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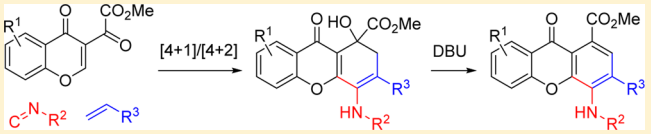
Regioselective Tandem [4 + 1]−[4 + 2] Synthesis of Amino-Substituted Dihydroxanthones and Xanthones

Ana Bornadiego, Jesús Díaz,* and Carlos F. Marcos*

Laboratory of Bioorganic Chemistry & Membrane Biophysics (L.O.B.O.), School of Veterinary Sciences, University of Extremadura, 10071 Cáceres, Spain

Supporting Information

ABSTRACT: A highly convergent and operationally simple approach to mycotoxin-related 4-amino-substituted 1-hydroxy-dihydroxanthones is described. The target compounds are obtained in one pot by the multicomponent reaction of 3-carbonylchromones, isocyanides, and nonsymmetric dienophiles. The reaction, which involves a tandem [4 + 1]−[4 + 2] cycloaddition, efficiently affords a variety of both monomeric and dimeric polysubstituted dihydroxanthones structurally similar to bioactive ergochromes. Further aromatization to the corresponding xanthones is readily achieved by treatment with DBU under microwave irradiation.



INTRODUCTION

Partially hydrogenated xanthones are the key structural motifs of secondary metabolites from fungi that exhibit potent biological activities.[1] Notably, monomeric dihydro- or tetrahydroxanthones containing both a hydroxyl and an ester group on position 1, such as globosuxanthones,[2] diversonolic esters,[3] and aspergillusones,[4] have demonstrated strong antifungal, antibiotic, and anticancer activities (Figure 1). Similarly, the related dimeric secalonic acids, ergoflavins, ergochrysins, and chrysergonic acid have shown potent and selective antitumor and anti-HIV properties.[5]

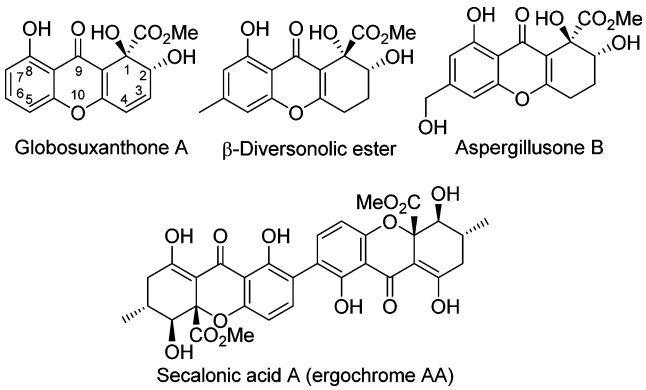


Figure 1. Natural hydrogenated monomeric and dimeric xanthones.

Although various synthetic routes to xanthones are known, they are largely limited to fully aromatized targets,[1,6] with reports on the syntheses of the more challenging, partially saturated xanthones being few and far between.[3a,7] Indeed, there is only one example in the literature, by the group of Nicolaou, detailing the synthesis of tetrahydroxanthones comprising a quaternary hydroxyl group on position 1.[3a] According to this procedure, a mixture of α- and β-diversonolic esters is obtained through a 10-step synthesis in a 14% yield. This synthesis is both elaborate and low yielding. The development of direct and efficient synthetic methods for hydrogenated xanthones is thus highly desirable.

Herein we describe the selective synthesis of 1-hydroxy-dihydroxanthones based on natural mycotoxins and their straightforward and high yielding transformation into the corresponding xanthones.

RESULTS AND DISCUSSION

In a previous manuscript, we reported the trapping of elusive 2-aminofurans by means of Diels−Alder reactions leading to a facile one-pot synthesis of anilines. These 2-aminofurans were readily obtained by the reaction of isocyanides and α,β-unsaturated carbonylic compounds, prior to *in situ* reaction with dienophiles.[8] Likewise, as a result of our interest in the synthesis of biologically relevant benzopyranones,[9] we investigated a similar [4 + 1] plus [4 + 2] cycloaddition of carbonylchromones (**1**), isocyanides (**2**), and cyclic maleic acid derivatives for the synthesis of fully aromatized polysubstituted 4-aminoxanthones (**7**).[10] In that work, we postulate a mechanism in which the oxygen bridge of intermediate amino-substituted 7-oxabicyclo[2.2.1]heptene (**5**) is opened with assistance of the nitrogen lone pair to give a 4-amino-1-hydroxy-1*H*-xanthen-9(2*H*)-one (Scheme 1; **6**; E^1 and E^2 are electron-withdrawing groups). We were unable to obtain the isolated compound (**6**), since the acidity of the hydrogen on position 2 enables spontaneous dehydration to aromatic 4-aminoxanthone **7**, even at room temperature and in the absence of bases (Scheme 1).

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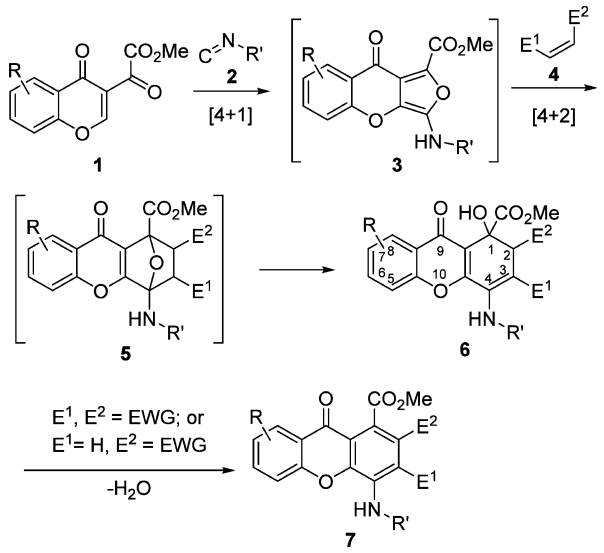
Scheme 1. Proposed Mechanism for the Synthesis of Amino-dihydroxanthones and the Expected Dehydration to the Corresponding Xanthones



We reason that elimination of water would be much more difficult in the absence of an electron-withdrawing group on position 2, and in that case it could be possible to isolate the intermediate 1-hydroxy-1*H*-xanthen-9(2*H*)-one (**6**). The use of asymmetric dienophiles containing only one electron-withdrawing group would lead to 1-hydroxy-1*H*-xanthen-9(2*H*)-ones, with the substituent on position C2 or C3, depending on the regiochemistry of the [4 + 2] cycloaddition. The regioisomer substituted on C2 would then be prone to conversion to aromatized products through dehydration. In contrast, the regioisomer substituted on C3 would most likely be stable under the conditions required for the [4 + 1]/[4 + 2] cycloaddition (Scheme 1).

Frontier molecular orbitals calculations were carried out in order to predict the possible products of the cycloaddition of the chromone-derived aminofurans (**3**) with classical dienophiles as acrylonitrile (**4a**) and methyl vinyl ketone (**4b**). Table 1 shows that these reactions should result from diene

Table 1. Energy Differences between Diene (3; R = H, R′ = Cy) and Dienophile (4) FMOs

	acrylonitrile (**4a**)	methyl vinyl ketone (**4b**)
$HOMO_3 - LUMO_4$	0.13918	0.13857
$HOMO_4 - LUMO_3$	0.21176	0.17041

HOMO−dienophile LUMO interactions, having the smaller energetic gap. The interaction of the diene HOMO and dienophile LUMO positions with higher coefficients would lead to the formation of the regioisomer with the nitrile or keto group on C3 (Figure 2). These results are consistent with previous reports dealing with the Diels−Alder reaction of furanamines.[11] Thus, to confirm the reliability of computer calculations, we decided to investigate the reaction of methyl 2-oxo-2-(4-oxo-4*H*-chromen-2-yl)acetate (**1a**) with cyclohexyl isocyanide (**2a**) and acrylonitrile (**4a**).

