1 H, Ar-H), 7.18 (dd, J = 4.9, 3.9 Hz, 1 H, Ar-H), 6.90 (d, J = 8.5 Hz, 1 H, Ar-H), 6.68 (s, 1 H, C=CH), 2.34 (s, 3 H, CH_3) ppm.

Determination of Effects of Non-Nucleophilic Base on Chromone 3a Formation: Compound **1a** (120 mg, 0.5 mmol) and Ac_2O (75 mg, 0.75 mmol) were added to four 10 mL round-bottomed flasks equipped with magnetic stirrers, and dissolved with Py (1.5 mL); parallel reactions were conducted at 25 °C with or without the addition of DMAP, DIEA, or NEt_3, respectively, (0.2 equiv.). After stirring for 1 h, the reaction mixture was acidified with 10% HCl and extracted with EtOAc, 0.1 mL of the EtOAc layer was taken and diluted to 1.0 mL with CH_3CN. Samples were analyzed by using DIONEX Ultimate 3000 HPLC at 254 nm with a gradient of 30–95% CH_3CN in double-deionized H_2O over 35 min, using the synthesized and purified **1a**, **2a**, and **3a** as references.

2-(3-Oxo-3-phenylpropanoyl)phenyl Acetate (2a): Compound **1a** (240.0 mg, 1.0 mmol) and Ac_2O (1.5 mmol, 150.0 mg) were mixed with Py (2.5 mL) and stirred at 25 °C for 1 h, and then the pH of the resulting mixture was adjusted to 5.0 with 10% HCl, and it was

extracted with EtOAc three times. After that, the organic layers were combined and washed with water three times, and then dried with $MgSO_4$. The evaporation of EtOAc resulted in a crude product, which was purified by column chromatography to give **2a** as a yellow powder (268.0 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.92 (m, 2 H, Ar-H), 7.80 (dd, J = 7.8, 1.6 Hz, 1 H, Ar-H), 7.59–7.46 (m, 4 H, Ar-H), 7.36 (td, J = 7.6, 1.1 Hz, 1 H, Ar-H), 7.16 (dd, J = 8.1, 1.0 Hz, 1 H, Ar-H), 6.70 (s, 1 H, C=CH), 2.32 (s, 3 H,CH_3) ppm.

2-[3-(Furan-2-yl)-3-oxopropanoyl]phenyl Acetate (2b): Compound **1b** (230.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, giving **2b** as a yellow powder (244.8 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.95 (s, 1 H, OH), 7.83 (dd, J = 7.8, 1.7 Hz, 1 H, Ar-H), 7.61 (dd, J = 1.7, 0.7 Hz, 1 H, Ar-H), 7.55–7.50 (m, 1 H, Ar-H), 7.35 (td, J = 7.6, 1.2 Hz, 1 H, Ar-H), 7.23 (dd, J = 3.6, 0.7 Hz, 1 H, Ar-H), 7.14 (d, J = 1.1 Hz, 1 H, Ar-H), 6.64 (s, 1 H, C=CH), 6.59 (dd, J = 3.6, 1.7 Hz, 1 H, Ar-H), 2.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.7, 177.1, 169.1, 150.6, 148.7, 146.2, 132.5, 129.5, 128.5, 126.2, 123.7, 116.0, 112.7, 96.2, 21.0 ppm. HRMS (ESI–TOF): calcd. for $C_{15}H_{12}O_5$ $[M + H]^+$ 273.0763; found 273.0753.

2-[3-(Furan-2-yl)-3-oxopropanoyl]-4-methoxyphenyl Acetate (2c): Compound **1c** (260.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, giving **2c** as a yellow powder (287.0 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.96 (s, 1 H, OH), 7.61 (d, J = 0.8 Hz, 1 H, Ar-H), 7.33 (d, J = 2.1 Hz, 1 H, Ar-H), 7.24 (d, J = 3.5 Hz, 1 H, Ar-H), 7.05 (d, J = 2.8 Hz, 2 H, Ar-H), 6.65 (s, 1 H,C=CH), 6.59 (dd, J = 3.5, 1.6 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OCH_3), 2.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.4, 177.1, 169.6, 157.3, 150.7, 146.3, 142.2, 129.1, 124.6, 118.2, 116.1, 113.8, 112.7, 96.3, 55.7, 21.0 ppm. HRMS (ESI–TOF): calcd. for $C_{16}H_{14}O_6$ $[M + H]^+$ 303.0869; found 303.0869.

2-[3-(Furan-2-yl)-3-oxopropanoyl]-4-methylphenyl Acetate (2d): Compound **1d** (244.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, except for the reaction time (2 h), giving **2d** as a yellow powder (211.6 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.97 (s, 1 H,OH), 7.62 (dd, J = 6.6, 1.7 Hz, 2 H, Ar-H), 7.32 (dd, J = 8.2, 1.6 Hz, 1 H, Ar-H), 7.23 (d, J = 3.6 Hz, 1 H, Ar-H), 7.03 (d, J = 8.2 Hz, 1 H, Ar-H), 6.63 (s, 1 H, C=CH), 6.59 (dd, J = 3.5, 1.7 Hz, 1 H, Ar-H), 2.40 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.8, 177.0, 169.4, 150.7, 146.5, 146.2, 136.0, 133.1, 129.8, 128.0, 123.4, 115.9, 112.6, 96.1, 20.9, 20.7 ppm. HRMS (ESI–TOF): calcd. for $C_{16}H_{14}O_5$ $[M + H]^+$ 287.0919; found 287.0912.

2-[3-Oxo-3-(thiophen-2-yl)propanoyl]phenyl Acetate (2e): Compound **1e** (246.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, giving **2e** as a yellow viscous liquid (242.0 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.09 (s, 1 H, OH), 7.79 (dd, J = 7.8, 1.7 Hz, 1 H, Ar-H), 7.76 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.63 (dd, J = 4.9, 1.1 Hz, 1 H, Ar-H), 7.51 (td, J = 7.8, 1.7 Hz, 1 H, Ar-H), 7.34 (td, J = 7.7, 1.1 Hz, 1 H, Ar-H), 7.17–7.13 (m, 2 H, Ar-H), 6.55 (s, 1 H, C=CH), 2.33 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.5, 180.2, 169.1, 148.7, 141.7, 132.8, 132.4, 130.5, 129.5, 128.5, 128.4, 126.3, 123.7, 96.9, 21.1 ppm. HRMS (ESI–TOF): calcd. for $C_{15}H_{11}O_4S$ $[M - H]^-$ 287.0378; found 287.0365.