We found the reaction proceeds very slowly at room temperature, and TLC analysis shows the transformation of the starting reagents into a new product, which, in contrast to xanthones (**7**), is not fluorescent. Spectroscopic data of the

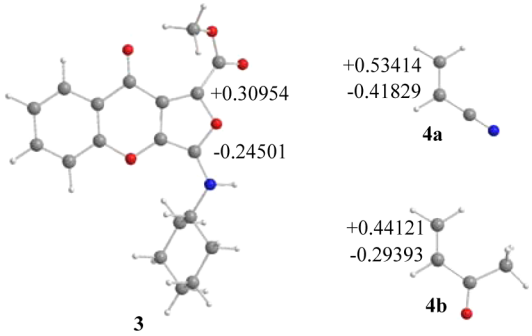
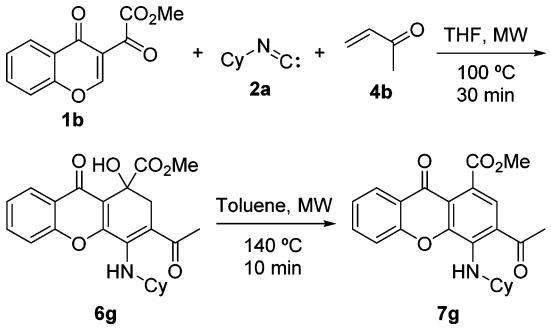


Figure 2. Calculated FMO coefficients of diene (**3**) HOMO and dienophile (**4a** and **4b**) LUMO at the B3LYP/6-31G* level.

resulting product are compatible with the structure of 4-amino-1-hydroxy-1*H*-xanthen-9(2*H*)-one (**6a**). Encouraged by this result, we proceeded to examine the effect of varying reaction temperatures and ratios of the dienophile. Satisfactory conditions were achieved when the reaction was performed with 2 equiv of acrylonitrile at 70 °C.

The reaction was also possible using methyl vinyl ketone (**4b**) as the dienophile, although higher reaction temperatures (100 °C) were required. This reaction gave satisfactory results with 4-amino-1-hydroxy-1*H*-xanthen-9(2*H*)-one (**6g**) being obtained in 74% yield using just 1.2 equiv of methyl vinyl ketone under microwave irradiation at 100 °C (Scheme 2). Spectroscopic analysis also supports the formation of the expected structure.

Scheme 2. Synthesis of Dihydroxanthone (6g) and Subsequent Dehydration to the Corresponding Xanthone (7g)



To further verify the structure of the cycloadducts, hydroxyxanthenone (**6g**) was dehydrated by treatment with DBU under microwave irradiation (Scheme 2). X-ray diffraction analysis of the resulting xanthone (**7g**) confirmed the predicted regiochemistry of the cycloaddition (Supporting Information; Figure S1).

To explore the scope of this reaction's applicability, chromones (**1a−d**) were treated with acrylonitrile (**4a**) or methyl vinyl ketone (**4b**) and different isocyanides (**2a−c**) under the optimized reaction conditions (Table 2). The reaction was shown to be tolerant of various isocyanides, dienophiles, and substituents on the chromone. No traces of aromatized products were detected under these conditions, and products were generally cleanly obtained in good yields (70−90%). An exception to this were the reactions with *p*-methoxyphenyl isocyanide, which led to complex reaction mixtures, affording the products in lower yields (Table 2,

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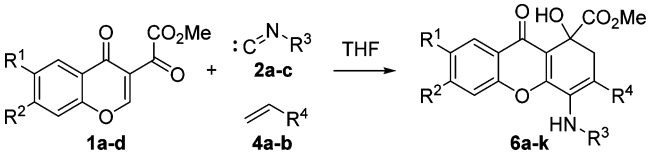
Table 2. Synthesis of 4-Amino-1-hydroxy-1*H*-xanthen-9(2*H*)-ones (6)



entry	R^1	R^2	R^3	R^4	time (h)	product (% yield)
1	Me	H	Cy	CN	2	**6a** (76)[a]
2	H	H	Cy	CN	2	**6b** (81)[a]
3	H	OMe	Cy	CN	4.5	**6c** (82)[a]
4	Cl	H	Cy	CN	2	**6d** (83)[a]
5	H	H	*p*MeOPh	CN	9	**6e** (28)[a]
6	Me	H	Cy	COMe	1	**6f** (78)[b]
7	H	OMe	Cy	COMe	0.5	**6g** (74)[b]
8	Cl	H	Cy	COMe	1	**6h** (90)[b]
9	H	H	Cy	COMe	0.5	**6i** (70)[b]
10	Me	H	*p*MeOPh	COMe	2	**6j** (62)[b]
11	Me	H	C_5H_{11}	COMe	1	**6k** (83)[b]

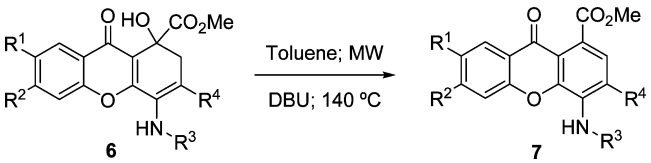
[a]*Method A*: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4a** (2 equiv) in THF was heated 2–9 h at 70 °C. [b]*Method B*: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4b** (1.2 equiv) in THF was irradiated with MW 0.5–2 h in a closed vial at 100 °C.

entries 5 and 10). This could be explained by the lower nucleophilicity of aromatic isocyanides,[12] resulting in longer reaction times for the [4 + 1] cycloaddition. *p*-Methoxyphenyl isocyanide has also been recently reported to require much longer reaction times and give poorer yields in Passerini reactions.[13] Furthermore, HOMO coefficients of *p*-methoxyphenylamino furanechromones are significantly smaller than the corresponding HOMO coefficients of cyclohexylamino furanechromones, leading to a less efficient overlap with the dienophile LUMO in the Diels–Alder reaction (see Tables S7 and S8 in the Supporting Information).

Importantly, hydroxydihydroxanthenones (**6**) were readily dehydrated by microwave irradiation at 140 °C in the presence of DBU to give the corresponding aromatic xanthones (**7b,c,g,h**; Table 3), demonstrating the feasibility of our method to afford both hydrogenated and fully aromatized xanthones.

We went on to explore the possibility of performing the synthesis of xanthones (**7**) using a one-pot sequential procedure and discovered that aromatic xanthones (**7a–p**) could be efficiently synthesized through the tandem cyclo-

Table 3. Dehydration of 1-Hydroxydihydroxanthones (6)

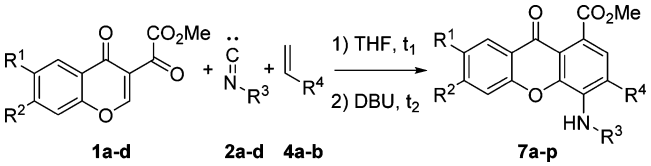


entry	R^1	R^2	R^3	R^4	time (min)	product (% yield)[a]
1	H	H	Cy	CN	5	**7b** (83)
2	H	OMe	Cy	CN	5	**7c** (75)
3	H	OMe	Cy	COMe	10	**7g** (80)
4	Cl	H	Cy	COMe	5	**7h** (82)

[a]General procedure: A solution of **6** and 2 equiv of DBU in toluene was heated at 140 °C under MW irradiation for 5–10 min.

addition of carbonylchromones (**1a–d**), isocyanides (**2a–d**), and asymmetric dienophiles (**4a–b**), followed by addition of DBU and further heating (Table 4). Comparable yields were

Table 4. One-Pot Synthesis of Xanthones (7)



entry	R^1	R^2	R^3	R^4	t_1/t_2 (h)	product (% yield)
1	Me	H	Cy	CN	5/1.5	**7a** (68)[a]
2	H	H	Cy	CN	2/0.5	**7b** (78)[a]
3	H	H	Cy	CN	0.5/0.2	**7b** (75)[b]
4	H	OMe	Cy	CN	9/1	**7c** (65)[a]
5	Cl	H	Cy	CN	2.5/0.5	**7d** (70)[a]
6	Me	H	Cy	COMe	6.5/1	**7f** (70)[b]
7	H	OMe	Cy	COMe	1/1.5	**7g** (75)[b]
8	Cl	H	Cy	COMe	1/0.3	**7h** (68)[b]
9	H	H	Cy	COMe	0.5/1	**7i** (76)[b]
10	Me	H	*p*MeOPh	COMe	3/0.5	**7j** (70)[b]
11	Me	H	C_5H_{11}	COMe	1.5/1	**7k** (44)[b]
12	H	OMe	*t*-Bu	CN	3/0.5	**7l** (69)[a]
13	H	OMe	*t*-Bu	CN	1/0.2	**7l** (69)[b]
14	Cl	H	*t*-Bu	CN	3.5/0.5	**7m** (78)[a]
15	Cl	H	*p*MeOPh	CN	8/0.5	**7n** (27)[a]
16	H	OMe	*p*MeOPh	CN	3/0.5	**7o** (40)[a]
17	Cl	H	C_5H_{11}	COMe	0.5/0.5	**7p** (48)[b]

[a]*Method A*: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (2 equiv) was heated in THF at 70 °C for 2–9 h before the addition of 2 equiv of DBU and further heating of the reaction mixture for 25–75 min at the same temperature. [b]*Method B*: A solution of **1** (1 equiv), **2** (1.2 equiv), and **4** (1.2 equiv) in THF was irradiated with MW in a sealed vial at 100 °C for 0.5–6 h before the addition of 2 equiv DBU, and further irradiation of the reaction mixture is for 10–90 min.

obtained when the reaction with acrylonitrile (**4a**) is performed under either thermal or microwave conditions (cf. Table 4, entries 2 and 3, 12 and 13), with considerably shorter reaction times when using microwaves. However, due to the high volatility of methyl vinyl ketone (**4b**), reactions with this dienophile are preferably accomplished under microwave irradiation in a sealed vial.

In order to evaluate our synthetic methodology toward the construction of the basic skeleton of more complex xanthone natural products, dimeric chromone **11** was synthesized from readily available bisphenol (**8**) and transformed to dimeric dihydroxanthone **12**. Thus, according to Scheme 3, acetylation and acid catalyzed Fries rearrangement[14] led almost quantitatively to 1,1′-(4,4′-dihydroxy-[1,1′-biphenyl]-3,3′-diyl)bis-(ethan-1-one) (**9**),[15] which was readily transformed into bischromone **11**, via the corresponding double enaminone (**10**). Finally, reaction with cyclohexyl isocyanide and acrylonitrile under reflux in toluene successfully afforded **12** in 55% yield over the three steps.

■ CONCLUSIONS

In conclusion, we have successfully designed a straightforward multicomponent synthesis of xanthone mycotoxin analogues. These compounds are structurally similar to natural globosuxanthones and diversolonic acids and hence may have interest

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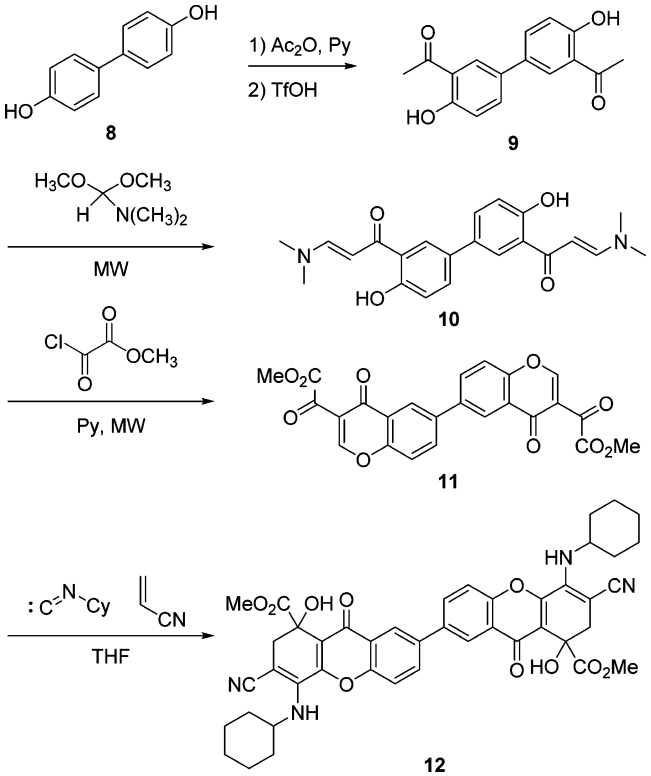
Scheme 3. Synthesis of Dimeric Dihydroxanthone 12



for their biological activities. The reaction takes place in very mild conditions and represents a significant improvement over previously reported synthesis. Both hydrogenated and fully aromatized xanthones can be selectively synthesized in a one-pot process. The highly convergent and atom economic tandem reaction affords the target compounds in high yields, with complete regioselectivity, starting from readily available 3-carbonylchromones, isocyanides, and dienophiles. We have demonstrated the utility of this methodology for the synthesis of structurally challenging dimeric dihydroxanthone **12**. This compound, closely related to mycotoxin secalonic acid, was obtained in a 55% yield in only three reaction steps starting from bisphenol **9**.

Next we will focus on the application of this approach for the synthesis of homochiral dihydroxanthones; thus, further research aimed to the development of an enantioselective version of this reaction is currently underway in our lab.

EXPERIMENTAL SECTION

General Techniques. Liquid reagents were measured using positive-displacement micropipettes with disposable tips and pistons. Thin layer chromatography was performed on aluminum plates, using 254 nm UV light or a mixture of *p*-anisaldehyde (2.5%), acetic acid (1%), and H_2SO_4 (3.4%) in 95% ethanol, as developer.

Materials. Isocyanides and dienophiles were purchased from commercial sources. Methyl 2-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxoacetate (**1a**), methyl 2-oxo-2-(4-oxo-4*H*-chromen-3-yl)acetate (**1b**), methyl 2-(7-methoxy-4-oxo-4*H*-chromen-3-yl)-2-oxoacetate (**1c**), methyl 2-(6-chloro-4-oxo-4*H*-chromen-3-yl)-2-oxoacetate (**1d**), and 1,1′-(4,4′-dihydroxy-[1,1′-biphenyl]-3,3′-diyl)bis(ethan-1-one) (**9**) were prepared according to literature procedures.[10,15]

Instrumentation. Melting points are uncorrected. IR spectra were recorded as KBr pellets. Proton and carbon-13 nuclear magnetic resonance (^{1}H NMR or ^{13}C NMR) spectra were obtained on a 400 or 500 MHz spectrometer. NMR signal assignment of compounds **6a**, **6g**, **7a**, and **7g** was made based on HSQC and NOE NMR experiments. Mass spectra (MS) and High Resolution Mass Spectra (HRMS) were recorded using Electron Impact (EI, 70 eV), Chemical Ionization (CI) with CH_4, or ESI-FIA-TOF. The assignments of signals in ^{13}C NMR were made by DEPT. Experiments under microwave irradiation were performed in closed vials, using a focused single-mode microwave reactor CEM Discover BenchMate, provided with an IR internal thermal probe.

Computational Details. Quantum chemical computations were carried out with the Gaussian 09 series of programs.[16] Full geometry optimizations of stable species were performed in the gas phase by employing the hybrid density functional B3LYP[17] with the 6-31G(d) basis set.[18] The B3LYP functional combines the Becke's three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang, and Parr. The nature of the stationary points was verified by analytical computations of harmonic vibrational frequencies.

General Procedure for the Synthesis of 4-Amino-1-hydroxy-1*H*-xanthen-9(2*H*)-ones (6a–k). *Method A*: To a solution of chromenones **1a–1d** (0.3 mmol) in dry THF (2 mL), isocyanide **2a–2c** (0.36 mmol) and dienophile **4a–4b** (0.6 mmol) are successively added. The resulting mixture is heated at 70 °C (bath temperature) under a nitrogen atmosphere until all the starting chromone is consumed, as judged by TLC. HCl (1 N) is then added to the reaction mixture, the crude is extracted with CH_2Cl_2, and the organic phase is dried (Na_2SO_4) and concentrated. In the case of having a precipitate, the solid is filtered and washed with hexane, giving the desired product **6a–6d**. Otherwise, the crude mixture is purified by column chromatography (silica gel, hexane–EtOAc gradient), giving the desired product **6e**.

Method B: To a solution of chromenones **1a–1d** (0.3 mmol) in dry THF (2 mL), isocyanide **2a–2c** (0.36 mmol) and dienophile **4a–4b** (0.36 mmol) are successively added. The resulting mixture is irradiated with MW in a closed vial at 100 °C until all the starting chromone is consumed, as judged by TLC. HCl (1 N) is then added to the reaction mixture, the crude is extracted with CH_2Cl_2, and the organic phase is dried (Na_2SO_4) and concentrated. In the case of having a precipitate, the solid is filtered and washed with hexane, giving the desired product **6f–6h**. Otherwise, the crude mixture is purified by column chromatography (silica gel, hexane–EtOAc gradient), giving the desired product **6i–6k**.