5-Methoxy-2-[3-oxo-3-(thiophen-2-yl)propanoyl]phenyl Acetate (2f): Compound **1f** (276.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, except for the reaction time (2 h), giving **2f** as yellow viscous liquid (251.2 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.32 (s, 1 H, OH), 7.79 (d, J = 8.8 Hz, 1 H, Ar-H), 7.75 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.61 (dd, J = 4.9, 1.1 Hz, 1 H, Ar-H), 7.15 (dd, J = 4.9, 3.8 Hz, 1 H, Ar-H), 6.87 (dd, J = 8.8, 2.5 Hz, 1 H, Ar-H), 6.66 (d, J = 2.5 Hz, 1 H, Ar-H), 6.55 (s, 1 H, C=CH), 3.86 (s, 3 H, OCH_3), 2.34 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.6, 180.7, 169.0, 163.1, 150.5, 141.7, 132.2, 130.9, 130.1, 128.3, 120.8, 112.2, 109.4, 95.9, 55.7, 21.1 ppm. HRMS (ESI–TOF): calcd. for $C_{16}H_{13}O_5S$ $[M - H]^-$ 317.0484; found 317.0480.

4-Methyl-2-[3-oxo-3-(thiophen-2-yl)propanoyl]phenyl Acetate (2g): Compound **1g** (260.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **2a**, except for the reaction time (2 h), giving **2g** as a yellow viscous liquid (226.5 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.10 (s, 1 H, OH), 7.77 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.63 (dd, J = 4.9, 1.1 Hz, 1 H, Ar-H), 7.59 (d, J = 1.8 Hz, 1 H, Ar-H), 7.31 (dd, J = 8.2, 2.1 Hz, 1 H, Ar-H), 7.16 (dd, J = 4.9, 3.8 Hz, 1 H, Ar-H), 7.03 (d, J = 8.2 Hz, 1 H, Ar-H), 6.54 (s, 1 H, C=CH) 2.40 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.4, 180.2, 169.3, 146.4, 141.7, 136.0, 133.0, 132.7, 130.4, 129.8, 128.3, 127.9, 123.7, 96.8, 21.0, 20.7 ppm. HRMS (ESI–TOF): calcd. for $C_{16}H_{13}O_4S$ $[M - H]^-$ 301.0535; found 301.0530.

3-Benzoyl-2-methyl-4*H*-chromen-4-one (3a): Compound **1a** (240.0 mg, 1.0 mmol), DMAP (24.5 mg, 0.2 mmol), and Ac_2O (150.0 mg, 1.5 mmol) were stirred at 25 °C for 1 h. Then, the pH of the resulting mixture was adjusted to 5.0 with 10% HCl, and extracted with EtOAc three times. The organic layer was then combined and washed with water and dried with $MgSO_4$. EtOAc was evaporated, resulting in a crude product, which was purified by column chromatography to give **3a** as a white powder (235.0 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, J = 8.0, 1.5 Hz, 1 H, Ar-H), 7.92 (dd, J = 8.4, 1.3 Hz, 2 H, Ar-H), 7.71 (ddd, J = 8.7, 7.2, 1.7 Hz, 1 H, Ar-H), 7.62–7.56 (m, 1 H, Ar-H), 7.51–7.40 (m, 4 H, Ar-H), 2.39 (s, 3 H, CH_3) ppm.

3-(Furan-2-carbonyl)-2-methyl-4*H*-chromen-4-one (3b): Compound **1b** (230.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, giving **3b** as a brown powder (216.0 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, J = 7.9, 1.6 Hz, 1 H, Ar-H), 7.71 (ddd, J = 8.7, 7.2, 1.7 Hz, 1 H, Ar-H), 7.63 (d, J = 1.0 Hz, 1 H, Ar-H), 7.47 (d, J = 8.4 Hz, 1 H, Ar-H), 7.46–7.40 (m, 1 H, Ar-H), 7.22 (d, J = 3.6 Hz, 1 H, Ar-H), 6.57 (dd, J = 3.6, 1.7 Hz, 1 H, Ar-H), 2.43 (s, 3 H, CH_3) ppm.

3-(Furan-2-carbonyl)-6-methoxy-2-methyl-4*H*-chromen-4-one (3c): Compound **1c** (260.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, giving **3c** as a yellow powder (258.0 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 1.5 Hz, 1 H, Ar-H), 7.56 (d, J = 3.1 Hz, 1 H, Ar-H), 7.41 (d, J = 9.1 Hz, 1 H, Ar-H), 7.27–7.30 (m, 1 H, Ar-H), 7.21 (d, J = 3.6, Hz, 1 H, Ar-H), 6.57 (dd, J = 3.6, 1.7 Hz, 1 H, Ar-H), 3.89 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.8, 175.3, 165.7, 157.1, 152.9, 150.6, 147.4, 124.0, 123.9, 121.7, 120.0, 119.2, 112.6, 105.1, 55.9, 19.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3122, 1658, 1627, 1484, 1028, 829, 786 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{16}H_{12}O_5$ $[M + H]^+$ 285.0763; found 285.0749.

3-(Furan-2-carbonyl)-2,6-dimethyl-4*H*-chromen-4-one (3d): Compound **1d** (244.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, except for the reaction time (2 h), giving **3d** as a brown powder (185.0 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 1.0 Hz, 1 H, Ar-H), 7.62 (dd, J = 1.6, 0.6 Hz, 1 H, Ar-H), 7.50 (dd, J = 8.6, 2.0 Hz, 1 H, Ar-H), 7.36 (d, J = 8.5 Hz, 1 H, Ar-H), 7.21 (d, J = 4.1 Hz, 1 H, Ar-H), 6.56 (dd, J = 3.6, 1.7 Hz, 1 H, Ar-H), 2.46 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 180.6, 175.4,

165.6, 154.0, 152.8, 147.3, 135.3, 135.1, 125.1, 122.9, 122.1, 120.0, 117.5, 112.5, 20.8, 18.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3122, 1632, 1568, 1463, 1016, 818, 774 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{16}H_{12}O_4$ $[M + H]^+$ 269.0814; found 269.0805.