*Methyl 3-Cyano-4-(cyclohexylamino)-1-hydroxy-7-methyl-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6a**).* Obtained as a light yellow solid (2 h, 93 mg, 76%); mp: 206–218 °C (CH_2Cl_2); IR (cm^{-1}): 3400, 2937, 2854, 2183, 1741, 1632, 1614, 1571; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H, H-8), 7.56 (d, J = 8.6 Hz, 1H, H-5 or H-6), 7.43 (d, J = 8.6 Hz, 1H, H-5 or H-6), 5.18 (d, J = 8.5 Hz, 1H, NH), 4.79 (bs, 1H, OH), 4.14 (m, 1H, C<u>H</u>-NH), 3.83 (s, 3H, $COOCH_3$), 3.12 (d, J = 16.4 Hz, 1H, H-2), 2.76 (d, J = 16.4 Hz, 1H, H-2), 2.21 (m, 2H, Cy), 2.47 (s, 3H, Ar–CH_3), 1.81–1.24 (m, 8H, Cy) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 177.0 (C), 175.2 (C), 154.0 (C), 153.6 (C), 141.4 (C), 137.0 (C), 136.4 (C-5 or C-6), 125.8 (C-8), 123.5 (C), 121.1 (C), 119.2 (C), 117.9 (C-5 or C-6), 71.6 (C), 70.9 (C), 53.6 ($COOCH_3$), 51.8 (CH–NH), 36.7 (C-2), 33.7 (CH_2), 25.2 (CH_2), 24.06 (CH_2), 24.02 (CH_2), 20.7 (Ar–CH_3) ppm; MS (CI) m/z (%) 409 (M + 1, 99), 408 (M^+, 40), 407 (53), 391 (100), 374 (100), 360 (100), 350 (82); HRMS (ESI-FIA-TOF) Calcd for $C_{23}H_{24}N_2NaO_5$: 431.1577. Found: 431.1574.

*Methyl 3-Cyano-4-(cyclohexylamino)-1-hydroxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6b**).* Obtained as a light yellow solid (1.7 h, 96 mg, 81%); mp: 206–215 °C (CH_2Cl_2); IR (cm^{-1}): 3381, 2932, 2854, 2180, 1740, 1623, 1607, 1567; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 7.6 Hz, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 5.18 (d, J = 7.4 Hz, 1H), 4.74 (bs, 1H), 4.15 (m, 1H), 3.84 (s, 3H), 3.13 (d, J = 16.4 Hz, 1H), 2.76 (d, J = 16.4 Hz, 1H), 2.20 (m, 2H), 1.81–1.26 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 177.8 (C), 174.7 (C), 154.8 (C), 153.7 (C), 140.9 (C), 134.8 (CH), 126.37 (CH), 126.30 (CH), 123.5 (C), 120.7 (C), 119.2 (C), 117.9 (CH), 71.9 (C), 70.9 (C), 53.8 (CH_3), 51.9 (CH), 36.9 (CH_2), 33.9 (CH_2), 25.6 (CH_2), 24.38 (CH_2), 24.35

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(CH_2) ppm; MS (CI) *m/z* (%) 395 (M + 1, 2), 394 (M^+, 2), 376 (23), 360 (41), 345 (100), 333 (23). HRMS (EI) Calcd for $C_{22}H_{22}N_2O_5$: 394.1529. Found: 394.1526.

*Methyl 3-Cyano-4-(cyclohexylamino)-1-hydroxy-6-methoxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6c**).* Obtained as a light brown solid (4.5 h, 104 mg, 82%); mp: 207−212 °C (CH_2Cl_2); IR (cm^{-1}): 3397, 2936, 2856, 2183, 1748, 1600, 1567; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.9 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.89 (s, 1H), 5.14 (d, *J* = 7.7 Hz, 1H), 4.89 (bs, 1H), 4.15 (m, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.11 (d, *J* = 16.2 Hz, 1H), 2.76 (d, *J* = 16.2 Hz, 1H), 2.21 (m, 2H), 1.82−1.26 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 176.2 (C), 175.1 (C), 165.5 (C), 157.1 (C), 153.8 (C), 141.4 (C), 127.9 (CH), 121.0 (C), 119.3 (C), 117.7 (C), 115.8 (CH), 100.5 (CH), 71.4 (C), 71.0 (C), 56.0 (CH_3), 53.6 (CH_3), 51.8 (CH), 36.6 (CH_2), 33.8 (CH_2), 25.3 (CH_2), 24.0 (CH_2) ppm; MS (EI) *m/z* (%) 425 (M + 1, 1), 424 (M^+, 3), 406 (46), 365 (100), 363 (91), 324 (24), 293 (96); HRMS (EI) Calcd for $C_{23}H_{24}N_2O_6$: 424.1634. Found: 424.1630.

*Methyl 7-Chloro-3-cyano-4-(cyclohexylamino)-1-hydroxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6d**).* Obtained as a green solid (2.2 h, 107 mg, 83%); mp: 205 °C (CH_2Cl_2); IR (cm^{-1}): 3402, 2934, 2852, 2186, 1737, 1627, 1605, 1562; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 5.12 (bs, 1H), 4.61 (bs, 1H), 4.14 (m, 1H), 3.84 (s, 3H), 3.12 (d, *J* = 16.4 Hz, 1H), 2.74 (d, *J* = 16.4 Hz, 1H), 2.20 (m, 2H), 1.79−1.27 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 175.0 (C), 174.4 (C), 154.0 (C), 153.0 (C), 140.6 (C), 135.0 (CH), 132.4 (C), 125.7 (CH), 124.5 (C), 120.5 (C), 119.6 (CH), 119.2 (C), 72.3 (C), 70.6 (C), 53.9 (CH_3), 52.0 (CH), 37.0 (CH_2), 33.9 (CH_2), 25.5 (CH_2), 24.38 (CH_2), 24.34 (CH_2) ppm; MS (CI) *m/z* (%) 429 (M + 1, 5), 411 (27), 379 (60), 367 (25), 346 (43), 285 (15). HRMS (CI) Calcd for $C_{22}H_{20}N_2O_4Cl$ (dehydrated): 411.1112. Found: 411.1115.

*Methyl 3-Cyano-1-hydroxy-4-((4-methoxyphenyl)amino)-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6e**).* Obtained as a yellow solid (8.7 h, 35 mg, 28%); mp: 181 °C (hexane−EtOAc); IR (cm^{-1}): 3350, 2194, 1742, 1605, 1563; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.7 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.92 (t, *J* = 8.9 Hz, 2H), 6.71 (bs, 1H), 4.84 (bs, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.14 (d, *J* = 16.9 Hz, 1H), 2.78 (d, *J* = 16.9 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): 176.3 (C), 174.5 (C), 158.6 (C), 154.9 (C), 154.0 (C), 142.0 (C), 135.0 (CH), 131.2 (C), 127.2 (CH), 126.4 (CH), 126.2 (CH), 123.8 (C), 119.4 (C), 118.0 (CH), 117.8 (C), 114.5 (CH), 71.0 (C), 55.6 (CH_3), 53.9 (CH_3), 36.8 (CH_2) ppm; MS (CI) *m/z* (%) 419 (M + 1, 9), 418 (2), 401 (26), 400 (16), 369 (45), 270 (20). HRMS (CI) Calcd for $C_{23}H_{19}N_2O_6$: 419,1243. Found: 419.1239.

*Methyl 3-Acetyl-4-(cyclohexylamino)-1-hydroxy-7-methyl-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6f**).* Obtained as a yellow solid (0.7 h, 100 mg, 78%); mp: 208−220 °C (CH_2Cl_2); IR (cm^{-1}): 3501, 2933, 2851, 1741, 1635, 1616, 1584; ^1H NMR (500 MHz, $CDCl_3$) δ 11.12 (d, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 1.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 5.75 (bs, 1H), 3.94 (m, 1H), 3.79 (s, 3H), 3.20 (d, *J* = 15.8 Hz, 1H), 2.87 (d, *J* = 15.8 Hz, 1H), 2.49 (s, 3H), 2.27 (s, 3H), 2.00 (m, 2H), 1.84−1.26 (m, 8H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): 197.4 (C), 177.2 (C), 174.4 (C), 156.0 (C), 153.4 (C), 146.6 (C), 136.4 (C), 136.2 (CH), 125.3 (CH), 123.5 (C), 120.8 (C), 117.6 (CH), 101.8 (C), 72.8 (CH), 55.0 (CH), 53.4 (CH_3), 35.9 (CH_2), 35.0 (CH_2), 34.8 (CH_2), 29.0 (CH_3), 25.6 (CH_2), 24.7 (CH_2), 21.2 (CH_3) ppm; MS (CI) *m/z* (%) 426 (M + 1, 97), 425 (M^+, 38), 408 (77), 376 (100), 366 (99), 294 (88); HRMS (ESI-FIA-TOF) Calcd for $C_{24}H_{27}NNaO_6$: 448.1731. Found: 448.1733.

*Methyl 3-Acetyl-4-(cyclohexylamino)-1-hydroxy-6-methoxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6g**).* Obtained as a yellow solid (0.6 h, 98 mg, 74%); mp: 193−200 °C (CH_2Cl_2); IR (cm^{-1}): 3425, 2937, 1747, 1637, 1607, 1581; ^1H NMR (500 MHz, $CDCl_3$) δ 11.11 (d, *J* = 7.6 Hz, 1H, NH), 8.13 (d, *J* = 8.9 Hz, 1H, H-7 or H-8), 7.05 (d, *J* = 8.9 Hz, 1H, H-7 or H-8), 6.82 (d, *J* = 1.8 Hz, 1H, H-5), 5.90 (bs, 1H, OH), 3.94 (s, 3H, $COOCH_3$ or Ar-OCH_3), 3.90 (m, 1H, CH-NH), 3.78 (s, 3H, $COOCH_3$ or Ar-OCH_3), 3.20 (d, *J* = 15.7 Hz, 1H, H-2), 2.86 (d, *J* = 15.7 Hz, 1H, H-2), 2.27 (s, 3H, $COCH_3$), 2.00 (m, 2H, Cy), 1.82−1.31 (m, 8H, Cy) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 197.4 (C), 176.6 (C), 174.4 (C), 165.1 (C), 156.9 (C), 155.7 (C), 146.7 (C), 127.6 (C-7 or C-8), 120.8 (C), 117.7 (C), 115.3 (C-7 or C-8), 101.8 (C), 100.4 (C-5), 73.0 (C), 56.1 ($COOCH_3$ or Ar−OCH_3), 54.9 (CH−NH), 53.4 ($COOCH_3$ or Ar−OCH_3), 35.9 (C-2), 35.0 (CH_2), 34.7 (CH_2), 29.0 ($COCH_3$), 25.5 (CH_2), 24.7 (CH_2) ppm; MS (EI) *m/z* (%) 441 (M^+, 7), 423 (13), 382 (14), 300 (47), 258 (45); HRMS (EI) Calcd for $C_{24}H_{27}NO_7$: 441.1788. Found: 441.1789.

*Methyl 3-Acetyl-7-chloro-4-(cyclohexylamino)-1-hydroxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6h**).* Obtained as a light brown solid (0.7 h, 120 mg, 90%); mp: 192−200 °C (CH_2Cl_2); IR (cm^{-1}): 3510, 3095, 2935, 2852, 1741, 1637, 1606, 1586; ^1H NMR (500 MHz, $CDCl_3$) δ 11.03 (d, *J* = 6.7 Hz, 1H), 8.18 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 5.40 (bs, 1H), 3.87 (m, 1H), 3.80 (s, 3H), 3.20 (d, *J* = 15.9 Hz, 1H), 2.87 (d, *J* = 15.9 Hz, 1H), 2.28 (s, 3H), 2.00 (m, 2H), 180−1.33 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 197.6 (C), 175.8 (C), 174.4 (C), 156.5 (C), 153.4 (C), 146.1 (C), 135.1 (CH), 132.4 (C), 125.6 (CH), 124.8 (C), 121.0 (C), 119.6 (CH), 102.4 (C), 72.3 (C), 55.1 (CH), 53.6 (CH_3), 35.9 (CH_2), 35.0 (CH_2), 34.8 (CH_2), 29.0 (CH_3), 25.5 (CH_2), 24.7 (CH_2) ppm; MS (CI) *m/z* (%) 446 (M + 1, 21), 445 (M^+, 12), 428 (31), 396 (70), 386 (22), 314 (15); HRMS (EI) Calcd for $C_{23}H_{24}ClNO_6$: 445.1292. Found: 445.1276.

*Methyl 3-Acetyl-4-(cyclohexylamino)-1-hydroxy-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6i**).* Obtained as a yellow solid (0.4 h, 86 mg, 70%); mp: 170−183 °C (hexane−EtOAc); IR (cm^{-1}): 3481, 2934, 2852, 1746, 1636, 1608, 1588; ^1H NMR (400 MHz, $CDCl_3$) δ 11.12 (d, J = 8.2 Hz, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.77 (t, *J* = 8.6 Hz, 1H), 7.52−7.47 (m, 2H), 5.67(s, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.21 (d, *J* = 15.8 Hz, 1H), 2.88 (d, *J* = 15.8 Hz, 1H), 2.28 (s, 3H), 2.03 (m, 2H), 1.80 (m, 2H), 1.47−1.30 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 197.5 (C), 177.1 (C), 174.4 (C), 165.2 (C), 155.1 (C), 146.5 (C), 135.0 (CH), 126.2 (CH), 126.1 (CH), 123.8 (C), 121.0 (C), 117.9 (CH), 101.9 (C), 72.7 (C), 55.0 (CH), 53.5 (CH_3), 35.9 (CH_2), 35.0 (CH_2), 34.8 (CH_2), 29.0 (CH_3), 25.5 (CH_2), 24.7 (CH_2) ppm; MS (CI) *m/z* (%) 412 (M + 1, 8), 411 (M^+, 5), 394 (11), 362 (75), 280 (16). HRMS (EI) Calcd for $C_{23}H_{25}NO_6$: 411.1682. Found: 411.1680.

*Methyl 3-Acetyl-1-hydroxy-4-((4-methoxyphenyl)amino)-7-methyl-9-oxo-2,9-dihydro-1H-xanthene-1-carboxylate (**6j**).* Obtained as a yellow solid (1.9 h, 84 mg, 62%); mp: 64−80 °C (hexane−EtOAc); IR (cm^{-1}): 3382, 2951, 2836, 1737, 1612, 1509; ^1H NMR (500 MHz, $CDCl_3$) δ 11.82 (s, 1H), 7.91 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 1H), 6.10 (bs, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.32 (d, *J* = 16.1 Hz, 1H), 2.98 (d, *J* = 16.1 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 200.0 (C), 179.9 (C), 175.1 (C), 157.6 (C), 156.9 (C), 155.7 (C), 144.0 (C), 136.5 (C), 136.4 (CH), 135.4 (C), 125.1 (CH), 124.5 (CH), 123.5 (C), 120.5 (C), 118.0 (CH), 114.6 (CH), 106.6 (C), 73.0 (C), 55.5 (CH), 53.4 (CH_3), 35.6 (CH_2), 29.0 (CH_3), 20.7 (CH_3) ppm; MS (CI) *m/z* (%) 450 (M^+, 4), 400 (9), 372 (7), 187 (16), 155 (15). HRMS (EI) Calcd for $C_{25}H_{23}NO_7$: 449.1474. Found: 449.1477.

*Methyl 3-Acetyl-1-hydroxy-7-methyl-9-oxo-4-(pentylamino)-2,9-dihydro-1H-xanthene-1-carboxylate (**6k**).* Obtained as a dark brown oil (1.0 h, 103 mg, 83%); IR (cm^{-1}): 3423, 2954, 1737, 1617; ^1H NMR (500 MHz, $CDCl_3$) δ 11.10 (t, *J* = 4.9 Hz, 1H), 8.00 (d, *J* = 1.0 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 3.80 (s, 3H), 3.68−3.59 (m, 2H), 3.20 (d, *J* = 15.8 Hz, 1H), 2.87 (d, *J* = 15.8 Hz, 1H), 2.48 (s, 3H), 2.27 (s, 3H), 1.69 (m, 2H), 1.38 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 198.1 (C), 177.7 (C), 175.2 (C), 156.5 (C), 153.9 (C), 147.9 (C), 136.8 (C), 136.5 (CH), 125.7 (CH), 123.8 (C), 121.1 (C), 118.0 (CH), 101.7 (C), 72.6 (C), 53.3 (CH_3), 46.6 (CH_2), 35.6 (CH_2), 30.6 (CH_2), 28.9 (CH_2), 28.6 (CH_3), 22.2 (CH_2), 20.8 (CH_3), 13.73 (CH_3) ppm; MS (CI) *m/z* (%) 414 (M + 1, 12), 413 (5), 396 (10), 364 (70), 354 (68), 322 (100). HRMS (EI) Calcd for $C_{23}H_{28}NO_6$: 414.1917. Found: 414.1938.

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General Procedure for the Synthesis of Xanthones (7a−p). *Method A*: To a solution of chromenones **1a−1d** (0.3 mmol) in dry THF (2 mL), isocyanide **2a−2d** (0.36 mmol) and dienophile **4a** (0.6 mmol) are successively added. The resulting mixture is heated at 70 °C under a nitrogen atmosphere until all the starting chromone is consumed, as judged by TLC. Then 2 equiv of DBU are added, and the reaction mixture is heated at the same temperature until the intermediate 1-hydroxydihydroxanthone is completely aromatized. HCl (1 N) is then added to the reaction mixture, the crude is extracted with CH_2Cl_2, and the organic phase is dried (Na_2SO_4) and concentrated. The residue is purified by column chromatography (silica gel, hexane−EtOAc gradient), giving the desired product **7a−7d**, **7l−7o**.