2-Methyl-3-(thiophene-2-carbonyl)-4*H*-chromen-4-one (3e): Compound **1e** (246.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, giving **3e** as a brown powder (218.7 mg, 81%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, J = 7.9, 1.5 Hz, 1 H, Ar-H), 7.75–7.68 (m, 2 H, Ar-H), 7.62 (dd, J = 3.8, 1.0 Hz, 1 H, Ar-H), 7.48 (d, J = 8.2 Hz, 1 H, Ar-H), 7.46–7.41 (m, 1 H, Ar-H), 7.12 (dd, J = 4.8, 3.9 Hz, 1 H, Ar-H), 2.42 (s, 3 H, CH_3) ppm.

7-Methoxy-2-methyl-3-(thiophene-2-carbonyl)-4*H*-chromen-4-one (3f): Compound **1f** (276.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, except for the reaction time (2 h), giving **3f** as a yellow powder (219.0 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.9 Hz, 1 H, Ar-H), 7.72 (dd, J = 4.9, 1.2 Hz, 1 H, Ar-H), 7.62 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.11 (dd, J = 4.9, 3.9 Hz, 1 H, Ar-H), 6.99 (dd, J = 8.9, 2.4 Hz, 1 H, Ar-H), 6.87 (d, J = 2.4 Hz, 1 H, Ar-H), 3.93 (s, 3 H, OCH_3), 2.38 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.5, 174.8, 164.5, 164.3, 157.6, 144.3, 135.1, 134.8, 128.3, 127.3, 123.1, 117.1, 114.6, 100.2, 55.8, 19.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3091, 1637, 1601, 1406, 1237, 840, 771 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{16}H_{12}O_4S$ $[M + H]^+$ 301.0535; found 301.0535.

2,6-Dimethyl-3-(thiophene-2-carbonyl)-4*H*-chromen-4-one (3g): Compound **1g** (260.0 mg, 1.0 mmol) was treated by using the same procedure as that used for the synthesis of **3a**, except for the reaction time (2 h), giving **3g** as a yellow powder (190 mg, 67%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 1.4 Hz, 1 H, Ar-H), 7.72 (dd, J = 4.9, 1.1 Hz, 1 H, Ar-H), 7.61 (dd, J = 3.8, 1.1 Hz, 1 H, Ar-H), 7.51 (dd, J = 8.6, 2.2 Hz, 1 H, Ar-H), 7.37 (d, J = 8.5 Hz, 1 H, Ar-H), 7.11 (dd, J = 4.9, 3.9 Hz, 1 H, Ar-H), 2.46 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3) ppm.

Determination of the Standard Curves and the HPLC Yields: Series of solutions of purified **5a**–**r** in acetonitrile were prepared at the following concentrations: for **5a**, **5e**–**g**, **5j**–**k**, and **5n**–**q**, 2.5, 1.25, 0.625, 0.313, and 0.156 mg mL^{-1}; for **5c**, 2.2, 1.1, 0.55, 0.275, and 0.138 mg mL^{-1}; for others, 2.0, 1.0, 0.5, 0.25, and 0.125 mg mL^{-1}. For each compound, 5 μL sample was used and eluted with a linear gradient of 55–99% CH_3CN in double-deionized H_2O over 30 min, using UV detection at 390 nm. The standard curve was plotted with the peak area versus the mass of 5 μL of purified **5a**–**r** at various concentrations, and was analyzed with linear regression to give a standard equation, $A = kM$, in which A is the obtained peak area in mAu min, mAu is the Absorbance unit × 1/1000, M is the determined mass of 5 μL sample in mg, and k is the slope. To determine the HPLC yield (Y_{HPLC}), the reaction mixture was centrifuged, and 80 μL of the supernatant was taken and diluted to 1.0 mL with acetonitrile for HPLC analysis. Signals of 5 μL of sample were recorded on a UV detector at 390 nm to avoid the noise from byproducts, and the product peak area was calculated by integration. The HPLC yield was calculated according to $Y_{HPLC} = 100\% \times [M \times (1.0\ mL/0.08\ mL) \times 10\ mL]/N = 100\% \times 125\ A/kN$, in which N is the theoretical yield in mg.

Reaction Optimization and Synthesis of 5a–r

First Synthesis of 5a: Fmoc-Lys(Boc)-OH (1.41 g, 3.0 mmol) was dissolved in CH_2Cl_2 (20 mL), and then DCC (1.8 mmol) was added. The mixture was stirred at 25 °C until the amino acid disappeared. After filtering off the insoluble byproduct, DCU, CH_2Cl_2 was evaporated to give a viscous residue; the freshly obtained residue was then mixed with **1a** (240.0 mg, 1.0 mmol) and DMAP (0.2 mmol) in Py (10 mL). A major yellow spot could be observed in 5 h, and a large excess of water was added and the pH of the mixture was adjusted to neutral with 10% HCl. The product was then extracted with EtOAc, washed with water three times, and dried with $MgSO_4$. The evaporation of EtOAc resulted in a crude product, which was purified by column chromatography to give **5a** as a yellow powder (185.7 mg, 43%). M.p. 156.9–158.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1 H, N-H), 8.32 (dd, J = 7.9, 1.6 Hz, 1 H, Ar-H), 8.04 (d, J = 7.6 Hz, 2 H, Ar-H), 7.55–7.61 (m, 1 H, Ar-H), 7.42 (t, J = 7.7 Hz, 2 H, Ar-H), 7.36 (d, J = 8.3 Hz, 1 H, Ar-H), 7.30 (t, J = 7.4 Hz, 1 H, Ar-H), 7.23 (d, J = 7.9 Hz, 1 H, Ar-H), 4.75 [s, 1 H, (C=O)-*N*-H], 3.24 (dd, J = 13.0, 6.5 Hz, 2 H, CH_2), 2.94 (t, J = 7.1 Hz, 2 H, CH_2), 1.79–1.70 (m, 2 H, CH_2), 1.62–1.56 (m, 2 H, CH_2), 1.34 (s, 9 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 156.8, 142.1, 133.4, 131.3, 128.3 (3×), 123.0 (2×), 127.7, 127.1, 122.6, 122.4, 117.3, 113.7, 108.1, 79.6, 39.0, 29.1, 28.3 (3×), 26.0, 22.2 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3337, 3227, 2967, 1684, 1619, 1475, 1282, 1169, 745 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{26}H_{28}N_2O_4$ $[M - H]^-$ 431.1971; found 431.1944.

Reaction Optimization: Reaction optimization was carried out by using the reaction of **1a** with Fmoc-Leu-OH as a model. Taking account of the contribution of DMAP in Fmoc cleavage, DMAP (0.6 equiv.) was used during the reaction. Several conditions were applied. **Method I:** Fmoc-Leu-OH (530 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (20 mL), and then DCC (0.9 mmol) was added, and the mixture was stirred at 15 °C until the amino acid disappeared. After filtering off the insoluble side product, DCU, CH_2Cl_2 was evaporated to give a viscous residue; the freshly obtained residue was then mixed with **1a** (120.0 mg, 0.5 mmol) and DMAP (0.3 mmol) in Py (exactly 10 mL). The reaction mixture was either stirred at 15 °C for 5 h, or warmed to 40 °C for another 2 h after 5 h of stirring at 15 °C. **Method II:** Fmoc-Leu-OH (265 mg, 0.75 mmol), **1a** (0.5 mmol, 120 mg), and DMAP (0.3 mmol, 36.6 mg) were dissolved in Py (exactly 10 mL). Then, DCC (0.9 mmol, 185.4 mg) was added, and the mixture was kept stirring at 15 °C until **1a** disappeared, as monitored by using TLC (about 30 min). After that, the reaction mixture was either stirred at 15 °C for 5 h, or warmed to 40 °C for another 2 h after 5 h of stirring at 15 °C, or directly warmed to 40 °C for 2 h soon after the disappearance of **1a**. Then, each reaction mixture was centrifuged and 80 μL of the supernatant was taken and diluted to 1.0 mL with acetonitrile for HPLC analysis and Y_{HPLC} calculation, according to procedures described above. In further investigations, more reactions were carried out by replacing DMAP with NEt_3 or DIEA, or simply by removing DMAP under conditions of direct acylation of **1a** with leucine/DCC followed with 2 h of stirring at 40 °C. The HPLC yields were determined as well.

Synthesis of 5a–r under the Optimized Conditions

***tert*-Butyl [4-(9-Oxo-1-phenyl-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl)butyl]carbamate (5a):** Compound **1a** (120.0 mg, 0.5 mmol), Fmoc-Lys(Boc)-OH (352 mg, 0.75 mmol), and DMAP (36.6 mg, 0.3 mmol) were dissolved in Py (10 mL), and then DCC (0.9 mmol, 185.4 mg) was added. The mixture was stirred at 15 °C until **1a** disappeared, as monitored by using TLC. Then, the reaction temperature was raised to 40 °C for 3 h, and a major yellow spot could be observed by TLC. The reaction mixture was then centrifuged, and 80 μL of the supernatant was taken and diluted to 1.0 mL with acetonitrile for HPLC analysis and Y_{HPLC} calculation, according to the procedures described above. The rest of the supernatant was concentrated under reduced pressure to remove Py, giving a residue that could be purified by column chromatography to give **5a** as a

yellow powder (164.2 mg, 76%). The characterization data are listed above.

3-Isobutyl-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5b): Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, except for the reaction time (40 °C for 2 h), giving **5b** as a yellow powder (128.4 mg, 81%). M.p. 146.7–148.6 °C. ^{1}H NMR (400 MHz, MeOD): δ = 8.16 (dd, J = 8.0, 1.6 Hz, 1 H, Ar-H), 7.94 (d, J = 1.3 Hz, 1 H, Ar-H), 7.92 (s, 1 H, Ar-H), 7.61 (ddd, J = 8.6, 7.2, 1.7 Hz, 1 H, Ar-H), 7.42–7.35 (m, 3 H, Ar-H), 7.29 (t, J = 7.4 Hz, 1 H, Ar-H), 7.23 (t, J = 7.5 Hz, 1 H, Ar-H), 2.68 (d, J = 7.2 Hz, 2 H, CH_2), 2.03 (dt, J = 13.6, 6.8 Hz, 1 H,CH), 0.96 (d, J = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.9, 157.0, 142.6, 133.5, 131.2, 128.5 (2×), 127.9, 127.8, 127.6 (2×), 127.0, 122.6, 122.4, 117.3, 113.3, 108.3, 33.4, 29.0, 22.3 (2×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3263, 2950, 1638, 1478, 1328, 1222, 754 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{21}H_{19}NO_2$ [M − H]$^-$ 316.1338; found 316.1335.

3-[2-(Methylthio)ethyl]-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5c): Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Met-OH (283 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a** synthesis, giving **5c** as a yellow powder (134.0 mg, 80%). M.p. 1146.0–149.2 °C. ^{1}H NMR (400 MHz, MeOD): δ = 8.16 (dd, J = 8.0, 1.6 Hz, 1 H, Ar-H), 7.94 (dd, J = 7.1, 5.8 Hz, 2 H, Ar-H), 7.62 (ddd, J = 8.6, 7.1, 1.7 Hz, 1 H, Ar-H), 7.39 (t, J = 7.6 Hz, 3 H, Ar-H), 7.30 (dd, J = 8.3, 6.4 Hz, 1 H, Ar-H), 7.26–7.21 (m, 1 H, Ar-H), 3.10 (t, J = 7.5 Hz, 2 H,CH_2), 2.84 (t, J = 7.5 Hz, 2 H, CH_2), 2.10 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 156.8, 142.4, 133.6, 131.1, 128.5 (2×), 128.4, 128.0, 127.6 (2×), 127.0, 122.6 (2×), 117.3, 112.4, 108.0, 33.9, 23.2, 15.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3063, 1608, 1456, 1306, 1187, 770 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{20}H_{17}NO_2S$ [M − H]$^-$ 334.0902; found 334.0892.