Method B: To a solution of chromenones **1a−1d** (0.3 mmol) in dry THF (2 mL), isocyanide **2a−2c** (0.36 mmol) and dienophile **4a−4b** (0.36 mmol) are successively added. The resulting mixture is irradiated with MW in a closed vial at 100 °C until all the starting chromone is consumed, as judged by TLC. Then 2 equiv of DBU are added, and the reaction mixture is heated at the same temperature until the intermediate 1-hydroxydihydroxanthone is completely aromatized. HCl (1 N) is then added to the reaction mixture, the crude is extracted with CH_2Cl_2, and the organic phase is dried (Na_2SO_4) and concentrated. The residue is purified by column chromatography (silica gel, hexane−EtOAc gradient), giving the desired product **7f−7k**, **7p**.

*Methyl 3-Cyano-4-(cyclohexylamino)-7-methyl-9-oxo-9H-xanthene-1-carboxylate (**7a**).* Obtained as a yellow solid (6.5 h, 80 mg, 68%); mp: 227−230 °C (hexane−EtOAc); IR (cm^{-1}): 3418, 2933, 2856, 2210, 1735, 1659, 1614; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 1.0 Hz, 1H, H-8), 7.57 (d, J = 8.8 Hz, 1H, H-5 or H-6), 7.43 (d, J = 8.6 Hz, 1H, H-5 or H-6), 7.32 (s, 1H, H-2), 5.33 (d, J = 8.7 Hz, 1H, NH), 4.29 (m, 1H, C<u>H</u>-NH), 3.97 (s, 3H, $COOCH_3$), 2.47 (s, 3H, Ar−CH_3), 2.22 (m, 2H, Cy), 1.85−1.27 (m, 8H, Cy) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 176.0 (C), 169.4 (C), 153.6 (C), 145.4 (C), 141.7 (C), 137.0 (C-5 or C-6), 135.8 (C), 128.1 (C-2), 126.6 (C-8), 121.8 (C), 121.1 (C), 120.2 (C), 118.6 (C), 117.7 (C-5 or C-6), 93.7 (C), 53.0 ($COO\underline{C}H_3$), 52.3 (CH-NH), 34.0 (CH_2), 25.2 (CH_2), 24.0 (CH_2), 20.7 (Ar−CH_3) ppm; MS (CI) m/z (%) 391 (M + 1, 53), 390 (M^+, 94), 389 (49), 374 (98), 308 (41); HRMS (ESI-FIA-TOF) Calcd for $C_{23}H_{22}N_2NaO_4$: 413.1474. Found $C_{23}H_{22}N_2NaO_4$: 413.1472.

*Methyl 3-Cyano-4-(cyclohexylamino)-9-oxo-9H-xanthene-1-carboxylate (**7b**).* Obtained as a yellow solid (2.7 h, 88 mg, 78%); mp: 204−214 °C (hexane−EtOAc); IR (cm^{-1}): 3382, 2942, 2851, 1735, 1665, 1609, 1561; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 7.9 Hz, 1H), 7.78 (t, J = 8.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.35 (s, 1H), 5.34 (d, J = 8.7 Hz, 1H), 4.30 (m, 1H), 3.98 (s, 3H), 2.22 (m, 2H), 1.85−1.26 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 175.2 (C), 168.6 (C), 154.8 (C), 145.0 (C), 141.2 (C), 135.4 (CH), 128.0 (CH), 127.0 (CH), 125.4 (CH), 121.9 (C), 120.9 (C), 119.9 (C), 118.2 (C), 117.7 (CH), 94.0 (C), 53.2 (CH_3), 52.6 (CH), 34.3 (CH_2), 25.6 (CH_2), 24.5 (CH_2) ppm; MS (CI) m/z (%) 377 (M + 1, 22), 376 (M^+, 32), 360 (74), 345 (100); HRMS (EI) Calcd for $C_{22}H_{20}N_2O_4$: 376.1423. Found: 376.1422.

*Methyl 3-Cyano-4-(cyclohexylamino)-6-methoxy-9-oxo-9H-xanthene-1-carboxylate (**7c**).* Obtained as a yellow solid (9.8 h, 83 mg, 65%); mp: 254−261 °C (hexane−EtOAc); IR (cm^{-1}): 3374, 2929, 2855, 2212, 1716, 1650, 1607, 1582; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 6.98 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 2.3 Hz, 1H), 5.27 (d, J = 8.7 Hz, 1H), 4.28 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 2.22 (m, 2H), 1.85−1.24 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 174.4 (C), 169.0 (C), 165.6 (C), 156.8 (C), 145.0 (C), 141.0 (C), 128.6 (CH), 127.8 (CH), 121.1 (C), 120.2 (C), 118.3 (C), 115.8 (C), 114.6 (CH), 100.2 (CH), 93.9 (C), 56.2 (CH_3), 53.1 (CH_3), 52.5 (CH), 34.3 (CH_2), 25.6 (CH_2), 24.5 (CH_2) ppm; MS (CI) m/z (%) 407 (M + 1, 29), 406 (M^+, 15), 390 (31), 375 (66), 263 (21); HRMS (EI) Calcd for $C_{23}H_{22}N_2O_5$: 406.1529. Found: 406.1526.

*Methyl 7-Chloro-3-cyano-4-(cyclohexylamino)-9-oxo-9H-xanthene-1-carboxylate (**7d**).* Obtained as a yellow solid (3.1 h, 86 mg, 70%); mp: 228 °C (hexane−EtOAc); IR (cm^{-1}): 3393, 2943, 2852, 2208, 1731, 1666, 1606, 1562; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 2.5 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.37 (s, 1H), 5.30 (d, J = 8.6 Hz, 1H), 4.31 (m, 1H), 3.97 (s, 3H), 2.21 (m, 2H), 1.85−1.25 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 174.3 (C), 168.5 (C), 153.2 (C), 144.9 (C), 141.2 (C), 135.6 (CH), 131.4 (C), 128.5 (CH), 126.4 (CH), 122.8 (C), 120.6 (C), 119.9 (C), 119.5 (CH), 118.1 (C), 94.3 (C), 53.2 (CH_3), 52.6 (CH), 34.3 (CH_2), 25.5 (CH_2), 24.4 (CH_2) ppm; MS (CI) m/z (%) 411 (M + 1, 35), 410 (M^+, 26), 394 (41), 379 (100), 369 (40), 351 (15); HRMS (EI) Calcd for $C_{22}H_{19}N_2O_4Cl$: 410.1033. Found: 410.1034.

*Methyl 3-Acetyl-4-(cyclohexylamino)-7-methyl-9-oxo-9H-xanthene-1-carboxylate (**7f**).* Obtained as a yellow solid (7.6 h, 89 mg, 70%); mp: 214−218 °C (hexane−EtOAc); IR (cm^{-1}): 3448, 2932, 2853, 1730, 1654, 1635, 1575; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (d, J = 7.3 Hz, 1H), 8.05 (s, 1H), 7.70 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 4.38 (m, 1H), 3.98 (s, 3H), 2.66 (s, 3H), 2.47 (s, 3H), 2.11 (m, 2H), 1.86−1.33 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.3 (C), 176.0 (C), 170.3 (C), 153.5 (C), 146.9 (C), 143.9 (C), 136.6 (CH), 134.9 (C), 126.7 (CH), 126.1 (CH), 122.2 (C), 121.6 (C), 119.0 (C), 117.7 (C), 117.5 (CH), 55.0 (CH), 53.0 (CH_3), 35.0 (CH_2), 28.9 (CH_3), 25.7 (CH_2), 24.9 (CH_2), 21.0 (CH_3) ppm; MS (CI) m/z (%) 408 (M + 1, 9), 407 (M^+, 5), 376 (24), 356 (10), 247 (24), 186 (62); HRMS (EI) Calcd for $C_{24}H_{25}NO_5$: 407.1733. Found: 407.1734.

*Methyl 3-Acetyl-4-(cyclohexylamino)-6-methoxy-9-oxo-9H-xanthene-1-carboxylate (**7g**).* Obtained as a yellow solid (2.5 h, 99 mg, 75%); mp: 206−208 °C (hexane−EtOAc); IR (cm^{-1}): 3428, 2926, 2849, 1724, 1689, 1654, 1620, 1604; ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, J = 7.0 Hz, 1H, NH), 8.16 (d, J = 8.9 Hz, 1H, H-7 or H-8), 7.68 (s, 1H, H-2), 6.97 (d, J = 8.9 Hz, 1H, H-7 or H-8), 6.79 (d, J = 2.3 Hz, 1H, H-5), 4.32 (m, 1H, <u>CH</u>-NH), 3.99 (s, 3H, $COOCH_3$), 3.95 (s, 3H, Ar−OCH_3), 2.65 (s, 3H, $COCH_3$), 2.13 (m, 2H, Cy), 1.87−1.25 (m, 8H, Cy) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.8 (C), 175.7 (C), 170.9 (C), 165.8 (C), 157.6 (C), 147.0 (C), 143.9 (C), 128.7 (C-7 or C-8), 126.8 (C-2), 122.7 (C), 119.4 (C), 118.3 (C), 116.2 (C), 114.5 (C-7 or C-8), 99.80 (C-5), 56.2 (Ar−O<u>C</u>H_3), 54.7 (CH-NH), 52.8 ($COO\underline{C}H_3$), 34.7 (CH_2), 28.7 ($CO\underline{C}H_3$), 25.6 (CH_2), 24.6 (CH_2) ppm; MS (CI) m/z (%) 424 (M + 1, 46), 423 (M^+, 47), 392 (73), 342 (15), 153 (100); HRMS (EI) Calcd for $C_{24}H_{25}NO_6$: 423.1682. Found: 423.1686.

*Methyl 3-Acetyl-7-chloro-4-(cyclohexylamino)-9-oxo-9H-xanthene-1-carboxylate (**7h**).* Obtained as a yellow solid (1.0 h, 87 mg, 68%); mp: 235 °C (hexane−EtOAc); IR (cm^{-1}): 3439, 2929, 2851, 1727, 1647, 1586; ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (d, J = 7.4 Hz, 1H), 8.22 (d, J = 2.6 Hz, 1H), 7.74 (s, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 4.33 (m, 1H), 3.98 (s, 3H), 2.66 (s, 3H), 2.10 (m, 2H), 1.86−1.25 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.3 (C), 174.9 (C), 169.9 (C), 153.5 (C), 146.7 (C), 143.8 (C), 135.4 (CH), 130.7 (C), 127.3 (CH), 126.2 (CH), 122.7 (C), 122.0 (C), 119.4 (CH), 119.3 (C), 117.5 (C), 55.1 (CH), 53.0 (CH_3), 35.0 (CH_2), 28.9 (CH_3), 25.7 (CH_2), 24.9 (CH_2) ppm; MS (CI) m/z (%) 428 (M + 1, 16), 427 (M^+, 17), 396 (29), 314 (24); HRMS (EI) Calcd for $C_{23}H_{22}NO_5Cl$: 427.1187. Found: 427.1180.

*Methyl 3-Acetyl-4-(cyclohexylamino)-9-oxo-9H-xanthene-1-carboxylate (**7i**).* Obtained as a yellow solid (1.6 h, 90 mg, 76%); mp: 169−173 °C (hexane−EtOAc); IR (cm^{-1}): 3431, 2936, 2847, 1724, 1659, 1639, 1590; ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (d, J = 7.6 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 8.6 Hz, 1H), 7.72 (s, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 4.39 (m, 1H), 3.99 (s, 3H), 2.66 (s, 3H), 2.14 (m, 2H), 1.86−1.32 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.3 (C), 175.9 (C), 170.2 (C), 155.2 (C), 146.8 (C), 143.9 (C), 153.3 (CH), 126.9 (CH), 126.8 (CH), 124.9 (CH), 122.3 (C), 122.0 (C),119.1 (C), 117.7 (CH), 117.6 (C), 55.1 (CH), 53.0 (CH_3), 35.0 (CH_2), 28.9 (CH_3), 25.7 (CH_2), 24.9 (CH_2) ppm; MS (CI) m/z (%) 394 (M + 1, 31), 393 (M^+, 33), 362 (77), 312 (20), 280 (22); HRMS (EI) Calcd for $C_{23}H_{23}NO_5$: 393.1576. Found: 393.1573.

*Methyl 3-Acetyl-4-((4-methoxyphenyl)amino)-7-methyl-9-oxo-9H-xanthene-1-carboxylate (**7j**).* Obtained as a red solid (3.5 h, 91 mg, 70%); mp: 178−184 °C (hexane−EtOAc); IR (cm^{-1}): 3242,

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2957, 1729, 1658, 1640, 1562; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 6.47 (d, J = 8.5 Hz, 2H), 4.02 (s, 3H), 3.83 (s, 3H), 2.72 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.8 (C), 175.9 (C), 170.1 (C), 156.8 (C), 153.0 (C), 147.3 (C), 140.1 (C), 136.6 (CH), 135.6 (C), 134.7 (C), 125.7 (CH), 125.3 (CH), 124.2 (CH), 122.0 (C), 121.9 (C), 121.3 (C), 120.8 (C), 117.6 (CH), 113.8 (CH), 55.8 (CH), 53.1 (CH_3), 28.9 (CH_3), 21.0 (CH_3) ppm; MS (CI) m/z (%) 433 (M + 2, 23), 432 (M + 1, 77), 431 (M^+, 100), 400 (88), 257 (17); HRMS (EI) Calcd for $C_{25}H_{21}NO_6$: 431.1369. Found: 431.1373.

*Methyl 3-Acetyl-7-methyl-9-oxo-4-(pentylamino)-9H-xanthene-1-carboxylate (**7k**).* Obtained as a yellow solid (2.4 h, 52 mg, 44%); mp: 120−123 °C (hexane−EtOAc); IR (cm^{-1}): 3442, 2949, 1731, 1716, 1656, 1634, 1578; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.05 (s, 1H), 7.70 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 3.98 (s, 3H), 3.93 (t, J = 7.0 Hz, 2H), 2.65 (s, 3H), 2.47 (s, 3H), 1.75 (m, 2H), 1.48−1.37 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 200.3 (C), 176.0 (C), 170.3 (C), 153.5 (C), 147.1 (C), 144.9 (C), 136.5 (CH), 134.9 (C), 126.6 (CH), 126.1 (CH), 122.3 (C), 121.6 (C), 118.7 (C), 117.6 (CH), 117.5 (C), 53.0 (CH_3), 47.2 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 28.9 (CH_3), 22.6 (CH_2), 21.1 (CH_3), 14.2 (CH_3) ppm; MS (CI) m/z (%) 396 (M + 1, 13), 395 (M^+, 10), 364 (34), 326 (83), 325 (64), 294 (100). HRMS (EI) Calcd for $C_{23}H_{25}NO_5$: 395.1733. Found: 395.1733.

*Methyl 4-(tert-Butylamino)-3-cyano-6-methoxy-9-oxo-9H-xanthene-1-carboxylate (**7l**).* Obtained as a yellow solid (3.6 h, 79 mg, 69%); mp: 169 °C (hexane−EtOAc); IR (cm^{-1}): 3343, 2968, 2229, 1729, 1651, 1622, 1603; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.00 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 4.02 (s, 3H), 3.97 (s, 3H), 1.50 (s, 9H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): 174.4 (C), 168.7 (C), 165.8 (C), 156.9 (C), 149.2 (C), 141.8 (C), 128.6 (CH), 126.3 (CH), 125.9 (C), 121.9 (C), 118.1 (C), 115.5 (C), 114.5 (CH), 107.3 (C), 100.2 (CH), 56.7 (C), 56.2 (CH_3), 53.3 (CH_3) 31.2 (CH_3) ppm; MS (CI) m/z (%) 381 (M + 1, 100), 380 (M^+, 52), 349 (100), 325 (97), 294 (76); HRMS (EI) Calcd for $C_{21}H_{20}N_2O_5$: 380.1372. Found: 380.1372.

*Methyl 4-(tert-Butylamino)-7-chloro-3-cyano-9-oxo-9H-xanthene-1-carboxylate (**7m**).* Obtained as a yellow solid (4.0 h, 90 mg, 78%); mp: 227−234 °C; IR (cm^{-1}): 3395, 2974, 2211, 1726, 1664, 1607, 1562; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 2.5 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.45 (s, 1H), 4.63 (bs, 1H), 4.01 (s, 3H), 1.52 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 174.4 (C), 168.2 (C), 153.2 (C), 148.7 (C), 142.0 (C), 135.8 (CH), 131.3 (C), 126.8 (CH), 126.3 (CH), 125.1 (C), 122.4 (C), 121.1 (C), 119.3 (CH), 117.8 (C), 106.6 (C), 56.6 (C), 53.2 (CH_3), 31.1 (CH_3) ppm; MS (CI) m/z (%) 385 (M + 1, 9), 384 (M^+, 8), 353 (23), 328 (21), 296 (35), 149 (46); HRMS (EI) Calcd for $C_{20}H_{17}N_2O_4Cl$: 384.0877. Found: 384.0874.