***tert*-Butyl 2-(9-Oxo-1-phenyl-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl)acetate (5d):** Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Asp(*t*Bu)-OH (310 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, except for the reaction time (40 °C for 4 h), giving **5d** as a red powder (140.6 mg, 75%). M.p. 167.2–168.9 °C. ^{1}H NMR (400 MHz, MeOD): δ = 8.12 (dd, J = 8.0, 1.6 Hz, 1 H, Ar-H), 7.88–7.91 (m, 2 H, Ar-H), 7.57 (ddd, J = 8.6, 7.1, 1.7 Hz, 1 H, Ar-H), 7.35 (dd, J = 10.2, 4.7 Hz, 3 H, Ar-H), 7.25 (t, J = 7.4 Hz, 1 H, Ar-H), 7.22–7.17 (m, 1 H, Ar-H), 3.73 (s, 2 H, CH_2), 1.38 (s, 9 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.4, 170.2, 156.6, 142.9, 133.5, 131.0, 129.0, 128.5 (2×), 128.1, 127.6 (2×), 127.1, 122.7, 122.6, 117.1, 108.0, 105.5, 82.4, 30.0, 28.1 (3×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3367, 1713, 1656, 1477, 1322, 1154, 757 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{23}H_{21}NO_4$ [M − H]$^-$ 374.1392; found 374.1368.

3-Methyl-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5e): Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Ala-OH (233 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a** synthesis, giving **5e** as a yellow powder (105.9 mg, 77%). M.p. 156.1–158.4 °C.^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.21 (s, 1 H, N-H), 8.16 (dd, J = 7.9, 1.5 Hz, 1 H, Ar-H), 8.10 (d, J = 7.4 Hz, 2 H, Ar-H), 7.73–7.68 (m, 1 H, Ar-H), 7.47 (dd, J = 14.7, 7.8 Hz, 3 H, Ar-H), 7.35 (d, J = 7.3 Hz, 1 H, Ar-H), 7.31 (d, J = 7.1 Hz, 1 H, Ar-H), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 174.0, 155.9, 141.4, 133.6, 131.0, 127.9 (2×), 127.4 (2×), 127.2, 126.7, 126.3, 122.4, 121.9, 117.1, 109.5, 107.3, 8.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3213, 1626, 1473, 1285, 750 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{18}H_{13}NO_2$ [M − H]$^-$ 274.0868; found 274.0872.

3-Benzyl-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5f): Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Phe-OH (290 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, except for the reaction time (40 °C for 4 h), giving **5f** as a yellow powder (89.5 mg, 51%). M.p. 151.8–154.6 °C. ^{1}H NMR (400 MHz, MeOD): δ = 8.13 (dd, J = 8.0, 1.6 Hz, 1 H, Ar-H), 7.88 (d, J = 1.3 Hz, 1 H, Ar-H), 7.86 (s, 1 H, Ar-H), 7.60–7.54 (m, 1 H, Ar-H), 7.33 (dd, J = 8.0, 6.7 Hz, 4 H, Ar-H), 7.25 (d, J = 7.4 Hz, 1 H, Ar-H), 7.22 (d, J = 0.8 Hz, 1 H, Ar-H), 7.21–7.18 (m, 4 H, Ar-H), 4.13 (s, 2 H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8, 156.8, 142.5, 138.5, 133.5, 130.9, 128.8, 128.7 (2×), 128.4 (4×), 128.0, 127.6 (2×), 127.0, 126.7, 122.6, 122.5, 117.3, 112.1, 108.2, 30.0 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3416, 1611, 1475, 1323, 745 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{24}H_{17}NO_2$ [M − H]$^-$ 350.1181; found 350.1174.

3-[4-(*tert*-Butoxy)benzyl]-1-phenylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5g): Compound **1a** (120.0 mg, 0.5 mmol) and Fmoc-Tyr(*p*-O*t*Bu)-OH (345 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5g** as a red powder (165.0 mg, 78%). M.p. 146.6–149.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.0 Hz, 1 H, Ar-H), 7.90–7.86 (m, 2 H, Ar-H), 7.56 (t, J = 7.7 Hz, 1 H, Ar-H), 7.32 (dd, J = 12.7, 5.0 Hz, 3 H, Ar-H), 7.24 (t, J = 7.4 Hz, 1 H, Ar-H), 7.19 (t, J = 7.5 Hz, 1 H, Ar-H), 7.11 (d, J = 8.3 Hz, 2 H, Ar-H), 6.83 (d, J = 8.4 Hz, 2 H, Ar-H), 4.08 (s, 2 H, CH_2), 1.28 (s, 9 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.7, 156.9, 154.2, 142.5, 133.6, 133.0, 131.0, 128.9 (2×), 128.6, 128.5 (2×), 128.1, 127.6 (2×), 127.1, 124.5 (2×), 122.6, 122.6, 117.3, 112.2, 108.4, 78.5, 29.4, 28.8 (3×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3416, 3220, 2932, 2382, 2293, 1609, 1471, 1158 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{28}H_{25}NO_3$ [M − H]$^-$ 422.1756; found 422.1761.

1-(Furan-2-yl)-3-isobutylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5h): Compound **1b** (115.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5h** as a red powder (109.0 mg, 71%). M.p. 143.0–145.1 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.36 (s, 1 H, N-H), 8.16 (dd, J = 7.9, 1.5 Hz, 1 H, Ar-H), 7.80 (d, J = 0.9 Hz, 1 H, Ar-H), 7.72 (d, J = 3.3 Hz, 1 H, Ar-H), 7.69 (dd, J = 11.2, 4.3 Hz, 1 H, Ar-H), 7.46 (d, J = 8.2 Hz, 1 H, Ar-H), 7.33 (t, J = 7.2 Hz, 1 H, Ar-H), 6.67 (dd, J = 3.3, 1.8 Hz, 1 H, Ar-H), 2.66 (d, J = 7.1 Hz, 2 H, CH_2), 2.09–2.01 (m, 1 H, CH), 0.93 (d, J = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 173.6, 156.3, 146.2, 142.3, 141.3,133.9, 126.2, 122.7, 122.0,117.7, 117.4, 113.6, 112.2, 109.0, 106.4, 32.5, 28.4, 22.0 (2×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3231, 2956, 1646, 1616, 1463, 1317, 919, 757 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{19}H_{17}NO_3$ [M − H]$^-$ 306.1130; found 306.1121.