*Methyl 7-Chloro-3-cyano-4-((4-methoxyphenyl)amino)-9-oxo-9H-xanthene-1-carboxylate (**7n**).* Obtained as a yellow solid (8.3 h, 37 mg, 27%); mp: 260−263 °C (hexane−EtOAc); IR (cm^{-1}): 3343, 2211, 1733, 1714, 1664, 1607, 1561; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 2.5 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.39 (s, 1H), 7.38 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.86 (bs 1H), 3.99 (s, 3H), 3.85 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 174.3 (C), 168.3 (C), 158.8 (C), 153.3 (C), 145.6 (C), 141.8 (C), 140.7 (C), 135.8 (CH), 131.6 (C), 131.5 (C), 128.0 (CH), 127.0 (CH), 126.4 (CH), 122.8 (C), 122.4 (C), 121.1 (C), 119.5 (CH), 115.5 (C), 114.7 (CH), 98.9 (C), 55.7 (CH_3), 53.3 (CH_3) ppm; MS (CI) m/z (%) 435 (M + 1, 16), 434 (M^+, 7), 400 (49), 340 (20), 152 (22); HRMS (EI) Calcd for $C_{23}H_{15}N_2O_5Cl$: 434.0669. Found: 434.0669.

*Methyl 3-Cyano-6-methoxy-4-((4-methoxyphenyl)amino)-9-oxo-9H-xanthene-1-carboxylate (**7o**).* Obtained as a yellow solid (3.5 h, 52 mg, 40%); mp: 219−230 °C (hexane−EtOAc); IR (cm^{-1}): 3394, 2951, 2225, 1745, 1655, 1620, 1607; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.9 Hz, 1H), 7.32 (s, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 8.9 Hz, 1H), 6.85 (bs, 1H), 6.80 (d, J = 2.3 Hz, 1H), 4.00 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 174.2 (C), 168.8 (C), 165.7 (C), 158.6 (C), 156.9 (C), 145.6 (C), 140.4 (C), 132.0 (C), 128.6 (CH), 127.4 (CH), 126.9 (CH), 122.6 (C), 121.6 (C), 115.8 (C), 115.7 (C), 114.73 (CH), 114.69 (CH), 98.4 (CH), 56.1 (CH_3), 55.7 (CH_3), 53.3 (CH_3) ppm; MS (CI) m/z (%) 432 (M + 2, 29), 431 (M + 1, 100), 430 (M^+, 53), 399 (59); HRMS (EI) Calcd for $C_{24}H_{18}N_2O_6$: 430.1165. Found: 430.1168.

*Methyl 3-Acetyl-7-chloro-9-oxo-4-(pentylamino)-9H-xanthene-1-carboxylate (**7p**).* Obtained as a yellow solid (1.2 h, 60 mg, 48%); mp: 161−163 °C (hexane−EtOAc); IR (cm^{-1}): 3428, 2952, 1725, 1655, 1602, 1573; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, J = 4.5 Hz, 1H), 8.20 (d, J = 2.5 Hz, 1H), 7.72 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 3.97 (s, 3H), 3.89 (m, 2H), 2.66 (s, 3H), 1.75 (m, 2H), 1.48−1.37 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): 200.3 (C), 174.8 (C), 169.9 (C), 153.5 (C), 146.9 (C), 144.7 (C), 135.3 (CH), 130.7 (C), 127.2 (CH), 126.1 (CH), 122.7 (C), 122.0 (C), 119.5 (CH), 118.9 (C), 117.4 (C), 53.0 (CH_3), 47.2 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 28.8 (CH_3), 22.6 (CH_2), 14.2 (CH_3) ppm; MS (CI) m/z (%) 417 (M + 2, 25), 416 (M + 1, 41), 415 (M^+, 41), 386 (35), 385 (24), 384 (100), 358 (27); HRMS (EI) Calcd for $C_{22}H_{22}NO_5Cl$: 415.1187. Found: 415.1188.

Synthesis of (2*E*,2′*E*)-1,1′-(4,4′-Dihydroxy-[1,1′-biphenyl]-3,3′-diyl)bis(3-(dimethylamino)prop-2-en-1-one) (10). A mixture of 1,1′-(4,4′-dihydroxy-[1,1′-biphenyl]-3,3′-diyl)bis(ethan-1-one) **9**[15] (10 mmol) and dimethylformamide dimethylacetal (10 mmol) is stirred and irradiated for 2 min at 150 °C in a microwave. The solid obtained is recrystallized from toluene, heated in the microwave reactor during 30 s at 150 °C, and then cooled at 4 °C. The collected crystals are then washed with hexane; obtained as a yellow solid (2.80 g, 74%); mp: 219 °C (toluene); IR (cm^{-1}): 2917, 1630, 1526; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.93 (s, 1H), 7.93 (d, J = 12.1 Hz, 1H), 7.77 (s, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 5.83 (d, J = 12.0 Hz, 1H), 3.22 (s, 3H), 3.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 129.2 (C), 162.7 (C), 155.6 (CH), 133.2 (CH), 131.8 (C), 126.9 (CH), 120.7 (C), 118.9 (CH), 90.2 (CH), 45.4 (CH_3), 37.5 (CH_3) ppm; MS (CI) m/z (%) 381 (M + 1, 100), 380 (M^+, 52), 335 (60), 290 (17); HRMS (EI) Calcd for $C_{22}H_{24}N_2O_4$: 380.1736. Found: 380.1735.

Synthesis of Dimethyl 2,2′-(4,4′-Dioxo-4*H*,4′*H*-[6,6′-bichromene]-3,3′-diyl)bis(2-oxoacetate) (11). A solution of methyl clorooxoacetate (1.1 mmol) in dichloromethane (1 mL) is added dropwise to an ice-cooled solution of enaminone **10** (1.0 mmol) and pyridine (2.2 mmol) in dichloromethane (1 mL). The resulting mixture is then stirred for 24 h at rt. The crude is washed with copper sulfate solution (to eliminate the pyridine) and brine; the organic phase is dried with Na_2SO_4, filtered, and evaporated, affording a solid, which is filtered and washed with cold hexane and ethyl acetate; obtained as a light brown solid (388 mg, 84%); mp: 204 °C (dec.; CH_2Cl_2); IR (cm^{-1}): 3435, 3072, 2956, 1753, 1688, 1597; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.50 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 4.02 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3 (C), 174.5 (C), 164.2 (C), 162.4 (CH), 156.1 (C), 137.7 (C), 133.8 (CH), 125.3 (C), 124.6 (CH), 120.2 (C), 119.8 (CH), 53.22 (CH_3). MS (CI) m/z (%) 463 (M + 1, 35), 462 (M^+, 13), 439 (35), 435 (43), 287 (38); HRMS (EI) Calcd for $C_{24}H_{14}O_{10}$: 462.0587. Found: 462.0558.

Synthesis of Dimethyl 6,6′-Dicyano-5,5′-bis(cyclohexylamino)-8,8′-dihydroxy-9,9′-dioxo-7,7′,9,9′-tetrahydro-8*H*,8′*H*-[2,2′-bixanthene]-8,8′-dicarboxylate (12). It was carried out according to *Method A* for the synthesis of dihydroxanthones **6**. Obtained as a yellow solid (8 h, 210 mg, 89%); mp: 230 °C (dec.; CH_2Cl_2); IR (cm^{-1}): 3429, 2932, 2855, 2183, 1742, 1632, 1609; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 12.3 Hz, 1H), 8.04 (t, J = 9.3 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 5.22 (t, J = 8.8 Hz, 1H), 4.68 (bs, 1H), 4.17 (m, 1H), 3.86 (s, 3H), 3.15 (d, J = 16.3 Hz, 1H), 2.77 (d, J = 16.3 Hz, 1H), 2.22 (m, 2H), 1.81−1.30 (m, 8H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0 (C), 175.9 (C), 174.62 (C), 174.59 (C), 154.55 (C), 154.53 (C), 154.04 (C), 154.03 (C), 140.7 (C), 137.03 (C), 137.02 (C), 133.51 (CH), 133.50 (CH), 124.3 (CH), 123.87 (C), 123.85 (C), 120.6 (C), 119.32 (C), 119.30 (C), 119.05 (CH), 72.3

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(C), 70.75 (C), 70.72 (C), 53.94 (CH_3), 53.92 (CH_3), 52.10 (CH), 52.08 (CH), 37.08 (CH_2), 37.06 (CH_2), 34.0 (CH_2), 33.2 (CH_2), 27.0 (CH_2), 25.60 (CH_2), 25.56 (CH_2), 24.9 (CH_2), 24.42 (CH_2), 24.38 (CH_2); HRMS (ESI-TOF) Calcd for $C_{44}H_{43}N_4O_{10}$: 787.2974. Found: 787.2971.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all products, single-crystal data of product **7g**, and computational data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00658.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jdal@unex.es (J.D.)

*E-mail: cfernan@unex.es (C.F.M.)

Notes

The authors declare no competing financial interest.

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