1-(Furan-2-yl)-3-isobutyl-7-methylchromeno[2,3-*c*]pyrrol-9(2*H*)-one (5i): Compound **1d** (122.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, except for the reaction time (40 °C for 4 h), giving **5i** as a red powder (101.1 mg, 63%). M.p. 142.3–144.4 °C. ^{1}H NMR (400 MHz, [D6]DMSO): δ = 12.30 (s, 1 H, N-H), 7.93 (d, J = 1.5 Hz, 1 H, Ar-H), 7.78 (d, J = 1.0 Hz, 1 H, Ar-H), 7.72 (d, J = 3.4 Hz, 1 H, Ar-H), 7.47 (dd, J = 8.5, 2.1 Hz, 1 H, Ar-H), 7.32 (d, J = 8.5 Hz, 1 H, Ar-H), 6.66 (dd, J = 3.4, 1.8 Hz, 1 H, Ar-H), 2.64 (d, J = 7.1 Hz, 2 H, CH_2), 2.38 (s, 3 H, CH_3) 2.03 (m, 1 H, CH), 0.91 (d, J = 6.6 Hz, 6 H, CH_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]-DMSO): δ = 173.7, 154.5, 146.3, 142.3, 141.4, 134.8, 131.8, 125.7, 121.7, 117.6, 117.3, 113.5, 112.2, 108.9, 106.5, 32.5, 28.4, 22.1 (2×), 20.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3208, 2956, 1644, 1468, 1307, 1218, 815, 742 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{20}H_{19}NO_3$ [M − H]$^-$ 320.1287; found 320.1278.

1-(Furan-2-yl)-3-isobutyl-7-methoxychromeno[2,3-*c*]pyrrol-9(2*H*)-one (5j): Compound **1c** (130.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5j** as a yellow powder (144.9 mg, 86%). M.p. 140.5–142.7 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.35 (s, 1 H, N-H), 7.80 (s, 1 H, Ar-H), 7.72 (d, J = 3.3 Hz, 1 H, Ar-H), 7.58 (d, J = 3.1 Hz, 1 H, Ar-H), 7.42 (d, J = 9.1 Hz, 1 H, Ar-H), 7.29 (dd, J = 9.1, 3.1 Hz, 1 H, Ar-H), 6.66 (dd, J = 3.1, 1.7 Hz, 1 H, Ar-H), 3.84 (s, 3 H, OCH$_3$), 2.65 (d, J = 7.1 Hz, 2 H, CH$_2$), 2.04 (m, 1 H, CH), 0.92 (d, J = 6.6 Hz, 6 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 173.4, 154.6, 150.8, 146.3, 142.2, 141.5, 122.3, 118.8, 117.3, 113.3, 112.2, 108.8, 106.9, 106.2, 55.5, 32.5, 28.4, 22.1 (2×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3153, 3041, 2953, 1608, 1468, 1301, 776, 732 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{20}H_{19}NO_4$ [M − H]$^-$ 336.1236; found 336.1206.

3-Isobutyl-1-(thiophen-2-yl)chromeno[2,3-*c*]pyrrol-9(2*H*)-one (5k): Compound **1e** (123.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, except for the reaction time (40 °C for 4 h), giving **5k** as a yellow powder (75.9 mg, 47%). M.p. 160.8–162.6 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.08 (s, 1 H, N-H), 8.16 (dd, J = 7.9, 1.4 Hz, 1 H, Ar-H), 8.01 (d, J = 3.6 Hz, 1 H, Ar-H), 7.73–7.66 (m, 1 H, Ar-H), 7.54 (d, J = 5.0 Hz, 1 H, Ar-H), 7.45 (d, J = 8.3 Hz, 1 H, Ar-H), 7.32 (t, J = 7.5 Hz, 1 H, Ar-H), 7.17–7.12 (m, 1 H, Ar-H), 2.67 (d, J = 7.2 Hz, 2 H, CH$_2$), 2.06 (m, 1 H, CH), 0.95 (d, J = 6.6 Hz, 6 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 173.9, 156.1, 141.3, 133.9, 133.3, 127.3, 126.3, 126.0, 122.7, 121.9, 121.3, 117.4, 113.5, 106.9, 32.6, 28.4, 22.1 (2×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3201, 2954, 1611, 1476, 1224, 919, 753 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{19}H_{17}NO_2S$ [M − H]$^-$ 322.0902; found 322.0898.

3-Isobutyl-6-methoxy-1-(thiophen-2-yl)chromeno[2,3-*c*]pyrrol-9(2*H*)-one (5l): Compound **1f** (138.0 mg, 0.5 mmol) and Fmoc-Leu-OH (265 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5l** as a yellow powder (139.4 mg, 79%). M.p. 110.6–111.4 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.01 (s, 1 H, N-H), 8.04 (d, J = 8.8 Hz, 1 H, Ar-H), 8.01–7.98 (m, 1 H, Ar-H), 7.53 (d, J = 5.0 Hz, 1 H, Ar-H), 7.13 (dd, J = 4.9, 3.8 Hz, 1 H, Ar-H), 6.95 (d, J = 2.3 Hz, 1 H, Ar-H), 6.89 (dd, J = 8.8, 2.3 Hz, 1 H, Ar-H), 3.88 (s, 3 H, OCH$_3$), 2.64 (d, J = 7.2 Hz, 2 H, CH$_2$), 2.05 (m, 1 H, CH), 0.94 (d, J = 6.6 Hz, 6 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 173.4, 163.8, 158.0, 141.6, 133.4, 127.6, 127.2, 125.8 (2×), 121.0, 115.7, 113.5, 111.6, 106.8, 100.1, 55.8, 32.6, 28.4, 22.1 (2×) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3414, 3171, 2952, 1608, 1473, 1286, 829, 772 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{20}H_{19}NO_3S$ [M − H]$^-$ 352.1007; found 352.0981.

***tert*-Butyl [4-(1-(Furan-2-yl)-9-oxo-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl)butyl]carbamate (5m):** Compound **1b** (115.0 mg, 0.5 mmol) and Fmoc-Lys(Boc)-OH (351 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5m** as a yellow powder (162.5 mg, 77%). M.p. 145.4–147.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.57 (s, 1 H, N-H), 8.31 (dd, J = 7.9, 1.5 Hz, 1 H, Ar-H), 7.85 (d, J = 3.3 Hz, 1 H, Ar-H), 7.56–7.61 (m, 1 H, Ar-H), 7.41 (d, J = 0.9 Hz, 1 H, Ar-H), 7.34 (d, J = 8.3 Hz, 1 H, Ar-H), 7.29–7.23 (m, 1 H, Ar-H), 6.54 (dd, J = 3.3, 1.7 Hz, 1 H, Ar-H), 4.67 [s, 1 H, (C=O)-*N*-H], 3.24 (d, J = 6.1 Hz, 2 H, CH$_2$), 2.90 (t, J = 7.4 Hz, 2 H, CH$_2$), 1.78–1.73 (m, 2 H, CH$_2$), 1.61–1.56 (m, 2 H, CH$_2$), 1.46 (s, 9 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.1, 157.0, 146.3, 141.6, 141.4, 133.5, 126.8, 122.7, 122.5, 119.1, 117.4, 113.1, 112.4, 109.8, 107.4, 79.4, 39.4, 29.5, 28.4 (3×), 26.1, 22.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3333, 3166, 2930, 1689, 1620, 1465, 1280, 918, 746 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{24}H_{26}N_2O_5$ [M −H]$^-$ 421.1763; found 421.1742.

***tert*-Butyl (4-{9-Oxo-1-(thiophen-2-yl)-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl}butyl)carbamate (5n):** Compound **1e** (123.0 mg, 0.5 mmol) and Fmoc-Lys(Boc)-OH (351 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5n** as a yellow powder (133.6 mg, 61%). M.p. 163.1–165.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.74 (s, 1 H, N-H), 8.32 (d, J = 7.0 Hz, 1 H, Ar-H), 8.00 (d, J = 2.6 Hz, 1 H, Ar-H), 7.58 (dd, J = 11.2, 4.1 Hz, 1 H, Ar-H), 7.34 (d, J = 8.3 Hz, 1 H, Ar-H), 7.30 (d, J = 5.0 Hz, 1 H, Ar-H), 7.24 (d, J = 7.6 Hz, 1 H, Ar-H), 7.10–7.07 (m, 1 H, Ar-H), 4.72 [s, 1 H, (C=O)-*N*-H], 3.24 (d, J = 6.0 Hz, 2 H, CH$_2$), 2.91 (t, J = 7.1 Hz, 2 H, CH$_2$), 1.77–1.72 (m, 2 H, CH$_2$), 1.62–1.57 (m, 2 H, CH$_2$), 1.41 (s, 9 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.5, 156.9, 141.7, 133.5, 133.4, 127.4, 126.9, 126.3, 125.2, 122.5, 122.5, 122.4, 117.3, 113.5, 108.0, 79.5, 39.3, 29.2, 28.3 (3×), 26.0, 22.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3415, 3227, 2935, 1685, 1618, 1473, 1283, 1171, 922, 755 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{24}H_{26}N_2O_4S$ [M − H]$^-$ 437.1535; found 437.1496.

***tert*-Butyl (4-{6-Methoxy-9-oxo-1-(thiophen-2-yl)-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl}butyl)carbamate (5o):** Compound **1f** (138.0 mg, 0.5 mmol) and Fmoc-Lys(Boc)-OH (351 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5o** as a yellow powder (102.9 mg, 44%). M.p. 143.8–145.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.58 (s, 1 H, N-H), 8.22 (d, J = 8.8 Hz, 1 H, Ar-H), 7.98 (d, J = 3.1 Hz, 1 H, Ar-H), 7.28 (dd, J = 5.1, 0.9 Hz, 1 H, Ar-H), 7.07 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 6.82 (dd, J = 8.8, 2.4 Hz, 1 H, Ar-H), 6.77 (d, J = 2.4 Hz, 1 H, Ar-H), 4.72 [s, 1 H, (C=O)-*N*-H], 3.90 (s, 1 H, OCH$_3$), 3.23 (dd, J = 12.9, 6.4 Hz, 2 H, CH$_2$), 2.88 (t, J = 7.2 Hz, 2 H, CH$_2$), 1.76–1.71 (m, 2 H, CH$_2$), 1.61–1.56 (m, 2 H, CH$_2$), 1.41 (s, 9 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.1, 164.2, 158.7, 142.0, 133.5, 128.4, 127.4, 126.2, 125.1, 122.2, 116.5, 113.4, 111.2, 108.0, 100.2, 79.6, 55.7, 39.4, 29.3, 28.4 (3×), 26.1, 22.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3261, 3073, 2971, 2929, 1680, 1641, 1475, 1271, 1168, 833, 780 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{25}H_{28}N_2O_5S$ [M − H]$^-$ 467.1641; found 467.1623.

***tert*-Butyl (4-{7-Methyl-9-oxo-1-(thiophen-2-yl)-2,9-dihydrochromeno[2,3-*c*]pyrrol-3-yl}butyl)carbamate (5p):** Compound **1g** (130.0 mg, 0.5 mmol) and Fmoc-Lys(Boc)-OH (351 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5p** as a yellow powder (155.9 mg, 69%). M.p. 152.4–153.3 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.09 (s, 1 H, N-H), 7.99 (d, J = 3.1 Hz, 1 H, Ar-H), 7.94 (s, 1 H, Ar-H), 7.54 (d, J = 5.0 Hz, 1 H, Ar-H), 7.51 (dd, J = 8.5, 1.6 Hz, 1 H, Ar-H), 7.37 (d, J = 8.4 Hz, 1 H, Ar-H), 7.11–7.17 (m, 1 H, Ar-H), 6.78 [s, 1 H, (C=O)-*N*-H], 2.97 (d, J = 6.1 Hz, 2 H, CH$_2$), 2.77 (t, J = 7.3 Hz, 2 H, CH$_2$), 2.40 (s, 3 H, CH$_3$), 1.64–1.71 (m, 2 H, CH$_2$), 1.41–1.48 (m, 2 H, CH$_2$), 1.35 (s, 9 H, CH$_3$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 175.7, 155.1, 141.9, 134.6, 133.5, 132.0, 127.4, 126.5, 126.2, 125.2, 122.3, 122.2, 117.0, 113.3, 108.1, 79.5, 39.4, 29.2, 28.4 (3×), 26.1, 22.7, 20.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3389, 3248, 2930, 1680, 1617, 1478, 1292, 1165, 824, 773 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{25}H_{28}N_2O_4S$ [M + H]$^+$ 453.1848; found 453.1839.

3-[4-(*tert*-Butoxy)benzyl]-6-methoxy-1-(thiophen-2-yl)chromeno-[2,3-*c*]pyrrol-9(2*H*)-one (5q): Compound **1f** (138.0 mg, 0.5 mmol) and Fmoc-Tyr(*p*-O*t*Bu)-OH (345 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5q** as a yellow powder (123.9 mg, 54%). M.p. 166.5–168.7 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.28 (s, 1 H, N-H), 8.08 (d, J = 8.9 Hz, 1 H, Ar-H), 8.06 (d, J = 3.6 Hz, 1 H, Ar-H), 7.56 (d, J = 4.9 Hz, 1 H, Ar-H), 7.20 (d, J = 8.4 Hz, 2 H, Ar-H), 7.17–7.14 (m,

1 H, Ar-H), 6.95 (d, J = 2.2 Hz, 1 H, Ar-H), 6.93 (s, 1 H, Ar-H), 6.92–6.89 (m, 2 H, Ar-H), 4.12 (s, 2 H, CH_2), 3.88 (s, 3 H, OCH_3),1.25 (s, 9 H,CH_3) ppm. ^{13}C NMR (400 MHz, [D_6]DMSO): δ = 173.3, 163.9, 157.9, 153.3, 141.6, 134.0, 133.3, 128.5 (2×), 127.7, 127.3, 126.1 (2×), 123.8 (2×), 121.7, 115.7, 112.6, 111.6, 107.0, 100.2, 77.6, 55.8, 28.5 (3×), 28.4 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2973, 1609, 1475, 1271, 1162, 925, 777 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{27}H_{25}NO_4S$ [M − H]$^-$ 458.1426; found 458.1387.

3-[2-(Methylthio)ethyl]-1-(thiophen-2-yl)chromeno[2,3-*c*]pyrrol-9(2*H*)-one (5r): Compound **1e** (123.0 mg, 0.5 mmol) and Fmoc-Met-OH (278 mg, 0.75 mmol) were treated by using the same procedure as that used for **5a**, giving **5r** as a yellow powder (151.7 mg, 89%). M.p. 143.6–145.6 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 12.20 (s, 1 H, N-H), 8.16 (d, J = 7.9 Hz, 1 H, Ar-H), 8.02 (d, J = 3.4 Hz, 1 H, Ar-H), 7.71 (t, J = 7.0 Hz, 1 H, Ar-H), 7.57 (d, J = 4.7 Hz, 1 H, Ar-H), 7.49 (d, J = 8.3 Hz, 1 H, Ar-H), 7.33 (t, J = 7.4 Hz, 1 H, Ar-H), 7.18–7.14 (m, 1 H, Ar-H), 3.07 (t, J = 7.5 Hz, 2 H, CH_2), 2.86 (t, J = 7.5 Hz, 2 H, CH_2), 2.13 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 173.8, 156.0, 141.4, 134.0, 133.2, 127.3, 126.2 (3×), 122.8, 121.9, 121.7, 117.4, 112.5, 106.9, 32.6, 23.7, 14.5 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3142, 2972, 1642, 1479, 1219, 823, 756 cm^{-1}. HRMS (ESI–TOF): calcd. for $C_{18}H_{15}NO_2S_2$ [M − H]$^-$ 340.0466; found 340.0412.

Synthesis of 4a′: The synthesis of **4a′** was performed under similar conditions as those used to synthesize **5a**–**r**. Boc-Lys(Boc)-OH (0.75 mmol, 0.26 g), **1a** (0.5 mmol, 120 mg), and DMAP (0.3 mmol, 36.6 mg) were dissolved in Py (10 mL). Then, DCC (0.9 mmol, 185.4 mg) was added, and the mixture was stirred at 15 °C until **1a** disappeared, as monitored by using TLC (about 30 min). After that, the reaction mixture was warmed to 40 °C for 2 h. Then, the reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to remove the Py, giving a residue that could be purified by column chromatography to give **4a′** as an off-white powder (210 mg, 76.3%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 7.9, 1.3 Hz, 1 H, Ar-H), 7.91 (s, 1 H, Ar-H), 7.89 (d, J = 1.2 Hz, 1 H, Ar-H), 7.74–7.68 (m, 1 H, Ar-H), 7.55 (t, J = 7.4 Hz, 1 H, Ar-H), 7.51 (d, J = 8.2 Hz, 1 H, Ar-H), 7.45–7.38 (m, 3 H, Ar-H), 5.02 [s, 1 H, (C=O)-N-H], 4.69 [s, 1 H, (C=O)-N-H], 4.64 (td, J = 8.6, 5.4 Hz, 1 H, CH), 3.08 (d, J = 5.0 Hz, 2 H, CH_2), 2.00–1.84 (m, 2 H, CH_2), 1.51–1.45 (m, 4 H, CH_2), 1.42 (s, 9 H, *t*Bu), 1.20 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.0, 176.3, 167.6, 156.0, 155.7, 154.6, 137.1, 134.1, 133.5, 129.4 (2×), 128.5 (2×), 125.9, 125.5, 123.3, 121.8, 117.9 (2×), 79.8, 78.9, 52.8, 39.8, 34.5, 28.3, 27.9, 22.9 ppm. ESI-MS: calcd. for $C_31H_{38}N_2O_7$ [M − H]$^-$ 550.3; found 549.3.

Supporting Information (see footnote on the first page of this article): X-ray data, HPLC analysis and spectroscopic data for all new compounds.

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